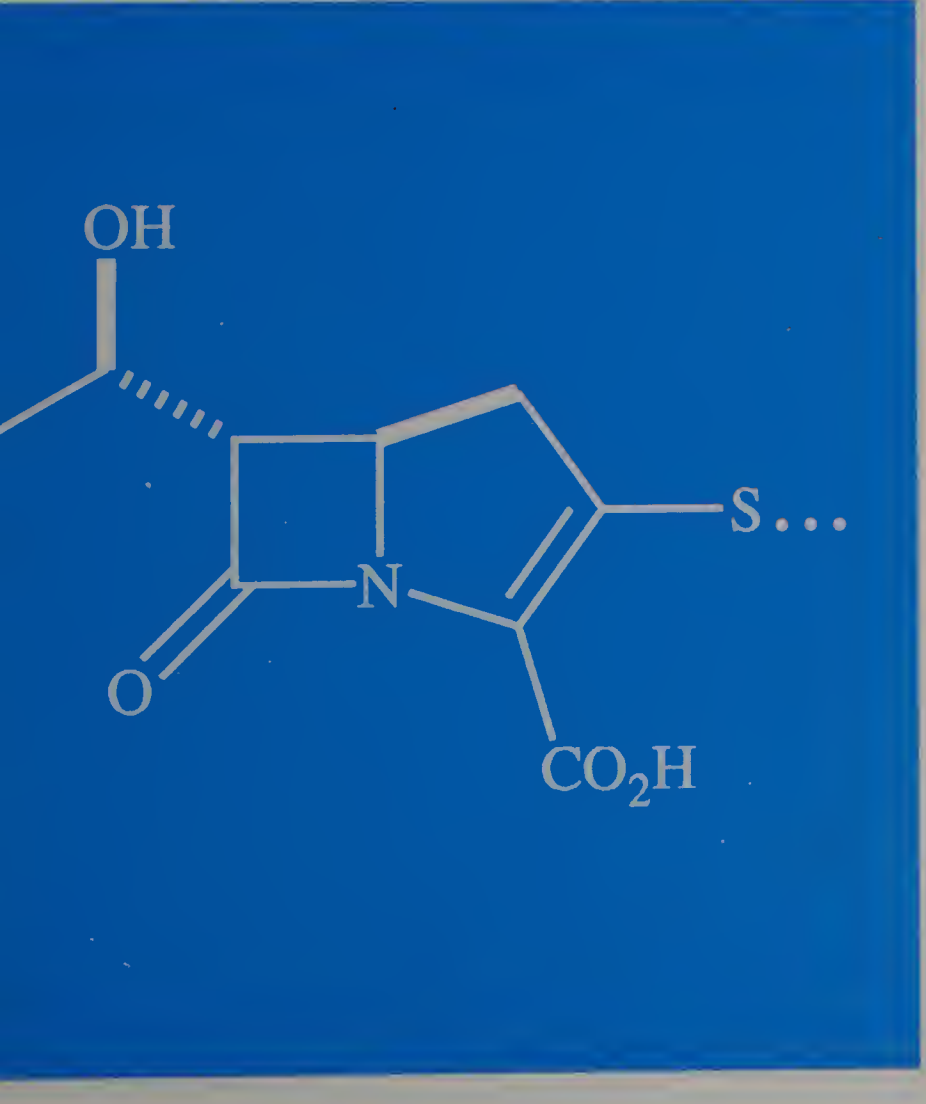
The Organic Chemistry of β-Lactams

Edited by
Gunda I. Georg



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The Organic Chemistry of β-Lactams

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Gunda I. Georg
EDITOR

Gunda I. Georg
Department of Medicinal Chemistry
University of Kansas
Lawrence, Kansas 66045

Library of Congress Cataloging-in-Publication Data
The Organic chemistry of b [beta]-lactams / Gunda I. Georg, editor.
p. cm.
Includes bibliographical references and index.
ISBN 1-56081-083-1
1. Lactams. I. Georg, Gunda I. II. Title: Organic chemistry of beta-lactams.
QD405.O58 1992
547'.592—dc20 92-34461

Printed in the United States of America
ISBN 1-56081-083-1 VCH Publishers
ISBN 3-527-28188-6 VCH Verlagsgesellschaft

Printing History:
10 9 8 7 6 5 4 3 2 1

Published jointly by

VCH Publishers, Inc.
220 East 23rd Street
New York, New York 10010

VCH Verlagsgesellschaft mbH
P.O. Box 10 11 61
D-6490 Weinheim
Federal Republic of Germany

VCH Publishers (UK) Ltd.
8 Wellington Court
Cambridge CB1 1HZ
United Kingdom

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Preface

The almost overwhelming wealth of publications in the area of β-lactam chemistry makes it necessary periodically to provide reviews of the work accomplished. With the publication of this book, we hope to provide a comprehensive and critical review of important topics in β-lactam chemistry, covering approximately the last 10 years. With the rapid and exciting developments in the field of asymmetric synthesis, the book is also intended to have a special focus on the preparation of β-lactams in optically active form.

Dr. Wild took on the task of writing two chapters. Chapters 1 and 2 on protective group chemistry and functional group conversions in β-lactam chemistry are of importance because of the special sensitivities of the β-lactam ring, particularly in bicyclic systems, toward chemical reactions. For the first time, he has compiled a multitude of information, mostly in the form of tables, on successful protective group chemistry and functional group transformations in β-lactam chemistry. This critical evaluation of the literature will be extremely useful for practicing β-lactam chemists—seasoned researchers and novices to the field alike.

With the discovery of the carbapenems, the penems, and the carbacephems as powerful antibacterial agents, much effort in recent years has focused on the search for novel methods for the construction of bicyclic β-lactam ring systems. Chapter 3 by Dr. Kant and Dr. Walker provides an extensive and critical review of developments in this area.

In recent years it has become additionally evident that β-lactams, and optically active β-lactams in particular, are powerful precursors for the synthesis of α- and β-amino acids and natural products. Chapter 4 by Dr. Ojima

focuses on the development of the so-called β-Lactam Synthon Method, under development in his laboratory as a powerful method for the synthesis of optically active amino acids and oligopeptides.

A centerpiece in β-lactam chemistry will always be the synthesis of the β-lactam ring system itself. In Chapter 5 Dr. Ternansky and Dr. Morin have provided an update on the last 10 years of synthesis of the "enchanted nucleus."

In the last chapter of the book, an overview on the mechanism and on recent developments in the Staudinger reaction is provided by Dr. Ravikumar and myself. Special emphasis is placed on asymmetric versions of the Staudinger reaction. Additionally, we suggest simple rules to predict *cis*- or *trans*-β-lactam formation in the Staudinger reaction.

With six chapters and a page limit we were not able to cover all of the important aspects of novel β-lactam chemistry. For example, some very interesting topics such as the ester enolate–imine cyclocondensation reaction and the utilization of transition metal carbenes in β-lactam formation are not covered in this book; however, citations of recent review articles on these and other topics can be found throughout this book.

I take this opportunity to sincerely thank the authors for their excellent work. Without their contributions this book would not have been possible. I also thank Dr. V. T. Ravikumar and D. Sharp for their help with the editing of this manuscripts.

I do hope that our readers and critics will find that we have embarked on a successful venture.

Gunda I. Georg

Contributors

Dr. Gunda I. Georg. Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66045, USA

Dr. Joydeep Kant. Bristol-Myers Squibb Company, Pharmaceutical Research Institute, P.O. Box 5100, Wallingford, Connecticut 06492-7600, USA

Dr. John M. Morin, jr. Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285, USA

Dr. Iwao Ojima. Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794, USA

Dr. Vasulinga T. Ravikumar. Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66045, USA

Dr. Robert J. Ternansky. Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285, USA

Dr. Donald G. Walker. Bristol-Myers Squibb Company, Pharmaceutical Research Institute, P.O. Box 4755, Syracuse, New York 13221-4755, USA

Dr. Hanno Wild. Bayer AG, Chemistry Science Laboratories Pharma, P.O. Box 10 17 09, 5600 Wuppertal 1, Germany

CHAPTER

1

Protective Groups in β-Lactam Chemistry

Hanno Wild

Bayer AG, Chemistry Science Laboratories Pharma, P.O. Box 10 17 09, 5600 Wuppertal 1, Germany

1.1 Introduction
1.2 Protection of Nitrogen in β-Lactam Chemistry
  1.2.1 Protection of the β-Lactam Nitrogen
  1.2.2 Protective Groups Suitable for Amino Functions in General
  1.2.3 Special Protective Groups for the 3-Amino Group in Monocyclic and Bicyclic β-Lactams
  1.2.4 Protective Groups for the 2-Aminothiazole Group
1.3 Protection of Hydroxyl Functions in β-Lactam Derivatives
1.4 Protective Groups for the Carboxylic Acid Functions in β-Lactam Derivatives
  1.4.1 Protective Groups That Can Be Removed Chemically
  1.4.2 Protective Groups That Can Be Removed Enzymatically (Prodrug Esters)
1.5 Protection of Carbonyl Groups in β-Lactam Derivatives
1.6 Protective Groups for Thiol Functions in β-Lactam Chemistry
1.7 Examples from Practice
1.8 Abbreviations
1.9 Literature

1.1 Introduction

The protection of functional groups in β-lactam derivatives presents special problems for the synthetic chemist because of the high reactivity of bicyclic β-lactams in particular. Many β-lactam systems would have been impossible to prepare but for the development of suitable protective groups. The following are just three of the many examples that could be cited:

- First preparation of penicillin G benzhydryl ester (1943), which was also the first esterification of the carboxylic acid of penicillin[1]
- Introduction of the trichloroethyl and trichloroethoxycarbonyl protective groups by Woodward et al. (1966) in the first total synthesis of cephalosporin C[2]
- Palladium-catalyzed cleavage of allyl esters, allyl carbonates, and allyl carbamates, which has been extensively used in penem and carbapenem syntheses[3]

Protective groups are used in β-lactam chemistry in three partly interconnected areas: (1) in the synthesis of the β-lactam itself, (2) for the temporary protection of functional groups during synthetic operations, and (3) for permanent protection during a synthesis, with simultaneous removal usually of several groups in the final stage. Whereas selective deprotection in the presence of other functional groups is the main criterion for the first two applications, an important requirement in the third is the ability to liberate the multifunctional and generally very unstable end product by the gentlest possible means.

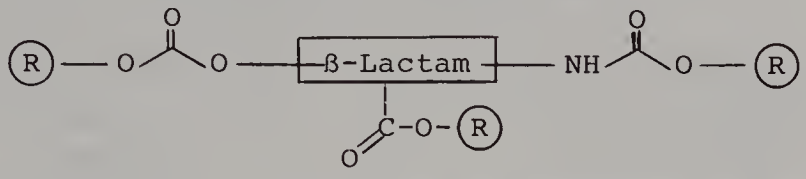
Table 1.1 is a rough ranking of the principal β-lactam systems in order of increasing stability, though the order may naturally be completely reversed by the presence of activating or deactivating groups. This table also lists a number of groups often used in β-lactams for the protection of carboxylic acid, amine, and alcohol functions.

In the following sections, the discussion of protective groups that can be used in β-lactam chemistry is organized according to the functional groups to be protected.

Section	Group Protected
1.2.1	β-Lactam nitrogen
1.2.2	Amino groups in general
1.2.3	C-3 amino group in β-lactams
1.2.4	2-Aminothiazole groups
1.3	Hydroxyl groups
1.4	Carboxylic acid groups
1.5	Carbonyl functions
1.6	Thiol groups

It is impossible in some cases to make a clear distinction between protective groups and activating groups that enable the introduction of other functional groups. This applies in particular to reactions in the β-lactam ring itself (e.g., methoxylation on C-3, synthesis of 3-methylene-β-lactams, substitutions on C-4). In case of doubt, the reader is referred to Chapter 2. The introduction of the protective groups is discussed in only a small number of cases. These groups are often introduced into acyclic precursors or stable β-lactam derivatives by standard methods.[4]

Table 1.1. STABILITY OF β-LACTAMS TO HYDROLYSIS AND COMMON PROTECTING GROUPS IN β-LACTAM CHEMISTRY



Stability to hydrolysis	— R	Deprotection
low		mild
carbapenem	-CH$_2$-C$_6$H$_4$-NO$_2$	H_2, Pd-C
	-CH$_2$-CH=CH$_2$	Pd(0), nucleophile
penem	-CH$_2$-C$_6$H$_4$-OMe	$AlCl_3$, anisole, -50°C
penicillin	-CH$_2$CCl$_3$	Zn, HOAc
	-CH$_2$-C$_6$H$_4$-OMe	
cephalosporin	-CHPh$_2$	CF_3CO_2H, anisole
monocyclic β-lactam	-tert-butyl	
high		moderate

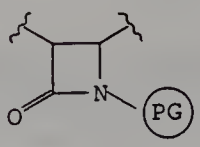
1.2 Protection of Nitrogen in β-Lactam Chemistry

Nitrogen functions that may require protection during a synthesis are the β-lactam nitrogen (Section 1.2.1) and usually primary amino groups. Apart from the amino group on C-3 of the β-lactam, these include the arylglycine side chain in penicillins and cephalosporins, amino functions in the side chain in position 2 of penems and carbapenems, and the aminothiazole group, which is a component of many important derivatives. Whereas some protective groups, particularly carbamate groups, can be used in all possible positions (Section 1.2.2), a number of methods are used especially for the protection of the C-3 amino group (Section 1.2.3) and of the aminothiazole group (Section 1.2.4).

1.2.1 Protection of the β-Lactam Nitrogen

Most protective groups for the β-lactam nitrogen are already present during the synthesis of the β-lactam ring from acyclic precursors, so that the only important consideration is their selective removal at the appropriate time. Benzyl groups (Table 1.2, entries 7–10) are often used, as is the *p*-methoxyphenyl group, which can be removed by oxidative methods (Table 1.2, en-

Table 1.2. PROTECTION OF THE β-LACTAM NITROGEN



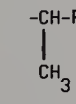
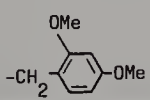
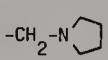
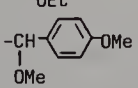
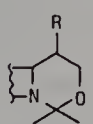
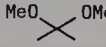
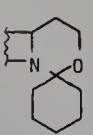
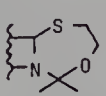
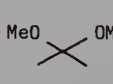
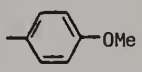
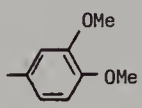
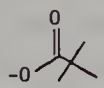
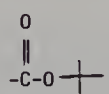
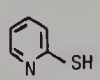
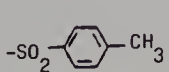
Entry	Protecting group	Protection	Ref.	Deprotection	Ref.
	Silyl				
1	$-SiMe_3$ (TMS)	-		1 % AcOH, MeOH	5
2	$-SiMe_2{}^tBu$ (TBOMS)	TBOMS-Cl, NEt_3, DMF	6	1 eq NaOH, THF/H_2O	6
3	"	1) $Li(NTMS)_2$ 2) TBOMS-Cl	7	$n\text{-}Bu_4NF$, AcOH, THF, 0°C	8
4	"	-		KF, MeOH, 0°C	9
5	"	-		c.HCl, MeOH	10
6	"	-		Ph_2BBr, -78°C	11
	Benzyl				
7	$-CH_2Ph$	-		Li, NH_3	12
8		-		Na, NH_3	13
9	"	-		$K_2S_2O_8$, AcOH, H_2O	14
10		-		$K_2S_2O_8$, CH_3CN/H_2O	15
	Acetals + ketals				
11		 , CH_2O, EtOH, Δ	16	HCl, THF	16
12		-		$1NH_2SO_4$, THF	17
13		$(MeO)_2CH$  OMe, $BF_3\text{-}OEt_2$	18	SO_2, H_2O	18
14		 , $BF_3\text{-}OEt_2$	19	H_2SO_4, CrO_3: -OH ⟶ $-CO_2H$	19
15	"	-		AcOH, H_2O	20
16		-		H_2SO_4, THF, 50°C	21
17		 , $BF_3\text{-}OEt_2$	22	AcOH, H_2O Δ	22

Table 1.2.

Entry	Protecting group	Protection	Ref.	Deprotection	Ref.
	Aryl				
18		-		$(NH_4)_2Ce(NO_3)_6$ [CAN], CH_3CN/H_2O	23
19	"	-		electrolysis, 1.5 V CH_3CN/H_2O	24
20	"	-		$AgNO_3$ (cat.), $(NH_4)_2S_2O_8$, CH_3CN/H_2O	25
21	"	-		1) O_3 2) $Na_2S_2O_4$	26
22		-		" "	26
	N-O				
23	-OH	-		$TiCl_3$, $MeOH/H_2O$	27
24	-OMe	-		Na, NH_3	28
25	"	-		Li, NH_3, t-BuOH, THF	29
26	$-OCH_2Ph$	-		1) H_2, Pd-C ⟶ OH 2) $TiCl_3$	30
27		-		1) NH_4OAc, THF/H_2O ⟶ OH 2) $TiCl_3$	31
	Miscellaneous				
28		-		$KMnO_4$, acetone (50 %)	32
29		-		$KMnO_4$, acetone	33
30	"	-		1 % HCl, THF, △	33
31		-		TFA, CH_2Cl_2	34
32	$-SCH_3$	1) LOA 2) $MeSO_2SMe$ 35		 , NEt_3	35
33		-		Na-naphthalide	36

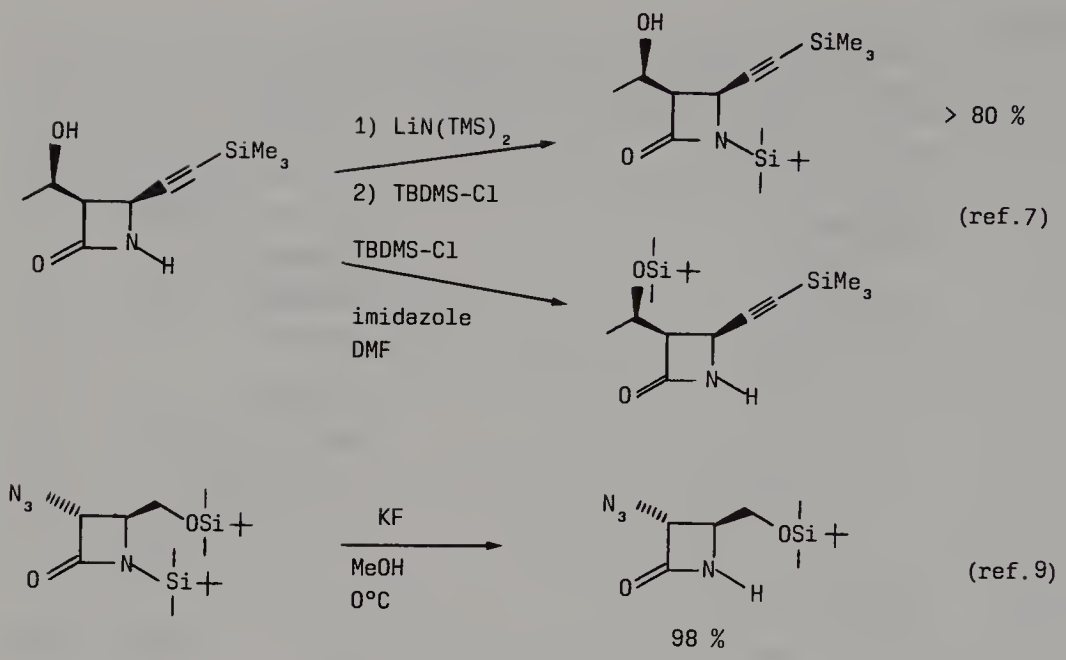


Figure 1.1. Selective reactions with the TBDMS protective group.

tries 18–22). N—O derivatives are formed on cyclization of hydroxamic acids. The N—O bond of *N*-hydroxyazetidinone can be broken by reduction with titanium(III) chloride (Table 1.2, entries 23, 26, 27).

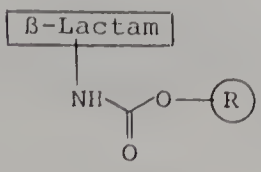
The main group used for temporary protection of the β-lactam nitrogen is the *tert*-butyldimethylsilyl group (TBDMS, Table 1.2, entries 2–6); a few acetal protective groups (Table 1.2, entries 11–17) are also suitable. Cyclic ketals of acetone or cyclohexanone allow the simultaneous protection of alcohol functions in the side chain on position 4 (Table 1.2, entries 14–17). Figure 1.1 shows two examples of selective reactions with the TBDMS protective group.

1.2.2 Protective Groups Suitable for Amino Functions in General

The most important of the protective groups for amino functions in general is the carbamate. The groups normally used are listed in Table 1.3 together with methods for their removal. The introduction of these groups either is described in the publications cited or is accomplished by standard methods.[4] The Boc (Table 1.3, entries 1–3) and Teoc (Table 1.3, entries 4 and 5) groups and the Cbz protective group (Table 1.3, entries 7–9) are used in penicillins and cephalosporins, but are less suitable, or even totally unsuitable, for the protection of the sensitive penems and carbapenems because of the acidic conditions usually required for their removal.

The *p*-nitro (Table 1.3, entries 10–15) and the *p*-methoxybenzyloxycar-

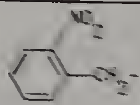
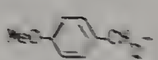
Table 1.3. CARBAMATE PROTECTIVE GROUPS



Entry	(R)	ß-Lactam	Deprotection	Ref.
1	t-Bu- (Boc)	penicillin, 6-side chain	TFA, 0°C	37
2	"	cephalosporin, phenylglycine	$AlCl_3$, anisole, CH_2Cl_2/CH_3NO_2, r.t.	38
3	"	monobactam, 3-amino	TFA, anisole, 0°C	39
4	Cl_3CCH_2- (Teoc)	cephalosporin C, 7-side chain	Zn, 90 % AcOH, 0°C	2
5	"	penicillin, 6-amino	Zn, pH4-phosphate buffer	40
6	Ph_2CH-	cephalosporin, 3-sida chain	TFA, anisole, 0°C	41
7	Ph-CH_2- (Cbz)	cephalosporin, phenylglycine	1 atm H_2, Pd-$BaCO_3$, H_2O, r.t.	42
8	"	monobactam, 3-amino	1 atm H_2, Pd-C, MeOH	43
9	"	oxacephem, 7-amino	$AlCl_3$, anisole, CH_2Cl_2, r.t.	44
10		carbapenem, 2-side chain	3 atm H_2, PtO_2, THF/phosphate buffer	45
11	"	penem 2-side chain	1 atm H_2, Pd-C, THF/phosphate buffer, r.t.	46
12	"	penem, 6-aminoethyl	3 atm H_2, Pd-Celite, THF/H_2O	47

(Continued)

Table 1.3. (Continued)

Entry	(R)	β-Lactam	Deprotection	Ref.
13	"	carbapenem, 6-aminoethyl	3 atm H_2, Pd-C, THF/EtOH/H_2O	48
14	"	penicillin, arylglycine	1 atm H_2, Pd-C, MeOH, r.t. (95 %)	49
15	"	cephamycin, 7-amino	1 atm H_2, Pd-C, MeOH/THF	50
16		carbapenem, 6-aminoethyl	hν (350 nm), dioxane, pH 7 phosphate buffer	51
17		carbapenem, 2-side chain	$AlCl_3$, anisole, CH_2Cl_2, −50°C	52
18	 (Alloc)	penicillin, 6-amino	$Pd(PPh_3)_4$, Ph_3P / +  CO_2K, CH_2Cl_2, r.t.	5
19	"	carbacephem, 7-amino	+ Bu_3SnH	53
20	"	penem, 2-side chain	+ dimedone	54
21	"	penem 2-side chain	+  $CO_2^{\ominus}$ Na$^{\oplus}$, AcOH	55
22	"	carbapenem 2-side chain	+ Bu_3SnH, THF, r.t.	56
23	"	cephalosporin, arylglycine	$Pd(OAc)_2$, Ph_3P, Bu_3SnH	57a
24	"	carbapenem, 2-side chain	Pd(0)-polymer bound, NMM	57b
25	Me_3Si 	monocyclic, N-amino	n-Bu_4NF, CH_3CN, 50°C	58a
26	Br_2CH-CH_2-	penicillin, phenylglycine	[illegible] phenol, CH_3CN, r.t.	58b

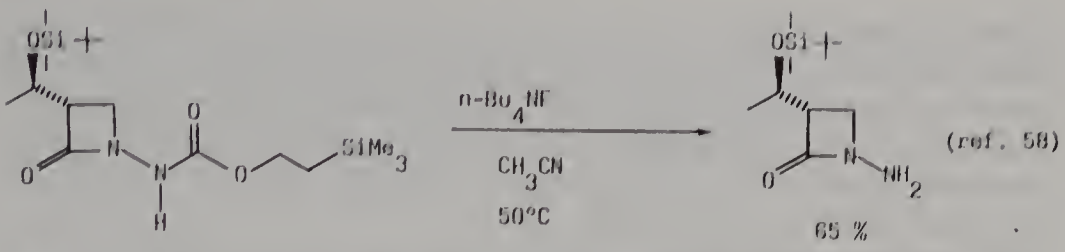


Figure 1.2. Selective removal of a 2-trimethylsilylethyl carbamate group.

bonyl group (Table 1.3, entry 17), as well as the Alloc protective group (Table 1.3, entries 18–24) have proved to be suitable in these cases. Multiple deprotection with simultaneous regeneration of hydroxyl groups (Section 1.3) and carboxylic acid groups (Section 1.4) is also readily possible with these protective groups. The *p*-methoxybenzyloxycarbonyl group can be removed with aluminum trichloride in anisole at very low temperatures. The *p*-nitrobenzyloxycarbonyl group is extremely easily removed by hydrogenolysis, so that it is even possible to prepare, for example, very unstable 6-aminoethylpenems (Table 1.3, entry 12) and 6-aminoethylcarbapenems (Table 1.3, entry 13).

During hydrogenolysis the nitro group is first reduced to the amine. The resulting *p*-aminobenzyl compound is so reactive that the entire deprotection can be carried out at 0°C in many cases. The palladium-catalyzed removal of the Alloc protective group is equally mild, and proceeds under almost neutral conditions. Special cases are the *o*-nitrobenzyloxycarbonyl group (Table 1.3, entry 16), which is removed photochemically, and the 2-trimethylsilylethyl carbamate group (Table 1.3, entry 25). A Boc group was not removed cleanly in the latter case (Figure 1.2).

The Dane group (Table 1.4, entries 1–3) is very suitable for penicillins and

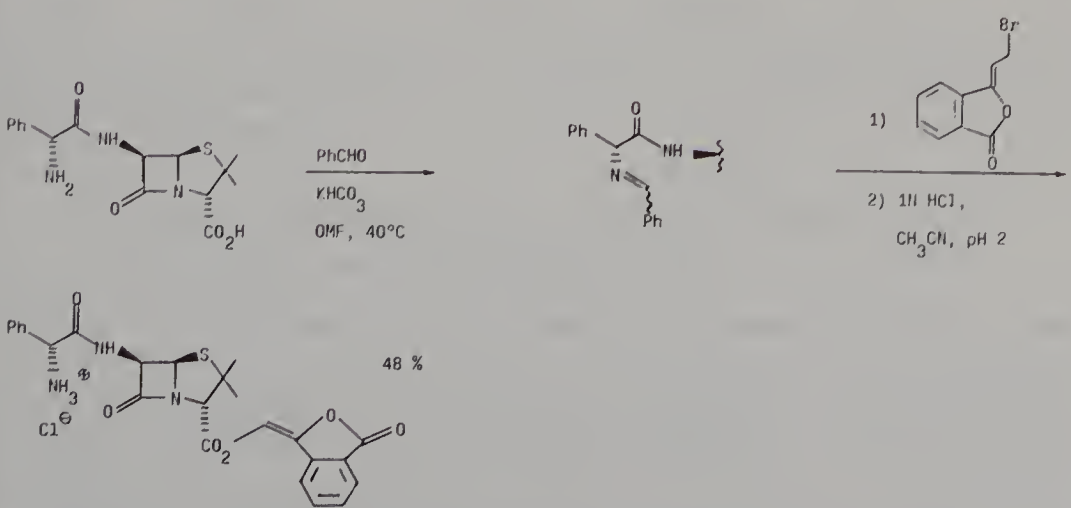


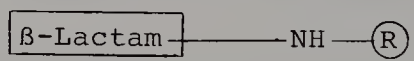
Figure 1.3. Utilization of an imino protective group.

cephalosporins. As the proton remaining on the nitrogen is stabilized by hydrogen bonding with the ester carbonyl group, the Dane group even permits reactions that are normally possible only in doubly protected derivatives (e.g., ketenimine cycloadditions). The *o*-nitrophenylsulfenyl (NPS) protective group, which is known from peptide chemistry, has only occasionally been used (Table 1.4, entries 4–6).

The imino group, which is described in more detail in Section 2.3, has also been used in one case to protect the amino function of ampicillin during the preparation of a prodrug ester (Figure 1.3).[67]

The azido group should also be mentioned under this heading (Table 1.5). Though this is not a protective group in the true sense, it is easy to introduce and inert to many synthetic operations, and even in very sensitive β-lactams it can readily be reduced to a primary amino group. Apart from hydrogenation (Table 1.5, entries 1, 6, and 10–13), reduction with triphenylphosphine in particular is characterized by mild reaction conditions. The phosphini-

Table 1.4. DANE AND *o*-NITROPHENYLSULFENYL PROTECTIVE GROUPS



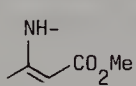
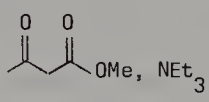
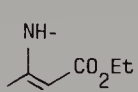
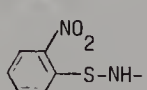
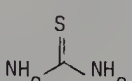
Entry	Ⓡ—NH-	ß-Lactam	Protection	Deprotection	Ref.
	DANE				
1		penicillin, 6-amino		TsOH, acetone	59
2		cephalosporin 7-amino		c.HCl, MeOH	60
3	"	penicillin, phenylglycine	———	1N HCl, pH 2.7	61, 62
	NPS				
4		monocyclic, 3-amino	NPS-Cl, pH 7-8	TsOH, 	63, 64
5	"	carbapenem, 2-side chain	NPS-Cl, pH 7, dioxane	AcOH, 	65
6	"	cephalosporin, 7-amino	NPS-Cl, NEt_3, r.t.	NaI, $MeOH/CH_2Cl_2$, 0°C	66

Table 1.5. AZIDE REDUCTION

Entry	ß-Lactam	Reduction conditions	Ref.
1	carbacephem, 7-amino	1 atm H_2, Pd-C, EE, r.t.	68
2	norcardicin, 3-amino	Zn, AcOH, r.t. (30 %)	69
3	cephalosporin, 7-amino	$(NH_4)_2S$, MeOH, r.t.	70
4	monocyclic, 3-amino	H_2S, NEt_3, CH_2Cl_2, r.t.	71
5	monocyclic, 3-amino	$SnCl_2$, AcOH, -20°C	72
6	penicillin, phenylglycine	3,5 atm H_2, Ra-Ni, H_2O, r.t.	73
7	cephalosporin, phenylglycine	1) Ph_3P 2) H_2O (46 %)	74
8	monocyclic, 3-amino	1) Ph_3P 2) O_2N-C$_6$H$_4$-CHO 3) 2,4-ONPH or	75
		1) Ph_3P 2) PhO-C(=O)-Cl *	
9	monocyclic, 3-amino	1) HS-(CH$_2$)$_3$-SH, NEt_3 2) aq. $CuSO_4$	76
10	penem, 2-side chain	6 atm H_2, Pd-C, OME/Et_2O/H_2O, r.t. (40 %)	55
11	carbapenem, 2-side chain	1 atm H_2, Pd-C, dioxane, pH 7-buffer, r.t.	77
12	carbapenem, 6-side chain	3 atm H_2, Pd-C, THF/Et_2O/H_2O, r.t.	48
13	carbapenem, 6-side chain	3 atm H_2, Pd-Celite, H_2O, pH 7, r.t. or	78
		1) Ph_3P, Ph-H, △ 2) O_2N-C$_6$H$_4$-CHO 3) H_2O, pH 6**	

* yields the corresponding amide

** during Pd(0)-cleavage of an allylester

mine intermediate formed can be either hydrolyzed (Table 1.5, entries 7, 8, and 13) or converted directly into an amide by reaction with an acyl chloride (Table 1.5, entry 8).

1.2.3 Special Protective Groups for the 3-Amino Group in Monocyclic and Bicyclic β-Lactams

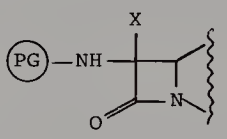
In addition to the protective groups described in Section 1.2.2 for amino groups in general, a number of groups are used specifically for the protection of the 3-amino position of β-lactams. These groups are important in the chemistry of penicillins, cephalosporins (and analogs), and monocyclic β-lactams.

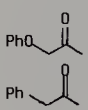
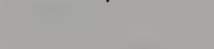
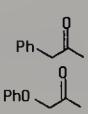
Investigations on the removal of acyl groups by chemical and enzymatic methods have a long history. This was an important step in the preparation of 6-aminopenicillanic acid (6-APA) from penicillin G and penicillin V, and

is still important in the preparation of new penicillin derivatives. Corresponding amido groups in the penicillin or cephalosporin system can therefore act as easily removable protective groups (Table 1.6, entries 1–5).

The mechanism of the removal of acyl groups by treatment with phosphorus pentachloride (intermediate formation of an imide chloride, followed by its hydrolysis) and the function of the alcohol used in the hydrolysis have been extensively studied.[80] The enzymatic removal of the phenacetyl or the phenoxyacetyl group with the aid of penicillin acylase is used industrially in the production of 6-APA. Very many penicillin acylases are obtainable from various strains of bacteria, and can also be used on the laboratory scale for

Table 1.6. MONOPROTECTION OF THE 3-AMINO GROUP



Entry	(PG)	ß-Lactam	Deprotection	Ref.
	Carbamates, DANE, NPS ⟶ section 2.2			
	Amides			
1		cephalosporin sulphoxide	$POCl_3$, MeOH, 50°C or PBr_3, MeOH, 10°C	79
2	 +	cephalosporin/ penicillin	1) PCl_5, Py 2) R-OH ROH=MeOH, n-BuOH,  , 	80,81
3		cephalosporin	1) PCl_5, Py 2)  , -20°C	82
4		cephamycin	1) PCl_5, Py, 0°C 2) MeOH, -20°C	83
5	 +	penicillin, cephalosporin, norcardicin	Panicillin acylase	84,85

			Protection	Deprotection	
	Trityl				
6	Ph_3C-	penicillin	Ph_3C-Cl (27 %)	1N HCl, , r.t. (29 %)	86
7	"	"	-	TsOH,  , r.t.	87
8	"	oxacephem	-	TsOH, CH_2Cl_2, 0°C	88
9	"	monocyclic	Ph_3C-Cl, NEt_3, r.t.	TsOH,  , r.t.	89
10	Me_3Si-	cephalosporin	HMDS, 3% TMS-I	MeOH, 0-5°C	90

the deprotection of synthetic cephalosporins, penicillins, and monocyclic β-lactams (Table 1.6, entry 5). An introduction to the literature is given in Reference 84. It should be noted that the penicillin acylases can naturally be used for acylations and transacylations, depending on the reaction conditions.

In addition to the well-established trityl protective group (Table 1.6, entries 6–9), Table 1.6 also includes an example of the use of the TMS group (entry 10). The most important use of this group, however, is in the conversion of 6-APA and 7-ACA derivatives into persilylated compounds to make them soluble in organic solvents in the coupling reaction with acids. This acylation is discussed in Section 2.3.2.

Double protection of the 3-amino group (Table 1.7) is desirable in many operations, particularly with strongly basic reagents. Imines are often used (Table 1.7, entries 1–5); a side effect of these protective groups is that they activate the C-3 position of the β-lactam and so facilitate the introduction of functional groups (e.g, OCH_3, SCH_3, NHCHO) and also epimerizations (see Section 2.2.3). Only derivatives that function mainly as protective groups are listed in the table.

Simple imino ethers, though rarely used (Table 1.7, entries 6–8), are perfectly suitable for use as protective groups for the amine or the amide, depending on the hydrolysis method (cf. cleavage of amides with PCl_5[80]). Cyclic imino ethers and imino thioethers of the type shown in Figure 1.4 are not listed in the table. These groups simultaneously activate position 4 of the β-lactam, and are discussed in Section 2.2.4.

The removal of phthaloyl protective groups (Table 1.7, entries 9–12) with hydrazine proceeds reasonably smoothly only if the β-lactam is very stable. Methylhydrazine or diamines must be used in other cases (Table 1.7, entries 10, 11). No selectivity between phthaloyl cleavage and β-lactam cleavage is found in less stable bicyclic systems. An indirect three-step method, involving hydrazinolysis of a cyclic imidate intermediate, has been developed for penicillin and cephalosporin derivatives (Table 1.7, entry 12).

Finally, Table 1.7 lists the stabase protective group (entries 13 and 14), as well as the 4-phenyloxazolidinone group (entry 15), which is both a protective group and a chiral auxiliary in highly diastereoselective ketene–imine cycloadditions.

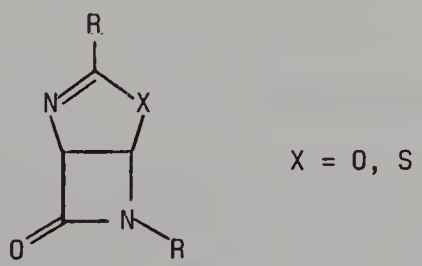
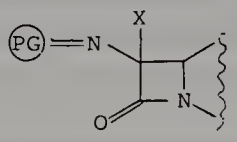


Figure 1.4. Cyclic imino esters and imino thioesters.

Table 1.7. DOUBLE PROTECTION OF THE 3-AMINO GROUP



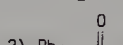
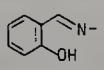
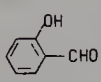
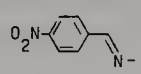
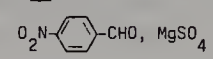
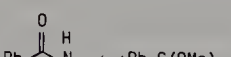
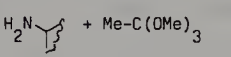
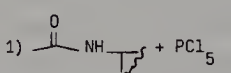
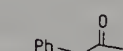
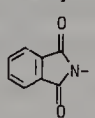
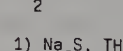
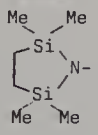
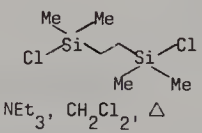
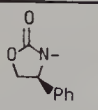
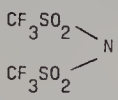
Entry	(PG)=N-	ß-Lactam	Protection	Deprotection	Ref.
	Imines				
1		cephalosporin	PhCHO, PhH, △	2N HCl or 	91a,91b
2	"	penicillin	-	2,4-ONPH, TsOH	92a
3	"	penicillin	-	1) $PdCl_2$, aq. THF, r.t. 2) 	92b
4		penicillin		3N HCl	87
5		cephalosporin		2,4-ONPH, TsOH	93
	Imidates				
6		cephalosporin		 , 1N HCl, r.t.** (49 %)	94
7		penicillin		-	95a
8	"	cephalosporin	1)  2) MeOH, -60°C	 MeOH (cat.), -30°C *	95b
	Phthaloyl				
9		isocephem	-	N_2H_4	96,97
10	"	monocyclic	-	NH_2NHMe, CH_2Cl_2 r.t.	98
11	"	norcardicin	-	 NMe_2, NEt_3, MeOH	99
12	"	penicillin / cephalosporin	-	1) Na_2S, THF, 0°C 2) DCC, 0°C or $ClCO_2Et$, NEt_3 3) N_2H_4 or NH_2NHMe	100, 101

Table 1.7.

Entry	(PG) = N	β-Lactam	Protection	Deprotection	Ref.
13	**Stabase** 	penicillin	 , NEt_3, CH_2Cl_2, △	TsOH, EE, r.t.	102
14	"	monocyclic	-	NaF, THF	103
15		monocyclic	-	Li, NH_3, t-BuOH, THF	12, 53, 104
16		penicillin	$(CF_3SO_2)_2O$, NEt_3	NEt_3, DMF/H_2O***	105

* yields the corresponding amide

** yields mixture of both possible amides

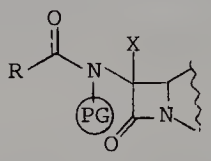
*** yields the monosulphonamide

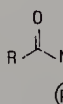
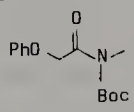
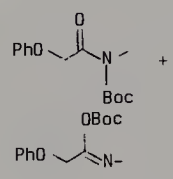
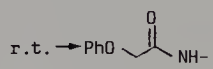
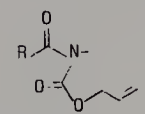
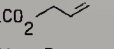
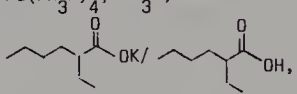
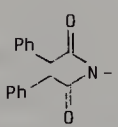
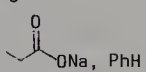
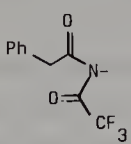
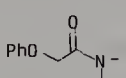
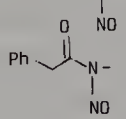
Table 1.8 lists a number of possible protective groups for replacement of the acidic amide proton in 3-amido-β-lactams. The derivatives are protected against deprotonation of the amide by basic reagents, and at the same time, the loss of the ability to act as a hydrogen bond donor, together with the increased steric hindrance of the groups, leads to altered selectivities in reactions in position 4 of the β-lactam.[107,109–111] Derivatives protected with Boc may be in the form of *N*-acyl compounds, the net result of basic hydrolysis of these compounds being transacylation with formation of the Boc-protected amine (Table 1.8, entries 1 and 2). In one case, however, the main product isolated was the *O*-acyl compound (Table 1.8, entry 3), from which the amide was regenerated on acid hydrolysis. In the case of a very unstable 6-amidocarbapenem, a corresponding *N*-Alloc protective group was removed in the final stage with catalysis by palladium (Table 1.8, entry 4). The last two examples in Table 1.8 are *N*-nitroso derivatives (entries 7 and 8), which were used for the selective preparation of penicillin α-sulfoxides.

1.2.4 Protective Groups for the 2-Aminothiazole Group

The 2-aminothiazole group, particularly in 2-(2-aminothiazol-4-yl)-2-methoximinoacetic acid, is present in many of the cephalosporin derivatives currently on the market. It is nearly always protected with the trityl group (Table 1.9, entries 1–4), which is easily removed under various acidic conditions. The choice of reagents is determined largely by the nature of the

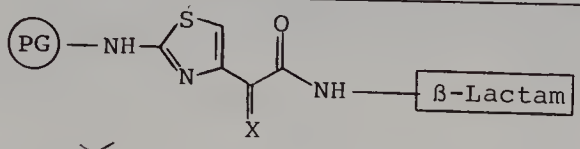
Table 1.8. PROTECTION OF THE 3-AMIDO GROUP

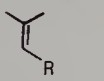
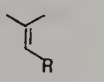
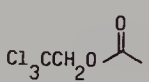
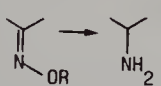
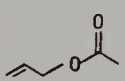
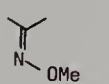
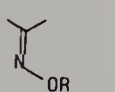
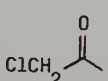
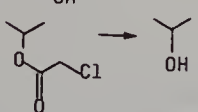
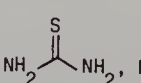


Entry		β-Lactam	Protection	Deprotection	Ref.
1		penicillin/ cephalosporin	Boc_2O, OMAP, NEt_3	NH_2⁄⁄NEt_2, CH_2Cl_2 → Boc-NH-	106
2	"	carbacephem	"	LiOH → Boc-NH-	53
3	 (1:B)	cephalosporin	Boc_2O, OMAP, DMF, 40°C	TFA, r.t. → 	107
4		6-amido-carbapenem	 , DMAP, Py	$Pd(Ph_3P)_4$, Ph_3P,  EE/CH_2Cl_2, 0°C	108
5		penicillin	1) PCl_5, Py 2) 	Zn, NH_4OAc, r.t.	109a
6		penicillin	Tf_2O, CH_2Cl_2	$NaHCO_3$, H_2O/acetone	109b
7		penicillin	N_2O_4	Zn, AcOH	110
8		penicillin	N_2O_4, 0°C	Zn, AcOH, 0°C	111

other protective groups in the molecule, which are generally removed together in the final stage. Other possibilities are protection of the amine as a carbamate (Table 1.9, entries 5–7) or as a formamide (Table 1.9, entry 8). The latter can be hydrolyzed under acidic conditions in the presence of *tert*-butyl esters. A further interesting variant is the chloroacetyl group (Table 1.9, entry 9), which is removed under very mild conditions by reaction with thiourea.

Table 1.9. PROTECTION OF THE 2-AMINOTHIAZOLE GROUP

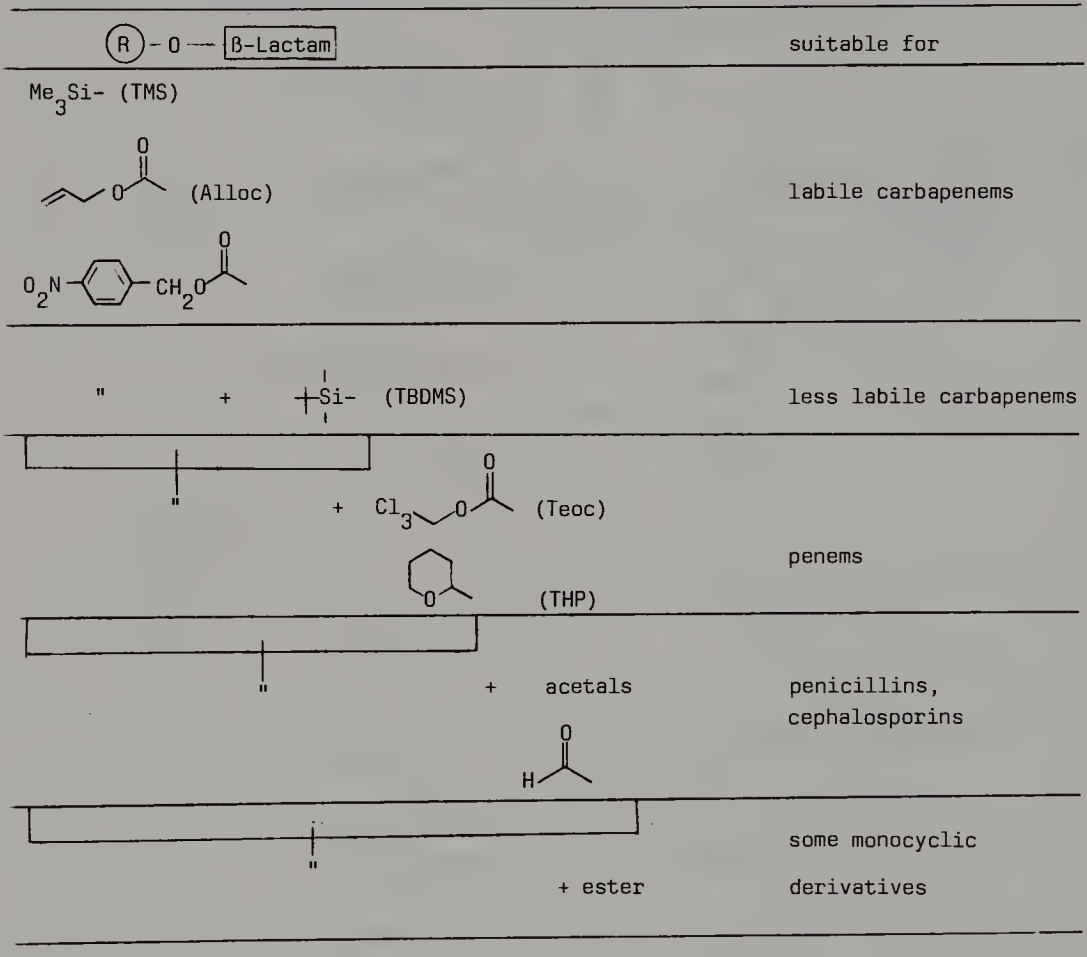


Entry	(PG)	X	Deprotection	Ref.
	Trityl			
1	Ph_3C-		HCO_2H, 50-60°C	112
2	"		TFA or c.HCl, HCO_2H, r.t.	113
3	"		TFA, anisole	114
4	"		$AlCl_3$, anisole or $SnCl_4$, anisole	115
5			$SnCl_4$, anisole	115
6			Zn, HCO_2H	116
7			$Pd(Ph_3P)_4$, Bu_3SnH, CH_3CN/Et_2O, r.t.	53
8			c.HCl, MeOH/THF	117
9			 NaOAc, THF, r.t.	118,119

1.3 Protection of Hydroxyl Functions in β-Lactam Derivatives

As far as the protection of hydroxyl functions in β-lactam derivatives is concerned, there are no special groups for particular positions in the molecule. The deciding factor, as in the protection of any other functional group, is the stability of the compounds under the conditions of removal of the protective group. Table 1.10 shows qualitative assignments of some important protective groups to certain types of β-lactams, arranged in order of increasing stability.

Table 1.10. HYDROXYL PROTECTING GROUPS ARRANGED IN ORDER OF INCREASING β-LACTAM STABILITY

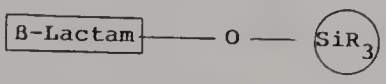


Suitable groups for the protection of very sensitive carbapenems, for example, apart from the trimethylsilyl group (Table 1.11, entries 1–4), are the Alloc and *p*-nitrobenzyloxycarbonyl groups (Table 1.12, entries 1–4 and 6–8, respectively), whereas removal of the TBDMS group is possible only from a few of the more stable carbapenems (Table 1.11, entries 11 and 12). At the other end of the scale are the monocyclic β-lactams, some of which can even withstand the alkaline removal of benzoyl groups (Table 1.12, entry 16).

The reaction conditions for the introduction of the protective groups listed in Tables 1.11 to 1.13 are indicated only in certain cases, as stable precursors are generally used in well-established reaction procedures.[4]

Table 1.11 lists silyl protective groups, including TBDMS, which is the group used most often for the protection of hydroxyl functions (entries 6–12). The trimethylsilyl group, because of its lability, is used only for short-term protection of the 6-hydroxyethyl side chain in very sensitive compounds (Table 1.11, entries 1–4). Tertiary alcohols (Table 1.11, entry 5) give

Table 1.11. SILYL PROTECTIVE GROUPS



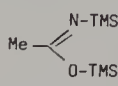
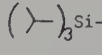
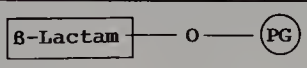
Entry	R_3Si	ß-Lactam	Protection	Deprotection	Ref.
1	Me_3Si-	penem, 6-hydroxyethyl	TMS-Cl, Py	during reaction with Cl-SO_2-NCO	120
2	"	carbapenem, 6-hydroxyethyl	TMS-OTf, NEt_3, -78°C	0.25-0.5 eq AcOH, 35°C	121
3	"	"	 , OMAP (cat.)	PPTS (cat.), THF/H_2O	122
4	"	"	TMS-Cl, Py	pH 2.5, H_2O, 0.5 min.	77
5	"	monocyclic, 3-hydroxyisopropyl	-	1N HCl, MeOH, r.t.	5
6		monocyclic, 3-hydroxyethyl	-	HF, CH_3CN, 0°C	123
7	"	"	-	HCl, MeOH	45
8	"	"	-	BF_3-OEt_2, CH_3CN	122
9	"	penem, 6-hydroxyethyl	TBDMS-Cl, imidazole, DMF, 55°C	n-Bu_4NF, AcOH, THF, r.t.	124
10	"	oxacephem 7-hydroxyethyl	-	BF_3-OEt_2	125
11	"	carbapenem, 6-hydroxyethyl	-	n-Bu_4NF, AcOH, THF, r.t.	126
12	"	"	-	not possible	127
13		penem, 2-side chain	-	n-Bu_4NF, AcOH, THF	128
14	"	monocyclic, 4-side chain	-	HCl, MeOH	36
15		monocyclic 3-hydroxyethyl	-	n-Bu_4NF, THF	129

Table 1.12. CARBONATE AND ESTER PROTECTIVE GROUPS



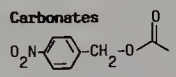
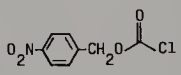
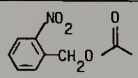
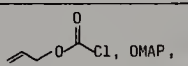
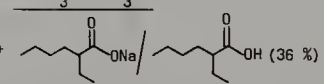
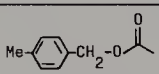
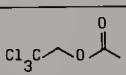
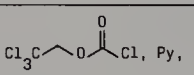
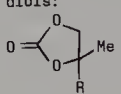
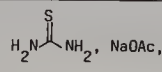
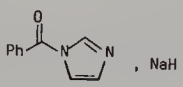
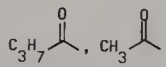
Entry	PG	β-Lactam	Protection	Deprotection	Ref.
	Carbonates				
1		carbapenem, 6-hydroxyethyl	-	1 atm H_2, Pd-C, dioxane/ $NaHCO_3$, r.t.	130
2	"	asparanomycin, 6-side chain	 OMAP, CH_2Cl_2	3 atm H_2, Pd-C, dioxane/ pH 7 buffer	131
3	"	penem, 6-hydroxyethyl	- -	6 atm H_2, Pd-C, OME/ Et_2O/H_2O, r.t.	55
4	"	oxapenem, 6-hydroxyethyl	-	1 atm H_2, Pd-C, EE/$NaHCO_3$, 0°C	132
5		carbapenem, 6-hydroxyethyl	-	1 atm H_2, Pd-C phosphate buffer, r.t.	130
6		carbapenem, 6-hydroxyethyl	 OMAP, CH_2Cl_2	$Pd(Ph_3P)$, Ph_3P 	133
7	"	penem, 6-hydroxyethyl	-	+ dimedone or Bu_3SnH	134
8	"	carbapenem, 6-hydroxyethyl	-	+ Bu_3SnH	56
9		cephalosporin, 3-side chain	-	$SnCl_4$, anisole, -40°C	135
10		monocyclic, 4-sida chain	 Py, THF	Zn, AcOH, 10-12°C	136
11	"	panem, 6-hydroxyethyl	" , CH_2Cl_2	Zn, AcOH, THF, 0°C	137, 138
12	diols: 	carbapanam/ asparenomycin, 6-side chain	 Py	O8U (cat.), CH_3CN, r.t. *	139, 140
	Esters				
13		cephalosporin, 7-side chain	-	K_2CO_3, $MeOH/H_2O$ or $NaHCO_3$, DMF/H_2O	141
14	"	monocyclic, 3-hydroxyathyl	-	OOWEX 50 or $NaHCO_3$, H_2O	142

Table 1.12.

Entry	(PG)	β-Lactam	Protection	Deprotection	Ref.
15		cephalosporin, 7-side chain	-		118
16		monocyclic, 3-hydroxyethyl		NaOMe, MeOH/THF, r.t.	143
17		monocyclic, 3-side chain	-	dibal-H, THF, -30°C	144
18		penicillin, 6-side chain	-	citrus acetylesterase	145
19		penem, 2-side chain	-	lipase	120

* causes elimination leading to 

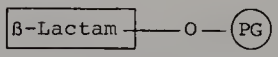
much more stable derivatives. Removal of the TBDMS group is possible only under drastic conditions in this case.

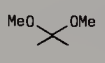
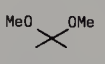
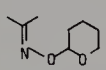
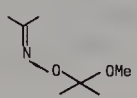
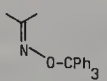
The carbonate protective groups listed in Table 1.12 (entries 1–12) are also widely used. The *p*-nitrobenzyloxycarbonyl group (Table 1.12, entries 1–4) and the Alloc group (Table 1.12, entries 6–8) are particularly suitable for sensitive systems, as exemplified by the deprotection of the 6-hydroxyethyl group of a very unstable oxapenem derivative at 0°C (Table 1.12, entry 4). Use of the corresponding carbamates (amino protection, Section 1.2.2) and esters (protection of carboxylic acid functions, Section 1.4) should also be mentioned.

Among the ester protective groups, formic acid esters (Table 1.12, entries 13 and 14) can be selectively saponified even in cephalosporins. In this connection, reference should also be made to cefmandole formate (Mandol, E. Lilly), a prodrug that is hydrolyzed enzymatically in vivo. The removal of chloroacetyl groups by treatment with thiourea was mentioned in Section 1.2.4 in connection with the protection of the aminothiazole group (Table 1.12, entry 15). Two interesting enzymatic deprotections are worth mentioning: Hydrolysis of a bis-acetylated dihydroxyphenylglycine derivative can be achieved without racemization with the aid of an acetyl esterase (Table 1.12, entry 18), and acyl groups in the side chain on position 2 of a penem can be removed by catalysis with lipase (entry 19).

The acetals listed in Table 1.13 (entries 1–4) are used mostly for temporary protection of monocyclic intermediates (but see entry 1). This table also includes a monothioacetal (Table 1.13, entry 5) and cyclic ketals, which simultaneously protect the β-lactam nitrogen (Table 1.13, entries 6–8; see Section 1.2.1). Acetals and ketals are also suitable for the protection of oximes

Table 1.13. ACETALS, KETALS, AND ETHERS AS PROTECTIVE GROUPS FOR HYDROXYL GROUPS



Entry	PG	ß-Lactam	Protection	Deprotection	Ref.
	Acetals + ketals				
1	 (THP)	penem, 6-hydroxyethyl	 , PPTS	PPTS, EtOH, 45°C	120, 146
2	CH_3OCH_2-(MOM)	monocyclic, 3-hydroxyethyl		TFA, H_2O, 0°C	26,48
3	$CH_3OCH_2CH_2OCH_2$- (MEM)	monocyclic, 3-hydroxyisopropyl	MEM-Cl, DIPEA	$TiCl_4$, CH_2Cl_2	147, 148
4	"	"	-	Ph_2BBr, CH_2Cl_2, -78°C	11
5	CH_3SCH_2-	monocyclic, 3-side chain	-	$HgCl_2$, $CaCO_3$ CH_3CN/H_2O	131
6		-	 , BF_3-OEt_2	TsOH, dioxane/H_2O	149
7		-	-	H_2SO_4, THF, 50°C	21
8		-	 , BF_3-OEt_2	AcOH, H_2O, △	22
	diols:				
9		monocyclic, 4-side chain	-	TFA, H_2O, r.t.	150
	oximes:				
10		cephalosporin	-	TFA, H_2O, r.t.	151
11		"	-	1 eq HCl, acetone, r.t. or 90 % HCO_2H/H_2O, r.t.	152 153
	Ethers				
12	Ph-CH_2-	monocyclic, 4-side chain	-	Li, $EtNH_2$, t-BuOH, THF	154
13	"	monocyclic, C-3-hydroxy	-	Pd-C, NH_4HCO_3, MeOH, △	143
14	"	norcardicin, N-1 side chain	-	1 atm H_2, Pd-C, r.t.	99
15	MeO-  -CH_2-	cephalosporin, 3-side chain	-	TFA, anisole, 0°C	41
	Oximes:				
16		cephalosporin	-	TFA, r.t.	155
17	O_2N-	monocyclic, 3-hydroxyethyl	-OMs + $Bu_4N^{\oplus}$ $NO_3^{\ominus}$, Ph-H, △	1 atm H_2, Pd-C, MeOH, r.t.	156

in the side chain of cephalosporins (Table 1.13, entries 10 and 11). Deprotection conditions are very mild, particularly for the mixed acetone ketals, with no attack on trityl protective groups or *tert*-butyl esters. With the use of the trityl group (Table 1.13, entry 16), on the other hand, trifluoroacetic acid is required for deprotection.

In addition to the relatively uncommon use of benzyl ethers for the protection of hydroxyl groups (Table 1.13, entries 12–15), use of the nitro group for the same purpose is mentioned as a curiosity (Table 1.13, entry 17). Once this group has been introduced under S_N2 conditions (inversion), it is stable in the course of a series of reactions, and can finally be removed by hydrogenolysis.

1.4 Protective Groups for Carboxylic Acid Functions in β-Lactam Derivatives

1.4.1 Protective Groups That Can Be Removed Chemically

With few exceptions (monobactams), a carboxylic acid function α to the β-lactam nitrogen is an essential condition for good antibacterial activity, and it is nearly always necessary to protect this carboxylic acid function during the preparation of derivatives. Just as in the protection of amino and hydroxyl functions, the groups that can be used for this purpose depend mainly on the stability of the β-lactam systems under the conditions required for deprotection (Figure 1.5).

The *p*-nitrobenzyl group (Table 1.15, entries 10–20) or the allyl group (Table 1.16, entries 1–7) is generally used for sensitive systems; both these groups are also very suitable, as far as deprotection is concerned, in derivatives with multiple protection. Also suitable are the less commonly used *p*-methoxybenzyl group (Table 1.15, entries 6–9, removal by treatment with $AlCl_3$) and the acetonyl ester group (Table 1.14, entries 4–7). The latter is extremely readily saponifiable (titration with NaOH in tetrahydrofuran at 0°C), but this instability also prevents its use in many synthetic operations.

Protective groups that can be removed under acidic conditions are most often used for penicillins and cephalosporins (benzhydryl: Table 1.15, entries 23–30; *tert*-butyl: Table 1.14, entries 19–23; *p*-methoxybenzyl: Table 1.15, entries 6–9). Favored reagents are trifluoroacetic acid (TFA)/anisole (as a cation scavenger) and $AlCl_3$ or $SnCl_4$ at low temperatures in anisole as a cosolvent. Most of the other protective groups listed in Tables 1.14 to 1.16 are less commonly used, but may be of interest for special cases.

Table 1.14 lists mainly substituted alkyl groups, which are activated for removal by the most diverse means. A few ester groups can be removed even from unstable systems. In addition to the acetonyl ester group mentioned earlier (Table 1.14, entries 4–7), these include the trimethylsilylethyl ester group (Table 1.14, entries 12 and 13) and two acetal groups (Table 1.14,

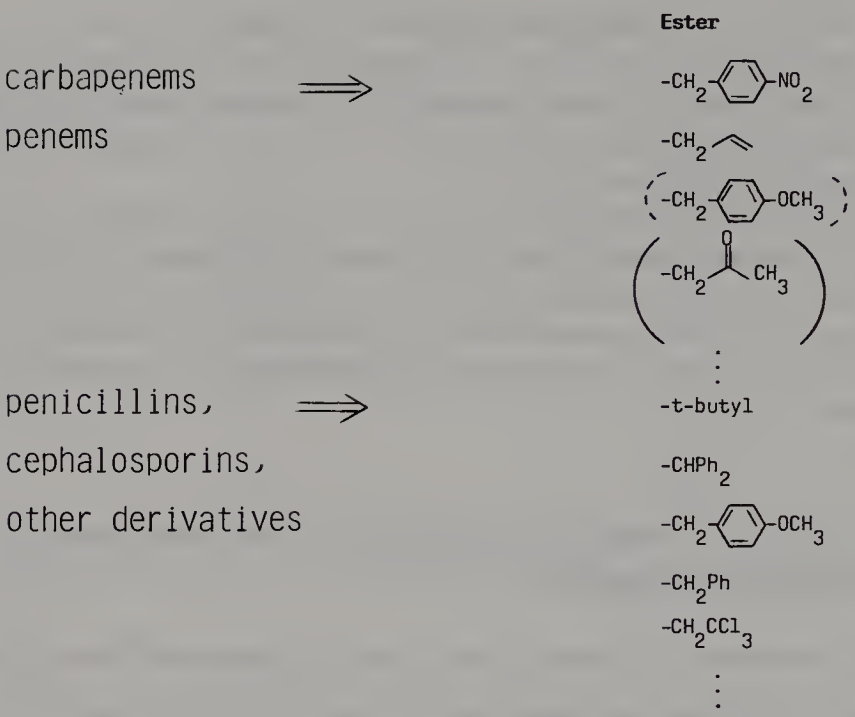


Figure 1.5. Typical ester protective groups for bicyclic β-lactams.

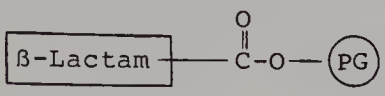
entries 17 and 18). Alkaline hydrolysis of an unsubstituted ester group (Table 1.14, entries 2 and 3) is possible only in a few monocyclic derivatives, as the β-lactam linkage may have a similar reactivity, depending on the substitution pattern.

The benzyl ester group (Table 1.15, entries 1–5) can be removed either by hydrogenolysis or by catalysis with a Lewis acid; however, *p*-methoxybenzyl and *p*-nitrobenzyl ester groups (entries 6–9 and 10–20, respectively) are preferable, as they are much more reactive under the deprotection conditions used. The *p*-nitrobenzyl ester group even permits the preparation of extremely unstable 6-amidopenems (Table 1.15, entries 16 and 17) and equally sensitive oxapenems (Table 1.15, entries 19 and 20). The hydrogenolysis here can be accomplished within a few minutes even at 0°C (Table 1.15, entry 20, see also Sections 1.2.2 and 1.3). The *p*-nitrobenzyl ester group can also be removed by several other reductive methods (Table 1.15, entries 10–14).

Other groups that should be mentioned are the *o*-nitrobenzyl group, which can be removed photolytically (Table 1.15, entries 21 and 22), and the *p*-methoxycarbonylbenzyl ester group, which can be removed even from carbapenems by electrolysis (Table 1.15, entries 31 and 32).

As was mentioned earlier, the allyl group (Table 1.16, entries 1–7) is one of the most easily removable protective groups. It can be removed even from a very unstable 6-amidocarbapenem (Table 1.16, entry 5). One disadvantage of this group, namely its reactivity toward some electrophilic reagents (e.g.,

Table 1.14. ALKYL ESTER PROTECTIVE GROUPS



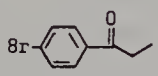
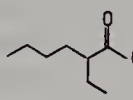
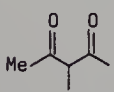
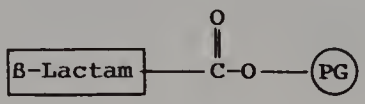
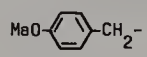
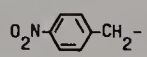
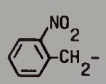
Entry	(PG)	ß-Lactam	Deprotection	Ref.
1	CH_3-	monocyclic	LiI, Py, △	99
2	"	"	1N KOH, MeOH, 0°C	157
3	C_2H_5-	"	LiOH, MeOH, 0°C	158
4		carbapenem	1 eq NaOH, THF/H_2O, 0°C	159
5	"	"	1 eq NaOH, dioxane, 5°C	160
6	"	penem	NaOH, CH_3CN/H_2O	161
7	"	"	NaOH, THF/H_2O, 0°C	162
8		penicillin	Ph-$S^{\ominus}$ $K^{\oplus}$, DMF, r.t.	163
9	Cl_3C	cephalosporin	Zn, 90 % AcOH, 0°C	2
10	"	penicillin	" " "	37
11	"	cephalosporin	Zn, AcOH, OMF, r.t.	164
12	Me_3Si	penem	Bu_4NF, THF, 	48
13	"	isoxacephem	Bu_4NF, THF, r.t.	165
14	Br	penicillin	aquocobalamin , Hg electrode, -1,95 V	166
15	"	penicillin, cephalosporin	Co(I)phthalocyanin, phenol, acetone, r.t.	58a
16		penicillin	$NaNO_2$, acetone/H_2O, r.t.	167
17	Me-O-CH_2-(MOM)	carbapenem	$AlCl_3$, anisole, 50°C	29
18		penem, penicillin, cephalosporin	AcOH, THF/H_2O, r.t.	168
19	t-Bu-	penicillin	TFA, r.t.	169
20	"	cephalosporin	TFA, anisole, CH_2Cl_2, r.t.	170
21	"	carbacephem	TFA, CH_2Cl_2, r.t.	68
22	"	cephalosporin	98 % HCO_2H/H_2O	170
23	"	"	HCO_2H, c.HCl, r.t.	113

Table 1.15. BENZYL AND SUBSTITUTED BENZYL ESTER PROTECTIVE GROUPS



Entry	PG	β-Lactam	Deprotection	Ref.
1	$Ph-CH_2-$	penicillin	1 atm H_2, Pd-C, dioxane, r.t.	171
2	"	cephalosporin	$AlCl_3$, anisole, CH_2Cl_2/CH_3NO_2	38
3	"	carbacephem	$AlCl_3$, anisole, CH_2Cl_2, 0°C	172
4	"	carbapenem	1 atm H_2, Pd-C, THF, r.t.	173
5	"	cephalosporin	$SnCl_4$, anisole	115
6		cephalosporin	TFA, anisole, 0°C	41
7	"	"	TFA or TsOH or c.HCl in phenol, 45°C	174
8	"	panem, carbapenem	$AlCl_3$, anisole, CH_2Cl_2, -40°C	175
9	"	carbapenem	" " " , -50°C	52
10		penem	Fe, NH_4Cl, H_2O/CH_3CN, r.t.	176
11	"	clavulanic acid	Fe, NH_4Cl, THF, 0°C	177
12	"	penicillin/cephalosporin	Na_2S, THF/H_2O	178a
13	"	2-oxopenam	$Na_2S_2O_4$, THF/H_2O, pH7, 0°C	178b
14	"	carbapenem	Zn, pH7 buffer	179
15	"	cephalosporin, 7-side chain	NaOH, pH12.5, r.t.	180
16	"	6-amidopenem	1 atm H_2, Pd-C, pH7 buffer, 15°C (25 %)	181
17	"	6-amidopenem	1 atm H_2, Pd-C, EE/$NaHCO_3$ (8 %, 55 %)	182
18	"	carbapenem	1 atm H_2, PtO_2, THF/pH7 buffer	45
19	"	oxapenem	1 atm H_2, Pd-C, EE, r.t.	183,184
20	"	oxapenam	1 atm H_2, Pd-C, EE/$NaHCO_3$, 0°C	132
21		carbapenem	hν (350 nm), dioxane/pH7 buffer	51
22	"	"	H_2, Pd-C, pH7 buffer, r.t.	130

chlorine), can be avoided through the use of less electron rich allyl ester groups (Table 1.16, entries 8 and 11). The very labile trimethylsilyl ester group (Table 1.16, entries 13–15) is used only for temporary protection of carboxylic acid functions. Its use in the acylation of 6-APA and 7-ACA derivatives is described in Section 2.3.2.

As the protective groups are usually introduced at a precursor stage

Table 1.15.

Entry	PG	β-Lactam	Deprotection	Ref.
23	Ph_2CH-	cephalosporin	98 % HCO_2H, 40-45°C	185
24	"	"	TMS-I, CH_2Cl_2, r.t.	186
25	"	oxacephem	$AlCl_3$, anisole, CH_2Cl, r.t.	44
26	"	cephalosporin	TFA, 0°C	187
27	"	"	TFA, anisole, 0°C	41
28	"	carbapenem	$AlCl_3$, anisole, CH_2Cl_2, -50°C	52
29	"	oxacepham	$SnCl_4$, anisole, -40°C	135
30	"	cephalosporin/ penicillin	TFA or TsOH or c.HCl in phenol, 45°C	174
31	MeO_2C-  -CH_2-	carbapenem	electrolysis, DMF, -1.9 V	188
32	"	"	" , Hg cathode, DMF	189

and by standard methods,[4] this subject is not discussed in detail here. The first esterifications of penicillin derivatives, which were performed with methyldiazomethane, benzyldiazomethane, and diphenylmethyldiazomethane,[1,86,197] are of historical significance. Procedures for the introduction of the *tert*-butyl ester group by treatment with isobutene/sulfuric acid are described in References 198 (6-APA) and 199 (7-ACA).

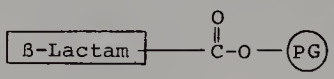
In base-catalyzed esterifications of cephalosporins, there is generally a danger of isomerization of the double bond.[200] This is avoided by using diazo compounds,[185] alkylating esterification,[201] or special mild activation methods.[202,203] Further examples of alkylating esterifications without isomerization are described in Section 1.4.2.

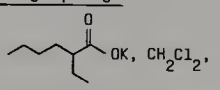
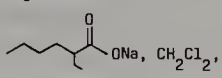
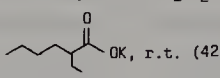
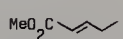
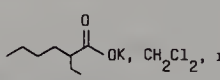
A special method for the synthesis of β-lactams known as the four-component reaction[204] leads to substituted amides as carboxylic acid derivatives. As methods are available for the conversion of these amides into carboxylic acids or esters, these groups can also be included under the protection of carboxylic acid groups (Table 1.17).

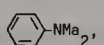
1.4.2 Protective Groups That Can Be Removed Enzymatically (Prodrug Esters)

A procedure that has been employed for some time to improve the absorption of penicillins and cephalosporins after oral administration is the use of special esters that readily undergo enzymatic hydrolysis in vivo, with liberation of the active drug (pivampicillin, bacampicillin, pivmecillinam, cefuroxime axetil, and many others). These esters, which are mostly bis-acyl derivatives of formaldehyde or acetaldehyde, can also provide protection for carboxylic acid functions during derivatization and synthetic operations.

Table 1.16. ALLYL AND MISCELLANEOUS ESTER PROTECTIVE GROUPS

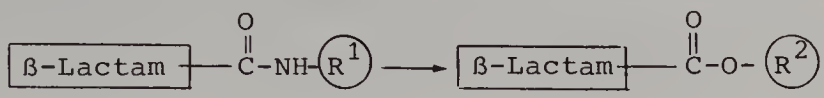


Entry	PG	ß-Lactam	Deprotection	Ref.
Allyl			$Pd(Ph_3P)_4$, Ph_3P	
1		penicillin, penem	+  OK, CH_2Cl_2, r.t.	3
2	"	penem	+ Bu_3SnH or dimedone	54
3	"	penem	+  ONa, CH_2Cl_2, r.t.	190
4	"	6-aminoethylcarbapenem	+  OK, r.t. (42 %)	78
5	"	6-amidocarbapenem	+ " , r.t. (20 %)	98
6	"	carbapenem	+ pyrrolidine, CH_3CN, 0°C	191
7	"	carbapenem, cephalosporin	Pd(0), polymer bound, NMM	57a
8		penicillin	+  OK, CH_2Cl_2, r.t.	3
9		"	+ " , " , "	3
10		"	+ " , " , "	3
11		penicillin, cephalosporin	+ " , " , "	3
12		cepholosporin, 7-side chain	$AlCl_3$, anisole, 30°C	192

			Protection	Deprotection	Ref.
13	Me_3Si-	penicillin	HMOS, $CHCl_3$, △	$NaHCO_3$, MeOH/H_2O, r.t.	193
14	"	cephalosporin	HMOS, 3 % TMS-I	MeOH, 5°C	90
15	"	penicillin	HMOS, $CHCl_3$, △	H_2O work-up	194
16	 *	penicillin	Me_2SiCl_2,  , CH_2Cl_2, r.t.	n-butanol	81
17	Bu_3Sn-	penicillin	$(Bu_3Sn)_2O$, PhH, △	Ph-$S^{\ominus}$ $K^{\oplus}$, r.t.	195
18		penicillin	-	$(NH_4)_2Ce(NO_3)_6$ CH_3CN/H_2O, pH 3, 0°C	196

* protects two carboxylic acids

Table 1.17. CONVERSION OF AMIDES TO ESTERS AND ACIDS



Entry	-NH(R1)	-O-(R2)	Conditions	Ref.
1	$-NH-CHPh_2$	$-O-CHPh_2$	N_2O_4, NaOAc, CH_2Cl_2, r.t.	205,206
2	-NH 	$-O-CH_3$	1) Boc_2O, DMAP, CH_3CN 2) NaOMe, MeOH	207
3	-NH	-O-H	1) H_2, Pd-C, MeOH 2) COI, CH_2Cl_2 3) H_2O, acetone	208
4	$-NH-CH_3$	-O-H	1) PCl_5, Py, CH_2Cl_2, 0°C 2) MeOH 3) KOH, MeOH, 0°C	157

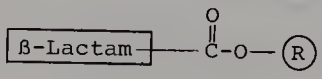
The list in Table 1.18 is not intended to be exhaustive, but merely to provide an overview of the types of groups used and the methods employed for their introduction, which is always by alkylating esterification. Methods for the removal of the ester group are described in two instances (Table 1.18, entries 3 and 5), immobilized PEN acylase being used in the case of the phenylacetic acid derivative (Table 1.18, entry 5).

1.5 Protection of Carbonyl Groups in β-Lactam Derivatives

Carbonyl groups are generally protected by the use of acetals or ketals, which can be readily hydrolyzed under weakly acidic to acidic conditions (Table 1.19, entries 1–8). The use of 1,3-dithiolans is less common (Table 1.19, entries 9–12), the main significance of these derivatives being acyl equivalents having reversed polarity. The thioacetal (thioketal) group can be removed by standard methods; a relatively commonly used method is oxidative transacetalization with thallium(III) nitrate in methanol, which leads to readily hydrolyzable dimethylacetals (dimethylketals) (Table 1.19, entries 9 and 12).

Enamines have occasionally been used for the protection of β-keto ester functions in the N-1 side chain (Table 1.19, entries 13 and 14). Figure 1.6 shows a unique example, in which an entire β-keto ester unit is protected as a cyclic ketal. The β-keto ester can be regenerated under neutral conditions with *p*-nitrobenzyl alcohol.[228]

Table 1.18. PRODRUG ESTERS



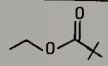
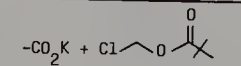
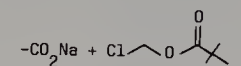
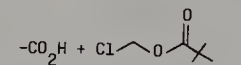
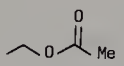
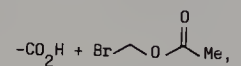
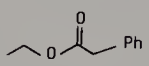
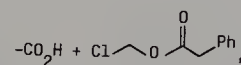
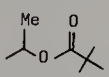
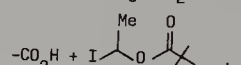
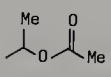
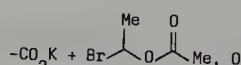
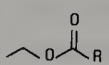
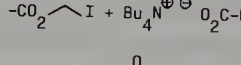
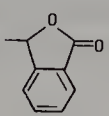
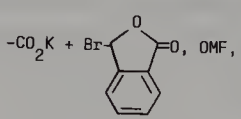
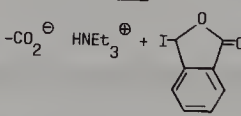
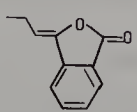
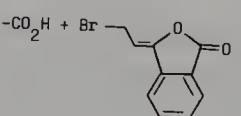
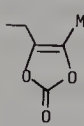
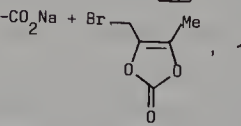
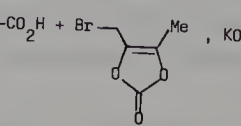
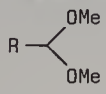
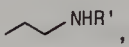
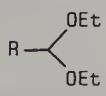
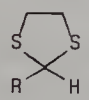
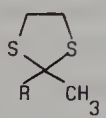
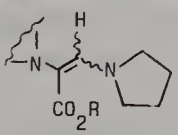
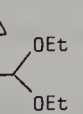
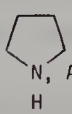
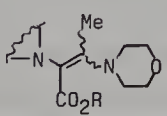
Entry	-R	ß-Lactam	Preparation	Ref.
1		penicillin	 , acetone (25 %)	209
2	"	carbapenem	 , HMPA, r.t.	65
3	"	penicillin	 , NEt_3, OMF	62
			cleavage: $(Bu_2Sn)_2O$, AIBN, Et_2O, -10°C (43 %)	210
4		cephalosporin	 , NEt_3, acetone, r.t. (34 %)	211
5		penicillin, cephalosporin	 , NEt_3, OMF	212
			cleavage: PEN-acylase on Eupergit C, CH_3CN/H_2O, pH 7.3	212
6		cephalosporin	 , OBU	153
7		"	 , OMF, 10°C	213,214
8		penicillin sulphone	 , acetone, r.t.	215
9		penicillin	 , OMF, 0°C (45 %)	216
10	"	cephalosporin	 , OMSO, CH_3CN	217
11		penicillin	 , K_2CO_3, 0°C (48 %)	67
12		penem	 ,  , r.t.	218
13	"	cephalosporin	 , KOAc, OMF, -20°C (50 %)	60

Table 1.19. PROTECTIVE GROUPS FOR THE CARBONYL FUNCTION (ALL DERIVATIVES ARE MONOCYCLIC)

Entry	PG	Deprotection	Ref.
	Acyclic acetals		
1		TsOH, acetone, r.t.	219
2	"	TMS-I, r.t.	220
3	"	 , TFA → Dithioacetal	221
4		95 % TFA, 50°C	222
	1,3-Dioxolans		
5		HCl, MeOH	6
6	"	HCl, acetone, r.t.	223
7	"	70 % $HClO_4$, CH_2Cl_2, 0°C	224
8	"	TFA, H_2O, r.t.	225
	1,3-Dithiolans		
9		$Tl(NO_3)_3$, MeOH, Ph-H → 	219
10	"	HgO, BF_3-OEt_2, THF/H_2O, r.t.	226
11	"	MeI, $BaCO_3$, acetone, (40-50 %)	88
12		1) $Tl(NO_3)_3$, MeOH, r.t. 2) $HClO_4$, dioxane/H_2O, r.t.	227
	Enamines		
13		HCl, acetone, △ (Formation:  ,  N, AcOH, PhH)	222
14		H_2SO_4, MeOH (Formation: ketone, Ts-Cl, NMM; then 	192
	Olefins		
15	→ Aldehydes	1) OsO_4 2) H_5IO_4	229
16	"	O_3 then Me_2S	162,182
17	→ Ketones	O_3 then Ph_3P	88
18	"	O_3 then Me_2S	230

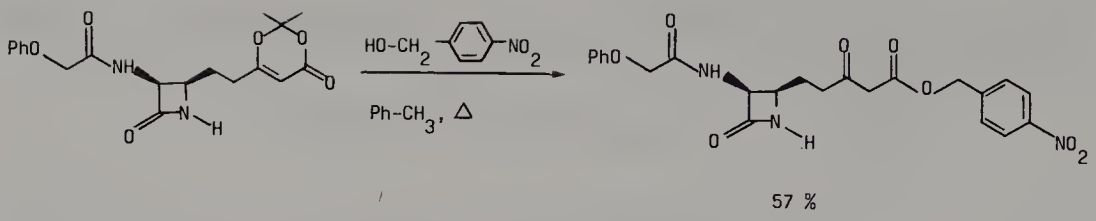


Figure 1.6. Deprotection of a β-keto ester protected as a cyclic ketal.

Instead of protected aldehydes or ketones, olefins are often used as carbonyl precursors (Table 1.19, entries 15–18), and the desired derivatives are then obtained by ozonolysis or similar oxidative cleavage methods. This provides a particularly elegant means of forming the aldehyde function in situ in syntheses of penems and carbapenems having no substituent in position 2.

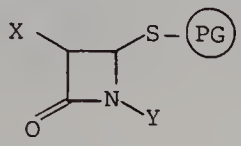
1.6 Protective Groups for Thiol Functions in β-Lactam Chemistry

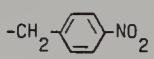
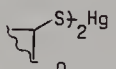
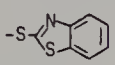
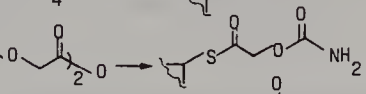
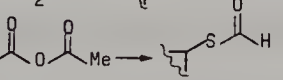
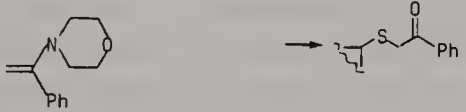
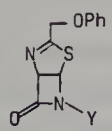
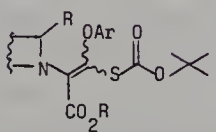
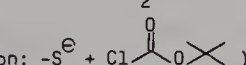
The thio group most frequently in need of protection is the 4-thio group in monocyclic β-lactams, whose conversion into a thioester, dithioester, or trithiocarbonate group is an important reaction in the synthesis of penem derivatives. A group that is often used is the tritylthio group (Table 1.20, entries 1–4); treatment of the resulting derivative with silver nitrate readily yields the silver thiolate, an intermediate that can be isolated and is particularly suitable for acylations. Reaction of the silver salt with H_2S leads to the free thiols (Table 1.20, entry 1). Alternatively, the corresponding mercury compounds may be prepared (Table 1.20, entry 2) and converted into thiols. Three further examples illustrate the use of tetrahydropyranyl, benzyl, and *p*-nitrobenzyl groups for the protection of thiol functions (Table 1.20, entries 5–7).

Bicyclic thiazolines, which are readily available from penicillin derivatives, are also viable precursors of 4-thio β-lactams (Table 1.20, entries 11–13). Benzothiazole disulfides are interesting in that acylations can be performed in the presence of phosphorus(III) compounds without isolation of intermediates (Table 1.20, entries 8 and 9), and nucleophilic substitutions on the sulfur (Table 1.20, entry 10) are also possible. The last example in Table 1.20 shows the protection of a very unstable thioketen acetal (entry 14). If R = Cl, deprotection with imidazole leads to immediate penem ring closure.

Finally, Figure 1.7 illustrates a possibility for the protection of the very unstable 4-sulfenic acid in the β-lactam. It can be intercepted from the equilibrium with the corresponding penicillin sulfoxide as the trimethylsilyl es-

Table 1.20. PROTECTIVE GROUPS FOR THIOL FUNCTIONS IN β-LACTAMS



Entry	(PG)	Deprotection	Ref.
1	$-CPh_3$	1) $AgNO_3$, MeOH, r.t. 2) H_2S	231
2	"	1) $Hg(OAc)_2$, MeOH 2) H_2S	231
3	"	$AgNO_3$, Py, MeOH, 0°C → 	232
4	"	$AgNO_3$, MeOH → 	233,234
5		$AgNO_3$, MeOH → 	235
6	$-CH_2Ph$	Na, NH_3, -70°C → 	236
7		1) H_2, Pd-C 2) $HgSO_4$, MeOH → 	237
8		$P(OEt)_3$, 	238
9	"	Ph_3P, NaI, OMAP, 	175
10	"		239
11		1) $AgClO_4$ or $AgBF_4$, THF, r.t. 2) H_2S, CH_2Cl	240
12	"	30 % $HClO_4$ or 30 % TsOH, CH_2Cl_2/acetone, r.t.	240
13	"	AcOH/H_2O, r.t.	241
14		imidazole, dioxane, H_2O, 0°C (Formation: )	242

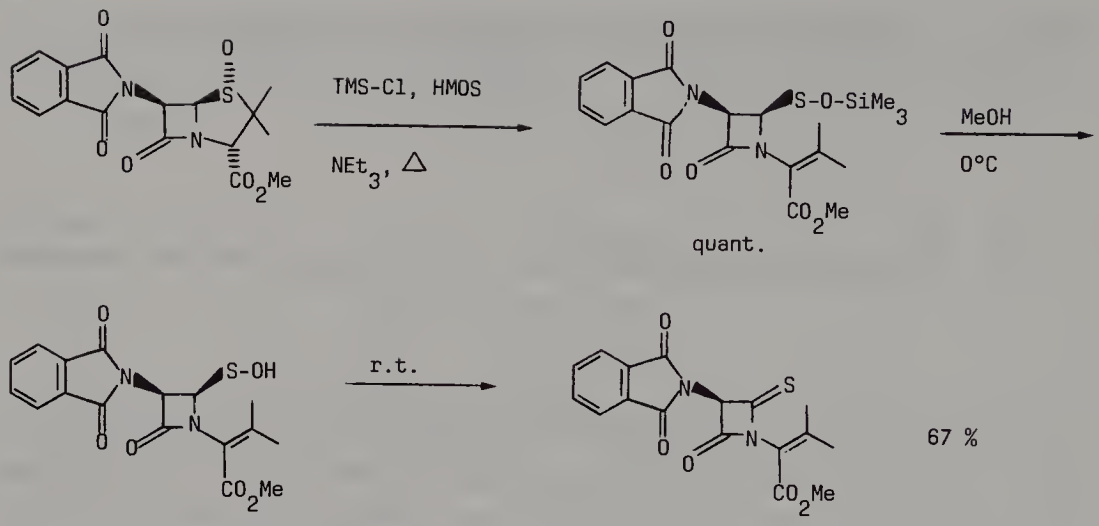


Figure 1.7. Protection of the 4-sulfenic acid.

