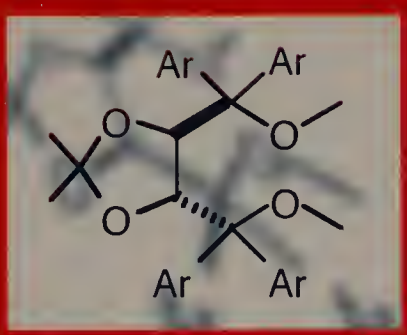
Tartaric and Malic Acids in Synthesis

A Source Book of Building Blocks, Ligands, Auxiliaries, and Resolving Agents



JACEK GAWROŃSKI • KRYSTYNA GAWROŃSKA

TARTARIC AND MALIC ACIDS IN SYNTHESIS

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A Source Book of Building Blocks, Ligands, Auxiliaries, and Resolving Agents

by

Jacek Gawroński

and

Krystyna Gawrońska

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To Paweł

CONTENTS

FOREWORD

It was with great pleasure that I accepted the request to write the Foreword to this book on tartaric and malic acid.

I have before me a copy of the paper written by Prof. Ernst L. Eliel entitled "Louis Pasteur and Modern Industrial Stereochemistry," published in *Croatica Chemica Acta* 1996, *69,* 519. The paper is based on a lecture given by the author at a symposium commemorating the Louis Pasteur Centennial sponsored by the New York section of the American Chemical Society on October 14, 1995. The paper is dedicated to Professor Vladimir Prelog on the occasion of his 90th birthday.

OF COURSE, THE STORY BEGINS WITH TARTARIC ACID

Although it is obvious that I did not know Louis Pasteur personally, I did know Professor Prelog and I do know Professor Eliel as well as the Gawroński family. From the publication by Prof. Eliel mentioned above, as well as from the original publication by Louis Pasteur exactly 150 years ago (L. Pasteur, *Ann. Chim. et Phys.* 1848, *24,* 442) it is possible to reconstruct the critical role that tartaric acid has played in the history of stereochemistry.

Louis Pasteur was just 26 years of age when he was asked to perform the physical separation of the enantiomorphic crystals of the sodium, ammonium salt of tartaric acid in front of the assembled academy members. Important was the presence of the 74-year-old Jean Baptiste Biot, the French physicist and astronomer who had invented the polariscope (among other things) and who had established the fundamental laws of the rotation of plane polarized light by optically active substances. Biot insisted on measuring the rotation of the enantiomorphic crystals himself. This event opened the door to the foundation of stereochemistry as well as to the chemistry of life.

STEREOCHEMISTRY HAD ITS START WHEN TARTARIC ACID WAS RESOLVED

The impact of Pasteur's discovery on chemistry was soon felt throughout the world. Whether we discuss the mechanism of drug action in the body, or the possibility of life on other planets, whether we study the mechanism of a reac-

tion or whether we attempt the total synthesis of a complex molecule, sooner or later the concept of chirality, the stereochemistry of the molecules involved, becomes the critical issue.

I have written these few historical notes in order to remind the prospective reader of the fact that it is not only the survey of the chemistry of tartaric and malic acids that makes this book from the Gawrońskis an important addition to chemical literature, but to emphasize the fact that these excellent Polish chemists, who themselves have made significant contributions to stereochemistry, also have added an important chapter to the history of chemistry. "If we do not know whence we came, we will never know where we are going."

This book should be on the shelf in every library.

Groningen, The Netherlands HANS WYNBERG

PREFACE

The use of renewable enantiomerically pure natural products as a source of chirality in synthesis has became routine in the past two to three decades. Tartaric and malic acids are among the most frequently used starting materials and their synthetic versatility has resulted in an amazing array of products made available by well-developed synthetic procedures. The chemistry of these hydroxyacids was developed over the period of more than a hundred years. However, some new areas, as for example the chemistry of tartrate boronates, or TADDOLs, and their complexes, have been uncovered only recently. The seminal work of Professor Dieter Seebach published in *Modern Synthetic Methods 1980* (Otto Salle Verlag–Verlag Sauerländer, R. Scheffold, Ed.) was the first to recognize the potential of the use of tartaric acid as a chiral building block. Subsequent rapid developments in this field led us to believe that while four-carbon intermediates based on a tartaric and malic acid framework are of primary importance for the synthesis of enantiomerically pure compounds, no comprehensive and updated review of the synthesis and applications of these compounds has appeared. The recent book of G. M. Coppola and H. F. Schuster, *α-Hydroxy Acids in Enantioselective Synthesis* (VCH, 1997), does serve the purpose stated in the title but it is product-oriented and does not deal with the many applications of tartaric and malic acids as resolving agents, ligands, and auxiliaries.

When starting the work we have seen this book as a unique source of detailed information on the vast number of four-carbon chiral compounds derived from tartaric and malic acids. This information was intended to include their synthesis and applications, as chiral building blocks, ligands, auxiliares, and resolving agents. We have searched over 2500 references to collect the data that make the foundation of the book.

We hope that the book will become a standard source of information and ideas for synthetic chemist already working in or entering the field of synthesis of enantiomerically pure compounds. We expect that the book will find its place not only in the research laboratories in academia but also in chemical, pharmaceutical, and agrochemical industries.

We are grateful to Mrs. Halina Kolbón, M.Sc. and to Mrs. Anna Pięta for their invaluable help in collecting the data and converting the raw manuscript into a readable publication.

JACEK GAWROŃSKI
KRYSTYNA GAWROŃSKA

Poznan, Poland

INTRODUCTION

WHY TARTARIC AND MALIC ACIDS?

The history of tartaric acid has long been associated with the most important discoveries in the fields of stereochemistry and organic chemistry. It was through Pasteur's discovery (1848) of two optical isomers of sodium ammonium tartrate that stereoisomerism was introduced to organic chemistry (the account of the development of structural studies of tartaric acid is given by Robinson[1]). One hundred years later, Bijvoet (1951) presented the method of determination of the absolute configuration of organic molecules by anomalous X-ray scattering using the sodium rubidium salt of natural tartaric acid. This experiment allowed for the first time to unequivocally establish the absolute configuration of a chiral molecule and to correlate the absolute stereostructures of other chiral molecules.

The unprecedented development of methods of asymmetric synthesis in the past two decades has been associated in many cases with the application of tartaric acid derivatives. Some spectacular methodologies, such as asymmetric epoxidation (Sharpless), asymmetric allylboration (Roush), asymmetric Diels–Alder and aldol reactions (Yamamoto), as well as asymmetric cyclopropanation (Charette) make use of simple tartaric acid derivatives as chiral ligands and provide a wide array of products of high enantiomeric purity.

More complex derivatives of tartaric acid such as TADDOLs have also entered the field of asymmetric synthesis as ligands for Lewis acid catalysts (the development of TADDOLates was due to Seebach and Duthaler–Hafner). TADDOLs were also helpful in developing the concept of enantioselective complex-forming hosts for organic guest molecules (Toda).

The chemistry of tartaric and malic acids has been marked by their extensive use as chiral building blocks (Seebach) and their recent application in *N*-acyliminium ion reactions (Hart, Chamberlin, Speckamp–Hiemstra.)

At present, tartaric and malic acids appear as unquestioned leaders among chiral organic compounds from which various highly functionalized nonracemic acyclic and heterocyclic compounds can be synthesized.

In a broader sense, tartaric and malic acids find countless applications in industry and in basic research (the number of citations of relevant reports and patents over the past 25 years exceeds 10,000). Their industral applications are broad and include pharmaceutical formulations, dental materials, ceramics, paints, electrochemical coatings and piezoelectronic devices. Malic diesters are known as mosquito repellents. For such applications racemic forms of tartaric

and malic acids are frequently adequate. However, with the development of methods of asymmetric synthesis, enantiomerically pure tartaric and malic acids were quickly recognized as basic commercial sources of chirality with highly functionalized structure.

Research papers, review articles[2,3] and books[4–6] published since 1980 are evidence of the increasing interest in such applications, although industrial application is still lagging in the use of derivatives of tartaric and malic acids as chiral building blocks[7]. Nevertheless, over the past 20 years the number of publications on the use of tartaric and malic acids in stereoselective synthesis has steadily increased, reaching 160 ± 20 papers published annually in the 1990s.

The field of synthetic use of tartaric and malic acids has now definitely approached the level of maturity.

The structural feature of the tartaric acid molecule—the C_2 symmetry—is highly desired for its application as chiral ligand, auxiliary, and resolving agent. For synthetic use it is often desirable to destroy molecular symmetry by selective transformation of one of the functional groups forming a pair. On the other hand, some applications of tartaric acid as a chiral building block may also have the advantage of molecular symmetry, such as in the case of two-directional synthesis.

Natural (+)-tartaric acid is one of the cheapest enantiomerically pure organic compounds; its low price is due to its ready availability as a by-product of the wine industry (potassium hydrogen tartrate, so-called cream of tartar). In fact, (+)-tartaric acid can be purchased at a price lower than the racemic acid, which is synthesized from maleic acid by catalytic addition of hydrogen peroxide. The price of natural tartaric acid varies with the source and the amount purchased, but it may be as low as several US dollars per kg.

Natural (−)-malic acid is considerably more expensive; its main source is the fermentative hydration of fumaric or maleic acids (acid-catalyzed hydration of fumaric acid is the method of production of racemic malic acid). Table 1 gives the comparison of relative prices of tartaric and malic acids in various configurational modifications.

Table 1. Relative price of tartaric and malic acids of 99% purity and 100 g quantity

L-(+)-tartaric acid (natural)	1
D-(−)-tartaric acid (unnatural)[a]	20–30
rac.-tartaric acid	2–4
meso-tartaric acid	150
L-(−)-malic acid (natural)	10
D-(+)-malic acid (unnatural)	150–300
rac.-malic acid	1

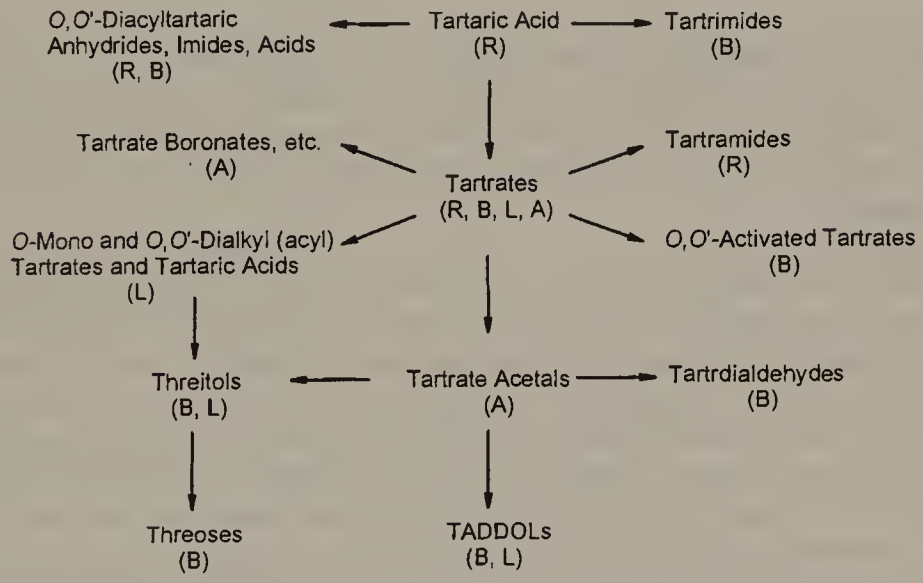
[a] This acid is nevertheless found in certain plants (Ref. 4)

HOW THE BOOK IS ORGANIZED

This book reviews the synthesis and applications of all four-carbon chiral building blocks, ligands, auxiliaries, and resolving agents derived from tartraric or malic acid. Some relevant properties of the derived compounds are mentioned. X-ray and other structural data are referred to, when appropriate. Although in a majority of cases the book mentions the derivatives of natural tartaric and malic acids, their enantiomers may be used as well.

The book is divided into **two parts** dealing with tartaric (**14 chapters**) and malic acid (**6 chapters**). Compounds within each part are divided according to their oxidation level, starting with the parent diacids and ending with the corresponding polyols: threitol and 1,2,4-butanetriol. The last chapter of the tartaric acid part is devoted to threonic acid, partly due to its unsymmetrical end-group structure and partly due to its synthetic relevance to both tartaric and ascorbic acids, from which it can be alternatively obtained.

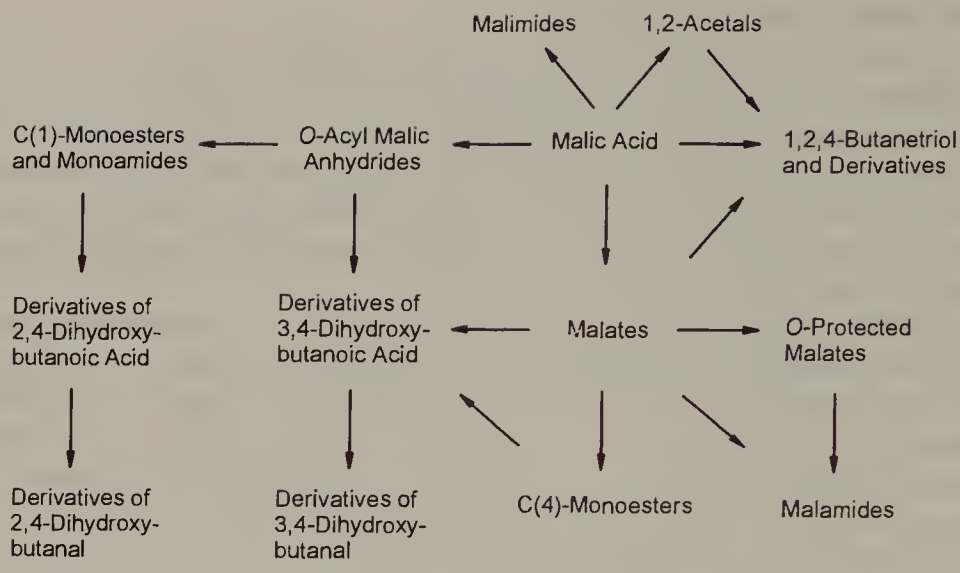
The main synthetic pathways to various derivatives of tartaric and malic acids are shown in Schemes 1 and 2.



Scheme 1. Main routes to various derivatives of tartaric acid (letters in parentheses indicate the most important types of application).

Chapters are further divided into **subchapters** allowing more easy access to the desired material. For example, chapters 13 on threitol and 20 on 1,2,4-butanetriol are divided into subchapters according to the position and number of the protecting groups.

Each chapter and subchapter has separate **sections** on the synthesis and applications of the derivatives. These sections are amply illustrated by **schemes** and **figures** (there are approximately 800 schemes throughout the book). For the



Scheme 2. Main routes to derivatives of malic acid (their principal applications are as chiral building blocks).

preparation of a specific tartaric or malic acid derivative, additional quick access to the information is provided by the **tables** of derivatives placed in the chapters. These tables (over 70 in the book) collect the basic data (melting or boiling point, specific rotation), if available, and the references for nearly 2000 specific compounds.

The data on specific rotation are helpful for identifying compounds and, in particular, for determining their optical purity and/or absolute configuration. However, care should be exercised when using these data, for two reasons. First, some of the data may come from measurements on tartaric or malic acid derivatives of uncertain purity, despite the effort to verify the data. Second, the optical rotation of malates and tartrates is strongly dependent on the solvent used.[8,9] L-Malates show negative $[\alpha]_D$ values in polar solvents and as pure liquids. Likewise, L-tartrates have positive $[\alpha]_D$ values under these conditions. However, when measured in chloroform solution, dimethyl and diethyl L-malate display positive rotation and L-tartrates are levorotatory. The change of the sign of rotation in chloroform solution is at least partly due to the association phenomena of tartrates and malates in nonpolar solvents. For such phenomena the effects of concentration and temperature may also be significant.

The commercial availability of tartaric and malic acid derivatives is mentioned in each chapter.

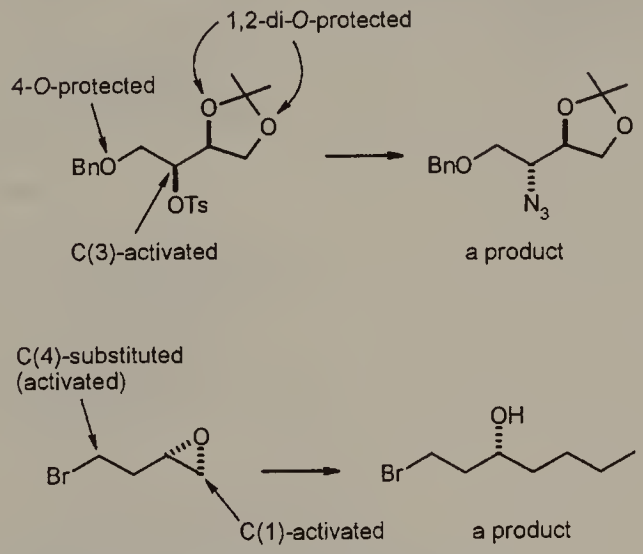
Sections on the application of the derivatives of tartaric and malic acid are organized within the four categories shown below.

- resolving agents 
- ligands 

- auxiliaries 
- chiral four-carbon building blocks 

Letters in diamonds on the left margins of the pages are **indicators** for flagging the relevant material. Each indicator is valid throughout the section or until the appearance of the next indicator.

The compound is considered a tartaric acid derivative as long as it carries the two oxygen substituents in *threo*-configuration in a four-carbon chain (the exception are α,α,α′,α′-tetraalkyl or aryl threitols and their derivatives—TADDOLs). Likewise, malic acid derivatives are defined as four-carbon compounds with an oxygen substituent at C(2). Products from these derivatives are obtained either by carbon chain elongation at C(1) or C(4) or by substitution at the stereogenic C(2) or C(3) atoms. Scheme 3 provides illustrations of these principles.



Scheme 3. From a tartaric or malic derivatives to a product.

As a rule, only the initial synthetic steps in a sequence leading from a tartaric or malic building block to a target product are shown in the schemes. After chain elongation (or shortening) or substitution at C(2)/C(3), further steps are shown only briefly with references to the original publication or more specialized monographs.

To further assist in finding specific applications of tartaric and malic acid derivatives, five **indexes** are provided. The first index refers to methods of desymmetrization of C_2-symmetric tartaric acid derivatives and to methods of differentiation of the C(1) and C(4) groups (site selectivity) in malic acid derivatives. Other indexes list resolutions, stereoselective reactions, and products obtained from tartaric or malic acids. The last index is the subject index.

The literature cutoff date for this work was approximately the first half of 1997.

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LIST OF ABBREVIATIONS

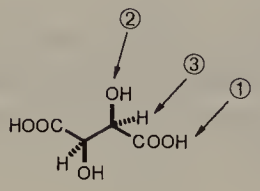
Ac	acetyl
AIBN	α,α′-azobisisobutyronitrile
All	allyl
An	4-methoxyphenyl
BINOL	1,1′-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
BSA	benzenesulfonic acid
Bu	butyl
Bz	benzoyl
Cbz	benzyloxycarbonyl
CDI	*N*,*N*′-carbonyldiimidazole
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl
CSA	10-camphorsulfonic acid
Cy	cyclohexyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBA	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N*′-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
d.e.	diastereomeric excess
DEAD	diethyl azodicarboxylate
DIAD	diisopropyl azodicarboxylate
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
e.e.	enantiomeric excess
EE	ethoxyethyl
ent	enantiomer of
eq.	molar equivalents
Et	ethyl

HMDS	hexamethyldisilazane
HMPA	hexamethylphosphorous triamide
Im	1-imidazolyl
Ipc	isopinocampheyl
LDA	lithium diisopropylamide
Me	methyl
ME	methoxyethyl
MEM	(methoxyethoxy)methyl
MOM	methoxymethyl
Ms	methanesulfonyl
MTM	methylthiomethyl
MTr	mono(4-methoxy)trityl
NBS	*N*-bromosuccinimide
NMM	*N*-methylmorpholine
Nps	2-naphthalenesulfonyl
Ns	4-nitrobenzenesulfonyl
PCC	pyridinium chlorochromate
Ph	phenyl
Pht	phthaloyl
Piv	pivaloyl
PMB	4-methoxybenzyl
PNB	4-nitrobenzyl
PNZ	4-nitrobenzyloxycarbonyl
PPTS	pyridinium 4-toluenesulfonate
Pr	propyl
2-Py	2-pyridyl
Red-Al	sodium bis(2-methoxyethoxy)aluminium hydride
SEM	2-(trimethylsilyl)ethoxymethyl
TBAF	tetra(n-butyl)ammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIBS	2,4,6-triisopropylbenzenesulfonyl
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Tol	4-tolyl
Tr	trityl
Ts	4-toluenesulfonyl

TARTARIC AND MALIC ACIDS IN SYNTHESIS

1 Tartaric Acid and Its Salts

1.1 TARTARIC ACID



1.1

Figure 1.1. L-Tartaric acid (L-threaric acid)
Butanedioic acid, 2,3-dihydroxy-[*R*-(*R**,*R**)] [*87-69-4*]
m.p. 170–172°C; $[\alpha]_D^{20}$ + 12 to 13 (c = 20, H_2O).

Overview of Properties

Tartaric acid is soluble in lower alcohols, dioxane, and tetrahydrofuran, and highly soluble in water. Solubility in water increases linearly with temperature[1,2] from 115g/100 ml at 0°C to 343g/100ml at 100°C. The solubility of racemic tartaric acid at 20°C is seven times lower compared to solubility of the pure enantiomer.

① This chiral dicarboxylic acid has the following pKa's:[1–3]

pKa_1	3.0 ± 0.1 (H_2O)	8.2 (MeOH)	8.1 (DMSO)
pKa_2	4.3 ± 0.1 (H_2O)	10.4 (MeOH)	12.2 (DMSO)

Salts of **1.1** with amines can be of either 1:1 or 1:2 stoichiometry; with diamines 1:1 stoichiometry is usual but 2:1 stoichiometry is also encountered. Diastereomeric salts often differ greatly in solubility, thus making tartaric acid one of the most frequently used resolving agents.

② Hydroxy groups enhance complexing properties of metal ions by tartrate anion. The molecules of tartrate salts, as well as the parent acid, have a planar carbon atom framework and metal ions are most frequently embedded into the planar five-membered chelate ring incorporating the C_α oxygen atom. Examples of such structures are provided by zinc and copper(II) tartrates (see below) as well as by the disilicate shown in **1.2** (Fig. 1.2), which has penta-coordinated silicon atoms.

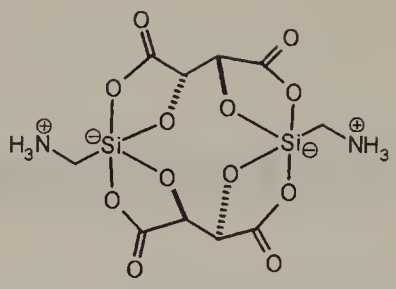


Figure 1.2. Structure of L-tartratodisilicate **1.2** from X-ray analysis.[4]

③ The acid is relatively stable in acidic solutions. However, the C_α proton can be removed under basic conditions. Heating tartaric acid in alkaline aqueous solutions causes its slow racemization. This process is used for the preparation of racemic tartaric acid.[5,6]

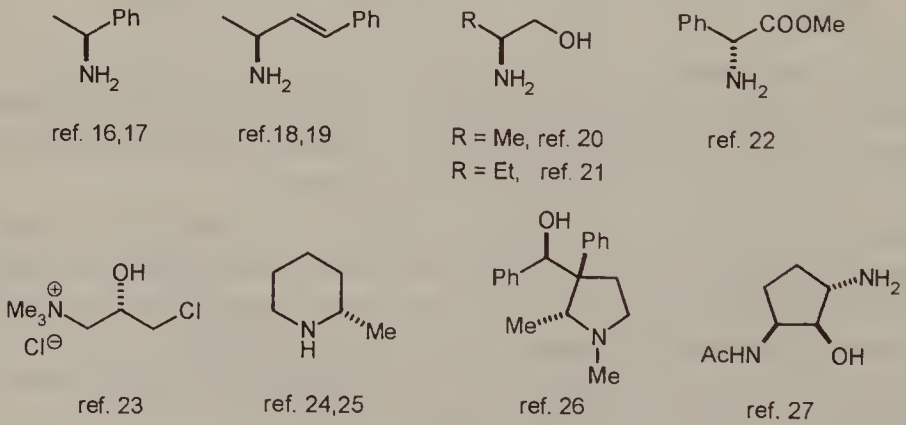
Source

Commercial. It is manufactured from potassium hydrogen tartrate (wine tartar, algol, cream of tartar—a by-product of the wine-making industry) via the calcium salt. D-tartaric acid [*147-71-7*] is also available commercially; it can be obtained from the racemic acid [*133-37-9*] by several resolution procedures[7–10] or from D-xylose.[11]

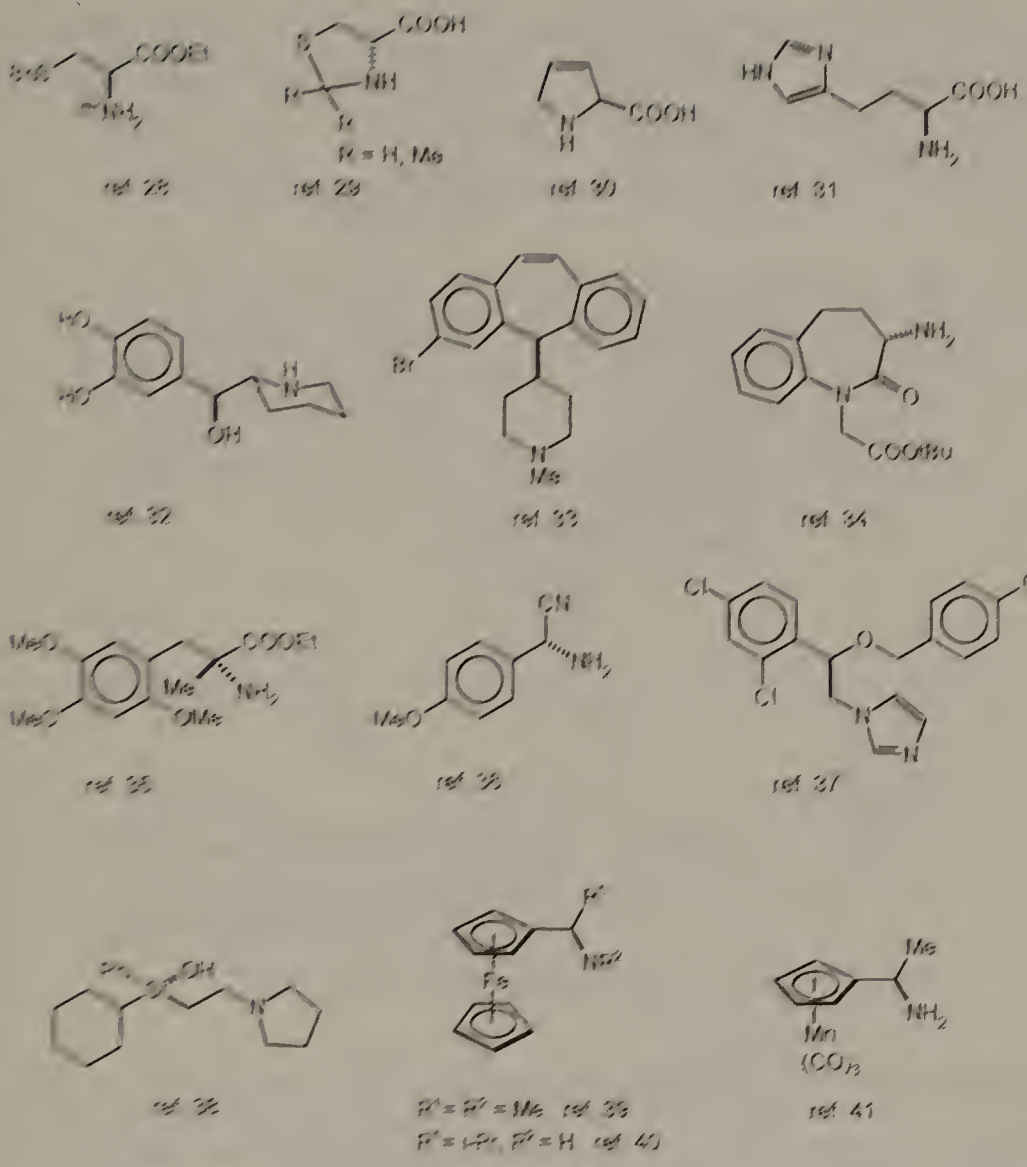
Applications

R

The highly functionalized and C_2-symmetric tartaric acid molecule is perfectly tailored for applications as a resolving agent and chiral ligand. In fact, tartaric acid is the most frequently used resolving agent for racemic amines.[12–15] Examples of *monoamines* resolved with L-tartaric acid are shown in Scheme 1.1.



Scheme 1.1 (*continued*)

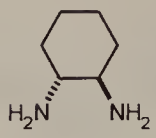


Scheme 1.1

Although in most cases salts of 1:1 monoamine–**1.1** stoichiometry are used in resolutions, amines of higher enantiomeric purity can frequently be obtained with a half molar amount of **1.1**. The use of two immiscible solvents can also be advantageous.[42]

Examples of *diamines* obtained by resolution with L-tartaric acid are shown in Scheme 1.2.

α-Amino acids and their esters can be obtained in enantiomerically pure form by tartaric acid mediated asymmetric transformation of intermediate racemic Schiff bases. The yield of this deracemization process can approach 100% (Scheme 1.3).



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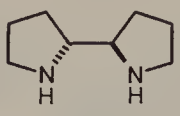

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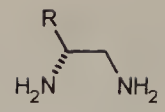
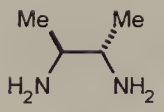
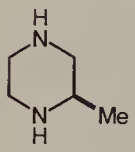


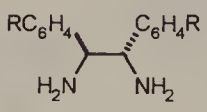
R = Me, ref. 47
Ph, ref. 48
2-BrC_6H_4, ref. 49



ref. 50

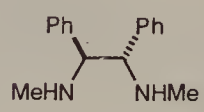


ref. 51

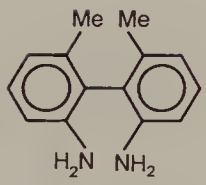


ref. 52,53

R = H; 3-Me; 4-Me
3,5-Me_2; 3-MeO
4-MeO; 3,5-$(MeO)_2$

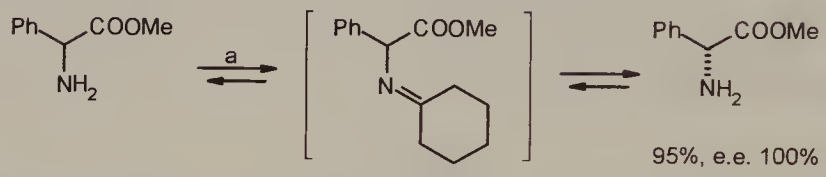


ref. 54



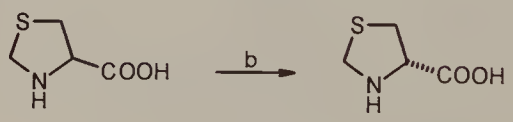
(*R*)-(-)
ref. 55

Scheme 1.2



95%, e.e. 100%

a: 1 eq. L-tartaric acid (**1.1**), 2 eq. cyclohexanone, EtOH, RT, 141h[56]



85%, e.e. 97%

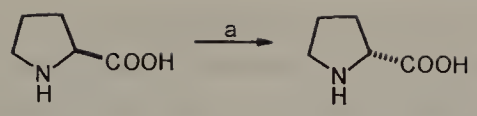
b: 0.5 eq. salicylaldehyde, 1 eq. L-tartaric acid, AcOH, 80°C, then 15°C[57]

Scheme 1.3

Likewise, tartaric acid can be used for asymmetric transformation of L-amino acids to D-amino acids in the presence of a catalytic amount of aldehyde (Scheme 1.4).

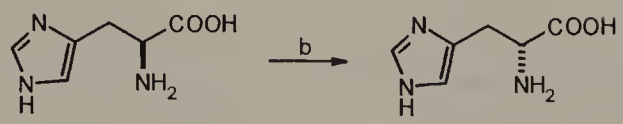
Asymmetric transformation of racemic homocysteine thiolactone to D-homocysteine (via racemic 1,3-thiazane-4-carboxylic acid) is accomplished with L-tartaric acid and salicylaldehyde (Scheme 1.5).

Enantiomers of phenylthiohydantoin amino acids were reportedly resolved on L-tartaric acid impregnated silica gel plates.[61]



85%, e.e. 100%

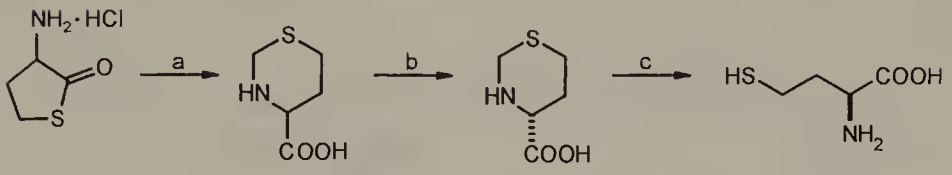
a: 1eq. D-tartaric acid (*ent*-**1.1**), 0.1 eq. n-PrCHO, 80°C, then 0°C[58]



95%, e.e. 100%

b: 1 eq. L-tartaric acid (**1.1**), 0.1 eq. salicylaldehyde, AcOH, 80-90°C, then 0°C[59]

Scheme 1.4



e.e. 100%

a: NaOH, then HCl, then aq. HCHO (62%)

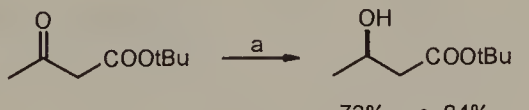
b: 1eq. L-tartaric acid (**1.1**), 1eq. salicylaldehyde, AcOH, 80°C, then RT (ca. 80%)

c: $H_2NOH \cdot HCl$, Et_3N, EtOH, reflux (92%)[60]

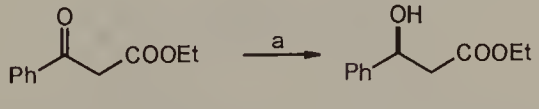
Scheme 1.5

Tartaric acid is used as a chiral additive in asymmetric reduction of functionalized ketones by sodium borohydride (Scheme 1.6).

Tai, Harada, and Izumi introduced tartaric acid as a chiral additive to Raney nickel catalyst (RNi) for hydrogenation of prochiral ketones.[63–66] This reaction is sensitive to conditions and catalyst preparation.[67–69] Additional treatment of



73%, e.e. 84%



87%, e.e. 86%

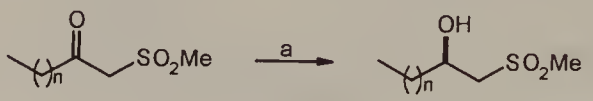
a: $NaBH_4$, **1.1**, THF, -20°C[62]

Scheme 1.6

RNi with a carboxylic acid (e.g. tBuCOOH) and with NaBr deactivates the catalyst's non-enantioface differentiating sites. This significantly improves enantioselectivity of the hydrogenation reaction.[70–73] On the other hand, addition of an amine to RNi allows repeated catalyst use.[74] Relevant examples are shown in Scheme 1.7.

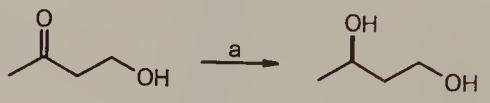
n = 0; R = Me, Et, i-Pr, i-Bu, n-hexyl — 95-98%; e.e. 86-88%[75,76]

n = 6, 8, 10, 12; R = Me — 79-82%, e.e. 83-87%[77]

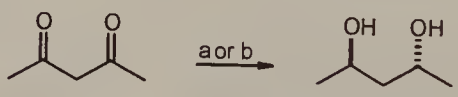


n = 1, 4, 7 — e.e. 67-69%; after recrystallization

20-40%, e.e. 100%[78]

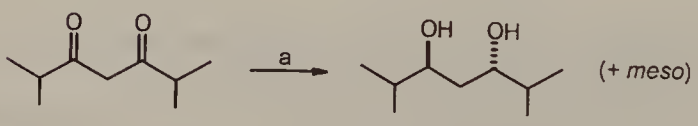


~100%, e.e. 69%[79]



a: d.e. 70%[80]; after recrystallization yield 65%, e.e. 100%[81]

b: 60%, e.e. 91%[82]



66%, e.e. 85%, after recrystallization

29%, e.e. 100%[83]

n = 3, 5 — e.e. 80%[84]

e.e 74%[85]

a: H_2/RNi, **1.1**, NaBr

b: H_2/ultrasonicated RNi, **1.1**, NaBr

c: H_2/RNi, **1.1**, NaBr, THF-tBuCOOH

d: H_2/RNi, **1.1**, NaBr, H_2O-tBuCOOH

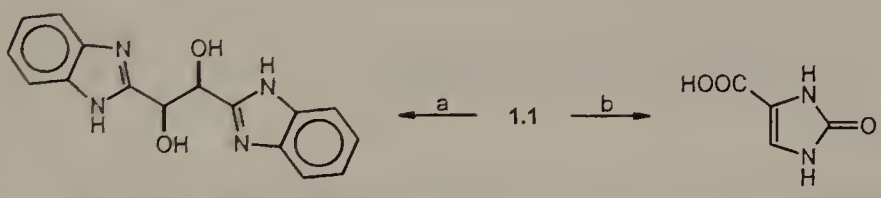
Scheme 1.7

With cyclic β-ketoesters, enantioselectivity of asymmetric hydrogenation is low, but diastereoselectivity is good.[86]

Brunner reported that commercial, easy to handle nickel powders, activated with hydrogen, can be used in place of RNi for the preparation of enantioselective catalysts. The efficiency of such tartaric acid–NaBr modified catalyst is high; for example methyl acetoacetate is hydrogenated to methyl 3-hydroxybutanoate with up to 77% e.e.[87]

Enantiomerically pure 3-hydroxybutanoic and 3-hydroxytetradecanoic acids can be obtained by saponification of their enantiomerically enriched methyl esters (Scheme 1.7) and crystallization of their dibenzylammonium[78] or dicyclohexylammonium[88] salts.

Diamino nucleophiles react with either carboxylic groups or the diol system of tartaric acid to give heterocyclic compounds. Tartaric acid was used for the preparation of a chiral bis-benzimidazole derivative,[89] as well as 4-carboxyimidazolin-2-one[90] (Scheme 1.8).



a. 2 eq. 1,2-diaminobenzene, 4M HCl, Δ (44%)[89]

b. urea, H_2SO_4, 80°C, 1h (53%)[90]

Scheme 1.8

Pyrolysis of tartaric acid in the presence of potassium hydrogen sulfate provides ready access to pyruvic acid with ca. 50% yield.[91] Tartaric acid has also been used as an equivalent of glyoxylic acid in condensations with resorcin.[92] Oxidation of tartaric acid with hydrogen peroxide in the presence of Fe(II) salts provides access to dihydroxyfumaric (dihydroxymaleic, hydroxyoxaloacetic) acid,[93,94] from which glycolaldehyde is prepared by decarboxylation.[95] The yield at each step does not exceed 20%.

1.2 ZINC L-TARTRATE (1.3)

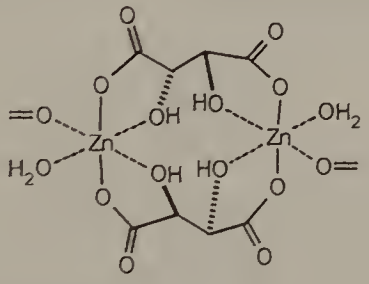


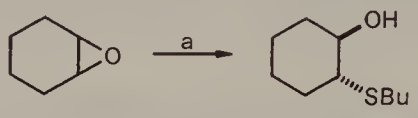
Figure 1.3. Structure of zinc L-tartrate (**1.3**) from X-ray analysis.[96]

Synthesis

The synthesis is accomplished from L-tartaric acid and zinc acetate or potassium-sodium L-tartrate (*Rochelle salt*) and zinc chloride (98%).[97]

Application

Zinc L-tartrate is used as heterogeneous chiral Lewis acid catalyst for enantioselective ring opening of prochiral epoxides[97,98] (Scheme 1.9).



82%, e.e. 85%

a: n-BuSH, 0.1 eq. **1.3**, CH_2Cl_2, RT, 5d

Scheme 1.9

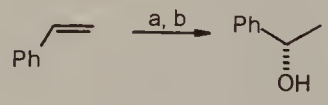
1.3 MERCURY(II) L-TARTRATE (1.4)

Synthesis

The synthesis is from L-tartaric acid and mercury(II) acetate (94%).[99]

Application

Mercury(II) L-tartrate is used as heterogeneous chiral reagent for asymmetric oxymercuration-demercuration of styrene[99] (Scheme 1.10).



20%, e.e. 30%

a: **1.4**, H_2O-THF (1:1), RT

b: NaOH, $NaBH_4$, RT

Scheme 1.10

1.4 COPPER(II) L-TARTRATE (1.5)

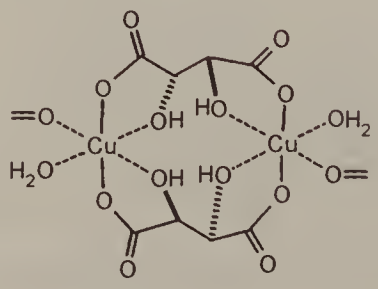


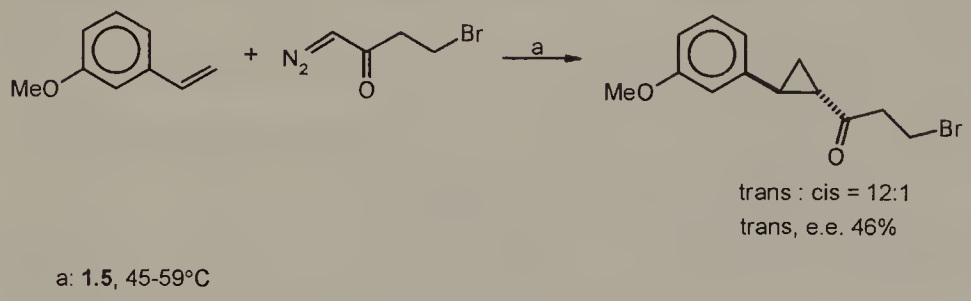
Figure 1.4. Structure of copper(II) L-tartrate (**1.5**) from X-ray analysis.[100]

Synthesis

The synthesis is achieved from potassium-sodium L-tartrate and copper(II) sulfate.[99]

Application

Copper(II) L-tartrate is used as chiral promoter of asymmetric cyclopropanation[101] (Scheme 1.11).



Scheme 1.11

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2 Tartrates and Their Metal Complexes

2.1 DIESTERS OF TARTARIC ACID

Table 2.1 Symmetrical diesters of L-tartaric acid ROOCCH(OH)CH(OH)COOR

R	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
	n-Alkyl		
Me (**2.1**)	58–61	+21.0 (H_2O)	1–4
Et (**2.2**)	107/0.7	+26.5 (H_2O)	5–11
n-Pr	108/0.01	+26.7 (H_2O)	12
n-Bu	21–22	+10.5 (EtOH)	13
n-C_7H_{15}	35–35.5	+14.0 (Me_2CO)	14,15
n-C_8H_{17}	43–44	+13.6 (Me_2CO)	14–18
n-C_9H_{19}	49–50	+11.0 (Me_2CO)	15,16
n-$C_{11}H_{23}$	62	+10.0 (Me_2CO)	15
	Branched alkyl		
i-Pr (**2.3**)	152/12	+20.9 (neat)	19
i-Bu	73	+12.4 ($CHCl_3$)	19–22
t-Bu	90–92	+12.0 (Me_2CO)	23
i-Pr$(CH_2)_2$	195/16	+11.7 (neat)	19
(*S*)-Et(Me)$CHCH_2$	195/0.08	+20.3 (EtOH)	16
(*R*)-Et(Me)$CHCH_2$[a]	195/0.03	+10.9 (EtOH)	16
n-Pr_2CH	35	+14.0 (Me_2CO)	15
i-Pr_2CH	168–176/0.3	+23.7 (MeOH)	24
(*R,S*)-Me$(CH_2)_5$CHMe	43–44	+31.0 (Me_2CO)	15,25
(*R*)-Me$(CH_2)_5$CHMe	165/0.03	−3.3 (EtOH)	16
(*S*)-Me$(CH_2)_5$CHMe	160/0.02	+20.4 (EtOH)	16
Me$(CH_2)_3$(Et)$CHCH_2$	222/2	—	26
(*R,S*)-Me$(CH_2)_6$CHMe	49–50	+10.0 (Me_2CO)	15
(*R,S*)-Me$(CH_2)_5$CHEt	49–50	+12.0 (Me_2CO)	15
(*R,S*)-Me$(CH_2)_4$CHn-Pr	49–50	+10.0 (Me_2CO)	15
n-Bu_2CH	49–50	+12.0 (Me_2CO)	15
$[Me(CH_2)_4]_2CH$	62	+9.0 (Me_2CO)	15
(*R,S*)-Me$(CH_2)_8$CHMe	62	+8.0 (Me_2CO)	15

(*continued*)

Table 2.1 (*continued*)

R	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
	Cyclic		
cyclopentyl	100/0.01	+20.0 (EtOH)	16
cyclohexyl	69.5–70.5	+15.0 (EtOH)	17,27
cycloheptyl	35	+18.0 (Me_2CO)	15
cyclododecyl	123	+8.2 (EtOH)	24,27
cis-4-(*tert*-butyl)-cyclohexyl	134–136	+16.8 (EtOH)	16
trans-4-(*tert*-butyl)cyclohexyl	181–183	+4.3 (EtOH)	16
3,3,5,5-tetramethylcyclohexyl	109	+8.1 (EtOH)	16
2-adamantyl	156–160	+7.6 (EtOH)	16
(1*R*,2*S*,5*R*)-menthyl	75–77	−71.0 (EtOH)	16,28
(1*S*,2*R*,5*S*)-menthyl	41–43	+80.6 (EtOH)	16
(1*S*,2*R*,5*R*)-isomenthyl	126	+31.6 (EtOH)	16
(1*R*,2*S*,5*S*)-isomenthyl[a]	64–66	212.1 (EtOH)	16
(1*S*,2*S*,5*R*)-neomenthyl[a,b]	108–110	+57.5 (EtOH)	16
(1*R*,2*R*,5*S*)-neomenthyl[b]	—	+23.9 (EtOH)	16
(1*R*,2*S*)-2-phenylcyclohexyl	110–140	−39.7 (EtOH)	16
(1*S*,2*R*)-2-phenylcyclohexyl[a]	100–130	+33.5 (EtOH)	16
(1*R*,2*S*,5*R*)-8-phenylmenthyl[c]	57–60	−3.7 (EtOH)	16
(1*S*,2*R*,5*S*)-8-phenylmenthyl[b,c]	147–149	+3.5 (EtOH)	16
(1*S*,2*S*,5*S*)-myrtanyl	78–80	−3.3 (EtOH)	16
(1*R*,2*R*,5*R*)-myrtanyl[b]	87–89	+26.4 (EtOH)	16
(1*S*)-bornyl	132.5–133.5	−12.4 (EtOH)	16,29,30
(1*R*)-bornyl	118–118.5	+63.2 (EtOH)	16,29,30
(1*R*)-fenchyl	124–126	+54.9 (EtOH)	16
(1*S*)-fenchyl[b]	—	−39.0 (EtOH)	16
	Functionalized		
Cl_3CCH_2	101.5–103.5	+9.0 ($CHCl_3$)	31
CH_2=CH	127/2	—	32
CH_2=$CHCH_2$	191/20	+15.5	19
MeCH=$CHCH_2$	—	—	33
Bn	68–69	+7.8 (EtOH)	16,17,19,34,35
		−10.2 ($CHCl_3$)	8,36
$C_6Me_5CH_2$	212–213.5	—	37
2-$O_2NC_6H_4CH_2$	131	+59.4 (pyridine)[d]	38
3-$O_2NC_6H_4CH_2$	119	+72.7 (pyridine)[d]	38
4-$O_2NC_6H_4CH_2$	163–164	+89.5 (pyridine)[d]	38–42
4-$PhC_6H_4C(O)CH_2$	203–204	—	43
4-$BrC_6H_4C(O)CH_2$	231	—	8
Ph_2CH	110.5–111	—	44

[a] Enantiomer prepared.

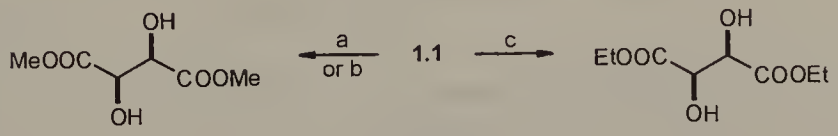
[b] Prepared by t-BuOOH /OsO_4 dihydroxylation of (–)-di(neomenthyl) fumarate.

[c] Prepared by $KMnO_4$ dihydroxylation of (–)-8-phenylmenthyl fumarate.

[d] At 546 nm.

Synthesis

The diesters listed in Table 2.1 are routinely obtained by acid-catalyzed esterification of primary and in many cases secondary alcohols with tartaric acid (**1.1**) or by acid-catalyzed transesterification of dimethyl or diethyl tartrate with higher boiling point alcohols. This reaction proceeds without detectable racemization of the tartrate molecule. Some examples of large scale preparations are shown in Scheme 2.1.



2.1 **2.2**

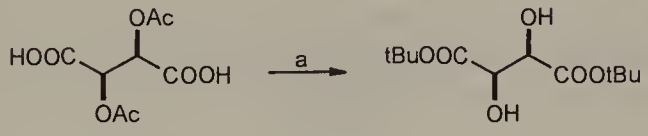
a: MeOH (1 ml/mmol), $MgSO_4$ (0.1 g/mmol), TsOH (cat.), RT (ca. 100%)[45]

b: MeOH, 2 eq. $HC(OMe)_3$, 2 eq. AcCl, Δ (90.5%)[4]

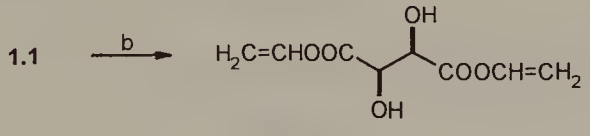
c: EtOH, cat. acidic resin (90%)[22,46]

Scheme 2.1

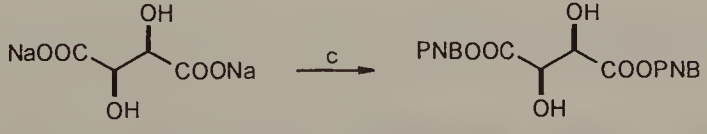
Other methods of preparation of dialkyl tartrates with less reactive or acid-sensitive alcohols are shown in Scheme 2.2.



a: $CH_2=CMe_2$, CH_2Cl_2, H_2SO_4 (cat.), -15°C → RT (100%) then MeOH, KOH (cat.), 4°C, 10 min. (54%)[23]

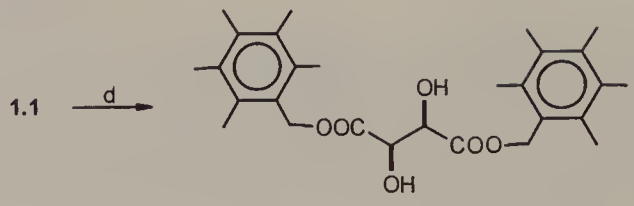


b: $CH_2=CHOAc$, $Hg(OAc)_2$, H_2SO_4 (cat.)[32]

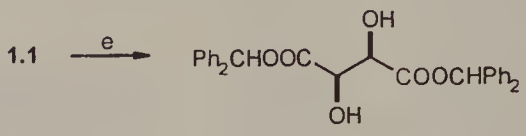


c: 2 eq. PNBBr, 2.1 eq. NEt_3, DMF, ca. 5°C, 1d (85%)[42]

Scheme 2.2 (*continued*)



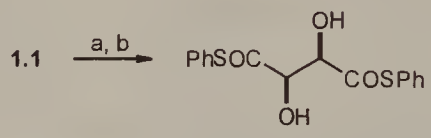
d: NEt_3, $Me_5C_6CH_2Cl$[37]



e: $Ph_2C{=}N_2$, AcOEt, RT (95%)[44]

Scheme 2.2

Except for a few cases[47] diaryl tartrates have not been reported. Similarly, thiol esters of tartaric acid are known only in isolated cases; an example of their preparation is shown in Scheme 2.3.[48]

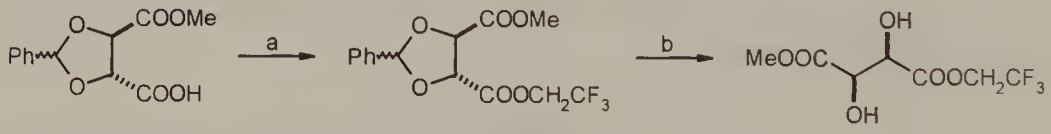


a: 2 eq. Me_2N-C≡C-COMe, THF, -50°C (98%)

b: 2 eq. PhSNa, THF, 0°C (72%)

Scheme 2.3

Unsymmetrical esters can be obtained by esterification of acetal-protected tartaric acid monoesters, with subsequent chemoselective removal of the acetal function. An example is shown in Scheme 2.4.



a: 1.5 eq. CDI, THF, 2h, RT, then 2 eq. CF_3CH_2OH, 8h (78%)

b: H_2, 10% Pd/C, CF_3CH_2OH (97%)[49]

Scheme 2.4

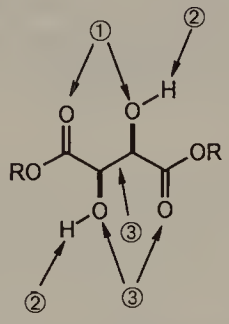
Several frequently used dialkyl tartrates are commercially available in both enantiomeric forms.

(+)-DMT: dimethyl L-tartrate (**2.1**) [*608-68-4*]
(−)-DMT: dimethyl D-tartrate (*ent*-**2.1**) [*13171-64-7*]
(+)-DET: diethyl L-tartrate (**2.2**) [*87-91-2*]

(−)-DET: diethyl D-tartrate (*ent*-**2.2**) [*13811-71-7*]
(+)-DIPT: diisopropyl L-tartrate (**2.3**) [*2217-15-4*]
(−)-DIPT: diisopropyl D-tartrate (*ent*-**2.3**) [*62961-64-2*]
dibutyl L-tartrate [*87-92-3*]
di-*tert*-butyl L-tartrate [*117384-45-9*]
di-*tert*-butyl D-tartrate [*117384-46-0*]
dibenzyl L-tartrate [*622-00-4*]
dibenzyl D-tartrate [*4136-22-5*]

Applications

Tartrates are excellent ligands for many metal ions, for which oxygen atoms of the hydroxy groups are the primary sites of coordination. Coordination may also involve oxygen atoms of the carbonyl groups (Fig. 2.1). Many asymmetric synthesis protocols mediated by metal ions are based on this property; the titanium(IV)-tartrate mediated asymmetric epoxidation of Katsuki–Sharpless is the best known example. Another synthetically useful structural feature of tartrates is their ability to act as chiral proton sources, for example in the desymmetrization of chiral carbonyl compounds via their prochiral enolates. Tartrates are also useful and inexpensive starting materials for the synthesis of unnatural (*R*)-malic acid esters as well as for the synthesis of (achiral) glyoxylic esters by the cleavage of the diol unit.



① Coordination sites for metal ions
② Proton source
③ Site of oxidative cleavage for glyoxylic esters synthesis

Figure 2.1

Tartrates were applied as chiral selectors in liquid chromatography of racemic aminoalcohols, such as ephedrine and analogues.[17,50]

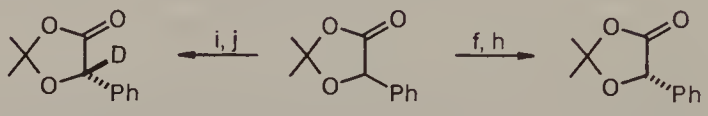
Tartrates are used as chiral auxiliaries for deracemization of carboxylic acid derivatives via enantioselective protonation of their enolates, or by stereoselective addition to ketenes (Scheme 2.5).

e.e. 78%

a: $SOCl_2$, DMF; b: NEt_3; c: **2.2**, -78°C; d: AcOH-H_2O; e: AcOH-2N HCl, 85°C[51]

e.e. 43%

f: LDA, -78°C; g: **2.3**[52]



> 95% D
e.e. 57%

e.e. 42-68%

h: dialkyl L-tartrates[52-55] i: LiHMDS, -78°C j: O-deuterated **2.3**[53]

Scheme 2.5

B

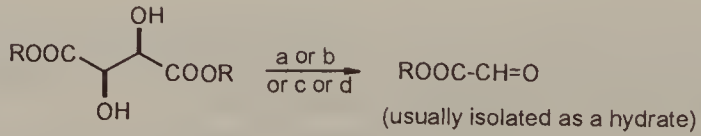
Esters of unnatural (*R*)-malic acid can be synthesized from (*R*,*R*)-tartrates. Several routes have been devised, differing in number of steps, yields, and reagents used (see Chapters 4 and 7). A remarkable direct deoxygenation of tartrates to malates with the use of samarium(II) iodide and ethylene glycol as additive has been reported by Inanaga[56] (Scheme 2.6).

R = Et (72%)
R = i-Pr (99%)

a: SmI_2, $HOCH_2CH_2OH$, THF, RT

Scheme 2.6

Oxidation of dialkyl tartrates (an alternative to ozonolysis of fumarates or maleates), yields synthetically useful glyoxylic esters (Scheme 2.7.).



(usually isolated as a hydrate)

a: $Pb(OAc)_4$, benzene c: Pb_3O_4, AcOH-H_2O

b: $NaIO_4$, H_2O or H_5IO_6, Et_2O d: NBS, K_2CO_3, cat. Ph_3Bi

(*continued*)

R	method	ref.
Me	a	41
Me	b	57,58
Et	a	59
Et	b	57,60
Et	c	61
n-Bu	a	62-64
n-Bu	b	65
t-Bu	a	66
$Me(CH_2)_3CH(Et)CH_2$	b	26
cyclo-C_6H_{11}	b	67
(-)-menthyl	b	67
(-)-bornyl	b	67
$MeCH{=}CHCH_2$	b	33
$ClCH_2CH_2$	a	68
Cl_3CCH_2	b	31,41
Bn	b	34
Bn	d	69
PMB	a	70
2-$O_2NC_6H_4CH_2$	a	71
4-$O_2NC_6H_4CH_2$	a	41,72
4-$O_2NC_6H_4CH_2$	b	42,73
Ph_2CH	a	44
PhOCH(Me)	a	71

Scheme 2.7

2.2 MONOESTERS OF TARTARIC ACID

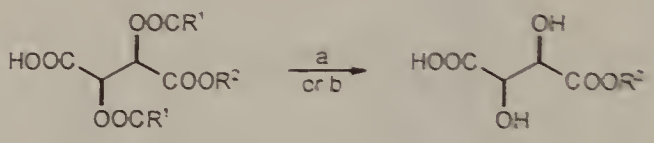
Table 2.2 Monoesters of L-tartaric acid ROOCCH(OH)CH(OH)COOH

R	m.p. (°C)	$[\alpha]_D$ (solvent)	References
Me	76[a]	+18.7 (H_2O)	74
t-Bu	85	+9.9 (Me_2CO)[b]	23
C_8H_{17}	51–51.5	+7.4 ($CHCl_3$)	75
(1*R*,2*S*,5*R*)-menthyl	82.5–83	−53.0 ($CHCl_3$)	76
(1*S*,2*R*,5*S*)-menthyl[c]	122–122.5	+71.1 ($CHCl_3$)	76
(1*S*)-bornyl	158–158.5	−6.5 (EtOH)	29,30
(1*R*)-bornyl	130.5–131.5	+51.8 (EtOH)	29,30

[a] Monohydrate.
[b] At 546 nm.
[c] Enantiomer prepared.

Synthesis

Only a few monoesters of tartaric acid have been reported. The monomethyl ester is formed in low yield by heating **1.1** with methanol.[74] Other monoesters such as monobornyl tartrates can be obtained by hydrolysis of the diesters with one equivalent of alcoholic hydroxide solution.[30] A more general access to monotartrates is through hydrolysis of their *O,O′*-diacyl derivatives (Scheme 2.8).



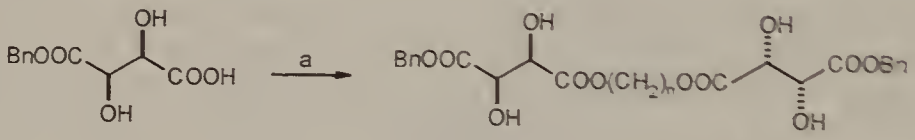
a: 3N NaOH, RT, then dil. HCl ($R^1 = CF_3$, $R^2 = C_8H_{17}$-), 88%[75]

b: 1.1 eq. KOH, EtOH, then Me_3SiCl, then H_2O ($R^1 = Me$, $R^2 = t$-Bu), 54%[73]

Scheme 2.8

Application

Monobenzyl ester was used for the preparation of bis-tartrate ligands for asymmetric epoxidation[77] (Scheme 2.9).



n = 3 (51%)

n = 4 (81%)

n = 5 (84%)

a: 1 eq. Bu_4NOH, 0.5 eq. $I(CH_2)_nI$, DMF, 50°C

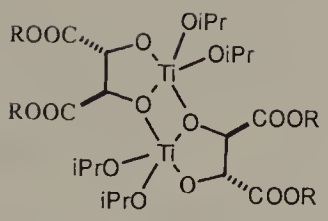
Scheme 2.9

2.3 TITANIUM(IV) TARTRATE COMPLEXES

Preparation

Titanium(IV) tartrate complexes are prepared *in situ*, in dichloromethane solution, from titanium tetraisopropoxide and diethyl tartrate (**2.2**) or diisopropyl tartrate (**2.3**), by ligand exchange reaction. For *enantioselective epoxidation reactions* the 1:1 complex **2.4** is used.[78] Dimeric catalyst structure as in Fig. 2.2 was established by the X-ray[79] and by spectroscopic[80] methods.

For *asymmetric sulfide to sulfoxide oxidations* best results are obtained with the complex $Ti(OiPr)_4$: tartrate: H_2O of 1:2:1 stoichiometry (Kagan reagent)[81] or with $Ti(OiPr)_4$: tartrate complex of 1:4 stoichiometry (Modena reagent).[82]



2.4a, R = Et

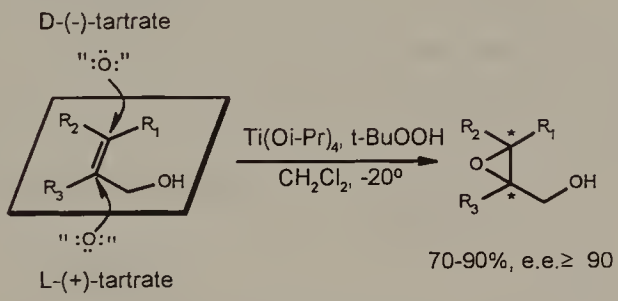
2.4b, R = i-Pr

Figure 2.2

For *enantioselective N-oxide formation* optimum results are obtained with the $Ti(OiPr)_4$: tartrate ratio 2 : 1.[83]

Applications

Chiral mediator/catalyst for Sharpless–Katsuki asymmetric epoxidation of allylic alcohols[84] (Scheme 2.10).

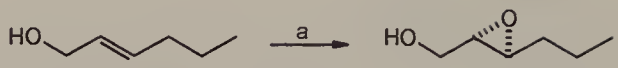


Scheme 2.10

Reaction features

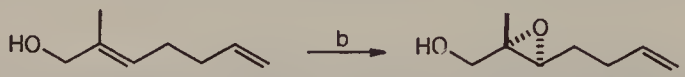
- relative insensitivity to resident chirality
- high reliability and predictability of absolute configuration (according to Scheme 2.10)
- high enantiomeric purity of the epoxide: generally above 90%, frequently above 95%
- all reagents are commercially available and inexpensive
- the titanium tartrate complex can be used in catalytic amounts (usually 0.05–0.15 eq.), with the addition of molecular sieves 4Å[27,85]
- the addition of silica gel and calcium hydride results in acceleration of some epoxidation reactions by the Sharpless reagent[86]
- the polymer-supported catalyst provides high chemical yield and enantiomeric excess of the reaction while facilitating recovery of the catalyst.[87]

Reviews: ref. 88–95. Examples of reactions under *standard conditions* are shown in Scheme 2.11.



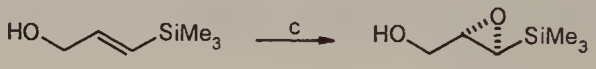
78%, e.e.>96.8%

a: 0.65 eq. (+)-DET (**2.2**), 0.54 eq. Ti(Oi-Pr)$_4$, 2.0 eq. t-BuOOH, CH_2Cl_2, -60°→ 0°C[96]



71%, e.e. 96%

b: 1.1 eq. (+)-DET (**2.2**), 1.1 eq. Ti(Oi-Pr)$_4$, 2.2 eq. t-BuOOH, CH_2Cl_2, -25°C[97]



60%, e.e. 95%

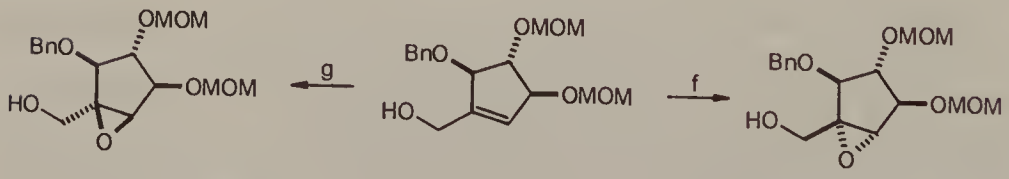
c: 1.5 eq. (+)-DIPT (**2.3**), 1.2 eq. Ti(Oi-Pr)$_4$, 2.0 eq. t-BuOOH, CH_2Cl_2, -20°C[98]

95%, e.e. 95%

d: 2.2 eq. (+)-DET (**2.2**), 2.2 eq. Ti(Oi-Pr)$_4$, 2.0 eq. t-BuOOH, CH_2Cl_2, -20°C[99]

82%, one diastereomer

e: 1.2 eq. (+)-DIPT (**2.3**), 1.1 eq. Ti(O-iPr)$_4$, 1.5 eq. t-BuOOH, mol. sieves 4Å, CH_2Cl_2, -20°C[100]



77%, one diastereomer

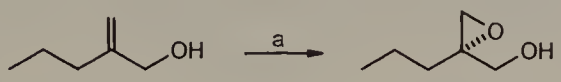
94%, one diastereomer

f: 1.4 eq. (+)-DIPT (**2.3**), 1.4 eq. Ti(Oi-Pr)$_4$, 2.0 eq. t-BuOOH, CH_2Cl_2, -25°C[101]

g: as f, except (-)-DIPT used in place of (+)-DIPT

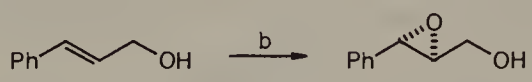
Scheme 2.11

Scheme 2.12 shows examples of reactions under *catalytic conditions*.



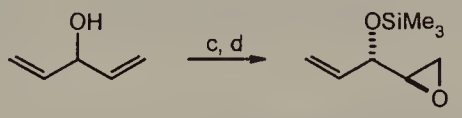
88%, e.e.95%

a: 0.06 eq. (+)-DET (**2.2**), 0.05 eq. $Ti(OiPr)_4$, 2.0 eq. t-BuOOH, mol sieves 3Å, CH_2Cl_2, -12°C[27]



86%, e.e. 98%

b: 0.1eq. (+)-DIPT (**2.3**), 0.05 eq. $Ti(OiPr)_4$, 1.5 eq. t-BuOOH, CH_2Cl_2, -20°→ 0°C[102]



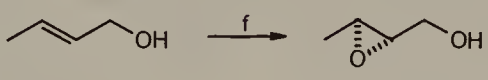
65%, e.e. 97%

c: 0.15 eq. (+)-DIPT (**2.3**), 0.16 eq. $Ti(OiPr)_4$, 1.8 eq. t-BuOOH, mol. sieves 4Å, CH_2Cl_2, -20°C

d: $MeSi_3Cl$, DMAP, NEt_3, CH_2Cl_2[103]

82%, one diastereomer

e: 0.09 eq. (-)-DIPT (*ent*-**2.3**), 0.07 eq. Ti(OiPr)4, 2.0 eq. t-BuOOH, mol. sieves 4Å, CH_2Cl_2, -25°C[104]



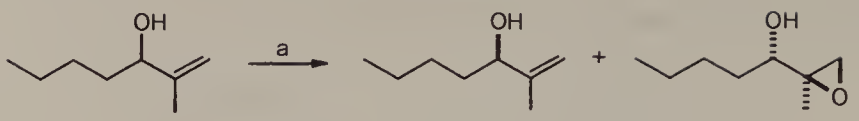
91%, e.e. 95%

f: 0.06 eq. (+)-DIPT (**2.3**), 0.03 eq. titanium-pillared montmorillonite, 1.2 eq. t-BuOOH, CH_2Cl_2, -20°C[105]

Scheme 2.12

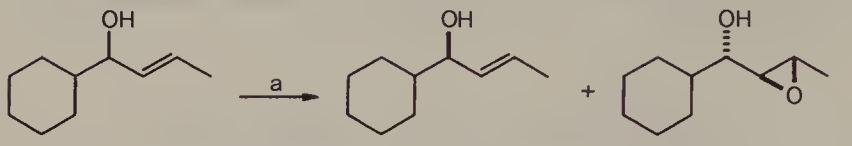
- *Chiral mediator for kinetic resolution of racemic allylic alcohols* in the asymmetric epoxidation, with ca. 55% conversion[106] (Scheme 2.13). *Review*: ref. 107.

Chiral mediator for asymmetric oxidation of prochiral sulfides to sulfoxides (Kagan–Modena method),[81,115–117] Scheme 2.14.



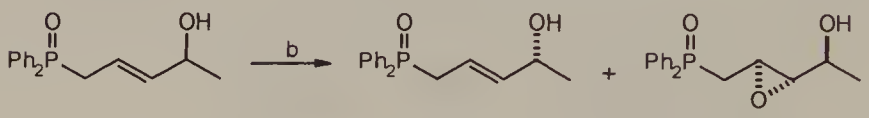
e.e.> 99.5% e.e.~ 90%

(*anti* : *syn* ~ 9 :1)[108]



e.e.> 96% (*anti* : *syn* ~ 49 :1)[106]

a: 1.2 eq. (+)-DIPT (**2.3**), 1.0 eq. $Ti(Oi\text{-}Pr)_4$, 0.6 eq. t-BuOOH, CH_2Cl_2, -20°C



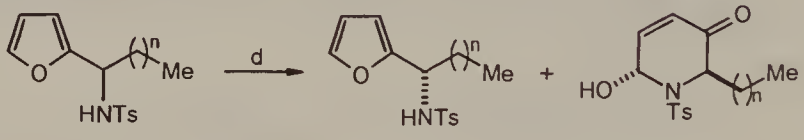
e.e.95% (*anti* only)

b: 0.6 eq. (+)-DET (**2.2**), 0.5 eq. $Ti(Oi\text{-}Pr)_4$, 0.5 eq. t-BuOOH, mol. sieves 4Å, CH_2Cl_2, -16°C →16°C[109]

n = 0, 1, 3, 5, 9

30-43%, e.e.≥ 90%

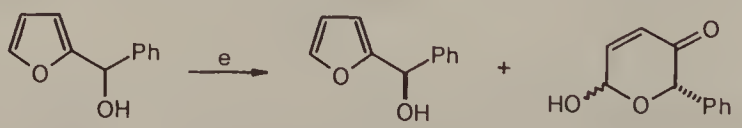
c: 1.2 eq. (+)-DIPT (**2.3**), 1.0 eq. $Ti(Oi\text{-}Pr)_4$, 1.0 eq. t-BuOOH, 0.05-0.1 eq. CaH_2, 0.1-0.2 eq. silicagel, CH_2Cl_2, -10°C[110]



n = 0-3, 5

45-47%, e.e.≥90%

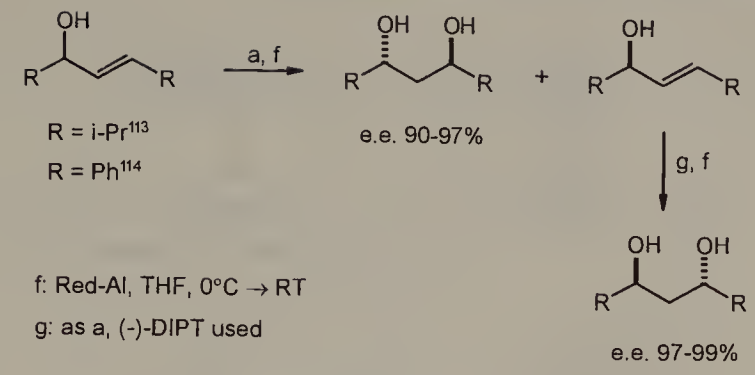
d: 1.0 eq. (+)-DIPT (**2.3**), 1.0 eq. $Ti(Oi\text{-}Pr)_4$, 2.5 eq. t-BuOOH, 0.05-0.1 eq. CaH_2, 0.10-0.15 eq. silicagel, CH_2Cl_2, RT[111]



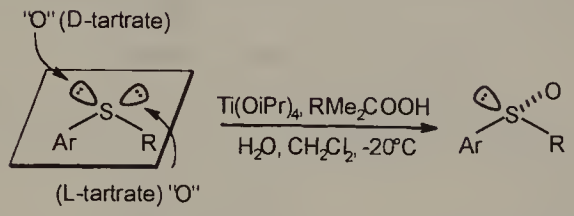
38%, e.e.> 99%

e: 0.24 eq. (+)-DIPT (**2.3**), 0.2 eq. $Ti(Oi\text{-}Pr)_4$, 0.6 eq. t-BuOOH, mol. sieves 4Å, CH_2Cl_2, -21°C[112]

(*continued*)



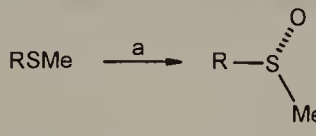
Scheme 2.13



(configuration for the L-tartrate mediated oxidation)

Scheme 2.14

Reviews: ref. 118–120. Examples are shown in Scheme 2.15.



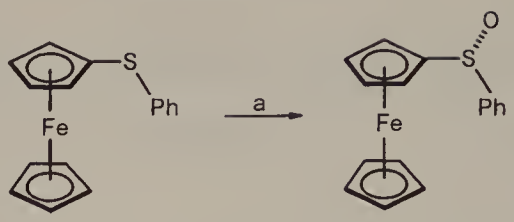
a: 2 eq. (+)-DET (**2.2**), 1 eq. Ti(Oi-Pr)$_4$,1 eq. H_2O, 1 eq. cumene hydroperoxide, CH_2Cl_2, -20°C

R	yield (%)	e.e. (%)[a]	ref.
Ph	93	93	118
	77	99.2	117
4-MeC_6H_4	93	96	116
	75	> 99.5	117
	85	89	121[b]
1-naphthyl	91	91.2	117
Bn	84	61.5	116
	87	95.4	117
Me$(CH_2)_7$	71	80	116
	63	85.1	117

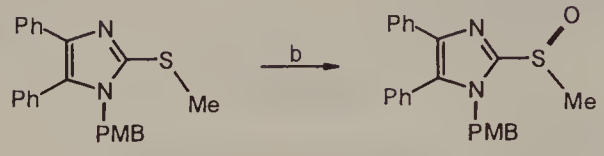
[a] all these sulfoxides can be obtained enantiomerically pure by recrystallization

[b] with (-)-DET (opposite configuration of the product)

Scheme 2.15 (*continued*)

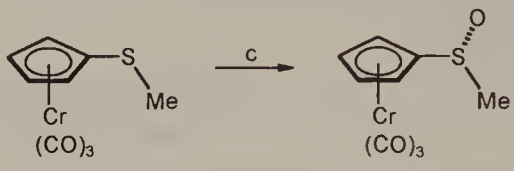


86%, e.e. > 99%[122]



75%, e.e. 98-99%

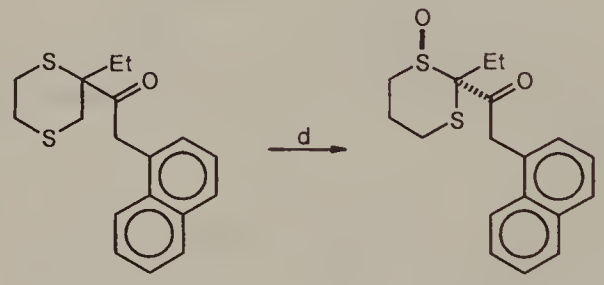
b: 1 eq. (-)-DET (**2.2**), 0.5 eq. $Ti(Oi\text{-}Pr)_4$, cumene hydroperoxide, CH_2Cl_2, -20°C[123]



65%, e.e. 83%

(e.e. ≥ 95% after recrystallization)

c: 4 eq. (+)-DET (**2.2**), 2 eq. $Ti(OiPr)_4$, 2 eq. H_2O, 1.3 eq. cumene hydroperoxide, CH_2Cl_2, -20°C[124]



64%, e.e. 94%

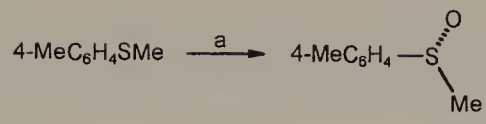
d: 2.2 eq.(+)-DET (**2.2**), 1.1 eq. $Ti(OiPr)_4$, 1 eq. H_2O, 1.5 eq. cumene hydroperoxide, CH_2Cl_2, -30°C[125]

Scheme 2.15

A modification of this reaction employs a titanium-pillared montmorillonite catalyst.[126]

The oxidation can be carried out efficiently under catalytic conditions with a reagent $Ti(OiPr)_4$:tartrate:i-PrOH of 1:4:4 stoichiometry[127] (Scheme 2.16).

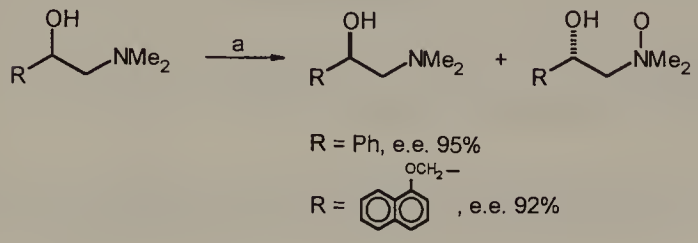
Chiral mediator for kinetic resolution of racemic β-hydroxy tertiary amines by enantioselective *N*-oxide formation[128] (Scheme 2.17).



77%, e.e. 96%

a: 0.4 eq.(+)-DET (**2.2**), 0.1 eq. $Ti(OiPr)_4$, 0.4 eq. i-PrOH, 2 eq. cumene hydroperoxide, mol. sieves, CH_2Cl_2, -22°C[127]

Scheme 2.16



R = Ph, e.e. 95%

R =

, e.e. 92%

R = C_8H_{17}, e.e. 94%

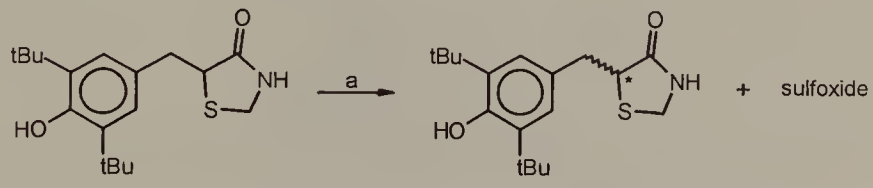
R = t-Bu, e.e. 92.5%[83]

e.e.> 95%

a: 1.2 eq.(+)-DIPT (**2.3**), 2.0 eq. $Ti(Oi\text{-}Pr)_4$, 0.6 eq. cumene hydroperoxide, CH_2Cl_2, -20°C[128]

Scheme 2.17

Chiral mediator for kinetic resolution of racemic sulfides by enantioselective sulfoxide formation[129] (Scheme 2.18).



$[\alpha]_D^{20}$ -57 (c = 1, MeOH)

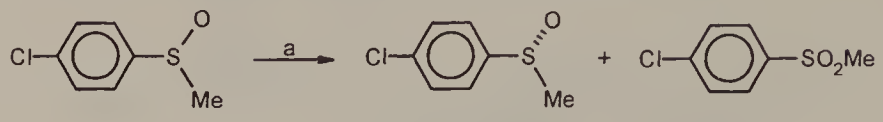
36%, e.e. 67%

(configuration unknown)

a: 1.2 eq. (+)-DIPT (**2.3**), 0.6 eq. $Ti(OiPr)_4$, 0.6 eq. H_2O, 0.6 eq. t-BuOOH, mol. sieves 4Å, CH_2Cl_2, -20°C[129]

Scheme 2.18

Chiral mediator for kinetic resolution of racemic sulfoxides by enantiospecific oxidation to sulfones (Scheme 2.19).[130]

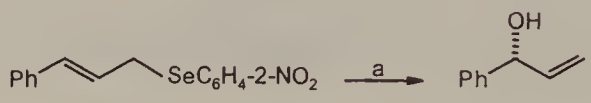


31%, e.e.94%

a: 2 eq. (+)-DET (**2.2**), 0.5 eq. $Ti(OiPr)_4$, 0.65 eq. cumene hydroperoxide, CH_2Cl_2,-23°C[130]

Scheme 2.19

Chiral mediator for the conversion of aryl cinnamyl selenides to 1-phenyl-2-propen-1-ol via the selenoxide[131] (Scheme 2.20).

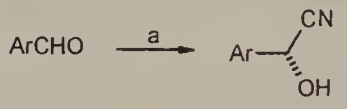


42%, e.e. 92%

a: 2 eq. (+)-DIPT (**2.3**), 1 eq. $Ti(OiPr)_4$, 1.1 eq. t-BuOOH, mol. sieves 4Å, CH_2Cl_2,-20°C[131]

Scheme 2.20

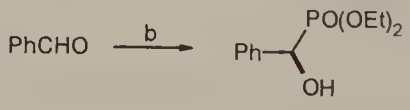
Chiral mediator in the enantioselective trimethylsilylcyanation[132] *and hydrophosphonylation*[93] of aryl aldehydes *and for asymmetric ring opening of epoxides* with trimethylsilylazide[133] (Scheme 2.21).



89-95%, e.e. 77-81%

Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-naphthyl

a: 1.1 eq. (+)-DIPT (**2.3**), 1 eq. $Ti(OiPr)_4$, 1 eq. TMSCN, CH_2Cl_2, 0°C[132]



75%, e.e. 53%

b: 0.2 eq. (+)-DIPT (**2.3**), 0.2 eq. $Ti(OiPr)_4$, 1 eq $HPO(OEt)_2$, Et_2O, 0°C[134]

60%, e.e. 46%

c: 0.11 eq. (+)-DIPT (**2.3**), 0.1 eq. $TiCl_2(Oi\text{-}Pr)_2$, 2 eq. $TMSN_3$, CH_2Cl_2, -10°C[133]

Scheme 2.21

Tartrate-$TiCl_4$ complexes were used as chiral Lewis acid catalysts in Diels–Alder reaction of cyclopentadiene and methyl acrylate (e.e. up to 83%, moderate chemical yield).[135]

2.4 MAGNESIUM TARTRATE COMPLEX

Preparation

The preparation is done *in situ* from dibutyl magnesium and diethyl tartrate (see Scheme 2.22).

Application

The application is as a chiral mediator for the asymmetric epoxidation of chalcones with t-butyl peroxide[136] (Scheme 2.22).

Ar	yield (%)	e.e. (%)
Ph	61	94
4-MeC_6H_4	36	87
2-naphthyl	46	92

a: 0.11 eq. (+)-DET (**2.2**), 0.1 eq. Bu_2Mg, 1.5 eq. t-BuOOH, PhMe/THF, RT, 1 day

Scheme 2.22

2.5 ZINC TARTRATE COMPLEXES

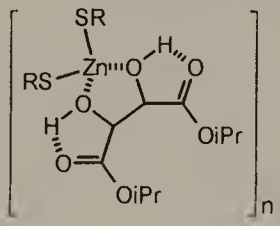


Figure 2.3

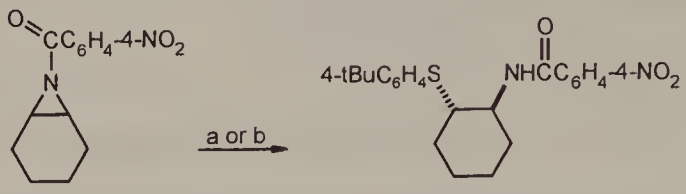
Preparation

The preparation is done *in situ* from diethyl zinc and dialkyl tartrate (see Schemes 2.23–2.26).

Application

L

The application is as a chiral mediator for the enantioselective addition of arenethiols to *N*-acylaziridines (Ogumi),[137(a)] also in the catalytic version[137(b)] (Scheme 2.23).



a: 98%, e.e. 88%

b: 95%, e.e. 78%

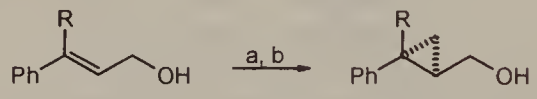
a: 1 eq. (+)-DIPT (**2.3**), 3 eq. Et_2Zn, 4.8 eq. 4-$tBuC_6H_4SH$, CH_2Cl_2, 0°C[137(a)]

b: 0.2 eq. (+)-dicyclohexyl tartrate, 1 eq. Et_2Zn, 3 eq. 4-$tBuC_6H_4SH$, CH_2Cl_2, 0°C[137(b)]

Scheme 2.23

The reactive species for the reaction are presumably zinc complexes of the formula in Fig. 2.3.[137(b)]

Fujisawa developed a protocol for the *asymmetric Simmons–Smith reaction of allylic alcohols* using zinc tartrate complexes as chiral mediators[138] (Scheme 2.24).



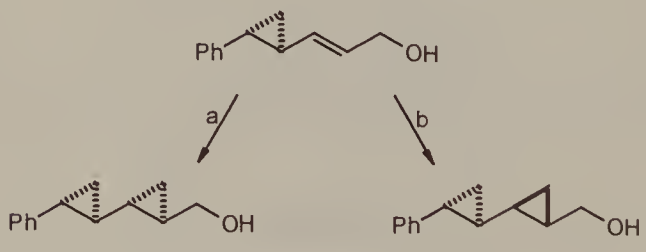
R = H 54%, e.e. 71-79%[138]

R = Me_3Si 84%, e.e. 80%[139]

a: 1 eq. Et_2Zn, 1 eq. (+)-DET (**2.2**), CH_2Cl_2 or $ClCH_2CH_2Cl$, 0°C

b: 2-3 eq. Et_2Zn, 2-3 eq. CH_2I_2, -20°C → 0°C

Scheme 2.24



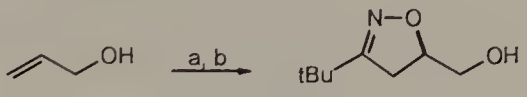
a: Et_2Zn, (+)-DET (**2.2**), CH_2I_2, $ClCH_2CH_2Cl$, -12°C (72%, d.e. 71%)

b: Et_2Zn, (-)-DET (*ent*-**2.2**), CH_2I_2, $ClCH_2CH_2Cl$, -12°C (84%, d.e. 71%)

Scheme 2.25

This reaction has been used by Barrett in the synthesis of the antifungal agent FR-900848[140] (Scheme 2.25). Note the opposite diastereoselectivity of cyclopropanation imposed by the two enantiomeric tartrate ligands, overriding the chirality of the substrate.

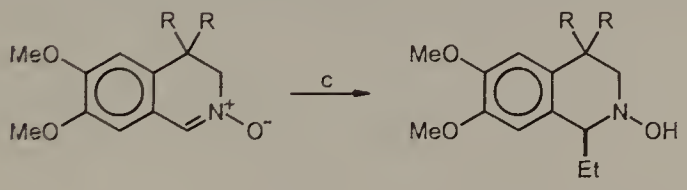
In addition, zinc tartrate complexes were applied by Ukaji and Inomata as chiral mediators in the enantioselective synthesis of 2-isoxazolines via 1,3-dipolar cycloaddition of a nitrile oxide to allyl alcohol,[141] as well as in addition of diethylzinc to nitrones[142] (Scheme 2.26).



92%, e.e. 96%

a: 1 eq. Et_2Zn, 1 eq. (+)-DIPT (**2.3**), $CHCl_3$, 0°C

b: 1.5 eq. Et_2Zn, 1.5 eq. t-BuC(Cl)=NOH, 0°C



R = H, 88%, e.e. 85%

R = Me, 91%, e.e. 94%

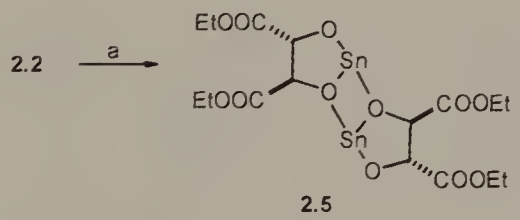
c: Et_2Zn, (+)-dicyclopentyl tartrate, MeMgBr, CH_2Cl_2, 0°C → RT

Scheme 2.26

2.6 TIN(II) AND TIN(IV) TARTRATE COMPLEXES

Preparation

Tin(II) tartrate complex (**2.5**) can be prepared from tin(II) dichloride and dialkyl tartrate (Scheme 2.27).



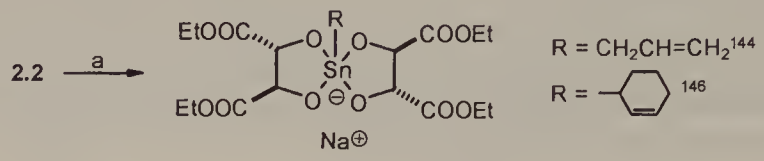
2.5

a $SnCl_2$, NEt_3, MeOH, RT, 85%[143]

Dimeric structure from ^{119}Sn NMR measurement[143]

Scheme 2.27

The tin(IV)-tartrate complex of the tentative structure **2.6** can be prepared *in situ* from tin(II) chloride, an allyl bromide, and dialkyl tartrate[144,145] (Scheme 2.28).



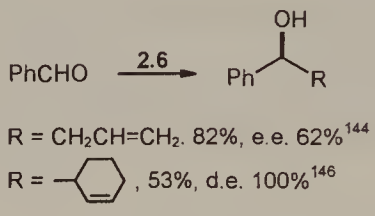
2.6

a: 2eq. NaH, 0.5 eq. $SnCl_2$, 1.5-2.0 eq. RBr, THF, 0°C[144]

Scheme 2.28

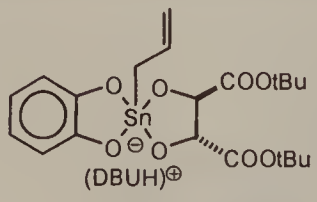
Applications

Tin(IV) complex **2.6** was developed by Umani-Ronchi *et al.* as a chiral reagent for the enantioselective allylation of aldehydes[144] (Scheme 2.29).



Scheme 2.29

The related chiral allylic tin reagent **2.7** developed by Mukaiyama *et al.* reacts with aromatic aldehydes to give homoallylic alcohols of high enantiomeric excess[147] (Scheme 2.30).



2.7

Ar	yield (%)	e.e. (%)
Ph	98	91
2-MeC_6H_4	99	94
1-naphthyl	97	92

a: **2.7**, CuI (cat.), CH_2Cl_2, -78°C

Scheme 2.30

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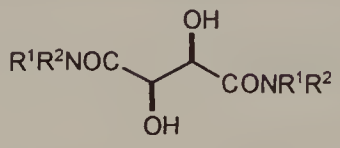
3 Tartramides, Tartaric Hydrazides, and Their Derivatives

3.1 DIAMIDES AND DIHYDRAZIDES OF TARTARIC ACID



I

Table 3.1 Symmetrical diamides and dihydrazides of L-tartaric acid (I)

R^1	R^2	m.p. (°C)	$[\alpha]_D$ (solvent)	References
H	H	195	+144.0 (MeOH)	1
Me	H	198–200	+148.8 (MeOH)	1–3
Et	H	210–211	+138.1 (MeOH)	1
n-Pr	H	216	+124.9 (MeOH)	2
i-Pr	H	189–190.5	+117.8 (MeOH)	2,4
n-Bu	H	193	+114.6 (MeOH)	2
i-Bu	H	183.5	+117.6 (MeOH)	2
$n\text{-}C_5H_{11}$	H	194–195	—	5
$n\text{-}C_7H_{15}$	H	183	+88.1 (MeOH)	2
$Cl(CH_2)_2$	H	191–192	—	6
$H_2N(CH_2)_2$	H	206–208	—	7
$BnOOCNH(CH_2)_2$	H	238–239	—	7
$(HOCH_2)_3C$	H	144	—	8
CH_2=CHCH	H	186–188	+119.8 (MeOH)	2
Bn	H	201–204	+91.5 (pyridine)	1
2-furylmethyl	H	178–180	+97.3 (pyridine)	9
Ph	H	255–256	+245.6 (pyridine)	1,10
$2\text{-}MeC_6H_4$	H	184–185	+199.0 (pyridine)	1
$3\text{-}MeC_6H_4$	H	184	+225.3 (pyridine)	1
$4\text{-}MeC_6H_4$	H	264–267	+241.0 (pyridine)	1,10
$2\text{-}ClC_6H_4$	H	185	+164.3 (MeOH)	11
$3\text{-}ClC_6H_4$	H	212	+182.3 (MeOH)	11
$4\text{-}ClC_6H_4$	H	276	+196.0 (MeOH)	10,11
$2\text{-}BrC_6H_4$	H	193	+120.9 (MeOH)	11
$3\text{-}BrC_6H_4$	H	220	+154.5 (MeOH)	11
$4\text{-}BrC_6H_4$	H	264	+181.1 (MeOH)	11

Table 3.1 (*continued*)

R^1	R^2	m.p. (°C)	$[\alpha]_D$ (solvent)	References
1-naphthyl	H	213–214	+97.6 (pyridine)	1,12
2-naphthyl	H	279	+292.0 (pyridine)	1,12
Me	Me	188–190	+46.0 (EtOH)	13,14
Ph	Me	152	+28.4 (benzene)	15
$-(CH_2)_4-$		132.5–135	+34.2 (EtOH)	13,16,17
$-(CH_2)_5-$		189–190	+1.2 (CH_2Cl_2)	18
BnO	H	183–185	—	16
NH_2	H	182.5–183	+97.1 (H_2O)	1,9,19
PhNH	H	231	+80.9 (AcOH)	1,2
3.1[a]		202–203	−79.9 (dioxane)	20
3.2[a]		145–147	−43.5 ($CHCl_3$)	21
3.3[a]		73–75	−28.9 ($CHCl_3$)	21

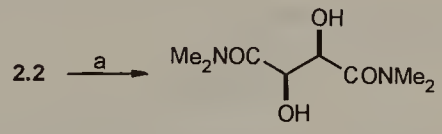
[a] See Scheme 3.5.

Unlike primary and secondary tartrdiamides, tertiary tartrdiamides in the lowest-energy conformation have a nonplanar (bent) four-carbon chain.[3,22]

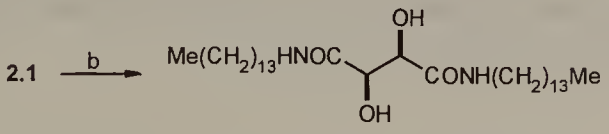
Synthesis

Three general methods are useful for the preparation of symmetrical tartaric acid diamides.

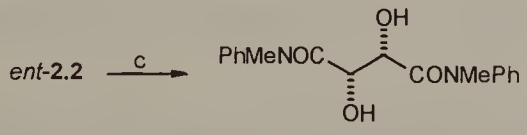
i. Aminolysis of dimethyl or diethyl tartrate (**2.1**, **2.2**) with excess alkyl amine in alcohol solvent or with more nucleophilic magnesium amides in ethereal solvents (Scheme 3.1).



a: excess Me_2NH, MeOH, RT, 3 days (95-98%)[13,14]



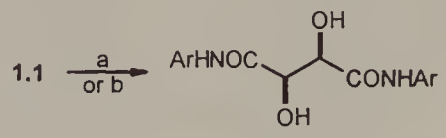
b: 2.2 eq. $Me(CH_2)_{13}NH_2$, MeOH, Δ, 20h (97%)[23]



c: excess PhMeNMgBr, Et_2O, Δ (63%)[15]

Scheme 3.1

ii. Thermal condensation of excess aryl amine with tartaric acid (**1.1**) or reaction of tartaric acid with *N*-sulfinylarylamine (Scheme 3.2).

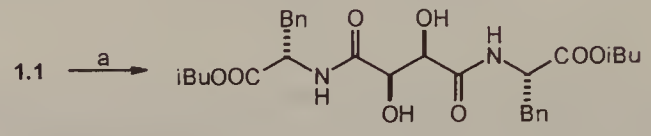


a: 2-5 eq. $ArNH_2$, 160-180°C[1,24]

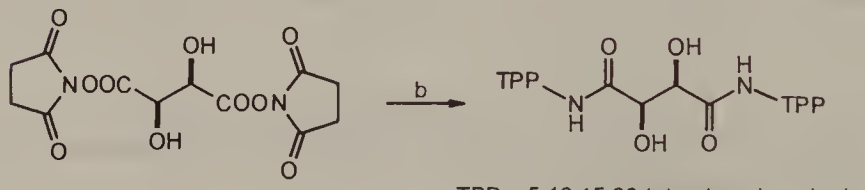
b: 2 eq. ArN=S=O, MeOH, 50°C (97-99%)[10]

Scheme 3.2

iii. Reaction of an amine with *in situ* prepared active esters of tartaric acid (Scheme 3.3).



a: 2 eq. (*S*)-Bn(N^+H_3)CHCOOiBu TsO^-, 2 eq. NMM, 2.2 eq. *N*-hydroxybenzotriazole, 2.2 eq. DCC, THF-CH_2Cl_2, 0°C → RT (55%)[25]



TPP = 5,10,15,20-tetraphenylporphyrin

b: 2 eq. TPP-NH_2, CH_2Cl_2, Δ, 5h (64%)[49]

Scheme 3.3

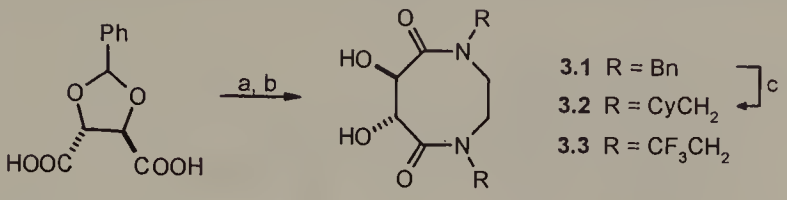
Unsymmetrical diamides can be obtained by aminolysis of tartramates or by reaction of tartramic acids or tartrimides with amines (see also Chapter 4).

Tartramides are also available by deacetylation of *O*,*O*′-diacetyltartramides with dilute methanolic ammonia (Scheme 3.4).

a: 0.6M NH_3 in MeOH (95-96%)[26]

Scheme 3.4

Cyclic diamides **3.1–3.3** were synthesized from *O,O′*-benzylidene-L-tartaric acid[20,21] (Scheme 3.5).



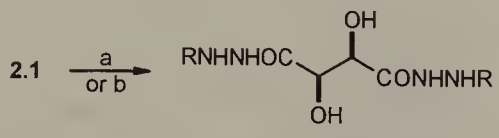
a: $RHNCH_2CH_2NHR$, DCC or *N*-methyl-2-chloropyridinium iodide, NEt_3 (38-52%)

b: AcOH-H_2O, reflux or H_2, 10% Pd, 10% AcOH-EtOH (87-97%)

c: H_2 (3.5 atm), 10% Rh-Al_2O_3 (90%)

Scheme 3.5

Tartaric dihydrazides are prepared by hydrazinolysis of tartrates (**2.1**, **2.2**) or by thermal condensation of tartaric acid (**1.1**) with substituted hydrazines (Scheme 3.6).



a (R = H): $H_2NNH_2 \cdot H_2O$, EtOH, RT[1]

b (R = Ph): $PhNHNH_2$, Δ[1]

Scheme 3.6

Tartaric polyamide was obtained by polycondensation of dimethyl L-tartrate with hexamethylenediamine at 30°C in various solvents, of which diglyme, THF, and DMSO were most favorable with respect to polymer yield.[32]

Several tartrdiamides are available commercially:

N,N′-diallyl-L-tartrdiamide [*58477-85-3*]

N,N′-dibenzyl-L-tartrdiamide [*88393-56-0*] and its enantiomer [*108321-43-3*]

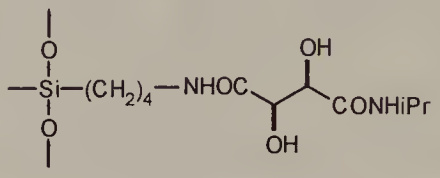
N,N,N′,N′-tetramethyl-L-tartrdiamide [*26549-65-5*] and its enantiomer [*63126-52-3*].

Applications

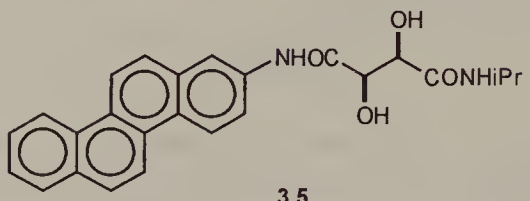
N,N′-Diisopropyltartrdiamide has been used as chiral additive in the resolution study of hydroxy and amino acid derivatives as well as diols by liquid chromatography.[4,27]

Chiral polysiloxanes of the structure **3.4** derived from (*R,R*)-*N*-isopropyltartramide were used for the GC separation of enantiomers.[28] Chiral stationary

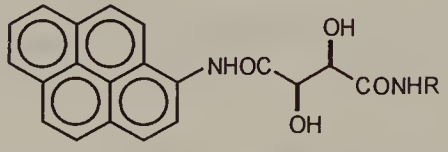
phases for HPLC exhibiting excellent enantioselectivity and stability have been obtained by adsorbing the unsymmetrical diamides **3.5–3.7** onto porous graphitic carbon.[26]



3.4



3.5

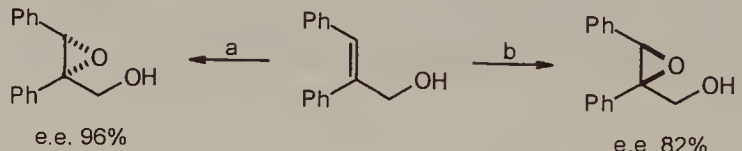


3.6 R = i-Pr

3.7 R = 3-$O_2NC_6H_4$

L

Tartrdiamides are used as chiral titanium(IV) ligands in Sharpless epoxidation; stereochemical outcome of the reaction is dependent on the ratio of $Ti(OiPr)_4$:tartrdiamide (Scheme 3.7).[29,30]



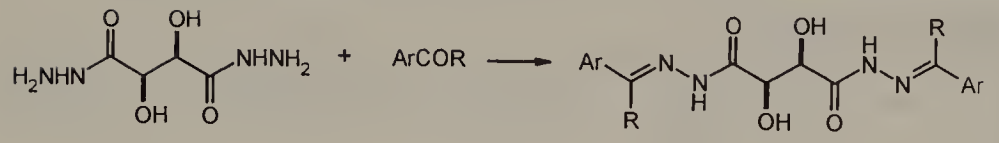
e.e. 96% e.e. 82%

a: 2.4 eq. (*R*,*R*)-*N*,*N*'-dibenzyltartrdiamide, 2 eq. $Ti(Oi\text{-}Pr)_4$, t-BuOOH, -20°C

b: as a, but 1.0 eq. of the diamide

Scheme 3.7

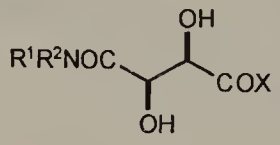
Tartaric dihydrazide readily forms with aromatic aldehydes and ketones tartaric bis-hydrazones, compounds of potential applications (Scheme 3.8).[31]



R	Ar	ref.
H	Ph	1,9
H	4-$NO_2C_6H_4$	31
H	4-pyridyl	31
H	2-furyl	1,9
Me	Ph	1,9

Scheme 3.8

3.2 MONOAMIDES OF TARTARIC ACID (TARTRAMIC ACIDS) AND THEIR DERIVATIVES



II

Table 3.2 L-Tartramic acids (II, X = OH), L-tartramates (II, X = OR) and L-tartramazides (II, X = $NHNH_2$)

R^1	R^2	X	m.p. (°C)	$[\alpha]_D$ (solvent)	References
H	H	OH	171–172	+63.7 (H_2O)	33,34
Me	H	OH	154–156	+86.8 (H_2O)	3
Me	Me	OH	—	+3.6 (MeOH)	3
i-Pr	H	OH	178–179	+75.1 (—)	28
C_8H_{17}	H	OH	150–151	+32.2 (AcOEt)	35
Ph	H	OH	182–182.5	+106.2 (H_2O)	36
2-MeC_6H_4	H	OH	152.5–154	+108.2 (EtOH)	37
2-ClC_6H_4	H	OH	180.5–182.5	+100.3 (EtOH)	37
2-BrC_6H_4	H	OH	171.5–172.5	+75.6 (EtOH)	37
2-$NO_2C_6H_4$	H	OH	196–198	+90.0 (H_2O)	37
3-$NO_2C_6H_4$	H	OH	205–207	+93.4 (H_2O)	38
4-ClC_6H_4	H	OH	193–195	+108.9 (EtOH)	37,39
4-BrC_6H_4	H	OH	198.5–201.5	+90.5 (EtOH)[a]	37
4-HOC_6H_4	H	OH	218	+108.3 (H_2O)	47
2,4-$Cl_2C_6H_3$	H	OH	181–191	+100.7 (EtOH)	37
2,4,6-$Cl_3C_6H_2$	H	OH	176.5–178.5	+72.4 (EtOH)[a]	37
H	H	OMe	136.5–140	+62.9 (H_2O)	40
Me	H	OMe	139–143	+130.5 (H_2O)	3
Me	Me	OMe	48–51	−20.0 (MeOH)	3

(*continued*)

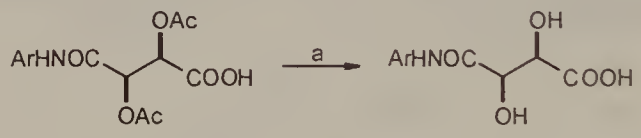
Table 3.2 (*continued*)

R^1	R^2	X	m.p. (°C)	$[\alpha]_D$ (solvent)	References
H	H	OEt	134–137	—	41
Bn	H	OEt	—	—	30
4-HOC_6H_4	H	OEt	118	+106.1 (MeOH)	42
H	H	$NHNH_2$	152	+124.0 (H_2O)	40,43

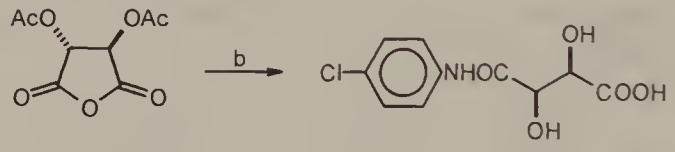
[a] Hydrate.

Synthesis

Tartramic acids can be obtained by hydrolysis or methanolysis of the corresponding *O,O′*-diacyl derivatives; the synthesis starts with the amine and *O,O′*-diacetyl tartaric anhydride and can be done in one step (Scheme 3.9).



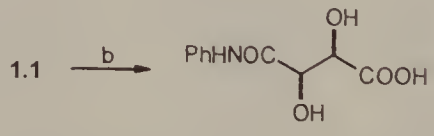
a: 3eq. 1.5M KOH, RT, 2h, then conc. HCl



b: 1 eq. 4-$ClC_6H_4NH_2$, CH_2Cl_2, Δ,15h, then 10% KOH, then conc. HCl (68%)[39]

Scheme 3.9

A mild synthetic method is based on the reaction of tartaric acid (**1.1**) with *N*-sulfinylanilines (Scheme 3.10).



b: 1eq. PhN=S=O, MeCN, 50°C (99%)[10]

Scheme 3.10

Tartramates can be obtained with moderate yields by aminolysis of dialkyl tartrates (side product—tartaric diamide), Scheme 3.11, or by esterification of the corresponding tartramic acids.

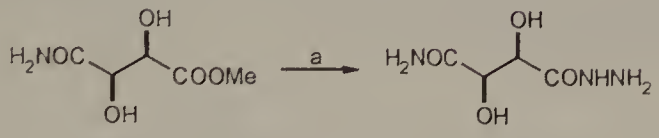
R = Me (34%)[40]

R = Et (55%)[41]

a: NH_3, ROH, 0-3°C, 2 h

Scheme 3.11

Tartramazides (hydrazides of tartramic acids) were prepared by hydrazinolysis of tartramates (Scheme 3.12).

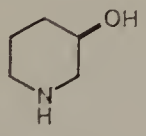


a: H_2NNH_2, MeOH, RT (92%)[44]

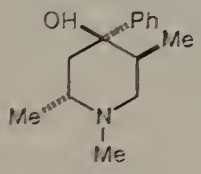
Scheme 3.12

Applications

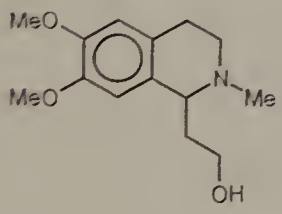
Tartranilic acids (monoanilides of tartaric acid) are useful as reusable resolving agents for amines (Scheme 3.13).



resolved with (*R*,*R*)-p-chlorotartranilic acid[39,45]



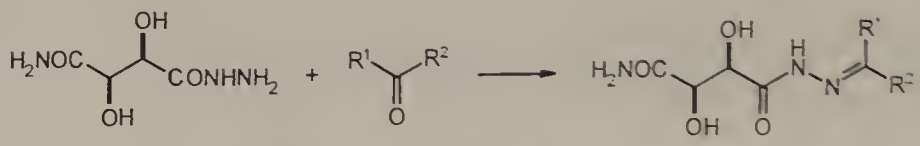
resolved with (*R*,*R*)-m-nitrotartranilic acid[37]



resolved with (*R*,*R*)-o-nitrotartranilic acid
(both enantiomers obtained)[37]

Scheme 3.13

Tartramazides form crystalline tartramazone derivatives of aldehydes and ketones[44] (Scheme 3.14).

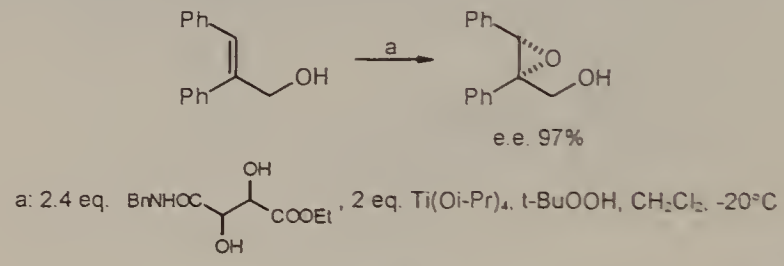


Scheme 3.14

These derivatives can be used for resolving racemic ketones, such as 2-phenylcyclopentanone,[43] α-methyllevulinic acid,[46] and 3-methoxy-14,17-dioxo-7(14)-*seco*-1,3,5(10),9(11)-estratetraene,[47] as well as 3,7-dimethyloctanal.[44]

N-Octyltartramic acid was applied as chiral mobile phase additive the resolution of racemic amino acids by liquid chromatography.[48]

Ethyl (*R,R*)-*N*-benzyltartramate is effective as a chiral titanium (IV) ligand in Sharpless epoxidation (Scheme 3.15).[30]



Scheme 3.15

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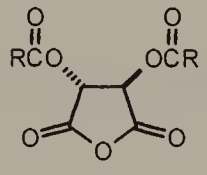
4 *O*-Acylated Tartaric Acids and Their Derivatives

O-Acylation provides simple and economic protection of the tartrate hydroxy groups. *O*-Acyl protection can be readily removed by base catalysed hydrolysis or methanolysis; the *O*-acetyl groups are particularly prone to deprotection (cf. Schemes 4.22 and 4.24). *O*-Acylation enhances the acidity of the neighboring carboxylic group.

4.1 *O,O'*-DIACYL TARTARIC ANHYDRIDES

In contrast to tartaric anhydride—a compound which is unstable and has not been isolated[1,2]—*O,O'*-diacyl tartaric anhydrides (**I**) are readily prepared from tartaric acid and widely used as resolving agents for alcohols.



I

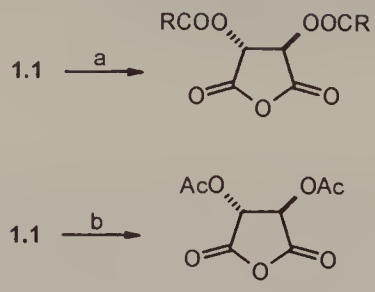
Table 4.1 ***O,O'*-Diacyl-L-tartaric anhydrides (I)**

R	m.p. (°C)	$[\alpha]_D$ (solvent)	References
Me	134–135	+62.0 (Me_2CO)	3,4,6–16
t-Bu	167	+76.0 (benzene)	17
Cy	139.5–141	+35.0 (dioxane)	18
$CyCH_2$	111–112.5	+40.0 (dioxane)	18
CyCH=CH	106–107	+66.0 (dioxane)	18
1-adamantyl	220	+34.8 (dioxane)	17
Bn	115.5–116	+60.8 (Me_2CO)	6,18
Ph	192–195[a]	+196.0 ($CHCl_3$)[a]	3,6,7,19–21
Tol	197–198	+195.0 (Me_2CO)	23
PhCH=CH	146–148	+291.0 (Me_2CO)	22
CF_3	54–55	+40.4 ($CHCl_3$)	24
CCl_3	176–177	+64.6 (benzene)	24

[a] Some authors report m.p. 173–174°C, $[\alpha]_D$ +142 (Me_2CO).[25,26]

Synthesis

O,O'-Diacyl tartaric anhydrides are synthesized from tartaric acid (**1.1**) by acylation with acyl halides at elevated temperatures or with acetyl anhydride in the presence of an acid catalyst (Scheme 4.1).



a: 3.5 eq. RCOCl, 100-150°C

b: 3.5 eq. Ac_2O, H_2SO_4 (cat.), Δ (dist. AcOH), 95%[15] or Δ, 10-30 min, 71-77%[10,14,16]

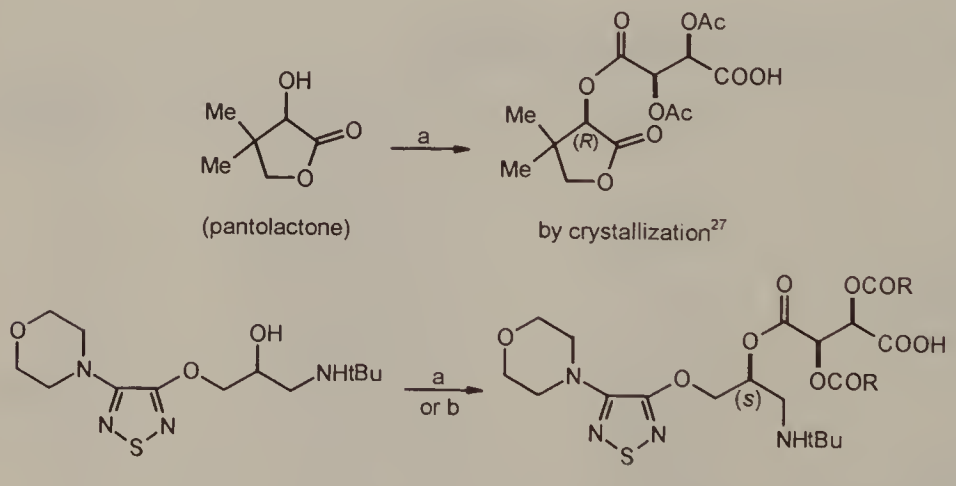
Scheme 4.1

Recent patents describe the synthesis of *O,O'*-(substituted)dibenzoyl tartaric anhydrides by benzoylation of **1.1** with (substituted) benzoyl chlorides at 105–110°C in the presence of a Lewis acid ($SOCl_2$, $FeCl_3$ or $BF_3{\cdot}Et_2O$).[28]

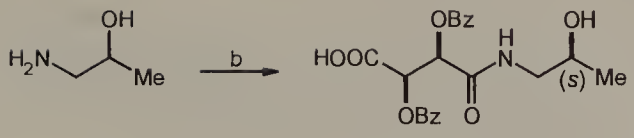
O,O'-Diacetyl-L-tartaric anhydride [*6283-74-5*] is commercially available.

Applications

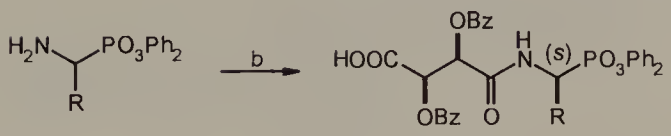
O,O'-Diacyl tartaric anhydrides were used for resolution of racemic alcohols and amines via diastereomeric monoesters, amides and imides (Scheme 4.2).



Scheme 4.2 (*continued*)

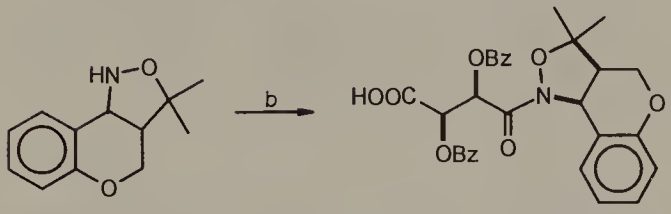


by chromatography,[31] d.e. 100%

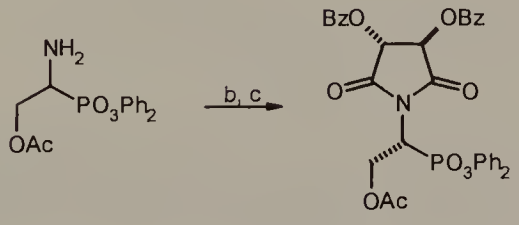


R = Me, i-Pr, i-Bu, Ph, Bn

yield 70-92%, by crystallization[32]



yield 91%, by crystallization[33]



yield 60%, d.e. 100% after three crystallizations[34]

a *O,O'*-diacetyl-L-tartaric anhydride

b: *O,O'*-dibenzoyl-L-tartaric anhydride

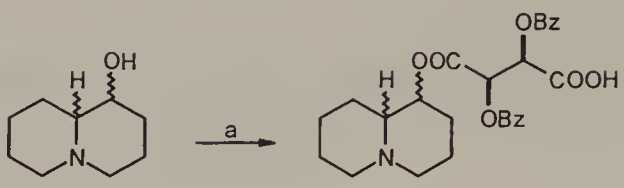
c: $SOCl_2$, benzene, Δ

Scheme 4.2

The resolved alcohols or amines are recovered from the monoesters or monoamides by alkaline hydrolysis. Partial kinetic resolution of racemic alcohols in the reaction with *O,O'*-diacyl tartaric anhydrides has been achieved.[35] Procedures for liquid chromatographic separation of diastereomeric *O,O'*-diacetyltartaric monoesters of pharmaceutical importance have been reported.[36–38]

Enantiomeric purity of diastereomeric 1-hydroxyindolizidines could be determined by HPLC separation or by ^{1}H NMR spectroscopy after conversion to esters **4.1** (Scheme 4.3).[39]

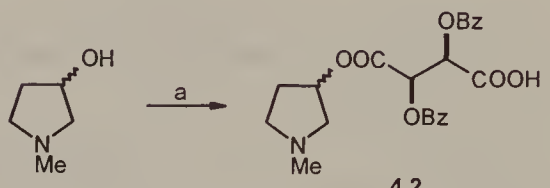
Similarly, enantiomeric purity of 1-methyl-3-pyrrolidinol[40] and 3-aminoquinuclidine[41] was determined by HPLC separation of the esters **4.2** or the amides **4.3** (Scheme 4.4).



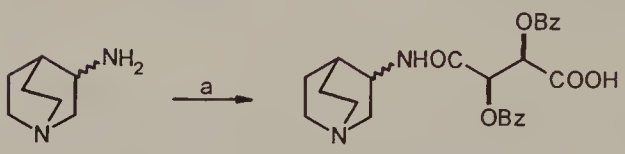
4.1

a: *O,O'*-dibenzoyl-L-tartaric anhydride

Scheme 4.3



4.2



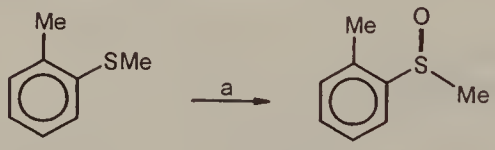
4.3

a: *O,O'*-dibenzoyl-L-tartaric anhydride

Scheme 4.4

L

O,O'-Diacyltartaric anhydrides can act as chiral ligands in the oxidation of prochiral sulfides to sulfoxides by iodine(III) compounds[42,43] (Scheme 4.5).



a: 2 eq. *O,O'*-dibenzoyl-L-tartaric anhydride, 2eq. PhIO, Me_2CO, RT (75%, e.e. 53%)[42]

Scheme 4.5

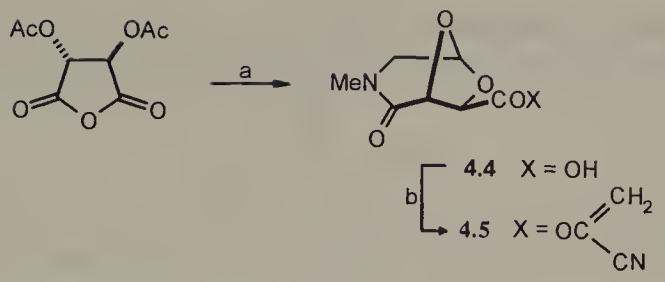
A

The chiral auxiliary, **4.4**, for the Diels–Alder reaction of 1-cyanovinyl ester derivative **4.5** was obtained from *O,O'*-diacetyl-L-tartaric anhydride and *N*-alkylaminoacetaldehyde by intramolecular acetalization[44] (Scheme 4.6).

Chiral 1-cyanovinylester **4.6** reacted with furan to give, after two recrystallizations, enantiomerically pure 7-oxabicyclo[2.2.1]hept-5-en-2-yl derivative **4.7** which was converted to (+)-6-deoxycastanospermine (**4.9**) via the "naked sugar" **4.8**[45] (Scheme 4.7).

B

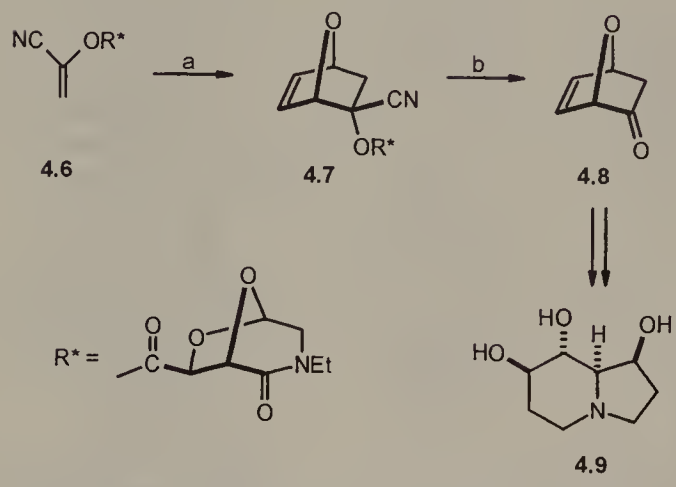
O,O'-Diacetyl tartaric anhydride readily undergoes elimination with pyridines to form salts of hydroxymaleic anhydride **4.10**.[4] These can be transformed into variety of derivatives, such as oxalacetic acid[4] and *O*-protected



a: $MeNHCH_2CH(OEt)_2$

b: $SOCl_2$, then pyruvonitrile, pyridine

Scheme 4.6

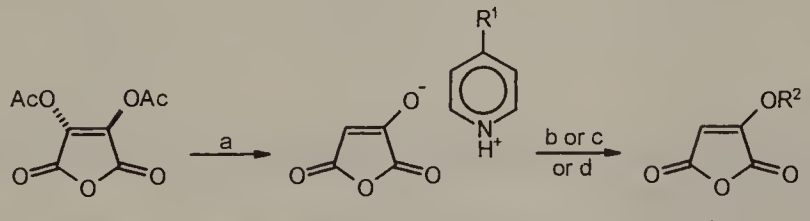


a: furan, $ZnBr_2$, mol. sieves 4Å, RT, 2 recrystallizations (35%)

b: 1M NaOH, 40% aq. HCHO, RT (96%)

Scheme 4.7

hydroxymaleic anhydrides **4.11** which are valuable synthetic intermediates[46] (Scheme 4.8).



m.p. 108-112° (R^1 = H)

122-123° (R^1 = Me)

a: pyridine or 4-picoline, AcOH, 65-80%[4,8,9,11,47,48]

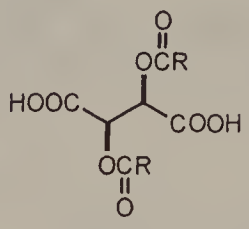
b (R^2 = Me): CH_2N_2, THF, 85%[47,49]

c (R^2 = Me_3Si): Me_3SiCl, benzene, 76.5%[48]

d (R^2 = Ac): AcCl, benzene, 96%[4,11]

Scheme 4.8

4.2 *O,O′*-DIACYL TARTARIC ACIDS



II

Table 4.2 ***O,O′*-Diacyl-L-tartaric acids (II)**

R	m.p. (°C)	$[\alpha]_D$ (solvent)	References
Me	117–118	−23.6 (Me_2CO)	50,51
t-Bu	135	−24.2 (dioxane)	17,52
t-$BuCH_2$	—	−21.1 (dioxane)	52
t-$Bu(CH_2)_2$	—	−24.4 (dioxane)	52
Cy	65–68	−29.0 (dioxane)	18
$CyCH_2$	125.5–126	−26.0 (dioxane)	18
CyCH=CH	82–85	−54.0 (dioxane)	18
1-adamantyl	273	−26.1 (dioxane)	17,52
$Ph(CH_2)_2$	—	−25.5 (dioxane)	52
Bn	133–135	−31.0 (dioxane)	18
Ph	152–155[a]	−117.0 (EtOH)	19
Tol	173	−140.0 (EtOH)	23,53
An	186	−162.8 (EtOH)	54
PhCH=CH	—	−207.4 (dioxane)	52
3,4-$(HO)_2C_6H_3CH$=CH	206	−384.2 (MeOH)	55
PhNH[b]	203–204	−94.8 (AcOEt)	56

[a] The monohydrate has m.p. 90–92°C, $[\alpha]_D$ −110 ± 3 (EtOH); for the anhydrous compound a m.p. of 138–139°C has also been reported (ref. 25, 57).

[b] Prepared from dibenzyl tartrate by the action of phenyl isocyanate followed by hydrogenolysis.

Synthesis

O,O′-Diacyl tartaric acids are obtained by hydrolysis of the corresponding *O,O′*-diacyl tartaric anhydrides.

Both enantiomers of *O,O′*-dibenzoyltartaric acid can be conveniently obtained from the racemate by preferential crystallization of its calcium salt-methoxyethanol complex which crystallizes as a conglomerate.[58] *O,O′*-Di-p-toluoyl-D-tartaric acid can be obtained by resolution of the racemate with cinchonine.[59]

The following *O,O′*-diacyl tartaric acids are commercially available:

O,O′-dibenzoyl-L-tartaric acid [*2743-38-6*] and its monohydrate [*62708-56-9*]

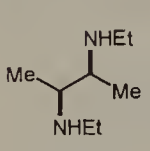
O,O′-dibenzoyl-D-tartaric acid [*17026-42-5*] and its monohydrate [*80822-15-7*]

O,O′-di-p-toluoyl-L-tartaric acid [*32634-66-5*] and its enantiomer [*32634-68-7*]
O,O′-dipivaloyl-L-tartaric acid [*65259-81-6*] and its enantiomer [*76769-55-6*].

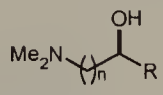
Applications

O,O′-Dibenzoyl and *O,O′*-di-p-toluoyl tartaric acids are excellent resolving agents for racemic amines and acid hydrazides via their diastereomeric salts.[60,61] These acids normally form 1:1 salts with monoamines.[62]

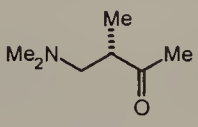
Examples of resolutions with *O,O′*-dibenzoyl-L-tartaric acid and with *O,O′*-di-p-toluoyl-L-tartaric acid are shown in Schemes 4.9 and 4.10, respectively.



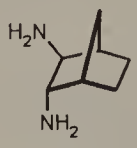
ref. 63



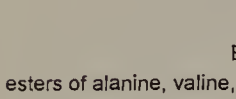
R = Et, n =1 (ref. 64)
R = Ph, n = 1,2 (ref. 65)

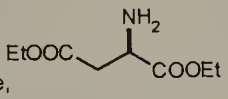


ref. 66

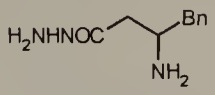


ref. 67

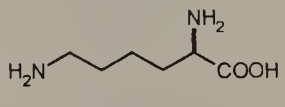

esters of alanine, valine, leucine, phenylalanine (ref. 68, 69)



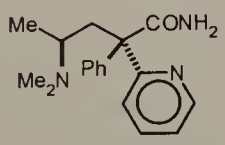
(and enantiomer) ref. 70



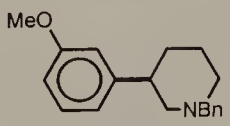
(both enantiomers) ref. 71



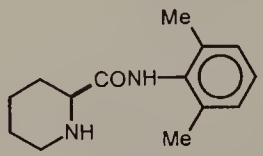
ref. 72



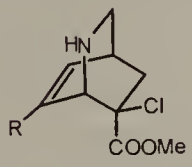
ref. 73



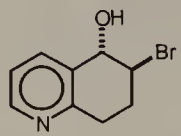
ref. 74



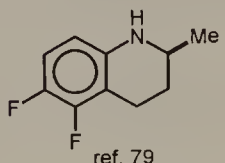
ref. 75



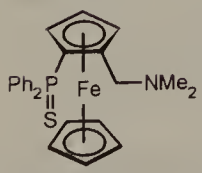
R = H (ref. 76)
R = Et (ref. 77)



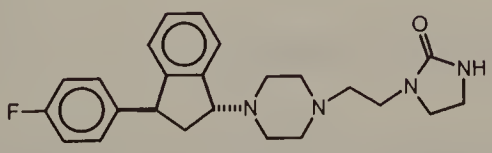
ref. 78



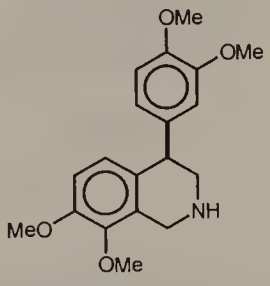
ref. 79



ref. 80

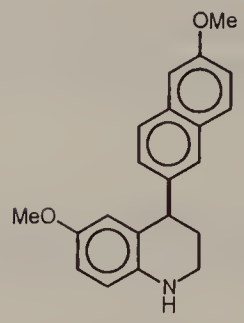


ref. 81

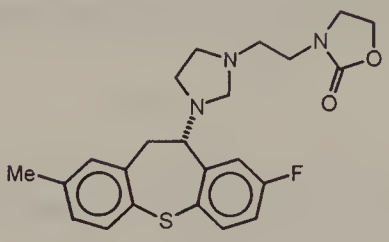


ref. 82

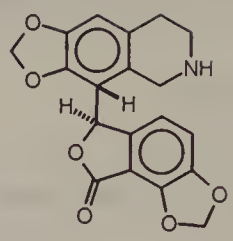
Scheme 4.9 (*continued*)



ref. 83

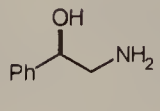


ref. 84

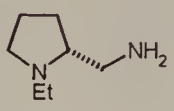


ref. 85

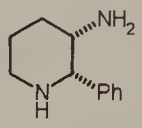
Scheme 4.9



ref. 86



ref. 87



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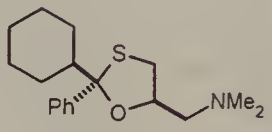
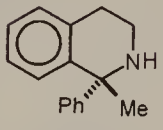
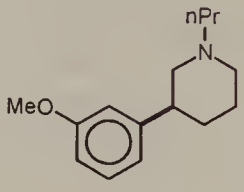


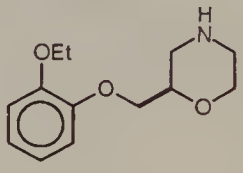
ref. 89



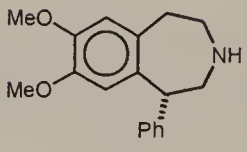
ref. 90



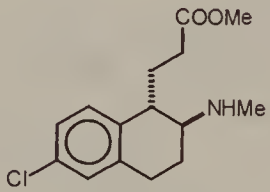
ref. 91



ref. 92

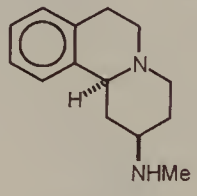


ref. 93

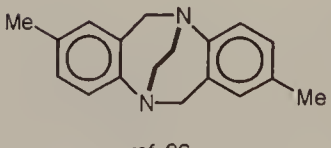


(and enantiomer)

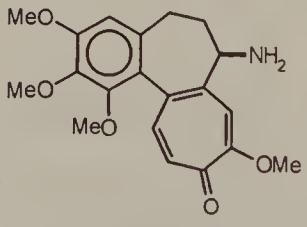
ref. 94



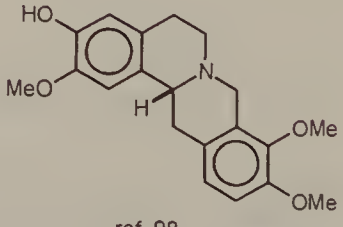
ref. 95



ref. 96



ref. 97



ref. 98

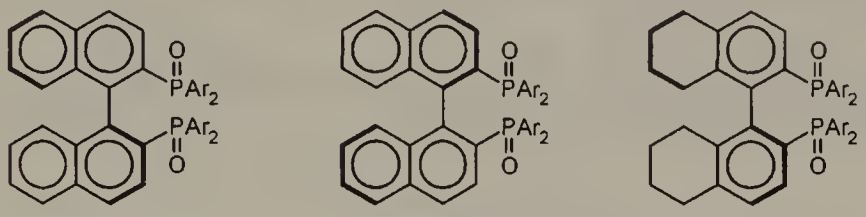
Scheme 4.10

O,O′-Di(phenylaminocarbonyl) tartaric acid was found to efficiently resolve racemic 2,2′-diamino-6,6′-dimethoxybiphenyl.[56] *O,O′*-Dibenzoyl tartaric acid was also used for resolution of racemic alkyl(benzyl)(methyl)(phenyl)phospho-

nium,[99,100] (hydroxyalkyl)triphenylphosphonium,[101] benzyl(methyl)(4-tolyl)(1-naphthyl)arsonium,[102] and (hydroxyalkyl)dimethyl sulfonium salts.[103]

O,O'-Dibenzoyl tartaric acid is known to give crystalline complexes with compounds acting as hydrogen bond acceptors, such as alcohols, ethers, and esters. This property can be used for the resolution of non-basic racemates. An example of this application is the resolution of racemic menthol by complex formation; *O,O'*-dibenzoyl-L-tartaric acid monohydrate gives a crystalline complex of d.e. 83% with (−)-menthol. From this complex (−)-menthol can be recovered by sublimation.[104]

Other examples of resolutions via hydrogen-bonded complexes with *O,O'*-dibenzoyl- or *O,O'*-ditoluoyl-L-tartaric acid include BINAPO and its analogues (Takaya, Akutagawa, Noyori[105–107]), Scheme 4.11.



(S)-BINAPO (Ar = Ph)[105]
Ar = 4-t-BuC$_6$H$_4$[105]
Ar = Cy[107]

Ar = 4-MeC$_6$H$_4$[105]
Ar = 4-ClC$_6$H$_4$[106]

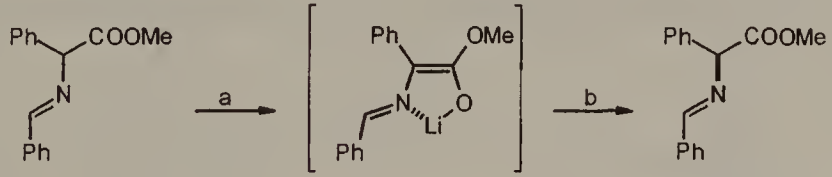
Ar = Ph[107]
Ar = Cy[107]

Scheme 4.11

In the case of methyl and ethyl mandelate, resolution is achieved by coordination complexes with calcium hydrogen *O,O'*-dibenzoyl tartrate; the salt of the L-acid gives (*R*)-mandelates of e.e. >99%.[108]

IR study of products of resolutions of *N*-alkyl pipecolic acid anilides with tartaric acid or *O,O'*-dibenzoyl tartaric acid led to the suggestion that even with bases tartaric acid may form complexes, rather than salts.[109]

O,O'-Diacyl tartaric acids were used by Duhamel *et al.* for deracemization of α-amino acids by protonation of their *N*-benzylidene enolates[52] (Scheme 4.12).

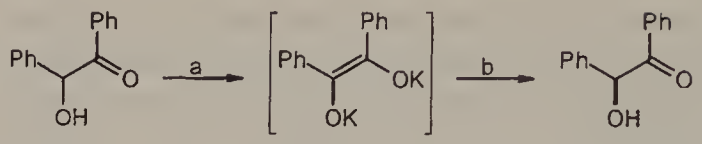


95%, e.e. 70%

a: LDA, THF, -70°C b: *O,O'*-dipivaloyl-L-tartaric acid , -105°C[110]

Scheme 4.12

O,O'-Dipivaloyl tartaric acid was applied for deracemization of benzoin via potassium (*Z*)-enediolate[111] (Scheme 4.13).

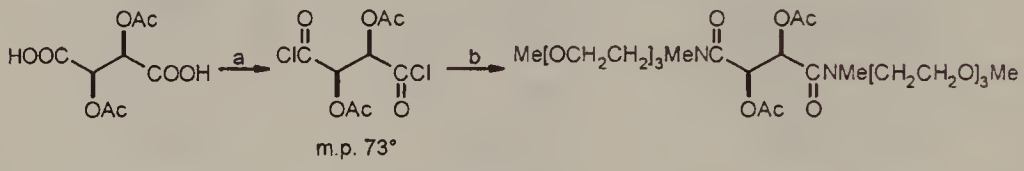


a: KH, THF, 0°C b: *O,O'*-dipivaloyl-L-tartaric acid, THF, -70°C, 15h

Scheme 4.13

It is essential for efficient enantiofacial protonation of enolates that the *O,O'*-diacyl tartaric acids, as a proton source, bear the bulky and rigid *O*-acyl substituent. This work has been extensively reviewed.[112–115]

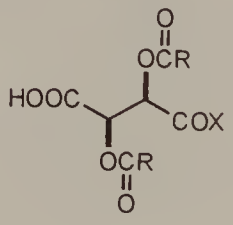
O,O'-Diacetyl tartaric acid can be converted to dichloride, which in turn can be used to prepare *O,O'*-diacetyl tartramides[51] (Scheme 4.14)



a: PCl_5, Δ b: $Me[OCH_2CH_2]_3NHMe$, NEt_3

Scheme 4.14

4.3 MONOESTERS AND MONOAMIDES OF *O,O'*-DIACYL TARTARIC ACIDS



III

Table 4.3 Monoesters and monoamides of *O,O'*-diacyl-L-tartaric acids (III)

R	X	m.p. (°C)	$[\alpha]_D$ (solvent)	References
Me	OMe	122–124	−16.2 ($CHCl_3$)	7,116
Me	Ot-Bu	112–113	−7.1 (Me_2CO)[a]	117
Me	OBn	—	+28.5 (CH_2Cl_2)	118
t-Bu	OMe	—	−12.9 ($CHCl_3$)	116
1-adamantyl	OMe	—	−16.1 ($CHCl_3$)	116
Ph	OMe	—	−90.0 ($CHCl_3$)	7
Ph	Ot-Bu	—	−100.0 (Me_2CO)[a]	117
Me	3,4-$(MeO)_2C_6H_3(CH_2)_2O$	220	—	119
Me	NHi-Pr	176.5–177	−22.0 (EtOH)	13,16,120
Me	$NH(CH_2)_3Si(OMe)_3$	—	+17.4 (THF)[b]	121

(*continued*)

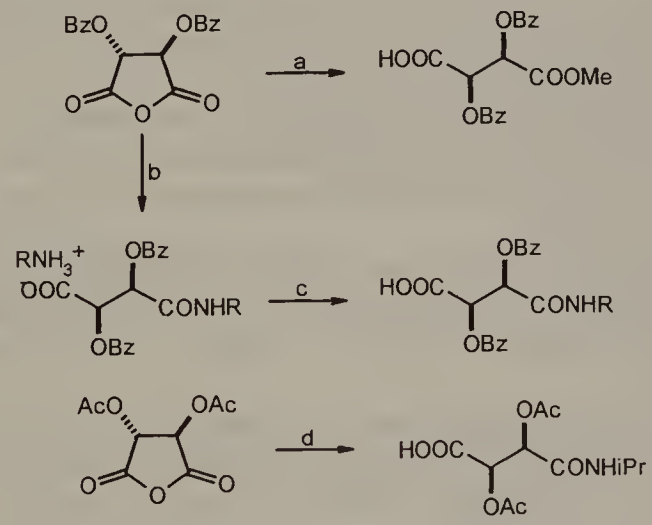
Table 4.3 (*continued*)

R	X	m.p. (°C)	$[\alpha]_D$ (solvent)	References
Me	NHBn	131.5–132	−13.7 (MeOH)	122
Me	NHPh	182	+106.2 (H_2O)	5
Me	NHC_6H_4-3-NO_2	144	+8.4 (THF)	16
Me	NHOBn[c]	—	—	118
Me	NHNHPh	168	—	123
Ph	NH_2	158–162	−142.8 (MeOH)	124
Ph	NHMe	124–132	−120.6 (dioxane)	124
Ph	NHn-Bu	136–138	−104.3 (Me_2CO)[d]	26
Ph	NHt-Bu	170–171	−106.9 (EtOH)	125
Ph	NMe_2	153–156	−79.0 (EtOH)	124
Ph	NEt_2	135–136	−74.4 (EtOH)	125,126
Ph	NHBn	123–124	−54.0 (EtOH)	125
Ph	(*S*)-NHCHMePh	100–101	−99.1 (EtOH)	127
Ph	(*R*)-NHCHMePh	116–117	−10.6 (EtOH)	127
Ph	NHPh	103–104	−77.8 (EtOH)	125

[a] At 546 nm [b] at 360 nm [c] unstable.
[d] m.p. 123–124°C, $[\alpha]_D$ −90.8 (EtOH) has been reported in ref. 125.

Synthesis

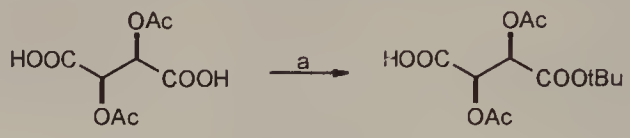
These monoesters and monoamides are readily available by alcoholysis or by aminolysis of the corresponding *O,O'*-diacyl tartaric anhydrides (Scheme 4.15).



a: 10 eq. MeOH, 1eq. pyridine, benzene, RT, then 5M HCl (96%)[125]
b: 2 eq. RNH_2, benzene or CH_2Cl_2
c: aq. Na_2CO_3, then 5M HCl, 89-95%[16,122,125]
d: 2 eq. i-$PrNH_2$, CH_2Cl_2, 0°, 20 min., then 5N HCl, 88%[13]

Scheme 4.15

Mono-t-butyl esters can be obtained by esterification of *O,O'*-diacyl tartaric acids with isobutene and concentrated sulfuric acid[117] (Scheme 4.16).



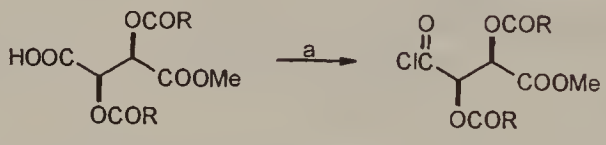
a: $Me_2C{=}CH_2$, H_2SO_4, CH_2Cl_2, -15°C → RT, 8h (52%)

Scheme 4.16

O,O'-Dibenzoyl-L-tartaric acid mono(dimethylamide) [*78761-37-2*] is available commercially.

Applications

B Monoesters of *O,O'*-diacyl tartaric acids are precursors of acid chlorides **4.12–4.14** (Scheme 4.17).



4.12 R = Me
4.13 R = t-Bu
4.14 R = Ph

a: $SOCl_2$, 45-60°C, 75-95%[7,128,129]

Scheme 4.17

Acid chloride **4.12** has been used in the synthesis of derivatives of L-pentoses[130] and L-apiose[128] via the threuronic acid derivative **4.15** or the diazoketone **4.16**, respectively (Scheme 4.18).

Ester **4.18** was synthesized by Schäfer by low-temperature photolysis of unsymmetrical diacyl peroxide **4.17** in the solid state. Under these conditions the radical pair generated by photochemical decarboxylation yielded a product with high diastereoselectivity.[131]

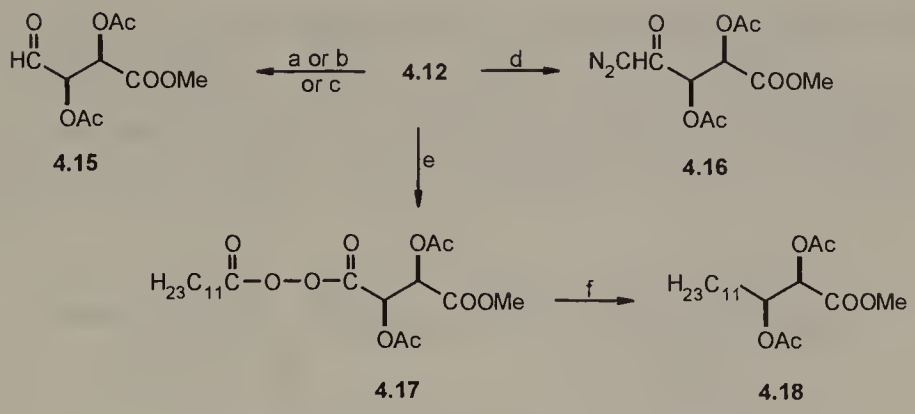
Acid chloride **4.13** provides easy access to optically pure γ-alkyl-α,β-dihydroxy lactones via the activated ester **4.19**[129] or by chemoselective reduction to the threuronic ester, **4.20**, followed by the addition of the Grignard reagent,[134] (Scheme 4.19).

Lactone **4.21** was used by Duhamel in the synthesis of L-biopterin.[134]

Acid chloride **4.14** was used as chiral auxiliary for the reduction of enamides in the synthesis of isoquinoline alkaloids such as *N*-acetylsalsolidine[119,135] (Scheme 4.20).

Monoamides of tartaric acid can be readily converted to *O,O'*-diacyl protected mononitriles of tartaric acid (Scheme 4.21).

Hydroxamate ester **4.24**, which can be obtained either from **4.22** or **4.23**, is an important entry to optically active functionalized β-lactams, according to the Miller's protocol[118,139] (Scheme 4.22).



a: $LiAlH(Ot\text{-}Bu)_3$, THF, -75°C[130]

b: $H_2/Pd\text{-}BaSO_4$[7]

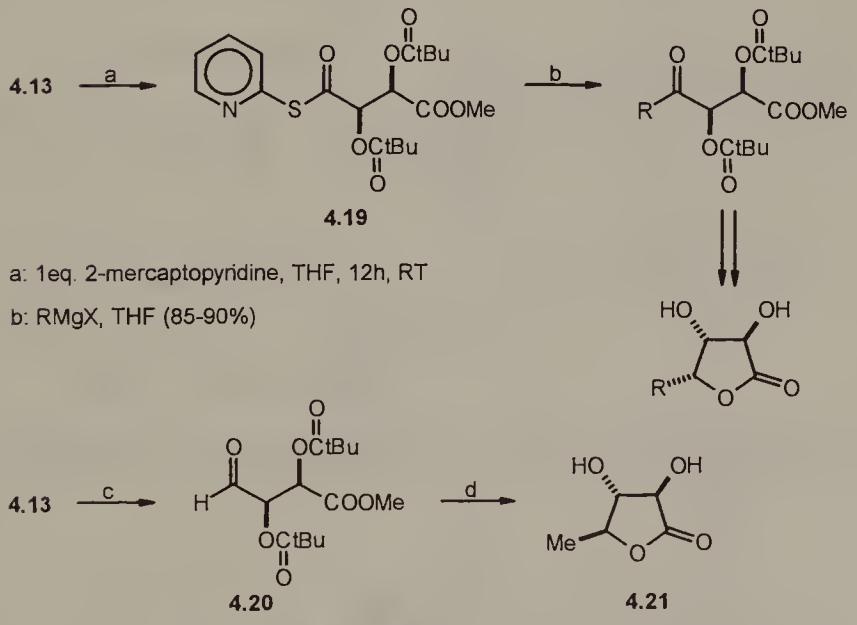
c: $n\text{-}Bu_3SnH$, THF, RT[132]

d: excess CH_2N_2, THF or dioxane, -10 → -17°C, 64-70%[128,133]

e: $H_{23}C_{11}COOH$, pyridine, Et_2O, -30°C (83-95%)[131]

f: medium-pressure Hg lamp, petroleum ether, -60°C (44-64%, d.e. 89-95.6%)[131]

Scheme 4.18



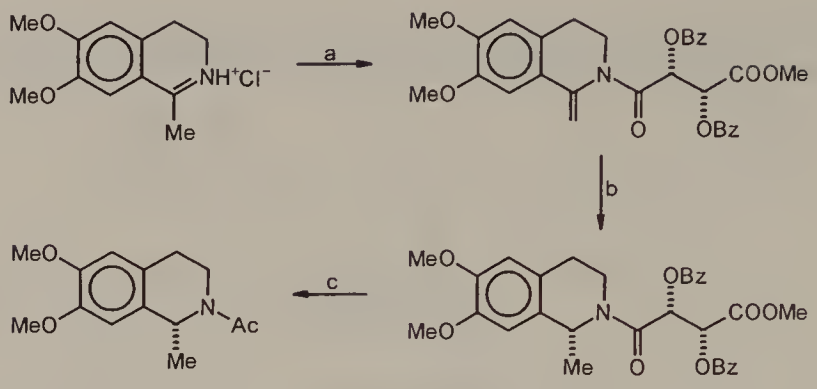
a: 1eq. 2-mercaptopyridine, THF, 12h, RT

b: RMgX, THF (85-90%)

c: 1 eq. $(Ph_3P)_2CuBH_4$, 2 eq. Ph_3P, Me_2CO, RT (90%)

d: 1.5 eq. MeMgBr, THF, -70°C (12h) → RT, then 3M HCl, dioxane (78%)

Scheme 4.19

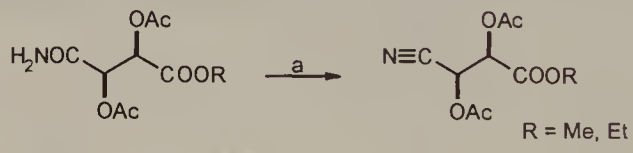


a: **4.14**, NEt_3, dioxane, RT

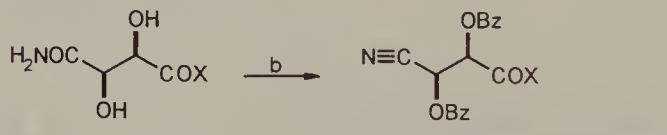
b: H_2, Pt, MeOH, RT

c: NH_2NH_2, ethylene glycol, Δ, 15 min. then Ac_2O, aq. NaOH[135]

Scheme 4.20

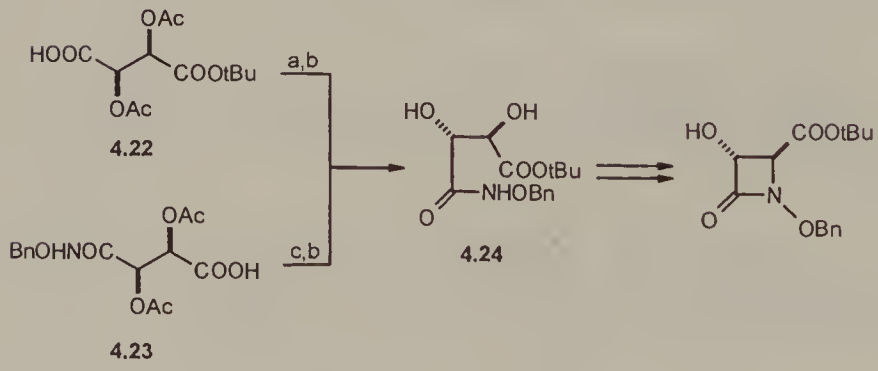


a: $POCl_3$, Δ (64-73%)[136-138]



b: BzCl, pyridine, RT (60-69%)[124]

Scheme 4.21



a: DCC, *N*-hydroxysuccinimide, then H_2NOBn (97%)

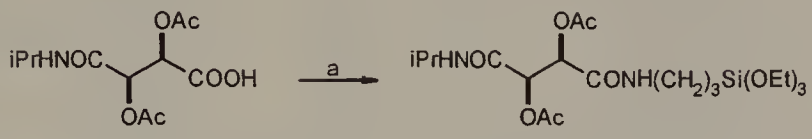
b: MeOH, DMAP (84%)

c: tBuOH, $HClO_4$ (55%)

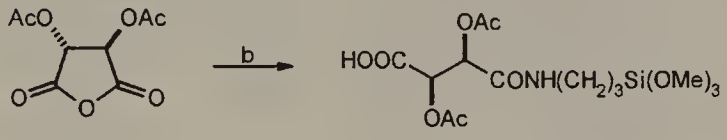
Scheme 4.22

O,O'-Dibenzoyl-L-tartaric acid mono(dimethylamide) is used for the resolution of racemic amines.

O,O'-Diacetyl tartramic acids chemically bonded to silica gel through a trialkoxysilane linker form chiral stationary phases bearing exposed amide or acid polar groups. These stationary phases were used in liquid chromatography for separation of enantiomers[13,120,121,140] (Scheme 4.23).



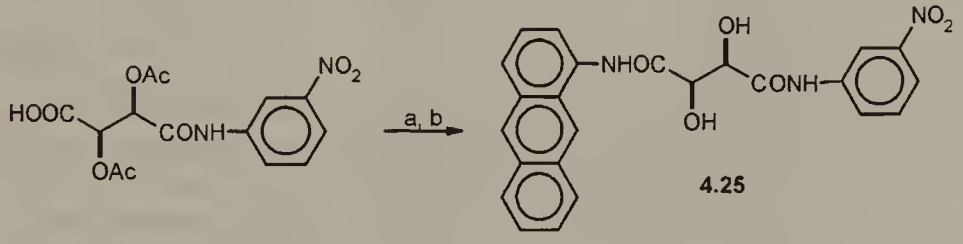
a: *N*-hydroxy-5-norbornene-2,3-dicarboxamide, DCC, then $H_2N(CH_2)_3Si(OEt)_3$[140]



b: $H_2N(CH_2)_3Si(OMe)_3$[121]

Scheme 4.23

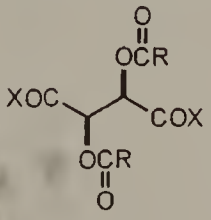
A further example of chromatography use is the synthesis of a chiral selector **4.25** for anchoring to a carbon-based stationary phase via the anthracene molecule. The ease of removal of the *O*-acetyl protecting groups in the final step is noteworthy (Scheme 4.24).



a: 1-aminoanthracene, peptide coupling b: $NaHCO_3$, Me_2CO[141]

Scheme 4.24

4.4 DIESTERS AND DIAMIDES OF *O,O'*-DIACYLTARTARIC ACIDS



IV

Table 4.4 Diesters and diamides of *O,O′*-diacyl-L-tartaric acids (IV)

R	X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
Me	OMe	106.5	−15.1 (EtOH)	142–144
Me	OEt	67–68	+0.4 (EtOH)	140,143,144
Me	On-Pr	21.5	+11.0 (neat)	50,143
Me	Oi-Pr	31.4	+8.6 (Et_2O)	50
Me	On-Bu	205/15	+22.2 (neat)	50
Me	Oi-Bu	183/11	+15.9 (neat)	146
Me	Ot-Bu[b]	65	+6.5 (Me_2CO)[a]	117
Me	O-(−)-menthyl	84.5/106–108	−51.0 (EtOH)	147
Me	$OCH_2C_6H_4$-2-NO_2	75	+11.7 (pyridine)[a]	148
Me	$OCH_2C_6H_4$-3-NO_2	107	+67.0 (pyridine)[a]	148
Me	$OCH_2C_6H_4$-4-NO_2	141.5	+46.8 (pyridine)[a]	148
Me	$OCH_2C(O)C_6H_4$-4-Br[c]	175-176	−9.3 ($CHCl_3$)	149
Cy	OEt	64-65	—	150
t-Bu	OMe	—	−14.2 ($CHCl_3$)	151
$ClCH_2$	OMe	—	−0.6 (neat)	143
Cl_2CH	OMe	—	+11.9 (neat)	143
Cl_3C	OMe	143	−5.0 (benzene)	152
Cl_3C	OEt	228–232/12	—	152
Cl_3C	Oi-Bu	208/4	—	152
OEt	OEt	173–174/0.4	+14.9 (EtOH)	153
Bn	OEt	—	+19.3 (neat)	154
Ph	OMe	135.5	−96.6 (EtOH)	25,142,144
Ph	OEt	62.5–63.5	−60.0 (EtOH)	144
Ph	On-Pr	45.5	−78.2 (pyridine)[a]	155
Ph	Oi-Pr	74–74.5	−67.8 ($CHCl_3$)	156
Ph	On-Bu	43	−57.6 (pyridine)[a]	155
Ph	Ot-Bu[b]	122	−90.0 (Me_2CO)[a]	117
Ph	OBn	76–77	+6.2 (Me_2CO)	157
Ph	$OCH_2C_6H_4$-2-NO_2	126.5–127	−11.5 (pyridine)[a]	148
Ph	$OCH_2C_6H_4$-3-NO_2	109	+112.4 (pyridine)[a]	148
Ph	$OCH_2C_6H_4$-4-NO_2	114	+185.6 (pyridine)[a]	148
2-ClC_6H_4	OMe	71	−52.0 (EtOH)	158
3-ClC_6H_4	OMe	80	−86.7 (EtOH)	158
4-ClC_6H_4	OMe	91	−108.1 (EtOH)	158
2-BrC_6H_4	OMe	59	−37.4 (EtOH)	158
3-BrC_6H_4	OMe	61–62	−72.2 (EtOH)	158
4-BrC_6H_4	OMe	66	−101.8 (EtOH)	158
2-IC_6H_4	OMe	95	—	158
3-IC_6H_4	OMe	103	—	158
2-$O_2NC_6H_4$	OMe	—	−184.9 (benzene)	159
2-$O_2NC_6H_4$	OEt	143	−119.5 (benzene)	159
3-$O_2NC_6H_4$	OMe	118	—	159
3-$O_2NC_6H_4$	OEt	96	—	159
4-$O_2NC_6H_4$	OMe	140	—	159

(*continued*)

Table 4.4 (*continued*)

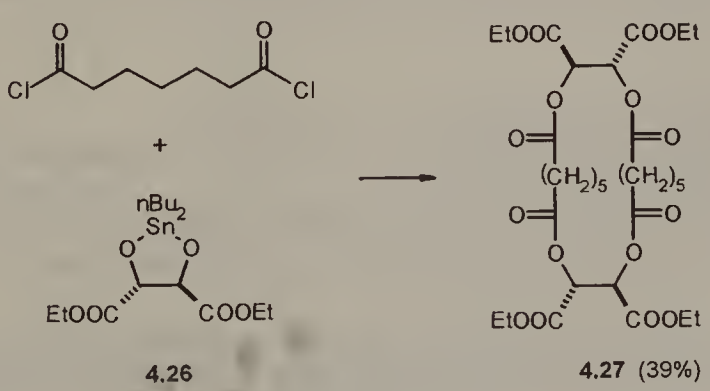
R	X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
4-$O_2NC_6H_4$	OEt	124–124.5	—	159
3,4-$Cl_2C_6H_3CH$=CH	OMe	150–151	−177.0 ($CHCl_3$)	160
PhCH=CH	OMe	200/0.5	−145.7 ($CHCl_3$)	161
4-(PhN=N)C_6H_4	OEt	130	−224.0 ($CHCl_3$)	162
1-bromo-2-naphthyl	OEt	127–129	−79.1 ($CHCl_3$)	163
2-furyl	OMe	131	—	164
2-furyl	OEt	76	−87.6 (EtOH)	164
Me	NHPh	227	—	165,166
Me	NH-C_6H_4-2-Me	229	+16.9 (pyridine)	167
Me	NH-α-naphthyl	260	—	166
Me	NH-β-naphthyl	240	—	166
Me	NHTMPO[d]	238–9	—	168
Ph	NH_2	252–255	−165.4 (MeOH)	124,169
Ph	NHMe	267–269	−158.0 (DMF)	124
Ph	NH-n-Bu	168–169	−107.7 (Me_2CO)	26
Ph	NHBn	194–195	—	125
Ph	NMe_2	190–192	+108.0 ($CHCl_3$)	124

[a] At 546 nm.
[b] Prepared by esterification of the corresponding *O,O'*-diacyltartaric acid with isobutene and concentrated H_2SO_4.
[c] Prepared by alkylation of disodium salt of *O,O'*-diacetyl tartaric acid with p-bromophenacyl bromide.
[d] TMPO = 4-(2,2,6,6-tetramethylpiperidinyl-*N*-oxide).

Synthesis

O,O'-Diacyl tartrates are commonly obtained by acylation of dialkyl tartrates with an acyl chloride in the presence of a tertiary amine or by esterification of *O,O'*-diacyl tartaric acids with trialkyl phosphite and benzyl azide.[145]

O,O'-Stannylene acetal of (+)-DET (**4.26**) was used as a template for the synthesis of a macrocyclic tartrate-based tetralactone **4.27**[170] (Scheme 4.25).

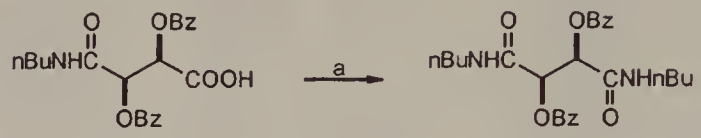


4.26 **4.27** (39%)

Scheme 4.25

O,O′-Diacyl tartramides can be obtained from tartaric diamides by *O,O′*-diacylation with acyl chlorides in alkaline-water solution.

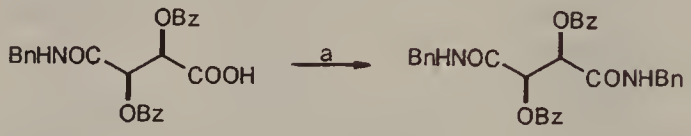
O,O′-Diacyl monotartramides can be converted to (unsymmetrical) diamides by the action of isocyanates (Scheme 4.26).



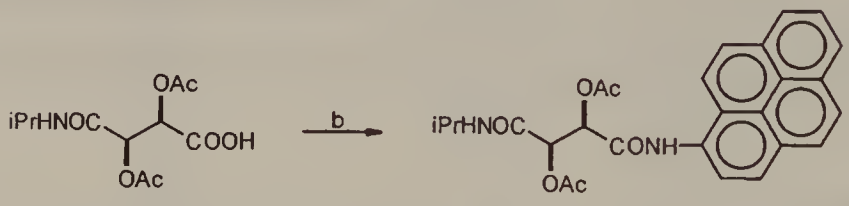
a: n-BuNCO, PhH, Δ (52%)[26]

Scheme 4.26

Alternatively the carboxyl group of the monotartramide can be activated prior to reaction with the amine by converting it to acid chloride or to a mixed carbonic anhydride (Scheme 4.27).



a: 1.1eq. $SOCl_2$, benzene, reflux, then $BnNH_2$ (88%)[125]



b: 1 eq. NMM, 1 eq. ClCOOEt, THF, -21°C, 20 min,
then 0.85 eq. 2-aminochrysene, 0°C, 24h (53%)[16]

Scheme 4.27

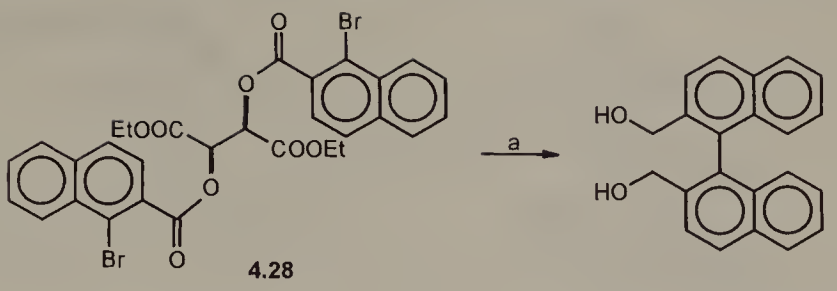
Polymeric esters and urethanes have been prepared by *O,O′*-diacylation of dibenzyl L-tartrate with chlorides of dicarboxylic acids or diisocyanates.[171]

Applications

Diester **4.28** has been used as a chiral auxiliary in the asymmetric Ullmann coupling[163] (Scheme 4.28).

The *O,O′*-diacyl tartrate moiety was used as a template in the photochemical dimerization of 1-carboxymethylthymine; the dimer had achiral *syn,cis* structure.[172]

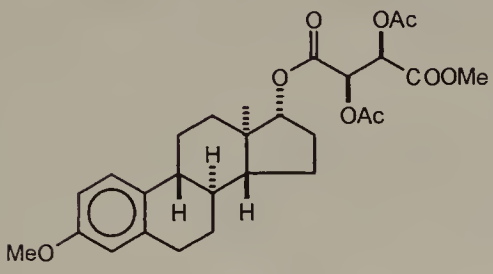
Racemic 3-methoxy-17β-hydroxy-1,3,5(10)-estratriene was resolved by crystallization of its 17-ester, prepared from acid chloride **4.12**; the less soluble diastereoisomer obtained had the structure **4.29**.[173]



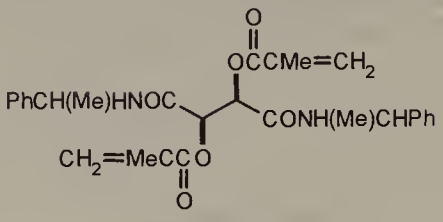
4.28

a: Cu, THF, Δ, then $LiAlH_4$, Et_2O e.e. 33%, (*S*)-configuration

Scheme 4.28



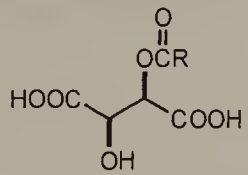
4.29



4.30

Diamide **4.30** is used in the preparation of chiral polymeric adsorbents.[174]

4.5 *O*-MONOACYL TARTARIC ACIDS



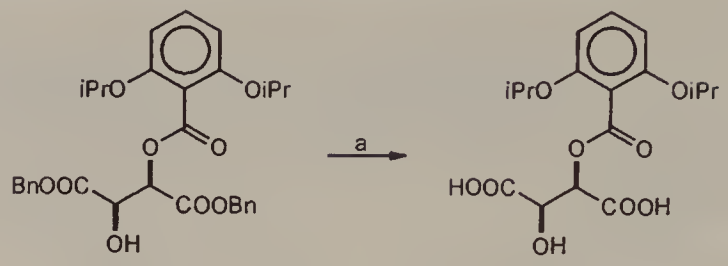
V

Table 4.5 ***O*-Monoacyl-L-tartaric acids (V)**

R	m.p. (°C)	$[\alpha]_D$ (solvent)	References
Me	—	—	175
t-Bu	—	—	175
Ph	211–212	−5.8 (MeOH)	68,176,177
2,6-$(MeO)_2C_6H_3$	187–188	−75.1 (EtOH)	175,177–179
2,6-$(i\text{-}PrO)_2C_6H_3$	81	−28.5 (EtOH)	177,180–182

Synthesis

The synthesis is performed by hydrogenolysis of *O*-monoacylated dibenzyl tartrates (Scheme 4.29).



a: H_2, 10% Pd/C (100%)[177,180-182]

Scheme 4.29

O-Monobenzoyl tartaric acid has been prepared by hydrolysis or aminolysis of *O,O′*-dibenzoyl tartaric acid, Scheme 4.30.

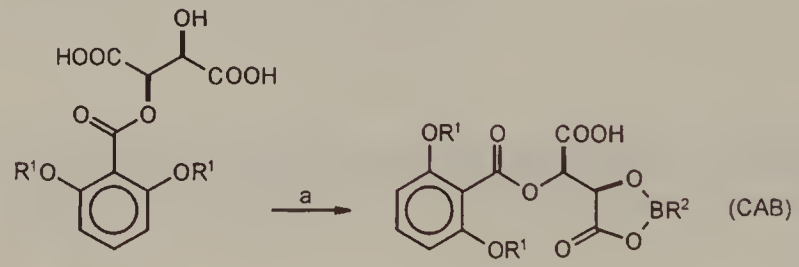
a: H_2O, Δ (45%)[67]

b: 10 eq. $BnNH_2$, benzene (isolated as bis-benzylammonium salt)[125]

Scheme 4.30

Applications

Yamamoto *et al.* used *O*-(2,6-dimethoxybenzoyl)tartaric acid and *O*-(2,6-diisopropoxybenzoyl)tartaric acid for *in situ* preparation of chiral acyloxyboranes (CABs), Scheme 4.31.

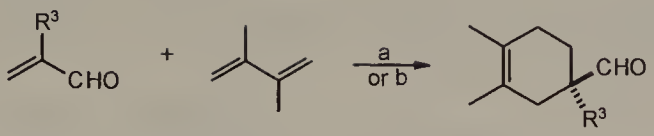


a: BH_3·THF or $ArB(OH)_2$

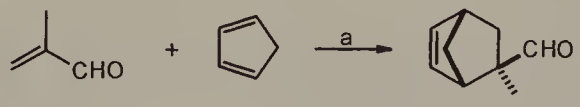
Scheme 4.31

CABs are widely used as catalysts for asymmetric Diels–Alder,[175,180,183,202] hetero Diels–Alder,[182,184] allylation[181,185] and aldol reactions[177,186–188] as well as in the synthesis of chiral α-methylene-β-hydroxyketones.[189] Examples are given in Scheme 4.32.

Diels-Alder reaction



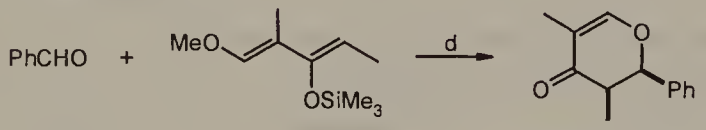
a (R^3 = Me): 0.1 eq. CAB (R^1 = Me, R^2 = H), CH_2Cl_2, -78°C (86%, e.e. 95%)[178]
b (R^3 = Br): 0.1 eq. CAB (R^1 = i-Pr, R^2 = H), CH_2Cl_2, -78°C (80%, e.e. 95%)[180]



85%, *endo* : *exo* = 11 : 89, e.e. 96%[183]
(*exo* diastereomer readily separated after oxidation to the acid[179])

c: 0.1 eq. CAB (R^1 = Me, R^2 = H), CH_2Cl_2, -40°C (84%, e.e. 92%)[190]

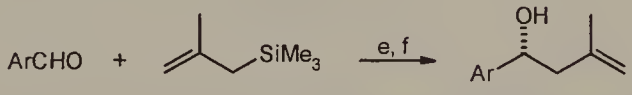
Hetero Diels-Alder reaction



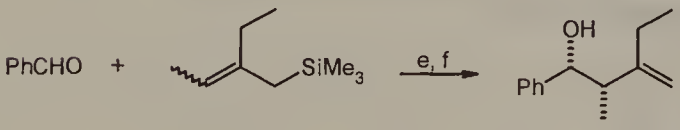
95%, e.e. 97%[182]

d: 0.2 eq. CAB (R^1 = i-Pr, R^2 = 2-$MeOC_6H_4$), -78°C

Allylation of aldehydes



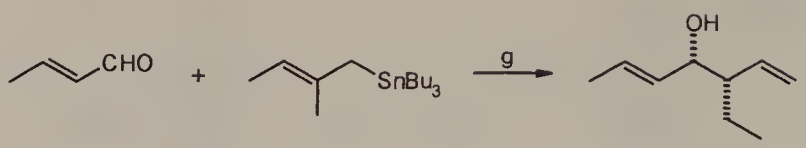
Ar = Ph, 99%, e.e. 84%[181]
Ar = PhCH=CH, 96%, e.e. 84%[181]



74%, syn:anti = 97:3, e.e. 96%[185]

e: 0.2 eq. CAB (R^1 = i-Pr, R^2 = 3,5-$(CF_3)_2C_6H_3$), EtCN
f: TBAF

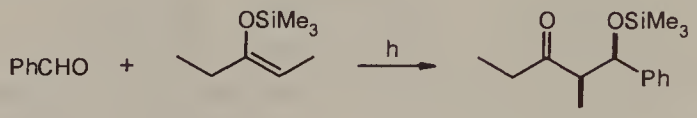
Scheme 4.32 (*continued*)



85%, syn:anti = 92:8, e.e. 95%[191]

g: 1 eq. CAB (R^1 = Me, R^2 = H), 2 eq. $(CF_3CO)_2O$, EtCN, -78°C

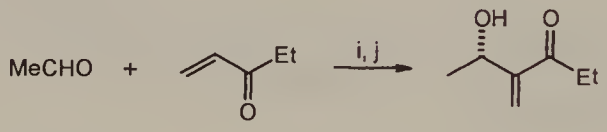
Aldol reaction



97%, syn:anti = 93:7, e.e. 94%[187,192]

h: 0.2 eq. CAB (R^1 = i-Pr, R^2 = H), EtCN, -78°C

Synthesis of α-methylene-β-hydroxyketones



e.e. 87%[189]

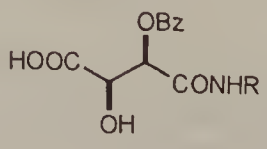
i: 0.2eq. CAB (R^1=iPr, R^2=H), Me_3SiSPh, EtCN, -78°C (38%)

j: 3-$ClC_6H_4CO_3H$, -10°, then 130-150°C (71%)

Scheme 4.32

O-Benzoyl-L-tartaric acid has been used as chiral modifying agent for Raney nickel catalyzed hydrogenation of methyl acetoacetate.[193]

4.6 MONOAMIDES OF *O*-ACYLTARTARIC ACIDS: 3-*O*-ACYLTARTRAMIC ACIDS



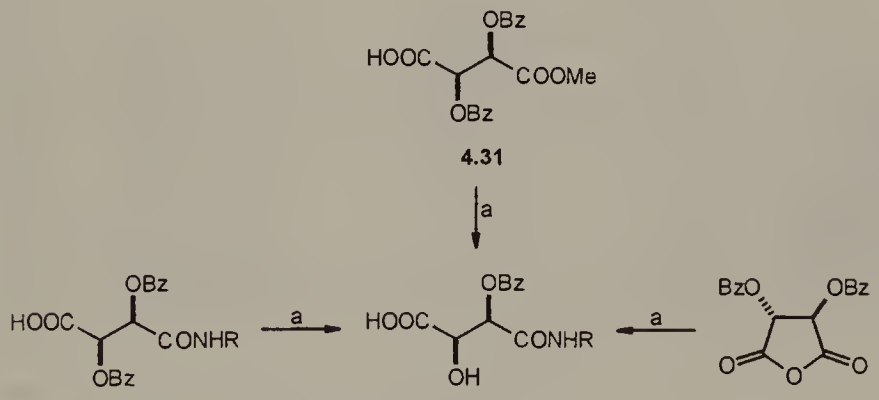
VI

Table 4.6 3-*O*-Benzoyl-L-tartramic acids (VI)

R	m.p. (°C)	$[\alpha]_D$ (solvent)	References
n-Bu	165–166	+49.6 (EtOH)	125
t-Bu	182–183	—	125
Bn	195–196	+39.7 (EtOH)	125
(*S*)-CHMePh	209.5–210	+29.5 (EtOH)	125,127
Ph	172–173	—	125

Synthesis

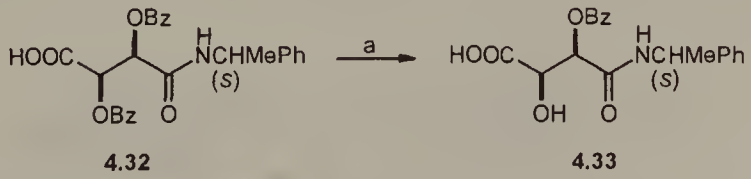
3-*O*-Benzoyl tartramic acids can be obtained by chemoselective aminolysis of *O,O'*-dibenzoyl tartaric anhydride, *O,O'*-dibenzoyl tartramic acids or the monoester **4.31** with excess amine[125] (Scheme 4.33).



a: 10 eq. RNH_2, benzene, RT, then 5M HCl (84-90%)

Scheme 4.33

3-*O*-Benzoyl tartramic acid **4.33** was prepared by chemoselective hydrolysis of *O,O'*-dibenzoyl monoamide **4.32**[127] (Scheme 4.34).

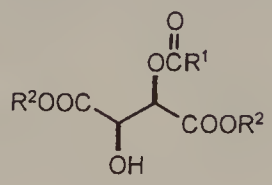


4.32 **4.33**

a: 1 eq. NaOH/MeOH-H_2O, RT, 10 min. (83%)

Scheme 4.34

4.7 DIESTERS OF *O*-MONOACYL TARTARIC ACIDS



VII

Table 4.7 Diesters of *O*-monoacyl-L-tartaric acid (VII)

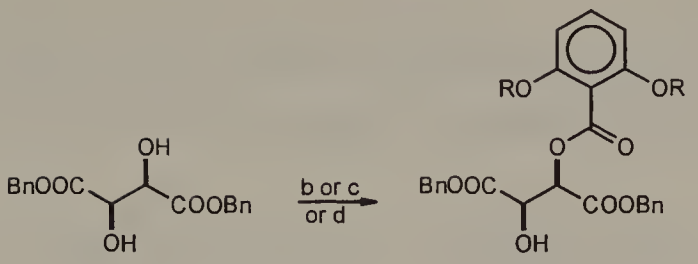
R^1	R^2	m.p. (°C) or b.p.(°C/torr)	$[\alpha]_D$ (solvent)	References
Me	Me	83–84	+19.0 ($CHCl_3$)	144,194,195
Me	Et	165–170/15	+12.4 (neat)	144,151
t-Bu	Me	100–101/0.06	−13.4 ($CHCl_3$)	151,196
CH_2=CMe	Bn	—	+11.3 (Me_2CO)	197
Bn	Et	—	+30.3 (neat)	154
Ph	Me	78	—	144,198
Ph	Et	66–66.5	+10.7 (benzene)	144,198
Ph	Bn	122–123	+36.8 ($CHCl_3$)	177
2-MeC_6H_4	Et	32.5	+4.5 (AcOH)	199
3-MeC_6H_4	Et	56	+7.5 (AcOH)	199
4-MeC_6H_4	Et	94	+15.1 (AcOH)	199
4-(PhN=N)C_6H_4	Et	126	+54.0 ($CHCl_3$)	162
2,6-$(MeO)_2C_6H_3$	Bn	—	−60.1 ($CHCl_3$)	177,178
2,6-$(i\text{-}PrO)_2C_6H_3$	Bn	—	−29.1 ($CHCl_3$)	177
OBn	Me	—	−0.6 ($CHCl_3$)	196

Synthesis

The synthesis is by monoacylation of dialkyl tartrates (Scheme 4.35).

a: AcCl (61%)[194]

Scheme 4.35 (*continued*)



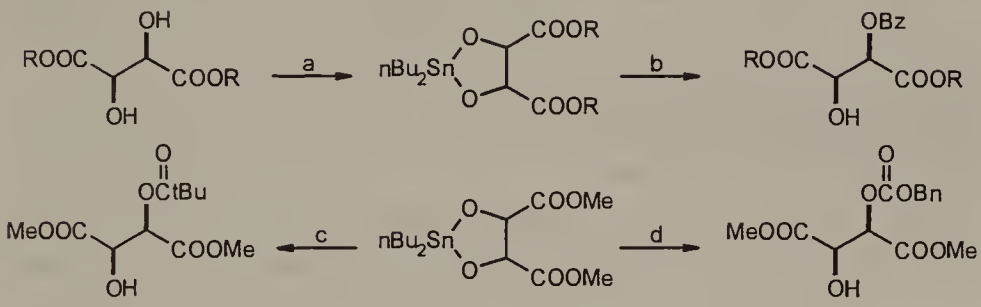
b: 1eq. 2,6-$(MeO)_2C_6H_3COCl$, NEt_3, DMAP, CH_2Cl_2 (78-82%)[178]

c: 1.3 eq. 2,6-$(i\text{-}PrO)_2C_6H_3COOH$, 1.3 eq. DCC, DMAP, CH_2Cl_2 (74%)[177]

d: 1eq. 2,6-$(RO)_2C_6H_3COOH$, 1.1 eq. $(CF_3CO)_2O$, CH_2Cl_2, RT (63-65%)[179-182]

Scheme 4.35

A more selective monoacylation method involves the use of *O,O'*-stannylene intermediates (Scheme 4.36).



a (R = Me): 0.2-1.0 eq. $(n\text{-}Bu_2SnO)_n$, microwave Δ (92%)[200]

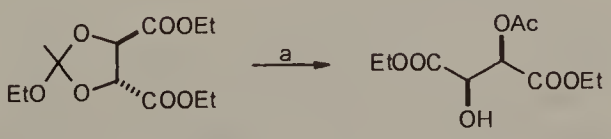
b (R = Et): 1 eq. BzCl, 1 eq. NEt_3, toluene, (86%)[198]

c: 1.06 eq. t-BuCOCl, $CHCl_3$, RT (100%)[196]

d: 1.05 eq. BnOCOCl, $CHCl_3$, RT (85%)[196]

Scheme 4.36

O-Monoacetyl tartrates are conveniently obtained by the cleavage of the corresponding orthoester acetals (Scheme 4.37).



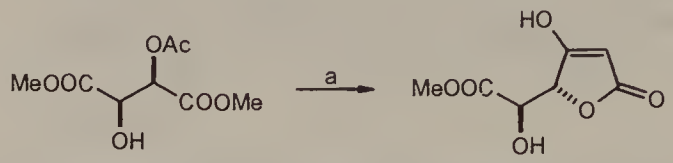
a: EtOH, TsOH (94%)[151]

Scheme 4.37

Applications

B

The *O*-monoacetyl derivative **4.34** is the substrate for the tetronic acid derivative **4.35** formed in the intramolecular Claisen condensation[201] (Scheme 4.38).

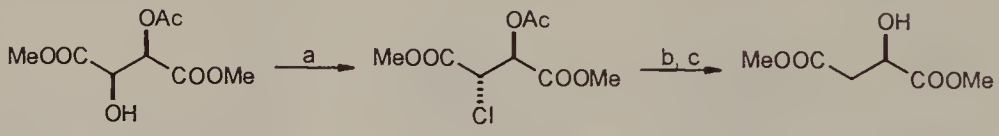


4.34 **4.35**

a: HMDS, n-BuLi, THF, -78°C (78%)

Scheme 4.38

(*R*)-Malates were synthesized from *O*-monoacetyl-(*R,R*)-tartrates[195] (Scheme 4.39).



a: $SOCl_2$, pyridine (79-82%)[151,194]

b: n-BuSnH, PhMe, AIBN (cat.), 80°C, 2h (94%)

c: MeOH, AcCl (cat.), 60°C, 15h (88%)

Scheme 4.39

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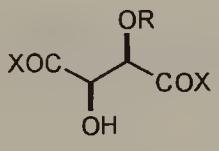
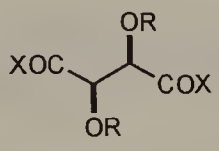
5 *O*-Alkylated and *O*-Silylated Tartaric Acid Derivatives

O-Alkylation of tartrates and tartramides found use primarily in the synthesis of tartaric acid derived crown ethers. Compared to *O*-methylation, *O*-benzylation and *O*-silylation offers much more operational flexibility, due to the possibility of selective removal of the benzyl group by hydrogenolysis and the silyl group by hydrolysis or by fluorodesilylation. *O*-Benzylation and *O*-silylation are the methods of choice for hydroxy group protection in cases where the tartrate is subjected to reactions requiring the use of strong bases.

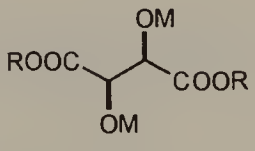
Both *O*-monoalkylated or monosilylated (**I**) and *O,O'*-dialkylated or disilylated (**II**) derivatives of tartaric acid found the use in synthesis. For their preparation various alkoxides of tartrates (**III**, M = Na, Ag, Tl^{I}) are used to enhance nucleophilicity of the hydroxy groups. Organotin alkoxides ("stannylene acetals," **III**, M,M = $SnBu_2$) are of particular interest because the nucleophilicity and low basicity of the oxygen enable the selective mono- and di-*O*-alkylation of tartrates.



I



II



III

5.1 *O*-MONOALKYL AND *O*-MONOSILYL TARTRATES AND TARTRAMIDES

Table 5.1 ***O*-Monoalkyl and *O*-monosilyl L-tartrates and L-tartramides (I)**

R	X	m.p. (°C) or b.p.(°C/torr)	$[\alpha]_D$ (solvent)	References
Me	OMe	119–122/1.6	+39.0 ($CHCl_3$)	1–3
Me	OEt	115/0.5	+37.0 ($CHCl_3$)	3,4
Me	NH_2	201	+140.0 (MeOH)	1,5,6
Me	NHMe	137	+103.0 (H_2O)	1,6
t-Bu	OMe	—	+33.0 (CH_2Cl_2)[a]	7

(*continued*)

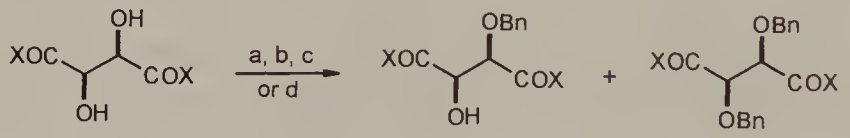
Table 5.1 (*continued*)

R	X	m.p. (°C) or b.p.(°C/torr)	$[\alpha]_D$ (solvent)	References
t-Bu	OEt	—	+16.8 ($CHCl_3$)	8
t-Bu	OBn	74	+22.5 (Me_2CO)[a]	7
All	OMe	—	+34.1 ($CHCl_3$)	2
Bn	OMe	69–70	+91.7 ($CHCl_3$)	2,3,9
Bn	OEt	—	+73.0 ($CHCl_3$)	3,4,10
Bn	Oi-Pr	79.5–80.5	+62.3 (AcOEt)	11
Bn	OBn	57–58	+60.2 ($CHCl_3$)	2,12,13
Bn	NMe_2	—	+53.2 (EtOH)	14
PMB	OMe	—	+84.0 ($CHCl_3$)	2
PMB	OEt	—	+67.6 (MeOH)	15
PNB	OMe	74.5–75.5	+68.1 ($CHCl_3$)	2
2,4,6-$(O_2N)_3C_6H_2$	OMe	142–143	—	16
TBS	OMe	—	+31.6 ($CHCl_3$)	2

[a] At 546 nm.

Synthesis

Both *O*-monobenzyl and *O,O′*-dibenzyl tartrates and tartramides can be obtained by one of several variants of the Williamson reaction (Scheme 5.1).



a (X = OMe)	35%	31%
b (X = OEt)	64%	
c (X = Oi-Pr)	12%	53%
d (X = NMe_2)	64%	

a: 3.0 eq. Ag_2O, 3.3 eq. BnBr, DME, RT→ 55°C[17]

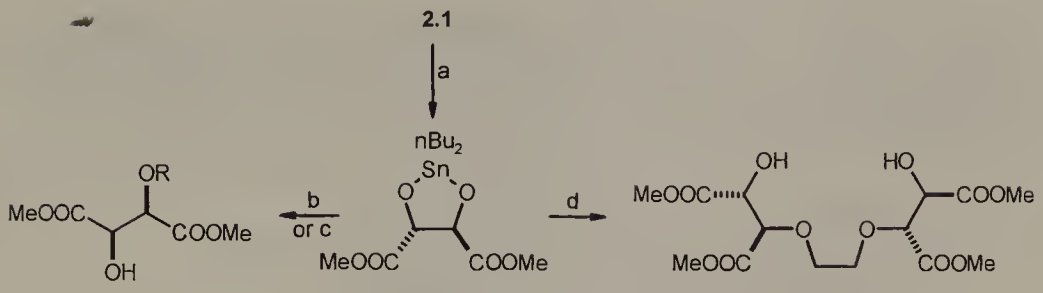
b: 1.2 eq. K_2CO_3, 1.2 eq. BnBr, 0.1 eq. Aliquat 336, 60°C, 6h[10]

c: 2.0 eq. NaH, 2.0 eq. BnBr, n-Bu_4NI (cat.), THF, 0°C→ RT, 7h[11] (yield of the diether increased to 80% when 18-crown-6 was added)[18]

d: 1 eq. NaH, 1.2 eq. BnBr, DMF, RT → 80°C, 8h[14]

Scheme 5.1

Selective *O*-monoalkylation or *O*-monosilylation of a tartrate is based on ring opening of *O,O′*-stannylene acetals at elevated temperature, or at room temperature with a fluoride ion promoter (Scheme 5.2).



a: 1eq. $(Bu_2SnO)_n$, PhMe, Δ (removal of water), 95%[2]

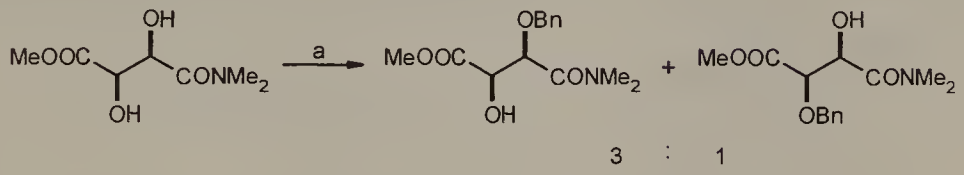
b (R = All): 1.5 eq. AllI, 1.6 eq. CsF, DMF, RT (98%)[2]

c: (R = TBS): TBSCl, CsF, $CHCl_3$, RT[2]

d: 0.5 eq. $BrCH_2CH_2Br$, 100°C (82%)[19]

Scheme 5.2

This reaction can be regioselective, as shown in the example of *O*-monobenzylation of a tartramate (Scheme 5.3).



a: 1 eq. $(Bu_2SnO)_n$, PhMe, Δ then 2.1 eq. BnI, 1.2 eq. CsF, DMF, 0-3°C (95%)[2]

Scheme 5.3

O-Monobenzyl derivatives can be obtained selectively and under non-basic conditions by trichloroacetimidation of a tartrate (Scheme 5.4).

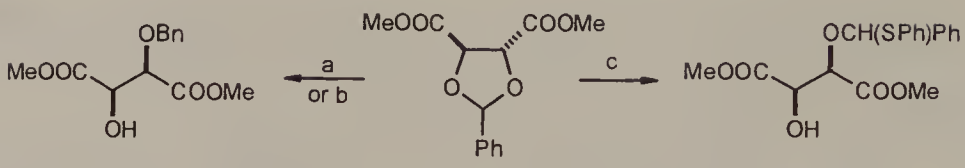
a: $Cl_3C(=NH)OBn$, CF_3SO_3H, RT (64%)[12]

Scheme 5.4

Or they may be obtained by the reduction of benzylidene acetals by various boron reducing agents compatible with the presence of the ester function (Scheme 5.5).

An allylation procedure, using allyl ethyl carbonate and palladium(0) catalyst, allows the synthesis of either *O*-monoallyl or *O,O'*-diallyl derivatives (Scheme 5.6).

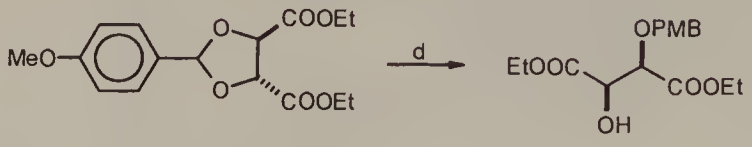
Selective *O*-monomethylation of diethyl tartrate (**2.2**) is based on enhanced nucleophilicity of the hydroxy group upon complexation with tin(II) chloride prior to alkylation with diazomethane (Scheme 5.7).



a: 1eq. $NaBH_3CN$, 1eq. $TiCl_4$ or $HCl\text{-}Et_2O$, RT (83-85%)[3,9]

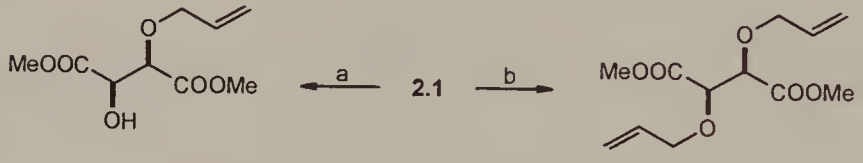
b: 2.2 eq. Me_2BBr, 2.0 eq. $BH_3\cdot THF$, 0.1 eq. NEt_3, -78° → -20°C (75%)[20]

c: 2.2 eq. Me_2BBr, 3.0 eq. PhSH, 3.5 eq. NEt_3, -78°C (92%)[20]



d: 6 eq. $NaBH_3CN$, 6 eq. TMSOTf, MeCN, RT, 2h (83%)[15]

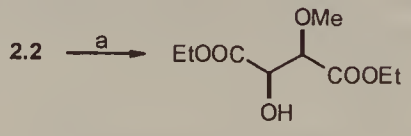
Scheme 5.5



a: 1.1eq. AllOCOOEt, 0.25 eq. $Pd_2(dba)_3$, THF, 65°C (50%)[21]

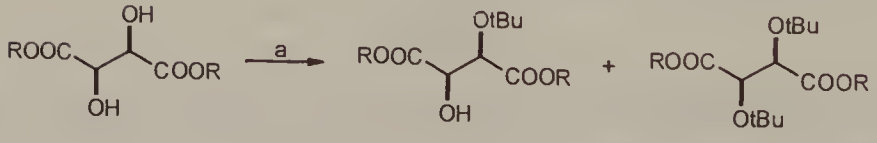
b: as a, but 4 eq. AllOCOOEt (75%)[21]

Scheme 5.6



a: $SnCl_2$ (cat.), then CH_2N_2, MeCN (75%)[3,4]

Scheme 5.7



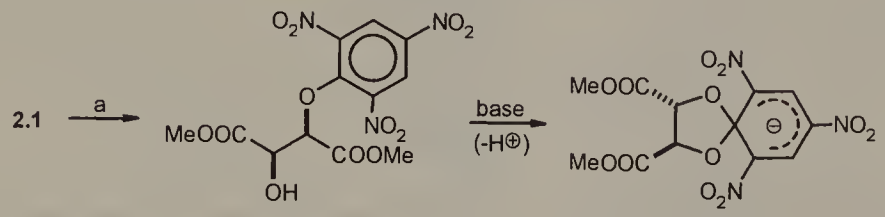
a: $CH_2{=}CMe_2$, H_2SO_4, diglyme, RT[7]

b: 1.2 eq. $CH_2{=}CMe_2$, H_2SO_4, CH_2Cl_2, -20°C to RT (50%)[8]

Scheme 5.8

O-tert-Butyl derivatives are obtained from tartrates by alkylation with isobutene in the presence of a strong acid (Scheme 5.8).

The *O*-monopicryl ether of dimethyl-L-tartrate, obtained by the action of one equivalent of picryl fluoride on **2.1**, readily forms the chiral Meisenheimer complex **5.1** with such weak bases as water[16] (Scheme 5.9).

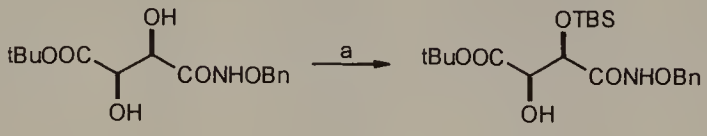


5.1

a: 0.9 eq. picryl fluoride, 3 eq. NEt_3, CH_2Cl_2, RT, 15 min. (62%)

Scheme 5.9

Highly regioselective *O*-monosilylation can be achieved in the preparation of the hydroxamate derivative **5.2** (Scheme 5.10).



5.2

a: TBSCl, imidazole, DMF, RT (94%)[22]

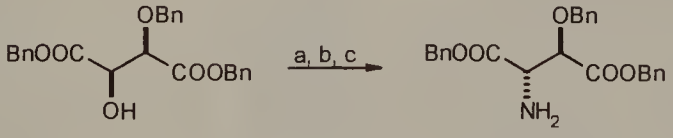
Scheme 5.10

This hydroxy group differentiation is important for the synthesis of functionalized β-lactams (see below).

Applications

O-Monoalkylation provides an entry to selective substitution of the residual hydroxy group. The syntheses shown below are based on the substitution of a non-alkylated hydroxy group after activation by sulfonylation.

The synthesis of protected (2*S*,3*R*)-3-hydroxyaspartic acid **5.3** is shown in Scheme 5.11.[12,13]



5.3

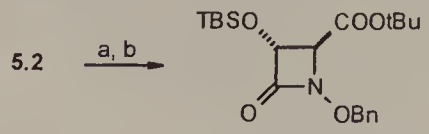
a: $(CF_3SO_2)_2O$, 2,6-lutidine, -78°C

b: tetramethylguanidinium azide, 120°C

c: H_2S, NEt_3, RT (49%)

Scheme 5.11

Miller obtained the chiral β-lactam **5.4** from *O*-monosilylated hydroxamate **5.2** by an intramolecular substitution of the mesylate (Scheme 5.12).[22]

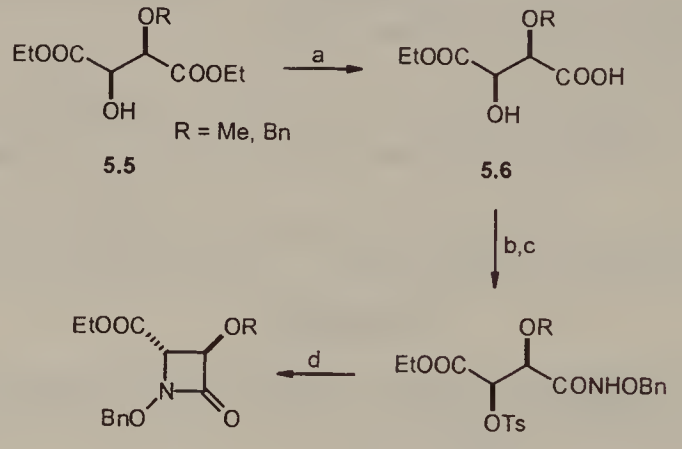


5.4

a: MsCl, pyridine, 0°C b: NEt_3, EtOH, RT (95%)

Scheme 5.12

Regioselective hydrolysis of *O*-monoalkylated tartrates **5.5** proceeds cleanly with the use of pig liver esterase (PLE) to exclusively yield the monoacids **5.6**. These were converted by Barton *et al.* to chiral substituted β-lactams **5.8**, with the use of intramolecular substitution of the tosylated hydroxamates **5.7** (Scheme 5.13).[3,4]

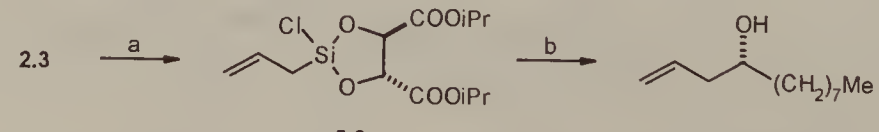


a: PLE, 0,1 M phosphate buffer (pH 8.0) c: TsCl, pyridine

b: $BnONH_2 \cdot HCl$, $EtN{=}C{=}N(CH_2)_3NMe_2 \cdot HCl$ d: K_2CO_3, acetone

Scheme 5.13

A The silylated derivative of diisopropyl tartrate (**5.9**) was used as a chiral auxiliary for asymmetric allylation of aldehydes with moderate enantioselectivity[23] (Scheme 5.14).



5.9

40%, e.e. 71%

a: $CH_2{=}CHCH_2SiCl_3$, CH_2Cl_2, Δ

b: $Me(CH_2)_7CHO$, CH_2Cl_2, DMF

Scheme 5.14

5.2 *O,O'*-DIALKYL AND *O,O'*-DISILYL TARTRATES AND TARTRAMIDES

Table 5.2 ***O,O'*-Dialkyl and *O,O'*-disilyl L-tartrates and L-tartramides (II)**

R	X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
Me	OMe	87–89/0.1[a]	+81.0 (MeOH)	24–28
Me	OEt	96–97/0.6	+85.4 (EtOH)	29–33
Me	O-n-C_5H_{11}	170/5	+77.6 (neat)	35
Me	O-(*R*)-$CHMeC_6H_{13}$	196/4	+53.0 (EtOH)[b]	34
Me	O-(*S*)-$CHMeC_6H_{13}$	190/4	+77.1 (EtOH)[b]	34
Me	OC_6Cl_5	179.5	−38.2 ($CHCl^3$)	28
Me	NH_2	275–276	+98.3 (H_2O)	25,26,36
Me	NHMe	204–205	+132.8 (H_2O)	6,26,31,32
Me	NHEt	—	+110.0 (H_2O)	31
Me	NHPh	137–139	+255.4 (Me_2CO)	37
Me	NMe_2	63.5	+116.0 ($CHCl_3$)	31,32,38,39
Me	$N(CH_2)_4$	—	+56.0 (benzene)	31
Me	$N(C_6H_{11})_2$	138–140	+57.7 ($CHCl_3$)	39,40
Et	OMe	141.5/22	+79.0 (H_2O)	37,41
Et	OEt	93–94/0.1	+93.5 (neat)	32,42
Et	NHPh	186–187	+263.1 (Me_2CO)	37
Et	NMe_2	74–76	—	32
n-Pr	OEt	93–98/0.03	+49.3 (neat)	32
n-Pr	NHMe	181–182	+121.0 (MeOH)	32
t-Bu	OMe	68	+55.9 (CH_2Cl_2)[b]	7
t-Bu	OBn	—	+28.5 (Me_2CO)[b]	7
n-C_6H_{13}	OEt	125–128/0.08	—	32
n-C_6H_{13}	NHMe	70	—	32
n-$C_{10}H_{21}$	NMe_2	48–49	+53.8 ($CHCl_3$)	43
n-$C_{16}H_{33}$	NMe_2	65–67	+40.4 ($CHCl_3$)	32
n-$C_{18}H_{37}$	NMe_2	75.6	+26.7 ($CHCl_3$)	31,32
All	OEt	96–98/0.3	—	44
All	OAll	115–117/0.5	+92.6 (EtOH)[b]	44
All	NMe_2	—	+94.0 (benzene)	32,45
Bn	OEt	40–48/1.2	+105.0 ($CHCl_3$)	10,32,46,47
Bn	Oi-Pr	76–77	+90.3 ($CHCl_3$)	11,18
Bn	NH_2	230	—	48
Bn	NHMe	181–183	+3.75 (MeOH)	32
Bn	NHEt	167–169	+46.3 (MeOH)	32
Bn	NMe_2	77–78	+89.2 (benzene)	31,32
$HO(CH_2)_2$	NMe_2	100–102	—	49,50
$TsO(CH_2)_2$	NMe_2	105–107	—	49,50
$PhtN(CH_2)_2$	NMe_2	204–205	+46.0 (CHCl3)	51
$TsHN(CH_2)_2$	NMe_2	82–84	+41.0 (CH2Cl2)	51
$Bn[O(CH_2)_2]_2$	NMe_2	—	+52.5 (CHCl3)	52
$Cl_2C{=}CH$	OMe	59	+11.0 (Me2CO)[b]	53
$Cl_2C{=}CH$	Ot-Bu	76–77	–9.4 (Me2CO)[b]	53

(*continued*)

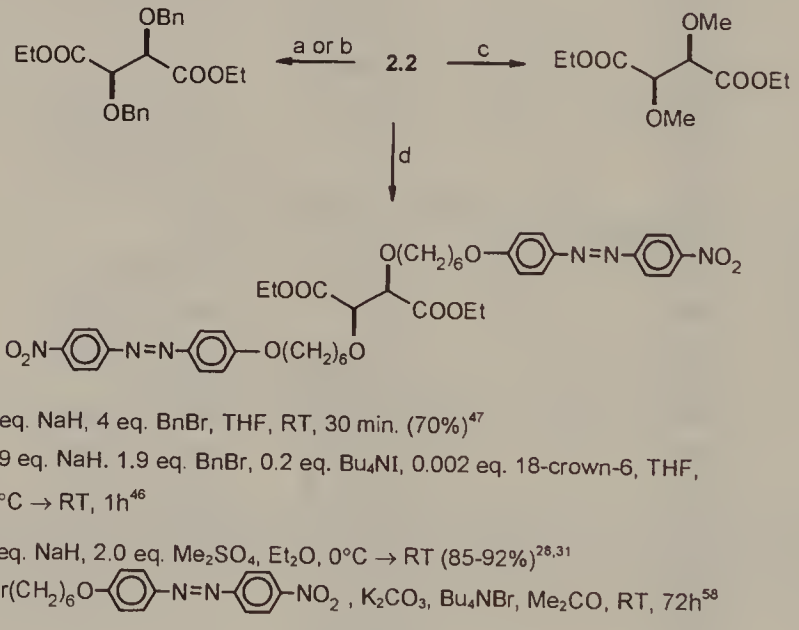
Table 5.2 (*continued*)

R	X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
$EtOOCCH_2$	NMe_2	—	+68.5 (benzene)	32,45
TMS	OEt	148–149/14	—	54
TMS	Oi-Pr	73/0.1	+57.0 ($CHCl_3$)	55
TMS	Ot-Bu	—	+61.8 ($CHCl_3$)	55
TBS	OMe	55.5–56.0	+49.1 ($CHCl_3$)	56,57
TBS	OEt	—	+47.0 ($CHCl_3$)	57
TBS	Oi-Pr	—	+50.1 ($CHCl_3$)	57
TBS	NMeOMe	131–132	+35.0 ($CHCl_3$)	56

[a] m.p. 51°C is given in ref. 24.
[b] At 546 nm.

Synthesis

O,O'-Dialkylated tartrates and tartramides can be obtained by a modified Williamson alkylation procedure, compatible with the presence of the ester or amide function (Scheme 5.15).



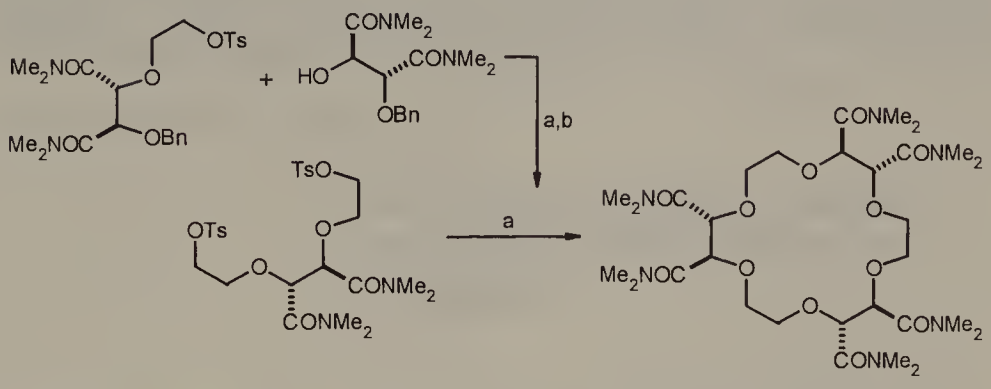
a: 2 eq. NaH, 4 eq. BnBr, THF, RT, 30 min. (70%)[47]
b: 1.9 eq. NaH. 1.9 eq. BnBr, 0.2 eq. Bu_4NI, 0.002 eq. 18-crown-6, THF, 0°C → RT, 1h[46]
c: 2 eq. NaH, 2.0 eq. Me_2SO_4, Et_2O, 0°C → RT (85-92%)[28,31]
d: $Br(CH_2)_6O$–N=N–NO_2 , K_2CO_3, Bu_4NBr, Me_2CO, RT, 72h[58]

Scheme 5.15

Bis-(*N,N*-dialkylamide) derivatives of tartaric acid are particularly useful in *O*-alkylation reactions, due to their lower sensitivity towards bases as compared to tartrate esters.

Chiral hexacarboxamide 18-crown-6 ether **5.10** has been synthesized in two steps by Dutton and Fyles from the three *O*-alkyl-*N,N,N',N'*-tetramethyl-

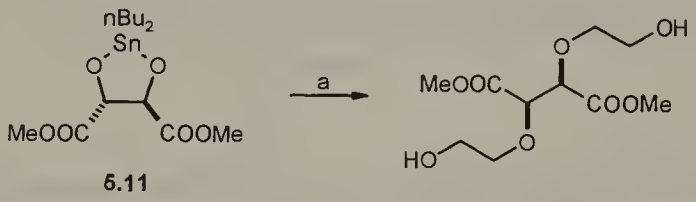
tartramide components using the Williamson reaction conditions[14] (Scheme 5.16).



a: NaH, DMF, 65°C b: H_2, Pd/C

Scheme 5.16

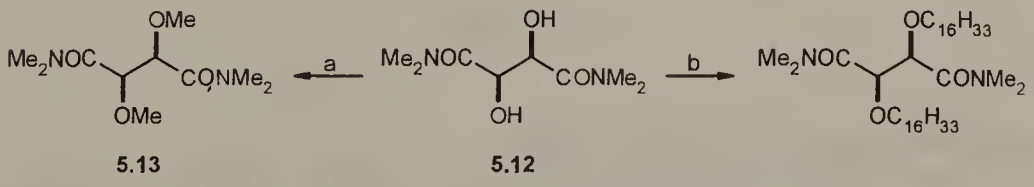
Dialkylation of *O,O'*-stannylene acetal **5.11** is possible at elevated temperatures; whereas at lower temperatures the monoalkylated product is formed exclusively[19] (Scheme 5.17).



a: 2 eq. $ClCH_2CH_2OH$, 170°C (78%)

Scheme 5.17

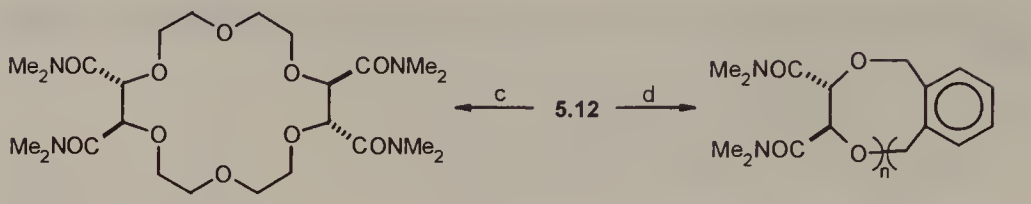
Seebach *et al.* demonstrated that *N,N,N',N'*-tetraalkyltartramides can be conveniently *O*-alkylated under phase transfer catalysis.[38] This method is preferred to another variant of the Williamson reaction based on the highly toxic thallium(I) alkoxides and used for the synthesis of macrocyclic tartrate ethers[45] (Scheme 5.18).



a: 2.1 eq. Me_2SO_4, 3 eq. 50% NaOH, CH_2Cl_2, $BnEt_3NCl$ (cat.), RT (95%)[38]

b: 2 eq. TlOEt, 2.2 eq. n-$C_{16}H_{33}I$, MeCN, RT, then 40°C (95%)[32]

Scheme 5.18 (*continued*)

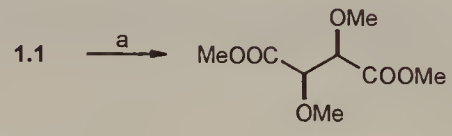


c: 2 eq. TlOEt, 1 eq. $I(CH_2)_2O(CH_2)_2I$, DMF, 90°C (20%)[59-61]

d: 2 eq. TlOEt, 1 eq. α,α'-dibromo-o-xylene, MeCN, 70°C[60]

Scheme 5.18

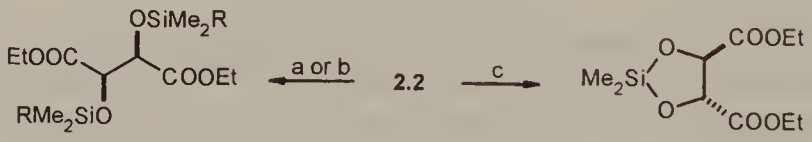
Dimethyl *O,O'*-dimethyl tartrate can be obtained with high yield by prolongated action of diazomethane on tartaric acid[62] (Scheme 5.19).



a: CH_2N_2, Et_2O, RT, 2 days (95%)

Scheme 5.19

O,O'-Disilyl tartrate derivatives are obtained by conventional silylation procedures (Scheme 5.20).



a (R = Me): 2 eq. HMDS, benzene, Δ, 8h (78%)[54]

b (R = tBu): 2.4-3 eq. $tBuMe_2SiCl$, 3-5 eq. imidazole, DMF, 35-60°C (100%)[57,63]

c: $(-SiMe_2NH-)_3$, $(NH_4)_2SO_4$, benzene, Δ, 8h (51%)[54]

Scheme 5.20

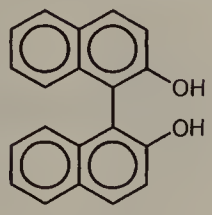
The following are commercially available:

N,N,N',N',O,O'-hexamethyl-L-tartaric acid diamide [*26549-29-1*] and its enantiomer [*63126-53-4*],

diisopropyl *O,O'*-bis(trimethylsilyl)-L-tartrate [*130678-42-1*] and its enantiomer.

Applications

Permetylated tartramide **5.13** is used for the effective resolution of racemic 2,2′-dihydroxy-1,1′-binaphthyl (**5.14**) by the formation of the crystalline 1:1 complex with (*S*)-(−)-enantiomer of **5.14** (Scheme 5.21).



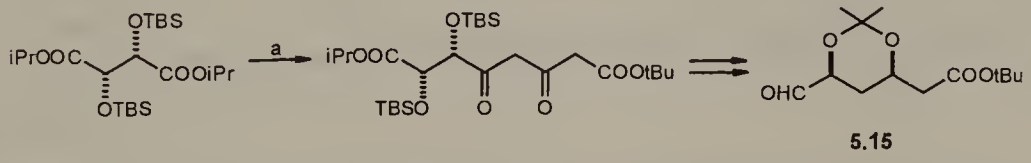
rac.-**5.14**

a: 1eq. **5.13**, benzene-hexane (82%)

Scheme 5.21

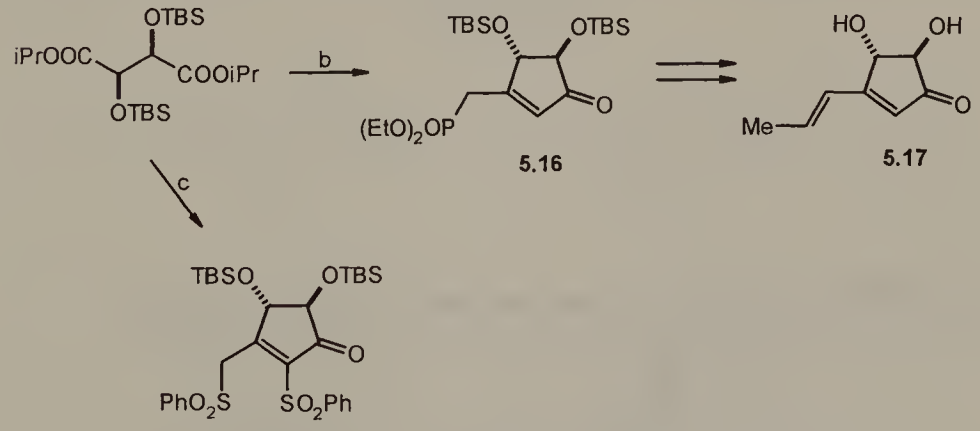
Enantiomerically pure (*S*)-(−)-**5.14** is obtained from the complex with a 72% yield.[39,40]

O,O'-Di-TBS protected tartrates are useful acylating agents for the aceto-acetate dianion,[57] α-methylphosphonate anion[64] or α-methylsulfonyl dianion[65] (Scheme 5.22).



5.15

a: 5 eq. $(CH_2COCHCOOtBu)^2{}^-Li^+Na^+$, THF, -78°C, 16h, then HCl (74%)[57]



5.16 **5.17**

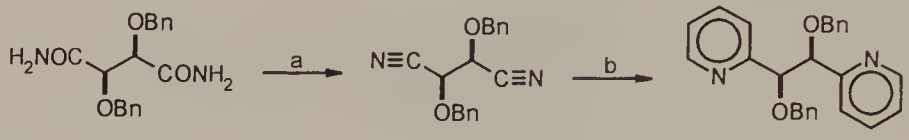
b: 4 eq. $LiCH_2PO(OEt)_2$, THF, -78 → -20°C, then 2 eq. AcOH, RT, 20h (61%)[64]

c: $PhSO_2CHLi_2$, THF, 0°C, 15 min., then HCl-H_2O (100%)[65]

Scheme 5.22

The latter two reagents provide access to chiral functionalized cyclopentenones. Product **5.15** is a precursor of artificial analogs of HMG-CoA reductase inhibitors, and cyclopentenone **5.16** is a precursor of (+)-terrein (**5.17**).

Diamide **5.18** was used as starting material in the synthesis of bis(2-pyridyl) ligand **5.20** through the dinitrile intermediate **5.19**[48] (Scheme 5.23).



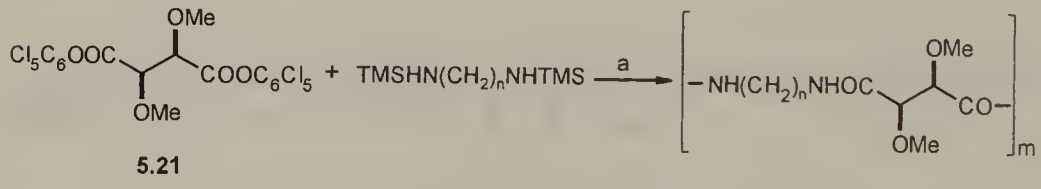
5.18 **5.19** **5.20**

a: MsCl, pyridine, 5h, 100°C (95%)

b: HC≡CH, CpCo(COD), PhMe, 14 bar, 36h,140°C (70%)

Scheme 5.23

Activated pentachlorophenyl ester **5.21** was used for the synthesis of a series of polyamides with *N,N'*-bis(trimethylsilyl)alkanediamines $TMSHN(CH_2)_nNHTMS$ (n from 2 to 12). Stereoregular, hydrophilic products of polycondensation had molecular weights between 7000 and 50,000[28] (Scheme 5.24).

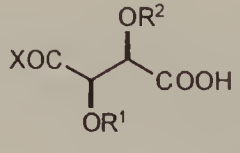


5.21

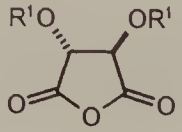
a: $CHCl_3$, 0°C → RT, 3 days

Scheme 5.24

5.3 *O*-ALKYLATED TARTARIC ACIDS AND ANHYDRIDES



IV



V

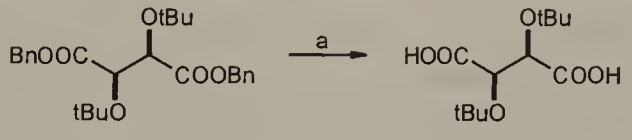
Table 5.3 ***O*-Alkylated tartaric acids (IV) and anhydrides (V)**

R^1	R^2	X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
			Formula IV		
Me	H	OH	179	+49.6 (H_2O)	66–68
Me	Me	OH	155–157	+84.0 (EtOH)	28,29,68
Me	Me	NH_2	185	+89.9 (H_2O)	37
Me	Me	NHPh	117–119	+129.6 (Me_2CO)	37
Et	Et	OH	127–128	+84.0 (Me_2CO)	37,41,42,47,53
Et	Et	NHPh	143–145	+145.5 (Me_2CO)	37
t-Bu	H	OH	67	+46.0 (Me_2CO)	7
t-Bu	t-Bu	OH	134	+54.7 (Me_2CO)	7
n-$C_{10}H_{21}$	n-$C_{10}H_{21}$	OH	56–58	+21.8 ($CHCl_3$)	43
n-$C_{10}H_{21}$	n-$C_{10}H_{21}$	NHBu	—	+25.2 ($CHCl_3$)	43
Cl_2C=CH	Cl_2C=CH	OH	120	−42.9 (MeOH)[a]	53
Cl_2C=CH	Cl_2C=CH	NH_2	185	−50.7 (MeOH)[a]	53
			Formula V		
Me	—	—	85–86	+156.0 (Me2CO)	29,69
Et	—	—	124–126/19	+143.6 (Me2CO)	37,53
Bn	—	—	95–96.5	—	47
Cl_2C=CH	—	—	35–38	—	53

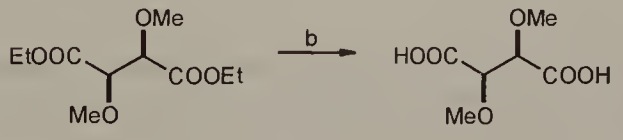
[a] At 546 nm.

Synthesis

The acids are readily obtained by hydrolysis or hydrogenolysis of the corresponding alkyl or benzyl tartrates (Scheme 5.25).



5.22 **5.23**



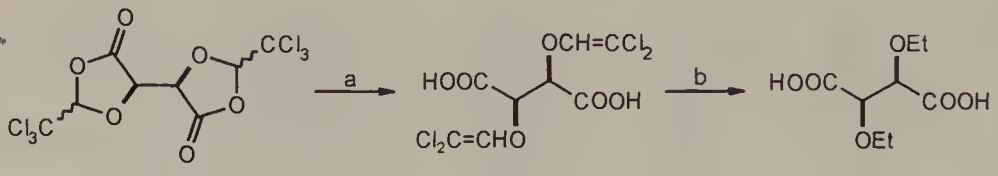
a: H_2, 10% Pd/C, AcOEt (93%)[7]

b: NaOH, H_2O-EtOH, 10-15°C, 1h, then HCl (64%)[29]

Scheme 5.25

It should be noted that alkaline hydrolysis (KOH in MeOH, reflux 80 hr) of **5.22** resulted in considerable racemization of diacid **5.23**.[7]

Diacid **5.25** can be synthesized by zinc reduction of chloralide **5.24**. Subsequent hydrogenation converts **5.25** to *O,O'*-diethyltartaric acid (**5.26**), Scheme 5.26.[7]



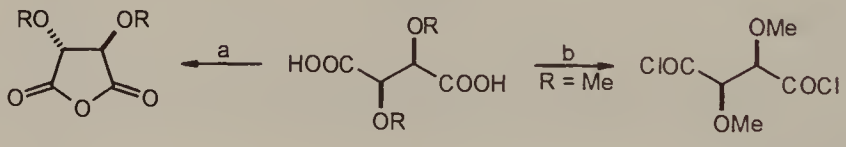
5.24 **5.25** **5.26**

a: Zn, AcOH, 60°C, 7 hr (78%)

b: H_2, 10% Pd/C, AcOK, MeOH, 50°C, 3-4 bar, then HCl (73%)

Scheme 5.26

O,O'-Dialkyltartaric anhydrides are prepared from the corresponding diacids by refluxing with acetyl chloride.[53] On the other hand, the action of phosphorus pentachloride allows the synthesis of *O,O'*-dimethyltartaroyl dichloride (**5.27**),[69] Scheme 5.27.



5.27
m.p. 90-93°C,
$[\alpha]_D$ +56.9 ($CHCl_3$)

a: AcCl, AcOEt, Δ b (R = Me): PCl_5, benzene, Δ

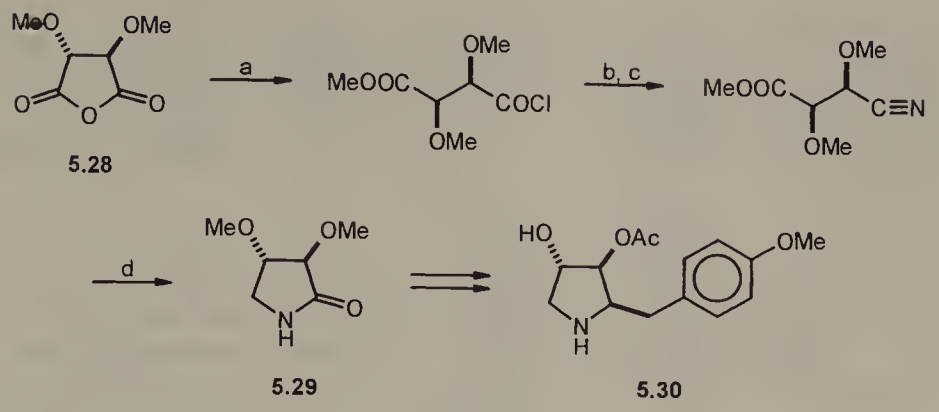
Scheme 5.27

O,O'-Dialkyltartramic acids are readily obtained from the corresponding anhydrides by the addition of ammonia or an amine.

Applications

B *O,O'*-Dimethyl-L-tartaric anhydride (**5.28**) was converted by rather conventional set of reactions to the pyrrolidone **5.29**, an intermediate in the total synthesis of antibiotic anisomycin **5.30** (Scheme 5.28).[29]

Macrocyclic tetra- and hexaamides have been prepared by Naemura by high dilution condensation of dichloride **5.31** with diamine **5.32** derived from L-threitol[41] (Scheme 5.29).



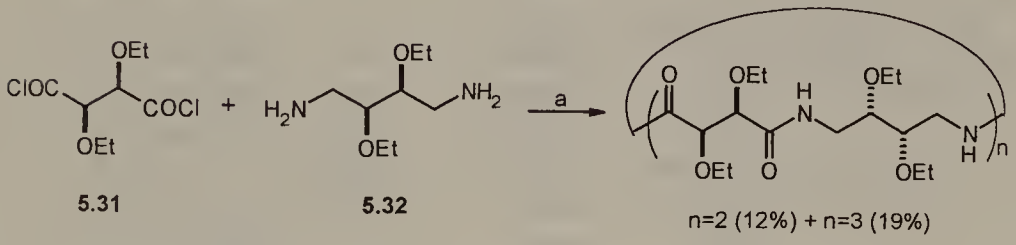
a: MeOH, 50°C, then PCl_5, CH_2Cl_2 (90%)

b: NH_3, CH_2Cl_2 (90%)

c: $SOCl_2$ (82%)

d: H_2, Pd/C, HCl-MeOH, then NH_3 (80%)

Scheme 5.28



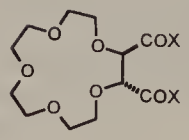
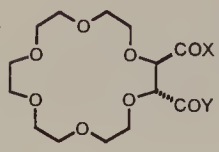
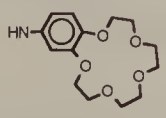
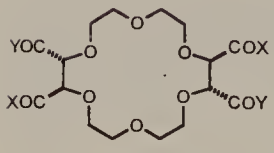
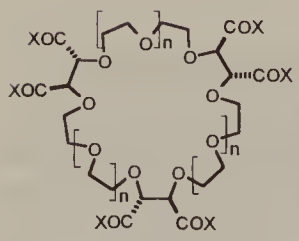
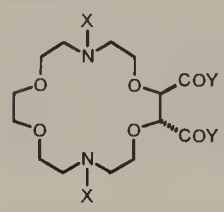
a: NEt_3, benzene, RT

Scheme 5.29

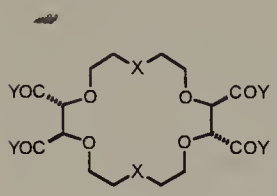
5.4 TARTARIC ACID DERIVED CROWN ETHERS AND RELATED MACROCYCLES

Tartaric acid based chiral crown ethers (Scheme 5.30) and other macrocycles (Scheme 5.31) are a group of *O,O'*-dialkyl derivatives of tartaric acid of well-established applications.[70,71] These acids and their amides display useful properties as, for example, cation selective ionophores,[72,73] chromoionophores,[51] selective ion carriers,[74–77] ion channel mimics,[78] synthetic molecular catalysts,[79,80] macro(poly)cyclic receptor molecules,[81–85] enantioselective optode membranes,[86] and as complexing resolving agents for racemic amines in capillary zone electrophoresis.[87–90]

Some selective transformations of the functional groups in 18-crown-6 diacid derivatives are shown in Scheme 5.32.

	X	Y	m.p.(°C)	$[\alpha]_D$ (solvent)	References
	OH	-	60-70	+24.0 (H_2O)	60
	OMe	-	-	+49.0 ($CHCl_3$)	60
	NMe_2	-	65	+84.0 ($CHCl_3$)	60
	OH	OH	108	+34.7(H_2O)	74,91
	NMe_2	NMe_2	-	+52.6 ($CHCl_3$)	61
	OH	HNTMP[a]	161-163	+29.0 (MeOH)	76
	OMe	HNTMP[a]	79-81	+25.1 ($CHCl_3$)	76
	OH	HNPh	143-145	+85.7 ($CHCl_3$)	76
	OH		-	+55.8 ($CHCl_3$)	77,92
	OH	OH[b]	213	+67.0 (H_2O)	60
	Cl	Cl	180	-	60,86,93
	NHMe	NHMe	255	+66.0 ($CHCl_3$)	60
	NMe_2	NMe_2	186	+112.0 ($CHCl_3$)	60,61
	NBu_2	NBu_2	81	+49.0 ($CHCl_3$)	60,94
	$N(C_8H_{17})_2$	$N(C_8H_{17})_2$	-	+35.8 ($CHCl_3$)	86
	OH	HNTMP[a]	190	+31.4 ($CHCl_3$)	76
	OMe	HNTMP[a]	200	+45.6 ($CHCl_3$)	76
	OH	HNTMPO[c]	160	+45.2 (EtOH)	95
	HNTMPO	HNTMPO[c]	106-109	+42.7 (EtOH)	95
	OH	HNPh	ca 110	-	96
	OMe	HNPh	-	+67.6 ($CHCl_3$)	76
	OH	HN-Ar[d]	170-173	-	96
	-O-		153-154	-	60
	-NMe-		128	+147.0 ($CHCl_3$)	76
	OH (n=0)	-	113-116	+122.1 (EtOH)	14
	NMe_2 (n=0)	-	-	+87.6 (EtOH)	14
	OH (n=1)	-	-	+40.0 (buffer)	82
	NMe_2 (n=1)	-	-	+111.0 ($CHCl_3$)	60
	H	OH	180	+39.0 (H_2O)[e]	50
	H	NMe_2	-	-	50
	CH_2COOH	OH	195	+32.0 (H_2O)[e]	50
	Ts	NMe_2	62-64	+46.0 (CH_2Cl_2)	50

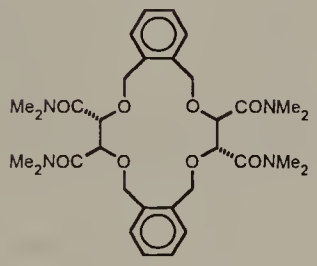
(*continued*)



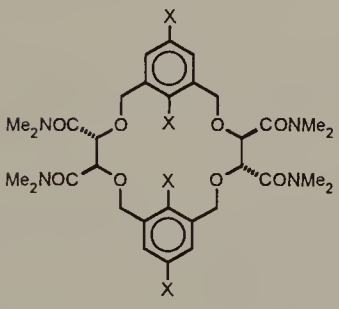
NH	OH	>200	+62.0 (H_2O)[e]	50
NH	NMe_2	-	-	50
NCH_2COOH	OH	188	-	50
NTs	NMe_2	194-196	+74.0 ($CHCl_3$)	50
S	OH	-	-	49
S	NMe_2	164-169	-	49

[a] TMP = 2,2,6,6-tetramethyl-4-piperidyl
[b] this (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid [*61696-54-6*] is available commercially
[c] TMPO = 2,2,6,6-tetramethyl-4-piperidyl-1-oxide
[d] Ar = 9-phenanthryl
[e] bis-TsOH salt

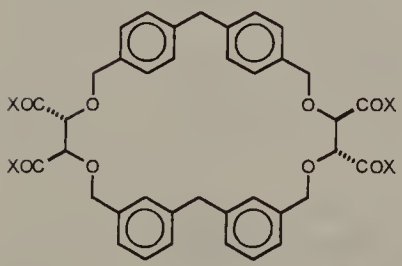
Scheme 5.30. L-Tartaric acid derived crown ethers and their aza and thia analogues.



X	m.p. (°C)	$[\alpha]_D$ (solvent)	Ref.
-	230	+114.0 ($CHCl_3$)	60

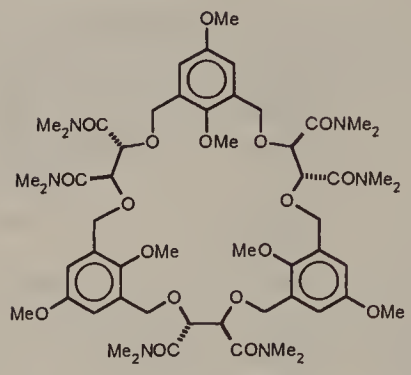


H	224	+107.0 ($CHCl_3$)	60
OMe	244-246	+139.8 ($CHCl_3$)	51

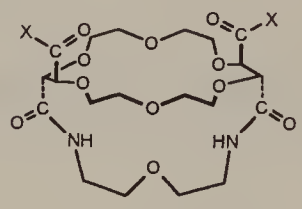


OH	>350	+10.4 (EtOH)	97
NMe_2	>350	-84.3 ($CHCl_3$)	97

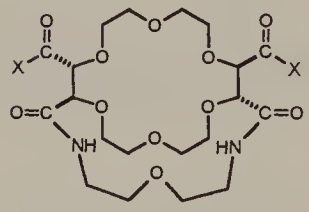
Scheme 5.31 (*continued*)



-	-	+84.4 ($CHCl_3$)	51

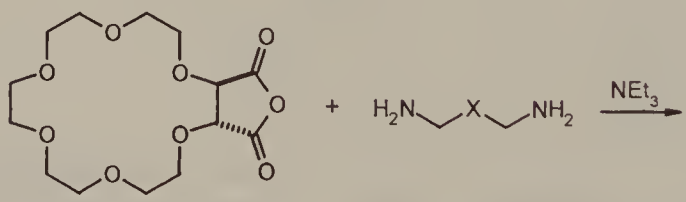


OH, OMe (*syn*)	-	-	98

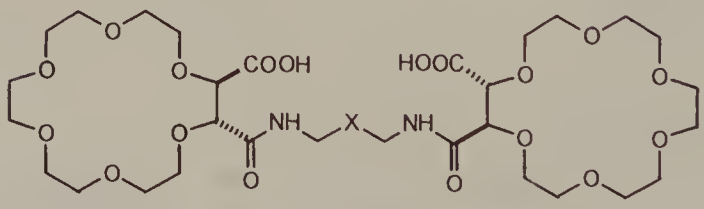


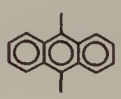
OH (*anti*)	-	-	98

Scheme 5.31. L-Tartaric acid derived speleands, ionophores, and cryptands.

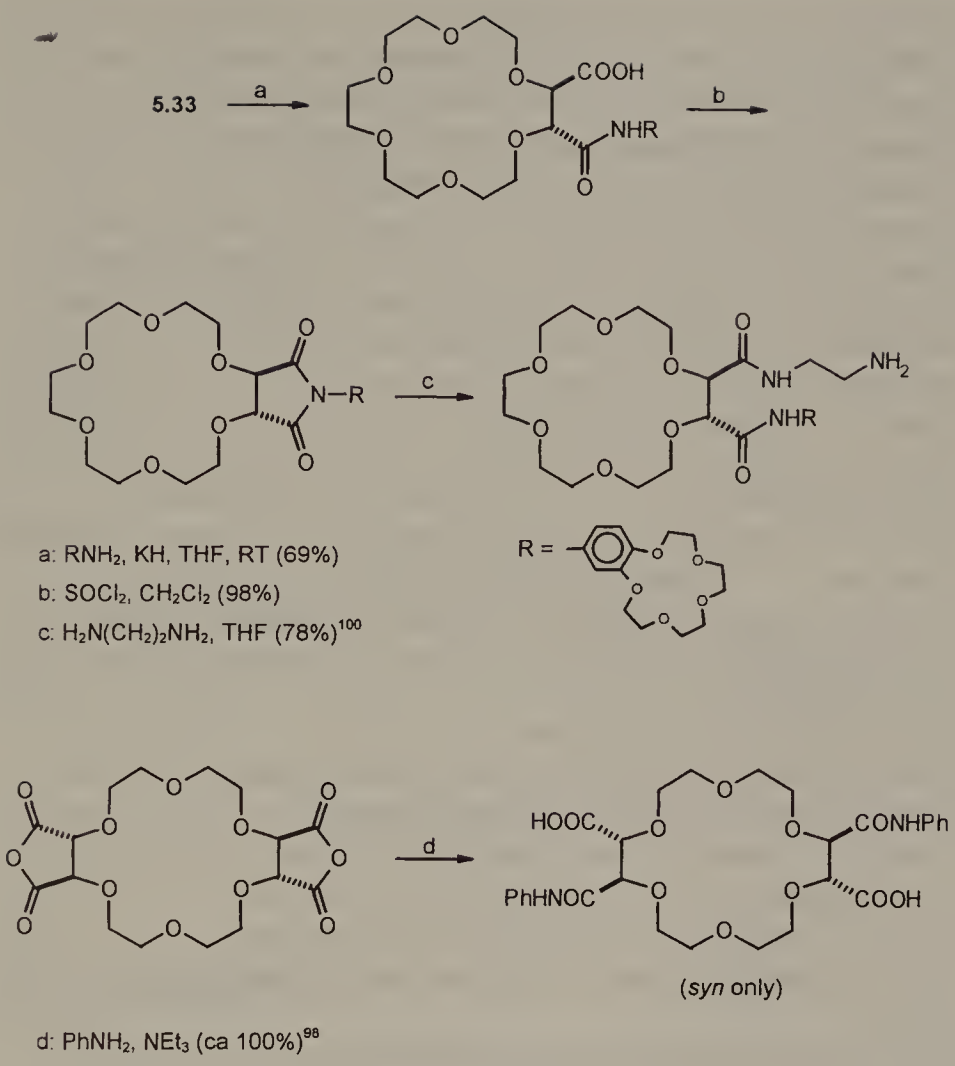


5.33



X = $(CH_2)_2OC(CH_2)_nCO(CH_2)_2$ (n = 14, 18)[99] or X =  [93]

(*continued*)



Scheme 5.32

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6 Tartrimides

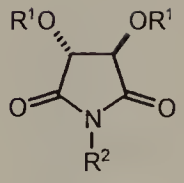

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Table 6.1 L-Tartrimides and their *O,O*-dialkyl, disilyl and diacyl derivatives (I)

R^1	R^2	m.p. (°C)	$[\alpha]_D$ (solvent)	References
H	H	205–206	+202.0 (H_2O)	1,2
H	Me	178	+194.0 (H_2O)	3
H	Et	171–174	+164.9 (H_2O)	3
H	n-$C_{12}H_{25}$	127–128	+113.0 (MeOH)	4
H	Bn	196–198	+138.0 (MeOH)	5–8
H	$(CH_2)_2Ph$	190–192	+156.6 (MeOH)	9
H	3,4-$(MeO)_2C_6H_3(CH_2)_2$	178	+123.3 (DMSO)	10
H	Ph	255-257	+130.0 (MeOH)	11,12
H	4-MeC_6H_4	235	+128.7 (MeOH)	13
H	4-HOC_6H_4	299	+119.6 (MeOH)	14
H	OH	86–89	+175.3 (EtOH)	15
H	OBn	173–175	+154.0 (EtOH)	15
Me	H	108–110	+235.5 (Me_2CO)	16
Me	Me	54–57	+228.8 (Me_2CO)	16
Me	CH_2COOH	60	+172.0 ($CHCl_3$)	17,18
Me	CH_2COOBn	55	+104.6 ($CHCl_3$)	18
Me	Ph	82	+198.2 (Me_2CO)	16
Me	SMe	79–80	+233.0 (Me_2CO)	19
Me	SPh	109–111	+182.0 (Me_2CO)	19
Et	Ph	56–58	+182.2 (Me_2CO)	16
t-Bu	H	154	+205.0 ($CHCl_3$)	2
Bn	H	58	+143.9 (Me_2CO)	20
Bn	Me	—	+177.0 (Me_2CO)	21
TBS	Me	—	+134.3 ($CHCl_3$)	22
TBS	Bn	—	+98.6 ($CHCl_3$)	23
Ac	H	132	+113.1 (Me_2CO)	24

(*continued*)

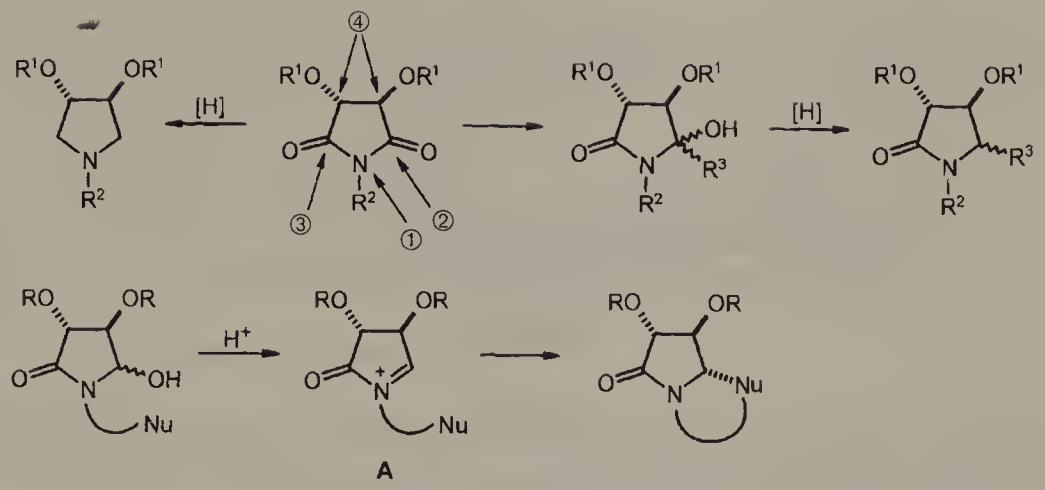
Table 6.1 (*continued*)

R^1	R^2	m.p. (°C)	$[\alpha]_D$ (solvent)	References
Ac	CH_2COOMe	—	—	25
Ac	Ph	125.5	+90.5 (Me_2CO)	26,27
Ac	2-MeC_6H_4	128	+99.4 (Me_2CO)	27
Ac	3-MeC_6H_4	146	+112.0 (Me_2CO)	27
Ac	4-MeC_6H_4	127	+118.5 (Me_2CO)	27
Ac	4-ClC_6H_4	173	+106.9 (Me_2CO)	27
Ac	4-BrC_6H_4	184	+81.6 (Me_2CO)	27
Ac	4-$MeOOCC_6H_4$	—	—	28
Ac	2,4-$Me_2C_6H_3$	118.5	+166.4 (Me_2CO)	27
Ac	2,4-$Cl_2C_6H_3$	158	+63.0 (Me_2CO)	27
Ac	2,4-$Br_2C_6H_3$	172	+58.0 (Me_2CO)	27
Ac	2-naphthyl	166	+134.6 (Me_2CO)	27
Ac	NHPh	156	—	29
Ac	OH	142–143	+115.6 (—)	15
Ac	OBn	62–63	—	15
i-PrCO	Ph	96–97	+60.3 (Me_2CO)	26
t-BuCO	H	166	+83.2 ($CHCl_3$)	24
t-BuCO	Cl	137–140	+53.9 ($CHCl_3$)	30
1-adamantylCO	H	229	+73.3 ($CHCl_3$)	24
BnCO	Ph	112	+80.9 (Me_2CO)	26
Bz	Me	106–107[a]	+189.0 (AcOEt)	3
Bz	Et	159–160	—	31
Bz	n-Bu	124–125	+148.0 (Me_2CO)	32
Bz	t-Bu	169–173	—	28
Bz	(*S*)-CHMePh	85–86	+217.4 (CH_2Cl_2)	33
Bz	CH_2COOMe	125–127	+158.7 (CH_2Cl_2)	33
Bz	(*R*)-MeCHCOOMe	144–145	+217.5 (CH_2Cl_2)	33
Bz	(*R*)-iPrCHCOOMe	78–80	+104.5 (CH_2Cl_2)	33
Bz	(*S*)-BnCHCOOMe	—	+20.0 (CH_2Cl_2)	33
Bz	Ph	173	+144.8 (benzene)	26
Bz	1-naphthyl	215–217	—	34
Bz	2-naphthyl	179–180	—	34
Bz	OH	140–141	+161.2 (THF)	35
PhCH=CHCO	Me	95	+311.6 (AcOEt)	31
PhCH=CHCO	Bn	129–131	+258.5 ($CHCl_3$)	28
PhCH=CHCO	Ph	169–170	+203.0 ($CHCl_3$)[b]	28
2-$Ph_2PC_6H_4CO$	Bn	—	+77.5 (CH_2Cl_2)	36

[a] Crystallizes with ethanol molecule (m.p. 56°).

[b] The data in ref. 26, m.p. 202°C, $[\alpha]_D$ −145.1 (Me_2CO), are apparently erroneous; they correspond to *O*,*O*′-dicinnamoyl-L-tartranilic acid.

Tartrimides are very useful as precursors of chiral derivatives of pyrrolidine and its bicyclic analogues. Several features of the tartrimide moiety that are of importance in the syntheses leading to these compounds are shown in Scheme 6.1.



Scheme 6.1

① The deprotonated form of a tartrimide (R^2 = H) is useful as a nucleophile.

② This is an electrophilic site: reduction either to the CHOH ($NaBH_4$) or to the CH_2 group ($LiAlH_4$ or BH_3); addition of carbanions, addition of nitrogen or oxygen nucleophiles with imide ring opening.

③ This group can be additionally reduced to the CH_2 group ($LiAlH_4$ or BH_3).

④ R^1O groups can be substituted when R^1 = Ms, Ts, Tf.

Various products of reduction or carbon nucleophile addition to tartrimides are used in synthesis and considerable part of synthetic utility of tartrimides is based on *N*-acyliminium ions, reactive intermediates formed from partially reduced imides under acidic conditions. Reactions proceeding through the intermediate *N*-acyliminium ion are frequently highly diastereoselective. For example, in intramolecular cyclizations of *N*-acyliminium ion (A), the incoming nucleophile forms the bond *anti* to the neighboring C–OR bond (Scheme 6.1). Similar considerations apply to cyclizations of *N*-acylimino radicals.

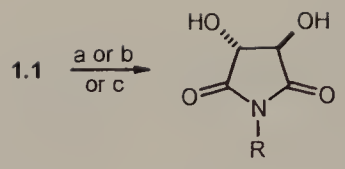
Synthesis

Tartrimides with unprotected hydroxy groups can be directly synthesized from tartaric acid (**1.1**) by thermal condensation with primary amines. The best results are obtained with aromatic amines, such as anilines; their 1:1 salts with **1.1** on heating yield *tartranils*. Examples are shown in Scheme 6.2.

A patent describes the manufacture of tartrimides by removing water from a slurry of the amine–**1.1** salt in organic solvent by azeotropic distillation.[37]

With methylamine, partially racemized imide *N*-methyltartrimide was obtained by thermal condensation.[3] Alternatively this imide can be prepared with high yield by methanolysis of its di-*O,O'*-diacetyl derivative.[22]

O,O-Diacyl and dialkyl imides can be conveniently obtained from the corresponding anhydrides. This can be done either in the one-step or in the two-step



a (R = Bn): 1eq. $BnNH_2$, xylene, Δ, removal water (81%)[6]

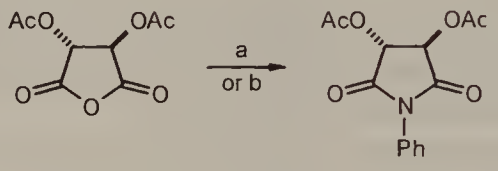
b (R = Bn): 1eq. $BnNH_2$, 170°C, 30 min. (95%)[7]

c (R = Ph): 1eq. $PhNH_2$, H_2O; the 1:1 salt is separated, then 140°C[11]

Scheme 6.2

sequence involving the formation of the intermediate *O,O*-protected tartramic acid.

In the one-step method the anhydride is fused with diacylurea at 135°C[26] or heated briefly with arylamine at 110°C[27] (Scheme 6.3).



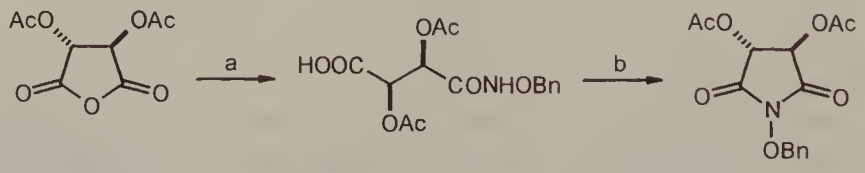
a: $(PhNH)_2CO$, 135°C[26]

b: 1eq. $PhNH_2$, 110°C, 5 min.[27]

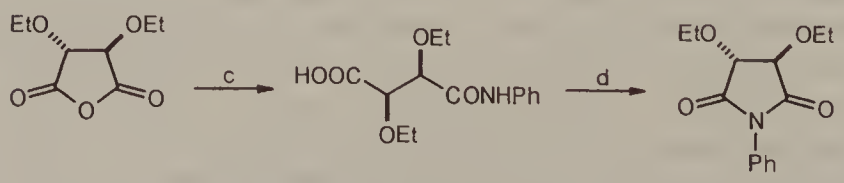
Scheme 6.3

The use of less basic urea instead of amine allows to avoid some side reactions (e.g. racemization).

In the two-step sequence the intermediate tartramic acid is cyclized to the imide by the addition of a condensing agent (Scheme 6.4).

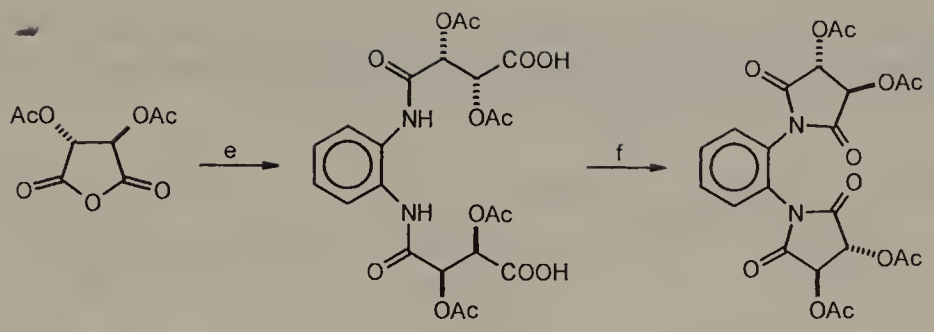


a: $BnONH_2$, THF, 0°C; b: Ac_2O, 90°C[15]



c: 1eq. $PhNH_2$, benzene, reflux; d: AcCl, reflux (85%)[16]

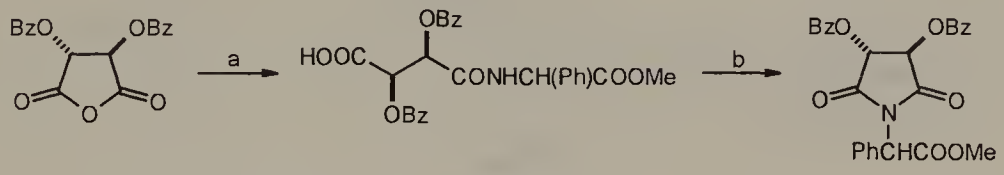
(continued)



e: 1,2-diaminobenzene (90%); f: $(PhO)_2PON_3$[38]

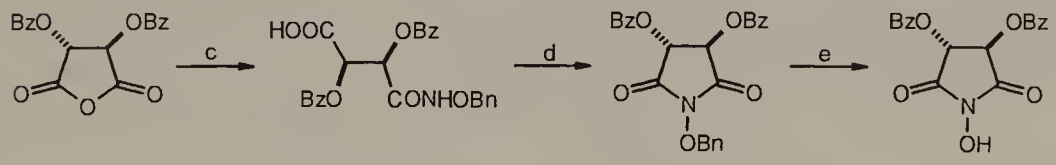
Scheme 6.4

In another method, particularly useful for esters of aminoacids as substrates, cyclization of the intermediate tartramic acid is induced by thionyl chloride (Scheme 6.5).



a: $PhCH(N^+H_3Cl^-)COOMe$, NEt_3, $CHCl_3$, RT, 30 min.

b: 2 eq. $SOCl_2$, 0°C → RT, 30 min. (97%)[33]



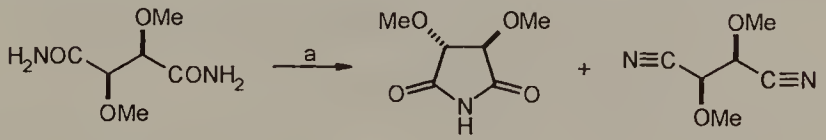
c: 1.1 eq. $BnONH_2$, THF, RT

d: 1.2 eq. $SOCl_2$, $CHCl_3$, 0°C → RT (95%)

e: H_2, 10% Pd/C, AcOEt (93%)[35]

Scheme 6.5

O,O-Dimethyl-L-tartrimide (**6.2**) along with the dinitrile **6.3** were obtained by the action of thionyl chloride on the diamide **6.1**[39] (Scheme 6.6).



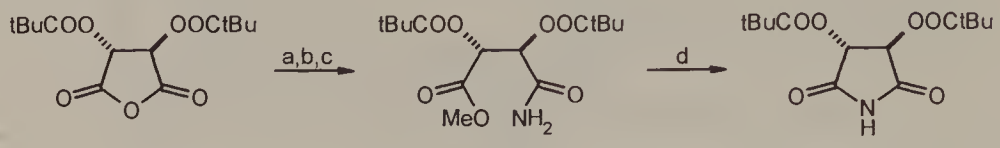
6.1 **6.2** **6.3**

m.p. 56°C; $[\alpha]_D$ + 170.4 ($CHCl_3$)

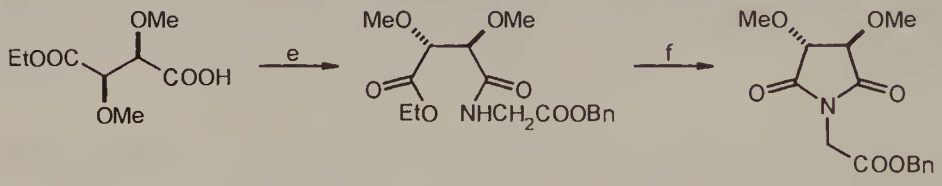
a: $SOCl_2$, Δ

Scheme 6.6

A more elaborate method involves initial conversion of the anhydride to the tartramate ester; the crucial cyclization step is effected by the action of sodium hydride on the intermediate ester[24] (Scheme 6.7).



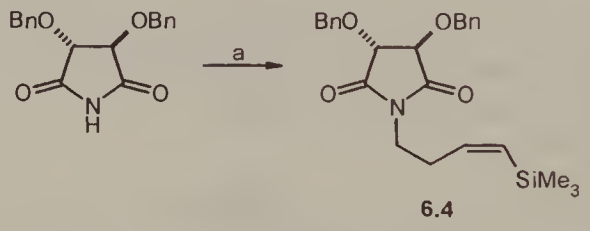
a: MeOH, RT; b: $SOCl_2$, 40°C; c: NH_3, THF, 0°C, 10 min.
d: 1.2eq. NaH, THF, RT (82%)[24]



e: Gly-OBn·TsOH, $(EtO)_2POCN$, NEt_3 (91%)
f: Na, PhMe (71%)[17,18]

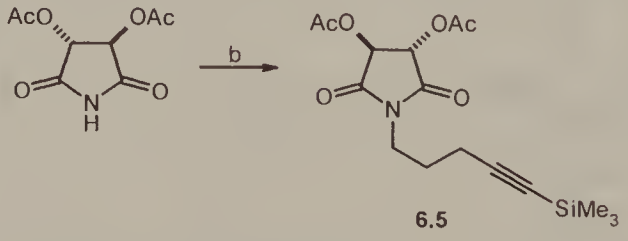
Scheme 6.7

N-Alkylation of tartrimides is a method for preparing functionalized tartrimides. Examples shown in Scheme 6.8 feature Mitsunobu-type substitution to produce *N*-substituted imides **6.4** and **6.5** and *N*-sulfenylation, leading to imides **6.6**.



6.4

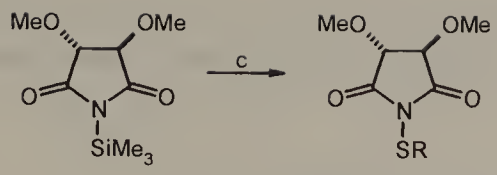
a: (*Z*)-$Me_3SiCH{=}CH(CH_2)_2OH$, PPh_3, DEAD, THF, RT, 30 min. (77%)[40]



6.5

b: $Me_3SiC{\equiv}C(CH_2)_3OH$, PPh_3, DEAD, THF, 0°C → RT, 8h (86%)[41]

(*continued*)



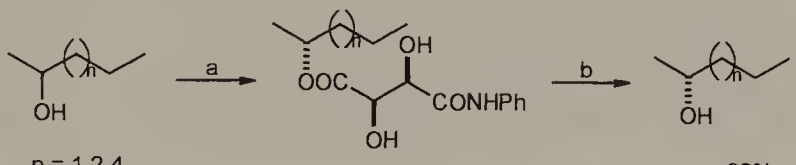
6.6 (R = Me, Ph)

c: 1.5 eq. RSCl, RT, 5 min. (70-76%)[19]

Scheme 6.8

Applications

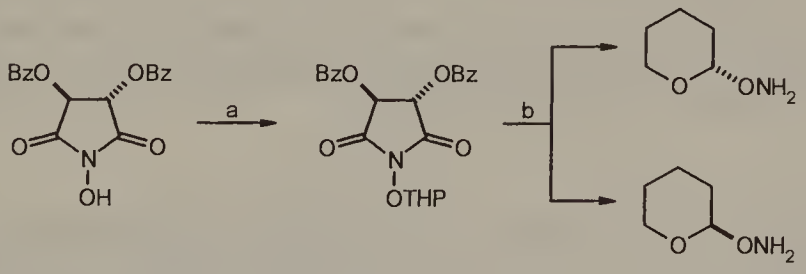
Racemic alcohols can be resolved by crystallization of their tartranilate esters **6.7** formed by acid-catalyzed esterification of tartranils; however yields are low[11] (Scheme 6.9).



a: (*R,R*)-*N*-phenyltartrimide, H_2SO_4, Δ; crystallization; b: aq. KOH

Scheme 6.9

Resolution of *O*-2-tetrahydropyranylhydroxylamine was achieved by Kolasa and Chimiak by crystallization of the diastereomeric THP-derivatives of *O,O′*-di-benzoyl-*N*-hydroxytartrimide[42] (Scheme 6.10).



a: dihydropyran, TsOH (cat.), dioxane (55%)

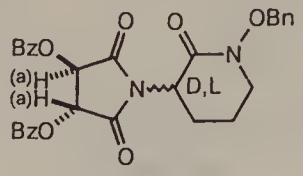
b: crystallization, then H_2NNH_2-H_2O, PhH, EtOH, Δ

Scheme 6.10

Diastereomeric *O,O′*-di-benzoyl-*N*-alkoxytartrimides were successfully resolved chromatographically.[35]

O,O′-Dibenzoyl tartrimides derived from chiral amines were used by Kolasa and Miller to determine the amine enantiomeric purity by ^{1}H NMR spectroscopy.[33] For example, the derivative of δ-*N*-(benzyloxy)cycloornitine (**6.8**)

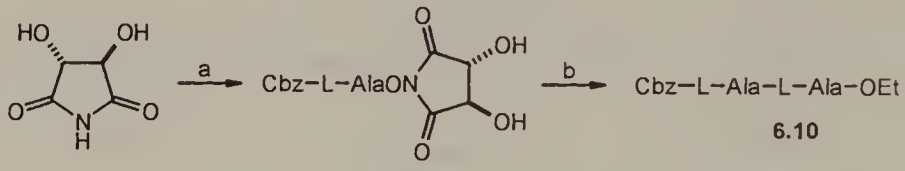
displayed signals of the tartrimide protons (a) of the L-amino acid isomer shifted downfield ($\Delta\delta = 0.055$ ppm) relative to those of the D isomer.[43]



6.8

A

The tartrimide moiety has been used as a chiral auxiliary. Nearly complete kinetic resolution was achieved in the reaction of the activated *N*-hydroxy-tartrimide ester of *Z*-L-alanine (**6.9**) with two equivalents of racemic ethyl alaninate. The L,L form of the dipeptide **6.10** was obtained selectively[15] (Scheme 6.11).



6.9 **6.10**

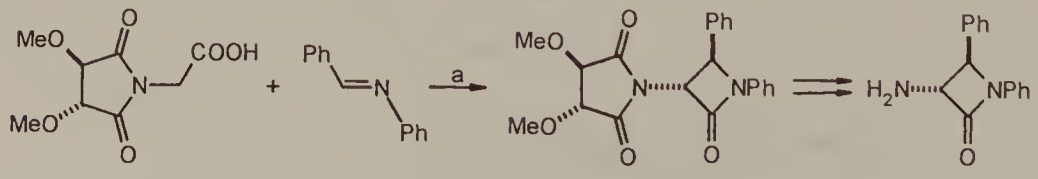
93%, e.e. 100%

a: 1 eq. Cbz-L-Ala-OH, DCC, THF, 0°C

b: 2 eq. D,L-Ala-OEt, THF-MeCN, 0°C

Scheme 6.11

Optically active azetidinones, such as **6.12**, which is useful in the synthesis of β-lactam antibiotics, can be obtained in the Staudinger reaction. The pendant chiral auxiliary derived from the tartrimide is attached to the ketene moiety (generated *in situ* from **6.11**), controlling the formation of the new chiral centers in the β-lactam ring (Scheme 6.12).[17,18,44]



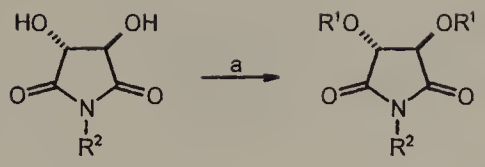
6.11 **6.12**

a: 1 eq. NEt_3, 1 eq. $(CF_3CO)_2O$, CH_2Cl_2, -20°C (40-47%, 100% *trans*, d.e. 60-74%)[17,18]

Scheme 6.12

L

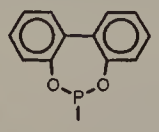
Chiral diposphinites **6.13** and **6.14** or diphosphite **6.15** of C_2-symmetry, prospective ligands for metal catalysts, were obtained from *N*-benzyl and *N*-phenyl tartrimide (Scheme 6.13).



a: R^1Cl, pyridine

6.13, $R^1 = Ph_2P$, $R^2 = Ph$[12]

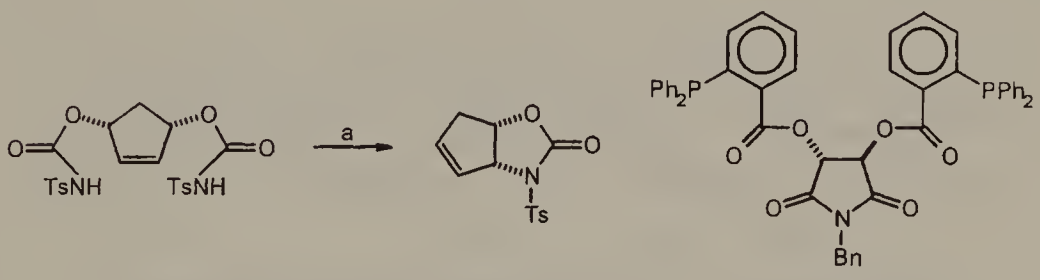
6.14, $R^1 = Ph_2P$, $R^2 = Bn$[7]

6.15, $R^1 =$  , $R^2 = Bn$[45]

Scheme 6.13

Diarylphosphinites derived from tartranil (e.g. **6.13** and 3,5-bis(trifluoromethyl)phenyl analogue) were used by RajanBabu and Casalnuovo as efficient ligands for Ni(0) catalyzed asymmetric hydrocyanation of vinylarenes.[46]

Trost developed a tartrimide-based 2-(diphenylphosphino)benzoate ligand **6.16** for palladium-catalyzed enantioselective allylation reactions[36] (Scheme 6.14). In this ligand, rotational freedom of the benzoate substituents is restricted, resulting in increased enantioselectivity of the catalyst.



6.16

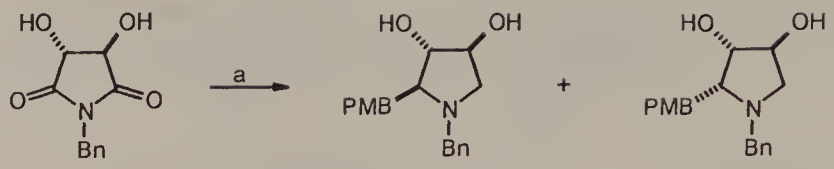
a: 0.025 eq. tris(DBA)dipalladium(0)-chloroform complex, 0.075 eq. **6.16**, THF, RT (68%, e.e. 75%)

Scheme 6.14

Tartrimide derivatives are widely used as building blocks for the synthesis of chiral heterocyclic compounds. Optically active deacetyl *N*-benzyl-anisomycin (**6.17**) was obtained from *N*-benzyltartrimide by sequential reaction with excess Grignard reagent followed by $LiAlH_4$ reduction; the yield of the mixture of epimeric products was low[5] (Scheme 6.15).

A related attempt to synthesize (−)-anisomycin via *N*-acyliminium route was reported by Weinreb *et al.*[47]

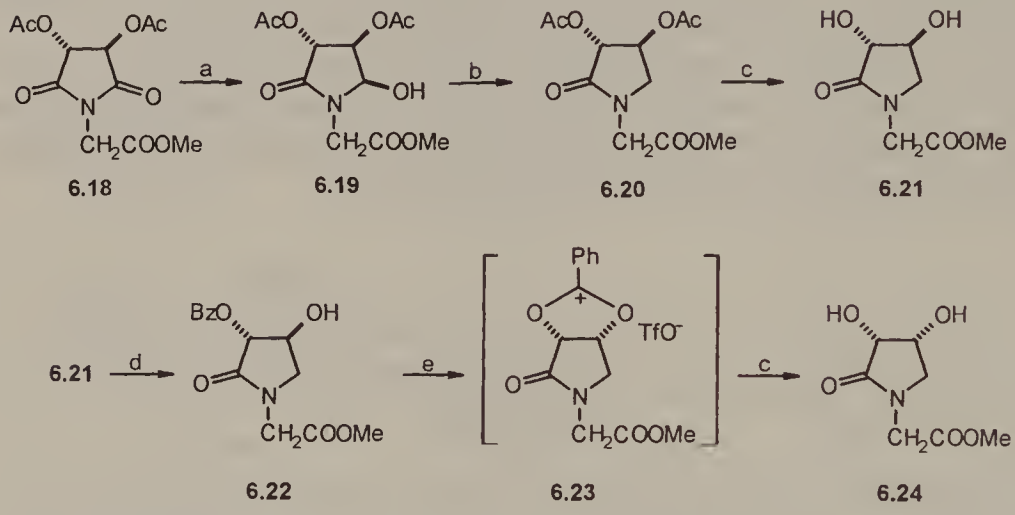
Lactams **6.21** and **6.24** related to the nootropic drug oxiracetam were synthesized from tartrimide **6.18**. Crucial for the synthesis was the selective two-step reduction of the imide **6.18** to lactam **6.20** via hydroxylactam **6.19** by the action of sodium borohydride followed by triethylsilane and trifluoroacetic acid. The



a: PMBMgCl, THF, 40°C, then $LiAlH_4$

Scheme 6.15

diastereoisomer **6.24** was obtained from **6.21** by selective monobenzoylation to give **6.22**, followed by an internal S_N2 displacement of the triflate through the benzoxonium ion **6.23**[25] (Scheme 6.16).



a: $NaBH_4$, THF, -40°C → 0°C (80%); b: $(CF_3CO)_2O$, then Et_3SiH, CF_3COOH (79%)

c: MeONa, MeOH; d: 1.1 eq. BzCl, pyridine, -30°C → 0°C, 3h (71%)

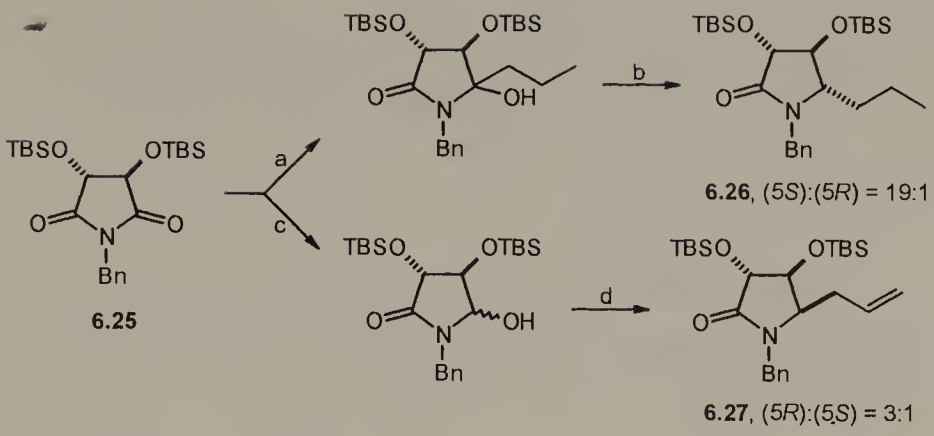
e: 1.2 eq. Tf_2O, 1.1 eq. pyridine, CH_2Cl_2, 5°C then H_2O (98%)

Scheme 6.16

The syntheses shown below are directly or indirectly implied to proceed through the intermediate *N*-acyliminium ion and are characterized by good to excellent diastereoselectivity.

A nucleophile addition-reduction sequence developed by Yoda and Takabe was used to synthesize epimeric chiral γ-alkylated lactams from imide **6.25** (Scheme 6.17).

The addition of a Grignard reagent followed by a low-temperature reduction of the intermediate *N*-acyliminium ion gave lactam **6.26** with high diastereoselectivity. When borohydride reduction preceded alkylation of the *N*-acyliminium ion intermediate, epimeric lactam **6.27** was obtained predominantly as a result of *syn*-alkylation.[48]



a: n-PrMgBr, THF, -78→0°C (98%)

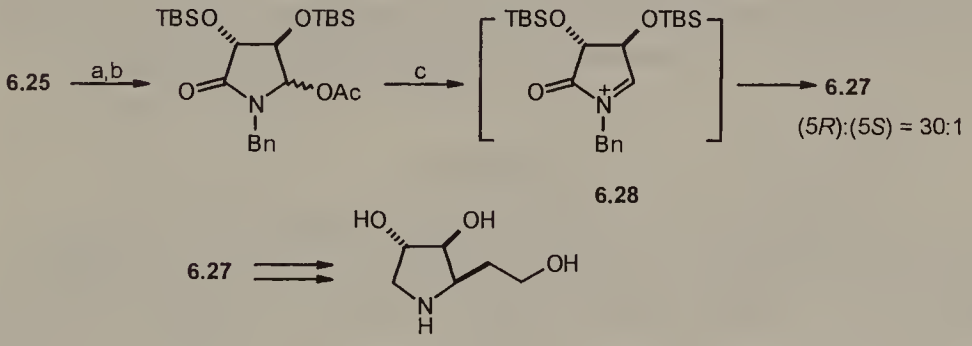
b: Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, -78°C (78%)

c: $NaBH_4$, MeOH, -15°C (91%)

d: $Me_3SiCH_2CH{=}CH_2$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0°C (96%)

Scheme 6.17

Another variant of *syn*-alkylation of *N*-acyliminium ion **6.28** involved tin reagents to give lactam **6.27** with much higher diastereoselectivity (Scheme 6.18).



a: 5eq. $NaBH_4$, 1eq. $SnCl_2$, EtOH-CH_2Cl_2, 0° (100%)

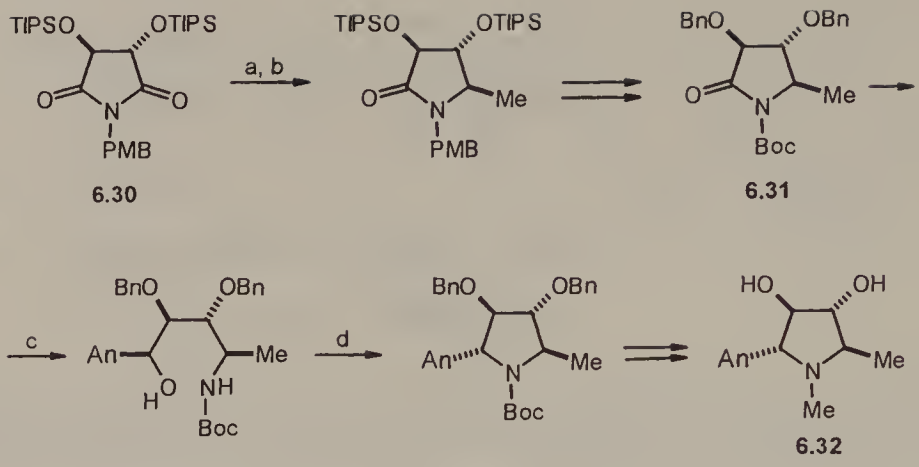
b: Ac_2O, pyridine, 0° (100%)

c: Bu_3SnAll, $MgBr_2$, PhMe, 0° (92%)

Scheme 6.18

Lactam **6.27** was converted to trihydroxylated pyrrolidine **6.29**, a potential glycosidase inhibitor.[23]

The synthesis of (−)-codonopsinine (**6.32**) from D-tartrimide **6.30** involved two Grignard addition-stereoselective reduction sequences targeting at the *trans* configuration of the substituents next to the resident C−O bonds in the molecule[49] (Scheme 6.19).



a: MeMgBr, THF, -78 → -10°C (91%)

b: Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, -78°C (98%)

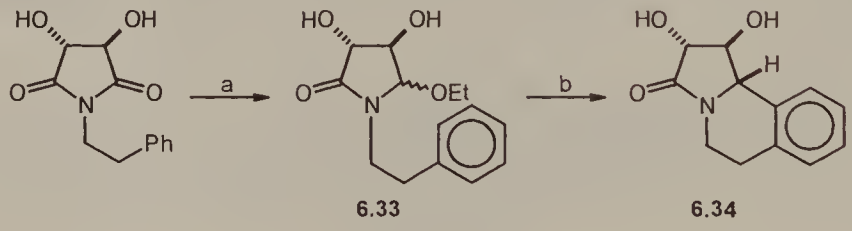
c: AnMgBr, THF, -78°C, then $NaBH_4$, $SmCl_3$, MeOH, -18°C (88%, d.e. 90%)

d: MsCl, NEt_3, CH_2Cl_2, then tBuOK, THF (92%)

Scheme 6.19

Intramolecular acyliminium ion cyclization[50] based on a tartrimide precursor was the pivotal step in several syntheses of bicyclic fused pyrrolidinones.

Cyclization of the acyliminium ion, derived from ethoxy lactam **6.33**, involved the aromatic ring of *N*-phenylethyl substituent. The reaction afforded one diastereomer of isoquinolinopyrrolidinone **6.34**[9] (Scheme 6.20).



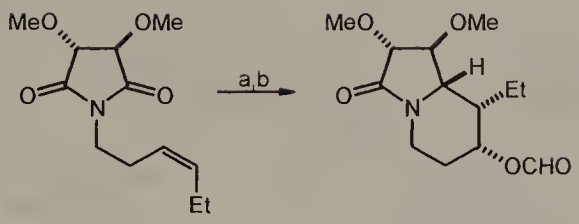
a: $NaBH_4$, EtOH, 0°C, 10 min., then 1N H_2SO_4, RT, 12h

b: HCOOH, Δ then EtOH, AcCl (total yield 55%)

Scheme 6.20

Formic acid induced cyclization of a hydroxylactam, obtained by borohydride reduction of **6.35**, gave exclusively one diastereoisomer of a bicyclic pyrrolidinone **6.36**[51] (Scheme 6.21). Cyclization reactions of other structurally related hydroxylactams were, however, less stereoselective.[20,51]

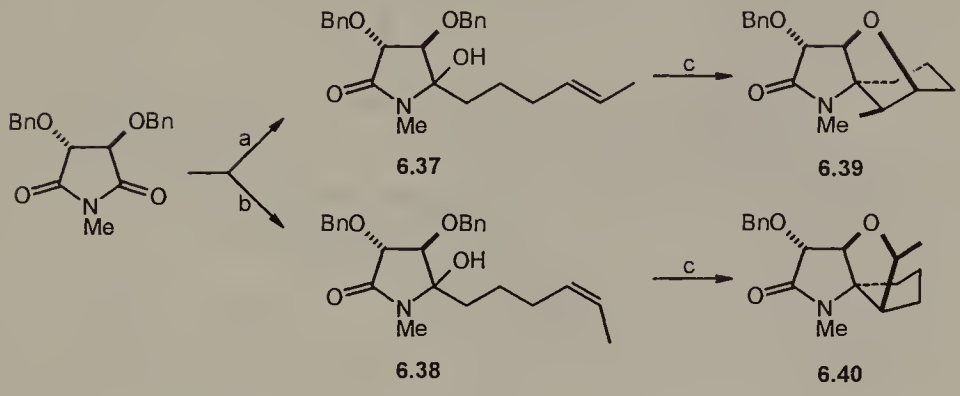
Formic acid induced cyclization and debenzylation of pyrrolidinones **6.37** and **6.38** shows a high degree of stereoselectivity directed by the C=C bond configuration. Two different products, **6.39** and **6.40**, were obtained from (*E*)- and (*Z*)-alkenes **6.37** and **6.38**, respectively (Scheme 6.22).[21]



6.35 **6.36**

a: $NaBH_4$; b: HCOOH, RT, 18h (~100%)

Scheme 6.21



a: (*E*)-$BrMg(CH_2)_3CH{=}CHMe$, Et_2O (70%)

b: (*Z*)-$BrMg(CH_2)_3CH{=}CHMe$, Et_2O (63%)

c: HCOOH, RT (81-100%)

Scheme 6.22

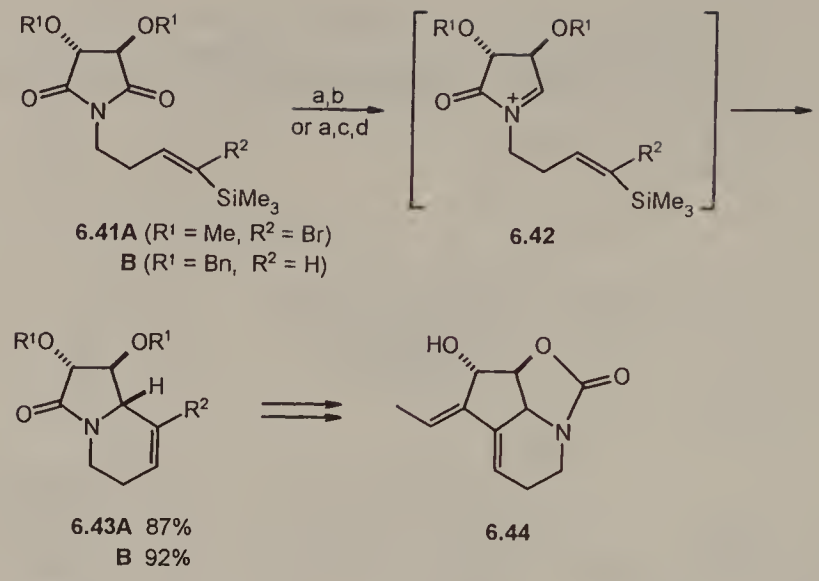
Acyliminium ion-vinylsilane cyclizations of **6.42**, obtained from imides **6.41** by borohydride reduction followed by acid treatment, afforded single bicyclic products **6.43**, which are precursors of the natural antibiotic (+)-streptazolin (**6.44**), Scheme 6.23.[40,52]

A sequence of intramolecular Wittig reaction and *N*-acyliminium ion cyclization was developed by Park for the synthesis of the tetracyclic isoquinoline derivative **6.46** from imide **6.45** (Scheme 6.24).[10]

Cyclization of the *N*-acylimino radical **6.48**, derived from thioether **6.47**, gave bicyclic lactam **6.49** as a mixture of diastereomers. Lactam **6.49** is a precursor of the indolizidine alkaloid (−)-swainsonine (**6.50**), Scheme 6.25.[41]

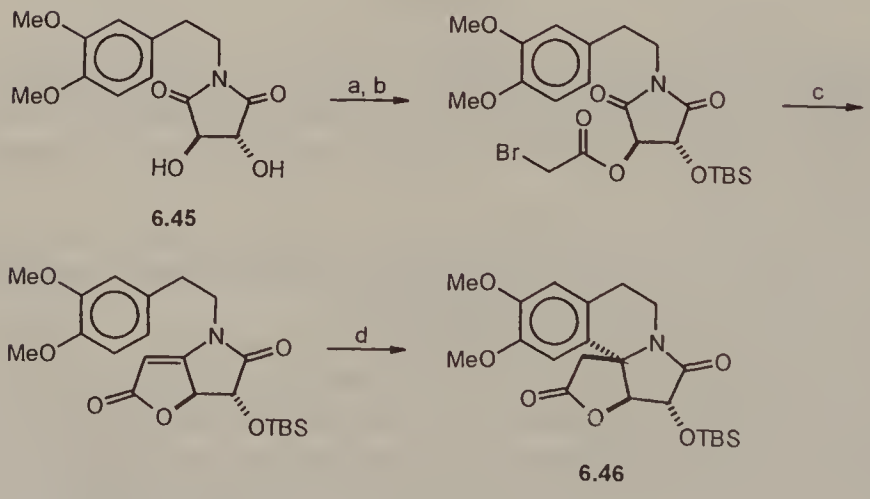
Derivatives of 2,3,4-trihydroxy carboxylic acids are readily available as the products of Grignard reagent addition-sodium borohydride reduction of protected tartrimides. The reduction step is diastereoselective; from L-tartrimides, trihydroxyacids of (2*R*,3*S*,4*R*)-configuration are predominantly obtained.

O,O-Disilyl protected tartrimides in the above mentioned two-reaction sequence give hydroxyamides **6.51**, which can be further converted under acidic conditions to (3*S*,4*R*)-3,4-dihydroxyfuran-2-ones **6.52** (Scheme 6.26).[22,53,54]



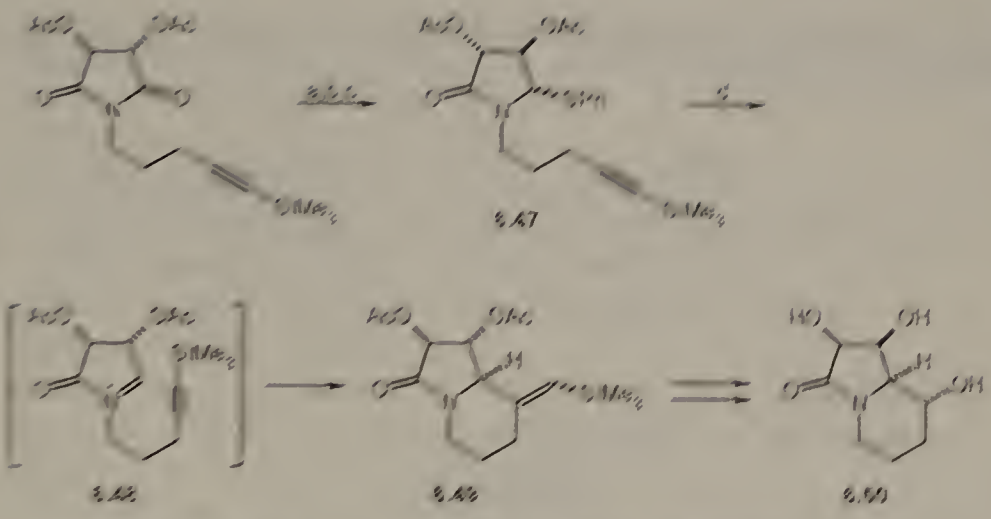
a: $NaBH_4$, MeOH, 0°C, 15 min.
b: CF_3COOH[52]
c: Ac_2O, NEt_3, DMAP, RT, 30 min.
d: $BF_3{\cdot}Et_2O$, CH_2Cl_2, RT[40]

Scheme 6.23

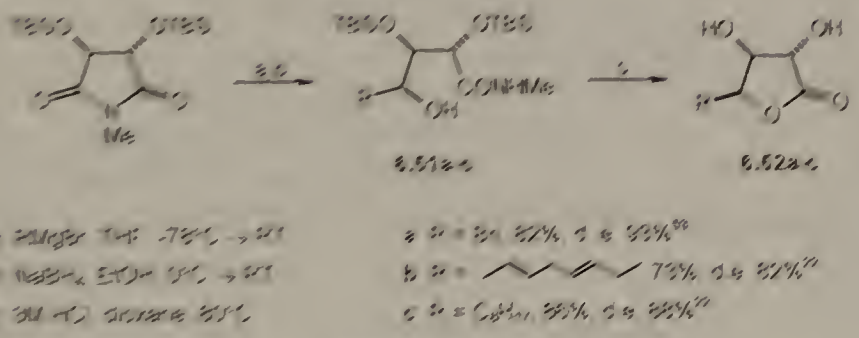


a: 1.1 eq. TBSCl, imidazole, DMF, RT, 16h (68%)
b: $BrCH_2COCl$, pyridine, CH_2Cl_2, 0°C → RT, 0.5h (98%)
c: Ph_3P, MeCN, 50°C, 2h then NEt_3, 50°C, 16h (90%)
d: TsOH, CH_2Cl_2, Δ, 1h (76%)

Scheme 6.24

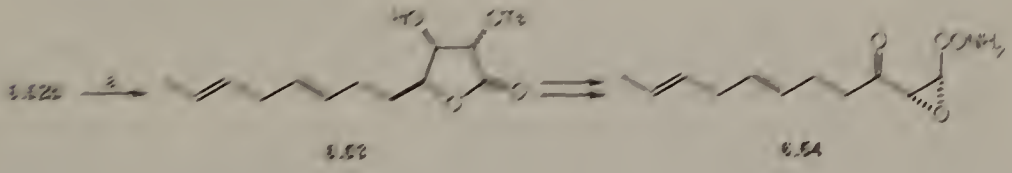


Scheme 6.25



Scheme 6.26

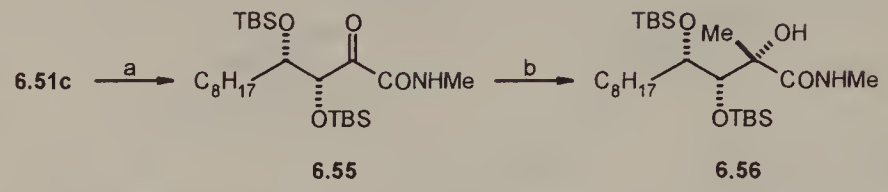
Lactone 6.52b was converted to the natural antifungal antibiotic (+)-cerulenin (6.54) via the regioselectively monosilylated derivative 6.53 (Scheme 6.27).[22]



Scheme 6.27

Hydroxyamide 6.51c underwent PCC oxidation gave α-ketoamide 6.55 as a product of TMS group transfer. Addition of Grignard reagent to 6.55 afforded

the 2,3,4-trihydroxylated carboxylic acid derivative **6.56** with high diastereoselectivity (Scheme 6.28).[55]



6.55 **6.56**

a: PCC, AcONa

b: MeMgBr, THF, -78°C (90%, d.e. 90%)

Scheme 6.28

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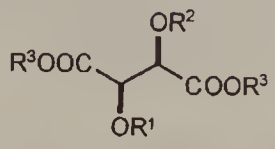
55. Yoda, H.; Kitayama, H.; Takabe, K.; Kakehi, A. *Tetrahedron: Asymmetry* 1993, *4*: 1759.

7 Derivatives of Tartrates with Activated Hydroxy Groups



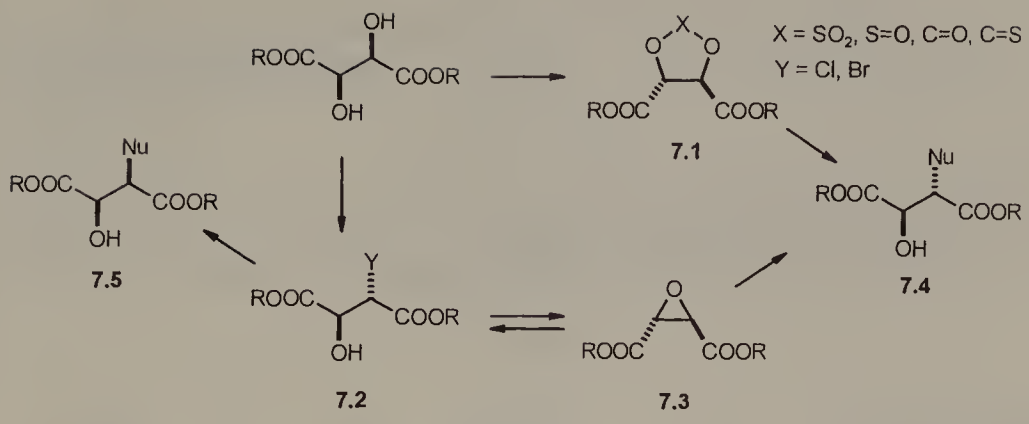
I

Table 7.1 ***O*-Sulfonate, *O,O'*-sulfate, sulfite and thionocarbonate derivatives of L-tartrates (I)**

R^1	R^2	R^3	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
$PhSO_2$	$PhSO_2$	H	193–194	+27.4 (Me_2CO)	1
$PhSO_2$	$PhSO_2$	Et	88–90	+29.3 ($CHCl_3$)	1
Ts	H	Me	86–89	—	2
Ts	Bn	Me	71–72	+55.4 ($CHCl_3$)	3
$-SO_2-$		Me	70–71	−73.0 ($CHCl_3$)	4
$-SO_2-$		Et	75–76	—	4,5
$-SO_2-$		i-Pr	—	−71.4 ($CHCl_3$)	4
$-SO_2-$		Bn	—	−69.0 ($CHCl_3$)	6
−SO−		Me	114–115/1	−164.9 ($CHCl_3$)	7
−SO−		Et	130–135/0.5	−189.0 (EtOH)	8–11
−SO−		i-Pr	120–121/1	−151.0 ($CHCl_3$)	7
−CS−		Me	59–60	−45.0 ($CHCl_3$)	12
−CS−		Et	—	—	13
−CS−		i-Pr	—	—	13

Products of *erythro*-configuration are accessible by substitution of *threo*-configured tartrates in which one or two C−O bonds were activated by suitable derivatization.The main synthetic routes are summarized in Scheme 7.1.

As seen in the scheme, *erythro*-products are available in one inversion step **7.1**→**7.4** by nucleophilic substitution of cyclic sulfates (X = SO_2), sulfites (X = SO), carbonates (X = CO) and thionocarbonates (X = CS), whereas triple inversion is involved in the reaction path through the *erythro*-halohydrin **7.2** and the *trans*-epoxide **7.3**.



Scheme 7.1

Reactivity of the cyclic activated derivatives in nucleophilic substitution reaction generally decreases in this order: cyclic sulfates > cyclic thionocarbonates, carbonates, sulfites > epoxides. Reactions of cyclic sulfates do not require catalysis by Lewis acids; and substitution of both C–O bonds is possible. A review of the reactions of cyclic sulfites and sulfates has been published elsewhere.[14] Synthetic use of *O*-sulfonate derivatives of tartrates for substitution is hampered by their tendency to undergo elimination under basic conditions.

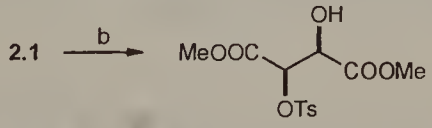
Threo-product **7.5** can be obtained by direct substitution of *erythro*-halohydrins **7.2**. For syntheses of *erythro*-halohydrins from tartrates see also Chapters 4 and 10.

7.1 *O*-MESYL AND *O*-TOSYL DERIVATIVES

Synthesis

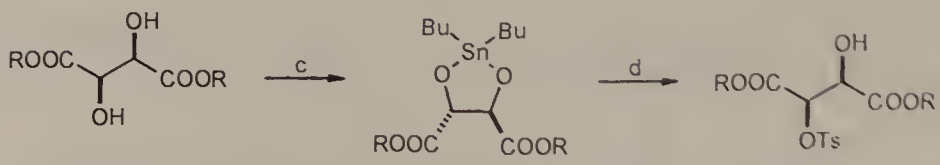
Conventional *O*-sulfonylation procedures give smoothly the corresponding tartrate mesylates or tosylates in good yield. With less then one equivalent amount of sulfonylating agent, monosulfonylation of the diol is possible. However, a much better yield of monosulfonylated diol is obtained when the reaction is carried out with the cyclic stannylene derivative (Scheme 7.2).

a: 2 eq. TsCl, pyridine, DMAP (cat.), CH_2Cl_2, 0°C → RT, 70h (93%)[3]



b: 0.5 eq. TsCl, pyridine, DMAP (cat.), CH_2Cl_2, 0°C → RT, 15h (34%)[2]

Scheme 7.2 (*continued*)



c: 1 eq. n-Bu_2SnO, benzene or toluene, Δ, 95%

d (R = Me): 1 eq. TsCl, $CHCl_3$, RT, 69h (94%)[15]

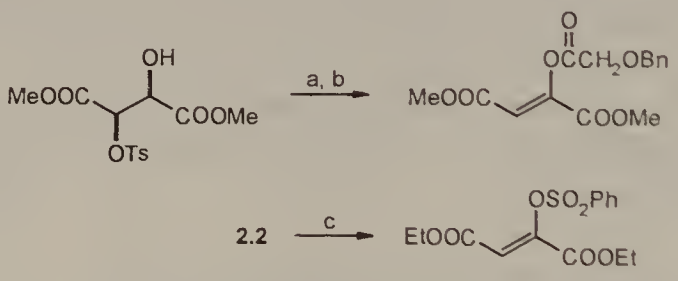
d (R = Et): 1 eq. TsCl, 1 eq. Et_4NCl, MeCN, RT, 24h (91%)[16]

Scheme 7.2

Applications

B

Achiral but synthetically useful hydroxyfumaric acid derivatives are available by a base-induced elimination reaction of a tartrate monotosylate, or directly by sulfonylation of a tartrate at ambient temperature in the presence of pyridine (Scheme 7.3).



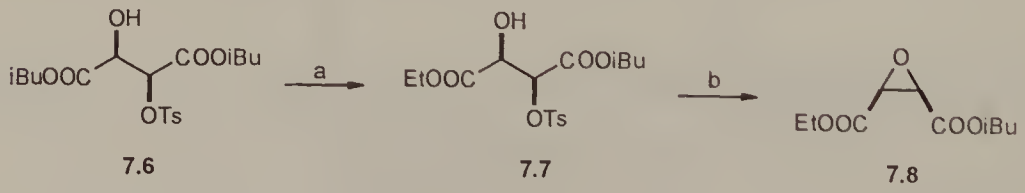
a: $BnOCH_2COCl$, pyridine, DMAP, CH_2Cl_2, 0°C

b: NEt_3, DBU (cat.), THF, RT (55%)[2]

c: 2 eq. $PhSO_2Cl$, pyridine, -5°C → RT (92% crude)[1]

Scheme 7.3

Substitution reactions of the tosylates are shown in Scheme 7.4. The *O*-tosyl derivative of diisobutyl tartrate (**7.6**) undergoes regioselective transesterification at the ester group distal to the tosyl group. The unsymmetrical diester **7.7** can be further converted to the chiral *cis*-epoxide **7.8**.



7.6 **7.7** **7.8**

a: EtOH, TsOH

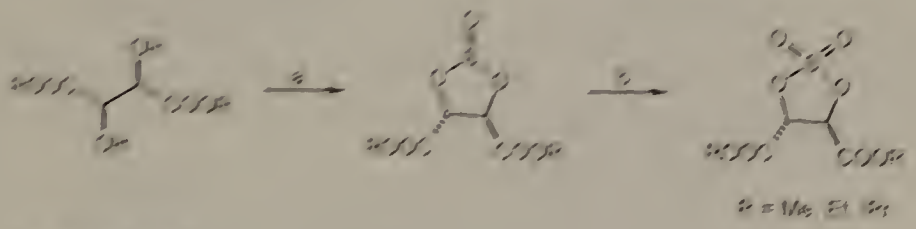
b: t-$BuMe_2SiCl$, imidazole, DMF, RT then n-Bu_4NF, THF (e.e. 94%)[16]

Scheme 7.4

7.2 CYCLIC SULFITES, SULFATES, CARBONATES, AND THIONOCARBONATES

Synthesis

Cyclic sulfites are readily obtained from tartrates by the reaction with thionyl chloride. They can be oxidized by ruthenium dioxide-periodate to the corresponding cyclic sulfates[6] (Scheme 7.5).



R = Me, Et, Pr

a = $SOCl_2$, CCl_4, 0 °C

b = $NaIO_4$, $RuO_2 \cdot nH_2O$ (cat.), CCl_4, MeCN, H_2O, 0 °C → RT (82–96%)

Scheme 7.5

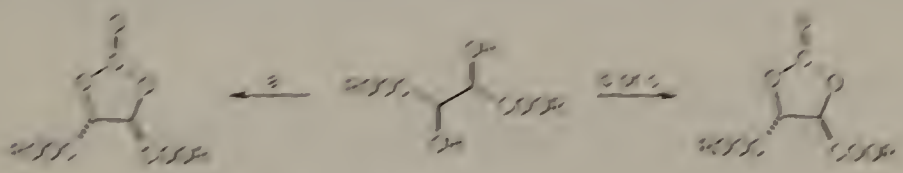
This method is subject of patent applications.[7]

Cyclic sulfites shown in Scheme 7.5 are also available commercially in both enantiomeric forms, as listed below.

(−)-Diethyl L-tartrate cyclic sulfite [117470-50-3] and its enantiomer [127854-46-5]

(−)-Dipropyl L-tartrate cyclic sulfite [117470-22-5] and its enantiomer [127854-45-4]

Cyclic carbonates can be synthesized from tartrates by the reaction with triphosgene and dibenzyl cyclic thionocarbonates are obtained from tartrates by reaction with ester thiocarbonyldiimidazole[4] or with thiophosgene[3] (Scheme 7.6).



a = Cl–C(=O)–Cl, pyridine (CH_2Cl_2, −78 °C → RT)[4]

b (R = Me): $Im_2C{=}S$, THF, RT, 2 h (75%)[4]

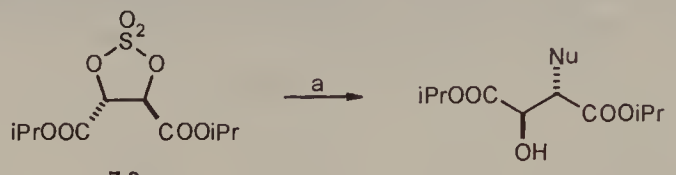
c (R = Et, iPr): Cl–C(=S)–Cl, pyridine, DMAP, CH_2Cl_2 (75%)[3]

Scheme 7.6

Applications

B

The synthesis of malates and various *erythro*-β-substituted malic acid esters is based on nucleophilic substitution reactions of cyclic sulfates[4] and sulfites[7,19] derived from tartaric acid. Products of nucleophilic monosubstitution of the sulfate **7.9** (Gao and Sharpless) are shown in Scheme 7.7.



7.9

a: nucleophile, then 20% H_2SO_4[4]

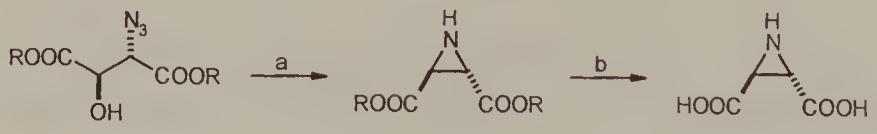
Nu^-	reaction conditions	yield (%)
H^-	$NaBH_3CN$, pH 4-5, THF, 65°C, 5h	55
N_3^-	NaN_3, acetone - H_2O, 0-25°, 1h	81
F^-	$Et_4NF{\cdot}2H_2O$, acetone, 25°C, 6h	90
BzO^-	$BzONH_4$, acetone, 25°C, 12h	95
NO_3^-	Bu_4NNO_3, acetone, 25°C, 12h	96
NCS^-	NH_4SCN, acetone, 25°C, 5h	87
Bn^-	BnMgCl, 0.01 eq. Li_2CuCl_4, THF, -78°C, 2h	73

Scheme 7.7

Azido alcohols **7.10** and **7.12** were utilized, respectively, in the synthesis of aziridinedicarboxylates **7.11** and in the synthesis of the building block **7.13** for penicillanic acid *S*,*S*-dioxide. The fluoride substitution product **7.14** was used in the synthesis of *threo*-3-fluoro-D-aspartic acid (**7.15**), shown in Scheme 7.8.

Mori synthesized wheat grain cerebroside from azidoalcohol *ent*-**7.10** (R = Et).[22] Komori claimed to synthesize a derivative of *erythro*-D-sphingosine from **7.10** (R = Et), but apparently the absolute configuration of either the substrate or the product was erroneous.[5]

A one-pot facile synthesis of D-malate esters from L-tartrate esters via cyclic sulfites has been reported by Gao[23,24] and Koert.[11] The sequence involves nucle-

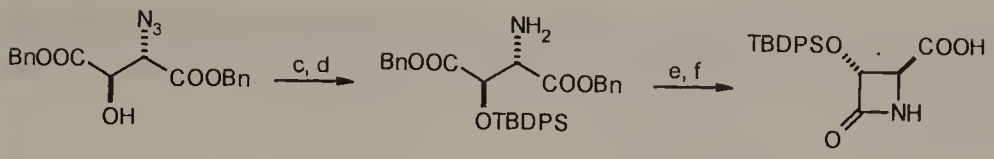


7.10 **7.11** (R = Me, Et, i-Pr)

a: Ph_3P, Δ[7,20]

b (R = Et): LiOH, EtOH, then Dowex 50W-X2 resin[20]

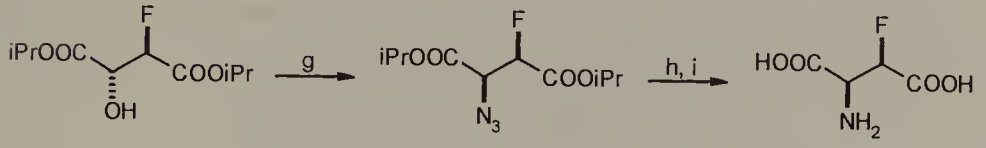
(*continued*)



7.12 **7.13**

c: TBDPSCl, i-Pr_2NEt, DMAP, CH_2Cl_2 e: NEt_3, Me_3SiCl, Et_2O then t-BuMgCl, 0°C

d: Ph_3P, THF, H_2O, 60°C (73%) f: H_2, Pd/C, THF (60%)[6]



7.14 **7.15**

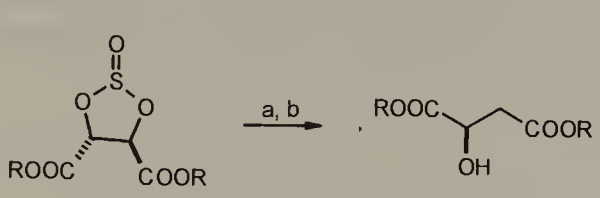
g: Tf_2O, 2,6-lutidine, CH_2Cl_2, -65°C, 5 min., then NaN_3, DMF, -5°C (56%)

h: H_2, Pd/C, EtOH, 4h (quant.)

i: 4N HCl, Δ, 20h (53%)[21]

Scheme 7.8

ophilic substitution with the bromide ion, followed by activated zinc powder reduction or catalytic hydrogenation (Scheme 7.9).



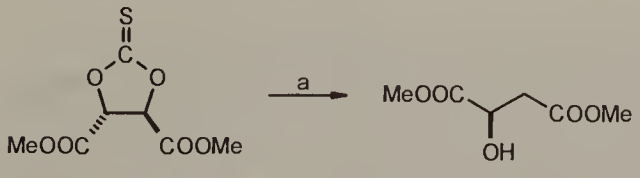
R = Me, Et, i-Pr

a: 1.5 eq. LiBr, acetone, Δ

b: Zn, H_2O, Δ or H_2, Pd/C, MgO, H_2O, RT (70-82%)

Scheme 7.9

Dimethyl D-malate is also available through the tri-*n*-butyltin hydride reduction of cyclic thionocarbonate derivative **7.16**[12] (Scheme 7.10).



7.16

a: *n*-Bu_3SnH, Δ (88%)

Scheme 7.10

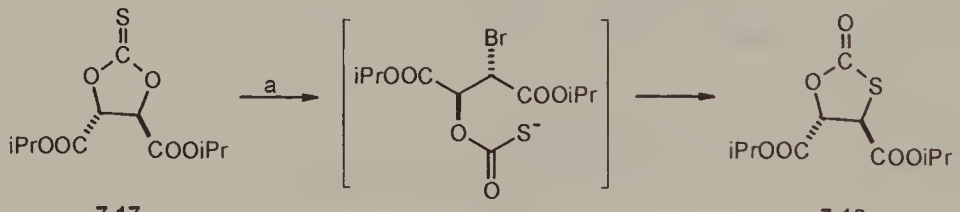
Products of the *erythro* configuration are available by nucleophilic substitution of cyclic carbonates and thionocarbonates derived from tartrates[25] (Scheme 7.11).

X	R	Nu^-	reaction conditions	yield (%)
O	Et	PhS^-	PhSH, NEt_3, THF, 0°C, 0.5h	95
O	Et	I^-	LiI, DMF, 25°C, 2h	85[a]
O	Et	N_3^-	NaN_3, DMF, 25°C, 4h	88
S	i-Pr	PhS^-	PhS, NEt_3, THF, O°C, 1h	100
S	i-Pr	BzO^-	BzOH, NEt_3, DMF, RT, 24h	59
S	i-Pr	N_3^-	NaN_3, PPTS, DMF, O°C, 1h	84

[a] 1:1 mixture of epimers

Scheme 7.11

The nucleophilic character of the thiolcarbonate anions formed in the initial substitution step of a cyclic thionocarbonate (**7.17**) with bromide ions makes it possible to obtain doubly inverted (net retention of configuration) thiolcarbonate product **7.18** by intramolecular substitution[13] (Scheme 7.12).

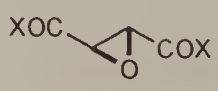


7.17 **7.18**

a: 0.1 eq. Bu_4NBr, THF, RT, 1h (98%)

Scheme 7.12

7.3 *TRANS*-EPOXIDES AND *ERYTHRO*-HALOHYDRINS



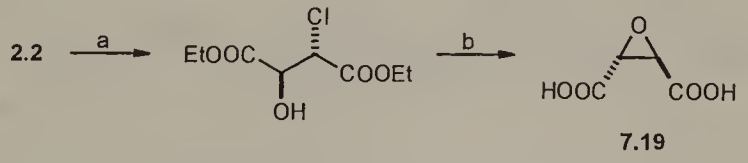
II

Table 7.2 Derivatives of (2*R*,3*R*)-2,3-epoxysuccinic acid (II)

X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
HO	178–180	−121.6 (EtOH)	26–28
MeO	74–75	−125.0 (EtOH)	29
EtO	80–82/0.2	−110.0 (EtOH)	29–33
t-BuO	—	−107.3 (Et2O)	34
n-$C_8H_{17}O$	120–140/0.05	−58.0 (MeOH)	29
n-$C_{12}H_{25}O$	43–44	−27.0 (dioxane)	29
AllO	78–85/0.1	−102.0 (EtOH)	29
$HC{\equiv}CCH_2O$	70–71	−123.0 (EtOH)	29
BnO	190–194/0.1	−66.0 (EtOH)	29
PhO	100–102	−144.0 (EtOH)	29
C_6Cl_5O	206–207	−68.0 ($CHCl_3$)	29
H_2N	208–209	−68.0 (H2O)	29
MeHN	238–242	−92.0 (EtOH)	29
AllHN	209–210	−93.0 (pyridine)	29
$HO(CH_2)_2HN$	156–160	—	29
BnHN	177–178	−71.0 (pyridine)	29
PhHN	221–224	—	29
H_2NHN	138	−97.0 (EtOH)	29
Cl	42–45	—	29

Synthesis

(2*R*,3*R*)-(−)-2,3-Epoxysuccinic acid (**7.19**) has been prepared by Kuhn[26,35] from diethyl L-tartrate. The synthesis involved double nucleophilic inversion at C-2 (Scheme 7.13).



7.19

a: 1 eq. $SOCl_2$, 1 eq. pyridine, $CHCl_3$, Δ

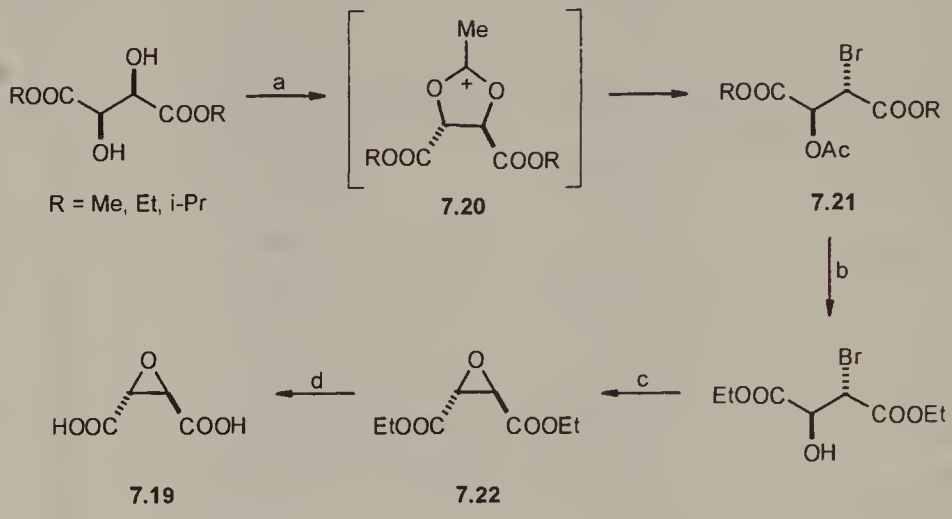
b: conc. HCl, then 1M NaOH[35]

Scheme 7.13

(2*S*,3*S*)-(+)-2,3-Epoxysuccinic acid (*ent*-**7.19**) has been obtained by resolution of the racemate with various optically active amines. Good results were obtained with L-arginine (yield 55%),[28] or with (−)-ephedrine (yield 48%).[27]

A reliable method of synthesis of diethyl *trans*-2,3-epoxysuccinate (**7.22**) by Mori is based on the formation of the intermediate *erythro*-*O*-acetylbromohydrin derivative **7.21**, resulting from the substitution of the acyloxyoxonium ion **7.20**

by the bromide ion (Scheme 7.14).[16,30-33,36,37] The acid **7.19** can be obtained from the diester **7.22** by alkaline hydrolysis.[38]



a: 30-33% HBr/AcOH, RT

b (R = Et): EtOH, HBr or HCl, Δ

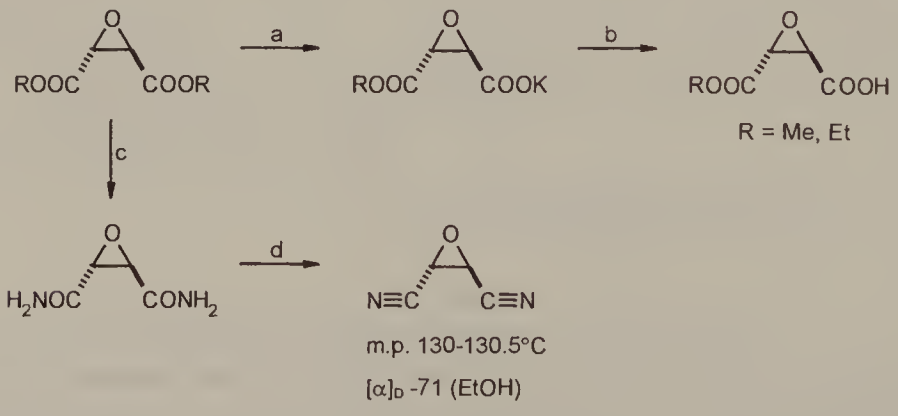
c: NEt_3 or EtONa, EtOH, RT, 1h (overall yield a-c 61-68%)[37]

d: 0.2M KOH, 0°C → RT, 3h (93%)

Scheme 7.14

Alternative synthesis of (2*R*,3*R*)-epoxysuccinic acid is by fermentation of D-glucose with *Aspergillus fumigatus*.[29]

Diesters of **7.19** can be selectively hydrolyzed to the corresponding monoesters[31,39] (Scheme 7.15).



a: 1 eq. KOH/EtOH, 0°C, 2h

b: $KHSO_4$ (61-69%)

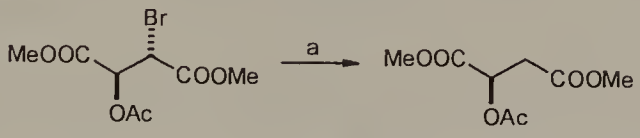
c (R = Me): 29% NH_4OH, RT, 10-15 min. (97%)[29]

d: $POCl_3$, 80-100°C, 30 min. (49%)[29]

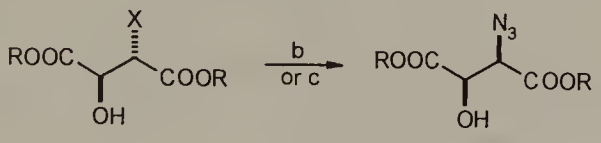
Scheme 7.15

Applications

Erythro-halohydrins (**7.2**) and *trans*-epoxides (**7.3**) derived from tartrates are pivotal compounds in the synthesis of *threo* (**7.5**) and *erythro* substituted (**7.4**) malates (Scheme 7.1). Thus, (*R*)-malates as well as their *threo*-β-substitution products are available from *erythro*-halohydrin **7.2** in nucleophilic or radical substitution reactions. It should be noted, however, that in contrast to intramolecular epoxide-formation reaction, diastereoselectivity of such reactions is not very high (Scheme 7.16).



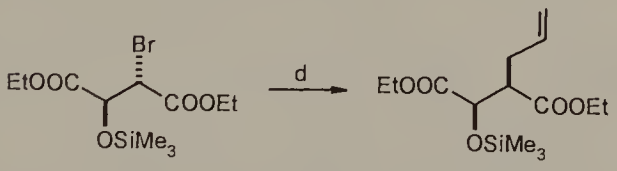
a: 1 eq. $NaBH_4$, 0.02 eq. Me_3SnCl, 0.008 eq. AIBN, EtOH, 10°C[36]



(d.e. 64-66%)

b (R = Me, X = Cl): HN_3· i-Pr_2NEt, DMF, RT (95%)[40]

c (R = Et, X = Br): NaN_3, 15-crown-5 (cat.), DMF, RT (90%)[41]



(d.e. 79%)

d: n-$Bu_3SnCH_2CH{=}CH_2$, AIBN, Eu(fod)$_3$, CH_2Cl_2, hν[42]

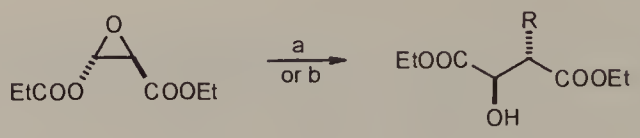
Scheme 7.16

(2*R*,3*R*)-2,3-Epoxysuccinates can be converted in quantitative yield to (*R*)-malates by catalytic hydrogenation.[43]

(2*R*,3*R*)-2,3-Epoxysuccinates were used for stereoselective alkylation to give *erythro*-β-alkylated malic acid derivatives (Scheme 7.17).

Product **7.23** is an important intermediate in the synthesis of (−)-δ-multistratin,[30] (+)-phyllantocin,[44] tetraene fragment of calyculins,[45] and an isomer of serricornin.[46]

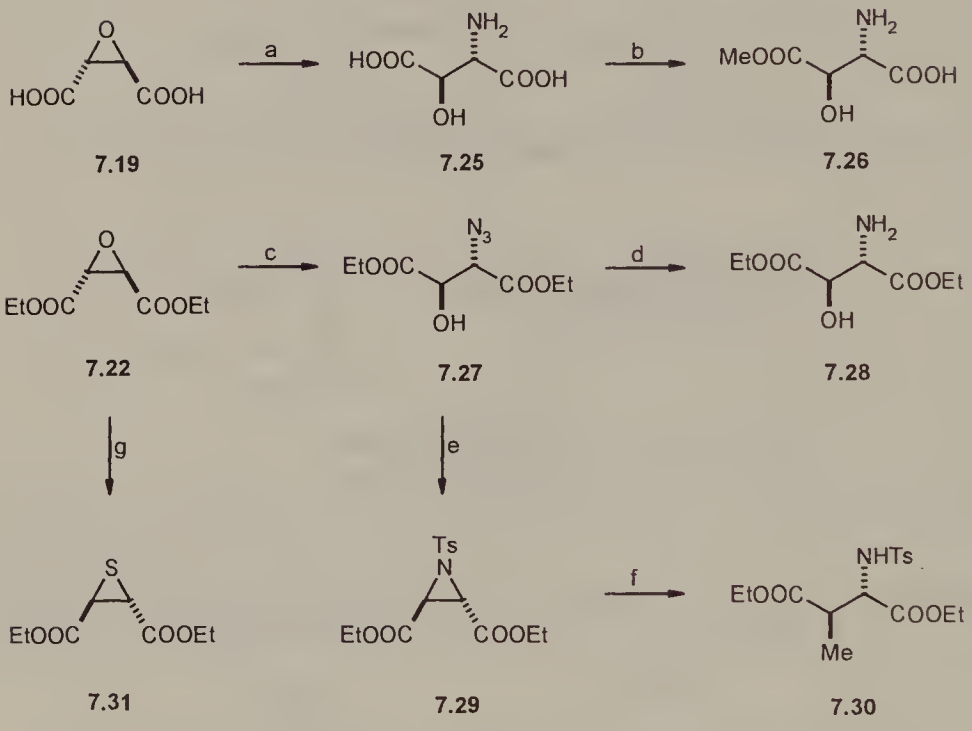
Addition of nitrogen nucleophiles to (2*R*,3*R*)-2,3-epoxysuccinic acid and its esters gives access to *erythro*-β-hydroxy L-aspartic acid derivatives **7.25**, **7.26** and **7.28** (Scheme 7.18).



7.23 (R = Me)
7.24 (R = i-Pr)

a (R = Me): $LiMe_2Cu$, ether, -78°C → 20°C[30,44]
b (R = i-Pr): i-PrMgBr, CuCN, ether, -20°C, 60%[32]

Scheme 7.17



a: NH_4OH, 110°-130°C (42%)[38,47] or NH_4OH, ca 45°C (82-94%)[29,48] or $BnNH_2$, Δ, then 5% Pd/C (42%)[27]

b: MeOH, HCl, Δ, then pyridine (73%)[48] or isolated as hydrochloride (99%)[38]

c: $TMSN_3$, MeOH, DMF, 60°C, 10-12h (86-97%)[37,41,49]

d: H_2, 10% Pd/C, AcOEt, RT, 6h (92-98%)[49]

e: PPh_3, benzene, Δ, then TsCl, pyridine (73%)[51]

f: 2 eq. Me_2CuLi, Et_2O, -78°C (68%)[50]

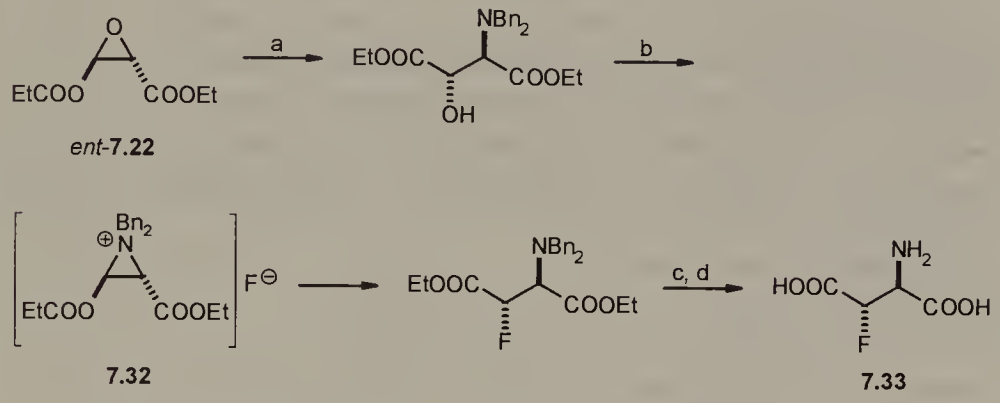
g: Ph_3PS, 1 eq, CF_3COOH, CH_2Cl_2, Δ then $NaHCO_3$ (48%)[51]

Scheme 7.18

Interestingly, acid-catalyzed esterification of **7.25** is selective, providing monoester **7.26**. Amino acid **7.26** was used in the synthesis of chiral 2-azetidinones.[38,48]

Chiral aziridine **7.29**, obtained in the intramolecular Mitsunobu reaction, was used by Tanner[50] for the synthesis of β-alkyl aspartic acid derivatives, such as **7.30**. Note also the facile synthesis of the chiral thiirane **7.31** from **7.22** by double substitution reaction with a sulphur nucleophile.[51]

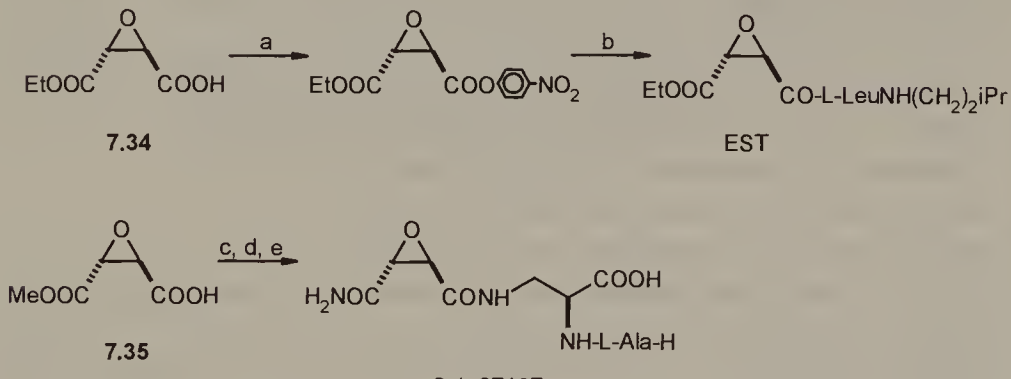
Erythro-3-Fluoro-D-aspartic acid **7.33** was synthesized from epoxyester *ent*-**7.22** using the DAST reaction for introducing the fluorine atom with retention of configuration, via the intermediate aziridinium ion **7.32** (Scheme 7.19).



a: Bn_2NH, $LiBF_4$, MeCN, Δ, 72h (62%)
b: Et_2NSF_3, THF, RT, 2h (94%)
c: H_2, Pd/C, EtOH, 4h (quant.)
d: 2N HCl, Δ, 48h (40%)[21]

Scheme 7.19

(2*R*,3*R*)-2,3-Epoxysuccinyl aminoacids[28] and dipeptides[31,39] were synthesized from monoesters **7.34** and **7.35** (Scheme 7.20).



a: 4-$O_2NC_2H_4OH$, DCC[28]
b: H-L-LeuNH$(CH_2)_2$i-Pr[28]
c: $H_2NCH_2CH(COOH)$NH-L-Ala-Cbz, DCC, NEt_3, BSA, THF (32%)[39]
d: NH_3, MeOH (73%)[39]
e: 10% Pd/C, 1,4-cyclohexadiene, MeOH (96%)[39]

Scheme 7.20

EST is a potential therapeutic agent for muscular dystrophy and Sch 37137 is known for its antifungal activity.

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8 Tartrate Borates and Boronates

8.1 TARTRATE AND TARTRAMIDE MODIFIED BORATES

Boric acid and tartrates in solution form borotartrate complexes, with stoichiometry and structure dependent on pH and the solvent used. The stoichiometry of the complexes has been suggested to be two boric acids per tartrate,[1] one tartrate to one boric acid molecule,[2,3] and one boric acid per two borates.[4–7] The dominant complex appears to be of 1:1 stoichiometry.[8] Lamandé *et al.* postulated the formation of a dimeric 1:1 complex of pKa 1.8 in dimethylformamide solution.[9] Typical structures of borotartrate complexes are shown in Fig. 8.1.

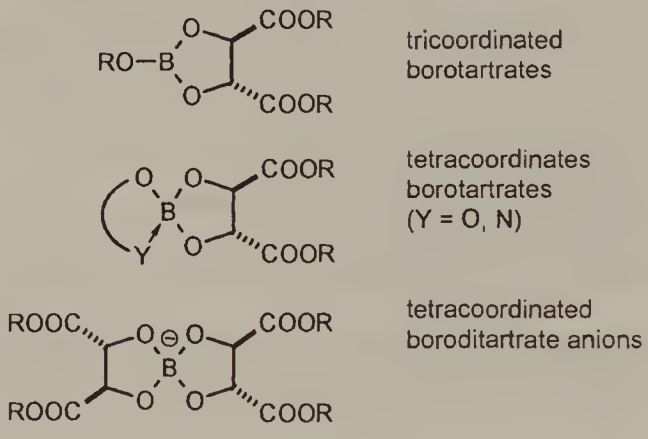
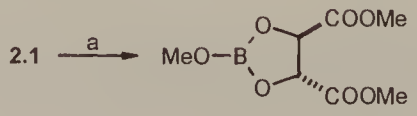


Figure 8.1

Synthesis

Cyclic borotartrates can be synthesized from tartrates and trialkyl borates by transesterification (Scheme 8.1).

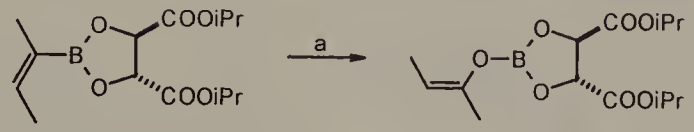


oil, $[\alpha]_D$ -34 (CH_2Cl_2)

a: $B(OMe)_3$, benzene, Δ^{10}

Scheme 8.1

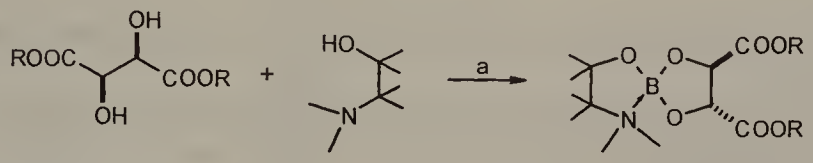
Enol borates can be obtained from boronates by oxidation with amine *N*-oxide[11,12] (Scheme 8.2).



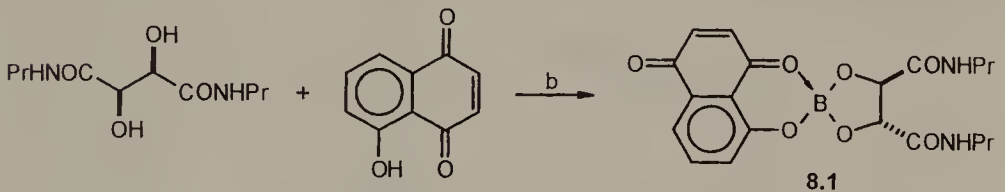
a: 1 eq. Me_3NO, CH_2Cl_2, RT[12]

Scheme 8.2

Stable tetracoordinated borotartrate or borotartramide complexes are formed from tartrates or tartramides and aminoalcohols or hydroxyketones (Scheme 8.3).



a: H_3BO_3, solvent

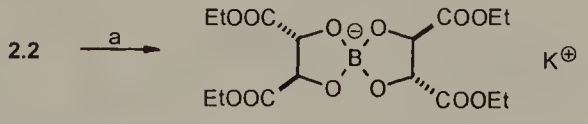


8.1

b: $B(OMe)_3$, CH_2Cl_2, Δ (removal of methanol)[13]

Scheme 8.3

In the presence of a base, salts of tetracoordinated boric acid are obtained from tartrates (Scheme 8.4).



a: $KHCO_3$, H_3BO_3, H_2O[14]

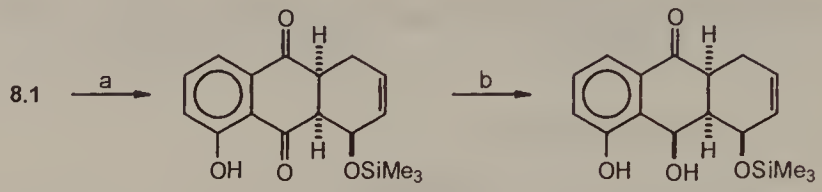
Scheme 8.4

Applications

Enantiomers of aminoalcohols can be partially separated due to the difference in distribution in a two-phase system consisting of a chloroform solution of a tartrate and an aqueous solution of boric acid.[15]

Borotartramide complexes can act as chiral Lewis acid promoters in a Diels–Alder reaction.[13,16] For example, the borotartramide complex of juglone

(**8.1**) undergoes an enantioselective Diels–Alder reaction with a siloxydiene to yield, after sodium borohydride reduction, chiral anthracycline intermediate **8.2** (Scheme 8.5).



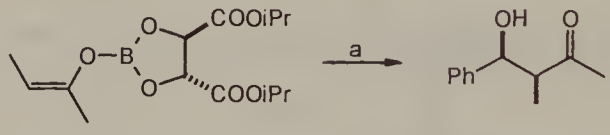
8.2 (e.e. 84%)

a: CH_2=CH-CH=CHOSiMe$_3$, CH_2Cl_2, RT, 23h (90%) b: $NaBH_4$, THF[13]

Scheme 8.5

For related applications of acyloxyboranes in a Diels–Alder reaction, see Section 4.5.

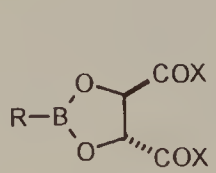
The aldol reaction of tartrate-modified enol borates with aldehydes has been reported by Umani-Ronchi to give *syn*-ketols with moderate enantioselectivity[11,12] (Scheme 8.6).



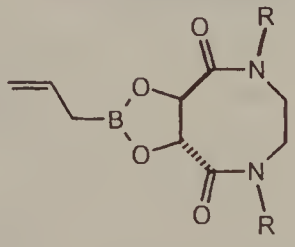
a: PhCHO, CH_2Cl_2, -78°→ -50°C, 14h, 75%, e.e. 65%

Scheme 8.6

8.2 TARTRATE AND TARTRAMIDE MODIFIED BORONATES



I



II

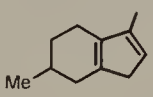
Table 8.1 Esters of boronic acids derived from tartrates and tartramides (2-substituted 1,3,2-dioxaborolane-4,5-dicarboxylic esters and amides), I and II

No.	R	X	m.p. (°C) or b.p.(°C/torr)	$[\alpha]_D$ (solvent)	References
			Formula I		
8.3	n-Bu	OEt	—	—	18
8.4	n-Bu	NMe_2	—	—	21,22

(*continued*)

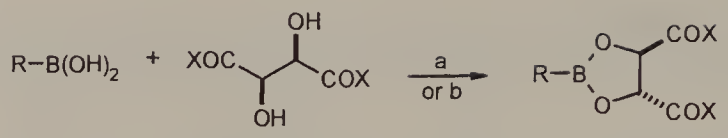
Table 8.1 (*continued*)

No.	R	X	m.p. (°C) or b.p.(°C/torr)	$[\alpha]_D$ (solvent)	References
8.5	CH_2=$CHCH_2$	OEt	90–180/0.07–1.1	—	23
8.6	CH_2=$CHCH_2$	Oi-Pr	115–120/0.15	−47.9 (CH_2Cl_2)	24
8.7	CH_2=$C(Br)CH_2$	$OCHi\text{-}Pr_2$	—	—	25
8.8	(*E*)-MeCH=$CHCH_2$	Oi-Pr	—	—	26
8.9	(*Z*)-MeCH=$CHCH_2$	Oi-Pr	—	—	26
8.10	n-BuMeC=$CHCH_2$	Oi-Pr	—	—	27
8.11	$Cl(CH_2)_2CH$=$CHCH_2$	$OCHi\text{-}Pr_2$	—	—	28
8.12	$PhMe_2SiCH$=$CHCH_2$	Oi-Pr	—	—	29
8.13	$CyOMe_2SiCH$=$CHCH_2$	Oi-Pr	—	—	29
8.14	$MfSiMe_2CH$=$CHCH_2$[a]	Oi-Pr	—	—	30
8.15	Me_2C=$CHCH_2$	Oi-Pr	—	—	31
8.16	CH_2=CH–C(=CH_2)CH_2	Oi-Pr	—	—	32
8.17	CH_2=C=CH–CH_2	Oi-Pr	—	—	33
8.18	CH_2=C=CH–CH_2	$OCHi\text{-}Pr_2$	—	—	33
8.19	CH_2=CH	OEt	80/0.05	−44.0 (dioxane)	17
8.20	CH_2=CMe	OEt	115–120/0.2	−33.4 ($CHCl_3$)	11
8.21	(*E*)-MeCH=CMe	Oi-Pr	—	—	12
8.22	(*Z*)-MeCH=CMe	Oi-Pr	140–145/0.2	—	12
8.23	n-BuCH=CH	Oi-Pr	—	—	34
8.24	n-BuCH=CH	NMe_2	—	—	34
8.25	BnCH=CH	Oi-Pr	—	—	34
8.26	BnCH=CH	NMe_2	—	—	34
8.27	PhCH=CH	Oi-Pr	—	—	34
8.28	PhCH=CH	NMe_2	—	—	34
8.29	CH_2=C=CH	OEt	—	—	35
8.30	CH_2=C=CH	Oi-Pr	—	—	35
8.31	CH_2=C=CH	$OCHi\text{-}Pr_2$	—	—	36
8.32	Ph	OEt	46–48	—	37
8.33	4-CH_2=CHC_6H_4	OEt	58–59	—	38
		Formula II			
8.34	Bn	—	—	—	19
8.35	$CyCH_2$	—	—	—	39
8.36	CF_3CH_2	—	—	—	39

[a] Mf = 

Synthesis

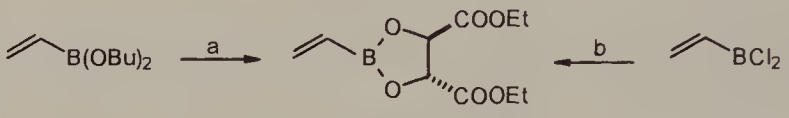
Cyclic esters of boronic acids can be obtained in good to high yield by azeotropic removal of water from a mixture of boronic acid and tartrate diol (Scheme 8.7).



a: benzene or $ClCH_2CH_2Cl$, Δ b: Et_2O, $MgSO_4$ or molecular sieves 4Å

Scheme 8.7

Transesterification of boronates with tartrates is another useful method of preparation of tartrate-modified boronic esters (Scheme 8.8). Dichloroboranes react with tartrates in the presence of a proton acceptor such as poly(4-vinylpyridine) to give cyclic esters of boronic acids.



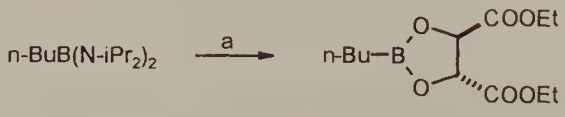
8.19

a: 1 eq. **2.2**, n-hexane, Δ (removal of n-BuOH), 66%[17]

b: 1 eq. **2.2**, poly(4-vinylpyridine), phenothiazine (cat.), CH_2Cl_2, 45%[17]

Scheme 8.8

Excellent yields of boronate esters are usually obtained in the reaction of bis(diisopropylamino)borane with tartrates (Scheme 8.9).

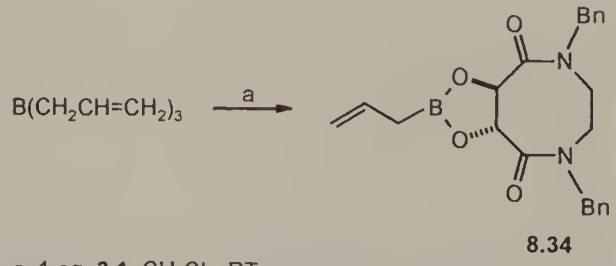


8.3

a: 1eq. **2.2**, 50°C, 20 torr, 95% (crude)[18]

Scheme 8.9

Allyl boronates are also obtained in the reaction of a tartrate diol with triallylborane[19] (Scheme 8.10).

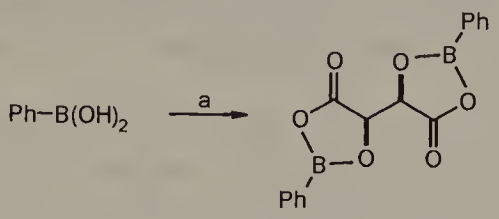


8.34

a: 1 eq. **3.1**, CH_2Cl_2, RT

Scheme 8.10

Phenylboronic acid reacts with tartaric acid to give a bis-boronate derivative (Scheme 8.11).



a: 0.5 eq. **1.1**, benzene, Δ (removal of water)[20]

Scheme 8.11

Applications

Cyclic esters of tartrates with boronic acids have found uses as chiral auxiliaries in several important synthetic procedures, such as allylboration of aldehydes, and cyclopropanation of olefins. Absolute configuration of products of such reactions is dictated by configuration of the tartrate auxiliary. Structural features of tartaroboronates which are of significance to these reactions are shown in Fig. 8.2.

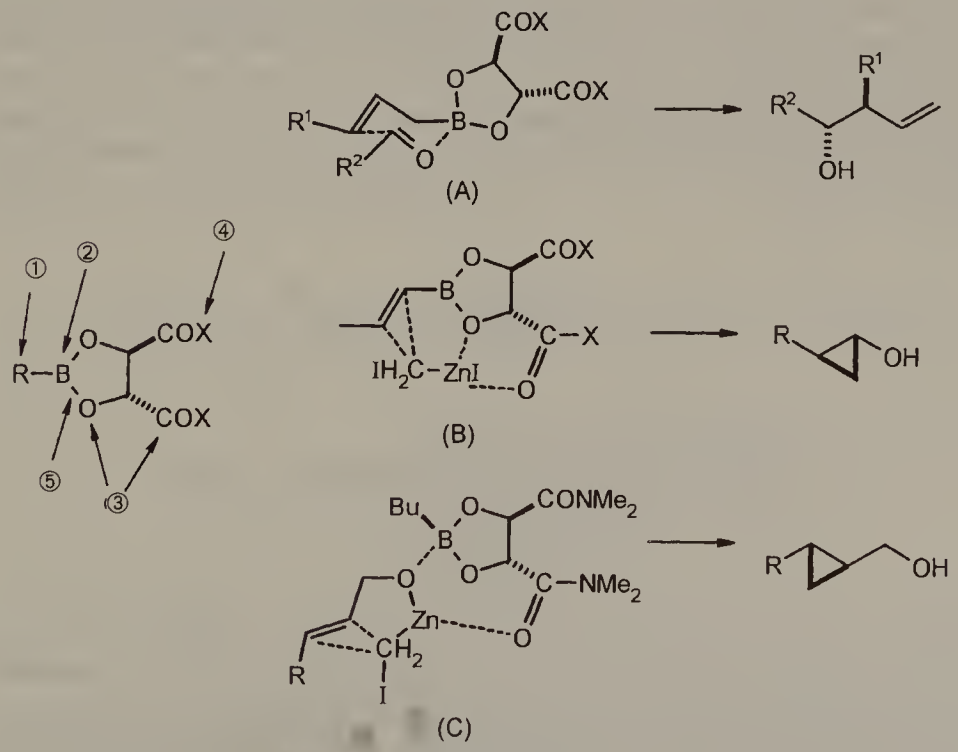


Figure 8.2

① Allyl or alkenyl groups undergo addition to aldehydes (see ②) or cyclopropanation (see ③).

② The boron atom (a Lewis acid) can coordinate an electron donor atom (nitrogen of the amine, oxygen of the carbonyl group, or the alkoxide anion). Fig. 8.2A shows a transition state in the allylboration of an aldehyde, coordinated to the boron atom.

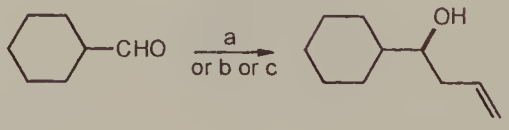
③ The basic oxygen atoms of the tartrate moiety can chelate organometallic species, such as the Simmon–Smith reagent ($IZnCH_2I$), thus directing diastereoselectivity in the cyclopropanation reaction of 1-alkenyl boronates (Fig. 8.2B). In the Charette catalytic cyclopropanation reaction of allylic alcohols, the boron atom additionally coordinates the intermediate zinc alkoxide species and the sterical outcome of the reaction follows from Fig. 8.2C.

④ The bulk of the X group has some effect on the enantioselectivity of reactions, but for practical reasons the isopropoxy or dimethylamino derivatives are most frequently used.

⑤ Boron–oxygen bonds hydrolyze rapidly under hydrolytic conditions (wet solvents, etc.). However, the reagents at low temperatures (−20°C) are stable for several months in the absence of moisture. As they are usually prepared *in situ*, many boronate esters have not been isolated nor characterized.

A

Allylboration of aldehydes. Tartrate modified allylboronates were developed by Roush[40] as chiral reagents for asymmetric synthesis of homoallylic alcohols by allylboration of aldehydes (Fig. 8.2A and Scheme 8.12). Allylboronates **8.34** and **8.36** modified with the conformationally rigid cyclic tartramide auxiliary display higher enantioselectivity than ordinary tartrate derivatives I (R = All), also in reactions with achiral aldehydes. The limiting factor is low solubility of **8.34** in toluene at –78°C.[19,39]



a: **8.6**, PhMe, -78°C, 72%, e.e. 87%[24,41]

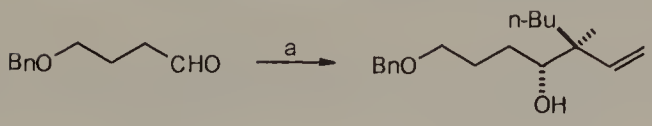
b: **8.34**, PhMe, molecular sieves 4Å, -78°C, 40%, e.e. 97%[19,39]

c: **8.36**, THF, molecular sieves 4Å, -78°C, 91%, e.e. 94%[19,39]

Scheme 8.12

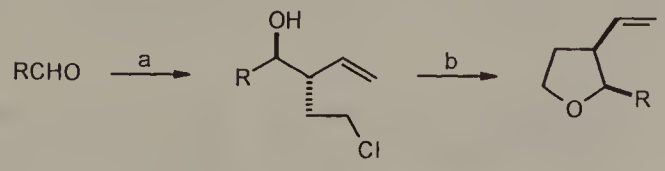
Hara demonstrated the usefulness of allylboronates for the stereoselective generation of a chiral quaternary carbon atom[27] (Scheme 8.13).

Brown synthesized enantiomerically pure α,β-disubstituted tetrahydrofurans with use of the allylboration reaction[28] (Scheme 8.14).



a: **8.10**, PhMe, molecular sieves 4Å, -78°C, 56%, d.e. 94%, e.e. 85%

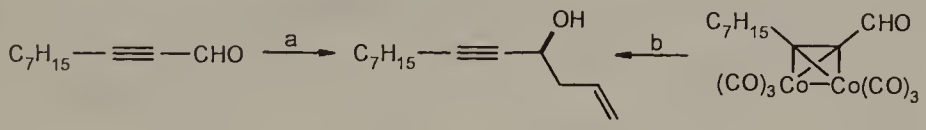
Scheme 8.13



a: **8.11** (70-85%, e.e. 91-96%) b: NaH

Scheme 8.14

α,β-Unsaturated aldehydes react with boronates with lower stereoselectivities but this problem can be circumvented by the use metal carbonyl complexes, as shown in Scheme 8.15.

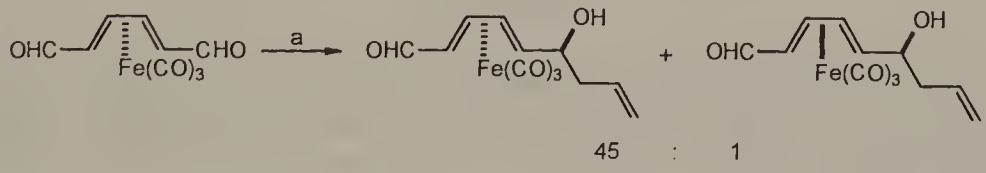


a: **8.6**, PhMe, molecular sieves 4Å, -78°C, e.e. 72%

b: as a, then $Fe(NO_3)_3$, EtOH, RT, 90%, e.e. 92%[42]

Scheme 8.15

Allylboration of a *meso* iron-dienedialdehyde complex proceeds with high group and face selectivity (Scheme 8.16).

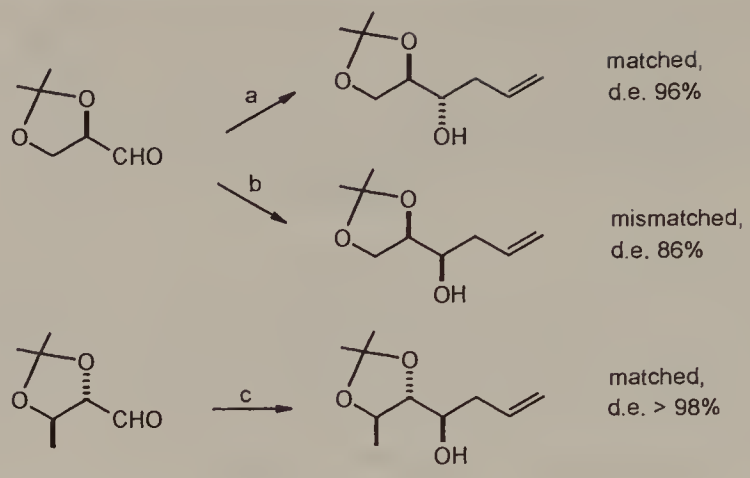


a: 0.95 eq. **8.6**, PhMe, molecular sieves 4Å, -78°C, 82%, e.e. 98% (major isomer)[43]

Scheme 8.16

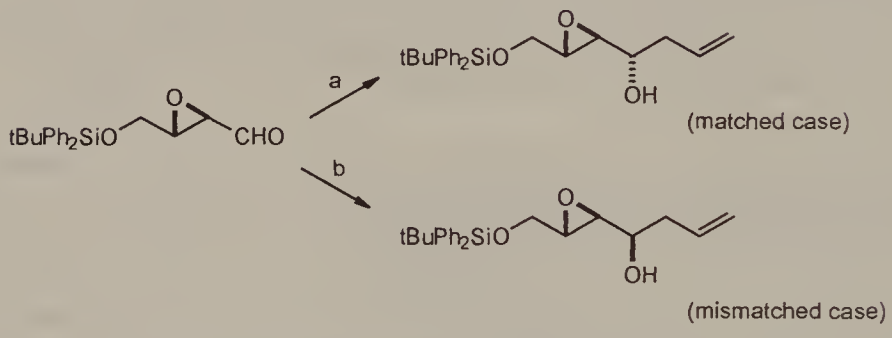
With chiral aldehydes the double diastereoselection principle is operative and in the matched cases high diastereoselectivity can be achieved[24,44–46] (Scheme 8.17).

Asymmetric allylboration of 2,3-epoxy aldehydes with matched double diastereoselection is the key step in the synthesis of 2-deoxyhexoses[23] (Scheme 8.18).



a: **8.6**, PhMe, molecular sieves 4Å, -78°C
b: *ent*-**8.6**, PhMe, molecular sieves 4Å, -78°C
c: ent-**8.5**, CH_2Cl_2, molecular sieves 4Å, -78°C

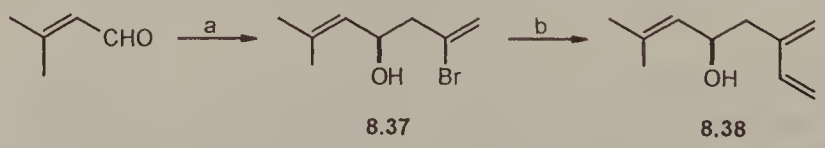
Scheme 8.17



a: **8.5**, benzene, molecular sieves 4Å, -78°C, d.e. 94%, e.e. > 96%
b: *ent*-**8.5**, benzene, molecular sieves 4Å, -78°C, d.e. 54%, e.e. > 97%

Scheme 8.18

Chiral 2-bromohomoallylic alcohols can be obtained from aldehydes by the action of tartrate modified (2-bromoallyl)boronic acid.[25] The product of such a reaction (**8.37**) was used by Hara for the synthesis of (−)-ipsdienol **8.38**[47] (Scheme 8.19).

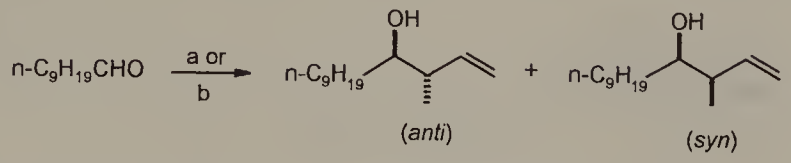


8.37 **8.38**

a: *ent*-**8.7**, PhMe, molecular sieves 4Å, -78°C, (98%, e.e. 88%)
b: CH_2=CHMgBr, $Pd(PPh_3)_4$, THF, 0°C (84%, e.e. 87%)[47]

Scheme 8.19

(*E*)- and (*Z*)-crotylboronates, which are propionate enolate equivalents, react diastereoselectively with aldehydes to give *anti* and *syn* products, respectively[26] (Scheme 8.20).



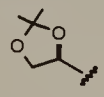
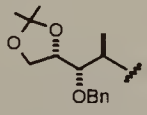
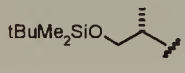
a: **8.8**, PhMe, molecular sieves 4Å, -78°C, 90%, d.e. > 98% *anti*, e.e. 88%

b: **8.9**, PhMe, molecular sieves 4Å, -78°C, 80%, d.e. 98% *syn*, e.e. 82%

Scheme 8.20

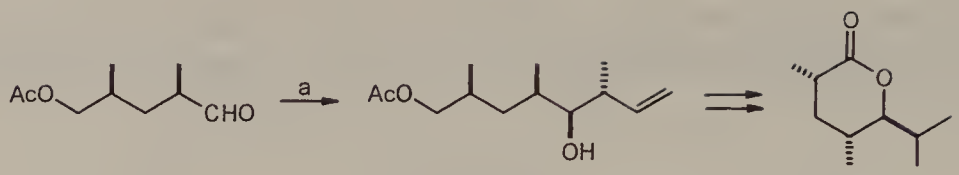
Diastereoselectivity of the reaction of (*E*)- and (*Z*)-crotylboronates with chiral aldehydes is detailed in Table 8.2. In all cases (*E*)-crotylboronates give predominantly *anti* products whereas (*Z*)-crotylboronates favor the formation of the *syn* products.

Table 8.2. Product distribution (%) in the reaction of crotyl boronates 8.8 and 8.9 with chiral aldehydes[48–50]

Boronate	R in RCHO	R, OH	R, OH	R, OH	R, OH
8.8[b]		9	87	—	4
ent-**8.8**[a]		96	2	—	2
8.8[b]		57	41	—	2
ent-**8.8**[a]		86	11	—	3
8.9[a]		5	—	1	94
ent-**8.9**[b]		3	—	15	82
8.8[a]		3	97	—	—
ent-**8.8**[b]		81	16	7	—
8.9[b]		2	12	45	41
ent-**8.9**[a]		4	—	95	1

[a] Matched reagents. [b] Mismatched reagents.

The reaction of (*E*)-crotylboronate *ent*-**8.8** with chiral aldehyde **8.39** was the key step in the synthesis of a sex pheromone *Macrocentrus grandii* (**8.40**)[51] (Scheme 8.21).

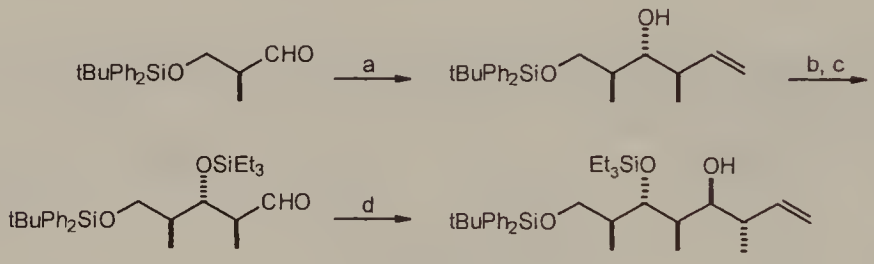


8.39 **8.40**

a: *ent*-**8.8**, PhMe, molecular sieves 4Å, -78°C

Scheme 8.21

Tartrate modified (*E*)- and (*Z*)-crotylboronates offer a solution to the synthesis of chiral dipropionate units of defined stereostructure.[49] For example, reactions of (*E*)-crotylboronates with chiral aldehydes were used in the stereoselective synthesis of the C(19)–C(29) segment of rifamycin S. Initial stages of the synthesis are shown in Scheme 8.22.[52,53]



a: *ent*-**8.8**, PhMe, molecular sieves 4Å, -78°C, 75%

b: Et_3SiCl, NEt_3, DMF

c: O_3, MeOH, -78°C, then Me_2S

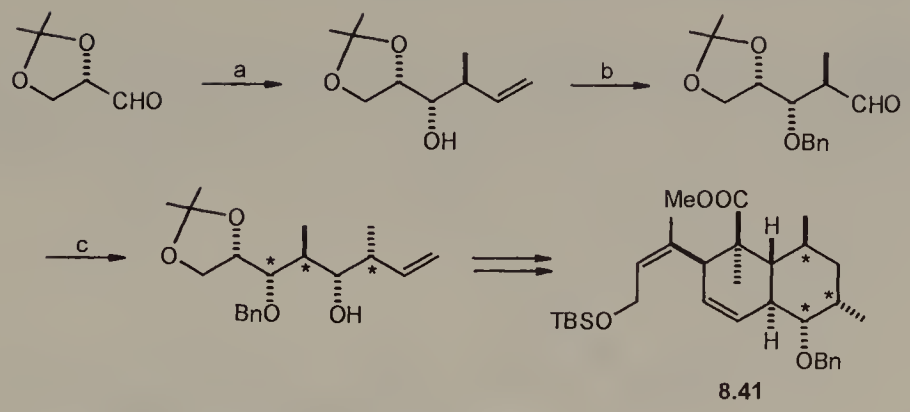
d: **8.8**, PhMe, molecular sieves 4Å, -78°C, 76%[52]

Scheme 8.22

Other applications of crotylboronates involved the syntheses of the C(1)–C(15) segment of streptovaricin D,[54] (−)-pre-swinholide A[55] and the octahydronaphthalene subunits of kijanolide and tetronolide.[50,56]

Two consecutive crotylborations, with the use of (*E*)- and (*Z*)-crotylboronates **8.8** and **8.9**, were applied by Roush in the early stages of a stereoselective synthesis of the kijanolide/tetronolide subunit **8.41** from L-glyceraldehyde acetonide[50] (Scheme 8.23).

Two silicon substituted allylboronate reagents were developed by Roush and Grover for the enantio- and diastereoselective synthesis of *anti* 1,2-diols and 2-butene-1,4-diols. These allylboronate reagents, **8.12** and **8.13**, formally constitute the γ- and α-hydroxyallyl anion equivalents, respectively[29] (Scheme 8.24), and have potential for application in the diastereoselective synthesis of carbohydrates.



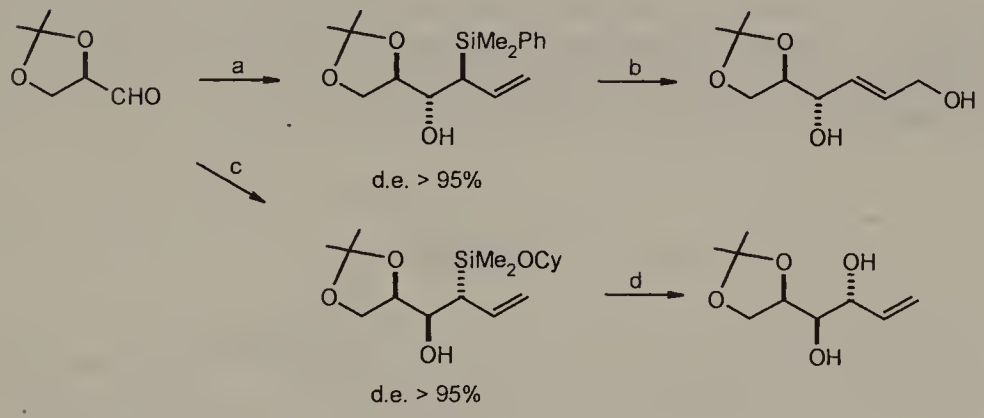
8.41

a: **8.8**, PhMe, molecular sieves 4Å, -78°C (77%)

b: BnBr, NaH, DMF (89%), then O_3, MeOH, -78°C, then Me_2S

c: **8.9**, PhMe, molecular sieves 4Å, -78°C (73%)

Scheme 8.23



a: **8.12**, PhMe, molecular sieves 4Å, -78°C, 90%

b: Me_2CO_2, Me_2CO, then AcOH, MeOH, 88%

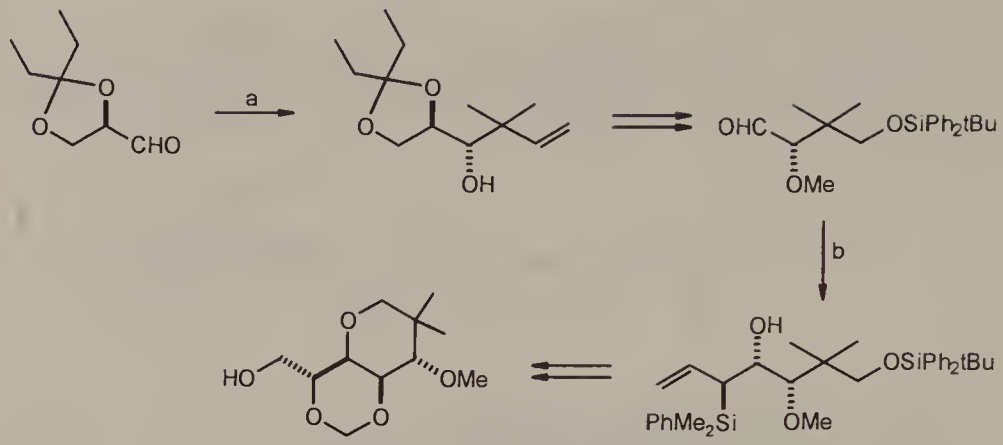
c: *ent*-**8.13**, PhMe, molecular sieves 4Å, -78°C, 82%

d: H_2O_2, KF, $KHCO_3$, MeOH, THF, RT, 92%

Scheme 8.24

Prenyl boronate **8.15** as well as silicon-substituted boronate **8.12** were applied to the synthesis of the trioxadecalin ring system of **8.42**[31] (Scheme 8.25).

Another silicon-modified allylboronate reagent **8.14** was introduced by Hunt and Roush to improve the low enantioselectivity observed in some reactions of allylboronate reagent **8.13**. Allylboronate reagent **8.14** is highly reactive toward protodesilylation-oxidation, allowing conversion of the silyl group in the product to the hydroxy group, with retention of configuration. The γ-(mentho-furyl)dimethylsilyl allylboronate reagent *ent*-**8.14** was used in the highly stereo-selective total synthesis of the indolizine alkaloid (−)-swainsonine. The crucial



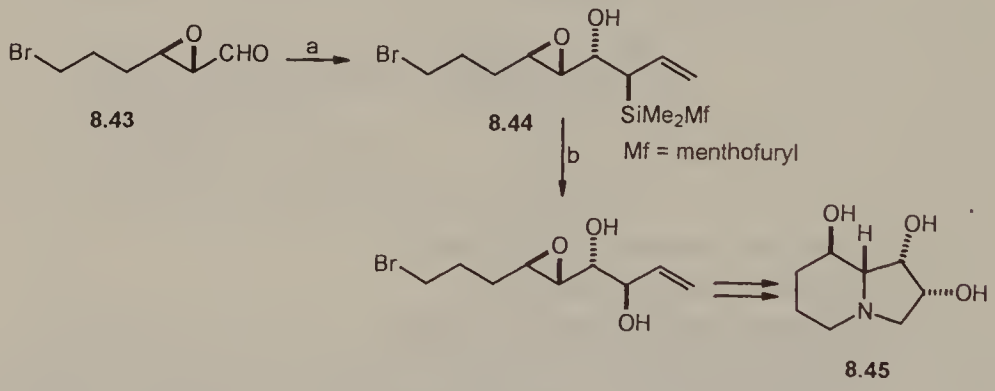
8.42

a: **8.15**, PhMe, molecular sieves 4Å, -78°C, 79%, d.e. > 98%

b: **8.12**, PhMe, molecular sieves 4Å, -78°C, 86%, d.e. > 98%

Scheme 8.25

step was the reaction of allylboronate *ent*-**8.14** with chiral aldehyde **8.43** (obtained via Sharpless asymmetric epoxidation). The major product **8.44** was obtained in enantiomerically pure form by recrystallization and then converted in six steps to (−)-swainsonine (**8.45**),[30] Scheme 8.26.



8.43 **8.44** **8.45**

a: *ent*-**8.14**, PhMe, molecular sieves 4Å, -78°C, d.e. 80%, 73% yield after recrystallization

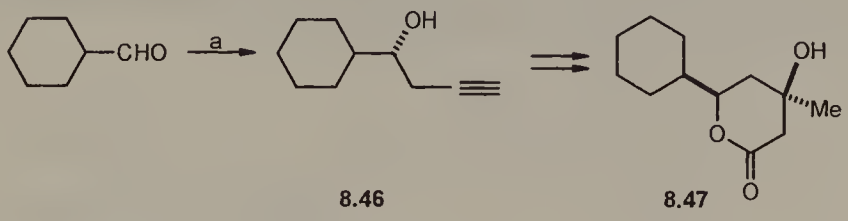
b: CF_3COOH, THF, 0°C → RT then $KHCO_3$, KF, H_2O_2, THF-MeOH, RT (85%)

Scheme 8.26

Renard and Lallemand have also reported the tandem Diels–Alder reaction–allylboration reaction of tartrate modified 1,3-dienyl-boronate.[57]

Allenylboration of aldehydes. Yamamoto *et al.* have developed a method of enantioselective synthesis of homopropargylic alcohols such as **8.46** by the addi-

tion of allenylboronic esters, modified with tartrate residues, to aldehydes[35] (Scheme 8.27). Product **8.46** was converted to optically active δ-lactone **8.47**, related to mevinolin.[58]



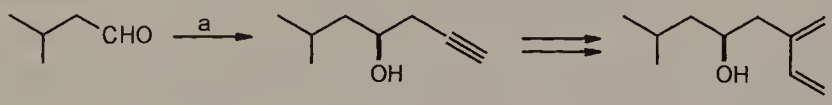
8.46 **8.47**

a: *ent*-**8.30**, PhMe, -78°C, 81%, e.e. 95%

Scheme 8.27

Enantioselectivity of the reaction is somewhat dependent on the bulk of the alkoxy group in the tartrate residue, the best result being obtained with X = $OCHiPr_2$ (Fig. 8.2A).[36]

The short synthesis of (−)-ipsenol (**8.48**) serves as an illustration of the application of allenylboronic reagents[36] (Scheme 8.28).

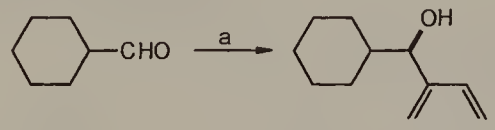


8.48

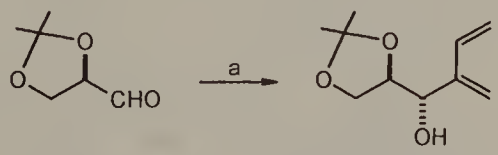
a: *ent*-**8.31**, PhMe, -78°C, 78%, e.e. 99%

Scheme 8.28

Homoallenylboration of aldehydes. Brown introduced a method of synthesis of chiral 2-substituted 1,3-butadienes by homoallenylboration of aldehydes with 2,3-butadien-1-ylboronate reagent modified with a tartrate[33] (Scheme 8.29). The reaction shows *anti*-selectivity, similar to that observed for the allylboration reaction (cf. Schemes 8.12 and 8.15).



94%, e.e. 88.9%

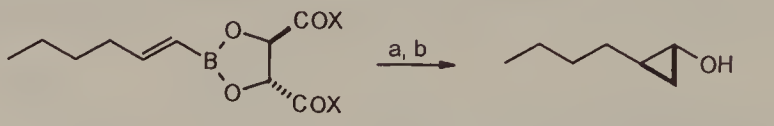


72%, e.e. 97%

a: **8.18**, PhMe, -78°C

Scheme 8.29

Cyclopropanation of tartrate modified 1-alkenylboronic esters. In the synthesis reported by Imai,[32] 1-alkenylboronic esters modified with tartrate residues (e.g. **8.23**, **8.24**) undergo a diastereofacial selective Simmons–Smith reaction (Fig. 8.2B) to give optically active 2-substituted cyclopropanols, after oxidative cleavage of the carbon–boron bond (Scheme 8.30).



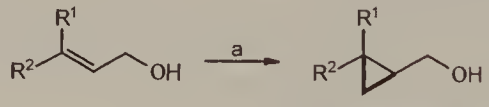
8.23 (X = OiPr): 44%, e.e. 86%

8.24(X = NMe_2): 48%, e.e. 93%

a: 3 eq. CH_2I_2, Zn-Cu, Et_2O, Δ b: H_2O_2, $KHCO_3$, THF

Scheme 8.30

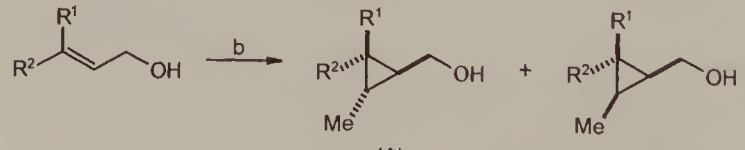
Enantioselective Simmons–Smith cyclopropanation of allylic alcohols with tartramide modified boronate ligand. A very useful procedure developed by Charette utilizes n-butylboronic acid modified with *N,N,N′,N′*-tetramethyltartramide (**8.4**) as a chiral amphoteric bifunctional ligand in the cyclopropanation of allylic alcohols. In contrast to the Imai's method in which the alkene is covalently bound to the boron, in Charette's procedure the acidic site (the boron atom) coordinates the alkoxide of the allylic alcohol while the basic site (the oxygen atom of the tartramide residue) chelates the acidic Simmons–Smith reagent (Fig. 8.2C). The reaction provides cyclopropylmethanols of high enantiomeric purity (>90%) with a range of allylic alcohols.[21,59] It can also be used for the synthesis of 1,2,3-trisubstituted cyclopropanes[60] (Scheme 8.31).