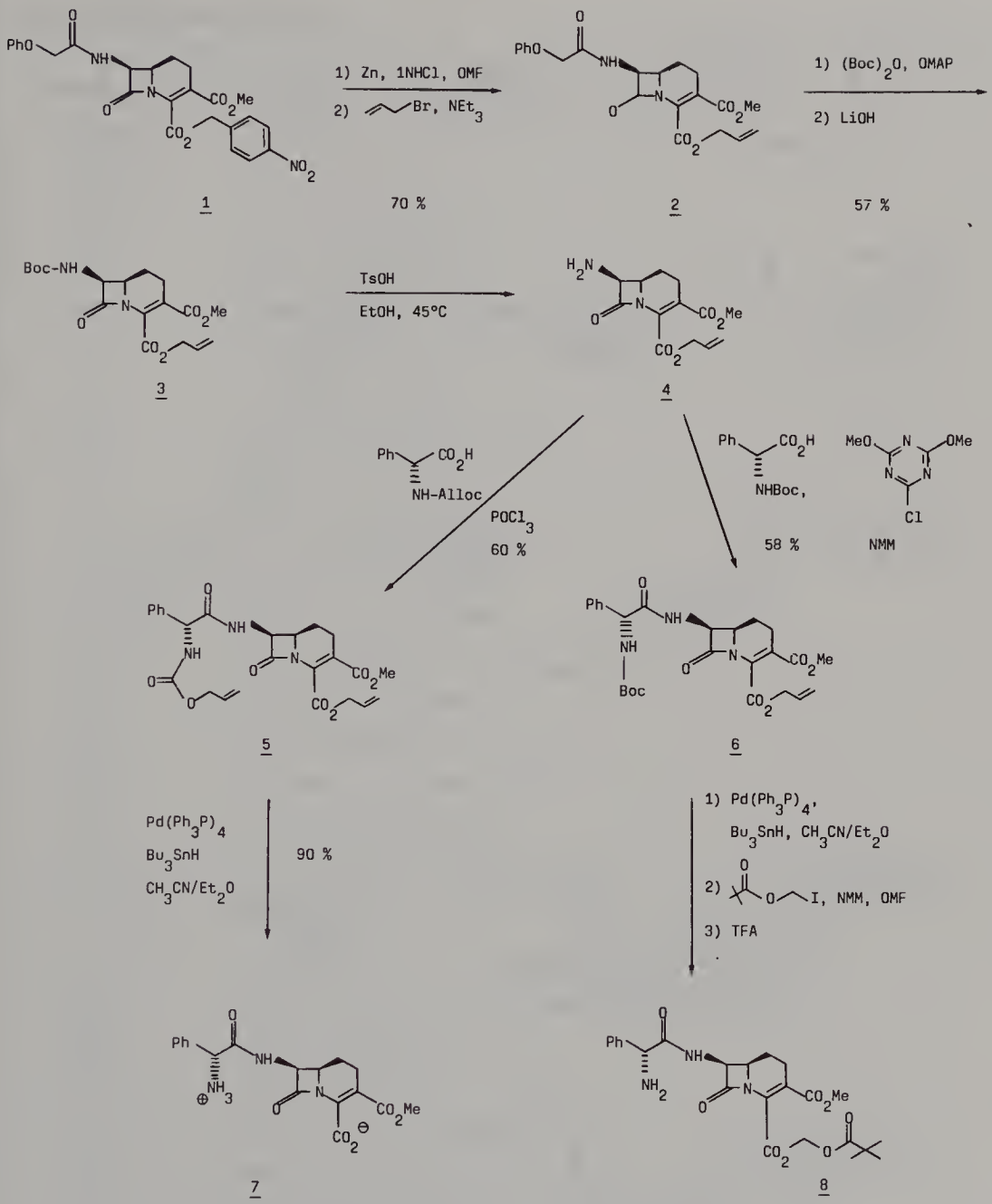
ter. The sulfenic acid is selectively liberated in methanol at 0°C and changes into the 4-thiono-β-lactam via a dimeric intermediate.[243,244]

1.7 Examples from Practice

In this section, some examples are described to illustrate the possibilities offered by the available protective group techniques.

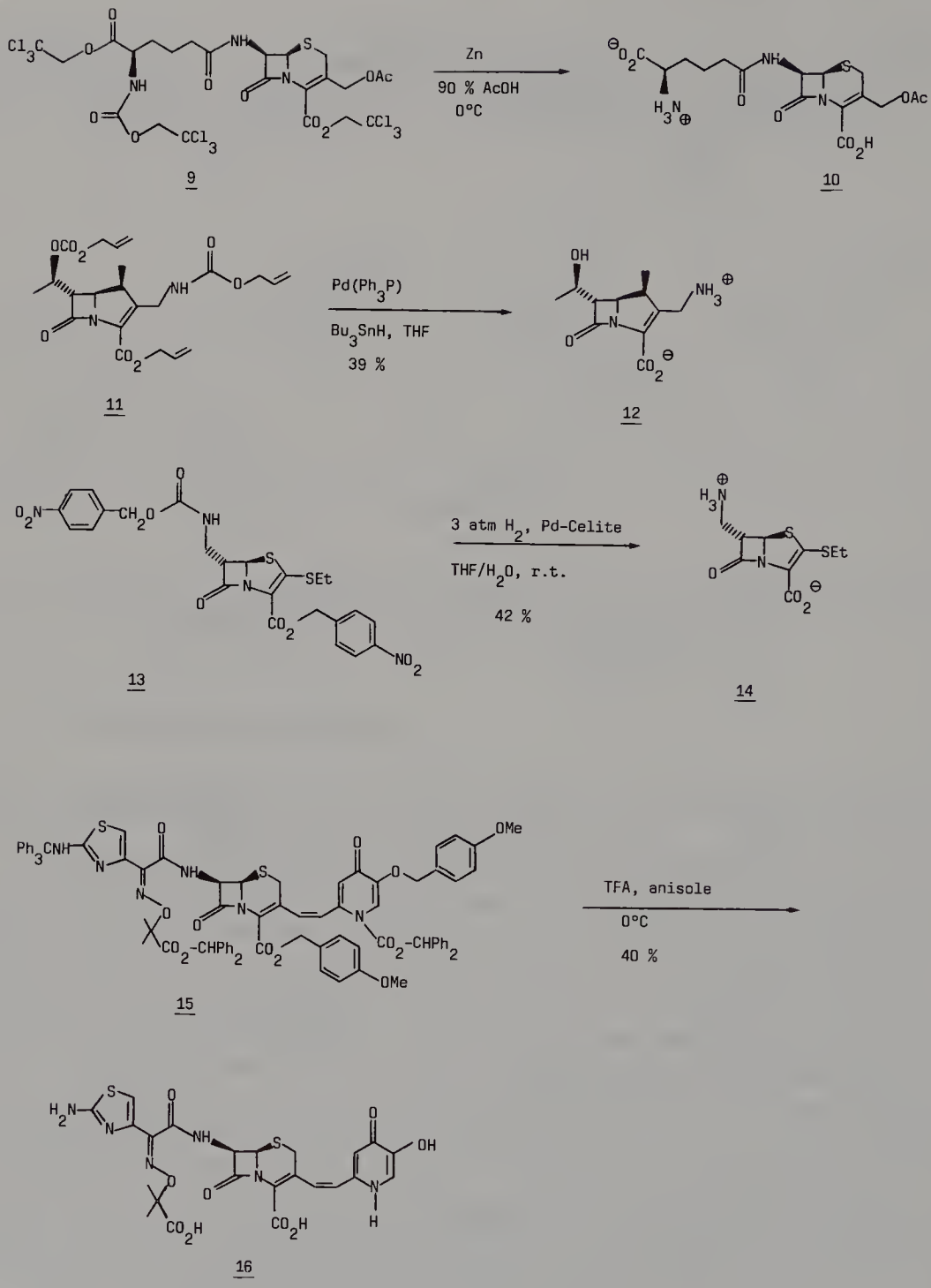
Scheme 1.1 shows a number of reaction steps carried out by J.E. Munroe and co-workers (E. Lilly) in their synthesis of carbacephem derivatives.[53] Beginning with intermediate **1** the *p*-nitrobenzyl protective group (which has been necessary up to this point) is removed by reduction and replaced by an allyl ester group. The phenoxyacetic acid unit in **2** is replaced by the Boc protective group by saponification of the bis-acyl intermediate (see Section 1.2.3). The free amine **4** is produced by treatment with *p*-toluenesulfonic acid. Coupling with Alloc-protected phenylglycine followed by simultaneous palladium-catalyzed removal of the two allyl groups leads to a good yield of the betaine **7.** By reaction of **4** with Boc-phenylglycine, on the other hand, the allyl ester group can be selectively replaced by a pivaloyloxymethyl ester group. Removal of the Boc group by treatment with trifluoroacetic acid then yields the amino ester **8,** which is a prodrug of the betaine **7.**

Scheme 1.2 shows some examples of the simultaneous removal of several protective groups, in some cases from very unstable systems. In the final step of Woodward's cephalosporin synthesis, the trichloroethyl groups are removed from the precursor **9** with zinc in glacial acetic acid, with formation of cephalosporin C (**10**).[2] Triple deprotection of a 2-aminomethylcarbapenem **11** can be achieved with palladium as a catalyst,[56] and a very unstable 6-aminomethylpenem **14** can be prepared by hydrogenolytic removal of the



Schema 1.1

p-nitrobenzyl protective group.[47] The final example shows the removal of five protective groups from a cephalosporin derivative **15**, again by trifluoroacetic acid. Compound **16** is obtained here in an acceptable yield by simultaneous cleavage of a tritylamine group, a benzhydryl ester group, a benzhydryl carbamate group, a *p*-methoxybenzyl ester group, and a *p*-methoxybenzyl ether group.[41]



9 10 11 12 13 14 15 16

Schema 1.2

1.8 Abbreviations

7-ACA	7-Aminocephalosporanic acid
AIBN	2,2′-Azobisisobutyronitrile
Alloc	Allyloxycarbonyl
6-APA	6-Aminopenicillanic acid
Boc	*tert*-Butyloxycarbonyl
BSA	Bistrimethylsilyl acetamide
Cbz	Carbobenzyloxy (benzyloxycarbonyl)
CDI	Carbonyldiimidazol
DAST	Diethylamino sulfur trifluoride
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DEAD	Diethylazodicarboxylate
Dibal-H	Diisobutylaluminum hydride
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME	1,2-Dimethoxyethane (glyme)
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
2,4-DNPH	2,4-Dinitrophenylhydrazine
EE	Ethyl acetate
EEDQ	*N*-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoric triamide
LDA	Lithium diisopropylamide
MCPBA	*meta*-Chloroperbenzoic acid
MEM	Methoxyethoxymethyl
MOM	Methoxymethyl
MoOPH	Oxodiperoxymolybdenum(pyridine)hexamethyl phosphoramide
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
NMM	*N*-Methylmorpholine
NPS	*o*-Nitrophenylsulfenyl

PCC	Pyridinium chlorochromate
PPTS	Pyridinium *p*-toluenesulfonate
Py	Pyridine
t-	*tert*-
TBDMS	*tert*-Butyldimethylsilyl
Teoc	Trichlorethoxycarbonyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoracetic acid
THP	Tetrahydropyranyl
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl (tosyl)

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Sendo, Y.; Tsuji, T.; Yoshioka, M. In *Recent Advances in the Chemistry of* β-*Lactam Antibiotics;* Elks, J., Ed.; Spec. Pub. No. 28, Roy. Soc. Chem.: London, **1977;** p. 243.

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CHAPTER

2

Introduction and Transformation of Functional Groups in β-Lactam Chemistry

Hanno Wild

Bayer AG, Chemistry Science Laboratories Pharma, P.O. Box 10 17 09, 5600 Wuppertal 1, Germany

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2.2 Introduction and Transformation of Functional Groups Directly on the β-Lactam Ring
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  2.2.2 At C-2
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2.1 Introduction

A detailed presentation of the introduction and transformation of functional groups in β-lactam chemistry should really take the following three areas into account:

1. Reactions that are specific to β-lactam systems: Above all, this means many of the transformations that take place directly on the ring system of monocyclic or bicyclic β-lactams.
2. Reactions that, owing to the presence of the β-lactam, demand reaction conditions that are particularly mild or special in some other way.
3. Standard reactions that can also be performed on β-lactams.

The enormous variety of reactions involved, however, extends beyond the scope of this chapter. Consequently, the following is merely a concentrated synopsis of the most important methods devised specifically for β-lactam systems (items 1 and 2). Standard reactions (item 3) are dealt with only in exceptional cases, when unusual conditions or selectivities so demand.

This chapter cannot give a complete overview of all the possible transformations at a specific position. A further restriction lies in the concentration on the chemistry of the main β-lactam systems: monobactams, penams, cephems and analogs, penems, carbapenems. Transformations on other systems (e.g., isocephems and oxapenams) are mentioned only in isolated instances. Furthermore, there is no further discussion of those fields that have already been dealt with at length in the two excellent books preceding this one: (1) E. H. Flynn, *Cephalosporins and Penicillins,* 1972,[1] and (2) R. B. Morin and M. Gorman, *Chemistry and Biology of β-Lactam Antibiotics,* 1982.[2] Reference are made to the appropriate chapters of these books in many cases.

The sections of this chapter are arranged as depicted in Figure 2.1. Section 2.2 deals with reactions occurring directly on the β-lactam ring. In this

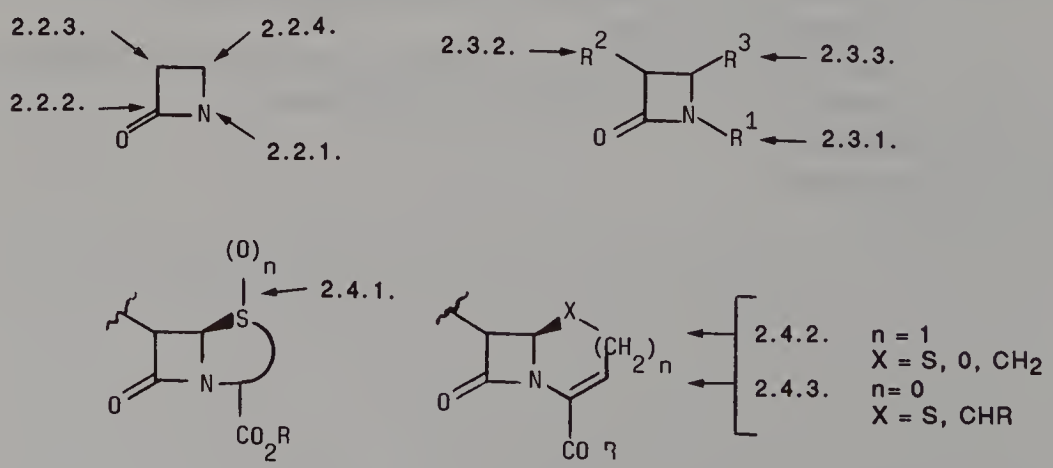


Figure 2.1. Index of functional group transformations covered in Chapter 2.

context, transformations on monocyclic and bicyclic derivatives are discussed in Sections 2.2.2 and 2.2.3. Section 2.3 discusses the most important reactions typical of the side chains of monocyclic β-lactams (2.3.1, 2.3.3) or monocyclic and bicyclic β-lactams (2.3.2). Section 2.4 deals with transformations on the second ring of bicyclic β-lactams. Typical methods for oxidizing and reducing the ring sulfur (2.4.1), reactions in positions 2 and 3 of cephems and their analogs (2.4.2), and reactions in position 2 of penems and carbapenems (2.4.3) are presented.

For reasons of space, the methods are summarized in the tables, the educts and products being shown only with those parts of the molecule relevant to the reaction. Typical reaction conditions are stated, but no yields, as several derivatives have often been transformed with varying results. Where possible, however, only those reactions have been included that offer reasonable product yields. The yields are noted where this is not the case.

2.2 Introduction and Transformation of Functional Groups Directly on the β-Lactam Ring

2.2.1 At N-1

The alkylation or hydroxyalkylation of the β-lactam nitrogen is an important reaction for building up cyclization precursors for bicyclic β-lactams (Table 2.1, entries 1–9). Further transformations of the hemiacetals (entries 1–3) and acetic acid derivatives (entries 4–6) obtained in this way are described in Section 2.3.1. Table 2.1 also shows a number of possibilities for introducing the sulfo group of the monobactams (entries 10–13). Reaction with the DMF–SO_3 complex (entry 12) has become widely accepted in this context. The sulfonation reagent of entry 13 is characterized by the fact that the resultant salt is readily soluble in organic solvents, thus facilitating further reactions.

The β-lactams, unsubstituted at N-1, that are required for the reactions shown in Table 2.1 are obtained either by total synthesis or, expediently, in optically pure form by degradation of penicillin derivatives. Starting with the latter, ring fission and basic isomerization of the double bond[14] lead to the olefins shown in Table 2.2. By oxidation, these can be converted into β-lactams unsubstituted at N-1 via intermediate oxalic acid amide esters which are highly sensitive to hydrolysis (entries 1–5). The double bond can be acetoxylated twice by electrolysis. The acetal formed is hydrolyzed under the reaction conditions (entry 6).

2.2.2 At C-2

Reactions at C-2 of azetidinones that take place without ring fission rank among the exceptions in β-lactam chemistry. Several such transformations

Table 2.1. ALKYLATION, HYDROXYALKYLATION, AND SULFONATION OF THE β-LACTAM NITROGEN

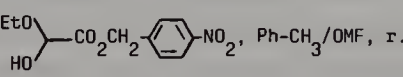
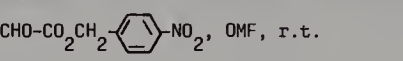
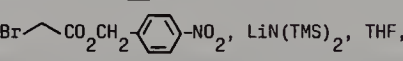
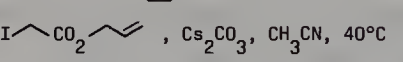
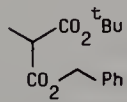
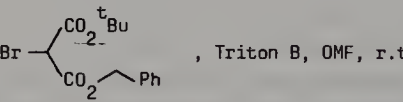
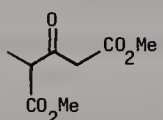
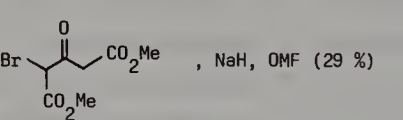
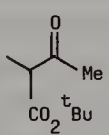
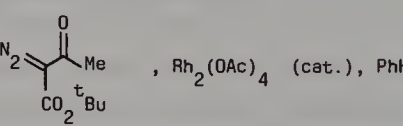
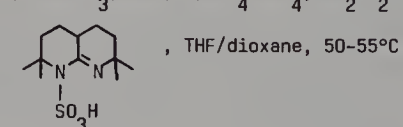
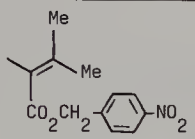
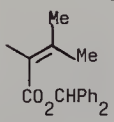
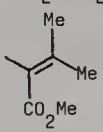
Entry	R	Reaction conditions	Ref.
1		$CHO-CO_2{}^tBu$, $Ph-CH_3$, 90°C	3
2	"		4
3	"		5
4	$-CH_2-CO_2R'$		6
5	"		7
6	"		8
7			9
8			10
9			11
10	$-SO_3^{\ominus}\,M^{\oplus}$, M = Py-H	$Py-SO_3$, CH_2Cl_2/OMF, r.t.	12
11	" , M = K	1) TMS-Cl, NEt_3, CCl_4 2) $TMS-OSO_2Cl$, CH_2Cl_2, 0°C; 3) KH_2PO_4	12
12	" , M = Bu_4N	1) OMF-SO_3, OMF, 2) Bu_4NHSO_4, CH_2Cl_2	12
13	" , M = HNR_3		13

Table 2.2. SYNTHESIS OF β-LACTAMS, UNSUBSTITUTED AT N-1

Entry	R	Reaction conditions	Ref.
1		1) O_3, AcOMe, -78°C then $NaHSO_3$ 2) MeOH, r.t.	4
2		1) O_3, CH_2Cl_2, -70°C then Me_2S 2) MeOH, SiO_2, CH_2Cl_2, r.t.	15
3		O_3, Py, MeOH/H_2O or O_3, MnO_2, MeOH/H_2O	16
4	"	1) O_3, CH_2Cl_2, -78°C then Me_2S 2) 2,4-DNPH, THF, r.t.	17
5	"	$KMnO_4$, AcOH, THF/H_2O, 50°C	18a
6	"	electrolysis, Ac_2O, AcOH, NEt_3, EE	18b

are listed in Table 2.3, namely thionations (entries 1–3) and Wittig reactions on penicillin and clavulanic acid derivatives (entries 4 and 5).

The carbonyl group can be regenerated both from the thiono-β-lactams and the Wittig products (Table 2.4, entries 1 and 3). In addition, Table 2.4 shows a number of further possibilities for producing β-lactams from precursors with four-membered rings: hydrolysis of iminium salts produced by 2 + 2 cycloaddition (entry 2), degradation of carboxylic acids (entries 4 and 5) and α-oxidation of azetidines (entry 6).

2.2.3 At C-3

From the mechanistic point of view, functional groups in position 3 of β-lactams can be introduced and transformed in the following ways: via "carbene" reactions based on 3-diazoazetidinones, by nucleophilic substitution, by reaction of β-lactam enolates, via radical reactions, and by nucleophilic addition on 3-oxoazetidinones or 3-iminoazetidinones.

3-Diazoazetidinones can be produced from penicillins and cephalosporins and isolated with good yields (Table 2.5, entries 1 and 2). Reacting them allows, among other things, selective introduction of heterosubstituents (entries 3–9). The diazo compound can readily be produced in situ (entries

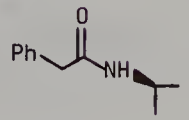
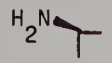
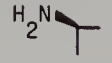
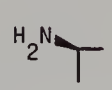
Table 2.3. REACTIONS AT THE CARBONYL GROUP OF 2-AZETIDINONES

Entry	X =	ß-Lactam	Reaction conditions	Ref.
1	S =	monocyclic	P_2S_5, Ph-CH_3, △	19,20
2	"	"	Lawesson's reagent, Ph-CH_3, △	19,20
3	"	cephalosporin	B_2S_3, $CHCl_3$, △ (20 %)	21
4	MeO_2C	penicillin	Ph_3P CO_2Me, Ph-CH_3, △ (Z:E=1:1)	22
5	MeO_2C	clavulanic acid	" , " , " (31 %, Z only)	22

Table 2.4. DEPROTECTION AND INTRODUCTION OF THE 2-AZETIDINONE CARBONYL GROUP

Entry	X =	ß-Lactam	Reaction conditions	Ref.
1	$S^{\oplus}$ =	monocyclic	MCPBA, CH_2Cl_2	23
2	$Me_2N^{\oplus}$ =	"	KOH, H_2O/CH_2Cl_2	23
3	MeO_2C	penicillin	1) O_3, EE, -78°C 2) Ph_3P	22
4	HO_2C H	monocyclic	1) $(COCl)_2$, 0°C 2) 70 % $HClO_4$, 0°C 3) MCPBA, Py, CH_2Cl_2, 0°C	24
5	"	"	1) LOA, THF, 0°C 2) h ν , O_2, ether, -78°C	24
6	H H	"	RuO_2, $NaIO_4$, EE/H_2O, r.t.	25

Table 2.5. FUNCTIONAL GROUP TRANSFORMATIONS AT C-3 OF 2-AZETIDINONES VIA DIAZO INTERMEDIATES AND NUCLEOPHILIC SUBSTITUTION

Entry			ß-Lactam	Reaction conditions	Ref.
diazo intermediates					
1			penicillin sulfoxide	N_2O_4, NaOAc, CH_2Cl_2, -5°C → △	27
2			cephalosporin sulfone	 , TFA (cat.), EE, 31°C	28
3			penicillin	DAST, $CHCl_3$, 10°C	29
4			penicillin	H_2SO_4, $NaNO_2$, KBr, EtOH/H_2O, 6-8°C	30
5			penicillin	H_2SO_4, $NaNO_2$, Br_2, CH_2Cl_2, 5°C	31

(*Continued*)

Table 2.5. (*Continued*)

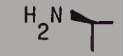
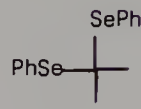
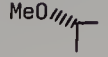
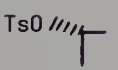
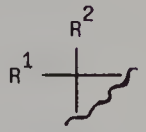
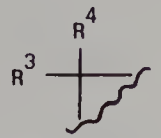
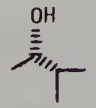
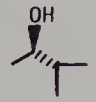
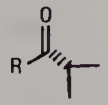
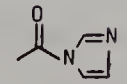
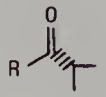
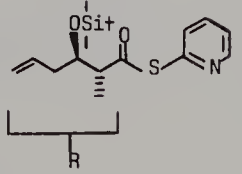
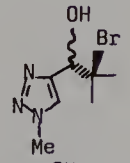
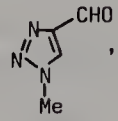
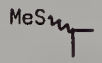
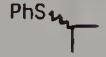
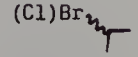
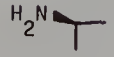
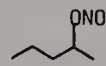
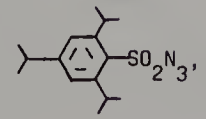
6			cephalosporin	H_2SO_4, $NaNO_2$, I_2, NaI, CH_2Cl_2, 5-10°C	32
7			penicillin	$(PhSe)_2$, BF_3-OEt_2, CH_2Cl_2, r.t.	33
8			penicillin	1NHClO$_4$, acetone/H_2O, 5°C	34
9			cephalosporin sulfone	$Rh_2(OCOC_7H_{15})_4$ (cat.), NEt_3 (cat.), MeOH/EE, -5°C	28
nucleophilic substitution					
10			monocyclic	OEAO, Ph_3P, Me-Br, THF, r.t.	35
11			penicillin	1) Tf-Cl, NEt_3, $CHCl_3$ 2) NaI, acetone	36
12			monocyclic	NaN_3, OMSO, 50°C	35
13			"	NaN_3, OMSO, 55°C	37
14			penicillin	PhSNa, OMF, r.t. (31 %)	38
15			penicillin	OAST, CH_2Cl_2, r.t. (retention!)	29

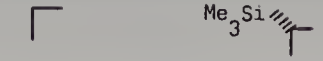
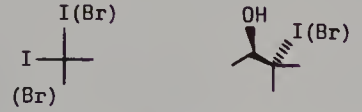
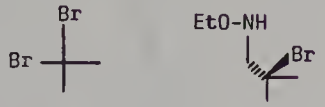
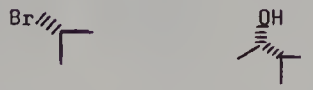
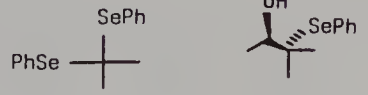
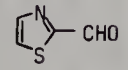
Table 2.6. REACTIONS OF C-3 ENOLATES OF 2-AZETIDINONES

Entry			ß-Lactam	Reaction conditions	Ref.
enolate intermediates					
1			monocyclic	LDA, CH_3CHO, THF, -78°C (main diastereomer)	41
2			"	1) LDA, THF, -78°C 2) Cp_2ZrCl_2, HMPA, -78°C 3) CH_3CHO (main diastereomer)	41
3			"	LDA,  , THF, -78°C	42
4			"	LDA,  , THF, -78°C	43

(*Continued*)

Table 2.6. (*Continued*)

5			penem, carbapenem	$LiNPh_2$,  , THF, -78°C	44,45
6			monocyclic	LOA, MoOPH, THF, -78°C	46
7			"	1) n-BuLi, THF, -78°C then O_2 2) Na_2S, r.t. (26 %)	47
8			penem	LOA, $MeSSO_2Me$, THF, -78°C (28 %)	48
9			bicyclic	LDA, PhSSPh, THF, -78°C	49
10			monocyclic	LDA, $PhSO_2Br$ (Ts-Cl), THF, -78°C	39
11			"	1) LOA,  , THF, -78°C 2) H_2, PtO_2, EE	50
12			bicyclic	1) LOA, Ts-N_3, THF, -78°C 2) TMS-Cl, -78°C ⟶ r.t.	51
13			monocyclic	1) LOA,  , THF, -78°C 2) TMS-Cl, -78°C ⟶ r.t.	13

14				LDA, TMS-Cl, THF, -78°C	39
15			penicillin	1) MeMgI, THF, -78°C 2) CH_3CHO	52,53
16			penicillin sulfone	1) MeMgBr, THF, -80°C 2) CH_2=NOEt, BF_3-OEt_2, -80°C	54
17			monocyclic	1) $LiCuBu_2$, THF, -78°C 2) CH_3CHO	55
18			penicillin	1) MeMgBr, THF, -78°C 2) CH_3CHO	33
19			penicillin sulfone	1) MeMgBr, THF, -78°C 2) 	56
radical intermediate					
20			penicillin (X=H, Br)		57

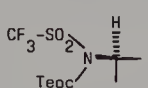
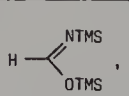
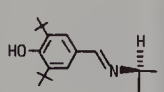
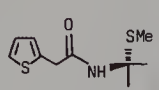
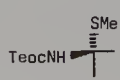
4–6). An overview of further reactions of 3-diazoazetidinones can be found in Reference 26. Nucleophilic substitutions in position 3 produce only reasonable yields if the nucleophiles are very good (entries 10–15).

β-Lactam enolates can easily be produced by deprotonation with strong bases and allow the introduction of numerous electrophiles (Table 2.6, entries 1–14).[39] Another possibility is to react magnesium enolates, which are obtained by halogen–metal exchange, from 3-halogenazetidinones and methyl Grignard compounds (entries 15–19).

Hydroxyalkylation is particularly important, especially hydroxyethylation (Table 2.6 (see page 57), entries 1, 2, 15, and 17), the stereochemistry of which has been investigated in depth.[40,41] The *R* configuration in the side chain is important for the antibacterial activity of penems and carbapenems, and can be obtained either by the use of zirconium enolates (entry 2) or magnesium enolates with subsequent dehalogenation (entry 15, cf. Table 2.9), or by acylation and subsequent selective reduction (entry 3, cf. Section 2.3.2). Table 2.6, entry 20, shows a singular example of radical allylation (cf. Table 2.9).

The production of additional functionality in 3-amino-β-lactams has largely been examined. The introduction of the 7-methoxyl group in cephalosporins or of the 6-methoxyl residue in penicillins is of special importance. Most of the methods developed to this end involve 3-iminoazetidones as

Table 2.7. INTRODUCTION OF THE 3-FORMAMIDE GROUP IN 3-AMINO-2-AZETIDINONES

Entry		R'	β-Lactam	Reaction conditions	Ref.
1		Teoc	penicillin	 , NEt_3, CH_2Cl_2, r.t.	59
2		H	cephalosporin	1) PbO_2, Ph-H, r.t. or OOQ, CH_2Cl_2, r.t. 2) $(TMS)_2NCHO$, CH_2Cl_2, r.t. 3) Girard T, AcOH, EE/MeOH, r.t.	60
3			cephalosporin	1) $Hg(OAc)_2$, NH_3, OMF, 0°C 2) HCO_2COMe, CH_2Cl_2, 0°C	61
4		Teoc	penicillin	$Hg(OAc)_2$,  , OMF, r.t.	62

intermediate stages. A basic overview can be found in Reference 58. Table 2.7 shows just a few examples of the introduction of the 3-formamido group, which has recently come to be of interest. These reactions also take place via intermediate imino stages in accordance with concepts developed for the methoxyl residue.

Table 2.8 shows a few of the ways to obtain 3-oxoazetidinones. Most of these compounds are highly instable and can serve as a starting point for the synthesis of 3-iminoazetidinones,[58] as well as 3-methylene β-lactams (Section 2.3.2). Reduction with sodium borohydride smoothly produces the alcohols.[72,73]

Table 2.8. SYNTHESIS OF 3-OXO-2-AZETIDINONES

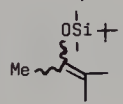
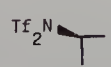
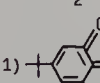
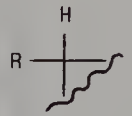
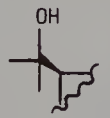
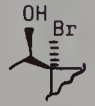
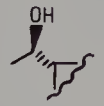
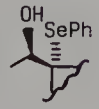
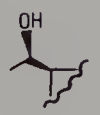
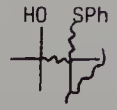
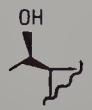
Entry		β-Lactam	Reaction conditions	Ref.
1		penicillin	Ag_2O, Na_2SO_4, CH_2Cl_2, r.t. (formation:  + HCN, 0°C)	63
2		monocyclic	O_3, -78°C	64
3		"	1) O_3, MeOH, -78°C 2) Zn, AcOH, r.t.	65
4		"	1) OsO_4, NMM oxide, acetone, r.t. 2) $NaIO_4$, THF/H_2O, r.t.	66
5		penicillin, cephalosporin	1) DBU or NEt_3, CH_2Cl_2, -78°C 2) dil. HCl, r.t.	67
6		monocyclic	1) SO_2Cl_2, CH_2Cl_2, -10°C 2) $ZnCl_2$ (cat.), SiO_2, $CHCl_3/H_2O$, △	68
7		"	1)  THF, 0°C 2) $(COOH)_2$, THF/H_2O, 0°C	69
8		cephalosporin, penicillin	OCC, OMSO, Ph-H, Cl_2CHOO_2H, r.t.	70
9	"	penicillin	TFA anhydride, DMSO, CH_2Cl_2, -78°C then NEt_3, r.t.	71

Table 2.9. REPRESENTATIVE METHODS FOR THE REMOVAL OF SUBSTITUENTS AT POSITION 3 OF 2-AZETIDINONES

Entry			ß-Lactam	Reaction conditions	Ref.
1			bicyclic	Bu_3SnH, AIBN, PH-CH_3, 95°C	74
2			penicillin	Zn(Ag), MeOH, r.t.	75
3			penicillin	Bu_3SnH, AIBN, THF, △	33
4			bicyclic	Ph_3SnH, AIBN, acetone, △	49

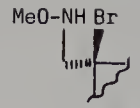
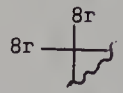
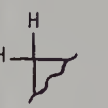
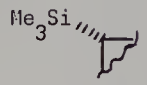
5			penicillin	Bu_3SnH, Ph-H, △	76
6			penicillin	1 atm H_2, Pd, r.t.	77
7			penicillin	Al, $PbCl_2$, NH_4Cl, r.t.	78
8	"	"	"	Pb-cathode, electrolysis, DMF/AcOH/MeOH	79
9		"	"	1) Zn, I_2, ultrasound, dioxane 2) NH_4Cl, r.t.	80
10	"	"	"	Bu_3P, MeOH, r.t.	81
11	"	"	"	2 atm H_2, Pd-$BaCO_3$, dioxane/H_2O, r.t.	82
12		"	monocyclic	KF, CH_3CN, r.t.	83

Table 2.9 (see page 62) lists a number of representative methods for removing substituents in the β-lactam position 3. The reaction can take place either radically or ionically via β-lactam enolates as intermediate stages. In combination with the hydroxyalkylations shown in Table 2.6, these methods are particularly important for stereoselective preparation of 3,4-*cis*-substituted azetidinones (Table 2.9, entries 1 and 3–5) or the synthesis of *trans* derivatives with the desired *R* configuration in the side chain (entry 2). Also of interest is the synthesis of penam derivatives that are unsubstituted in position 6, such as the β-lactamase inhibitor sulbactam (Table 2.9, entries 7–11).

2.2.4 At C-4

Introduction or transformation of functional groups at C-4 of the azetidinone is a necessary step in most total syntheses of β-lactams (Figure 2.2). It is facilitated by the capacity of the β-lactam to enter into S_N1 reactions very easily at this position, these taking place via intermediate acyliminium or acylimine stages.[84] In many cases, the new substituent Y is added *trans*, relative to an existing residue in position 3, and often with very great selectivity; however, residues with an effect on adjacent groups, for example, unprotected hydroxyethyl or amides, can also induce *cis* selectivity.[140,146]

Tables 2.10 to 2.15 describe the most important functionalities and the most common ways of introducing them. Table 2.10 shows the preparation of halides and other reactive substituents, of which the chlorides in particular (entries 1–6) are frequently used for synthesis.

Substituents bonded via oxygen can be introduced by oxidation, starting with 4-unsubstituted β-lactams (Table 2.11, entries 1–4); however, the replacement of other substituents is suitable for a wider range of applications. In this context, particular importance is attached to the oxidative degradation of the easily accessible 4-carboxylic acids and 4-benzoyl compounds (entries 6–9), as well as substitution reactions on bicyclic oxazolines (entries 13–15), for which several methods of preparation are listed in Table 2.12. The unstable 4-hydroxyazetidinone, which breaks down under ring fission at as low as −15°C, is only of theoretical interest (Table 2.12, entry 15).

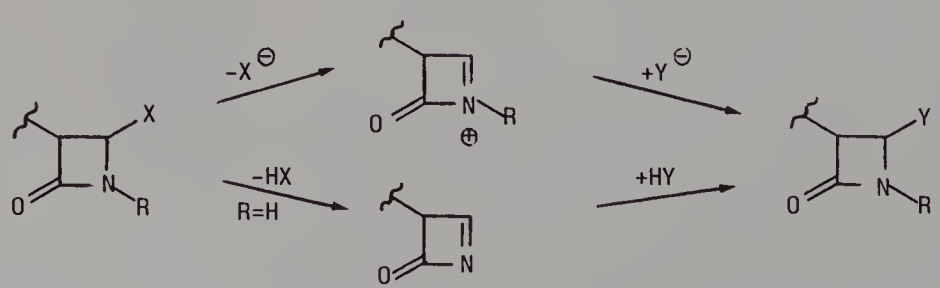
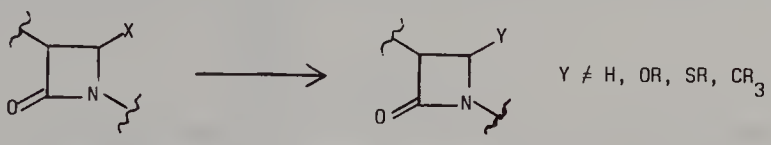


Figure 2.2. Mechanism of substitution reactions at C-4 of 2-azetidinones

Table 2.10. PREPARATION OF C-4 HALIDES AND OTHER REACTIVE C-4 SUBSTITUENTS



Y ≠ H, OR, SR, CR_3

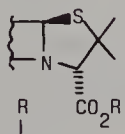
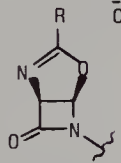
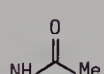
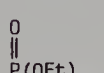
Entry	X	Y	Reaction conditions	Ref.
1	SCH_3	Cl	Cl_2, CH_2Cl_2, -78°C	85
2	"	"	SO_2Cl_2, CH_2Cl_2, r.t.	86
3	"	"	CH_3SCl, CH_2Cl_2, 0°C	87
4		"	Cl_2, CH_2Cl_2, -78°C	88
5		"	HCl, CH_2Cl_2, r.t.	89
6	SO_2H	"	NCS, CH_2Cl_2, r.t.	90
7	"	F	$FClO_3$, DMF, -78°C	"
8	"	Br	NBS, CH_2Cl_2, 0°C	"
9	"	I	NIS, CH_2Cl_2, 0°C	"
10	OAc	N_3	NaN_3, H_2O, r.t.	91a
11	SO_2Ph	"	NaN_3, H_2O, r.t.	"
12	SOPh	"	TMS-N_3, ZnI_2 (cat.) or $TiCl_4$, CH_3CN, r.t.	91b
13	SOPh		BSA, ZnI_2 (cat.), CH_3CN, -20°C	"
14	OAc		$P(OEt)_3$, 120-130°C	91a
15	"	$SiMe_3$	$LiSiMe_3$, CuCN, -30°C ⟶ r.t.	92
16	"	$Sn Bu_3$	$LiSn Bu_3$, CuBr · Me_2S, -50°C	"

Table 2.11. INTRODUCTION OF C-4 SUBSTITUENTS BONDED VIA OXYGEN

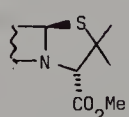
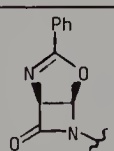
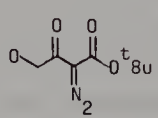
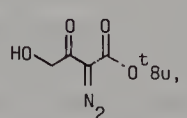
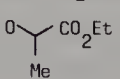
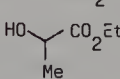
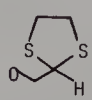
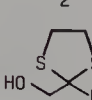
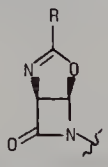
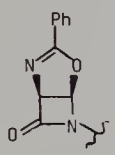
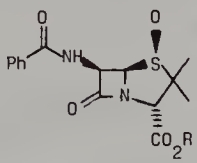
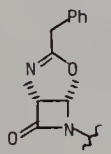
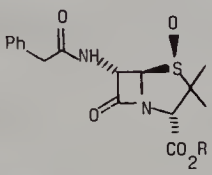
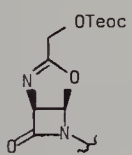
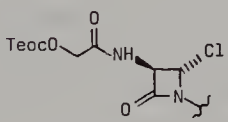
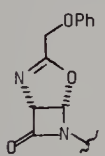
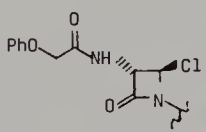
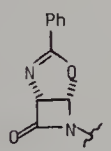
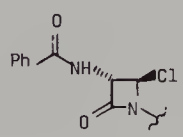
Entry	X	OR	Reaction conditions	Ref.
1	H	OAc	Ru-C, CH_3CO_3H, Ph-H, r.t.	93a
2	H	"	$OsCl_3$, CH_3CO_3H, NaOAc, EE, r.t.	93b
3	H	"	electrolysis, CH_3CN/AcOH, NaOAc	94
4	H		$PhCO_3{}^tBu$, $Cu(O_2CC_7H_{15})_2$ (cat.), Ph-H, △	95
5	$OSiMe_3$	OAc	Ac_2O, DMAP, CH_2Cl_2, -35°C	96
6	CO_2H	"	$Pb(OAc)_4$, DMF/AcOH, 70°C	97,98
7	"	"	$Pb(OAc)_4$, $Cu(OAc)_2$ (cat.), CH_3CN	99
8			MCPBA, CH_2Cl_2	100
9	"	"	$KHSO_5$, R_4NCl, EE/H_2O	101a
10	SPh, SMe	OAc	$Cu(OAc)_2$, TFA, AcOH, 80°C	101b
11		OAc	$Hg(OAc)_2$, Ac_2O, AcOH, 85°C	102
12	SOPh	OAc	AcO-TMS, ZnI_2 (cat.), CH_3CN, r.t.	91b
13			 BF_3-OEt_2, THF, r.t.	103
14	"			104
15	"	OH	1) H_2O_2, Na_2WO_4 (cat.), CH_2Cl_2/AcOH → OOH 2) Me_2S, CH_2Cl_2, -50°C	105
16	SO_2Me		 , $Zn(DAc)_2$, Ph-H, △	106
17	SO_2Me		 , 90°C	107

Table 2.12. SYNTHESIS OF BICYCLIC OXAZOLINES



formation

Entry	Product	Starting material	Reaction conditions	Ref.
1			Ph_3P, squaric acid, CH_3CONMe_2, $PhCH_3$	108
2			Ph_3P, CH_2Cl-CH_2Cl, △	109
3			Ag_2O, $Ag8F_4$, CH_2Cl_2, -30°C	85
4			silicagel chromatography	86
5			$NaHCO_3$, H_2O, 20-30°C	110

On one hand, the thio substituents shown in Table 2.13 are of interest for the preparation of penems; on the other hand, both alkyl and arylthio residues can serve as a kind of protective group for the β-lactam position 4, which can later be reactivated by chlorination (Table 2.10).

Numerous reactions, catalyzed mostly with Lewis acid, are available for introducing carbon-bonded residues that are important for carbapenem and carbacephem syntheses. Silylenol ethers (Table 2.14, entries 1–9) and allyl stannanes and silanes (entries 10–13) can be used, but the substitution reaction with Grignard compounds and cuprates is also possible (entries 14, 15, and 17–20). Exceptions are two radical bondings (entries 16 and 24) and one palladium-catalyzed coupling reaction (entry 23).

Complete removal of the C-4 substituent can be important for the synthesis of a number of monobactam antibiotics. Table 2.15 (see page 70) shows some examples.

Table 2.13. FORMATION OF 4-THIO-SUBSTITUTED 2-AZETIDINONES

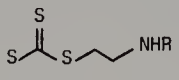
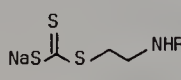
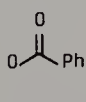
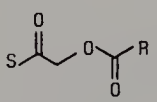
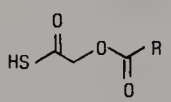
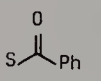
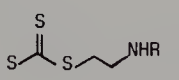
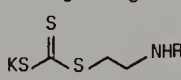
Entry	X	SR	Reaction conditions	Ref.
1	OAc	SPh	NaSPh, EtOH, 0-10°C	91
2	OAc		 , MeOH, -10°C	111
3			 , NEt_3, acetone/H_2O, r.t.	112
4	SOPh		PhCOS-TMS, ZnI_2 (cat.), CH_3CN, r.t.	91b
5	SOPh	SMe	MeS-TMS, ZnI_2 (cat.), CH_3CN, r.t.	"
6	SO_2Ph	SPh	PhSH, cinchonidine, Ph-H, 35°C (96 %, 54 % ee; 28 %, optically pure)	113
7	Cl	$SCPh_3$	$NaSCPh_3$, MeOH, -15°C	17
8	Cl	$SCMe_3$	$HSCMe_3$, NEt_3, $ZnCl_2$	114
9	Cl		 , EtOH, 0°C	115

Table 2.14. INTRODUCTION OF C-4 CARBON-BONDED SUBSTITUENTS

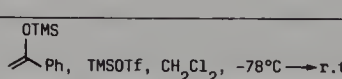
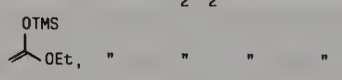
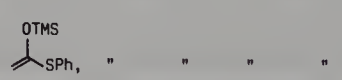
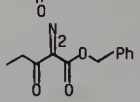
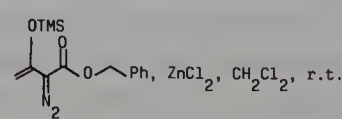
Entry	X	CR_3	Reaction conditions	Ref.
1	OAc			116
2	"			116
3	"			116
4	"			117

Table 2.14.

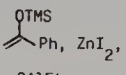
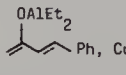
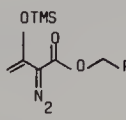
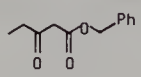
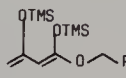
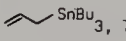
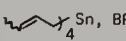
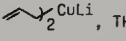
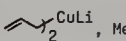
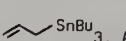
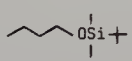
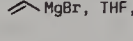
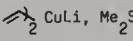
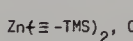
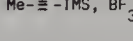
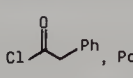
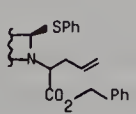
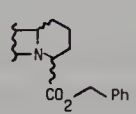
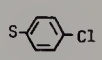
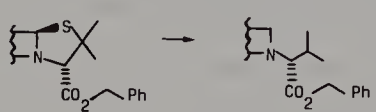
5	"			117
6	"			118
7				119
8	Cl	"	" , $AgBF_4$, CH_2Cl_2, -30°C	114
9	Cl			120
10	OAc			121
11		"	" " " "	121
12	OAc			122
13	OAc			123
14	SO_2Me	"		124
15	OAc	"		125
16	SePh	"		126
17	OAc			125
18	SO_2Me		$n\text{-}Bu_2CuLi$, THF, -78→0°C	124
19	"			124
20	OAc			125
21	SPh			127
22	OAc			128
23	$SnBu_3$			92
24			Bu_3SnH, AIBN, Ph-H, Δ	129

Table 2.15. REMOVAL OF C-4 SUBSTITUENTS FOR THE FORMATION OF C-4 UNSUBSTITUTED 2-AZETIDINONES

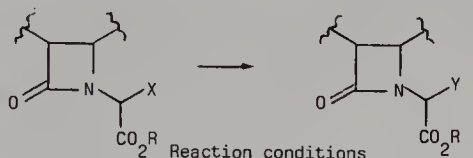
Entry	X	Reaction conditions	Ref.
1	OAc	$NaBH_4$, isopropanol/H_2O, r.t. or KBH_4, H_2O, r.t.	130
2	"	$(HMe_2Si)_2O$, TMSOTf, CH_2ClCH_2Cl, Δ (30 %)	131
3	Cl	Bu_3SnH, AIBN, Ph-H, Δ	132
4	CN	Na, NH_3, -78°C	133
5	SMe	Ra-Ni, dioxane, 50°C	134
6	SO_2Ph	$Li[AlH(O^tBu)_3]$, THF, 0°C	135
7		Bu_3SnH, AIBN, Ph-CH_3, 90°C	136
8		Ra-Ni, H_2O, 76°C	137
9		Ra-Ni, $NaHCO_3$, H_2O, Δ	138
10		Ph_3SnH, AIBN, Ph-H, Δ	139

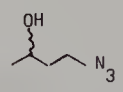
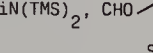
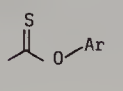
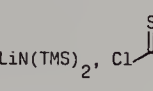
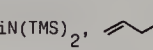
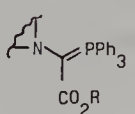
2.3 Selected Reactions for the Introduction and Transformation of Functional Groups in β-Lactam Side Chains

2.3.1 At N-1

The reactions in the N-1 side chain listed in Table 2.16 are used almost without exception for building up cyclization precursors for bicyclic β-lactam systems. The α position of 2-azetidinyl acetates (Table 2.16) can be selectively deprotonized and reacted with electrophiles. This permits the buildup of β-keto esters (entry 1) and malonic semiesters (entry 2), for example.

Table 2.16. REACTIONS OF N-1 SIDE-CHAIN ACETYL ESTERS

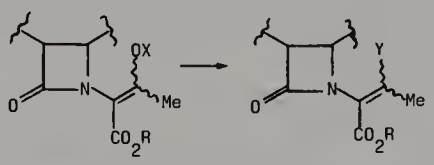


Entry	X	Y	Reaction conditions	Ref.
1	H		$2LiN(TMS)_2$, Ac-Cl, THF, -78°C	6
2	"		$4LiN(TMS)_2$, CO_2, THF, -78°C	141
3	"		$LiN(TMS)_2$,  , -70°C	142
4	"		$2LiN(TMS)_2$,  , -78°C → r.t.	143
5	"		$LiN(TMS)_2$,  , THF, -78°C	144
6	OH	Cl	$SOCl_2$, base, dioxane or THF, -20°C/r.t.	3-5
7	Cl		Ph_3P, base, dioxane, 50-60°C	3-5

Given suitable substitution of the β-lactam, alkylations (entry 5) are highly diastereoselective. This fact has been exploited in the synthesis of α-amino acids.[144] Preparation of the important α-phosphoranylidene acetic acid derivatives from glyoxylic acid hemiacetals (cf. Table 2.1) is shown in entries 6 and 7 of Table 2.16. β-keto ester derivatives (Table 2.17), which are usually completely enolized (X = H), among other compounds are used as intermediate stages for the synthesis of penems, oxapenems, and also isoxacephems. It is possible to convert the enol into a leaving group (mesylate, triflate).

Tables 2.18 and 2.19 show a number of representative reactions into which α-azetidinyl-β,γ-unsaturated esters can enter. These are easily accessible from penicillin S oxides by ring fission and are important intermediate stages in the synthesis of penicillin and cephalosporin derivatives. Reactions in the allyl position allow the introduction of substituents (Table 2.18). Under suitable reaction conditions, benzothiazole disulfides yield penicillins substituted directly in the β-methyl group (Table 2.19). This process involves intermediate allyl oxidations, similar to those shown in Table 2.18. The com-

Table 2.17. REACTIONS OF N-1 β-KETO ESTER DERIVATIVES



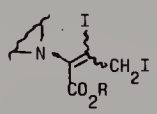
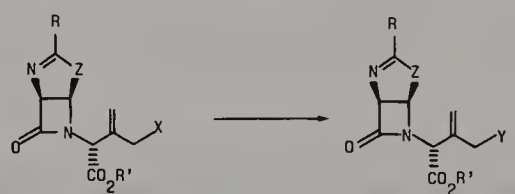
Entry	X	Y	Reaction conditions	Ref.
1	H	OCH_3	CH_2N_2	145
2	H	OSO_2CH_3	MsCl, NEt_3, CH_2Cl_2, -20°C	146
3	H	OSO_2CF_3	Tf_2O, NEt_3, CH_2Cl_2, 0°C ⟶ r.t.	147
4	SO_2CH_3	SPh	PhSH, OIPEA, CH_3CN/CH_2Cl_2, -70°C ⟶ r.t.	148
5	SO_2CF_3		I_2, NEt_3, CH_2Cl_2, r.t.	149

Table 2.18. FUNCTIONAL GROUP TRANSFORMATIONS OF α-AZETIDINYL-β,γ-UNSATURATED ESTERS OF BICYCLIC OXAZOLINES AND THIAZOLINES



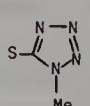
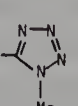
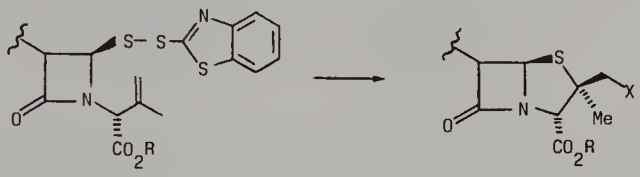
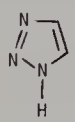
Entry	X	Y	Z	Reaction conditions	Ref.
1	H	Cl	S	t-butyl-OCl, HCO_2Me, r.t.	150
2	H	Cl	S	electrolysis, NaCl, CH_2Cl_2/H_2O	151
3	H	Cl	S	Cl_2O, $CH_2Cl_2/CCl_4/H_2O$, r.t.	152
4	H	Cl	O	Cl_2, EE, r.t.	153
5	Cl	I	O	NaI, acetona, r.t.	153
6	I	OH	O	Cu_2O, OMSO, 50-60°C or 1) $NaNO_3$, Ts-OMe, OMSO, 55°C 2) Zn, AcOH, CH_2Cl_2, 0°C	153
7	I		S	 , acetone, r.t.	154

Table 2.19. UTILIZATION OF BENZOTHIAZOLE DISULFIDES CARRYING AN N-1 β,γ-UNSATURATED ESTER SIDE CHAIN IN THE SYNTHESIS OF PENICILLINS DIRECTLY SUBSTITUTED AT THE β-METHYL GROUP



Entry	X	Reaction conditions	Ref.
1	Cl	$CuCl_2$, CH_2Cl_2, r.t.	30
2	Br	Br_2, Ac-NH_2, CCl_4, r.t.	155
3	Br	Br_2, Ac-NH_2, THF, r.t.	156
4	Br	Br_2, CaO, CH_2Cl_2, 0°C	157
5		I_2, AgO_2C-Ar, Ph-H, r.t.	155, 156
6		 , HgOAc, CH_3CN, 70°C	158

plex chemistry surrounding these allyl derivatives, their preparation, and reactions that start with penicillin S oxides and lead to substituted penicillins and cephalosporins are dealt with exhaustively in References 145 and 159 to 161.

2.3.2 At C-3

This section deals with three important areas relating to transformations in side chain 3 of both monocyclic and bicyclic β-lactams: manipulation of functional groups in the α position of 3-ethyl-β-lactams (Table 2.20), synthesis of 3-methylene azetidinones (Table 2.21), and acylation of the 3-amino group (Table 2.22 (see page 76)).

For carbapenem and penem derivatives to have good antibacterial activity, it is important for the hydroxyethyl side chain to have the *R* configuration; however, many syntheses produce diastereomer mixtures or even pure *S* diastereomers. The standard methods for obtaining the desired configuration are oxidation (Table 2.20, entries 5–7) and subsequent selective reduction (entries 1–4), as well as configuration inversion under Mitsunobu

Table 2.20. TRANSFORMATIONS OF FUNCTIONAL GROUPS IN THE α POSITION OF 3-ETHYL β-LACTAMS

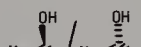
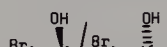
Entry			β-Lactam	Reaction conditions	Ref.
1			bicyclic	K-selectride, KI, Et_2O, r.t. (86:14) L-selectride, THF, -78°C (8:92)	162
2	"	"	monocyclic	K-selectride, Et_2O, r.t. (88.5:11.5) L-selectride, THF, -78°C (14:86) $NaBH_4$, THF/Et_2O, r.t. (45:55)	163
3	"		"	 NH/BH_3, $MgTf_2$	164
4			"	$NaBH_4$, MeOH, -78°C (78:12)	165
5			monocyclic	PCC, NaOAc, mol. sieves, CH_2Cl_2, r.t.	166
6	"	"	"	$Na_2Cr_2O_7$, H_2SO_4, H_2O	164
7		"	"	CrO_3, H_2SO_4, KF, acetone, 0°C	167
8			monocyclic	1) Ph_3P, OEAO, HCO_2H, THF, 0°C ⟶ r.t. 2) HCl, MeOH, r.t.	98,100, 168
9	"	"	"	1) Ph_3P, OEAO, $PhOCH_2CO_2H$, THF, -5°C ⟶ r.t. 2) NaOMe, MeOH, THF, -3°C	55
10	"		penam	OAST, CH_2Cl_2, -78°C ⟶ r.t.	169
11	"	"	carbapenem	" " , -68°C	
12	"	"	monocyclic	 , CH_2Cl_2, -78°C	171
13	"	"	"	CF_3-CHF-CF_2-NEt_2, CH_2Cl_2, -20°C ⟶ r.t.	172
14	"	"	"	" , " , 15°C	173
15			carbapenem	Ph_3P, OEAO, HN_3, THF/Ph-CH_3	174,175
16			penem	NaN_3, HMPA/H_2O, r.t.	48

Table 2.20.

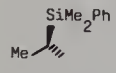
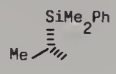
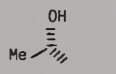
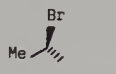
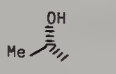
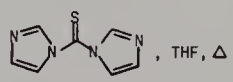
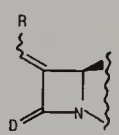
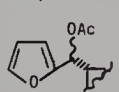
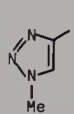
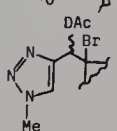
17	"	"	bicyclic	LiN_3, DMSD, r.t.	176
1B			monocyclic	1) HBF_4-OEt_2, CH_2Cl_2, r.t. 2) MCPBA, KF, DMF, r.t.	177
19			"	1) HBF_4-DEt_2, CH_2Cl_2, r.t. 2) AcDDH, NEt_3, r.t. (32 %)	17B
2D			monocyclic	CBr_4, Ph_3P, THF	179
21			"	Zn, HCD_2H, DMF	179
22			"	1)  , THF, Δ 2) $NaBH_4$, DMSD, 9D°C	1BD

Table 2.21. SYNTHESIS OF 3-METHYLENE-2-AZETIDINONES



formation

Entry	R	Starting material	E:Z	β-Lactam	Reaction conditions	Ref.
1	Me		9:91	penem	Ph_3P, DEAD, CH_2Cl_2, r.t.	181
2	"		1B:B2	"	OBU, CH_2Cl_2, -2D°C	1B1
3	"		-	carbapenem	MsCl, NEt_3, CH_2Cl_2	182
4	"		-	"	1) $Et_3D^{\oplus}$ $BF_4^{\ominus}$, CH_2Cl_2 2) K_2CD_3, OMF, r.t.	182
5	Ph		D:100	penicillin	Ph_3P, NCS, THF, r.t.	1B3
6			mainly Z	penem	OBU, CH_2Cl_2, -4D°C	1B4
7			12:88	penem	Zn, TMEDA·2HCl, NH_4Cl, OMF, r.t.	44
8	"	"	75:25	carbapenem	Zn, AcDH, THF, r.t.	45

(Continued)

Table 2.21. (*Continued*)

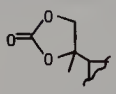
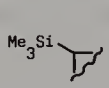
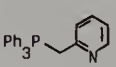
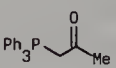
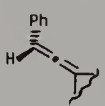
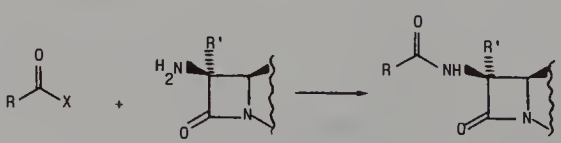
9			100:0	"	O8U (cat.), $CHCl_3$, r.t.	185
10	Me		-	monocyclic	SiO_2, Ph-CH_3, △	186
11			-	monocyclic	LOA, acetone, THF, -78°C	187
12	NO_2		-	cephem, penam	1) Me-NO_2, KO^tBu, THF, 0°C 2) MsCl, NEt_3, CH_2Cl_2, -40°C	70
13	CO_2Et	"	100:0	monocyclic	1) Br  CO_2Et, TMS-Cl, Zn, THF 2) HF, MeOH 3) MsCl, NEt_3, CH_2Cl_2, r.t.	188
14	OMe	"	25:75	penam	1)  Li, THF, -100°C 2) Ac_2O, NEt_3, OMAP, r.t. 3) CsF, OMSO, 80°C	189
15	$CO_2{}^tBu$		-	penam	Ph_3P  CO_2H , Ph-H, r.t.	190
16			mainly Z	"	Ph_3P  , THF, -78°C	71
17		"	2:98	"	Ph_3P  , CH_2Cl_2, r.t.	191
18			-	penam	1) Cl_2Ce-≡-H, THF, -78°C 2) Tf_2O, Py 3) $Ph_2CuCNLi_2$, THF, -78°C	192

Table 2.22. REPRESENTATIVE ACYLATION REACTIONS AT THE 3-AMINO GROUP



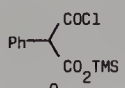
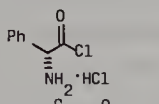
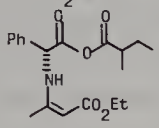
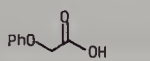
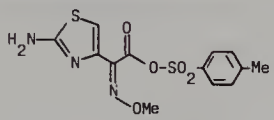
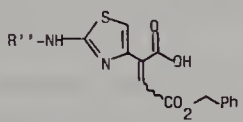
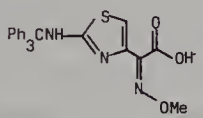
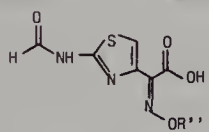
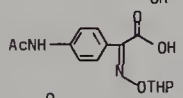
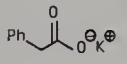
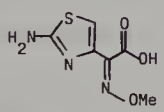
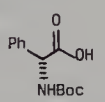
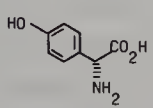
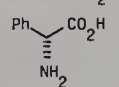
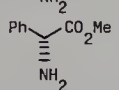
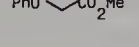
Entry		β-Lactam	Reaction conditions	Ref.
1		penicillin	Py, THF, r.t.	196
2		APA	1) HMDS, $CHCl_3$, △ 2) R  Cl, NEt_3, r.t.	197

Table 2.22.

3		cephalosporin	1) TMS-NH-CO-NHTMS; 45°C 2) RCOCl, Py, -50°C → r.t.	198
4		penicillin	EE, -10 → +10°C	199
5		APA	1) HMOS, $CHCl_3$, Δ 2) R-CO_2H, $ClCO_2Et$, NEt_3, r.t.	197
6		cephalosporin	1) BSA, CH_2Cl_2, Δ 2) R-CO_2-Ts, CH_2Cl_2, -10°C	200
7		cephalosporin	$POCl_3$, NMM, CH_2Cl_2, -20°C	201
8		cephalosporin	1) BSA, CH_2Cl_2, Δ 2) RCO_2H, PCl_5, CH_2Cl_2, r.t.	202
9		cephalosporin	1) Ac-NHTMS, EE 2) RCO_2H, $POCl_3$/OMF, THF, -20°C	203
10		ACA	1) BSA 2) RCO_2H, OMF/$SOCl_2$, NMM	204
11		cephalosporin	 $MeSO_4^{\ominus}$, CH_2Cl_2, r.t.	205
12		ACA	OCC, HOBT, OMF, NEt_3, CH_2Cl_2	206
13		cephalosporin	EEOQ, THF, r.t.	207
14		cephalosporin	Xanthomonas citrii (36 %)	208
15		APA	Penicillin amidase (E. coli; 52 %)	209
16		carbacephem (racemic)	Pseudomonas melanogenum (50 %, optically pure)	210
17		monocyclic (racemic)	Penicillin G amidase on Eupergit (45 %; optically pure)	211

conditions (entries 8 and 9). In the latter reaction, and in the other transformations occurring on the basis of an S_N mechanism, one of the side reactions frequently observed is elimination with formation of 3-methylene β-lactams, this taking place very readily in high-energy bicyclic systems, in particular (see Table 2.21). The processes that have been described include fluorination with diethylamino sulfur trifluoride (DAST, entries 10–12) or the Ishikawa reagent (entries 13 and 14), preparation of azides as amino precursors (entries 15–17), and deoxygenations (entries 21 and 22).

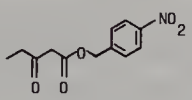
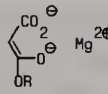
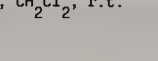
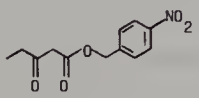
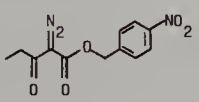
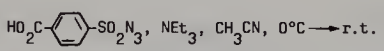
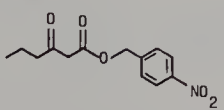
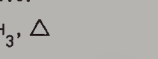
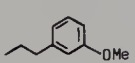
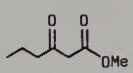
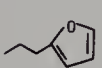
The reactions described in Table 2.21 lead to 3-methylene β-lactams, a structural type which can be found in many β-lactamase inhibitors. Common preparation methods are, on the one hand, elimination of suitably activated groups,[193] preferably at a late stage in synthesis (entries 1–10), and, on the other hand, olefinations of 3-oxo β-lactams (cf. Section 2.2.3) according to Wittig or Peterson (entries 15–17).

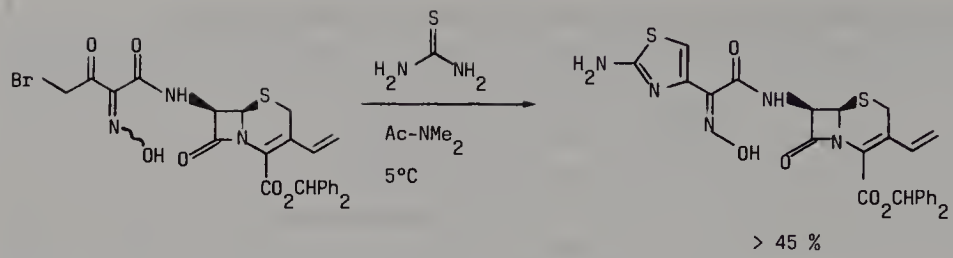
Eliminations under nonequilibrating conditions take place stereospecifically according to *E*2 and permit conclusions as to the stereochemistry of the underlying alcohols to be drawn from the nuclear magnetic resonance spectroscopic analysis of the resultant olefins (Table 2.21, entries 1 and 3–5). Entry 18 shows a special case: the first-ever synthesis of 3-allenyl azetidinones. The extremely high elimination tendency in the case of penem and carbapenem systems is striking, even though a further sp^2 center is formed in the 4-membered ring in the process; however, it would seem that the additional ring strain is overcompensated for by the disappearance of the steric interactions of the two *cis* substituents in positions 5 and 6 of the educt.

The methods shown in Table 2.22 for acylating 3-amino-β-lactams are intended only as a representative cross section of the host of available possibilities. Fundamental papers on this subject are listed in Reference 194. One important way of shortening synthesis processes by avoiding protective groups is direct conversion of APA or ACA and their derivatives into the amides via doubly silylated intermediate stages that are soluble in organic solvents. The silyl groups protect the acid, activate the amine, and are split off during processing (Table 2.22, entries 2, 3, 5, 6, and 8–10). A good overview, containing numerous quotations from patent literature, can be found in Reference 195. The enzymatic coupling involved in amide formation has also been frequently described (Table 2.22, entries 14–17); however, in contrast to enzymatic deacylation (see Section 1.2.3 where chemical deacylation is also dealt with in detail), it has not yet been possible to find a universally applicable method for this.

The 2-aminothiazole residue is a constituent of many of the cephalosporins available on the market. In some cases, it can be favorable not to build up the heterocycle in side chain 7 until a later stage (Figure 2.3).[212]

Table 2.23. BUILDING UP AND BREAKING DOWN CARBON CHAINS AT C-4

Entry	R^1	R^2	Reaction conditions	Ref.
1		$-CO_2H$	RuO_2, $NaIO_4$, acetone/H_2O or 1) O_3, Zn, AcOH, CH_2Cl_2 2) polymer bound $R_4N^{\oplus}ClO_2^{\ominus}$	99
2	"	"	1) OsO_4, $NaIO_4$, THF/H_2O, r.t. 2) $KMnO_4$, THF/H_2O, r.t.	98
3			1) COI, THF, r.t. 2)  , THF, r.t.	42
4	"	"	1) COI, CH_2Cl_2, r.t. 2) Meldrum's acid, OMAP, CH_2Cl_2, r.t. 3)  , △	213
5				42
6	"	"	Ts-N_3, NEt_3, EE, r.t.	213
7	-CHO		1)  , CH_3CN, r.t. 2) Pd/C, 1 atm H_2, EE, r.t. 3)  , Ph-CH_3, △	214
8			1) Li, NH_3, ^{t}BuOH, THF, -78°C 2) O_3, CH_2Cl_2/MeOH, -78°C 3) Me_2S	215
9			1) O_3, CH_2Cl_2/MeOH 2) H_2O_2	216



(ref. 212)

Figure 2.3. An example for the formation of the 2-aminothiazole residue as a late step in the synthesis of a cephalosporin.

2.3.3 At C-4

Transformations in the C-4 side chain of azetidinones are necessary in almost all total syntheses of β-lactam derivatives. Many of these reactions are not specific to β-lactams and are thus not referred to in this section. Only three specific areas are discussed. By way of example, Table 2.23 (see page 79) shows a number of important methods for building up and breaking down carbon chains. Of particular importance are the oxidative degradation of the styryl derivatives, which are easily accessible by 2 + 2 cycloaddition (entries 1 and 2), transformation of an acetic acid residue into the β-keto or diazo-β-keto acid in carbapenem syntheses (entries 3 to 6), and the buildup of homologous derivatives for the preparation of carbacephems (entries 7–9).

Table 2.24. TRANSFORMATIONS OF 4-METHYL-2-AZETIDINONES AT THE α POSITION

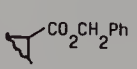
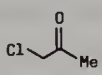
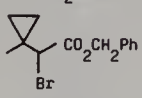
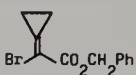
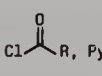
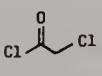
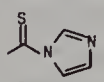
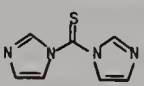
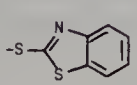
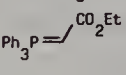
Entry	X	Y	Reaction conditions	Ref.
1		OH	$NaBH_4$, CH_2Cl_2, 0°C	217
2		OH	$NaBH_4$, MeOH	42
3	OH	I	1) Ts-Cl, Py, 5°C 2) NaI, acetone, △	217
4	"	"	1) Ms-Cl, NEt_3, CH_2Cl_2, 0°C 2) NaI, acetone, △	42
5	"	"	DCC·MeI, THF, 40–50°C	218
6	OTs	F	KF, 18-crown-6, CH_3CN, △ (23 %)	219
7	Cl	SH	1) NaI, DMF, 120°C 2) H_2S, DIPEA, DMF, 30°C	220

Table 2.25. CONVERSION OF 4-THIO-SUBSTITUTED β-LACTAMS WITH RETENTION OF THE SULFUR β-LACTAM BOND

Entry	X	Y	Reaction conditions	Ref.
1	H		 , HMPA, r.t.	221
2	H		$MeO_2C-\equiv-CO_2Me$, HMPA, r.t.	222
3	H		 K_2CO_3 (cat.), DMF, r.t.	223
4	Hg		 R, Py, CH_2Cl_2, 0°C	224
5	Ag		 , Py, DMAP, r.t.	225
6	Ag		 , r.t.	226
7	$SnBu_3$		1) n-BuLi, Et_2O, 0°C 2) Ac-Cl, 0°C	227
8			Ac_2O, AcOH, Zn, r.t.	82
9	"		AcOH, Ph_3P, CH_2Cl_2, r.t.	228
10	"			229

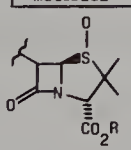
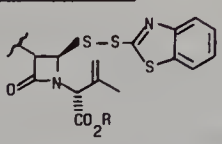
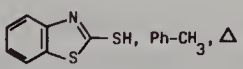
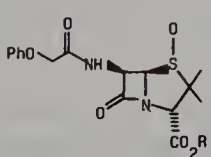
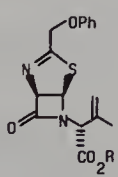
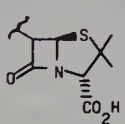
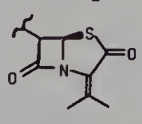
	Starting material	Product		
11			 SH, Ph-CH_3, △	44, 230, 231
12			$P(OMe)_3$, Ph-H, △	108, 232
13			TFA-anhydride, Py, NEt_3, CH_2Cl_2, r.t.	233

Table 2.24 (see page 80) shows some of the possibilities for transformation of 4-methyl-β-lactams in the α position. The starting point is usually a carboxylic acid derivative or an aldehyde which is converted into further derivatives (halides, thiols) via the alcohols.

The conversions of 4-thio-substituted β-lactams shown in Table 2.25 (see page 81), where the sulfur β-lactam bond is retained, are of major importance (cf. Section 2.2.4 for reactions in which this bond is broken). These reactions usually take place via free thiols (entries 1–3) or their salts (entries 4–6), which can easily be prepared from protected precursors. Transformations of benzothiazolyl disulfides (Table 2.25, entries 8–10) are universally applicable. Their preparation is shown in entry 11. Further reactions of these derivatives and the use of the thiazolidines shown in entry 12 as protective groups can be found in section 1.6.

2.4 Reactions on Bicyclic β-Lactam Derivatives

The introduction and transformation of functional groups in position 6 of penams, penems, and carbapenems and in position 7 of cephems and their analogs have already been dealt with in Sections 2.2.3 and 2.3.2. The following sections consider reactions in the second ring of bicyclic β-lactam derivatives; S oxidation and reduction (2.4.1), reactions in positions 2 and 3 of cephems and analogs (2.4.2), and reactions in position 2 of penems and carbapenems (2.4.3).

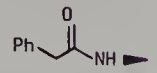
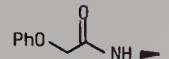
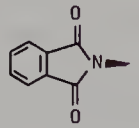
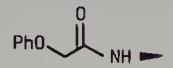
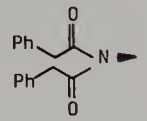
2.4.1 Oxidation and Reduction of the Ring Sulfur of Bicyclic β-Lactam Derivatives

The sulfur in penicillins and cephalosporins is oxidized mainly for one of three reasons:

1. Sulfoxide formation to obtain reactive intermediates for further transformations (ring fissions, Pummerer reaction, etc.)
2. Sulfoxide formation with subsequent reduction in cephems to shift the double bond from position 2 to position 3
3. Preparation of penam sulfones as β-lactamase inhibitors and of cephem sulfones as elastase inhibitors

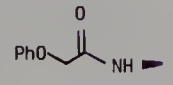
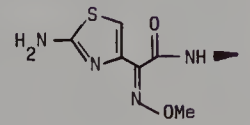
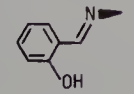
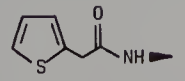
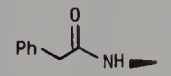
Depending on the oxidant used, oxidation of penicillin derivatives leads mainly to a surplus of β-(*S*)-sulfoxide as a result of the involvement of adjacent groups, if there is an amide/amine proton in position 6 (Table 2.26), entries 2 and 5–7). If the 6-amino group is doubly blocked, only the less sterically hindered α side is attacked (entries 4 and 8). The same is true for the oxidation of cephalosporins (entries 10–12). In the case of 2-cephem, the double bond is rearranged into position 3 following oxidation in the presence

Table 2.26. OXIDATION OF BICYCLIC β-LACTAMS TO SULFOXIDES AND SULFONES

Entry	R	α : β	β-Lactam	Reaction conditions	Ref.
Sulfoxides (n=1)					
1		-	penicillin	$NaIO_4$, dioxane/H_2O	234
2		1 : 4	APA	O_3, H_2O, 5°C	235
3		1 : 1	penicillin	O_3, H_2O/acetone, 5°C	"
4		α only	"	" " " "	"
5		β only	"	H_2O_2, AcOH, CH_2Cl_2, r.t.	236
6	"	"	"	H_2O_2, CH_2Cl_2, r.t.	237
7	"	"	"	H_2O_2, AcOH, PPA (cat.), CH_2Cl_2, 0°C	238
8		α only	"	MCPBA, Ph-H, r.t.	239

(*Continued*)

Table 2.26. (*Continued*)

9		-	△ 2-cephem→ △ 3-cephem	1) MCPBA, CH_2Cl_2, r.t. 2) CH_3OH or H_2O_2, AcOH, CH_2Cl_2, r.t. or HIO_4, Et_2O, r.t.	240
10		ß only	△ 3-cephem	MCPBA	241
11		α only	"	"	"
12		ß only	"	H_2O_2, AcOH, CH_2Cl_2, r.t.	236
13		-	△ 3-cephem	H_2O_2, AcOH, PPA (cat.), CH_2Cl_2, 0°C	238
14		1 : 4	penem	MCPBA, CH_2Cl_2	242

Sulfones (n=2)

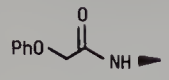
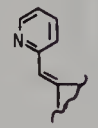
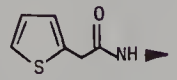
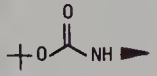
15		-	penicillin	H_2O_2, HCO_2H, CH_2Cl_2, r.t.	236
16		-	APA	$KMnO_4$, H_2SO_4 or H_3PO_4, H_2O/CH_3CN	243
17	H	-	penicillin	$KMnO_4$, AcOH, H_2O, r.t.	244
18		-	"	MCPBA, CH_2Cl_2, r.t.	71
19		-	△ 3-cephem	H_2O_2, HCO_2H, CH_2Cl_2, r.t.	236
20		-	"	H_2O_2, Na_2WO_4 (cat.), EE, r.t.	28
21		-	"	MCPBA	241

Table 2.27. REDUCTION OF PENICILLIN AND CEPHALOSPORIN SULFOXIDES TO SULFIDES

Entry	β-Lactam	Reaction conditions	Ref.
1	penicillin	KI, Ac-Cl, DMF, 0-5°C	245
2	cephalosporin	PCl_3, CH_2Cl_2, Δ or $SnCl_2$, Ac-Cl, DMF/CH_3CN, 0°C ⟶ r.t.	240
3	"	PBr_3, DMF, 0°C	246
4	"	PCl_3, DMF, -30°C	247
5	"	P_2S_5, Py, CH_2Cl_2	248

of protic solvents (Table 2.26, entry 9). The preparation of a penem sulfoxide is also worthy of note (entry 14).

The reduction of sulfoxides to sulfides is a particularly common process in the case of cephalosporins. The reagents of choice are phosphorus(III) compounds (Table 2.27, entries 2–4).

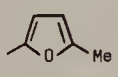
2.4.2 Reactions at C-2 and C-3 of Cephalosporins and Their Analogs

On the cephem system, in addition to transformations of the ring sulfur, reactions at positions 2, 3, 4, 6, and 7 are conceivable. Derivations in position 4 or 6 lead to derivatives with little or no antibacterial effect. Position 1 (sulfur) has been dealt with in Section 2.4.1 and position 7 in Sections 2.2.3 and 2.3.2. Thus, in the following paragraphs are discussed a few reactions at C-2 and mainly those at C-3 of the cephem system, an important chapter in the chemistry of cephalosporins, in the framework of which thousands of derivatives have already been prepared.

Reference 249 offers an exhaustive overview of the possibilities for introducing and transforming functional groups at C-2, specifically using cephem-*S*-oxides. Table 2.28 shows a number of possibilities for introducing a methoxyl group directly by way of oxidation of the sulfides, as well as various other transformations.

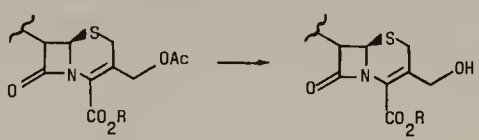
Fundamental overviews of cephem derivations in position 3 can be found in References 249 and 255. Most partially synthetic ways of arriving at ceph-

Table 2.28. REACTIONS AT C-2 OF CEPHALOSPORINS

Entry	X	Y	Reaction conditions	Ref.
1	H	OMe	Cl_2, MeOH/CH_2Cl_2, r.t.	250
2	"	"	electrolysis, MeOH or $(NH_4)_2Ce(NO_3)_6$, MeOH/THF, r.t.	251,252
3	"	"	t-BuOCl, MeOH/CH_2Cl_2, r.t.	253
4	OMe	SC_4H_9	C_4H_9-SH, $TiCl_4$, CH_2Cl_2, -30°C	254
5	OAc		 Me, $AlCl_3$, CH_2Cl_2, 0°C	"
6	OMe		 , $TiCl_4$, CH_2Cl_2, 0°C	"

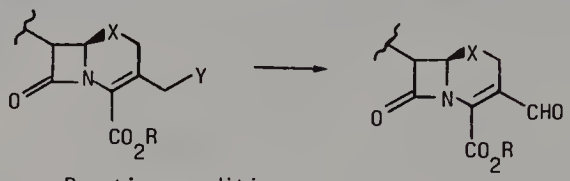
alosporin antibiotics use 3-acetoxymethyl cephalosporins obtained by fermentation as the starting material. Therefore, transformations of these 3-acetoxymethyl compounds are of central importance. Table 2.29 shows possibilities for splitting off the acetyl residue. This critical reaction can be carried out both enzymatically and chemically under the mildest possible conditions. One potential secondary reaction here is the formation of the

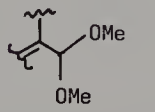
Table 2.29. DEACETYLATION OF THE 3-ACETOXYMETHYL GROUP IN CEPHALOSPORINS



Entry	R	Reaction conditions	Ref.
1	H	Citrus ecetylesterase	256
2	H	Esterase (Bacillus subtilis)	257
3		1) TMS-I→  I 2) $NH_4^{\oplus}CF_3CO_2^{\ominus}$, DMF, 50°C 3) pH7 buffer	258
4	-t-butyl	Ti(O )$_4$,  , 50°C	259
5	H	NaOH, H_2O/MeOH, -20/-10°C	260

Table 2.30. FORMATION OF 3-FORMYL CEPHALOSPORIN DERIVATIVES



Entry	X	Y	Reaction conditions	Ref.
1	O	OH	Py dichromate, CH_2Cl_2, r.t.	261
2	S	OH	CrO_3, Py, CH_2Cl_2, 30°C	257,262
3	O	OH	$(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -40°C	263
4	S	I	O_2, $RhCl_3$ (cat.), Al, DMF, r.t. or O_2, $VOSO_4$, DMF, r.t.	264
5	S	Cl	air, NaI, MeOH/CH_2Cl_2 →  (41 %)	265

five-ring lactone. Oxidation of the alcohols obtained in this way or of halides allows preparation of the corresponding aldehydes (Table 2.30), which, for example, can enter into Wittig reactions (cf. Table 2.33).

As shown in Figure 2.4, aldehydes have also been used to synthesize 3-cyanocephems.[262]

Tables 2.31 and 2.32 (see page 90) deal with substitution reactions in the α position. First, they show the preparation of halides (Table 2.31), which

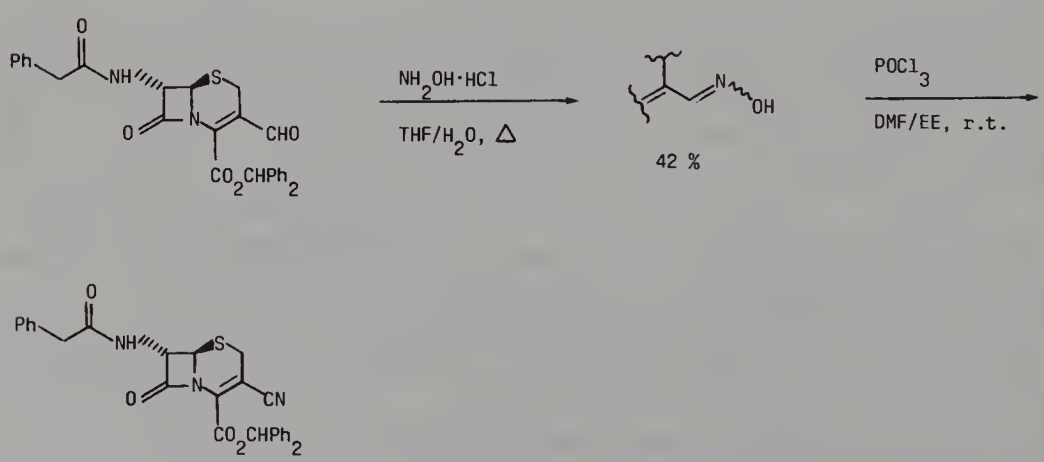


Figure 2.4. Synthesis of a 3-cyanocephem from its corresponding aldehyde.

usually act as intermediate stages for further transformations. Second, the introduction of residues bonded via O, S, N, or C is also shown (Table 2.32). Thioheterocycles (entries 5–8) and *N*-heterocycles (entries 9–15) occupy an outstanding position here, owing to the enormous number of known derivatives. Reactions that can be carried out directly with 3-acetoxymethyl cephalosporins are particularly important in this context, as they offer the quickest access to new derivatives. Common activation methods are those employing trimethylsilyl iodide (in situ transformation into the iodide, entry 12) and borotrifluoride etherate (entry 15). The introduction of a tetrazolylthio residue in concentrated sulfuric acid is an astounding reaction (entry 8).

C—C bonding with aryl and vinyl residues is also described, this taking place either as electrophilic aromatic substitution (Table 2.32, entries 16 and 18) or via metallo-organic intermediate stages (entries 17, 19, and 20).

Recently, interest has begun to center on 3-vinyl derivatives of cephalosporins. Typical methods of preparation are given in Table 2.33 (see page 92). On the one hand, 3-phosphoranylidene methyl cephem can be reacted with reactive aldehydes (entries 1–4); on the other hand, it is also possible to use aldehydes at position 3 (entries 5–10). In the latter case, however, 2-cephems or Δ-3-sulfoxides must be used to avoid secondary reactions.