R^1 = H, R^2 = Ph > 98%, e.e. 93%

R^1 = R^2 = Me 85%, e.e. 94%

a: 1.1 eq. **8.4**, 2.2 eq. $Zn(CH_2I)_2$, CH_2Cl_2, RT, 2h

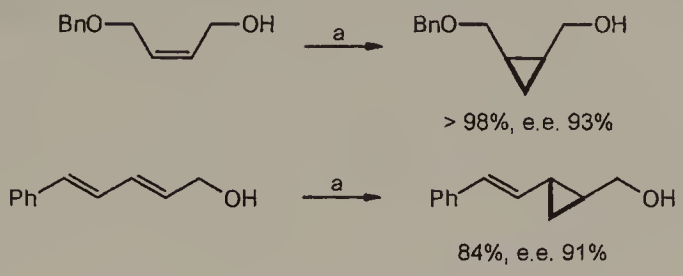


R^1	R^2	yield (%)	(A) : (B)	e.e. (%)
H	Ph	96	>50 : 1	98
$BnOCH_2$	H	80	>50 : 1	94
H	n-Pr	80	10 : 1	93

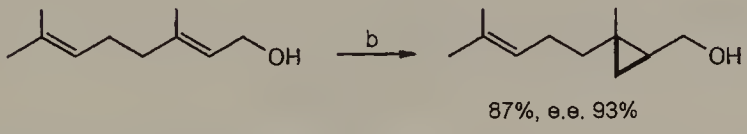
b: 1.1 eq. **8.4**, 2.2 eq. $Zn(CH_2I)_2$, CH_2Cl_2, 0°C

Scheme 8.31

An improved asymmetric cyclopropanation suitable for a large scale synthesis of cyclopropylmethanols by Charette's procedure (including the recovery of the boronate controller) has appeared[22,61] (Scheme 8.32).



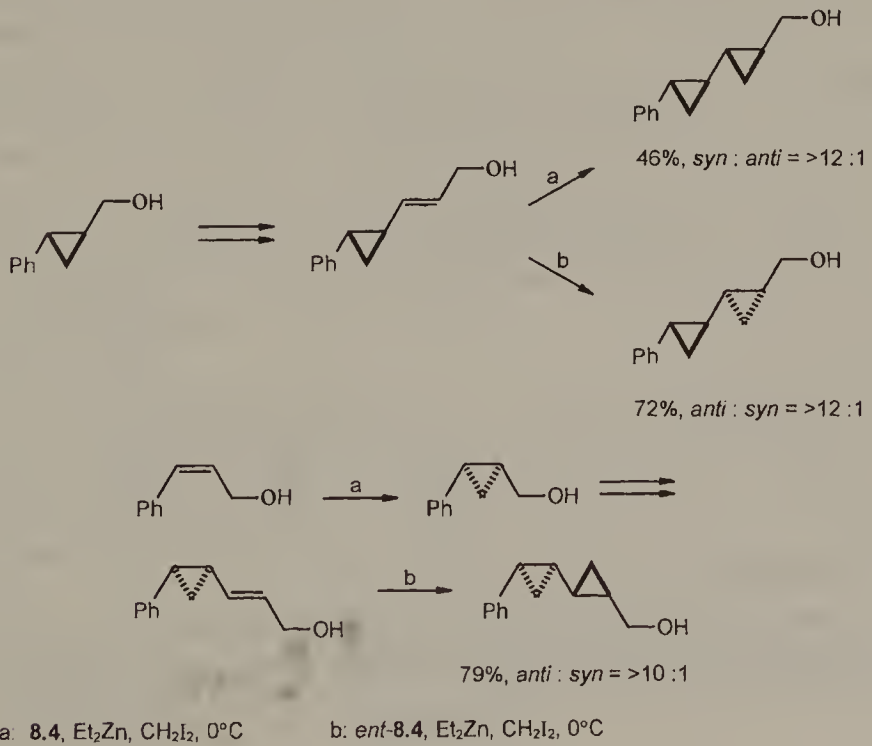
a: 1.1 eq. **8.4**, 3 eq. $Zn(CH_2I)_2 \cdot DME$, CH_2Cl_2, -10°C, 2h



b: 1.1 eq. **8.4**, 1.6 eq. $Zn(CH_2I)_2 \cdot DME$, CH_2Cl_2, 0°C

Scheme 8.32

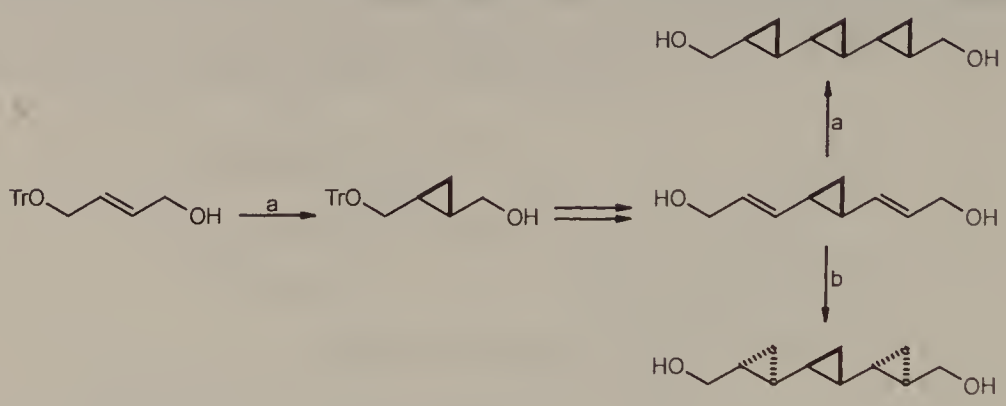
Zercher applied an interative cyclopropanation process to the synthesis of diastereomeric bis-cyclopropanes. Examples of this process are shown in Scheme 8.33. In these reactions control of stereochemistry by an external chiral dioxaborolane auxiliary overrides the effect of the resident cyclopropane stereocenters.[62,63]



a: **8.4**, Et_2Zn, CH_2I_2, 0°C b: *ent*-**8.4**, Et_2Zn, CH_2I_2, 0°C

Scheme 8.33

Zercher extended Charette's cyclopropanation methodology to bi-directional synthesis of stereoisomeric tercyclopropanes[64] (Scheme 8.34).

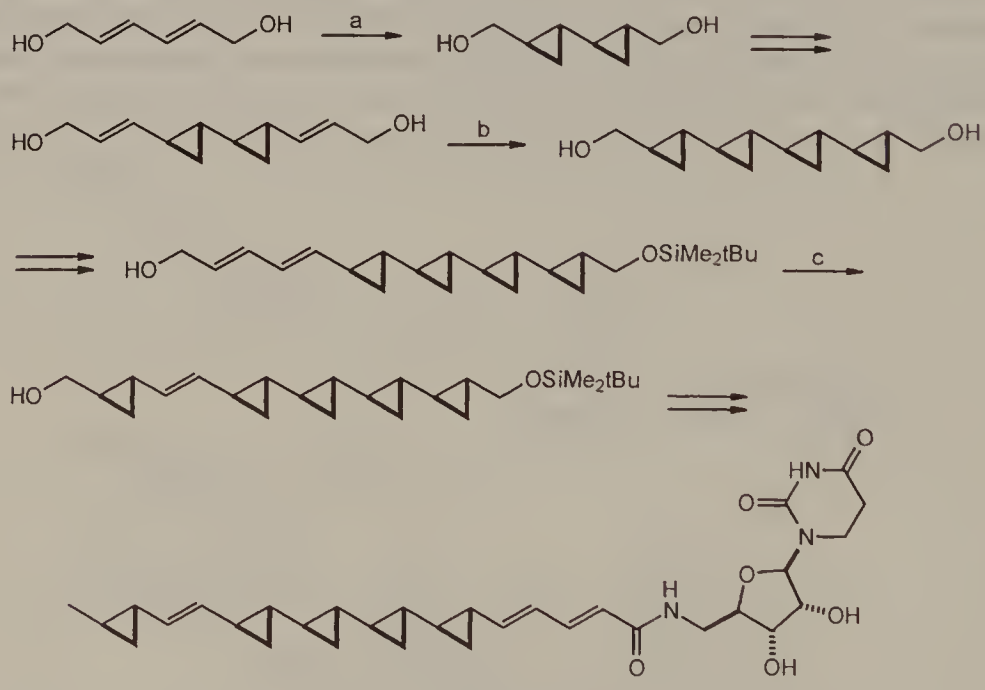


a: **8.4**, Et_2Zn, CH_2I_2, -5°C → RT (83-89%)

b: *ent*-**8.4**, Et_2Zn, CH_2I_2, -5°C → RT (65%)

Scheme 8.34

Barrett reported the total synthesis of antifungal agent FR-900848 (**8.49**), using Charette asymmetric cyclopropanation to effectively control the configuration of ten stereocenters[65-67] (Scheme 8.35).



8.49

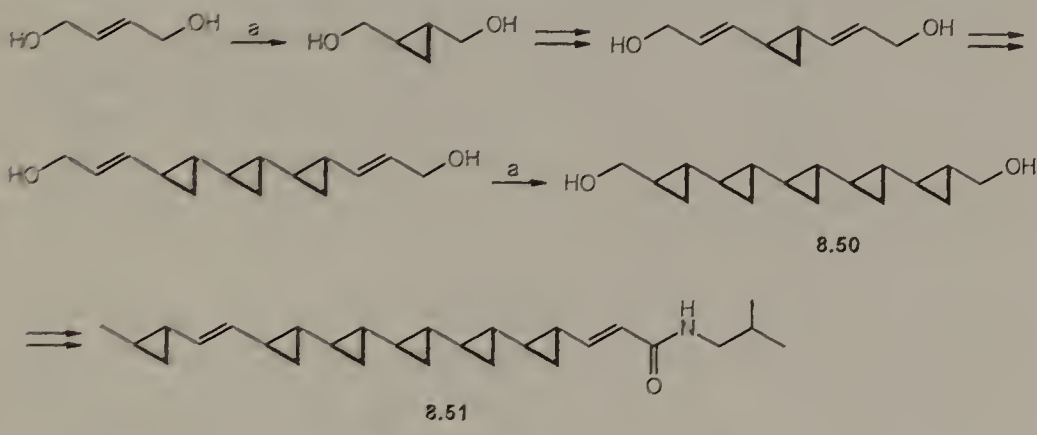
a: *ent*-**8.4**, Et_2Zn, CH_2I_2, CH_2Cl_2, -15°→ 25°C, 89%

b: *ent*-**8.4**, Et_2Zn, CH_2I_2, DME, CH_2Cl_2, -15°→ 25°C, 93%

c: *ent*-**8.4**, Et_2Zn, CH_2I_2, DME, CH_2Cl_2, - 40°C, 90%

Scheme 8.35

Barrett's group has synthesized the cholesteryl ester transfer protein inhibitor (−)-U-106305 (**8.51**) by sequential assembly of the C_2-symmetrical quinquecyclopropane unit **8.50** using a similar methodology[68] (Scheme 8.36). Independently, Charette synthesized the (+)-enantiomer of U-106305.[69] These syntheses established absolute stereochemistry of U-106305.



a *ent*-**8.4**, Et_2Zn, CH_2I_2, DME, CH_2Cl_2, -40°C → RT (83-91%)[68]

Scheme 8.36

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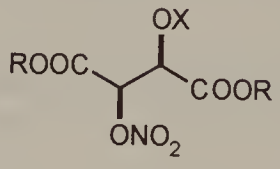
9 Tartrate Nitrates and Tartrate Modified Phosphorous Compounds

9.1 TARTRATE NITRATES

Several *O*-mono- and *O,O′*-dinitro derivatives of tartrates (**I**) have been synthesized (Table 9.1).



I

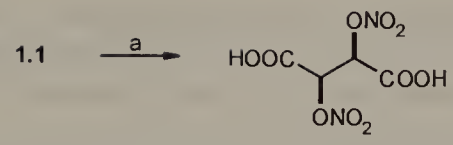
Table 9.1 ***O*-Nitro derivatives of L-tartrates (I)**

X	R	m.p. (°C)	$[\alpha]_D$ (solvent)	References
NO_2	H	(dec.)	+14.4 (MeOH)	1–3
H	Me	96–97	+27.3 (MeOH)	1,3,4
NO_2	Me	75	+21.0 (MeOH)	1,3
H	Et	46–47	+31.6 (MeOH)	1,3
NO_2	Et	26–27	+27.8 (MeOH)	1,3,4

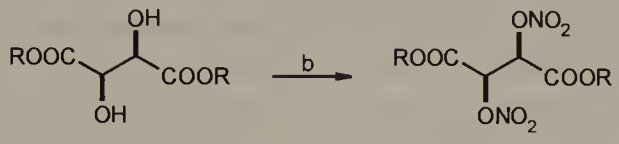
The *O,O′*-dinitro derivative of tartaric acid ("dinitrotartaric acid"), due to its instability, is seldom isolated in pure form (hydrolysis of the nitrate ester groups or formation of "dihydroxytartaric acid" contribute to its instability in the presence of moisture).[5] This is an important synthetic intermediate and it is used directly in subsequent reactions (see below).

Synthesis

Nitration of tartrates or tartaric acid with a mixture of concentrated sulfuric and nitric acids provides nitrates in moderate to good yield (Scheme 9.1). (**Caution:** Although no accidents have been reported with nitrates of tartrates they should be handled with due care, as any polynitrates of potentially hazardous nature).



a: 70% HNO_3, 90% (fuming) HNO_3, conc. H_2SO_4, ~ 40°C, 1h (78%)[2,5-7]

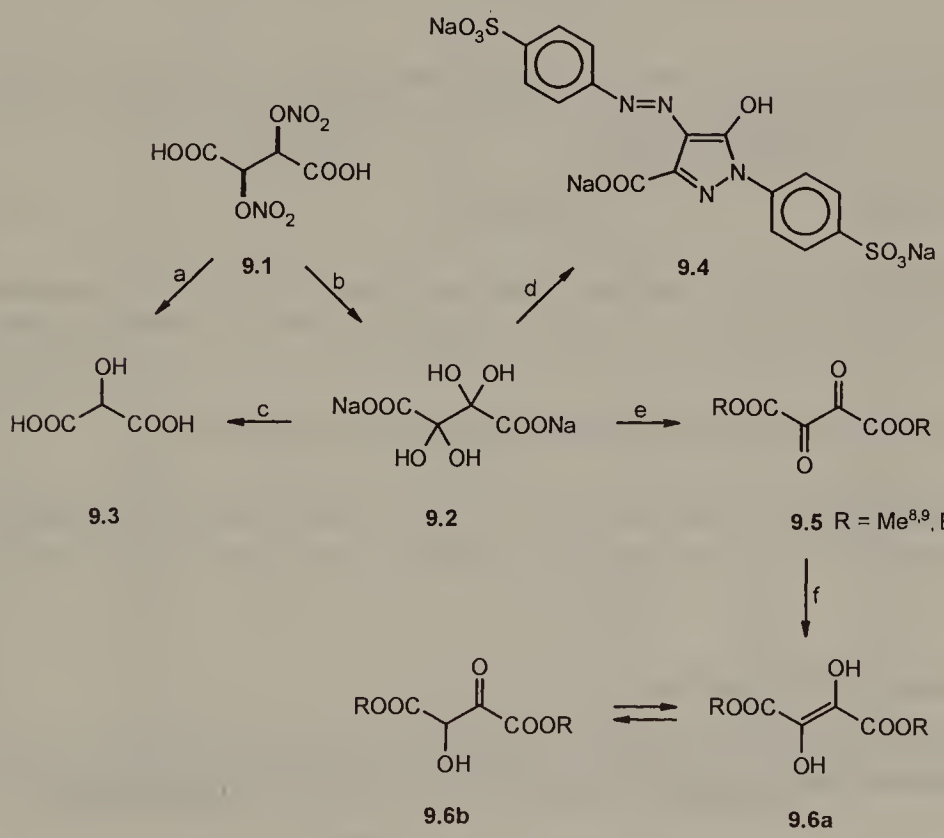


b: fuming HNO_3, conc. H_2SO_4, 0°C, 1h[1]

Scheme 9.1

Applications

O,O′-Dinitrotartaric acid (**9.1**), due to its masked α-dicarbonyl character, is readily transformed to several useful achiral products (Scheme 9.2).



a: EtOH-H_2O, Δ (42-48%)[2,11,12]

b: aq. Na_2CO_3, aq. NaOAc, 0°C, 2-3d[13,14]

c: aq. HCl, Δ[15]

d: 4-$NaO_3SC_6H_4NHNH_2$

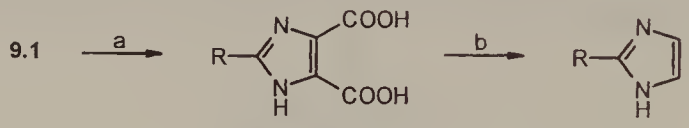
e: ROH, HCl, 0°-5°C, 3-5d

f: $Na_2S_2O_4$[16]

Scheme 9.2

The α-dicarbonyl function is unmasked by the action of a weak base on **9.1** (elimination of nitrous acid) to give **9.2**, *disodium dihydroxytartrate*. The sodium salt is readily isolated due to its sparing solubility.[17] The parent acid of **9.2** is easily decarboxylated to hydroxymalonic acid (*tartronic acid*), **9.3**, which can be obtained directly and more conveniently from **9.1**. Condensation of **9.2** with 4-(phenylhydrazine)sulfonic acid produces dyestuff *tartrazine* (**9.4**). Esterification of the acid form of **9.2** gives access to 2,3-dioxobutanedioates **9.5**, which can be reduced to dihydroxyfumarates **9.6a**. A keto tautomer **9.6b** (R=Et) of dihydroxyfumarate has been reportedly obtained in optically active form by SeO_2 oxidation of diethyl L-tartrate.[18] Dihydroxytartaric acid (**9.2**) can be used as precursor of glyoxal, as demonstrated by its conversion to 2,3,5,6-tetrahydroxy-1,4-benzoquinone.[19]

O,O'-Dinitrotartaric acid (**9.1**) is also used in the synthesis of imidazole and substituted imidazoles by condensation with aldehydes in the presence of ammonia (Scheme 9.3).



R = H,[6] Me,[20] Ph[7]

a: NH_4OH, -5° to -10°C, then RCHO, NH_4OH, 0°C → RT (43-62%)[6,7,20,21]

b (R = H): CuO, Δ (68-78%)[6]

Scheme 9.3

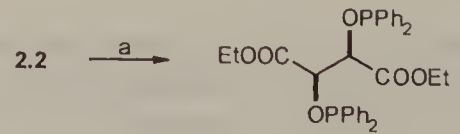
Although yields of the syntheses shown in Schemes **9.2** and **9.3** are moderate, they are compensated by the simplicity of operations and low cost of materials.

9.2 TARTRATE MODIFIED PHOSPHOROUS COMPOUNDS

Diverse derivatives of tartrates with tri-, tetra-, and pentavalent phosphorous compounds have been synthesized and some of them have synthetic applications.

Synthesis and Applications

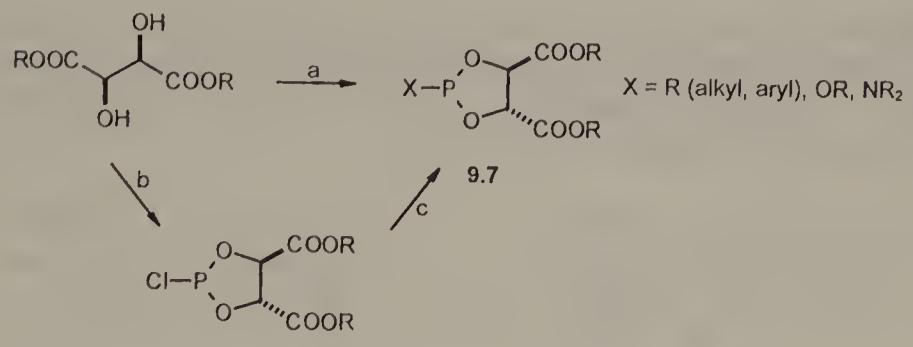
Trivalent phosphorous derivatives. Brunner reported a potential ligand, a chiral bis-phosphite that has been derived from diethyl L-tartrate (Scheme 9.4).



a: Ph_2PCl, pyridine, Et_2O, 0°C → RT (94% crude)[22]

Scheme 9.4

A number of cyclic 1,3,2-dioxaphospholanes derived from L-tartrates have been synthesized according to Scheme 9.5.



a: $RPCl_2$, pyridine or NEt_3, Et_2O or benzene

b: PCl_3, pyridine or NEt_3, THF or CH_2Cl_2

c: ROH, NEt_3, toluene or THF

Scheme 9.5

Table 9.2 Synthesis of 1,3,2-dioxaphospholanes 9.7 from L-tartrates (Scheme 9.5)

X	R	Method of Synthesis	Yield (%)	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (benzene)	References
Ph	Et	a	55	126/0.3	—	23,24
Cl	Et	b	93	93–95/0.001	—	25
Cl	i-Pr	b	46	108–110/0.001	—	25
Cl	Me	b	31	—	—	26
$O(CH_2)_3O$[a]	Et	c	77	—	—	25
$O(CH_2)_3O$[a]	i-Pr	c	71	—	—	25
OAr[b]	Et	a	—	114–116	—	27
OTES	Me	c	70	—	—	26
OTBS	Me	c	66	—	—	26
$OSiPh_3$	Me	c	70	—	—	26
NEt_2	Me	a	30	122–123/1	—	28
NEt_2	Et	a	45	142–144/2.5	−52.5	28
NEt_2	n-Pr	a	57	155–156/1.5	−51.8	28
NEt_2	i-Pr	a	43	138–139/1	−49.9	28
NEt_2	n-Bu	a	40	174–175/2	−39.1	28
NEt_2	i-Bu	a	40	161–162/1.5	−41.1	28

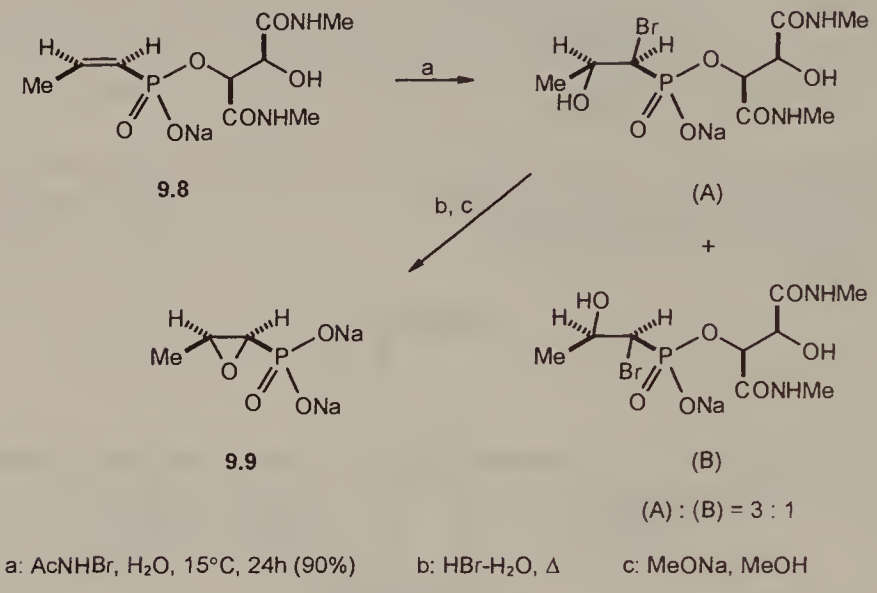
[a] Bis(dioxaphospholane) [b] Ar = 2,6-di(t-butyl)-4-methylphenyl

2-Chloro-1,3,2-dioxaphospholanes, prepared *in situ* from tartrates and PCl_3 (method b, Scheme 9.5), were used as chiral derivatizing agents for the determination of enantiomeric purity of alcohols by ^{31}P NMR. The diastereomeric deriv-

atives **9.7**, X=OR*, prepared *in situ* by method c (Scheme 9.5), display ^{31}P chemical shift differences up to 1.5 ppm.[29]

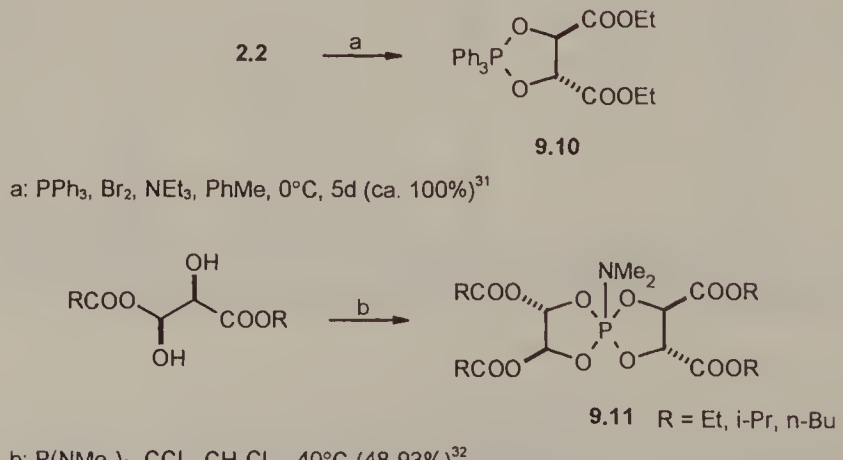
A

Tetravalent phosphorous derivatives. Asymmetric synthesis of fosfomycin (**9.9**) is based on the bromohydroxylation of a phosphonic acid derivative **9.8**, modified with chiral D-tatramide auxiliary. The best diastereoselectivity obtained was 50%[30] (Scheme 9.6).



Scheme 9.6

Pentavalent phosphorous derivatives. Compounds synthesized from tartrates include 1,3,2-dioxaphospholane **9.10** as well as spirophosphoranes **9.11** (Scheme 9.7).



Scheme 9.7

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10 Acetals of Tartaric Acid Derivatives

10.1 DERIVATIVES OF (4*R*,5*R*)-1,3-DIOXOLANE-4,5-DICARBOXYLIC ACID

Overview of Properties

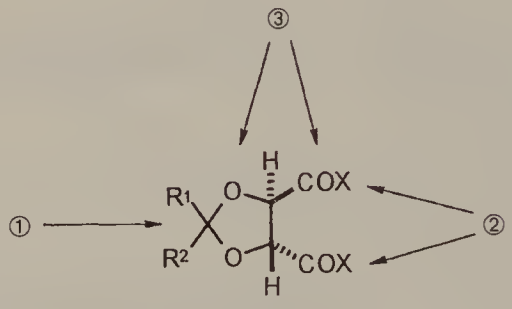


Figure 10.1

① The acetal function provides suitable protection of the hydroxy groups in reactions of the carboxy groups with organometallic reagents. This protecting group is used widely for the synthesis of TADDOLS (Chapter 12) and derivatives of threitol (Chapter 13), as well as tartrdialdehydes (Chapter 11) from tartrates (X = OR) and tartramides ($X = NR_2$).

② The *trans*-relationship of the carbonyl substituents adds some stability to the reactive products of reduction (X = H) by preventing intramolecular cyclization reactions.

③ The acetal and the carbonyl oxygen atoms act as chelators for Lewis acid type reagents. The chelated transition states make some reactions, such as Simmons–Smith cyclopropantion or 1,4-addition of Me_3Al (see below), highly diastereoselective.

The conformation of the tartrate-derived 1,3-dioxolanes has been studied in solution and in the solid state.[1]

Table 10.1 Symmetrical derivatives of (4*R*,5*R*)-1,3-dioxolane-4,5-dicarboxylic acid (Figure 10.1)

R^1	R^2	X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
			Alkyl aldehyde acetals		
H	H	OH	165	−81.3 (H_2O)	2–5
H	H	OMe	31.5	−80.7 (EtOH)	3,5–8
H	H	OEt	150/15	−73.4 (EtOH)	8–13
H	H	OAr[a]	111–113	—	4
H	H	OC_6Cl_5	224–225	—	5
H	H	NMe_2	—	−56.2 ($CHCl_3$)	14
H	H	Cl	55–58/0.7	—	4
Me	H	OMe	142/18	−62.5 ($CHCl_3$)	6,8,15,16
Me	H	OEt	151/19	−74.7 (neat)	8,9,15
i-Pr	H	OMe	—	—	17
t-Bu	H	OMe	85–90/0.01	−55.3 (Et_2O)	7,11,18,19
Cy	H	OMe	118/0.01	−27.7 ($CHCl_3$)	11,17
C_6H_{13}	H	OMe	105/0.001	—	20
C_7H_{15}	H	OMe	110/0.001	—	20
C_8H_{17}	H	OMe	120/0.001	—	20
C_9H_{19}	H	OMe	130/0.001	—	20
i-Pr$(CH_2)_3$MeCHCH_2	H	Oi-Pr	200/0.1	−33.8 ($CHCl_3$)	21
i-Pr$[(CH_2)_3CHMe]_2$	H	Oi-Pr	—	−28.2 (CH_2Cl_2)	21
i-Pr$[(CH_2)_3CHMe]_2CH_2$	H	OMe	—	−26.3 (CH_2Cl_2)	21
i-Pr$[(CH_2)_3CHMe]_2CH_2$	H	Oi-Pr	—	−27.7 ($CHCl_3$)	21
i-Pr$[(CH_2)_3CHMe]_2CH_2$	H	Oi-Bu	—	−25.0 ($CHCl_3$)	21
i-Pr$[(CH_2)_3CHMe]_2CH_2$	H	OCH_2tBu	—	−23.4 ($CHCl_3$)	21
i-Pr$[(CH_2)_3CHMe]_2CH_2$	H	OCy	—	−26.2 ($CHCl_3$)	21
CH_2=CH	H	OEt	169/36	−29.9 (EtOH)	9
CH_2=CMe	H	Oi-Pr	—	—	22
MeCH=CH	H	OEt	110–120/0.3	−26.7 ($CHCl_3$)	23
MeCH=CH	H	Oi-Pr	—	—	24,25
MeCH=CH	H	NMe_2	—	—	26
$AcOCH_2$CH=CH	H	Oi-Pr	—	−23.6	27
MeCH=CH$(CH_2)_2$	H	OMe	125/0.01	−32.7 ($CHCl_3$)	28
EtCH=CMe	H	Oi-Pr	—	—	24
n-PrCH=CH	H	Oi-Pr	—	—	24
n-PrCH=CH	H	NMe_2	—	−42.7 (MeOH)	26
Me_2C=CH$(CH_2)_2$CH=CH	H	NMe_2	—	—	26
OHC$(CH_2)_3$CH=CH	H	NMe_2	—	−21.5 (AcOEt)	29
O(Me)C$(CH_2)_3$CH=CH	H	NMe_2	—	−19.0 (AcOEt)	29
Bu_3Sn	H	NMe_2	—	−36.7 ($CHCl_3$)	30
			Aryl aldehyde acetals		
Ph	H	OH	128.5–129.5	+39.0 (Me_2CO)	31
Ph	H	OMe	74–76	−48.1 (MeOH)	6,32–38
Ph	H	OEt	75	−46.5 (MeOH)	11,39–41

(*continued*)

Table 10.1 (*continued*)

R^1	R^2	X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
Ph	H	NMe_2	—	—	42
Ph	H	$N(Bn)CH_2$	110–111	+58.6 ($CHCl_3$)	31
Ph	H	$N(CF_3CH_2)CH_2$	86–88	−5.5 ($CHCl_3$)	43
2-MeC_6H_4	H	NMe_2	—	—	42
3-MeC_6H_4	H	OEt	165–166/3	−43.0 (EtOH)	9
4-MeC_6H_4	H	OEt	189.5–190/5	−39.5 (EtOH)	9
4-CH_2=CHC_6H_4	H	OMe	58–59	−2.45 ($CHCl_3$)	44
2,5-$Me_2C_6H_3$	H	OEt	183–184/3	−31.3 (EtOH)	9
2,4,6-$Me_3C_6H_2$	H	OMe	96–97	−29.9 ($CHCl_3$)	11
2-$O_2NC_6H_4$	H	OMe	170/0.1	—	45
2-$O_2NC_6H_4$	H	OEt	60	+40.1 (EtOH)	9
3-$O_2NC_6H_4$	H	OEt	42–43	−35.6 (EtOH)	9
4-$O_2NC_6H_4$	H	OEt	57–58	−22.3 (EtOH)	9
2-HOC_6H_4	H	OEt	67–68	−73 ($CHCl_3$)	46
3-HOC_6H_4	H	OMe	65	−20.8 (THF)	47
4-$MeOC_6H_4$	H	OMe	73–74.5	−35.1 (MeOH)[b]	48,49
4-$MeOC_6H_4$	H	OEt	35	−23.6 ($CHCl_3$)	50,51
4-$BzOCH_2C_6H_4$	H	OMe	64–65	−6.4 ($CHCl_3$)	44
2-ClC_6H_4	H	OEt	34–35	−39.0 (EtOH)	9
4-ClC_6H_4	H	OEt	186–187/4	−26.7 (EtOH)	9
2-IC_6H_4	H	OEt	34	−65.7 (EtOH)	9
4-IC_6H_4	H	OEt	198/6	−4.9 (EtOH)	9
2-$BrC_6H_4CH_2$	H	OMe	—	—	52
2-$BrC_6H_4CH_2$	H	NMe_2	—	—	52
$PhSO_2CH_2$	H	OMe	—	−19.3 (CH_2Cl_2)	53
4-$MeC_6H_4SO_2(CH_2)_2$	H	OEt	96–98	−21.0 ($CHCl_3$)	54,55
PhCH=CH	H	OEt	55.5–56	−4.2 ($CHCl_3$)	24,56,57
PhCH=CH	H	Oi-Pr	56–57.5	—	24,58,59
PhCH=CH	H	NMe_2	—	—	26
1-naphthyl	H	OMe	64–65	−9.2 (CH_2Cl_2)	16
1-naphthyl	H	OEt	63–64	−19.3 (EtOH)	9
2-naphthyl	H	OMe	48.5–49.0	+1.4 ($CHCl_3$)	16
		Alkyl ketone acetals			
Me	Me	OH	92	−51.4 (MeOH)	4,60
Me	Me	OMe	80–82/0.1	−44.2 ($CHCl_3$)	7,8,11,61–65
Me	Me	OEt	115–117/5	−40.2 ($CHCl_3$)	61,66–68
Me	Me	Oi-Pr	43–45	−40.8 ($CHCl_3$)	69,70
Me	Me	OAr[a]	140–142	—	4
Me	Me	NH_2	157–160	−16.4 (MeOH)	71–73
Me	Me	NHAll	145–154/0.07	−19.3 (Me_2CO)	74
Me	Me	NHBn	83–84	—	75
Me	Me	NMe_2	88–90	+2.5 ($CHCl_3$)	76
Me	Me	$N(iPr)_2$	123–124	—	75

(*continued*)

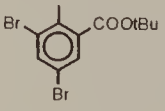
Table 10.1 (*continued*)

R^1	R^2	X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
Me	Me	$N(iBu)_2$	—	—	75
Me	Me	NCy_2	148–149	—	75
Me	Me	Cl	42–44	—	4,75
Et	Me	OMe	141/15	−35.8 (neat)	77
Et	Me	OEt	158/17	−35.0 (EtOH)	77
Et	Me	OnPr	167/15	−30.1 (neat)	77
Et	Me	Oi-Pr	115–117/0.5	−30.3 (neat)	77
n-Pr	Me	OEt	167.5/20	−31.8 (EtOH)	77
$CH_3(CH_2)_4$	Me	OEt	180/15	−26.6 (EtOH)	77
$CH_3(CH_2)_8$	Me	OEt	218/15	−21.3 (EtOH)	77
i-Pr$(CH_2)_3$CHMe$(CH_2)_3$	Me	Oi-Pr	—	−17.4 ($CHCl_3$)	21
i-Pr$(CH_2)_3$CHMe$(CH_2)_3$	Me	OBn	—	−20.4 ($CHCl_3$)	21
i-Pr$(CH_2)_3$CHMe$(CH_2)_3$	Me	NHAll	—	−0.6 ($CHCl_3$)	21
i-Pr$[(CH_2)_3$CHMe$]_2(CH_2)_3$	Me	Oi-Pr	—	−15.1 ($CHCl_3$)	21
CH_2=CH$(CH_2)_2$	Me	OEt	95–98/0.2	−28.4 (EtOH)[c]	78
Et	Et	OMe	102–104/0.05	−16.8 ($CHCl_3$)	79
Et	Et	OEt	169/22	−23.1 (EtOH)	77
n-Pr	n-Pr	OEt	175/16	−19.8 (EtOH)	77
		Aryl ketone acetals			
Ph	Me	OMe	140/0.15	+11.0 (CH_2Cl_2)	80,81
Ph	Me	NMe_2	—	—	42
2-MeC_6H_4	Me	NMe_2	—	—	42
4-CH_2=CHC_6H_4	Me	OMe	—	+21.8 ($CHCl_3$)	44
PhCH=CH	Me	NMe_2	—	—	82
PhS$(CH_2)_2$	Me	OEt	—	—	83
$PhSO_2(CH_2)_2$	Me	OEt	—	−16.4 ($CHCl_3$)	83,84
Ph	Et	OMe	—	+18.5 ($CHCl_3$)	85
3-BnC_6H_4	Et	OMe	—	+10.0	86
4-MeOC_6H_4	Et	OMe	—	+15.6 ($CHCl_3$)	85,87
4-ClC_6H_4	Et	OMe	—	+20.6 ($CHCl_3$)	85
6-methoxy-2-naphthyl	Et	OMe	77–78	+35.0 ($CHCl_3$)	87
6-methoxy-2-naphthyl	Et	OEt	—	+20.6 ($CHCl_3$)	87
6-methoxy-2-naphthyl	Et	Oi-Pr	—	+21.6 ($CHCl_3$)	87
6-methoxy-2-naphthyl	Et	OnBu	—	+14.0 ($CHCl_3$)	87
4-ClC_6H_4	iPr	OMe	40	+21.6 ($CHCl_3$)	87
5-bromo-6-methoxy-2-naphthyl	(*S*)-CHBrMe	OH	187–88	+39.9 (Me_2CO)	88
Ph	Ph	OMe	80–81	+54.2 ($CHCl_3$)	89
4-CH_2=CHC_6H_4	Ph	OMe	52.5–54	+63.8 ($CHCl_3$)	44
		Cyclic ketone acetals			
$-(CH_2)_4-$		OEt	170–171/12	−40.5 (neat)	90
$-(CH_2)_4-$		OtBu	64–65	−36.0 (CH_2Cl_2)	91,92

(*continued*)

Table 10.1 (*continued*)

R^1	R^2	X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
$-(CH_2)_5-$		OH	142–143	−24.0 (EtOH)	93,94
$-(CH_2)_5-$		OMe	123/0.06	−27.0 ($CHCl_3$)	7,11,95
$-(CH_2)_5-$		OEt	124–126/0.15	−35.6 (neat)	90,93,96–99
$-(CH_2)_5-$		NH_2	181–185	—	94
$-(CH_2)_5-$		NHPh	185.5–187	—	94
$-(CH_2)_5-$		NEt_2	—	+14.9 (CCl_4)	93
$-CHMe(CH_2)_4-$		OEt	184/14	−21.8 (neat)	90
$-CH_2CHMe(CH_2)_3-$		OEt	186/14	−35.4 (neat)	90
$-(CH_2)_2CHMe(CH_2)_2-$		OEt	188/14	−30.5 (neat)	90
$-CH_2(CHMe)_2(CH_2)_2-$		OEt	—	—	91
$-(CH_2)_2CH=CH-$		Oi-Pr	—	—	100
$-(CH_2)_2CH=CMe-$		Oi-Pr	—	−35.1 ($CHCl_3$)	101
$-(CH_2)_3CH=CH-$		OMe	—	−8.5 ($CHCl_3$)	101
$-(CH_2)_3CH=CH-$		NMe_2	—	—	82
$-CH(iPr)(CH_2)_2CHMeCH_2-$[d]		OMe	114/0.005	−23.8 ($CHCl_3$)	11
$-2-(CH_2)_3C_6H_4-$		OMe	54	−9.4 ($CHCl_3$)	102
5′α-cholestan-3′,3′-ylidene		OEt	103–104	+4.2 (dioxane)	103
		Orthoesters			
H	OEt	OEt	150–154/20[e]	−25.7 ($CHCl_3$)	104–106
H	OEt	Oi-Pr	100–104/0.01	—	107
H	NMe_2	OEt	—	—	108
Me	OMe	OMe	—	−28.4 ($CHCl_3$)	1,109
Me	OMe	OEt		−22.2 ($CHCl_3$)	109
Me	OMe	Oi-Pr	—	−30.8 ($CHCl_3$)	109
Me	OMe	NMe_2	58	−1.1 ($CHCl_3$)	109
Me	OEt	OEt	—	—	110
Me	OEt	Oi-Pr	112/0.01	—	107
Et	OMe	OEt	—	—	111
Et	OEt	OEt	—	−24.5 ($CHCl_3$)	109,110
Ph	OMe	OEt	—	+10.2 ($CHCl_3$)	109,111
Ph	OEt	OEt	—	—	110
Ph	OEt	Oi-Pr	148/0.01	—	107

[a] Ar = 

[b] $[\alpha]_D$ −18.8[48] and + 46.3 for the (4*S*,5*S*)-enantiomer[34] are also reported.

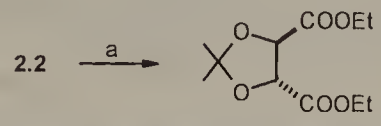
[c] At 546 nm.

[d] From (−)-menthone

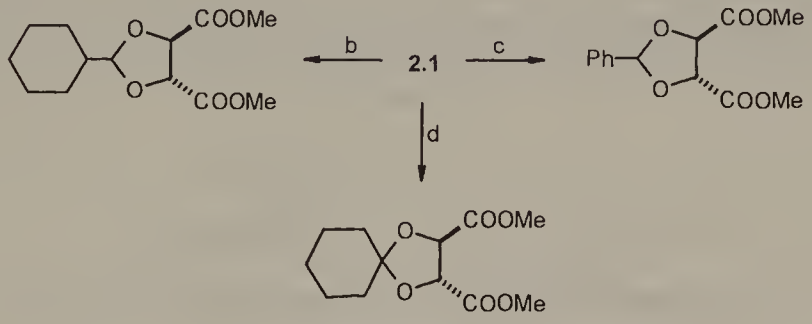
[e] At 180–200°C the orthoester undergoes decomposition to diethyl fumarate.[104]

Synthesis

Acetals from tartrate diols and aldehydes or ketones. Tartrate acetals can be simply prepared by acetalization of aldehydes or ketones by a tartrate diol; the reaction requires prolonged refluxing with removal of water or the use of one equivalent of boron fluoride etherate (Scheme 10.1).



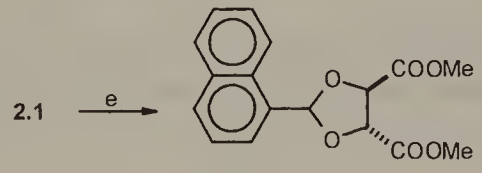
a: Me_2CO, petroleum ether, H_2SO_4, Δ, 9 days (removal of water), 69-83%[64,67]



b: 1 eq. CyCHO, $ZnCl_2$ (cat.), benzene, Δ, 28h (removal of water), 85%[11]

c: PhCHO, benzene or toluene, TsOH (cat.), Δ (removal of water), 83-91%[35,38]

d: 1eq. cyclohexanone, TsOH (cat.), toluene, Δ, 21h (removal of water), 60%[95]



e: 1 eq. 1-naphthaldehyde, 1 eq. $BF_3{\cdot}Et_2O$, AcOEt, 0°C → RT, 20h (high yield)[16]

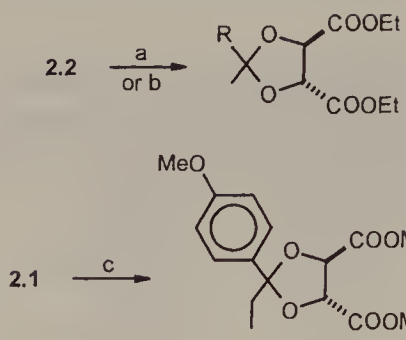
Scheme 10.1

The addition of trimethyl orthoformate to the reaction mixture brings about formation of the intermediate dimethyl acetal and accelerates the formation of the tartrate acetal. The reaction can be effectively catalysed by scandium tris(trifluoromethanesulfonate), Scheme 10.2.

A one-step procedure employing trimethyl orthoformate allows to simultaneously esterify tartaric acid and to form the acetal with benzaldehyde (Scheme 10.3).

Methylene acetals are usually prepared with the use of 1,3,5-trioxane or paraformaldehyde as formaldehyde equivalents (Scheme 10.4)

A procedure of Noyori[114] allows preparation of tartrate acetals from sensitive aldehydes or their acetals and *O,O*-silylated tartrates under catalysis by trimethylsilyl trifluoromethanesulfonate (Scheme 10.5).

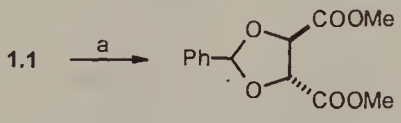


a (R = Me): Me_2CO, 1.3 eq. $HC(OEt)_3$, 6N HCl/DMF (cat.), RT, 3 days (89.5%)[112]

b (R = $(CH_2)_2Ph$): $Ph(CH_2)_2Ac$, 1.2 eq. $HC(OMe)_3$, 0.01 eq. $Sc(OTf)_3$, MeCN, RT, 3h (95%)[113]

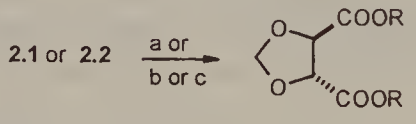
c: 0.5 eq. AnCOEt, 1 eq. $HC(OMe)_3$, MsOH (cat.), 3h, 100°C (90%)[87]

Scheme 10.2



a: PhCHO, MeOH, $HC(OMe)_3$, TsOH (cat.), Δ (removal of HCOOMe), 83-91%[37]

Scheme 10.3

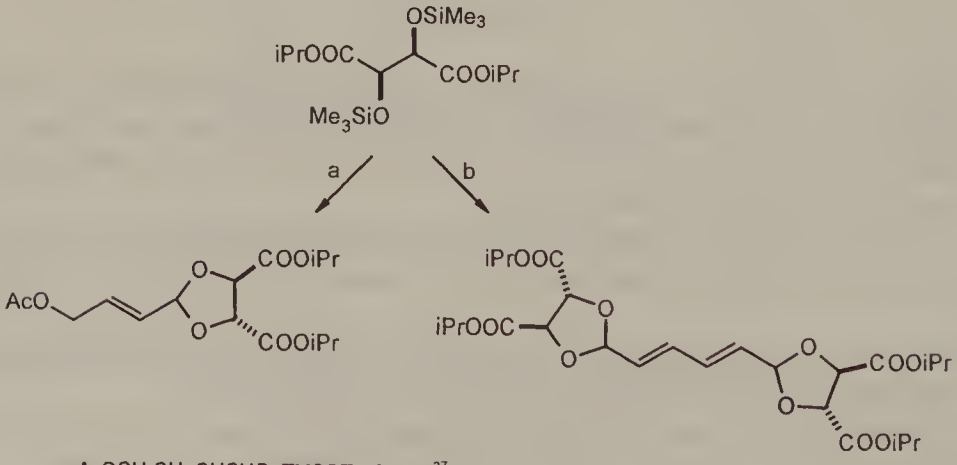


a (R = Me): $(CH_2O)_3$, benzene, TsOH (cat.), Δ, (removal of water), 59%[6]

b (R = Et): 2 eq. paraformaldehyde, benzene, TsOH (cat.), Δ, (removal of water), 83%[10]

c (R = Et): 2.6 eq. polyoxymethylene, 0.6 eq. $ZnCl_2$, 150°C, 1h, 52% [11]

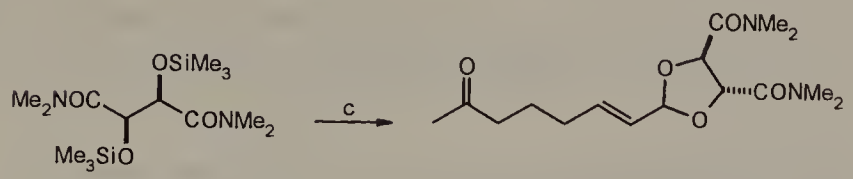
Scheme 10.4



a: $AcOCH_2CH{=}CHCHO$, TMSOTf, CH_2Cl_2[27]

b: $OHC(CH{=}CH)_2CHO$, TMSOTf, Me(OTMS)=NTMS, CH_2Cl_2, -78°C → RT (73%)[115]

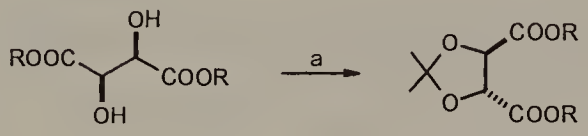
(continued)



c: $MeCO(CH_2)_3CH{=}CHCH(OMe)_2$, TMSOTf, CH_2Cl_2, -78°C → -20°C (57%)[29]

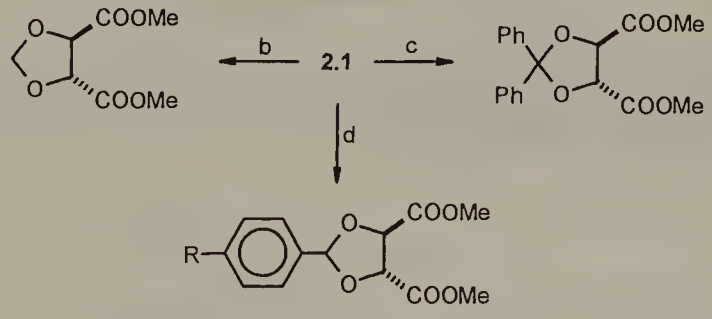
Scheme 10.5

Transacetalization of acetals, vinyl acetates or orthoesters by tartrate diols. Transacetalization of an acetal with a tartrate diol requires considerably shorter time than acetalization of the corresponding carbonyl compound (Scheme 10.6). The reaction may yield a mixture of products due to simultaneous transesterification of the tartrate.



R = Me, Et, i-Pr

a: 1.2-1.5 eq. $Me_2C(OMe)_2$, benzene, TsOH (cat.), Δ (removal of MeOH), ca. 100%[29,61,68,116-118]



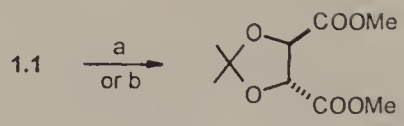
b: 1.2 eq. $CH_2(OMe)_2$, 1.2 eq. $BF_3{\cdot}Et_2O$, i-PrOAc, Δ (82%)[7]

c: 1 eq. $Ph_2C(OMe)_2$, benzene, TsOH (cat.), Δ (removal of MeOH), 82%[89]

d (R = H): 1.1 eq. $PhCH(OMe)_2$, benzene, TsOH (cat.), Δ (removal of MeOH), 94%[36]
(R = OMe): 3 eq. $AnCH(OMe)_2$, benzene, TsOH (cat.), mol. sieves, Δ (removal of MeOH), 97%[49]

Scheme 10.6

Simultaneous esterification and acetalization of tartaric acid (**1.1**) can be accomplished with excess 2,2-dimethoxypropane to yield the acetal directly[61] (Scheme 10.7).

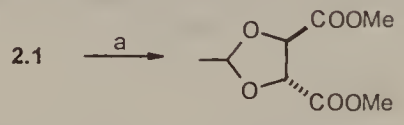


a: 3.3 eq. $Me_2C(OMe)_2$, MeOH, cyclohexane, TsOH (cat.), Δ (removal of acetone and MeOH), 85-92%[61]

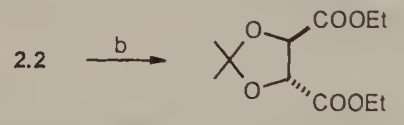
b: 3 eq. $Me_2C(OMe)_2$, Me_2CO,TsOH (cat.), Δ, 5h, 97%[119]

Scheme 10.7

Vinyl or isopropenyl acetate can be transacetalized with a tartarte diol at ambient temperature to give either ethylidene or isopropylidene acetal (Scheme 10.8).



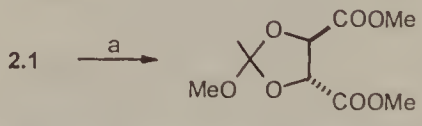
a: 1.2 eq. CH_2=CHOAc, HgO (cat.), $BF_3{\cdot}Et_2O$ (cat.), Et_2O (90%)[16]



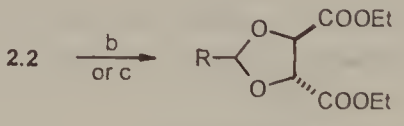
b: 1.1 eq. CH_2=C(Me)OAc, HgO (cat.), $BF_3{\cdot}Et_2O$ (cat.), Me_2CO, RT (71-88%)[120]

Scheme 10.8

In a similar way transacetalization of an orthoester or *N,N*-dimethylformamide acetal with a tartrate diol yields cyclic tartrate orthoester or dimethylamino(methylene) acetal (Scheme 10.9).



a: 1.2 eq. $MeC(OMe)_3$, benzene, PPTS (cat.), Δ, 51%[1]



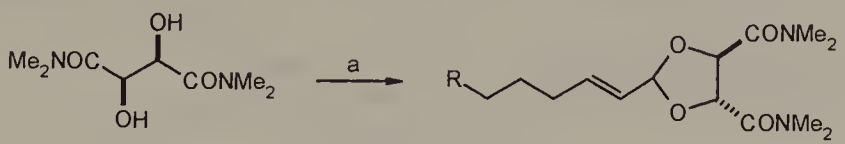
R = OEt, NMe_2

b (R = OEt): 2.7 eq. $HC(OEt)_3$, AcOH (cat.), PhMe, Δ (removal of EtOH), 94%[105]
or 1.2 eq $HC(OEt)_3$, PPTS (cat.), Δ (96%)[106]

c (R = NMe_2): 2-10 eq. $Me_2NCH(OMe)_2$, CH_2Cl_2, RT, quantitative[108]

Scheme 10.9

For the synthesis of α,β-unsaturated acetals, a method of Molander provides products of transacetalization with (*E*)-configuration[121] (Scheme 10.10).

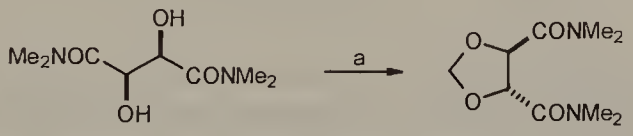


R	yield (%)	(*E*):(*Z*)
Ac	57	99 :1
Bz	89	98 :2
Cl	85	98 :2

a: $R(CH_2)_3CH{=}CHCH(OMe)_2$, PPTS (cat.), DMF, RT

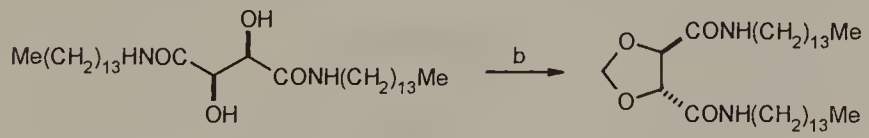
Scheme 10.10

Other methods of acetal formation from tartrate diols. Seebach *et al.* used alkylation of the thallium alkoxide, derived from *N,N,N′N′*-tetramethyltartramide with diiodomethane, to synthesize methylene acetal **10.1**. Alternately the two-phase alkylation reaction mediated by 18-crown-6 ether can be applied to prepare the methylene acetals, without intervention of toxic thallium compounds (Scheme 10.11).



10.1

a: 2 eq. TlOEt, benzene, then 1 eq. CH_2I_2, MeCN, RT, 12h, then 60°C, 3h (25%)[14]



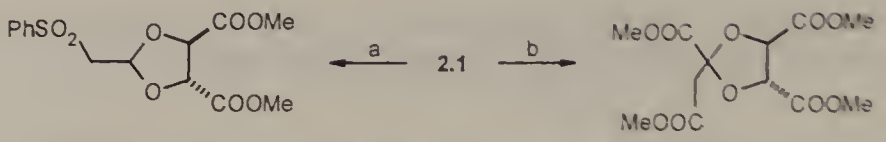
b: CH_2I_2, K_2CO_3, 18-crown-6, CH_2Cl_2, Δ (89%)[122]

Scheme 10.11

Michael-type addition of a tartrate to 1,2-bis(phenylsulfonyl)ethylene or to acetylenedicarboxylate allows preparation of functionalized tartrate acetals (Scheme 10.12).

Modification of the carboxy groups in tartrate acetals. Seebach has reported titanate-mediated transesterification of acetals of tartrates (Scheme 10.13).

Acetals of tartramides are readily obtained from acetals of tartrates by the action of ammonia or its derivatives (Scheme 10.14).



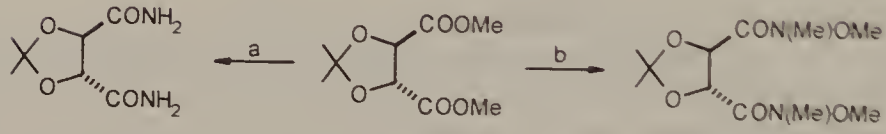
a: (*E*) or (*Z*)-$PhSO_2CH{=}CHSO_2Ph$, NaH, THF, RT, 6h (60%)[53]

b: MeOOCC≡CCOOMe, $La(Oi\text{-}Pr)_3{\cdot}3LiCl$, i-PrOH, 90°C, 24h (50%)[123]

Scheme 10.12

a: i-PrOH (excess), 0.05 eq. $Ti(Oi\text{-}Pr)_4$, 70°C, 3h (91-95%)[89]

Scheme 10.13

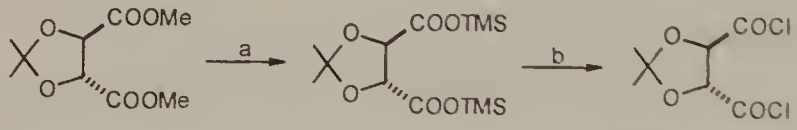


a: NH_3, MeOH, RT, 10 days, ca. 100%[73]

b: MeNHOMe·HCl, $AlMe_3$, CH_2Cl_2, -10°C (83%)[124]

Scheme 10.14

Alkaline hydrolysis of acetals of tartrates leads to acetals of tartaric acid which can further be converted to the corresponding acid chlorides.[4] In a modification of this synthesis, the acid chloride is obtained from the lithium salt via the trimethylsilyl ester[75] (Scheme 10.15)



a: $LiOH{\cdot}H_2O$, MeOH, RT, 2d, evaporation, then TMSCl, 18-crown-6 (cat.), THF, RT, 3h

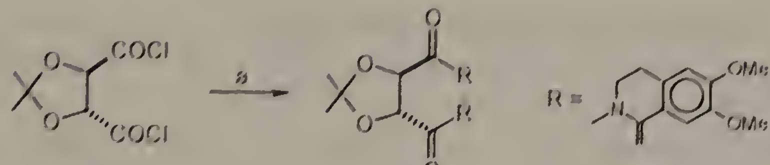
b: $(COCl)_2$, DMF (cat.), THF, RT (94%)[75]

Scheme 10.15

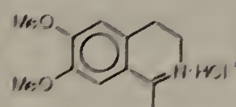
Acid chloride **10.2** is useful for preparing amides,[75] particularly from unstable amines (Scheme 10.16).

Bicyclic acetals **10.4** and **10.5** were obtained from diacid **10.3** by coupling with *N,N′*-disubstituted ethylenediamine (Scheme 10.17).

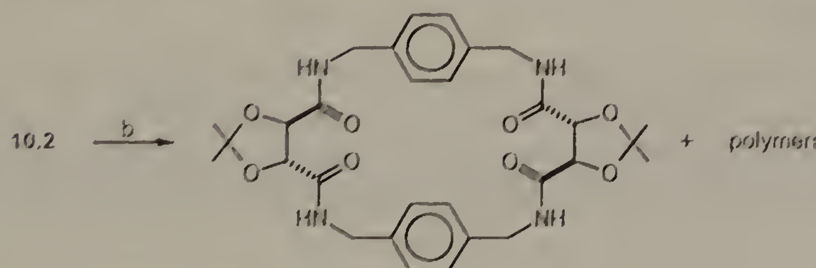
The use of an equimolar amount of base or pig liver esterase for hydrolysis of tartrate acetals allows the preparation of monoester derivatives (Scheme 10.18).



10.2

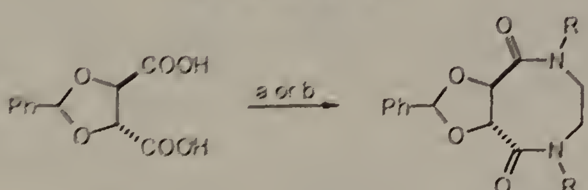
a 

, NEt_3, dioxane, RT, 68%[126]



b *p*-xylylenediamine, NEt_3, THF, RT (5%)[126]

Scheme 10.16



10.3

10.4 R = Bn

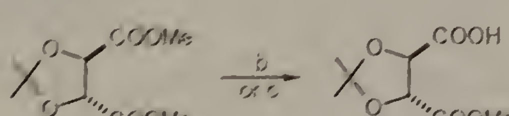
10.5 R = CF_3CH_2

a 1 eq. $BnHN(CH_2)_2NHBn$, 3 eq. *N*-methyl-2-chloropyridinium iodide, NEt_3, CH_2Cl_2, Δ (52%)[34]

b 1 eq. $CF_3CH_2HN(CH_2)_2NHCH_2CF_3$, 3 eq. DCC, 0.5 eq. DMAP, CH_2Cl_2, RT (38%)[43]

Scheme 10.17

a 1 eq. KOH, MeOH, RT, 8h (80%)[1]



b 1 eq. KOH, MeOH, RT, 1h (48–58%)[54,127]

c PLE, 0.1M phosphate buffer (pH 8), RT (81%)[128]

Scheme 10.18

The following acetals are available commercially:

dimethyl 2,3-*O*-benzylidene-L-tartrate [32278-72-3] and its enantiomer [91526-83-9]

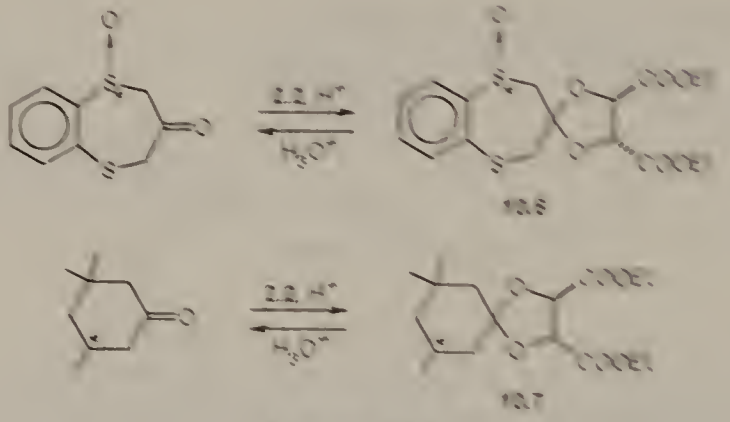
dimethyl 2,3-*O*-isopropylidene-L-tartrate [37031-29-7] and its enantiomer [37031-30-0]

N,N,N',N'-tetramethyl-2,3-*O,O'*-isopropylidene-L-tartramide.

Applications

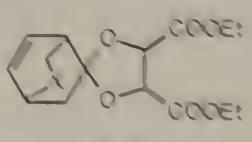
R

Tartrate acetals as resolving agents. Chiral racemic ketones can be resolved into enantiomers via their diastereomeric acetals with tartrates, see for example **10.6**.[28] Diastereomeric acetals of 3,3,5-trimethylcyclohexanone (**10.7**) can be separated by gas chromatography[28] or by controlled distillation[31] (Scheme 10.19).



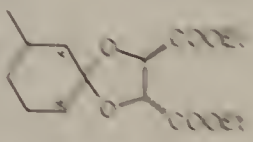
Scheme 10.19

Preparative separation of diastereomeric acetals **10.8** and **10.9** derived from diethyl tartrate and the corresponding bicyclic ketones was accomplished by liquid chromatography. The resolved ketones were used in the syntheses of loganin aglucon 6-acetate[32] and (−)-coriolin.[33]



10.8 X = CH_2[32]

10.9 X = CO[33, 34]

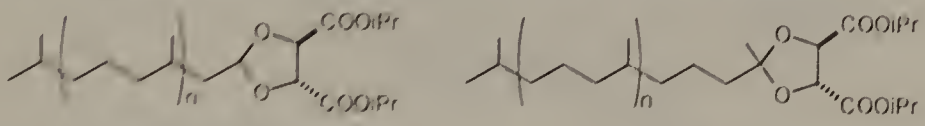


10.10

Enantiomeric excess of a chiral ketone or an aldehyde can be determined by converting it to a mixture of diastereomeric tartrate acetals. In the case of acetals **10.10** the composition of the diastereomeric mixture could be determined by

either ^{13}C NMR ($\Delta\Delta\delta \approx 0.4$ ppm for the starred carbon atoms)[134,135] or by gas chromatography.[136]

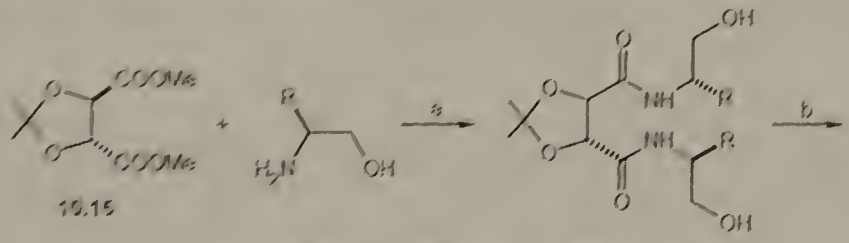
Diastereoisomeric acetals derived from dihydrocitronellal (**10.11**), hexahydrofarnesal (**10.12**), hexahydropseudoionone (**10.13**) and hexahydrofarnesylacetone (**10.14**) have been separated by capillary gas chromatography.[21]



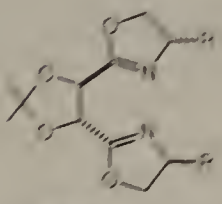
n=1 **10.11**
n=2 **10.12**

n=1 **10.13**
n=2 **10.14**

Tartrate acetals as ligands. Novel C_2-symmetric bis-oxazoline ligands **10.16** for the Cu-catalyzed asymmetric cyclopropanation and Rh(I)-catalyzed asymmetric hydrosilylation have been prepared from tartrate acetal **10.15** and chiral amino-alcohols by the groups of Andersson,[137] Ikeda,[138] and Knight[139] (Scheme 10.20).



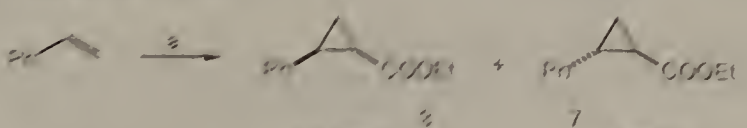
R	m.p. (°C)	$[\alpha]_D$ (CH_2Cl_2)	ref
H	oil	-61.6	138
i-Pr	oil	-143.0	138,139
t-Bu	oil	-120.9	137
t-Bu	81-83	-151.0	137,138
Bn	oil	-82.5	137
Ph	60-62	-128.3	138,139


10.16

a) i) *n*-BuLi (cat.), MeOH, 45°C (85-95%)
b) $MsCl$, NEt_3, CH_2Cl_2, 0°C → RT then NaOH (75-98%)

Scheme 10.20

Examples of enantioselective reactions catalyzed by complexes of ligands **10.16** are shown in Scheme 10.21.



a) $N_2CHCOOEt$, cat. $Cu(OTf)_2$, cat. **10.16** (R = *t*-Bu) 76%[137]

Scheme 10.21 *(continued)*

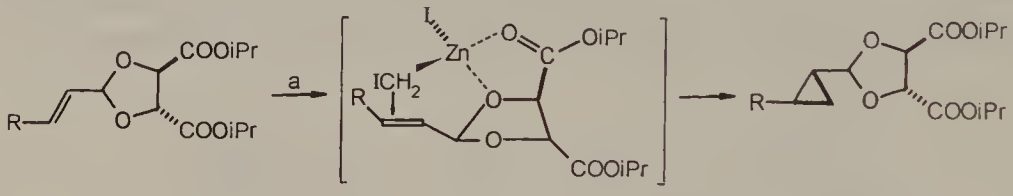
e.e. 64%

b: 1.6 eq. Ph_2SiH_2, 0.005 eq. $[Rh(COD)Cl]_2$, 0.04 eq. **10.16** (R = i-Pr), CCl_4, -5°C, 72h (90%)[138]

Scheme 10.21

A

Tartrate acetals as chiral auxiliaries. Yamamoto reported an asymmetric Simmons–Smith reaction employing tartrate acetal as the chiral auxiliary. The asymmetric induction in this reaction is entirely controlled by the chirality of the tartrate auxiliary which chelates the Lewis acid reagent[24,140] (Scheme 10.22).

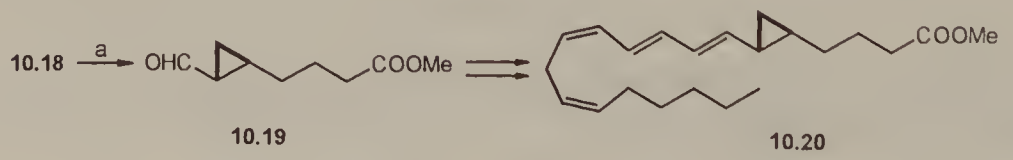


	R	yield (%)	d.e. (%)
10.17	Me	90	94
	n-Pr	80	91
	Ph	92	91
10.18	$MeOOC(CH_2)_3$	94	90

a: 5 eq. Et_2Zn, 10 eq. CH_2I_2, hexane, -20°→ 0°C

Scheme 10.22

Chiral cyclopropane **10.18** on hydrolysis yielded aldehyde **10.19**, a key intermediate in the synthesis of 5,6-methanoleukotriene A_4 (**10.20**)[24,140] (Scheme 10.23).

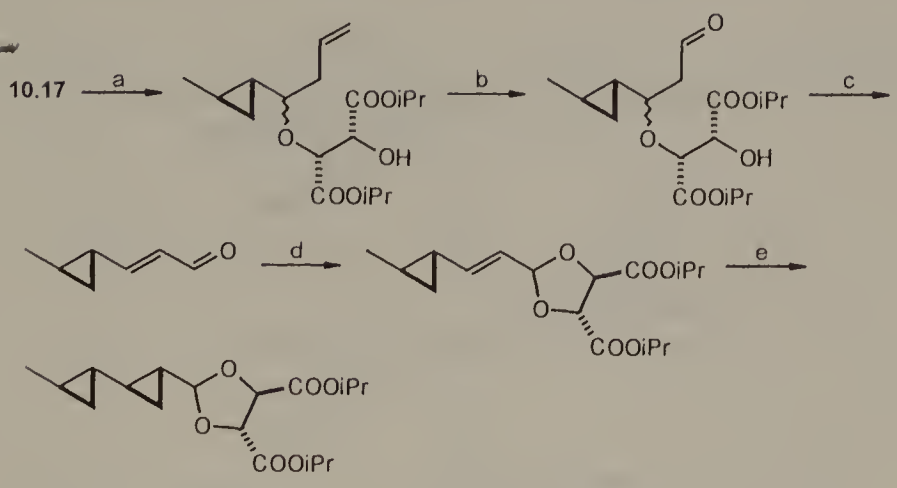


10.19 **10.20**

a: TsOH, MeOH-H_2O, RT, 72h (74%)

Scheme 10.23

Chiral vicinal bis-cyclopropanes are available by application of the Yamamoto procedure. An iterative strategy developed by Armstrong employs the cyclopropane **10.17** as the starting material[142] (Scheme 10.24).



a: AllTMS, $TiCl_4$ (59%)
b: O_3, then PPh_3 (90%)
c: CF_3COOH, Δ (90%)
d: $HC(OEt)_3$, PPTS, EtOH, PhH, then **2.3**, Δ (35%)
e: Et_2Zn, CH_2I_2 (65%)

Scheme 10.24

Sequential asymmetric bis-cyclopropanation reactions were applied by Barrett in an approach to the synthesis of the antifungal agent FR-900848.[115] The sequence utilized the Yamamoto procedure followed by the Charette protocol (see Chapter 8) to prepare the two diastereomeric tetracyclopropanes **10.21** and **10.22** (Scheme 10.25).

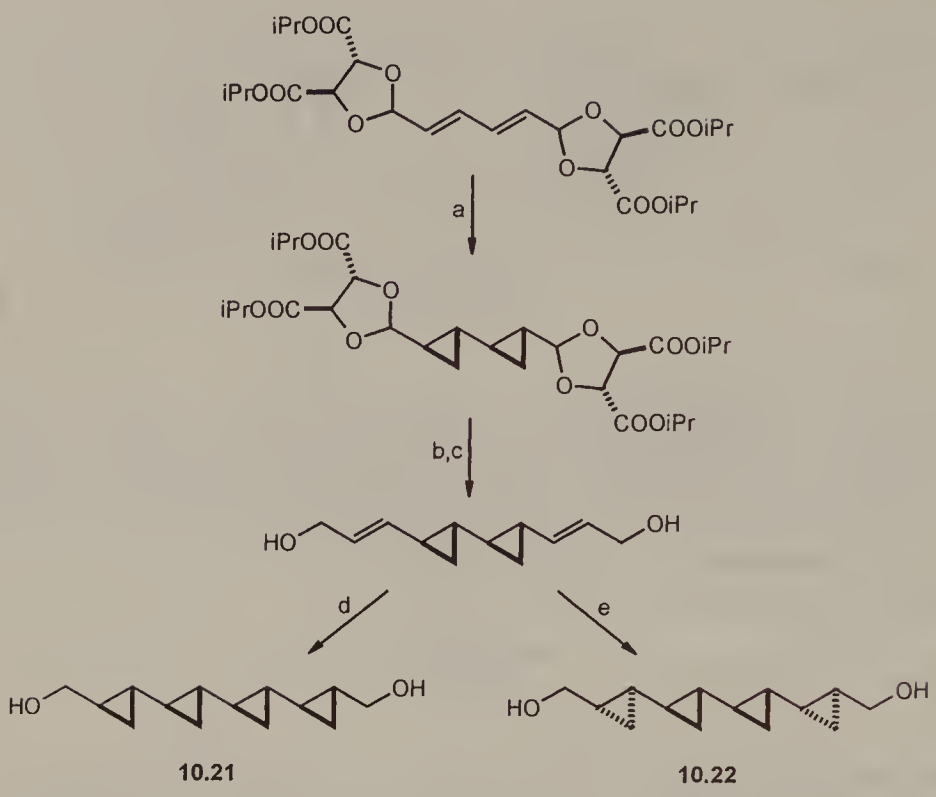
Asymmetric conjugate addition of organometallic reagents to α,β-unsaturated tartrate acetals proceeds with the opening of the acetal ring, but stereochemically it is related to the chelated transition state model proposed for asymmetric Simmons–Smith cyclopropanation (see above). Yamamoto *et al.* demonstrated high regio- and stereochemical control in the addition of organoaluminum reagents to tartramide acetals of α,β-unsaturated aldehydes. The reaction produces 1,4- or 1,2-adducts; the regioselectivity can be manipulated by the polarity of the solvent[26] (Scheme 10.26).

Asymmetric conjugate addition has been applied to the synthesis of the side-chain of biologically important vitamins E and K (alcohol **10.23**) and to the synthesis of various optically active ketones and aldehydes (Scheme 10.27).

Optically active secondary alcohols can be obtained from tartrate acetals of aldehydes upon reaction with dialkylboron bromides and higher order cuprates[17] (Scheme 10.28).

Tagliavini and Umani-Ronchi reported a similar 1,2-addition of a Reformatsky reagent to a tartrate acetal in the presence of $TiCl_4$; the reaction diastereoselectivity was low.[144]

Castaldi and Giordano reported the asymmetric bromination of alkyl aryl ketones via their tartrate acetals.[85] High diastereoselectivity was achieved for both acyclic and cyclic ketones and the brominated ketones were obtained in



10.21 **10.22**

a: Et_2Zn, CH_2I_2, $ClCH_2CH_2Cl$, -20°C (78%)

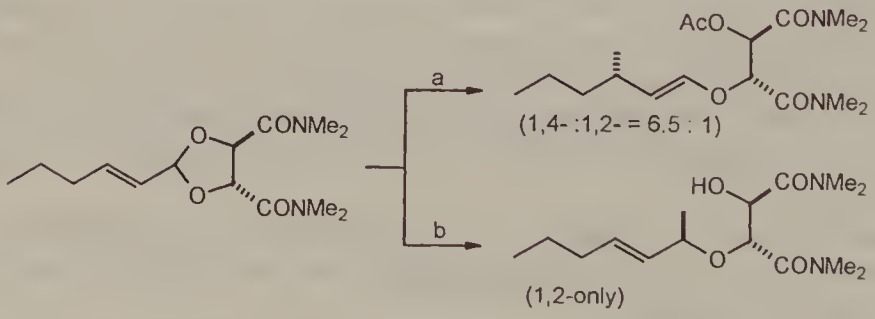
b: TsOH, THF, H_20, 55°C, then Ph_3P=CHCOOEt, CH_2Cl_2 (61%)

c: i-Bu_2AlH, CH_2Cl_2, -78°C (91%)

d: *ent*-**8.4**, $Zn(CH_2I)_2$, CH_2Cl_2, 0°→ 25°C (94%)

e: **8.4**, $Zn(CH_2I)_2$, CH_2Cl_2, 0°→ 25°C (100%)

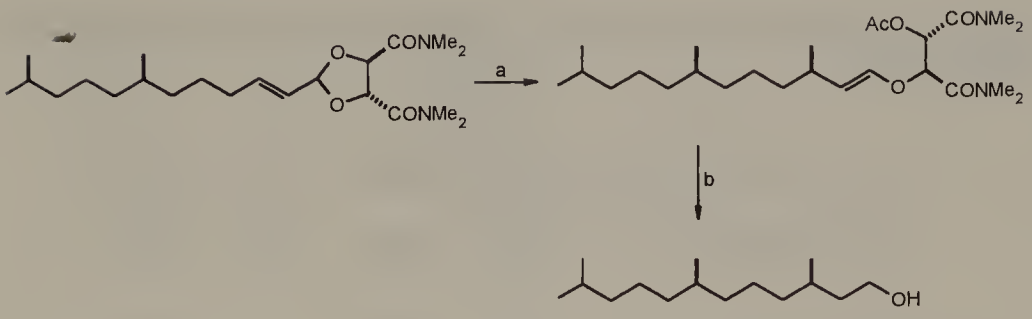
Scheme 10.25



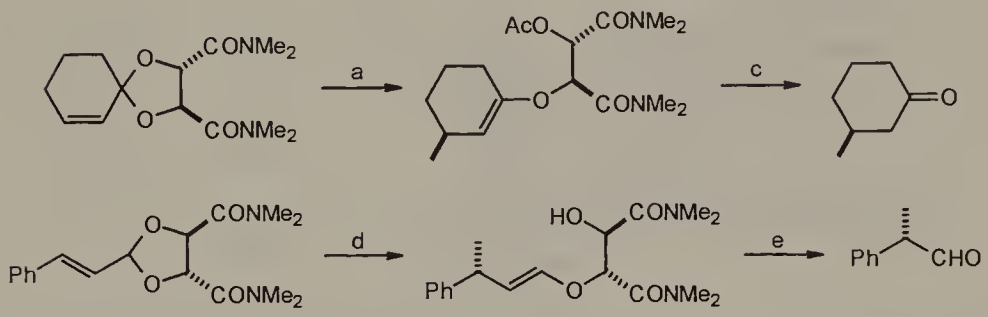
a: 5 eq. Me_3Al, $Cl(CH_2)_2Cl$, RT, then Ac_2O, pyridine, DMAP (97%, d.e. 88%)

b: 5 eq. Me_3Al, $CHCl_3$, RT (85%, d.e. 88%)

Scheme 10.26



10.23



a: 5 eq. Me_3Al, PhMe, RT, then Ac_2O, pyridine

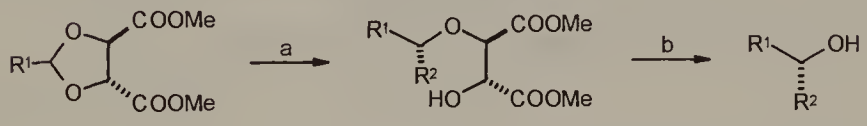
b: 6N HCl, dioxane, then $NaBH_4$ (92%, e.e. 96%)[26]

c: 6N HCl, dioxane (80%, e.e. 77%)[82]

d: 5 eq. Me_3Al, PhMe, RT (91%, d.e. 70%)

e: O_3, MeOH, -78°C (82%, e.e. > 95%)[143]

Scheme 10.27



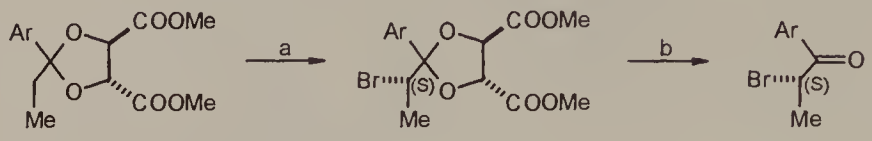
R^1	R^2	yield (%)	d.e. (%)
n-C_9H_{19}	Me	80	94
Cy	Me	83	89
n-C_9H_{19}	$CH{=}CH_2$	62	92

a: 1.2 eq. Me_2BBr, CH_2Cl_2, RT, then 3 eq. $R^2{}_2Cu(CN)Li_2$, -30°C

b: MsCl, NEt_3, then DBU, then MeONa, MeOH

Scheme 10.28

high enantiomeric purity by non-conventional removal of the acetal auxiliary[145] (Scheme 10.29).



Ar	yield (%)	d. e.(%)	yield (%)
Ph	94	86	92
4-ClC_6H_4	93	88	-
4-$MeOC_6H_4$	95	84	96[#]
5-bromo-6-methoxy-2-naphthyl	98	80	99[#]

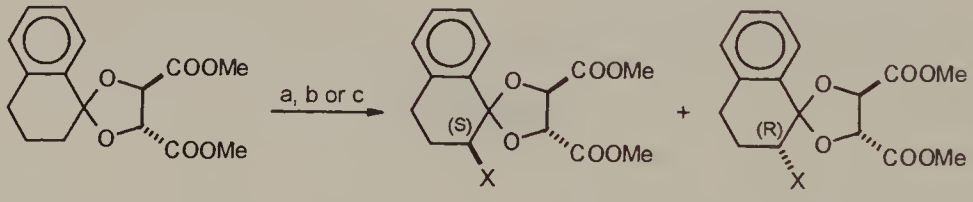
[#] enantiomerically pure after crystallization

a: 1 eq. Br_2, HBr (cat.), CCl_4, 15°C[85]

b: MsOH, H_2O, 20°C or CF_3SO_3H, $Cl(CH_2)_2Cl$, 15°C[145]

Scheme 10.29

The direction of asymmetric induction in the halogenation of tartrate acetals can be varied by the nature of the halogenating species used (Scheme 10.30).



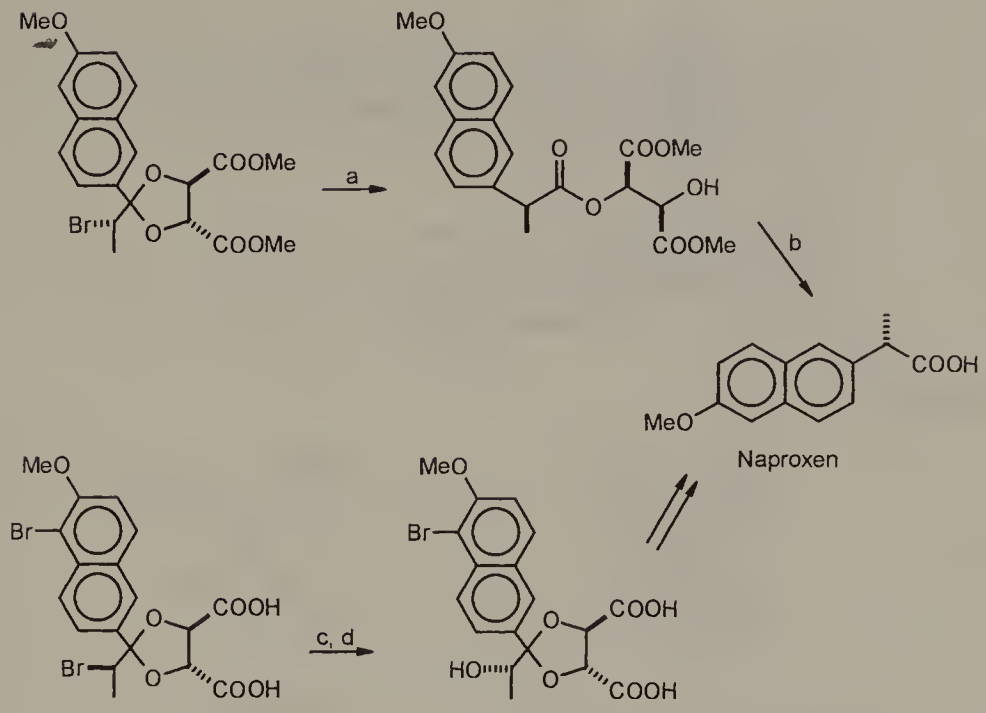
	(S) : (R)
a (X = Cl): 1eq. SO_2Cl_2, CH_2Cl_2, -10°C, 2.5h (98%)	88 : 12[102]
b (X = Br): 1eq. Br_2, CH_2Cl_2, -10°C, 1.5min. (99%)	86 : 14[102]
c (X = Br): 1 eq. pyridinium tribromide, THF, 0°C, 30 min. (95%)	5 : 95[146]

Scheme 10.30

Brominated acetals derived from arylalkyl ketones can be stereospecifically rearranged to 2-alkyl-2-arylacetic acids; among these are the antiinflammatory agents Naproxen and Ketoprofen (Scheme 10.31).

The synthesis of Naproxen has been scaled up to an industrial process by the Zambon Group.

Examples of addition reactions to the C=C bonds, in which asymmetric induction is due to the steric effects exerted by the tartaric acid acetal auxiliary rather then by chelation, are shown in Schemes 10.32–10.34.

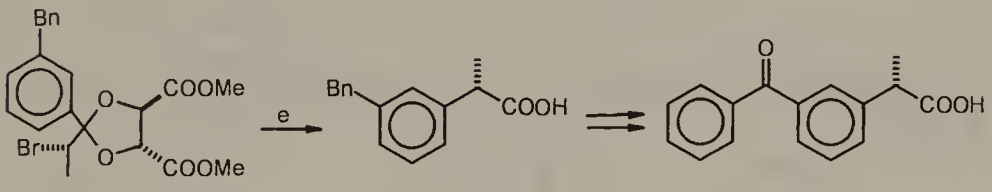


a: $AgBF_4$, $Cl(CH_2)_2Cl$, H_2O, 15°C, 18h (97%, d.e. 98%)

b: HCl, H_2O, 85°C (96%, d.e. 98%)[87]

c: NaH, DMF, 110°C

d: NaOH, then HCl[88]

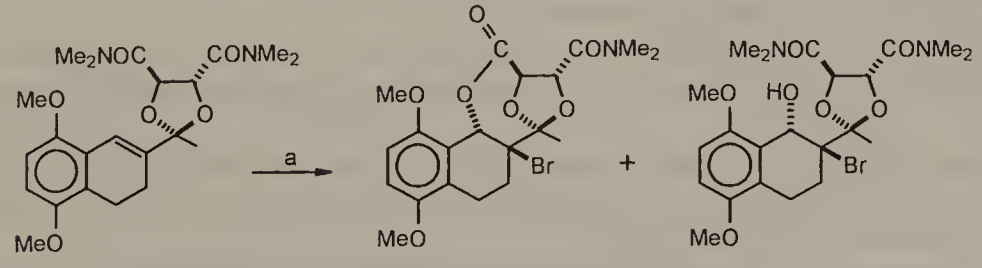


(d.e. 75%) (e.e. 88%)

e: NaOH, H_2O, DME, RT, then phosphate buffer, Δ (33%)[86]

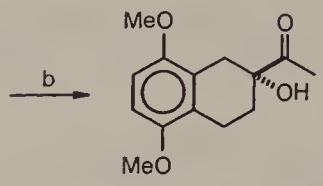
Scheme 10.31

Bromolactonization (Terashima)[147–149]



83%, d.e. 95% 7%

Scheme 10.32 (*continued*)



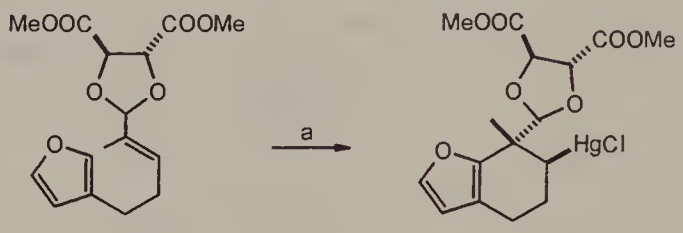
(intermediate for the synthesis of anthracyclinones)

a: AcNHBr, DMF-H_2O (100:1), 0°C, 15.5h

b: K_2CO_3, MeOH, then H_2, Pd/C, then HCl, Δ[149]

Scheme 10.32

Olefin cyclization[150]

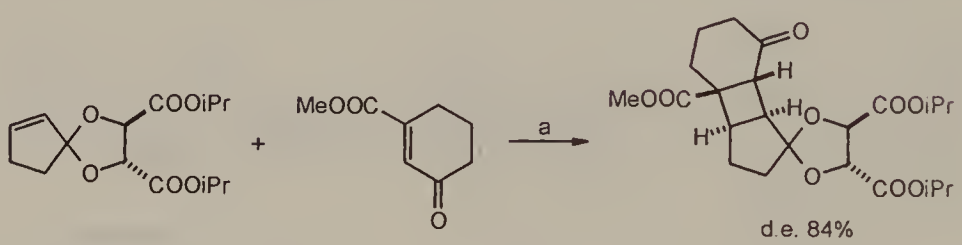


44%, d.e. 76%

a: 1.2 eq. $Hg(OTf)_2$, CH_2Cl_2, -78°C, 4h

Scheme 10.33

Photocycloaddition[100]



d.e. 84%

a: hν (350 nm), benzene

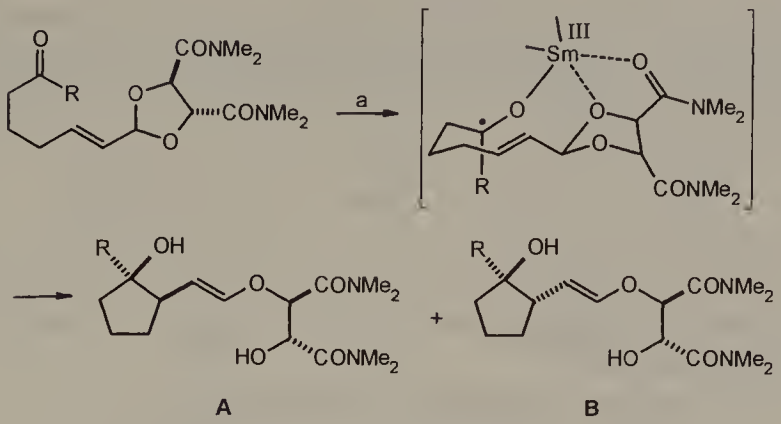
Scheme 10.34

Ketyl-olefin radical cyclization (Molander)[29] is highly diastereoselective; the two *cis*-isomers **A** and **B** are formed in more than 97% total yield and **A** is the main product of the reaction (Scheme 10.35).

Tagliavini and Umani-Ronchi used chiral orthoesters derived from tartrates as enantioselective acylating agents in the reactions with silyl enol ethers (Scheme 10.36).

Chiral chromium tricarbonyl-arene complexes were obtained with the aid of a tartrate acetal auxiliary. Two examples reported by Aubé *et al.*[42] and by Levine *et al.*[45] are shown in Scheme 10.37.

Watanabe *et al.*[151] used monoethyl *O,O'*-cyclohexylidene tartrate for highly diastereoselective desymmetrization of *myo*-inositol derivative **10.24** of *meso* structure (Scheme 10.38).

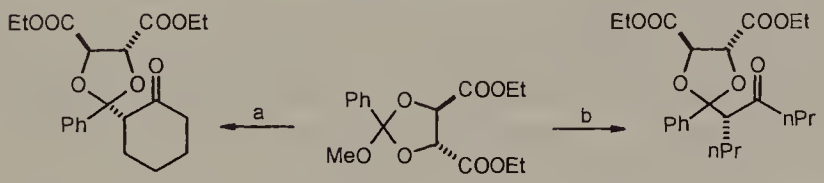


A B

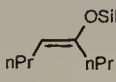
a: 2.6-2.8 eq. SmI_2, THF, 0°→ 35°C (53-83%)

R	A : B
H	95 : 5
Me	97 : 3
Et	97 : 3
i-Pr	93 : 7

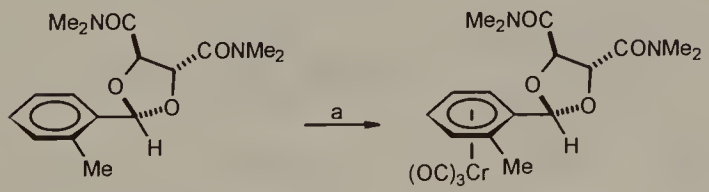
Scheme 10.35



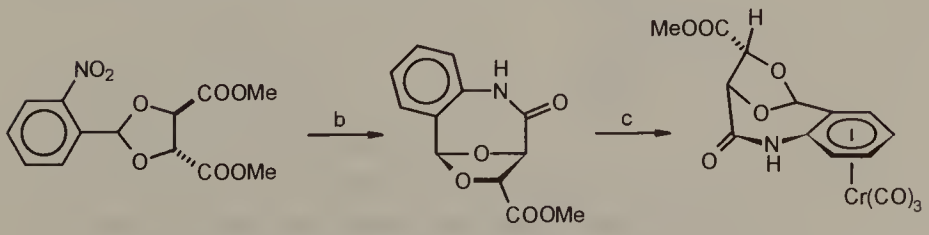
a:  , $BF_3{\cdot}Et_2O$, CH_2Cl_2, -60°C, 8h (93%, d.e. 89%)[109,110]

b:  , $BF_3{\cdot}Et_2O$, CH_2Cl_2, -60°C (90%, d.e. 88%)[109,111]

Scheme 10.36



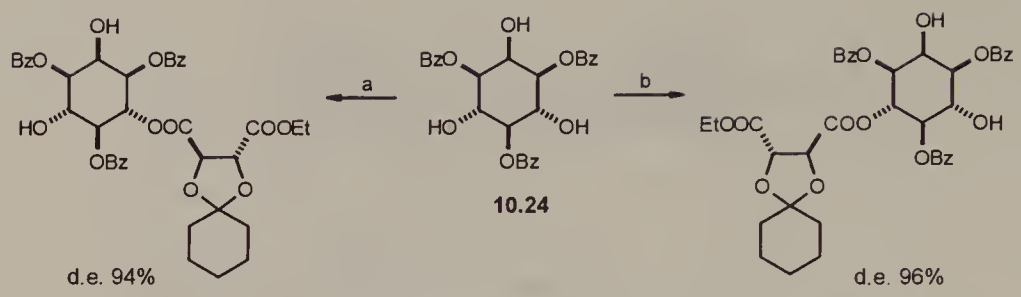
a: (naphthalene)$Cr(CO)_3$, THF, Δ (61%, d.e. 48%)[42]



b: H_2, 10% Pd/C, EtOH (98%), then Δ (88%)

c: $Cr(CO)_6$, Δ (42%, d.e. 96%)[45]

Scheme 10.37



a: 1 eq. monoethyl *O,O'*-cyclohexylidene L-tartrate, 1.1 eq. MsCl, 2.5 eq. NMM, DMAP (cat.), THF, 0°C

b: as a, 1 eq. monoethyl *O,O'*-cyclohexylidene D-tartrate was used

Scheme 10.38

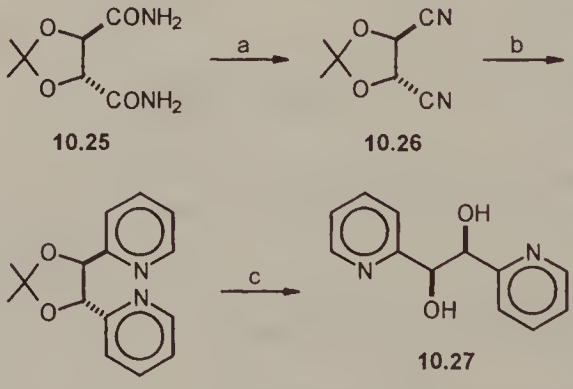
The unsymmetrical ester obtained with D-tartrate acetal was converted to D-*myo*-inositol 1,3,4,5-tetrakis-phosphate.[151]

Stankovic and Schreiber[152] reported the synthesis of transmembrane ion channels based on tartrate acetals.

B

Tartrate acetals as building blocks. Most obviously tartrate acetals can be incorporated into the target compounds by modification of the terminal carboxy or carbamide groups. For example, Schreiber used *O,O'*-methylene L- and D-tartaric acid for the construction of acid-gramicidin A hybrids by formation of the amide bonds.[153]

Chelucci used the acetal protected tartrate building block **10.25** in the synthesis of the chiral bis(2-pyridine) derivative **10.27** via the tartarodinitrile **10.26**[72,154] (Scheme 10.39).



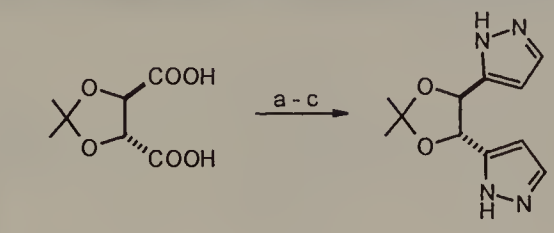
a: 4 eq. MsCl, pyridine, 100°C, 5h, (81%)

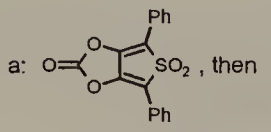
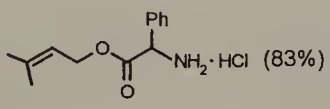
b: HC≡CH, CpCo(COD), PhMe, 14 bar, 140°C (72%)

c: 0.1M H_2SO_4, EtOH, Δ, 4h (85%)

Scheme 10.39

Another heterocyclic pyrazole derivative **10.29** was synthesized by Stieglich from *O*,*O*′-isopropylidene L-tartaric acid (**10.28**)[60] (Scheme 10.40).



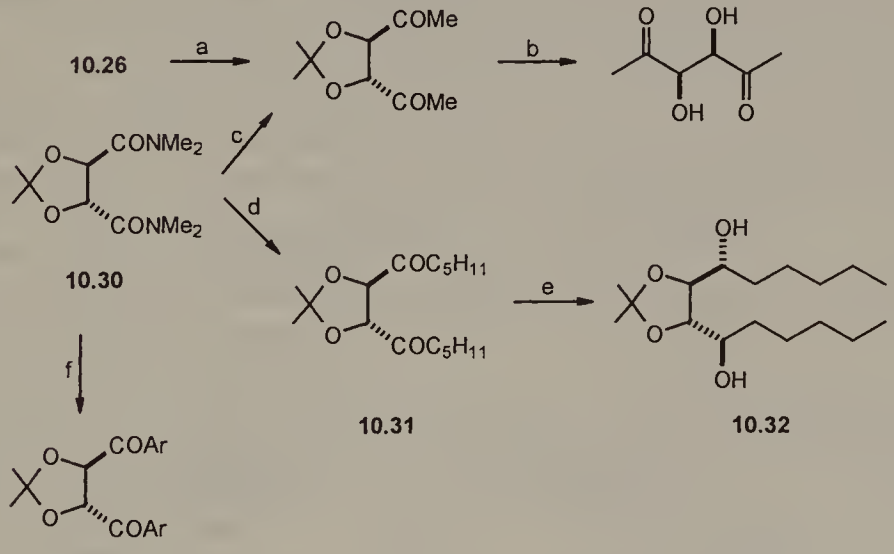
a:  , then  (83%)

b: Ph_3P, NEt_3, $Cl_3C\text{-}CCl_3$ (85%)

c: O_3, Me_2S, then $N_2H_4\cdot H_2O$ (57%)

Scheme 10.40

Dinitrile **10.26** and diamide **10.30** were used by Haines *et al.*,[71] Wicha and Achmatowicz [155] and Di Mare *et al.*[156] for the synthesis of chiral 1,4-diketones. Acetal derivative of a tetraol **10.32** was obtained by stereoselective reduction of diketone **10.31** (Scheme 10.41).



a: MeMgI, PhMe-Et_2O (43%)[71]

b: CF_3COOH-H_2O (9:1), 0°C, 10 min. (89%)[71]

c: 4 eq. MeMgCl, THF, RT ,1h (50%)[71]

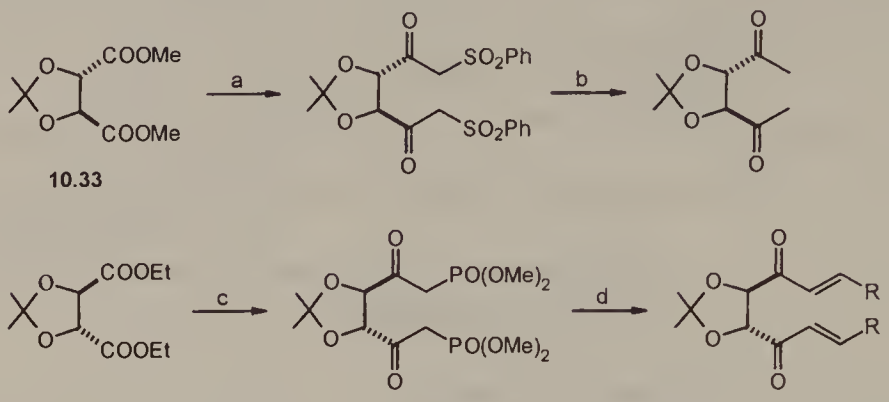
d: n-$C_5H_{11}MgBr$, THF (50-70%)[155]

e: K-Selectride, THF, -78°C, 2h (95%, d.e. 88%)[155]

f: 3 eq. ArMgX, Et_2O (Ar = 4-FC_6H_4, 66% or Ar = 3,5-$Me_2C_6H_3$, 49%)[156]

Scheme 10.41

Derivatives of chiral 1,4-diketones are also available in the reaction of acetal **10.33** with the dilithioderivative of methyl phenyl sulfone or with the lithium derivative of dimethyl methylphosphonate[157,158] (Scheme 10.42).



a: 2 eq. $PhSO_2CHLi_2$, THF, 0°C, 15 min (85%)

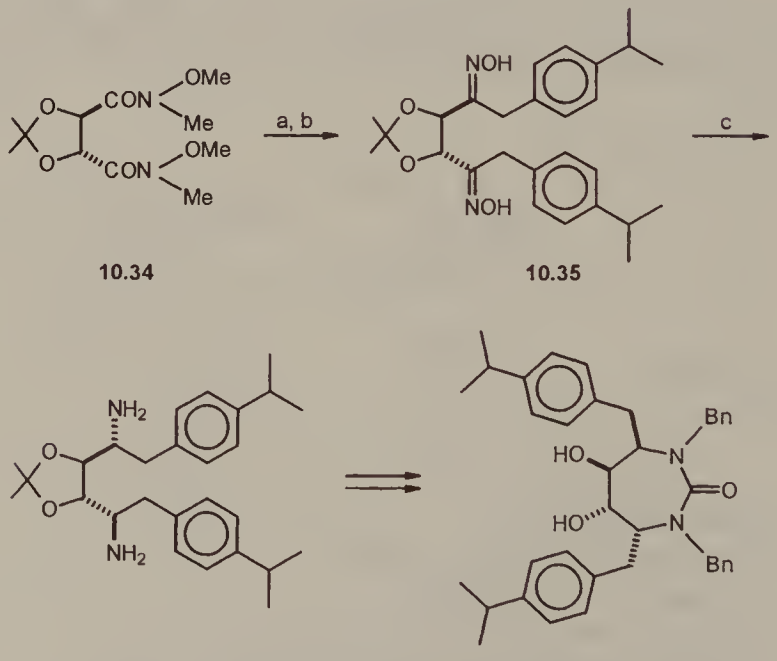
b: Al(Hg), THF-H_2O (9:1), 0°C, 4h (73%)[157]

c: 2.2 eq. $LiCH_2PO(OMe)_2$, THF, -78°C → RT, 2h (100%)

d: RCHO (R = protected sugar), Cs_2CO_3, i-PrOH (44-54%)[158]

Scheme 10.42

The synthesis of the novel HIV-1 protease inhibitor **10.36** is based on the addition of a Grignard reagent to the hydroxamate ester **10.34** and subsequent stereoselective reduction of the dioxime **10.35**[124] (Scheme 10.43).



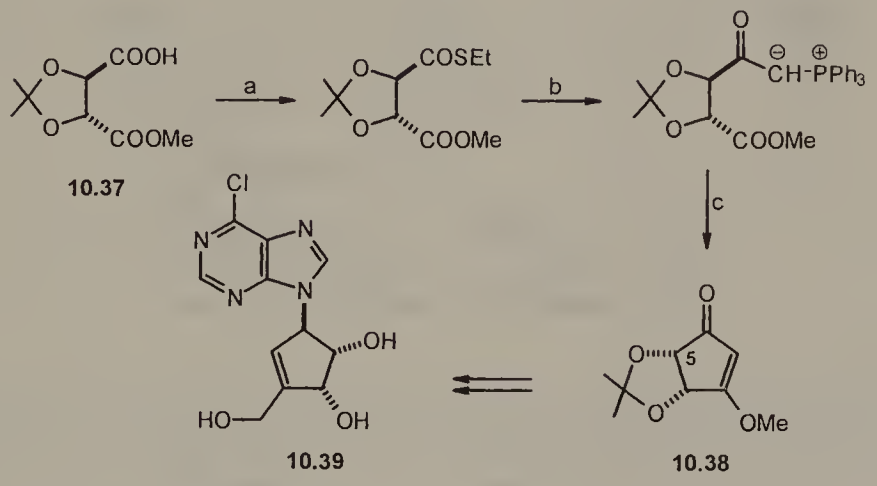
a: p-(i-Pr)$C_6H_4CH_2MgCl$, THF (95%)

b: NH_2OH·HCl, EtOH, H_2O (82%)

c: i-Bu_2AlH, PhMe (58%)

Scheme 10.43

The optically active cyclopentenone building block **10.38** was synthesized by Bestmann from monoester **10.37**. The key step in the synthesis was an intramolecular Wittig reaction accompanied by epimerization at C(5)[159,160] (Scheme 10.44).



a: EtSH, DCC, DMAP, CH_2Cl_2 (83%) c: PhMe, 110 bar, 150°C, 80h (60%)

b: $Ph_3P{=}CH_2$, PhMe, Δ (70%)

Scheme 10.44

Cyclopentenone **10.38** was converted to the naturally occuring carbocyclic nucleoside analogues (−)-neplanocin A (**10.39**)[160a] and (−)-aristeromycin.[160b]

Barton applied the radical decarboxylative process developed in his laboratory for substitution of the carboxy group of the monoacid acetal **10.37**. The substitution products **10.41**, **10.42** and **10.43** were obtained with essentially complete retention of configuration[161] (Scheme 10.45).

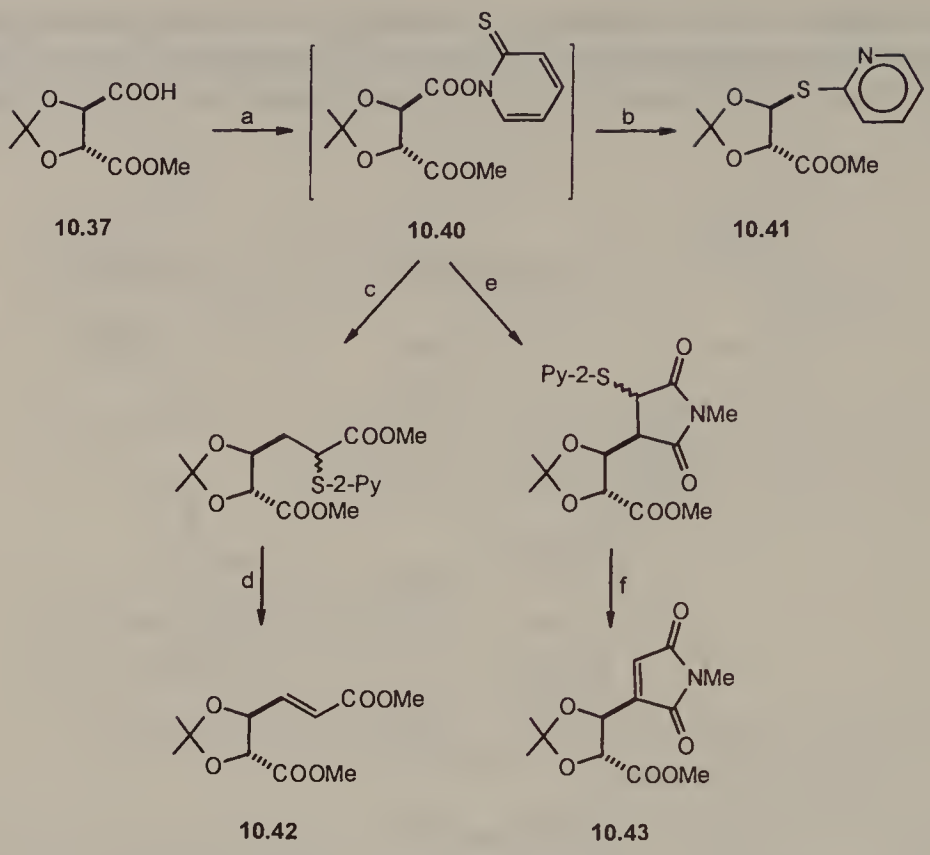
The substitution product **10.44**, obtained from the Barton ester **10.40** and phenyl vinyl sulfone, was transformed in seven steps into a highly functionalized β-lactam **10.45**[162] (Scheme 10.46).

Stereoregular polyamides were prepared by a room-temperature polycondensation of bis(pentachlorophenyl) *O,O'*-methylene-L-tartrate with bis-TMS derivatives of α,ω-alkane-diamines[5] (Scheme 10.47).

These polytartramides were readily soluble in chloroform and formed highly crystalline films.

Further synthetic applications of tartrate acetals as chiral building blocks are based on reactions at C(2) or C(3).

Tartrate acetals can be directly allylated and benzylated through the enolate ions of moderate stability, generated at low temperatures. Additions occur preferentially from the *Si*-face of the L-tartrate derived enolate.[163a] Seebach demonstrated synthetic utility of this reaction, giving predominantly *threo* products[163] (Scheme 10.48).



a: ClCOOi-Bu, NMM, THF, 15 min. -20°C, then *N*-hydroxy-2-thiopyridone sodium salt, THF, 90 min., -20°C

b: hν (tungsten lamp), 78%

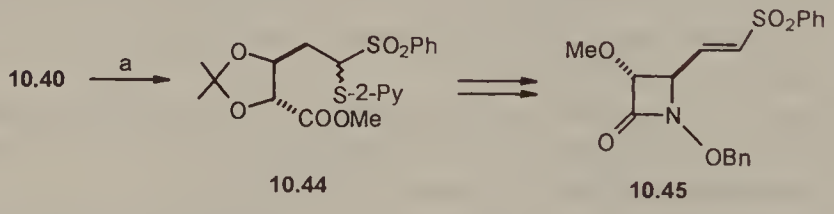
c: methyl acrylate, hν (70%)

d: 3-$ClC_6H_4CO_3H$, then Δ (PhMe), 75%

e: *N*-methylmaleimide, hν (93%)

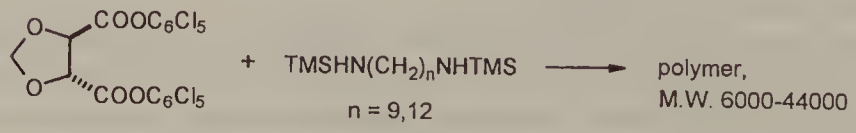
f: Cu powder, Δ (52%)

Scheme 10.45

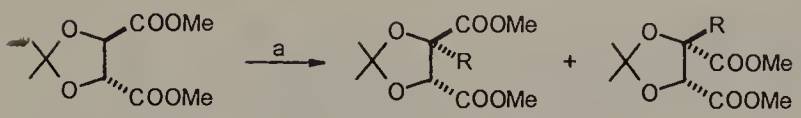


a: $CH_2=CHSO_2Ph$, hν (70%)

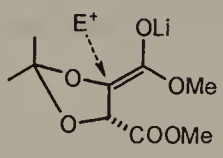
Scheme 10.46



Scheme 10.47



ent-**10.33** *threo* *erythro*



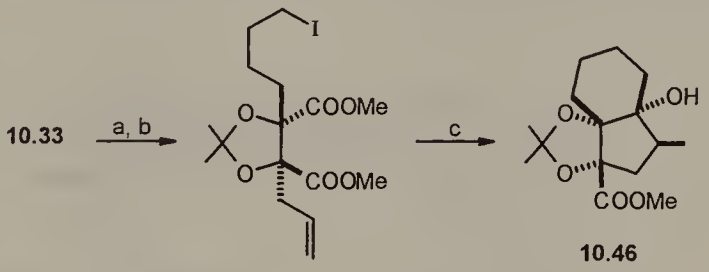
R	*threo* : *erythro*	yield (%)
All	87 : 13	65
$CH_2CH{=}CMe_2$	82 : 18	75
Bn	84 : 16	54
CH_2An	82 : 18	77

a: 1.1 eq. LDA, THF, HMPA, 1.2 eq. RBr, -70° → 10°C

Scheme 10.48

This procedure has been applied to the synthesis of (+)−malyngolide.[164]

Molander used the product of double alkylation of tartrate acetal **10.33** for the synthesis of a tricyclic product **10.46** by a tandem reaction of intramolecular nucleophilic acyl subsitution and ketyl-olefin coupling, promoted by samarium(II) iodide[165] (Scheme 10.49).



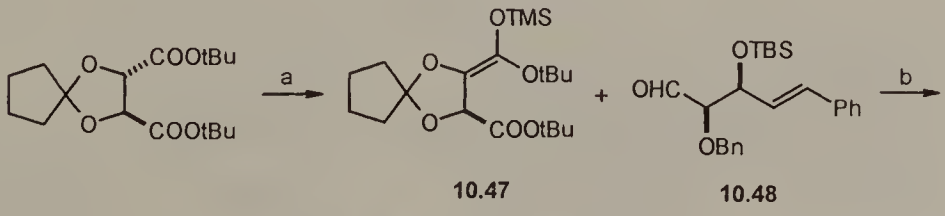
a: LDA, THF, HMPA, All-Br

b: LDA, THF, HMPA, $I(CH_2)_4I$

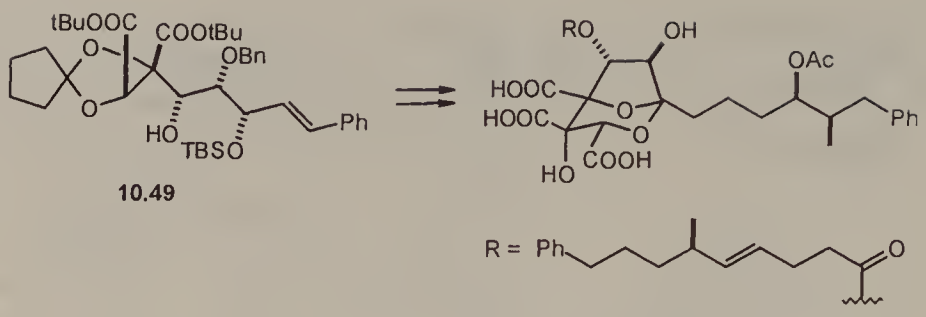
c: 4 eq. SmI_2, THF, HMPA (26%)

Scheme 10.49

Aldol products of *erythro* configuration were obtained in the reaction of acetone with the enolate derived from **10.33**.[163] Evans used a Lewis acid catalyzed aldol reaction of silylketene acetal **10.47** with chiral aldehyde **10.48** to construct the core carbon framework of zaragozic acid C[166] (**10.50**) (Scheme 10.50).



Scheme 10.50 (*continued*)



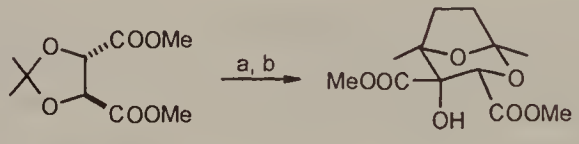
10.49 10.50

a: LiHMDS, TMSCl, THF, -78°C, 30 min., 0°C, 30 min. (97%)

b: $(i\text{-PrO})TiCl_3$, CH_2Cl_2, -78°C, 2h, -40°C, 2.5h (76%)

Scheme 10.50

Again, the aldol product (**10.49**) obtained in the above reaction had *erythro* configuration. Evans published efficient syntheses of cinatrins C_1 and C_3 based on a similar methodology.[92] Aggarwal used an aldol reaction of acetonylacetone and the enolate generated from **10.33** to prepare, after acidic cyclization, a derivative of 2,8-dioxabicyclo[3.2.1]octane **10.51**, a core of the squalestatin family of fungal metabolites[167] (Scheme 10.51).



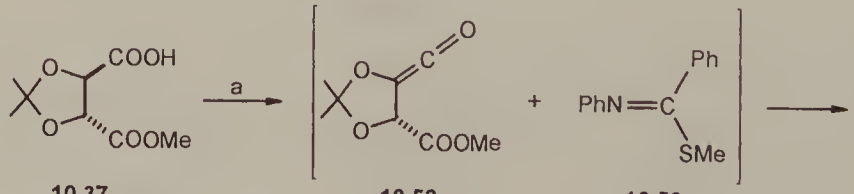
10.33 10.51

a: LDA, 12-crown-4, THF, -78°C, 5h, $MeCO(CH_2)_2COMe$ (77%)

b: HCl, MeOH, 1.5h, 65°C (30%)

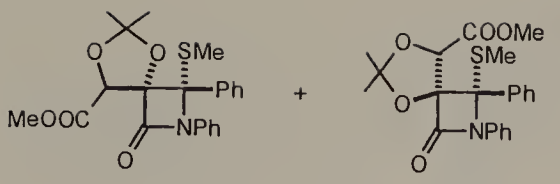
Scheme 10.51

[2 + 2] Cycloaddition of imine **10.53** and ketene **10.52**, generated from acetal **10.37**, gives a 6 : 4 mixture of diastereomeric β-lactams **10.54** and **10.55**[168] (Scheme 10.52).



10.37 10.52 10.53

Scheme 10.52 *(continued)*

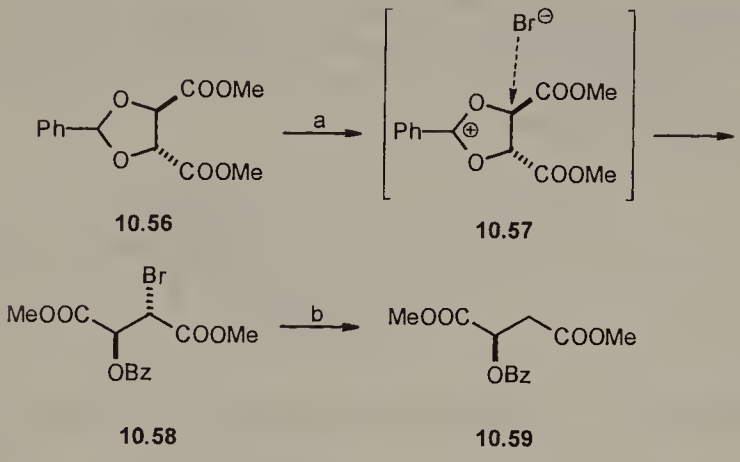


10.54 **10.55**

a: Ph(MeS)C=NPh, $PhOP(O)Cl_2$, NEt_3, CH_2Cl_2, 0°C → RT

Scheme 10.52

Substitution of the tartrate C(α)–O bond is possible through the intermediate cyclic 1,3-dioxolan-2-ylium ion **10.57**, formed by the oxidation of benzylidene acetal **10.56**. An example of this stereochemically well defined transformation is shown in Scheme 10.53. The *erythro* bromobenzoate **10.58** can be converted to (*R*)-malic derivative **10.59**.[169]



10.56 **10.57**

10.58 **10.59**

a: 1 eq. NBS, HBr (cat.), CCl_4, Δ (90%)

b: 1.2 eq. Bu_3SnH, AIBN, PhMe, 80°C, 2h, (88%)[169]

Scheme 10.53

10.2 OTHER ACETALS

Synthesis

Table 10.2 Physical properties of acetals 10.60–10.73

No.	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
10.60	118.5–119	+130.6 (Me_2CO)[a]	3,170
10.61 (2*S*,2′*S*)	176	+28.4 (Me_2CO)	171,172
10.61 (2*R*,2′*S*)	162	+49.0 (Me_2CO)	171,172
10.61 (2*R*,2′*R*)	205	+54.0 (Me_2CO)	172

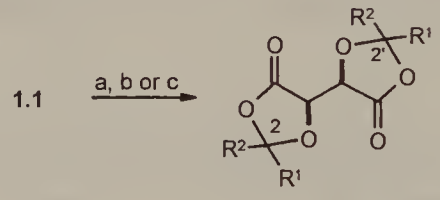
(*continued*)

Table 10.2 (*continued*)

No.	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
10.62	102	+63.3 ($Cl_2HCCHCl_2$)	173
10.63	73–74	+116.0 ($CHCl_3$)	174
10.66	152–154/0.6	+141.0 ($CHCl_3$)	175,176
10.67	—	+102.6 ($CHCl_3$)	177
10:69	107–115/0.03	−66.3 (EtOH)	7
10.70	107	−110.4 ($CHCl_3$)	178
10.71	115/0.01	−111.5 ($CHCl_3$)	178,179
10.72	76–77	−65.5 (MeOH)	180,181
10.73	93–93.5	−56.4 (EtOH)	180,182

[a] At 546 nm.

Bis-(1,3-dioxolan-4-one) acetals from L-tartaric acid. Reaction of tartaric acid with reactive carbonyl compounds (paraformaldehyde, chloral, acetone) or with 2,2-dimethoxypropane gives, among other products, bis-acetals of 1,3-dioxolan-4-one type (Scheme 10.54).



	R^1	R^2
10.60	H	H
10.61	CCl_3	H
10.62	Me	Me

a (**10.60**): 2.1 eq. $(CH_2O)_n$, 0.2 eq. H_2O, 150°C, then H_2SO_4, RT (ca. 40%)[2]

b (**10.61**): 2.2 eq. $CCl_3CH(OH)_2$, H_2SO_4, RT, 30 min. (ca. 100%, mixture of diastereomeric tartaric acid *chloralides*[183,184]

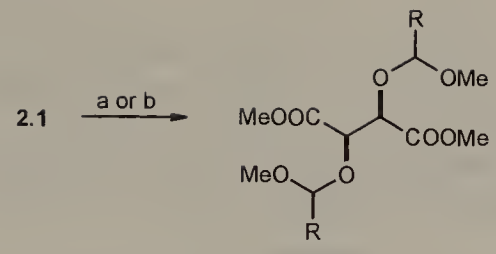
c (**10.62**): Me_2CO, $ZnCl_2$, RT, 12h (30%)[173] or Me_2CO, $Me_2C(OMe)_2$, BF_3, 4h, 0°C[185]

Scheme 10.54

Bis-(1,3-dioxolan-4-one) acetals of L-tartaric acid with benzaldehyde (mixture of diastereomers) were also described.[186]

Mono- and bis-(alkoxyalkyl) acetals of L-tartrates. Compounds of this type include methoxymethyl (MOM), methoxyethyl (ME), ethoxyethyl (EE), and tetrahydropyranyl (THP) derivatives (Scheme 10.55).

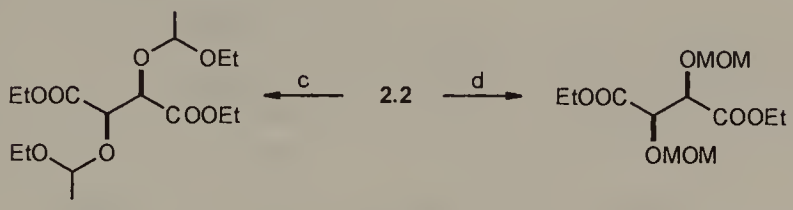
The unsymmetrical mono-MOM protected tartrate diol can be readily obtained by alkylation of diethyl tartrate (**2.2**) with one equivalent of base and



10.63, R = H
10.64, R =Me

a (R = H): 1.1 eq. $CH_2(OMe)_2$, 0.6 eq. P_2O_5, $CHCl_3$, RT (58%)[174]

b (R = Me): 6 eq. $MeOCH{=}CH_2$, CF_3COOH (cat.), CH_2Cl_2, RT, 2 days (100%, mixture of diastereomers)[187]



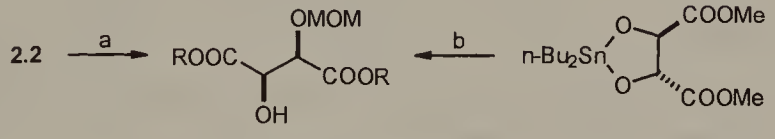
10.65 **10.66**

c: $EtOCH{=}CH_2$ (excess), CF_3COOH (cat.), RT, 36h (ca. 100%)[188]

d: 10 eq. $CH_2(OMe)_2$, 5 eq. P_2O_5, $CHCl_3$, RT (100% crude)[13,176,189] or 2.5 eq. $ClCH_2OMe$, 2.5 eq. i-Pr_2NEt, $CHCl_3$, Δ (79%)[175]

Scheme 10.55

methoxymethyl chloride or from the stannylene derivative of dimethyl tartrate (Scheme 10.56).



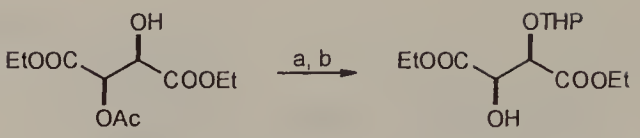
10.67, R = Me
10.68, R = Et

a R = Et): 1 eq. NaH, 1 eq. $MeOCH_2Cl$, DMF, -40°C (85%)[13]

b (R = Me): 1.6 eq. $MeOCH_2Cl$, $CHCl_3$, RT (86%)[177]

Scheme 10.56

Mono-tetrahydropyranyl protection of the tartrate hydroxy groups can be executed effectively through the *O*-monoacetyl derivative of diethyl tartrate; direct tetrahydropyranylation of diethyl tartrate with one equivalent of dihydropyran yields a mixture of mono- and bis-tetrahydropyranyl derivatives (Scheme 10.57).



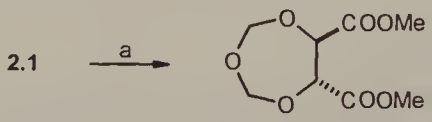
a: 1.2 eq. dihydropyran, CSA (cat.), CH_2Cl_2, RT, 0.5h (99%)

b: EtONa, EtOH, 1h, 0°C (82%)

Scheme 10.57

With two equivalents of dihydropyran the *O,O'*-bis-tetrahydropyranyl derivative is cleanly obtained from diethyl tartrate.[190]

The reaction of dimethyl tartrate with excess paraformaldehyde under BF_3 catalysis yields a trioxepane acetal **10.69** (Scheme 10.58).

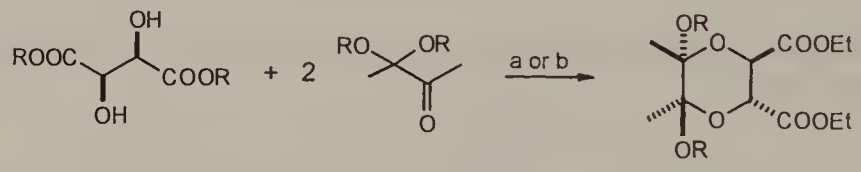


10.69

a: 3 eq. $(CH_2O)_n$, 0.3 eq. $BF_3{\cdot}Et_2O$, AcOi-Pr, RT, 3.5h, (68%)[7,191]

Scheme 10.58

1,4-Dioxane derivatives from tartrates. Monoacetals of butane-2,3-dione on transacetalization with a tartrate afford 1,4-dioxane derivatives **10.70** and **10.71** (Scheme 10.59).



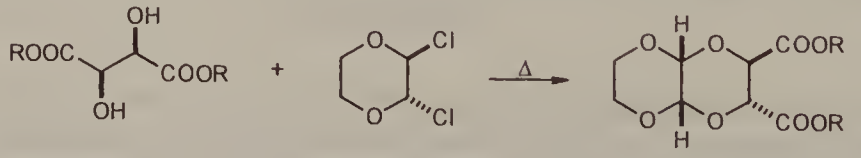
10.70, R = Me

10.71, R = Et

a: TsOH (cat.), 60-70°C, 73-88%[178,179]

Scheme 10.59

trans-2,3-Dichloro-1,4-dioxane reacts with tartrates to give 1,4,5,8-tetraoxadecalin-2,3-dicarboxylic acid derivatives **10.72**, **10.73**[180,182] (Scheme 10.60).



10.72, R = Me

10.73, R = Et

Scheme 10.60

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11 Tartraldehydes

11.1 TARTARIC DIALDEHYDES

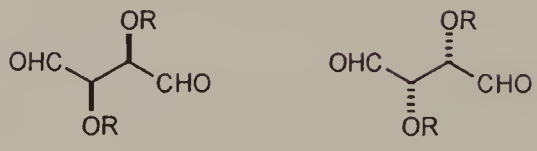
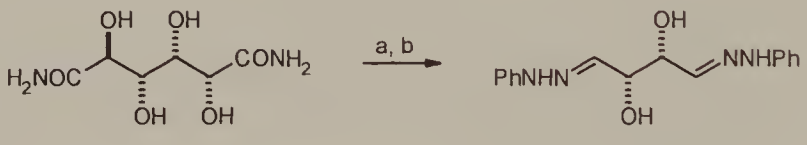


Figure 11.1

Overview of Earlier Work

Tartaric dialdehydes, either unprotected or protected, are highly reactive and unstable compounds seldom isolated and characterized in pure form. Earlier these dialdehydes were prepared from the carbohydrate substrates and isolated in the form of stable derivatives. Bergmann prepared mono- and bis-phenylhydrazone derivatives of D-tartrdialdehyde from D-glucaric acid diamide[1] (Scheme 11.1).



m.p. 177-179°C (dec.)

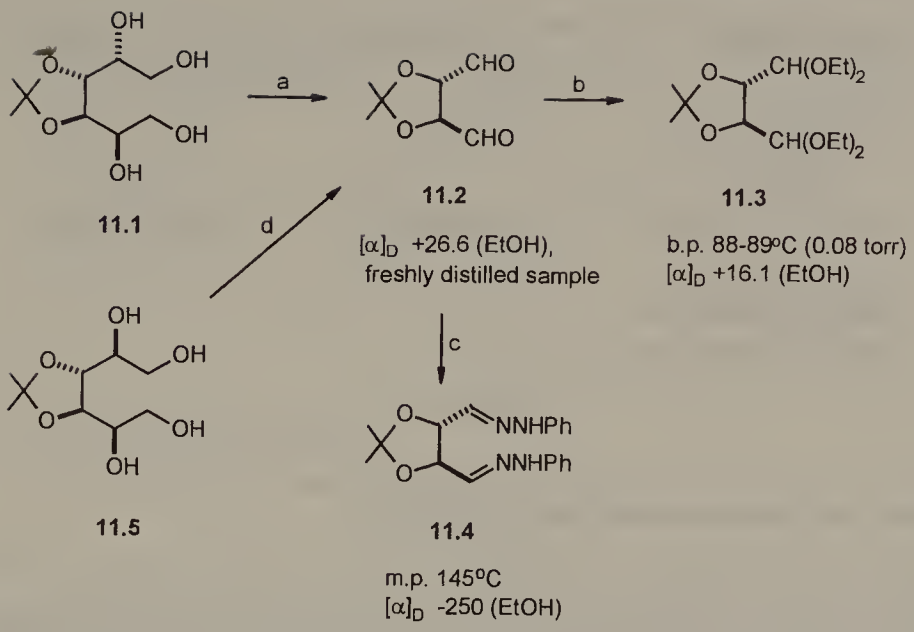
$[\alpha]_D$ -114.3 (pyridine)[2]

a: Br_2, KOH

b: $PhNHNH_2$

Scheme 11.1

The 2,3-*O*-isopropylidene derivative of tartrdialdehyde received more attention. Fischer obtained 2,3-*O*-isopropylidene D-tartraldehyde (**11.2**) and its derivatives **11.3** and **11.4** from 3,4-*O*-isopropylidene D-mannitol (**11.1**)[2] (Scheme 11.2). Similar synthesis of **11.2** was accomplished starting from 3,4-*O*-isopropylidene D-glucitol (**11.5**).[3]



a: $Pb(OAc)_4$, benzene, Δ

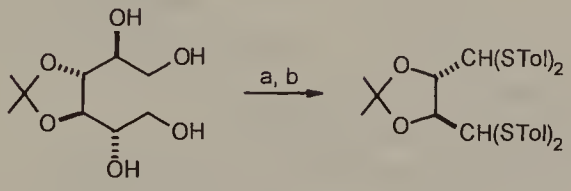
b: $HC(OEt)_3$, EtOH, NH_4Cl, RT, 10 days

c: $PhNHNH_2$, EtOH

d: $NaIO_4$, H_2O, RT

Scheme 11.2

Thioacetal derivatives of 2,3-*O*-isopropylidene D-tartrdialdehyde were obtained from derivatives of L-iditol (**11.6**)[4] and D-arabinose (**11.7**)[5,6] (Scheme 11.3).



11.6

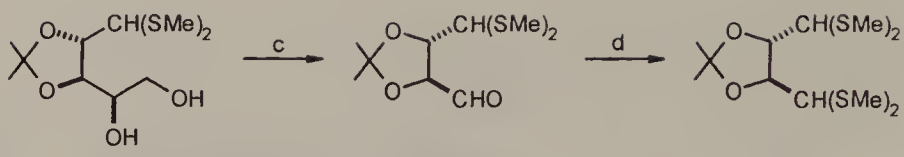
m.p. 101°C

[α]D +70 (pyridine)

a: $NaIO_4$, H_2O, RT

b: TolSH, conc. HCl

Scheme 11.3 (*continued*)



11.7

$[\alpha]_D$ +95.7 (MeOH)

m.p. 116°C
$[\alpha]_D$ +5.5 (MeOH)

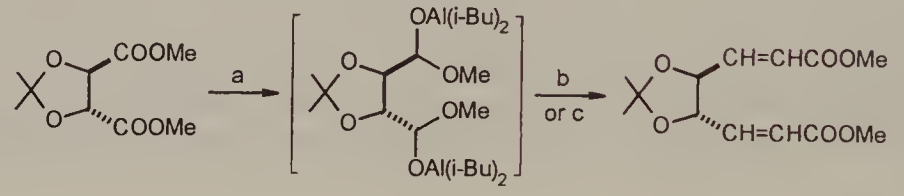
c: $Pb(OAc)_4$, benzene, RT

d: MeSH, 10% HCl in dioxane, RT (64%)[5]

Scheme 11.3

Synthesis and Application as Building Blocks

Presently, protected tartaric dialdehydes are conveniently prepared *in situ* by the i-Bu_2AlH reduction of protected tartrates and used directly in the following synthetic step. C_2-Symmetry makes tartaric dialdehydes ideal chiral building blocks for the two-directional construction of highly functionalized carbon chains. Synthetically very useful are Wittig or Horner–Emmons olefination reactions, introduced to tartraldehyde chemistry by Krief[7,8] (Scheme 11.4). These reactions can be directly performed on the dialuminate intermediate **11.8**, thus eliminating tedious separation of the unstable dialdehyde.



11.8 **11.9**

	(*E*,*E*)	: (*Z*,*Z*)	: (*E*,*Z*)
Wittig (b)	2	60	38
Horner-Emmons (c)	96	-	4

a: 2 eq. i-Bu_2AlH, PhMe, -78°C, 2h

b: 2.5 eq. Ph_3P=CHCOOMe, MeOH, -78°C → RT, 3h (83%)

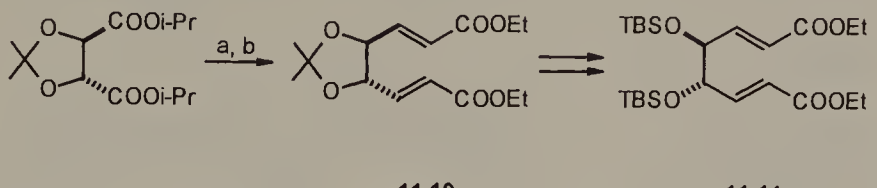
c: 2.5 eq. $(EtO)_2P(O)CH(Na)COOMe$, DME, -78°C → RT, 4h (60%)

Scheme 11.4

The (*Z*,*Z*)- and (*E*,*E*)-diastereomers **11.9** can be separated through chromatography in 55% and 51% overall yield, respectively, from the reactions b and c.

O-Isopropylidene protection is essential for successful execution of this transformation as it suppresses intramolecular side reactions by keeping apart the two carbonyl functional sites.[9] In a slightly modified procedure Saito *et al.* obtained

(*E*,*E*)-diester **11.10** in high yield and further converted it to the *O*-TBS protected derivative **11.11**[9,10] (Scheme 11.5).



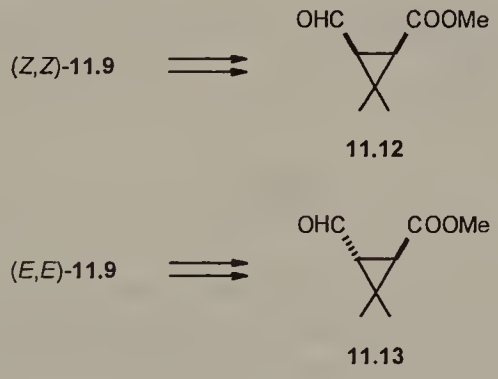
11.10 **11.11**

a: 2 eq. i-Bu_2AlH, PhMe, -78°C, 4h

b: 6 eq. $(i\text{-}PrO)_2P(O)CH(Na)COOEt$, THF, -78°C → RT (98%)

Scheme 11.5

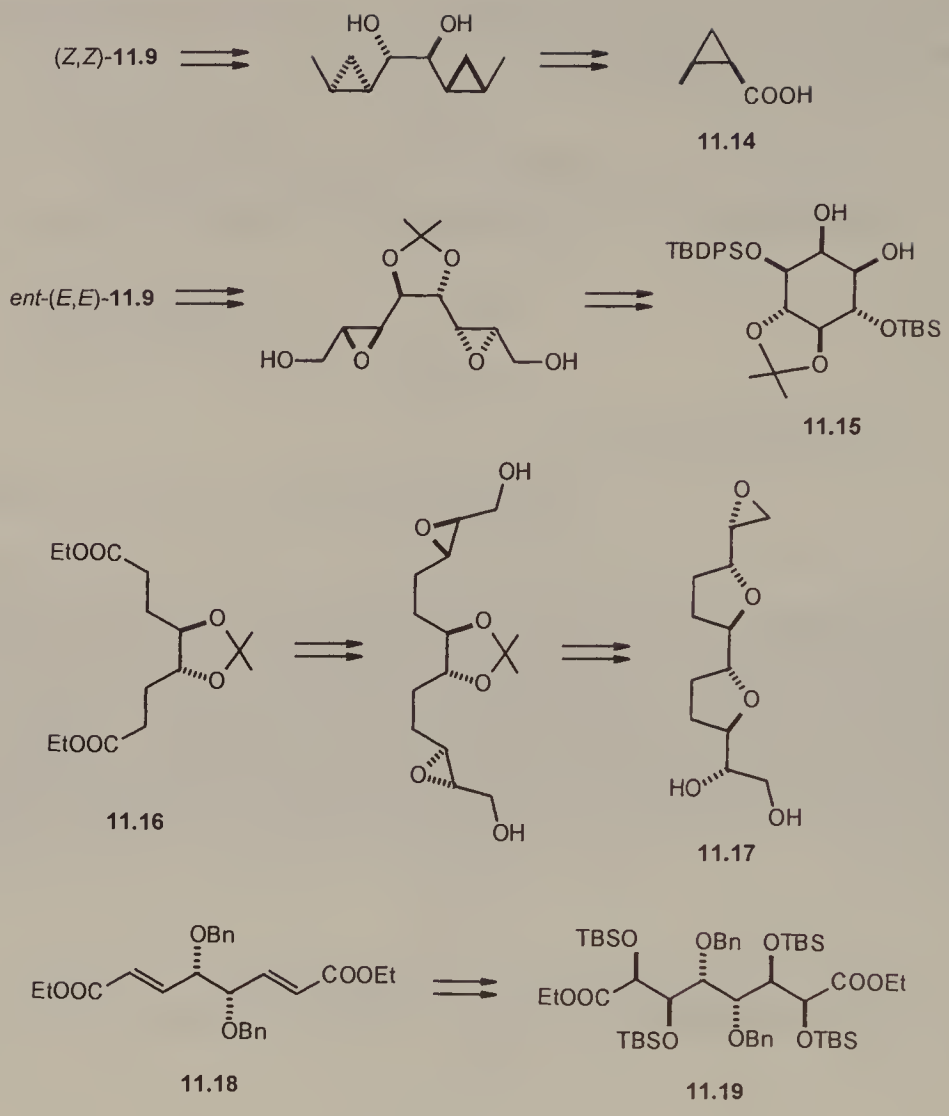
Diester **11.10** has been used in a variety of stereoselective reactions including the Diels–Alder reaction,[11] cyclopropanation, dihydroxylation, epoxidation, and conjugate addition (see below). Products **11.9** were used in the synthesis of (1*R*)-*cis* and (1*R*)-*trans* hemicaronaldehydes **11.12** and **11.13**, precursors of (1*R*)-*trans*-chrysanthemic acid. The synthesis employed the C_2-symmetry of (*E*,*E*)- and (*Z*,*Z*)-**11.9** which allowed the production of two moles of hemicaronaldehydes by the cleavage of one mole of the deprotected diol[7,8] (Scheme 11.6).



11.12 **11.13**

Scheme 11.6

Iwasaki used the (*Z*,*Z*)-diester **11.9** in the synthesis of *cis*-2-methylcyclopropanecarboxylic acid **11.14**, a component of curacin A[12] and the (*E*,*E*)-diester *ent*-**11.9** in the synthesis of the D-*myo*-inositol derivative **11.15**.[13] Further applications included Sasaki's synthesis of bis-tetrahydrofuran skeleton **11.17** of (+)-bullatacin from the hydrogenated diester **11.16**[14] and Schreiber's total synthesis of anthelmintic agent (−)-hikizimycin fragment **11.19** from the (*E*,*E*)-diester **11.18**[15] (Scheme 11.7).



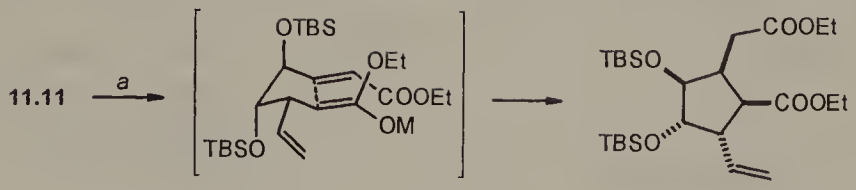
Scheme 11.7

Compared to **11.10**, the *O,O*-di-TBS derivative **11.11** (Scheme 11.5) shows enhanced diastereoselectivity in many reactions involving the C=C bonds. This can be attributed to the *anti*-arrangement of the bulky TBSO substituents, causing mutual shielding of the pair of "inside" C=C diastereofaces.[10] Examples of such diastereoselective reactions are shown in Scheme 11.8.

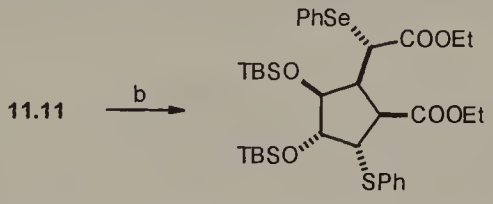
Dithioacetal protected aldehyde **11.20** was converted in one step to the two-carbon homologated enal **11.21**, from which two naturally occurring 2,6-dideoxyhexoses, D-diginose (**11.22**) and D-sermentose (**11.23**), as well as *N*-acetyl-D-daunosamine (**11.24**), could be obtained[6,20] (Scheme 11.9).

Apart from olefination reactions, tartaric dialdehydes are used in syntheses involving addition of nitrogen nucleophiles to the aldehyde groups. *cis*-4-Formyl β-lactams **11.27** were obtained by the stereoselective [2+2] cycloaddition of ketenes to tartrate derived diimines **11.25**. C_2-Symmetry of the tartrate frame-

Double Michael addition

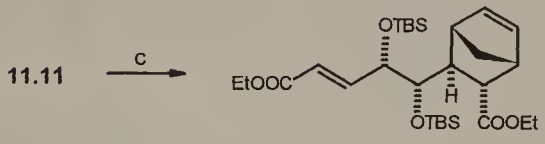


a: excess CH_2=CHMgBr, CuI, Et_2O, -20°C, 1h (94%, d.e. > 99%)[16]



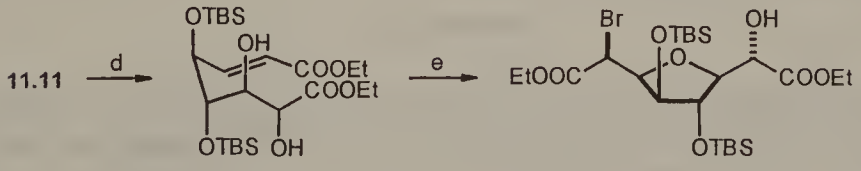
b: PhSLi, THF, -40° → -20°C, then PhSeCl, HMPA, -78° → 0°C (88%, d.e. > 99%)[17]

Diels-Alder reaction



c: cyclopentadiene, Et_2AlCl, CH_2Cl_2, -20°C (90%, d.e. > 99%)[18]

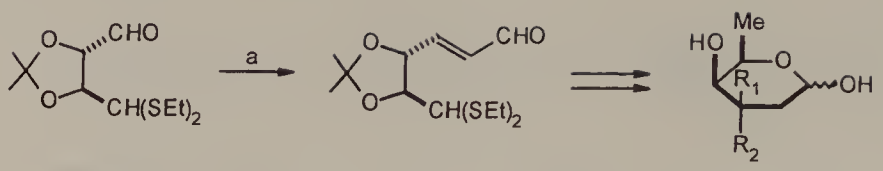
Dihydroxylation and haloetherification



d: OsO_4 (cat.), 2 eq. NMM oxide, Me_2CO-H_2O, RT (94%)

e: NBS, MeCN, RT (87%, d.e. >99%)[19]

Scheme 11.8



11.20 **11.21**

11.22 R_1 = OMe, R_2 = H

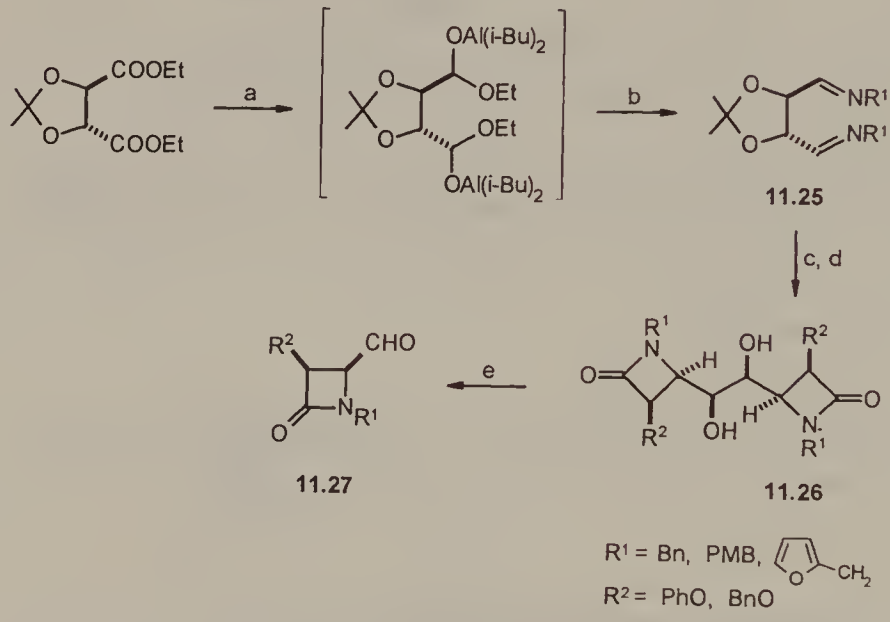
11.23 R_1 = H, R_2 = OMe

11.24 R_1 = NHAc, R_2 = H

a: Ph_3P=CHCHO, benzene, Δ, 1h (77%)

Scheme 11.9

work allowed the production of two moles of lactams **11.27** from one mole of **11.26** by the cleavage of the diol functional group[21] (Scheme 11.10).



a: 2 eq. $i\text{-}Bu_2AlH$, PhMe, -78°C, 3h

b: 2 eq. R^1NH_2 (86-98%)

c: 3 eq. R^2CH_2COCl, NEt_3, CH_2Cl_2, -23°C → RT (52-73%)

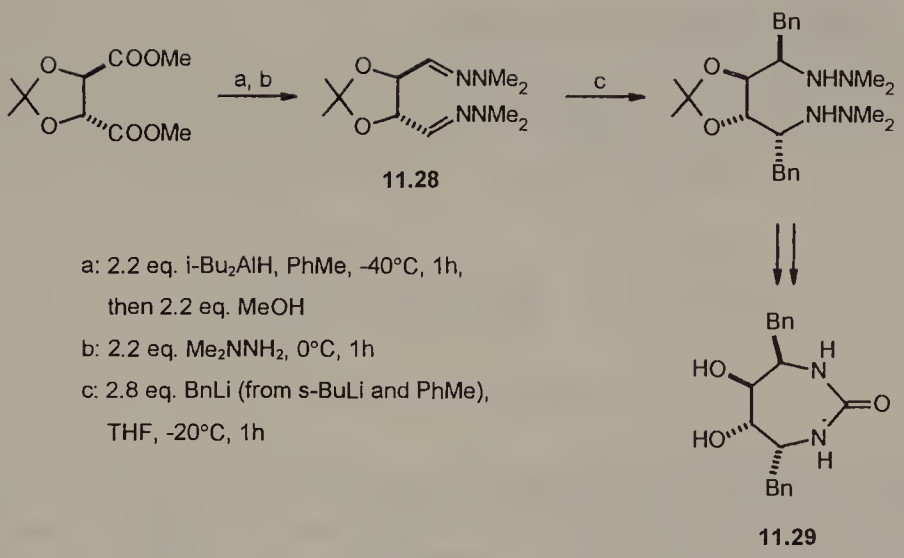
d: 2.5M $HClO_4$, THF, RT, 4-8h (100%)

e: $NaIO_4$, H_2O-MeOH, RT (100%)

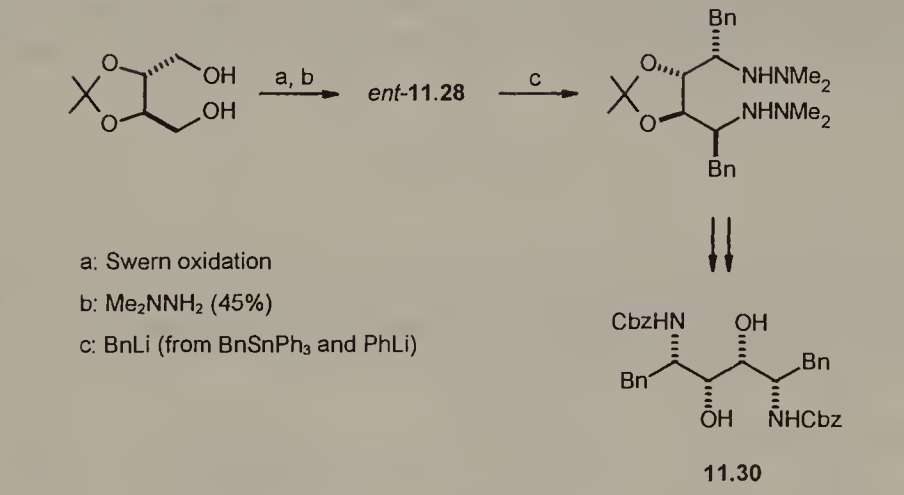
Scheme 11.10

A practical synthesis of nonpeptide cyclic ureas **11.29**, inhibitors of HIV protease, was developed at Du Pont Merck. It utilized the stereoselective, chelation-controlled addition of benzyllithium to bis-hydrazone **11.28** as the pivotal step[22] (Scheme 11.11).

Baker and Condon obtained the enantiomer of bis-hydrazone **11.28** from 2,3-*O*-isopropylidene-D-threitol and converted it to the diaminodihydroxyethylene dipeptide isostere **11.30**[23] (Scheme 11.12).

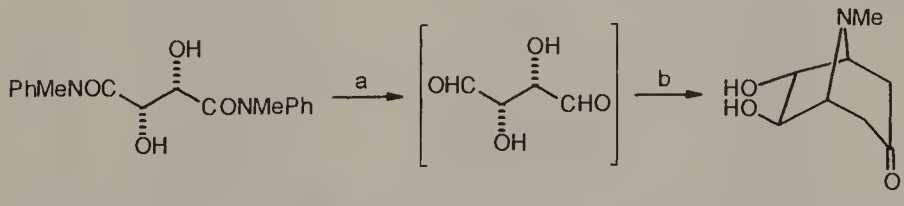


Scheme 11.11



Scheme 11.12

Unprotected D-tartrdialdehyde, obtained in a crude form by the $LiAlH_4$ reduction of bis-*N*-methylanilide of D-tartaric acid, was used in a straightforward synthesis of (+)-*trans*-6,7-dihydroxy-3-tropanon in a Mannich-type condensation[24] (Scheme 11.13).



Scheme 11.13

11.2 DERIVATIVES OF THREOSES

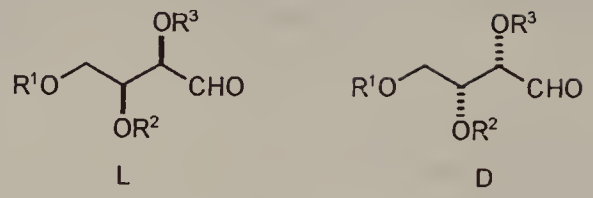


Figure 11.2

Variously protected threose derivatives are widely used in synthesis, mainly as four-carbon chirons for unidirectional chain elaboration. Because of their limited stability and susceptibility to epimerization at C(2) they are customarily used freshly prepared but not necessarily thoroughly purified. Noteworthy is the ability of threoses to form hydrates. However, some L-threose derivatives have been separated, purified, and characterized; these derivatives are collected in Table 11.1.

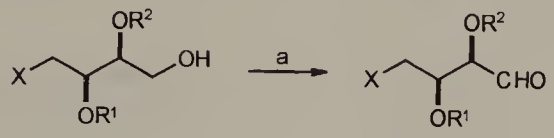
Table 11.1 Isolated and characterized L-threose derivatives (Figure 11.2)

R^1	R^2	R^3	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
H	H	H	—	+12.5 (H_2O)[a,b]	25–27
H	Me	Me	—	+12.0 (MeOH)[b]	28
H	Ac	Ac	140–142	−34.3 ($CHCl_3$)[b,c]	29
H	MOM	MOM	—	−20.8 (MeOH)[b]	30
Bn	MOM	MOM	—	+13.3 (MeOH)	30
TBS	Bn	Bn	—	+38.1 ($CHCl_3$)	31
–CMe_2–		OBn	—	+14.6 ($CHCl_3$)	32
–CMe_2–		TBS	—	−187.1 ($CHCl_3$)	32
–CMe_2–		THP	—	+30.0 ($CHCl_3$)	33
H	–CMe_2–		84–85	+15.1 (Me_2CO)[c]	26,34
Bn	–CMe_2–		121/0.4	+16.8 ($CHCl_3$)	35–37
Tr	–CMe_2–		—	−3.3 ($CHCl_3$)	38a
Bz	–CMe_2–		107–109/0.05	+17.1 ($CHCl_3$)	39
TBS	–CMe_2–		93–95/0.4	+8.9 ($CHCl_3$)	40
TBDPS	–CMe_2–		—	−11.6 ($CHCl_3$)	41

[a] The m.p. and $[\alpha]_D$ in ref. 29 are apparently erroneous.
[b] Hemiacetal form.
[c] Obtained in D-form.

Synthesis

As a rule, protected threoses are prepared from 1,2,3-tri-*O*-protected threitols by mild and selective oxidation reactions, of which the Swern method[42] is most frequently used (Scheme 11.14).



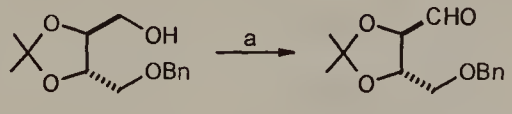
a: $(COCl)_2$, DMSO, CH_2Cl_2, -50° → -78°C, then NEt_3, -78°C → RT

X	R^1	R^2	yield (%)	ref.
BnO	-CMe_2-		85	36
BzO	-CMe_2-		65	39
TBSO	-CMe_2-		56-85	40,43,44
Br	-CMe_2-		96	38b
BnO	MOM	MOM	82	30
EtOOCHN	MOM	MOM	100	45
BzHN	MOM	MOM	96	45

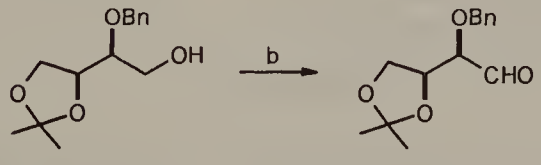
Scheme 11.14

Fully protected threoses can also be obtained from 1,2,3-tri-*O*-protected threitols by other selective oxidation reactions; see the examples in Scheme 11.15.

PCC oxidation (with sodium acetate buffer)



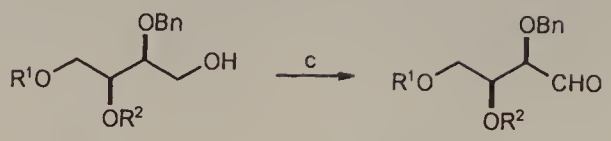
a: PCC, AcONa, mol. sieves 4Å, CH_2Cl_2, RT (87%)[37]



b: PCC, AcONa, mol. sieves 3Å, CH_2Cl_2, RT (70-90%)[46]

Scheme 11.15 (*continued*)

Dess-Martin oxidation



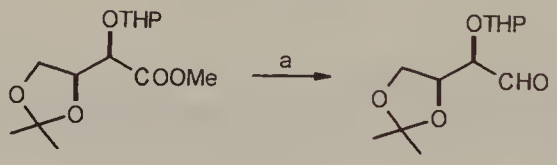
R^1 = TBS, R^2 = Bn, 93%[31]

R^1, R^2 = CMe_2, ca 100%[47]

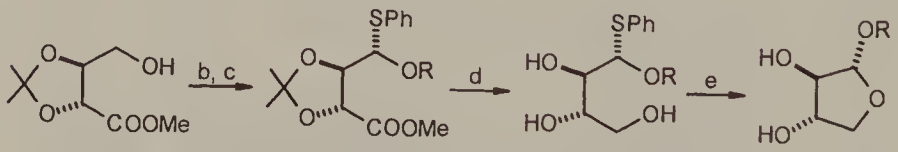
c: Dess-Martin reagent, CH_2Cl_2, RT

Scheme 11.15

Protected threoses can be obtained by DIBAL reduction of threonic acid derivatives, as shown in Scheme 11.16. α-L-Threofuranosides **11.32** are available selectively from the L-threonic acid derivative **11.31** according to the procedure of Mukaiyama *et al.*[48]



a: 1.1 eq. i-Bu_2AlH, CH_2Cl_2, -78°C, 1h (100%)[33]



11.31

(diastereoselectivity 6 : 1 to > 10 : 1)

11.32

b: $(PhS)_2$, Bu_3P, pyridine then NCS (92%)

c: ROH, $SnCl_2$, $AgClO_4$, mol. sieves 3Å, Et_2O, 0°C

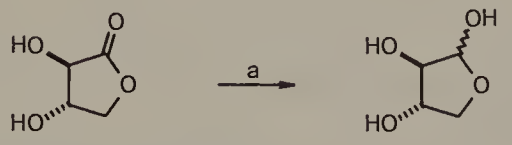
d: $LiAlH_4$, THF then 2N HCl, MeOH (52-67%)

e: $Pd(OAc)_2$, DME-H_2O, RT (68-93%)[48]

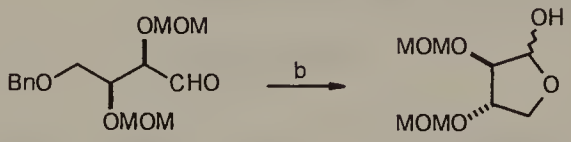
Scheme 11.16

4-*O*-Unprotected threoses **11.33**, **11.37** were obtained in the hemiacetal form. L-Threose (hemiacetal form) is available directly from L-threonolactone by reduction with disiamylborane. Acetal protected L-threose derivative **11.35** was

prepared from aldehyde **11.34** by deprotection-isopropenylation[33] as well as from the fully protected form of L-tartrdialdehyde (**11.36**), in turn available from diacetone-D-glucose.[49] Chiral dihydrofuran **11.38** was used by Smith for asymmetric [2+2] photocycloaddition reactions directed toward synthesis of (−)-echinosporin[33] (Scheme 11.17).

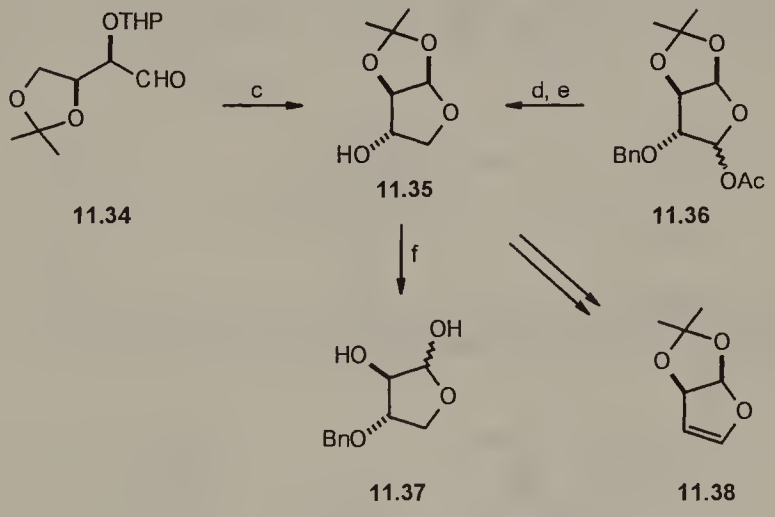


a: $(Me_2CHCHMe)_2BH$, THF, RT (100%)[27]



11.33

b: H_2, 10% Pd/C, MeOH, RT (91%)



11.34 **11.35** **11.36**

11.37 **11.38**

c: MeOH, PPTS (cat.), RT, 3h, then Me_2CO, H_2SO_4 (cat.) RT, 2h (53%)[33]

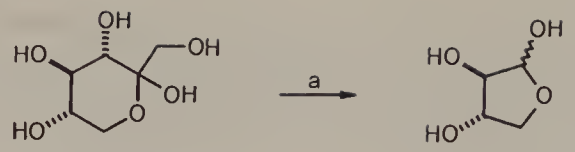
d: 4 eq. Et_3SiH, 2.5 eq. $MgBr_2$, CH_2Cl_2, 15°C, 19h (90%)[49]

e: H_2, Pd-C (cat.), 15°C (92%)[49]

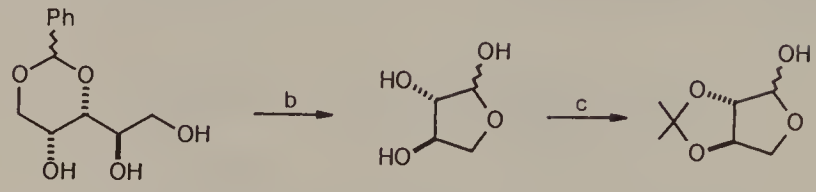
f: 2N HCl, THF, 60°C (80%)[49]

Scheme 11.17

Threoses were also synthesized from carbohydrate precursors of suitable configuration. For example, L-threose was obtained from L-sorbose by oxidation with silver carbonate.[26] Reichstein prepared D-threose and its 2,3-*O*-isopropylidene derivative from 1,3-*O*-benzylidene-D-arabitol[50] (Scheme 11.18).



a: Ag_2CO_3/Celite, MeOH, 40°C (ca 40%)

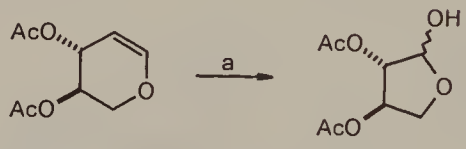


b: $Pb(OAc)_4$, AcOH then 10% AcOH, Δ (95% crude)

c: Me_2CO, $CuSO_4$, H_2SO_4 (cat.), RT

Scheme 11.18

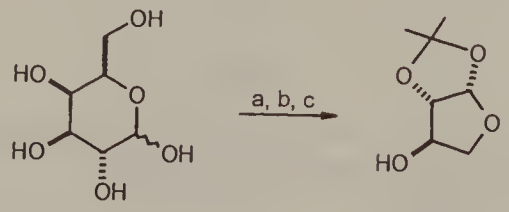
Freudenberg prepared 2,3-di-*O*-acetyl-D-threose from 3,4-di-*O*-acetyl-D-xylal[29] (Scheme 11.19).



a: O_3, AcOH, then Zn (75%)

Scheme 11.19

1,2-*O*-Isopropylidene protected D-threose can be synthesized in three steps from D-galactose by the procedure of Perlin[33,51] (Scheme 11.20).



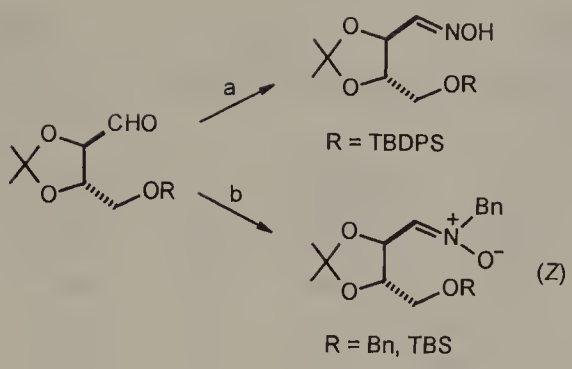
a: $Pb(OAc)_4$, AcOH, RT

b: Me_2CO, H_2SO_4 (cat.), RT

c: K_2CO_3, MeOH (30% combined yield)[33]

Scheme 11.20

Preparation of some isolated and characterized oxime and *N*-benzyl nitrone derivatives of protected L-threoses is shown in Scheme 11.21.



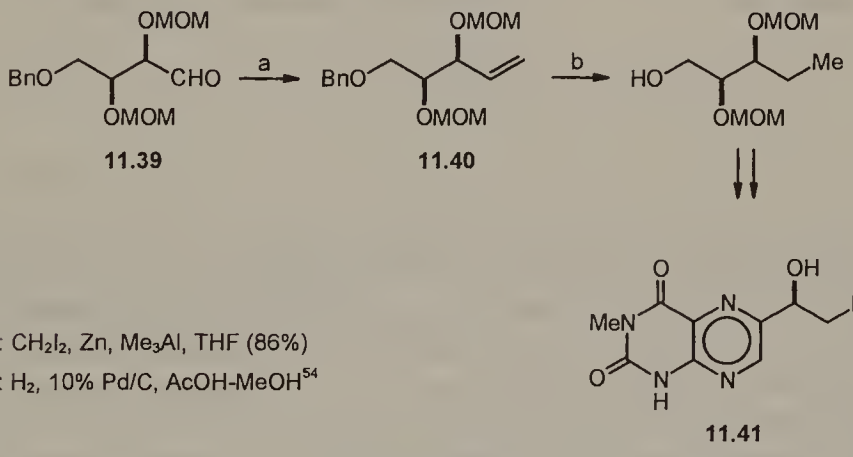
a: 1.3 eq. $H_2NOH{\cdot}HCl$, AcONa, MeCN-H_2O (1:1), RT, 24h (83%)[52]

b: BnNHOH, CH_2Cl_2, $MgSO_4$ (80-85%)[53]

Scheme 11.21

Applications

Olefination of threoses. Many variants of this reaction are commonly used in the early stages of synthesis of natural products from protected threoses. For example (*S*)-6-(1-hydroxypropyl)-3-methyllumazine (**11.41**) was synthesized from the olefination product **11.40** derived from protected L-threose **11.39**[54] (Scheme 11.22).



11.39 **11.40** **11.41**

a: CH_2I_2, Zn, Me_3Al, THF (86%)

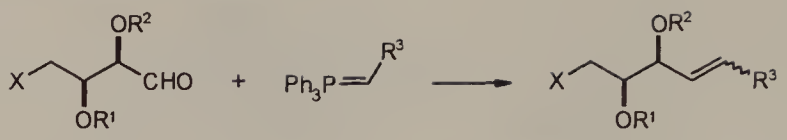
b: H_2, 10% Pd/C, AcOH-MeOH[54]

Scheme 11.22

Standard Wittig reaction of non-stabilized ylides with threoses yields a mixture of (*Z*) and (*E*) olefins, with the (*Z*)-diastereomer predominating (Scheme 11.23, entries 5–7, 10–12).

Schlosser's modification of the Wittig olefination[64] yields predominantly (*E*)-alkenes from protected threoses (entries 13, 14 in Scheme 11.23).

In a number of cases the (*E*)/(*Z*) mixture of olefins obtained from the Wittig reaction of threoses could be used without isomer separation in a subsequent



entry	X	R^1	R^2	R^3	yield (%)	(Z)/(E)	ref.
1	HO[a]	Bn	H	H	85	-	49
2	BocNH	Bn	THP	H	68[b]	-	55
3	TBSO	-CMe_2-		H	78[b]	-	56
4	BnO	-CMe_2-		n-Pr	70[b]	c	57
5	TBSO	-CMe_2-		n-C_9H_{19}	77	>1	40
6	BnO	-CMe_2-		n-$C_{10}H_{21}$	63[b]	19	58
7	BzO	-CMe_2-		n-$C_{13}H_{27}$	52[b]	>1	59
8	BnO	-CMe_2-		2-(1,3-dioxanyl)CH_2	63	c	60
9	BzO	-CMe_2-		2-(1,3-dioxanyl)CH_2	47	c	39
10	BnO	-CMe_2-		TMS$O(CH_2)_3$	73[d]	32	61
11	TIPSO	-CMe_2-		Bn$O(CH_2)_2$	74[b]	(Z) only	44
12	TBSO	-CMe_2-		HOOC$(CH_2)_4$	62[b]	(Z) only	44
13	TBSO	-CMe_2-		Me	55	0.16	62
14	-$OCEt_2$-		PMB	n-$C_{13}H_{27}$	62[b]	(E) only	63

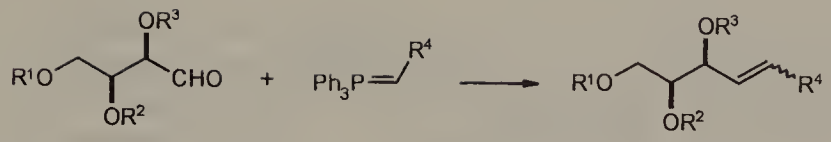
[a] hemiacetal form
[b] including aldehyde preparation step by oxidation
[c] not reported
[d] including subsequent oxidation to the aldehyde

Scheme 11.23

hydrogenation step;[39,40,57,58,60] this two-reaction sequence provides a convenient method for the elongation of the threitol carbon chain. Alternatively, when needed, the (*E*)/(*Z*) mixture of olefinic products can be isomerized by irradiation with a high pressure mercury lamp in the presence of diphenyl disulfide to give the (*E*)-diastereomer.[59]

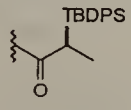
Olefins prepared according to Scheme 11.23 were used in the synthesis of the anti-mite substance AB3217-A (entry 2),[55] (−)-anisomycin (entry 3),[56] koninginin A (entry 4),[57] epoxide pheromones (entry 5),[40] corossoline (entry 6),[58] precursors of sphingosine (entry 7),[59] punaglandin 4 (entry 8),[60] 6-epileukotrienes (entry 9),[39] precursor of chlamydocin (entry10),[61] modified trapoxins (entries 11,12),[44] antifungal agent FR-900848 (entry 13),[62] and *erythro*-sphingosine (entry 14).[63]

With stabilized ylides, protected threoses react unexceptionally to give predominantly (*E*)-olefinic products in aprotic solvents and (*Z*)-olefins in methanol (Mukaiyama *et al.*[65]), Scheme 11.24.



entry	R^1	R^2	R^3	R^4	reaction conditions	yield (%)	(*Z*):(*E*)	ref.
1	Bn	$-CMe_2-$		COOEt	DMF, RT	77	27:73	65
2	Bn	$-CMe_2-$		COOEt	benzene, Δ	83	30:70[a]	65
3	Bn	$-CMe_2-$		COOEt	MeOH, RT	88	89:11	36,65
						98	95:5	66
4	TBS	$-CMe_2-$		COOEt	CH_2Cl_2, RT	87	32:68	43
5	TBDPS	$-CMe_2-$		COOMe	MeOH, -70°C → RT	81	(*Z*) only	41
6	$-CMe_2-$		Bn	COOMe	MeOH, RT	77	92:8	46,67
7	TBS	$-CMe_2-$		[b]	benzene, Δ	90	(*E*) only	68.
8	Bn	$-CMe_2-$		2-thiazolyl	benzene, RT	95	40:60	69
9	Ac	MOM	MOM	An	THF, RT	78	20:80	70

[a] (*Z*):(*E*) = 1:1 was obtained in the presence of cat. PhCOOH[37], but reportedly only (*E*)-isomer was formed in refluxing toluene[71]

b 

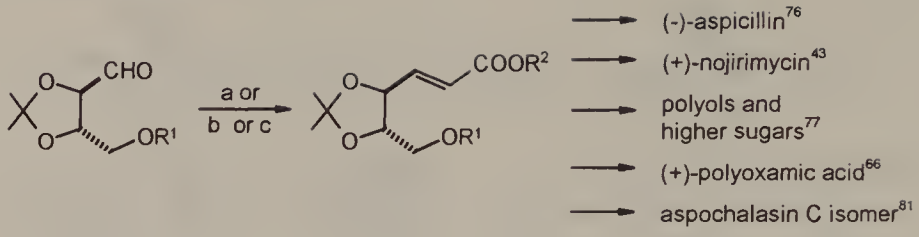
Scheme 11.24

Synthetic applications of products in Scheme 11.24 are as follows.

deoxypolyoxin C [from (*Z*)-olefin, entry 3][36,65]
(+)-castanospermine[72] and (+)-galactostatin[73] [from (*E*)-olefin, entry 4]
(+)-anamarine[74] and unsaturated lactones[46] [from (*Z*)-olefin, entry 6]
(+)-polyoxamic acid (entry 7)[68]
(+)-*N*-methylanisomycin (entry 9)[70]

While the classical Horner–Emmons reaction of protected threoses gives (*E*)-olefinic products, entries a–d, its Still's modification[75] is (*Z*)-selective, entry e. (*Z*)-Selective is also reaction of a protected threose with carbonyl-stabilized ylide, activated *in situ* by the formation of the enolate derivative, entry f (Scheme 11.25).

Horita and Yonemitsu demonstrated the utility of the (*E*)-selective Horner–Emmons reaction of protected L-threose **11.42** for the synthesis of bicyclic JK-ring part of halichondrin B (**11.44**). Two molecules of **11.42** were used to construct the target molecule **11.44** via the C_2-symmetrical chiral ketone **11.43**, using two olefination reactions and two stereocontrolled conjugate additions of Me_2CuLi,[82] as outlined in Scheme 11.26.

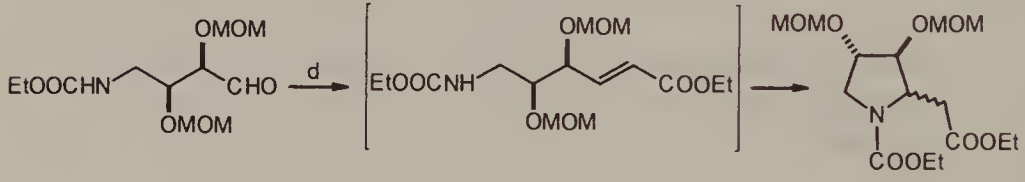


a (R^1 = Bn, R^2 = Et): $(EtO)_2P(O)CH_2COOEt$, LiCl, i-Pr_2NEt, MeCN (90%)[76] or
$(EtO)_2P(O)CH_2COOEt$, NaH, THF (100%)[66]

b (R^1 = TBS, R^2 = Me): $(MeO)_2P(O)CH_2COOMe$, NaH, benzene (95%)[43]

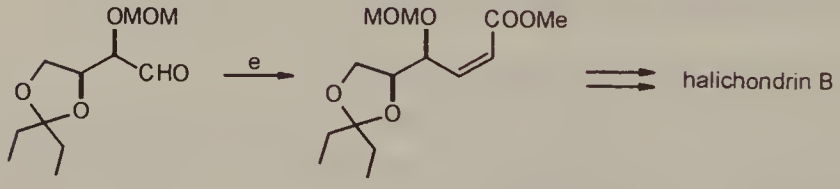
c (R^1 = TBS, R^2 = Et): $(EtO)_2P(O)CH_2COOEt$, NaH, THF (83%, including Swern oxidation)[77]

(R^1 = Bz, R^2 = Et): $(EtO)_2P(O)CH_2COOEt$, NaH, DME (60%, including Swern oxidation)[81]

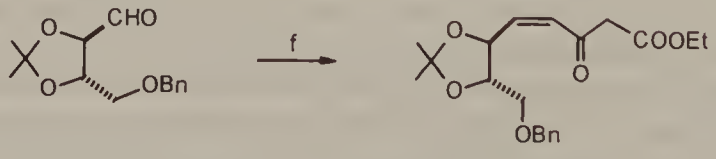


d: $(EtO)_2P(O)CH_2COOEt$, NaH, DME, RT (70%)[78]

pyrrolizidine alkaloids

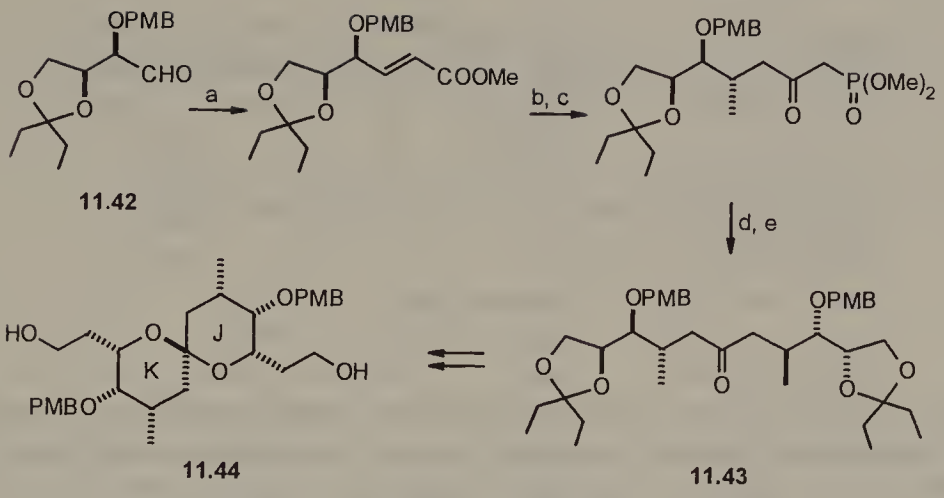


e: $(CF_3CH_2O)_2P(O)CH_2COOMe$, $KN(TMS)_2$, 18-crown-6, THF, -78°C
(90%, including Swern oxidation)[79]



f: $Ph_3P{=}CHC(O)CH_2COOEt$, NaH, THF, H_2O (cat.), 35-40°C (65%)[80]

Scheme 11.25



a: $(EtO)_2P(O)CH_2COOMe$, n-BuLi, THF, -78°C, (*E*):(*Z*) = 4:1

b: Me_2CuLi, TMSCl, THF-Et_2O, -20°C (93%)

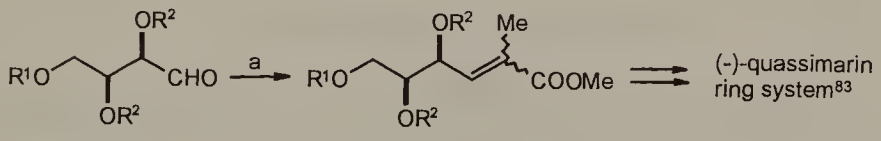
c: $(MeO)_2P(O)Me$, n-BuLi, THF, -78°C (89%)

d: n-BuLi, THF, -78°C, then **11.42** (96%)

e: Me_2CuLi, THF-Et_2O, -78°C (98%)

Scheme 11.26

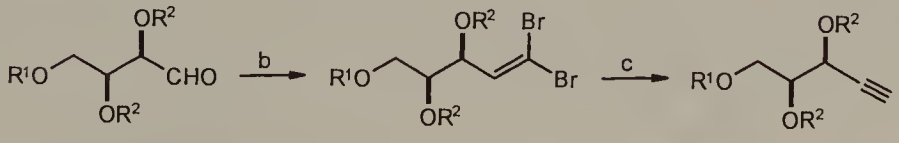
A potpourri of trisubstituted products of olefination of protected threoses is shown in Scheme 11.27.



R^1 = Bn, R^2,R^2 = $C(CH_2)_5$, 92%[83a]

R^2 = TBS, R^2 = Me, (*E*):(*Z*) = 20:1[83b]

a: Ph_3P=C(Me)COOMe, benzene, Δ



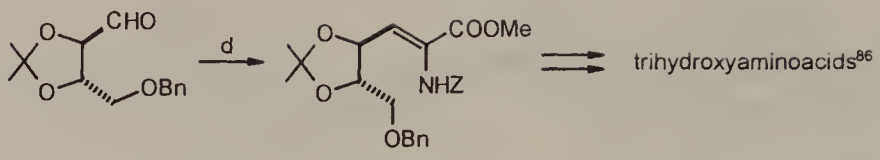
R^1 = TBS, R^2 = Bn

R^1 = PMB, R^2,R^2 = CMe_2

b: CBr_4, Ph_3P, CH_2Cl_2, 0°C (65-70%)

c: n-BuLi, THF or Et_2O, -78°C or 0°C (75-96%)[84,85]

Scheme 11.27 (*continued*)



d: $(MeO)_2P(O)CH(NHZ)COOMe$, t-BuOK, CH_2Cl_2, -70°C → +35°C (87%, (*Z*):(*E*) = 92:8)[86]

Scheme 11.27

Chain extension by the addition of carbon nucleophiles to threoses. Addition of a carbon nucleophile to a protected threose is diastereomerically biased with regard to the *syn* (*xylo*) or *anti* (*lyxo*) configuration of the products. As demonstrated by the work of Mukaiyama, Kibayashi, and others, *anti*-configured products result when non-chelated Felkin–Ahn model is operative whereas *syn*-selectivity is observed in cases where α-chelation occurs (Figure 11.3).

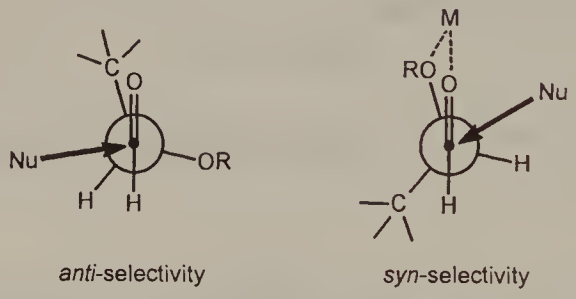
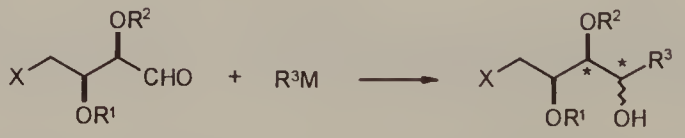


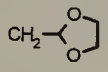
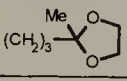
Figure 11.3

The former case is illustrated by entries 2 (addition of an alkyllithium), 5,12,16,17 (organozinc nucleophiles) and 7 (an organotin nucleophile), whereas the latter case is due to the magnesium ion chelation (entries 3,4,11,14,15,20, Scheme 11.28).



entry	X	R^1	R^2	R^3	M	yield (%)	*anti*:*syn*	ref.
1	$-OCMe_2$		Bn	Me	MgBr	85	50:50	47
2	OTBS	$-CMe_2-$		Me	Li	79	90:10	87
3	OBn	MOM	MOM	Me	MgBr	95	23:77	88
4	OBn	MOM	MOM	n-Pr	MgBr	82	22:78	88

Scheme 11.28 (*continued*)

5	OBn	-CMe_2-		n-Bu	$Li/ZnBr_2$	87	91:9	89
6	OBn	MOM	MOM	n-Bu	MgBr	a	a	90
7	OBn	-CMe_2-		All	R^3SnBr_2	100	90:10	36
8	-$OCMe_2$-		Bn	All	MgCl	88	45:55	91
9	-$OCMe_2$-		Bn	All	R^3Zn	95	65:35	91
10	-$OCMe_2$-		Bn	All	b	83	40:60	91
11	-$OCMe_2$-		Bn	All	$SiMe_3/MgBr_2$	78	2:98	91
12	OBn	-CMe_2-		$HC{\equiv}CCH_2$	ZnBr	91	30:1	92,93
13	I	-CMe_2-		$HC{\equiv}C$	MgBr	84	63:37	94
14	OH	MOM	MOM	PMB	MgCl	69	21:79	95
15	OBn	MOM	MOM	4-$MeOC_6H_4$	MgBr	83	23:77	30
16	OBn	-CMe_2-		2-furyl	$Li/ZnBr_2$	97	98:2	36,96
17	OTBDPS	-CMe_2-		2-furyl	$Li/ZnBr_2$	90	12:1	97
18	OBn	-CMe_2-		3-furyl	Li	72	1:1	98
19	OTBS	MOM	MOM	CH_2OEE	$SnBu_3$	a	a	99
20	OBn	MOM	MOM		MgBr	70	0:100	100
21	OBn	-CMe_2-		CH_2COOEt	Li	72	83:17	35
22	Br	-CMe_2-			MgBr	a	5:1	38b

[a] not determined

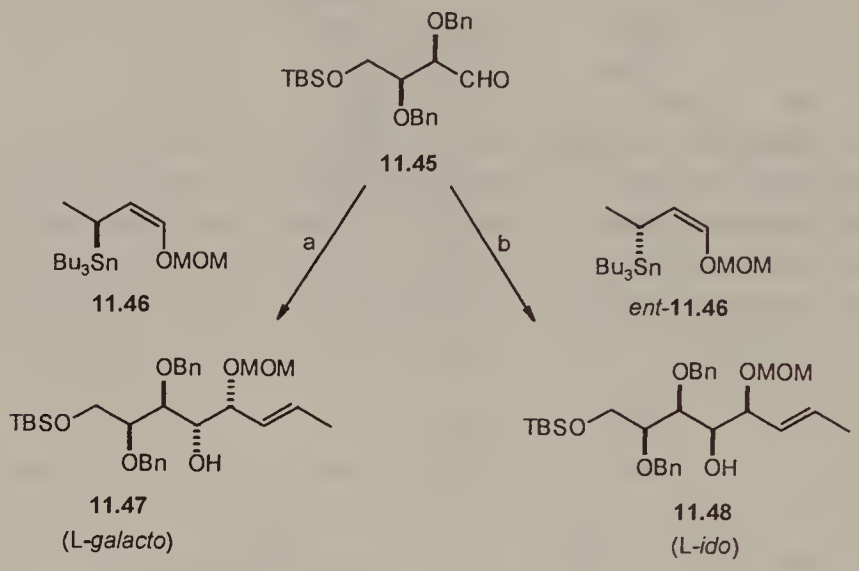
[b] 

Scheme 11.28

Synthetic applications of products in Scheme 11.28 are as follows.

1-deoxy-D-*threo*-2-pentulose (from enantiomer of entry 1)[47]
(+)-indolizidine 195 B and (−)-pinidine (entry 6)[90]
2-deoxy-L-galactose and L-diginose (entry 7)[36]
L-hexose derivatives (entries 8–11)[91]
(10*R*)-hepoxilin B_3 methyl ester and (10*R*)-trioxilin B_3 methyl ester (entry 12)[93]
cyclitols (entry 13)[94]
(+)-codonopsinine (entry 15)[30]
L-tagatose (entry 16)[96]
1-deoxy-8,8a-di-*epi*-castanospermine (entry 17)[97]
zaragozic acid core (entry 18)[98]
(−)-syringolides 1 and 2 (from enantiomer of entry 19)[99]
N-benzoyl-L-daunosamine (entry 20)[100]
endo-and *exo*-brevicomins (entry 22)[38b]

Marshall *et al.* established that additions of γ-alkoxy allylic stannanes **11.46** and *ent*-**11.46** to protected L-threose **11.45** led to different stereoisomeric products in the presence of Lewis acid promoters. With $BF_3 \cdot Et_2O$, **11.45** and **11.46** gave *syn-anti-syn* (L-*galacto*) adduct **11.47**; whereas the $MgBr_2$ promoted reaction led to the *syn-syn-syn* (L-*ido*) adduct **11.48** from **11.45** and *ent*-**11.46**[31] (Scheme 11.29).

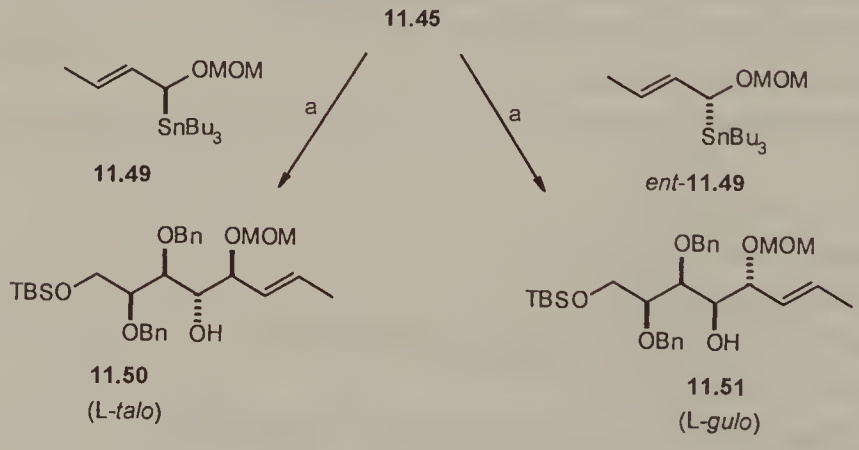


a: $BF_3 \cdot Et_2O$, CH_2Cl_2, -78°C (72%)

b: $MgBr_2 \cdot Et_2O$, CH_2Cl_2, -23°C (68%)

Scheme 11.29

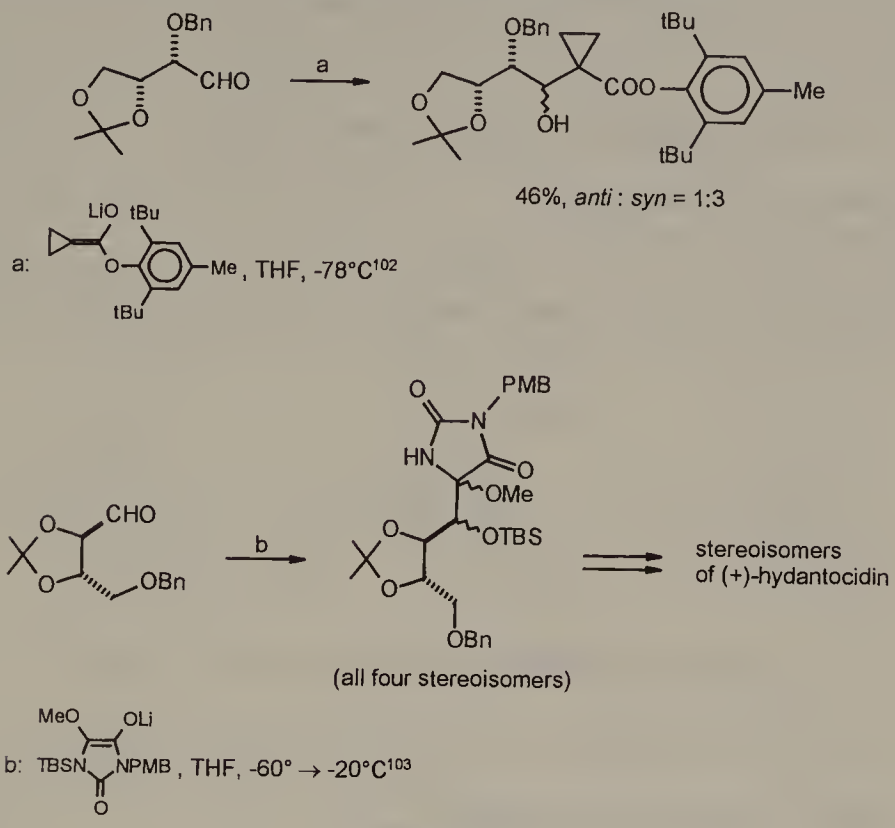
Adducts of L-*talo* (**11.50**) and L-*gulo* (**11.51**) configuration were stereoselectively synthesized from L-threose **11.45** and indium trichloride transmetallated allylic stannanes **11.49** and *ent*-**11.49**[101] (Scheme 11.30).



a: $InCl_3$, AcOEt, -78°C → RT (89-95%)

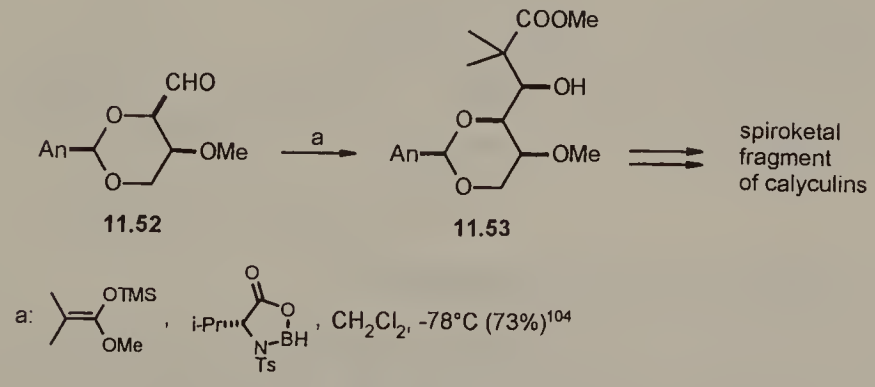
Scheme 11.30

Two examples of aldol reactions of lithium enolates and protected threoses are shown in Scheme 11.31. These reactions display low stereoselectivity.



Scheme 11.31

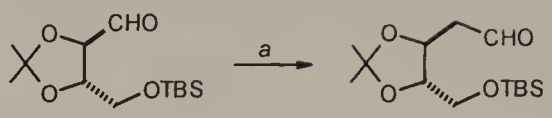
Hamada and Shioiri reported that aldol reaction of protected aldehyde **11.52** with methyl trimethylsilyl dimethylketene acetal gave the desired *syn*-product **11.53** when chiral borane catalyst derived from D-valine was used[104] (Scheme 11.32).



Scheme 11.32

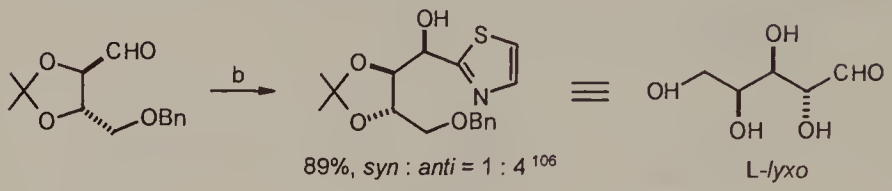
A number of carbon chain elongation reactions with important synthetic applications in the carbohydrate field have been implemented into threose

Homologation with a CH_2 group equivalent



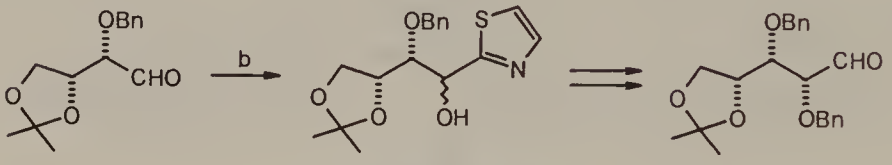
a: 1.5 eq.  $NCH_2P(O)Ph_2$, 1.2 eq. n-BuLi, THF-HMPA, 0°C (≥83%)[105]

Addition of a formyl anion equivalent



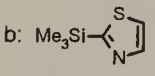
89%, *syn* : *anti* = 1 : 4 [106]

L-*lyxo*

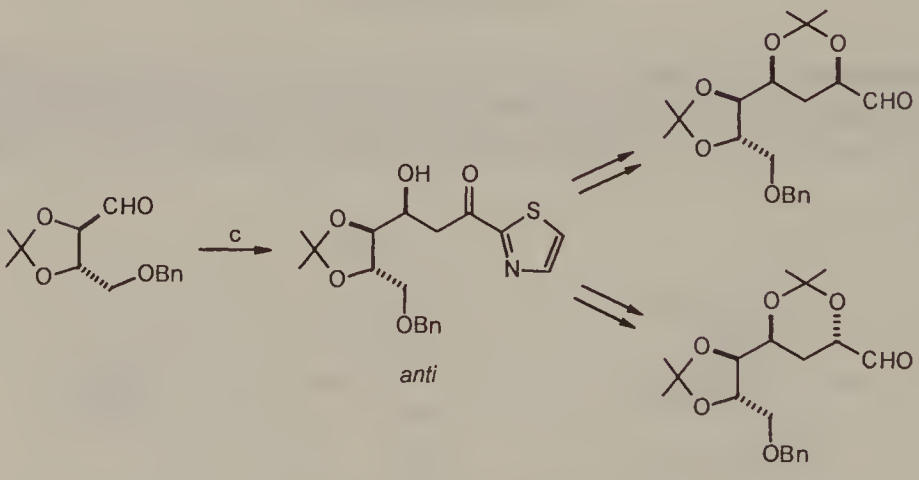


92%, *syn* : *anti* = 81 : 19 [32]

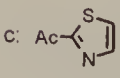
D-*xylo*

b:  , THF then Bu_4NF

Addition of a lactaldehyde anion equivalent



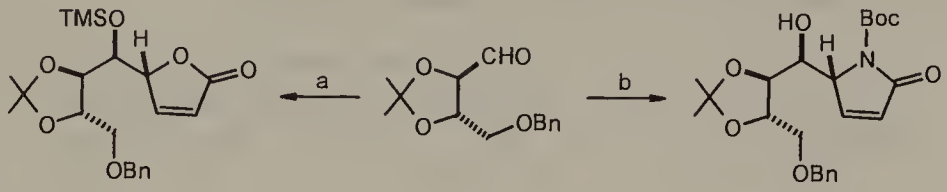
anti

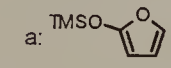
c:  , t-BuOLi, THF, -50°C, 2h (58-62%)[107]

Scheme 11.33

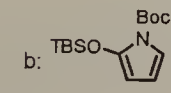
chemistry. Simple homologation was carried out by Nagata *et al.*[105] with the use of aminomethylphosphonate anion. Two chain elongation protocols were developed by Dondoni. The first one, using 2-(trimethylsilyl)thiazole as a formyl anion equivalent, with threose derivatives, gave predominantly either *anti* or *syn* addition products, depending on the threose protection scheme.[32,106] *Anti*-selectivity was observed in a chain elongation procedure with the enolate of 2-acetylthiazole as a lactaldehyde anion equivalent[107] (Scheme 11.33).

Anti-selectivity was also dominant in the addition reactions of a butenolide equivalent (Rassu–Casiraghi)[108] and of an α,β-unsaturated lactam equivalent (Casiraghi–Spanu)[109,110] to the protected threose (Scheme 11.34). The product of the latter reaction could be used for the synthesis of a polyhydroxy-α-amino acid.[111]



a: 

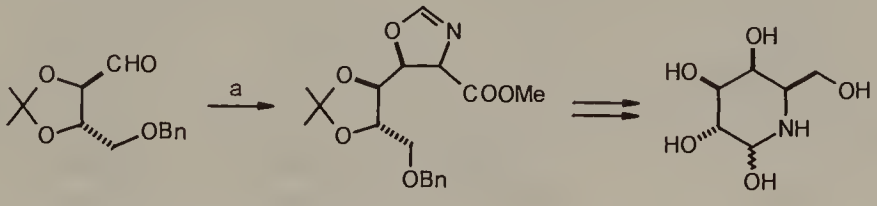
, $BF_3{\cdot}Et_2O$, CH_2Cl_2, -80°C, then TMSCl, pyridine, RT (66%)[108]

b: 

, $SnCl_4$, Et_2O, -80°C (80%)[109]

Scheme 11.34

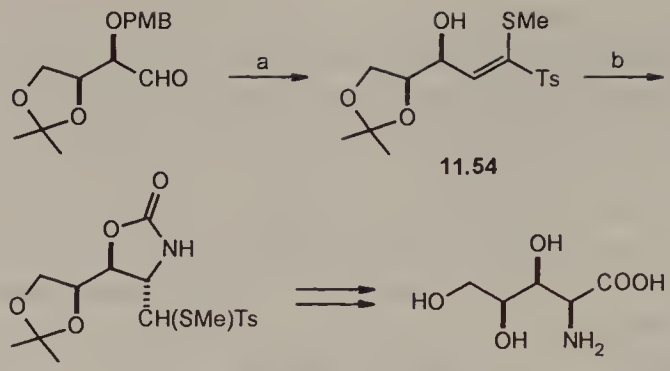
The addition of methyl isocyanoacetate to a protected threose is *anti*-selective, with the ratio of diastereoisomeric products 5.5:1; the major diastereoisomer was used for the synthesis of (+)-galactostatin[112] (Scheme 11.35).



a: $:CNCH_2COOMe$, NaCN, MeOH (81%)[112]

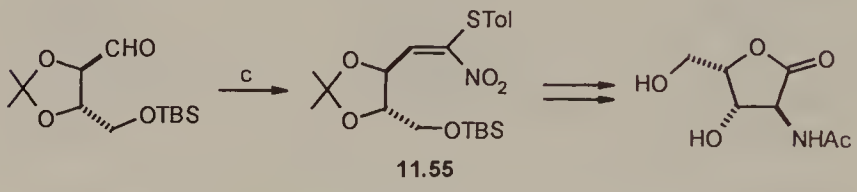
Scheme 11.35

Two syntheses of (+)-polyoxamic acid derivatives of Hirama *et al.*[113] and Jackson *et al.*[114] employed the addition of a stabilized carboanion to L-threose derivatives followed by a dehydration step to give the functionalized olefinic products **11.54** and **11.55** as the five-carbon intermediates, with the desired C(3)-C(5) substitution pattern and stereochemistry (Scheme 11.36).



a: $MeSCH_2Ts$, n-BuLi, -78°C, then MsCl, pyridine, NEt_3, then DDQ, CH_2Cl_2, H_2O (57%)

b: CCl_3CONCO, CH_2Cl_2, 0°C, then K_2CO_3, MeOH-CH_2Cl_2 (73%)[113]

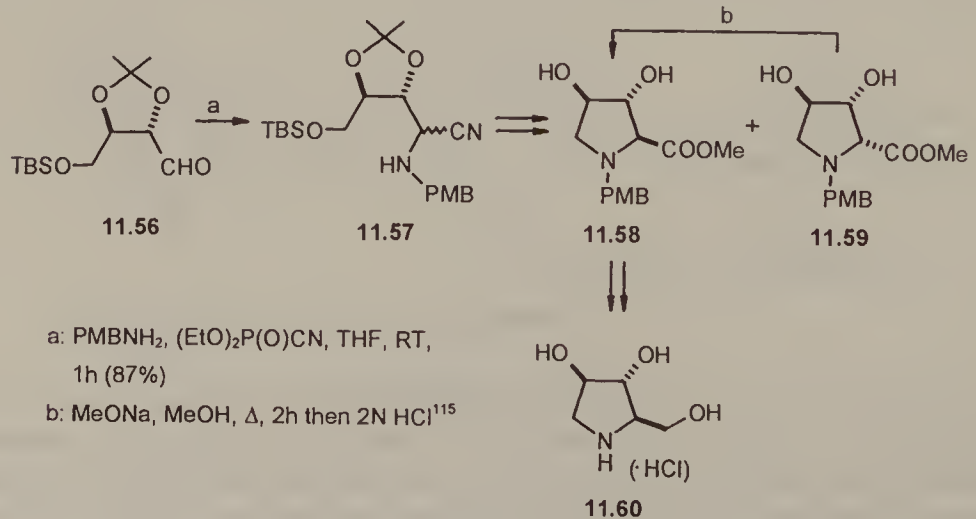


11.55

c: $TolSCH_2NO_2$, t-BuOK, t-BuOH -THF, 0°C → RT, then MsCl, i-Pr_2NEt, -78°C (61%)[114]

Scheme 11.36

A modified Strecker reaction of aldehyde **11.56** gave a mixture of diastereomeric aminonitriles **11.57** from which an epimerizable mixture of 3,4-dihydroxyproline derivatives **11.58** and **11.59** was obtained. Kitahara used this reaction sequence for the synthesis of a glucosidase inhibitor DAB-1 (**11.60**),[115] Scheme 11.37.



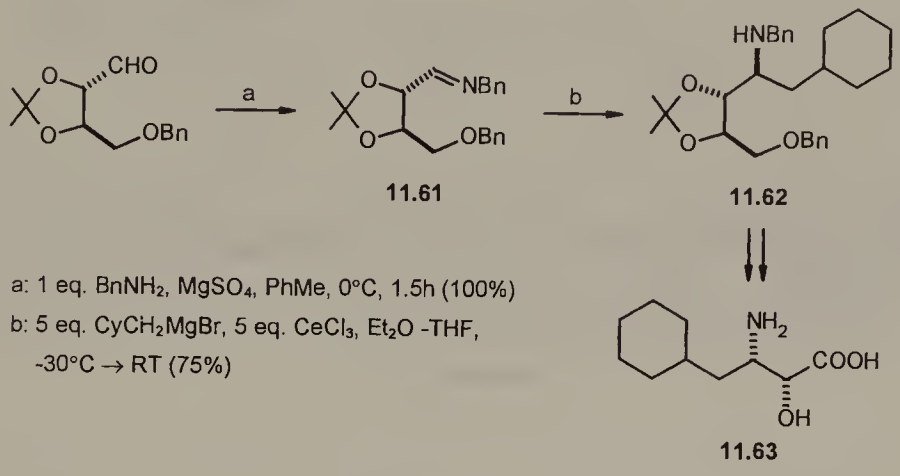
11.56 11.57 11.58 11.59 11.60

a: $PMBNH_2$, $(EtO)_2P(O)CN$, THF, RT, 1h (87%)

b: MeONa, MeOH, Δ, 2h then 2N HCl[115]

Scheme 11.37

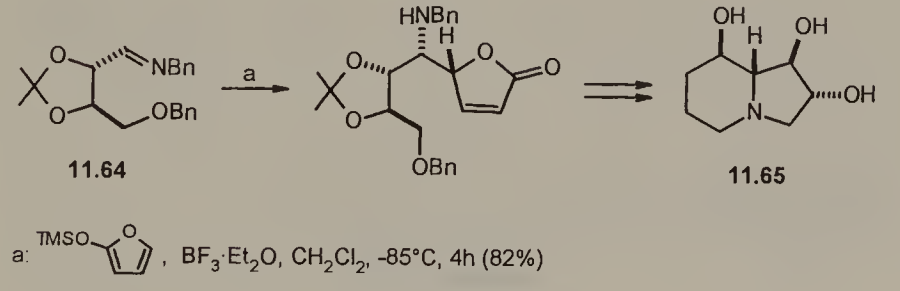
Synthetic applications of the imine, nitrone, and tosylhydrazone derivatives of threoses. Addition of a Grignard reagent to imine **11.61** in the presence of cerium(III) chloride is highly *syn*-selective due to α-chelation and exclusively yields product **11.62**. This product has been used by Terashima for the synthesis of cyclohexylnorstatine (**11.63**), the key component of a renin inhibitor[116] (Scheme 11.38).



Scheme 11.38

Addition of phenyllithium to a related imine is apparently also predominantly *syn*-selective.[117]

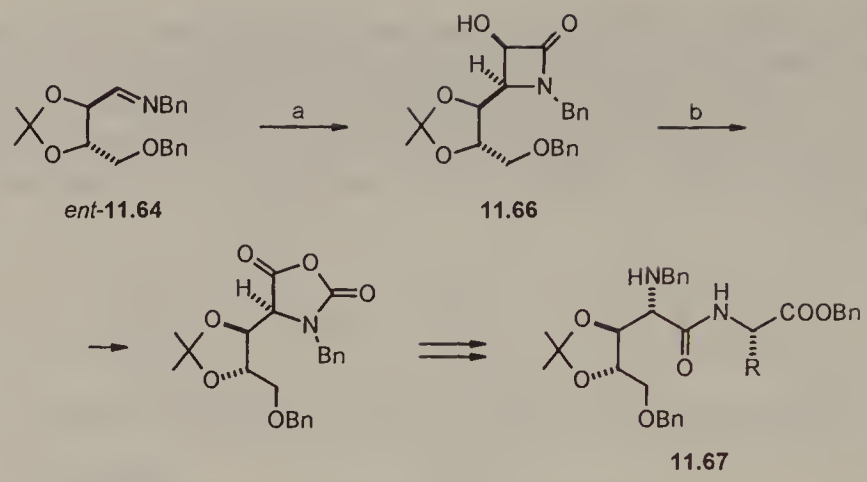
In the synthesis of 1-*epi*-swainsonine (**11.65**) the crucial step was the highly stereoselective *anti*-addition of a butenolide equivalent to imine **11.64** by the procedure of Casiraghi–Rassu[118] (Scheme 11.39).



Scheme 11.39

Palomo synthesized the polyoxamic acid derivative **11.67** by a highly diastereoselective [2+2] cycloaddition of acetoxyketene to imine *ent*-**11.64**. The β-lactam intermediate **11.66** was isolated as the only product of the cycloaddition[119] (Scheme 11.40).

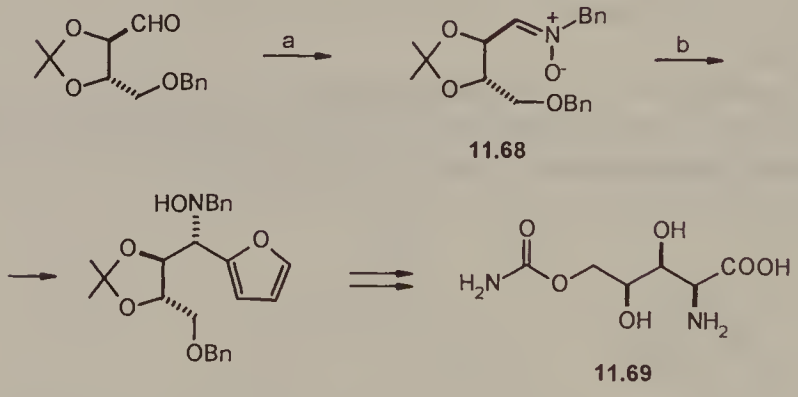
Dondoni *et al.* used *syn*-selective addition of 2-lithiofuran to nitrone **11.68** in the synthesis of 5-*O*-carbamoylpolyoxamic acid (**11.69**), a building block of the nucleoside antibiotic polyoxin J[120] (Scheme 11.41).



a: $AcOCH_2COCl$, NEt_3, CH_2Cl_2, 0°C → RT, 16h then LiOH, H_2O_2, THF-H_2O, 0°C, 3h (90%)

b: NaOCl, CH_2Cl_2, TEMPO (cat.), pH 7.0, 0°C, 1min.

Scheme 11.40



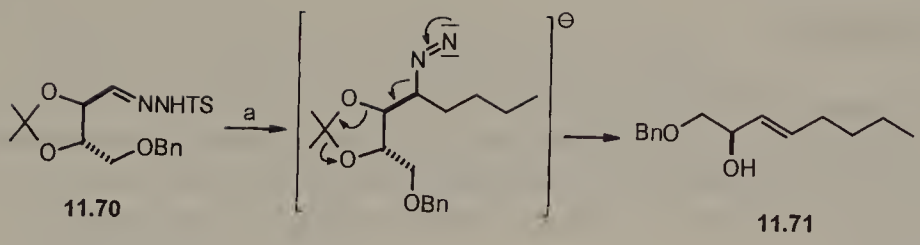
a: BnNHOH, $MgSO_4$, CH_2Cl_2 (85%)[53]

b: 2-lithiofuran, THF, -80°C, 15 min. (82%, *syn* : *anti* = 96 : 4)[120]

Scheme 11.41

It should be noted that in the presence of the Lewis acid Et_2AlCl, the addition of the Grignard reagent to nitrone **11.68** was predominantly *anti*-selective.[121]

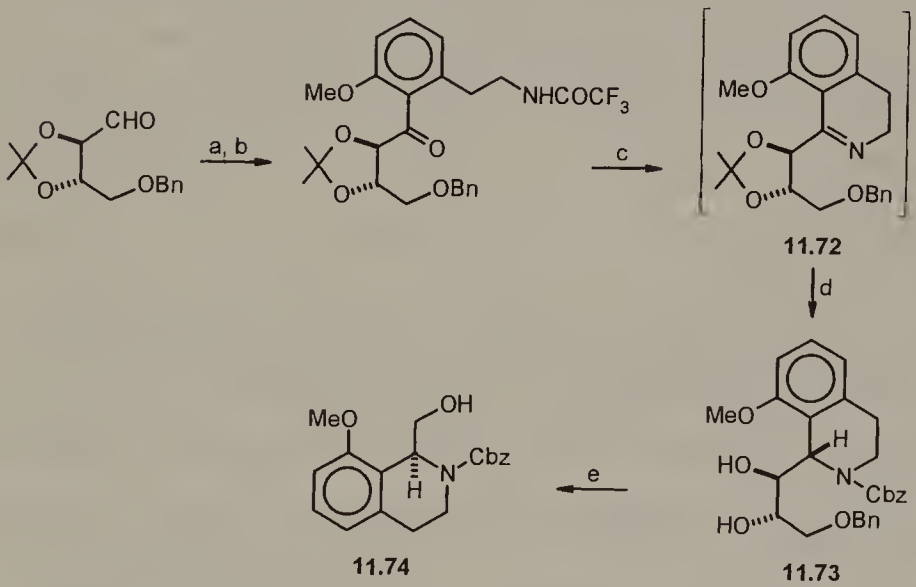
Optically active allyl alcohol **11.71** is readily available by the alkylation-fragmentation reactions of L-threose tosylhydrazone **11.70** bearing an adjacent *O*-isopropylidene group[122] (Scheme 11.42).

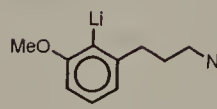


a: 3 eq. n-BuMgBr, Et_2O, RT, 1h (66%)

Scheme 11.42

Terashima used protected threose as chiral scaffold in the synthesis of quinocarcin.[123] Crucial to the synthesis was a highly diastereoselective reduction of 3,4-dihydroisoquinoline **11.72** to **11.73** by sodium cyanoborohydride. Oxidative cleavage of the chiral auxiliary gave the bicyclic intermediate **11.74** (Scheme 11.43).



a. 

, Et_2O, -78°C → 0°C (63%)

b: $CrO_3 \cdot 2Py$, CH_2Cl_2, RT (84%)

c: K_2CO_3, aq. MeOH, RT

d: $NaBH_3CN$, -20°C, then HCl, MeOH, RT, then ClCOOBn, NaOH, CH_2Cl_2 (81%)

e: $NaIO_4$, MeOH, then $NaBH_4$ (78%)

Scheme 11.43

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12 TADDOLs, Their Complexes, and Related Compounds

12.1 TADDOLS

Overview of Structure and Properties

The acronym TADDOL has been coined for $\alpha,\alpha,\alpha',\alpha'$-tetraaryl-1,3-dioxolane-4,5-dimethanols (2,3-acetals of 1,1,4,4-tetraarylthreitols). Their basic structural features are shown in Figure 12.1.

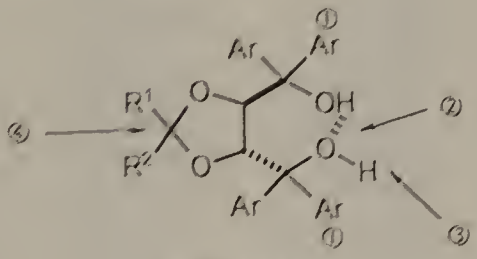
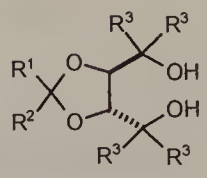


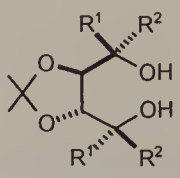
Figure 12.1

1. One of the Ar groups on each side arm occupies the axial position.
2. The intramolecular hydrogen bond adds to the molecule's conformational rigidity.
3. This hydrogen bonding site is accessible to polar guests, inducing the formation of a host-guest inclusion complex. Intermolecular hydrogen bonding leads to dimerization of TADDOLs in the solid state in the absence of guests.
5. The acetal ring makes TADDOLs molecules rigid; it shows remarkable resistance to acid hydrolysis.

With very few exceptions, TADDOLs are solids and possess very good crystallization properties. They enantioselectively form inclusion compounds with various chiral guests in the crystalline state. The guest molecules include (moderately) polar compounds, acting as hydrogen bond acceptors or donors. This useful property must be borne in mind also when isolating and purifying TADDOLs. In addition, TADDOLs are excellent bidendate chelators for many ions, a property extensively explored for the preparation of chiral catalysts.



I



II

Table 12.1 (4*R*,5*R*)-α,α,α′,α′-Tetraaryl (alkyl)-1,3-dioxolane-4,5-dimethanols (I)

No.	R^1	R^2	R^3	m.p. (°C)	$[\alpha]_D$ ($CHCl_3$)	References
12.1	H	H	Ph	oil	−23.5	1,2
12.2	H	H	4-$Me_2NC_6H_4$	134.8–137.6[a]	−61.0	3
12.3	H	H	1-naphthyl	255–257	−32.6	4
12.4	H	Me	Ph	162–163	−47.4	5
12.5	H	t-Bu	Me	128–129	−20.5	1
12.6	H	t-Bu	Ph	154–156	−91.6	1,2,5[b]
12.7	H	t-Bu	1-naphthyl	195–203	−224.1[c]	2
12.8	H	t-Bu	2-naphthyl	208.5–210	−5.5[c]	2
12.9	H	Cy	Ph	190–191	−52.5	1
12.10	H	Ph	Me	106	−13.2	5,6
12.11	H	Ph	Ph	196.4–198.2	+10.4	1,3,5[b]
12.12	H	3-HOC_6H_4	Ph	135–140	+7.4[d]	7
12.13	H	3-HOC_6H_4	3,5-$Me_2C_6H_3$	145–158	+129.0[d]	7
12.14	H	3-HOC_6H_4	2-naphthyl	165–173	+137.0[d]	7
12.15	H	3-HOC_6H_4	4-$MeOC_6H_4$	113–118	+25.0[d]	7
12.16	H	3-$BnOC_6H_4$	Ph	80–85	+35.0[d]	7
12.17	H	3-$BnOC_6H_4$	3,5-$Me_2C_6H_3$	103	+75.0[d]	7
12.18	H	4-$BrCH_2C_6H_4$	Ph	105–108	+36.0	8
12.19	H	4-$HOCH_2C_6H_4$	Ph	128–132	+28.0	8
12.20	H	4-$MeOC_6H_4$	Ph	104–109	+28.2[e]	9
12.21	H	4-CH_2=CHC_6H_4	Ph	104–105	+63.2	8
12.22	H	4-CH_2=CHC_6H_4	1-naphthyl	200–210	+12.8	8
12.23	H	4-CH_2=CHC_6H_4	2-naphthyl	165–170	+20.0	8
12.24	H	2,4,6-$Me_3C_6H_2$	Ph	91–93	−42.5	1
12.25	H	1-naphthyl	Ph	229.4–231.5	+25.2	5
12.26	H	2-naphthyl	Ph	109–110	+70.9	5
12.27	Me	Me	Me	154.0–154.6	+7.6	1,10–13
12.28	Me	Me	Bn	glass	+70.7	5
12.29	Me	Me	Ph	194–195	−68.5	1,2[b],14–16
12.30	Me	Me	2-MeC_6H_4	160–162	−32.7	16,17
12.31	Me	Me	4-MeC_6H_4	103–105	−52.0	16,18
12.32	Me	Me	4-$CF_3C_6H_4$	205–206	+114.2	18
12.33	Me	Me	4-$tBuC_6H_4$	222–223	−64.5	4
12.34	Me	Me	4-PhC_6H_4	231	−71.8	2
12.35	Me	Me	4-FC_6H_4	169–170	−65.6	18
12.36	Me	Me	4-ClC_6H_4	124	−62.9[e]	18
12.37	Me	Me	4-BrC_6H_4	151–154	−30.0[f]	19
12.38	Me	Me	4-$MeOC_6H_4$	107.2–107.8[g]	−55.6	2
12.39	Me	Me	4-$Me_2NC_6H_4$	232–234	−69.0[f]	19

(*continued*)

Table 12.1 (*continued*)

No.	R^1	R^2	R^3	m.p. (°C)	$[\alpha]_D$ ($CHCl_3$)	References
12.40	Me	Me	4-$IPh_3PC_6H_4$	240	−48.0[f]	19
12.41	Me	Me	4-$Ph_4BPh_3PC_6H_4$	175	−37.0[f]	19
12.42	Me	Me	3,5-$Me_2C_6H_3$	92.0–93.2	−42.6	4,20,21
12.43	Me	Me	3,5-$F_2C_6H_3$	145–147	−76.2	18
12.44	Me	Me	C_6F_5	—	—	22
12.45	Me	Me	1-naphthyl	199–200[g]	−288.3[c]	2,4[b]
12.46	Me	Me	2-naphthyl	213–215	−115.4[c]	2
12.47	Me	Me	2-furyl	—	—	22
12.48	Et	Et	Ph	—	—	21,23
12.49	Et	Et	3,5-$Me_2C_6H_3$	175.8–179.2	−92.2	23,24
12.50	Et	Et	3,5-$(CF_3)_2C_6H_3$	—	—	23
12.51	Et	Et	3,5-$Cl_2C_6H_3$	—	—	23
12.52	Et	Et	2-naphthyl	—	—	23
12.53	Et	Et	6-MeO-2-naphthyl	—	—	23
12.54	$-(CH_2)_4-$		Me	156	—	24
12.55	$-(CH_2)_4-$		Ph	165	—	25
12.56	$-(CH_2)_5-$		Ph	197.5–198.5	−78.4	1,2
12.57	$-(CH_2)_5-$		1-naphthyl	197–204[h]	−267.4	2,4[b]
12.58	Me	Ph	Ph	96–99	+71.4	4[b],26,27
12.59	Me	Ph	4-MeC_6H_4	103–106	+67.0	28
12.60	Me	Ph	4-$tBuC_6H_4$	147–151	−6.0	28
12.61	Me	Ph	3,5-$Me_2C_6H_3$	237–239	+88.0	28
12.62	Me	Ph	2-naphthyl	160–170	+289.9	4
12.63	Me	4-CH_2=CHC_6H_4	Ph	76–78	+83.9	8
12.64	Me	4-HOC_6H_4	Ph	110–115	+53.7[d]	7
12.65	Me	4-HOC_6H_4	4-$MeOC_6H_4$	122.5	+55.4[d]	7
12.66	Ph	Ph	Ph	156–157[i]	+187.7	29[b]
12.67	Ph	4-CH_2=CHC_6H_4	Ph	105–106	+177.8	8
12.68	2,2′-biphenyl		Ph	225–226.4[j]	−62.9	4,30

[a] 1:1 Complex with toluene.
[b] X-ray structure reported.
[c] Measured in ethyl acetate.
[d] Measured in THF.
[e] Measured in methanol.
[f] Measured in acetone.
[g] 1:1 Complex with methanol.
[h] 1:1 Complex with ethanol.
[i] Ref. 30 reports m.p. 90–94°C.
[j] Ref. 30 reports m.p. 128–130°C.

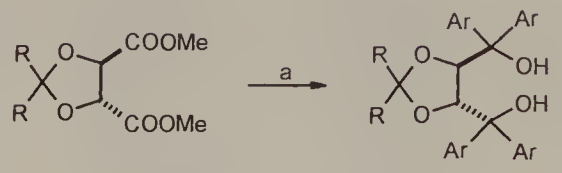
Table 12.2 C_2-symmetrical TADDOLs with two different substituents (II)

No.	R^1	R^2	m.p. (°C)	$[\alpha]_D$ ($CHCl_3$)	References
12.69	Me	Ph	131–133	−24.6	31
12.70	Ph	Me	192–193	+46.4	31[a]
12.71	Ph	4-FC_6H_4	151–153	−63.3	20
12.72	4-FC_6H_4	Ph	188–191	−59.3	20
12.73	Ph	3,5-$Me_2C_6H_3$	78–80	−30.5	20
12.74	3,5-$Me_2C_6H_3$	Ph	82–85	−38.3	20

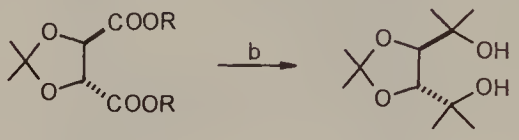
[a] X-ray structure reported.

Synthesis

TADDOL synthesis is achieved by the reaction of a tartrate acetal with a Grignard reagent in tetrahydrofuran or ether solution. Aryl, methyl, and allyl Grignard reagents are suitable for the reaction. Examples of these procedures are shown in Scheme 12.1.

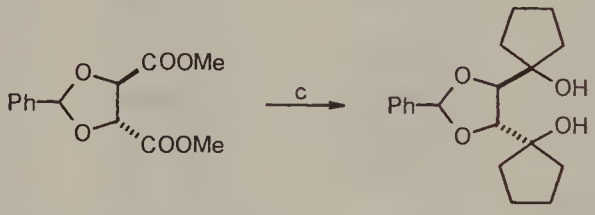


a: 4.4 eq. ArMgBr, THF, 20°C, then Δ, 2h[2] (yield 88% for R = Et, Ar = 3,5-$Me_2C_6H_3$[23])



R = Me, Et

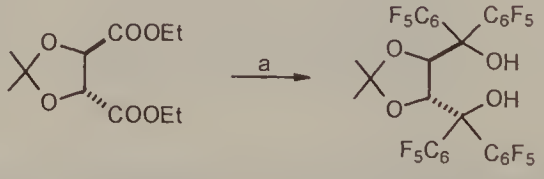
b: 6 eq. MeMgBr, Et_2O or THF (93%)[1,12,32]



c: $BrMg(CH_2)_4MgBr$, THF, 0°C → RT (50%)[33]

Scheme 12.1

Certain TADDOLs were also prepared by the reaction of tartrate acetals with aryllithium reagents (Scheme 12.2).

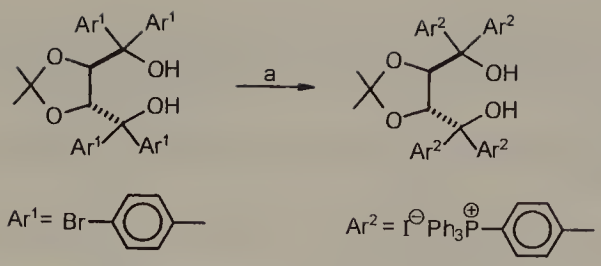


a: BrC_6F_5, n-BuLi, hexane-Et_2O, -78°C, then 0°C (51%)[22]

Scheme 12.2

Modified TADDOLs can be obtained by substitution reactions of aromatic groups, without changing the integrity of the compound (Scheme 12.3).

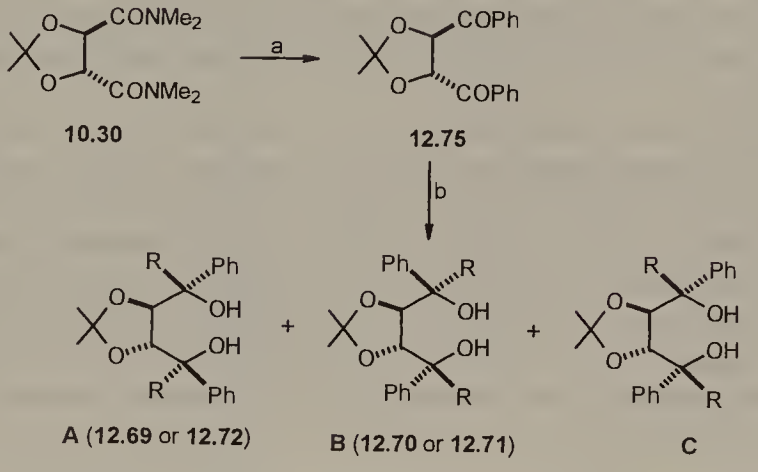
C_2-Symmetrical TADDOLs with two different substituents on each side arm were synthesized from the tartramide acetal **10.30** via the intermediate bis(aryl ketone), for example, **12.75** (Scheme 12.4). The three diastereomeric products



a: Ph_3P, $NiBr_2$, EtOH, 110-120°C, 72h, then NaI[19]

Scheme 12.3

A–C were obtained in varying proportions, depending on the nature of the second nucleophile used.



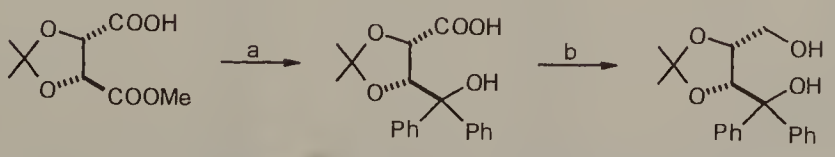
a: 4 eq. PhMgBr, THF, RT (77%)[31]

b: 4 eq. MeLi-$CeCl_3$, THF, -78°C (67%)[31]
or 4 eq. MeMgCl, Et_2O, 0°C (93%)[31]
or 2.5 eq. 4-FC_6H_4MgBr, CH_2Cl_2-Et_2O, -78°C (71%)[20]

	A	B	C
	75	2	23
	2	65	33
	94	1	5

Scheme 12.4

An example of the synthesis of an unsymmetrical "half-TADDOL" derivative is shown in Scheme 12.5.



a: PhMgBr, THF, RT (67%) b: MeI, Na_2CO_3, DME then $NaBH_4$, MeOH (87%)[34]

Scheme 12.5

The following TADDOLs are availabe commercially:

(4*R*,5*R*)-2,2-dimethyl-α,α,α′,α′-tetraphenyldioxolane-4,5-dimethanol [*93379-48-7*]

(4S,5S)-2,2-dimethyl-α,α,α′,α′-tetraphenyldioxolane-4,5-dimethanol [*93379-49-8*]

(4*R*,5*R*)-2,2-dimethyl-α,α,α′,α′-tetra(2-naphthyl)dioxolane-4,5-dimethanol, (−)-DINOL [*137365-09-4*]

(4*S*,5*S*)-2,2-dimethyl-α,α,α′,α′-tetra(2-naphthyl)dioxolane-4,5-dimethanol, (+)-DINOL [*137365-16-3*].

Applications

In relation to the synthesis of enantiomerically pure compounds, TADDOLs are used as unconventional yet efficient resolving agents and as chiral ligands for solid state enantioselective reactions. The most frequently used for these purposes are TADDOLs **12.29**, **12.30**, **12.55**, and **12.56** (for numbering see Table 12.1).

TADDOLs display a high ability for the formation of clathrates with a variety of uncharged guests molecules. The guest molecules include alcohols, amines, ketones, esters, lactones, amides, anhydrides, cyanohydrins, acetals, sulfoxides, and sulfinates as well as aromatic and heterocyclic compounds. Inclusion crystals are formed by cocrystallization of the TADDOL with the guest compound which can be used as a solvent, or by crystallization of the TADDOL and the guest compound from the solution in nonpolar solvent. A list of inclusion compounds with simple guests and their X-ray determined structures is given in Tables 12.3 and 12.4.

Table 12.3 Crystalline inclusion compounds of TADDOL 12.29 and references to the X-ray determined structures

Guest	**12.29**: guest stoichiometry	Ref.	X-ray ref.
MeOH	1:1	18	
EtOH	1:1	18	
t-BuOH	1:2	18	
n-$PrNH_2$	1:1	8,30	15
i-$PrNH_2$	1:1	30	
n-$BuNH_2$	1:1	30	
i-$BuNH_2$	1:1	30	
n-$C_8H_{17}NH_2$	1:1	30	
cyclo-$C_5H_9NH_2$	1:1	30	
cyclo-$C_6H_{11}NH_2$	1:1	18,30	
$PhNH_2$	1:1	30	
Et_2NH	1:1	30	

(*continued*)

Table 12.3 (*continued*)

Guest	**12.29**: guest stoichiometry	Ref.	X-ray ref.
n-Pr_2NH	1:1	18,30	15
i-Pr_2NH	1:1	30	
n-Bu_2NH	1:1	30	
i-Bu_2NH	1:1	30	
piperidine	1:1	18,30	
morpholine	1:1	18	
Et_3N	1:1	30	
n-Pr_3N	1:1	18,30	15
n-Bu_3N	1:1	30	
pyridine	1:1	18,30	
2-picoline	1:1	30	
3-picoline	1:1	30	
4-picoline	1:1.5	30	
acetone	1:1	18	
cyclohexanone	1:1	18	
MeCN	3:2	18	
$MeNO_2$	3:2	18	
DMF	1:1	18	
DMSO	1:1	kx	
THF	4:1	18	
dioxane	1:2	18	
benzene	2:1	18	
CCl_4	1:2	2	2

Table 12.4 Crystalline inclusion compounds of various 2,2-dimethyl substituted TADDOLs[18]

	Host TADDOL: guest stoichiometry				
Guest	**12.31**	**12.32**	**12.35**	**12.36**	**12.43**
MeOH	1:1[a]	1:1	1:1[a]	2:3[a]	3:1
EtOH	1:1	1:1	2:1	1:2	2:1[a]
i-PrOH	1:1	1:1	2:1[a]	1:2	2:1
t-BuOH	[b]	1:1	3:2	1:2	3:2
cyclo-$C_6H_{11}OH$	[b]	[b]	2:1	1:1	3:2
n-$PrNH_2$	1:1	1:1	1:1	1:1	1:1
n-Pr_2NH	1:1	1:1	1:1	1:1	1:1
n-Pr_3N	[b]	1:1	2:1	[b]	1:1
cyclo-$C_6H_{11}NH_2$	[b]	1:1	1:2	1:2	1:1
morpholine	[b]	3:2	2:3	[b]	[b]
pyridine	1:1	1:1	2:1	2:1	1:1
acetone	2:1	2:1	2:1	2:1	2:1
cyclohexanone	1:1	1:1	1:1	2:3	[b]

(*continued*)

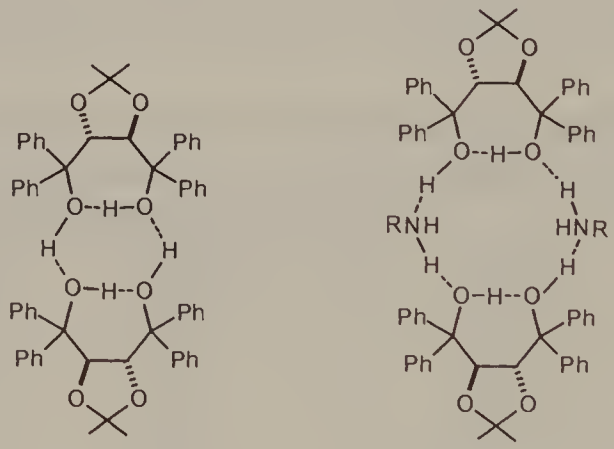
Table 12.4 *(continued)*

	Host TADDOL: guest stoichiometry				
Guest	**12.31**	**12.32**	**12.35**	**12.36**	**12.43**
MeCN	2:1	2:1	3:2	2:1	2:1
$MeNO_2$	2:1	1:1	3:2	2:1	—
DMF	1:1	2:1	1:1	1:1	[b]
DMSO	1:1	1:1	1:1	1:3	1:2
THF	4:3	2:1	2:1	[b]	1:1
dioxane	1:1	1:1	4:3	1:1	4:3
benzene	[b]	1:1	—	2:1	2:1

[a] Structure determined by X-ray diffraction. [b] Difficult to crystallize.

Selectivity in the formation of the inclusion compounds in the crystalline state can be used for separation of compounds from mixtures. For example, **12.29** forms inclusion compounds with amines in this order of preference: R_2NH > RNH_2 > R_3N.[30] Thus secondary amines can be isolated from mixtures by complexation with TADDOLs.

A schematic summary of hydrogen bonding in crystals of host **12.29** and its inclusion compound (1:1) with a primary amine, as determined by Weber and Goldberg,[15] is shown in Figure 12.2.



12.29 **12.29** x RNH_2

Figure 12.2

Inclusion complexation with TADDOL hosts has been widely used by Toda *et al.* for solid state resolution of racemic guests.[35] A variety of racemic organic compounds with hydrogen bonding capabilities can cocrystallize with chiral TADDOL hosts, thus providing a means for enantiomer resolution. Apart from

cocrystallization, other less conventional techniques of optical resolution have been developed.

- enantioselective transfer of the guest molecule from the racemic guest crystal to the host crystal with the formation of an inclusion crystal[36]
- enantioselective transfer of the guest molecule from the solution to the host crystal suspended in the solution (usually in hexane or water)[37]

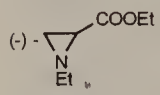
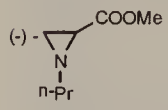
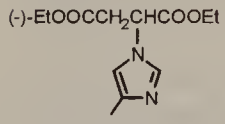
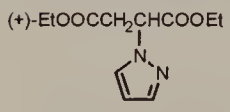
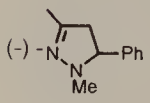
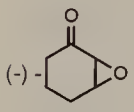
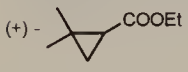
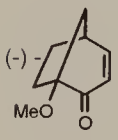
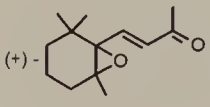
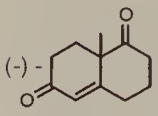
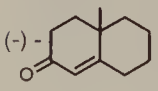
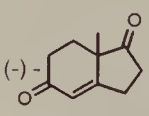
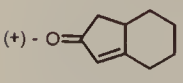
Table 12.5 shows representative examples of resolutions via inclusion complexation with TADDOL hosts.

Table 12.5 Resolution of racemates by enantioselective inclusion complexation with the TADDOL hosts 12.29, 12.30, 12.55, and 12.56

Guest in the complex	Host	Stoichiometry, H:G	Method[a]	Yield (%)	e.e. (%)	Ref.
(−)-PhCH(OH)Me	12.29	2:1	C	72	75	38
			S	85	98	37,39
(−)-PhCH(OH)Et	12.29	2:1	C	40	91	38
			S	75	100	37,39
(+)-PhCH(OH)C≡CH	12.29	2:1	C	69	97	38
			S	76	100	37,39
(−)-3-MeOC$_6$H$_4$CH(OH)C≡CH	12.55	2:1	C	65	92	38
	12.55	—	C	79	79	38
(+)-PhCH(OH)C≡N	12.29	2:1	C	54	100	38
	12.55	2:1	C	51	100	38
	12.55	1:1	C	72	100	38
	12.56	1:1	C	44	100	38
(−)-HOCH$_2$CH(OH)Me	12.55	—	C	—	100	40
(+)-MeCH(OH)CH$_2$COOEt	12.55	2:1	S	93	78	37,39
(+)-PhCH$_2$CH(NH$_2$)COOMe	12.55	2:1	C	45	100	41[b]
(+)-PhCH$_2$CH(NH$_2$)COOMe	12.55	2:1	C	40	100	41
(−)-PhCH(Me)NH$_2$	12.29	2:1	C	52	100	42[b]
	12.55	1:1	C	30	100	42[b]
	12.55	2:1	C	52	100	36

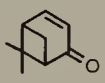
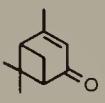
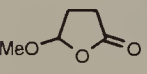
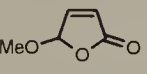
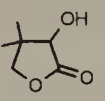
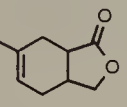
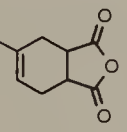
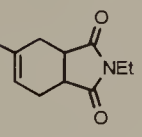
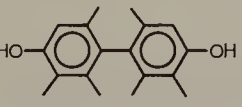
(continued)

Table 12.5 (*continued*)

Guest in the complex	Host	Stoichiometry, H:G	Method[a]	Yield (%)	e.e. (%)	Ref.
	**12.56**	1:1	C	34	100	43
	**12.55**	1:1	C	44	100	43
	**12.29**	—	S	100	100	44
	**12.56**	2:1	C	93	98	44
	**12.30**	1:1	C	45	96	45[b]
	**12.55**	—	S	82	100	37,39
	**12.56**	—	S	80	100	37,39
	**12.29**	1:1	C	48	100	46[b]
	**12.56**	1:1	T	24	88	36,47
	**12.29**	1:1	C	70	100	16,48[b]
	**12.29**	1:1	C	62	100	16,48[b]
	**12.29**	1:1	C	58	100	16
	**12.29**	1:1	C	80	100	16

(*continued*)

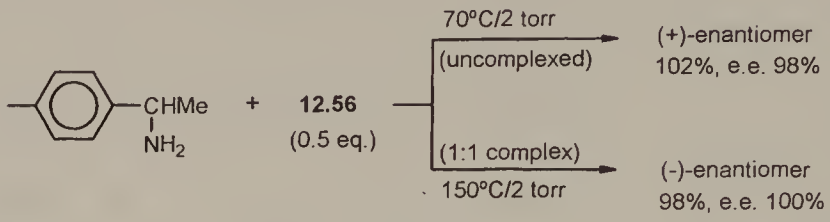
Table 12.5 (*continued*)

Guest in the complex	Host	Stoichiometry, H:G	Method[a]	Yield (%)	e.e. (%)	Ref.
(+)- 	**12.29**	1:1	C	47	100	49
(-)- 	**12.30**	1:1	C	48	100	49[b]
(-)-MeO 	**12.30**	1:1	C	50	96	17
(-)-MeO 	**12.30**	1:1	C	41	92	17[b]
(-)- 	**12.56**	1:1	C	30	99	50[b]
(+)- 	**12.55**	1:1	C	56	100	47
(+)- 	**12.29**	1:1	C	52	100	47,51
(+)- 	**12.56**	1:1	C	50	100	47
(-)-HO 	**12.55**	1:1	C	34	100	52
(+)-PhSMe 	**12.56**	1:1	C	61	100	53
(+)-PhSOMe 	**12.56**	1:1	C	18	69	53

[a] C—crystallization from a solution in nonpolar solvent(s).
S—transfer in suspension in hexane or water.
T—transfer in the solid state (crystal-to-crystal).
[b] X-ray structure reported.

If the resolution by complexation is incomplete, enantiomerically pure guest compounds can be obtained by repeated crystallization or complexation. The guest and host compounds can be recovered from the complexes by any suitable

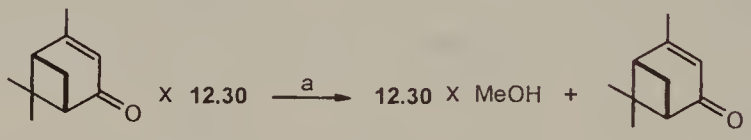
method: chromatography, distillation or extraction. Fractional distillation is particularly effective, as it allows for separation of both enantiomers of the guest.[36,37,54] An example is shown in Scheme 12.6.[36]



Scheme 12.6

The process for separating enantiomers of amphetamine by differential distillation in the presence of **12.29** has been patented.[55]

Still another method for recovering guest compound from the TADDOL complex is based on replacement by a more strongly interacting compound or solvent (Scheme 12.7).



a: crystallization from methanol (yield 99%)[49]

Scheme 12.7

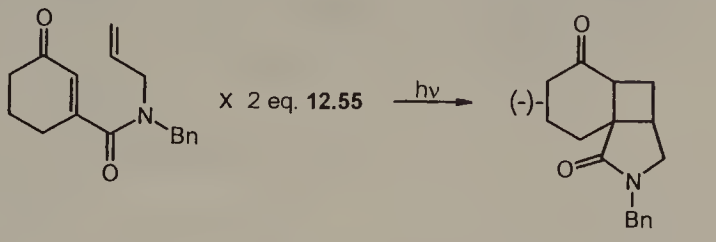
Molecular complexes of TADDOLs with organic molecules can be used for the isolation of unstable conformers of these molecules. For example, β-ionone forms a 1:1 inclusion compound with **12.56** in which β-ionone molecules are in the energetically less favorable *s-cis* conformation.[56]

Molecular association of TADDOLs with compounds capable of forming hydrogen bonds in solution is the basis of their application as chiral resolving agents in NMR spectroscopy. The enantiomeric excess of alcohols, amines, amino acid esters, and cyanohydrins can be determined from the nonequivalence of signals in the ^{1}H, ^{13}C, and ^{19}F NMR spectra.[3,42,57]

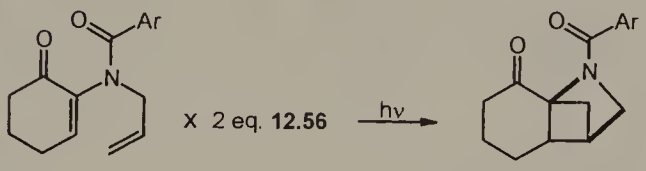
Molecules included in TADDOL complexes can undergo enantioselective reactions in the solid state.[58,59] Several examples of such synthetically useful and conveniently performed transformations, developed by Toda *et al.*, are shown in Scheme 12.8. Molecular complexes for the reaction can be formed either by recrystallization or simply by mixing[60] powdered components.

Note the opposite enantioselectivity in the photocyclizations of 1:1 and 2:1 complexes of **12.55** and *N*-allylfuran-2-carboxanilide.[69]

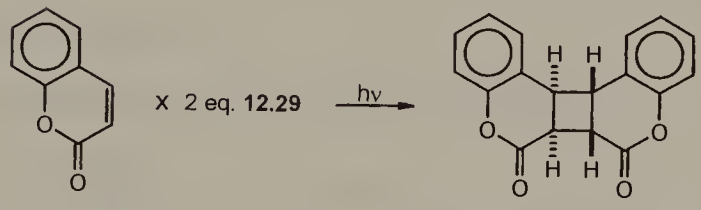
Intramolecular photocyclizations of achiral molecules arranged in the crystalline complex in a chiral form



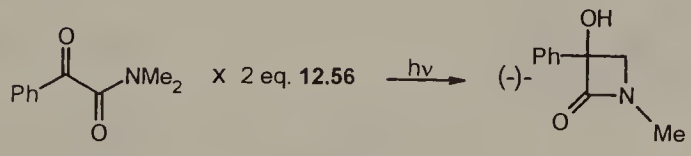
90%, e.e. 100%[60,61]



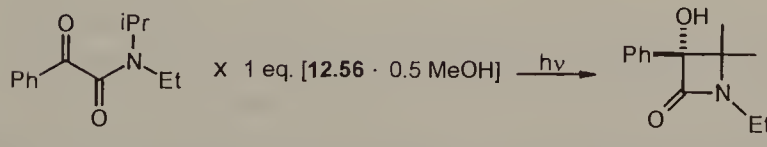
Ar = Ph, 81%, e.e. 99%
3-ClC_6H_4, 71%, e.e. 99.9%
4-MeC_6H_4, 65%, e.e. 99%[62]



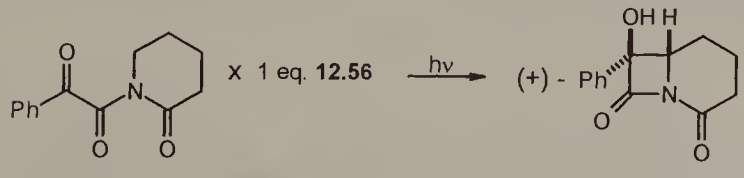
96%, e.e. 96%[63]



40%, e.e. 100%[64,65]

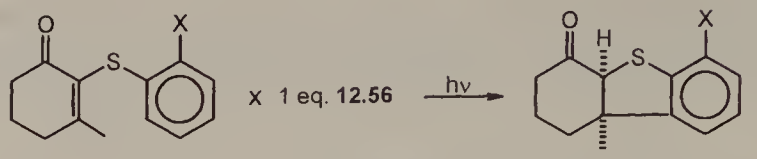


72%, e.e. 76%[27,60]



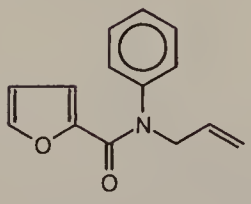
87%, e.e. 94%[66,67]

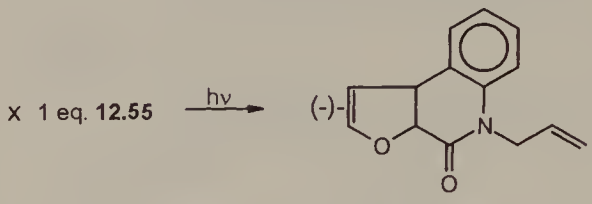
Scheme 12.8 (*continued*)



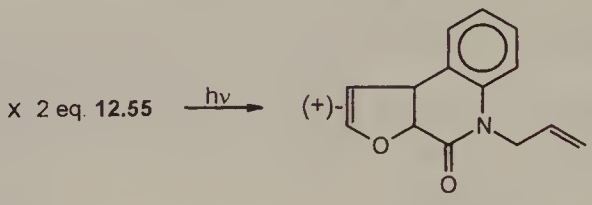
X = Cl, 92%, e.e. 81%

X = Br, 91%, e.e. 83%[68]



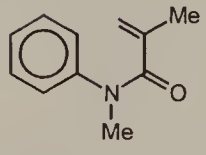


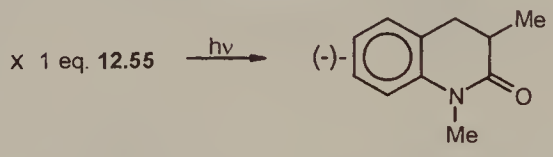
50%, e.e. 96%[69]



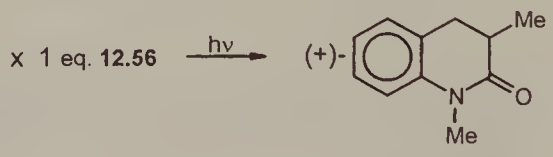
86%, e.e. 98%[69]

(note the opposite enantioselectivity in the above two reactions)





65%, e.e. 98%[70]

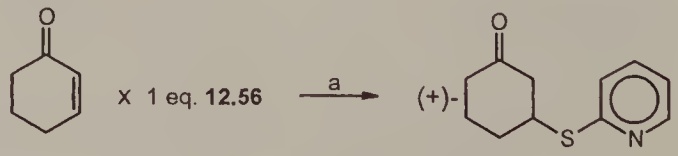


44%, e.e. 98%[70]

(note the opposite enantioselectivity controlled by the two closely related hosts)

The above photocyclizations are usually conducted in water suspension containing a small amount of a surfactant, $C_{16}H_{33}Me_3N^+Br^-$, with a high-pressure Hg lamp.

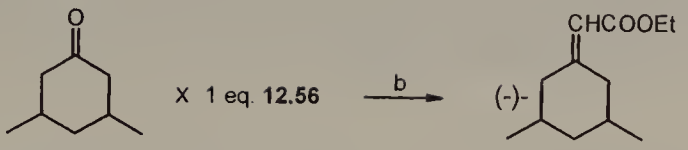
Michael addition



a: 2-mercaptopyridine, aq. $BnMe_3N^+OH^-$, ultrasound, RT (51%, e.e. 80%)[39,71]

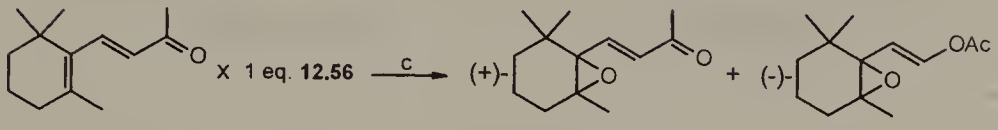
(continued)

Wittig-Horner reaction

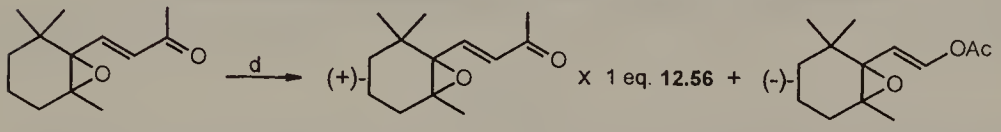


b: Ph_3P=CHCOOEt, 2h, 80°C (58%, e.e. 57%)[25]

Bayer-Villiger oxidation (kinetic resolution)

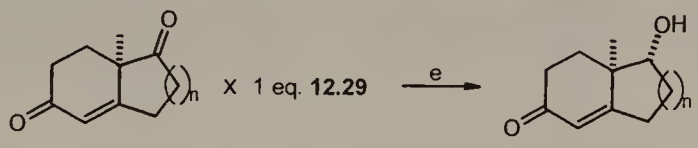


c: 2 eq. MCPBA, 2 days, RT[72] (first step - epoxidation - is non-enantioselective)



d: 1 eq. **12.56**, 1 eq. MCPBA, RT[47]

Diastereoselective ketone reduction



n = 1 55%, d.e. 100%

n = 2 54%, d.e. 100%[73]

e: $NaBH_4$, 3 days, RT

Scheme 12.8

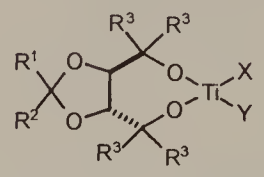
12.2 TITANIUM TADDOLATES

Overview of Structure and Reactivity

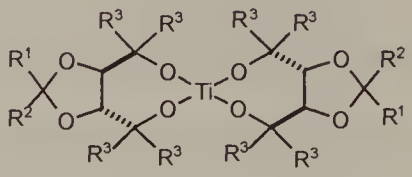
Titanium(IV) TADDOLates are Lewis acids used for stoichiometric and catalytic enantioselective transformations.[74] Their catalytic activity resides in the acceleration of the asymmetric processs by the chiral catalyst with a TADDOL ligand over the competing process catalyzed by an achiral titanate.

Titanium(IV) chelation by TADDOLs in solution is spontaneous; most Ti-TADDOLates are prepared *in situ*, with the exception of the *Duthaler–Hafner reagent*, **12.85** and the spirotitanate **12.97**. The TADDOLates in solution can be either monomeric or aggregated. The conformation of the seven-membered chelate ring is such that the four carbon atoms of the tartrate residue are in the

gauche arrangement and the Ar groups occupy outer positions. The acidity of titanium(IV) TADDOLates can be modulated by the choice of substituents X, Y: Cl, Cp, allyl, or i-PrO (see Table 12.6).



Ti-TADDOLates(**III**)



Spirotitanates(**IV**)

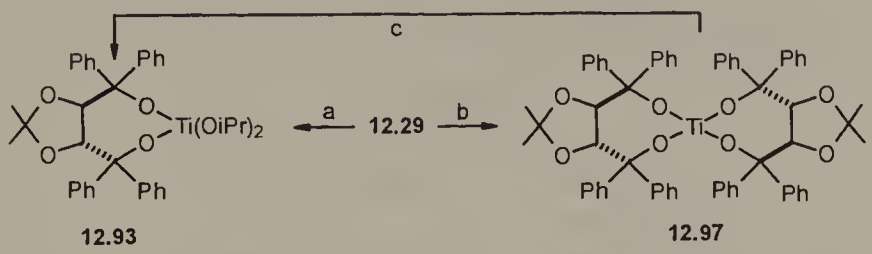
Table 12.6 Titanium(IV) TADDOLates (III) and spirotitanates (IV)

No.	X	Y	R^1	R^2	R^3	References
			Formula III			
12.76	Cl	Cl	Me	Me	Ph	20,75
12.77	Cl	Cl	Me	Me	3,5-$Me_2C_6H_3$	20
12.78	Cl	Cl	Me	Me	2-naphthyl	20
12.79	Cl	Cl	Et	Et	3,5-$Me_2C_6H_3$	23
12.80	Cl	Cl	Ph	H	Ph	76
12.81	Cl	Cl	Ph	Me	Ph	77
12.82	Cl	Cp	H	H	Ph	22
12.83	Cl	Cp	Me	Me	Me	22[a]
12.84	Cl	Cp	Me	Me	All	22
12.85	Cl	Cp	Me	Me	Ph[b]	22[a],78–80
12.86	Cl	Cp	Ph	Ph	Ph	22
12.87	Cl	Cp	2,2′-biphenyl		Ph	22
12.88	Cl	Me_5Cp	Me	Me	Me	22[a],81
12.89	Cl	Me_5Cp	Me	Me	Ph	22
12.90	Cl	OiPr	Me	Me	Ph	1
12.91	All	Cp	Me	Me	Ph	22
12.92	MeCH=$CHCH_2$	Cp	Me	Me	Ph	22
12.93	OiPr	OiPr	Me	Me	Ph[c]	82,83
12.94	OiPr	OiPr	Me	Me	2-naphthyl	75,82
12.95	OiPr	OiPr	Ph	H	Ph	82
12.96	OiPr	OiPr	Ph	Me	Ph	28,84
			Formula IV			
12.97	—	—	Me	Me	Ph	5,82,83,85[a]
12.98	—	—	Et	Et	3,5-$(CF_3)_2C_6H_3$	86

[a] X-ray structure reported.
[b] m.p. 209–213°C; $[\alpha]_D$ −246 ($CHCl_3$).
[c] m.p. 79–83°C.

Synthesis

Diisopropoxytitanium TADDOLates are conveniently prepared in solution from TADDOLs and titanium tetraisopropoxide by distilling off or azeotropically removing isopropanol (Scheme 12.9).[1,5,14,82,83,87]



a: 1 eq. $(i\text{-PrO})_4Ti$, PhMe, Δ (removal of i-PrOH)[82,83]

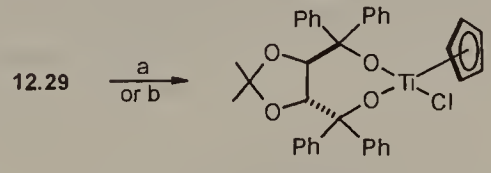
b: 0.5 eq.$(i\text{-PrO})_4Ti$ or 0.5 eq. $(EtO)_4Ti$[82,83]

c: 1 eq. $(i\text{-PrO})_4Ti$[83]

Scheme 12.9

Spirotitanate **12.97** is obtained in an analogous reaction with a half equivalent of titanium tetraalkoxide. Note the facile conversion of **12.97** to **12.93** by the reaction with titanium tetraisopropoxide.

Cyclopentadienylchlorotitanium TADDOLate (**12.85**), the Duthaler–Hafner reagent, is a stable and easy to handle reagent, prepared according to Scheme 12.10, in molar batches.[88,89]



a: $CpTiCl_3$, NEt_3, 12h, RT (87%) or $CpTiCl_3$, Δ (evaporation of HCl), 98%[22]

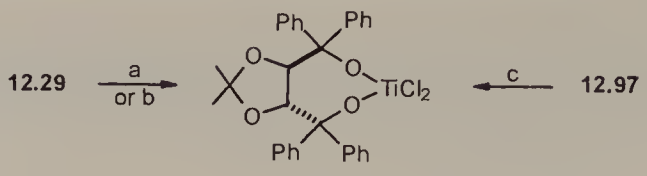
b: Cp_2TiCl_2, NEt_3, MeCN, 3d, 30°C (60%)[79]

Scheme 12.10

The less expensive bis(cyclopentadienyl)titanium dichloride can be used in place of cyclopentadienyltitanium trichloride.[79]

Dichlorotitanium TADDOLates are best obtained *in situ* by the exchange reaction of TADDOL with dichlorotitanium diisopropoxide in the presence of molecular sieves of size 4Å[77,90–93] or by the reaction of dilithium TADDOLate with titanium tetrachloride.[4] Alternatively, **12.76** can be obtained from the spirotitanate **12.97** by the reaction with titanium tetrachloride[4] (Scheme 12.11).

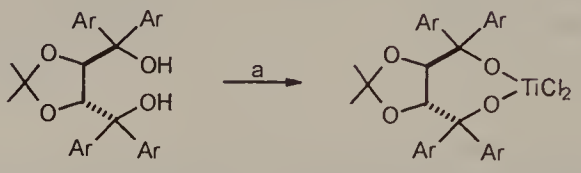
A number of dichlorotitanium TADDOLates have been cleanly obtained by Corey's procedure from TADDOLs under sequential treatment with titanium tetraisopropoxide and silicon tetrachloride[20,23] (Scheme 12.12).



12.76

a: $(i\text{-PrO})_2TiCl_2$, molecular sieves 4Å b: 2 eq. n-BuLi, then $TiCl_4$ c: $TiCl_4$

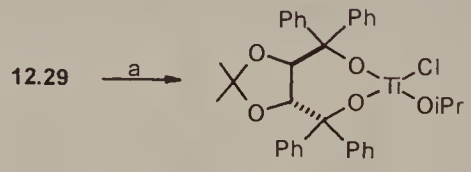
Scheme 12.11



a: $Ti(O\text{-}iPr)_4$, then $SiCl_4$

Scheme 12.12

Chloroisopropoxytitanium TADDOLate (**12.90**) can likewise be obtained by the exchange reaction of TADDOL with chlorotitanium triisopropoxide[14] (Scheme 12.13).

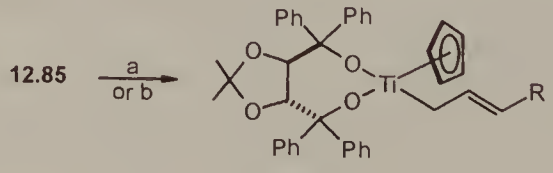


12.90

a: 1 eq. $ClTi(Oi\text{-}Pr)_3$, PhMe, Δ (removal of i-PrOH)

Scheme 12.13

Allyl cyclopentadienyl titanates are obtained by chloride substitution with allylic organometallic reagents[22] (Scheme 12.14).



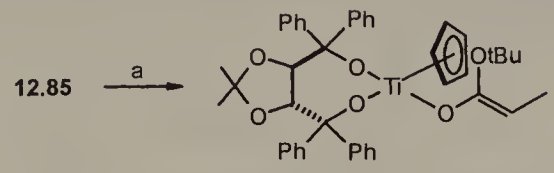
12.91, 12.92

a (R = H): 0.9 eq. $CH_2{=}CHCH_2MgBr$, THF, 1h, RT (93%)

b (R = Me): 1 eq. $MeCH{=}CHCH_2MgCl$, Et_2O, 1h, 0°C (78%)

Scheme 12.14

Chiral cyclopentadienyl titanium enolates are prepared *in situ* from the corresponding lithium enolates[81] (Scheme 12.15).



12.99

a: CH_2=C(OLi)OtBu, Et_2O, -78° to -30°C

Scheme 12.15

The following titanium(IV) TADDOLates are available commercially:

[(4*R*,5*R*)-2,2-dimethyl-1,3-dioxolan-4,5-bis(diphenylmethoxy)]cyclopentadienyl-chlorotitanium, (*R*,*R*)-Duthaler–Hafner reagent [*132068-98-5*]

[(4*S*,5*S*)-2,2-dimethyl-1,3-dioxolan-4,5-bis(diphenylmethoxy)]cyclopentadienyl-chlorotitanium, (*S*,*S*)-Duthaler–Hafner reagent [*140462-73-3*].

Applications

Mediators for asymmetric nucleophilic additions of organometallics to aldehydes. TADDOLs have been shown to be superior chiral titanium ligands for enantioselective additions of organometallics to aldehydes. As amply demonstrated by Seebach *et al.*, the reaction of Grignard, alkyllithium, dialkylzinc, and other polar organometallic reagents with aldehydes in the presence of stoichiometric or catalytic amount of titanium (*R*,*R*)-TADDOLates gives rise to products of *Si* addition[31,74] (Figure 12.3).

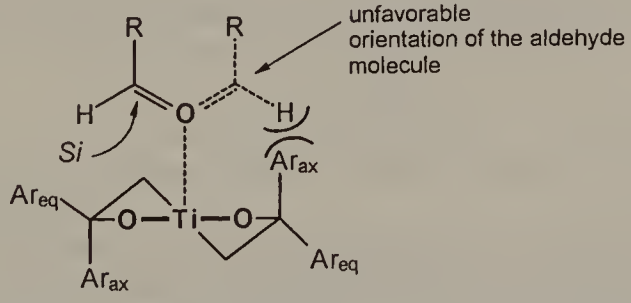
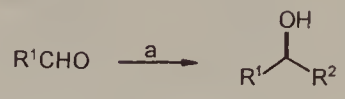


Figure 12.3 Prediction of the face selectiveity in the transition-state model for Ti-TADDOLate mediated nucleophilic additions to aldehydes.[5,31] For the 1,3-dioxolane ring (not shown for clarity) of (4*R*,5*R*) configuration the preferred face selectivity is *Si*.

Particularly effective are the additions of $RTi(OiPr)_3$ reagents to aldehydes, in the presence of 0.2 eq. **12.93**. Alkyltriisopropoxytitanium reagents are prepared

in situ from Grignard or alkyllithium reagents and $ClTi(OiPr)_3$ and should be made free of salts in order to increase enantioselectivity of the addition.[83] The resulting chiral alcohols have in general high enantiomeric excesses, as illustrated by examples of Scheme 12.16.

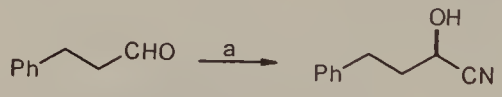


a: R^2M, Ti-TADDOLate, $(i\text{-PrO})_4Ti$, temperature between -78°C and 0°C

R^1	R^2M	Ti-TADDOLate (eq.)	$(i\text{-PrO})_4Ti$ (eq.)	yield (%)	e.e. (%)	ref.
$n\text{-}C_6H_{13}$	MeLi	**12.90** (1.0)	none	67	83	1
$CH_2{=}CH(CH_2)_3$	MeMgI, $ZnCl_2$	**12.97** (0.15)	1.2	69	95	94
PhCH=CH	Et_2Zn	**12.97** (0.1)	1.2	89	96	85
$Me_3SiC{\equiv}C$	Me_2Zn	**12.96** (0.2)	1.4	56	96	28
$PhC{\equiv}C$	Et_2Zn	**12.94** (0.2)	1.2	83	>99	75
$PhC{\equiv}C$	$[CH_2{=}CH(CH_2)_2]_2Zn$	**12.94** (0.2)	1.2	78	96	95
Ph	MeLi	**12.90** (1.0)	none	95	70	1
Ph	Et_2Zn	**12.93** (1.2)	none	85	90	83
Ph	Et_2Zn	**12.93** (0.2)	1.2	99	98	83,95
Ph	$[Me_2C{=}CH(CH_2)_2]_2Zn$	**12.97** (0.17)	1.2	89	96	82
Ph	n-BuTi(Oi-Pr)$_3$	**12.93** (0.2)	none	97	>98	83

Scheme 12.16

Cyanohydrins are formed enantioselectively from aldehydes and cyanotrimethylsilane under catalysis by titanium TADDOLate[26,96] (Scheme 12.17).



a: Me_3SiCN, **12.81**, PhMe, -78°C (88%, e.e. 91%)[26]

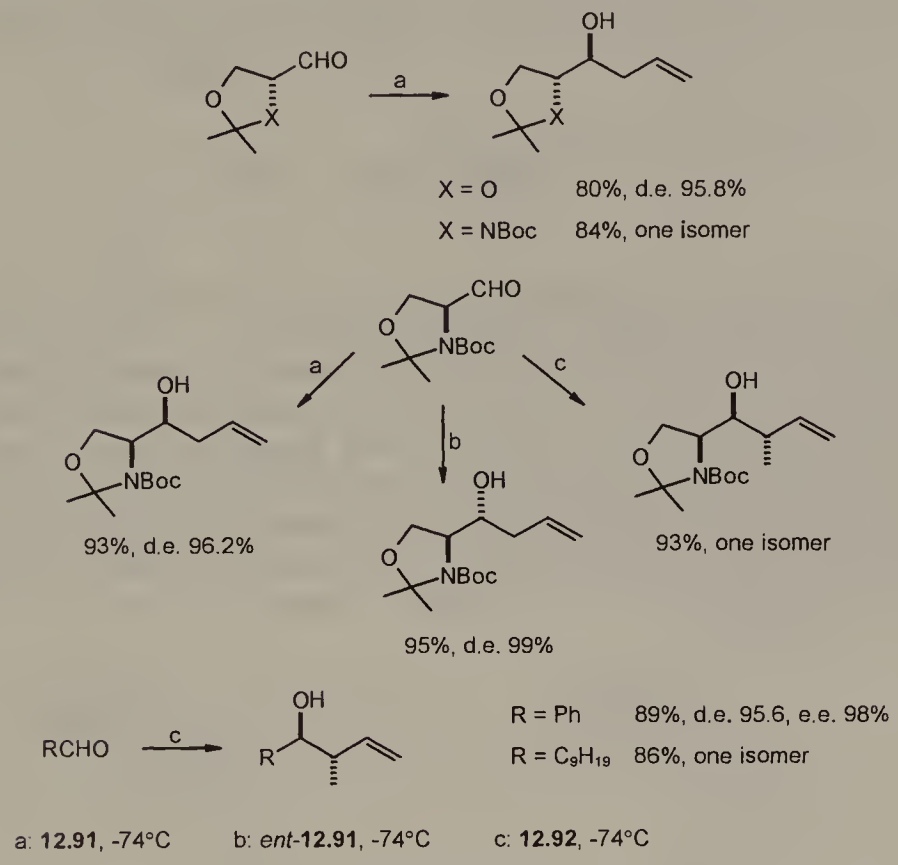
Scheme 12.17

Compounds of this type are used as chiral dopants for ferroelectric liquid crystals.[97]

Seebach *et al.* found that nucleophilic additions to aldehydes can be catalyzed with polymer- or dendrite-bound TADDOLs. The enantioselectivities obtained were comparable to those observed with the soluble analogues and the activity of the polymer-bound Lewis acids was only slightly reduced as compared to that observed in homogenic solution. The polymer-bound TADDOLs could be used up to ten times without decreasing performance.[8]

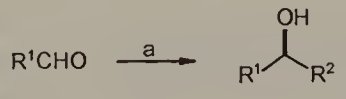
Duthaler, Hafner, and Riediker found that enantio- and diastereoselective addition of the allyl groups and ester enolates to aldehydes is very efficient with titanium TADDOLates coordinated to cyclopentadienyl ligand, which attenuates

the Lewis acidity of titanium.[88,89,98] The reactive intermediates are the cyclopentadienyl-dialkoxy-alkyltitanium complexes. Allyltitanium complexes **12.91** and **12.92** add to aldehydes with high *Si*- and *anti*- selectivity[22] (Schemat 12.18).



Scheme 12.18

Results of representative enantioselective addition reactions of cyclopentadienyl titanium complexes to aldehydes are collected in Scheme 12.19.

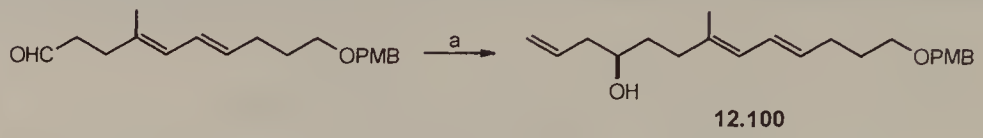


a: Ti-TADDOLate, -78°

R^1	R^2	TADDOLate	yield (%)	e.e. (%)	ref.
$Me(CH_2)_8$	All	**12.91**	95	97	88
i-Pr	All	**12.91**	93	97	88
t-Bu	All	**12.91**	83	97	88
CH_2=CH	All	**12.91**	67	95	88
Ph	All	**12.91**	93	95	22,88
i-Bu	CH_2COOt-Bu	**12.99**	80	78	81

Scheme 12.19

An application of aldehyde allylation reaction to the synthesis of curacin A side chain (**12.100**) as reported by Iwasaki is shown in Scheme 12.20.

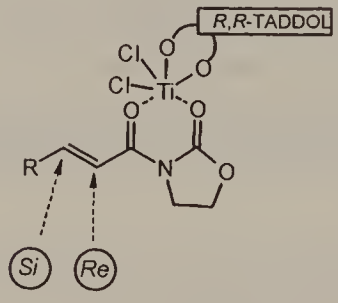


12.100

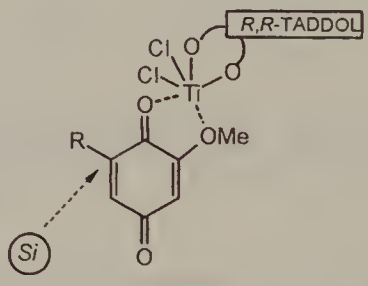
a: **12.91**, THF, 1h, -78°C (95%, e.e.>99%)[99]

Scheme 12.20

Chiral catalysts for cycloadditions. Highly enantioselective Diels–Alder reactions can be carried out under catalysis by equimolar or catalytic amounts of dichlorotitanium TADDOLate complexes. The reaction is particularly effective with chelating dienofiles, such as *N*-acyl-1,3-oxazolidin-2-ones (Narasaka, Corey) and *o*-methoxyquinones (Engler). With these complexes (**V** and **VI**) reaction topicity is greatly enhanced, thus leading to higher and more predictable product stereoselectivity. The stereochemical outcome of the reactions of dienes with *N*-acyl-1,3-oxazolidin-2-one and *o*-methoxyquinone dienofiles, activated by titanium chelation, according to Seebach[4,74] is predicted by the models **V** and **VI**.



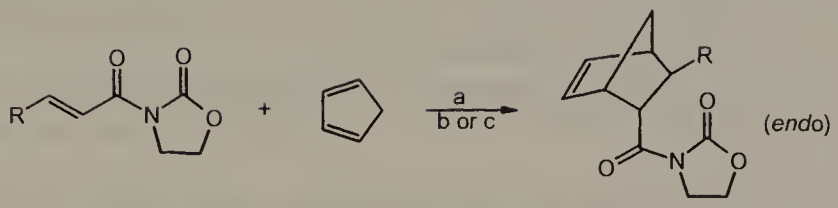
V



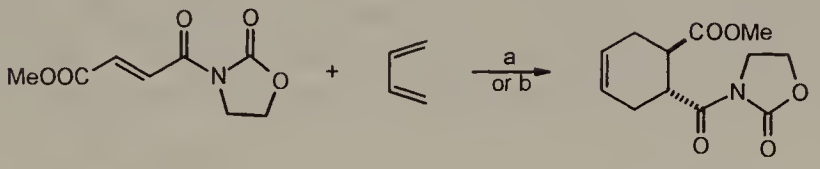
VI

The X-ray structure the complex **V** (R = Ph, TADDOL = **12.29**) has been reported. According to the X-ray structure determination, one of the phenyl groups of TADDOL blocks one face of the alkene, allowing the diene to approach from the less hindered face.[100] However, the solid state conformer may not necessarily be the most reactive one in solution. Examples of enantioselective Diels–Alder reactions catalyzed by TADDOLates and reported by Narasaka,[27] Corey,[23] and Seebach[4] are shown in Scheme 12.21.

The catalytic reaction usually requires the use of molecular sieves of size 4Å[103] and is highly sensitive to the solvent used. The best results were obtained with solvents of low donor and acceptor properties (polyalkylated benzenes and/or aliphatic hydrocarbons).[27] Such solvents provide optimum conditions for complexation of titanium by the acyl oxazolidinone moiety. For example, Narasaka demonstrated that 1,3,5-trialkylbenzenes (e.g. mesitylene) as solvents



R	yield (%)	d.e. (%)	e.e. (%)
a: Me	93	80	92
b: Me	91	74	94
c: Me	96	80	88
a: Ph	97	84	81
b: Ph	76	84	80



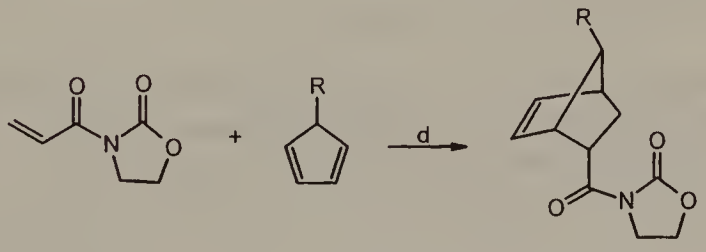
a: 86%, e.e. 85%

b: 84%, e.e. 91%

a: 2 eq. **12.81**, PhMe, -15°→ 0°C[27,101]

b: 0.1 eq. **12.81**, molecular sieves 4Å, PhMe-petroleum ether (1:1), 0°C → RT[27]

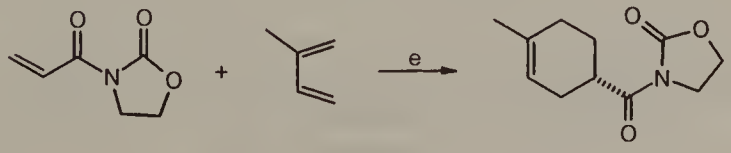
c: 0.1 eq. **12.78**, PhMe, -78°→ -13°C[4]



R = H, 80%, d.e. 90%, e.e. 94%[23]

R = CH_2OBn, 83%, d.e. >98%, e.e. 95%[23]

d: 0.2 eq. **12.79**, PhMe, -30°C



93%, e.e. >96%

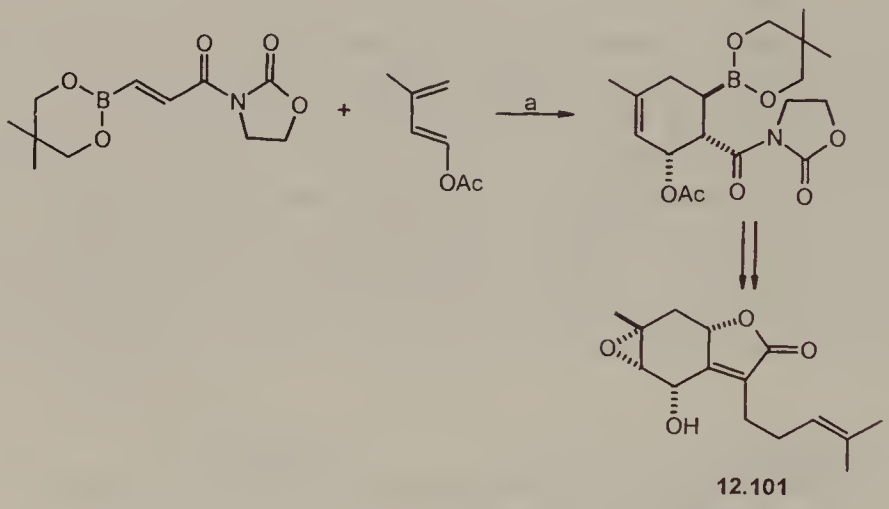
e: 0.1 eq. **12.81**, p-xylene-petroleum ether (1:1), 0°C[102]

Scheme 12.21

are superior to other solvents in catalytic Diels–Alder reactions.[104] Since polyalkylated benzene derivatives are inconvenient to use (because they are difficult to remove during work-up), using 1:1 mixtures of petroleum ether and toluene or xylenes is a more practical solution.

The increase in the enantioselectivity of hetero Diels–Alder reaction catalyzed by dichlorotitanium TADDOLate under high pressure has been noted by Tietze *et al.*[105]

A Diels–Alder reaction catalyzed by dichlorotitanium TADDOLates has been used successfully by Narasaka in the synthesis of sesquiterpene (+)-paniculide A[106] (**12.101** in Scheme 12.22).

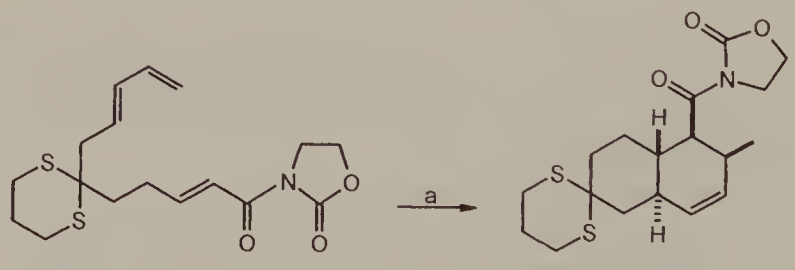


12.101

a: 0.1 eq. **12.81**, mol. sieves 4Å, PhMe-petroleum ether (1:1), RT (82%, e.e. 94%)

Scheme 12.22

The octahydronaphthalene moiety **12.102** of mevinic acids was synthesized enantioselectively by the use of asymmetric intramolecular Diels–Alder reaction catalyzed by dichlorotitanium TADDOLate[107] (Scheme 12.23).

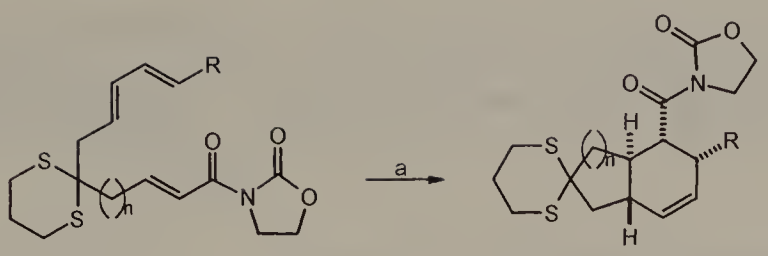


12.102

a: 0.3 eq. *ent*-**12.81**, mol. sieves 4 Å, PhMe-petroleum ether (1:1), RT (70%, e.e. >95%)

Scheme 12.23

This type of intramolecular Diels–Alder reaction is more general,[107,108] as shown by examples of Scheme 12.24.

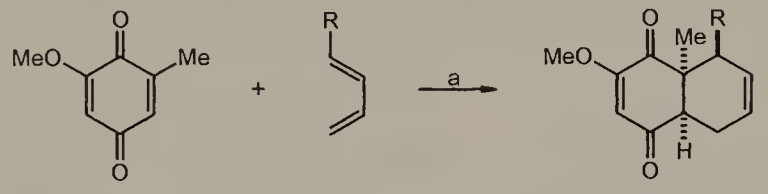


n = 1 R = H 62%, e.e. 95%
n = 2 R = H 64%, e.e. 86%
n = 2 R = Me 70%, e.e. 87%

a: 0.1 eq. **12.81**, mol. sieves 4Å, mesitylene, RT

Scheme 12.24

An enantioselective Diels–Alder reaction promoted by a $TiCl_4$-$Ti(OiPr)_4$-**12.58** complex was applied by Engler *et al.* to 2-methoxy-1,4-benzoquinones. The products were obtained in good to excellent enantiomeric excess and some could be made enantiomerically pure by recrystallization.[109,110] (Scheme 12.25).



R = Me 94%, e.e. 80%
(54% after recrystallization)[110]
R = i-Pr 90%, e.e. 92%[109]

a: **12.58**, $TiCl_4$/$Ti(Oi\text{-}Pr)_4$ (5:1), PhMe, -78°C

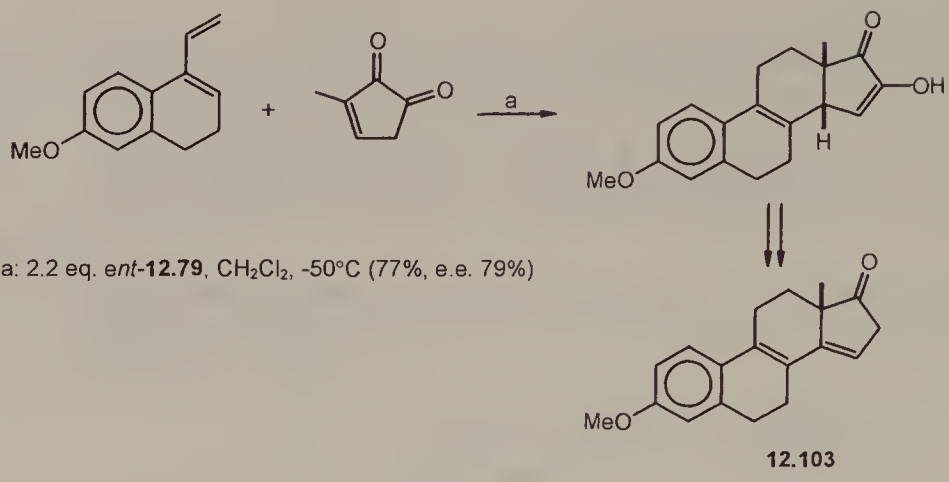
Scheme 12.25

A Diels–Alder reaction mediated by the TADDOLate *ent*-**12.79** was used by Quinkert in the enantioselective AB + D → ABCD type steroid synthesis (Scheme 12.26). The initial Diels–Alder product was readily converted to Torgov's pentaenone **12.103**.[111]

Posner has shown that dichlorotitanium TADDOLates can also be used to promote asymmetric [4 + 2] cycloaddition of electron-poor 2-pyrone-3-carboxylates to electron-rich vinyl ethers (Scheme 12.27).[112]

A shown by Narasaka and others, variety of electron deficient olefins undergo enantioselective [2 + 2] cycloaddition to electron-rich sulfenylated alkynes, ketene ditioacetals, and allenyl sulfides under titanium TADDOLate catalysis to give functionalized cyclobutenes and cyclobutanes (Scheme 12.28).

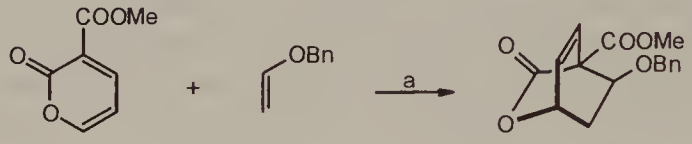
The enantiomer of product **B** (R^1 = H), optically pure after two recrystallizations, was used by Narasaka *et al.* for the synthesis of an insect pheromone, (+)-grandisol,[116] as well as in the synthesis of carboxylic oxetanocin analogues.[117]



a: 2.2 eq. *ent*-**12.79**, CH_2Cl_2, -50°C (77%, e.e. 79%)

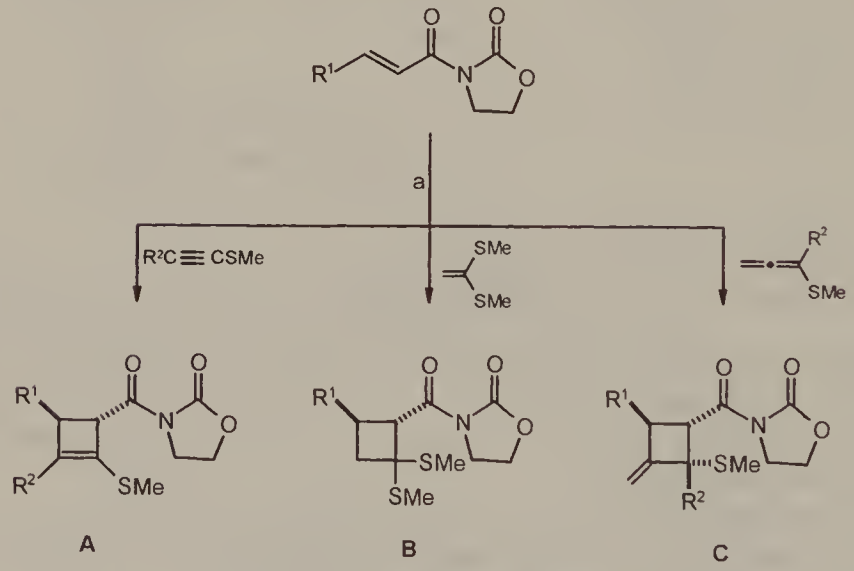
12.103

Scheme 12.26



a: **12.76**, PhMe-CH_2Cl_2 (2.5:1), -78°→ - 40°C (63%, e.e. 55%)

Scheme 12.27



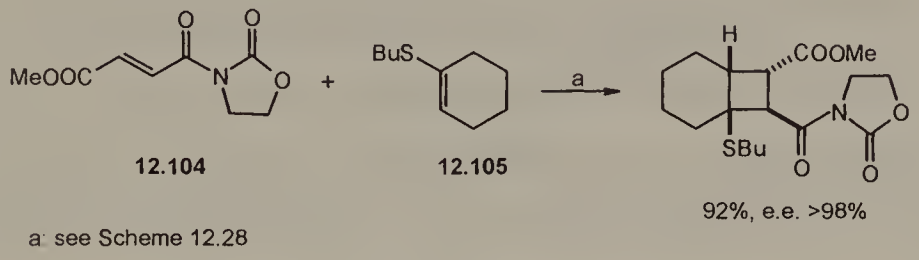
a: 0.1-0.2 eq **12.76**, mol. sieves 4Å, PhMe-petroleum ether

product	R^1	R^2	yield (%)	e.e. (%)	ref.
A	H	n-Bu	80	98	90,113
	COOMe	H	83	>98	90,113
B	H	-	74	88	113
	COOMe	-	96	98	113
C	H	$(CH_2)_3CH{=}CH_2$	86[#]	97	114
	COOMe	$SiMe_3$	100	>98	115

[#] *cis* : *trans* = 4:1

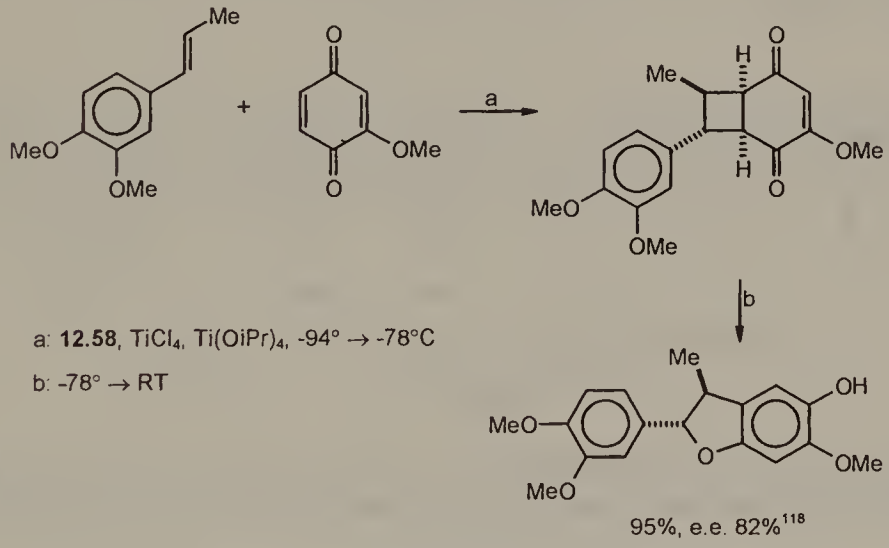
Scheme 12.28

Different diastereoselectivity was observed for [2+2] cycloaddition of the fumaric acid derivative **12.104** to cyclic vinyl sulfide **12.105** under conditions similar to those indicated in Scheme 12.28. The product was nevertheless obtained with high yield and enantiomeric excess (Scheme 12.29).[90]



Scheme 12.29

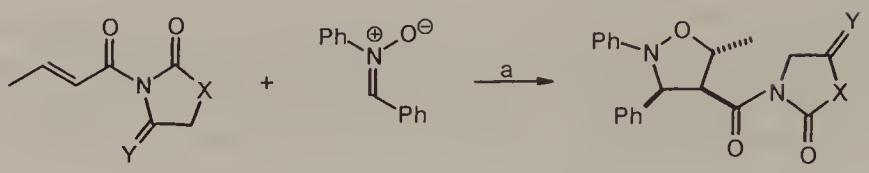
The titanium TADDOLate complex developed by Engler promotes a similar [2+2] cycloaddition reaction of 1,4-benzoquinones to styrenes at −78°C; at higher temperatures the Ti complex promotes the rearrangement of the initial cycloaddition product to a 2,3-dihydrobenzofuran with no loss of enantiomeric purity (Scheme 12.30).



Scheme 12.30

The enantioselective 1,3-dipolar cycloaddition of alkenes to nitrones catalyzed by dichlorotitanium TADDOLate has been reported by Jørgensen[119,120] (Scheme 12.31). There was observed improvement in the stereoselectivity of the cycloaddition by substitution of the oxazolidinone auxiliary of the alkene with the succinimide.[120]

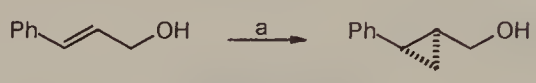
Enantioselective cyclopropanation of *trans*-3-aryl-2-propen-1-ols catalyzed by titanium TADDOLate **12.93** was reported by Charette to proceed with good enantioselectivity[121] (Scheme 12.32).



a (X = O, Y = H_2): 0.1 eq. **12.76**, PhMe-petroleum ether (1:1), 0°C (94%, d.e. 76%, e.e. 60%)

b (X = CH_2, Y = O):0.05 eq. **12.76**, PhMe, -18°C (76%, d.e. >90%, e.e. 72%)

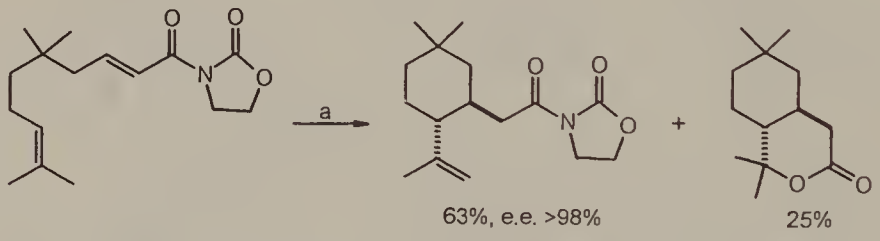
Scheme 12.31



a: 1 eq. $Zn(CH_2I)_2$, 0.25 eq. **12.93**, CH_2Cl_2, 0°C, 1.5h (80%, e.e. 90%)

Scheme 12.32

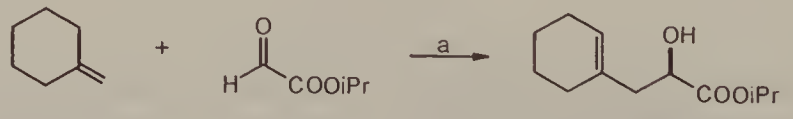
Other reactions mediated by TADDOLates. An asymmetric intramolecular ene reaction, accompanied by hetero Diels–Alder reaction, has been reported by Narasaka to proceed with high enantioselectivity in Freon 113 solvent[122] (Scheme 12.33).



a: 1.1 eq. **12.81**, mol. sieves 4Å, $CFCl_2CF_2Cl$, 0°C

Scheme 12.33

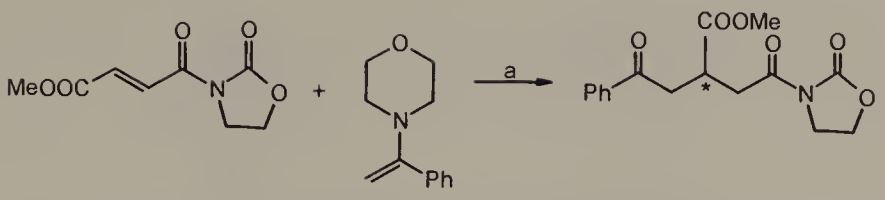
On the other hand, the glyoxylate-ene reaction, catalyzed by dichlorotitanium TADDOLate, turned out to be moderately enantioselective[123] (Scheme 12.34).



a: 0.1 eq. **12.81**, mol. sieves 4Å, CH_2Cl_2, -70° → -30°C (70%, e.e. 44%)

Scheme 12.34

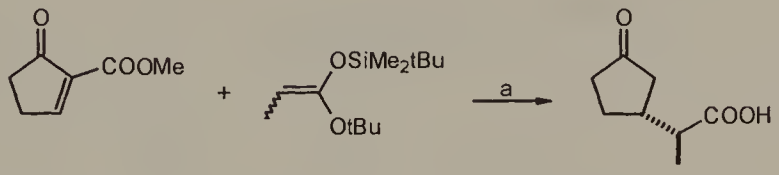
An asymmetric Michael reaction between enamines and butenoates catalyzed by dichlorotitanium TADDOLate has been reported by Narasaka *et al.*[92] (Scheme 12.35).



a: 0.1 eq. **12.81**, mol. sieves 4Å, Et_2O, 0°C, then HCl (68%, e.e. 55%)

Scheme 12.35

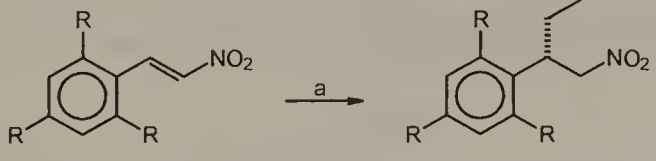
A related enantioselective Michael–Mukaiyama reaction promoted by dichlorotitanium TADDOLates has been reported by Bernardi *et al.*[124] (Scheme 12.36).



a: 1 eq. **12.78**, mol. sieves 4Å, PhMe, -78°C, then HCl, reflux (50%, d.e. 96%, e.e. 47%)

Scheme 12.36

Seebach reported enantioselective conjugate addition of primary dialkylzinc reagents to 2-arylnitroolefins mediated by dichlorotitanium TADDOLates (Scheme 12.37). Products of this reaction can be readily hydrogenated to the corresponding chiral amines with no loss of enantiomeric purity.[76]



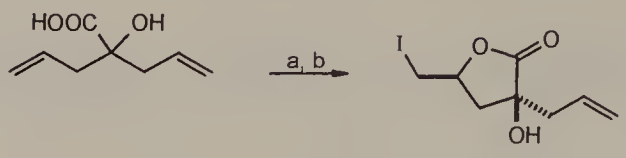
R = H 92%, e.e. 76%
(e.e. 98% after recrystallization)
R = Me 92%, e.e. 90%

a: 1.2 eq. **12.80**, 3.8 eq. Et_2Zn, PhMe, mol. sieves 4Å, -90°→ -75°C

Scheme 12.37

Enantioselective iodolactonization of 2-allyl-2-hydroxy-4-pentenoic acid mediated by titanium TADDOLate is highly *cis*-diastereoselective and it gives optically active iodolactone **12.106** with moderate enantioselectivity, as shown in Scheme 12.38.

Taguchi developed a highly diastereoselective iodocarbocyclization reaction of (substituted) 4-pentenylmalonates **12.107** with titanium spiro-TADDOLate



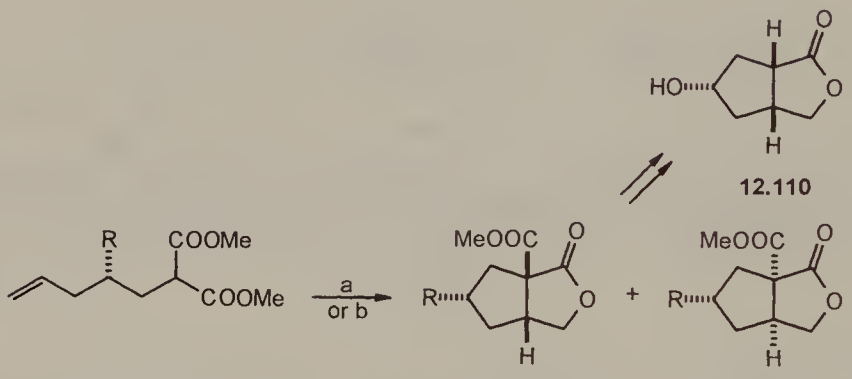
12.106

a: 1 eq. **12.58**, $Ti(OiPr)_4$, I_2, pyridine, CH_2Cl_2, -75° → 0°C

b: TsOH, benzene, Δ (67%, e.e. 65%)[125]

Scheme 12.38

12.97 as the catalyst.[126] The main product of the reaction (**12.108**, R = OTBS) can be readily converted to **12.110**, an intermediate in the synthesis of brefeldin A (Scheme 12.39).



12.107 12.108 12.109

a: R = H,	86%,	96	:	4
a: R = OTBS,	87%,	90	:	1
b: R = OTBS	91%,	2	:	1

a: 0.2 eq. **12.97**, I_2, 2,6-dimethoxypyridine, CH_2Cl_2, -78°C

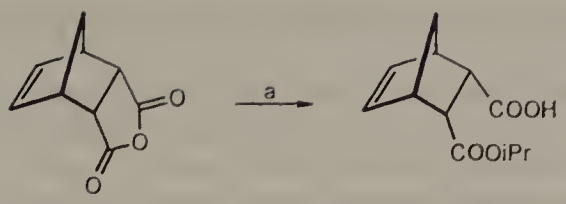
b: as a, *ent*-**12.97** used (mismatched pair)

Scheme 12.39

Seebach reported highly enantioselective opening of cyclic *meso*-anhydrides to isopropyl monoesters using a stoichiometric amount of titanium TADDOLate. The reactions proceeded with e.e. in excess 90% with simple recovery of the product and the TADDOL[127] (Scheme 12.40). Related kinetic resolutions of dioxolanones, azlactones, and biaryl lactones by transesterification mediated by titanium TADDOLates have also been reported.[128]

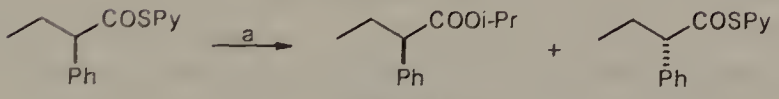
Racemic 2-pyridyl 2-phenylthiobutyrate is transesterified with titanium TADDOLate and kinetically resolved due to the high ratio of solvolysis rates of the two enantiomers, $K_R : K_S = 39$[129] (Scheme 12.41).

The chiral titanium enolate of propiophenone, obtained from lithium enolate and chlorocyclopentadienyltitanium TADDOLate, undergoes moderately enantioselective oxidation with dimethyldioxirane to 2-hydroxy-1-phenyl-1-propanone[130] (Scheme 12.42).



a: 1.2 eq **12.93**, THF, -30°C, 5d (91%, e.e. 94%)

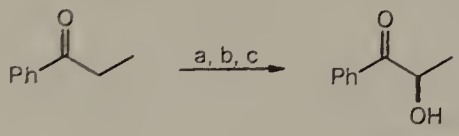
Scheme 12.40



69%, e.e. 92%

a: 0.1 eq **12.58**, $Ti(OiPr)_4$, mol. sieves 4Å, 5 eq. i-PrOH, PhMe, -75°C

Scheme 12.41

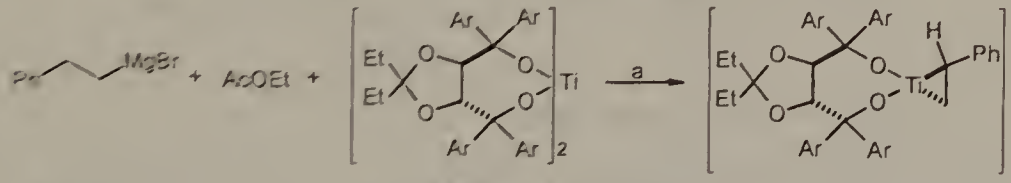


95% (67% conversion), e.e. 40%

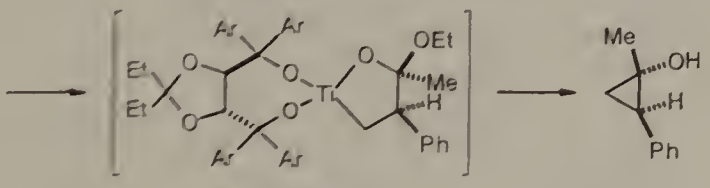
a: LDA, THF, -78°C b: **12.85** c: Me_2CO_2, then NH_4F-H_2O

Scheme 12.42

Corey reported the enantioselective synthesis of *cis*-1,2-disubstituted cyclopropanol **12.114** from ethyl acetate and Grignard reagent **12.111** under the catalysis by spirotitanate **12.98**.[99] The reaction pathway presumably leads through the more stable diastereomeric titanocyclopropane intermediate **12.112** which subsequently undergoes ring expansion by insertion of the ester carbonyl group with high bond selectivity and diastereoselectivity (**12.113**), Scheme 12.43.



12.111 **12.98** *Ar* = 3,5-$(CF_3)_2C_6H_3$ **12.112**



12.113 **12.114**

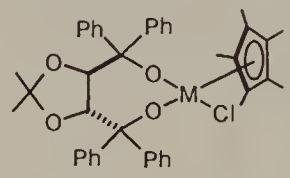
a: Et_2O, RT, 2h (65-72%, e.e. 70-73%)

Scheme 12.43

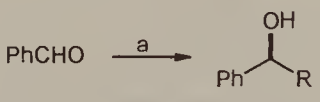
12.3 TADDOLATES OF OTHER METALS: Zr, Hf, Mg, Al, Ce

Duthaler and Hafner have found that chlorocyclopentadienyl zirconium and hafnium TADDOLates have much higher reactivity compared to their titanium analogues and that their alkyl derivatives react with aldehydes even at −78°C. The enantioselectivity of zirconium and hafnium TADDOLates is also higher than that of titanium TADDOLates; however the best results are obtained with the transfer of the methyl group.[89]

The synthesis of zirconium and hafnium TADDOLates is a subject of a patent.[78] Some examples of enantioselective addition of organolithium and Grignard reagents to aldehydes, mediated by pentamethylcyclopentadienyl zirconium and hafnium TADDOLates, are shown in Scheme 12.44.[89]



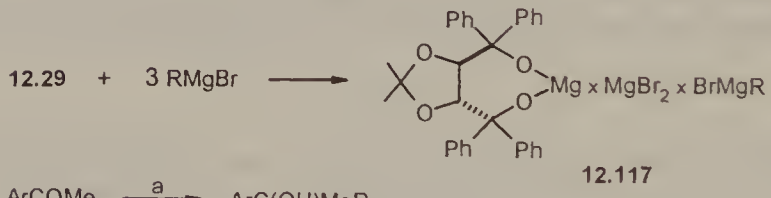
12.115 M = Zr
12.116 M = Hf



a: RLi or RMgBr, **12.115** or **12.116**, -78°C

	12.115, e.e. (%)	**12.116**, e.e (%)
MeMgBr	98	97
MeLi	97	-
EtMgBr	52	47
n-BuLi	68	65

Scheme 12.44



12.117

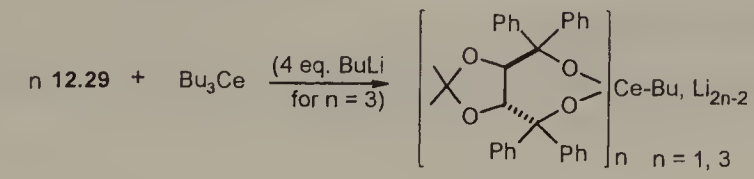
a: **12.117**, THF, -100°C

Ar	R	ArC(OH)MeR yield (%)	e.e. (%)
Ph	Et	62	98
Ph	n-Pr	84	>98
Ph	$(CH_2)_2CH{=}CH_2$	60	>98
4-BrC_6H_4	Et	60	98
2-naphthyl	Et	41	98
4-pyridyl	Et	96	>99

Scheme 12.45

Magnesium TADDOLate complexes, such as **12.117**, enantioselectively react with aryl ketones to give tertiary alcohols in high enantiomeric purity. These complexes are considered, according to Weber and Seebach, to be chiral Grignard reagents[131,132] (Scheme 12.45).

Greeves *et al.* have found that organocerium TADDOLates of the type **12.118** add to aldehydes to give secondary alcohols with moderate to good enantioselectivity.[21] Tris-TADDOL organocerium reagents show improved enantioselectivity[133] (Scheme 12.46).



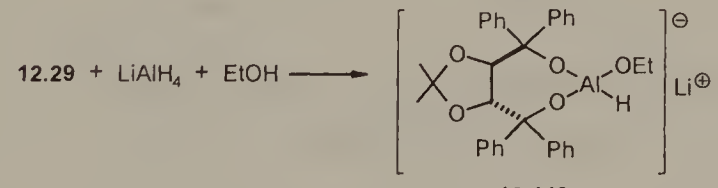
R = Ph (n = 1) 66%, e.e. 66%[21] (n = 3) 66%, e.e. 83%[133]

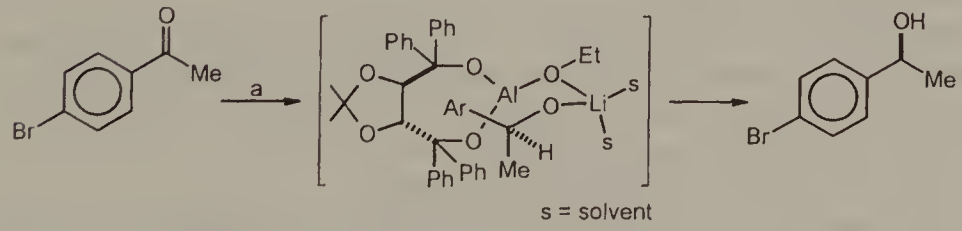
R = Cy (n = 1) 65%, e.e. 70%[21] (n = 3) 42%, e.e. 92%[133]

a: 2 eq. **12.118**, Et_2O, -100°C

Scheme 12.46

Aluminum TADDOLate **12.119**, obtained *in situ* from $LiAlH_4$, **12.29** and one equivalent of ethanol, reduces enantioselectively aryl alkyl ketones. An example of such a reaction, with the proposed complex formed after hydride transfer to the carbonyl group, is shown in Scheme 12.47.[134]





a: 2 eq **12.119**, THF, -80°C → RT (62%, e.e. 92%)

Scheme 12.47

The crude alcohol products of the reaction can be isolated with enhanced enantiopurity by clathrate formation with TADDOL **12.29**.[134]

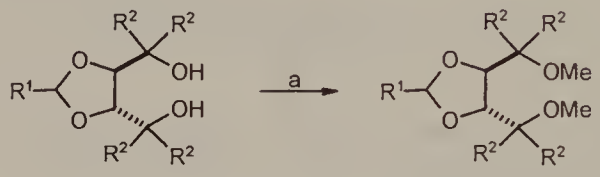
Finally, it should be noted that Mo(CHCMe$_2$Ph)(NAr) (TADDOLate) complexes were successfully used by Schrock for highly tactic polymerization of 2,3-bis(trifluoromethyl)- and 2,3-bis(carbomethoxy)norbornadiene.[135]

12.4 OTHER COMPOUNDS RELATED TO TADDOLS

12.4.1 Compounds with Modified Hydroxy Groups

Synthesis and Applications

O-Alkylation of the tertiary hydroxy groups of TADDOLs is easily done by the modified Williamson method (Scheme 12.48).



12.120 R^1 = Ph, R^2 = Me[6,33,136]

12.121 R^1 = 4-MeOC$_6$H$_4$, R^2 = Ph (85%)[9]

a: NaH, MeI, DMSO or DMF or PhMe

12.122

12.123 R = Bn

12.124 R = MEM

b: 1.2 eq. NaH, 1.1 eq. BnBr or MEMCl, THF, HMPA, RT (85-89%)[11]

Scheme 12.48

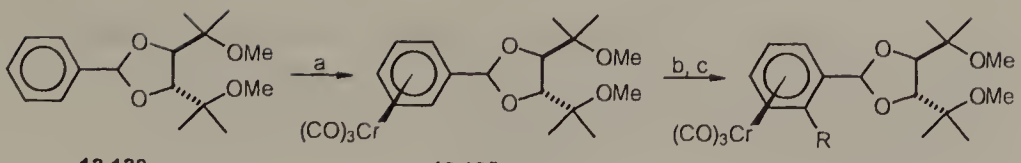
A

The chromium tricarbonyl complex of *O*-dialkylated TADDOL **12.120** can be diastereoselectively *ortho*-lithiated, with preferential *pro-R* deprotonation. Green *et al.* have shown that the lithium derivative of the chromium tricarbonyl complex **12.125** reacts with electrophiles to give products **12.126** with high diastereoselectivity (Scheme 12.49).[6,137]

Other applications of *O*-methylated TADDOLs as chiral auxiliaries involve cyclopropanation of 2-cyclohexen-1-one acetals and alkylation of aldehydes with α-(1,3-dithian-2-yl)acetals (Scheme 12.50). These reactions proceed with low to moderate diastereoselectivity.

B

An acetate elimination-hydrogenation sequence, when applied to TADDOL **12.122**, allows for the preparation of enantiomerically pure (3*S*,4*S*)-2,5-dimethyl-3,4-hexanediol [(*S*)-DIPED, **12.127**],[10] Scheme 12.51.



12.120 12.125 12.126

R = $SiMe_3$ 77%, d.e. 86%

R = Me 62%, d.e. 92%

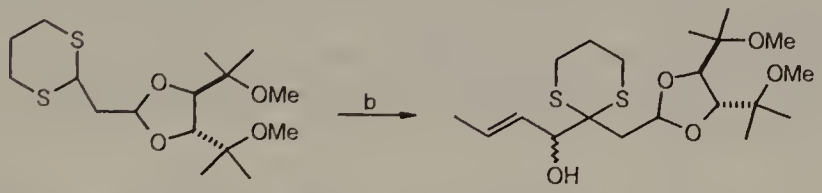
R = PPh_2 69%, d.e.>94%

a 2 eq. $Cr(CO)_6$, n-Bu_2O, Δ (88%)

b: 2.4 eq. n-BuLi, Et_2O, -30°C c: Me_3SiCl or MeI or Ph_2PCl

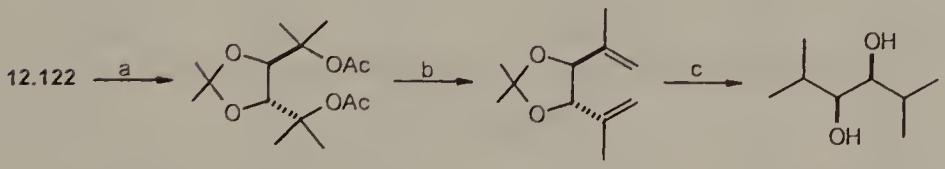
Scheme 12.49

a: CH_2I_2, Zn(Cu), 91%, d.e. 60%[12]



b: BuLi, THF, -78°C, then MeCH=CHCHO, 92%, d.e. 64%[138]

Scheme 12.50



12.127

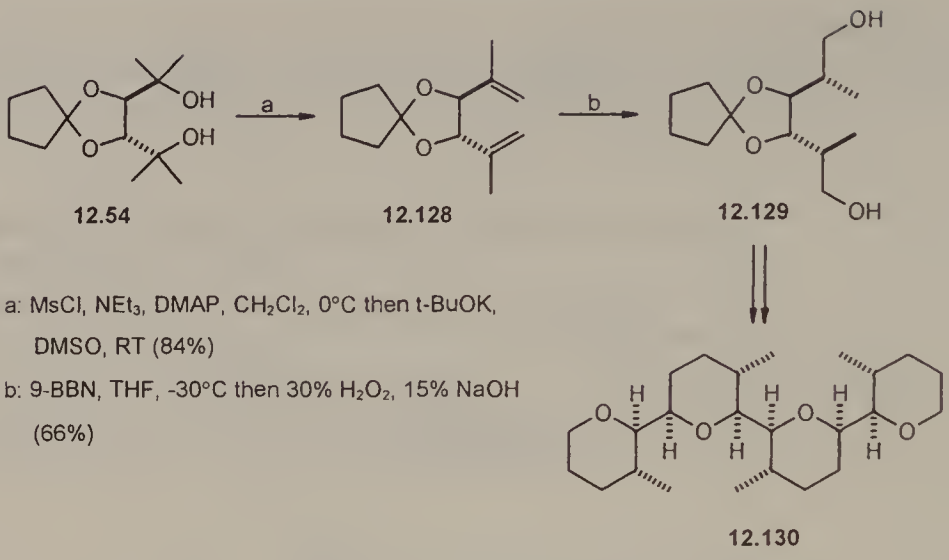
a: Ac_2O, TMSCl, 85-95°C, 16-24h (98%)

b: Δ (450-470°C) (crude 77-90%)

c: H_2, 5% Rh/Al_2O_3 then HCl, H_2O-EtOH, Δ (89%)

Scheme 12.51

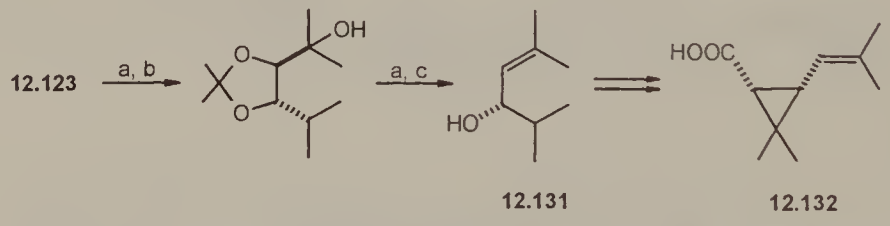
Still used TADDOL **12.54** in the synthesis of a C_2-symmetrical tetraether podand ionophore **12.130**[24,139] (Scheme 12.52).



Scheme 12.52

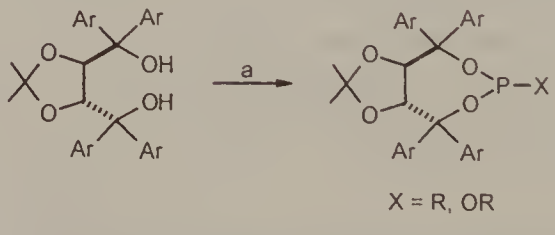
The sequence involved dehydratation of **12.54** to the diene **12.128**; this was best done by the elimination of the dimesylate (the monoolefin byproduct was subjected to the same dehydration procedure). Hydroboration-oxidation of **12.128** gave the diol **12.129** with good diastereoselectivity (80%).

O-Monobenzylated derivative **12.123** was converted in several steps to the allylic alcohol **12.131**, from which (*1R*)-*cis*-chrysanthemic acid (**12.132**) was obtained[11] (Scheme 12.53).



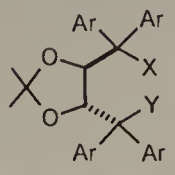
Scheme 12.53

Seebach synthesized several cyclic phospite and phosphonite derivatives of TADDOLs[140,141] (Scheme 12.54).



Scheme 12.54

For specific derivatives see Table 12.7, entries **12.133–12.143**.



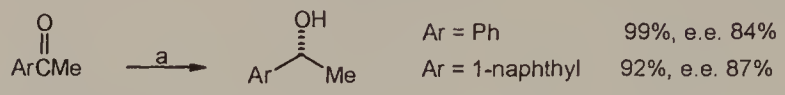
VII

Table 12.7 P, N, S and Cl substituted TADDOLs (VII)

No.	X	Y	Ar	m.p. (°C)	$[\alpha]_D$ ($CHCl_3$)	References
12.133	–OP(OMe)O–		Ph	190–192	−236.7	141
12.134	–OP(OPh)O–		Ph	177–177.5	−172.8	141
12.135	–OP(Me)O–		Ph	193–196	−87.4	141
12.136	–OP(Ph)O–		Ph	206–209	−85.9	141
12.137	–OP(Ph)O–		2-naphthyl	174.5–176	−140.9	141
12.138	–OP(4-MeC_6H_4)O–		Ph	207–211	−80.7	140
12.139	–OP(4-MeC_6H_4)O–		2-naphthyl	167–168	−129.9	140
12.140	–OP(2,4,6-$Me_3C_6H_2$)O–		Ph	205–208	−133.0	140
12.141	–OP(2,4,6-$Me_3C_6H_2$)O–		2-naphthyl	174–178	−185.4	140
12.142	–OP(2-naphthyl)O–		Ph	201–202	−71.4	140
12.143	–OP(2-naphthyl)O–		2-naphthyl	171–173.5	−133.3	140
12.144	–OS(O)O-		Ph	165–168	−87.6	141
12.145	OH	N_3	Ph	—	−52.5	141
12.146	OH	NH_2	Ph	211–212	−59.9	141
12.147	OH	NHMe	Ph	189–191	−63.7	141
12.148	OH	NHBn	Ph	204–206	−32.3	141
12.149	OH	NMe_2	Ph	181–183	−23.0	141
12.150	N_3	N_3	Ph	127–129	−13.1	141
12.151	NH_2	NH_2	Ph	200–201	−43.0	141
12.152	NHMe	NHMe	Ph	201–203	−49.2	141,142
12.153	NHMe	NMe_2	Ph	161–163	−39.5	141,142
12.154	NMe_2	NMe_2	Ph	239	−95.4	141
12.155	NHCHO	NHCHO	Ph	>225	−10.3	142
12.156	$NHCOCF_3$	$NHCOCF_3$	Ph	104–107	−26.1	141
12.157	–NH–		Ph	140–141	−222.6	141[a]
12.158	OH	SH	Ph	120–121	−31.8	143
12.159	OH	SMe	Ph	128–129	−108.1	143
12.160	$–OCH_2S–$		Ph	222–224	−291.5	143
12.161	$–OCMe_2S–$		Ph	267–268	−65.0	143[a]
12.162	–OCH_2-(*S*)-S(O)–		Ph	223.5–224.5	−344.8	143
12.163	$–OCH_2SO_2$-		Ph	279–280	−250.5	143
12.164	SCN	SCN	Ph	196–197	+12.6	141
12.165	–S–		Ph	179	−428.3	141
12.166	Cl	Cl	Ph	165–170	−11.2	141

[a] X-ray structure determination reported

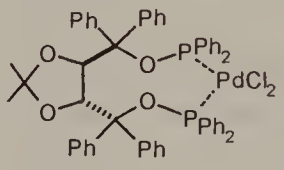
The phosphite and phosphonite derivatives were tested as ligands for Rh(I)- and Pd(0)-catalyzed reactions; one ligand, **12.143** (Table 12.7), when used with Rh(I), catalyzed hydrosilylation of aryl alkyl ketones with high enantioselectivity[140] (Scheme 12.55).



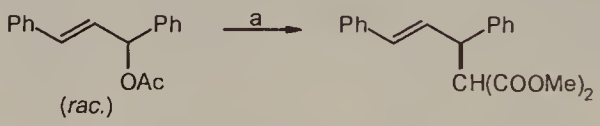
a: 1.2 eq. Ph_2SiH_2, 0.1 eq. **12.143**, 0.01 eq $[Rh(COD)Cl]_2$, benzene, 0°→ 20°C, then

Scheme 12.55

The bis(diphenylphosphinite) derivative of TADDOL, abbreviated TADDOP, as a complex with $PdCl_2$, was used by Seebach *et al.* in enantioselective 1,3-diphenylallylations of C-nucleophiles;[34] see the example in Scheme 12.56.

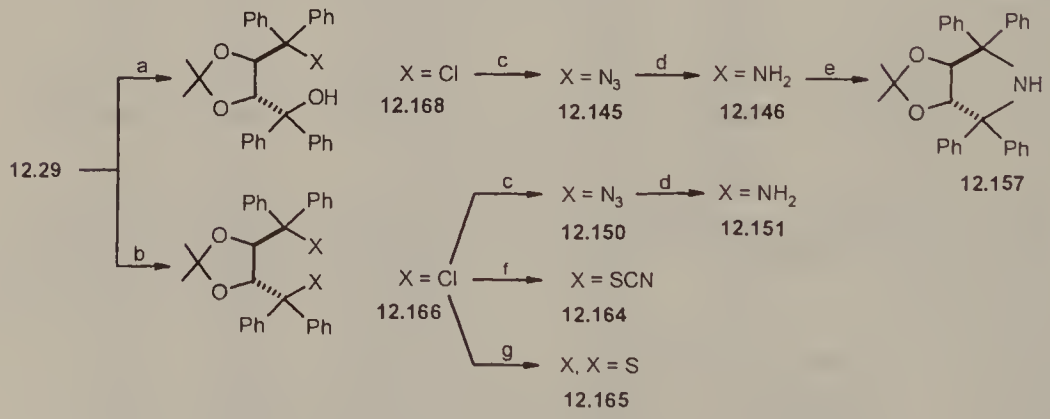


12.167



a: $CH_2(COOMe)_2$, NaH, 0.02 eq. **12.167**, 0.02 eq. BH_3·THF, THF, RT (72%, e.e. 76%)

Scheme 12.56



a: 2 eq. n-BuLi, THF, -70°C, then 2 eq. $MeSO_2Cl$ (unstable)

b: $SOCl_2$, NEt_3, CH_2Cl_2, Δ (73%)

c: NaN_3, DMF, 80°C (70%)

d: $LiAlH_4$, THF, RT (85%)

e: TsCl, pyridine, DMAP, 80°C (50%)

f: KSCN, DMF, 80°C (55%)

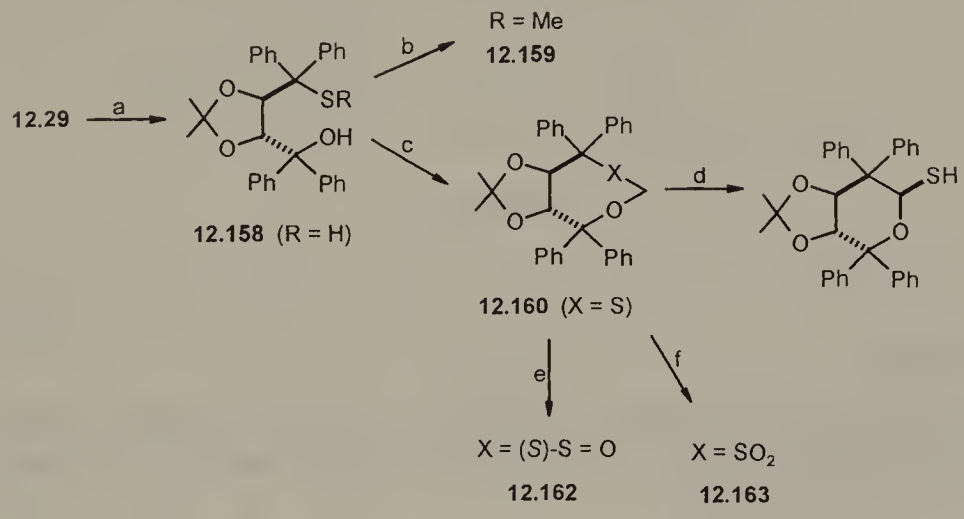
g: NaSH-H_2O, DMF, 80°C (39%)

Scheme 12.57

A number of amine and diamine analogs of TADDOLs (i.e. TADDAMINEs, Table 12.7, entries **12.146–12.149**, **12.151–12.154**) as well as sulfur derivatives were obtained by Seebach *et al.* from the readily available mono- and dichloro-derivatives **12.168** and **12.166**[141] (Scheme 12.57).

N-Alkylated derivatives of TADDAMINEs were synthesized from the parent compounds (**12.146** and **12.151**) by conventional alkylation.[141] The TADDAMINEs and their *N*-lithium derivatives were used as chiral mediators in Michael addition of cyclohexanone lithium enolate to (*E*)-nitropropene, with moderate stereoselectivity.[142]

The monothiol analogue of TADDOL (**12.158**) was synthesized by De Lucchi *et al.*, together with several compounds derived from the oxathiepane **12.160**[143] (Scheme 12.58).



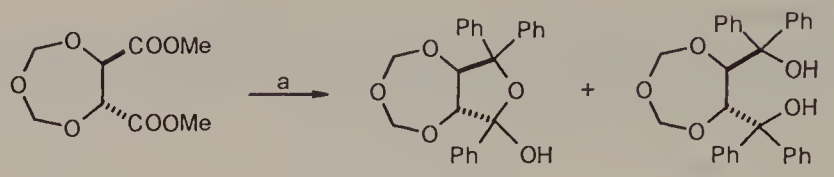
Scheme 12.58

12.4.2 Other Acetals Related to TADDOLs

Synthesis

The 1,3,5-trioxepane analogue of TADDOL (**12.170**) can be obtained from the corresponding ester acetal (**10.69**) in low yield and only when a large excess of Grignard reagent is used; otherwise cyclic hemiacetal **12.169** is the major product[5] (Scheme 12.59).

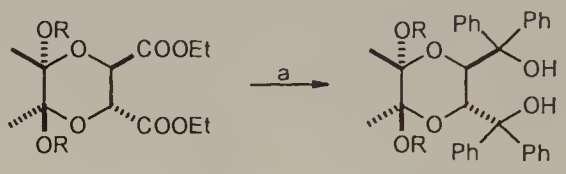
Diols **12.171** and **12.172**, called TARTROLS, have been obtained by Berens from the corresponding ester acetals **10.70** and **10.71** (Scheme 12.60). TARTROLs, like TADDOLs, show a tendency to form inclusion compounds with solvents.[144]



10.69 12.169 12.170

a: PhMgBr (excess), THF

Scheme 12.59



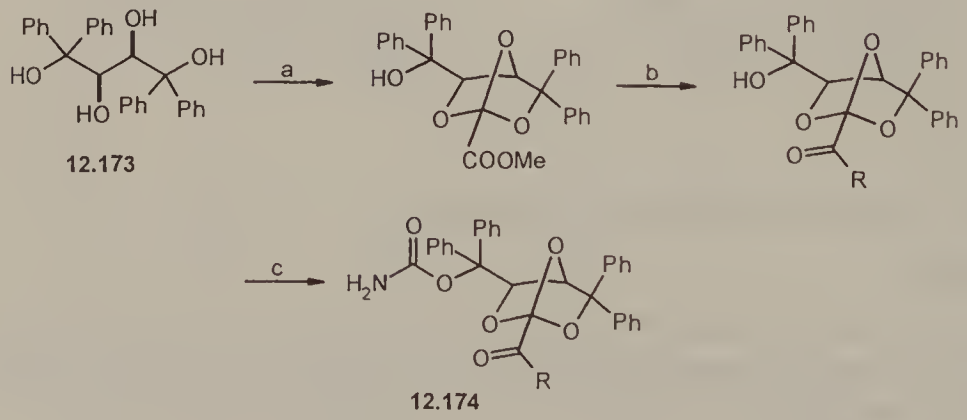
10.70 12.171 R = Me (32%)
10.71 12.172 R = Et (28%)

a: 5-8 eq. PhMgBr, THF, RT

Scheme 12.60

Application

Bicyclic orthoester **12.174** derived from 1,1,4,4-tetraphenyl-L-threitol (**12.173**) has been devised by Dubé as a chiral auxiliary for the synthesis of α-hydroxy acids[145] (Scheme 12.61).



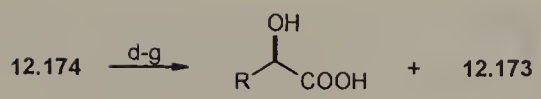
12.173 12.174

a: $MeOCl_2CCOOMe$, pyridine (90%)

b: MeO(Me)NMgBr, THF, -78°→ 0°C, then RMgX or RLi, THF (83-92%)

c: CCl_3CONCO, then NH_3, MeOH (75-85%)

Scheme 12.61 (*continued*)



e.e. ≥ 98% 81-95% recovery

d: 1.1 eq. L-Selectride®, THF, -78°C, then EtONa, EtOH, RT

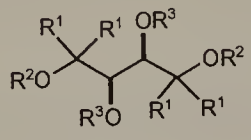
e: Ac_2O, pyridine, DMAP (cat.), 81-92%

f: TFA, THF/MeOH/H_2O (4:4:1), RT

g: 1N NaOH, THF, RT (71-95%)

Scheme 12.61

12.4.3 1,1,4,4-Tetraaryl (Alkyl) Threitols and Derivatives



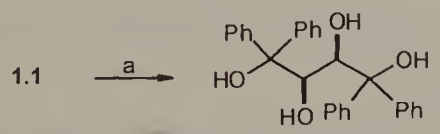
VIII

Table 12.8 1,1,4,4-Tetraaryl (alkyl) L-threitols and their *O*-methyl derivatives (VIII)

No.	R^1	R^2	R^3	m.p. (°C) or b.p.(°C/torr)	$[\alpha]_D$ (solvent)	References
12.175	Me	Me	H	90/0.01	−8.5 ($CHCl_3$)	12,32,136
12.176	Me	H	Me	71	−30.9 (MeOH)	146
12.177	$(CH_2)_4$	Me	H	62.5	−28.0 ($CHCl_3$)	33,147
12.178	Ph	H	H	148–151	+182.8 (EtOH)	16,145,148
12.179	Ph	Me	H	76–78	+17.6 (MeOH)	9
12.180	Ph	H	Me	125–126	−158.6 ($CHCl_3$)	16,143,149

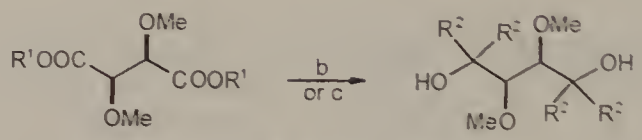
Synthesis

These compounds can be obtained either directly from tartrates or from their *O*-alkyl derivatives by the action of excess Grignard reagents. 1,1,4,4-Tetraphenyl-L-threitol was synthesized by Frankland as early as in 1904[148] (Scheme 12.62).



a: excess PhMgBr (84%)[145,148]

Scheme 12.62 (*continued*)

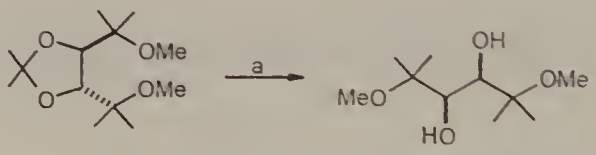


b ($R^1 = R^2 = Me$): 4.5 eq. MeMgI, Et_2O, Δ (45%)[145]

c ($R^1 = Et$, $R^2 = Ph$): 5 eq. PhMgBr, THF, RT (20%)[149]

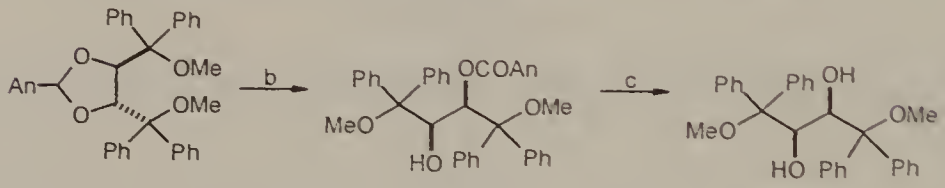
Scheme 12.62

Hydrolytic, oxidative, or hydrogenolytic cleavage of TADDOLs is another route to 1,1,4,4-tetrasubstituted threitols (Scheme 12.63).



12.175

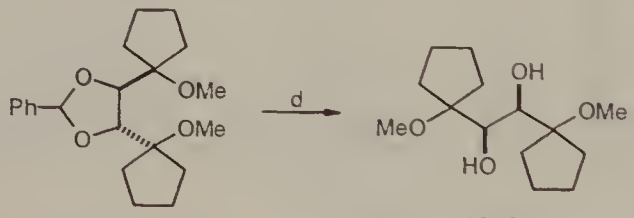
a: TsOH, H_2O-MeOH, Δ (79%)[12] or 8N H_2SO_4-MeOH (1:2), RT, 48h (92%)[32]



12.179

b: DDQ, CH_2Cl_2, H_2O, RT (99%)[9]

c: $LiAlH_4$, Et_2O, RT (80%)[9]



12.177

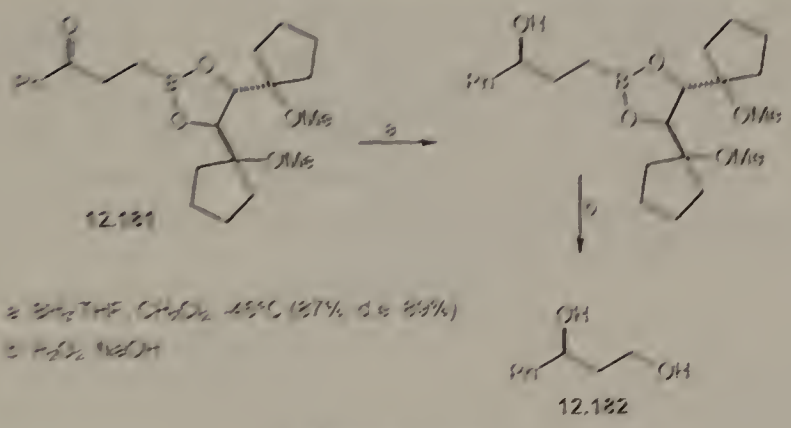
d: H_2, 10% Pd/C, RT, 48h (98%)[33]

Scheme 12.63

Applications

Chiral γ-carbonyl boronate **12.181** derived from diol **12.177** can be reduced with a borane-THF complex with good diastereoselectivity and then converted to diol **12.182**[33,147] (Scheme 12.64).

Optically active phosphonic acid analogues of D- and L-penicillamine were obtained by asymmetric addition of chiral cyclic phosphite **12.183** derived from diol **12.175** to cyclic prochiral imine **12.184**[32] (Scheme 12.65).

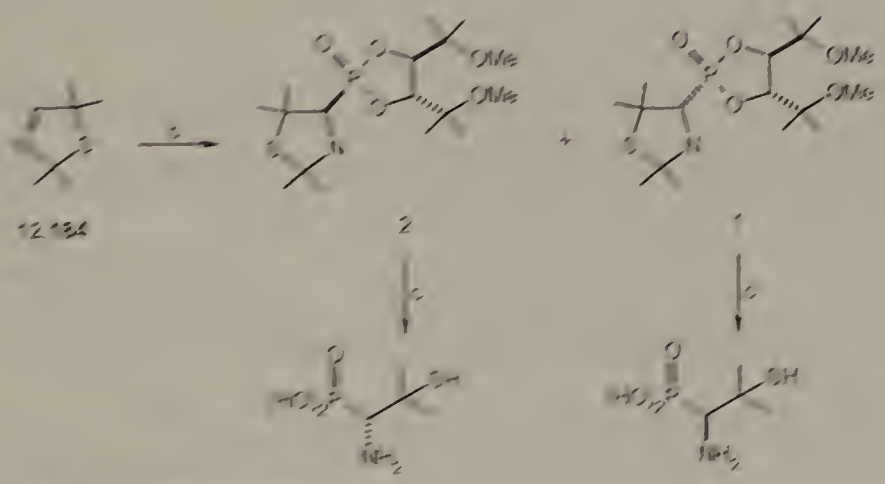


12.181

12.182

Scheme 12.64

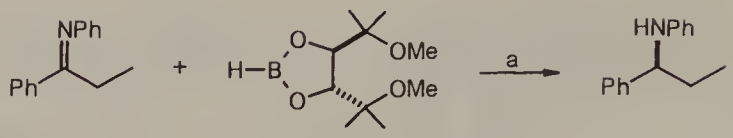
12.183



12.184

Scheme 12.65

Optically active *N*-arylamines were obtained by Nakagawa *et al.*,[205] by asymmetric reduction of aryl imines with dialkoxyboranes **12.185** derived from diol **12.175** (Scheme 12.66).



12.185

a: $MgBr_2 \cdot Et_2O$, THF, RT (91%, e.e. 73%)[150,151]

Scheme 12.66

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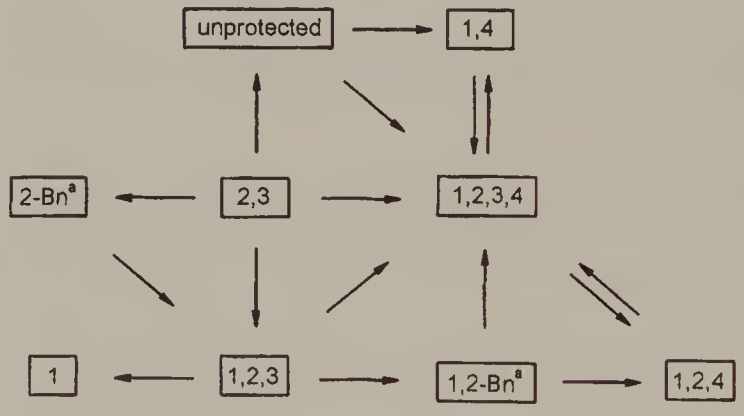
13 Threitol and Its Derivatives

The derivatives of L-threitol listed in this chapter are divided according to the position and number of the hydroxy protecting groups. The protecting groups include acetal, alkyl or silyl ether, and ester functions. The remaining unprotected hydroxy groups can either be left free or activated for substitution (e.g. in the form of an epoxide or sulfonate). A number of 1- and 1,4-heteroatom (halogen, S, N, P) substituted L-threitol derivatives are also included in this chapter.

There are many pathways for interconversion of differently protected threitol derivatives. Most of them are established, reliable, high yield procedures. The general scheme shown in Figure 13.1 is supported by numerous examples cited throughout this chapter and it also clearly indicates the pivotal role of 2,3-diprotected threitols (which are directly available from 2,3-acetal protected tartrates) in the synthesis.

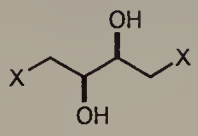


[a] from 2,3-benzylidene acetal

Figure 13.1 Most common pathways to the differently protected threitols.

The derivatives of threitol with variously protected/activated hydroxy groups, both acyclic and cyclic, are used primarily as chiral building blocks in synthesis. Their further well established application is as chiral ligands, for example as analogues of DIOP, chiral bis(diphenylphosphine) ligand used in asymmetric hydrogenation.

13.1 UNPROTECTED L-THREITOL AND ITS SUBSTITUTION PRODUCTS



I

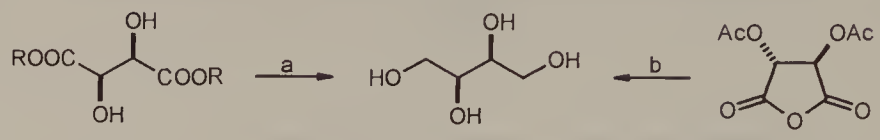
Table 13.1 L-Threitol and its C_2-symmetrical derivatives (I)

X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
OH	89–91	+14.0 (EtOH)[a]	1–3
OMs	102–103	−5.5 (Me_2CO)	4
OTs	76–77	−5.7 (DMF)	5–7
NH_2·HCl	210–212	—	8
$NH(CH_2)_2Cl$·HCl	234–235	−31.1 (H_2O)	9
$NH(CH_2)_nAr$·HCl (n = 1–5, Ar = Ph, 1-naphthyl, 4-ClC_6H_4, An)	—	—	10
NMe_2	43.0–43.6	−34.8 (benzene)	11–13
NEt_2	85–86/0.2	−51.0 (EtOH)[b]	14,15
NBu_2	156–158/0.2	−26.3 (EtOH)	15
$NMeC_8H_{17}$	—	−16.5 (MeOH)	13
NMePh	76.5	+53.0 ($CHCl_3$)	13
$N(CH_2)_2$	98–99	—	9
$N(CH_2)_4$	68–69	−30.4 (EtOH)	13,15
$N(CH_2)_5$	44–45	−18.5 (EtOH)	13,15
$N(CH_2)_6$	49–50	−34.3 (EtOH)	15
N-(4-methylpiperidinyl)	69–70	−19.7 (CCl_4)	16
N-(3,5-dimethylpiperidinyl)	82–85	−18.8 (MeOH)	16
N-morpholinyl	89–90	−14.2 (EtOH)	15
N_3	—	+13.1 (Me_2CO)	17
NHCOOEt	112–113.5	+21.2 (EtOH)	18
NHMs	128.5–129.5	−12.2 (H_2O)	19
NPht	263–264.5	−71.1 (DMF)	20
PPh_2	99–100	−35.8 ($CHCl_3$)	7,21,22
$P(O)Ph_2$	226–228	—	23
SH	50–52	−14.0 ($CHCl_3$)	24
SBn	105–106	—	25
SPh	117–118	+30.5 ($CHCl_3$)	23,26,27
SAn	—	+29.5 ($CHCl_3$)	27
SO_2Ph	142.5–143	—	23
Cl	68–69	+16.3 (MeOH)[c]	28–30
Br	82–82.5	+13.5 (MeOH)	28

[a] $[\alpha]_D$ −4.2 in water has been reported[3,31-35].
[b] $[\alpha]_D$ +5.3 in CCl_4 has been reported[14].
[c] $[\alpha]_D$ −11.7 in CH_2Cl_2 has been reported[30].

Synthesis

L-Threitol (**13.1**) is readily obtained by reduction of either L-tartrates or *O,O'*-diacetyl L-tartaric anhydride (Scheme 13.1).



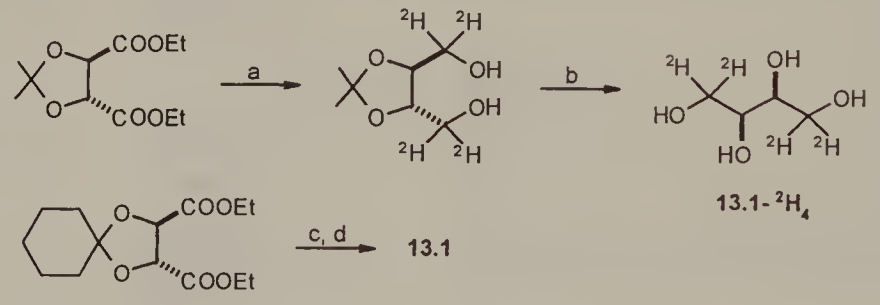
13.1

a (R = Me or Et): 2.6 eq. $NaBH_4$, EtOH, 5°C → reflux[36]
or (R = Me): 3 eq. KBH_4, EtOH, 70°C (71%)[37]
b: $LiAlH_4$, THF-Et_2O, RT, then Amberlite IR-120 and Duolite A-4 (18%)[2]

Scheme 13.1

L-Threitol was also obtained by catalytic high pressure hydrogenation of diethyl tartrate over copper-chromium oxide or W-6 Raney nickel catalysts;[1] however under rather harsh conditions (high temperature) partial racemization was observed.[38]

L-Threitol is readily available by reduction of ethyl *O,O'*-isopropylidene (or cyclohexylidene) L-tartrate followed by acetal hydrolysis (Scheme 13.2).



a: $LiAl^2H_4$, Et_2O
b: Amberlite IR 120, H_2O[39]
c: $LiAlH_4$, THF, RT
d: HCl, H_2O, Δ (removal of cyclohexanone), 90%[34,40]

Scheme 13.2

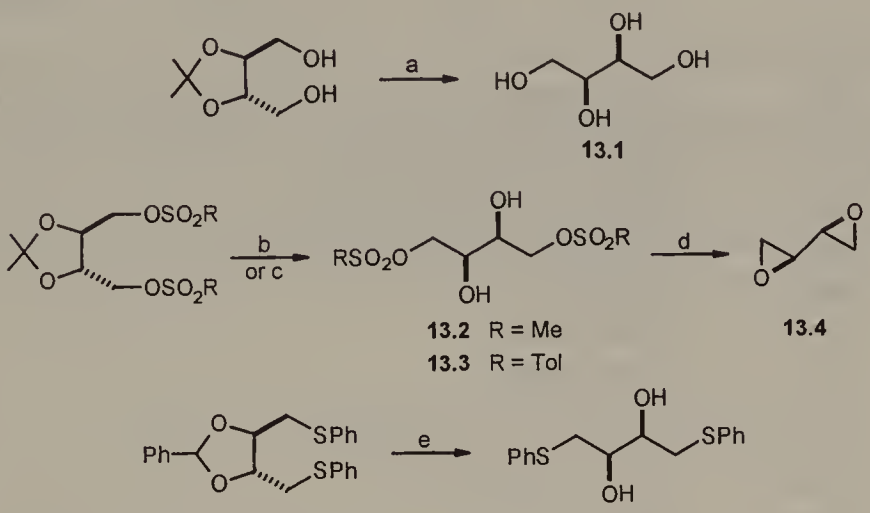
threo-1,4-Diamino-2,3-butanediols are available through $LiAlH_4$ reduction of the corresponding tartaric diamides (Scheme 13.3).

R = Me 77%[11]
R, R = $(CH_2)_4$ 80%[13]

a: $LiAlH_4$, Et_2O

Scheme 13.3

A general method of obtaining threitol and its *O*-activated derivatives is based on deprotection of the corresponding acetals. For example, 1,4-*O*-disulfonylated 2,3-*O*-isopropylidene threitols can be selectively deprotected to give the corresponding 1,4-dimesylate **13.2** or 1,4-ditosylate **13.3** which can in turn be converted to the reactive diepoxide **13.4** according to Feit[4] (Scheme 13.4). The three derivatives are good substrates for 1,4-disubstituted threitols. (**Warning**: diepoxybutane is mutagenic[41]).



a: 0.5 N HCl, MeOH, Δ (removal of volatiles), 72-95%[35,42]

b: MsOH or TsOH (cat.), EtOH-H_2O (100%)[6,43]

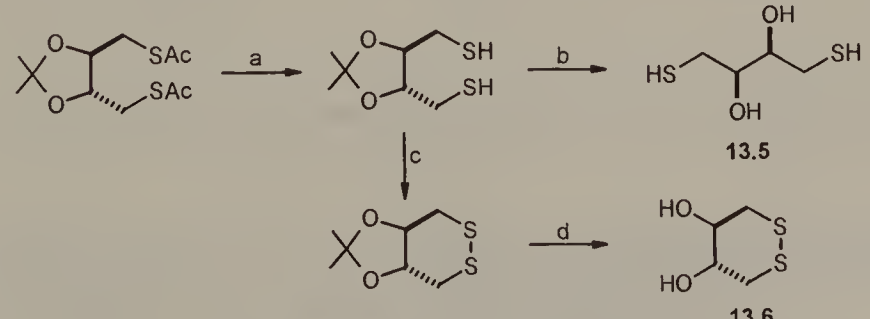
c: 2N HCl, MeOH or EtOH, Δ (70-85%)[4,5,7]

d: KOH/H_2O, Et_2O (76-81%)[4,5,7,43,44] e: 10% HCl, THF, RT(85%)[26]

Scheme 13.4

An alternative route to diepoxide **13.4** is based on the asymmetric dihydroxylation of *trans*-1,4-dichloro-2-butene.[30]

The synthesis of the optically active Cleland's reagent **13.5** and the related dithiane **13.6** by Carmack and Kelley[24] employs the acetal deprotection step (Scheme 13.5).



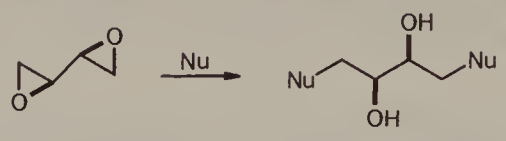
a: MeOH, MeONa (cat.), Δ (100%) c: O_2, KOH, MeOH-H_2O (72%)

b: 0.1 N HCl, H_2O-MeOH, Δ (80%) d: 0.1 N HCl, H_2O-MeOH, RT (93%)

Scheme 13.5

The structure of dithiane **13.6** has been determined by X-ray diffraction.[45]

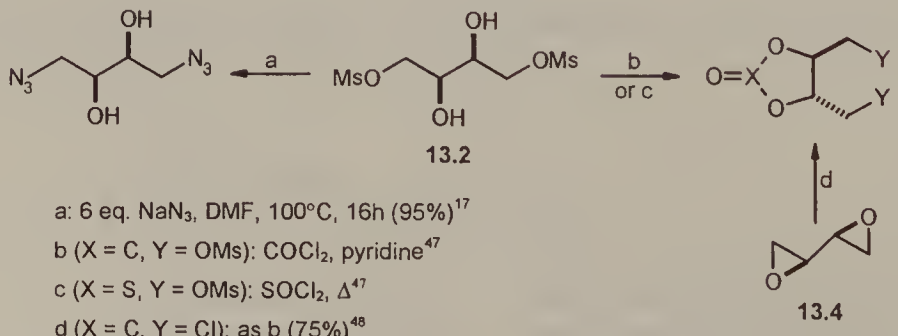
Diepoxide **13.4** cleanly undergoes ring opening in the 1 and 4 positions with a variety of nucleophiles to give 1,4-disubstituted L-threitol derivatives (Scheme 13.6).



Nu	reaction conditions	yield (%)	ref.
Me	MeMgBr, CuI, THF, Et_2O, -30°→ 0°C	89	43
i-Pr	i-PrMgCl, CuI, THF, Et_2O, -30°→ 0°C	66	43
Ph	PhMgBr, CuI, THF, Et_2O, -30°→ 0°C	85	43
HC≡C	HC≡CLi ·EDA, THF, DMSO, 0°C	57	44
Me_2N	Me_2NH, Et_2O, RT	80	13
PhMeN	PhMeNH, benzene, Δ	89	13
	aziridine, 50°C	73	9
	 (n = 4,5), Et_2O, RT	62-88	46
MsHN	$MsNH_2$, PhMe, Δ	-	19
Ph_2P	Ph_2PLi, 0°C	-	7
Br or Cl	conc. HBr or HCl, Et_2O, 8-10°C	-	28

Scheme 13.6

Products of 1,4-disubstitution of threitol as well as cyclic 2,3-*O*-carbonate and sulfite derivatives are available directly from bis-mesylate **13.2** or diepoxide **13.4** (Scheme 13.7).



a: 6 eq. NaN_3, DMF, 100°C, 16h (95%)[17]
b (X = C, Y = OMs): $COCl_2$, pyridine[47]
c (X = S, Y = OMs): $SOCl_2$, Δ[47]
d (X = C, Y = Cl): as b (75%)[48]

Scheme 13.7

The following are commercially available:

L-threitol [*2319-57-5*] and D-threitol [*2418-52-2*]

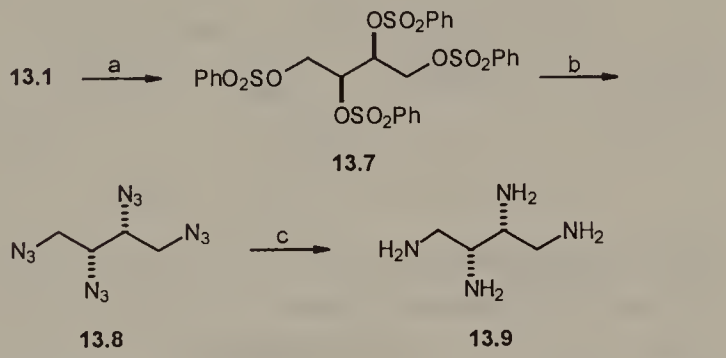
L-threitol 1,4-ditosylate [*57495-46-2*]

1,4-dithio-L-threitol (chiral Cleland's reagent) [*16096-97-2*].

Applications

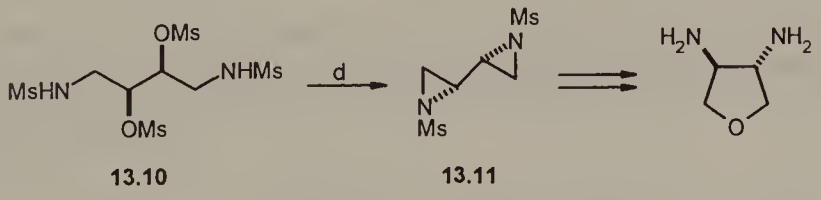
Substitution reactions at C(2) and C(3) with nitrogen or sulfur nucleophiles lead to products having inverted *threo* configuration.

O-Tetrabenzenesulfonate of threitol (**13.7**) yields on reaction with sodium azide in DMF *threo*-1,2,3,4-tetraazidobutane (**13.8**) which can be catalytically hydrogenated to *threo*-1,2,3,4-tetraaminobutane (**13.9**).[40] A related intramolecular substitution of tetramethanesulfonate **13.10** provides access to bis-aziridine **13.11** and further to *trans*-3,4-diaminotetrahydrofuran[19] (Scheme 13.8).



a: $PhSO_2Cl$, pyridine, 0°C → RT (88%)

b: NaN_3, DMF, 100°C c: H_2, 10% Pd/C (cat.), EtOH

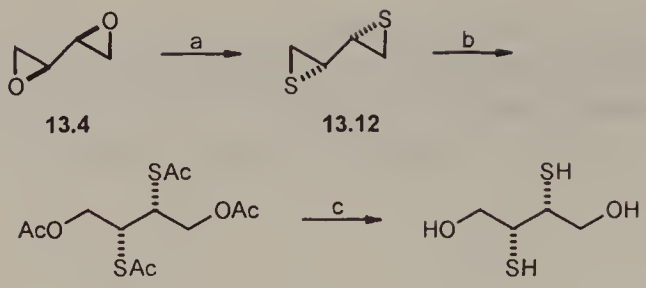


d: 10% NaOH, RT

Scheme 13.8

(*S,S*)-Diepoxybutane (**13.4**) was converted to the unstable (*R,R*)-diepithiobutane (**13.12**) with inversion of configuration at both chiral centers, and further to (2*R*,3*R*)-2,3-dideoxy-2,3-dithiothreitol (**13.13**), Scheme 13.9.

A derivative **13.14** of 2,3-dithiothreitol (**13.13**) has been used by Samuelsson for the synthesis of [4,5-bis(hydroxymethyl)-1,3-dithiolan-2-yl]nucleosides, potential inhibitors of HIV[41] (Scheme 13.10).

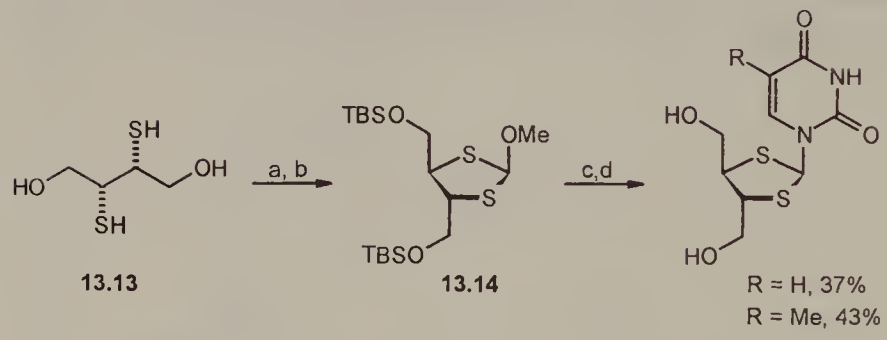


a: KSCN, then $(H_2N)_2C{=}S$[41,49]

b: Ac_2O, AcONa, AcOH, 120°C, 20h (51%)[41]

c: HCl, MeOH, RT (91%)[41]

Scheme 13.9



a: TBSCl, imidazole, DMF, RT

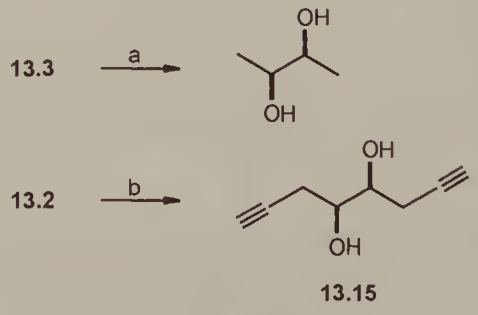
b: $HC(OMe)_3$, CH_2Cl_2, CSA (cat.), RT (80%)

c: TMSOTf, CH_2Cl_2, -80°C then silylated thymine or uracil

d: Bu_4NF, THF, RT

Scheme 13.10

1,4-Di-*O*-sulfonylated threitols can be directly reduced or substituted with carbon nucleophiles. Enantiomerically pure (2*S*,3*S*)-2,3-butanediol has been



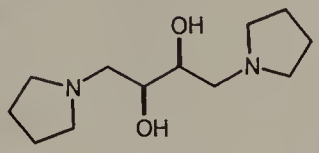
a: $LiAlH_4$, Et_2O (69%)[6]

b: 4 eq. HC≡CLi·EDA, DMSO, 0°C (87%)[44]

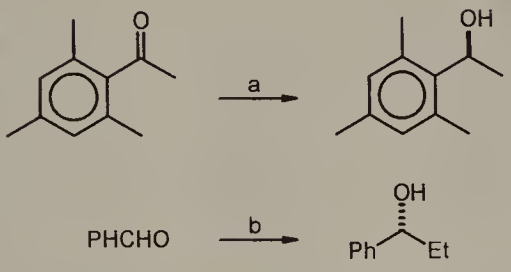
Scheme 13.11

obtained by Schurig[6] in a simple reduction step of 1,4-ditosylate **13.3** while bis-acetylene **13.15**, an intermediate in the synthesis of (+)-(4*S*,5*S*)-muricatacin, was obtained by Quayle[44] by substitution of 1,4-dimesylate **13.2** (Scheme 13.11).

1,4-Diamino derivatives of L-threitol are useful as chiral Al and Zn ligands in the reduction of prochiral ketones with $LiAlH_4$,[11,13] as well as in the catalytic enantioselective addition of diethylzinc to aldehydes.[15] Examples are shown in Scheme 13.12.



13.6



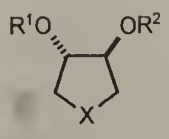
a: 0.5 mol. eq. $LiAlH_4$, 6.5 mol. eq. **13.16**, pentane, -78°C, e.e. 87%[13]

b: 2 eq. Et_2Zn, 0.05 eq. **13.16**, PhMe, RT, 93%, e.e. 72%[15]

Scheme 13.12

13.2 L-THREITOL DERIVED TETRAHYDROFURANS, THIOLANES AND PYRROLIDINES

For convenience these heterocyclic derivatives of threitol (II) are collected in this section regardless of the nature of the substituents at the C(2) and C(3) oxygen atoms.



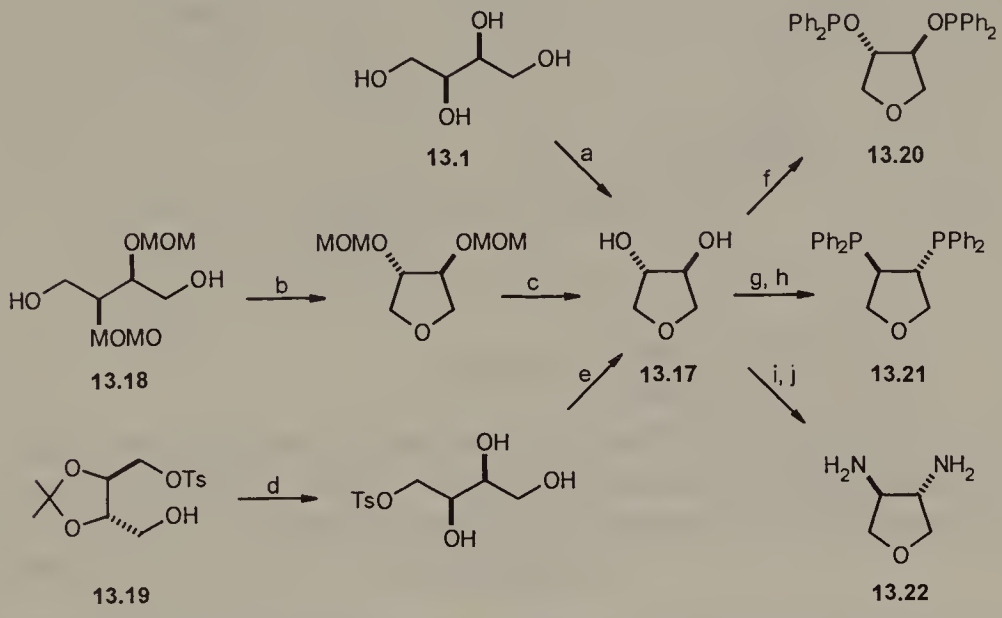
II

Table 13.2 Heterocyclic derivatives of L-threitol (II)

R^1	R^2	X	m.p. (°C) or b.p.(°C/torr)	$[\alpha]_D$ (solvent)	References
H	H	O	63–64	−5.0 (H_2O)	32,33,50,51
Ms	H	O	107–108	+16.5 (Me_2CO)	52,53
Ms	Bn	O	—	+1.2 ($CHCl_3$)	53
Me	Me	O	98/50	−31.8 (neat)	5
MOM	MOM	O	—	−25.0 (MeOH)	51,54
Bz	Bn	O	175–185/0.4	+34.1 ($CHCl_3$)	26
Bz	Bz	O	89–90	+174.2 ($CHCl_3$)	26
PPh_2	PPh_2	O	64–65	+69.0 (−)	50
H	H	S-S	116–117.8	+260.0 ($CHCl_3$)	24
Me	Me	S	55–57/1–2	+94.1 (neat)	5
TBS	TBS	S	—	+29.0 (Me_2CO)	55
MOM	MOM	NH	—	−1.5 ($CHCl_3$)	56
TBS	TBS	NH	—	+35.9 ($CHCl_3$)	57
TBDPS	TBDPS	NH	—	+6.9 ($CHCl_3$)	58
Bz	Bz	NH	178.5–179	+56.1 ($CHCl_3$)	57
Me	Me	NMe	118/100	+29.9 (neat)	5
All	All	NMe	—	+17.7 ($CHCl_3$)	59
Me	Me	Nn-Bu	40/0.03	+43.6 (neat)	5
Me	Me	Nt-Bu	99–102/10	+45.7 (neat)	5
H	H	$NC_{12}H_{25}$	70.5–71.5	+15.0 (MeOH)	54
H	H	NBn	109–110	+8.5 ($CHCl_3$)	57,60,61
Ms	Ms	NBn	56	+36.4 (MeOH)	61
Me	Me	NBn	80/0.03	+36.7 (neat)	5
All	All	NBn	—	+39.5 ($CHCl_3$)	59
MOM	MOM	NBn	—	+11.9 ($CHCl_3$)	56
Bz	Bz	NBn	110–112	+86.6 ($CHCl_3$)	57
TBS	TBS	NBn	—	+58.3 ($CHCl_3$)	57
TBDPS	TBDPS	NBn	—	+47.0 ($CHCl_3$)	58
Ph_2P	Ph_2P	NBn	—	+50.4 (benzene)	60
H	H	$N(CH_2)_2NMe_2$	—	+2.9 ($CHCl_3$)	62
Me	Me	$N(CH_2)_2NMe_2$	59–61/0.005	+34.2 (neat)	5
H	H	$N(CH_2)_3NMe_2$	—	—	62
Ph_2P	Ph_2P	$N(CH_2)_2$i-Pr	54.5–57.2	+59.8 (benzene)	62
Ph_2P	Ph_2P	$N(CH_2)_2NMe_2$	—	+55.4 (benzene)	62
Ph_2P	Ph_2P	$N(CH_2)_3NMe_2$	—	+56.0 (benzene)	62
Tol_2P	Tol_2P	$N(CH_2)_2NMe_2$	74.5–76.5	+60.4 (benzene)	62
An_2P	An_2P	$N(CH_2)_2NMe_2$	62.8–65.7	+58.9 (benzene)	62
An_2P	An_2P	$N(CH_2)_2$i-Pr	—	+53.3 (benzene)	60
H	H	NPh	154	+45.0 ($CHCl_3$)	29
Me	Me	NOH	—	+16.9 ($CHCl_3$)	63
tBu	tBu	NOH	65–66	+78.2 ($CHCl_3$)	63
Bn	Bn	NOH	64–65	+26.3 (CCl_4)	63

Synthesis and Applications

(*S*,*S*)-*trans*-3,4-Dihydroxytetrahydrofuran (L-threitan, **13.17**) is available from L-threitol (**13.1**) or its derivatives **13.18** and **13.19** as shown in Scheme 13.13. Although direct synthesis of L-threitan from L-threitol by acid induced cyclization appears attractive, a route from *O*,*O*′-bis-MOM protected L-threitol (**13.18**) is far more practical and high-yielding.



a. TsOH (cat.), 220°C/0.0005 torr (distill), 35-50%[36]
or 50% H_2SO_4, 120°C, 24h (68%)[32,33]

b: 3 eq. TsCl, pyridine, CH_2Cl_2, Δ, 4h (96%)[51] or 1.2 eq. Ph_3P, 1.2 eq. DEAD, benzene, RT (93%)[54]

c: Amberlyst 15 resin, CH_2Cl_2, Δ, 24h (99%)[51]

d: CF_3COOH-H_2O, RT, 10 min.[50]

e: Amberlite IR 45 basic resin, H_2O[50]

f: Ph_2PCl, pyridine, THF, RT (70%)[50]

g: MsCl, pyridine, CH_2Cl_2, -30°C → RT (77-82%)[36]

h: Ph_2PLi, dioxane, 0° - 5°C (30%)[36]

i: Ph_3P, DEAD, HN_3, benzene, 0°C → RT (54%)[54]

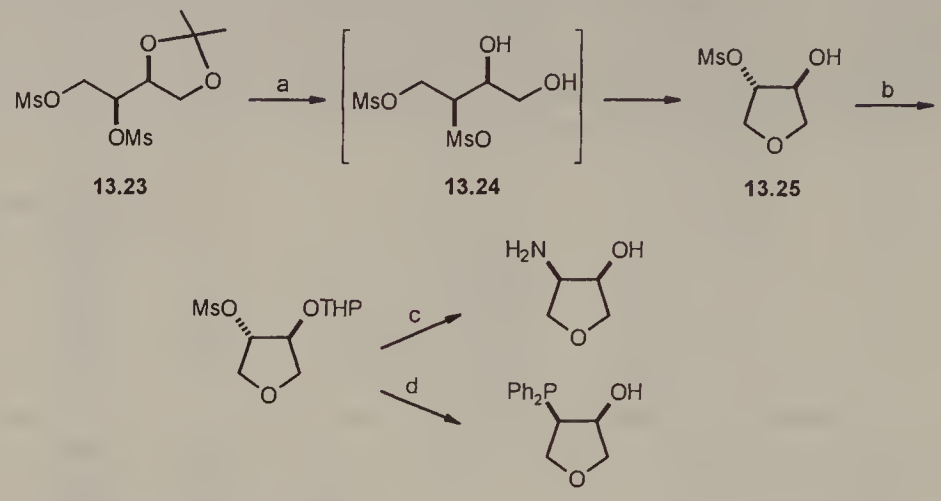
j: H_2, 10% Pd/C, EtOH, RT (57%)[54]

Scheme 13.13

From L-threitan, two ligands, that is, 3,4-bis(diphenylphosphino) derivative **13.20** and diphosphinite DIPHIN (**13.21**), as well as diamine **13.22**, have been obtained (Scheme 13.13).