Table 2.31. PREPARATION OF 3-HALOMETHYL CEPHALOSPORINS VIA SUBSTITUTION REACTIONS

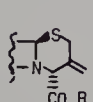
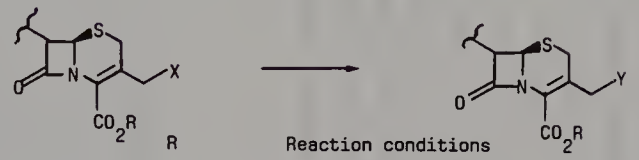
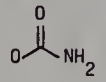
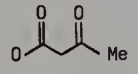
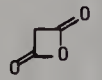
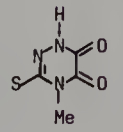
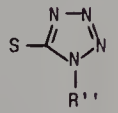
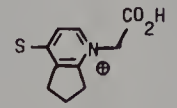
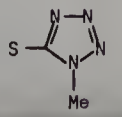
Entry	X	Hal	Reaction conditions	Ref.
1	OH	F	$CHCl_2$-CF_2-NEt_2, CH_2Cl_2, 0°C (Δ 2-cephem)	266
2	OH	Cl	PCl_5, Py, CH_2Cl_2, -10/-20°C	260
3	OAc	I	TMS-I, CH_2Cl_2, r.t.	267
4	Cl	I	NaI, acetone, r.t.	268
5	Cl	I	NaI, CCl_4/pH7 buffer, r.t.	269
6	H	Br	NBS, hν, CH_2ClCH_2Cl, 0°C, (cephem-S-oxide)	270
7	H	Br	NBS, hν, Ph-H, Δ (cephem sulfone)	271
8		Br	1) Br_2, $CHCl_3$, 0°C 2) DBU, Py, -65°C	272
9	"	I	I_2, OBU, THF, -80°C → 0°C	273
10	"	F	$FClO_3$, OBU, OMF	"

Table 2.32. FORMATION OF 3-(SUBSTITUTED METHYL) CEPHALOSPORINS WITH SUBSTITUENTS BONDED VIA OXYGEN, SULFUR, NITROGEN, OR CARBON



Entry	X	Y	R	Reaction conditions	Ref.
1	OH		H	1) Cl_2PNCO, THF, r.t. 2) pH 3-5, 40-45°C	274
2	OH	"		1) $ClSO_2NCO$, DMF, 0°C 2) HCl, EE, r.t.	275
3	OH		H		276
4	Br	OAc	CH_2CCl_3	KOAc, AcOH, DMF, r.t.	277
5	OAc		H	R'-SH, THF/H_2O, pH7, 60°C	278
6			H	R'-SH, $NaHCO_3$, H_2O, r.t.	276
7	OAc		H	R'-SH, NaI, CH_3CN/H_2O, 70°C	279
8	OAc		H	R'-SH, c.H_2SO_4, <45°C	280

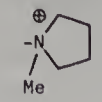
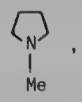
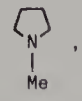
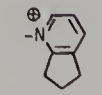
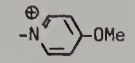
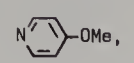
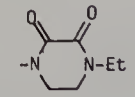
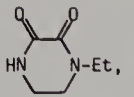
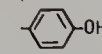
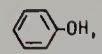
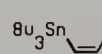
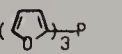
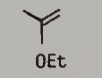
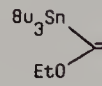
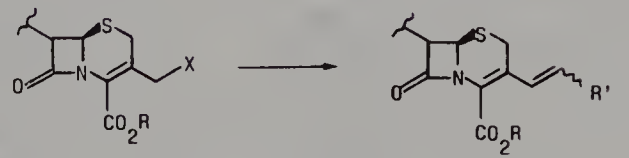
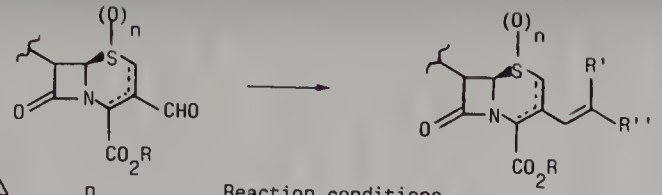
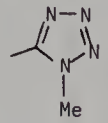
9	OAc		H	1) KSCN 2) Py, H_2O, 60°C	281
10	OH	"	t-butyl	Py, Tf_2O	282
11	I		$CHPh_2$	 , CCl_4, 0°C	283
12	OAc	"	TMS	1) TMS-I, Freon- TF, r.t. 2)  , 5°C	284
13	OAc		H	TMS-I,  , CH_2Cl_2, Δ	285
14	OAc		H	 , KI, H_2O, Δ	286
15	OAc		H	 , $8F_3$-OEt_2, EE, r.t.	287
16	OAc		H	 ,TFA (Δ 2-cephem)	288
17	8r	-Ph	CH_2CCl_3	Ph_2CuLi, THF, -70°C	289
18	8r		Me	 , CH_3CN, r.t.	290
19	Cl		$CHPh_2$	 , $Pd(dbe)_2$,  , THF, Δ	291
20	Cl		$CHPh_2$	 , " " " "	291

Table 2.33. METHODS FOR THE PREPARATION OF 3-VINYL CEPHALOSPORINS



Entry	X	R'	Reaction conditions	Ref.
1	Cl	H	1) NaI, Ph_3P, DMF, 35°C 2) CH_2O, CH_2Cl_2/H_2O, pH9	260
2	I	CH_3 (mainly Z)	1) Ph_3P, EE, r.t. 2) NaOH, CH_2Cl_2, r.t. 3) CH_3CHO, $CHCl_3$, r.t. (31 %)	268
3	$\overset{\oplus}{P}Ph_3$	CH_2Cl (mainly Z)	1) base 2) $ClCH_2CHO$, BSA, -10°C	292
4	"	$CH_2OTBDMS$ (E:Z = 6:4)	CHO⟨ ⟩OTBDMS, LiO^tBu (isocephem)	282, 293



Entry	R	R''	Δ	n	Reaction conditions	Ref.
5	Cl	Cl	2	0	Zn, Ph_3P, CCl_4, $AcNMe_2$, 60°C	294
6	Br	Br	2	0	", " , CBr_4, " , "	"
7	F	F	2	0	Zn, CBr_2F_2, HMPA, $AcNMe_2$, 35°C	"
8	H	CH_2OAc	2	0	1)  MgCl, THF, -70°C 2) AcOH, TsOH, THF, 40°C	295
9	H	CO_2Et	3	1	Ph_3P  CO_2Et, Ph-H, r.t.	296
10	H		3	1	, THF	297

2-Cephems can easily be prepared from 3-cephems by base-catalyzed isomerization of the double bond (e.g., with pyridine).[257,288] Reverse isomerization to obtain the 3-cephems is possible via sulfoxides as intermediate stages, as shown in Section 2.4.1.

As shown in Figure 2.5, 3-aminoethylidene cephems, which can also be transformed in a variety of ways, are directly accessible from the methyl compounds by way of a Mannich reaction.[298]

The preparation of 3-vinyl cephalosporins on the basis of 3-hydroxycephems is described in Table 2.36.

3-Methylene cephams are an important intermediate stage, inter alia, for the synthesis of 3-hydroxycephems (Table 2.35, cf. also Table 2.31). Typical methods of synthesis with good yields are shown in Table 2.34.

Ozonolysis of 3-methylene cephams produces 3-hydroxycephems (Table 2.35). In many cases, ozonolysis of derivatives with unprotected nitrogen leads to a marked improvement in yield.

Table 2.36 (see page 97) summarizes the various possibilities for direct transformation of functional groups in position 3 of the cephem skeleton. The keto/enol equilibrium of the β-keto ester is mainly on the enol side, and 3-hydroxycephems enter into numerous reactions typical for enols. For many transformations, it is advantageous to activate the position as well, generally as isolatable sulfonates (entries 1–4) but also as phosphonates, which can be prepared in situ (entry 9).

Tables 2.36 shows a wide variety of ways of introducing substituents that are bonded via oxygen (entries 5–8), sulfur (entries 9–12), or nitrogen (entries 13–16). 3-Halogen cephems are also accessible (entries 17–19) and 3-unsubstituted cephems can be obtained by decarbonylation (entry 20) or reduction (entries 21–23).

There have been interesting developments in the introduction of side chains bonded via carbon. Triflates, in particular, can be reacted not only with cuprates (Table 2.36, entries 26 and 27), but also with tin compounds, namely under palladium catalysis (entries 28–34). The decisive factor for the success of this reaction, which permits the introduction of a wide variety of residues, is the selection of trifurylphosphine as the ligand (entries 23 and 28–30) or the use of a "bare" palladium catalyst (entries 31–34).

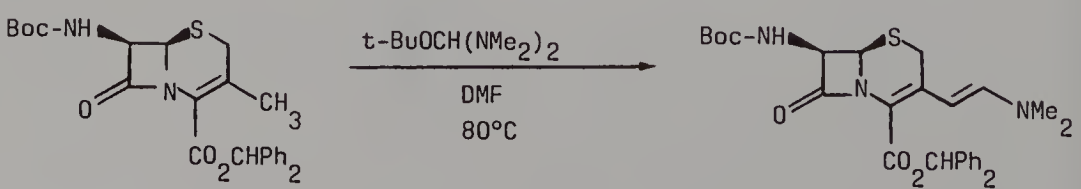
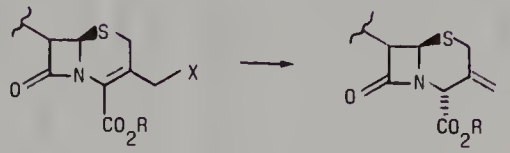


Figure 2.5. Synthesis of a 3-aminoethylidene cephem by way of a Mannich reaction.

Table 2.34. PREPARATION OF 3-METHYLENE CEPHAMS



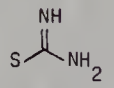
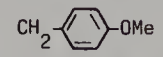
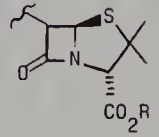
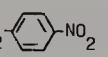
Entry	X	R	Reaction conditions	Ref.
1	OAc	Na	$Cr(OAc)_2$, H_2O/OMSO, r.t.	299
2	OAc	H	electrolysis, pH6.9	300
3		H	1atm H_2, Ra-Ni, EtOH/H_2O, r.t.	301
4	OAc	$CHPh_2$	Zn, NH_4Cl, OMF/H_2O, 0°C (cephem-S-oxide)	302
5	Cl		Zn, NH_4Cl, OMF, -30°C	303
6	Cl	"	electrolysis, THF	304
7			1) NCS or NBS 2) Lewis acid ($TiCl_4$, $AlCl_3$, ...)	305

Table 2.35. SYNTHESIS OF 3-HYDROXYCEPHEMS

Entry	R^1	R^2	Reaction conditions	Yield	Ref.
1		$CHPh_2$	1) O_3, CH_2Cl_2, -70°C 2) Me_2S	42 %	306
2	H • TsOH	"	" "	75 %	"
3		$CHPh_2$	1) O_3, MeOH, -75°C 2) Me_2S	37 %	307
4	H • HCl	H	O_3, MeOH, -75°C	quant.	"
5		$CHPh_2$	1) O_3, MeOH/CH_2Cl_2, -78°C 2) Zn, AcOH	quant.	308
6	H		1) O_3, MeOH, -70°C 2) SO_2	75 %	309

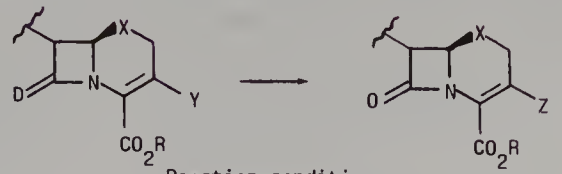
2.4.3 Reactions at C-2 of Penems and Carbapenems

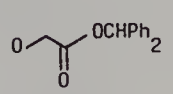
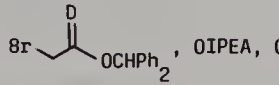
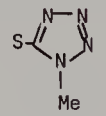
The introduction and transformation of functional groups in penems and carbapenems are possible mainly in positions 2 and 6. Substituents in position 1 of carbapenems (cf. the corresponding Chapter in this book) and in position 5 are generally introduced on monocyclic precursors. As reactions at C-6 have already been discussed (Sections 2.2.3 and 2.3.2), the following is a discussion of possible transformations in position 2.

The starting point for many derivations is a 2-oxopenam or a 2-oxocarbapenam, direct cyclization products of activated monocyclic precursors. Two methods for producing the ketone subsequently by ozonolysis are shown in Figure 2.6 (see page 100). To substitute the 2-keto group by other residues, it is first transformed into a leaving group (sulfonate or phosphonate), as shown in Table 2.37 (see page 100). Even the unstable triflates can be isolated (entries 4–6). These reactive intermediates can then be reacted with sulfur nucleophiles (Table 2.38 (see page 101), entries 1–6) or nitrogen nucleophiles (entries 7 and 8). Triflates also permit the introduction of carbon nucleophiles, such as cuprates (entry 9) and palladium-catalyzed coupling with aryl tin compounds (entries 10–13). In the case illustrated in Figure 2.7 (see page 102), a 2-oxocarbapenem was successfully reacted with a stabilized phosphorus ylide.[338]

Another way of introducing new substituents consists of the reactions of 2-sulfoxides listed in Table 2.39 (see page 102). These are readily obtained from the corresponding alkylthio residues by oxidation with *meta*-chloro-

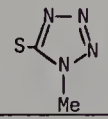
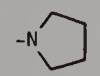
Table 2.36. REACTIONS OF 3-HYDROXYCEPHEMS AND RELATED DERIVATIVES

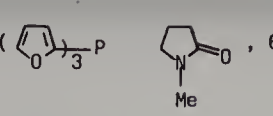
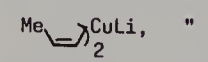
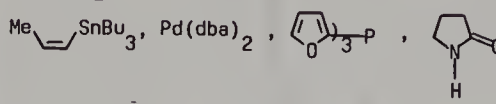
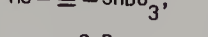
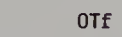
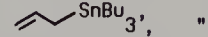
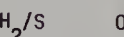
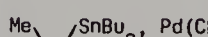
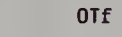
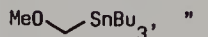
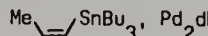
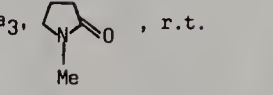


Entry	X	Y	Z	Reaction conditions	Ref.
1	CH_2	OH	OMs	Ms-Cl, NEt_3, CH_2Cl_2, r.t.	310
2	CH_2	OH	OTs	Ts_2O, NEt_3, CH_2Cl_2, 0°C	311
3	S	OH	OTf	Tf_2O, DIPEA, CH_2Cl_2, -78°C	312
4	CH_2	OH	OTf	Tf_2O, DIPEA, $CHCl_3$, 0°C	215
5	S	OH	OMe	CH_2N_2, CH_2Cl_2, r.t.	309
6	CH_2	OH	OMe	CH_2N_2, BF_3-OEt_2, CH_2Cl_2, r.t.	313
7	SO	OH		 , OIPEA, OMSO, r.t.	314
8	S	OH	OR (R = Me,  , ..)	Ph_3P, OEAD, ROH, THF or CH_2Cl_2	315
9	S	OH	SMe	1) $(PhO)_2POCl$, OIPEA, CH_3CN, -20/-10°C 2) MeSH, -20°C	316
10	CH_2	OMs		R'-SNa, DMF, r.t.	310
11	SO	OTs	SPh	PhSH, OIPEA, OMF, r.t.	317

(Continued)

Table 2.36. (*Continued*)

12	S	OTf		R'-SNa, THF, r.t.	312
13	S	OH	NH_2	NH_4Cl, Py, 50°C	317
14	S	OMs	N_3	NaN_3, DMF, r.t.	310
15	S	OTf		Py, CH_2Cl_2, r.t.	312
16	S	OTf		 , THF, -78°C	"
17	S	OH	Cl	PCl_3, DMF, r.t.	309
18	O	OH	Cl	Ph_3P, Cl_2, CH_2Cl_2, 0°C	318
19	S	OTf	Cl, Br, I	LiHal, THF, r.t.	312
20	S	CHO	H	$(Ph_3P)_3RhCl$, Ph-H, 70°C	257
21	S	Cl	H	Zn, AcOH, CH_2Cl_2, r.t.	318
22	S	OMs	H	" , " , " , "	"

23	S	OTf	H	Bu_3SnH, $Pd(dba)_2$,  , 65°C	319
24	S	OH		Ph_3P, $Ph\text{-}CH_3$, 100°C	320
25	S	Cl	Me	Me_2CuLi, THF, -50°C	321
26	S	OTf	t-Bu	$(t\text{-}Bu)_2CuLi$, $BF_3\text{-}OEt_2$, THF, -78°C	322
27	S	OTf		 , " , " , " (29 %)	"
28	S	OTf		 , r.t.	319
29	S	OTf		 , " , " , " , r.t.	"
30	S	OTf		 , " , " , " , 50°C	"
31	CH_2/S	OTf		 , $Pd(CH_3CN)_2Cl_2$, LiCl, DMF, r.t.	323
32	CH_2	OTf		 , " , " , " , "	324
33	CH_2/S	OTf	CO_2R'	CO, $Pd(CH_3CN)_2Cl_2$, NEt_3, R'OH, DMF	323,324
34	S	OTf		 , Pd_2dba_3,  , r.t.	325

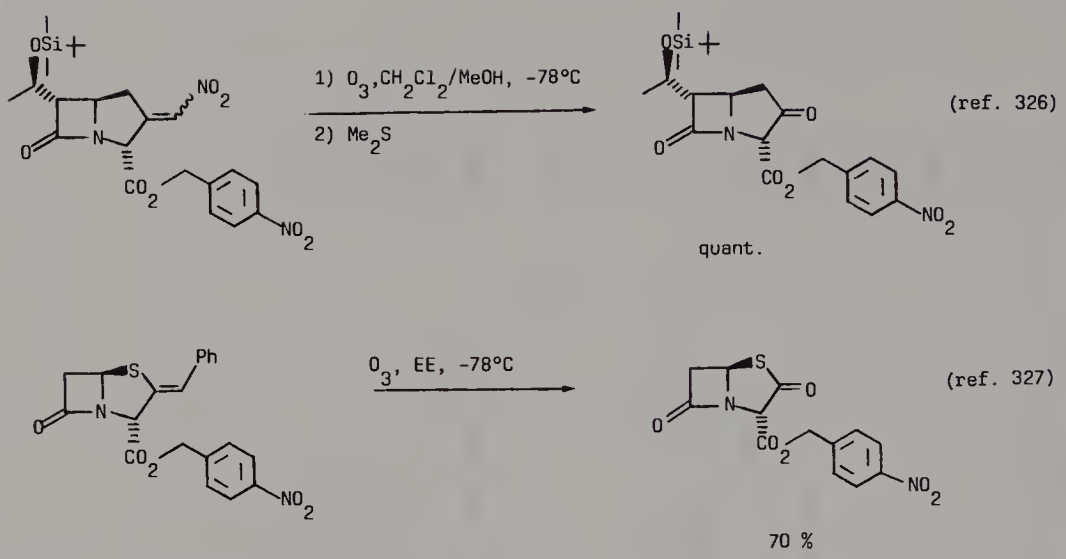
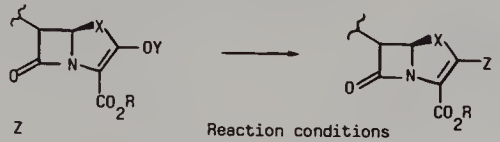


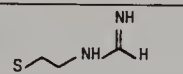
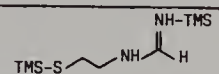
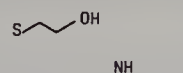
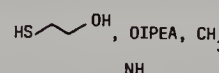
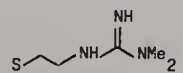
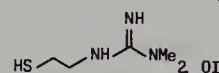
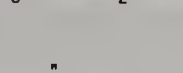
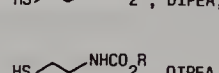
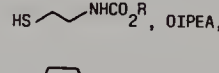
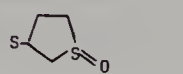
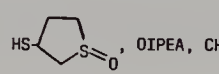
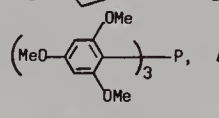
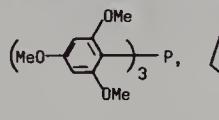
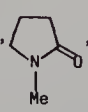
Figure 2.6. Formation of 2-oxocarbapenams and 2-oxopenams via ozonolysis.

Table 2.37. SYNTHESIS OF PENEM AND CARBAPENEM ENOL PHOSPHONATES, SULFONATES, AND TRIFLATES

Entry	X	Y	Reaction conditions	Ref.
1	S	Me	CH_2N_2, Et_2O/CH_2Cl_2, r.t.	328
2	CH_2, $CHCH_3$	$P(OPh)_2$ (O)	$(PhO)_2$ POCl, DIPEA, CH_3CN, 0°C	213,329-331
3	CH_2	Ts	Ts_2O, OIPEA, CH_3CN	330
4	CH_2	Tf	Tf_2O, DIPEA, CH_2Cl_2, 0°C	"
5	CH_2	Tf	Tf_2O, OIPEA, THF, -78°C	332 a
6	S	Tf	Tf_2O, OIPEA, CH_2Cl_2, -78°C	333

Table 2.38. SUBSTITUTION REACTIONS OF PENEM AND CARBAPENEM ENOL PHOSPHONATES, SULFONATES, AND TRIFLATES TO FORM SULFUR, AMINO, AND CARBON BONDS AT C-2



Entry	X	Y	Z	Reaction conditions	Ref.
1	CH_2	$P(OPh)_2$		 , OIPEA	329
2	CH_2	"		 , OIPEA, CH_3CN, 0°C	334
3	CH_2	"		 , OIPEA, CH_3CN, -20°C	335
4	CH_2, $CHCH_3$	"		 , DIPEA, CH_2Cl_2, 0°C	213, 330, 331
5	CH_2	Ts, Tf	"	 , OIPEA, OMF or CH_2Cl_2	330
6	S	Tf		 , OIPEA, CH_2Cl_2 -78°C→r.t.	333
7	CH_2	Ts	N_3	KN_3, CH_3CN/CH_2Cl_2, 0°C	336
8	S			 , DMF	337
9	S	Tf	Me	$Me_2CuCNLi_2$, THF, -78°C	333
10	CH_2	Tf		 , $Pd(dba)_3 \cdot CHCl_3$,  , r.t.	332 a
11	CH_2	Tf		 , $Pd(dba)_3 \cdot CHCl_3$,  , r.t.	332 a
12	CH_2	Tf		 , $Pd(dba)_2$,  ,  , 50°C	332b
13	CH_2	Tf	CH_2Ph	Bu_3SnCH_2Ph, $Pd(dba)_2$, " , " r.t.	332b

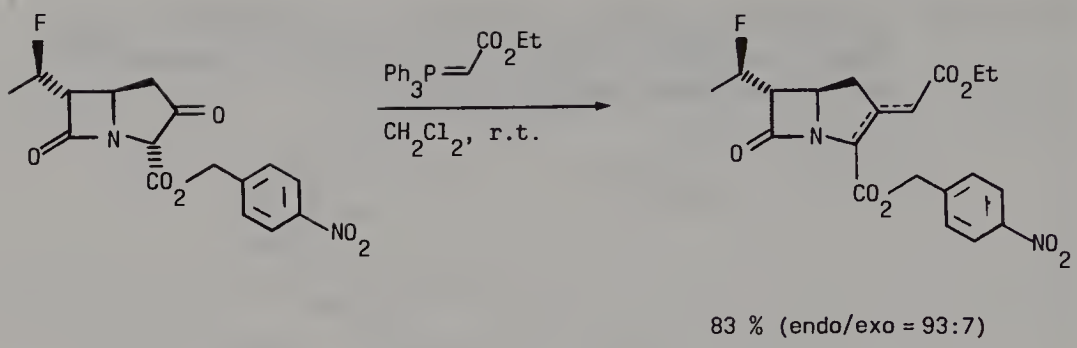


Figure 2.7. Reaction of a 2-oxocarbapenem with a stabilized phosphorus ylide.

perbenzoic acid in methylene dichloride at temperatures between −25 and −35°C.[339–344] They can be converted, inter alia, into the free sulfides (entries 3 and 4), which are present in the thiono form in the case of penems.

The carbapenem-2-thiols and penem-2-thiols can be converted into sulfides with the aid of alkylating agents, as shown in Table 2.40.

There follow three somewhat special reactions for the preparation of 2-unsubstituted carbapenems and for the transformation of carbapenams into

Table 2.39. 2-SULFOXIDES AS PRECURSORS FOR 2-THIO- AND 2-CARBON-SUBSTITUTED PENEMS AND CARBAPENEMS

Entry	X	Y	Z	Reaction conditions	Ref.
1	S	Et	SCH_2–pyridyl	$HSCH_2$–pyridyl, DIPEA, CH_3CN, -20°C	339
2	CH_2	NHAc	S–OH	HS–OH, NEt_3, DMF, -50°C	340
3	S	tBu	SH*	Ph_3P, CH_2Cl_2, △	341
4	CH_2	NHAc	SH	NaHS, DMF, -45°C	342
5	CH_2	"	CH_2NO_2	CH_3NO_2, tetramethyl guanidine, -25°C	343

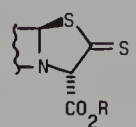
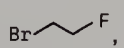
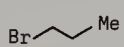
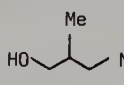
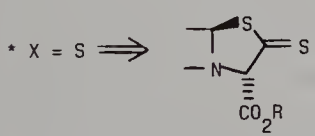
* ≙ 

Table 2.40. CONVERSION OF CARBAPENEM-2-THIOLS AND PENEM-2-THIOLS TO SULFIDES VIA ALKYLATION REACTIONS

Entry	X	Y	Reaction conditions	Ref.
1	CH_2	CH_3	CH_2N_2	342
2	S		 NEt_3, CH_3NO_2, r.t. (23 %)	344
3	S		 DIPEA, CH_2Cl_2, r.t.	8
4	S		≡ – CD_2Me, DIPEA, CH_2Cl_2, r.t.	"
5	S		 $NHCO_2R'$, Ph_3P, DEAD, THF, r.t.	345



carbapenems: (1) 2-Alkylthio residues can be split off by hydrogenolysis (Figure 2.8).[346] (2) Elimination of a carbapenam-2-mesylate permits the preparation of the carbapenem parent substance (Figure 2.9).[347,348] (3) 2-Alkylthio carbapenams can be converted into carbapenems by oxidation with iodophenyl dichloride and subsequent elimination. The resultant sulfoxides can be reacted with nucleophiles (Table 2.39) or can also be reduced in the manner shown in Figure 2.10.[349,350]

To conclude, only a few examples are given of the transformation of functionalities in side chain 2 of penems and carbapenems. Table 2.41 shows

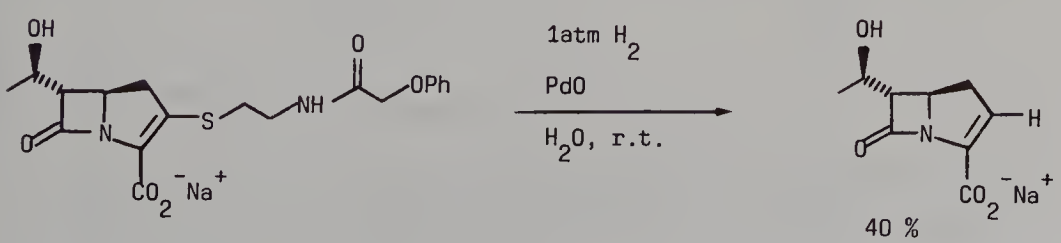


Figure 2.8. Removal of the 2-alkylthio group of a carbapenem by hydrogenolysis.

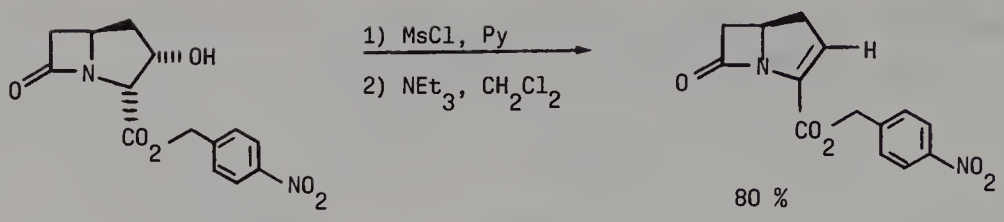


Figure 2.9. Formation of the parent carbapenem structure via elimination of a carbapenam-2-mesylate.

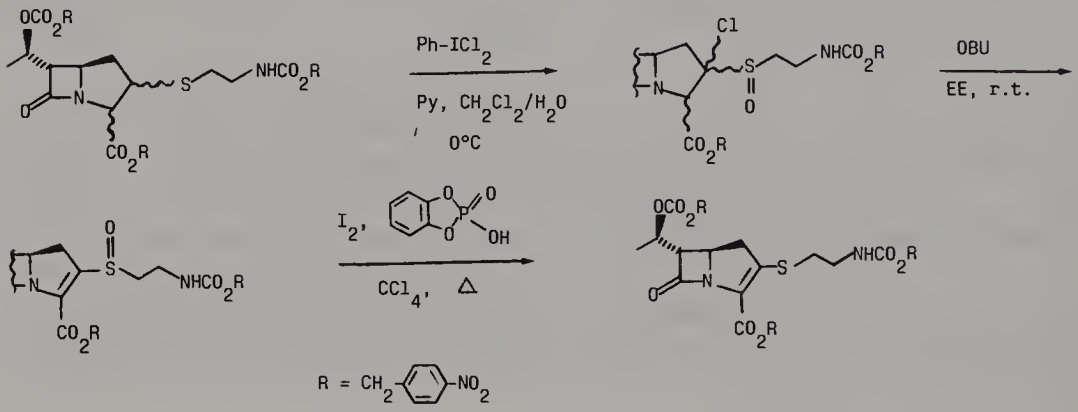
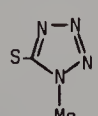
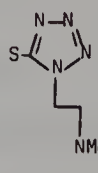


Figure 2.10. Conversion of a 2-alkylthio carbapenam to a 2-alkylthio carbapenem.

Table 2.41. TYPICAL METHODS FOR THE NUCLEOPHILIC SUBSTITUTION OF 2-HYDROXYMETHYLPENEMS

Entry	X	Reaction conditions	Ref.
1		Tf_2O, Py, CH_2Cl_2, -40°C	351
2		1) Ms-Cl, NEt_3, CH_2Cl_2, -40°C 2) R'-SH, NEt_3, THF, 0°C	352
3	Cl	OEAO, Ph_3P, $MeONH_2 \cdot HCl$, THF, 0°C	353
4		OEAO, PH_3P, R'-SH, 0°C	354

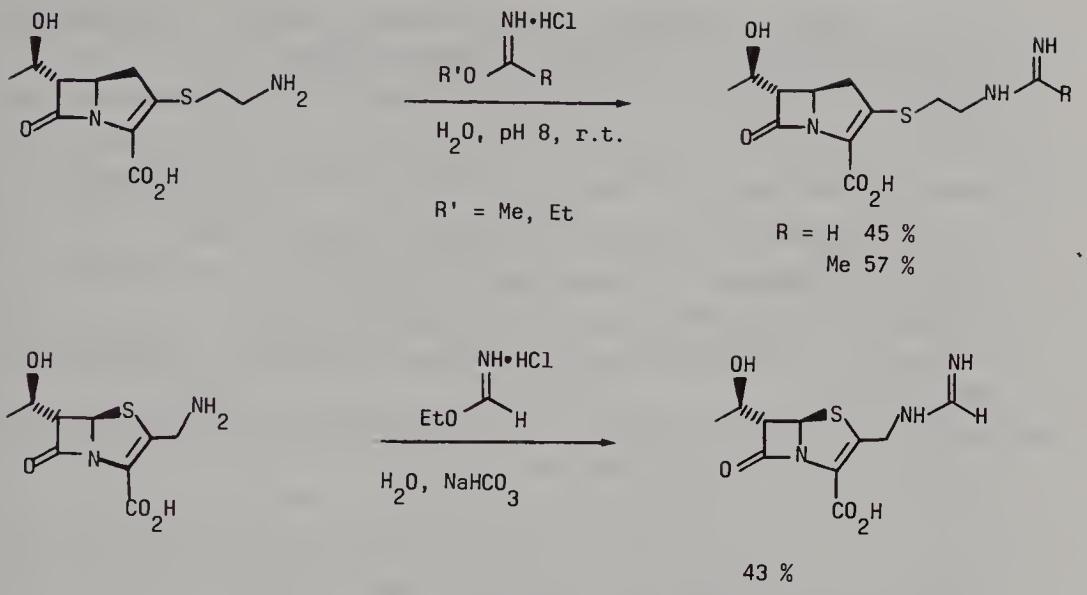


Figure 2.11. Conversion of amino groups in the C-2 side chain to amidines.

typical methods for nucleophilic substitution on 2-hydroxymethylpenems. Here, the hydroxyl group is either first transformed into a sulfonate or activated under Mitsunobu conditions.

Amino groups can be converted under gentle conditions to form amidines, which are often pharmacologically better and more stable (Figure 2.11). The reaction shown in Figure 2.11 was first used to prepare imipenem from thienamycin.

2.5 Abbreviations

See Chapter 1.

2.6 Acknowledgment

I thank Ms. C. Lettner for typing the manuscript and compiling the tables and drawings for this and the preceding chapter.

2.7 Literature

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CHAPTER

3

Strategies for the Synthesis of Bicyclic β-Lactams

Joydeep Kant

Bristol–Myers Squibb Company, Pharmaceutical Research Institute, P. O. Box 5100, Wallingford, Connecticut 06492–7600

Donald G. Walker

Bristol–Myers Squibb Company, Pharmaceutical Research Institute, P. O. Box 4755, Syracuse, New York 13221–4755

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3.1 Introduction

The unique structural and chemotherapeutic properties of β-lactam antibiotics continue to attract the attention of the synthesis community as they present a variety of synthetic challenges. During the last two decades, much of the effort was directed toward developing new strategies for the stereoselective synthesis of β-lactam antibiotics. The syntheses usually relied on

the prior construction of a monocyclic β-lactam leaving an appropriate tether for ring closure. The chemical reactivity of the azetidinone usually controlled the annulation of the second ring at a later stage in the synthesis.

The two most frequently used methods for ring closure are Woodward's intramolecular Wittig condensation and Merck's elegant carbene insertion reaction. By contrast, there are numerous methods in the literature for the synthesis of monocyclic β-lactams. To date, a number of comprehensive reviews have appeared detailing the chemistry of β-lactams.[1] This account focuses attention only on a variety of chemical strategies for construction of bicyclic β-lactam ring systems, including applications of both Woodward's and Merck's cyclization approaches. In the following, we discuss the synthetic strategies for the synthesis of bicyclic β-lactams, based on the final bond-forming step.

3.2 Closure to C-4 of the Azetidinone

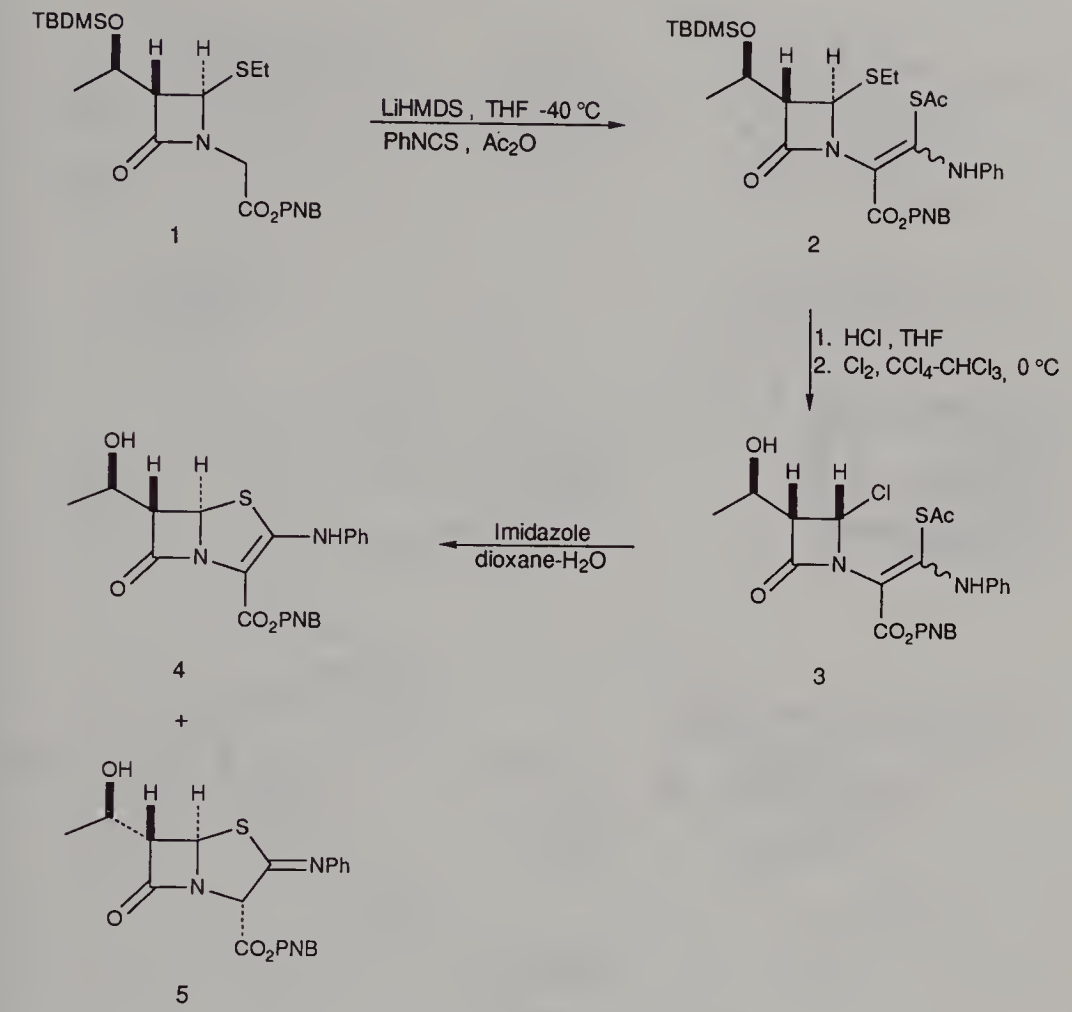
Closure to C-4 of the azetidinone is exemplified by bond formation to a heteroatom at C-4 of the azetidinone.

Barker and co-workers[2] used this strategy to synthesize substituted 3-aminopenems **4.** Treatment of the azetidinone **1** with lithium hexamethyldisilylamide (LiHMDS) in tetrahydrofuran (THF) at $-40°C$ generated an enolate anion, which on reaction with phenyl isothiocyanate and acetic anhydride afforded **2** (Scheme 3.1). Deprotection followed by stereospecific halogenation provided the 4-chloro derivative **3**, which in the presence of base cyclized to give the phenylamino penem **4** and its penam tautomer **5.**

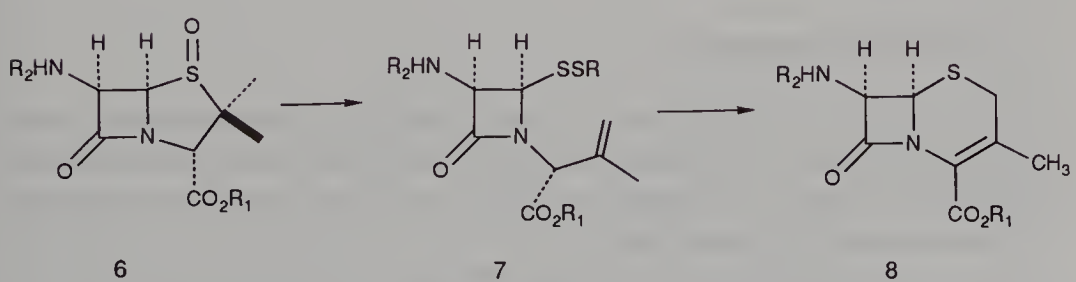
3.3 1,2 Bond Formation

Woodward's total cephalosporin synthesis exemplifies this approach and involves formation of a 1,2 bond by Michael addition of a sulfhydryl group to a highly activated double bond. This methodology was exploited using azetidinone disulfide esters **7,** usually obtained in high yields from penicillin sulfoxides **6** (Scheme 3.2). In the presence of base, intermediates **7** cyclized to the corresponding cephems **8.** Over a period of time, process improvements were made through selection of an appropriate base which facilitated cyclization to the Δ^3-cephem without isomerization to the undesired Δ^2 isomer.

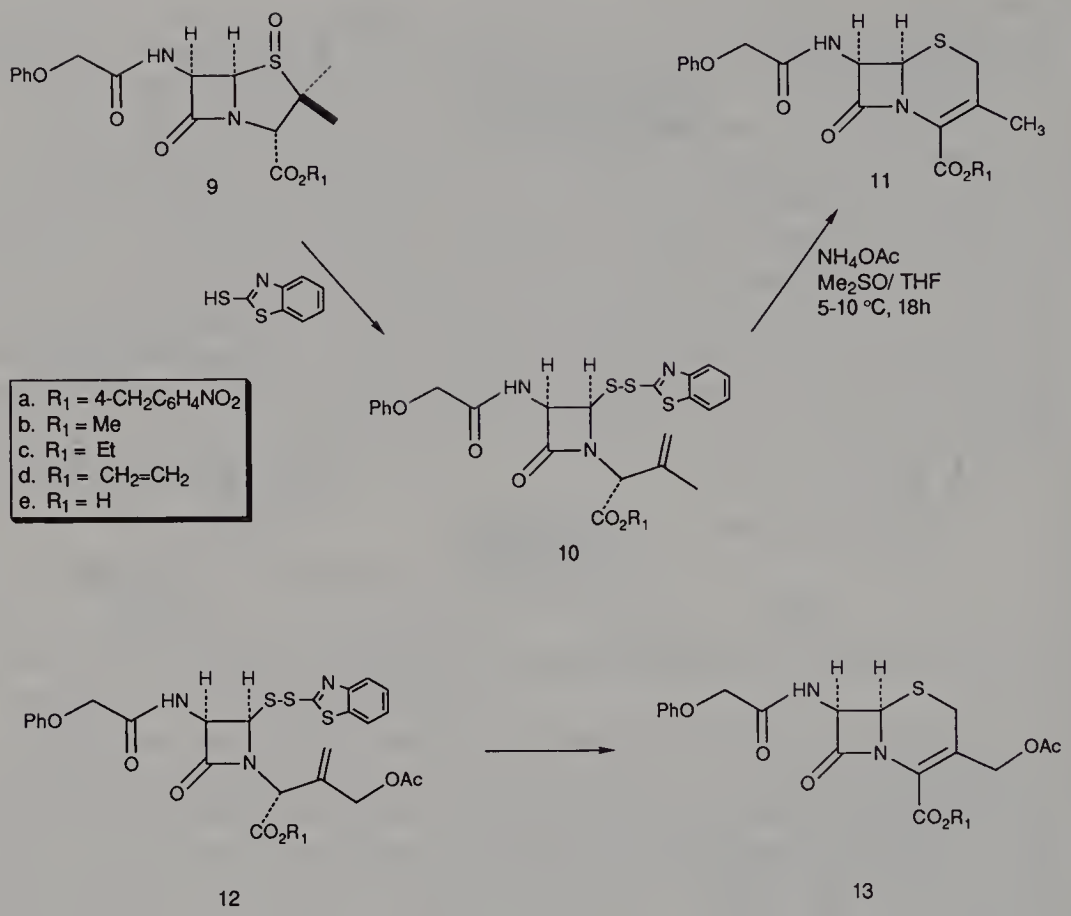
A comprehensive account of this chemistry was presented in texts edited by Morin and Gorman.[1c] Very recently, Davis and Wu[3] reported the use of ammonium acetate in a solution of dimethylsulfoxide (Me_2SO)/THF for cyclizing azetidinones **10** and **12** to the corresponding Δ^3-cephem esters **11** and **13,** respectively, in satisfactory yields. The mild reaction conditions pre-



Scheme 3.1



Scheme 3.2



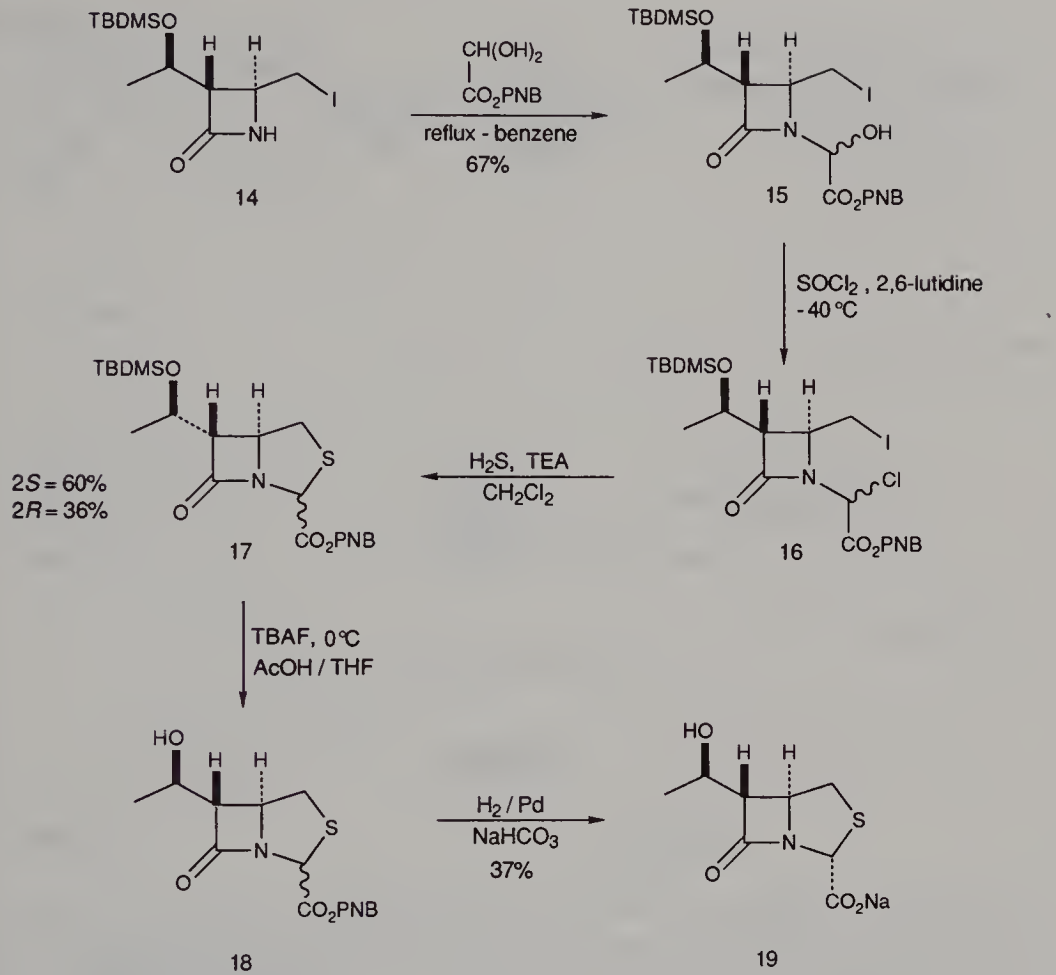
Scheme 3.3

vented double bond isomerizations into the undesired Δ^2 position (Scheme 3.3).

3.4 2,3 Bond Formation

The synthesis of isocephems was the most widely reported application of this type of β-lactam ring closure strategy. Hirai and co-workers[4] reported the synthesis of the *S*-2 isopenam derivative **19** employing this 2,3 bond formation technique (Scheme 3.4).

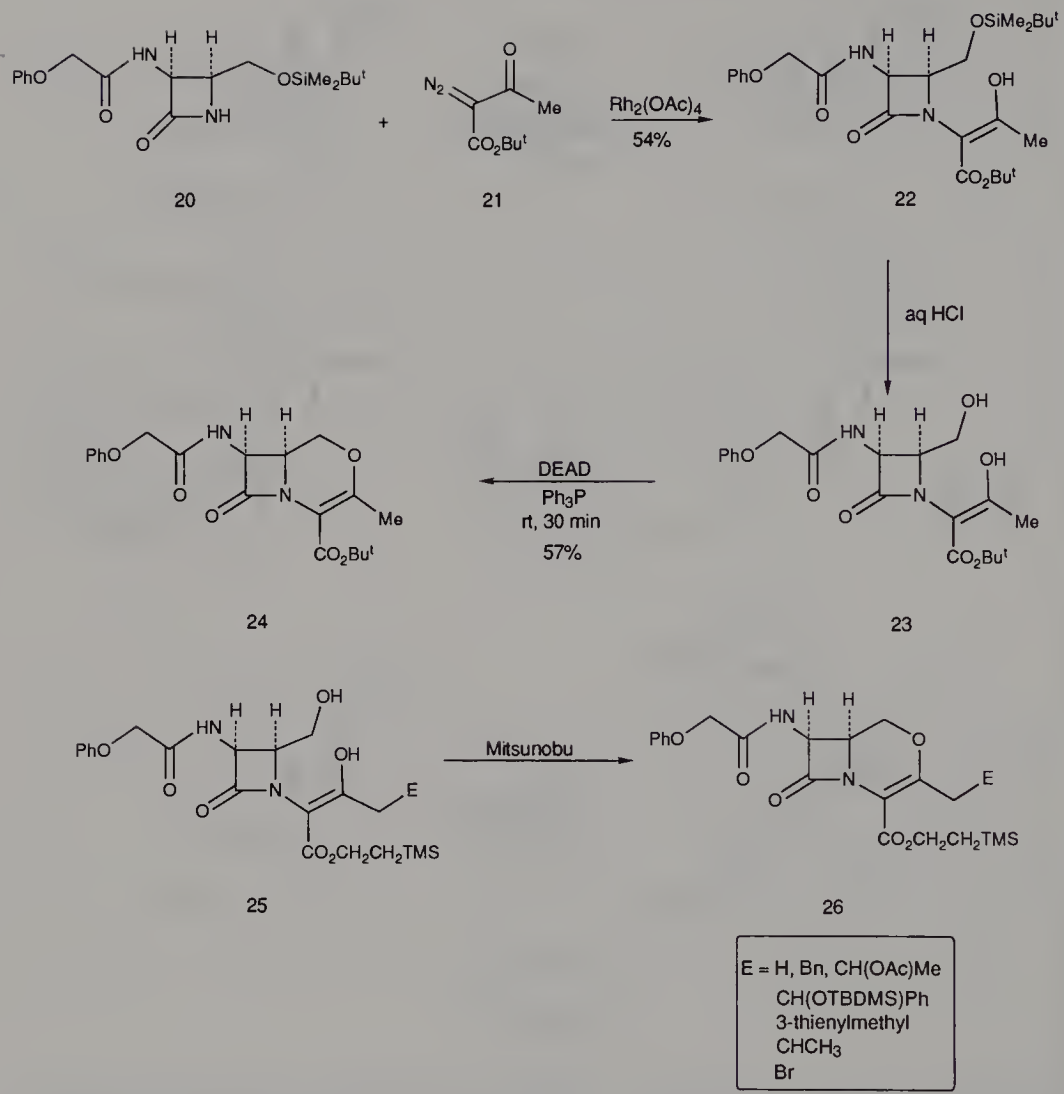
The starting iodomethyl azetidinone **14** was treated with *p*-nitrobenzyl glyoxylate in refluxing benzene to give the aminal **15.** Chlorination followed by treatment of **16** with hydrogen sulfide and triethylamine afforded the desired cyclized product **17,** which was then desilylated to **18.** Reductive removal of the *p*-nitrobenzyl (PNB) ester in the presence of sodium bicarbonate gave **19** in 37% yield.



Scheme 3.4

Hrytsak and Durst[5] recently employed intramolecular Mitsunobu reactions of enol alcohols to synthesize a variety of *O*-2 isooxacephems (Scheme 3.5). The rhodium acetate ($Rh_2(OAc)_4$) catalyzed carbene insertion reaction of *tert*-butyl-2-diazo-3-oxobutyric acid **21** with azetidinone **20** afforded the enol **22.** Acid catalyzed deprotection of the C-4 hydroxymethyl group followed by cyclization of the intermediate enol alcohol **23** with diethyl azodicarboxylate (DEAD) and triphenylphosphine (Ph_3P) provided the desired *O*-2 isooxacephem **24** in 57% yield. This chemistry was further extended by replacing **21** with other α-diazo-β-keto esters to provide **25,** which subsequently gave a variety of *O*-2 isooxacephem derivatives **26.**

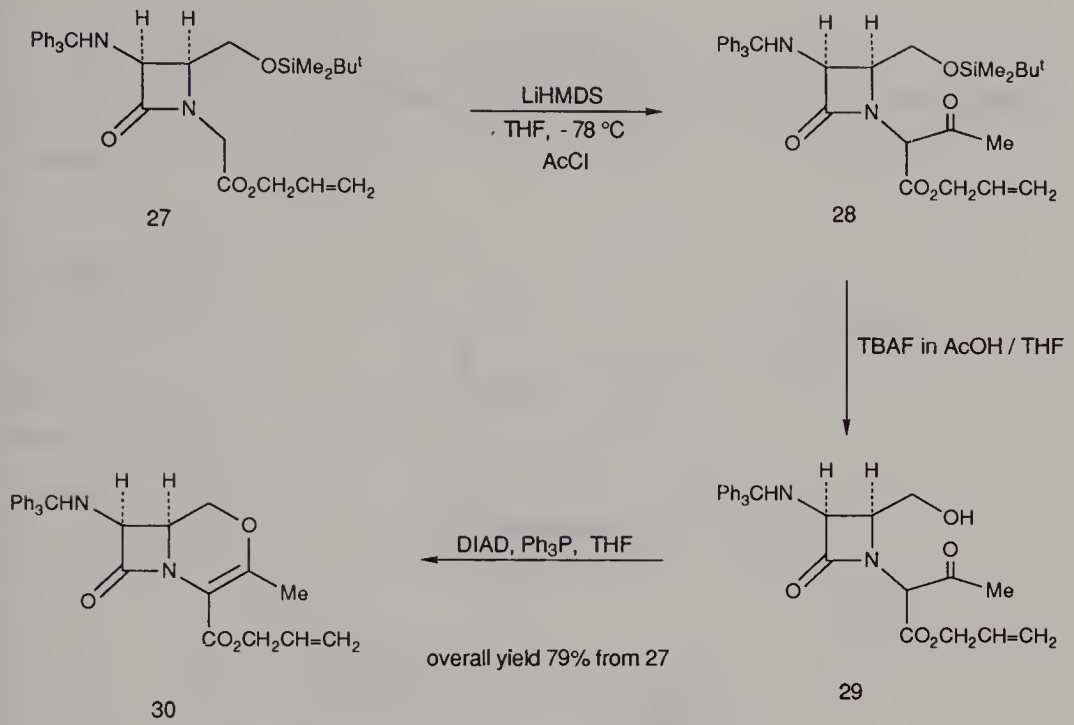
A similar approach was reported by Mastalerz and Vinet[6] in the enantioselective synthesis of *O*-2 isooxacephems **30.** The required acetate derivative **28** was prepared by the reaction of the enolate, derived from chiral, nonracemic azetidinone **27**, with acetyl chloride. Deprotection of the hydroxymethyl group by tetrabutylammonium fluoride (TBAF) followed by



Scheme 3.5

treatment of **29** with diisopropyl azodicarboxylate (DIAD) and Ph_3P in THF at room temperature afforded **30** in 79% yield (Scheme 3.6).

Hatanaka and co-workers[7] reported syntheses of *O*-2 isooxacephem **35** and *S*-2 isocephem **36** starting from L-aspartic acid (Scheme 3.7). The cyclization step employed was similar to that previously reported by Doyle and co-workers[8] for the synthesis of *O*-2 isooxacephems. The amino acid **31** was subjected to a four component condensation for construction of the azetidinone **32.** Mesylation followed by conversion of the *p*-nitrobenzylamide group into the corresponding ester via *N*-nitrosation gave the azetidinone **33** in 57% yield. Further treatment with trifluoroacetic acid (TFA) followed by triethylamine (TEA) gave the *O*-2 isooxacephem **35.** On the other hand, mesylation of azetidinone **34** followed by treatment with hydrogen sulfide and TEA provided *S*-2 isocephem **36.**

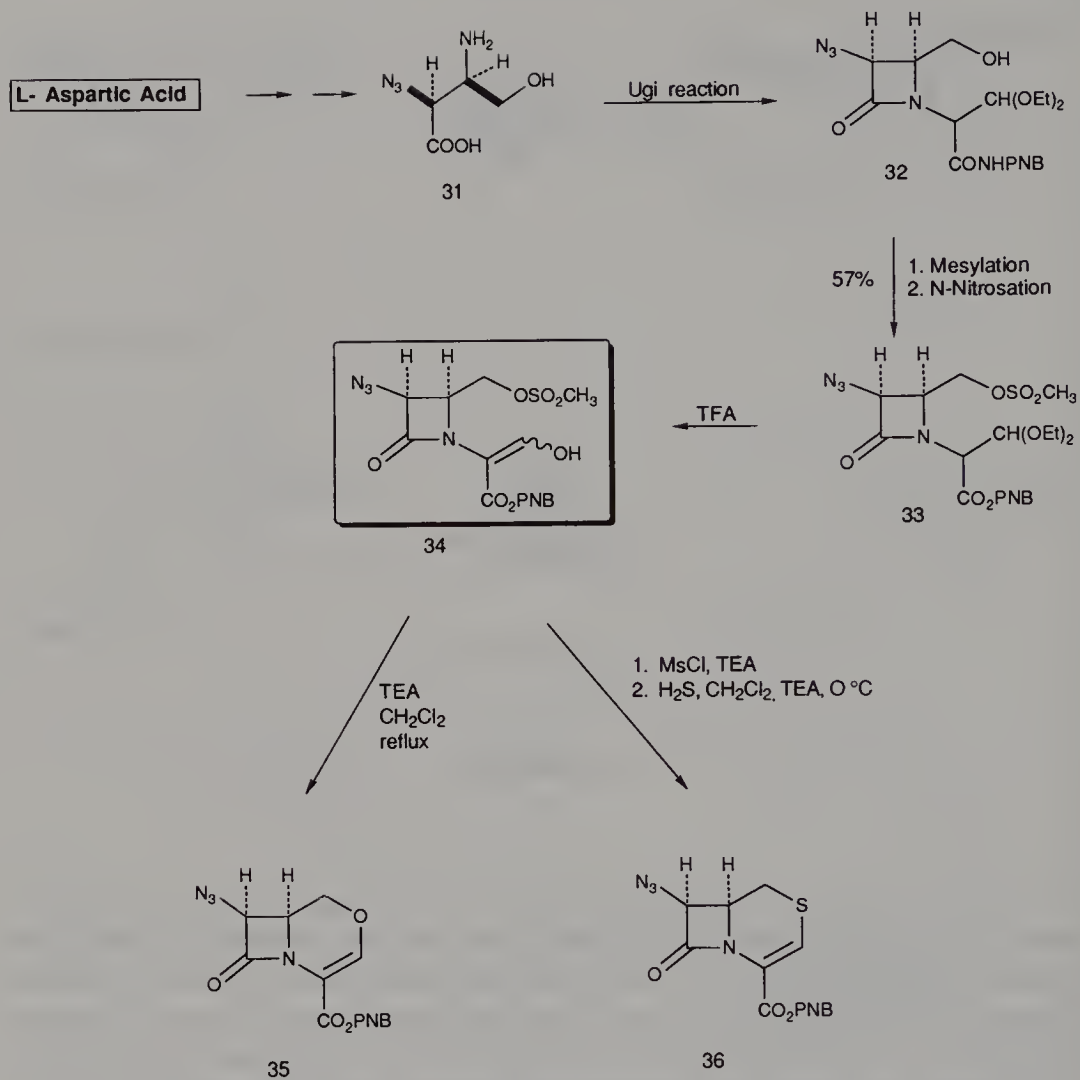


Scheme 3.6

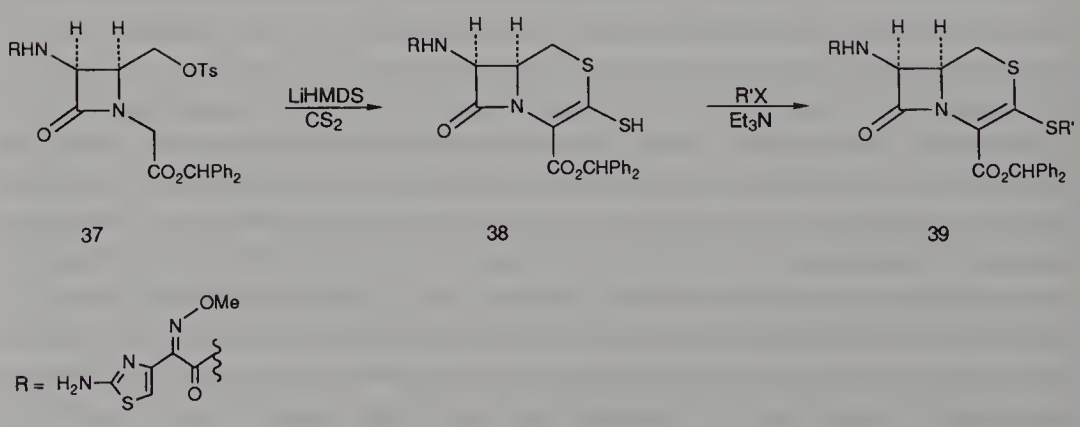
A novel synthesis of *S*-2 isocephems **39** was reported by French scientists.[9] Treating **37** with LiHMDS and quenching the resulting enolate with carbon disulfide followed by intramolecular displacement of the tosylate afforded **38** (Scheme 3.8). Subsequent alkylation followed by protecting group removal gave **39,** which showed interesting levels of antibacterial activity.

Recently, Hatanaka and co-workers[10] reported the synthesis of the *O*-2,3-methoxyisocephem **44** via an intramolecular acylation reaction. The key azetidinone **40,** synthesized using an Ugi condensation reaction, was converted to PNB ester **41** (Scheme 3.9). Deprotection to the alcohol **42** followed by treatment with 1,1′-carbonyldiimidazole afforded the carbamate **43,** which was cyclized on reaction with 2 equivalents of base. The crude ester was not isolated but converted to **44** using diazomethane.

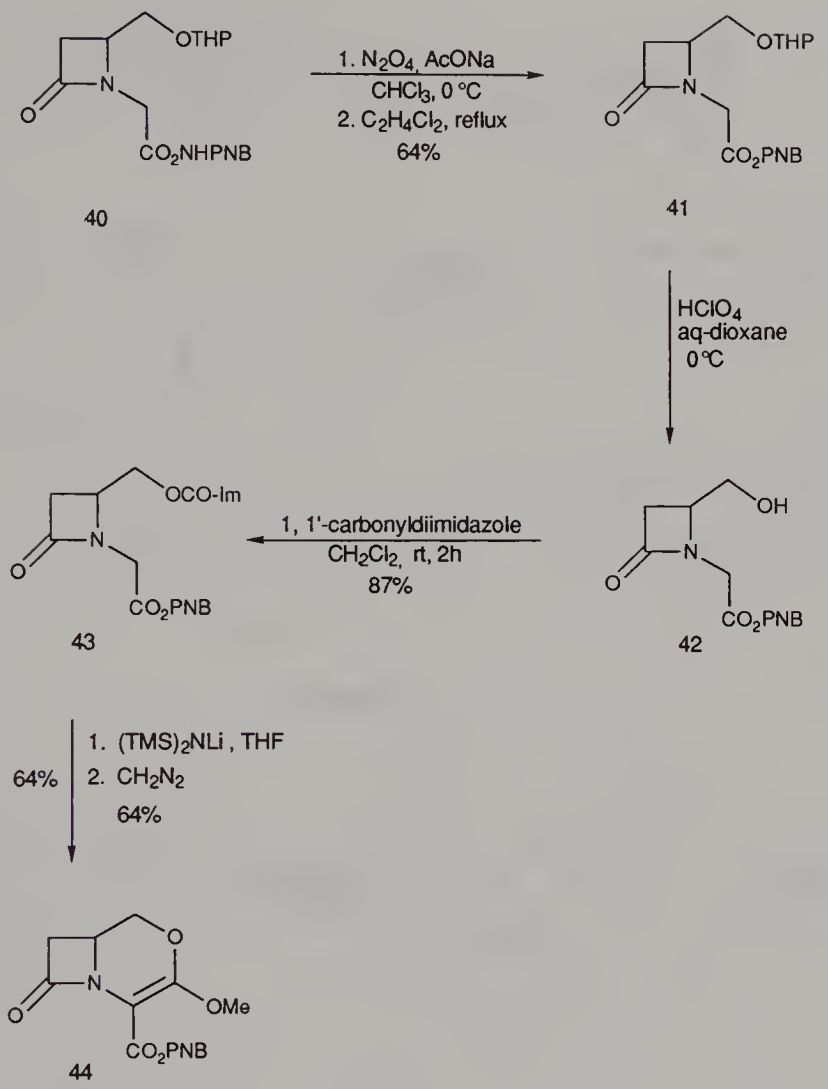
A similar intramolecular acylation reaction was also used by Schering researchers[11] to synthesize chiral, nonracemic penem **52** (Scheme 3.10). The readily accessible starting azetidinone **45** was converted via **46** to the unstable silver thiolate **47,** which was immediately converted to the corresponding thiothionocarbonates **48** and **49** by treatment with 1,1-thiocarbonyldiimidazole (CTBI) and β-naphthalenyl carbonochloridothioate (NCCT), respectively. These intermediates underwent smooth cyclizations in the presence of LiHMDS to the unstable intermediate **50,** which was not isolated but immediately *S*-alkylated to **51.** Deprotections then yielded the target compound **52.**



Scheme 3.7



Scheme 3.8

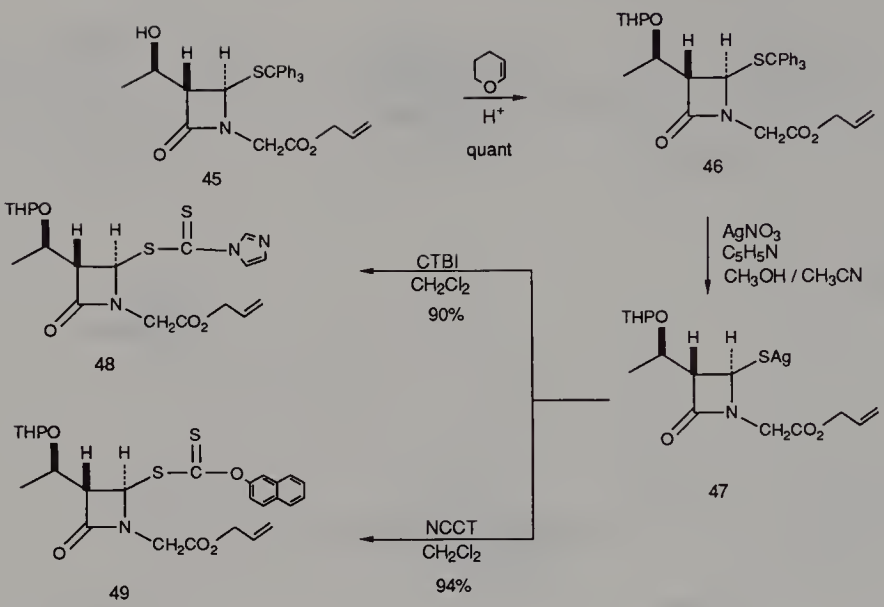


Scheme 3.9

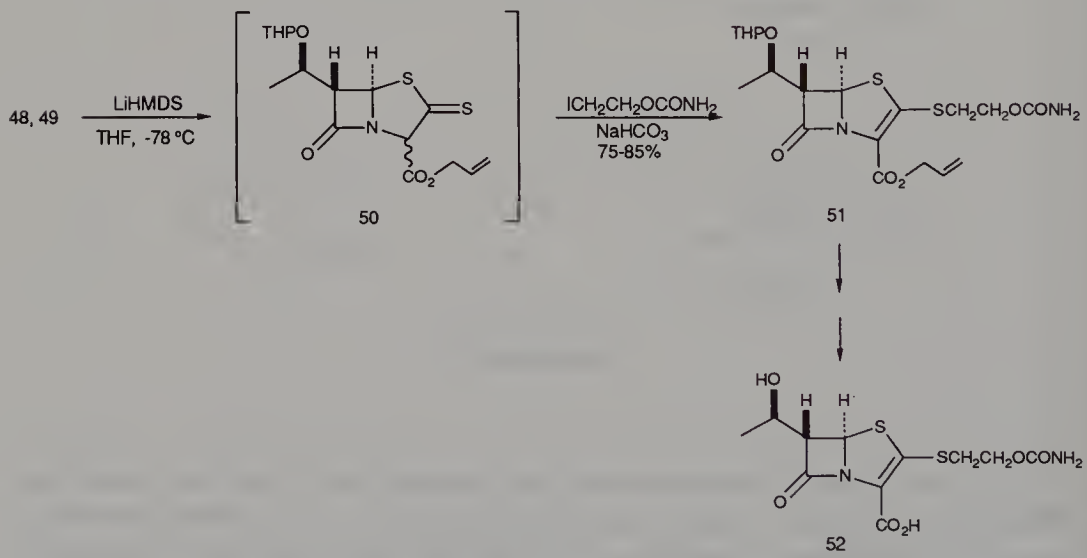
Lilly researchers[12] reported a one pot preparation of 3-acylcarbacephems **57** based on a Michael addition/cyclization/pyrolytic elimination reaction sequence of azetidinone **53** with α,β-unsaturated sulfoxides **54** (Scheme 3.11). Initially formed Michael adduct **55** underwent intramolecular 2,3 bond formation by nucleophilic displacement of iodide to give the carbapenam **56,** which lost phenylsulfenic acid by thermal *cis* elimination at 100°C to yield **57** in modest overall yields.

3.5 Carbon–Carbon Bond Formation

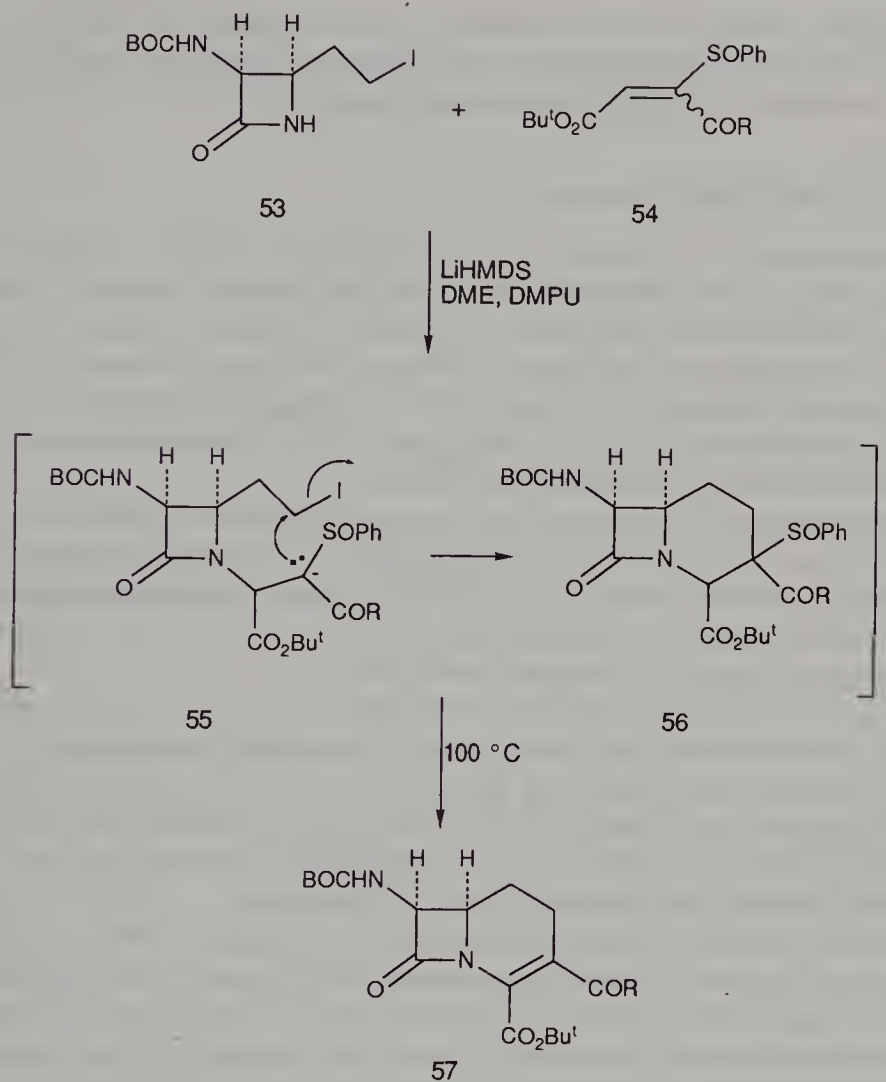
One of the most effective and widely used C—C bond formation strategies for constructing the bicyclic β-lactam system was Woodward's intramole-



Cyclizations



Scheme 3.10



R	% yield
OMe	30
Me	16

Scheme 3.11

cular Wittig condensation. In addition to this approach, however, other methods for C—C bond formation were reported based on carbanion, free radical, carbene, and aldol condensation chemistries.

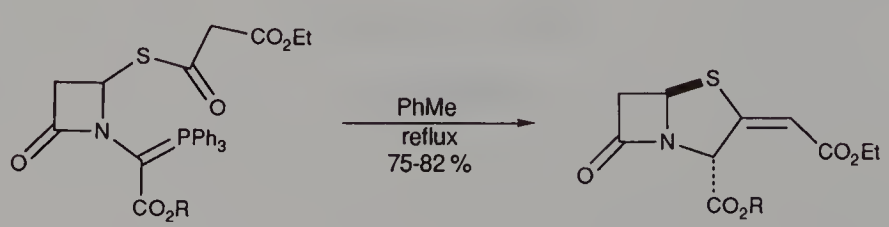
3.5.1 The Wittig Approach

Total syntheses of both natural and nontraditional β-lactam antibiotics employing Woodward's intramolecular Wittig ring closure strategy[13] continue to be exploited by the synthesis community. Penems, carbapenems, cephems, 1-oxacephems, and other classes of β-lactam antibacterial agents were (and most assuredly will continue to be) prepared using this C—C bond forming methodology.[1b,c,e,f,i–l] A discussion of selected applications of this annulation technology through 1990 follows.

The synthesis of a thia analog of clavulanic acid was reported by Lombardi and co-workers (Scheme 3.12).[14] Cyclizations of **58** in refluxing toluene gave thiaclavulanoids **59** in 75 to 82% yields after chromatographic purifications. The relative stereochemistries at C-3 and C-5 of **59** were found to be identical to those of the natural penicillins.

Italian researchers described preparations of chiral, nonracemic, and biologically active penems **62** derived from (5*R*)-methyl penicillanate *S*-oxide (**60**).[15] Structural modification of **60** gave the phosphoranes **61.** Intramolecular Wittig reactions yielded targets **62** (R″ = CH_2OAc) in good yields after refluxing in toluene (Scheme 3.13). The penem-3-carboxylate **62** (R″ = H) was produced after hydrogenolysis of the PNB ester.

A series of racemic C-6 α-ethylpenems **66** showing in vitro activity were synthesized from the common intermediate **63** (Scheme 3.14).[16] Acylation of **63** with 1.5 equivalents of acid chloride at ambient temperature for 5 minutes gave phosphoranes **64** in about 60% yields after workup. Conversion to penems **65** by refluxing in toluene proceeded with variable yields. The carboxylic acids **66** were obtained either by hydrogenolysis (R_2 = PNB) or by hydrolysis in pH 7.5 phosphate buffer (R_2 = CH_2OAc).

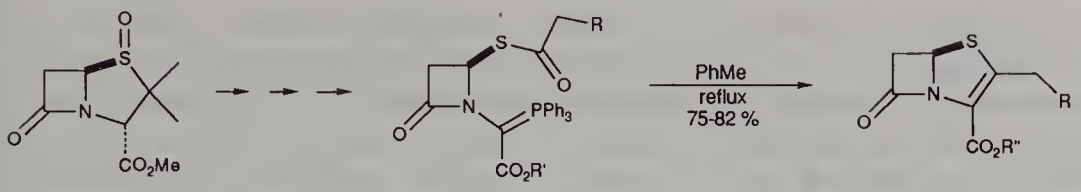


58

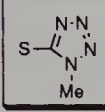
R = Me, Bn, CH_2OAc

59

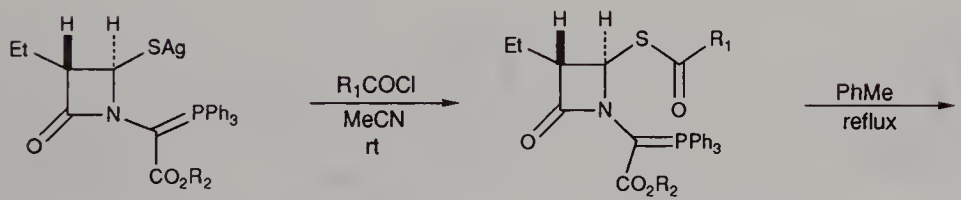
Scheme 3.12



60 61 62

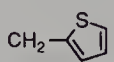
R	R'	R''
OAc	PNB	H
OAc	CH_2OAc	CH_2OAc
	CH_2OAc	CH_2OAc

Scheme 3.13



63 64

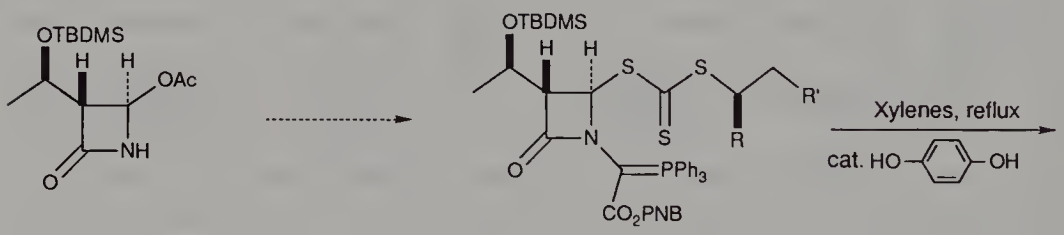
65 66

R_1	R_2
Me	PNB
CH_2OAc	CH_2OAc
CO_2Et	PNB
	PNB

Scheme 3.14

As shown in Scheme 3.15, Sankyo researchers reported syntheses of 1-thiathienamycins **70**.[17,18] The azetidinone **67** was elaborated to phosphoranes **68** which subsequently afforded penems **69** in 74 to 76% yields on heating in xylenes. Catalytic hydroquinone (HQ) was used to suppress decomposition of both **68** and **69** under the reaction conditions. Deprotections under standard conditions gave **70** (R = H, Me; R″ = NH_2), which showed good antibacterial and antipseudomonal activities. The β-fluoroethyl penem **70** (R″ = F) exhibited potent in vitro activity against both gram-positive and gram-negative organisms.[19]

Girijavallabhan and co-workers[20] described some C-2 nitrogen substituted penems **74** (Scheme 3.16). Thermal Wittig condensation of **71** proceeded to give a mixture of **72** and the undesired *cis*-penem **73.** This latter material was converted by thermal isomerization to **72.** Deblocking to the sodium salt **74** was performed by Pd(0) catalysis.[21] These penems were found to be slightly less active antibacterials than Schering's **52**[11,22] and Farmitalia's **75** (Scheme 3.17).[23] Azetidinone **67** was converted over numerous steps to **76.** Selective removal of the primary hydroxyl protecting group of **76** with TBAF followed by thermal intramolecular Wittig cyclization gave the key intermediate **77.**

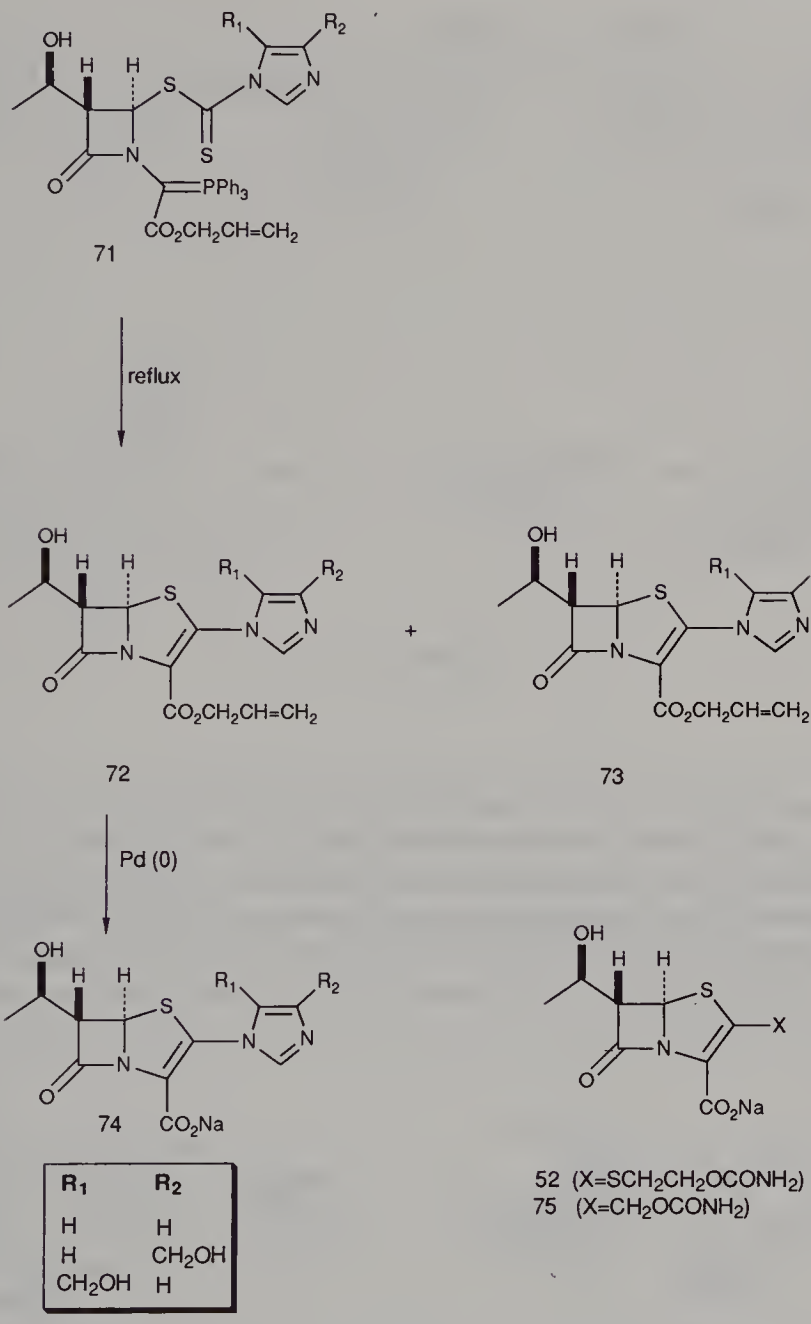


67 68

69 70

R	R'	R"
H	$NHCO_2PNB$	NH_2
Me	$NHCO_2PNB$	NH_2
H	F	F

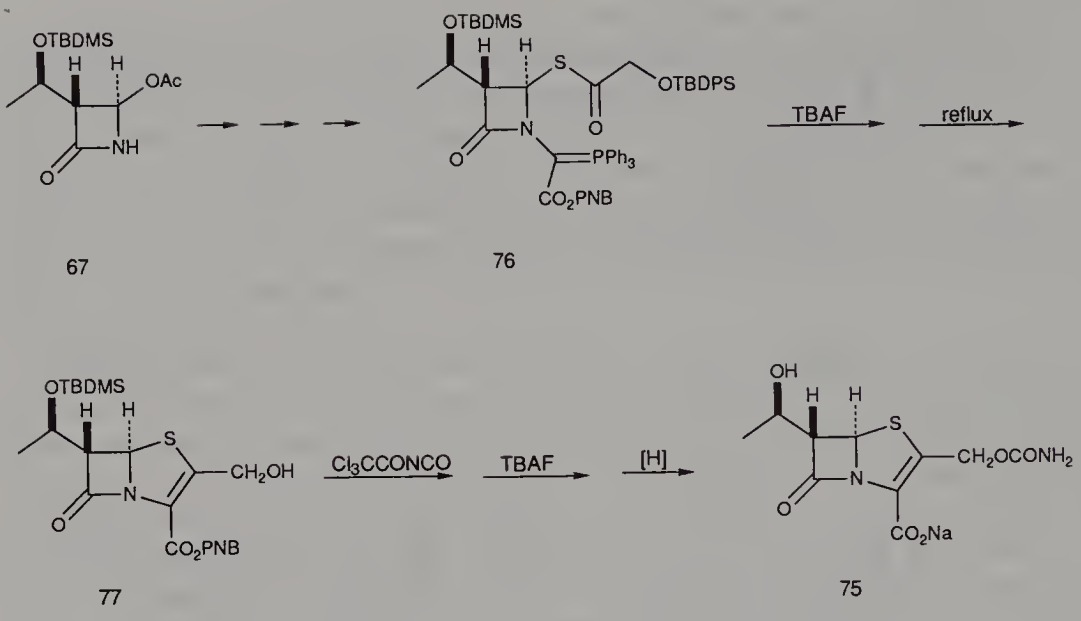
Scheme 3.15



Scheme 3.16

Further reaction with trichloracetyl isocyanate, removal of the TBDMS and trichloracetyl protecting groups with TBAF, and hydrogenolysis of the PNB ester afforded **75.**

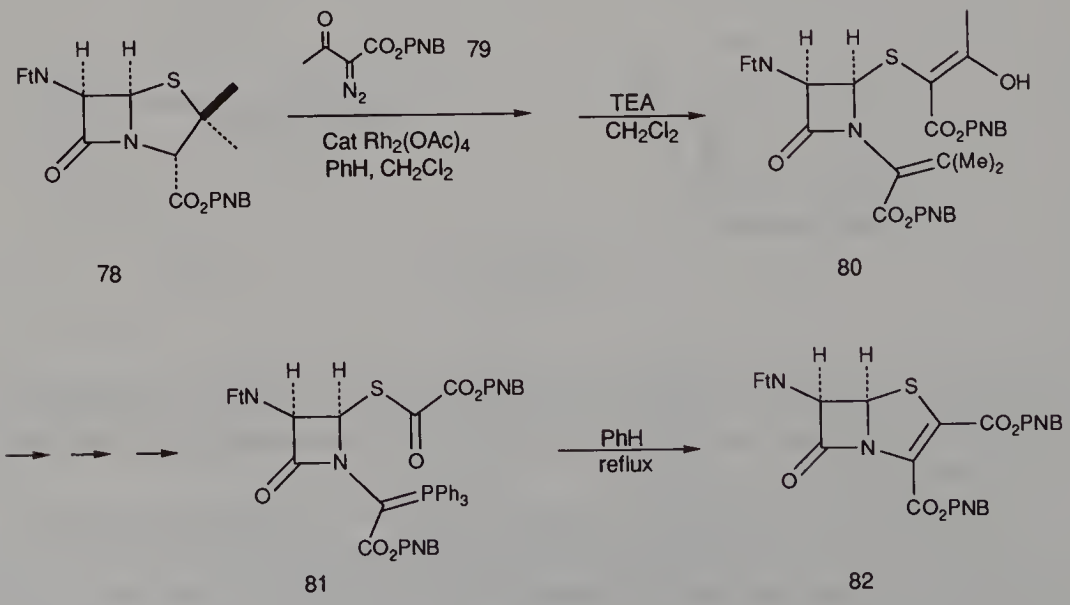
The synthesis of a penem-2,3-dicarboxylate which featured the novel reaction of a protected penicillin with α-diazoacetate catalyzed by $Rh_2(OAc)_4$ as a key step was reported by Kametani and co-workers.[24] Reaction of **78** with **79** in CH_2Cl_2/PhH (1:1) at reflux with catalytic rhodium(II) followed by



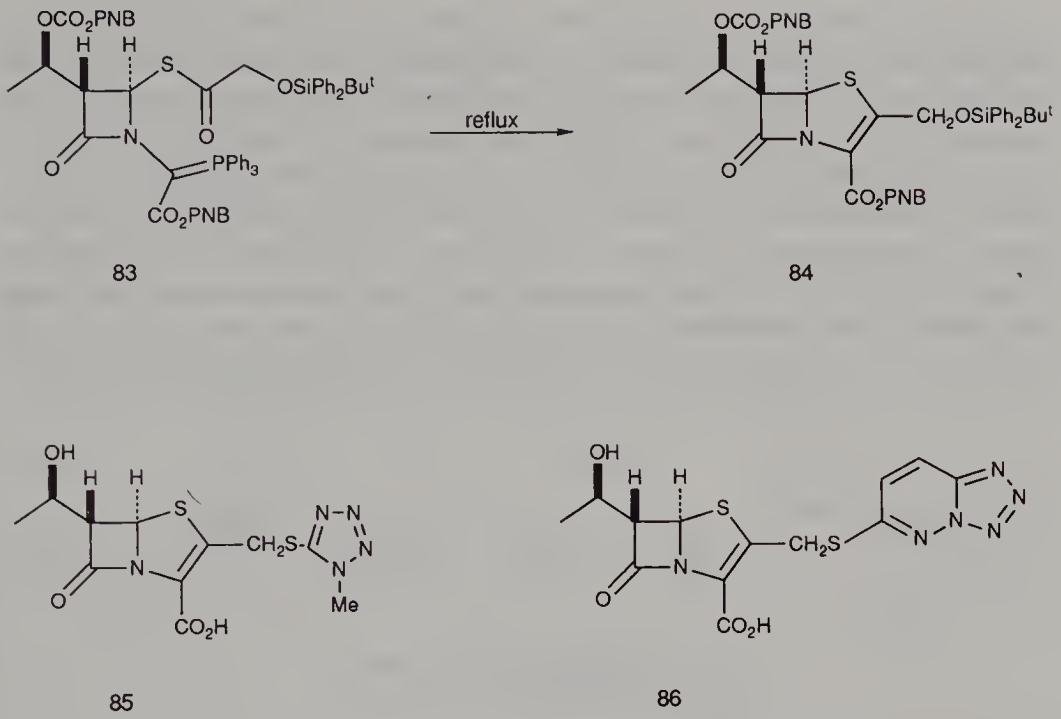
Scheme 3.17

olefin isomerization with TEA in CH_2Cl_2 gave azetidinone **80** in 79% yield (Scheme 3.18). Further transformations gave **81,** which smoothly cyclized in refluxing benzene to afford the penem **82.**

A number of other papers also appeared related to the synthesis of penems bearing C-2 carbon tethers. For example, Farmitalia scientists[25] com-



Scheme 3.18

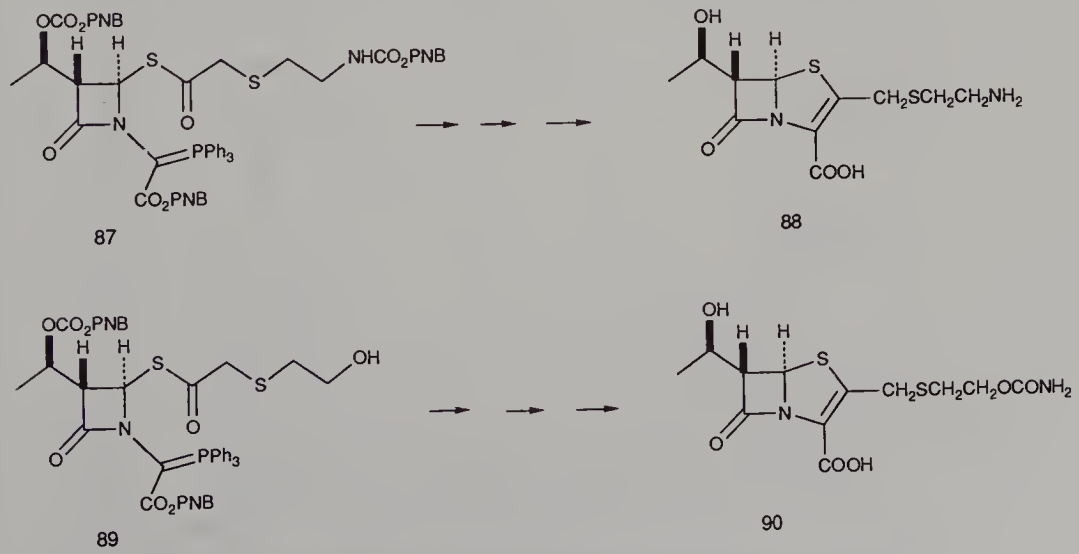


83 84

85 86

Scheme 3.19

municated syntheses of antibacterially active penems **85** and **86** from phosphorane **83** via the Wittig product **84** (Scheme 3.19); the C-2 homolog **88** of 1-thiathienamycin **70**[17,18] by intramolecular Wittig closure of **87** and subsequent deprotections; and the C-2 homolog **90** of SCH-34343 (**52**),[11,22] produced from the Wittig precursor **89** in a similar fashion (Scheme 3.20).

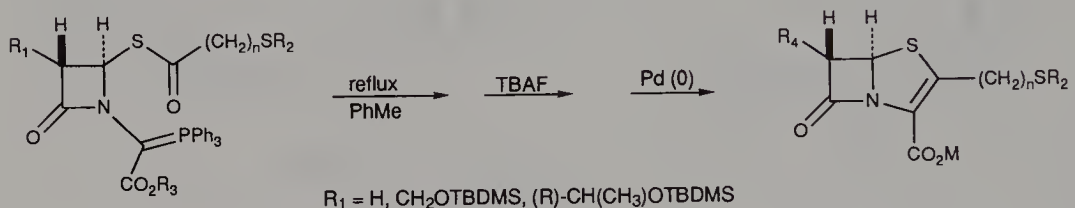


87 88

89 90

Scheme 3.20

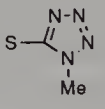
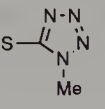
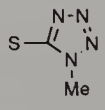
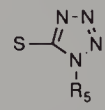
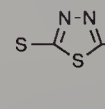
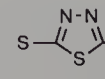
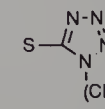
Lang and co-workers[26] prepared a number of C-2 heterocyclylmercaptoalkylpenems **92** with different C-6 substitution patterns in search of antibacterial agents with good activity. The majority of these materials were prepared by intramolecular Wittig cyclizations of phosphoranes **91** in toluene followed by standard TBAF and palladium(0)-catalyzed[21] deprotections. Representative examples of **92** synthesized by this protocol are listed in Scheme 3.21 (R_5 = CH_2CO_2Na, CH_2CONH_2, $(CH_2)_2NMe_2$, $(CH_2)_2NHCOMe$). Although displaying good gram-positive and gram-negative activity, none of **92** possessed significant antipseudomonal activity. Unsubstituted C-6 penems proved to be inferior to those with substitution from



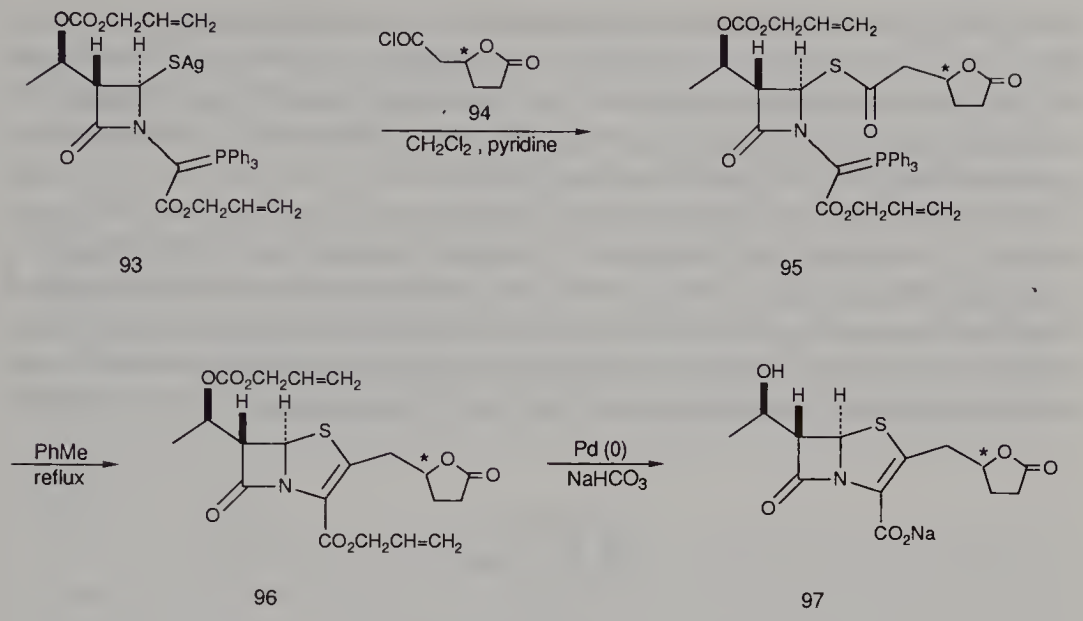
91

R_1 = H, $CH_2OTBDMS$, (R)-$CH(CH_3)OTBDMS$
R_3 = allyl, CH_2CH_2TMS
n = 1-3
M = Na, H

92

R_4	n	M	SR_2
CH_2OH	1,2,3	Na	
(R)-CH(Me)OH	1	Na	
H	3	Na	
CH_2OH	1	Na	
CH_2OH	1	Na	 , 
H, CH_2OH	3	H or Na	

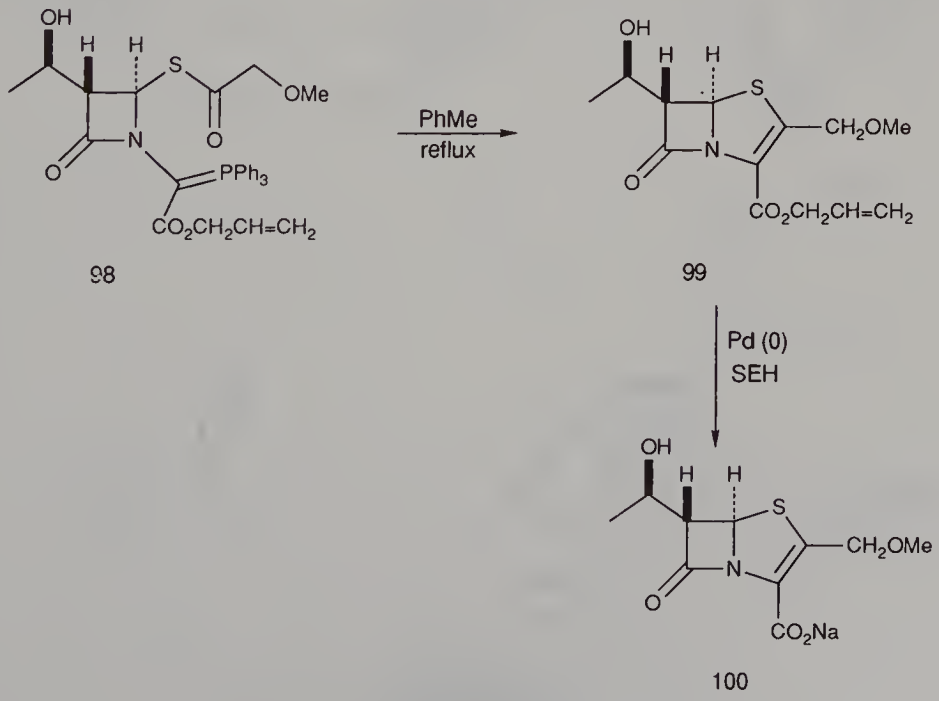
Scheme 3.21



Scheme 3.22

a β-lactamase stability viewpoint. Also, increasing the length of the C-2 carbon tether resulted in decreased gram negative activity.

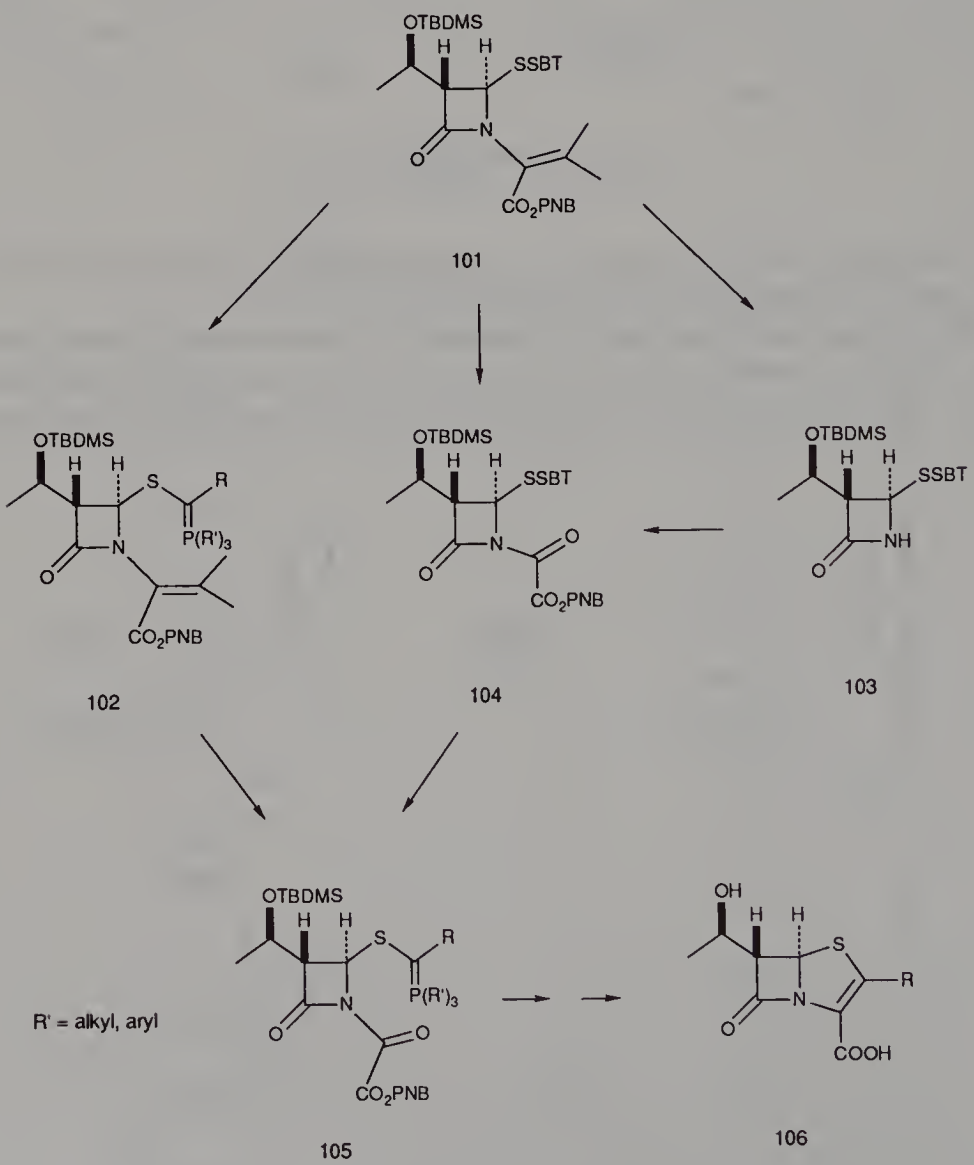
Researchers at Ciba–Geigy[27] described the synthesis and activity of a series of C-2 lactonylpenems **97** (Scheme 3.22). Acylation of **93** with either the *(R)* or *(S)* acid chloride **94** (prepared in situ) gave intermediates **95**, which



Scheme 3.23

smoothly underwent Wittig cyclization to **96** in refluxing toluene with catalytic 2,6-di-*tert*-butyl-*p*-cresol (BHT). Conversion to penems **97** followed use of the Pd(0) catalyzed removal of the blocking groups[21] and an aqueous $NaHCO_3$ quench. These penems displayed a well-balanced antibacterial spectrum and showed good in vivo activity.

Prompted by the improved oral bioavailability of 2-alkoxymethylcephems, Franceschi and co-workers[28] prepared a series of 2-alkoxymethylpenems (Scheme 3.23). Wittig cyclization of the phosphorane **98,** prepared by acylation of the corresponding silver azetidinyl mercaptide with methoxyacetyl chloride, afforded penem **99** in good yield. Removal of the allyl protecting group[21] in the presence of sodium ethylhexanoate (SEH) gave **100.**



Scheme 3.24

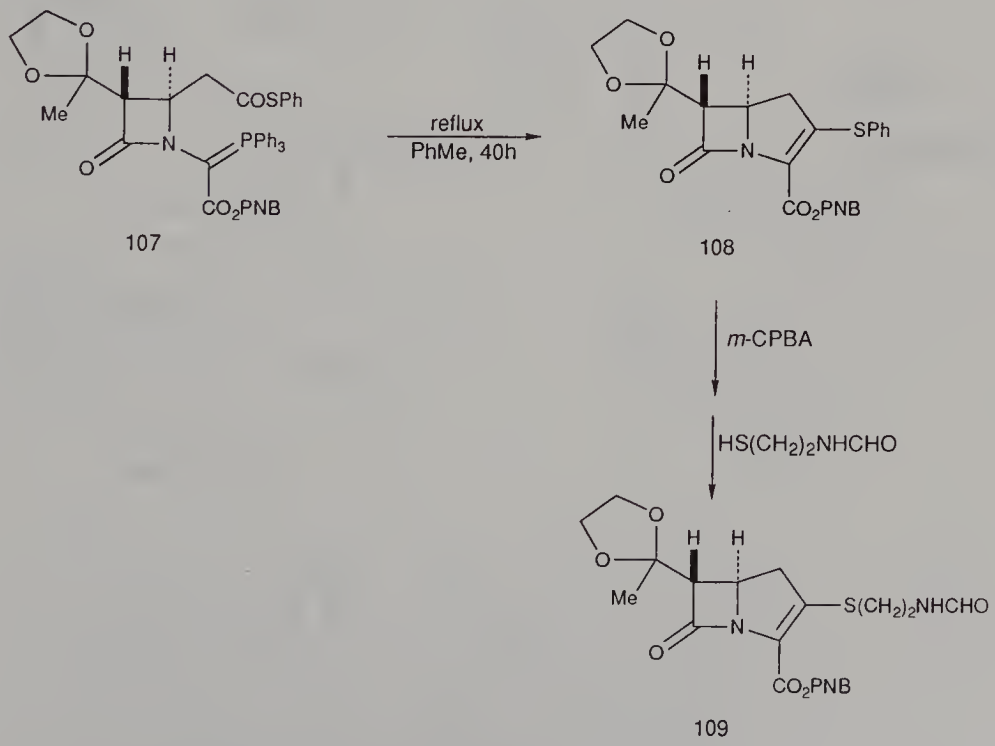
The antibacterial activity profile of this penem warranted its further evaluation.[28]

Finally, researchers at Hoechst[29] reported a general synthesis of a wide variety of C-2 functionalized penems **106** by an intramolecular Wittig condensation of C-4 tethered azetidinyl phosphoranes **105.** These trialkyl (tri-*n*-butyl preferred) or triaryl (especially triphenyl) phosphoranes were readily accessible from azetidinone **101** via **102** or **104** (Scheme 3.24).

Numerous syntheses of carbapenem antibiotics using the intramolecular Wittig annulation as a key step for ring construction appeared in the literature. Fetter and co-workers[30] (Scheme 3.25) prepared the carbapenem intermediate **108** from phosphorane **107** by heating its toluene solution for 40 hours. Peracid oxidation to the sulfoxide and displacement by *N*-formylcysteamine gave **109.**

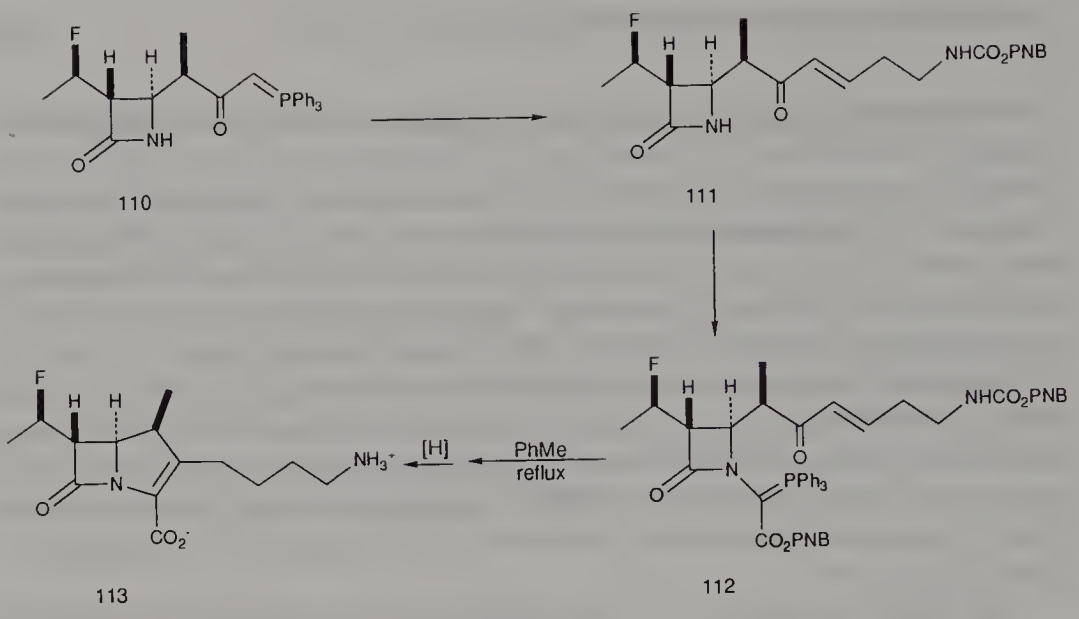
Synthesis of the novel C-6 α-fluoroethylcarbapenem **113** was detailed by deVries and Sigmund.[31] The Wittig reaction of azetidinone **110** with an *N*-protected β-aminoaldehyde gave **111** (*trans* only), which was converted to phosphorane **112** by Woodward's method.[13,32] Intramolecular olefination in refluxing toluene followed by prolonged hydrogenation (10% Pd/C, EtOAc/pH 7 phosphate buffer) produced the 1β-methylcarbapenem **113** (Scheme 3.26).

Shah and Cama described the synthesis of a C-1 geminal difluorocarbapenem **119** which featured the use of the acid and base stable —SMe group



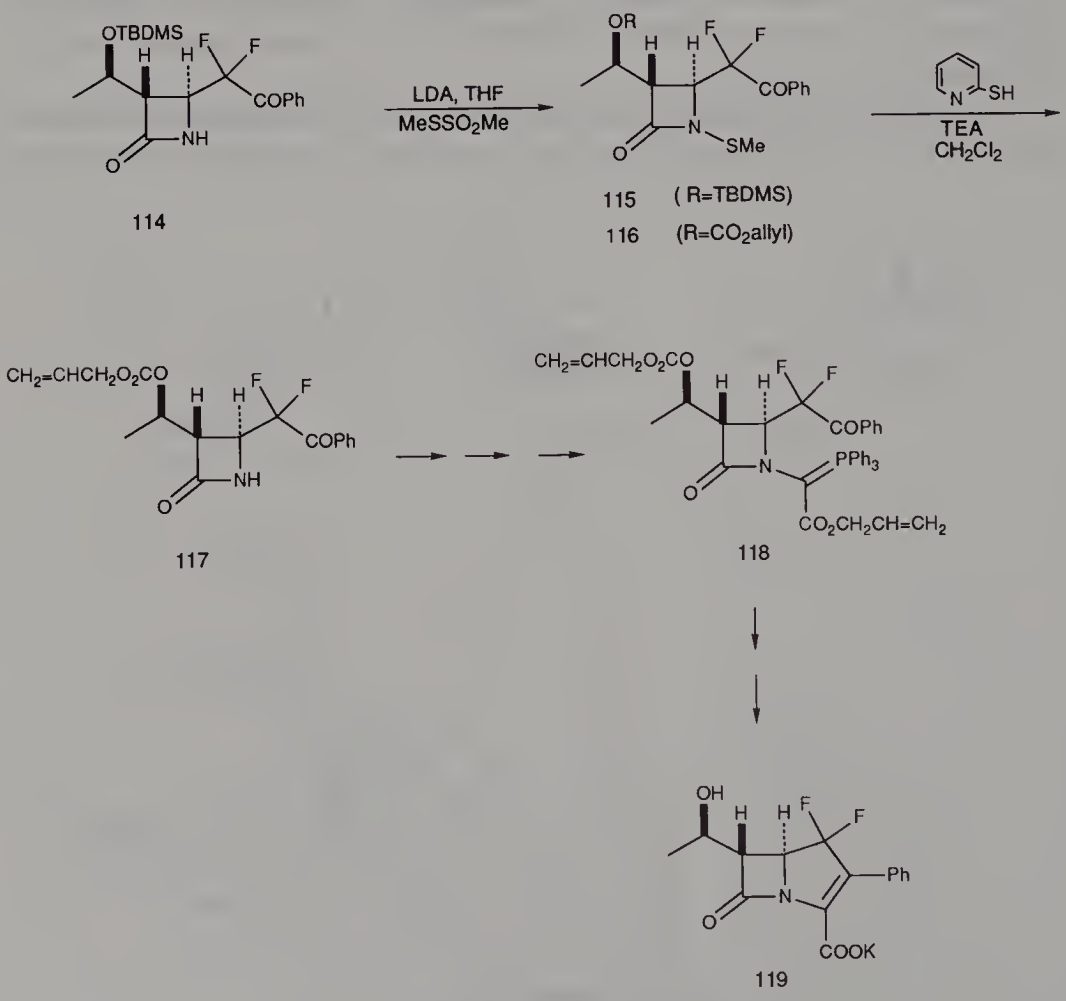
Scheme 3.25

(Reprinted, with permission, from Fetter et al.[30])



Scheme 3.26

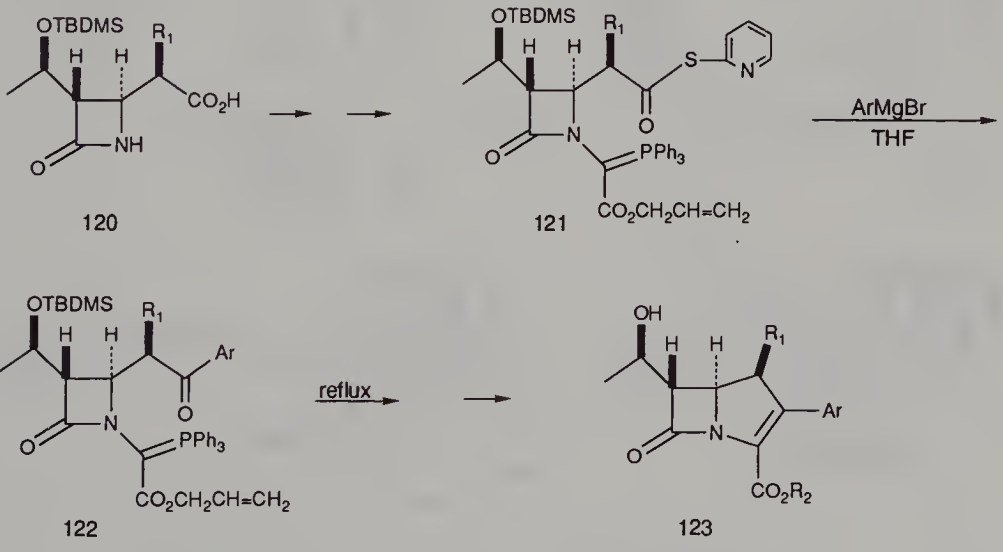
(Reprinted, with permission, from de Vries et al.[31])

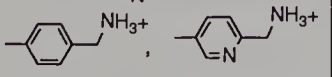


Scheme 3.27

for *N*-1 protection of the azetidinone (Scheme 3.27).[33] Difluoroazetidinone **114** was converted in 68% yield to the *N*-methylsulfenamide **115** on reaction with methyl methanethiolsulfonate ($MeSSO_2Me$) under anionic conditions. Exchange of the TBDMS protecting group in favor of the allyl carbonate gave **116,** which was reduced to azetidinone **117** in 97% yield on reaction with 2-mercaptopyridine and TEA in CH_2Cl_2. Functionalization to in situ generated phosphorane **118,** intramolecular Wittig cyclization in THF, and Pd(0) catalyzed[21] deprotection in the presence of potassium ethylhexanoate (KEH) gave the chemically unstable carbapenem **119.** Because of its instability, an accurate in vitro activity determination was not possible; however, the infrared absorption of 1795 cm^{-1} for the bisallyl protected **119** resulting from Wittig closure of **118** indicated a very reactive β-lactam.

Merck researchers[34] reported the syntheses and antibacterial activities of a number of C-2 aryl-substituted carbapenems (Scheme 3.28). Multistep transformations of azetidinones **120** gave 2-pyridylthioesters **121.** Further reactions with the appropriate aryl Grignard reagents produced **122.** Intramolecular Wittig condensations proceeded in 58 to 90% yields in refluxing toluene or xylenes. Removal of the protecting groups afforded carbapenems **123.** The 1β-methylcarbapenems **123** in this series (R_1 = Me) exhibited

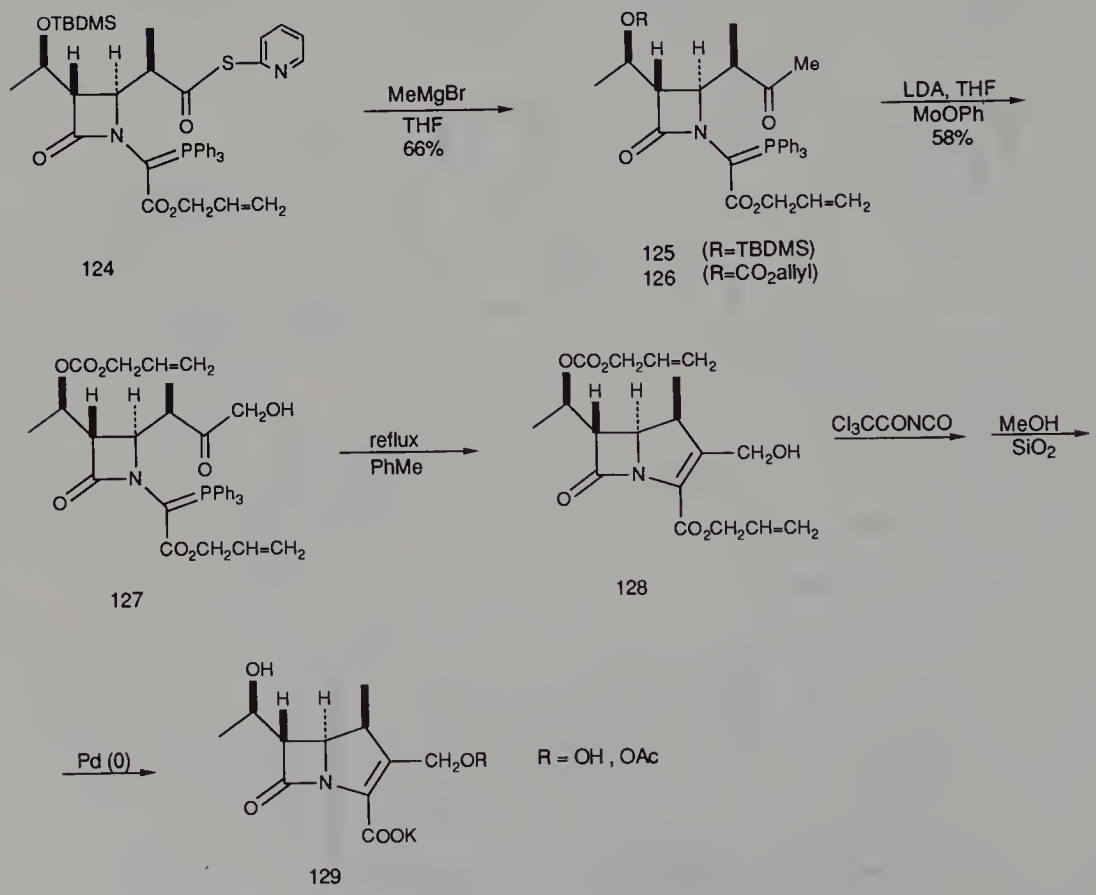


R_1	R_2	Ar
H, Me	K	Ph, 
H, Me	-	

Scheme 3.28

poorer dehydropeptidase I (DHP-I) stabilities and antibacterial activities than their carbapenem counterparts (R_1 = H).

A similar approach to 1β-methyl-C-2-CH_2OR carbapenems, shown in Scheme 3.29, was published by another group of Merck scientists.[35] Treatment of the 2-thiopyridyl ester **124** with methylmagnesium bromide (MeMgBr) in THF at −78°C gave the methyl ketone **125** in 66% yield. As removal of the TBDMS group later in the synthesis by flouride ion caused Δ^2-carbapenem to 2-alkylidenecarbapenam isomerization, a protecting group exchange sequence of **125** to **126** was performed. Oxidation of the lithium enolate at −78°C with molybdenum peroxide reagent MoO_5·pyridine·HMPA (MoOPh) gave the α-hydroxy ketone **127** in 58% yield. Intramolecular Wittig cyclization in refluxing toluene afforded intermediate **128** (76%). Acylation with trichloroacetyl isocyanate, methanolysis of the resulting imide, and Pd(0) catalyzed[21] removal of the allyl ester in the presence of potassium ethylhexanoate gave the 1β-methylcarbapenem **129**, the most active 2-CH_2OR compound in the series prepared (R = OH, OAc, **129**, OCONHMe, OCONHPh, $OCON(Me)_2$, $OCONH(CH_2)_2$-*N*-pyridyl). Disappointingly, **129** showed only 40% of the antipseudomonal activity of thienamycin.

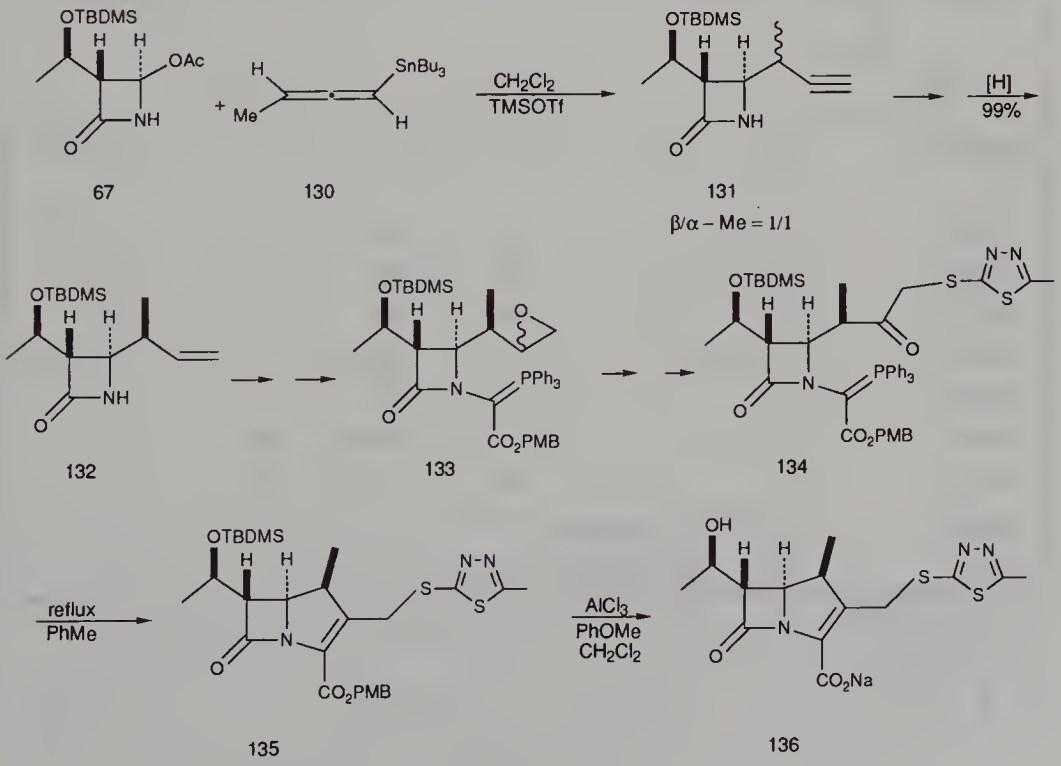


Scheme 3.29

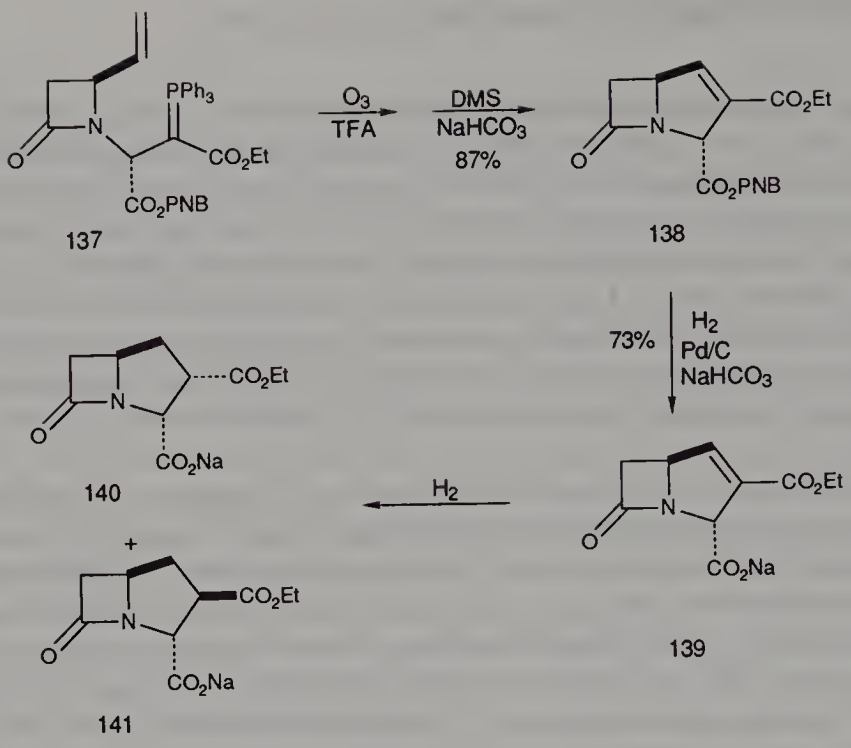
Haruta and co-workers[36] described the synthesis of the 1β-methylcarbapenem **136.** Lewis acid mediated propargylation of **67** by allenylstannane **130** gave azetidinone **131** in 98% yield as a 1/1 mixture of β-/α-Me diastereomers (Scheme 3.30). After a high yielding four step chemical resolution, reduction of the β-methyl diastereomer **131** in methanol afforded **132** (99%). Olefin oxidation and *N*-1 functionalization yielded phosphorane **133.** Reaction with the appropriate thiolate anion and Swern oxidation gave **134,** which underwent Wittig condensation in refluxing toluene to **135** in good yield. Deprotection with $AlCl_3$ and anisole in CH_2Cl_2 followed by basification gave **136.**

British chemists[37] synthesized C-2 carboxyethylpenem **139** and penams **140** and **141** via an intramolecular Wittig annulation strategy (Scheme 3.31). Oxidation of **137** with ozone and TFA followed by dimethyl sulfide reduction and phosphorane regeneration with aqueous $NaHCO_3$ gave the Δ^1-carbapenem **138** in 87% yield. Hydrogenolysis of the PNB ester (EtOAc, EtOH, aqueous $NaHCO_3$, 10% Pd/C) gave **139,** which was void of antibacterial activity. Extended hydrogenation of **138** afforded **140** (46%) and **141** (22%), which also lacked antibacterial activity.

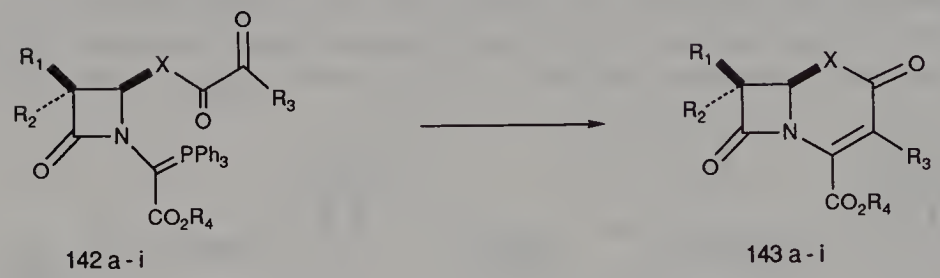
Numerous research groups published syntheses of highly reactive 2-oxo-β-lactams in which bicyclic ring construction was accomplished via intramolecular Wittig reactions.[38–41] The azetidinones **142a–i,** prepared in situ either by low temperature ozonolysis of an alkene precursor[38,40,41] or by



Scheme 3.30

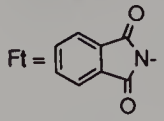


Scheme 3.31



compound	R_1	R_2	R_3	R_4	X	reference
143 a	V	H	H	Bu^t	S	38
143 b	V	H	Me	Bu^t	S	38
143 c	Ft	H	Me	Bu^t	S	38
143 d	V	H	H	Bn	O	39
143 e	H	H	H	Bu^t	O	40
143 f	H	H	H	CH_2Ac	O	40
143 g	H	H	Me	Bu^t	O	40
143 h	H	(R)-CH(OH)Me	H	Bn	O	41
143 i	H	(R)-CH(OH)Me	Me	Bn	O	41

V = $PhOCH_2CONH$

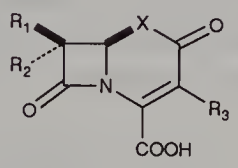
Ft = 

Scheme 3.32

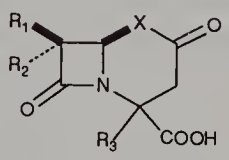
Swern oxidation of a primary alcohol,[39] were short-lived and spontaneously cyclized to the cephems **143a–i** (Scheme 3.32).

Acidic hydrolysis of **143a–c**,[38] exchange of C-7 amide functionality followed by hydrogenolysis of **143d**,[39] or direct hydrogenolysis of **143h** and **i**[41] afforded β-lactam carboxylic acids **144a–f** and **145a** and **b** (Scheme 3.33). None of the 2-oxocephems **143e–g, 144a–f** or others (prepared by non Wittig routes)[42,43] or 2-oxocephams **145a,b** showed measurable and/or significant antibacterial[38–41] or β-lactamase inhibitory[40] activities. As listed in Scheme 3.33, these compounds possessed very reactive β-lactam carbonyl groups, as reflected in their infrared stretching frequencies. It was proposed that the poor antibacterial activities of the cephems were a result of their hydrolytic lability in the media used for activity determinations.[38–43]

Two industrial firms recently reported syntheses of 1-oxacephems bearing α-face *(R)*-CH(OH)Me substitution at C-7.[41,44] Fujisawa scientists[44] elabo-



144a - f

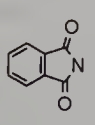


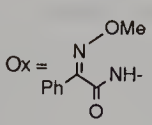
145 a , b

Compound	R_1	R_2	R_3	X	β-lactam, cm^{-1}	reference
144a	V	H	H	S	1805 [a]	38
144b	V	H	Me	S	1799 [a]	38
144c	Ft	H	Me	S	1805 [b]	38
144d	Ox	H	H	O	1815 [c]	39
144e	H	(R) - CH(OH)Me	H	O	1800 [d]	41
144f	H	(R) - CH(OH)Me	Me	O	1792 [d]	41
145a	Ox	H	α - H	O	1800 [c]	39
145b	Ox	H	β - H	O	1790 [c]	39

a. in 9% EtOH / CH_2Cl_2
b. in CH_2Cl_2
c. Nujol
d. KBr

V = $PhOCH_2CONH$

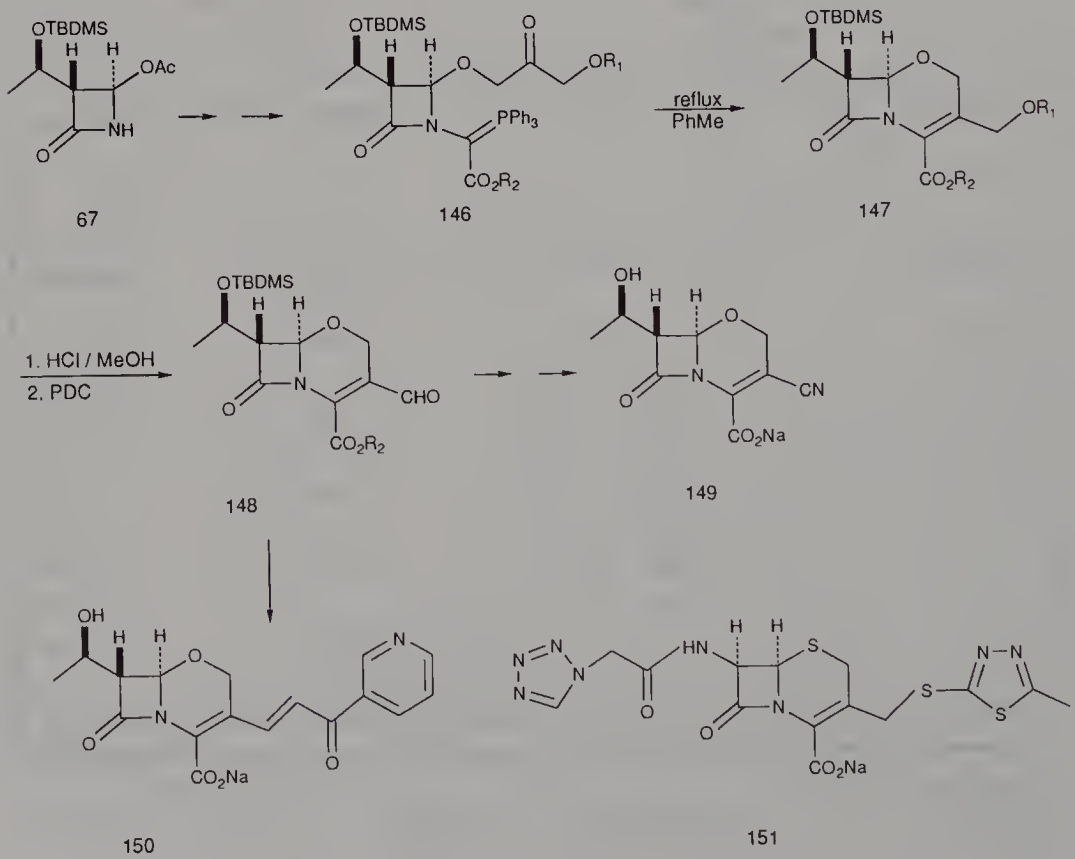
Ft = 

Ox = 

Scheme 3.33

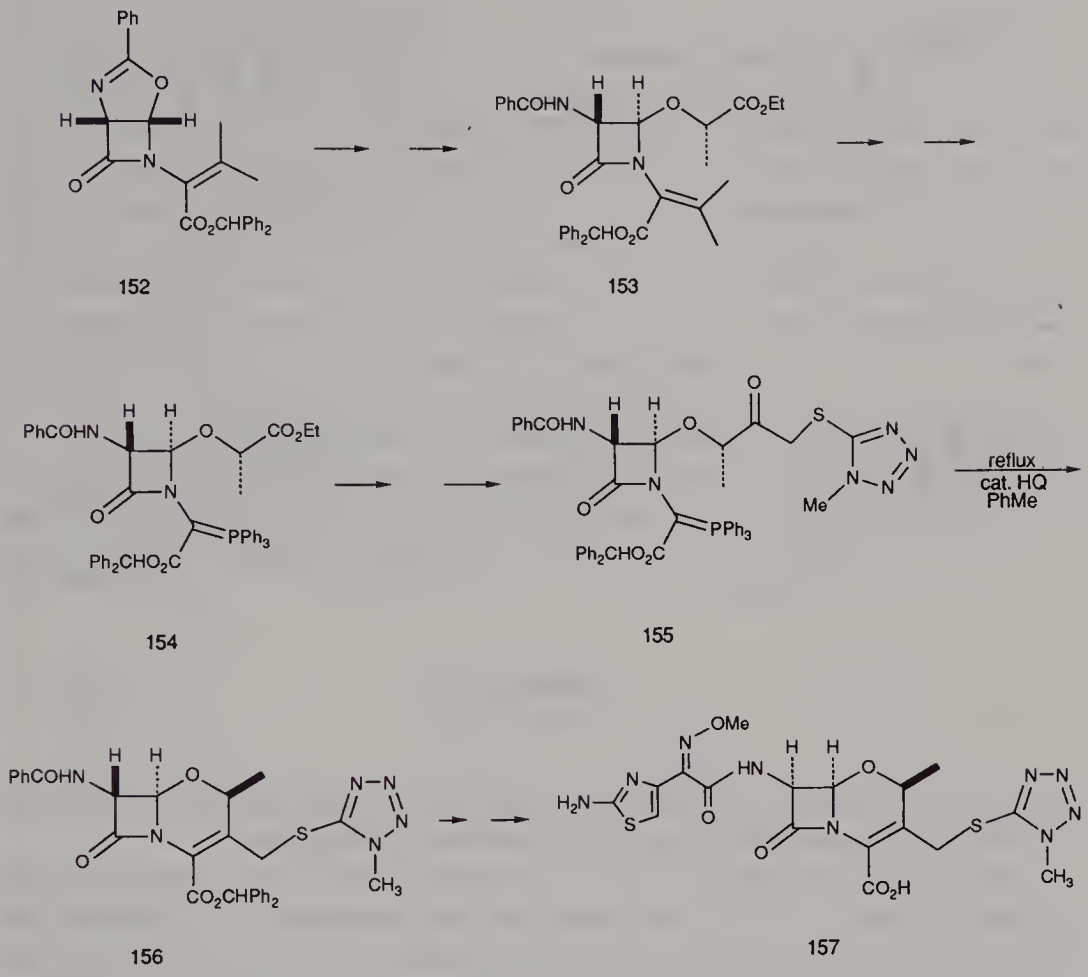
rated **67** to phosphorane **146** (R_1 = TBDMS, R_2 = allyl) which produced 1-oxacephem **147** (62%) on refluxing in toluene with catalytic hydroquinone (HQ) (Scheme 3.34). Selective hydrolysis to the primary hydroxyl group with HCl in MeOH/THF followed by pyridinium dichromate (PDC) oxidation gave aldehyde **148** (R_2 = allyl). Conversion to the C-3 nitrile via a hydroxyimino intermediate and protecting group removal afforded **149.** Nagata and co-workers[41] followed a similar path to **149** by way of phosphorane **146** (R_1 = H, R_2 = benzyl), 1-oxacephem **147** (87%), and aldehyde **148** (R_2 = benzyl). The 1-oxacephem **149** and the more antibacterially potent **150** (derived from **148** by Wittig reaction with 3-(1-triphenylphosphoranylideneacetyl)pyridine and protecting group removal)[44] were found to be inferior to cefazolin **151** in both antibacterial and β-lactamase inhibitory activities.

A new 2β-methyl-1-oxacephem **157** showing a good antibacterial activity spectrum was recently described[45] using an intramolecular Wittig condensation for ring annulation (Scheme 3.35). Ring opening of oxazoline **152** in ethyl *(S)*-lactate containing triflic acid gave **153** (53%). Ozonolysis in CH_2Cl_2 followed by reduction with zinc in acetic acid gave the carbinol, which was then transformed into the phosphorane **154** in the usual way.[13,32] Further modification of the C-4 functionality (alkaline hydrolysis, α-diazo ketone



Scheme 3.34

(Reprinted, with permission, from Murakami et al.[41] and Nishimura et al.[44])

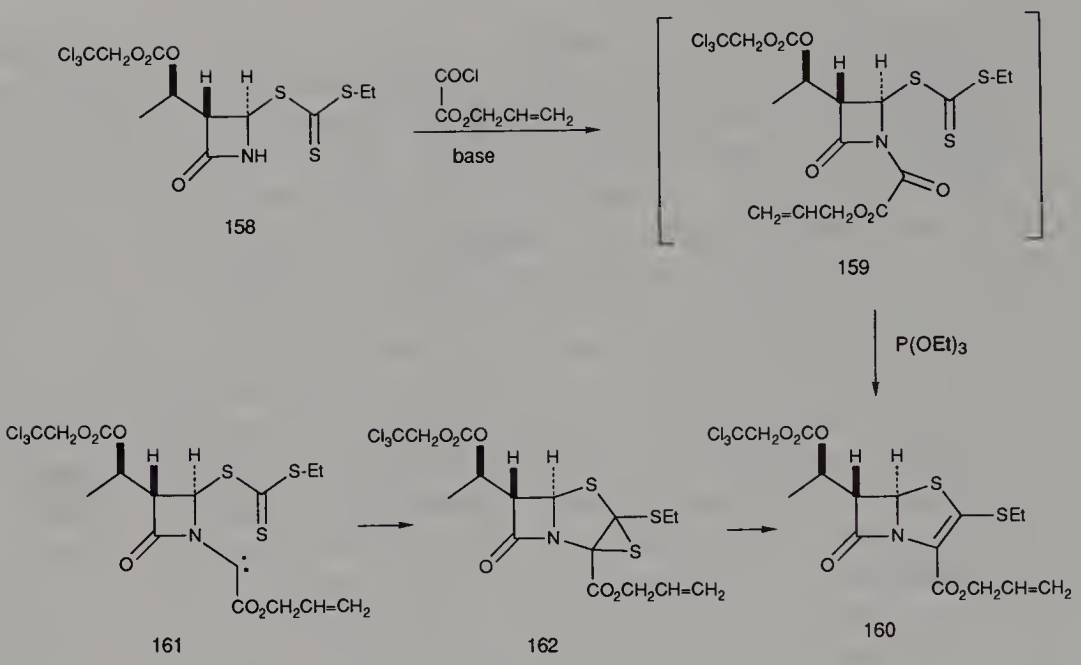


Scheme 3.35

preparation, $Rh_2(OAc)_4$ catalyzed carbene formation in refluxing benzene in the presence of 1-methyl-5-mercaptotetrazole) gave **155.** Intramolecular Wittig condensation in refluxing toluene with catalytic HQ gave an 81% yield of **156,** isolated as its DMF solvate. Epimerization to the C-7 β-amino group, acylation, and removal of protecting groups afforded **157** as its TFA salt.

3.5.2 Phosphite Mediated Reductive Cyclizations

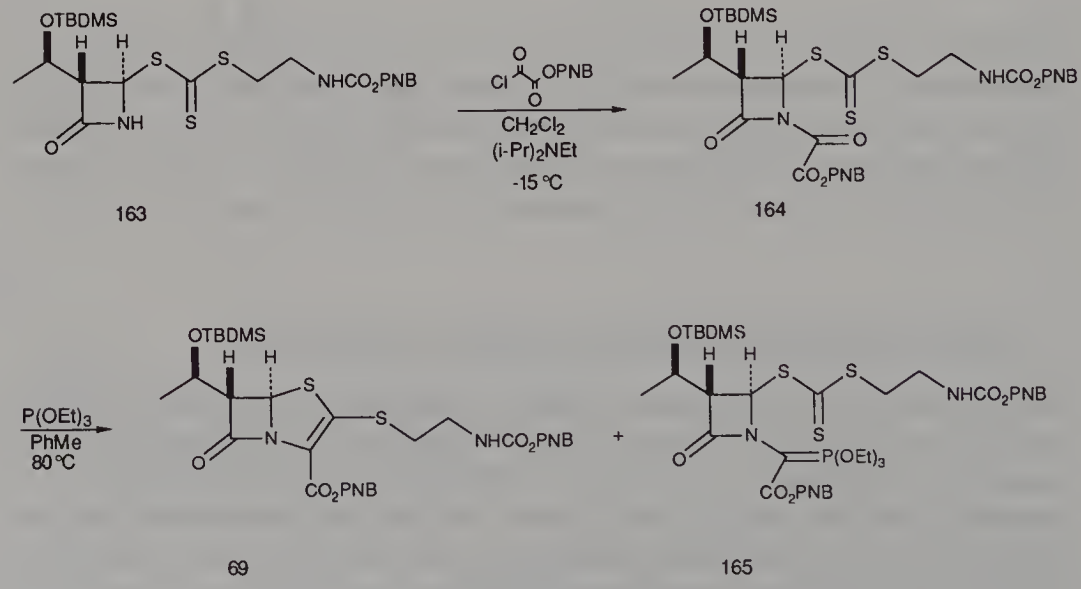
Schering scientists[46] developed a high yielding one step penem cyclization reaction starting from an azetidinone trithiocarbonate (Scheme 3.36). The chemistry relied on the reaction of oxalimides with triethylphosphite and complemented Woodward's Wittig approach. The key intermediate **159,** prepared from **158** and allyloxalyl chloride, on treatment with triethylphosphite ($P(OEt)_3$) under dilute conditions afforded the cyclized penem **160** in 50% yield. It was proposed that the reaction proceeded through a carbene inter-



Scheme 3.36

mediate **161**, which added intramolecularly to the trithiocarbonate C-4 tether to give an episulfide **162**; desulfurization then afforded **160.**

Yoshida and co-workers[47] reported a second preparation of **69**, a material previously converted to 1-thiathienamycin **70.**[17] Acylation of azetidinone **163** with 2 equivalents each of *p*-nitrobenzyloxalyl chloride and $(i\text{-Pr})_2NEt$ in CH_2Cl_2 at $-15°C$ gave **164** in 77% yield (Scheme 3.37). Reductive cyclization

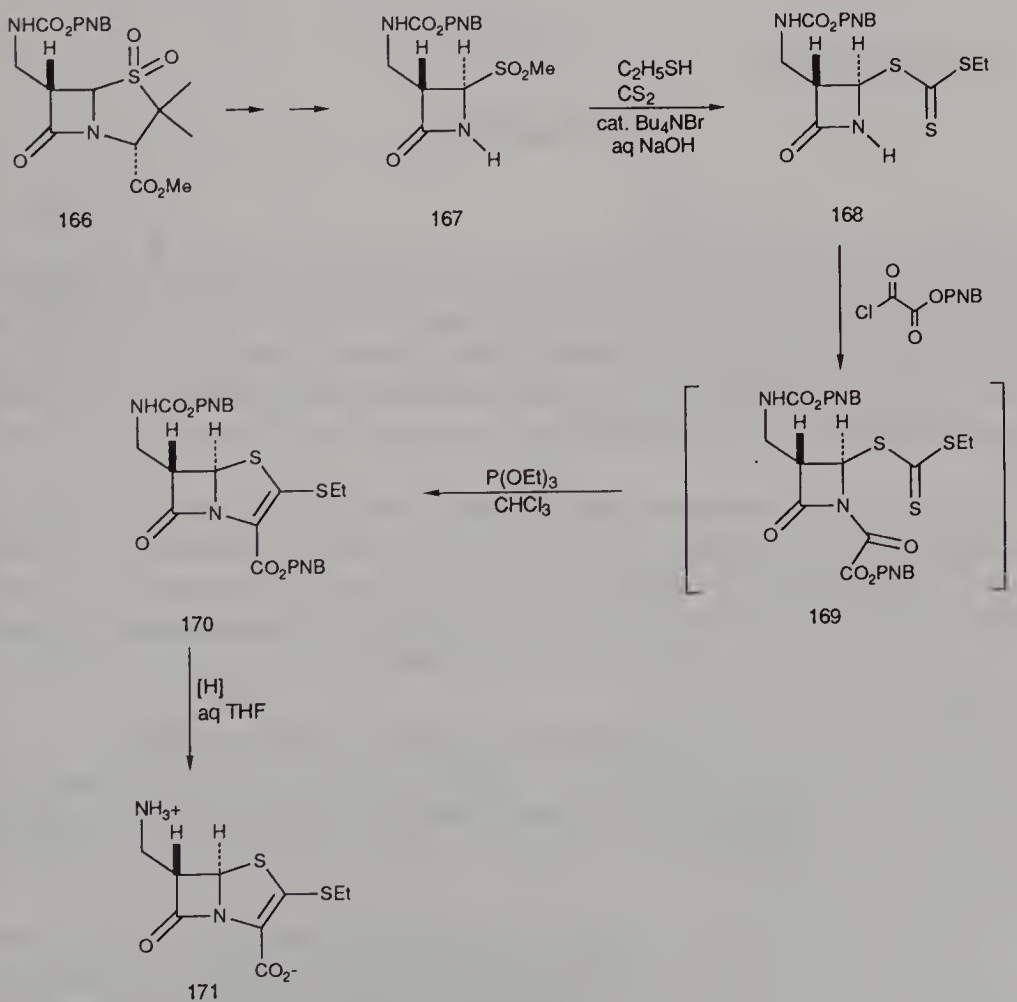


Scheme 3.37

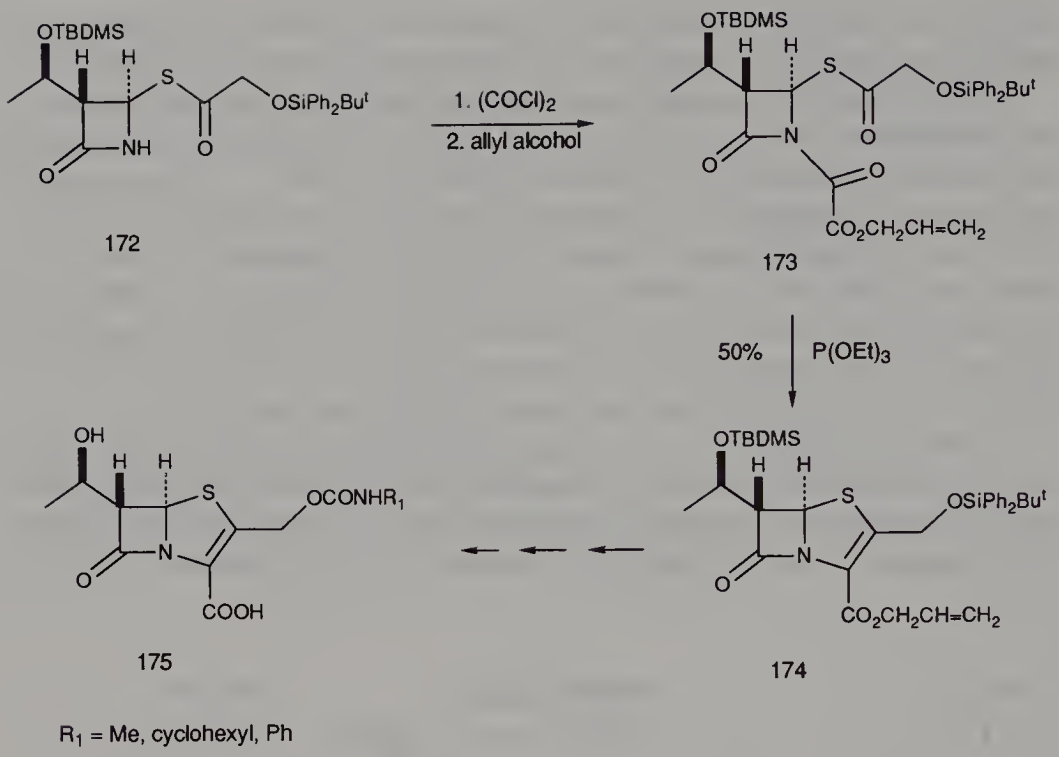
in toluene at 80°C for 1 hour with 5 equivalents of $P(OEt)_3$ afforded penem **69** (29%) and phosphorane **165** (43%) after chromatographic separation.

Application of this annulation strategy to the C-6 aminomethylpenem **171** was described by Welch and Guarino.[48] Multistep conversions of sulfone **166** yielded **167** (Scheme 3.38). Exchange of the C-4 tether in preparation for cyclization was performed on reaction of **167** with ethanethiol, CS_2, and catalytic tetrabutylammonium bromide (Bu_4NBr) in aqueous NaOH (31%). Acylation of **168** with *p*-nitrobenzyloxalyl chloride in $CHCl_3$ gave **169**, which was directly converted in situ to penem **170** (23%) using 3 equivalents of $P(OEt)_3$. Hydrogenolysis of the protecting groups in aqueous THF gave zwitterion **171**, which showed weak gram positive activity in vitro.

A similar type of reductive cyclization involving dicarbonyl precursors instead of Schering's carbonyl/thiocarbonyl system was reported by Battistini and co-workers[49] in preparing alkylcarbamate derivatives of **75** (Scheme 3.39). Reaction of azetidinone **172** with oxalyl chloride followed by allyl al-



Scheme 3.38



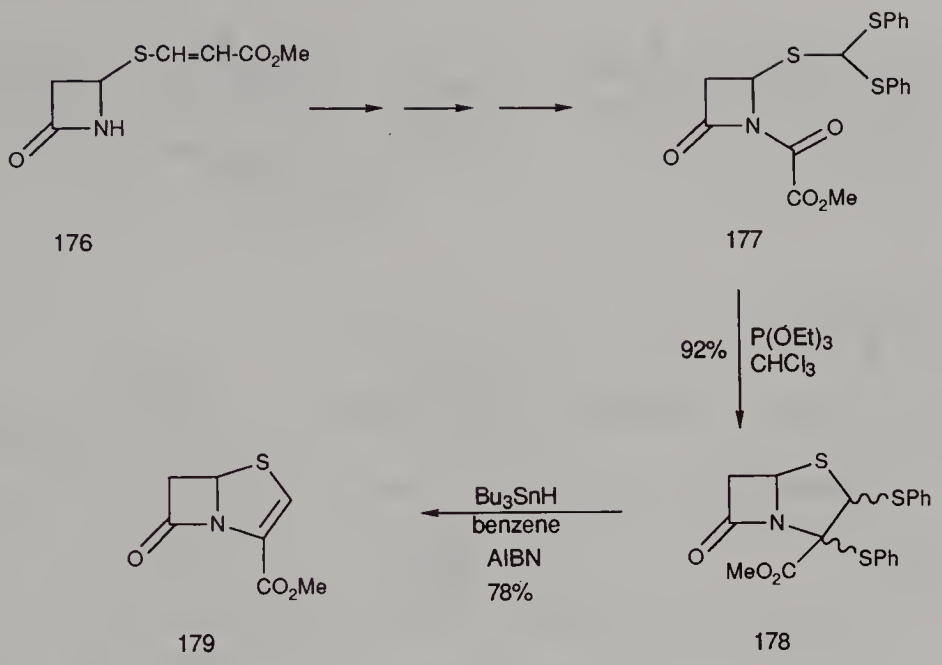
Scheme 3.39

cohol gave **173,** which produced **174** in 50% yield on heating with $P(OEt)_3$. Selective cleavage of the *tert*-butyldiphenylsilyl (TBDPS) ether, acylation with R_1NCO and 4-dimethylaminopyridine (DMAP), and TBAF cleavage of the TBDMS ether followed by Pd(0) catalyzed deprotection[21] of the allyl ester in the presence of SEH afforded penems **175** (R_1 = Me, cyclohexyl, Ph).

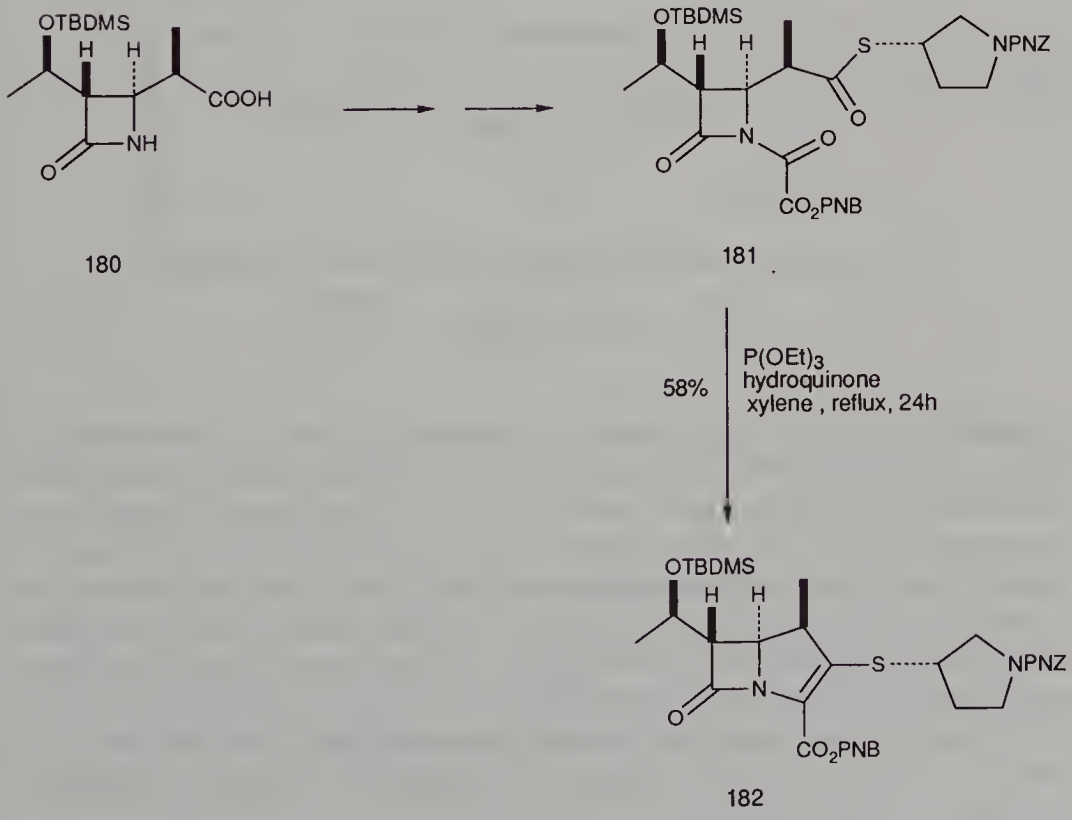
Kametani and co-workers[50] demonstrated further utility of the oxalimide cyclization reaction in the synthesis of penem ring systems also. The azetidinone **176** provided the oxalimide **177** which smoothly cyclized in 92% yield to the penam **178,** obtained as a 1:2:2:4 mixture of diastereomers (Scheme 3.40). Further treatment of **178** with tributyltin hydride (Bu_3SnH) afforded the penem **179** in 78% yield.

Shibata and Sugimura[51] applied the oxalimide cyclization chemistry to the synthesis of 1β-methylcarbapenem antibiotics. The bicyclic β-lactam precursor **181** was prepared in a few steps from carboxylic acid **180.** Cyclization to **182** was accomplished by refluxing in xylene in the presence of $P(OEt)_3$ and HQ (Scheme 3.41).

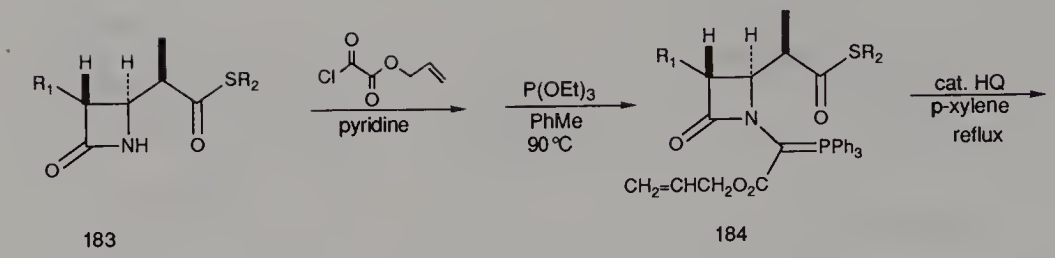
In an effort to prepare C-6 amido-1β-methylcarbapenems with enhanced antibacterial activities and chemical stabilities, Merck researchers[52] reported syntheses of **186** based on a dicarbonyl reductive cyclization approach (Scheme 3.42). For the C-6 α-phthalimido series, **183** were converted by



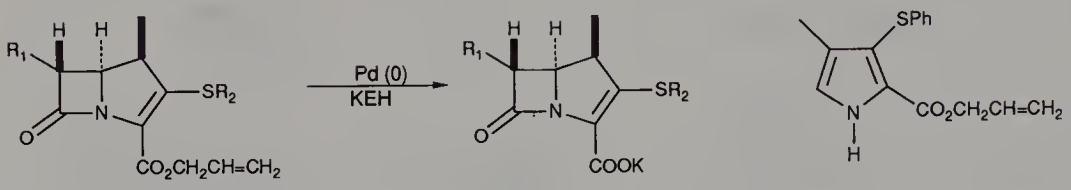
Scheme 3.40



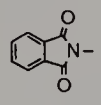
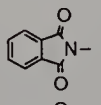
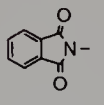
Scheme 3.41



183 184



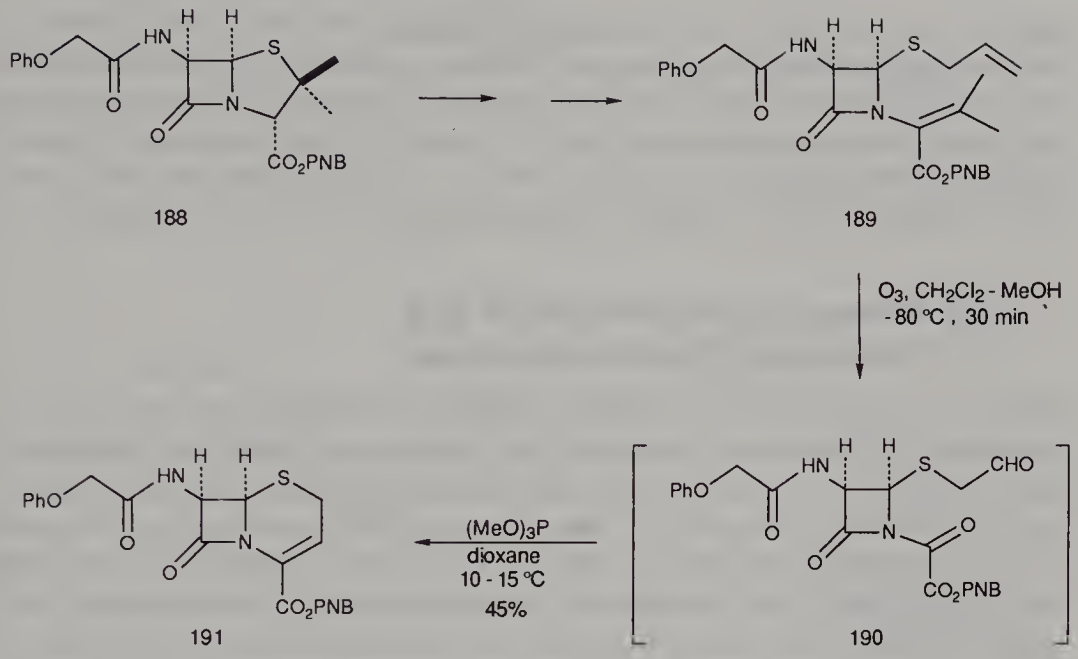
185 186 187

R1	SR2	% yield 185	% yield 186
	SPh	60	50
	SCH_2CH_2CN	60	71
	$SCH_2CH_2NHCO_2PNB$	20	-
PNBOCONH	SPh	18	20

Scheme 3.42

acylation with allyloxalyl chloride in pyridine followed by treatment with $P(OEt)_3$ in toluene at 90°C to phosphoranes **184.** Cyclizations to **185** occurred on refluxing in *p*-xylene with catalytic HQ. Deblocking with Pd(0) in the presence of KEH[21] gave **186** in good yields, with the exception of the C-2-protected (β-aminoethyl)thiocarbapenem **185.** These 1β-methylcarbapenems showed low levels of antibacterial activity. Replacement of the C-6 α-phthalimido group with the more biologically active C-6 α-carbamate side chain was therefore pursued next. In this series, cyclization to **185** (18%) proved more sensitive because of its thermal decomposition to pyrrole **187** (15%) under the reaction conditions. Deprotection afforded 1β-methylcarbapenem **186** (20%).

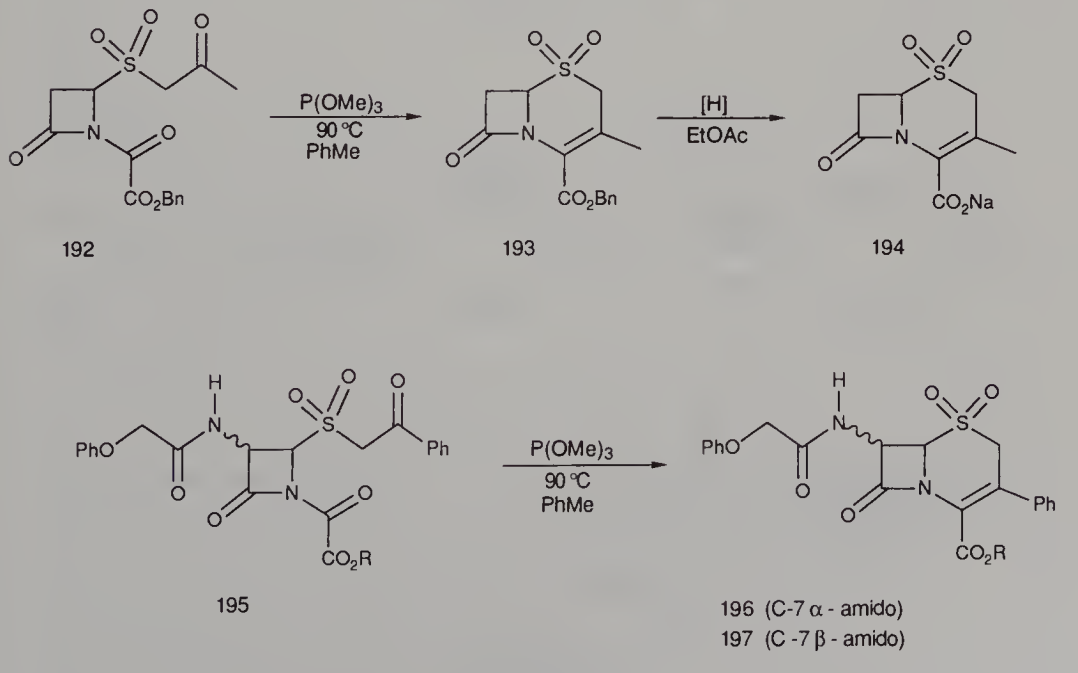
Davis and Wu[53] reported a preparative route to the 3-unsubstituted cephalosporin **191** from penicillin V PNB ester **188** using an oxalimide cyclization



Scheme 3.43

reaction of **190** with trimethylphosphite ($P(OMe)_3$) as the key step for ring closure (Scheme 3.43).

Sriyani Ananda and Stoodley[54] described syntheses of cephem sulfones **194** and **197** as part of a structure activity program (Scheme 3.44). Heating of azetidinone **192** in toluene at 90°C with $P(OMe)_3$ gave **193** (84%). Hydro-

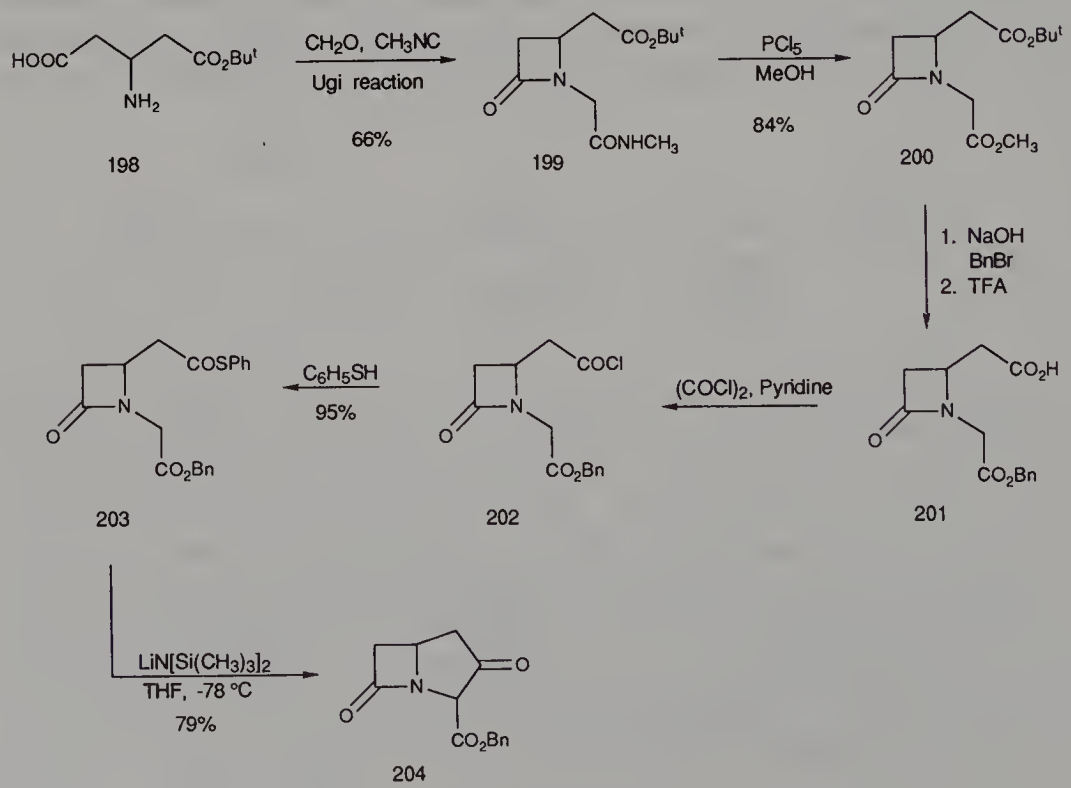


Scheme 3.44

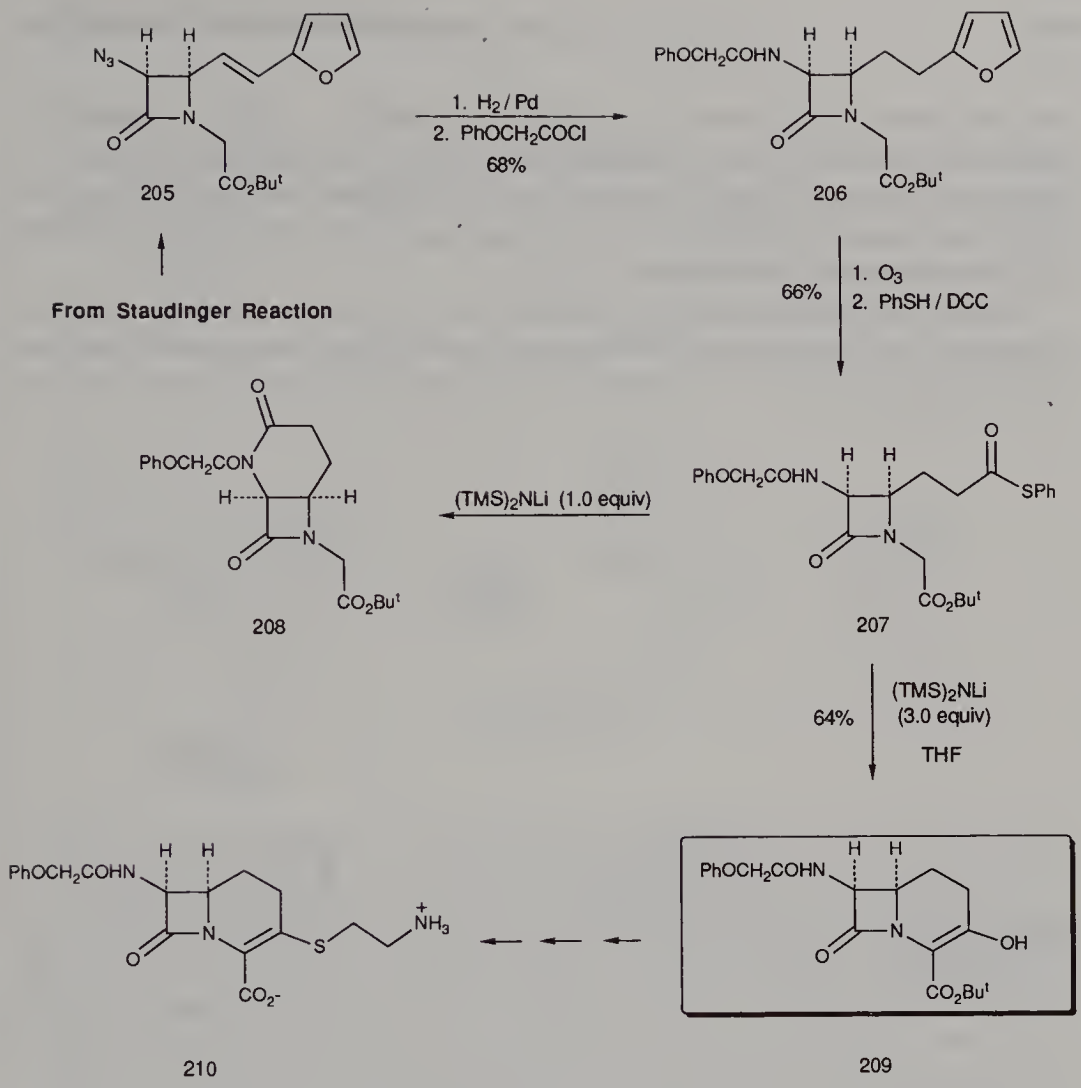
genolysis of the benzyl protecting group afforded **194** (30%), which showed low antibacterial and β-lactamase inhibitory activities. Also investigated were the preparations of C-7 amidocephem sulfones **196** and **197.** Attempted cyclization of *trans*-azetidinone **195** (R = benzyl) yielded only non β-lactam products, whereas the *cis* compound **195** (R = $CHPh_2$) afforded **197** in 30% yield on reaction with $P(OMe)_3$ in toluene at 90°C.