The *O*-monomesyl derivative of L-threitan (**13.25**) was synthesized by Börner and Kagan by acid-catalyzed cyclization of bis-*O*-mesylate **13.24**, a product of

hydrolysis of acetal **13.23**. *O*-Monomesylate **13.25** can be used for the preparation of unsymmetrically substituted threitans (see Scheme 13.14).



a: HCl, MeOH-H_2O, Δ (90%)[52,53]

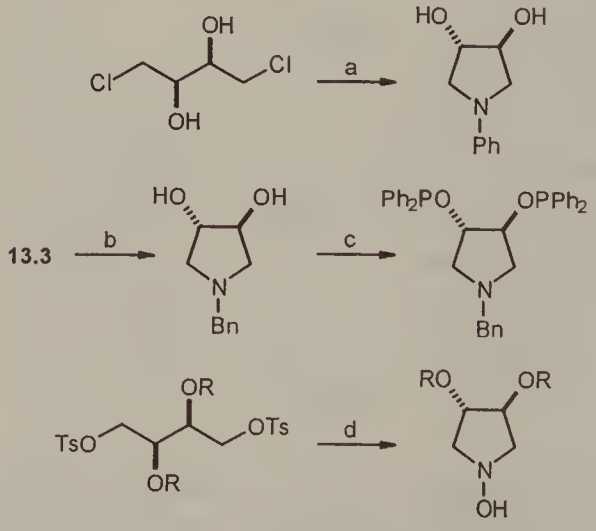
b: dihydropyran, PPTS (80%)[52,53]

c: LiN_3,n-Bu_4NI, DMF, RT then CF_3COOH, MeOH-H_2O, RT, then H_2, Pd/C, MeOH, RT (76%)[52]

d: Ph_2PLi, THF, RT, then $MeSO_3H$ (cat.), MeOH, H_2O, Δ (27%)[53]

Scheme 13.14

Chiral pyrrolidine derivatives are available from 1,4-activated threitols by condensation with primary amines. A series of chiral diphosphinite containing pyrrolidines, useful as Rh(I) ligands for highly diastereoselective hydrogenation



a: $PhNH_2$, 100-140°C[29]

b: $BnNH_2$, dioxane (64%)

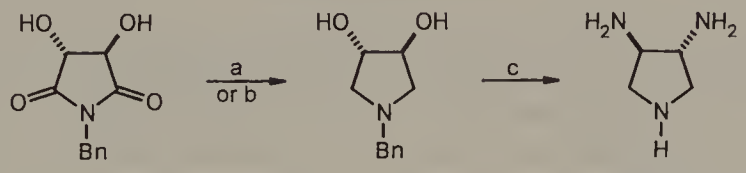
c: Ph_2PCl, NEt_3 (90%)[60]

d: NH_2OH HCl, NEt_3, EtOH, Δ (85-98%)[63]

Scheme 13.15

of dehydropeptides, was synthesized from 1,4-ditosylate **13.3**.[60,62] Examples are shown in Scheme 13.15.

Chiral 3,4-diaminopyrrolidine **13.26** is available directly by reduction of *N*-benzyltartrimide by the procedure of Nagel,[61,64] followed by Mitsunobu reaction and deprotection (Scheme 13.16).



13.26

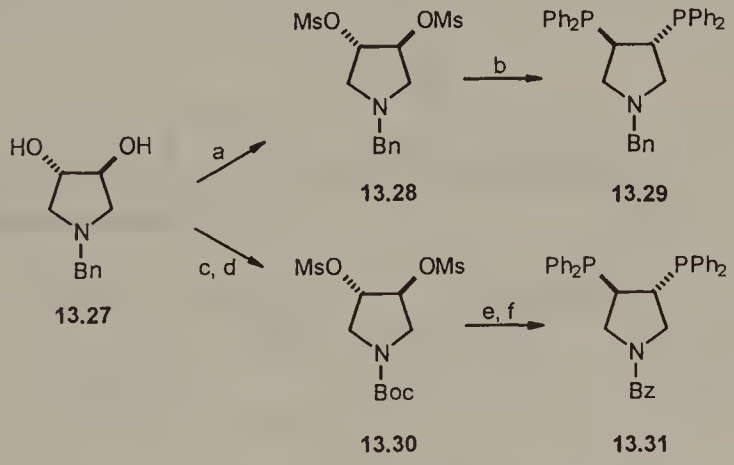
a: BF_3 or I_2, $NaBH_4$, $(MeOCH_2CH_2)_2O$ or THF, Δ (70-86%)[54,61]

b: $LiAlH_4$, THF, Δ, 12h (70%)[57,64]

c: Ph_3P, DEAD, HN_3, benzene, 0°C → RT (72%), then H_2, 10% Pd/C, EtOH, RT (93%)[54]

Scheme 13.16

Chiral bis-diphenylphosphines **13.29** ("Deguphos") and **13.31**, useful for the synthesis of cationic 1,5-cyclooctadiene-bisphosphane-rhodium complexes, were synthesized from **13.27** by nucleophilic substitution of *N*-protected bis-mesylates **13.28** and **13.30** (Scheme 13.17).



a: MsCl, NEt_3, CH_2Cl_2, 0°C → RT, (87%)

b: Ph_2PNa, DMF, -40°C (76%)[61]

c: Pd/C, H_2 (95%)

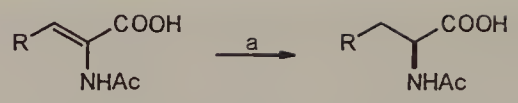
d: $(Boc)_2O$ then Ms_2O (86%)[64]

e: HBr then Ph_2PNa (75%)[65]

f: BzCl (89%)[64]

Scheme 13.17

Chiral bis(diphenylphosphino) ligands **13.29** and **13.31** are used as ligands for highly enantioselective rhodium catalyzed hydrogenation of α-(acetylamino)acrylic acids to (*S*)-*N*-acetylamino acids (Scheme 13.18).

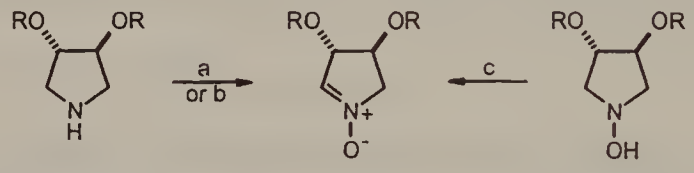


a: H_2, $[Rh(COD)Cl]_2$ or $[Rh(COD)^+]BF_4^-$ (cat.), **13.29** or **13.31**, (>90%, e.e. 85-99%)[36,64]

Scheme 13.18

B

O-Protected 3,4-dihydroxy and 1,3,4-trihydroxypyrrolidines can be oxidized to nitrones **13.32**. These compounds are important intermediates in the synthesis of various heterocyclic compounds via nucleophile addition or stereo- and regioselective 1,3-dipolar cycloaddition. Examples include synthesis of lentiginosine (Petrini;[66] Brandi, Goti[58,67,68]), pyrrolizidines (Wightman[69]), and indolizidines (Brandi, Goti[70]), Scheme 13.19.

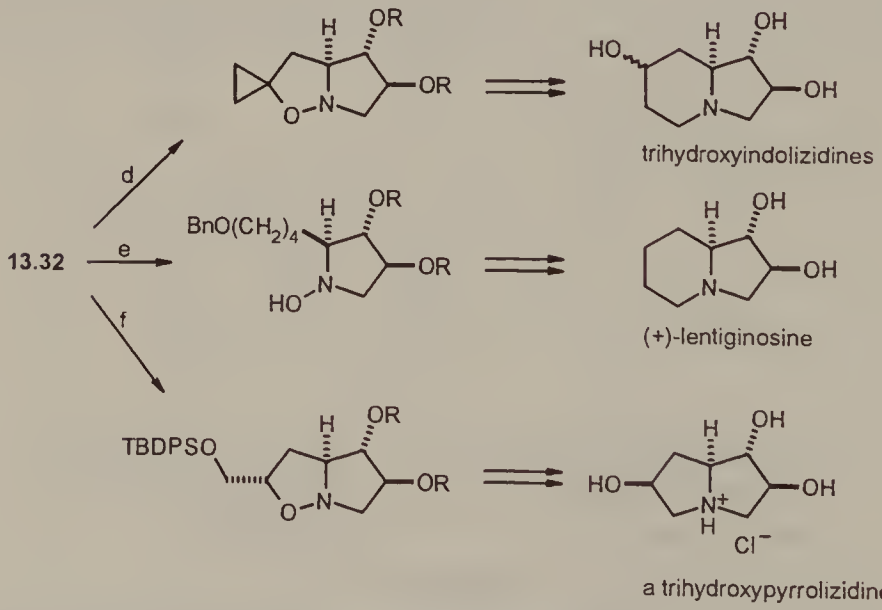


R = MOM, TBDPS **13.32** R = Me, Bn, t-Bu

a: 30% H_2O_2, SeO_2 (cat.), Me_2CO, RT (53-60%)[58]

b: 30% H_2O_2-urea. Na_2WO_4 (cat.), MeOH, RT (70%)[71]

c: HgO (yellow), CH_2Cl_2, RT (91-93%)[63]



d (R = TBDPS): methylenecyclopropane, 35°C, 8d (94%)[58,67]

e (R = MOM): 2 eq. $BnO(CH_2)_4MgBr$, THF (reverse addition), RT (82%, d.e. 90%)[66]

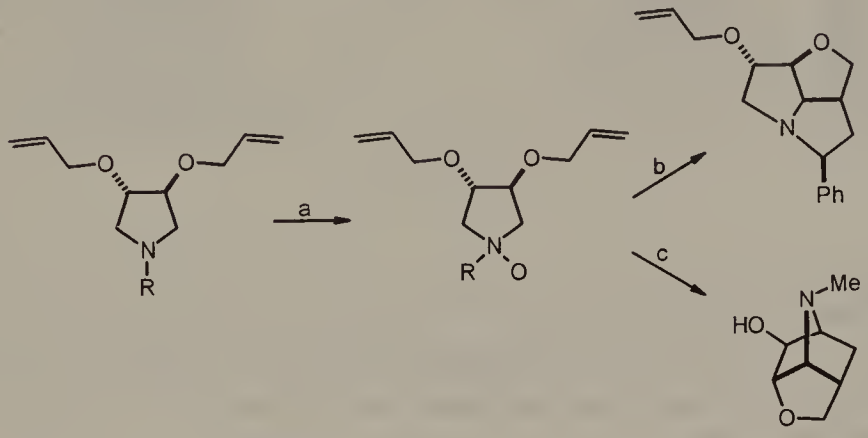
f (R = MOM): CH_2=$CHCH_2OTBDPS$, $CHCl_3$, Δ[69]

Scheme 13.19

Nitrones **13.32** (R = Me, t-Bu, TBDPS) were applied by Brandi and Pietrusiewicz to kinetic resolution of 2,3-dihydro-1-phenyl-1*H*-phospholes in 1,3-dipolar cycloaddition.[72]

Nitrone **13.32** (R = MOM) has been used by Petrini in the enantioselective synthesis of (−)-anisomycin.[56]

Interesting examples of intramolecular 1,3-dipolar cycloaddition of azomethine ylides generated from chiral tertiary amine *N*-oxides were reported by Takano. Different reaction products were obtained from *N*-benzyl and *N*-methyl *O,O′*-diallyl pyrrolidine-1-oxides[59] (Scheme 13.20).



a: t-BuOOH, $VO(acac)_2$, CH_2Cl_2, RT

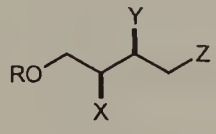
b: 3.5 eq. LDA, THF, -78° → -20°C

c: Me_3Al, PhMe, -30°C → RT, then t-BuLi, -90°C

Scheme 13.20

13.3 MONOPROTECTED L-THREITOLS AND THEIR SUBSTITUTION PRODUCTS

13.3.1 1-*O*-Protected L-Threitols



III

Table 13.3 1-*O*-Protected L-threitols and their derivatives (III)

R	X	Y	Z	m.p (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
Me	OH	OH	OH	—	−9.6 (MeOH)	73,74
Me	OH	OH	OTs	78–80	—	75
Bn	OH	OH	OH	—	−2.6 (−)	76

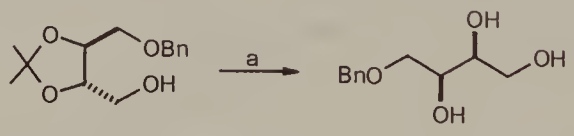
(continued)

Table 13.3 (*continued*)

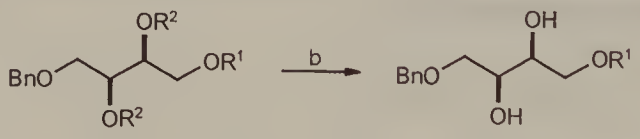
R	X	Y	Z	m.p (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
Bn	OH	OH	OTs	—	—	77
Bn	OH	OH	NMe_2	53–54	−18.4 ($CHCl_3$)	78
Bn	OH	OH	SPh	—	+11.4 ($CHCl_3$)	79
Bn	–O–		OH	135/0.01	−22.0 ($CHCl_3$)	77,79
Bn	–O–		OC(O)NHPh	—	—	79
Bn	OH	–O–		130/0.01	+16.0 ($CHCl_3$)	26,77,78
Bn	OH	–O–C(O)O–		—	+44.1 ($CHCl_3$)	79,80
Bn	OTs	–O–C(O)O–		83–84	+28.0 ($CHCl_3$)	77
PMB	OMs	OH	OH	—	+1.0 ($CHCl_3$)	81
PMB	OH	–O–		—	+13.6 ($CHCl_3$)	82

Synthesis

1-*O*-Benzyl L-threitol and its 4-tosylate are available by acidic hydrolysis of the corresponding 2,3-acetal protected derivatives (Scheme 13.21). This reaction is also applicable to other 1-*O*-alkylated acetals of threitol.

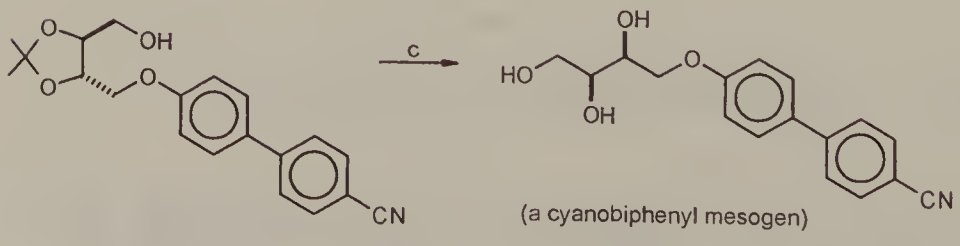


a: Dowex 50Wx8, MeOH, RT (81%)[80]



13.33

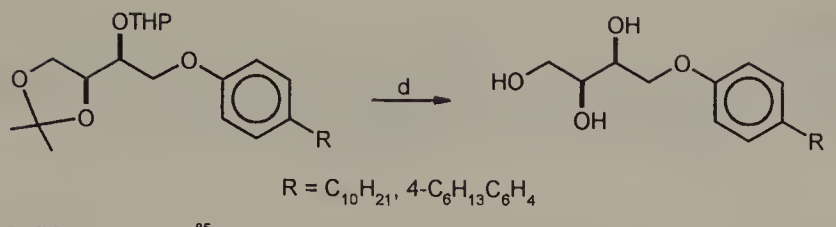
b: HCl, H_2O, Me_2CO (R^1 = Ts, R^2 = ME[77,78]; R^1 = Ms, R^2 = EE[83])



(a cyanobiphenyl mesogen)

c: acid hydrolysis[84]

Scheme 13.21 (*continued*)



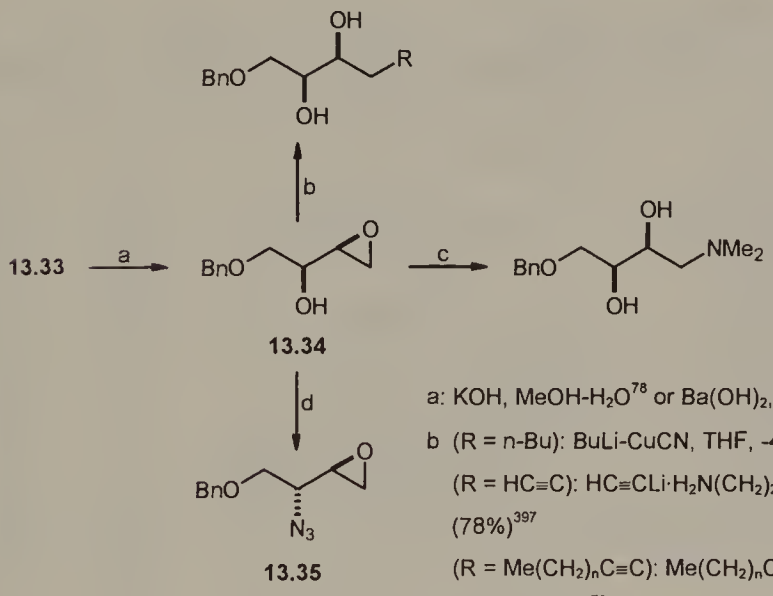
$R = C_{10}H_{21}$, 4-$C_6H_{13}C_6H_4$

d: PPTS, MeOH-H_2O[85]

e: conc. HCl, MeOH, RT (97%)[81]

Scheme 13.21

The tosylate **13.33** can be further converted to the epoxide **13.34** (see also Section 13.8.2) from which a variety of 1-monoprotected threitol substitution products are available; see the examples in Scheme 13.22.



a: KOH, MeOH-H_2O[78] or $Ba(OH)_2$, H_2O[77]

b (R = n-Bu): BuLi-CuCN, THF, -45°C, 2h (100%)[396]

(R = HC≡C): $HC{\equiv}CLi{\cdot}H_2N(CH_2)_2NH_2$, DMSO, RT, 15h (78%)[397]

(R = $Me(CH_2)_nC{\equiv}C$): $Me(CH_2)_nC{\equiv}CLi$, BF_3, Et_2O,-70°C[398]

c: Me_2NH (62%)[78]

d: Ph_3P, $(PhO)_2P(O)N_3$, DIAD, THF (61%)[86]

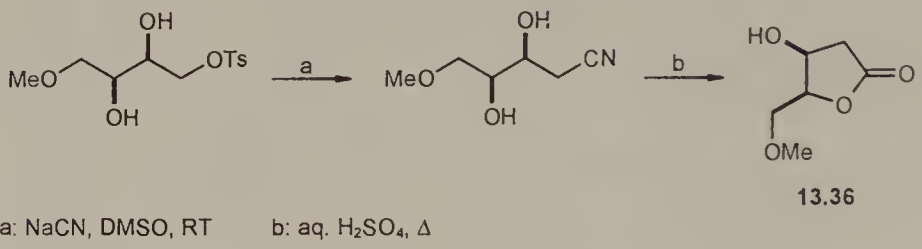
Scheme 13.22

Chain-extended triols were used in the synthesis of (6*S*,7*S*)-*trans*-lauradiol[397] and a component of the sex pheromone of *Phragmatobia fuliginosa*.[398] Product **13.35** has been used by Takano in the synthesis of (−)-kainic acid.[86]

Applications

B

1-*O*-Methyl-4-*O*-tosyl L-threitol was applied by Font *et al.* to the synthesis of 5-*O*-methyl-2-deoxy-L-xylono-1,4-lactone (**13.36**), Scheme 13.23.

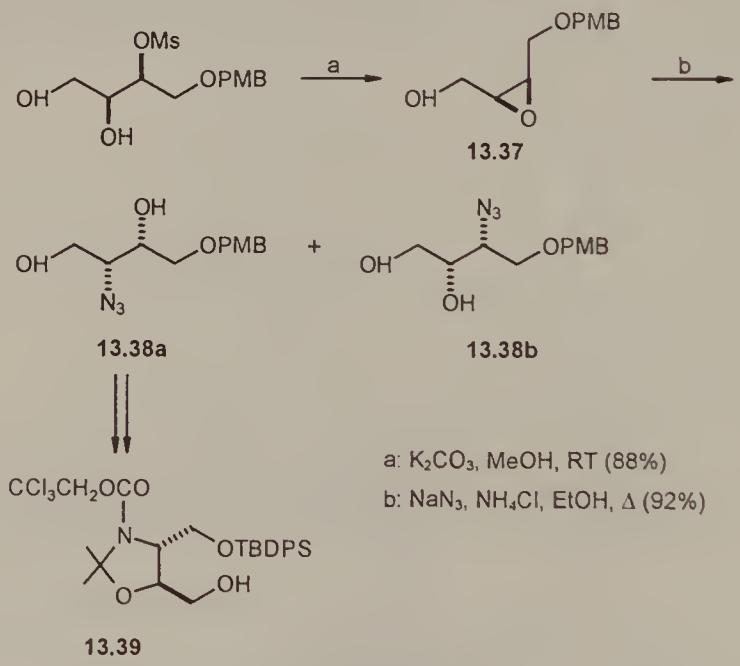


13.36

a: NaCN, DMSO, RT b: aq. H_2SO_4, Δ

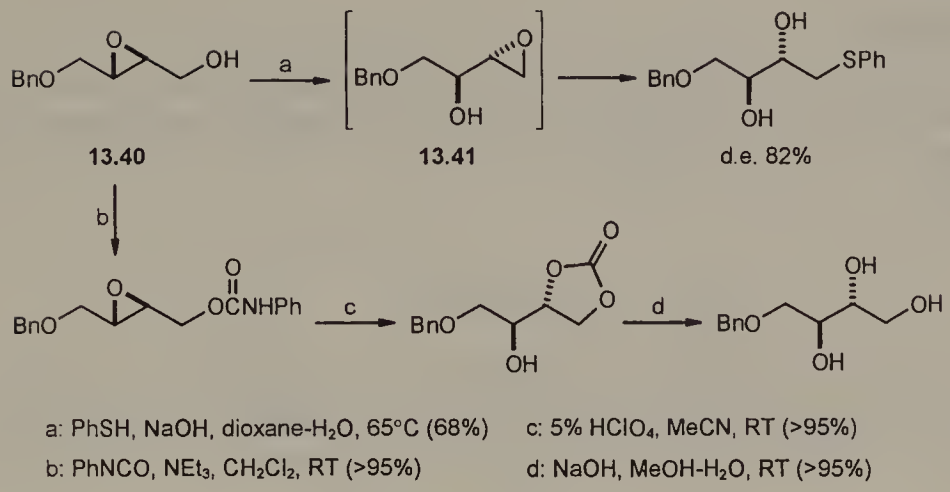
Scheme 13.23

1-*O*-PMB-Protected-2-*O*-mesyl L-threitol was converted by Terashima to the *cis*-epoxide **13.37**. Opening the epoxide ring with the azide nucleophile gave a 3:2 mixture of regioisomers **13.38a**,**b**, from which the undesired isomer **13.38b** could be removed by periodate oxidation. The other isomer was converted to the product **13.39**, an aliphatic fragment of the natural secondary metabolite (+)-FR 900482[81] (Scheme 13.24).



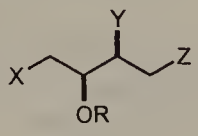
Scheme 13.24

The 1-*O*-benzyl protected 2,3-epoxide **13.40** (readily available by Sharpless asymmetric epoxidation[79]) can be converted to *erythro* configured products with good regioselectivity. Under basic conditions the reaction may proceed through the intermediate isomeric hydroxyepoxide **13.41**, a product of Payne rearrangement[79] (Scheme 13.25).



Scheme 13.25

13.3.2 2-*O*-Protected L-Threitols



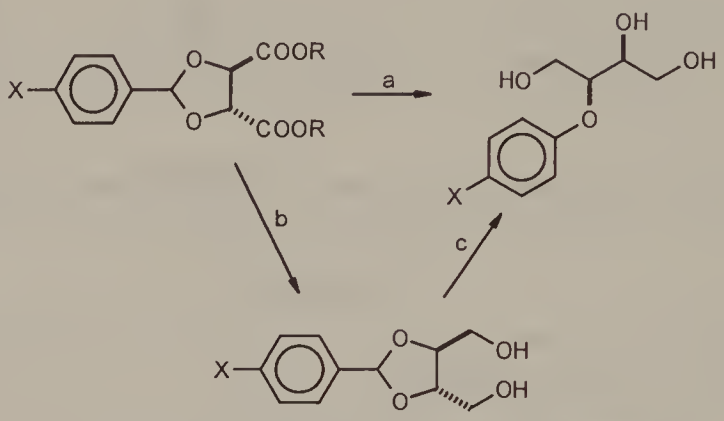
IV

Table 13.4 2-*O*-Protected L-threitols and derivatives (IV)

X	R	Y	Z	m.p (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
OH	C_7H_{15}	OH	OH	—	+10.8 (MeOH)	87
OH	C_8H_{17}	OH	OH	—	+9.9 (MeOH)	87
OH	C_9H_{19}	OH	OH	—	+9.5 (MeOH)	87
OH	$C_{10}H_{21}$	OH	OH	—	+9.3 (MeOH)	87
OH	Bn	OH	OH	75.5–76.5	+16.0 (MeOH)	26,88–93
OH	Bn	OTs	OH	77.5–78	−5.3 ($CHCl_3$)	94
OH	Bn	–O–		130–135/0.5	+33.3 ($CHCl_3$)	26
Br	Bn	OH	OH	—	—	95
SPh	Bn	OH	OH	—	−17.9 (MeOH)	26
OMs	Bn	OH	OMs	—	—	96
OTs	Bn	OH	OTs	—	—	96
Cl	Bn	OH	Cl	—	—	96
Br	Bn	OH	Br	—	—	96
SPh	Bn	OH	SPh	—	+88.1 (MeOH)	26
OMs	Bn	–O–		—	—	96
OTs	Bn	–O–		—	—	96
Cl	Bn	–O–		—	—	96
Br	Bn	–O–		—	—	96
OH	MOM	OH	OH	—	+3.3 (MeOH)	97
OH	An	OH	OH	54–55	+29.6 ($CHCl_3$)	98

Synthesis

2-*O*-Benzyl and 2-*O*-(4-methoxybenzyl) L-threitols are readily available by either one- or two-step reductive cleavage of L-tartrate benzylidene acetals (Scheme 13.26); the two-step procedure appears superior in terms of overall yield.



a (R = Me, X = H): $LiAlH_4$-$AlCl_3$(1:1), Et_2O-CH_2Cl_2 (1:1) (50-97%)[88,89,91-93,99,100]

(R = Et, X =H): 6.5 eq. i-Bu_2AlH, PhMe, RT (77%)[101]

b (R = Et, X = H): $NaBH_4$, EtOH, 0°C (82%)[26]

(R = Et, X = OMe): $NaBH_4$, LiCl, THF, EtOH, RT (100%)[98]

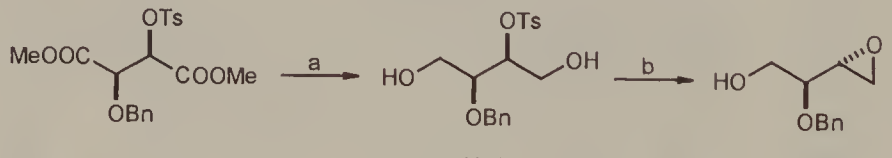
c (X = H): i-Bu_2AlH, CH_2Cl_2, PhMe, RT (87%)[26]

(X = OMe): BH_3·THF, THF, -20°C → RT → reflux (94%)[98]

Scheme 13.26

This procedure also works for the cleavage of 3,4-methylenedioxycinnamaldehyde acetal of threitol.[102]

Reduction of *O'*-benzyl-*O*-tosyl tartrate leads to the corresponding threitol derivative **13.42** which is readily converted to the *erythro*-epoxide **13.43** (Scheme 13.27).



13.42 **13.43**

a: $LiBH_4$, $LiBEt_3H$, THF-Et_2O, 0°C → RT, 60h (61%)

b: NaOH, MeOH-H_2O, CH_2Cl_2, 30°C (93%)

Scheme 13.27

Reductive cleavage of phenylthio substituted benzylidene acetals was applied by Takano *et al.* in the synthesis of phenylthio substituted 2-*O*-benzylthreitols[26] (Scheme 13.28).

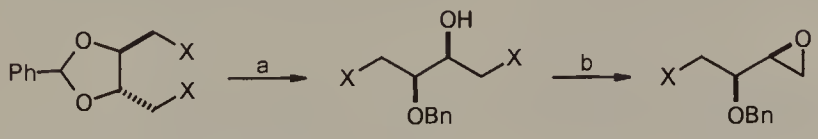
X = OH (40-77%)

X = SPh (92%)

a: i-Bu_2AlH, benzene, RT

Scheme 13.28

Géro *et al.* reported sodium cyanoborohydride reductions of 1,4-disubstituted benzylidene acetals **13.44** to the corresponding 2-*O*-benzyl L-threitol derivatives and their further transformation to epoxides **13.45**[96] (Scheme 13.29).

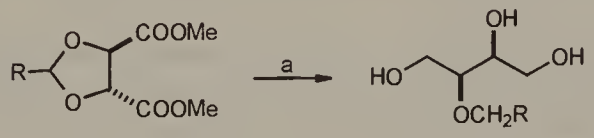


13.44 (X = OMs, OTs, Br) **13.45**

a: $NaBH_3CN$, MeCN (80-85%) b: MeONa, MeOH ("excellent yield")

Scheme 13.29

2-*O*-Alkyl protected L-threitols were obtained by the reductive cleavage of L-tartrate alkylidene acetals with ethyl diboranes in the presence of 9-mesyloxy-9-BBN[87] (Scheme 13.30).

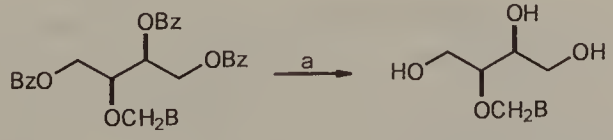


R = C_6H_{13} to C_9H_{19}

a: ethyl diboranes, Δ, then MsO-9-BBN (cat.), Δ (35-42%)

Scheme 13.30

2-*O*-(Nitrogen base)methyl protected L-threitols (1′,2′-*seco*-nucleosides) were obtained by deprotection of their 1,3,4-*O*-tribenzoyl precursors (Scheme 13.31).



B = adenine, cytosine
guanine, thymine

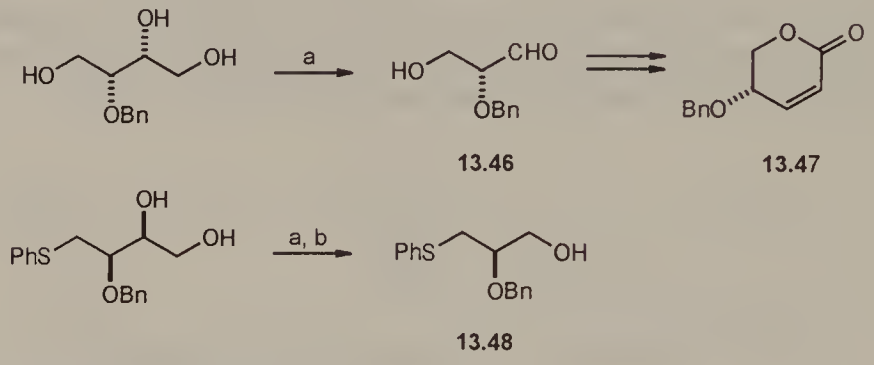
a: NH_3/MeOH, -4°C, 2-4 days (98%)[97]

Scheme 13.31

Commercially available are 2-*O*-benzyl L-threitol [*84379-51-1*] and its enantiomer [*84379-52-2*].

Applications

2-*O*-Benzyl threitol and its 1-substituted derivatives are convenient substrates for the synthesis of 2-*O*-benzyl glyceraldehyde (**13.46**) and 2-*O*-benzyl-1-substituted glycerol (**13.48**), Scheme 13.32.



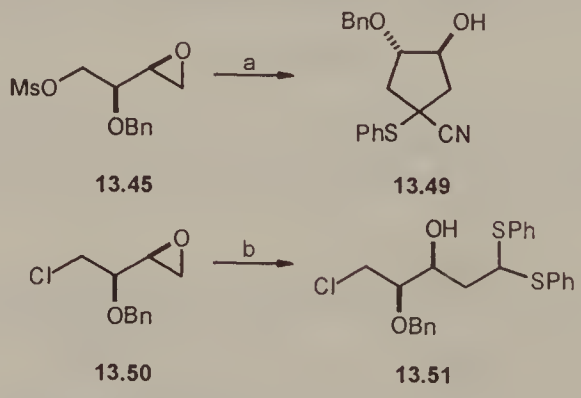
a: $NaIO_4$, H_2O, RT (90-96%)[103]

b: $NaBH_4$, MeOH[26]

Scheme 13.32

Although aldehyde **13.46** rapidly oligomerizes to (hemi)acetals, it could be successfully used for the synthesis of pentenolide **13.47** of high enantiomeric purity.[103]

Chiral cyclopentane derivative **13.49** is available through (4+1) fragment assembly using epoxide **13.45**. Géro *et al.* have found that the success of cyclization is highly dependent on the reactants; with epoxide **13.50** only the acyclic derivative **13.51** was obtained[96] (Scheme 13.33).

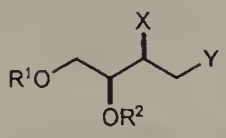


a: $PhSCH_2CN$, NaHMDS, DMF, 0°C (70%)

b: $(PhS)_2CH_2$, n-BuLi, Et_2O, TMEDA, 0°C (72%)

Scheme 13.33

13.4 1,2-DI-*O*-PROTECTED L-THREITOLS



V

Table 13.5 1,2-Di-*O*-protected L-threitols and their derivatives (V)

R^1	R^2	X	Y	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
$-CMe_2-$		OH	OH	101–102/0.1	+3.9 (MeOH)	57,65,92,104,105
$-CMe_2-$		OTs	OH	—	+10.6 (EtOH)	106
$-CMe_2-$		OH	OTs	—	+5.8 ($CHCl_3$)	107
$-CMe_2-$		OH	ONs	40	+10.0 (CH_2Cl_2)	105
$-CMe_2-$		OH	SPh	—	+1.4 ($CHCl_3$)	107
$-CMe_2-$		OMs	OMs	85–86.5	−6.0 (Me_2CO)	52,53,108
$-CMe_2-$		OTs	OTs	70–72	+12.1 ($CHCl_3$)	109
$-CMe_2-$		–O–		72.5/15	−5.3 ($CHCl_3$)[a]	110,111
n-$C_{16}H_{33}$	Me	OH	OH	44–46	+8.6 (MeOH)	93
n-$C_{16}H_{33}$	Bn	OH	OH	40–41	+6.2 (MeOH)	89,93
n-$C_{18}H_{37}$	Bn	OH	OH	44–46	+6.2 (MeOH)	93
Bn	$MeCH{=}CHCH_2$	OH	OH	—	+12.7 ($CHCl_3$)	112
Bn	$HC{\equiv}CCH_2$	–O–		—	−16.9 ($CHCl_3$)	112
Bn	Bn	OH	OH	190–200/0.6	+35.3 ($CHCl_3$)	26,113
Bn	TBDPS	OH	OH	—	+27.8 ($CHCl_3$)	113
Bn	$MeOCMe_2$	–O–		—	−7.0 ($CHCl_3$)	83
Bn	4-$NO_2C_6H_4CO$	–O–		51–52	+11.0 ($CHCl_3$)	77
PMB	THP	–O–		—	—	82
Tr	Bn	OH	OH	—	—	93
Bz	Bz	OH	OH	124–125	−5.4 ($CHCl_3$)	37
TBDPS	Bn	OH	OH	—	+29.6 ($CHCl_3$)	113
TBDPS	TBDPS	OH	OH	—	+18.4 ($CHCl_3$)	113

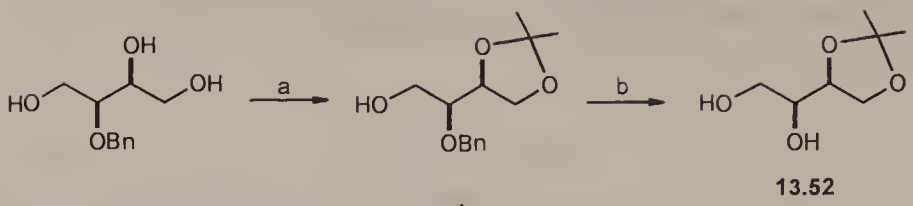
[a] $[\alpha]_D$ +1.1 in EtOH (ref. 110).

Synthesis

1,2-*O*-Isopropylidene-L-threitol (**13.52**) is the most frequently used 1,2-diprotected threitol derivative. In addition to its availability from L-tartaric acid (Scheme 13.34) it can also be obtained by reduction of methyl 3,4-*O*-isopropylidene L-threonate, which is synthesized from L-ascorbic acid (see Chapter 14).

1,2-*O*-Isopropylidene-L-threitol can be selectively activated and substituted in the 4-position, as shown in Scheme 13.35.

Diprotected L-threitols are available by hydrolysis of the 3,4-acetal group of the corresponding tetraprotected L-threitols (Scheme 13.36).



a: 1.5 eq. $Me_2C(OMe)_2$, TsOH, mol. sieves 4Å, CH_2Cl_2, Δ (45%)[92]

b: H_2, Pd/C (cat.), MeOH (61-85%)[92,93] or Na/NH_3, THF, -78°C (ca. 100%)[114]

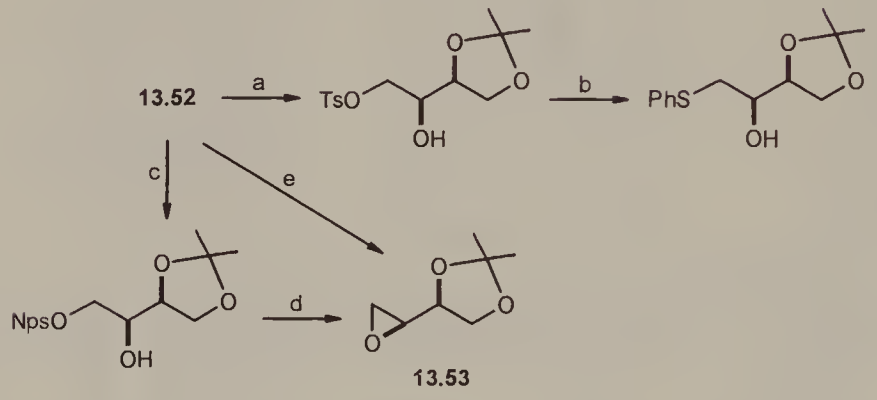
c (R = H, Piv): $LiAlH_4$, THF (91-94%)[111,115]

d (R = Ts): AlH_3, THF, 0°C, 1h (99%)[106]

e (R = H): $NaBH_4$, EtOH, 0°C → RT (83%)[116]

(R = H, Piv, Ts)

Scheme 13.34



a: 1.1 eq. TsCl, pyridine, 5°C, 16h (96%)[107]

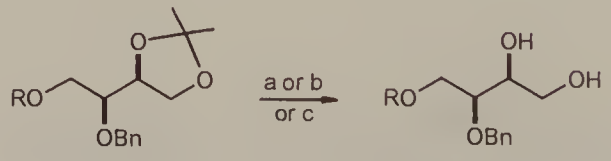
b: PhSNa, MeOH, RT (85%)[107]

c: NpsCl, pyridine, 0°C, 4h (70%)[104]

d: Amberlite IRA 400 (basic), Et_2O, RT (100%)[104]

e: DEAD, PPh_3, benzene, RT (72-89%)[99,110,111,117]

Scheme 13.35



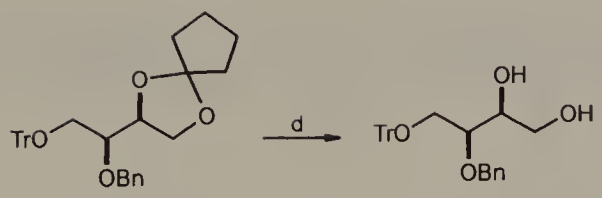
R = n-$C_{16}H_{33}$, n-$C_{18}H_{37}$, Bn, TBDPS

a (R = n-$C_{16}H_{33}$, n-$C_{18}H_{37}$): 2N HCl, THF, RT (91-95%)[93]

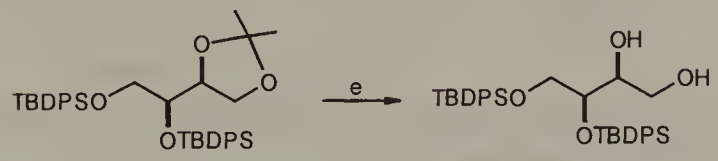
b (R = Bn): AcOH-H_2O (4:1), RT, 18h (89%)[113]

c (R = TBDPS): AcOH-H_2O) (7:3), 40°C, 4h (92%)[408]

Scheme 13.36 *(continued)*



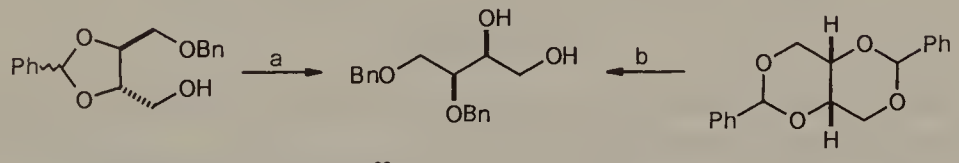
d: AcOH-EtOH (1:1), RT, 2d (90%)[93]



e: AcOH-H_2O-THF (3:1:3), RT, 18h (40%)[113]

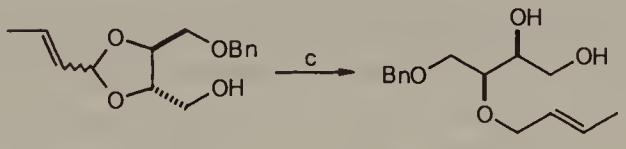
Scheme 13.36

Another useful synthesis of 1,2-diprotected L-threitols is based on the regioselective reductive cleavage of 1-*O*-protected 2,3-*O*-benzylidene or alkylidene acetals, as well as 1,3; 2,4-*O*-dibenzylidene acetal (Scheme 13.37).

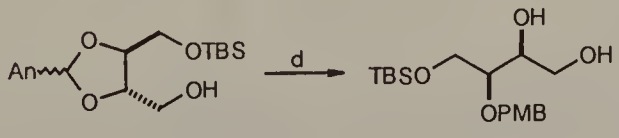


a: i-Bu_2AlH, PhMe, 0°C → RT (94%)[26]

b: i-Bu_2AlH, CH_2Cl_2, PhMe, 0°C → RT (73%)[26]



c: i-Bu_2AlH, PhMe, 0°C (74%)[112]

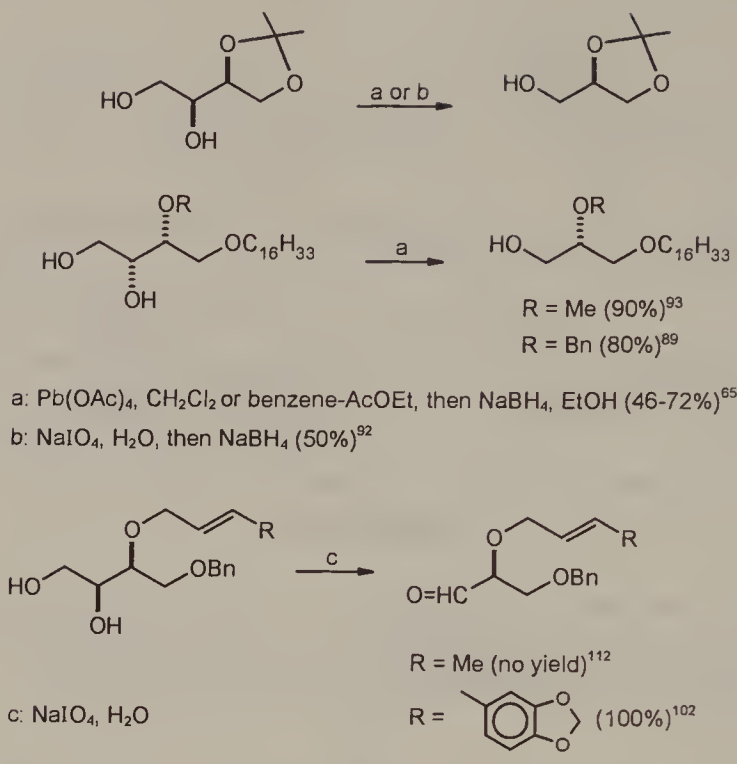


d: $LiAlH_4$, $AlCl_3$, Et_2O, -50°C (80%)[55]

Scheme 13.37

Applications

1,2-Diprotected threitols are valuable substrates for the synthesis of suitably substituted chiral glyceraldehydes[90] and glycerols. The synthesis involves lead tetraacetate or periodate cleavage of the diol derived from threitol and subsequent sodium borohydride reduction of the aldehyde (Scheme 13.38).

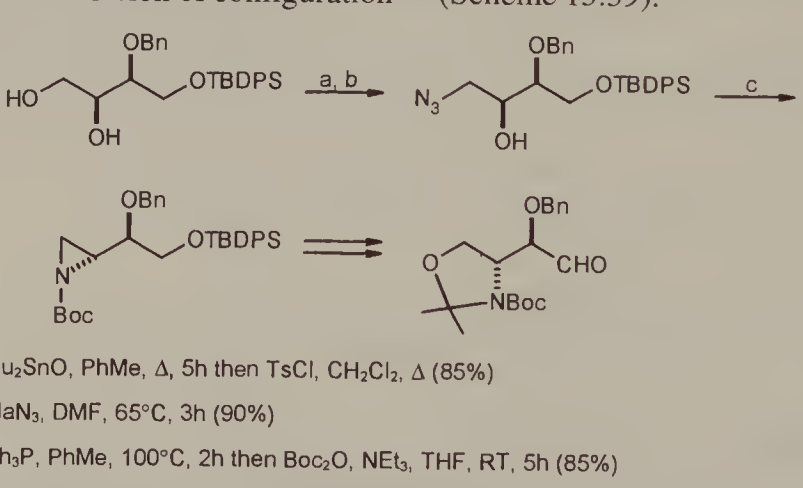


Scheme 13.38

Chiral *O,O*-dialkylated glycerols were used Ohno *et al.* in the synthesis of platelet-activating factors (PAFs).[89,93]

4-Substituted 1,2-diprotected threitols can be oxidized to derivatives of L-erythrulose.[107]

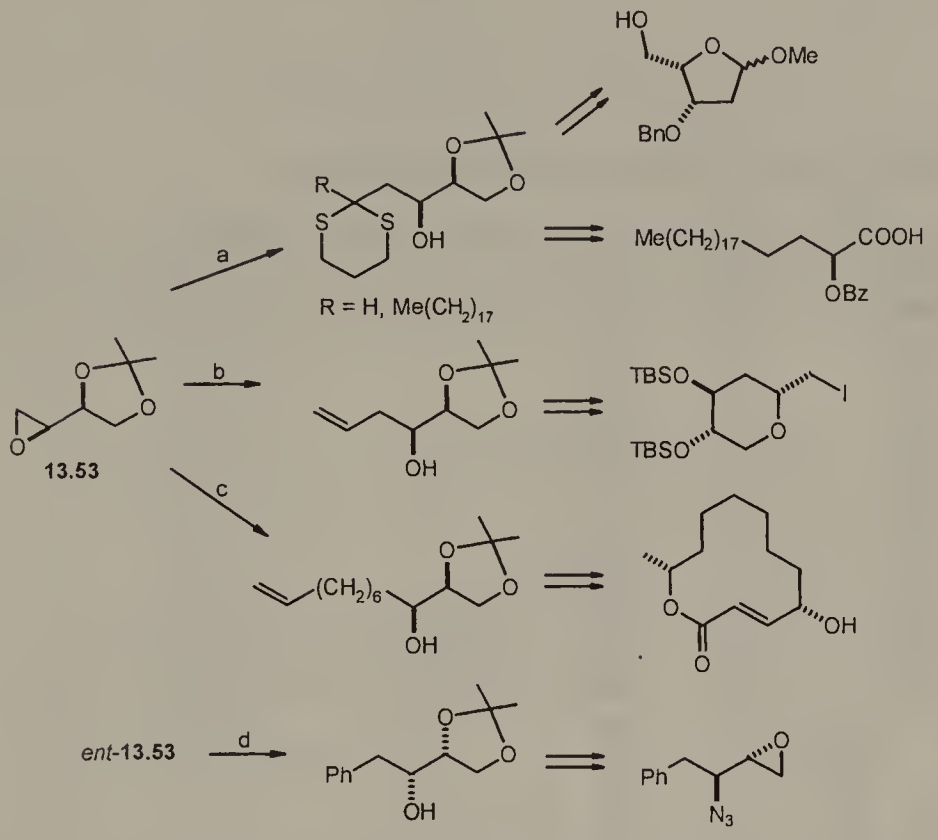
Depezay used 4-activated 1,2-diprotected threitol derivative for the synthesis of a derivative of 3-amino-3-deoxy-D-erythrose, via intramolecular aziridine formation with inversion of configuration [408] (Scheme 13.39).



Scheme 13.39

1,2-Diprotected epoxide **13.53** or its enantiomer have been used by Abushanab[106] in the synthesis of 2-deoxy-pentofuranoses; by Kamikawa[110] in the synthesis of long chain α-hydroxyacids; by Hanaoka[118] for the stereoselec-

tive synthesis of tetrahydropyrans; by Irie[111] in the synthesis of patulolide C; and by Ghosh[99] in the synthesis of [1′-(*S*)-azido-2′-phenylethyl]oxirane (Scheme 13.40).



a: R–(S,S-dithiane), n-BuLi, THF, HMPA, -30°→ -20°C (99%)[106,110]

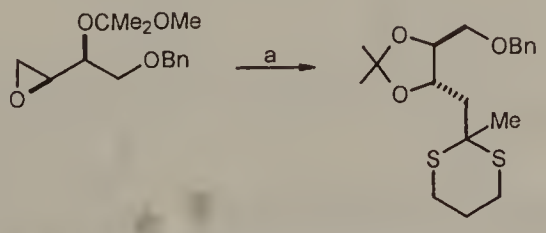
b: CH_2=CHMgBr, CuI (cat.), THF, 0°C[118]

c: CH_2=CH$(CH_2)_5$MgBr, CuI (cat.), THF, -40°C → RT (78%)[111]

d: PhMgBr, CuCN (cat.), THF, -40°C → 0°C (93%)[99]

Scheme 13.40

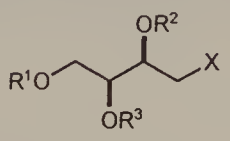
An analogous substitution reaction of the 3-O-methoxyisopropyl protected epoxide with a carbon nucleophile gives rise to a 2,3-*O*-isopropylidene protected product, as reported by Seebach[83] (Scheme 13.41).



a: 2 eq. 2-methyl-1,3-dithiane, 2 eq. n-BuLi, THF, -60°→ 32°C, 12h (89%)

Scheme 13.41

13.5 1,3-DI-*O*-PROTECTED L-THREITOLS



VI

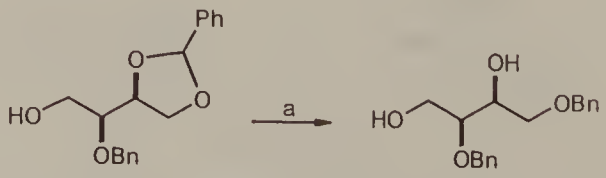
Table 13.6 1,3-Di-*O*-protected L-threitol derivatives (VI)

R^1	R^2	R^3	X	m.p. (°C)	$[\alpha]_D$ (solvent)	References
$-CH_2-$		H	OH	—	+2.3 ($CHCl_3$)[a]	51,119
$-CH_2-$		H	OTs	89–90	+16.9 (EtOH)[a]	119
$-CH_2-$		H	N_3	—	+6.1 (EtOH)[a]	119
$-CH_2-$		H	NH_2	—	+12.1 (EtOH)[a]	119
$-CH_2-$		H	n-PrNH	—	+4.7 (EtOH)[a]	119
$-CH_2-$		H	i-PrNH	—	+2.5 (EtOH)[a]	119
$-CH_2-$		H	t-BuNH	—	−1.6 (EtOH)[a]	119
$-CH_2-$		H	Et_2N	—	+10.0 (EtOH)[a]	119
$-CH_2-$		H	$(CH_2)_4N$	—	+15.0 (EtOH)[a]	119
$-CH_2-$		H	$(CH_2)_5N$	—	+12.6 (EtOH)[a]	119
–CHPh–[b]		H	OH	133–134	+8.0 (pyridine)	120
–CHPh–[b]		Ms	OMs	155–157	+31.0 ($CHCl_3$)	120
–CHPh–[b]		Ts	OTs	116–118	+37.0 ($CHCl_3$)	120
Me	Me	H	OH	—	—	121
Bn	Bn	H	OH	57–58	+22.4 ($CHCl_3$)	26
Tr	THP	H	OH	—	—	122
TBDPS	Bn	H	OH	—	+6.0 (CH_2Cl_2)	123

[a] Measured at 546 nm.
[b] Configuration at the acetal carbon atom unknown.

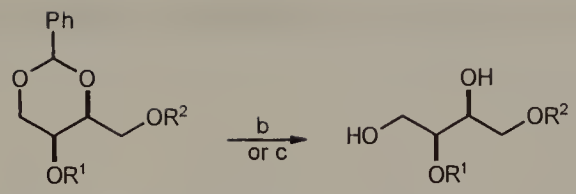
Synthesis

As in the case of monoprotected threitols, 1,3-diprotected threitols are available by regioselective reductive cleavage of triprotected benzylidene acetals, and by acetal hydrolysis of tetraprotected derivatives (Scheme 13.42).



a: i-Bu_2AlH, CH_2Cl_2, PhMe, RT (76%)[26]

Scheme 13.42 (*continued*)

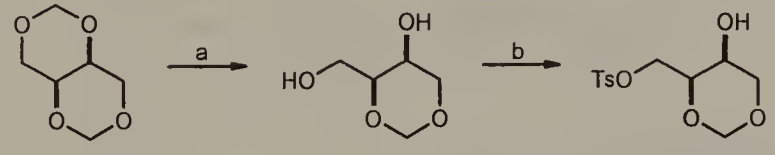


b (R^1 = R^2 = Me): 0.05 M H_2SO_4, 100°C, 4h (86%)[121]

c (R^1 = Bn, R^2 = TBDPS): AcOH-H_2O (4:1), 40°C, 15h (88%)[123]

Scheme 13.42

1,3-*O*-Methylenethreitol (**13.55**) was obtained by acetolysis of 1,3; 2,4-di-*O*-methylenethreitol (**13.54**); it could be further selectively mono-1-*O*-activated by tosylation (**13.56**) or cyclized under Mitsunobu conditions to oxetane **13.57** (Scheme 13.43).



13.54 **13.55** **13.56**

13.57

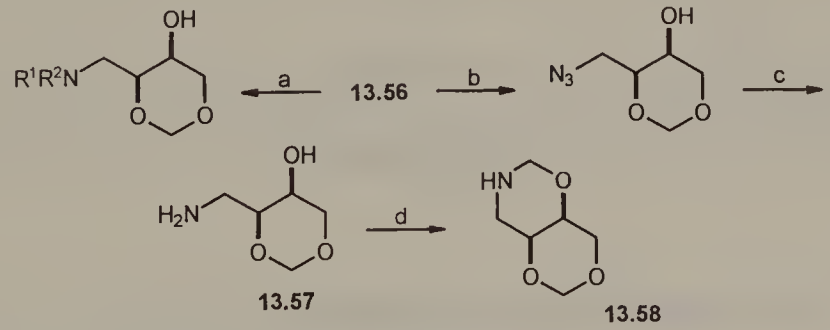
a: TFA, AcOH, 0°C then K_2CO_3, MeOH (97%)[124]

b: TsCl, pyridine, -20°C, 2h (80% + 8% of the isomeric 3-*O*-tosylate)[119]

c: Ph_3P, DEAD, THF, RT (71%)[51]

Scheme 13.43

Tosylate **13.56** readily undergoes substitution with various nitrogen nucleophiles (Scheme 13.44). Aminoalcohol **13.57** can further be cyclized to tetrahydro-1,3-oxazine **13.58**.[119]



13.57 **13.58**

a: R^1R^2NH, 0.5M t-BuOK, t-BuOH, $CHCl_3$ (64-88%)

b: NaN_3, EtOH, Δ (95%)

c: H_2, Pd/C, MeOH (74%)

d: HCHO, CH_2Cl_2, RT (79%)

Scheme 13.44

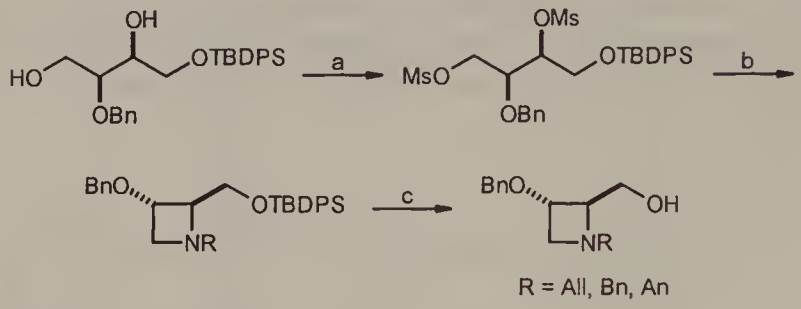
1,3-*O*-Benzylidene L-threitol can be obtained from 1,3-*O*-benzylidene-L-arabinitol.[125]

Applications

B

1,3-Di-*O*-protected threitols are used as starting materials for the synthesis of chiral four membered heterocycles.

Enantiomerically pure functionalized azetidines were synthesized by Depezay[123] from 1,3-di-*O*-protected L-threitol (Scheme 13.45).



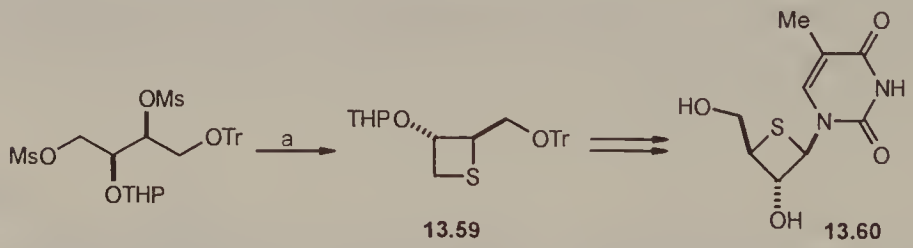
a: MsCl, NEt_3, DMAP, CH_2Cl_2 (92%)

b: RNH_2, PhMe, Δ (67-95%)

c: $(n\text{-}Bu)_4NF/SiO_2$, THF, RT (84-88%)

Scheme 13.45

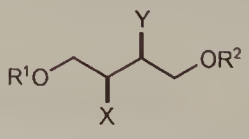
A similar synthetic pathway was devised for a chiral thietane derivative **13.59** from which thymine thietane nucleoside **13.60** was obtained[122] (Scheme 13.46).



a: Na_2S, aq. EtOH, Δ

Scheme 13.46

13.6 1,4-DI-*O*-PROTECTED L-THREITOLS



VII

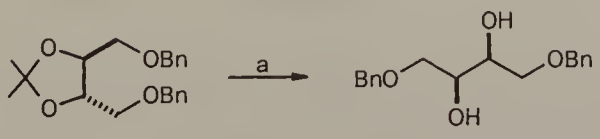
Table 13.7 1,4-Di-*O*-protected L-threitols and their derivatives (VII)

R^1	R^2	X	Y	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
Me	Me	OH	OH	28–30	−1.8 (MeOH)[a]	5,13,126,127
Me	Me	OMs	OMs	52	−25.9 ($CHCl_3$)	5
n-Bu	n-Bu	OH	OH	33	+7.1 (benzene)	5
i-Pr	i-Pr	OH	OH	—	−1.4 ($CHCl_3$)	128
Et_2CH	Et_2CH	OH	OH	—	−0.4 ($CHCl_3$)	128
cyclo-C_5H_9	*cyclo*-C_5H_9	OH	OH	—	−0.7 ($CHCl_3$)	128
cyclo-C_6H_{11}	*cyclo*-C_6H_{11}	OH	OH	—	−1.6 ($CHCl_3$)	128
t-Bu	t-Bu	OH	OH	98–100/1	+4.8 ($CHCl_3$)	129
i-$PrMe_2C$	i-$PrMe_2C$	OH	OH	124–126/1	+5.5 ($CHCl_3$)	129
$MeEt_2C$	$MeEt_2C$	OH	OH	—	+1.7 ($CHCl_3$)	128
$(CH_2)_4CMe$	$(CH_2)_4CMe$	OH	OH	—	+2.1 ($CHCl_3$)	128
$(CH_2)_5CMe$	$(CH_2)_5CMe$	OH	OH	—	+1.5 ($CHCl_3$)	128
Bn	Bn	OH	OH	60–61[b]	−5.8 ($CHCl_3$)[a]	126,130–133
Bn	Bn	OMs	OMs	76.5–77.5	−11.7 ($CHCl_3$)	18,134
Bn	Bn	OTs	OTs	—	—	135
Bn	Bn	–O–		30–31	−10.2 ($CHCl_3$)	136–138
Bn	$MeOCMe_2$	–O–		—	−13.0 ($CHCl_3$)	77
Bn	2-$MeOC_6H_4$	OH	OH	78–80	−8.2 ($CHCl_3$)	139
Bn	4-$O_2NC_6H_4CO$	–O–		52–53	−27.0 ($CHCl_3$)	77
$Bn(OCH_2CH_2)_2$	$Bn(OCH_2CH_2)_2$	OH	OH	—	−4.1 (EtOH)	140
4-$ClC_6H_4CH_2$	4-$ClC_6H_4CH_2$	OH	OH	76–77	−6.4 ($CHCl_3$)	141
3-$MeOC_6H_4CH_2$	3-$MeOC_6H_4CH_2$	OH	OH	—	−4.7 ($CHCl_3$)	27
Ph	Ph	OH	OH	133	−11.0 (MeOH)	13
1-naphthyl	1-naphthyl	OH	OH	158–159	−17.3 (THF)	142
TBS	TBS	OH	OH	—	+4.4 ($CHCl_3$)	143

[a] Reported values vary.
[b] m.p. 66–68°C reported in ref. 131.

Synthesis

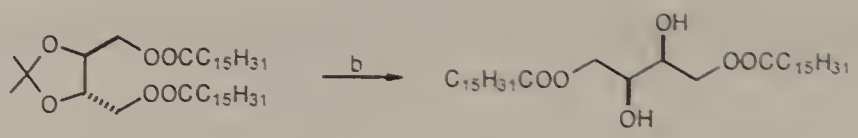
1,4-Di-*O*-protected threitols are readily available from 2,3-acetal protected precursors, which are in turn obtained from tartrate acetals. Examples, including the most frequently used 1,4-di-*O*-benzyl-L-threitol (**13.61**), are shown in Scheme 13.47.



13.61

a: 0.5N HCl, MeOH, Δ (removal of acetone), 95-100%[130,132,144,145]

Scheme 13.47 (*continued*)

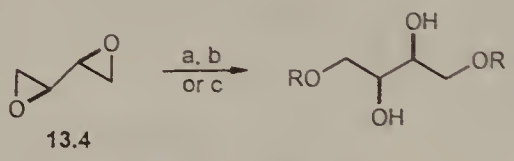


b: CF_3COOH-H_2O (4:1), RT, 1h (95%))[146]

c. MeOH-H_2O (4:1), CF_3COOH (cat.), RT (90%)[127]

Scheme 13.47

1,4-Di-*O*-protected threitols were obtained by Feit[18] and Seebach[13] by nucleophilic ring opening of diepoxide **13.4** (Scheme 13.48).



13.4

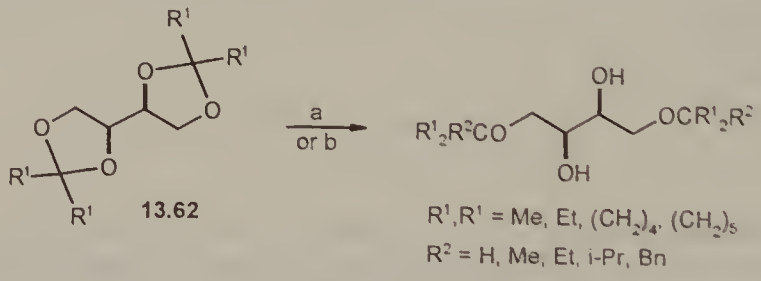
a (R = Me): MeOH, $HClO_4$ (cat.), Δ (80%)[13]

b (R = Ph): PhONa, H_2O, 100°C (57%)[13]

c (R = Bn): BnONa, BnOH, 55-85°[18]

Scheme 13.48

Grignard reagent ring-opening reactions of 1,2:3,4-bisacetals of threitol **13.62** are convenient routes to 1,4-di-*O*-tert-alkyl protected threitols (useful as a tailor-made ligands in asymmetric reactions).[128,129] Reduction of **13.62** with $LiAlH_4$-$AlCl_3$ provides 1,4-di-*O*-*sec*-alkyl protected threitols[128] (Scheme 13.49).



13.62

R^1,R^1 = Me, Et, $(CH_2)_4$, $(CH_2)_5$

R^2 = H, Me, Et, i-Pr, Bn

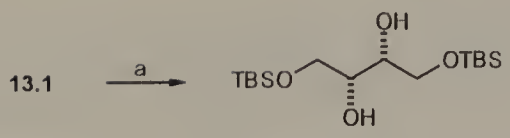
a (R^2 = H): $LiAlH_4$, $AlCl_3$ (cat.), PhMe, Δ (58-77%)[128]

b: R^2MgX, benzene, Δ (56-89%)[128,129]

Scheme 13.49

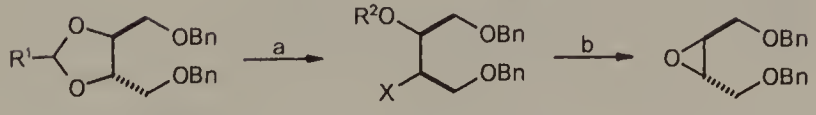
The 1,4-di-*O*-TBS derivative is directly obtained from threitol in good yield (Scheme 13.50).

The epoxide **13.65** is a useful 2,3-activated 1,4-di-*O*-protected L-threitol derivative. It can be obtained by the cleavage of cyclic orthoformate **13.63** or by oxidative cleavage of benzylidene acetal **13.64** followed by treatment with a base (Scheme 13.51).



a: 2.0 eq. TBSCl, 2.0 eq. imidazole, DMF, RT (73%)[143]

Scheme 13.50



13.63, R^1 = OEt
13.64, R^1 = Ph

R^2 = HCO, X = Cl
R^2 = Bz, X = Br

13.65

a (R^1 = OEt): PCl_5, CH_2Cl_2, 0°C → RT (86-99%)[136,138]
(R^1 = Ph): 1 eq. NBS, CCl_4, RT (91%)[28,137,147]
b (R^2 = HCO): K_2CO_3, MeOH, RT (88%)[136,138]
(R^2 = Bz): 10N KOH, EtOH, RT (97%)[137,147]

Scheme 13.51

1,4-Di-*O*-methyl D-threitol was synthesized from D-mannitol.[148]

It should be noted that 1,4-diprotected threitols are also available from 1,4-diprotected 2-butene-1,4-diols by Sharpless asymmetric dihydroxylation.[149]

The following 1,4-diprotected threitols are available commercially:

1,4-di-*O*-methyl-L-threitol [*50622-10-1*] and its enantiomer [*33507-82-3*]

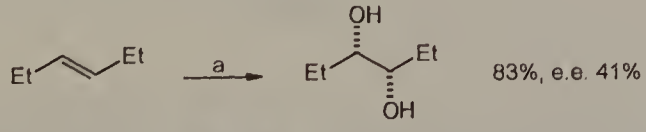
1,4-di-*O*-benzyl-L-threitol [*17401-06-8*] and its enantiomer [*91604-41-0*]

1,4-bis-*O*-(4-chlorobenzyl)-D-threitol [*85362-86-3*].

Applications

A number of synthetically important reactions can be carried out with moderate to good enantio- or diastereoselectivity in the presence of chiral ligands **13.61**, **13.66**, and **13.67** derived from L-threitol (Scheme 13.52).

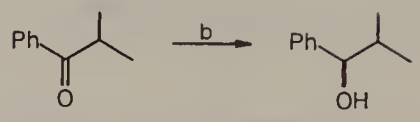
Asymmetric dihydroxylation



a: 0.01 eq. OsO_4, 0.05 eq. **13.66**, 3 eq. $K_3Fe(CN)_6$, 3 eq. K_2CO_3, t-BuOH-H_2O (1:1)[134]

Scheme 13.52 (*continued*)

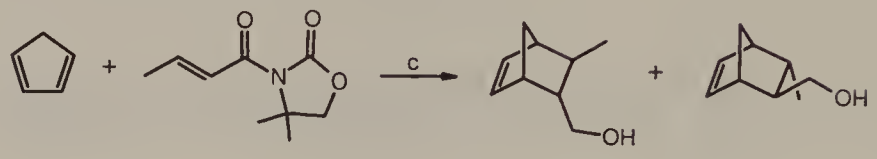
Asymmetric hydrosilylation



63%, e.e. 69%

b: 1.2 eq. $HSi(OMe)_3$, 2.4 eq. **13.67**, THF, 0°C[126]

Asymmetric Diels-Alder reaction

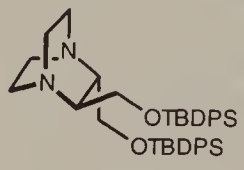


73 : 27

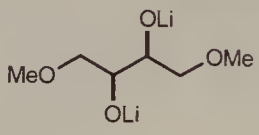
d.e. 91%

c: 2 eq. $EtAlCl_2$, 1 eq. **13.61**, CH_2Cl_2,-78°C, then $LiAlH_4$[150]

Ligands:



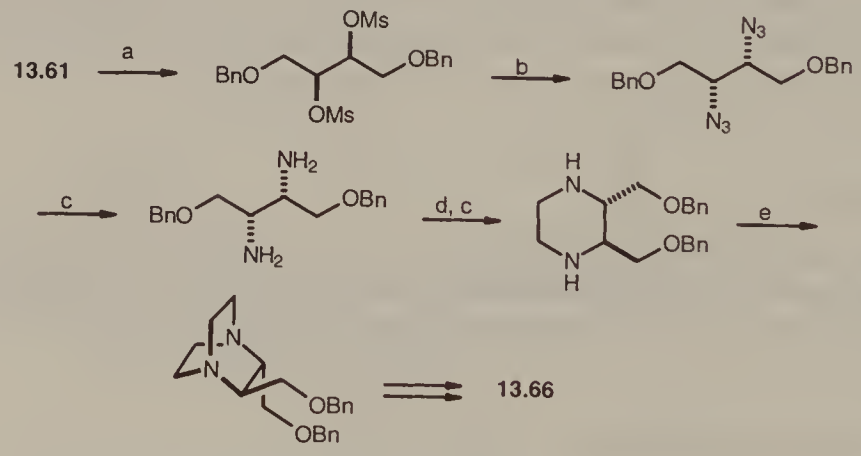
13.66



13.67

Scheme 13.52

Chiral ligand **13.66** was synthesized by Hirama[134] according to Scheme 13.53 (see also Feit,[18] Saito[135] and Saalfrank[151]).



a: 2.4 eq. MsCl, 3 eq. NEt_3, CH_2Cl_2, 0°C, 1h (98%)

b: 3.0 eq. NaN_3, DMF, 100°C (89%)

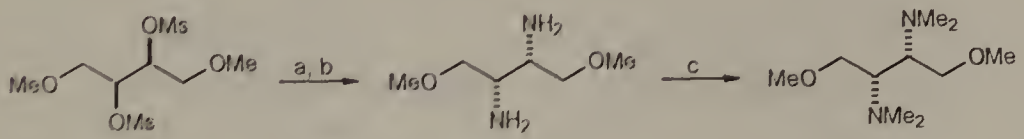
c: $LiAlH_4$, THF, Δ (66-70%)

d: 1.1 eq. $(COOEt)_2$, PhMe, Δ (83%)

e: $(CH_2Br)_2$, EtOH, K_2CO_3, Δ then Zn, AcOH, Δ (39-63%)

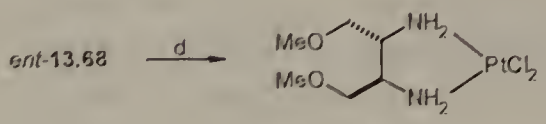
Scheme 13.53

A synthesis of the bis-(*N*,*N*-dimethylamino) substituted ligand **13.69** was reported by Seebach[5] (Scheme 13.54). Enantiomer of **13.68** was used by Haines *et al.*[152] in the synthesis of the analogue of the anticancer drug cisplatin (**13.70**).



13.68 **13.69**

a: NaN_3, HMPA-H_2O, 80°C
b: $LiAlH_4$, Et_2O, RT (46%)
c: HCHO, HCOOH, 95°C, 7 days (27%)

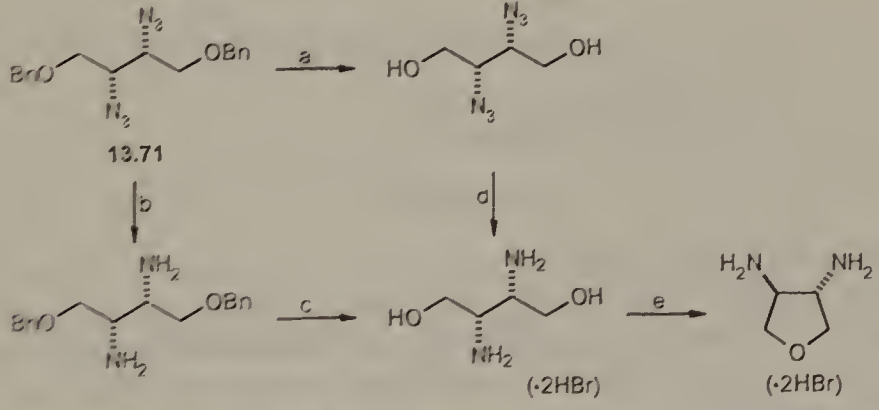


13.70

d: K_2PtCl_4

Scheme 13.54

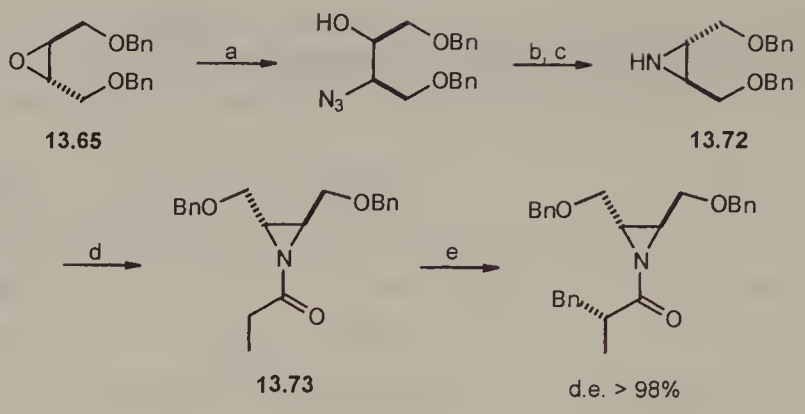
Synthesis of other chiral diamino ligands from the intermediate **13.71** is shown in Scheme 13.55 (See also schemes 13.8 and 13.13).



a: BCl_3·Me_2S, CH_2Cl_2, RT (81%)[151]
b: H_2, Pd/C, RT (100%)[151]
c: Ac_2O, then H_2, 10% Pd/C, EtOH-HBr[152]
d: H_2, PtO_2, MeOH-H_2O (3:2), RT (98%)[151]
e: 48% HBr, Δ[153]

Scheme 13.55

Electrophilic alkylation of chiral propionamide **13.73** derived from epoxide **13.65** via aziridine **13.72** proceeds with high diastereoselectivity owing to the chelating properties of the oxygen atom of the threitol auxiliary[153] (Scheme 13.56).



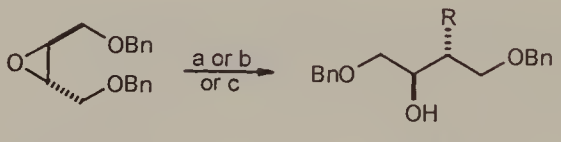
a: NaN_3, NH_4Cl, PrOH, H_2O, Δ (94%) d: $(EtCO)_2O$, NEt_3, DMAP, CH_2Cl_2, RT (89%)

b: MsCl, NEt_3, CH_2Cl_2, 0°C (88%) e: 1.1 eq. LiHMDS, THF, -78°C, then 1.2 eq. BnBr, -78° → RT (88%)

c: $LiAlH_4$, THF, 0°C, then Δ (74%)

Scheme 13.56

Some substitution reactions shown in Scheme 13.57 exemplify the usefulness of the epoxide **13.65** for the synthesis of *erythro* configured products.



a (R = Me): Me_2CuLi, Et_2O, -78°→ - 40°C (89-100%)[136,137,147]

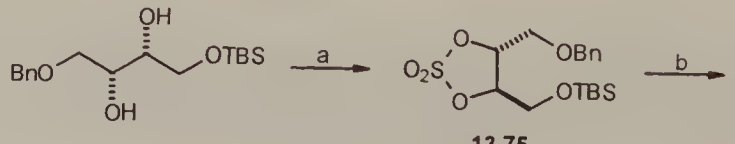
b (R = All): AllMgBr, THF, -20°C (93%)[399]

c (R = CH=CH_2): CH_2=CHMgBr, CuI, Et_2O, -10°C (94%)[138]

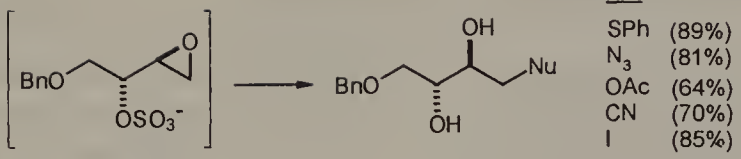
Scheme 13.57

Products **13.74** and **13.75** were used in the synthesis of the ionophore antibiotic X-14547A (Nicolaou[136]), amphoteronolide B and amphotericin B (Nicolaou[407]), C16-C23 segment of the immunosuppresant FK-506 (Kocieński[399]), and the bis(hydroxymethyl)azetidin-1-yl pyrimidine nucleosides (Kato[138]), respectively.

Erythro configured diols can be obtained from unsymmetrically protected 1-*O*-TBS, 4-*O*-Bn threitol. The sequence of reactions includes Payne-type rearrangement of 1-deprotected cyclic sulfate **13.75** via the epoxide **13.76**[149] (Scheme 13.58).



Scheme 13.58 (*continued*)

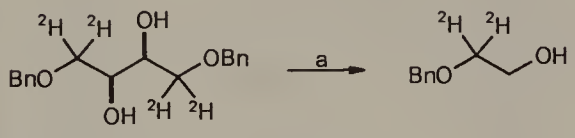


a: $SOCl_2$, NEt_3, CH_2Cl_2, 0°C, then $NaIO_4$, $RuCl_3 \cdot 3H_2O$ (cat.), CCl_4-MeCN-H_2O, 0°C (93%)

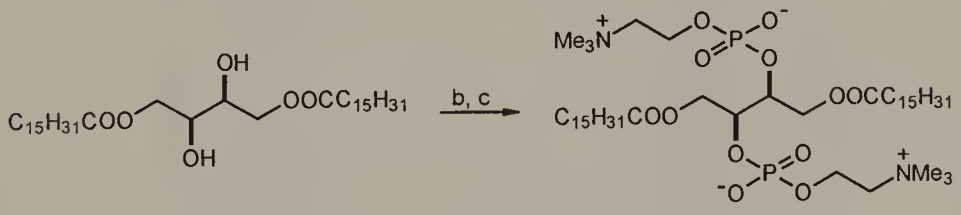
b: TBAF, THF, then Nu^-, RT, then H_2SO_4[149]

Scheme 13.58

Other syntheses from 1,4-diprotected threitols are shown in Scheme 13.59. The products are deuterated 2-(benzyloxy)ethanol, a bis-phosphatidylcholine lipid, and a chiral bis-azafulleroid.

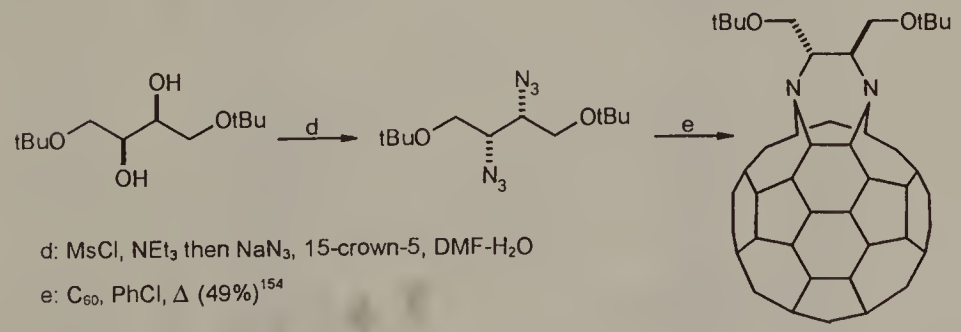


a: $Pb(OAc)_4$, benzene, 0°C then $NaBH_4$, EtOH (69%)[145]



b: i-$Pr_2NP(CH_2CH_2Cl)OCH_2CH_2CN$, tetrazole, THF, RT, then H_2O_2 (73%)

c: Me_3N, MeCN-$CHCl_3$, NaI, 65°C (55%)[146]



d: MsCl, NEt_3 then NaN_3, 15-crown-5, DMF-H_2O

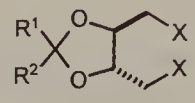
e: C_{60}, PhCl, Δ (49%)[154]

Scheme 13.59

13.7 2,3-DI-*O*-PROTECTED L-THREITOLS

2,3-Diprotected L-threitols are the most frequently used derivatives of L-threitol; they include both 2,3-acetal and 2,3-di-*O*-alkyl derivatives. Their popularity stems from their direct availability from suitably protected tartrates and from the well-established synthetic routes for converting these compounds to other unprotected and protected derivatives of threitol (see Figure 13.1). Because of the large body of published material involved, 2,3-acetal and 2,3-di-*O*-alkyl protected threitols are treated separately.

13.7.1 2,3-Acetals of L-Threitol and Their Derivatives



VIII

Table 13.8 Symmetrical 2,3-acetal protected L-threitol derivatives and 1,4-substitution products[a] (VIII)

R^1	R^2	X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
			Aldehyde acetals		
H	H	OH	—	−30.0 (MeOH)[b]	51,124
H	H	OMs	94.5–95.5	−45.2 (Me_2CO)	4
H	H	NH_2	—	—	17
H	H	N_3	—	−122.0 (Me_2CO)	17
Me	H	OMs	108.5–110	−37.1 (Me_2CO)	4,155
Me	H	NH_2	—	—	17
Me	H	N_3	—	−140.7 (Me_2CO)	17
CF_3	H	OMs	68–69	−32.2 (Me_2CO)	4
CCl_3	H	OMs	105–106.5	−21.8 (Me_2CO)	4
CBr_3	H	OMs	110.5–112.5	−14.0 (Me_2CO)	4
Et	H	OMs	65–66	—	17
Et	H	NH_2	—	—	17
Et	H	N_3	—	−127.5 (Me_2CO)	17
i-Pr	H	OMs	70–71	—	17
i-Pr	H	NH_2	—	—	17
i-Pr	H	N_3	—	−110.9 (Me_2CO)	17
Bn	H	OMs	80–81.5	−19.0 (Me_2CO)	4
Ph	H	OH	72–74	−11.4 (MeOH)[c]	3,26,133,137,147,156
Ph	H	OMs	116–117.5	−14.9 (Me_2CO)	4,156
Ph	H	OTs	132–135	—	157
Ph	H	SPh	—	−13.2 (MeOH)	26
Ph	H	$N(CH_2)_5$	—	−12.8 (CH_2Cl_2)	158
2-$AcOC_6H_4$	H	OTs	—	−16.5 ($CHCl_3$)	159

(*continued*)

Table 13.8 (*continued*)

R^1	R^2	X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
4-$AcOC_6H_4$	H	OTs	94	−19.0 ($CHCl_3$)	159
4-$MeOC_6H_4$	H	OH	52–53	+10.5 ($CHCl_3$)	160
PhCH=CH	H	OH	66–67	+12.3 ($CHCl_3$)	161
PhCH=CH	H	Br	—	+46.6 ($CHCl_3$)	161
2-naphthyl	H	OTs	120.0–120.8	—	162
1-naphthyl	H	$N(CH_2)_5$	—	+12.8 (CH_2Cl_2)	158
1-pyrenyl	H	OTs	54.2–55.0	—	162
			Ketone acetals		
Me	Me	OH	49–51	+5.1 ($CHCl_3$)	4,35,141,163–166
Me	Me	OMs	85.5–86.5[d]	−23.5 (Me_2CO)	167,168
Me	Me	OTs	91.7–92.7	−12.9 ($CHCl_3$)	5,7,24,163,166,169,170
Me	Me	OBz	83–84	−14.3 (DMF)	171
Me	Me	$OPPh_2$	240–250/0.0001	—	29
Me	Me	NMe_2	54/0.8	+7.8 (neat)	5
Me	Me	$N(Me)C_8H_{17}$	145–147/0.003	—	13
Me	Me	$N(CH_2)_5$	35	−37.8 (MeOH)	13
Me	Me	$AsPh_2$	74–75	−3.1 ($CHCl_3$)	169
Me	Me	SH	60/0.15	−13.3 ($CHCl_3$)	24,172
Me	Me	SAc	—	−39.3 ($CHCl_3$)	24
Me	Me	SMe	66/0.02	−6.8 ($CHCl_3$)	172
Me	Me	SC_8H_{17}	—	−4.3 ($CHCl_3$)	173
Me	Me	SBn	86–88	−56.7 ($CHCl_3$)	25,172
Me	Me	SPh	—	—	23
Me	Me	SO_2Ph	—	—	23
Me	Me	F	56–57/16	−23.5 ($CHCl_3$)	174
Me	Me	Cl	47–48/3	+13.4 ($CHCl_3$)	170,174
Me	Me	Br	75–77/3	+8.4 ($CHCl_3$)	170,174
Me	Me	I	80–82/0.05	−17.6 (MeOH)	163,164,175
CH_2OH	Me	N_3	—	−107.1 (Me_2CO)	17
CH_2OAc	Me	OTs	67–68	−10.0 ($CHCl_3$)	159
$CH_2=CH(CH_2)_2$	Me	OH	98–100/0.2	+3.6 (EtOH)[b]	176
$CH_2=CH(CH_2)_2$	Me	OTs	67–68	−16.3 (EtOH)[b]	176
$(EtO)_3Si(CH_2)_4$	Me	OTs	—	−11.5 (benzene)	176
$-(CH_2)_4-$		OMs	90–91	−11.8 ($CHCl_3$)[b]	177
$-(CH_2)_4-$		OTs	117–118	—	17
$-(CH_2)_4-$		NH_2	—	—	17
$-(CH_2)_4-$		N_3	—	−122.9 (Me_2CO)	17
$-(CH_2)_5-$		OH	53–54	−3.35 (EtOH)	34,177–179
$-(CH_2)_5-$		OMs	95.5–97	−20.4 (Me2CO)	4,178
$-(CH_2)_5-$		OTs	107.5–108	−13.8 ($CHCl_3$)	157,177
$-(CH_2)_5-$		NH_2	—	—	17
$-(CH_2)_5-$		N_3	—	−122.5 (Me_2CO)	17
$-(CH_2)_5-$		NMeEt	—	−8.3 (CH_2Cl_2)	180

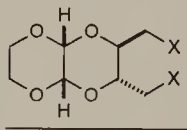
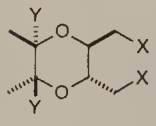
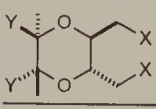
(*continued*)

Table 13.8 (*continued*)

R^1	R^2	X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
$-(CH_2)_5-$		SEt	—	-7.3 ($CHCl_3$)	180
$-(CH_2)_5-$		SPh	—	$+15.7$ (CH_2Cl_2)	180
$-(CH_2)_3CH{=}CH-$		OH	77–78	$+17.7$ ($CHCl_3$)	181
5α-cholestan-3,3-ylidene		OH	199–200	$+13.9$ (dioxane)	182
5α-cholestan-3,3-ylidene		OTs	122–125	—	182
Ph	Me	OTs	166–169	-11.0 ($CHCl_3$)	159
Ph	CH_2OAc	OTs	79–80	$+1.3$ ($CHCl_3$)	159
Ph	CH_2OH	OTs	154–155	-12.5 ($CHCl_3$)	159
$PhS(CH_2)_2$	Me	OH	60–61	$+10.8$ ($CHCl_3$)	183
$PhSO_2(CH_2)_2$	Me	OTs	98–100	-3.3 ($CHCl_3$)	183
Ph	Ph	OTs	121–122	-6.4 (benzene)	87,184
9,9′-xanthenylidene		OTs	—	—	87

[a] For 1,4-phosphine substituted derivatives see Tables 13.10 and 13.11.
[b] At 546 nm.
[c] $[\alpha]_D$ +7.4 in $CHCl_3$[137].
[d] For an apparently isomorphic substance m.p. 78.5–80°C was reported[108].

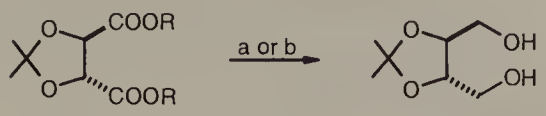
Table 13.9 1,4-Dioxane-type acetals of 2,3-diprotected L-threitol and derivatives

Formula	X	Y	m.p. (°C)	$[\alpha]_D$ (solvent)	References
	OH	—	90–91	-86.2 ($CHCl_3$)	185
	OTs	—	188–189	-38.9 ($CHCl_3$)	185
	I	—	148	-88.3 ($CHCl_3$)	185
	OTs	H	138	-7.0 ($CHCl_3$)	186
	PPh_2	H	81	-77.5 (THF)	186
	OH	OMe	121	-170.2 ($CHCl_3$)	187,188
	OH	OEt	121	-136.2 ($CHCl_3$)	187,188
	OTs	OMe	126	-93.8 (THF)	187
	OTs	OEt	64	-74.0 (THF)	187
	PPh_2	OMe	73	-125.6 (THF)	187
	PPh_2	OEt	99	-98.0 ($CHCl_3$)	187
	OH	OMe	74	$+100.4$ ($CHCl_3$)	188
	OH	OEt	64	$+68.1$ ($CHCl_3$)	188

Synthesis

Symmetrically substituted 2,3-acetals. 2,3-*O*-Isopropylidene protected threitol **13.77** is readily available by reduction of 2,3-*O*-isopropylidene tartrates with

either $LiAlH_4$ or $NaBH_4$; in the latter case the successful reduction of the ester group is made possible by the activating effect of the α-C–O bonds. (Scheme 13.60).



13.77

a (R = Me): $LiAlH_4$, Et_2O, Δ (59-88%)[165,189-192]

(R = Et): $LiAlH_4$, Et_2O, Δ (63-87%)[4,132,164,169,193]

b (R = Me): excess $NaBH_4$, MeOH, RT (89%)[194]

(R = Et): $NaBH_4$, EtOH (99%), 0°C → RT (65-69%)[171,195]

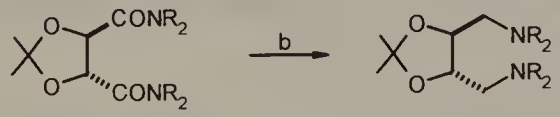
Scheme 13.60

Other 2,3-acetals of (substituted) threitol can be obtained similarly from suitably protected tartrates and tartramides (Scheme 13.61).

R = H (97%)[51]

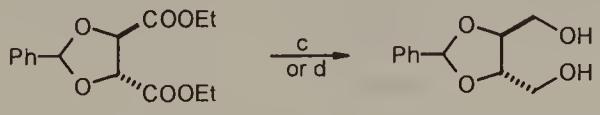
R,R = $(CH_2)_5$ (74%)[34,178,179]

a: $LiAlH_4$, THF, 0°C or $LiAlH_4$, Et_2O, Δ



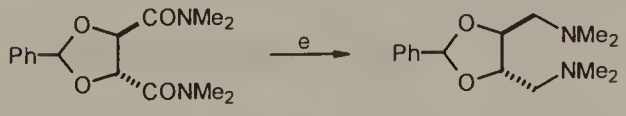
R = H[152], Me[5]

b: $LiAlH_4$, THF, Δ



c: $LiAlH_4$, THF, Δ (85%)[3,137,147]

d: $NaBH_4$, EtOH, 0°C (82%)[26]

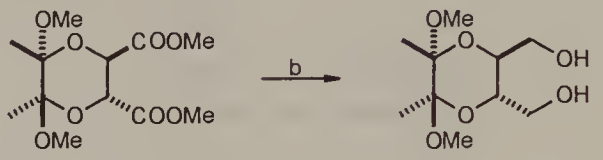


e: $NaH_2Al(OCH_2CH_2OMe)$[196]

Scheme 13.61

The reduction can also be applied to other acetal and orthoester derivatives of tartrates to give the corresponding 2,3-diprotected threitols (Scheme 13.62).

a: $LiAlH_4$, THF, 0°C[138,138]



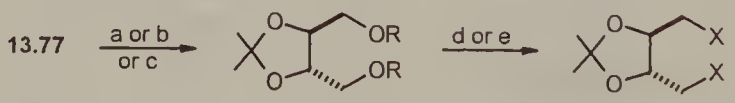
b: $LiAlH_4$,THF, Δ, 3h (95%)[188]

R = MOM (85-97%)[51,197-200]
ME (86-88%)[77]
EE (95%)[83]
THP (73-92%)[78,127]

c: $LiAlH_4$, THF or Et_2O

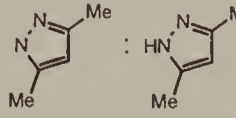
Scheme 13.62

After activation by mesylation (**13.78**), tosylation (**13.79**), or trifylation (**13.80**), derivative **13.77** was used as a substrate for the preparation of numerous threitol substitution products (Scheme 13.63).



13.78 R = Ms
13.79 R = Ts
13.80 R = Tf

a: MsCl, NEt_3 or pyridine, RT (75 → 82%)[4,167,168]
b: TsCl, pyridine, -15°→ -25°C, 18h (94%)[24,163,166,169]
c: Tf_2O, pyridine, CH_2Cl_2, -15°C[201]

d (from **13.78**) X =  , NaH, MeCN, 50°C (85%)[23]

X = SPh: Ph_2S_2, KBH_4, i-PrOH, RT (86%)[23]

Scheme 13.63 *(continued)*

e (from **13.79**) X = $N(CH_2)_5$: piperidine, 3h, 60°C, then 12h, RT (88%)[13]

X = Ph_2As: Na-K, Ph_3As, dioxane-PhMe, RT (66%)[169]

X = SAc: AcSK, EtOH, Δ[24]

X = SBn: BnSH, NaOH, EtOH-THF, Δ (92%)[25]

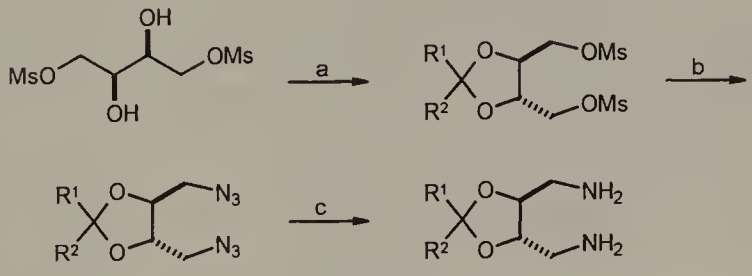
X = F: KF, $HOCH_2CH_2OH$, 130°C (63%)[174]

X = Cl or Br: LiCl or LiBr, DMSO or DMF, 55-60°C (88-95%)[170,174]

X = I: NaI, Me_2CO, Δ (96%)[163,164,166]

Scheme 13.63

2,3-Acetal diprotected threitol derivatives can be prepared by acetalization of 1,4-bis-*O*-mesyl threitol followed by the usual substitution procedures[4,17] (Scheme 13.64).



a [R^1 = i-Pr, R^2 = H]: i-PrCHO, $CuSO_4$, MsOH (cat.), PhMe, RT (98%)[17]

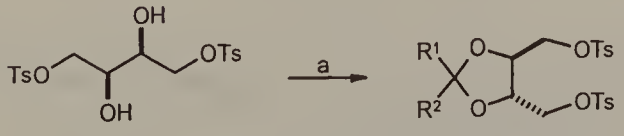
[R^1, R^2 = $(CH_2)_4$]: cyclopentanone, MsOH (cat.), benzene, Δ (89%)[17]

b: 4 eq. NaN_3, DMF, 100°C (90-98%)[17]

c: H_2, 10% Pd/C (cat.), EtOH, 50 psi, 40°C (93-99%)[17]

Scheme 13.64

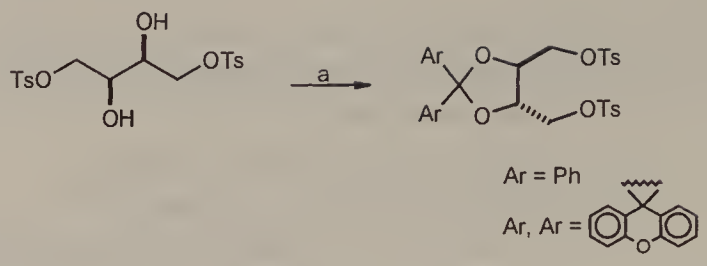
Similar acetalization reactions are known for 1,4-bis-*O*-tosyl threitol;[162] they can also be accomplished by the Noyori method, as shown in Scheme 13.65.



a: 1 eq. R_1R_2CO, TMSOTf, $CHCl_3$, RT (60-89%)[159]

Scheme 13.65

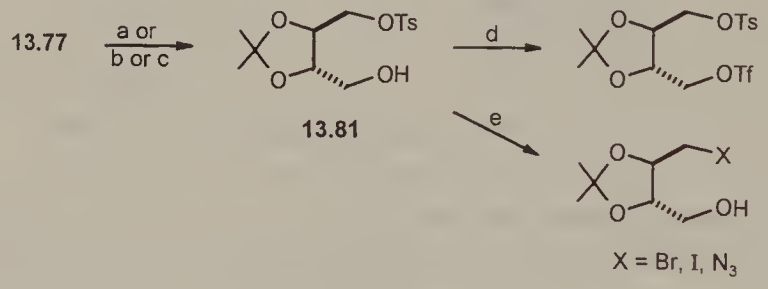
2,3-Acetal diprotected threitol derivatives bearing two aryl groups are available from the corresponding diaryl dichloromethanes[184,202] (Scheme 13.66).



a: Ar_2CCl_2, o-dichlorobenzene, Δ

Scheme 13.66

Unsymmetrically substituted 2,3-acetals. The mono-*O*-tosyl derivative of 2,3-*O*-isopropylidene threitol (**13.81**) is available by tosylation of **13.77** with one equivalent of tosyl chloride, reaction (a). The mono-*O*-tosylation procedure is more efficient when conducted under phase-transfer conditions (b), or when diol **13.77** is ionized with one equivalent of n-butyllithium (c). The tosyloxy group of **13.81** can be substituted by the bromide, iodide, or azide nucleophiles. The hydroxy group of the mono-*O*-tosyl derivative **13.81** can be triflate-activated for further substitution (d) by the procedure of Kotsuki[203,204] (Scheme 13.67).



a: 1 eq. TsCl, pyridine (54.5% + **13.79**, 14.8%)[50,75,205-207]

b: 1.1 eq. TsCl, 1.1 eq. 15% NaOH, CH_2Cl_2, n-$Bu_4N{\cdot}HSO_4$ (cat.), 89%[190]

c: 1.1 eq. n-BuLi, 1.1 eq. TsCl, THF-DMSO, -15°C → RT (89%)[203,208]

d: Tf_2O, NEt_3, CH_2Cl_2, -15°C[203,204]

e: LiBr or NaI, pyridine (cat.), Me_2CO, 100°C[205] or NaN_3, DMF (88%)[209]

Scheme 13.67

2,3-*O*-Isopropylidene-D-threitol can be alternatively obtained from D-mannitol (see for example refs. 141 and 148).

The following are commercially available:

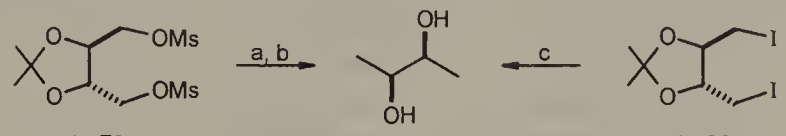
2,3-*O*-benzylidene-L-threitol [*35572-34-0*] and its enantiomer [*58383-35-0*]

2,3-*O*-isopropylidene-L-threitol [*50622-09-8*] and its enantiomer [*73346-74-4*]

1,4-di-*O*-tosyl-2,3-*O*-isopropylidene-L-threitol [*37002-45-2*] and its enantiomer [*51064-65-4*].

Applications

1,4-Activated 2,3-acetals of threitol are widely used as chiral bulding blocks. An important application is the synthesis of *threo*-2,3-butanediol in the optically active form. Thus (*S*,*S*)-2,3-butanediol was obtained either by $LiAlH_4$ reduction of the dimesylate **13.78** or by hydrogenolysis of the diiodide **13.82** followed by hydrolysis of the acetal protecting group (Scheme 13.68).



13.78 **13.82**

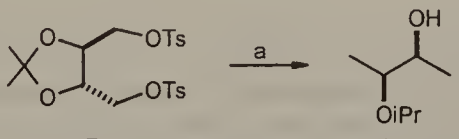
a: $LiAlH_4$, THF, 0°C → RT, 24h, then Δ, 1h (78%)[167]

b: 0.5N HCl, Δ (distill acetone), 91%[167]

c: H_2, Raney nickel, KOAc, MeOH, RT[163,175]

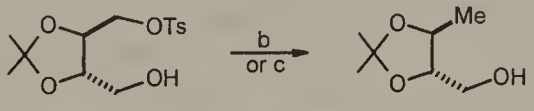
Scheme 13.68

Interestingly, $LiAlH_4$ reduction of the ditosylate **13.79** leads to the cleavage of the acetal function and to the formation of the mono-*O*-isopropyl ether of *threo*-2,3-butanediol (**13.83**). However, monotosylate **13.81** can be effectively reduced with $NaBH_4$ in acetonitrile to (2*S*,3*S*)-2,3-*O*-isopropylidene-1,2,3-butanetriol (**13.84**). This compound has been used for the synthesis of *erythro*-9-[(2*S*)-hydroxy-(3*R*)-nonyl]adenine[210] (Scheme 13.69).



13.79 **13.83**

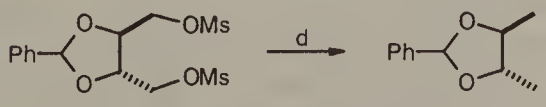
a: $LiAlH_4$, Et_2O, Δ (85%)[6,175]



13.81 **13.84**

b: $NaBH_4$, MeCN, Δ

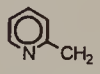
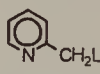
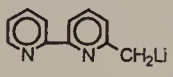
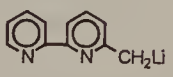
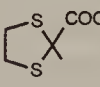
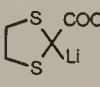
c: NaI, Me_2CO, 100°C then H_2, 10% Pd/C, EtOH (80%)[210]



d: $NaBH_4$, DMSO, 100-140°C, 87%[156]

Scheme 13.69

1,4-Activated 2,3-acetals of threitols react with a variety of carbon nucleophiles, providing access to protected chiral *threo*-diols (Scheme 13.70).

entry	X	R	Nu	yield (%)	ref.
1	OTs	n-Bu	$(n\text{-Bu})_2CuLi$	39	207
2	OTs	Ph	Ph_2CuLi	47	211
3	OTs	1-naphthyl	(1-naphthyl)MgBr	22[a]	142
4	OTs	1-indenyl	(1-indenyl)MgBr	76	212
5	OTf	$n\text{-}C_5H_{11}$	$C_5H_{11}MgBr$	56	213
6	OTf	PhC≡C	PhC≡CLi	55	214
7	OTf			80	215
8	OTf			43	215
9	OTf	$t\text{-BuOOCCH}_2$	$t\text{-BuOOCCH}_2Li$	76	216
10	I	$t\text{-BuOOCCH}_2(O)CCH_2$	$t\text{-BuOC(ONa)=CH(OLi)=CH}_2$	-	217
11	I			47	218

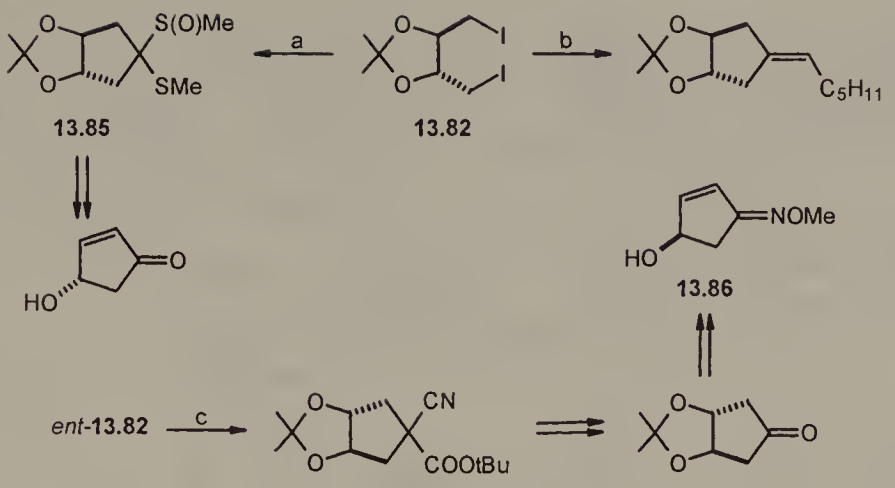
[a] including hydrolysis of the isopropylidene group

Scheme 13.70

Products of the reactions shown in Scheme 13.70 found application in the synthesis of (+)-1,4-diphenyl-2,3-butanediol; a natural diol isolated from bull testicular tissue (entry 2);[211] and the chiral (*R*,*R*)-2,2′-bipyrrolidine derivatives (entry 9).[216] Kotsuki used a reaction analogous to that shown in entry 9 (with 2,3-*O*-benzylidene acetal of D-threitol) to synthesize the cyclohexyl fragment of the immunosuppressant FK-506.[201] Hoye used the reaction of entry 10 in the initial stage of his synthesis of (+)-(15,16,19,20,23,24)-*hexepi*-uvaricin, an analogue of *Annonaceous* acetogenins.[217] Products of entries 9 and 11 can be used for four-carbon extension of the threitol chain.

1,4-Diiodides **13.82** and *ent*-**13.82** as well as 1,4-ditosylate **13.79** react with 1,1- or 1,2-dianions to give five- or six-membered carbocyclic products, respectively, as shown in Scheme 13.71.

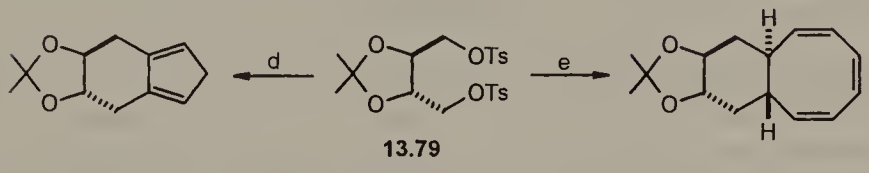
Product **13.85** (mixture of diastereomers) was used by Rokach[166] in the efficient, large-scale synthesis of (*S*)-4-hydroxycyclopent-2-enone, while *O*-methyloxime **13.86** served as a key intermediate in the synthesis of prostaglandins developed by Corey.[221] Revised specific rotation data[224] point, however, to partial racemization of the (*S*)-4-hydroxycyclopent-2-enone prepared by Ogura[219] and Rokach.[166]



a: $MeSCH_2S(O)Me$, n-BuLi, THF, -78°C (58-76%)[166,394]

b: 2 eq. $Ph_3P{=}CH_2$, $(MeSi)_2NNa$, $C_5H_{11}CHO$[220]

c: $NCCH_2COOt\text{-}Bu$, t-BuOK, t-BuOH, 60°C, 18h (77%)[221]

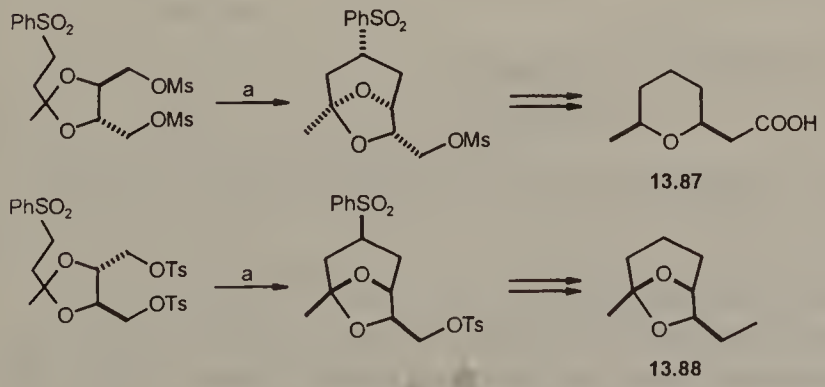


d: cyclopentadiene, NaH, THF, RT, 23h, Δ, 2h (31%)[222]

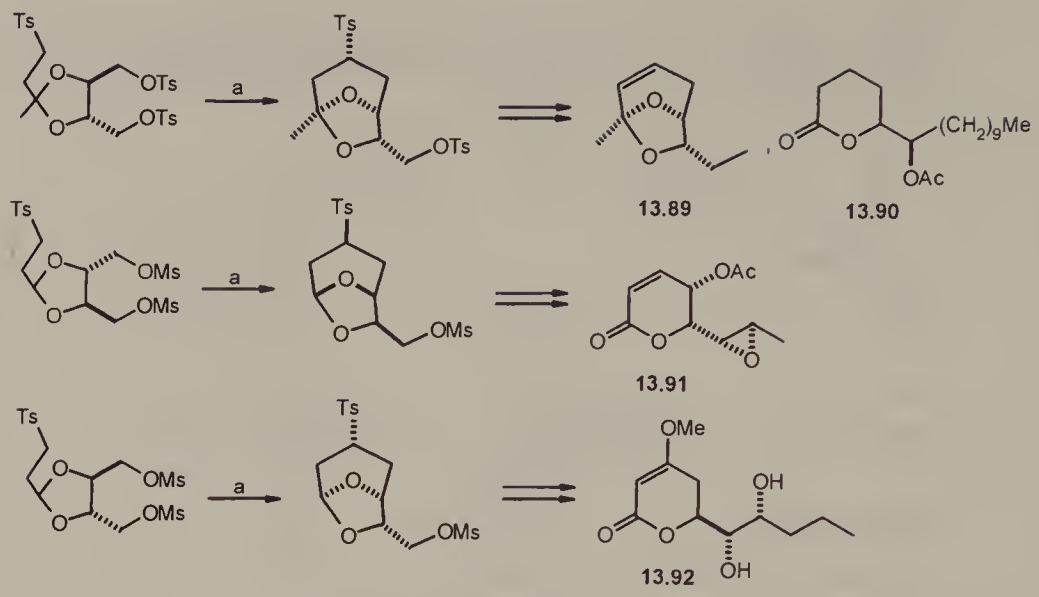
e: cyclooctatetraene, Li, THF, 33°C, 7h (13%)[223]

Scheme 13.71

Masaki has extensively used an intramolecular version of alkylation by a carbon nucleophile generated from the alkylsulfonyl group in the acetal side chain in the synthesis of various naturally occuring compounds (Scheme 13.72).



Scheme 13.72 (*continued*)

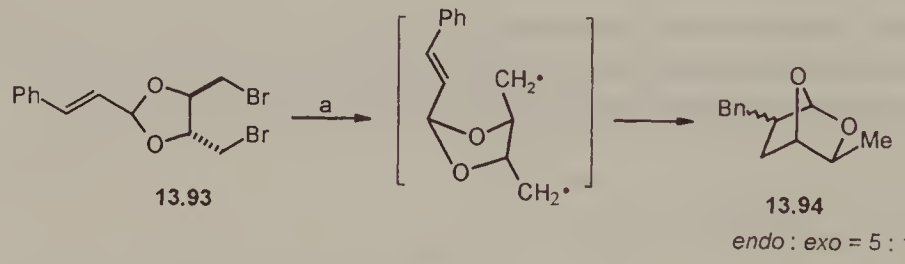


a: 1.2-1.5 eq. n-BuLi, THF, -20°→ 0°C, 1h

Scheme 13.72

Among the products synthesized according to the above scheme are **13.87**, a constituent of civet;[225] *exo*-brevicomin (**13.88**);[183] an optically active form of the house mouse pheromone (**13.89**);[226] a component of a mosquito oviposition attractant pheromone (**13.90**);[227] metabolite (+)-asperlin (**13.91**);[228] and a fungal metabolite LL-P880β (**13.92**).[229] In addition, Masaki reported the synthesis of the hemlock alkaloid (+)-conhydrine.[400]

Intramolecular cyclization of the suitably substituted acetal **13.93**, derived from L-threitol, was induced by a bis-radical intermediate[161] (Scheme 13.73).



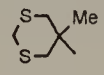
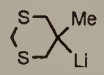
a: 3 eq n-Bu_3SnH, AIBN (cat.), benzene, Δ (87%)

Scheme 13.73

The *exo* product **13.94** was converted by Takano *et al.* to (*S*)-4-benzyl-2-furanone.[230]

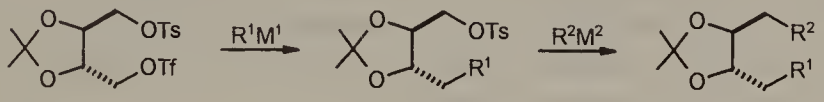
Mono-*O*-tosyl 2,3-acetals of threitol react with carbon nucleophiles to give 2,3-protected *threo*-1,2,3-triols (Scheme 13.74).

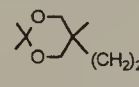
Enantiomers of triol derivatives, entries 2 and 3, were converted, respectively, to (2*R*,3*R*)-2,3-hexanediol (a component of the longhorn beetle male pheromone)[208] and to panaxacol, an anticancer compound of *Panax gingeng*.[214]

entry	R	Nu	yield (%)	ref.
1	Me	Me_2CuLi	90	203
2	Et	EtMgBr, CuBr · Me_2S	83	208
3	n-C_6H_{13}	(n-C_6H_{13})$_2$CuLi	81	214
4	All	AllMgBr, CuBr	83	204
5	4-$BnOC_6H_4$	4-$BnOC_6H_4$MgBr, CuBr	(low)	231
6			77	205

Scheme 13.74

Unsymmetrical activation of the C(1) and C(4) hydroxy groups by the protocol of Kotsuki allows to selectively substitute the *O*-triflate group in the presence of the *O*-tosyl group; the latter can be subsequently substituted by another nucleophile to give a protected unsymmetrical *threo*-diol (Scheme 13.75).



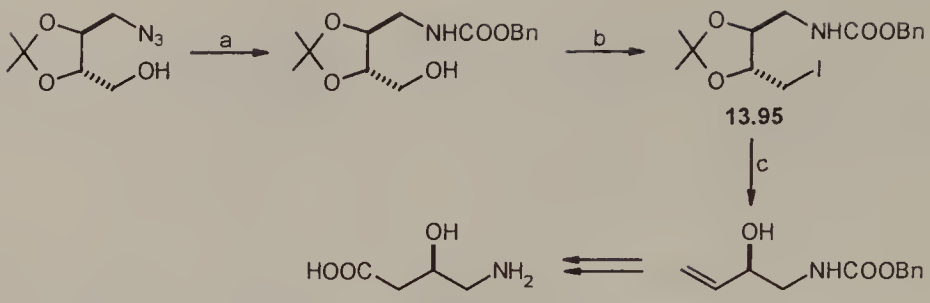
entry	R^1	M^1	R^2	M^2	yield (%)	ref.
1	All	MgBr, CuBr	Ph	[PhCuLi]	33	204
2		MgBr	Me	[MeCuLi]	63	203,232
3	$TBSOCH_2C{\equiv}C$	Li	-	-	88	214
4	4-$BnOC_6H_4$	MgBr, CuBr	-	-	75	231

Scheme 13.75

Some of the compounds obtained according to Scheme 13.75 were used in the synthesis of lateral root inducing compounds (entry 1),[204] (+)-*exo*-brevicomin (entry 2)[203,232] and (+)-diolmycin A2 (entry 4).[231]

One of the syntheses of (*R*)-(−)-γ-amino-β-hydroxybutyric acid (GABOB) is based on the elimination reaction of the iodo substituted acetal **13.95**[209] (Scheme 13.76).

Of potential synthetic interest is the related pyrolysis of formates of 2,3-*O*-isopropylidene threitol which gives, among other elimination products, (*R*)-but-1-ene-3,4-diol; this product can be isolated by flash chromatography[233] (Scheme 13.77).

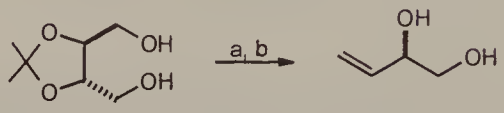


a: H_2, Pd/C, then ClCOOBn, $NaHCO_3$ (80%)

b: TsCl, pyridine, then NaI, Me_2CO (70%)

c: Zn, EtOH (91%)

Scheme 13.76

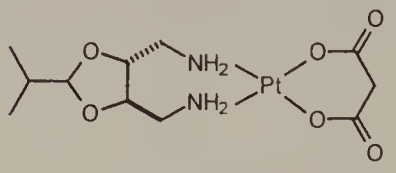


a: HCOOH, Δ (evaporate), then pyrolysis

b: NaOH, H_2O

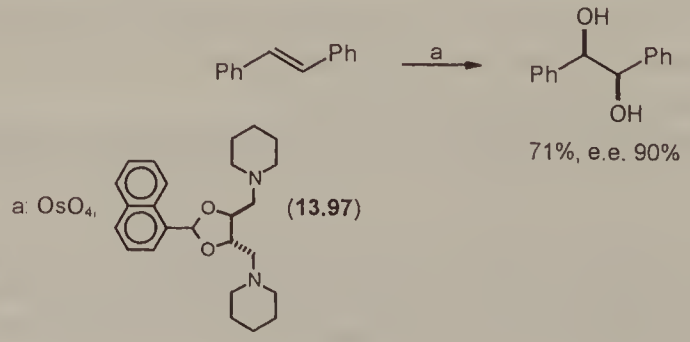
Scheme 13.77

2-Substituted-4,5-bis(aminomethyl)-1,3-dioxolane platinum(II) complexes show excellent antitumor activity against murine L1210 leukemia cells. An example is SKI 2053R (**13.96**) which is characterized additionally by high solubility and stability in aqueous solution.[17,234]



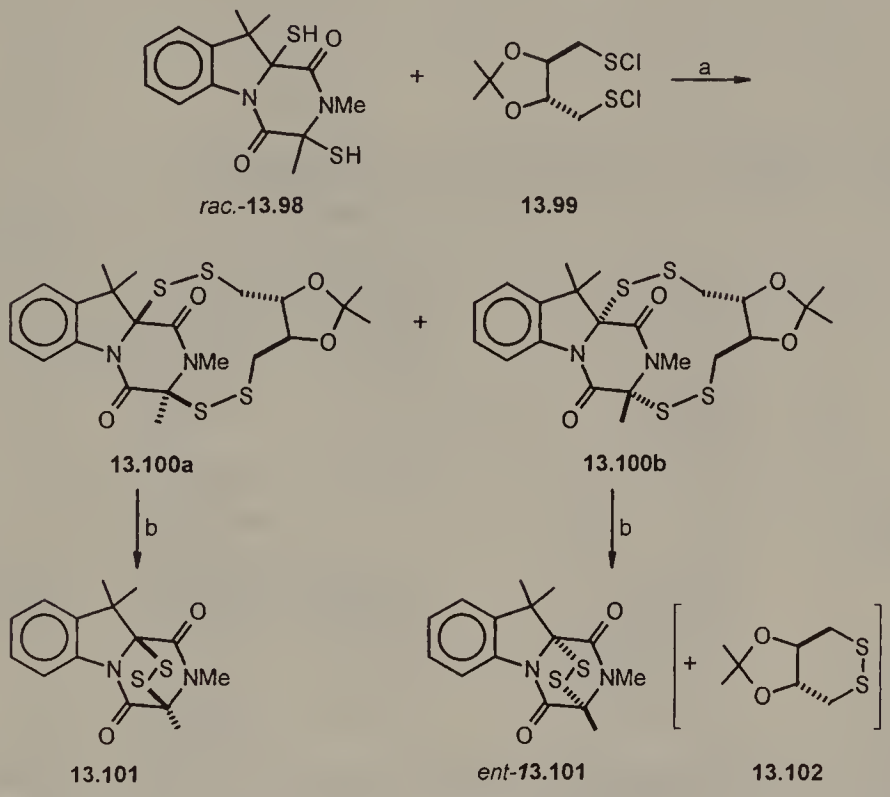
13.96

Narasaka successfully used 1,4-diamino substituted acetal **13.97** as a ligand in the asymmetric dihydroxylation of stilbene [158] (Scheme 13.78).



Scheme 13.78

Racemic dithiol **13.98** was resolved by conversion to a mixture of diastereomeric disulfides **13.100a** and **13.100b**, followed by column chromatography. The disulfides were formed by the reaction of dithiol **13.98** with bis-(sulfenyl chloride) **13.99**. Reduction of **13.100a** and **13.100b** with $NaBH_4$ followed by reoxidation with iodine/pyridine gave disulfides **13.101** and *ent*-**13.101**, analogues of a fungal metabolite dehydrogliotoxin. Disulfide **13.102**, the precursor of the resolving agent **13.99**, was recovered in the process[235] (Scheme 13.79).

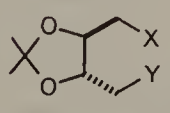


a: 2 eq. pyridine, CCl_4, then column chromatography (28% each)

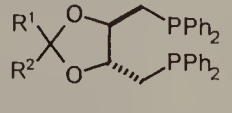
b: $NaBH_4$, EtOH, then I_2, pyridine, CH_2Cl_2 (82%)

Scheme 13.79

13.7.2 Mono- and Diphosphine Ligands Derived from 2,3-Acetals of L-Threitol



IX



X

Overview

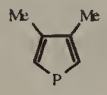
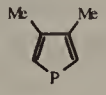
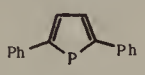
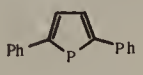
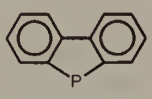
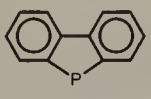
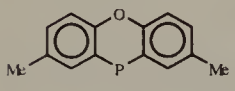
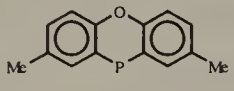
The prototype of the tartrate-based diarylphosphine ligands for asymmetric hydrogenation—DIOP (**IX**: X=Y=PPh_2) has been synthesized by Kagan.[236-238] Compounds structurally related to DIOP are successfully used as ligands for various Rh(I) and Ir(I) catalyzed reactions. A large number of derivatives with structural modifications were prepared with the aim of optimizing the stereochemical efficiency of the ligand (Tables 13.10 and 13.11).

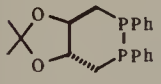
Table 13.10 Analogues of (−)-DIOP and related compounds (IX)

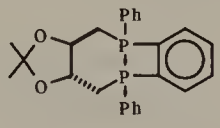
	X	Y	m.p (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
	PEt_2	PEt_2	90–91/0.001	−25.5 ($CHCl_3$)	174
	$Pi\text{-}Pr_2$	$Pi\text{-}Pr_2$	125–130/0.001	−31.0 (benzene)	174
	PCy_2	PCy_2	90–92	−24.1 (benzene)	174
	PCy_2	PPh_2	52.5–54	−24.1 (benzene)	157,239,240
	$P(O)Cy_2$	OH	81–82	+22.2 ($CHCl_3$)	240
	$P(O)Cy_2$	OMs	91.5–92.5	—	240
	PPh_2	Cl	—	−27.5 (benzene)	241
	$P(4\text{-}MeC_6H_4)_2$	Cl	—	−26.5 (benzene)	241
	$P(4\text{-}MeOC_6H_4)_2$	Cl	—	−22.6 (benzene)	241
A	PPh_2	PPh_2	89–90	−12.5 (benzene)	7,169,236,237,242
	$P(O)Ph_2$	$P(O)Ph_2$	218–220	+15.0 ($CHCl_3$)	23,243
	$P(2\text{-}MeC_6H_4)_2$	$P(2\text{-}MeC_6H_4)_2$	—	—	157
	$P(2\text{-}CF_3C_6H_4)_2$	$P(2\text{-}CF_3C_6H_4)_2$	140.6–142.9	−27.0 ($CHCl_3$)	244
B	$P(2\text{-}MeOC_6H_4)_2$	$P(2\text{-}MeOC_6H_4)_2$	147.5–150	−12.5 (benzene)	245,246
	$P(3\text{-}MeC_6H_4)_2$	OTs	—	−24.6 (benzene)	240
	$P(3\text{-}MeC_6H_4)_2$	$P(3\text{-}MeC_6H_4)_2$	100	—	157,170
	$P(3\text{-}CF_3C_6H_4)_2$	$P(3\text{-}CF_3C_6H_4)_2$	—	+3.2 (toluene)	184
	$P(3\text{-}MeOC_6H_4)_2$	$P(3\text{-}MeOC_6H_4)_2$	—	−10.4 (benzene)	245
	$P(3\text{-}ClC_6H_4)_2$	$P(3\text{-}ClC_6H_4)_2$	—	−4.5 (benzene)	245
	$P(4\text{-}MeC_6H_4)_2$	PPh_2	—	−6.6 (benzene)	162,241
	$P(4\text{-}MeC_6H_4)_2$	$P(4\text{-}MeC_6H_4)_2$	80.5–82	+2.1 (benzene)	242,247
	$P(4\text{-}MeOC_6H_4)_2$	PPh_2	—	−6.2 (benzene)	162,240,241
	$P(4\text{-}MeOC_6H_4)_2$	$P(4\text{-}MeC_6H_4)_2$	—	−1.2 (benzene)	241
	$P(4\text{-}MeOC_6H_4)_2$	$P(4\text{-}MeOC_6H_4)_2$	84–86.5	−13.3 ($CHCl_3$)	240,242
	$P(4\text{-}Me_2NC_6H_4)_2$	PPh_2	—	−1.7 (benzene)	240
	$P(4\text{-}Me_2NC_6H_4)_2$	$P(3\text{-}MeC_6H_4)_2$	—	+8.4 (benzene)	240
	$P(4\text{-}Me_2NC_6H_4)_2$	$P(4\text{-}Me_2NC_6H_4)_2$	78	+23.5 (benzene)	240,242,248
	$P(4\text{-}Me_3SiC_6H_4)_2$	PPh_2	—	−1.1 (benzene)	241
	$P(4\text{-}Me_3SiC_6H_4)_2$	$P(4\text{-}MeC_6H_4)_2$	—	+5.1 (benzene)	241
	$P(4\text{-}Me_3SiC_6H_4)_2$	$P(4\text{-}MeOC_6H_4)_2$	92–99	+6.1 (benzene)	241
	$P(4\text{-}Me_3SiC_6H_4)_2$	$P(4\text{-}Me_3SiC_6H_4)_2$	78–83	+10.8 (benzene)	242
	$P(2,5\text{-}Me_2C_6H_3)_2$	$P(2,5\text{-}Me_2C_6H_3)_2$	66–68	—	157
	$P(3,4\text{-}Me_2C_6H_3)_2$	$P(3,4\text{-}Me_2C_6H_3)_2$	—	+7.4 (benzene)	245
	$P(3,5\text{-}Me_2C_6H_3)_2$	$P(3,5\text{-}Me_2C_6H_3)_2$	—	+1.9 (benzene)	245
C	$P(3,5\text{-}Me_2,4\text{-}MeOC_6H_2)_2$	$P(3,5\text{-}Me_2,4\text{-}MeOC_6H_2)_2$	128–129	+14.4 (benzene)	240,249

(*continued*)

Table 13.10 (*continued*)

X	Y	m.p (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
$P(3,5\text{-}Me_2,4Me_2NC_6H_2)_2$	$P(3,5\text{-}Me_2,4\text{-}Me_2NC_6H_2)_2$	—	+25.7 (benzene)	250
$P(1\text{-naphthyl})_2$	PPh_2	—	—	162
$P(2\text{-naphthyl})_2$	PPh_2	—	—	162
$P(1\text{-naphthyl})_2$	$P(1\text{-naphthyl})_2$	104–106	−0.46 (benzene)	184
$P(2\text{-naphthyl})_2$	$P(2\text{-naphthyl})_2$	110–125	+13.9 (benzene)	184
		—	+16.0 ($CHCl_3$)	251
		58	−15.1 ($CHCl_3$)	252,253
		192–193	−66.0 (benzene)	157,184,254
		—	−43.1 (toluene)	184
	a	114–116	−643.0 (benzene)	255
	b	156–157	−26.1 ($CDCl_3$)	256
	c	—	—	257

a 

b 

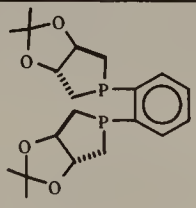
c 

Table 13.11 1,4-Dideoxy-1,4-bis(diphenylphosphino) substituted 2,3-acetals of L-threitol (X)

R^1	R^2	m.p. (°C)	$[\alpha]_D$ (solvent)	References
$2\text{-}HOC_6H_4$	H	—	−20.5 ($CHCl_3$)	159
$4\text{-}HOC_6H_4$	H	—	−1.0 ($CHCl_3$)	159
$4\text{-}(CH_2{=}CH)C_6H_4$	H	—	−29.2 (benzene)	21
2-naphthyl	H	122–123	−48.8 (benzene)	162
1-pyrenyl	H	158.5–159.1	−70.0 (benzene)	162
CH_2OH	Me	—	−22.6 ($CHCl_3$)	159
$i\text{-}Pr(CH_2)_3CH(Me)(CH_2)_3$	Me	—	−13.5 (hexane)	258
$(EtO)_3Si(CH_2)_4$	Me	—	−15.1 (benzene)	176
$-(CH_2)_4-$		90–91.5	−19.9 (benzene)	177
$-(CH_2)_5-$		118.5–120	−19.6 (benzene)	177
5α-cholestan-3,3-ylidene		137–140	−17.7 (dioxane)	182
Ph	Me	—	−40.4 ($CHCl_3$)	159
Ph	CH_2OH	38–42	−30 ($CHCl_3$)	159,259
Ph	Ph	135–137	−40.4 (benzene)	184

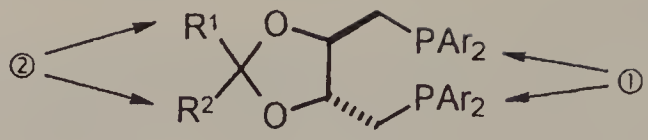
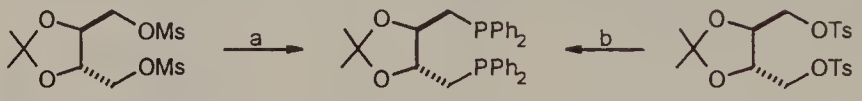


Figure 13.2

These modifications addressed the steric and electronic properties of the ligating phosphorous atoms by changing the aryl substituents (① in Fig.13.2) and the conformation of the seven-membered chelate ring, that is, the dihedral "bite" angle associated with ligation, by altering the acetal substituents (② in Fig. 13.2).

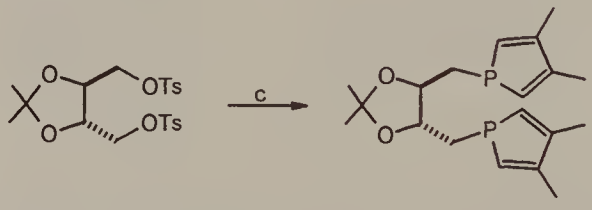
Synthesis

The important diphosphine ligands are available by nucleophilic substitution of the corresponding 1,4-activated 2,3-acetals of threitol, that is, bis-mesylate, bis-tosylate, difluoride, and dichloride derivatives (Scheme 13.80).

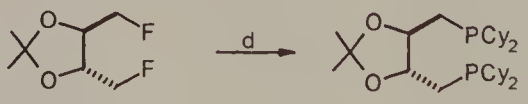


a: $Ph_2P(BH_3)Li$, THF, RT, then DABCO, PhMe, 40°C (80%)[168]

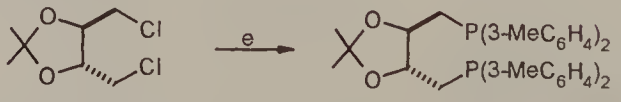
b: Ph_3P, Na-K, dioxane-PhMe, RT (72%)[169]



c:  PPh , Li, t-BuCl, THF (71%)[251]



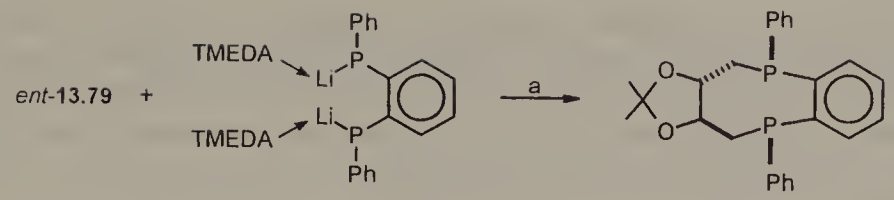
d: Cy_2PLi, dioxane, 35°C (74%)[174]



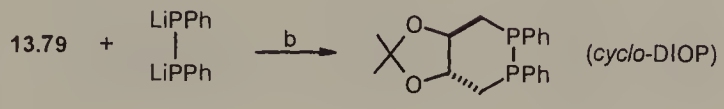
e: 2 eq. $(3\text{-}MeC_6H_4)_2PLi$, THF, -70°C → RT (87%)[170]

Scheme 13.80

Cyclic diphosphines **13.104** and **13.106** have been obtained by the reactions of bis-*O*-tosyl derivatives *ent*-**13.79** and **13.79** with dilithiodiphosphides **13.103** and **13.105**, respectively (Scheme 13.81).



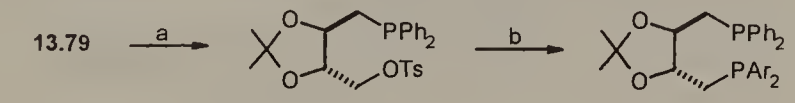
a: THF, RT (75%)[256]



b: THF, 35°C (57%)[255]

Scheme 13.81

Unsymmetrical 1,4-dideoxy-1,4-bis(diarylphosphino) substituted 2,3-*O*-isopropylidene threitols can be obtained with moderate yield by sequential substitution of the 1,4-bis-*O*-tosyl derivative **13.79** (Scheme 13.82).

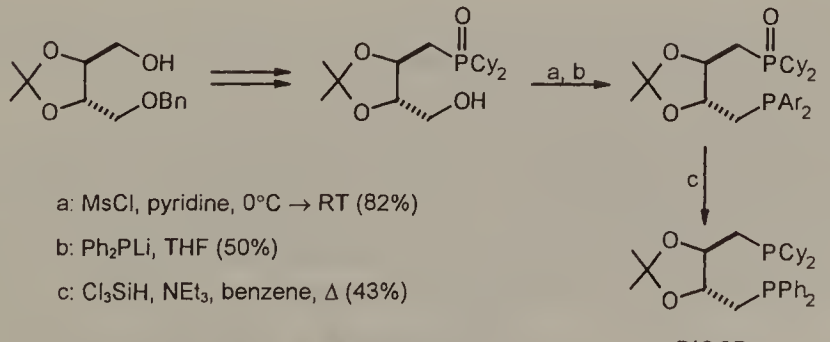


a: 0.5 eq. Ph_2PLi, THF (44-49%)

b: Ar_2PLi, THF (25-68%)[162,240]

Scheme 13.82

Another route to unsymmetrical 2,3-*O*-isopropylidene threitol derived diphosphines starts with triprotected 1-*O*-benzyl-2,3-*O*-isopropylidene threitol. By sequential substitution and removal of the *O*-benzyl protecting group unsymmetrical diphosphine ligand for Rh(I) catalyzed asymmetric hydrogenations, DIOCP, was obtained[239,240] (Scheme 13.83).



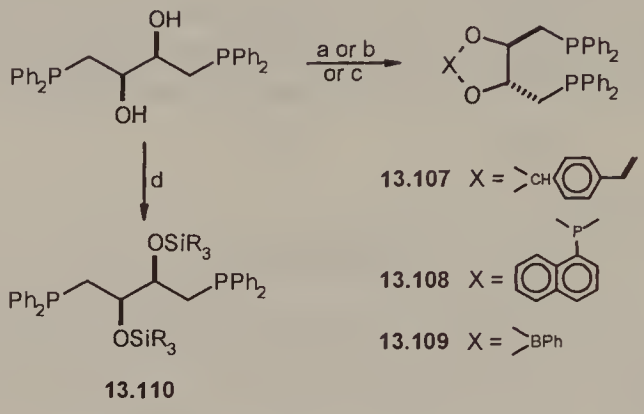
a: MsCl, pyridine, 0°C → RT (82%)

b: Ph_2PLi, THF (50%)

c: Cl_3SiH, NEt_3, benzene, Δ (43%)

Scheme 13.83

1,4-Dideoxy-1,4-bis(diphenylphosphino) L-threitol was used to synthesize analogues of DIOP, both acyclic (**13.110**), and with the modified acetal ring (**13.107**), or with additional phosphorous (**13.108**) or boron (**13.109**) functionalities (Scheme 13.84). In the 2,3-bis(siloxy) substituted analogue **13.110** (R_3Si = TBS) the two siloxy groups occupy *anti* positions, as shown by the X-ray structure analysis.[260]



13.110

a: 4-(CH_2=CH)C_6H_4CHO, mol. sieves 4Å, TsOH (cat.), benzene, Δ (60%)[21]

b: 1-naphthyl-$OPCl_2$, NEt_3, Et_2O, RT (45%)[261]

c: $PhBCl_2$, CH_2Cl_2, -78°C → RT (87%)[22] or $PhB(OH)_2$, THF, RT (84%)[262]

d: 3-4 eq. R_3SiOTf, 5 eq. NEt_3, CH_2Cl_2, RT (58-90%)[260]

Scheme 13.84

The following are commercially available:

(+)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane, (+)-DIOP [*37002-48-5*], and its enantiomer, (−)-DIOP [*32305-98-9*].

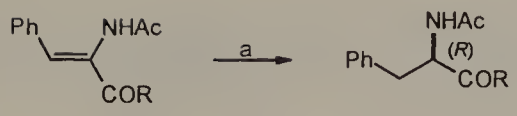
Applications

L

Chiral DIOP-type ligands are widely used for homogeneous asymmetric hydrogenation reactions of alkenes, imines, and reactive carbonyl compounds, using Rh(I) or Ir(I) catalysts. Some examples are shown in Scheme 13.85.

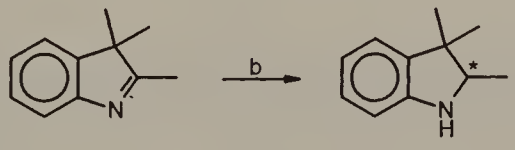
Modified diphosphine ligands in Rh^+ catalyzed hydrogenation show decreasing enantioselectivity approximately in the order (shown with positions of substituents in the phenyl ring) 4-MeO > H > 3-Me > 4-Me_2N > 4-MeO, 3,5-Me_2.[85] Interestingly, Brown found that 2-methoxy substitution in DIOP causes a reversal of configuration in asymmetric hydrogenation of enamides[246] (Scheme 13.86).

Other enantioselective reactions catalyzed by the Rh(I)-diphosphine ligand system include hydroboration and [4+2] cycloaddition (Scheme 13.87).



R	diphosphine ligand (tables 13.10, 13.11)	e.e.(%)	ref.
OH	**A**, (-)-DIOP	72	237
OiPr	**A**, (-)-DIOP	85	162
NH_2	**A**, (-)-DIOP	71	237
(*S*)-HNCH(Me)COOMe	**A**, (-)-DIOP	94	162
OH	**E**, (-)-DIOCOL	93	182

R^1	R^2	diphosphine ligand (Table 13.10)	e.e.(%)	ref.
H	OH	**C**, (+)-MOD-DIOP	86	249
Ph	OH	**C**, (+)-MOD-DIOP	70	249
(3,4-OCH_2O)C_6H_3	OMe	**C**, (+)-MOD-DIOP	94	249
(3,4-OCH_2O)C_6H_3	OMe	**D**, (+)-XYL-DIOP	94	240,250

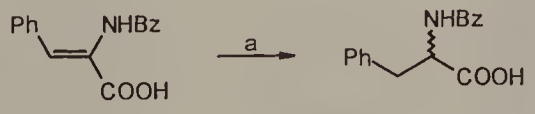


e.e. 81.4%,
(+)-enantiomer

a: H_2, [Rh(COD)Cl]$_2$, diphosphine ligand

b: H_2 (100 atm.), [Ir(COD)Cl], ligand **C**, n-Bu_4NI, benzene-MeOH, RT[263]

Scheme 13.85

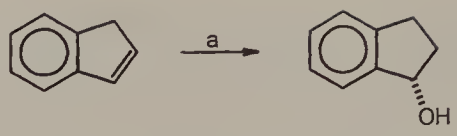


ligand **A:** (*R*), e.e. 70%

ligand **B:** (*S*), e.e. 66%

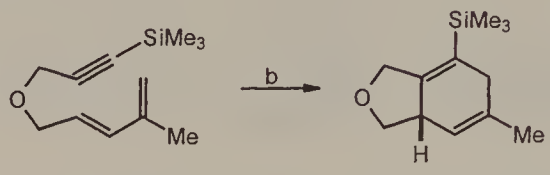
a: H_2, [Rh^+(norbornadiene)BF_4^-]

Scheme 13.86



e.e. 74%

a: catecholborane, 0.01 eq. $[Rh(COD)Cl]_2$, 0.02 eq. ligand **A**, PhMe, -30°C then H_2O_2, aq. NaOH, 0°→ RT[264]

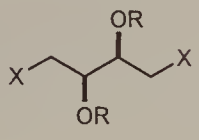


e.e. 87%

b: 0.025 eq. $[Rh(COD)Cl]_2$, 0.06 eq. ligand **F**, CF_3CH_2OH, CH_2Cl_2, 55°C[244]

Scheme 13.87

13.7.3 2,3-Di-*O*-Alkyl and 2,3-Di-*O*-Silyl L-Threitols



XI

Table 13.12 Symmetrical 2,3-*O*-dialkyl and 2,3-*O*-disilyl protected L-threitol derivatives (XI)

R	X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
Me	OH	39–41	+9.0 (EtOH)	73,265–267
Me	OTs	65	+9.6 ($CHCl_3$)	265–268
Me	Br	96–99/5	+7.0 (neat)[a]	268
Me	I	73–75/0.05	−7.9 ($CHCl_3$)	265,269
Me	N_3	71–73/0.1	+19.8 ($CHCl_3$)	267
Me	NH_2	58–62/0.1	−23.1 ($CHCl_3$)	267
Me	NHMe	70/6	−10.9 (neat)	5
Me	NHEt	76/5	−10.2 (neat)	5
Me	NHBz	135	−10.9 (EtOH)	269
Me	NMe_2	62–64/2	+14.7 (neat)	270
Me	NMeEt	—	+23.9 (benzene)	271
Me	NEt_2	—	+23.4 (benzene)	271
Me	$N(CH_2)_4$	80–81/0.01	+5.8 (neat)	5
Me	PPh_2	—	+4.0 (benzene)	236
Me	SMe	62/0.05	+29.5 (neat)	5
Et	OH	95/0.8	+43.6 (Me_2CO)	272
Et	NH_2	104–106/7	−39.2 ($CHCl_3$)	272

(continued)

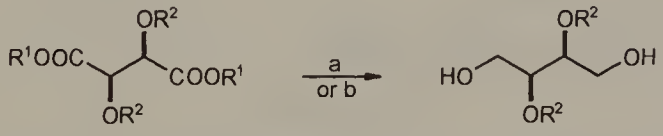
Table 13.12 (*continued*)

R	X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
Et	NHTs	110–112	−5.9 ($CHCl_3$)	272
Bn	OH	50–52	+17.3 ($CHCl_3$)	273–276
Bn	OTs	121	+14.6 ($CHCl_3$)	273
Bn	Br	—	+11.7 ($CHCl_3$)	273
$C_{18}H_{37}$	NMe_2	34.5	+3.9 ($CHCl_3$)	5
$[(CH_2)_2O]_2Me$	OTs	—	+0.3 ($CHCl_3$)	274
$[(CH_2)_2O]_2Me$	SH	240/1	+10.0 ($CHCl_3$)	274
$(CH_2)_2NMe$	NMe_2	—	−33.3 (MeOH)	271
MOM	OH	62–63	−7.7 (MeOH)	54,197
Bz	NHBz	157–158	−28.5 (DMF)	20
$SiMe_3$	OTs	—	−14.4 ($CHCl_3$)	159
$SiMe_2$t-Bu	OH	—	—	277
$SiMe_3$	PPh_2	44–46	−10.2 ($CHCl_3$)	260
$SiMe_2$t-Bu	PPh_2	95–97	−13.4 ($CHCl_3$)	260
$Si(i\text{-}Pr)_3$	PPh_2	73–75	+63.8 ($CHCl_3$)	260
$SiPh_3$	PPh_2	118–119	+10.1 ($CHCl_3$)	260

[a] At 546 nm.

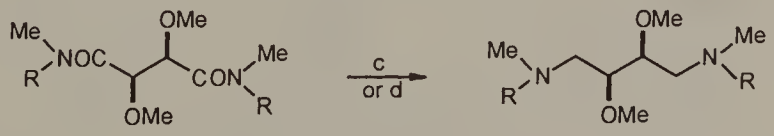
Synthesis

2,3-Di-*O*-alkyl or di-*O*-silyl protected threitol derivatives are readily prepared from the corresponding 2,3-di-*O*-protected tartrates and tartramides by $LiAlH_4$ reduction (Scheme 13.88).



a (R^1 = Me, Et; R^2 = Me, Et, Bn): $LiAlH_4$, Et_2O, RT to reflux (62-87%)[5,265-267,272,273]

b (R^1 = Et; R^2 = TBS): 6 eq. $LiEt_3BH$, THF, 0°C (75%)[277]

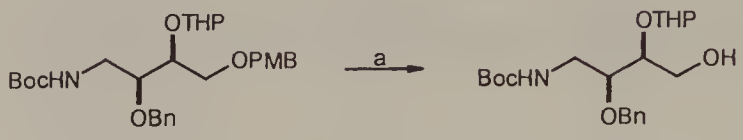


c (R = H): $LiAlH_4$, dioxane, Δ, (39%)[5]

d (R = Me): $LiAlH_4$, THF, Δ, (88-90%)[5,270]

Scheme 13.88

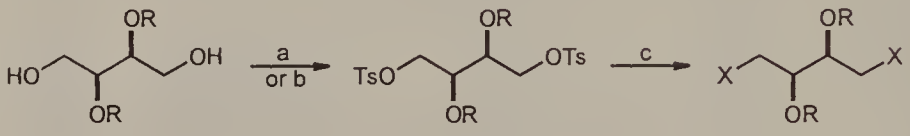
Selective removal of the protecting group(s) from tri- or tetra-*O*-protected threitols constitutes another method of preparing 2,3-di-*O*-protected threitol derivatives (Scheme 13.89).



a: DDQ, CH_2Cl_2-H_2O (18:1), RT, 0.5h (95%)[82]

Scheme 13.89

1,4-Diactivated derivatives are available through tosylation of the 2,3-diprotected threitols (Scheme 13.90).



a (R = Me): TsCl, pyridine, -20°C → RT (79-95%)[5,265,266]

b (R = Bn): TsCl, pyridine, -5°C → 0°C (86%)[273]

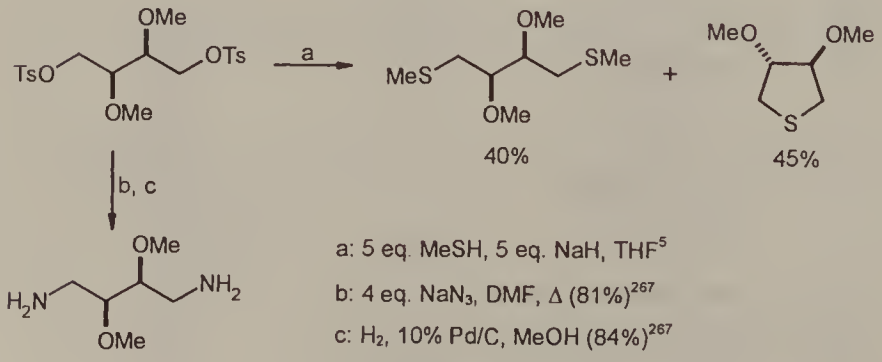
c (R = Me): LiBr or LiI, Me_2CO, Δ (91-92%)[268,278]

Scheme 13.90

2,3-Bis-*O*-trimethylsilyl-1,4-di-*O*-tosyl threitol is available from 1,4-di-*O*-tosyl threitol (Scheme 13.91).

a: TMSCl, HMDS, CH_2Cl_2, RT (82%)[159]

Scheme 13.91



a: 5 eq. MeSH, 5 eq. NaH, THF[5]

b: 4 eq. NaN_3, DMF, Δ (81%)[267]

c: H_2, 10% Pd/C, MeOH (84%)[267]

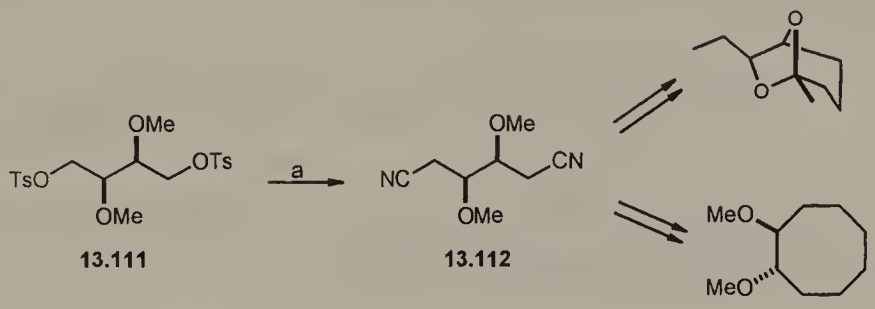
Scheme 13.92

1,4-Di-*O*-tosyl derivatives of threitol react with N- or S-nucleophiles to give acyclic or cyclic substitution products (Scheme 13.92).

(*S*,*S*)-2,3-Dimethoxy-1,4-bis(dimethylamino)butane [*26549-21-3*] is available commercially.

Applications

Dinitrile **13.112**, obtained by substitution of ditosylate **13.111** with a cyanide ion, served as an intermediate in the syntheses of (1*S*,2*S*)-1,2-dimethoxycyclooctane (Cope[265]) and of the enantiomer of natural (+)-*exo*-brevicomin (Mori[266]), Scheme 13.93.



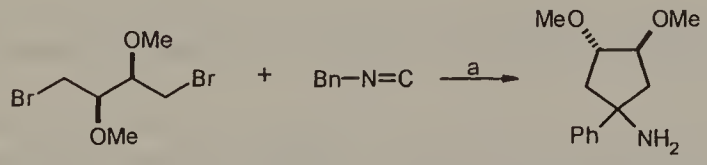
13.111 **13.112**

a: NaCN, DMSO, RT, 6d (65-78%)

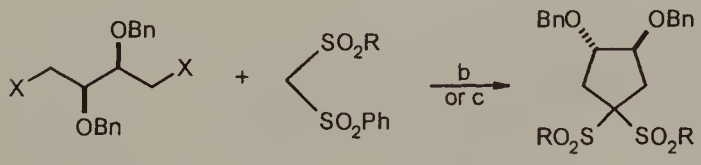
Scheme 13.93

These syntheses helped to establish the absolute configuration of the target compounds.

Unlike the 2,3-acetal protection, 2,3-di-*O*-alkyl protection makes it feasible to carry out one-step synthesis of functionalized cyclopentane derivatives from 1,4-diactivated threitols (Scheme 13.94).



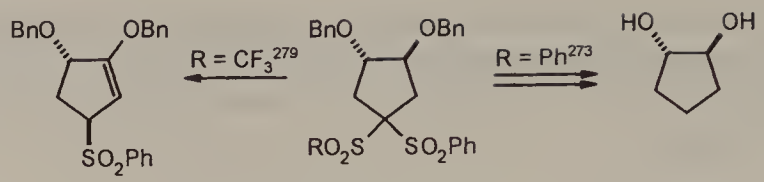
a: 2 eq. LDA, THF, -60°C, then HCl-MeOH, -55°C, then 20% NaOH (55%)[268]



b (X = Br, R = Ph): K_2CO_3, DMF, 75°C, 20h (92%)[273]

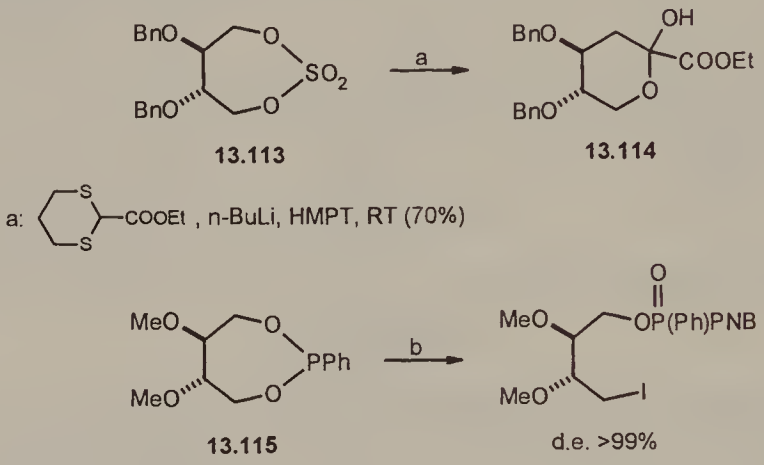
c (X = OTf, R = CF_3): 2.3 eq. n-BuLi, THF, HMPA, -78°C (95%)[279]

Scheme 13.94 (*continued*)



Scheme 13.94

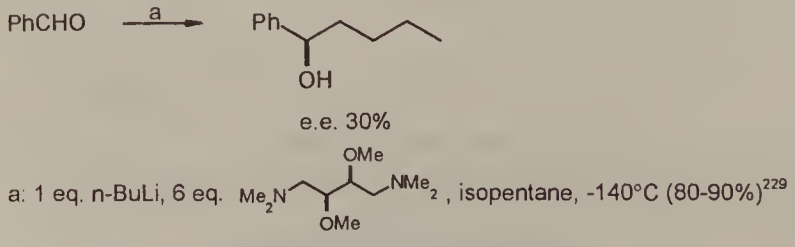
Desymmetrization of 2,3-di-*O*-alkyl threitols is possible via cyclic derivatives. Cyclic sulfate **13.113** reacts with the anion of 2-ethoxycarbonyl-1,3-dithiane to give ester **13.114**, an intermediate in the synthesis of 3-deoxy-L-*threo*-2-hexulosonic acid.[280] Chiral phosphonite **13.115** bearing the 2,3-di-*O*-methyl-L-threitol ligand was reported to undergo a diastereoselective Arbuzov reaction[281] (Scheme 13.95).



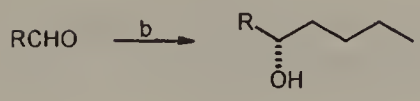
Scheme 13.95

(*S*,*S*)-2,3-Dimethoxy-1,4-butanediamine was used for the synthesis of stereoregular polyamides by condensation with pentachlorophenyl esters of aliphatic C_4 to C_{12} diacids.[267]

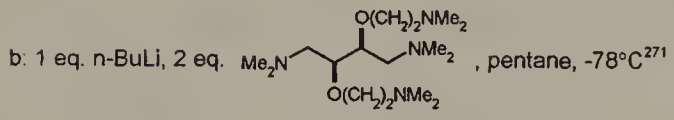
Various alkoxyamines derived from threitol were used by Seebach as chiral ligands in the asymmetric nucleophilic additions of organometallics to carbonyl compounds.[219,270,271,282,283] Enantioselectivity induced by the chiral ligand (cosolvent) was found to be generally moderate, as shown in the examples in Scheme 13.96.



Scheme 13.96 (*continued*)



R	e.e. (%)
Me	46
i-Pr	53
Cy	48
Ph	52
2-MeC_6H_4	56
4-MeC_6H_4	49

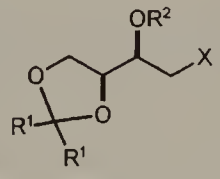


Scheme 13.96

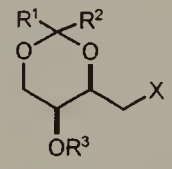
13.8 1,2,3-TRI-*O*-PROTECTED L-THREITOLS AND THEIR DERIVATIVES

The most frequently used 1,2,3-triprotection scheme is based on the 1,2- and 2,3-acetals of threitol (**XII** and **XIV**) while the use of 2-*O*-alkyl-1,3-acetals of threitol (**XIII**) and 1,2,3-*O*-trialkyl threitols (**XV**) is limited by their availability.

13.8.1 3-*O*-Protected-1,2-Acetals and 2-*O*-Protected-1,3-Acetals of L-Threitol and Derivatives



XII



XIII

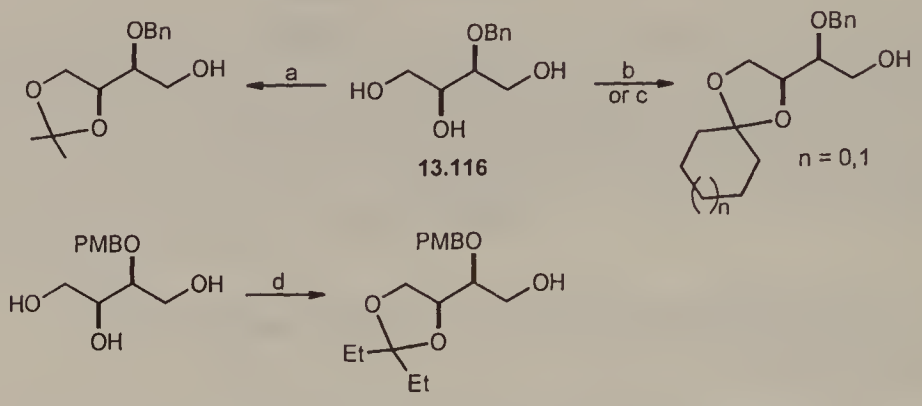
Table 13.13 3-*O*-Protected-1,2-cyclic acetals of L-threitol and their derivatives (XII)

R^1	R^2	X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
Me	Bn	OH	140–145/0.05	−22.1 ($CHCl_3$)	81,89,91–93,100,284
Me	Bn	OMs	—	—	89
Me	Bn	OTs	—	+11.1 ($CHCl_3$)	285
Me	Bn	Br	—	—	95
Me	Bn	I	130–150/1	−8.6 ($CHCl_3$)	284,285
Me	THP	OH	123/0.03	—	107,286
Me	THP	OMs	—	—	107
Me	THP	SPh	—	—	107
Et	PMB	OH	—	−28.3 ($CHCl_3$)	98,160
[a]	Bn	OH	—	−4.0 ($CHCl_3$)	93

[a] $R^1,R^1 = (CH_2)_4$.

Synthesis

A very useful synthetic scheme involves formation of the dioxolane acetals of 2-*O*-benzyl (or p-methoxybenzyl) monoprotected threitol, which is in turn obtained from the 2,3-*O*-benzylidene acetal of threitol (see Section 13.3.2), Scheme 13.97.



a: $Me_2C(OMe)_2$, TsOH (cat.), CH_2Cl_2 or benzene, Δ (45-98%)[89,92,95] or Me_2CO (excess), 0.4 eq. TsOH, benzene, RT (58-98%)[83,91,93,99,100]

b (n = 0): cyclopentanone, $HC(OEt)_3$, TsOH, PhMe, RT (77%)[93]

c (n = 1): 1,1-dimethoxycyclohexane,TsOH (cat.), benzene, Δ[287]

d: Et_2CO (excess), TsOH, THF or benzene, RT (89-95%)[98,160]

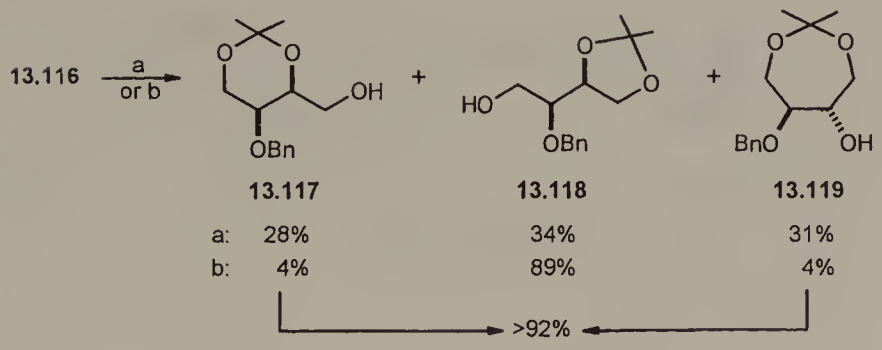
Scheme 13.97

Despite the generally observed preference for the formation of five-membered 1,3-dioxolane acetals from ketones, the isopropylidenation reaction of 2-*O*-benzylthreitol (**13.116**) produces mixtures of acetals. Valverde and Herradón have shown that with the use of 2-methoxypropene, nearly equal amounts of the isomeric acetals **13.117–13.119** are obtained. The desired five-membered acetal can be selectively obtained using large excess acetone as the isopropylidenation agent; for practical preparations the recommended procedure employs acetone with perchloric acid for acetalization, combined with isomerisation of the undesired acetals to the 1,3-dioxolane derivative **13.118**[91,100] (Scheme 13.98).

Transacetalization of 2-*O*-benzyl-threitol with benzaldehyde diethyl acetal may lead to a mixture of five- and six-membered benzylidene derivatives—a reaction of low synthetic utility (Scheme 13.99).

However, the yield of six-membered benzylidene acetal **13.120** can be increased significantly by acetalization of 2-*O*-benzylidene threitol with benzaldehyde—a result consistent with the generally observed preference of aldehydes for the formation of 1,3-dioxane acetals. A recent report claims an 83% yield of the acetal **13.120** by transacetalization of benzaldehyde dimethyl acetal with **13.116**.[288]

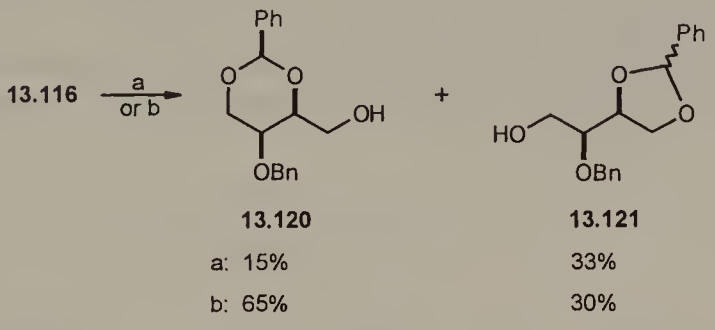
Six-membered aldehyde acetal is preferentially obtained by DDQ oxidation of 2-*O*-PMB-3-*O*-methyl protected L-threitol[289] (Scheme 13.100).



a: 2.5 eq. CH_2=C(OMe)Me, TsOH (cat.), DMF, 0°C, 0.75h

b: acetone (25mL/mmol), 1 eq. $HClO_4$, mol sieves 4Å, RT, 28h

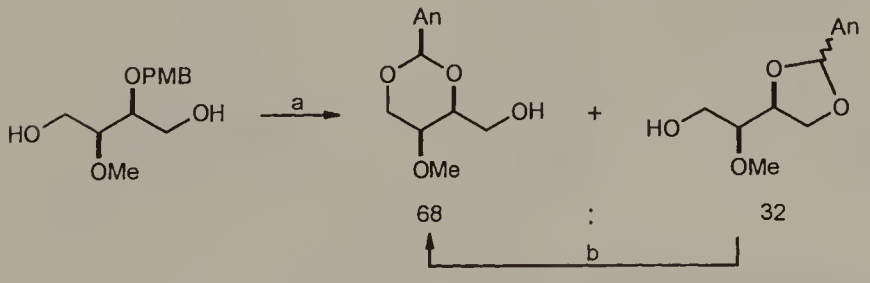
Scheme 13.98



a: $PhCH(OEt)_2$, TsOH (cat.), DMF, RT[26]

b: PhCHO, CF_3COOH (cat.), CH_2Cl_2, Δ[123]

Scheme 13.99

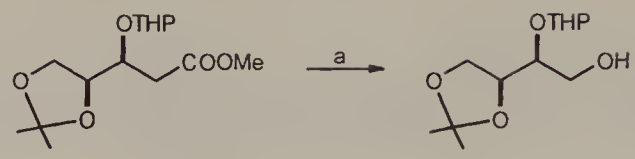


a: DDQ, mol. sieves 4Å, CH_2Cl_2, RT, 1h

b: TsOH, PhMe, RT, 15 min (65%)

Scheme 13.100

3-*O*-Protected-1,2-*O*-isopropylidene-L-threitol can be alternatively obtained from suitably protected L-threonic acid, which is readily available from L-ascorbic acid (see Chapter 14), Scheme 13.101.



a: $LiAlH_4$, Et_2O, RT (87-90%)[107,286]

Scheme 13.101

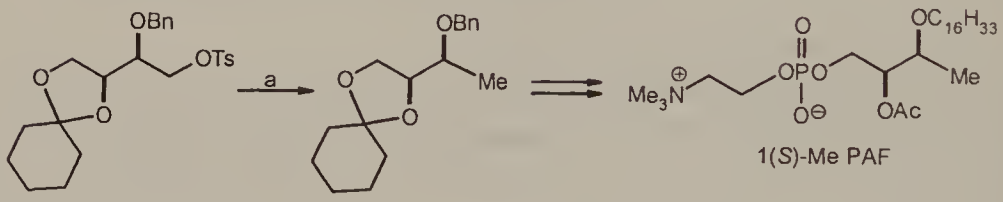
Applications

B

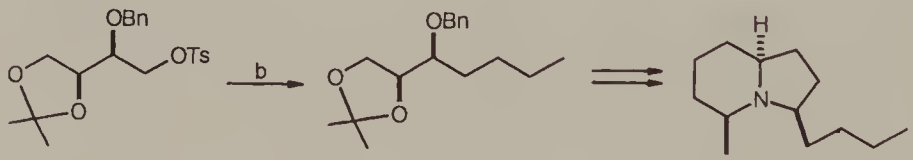
Various protected 1,2,3-triols of 2,3-*threo* configuration are available from 1,2,3-tri-*O*-protected threitols by the reaction of 4-activated derivatives with reducing or C-nucleophilic reagents. The target compounds obtained from the protected triols are also shown in Scheme 13.102.

A

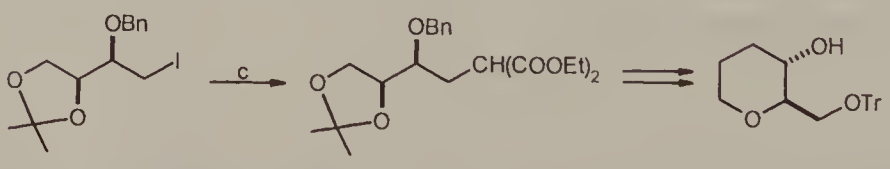
The 1,3-dioxane type acetal **13.122** is useful as a chiral auxiliary in the Diels–Alder reaction of acrylate **13.123** with cyclopentadiene[293] (Scheme 13.103).



a: $LiAlH_4$, Et_2O[287]

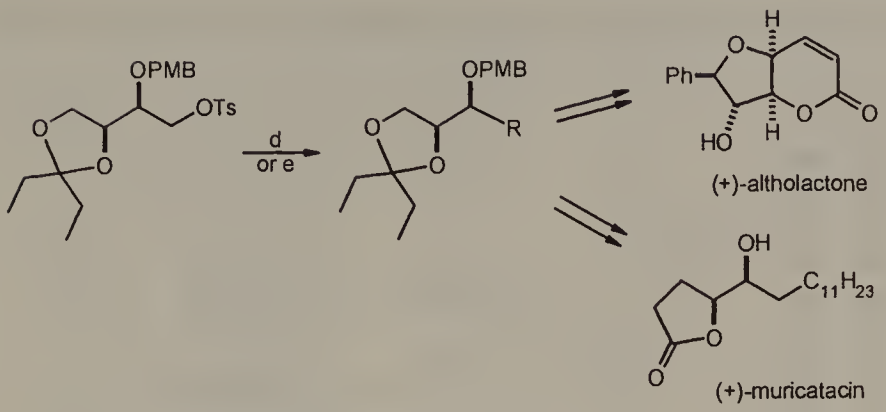


b: n-PrMgBr, Li_2CuCl_4 (cat.), THF, -78°C → RT (87%)[285,290]



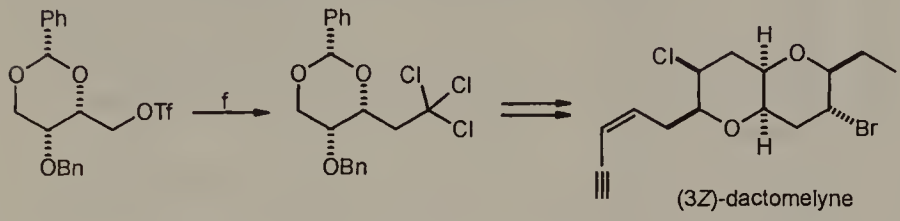
c: $CH_2(COOEt)_2$, NaH, DMF[284]

Scheme 13.102 (*continued*)



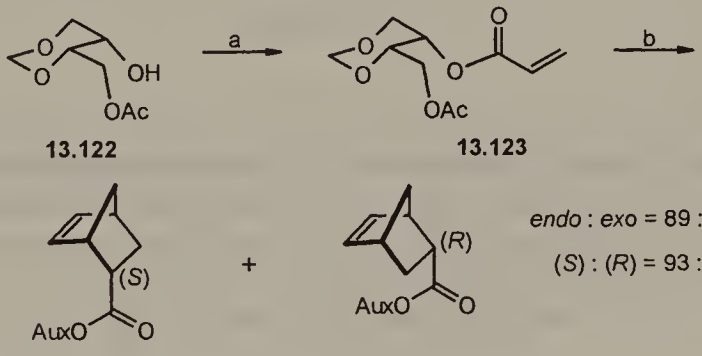
d: (R = All) : AllMgCl, CuI (cat.), THF, -30°C (84%)[291]

e (R = $C_{11}H_{23}$) : $C_{11}H_{23}MgBr$, CuI (cat.), THF, -30°C (82%)[292]



f: $CHCl_3$, LDA, THF-Et_2O-HMPA (1:1:0.2), -110°C (60%)[288]

Scheme 13.102

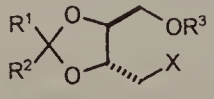


a: ClOCCH=CH_2, NEt_3, 0°C

b: 3 eq. cyclopentadiene, 1.5 eq. $EtAlCl_2$, CH_2Cl_2, -70°C

Scheme 13.103

13.8.2 1-*O*-Protected-2,3-Acetals of L-Threitol and Derivatives



XIV

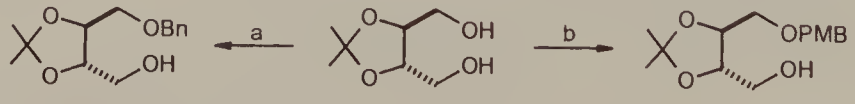
Table 13.14 1-*O*-Protected-2,3-cyclic acetals of L-threitol and their derivatives (XIV)

R^1	R^2	R^3	X	m.p. (°C) or b.p. (C/torr)	$[\alpha]_D$ (solvent)	References
Me	Me	Me	OTs	—	+16.5 ($CHCl_3$)	75
Me	Me	Bn	OH	123/0.005	+9.0 ($CHCl_3$)	77,79,83,139,240
Me	Me	Bn	OTs	—	−14.6 ($CHCl_3$)[a]	77,139
Me	Me	Bn	I	135/0.05	−10.1 ($CHCl_3$)	294–296
Me	Me	Bn	Br	160/0.01	+2.0 ($CHCl_3$)	83,297
Me	Me	Bn	Cl	—	+1.5 ($CHCl_3$)	296
Me	Me	Bn	$P(O)Ph_2$	91–92	+1.9 ($CHCl_3$)	240
Me	Me	PMB	OH	—	+10.6 ($CHCl_3$)	82,296
Me	Me	PMB	Cl	—	+2.1 ($CHCl_3$)	402
Me	Me	Bz	OH	123–127/0.05	−7.5 ($CHCl_3$)	393
Me	Me	Bz	OTs	85–86	—	171
Me	Me	TBS	OH	—	+16.1 ($CHCl_3$)[b]	298–300
Me	Me	TIPS	OH	—	+9.5 (CH_2Cl_2)	300
Me	Me	Ph	Cl	—	—	301
Me	Me	4-t-BuC_6H_4	OTs	65–67	—	302
$-(CH_2)_5-$		Bn	OH	—	+0.9 ($CHCl_3$)	179
MeCH=CH	H	Bn	OH	—	—	112

[a] $[\alpha]_D$ −9.8 ($CHCl_3$) was reported in ref. 240.
[b] $[\alpha]_D$ −5.4 (MeOH) was reported in ref. 303.

Synthesis

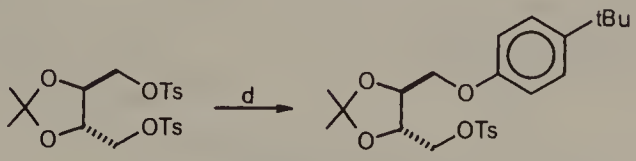
The synthesis is based on monoprotection of the readily available 2,3-acetals of threitol. The most frequently used 1-*O*-protecting groups are the benzyl and the TBS groups; but other groups like methyl, phenyl, tetrahydropyranyl, and benzoyl are also encountered. Some examples of monoprotection of 2,3-acetals of threitol and their derivatives are shown in Scheme 13.104.



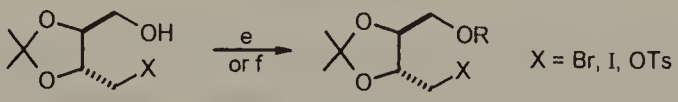
a: 1.1 eq. NaH, 1.1 eq. BnBr or BnCl, DMF, -20°C (72-89%)[77,83,193,296, 297,304]
or 1.1 eq. NaH, 1.1 eq. BnCl, DMSO, RT, 1.5h (54%)[305]
or 1 eq. NaH, 1 eq. BnBr, Bu_4NI, THF (63%)[239]
or 1 eq. KOH, 1 eq. BnCl, benzene, Δ (66%)[139]
b: 1.1 eq. NaH, 1 eq. PMBCl, DMF, -30°C, 2h (76-80%)[82,306]
or 1 eq. NaH, 1 eq. PMBBr, THF, RT, 1h (90%)[401]

Scheme 13.104 (*continued*)

c: PhOH, NaOH, $MeOCH_2CH_2OH$-H_2O, Δ (≥65%)[301]

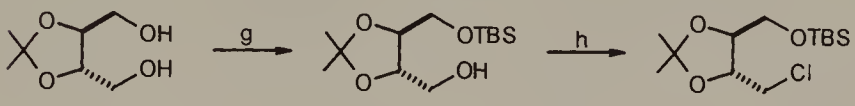


d: 0.5 eq. 4-t-BuC_6H_4OH, K_2CO_3, DMF (74%)[302]



e (R = THP): dihydropyran, CSA (cat.), CH_2Cl_2, RT, 30 min. (93-99%)[205,206]

f (R = CMe_2OMe): $MeOC(Me)=CH_2$, $POCl_3$ (cat.), hexane-Et_2O, RT, 1h (97-100%)[205]

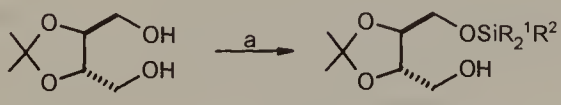


g: 1.1 eq. $tBuMe_2SiCl$, 1 eq. n-BuLi, THF, 0°C → RT (88%)[298]

h: MsCl, NEt_3, CH_2Cl_2, RT then LiCl, DMF, 80°C (85%)[301]

Scheme 13.104

A convenient, high-yield, and general method of monosilylation of 2,3-*O*-isopropylidene threitol requires the use of one equivalent each sodium hydride and a silyl chloride (Scheme 13.105).



R^1 = Me, R^2 = t-Bu (TBS), 64-100%[191,299-301,303,307]

R^1 = Ph, R^2 = t-Bu (TBDPS), 75%[308]

R^1 = R^2 = i-Pr (TIPS), 100%[300]

(100%)[392]

a: 1 eq. NaH, 1 eq. $R^1R_2^1SiCl$, THF or DME, RT

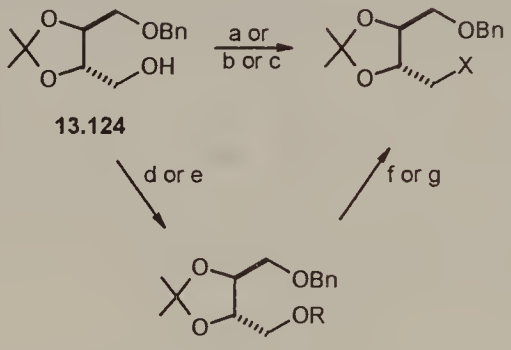
Scheme 13.105

A unique chemoselective 2,3-*O*-protection/activation reaction of 1-*O*-benzyl threitol is carried out with dimethyl carbonate under basic conditions (the reaction with triphosgene provides the less stable 1,2,4-tri-*O*-protected derivative), Scheme 13.106.

a: Me_2CO_3, NaH, RT, 30 min. (65%)[80]

Scheme 13.106

Synthesis of some useful 4-activated derivatives of the versatile 1-*O*-benzyl-2,3-*O*-isopropylidene-L-threitol (**13.124**) is shown in Scheme 13.107.



a (X = Cl): CCl_4, Ph_3P, 70°C, 2h (95%)[296]

b (X = Br): CBr_4, Ph_3P, Et_2O-CH_2Cl_2, 35 min (85%)[83,297]

c (X = I): I_2, Ph_3P, imidazole, PhMe, 60°C, 3h (80%)[295]

d (R = Ms): MsCl, NEt_3, PhMe (99.8%)[83,294]

e (R = Ts): TsCl, pyridine, -20°C, 24h (97-99.5% crude)[139,240]

f (X = I, R = Ms or Ts): NaI (excess), $NaHCO_3$, DMF or MeCN, 70°C, 96h (≥92%)[294,309]

g (X = Br, R = Ms): LiBr, CuBr, Me_2CO, 100°C/4 atm. (70%)[83]

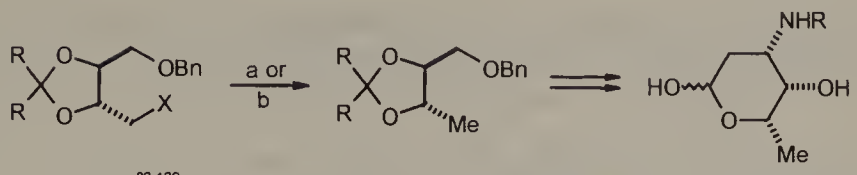
Scheme 13.107

Applications

B

As in the case of 1,2-acetals of 3-*O*-protected threitols, the reaction of 4-activated 1-*O*-protected 2,3-acetals of threitol with reducing or C-nucleophilic reagents gives access to the 1,2,3-triols of 2,3-*threo* configuration. These products can be further transformed to the target compounds, shown in Scheme 13.108.

Tri-*O*-protected iodide **13.125** is a suitable educt for a carbon chain elongation via the radical addition to the C=C bond (Scheme 13.109).