3.5.3 Intramolecular Dieckmann and Wadsworth–Emmons Reactions

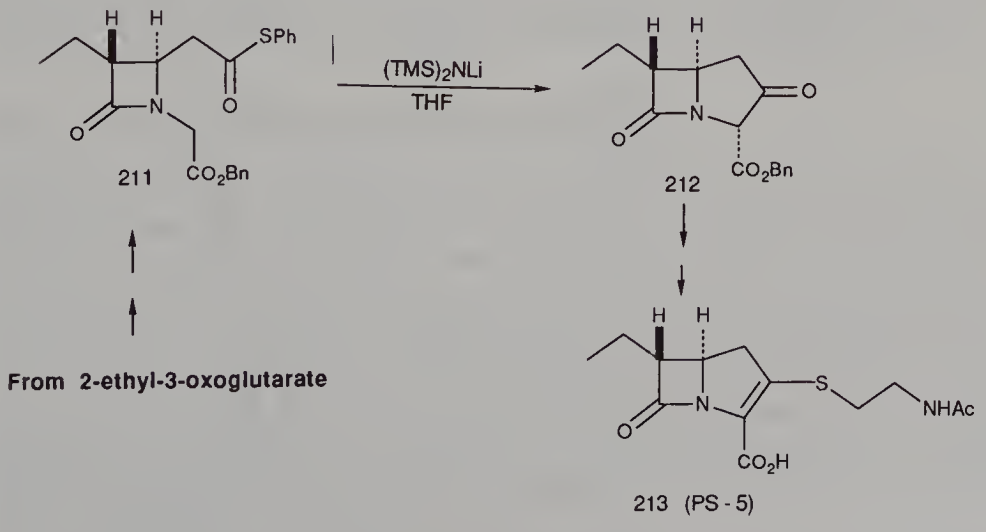
Hatanaka and co-workers[55] introduced another synthesis of carbapenem derivatives that involved an intramolecular Dieckmann type condensation reaction of an *N*-1, C-4-substituted monocyclic β-lactam. The three component condensation reaction of **198,** formaldehyde, and methyl isonitrile readily provided the azetidinone **199** (Scheme 3.45). Conversion to ester **200** was accomplished with phosphorus pentachloride (PCl_5) and methanol. Alkaline hydrolysis, reaction with benzyl bromide (BnBr), and TFA hydrolysis of the *tert*-butyl ester gave **201,** which was next converted to acid chloride **202.** As Dieckmann-type condensation reactions were examined with active esters, **202** was converted to the phenyl thioester **203.** Treatment of the



Scheme 3.45



Scheme 3.46

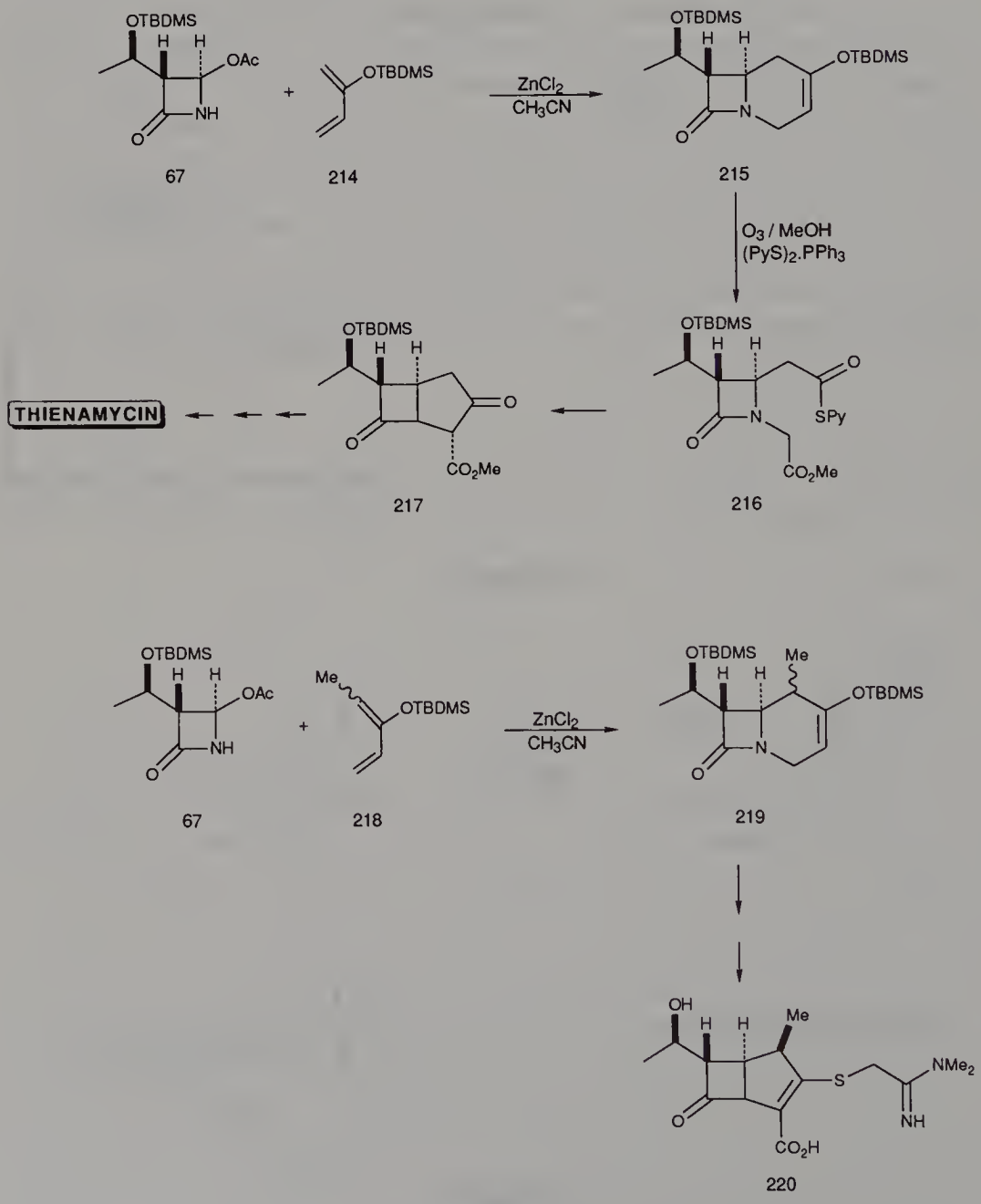


Scheme 3.47

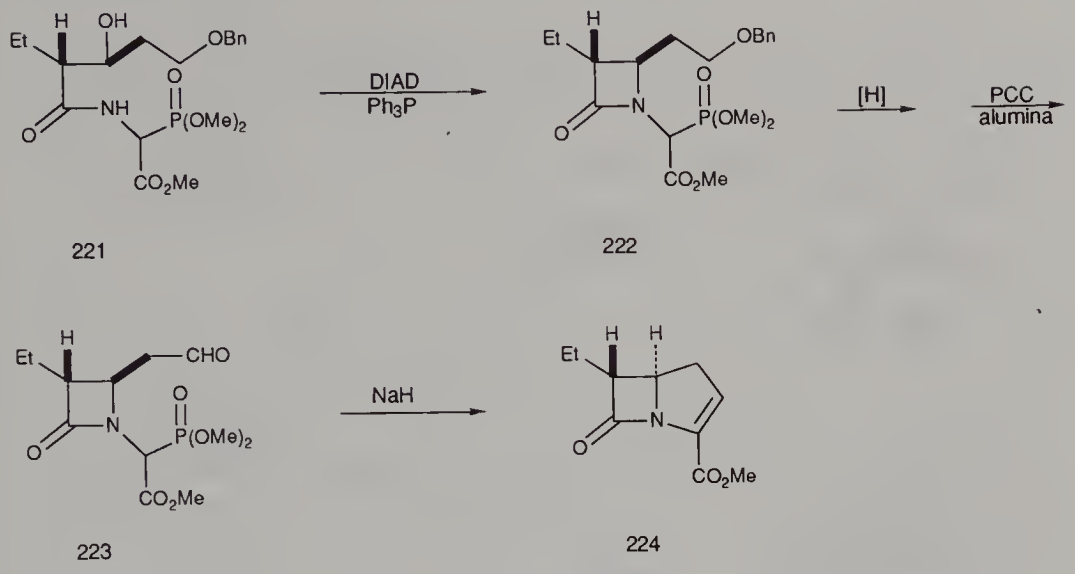
thioester with 3.5 equivalents of LiHMDS in THF at −78°C for 5 minutes afforded the bicyclic β-keto ester **204** in 79% as a single diastereomer.

A similar approach was reported for the synthesis of carbacephem **210** from azetidinone **205** (Scheme 3.46)[56] and the carbapenem antibiotic PS-5 (**213**) from thioester **211** (Scheme 3.47).[57]

Meyers and co-workers used azetidinone **67** in a Lewis acid mediated annulation with siloxydiene **214** as an entry into the carbacephem ring system **215** (Scheme 3.48).[58] Treatment of the crystalline carbacephem **215** with



Scheme 3.48



Scheme 3.49

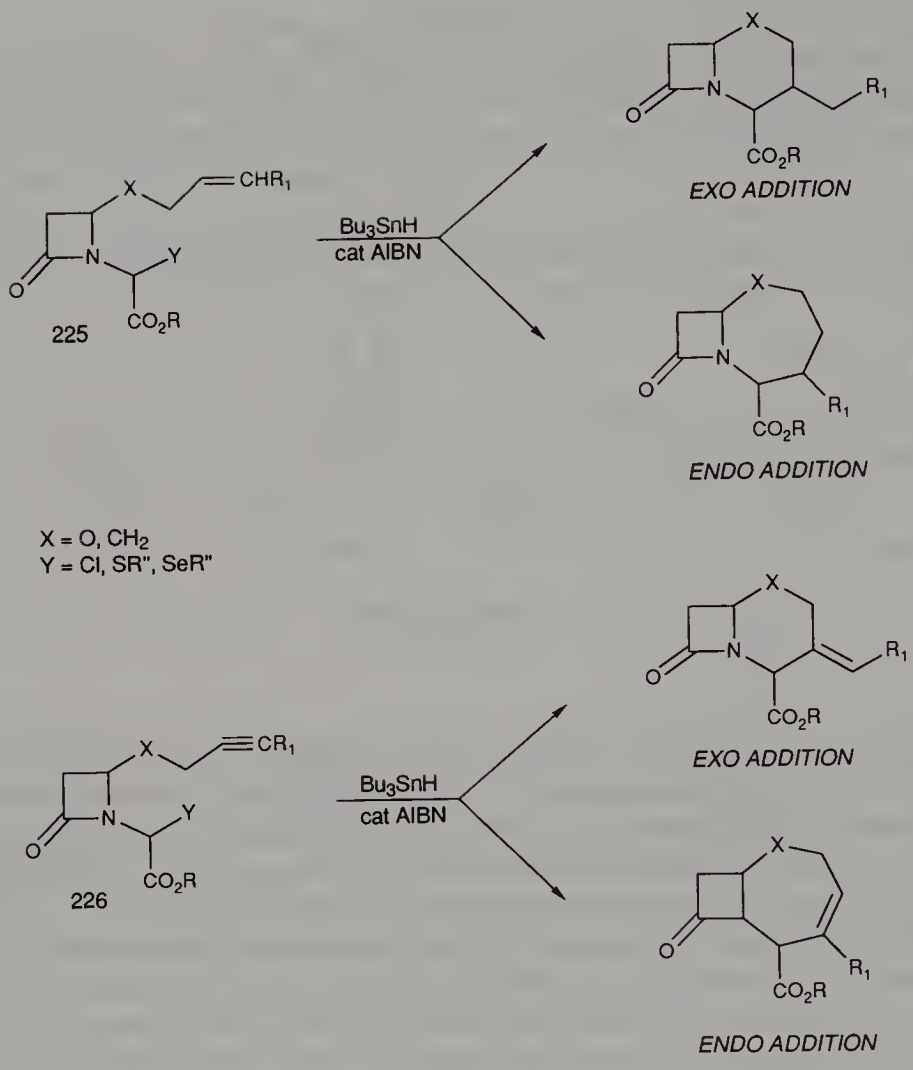
ozone gave the acid ester, which was then converted to the thiopyridyl ester **216.** The Dieckmann cyclization was carried out with 1.1 equivalents of sodium bis(trimethylsilyl)amide in THF at −30°C and afforded carbapenam-2-one **217,** a material previously converted to theniamycin.[58] Substitution of **214** with diene **218** in the aforementioned reaction sequence ultimately afforded the 1β-methylcarbapenem **220** via intermediate **219** (Scheme 3.48).[59]

Miller and co-workers described the synthesis of carbapenem **224** based on an intramolecular Wadsworth–Emmons annulation strategy (Scheme 3.49).[60] Reaction of **221** with DIAD and Ph_3P gave azetidinone **222.** Hydrogenolysis of the benzyl protecting group and pyridinium chlorochromate (PCC)/alumina oxidation furnished aldehyde **223.** A clean cyclization to the unstable carbapenem **224** was observed on reaction with sodium hydride.

3.5.4 Free Radical Cyclization Reactions

Generation of a free radical in the presence of a carbon–carbon double or triple bond leads to cyclic products as a result of an intramolecular annulation. This chemical ring closure concept employing suitably constituted alkenyl radicals and related species was exploited in recent years for the synthesis of bicyclic β-lactams. Bachi and co-workers[61] detailed the use of azetidinone intermediates **225** and **226** bearing appropriate *N*-1 and C-4 tethers for ring closure (Scheme 3.50). The radical intermediates were prepared from the corresponding chloro-, thio-, and seleneno- derivatives by employing Bu_3SnH along with a catalytic amount of 2,2′-azobisisobutyronitrile (AIBN) in toluene or benzene.

The seven membered 1-oxahomocepham **229** and 1-oxahomocephem **232** ring systems were synthesized by regiospecific intramolecular *endo* addi-

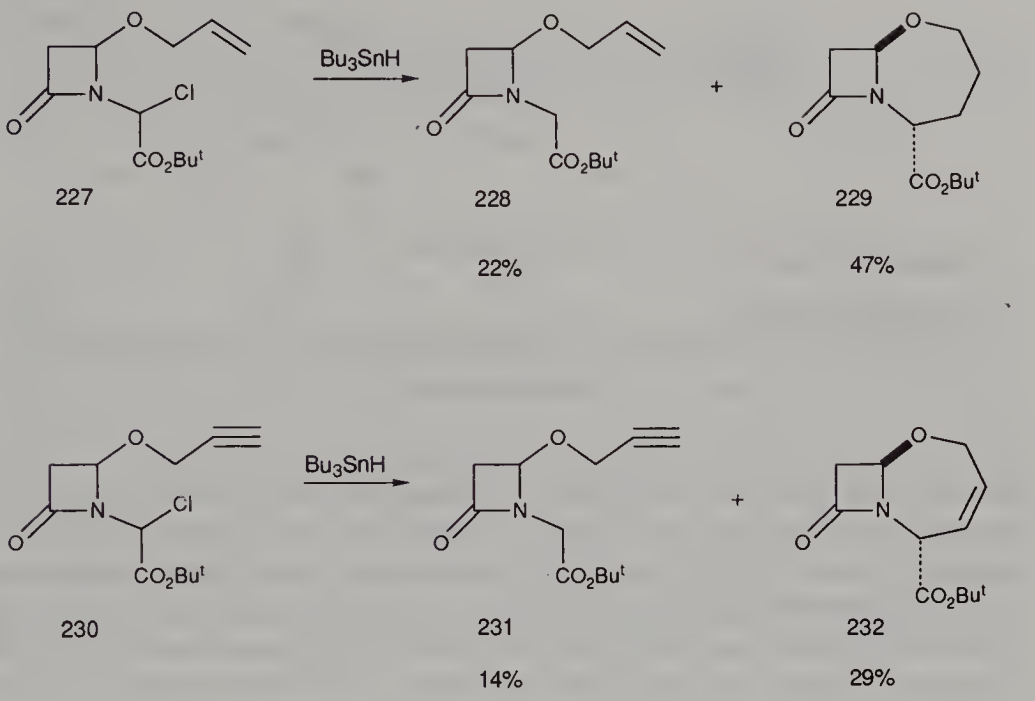


Scheme 3.50

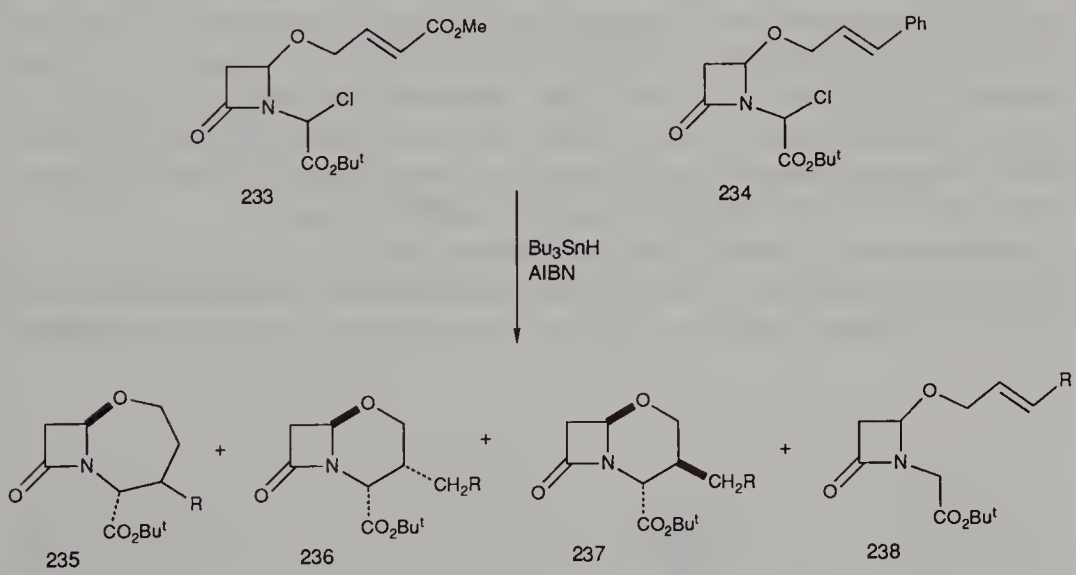
tions of radicals generated from the corresponding chloro-β-lactams **227** and **230,** respectively, to the olefinic residues in their C-4 tethers (Scheme 3.51).[62]

Radicals generated from **233** and **234** bearing terminal phenyl or carbomethoxy substituents on the C-4 oxyallyl chains, however, underwent *exo* additions to provide six membered 1-oxacephams **236** and **237** as the major products (Scheme 3.52).[62] The differences in the modes of cyclization were attributed to a variety of factors such as steric strain, bond polarity, and thermochemical accelerating effects.[62]

Treatment of chloroazetidinone **239** with Bu_3SnH (1.1 equivalent) and AIBN (5 mole%) in refluxing benzene (0.02 *M* solution) afforded three products (Scheme 3.53). The major reduction product **240** (50%) was obtained from a direct hydrogen transfer to the parent free radical, whereas the desired carbacephem **241** accounted for only 20% of the product mixture.[63] The

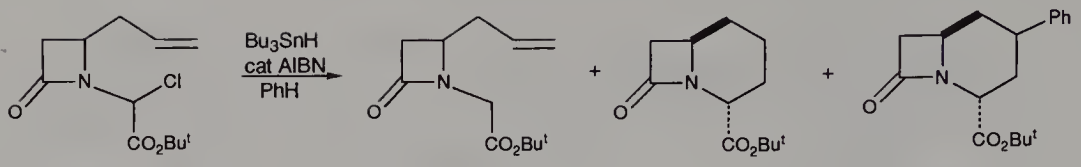


Scheme 3.51



(A)	R=CO_2Me	4%	68% (3.3 : 1)	16%
(B)	R=Ph	--	68% (1:1)	10%

Scheme 3.52



239 240 241 242

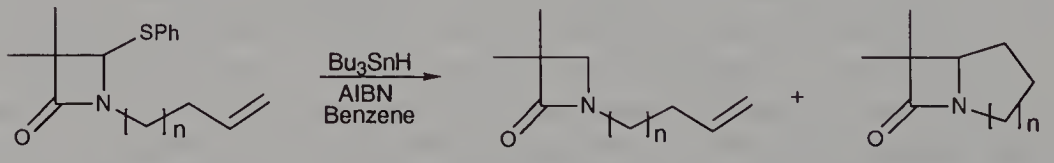
STANDARD COND (0.02 M)	50%	20%	—
HIGH DILUTION COND (0.003 M)	9%	62%	20%

Scheme 3.53

product ratio was reversed when the reaction was performed under high dilution (0.003 *M* solution). Thus, addition of a solution of Bu_3SnH (1.1 equivalent) and AIBN (3 mole%) in benzene over a period of 90 minutes to a refluxing solution of **239** resulted in conversion to a mixture of the carbacephams **241** (62%) and **242** (20%) and only 9% of the reduced product **240.** The phenyl derivative **242** formed as a result of the addition of the C-2 carbacepham radical to benzene.

Preference for *endo* cyclization to form bicyclic β-lactams was also observed by Beckwith and Boate (Scheme 3.54).[64] Treatment of **243a** with Bu_3SnH in the presence of catalytic AIBN in benzene at 80°C gave the reduction product **244a** (48%), carbapenam **245a** (26%), and recovered starting material (22%). The $n = 2$ homolog **243b** behaved similarly; besides recovered starting material (19%), **244b** (25%) and **245b** (55%) were also isolated. The preference for *endo* ring closure was attributed to the strain imposed on the *exo* transition state by the azetidinyl ring.[64]

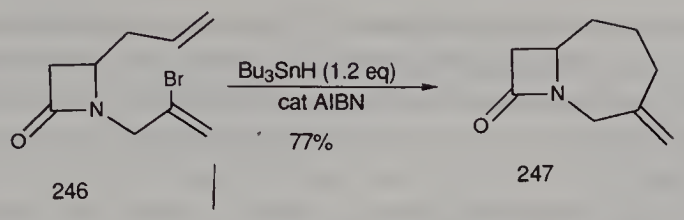
Parsons and co-workers[65] observed formation of the seven membered bicyclic β-lactam **247** in 77% yield from the azetidinone **246** on treatment with Bu_3SnH (1.2 equivalents) and AIBN (8 mole%) in benzene under photolytic



243 244 245

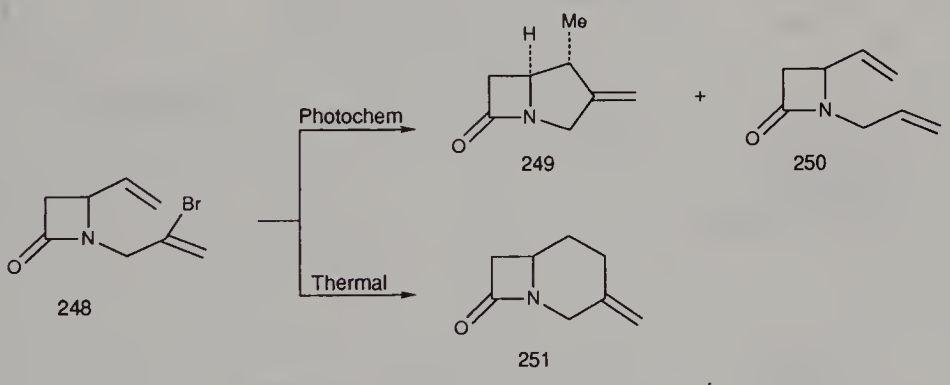
a	n = 1	48%	26%
b	n = 2	25%	55%

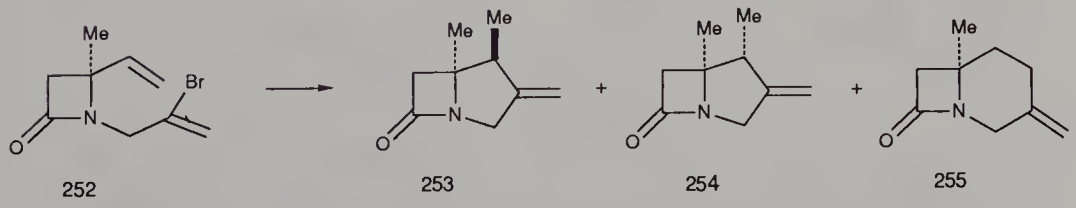
Scheme 3.54



Scheme 3.55

conditions (Scheme 3.55); however, photolysis of vinylazetidinone **248** in the presence of Bu_3SnH and AIBN gave 1α-methylcarbapenam **249** (30%) as a single diastereomer along with 70% of the reduction product **250** (Scheme 3.56).[65,66] Under more dilute conditions, the yield of **249** increased to 50%. Interestingly, when a toluene solution of azetidinone **248** was refluxed for 4 days with Bu_3SnH and AIBN, a 58% yield of carbacepham **251** was isolated. This chemistry therefore presented a synthetic approach to both the carbacepham and the carbapenam ring systems starting from a common intermediate. On the other hand, thermal and photochemical reactions of the



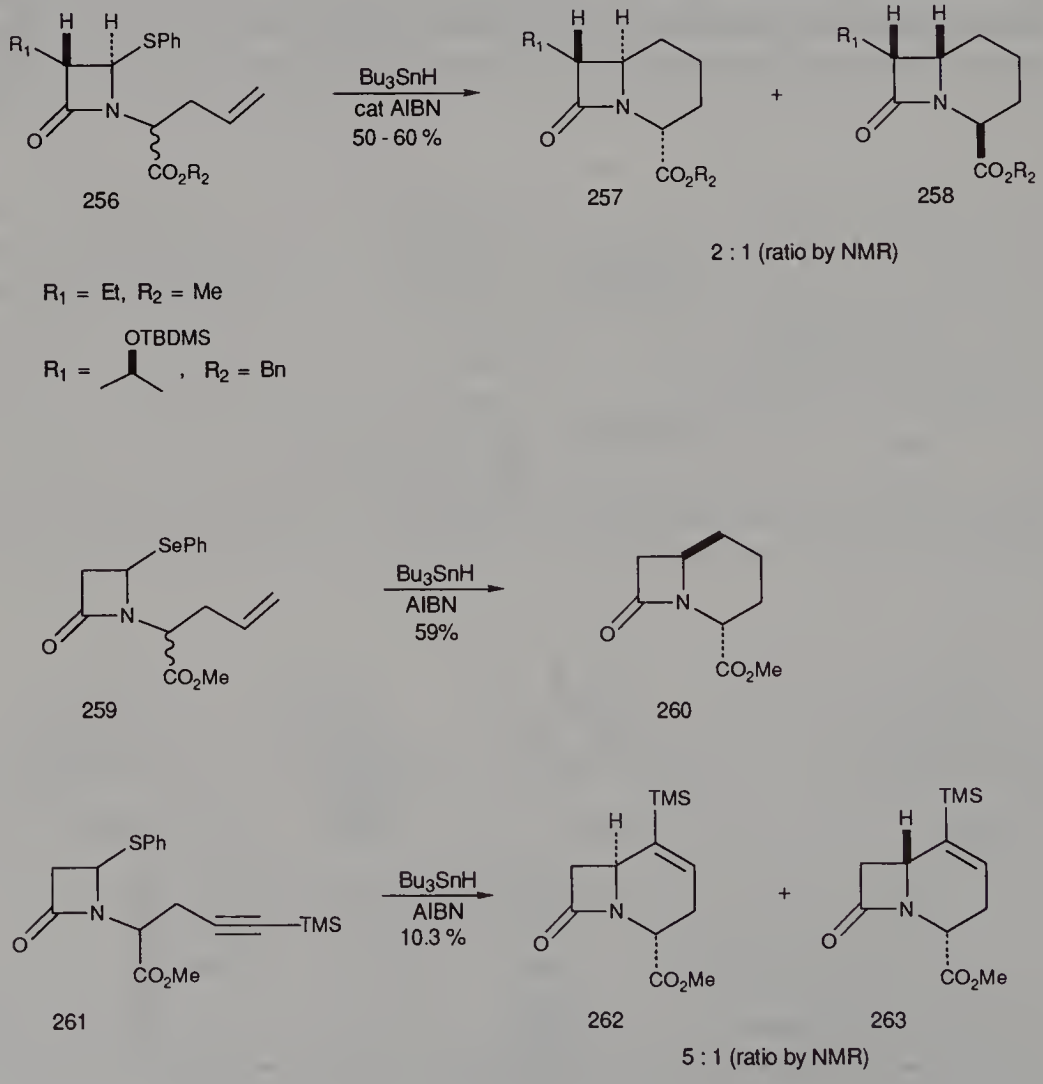


	253	254	255
THERMAL CYCLIZATION	59%	3%	30%
PHOTOCHEMICAL	58%	10%	10%

Scheme 3.56

C-4 α-methyl substituted azetidinone **252** provided carbapenam **253** as the major product. The steric strain imposed by the angular methyl group of **252** on the olefin during the radical closure was speculated to be responsible for the preferential formation of the carbapenam **253** (58%) over the carbacepham **255** (10%).[65,66]

Kametani and co-workers[67] used a radical cyclization strategy to construct C-7-substituted carbacepham and carbacephem ring systems (Scheme 3.57). Treatment of a mixture of azetidinones **256** with Bu_3SnH and catalytic AIBN in refluxing benzene afforded the diastereomeric mixture of carbacephams **257** and **258** in moderate yields. The 4-phenylselenenoazedtidinone **259** was found to be a superior substrate for this radical cyclization chemistry. Treatment with Bu_3SnH in the presence of AIBN in refluxing benzene

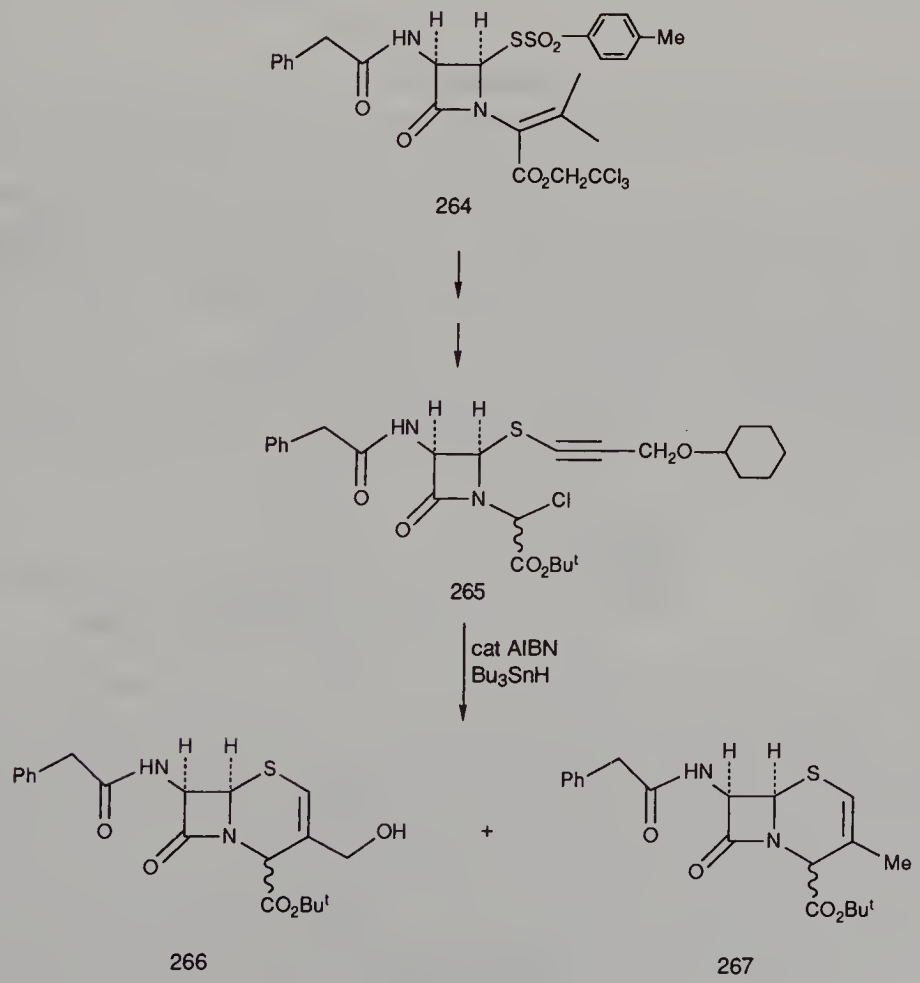


Scheme 3.57

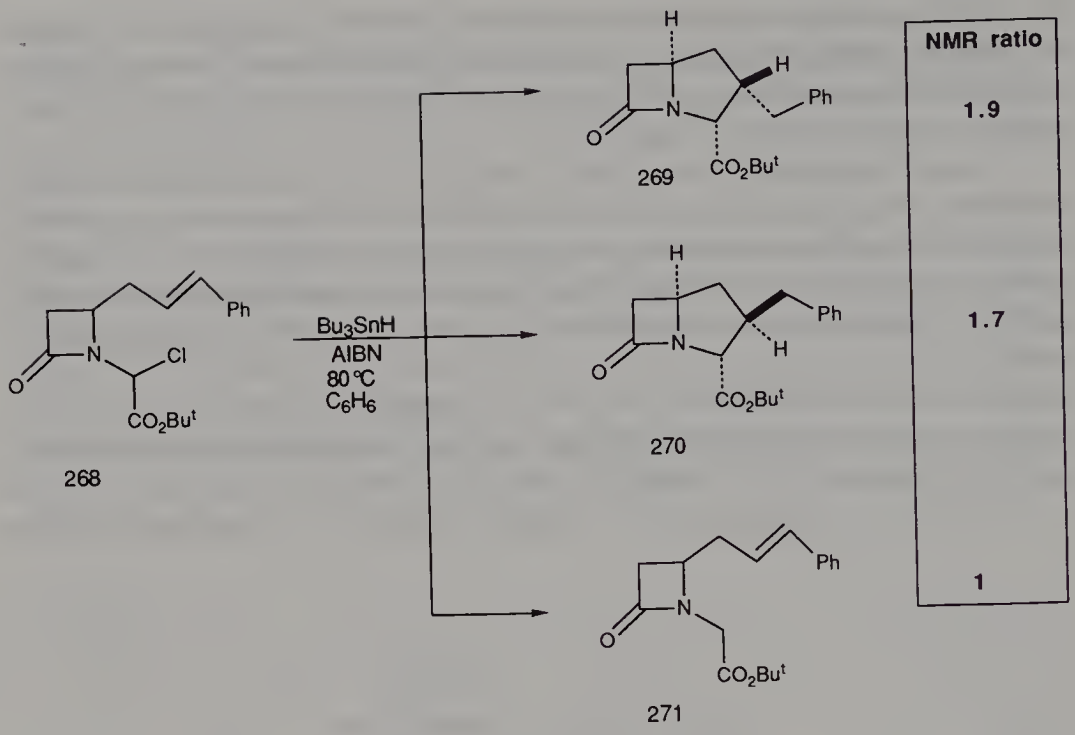
furnished a single diasteromer of carbacepham **260.** An attempt to prepare the Δ^1-carbacephem nucleus via the radical cyclization reaction of azetidinone **261** provided only a 10% yield of the cyclized carbacephems **262** and **263** as a diasteromeric mixture (5:1).

A radical cyclization route for the synthesis of Δ^2-cephalosporins was reported by Schering scientists (Scheme 3.58).[68] The target azetidinone **265,** bearing an acetylenic substituent directly bonded to sulfur, was prepared by synthetic manipulations of the readily available azetidinone **264.** Reaction with Bu_3SnH and catalytic AIBN in dry toluene at 90°C afforded **266** and **267.**

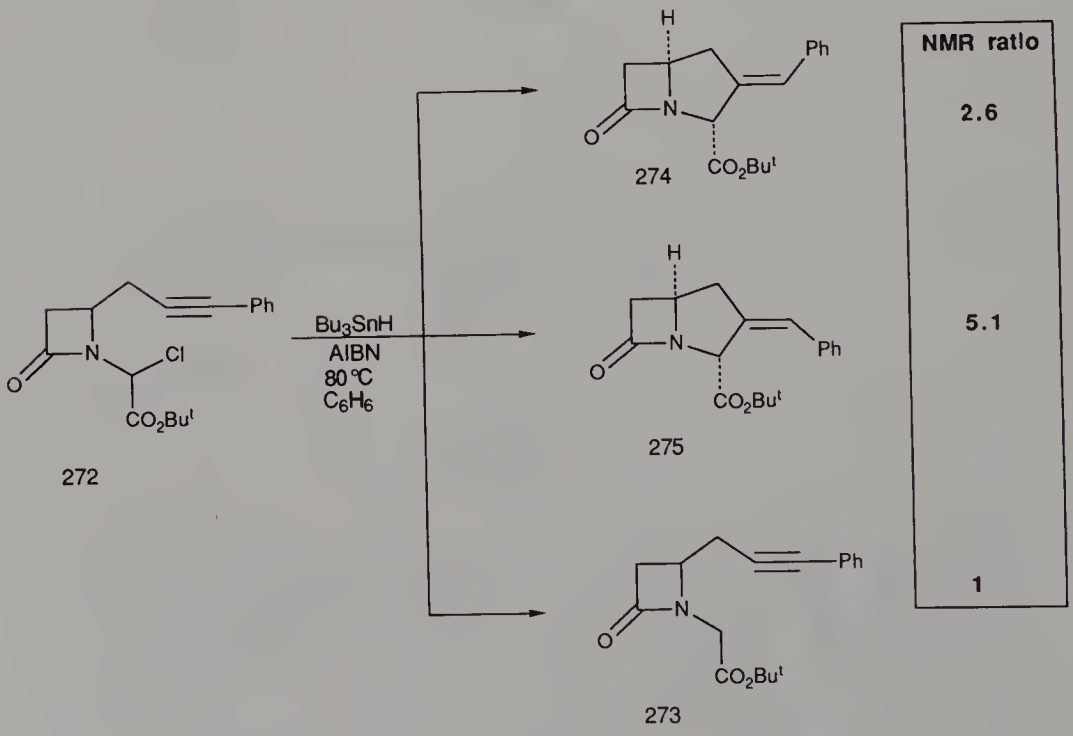
Bachi and co-workers[61] were also successful in synthesizing the carbapenam and carbaclavam ring systems. In line with previously reported results (cf. Scheme 3.52),[62] radical cyclization of **268** in benzene at 80°C with 1.1 equivalents of Bu_3SnH and 5 mole% AIBN gave carbapenams **269/270**



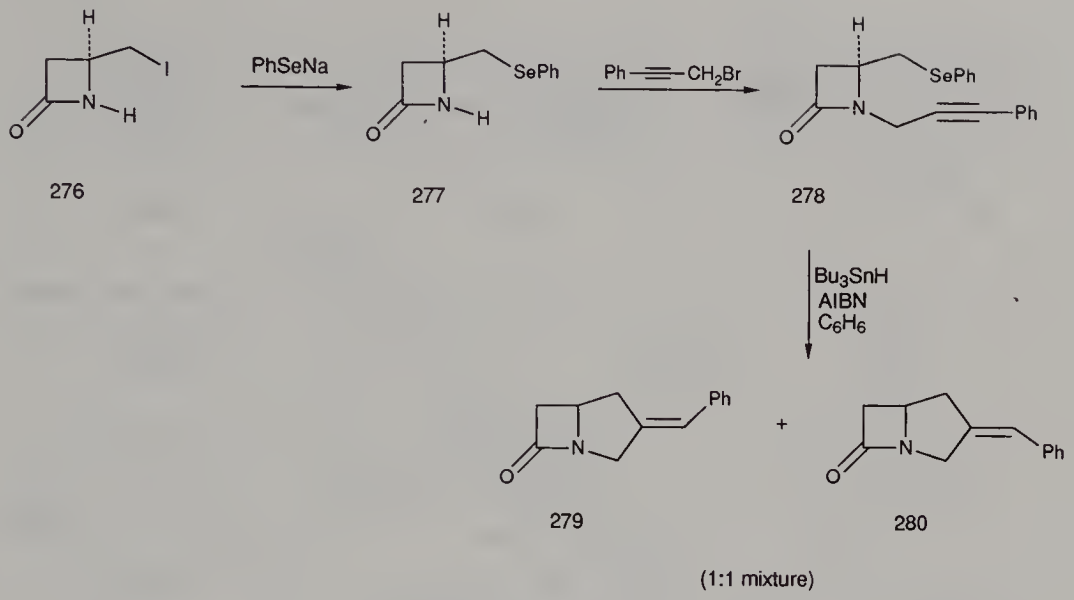
Scheme 3.58



Scheme 3.59



Scheme 3.60



Scheme 3.61

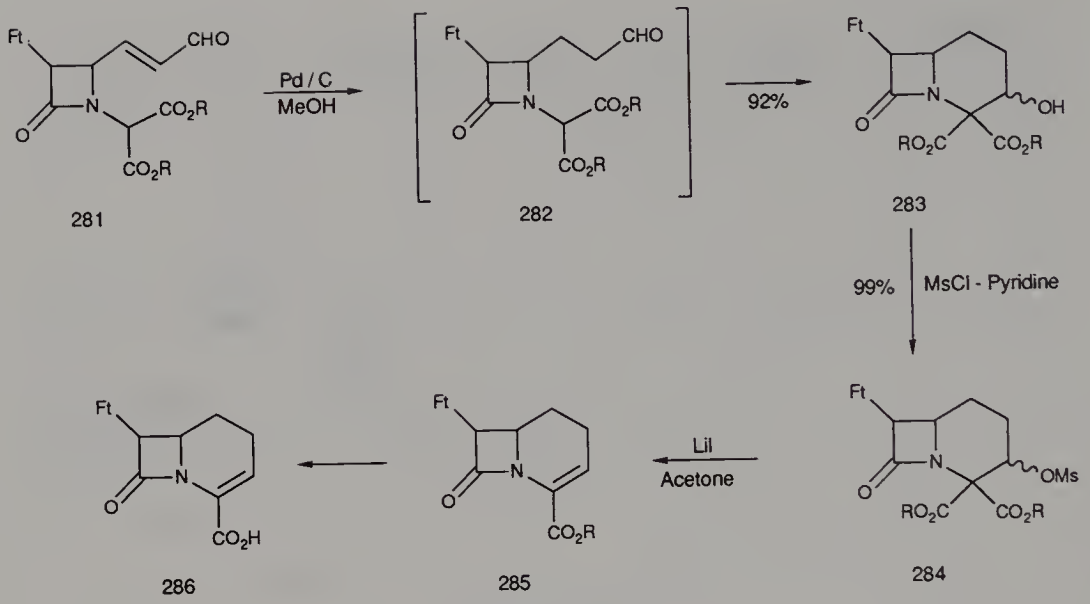
and the reduction product **271** in yields of 62 and 20%, respectively, after chromatographic purification (Scheme 3.59).[63]

Similarly, carbaclavams **274** and **275** and the reduction product **273** were prepared in near quantitative yield by simultaneously adding benzene solutions of Bu_3SnH (1.1 equivalents) and AIBN (5 mole%) over 3 hours to a 0.003 *M* isolution of **272** under reflux.[69] A chromatographic purification gave **274/275** and **273** in overall yields of 66 and 10%, respectively (Scheme 3.60).

Another approach[61] to the synthesis of C-2 benzylidene carbapenams **279** and **280** was reported by radical cyclization from the C-4 phenylselenenomethyl-substituted azetidinone **278** (Scheme 3.61).

3.5.5 Aldol Condensation and Peterson Olefination Approaches

An interesting approach to the synthesis of 3*H*-carbacephems was developed by Mochida and Hirata[70] that involved an intramolecular aldol condensation for the construction of the bicyclic β-lactam. The key azetidinone **281** was obtained by reaction of the appropriate Schiff base and phthaloylglycyl chloride in the presence of triethylamine at room temperature (Scheme 3.62). When **281** was hydrogenated carbacephem **283** was isolated in 92% yield after workup. It was of interest to note that the malonate system in **282** was reactive enough to undergo the intramolecular aldol condensation spontaneously under neutral conditions. Subsequent treatment of **283** with mesyl

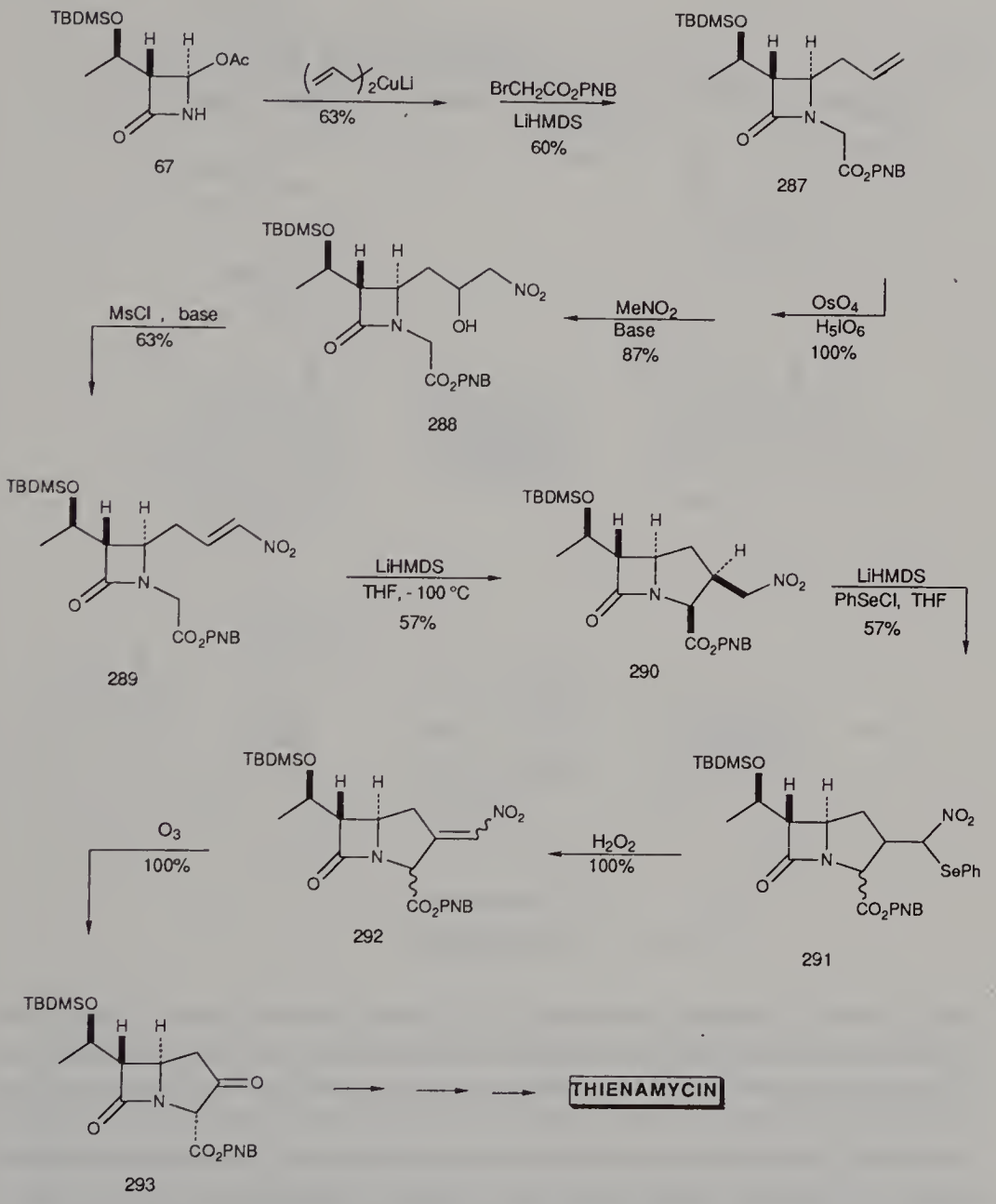


Scheme 3.62

chloride in pyridine and lithium iodide in acetone and ester group removal gave carbacephem **286.**

Hanessian and co-workers[71] used the concept of an intramolecular Michael addition for ring closure in their total synthesis of thienamycin. The strategy involved the conversion of **67** to key intermediate **289** bearing an appropriate C-4 tether for reaction as a Michael acceptor. Treatment of the nitroolefin **289** with a slight excess of LiHMDS in THF at $-100°C$ followed by quenching the reaction at $-50°C$ gave the desired bicyclic product **290** in 57% yield (Scheme 3.63), whose structure was confirmed by single crystal x-ray analysis. The success of the cyclization was found to be temperature dependent. An attempt to form the desired enolate of **289** at $-78°C$ was unsuccessful and led to the isolation of the starting material. Presumably, kinetic deprotonation at this higher temperature gave the nitro dienolate anion instead of the requisite enolate anion. The bicyclic β-lactam **290** was converted to thienamycin via further synthetic manipulations.

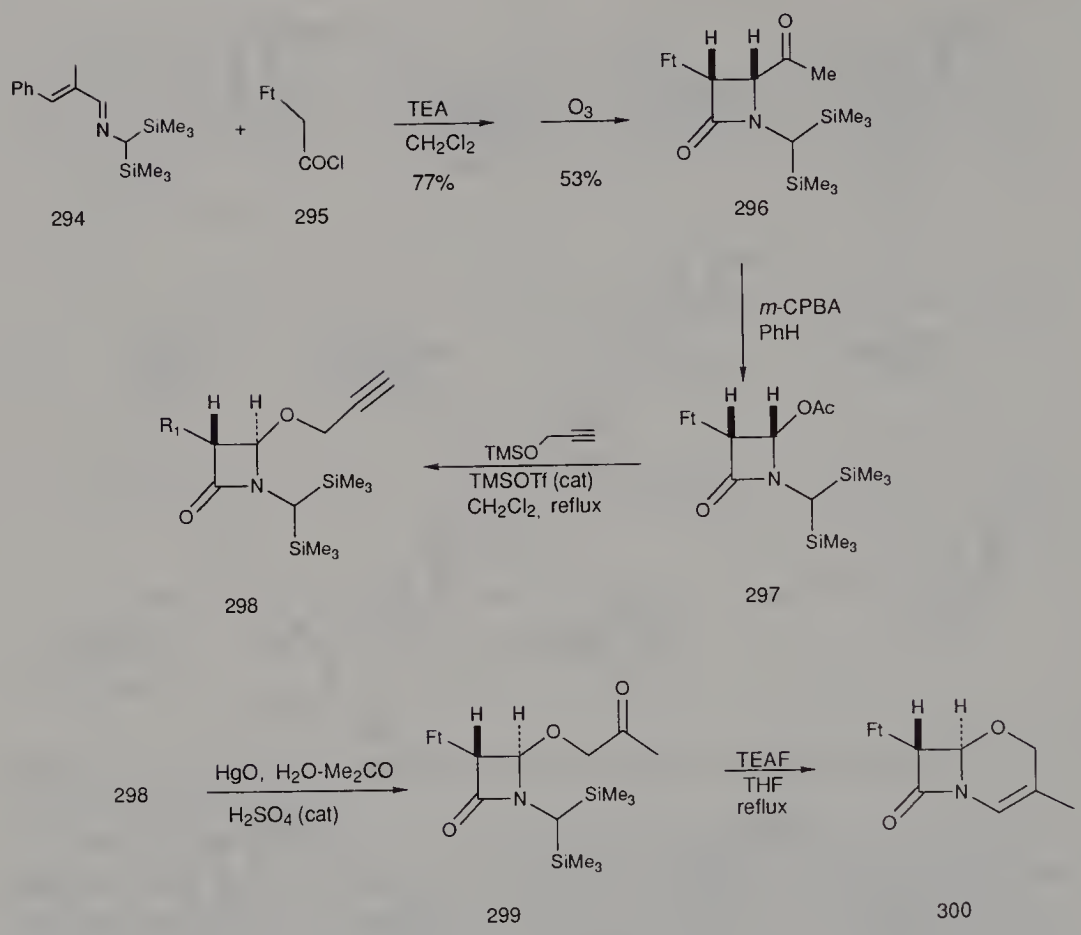
Another example of carbon–carbon bond formation involved an intramolecular Peterson olefination catalyzed by fluoride ion and was reported by Palomo and co-workers (Scheme 3.64).[72] Preparation of the acetoxyazetidinone **297** was achieved via a Staudinger reaction followed by ozonolysis and peracid oxidation. Treatment of **297** with the trimethylsilyl ether (TMSOTf) of propargyl alcohol and catalytic trimethylsilyl triflate (TMSOT) afforded **298,** which on hydration with mercuric oxide gave **299** in 70% yield. This azetidinone was then subjected to a Peterson olefination by treatment with tetraethylammonium fluoride (TEAF) in boiling THF and furnished the 1-oxacephem **300.**



Scheme 3.63

3.6 Closure to *N*-1 of the Azetidinone

Numerous methods of β-lactam synthesis by closure to *N*-1 of the azetidinone were published and previously reviewed in the literature,[1b,c,i,k,l] indicating the degree of interest and importance in this area of medicinal chemistry. The most popular ring closure approach in this category was Merck's car-



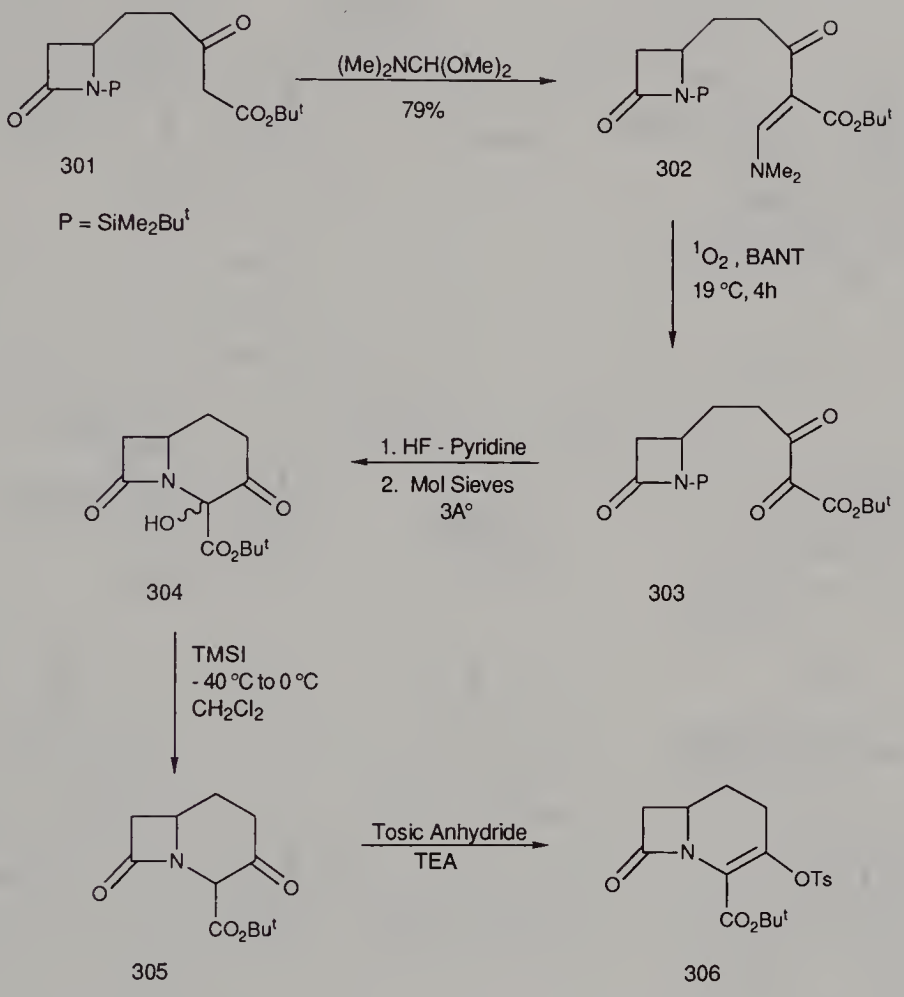
Scheme 3.64

(Reprinted, with permission, from Palomo et al.[72])

bene insertion reaction; however, a few more methods were recently reported that employed other chemistries for closure to *N*-1 of the azetidinone.

Wasserman and Han[73] reported an interesting and concise synthesis of the carbacephem nucleus. The chemistry relied on the synthesis of vicinal tricarbonyls formed from the reaction of a β-ketoester precursor and DMF acetal followed by photooxidative cleavage. The azetidinone **301** was treated with DMF dimethyl acetal to afford enamine **302** (Scheme 3.65). Photooxygenation using singlet O_2 along with a catalytic amount of the sensitizer bisacenaphthalenethiophene (BANT) gave the vicinal tricarbonyl derivative **303.** Desilylation followed by stirring with activated molecular sieves provided the cyclized product **304.** Subsequent low-temperature reduction with trimethylsilyl iodide (TMSI) followed by tosylation yielded the carbacephem **306.** A similar sequence of reactions was used for a formal total synthesis of (±)-PS-5 (**213**) from azetidinone **307** (Scheme 3.66).[74]

Shibuya and co-workers[75] demonstrated an *N*-1 bond closure for synthesis of the carbapenam ring system using an intramolecular Michael reaction. Treatment of nitroazetidinone **314,** obtained from **312** in a few steps, with



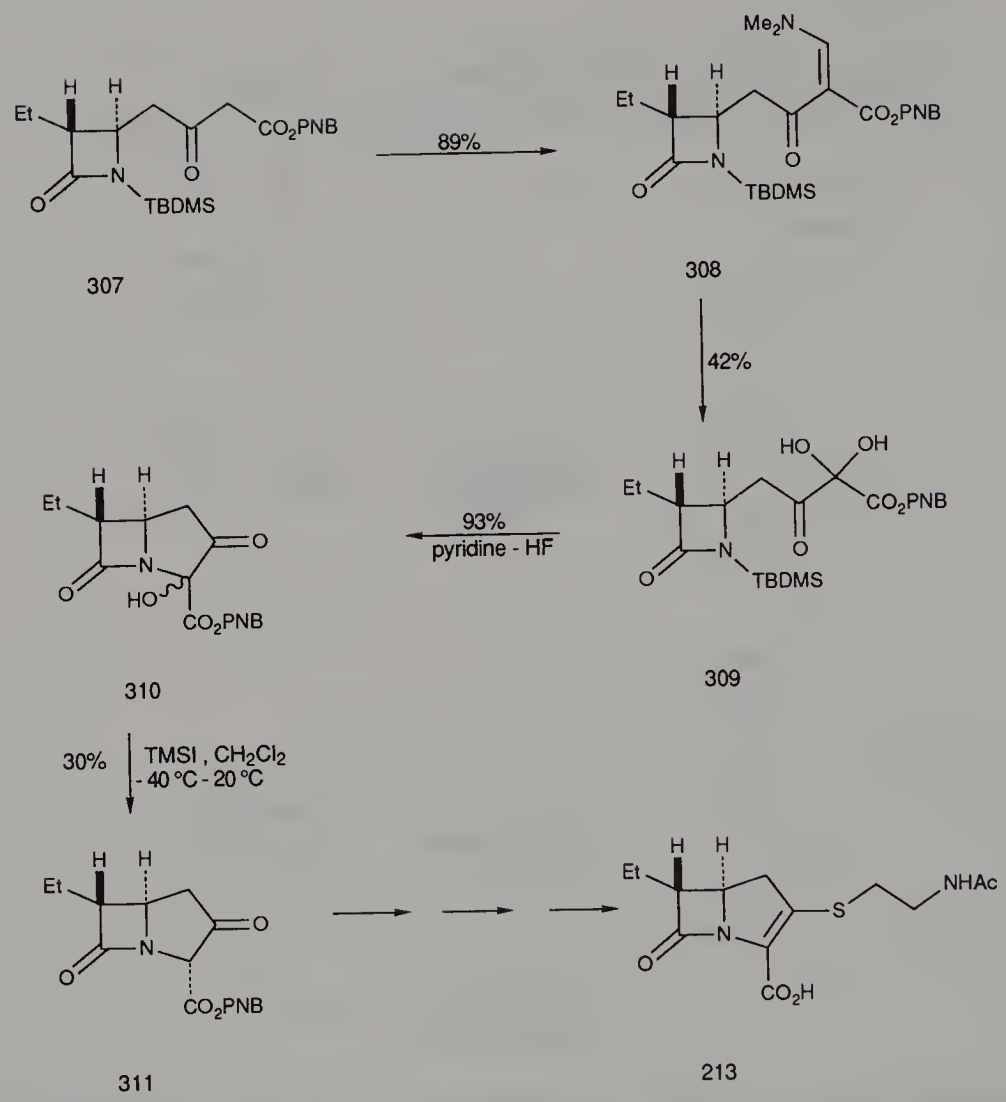
Scheme 3.65

potassium fluoride in methanol afforded a C-3 epimeric mixture of **315** (ca. 2:1). Further functional group conversions gave the carbapenam **317** (Scheme 3.67).

A complementary approach to Shibuya's method of intramolecular Michael cyclization was improved on by Barrett and co-workers (Scheme 3.68).[76] In four steps azetidinone **318** was synthesized and, on *N*-silylation and ozonolysis, afforded the aldehyde **319.** Aldol condensation followed by elimination provided the key azetidinone **320.** Desilylation, potassium salt formation, cyclization, and ozonolysis produced the bicyclic β-lactam **321** as a 1:1.1 diastereomeric mixture.

This chemistry was also extended to the synthesis of 1-oxapenam **325** from azetidinone **322** (Scheme 3.69).[76]

In these studies[76] Barrett and co-workers recognized the potential problem of selective hydrolysis of the phenylthioesters **321** and **325** to the corresponding β-lactam carboxylic acids. To circumvent the problem, use of (benzyloxy)nitromethane was introduced. Its utility was demonstrated in the

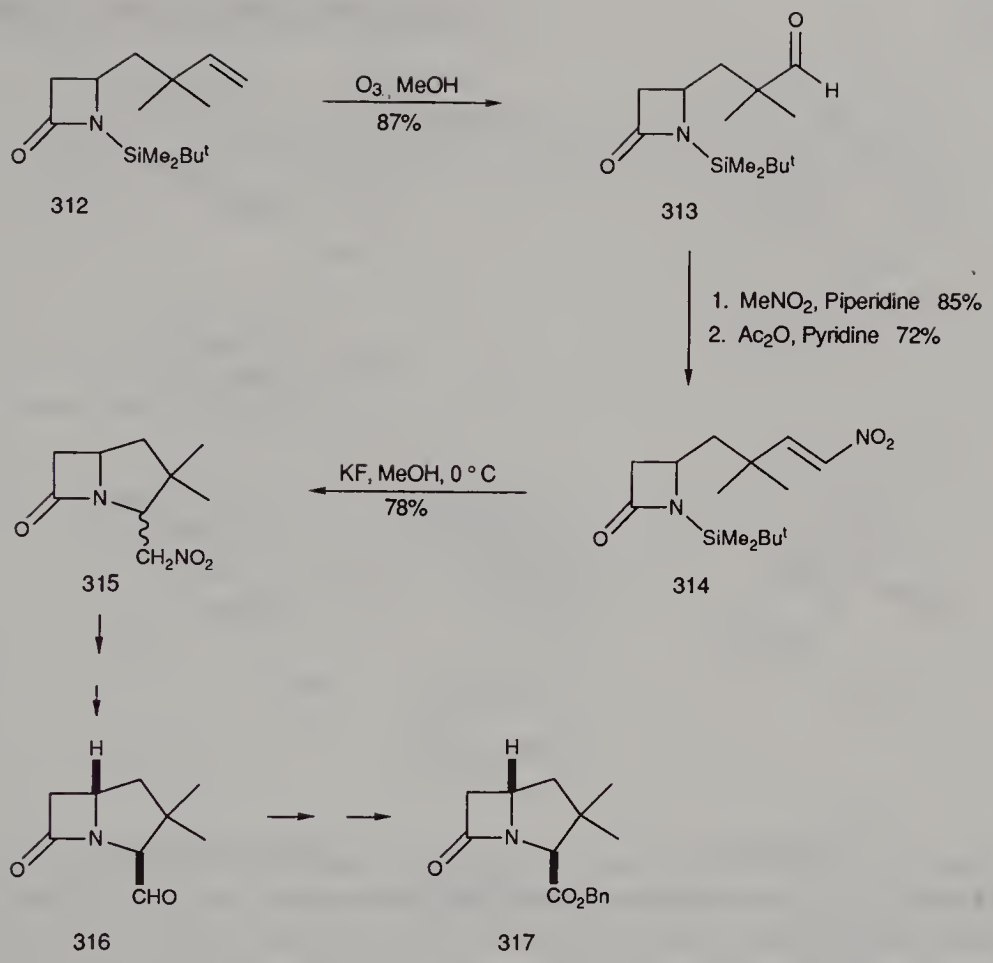


Scheme 3.66

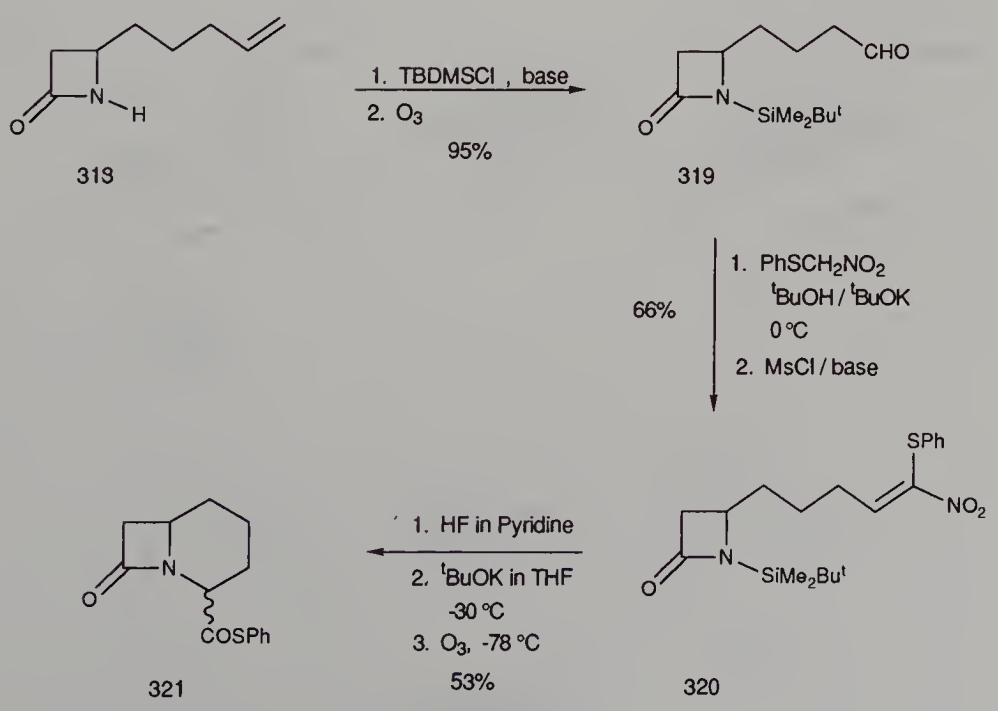
construction of benzyl penicillinate **329** (Scheme 3.70)[77] and benzyl 1-oxapenam **333** (Scheme 3.71).[78]

An interesting approach to the carbapenam ring system using an intramolecular cyclization to *N*-1 of the azetidinone was described by Dumas and d'Angelo.[79] The ester **334** was readily converted to the azetidinyl organomercurate **335** (98%) via a stereoselective solvo-mercuration reaction employing mercuric trifluoroacetate (Scheme 3.72). Further treatment with potassium bromide followed by addition of iodine under photochemical conditions afforded an equimolar mixture of iodoazetidinones **337.** Desilylation and Triton-B induced cyclization afforded the carbapenam **339** in 80% yield as a single diastereomer.

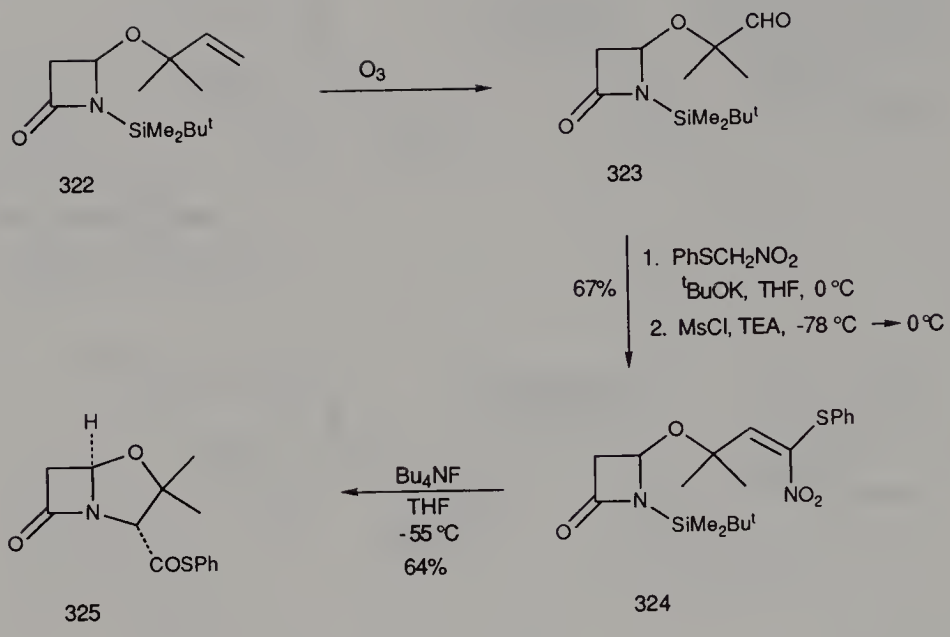
Hoppe and Hilpert[80] reported the enantioselective synthesis of the fungicidal β-lactam antibiotic (−)-(2*S*, 5*S*)-2-(2-hydroxyethyl)clavam **345** and its (+)-(2*S*,5*R*) epimer **344.** The key intermediate prior to ring cyclization was



Scheme 3.67

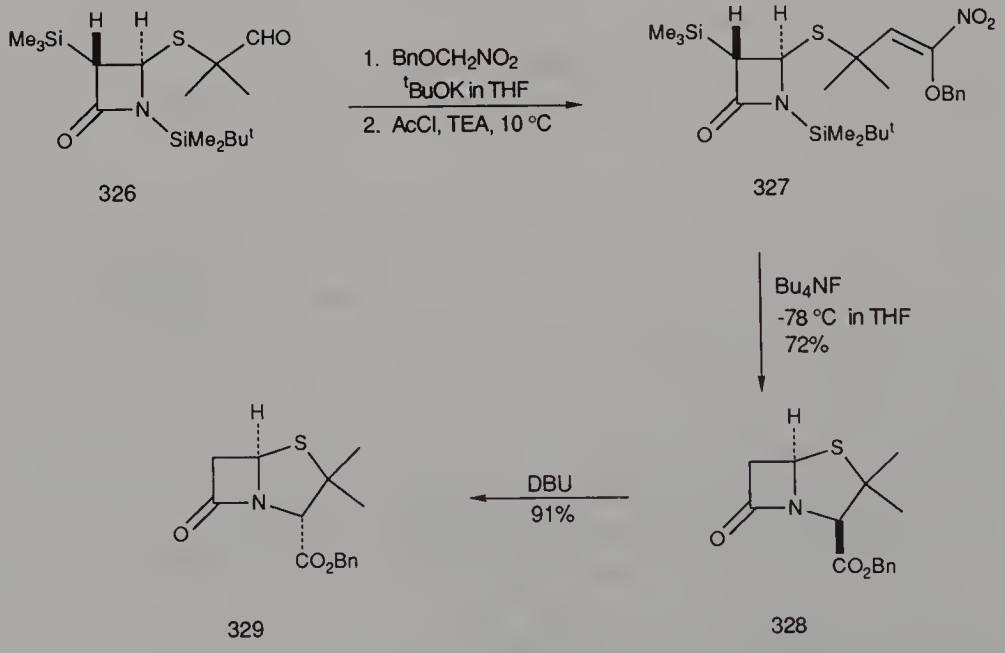


Scheme 3.68

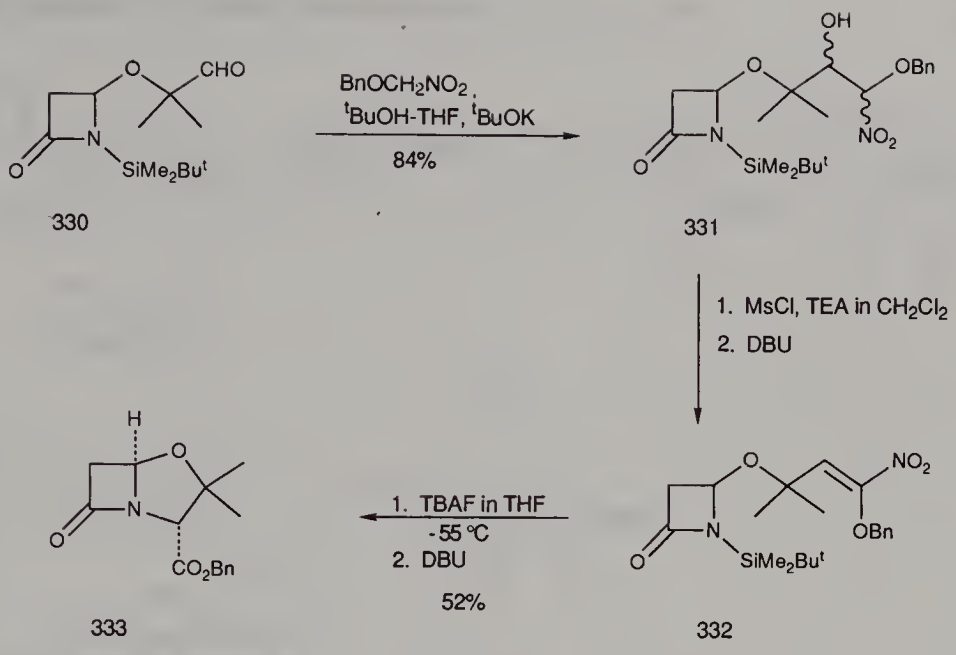


Scheme 3.69

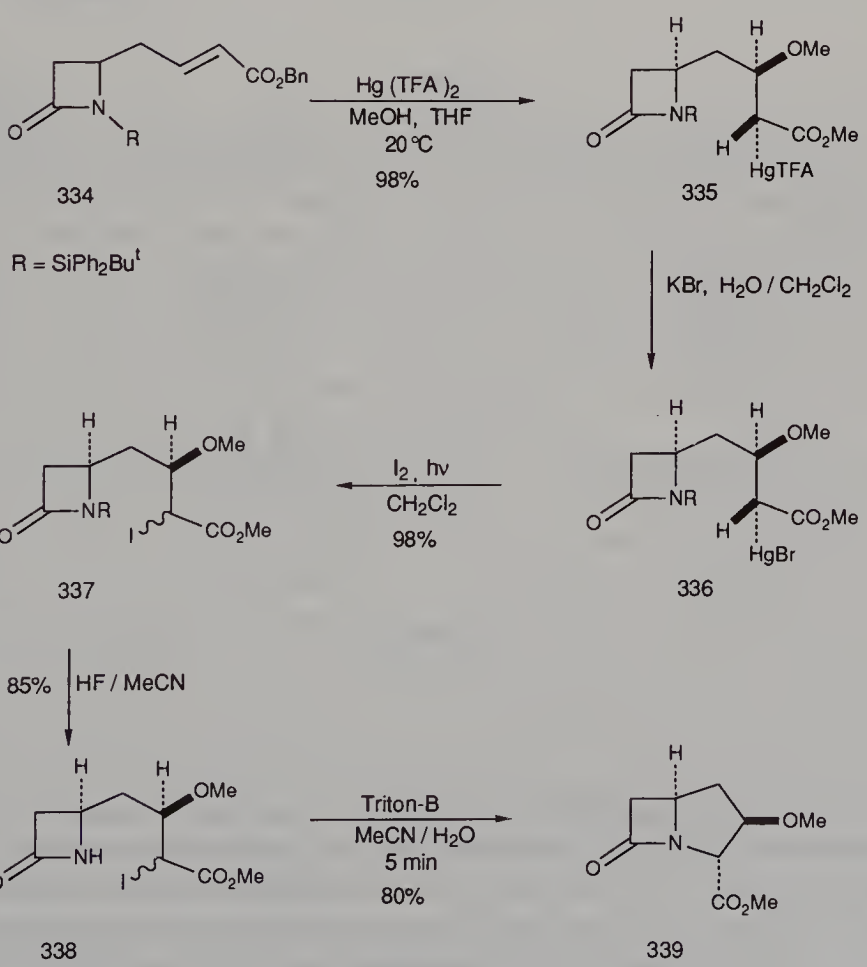
prepared by palladium(II) acetate catalyzed coupling of the chiral alcohol **341** with 4-acetoxyazetidinone **340.** The intermediate **342** was cyclized by treating its solution in hexamethylphosphoric triamide (HMPT) with 3 equivalents each of K_2CO_3 and NaI (Scheme 3.73). Reduction over 10% Pd/C in THF afforded the corresponding 4-methoxy-3-aminobenzyl protected inter-



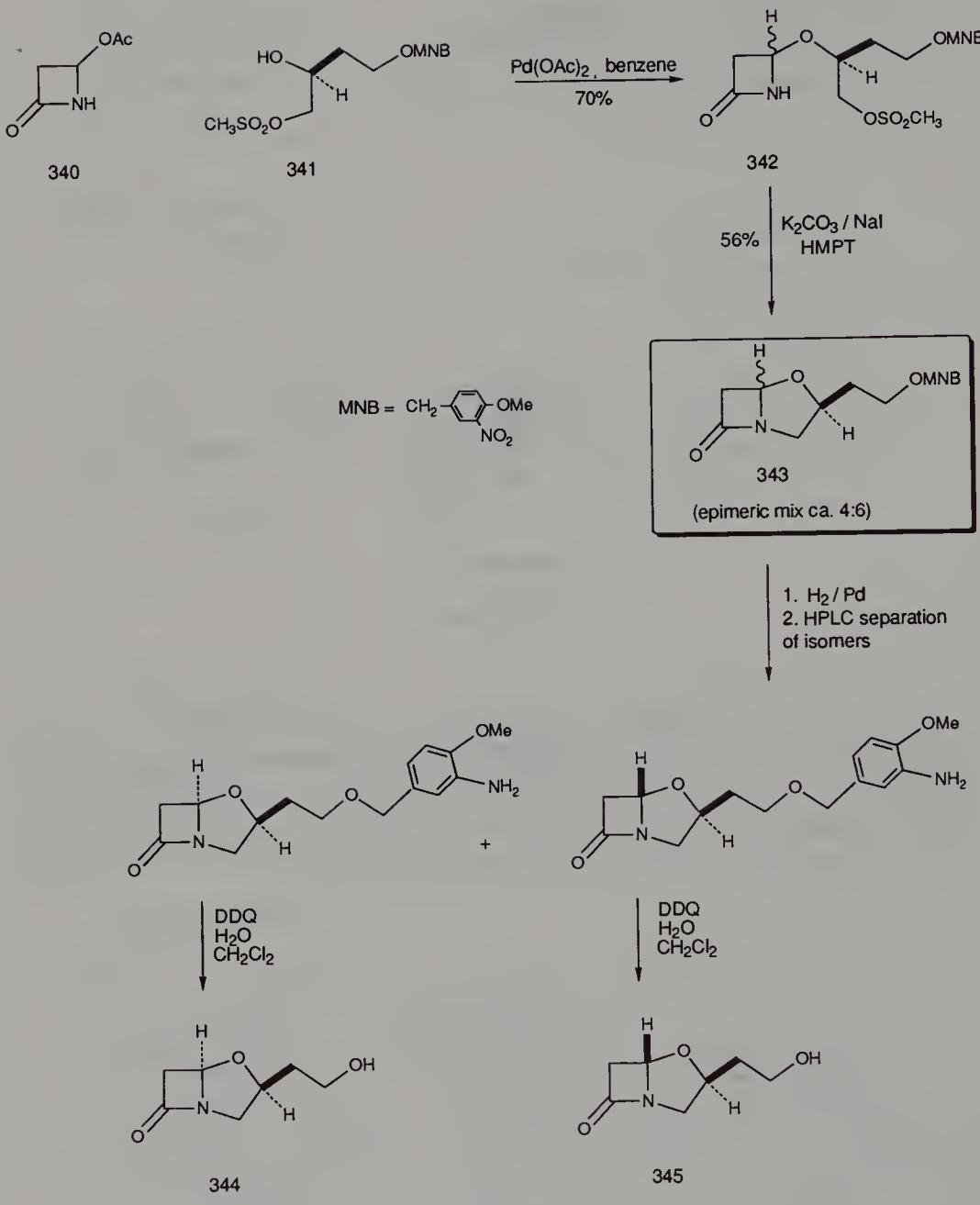
Scheme 3.70



Scheme 3.71



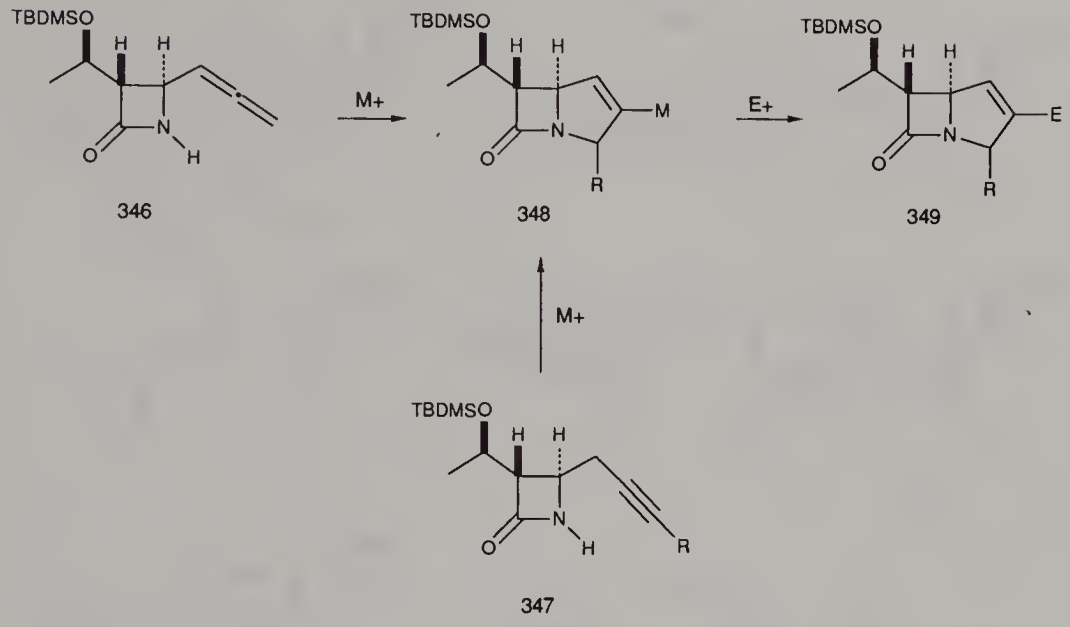
Scheme 3.72



Scheme 3.73

mediates which were chromatographically separated. Conversion of each diastereomer to **344** (20%) and **345** (19%) was performed by reaction with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in aqueous CH_2Cl_2.

A novel organotransition metal approach to the carbapenem ring system **349** from C-4 allenyl (**346**) and C-4 2-propynylazetidinones (**347**) was recently developed by Liebeskind and Prasad (Scheme 3.74).[81,82]

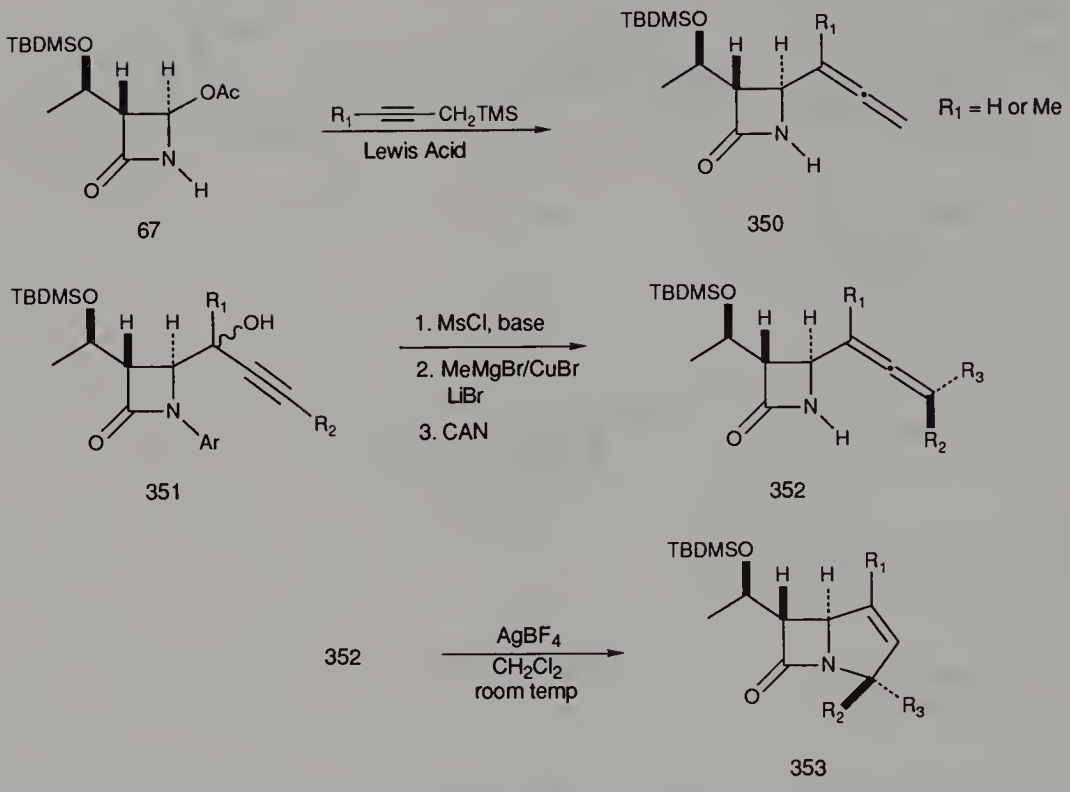


Scheme 3.74

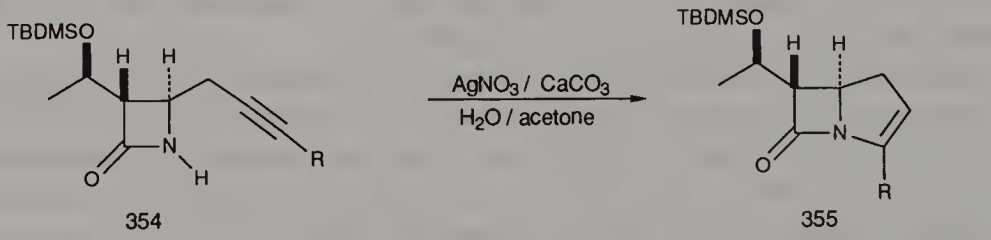
The allenes **350** (R_1 = H, Me) were prepared from the Lewis acid induced reaction of C-4 acetoxyazetidinone **67** with 1-trimethylsilyl-2-propyne and 1-trimethylsilyl-2-butyne, respectively (Scheme 3.75). The substituted allenes **352** were obtained from the S_N2' reaction of MeMgBr/CuBr/LiBr with the mesylates derived from propargyl alcohols **351.** In the presence of silver tetrafluoroborate in methylene chloride, the allenes **352a–e** cyclized readily to the Δ^1-carbapenems **353a–e.** The alkynyl substituted azetidinones **354** (R = Me, Ph) also underwent slow cyclizations to Δ^2-carbapenems **355** in the presence of silver nitrate, albeit in low yields.[81]

Treatment of allene **352b** with a variety of palladium(II) salts produced only traces of the carbapenem **356**[82]; however, in the presence of excess allyl bromide and a Pd^{2+} species, a 60% yield of the carbapenem **357** was isolated (Scheme 3.76). The transformation was proposed to proceed by an initial palladium induced *N*—C3 bond formation to afford a vinylpalladium species followed by insertion of the allyl halide. The subsequent β-elimination gave the product and the Pd^{2+} catalyst.[82] This chemistry was also extended to the preparation of C-2 substituted Δ^1-carbapenems **358** by reaction of the intermediate vinylpalladium species with various acrylates and methyl vinyl ketone (Heck reaction). The aryl substituted alkynes **359** also underwent palladium-mediated cyclizations to afford the unstable Δ^2-carbapenems **360** (R = phenyl, 4-methoxyphenyl).

Another report of a metal assisted *N*—C3 closure was made by French scientists.[83] The azetidinone **362,** prepared from **340,** NaH, and vinyl bromide **361** in THF, was cyclized under harsh conditions to carbacephem **363**



352a	$R_1 = R_2 = R_3 = H$	0.05 equiv	75%	
352b	R_1 = Me , $R_2 = R_3 = H$	0.14 equiv	70%	
352c	$R_1 = H$, R_2, R_3 =H, Me	1.0 equiv	65%	(diast. 1:2)
352d	$R_1 = H$, R_2, R_3 = H, Me	1.3 equiv	62%	(diast. 1:2.8)
352e	$R_1 = H$, R_2, R_3 = Me, n-Bu	0.5 equiv	58%	(diast. 1.2.2)

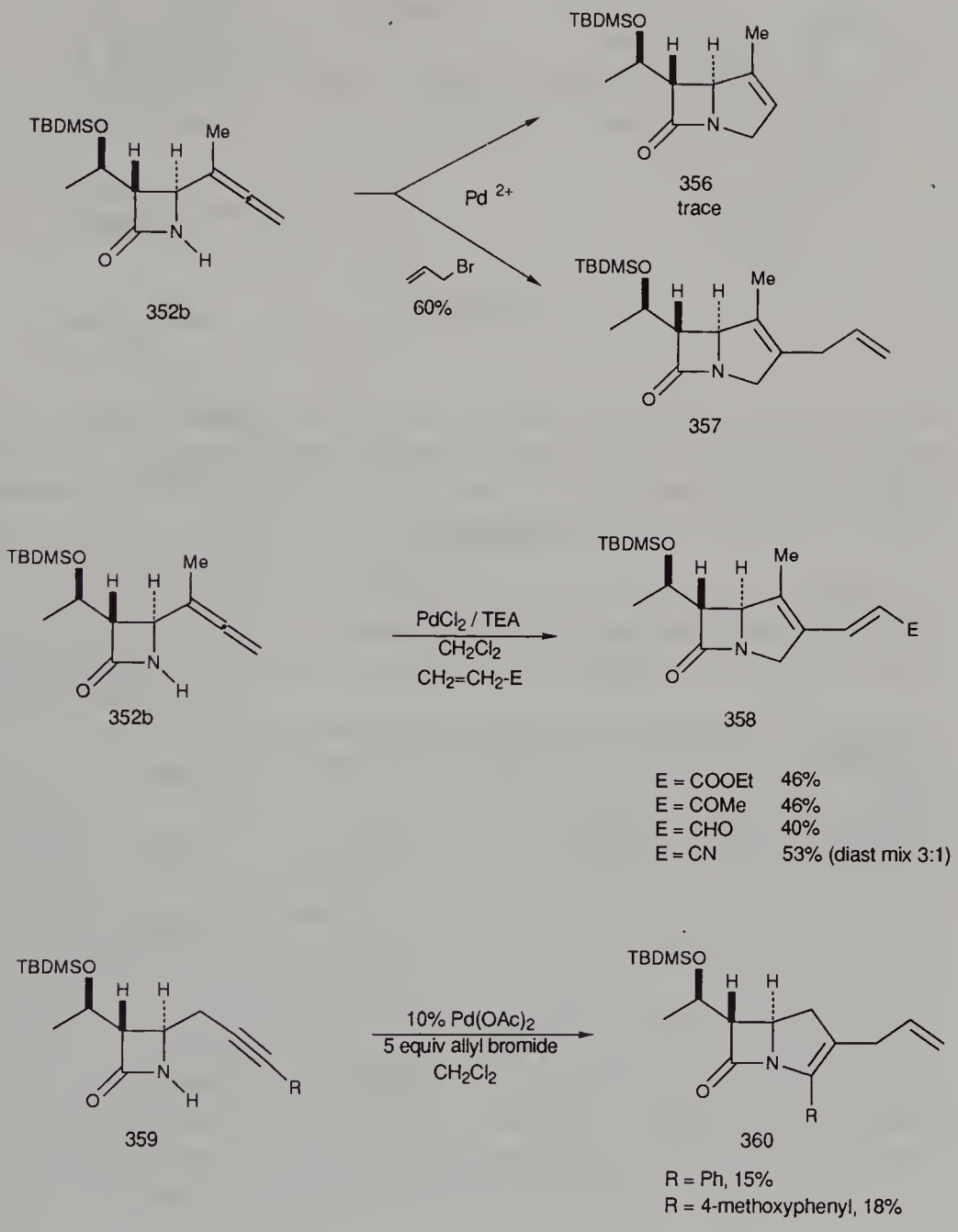


R = Me, 7- days, 45% yield
R = Ph, 10 - days, 20% yield

Scheme 3.75

by heating in DMF at 110 to 120°C in the presence of metallic copper (Scheme 3.77).

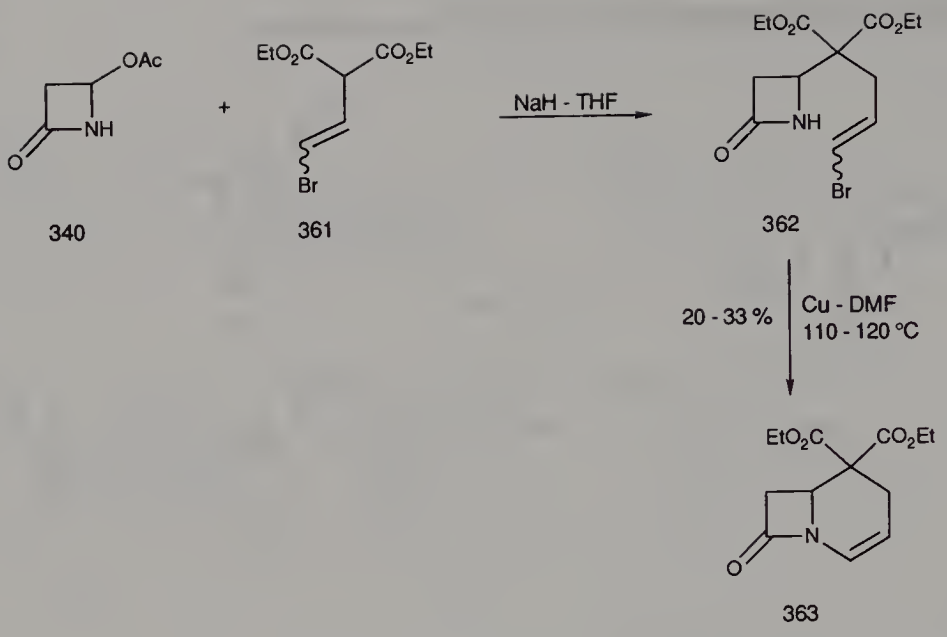
A similar type of closure was reported by Greengrass and Hoople (Scheme 3.78).[84] Reaction of azetidinone **340** with the sodium (THF, NaH, 0°C) or copper(II) salt (from $Cu(OAc)_2$) of **364** gave **365** in greater than 80%



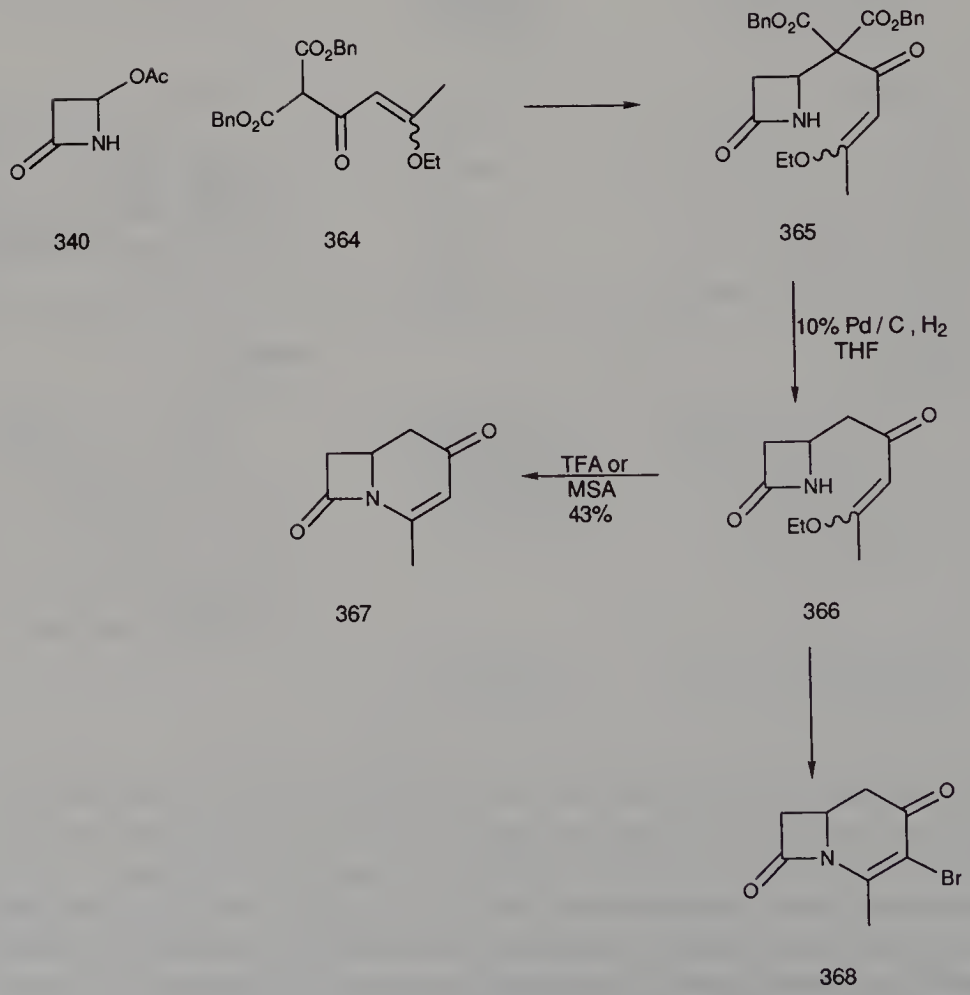
Scheme 3.76

yields. Extended hydrogenation over 10% Pd/C in THF gave **366** (45%), which was cyclized to the carbacephem **367** (43%) on treatment with TFA or methanesulfonic acid (MSA). Alternately, closure to the bromo derivative **368** occurred in 93% yield on reaction with pyridinium bromide perbromide.

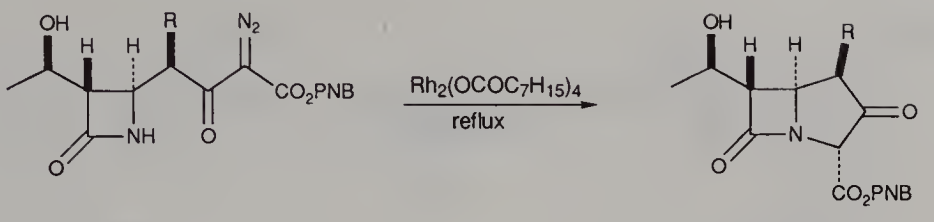
By far the most frequently exploited method of β-lactam synthesis for this type of closure was via the Merck carbene protocol (Scheme 3.79).[85–88] This technology afforded efficient syntheses of the carbapenems **370** (R = H, Me) from their respective precursors **369.** These β-lactams continue to serve



Scheme 3.77



Scheme 3.78



369 370

R = H, Me

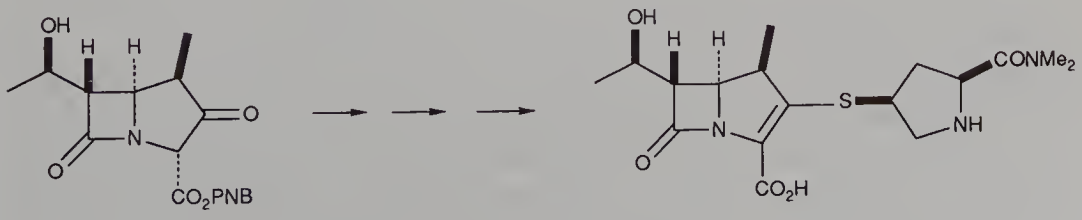
Scheme 3.79

as springboards toward the discovery of new antibacterial agents, as shown in Scheme 3.80. Elaboration of **370** in the usual way[88] recently gave mercaptopenem **371.**[89] Good DHP-I stability and a well balanced antibacterial spectrum including antipseudomonal activity were exhibited by this compound, this warranting its further investigation.

As the aforementioned example showed, this annulation technique consistently proved useful as a general synthetic method for β-lactam synthesis. The remainder of this chapter outlines other applications of this facile methodology through 1990.

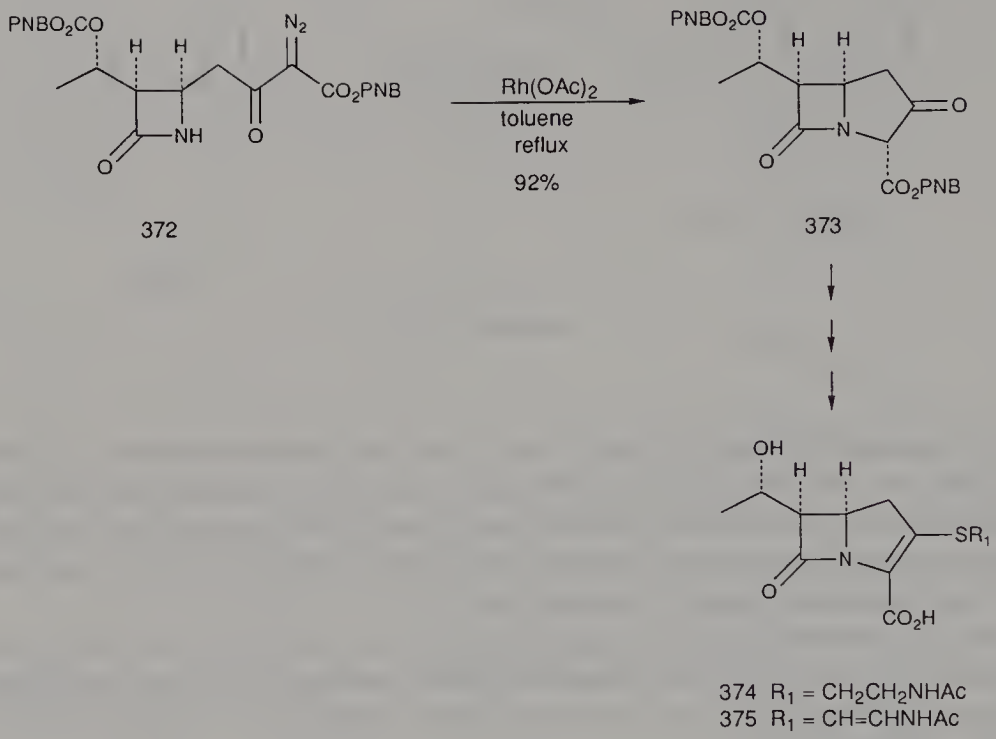
Kametani and co-workers[90] reported the total synthesis of (±)-epithienamycins A (**374**) and B (**375**) by employing Merck's carbene cyclization methodology. The key intermediate **372,** prepared in a few steps from an isoxazoline derivative, was subjected to $Rh_2(OAc)_4$ mediated cyclization conditions to afford the bicyclic ketone **373,** which was further elaborated to the respective target compounds (Scheme 3.81).

Other research groups described syntheses of 3-hydroxy-l-oxacephems **377** from **376** (Scheme 3.82). Cyclization of **376** (R_1 = H; R_2 = Bu^t) in refluxing benzene with catalytic $Rh_2(OAc)_4$ gave **377** in 82% yield.[91] This provided a direct and easy access to 1-oxacephems **378** (X = OMe, Cl) of medicinal interest. Similarly, annulation of **376** (R_1 = Me, R_2 = $CHPh_2$) with catalytic $Rh_2(OAc)_4$ in refluxing ethyl acetate gave the unstable intermediate **377**[92] in quantitative yield. Further elaboration gave **379,** a potent new antibacterial agent with a broad activity spectrum.[93]



370 371

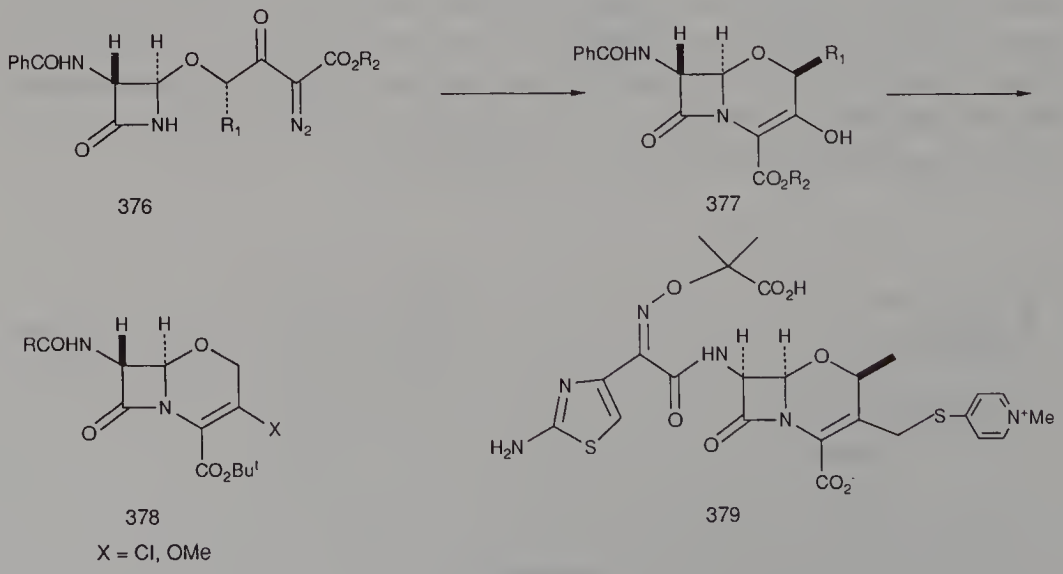
Scheme 3.80



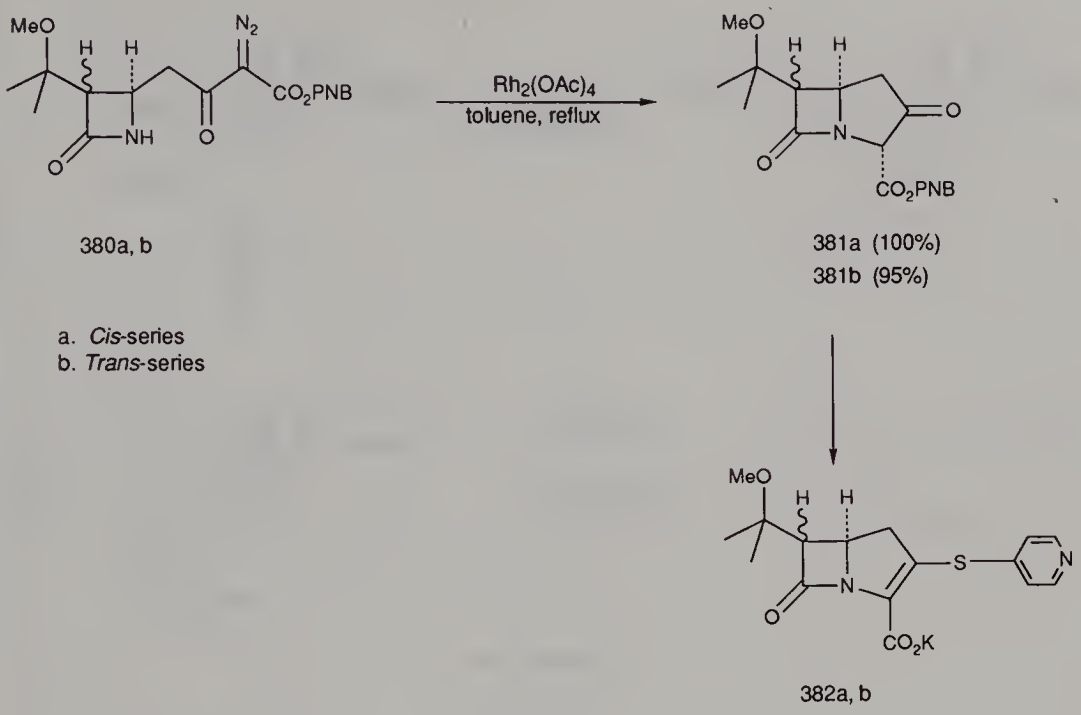
Scheme 3.81

(Reprinted, with permission, from Kametani et al.[90])

In an effort to gain structure activity relationship information versus their hydroxy counterparts, *O*-methylcarpetimycin **382a** and *O*-methyl-6-epicarpetimycin **382b** were prepared by Hoshimoto and co-workers (Scheme 3.83).[94] Excellent yields were obtained for the $Rh_2(OAc)_4$ catalyzed reactions of **380a** and **b** to **381a** and **b.** Subsequent transformations (enol triflate for-



Scheme 3.82



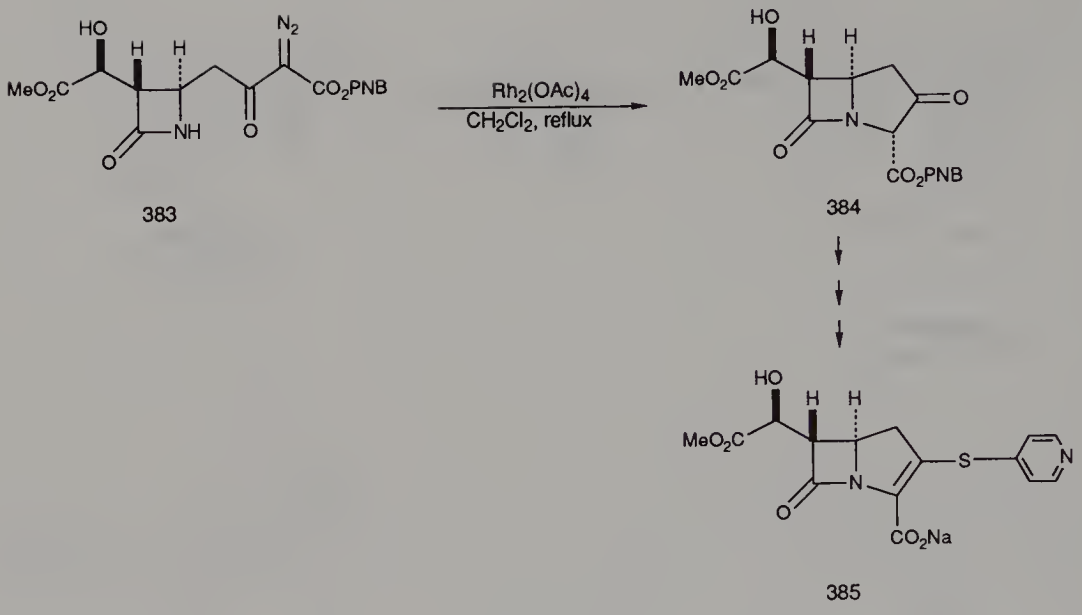
Scheme 3.83

mation, mercaptan displacement, deprotection) gave **382a** and **b,** which were found to be less active than the parent carpetimycins.

As shown in Scheme 3.84, Habich and Hartwig attempted to improve in vivo metabolic stability against DHP-I while increasing antibacterial activity with the C-6 modified carbapenem **385.**[95] Treatment of **383** with catalytic $Rh_2(OAc)_4$ in refluxing dichloromethane gave β-ketoester **384** (57%), which was converted to **385** via an enol diphenyl phosphate.[88]

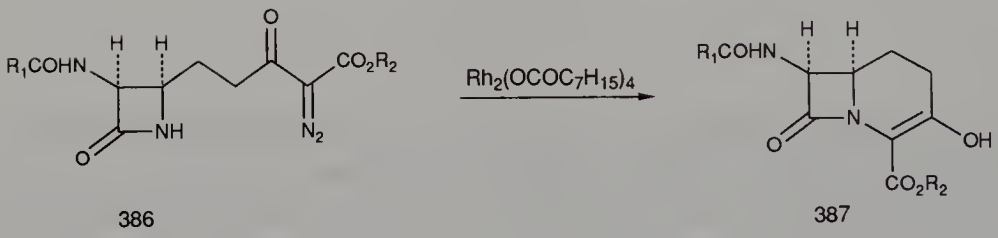
Carbacephems were also readily accessible via this carbene insertion procedure. Azetidinones **386** were prepared in good overall yields and with excellent diastereoselectivities based on the elegant work of Evans and Sjogren.[96] Cyclizations[97,98] gave the 3-hydroxycarbacephems **387** as expected (Scheme 3.85), which were subsequently elaborated to **210**[97] and loracarbef monohydrate (**388**),[98] respectively.

Uyeo and co-workers[99] described syntheses of (±)-asperenomycin A (**394**), B (**396**), and C (**393**). The $Rh_2(OAc)_4$ catalyzed carbene insertions to **390a** (80%) and **390b** (79%) were straightforward, as were further conversions to **391a** (46%) and **391b** (70%) (Scheme 3.86). Interestingly, **392** was produced from **391a** in 74% yield under ElcB conditions, whereas **391b** gave **392** in 58% yield by *E*2 elimination. Removal of the ester protecting group with $AlCl_3$ and anisole in dichloromethane gave (±)-asperenomycin C (**393**). Oxidation with *m*-CPBA in a two-phase dichloromethane aqueous phosphate buffer provided (±)-asperenomycin A (**394,** *R*-sulfoxide) after chromatographic purification. In an exactly analogous fashion, (±)-aspereno-



383 384 385

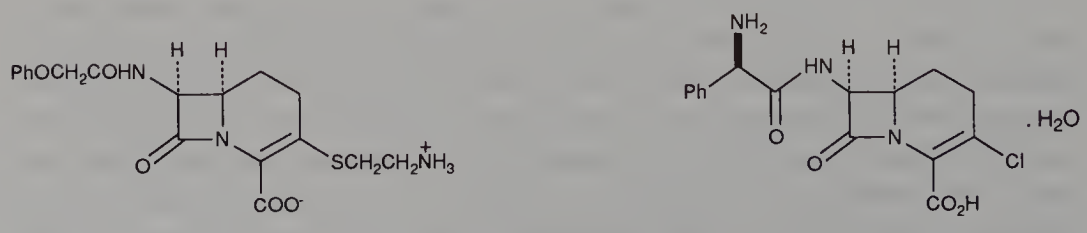
Scheme 3.84



386 387

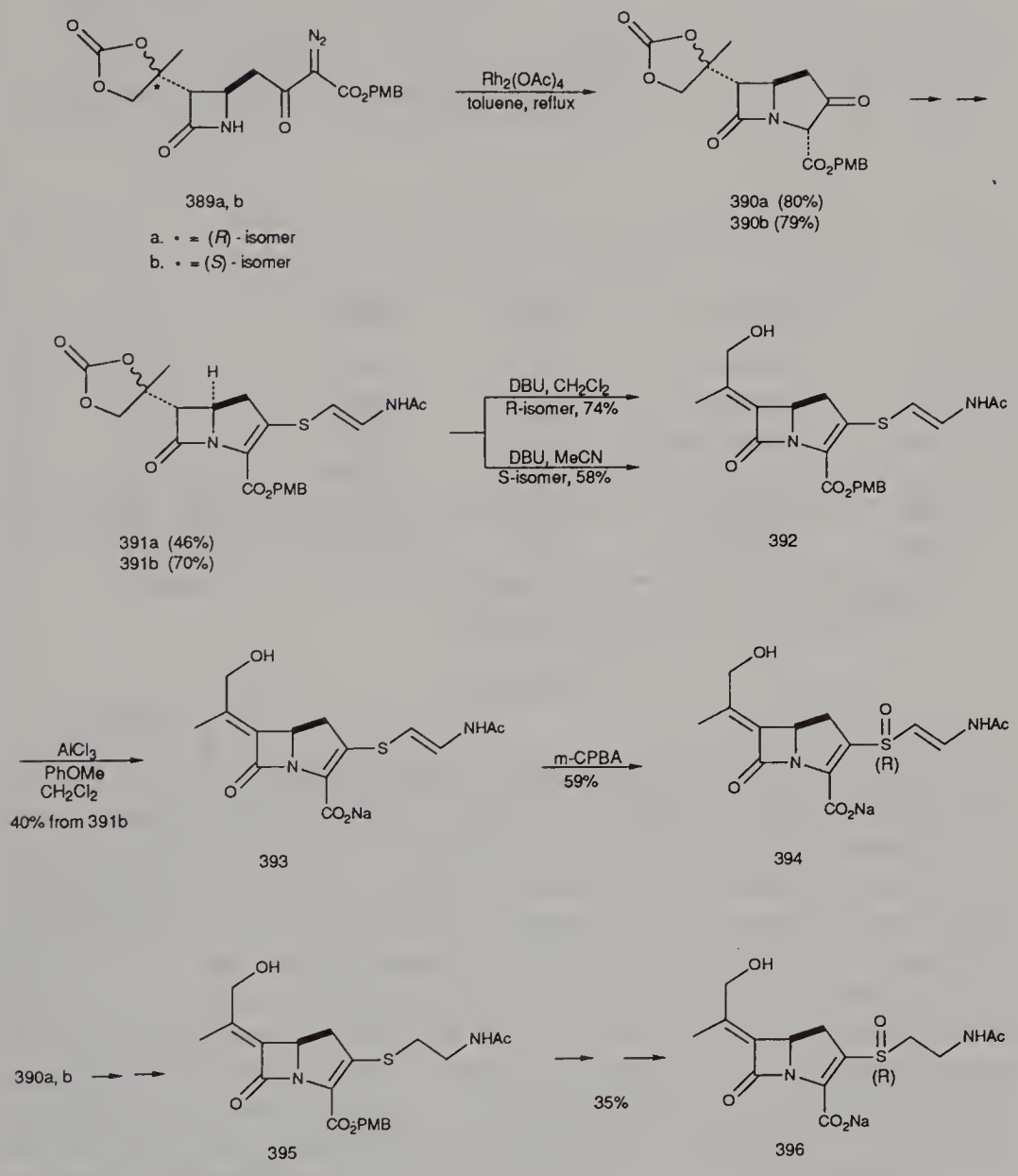
R_1	R_2	solvent	% yield	ref
OBu^t	Bn	$CHCl_3$[a]	b	97
CH_2OPh	PNB	CH_2Cl_2	72	98

a. alcohol free
b. derivatized to an enol triflate without isolation



210 388

Scheme 3.85

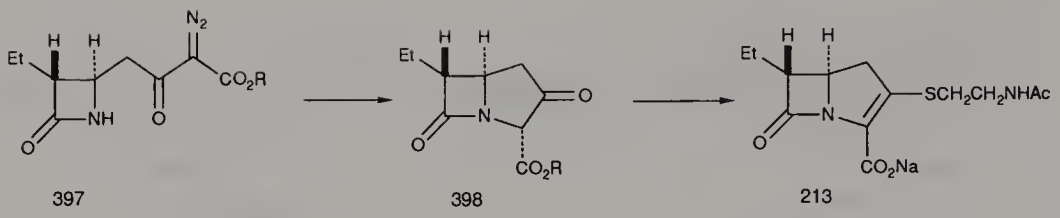


Scheme 3.86

mycin B (**396**) was also produced from common intermediates **390a** and **b**. Ester hydrolysis of **395** and *m*-CPBA oxidation gave the desired product in 35% overall yield after purification.

Several research groups reported enantioselective syntheses of the carbapenem antibiotic PS-5 (**213**) from **397**, as summarized in Scheme 3.87.[100–104] Again, the carbene insertion reactions to **398** were uneventful and proceeded in high yields.

Also described by several investigators were vastly improved procedures for construction of carbapenem precursors **400** based on diastereoselective



397 398 213

R	catalyst	solvent	% yield	ref
Bu^t	$Rh_2(OAc)_4$	PhH	95	100
Bn	$Rh_2(OAc)_4$	PhH	93	100
MOM	$Rh_2(OCOC_7H_{15})_4$	$CHCl_3$[a]	b	101
PNB	$Rh_2(OCOC_7H_{15})_4$	hexane	94	102
PNB	$Rh_2(OAc)_4$	$C_2H_4Cl_2$	91	103
PNB	$Rh_2(OAc)_4$	PhH	84	104

a. alcohol free
b. immediately derivatized to the enol triflate without isolation

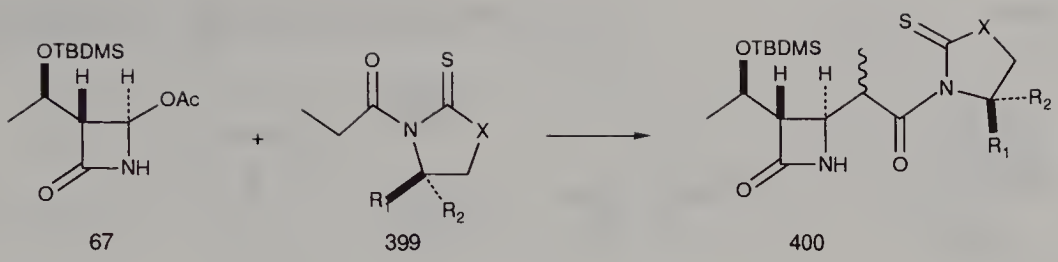
Scheme 3.87

aldol type reactions of azetidinone **67** and **399** (Scheme 3.88).[105–107] Hydrolytic removal of the auxiliaries gave the key 1β-methylcarbapenem intermediate **180** in overall yields of 73%[106] and 70%[107,108] from **67** (Scheme 3.89).

Endo and Droghini[109] demonstrated the stereoselective and direct introduction of the entire carbon chain needed for 1β-methylcarbapenems (Scheme 3.90). The dianion of methyl propionylacetate **401** was coupled with **67** under Lewis acid conditions at low temperature. Moderate to good diastereoselectivities were observed for **402** after chromatographic purification. Reaction yields were generally low because of coproduction of 2-pyridone **403**, which resulted from α-site alkylation of **401**. Substitution of the dianion **401** with the bistrimethylsilyl enol ether **404** afforded **402** in comparable yields but with poorer β-diastereoselectivities (Scheme 3.91).

A more direct preparation of the key 1β-methylcarbapenem intermediate **407** was reported shortly thereafter by Deziel and Endo.[110] Diastereoselective coupling of **67** with in situ-generated tin(II) enolate **405** and catalytic $AgBF_4$ gave **406** in 75 to 80% yield (Scheme 3.92). As separation of the diastereomers was unsuccessful, hydrolysis to the β-methyl isomer **407** was performed. The isolated material contained less than 1% of the undesired α-isomer. Overall yields of **407** from **67** by this two-step process were 40 to 45%.

A series of 6β-methylcarbapenems were synthesized by Satoh and Tsuji.[111] Treatment of a diastereomeric mixture of **408** with catalytic $Rh_2(OAc)_4$ gave **409** (31%) and **410** (52%) after chromatographic purification

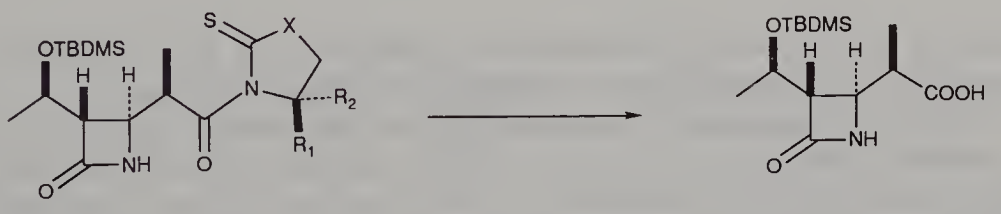


67 399 400

R_1	R_2	X	Lewis Acid	solvent	% yield	β/α - Me-400	ref
H	Et	S	$Sn(OTf)_2$	THF	80	90/10 [a]	105
H	i-Pr	S	$Sn(OTf)_2$	THF	74	91/9	105
H	i-Pr	O	Et_2BOTf $ZnBr_2$	CH_2Cl_2	>95	>99/1	106
Me	Me	O	$Sn(OTf)_2$	CH_2Cl_2	79	24/1	107

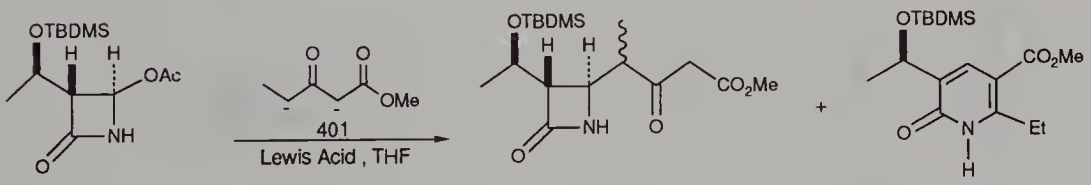
a. ratio of desired β-methyl isomer **400** to all others

Scheme 3.88



400 180

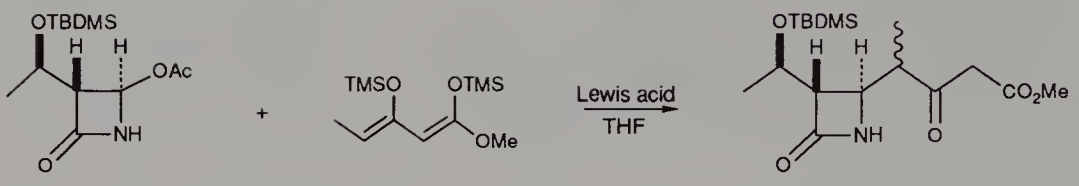
Scheme 3.89



67 402 403

Lewis acid	β/α - Me-402	% yield
-	77/23	38
$SnCl_2$	88/12	30
$ZnCl_2$	78/22	75
BBu_3	93/7	28

Scheme 3.90



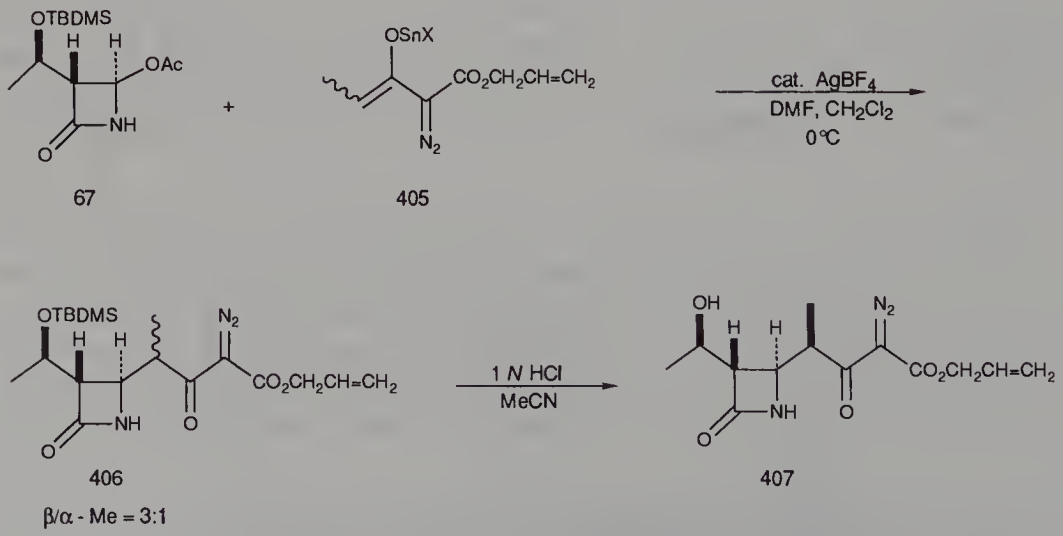
Lewis acid	β/α - Me-402	% yield
$SnCl_2$	69/31	70
$Sn(OTf)_2$	73/27	41
$ZnCl_2$	33/67	75 [a]
BBu_3	20/80	100

a. reaction run in CH_2Cl_2

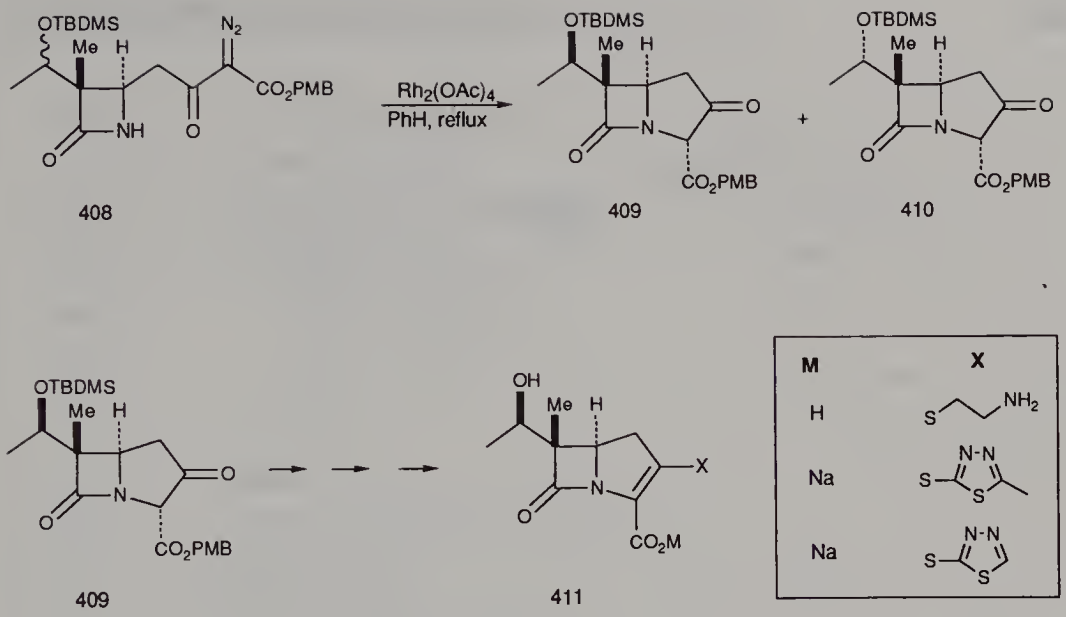
Scheme 3.91

(Scheme 3.93). Further manipulations of **409** afforded 6β-methylcarbapenems **411,** all of which were less potent in vitro than thienamycin.

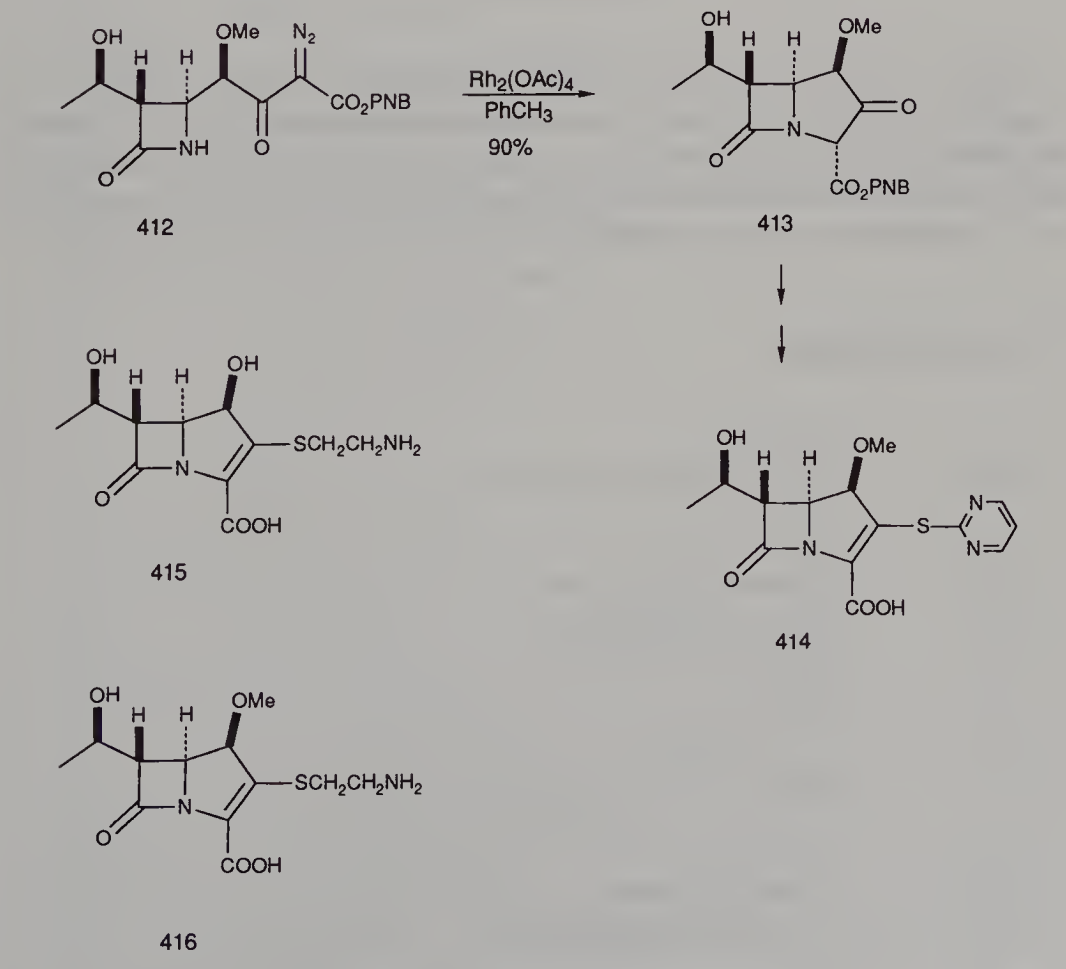
Nagao and co-workers[112] communicated an asymmetric synthesis of the 1β-methoxycarbapenem **414** (Scheme 3.94). Annulation of the C-4 tether of azetidinone **412** in toluene/EtOAc (1/1) with catalytic $Rh_2(OAc)_4$ yielded **413** (90%), which was then converted to **414.** Similar C-1 oxygenated carbapenems **415** and **416,** although retaining good DHP-I stability, showed diminished antibacterial activities relative to thienamycin.[113]



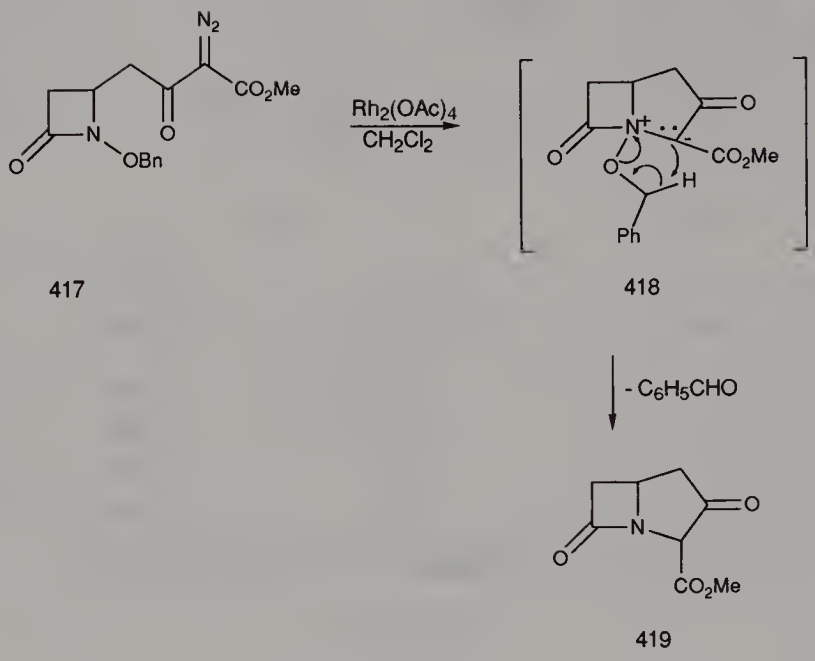
Scheme 3.92



Scheme 3.93



Scheme 3.94



417 418 419

Scheme 3.95

Finally, a novel synthesis of the carbapenem ring system through rearrangement of an *N*-benzyloxyazetidinone was recently reported by Williams and Miller.[114] The α-diazoester **417** on reaction with $Rh_2(OAc)_4$ (5 mole%) in CH_2Cl_2 gave 40% of **419** and benzaldehyde (Scheme 3.95). The conversion was hypothesized to proceed through fragmentation of intermediate **418.**

3.7 Abbreviations

Ac	Acetyl
AIBN	2,2′-Azobisisobutyronitrile
Ar	Aryl
BANT	Bisacenaphthalenethiophene
BHT	2,6-Di-*tert*-butyl-*p*-cresol
Bn	Benzyl
BnBr	Benzyl bromide
Bu	Butyl
Bu^t	*tert*-Butyl
Bu_3SnH	Tributyltin hydride
CTBI	1,1-Thiocarbonyldiimidazole
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DEAD	Diethyl azodicarboxylate
DHP-I	Dehydropeptidase I
DIAD	Diisopropyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMS	Dimethyl sulfide
Et	Ethyl
EtOAc	Ethyl acetate
HMPT	Hexamethylphosphoric triamide
HQ	Hydroquinone
KEH	Potassium ethylhexanoate
LDA	Lithium diisopropylamide
LiHMDS	Lithium hexamethyldisilylamide
Me	Methyl
Me_2SO	Dimethylsulfoxide
$MeSSO_2Me$	Methyl methanethiosulfonate
MoOPh	MoO_5·pyridine·HMPA
MSA	Methanesulfonic acid
NCCT	β-Naphthalenylcarbonochloridate
PCC	Pyridinium chlorochromate
PCl_5	Phosphorus pentachloride
PDC	Pyridinium dichromate
Ph	Phenyl
PhNCS	Phenyl isothiocyanate
Ph_3P	Triphenylphosphine
PMB	*p*-Methoxybenzyl
PNB	*p*-Nitrobenzyl
$Rh_2(OAc)_4$	Rhodium acetate
SEH	Sodium ethylhexanoate
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TEA	Triethylamine
TEAF	Tetraethylammonium fluoride

TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMS	Trimethylsilyl
TMSI	Trimethylsilyl iodide
TMSOTf	Trimethylsilyl triflate

3.8 Literature

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CHAPTER

4

β-Lactam Synthon Method: Enantiomerically Pure β-Lactams as Synthetic Intermediates

Iwao Ojima

Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794

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4.1 Introduction

In recent years, the β-lactam skeleton has been recognized as providing useful synthetic building blocks by exploiting its strain energy, in addition to its use in the synthesis of a variety of β-lactam antibiotics.[1–3] We have been exploring such new aspects of β-lactam chemistry using enantiomerically pure β-lactams as versatile intermediates for the synthesis of aromatic α-amino acids and their derivatives,[4] oligopeptides,[5–8] labeled peptides,[9] and azetidines which are further converted to polyamines, polyamino alcohols, and polyamino ethers.[10]

Based on the hydrogenolysis of chiral 4-aryl-β-lactam intermediates on palladium catalyst, we developed the first-generation β-*Lactam Synthon Method* for peptide synthesis and successfully applied it to the synthesis of potent enkephalin analogs.[11,12] We have been further developing the second-generation β-Lactam Synthon Method, which is based on a highly efficient asymmetric synthesis of β-lactams, dissolving metal reduction in addition to hydrogenolysis on palladium catalyst, and extremely stereoselective alkylations of β-lactam enolates as well as β-lactam ester enolates.[13–19] The second-generation β-Lactam Synthon Method provides newer and efficient routes to nonprotein amino acids and their derivatives, which serve as enzyme inhibitors as well as effective modifiers of biologically active peptides. Variations of the second-generation β-Lactam Synthon Method have brought about new aspects of this methodology including N—C(O) bond cleavage revisited, rearrangements, and further manipulations of substi-

tuents on the β-lactam skeleton, which furnish versatile chiral building blocks, reagents, and ligands in asymmetric synthesis.[20–22]

This chapter describes accounts of our research on the development of the β-Lactam Synthon Method, in which the unique nature of the β-lactam skeleton has been thoroughly exploited.

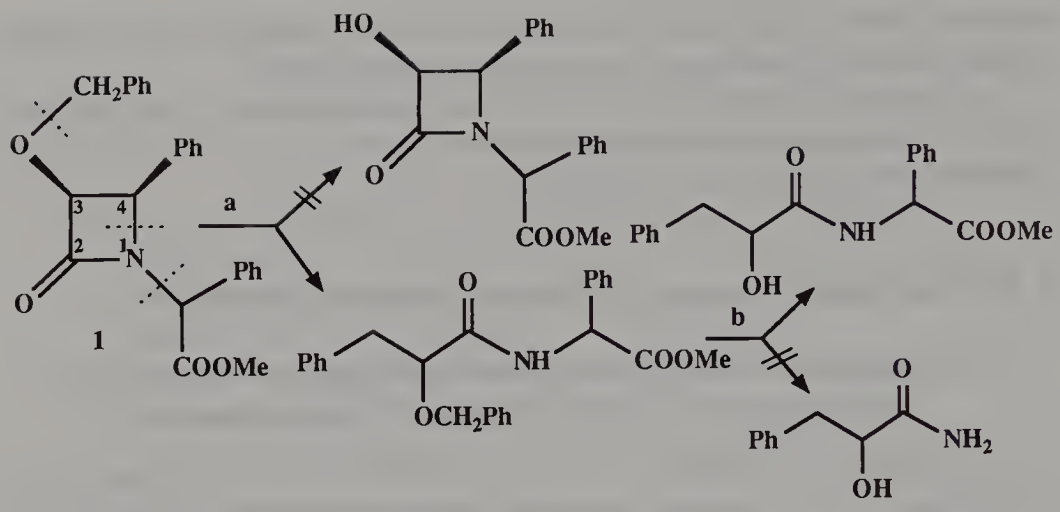
4.2 β-Lactam Synthon Method for Peptide Synthesis

4.2.1 Synthesis of α-Amino Acids, α-Hydroxy Acids, and Oligopeptides by the β-Lactam Synthon Method

The synthesis of β-lactams has been extensively studied for a long time in connection with the naturally occurring β-lactam antibiotics; however, only limited attention had been drawn to the use of β-lactam as a synthetic intermediate when we started development of the β-Lactam Synthon Method. It is well known that cleavage of the β-lactam ring takes place usually at the N—C(O) bond by nucleophilic reagents including water. For example, Wasserman et al. have developed a useful methodology using the cleavage of the N-C(O) bond for the synthesis of macrocyclic alkaloids.[3] Conceptually, however, other types of cleavages are also possible. Among these possibilities, we have found that cleavage of the N-C^4 bond proceeds exclusively in a palladium-catalyzed hydrogenolysis (e.g., ambient pressure of hydrogen at 50°C in methanol) when an aryl substituent is attached to the C^4 position.[4] As 3-azido- and 3-benzyloxy-4-arylazetidin-2-ones can easily be synthesized by the [2+2] cycloaddition of azidoketene and benzylketene to imines, respectively, this type of cleavage can serve as a useful synthetic route to the amides of α-amino acids and α-hydroxy acids.[4] In the same manner, dipeptides are obtained when the imines of α-amino esters are employed.[5,6]

It should be noted that the observed facile reductive N—C^4 bond cleavage is ascribed to the strain energy of the β-lactam skeleton. For instance, the β-lactam (**1**) shown in Scheme 4.1 has three bonds to be cleaved by the palladium-catalyzed hydrogenolysis. It is well known that cleavage of the benzyl–oxygen bond is by far faster than that of the benzyl–nitrogen bond; in particular, the benzyl–nitrogen bond in *N*-benzylamides can hardly be cleaved under ordinary conditions.[23] It is therefore reasonable to anticipate that cleavage of the benzyl–oxygen bond is the only reaction observed. To our surprise, however, the cleavage of the β-lactam ring was much faster than that of the benzyl–oxygen bond; the other benzyl–nitrogen bond remains intact as expected, as shown in Scheme 4.1. The result clearly indicates that the ring strain of the β-lactam greatly accelerates the cleavage.[5]

This finding led us to develop the first-generation β-Lactam Synthon Method for the synthesis of aromatic α-amino acids, aromatic α-hydroxy acids, and their peptides. The formation of peptide bonds has been extensively studied because of its significance as a unit reaction of peptide syn-

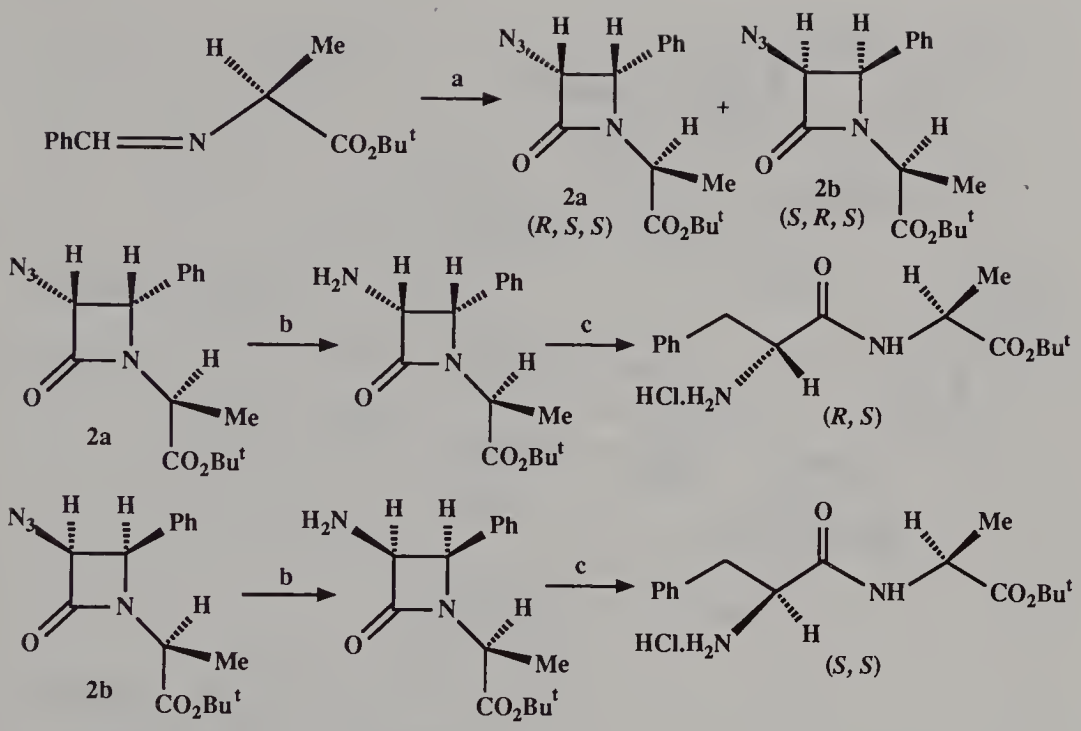


a: H_2 (1 atm), 10% Pd-C, MeOH, room temperature, 12 h.
b: H_2 (1 atm), 10% Pd-C, MeOH, 50 °C, 48 h.

Scheme 4.1

thesis. The standard methods of amide linkage formation essentially include dehydration from two amino acids, for example, by means of dicyclohexylcarbodiimide (DCC), activated ester, enzyme, or other dehydrating agents. Accordingly, it is important to develop synthetic methods for peptides without using the conventional dehydrating process, which would complement the standard methods. Along this line, we have developed a highly efficient method for the synthesis of peptide building blocks using asymmetric hydrogenation of dehydropeptides catalyzed by chiral rhodium complexes.[24] The β-Lactam Synthon Method would provide another route to peptide building blocks with excellent optical purity.

As the dipeptide is the most fundamental unit in peptides, the syntheses of optically pure Ac-*(S)*-Phe–*(S)*-Ala-OBu^t and Ac-*(R)*-Phe–*(S)*-Ala-OBu^t are described (Scheme 4.2) as typical examples.[8] 3-Azido-4-phenyl-β-lactam (**2**,*cis*) was obtained in 80–85% yield by the reaction of t-butyl-*N*-benzylidene-(**S**)-alaninate with azidoketene. Because the β-lactam ester *(2)* was obtained as a ca. 1:1 mixture of two diastereomers, the mixture was submitted to flash chromatography or medium-pressure liquid chromatography (MPLC) on silica gel using *n*-hexane/AcOEt as eluant to give pure **2a** and **2b** in virtually quantitative recovery yield. Then, each separated β-lactam was converted to the corresponding dipeptide (>99.5% d.e. by HPLC). At this stage, it turned out that **2a** gave Ac-*(R)*-Phe–*(S)*-Ala-OBu^t and **2b**, the *(S,S)*-isomer. Consequently, optically pure β-lactams derived from the imines of α-amino esters were proven to be the synthetic equivalents of dipeptides. It is confirmed that no racemization takes place during the reductive cleavage. Once these dipeptide synthon fragments are obtained, oligopeptide synthons



a: N_3CH_2COCl, Et_3N, CH_2Cl_2, -78 °C - room temperature.
b: H_2 (1 atm), 10% Pd-C, MeOH, room temperature.
c: H_2 (1 atm), 10% Pd-C, MeOH, HCl (1 eq.), 50 °C.

Scheme 4.2

can easily be synthesized through combinations of them as exemplified in Chart 4.1. Although Chart 4.1. exhibits only mono- and bis-β-lactam combinations, we have synthesized up to tetra-β-lactams,[2,11] and poly-β-lactams can also be obtained by using solid-phase synthesis.

A striking feature of these oligopeptide synthons is that they are highly soluble in regular organic solvents such as ether, ethyl acetate, and chloroform; even octa- and nonapeptide synthons are readily soluble in chloroform. Thus, these compounds can be chromatographed on an ordinary silica gel column in conventional fashion unlike other standard peptide precursors. These characteristics should provide a unique advantage in certain peptide syntheses in which a low solubility of the peptide precursors hampers smooth reactions or scaleup.

We applied this first-generation β-Lactam Synthon Method to the synthesis of a potent analog of enkephalin (**8**), which is an opioid peptide in the brain (Scheme 4.3).[12] As Scheme 4.3 illustrates, the coupling of Tyr–*(R)*–Ala synthon (**4**) and Gly–Phe–Leu-ol synthon (**6**) by using DCC and 1-hydroxybenzotriazole (HOBT) gave the bis-β-lactam (**7**), which is the direct precursor of **8**, in 84% yield after purification on silica gel column (eluant =

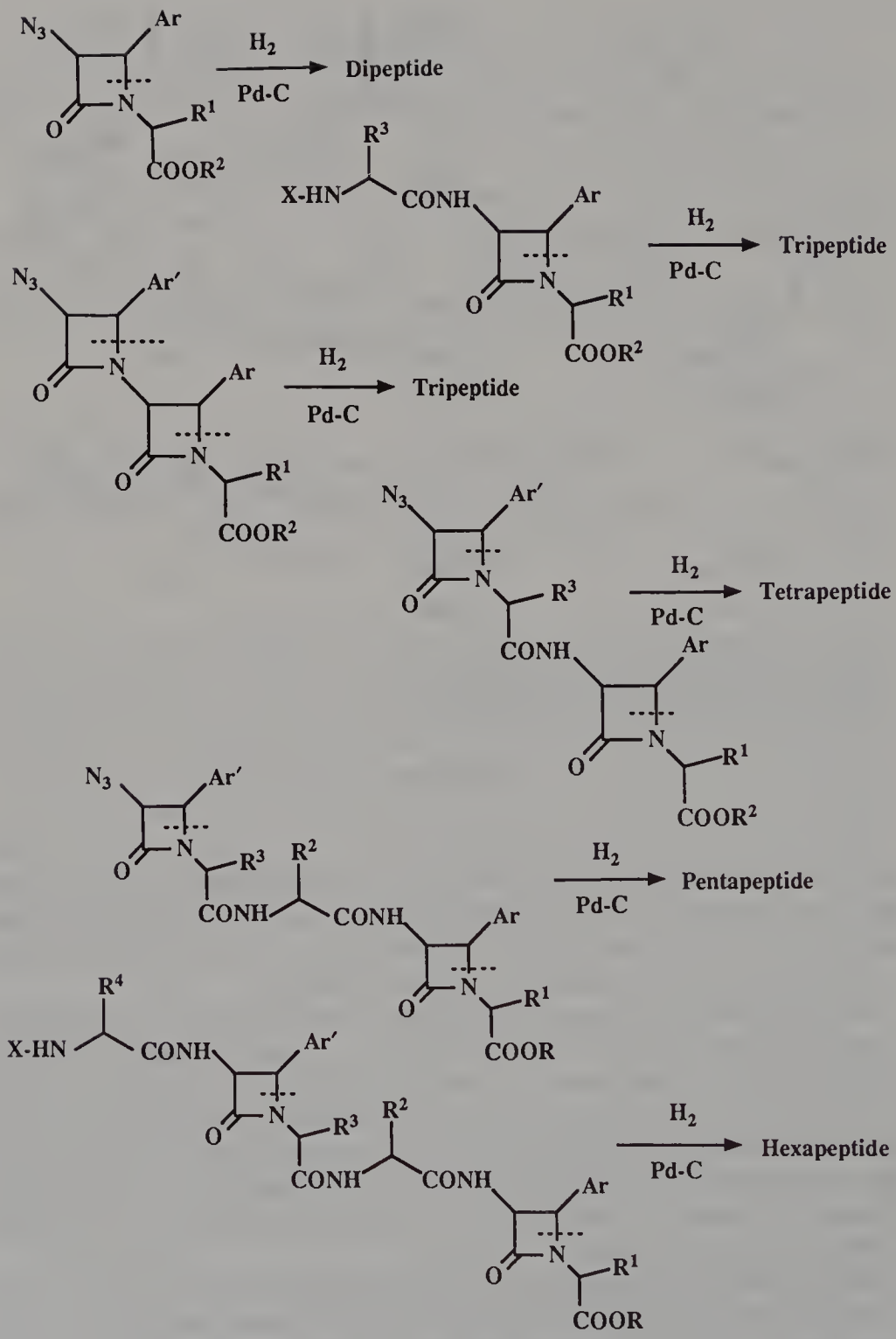
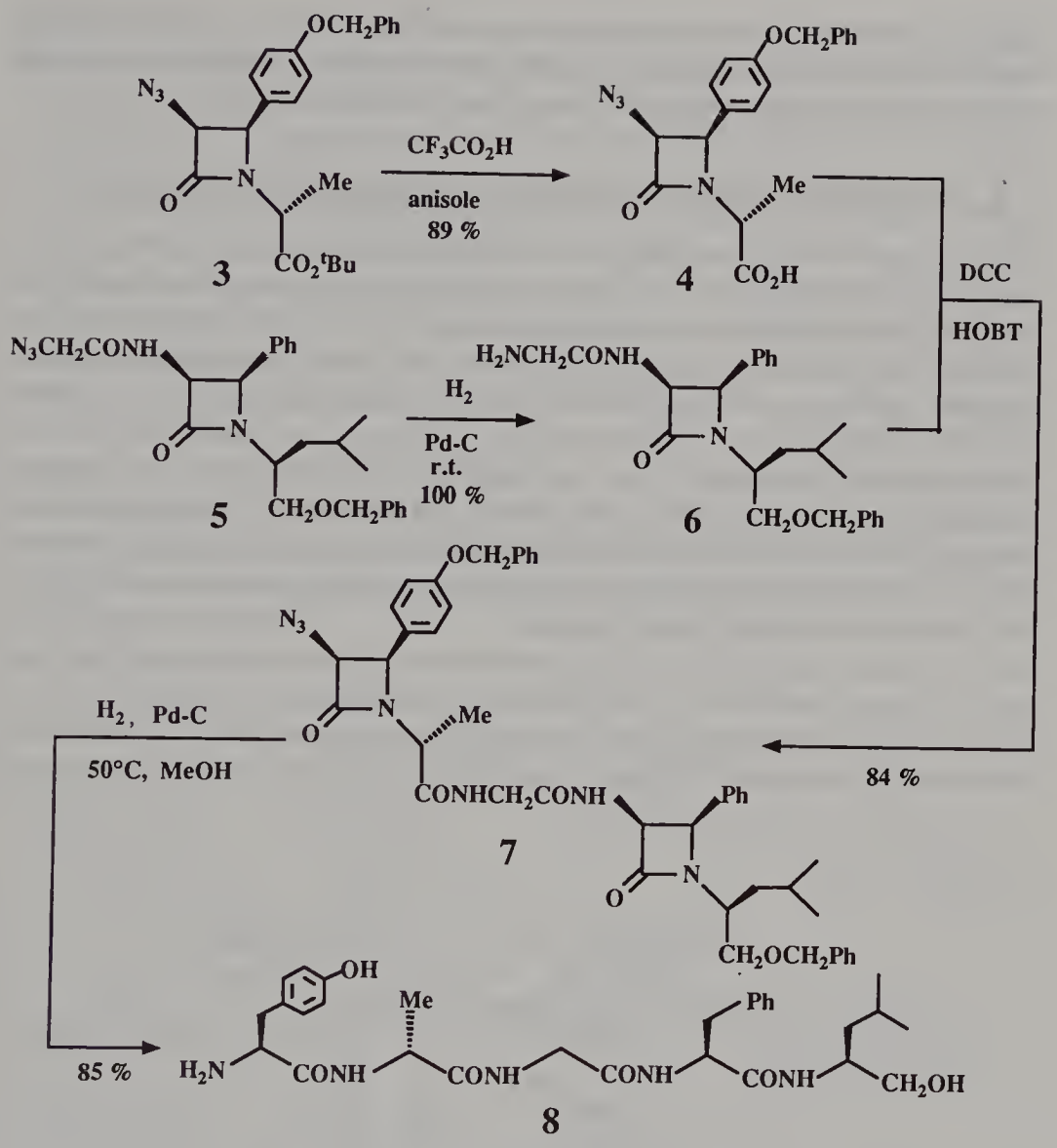


Chart 4.1. Synthesis of oligopeptides via β-lactams.



Scheme 4.3

AcOEt). Then, the pentapeptide synthon (**7**) was submitted to hydrogenolysis on 10% Pd—C in methanol at 50°C to give **8** in 85% yield through the reductive cleavage of two β-lactam rings, deprotection of two hydroxy groups, and reduction of the azide group all at once.

It is noteworthy that the β-lactam ring of **4** acts not only as a tyrosine synthon, but also as an excellent protecting group of *(R)*-alanine. According to the widely accepted mechanism of racemization during peptide coupling, the formation of oxazolone involving an acylamino proton or an alkoxycarbonylamino proton is crucial,[25] which is more or less inevitable as far as ordinary protecting groups are employed. In the Tyr–*(R)*-Ala synthon (**4**), however, the two amino protons of *(R)*-alanine are protected by the β-lactam

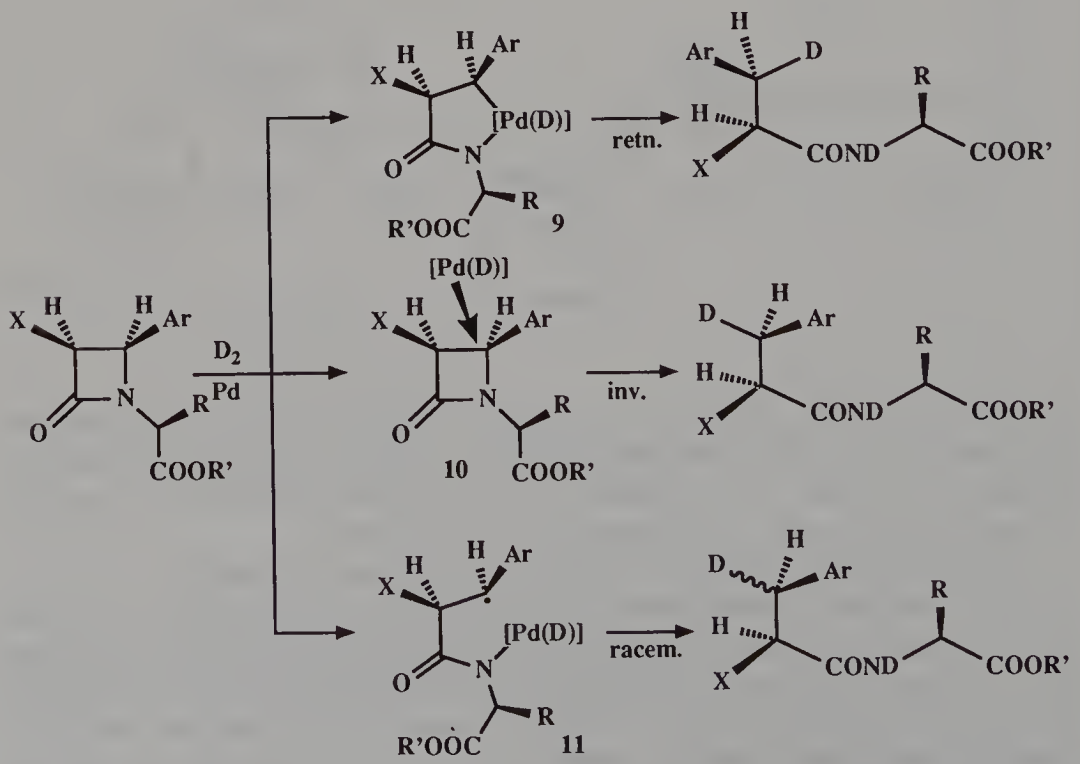
ring; racemization at the chiral center cannot take place via oxazolone formation. In fact, no racemization is detected during the coupling of **4** and **6.** This is another advantageous feature of the β-Lactam Synthon Method.

4.2.2 Efficient Route to Labeled Optically Pure Peptides

As described in the preceding section, it was found that no racemization took place at the original C-3 position of optically pure 4-aryl-β-lactams during the hydrogenolysis on palladium catalyst (Pd—C or Pd black)[5,7,11,12]; however, the stereochemistry of the cleavage of the N—C^4 bond was not yet studied. Therefore, we closely investigated the stereochemical course of the reductive cleavage.[9]

Conceptually, there are three possibilities (Scheme 4.4): (1) retention of configuration via a palladometallacycle (**9**), (2) inversion of configuration via an S_N2-type mechanism (**10**), and (3) racemization via a free radical mechanism (**11**). To look at the stereochemistry, D_2 was employed so that the products would have a chiral benzyl group.

First, a pair of optically pure diastereomeric β-lactams, **12a** and **12b,** were used as typical substrates. Compound **12** in methanol-d_1 was added to a reaction flask containing 5% Pd—C, which was equipped with a standard hydrogenation/hydrogenolysis apparatus filled with an atmospheric pressure of



Scheme 4.4

D_2. The reaction mixture was stirred for 24 hours at room temperature. The disappearance of **12** and the formation of a dipeptide derivative (**13**) were monitored by TLC. A simple filtration of the catalyst and evaporation of the solvent gave **13** in quantitative yield. In a similar manner, the usual hydrogenolysis of **12a** and **12b** was carried out for the purpose of comparison. The reaction proceeded with virtually complete stereoselectivity (by ^1H NMR) and one of the two benzylic hydrogens that appeared at a lower field and had a smaller coupling constant (**13a:** δ 3.296, J = 3.8 Hz; **13b:** δ 3.300, J = 3.5 Hz) disappeared through the reductive cleavage with D_2 in both cases.

We also employed two sets of enantiomerically pure diastereomeric β-lactams, **14a/14b 14a–d/14b–d,** which are the precursors of monodeuterated Ac-Phe–Ala-OBu^t: **14a** and **14b,** a pair of enantiomerically pure diastereomers, were reductively cleaved with D_2 to give **15a-D** and **15b-D,** respectively, whereas the monodeuterated pair, **14a–d** and **14b–d,** was cleaved with H_2 under the same reaction conditions to give **15a–d-H** and **15b–d-H,** respectively. All reactions gave the corresponding dipeptides with virtually complete stereoselectivity.[9]

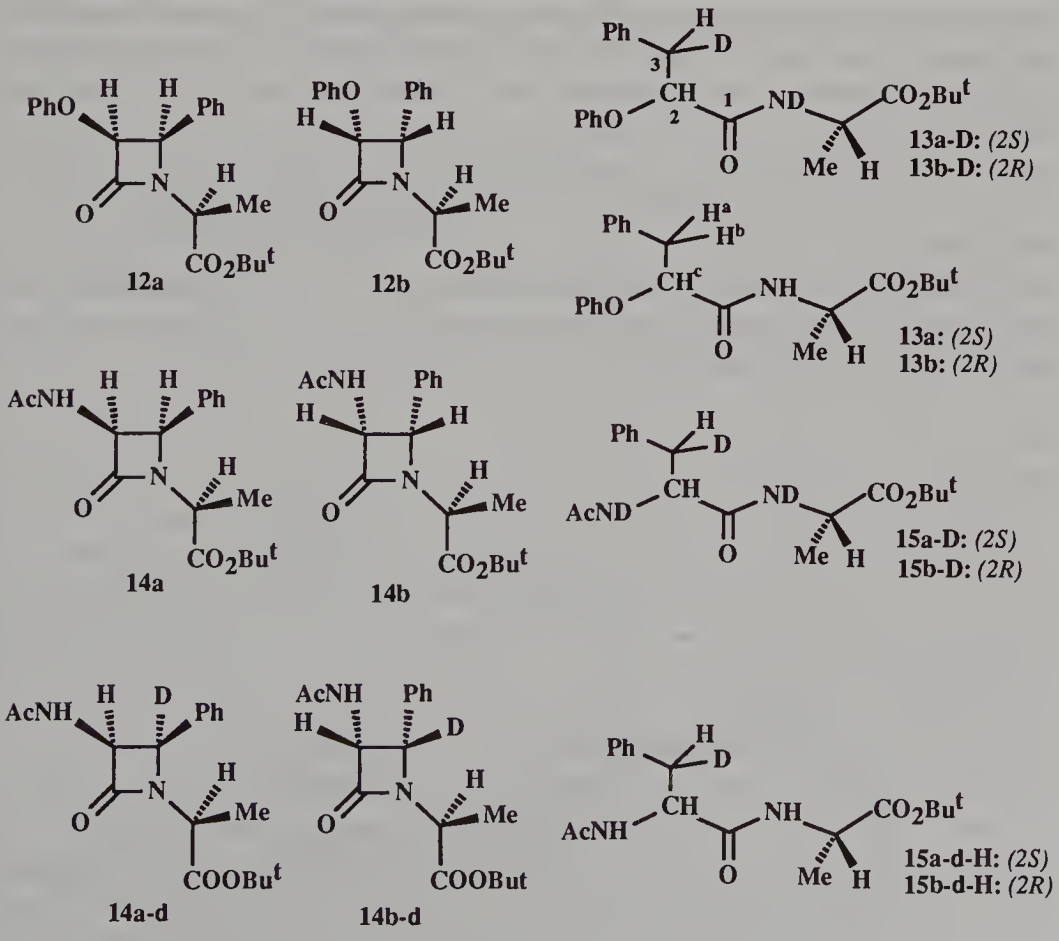
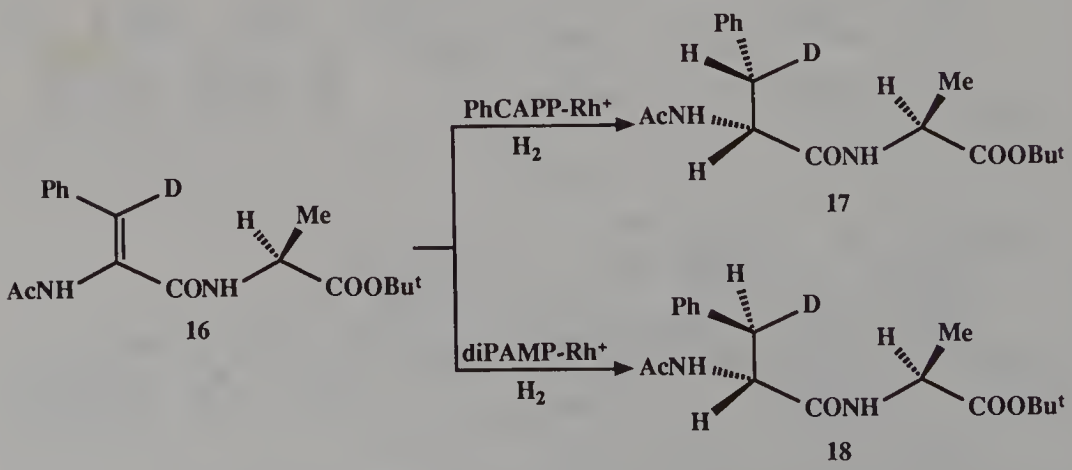


Chart 4.2. Optically pure β-lactams and labeled dipeptides therefrom.

Elucidation of the absolute configurations of the monodeuterated dipeptides obtained was not a straightforward task; neutron diffraction might be the only physical analysis method as conventional X-ray diffraction could hardly distinguish deuterium from hydrogen; however, we were fortunate to find a convenient and solid way to elucidate the stereochemistry based on ^{1}H NMR spectroscopy using authentic samples prepared by asymmetric hydrogenation of *(Z)*-Ac-dehydro-Phe(3-*d*)–*(S)*-Ala-OBu^t **(16).** The stereochemical course of the asymmetric hydrogenation of dehydro-α-amino acids and dehydropeptides has been unambiguously established.[24,26] Thus, **(16)** was subjected to asymmetric hydrogenation with the use of PhCAPP-Rh$^+$ and diPAMP-Rh$^+$ as catalysts at 40°C and 10 atm of H_2 for 22 hours following a well-established procedure.[24] The reactions proceeded in quantitative yields, and after recrystallization from AcOEt/*n*-hexane, **17** and **18,** Ac-(2*R*,3*S*)-Phe(3-*d*)–*(S)*-Ala-OBu^t and Ac-(2*S*,3*R*)-Phe(3-*d*)–*(S)*-Ala-OBu^t, respectively, were obtained optically pure (Scheme 4.5).

Comparison of the ^{1}H NMR data unambiguously indicates that **17** coincides with **15b–d-H** as **18** does with **15a–d-H.** Consequently, it is established that the stereochemical course of the reductive cleavage is essentially complete inversion of configuration! This result was surprising for us as our initial prediction was retention of configuration through a metallacycle **(9)** based on the well-known fact that low-valent metal species can insert into strained molecules to form metallacycles.[27] Although it has been shown that the hydrogenolysis of chiral benzylamines over palladium catalysts tends to proceed with inversion of configuration,[28] the stereoselectivity is not necessarily high and sometimes racemization[29] and even retention of configuration[30] are observed; the rationalization for those results is still controversial.[28–31] The present results provide the first clear evidence for the stereochemical course (complete inversion) of the hydrogenolysis of strained chiral benzyl–amide bonds over palladium catalysts.[9]

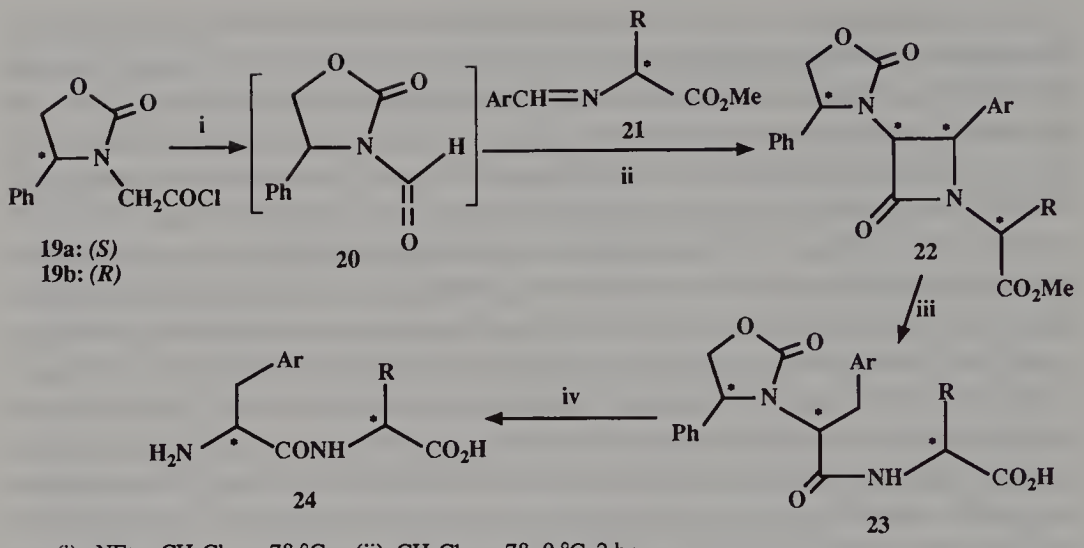


Scheme 4.5

The significance of the findings described in this section is not only the elucidation of the stereochemistry of the reaction but also its application to the synthesis of deuterium- or tritium-labeled optically pure peptides, as regiospecific and stereoselective labeling of C^3 positions of α-amino acid residues is extremely difficult based on conventional organic transformations.[32] The C^3-labeled optically pure peptides will play an important role (1) for the study of metabolism, as C^3 labeling does not disappear through racemization (C^2 labeling will be lost by racemization; (2) for the conformational analysis of physiologically active peptides in their binding sites by NMR spectroscopy; and (3) for the mechanistic study of oxygenases which may produce phenylserine derivatives, as such oxidation by enzymes will proceed stereoselectively distinguishing two diastereotopic benzyl protons. Although we demonstrated the usefulness of our stereoselective as well as regio- and stereospecific labeling method only with deuterium, its extension to tritium labeling is straightforward. In fact, diastereoselective synthesis of C^3-tritiated dipeptides was successfully carried out following the aforementioned procedure with the use of T_2 instead of D_2 and THF instead of methanol-d_1.[33] At present the applicability of this method is restricted to the labeling of aromatic amino acid residues such as phenylalanine, tyrosine, tryptophan, histidine, and dopa. Nevertheless, its usefulness is obvious as there are so many physiologically important peptides that include aromatic amino acid residues.

4.2.3 Asymmetric Synthesis of Optically Pure Dipeptide Synthons

The first-generation β-Lactam Synthon Method has demonstrated its uniqueness and high potential as a new synthetic method as described in the previous sections; however, the first-generation β-Lactam Synthon Method is based on enantiomerically pure diastereomeric β-lactams which are obtained through chromatographic separations of two diasteromers, as only cycloadditions of *achiral* ketenes such as azidoketene, phenoxyketene, and benzyloxyketene to chiral imines were employed. In 1984–1985 it was reported that the asymmetric cycloaddition of chiral ketenes to achiral imines yielded chiral β-lactams with good to excellent stereoselectivity by Ikota and Hanaki[34] and Evans and Sjogren.[35] Those reports inspired us to examine the applicability of those chiral ketenes to the reaction with chiral imines in which it is necessary to take into account both favorable and unfavorable double asymmetric inductions. If the asymmetric cycloaddition can achieve excellent stereoselectivity regardless of the chiral centers in imines, the process would provide an extremely effective route to the direct precursors of optically pure dipeptides with desired configurations. Actually, this approach was successful[13,17] and thus opened a new avenue for the β-Lactam Synthon Method. This section describes a newer and more effective asymmetric synthesis of dipeptides through optically pure β-lactams as a basic



(i) NEt_3, CH_2Cl_2, −78 °C; (ii) CH_2Cl_2, −78~0 °C, 2 h;
(iii) a) H_2, Pd / C, MeOH, 50°C, 5 h, b) 1 N NaOH / THF, r.t., 1 h, c) H_3O^+;
(iv) Li / NH_3 / ^tBuOH, −78 °C, 15 min.

Scheme 4.6

(Reprinted, with the permission of Pergamon PLC, from Ojima et al.[17])

methodology for developing the "second-generation" β-Lactam Synthon Method.

First, we examined the effectiveness of asymmetric induction of the chiral ketene (**20**) generated in situ from enantiomerically pure 4-phenyloxazolidinylacetyl chloride (**19a:** *S*, **19b:** *R*) in the [2+2] cycloaddition to chiral imines (**21**) derived from esters of alanine, valine, phenylalanine, and methionine (Scheme 4.6). Results are summarized in Table 4.1. As Table 4.1 shows, we were very fortunate to find that the chiral centers in the imines (**21**) do not have any significant influence on the asymmetric induction and no appreciable double asymmetric induction is observed; that is, only the chiral

Table 4.1. ASYMMETRIC [2+2] CYCLOADDITIONS OF CHIRAL KETENES (**20**) TO CHIRAL IMINES (**21**).

		Imine (21)		β-Lactam (22)		
Entry	Ketene	Ar	R	Yield(%)	Config.	%d.e.[a]
a	**20a**	Ph	Me (*R*)	82	(*3S,4R*)	>99
b	**20a**	Ph	Me (*S*)	76	(*3S,4R*)	>99
c	**20b**	Ph	^{i}Pr(*S*)	92	(*3R,4S*)	>99
d	**20b**	Ph	^{i}Pr(*R*)	86	(*3R,4S*)	>99
e	**20b**	Ph	$PhCH_2$(*S*)	91	(*3R,4S*)	>99
f	**20b**	Ph	$MeS(CH_2)_2$(*S*)	79	(*3R,4S*)	>99

[a] Determined by HPLC analysis

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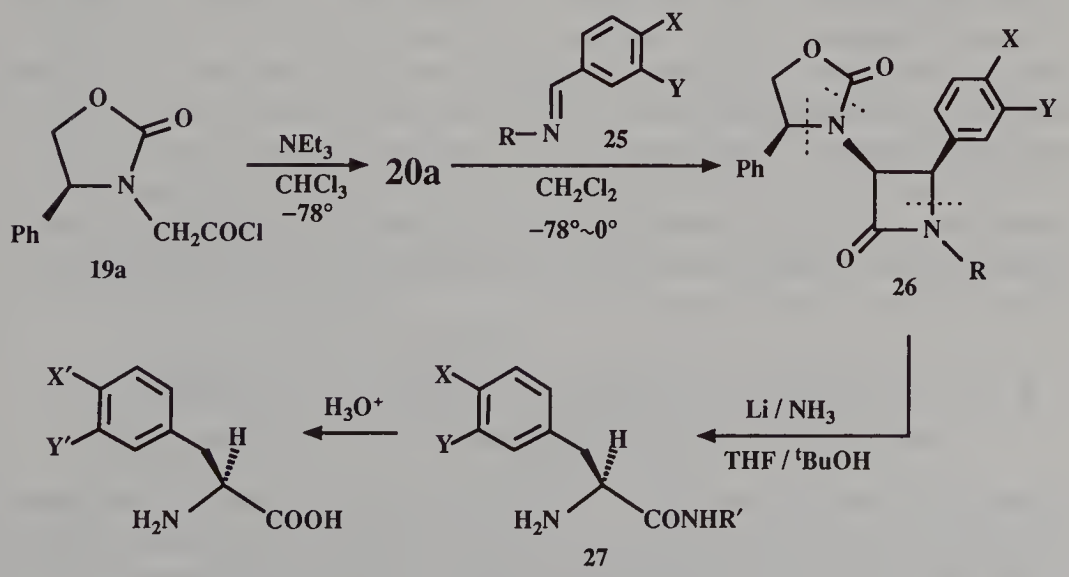
center in the ketene (**20**) plays a key role in this symmetric synthesis. In each case, the reaction gave only one of the two possible diastereomers: In spite of extensive search by HPLC and ^{1}H NMR spectroscopy, the other diastereomer of **22** was not detected in any case examined.