R = Me[83,139]

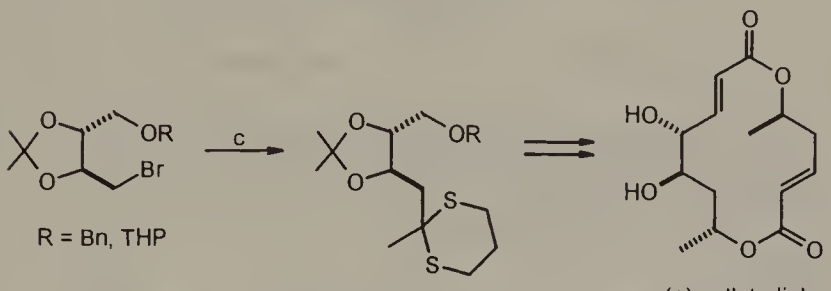
R,R = $(CH_2)_5$[310]

N-acetyl-L-daunosamine[310]

N-benzoyl-L-daunosamine[311]

a (X = OTs): $LiAlH_4$, THF, Δ (82%)[139]

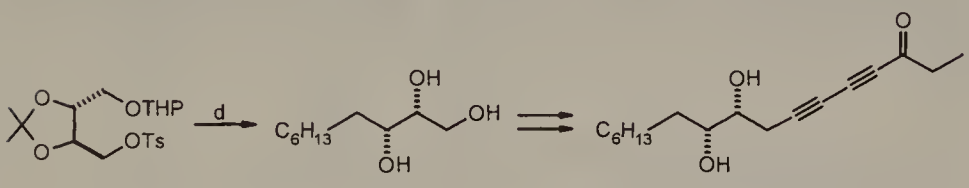
b (X = Br): H_2, Pd/C, $Ba(OH)_2{\cdot}8H_2O$, MeOH, RT (77%)[83]



R = Bn, THP

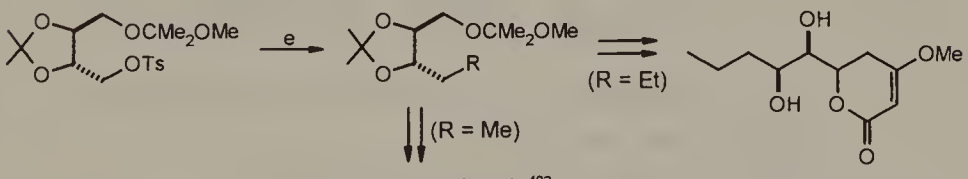
(+)-colletodiol

c:  , n-BuLi, THF, -78° [205,297]



panaxacol

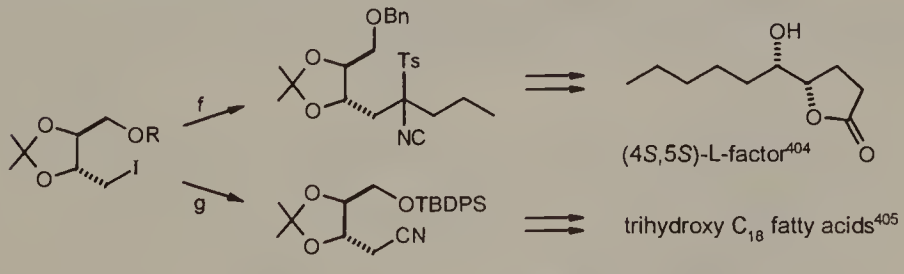
d: $(C_6H_{13})_2CuLi$, THF, -30°C, then 2M HCl/MeOH (66%)[206]



(-)-*exo*-brevicomin[403]

a fungi metabolite[205]

e: Et_2CuLi, Et_2O,-78°C (52-74%)[205,403]



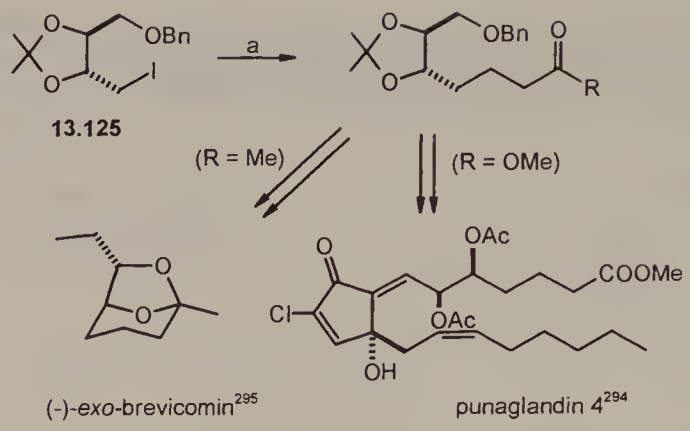
(4*S*,5*S*)-L-factor[404]

trihydroxy C_{18} fatty acids[405]

f (R = Bn): NaH, n-PrCH(NC)Ts, DMSO-Et_2O, RT, 3h (50%)[404]

g (R = TBDPS): NaCN, DMF, RT, 20h[405]

Scheme 13.108



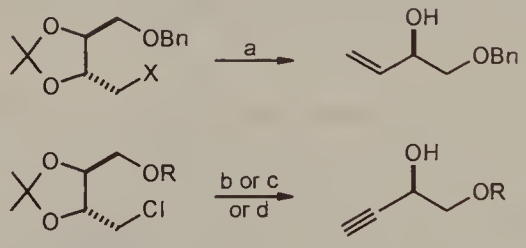
a (R = Me): MVK, n-Bu_3SnH, AIBN, benzene, Δ (53%)[295]

b (R = OMe): CH_2=CHCOOMe, n-Bu_3SnCl, $NaBH_4$, hν, MeOH (70%)[294]

Scheme 13.109

The addition products were used in the synthesis of *exo*-brevicomin (Giese[295]) and punaglandin (Mori[294]).

1-Halogen substituted threitol derivatives undergo base induced elimination to give protected chiral allylic and propargylic diols of synthetic utility (Scheme 13.110).



a (X = Br): Zn, AcOH, ultrasound, ca. 50°C (85%)[83] or Mg, MeOH (99%)[312]

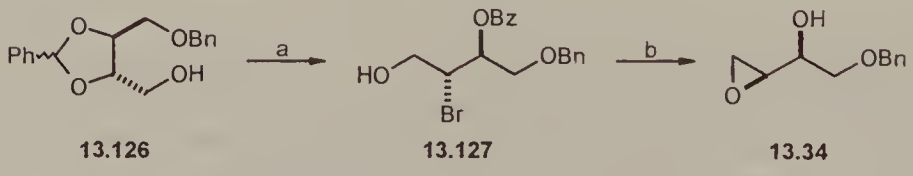
(X = I): Zn, EtOH, Δ (ca. 100%)[309]

b (R = Bn or PMB): $LiNH_2$, NH_3, -33°C, 0.5h (70-90%)[296,401]

c (R = Ph): LDA, THF, 0°C (78%, isolated as a O-TBS derivative)[301]

d (R = PMB): BuLi, HMPA, -30°C, 1h (97%)[402]

Scheme 13.110



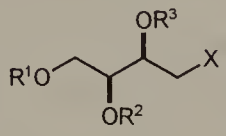
a: NBS, CCl_4, RT (ca. 100% crude)

b: NaOH, DME, RT (49%)[26]

Scheme 13.111

1-*O*-Protected 2,3-*O*-benzylidene threitol **13.126** can be regioselectively cleaved to the *erythro* bromohydride derivative **13.127** from which 1-*O*-protected epoxide **13.34** is readily prepared (Scheme 13.111).

13.8.3 1,2,3-Tri-*O*-Protected Acyclic L-Threitols and Derivatives (XV)



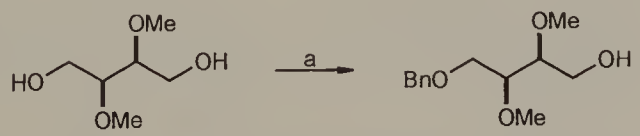
XV

Table 13.15 1,2,3-Tri-*O*-protected acyclic L-threitol derivatives

R^1	R^2	R^3	X	b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
Bn	Me	Me	OH	130–151/0.2	+14.2 ($CHCl_3$)	313
Bn	MOM	MOM	OH	—	−2.5 ($CHCl_3$)	197,199
Bn	MOM	MOM	OMs	—	−8.5 (MeOH)	314
Bn	MOM	MOM	NHCOOEt	—	−0.6 ($CHCl_3$)	199
Bn	MOM	MOM	NHBz	—	−17.9 ($CHCl_3$)	199
Bn	MOM	MOM	NPht	—	−43.3 ($CHCl_3$)	199
PMB	THP	Bn	N_3	—	—	82
PMB	THP	Bn	NHBoc	—	—	82
4-$BrC_6H_4CH_2$	Ac	Ac	SAc	—	−19.0 ($CHCl_3$)	315
Ac	MOM	MOM	OH	—	−22.9 (MeOH)	200
TBS	Me	Me	OH	—	+16.7 ($CHCl_3$)	313
TBS	Bn	Bn	OH	—	+15.7 ($CHCl_3$)	276,316
TBS	MOM	MOM	OH	—	+1.3 ($CHCl_3$)	317
TBS	CH=CHCOOEt	Bn	Br	—	—	95

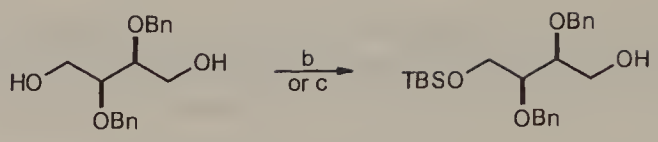
Synthesis

1,2,3-Tri-*O*-protected threitols are usually obtained by monoalkylation or monosilylation of the 2,3-di-*O*-alkyl or 2,3-di-*O*-alkoxyalkyl threitol derivatives (Scheme 13.112).



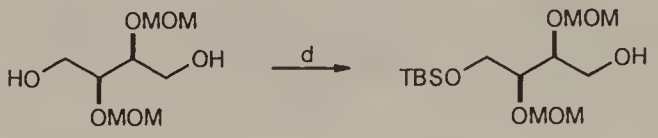
a: 1 eq. NaH, 1 eq. BnBr, DMF, -30°C, 1h (73%)[313]

Scheme 13.112 (*continued*)



b: 1 eq. NaH, 1 eq. TBSCl, THF, RT (90%)[276]

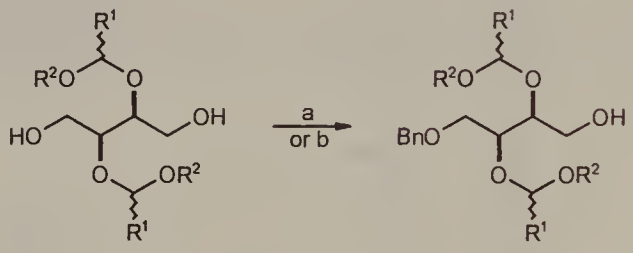
c: 1 eq. n-BuLi, 1.1 eq. TBSCl, THF, 0°C (95%)[316]



d: 1.1 eq. NaH, 1.1 eq. TBSCl, THF, 0°C (91%)[317]

Scheme 13.112

Similarly, acyclic 2,3-acetal protected threitols can be *O*-monobenzylated with high yield (Scheme 13.113).



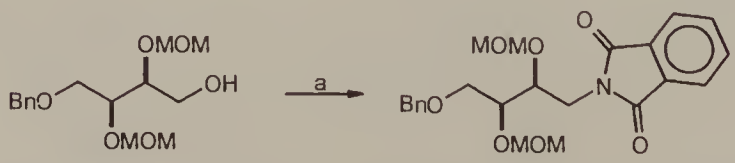
R^1	R^2	method	yield (%)	ref.
H	Me (MOM)	a	99	197,199
		b	74-85	198,200
Me	Me (ME)	a	84-89	77,78
Me	Et (EE)	a	97	83

a: 1.0 eq. NaH, 1.0 eq. BnBr, DMF, -55°→ -20°C

b: 1.0 eq. BnCl or BnBr, 4N NaOH, Bu_4NCl, CH_2Cl_2, 50°C

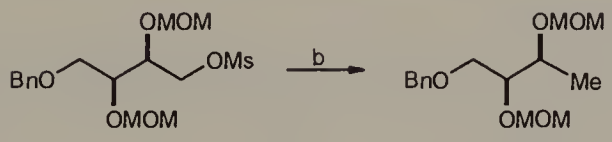
Scheme 13.113

These derivatives undergo uneventful substitution reactions at C-4 (Scheme 13.114).



a: phthalimide, PPh_3, DEAD, THF, 0°C → RT (92%)[198,199]

Scheme 13.114 (*continued*)

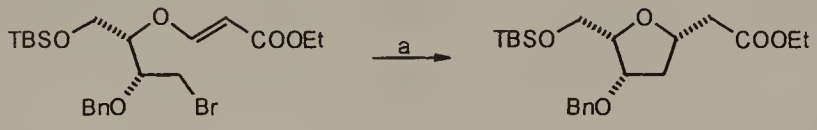


b: $LiAlH_4$, THF- Et_2O (1:1), Δ, 9h (72%)[314]

Scheme 13.114

Application

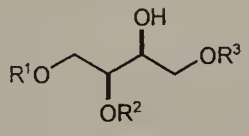
1,2,3-Tri-*O*-protected derivative of L-threitol bearing a β-alkoxyacrylate moiety as a radical acceptor is an excellent substrate for C-furanoside synthesis (Scheme 13.115).



a: Bu_3SnH, AIBN (cat.), benzene, Δ (84%)[95]

Scheme 13.115

13.9 1,2,4-TRI-*O*-PROTECTED L-THREITOL DERIVATIVES



XVI

Table 13.16 1,2,4-Tri-*O*-protected L-threitol derivatives (XVI)

R^1	R^2	R^3	b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
$-CMe_2-$		$C_{16}H_{33}$	—	—	93
$-CMe_2-$		Bn	—	+6.8 ($CHCl_3$)	113
$-CMe_2-$		PMB	—	+5.7 ($CHCl_3$)	81
$-CMe_2-$		Ac	104/0.95	+2.4 ($CHCl_3$)	318
$-CMe_2-$		Tr	—	+2.5 ($CHCl_3$)	319
$-CMe_2-$		Piv	—	−6.2 ($CHCl_3$)	319,320
$-CMe_2-$		Bz	—	+1.9 ($CHCl_3$)	104
$-CMe_2-$		TBS	—	+7.3 ($CHCl_3$)	319
$-CMe_2-$		TBDPS	—	+4.4 ($CHCl_3$)	313
t-Bu	CH(Ph)*cyclo*-C_5H_9	t-Bu	—	−53.2 ($CHCl_3$)	129

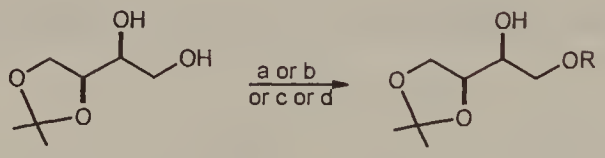
(*continued*)

Table 13.16 (*continued*)

R^1	R^2	R^3	b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
t-Bu	CH(Ph)*cyclo*-C_6H_{11}	t-Bu	—	−38.0 ($CHCl_3$)	129
t-Bu	CH(4-PhC_6H_4)*cyclo*-C_5H_9	t-Bu	—	−54.9 ($CHCl_3$)	129
t-Bu	CH(4-BrC_6H_4)*cyclo*-C_5H_9	t-Bu	—	−51.2 ($CHCl_3$)	129
t-Bu	CH(3-$MeOC_6H_4$)CH_2tBu	t-Bu	—	−63.5 ($CHCl_3$)	129
t-Bu	CH(3-$MeOC_6H_4$)*cyclo*-C_6H_{11}	t-Bu	—	−41.8 ($CHCl_3$)	129
t-Bu	CHPh(3-$MeOC_6H_4$)	t-Bu	—	+41.6 ($CHCl_3$)	129
Bn	Bn	TBDPS	—	+5.7 ($CHCl_3$)	113
Bn	THP	Tr	—	—	321
Tr	$[(CH_2)_2O]_2$Ts	Bn	—	—	321
TBS	Bn	TBS	170/0.07	+21.0 ($CHCl_3$)	83
TBS	PMB	TBS	—	+23.4 ($CHCl_3$)	160
TBDPS	Bn	TBDPS	—	+12.6 ($CHCl_3$)	113
TBDPS	TBDPS	TBDPS	—	+11.3 ($CHCl_3$)	113

Synthesis

Access to the 1,2,4-tri-*O*-protected threitols is provided by the 1,2-di-*O*-protected precursors in which a number of reaction can differentiate between the more reactive 4-hydroxy group and the secondary 3-hydroxy group[319] (Scheme 13.116).



a (R = Bz): 1 eq. BzCl, pyridine, CH_2Cl_2, -70°C, 2h (70%)[104]

or 1 eq. BzCl, pyridine, Et_2O, 0°→ 5°C (81%)[322]

b (R = Piv): 1 eq. PivCl, pyridine, CH_2Cl_2, -15°C → RT (77-83%)[110,320]

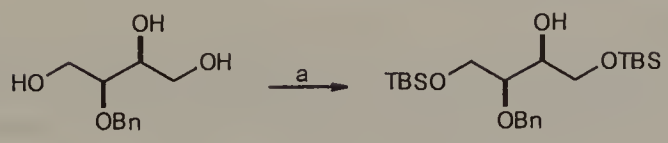
c (R = TBDPS): TBDPSCl, imidazole, DMF, RT (85%)[113]

d (R = Bn): Bu_2SnO, mol sieves 4Å, PhMe, Δ, 20h then BnBr, n-Bu_4NI, 70°C, 10h (84%)[113] or Bu_2SnO, MeOH, Δ, 5h then BnBr, DMF, 70-80°C (90%)[116]

e: TrCl, pyridine (≥ 96%)[321]

Scheme 13.116

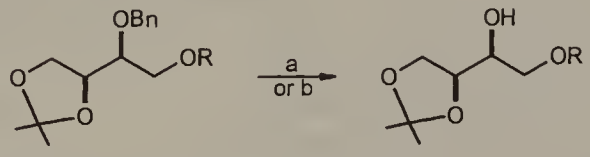
The process of 1,4-di-*O*-protection of 2-*O*-benzyl threitol by the bis-TBS ether formation is also applicable (Scheme 13.117).



a: 2 eq. TBSCl, 2 eq. imidazole, DMF, -20°C → RT, 16h (94%)[83]

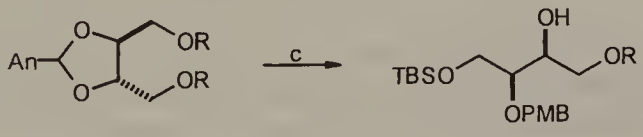
Scheme 13.117

Chemoselective removal (or cleavage) of one of the internal protecting groups in tetraprotected threitol derivaties is another route to 1,2,4-tri-*O*-protected threitols. Noteworthy is the chemoselective hydrogenolytic removal of the benzyl group in the presence of the *p*-methoxybenzyl group and diastereoselectivity in the formation of the new chiral center in the reaction of benzylidene acetals with Grignard reagents (Scheme 13.118).



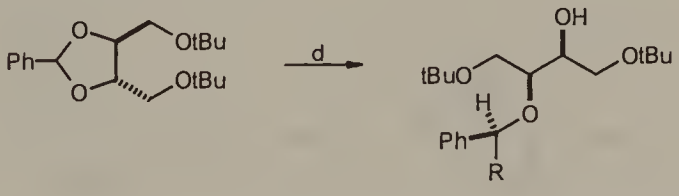
a (R = $C_{16}H_{33}$): H_2, Pd, 2% AcOH-MeOH, RT (87%)[93]

b (R = PMB): H_2, Raney nickel, EtOH, RT (93%)[81]



c (R = TBS): i-Bu_2AlH, CH_2Cl_2, -78°→ -30°C (81%)[160]

(R = Bn): i-Bu_2AlH, PhMe (97%)[323]



d: RMgX, benzene, Δ[129]

R	yield (%)	d.e. (%)
i-Pr	77	48
cyclo-C_5H_9	83	96
cyclo-C_6H_{11}	84	>98

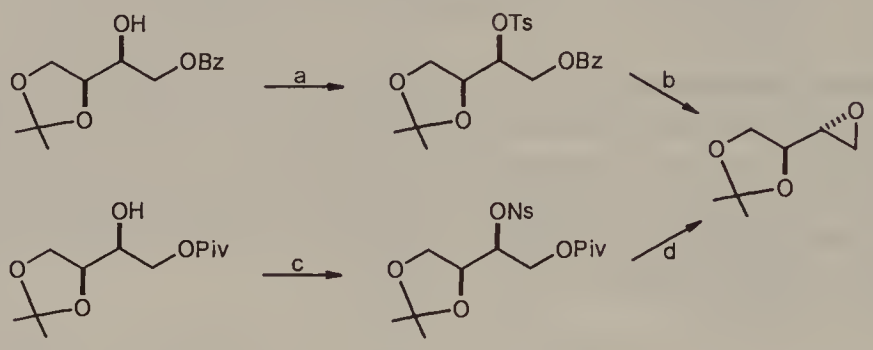
e: PhSH, NEt_3, Me_2BBr, CH_2Cl_2, -78°C (88%)[324]

Scheme 13.118

Applications

B

1,2,4-Tri-*O*-protected L-threitol derivatives can be converted to the 3,4-di-*O*-protected 1,2-epoxides of *erythro* configuration after activation of the 3-hydroxy group and removal of the 4-protecting group (Scheme 13.119).



a: TsCl, NEt_3, DMAP, CH_2Cl_2, 0°C → RT[104,105]

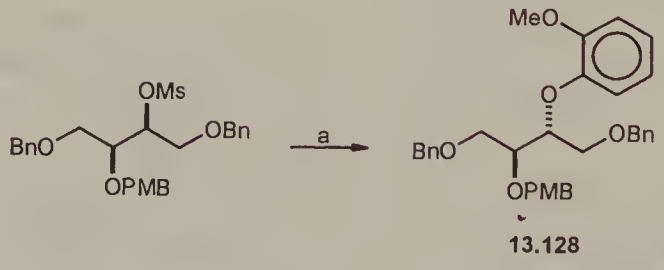
b: K_2CO_3, MeOH, CH_2Cl_2, RT, 6h (95%)[104]

c: 3-$O_2NC_6H_4SO_2Cl$, pyridine, DMAP, CH_2Cl_2, RT

d: KOH, MeOH, 0°C → RT, 2h (51-56%)[110,320]

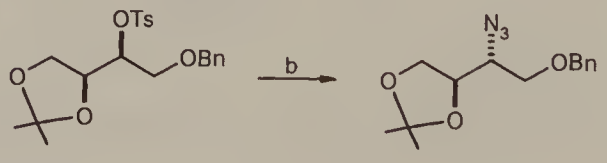
Scheme 13.119

Erythro configured products, such as intermediates **13.128**, useful in the synthesis of neolignans, and **13.129**, used in the synthesis of the 1,4-diazepan-2-one moiety of liposidomycins, are available by substitution of the 3-activated hydroxy group (Scheme 13.120).



13.128

a: 2-$MeOC_6H_4OCs$, 18-crown-6, benzene, Δ, 24h (85-90%)[323]

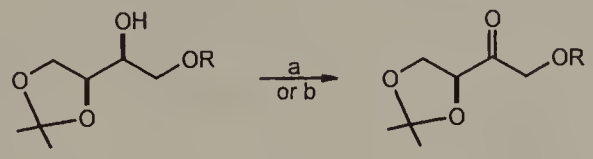


13.129

b: NaN_3, DMF, 70-80°C, 12h (90%)[116]

Scheme 13.120

Derivatives of L-erythrulose bearing various protecting groups can be obtained by oxidation of the corresponding 1,2,4-tri-*O*-protected L-threitols[319] (Scheme 13.121).



a (R = Bz): CrO_3, pyridine, CH_2Cl_2, RT (76%)[322]

b (R = TBDPS): $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -60°C → RT (86%)[113]

c: as a (98%)[83]

$R^1 = R^2$ = Bn (94%)

R^1 = TBDPS, R^2 = Bn (74%)

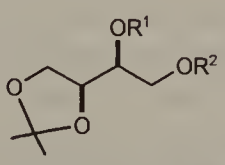
$R^1 = R^2$ = TBDPS (78%)

d: as b[113]

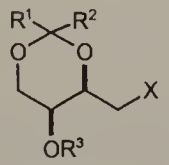
Scheme 13.121

13.10 TETRA-*O*-PROTECTED L-THREITOLS

13.10.1 Tetra-*O*-Protected L-Threitols with 1,2-Acetal or 1,3-Acetal Groups



XVII



XIII

Table 13.17 Tetraprotected L-threitol derivatives with 1,2- and 1,3-acetal groups (XVII, XVIII)

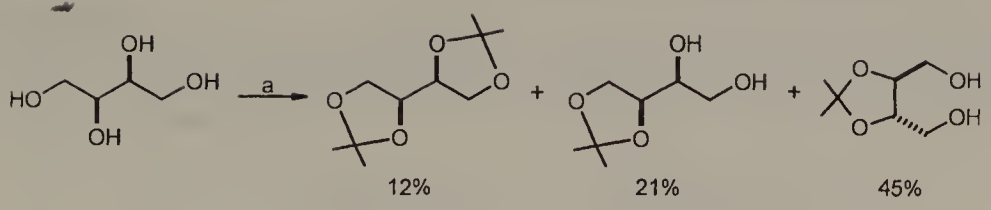
R^1	R^2	R^3	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
		Formula XVII			
$-CMe_2-$		—	35–36	-11.4 ($CHCl_3$)[a]	108
Me	$C_{16}H_{33}$	—	—	-4.2 ($CHCl_3$)	93
Bn	$C_{16}H_{33}$	—	—	—	93
Bn	$C_{18}H_{37}$	—	—	-0.7 ($CHCl_3$)	93
Bn	Bn	—	180/0.5	-3.3 (CH_2C_{12})	113,325
Bn	PMB	—	—	-3.9 ($CHCl_3$)	81
Bn	Tr	—	90–92	—	93
Bn	Ac	—	147/0.7	-12.4 ($CHCl_3$)	318
Bn	TBDPS	—	—	$+10.1$ ($CHCl_3$)	113
TBDPS	Bn	—	—	$+9.0$ ($CHCl_3$)	113
TBDPS	TBDPS	—	—	$+7.4$ ($CHCl_3$)	113
4-(PhN=N)C_6H_4CO	4-(PhN=N)C_6H_4CO	—	198–199	-39.0 ($CHCl_3$)[b]	326
PPh_2	PPh_2	—	—	$+2.8$ ($CHCl_3$)	109
$P(C_6F_5)_2$	$P(C_6F_5)_2$	—	—	$+0.4$ ($CHCl_3$)	109
		Formula XVIII			
H	$-CH_2-$		180–180.5	$+10.7$ ($CHCl_3$)	34,51,327
Ph	–PhCH–		231	$+79.3$ ($CHCl_3$)	31,33,37,163
4-($C_5H_{11}O$)C_6H_4	–4-($C_5H_{11}O$)C_6H_4CH–		188–190	$+80.0$ ($CHCl_3$)	329
4-($C_6H_{13}O$)C_6H_4	–4-($C_6H_{13}O$)C_6H_4CH–		175–178	$+68.0$ ($CHCl_3$)	329
4-($C_7H_{15}O$)C_6H_4	–4-($C_7H_{15}O$)C_6H_4CH–		177–179	$+60.0$ ($CHCl_3$)	329
2-$O_2NC_6H_4$	–2-$O_2NC_6H_4$CH–		—	—	330
3-$O_2NC_6H_4$	–3-$O_2NC_6H_4$CH–		—	—	330
4-$O_2NC_6H_4$	–4-$O_2NC_6H_4$CH–		—	—	330
H	MOM	Ac	—	$+53.3$ ($CHCl_3$)[b]	51
H	C(O)CH=CH_2	Ac	—	—	293
Ph	Me	Me	65	$+53.0$ ($CHCl_3$)	121
Ph	Bn	TBDPS	—	$+22.0$ (CH_2Cl_2)	123

[a] $[\alpha]_{546}$ $+3$ ($CHCl_3$) is given in ref. 326 [b] at 546 nm.

Synthesis

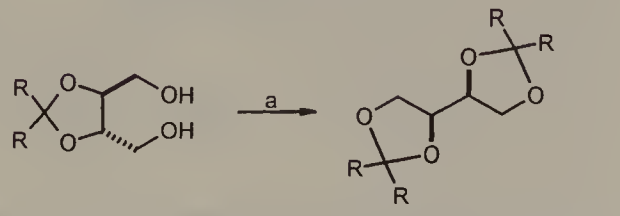
Direct isopropylidenation of L-threitol with acetone gives, not unexpectedly, a mixture of 1,2;3,4-di-*O*-isopropylidene-L-threitol and two other five-membered mono-*O*-isopropylidene-L-threitols.[108,326] The reaction is apparently of limited synthetic use (Scheme 13.122).

However, transacetalization of 2,3-*O*-isopropylidene-L-threitol with ketones makes 1,2;3,4-bisacetals readily available (Scheme 13.123).



a: Me_2CO, 2N HCl (cat.), RT, 3d[108]

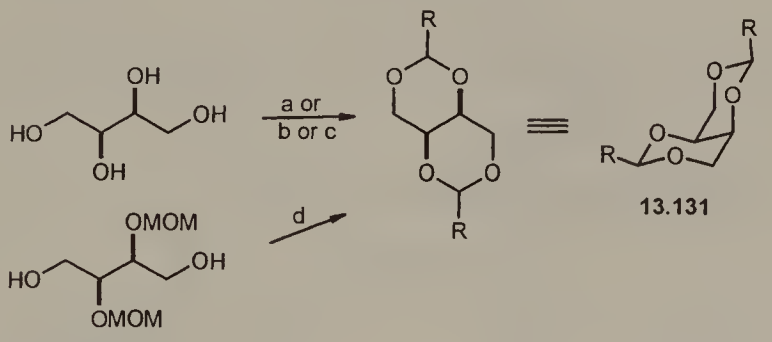
Scheme 13.122



a: R_2CO, TsOH (cat.)[128]

Scheme 13.123

In contrast to isopropylidenation, the reaction of threitol with aldehydes or their acetals gives cleanly the six-membered 1,3;2,4-bisacetals, as detailed in Scheme 13.124. 1,3;2,4-Di-*O*-methylenethreitol is obtained in high yield also by transacetalization of the bis-MOM acetal **13.130**. The course of the reaction has its origin in the preferred conformation of the substrate.[331]



a (R = H): $CH_2(OMe)_2$ (excess), H_2SO_4 (cat.), $CaCl_2$ (removal of MeOH), Δ (59%)[34]

b (R = H): $CH_2(OMe)_2$, MeOH, 0.4M HBr in $CH_2(OMe)_2$, dioxane, mol. sieves 4Å, Δ, 23h (removal of MeOH), 92%[327]

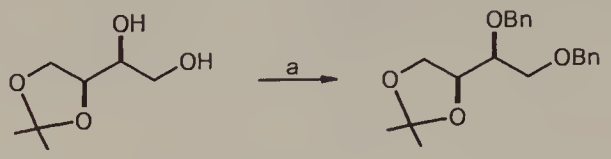
c (R = Ph): PhCHO, $ZnCl_2$, RT (63%)[37]

d (R =H): Amberlyst 15, CH_2Cl_2, Δ (99%)[51]

Scheme 13.124

The product obtained according to procedure (a) was found to be impure.[327] The 1,3;2,4-bisacetals of threitol have the structure of *cis*-1,3,5,7-tetraoxadecalin (**13.131**).

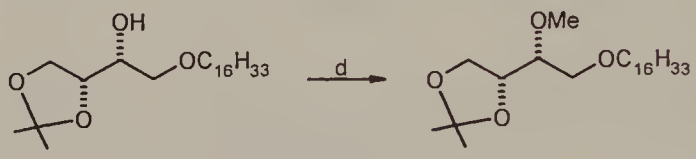
Tetraprotected threitols were also obtained from di- or tri-*O*-protected acetal precursors by the usual *O*-alkylation or silylation reactions (Scheme 13.125).



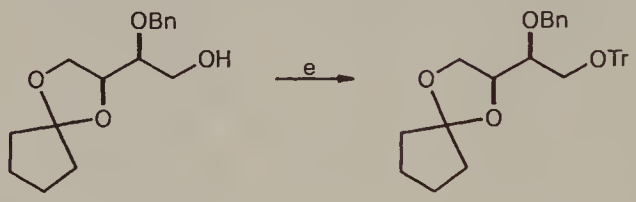
a: NaH, THF, Δ then BnBr, n-Bu_4NI, Δ (84%)[113]

b (R = PMB): NaH, PMBCl, DMF, RT (97%)[81]

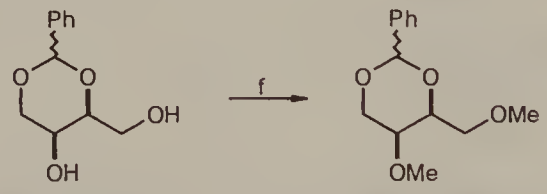
c (R = $C_{16}H_{33}$): 2.5 eq. KH, 1.25 eq. $C_{16}H_{33}OMs$, benzene, Δ (88%)[93]



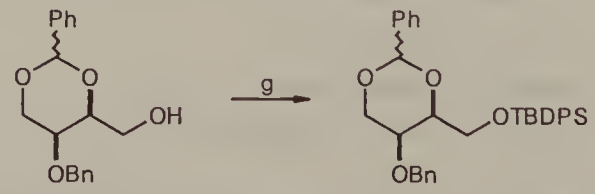
d: KH, MeI, benzene, RT, 12h (98%)[93]



e: 2 eq. Ph_3CCl, pyridine, DMAP (cat.), 50°C (74%)[93]



f: MeI, Ag_2O, DMF (58%)[121]

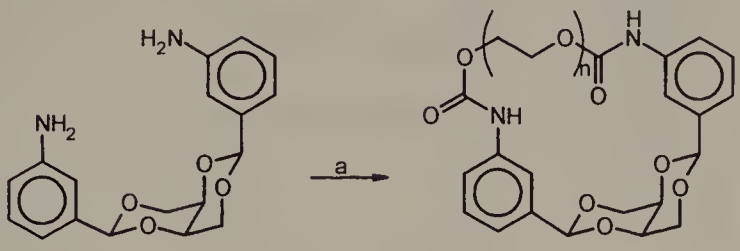


g: TBDPSCl, imidazole, DMF, RT, 2h (90%)[123]

Scheme 13.125

Application

Bisacetal **13.132** has been converted to macro-*m*-cyclophanes **13.133** and **13.134**[330] (Scheme 13.126).

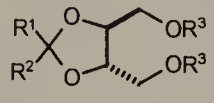


13.132 **13.133** (n = 1), 17%
13.134 (n = 2), 10%

a: $COCl_2$, $NaHCO_3$; then $HO(CH_2CH_2O)_nH$

Scheme 13.126

13.10.2 Tetra-*O*-Protected L-Threitols with 2,3-Acetal Group



XIX

Table 13.18 Symmetrical derivatives of tetra-*O*-protected L-threitol with 2,3-acetal group (XIX)

R^1	R^2	R^3	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
		Aldehyde acetals			
H	H	Ac	—	—	332
H	Me_2C=CH	Bn	—	+8.85 ($CHCl_3$)	333
H	n-PrCH=CH	Me	—	—	334
H	1-cyclohexenyl	Bn	—	+3.6 ($CHCl_3$)	333
H	$MeOOC(CH_2)_3CH$=CH	Bn	—	+5.5 ($CHCl_3$)	333
H	$BrCH_2$	Bn	—	—	335
H	Me(OH)CH	Me	—	—	336
H	Ac	Me	—	−9.6 ($CHCl_3$)	336
H	(2-dithianyl)CH_2	Me	—	—	337
H	(2-dithianyl)CH_2	Bn	—	—	337
H	Ph	Me	—	+10.1 ($CHCl_3$)	137
H	Ph	t-Bu	—	+4.7 ($CHCl_3$)	129
H	2-BrC_6H_4	Me	—	—	338
H	3-$MeOC_6H_4$	t-Bu	—	+6.0 ($CHCl_3$)	129
H	3-$MeOC_6H_4$	CMe_2i-Pr	—	+5.8 ($CHCl_3$)	129
H	4-$MeOC_6H_4$	TBS	—	+10.5 ($CHCl_3$)	160

(*continued*)

Table 13.18 (*continued*)

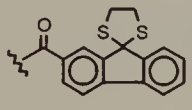
R^1	R^2	R^3	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
H	4-BrC_6H_4	t-Bu	—	+14.1 ($CHCl_3$)	129
H	4-PhC_6H_4	t-Bu	—	+11.7 ($CHCl_3$)	129
H	4-PhC_6H_4	CMe_2i-Pr	—	+15.0 ($CHCl_3$)	129
		Acyclic ketone acetals			
Me	Me	Me	49/0.15	+7.4 (CCl_4)	5
Me	Me	n-Bu	92–93.5/0.5	−1.06 (neat)	5
Me	Me	Bn	115/0.1	−7.5 ($CHCl_3$)	130,132,144
Me	Me	4-$ClC_6H_4CH_2$	—	−8.2 ($CHCl_3$)	141
Me	Me	Het[a]	—	+28.4 (benzene)	339
Me	Me	$C_{15}H_{31}CO$	—	—	146
Me	Me	Bz	83–84	+14.3 (DMF)	171
Me	Me	Ar[b]	173–175	−10.2 ($CHCl_3$)	340
Me	Me	4-(PhN=N)C_6H_4CO	192–194	−20.0 ($CHCl_3$)[f]	326
R[c]	Me	$CH_2C(=CH_2)Me$	—	−1.4 ($CHCl_3$)	258
R[c]	Me	4-$ClC_6H_4CH_2$	—	−3.2 ($CHCl_3$)	258
R[c]	Me	$C_7H_{15}CO$	—	−11.0 ($CHCl_3$)	258
R[c]	Me	$C_9H_{19}CO$	—	−10.0 ($CHCl_3$)	258
R[c]	Me	i-Pr_3Si	—	+1.3 ($CHCl_3$)	258
R[c]	Me	$MePh_2Si$	—	−2.3 ($CHCl_3$)	258
Me_2C=CH	Me	Bn	—	−2.5 ($CHCl_3$)	333
1-cyclohexenyl	Me	Bn	—	−3.4 ($CHCl_3$)	333
Ph	Me	Me	—	—	341
CH_2OH	Me	Me	90/0.1	—	342
CHO	Me	Me	70/0.5	—	342
CH(OH)Me	Et	Me	—	—	346
Ac	Et	Me	—	−6.1 ($CHCl_3$)	336
CH_2OH	Ph	Me	—	+16.2 ($CHCl_3$)	343
CH_2OAc	Ph	Me	—	+12.8 ($CHCl_3$)	343
CH(OH)Me	Ph	Me	—	—	336
Ac	Ph	Me	—	+65.0 ($CHCl_3$)	336
CH=NOBn	Ph	Me	—	+15.2 ($CHCl_3$)	343
		Cyclic ketone acetals			
$-(CH_2)_5-$		Me	—	−8.25 (CH_2Cl_2)	344
$-(CH_2)_5-$		Bn	—	−9.3 (CH_2Cl_2)	344
$-(CH_2)_3CH=CH-$		Me	—	+13.4 ($CHCl_3$)	181
$-(CH_2)_2CH=CMe-$		Me	—	−1.0 ($CHCl_3$)	181
$-(CH_2)_3CH=CH-$		t-Bu	—	+4.3 ($CHCl_3$)	345
$-(CH_2)_3CH=CH-$		CMe_2Et	—	+0.2 ($CHCl_3$)	345
$-(CH_2)_3CH=CH-$		CEt_2Me	—	−7.7 ($CHCl_3$)	345
$-(CH_2)_3CH=CH-$		CMe_2i-Pr	—	+1.7 ($CHCl_3$)	345
$-(CH_2)_4CH=CH-$		CMe_2i-Pr	—	−3.1 ($CHCl_3$)	345
$-(CH_2)_3CMe=CH-$		CMe_2i-Pr	—	+4.4 ($CHCl_3$)	345
$-(CH_2)_2CH=CMe-$		CMe_2i-Pr	—	−2.0 ($CHCl_3$)	345
$-(CH_2)_2CH=CH-$		Bn	—	+0.2 ($CHCl_3$)	333
$-(CH_2)_2CH=CMe-$		Bn	—	−1.0 ($CHCl_3$)	333
$-(CH_2)_2C$(i-Pr)=CH–		Bn	—	+8.8 ($CHCl_3$)	333

(*continued*)

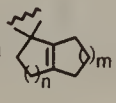
Table 13.18 (*continued*)

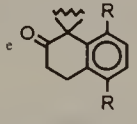
R^1	R^2	R^3	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
	$-(CH_2)_3CH=CH-$	Bn	—	+9.3 ($CHCl_3$)	333
	$-(CH_2)_3CH=CH-$	4-$PhC_6H_4CH_2$	63–65	+4.7 ($CHCl_3$)	181
	$-(CH_2)_3CH=CH-$	2-naphthyl-CH_2	74.5–79	+2.3 ($CHCl_3$)	181
	$-(CH_2)_2CH=CHCH_2-$	Bn	—	−9.7 ($CHCl_3$)	333
	$-(CH_2)_3CH=CMe-$	Bn	—	+14.7 ($CHCl_3$)	333
	$-(CH_2)_4CH=CH-$	Bn	—	+1.7 ($CHCl_3$)	333
	$-(CH_2)_2CMe=CHC(O)-$	Me	—	−30.1 ($CHCl_3$)	346
	$-(CH_2)_2CPh=CHC(O)-$	Me	—	−10.9 ($CHCl_3$)	346
	$-(CH_2)_3CH(COOEt)-$	Me or Bn	—	—	347
	$-(CH_2)_4CH(COOEt)-$	Me or Bn	—	—	347
	-(*E*)-$(CH_2)_{12}CH=CH$	Me	—	+2.65 ($CHCl_3$)	348
	-(*Z*)-$(CH_2)_{12}CH=CH$	Me	—	+4.2 ($CHCl_3$)	348
	-(*E*)-$(CH_2)_{12}CH=CH-$	Bn	—	−2.1 ($CHCl_3$)	333
	-(*Z*)-$(CH_2)_{12}CH=CH-$	Bn	—	−2.8 ($CHCl_3$)	348
	n = 1, m = 1[d]	Bn	—	+2.3 ($CHCl_3$)	333
	n = 1, m = 2[d]	Bn	—	+4.3 ($CHCl_3$)	333
	n = 1, m = 3[d]	Bn	—	+2.3 ($CHCl_3$)	333
	n = 2, m = 2[d]	Bn	—	+25.3 ($CHCl_3$)	333
	R = H[e]	Me	—	−4.8 (CHCl3)	349
	R = OMe[e]	Me	—	+29.7 ($CHCl_3$)	349
		Orthoesters			
H	OMe	Bn	—	−10.0 ($CHCl_3$)	143
H	OMe	Bz	—	−16.5 ($CHCl_3$)	143
H	OMe	TBS	—	−4.8 ($CHCl_3$)	143
H	OEt	Me	—	−17.4 ($CHCl_3$)	350
H	OEt	Bn	—	−14.3 ($CHCl_3$)	136,138

[a] Het = 

[b] Ar = 

[c] R = i-Pr$(CH_2)_3$CH(Me)$(CH_2)_3$–

[d] 

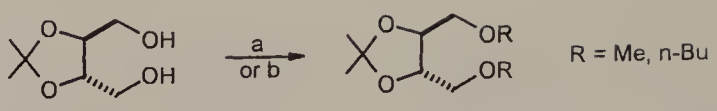
[e] 

[f] at 546 nm

Synthesis

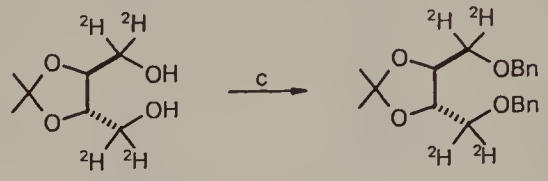
These tetraprotected threitol derivatives are obtained simply from 2,3-acetals of threitol by 1,4- di-*O*-alkylation, di-*O*-acylation, or di-*O*-silylation reactions. Examples of such transformations are shown in Scheme 13.127.

Otherwise, tetra-*O*-protected 2,3-acetals of threitol are available by the reaction of aldehydes and ketones or their acetals with 1,4-di-*O*-protected threitols (Scheme 13.128).

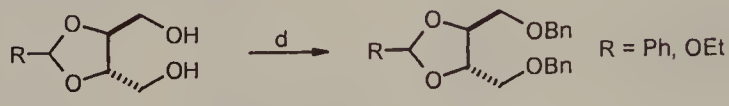


a (R = Me): Me_2SO_4, 50% NaOH, Et_3BnNCl (cat.), CH_2Cl_2 (79%)[5]

b (R = n-Bu): 2 eq. n-BuI, 2 eq. NaH, dioxane, Δ (43%)[5]

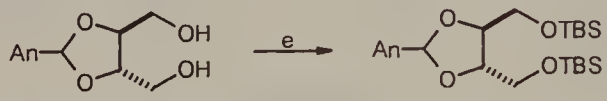


c: BnBr, NaH, DMF (90%)[145] or THF[130]

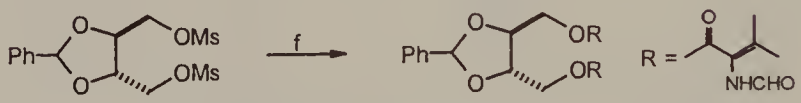


d (R = Ph): BnBr, KOH, PhMe, 80°C, 15h (90%)[137]

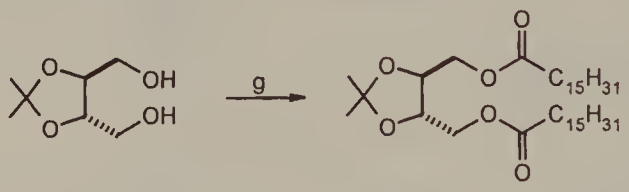
(R = OEt): BnBr, NaH, THF, 0°→ 65°C (92%)[136,138]



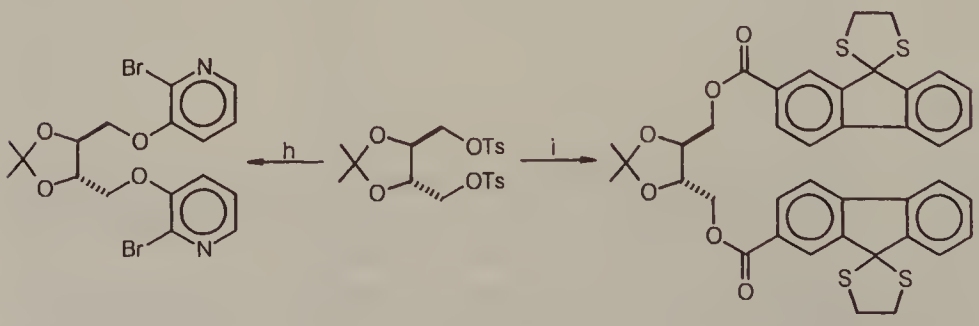
e: 2.2 eq. TBSCl, 2.2 eq. imidazole, CH_2Cl_2, 0°C → RT (97%)[160]



f: 2.2 eq. $Me_2C{=}C(NHCHO)COOH$, NEt_3, HMPT (72%)[351]

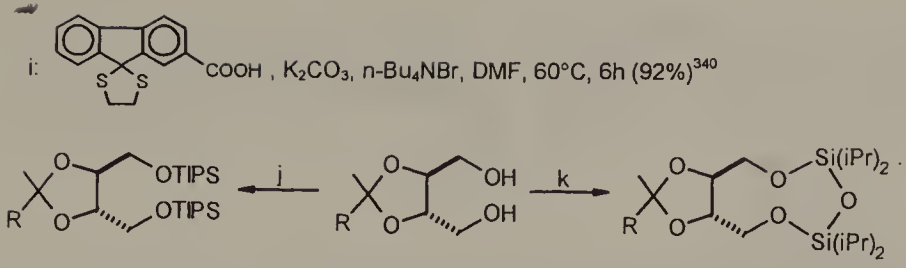


g: $C_{15}H_{31}COOH$, DCC, DMAP, CH_2Cl_2, RT, 16h (96%)[146]

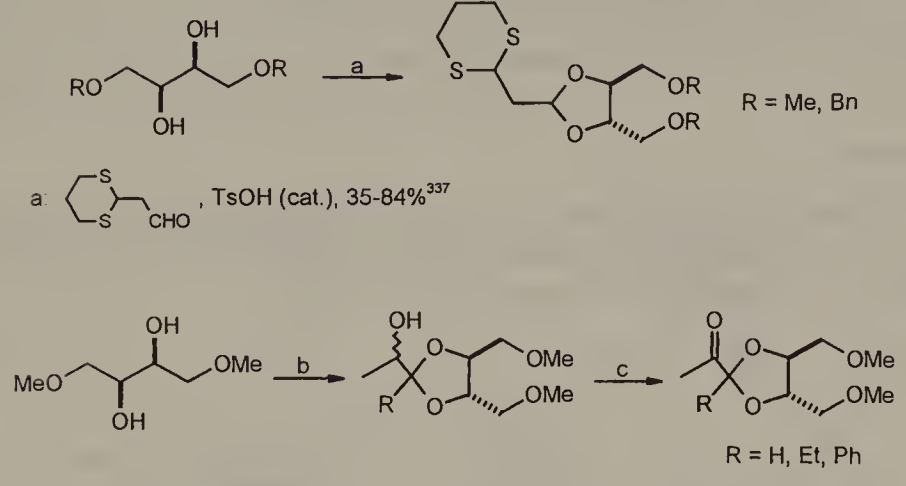


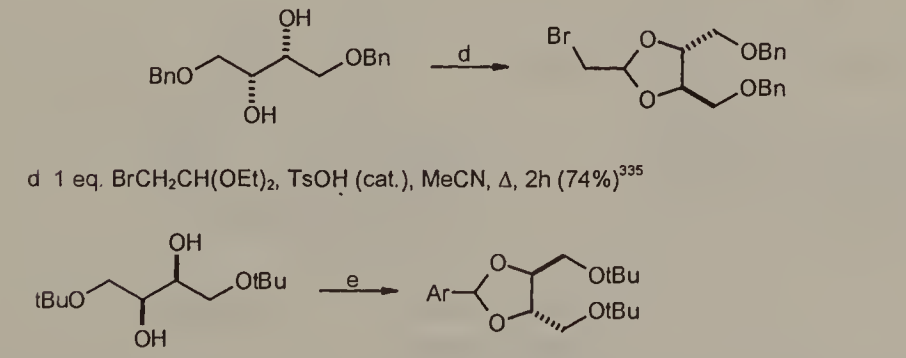
h: 2-bromo-3-hydroxypyridine, NaOH, $n\text{-}Bu_4NBr$, PhMe, 85°C, 48h (95%)[339]

Scheme 13.127 (*continued*)

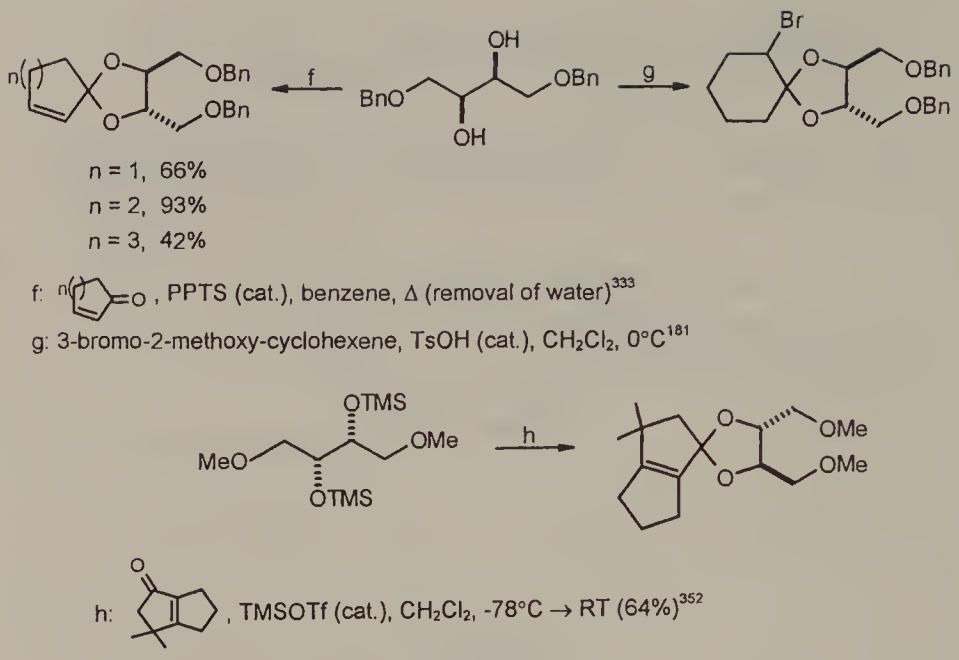


Scheme 13.127





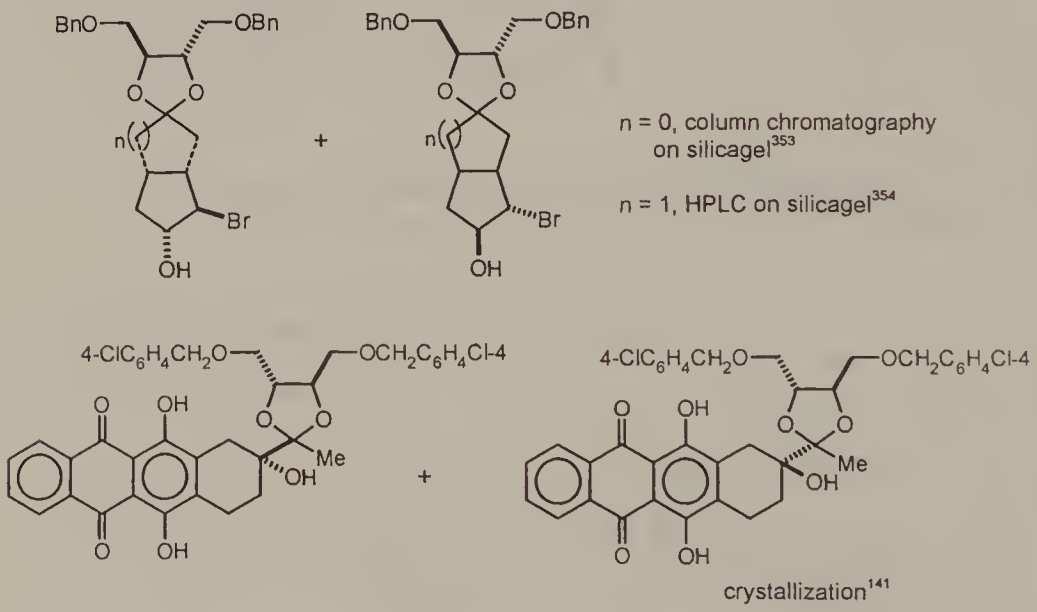
Scheme 13.128 *(continued)*



Scheme 13.128

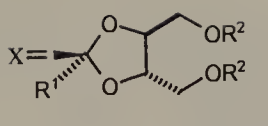
Applications

Racemic ketones after conversion to the diastereomeric acetals of 1,4-*O*-di-benzyl or 1,4-*O*-di(4-chlorobenzyl) threitol can be resolved by HPLC, column chromatography, or crystallization (Scheme 13.129).



Scheme 13.129

The resolved compounds are useful as substrates in the synthesis of prostanoids[353,354] as well as 4-demethoxydaunomycinone and 4-demethoxyadriamycinone.[141]



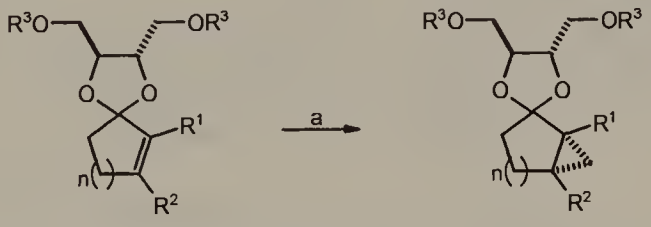
X: CR_1R_2, NR, O
R^1: alkyl, H
R^2: alkyl

Figure 13. 3

1,4-Di-*O*-alkylated threitols are frequently used as excellent chiral auxiliaries in the diastereoselective reactions of acetals of α-functionalized ketones and aldehydes (Fig. 13.3).

Synthetic applications involve reactions of the C=C bond (cyclopropanation, conjugate addition, Diels–Alder cycloaddition) and nucleophilic additions to the C=N and C=O bonds. Other reactions mentioned here are asymmetric deprotonation, asymmetric alkylation and formation of the axially chiral molecules.

Mash has demonstrated high effectiveness of the threitol derived 2,3-acetal auxiliary in diastereoselective cyclopropanation.[333,355,356] Examples of cyclopropanation reactions of α,β-unsaturated acetals of 1,4-di-*O*-benzyl-L-threitol are shown in Scheme 13.130. For comparison, the parenthetical values are yields and diastereoselectivities of these reactions with the 1,4-di-*O*-(2,3-dimethyl-2-butyl)-L-threitol derivatives reported by Luh.[345]



a: Zn-Cu couple, 3 eq. CH_2I_2, I_2 (cat.), Et_2O, Δ

n	R^1	R^2	yield (%) R^3 = Bn (R^3 = CMe_2i-Pr)	d.e. (%) R^3 = Bn (R^3 = CMe_2i-Pr)
1	H	H	72	80
1	Me	H	88 (81)	80 (>98)
1	-$(CH_2)_3$-		78	80
1	-$(CH_2)_4$-		72	75
1	-$(CH_2)_5$-		72	80
2	H	H	90-98 (76)	80 (>98)
2	Me	H	99	90
3	-$(CH_2)_4$-		80	75
3	H	H	90 (90)	78 (>98)

Scheme 13.130

All of these cyclopropanation reactions occur in accordance with the simple mechanistic model, shown in Fig. 13.4. The observed diastereoselectivity in the reaction is presumably due to the chelation control by the threitol acetal oxygen atoms.

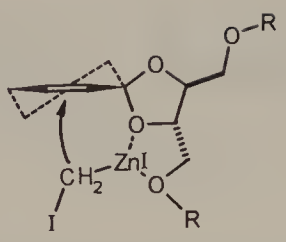
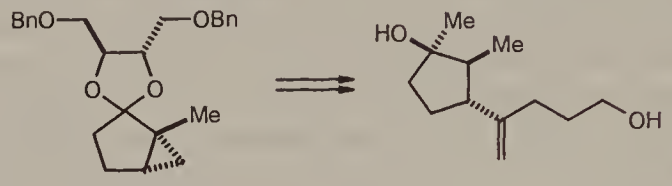
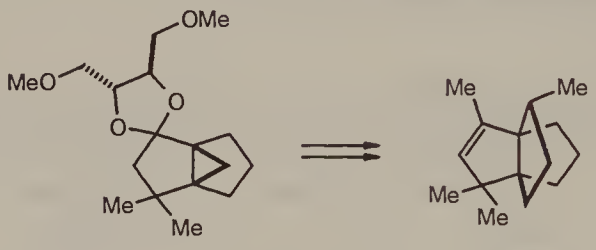


Figure 13.4

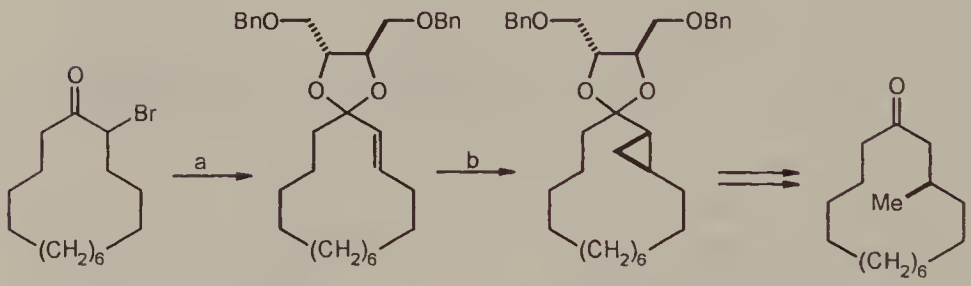
Reactions of this type were used by Mash in the enantioselective synthesis of (−)-chokol A (**13.135**), (−)-modhephene (**13.136**), and (−)-muscone (**13.137**), Scheme 13.131.



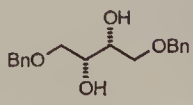
d.e. 80% **13.135** (d.e. 80%)[357]



d.e. 77% **13.136** [352,358]



d.e. 100% **13.137**[348]

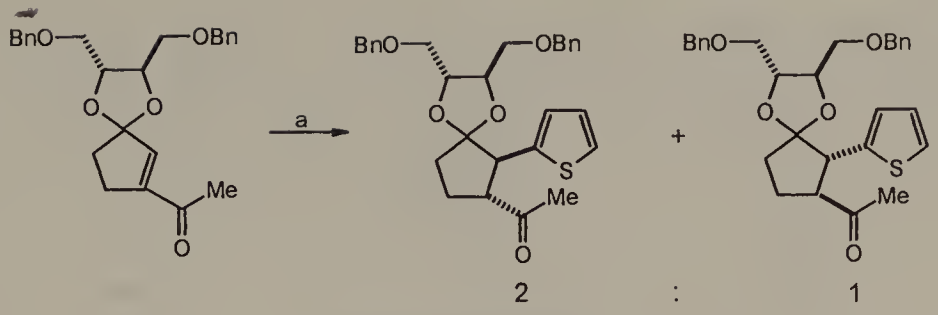
a: 

, TsOH, benzene, Δ, then MeONa, DMSO (56%)

b: Zn-Cu couple, 3 eq. CH_2I_2, K_2CO_3, I_2 (cat.), Δ (88%)

Scheme 13.131

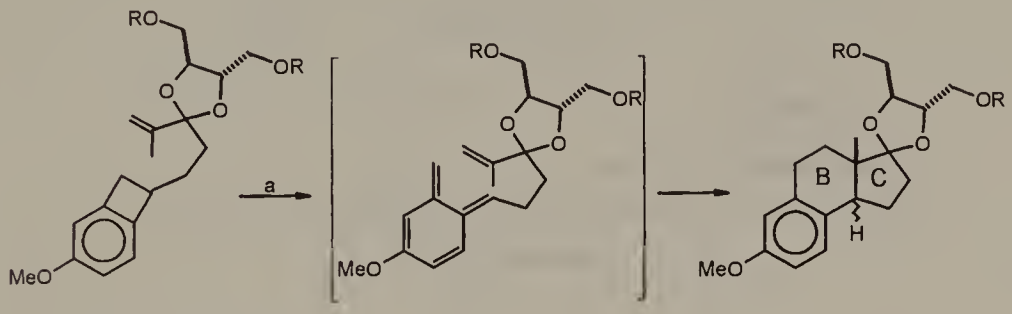
In contrast, conjugate organocuprate addition to 1,4-di-*O*-benzyl threitol acetals of 3-acetylcyclopent-2-en-1-one proceeds with low to moderate diastereoselectivity[359] (Scheme 13.132).



a: (2-thienyl)MeCu(CN)Li_2, Et_2O, -78°C, then MeONa, MeOH, RT

Scheme 13.132

Intramolecular Diels–Alder reactions of chiral *o*-quinodimethanes generated by thermal ring opening of the chiral acetal derivatives of benzocyclobutenes occur with high diastereofacial selection but with low d.e.[360] (Scheme 13.133).



a: *o*-dichlorobenzene, Δ

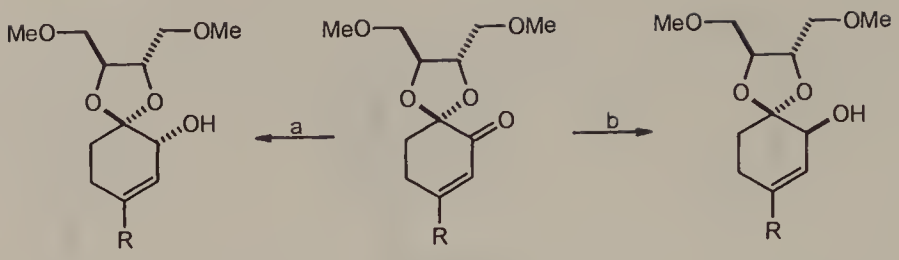
R, R	yield (%)	*trans* B/C : *cis* B/C	*trans* B/C, d.e. (%)
Me, Me	95	91 : 9	12
$(i\text{-}Pr_2Si)_2O$	82	97 : 3	29

Scheme 13.133

Fujioka, Tamura *et al.* found that diastereoselectivity of the $LiAlH_4$ reduction of acetal **13.138** bearing the enone functional group can be tuned by the choice of the salt additive. The reduction products, R = 3,4-$(MeO)_2C_6H_3$, were used for the synthesis of enantiomers of 3′-methoxy-4′-*O*-methyl-joubertiamine (**13.141**), a *Sceletium* alkaloid, using the Claisen–Eschenmoser rearrangement to create the quaternary chiral carbon atom [346] (Scheme 13.134).

Diastereoselective nucleophilic additions to threitol α-ketoacetals were reported by Mioskowski *et al.*[334] and Tamura *et al.*[336,349] Good to excellent diastereoselectivies were obtained with Grignard reagents as nucleophiles (Scheme 13.135).

In the reactions shown in Scheme 13.135, the observed high diastereoselectivity is undoubtedly due to the chelation of the magnesium cation by the oxygen

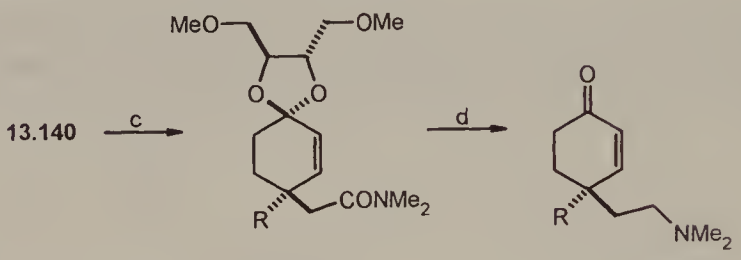


13.139 13.138 13.140

R = Me; Ph; 3,4-$(MeO)_2C_6H_3$

a: $LiAlH_4$, LiBr, Et_2O, -100°C (95%, d.e. 92%)

b: $LiAlH_4$, $MgBr_2$, Et_2O, -100°C (85-95%, d.e. 80%)

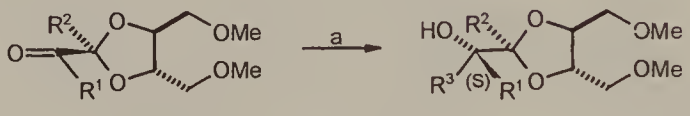


[R = 3,4-$(MeO)_2C_6H_3$] (*S*)-(+)-**13.141**

c: $MeC(OMe)_2NMe_2$, 110°C (90%)

d: $LiAlH_4$, Et_2O, then 80% AcOH, H_2SO_4 (cat.), Δ (82%)[346]

Scheme 13.134



a: R^3MgX, THF or Et_2O, -78°C

R^1	R^2	R^3	yield (%)	d.e. (%)	ref.
H	H	Me	70	80	334
H	H	n-Bu	65	74	334
Me	H	Et	91	76	336
Me	Et	Et	96	>98	336
Me	Et	CH_2=CH	93	>98	336
Me	Et	TMSC≡C	98	>98	336
Me	Et	Ph	81	96	336
Me	Ph	Et	98	>98	336
Me	Ph	CH_2=CH	90	96	336
Me	Ph	TMSC≡C	91	94	336
Me	Ph	Ph	84	94	336

Scheme 13.135

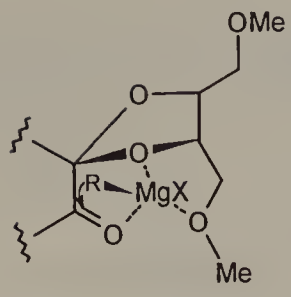
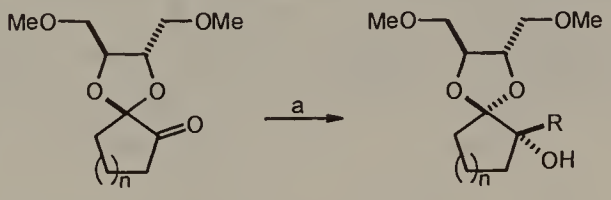


Figure 13.5

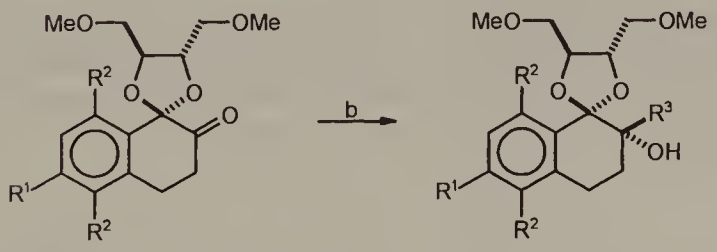
atoms of the threitol auxiliary and the carbonyl group[336] (Fig. 13.5, see also Fig. 13.4).

Reactions of chiral monoacetals of cyclic 1,2-diones with Grignard reagents follow the pattern shown in Fig. 13.5 to give acetals of α-hydroxy-α-alkyl ketones with excellent diastereoselectivity (see examples in Scheme 13.136).



a: RMgBr, THF, -78°C[361]

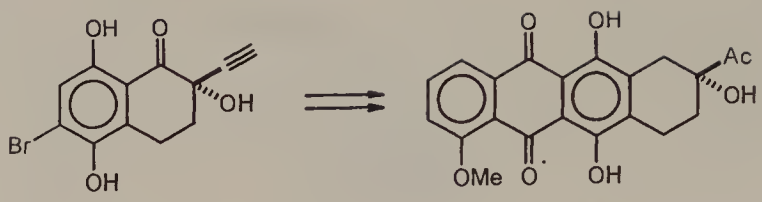
n	R	yield (%)	d.e. (%)
1	Me	91	96
2	Me	93	100
2	All	95	94
2	Ph	90	90



b: R^3MgBr, THF, -78°C[349,362]

R^1	R^2	R^3	yield (%)	d.e. (%)
H	H	Me	92	96
H	OMe	Me	95	100
Br	OMOM	Me	96	100
Br	OMOM	Et	94	100
Br	OMOM	TMSC≡C	98	100

Scheme 13.136 (*continued*)

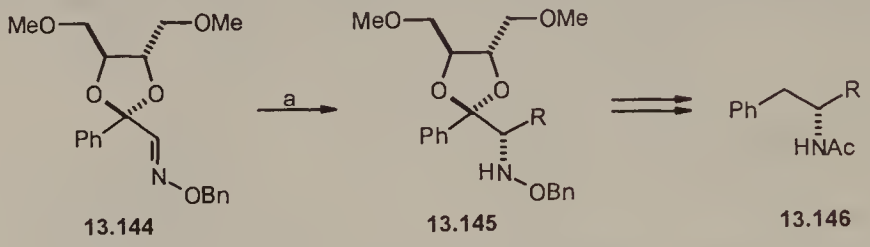


13.142 13.143

Scheme 13.136

The chiral tetralone derivative **13.142** obtained by the above route was used by Tamura in the synthesis of (−)-7-deoxydaunomycinone (**13.143**).[362]

Organocerium reagents, generated from Grignard reagents and cerium trichloride, add to the chiral α-aldoxime acetal **13.144** in a manner similar to that observed for the addition of Grignard reagents to ketones (Scheme 13.137).



13.144 13.145 13.146

R = Me, 84%, d.e. >98%

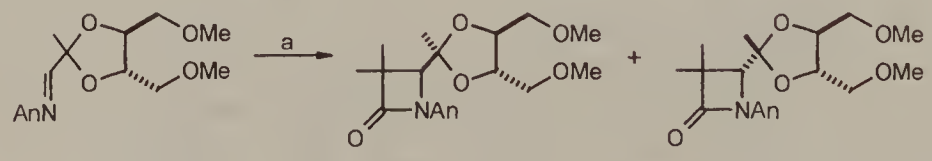
R = n-Bu, 81%, d.e. 94%

a: RMgX, $CeCl_3$, THF, 0°C[343]

Scheme 13.137

The addition product **13.145** can be converted to chiral *N*-acetylamine **13.146** in three steps with high yield.[343] Chastrette reported related additions of alkyllithiums to the hydrazonoacetal derived from 1,4-di-*O*-methyl-L-threitol.[406]

Diastereoselective addition of ester enolates to the chiral imine **13.147** derived from 1,4-di-*O*-methyl-L-threitol is a convenient method of stereodivergent synthesis of β-lactams. Fujisawa has found that by varying metal enolates, different diastereomeric products could be obtained,[342] as shown in the examples in Scheme 13.138.



13.147

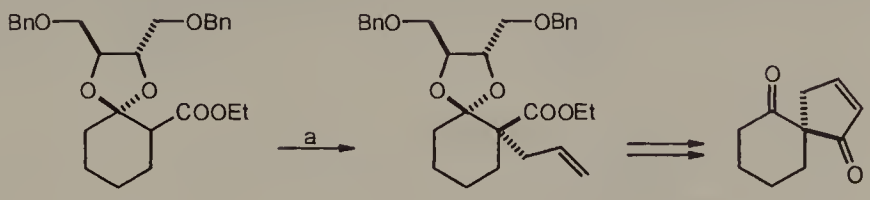
M = Li, 96% 99 : 1

M = $Ti(Oi\text{-}Pr)_3$, 94% 4 : 96

a: $Me_2C{=}C(OEt)OM$, -78°C → RT

Scheme 13.138

Asymmetric allylation of chiral acetal **13.148** gave product **13.149** with good diastereoselectivity; the product was further converted to spiro[4.5]dec-2-ene-1,6-dione[347] (Scheme 13.139).

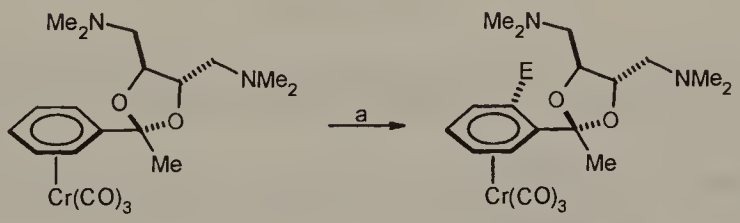


13.148 **13.149** e.e. 88%

a: 3 eq. LDA, THF-TMEDA (10 : 1), 1 eq. AllBr, -78°C, then TsOH, benzene, Δ (95%, d.e. 88%)

Scheme 13.139

Asymmetric ortho deprotonation of (η^6-arene)$Cr(CO)_3$ complexes of chiral acetals, derived from aryl ketones or aldehydes and 1,4-disubstituted L-threitols, proceeds in a number of cases with good diastereoselectivity (Aube[341] and Green[196]). The deprotonated species were quenched with carbon, phosphorous, or silicon electrophiles (Scheme 13.140).

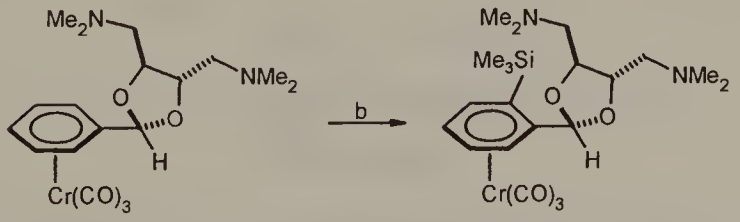


E = $SiMe_3$, 62%, d.e. 88%

E = PPh_2, 85%, d.e. 88%

E = $C(OH)Ph_2$, 80%, d.e. 96%

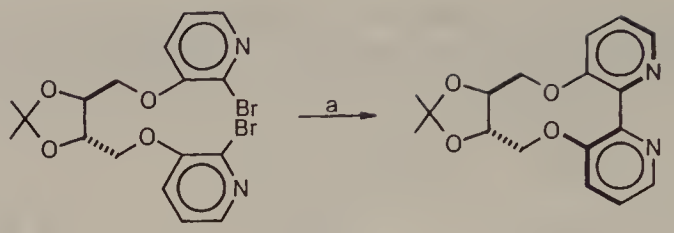
a: 1.1 eq. t-BuLi, THF, -78°C, 2.5 h, then 1.2 eq. Me_3SiCl or Ph_2PCl or $Ph_2C{=}O$[341]



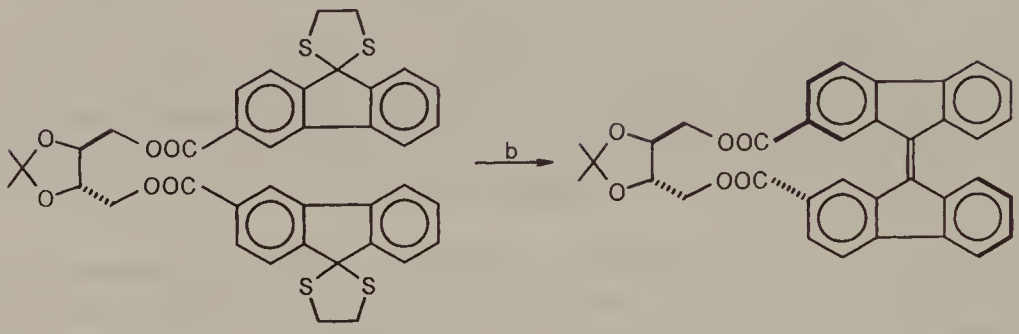
b: n-BuLi, Et_2O, -78°C, 1h, then Me_3SiCl (70%, d.e. 74%)[196]

Scheme 13.140

2,3-*O*-Isopropylidene threitol is useful as a chiral auxiliary in the formation of C_2-chiral macrocyclic rings incorporating twisted 2,2′-bipyridine (De Lucchi[339]) or bifluorenylidene (Luh[340,363]) units (Scheme 13.141).



a: $NiCl_2$, PPh_3, Zn, DMF, 50°C, 20h (38%)[339]

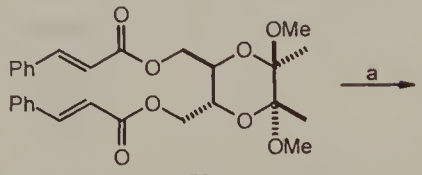


b: $W(CO)_6$, PhCl, Δ, 48h (40%)[340,363]

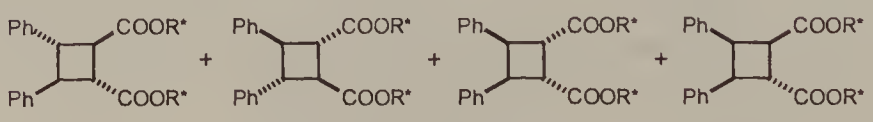
Scheme 13.141

It is of interest to note that removal of the 2,3-*O*-isopropylidene-L-threitol auxiliary from the macrocyclic products shown in Scheme 13.141 leads to optically inactive biaryl compounds.

Furthermore, a dioxane-type threitol acetal was used by Scharf as a template for asymmetric intramolecular [2+2] photocycloaddition of the cinnamate residues in the bis-cinnamate **13.150**. A separable mixture of (+)-δ-truxinate (**13.151**), (−)-δ-truxinate (**13.152**), β-truxinate (**13.153**), and neotruxinate (**13.154**) esters was obtained[188] (Scheme 13.142).



13.150

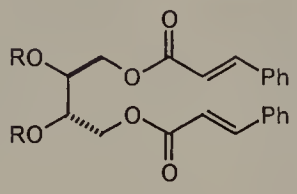


13.151 **13.152** **13.153** **13.154**

a: hν (high-pressure Hg lamp), PhMe, -28°C, 60h (89% total)

Scheme 13.142

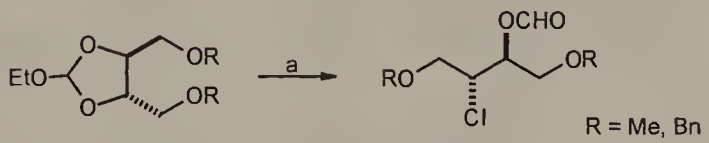
An earlier study by Green *et al.* has shown that while (+)-δ-truxinate ester (**13.151**) was the main product of photocyclization of the less rigid bis-cinnamate **13.155**, photocyclization of the more rigid bis-cinnamate **13.156** gave (−)-δ-truxinate ester (**13.152**) in only low preference over the (+)-δ-stereoisomer **13.151**.[364]



13.155 R = Me

13.156 R,R = CMe_2

Erythro-configured products are available from the fully protected orthoformates derived from L-threitol (Scheme 13.143).

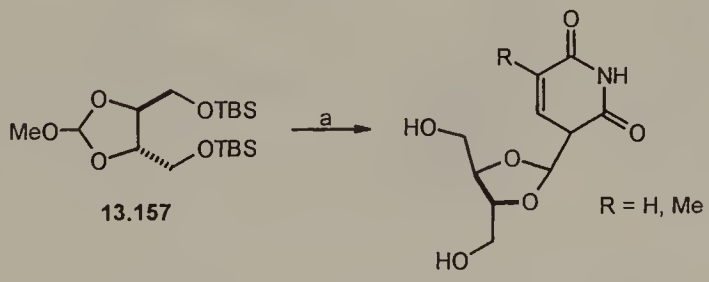


a: 1.5 eq. PCl_5, CH_2Cl_2, 0°C → RT, 3-8h (86-99%)[87,138,350]

Scheme 13.143

These chloroformates can be further converted to 2,3-epoxides of L-threitol (see Section 13.6).

[4,5-Bis(hydroxymethyl)-1,3-dioxolan-2-yl]nucleosides, potential inhibitors of HIV, were obtained from 2-methoxy-1,3-dioxolane **13.157** (Scheme 13.144).

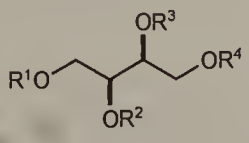


13.157

a: silylated thymine or uracil, TMSOTf (53-63%), then Bu_4NF (95-97%)[143]

Scheme 13.144

13.10.3 Tetra-*O*-Protected Acyclic L-Threitol Derivatives



XX

Table 13.19 Non-acetal 1,2,3,4-tetra-*O*-protected L-threitol derivatives (XX)

R^1	R^2	R^3	R^4	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
Me	THP	THP	Me	—	—	127
Me	1-cyclohexenyl	TMS	Me	—	+4.8 (CH_2Cl_2)	344
Me	Ar[a]	Me	Ar[a]	112–113	+230.0 ($CHCl_3$)[b]	121
$HS(CH_2)_2$	Me	Me	$HS(CH_2)_2$	175/5	—	366
Bn	Me	Me	TBS	—	+18.6 ($CHCl_3$)	313
Bn	1-cyclohexenyl	TMS	Bn	—	−6.8 (CH_2Cl_2)	344
Bn	MOM	MOM	Ac	—	−14.3 (MeOH)	200
Bn	$HO(CH_2)_2$	$HO(CH_2)_2$	Bn	—	+2.5 ($CHCl_3$)	130,366
Bn	$TsO(CH_2)_2$	$(CH_2)_2OTs$	Bn	—	—	366
Bn	$THPO(CH_2)_2$	$THPO(CH_2)_2$	Bn	—	+3.0 ($CHCl_3$)	366
Bn	$Ts[O(CH_2)]_2$	$Ts[O(CH_2)]_2$	Bn	—	—	367
Bn	$THP[O(CH_2)]_2$	$THP[O(CH_2)]_2$	Bn	—	—	367
Bn	$Pr[O(CH_2)]_2$	$Pr[O(CH_2)]_2$	Bn	—	+5.3 ($CHCl_3$)	367
Bn	$I(CH_2)_2O(CH_2)_2$	$I(CH_2)_2O(CH_2)_2$	Bn	—	—	131
Bn	$HOOCCH_2$	$HOOCCH_2$	Bn	—	+7.4 ($CHCl_3$)	130,368
Bn	Ar[c]	Ar[c]	Bn	—	+14.7 (THF)	368
Ac	Ac	$BrCH_2$	Ac	—	—	332
Ac	Ac	Ac	Ac	54	+13.8 ($CHCl_3$)[d]	124
Bz	Bz	$MeOCH_2$	Bz	—	+7.4 ($CHCl_3$)	97
Bz	Bz	$AcOCH_2$	Bz	—	+11.0 ($CHCl_3$)	97
Bz	Bz	$BrCH_2$	Bz	—	—	97
Bz	Bz	RCH_2[e]	Bz	95–97	+18.7 ($CHCl_3$)	97
Bz	Bz	RCH_2[f]	Bz	>300	+2.0 ($CHCl_3$)	97
Bz	Bz	RCH_2[g]	Bz	235	+13.5 (MeOH)	97
Bz	Bz	RCH_2[h]	Bz	142–143	+14.0 ($CHCl_3$)	97
Bz	Bz	Bz	Bz	97	+4.3 ($CHCl_3$)	37
4-ClC_6H_4CO	4-ClC_6H_4CO	4-ClC_6H_4CO	4-ClC_6H_4CO	112–114	+1.2 ($CHCl_3$)	369
Ar[a]	Ar[a]	Ar[a]	Ar[a]	207–208	−36.0 ($CHCl_3$)[b]	326
4-$O_2NC_6H_4CO$	Me	Me	4-$O_2NC_6H_4CO$	143–144	—	73
Ar[i]	Me	Me	Ar[i]	181	—	269

[a] Ar = 4-(PhN=N)C_6H_4CO.
[b] At 546 nm.
[c] Ar = 1-bromo-2-naphthyl.
[d] $[\alpha]_D$ −21.9 ($CHCl_3$) in ref. 79.
[e] R = 9-adenyl.
[f] R = 1-cytosyl.
[g] R = 9-guanyl.
[h] R = 1-thymyl.
[i] Ar = 3,5-$(O_2N)_2C_6H_3CO$.

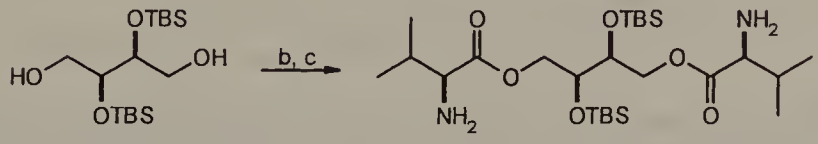
Synthesis

These products are obtained from mono-, di-, or tri-*O*-protected threitol derivatives by standard procedures. A few examples are given in Scheme 13.145.

Product **13.158** has been used in the synthesis of a biologically active analogue of antibiotic A-32390A.[277]

Acetal cleavage reactions provide access to acyclic tetra-*O*-protected threitols with enol ether, halomethyl, or acetoxymethyl substituents (Scheme 13.146). The latter products have been further converted to acyclic nucleosides.

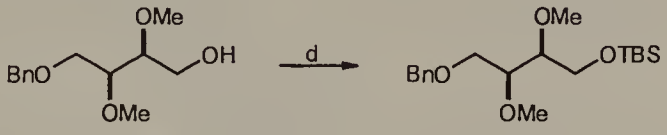
a: NaH, MeI, imidazole (cat.), n-Bu_4NBr (cat.), THF, 0°C, 2h (100%)[127]



13.158

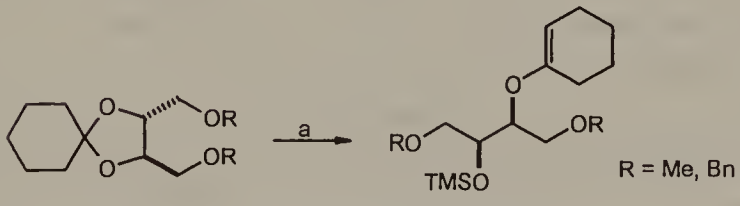
b: 2.1 eq. L-*N*-*Z*-valine, 2.1 eq. DCC, 0.2 eq. DMAP, CH_2Cl_2, RT, 24h (quant.)

c: H_2, 10% Pd/C, AcOEt (quant.)[277]

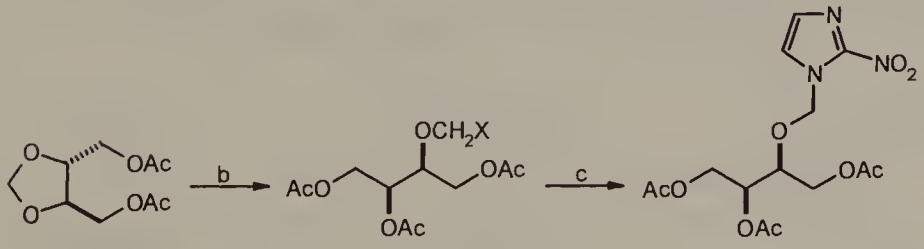


d: TBSCl, imidazole, DMAP (cat.), CH_2Cl_2, RT (100%)[313]

Scheme 13.145



a: TMSOTf, i-Pr_2NEt, CH_2Cl_2, -20°C → RT, 24h (96-98%)[344]

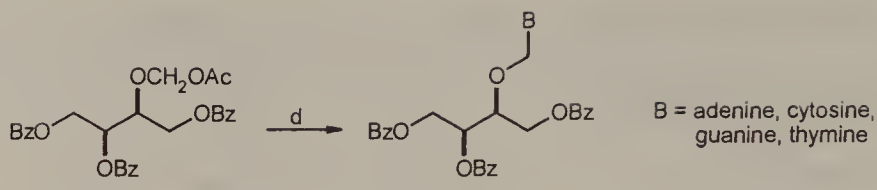


b (X = Br): AcBr, $ZnCl_2$, 0°C → RT, 1h[332]

(X = AcO): Ac_2O, AcOH, $ZnCl_2$, RT, overnight[370]

c: 2-nitroimidazole, NEt_3, DMF, RT, 3h[332]

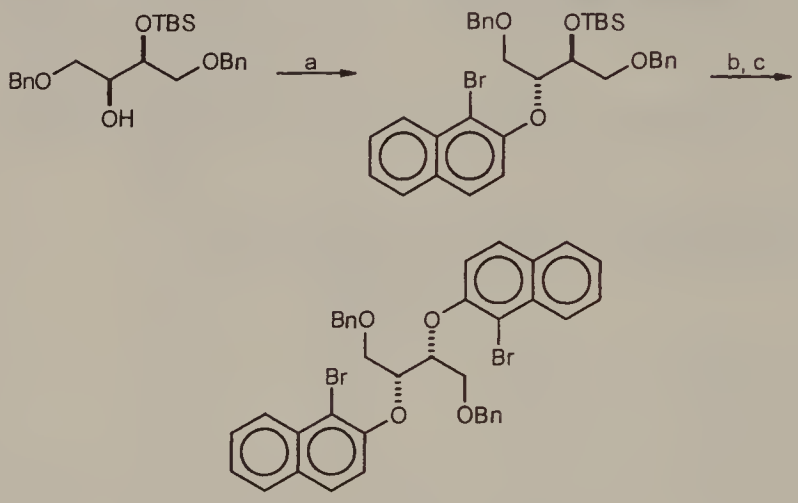
Scheme 13.146 (*continued*)



d: B-$SiMe_3$, KI, dibenzo-18-crown-6, MeCN, PhMe, Δ (78-88%)[97]

Scheme 13.146

2,3-Di-aryloxy substitution with inversion of configuration was effectively executed by consecutive Mitsunobu reactions of the 1,2,4-tri-*O*-protected threitol with 1-bromo-2-naphthol as a nucleophile[368] (Scheme 13.147).



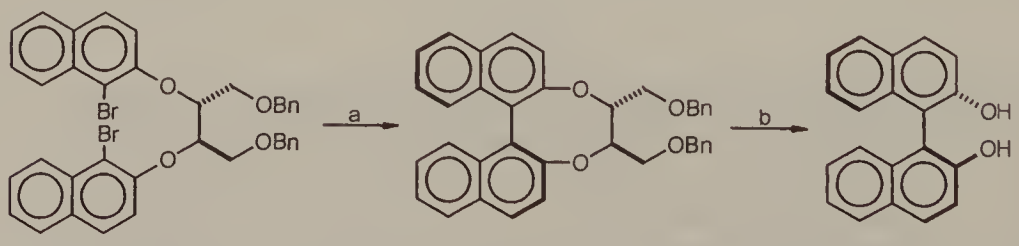
a: 1-bromo-2-naphthol, DEAD, PPh_3, THF, 0°C → RT, 14h (93%)

b: n-Bu_4NF (92%) c: repeat a (67%)

Scheme 13.147

Applications

Nearly complete asymmetric induction was obtained by Lipshutz *et al.* in the asymmetric synthesis of (*S*)-2,2′-binaphthol by intramolecular oxidative cou-



a: 2 eq. t-BuLi, CuCN, -78° (78%, d.e. ~100%)

b: NBS, then aq. KOH (86%)

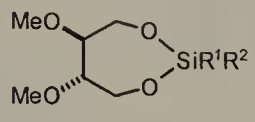
Scheme 13.148

pling of the above-mentioned tetra-*O*-substituted D-threitol derivative bearing two 1-bromo-2-naphthyl residues[368] (Scheme 13.148). In this "sacrificial" synthesis the threitol auxiliary could not be recovered.

A similar protocol was used for the synthesis of the fungal metabolite (+)-kotanin.[371]

13.10.4 Cyclic Siloxanes and Boronates of L-Threitol

Cyclic silyl ether derivatives **XXI** were synthesized from 2,3-di-*O*-methyl-L-threitol and dichlorodialkylsilanes[372] (Table 13.20).

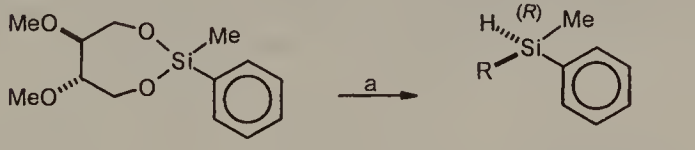


XXI

Table 13.20 Properties of 1,4-cyclic siloxane derivatives of L-threitol[372] (XXI)

R^1	R^2	b.p. (°C/torr)	$[\alpha]_D$ (benzene)
Me	All	100/6	+61.8
Me	Ph	133/0.6	+46.1
Me	1-naphthyl	154/0.4	+38.2
Et	Ph	128/0.2	+48.3
Ph	1-naphthyl	220/0.2	+79.5

Compounds having chiral silicon atom were obtained by Kobayashi *et al.* from siloxanes bearing the 2,3-di-*O*-methyl-L-threitol ligand[372,373] (Scheme 13.149).



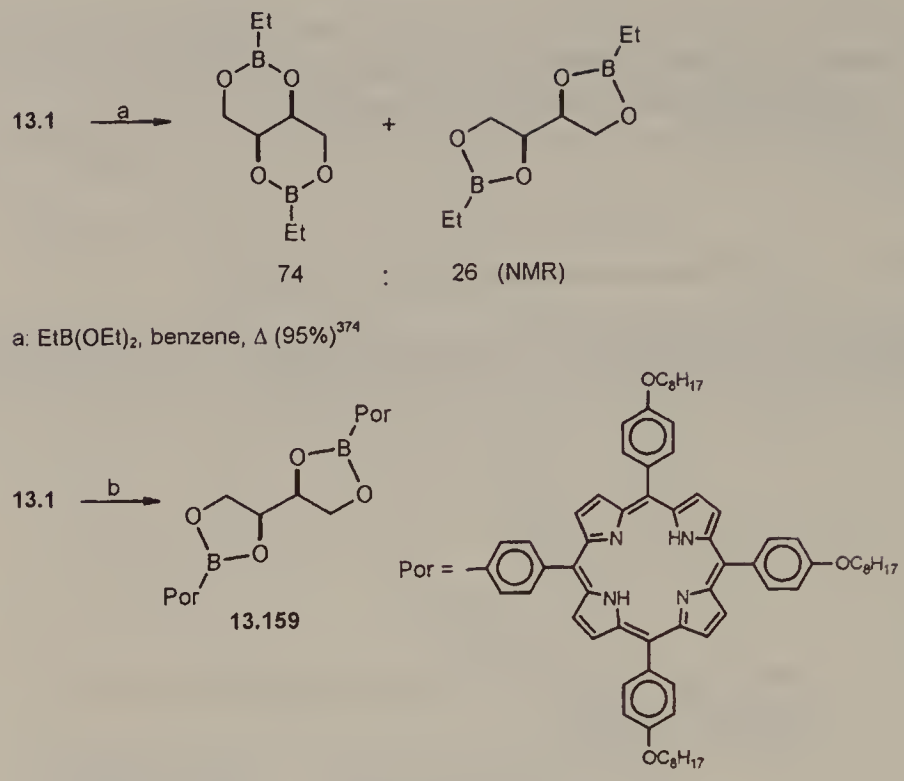
R = Et: 70%, e.e. 93%

R = n-Pr: 50%, e.e. 98%

a: RMgBr, then $LiAlH_4$

Scheme 13.149

Boronic acids with L-threitol readily form bis-boronate esters which may find interesting applications as chiral ligands and auxiliaries (Scheme 13.150).



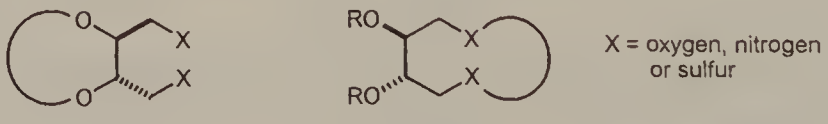
Scheme 13.150

Shinkai used the dimeric porphyrin boronate-threitol ester **13.159** for photochemical and chiroptical studies.[375]

13.11 L-THREITOL BASED CROWN ETHERS AND RELATED COMPOUNDS

13.11.1 Crown Ethers, Their Aza- and Thiaanalogues, and Cryptands

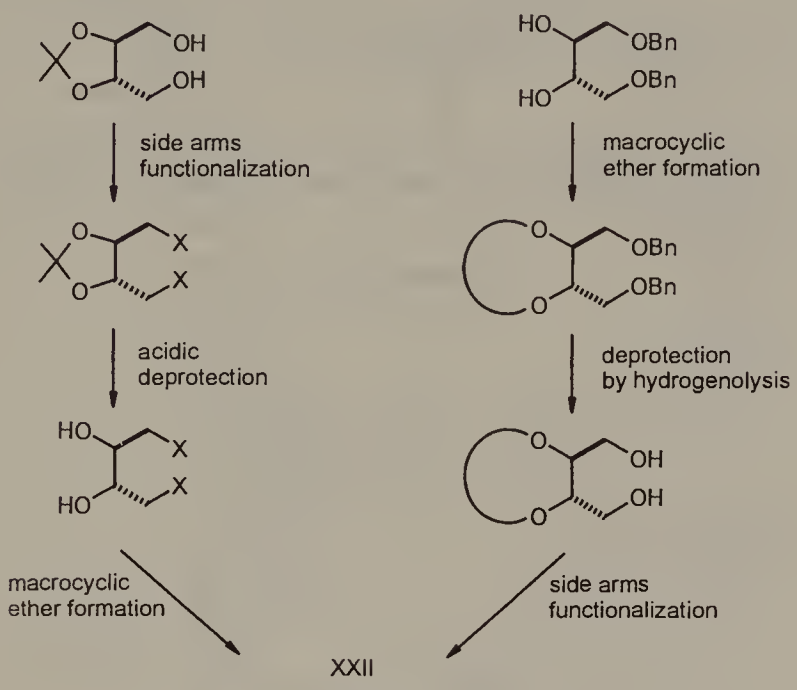
Crown ethers and aza-crown ethers based on L-threitol belong to the two structural types, **XXII** and **XXIII**, in which the macrocycle incorporates either the $O–C_2–C_3–O$ or the $X–C_1–C_2–C_3–C_4–X$ structural unit.



XXII **XXIII**

Crown ethers of the type **XXII** (in some cases properly described as lariat-type crown ethers) are by far more frequently encountered than crown ethers of the type **XXIII**. Structures of these compounds are listed separately below; in

addition some other threitol-incorporating macrocycles, such as porphyrins, hemispherands, and dendrimers, are mentioned at the end of this chapter.
Crown ethers of the type **XXII** are commonly synthesized according to either of the two complementary routes shown in Scheme 13.151.



Scheme 13.151

Macrocyclic polyether synthesis is discussed in detail in a number of reference works.[376-378]

Crown ethers of the type **XXIII** can act as regio- and enantioselective ligands, due to the features characteristic of their structure (Koga[218,379]), Fig. 13.6.

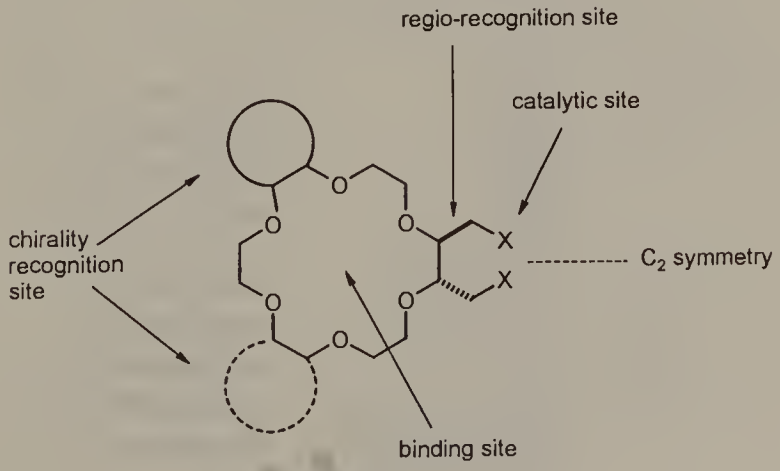
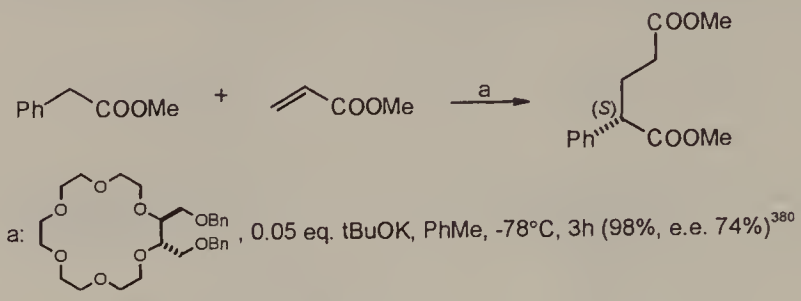


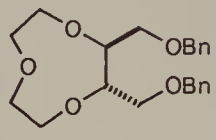
Figure 13.6

An example of application of the chiral crown ether based on threitol as a C_2-symmetric ligand in the asymmetric Michael addition is shown in Scheme 13.152.

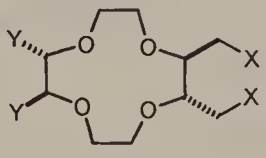


Scheme 13.152

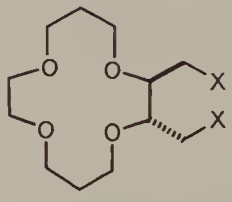
9-crown-3[133]



12- and 14-crown-4

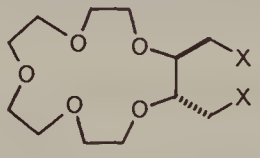


X = OH, OBn, OBz
Y = H, CH_2X[366]



X = OH, OTs, OBn[144]

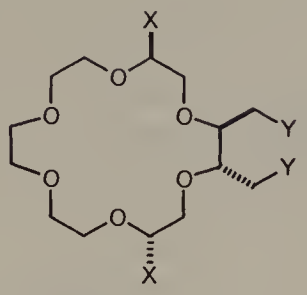
15-crown-5



X =	OH[132,366]	OOC(2-$HOOCC_6H_4$)[367]
	OBn[132,366]	OOCCH(OH)Ph[367]
	SBn[25]	OOC(4-$tBuC_6H_4$)[132]
	OTs[367]	OOC(2-ClC_6H_4)[132]
	OCH_2(2-IC_6H_4)[367]	OOC(3-ClC_6H_4)[132]
	OCH_2(4-FC_6H_4)[367]	OOC(4-ClC_6H_4)[132]
	OCH_2(3-$O_2NC_6H_4$)[367]	OOC(2,4-$Cl_2C_6H_3$)[132]
	OBz[132,366]	OOC(4-$MeOC_6H_4$)[132]
	OCH_2[3,5-$(O_2N)_2C_6H_3$][367]	OOC(3,4-$(MeO)_2C_6H_3$)[132]
	OCH_2(4-$OHCC_6H_4$)[367]	O(2-naphthoyl)[132]

Figure 13.7 (*continued*)

18-crown-6



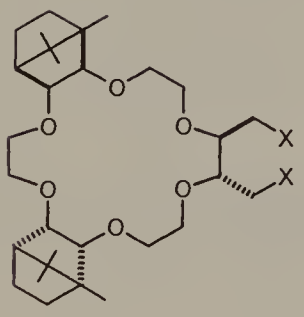
X = H, Y = OH[130]
OTs[218]
OMe[380]
OBn[130,165,218]
$OCHPh_2$[380]
$O(CH_2)_2OTs$[218]
$O(CH_2)_2OBn$[218]
$O(CH_2)_2SH$[218]
$O(CH_2)_2SBz$[218]
$[O(CH_2)_2]_2OTs$[365]
$[O(CH_2)_2]_2SH$[365]
$O(2\text{-}MeOC_6H_4)$[380]
OAc[130]
$OOC(2,4\text{-}Cl_2C_6H_3)$[367]
SH[218]
SBn[25]
$S(2\text{-}HSC_6H_4)$[365]
$S(3\text{-}HSC_6H_4)$[365]
SBz[218]

X = n-Pr, Y = OH[139]
OTs[139]
OBn[139]
SH[139]
SBz[139]

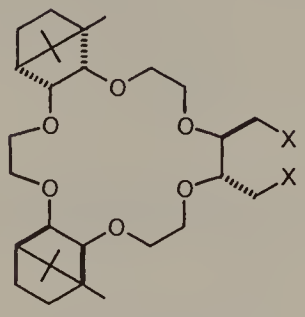
X = CH_2OH, Y = SH[139]

X = CH_2OMe, Y = OH[139]
OTs[139]
OBn[139]
SH[139]
SBz[139]

X = CH_2OMOM, Y = OH[139]
OTs[139]
OBn[139]
SH[139]
SBz[139]

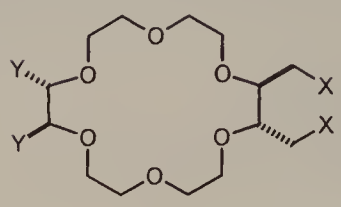


X = OH[379]
OTs[139]
OBn[139]
SH[139,379]
SBz[139]

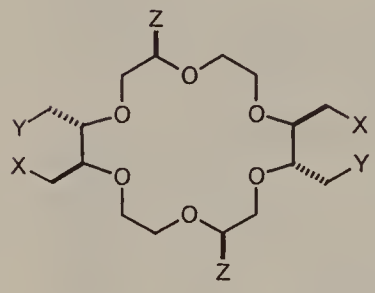


X = OH[139,379]
OTs[139]
OBn[139]
SH[139,379]

Figure 13.7 (*continued*)

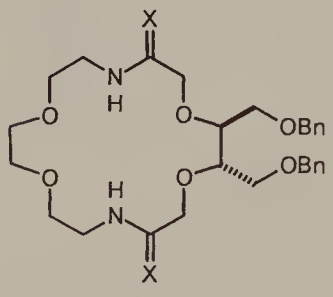


X	Y
OH	CH_2OH[131,382]
OH	$CON(C_8H_{17})_2$[131]
OBn	CH_2OBn[133,366]
OBn	$CONMe_2$[131]
OBn	$CON(C_8H_{17})_2$[131]
OTr	CH_2OTr[133]
OAc	CH_2OAc[133]
$OOC(4\text{-}ClC_6H_4)$	$CH_2OOC(4\text{-}ClC_6H_4)$[367]
$OOC(2,4\text{-}Cl_2C_6H_4)$	$CH_2OOC(2,4\text{-}Cl_2C_6H_3)$[367]
NMe_2	CH_2NMe_2[381]

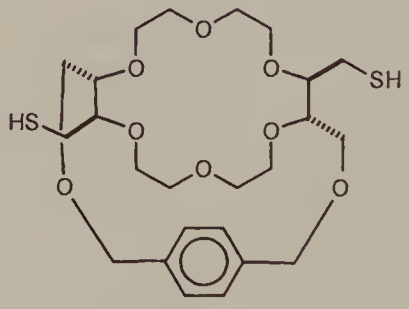


X	Y	Z
OH	OMOM	H[321]
OBn	OTr	H[321]
SH	$O(2\text{-}MeOC_6H_4)$	H[321]
SH	$O(2\text{-}MeOC_6H_4)$	COOH[382]
SH	$O(2\text{-}MeOC_6H_4)$	COOMe[382]
SH	$O(2\text{-}MeOC_6H_4)$	CONHMe[382]

Azacrown ethers and cryptands



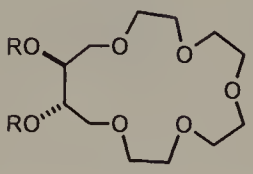
$X = H_2$; O[130]



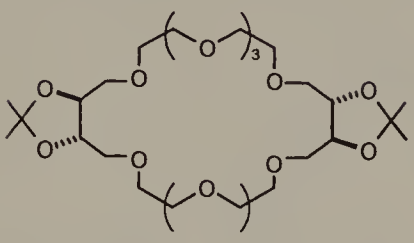
ref. 321

Figure 13.7 Crown ethers, aza-crown ethers and cryptands based on the 2,3-diol unit of L-threitol.

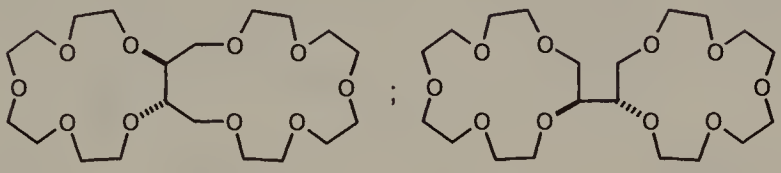
Crown ethers



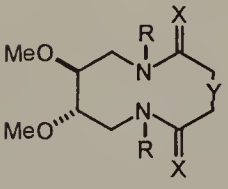
R = H; R,R = CMe_2[35]



ref. 35



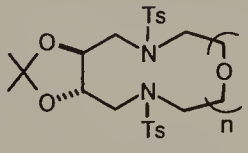
ref.35



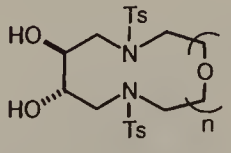
R = Me, X = H_2, Y = O;[96] [5,96] [383]

R = Et, X = H_2, Y = [5]

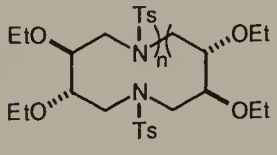
R = Me or Et, X = O, Y = [5]



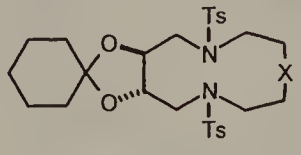
n = 1, 2[384]



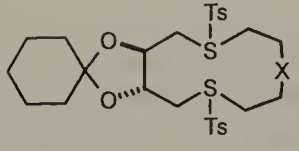
n = 1, 2, 3[385]



n = 1, 2, 3[272]

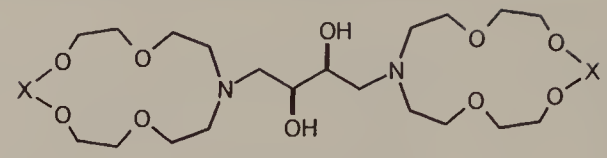


X = NTs; $(CH_2)_6$[178]

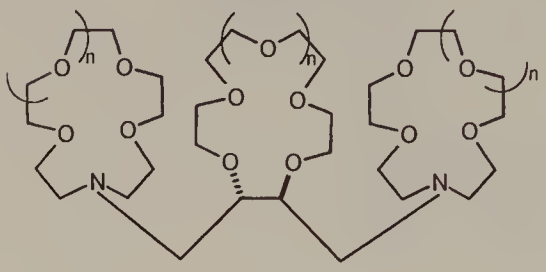


X = [O]; S; [S]; [S]; [S] [180]

Figure 13.8 (*continued*)

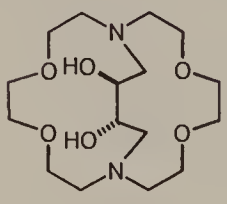


X = $(CH_2)_2$[46]
$(CH_2)_2O(CH_2)_2$[46]
$(CH_2)_2NH(CH_2)_2$[46]

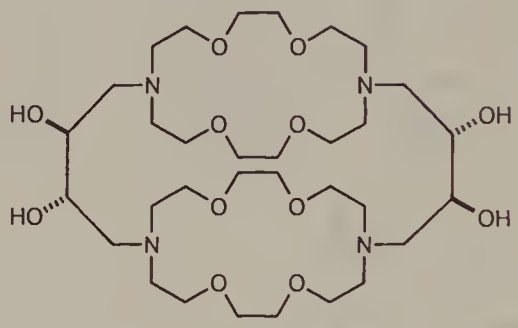


n = 1, 2[46]

Cryptands

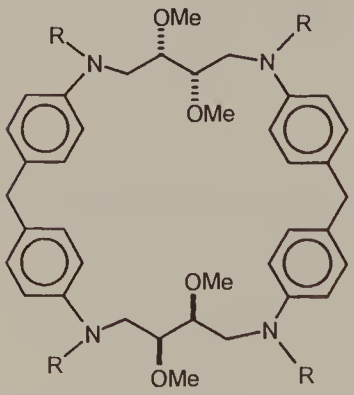


ref.46, 386



ref. 46

Paracyclophanes

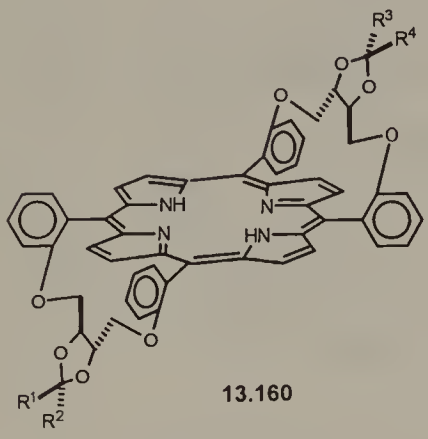


R = H, Ts[395]

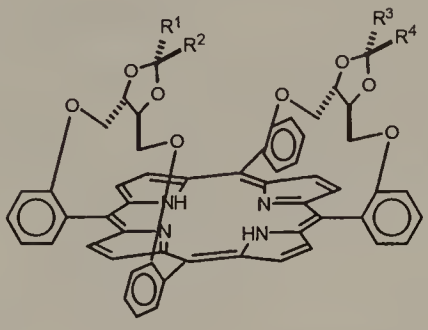
Figure 13.8 Crown ethers, their aza- and thiaanalogues, polynuclear crown ethers, cryptands and paracyclophanes based on the 1,4-diol unit of L-threitol.

13.11.2 L-Threitol-Strapped Porphyrins, Hemispherands, and Dendrimers

Collman *et al.* prepared chiral porphyrins **13.160** and **13.161** whose frameworks were constructed from L-threitol straps that could be varied by changing the 2,3-acetal protecting group. The manganese derivatives of these systems were used as asymmetric catalysts in the epoxidation of unfunctionalized olefins, with up to 88% e.e. obtained in the epoxidation of 1,2-dihydronaphthalene.[202,387]

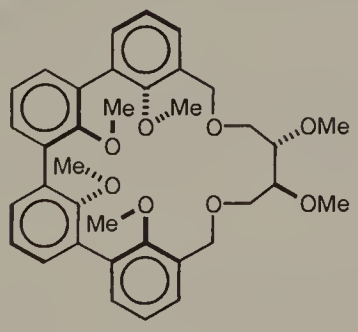


13.160

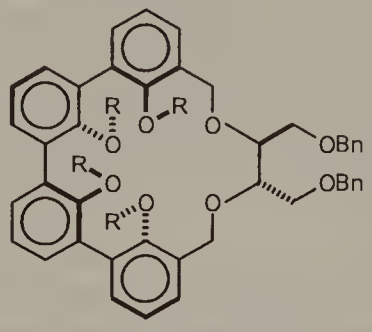


13.161

Cram *et al.* synthesized chiral hemispherands which have either a 1,4- (**13.162**) or a 2,3- (**13.163**) L-threitol bridging unit and investigated their binding properties. Of these hemispherands, only **13.163**, R = Bn bearing four bulky benzyloxy substituents in the quaterphenyl unit, was characterized as configurationally stable and consisting of a single diastereomer.[388,389]

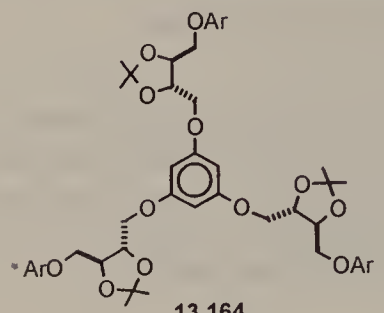


13.162

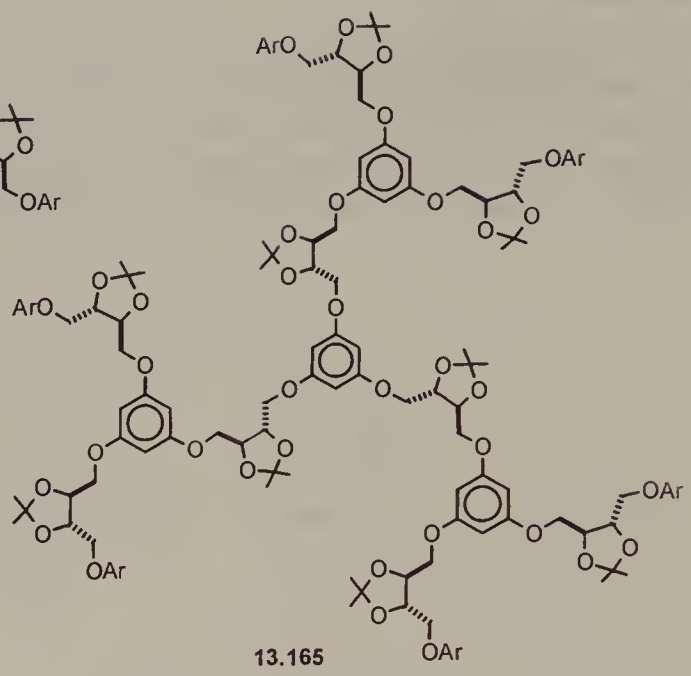


13.163 R = Me, Et, Bn

Chow *et al.* synthesized chiral dendrimers based on the 1,4-linked unit of 2,3-isopropylidene L-threitol. Both zeroth generation (**13.164**) and first generation (**13.165**) dendrimers were obtained,[302,390] as well as mixed D/L diastereomeric dendrimers.[391]



13.164



13.165

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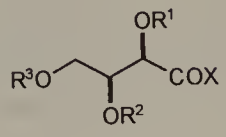
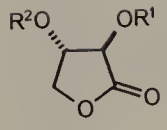
14 Threonic Acid



I



II

Table 14.1 Derivatives of L-threonic acid (I) and of L-threonolactone (II)

R^1	R^2	R^3	X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
				Formula I		
epoxy[c]		H	OEt	45–46	−33.8 (EtOH)	1
epoxy[c]		Ac	OMe	25–26	−65.8 (MeOH)	1
epoxy[c]		TBS	OMe	90–91/0.7	−24.7 ($CHCl_3$)	2,3
H	epoxy[c]		ONa	—	+16.2 (H_2O)	1
H	epoxy[c]		NH_2	43–48	−18.3 (MeOH)	1
H	H	H	NH_2	105–107	+77.5 (MeOH)	4,5
H	H	H	NHOBn	125–126	+50.8 (MeOH)	5
H	H	TBS	NHOBn	70–72	+12.5 ($CHCl_3$)	5
H	Me	H	NH_2	78–81	+57.4 (MeOH)	6
H	Me	Me	NH_2	149–150	+64.8 (MeOH)	6
H	$-CMe_2-$		OH	90	+14.1 ($CHCl_3$)	7
H	$-CMe_2-$		OMe	70–75/0.001	+18.4 ($CHCl_3$)	5
H	$-CMe_2-$		OBn	52–54	+31.5 ($CHCl_3$)	7,8
H	$-CMe_2-$		NH_2	77–79	+29.4 ($CHCl_3$)	5
Me	Me	Me	OMe	147–149/12	+40.2 (MeOH)	6
Me	Me	Me	NH_2	79	+63.7 (MeOH)	6
t-Bu	$-CMe_2-$		OEt	—	+18.2 ($CHCl_3$)	3
Bn	$-CMe_2-$		OMe	150/0.05	+18.5 ($CHCl_3$)[a]	3,9
THP	H	H	OEt	—	—	10
THP	H	Tr	OEt	—	—	10
THP	$-CMe_2-$		OMe	78–83/0.01	+24.3 ($CHCl_3$)	11–13
$-CMe_2-$		H	OMe	80–85/0.1	−19.2 (MeOH)	14,15
$-CMe_2-$		Ms	OMe	100/0.03	−25.7 (Me_2CO)	14
$-CMe_2-$		Ts	OMe	47–49	−22.1 (MeOH)	16
$-CMe_2-$		TBS	OMe	—	−15.0 (Me_2CO)	17,18
Ac	epoxy[c]		NH_2	135–136	−53.5 (MeOH)	1

(*continued*)

Table 14.1 (*continued*)

R^1	R^2	R^3	X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
Ac	H	H	OMe	66–67	+36.2 (MeOH)	19
Ac	$-CMe_2-$		OMe	135–138/14	+37.4 (MeOH)	19
Ac	Ac	Ac	OH	76–78	−29.0 ($CHCl_3$)	4
Ac	Ac	Ac	OMe	100/0.005	−30.0 (MeOH)	20
Ac	Ac	Ac	NH_2	124–125	−27.0 ($CHCl_3$)	4
Ac	Ac	Ac	NHAc	120–122	−25.0 ($CHCl_3$)	4
Piv	H	H	OMen[b]	147–148	−25.4 ($CHCl_3$)	21
Piv	H	TBDPS	OBn	—	+7.5 ($CHCl_3$)	21
Piv	$-CMe_2-$		OBn	76.5–77	+35.6 ($CHCl_3$)	21
Piv	$-CMe_2-$		OMen[b]	86–88	−8.8 ($CHCl_3$)	21
Piv	$-CMe_2-$		Cl	45–47	—	21
Piv	$-CMe_2-$		OMe	43–44	+28.2 ($CHCl_3$)	3
Piv	Ms	TBDPS	OBn	—	+6.2 ($CHCl_3$)	21
Bz	H	Bz	OEt	106–107	−64.1 (EtOH)	22
Bz	Bz	H	OEt	60–73	−63.8 (EtOH)	22
Bz	Bz	H	Oi-Pr	—	−41.4 (EtOH)	22
Bz	Bz	Bz	OH	122–123	−56.0 ($CHCl_3$)	4
Bz	Bz	Bz	OEt	—	−60.0 (EtOH)	22
Bz	Bz	Bz	Oi-Pr	72	−70.4 (EtOH)	22
Bz	Bz	Bz	NH_2	114–116	−45.0 ($CHCl_3$)	4
C(S)OPh	$-CMe_2-$		OMe	102–103	+4.2 ($CHCl_3$)	23
TBS	H	TBS	NHOBn	55–57	+44.9 ($CHCl_3$)	5
Ms	$-CMe_2-$		OMe	105–106	+36.3 ($CHCl_3$)	24
Ts	$-CMe_2-$		OEt	69–71	+45.1 (EtOH)	25
Ts	$-CMe_2-$		NH_2	136–138	+57.7 ($CHCl_3$)	20
				Formula II		
H	H	—	—	75–76	+51.2 (MeOH)	4,5,20,26
H	Me	—	—	—	+20.0 (MeOH)	6
Bn	Bn	—	—	—	+58.0 ($CHCl_3$)	27
Bz	Bz	—	—	116–117	+188.0 (EtOH)	22,28

[a] $[\alpha]_D$ +62.3 ($CHCl_3$) in ref. 9.

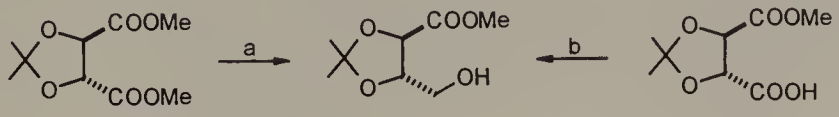
[b] Men = (−)-menthyl.

[c] Epoxy group in place of the two OR groups.

Synthesis

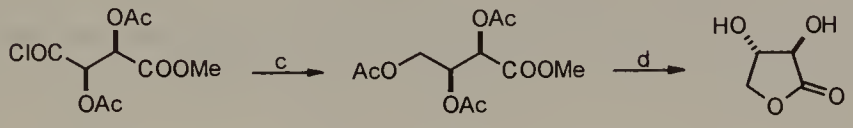
Derivatives of threonic acid are available from suitably protected tartaric acid derivatives by various reduction or hydrogenation reactions. Although the reduction or hydrogenation step is usually not high-yielding, it is nevertheless an attractive route to threonates from readily available symmetrical tartrate precursors. Note that desymmetrization of tartrate epoxide by reduction gives threonic acid derivative **14.2** in high yield, as reported by Manchand *et al.*[1]

L-Threonolactone (**14.1**) is obtained most conveniently from methyl hydrogen di-*O*-acetyl L-tartrate by simple $NaBH_4$ reduction[29] (Scheme 14.1).



a: 0.6 mol eq. $NaBH_4$, MeOH, 0°C → RT, 30 min. (35%, other products: 2,3-*O*-isopropylidene-L-threitol, 25% and substrate, 30%)[18]

b: 0.4 M BH_3, THF, 0°C, 8.5h (58%)[14,16]

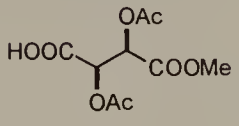


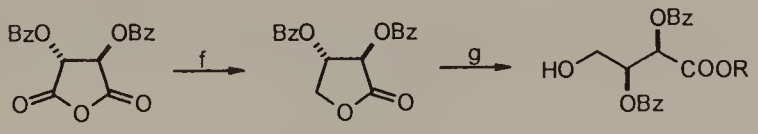
14.1

c: $LiAlH(Ot\text{-}Bu)_3$, THF, 0°C, 1h then Ac_2O, HCl, RT, 2h (58%)[20]

d: KOH, MeOH-H_2O, RT, 30 min., then Δ, then HCl (71%)[20]

e: $NaBH_4$, H_2O, RT, 4h, then KOH, MeOH-H_2O, Δ, then HCl (74%)[29]



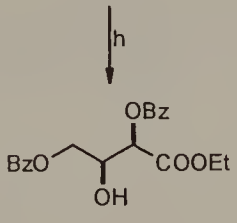


R = Et, i-Pr

f: H_2, 7% Pd/$BaSO_4$, 90°C, 14h (31-42%)[22]

g (R = Et, i-Pr): ROH, HCl, Δ, 5 -15 min. (>95%)[22]

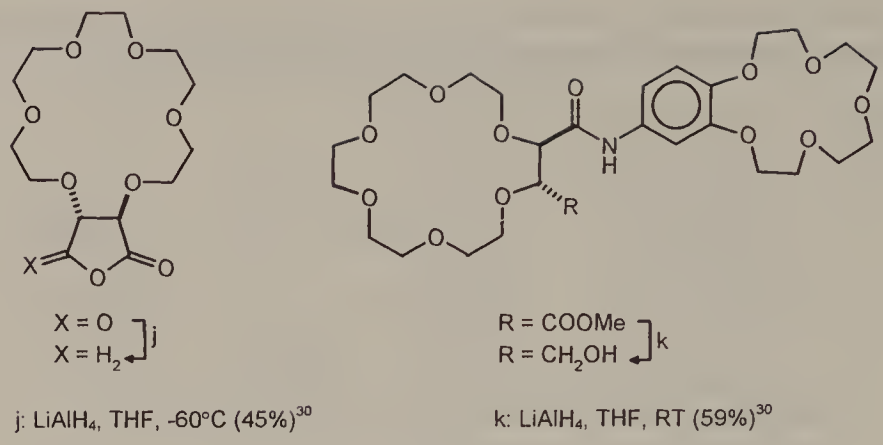
h: K_2CO_3 (cat.), EtOH, RT, 48h (38%)[22]



14.2

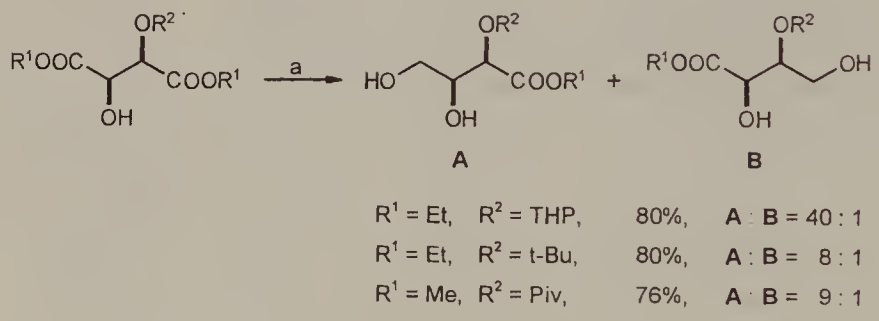
i: 0.8 mol eq. $NaBH_4$, EtOH, 0° → 15°C (86%)[1]

Scheme 14.1 (*continued*)



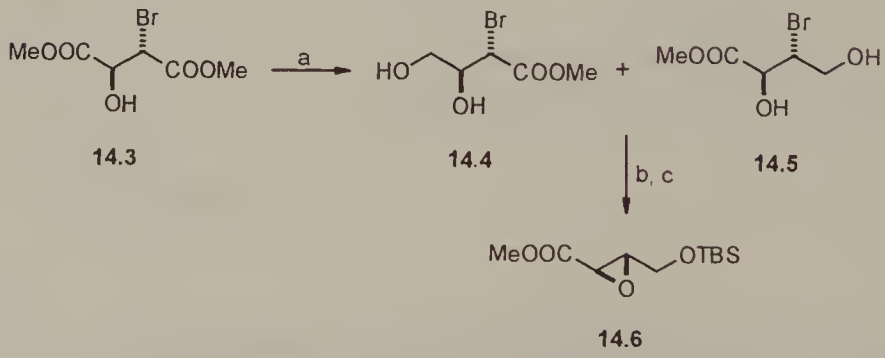
Scheme 14.1

Reduction of mono-*O*-protected tartrates to threonates with one equivalent of borane tends to be highly chemoselective due to the BH_3 coordination by the neighboring hydroxy group, as shown by Saito, Moriwake *et al.*[2,3] (Scheme 14.2).



a: 1.02 eq. $BH_3{\cdot}Me_2S$, THF, RT, 2h, then 0.05 eq. $NaBH_4$, RT, 2h

Scheme 14.2



a: 1 mol eq. $BH_3{\cdot}Me_2S$, THF, RT, 2h, then 0.05 mol eq. $NaBH_4$, 2h

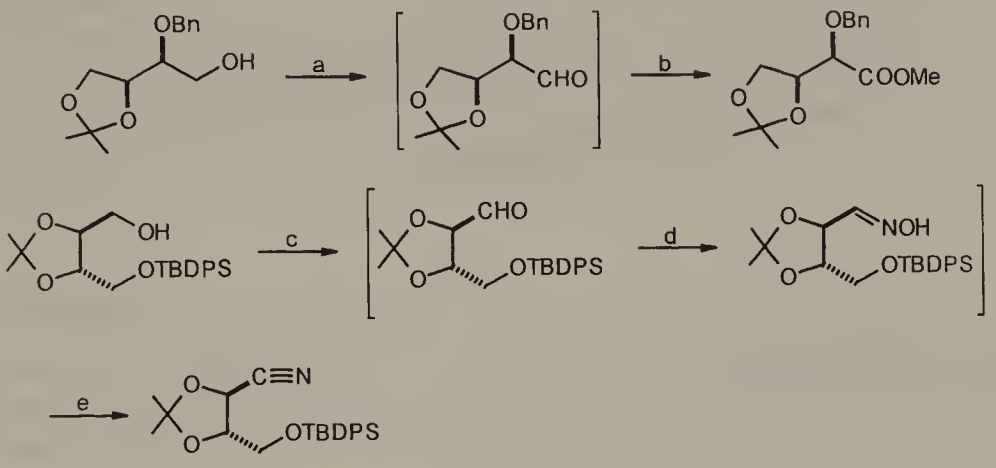
b: 1 eq. $tBuMe_2SiCl$, imidazole, THF, 0°C → RT, 20 min.

c: 1.1 eq. MeONa, MeOH, 0°C → RT, 2h (71% overall)

Scheme 14.3

Saito, Moriwake *et al.* have also developed a route to stereoisomerically pure *trans*-epoxide **14.6** from Mori's *erythro* bromohydrin **14.3**. Although borane reduction of **14.3** gave two intermediates **14.4** and **14.5** in the ratio 4:1, they cleanly converged to a single product **14.6** in the next two synthetic steps[2] (Scheme 14.3).

Protected threonates and threononitriles can be obtained without racemization by Swern-type oxidation of 1,2,3-tri-*O*-protected threitols. The intermediate threose derivative is subjected to a standard bromine oxidation or to an oxime formation-dehydration reaction (Scheme 14.4).



a: $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78°→ -20°C

b: Br_2, MeOH-H_2O (9 :1), $NaHCO_3$, RT (78% overall)[9]

c: $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78°C

d: NH_2OH·HCl, 10% K_2CO_3

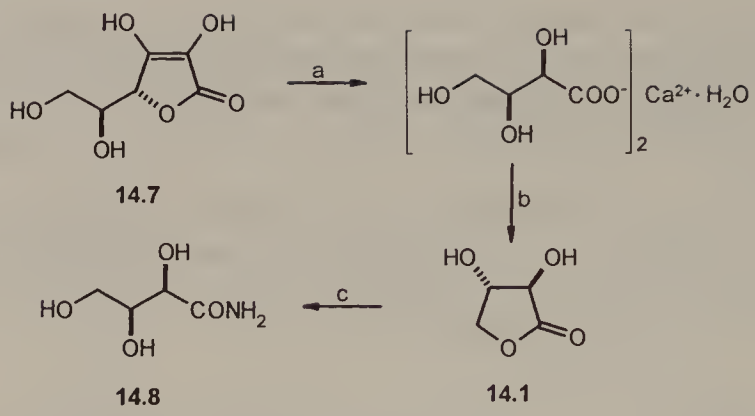
e: CDI (89% overall)[31]

Scheme 14.4

L-Threonic acid calcium salt is conveniently obtained by hydrogen peroxide oxidation of l-ascorbic acid (14.7) according to Isbell and Frush.[5,32] The salt can further be converted to L-threonolactone (14.1) and to L-threonamide (14.8) (Scheme 14.5).

Following the classical method of Reichstein,[33] cleavage of 5,6-*O*-isopropylidene-L-ascorbic acid (**14.9**) with potassium permanganate affords the potassium salt of L-threonic acid. The salt can be directly converted to esters of L-threonic acid or to L-threonolactone (**14.1**) (Scheme 14.6).

Acetal protected L-threonic acid derivatives are conveniently prepared from L-ascorbic acid by a three-step sequence developed at Hoffmann-La Roche.[5] The synthesis involves acetal protection of **14.7** to give **14.9**, oxidation of **14.9** with hydrogen peroxide, and methylation of calcium 3,4-*O*-isopropylidene-L-threonate (**14.10**) to the pivotal ester **14.11** (Scheme 14.7).

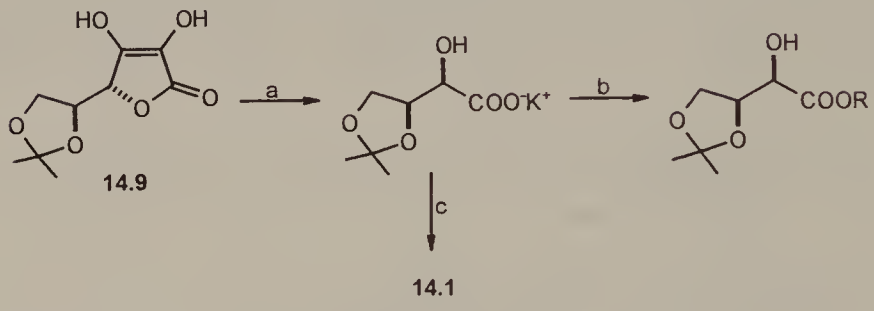


a: $CaCO_3$, 30% H_2O_2, RT, 16h, then 75°C (78.8%)

b: 50 W-X4 (H^+) resin, H_2O, Δ, 30 min., then TsOH (cat.), MeCN, Δ, 1h (76%)

c: NH_3, MeOH, RT, 48h (96%)

Scheme 14.5



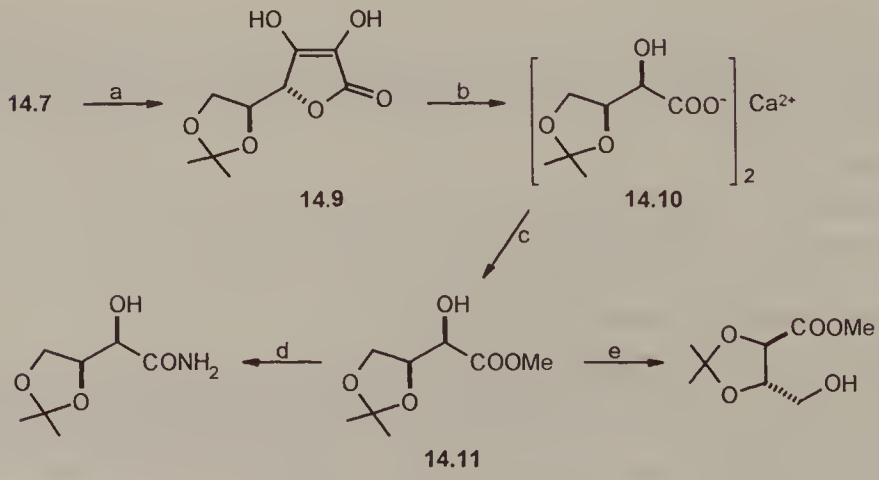
a: $KMnO_4$, K_2CO_3, H_2O, 0-5°C (78%)[26,33]

b (R = Me): MeI, MeCN (75% overall)[34]

b (R = Bn): BnBr, HMPA, 30°C, 20h (75%)[8]

c: Amberlite IR-120 (H^+) resin, H_2O (65%)[26]

Scheme 14.6



Scheme 14.7 (*continued*)

a: Me_2CO, $Me_2C(OMe)_2$, HCl, RT, 1h (96.7%)[5]

b: 2 eq. $CaCO_3$, 4 eq. 30% H_2O_2, H_2O, 0° → 40°C, 30 min. (78-81%)[5,21]

c: Me_2SO_4, aq. $NaHCO_3$, 40°C, 6h (72%)[5]

d: 29% aq. NH_4OH, THF, NH_3, RT, 12h (89%)[5]

e: Me_2CO, $Ph_3P{\cdot}HBr$ (cat.), 38%[15]

Scheme 14.7

D-Threonic acid was obtained by oxidation of D-xylose with oxygen in an alkaline medium.[35,36]

The following are commercially available:

L-threonic acid, calcium salt [*70753-61-6*]

3,4-*O*-isopropylidene-L-threonic acid, calcium salt [*98733-24-5*]

methyl 3,4-*O*-isopropylidene-L-threonate [*92973-40-5*].

Applications

Substitution reactions at either carbon atom of threonic acid derivatives lead to an array of chiral products, with either an elongated carbon chain at C(1) or with heteroatom substituents at C(2), C(3), or C(4).

Chain elongation at C(1). Dieckmann condensation of methyl 2-*O*-acetyl L-threonate (**14.12**) was used by Kirk to synthesize 2-deoxy-L-ascorbic acid (**14.17**).[19] While Dieckmann condensation of **14.12** gave product **14.17** with low yield, protection of the 4-hydroxy group as the trityl ether significantly improved the overall yield even though both γ- and δ-lactones **14.16** and **14.15** were formed in the cyclization step from the isomeric acetates **14.14** and **14.13**. The formation of 3-*O*-acetate **14.13** as the major product of the tritylation reaction was due to the base-catalyzed acetyl migration (Scheme 14.8).

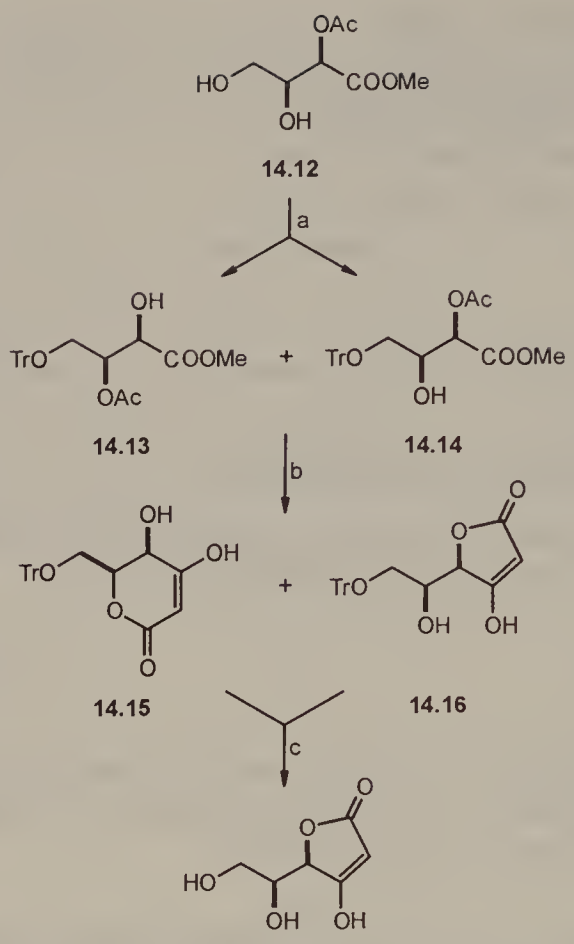
The diazoketone route is useful for converting protected threonic acid into five-carbon chain products. Thus, L-*threo*-pentulose (**14.19**) was synthesized by Wolfrom and Bennett from L-threonic acid derivative **14.18**[4] (Scheme 14.9).

For a related synthesis of the isotopically labelled 1-deoxy-D-xylulose see ref. 37.

Intramolecular butenolide formation (**14.21**) was the key step in the synthesis of (−)-syringolides 1 (**14.22**) and 2 (**14.23**) by Wood *et al.*, from the chain-elongated intermediate **14.20**[38] (Scheme 14.10).

Chiral diphenylphosphino ligand PYDIPHOS (**14.25**) was synthesized by Chelucci *et al.* from threononitrile **14.24**[31] (Scheme 14.11).

The C(10)–C(19) portion of antineoplastic macrolide amphidinolide A (**14.28**) was assembled by Williard from protected threonate **14.26** and chiral sulphone **14.27**[17] (Scheme 14.12).

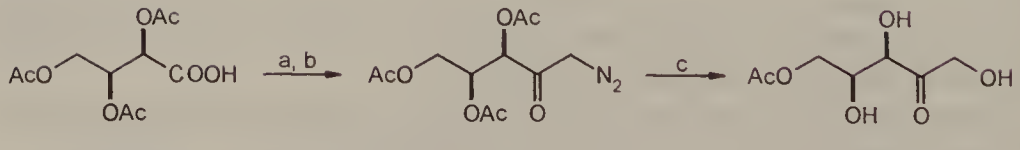


a: 1.6 eq. TrCl, 1.5 eq. DMAP, CH_2Cl_2, RT, 20h

b: $(Me_3Si)_2NLi$, THF, -78°C → RT (95%)

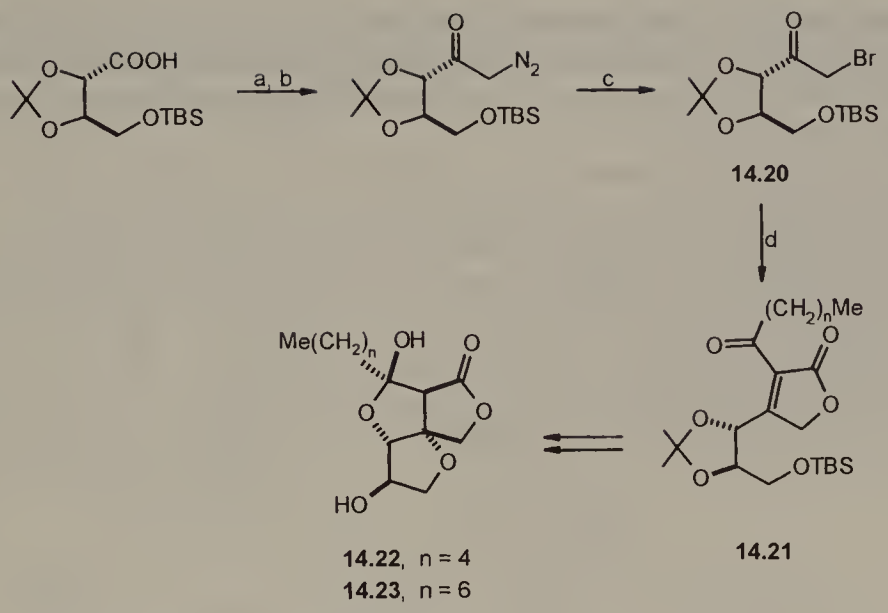
c: 2.5N HCl, THF, RT, 3h (75%)

Scheme 14.8



a: $SOCl_2$, benzene, Δ b: CH_2N_2, Et_2O, 0°C → RT c: AcOH, then $Ba(OH)_2$

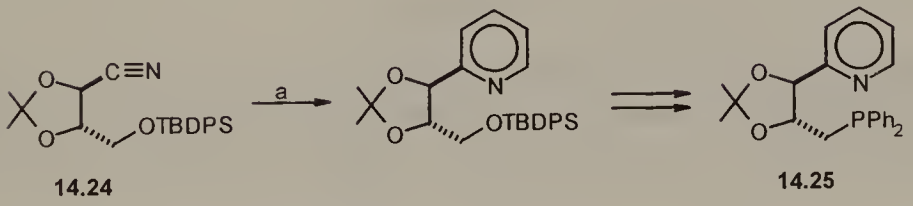
Scheme 14.9



a: ClCOOEt, NEt_3 c: HBr, Et_2O, -78°C

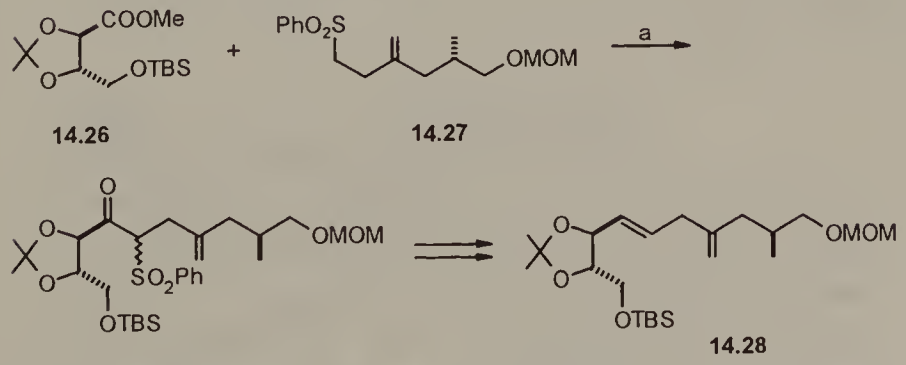
b: CH_2N_2 d: $Me(CH_2)_nC(O)CH_2COOCs$, DMF

Scheme 14.10



a: CpCo(COD), HC≡CH, PhMe, 120°C, 14 atm (91%)

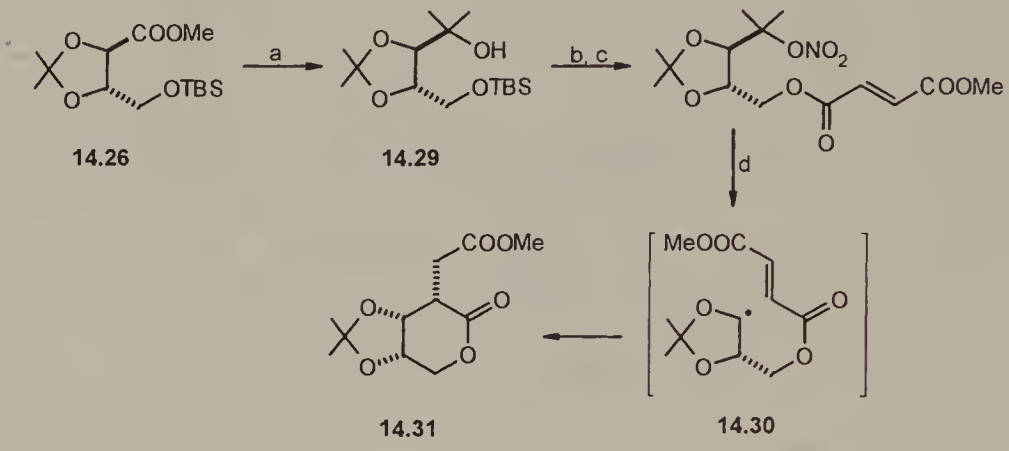
Scheme 14.11



a: 1 eq. n-BuLi, then 0.5 eq. LDA, THF, -78°C → RT (65%)

Scheme 14.12

Nitrate ester of tertiary alcohol **14.29**, obtained from threonate acetal **14.26**, can be thermally or photolytically cleaved to generate the radical **14.30** which cyclizes stereoselectively to give *erythro*-configured lactone product **14.31**, as shown in Scheme 14.13.[18]



a: 2.5 eq. MeLi, THF, -60°C → RT (95%)

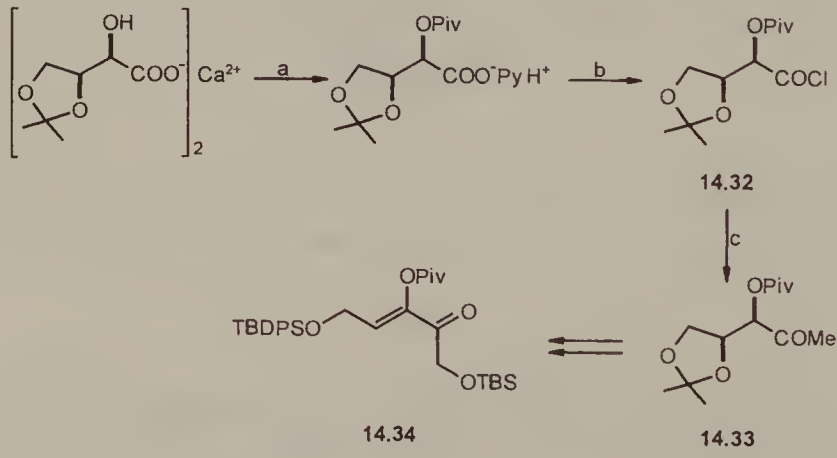
b: HNO_3, Ac_2O, 0°C (89%)

c: TBAF, THF, RT, then (*E*)-MeOOCCH=CHCOOH, DCC, DMAP, Et_2O (74%)

d: Bu_3SnH, AIBN (cat.), benzene, Δ (39%)

Scheme 14.13

Ireland synthesized achiral dienophile **14.34** en route to the hexahydrobenzofuran portion of the avermecitins and milbemycins, starting from calcium L-threonate (Scheme 14.14). Interestingly, the method of Stille for converting the



a: tBuCOCl, pyridine, DMAP (cat.), CH_2Cl_2, 0°C → RT (93%)

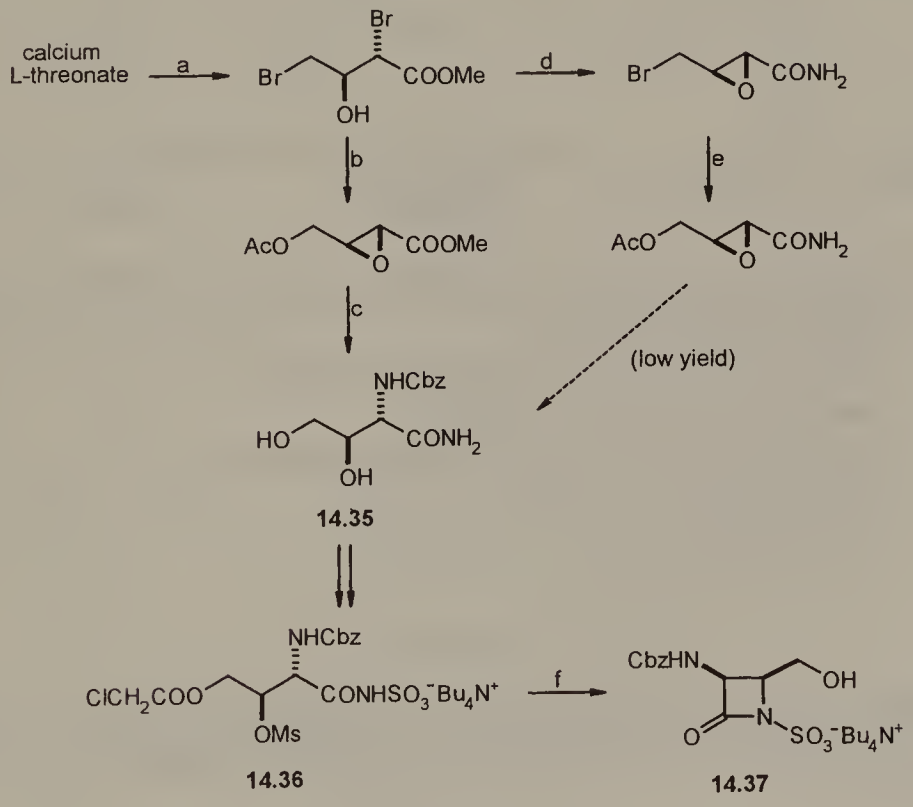
b: $(COCl)_2$, THF, -20°C → RT (93%)

c: Me_4Sn, $[Pd(Ph_3P)_2(Bn)Cl]$, HMPA, RT (87%)

Scheme 14.14

acid chloride **14.32** to the methyl ketone **14.33**, using Me_4Sn and Pd(II) as the catalyst, gave high yield of the product, with very little epimerization at the carbon atom next to the carbonyl group.[21]

Manipulations at C(2) and C(3). Many useful threonic acid substitution reactions at C(2) and C(3) have been developed for the synthesis of β-lactams of varying structure and configuration. *Erythro-* and *threo*-configurated products are available from threonic acid in a cycle of substitution reactions at C(2), proceeding with clean inversion of configuration. The transformations shown in Scheme 14.15 were developed by Manchand *et al.* at Hoffmann-La Roche for the synthesis of the β-lactam moiety of the antibiotic carumonam (**14.37**). The β-lactam ring of **14.37** was formed in an intramolecular substitution reaction of the 3-*O*-mesyl derivative **14.36**.



a: 10M HBr in AcOH, 10°C → RT, 24h, then MeOH, RT (95%)

b: 2.2 eq. AcOK, KI (cat.), DMF, 50-55°C, 4-6h (90%)

c: NaOH, MeOH, 5°C, 3h, then NH_4OH, 50-55°C, 45h, then HCl in MeOH, 5°C, 20 min., then NH_3 in MeOH, then BnOC(O)Cl, $NaHCO_3$, MeOH-H_2O, 10°C → RT, 4h (40%)

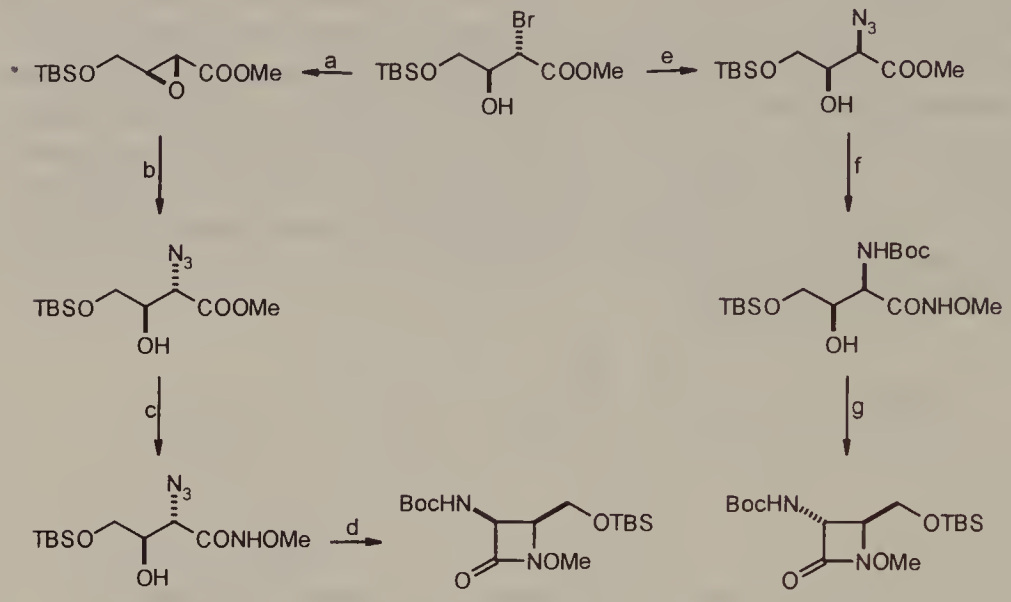
d: NH_4OH, RT, 2h (60%)

e: as b, yield 52%

f: $KHCO_3$, $ClCH_2CH_2Cl$, H_2O (68% from **14.35**)

Scheme 14.15

Related substitution reactions at C(2) leading to either *erythro-* or *threo-* products are shown in Scheme 14.16. These reactions were developed by Saito and Moriwake for the synthesis of diastereomeric β-lactams **14.38** and **14.39** according to the method of Miller.[3,39]



a: MeONa, MeOH, 0°C → RT (78%)

b: $N_3H{\cdot}NEt_2i\text{-}Pr$, DMF, RT (74%) or Bu_3SnN_3, 60°C, 46h (62%)[47]

c: $MeONH_2$, Me_3Al, benzene, 50°C, 3-4h (62%)

d: Ph_3P, DEAD, THF, RT then H_2, 10% Pd/C, Boc_2O, AcOEt, RT, 3h

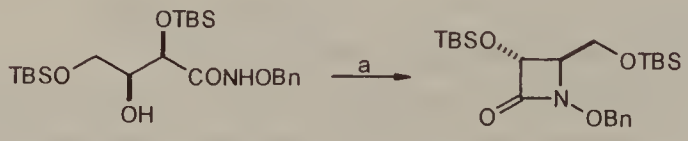
e: $N_3H{\cdot}NEt_2i\text{-}Pr$, DMF, 40°C, 10h (75%)

f: H_2, 10% Pd/C, Boc_2O, AcOEt, RT, 3h then c (56%)

g: Ph_3P, DEAD, THF, RT (73%)[3]

Scheme 14.16

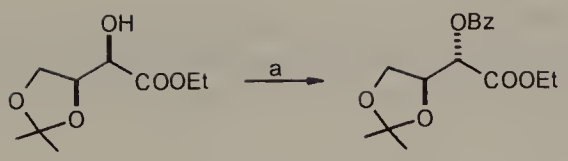
Miller's protocol is also useful for the formation of the β-lactam ring from the protected *N*-benzyloxy threonamide via intramolecular substitution at C(3)[5] (Scheme 14.17).



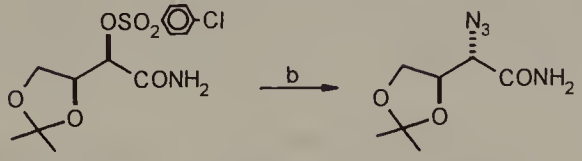
a: 1.1 eq. PPh_3, 1.5 eq. NEt_3, 1.1 eq. CCl_4, MeCN, RT (77%)

Scheme 14.17

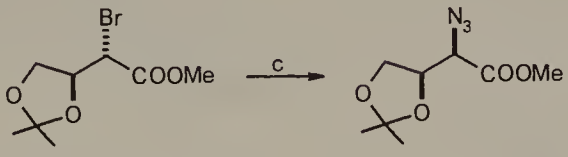
Examples of other useful substitution reactions with inversion at C(2) are shown in Scheme 14.18.



a: BzOH, Ph_3P, DIAD, THF, RT, 12h (72%)[40]



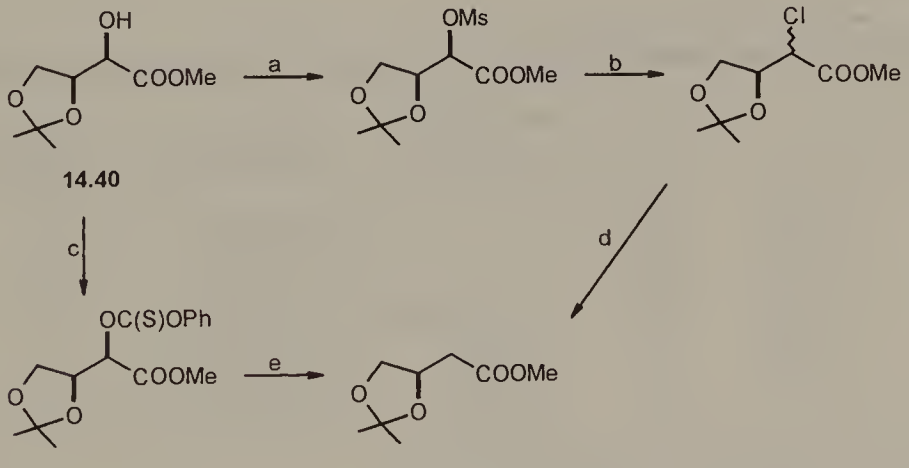
b: 1.2 eq. NaN_3, DMF, 60°C, 48h (70%)[5]



c: $N_3H{\cdot}NEt_2i$-Pr, DMF, RT, 24h (85%)[39]

Scheme 14.18

Deoxygenation at C(2) of 3,4-*O*-acetal protected threonate **14.40** provides access to 3,4-dihydroxybutanoate **14.41** and can be done in two different ways, as shown in Scheme 14.19.



a: MsCl, pyridine, CH_2Cl_2, RT (90%)[24]

b: LiCl, DMF, 85°C (71%)[24]

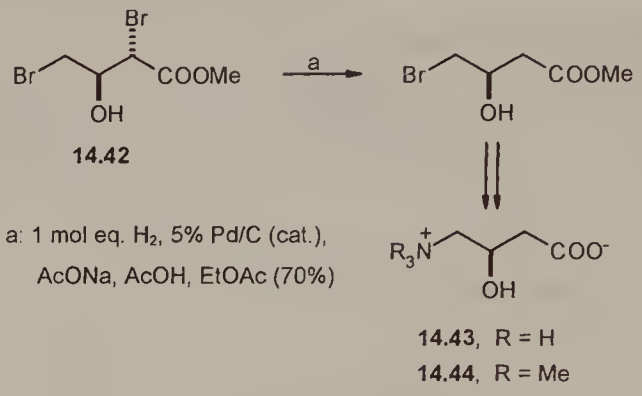
c: PhOC(S)Cl, pyridine, CH_2Cl_2, 0°C → RT (84%)[23]

d: H_2, 10% Pd/C, NEt_3, MeOH, RT (92%)[24]

e: Bu_3SnH, AIBN, PhMe, 80°C (~90%)[23]

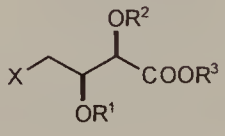
Scheme 14.19

(*R*)-GABOB (**14.43**) and (*R*)-carnitine (**14.44**) were synthesized by Bock *et al.* from the pivotal *erythro*-bromohydrin **14.42** (cf. Scheme 14.15) with the use of site-selective hydrogenolysis of the C–Br bond[41] (Scheme 14.20).



Scheme 14.20

Substitution at C(4)



III

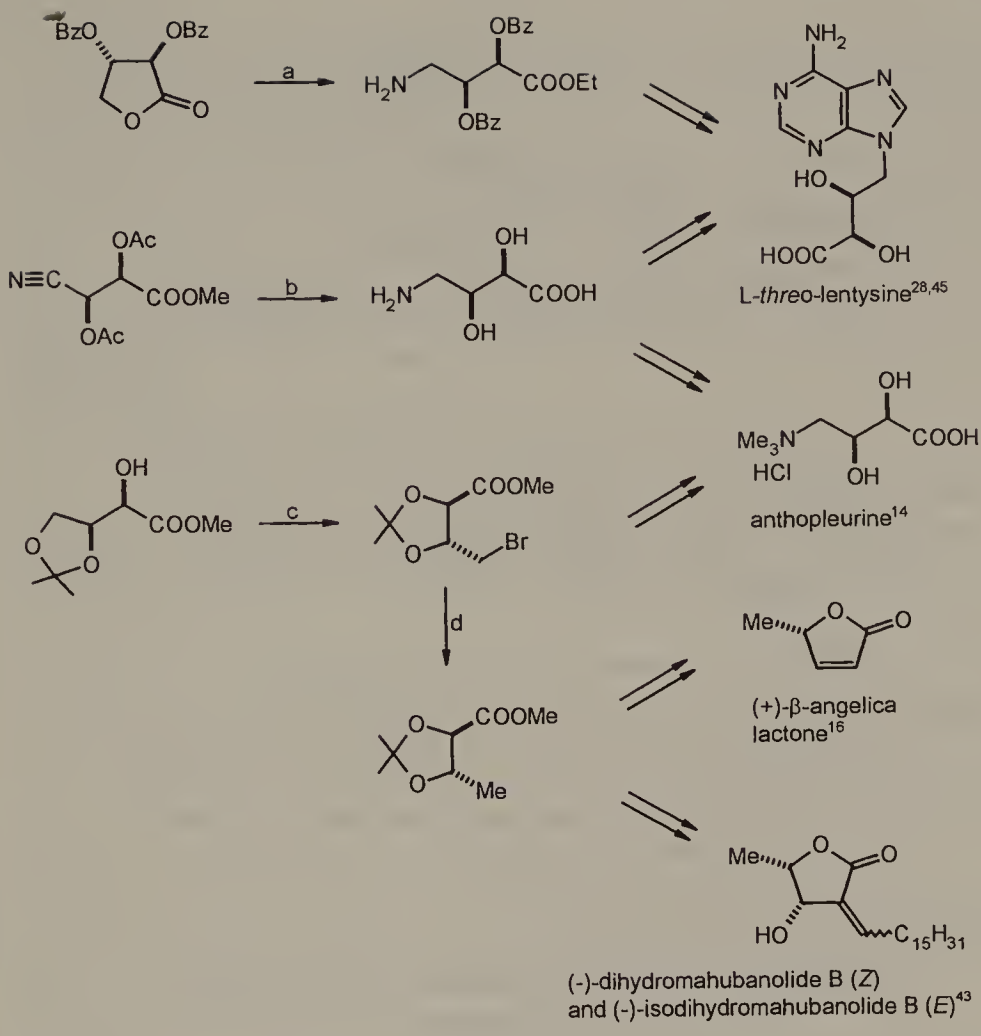
Table 14.2 4-Deoxy L-threonic acid derivatives with 4-heteroatom substituent (III)

X	R^1	R^2	R^3	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
F	$-CMe_2-$		Me	—	—	42
Br	$-CMe_2-$		Me	—	−5.0 ($CHCl_3$)	15
I	$-CMe_2-$		Me	—	−12.3 ($CHCl_3$)	18,43
N_3	$-CMe_2-$		Me	70/0.25	−96.3 ($CHCl_3$)	14
N_3	$-CMe_2-$		H	49–52	−98.5 (MeOH)	14
H_2N	$-CMe_2-$		H	225–226	+20.5 (Me_2CO-H_2O)	14
H_2N	H	H	H	222–224	+4.9 (H_2O)[a]	14

[a] $[\alpha]_D$ +42 to +43 (H_2O) has been reported in refs. 44,45.

Some less typical syntheses of 4-deoxy, 4-heteroatom substituted threonic acid derivatives and their applications are shown in Scheme 14.21.

In the case of poor nucleophiles such as the fluoride ion, 4-*O*-triflate activation is essential for effective substitution.[46] 4-Fluoromethyl substituted azetidin-



a: EtOH, HBr, then TsCl, pyridine, then NaN_3, DMSO, then H_2, Pd/C[28]

b: H_2 (85 atm.), Raney Co, 80°C, 6h, then 6N HCl, Δ (71%)[45]

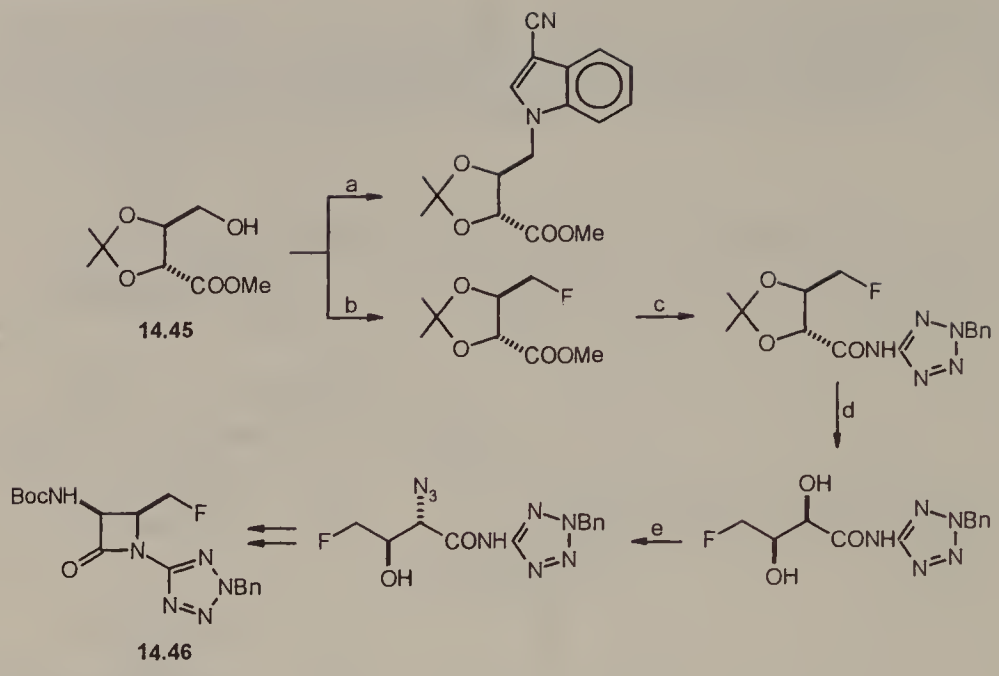
c: 1.1 eq. PPh_3, 1.1 eq. CBr_4, MeCN, RT, 30 min. (93%)[15]

d: H_2, 10% Pd/C, NEt_3, MeOH, RT (80%)[15]

Scheme 14.21

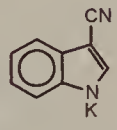
2-one **14.46** was synthesized by Klich and Teutsch from threonate acetal **14.45** by a combination of substitutions at C-4 (triflate activation) and C-3 (tosyl activation)[42] (Scheme 14.22).

Ziegler and Harran used aldehyde **14.47**, available from threonate **14.45**, for the synthesis of carbocycle **14.49**. The key step (d,e) was Barton decarboxylation for the conversion of alkyne **14.48** to the methylenecyclopentane derivative **14.49** with inversion of configuration[48] (Scheme 14.23).

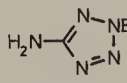


14.45

14.46

a: Tf_2O, pyridine, CH_2Cl_2, -23°C, 10 min., then  , THF, RT (86%)[46]

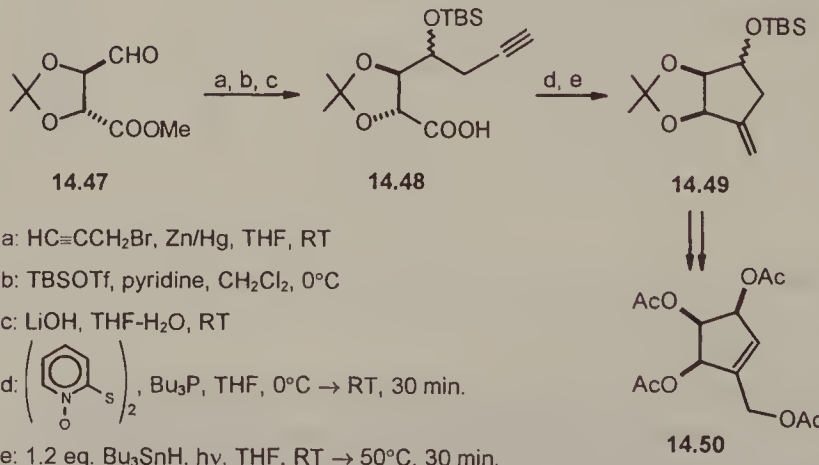
b: Tf_2O, pyridine, CH_2Cl_2, -20°C, 30 min., then Bu_4NF, MeCN, RT, 1h (51%)

c:  , MeOK, THF, RT, 1h (91%)

d: 2N HCl, MeCN, 50°C, 8h (79%)

e: TsCl, pyridine, 0°C, 2h (36%), then NaN_3, DMF, 70°C, 30 min. (48%)[42]

Scheme 14.22



14.47 14.48 14.49 14.50

a: $HC{\equiv}CCH_2Br$, Zn/Hg, THF, RT

b: TBSOTf, pyridine, CH_2Cl_2, 0°C

c: LiOH, $THF-H_2O$, RT

d: , Bu_3P, THF, 0°C → RT, 30 min.

e: 1.2 eq. Bu_3SnH, hv, THF, RT → 50°C, 30 min.

Scheme 14.23

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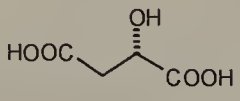
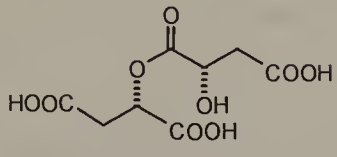
15 Malic Acid, Its Anhydride, and *O*-Protected Derivatives

15.1 MALIC ACID AND ITS DERIVATIVES



15.1

L-malic acid



15.2

L-malomalic acid

Butanedioic acid, hydroxy-(*S*) [97-67-6]

m.p. 101-103°C; $[\alpha]_D$ -28.6 (c = 5.5 pyridine)

Optical rotation of L-malic acid (**15.1**) is strongly dependent on solvent and concentration. The two carboxylic groups of L-malic acid differ significantly in acidity; the pKa's in water solutions are as follows: pKa_1 3.4, pKa_2 5.1.

Of the two carboxylic groups of malic acid, the C(1) group is more reactive in nucleophilic substitution reactions, such as estrification, aminolysis, and reactions with hydrides and organometallics. Malic acid racemizes slowly in alkaline solutions at room temperature, and racemizes much faster at elevated temperatures.[1] Malic acid undergoes self-esterification at elevated temperatures to form malomalic acid (**15.2**) and at 140–150°C it is dehydrated to fumaric acid.

The conformational population of malic acid has been studied by a variety of methods.[2]

In addition to L-malic acid, D-malic acid [*636-61-3*] and D,L-malic acid [*617-48-1*] are commercially available.

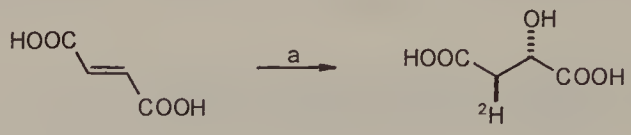
Synthesis

Naturally occurring L-malic acid can be isolated from apples and many other fruits and plants; however its main source is synthesis.

Asymmetric synthesis. The main synthetic route to L-malic acid is asymmetric hydration of salts of fumaric acid with the enzyme fumarase or fermentation with bacterial cells, such as *Brevibacterium flavum*, *Brevibacterium ammonia-*

genes, or *Corynebacterium sp.* The use of an immobilized biocatalyst and a continuous flow reactor greatly improves catalyst stability and production output. Numerous variants of the process have been described.[3–9] The reaction was carried out with the use of immobilized cells of *Saccharomyces cerevisiae* amplified for fumarase by cloning.[10]

Stereospecifically (*3R*)-deuterated L-malic acid was synthesized by Young[11] by asymmetric *anti*-hydratation of fumaric acid with fumarase in ^2H_2O (Scheme 15.1).

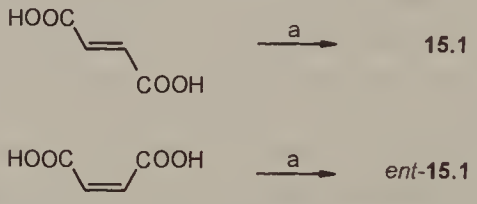


a: fumarase, ^2H_2O, 28°C, p^{2}H 7.7±0.2, 5d (54%)

Scheme 15.1

Similarly 1,4-$^{13}C_2$, 3-$^2H_1$ labelled L-malic acid was prepared from 1,4-$^{13}C_2$ labelled fumaric acid by Keller *et al.*[12] and Jordan.[13]

It is well established that asymmetric hydration of maleic acid catalyzed by maleases from many strains of molds and yeasts is enantiocomplementary to hydration of fumaric acid and yields D-malic acid.[14–16] As an example, both enantiomers of malic acid were synthesized from fumaric and maleic acid with the use of resting cells of *Clostridium formicoaceticum*[17] (Scheme 15.2).



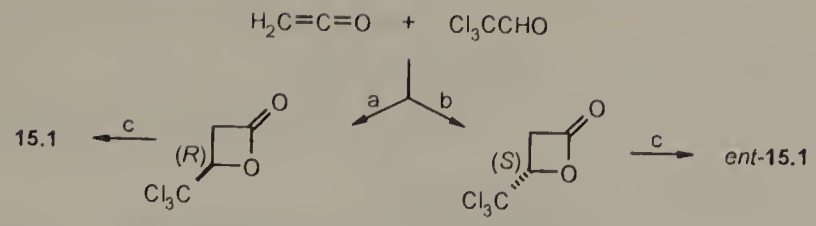
a: *Clostridium formicoaceticum*, 0.1 M phosphate buffer pH 8.0 (e.e. 99.9%)

Scheme 15.2

(*3R*)-Deuterated D-malic acid can be obtained from malic acid by hydration with maleate hydratase in ^2H_2O.[18]

Wynberg and Staring synthesized L- and D-malic acids by asymmetric addition of ketene to chloral, catalyzed respectively by quinidine or quinine, followed by hydrolysis of the intermediate β-(trichloromethyl)-β-propiolactone (Scheme 15.3).[19] Note that the hydrolysis step proceeded with inversion of configuration.[20]

A promising synthetic method is homogeneous catalytic asymmetric hydrogenolysis of sodium epoxysuccinate with rhodium catalysts containing chiral phosphine ligands. However, the highest enantiomeric excess obtained by this method was only 62%.[21]



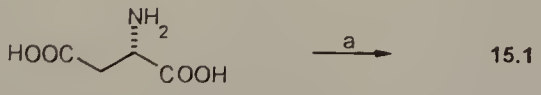
a: quinidine (cat.), PhMe, -50°C (89%, e.e. 98%)

b: quinine (cat.), PhMe, -50°C (e.e. 76%)

c: 4N HCl, Δ then aq. NaOH, RT, then Dowex 50W

Scheme 15.3

Synthesis from chiral substrates. D-Malic acids can be synthesized from L-tartaric acid by a number of methods, described in earlier parts of the book (Chapters 2, 4, 7 and 10). Additionally, L- or D-malic acids can be readily obtained by treatment of much less expensive L- or D-aspartic acids with nitrous acid. This reaction proceeds with net retention of configuration[11,22,23] (Scheme 15.4).

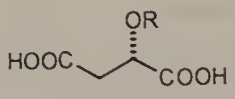


a: $NaNO_2$, 0.5 H_2SO_4, RT (73%)[11]

Scheme 15.4

Resolution. Racemic malic acid can be resolved by a number of methods. The classical resolution via diastereoisomeric salts formation with enantiomerically pure amines is exemplified by the use of equimolar amount of inexpensive 1-phenylethylamine (yield 26%)[24] or its less common *p*-isopropyl derivative (yield 39%).[25] A method of mutual resolution of 1-phenylethylamine and malic acid was developed by Ingersoll.[26] The resolution of racemic malic acid can also be achieved by preferential crystallization of its salts with ammonia[27] or achiral amines,[28] which are conglomerates at room temperature. A rather unusual but very effective resolution of malic acid with tartaric acid was reported by Arsenijević: crystallization of a mixture of racemic malic acid and L-tartaric acid from isopropanol-benzene yields cocrystals of D-malic and L-tartaric acids (1:1) from which pure D-malic acid can be efficiently isolated (yield ca. 65%).[29] The crystal structure of the cocrystal of L-malic and L-tartaric acids (1:1) was reported.[30]

O-Protected malic acids (**I**) are usually prepared by hydrolysis of the corresponding anhydrides (*O*-alkyl, *O*-acyl) or by hydrolysis of *O*-alkyl malates (Table 15.1).



I

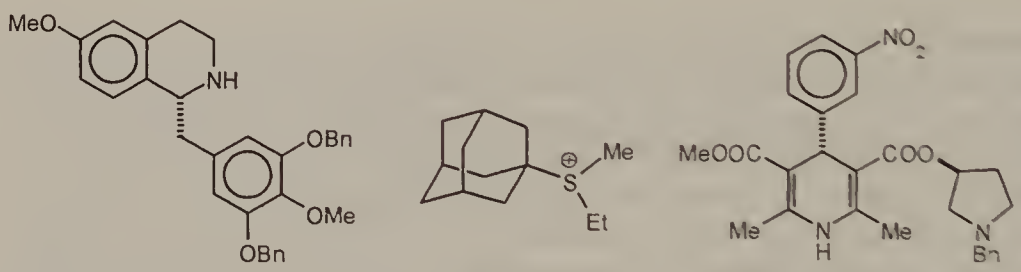
Table 15.1 ***O*-Protected L-malic acids (I)**

R	m.p. (°C)	$[\alpha]_D$ (solvent)	References
Me	88–90	−33.8 (H_2O)	31,32
Et	76–80	−33.2 (H_2O)	33
Pr	66–67	−64.4 (Me_2CO)	34
i-Pr	—	−36.3 (H_2O)	34
β-D-glucopyranosyl	—	−29.0 (H_2O)	35
Ac	134–135	−10.7 (H_2O)	36
Bz	162	−1.2 (Me_2CO)	37
NO_2	114–115	−38.0 (MeOH)	38–41
C(S)SEt	150–151	+33.5 (Me_2CO)	42
$C(S)NMe_2$	117–118	+50.9 (EtOH)	42
$C(S)NEt_2$	70–71	+56.5 (EtOH)	42

Applications

R

L-malic acid is used as acidic resolving agent, but its relatively high price limits its use to small-scale resolutions and to those cases where less expensive resolving agents fail. Examples are shown in Scheme 15.5.



ref. 43 ref. 44 ref. 45

Scheme 15.5

Lanthanide(III) salts of *O*-carboxymethyl-L-malic acid are useful as chiral lanthanide shift reagents for determining the enantiomeric excess of carboxylic acids in aqueous solutions.[46]

B

Optically active 2-chloro- and 2-bromobutanedioic acids are available from L- or D-malic acid by substitution involving Walden inversion[47] (Scheme 15.6); however, 2-bromobutanedioic acid is more conveniently prepared from aspartic acid by deamination with net retention of configuration.[104]

a: 3.2 eq. PCl_5, RT, then H_2O (40%)[48] or 4 eq. $SOCl_2$, Δ, then H_2O[49]

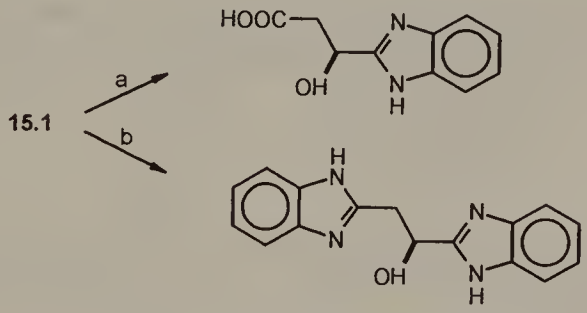
Scheme 15.6

Enantiomeric purity of the products is dependent on reaction conditions. Data for halobutanedioic acids and their derivatives of presumably high enantiomeric purity are collected in Table 15.2.

Table 15.2 Data for (*R*)-halobutanedioic acids and their derivatives

Halogen substituent	Compound	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
Cl	diacid	174–176	+21.3 (H_2O)	47,49,50
Cl	dichloride	91–93/11	+29.5 (neat)	50
Cl	dimethyl ester	107/15	+41.4 (neat)	50
Cl	diethyl ester	131/18	+27.5 (neat)	50
Cl	anhydride	80	+30.8 (AcOEt)	50
Br	diacid	179	+70.2 (AcOEt)	51
Br	dichloride	56/1	+58.4 (neat)	51
Br	dimethyl ester	129/23	+65.3 (neat)	50,51
Br	diethyl ester	143/28–30	+48.2 (neat)	50,51

O-(Phosphonoacetyl)-L-malic acid, synthesized via the dibenzyl ester, exhibits the properties of an inhibitor of aspartate transcarboxylase.[52] Chiral derivatives of benzimidazole were prepared from L-malic acid[53] (Scheme 15.7).