The β-lactams (**22**) thus obtained were saponified and then converted to the corresponding N-protected dipeptides (**23**) quantitatively through hydrogenolysis over Pd-C in MeOH: The N-protected dipeptides (**23**) can be used for fragment condensation with other N-terminus-free peptide units. The modified Birch reduction[17,35] of **23** with lithium in liquid NH_3/THF/t-BuOH gave the corresponding optically pure dipeptides (**24**) in excellent yields (Scheme 4.6).[17]

The simple asymmetric synthesis of enantiomerically pure α-amino acids is achieved by asymmetric [2+2] cycloaddition followed by reductive cleavage as well. For example, the amides of phenylalanine (**27a:** X=Y=H, R′=Me) and *O,O*-dimethyldopa (**27b:** X=Y=MeO, R′=H) with greater than 99.5% e.e. were synthesized via β-lactams, **26a** (X=Y=H, R=Me) and **26b** (X=Y=MeO, R=$PhCH_2$), which were obtained through asymmetric [2+2] cycloadditions of the chiral ketene (**20**) to imines, **25a** and **25b,** respectively, in high yields (Scheme 4.7).[17]

The asymmetric cycloaddition–reductive cleavage process will open an effective route to optically pure peptides, as it is demonstrated that the desirable absolute configurations can be introduced to the chiral β-lactams **22** regardless of the chiral centers in the imines and no racemization is observed during the modified Birch reduction. This newer method, that is, the second-generation β-Lactam Synthon Method, is particularly useful for the introduction of unnatural amino acid residues with desired absolute configura-



Scheme 4.7

(Reprinted, with the permission of Pergamon PLC, from Ojima et al.[17])

tions into physiologically active peptides and enzyme inhibitors (see later text).

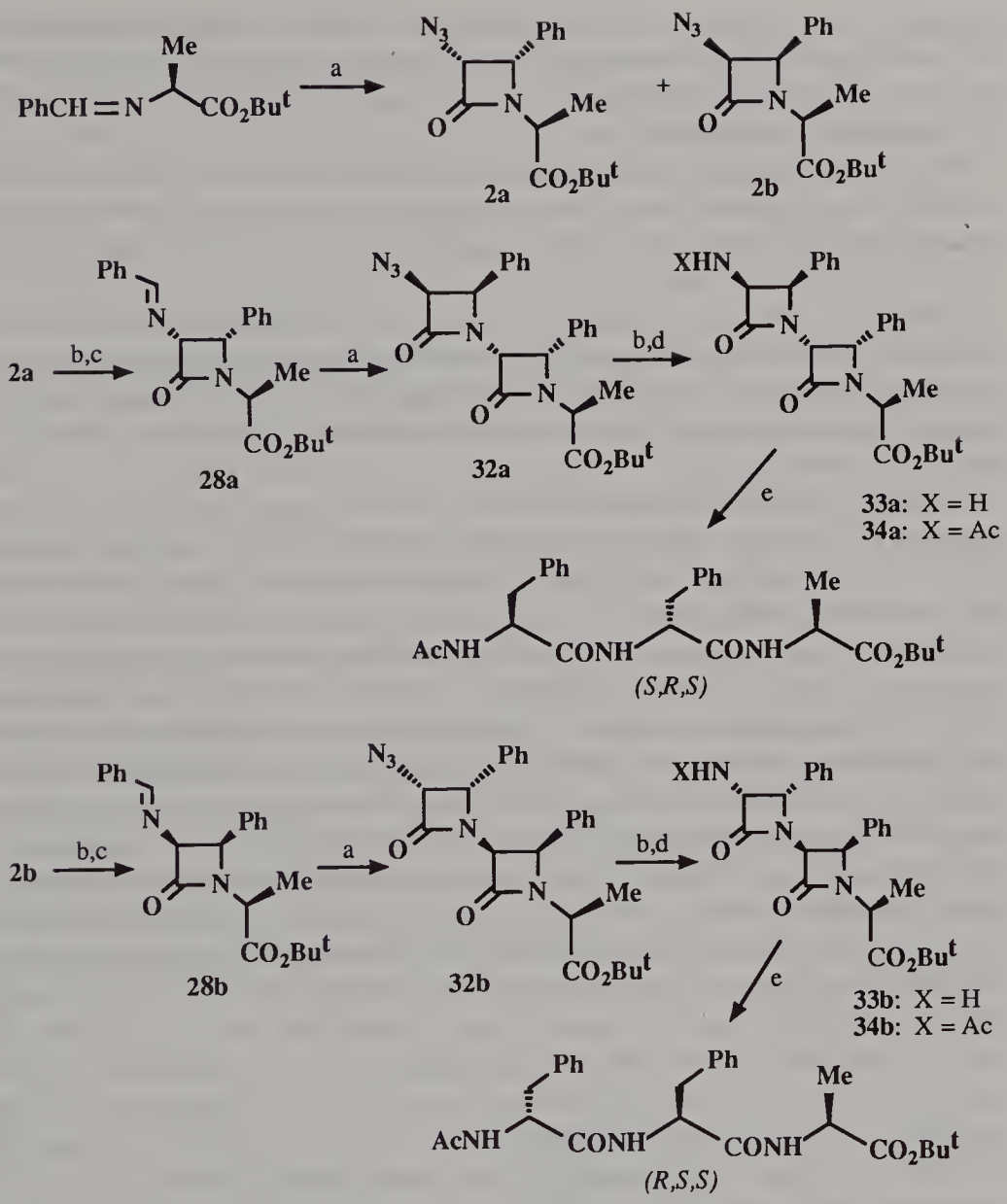
4.3 Application of the β-Lactam Synthon Method to a Mechanistic Study on [2+2] Cycloadditions

Besides its significance as a synthetic method, the β-Lactam Synthon Method provides a convenient and useful protocol for rapid elucidation of the absolute configurations of β-lactams obtained through asymmetric synthesis. This section describes such an application of the β-Lactam Synthon Method to the mechanistic study of the extremely stereoselective [2+2] cycloaddition of azidoketene to 3-imino-β-lactams.

The [2+2] cycloaddition of ketene species to imines serves as one of the most convenient methods for the synthesis of the β-lactam skeleton, and thus the reaction has been used for a variety of β-lactam antibiotic syntheses.[36] In the course of our study on the use of enantiomerically pure β-lactams as key intermediates of oligopeptide syntheses (see earlier text), we found that the [2+2] cycloaddition of azidoketene to a benzylideneamine bearing a β-lactam backbone (**28a,28b**) proceeded with extremely high stereoselectivity to give an optically pure bis-β-lactam.[7] Although the synthetic importance of the reaction was obvious, we could not rationalize such high stereoselectivity at all based on the usual stereochemical considerations using Dreiding models and CPK models; that is, the conformation of the imine and the approach of the ketene seemed to have so much freedom that any predictions seemed arbitrary. Accordingly, we planned to clarify the crucial factors that governed the stereochemical course of this unique asymmetric [2+2] cycloaddition by using a series of enantiomerically pure *cis*-3-imino-β-lactam (**29**), *trans*-3-imino-β-lactam (**30**), and *cis*-3-iminoazetidine (**31**) as substrates and found unexpectedly strong lone pair–lone pair interactions (dipole–dipole interaction and/or electrostatic interaction) which controlled the stereochemistry of the reaction. This section discusses remarkable effects of β-lactam carbonyl lone pairs as a crucial factor for extremely stereoselective [2+2] cycloadditions.[7] In this study, the β-Lactam Synthon Method plays an important role in determining the absolute configurations of newly formed β-lactam moieties.

4.3.1 Observation of Extremely High Stereoselectivities in the Bis-β-lactam Syntheses via [2+2] Cycloaddition

t-Butyl *(S)-N*-benzylidenealaninate was treated with azidoketene generated in situ from azidoacetyl chloride in the presence of triethylamine in dichloromethane to give a diastereoisomeric mixture of the *cis*-β-lactams, **2a** and **2b**, which were readily separated by column chromatography on silica gel (80% yield, **2a**/**2b** = 51/49). The azide moiety in **2a** or **2b** was converted into



a: N_3CH_2COCl, Et_3N, CH_2Cl_2, -78 °C-r.t.
b: H_2 (1 atm), 5% Pd-C, MeOH, 0-5 °C
c: PhCHO, Na_2SO_4, CH_2Cl_2
d: Ac_2O, *N*-Methylmorpholine, $CHCl_3$
e: H_2 (1atm), 10% Pd-C, EtOH, 50 °C

Scheme 4.8

an amino group under 1 atm of hydrogen on 5% Pd—C in methanol at 0–5°C, and the 3-amino-β-lactams produced were condensed with benzaldehyde to give the 3-benzylideneamino-β-lactams **28a** [(3*R*,4*S*), 96%] and **28b** [(3*S*,4*R*), 96%], respectively.

Each 3-benzylideneamino-β-lactam (**28**) was converted into the corresponding bis-β-lactam **32a** or **32b** by cycloaddition with azidoketene; **32a** was obtained from **28a** in 48% yield, and **32b** from **28b** in 74% yield (Scheme 4.8).

In these cycloadditions, only one of the two possible stereoisomers was formed in each case, and none of the other isomer was found in the reaction mixture in spite of the extensive chromatographic search. The relatively low yield of **32a** is due mainly to the low conversion of the reaction; that is, the reaction itself was clean.

The newly formed β-lactam ring was proven to have a *cis* relationship between the 3′-azide and 4′-phenyl groups based on the coupling constants ($J_{3'-4'}$ = 5–5.5 Hz) in the ^{1}H NMR spectra of **32a** and **32b;** however, the absolute configurations of the newly formed β-lactam rings in **32a** and **32b** remained to be determined. To solve this problem, we employed the β-Lactam Synthon Method; that is, bis-β-lactams thus obtained were converted to the corresponding tripeptides by reductive cleavage of the β-lactam rings, and absolute configurations of the bis-β-lactams were unambiguously determined by comparing the tripeptides derived therefrom with authentic samples. Thus, the azide moiety in **32a** or **32b** was reduced to an amino group and then acetylated to give *N*-acetyl-bis-β-lactam, **34a** (80%) or **34b** (85%). Reductive cleavage of the *N*-acetyl-bis-β-lactam, **34a** or **34b,** with hydrogen (1 atm) on 5% Pd—C at 50°C gave the corresponding tripeptides. All four of the possible tripeptides, Ac-*(S)*-Phe–*(S)*-Phe–*(S)*-Ala-OBu^t, Ac-*(R)*-Phe–*(S)*-Phe–*(S)*-Ala-OBu^t, Ac-*(S)*-Phe–*(R)*-Phe–*(S)*-Ala-OBu^t, and Ac-*(R)*-Phe–*(R)*-Phe–*(S)*-Ala-OBu^t, were prepared independently by conventional peptide synthesis and compared with the tripeptides from bis-β-lactams by ^{1}H NMR and HPLC analysis. It was found that Ac-*(S)*-Phe–*(R)*-Phe–*(S)*-Ala-OBu^t was obtained from **34a** in 92% yield, and Ac-*(R)*-Phe–*(S)*-Phe–*(S)*-Ala-OBu^t from **34b** in 93% yield. Consequently, the stereochemistry of **32a** was determined to be (3′*S*,4′*R*,3*R*,4*S*), and that of **32b** (3′*R*,4′*S*, 3*S*,4*R*). In both cases the newly formed β-lactam ring had a configuration opposite to that of the parent (Scheme 4.8). The results indicate that the chiral ester moiety attached to the β-lactam nitrogen does not have any significant effects on the asymmetric induction although it affects the reactivity to some extent; **28b** is more reactive than **28a** judging from the yields of **32a** and **32b.**

4.3.2 Asymmetric [2+2] Cycloaddition of Azidoketene to *cis*- and *trans*-Imino-β-lactams (29,30) and *cis*-Iminoazetidine (31)

To investigate the stereochemical course of the asymmetric [2+2] cycloaddition of azidoketene to 3-imino-β-lactams in detail, we prepared *cis*-3-

imino-β-lactams (**29a,29b**) and *trans*-3-imino-β-lactam (**30**) as substrates that have the same substituents on N^1, C^3, and C^4 positions. Fortunately, the *cis*-3-imino-β-lactam (**29a**) gave a good single crystal, and thus X-ray analysis of the crystal was carried out. The crystal structure of **29a** is depicted in Figure 4.1, which clearly shows the *trans* and coplanar structure of the benzylideneamino moiety.

The conformational analysis based on MM2 calculations implies that the 4-phenyl moiety in **29** may have a considerable influence on the stereoselection because the phenyl group in the *cis* position is close to the 3-imino moiety: The minimum energy conformer of **29a** using the Model-MM2-Rotochem program[37] is shown in Figure 4.2. In the *trans* isomer (**30**) however, the 4-phenyl group does not seem to have any appreciable influence on the conformation of the imino moiety with regard to the approach of azidoketene: The MM2 calculations for **30** give the energy minimum conformation as shown in Figure 4.3. Therefore, it was reasonable to assume that the reaction of **29a** would be highly stereoselective, whereas the reaction of **30** would proceed with a low stereoselectivity and even the inversion of the preferred configuration could be expected.

The *cis*-3-imino-β-lactam (**29a**) was prepared from (3*R*,4*S*)-3-azido-4-phenyl-β-lactam (**35a**) by selective reduction of the azide group with 5% Pd—C and H_2 (100%) followed by condensation with benzaldehyde (100%). The enantiomerically pure β-lactam (**35a**) was prepared through the [2+2] cycloaddition of azidoketene with *N*-benzylideneleucinol benzyl ether and subsequent separation of diastereomers (**35a,35b**) on a silica gel column. The *trans*-3-imino-β-lactam (**30**) was prepared by isomerization of **15a** with LDA (1.0 equivalent) in THF at −78°C followed by purification on a silica gel column (90%). The *cis*-3-iminoazetidine (**31**) was prepared through $AlClH_2$

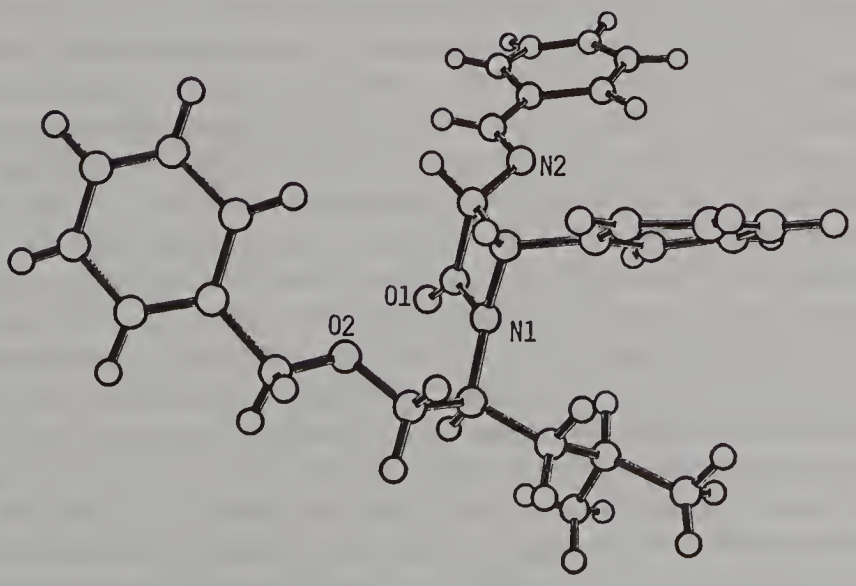


Figure 4.1. X-ray crystal structure of **29a**.

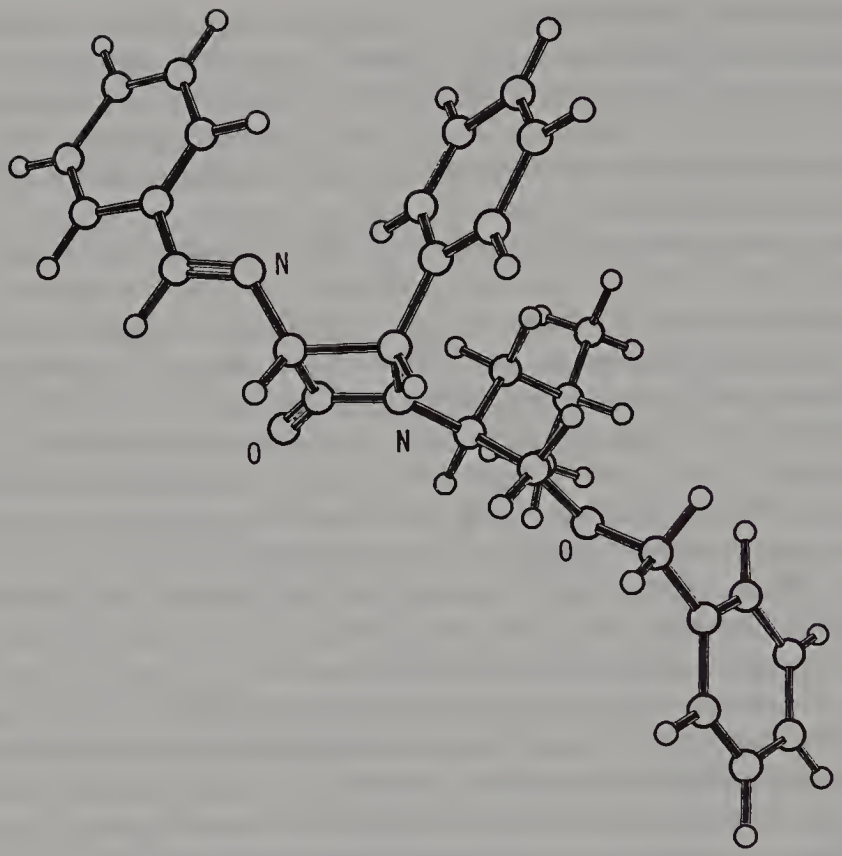
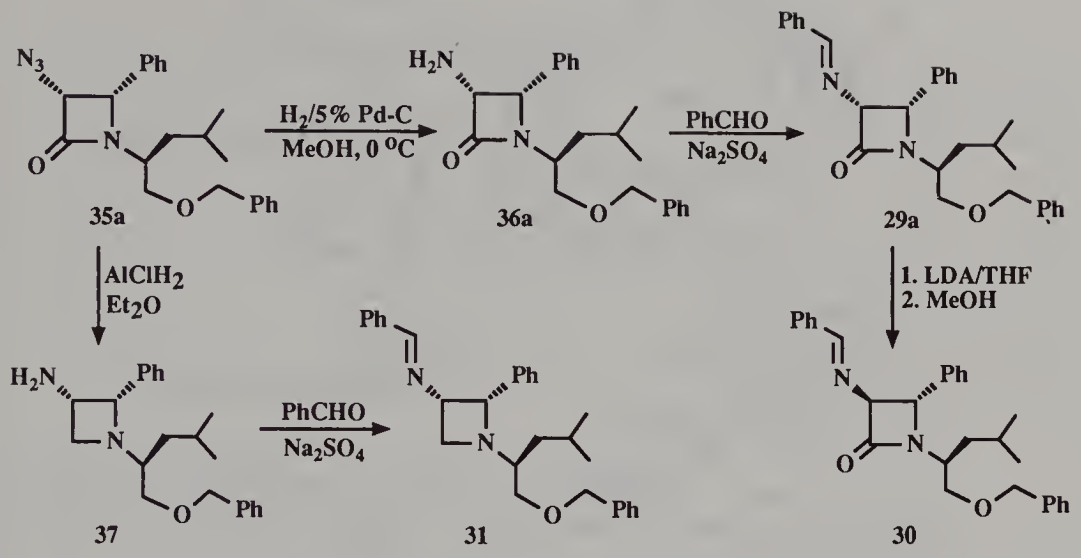


Figure 4.2. Energy minimum conformation of **29a.**

reduction[10] of **35a** (70%) followed by condensation with benzaldehyde (100%) (Scheme 4.9).

The [2 + 2] cycloaddition of azidoketene to **29a** was carried out to give the corresponding (3′*S*,4′*R*,3*R*,4*S*)-bis-β-lactam (**38a**) (46%) with greater than 99.5% d.e. (^{1}H NMR, HPLC) as expected. The absolute configuration was determined by HPLC analysis of the tripeptide, t-Boc-Phe–Phe–Leu-ol, obtained from **38** via hydrogenolysis on 5% Pd—C; however, contrary to our prediction, the reaction with **30** gave a (3′*R*,4′*S*,3*S*,4*S*)-bis-β-lactam (**39**) (67%) with a good diastereoselectivity (**39a/39b** = 81/19, ^{1}H NMR, HPLC). This unexpected result indicates that the steric hindrance of the 4-phenyl moiety in **29** is not the single crucial factor for the observed extremely high stereoselectivity. To exclude the possibility of asymmetric induction caused by the chiral *N*-substituent, that is, the *(S)*-leucinol benzyl ether moiety, we also carried out the [2 + 2] cycloaddition of azidoketene to **29b,** (3*S*,4*R*)-isomer. The reaction with **29b** gave (3′*R*,4′*S*,3*S*,4*R*)-bis-β-lactam (**38b**) with greater than 99.5% d.e. (HPLC) in 60% yield. Thus, it is reconfirmed that the chiral center at the *N*-substituent does not have any significant effects on the asymmetric induction (see earlier text). At this point, we recognized that the only other crucial factor conceivable should be the β-lactam car-

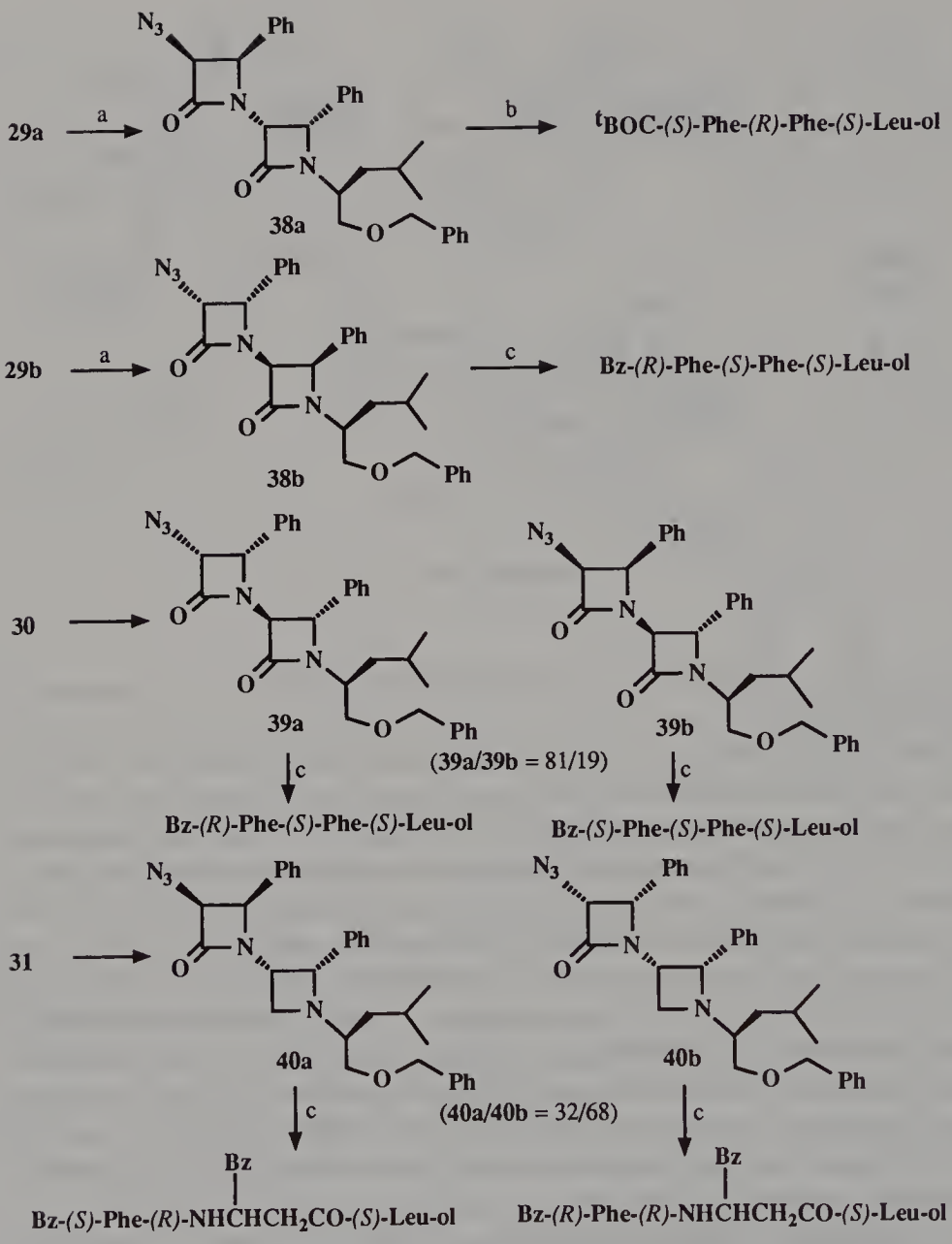


Scheme 4.9

bonyl moiety, which might have strong directing effects on the approach of the azidoketene.

These results prompted us to examine the reaction with the *cis*-3-iminoazetidine **31,** which has the same substituents on C^2 and C^3 positions as **29a** and **30** (C^3 and C^4 for β-lactams). Surprisingly, not only the stereoselectivity was decreased but also the direction of asymmetric induction was reversed by eliminating the β-lactam carbonyl! Namely, the reaction gave a diastereomeric mixture of azetidin-2-onylazetidine **(40)** (71%) with a 32/68 ratio: The HPLC analysis of Bz-Phe-NH-CH(CH_2Ph)-CH_2-CO-Leu-ol, which was obtained via the hydrogenelysis of **40,** disclosed that the major product was (3′*R*,4′*S*,2*S*,3*S*)-isomer **(40b)** and the minor, *(3′S,4′R,2S,3S)*-isomer **(40a).** The result is even more surprising by considering the fact that the most favorable conformation of **31** based on MM2 calculations, which is shown in Figure 4.4, has almost the same stereochemical arrangements as its β-lactam counterpart **(29a)** (Figure 4.2).

The remarkable effects of the β-lactam carbonyl are best interpreted by taking into account the interaction between the oxygen lone pair of the β-lactam carbonyl and the oxygen lone pair of the betaine **II,** which is the key intermediate for the reaction (Scheme 4.11). The stereo model inspections considering such lone pair–lone pair interactions give us a clear rationale of the extremely stereoselective reaction. Based on stereo models, it is very likely that the azidoketene approaches the lone pair of the imine nitrogen perpendicular to the plane of the benzylideneamine moiety, in which the *p* lobe of the azidoketene *anti* to the azide moiety is expected to react with the imine lone pair exclusively, as this lobe is sterically much more favorable for the reaction than the other. There are two directions for the approach and one of them gives **IIA** and the other **IIB.** As shown in Scheme 4.11, the



a: N_3CH_2COCl, Et_3N, -78 °C-rt; b: (i) H_2 (1 atm), 5% Pd-C, 0-5 °C; (ii) *t*-BOC-S, Et_3N, THF, rt; (iii) H_2 (1 atm), 5% Pd-C, MeOH, 55 °C; c: (i) and (iii), same as b; (ii) PhCOCl, *N*-methylmorpholine, THF, 0-5 °C.

Scheme 4.10

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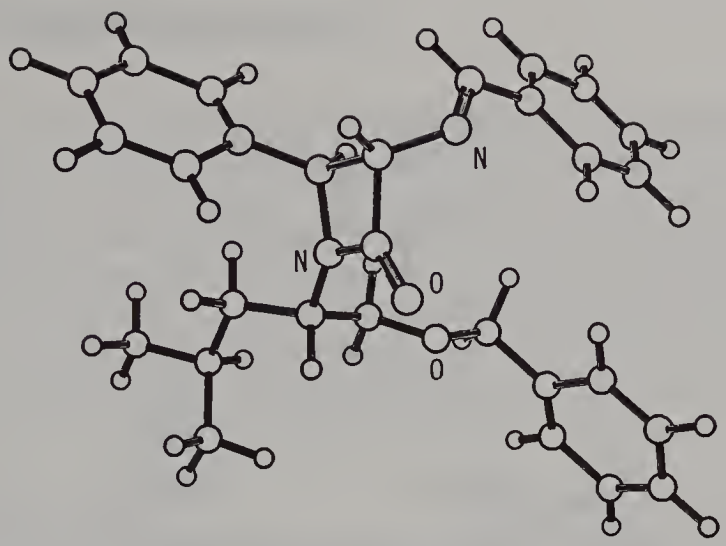

Figure 4.3 Energy minimum conformation of **30.**

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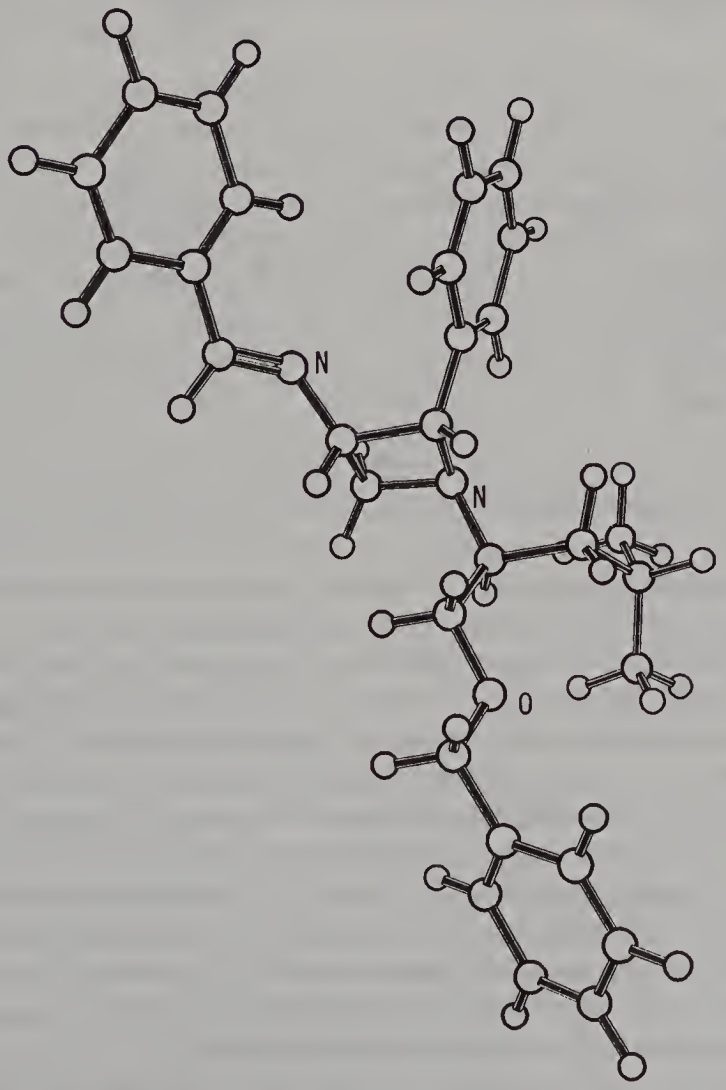

Figure 4.4 Energy minimum conformation of **31.**

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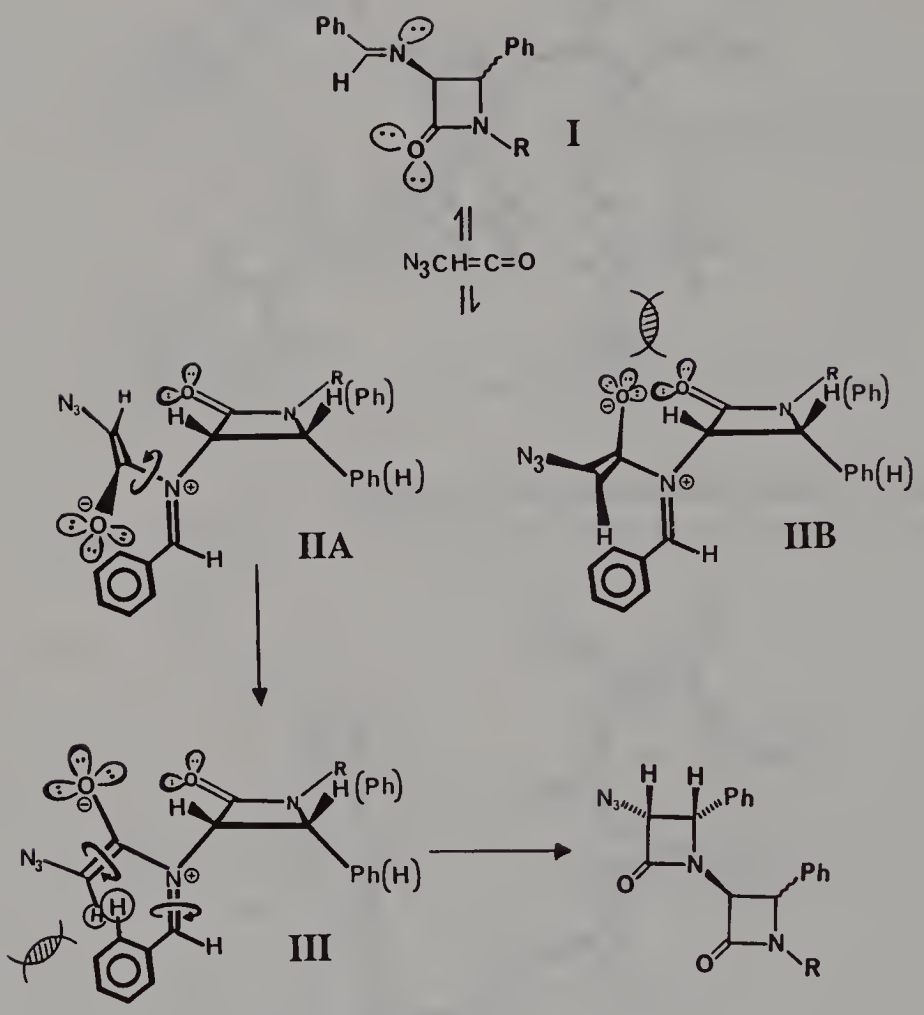

Scheme 4.11

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betaine **IIB** is very unfavorable because of the severe repulsion between the oxygen lone pair of the betaine and that of the β-lactam-carbonyl, whereas the betaine **IIA** does not have any nonbonded interactions between these lone pairs. Thus, betaine **IIA** is much more favorable than **IIB.** From the initial conformation thus formed, the azido-enolate moiety may rotate ca. 90° along the C—N bond of the betaine following the "principle of least motion"[38] to give a quasi-coplanar transition state for the conrotatory ring closure. In the quasi-coplanar transition state **(III),** there is steric conflict between two periplanar hydrogens, that is, the *ortho* hydrogen of the phenyl group and the vinyl hydrogen of the azido-enolate moiety. Because of this *syn*-periplanar repulsion of the two hydrogens, the conrotatory ring closure of **IIA** proceeds in a direction that releases the repulsion to give the bis-β-lactams **(38b,39)** with the configurations observed.

As a summary of this section, it is disclosed that the lone pair–lone pair interaction of the β-lactam carbonyl oxygen with the betaine oxygen is the

crucial factor for the extremely stereoselective [2 + 2] cycloadditions in the bis-β-lactam synthesis in addition to the conventional steric effects of the 4-phenyl group. This finding is very important not only because the nonbonded lone pair–lone pair interaction plays a key-role in asymmetric induction but also because the concept of the lone pair–lone pair interaction of this type can be applied to many cycloaddition reactions as a crucial stereocontrolling factor. It is also demonstrated that the β-Lactam Synthon Method can play a key role in the determination of absolute configurations of the newly formed β-lactam moiety of the bis-β-lactams.

4.4 Asymmetric Synthesis of Nonprotein Amino Acids by the β-Lactam Synthon Method

4.4.1 Asymmetric Synthesis of α-Alkyl-α-amino acids and Their Derivatives

The significance of nonprotein amino acids has recently been recognized in connection with design and synthesis of enzyme inhibitors as potential pharmaceutical drugs and also for the study of enzymatic reaction mechanisms.[38–41] Among those nonprotein amino acids, α-alkyl-α-amino acids have been attracting medicinal and biochemical interest for two reasons: (1) these amino acids are known to be powerful enzyme inhibitors, for example, for the decarboxylases of dopa,[38] ornithine,[39] glutamate,[39] and *S*-adenosylmethionine,[40] and the aminotransferase of aspartate[41]; (2) these amino acids act as conformational modifiers for physiologically active peptides.[42] Some α-alkyl-α-amino acids have been found in the metabolites of bacteria and act as antibiotics such as amicetin[43] and antiamoebin I.[44] α-Alkyl-α-amino acids also provide a challenging synthetic problem for chemists, as the α-alkyl-α-amino acids have chiral quaternary carbons and thus conventional enzymatic optical resolution technology cannot be applied effectively; no racemization can take place at the chiral α-carbons and thus D-isomers cannot be recycled to the optical resolution process. Therefore, the asymmetric synthesis of optically pure α-alkyl-α-amino acids is the method of choice. Schöllkopf and co-workers[45] developed a general method based on bis(lactim) ethers and Seebach et al.[46] reported a method based on chiral proline derivatives using "self-reproduction of chirality." Karady,[47] Williams,[48] and Georg[49] and their coworkers developed effective methods based on oxazolidinone, aza-δ-lactone, and Schmidt rearrangement, respectively. We have successfully been working on this important problem through extremely stereoselective alkylations of chiral β-lactams followed by the reductive cleavage of the aklylated β-lactams.[14–18] This section describes effective methods for the asymmetric synthesis of α-alkyl-α-amino acids and their dipeptides as an application of the second-generation β-Lactam Synthon Method.

4.4.1.1 Asymmetric Synthesis via Type 1 and Type 2 Alkylations

We have studied two types of asymmetric alkylations: the alkylation of the C-3 carbon of a β-lactam (type 1) and the alkylation of a side-chain carbon bonding to the β-lactam nitrogen (type 2) as illustrated in Chart 4.3.[17,18]

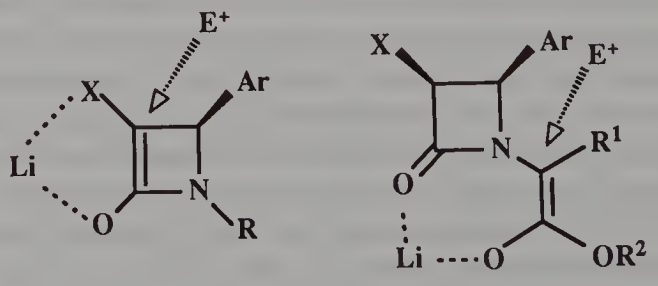
In the type 1 alkylation, an electrophile should attack the C-3 position from the opposite side of the bulky 4-aryl group of the β-lactam enolate to avoid steric conflict. In the type 2 alkylation, the enolate is supposed to form a chelate with the β-lactam oxygen and then an electrophile should attack from the back side of the 4-aryl group.

If the reactions proceed following our hypotheses, chiral quaternary carbons should be created in a highly predictable manner, which is very beneficial for the synthesis of a series of new α-substituted α-amino acids and their derivatives.

4.4.1.1.1 Type 1 Alkylation

We applied the type 1 alkylation to the asymmetric synthesis of the amides of *(S)*-α-methylphenylalanine (**42a:** X = Y = H) and *(S)*-α-methyl-dopa (**42b:** X = Y = MeO) (Scheme 4.12). *(S)*-α-Methyl-dopa (**43b:** X′ = Y′ = OH) is an inhibitor of dopa decarboxylase and is widely used as antihypertensive drug.[38]

Chiral-β-lactams (**26a,b:** >99.5% d.e.) were synthesized through the asymmetric [2+2] cycloadditions of the chiral ketene (**20a**) generated in situ from **19a** and triethylamine to arylmethylidene-*N*-methylamines (**25a,b**). Second, to a β-lactam (**26**) was added lithium hexamethyldisilazide (LHMDS) in THF at −78°C to generate the type 1 chiral β-lactam enolate. Methyl iodide was then added to the enolate and the mixture was stirred overnight at −78°C (room temperature). A usual workup and purification on a short silica gel column gave a (3*S*)-3-methyl-3-oxazolidinyl-β-lactam (**41:** >99.5% d.e.) in excellent yield. The 3-methyl-β-lactams (**41**) thus obtained



Type 1 Type 2

Chart 4.3. Type 1 and type 2 asymmetric alkylations.

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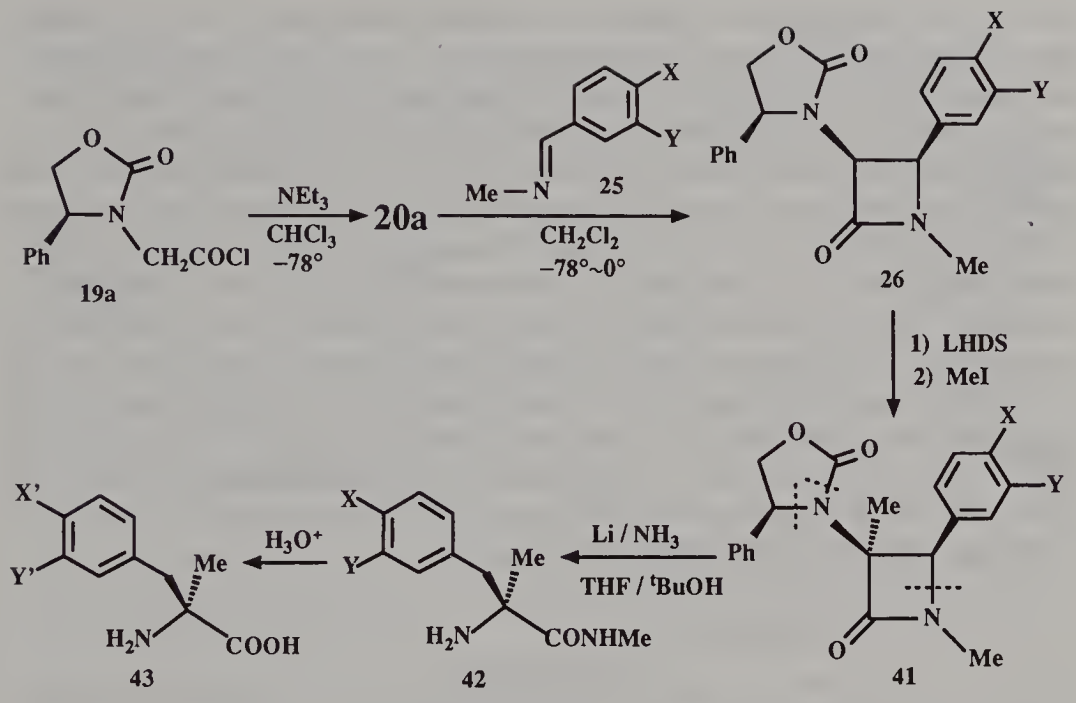
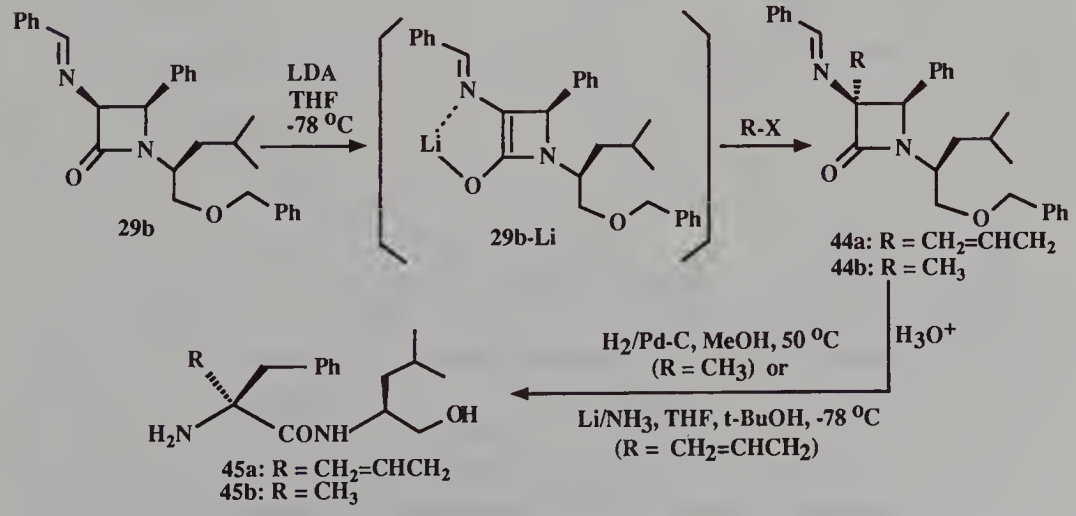


Scheme 4.12

(Reprinted, with the permission of Pergamon PLC, from Ojima et al.[17])

were submitted to the modified Birch reduction to give in excellent yields the corresponding *N*-methylamides of α-methyl-α-amino acids (**42**), which are the direct precursors of *(S)*-α-methylphenylalanine (**43a**) and *(S)*-α-methyl-dopa (**43b**).

The type 1 alkylation was also applied to the enolate of 3-benzylidene-amino-β-lactam (**29b-Li**) which was generated by adding LHMDS in THF at



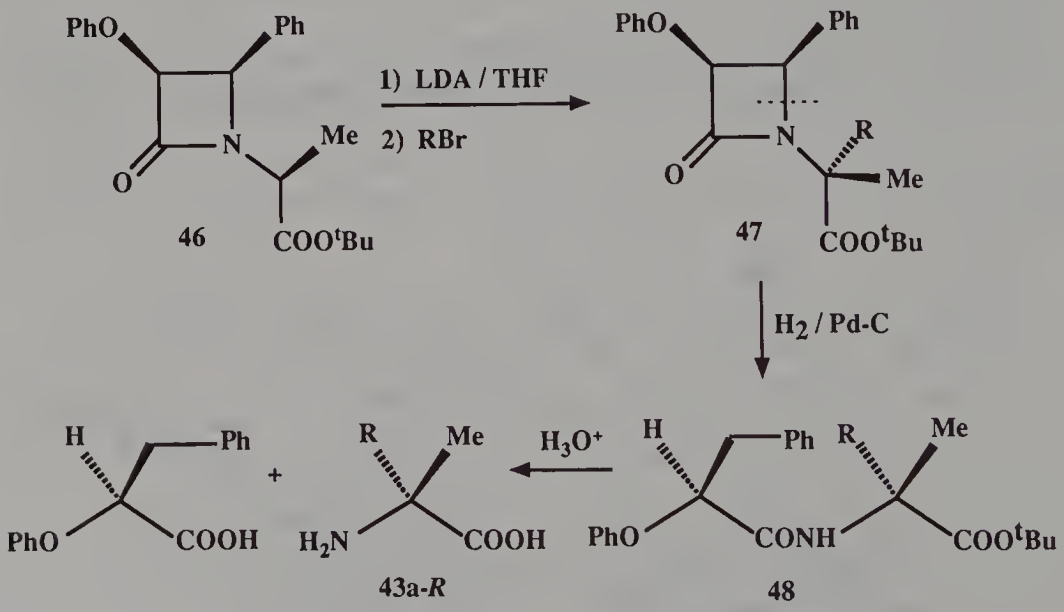
Scheme 4.13

−78°C. Allyl bromide was added at the same temperature. Then, the reaction mixture was allowed to warm gradually to room temperature overnight, and quenched with 1 *N* HCl. A usual workup gave 3-allyl-3-benzylideneamino-β-lactam (**44a**) in 95% yield. 3-Methyl-3-benzylidene-amino-β-lactam (**44b**) was also obtained in 94% yield by using methyl iodide. HPLC analysis showed that the type 1 alkylations proceeded with extremely high stereoselectivities (>99.5% d.e.) in both cases (Scheme 4.13). The difference NOE experiments clearly showed the *cis* arrangement of the C^3-allyl and the C^4-hydrogen. Thus, it was proven that the electrophile did attack from the opposite side of the 4-phenyl group as originally designed. Deprotection of the 3-benzylideneamino group of **44** by hydrolysis, followed by hydrogenolysis over 10% Pd—C (for **44b:** R = Me) or dissolving metal reduction (Li/NH_3/THF/t-BuOH) (for **44a:** R = allyl) gave the corresponding optically pure dipeptide (**45**) bearing the α-alkyl-α-amino acid residue at the *N* terminus in high yield (**45a,** 90%; **45b,** 88%) (Scheme 4.13).

4.4.1.1.2 Type 2 Alkylation

The type 2 alkylation was applied to the asymmetric synthesis of *(S)*-α-alkylalanines and *(R)*-phenylalanyl–*(S)*-α-methylphenylalanine.[14,17]

A β-lactam enolate was generated by treating a β-lactam (**46**) with LDA (1.0 equivalent) in THF at 0 to 5°C and the solution was cooled to −78 to −90°C (Scheme 4.14). The asymmetric alkylation was carried out by adding



Scheme 4.14

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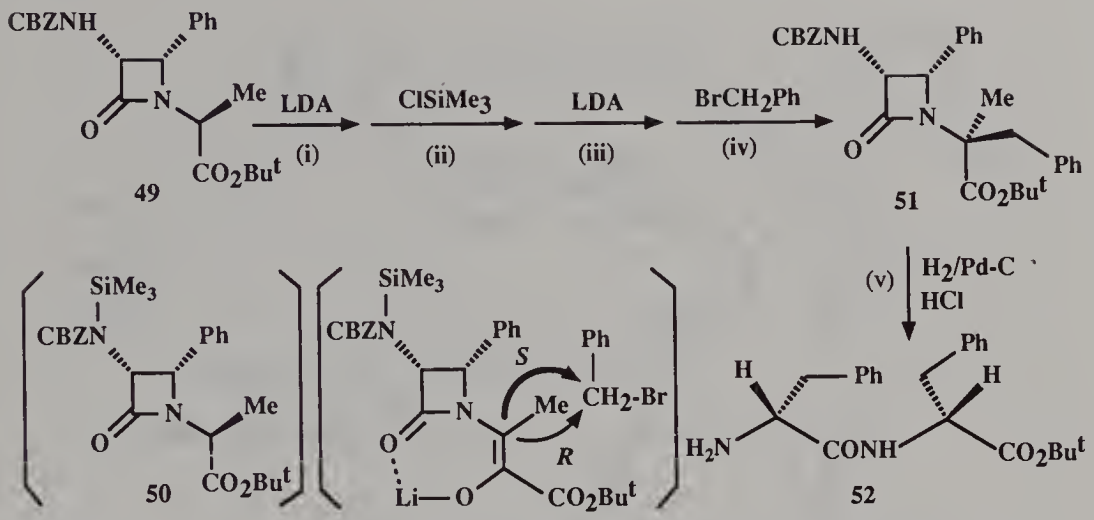


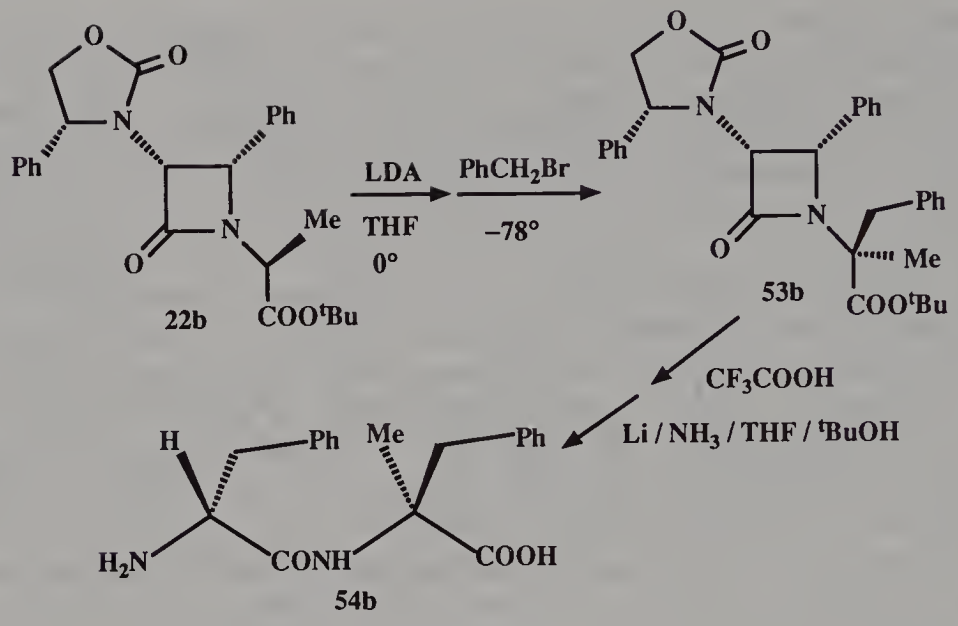
(i) 1 eq., THF, -78 °C, 3 min; (ii) 1 eq., -78 - 0 °C, 75 min; (iii) 1 eq., THF, 0 °C, 10 min, then -78 °C; (iv) 3 eq., -78 °C, 2 h, -78 - 0 °C 3 h, 0 °C, 2 h, then sat. NH_4Cl in MeOH; (v) H_2 (1 atm),10% Pd-C, 1N HCl (1 eq.), MeOH, 50 °C, 12 h.

Scheme 4.15

an aklyl bromide to the enolate to give an alkylated β-lactam ester (**47**) with greater than 98% d.e. in excellent yield. The hydrogenolysis of **47** on Pd—C gave the corresponding dipeptide analog (**48**) in quantitative yield. The hydrolysis of **48** with 6 *N* HCl in aqueous THF at 110°C gave enantiomerically pure *(R)*-α-alkyl-alanine (**43a-R**) in high yield.

When 3-CBZ-NH-β-lactam ester (**49**) was employed as a substrate for the asymmetric alkylation, the reaction using 2 equivalents of LDA and 1 equivalent of benzyl bromide gave a poor result (ca. 20% d.e.). This may indicate that the β-lactam oxygen cannot hold double coordination of lithium. Accordingly, TMS-Cl was added after the addition of 1 equivalent of LDA at −78°C to form 3-CBZ-*N*(TMS)-β-lactam ester (**50**), and then another equivalent of LDA was added at 0°C followed by the addition of benzyl bromide at −78°C. The stereoselectivity of this reaction was 14:1 as we expected (Scheme 4.15). The hydrogenolysis of the alkylated β-lactam ester **51** on 10% Pd-C gave *(R)*-phenylalanyl–*(S)*-α-methylphenylalanine *tert*-butyl ester hydrochloride (**52**) in nearly quantitative yield.

The asymmetric alkylation of a chiral β-lactam ester (**22a**) prepared via the asymmetric ketene addition (see earlier text) in which the 3-amino group of the β-lactam was protected as an oxazolidinone structure, proceeded with extremely high stereoselectivity (>99% d.e.) to give the methylated β-lactam ester (**53**) in 90% yield (Scheme 4.16). Deprotection of **53** with trifluoroacetic acid (TFA) and the dissolving metal reduction gave *(R)*-phenylalanyl–*(S)*-α-methylphenylalanine (**54**: >99% d.e.) in 76% isolated yield.



Scheme 4.16

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4.4.1.1.3 Kinetic versus Thermodynamic Enolates in the Type 2 Alkylation

In the type 2 asymmetric alkylation of **46** (Scheme 4.14), we observed an interesting dependence of stereoselectivity on the reaction temperature as shown in Table 4.2. When the reaction was carried out at −78 to −95°C, the results of the alkylations were discouraging because the ratios of the two diastereomers were only 2:1 to 3:1, and the enolate generated showed an intense violet color. When the enolate was generated at 0 to 5°C, however, the stereoselectivities of the alkylations were excellent, and the enolate generated exhibited a pale yellow color. The observed remarkable color change strongly suggests the interconversion of one enolate form to the other. As no strong intramolecular charge transfer can be envisioned as an origin of the violet color of the enolate, formation of some aggregate may well be responsible for the color. A possible formation of dianion species can be eliminated because of no epimerization at the C-3 position of the β-lactam ring. Similar dependence of stereoselectivity on the temperature of enolate formation was observed for the reactions of **22a** (Scheme 4.16), although strong coloration was not observed at low temperature in this case.

On treatment with LDA or LHMDS, a β-lactam ester, for example, **46** and **22,** should generate a chelating enolate **(I)** and/or a nonchelating enolate **(II).** Based on the widely accepted transition-state model for the kinetic enolate formation, the nonchelating enolate **(II)** is favorable when generated at −78 to −90°C (Scheme 4.17). As the kinetic enolate cannot form a rigid

Table 4.2. ASYMMETRIC ALKYLATION OF β-LACTAM ESTERS (**46**).[14]

β-Lactam ester[a]	Alkyl Bromide	Base[b]	Generation of Enolate (I)		Addition of RBr		Product	Yield (%)[c]	Stereo-selectivity[d] (% d.e.)
			Temp.(°C),	Time (min)	Temp.(°C),	Time (h)			
46a	$CH_2=CH-CH_2Br$	LDA	0	15	−78	5	**47a–1**	95	>98 (*R*)
46a	$CH_2=CH-CH_2Br$	LHMDS	0	15	0–5	5	**47a–1**	94	95 (*R*)
46b	$CH_2=CH-CH_2Br$	LDA	−78	15	−78	5	**47b–1**	95	34 (*S*)
46a	$PhCH_2Br$	LDA	0	15	−78	5	**47a–2**	96	>98 (*R*)
46a	$PhCH_2Br$	LDA	0	15	0–5	5	**47a–2**	95	93 (*R*)
46a	$PhCH_2Br$	LDA	−10	15	−10	5	**47a–2**	93	75 (*R*)
46a	$PhCH_2Br$	LDA	−90	15	−90	5	**47a–2**	95	50 (*R*)
46b	C_2H_5Br	LDA	0	15	−78	5	**47b–3**	95	>98 (*R*)
46b	$3,5\text{-}(MeO)_2C_6H_3CH_2Br$	LDA	0	15	0–5	5	**47b–4**	95	93 (*R*)

[a] **46a** = (*3S,4R*)-isomer; **46b** = (*3R,4S*)-isomer.

[b] LDA = lithium diisopropylamide; LHMDS = lithium hexamethyldisilazide.

[c] Determined by ^1H NMR. Conversion yield for the reaction is >99% in every case.

[d] Determined by ^1H NMR. No the other diastereomer was detected for the cases with >98% d.e. *R* or *S* in the parentheses is the configuration of the newly formed quaternary center.

chelate ring with the β-lactam oxygen by any means, it is reasonable that the stereoselectivity of the alkylation is low. The experiments at 0 to 5°C imply that the thermodynamic enolate (**I**), which has a rigid chelate structure, is generated at this temperature as originally designed and achieves excellent stereoselectivity. Thus, there is an isomerization process from the kinetic enolate (**II**) to the chelated enolate (**I**) when the reaction is carried out at 0 to 5°C. In fact, we observed a short-lived violet color at 0°C when LDA in THF was added dropwise to a solution of the β-lactam ester (**46**) in THF. The intense violet color of the kinetic enolate (**II**) of **46** was gradually decolorized upon warming to 0 to 5°C to show a pale yellow color indicating the formation of the chelated enolate (**I**). Once the chelated enolate was formed, its pale yellow color did not change upon cooling to −78°C, which clearly indicates that this isomerization is irreversible. As Table 4.2 shows, the best results are obtained when the enolate is formed at 0 to 5°C and the alkylation is carried out at −78°C, which is quite reasonable by taking into account the entropy factor of the reaction. A stereo model of the type 2 lithium enolate of **43** on the basis of the Model-MM2-Rotochem program[37] is depicted in Figure 4.5, in which the coplanar structure regarding the β-lactam amide moiety and the enolate moiety is assumed. This model clearly supports the hypothetical transition state shown in Scheme 4.17.

Consequently, it was demonstrated that the type 1 and type 2 asymmetric alkylations of chiral β-lactams provide unique and effective routes to a variety of α-substituted aromatic α-amino acids and their derivatives that have chiral quaternary centers.

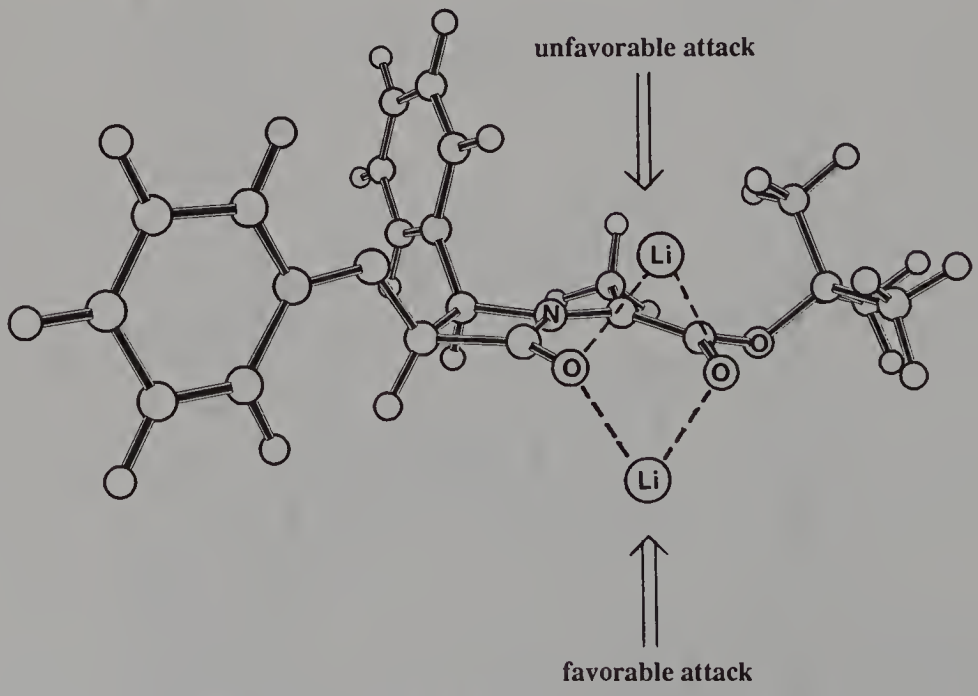
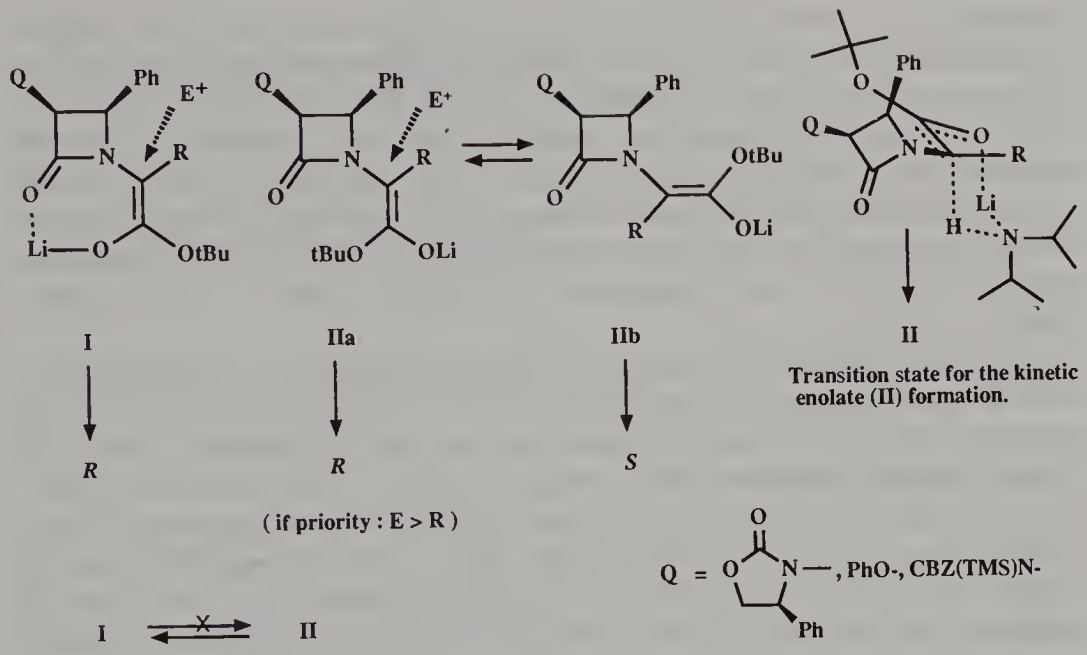


Figure 4.5 A stereo model of the type 2 lithium enolate.



Scheme 4.17

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4.4.1.2 Asymmetric Alkylations of Phenylalanylglycinate Equivalent

We have extended the type 2 alkylation to the asymmetric single and double alkylations of chiral-β-lactam acetate (**55**), which is a chiral glycinate as well as a phenylalanylglycinate equivalent (Chart 4.4).[18]

First, we performed sequential asymmetric double alkylation of the β-lactam ester [**55a**, (3*S*,4*R*)] which was prepared through asymmetric [2+2] cycloaddition of the chiral ketene [(*S*)-**20**] (see earlier text) to *tert*-butyl *N*-benzylideneglycinate in 83% yield; **55b** was prepared in the same manner

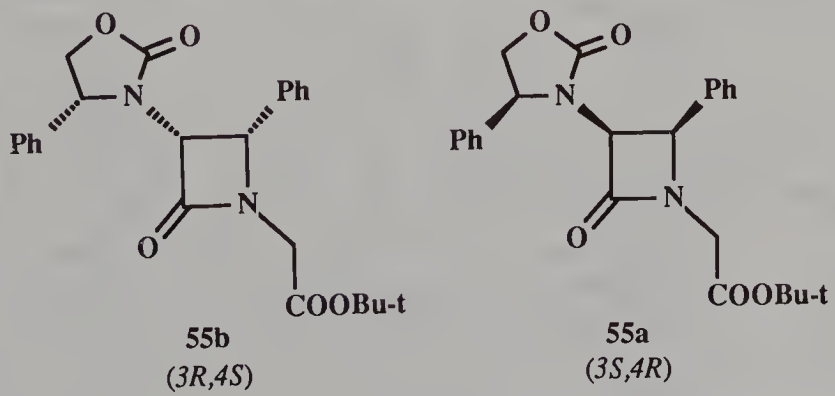

Chart 4.4. β-Lactam **55**, a chiral glycinate and phenylalanylglycinate equivalent.

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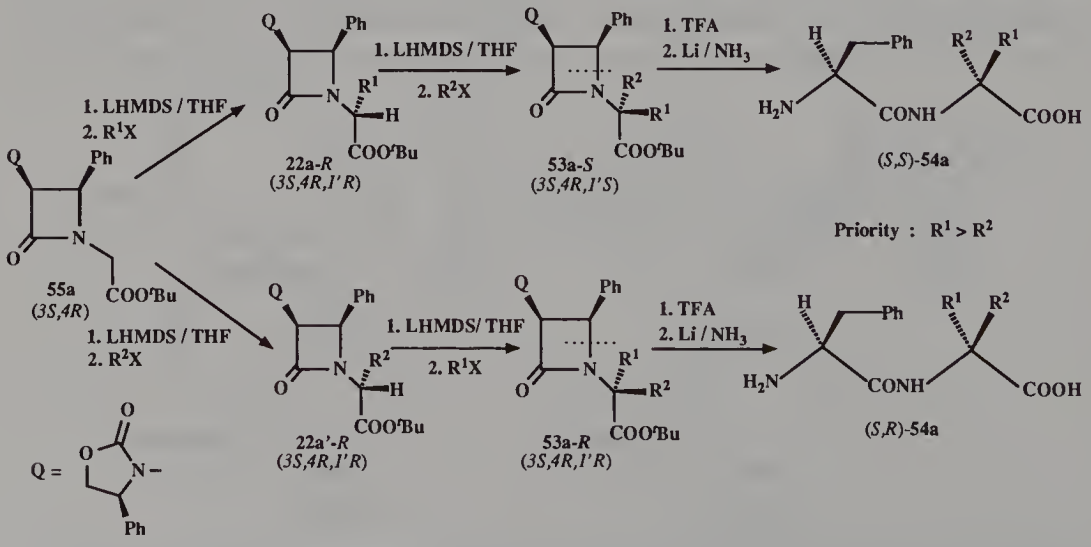
from *(R)*-**20.** As shown in Scheme 4.18, the salient advantage of this method is that a quaternary chiral center of desired configuration can be created just by changing the order of the addition of two alkyl halides used ($R^1 \neq R^2$). Reactions were carried out using methyl iodide, allyl bromide, and benzyl bromide, and doubly alkylated β-lactam esters **(53)** were obtained in high yields. Results are summarized in Table 4.3. The doubly alkylated β-lactams **(53)** thus obtained can readily be converted to the corresponding dipeptides **(54)** via dissolving metal reduction ($Li/HN_3/THF/t\text{-}BuOH, -78°C$) in good yield.

As Table 4.3 shows, the stereoselectivity of the asymmetric double alkylation is extremely high (>99% d.e. by HPLC analysis). As discussed in the preceding section, a chelated lithium ester enolate **(I,** Scheme 4.17) must be formed through thermodynamic control to achieve high stereoselectivity, and a temperature of 0 to 5°C is necessary for the smooth transformation of a kinetic enolate **(II)** of **22** (R^1 or R^2 = Me) to the corresponding chelated enolate **(I).** Thus, we employed 0 to 5°C for the generation of the chelated enolate in the second alkylation. For the first alkylation, however, we had to use much lower temperature, typically −78°C, as the lithium enolate generated from **55** was found to be unstable at temperatures higher than −30°C.

Next, we looked at the efficiency of the asymmetric single alkylation of **55a** (Scheme 4.19). Results are summarized in Table 4.4.[18] As Table 4.4 shows, remarkable dependence of stereoselectivity on the reaction temperature was observed for the reactions with allyl bromide, methyl iodide, and benzyl bromide.

The best results for these alkyl halides (1′*R*/1′*S* > 50/1) were obtained at −78°C. The results clearly indicate that (1) a kinetic enolate (nonchelated)



Scheme 4.18

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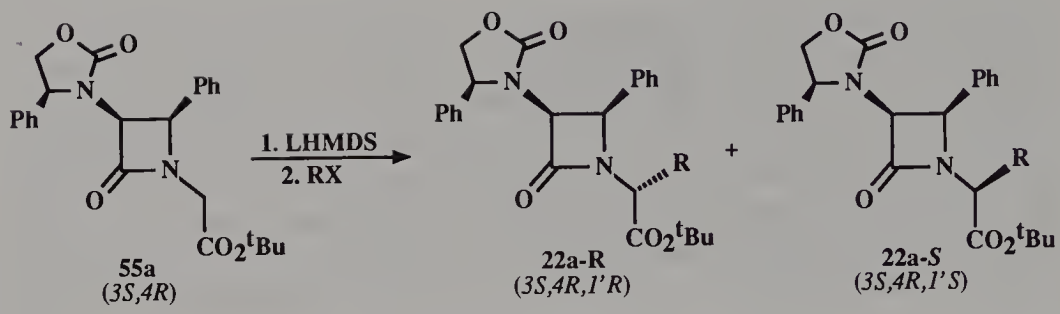
Table 4.3. ASYMMETRIC SINGLE AND DOUBLE ALKYLATIONS OF β-LACTAM ESTER (**55**).

			22				53		
Entry	β-Lactam ester	R^1X	Yield(%)[a]	%d.e.[b]	Config.[c]	R^2X	Yield (%)[a]	% d.e.[d]	Config.
1	**55a**	MeI	90			$CH_2=CHCH_2Br$	85	>99	*3S,4R,1'R*
2	**55b**	MeI	86			$CH_2=CHCH_2Br$	77	>99	*3R,4S,1'S*
3	**55b**	$CH_2=CHCH_2Br$	85			MeI	94	>99	*3R,4S,1'R*
4	**55b**	MeI	86			$PhCH_2Br$	79	>99	*3R,4S,1'S*
5	**55a**	MeI	89 (95)[e]	>96	*R*				
6	**55a**	$CH_2=CHCH_2Br$	80 (95)[e]	>96	*R*				
7	**55a**	$PhCH_2Br$	73 (93)[e]	>96	*R*				
8	**55a**	$BrCH_2COOEt$	79 (94)[e]	>96	*R*				

[a] Isolated yield unless otherwise noted.
[b] Determined by ^1H NMR analysis.
[c] Configuration of substituted glycinate moiety.
[d] Determined by HPLC analysis.



Scheme 4.19

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is generated as major species at −95°C, but a chelated enolate is formed at −78°C (see Scheme 4.17), and (2) higher temperatures substantially attenuate stereoselectivity, which may well be due to a large entropy term of this reaction, for example, possible change in aggregation mode. When ethyl bromoacetate was used as an electrophile, the reaction gave the highest stereoselectivity at −97°C rather than at −78°C, and the stereoselectivity decreased along with the increase of temperature. The results imply that the ester moiety of ethyl bromoacetate contributes to a facile conversion of the kinetic enolate to the chelated enolate and/or the generation of a particular aggregate. Consequently, it was found that the asymmetric single alkylation proceeds with extremely high stereoselectivity as well. As the single alkylation products can readily be converted to the corresponding dipeptides through dissolving metal reduction and then to amino acids by hydrolysis, this asymmetric single alkylation serves as an effective method for the synthesis of enantiomerically pure nonprotein amino acids and their dipeptides.

Finally, we performed the sequential asymmetric triple alkylation of **55a** by the combination of type 1 and type 2 alkylations as exemplified in Scheme 4.20.[18] After completion of the asymmetric double alkylations of the glycinate moiety with methyl iodide and allyl bromide, the side chain of the re-

Table 4.4. DEPENDENCE OF STEREOSELECTIVITY ON REACTION TEMPERATURE IN ASYMMETRIC SINGLE ALKYLATION

	22a–*R*/22a–*S*[a] (% Yield)[a]			
RX	−97 °C	−78 °C	−50 °C	−30 °C
CH_2=CHCH2Br	7.6/1 (94)	>50/1 (95)	7.9/1 (95)	4.4/1 (92)
$PhCH_2Br$	17/1 (93)	>50/1 (93)	36/1 (93)	8.4/1 (92)
MeI	37/1 (94)	>50/1 (95)	12/1 (94)	8.0/1 (93)
$EtOCOCH_2Br$	>50/1 (94)	40/1 (95)	18/1 (92)	6.0/1 (90)

[a] Determined by ^{1}H NMR analysis. **22a–*R*/22a–*S*** = (*3S,4R,1'R*)–**2a**/(*3S,4R,1'S*)–**2a**

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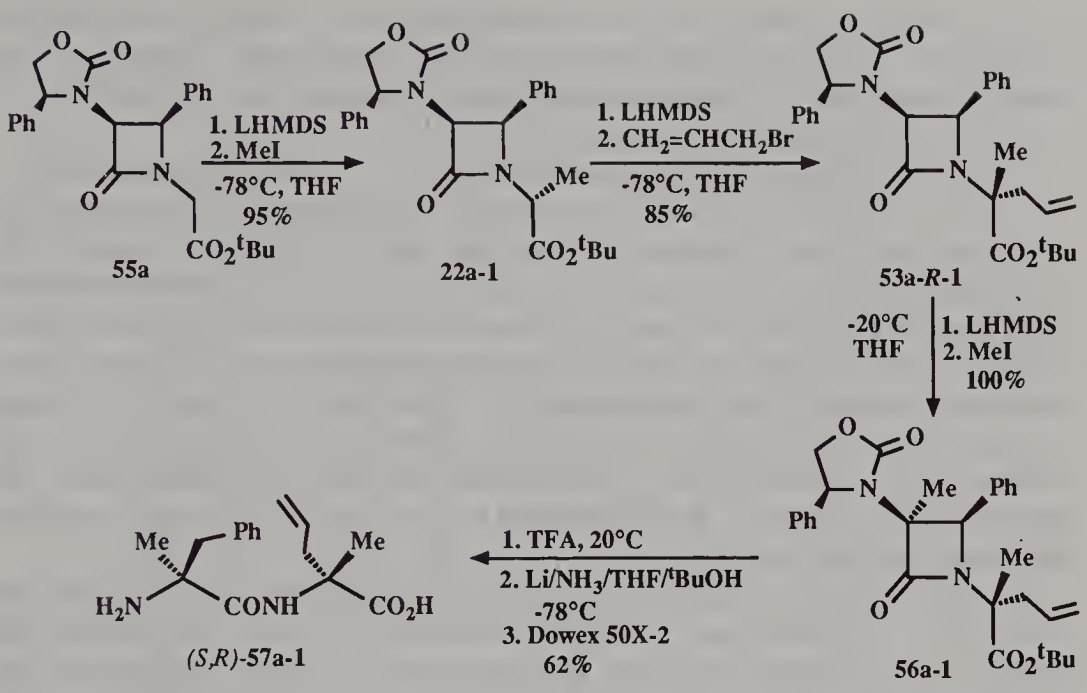

Scheme 4.20

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sulting β-lactam ester (**53a-R-1**) does not have any acidic proton. Thus, a type 1 enolate is generated and the third alkyl substituent (methyl) is introduced to the C-3 position of **53a-R-1**; hence the whole process constitutes a unique and highly selective sequential asymmetric triple alkylation to give **56a-1.** It was found that the third alkylation also proceeded with virtually complete stereoselectivity.

Deprotection of the *tert*-butyl ester of **56a-1** by TFA in dichloromethane at 20°C, followed by cleavage of the β-lactam ring as well as removal of N-protection with $Li/NH_3/THF/t\text{-}BuOH$ at −78°C, gave *(S)*-α-methylphenylalanyl-*(R)*-α-allylalanine, *(S,R)*-**57a-1,** in 62% yield after purification on an ion-exchange column (Scheme 4.20).

4.4.1.3 Asymmetric Synthesis Based on Chiral Ester Enolate–Imine Cyclocondensation Followed by Stereoselective Alkylation

4.4.1.3.1 Asymmetric Synthesis of β-lactams

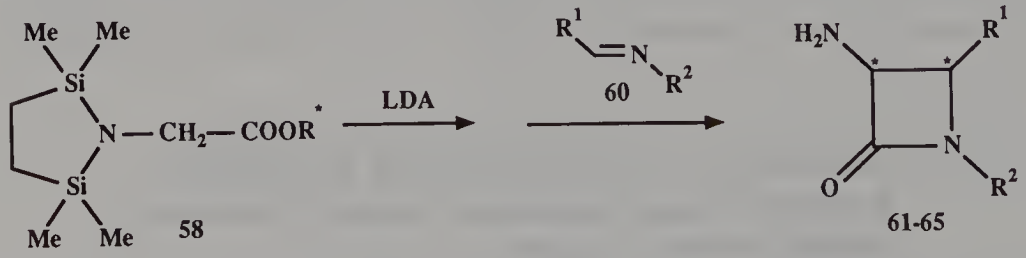
The enantiomerically pure β-lactam discussed in the previous sections are all synthesized through [2+2] cycloaddition of ketenes to imines. This section describes a successful application of the lithium chiral ester enolate–imine cyclocondensation strategy[51] to the asymmetric synthesis of 3-amino-β-lactams.

We carried out the reactions of chiral lithium ester enolates (**59**) generated in situ from *N,N*-bis(silyl)glycinates (**58**) with imines (**60**), which gave the corresponding chiral β-lactams (**61–65**) in fairly good isolated yields (Scheme 4.21).[19,52] Results are summarized in Table 4.5.[19]

As Table 4.5 shows, the reactions of **58a** [R* = (−)-menthyl] and **58d** [R* = (−)- or (+)-*trans*-2-phenyl-1-cyclohexyl) with **60a–c** give exclusively the corresponding *trans*-β-lactams (**61a, 62,** and **63**) in fairly good yields with extremely high enantiomeric purity (entries 1 and 4–7). The reactions of **58a** with **60d** and **60e** also give *trans*-β-lactams (**64a** and **65a**) as the predominant products with greater than 99% e.e. accompanied by a small amount of *cis*-β-lactams (**64b** and **65b**) (entries 8 and 9). When the (+)-neomenthyl group is used as the chiral auxiliary, the reaction gives a 1:3 mixture of *trans:cis* isomers (**61a** and **61b**) with *S* configuration at the C-3 positions (entry 2), which is opposite to that of **61a** obtained by using the (−)-menthyl group as the chiral auxiliary (entry 1).

A mixture of *trans*- and *cis*-β-lactams (**61a** and **62b**) is also obtained on using the (+)-bornyl group as the chiral auxiliary, in which (3*R*)-isomers are formed with very low enantiomeric purity (entry 3). Accordingly, it is obvious that the use of (−)- and (+)-*trans*-2-phenyl-1-cyclohexyl[53] as well as (−)-menthyl groups as the chiral auxiliaries is the most efficient.

The formation of *trans*- and *cis*-β-lactams can be explained by taking into account the stereochemistry of the lithium enolates (*Z*-**59** and *E*-**59**) and a chairlike transition state[51,52c,54]; that is, the reaction of the *Z*-enolate proceeds through a chairlike transition state **A** to give *trans*-β-lactams, whereas the *E*-enolate gives *cis*-β-lactams via a similar transition state (Scheme 4.22). When (−)-menthyl and (−)-2-phenyl-1-cyclohexyl groups are used as the chiral auxiliaries, it is indicated that the imines (**60a–e**) approach exclusively from the *re*-face of *Z*-**59a** and *Z*-**59d**(−) [*si* face of *Z*-**59d**(+)] to give *N*-



58a : R^* = (-) - menthyl
58b : R^* = (+) - neomenthyl
58c : R^* = (-) - bornyl
58d(-) : R^* = (-) - *trans* -2- phenylcyclohexyl
58d(+) : R^* = (+) - *trans* -2- phenylcyclohexyl

60 a: R^1 = Ph ; R^2 = *p*-MeO-C_6H_4
60 b: R^1 = *p*-F-C_6H_4 ; R^2 = *p*-MeO-C_6H_4
60 c: R^1 = *p*-CF_3-C_6H_4 ; R^2 = *p*-MeO-C_6H_4
60 d: R^1 = *p*-MeO-C_6H_4 ; R^2 = *p*-MeO-C_6H_4
60 e: R^1 = 3,4-$(MeO)_2$-C_6H_3 ; R^2 = *p*-MeO-C_6H_4

Scheme 4.21

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Table 4.5. ASYMMETRIC SYNTHESIS OF β-LACTAMS (**61–65**) THROUGH ESTER ENOLATE–IMINE CONDENSATION.

Entry	Ester	Imine	Condition[a]	β-Lactam	Isolated Yield (%)	Product Ratio and Enantioselectivity[b]	
						trans (%)	*cis* (%)
1	**58a**	**60a**	A	**61a**	65	100 (>99% e.e.; *3R,4R*)	
2	**58b**	**60a**	A	**61a**	65	26 (54% e.e.; *3S,4S*)	
				61b			74 (21% e.e.; *3S,4R*)
3	**58c**	**60a**	A	**61a**	53	37 (5% e.e.; *3R,4R*)	
				61b			63 (2% e.e.; *3R,4S*)
4	**58d(−)**	**60a**	A	**61a**	58	100 (>99% e.e.; *3R,4R*)	
5	**58d(+)**	**60a**	A	**61b**	58	100 (>99% e.e.; *3S,4S*)	
6	**58a**	**60b**	A	**62a**	55	100 (>99% e.e.; *3R,4R*)	
7	**58a**	**60c**	A	**63a**	59	100 (>99% e.e.; *3R,4R*)	
8	**58a**	**60d**	A	**64a**	70	89 (>99% e.e.; *3R,4R*)	
				64b			11 (38% e.e.; *3S,4R*)
9	**58a**	**60e**	A	**65a**	54	91 (>99% e.e.; *3R,4R*)	
				65b			9 (27% e.e.; *3S,4R*)

[a] Condition A, at −78°C for 4h; Condition B, at −78°C for 4 h and at −50°C for 72 h.

[b] Enantiomeric purity was determined by Mosher's MTPA method [55] on ^{1}H NMR and/or ^{19}F NMR. Absolute configurations were determined based on chemical correlation (specific rotation) with authentic samples (for 4-aryl-β-lactams, their conversion to the corresponding α-amino acid amides by hydrogenolysis was used), and also based on the NMR chemical shift correlation of 3-MTPA-amino-β-lactams.

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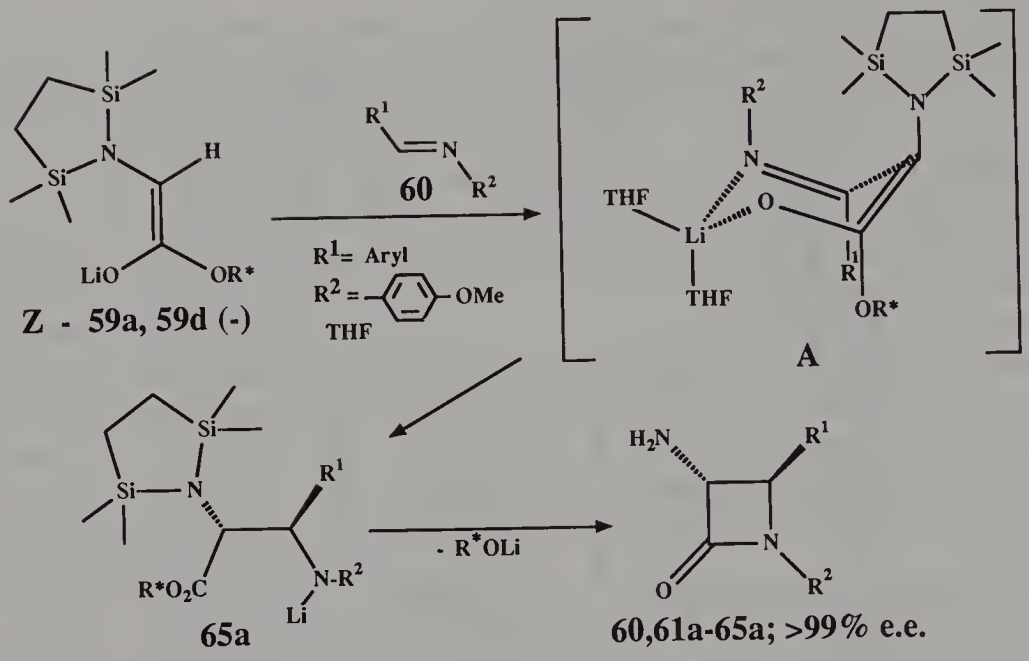


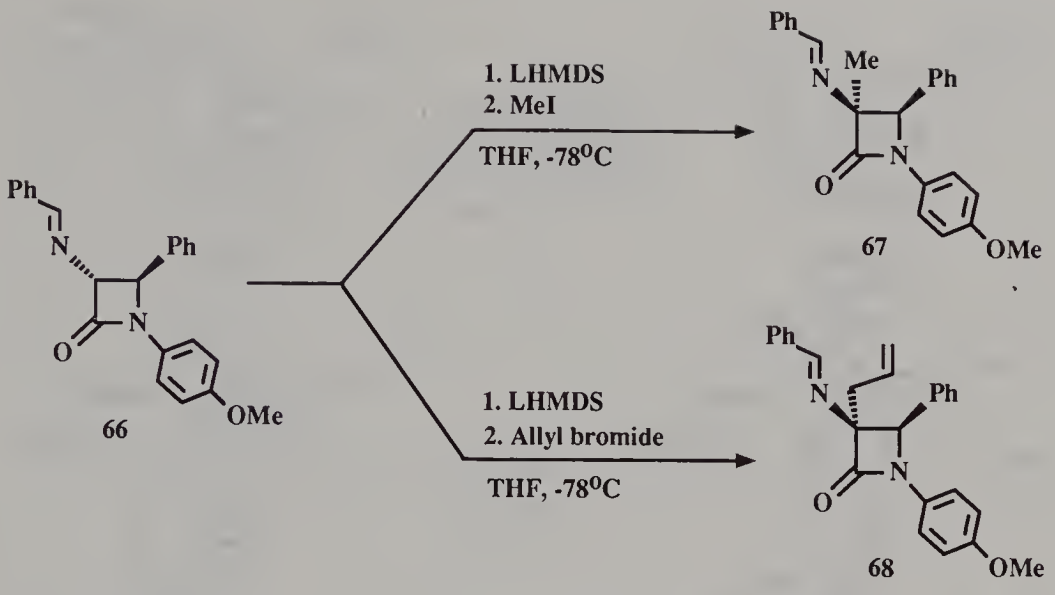
Scheme 4.22

(Reprinted, with the permission of Pergamon PLC, from Ojima and Habus.[19])

lithiated β-amino esters **(65a)**, which then cyclize to afford the corresponding *trans*-β-lactams **(61a–65a)** with greater than 99% e.e. (Scheme 4.22).