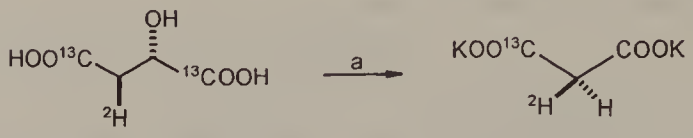
a: 1 eq. *o*-phenylenediamine, 4N HCl, Δ, 8h (80%)

b: 2 eq. *o*-phenylenediamine, 4N HCl, Δ (75%)

Scheme 15.7

Optically active (*R*)-[1-$^{13}C_1$, 2-$^{2}H_1$]malonate was synthesized by permanganate oxidation of suitably labeled (*S*)-malic acid. The product racemizes in

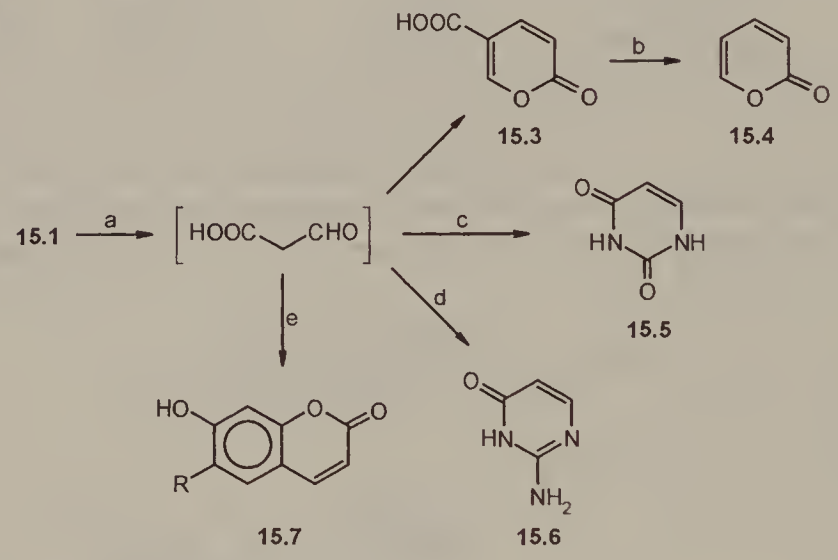
aqueous solution; hence it must be generated and used on a time scale of minutes[12,13] (Scheme 15.8).



a: $KMnO_4$, H_2O, pH 10

Scheme 15.8

Furthermore, malic acid is used as an equivalent of monomalonaldehyde in the synthesis of pyrones developed by von Pechmann.[54] The condensation, induced by fuming sulfuric acid which converts malic acid to monomalonaldehyde,[55,56] provides 2*H*-pyran-2-one-5-carboxylic acid (**15.3**), *coumalic acid*, by self-condensation of monomalonaldehyde. Coumalic acid can be further decarboxylated to 2*H*-pyran-2-one (**15.4**). Malic acid as a source of monomalonaldehyde is also used for the synthesis of uracil (**15.5**), isocytosine (**15.6**), and coumarin derivatives (**15.7**) (Scheme 15.9).

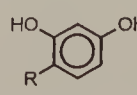


a: SO_3, H_2SO_4, RT, then 100°C (65-70%)[57]

b: 650°C (65-70%)[58]

c: $(NH_2)_2CO$ (50-55%)[59]

d: $(NH_2)_2C{=}NH{\cdot}HCl$ (32%)[60]

e: 

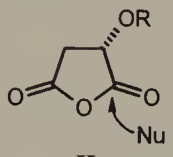
, (43-65%)[61,62]

Scheme 15.9

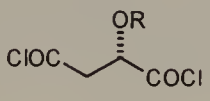
15.2 MALIC ANHYDRIDE AND ITS DERIVATIVES

Unlike the unstable tartaric anhydride, malic anhydride was prepared and isolated as early as 1913.[63] Malic anhydrides are frequently used as chiral building blocks; addition of an oxygen or nitrogen nucleophile is biased, with strong preference toward the α-oxygen substituted carbonyl group in **II**.

Products of such reaction are 1-monoesters and 1-monoamides of malic acid (see Chapters 16 and 17). "Activated" anhydrides (**II**, R = $COCF_3$, $COCCl_3$) on reaction with alcohols or amines undergo removal of the *O*-protecting group, in addition to the previously mentioned reaction.



II



III

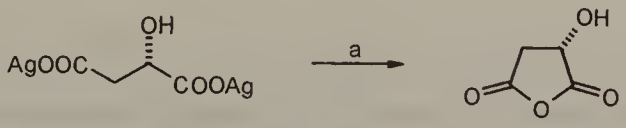
Table 15.3 L-Malic anhydrides (II) and acid chlorides (III)

Formula	R	m.p. (°C) or b.p.(°C/torr)	$[\alpha]_D$ (solvent)	References
II	H	75–76	—	64
	Me	125/15	−104.0 (benzene)	65,66
	t-Bu	64	−51.5 (benzene)	66
	Ac	58	−28.4 (Me_2CO)	67,68
	$COCF_3$	77–78	−50.5 ($CHCl_3$)	69,70
	$COCCl_3$	167–169	−26.1 ($CHCl_3$)	70
III	Me	114–117/56	−54.0 (benzene)	51,65
	Ac	75–80/0.05	−10.0 ($CHCl_3$)	37,51,71

Malic anhydrides are quite unstable; they easily hydrolyse to the corresponding diacids. *O*-Acetylmalic anhydride readily forms maleic anhydride upon distillation above 200°C.[72]

Synthesis

O-Unprotected malic anhydride was obtained from disilver malate by the action of thionyl chloride (Scheme 15.10).

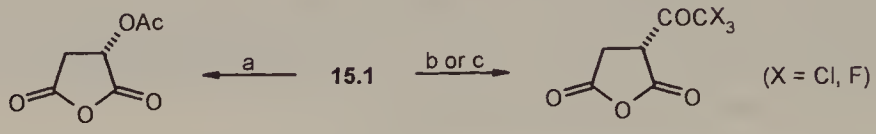


a: $SOCl_2$, THF or Et_2O, RT (50-70%)[63,64,73]

Scheme 15.10

It is also formed along with varying amounts of polymeric products by treatment of malic acid with dicyclohexylcarbodiimide.[74]

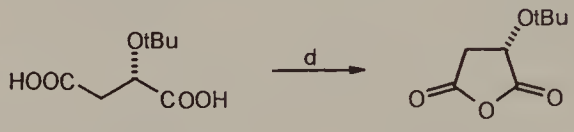
Malic acid and *O*-protected malic acids readily form cyclic anhydrides by the action of acid chlorides and/or acid anhydrides (Scheme 15.11).



a: AcCl, Ac_2O, Δ, 1-3h (94-100%)[23,62,72,75,76]

b: 2.2 eq. $(CX_3CO)_2O$, dioxane, 75°C, 2h (92-97%)[70]

c: 2.0 eq. $(CF_3CO)_2O$, 0°C → RT, 2h (100%)[77]



d: Ac_2O, RT, 24h (81%)[66]

Scheme 15.11

(*S*)-Acetoxysuccinic anhydride [*59025-03-5*] and its enantiomer [*79814-40-7*] are commercially available.

Dichlorides of *O*-protected malic acid can be prepared by chlorination of the corresponding anhydrides (Scheme 15.12).

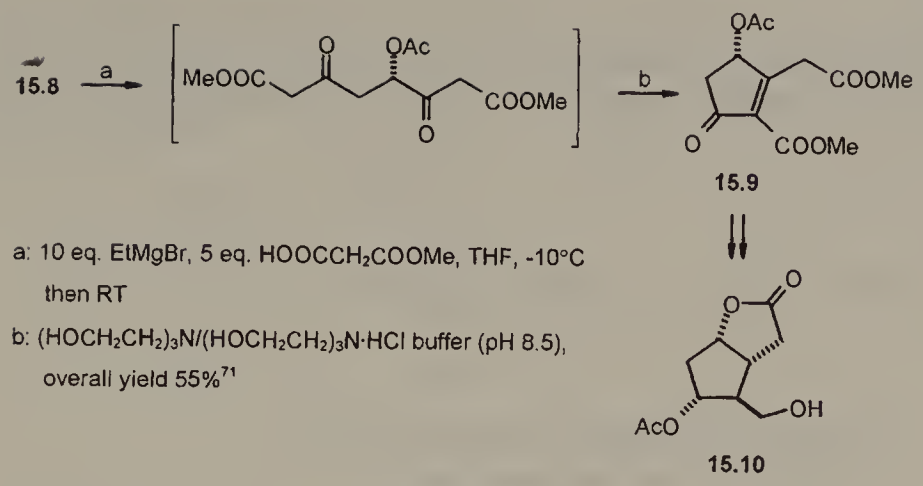
a: Cl_2CHOMe, $ZnCl_2$, Δ (80%)[71]

Scheme 15.12

Application

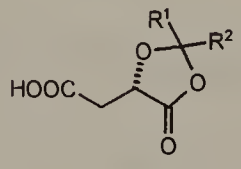
B

Johnson prepared chiral cyclopentenone **15.9**, an intermediate in the synthesis of prostaglandins, via Corey lactone intermediate **15.10**, in a one-step reaction of dichloride **15.8** with the dianion of methyl hydrogen malonate followed by chemoselective cyclization under controlled pH[71] (Scheme 15.13).



Scheme 15.13

15.3 1,2-ACETALS OF MALIC ACID: DIFFERENTIATION OF THE CARBOXY GROUPS



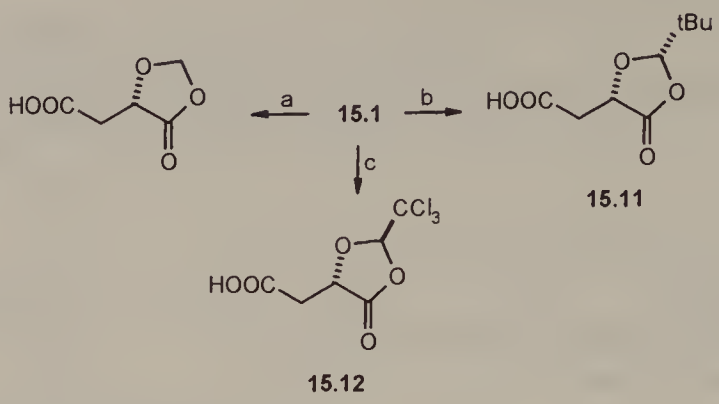
IV

Table 15.4 1,2-Acetal derivatives of L-malic acid (IV)

R^1	R^2	m.p. (°C)	$[\alpha]_D$ (solvent)	References
H	t-Bu	114–117	+23.1 ($CHCl_3$)	78
t-Bu	H	104–105	−2.3 ($CHCl_3$)	78–80
H	CCl_3	141–142	+96.5 (benzene)	81–83
Me	Me	115–117	+6.9 ($CHCl_3$)	84–86
CF_3	CF_3	75	−12.7 (Me_2CO)	87
$-(CH_2)_5-$		104–105	—	88

Synthesis

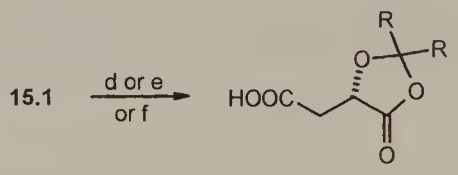
C(1) Protected malic acids are readily obtained by the formation of 1,3-dioxolan-4-one derivatives (**IV**) from aldehydes and ketones. This reaction is chemoselective because the formation of isomeric six-membered 1,3-dioxan-4-ones is strongly disfavored[85,89] (Scheme 15.14). The same preference for the formation of five-membered ring product was observed in the synthesis of a spirophosphorane from L-malic acid.[90]



a: paraformaldehyde, TsOH (cat.), $CHCl_3$, Δ, (no yield)[91]

b: t-BuCHO, TsOH (cat.), H_2SO_4 (cat.), pentane (67%, *cis* : *trans* = 98 : 2 after crystallization)[78]

c: $CCl_3CH(OH)_2$, H_2SO_4, RT (96-99%),[92,93] *trans* : *cis* = 6 : 1[93]



d (R = Me): $MeC(OMe)_2$ or $MeC(OMe)=CH_2$, TsOH or PPTS (cat.), RT (74-96%)[84,85,94]

e (R = CF_3): 2.1 eq. $(CF_3)_2CO$, DMSO, RT (92%)[93]

f (R,R = $(CH_2)_5$): 1 eq. Me_2CO, $BF_3 \cdot Et_2O$, Et_2O, 0°C, 1h (100%)[88]

Scheme 15.14

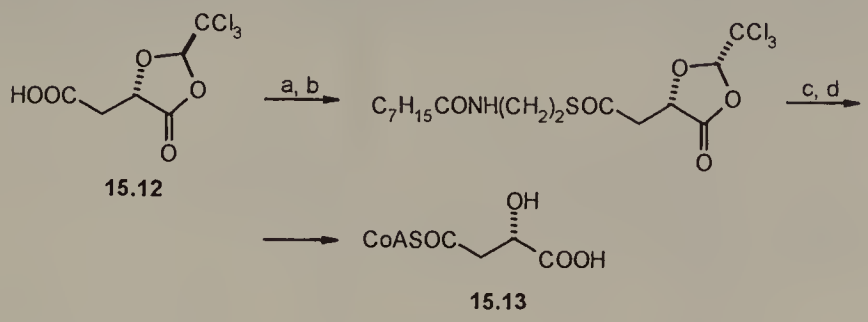
It is of interest to note that the preference for the formation of *cis*- (**15.11**) or *trans*-substituted 1,3-dioxolan-4-ones (**15.12**) from malic acid and pivalaldehyde or chloral is opposite (Scheme 15.14). The selectivity of the reaction with pivalaldehyde, in benzene under equilibrium conditions (*cis*:*trans* = 3:2)[78] can be improved significantly (*cis*:*trans* = >100:1) under Noyori ketalization conditions.[80] *Cis*-acetal **15.11** can be thermally isomerized to the more stable *trans* isomer.[78,79] The crystal and molecular structure of the *cis*-substituted acetal **15.11** has been determined by X-ray diffraction.[79]

Applications

B

C(1)–C(2) Acetal protected malic acids exhibit sufficiently different reactivity of the two carbonyl groups to permit selective transformations of either end of the molecule. The C(4)-carboxy group can be selectively subjected to reactions typical for the free carboxylic acid (derivatization, decarboxylation), including reduction with diborane (see Chapter 18). The C(1)-carboxy group, on the other hand, is the site of selective addition of Grignard reagents and of enolization,

leading to selective alkylation at C(2). For example, malyl-coenzyme **15.13** was synthesized from malic acid chloralide **15.12** by selective tioester formation at C(4) with *N*-capryloylcysteamine, followed by transestrification with coenzyme A[82] (Scheme 15.15).



15.12 **15.13**

a: $SOCl_2$, Δ (87%)

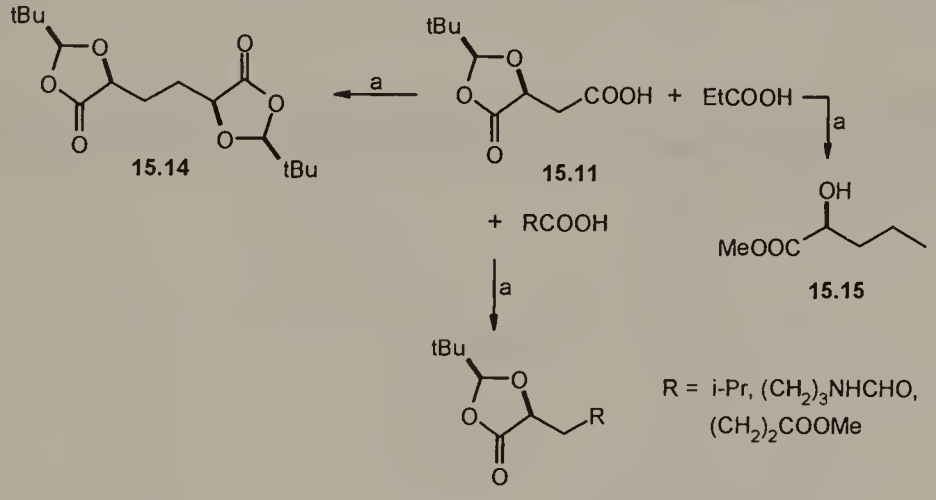
b: $C_7H_{15}CONH(CH_2)_2SH$, pyridine, THF, RT (89%)

c: conc. HCl, DMF, 50°C (71%)

d: CoASH, $KHCO_3$, KBH_4, H_2O, RT

Scheme 15.15

Syntheses involving decarboxylation of C(4) carboxylic group. An obvious application is Kolbe electrolytic cross-coupling of C(4) acid **15.11** with other carboxylic acids, for the synthesis of enantiomerically pure α-hydroxyacids, as amply demonstrated by Seebach *et al.* (Scheme 15.16).



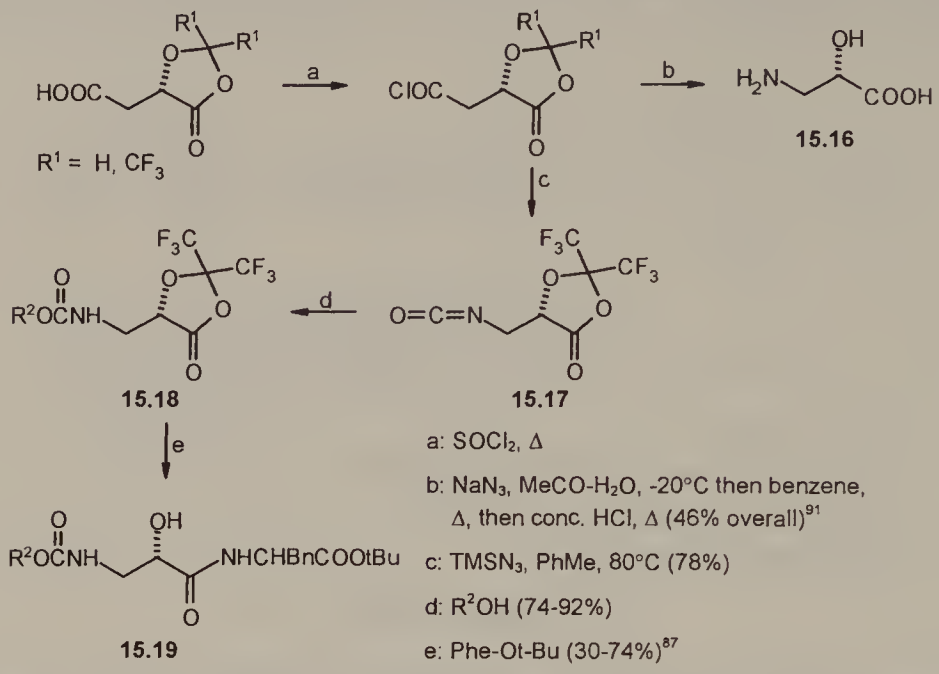
15.14 **15.11** **15.15**

a: Pt anode, NEt_3, MeOH, RT (35-56%)[95]

Scheme 15.16

The dimeric product **15.14** is a protected form of (2*S*,5*S*)-2,5-dihydroxyhexanedioic acid; and methyl (2*S*)-2-hydroxypentanoate (**15.15**), obtained directly from the electrolysis, was used for the synthesis of (+)-myxovirescine M_2.[96]

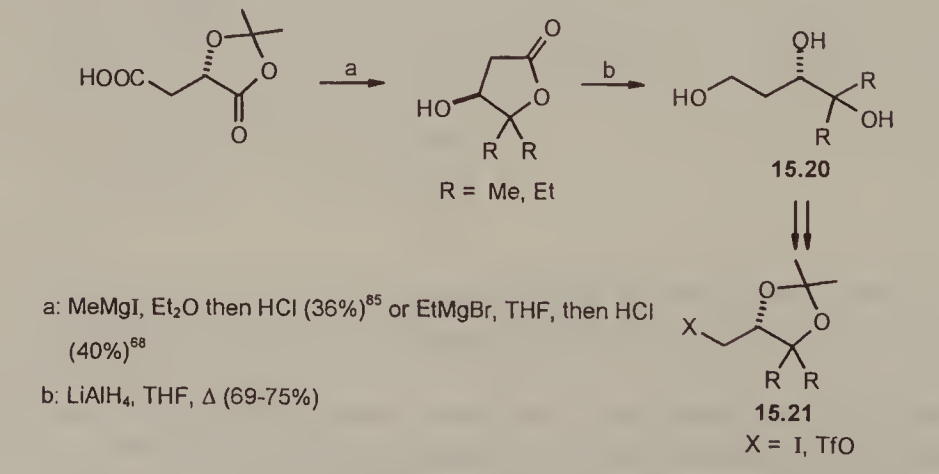
(*S*)-Isoserine (**15.16**) and its derivatives are readily available from C(1)–C(2) acetal protected malic acid chlorides by Curtius rearrangement (Scheme 15.17).



Scheme 15.17

^{2}H-Labeled isoserine was obtained by the above procedure.[97] *N*-Protected C(1)-activated isoserine derivatives **15.18** can be obtained from the intermediate isocyanate **15.17** and directly coupled with amino acid esters to give dipeptides **15.19**.[87]

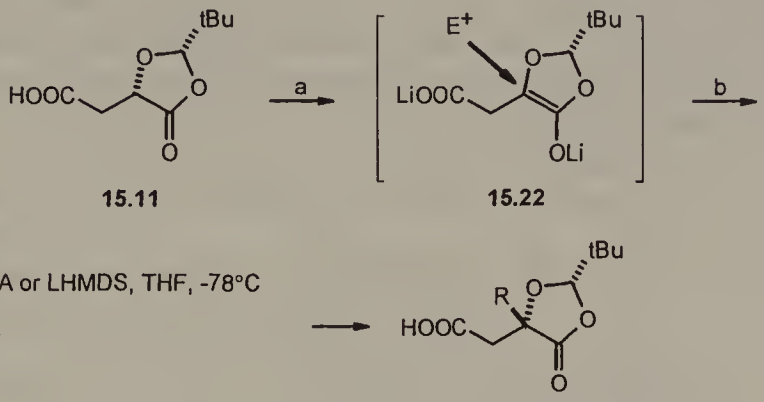
Syntheses involving C(1) carboxylic group. Chiral triols **15.20** are available from C(1)–C(2) acetals of malic acid by the chemoselective addition of Grignard reagents (Scheme 15.18).



Scheme 15.18

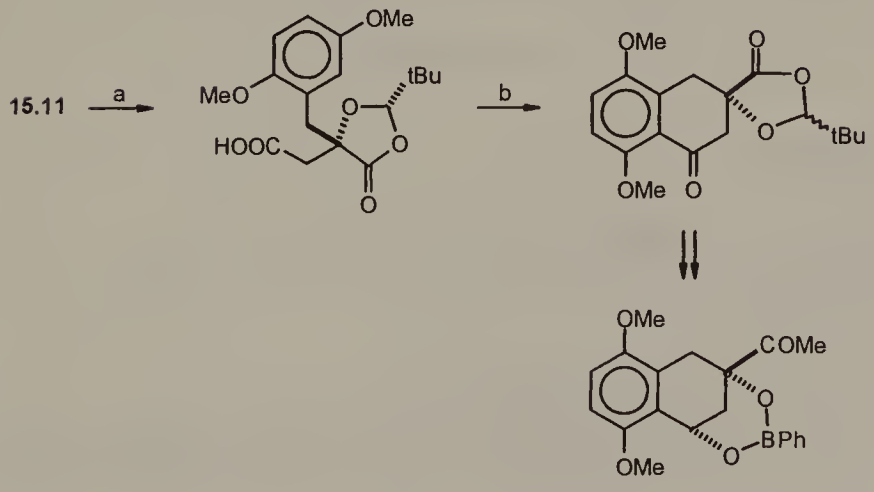
The triols **15.20** were converted to reactive chirons **15.21** for introduction of the hydroxylated side chain in steroids.[68,85]

t-Butyl substituted 1,3-dioxolan-4-one **15.11** can be regioselectively deprotonated to enolate **15.22** in which the residual chiral center controls *Re*-addition of the electrophile to the C(2) atom. This synthesis provides access to alkylated malic acid derivatives **15.23** with retention of configuration at C(2) (Scheme 15.19).



R	yield (%)	d.e. (%)	ref.
Me	79-80	>90	78, 98
All	76	>90	78
Bn	77	>90	78
(*R*)-CH(Me)CH_2NO_2	38	70	99

Scheme 15.19



a: LDA, THF, -78°C, then 2,5-dimethoxybenzyl iodide (63%)

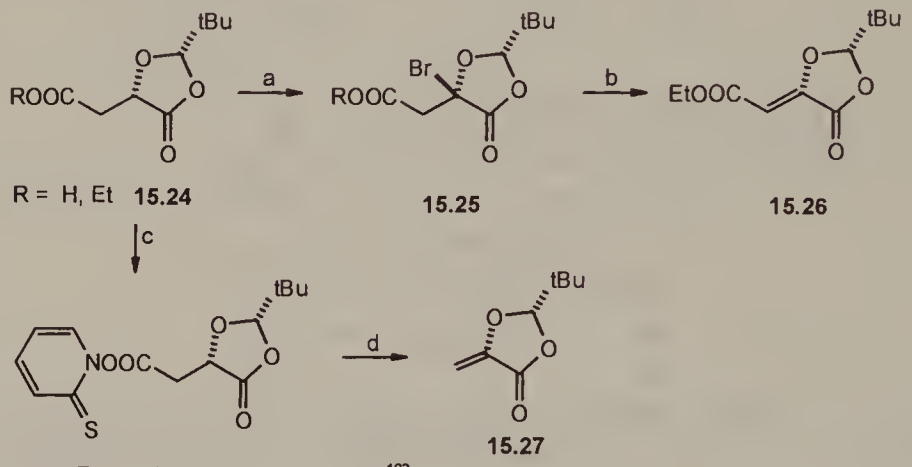
b: $SOCl_2$, then $SnCl_4$, 0°C (82%, 2.7:1 mixture of diastereomers)

Scheme 15.20

The structure of the enolate **15.22** is apparently solvent-dependent.[100] This synthetic scheme was developed by Seebach[78] and the procedure was subsequently used by Krohn for the synthesis of labeled enantiomerically pure (*R*)-mevalonolactone from L-malic acid.[98]

A further example of the application of the 1,2-acetal **15.11** of L-malic acid is in the synthesis of the AB-ring fragment of daunomycinone, reported by Krohn[101] (Scheme 15.20).

Free-radical bromination of acetal **15.24** proceeds stereoselectivity at C(2) to give bromoacetal **15.25**, from which chiral dienophile **15.26** can be obtained. Dienophile **15.27** is available from **15.24** through decarboxylation-elimination reactions (Scheme 15.21).



a (R = Et): NBS, AIBN, CCl_4, Δ (88%)[102]

b: NEt_3, CCl_4, RT (62%)[102]

c (R = H): *N*-hydroxypyridine-2-thione, DCC, DMAP (cat.), RT (> 90% crude)[103]

d: $BrCCl_4$, hν, then DBU (54%)[103]

Scheme 15.21

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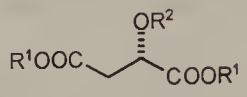
16 Malates and Their *O*-Protected Derivatives

16.1 DIESTERS OF MALIC ACID



I

Table 16.1 L-Malates and their *O*-protected derivatives (I)

R^1	R^2	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
Me	H	74–76/1.5	−8.4 (neat)	1
			−9.9 (MeOH)	2,3
Et	H	128/10	−10.7 (neat)	4
			−11.1 (MeOH)	5–9
n-Pr	H	151/10	−11.6 (neat)	5
i-Pr	H	147/14	−10.4 (neat)	10
n-Bu	H	170/12–13	−8.0 (CH_2Cl_2)	11
n-C_5H_{11}	H	191–192/20	−6.9 (neat)	10
n-C_6H_{13}	H	185–189/6-7	—	12
n-C_7H_{15}	H	212–214/6-7	—	12
n-C_8H_{17}	H	220–221/6-7	—	12
n-C_9H_{19}	H	240–247/6-7	—	12
n-$C_{10}H_{21}$	H	245–250/6-7	—	12
Bn	H	—	−18.6 ($CHCl_3$)	13,14
4-$O_2NC_6H_4CH_2$	H	124.5	—	15
$BzCH_2$	H	109–110	−2.4 (pyridine)	16
4-$BrC_6H_4C(O)CH_2$	H	179	—	17
Me	Me	113–114/15	−55.0 (neat)	18–20
			−50.7 (Me_2CO)	21–22
Et	Me	96/16	−50.4 (neat)	18,23,24
n-Pr	Me	145–146/12	−47.0 (neat)	18
Me	Et	110/12	−61.1 (neat)	10

(continued)

Table 16.1 (*continued*)

R^1	R^2	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
Et	Et	124/10	−54.1 (neat)	25
n-Pr	Et	147/17	−51.2 (neat)	10
n-Bu	Et	158/13	−46.4 (neat)	10
Me	t-Bu	120–122/15	−56.8 (neat)	26
Et	t-Bu	110/0.03	−38.9 (CH_2Cl_2)	27
Me	$CH{=}CH_2$	—	−34.0 (MeOH)	27
Me	Bn	100/0.1	−72.6 ($CHCl_3$)	29,30
Me	Ph_2CH	—	−99.5 (MeOH)	31
Me	4-$BrC_6H_4C(O)CH_2$	113–115	+29.7 (Me_2CO)	32
Et	HCO	120–121/2	−28.8 (neat)[a]	33
Et	$EtOOCCH_2$	115–120/0.2	—	34
Me	Ac	132–134/12	−21.6 (EtOH)	25
Et	Ac	137/10	−23.6 (EtOH)	5,8,33,36
Me	EtCO	145–147/10	−22.9 (neat)	10
Et	EtCO	150/9	−22.2 (neat)	36,37
Et	PrCO	162–163/12	−22.2 (neat)	36
Et	i-PrCO	160/15	−22.0 (neat)	36
Et	n-BuCO	176–177/19	−21.4 (neat)	10
Et	$C_5H_{11}CO$	182/17	−20.3 (neat)	10
Et	$C_6H_{13}CO$	140/2	−22.0 (neat)	33
Et	$C_9H_{19}CO$	199/15	−18.2 (neat)	10
Me	$ClCH_2CO$	187–188/37	−23.3 (neat)	10
Me	$BrCH_2CO$	194–195/22	−22.4 (neat)	10
Et	$BrCH_2CO$	178−182/10	−22.5 (neat)	36
Me	Bz	150/0.001	−3.0 ($CHCl_3$)	38
Et	Bz	152/0.5	−3.9 (neat)	33,39
Et	2-MeC_6H_4CO	—	−6.2 (neat)	39
Et	3-MeC_6H_4CO	—	−4.7 (neat)	39
Et	4-MeC_6H_4CO	—	−0.2 (neat)	39
Me	4-$O_2NC_6H_4CO$	—	−5.1 (MeOH)	40
Me	PhCH=CHCO	—	−0.5 ($CHCl_3$)	41
Et	PhCH=CHCO	190/0.25	+9.9 ($CHCl_3$)	33,42
Me	THP	112–114/0.55	−48.3 (EtOH)	43
Et	THP	118.5–119/0.4	−59.0 (Me_2CO)	44,45
MOM	MOM	116–122/0.04	−42.7 (EtOH)	46
Et	$MeOCMe_2$	—	—	47
Me	EE	—	−52.4 (Me_2CO)	48
Et	EE	116–118/0.3	—	49,50
Me	BOM	—	−40.9 ($CHCl_3$)	51
Et	Acgl[b]	73.5–75	−36.4 ($CHCl_3$)	52
Me	NO_2	24–25	−33.0 (neat)	53

(*continued*)

Table 16.1 (*continued*)

R^1	R^2	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
Et	NO_2	148/25	−33.8 (MeOH)	7,53
Et	PCl_2	92–93/0.2	−84.6 (neat)	54
Me	$EtSO_2$	167–168/1	−43.4 (neat)	33
Et	$EtSO_2$	154–155/0.5	−41.9 (neat)	33
Et[a]	Ts	197–198/1	−34.5 (neat)	33
TMS	TMS	137–140/11	−43.2 (neat)	124

[a] At 546 nm.
[b] Acgl = *O*-tetraacetyl-β-D-glucopyranosyl.

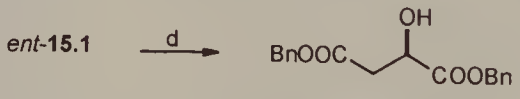
Synthesis

Synthetic methods reported for diesters of tartaric acid (Chapter 2), and their *O*-acyl and *O*-alkyl derivatives (Chapters 4 and 5), are entirely applicable to malates and their *O*-protected derivatives. A few representative examples of syntheses are shown in Scheme 16.1.

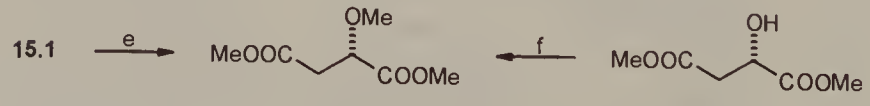
a: MeOH, $SOCl_2$, 0°C → RT, 24h (98%)[55]

b: MeOH, HCl or AcCl, RT, 24h (88-91%)[1,43,56,57]

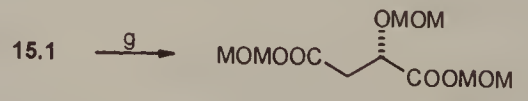
c: EtOH, AcCl, benzene, Δ (removal of water), ca 100%[58]



d: 2 eq. BnOH, TsOH (cat.), PhMe, Δ (removal of water), 95%[14]

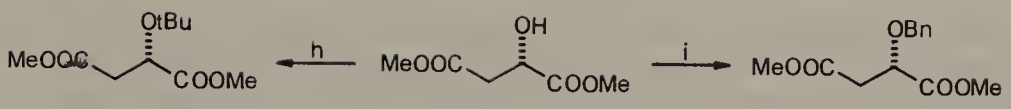


e: $TMSCHN_2$, HBF_4, CH_2Cl_2, 0°C (46%)[20] f: Ag_2O, MeI (37-74%)[21,22]



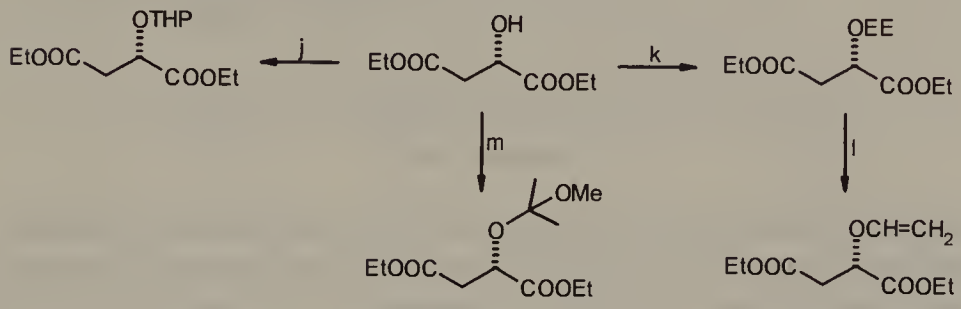
g: 1.5 eq. MOMCl, 1.5 eq. i-Pr_2NEt, $MeOCH_2CH_2OMe$, Δ, 2h (75%)[46]

Scheme 16.1 (*continued*)



h: $CH_2=CMe_2$, H_2SO_4 (cat.), CH_2Cl_2, RT (75%)[26]

i: 1.2-3.0 eq. $Cl_3CC(NH)OBn$, TfOH (cat.), CH_2Cl_2-cyclohexane (1:2), RT (60-68%)[29,30] or 1.5 eq. Ag_2O, 1.5 eq. BnBr, AcOEt, RT, 15h (65%)[59]

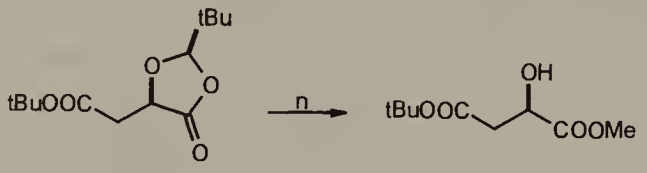


j: 2,3-dihydro-4*H*-pyran, TsOH (cat.), Et_2O, RT 12h (100%)[45]

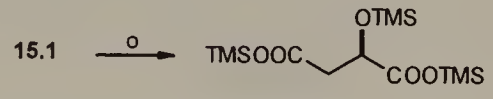
k: $EtOCH=CH_2$, CF_3COOH (cat.), 0°C → RT (99%)[49]

l: NEt_3, TMSOTf, CH_2Cl_2, 0°C → RT, 15h (60% crude)[60]

m: $CH_2=CH(OMe)Me$, $POCl_3$ (cat.), 0°C (99%)[9]



n: MeOH, $NaHCO_3$, RT, 1h (98%)[61]

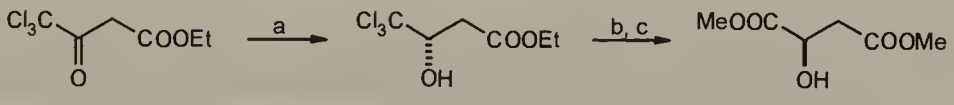


o: 1.1 eq. HMDS, 1.1 eq. TMSCl, RT, 12h (85%)[124]

Scheme 16.1

Specific compounds are listed in Table 16.1.

Optically active malates can also be obtained by biocatalytic methods of enantioselective synthesis. Seebach *et al.* used a baker's yeast reduction of ethyl-4,4,4-trichloro-3-oxobutanoate (**16.1**) for conversion to optically active dimethyl



16.1 **16.2**

a: baker's yeast, saccharose, H_2O, 30°C, 20h (70%, e.e. 84%); after crystallization 52%, e.e. 100%

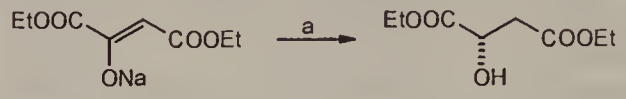
b: 4N HCl, Δ, 2.5h, then aq. NaOH, RT, 24h, then acid resin

c: MeOH, TsOH (cat.), Δ (61%)

Scheme 16.2

D-malate (Scheme 16.2). Note the inversion of configuration during the course of hydrolysis of 4,4,4-trichloro-3-hydroxybutanoate (**16.2**) to malic acid.[62]

Of practical significance is the direct synthesis of enantiomerically pure diethyl L-malate from commercially obtained sodium diethyl oxalacetate by fermenting baker's yeast, as reported by Santaniello *et al.*[35] (Scheme 16.3).



a: baker's yeast, saccharose, H_2O, 30°C, 96h (72%, e.e. > 98%)

Scheme 16.3

This reaction was applied to the synthesis of ^{13}C-labeled diethyl L-malate.[63]

Dimethyl D-malate of e.e. up to 93% was obtained by kinetic resolution of racemic dimethyl malate with the use of porcine liver esterase (PLE). However the authors encountered difficulties in the separation of the D-diester from the L-monoester formed.[35]

Dimethyl L-malate [*617-55-0*], its D-enantiomer [*70681-41-3*], diisopropyl L-malate, and its D-enantiomer are available commercially.

Applications

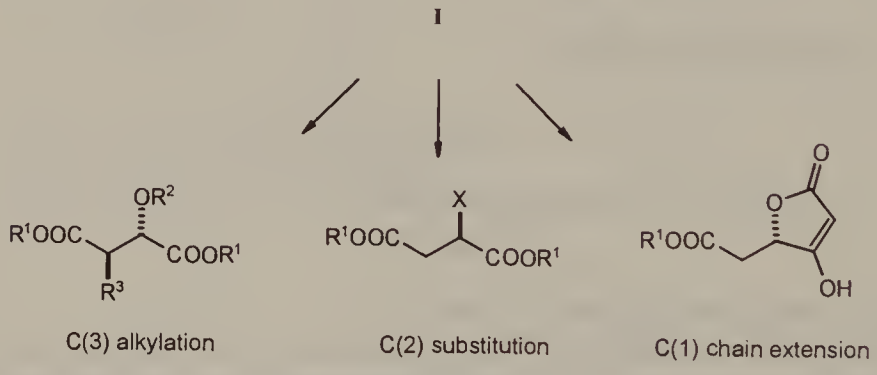
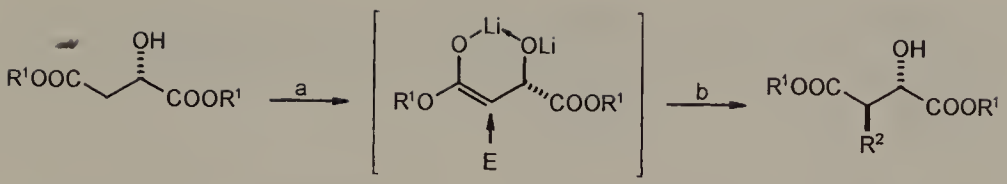


Figure 16.1

B

Synthesis of 3-alkyl-2-hydroxysuccinates. *Anti (erythro)*-3-alkyl-2-hydroxysuccinates (**16.4**) are readily available by diastereoselective alkylation of alkoxide enolates **16.3** derived from malates by double deprotonation. The *anti*-selectivity results from the direction of approach of the electrophile to enolate **16.3** (Scheme 16.4).

The reaction, originally developed by Seebach,[64] is characterized by high diastereoselectivity (typically over 90% *anti*) and versatility. The usefulnes of *anti*-3-alkyl-2-hydroxysuccinates is documented by numerous examples of synthesis in which they served as chiral intermediates (Scheme 16.5).



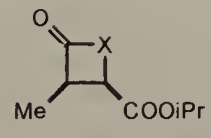
16.3 16.4

a: 2 eq. LDA, THF, -78°C → -20°C b: R^2X, -78° → -5°C

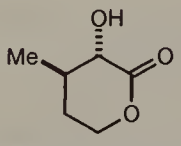
entry	R^1	R^2	electrophile	*anti* : *syn*	*anti*, yield (%)	ref.
1	Me	Me	MeI	>10 : 1	65	64,65
2	Et	Me	MeI	>10 : 1	88	64,66
3	Me	Et	EtI	9 : 1	64	65
4	i-Pr	Et	EtI	6.7 : 1	84	67
5	Et	n-C_5H_{11}	n-C_5H_{11}I	46 : 1	48	68[a]
6	Me	All	AllBr	>15 : 1	-	64
7	Et	All	AllBr	12 : 1	70-85	64,69,70
8	Et	Bn	BnBr	10 : 1	48	64
9	Et	Bn	BnBr	>35 : 1	70	71[a]
10	i-Pr	Bn	BnBr	10 : 1	80-85	72[b]
11	Bn	Bn	BnBr	*anti* only	47-52	14
12	Me	$Me_3SiC{\equiv}CCH_2$	$Me_3SiC{\equiv}CCH_2Br$	9 : 1	51	73[b]
13	i-Pr	i-$Pr_3SiO(CH_2)_2$	i-$Pr_3SiO(CH_2)_2$I	9 : 1	70	74
14	Me	$O_2N(CH_2)_2$	$O_2NCH{=}CH_2$	5.7 : 1	31	75
15	Me/tBu[c]	$CH_2{=}C(Me)CH_2$	$CH_2{=}C(Me)CH_2Br$	20 : 1	59	61[a,b]

[a] $(TMS)_2NLi$ used as a base [b] enantiomer prepared [c] unsymmetrical ester

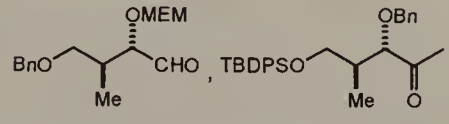
Scheme 16.4



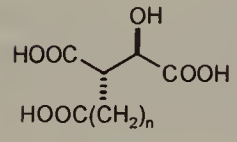
(X = O, NH), from entry 2 (Miller[76])



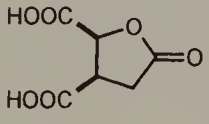
verrucarinolactone, from entry 13 (Tamm[74])



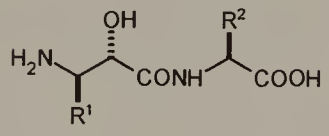
intermediates for the synthesis of avermectins, from entry 1 (Hanessian,[77] Hirama[78])



(n = 1, 2) (-)-isocitric and (-)-homo-isocitric acids, from enantiomer of entry 12 (Biellmann)[73]

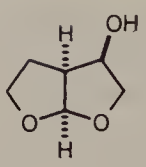


(+)-isocitric acid lactone, from entry 6 (Seebach[79])

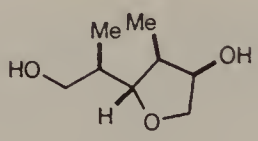


valinoctin A (R^1 = n-C_5H_{11}, R^2 = i-Pr), from entry 5 (Umezawa[68])
(-)-bestatin (R^1 = Bn, R^2 = i-Bu), from entry 9 (Norman[71])

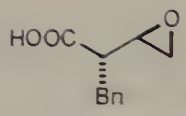
Scheme 16.5 (*continued*)



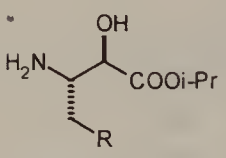
HIV-1 protease inhibitor, from enantiomer of entry 7 (Ghosh *et al.*[70])



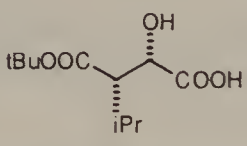
C(17)-C(22) subunit of ionomycin, from enantiomer of entry 2 (Guindon *et al.*[66])



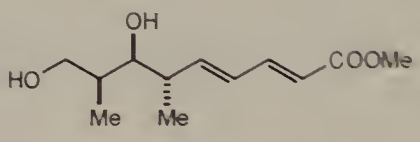
carboxypeptidase A inactivator, from enantiomer of entry 11 (Kim *et al.*[14])



norstatine, R = i-Pr
nor-C-statine, R = Cy
from enantiomer of entry 10 (Dugger *et al.*[72])



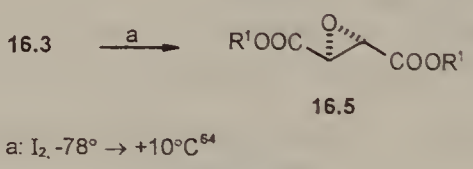
subunit of a peptidyl boronate, from enantiomer of entry 15 (Bartlett *et al.*[61])



subunit of the macrolide antibiotic elaiophylin, from entry 2 (Seebach *et al.*[123])

Scheme 16.5

The reaction of enolate **16.3** with iodine as electrophile is an alternative method for the synthesis of epoxydiesters **16.5** (Scheme 16.6). This products is otherwise available from tartrates (Chapter 7). Diastereoselectivity of the iodination reaction is, however, moderate to low.



16.3 —a→ **16.5**

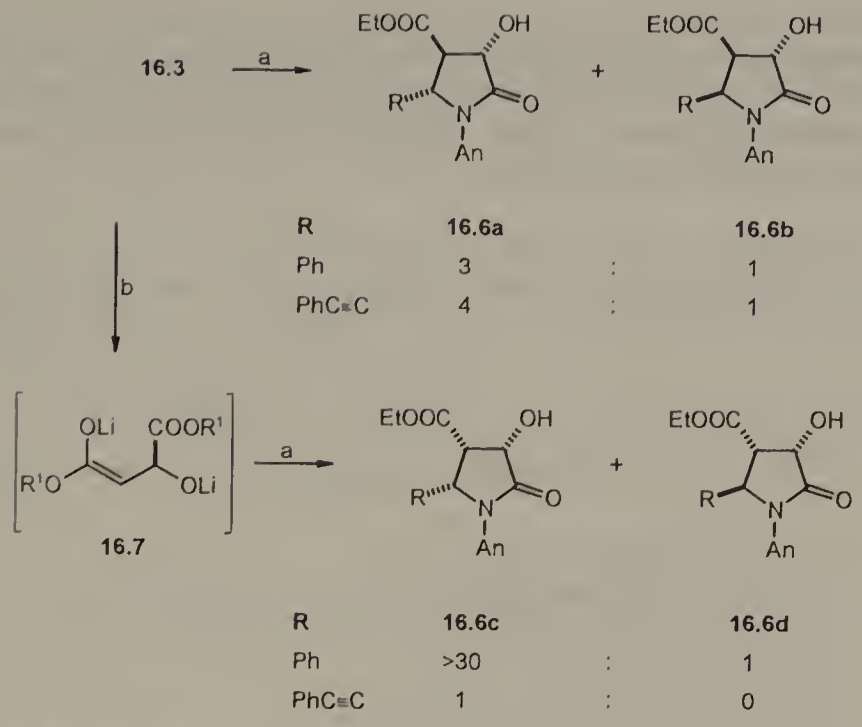
a: I_2, -78° → +10°C[64]

Scheme 16.6

Addition of dianion **16.3** to non-enolizable *N*-arylimines is accompanied by cyclization to 2-pyrrolidinone derivatives. In THF solution normal *anti*-selective addition gives rise to two diastereoisomeric products **16.6a** and **16.6b**. In the presence of HMPA, *syn*-selective addition dominates (products **16.6c** and **16.6d**), presumably due to the non-chelated structure of the enolate **16.7**. Yields of the products were moderate (32–60%)[80] (Scheme 16.7).

3,3-Dialkyl-2-hydroxysuccinates can be synthesized from malates following the route to monoalkyl derivatives. Good diastereoselectivity is maintained throughout when the two alkyl substituents are different: the second alkylation step occurs from the *Re*-face in the case of L-malate. Relevant examples are shown in Scheme 16.8.

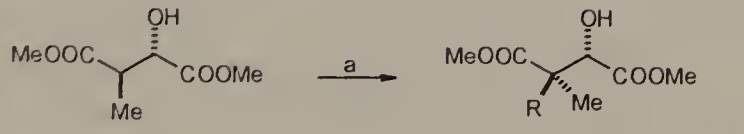
Products shown in Scheme 16.8 were used for the synthesis of (+)-pantolactone and its ^{13}C labeled analogue,[65] as well as for the synthesis of the (−)-ring-B imide related to vitamin B_{12}.[81] Electrochemical decarboxylation of C(1) acid function of 3,3-dialkyl-2-hydroxysuccinates gave enantiomerically pure dialkylmalonaldehydic esters.[122]



a: An N=CHR, THF

b: 4 eq. HMPA

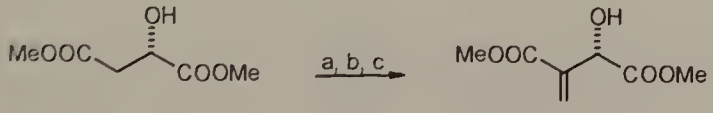
Scheme 16.7



a: 2 eq LDA, THF, -78°C, then RX, -78° (36-94%, d.e. 76-90%)

Scheme 16.8

A sequence of aminomethylation-quaternization-Hoffman degradation reactions led to 3-methylenation of a malate, with low yield[82] (Scheme 16.9).

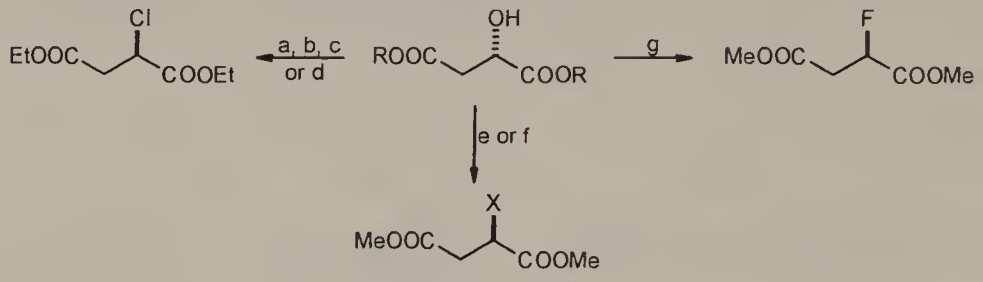


a: 2 eq LDA, $CH_2=\overset{+}{N}Me_2I^-$; b: MeI; c: $NaHCO_3$ (10% overall)

Scheme 16.9

2-Heteroatom substituted succinates. 2-Halo-, nitrogen- and sulfur-substituted succinates can be obtained from malates by nucleophilic substitution with inversion of configuration. Two general methods are used for this transformation.

2-Halosubstituted succinates are available directly from malates by a Walden-type substitution with halogenating agents. Depending on reaction conditions, the 2-chlorosuccinate obtained in such a reaction can be partially racemized.[83] Reaction with diethylaminosulphur trifluoride (DAST) produces 2-fluorosuccinates from malates (Scheme 16.10).



a: 1 eq. $SOCl_2$, RT, 4d (72%), $[\alpha]_D$ +32.7 (neat)[83]

b: 0.33 eq. PCl_3, 1 eq. pyridine, Et_2O, -10°C, then HCl, $[\alpha]_D$ +32.4 (neat)[54]

c: Et_2PCCl_3, NEt_3, CH_2Cl_2 (72%), $[\alpha]_D$ +29.8 ($CHCl_3$)[84]

d: CCl_4, Ph_3P, Δ, $[\alpha]_D$ +31 (neat)[58]

e (X = Cl): $POCl_3$, pyridine (36%), $[\alpha]_D$ +36.6 (neat)[85]

f (X = Br): PBr_5, $CHCl_3$, Δ, 0.5h (54%), $[\alpha]_D$ +50.8 (neat)[86]

g: 1 eq. DAST, $CHCl_3$, 0°C → RT, 0.5h (ca. 80%)[87]

Scheme 16.10

entry	R^1	R^2	Nu	yield (%)	ref.
1	Et	Ms	AcS^-Cs^+	89[a]	88
2	Et	Tf	$(MeO)_2P(S)S^-Na^+$	80[b]	89
3	Et	Tf	$EtCOO^-K^+$	52	37
4	Et	Tf	$PhCOO^-K^+$	58[c]	37
5	Bn	Tf	$BocNHO^-Li^+$	40	90
6	Me	Ns	N_3^- $(Me_2N)_2C^+NH_2$	78	91
7	Et	Tf	$n\text{-}C_6H_{13}NH_2$	40	92
8	Et	Tf	$AllNH_2$	55	92
9	Et	Tf	$BnNH_2$	93	92
10	Et	Tf	$PhNH_2$	94	92
11	Me	Tf	$N_3CH_2CH(COOBn)NH_2$	61-73[b]	93
12	Me	Tf	$BnONH_2$	88[c]	94
13	Me	Ns	$BocNHNH_2$	91	95
14	Bn	Tf	$CbzNHNH_2$	89-97	90

[a] side product diethyl fumarate (3%)

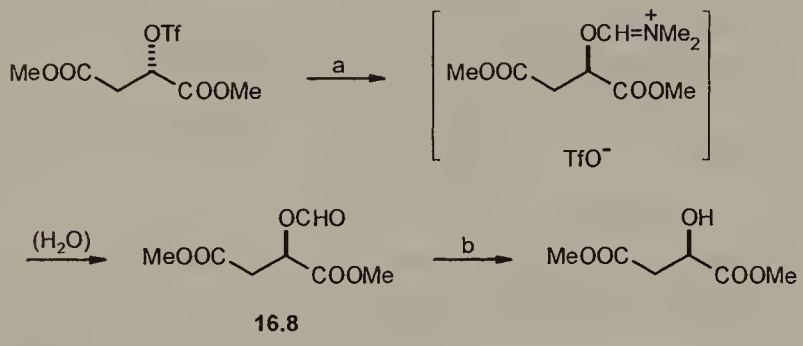
[b] overall yield from diethyl malate [c] e.e. 95%

Scheme 16.11

2-Sulfur-, oxygen- and nitrogen-substituted succinates are readily prepared by substitution of *O*-sulfonyl activated malates with suitable nucleophiles. The reaction is generally believed to proceed without racemization, particularly at low temperatures (−78°C) with highly reactive triflates (usually prepared from malates *in situ*). With less reactive mesylates and tosylates elimination can be highly competitive (Scheme 16.11).

Entry 2 represents the first synthesis of enantiomerically pure malathion.[89] 2-Azidoesters prepared according to entry 6 were used for the synthesis of L-D and D-L dipeptides and L-D-L tripeptides.[91] Entries 7–14 represent syntheses of variously *N*-substituted aspartates from malates.

The triflate methodology makes possible the synthesis of D-malates from L-malates in a one-pot reaction and without the necessity of isolating the intermediate formate **16.8**, by using DMF as a nucleophile (Scheme 16.12).



16.8

a: DMF, 0°C → RT, 15 min.

b: MeOH, TsOH (cat.), RT, 1h (93%, e.e. 98%)[94(b)]

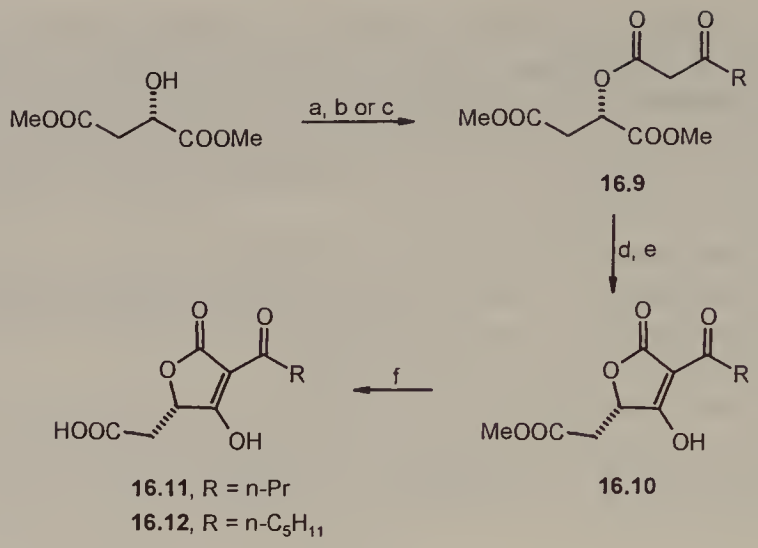
Scheme 16.12

Synthesis of tetronic acid derivatives. Dieckman cyclization of *O*-acylacetate derivatives of malates (**16.9**) gives access to chiral tetronic acid derivatives **16.10**. Several variants of this reaction have been developed by Bloomer,[96] Ley,[97] Sakaki and Kaneko,[98] and Schobert.[99] These variants differ chiefly in the method of preparing the acylacetate derivative **16.9** (Scheme 16.13).

Following these methodologies (*S*)-carlosic acid (**16.11**)[97-98] and (*S*)-viridicatic acid (**16.12**)[98] have been synthesized.

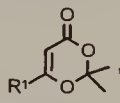
Substituted tetronic acid **16.15** is available by one-pot synthesis, involving an intramolecular Wittig reaction of the intermediate ester-ylide **16.14**, derived from dimethyl L-malate and ketenylidene triphenylphosphorane **16.13**[99] (Scheme 16.14).

In a related C-1 chain extension reaction of unsymmetrical malic acid diester **16.16** with the (*R*)- and (*S*)-methyl p-tolylsulfoxide anion, followed by DIBAL reduction, there are obtained diastereomeric products **16.17** and **16.18**, precursors of derivatives of 2-deoxy-D-ribose and 2-deoxy-L-xylose, respectively[100] (Scheme 16.15).



a (R = Me): diketene, NEt_3 (cat.), PhH (80%)[96]

b (R = n-Pr): n-$PrCOCH_2COSt$-Bu, CF_3COOAg, THF (71-75%)[97]

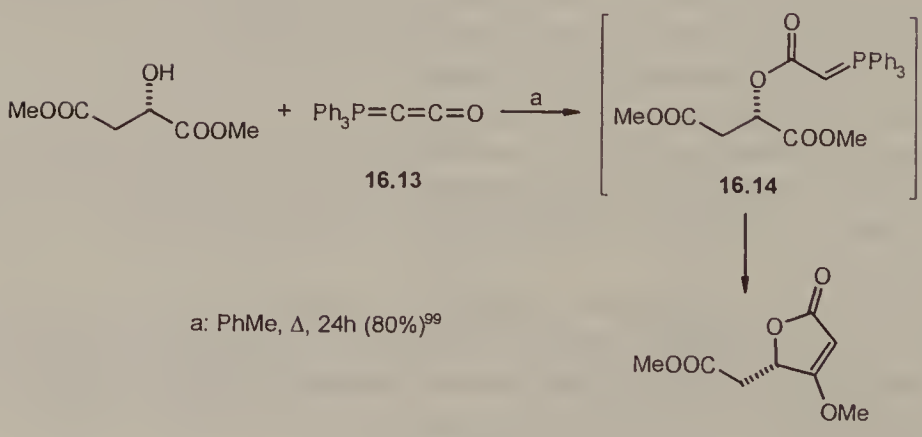
c (R =Me, n-Pr, n-C_5H_{11}):  , PhMe, Δ, 1h (81-98%)[98]

d (R = Me): t-BuOK, t-BuOH (39%)[96]

e (R = Me, n-Pr, or $(CH_2)_2OTHP$): 1 eq. n-Bu_4NF, THF (44-84%)[97,98]

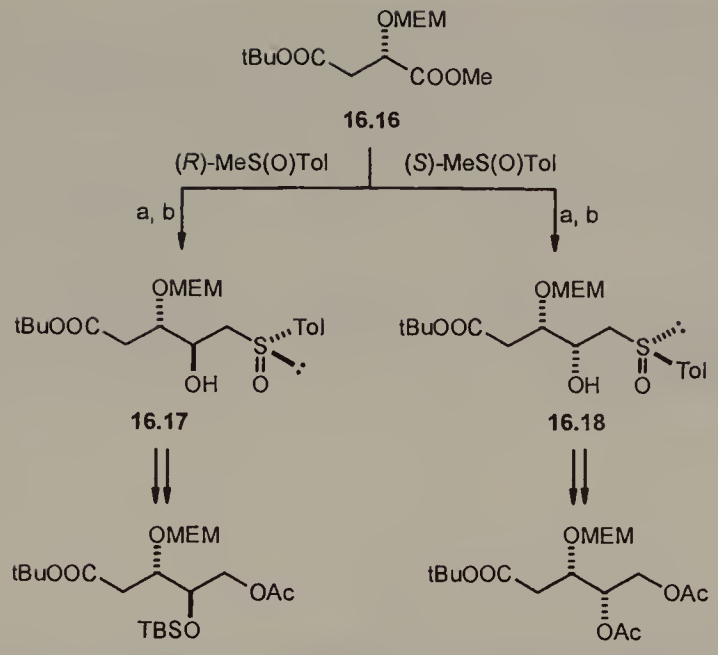
f: 10% HCl, RT, one week (56-71%)[97,98]

Scheme 16.13



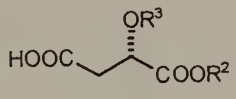
a: PhMe, Δ, 24h (80%)[99]

Scheme 16.14

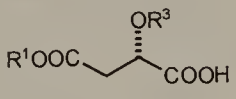


Scheme 16.15

16.2 MONOESTERS OF MALIC ACID: DIFFERENTIATION OF THE CARBOXY GROUPS



II



III

Table 16.2 Monoesters of L-malic acid and *O*-protected L-malic acids (II and III)

R^1	R^2	R^3	m.p. (°C)	$[\alpha]_D$ (solvent)	References
			C(1) monoesters (II)		
—	Me	H	79–80	+5.8 (MeOH)[a]	67,101
—	Et	H	48–49.5	—	67
—	(*S*)-Et(Me)CHCH_2	H	—	−9.0 (THF)	101
—	Me$(CH_2)_7$	H	—	−9.4 ($CHCl_3$)	102
—	Bn	H	—	−16.0 (THF)[b]	101,103
—	Me	Me	46–48	−55.9 (Me_2CO)	22,104
—	Me	Ac	48–50	−27.9 (MeOH)	105,106
—	Et	Ac	53	−32.4 ($CHCl_3$)	108–110

(continued)

Table 16.2 (*continued*)

R^1	R^2	R^3	m.p. (°C)	$[\alpha]_D$ (solvent)	References
		C(4) monoesters (III)			
Me	—	H	—	+1.5 ($CHCl_3$)	111
Me	—	Me	—	−45.8 (Me_2CO)	22
Et	—	Et	—	−46.0 (EtOH)[c]	112
Et	—	Ac	52–54	−16.8 (EtOH)	8

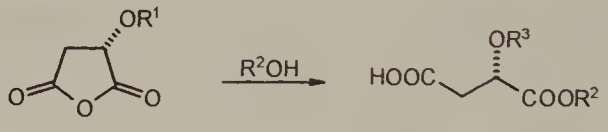
[a] $[\alpha]_D$ -5.0 (dioxane) in ref. 101.
[b] $\alpha]_D$ +13.2 (DMF) in ref. 103.
[c] e.e. 95.8%.

Synthesis

Differentiation of malic acid carboxy groups can be readily achieved by taking advantage of the higher reactivity of the C(1) carboxy group. This property of α-hydroxyacids allows to selectively synthesize C(1) and C(4) monoesters of malic acid.

To this end two general approaches have been developed; alcoholysis of malic anhydrides yields predominantly C(1) monoesters **II** (Scheme 16.16), whereas enzymatic hydrolysis of malates provides accesss to C(4) monoesters **III** (Scheme 16.17).

C(1) monoalkyl malates (II)



R^1	R^2	R^3	isolated yield (%)	ref.
H	Me	H	64	67
H	Bn	H	64	67
Me	Me	Me	-	104
Ac	Me	Ac	73-100	105,106
Ac	Et	Ac	60-95	107-110
CF_3CO	Me	H	26-100	67,101,113
CF_3CO	Et	H	99	67
CF_3CO	i-Pr	H	98	67
CF_3CO	$Me(CH_2)_7$	H	50	102
CF_3CO	(*S*)-Et(Me)$CHCH_2$	H	80	101
CF_3CO	Bn	H	76-100	101,103

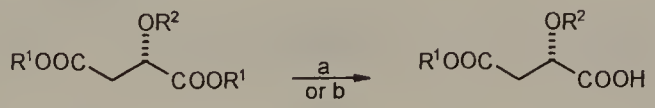
Scheme 16.16

C(1) monoesters are usually prepared from crude anhydrides and the reaction is best carried out at ambient temperature; heating the reaction mixture has an adverse effect on monoester yield.

The use of *O*-trifluoroacetyl malic anhydride appears to offer the highest yield and selectivity in the formation of the C(1) monoester. Note that the *O*-trifluoroacetyl group is removed in the process of solvolysis of the anhydride[67] (Scheme 16.16).

Enzymatic hydrolysis of diesters of malic acid with α-chymotrypsin[8] and pig liver esterase[111] is C(1) selective in that it provides C(4) monoesters (Scheme 16.17), but it is not enantioselective: both dimethyl L- and D-malates are preferentially hydrolysed at C(1) by PLE.[114]

C(4) monoalkyl malates (III)

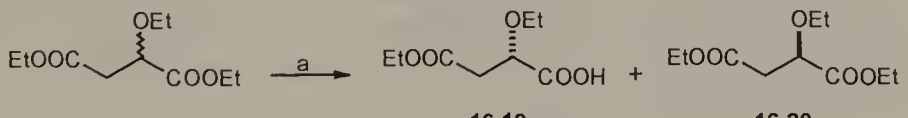


a (R^1 = Et, R^2 = H or Ac): α-chymotrypsin, pH 7.2, RT, (94-100% conversion)[8]

b (R^1 = Me, R^2 = H): PLE, pH 8.0, RT (100% conversion)[111]

Scheme 16.17

In contrast, enzymatic hydrolysis of racemic diethyl *O*-ethyl malate is both site selective and enantioselective with lipase from *Candida rugosa*, as reported by Wirz (Scheme 16.18).



16.19 **16.20**

39%, e.e. 95.8%

a: lipase OF 360, cyclohexane, 0.1M NaCl/0.01M sodium phosphate, pH 6.5, 3-4°C[112]

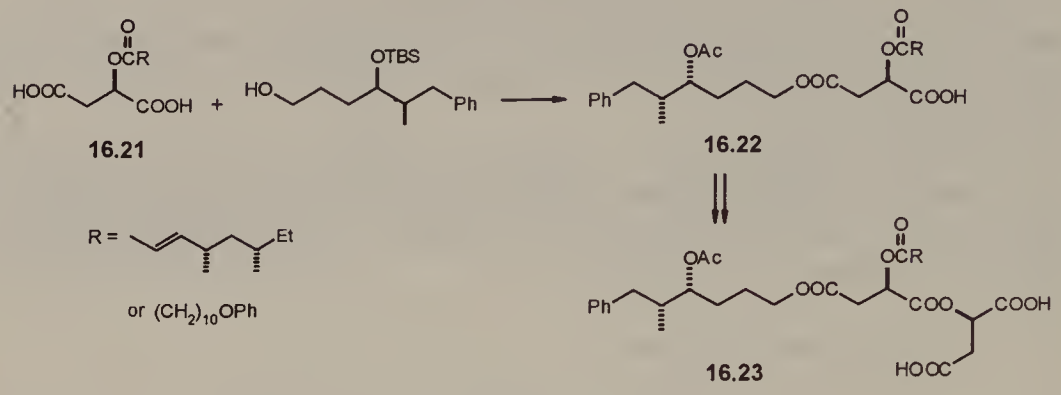
Scheme 16.18

High enantiomeric excess of the monoester **16.19** could only be achieved after careful optimization of reaction conditions: use of water-immiscible cosolvent, low substrate concentration, low temperature and pH, and relatively high enzyme concentration. Since the recovered diester **16.20** could be easily racemized (EtONa/EtOH) and recycled, the overall efficiency of the enzymatic deracemization and functional group differentiation could be significantly improved.[112]

Simple saponification of *O*-methyl dimethyl malate with one equivalent of potassium hydroxide in methanol is C(1) selective.[22]

It should be noted that esterification of *O*-acylated diacids **16.21** proceeds at the less hindered C(4) carboxy group and gives C(4) monoesters **16.22** in

excellent yield (no experimental details were reported). Monoesters **16.22** were used for the synthesis of squalene synthase inhibitors **16.23** [115](Scheme 16.19).

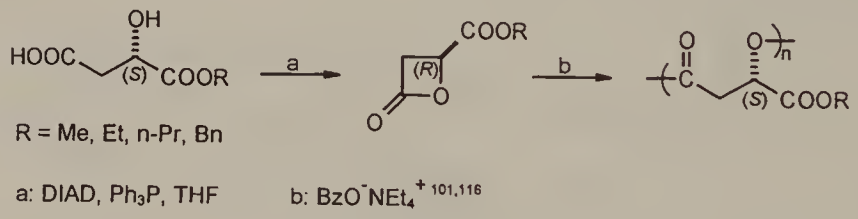


Scheme 16.19

Applications

B

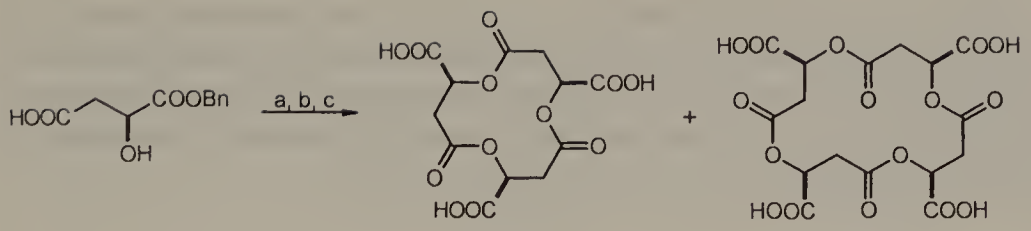
C(1) Monoesters of malic acid are used in synthetic transformations involving substitution at the C(4) carboxy group. For example, both 4-alkoxycarbonyl-2-oxetanones (β-lactones) and 4-alkoxycarbonyl-2-azetidinones (β-lactams) were obtained from C(1) monoesters of malic acid by intramolecular substitution (Scheme 16.20).



Scheme 16.20

These β-lactones were polymerized to high molecular weight poly(β-malic acid) having (*S*)-configuration of the stereogenic center. This indicates double inversion of configuration: one at the stage of Mitsunobu β-lactam formation; and the other at the polymerization step.[101,116] 12- And 16-membered oligolides, related model compounds for the biopolymer poly(β-malic acid), have been synthesized by Seebach and Hoffmann. The yields of isolated oligolides **16.24** and **16.25** were low (<10%) due to the formation of other oligomeric and polymeric products[121] (Scheme 16.21). Note that under reaction conditions the configuration of the stereogenic center remained unchanged.

The synthesis of β-lactams, developed by Miller *et al.*, is based on the intramolecular Mitsunobu reaction of malic acid monohydroxamates **16.27**, synthesized from C(1) monoesters **16.26**, and it proceeds with inversion of configuration[67] (Scheme 16.22).



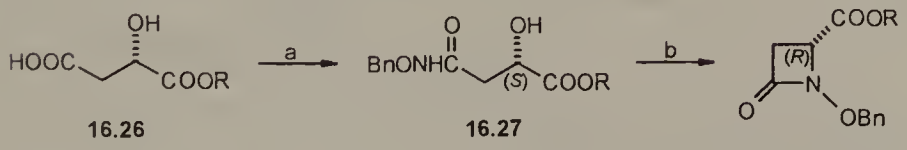
16.24 16.25

a: 2,6-$Cl_2C_6H_3COCl$, pyridine, THF

b: DMAP, high dilution (CH_2Cl_2 or PhMe), RT

c: H_2, Pd/C, AcOEt[121]

Scheme 16.21



16.26 16.27

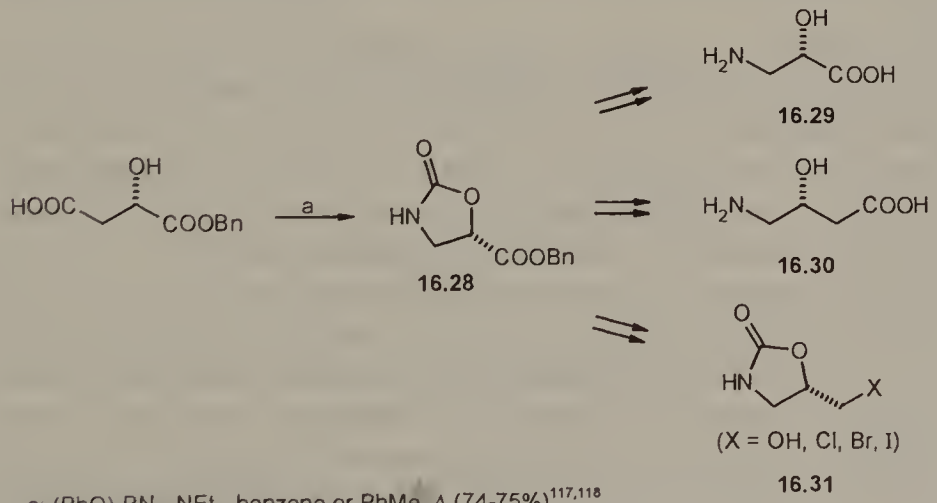
R = Me, Et, i-Pr, Bn

a: $BnONH_2 \cdot HCl$, $EtN{=}C{=}N(CH_2)_3NMe_2$, THF-Et_2O, pH 4.5 (60-84%)

b: DEAD, Ph_3P, THF, RT (78-96%)[67]

Scheme 16.22

The presence of the $-CH_2COOH$ unit in C(1) monoesters of malic acid enables syntheses involving decarboxylation, while retaining the integrity of the chiral center in the remaining three-carbon unit. One such example is the use of Curtius rearrangement on the C(1) monoesters of malic acid. The intermediately formed 2-oxazolidinone-5-carboxylic ester **16.28** can further be transformed into a variety of useful products, such as (*S*)-isoserine (**16.29**),[117] (*R*)-GABOB (**16.30**)[118] and 5-substituted 2-oxazolidinones **16.31**[103] (Scheme 16.23).



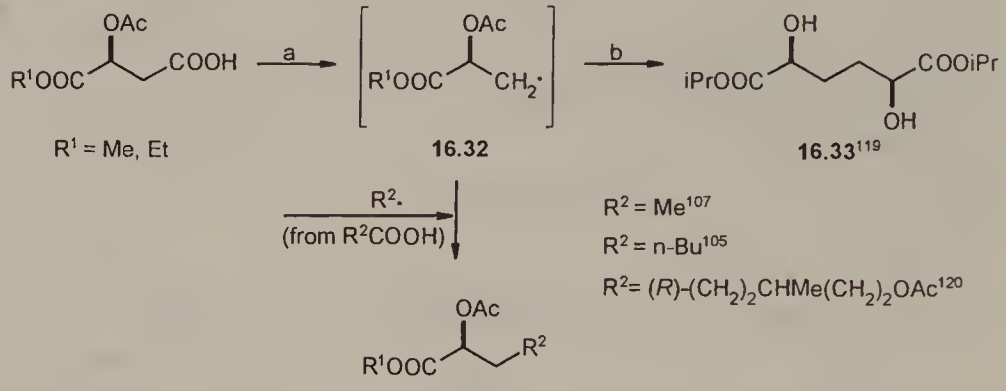
16.29 16.28 16.30 16.31

(X = OH, Cl, Br, I)

a: $(PhO)_2PN_3$, NEt_3, benzene or PhMe, Δ (74-75%)[117,118]

Scheme 16.23

Furthermore, Kolbe decarboxylation of C(1) monoesters of malic acid is useful for chain elongation of the chiral three-carbon unit either by dimerization of the initially formed radical **16.32** to the dimeric product, (2*S*,5*S*)-2,5-dihydroxyadipate **16.33**, or by its cross-coupling with radicals derived from other carboxylic acids (Scheme 16.24, see also Scheme 15.16).



Scheme 16.24

Diester **16.33** was tested by Sharpless *et al.* as a ligand in the asymmetric epoxidation.[119] The last of the products listed in Scheme 16.24 was used by Stork in the synthesis of cytochalasin B.[120]

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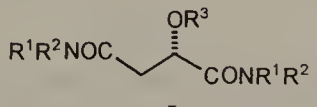
17 Malamides and Malimides

17.1 DIAMIDES OF MALIC ACIDS (MALAMIDES) AND THEIR *O*-PROTECTED DERIVATIVES



I

Synthesis

Malamides and their *O*-acyl and *O*-alkyl derivatives are synthesized in a way analogous to the synthesis of tartramides (Chapter 3) and their *O*-protected derivatives (Chapters 4 and 5). Specific compounds are listed in Table 17.1.

Table 17.1 L-Malamides and their derivatives (I)

R^1	R^2	R^3	m.p. (°C)	$[\alpha]_D$ (solvent)	References
H	H	H	156–158	−60.3 (MeOH)	1–4
Me	H	H	99	−68.5 (MeOH)	1
Et	H	H	122	−58.7 (MeOH)	1
Pr	H	H	126	−52.9 (MeOH)	1,5
i-Pr	H	H	150–151	−42.6 (MeOH)	1
n-Bu	H	H	125	−47.7 (MeOH)	1
i-Bu	H	H	121	−48.1 (MeOH)	1
n-C_5H_{11}	H	H	146	—	6
n-C_7H_{15}	H	H	131	−35.4 (MeOH)	1
All	H	H	117.5	−48.3 (MeOH)	1
Bn	H	H	157	−36.1 (MeOH)	5,7,8
Ph [a]	H	H	198	−101.1 (pyridine)	9
2-MeC_6H_4	H	H	179	−61.8 (pyridine)	9
3-MeC_6H_4	H	H	153	−75.9 (pyridine)	9
4-MeC_6H_4	H	H	206	−92.5 (pyridine)	9
(S)-BnCHCOOiBu	H	H	76	—	10
NH_2	H	H	177–179	−52.0 (EtOH-H_2O)	11
PhNH	H	H	214	−17.2 (pyridine)	1

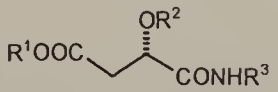
(continued)

Table 17.1 (*continued*)

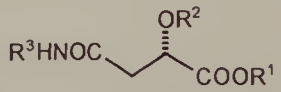
R^1	R^2	R^3	m.p. (°C)	$[\alpha]_D$ (solvent)	References
$-(CH_2)_4-$		H	157.5	−27.5 (MeOH)	1
H	H	Me	183–184	−57.5 (MeOH)	12–14
Bn	H	Me	157	−36.9 (MeOH)	15
Ph	H	Me	158–159	−77.7 (MeOH)	12
H	H	Et	192–193	−44.6 (H_2O)	2
Ph	H	Ac	177	+50.5 (EtOH)	16
Ph	Me	Ac	116	+26.8 (MeOH)	16

[a] This amide is known as *malanilide.*

17.2 MONOAMIDES OF MALIC ACID (MALAMIC ACID): DIFFERENTIATION OF THE CARBOXY GROUPS



II



III

R^1 = H : C(4) malamic acids

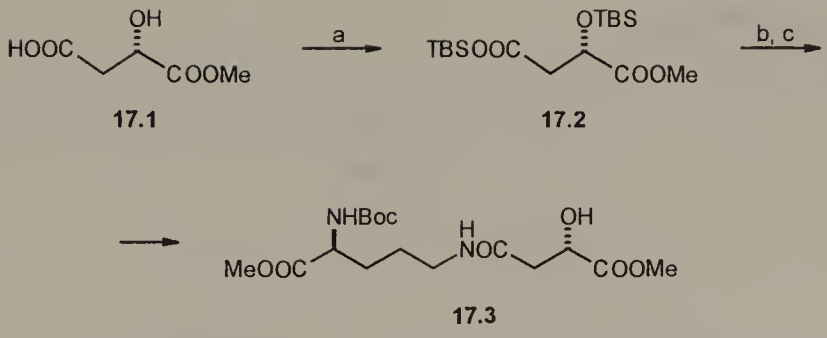
C(1) malamic acids

Table 17.2 Monoamide derivatives of L-malic acid (II, III)

Formula	R^1	R^2	R^3	m.p. (°C)	$[\alpha]_D$ (solvent)	References
II	H	H	H	83–84	−16.5 (AcOEt)	17
	H	Me	H	144	−46.7 (MeOH)	18
	H	H	Bn	131–132	−42.6 (H2O)	15
	Me	H	H	66–67	−48.5 (EtOH)	15,19
	Me	t-Bu	H	79–82	−53.1 (MeOH)	19
	Me	THP	H	52–53	+0.4 (MeOH)	19
	Et	H	H	102–103	−49.0 (H_2O)	15
III	H	H	H	149	−9.8 (H_2O)	4,15,20
	H	H	Bn	130–131	−13.8 (H_2O)	15
	Me	H	H	75–76	−12.5 (H_2O)	15
	Me	H	Bn	105	−12.8 (H_2O)	15
	Bn	H	H	78–79	—	21
	$-C(CF_3)_2-$		H	75	−19.0 (CH_2Cl_2)	22

Synthesis and Applications

Monoamides of malic acid are available from monoesters of malic acid, as shown in the example in Scheme 17.1.



17.1 17.2 17.3

a: TBSCl, imidazole, DMF

b: $(COCl)_2$, DMF (cat.), CH_2Cl_2

c: *N*(2)-Boc-Lys-OMe, pyridine, CH_2Cl_2[23]

Scheme 17.1

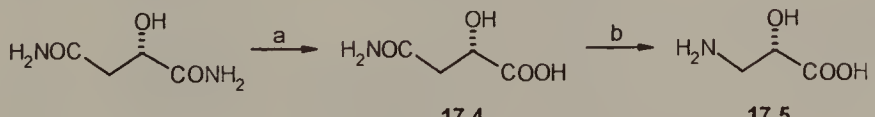
In this synthesis, the coupling of the *N*(2)-protected lysine ester with the C(1) ester of malic acid **17.1** requires the temporary protection of the malate hydroxy group as the TBS ether, prior to the generation of the C(4) acid chloride directly from the bis-TBS derivative **17.2**. Monoamide **17.3** was used by Smith[23] in the synthesis of a siderophore rhizobactin.

C(4) Malamic acids (**II**) are generally available by aminolysis of *O*-protected malic anhydrides. Chemoselectivity of this reaction closely resembles that of alcoholysis of malic anhydrides, which was covered in Chapter 16 (Scheme 17.2).

a: $Me(CH_2)_7NH_2$, THF, 0°C→RT (92% crude)[17]

Scheme 17.2

C(1) Malamic acids (**III**) can be obtained by controlled hydrolysis of malamides in alkaline solution. Malamic acid **17.4** obtained in this way (or alternatively by deamination of L-asparagine [77, 78]) was readily converted to (*S*)-isoserine (**17.5**) (Scheme 17.3).



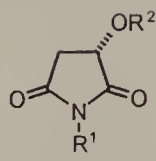
17.4 17.5

a: 1M KOH, Δ, 3d, then conc. HCl (62-75%)[4,20]

b: pyridine, Ac_2O, MeCN, 1h then $PhI(OCOCF_3)_2$, 4 h, then HCl , Δ, then Dowex/OH^- (66-82%)[4,24]

Scheme 17.3

17.3 MALIMIDES



IV

Table 17.3 L-Malimides and their *O*-protected derivatives (IV)

R^1	R^2	m.p. (°C)	$[\alpha]_D$ (solvent)	References
H	H	95	−92.0 (MeOH)	25
H	Me	70	−76.0 (MeOH)	25
H	t-Bu	108–109	−62.0 ($CHCl_3$)	25
H	Ac	112–114	−48.0 (MeOH)	26
Me	H	87–89	−81.8 (EtOH)	27,28
i-Pr	Ac	54–55	−31.1 (MeOH)	29
$(CH_2)_2C{\equiv}CSiMe_3$	Ac	—	−17.4 ($CHCl_3$)	30
$CH_2CMe_2CH{=}CHCH_2OBn$	Ac	—	−15.3 ($CHCl_3$)[a]	31
$(CH_2)_2CN$	Ac	84–86	−30.6 ($CHCl_3$)	32
$(CH_2)_2Ph$	H	130–132	−85.4 ($CHCl_3$)	33,34
$(CH_2)_2Ph$	Ac	97–99	−19.6 ($CHCl_3$)	33
$(CH_2)_2Ph$	$C(O)CH_2Br$	—	−15.3 ($CHCl_3$)	34
3,4-$(MeO)_2C_6H_3(CH_2)_2$	H	125	−67.2 ($CHCl_3$)	35
3,4-$(MeO)_2C_6H_3(CH_2)_2$	$C(O)CH_2Br$	—	−15.2 ($CHCl_3$)	35
$(CH_2)_2$-3-indolyl	H	168–170	−31.4 (DMSO)	34
$(CH_2)_2$-3-indolyl	$C(O)CH_2Br$	98–100	−21.3 (DMSO)	34
$(CH_2)_2OH$	H	77–78	−71.2 (Me_2CO)[a]	36
$(CH_2)_2OAc$	Ac	—	−16.5 ($CHCl_3$)[a]	36
$(CH_2)_2OPiv$	H	—	−56.1 ($CHCl_3$)[a]	36
$(CH_2)_2OPiv$	$C(O)CH_2Br$	—	−9.4 ($CHCl_3$)[a]	36
$(CH_2)_2OBz$	Ac	75–76	−10.2 ($CHCl_3$)	37
$CH_2CH{=}C{=}CH_2$	Ac	46–48	−23.0 ($CHCl_3$)	38
Bn	H	101–103	−62.7 (MeOH)[a,b]	39,40
Bn	Bn	76–77.5	−34.7 ($CHCl_3$)	41
Bn	Ac	61–62.5	−25.8 ($CHCl_3$)	40,42,43
PMB	Ac	—	−32.1 ($CHCl_3$)	43
3,4-$(MeO)_2C_6H_3CH_2$	Ac	—	−18.9 ($CHCl_3$)	43
CH_2COOMe	Ac	—	−26.4 (MeOH)	44
Ph[c]	H	179.5–180	−43.9 (MeOH)	45
Ph	Ac	137	—	46
OBn	H	125–126	—	47

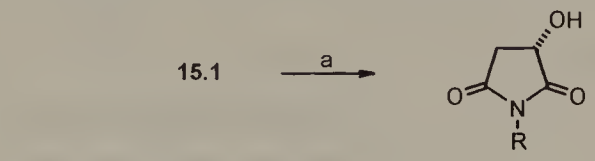
[a] Enantiomer has been prepared.

[b] m.p. 110–111°C; $[\alpha]_D$ −16.2 (MeOH) for apparently partially racemized imide is given in ref. 76. Racemic imide: m.p. 113–114°C (ref. 48).

[c] This imide is known as *malanil*.

Synthesis

Malimides with an unprotected hydroxy group are directly available by thermal condensation of malic acid with amines (Scheme 17.4).



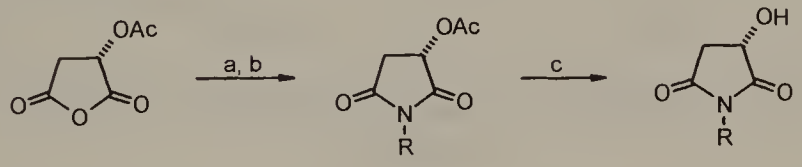
R = Me (65-78%)[27,28] 3,4-$(MeO)_2C_6H_3(CH_2)_2$ (70%)[35]
$BnCH_2$ (73%)[33] BnO (69%)[47]
Bn (62-85%)[39,49,50] Ph (72%)[51]

a: RHN_2, Δ, 150-170°C (neat or in xylene), water separation

Scheme 17.4

This method has the disadvantage of potential racemization of the product (see footnote b in Table 17.3).

O-Acetyl protected malimides can be prepared under mild conditions by a three step, one-pot sequence from *O*-acetyl malic anhydride (crude anhydride directly obtained from malic acid can be used for this purpose). Examples are shown in Scheme 17.5.



a: RNH_2, CH_2Cl_2
then removal of solvents
b: AcCl, Δ
c: EtOH, AcCl, 50°C (84-98%)

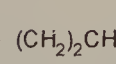
R = H (52%)[26]
Me (94%)[52]
i-Pr (68%)[29,53]
$CH_2CMe_2CH{=}CHCH_2OBn$ (81%)[31]
$(CH_2)_2OAc$ (62%)[36]
$(CH_2)_2CN$ (76%)[32]
CH_2COOMe (74-77%)[44]
Bn (78-100%)[42,43,54,55]
PMB (93%)[43]
3,4-$(MeO)_2C_6H_3CH_2$ (93%)[43]

Scheme 17.5

O-Acetyl protection can be removed by mild acidic solvolysis to give the hydroxy imides of unaltered enantiomeric purity.

Numerous *O*-protected malimides have been synthetized from the parent N–H imides by nucleophilic substitution. Particularly useful for this purpose is the Mitsunobu reaction (Scheme 17.6).

a: R^2OH, DEAD, PPh_3, THF, RT

R = $(CH_2)_2CH$=  (70%[26]

$(CH_2)_2CH$=$CHSiMe_3$ (87%)[56]

$(CH_2)_2CH$=$CHCH_2SnBu_3$ (75%)[57]

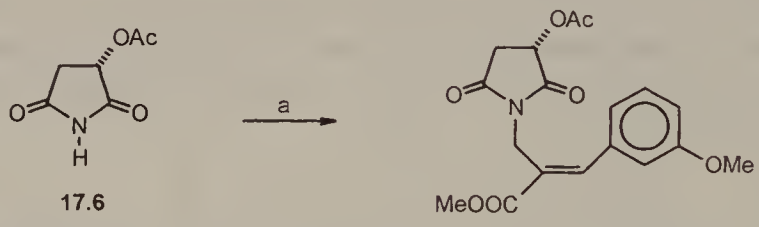
$(CH_2)_2C{\equiv}CSiMe_3$ (97%)[30]

$(CH_2)_2OBz$ (95.5%)[37]

CH_2CH=C=CH_2 (87%)[38]

Scheme 17.6

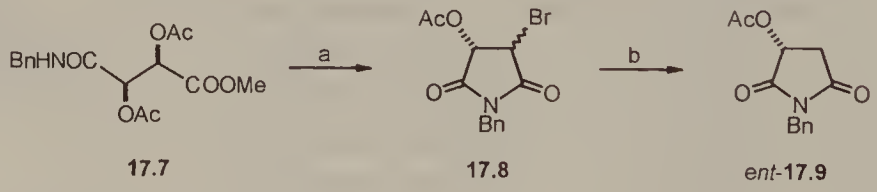
An example of nucleophilic substitution with the potassium derivative of imide **17.6** is shown in Scheme 17.7.



a: 1.0 eq. 3-$MeOC_6H_4CH$=$C(COOMe)CH_2Br$, 1.0 eq. K_2CO_3, DMF, RT (62%)[58]

Scheme 17.7

An efficient synthesis of D-malimide *ent*-**17.9** from L-tartaric acid monoamide **17.7** has been devised by Ogura *et al.*[40] (Scheme 17.8).



17.7 **17.8** *ent*-**17.9**

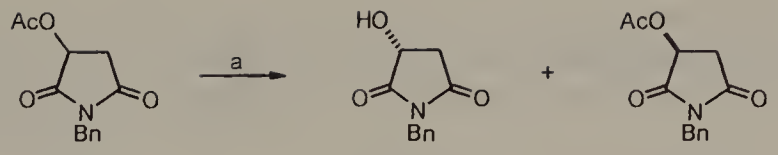
a: 30% HBr/AcOH, Ac_2O, 50°C

b: H_2, 5% Pd/C (74% overall)

Scheme 17.8

Note the highly regioselective formation of the intermediate *O*-acetyl bromohydrin **17.8**.

Ogura *et al.* have also developed a highly enantioselective kinetic resolution of racemic malimide **17.9** with lipase PS from *Pseudomonas cepacia* in a mixed solvent[48] (Scheme 17.9).



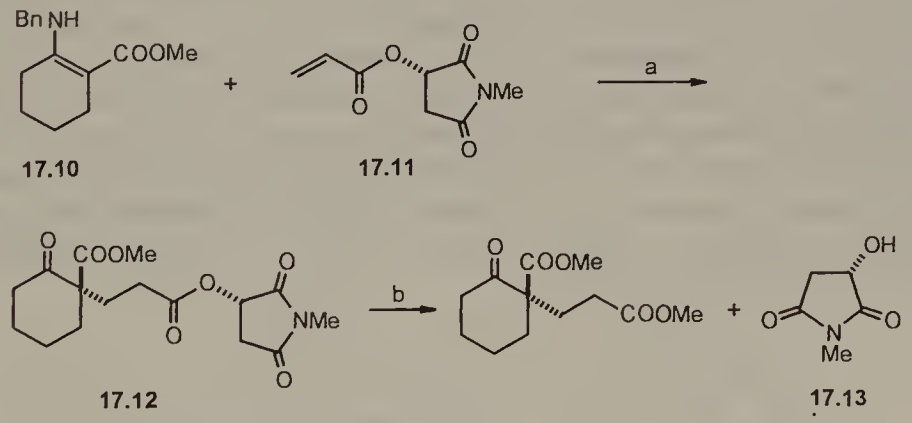
a: lipase PS (5%/wt), phosphate buffer (pH 7) - dioxane (1:1), 49.9 % conversion

Scheme 17.9

(*S*)-2-Hydroxy-*N*-methylsuccinimide [*104612-35-3*] is commercialy available.

Applications

Malimides have been used as chiral auxiliaries in conjugate addition reactions and Diels–Alder reactions of acrylic acid derivatives. In the former case, addition of β-enaminoester **17.10** to acrylate **17.11** catalyzed by $TiCl_4$ gave the product **17.12** of high enentiomeric excess, from which the chiral auxiliary, *N*-methyl-L-malimide (**17.13**), could be efficiently recovered by transestrification[59] (Scheme 17.10).



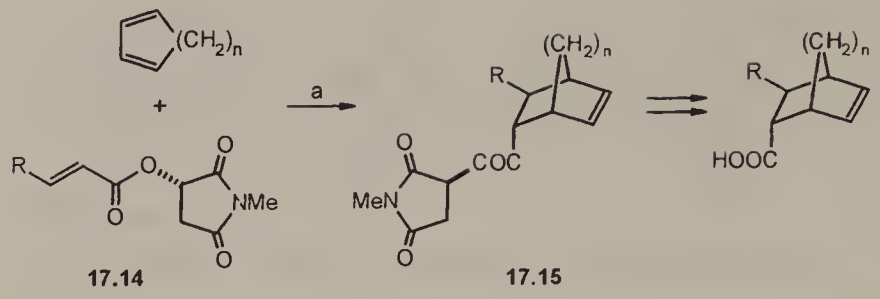
a: 1eq. $TiCl_4$, CH_2Cl_2, RT, 3h (75%, d.e. 94%)

b: MeONa, MeOH, RT (88%, e.e. 95%)

Scheme 17.10

In the latter case acrylates **17.14** derived from *N*-methyl-L-malimide were introduced by Helmchen as chiral dienophiles for syntheses employing a Diels–Alder reaction (Scheme 17.11).

The reaction was highly *endo* selective as well as highly diastereoselective; products **17.15** could be obtained diastereomerically pure by simple recrystallization. Products **17.15** having nonbornene skeleton (n = 1) were used by Helmchen for the synthesis of cyclosarcomycin[61] and *ent*-β-santalene,[62] and by



a: 0.75 eq. $TiCl_4$, CH_2Cl_2, -78°→0°C

n	R	*endo* : *exo*	yield[a]	ref.
0[b]	H	-	85	60
1	H	52 : 1	86	27
1	Me	13 :1	62	27
1	Br	38 : 1	70	27
2	H	82 : 1	89	27

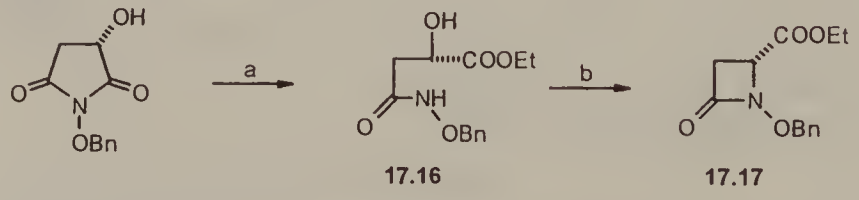
[a] diastereomerically pure product after recrystallization

[b] 1,3- butadiene

Scheme 17.11

Natsume in the synthesis of natural herbindoles.[63] Ireland devised a method for the addition of 1,3-butadiene to acrylate **17.14** (R = H), shown in entry 1 of Scheme 17.11, for the synthesis of (*R*)-3-cyclohexenecarboxylic acid, a building block for the analogue of immunosuppresant FK-506.[60]

Malimides are versatile chiral building blocks for the synthesis of chiral heterocycles. Shibuya reported that through highly regioselective ring opening of *N*-benzyloxy-L-malimide, hydroxamate **17.16** was produced exclusively.[47] Cyclization of **17.16** by Miller's method using the Mitsunobu reaction gave azetidinone **17.17** (Scheme 17.12).



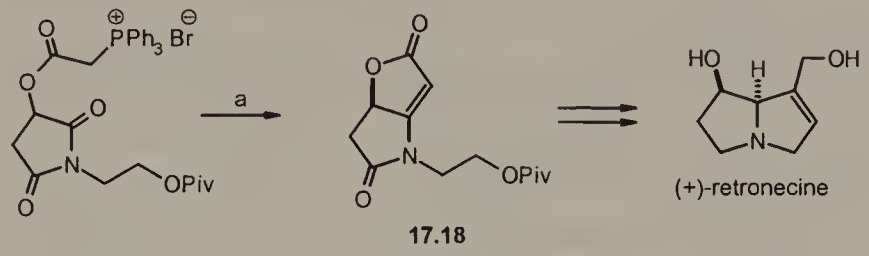
a: EtOLi, THF, 78°C→RT (85%)

b: DEAD, PPh_3, THF, 0°C→RT, 4h (58%)[47]

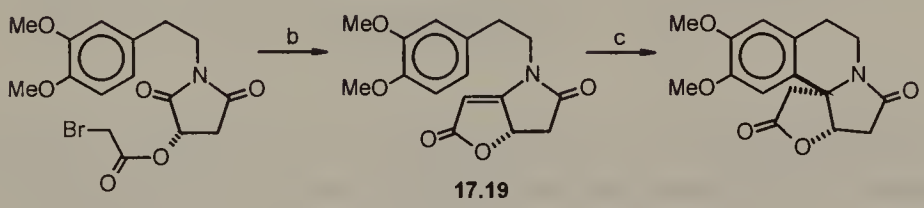
Scheme 17.12

The regioselectivity of malimide ring opening in this case may be assisted by the electronic effect of the lithium ion complexation by the hydroxyl group and the adjacent carbonyl group.

Chiral enamides **17.18** and **17.19** were synthesized from malimides by an intramolecular Wittig reaction. These products were further converted to chiral bi- and tetracyclic heterocycles via a diastereoselective *N*-acyliminium ion cyclization[34] (Scheme 17.13).



a: NEt_3, MeCN, 50°C (85%)[36]



b: PPh_3, MeCN, 50°C, 2h then NEt_3, 50°C, 16h (77%)

c: TsOH, PhMe, Δ, 1h (85%)[35]

Scheme 17.13

As in the case of tartrimides (Chapter 6) a large portion of synthetic utility of malimides is based on the reactions of *N*-acyliminium ions; their formation is, as expected, regioselective, since it involves regioselective reduction of the C(1) carbonyl group with $NaBH_4$ (Scheme 17.14).

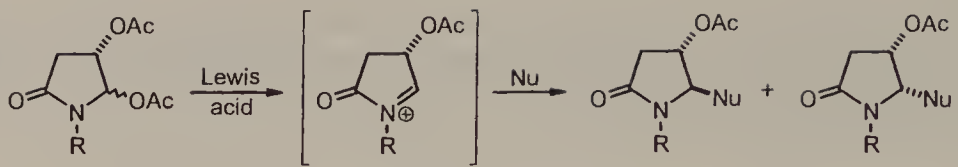
a (R^3 = H): $NaBH_4$, MeOH or EtOH, below 0°C then sat. $NaHCO_3$

b (R^3 = Et): $NaBH_4$, EtOH, -15°C then H_2SO_4, EtOH[53]

c (R^3 = Ac): as a, then AcCl, pyridine, CH_2Cl_2 (*cis*-2,3-diacetoxy product[43,64])

Scheme 17.14

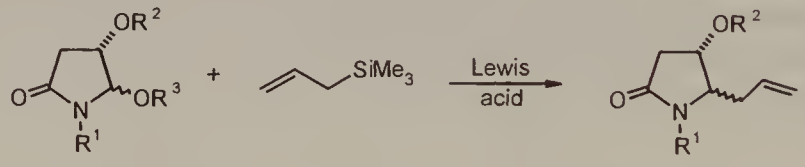
The *N*-acyliminium ion **17.20** can react with a variety of nucleophiles, providing access to *trans*- or *cis*-substituted lactams **17.21**. Although *trans*-lactams are normally the main reaction products, the *trans*:*cis* ratio is influenced by the reaction conditions and the size of the incoming nucleophile, but not by the configuration of the leaving acetoxy group[64] (Scheme 17.15).



entry	R	Lewis acid	Nu	*trans* : *cis*	yield (%)	ref.
1	PMB	TMSOTf	MeC(OTMS)=CHCOOMe	100 : 0	95	43
2	Bn	TMSOTf	MeC(OTMS)=CHCOOMe	100 : 0	98	43
3	Bn	$BF_3{\cdot}Et_2O$	CH_2=$CMeCH_2SiMe_3$	92 : 8	ca 100	54
4	Bn	TMSOTf	CH_2=$CHCH_2SiMe_3$	72 : 28	81	50
5	Bn	TMSOTf	(BnO)(TMSO)C=CH$(CH_2)_2$OBn	50 : 50	45	64
6	H	$ZnBr_2$,TMSCl	furan	67 : 33	71	65,66

Scheme 17.15

Trans-substituted lactams **17.21** (Scheme 17.15) were used in the synthesis of ptilomycalin A intermediate (entries 1 and 2, Hiemstra[43]), 4-*epi*-statine (entry 3, Hiemstra and Speckamp[54]), pyrrolizidines (entry 5, Pilli[64]) and *erythro*-L-β-hydroxyglutamic acid (entry 6, Nozoe[66]). *Trans* substitution is undoubtedly due to the known ability of the C(3)-acetoxy group to bridge to the adjacent cationic center;[50] C(3)-alkoxy or siloxy substituted aminals give preferentially *cis*-disubstituted lactams (Scheme 17.16).

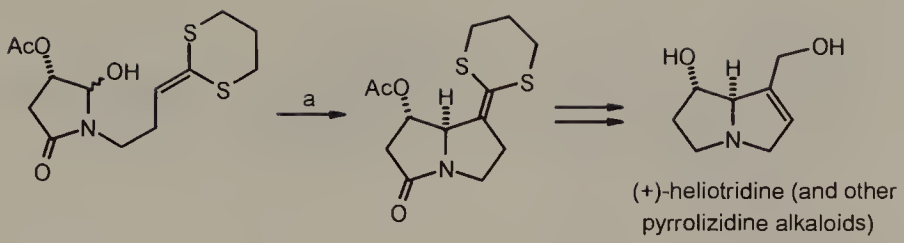


R^1	R^2	R^3	Lewis acid	*cis* : *trans*	ref.
Bn	Bn	Ac	$SnCl_4$	2 : 1	50
Me	TBS	Me	$TiCl_4$	6 : 1	52

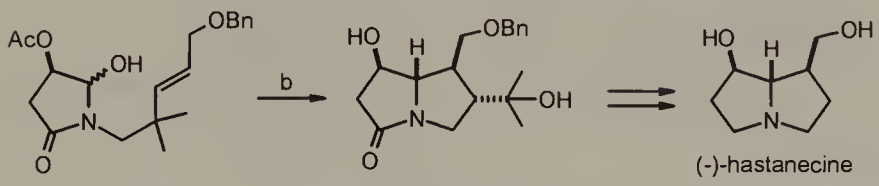
Scheme 17.16

Stereoselective acyliminium ion cyclizations directed by the C(3)-acetoxy substituent in the aminal substrate were devised independently by Chamberlin and Hart for the synthesis of optically active pyrrolizidinediols. Examples shown in Scheme 17.17 also include the acylamino radical cyclization procedure, developed by Hart[30,38] (entry d).

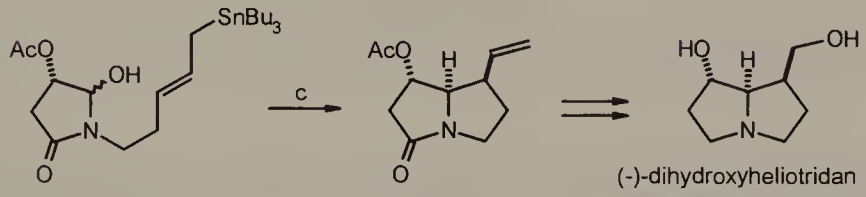
Indolizidines and other nitrogen heterocycles are also available from *O*-acetyl malimides by acyliminium ion cyclizations (Scheme 17.18).



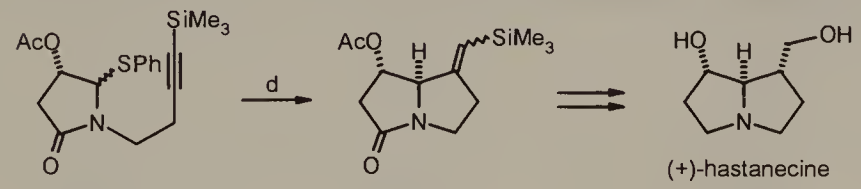
a: MsCl, NEt_3, CH_2Cl_2, -20°C→RT (75-80%)[26]



b: HCOOH, RT, 1d then NaOH , MeOH-H_2O (73%)[31]

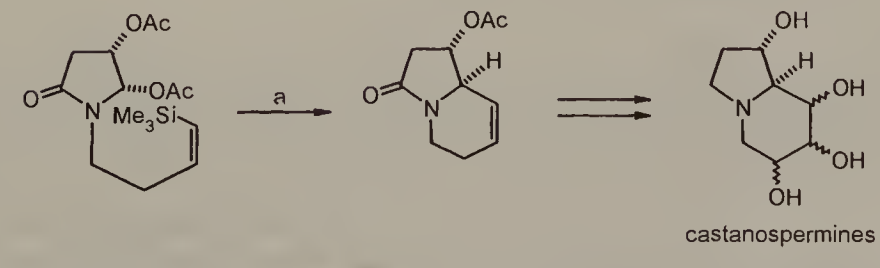


c: as a (77%)[57]



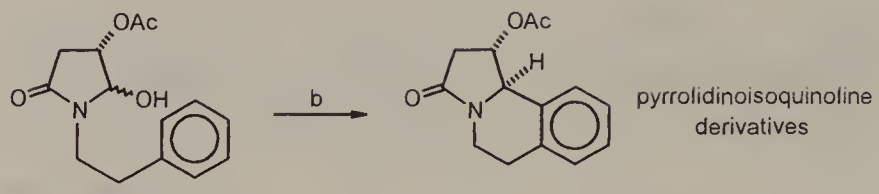
d: Bu_3SnH, AIBN, benzene, Δ (60-71%)[30,67]

Scheme 17.17

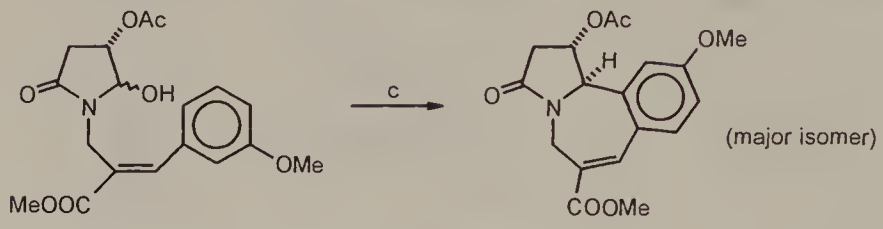


a: $BF_3{\cdot}Et_2O$ (72%)[56]

Scheme 17.18 (*continued*)



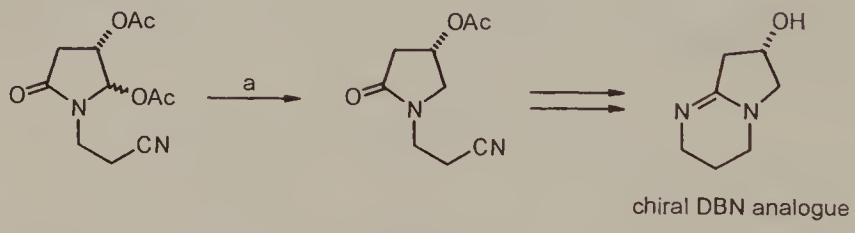
b: as a (74%)[33]



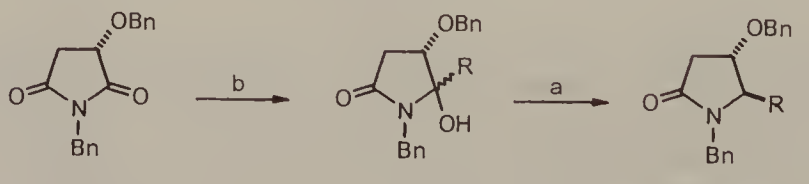
c: CF_3SO_3H, CH_2Cl_2 (55% + 25% other isomers)[58]

Scheme 17.18

Reductive deoxygenation of C(4)-oxygenated lactams is an alternative route to chiral lactams from malimides. C(4)-oxygenated lactams can be obtained from malimides by reduction with $NaBH_4$ (Scheme 17.14) or by the action of Grignard reagents (Scheme 17.19).

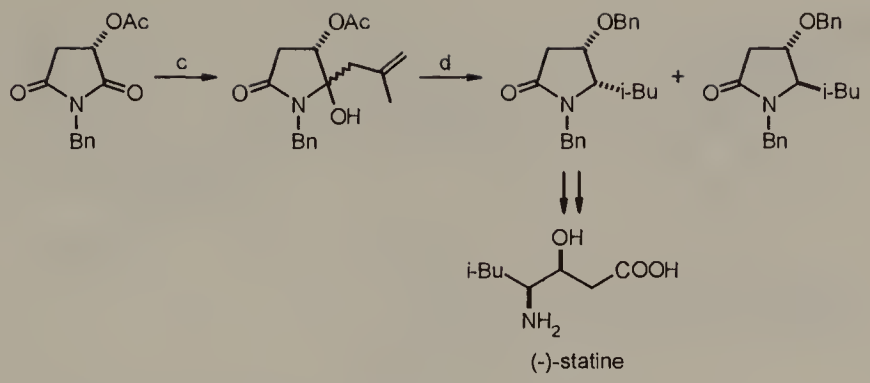


a: Et_3SiH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, -70°C→RT (80%)[32]



b: RMgX, THF, -78°C (83-94%)[41]

Scheme 17.19 (*continued*)

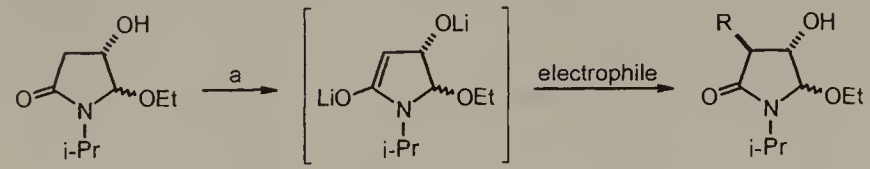


c: CH_2=$CMeCH_2MgCl$, THF, -50°C (46%)

d: H_2, Pd/C, CH_2Cl_2 (73%, *cis* : *trans* = 3 : 1)[68]

Scheme 17.19

Hiemstra and Speckamp developed a method of diastereoselective C(2)-alkylation of the enolate **17.23** generated from the ethoxylactam **17.22**[53] (Scheme 17.20).



17.22 **17.23** **17.24**

a: 2.1 eq. LDA, THF, -78°C

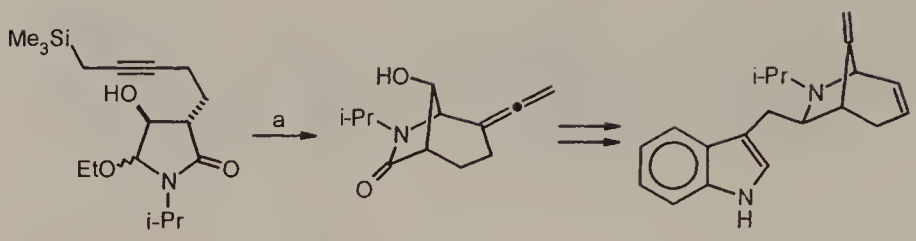
electrophile	R	yield (%)
MeI	Me	69
Me_2CO	CMe_2OH	60
$Me_3SiCH_2C{\equiv}C(CH_2)_nI$	$Me_3SiCH_2C{\equiv}C(CH_2)_n$	50-78 (n = 1, 2, 3)

Scheme 17.20

The configuration at C(4) apparently exerts no effect on the stereochemistry of alkylation; both the substrate **17.22** and the product **17.24** were 85:15 mixtures of the C(4) epimers. This reaction extends the usefulness of the acyliminium ion reactions to the formation of azabicyclic compounds such as **17.25**, a precursor of peduncularine (**17.26**)[29,59] (Scheme 17.21).

Hiemstra–Speckamp and Yoda–Takabe developed a method of converting 5-alkoxy-2-pyrrolidinones to 5-alkoxy-3-pyrrolin-2-ones[69–71] (Scheme 17.22).

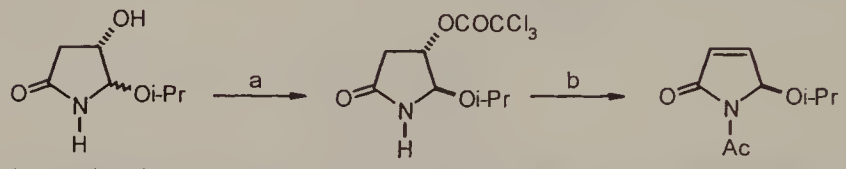
Chiral 3-pyrrolin-2-ones are synthetically useful as building blocks in



17.25 17.26

a: HCOOH, 3h then NH_3/MeOH, 18h (87%)

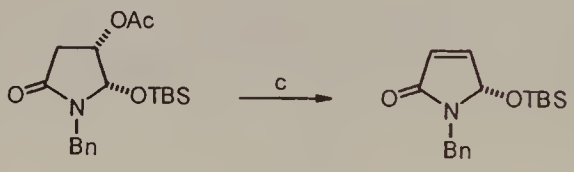
Scheme 17.21



trans : *cis* = 4 : 1

a: 1.1 eq. $(Cl_3CCO)_2O$, DMAP, Et_2O, -60°C→RT (86%)

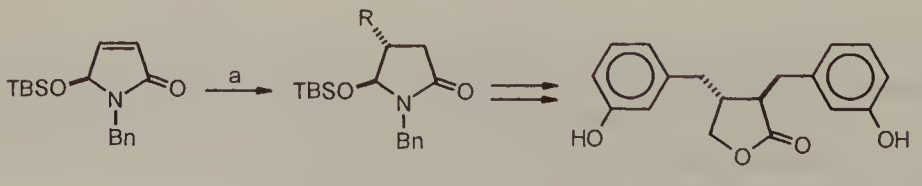
b: Ac_2O, pyridine, DMAP (cat.), 0°C→RT (85%)[70]



c: NaH, THF, 0°C (48%)[42,71]

Scheme 17.22

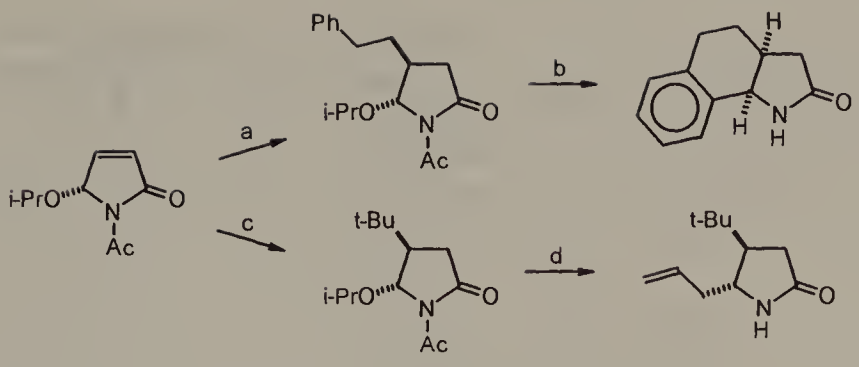
diastereoselective conjugate addition reactions[71] and in diastereoselective Diels–Alder reactions.[70] The former reaction can be coupled with the substitution at C(4) via the *N*-acyliminium ion. Examples are shown in Schemes 17.23 and 17.24.



(R= 3-$MeOC_6H_4CH_2$) (-)-enterolactone

a: R_2CuLi or RMgBr, CuI, THF, -78°C→RT (41-91% d.e. >99%)[42,71]

Schemes 17.23 (*continued*)



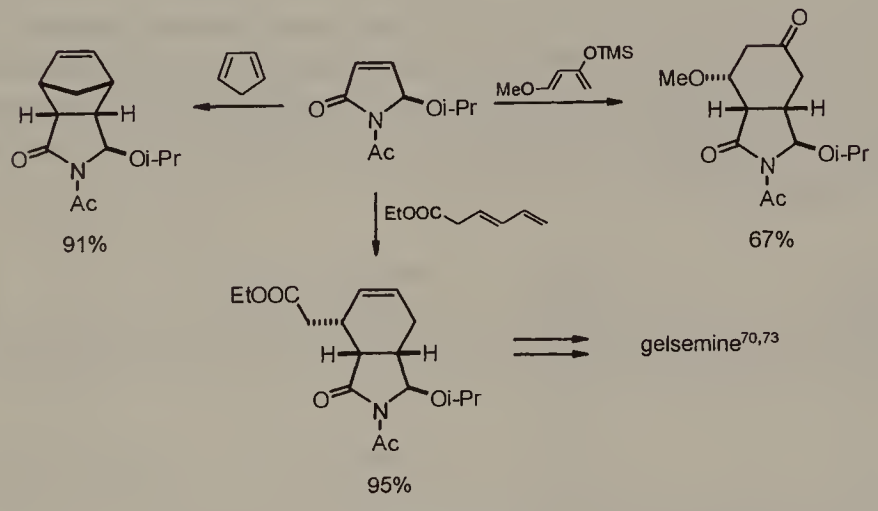
a: $PhCH_2CH_2Li$, CuI, THF, -78°C→RT, then Me_3SiCl (92%)

b: Me_2NH (excess), DMF, RT then $TiCl_4$, CH_2Cl_2, -78°C→RT (95%)

c: t-BuLi, CuI (84%)

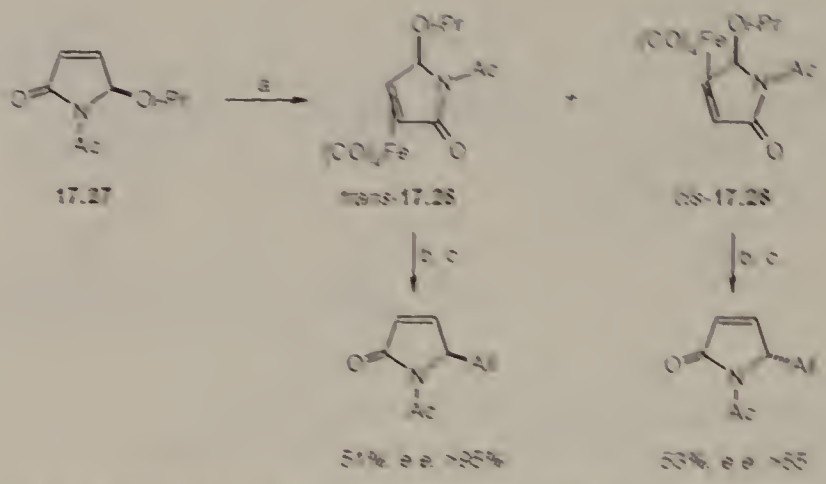
d: $AllSiMe_3$, $TiCl_4$, CH_2Cl_2, RT (77%)[72]

Scheme 17.23



Scheme 17.24

Chiral 5-alkyl-3-pyrrolin-2-ones are available indirectly in *N*-acyliminium ion reactions. Chirality of the *N*-acyliminium ion precursor **17.27** can be preserved in nucleophilic substitution reactions at C(4) by formation of the enantiopure tetracarbonyliron complexes **17.28**. The diastereomeric iron complexes are formed in different ratios under kinetic and thermodynamic conditions and can be separated; *trans*-complex **17.28** reacts quickly and with complete retention of configuration at C(4) whereas the reaction of *cis*-complex **17.28** proceeds slowly and with predominant inversion of configuration[69,74] (Scheme 17.25).



17.27 trans-17.28 cis-17.28

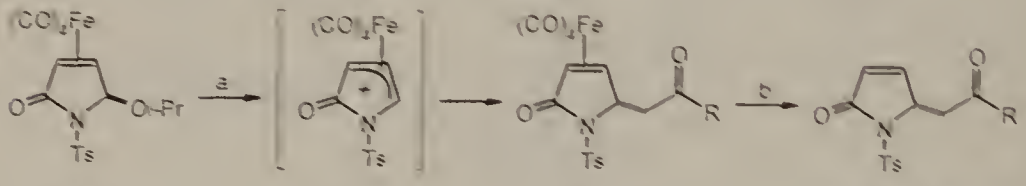
a. $Fe_2(CO)_9$, benzene or Et_2O (73%, trans : cis = 5 : 95 after 3h, 33 : 67 after 18h)

b. $AcSSiMe_3$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, RT

c. $Me_3N{\cdot}O$

Scheme 17.25

In contrast, Hiemstra and Speckamp found that the *N*-tosyl substituted *cis*-tetracarbonyliron complex **17.29** reacted faster than the corresponding *N*-acetyl complex and gave cleanly *trans*-substituted products **17.31** in reactions with enol acetates[75] (Scheme 17.26). The reaction most probably proceeded via the η^3-alkyl iron cation **17.30**.



17.29 17.30 17.31 R= Me, Ph, 2-furyl

a. $CH_2{=}C(OAc)R$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, RT

b. $Me_3N{\cdot}O$, RT (overall yield 49–60%)

Scheme 17.26

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18 2,4- and 3,4-Dihydroxybutanoic Acids

Derivatives of these dihydroxybutanoic acids are most frequently obtained by chemoselective reduction of malic acid monoesters, diesters, and anhydrides according to Fig.18.1.

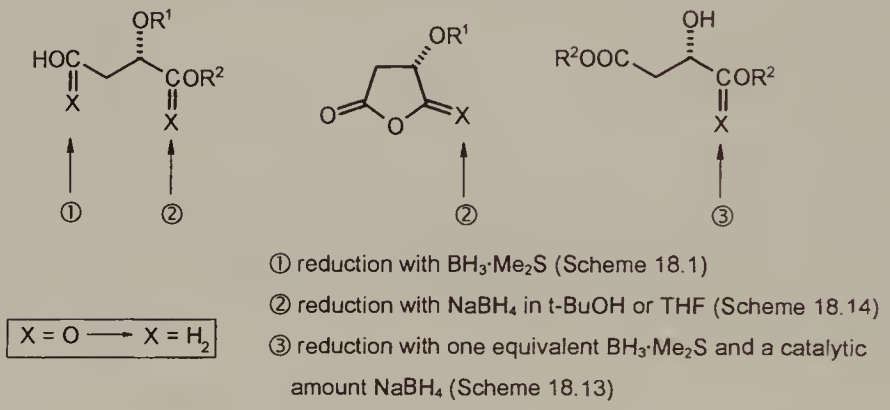


Figure 18.1

18.1 2,4-DIHYDROXYBUTANOIC ACID AND DERIVATIVES

I II

Table 18.1 Derivatives of (2*S*)-2,4-dihydroxybutanoic acid (I) and (2*S*)-2-hydroxybutyrolactone (II)

R^1	R^2	R^3	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
			Formula I		
H	H	Bn	70–72	−12.0 ($CHCl_3$)	1
H	Me	Tr	—	+2.3 ($CHCl_3$)	2

(*continued*)

Table 18.1 (*continued*)

R^1	R^2	R^3	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
H	–CHPh–		120–121	−31.0 ($CHCl_3$)	1
H	-(*S*)-CH(2-BrC_6H_4)-		142	−32.0 ($CHCl_3$)	3
Me	H	TBDPS	—	+1.3 ($CHCl_3$)	4
Me	Bz	Bz	—	−21.0 ($CHCl_3$)	5
Me	–CHPh–		51–52	−21.0 ($CHCl_3$)	1
Me	-(*S*)-CH(2-BrC_6H_4)-		—	−17.0 ($CHCl_3$)	3
Et	Ac	H	90/0.12	−37.9 ($CHCl_3$)	6–8
Et	Ac	THP	130–135/0.01	—	7
Et	Ac	CMe_2OMe	—	−26.5 ($CHCl_3$)	6
t-Bu	H	H	61–63	−16.3 ($CHCl_3$)	9
t-Bu	H	Bn	41–43	−6.0 ($CHCl_3$)	1
t-Bu	TBS	H	—	−41.1 ($CHCl_3$)	9
t-Bu	TBS	TBS	—	−21.3 ($CHCl_3$)	9
t-Bu	Ac	Ac	—	−39.4 ($CHCl_3$)	9
t-Bu	–CHPh–		55–56	−11.0 ($CHCl_3$)	1
Bn	Me	H	—	−5.1 (Me_2CO)	10
Bn	BOM	H	—	−45.3 (CH_2Cl_2)	11
Bn	THP	H	—	−117.0 ($CHCl_3$)	12
$–CMe_2–$		H	—	+3.7 ($CHCl_3$)	13
$–CMe_2–$		TBS	—	−7.2 ($CHCl_3$)	14
$–C(CH_2)_5–$		TBDPS	—	−5.8 ($CHCl_3$)	4
			Formula II		
—	H	—	95/0.1	−65.2 ($CHCl_3$)	8,15
—	Me	—	—	−8.7 (Me_2CO)	10
—	MEM	—	—	−80.6 ($CHCl_3$)	3
—	BOM	—	—	−81.7 ($CHCl_3$)	13
—	THP	—	—	−17.2 ($CHCl_3$)	12

The acid **I** (R^1, R^3 = H) spontaneously forms the lactone **II**.

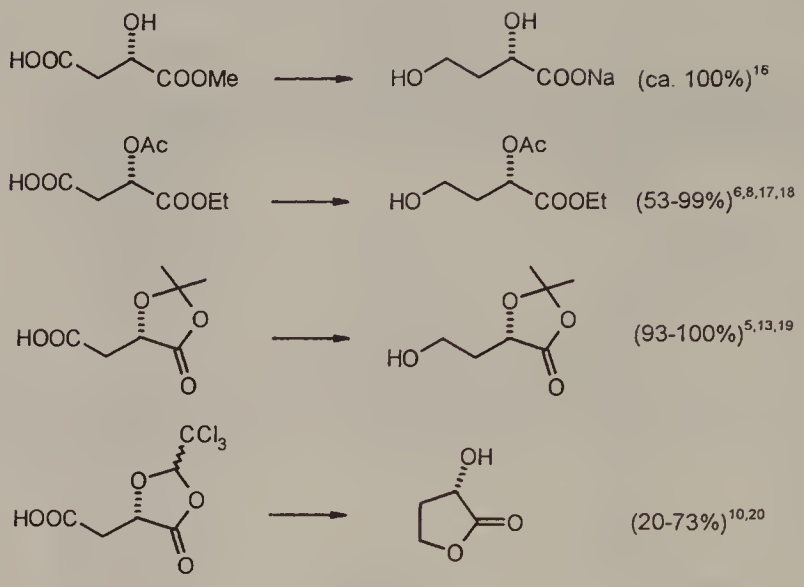
Synthesis

The common synthetic route to chiral 2,4-dihydroxybutanoic acid derivatives is based on borane reduction of C(4) monoacids, derived from malic acid by selective protection of the C(1) carboxylic group. The protection is introduced in the form of either a dioxolanone (Chapter 15) or a monoester (Chapter 16). Examples are shown in Scheme 18.1.

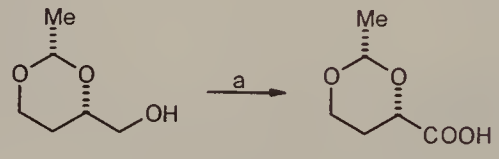
Acetal protected 2,4-dihydroxybutanoic acid was obtained by $RuCl_3$-$NaIO_4$ oxidation of the corresponding protected triol (Scheme 18.2)

Both enantiomers of 2,4-dihydroxybutanoic acid were obtained (in a form of 2-hydroxybutyrolactones) by resolution of the racemate.[15]

Reduction with BH_3·Me_2S in THF:



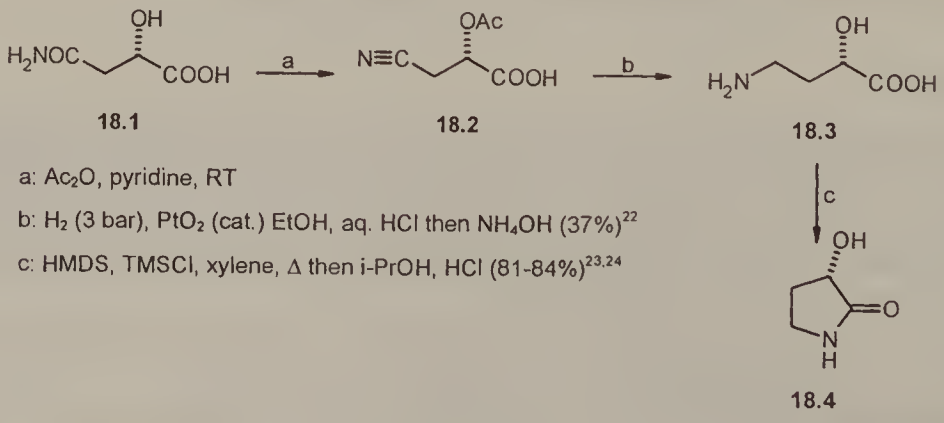
Scheme 18.1



a: $RuCl_3 \cdot 3H_2O$, $NaIO_4$, CCl_4-MeCN-H_2O (2:2:3), RT (90%)[21]

Scheme 18.2

(2*S*)-4-Amino-2-hydroxybutanoic acid (**18.3**) was obtained from malamic acid **18.1** by dehydration to nitrile **18.2** followed by its catalytic hydrogenation. The acid can be easily cyclized to (3*S*)-3-hydroxy-2-pyrrolidinone **18.4** (Scheme 18.3).



a: Ac_2O, pyridine, RT

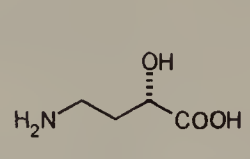
b: H_2 (3 bar), PtO_2 (cat.) EtOH, aq. HCl then NH_4OH (37%)[22]

c: HMDS, TMSCl, xylene, Δ then i-PrOH, HCl (81-84%)[23,24]

Scheme 18.3

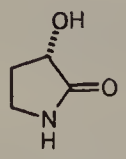
A similar synthesis of **18.4** used 1,2-acetal of malic acid with hexafluoroacetone as starting material.[25]

For a comparison of the properties of 4-amino-2- or 3-hydroxybutanoic acids and the derived lactams see Fig. 18.2.



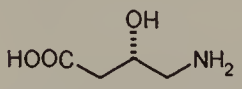
m.p. 208-209°C

$[\alpha]_D$ -31.3 (H_2O)[23]



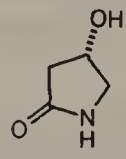
m.p. 103-104°C

$[\alpha]_D$ -125.0 ($CHCl_3$)[25-27]



m.p. 213-214°C

$[\alpha]_D$ +20.5 (H_2O)[24,28,29]



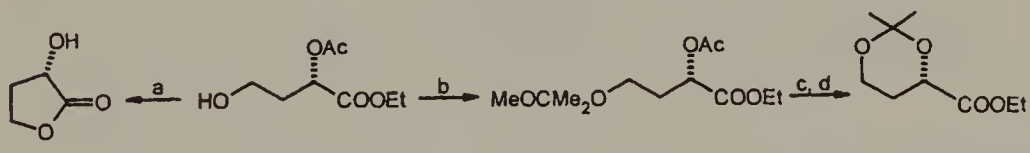
m.p. 155-157°C

$[\alpha]_D$ -58.6 (H_2O)[29,30]

Figure 18.2

(*S*)-α-Hydroxy-γ-butyrolactone (**II**, R^2 = H) and its enantiomer are available commercially.

Some useful functional group manipulations allowing selective protection of the hydroxy groups in 2,4-dihydroxybutanoates are shown in Scheme 18.4.

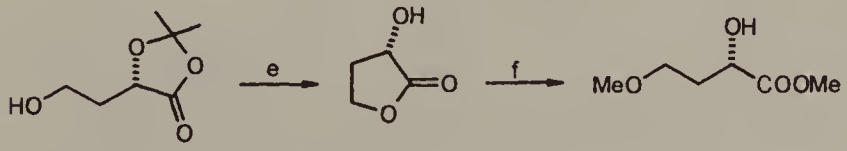


a: NaOH, H_2O, then HCl (47%)[6]

b: $MeC(OMe)=CH_2$, PPTS (cat.), 0°C → RT (90%)[6]

c: EtOH, EtONa (cat.), RT, 30 min. (94%)[6]

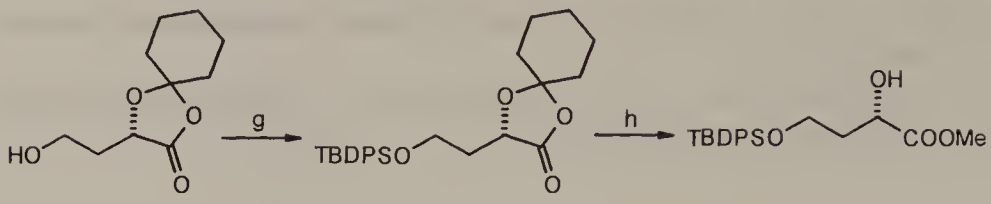
d: $BF_3{\cdot}Et_2O$ (cat.), Et_2O, RT (isolated yield 28% due to volatility)[6]



e: TsOH, CH_2Cl_2, RT, 1h (100%)[14]

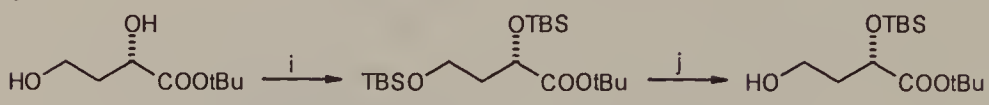
f: $HC(OMe)_3$, H_2SO_4, MeOH (>88%)[31]

Scheme 18.4 (*continued*)



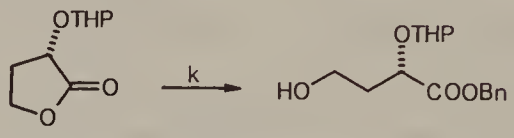
g: TBDPSCl, imidazole, DMF (>85%)[4]

h: MeONa (cat.), MeOH (94%)[4]

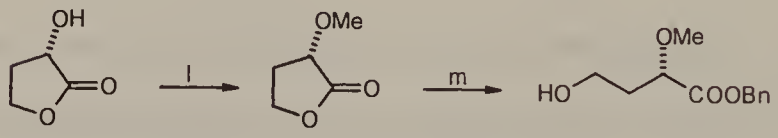


i: 3 eq. TBSCl, 4 eq. imidazole, DMF, 50°C, 40h (97%)

j: AcOH-THF-H_2O (9:1:2), RT, 20h (76%)[9]



k: 1 eq. 2.5% KOH, THF, RT, 1h then BnBr, 18-crown-6 (cat.), DMF-H_2O (4:1), RT, 6h (84%)[12]

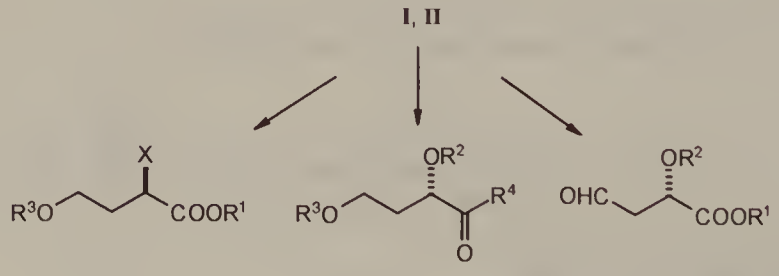


l: MeI, NaH, THF (63%)[10]

m: 2N NaOH, MeOH then BnBr, 18-crown-6 (cat.), DMF (69%)[10]

Scheme 18.4

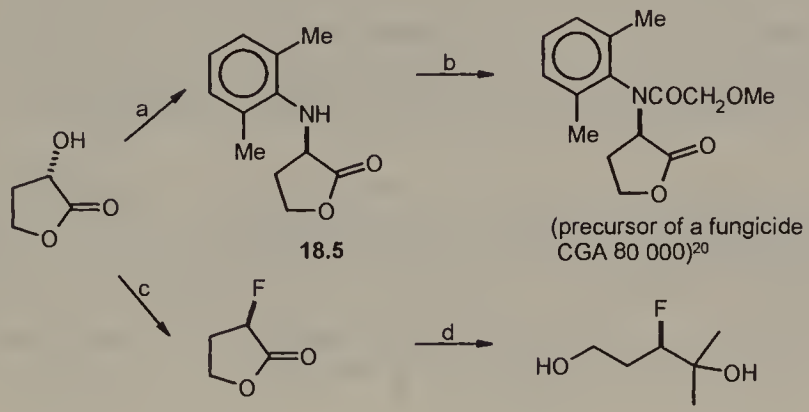
Applications



substitution at C(2) chain elongation at C(1) aldehyde intermediate for chain elongation at C(4)

Figure 18.3

Products of substitution at C(2). Substitution of the hydroxy group in 2-hydroxybutyrolactone gives access to lactones **18.5** and **18.6** which are useful in the synthesis of biologically active compounds (Scheme 18.5).



a: Tf_2O, pyridine, CCl_4 then 2,6-dimethylaniline, K_2CO_3 (49%)

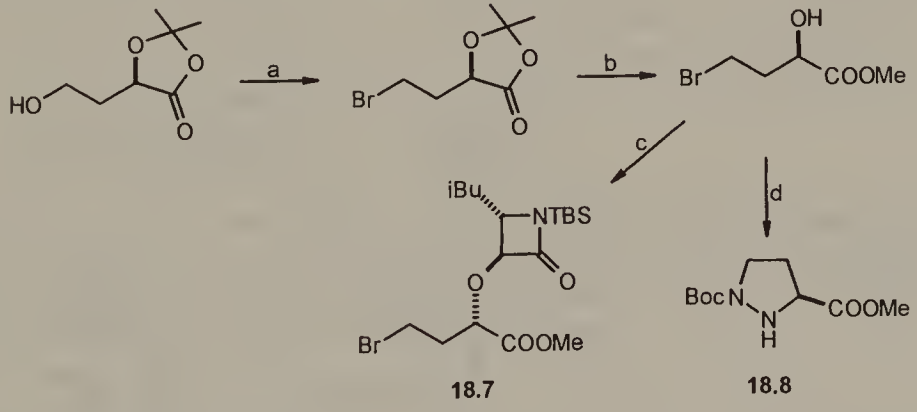
b: $MeOCH_2COCl$, DMF (cat.), PhMe (96%)[20]

c: Et_2NSF_3, CH_2Cl_2, -70°C → RT (76%)

d: MeLi, Et_2O, 0°C → RT (62%)[8]

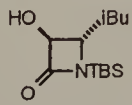
Scheme 18.5

Precursors of peptide secondary structure mimetics **18.7** and **18.8** were synthesized by substitution of the hydroxy groups in 2,4-dihydroxybutanoic acid using the triflate methodology[32] (Scheme 18.6).



a: PPh_3, CBr_4, THF (86%)

b: MeOH, TsOH (cat.), 67%

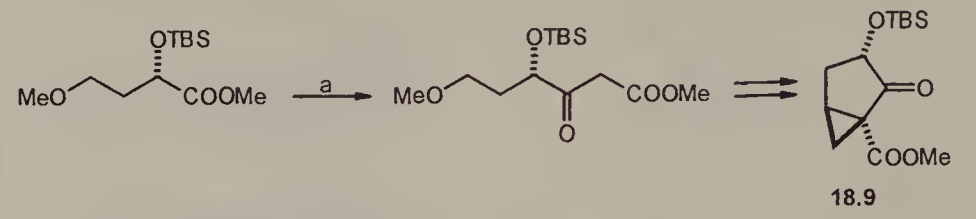
c: Tf_2O, then 

, NaHMDS (30%)

d: Tf_2O, 2,6-lutidine then $BocNHNH_2$ (38%)[32]

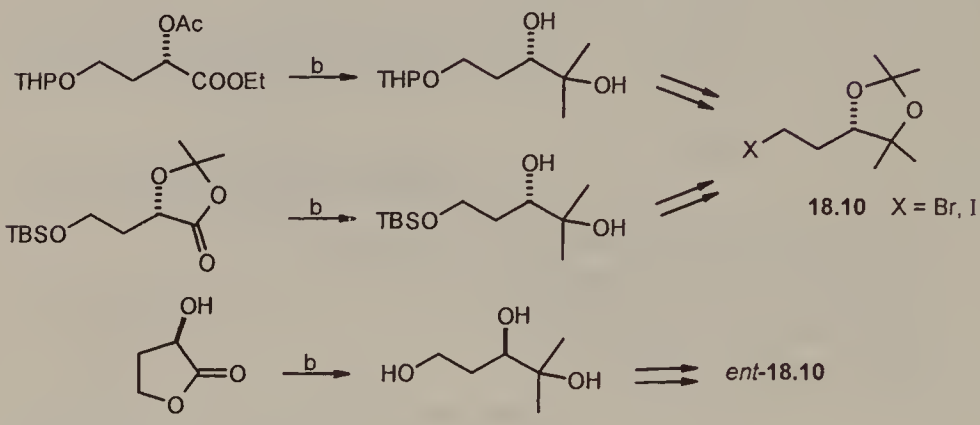
Scheme 18.6

Products of chain elongation at C(1). Chiral building blocks were obtained in reactions involving nucleophilic addition to the carboxy group of 2,4-dihydroxybutanoic acid (Scheme 18.7).



18.9

a: NaOH, MeOH-THF-H_2O, then CDI, then $Mg(OOCCH_2COOMe)_2$[31]

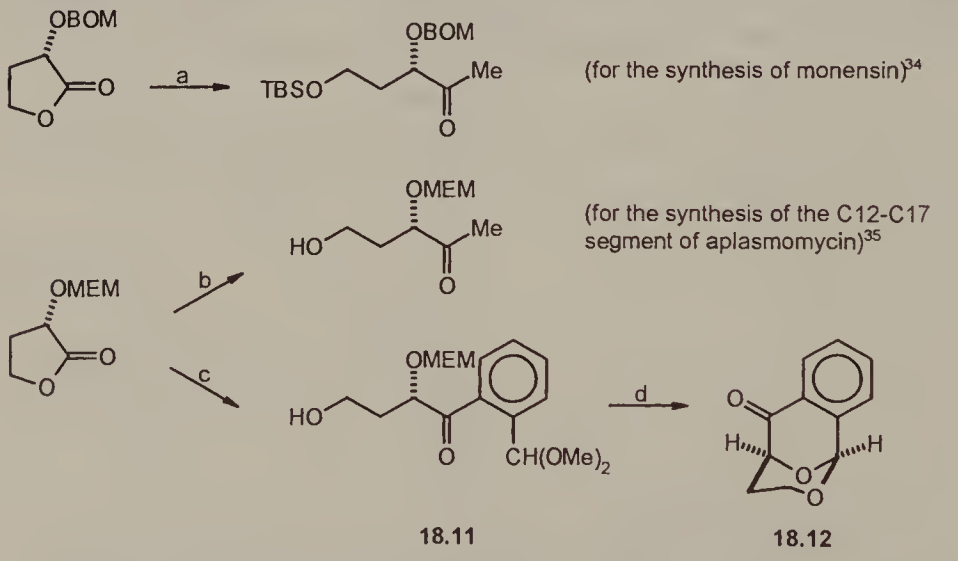


18.10 X = Br, I

ent-18.10

b: MeLi, Et_2O (55-69%)[7,14,33]

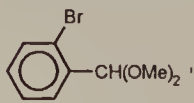
Scheme 18.7



18.11 18.12

a: 1 eq. MeMgBr, THF, -78°C then TBSCl, imidazole, DMF[34]

b: MeLi, THF, -78°C, 2h (98%)[35]

c: 

, n-BuLi, THF, -78°C

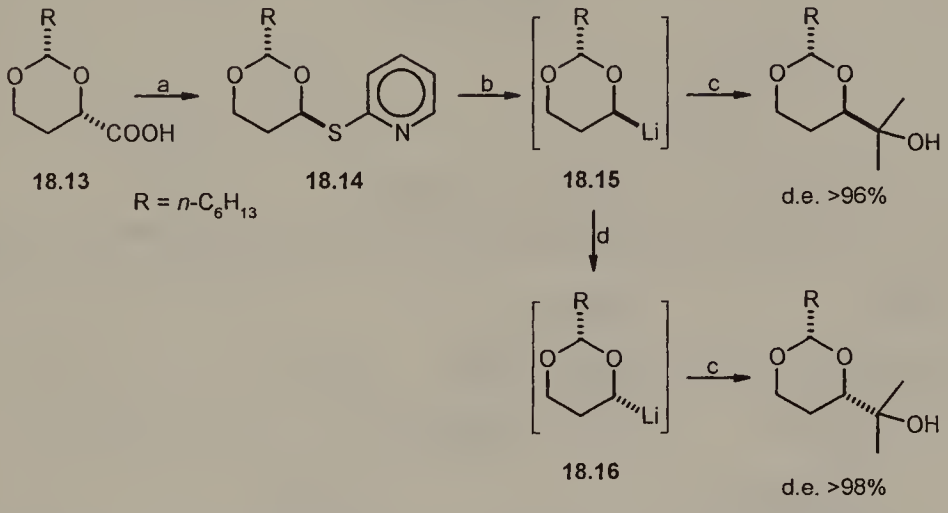
d: TsOH, PhMe, 60°C (53% overall)[3]

Scheme 18.8

Compound **18.9** is a precursor of ring A in 1α,25-dihydroxyvitamin D_3[31] while haloacetals **18.10** were designed for the synthesis of chiral carotenoids[7] and a triterpene saponaceolide B.[14]

O-Protected 2-hydroxybutyrolactone reacts at low temperatures with alkyl- or aryllithiums to give optically active ketones (Scheme 18.8). Note the remarkably facile formation of chiral benzoxocine **18.12** by intramolecular transacetalization of the aryllithium addition product **18.11**, as reported by Wünsch.[3]

Products of C(1) decarboxylation. Enantiomerically pure α-alkoxylithium reagent **18.15** can be generated from 2-thiopyridyl ether **18.14** by reductive lithiathion, as reported by Rychnovsky.[21] 2-Thiopyridyl ether **18.14** was in turn obtained by Barton radical decarboxylation of the protected acid **18.13**, proceeding with inversion of configuration (Scheme 18.9).



a: *N*-hydroxypyridine-2-thione, i-PrN=C=Ni-Pr, CH_2Cl_2, 0°C, then hν, 0°C (65-73%)
b: lithium di-*t*-butylbiphenylide, THF, -78°C c: Me_2CO, -78°C d: -20°C, 30 min.[21]

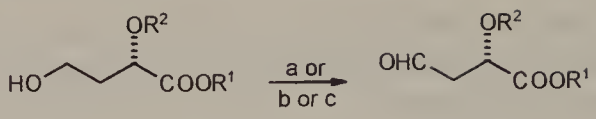
Scheme 18.9

Initially formed axial alkylithium reagent **18.15** can be epimerized to the equatorial alkyllithium reagent **18.16**. Both lithium reagents give products of trapping with an electrophile having high stereochemical integrity, thus proving their potential for the use in stereoselective synthesis.

Products from C(4) aldehyde intermediate. 1,2-Diprotected 2,4-dihydroxybutanoic acids can be readily oxidized to the corresponding C(4) aldehydes, as shown in Scheme 18.10.

These aldehydes can be reductively coupled with amines without affecting the C(1) carboxylic group. This reaction was used for the synthesis of several iron-chelating agents, as shown in Scheme 18.11.

An example of application of aldehyde **18.17** in the Horner–Wadsworth–Emmons reaction is shown in Scheme 18.12.

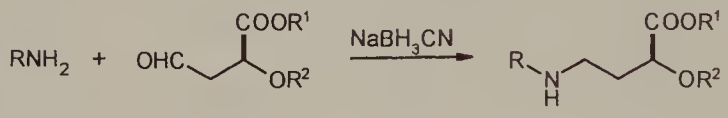


R^1	R^2	method	yield (%)	$[\alpha]_D$ (solvent	ref.
-CMe_2-		a	65	-	19
Me	TBS	a	90	-	36
Et	Ac	a	35	-31.7 ($CHCl_3$)	17,37
Bn	THP	a	72	-120.0 ($CHCl_3$)	12
Bn	BOM	b	70	-45.3 ($CHCl_3$)	11
t-Bu	TBS	c	92	-37.1 ($CHCl_3$)	9

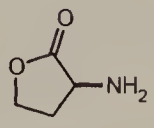
a: PCC, CH_2Cl_2, RT b: SO_3-pyridine, NEt_3, DMSO-CH_2Cl_2, RT

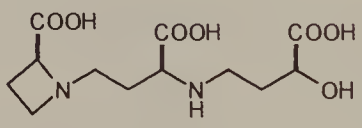
c: $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78°→ 0°C

Scheme 18.10

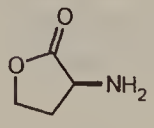


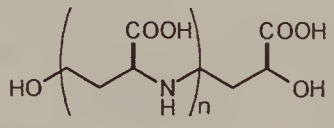
amines: *products:*



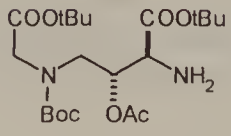


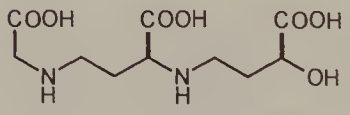
2'-deoxymugineic acid[12]



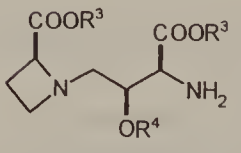


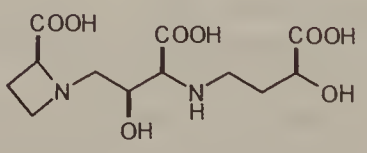
avenic acids B (n = 1)[37] and A (n = 2)[38]





2'-epi-distochonic acid A[17]



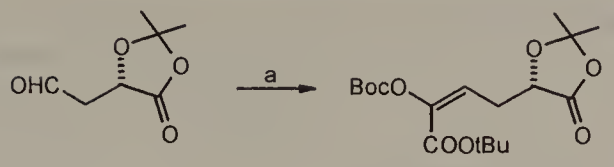


mugineic acid

R_3 = t-Bu, R_4 = MOM[9]

R_3 = Bn, R_4 = TBS[11]

Scheme 18.11



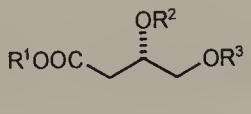
18.17 **18.18**

a: $(MeO)_2P(O)CH(OBoc)COOtBu$, LiHMDS, THF, -78°C (80%, *E*:*Z* = 7:1)[19]

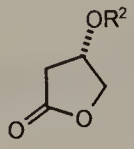
Scheme 18.12

Product **18.18** was used for the synthesis of a transition state analogue of hydrated tetrahydrodipicolinic acid.[19]

18.2 3,4-DIHYDROXYBUTANOIC ACID AND DERIVATIVES



III



IV

Table 18.2 Derivatives of (3*S*)-3,4-dihydroxybutanoic acid (III) and (3*S*)-3-hydroxybutyrolactone (IV)

R^1	R^2	R^3	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
			Formula III		
H	H	MOM	—	−2.3 ($CHCl_3$)[a]	39
H	H	4-$MeOC_6H_4$	81–82	−9.5 ($CHCl_3$)	40
Me	H	H	158/0.3	−18.9 (MeOH)	41,42
				−24.6 ($CHCl_3$)[b]	43
Me	H	Ts	—	−6.7 ($CHCl_3$)	43
Me	H	4-$MeOC_6H_4$	81	−3.3 (MeOH)	40,44
Me	H	1-naphthyl	—	−4.9 (MeOH)	40
Me	H	Tr	80–82	−5.5 (CH_2Cl_2)	45
Me	H	TBS	—	−10.2 ($CHCl_3$)	46
Me	H	TBDPS	—	−8.0 ($CHCl_3$)	3,47
Et	H	H	—	+6.2 ($CHCl_3$)[c]	48
Et	H	t-Bu	80–82/0.1	−13.2 ($CHCl_3$)[a]	49
Et	H	Bn	114–116/0.01	−9.0 (EtOH)	50
Et	H	TBS	—	−6.0 ($CHCl_3$)[d]	48
t-Bu	H	Bn	—	−10.0 (neat)	51
Bn	H	H	—	−14.0 (MeOH)	52
Me	Me	Me	—	−5.3 ($CHCl_3$)	53
Me	Bn	H	—	−2.4 ($CHCl_3$)	54
Me	MEM	TBDPS	—	−15.6 ($CHCl_3$)	3
Me	SEM	TBS	—	−12.9 ($CHCl_3$)	55

(*continued*)

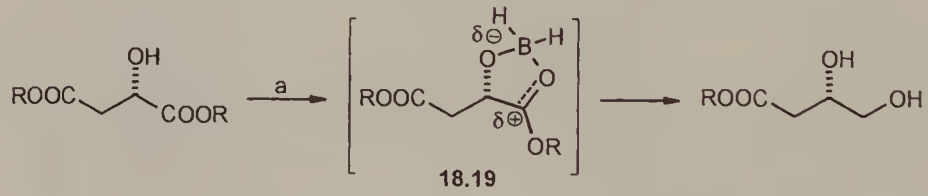
Table 18.2 (*continued*)

	R^2	R^3	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
Me	Ac	4-$MeOC_6H_4$	—	−25.0 ($CHCl_3$)[a]	40
Me	Ac	1-naphthyl	—	−28.0 ($CHCl_3$)[a]	40
Me	TBS	Ts	—	−18.3 ($CHCl_3$)	43
Me	TBDPS	Ts	83–84	—	56
Me	$-CMe_2-$		89–90/15	−18.2 ($CHCl_3$)	41,48,57
Me	$-C(CH_2)_5-$		106–109/5	+10.9 ($CHCl_3$)	58
Et	$-CMe_2-$		110/23	+27.0 ($CHCl_3$)	48
Et	3,5-$(O_2N)_2C_6H_3CO$	t-Bu	59–60	−20.1 ($CHCl_3$)[a]	49
		Formula IV			
—	H	—	98–100/0.3	−94.0 (EtOH)	49,58–60
—	Bn	—	70–71	−29.7 ($CHCl_3$)	54,61,62

[a] Enantiomer obtained.
[b] $[\alpha]_D$ values reported in the literature vary to a great extent; for example −51.2 ($CHCl_3$) in ref. 53. This may be due to the concentration effect or to the formation of lactone **IV** (R_2 = H).
[c] $[\alpha]_D$ −30 ($CHCl_3$) in ref. 63.
[d] $[\alpha]_D$ −15 ($CHCl_3$) in ref. 63.

Synthesis

Like other α-hydroxyesters, malates are readily reduced to 3,4-dihydroxybutanoates by borane-dimethyl sulfide with the addition of a catalytic amount of sodium tetrahydroborate. As demonstrated by Saito and Moriwake,[48,64] this reaction is highly C(1) chemoselective and is the most convenient route to 3,4-dihydroxybutanoates. The reaction involves the formation of a five-membered intermediate **18.19**, which then undergoes hydride addition (Scheme 18.13).



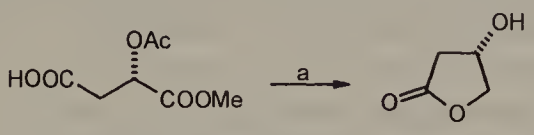
R = Me (80-95%)[41-43,53,64-66]
R = Et (86-97%)[48,63]
R = Bn (60-70%)[52]

a: 1.0 eq. $BH_3 \cdot Me_2S$, THF, 1h, then 0.05 eq. $NaBH_4$, 10°C → RT

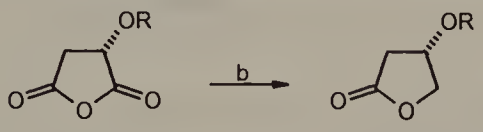
Scheme 18.13

Reduction of the C(1) carboxy group to the hydroxymethyl group can be performed chemoselectively also by the action of sodium tetrahydroborate on either

C(1) monoesters of malic acid or on malic acid anhydrides. Relevant examples are shown in Scheme 18.14.



a: $NaBH_4$, t-BuOH, Δ (removal of MeOH), 83%[59]

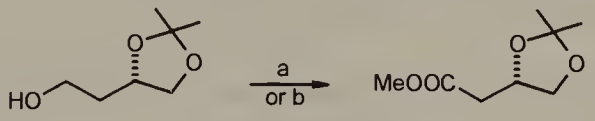


b (R = Bn): $NaBH_4$, THF (>61%)[61]

b (R = Ac): $NaBH_4$, t-BuOH, Δ (81%)[67]

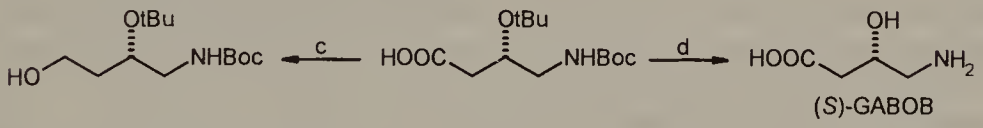
Scheme 18.14

Derivatives of 3,4-dihydroxybutanoic acid were also prepared by the oxidation of suitably protected 1,2,4-butanetriols (Scheme 18.15).



a: $KMnO_4$, 18-crown-6 (cat.), benzene, then MeI (43%)[68]

b: DMSO, $(COCl)_2$, CH_2Cl_2, -78°C, then i-Pr_2NEt, then Br_2, $NaHCO_3$, MeOH-H_2O (9:1), RT (84%)[57]



c: $Zn(MnO_4)_2$, Me_2CO (55%)

d: 4N HCl, dioxane (95%)[113]

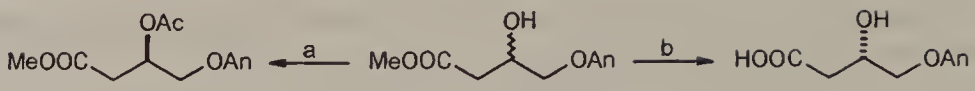
Scheme 18.15

For the synthesis of 3,4-dihydroxybutanoates from threonates see Chapter 14.

Racemic 3,4-dihydroxybutanoic acid was resolved by crystallization of the brucine salt and isolated as lactone **IV** (R^2 = H).[69] Kinetic resolution of 4-*O*-protected esters of 3,4-dihydroxybutanoic acid was carried out effectively in two ways: either by *O*-acylation of the 3-hydroxy group or by hydrolysis of the ester group, both with *Pseudomonas cepacia* lipase (PCL)[40] (Scheme 18.16).

(3*S*)-3,4-Epoxybutanoic acid of high enantiomeric purity was obtained by kinetic resolution of the racemic methyl ester with pig liver esterase (PLE).[70]

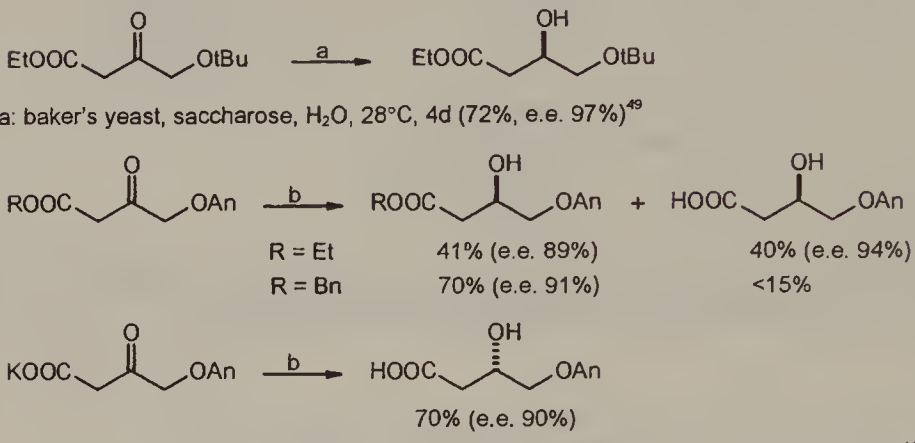
4-*O*-Protected 3,4-dihydroxybutanoates of high enantiomeric excess were synthesized from the corresponding 3-oxo esters by the reduction with either free or immobilized baker's yeast (Scheme 18.17).



a: CH_2=CHOAc, PCL, hexane, 4h, conversion 49%,
unreacted substrate: e.e. 99%, product: e.e. 99%

b: PCL, phosphate buffer, PhMe, 13h, conversion 49%,
unreacted substrate: e.e. 99%, product: e.e. 99%

Scheme 18.16



a: baker's yeast, saccharose, H_2O, 28°C, 4d (72%, e.e. 97%)[49]

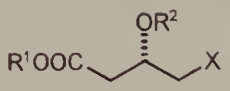
b: baker's yeast immobilized on calcium alginate, saccharose, H_2O-EtOH, 29°C, 20-36h[44]

Scheme 18.17

Analogously, 4-heteroatom substitued 3-hydroxybutanoates can be obtained from the 3-oxoesters or 3-oxoamides by the reduction with enzymes or microorganisms; enantioselectivity of such a reaction is often above 90%, but it is dependent on the substrate structure, the nature of the enzyme, and the reaction conditions. 4-Heteroatom substituents include chlorine,[71-78] bromine,[79] sulfur (phenylthio or phenylsulfonyl groups),[80-83] and nitrogen (azido or amido groups).[74,79] Enantiomerically pure 4-halogen substituted 3-hydroxybutanoates are of importance for the synthesis of GABOB and carnitine (see Applications below).

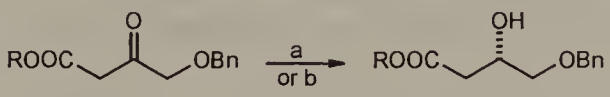
Table 18.3 Derivatives of 4-halogen substituted (3*S*)-hydroxybutanoic acid (V)

R^1	R^2	X	$[\alpha]_D$ (solvent)	References
Me	H	Cl	−21.6 ($CHCl_3$)	55
Et	H	Cl	−13.7 (MeOH)	78
			−21.1 ($CHCl_3$)	84
Et	H	Br	−11.0 (EtOH)	79
Me	Bn	Br	−12.6 ($CHCl_3$)	85
Me	TBS	Br	−26.4 ($CHCl_3$)	86
Me	TBS	I	−32.5 ($CHCl_3$)	86



V

4-Benzyloxy-3-hydroxybutanoates were obtained in high enantiomeric excess by asymmetric hydrogenation of the corresponding 3-oxoderivatives with a ruthenium-BINAP catalyst (Scheme 18.18). The first synthesis (entry a) was scaled up to a 10 kg batch.[50]



a (R = Et): H_2 (4 atm.), $RuCl(C_6H_6)$ (*R*)-BINAP (cat.), EtOH, 100°C, 6h (96%, e.e. 97-98%)[50]

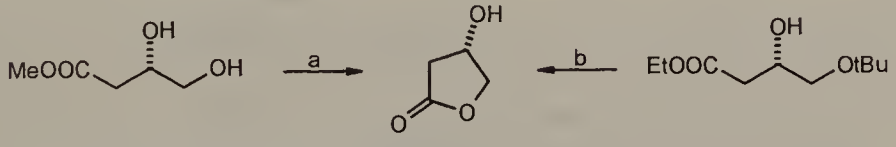
b (R = t-Bu): H_2 (100 atm.), $Ru_2Cl_4(NEt_3)$ (*R*)-BINAP (cat.), MeOH, 50°C, 48h (85%, e.e. 94%)[51]

Scheme 18.18

Similar catalytic hydrogenation when applied to ethyl 4-chloro-3-ketobutanoate yielded the 3-hydroxy derivative with high yield and enantiomeric purity.[87,88]

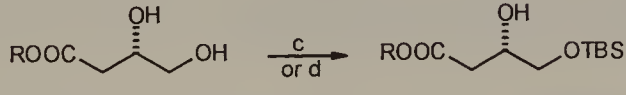
Some useful hydroxy group protection procedures for 3,4-dihydroxybutanoates are collected in Scheme 18.19.

4-O or *3-O monoprotection*



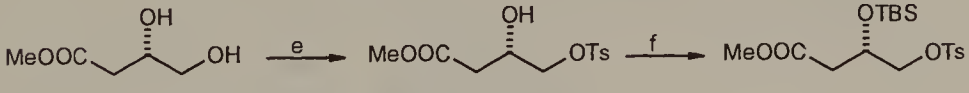
a: CF_3COOH, CH_2Cl_2, RT, 1d (>94%)[60]

b: CF_3COOH, -5°C, 2h (68%)[49]



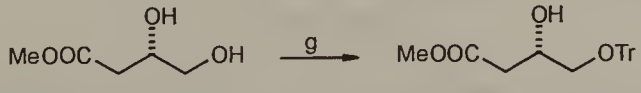
c (R = Me, Et): 1.0 eq. TBSCl, imidazole, THF or DMF (71-95%)[48,55,62,89]

d (R = Me): 1.1 eq. TBSCl, NEt_3, DMAP (cat.), CH_2Cl_2 (73%)[46]



e: 1.0 eq. TsCl, pyridine, CH_2Cl_2, 12h (75%)[43,56]

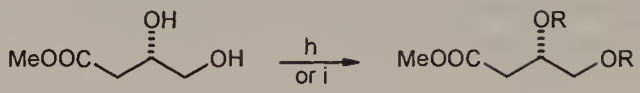
f: 1.5 eq. TBSCl, imidazole, DMF, RT (92%)[43]



g: TrCl, pyridine,CH_2Cl_2, 0°C → RT,18h (85%)[45] or TrCl, NEt_3, DMAP, DMF, RT, 12h (90 %)[90]

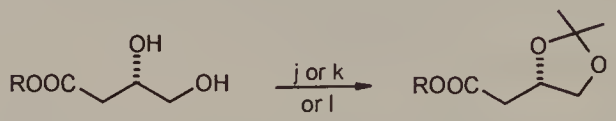
Scheme 18.19 *(continued)*

3,4-O-diprotection



h (R = Me): SiO_2, excess CH_2N_2/Et_2O, 0°C → RT (80%)[53]

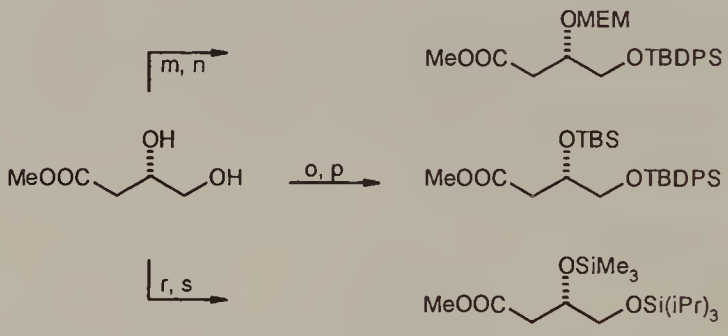
i (R = Bn): $Cl_3CC(=NH)OBn$, CF_3SO_3H, cyclohexane-CH_2Cl_2, 0°C → RT (52%)[91]



j (R = Me): Me_2CO, TsOH (cat.), mol. sieves 4Å, benzene, Δ (85%)[64]

k (R = Me): $Me(MeO)C=CH_2$, PPTS (70-90%)[41,64,65]

l (R = Me, Et): Me_2CO, $Me_2C(OMe)_2$, TsOH (cat.), RT (85-95%)[42,48,90]



m: 1.1 eq. TBDPSCl, NEt_3, DMAP (cat.), CH_2Cl_2, RT, 14h (91%)[92]

n: TBSOTf, 2,6-lutidine, CH_2Cl_2, RT, 2h (86%)[92]

o: 1.2 eq. TBDPSCl, imidazole, DMF, (75%)[3,93]

p: MEMCl, i-Pr_2NEt, CH_2Cl_2, RT, 48h (63%)[3]

r: $(i\text{-}Pr)_3SiOTf$, lutidine, CH_2Cl_2, -20°C (71%)[94]

s: Me_3SiCl, NEt_3, DMAP, CH_2Cl_2, RT (92%)[94]

COOR deprotection

R^1 = Bn, R^2 = Bn	90%
R^1 = H, R^2 = Bn	96%
R^1 = H, R^2 = BOM	100%

t: 1,4-cyclohexadiene, 10% Pd/C (cat.), EtOH, RT, 30 min.[95]

Scheme 18.19

It should be noted that *O*-alkylation of 3,4-dihydroxybutanoates under *basic* conditions invariably leads to the formation of lactones **IV** rather than to *O*-diprotected 3,4-dihydroxybutanoates.

(*S*)-β-Hydroxy-γ-butyrolactone, (**IV**, R^2 = H) [*7331-52-4*], (*R*)-β-hydroxy-γ-butyrolactam [*22677-21-0*], its enantiomer [*68108-18-9*], and methyl (*S*)-4-bromo-3-hydroxybutanoate (from isoascorbic acid) are available commercially.

Applications

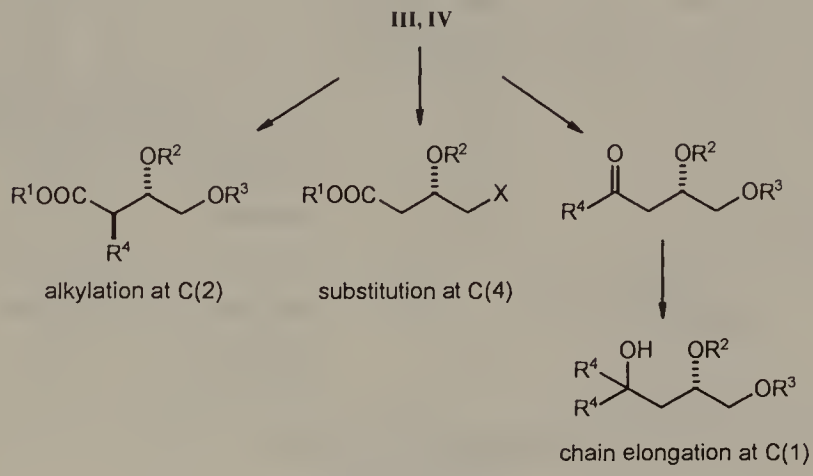
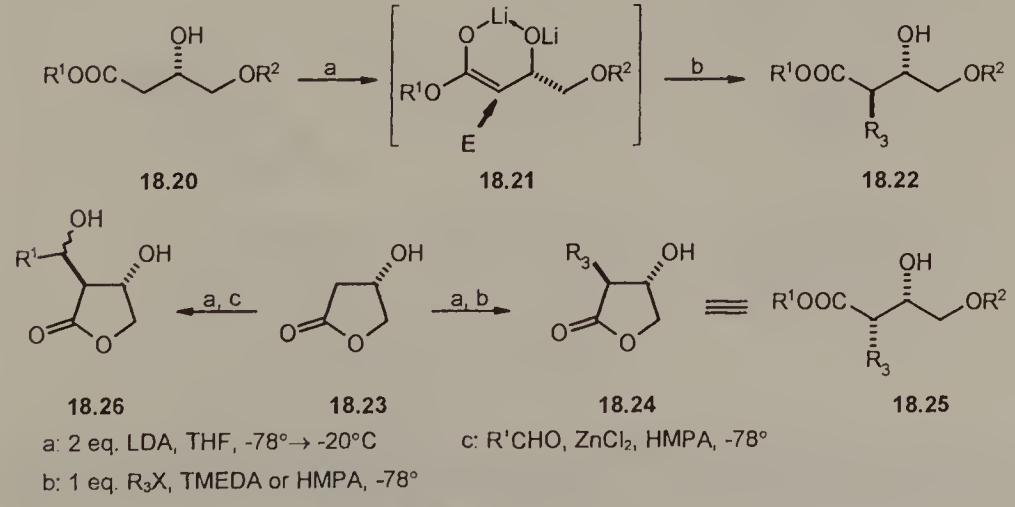


Figure 18.4

Synthesis of 2-substituted-3,4-dihydroxybutanoates. 4-*O*-Protected 3,4-dihydroxybutanoates **18.20** are readily doubly deprotonated and the resulting enolate ion **18.21** can be alkylated to give *anti*-2-alkyl derivatives **18.22**. The reaction proceeds similarly to the alkylation of malates, as described in Chapter 16, and can be extended to reactions with other electrophiles (Scheme 18.20).

Alkylation or aldol reaction of 3-hydroxybutyrolactone (**18.23**) is likewise *trans*-selective with respect to the vicinal C–O bond; effectively the product **18.24** is equivalent to the *syn*-OH/alkyl configured acyclic product **18.25**.



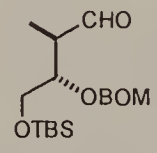
Scheme 18.20 (*continued*)

product	entry	R^1	R^2	R^3	*anti* : *syn* (*trans* : *cis*)	yield (%) *anti*/*trans*	ref.
18.22	1	Me	TBS	Me	-	86	46
	2	Me	TBS	All	30 :1	53	66
	3	Me	TBS	CH_2OBn	*anti* only	42	96
	4	Et	*t*-Bu	Me	4.5 :1	75	49
	5	Bn	An	N(Boc)NH(Boc)	-	37	44
	6	Me	TBDPS	N(Boc)NH(Boc)	2 :1	42	89
18.24	7	-	-	Me	49 :1	65	60,97,98
	8	-	-	All	300 :1	65	67
	9	-	-	R[a]	*trans* only	35	99
	10	-	-	Bn	*trans* only	34	100
18.26	11	$C_{13}H_{27}$	-	-	*trans* only	60	100
	12	Bn	-	-	*trans* only	89	100
	13	t-Bu	-	-	*trans* only	48	100
	14	Ph	-	-	*trans* only	85	100

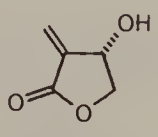
[a] R = $(CH_2)_2CH{=}C(Me)(CH_2)_2CH{=}CMe_2$

Scheme 18.20

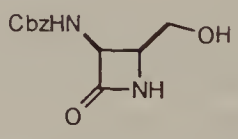
Products of the above reactions were used as chiral building blocks in several syntheses (Scheme 18.21).



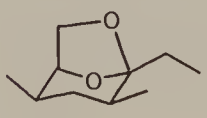
C(15)-C(18) fragment of lankacidins, from entry 1 (Thomas[46])



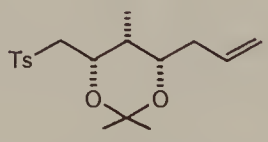
(-)-tulipalin, from entry 3 (Momose[96])



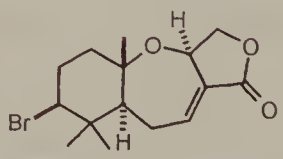
from enantiomer of entry 5 (Guanti[44])



(-)-α-multistratin, from entry 7 (Larchevêque[97])



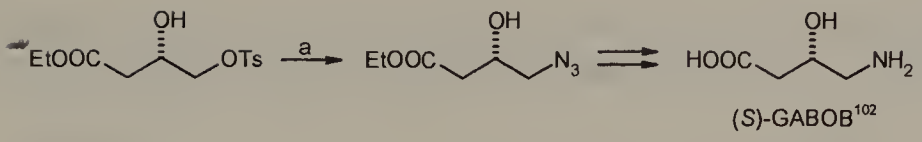
C(20)-C(25) fragment of calyculin A, from entry 7 (Shioiri[60])



(-)-aplysistatin, from entry 9 (Prestwich)[99]

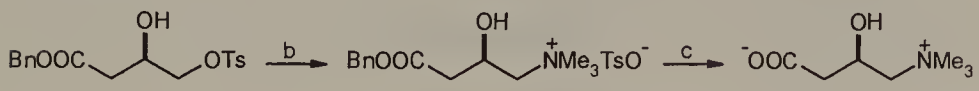
Scheme 18.21

Products of substitution reactions at C(4). A number of useful 4-heterosubstituted 3-hydroxybutanoates were obtained by substitution of the 4-*O*-tosyl derivatives (Scheme 18.22).



(*S*)-GABOB[102]

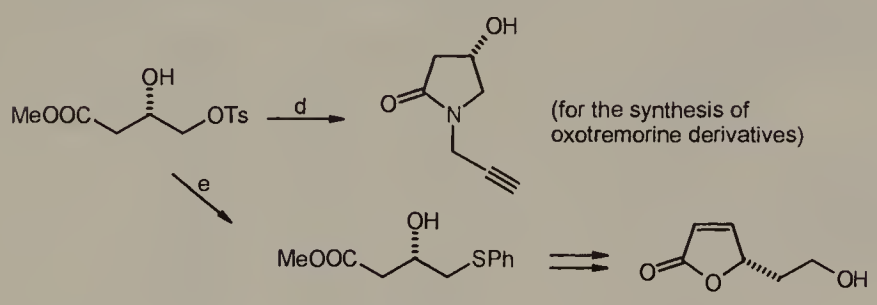
a: $HN_3 \cdot Et_2NH$, DMF, 60°C (76%)[101]



(*R*)-carnitine

b: NMe_3, PhMe (90%)

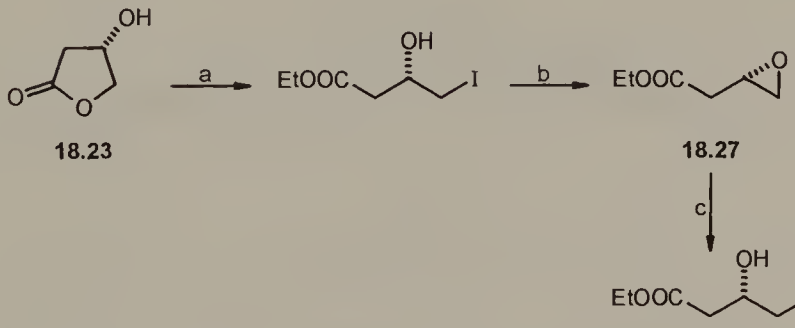
c: H_2, 10% Pd/C, MeOH then ion exchange (95%)[52]



d: $HC{\equiv}CCH_2NH_2$[103] e: PhSNa (55%)[104]

Scheme 18.22

3,4-Epoxybutanoates **18.27** and **18.28**, available from 3-hydroxybutyrolactone **18.23**, can be reacted with soft carbon nucleophiles to give C(4) chain extended hydroxyesters (Scheme 18.23). Epoxides **18.27** and **18.28** can also be used for the synthesis of GABOB.[98]



18.23 **18.27**

a: Me_3SiI, EtOH, CH_2Cl_2 (80%)

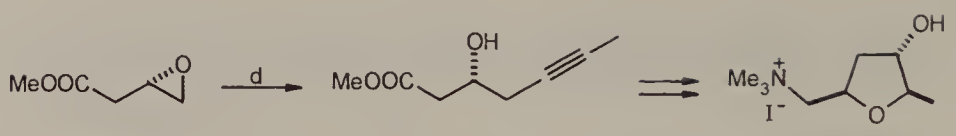
b: Ag_2O, $MeOCH_2CH_2OMe$ (75%)

c (R = Et): EtMgBr, CuI, THF (73%)

(R = n-Bu): Bu_2CuLi, Et_2O (80%)

(R = $Me_2C{=}CH$): $(Me_2C{=}CH)_2CuLi$, Et_2O (81%)[98]

Scheme 18.23 (*continued*)



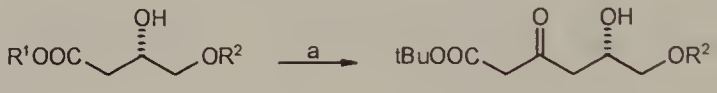
18.28

(-)-muscarine

d: MeC≡CLi, $BF_3 \cdot Et_2O$, THF, -78°C (80%)[105]

Scheme 18.23

Products of chain elongation at C(1). Claisen condensation of 4-*O*-protected 3,4-dihydroxybutanoates is the simplest entry to chiral δ-hydroxy-β-ketoesters **18.29**. The reaction requires two moles of base and is remarkably high-yielding (Scheme 18.24).



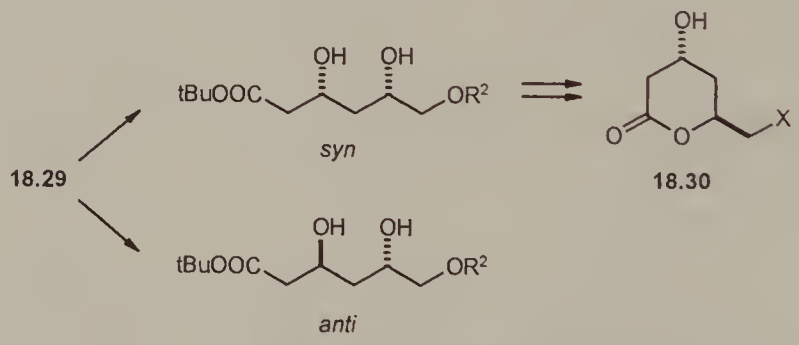
18.29

R^1	R^2	yield (%)
Et	Bn	ca. 100[50]
t-Bu	Bn	68[51]
Me	Tr	80[45]
Me	TBDPS	100[106]

a: 3-4 eq, CH_2=C(OtBu)OLi, THF, -78°→ 0°C

Scheme 18.24

Ketoesters **18.29** can be stereoselectively reduced to either *syn* or *anti* 1,3,5-triol derivatives (Scheme 18.25).



18.30

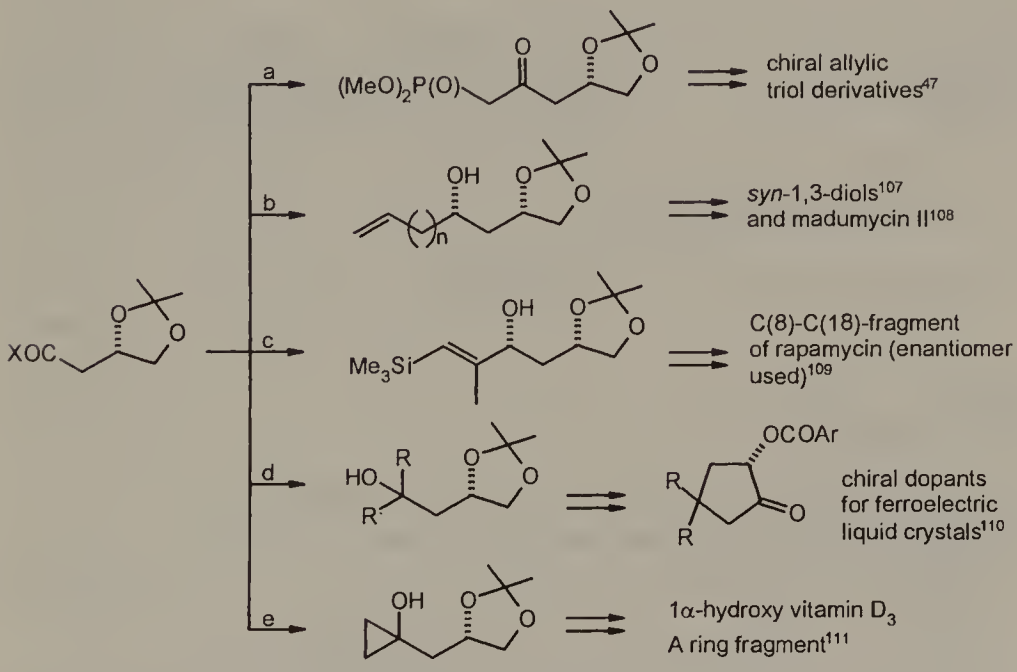
a: Et_3B, $NaBH_4$, MeOH-THF, -70°C, then H_2O_2[45,50,51,106]

b: $Me_4NHB(OAc)_3$, MeCN, AcOH, 0°C[45,51]

Scheme 18.25

The triols were used for the synthesis of HMG-CoA reductase inhibitors[50,106] as well as compactin and mevinolin,[51] all of them incorporating the hydroxylactone **18.30** unit.

Products of reactions of *O*-isopropylidene-protected 3,4-dihydroxybutanoates with other carbon nucleophiles are shown in Scheme 18.26.



a (X = OMe): $(MeO)_2P(O)CH_2Li$, THF, -78°C (95%)[47]

b (X = OH, n=3): $CH_2=CH(CH_2)_3Li$ then $LiAlH_4$ - LiI, -78°C[107]

(X = N(Me)OMe, n=1): $CH_2=CHCH_2MgBr$, THF, -78°C then $LiAlH_4$ - LiI, -100°C (92%)[108]

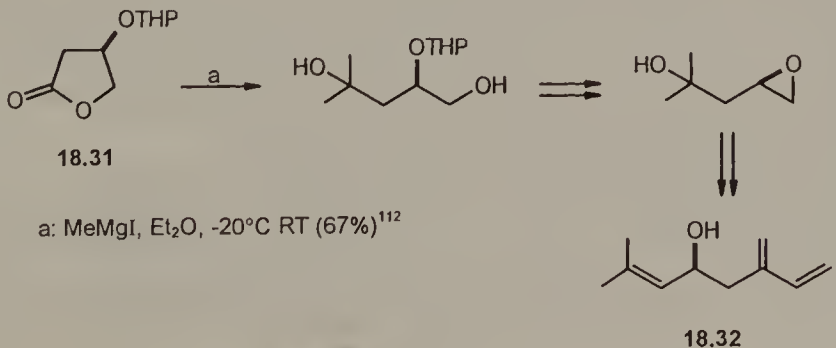
c (X = N(Me)OMe): $Me_3SiCH=C(Me)Li$, Et_2O, -78°C then $LiAlH_4$ - LiI, -100°C (60%)[109]

d (X = OEt): RMgBr, Et_2O[110]

e (X = OMe): EtMgBr-Ti(Oi-Pr)$_4$, 80%[111]

Scheme 18.26

Mori synthesized naturally occuring (+)-ipsdienol (**18.32**) from *O*-THP protected lactone **18.31**[112] (Scheme 18.27).



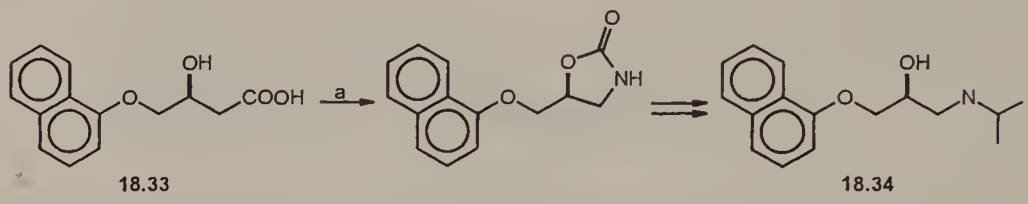
18.31

a: MeMgI, Et_2O, -20°C RT (67%)[112]

18.32

Scheme 18.27

Other syntheses. (−)-(*S*)-Propranolol (**18.34**) was synthesized from the acid **18.33** by Curtius rearrangement (Scheme 18.28).



a: $(PhO)_2PON_3$, NEt_3, PhMe (81%)[40]

Scheme 18.28

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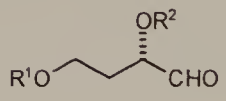
19 2,4- and 3,4-Dihydroxybutanals

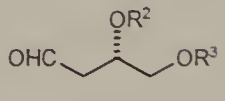
Overview



I

(2*S*)-2,4-dihydroxybutanal

(3-deoxy-L-threose)



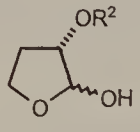
II

(3*S*)-3,4-dihydroxybutanal

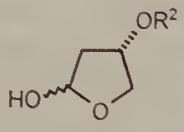
(2-deoxy-L-tetrose, L-homoglyceraldehyde)

These aldehydes are relatively unstable and are commonly prepared prior to use. For example, aldehydes **II** undergo β-elimination in the presence of acid or base impurities and heat. Some aldehydes have been isolated and characterized; see the examples in Schemes 19.1 and 19.2.

The butanals **I** and **II** with an unprotected 4-hydroxy group spontaneously from lactols **III** and **IV**, respectively.



III



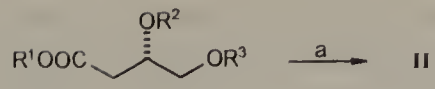
IV

(*S*)-3,4-Dihydroxybutanal (lactol **IV**, R^2 = H) has been reported;[1,2] its properties are m.p. 67–69°C, $[\alpha]_D$ + 3.6 (H_2O).

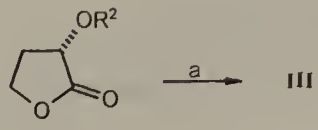
Synthesis

Dihydroxybutanals can be prepared either by reduction of the corresponding *O*-diprotected butanoates or *O*-protected butyrolactones with i-Bu_2AlH at low temperature (Scheme 19.1) or by selective oxidation of *O*-diprotected butanetriols (Scheme 19.2).

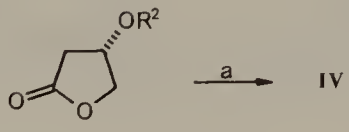
It should be noted that i-Bu_2AlH reduction is incompatible with the *O*,*O*′-benzylidene protective group as the reducing agent brings about the protective group's cleavage to the *O*-benzyl group.



R^1	R^2	R^3	yield (%)	ref.	$[\alpha]_D$ (solvent)
Et	Bn	Bn	87	3	
Me	TMS	TIPS	85	4	
Me	$-CMe_2-$		67-95	5-7	-3.1 ($CHCl_3$)[8]
Me	TBS	Ts	78	9	-12.2 ($CHCl_3$)
Me	Me	Me	83	10	-5.9 ($CHCl_3$)
t-Bu	MEM	TBS	80	11	-28.0 ($CHCl_3$)
Me	TBS	TBDPS	96	12	
Me	TES	TBDPS	93	13	



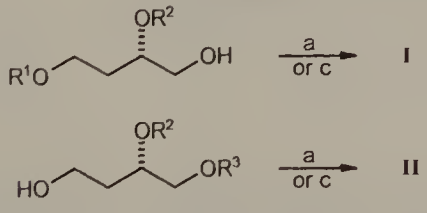
R^2	yield (%)	ref.	$[\alpha]_D$ (solvent)
Me	86	77	
BOM	53-73	14-16	+33.7 ($CHCl_3$)[16]
THP	95	17	



R^2	yield (%)	ref.
Bn	65	18

a: 1.1 eq. i-Bu_2AlH, CH_2Cl_2 or THF or Et_2O or PhMe, ca. -78°C, 30 min-1h

Scheme 19.1



a: Swern oxidation

b: pyridinium dichromate, pyridinium chlorochromate, pyridinium fluorochromate or Collins reagent oxidation

c: pyridine·SO_3, DMSO, NEt_3

Scheme 19.2 (*continued*)

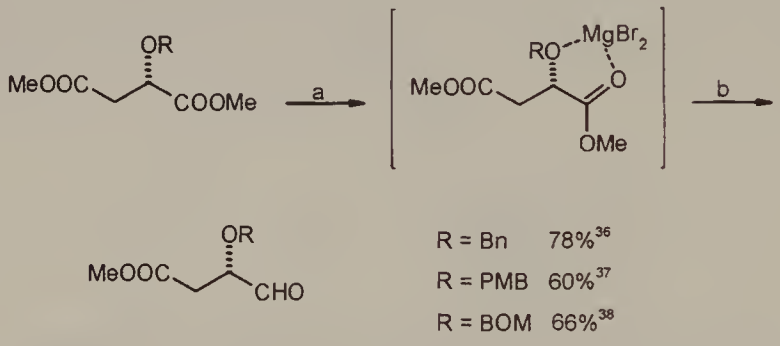
R^1	R^2	R^3	method	yield (%)	ref.
-CHPh-		-	a	78-86	19-21
-CH(2-BrC_6H_4)-		-	a	90	22
THP	MOM	-	a	>68	23
TBDPS	MOM	-	c	83	24
-	-CMe_2-		a	74-95	25,26#,27
-	-CMe_2-		b	67-88	6,28,29
-	-CEt_2-		a	74	30
-	-CEt_2-		b	69	31
-	Bz	Bn	b	73	32
-	TBDPS	Bn	b	high	33
-	Me	Me	a	98	34§

b.p. 57°C/3 torr, $[\alpha]_D$ +16.5 ($CHCl_3$)[35]

§ b.p. 110°C/15 torr, $[\alpha]_D$ -7.8 ($CHCl_3$)[34]

Scheme 19.2

Reduction of the ester group with i-Bu_2AlH shows high chemoselectivity when applied to malates; Keck demonstrated that only the C(1) ester group is reduced to the aldehyde group when it is activated by prior complexation with a Lewis acid along with the formation of a five-membered ring[36] (Scheme 19.3).



a: $MgBr_2 \cdot OEt_2$, CH_2Cl_2, 0°C, 1h

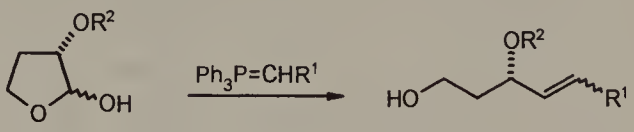
b: 1.2 eq. i-Bu_2AlH, -90°C, 1.5h

Scheme 19.3

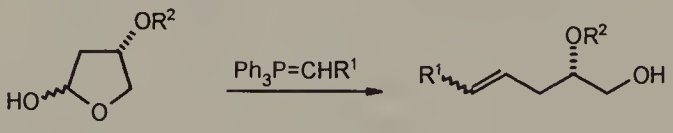
Applications

Aldehydes **I**, and **II** and lactols **III**, and **IV** are widely used as chiral building blocks for chain elongation reactions which can originate either at C(1) or at C(4). Reactions with the C(1) aldehyde are by far more popular and are based either on reactions with phosphorous ylides or on additions of various carbon nucleophiles.

Chain elongation based on C=C bond formation. Both lactols and aldehydes derived from malic acid react with phosphorous ylides in typical way, to give *cis* and/or *trans* alkenes according to general rules governing the Wittig reaction. Examples are shown in Schemes 19.4 and 19.5.



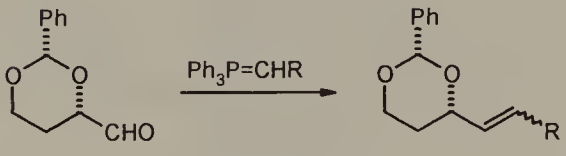
III



IV

entry	R^1	R^2	yield (%)	(*Z*):(*E*)	ref.
1 (III)	H	BOM	72	-	15
2 (III)	$(CH_2)_2COOEt$	BOM	57-73 (*Z*)	>1	14
3 (III)	$C{\equiv}CSiMe_3$	THP	85	1:2.4	17
4 (IV)	Et	PMB	87 (*Z*)	>1	39
5 (IV)	$(CH_2)_3COOMe$	PMB	69 (*Z*)	>1	40

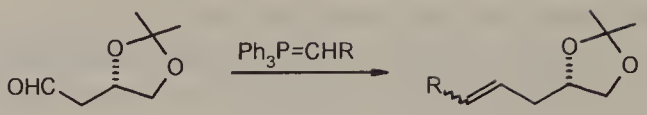
Scheme 19.4



entry	R	yield (%)	(*Z*):(*E*)	ref.
1	H	60	-	21
2	Me	65	99 :1	21
3	n-Bu	72	99 :1	21
4	$CH{=}CH_2$	60	> 1	41
5	CH=CHEt	95	3 :1	42
6	COOEt	60 (*E*)	< 1	43
7	COOMe	62	92 : 8[a]	20

[a] reaction in methanol at -70°C

Scheme 19.5 (*continued*)



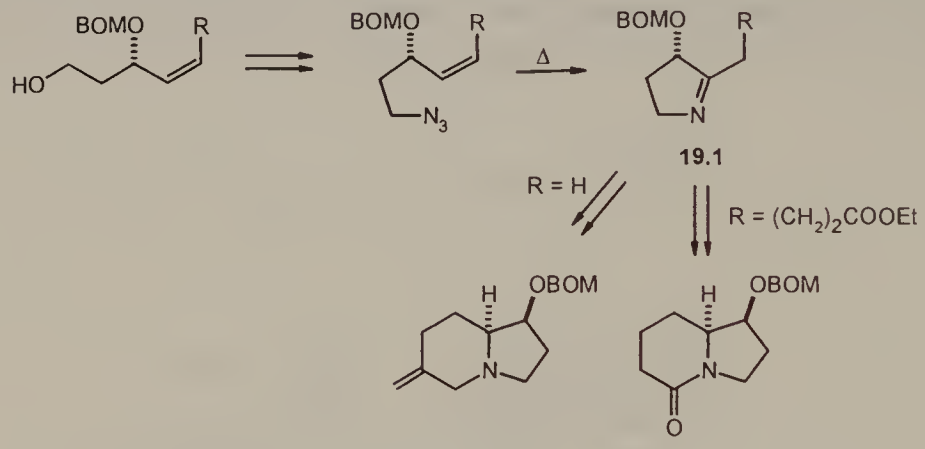
entry	R	yield (%)	ref.
8	Et	70 (*Z*)	44
9	C_5H_{11}	68 (*Z*)[a]	45
10	(*Z*)-CH_2CH=CHC_5H_{11}	87-91 (*Z*)	46
11	$(CH_2)_3COOMe$	61 (*Z*)[a]	47
12	COOEt	84 (*E*)[a]	48

[a] yield includes aldehyde preparation step

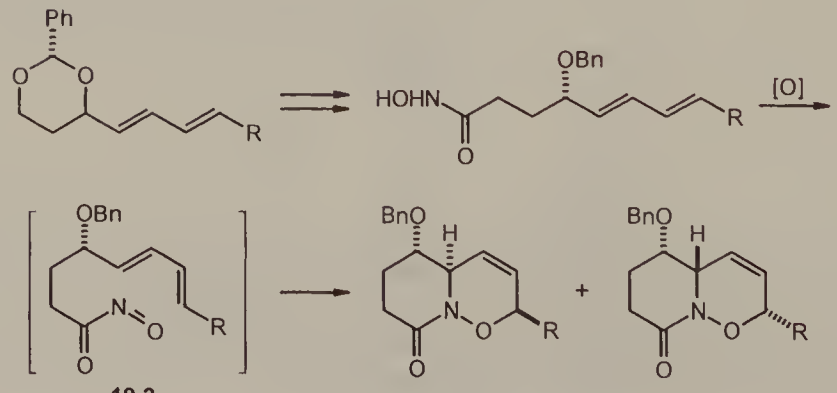
Scheme 19.5

The enantiomer of the product from entry 4, Scheme 19.4, was the intermediate in the synthesis of neohalicholactone (Wills[39]).

Chiral dihydroxyalkene derivatives synthesized according to entries 1 and 2 in Scheme 19.4 were used by Cha[14] and by Pearson[15] for the synthesis of indolizidine alkaloids via the pivotal 1-pyrrolines **19.1**, as outlined in Scheme 19.6.



Scheme 19.6

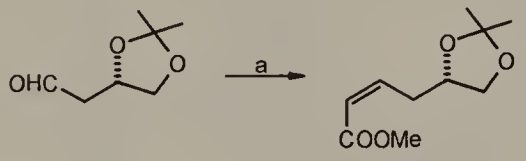


Scheme 19.7

Kibayashi devised a route to (−)-swainsonine[41] and to (−)-pumilitoxin C[42] based on intramolecular acylnitroso cycloaddition of dienes **19.2** derived from products *ent*-4 and 5 in Scheme 19.5. This crucial step is shown in Scheme 19.7.

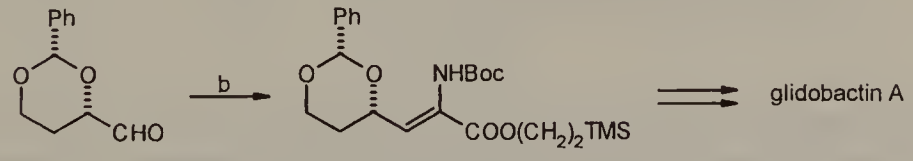
Further applications of the alkene products include the synthesis of 8(*S*),15(*S*)-dihydroxy-5,11-*cis*-9,13-*trans*-eicosatetraenoic acid (8,15-DiHETE) by Nicolaou[17] (Scheme 19.4, entry 3); the right-hand fragment of halicholactone by Wills[40] (Scheme 19.4, entry 4); 12(*S*)-hydroxy-5,8,14-*cis*-10-*trans*-eicosatetraenoic acid (HETE) by Corey[45](Scheme 19.5, entry 9); prostaglandins E_3 and $F_{3\alpha}$ by Corey[44] (Scheme 19.5, entry 8); 5(*S*),20- and 15(*S*),20-dihydroxyeicosatetraenoic acid as well as 5(*S*),6(*R*)-epoxy-20-hydroxy- and 14(*R*),15(*S*)-epoxy-20-hydroxyeicosatrienoic acids by Falck[47] (Scheme 19.5, entry 11); and 8,9- and 11,12-epoxyeicosatrienoic acids by Falck[46] (Scheme 19.5, entry10). Guindon synthesized tetrahydrofuran chirons from the products shown in Scheme 19.5, entries 6 and 12.[43,48] The enantiomer of the product of entry 12 served as a chiral building block for the synthesis of (+)-negamycin by Tanner and Somfai.[49] Herradón synthesized (*R*)-5-(2-hydroxyethyl)-2(5*H*)-furanone from the enantiomer of product 7 of Scheme 19.5.[20] Chiral δ-lactones were obtained from hydrogenated product 12 (Scheme 19.5).[50,51]

The (*Z*)-conjugated ester **19.4** was obtained from the protected aldehyde **19.3** by olefination with Still's reagent. This procedure was not practical on a larger scale due to the tedious separation of the diastereoisomeric products. (*E*)-Olefinic products were obtained by either Horner–Emmons reaction or by reductive addition of (tributylstannyl)dibromomethane (Scheme 19.8).

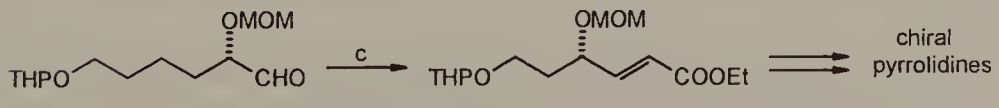


19.3 **19.4**

a: $(CF_3CH_2))_2P(O)CH_2COOMe$, NaH, Et_2O, -78°C (89%, (*Z*) : (*E*) = 5 :1)[52]

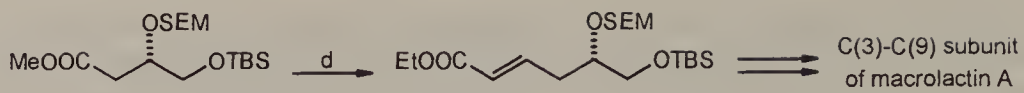


b: $(MeO)_2P(O)CH(NHBoc)COO(CH_2)_2TMS$, DBU, RT (95%, *trans*: *cis* = 49 :1)[53]

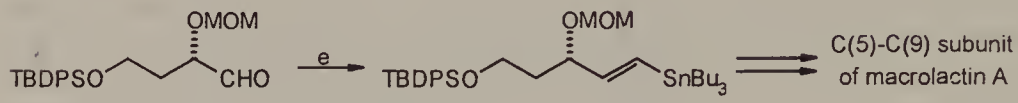


c: $(i\text{-}PrO)_2P(O)CH_2COOEt$, NaH, THF, 0°C (93%)[23]

Scheme 19.8 (*continued*)



d (*in situ* formation of the aldehyde): $(EtO)_2P(O)COOEt$, n-BuLi, i-Bu_2AlH, CH_2Cl_2, -78°C (75%)[54]

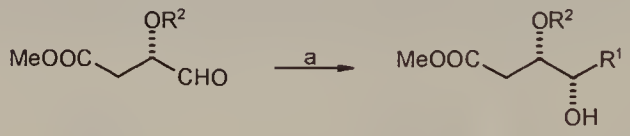


e: $Bu_3SnCHBr_2$, $CrCl_2$, LiI, THF-DMF (54%)[24]

Scheme 19.8

For an application of similar (*E*)-selective Horner–Emmons olefination to the synthesis of the caprolactam portion of bengamide B, see ref. 55.

Chain elongation reactions based on the addition of carbon nucleophiles. 2-Alkoxybutanals display high levels of diastereoselectivity in addition reactions of carbon nucleophiles under conditions of chelation control. Several examples of these reactions, leading to *syn* addition products, are shown in Scheme 19.9.



entry	R^1	R^2	yield (%)	*syn* : *anti*	ref.
1	$CH{=}CH_2$	Bn	83	155 : 1	36
2	$CH_2CH{=}CH_2$	Bn	77	49 : 1	36
3	$CH_2CH{=}CH_2$	PMB	62	200 : 1	37

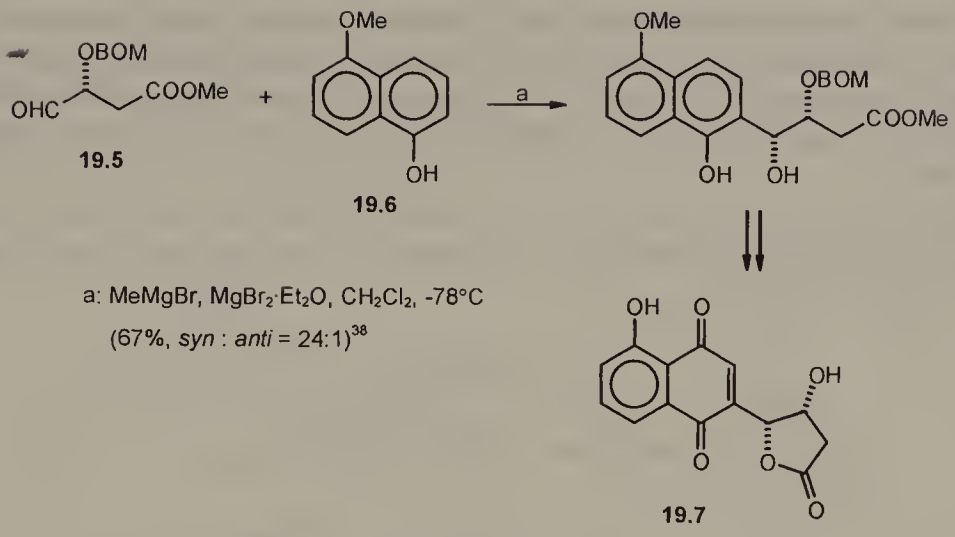
a: RMgBr, $MgBr_2{\cdot}Et_2O$, CH_2Cl_2, -78°C

Scheme 19.9

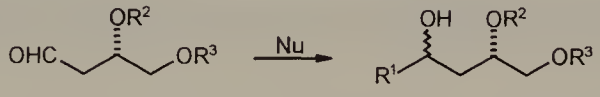
Keck established that in the absence of $MgBr_2$ reaction 1 in Scheme 19.9 shows low diastereoselectivity, *syn*:*anti* = 1:1.5.[36] The enantiomer of product 3 in Scheme 19.9 was used for the synthesis of (+)-carbonolide B.[37]

Kraus has synthesized juglomycin A (**19.7**) in four steps, starting with the chelation controlled addition of an anion of naphthol **19.6** to aldehyde **19.5**[38] (Scheme 19.10).

In contrast to 2-alkoxybutanals, protected 3,4-dihydroxybutanals show little diastereoselectivity in nucleophilic carbon chain elongation reactions; this is due to the separation of the aldehyde group from the chiral center by one CH_2 group. Examples of such reactions are collected in Scheme 19.11.

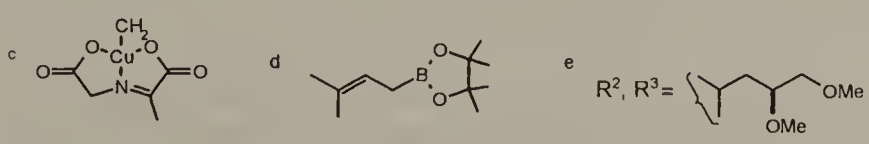


Scheme 19.10



entry	R^1	R^2	R^3	Nu	yield (%)	*syn* : *anti*	ref.
1	Me	$-CMe_2-$		MeMgBr	88	1 : 1	7
2	All	$-CMe_2-$		AllMgBr(Cl)	75-91	1 : 1	7,28,56,57
3	CH_2=CH	$-CMe_2-$		CH_2=CHMgBr	85-95	1 : 1	26,58,59
4	HC≡CCH_2	$-CMe_2-$		HC≡CCH_2ZnBr	79	1.6 : 1[a]	60
5	$PhSCH_2$	$-CMe_2-$		$PhSCH_2$Li	68	[b]	61
6	$MeOOCCH_2$	$-CMe_2-$		CH_2=C(OMe)OLi	[b]	1 : 1	62
7	$EtOOCCH_2$	$-CMe_2-$		CH_2=C(OEt)OLi	58	1 : 1	27
8	i-PrOOCCHMe	$-CMe_2-$		MeCH=C(Oi-Pr)OLi	64	[b]	63
9	$EtOOCCMe_2$	$-CMe_2-$		Me_2(=C(OEt)OLi	74	[b]	64
10	$HOOCCHNH_2$	$-CMe_2-$		[c]	50	[b]	6
11	CH_2=$CHCMe_2$	Me	Me	[d]	82	1 : 2	10
12	$BnOOCCH_2$	Bn	Bn	CH_2=C(OBn)OLi	78	[b]	3
13	$EtOOCCH_2$	TBDPS	Bn	$EtOOCCH_2ZnBr,Et_2AlCl$	85	1 : 1	33
14	CH_2=CMe	[e]		CH_2=C(Me)MgBr	88	[b]	34

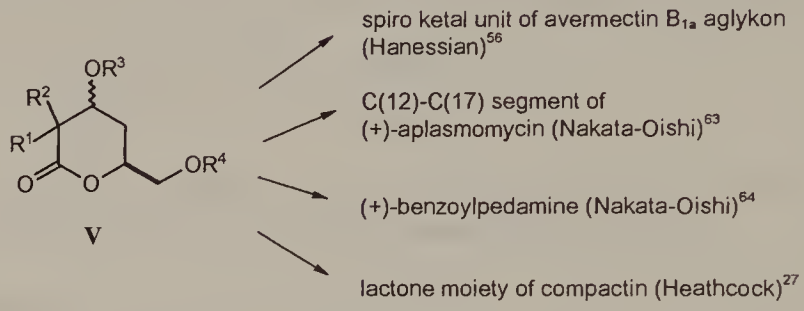
[a] relative configurations not assigned [b] not reported



Scheme 19.11

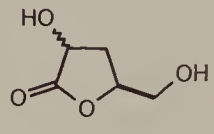
Despite poor stereoselectivity of the addition reactions, their products were used in the following synthetic steps, either as a mixture of diastereomers or after chromatographic separation.[26] In particular, stereoselectivity of the addition was of no significance, if the products were oxidized to the corresponding ketones.

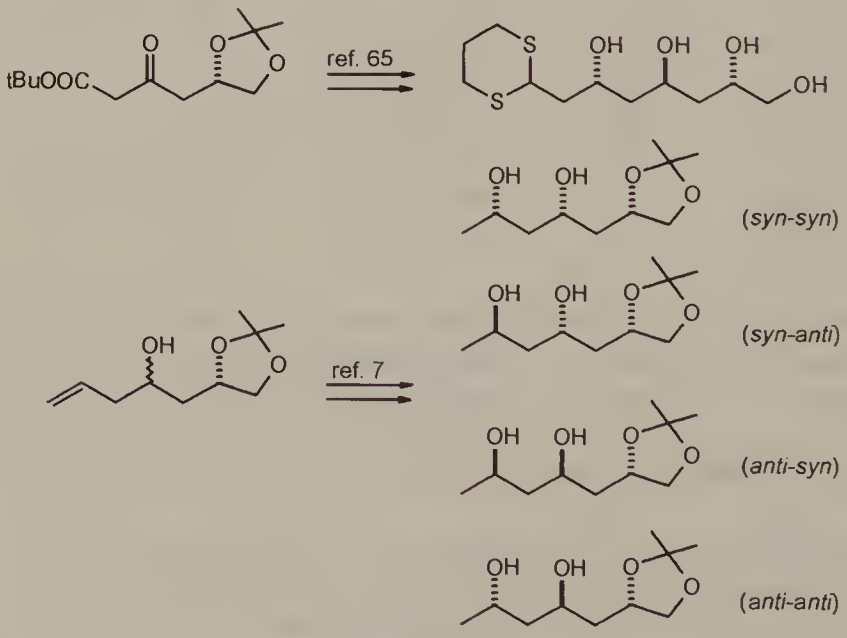
Products of two-carbon elongation or allylation reactions were converted to lactones of the general formula **V**[33] and further to more advanced natural products (Scheme 19.12).



Scheme 19.12

Chiral γ-lactones of formula **VI** were prepared from the addition products of entry 3, Scheme 19.11.[58]

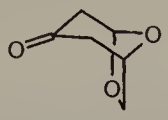




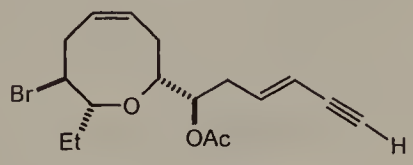
Scheme 19.13

Further important applications of chain elongation products were found in the synthesis of 1,3,5-*anti-anti*-triol systems[65] as well as in other stereoisomeric triol systems[7] (Scheme 19.13).

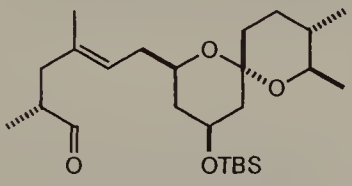
Other target compounds synthesized from the addition products of Scheme 19.11 are collected in Scheme 19.14.



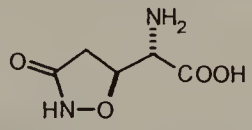
1,6-anhydropyranose skeleton (Léger[66]), from entry 1



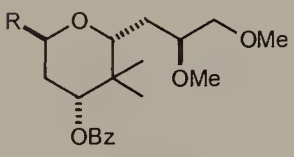
(+)-laurencin (Holmes[59]), from enantiomer of entry 3



a fragment of (+)-milbemycin β_3 (Kocieński[28,61]), from entry 2 or 5

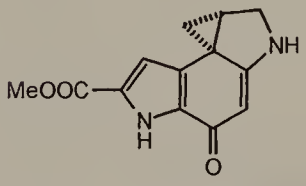


tricholomic acid (Hanessian[6]), from entry 10



R = $CONH_2$, benzoyl-pedamine (Hoffmann[10]), from entry 11

R = CH_2OBz, pederol dibenzoate (Kocieński[34]), from entry 14



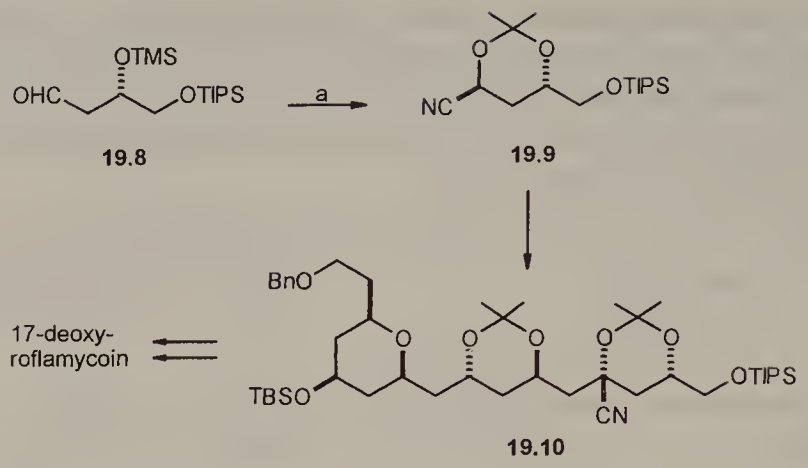
a fragment of (+)-duocarmycin SA (Natsume[3]), from entry 12

(entry numbers refer to Scheme 19.11)

Scheme 19.14

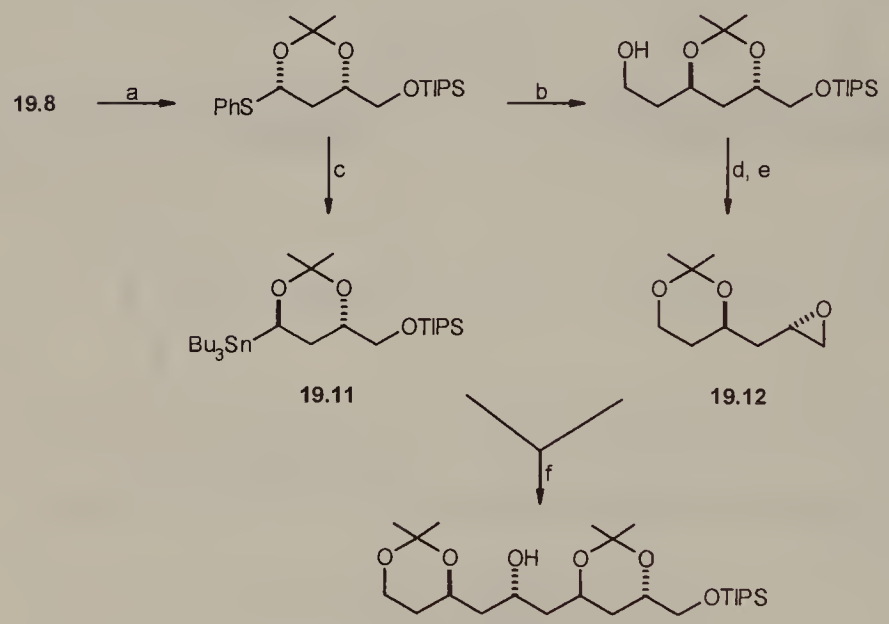
The lack of stereoselectivity in the addition reactions to 3,4-dialkoxybutanals can be compensated for by the formation of a 1,3-dioxane acetal ring including the hydroxy group of the newly formed chiral center. Rychnovsky obtained cyanohydrin acetonide **19.9** as a single diastereomer from the product of addition of cyanide ion to the protected aldehyde **19.8** (Scheme 19.15). Protected cyanohydrin **19.9** was stereoselectively alkylated (presumably with retention of configuration) to give intermediate **19.10** for the synthesis of 17-deoxyroflomycoin.[67]

The related convergent synthesis of skipped polyol chains, also developed by Rychnovsky,[4] is based on coupling the chiral tin reagent **19.11** with the epoxide **19.12**, both derived from aldehyde **19.8** (Scheme 19.16).



a: TMSCN, KCN/18-crown-6 (cat.) then Me_2CO, $Me_2C(OMe)_2$, CSA (cat.) (78%)[67]

Scheme 19.15



a: $PhSSiMe_3$, TMSOTf, CH_2Cl_2, -78°C then Me_2CO, TMSOTf, CH_2Cl_2, -78°C (51%)

b: lithium di-t-butylbiphenylide, ethylene oxide, $BF_3{\cdot}Et_2O$, THF, -78°C (77%)

c: lithium di-t-butylbiphenylide, Bu_3SnCl, THF, -78°C (82%)

d: PPTS, Me_2CO, $CuSO_4$, RT then Bu_4NF, THF, RT (84%)

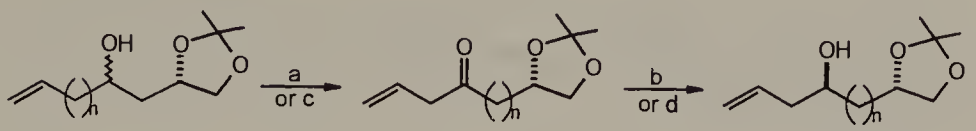
e: TsCl, NaOH, THF, RT (82%)

f: n-BuLi, THF, -78°C, 10 min. then $BF_3{\cdot}$ Et_2O, -78°C (62%)[4]

Scheme 19.16

Another way of circumventing the diastereoselectivity problem in the addition of carbon nucleophile to protected 3,4-dihydroxybutanal is oxidation of the secondary alcohol mixture to a β-alkoxyketone followed by its diastereoselective reduction. For example, highly *syn*-selective reduction was achieved with a

$LiAlH_4$-LiI reducing system or with L-Selectride, due to β-chelation control by the lithium cation (Scheme 19.17).



n = 0 *syn* : *anti* = 7 : 1

n = 3 *syn* : *anti* = 22 : 1

a (n = 0): MnO_2, CH_2Cl_2 (60%)

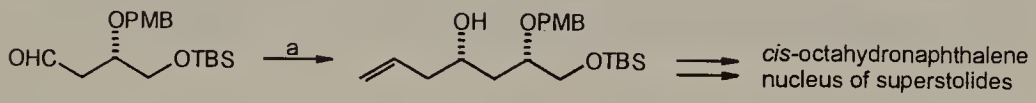
b (n = 0): L-Selectride, Et_2O, -100°C (63%)[26]

c (n = 3): PCC, AcONa, CH_2Cl_2, RT, 6h (>70%)

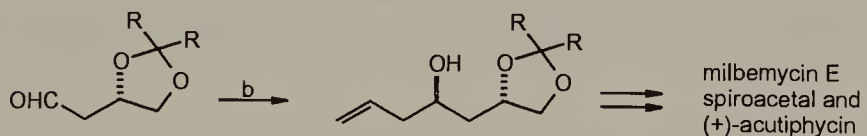
d (n = 3): $LiAlH_4$, LiI, Et_2O), -78°C, 1h (88%)[68]

Scheme 19.17

The addition of chiral carbon nuclophiles to protected 3,4-dihydroxybutanals (double diastereoselection) is the ultimate way for carbon chain elongation with concomitant control of configuration of the newly formed chiral center. By proper choice of chiral nucleophile either *syn* or *anti* addition product can be obtained (Scheme 19.18).



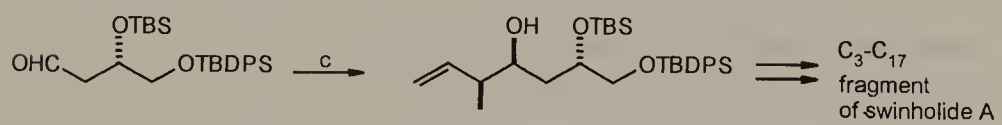
a: Bu_3SnAll, $Ti(OiPr)_4$, (*S*)-BINOL, CH_2Cl_2, -20°C, 6d (79%, d.e. 88%)[69]



R = Me 40-65%, d.e. 80%[25,70]

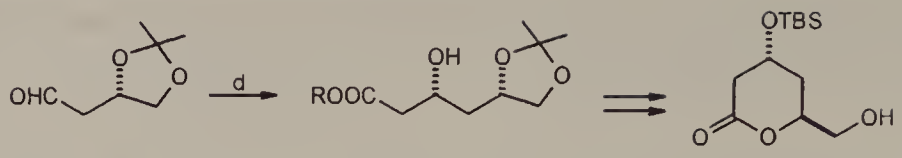
R = Et 75%, d.e. 90%[31]

b: (-)-Ipc_2BAll, then H_2O_2, NaOH;

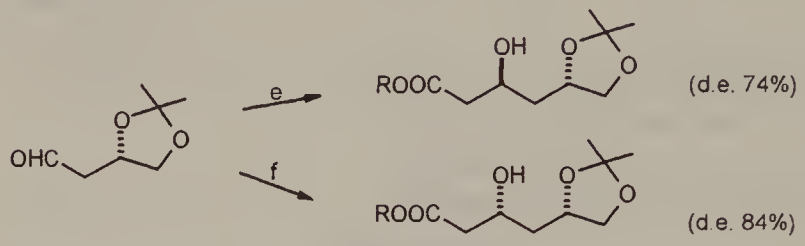


c: (*Z*)-MeCH=CHMe, t-BuOK, n-BuLi, (+)-Ipc_2BOMe, $BF_3 \cdot Et_2O$, THF, -78°C, 12h
then H_2O_2, NaOH (90%, d.e. 90%)[12]

Scheme 19.18 (*continued*)



d (R = Me, Et): (*R*)-TolS(O)CH_2COOR, t-BuMgCl, THF, -78°C then Al/Hg, THF-H_2O (10 :1), 0°C (41-50%)[71]

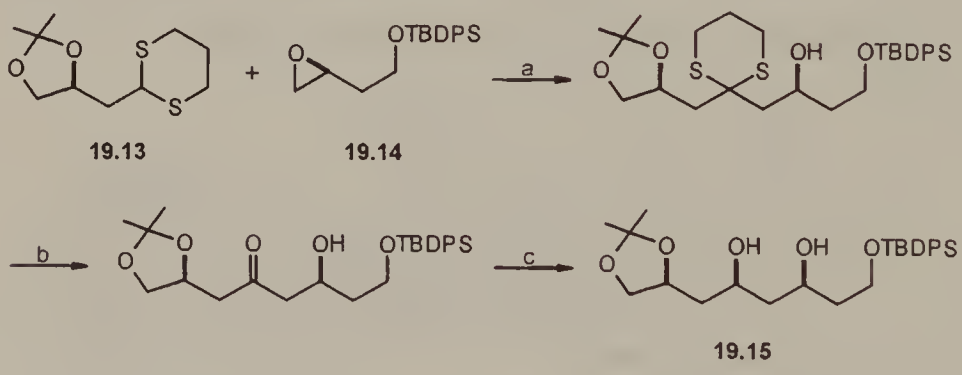


e: (*R*)-AcOCH(Ph)CPh_2OH, LDA, MgI_2, THF/2-methylbutane, -125°C

f: (*S*)- AcOCH(Ph)CPh_2OH, as e[62]

Scheme 19.18

Synthesis of 1,3-polyols via the 1,3-dithiane derivatives. *Umpolung* of the aldehyde functional group by formation of the dithiane derivative provides yet another way to 1,3-hydroxylated carbon chain of defined stereostructure. Thus dithiane **19.13**, derived from 3,4-dihydroxybutanal, was coupled with epoxide **19.14**, also derived from L-malic acid, to give *all-syn* pentaol **19.15**, after stereoselective reduction of the keto group (Suzuki and Mori,[72a,c] Scheme 19.19).



a: n-BuLi, THF, -20°C (98%)

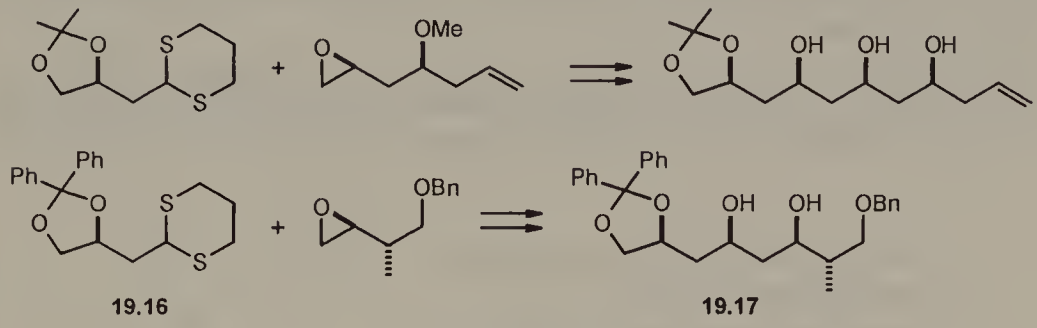
b: NBS, $AgNO_3$, 2,6-lutidine, 85% aq MeCN, 7 min. (78%)

c: $LiAlH_4$, LiI, Et_2O, -100°C (95%, *syn*:*anti* = 19:1)[72a,c]

Scheme 19.19

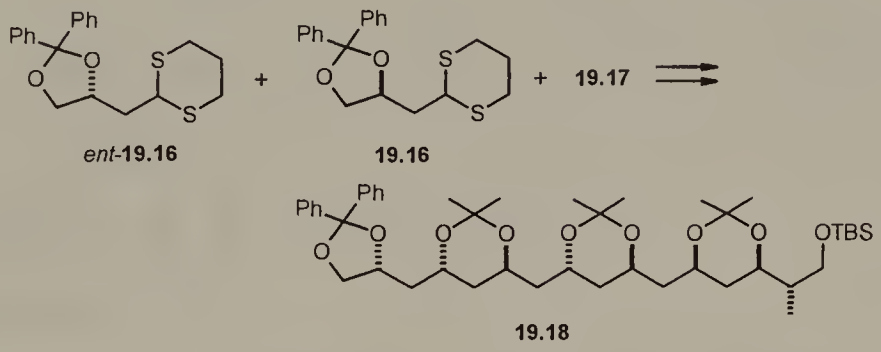
Anti-1,3-polyols can be synthesized accordingly, using the enantiomer of the aldehyde **19.14**, derived from D-malic acid.[72b]

Modification of the above synthetic scheme provided a synthetic route to skipped 1,3-polyol units of differing architecture[73,74] (Scheme 19.20). The epoxide components were also synthesized from L-malic acid.



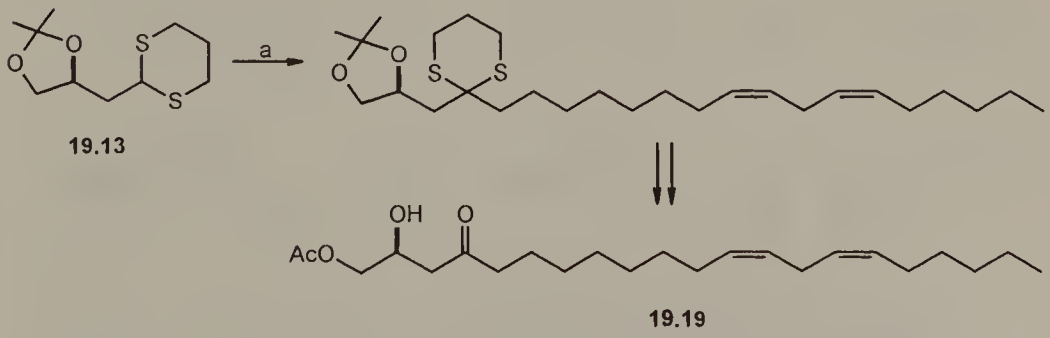
Scheme 19.20

Pentaol derivative **19.17** was prepared by Mori for the synthesis of the polyol fragment of roxaticin.[74] This C_{16} fragment **19.18** was assembled by stepwise coupling of **19.17** with dithiane **19.16** and its enantiomer[75] (Scheme 19.21).



Scheme 19.21

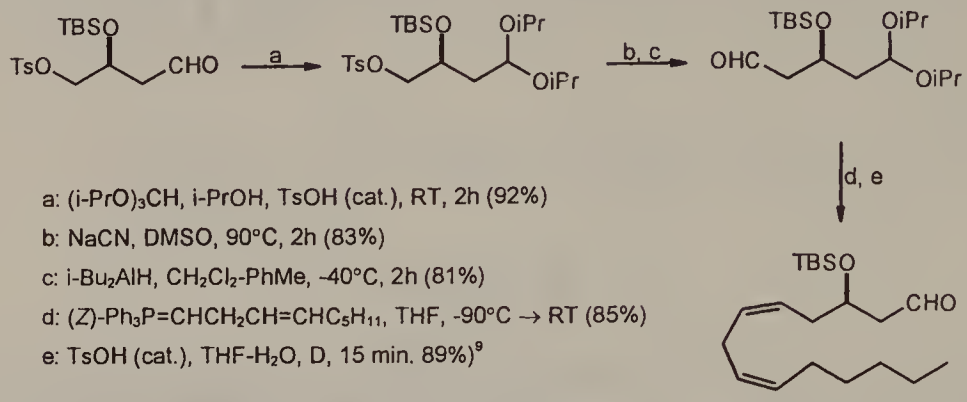
Finally, dithiane **19.13** was used for the synthesis of the avocado antifungal **19.19**[76] (Scheme 19.22).



a: n-BuLi, t-BuOK, (Z,Z)-Me$(CH_2)_4$CH=CHCH$_2$CH=CH$(CH_2)_7$Br, THF

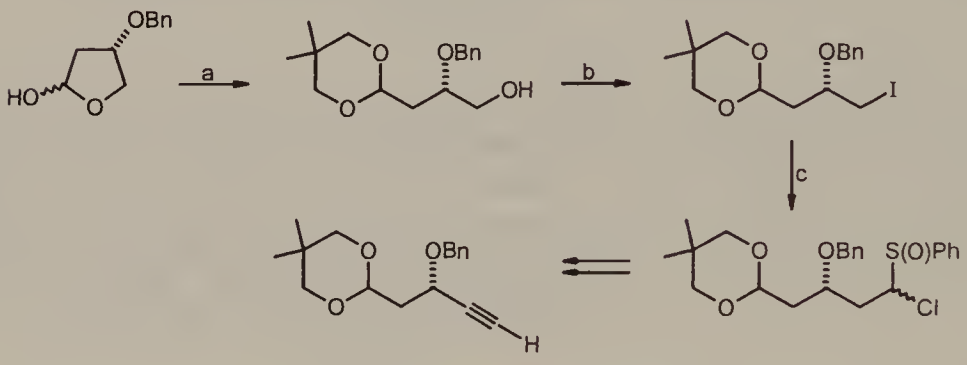
Scheme 19.22

Chain elongation at C(4). Protection of the aldehyde group as an acetal or dithioacetal derivative, combined with activation of the 4-hydroxy substituent, has been occasionally used for attachment of the functionalized carbon chain at C(4) in 3,4-dihydroxybutanals. Examples of such synthetic procedures are shown in Schemes 19.23 and 19.24.

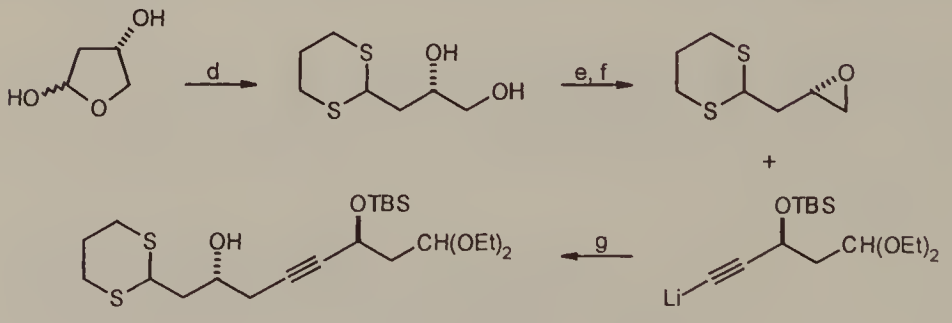


a: $(i\text{-}PrO)_3CH$, i-PrOH, TsOH (cat.), RT, 2h (92%)
b: NaCN, DMSO, 90°C, 2h (83%)
c: $i\text{-}Bu_2AlH$, CH_2Cl_2-PhMe, -40°C, 2h (81%)
d: (*Z*)-$Ph_3P{=}CHCH_2CH{=}CHC_5H_{11}$, THF, -90°C → RT (85%)
e: TsOH (cat.), THF-H_2O, D, 15 min. 89%)[9]

Scheme 19.23



a: $Me_2C(CH_2OH)_2$, TsOH (cat.) then acidic equilibration (80%)
b: TsCl, pyridine then NaI, Me_2CO (quant.)
c: PhS(O)CH(Cl)Li (72%)[18]



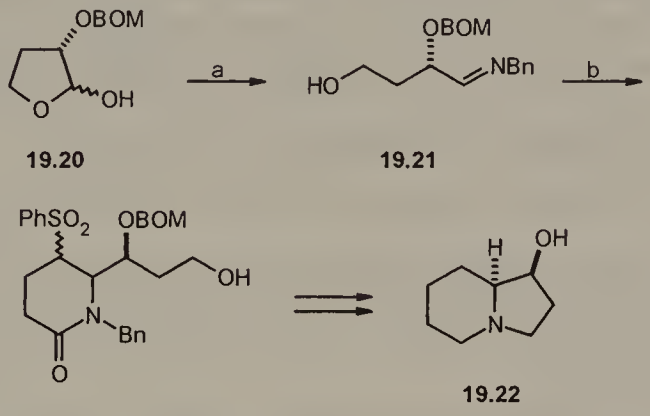
d: $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 2d, RT (77%)
e: 2 eq. Ph_3P, CCl_4, PhMe, 70°C, 3h (66%)
f: MeONa, MeOH, RT, 15 min. (74%)
g: 1 eq. $BF_3{\cdot}OEt_2$, THF, -78°C (70%)[29]

Scheme 19.24

The product of the synthesis of Scheme **19.23** was one of the key ingredients in the total synthesis of (−)-lipstatin by Kocieński.[9]

The products of Scheme 19.24 were obtained by Barton and Khuong-Huu for the synthesis of maytansinoids.[18,29]

Miscellaneous syntheses. Thompson *et al.* synthesized 1-hydroxyindolizidine (**19.22**) by *syn*-addition of the dianion of 4-phenylsulfonylbutanoic acid to imine **19.21**. The imine was directly obtained from lactol **19.20**[16] (Scheme 19.25).



a: $BnNH_2$, PhMe, RT, 10h (>99%)

b: $HOOC(CH_2)_3SO_2Ph$, 2 eq. n-BuLi, THF, $BF_3{\cdot}OEt_2$, -78°→ O°C then CF_3COOH (~100% crude)

Scheme 19.25

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20 1,2,4-Butanetriol and Its Derivatives

Overview

As in the case of threitol, derivatives of 1,2,4-butanetriol with various protecting and/or activating groups are primarily used as chiral four-carbon building blocks. These building blocks include also 1-, 4-, and 1,4-heteroatom (halogen, S, N, P) substitution products. Compounds included in this chapter are divided according to the number of the hydroxy protecting groups and further divided according to the position of the protecting group(s). The most frequently used synthetic pathways between differently protected 1,2,4-butanetriol derivatives are shown in Figure 20.1.

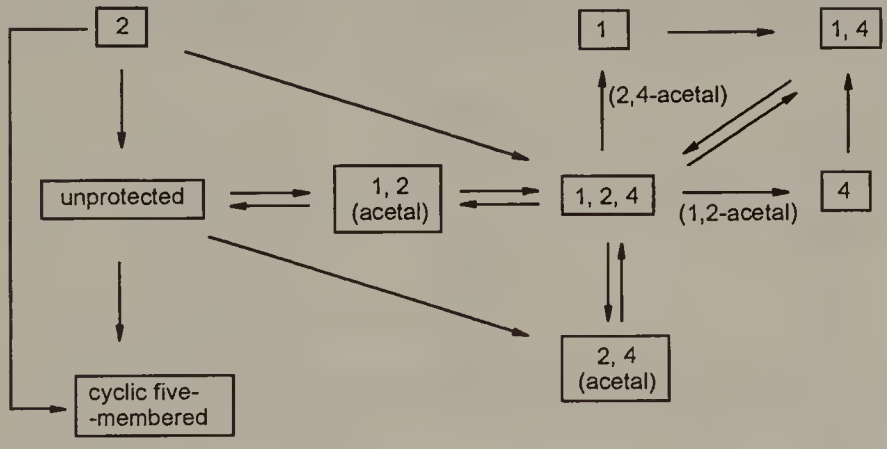
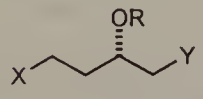
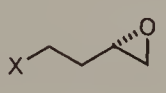


Figure 20.1 Most common pathways to the differently protected 1,2,4-butanetriols.

20.1 UNPROTECTED 1,2,4-BUTANETRIOL AND ITS SUBSTITUTION PRODUCTS



I



II

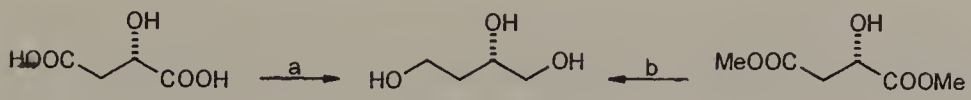
Table 20.1 (*S*)-1,2,4-Butanetriol and its substitution products (I, II)

X	Y	R	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
			Formula I		
OH	OH	H	145–148/1.1	−29.5 (MeOH)	1–4
OH	OH	Ts	—	−7.1 (MeOH)	2
OH	9-adenyl	H	212–214	+2.6 (0.1M HCl)	5
OH	SO_2Ph	H	—	−3.2 (EtOH)	6
OMs	OMs	H	68–70	−17.9 (CH_2Cl_2)	7,8
OTs	OTs	H	56–58	−5.0 ($CHCl_3$)	9
OMs	OMs	Ms	79.5–80	−24.4 ($CHCl_3$)	10
OTs	OTs	Ts	107.7	−28.7 ($CHCl_3$)	11,12
Br	OH	H	—	−38.4 ($CHCl_3$)	13
Br	Br	H	28–30	−39.3 ($CHCl_3$)	14,15
NH_2	OH	H	172–175/0.1	−23.0 (MeOH)	16
NMe_2	OH	H	53/0.08	−17.4 (MeOH)	17
NHCbz	OH	H	67–68	−6.0 ($CHCl_3$)	16
NHCbz	OTs	H	68–69	−3.1 (AcOEt)	16
NHCbz	Br	H	—	−15.0 (AcOEt)	16
NH_2·HCl	NH_2·HCl	H	249–250	+3.2 (H_2O)	18
9-adenyl	OH	H	226–227	−25.9 (0.1M HCl)	19
PPhBn	PPhBn	H	268–269	−39.2 (MeOH)	20
PPh_2	PPh_2	H	107–112	+1.0 ($CHCl_3$)	9
$PO(OH)_2$	OH	H	—	−16.0 (EtOH)	21,22
			Formula II		
OH	—	—	—	−19.0 (Me_2CO)	23
				−32.0 (CH_2Cl_2)	2,24
OMs	—	—	—	−21.5 (Me_2CO)	7
OTs	—	—	28–32	−14.6 (Me_2CO)	25
Br	—	—	75/35	−23.9 ($CHCl_3$)	14,15,26
I	—	—	—	−13.5 (CH_2Cl_2)	7
NMe_2	—	—	53/22	−23.8 (Et_2O)	17

Synthesis

1,2,4-Butanetriol is readily available by reduction of malic acid with BH_3·Me_2S or reduction of malates with $LiAlH_4$. The latter procedure appears to be inferior due to the difficulty in separation and purification of the product, lowering its yield. A similar diborane reduction of malamic acid (**20.1**) or malamide (**20.3**) yields 4-amino-1,2-butanediol (**20.2**) or 2-hydroxyputrescine (**20.3**). These procedures are shown in Scheme 20.1.

Indirectly, 1,2,4-butanetriol was quantitatively obtained by hydrolysis of the 1,2-*O*-isopropylidene derivative in aqueous acetic acid.[9]



a: $B(OMe)_3$, 2-4 eq. $BH_3 \cdot Me_2S$, THF, 0°C → RT, 24h (84-100%)[3,4,27-29]

b: $LiAlH_4$, THF or Et_2O, Δ, 1-3d (50-100%)[1,30-32]

20.1 (X = OH) **20.2** (X = OH)[16]

20.3 (X = NH_2) **20.4** (X = NH_2)[18]

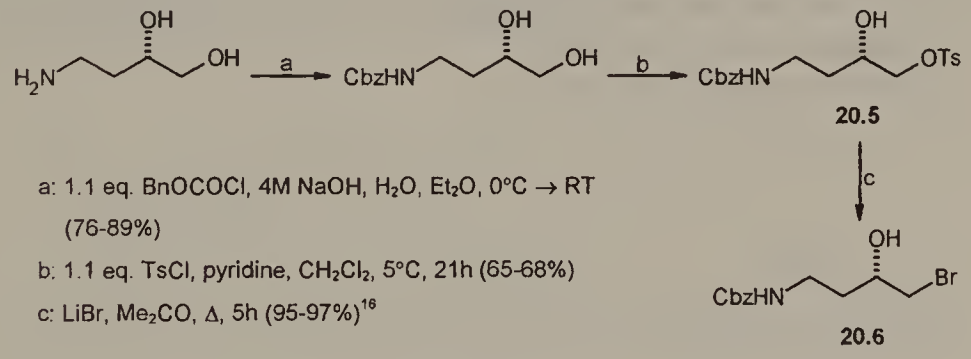
c: B_2H_6, THF, then Δ (56-75%)

Scheme 20.1

(*R*)-1,2,4-Butanetriol can be alternatively synthesized by deoxygenation of (*S*)-(+)-erythrulose (Vandewalle[33]).

(*S*)-(−)-1,2,4-Butanetriol [*42890-76-6*] and its enantiomer [*70005-88-8*] are commercially available .

An essential step for any application of 1,2,4-butanetriol and its derivatives as chiral building blocks in the synthesis is the selective activation of the hydroxy groups. A simple yet efficient method of activation of the C(1) hydroxy group for substitution is to convert it to the tosyl ester, or to the bromide in 4-amido derivatives **20.5** and **20.6** (Scheme 20.2).



a: 1.1 eq. BnOCOCl, 4M NaOH, H_2O, Et_2O, 0°C → RT (76-89%)

b: 1.1 eq. TsCl, pyridine, CH_2Cl_2, 5°C, 21h (65-68%)

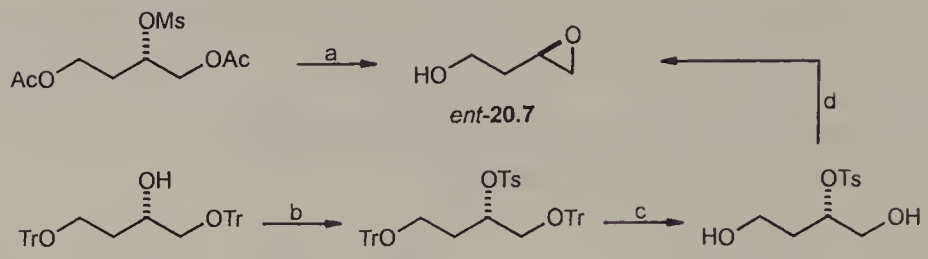
c: LiBr, Me_2CO, Δ, 5h (95-97%)[16]

Scheme 20.2

A convenient way of activating the C(1) hydroxy group in 1,2,4-butanetriol is by the formation of the 1,2-epoxide **20.7** from 2-*O*-sulfonyl derivatives (Scheme 20.3). The starting materials for this synthesis are 1,4-diprotected butanetriols.

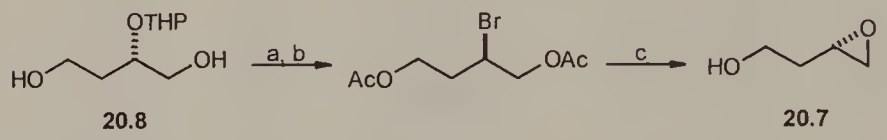
The inversion of configuration at C(2) in this process makes accessible derivatives of (*R*)-1,2,4-butanetriol from (*S*)-malic acid.

Epoxide **20.7** was obtained from the 2-*O*-THP derivative of 1,2,4-butanetriol (**20.8**) in a three-step sequence involving double inversion of configuration at C(2) (Scheme 20.4).



a: K_2CO_3, MeOH-THF, RT, 10h (85%)[7]
b: TsCl, pyridine (88%)
c: H_2SO_4, dioxane (80%)
d: K_2CO_3, MeOH (67%)[2]

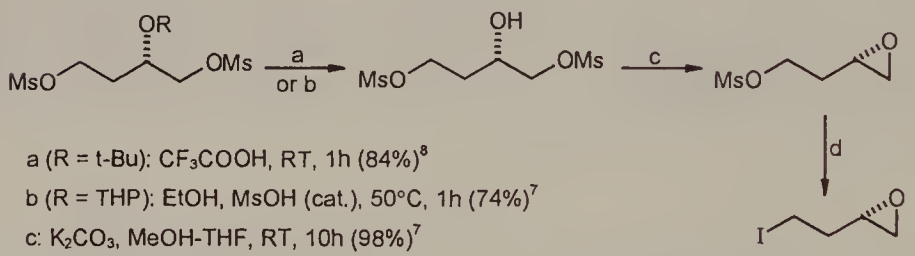
Scheme 20.3



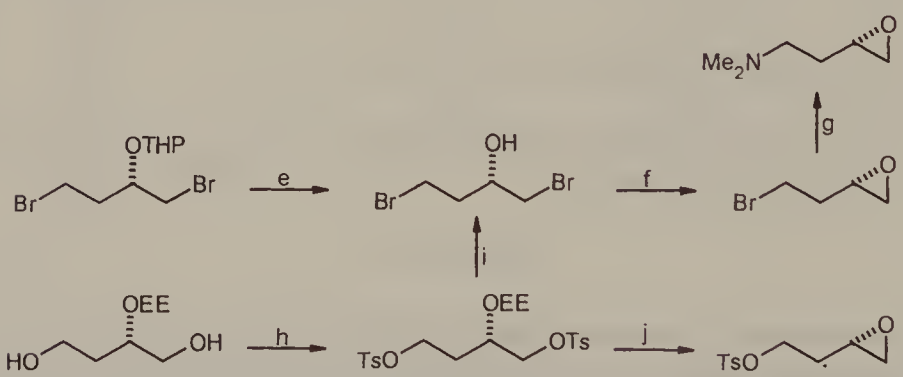
20.8 **20.7**

a: Ac_2O, pyridine, DMAP (cat.), CH_2Cl_2 (77%)
b: 45% HBr/AcOH, RT, 1h (88%)
c: K_2CO_3, MeOH-THF, RT (85%)[23]

Scheme 20.4



a (R = t-Bu): CF_3COOH, RT, 1h (84%)[8]
b (R = THP): EtOH, MsOH (cat.), 50°C, 1h (74%)[7]
c: K_2CO_3, MeOH-THF, RT, 10h (98%)[7]
d: NaI, K_2CO_3, Me_2CO, 0°-25°C, 2d (81%)[7]

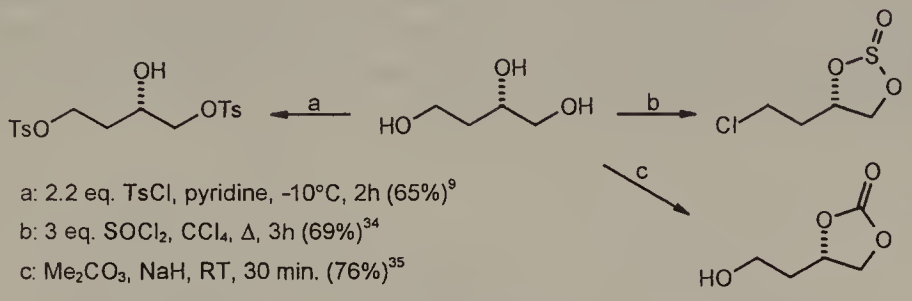


e: 5% HCl, MeOH-Me_2CO, RT, 6h (97% crude)[14]
f: KOH, H_2O, 40°C (76%)[14]
g: Me_2NH, Et_2O, RT (83%)[17]
h: TsCl, pyridine, 0°C (89-92%)[15,25]
i: LiBr, CuBr (cat.), $NaHCO_3$, Me_2CO, RT→ 50°C (79%)[15]
j: MeOH, PPTS (cat.), RT, 14h then K_2CO_3, RT, 7h (90%)[25]

Scheme 20.5

1,4-Di-*O*-activated butanetriol derivatives are of particular significance in synthesis. Differential activation of the C(1) and C(4) substituents is achieved by formation of the 1,2-epoxy group followed by sulfonylation and halogen substitution of the 4-hydroxy group (Scheme 20.5).

One-pot procedures for 1,4-diactivation of butanetriol by the formation of the ditosyl or the chlorosulfite derivatives have been reported (Scheme 20.6). Note the analogous selective formation of the 1,2-carbonate derivative of 1,2,4-butanetriol.

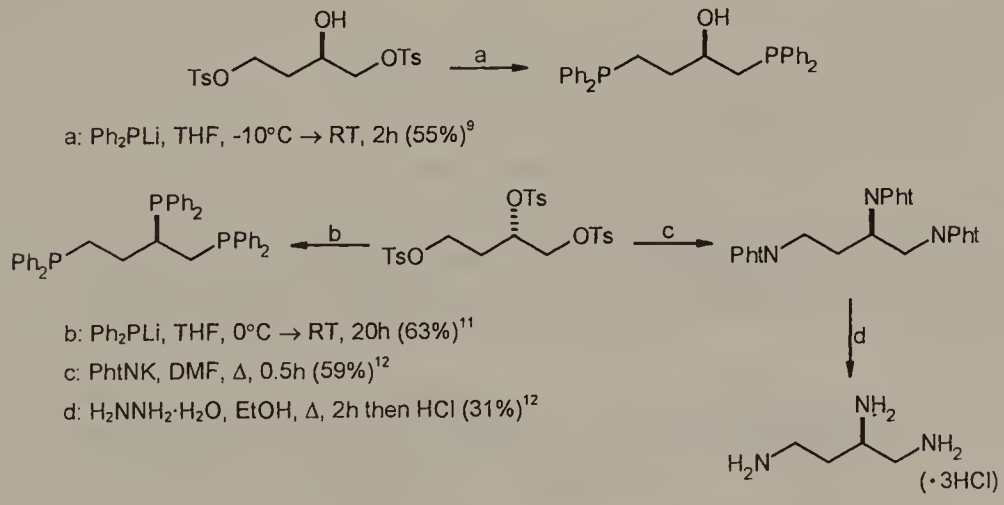


Scheme 20.6

(*S*)-4-Bromo-1,2-epoxybutane [*61847-07-2*] is commercially available.

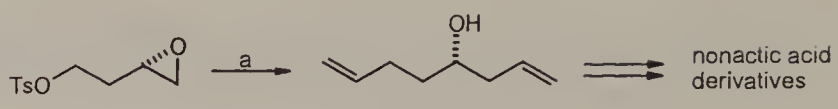
Applications

Nucleophilic substitution of the doubly or triply activated butanetriols with N- and P-nucleophiles yields the corresponding triamine or bis- and tris (diphenylphosphine) derivatives (Scheme 20.7).



Scheme 20.7

Doubly activated 1,2,4-butanetriol derivatives have found widespread use as electrophilic chiral building blocks. Bartlett used epoxytosylate **20.9** in the synthesis of nonactin[25] (Scheme 20.8).

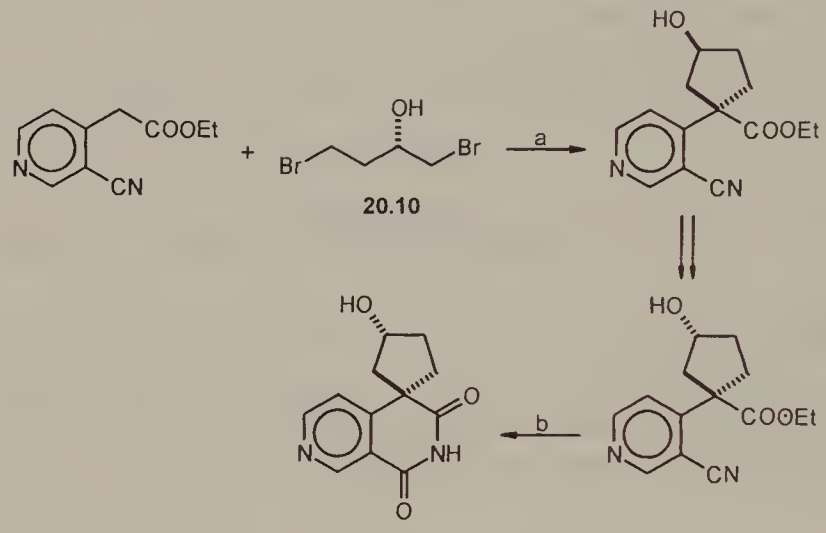


20.9

a: H_2C=CHLi, CuCN, THF, -78°→ 0°C, 6h (92%)[25]

Scheme 20.8

Tomioka and Koga synthesized (+)-sesbanine (**20.11**) in a series of reactions in which the highly stereoselective cycloannelation step with the dibromide **20.10** as an electrophile allowed generation of a chiral quaternary carbon center[36] (Scheme 20.9). The synthesis also involved inversion of configuration at the carbinol carbon atom by Mitsunobu reaction.

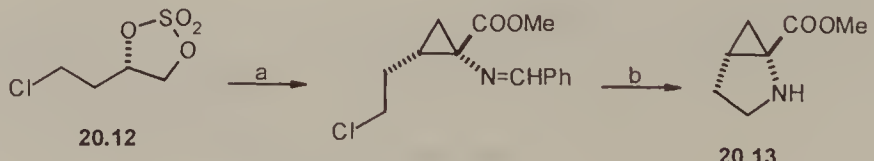


a: K_2CO_3, EtOH, 15°C, 24h (27%, single diastereoisomer)

b: H_2O_2, NaOH (cat.)[36]

Scheme 20.9

(−)-(2*S*,3*R*)-Methanoproline methyl ester (**20.13**) was synthesized for the first time by Hercouet from cyclic chlorosulfate **20.12**[34] (Scheme 20.10).



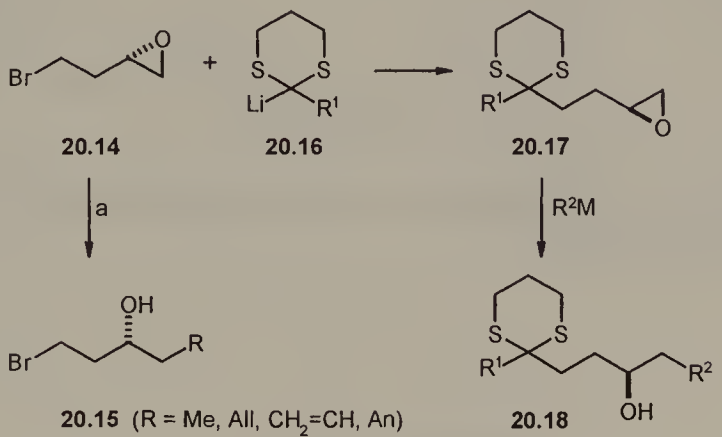
20.12 **20.13**

a: PhCH=NCH$_2$COOMe, 2 eq. NaH, DME, RT (quant.)

b: 1N HCl then K_2CO_3[34]

Scheme 20.10

Bromoepoxide **20.14** can be selectively substituted with carbon nucleophiles at either C(1) or C(4). Grignard reagents in the presence of Cu(I) salts selectively add to the epoxide at C(1) to give 1,3-bromohydrins **20.15**, as shown in Scheme 20.11.[37]

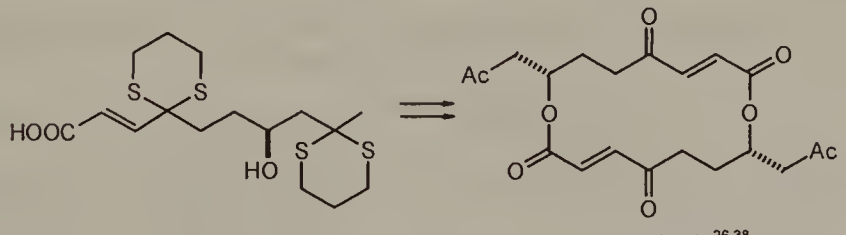


a: RMgX, CuI (cat.), THF, -30°→ 0°C (72-86%)[13,37]

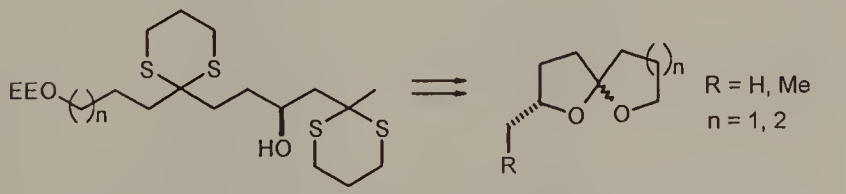
Scheme 20.11

Seebach *et al.* developed a highly useful and versatile protocol for chemoselective substitution of the bromoepoxide **20.14** at C(4) by 2-lithio-1,3-dithiane derivatives **20.16**. The resulting adduct **20.17** with the masked carbonyl group could further be functionalized at the oxirane terminus by either reduction with Selectride or by addition of organometallics (Scheme 20.11).

Some specific products **20.18** synthesized according to the above protocol are shown in Scheme 20.12.

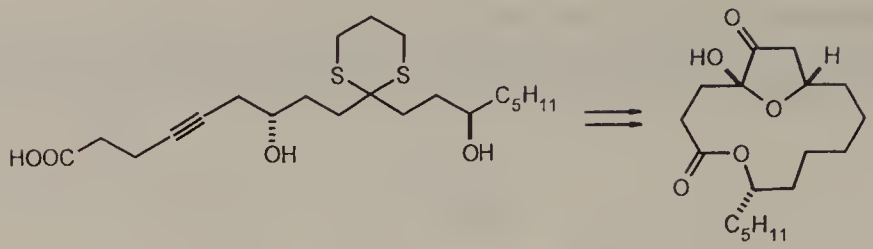


vermiculin[26,38]



1,6-dioxaspiro[4,4]nonane and
1,6-dioxaspiro[4,5]decane pheromones[15]

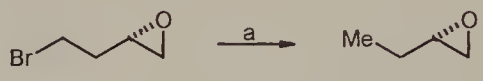
Scheme 20.12 (*continued*)



(+)-gloeosporone[39]

Scheme 20.12

Tributyltin hydride reduction of bromoepoxide **20.14** provides (*S*)-1,2-epoxy butane (Scheme 20.13).

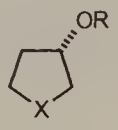


20.14

a: n-Bu_3SnH, 90°C (quant.)[14]

Scheme 20.13

20.2 DERIVATIVES OF 3-HYDROXYTETRAHYDROFURAN, 3-HYDROXYTETRAHYDROTHIOPHENE AND 3-HYDROXYPYRROLIDINE



III

Table 20.2 Five-membered heterocycles derived from (*S*)-1,2,4-butanetriol (III)

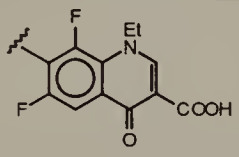
X	R	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
O	H	80/15	+17.5 (MeOH)	31
S	H	—	—	40
S	Ms	—	−19.9 (MeOH)	41
S	Ts	—	−16.8 (MeOH)	41
NH	H	108–110/8	−5.7 (MeOH)	42
NMe	H	103–106/37–40	+0.8 (neat)	43
NBn	H	116/0.9	−3.8 (MeOH)	42,44
NBn	Ts	68	−30.0 (MeOH)	45
NBn	Ac	—	−22.0 (MeOH)	45
NPh	H	80–82	+7.3 ($CHCl_3$)	46
NAc	TBS	—	+23.4 ($CHCl_3$)	47
NBoc	H	60–61	+22.7 ($CHCl_3$)	48
NBoc	Ac	—	+11.7 ($CHCl_3$)	48

(*continued*)

Table 20.2 (*continued*)

X	R	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
NCbz	H	—	+26.2 (MeOH)	49,50
NCbz	Ms	—	+27.3 (MeOH)	50
NPNZ	H	99–100	+18.5 ($CHCl_3$)	10
NPNZ	Ms	101–102	+25.6 ($CHCl_3$)	10
NHet[a]	H	—	−125.0 (0.1N NaOH)	51
NOH	All	—	+8.6 ($CHCl_3$)	8
NOH	t-Bu	—	+1.7 (CH_2Cl_2)	52
NOH	Bz	125	+3.7 (MeOH)	8
NOH	TBS	—	−0.1 ($CHCl_3$)	8

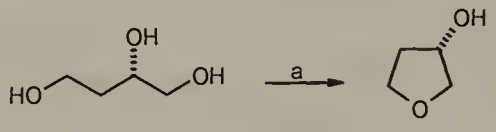
[a] Het =



Synthesis

Five-membered saturated heterocycles with tetrahydrofuran, tetrahydrothiophene, and pyrrolidine skeleton are available either by cyclization of 1,2,4-butanetriol derivatives or, in the case of 3-hydroxypyrrolidine derivatives, directly by reduction of malimides.

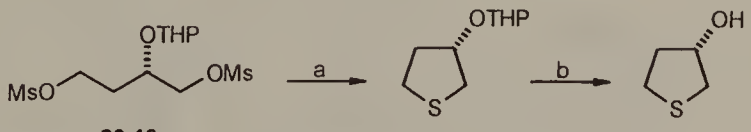
3-Hydroxytetrahydrofuran is available by acid-catalyzed cyclodehydration of 1,2,4-butanetriol, as reported by Wynberg *et al.*[31,53] (Scheme 20.14). The reaction proceeds without racemization.



a: TsOH (cat.), Δ (87%)[31]

Scheme 20.14

3-Hydroxytetrahydrothiophene was obtained by reaction of 2-*O*-protected 1,4-bis-mesylate **20.19** with lithium sulfide followed by deprotection[40] (Scheme 20.15).



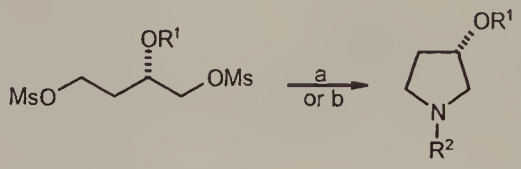
20.19

a: Li_2S (excess), DMF, 60°C, 6h (73%)

b: MeOH, TsOH (cat.), RT, 12h (88%)[40]

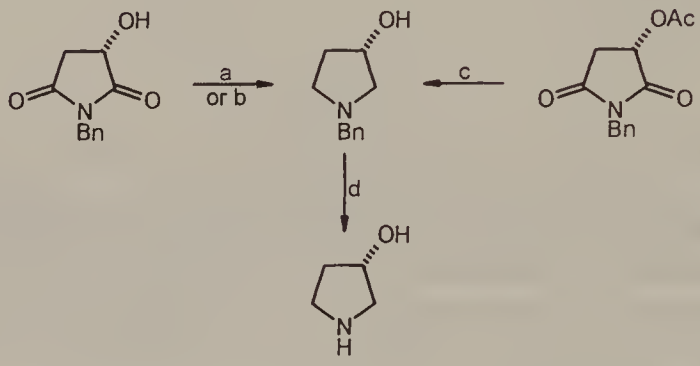
Scheme 20.15

Derivatives 3-hydroxypyrrolidine were synthesized by reactions of amines (or hydroxylamine) with 1,4-bis-*O*-mesylates of butanetriol (Scheme 20.16), or by reductions of malimides (Scheme 20.17). The latter method, although more direct, may proceed with partial racemization.



a(R^1 = Ms, R^2 = PNZ): NH_3, NEt_3, EtOH, RT then PNZCl, NEt_3, CH_2Cl_2, 0°C (67%)[10]
b(R^1 = t-Bu, All, Bz, TBS, R^2 = OH): $NH_2OH{\cdot}HCl$, NEt_3, Δ[8,52]

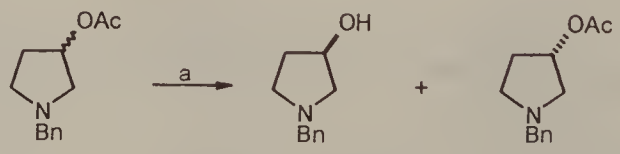
Scheme 20.16



a: $NaBH_4$, $BF_3{\cdot}OEt_2$, diglyme, 0°→100°C, 15h (73%, e.e. 80%)[44]
b: $LiAlH_4$, THF, Δ (66%)[48]
c: as b (64%)[42]
d: H_2 (5 atm.), 10% Pd/C (cat.), EtOH-AcOH (88%)[42]

Scheme 20.17

Enantiomerically pure 1-methyl- and 1-benzyl-3-hydroxypyrrolidines were readily obtained by resolution of the racemates with tartaric acid[43] and mandelic acid,[44] respectively. In addition, 3-acetoxy-1-benzylpyrrolidine was kinetically resolved by lipase PS-catalyzed hydrolysis[54] (Scheme 20.18).



40%, e.e. >99.5% 45%, e.e. >99.5%

a: lipase PS, phosphate buffer (pH 7.0)-dioxane, 25°C, 24h (conversion 50%)[54]

Scheme 20.18

The following are commercially available:

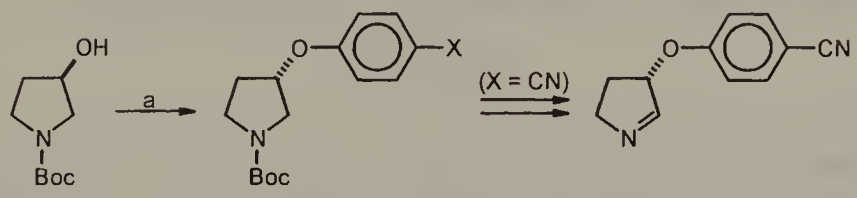
(*S*)-3-hydroxytetrahydrofuran [*86087-23-2*] and its enantiomer

(*R*)-3-pyrrolidinol [*2799-21-5*] and its hydrochloride [*104706-47-0*]

(*S*)-1-benzyl-3-pyrrolidinol [*101385-90-4*] and its enantiomer [*101930-07-8*].

Applications

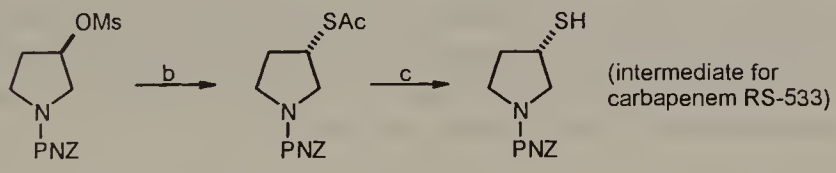
Derivatives of 3-pyrrolidinol were widely used in the synthesis of drugs, prodrugs, and naturally occuring compounds.[10,44,50,55] For this purpose 3-hydroxy substitution reactions were of significance; see the examples shown in Scheme 20.19.



X = CN (85%)[55]

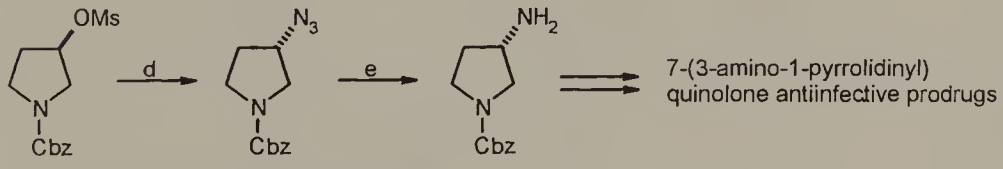
X = CHO, COCOOEt[56]

a: 4-XC_6H_4OH, PPh_3, DEAD, THF, RT (85%)[55]



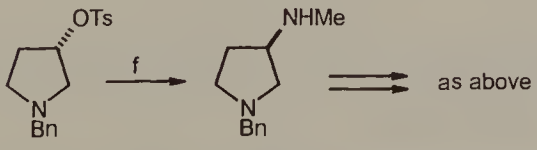
b: AcSNa, DMF, 65°C (92%)

c: MeONa, MeOH, RT then AcOH (98%)[10]



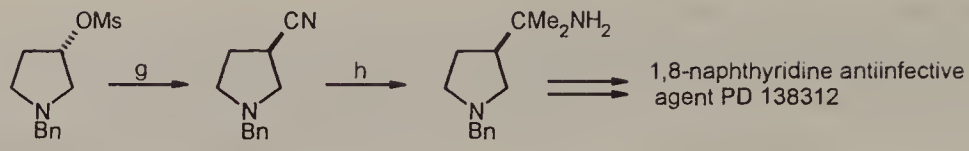
d: NaN_3, DMF, 100°C, 2h (98%)

e: H_2 (3.5 atm), Raney nickel (cat.), MeOH, RT (95%)[50]



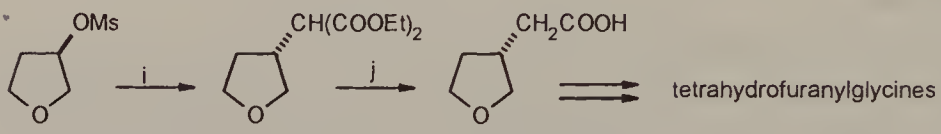
f: $MeNH_2$, EtOH, 140°C (pressure bottle), 20h (72%)[45]

Scheme 20.19 (*continued*)



g: 1.85 eq. n-Bu_4NCN, MeCN, 65°C, 6h (91%)

h: 4 eq. $MeCeCl_2$, THF, -70°C, 3h (86%)[57]



i: 5 eq. $CH_2(COOEt)_2$, NaH, DMF, 100°C, 12h (80%)

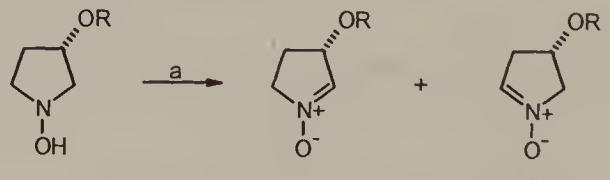
j: 1N NaOH, EtOH, 48h, then HCl, then 0.05 eq. Cu_2O, MeCN, Δ, 6h (87%)[58,59]

Scheme 20.19

For the application of *N*-phenyl substituted 3-pyrrolidinol in nonlinear optics see ref. 46.

Goti and Brandi developed a useful synthetic protocol for the synthesis of bicyclic heterocycles based on the regioselective formation of nitrones from *O*-protected 3-hydroxypyrrolines and their 1,3-dipolar cycloaddition to alkenes.

The regioselectivity in the HgO oxidation of *N*-hydroxy-3-substituted pyrrolidines to nitrones **A** and **B** is summarized in Scheme 20.20. The regioselectivity is influenced by the degree of electronegativity of the substituent in the 3-position; the greater the ability of the substituent to stabilize the negative charge, the higher the regioselectivity in the oxidation reaction.[8,52]



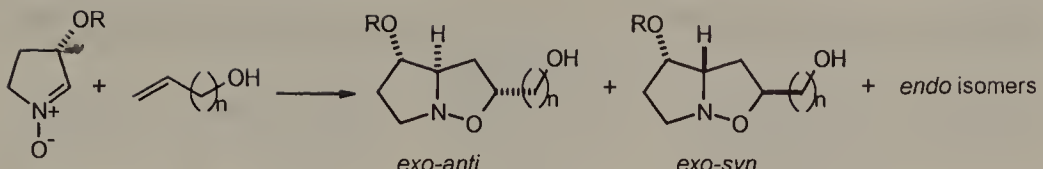
A **B**

R	yield A+B (%)	A : B
H	>24	5 : 1
t-Bu	80	9 : 1
All	100	9 : 1
TBS	>64	12 : 1
Bz	>50	>20 : 1

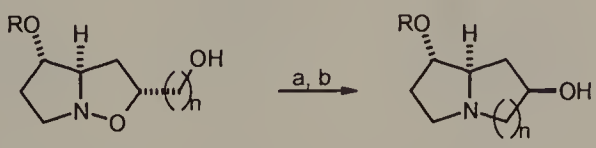
a: HgO (yellow), CH_2Cl_2, RT

Scheme 20.20

The major isomeric nitrones **A** were applied to the synthesis of pyrrolizidine and indolizidine derivatives by 1,3-dipolar cycloaddition (Scheme 20.21).



R = TBS (n =1)	4.6	:	1^{8}
R = t-Bu (n = 2)	8	:	1^{52}

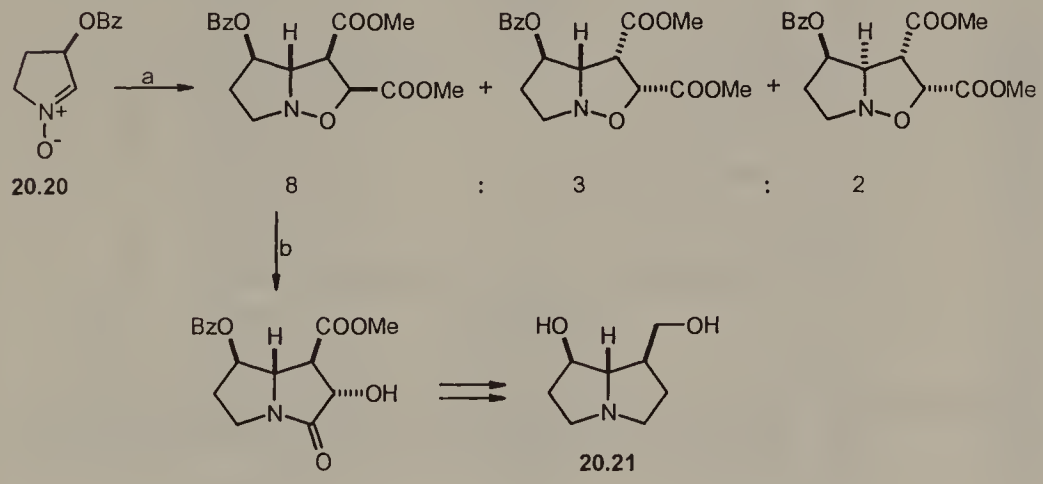


a: MsCl, NEt_3 or pyridine

b: H_2 (3 atm.), 10% Pd/C (70-82%)[8,52]

Scheme 20.21

According to the above synthetic protocol, the necine base (−)-hastanecine (**20.21**) has been synthesized by cycloaddition of the enantiopure nitrone **20.20** to dimethyl maleate[60] (Scheme 20.22).

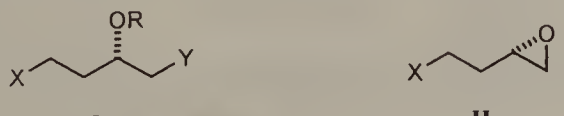


a: dimethyl maleate, benzene, RT (91%)

b: $Mo(CO)_6$, MeCN-H_2O, Δ (93%)[60]

Scheme 20.22

20.3 MONO-*O*-PROTECTED 1,2,4-BUTANETRIOLS



I **II**

Table 20.3 Mono-*O*-protected (*S*)-1,2,4-butanetriols and their derivatives (I, II)

Y	R	X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
			Formula I		
			1-protected		
OMe	H	OH	—	−28.8 ($CHCl_3$)	61
$OC_{18}H_{37}$	H	OH	60–61	+1.3 ($CHCl_3$)	62
OBn	H	OH	—	−7.7 (MeOH)	61,63
OBn	H	Br	—	−16.4 ($CHCl_3$)	37
OTr	H	OH	—	+15.8 ($CHCl_3$)	61
OBz	H	OH	—	−7.6 (MeOH)	64
OTBS	H	OH	—	−1.0 ($CHCl_3$)	65
OTBS	H	Br	—	−10.7 ($CHCl_3$)	13
OTBDPS	H	Br	—	−17.0 ($CHCl_3$)	13
$OP(O)O_2Ba$	H	OH	—	−2.5 (H_2O)[a]	66
			2-protected		
OH	Me	OH	90–95/0.04	−23.5 (Me_2CO)	67,68
OTs	Me	OTs	38–41	−15.4 (Me_2CO)	9,69
I	Me	I	30–40/0.1	−26.9 (Me_2CO)	69
OH	t-Bu	OH	100/0.05	+1.4 (CH_2Cl_2)	52
OMs	t-Bu	OMs	63	−15.4 (CH_2Cl_2)	52
OMs	All	OMs	—	−29.4 ($CHCl_3$)	8
OH	Bn	OH	—	−15.0 ($CHCl_3$)	70
NH_2	Bn	OH	—	+7.0 ($CHCl_3$)	70
OMs	Ph_2CH	OMs	—	−49.9 ($CHCl_3$)	71
OMs	Bz	OMs	68–69	−29.6 ($CHCl_3$)	8
OH	MOM	OH	—	−13.9 ($CHCl_3$)[b]	72
OH	MOM	NHCOOEt	—	+12.0 ($CHCl_3$)	73
OH	EE	OH	99/0.01	−21.7 (MeOH)	15,25
OTs	EE	OTs	—	−16.3 (Me_2CO)	25
OH	THP	OH	115–123/0.2	−47.1 (Me_2CO)	14,74
OMs	THP	OMs	68.5–70	−16.5 (Me_2CO)	74
OTs	THP	OTs	60–68	—	9,14
OMs	TBS	OMs	41–42	−13.3 ($CHCl_3$)	8
			4-protected		
OH	H	OBn	130/0.001	−22.6 (EtOH)[c]	33,75,76
OTs	Ts	OBn	—	−18.6 ($CHCl_3$)	77
OH	H	OMNB	—	−14.5 (Me_2CO)	78
OMs	H	OMNB	—	−11.1 ($CHCl_3$)	78
OH	H	OAn	64–65	−2.3 (MeOH)[a]	79
OH	H	OTBDPS	72–74	+5.4 ($CHCl_3$)	80,81
OH	H	OSEM	—	+1.2 ($CHCl_3$)	77
OTs	Ts	OSEM	—	−11.2 ($CHCl_3$)	77
OTs	Ts	OTHP	61.5–65	—	9
OH	H	OMTM	—	−12.9 ($CHCl_3$)	77

(*continued*)

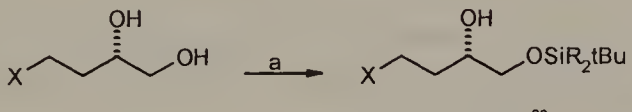
Table 20.3 (*continued*)

Y	R	X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
OTs	Ts	OMTM	—	−1.4 ($CHCl_3$)	77
OH	H	OPiv	—	−11.5 ($CHCl_3$)	82
OH	H	$OPO(OH)_2$	—	−20.4 (EtOH)	21
			Formula II		
—	—	OBn	57–60/0.005	−16.3 ($CHCl_3$)	33,76,83–86
—	—	OTBS	64–67/5	−12.8 ($CHCl_3$)	24,87
—	—	OTBDPS	46.5–47.5	−6.6 ($CHCl_3$)	80,88

[a] Enantiomer prepared. [b] At 546 nm.
[c] $[\alpha]_D$ in $CHCl_3$ appears highly concentration dependent (ref. 33,75,76,89).

Synthesis

Several methods are available for the synthesis of 1-protected 1,2,4-butanetriols. 4-Activated or substitued 1,2,4-butanetriols can be selectively 1-*O*-protected with bulky silylating agents (Scheme 20.23).

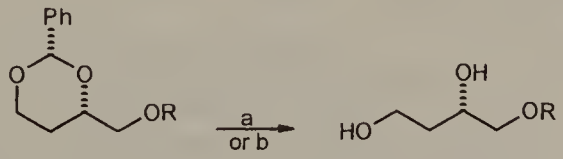


X = MsO, R = Ph[90]
X = Br, R = Ph[13]
X = EtOOCNH, R = Me[73]

a: t-BuR_2SiCl, imidazole and/or DMAP, NEt_3

Scheme 20.23

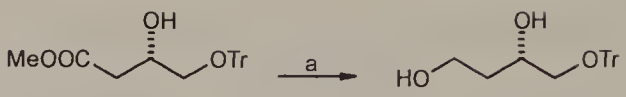
1-*O*-Protected 2,4-acetals of butanetriol afford 1-*O*-monoprotected derivatives on acidic hydrolysis or hydrogenolysis (Scheme 20.24).



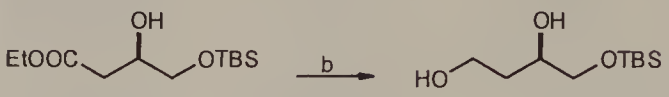
a (R = Me, Bn): H_2O-EtOH or THF, Amberlite resin or TsOH (cat.), RT, 12h[61,91]
b (R = $C_{18}H_{37}$): H_2, 10% Pd/C, AcOH (78%)[62]

Scheme 20.24

Reduction of 4-*O*-protected 3,4-dihydroxybutanoates is another preparative way to 1-*O*-protected butanetriols (Scheme 20.25).



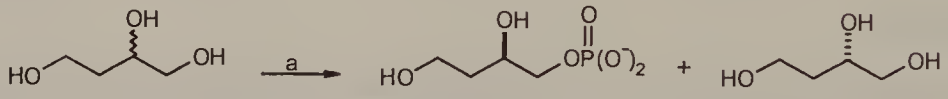
a: $LiAlH_4$, THF, RT, 2h (78%)[61]



b: $BH_3{\cdot}Me_2S$, THF, RT then $NaBH_4$ (cat), 10°C → RT (85.5%)[65]

Scheme 20.25

Whitesides kinetically resolved racemic 1,2,4-butanetriol by a highly enantioselective phosphorylation reaction catalyzed by glycerol kinase (E.C.2.7.1.30, ATP: glycerol-3-phosphotransferase; Scheme 20.26).



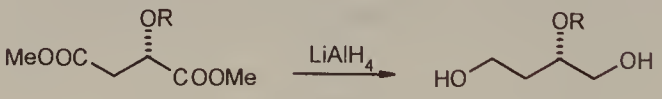
a: glycerol kinase, PK, ATP, PEP^-K^+ (0.5 equiv.), pH 7.5, 9d (97%, e.e. 95%)[66]

Scheme 20.26

Regioselective reductive opening of 2,3-epoxy-4-benzyloxy-1-butanol (prepared by Sharpless epoxidation) with Red-Al is an alternative route to 1-*O*-benzyl-1,2,4-butanetriol (Scheme 20.27).

a: Red-Al, THF, -20°→ 0°C (95-98%, regioselectivity 100 : 1)[92,93]

Scheme 20.27



R	yield (%)	ref
Me	64-69	9,67
t-Bu	83	52
Bn	98	70
Ph_2CH	>95	71
EE	92	15,25
$MeOCMe_2$	77	94
THP	55-89	9,14,23,95

Scheme 20.28 (*continued*)

R = t-Bu, THP (90-98%)[96]

Scheme 20.28

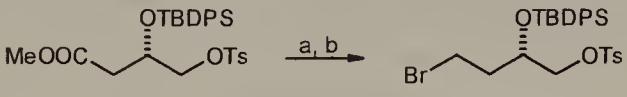
2-*O*-Protected 1,2,4-butanetriols are readily synthesized by the reduction of suitably 2-*O*-protected malates or malamates with $LiAlH_4$ in THF or diethyl ether (Scheme 20.28).

The reduction procedure is also applicable to 2-*O*-protected 3-*O*-sulfonylated tartrates (Scheme 20.29).

a: $LiAlH_4$, Et_2O, RT, 3d[72]

Scheme 20.29

Unsymmetrically 1,4-activated 2-*O*-protected butanetriol **20.23** was obtained from a derivative of 3,4-dihydroxybutanoic acid **20.22** (Scheme 20.30).



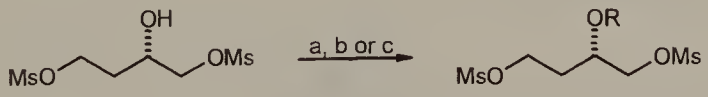
20.22 **20.23**

a: i-Bu_2AlH, CH_2Cl_2, -78°C, 2h

b: CBr_4, PPh_3, CH_2Cl_2, 0°C, 0.5h (75% overall)[97]

Scheme 20.30

1,4-Di-*O*-activated butanetriols can also serve as substrates for the preparation of 2-*O*-protected derivatives (Scheme 20.31).

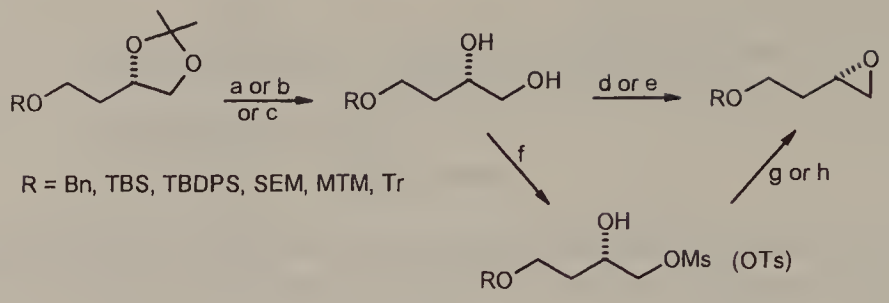


a (R =TBS): TBSCl, imidazole, DMF, 0°C → RT, 1d (84%)[8]

b (R = All): $Cl_3C(=NH)OAll$, TfOH, CH_2Cl_2, RT, 7d (58%)[8]

Scheme 20.31

4-*O*-Protected 1,2,4-butanetriols are most readily synthesized from their 1,2-*O*-isopropylidene derivatives according to Scheme 20.32. They can be further converted to the activated 1-*O*-sulfonyl or 1,2-epoxy derivatives.



a (R = Bn, MTM, SEM): MeOH, TsOH or HCl, RT (93%)[86,98]
or THF-H_2O, TsOH or H_2SO_4 or HCl (92-100%)[75,76,99,100]
or AcOH-H_2O (3:1), 40-50°C, 1h (95%)[77,83]

b (R = TBDPS): $HS(CH_2)_2SH$, TsOH, $CHCl_3$, Δ (60%)[101]
or MeOH, PPTS (cat.), RT (83%)[80]

c (R = Tr): EtOH-H_2O (5:1), Amberlite, RT, 12h (95%)[61]

d (R = Bn): Ph_3P, DEAD, benzene, Δ (63%)[98]
or Ph_3P, CCl_4, Δ then KOH, DMSO-H_2O, 55°C, 45 min. (52%)[76,85]

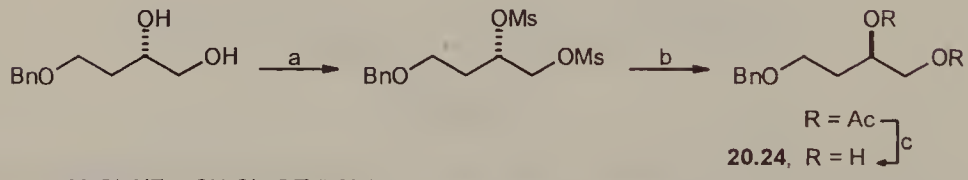
e (R = Bn): 2.5 eq. NaH, 1 eq. *N*-tosylimidazole, THF, 0°C (88%, e.e. 84%)[102]

f (R = Bn): 1.1 eq. MsCl or TsCl, pyridine, 0°C → RT, 20h (78-94%)[33,84,100,103]

g (R = Bn): DBU, THF, RT, 20h (63%)[84,100]
or NaOH, DMSO-H_2O, 0°C, 15 min.[33]
or K_2CO_3, MeOH, -10°C (98%)[103]

h (R = TBDPS): $BnMe_3N^+OH^-$, MeOH-Et_2O, RT, 30 min. (91%)[104]

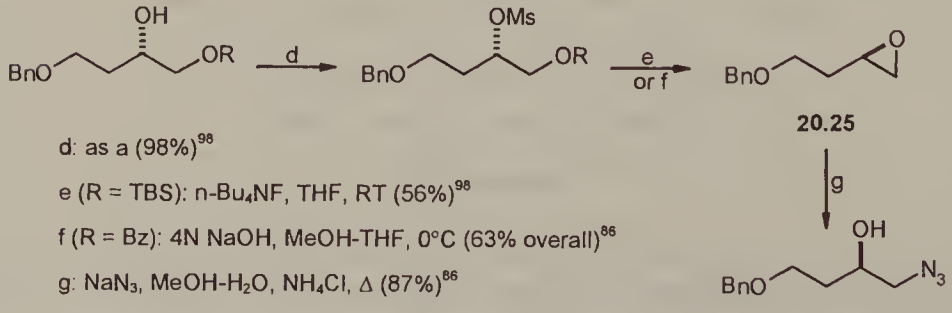
Scheme 20.32



a: MsCl, NEt_3, CH_2Cl_2, RT (79%)

b: AcOK, Ac_2O, Δ (41%)

c: K_2CO_3, MeOH (90%)[89]



d: as a (98%)[98]

e (R = TBS): n-Bu_4NF, THF, RT (56%)[98]

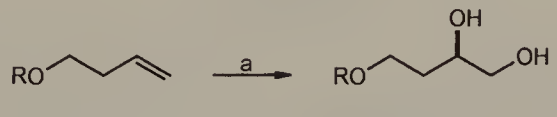
f (R = Bz): 4N NaOH, MeOH-THF, 0°C (63% overall)[86]

g: NaN_3, MeOH-H_2O, NH_4Cl, Δ (87%)[86]

Scheme 20.33

A modification of the above synthetic scheme was devised to produce 4-*O*-protected 1,2,4-butanetriol **20.24** or the epoxy derivative **20.25** with inverted configuration, thus making compounds of (*R*)-configuration available from the (*S*)-precursors (Scheme 20.33).

4-*O*-Protected 1,2,4-butanetriols were also synthesized by alternative methods, that is, from prochiral substrates by asymmetric synthesis. Corey introduced a modification of Sharpless asymmetric dihydroxylation which yielded the diol with good enantioselectivity in the case of 4-methoxyphenyl ether **20.26**[79] (Scheme 20.34).



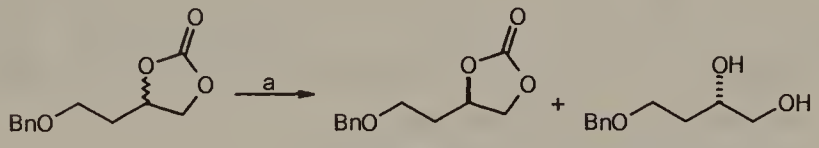
20.26 R = An 96%, e.e. 91%

R = Bn 97%, e.e. 52%

a: $K_3Fe(CN)_6$, K_2CO_3, $K_2OsO_4 \cdot 2H_2O$ (cat.), $(DHQD)_2PYDZ$ (cat.), t-BuOH-H_2O, RT[79]

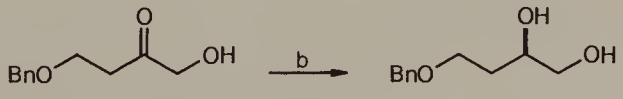
Scheme 20.34

4-*O*-Benzyl-1,2,4-butanetriol was kinetically resolved by hydrolysis of the cyclic 1,2-carbonate derivative catalyzed by porcine pancreas lipase (PPL).[105] Gerlach prepared (*R*)-4-*O*-benzyl-1,2,4-butanetriol of high enantiomeric excess by reduction of 4-benzyloxy-1-hydroxy-2-butanone with fermenting baker's yeast[76] (Scheme 20.35).



31% (e.e. >95%) 65% (e.e. 52%)

a: PPL, 0.1M phosphate buffer (pH 6.5), 10% i-Pr_2O, 30°C, 12h[105]

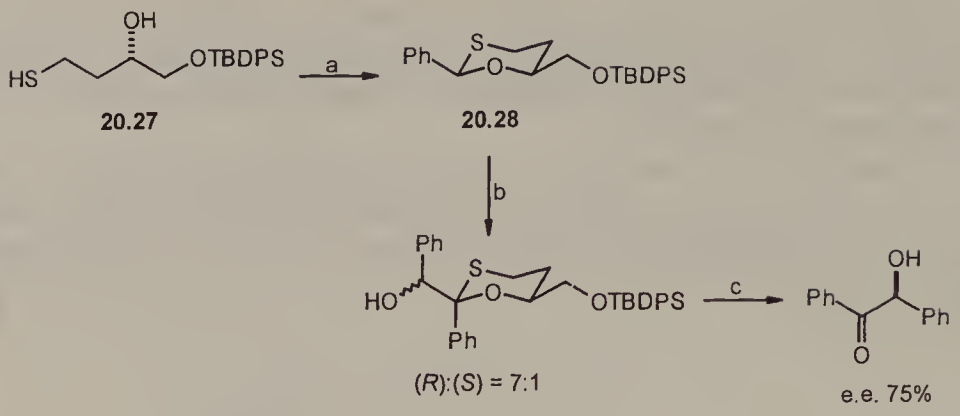


b: baker's yeast, sucrose, H_2O, RT, 2d (68%)[76]

Scheme 20.35

Applications

Chiral 1,3-oxathiane **20.28**, derived from benzaldehyde and 1-*O*-protected 4-deoxy 4-mercapto-1,2-butanediol (**20.27**), was diastereoselectively alkylated with benzaldehyde to give, after removal of the auxiliary, the optically active benzoin[90] (Scheme 20.36).



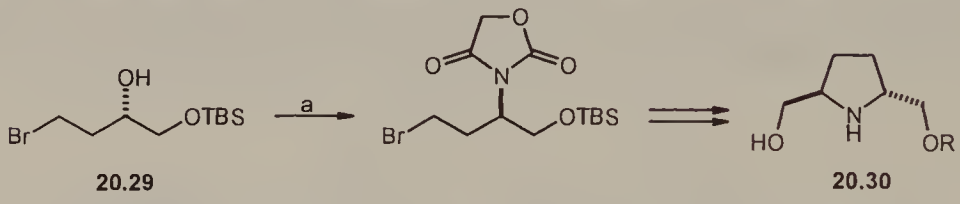
a: PhCHO, $BF_3{\cdot}Et_2O$, Et_2O

b: s-BuLi, THF, -78°C then $MgBr_2$, PhCHO

c: NCS, $AgNO_3$

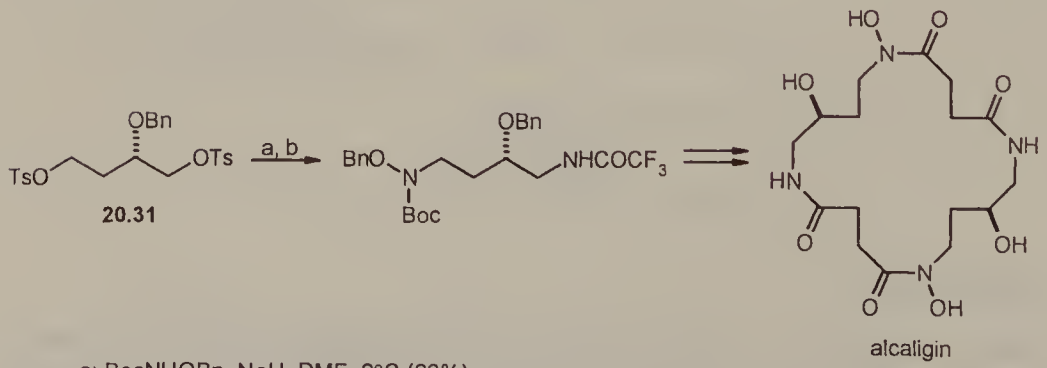
Scheme 20.36

trans-2,5-Disubstituted pyrrolidine derivative **20.30** was synthesized by Shibuya[13] from 1-*O*-protected 1,2,4-butanetriol derivative **20.29** (Scheme 20.37).



a: oxazolidine-2,4-dione, Ph_3P, DIAD, THF[13]

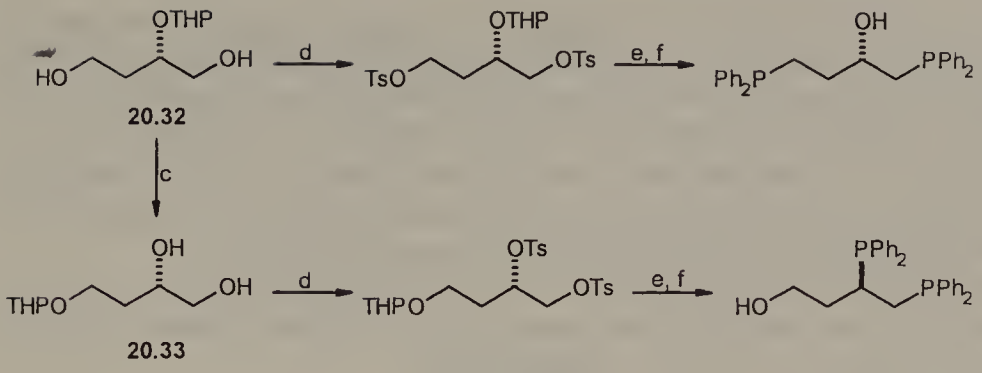
Scheme 20.37



a: BocNHOBn, NaH, DMF, 0°C (83%)

b: CF_3CONH_2, NaH, DMF, 80°C (62%)[106]

Scheme 20.38 (*continued*)



c: distillation (103-110°C/0.12 torr), yield 15-50%

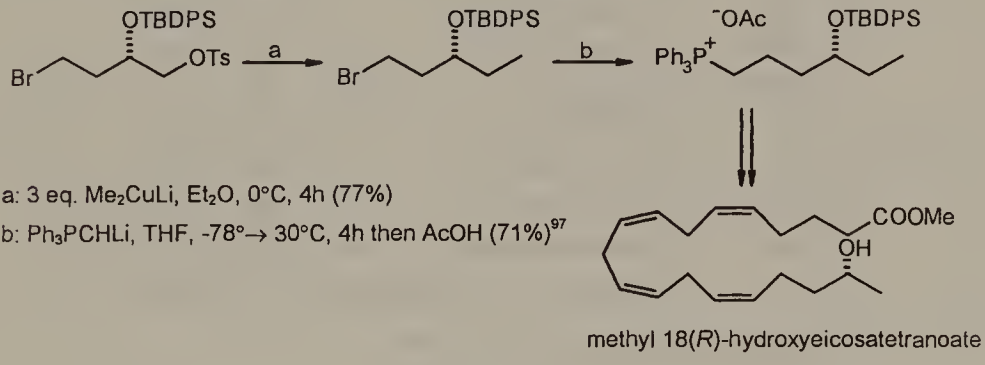
d: TsCl, pyridine, 0°C → RT (70-75%)

e: Ph_2PCl, Li, THF, 0°C → RT (27-43%)

f: CF_3COOH, MeOH-H_2O, Δ[9,77]

Scheme 20.38

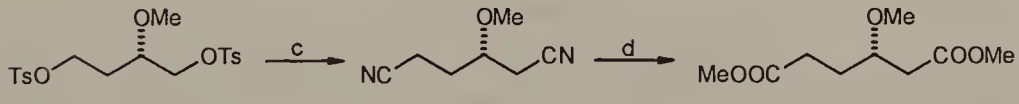
2-*O*-Protected 1,4-diactivated butanetriols were used as chiral four-carbon building blocks for the synthesis of 1,4-heteroatom substituted, carbon chain elongated, or carbocylic compounds (Schemes 20.38 and 20.39).



a: 3 eq. Me_2CuLi, Et_2O, 0°C, 4h (77%)

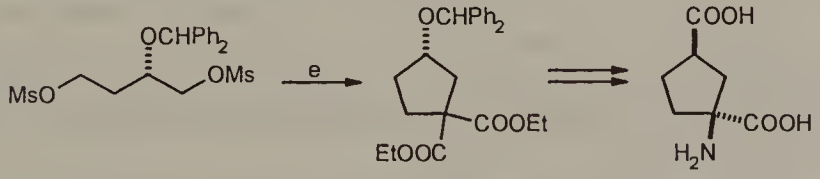
b: Ph_3PCHLi, THF, -78°→ 30°C, 4h then AcOH (71%)[97]

methyl 18(*R*)-hydroxyeicosatetranoate



c: NaCN, DMSO, RT (65% + 26% monosubstituted)[107]

d: MeOH, HCl, Δ then H_2O (78%)[107]



(1*S*,3*R*)-aminocyclopentane-1,3-dicarboxylic acid

e: $CH_2(COOEt)_2$, EtONa, EtOH, Δ (70%)[71]

Scheme 20.39

The first of the syntheses of Scheme 20.38 included regioselective sequential substitution of ditosylate **20.31** with nitrogen nucleophiles; the less sterically hindered C(4) tosylate was preferentially substituted in competition with the more sterically encumbered C(1) tosylate.[106] The second synthesis shown in Scheme 20.38 utilized the heat-induced isomerisation of 2-*O*-THP derivative of 1,2,4-butanetriol (**20.32**) to the 4-*O*-THP derivative **20.33**; both isomers were used for the synthesis of chiral bis(diphenylphosphine) ligands.[9]

4-*O*-Protected 1,2-epoxybutanols are excellent functionalized chirons for chain elongation reactions with organometallic reagents. Variants of this synthetic procedure are collected in Scheme 20.40.

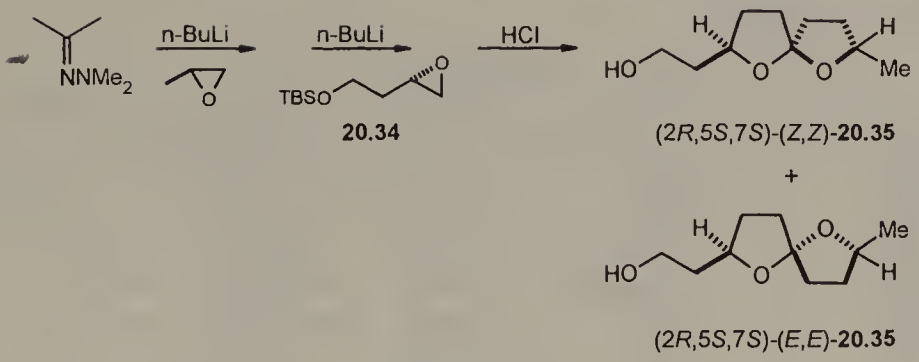
entry	R^1	R^2M	yield (%)	ref.
1	TBS	MeMgBr, CuBr	100	24
2	Bn	n-$C_{12}H_{25}$MgBr, COD·CuCl	92	76
3	Bn	CH_2=CH$(CH_2)_2$MgCl, Li_2CuCl_4	98	89,108
4	Bn	CH_2=CHMgBr, CuI	92-96	83,102
5	Bn	CH_2=C(Me)MgBr, CuI	97	109
6	TBDPS	n-$C_{10}H_{21}$Li, BF_3·Et_2O	90	88
7	TBDPS	CH_2=CHLi, CuCN	96	104
8	Bn	PhC≡CLi, BF_3· Et_2O	93	102
9	Bn	2-dithianyllithium	97	102
10	Bn	$TMSCH_2CHLiSO_2Ph$	92[a]	98
11	TBDPS	$TMSCH_2CHLiSO_2Ph$	87[a]	80
12	TBS	(*R*)-$BnOCH_2CH(Me)CHLiSO_2Ph$	94[a]	87,110

[a] mixture of diastereoisomers

Scheme 20.40

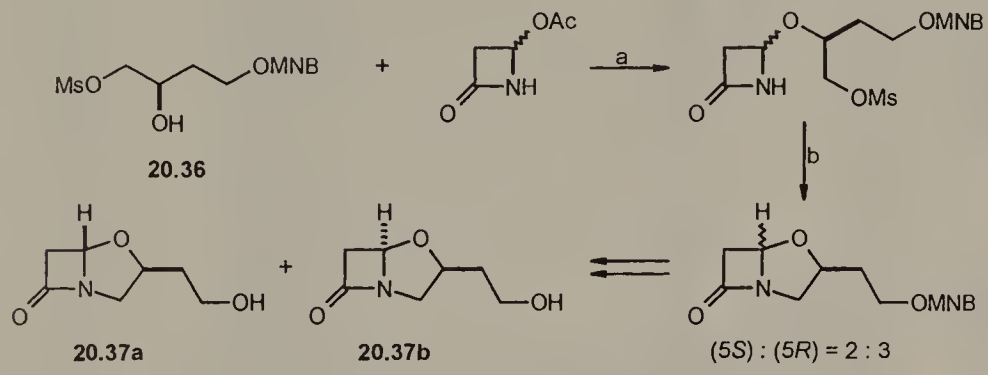
Some applications of the products shown in Scheme 20.40 include synthesis of (*S*)-α-lipoic acid (Golding,[89,108] from entry 3); the lactone portion of (+)-compactin and (+)-meviolin (Clive,[83,104] from entries 4 and 7); (+)-milbemycin β_3 (Kocieński,[109] from entry 5); tetrahydrolipstatin (Hanessian,[88] from entry 6); (methylenecyclopropyl)acetyl-CoA (Liu,[98] from entry 10); (methylenecyclopropyl)acetic acid and *syn*-1,3,5-triol chain (Wicha,[80] from entry 11); and (+)-lantrucunlin A (White,[110] from entry 12); see also the application in the synthesis of bryostatins (Vandewalle[111]).

An interesting application of the alkylation reaction of the acetone *N,N*-dimethylhydrazone anion sequentially with (*S*)-1,2-epoxypropane and epoxide **20.34**, is found in the synthesis of diastereomeric exogonols **20.35** by Kitching *et al.*[23] (Scheme 20.41).



Scheme 20.41

4-*O*-Protected 1-*O*-activated butanetriol derivative **20.36** with a carefully chosen 3-nitrobenzyl protecting group was used by Hoppe for the construction of the bicyclic skeleton of clavams in the sensitive β-lactam antibiotics **20.37**[78] (Scheme 20.42).

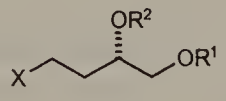


a: $Pd(OAc)_2$ (cat.), NEt_3, benzene, RT, 2d (70%)

b: K_2CO_3, NaI, HMPA, 70°C, 5h (56%)[78]

Scheme 20.42

20.4 1,2-DI-*O*-PROTECTED 1,2,4-BUTANETRIOLS



IV

Table 20.4 1,2-Di-*O*-protected (*S*)-1,2,4-butanetriols and their derivatives (IV)

R^1	R^2	X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
	$-CMe_2-$	OH	70–71/0.2	−2.2 to −3.2 (MeOH)	32,112–115
				+3.7 (Me_2CO)	86,116
	$-CMe_2-$	OTs	—	−15.7 (Me_2CO)	17,32,116

(*continued*)

Table 20.4 (*continued*)

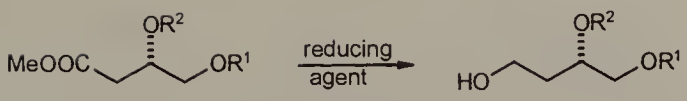
R^1	R^2	X	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
$-CMe_2-$		Cl	80/0.1	−14.3 ($CHCl_3$)	21,117
$-CMe_2-$		Br	89–90/19	−27.9 ($CHCl_3$)	13,118,119
$-CMe_2-$		I	112/26	−23.0 ($CHCl_3$)	82,116,120
$-CMe_2-$		NMe_2	40/0.6	+6.5 (neat)	17
$-CMe_2-$		9-adenyl	150	−9.8 (DMF)	19
$-CMe_2-$		Glu[a]	58–60	−15.6 ($CHCl_3$)	121
$-CEt_2-$		OH	100/0.5	+1.5 (CH_2Cl_2)	22,122
$-CEt_2-$		OTs	—	−15.4 (CH_2Cl_2)	122
$-CEt_2-$		I	73–75/0.5	—	22
$-CEt_2-$		NHCOOEt	—	+1.9 ($CHCl_3$)	73
$-CEt_2-$		$NHCOCF_3$	—	+18.1 (CH_2Cl_2)	122
$-CEt_2-$		NPht	—	+11.8 ($CHCl_3$)	73
$-CEt_2-$		$PO(OEt)_2$	125/0.5	−17.8 (Et_2O)	22
$-C(CH_2)_5-$		OH	—	−10.6 (MeOH)	27
$-C(CH_2)_5-$		Cl	—	−1.7 (CH_2Cl_2)	117
Me	Me	OH	68–70/0.02	−22.6 ($CHCl_3$)	75
n-$C_{16}H_{33}$	Bn	OH	—	−24.5 ($CHCl_3$)	113
n-$C_{18}H_{37}$	Ac	OH	—	−9.5 (EtOH)	103
n-$C_{18}H_{37}$	Ac	Cl	—	−11.8 (EtOH)	103
n-$C_{18}H_{37}$	Ac	$PO(OH)_2$	—	−5.0 (EtOH)	103
Bn	Bn	OH	—	−32.0 ($CHCl_3$)	82
Bn	Bn	I	—	−39.3 ($CHCl_3$)	82
Bn	THP	OH	—	−5.5 ($CHCl_3$)	37
Bz	Bz	OH	—	−9.1 ($CHCl_3$)	123
$C_{15}H_{31}CO$	$C_{15}H_{31}CO$	OH	58–60	−13.0 ($CHCl_3$)	21
MOM	$CH_2PO(Oi\text{-}Pr)_2$	OH	—	+3.4 (MeOH)	124
MOM	$CH_2PO(Oi\text{-}Pr)_2$	OMs	—	−17.9 (MeOH)	124
TBS	MOM	NHCOOEt	—	−50.0 ($CHCl_3$)	73
TBDPS	MEM	OH	—	−40.8 ($CHCl_3$)	125
TBDPS	THP	OH	—	+11.0 ($CHCl_3$)[b]	125
TBDPS	THP	OH	—	−25.1 ($CHCl_3$)[b]	125

[a] Tetra-*O*-acetyl-β-D-glucopyranosyl. [b] Rotations of the two diastereomers.

Synthesis

Reduction of suitably protected 3,4-dihydroxybutanoates is one of the frequently used methods for the synthesis of 1,2-*O*-diprotected butanetriols (Scheme 20.43).

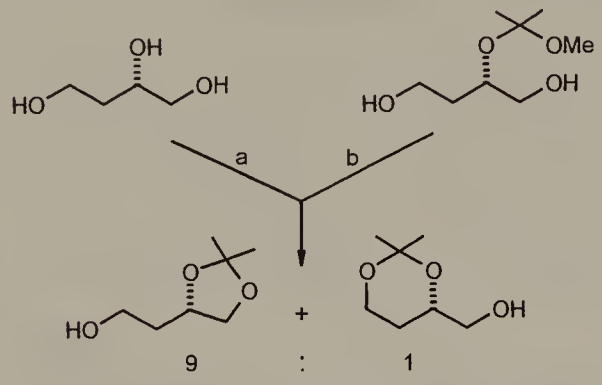
Since 1,2,4-butanetriol is directly available from malic acid, its 1,2-diprotection by the formation of a five-membered acetal appears to be an obvious choice. Indeed, ketones do form such acetals when reacted with 1,2,4-butanetriol under acidic conditions. For example 1,2-*O*-isopropylidene 1,2,4-butanetriol can be synthesized from diethyl malate in high overall yield (69%), without isolation of the intermediate 1,2,4-butanetriol.[82] However, contrary to the earlier reports,[128,129] a careful study of Meyers revealed that although the thermody-



reducing agent	R^1	R^2	yield (%)	ref.
$LiAlH_4$	$-CMe_2-$		70-92	86,98,113,115, 116,126,127
$LiAlH_4$	THP	Bn	>90	113
$LiBH_4$	TBDPS	MEM	90	125
$LiBH_4$	TBDPS	THP	89	125

Scheme 20.43

namic product of the reaction of acetone with 1,2,4-butanetriol is the five-membered 1,2-acetonide, it is invariably accompanied by 10% side product, the six-membered 2,4-acetonide[112,114] (Scheme 20.44).



a: Me_2CO, TsOH (cat.), RT, 14h (95-98% total yield)[1,32,112]

b: $BF_3{\cdot}Et_2O$ (cat.), Et_2O, 0°C→ RT, 48h (86-90% total yield)[112,114,129]

Scheme 20.44

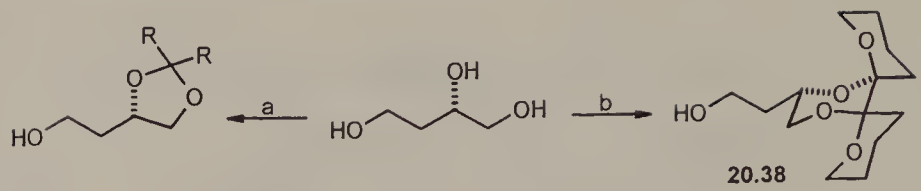
The acetonides could only be separated and purified by recrystallization of their 3,5-dinitrobenzoate derivatives.

The use of more bulky ketones such as diethyl ketone further destabilizes the six-membered 2,4-acetal; this allows the preparation of almost pure 1,2-acetals of 1,2,4-butanetriol (Scheme 20.45). Ketal **20.38** was used by Ley for the preparation of a stable glyceraldehyde derivative.[131]

A number of 4-activated derivatives of 1,2-*O*-isopropylidene-1,2,4-butanetriol have been synthesized according to Scheme 20.46.

Interestingly, 1,2-acetal diprotected 1,2,4-butanetriol was obtained by the isomerization reaction of the 2-*O*-ethoxyethyl protected precursor (Scheme 20.47). Note that direct protection of 1,2,4-butanetriol with aldehydes gives predominantly 2,4-acetals.

Moderate selectivity in the formation of the 1,2-diprotected derivative was observed in the acetylation of (*S*)-2-*O*-benzyl 1,2,4-butanetriol with vinyl acetate, catalyzed by PFL (*Pseudomonas fluorescens* lipase; Scheme 20.48).



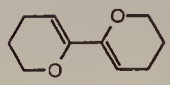
20.38

a (R, R = $(CH_2)_5$): cyclohexanone, TsOH (cat.), RT (85%), 95 : 5 mixture of isomers[27]

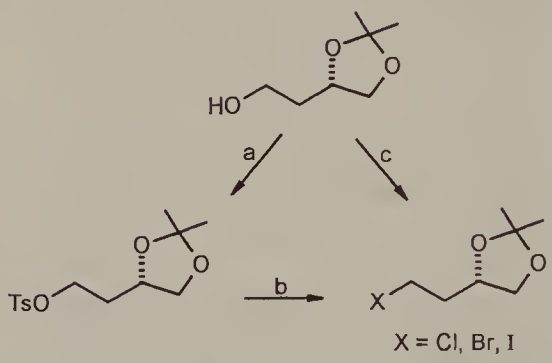
(R = Et): 3,3-dimethoxypentane, TsOH (cat.), CH_2Cl_2 or DMF, RT (71-93%),[104,130] 45 :1 ratio of isomers[130]

or 3-pentanone, TsOH (cat.), (71-92%)[22,122]

(R = i-Pr): 2,4-dimethyl-3-pentanone, TsOH (cat.), benzene, Δ (84%), single isomer[124]

b:  , CSA (cat.), PhMe, Δ (96%, single isomer)[131]

Scheme 20.45



a: TsCl, pyridine or NEt_3, CH_2Cl_2, 0°C→ RT (84-98%)[17,32,116,118,127,132]

b (X = Br): LiBr, THF or DMF (54-80%)[118,119,133]

b (X = I): NaI, Me_2CO (62-97%)[82,116,120,127]

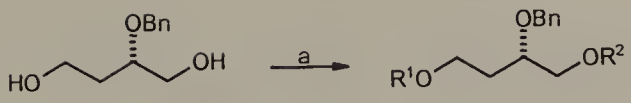
c (X = Cl): CCl_4, 1 eq. PPh_3, RT (61-86%)[17,21,134]

c (X = Br): 1.5 eq. CBr_4, 1eq. PPh_3, CH_2Cl_2, RT (77%)[1,128]

Scheme 20.46

a: $BF_3 \cdot Et_2O$ (cat.), Et_2O, RT (95%)[5,24]

Scheme 20.47

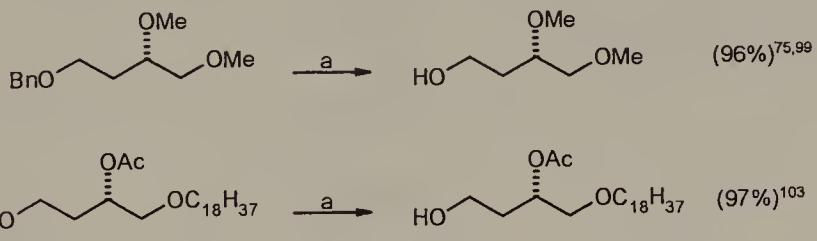


R^1 = H, R^2 = Ac 64%
R^1 = Ac, R^2 = H 7%
R^1 = R^2 = Ac 24%

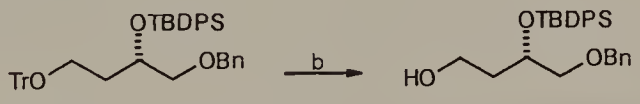
a: CH_2=CHOAc, PFL, $CHCl_3$, 24h (95% conversion)[135]

Scheme 20.48

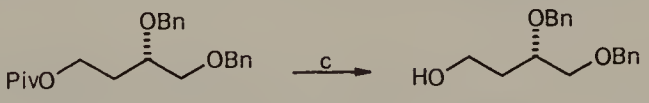
1,2-*O*-Diprotected derivatives are also available from the *O*-triprotected 1,2,4-butanetriols by selective removal of the 4-*O*-protecting group (Scheme 20.49).



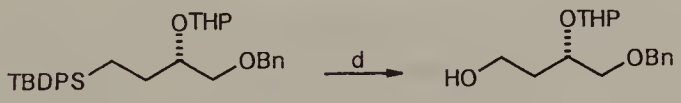
a: H_2, Pd/C, EtOH, RT



b: CF_3COOH-H_2O, CH_2Cl_2, -20°C[136]



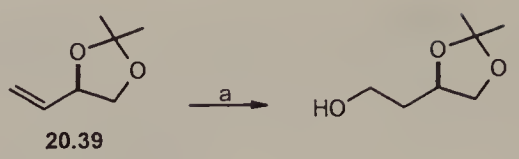
c: $LiAlH_4$, THF, Δ (97%)[82]



d: n-Bu_4NF, THF, RT (91%)[37]

Scheme 20.49

For the synthesis of (*R*)-1,2-*O*-isopropylidene 1,2,4-butanetriol the hydroboration-oxidation of the alkene **20.39**, available from L-ascorbic acid, appears to be a highly competitive method (Scheme 20.50).



20.39

a: 9-BBN, THF then H_2O_2, NaOH (79%)[137]

Scheme 20.50

Applications

B

4-Halo derivatives of 1,2-*O*-isopropylidene 1,2,4-butanetriol are versatile four-carbon chiral building blocks with masked diol functionality which can be used as both electrophilic and nucleophilic (*umpolung*) reagents (Fig. 20.2).

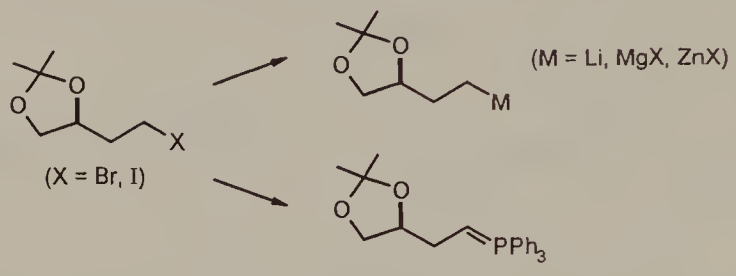
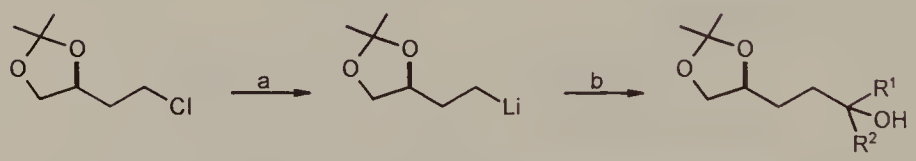
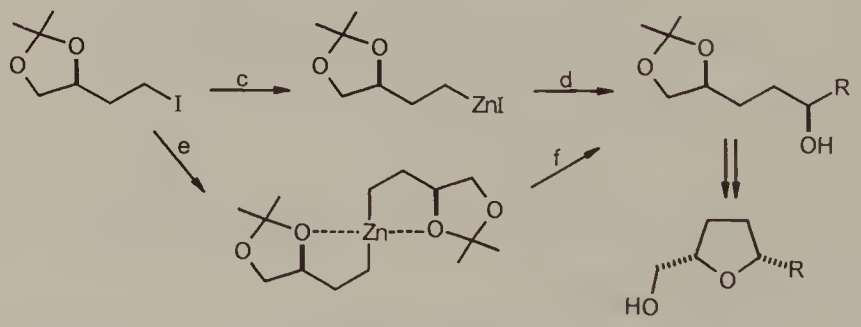


Figure 20.2



a: Li, 4,4'-di-*tert*-butylbiphenyl (cat.), THF, -78°C

b: R^1COR^2, -78°C, 20 min. then H_2O (m.d.)[117]



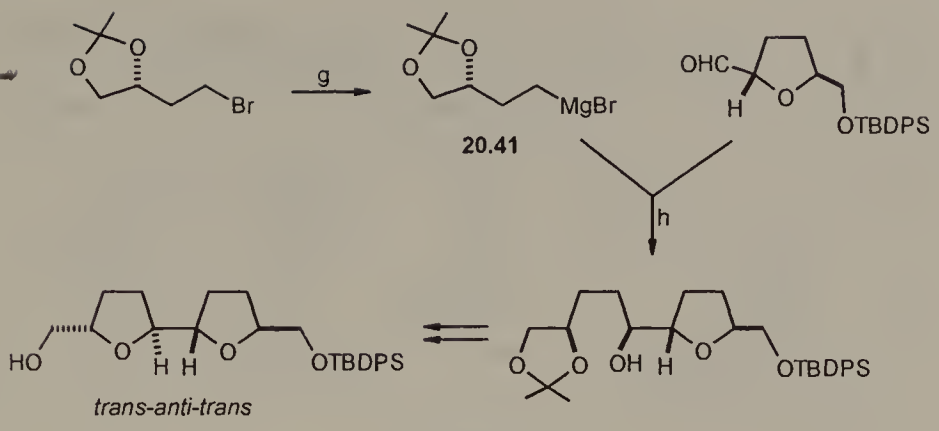
c: activated Zn, THF, 45-50°C (80-85%)

d: RCHO, $BF_3 \cdot Et_2O$, CH_2Cl_2,-30°→ 0°C, 3h (51-96%, 69-85% *syn*)[82]

e: 2 eq. Et_2Zn, CuI (cat.), 50°C

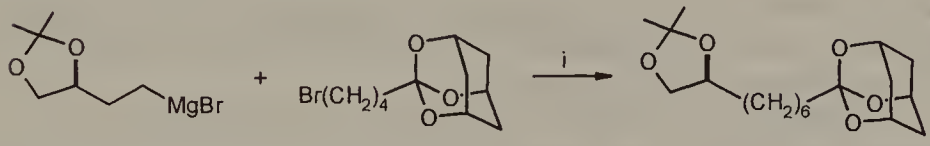
f: RCHO, $BF_3 \cdot Et_2O$, PhMe, -78°→ -30°C (52-89%, 84-95% *syn*)[138]

Scheme 20.51 (*continued*)

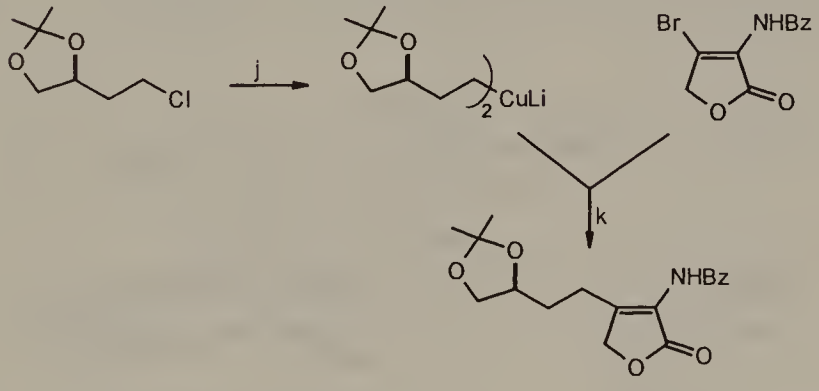


g: Mg, Et_2O, RT

h: 0.1 eq. $CuBr{\cdot}Me_2S$, Et_2O, -78°→ 0°C (70%, diastereoselectivity 92 : 8)[133]



i: Li_2CuCl_4 (cat.), THF, -78°C → RT (55%)[139]



j: Li, pentane, than CuI

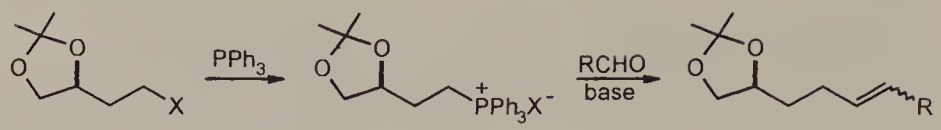
k: THF, -65°C, $PhNO_2$ quenching (91%)[134]

Scheme 20.51

In the latter case a number of organometallic reagents have been prepared and used for carbon-carbon bond formation (Scheme 20.51). Organozinc (**20.40**) and organomagnesium (**20.41**) reagents showed good diastereoselectivity in the addition to aldehydes; products of these reactions were further elaborated by Koert *et al.* to 2,6-disubstituted tetrahydrofurans of defined stereostructure.[82,138]

The chelation-controlled addition of *ent*-**20.41** to a chiral aldehyde allowed the construction of the bis-tetrahydrofuran moiety of (+)-rolliniastatin 1 in the highly stereoselective *cis-anti-cis* manner (Koert[140]).

Furthemore, 4-halo-1,2-*O*-isopropylidene derivatives were converted to chiral Wittig reagents and used for the carbon-carbon double bond formation (Scheme 20.52).



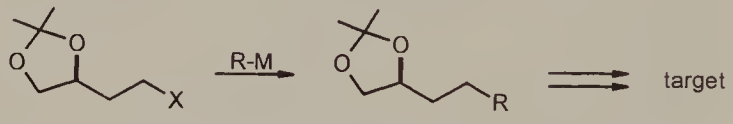
entry	R	X	base	yield (%)	config.	ref.
1	Bn	Br	n-BuLi	60	*E*	1,128
2	n-Pr	I	n-BuLi	84	*Z*[a]	141
3	n-C_5H_{11}	I	n-BuLi, HMPA	84	*Z*	116
4	(*S*)-MeCHNHCbz	I	KH	81	*Z*	142

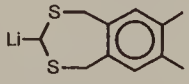
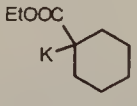
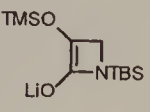
[a] in addition 14% *E*

Scheme 20.52

Products of Scheme 20.52 were used for the synthesis of (+)-5-(4′,5′-dihydroxypentyl)uracil (entry 1, Nakanishi[1,128]), 12(*S*)-HETE (entry 3, Mosset[116]), and 6-*epi*-D-purpurosamine (entry 4, Ohno[142]).

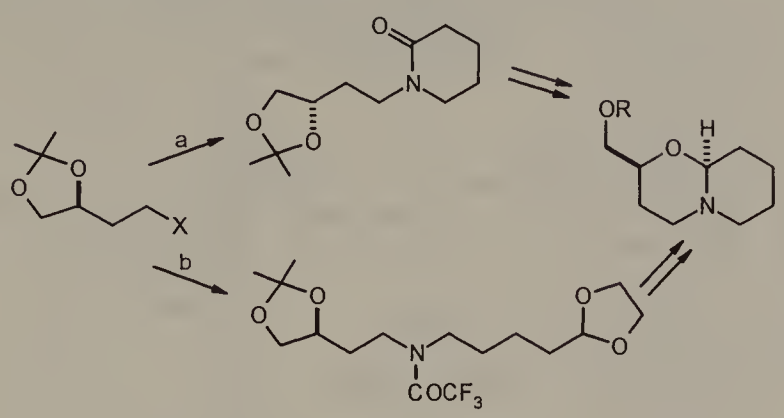
As electrophiles, 4-activated 1,2-*O*-diprotected derivatives of 1,2,4-butanetriol were used for the formation of C–C, C–N, C–P, and C–S bonds. Examples of such reactions are shown in Schemes 20.53 and 20.54.



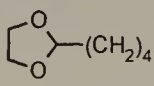
X	RM	yield (%)	target compound(s)
Br	n-PrMgBr	77	(+)-pulvilloric acid (Gerlach[143])
Br	LiC≡CLi (0.5 eq.)	41	2,5-linked dimeric tetrahydrofurans (Koert[144])
Br		88	3-hydroxy-1,7-dioxaspiro [5.5]undecane (Mori[118])
I	n-PrC≡CLi	-	(-)-bullatacin (Hoye[145])
I		60	phoracantholide (Sakai[146])
I	$LiCH_2C(OLi)=CHCOOEt$	96	*cis*-2,6-disubstituted tetrahydropyran (Kotsuki[147])
I	$LiCH_2C(ONa)=CHCOOMe$	63	2,8-dimethyl-1,7-dioxaspiro [5.5]undecane (Mori[120])
I		72	3-alkyl-3-hydroxyazetidin-2-ones (Dolle[148])
OTs	NaCN	82	(*S*)-(-)-3-piperidinol (Olsen[132])

Scheme 20.53

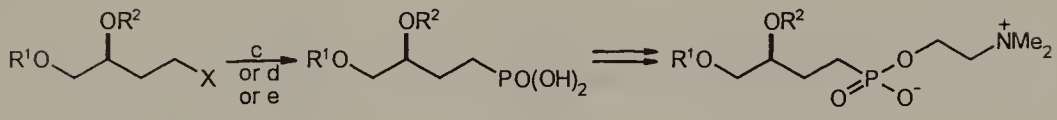
Synthesis of 1-oxaquinolizidines (Ahn,[127] Welch,[32,122])



a (X = I): δ-valerolactam, t-BuOK, THF, 50°C (70%)[127]

b (X = OTs):  , NaH, DMF, 80°C (42%)[32]

Synthesis of PAF (Nakamura,[113] Engel[103]) and phospholipid (Martin[149]) analogues

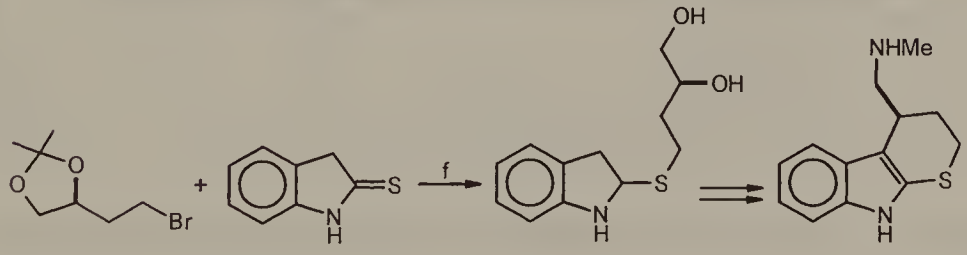


c ($R^1 = C_{16}H_{33}$, R^2 = Bn, X = Br): $P(OSiMe_3)_3$, 150°C, 22h then EtOH (79%)[113]

d ($R^1 = C_{18}H_{37}$, R^2 = Ac, X = Cl): $P(OMe)_3$,140°C, 48h (59%)[103]

e (R^1,$R^2 = CMe_2$, X = Br): $P(OEt)_3$, 165-175°C, 6h (86%)[149]

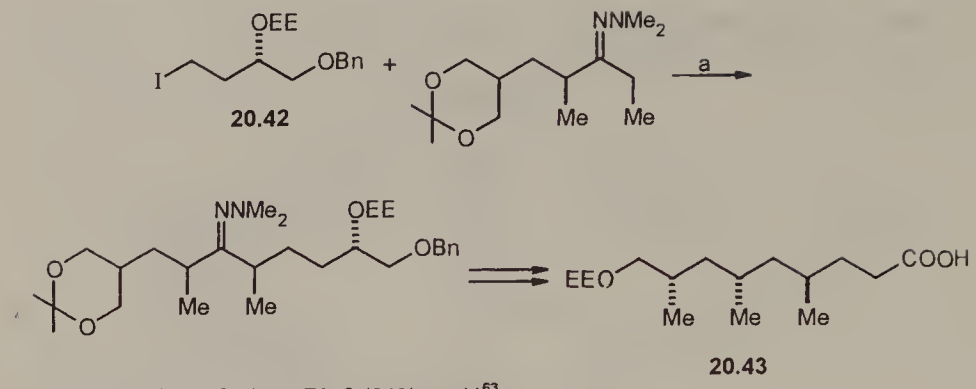
Synthesis of 4-methylaminomethyl-2,3,4,9-tetrahydrothiopyrano[2,3-*b*]indole (Makisumi[119])



f: K_2CO_3, Me_2CO, RT, 4h then MeOH, HCl, RT (84%)[119]

Scheme 20.54

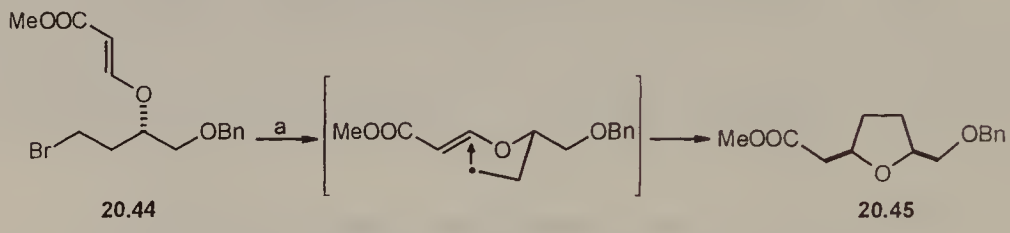
An outline of Schreiber's synthesis of ionomycin fragment **20.43** from iodide **20.42** is shown in Scheme 20.55. Note that the carboxylic group of the product is introduced by oxidative destruction of the chiral center provided by **20.42**.



a: LDA, THF, 0°C, then -78°C (91%, m.d.)[63]

Scheme 20.55

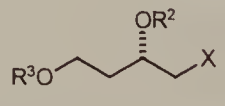
Shibuya *et al.* obtained *cis*-2,5-disubstituted tetrahydrofuran **20.45** by a highly diastereoselective radical cyclization of acrylate **20.44** derived from 1,2,4-butanetriol[37] (Scheme 20.56).



a: n-Bu_3SnH, Et_3B, PhMe, 0°C (93%, single isomer)[37]

Scheme 20.56

20.5 1,4- AND 2,4-DI-*O*-PROTECTED 1,2,4-BUTANETRIOLS



V

Table 20.5 1,4- and 2,4-Di-*O*-protected (*S*)-1,2,4-butanetriols and their derivatives (V)

X	R^2	R^3	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
			1,4-diprotected		
$C_{18}H_{37}O$	H	Bn	—	−15.7 (EtOH)	103
BnO	H	Bn	—	−7.3 (EtOH)	150
BnO	NH_2	Bn	—	−13.2 (EtOH)	150

(*continued*)

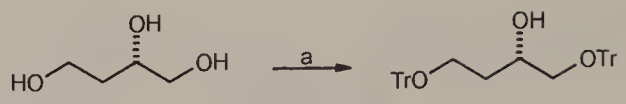
Table 20.5 (*continued*)

X	R^2	R^3	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
BnO	NPht	Bn	—	−17.4 (EtOH)	150
BnO	H	TIBS	—	−7.3 (CH_2Cl_2)	151
BnO	H	TBDPS	—	−1.0 ($CHCl_3$)	81
TrO	H	Tr	—	+10.4 (CH_2Cl_2)	2
TrO	Ts	Tr	—	+3.2 (CH_2Cl_2)	2
AcO	H	Ac	—	−16.8 (neat)	7
AcO	Ms	Ac	—	−8.7 (CH_2Cl_2)	7
BzO	H	Bn	—	−4.3 (EtOH)	86
Bz	H	Tr	—	−6.2 ($CHCl_3$)	64
TIBSO	H	Bn	—	−5.0 (CH_2Cl_2)	151
Ph_3SiO	H	Bn	—	−0.55 (CH_2Cl_2)	151
			2,4-diprotected		
HO	–CH_2–		—	+24.8 ($CHCl_3$)[a]	72
MsO	–CH_2–		73.5–74.5	+13.3 (CH_2Cl_2)	30
HO	–CMe_2–		—	+16.7 ($CHCl_3$)	65,152
TsO	–CMe_2–		57.5–59	+1.7 ($CHCl_3$)	152
I	–CMe_2–		94–95/9	+24.3 ($CHCl_3$)	152
HO	–CHPh–		63–64	+7.6 (MeOH)[b]	61
TsO	–CHPh–		64–65	−2.3 ($CHCl_3$)	118,153
Br	–CHPh–		111–114/0.4	+35.3 ($CHCl_3$)	118
N3	–CHPh–		—	+6.4 ($CHCl_3$)	154
HO	–2-BrC_6H_4CH–		—	−15.7 ($CHCl_3$)	125
$PhSO_2O$	–2-BrC_6H_4CH–		—	−5.4 ($CHCl_3$)	125
HO	–4-MeC_6H_4CH–		—	+8.0 ($CHCl_3$)	155
HO	–CHAn–		—	+10.3 ($CHCl_3$)	156
HO	Me	Tr	—	+2.3 ($CHCl_3$)	68
HO	Bn	MEM	—	−1.0 ($CHCl_3$)	113
HO	Bn	TIPS	—	−2.8 ($CHCl_3$)	70
H_2N	Bn	TIPS	—	−4.8 ($CHCl_3$)	70
BzNH	Bz	Bz	54–55	−26.0 ($CHCl_3$)	157

[a] At 546 nm [b] $[\alpha]_D$ +106 ($CHCl_3$) was reported erroneously in ref. 4 (cf. ref. 156,158)

Synthesis

1,4-Di-*O*-protected butanetriols are available from 4-*O*-monoprotected precursors, taking advantage of the difference in reactivity of the primary C(1) and the secondary C(2) hydroxy groups. The 1,4-di-*O*-trityl derivative can be synthesized directly from 1,2,4-butanetriol (Scheme 20.57).



a: TrCl, pyridine (75%)[2]

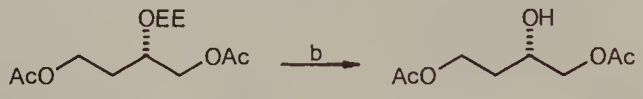
R^1	R^2	reagents	yield (%)	ref.
Bn[a]	$C_{18}H_{37}$	$C_{18}H_{37}OH$, BF_3, CH_2Cl_2	97	103
Bn	MTr	MTrCl, NEt_3, CH_2Cl_2	84	159
Bn	Bz	BzCl, pyridine, CH_2Cl_2	75[b]	86
Bn	TBDPS	TBDPSCl, DMAP, CH_2Cl_2 or pyridine	94-97	98,160
TBDPS	Bn	Bu_2SnO, BnBr, Bu_4NBr, PhMe	87	81
TBDPS	Piv	PivCl, NEt_3, CH_2Cl_2	93	101

[a] reaction with 1,2 epoxide [b] side product: 1,2-dibenzoate (10%)

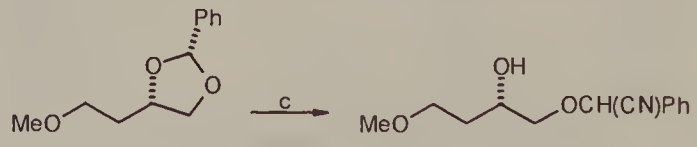
Scheme 20.57

Another synthetic entry to the 1,4-di-*O*-protected butanetriols is from the triprotected derivatives (Scheme 20.58).

a: HCl-MeOH, RT (84%)[150]



b: HCl, THF-H_2O, RT (100% crude)[24]

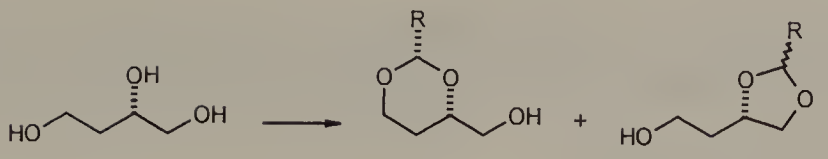


c: Me_3SiCN, $TiCl_4$, CH_2Cl_2 (82-98%, regioselectivity 22 :1 to 250 :1)[91]

Scheme 20.58

The most important route to 2,4-di-*O*-protected butanetriols is based on the acetalization of 1,2,4-butanetriol with aldehydes or their dimethyl acetals. In contrast to the analogous reaction of ketones, the reaction preferentially gives 2,4-acetals having *cis*-configuration (**A**) (Scheme 20.59).

The side products of this reaction are diastereoisomeric 1,2-acetals (**B**) and traces of the *trans* diastereomer of **A**. Acetal **A** (R = Ph) was also obtained by transacetalization of 1,2-*O*-isopropylidene-1,2,4-butanetriol with benzaldehyde.[158]



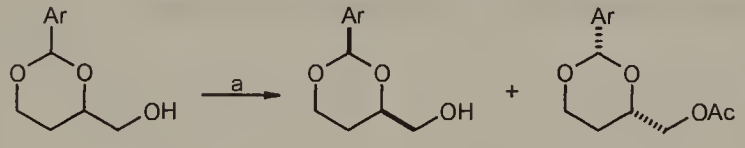
A B

R	reagents	yield (%)	A : B	ref.
H	paraformaldehyde, MsOH	77 (A+B)	77 : 23	90
H	$H_2C(OMe)_2$,TsOH	[a]	A only	161
Me	$MeCH(OEt)_2$,CSA	77 (A)	[a]	162
Ph	PhCHO, TsOH	87 (A)	ca. 9 : 1	29
Ph	PhCHO, CF_3COOH	82 (A+B)	85 : 15	153
Ph	$PhCH(OMe)_2$, HBF_4 or TsOH	80 (A)	ca. 10 : 1	4,29,91
2-BrC_6H_4	2-$BrC_6H_4CH(OMe)_2$, TsOH	82 (A)	91 : 9	125
3,4,5-$(MeO)_3C_6H_2$	3,4,5-$(MeO)_3C_6H_2CH(OMe)_2$, TsOH	79 (A)	a	163
Fer[b]	$FerCH(OMe)_2$, TsOH	85 (A)	a	164

[a] not determined [b] Fer = ferrocenyl

Scheme 20.59

Herradón developed a kinetic resolution of racemic acetals **A** by lipase catalyzed transesterification in organic solvents. The best results were obtained with *Pseudomonas fluorescens* lipase (PFL).[155,165] The enantioselectivity of the reaction was found to be solvent-dependent[156] (Scheme 20.60).



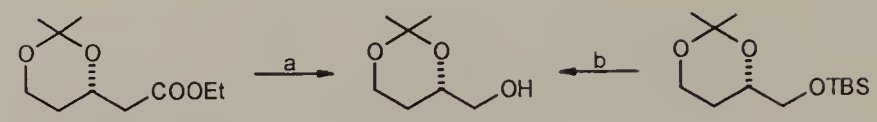
A

Ar	solvent	yield, % (e.e., %) alcohol	ester	ref.
Ph	THF	31 (>98)	42 (86)	165
Ph	benzene	32 (>98)	49 (83)	165
An	toluene	38 (91)	40 (90)	156
An	wet $CHCl_3$	44 (98)	44 (83)	156

a: CH_2=CHOAc, PFL, RT, conversion 50-54%

Scheme 20.60

The 2,4-*O*-isopropylidene derivative of 1,2,4-butanetriol is available either by reduction of the 2,4-*O*-isopropylidene derivatives of 2,4-dihydroxybutanoates or by selective deprotection of the tri-*O*-protected precursors (Scheme 20.61).



a: $LiAlH_4$, Et_2O, RT (82%)[152]

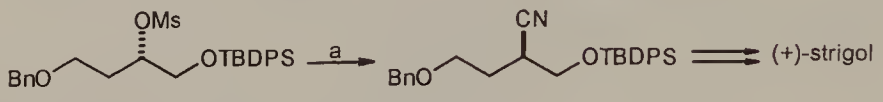
b: Bu_4NF, THF, RT (85%)[65]

Scheme 20.61

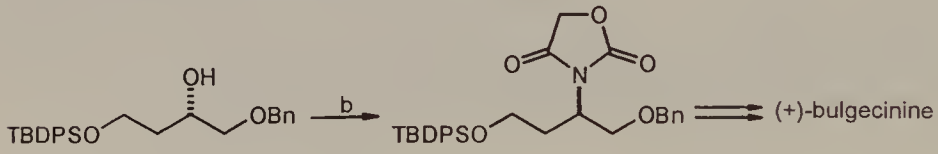
Applications

B

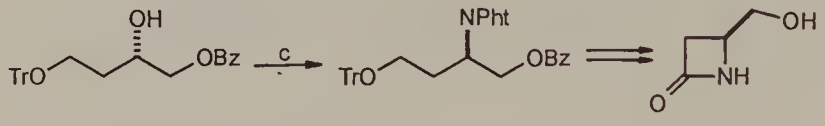
1,4-Di-*O*-protected butanetriols are commonly used as chiral substrates for the introduction of a new substituent at the chiral center with full control of stereochemistry. Some examples are shown in Scheme 20.62.



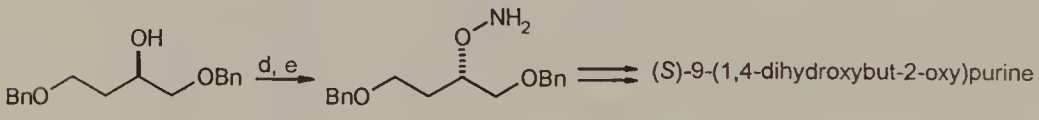
a: $BnNBu_3CN$, Me_3SiCN, MeCN, Δ (56%)[160]



b: oxazolidine-2,4-dione, PPh_3, DIAD, THF, 0°C → RT, 12h (65%)[81]



c: phthalimide (Mitsunobu reaction), 78%[64]



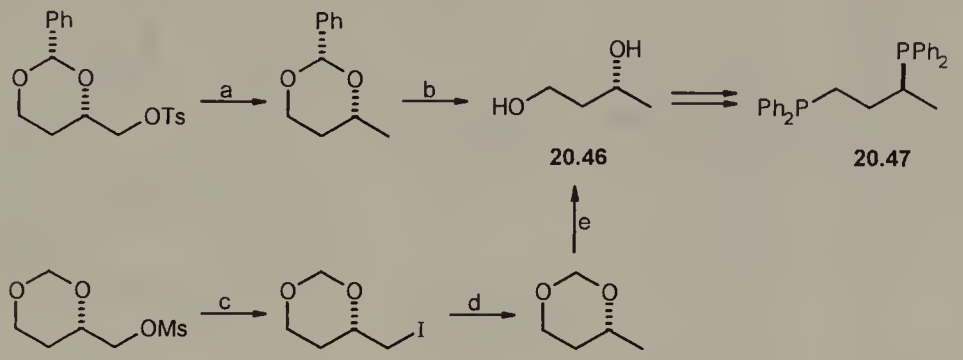
d: *N*-hydroxyphthalimide, PPh_3, DEAD, THF, 0°C → RT (91%)

e: $MeNHNH_2$, CH_2Cl_2, 0°C (76%)[150]

f: PhSNa, THF-DMF (71%)[2]

Scheme 20.62

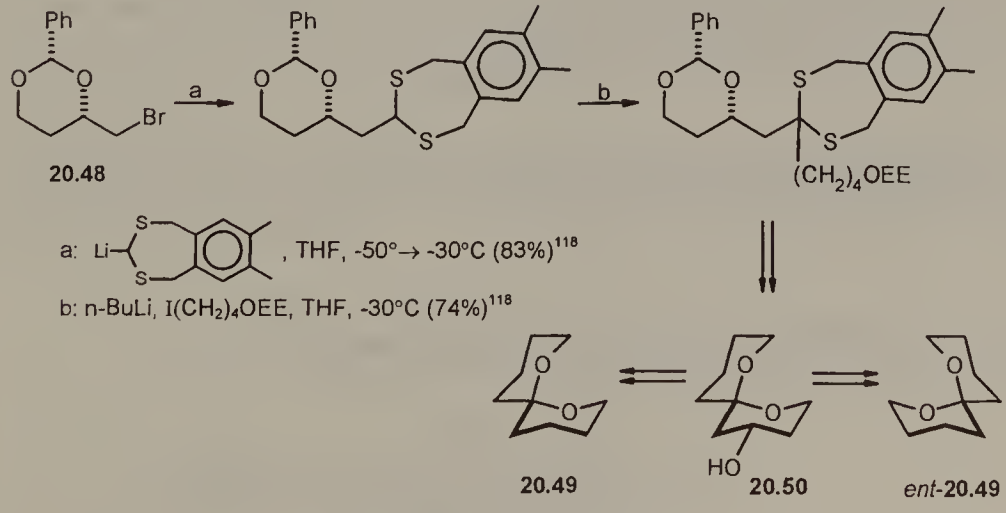
Likewise, 2,4-di-*O*-protected 1-activated butanetriols were used for substitutions at C(1) with a variety of nucleophiles. An example is the synthesis of enantiomerically pure (*R*)-1,3-butanediol (**20.46**), a precursor of chiral diphosphine ligand (*S*)-chairphos[30] (**20.47**), Scheme 20.63.



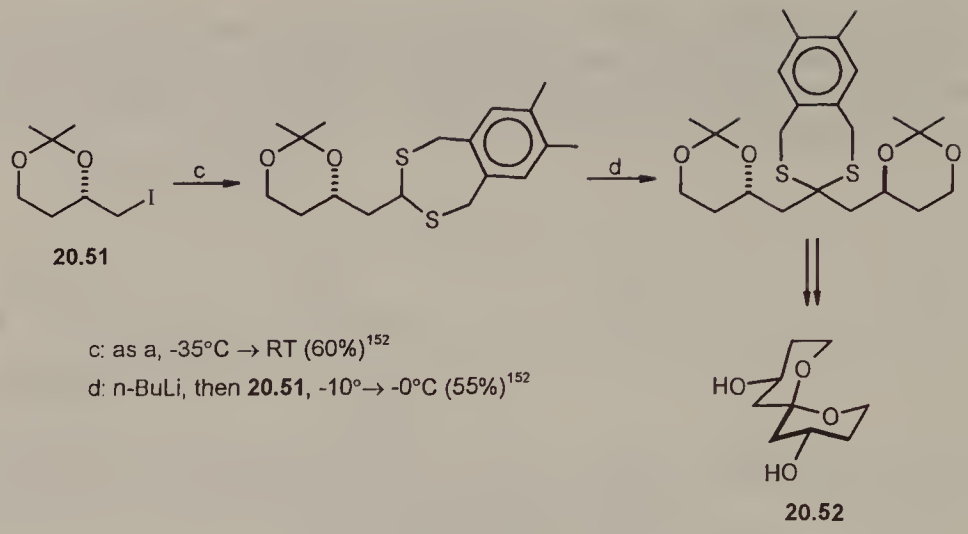
a: $LiBHEt_3$, THF, -60°C → RT (90%)[153]
b: H_2, 20% $Pd(OH)_2/C$, AcOEt, RT (87%)[153]
c: KI, DMF, 100-120°C[30]
d: H_2, 10% Pd/C, NEt_3, Et_2O (98%)[30]
e: 2,4-dinitrophenylhydrazine, HCl (75%)[30]

Scheme 20.63

Enantiomers of 1,7-dioxaspiro[5.5]undecane **20.49** and *ent*- **20.49**, the olive fly pheromone, and its hydroxy derivatives (**20.50** and **20.52**) were synthesized by Mori from 2,4-acetals of butanetriol **20.48** and **20.51** by C(1) substitution with 1,3-dithiane nucleophile, a formyl anion equivalent, followed by alkylation (Scheme 20.64).

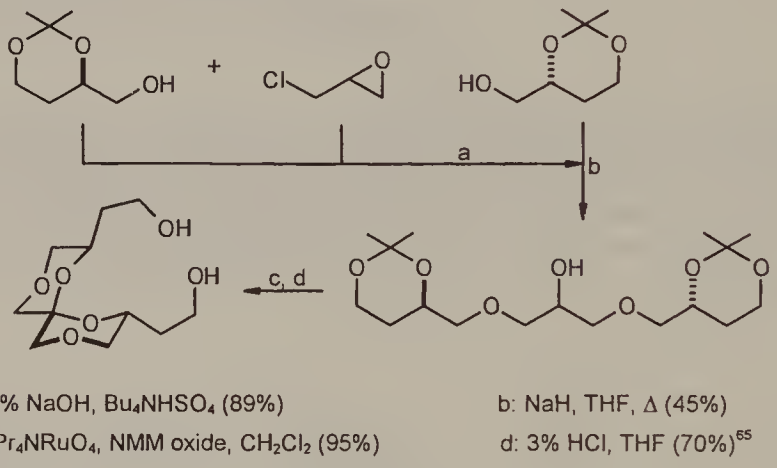


Scheme 20.64 (*continued*)



Scheme 20.64

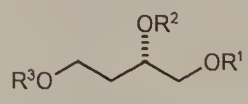
The substituted 1,4,7,10-tetraoxaspiro[5.5]undecane system has been synthesized from 2,4-*O*-isopropylidene butanetriol by condensation with an equivalent of 1,3-dihydroxyacetone (Scheme 20.65).



Scheme 20.65

1-Pyrrole substituted 2,4-*O*-benzylidene butanetriol was used for the synthesis of *C*-acyclic nucleoside analogues.[166]

20.6 TRI-*O*-PROTECTED 1,2,4-BUTANETRIOLS



VI

Table 20.6 Tri-*O*-protected (*S*)-1,2,4-butanetriols (VI)

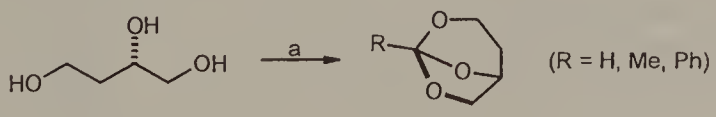
R^1	R^2	R^3	m.p. (°C) or b.p. (°C/torr)	$[\alpha]_D$ (solvent)	References
Me	Me	Bn	96–100/0.3	−13.2 ($CHCl_3$)	75
$C_{18}H_{37}$	Ac	Bn	—	−14.9 (EtOH)	103
$C_{18}H_{37}$	–CHPh–		58–59	+0.7 ($CHCl_3$)	62
Bn	Bn	Bn	—	−49.6 ($CHCl_3$)	167
Bn	MOM	Bn	—	−16.0 (EtOH)	150
–CHMe–		Ac	108–109/27	+19.4 ($CHCl_3$)	24
$–CMe_2–$		Bn	98–102/0.05	−1.7 ($CHCl_3$)[a]	75,76,86,100
$–CMe_2–$		MTM	—	+8.3 ($CHCl_3$)	77
$–CMe_2–$		DNB	62–63	−13.7 ($CHCl_3$)	114,115,168
$–CMe_2–$		SEM	—	+7.5 ($CHCl_3$)	77
$–CMe_2–$		TBDPS	—	+3.0 ($CHCl_3$)	80
Ac	–CHPh–		—	+27.1 ($CHCl_3$)	156
Ac	Ac	Bn	—	−20.5 (CCl_4)	169
Ac	Ac	Ac	—	−10.8 (MeOH)	27,170
$C_{15}H_{31}CO$	$C_{15}H_{31}CO$	Bn	40–41	−9.4 ($CHCl_3$)	21
Bz	Bz	Bn	—	+26.9 ($CHCl_3$)[b]	123
Bz	Bz	Ac	—	−30.9 ($CHCl_3$)	123
DNB	DNB	DNB	172–174	−40.7 (pyridine)	27
TBS	$–CMe_2–$		—	−7.0 ($CHCl_3$)	65
TBS	Bn	TBS	—	−24.0 ($CHCl_3$)	70
TIPS	Bn	TIPS	—	−20.0 ($CHCl_3$)	70
TBDPS	Bn	TBDPS	—	−13.0 ($CHCl_3$)	70

[a] $[\alpha]_D$ +3.1 ($CHCl_3$) in ref. 123. [b] $[\alpha]_D$ −4.0 ($CHCl_3$) in ref. 86.

Synthesis

Triprotected 1,2,4-butanetriols play a central role in the protection scheme (Fig. 20.1) and can be obtained by a variety of conventional methods from precursors bearing a smaller number of protecting groups, such as 2-, 1,2-, 1,4- and 2,4-*O*-protected derivatives. A number of specific compounds with differing protecting groups are displayed in Table 20.6.

A rather non-conventional bicyclic orthoesters **20.53**, derivatives of 2,7,8-trioxabicyclo[3.2.1]octane, were synthesized by Verkade *et al.* from (*S*)-1,2,4-butanetriol[171] (Scheme 20.66).



20.53

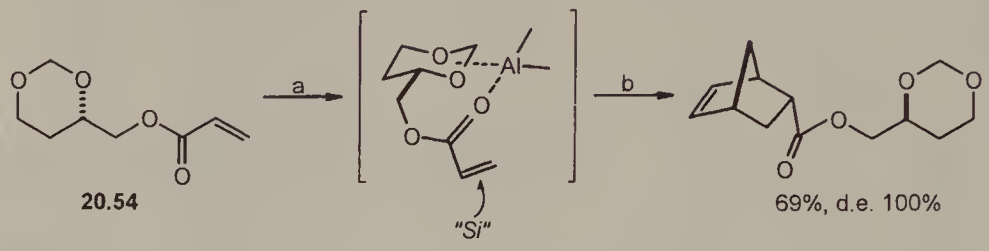
a: $RC(OMe)_3$, THF, dry HCl (cat.), RT, 6-8h (13-63%)[171]

Scheme 20.66

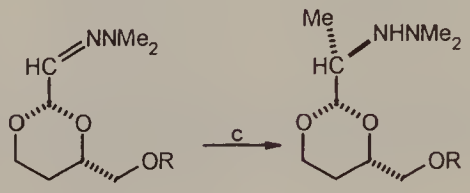
Applications

A

1,2,4-Tri-*O*-protected butanetriols are used as chiral auxiliaries in the Diels–Alder reaction (chiral dienophile **20.54**)[172] and in the nucleophilic alkylation of chiral hydrazones **20.55**[173] (Scheme 20.67).



a: $EtAlCl_2$, CH_2Cl_2, -60°C b: cyclopentadiene[172]



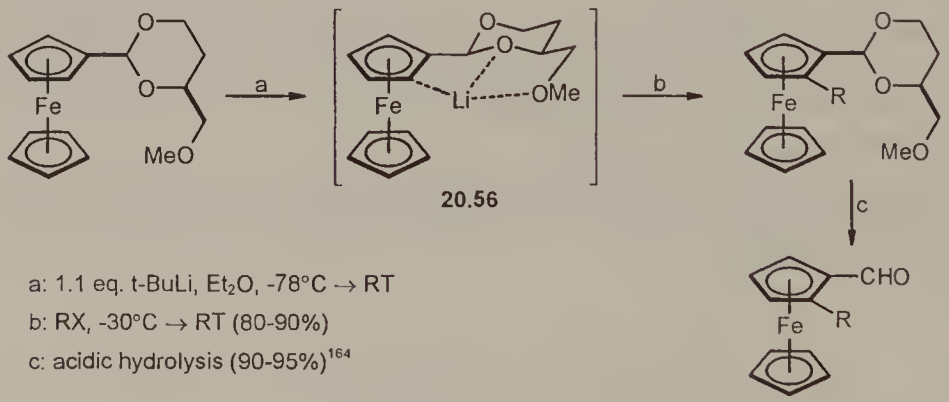
R = Me, d.e. 60%
Bn, d.e. 80%
Tr, d.e. 100%

20.55

c: 3 eq. MeLi, Et_2O, -12°C (72-78%)[173]

Scheme 20.67

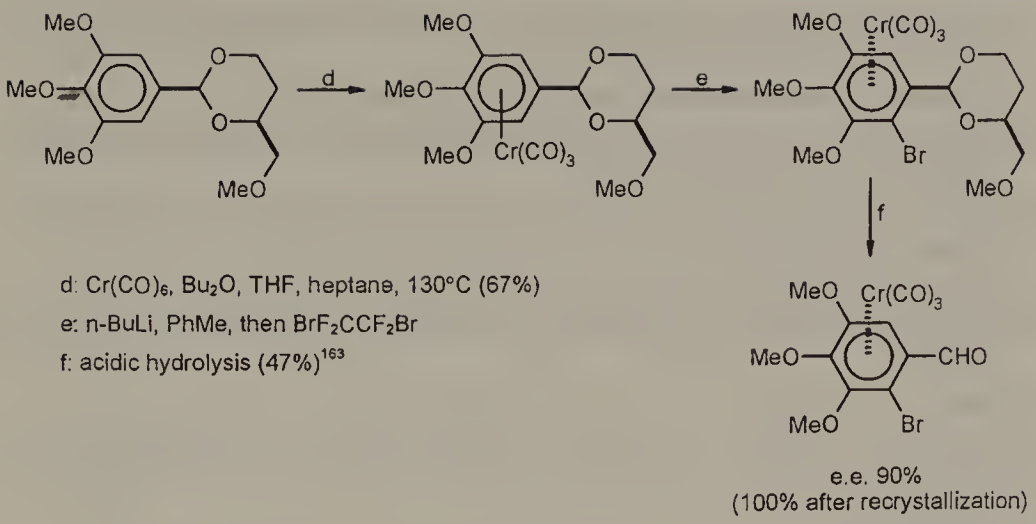
The high diastereoselectivity of the Diels–Alder reaction with the unhindered and flexible chiral butanetriol auxiliary undoubtedly results from the coordination of the Lewis acid to both the dienophile carbonyl group and the dioxane oxygen atoms of the auxiliary, making the *Si*-face of the dienophile more accessible for the diene.



a: 1.1 eq. t-BuLi, Et_2O, -78°C → RT
b: RX, -30°C → RT (80-90%)
c: acidic hydrolysis (90-95%)[164]

R = TMS, $SnBu_3$, PPh_2, COOMe, I,
C≡CTMS, C≡CPh
d.e. >98% in all cases

Scheme 20.68 (*continued*)



Scheme 20.68

The 1-*O*-methyl butanetriol 2,4-acetal auxiliary aided in the synthesis of chiral ferrocenes and of chiral (arene)chromium complex by Kagan[164] and Uemura[163] respectively (Scheme 20.68).

The similarity of asymmetric induction in the above two reactions suggests a common mechanistic rationalization, as it is shown for the substitution of the ferrocenyl derivative (**20.56**).

A number of 1-*O*-octadecyloxy 2,4-cyclic phosphates and phosphoramidates of (*S*)-1,2,4-butanetriol were prepared by Weller as conformationally restricted analogues of the platelet-activating factor.[62]

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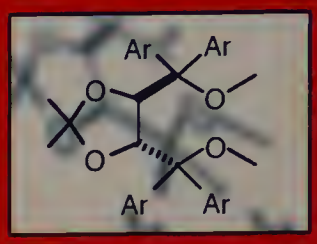
AN EXHAUSTIVE GUIDE TO THE STRUCTURE, PROPERTIES, AND APPLICATIONS OF 20 CLASSES OF TARTARIC AND MALIC ACID DERIVATIVES



The many exciting advances made in asymmetric synthesis over the past two decades have been due, in great part, to applications of tartaric and malic acid derivatives. Because of their unparalleled usefulness in synthesizing nonracemic acyclic and heterocyclic compounds, tartaric and malic acids are now considered indispensable "tools of the trade" for chemists working in natural products, fine chemicals, and pharmaceutical research.

Tartaric and Malic Acids in Synthesis provides chemists with a concise, yet comprehensive, review of the chemical properties and synthetic applications of derivatives of tartaric and malic acids. Intended as a source of information and inspiration, it contains a gold mine of ideas on the use of tartaric and malic acids in synthesis not only as chiral building blocks, but as chiral ligands, auxiliaries, and resolving agents as well. Throughout, the primary focus is on four-carbon building blocks derived from tartaric and malic acids and their synthetically useful reactions.

Designed for ready reference, this book follows a simple, hierarchical organization—moving from derivatives of carboxy groups to derivatives of hydroxy groups, and, finally, to products of reduction of the carboxy groups—and includes:

- Hundreds of reaction schemes and figures
- More than 70 tables with data and references for 2,000 compounds
- Over 2,500 references to primary, secondary, and patent literature sources

Tartaric and Malic Acids in Synthesis is a valuable working resource for chemists involved in the design of enantioselective syntheses. It is also an excellent supplementary text for graduate students of synthetic organic chemistry and natural products chemistry.

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