4.4.1.3.2 Type 1 Alkylation of *trans*-3-Imino-β-lactams

The *trans*-3-amino-β-lactams **(61–65)** thus obtained through the chiral ester enolate–imine cyclocondensation were converted to the corresponding *trans*-3-*N*-benzylideneamino-β-lactams and subjected to type 1 alkylation. Since the type 1 enolate generated from *trans*-β-lactam must have the same structure as that from its *cis*-isomer, the type 1 alkylation should take place in exactly the same manner as that described for the enolates from *cis*-β-lactams (see section 4.3.1.1.1). In fact, we found that, for example, the type 1 alkylation of the *trans*-3-imino-β-lactam **(66)** with methyl iodide and allyl bromide proceeded smoothly and cleanly to give the corresponding alkylated β-lactams, **67** and **68**, respectively, in high yields (Scheme 4.23), in which the attack of electrophiles took place from the backside of the 4-phenyl moiety.[56] The C^3-alkylated optically pure β-lactams thus obtained can be converted to aromatic α-alkyl-α-amino acids as discussed in the previous sections (see earlier text). Consequently, the chiral ester enolate–imine cyclocondensation followed by the type 1 alkylation protocol serves as an efficient and convenient alternative method for the synthesis of a variety of enantiomerically pure aromatic α-alkyl-α-amino acids.



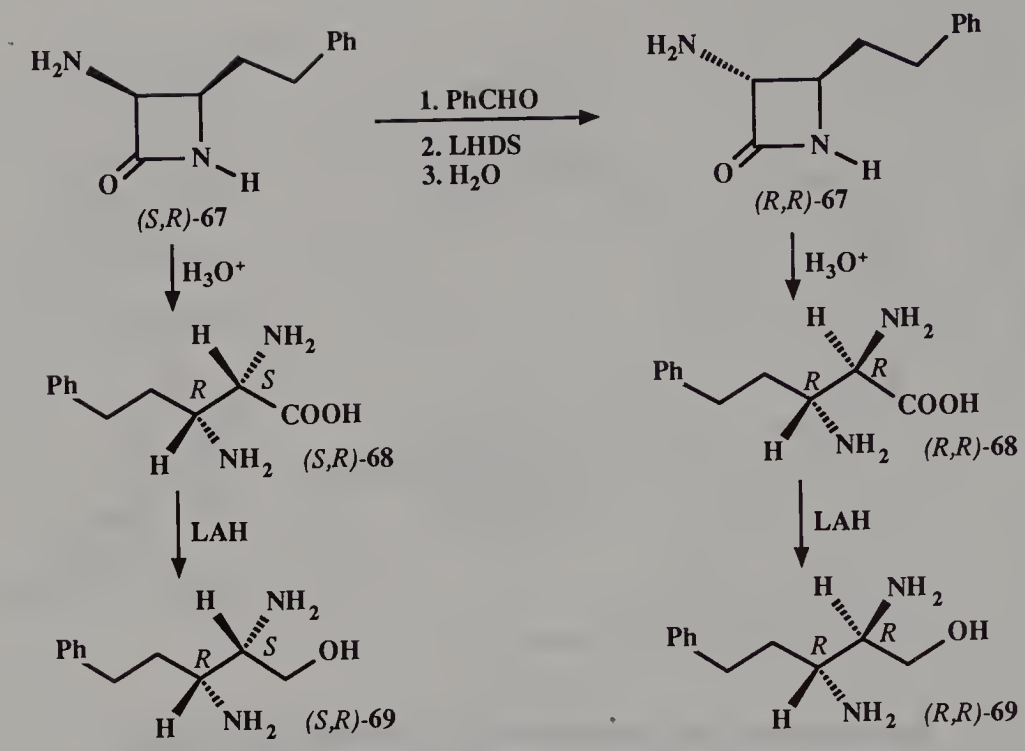
Scheme 4.23

4.4.2 Asymmetric Synthesis of α,β-Diamino Acids and Their Derivatives via Cleavage of the N—C(O) Bond of β-Lactams

The β-Lactam Synthon Method discussed earlier is based on reductive cleavage of the N—C^4 bond of 4-aryl-β-lactams. This section describes the expansion of the β-Lactam Synthon Method to the synthesis of enantiomerically pure nonaromatic amino acids and their derivatives, in which the cleavage of the N-C(O) bond of β-lactams is used for the transformation of β-lactams.

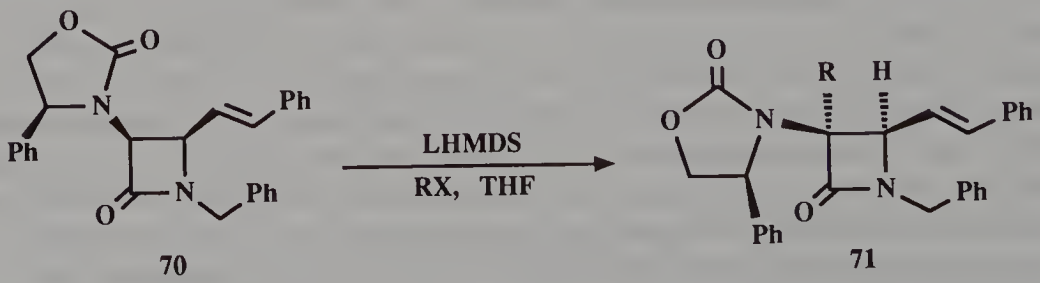
As Scheme 4.24 illustrates, 3-amino-β-lactams, *(S,R)*-**67** and *(R,R)*-**67**, are readily converted to the corresponding α,β-diamino acids, *(S,R)*-**68** and *(R,R)*-**68**, respectively, in quantitative yield by acidic hydrolysis, which are further transformed to their diamino alcohols, *(S,R)*-**69** and *(R,R)*-**69**, in high yield through lithium aluminum hydride (LAH) reduction.[57] The *cis*-β-lactam, *(S,R)*-**67**, can be epimerized to its *trans*-isomer, *(R,R)*-**69**, via protection, deprotonation, protonation, and deprotection. Accordingly, from (*S,R*)-**67** obtained via asymmetric [2+2] cycloaddition of the chiral ketene (**22a**) with imines (cf. Scheme 4.12), *(S,R)*- and *(R,R)*-isomers of **68** and **69** have been synthesized.[57] As the enantiomeric *cis*-β-lactam, *(R,S)*-**67**, can readily be obtained by using **22b**, all four stereoisomers of **68** and **69** can be synthesized by this protocol. It should be noted that *trans*-β-lactams, *(R,R)*- and *(S,S)*-**67**, can be obtained directly by the chiral ester enolate–imine cyclocondensation protocol (cf. Scheme 4.22).

The protocol illustrated in Scheme 4.24 can be combined with the type I alkylation. For example, we carried out the asymmetric alkylation of



Scheme 4.24

(3*S*,4*R*)-4-styryl-β-lactam (**70**), prepared through asymmetric [2+2] cycloaddition of **22a** to *N*-benzylcinnamaldimine, at the C-3 position with methyl iodide (at −100°C) and allyl bromide (at −78°C). The electrophiles attacked from the backside of the 4-styryl group to give the corresponding alkylated β-lactams, **71a** and **71b,** respectively, with extremely high stereoselectivity and in high yields (Scheme 4.25). The stereochemistry at the quaternary C-3 position was unambiguously confirmed by two-dimensional NMR (NOESY).



Scheme 4.25

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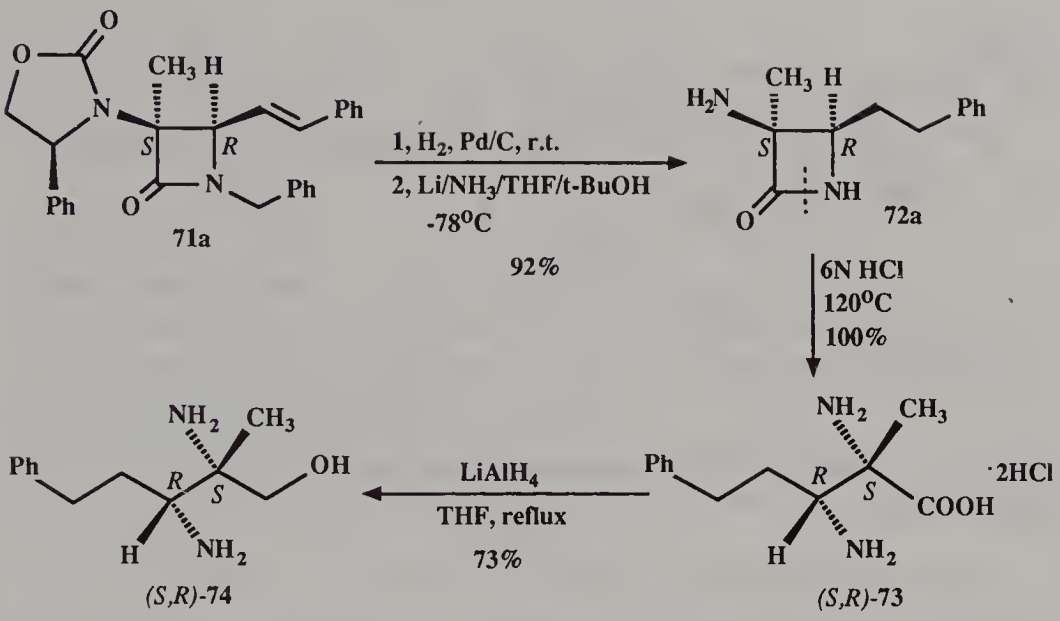

Scheme 4.26

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The 3-methyl-β-lactam (**71a**) was further converted to optically pure (2*S*,3*R*)-diamino acid, *(S,R)*-**73a**, and (2*S*,3*R*)-diamino alcohol, *(S,R)*-**74a**, bearing chiral quaternary center at the C-2 position in high yields through the optically pure β-lactam (**72a**) (Scheme 4.26).

As a variety of substituents can be introduced to the C-3 and C-4 positions of β-lactams with extremely high stereoselectivity, this newer version of the β-Lactam Synthon Method provides efficient and convenient routes to various optically pure diamino acids and diamino alcohols, which are useful intermediates for the synthesis of enzyme inhibitors, modified peptides, chiral macrocycles, and chiral ligands or reagents for asymmetric synthesis.

4.4.3 Asymmetric Synthesis of the Taxol C-13 Side Chain and Its Analogs via Chiral 3-Hydroxy-4-aryl-β-lactams

Taxol (**75**), a complex diterpene[58] isolated from the bark of *Taxus brevifolia* (Pacific yew), is currently considered the most exciting lead in cancer chemotherapy. Taxol possesses high cytotoxicity and strong antitumor activity, and is currently in phase II clinical trial in the United States.[59,60] Significant activity against cisplatin-refractory advanced ovarian cancer as well as breast cancer has been established.[60] A recent report has now shown that a more readily available taxol precursor can be isolated from the leaves of *Taxus baccata* (English yew).[61] Extraction of the fresh leaves yields 10-deacetyl baccatin III (**76**), (1g/1 kg), which has been converted to **75**.[61]

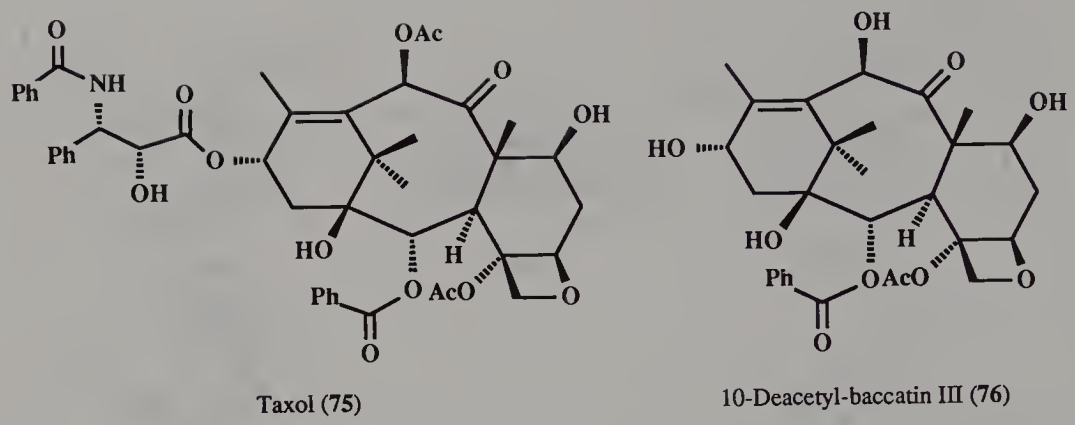

Chart 4.5. Structures of taxol (**75**) and 10-deacetyl-baccatin III (**76**).
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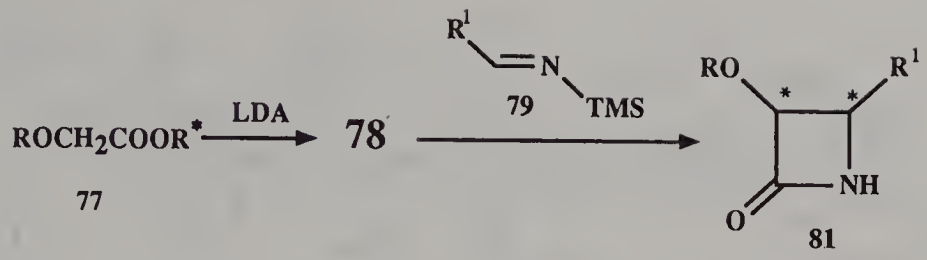
With the availability of **76,** it appears that sufficient supplies of **75** can now be produced in a semisynthetic fashion. It should be noted that the C-13 side chain, that is, the *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine (**84**) moiety, is crucial for the strong antitumor activity of **75.**[62] The first enantioselective synthesis of the important side chain **84** was performed in eight steps and 23% yield via a Sharpless epoxidation from *cis*-cinnamyl alcohol with an enantiomeric excess of 76–80%.[63] A recent publication describes the chemoenzymatic synthesis of a derivative of **84,** in which the racemic mixture was resolved by enzymatic hydrolysis with lipases.[64]

This section describes a successful application of the β-Lactam Synthon Method to the asymmetric synthesis of the C-13 side chain of taxol, **84,** and its derivatives via 3-hydroxy-4-aryl-β-lactams as the key intermediates. In this synthesis, **84** and its derivatives can be obtained in three steps in good yields with virtually 100% e.e.

First, we carried out the reactions of chiral lithium ester enolates (**4**) generated in situ from silyloxyacetates (**77**) with *N*-trimethylsilylimines (**79**), which gave the corresponding chiral β-lactams **81** (Schemes 4.27). Results are summarized in Table 4.6.

As Table 4.6 shows, the chiral auxiliary and the O-protecting group exert marked effects on the enantioselectivity as well as on the chemical yield of the reaction. [*Note:* When chiral benzyloxyacetate or phenoxyacetate was used, chemical yield was in the range 15–25%, and enantioselectivity was 15–67% e.e. See Reference 19.] For example, the reactions of **77d,** bearing (−)- or (+)-*trans*-2-phenyl-1-cyclohexyl as the chiral auxiliary[53] and triisopropylsilyl as the O-protecting group, with **79a–c** give exclusively the corresponding *cis*-β-lactams **81** in high yields with extremely high enantiomeric purity (96–98% e.e.) (entries 4–7). When (−)-menthyl is used as the chiral auxiliary and *tert*-butyldimethylsilyl as the O-protecting group (**77a**), the reaction with **5a** gives **81-A** in 52% yield with only 50% enantiomeric purity



77a : R= t-BuMe$_2$Si ; R*= (-)-menthyl
77b : R= t-BuMe$_2$Si ; R*= (-)-*trans*-2-phenyl-1-cyclohexyl
77c : R= t-BuMe$_2$Si ; R*= (-)-10-dicyclohexylsulfamoyl--D-isobornyl
77d(-) : R= *i*-Pr$_3$Si ; R*= (-)-*trans*-2-phenyl-1-cyclohexyl
77d(+): R= *i*-Pr$_3$Si ; R*=(+)-*trans*-2-phenyl-1-cyclohexyl

79a : R^1 = Ph
79b : R^1 = *p*-MeOC$_6$H$_4$
79c : R^1 = 3,4-(MeO)$_2$C$_6$H$_3$

Scheme 4.27

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(entry 1). The reaction of **77b** (t-BuMe$_2$Si; (−)-*trans*-2-phenyl-1-cyclohexyl) with **5a** gives **81-A** in 90% yield with 76% e.e., while on using (−)-10-dicyclohexylsulfamoyl-D-isobornyl as the chiral auxiliary,[65] **81-A** is obtained with 97% e.e., but in only 5% yield.

The exclusive formation of cis-β-lactams **81-B,C,D(+)** with 96 to 98% e.e. is rationalized by taking into account the highly selective generation of *E*-lithium enolates, *E*-**78d(−)**, and the transition state A depicted in Scheme 4.28. It is apparent that the chiral auxiliary, (-)-*trans*-2-phenyl-1-cyclohexyl, extremely effectively directs the approach of the *N*-TMS-imines (**79a-c**) from the *si* face of *E*-**78d(−)** to give *N*-lithio-β-amino esters (**80**), which then cyclize to afford the corresponding *cis*-β-lactams **81-B,C,D.** In the same man-

Table 4.6. ASYMMETRIC SYNTHESIS OF β-LACTAMS (**81**) THROUGH CHIRAL ESTER ENOLATE–IMINE CYCLOCONDENSATION.

Entry	Ester	Imine	β-Lactam	Isolated Yield (%)	Config.[a]	% e.e.[b]
1	**77a**	**79a**	**81–A**	52	*3R,4S*	50
2	**77b**	**79a**	**81–A**	90	*3R,4S*	76
3	**77c**	**79a**	**81–A**	5[c]	*3R,4S*	97
4	**77d(−)**	**79a**	**81–B(+)**	85	*3R,4S*	96
5	**77d(+)**	**79a**	**81–B(−)**	80	*3S,4R*	97
6	**77d(−)**	**79b**	**81–C(+)**	80	*3R,4S*	96
7	**77d(−)**	**79c**	**81–D(+)**	80	*3R,4S*	98

[a] Determined by chemical correlation with authentic samples.
[b] Determined by ^{1}H NMR analysis using a chiral shift reagent, (+)-Eu(hfc)$_3$, (entries 1,2) and by HPLC analysis on a chiral column.
[c] Substantial amount (55%) of **79c** was recovered.

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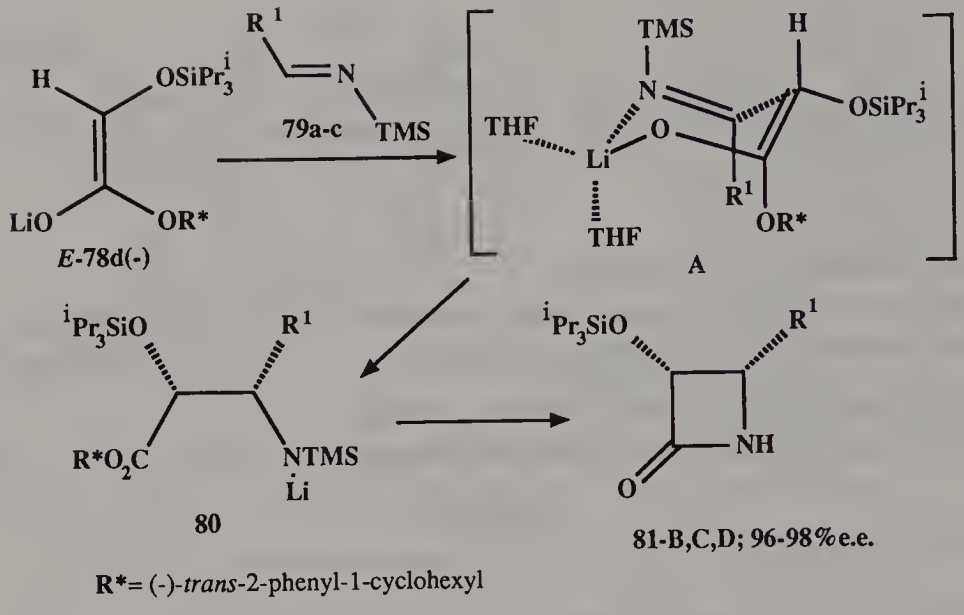

Scheme 4.28

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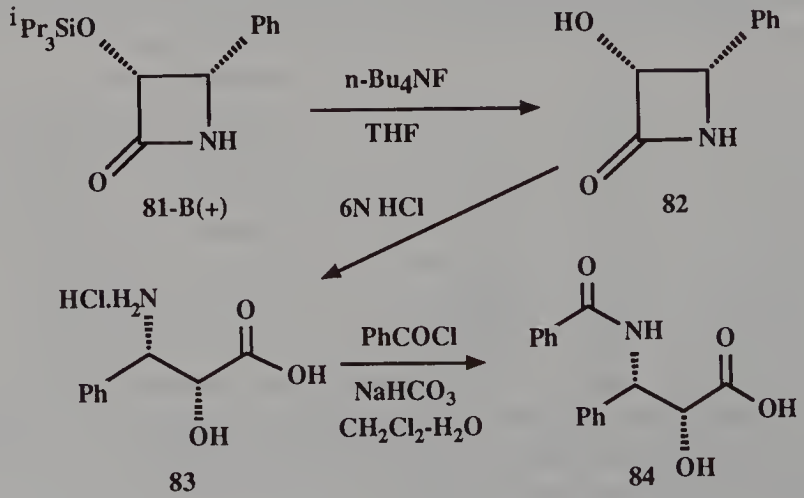
ner, the enantiomeric **81-B(−)** is yielded from *E*-**78d**(+) with 97% e.e. It is worthy of note that the asymmetric synthesis of 3-hydroxy-β-lactam has been suffering from low stereoselectivity and often low chemical yield.[66] Thus, our current method provides the first efficient and practical route to 3-hydroxy-β-lactams with extremely high enantiomeric purity.

Next, **81-B(+)** thus obtained was converted to the desired *N*-benzoyl-(2*R*,3*S*)-phenylisoserine (**84**) through the procedure illustrated in Scheme 4.29. As Scheme 4.29 shows, **81-B(+)** was deprotected by reacting with



Scheme 4.29

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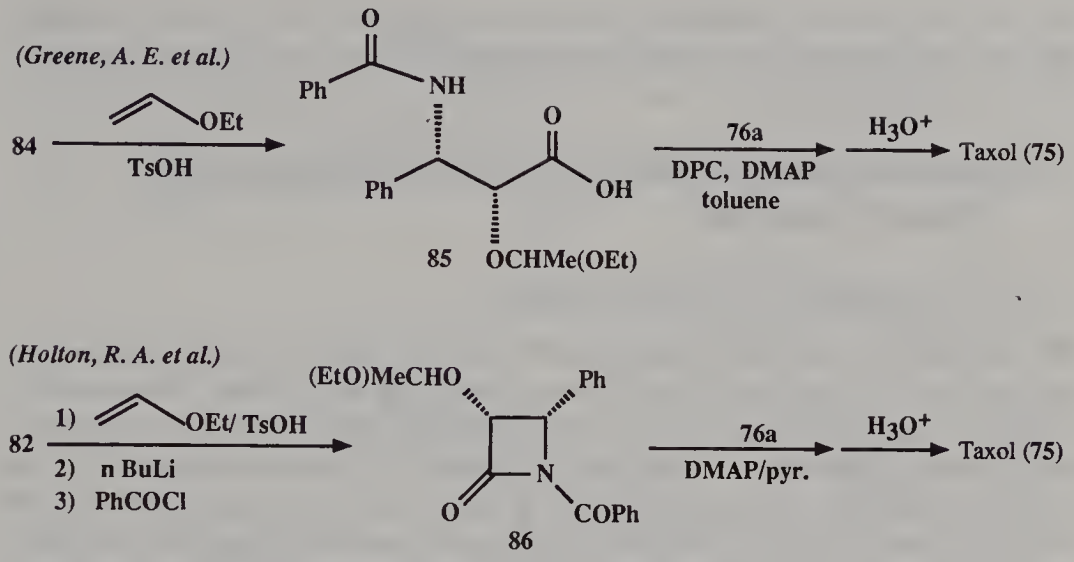

Scheme 4.30

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tetra-*n*-butylammonium fluoride to give the 3-hydroxy-β-lactam **82** in 97% yield. Then, **82** was hydrolyzed with 6 *N* HCl to afford **83** as hydrochloric acid salt in quantitative yield. The phenylisoserine **83** was benzoylated by the usual Schotten–Baumann procedure followed by purification on a short silica gel column to give enantiomerically pure *N*-benzoyl-(2*R*,3*S*)-phenylisoserine (**84**) in 70% yield. Other 3-silyloxy-4-aryl-β-lactams, **81-C(+)** and **81-D(+)**, can be converted to the corresponding substituted *N*-benzoylphenylisoserines in the same manner.

The *N*-benzoylphenylisoserine (**84**) has already been coupled with 10-acetyl-7-(triethylsilyl)-**76** (**76a**) by Greene et al.[63] (Scheme 4.30). Quite recently Holton[67] developed a more efficient coupling method directly from **82** (Scheme 4.30); thus our method described here provides the most efficient route to taxol (**75**) to date.

It is worth mentioning that this protocol based on enantiomerically pure 3-hydroxy-β-lactams is readily applicable to the synthesis of norstatin (**87**), cyclohexylnorstatin (**88**) (Chart 4.6), and their analogs and homologs, which

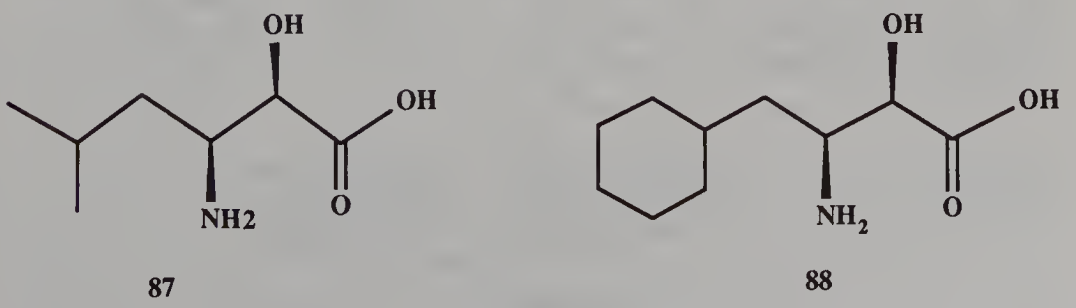


Chart 4.6. Structures of norstatin (**87**) and cyclohexylnorstatin (**88**).

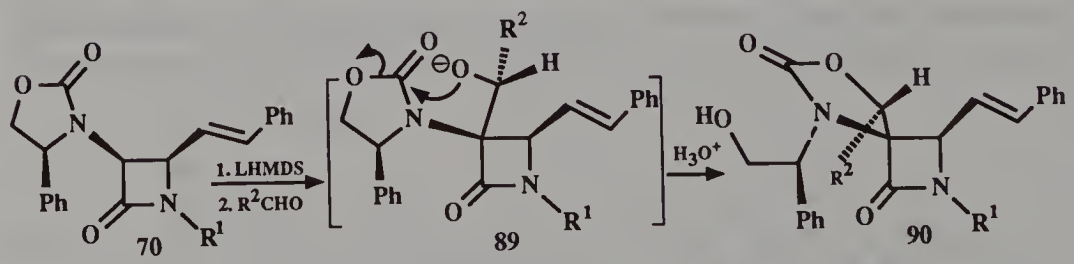
are very important constituents of enzyme inhibitors for a variety of peptidases including renin and human immunodeficiency virus type 1 protease.[68]

4.5 Miscellaneous Asymmetric Transformations with Chiral β-Lactams

4.5.1 Asymmetric Aldol Reaction

We investigated the aldol reaction of **70**, which would create two chiral centers at the C-3 position of the β-lactam and at its side chain. The approach of these aldehydes should be from the opposite side of the 4-styryl group, but the stereochemistry at the side chain and the stereoselectivity of the reaction were not easily predictable. It was found that the reactions of **70** with 2-methylpropranal, butanal, and 3-methylbutanal proceeded smoothly at −100°C to give products in high chemical yields with greater than 99% d.e.[20] When *N*-(4-bromophenyl)-β-lactam (**70-Br**) was employed, the reaction also gave the corresponding product with greater than 99% d.e. in 97% yield. At first, we naturally assumed that these products were simple aldols (**89**).[20] To our surprise, however, the X-ray crystallographic analysis of one of the products (R = isopropyl, *N*-4-bromophenyl) revealed that it was a unique spiro-β-lactam (**90-Br**) (Figure 4.6).[57] ^{1}H, ^{13}C, and two-dimensional NMR measurements, that is, COSY, CSCM, and NOESY, for **90a–c** and **90-Br** clearly showed that all the products had the same spiro-β-lactam skeleton.[57] It is apparent that the initially formed aldol **89** (lithium salt) is rearranged to the spiro-β-lactam as illustrated in Scheme 4.31.

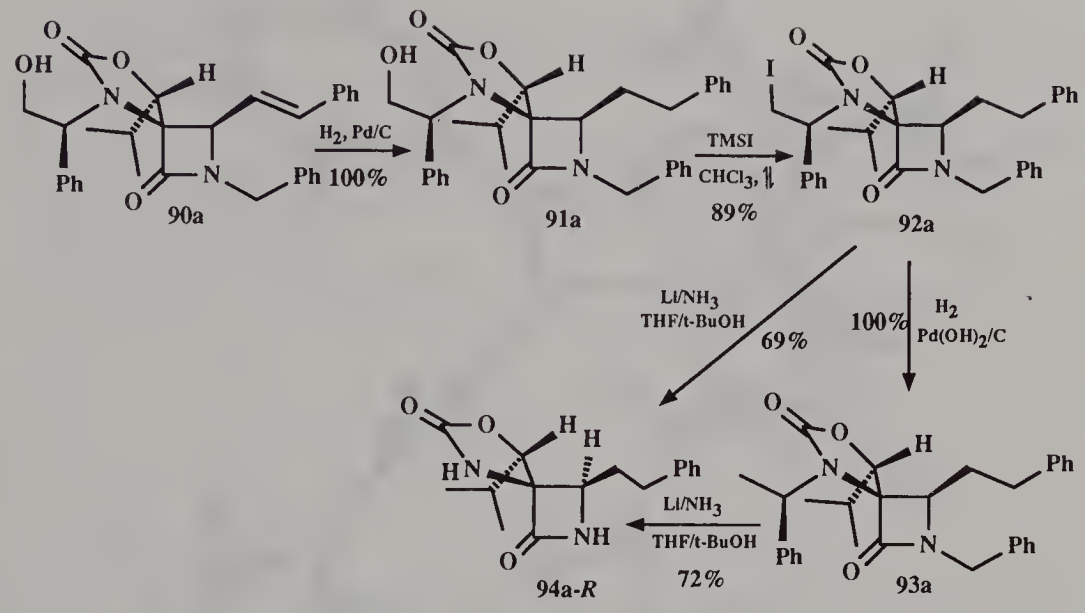
To determine the absolute configuration of the newly formed chiral center at the side chain, the spiro-β-lactam **90a** (R = isopropyl) was converted to the corresponding *N,N'*-spiro-β-lactam (**94a-R**) via hydrogenation, reaction with trimethylsilyl iodide (TMSI), and modified Birch reduction as shown in Scheme 4.32.[57] The stereochemistry of **94a-R** was determined on the basis



R^1 = -CH_2Ph
-C_6H_4-Br-*p* (**70-Br**)

a: $R^2 = (CH_3)_2CH$- >99% d.e. (96%)
b: $R^2 = CH_3CH_2CH_2$ >99% d.e. (92%)
c: $R^2 = (CH_3)_2CHCH_2$ >99% d.e. (95%)

Scheme 4.31



Scheme 4.32

of two-dimensional NMR analysis; that is, the NOESY spectrum of **94a-R** clearly showed that the isopropyl group at $C^{4'}$ of the oxazolidinone moiety was in the opposite side of the hydrogen at C^4 of the β-lactam moiety. Thus, the configuration at the newly formed chiral center ($C^{1'}$) at the side chain of **94a-R** was unambiguously determined to be R.[20,57] This assignment is consistent with the X-ray crystallographic analysis for **90-Br,** which has *R* configuration at the side chain (Figure 4.6).

We also looked at the participation of the chiral 4-phenyloxazolidinone moiety in asymmetric induction. Thus, **70** was converted to 3-amino-β-lactam (**95**) through hydrogenation and modified Birch reduction, and then to 3-imino-β-lactam (**96**). The aldol reaction of **96** with 3-methylpropanal in a manner similar to that for the formation of **90** gave the desired aldol product (**98**) with 90% d.e. (Scheme 4.33). The stereochemistry at $C^{1'}$ was unambiguously determined by converting **98** to the spirobicyclic β-lactam **94a-S** followed by the NOESY analysis; that is, it turned out that the newly formed chiral center ($C^{1'}$) of **94a-S** was *S*. It should be noted that the NMR spectra of the minor isomer coincided with those of **94a-R.**

Consequently, it was found that (1) the β-lactams **70** and **96** gave opposite configurations at the newly formed chiral centers ($C^{1'}$) of the aldol products, and (2) a simple β-lactam skeleton such as **96** possesses relatively high stereogenicity (90% d.e.) in this aldol reaction. Possible mechanisms that can accommodate these findings are proposed in Scheme 4.34. In the Newman projections of the cyclic transition states for the aldol reaction of 2-methylpropanal with lithium β-lactam enolates, the top position is the least hindered in the case of **96,** and thus the bulky isopropyl group takes this position to give the *S* configuration, whereas the top position is very crowded in the

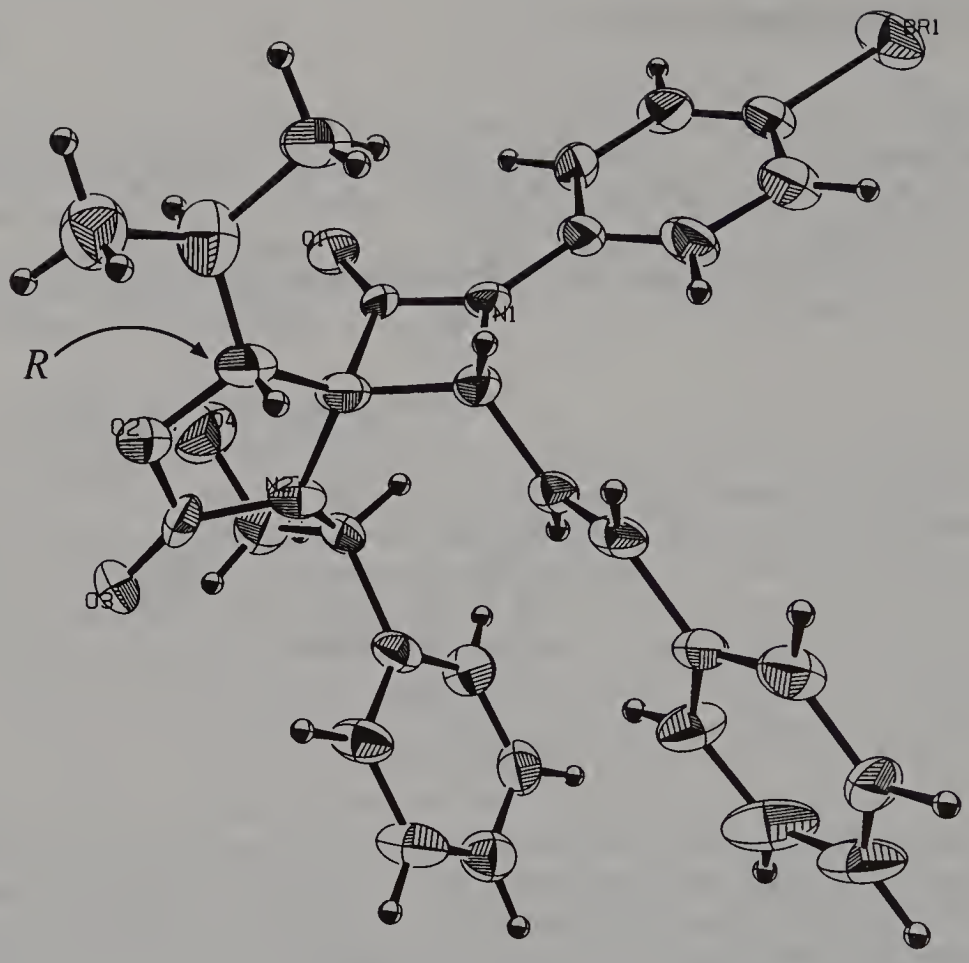
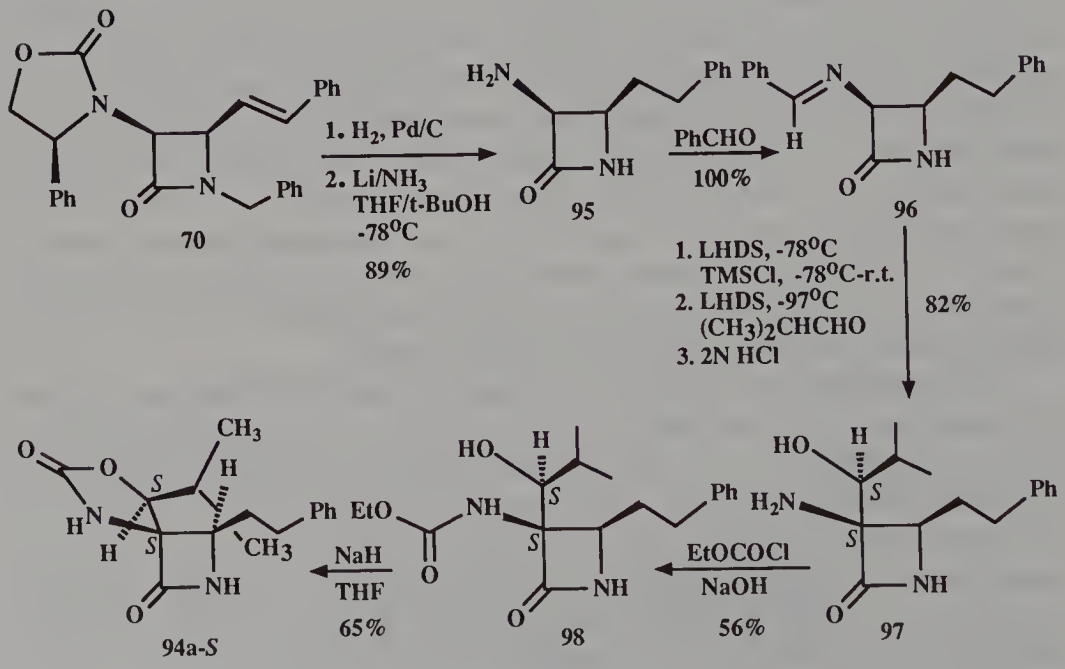


Figure 4.6 X-ray crystal structure of the spiro-β-lactam (**90-Br**).



Scheme 4.33

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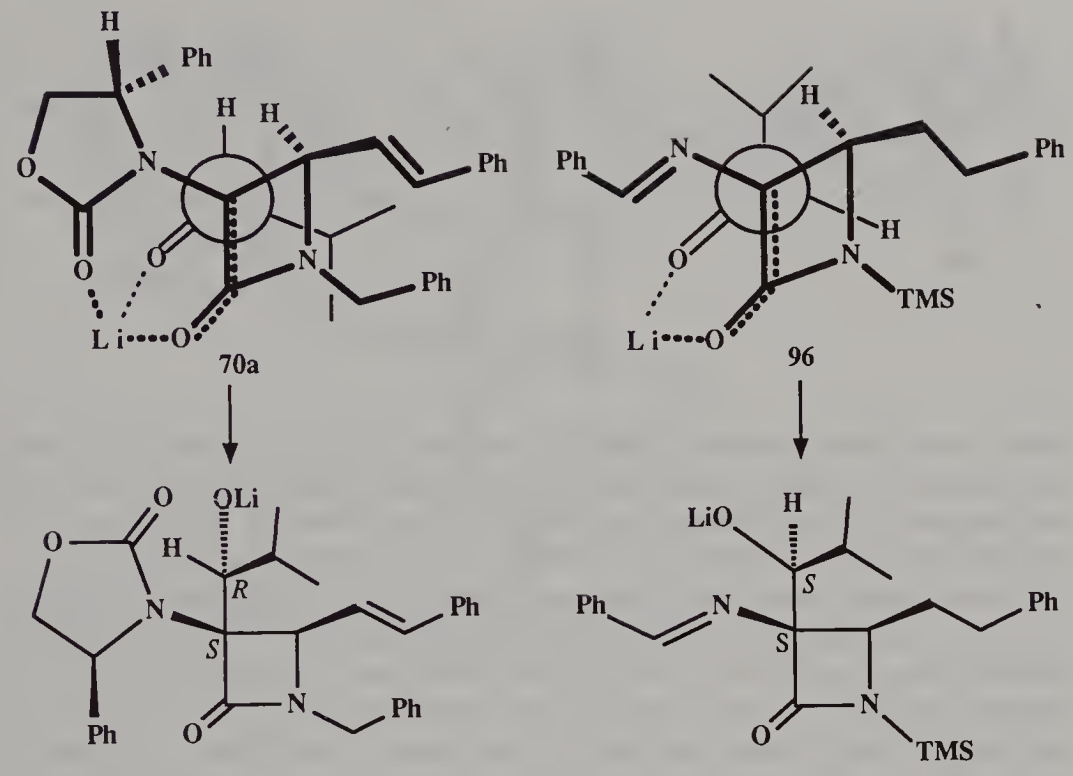

Scheme 4.34

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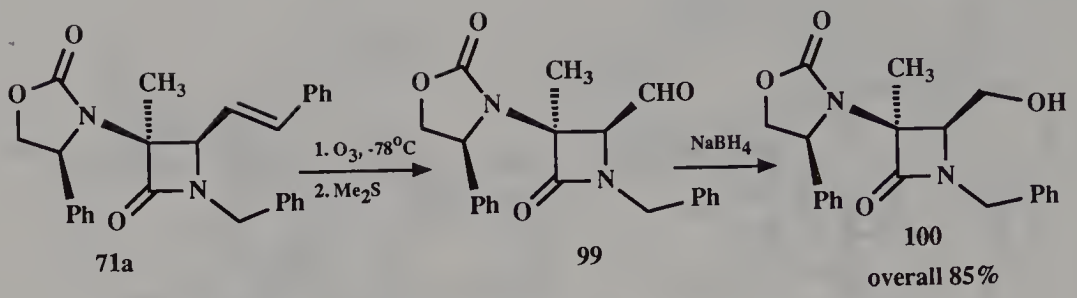
case of **70** because of the 4-phenyl group of the oxazolidinone moiety directing toward this top position, and thus the isopropyl group can no longer occupy this position to give the *R* configuration.

4.5.2 Unique Rearrangements of Chiral 3-Oxazolidinyl-β-lactams

In the course of our study on the transformations of chiral 3-oxazolidinyl-β-lactams, we discovered novel rearrangements of these β-lactams. This section describes these arrangements and discusses possible mechanisms.

First, the 4-styryl-β-lactam (**71a**) was converted to the corresponding 4-hydroxymethyl-β-lactam (**100**) by ozonolysis followed by sodium borohydride reduction in 85% overall yield (Scheme 4.35).[57]

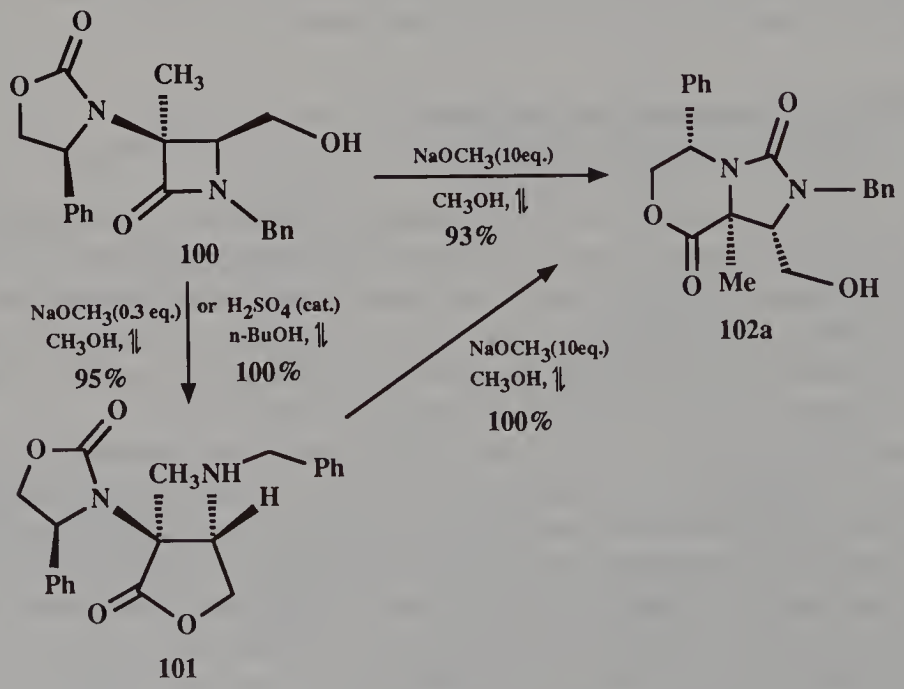
Next, **100** was treated with excess sodium methoxide (10 equivalents) in methanol at refluxing temperature, with the intention of converting **100** to the lactone (**101**); however, contrary to our prediction, a bicyclic diazolidinone (**102**) was obtained in nearly quantitative yield, which consisted of a single stereoisomer (Scheme 4.36).[57] When the reaction was carried out in methanol in the presence of a catalytic amount sodium methoxide (0.3 equivalent), the initially expected lactone (**101**) was formed in 95% yield.[69] This lactone (**101**) was also obtained in quantitative yield by using a catalytic amount of sulfuric acid in refluxing *n*-butanol.[69] When the lactone **101** was



Scheme 4.35

treated with excess sodium methoxide (10 equivalents) in refluxing methanol, **102a** was obtained in quantitative yield. Thus, **101** is likely to be a key intermediate for the formation of **102a.** The structures of **101** (Figure 4.7) and **102a** (Figure 4.8) were elucidated by X-ray crystallographic analyses.

A likely mechanism for these rearrangements is proposed in Scheme 4.37.[69] As Scheme 4.37 illustrates, the 4-hydroxymethyl of **100** becomes an alkoxide on treatment with sodium methoxide, and the alkoxide attacks intramolecularly the β-lactam carbonyl to cleave the β-lactam ring, forming the lactone (**101**) stereospecifically. Under acidic conditions, protonation takes place on the β-lactam carbonyl oxygen, and the 4-hydroxymethyl group attacks the β-lactam carbonyl, opening the β-lactam ring to give **101** with complete stereospecificity. When the base is used in excess, methoxide ion attacks the chiral oxazolidinone moiety to open the ring, generating the



Scheme 4.36

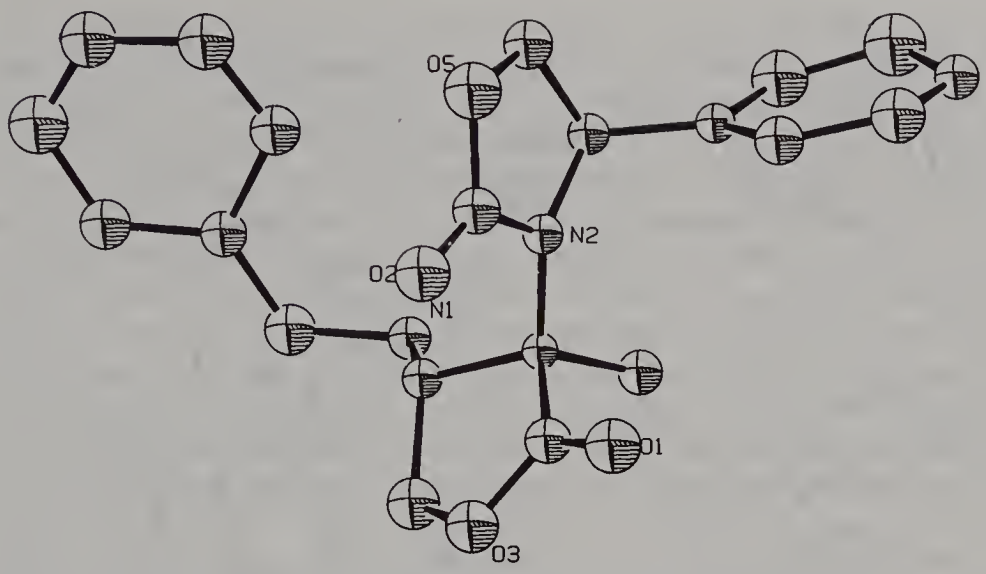


Figure 4.7 X-ray crystal structure of the lactone (**101**).

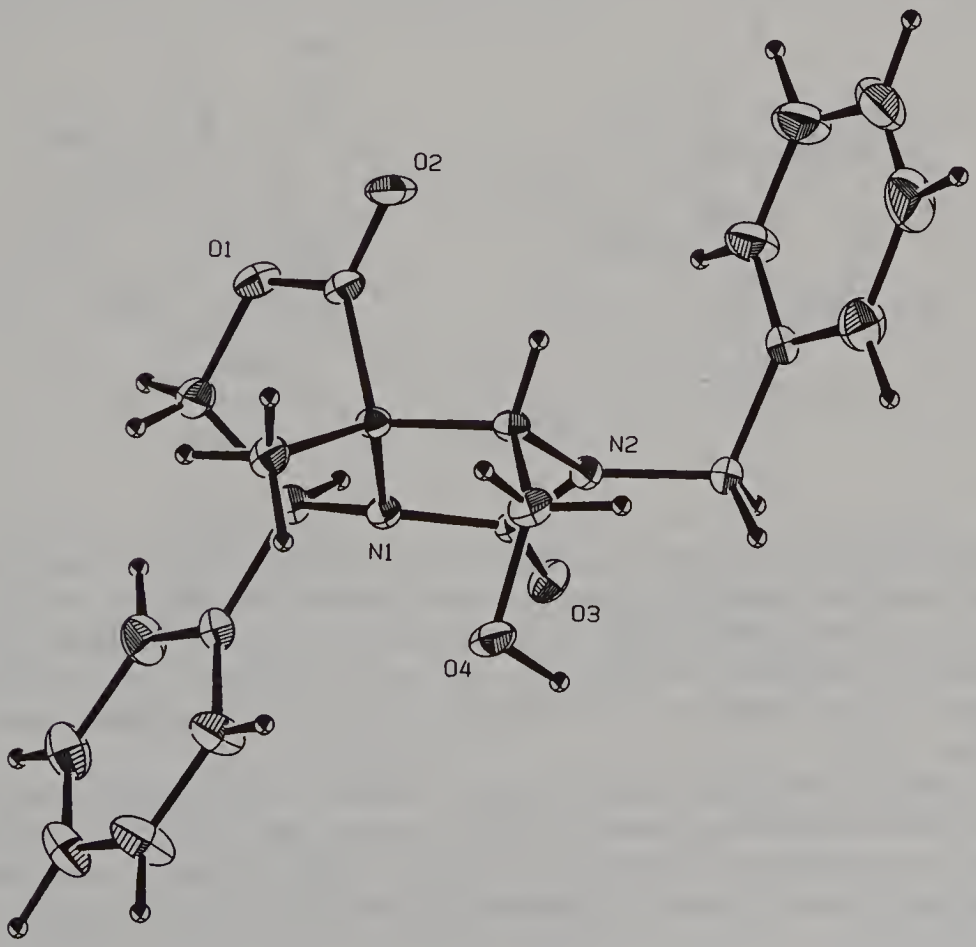
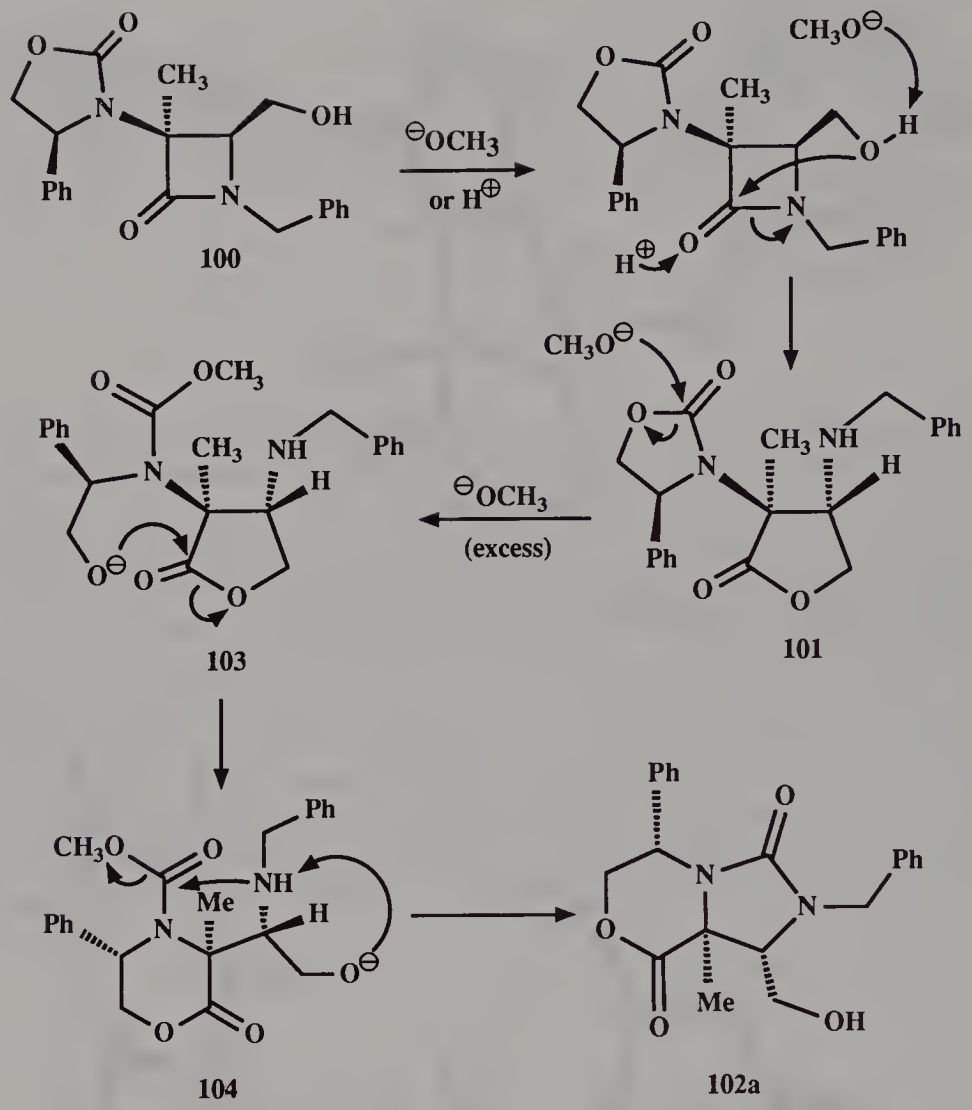


Figure 4.8 X-ray crystal structure of bicyclic diazolidinone (**102a**).



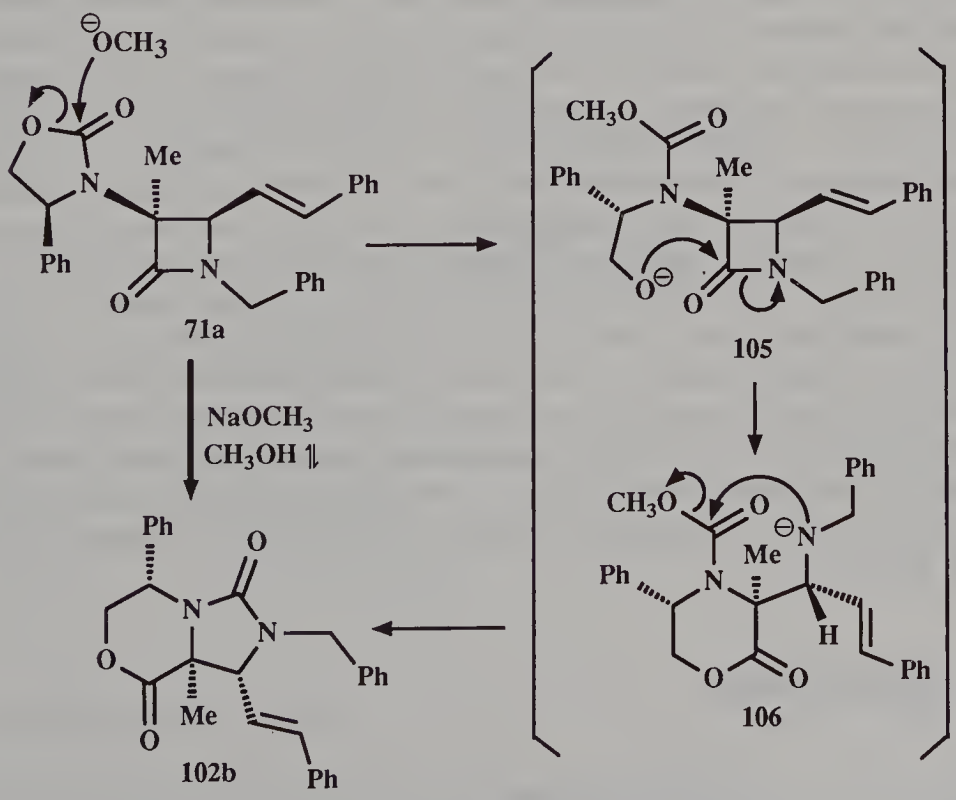
Scheme 4.37

alkoxide ion-bearing methyl carbamate moiety (**103**). The alkoxide (**103**) then undergoes lactone exchange to form another alkoxide-bearing morpholinone moiety (**104**). Finally, the alkoxide ion abstracts the amine proton and the amide thus generated attacks the carbamate moiety, all intramolecularly, to give the bicyclic diazolidinone having the morpholinone moiety (**102a**).

According to the proposed mechanism (Scheme 4.37), methoxide ion attacks the oxazolidinone moiety of **101** to generate **103**. If this is indeed the case, 3-oxazolidinyl-β-lactams not bearing a 4-hydroxymethyl group might undergo the same type of rearrangement to yield the corresponding bicyclic diazolidinones.

To examine this hypothesis, we carried out the reaction of the 4-styryl-β-lactam (**71a**) with excess sodium methoxide in refluxing methanol. The reaction indeed gave the expected rearrangement product, **102b** (Scheme 4.38), but in somewhat reduced isolated yield (50%).[57] A substantial amount of cinnamaldehyde was recovered, which indicates the occurrence of a retro-imine condensation process. This side reaction may well be ascribed to the competing methoxide attack on the β-lactam carbonyl to open the β-lactam ring first, promoting the retro-imine condensation. Nevertheless, the major pathway is to generate **105**, which then rearranges to form the morpholinone intermediate (**106**), which is very similar to **104** (Scheme 4.38). This reaction gives only one stereoisomer as well. The structure was elucidated by chemical correlation of **102b** to **102a** through conversion of the styryl moiety to the hydroxymethyl group via ozonolysis followed by sodium borohydride reduction.

Consequently, it was demonstrated that β-lactams are useful chiral precursors for the asymmetric synthesis of heterocycles. The asymmetry of the chiral β-lactams is successfully transferred to the chiral centers in the final heterobicyclic products. Since the 1- and 4-substituents on the β-lactam ring and the substituent in the oxazolidinyl moiety can readily be modified, the



Scheme 4.38

novel rearrangements may serve as new and useful methods for the asymmetric synthesis of a variety of azaoxabicyclo[4.3.0] systems.

4.6 Conclusion

This chapter has described the development of the unique β-Lactam Synthon Method in our laboratory. The first-generation β-Lactam Synthon Method is based on the facile reductive cleavage of the N—C^4 bond of optically pure 4-aryl-β-lactam esters, which are obtained through the [2+2] cycloaddition of azidoketene or other achiral ketenes to chiral imino esters followed by diastereomer separation. The method has been applied to (1) biologically active oligopeptide syntheses, (2) the rapid elucidation of absolute configurations in the mechanistic study of asymmetric [2+2] cycloadditions, and (3) extremely stereoselective labeling of dipeptides. The second-generation β-Lactam Synthon Method is based on the control of absolute configurations by asymmetric synthesis. The newer features in the second-generation method include (1) enantioselective as well as diastereoselective [2+2] cycloaddition of chiral ketenes to imines or imino esters, (2) enantioselective chiral ester enolate–imine cyclocondensation, (3) stereoselective alkylations through the type 1 and type 2 chiral β-lactam enolates, (4) dissolving metal reduction conditions for the N—C^4(Ar) bond cleavage, and (5) hydrolytic cleavage of the N—C(O) bond, which is applicable to any optically pure β-lactam. These reactions proceed with extremely high selectivity and constitute the basis for subsequent various transformations. The second-generation β-Lactam Synthon Method has been applied to the asymmetric syntheses of nonprotein amino acids, their dipeptides, and their derivatives, which are very important as the key structures in enzyme inhibitors as well as modifiers of biologically active peptides, and to the highly efficient and practical synthesis of the C-13 side chain of taxol, a highly potent anticancer agent. The β-Lactam Synthon Method is further expanding its applicability; for example, the highly stereoselective aldol reaction gives novel spirobicyclic-β-lactams, and the unique skeletal rearrangements provide new routes to a variety of heterocyclic compounds. Although the β-lactam skeleton is just a four-membered cyclic amide, it has been giving us unexpectedly rich organic chemistry and still more to come in the future.

4.7 Abbreviations

Ac	Acetyl
Boc	*tert*-Butoxycarbonyl
Bu	Butyl

Bu^t	*tert*-Butyl
CBZ	Carbobenzoxy
COSY	Correlated Spectroscopy
CSCM	Chemical shift correlation map
DCC	Dicyclohexylcarbodiimide
diPAMP-Rh^+	Bis[(2-methoxyphenyl)phenylphosphino]ethane-rhodium complex
d.e.	Diastereomeric excess
DMAP	4-Dimethylaminopyridine
DPC	2,2′-Dipyridyl carbonate
e.e.	Enantiomeric excess
Et	Ethyl
HOBT	1-Hydroxybenzotriazole
HPLC	High performance liquid chromatography
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
LHMDS	Lithium hexamethyldisilazide
Me	Methyl
MPLC	Medium-pressure liquid chromatography
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser and exchange spectroscopy
Ph	Phenyl
Ph-CAPP-Rh^+	1-Phenylcarbamoyl-2-diphenylphosphino-methyl-4-diphenylphosphinopyrrolidine-rhodium complex
r.t.	Room temperature
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMS	Trimethylsilyl
TMS-Cl	Chlorotrimethylsilane
TMSI	Trimethylsilyl iodide

4.8 Acknowledgments

This work has been supported by grants from the National Institutes of Health (NIGMS). Generous support from Ajinomoto Company, Inc., as well as the Center for Biotechnology at Stony Brook, which is sponsored by the New York State Science and Technology Foun-

dation, is also gratefully acknowledged. The author thanks Dr. Hauh-Jyun C. Chen, Dr. Xiaogang Qiu (George Chiu), Dr. Yazhong Pei, Dr. Ivan Habus, Dr. Mangzhu Zhao, Dr. Kazuaki Nakahashi, Dr. Thierry Briguard, Mr. Takeo Komata, and Mr. Young Hoon Park for their dedication and fruitful collaboration. He also thanks Dr. Naoto Hatanaka, Mr. Shigemi Suga, and Ms. Rumiko Abe for their excellent collaboration in the discovery and initial development of the first-generation β-Lactam Synthon Method at the Sagami Chemical Research Center.

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68. For example, (a) Harada, H.; Iyobe, A.; Tsubaki, A.; Yamaguchi, T.; Hirata, K.; Kamijo, T.; Iizuka, K.; Kiso, Y. *J. Chem. Soc., Perkin Trans. 1* **1990,** 2497. (b) Matsumoto, T.; Kobayashi, Y.; Takemoto, Y.; Ito, Y.; Kamijo, T.; Harada, H.; Terashima, S. *Tetrahedron Lett.* **1990,** *31,* 4175. (c) Rich, D.; Green, J.; Toth, M. V.; Marshall, G. R.; Kent, S. B. H. *J. Med. Chem.* **1990,** *33,* 1285.

69. Ojima, I.; Pei, Y. *Tetrahedron Lett.* **1992,** *33,* 887.

CHAPTER

5

Novel Methods for the Construction of the β-Lactam Ring

Robert J. Ternansky and John M. Morin, Jr.

Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana 46285

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5.1 Introduction

Since the determination of the chemical structure of penicillin[1] and the identification of the β-lactam subunit as the key structural element endowing these compounds with life-saving antibacterial activity, the significance of this small-ring heterocycle to the field of organic synthesis was established. Indeed, early preparations of the azetidinone ring, most notably by Staudinger in 1907,[2] were mere curiosities prior to the unraveling of the molecular framework of penicillin. The crystallographic confirmation of the structure of penicillin[3] led practitioners of the art of organic synthesis to focus their attention on the β-lactam ring as an important and practical synthetic target. The discovery of other β-lactam-containing antibacterials such as the cephalosporins, carbapenems, monobactams, and carbacephalosporins served to

lend further support to the need for efficient methods of construction of the β-lactam ring.

Of the many challenges presented to the synthetic chemist by these azetidinone-based antimicrobial agents, the preparation of the β-lactam ring proved most formidable. Early studies directed toward the construction of this four-membered lactam ring have been extensively reviewed. An initial progress report was described in 1949 by Bachmann and Croyn.[4] The chemical methodology required to construct these important heterocycles developed rapidly throughout the following years as reviewed in a work edited by Flynn.[5] A three-volume treatise entitled *Chemistry and Biology of β-Lactam Antibiotics* edited by Morin and Gorman was published in 1982.[6] This work summarized the major chemical and biological contributions to the field of β-lactam-containing antibacterials and remains today as the key reference to practitioners in this area. In 1983, a chapter reviewing the major syntheses of the β-lactam ring was presented by Koppel in a book edited by Hassner.[7] Also during these years, the proceedings of the First through Fourth International Symposia on Recent Advances in the Chemistry of β-Lactam Antibiotics were published by the Royal Society of Chemistry.[8] These compilations serve as periodic updates to the ever-progressing field of β-lactam chemistry and biology. In addition, many other topical reviews have appeared throughout the scientific literature.[9]

The goal of this chapter will be to highlight significant contributions to the synthesis of the β-lactam ring that have been reported over the last decade. When reviewing this scientific literature, one is immediately overwhelmed with the sheer number of citations. Many of the reported contributions to the synthesis of the azetidinone ring have been based on cycloaddition strategies, which have been covered in previous chapters, or organometallic-mediated processes, which will be excluded from this discussion. Nonetheless, after eliminating these references, the literature abounds with novel ways to prepare the four-membered lactam ring. Indeed, a search of the chemical literature has led to the identification of over 2000 references related to the novel methods that constitute the subject of this chapter. Clearly, it is not possible within the scope of this presentation to document all of these reports. Rather, it will be our goal to focus on those methodologies that are unique as well as those most suitable for use in the preparation of biologically active molecules. In this regard, methods that allow for appropriate substitution at carbons 3 and 4 of the β-lactam will be most useful for those interested in the conversion of such intermediates into biologically active compounds.

This chapter is divided into five main sections, each concentrating on the formation of a particular bond that results in the construction of an azetidinone ring. Thus (Figure 5.1), novel methods for the formation of the amide bond (N_1—C_2) and the C_2—C_3, C_3—C_4, and C_4—N_1 bonds are treated separately. Following these discussions, new methodologies that involve multiple-bond formations are presented. Ring contraction reactions leading to the

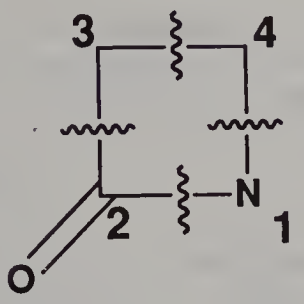


Figure 5.1 Sites for β-lactam bond formation.

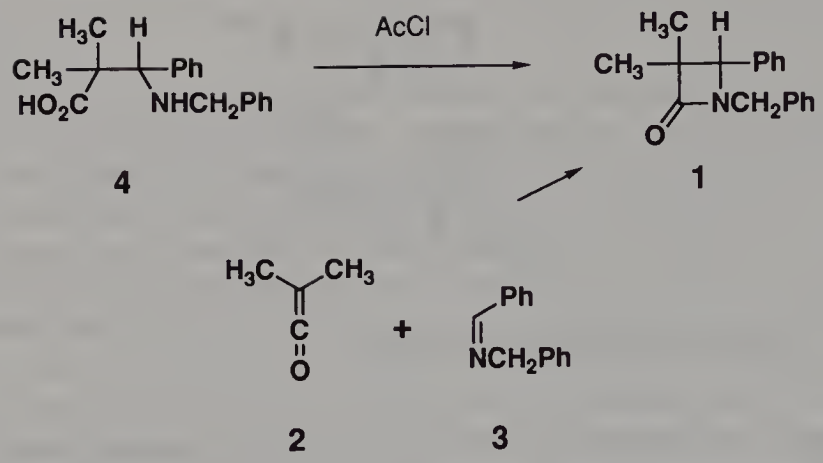
formation of a β-lactam ring are treated as single azetidinone bond-forming reactions and are included in the appropriate section. In addition, stereoselective syntheses of the precursor molecules used in the azetidinone bond-forming reactions are considered beyond the scope of this chapter and are not covered; however, some aspects of this important topic are covered in other chapters and have recently been reviewed.[10]

5.2 Formation of the Amide (N_1—C_2) Bond

The most obvious approach to the synthesis of the azetidinone structures is via dehydration of β-amino acids. Unfortunately, in contrast to their γ and δ analogs, β-amino acids do not normally cyclize thermally.[11] This is in part due to the high degree of ring strain present in the desired product, the possibility of intermolecular condensation, and the propensity of the starting material to undergo β-elimination. In spite of these complications, a limited number of specialized methods have been developed for the efficient cyclization of β-amino acids and their derivatives through the use of condensation reagents. The success of these methods is normally dependent on the structural features of the substrate and product. This section reviews the use of these amide-forming reagents over the last decade with an emphasis on the most commonly employed practical methods; however, because of the rich history of some approaches, a historical perspective is given where appropriate.

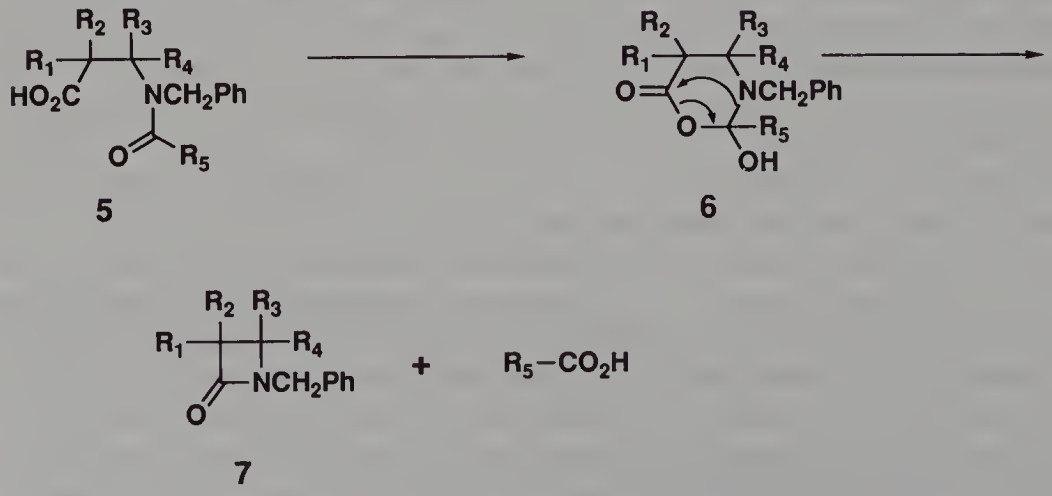
The first example of such an approach was reported by Staudinger, Klever, and Kober in 1910 (Scheme 5.1).[12]

To verify the structure of azetidinone **1**, derived via a cycloaddition reaction of dimethyl ketene **2** and Schiff base **3**, β-amino acid **4** was treated with acetyl chloride. The dehydration product **1** was obtained in 70% yield. In addition, they found that β-acylamino acids **5** cyclized readily to the parent azetidinone structure **7**. Sheehan and Corey have hypothesized the intermediacy of a hydroxylactone **6** that facilitates β-lactam formation.[13] Acetic anhydride has also been used with good success with β-acylamino acids (Scheme 5.2).[14,15]

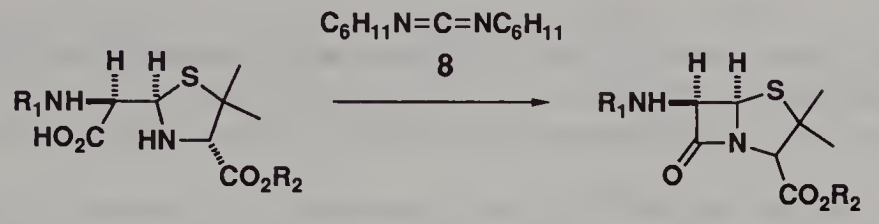


Scheme 5.1

The use of dicyclohexylcarbodiimide **8** as a condensing agent in peptide synthesis was pioneered by Sheehan and Hess (Scheme 5.3).[16,17] This reagent was used by Sheehan and Henery-Logan in their landmark synthesis of penicillin.[18,19] Cyclization of the monosodium salt **9** with dicyclohexylcarbodiimide in aqueous dioxane afforded penicillin V **11** in 5% yield. Improved conditions for the carbodiimide coupling reaction of these structures were reported in subsequent studies.[20] Reaction of the trityl-protected benzyl ester **10** with diisopropylcarbodiimide in aqueous dioxane afforded penicillin **12** in 67% yield. In this case, problematic azalactone formation **(9–13)**, a well-known occurrence in peptide bond-forming reactions, was obviated by judicious use of the trityl protecting group in the key coupling reaction. Aside from its historical significance, the Sheehan carbodiimide coupling procedure continues to be a method of choice for the cyclization of β-amino acids.[21]

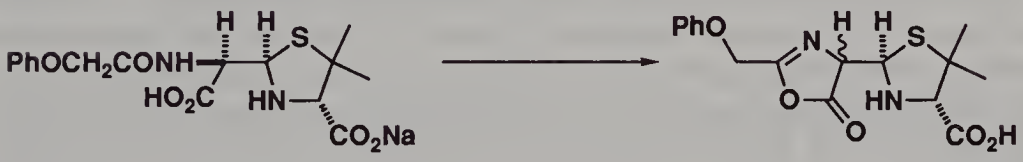


Scheme 5.2



9: R_1 = $PhOCH_2CO$, R_2 = Na
10: R_1 = Ph_3C, R_2 = CH_2Ph

11: R_1 = $PhOCH_2CO$, R_2 = H
12: R_1 = Ph_3C, R_2 = CH_2Ph

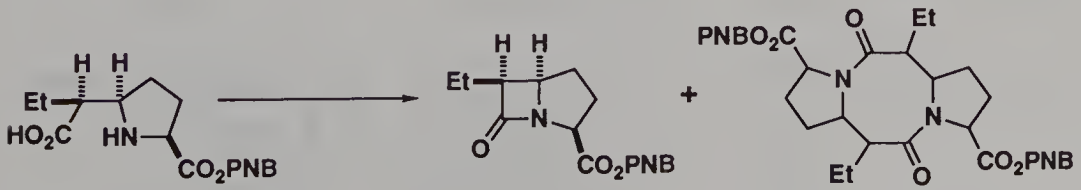


9 **13**

Scheme 5.3

Water-soluble carbodiimide has also been used effectively as a dehydrating agent. Bachi and co-workers found that attempted cyclization of β-amino acid **14**, derived from ethyl glutamate, gave an unstable crude β-lactam product which decomposed on attempted purification (Scheme 5.4).[22] To obviate any detrimental side reactions involving the starting materials or products, a high-dilution reaction using 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride in methylene chloride was employed. After 22 hours, residual carbodiimide and its corresponding derivatives, as well as any other water-soluble contaminants, were extractively removed. The desired β-lactam product **15** and its corresponding dimer **16** were obtained after flash chromatography in 41 and 10% yields, respectively.

An interesting variation of the classical carbodiimide method was described by Tanner and Somfai in their enantioselective synthesis of the car-



14 **15** **16**

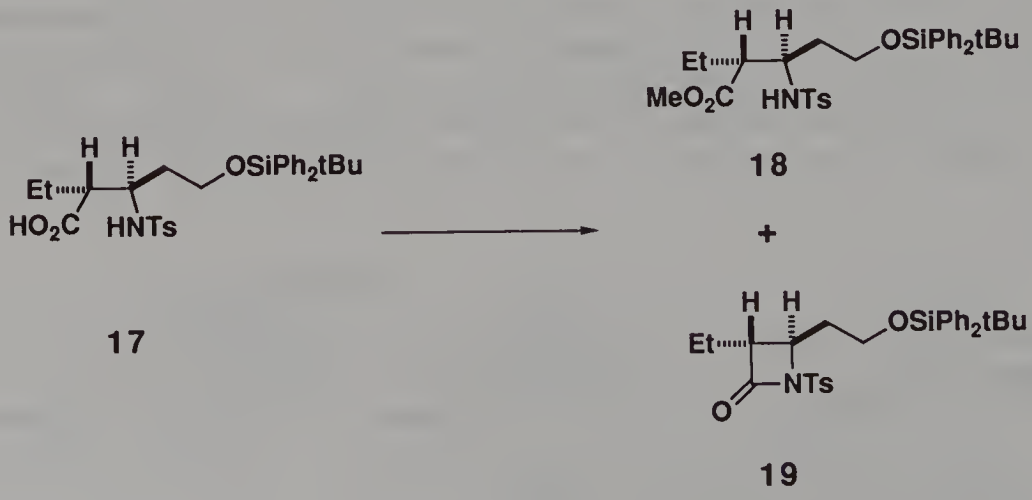
Scheme 5.4

bapenem antibiotic (+)-PS-5 (Scheme 5.5).[23] They reported that *N*-tosyl amides can be prepared in good yield under mild conditions by the inter- or intramolecular condensation of secondary sulfonamides and carboxylic acids using dicyclohexylcarbodiimide and the presence of 4-pyrrolidinopyridine.

This reaction was serendipitously discovered in an attempt to esterify acid **17** under Hassner conditions.[24] Treatment of **17** with dicyclohexylcarbodiimide, methanol, and 4-pyrrolidinopyridine in methylene chloride yielded only a modest amount of the expected methyl ester **18** and a significant amount of β-lactam **19**. Exclusion of the methanol from the reaction procedure produced compound **19** in 83% yield. High-dilution conditions were found to be unnecessary, but 4-pyrrolidinopyridine was essential for β-lactam formation, as little or no **19** was produced in its absence. A possible mechanism for this transformation (Figure 5.2) involving the intermediacy of an acylpyridinium species, has been suggested by these authors.[23] This procedure was found to proceed with little or no racemization and was also applicable to the synthesis of five-, six-, seven-, and nine-membered lactams.

Watanabe and Mukaiyama have reported phase-transfer conditions for the cyclodehydration of β-amino acids.[25] They found that reaction of β-amino acids with methanesulfonyl chloride, potassium hydrogen carbonate, and a tetrabutylammonium salt as catalyst in a chloroform–water system gave good yields of the corresponding azetidinones (Figure 5.3).

High-dilution techniques were not required as the concentration of the reactive species in the organic phase is low as a result of the phase-transfer nature of the reaction. A single-phase modification of this procedure has been used by French workers for the preparation of simple[26] and complex β-lactam derivatives.[27] For example, acid **21**, derived from methoxyglycinate, was converted to cephem **22** in 60% yield with methanesulfonyl chlo-



Scheme 5.5

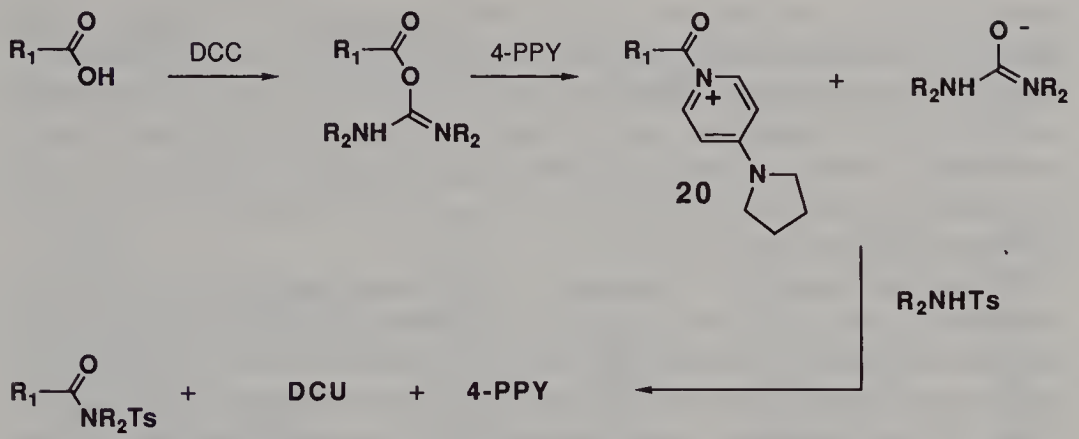
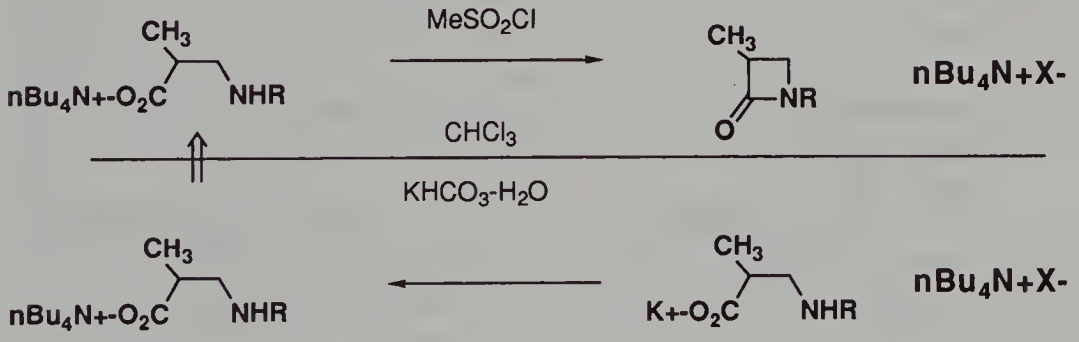


Figure 5.2 Mechanism for the formation of *N*-tosyl amides.

ride, tetrabutylammonium hydrogen sulfate, and triethylamine in anhydrous chloroform. More recently, conditions have been found that eliminate the necessity of the phase-transfer catalyst.[28] Chemists at Merck have developed a process in which acid **23**, when added to a solution of methanesulfonyl chloride and suspended sodium bicarbonate in acetonitrile at 45°C, afforded a 97% yield of 97% pure β-lactam **24** after filtration and solvent evaporation. Compound **24** is a key intermediate in carbapenem synthesis. This process has been carried out on a kilogram scale and compared favorably with other

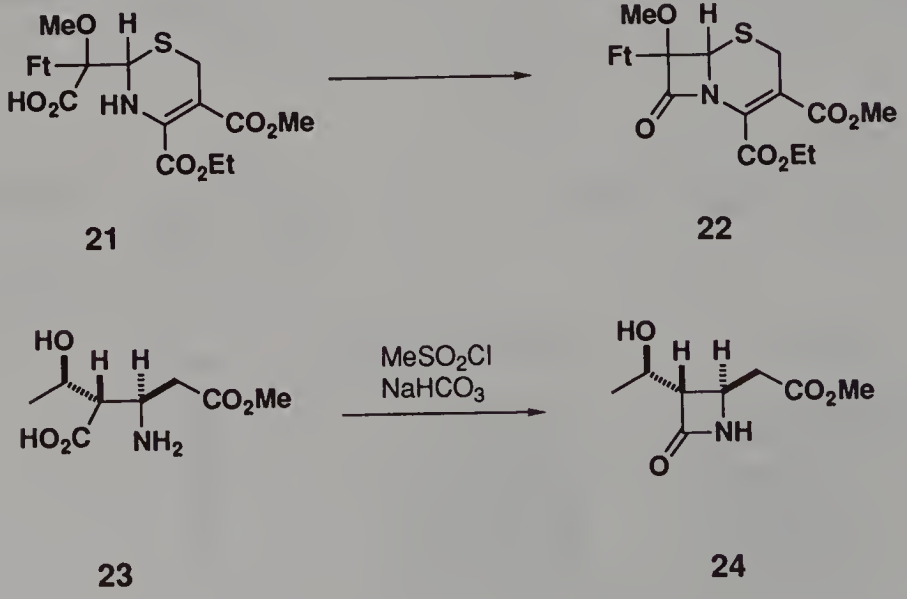


substrate	ammonium salt (mol%)	yield %
R = CH_2Ph	nBuN+Br-(15)	68
R = CH_2Ph	nBuN+HSO_4-(15)	87
R = cyclohexyl	nBuN+Br-(30)	48
R = cyclohexyl	nBuN+HSO_4-(15)	81
R = cyclohexyl	nBuN+HSO_4-(50)	59
R = nhexyl	nBuN+HSO_4-(15)	80

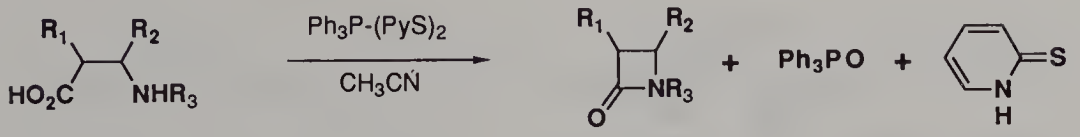
Figure 5.3 Phase-transfer conditions for the cyclodehydration of β-amino acids.

β-lactamization procedures on **23**, including dicyclohexylcarbodiimide (88%),[21] *N*-chloro-*N*-methylpyridinium iodide (93%),[29] and triphenylphosphine/2,2′-dibenzothiazyl disulfide (90%).[30] The generality of this method was found to be dependent on the solubility of the cyclization substrate in acetonitrile. Other sulfur-based agents such as thionyl chloride[31] (via the acid chloride) and di-2-pyridyl sulfite[32] have also been used for β-lactam synthesis (Scheme 5.6).

Phosphorus reagents are known to be efficient agents for activation of carboxylic acids.[33] For this reason, a number of excellent phosphorus-derived condensation agents have been developed for the preparation of β-lactams.[34] Among the most useful is Mukaiyama's reagent (triphenyl phosphine–pyridine disulfide)[35] in an acetonitrile solution developed for β-amino acids by Ohno and co-workers (Figure 5.4).[36,37] High yields of β-lactams are normally obtained under neutral conditions. Other functional groups such as the amino, hydroxy, and ester moieties are normally unaffected by the reaction conditions. In addition, wet acetonitrile can be used for water-soluble amino acids. The use of acetonitrile as solvent was critical for this reaction sequence as polymers were the main products in methylene chloride or dimethylformamide. High-dilution (0.01–0.05 *M*) conditions and reflux temperatures were preferred for highest yields. This method (yields ranged from 80 to 97%) compared very favorably to the carbodiimide method (yields ranged from 10 to 30%) in terms of efficiency when used in the same cases under the similar conditions. One limitation of the method is that the product normally has to be separated from the thione and triphenylphosphine oxide by-products chromatographically.



Scheme 5.6



substrate	solvent	concentration	temp	time h	yield %
$R_1 = R_3 = H$, $R_2 = CH_2CO_2Me$, *S*	CH_3CN	0.05M	55°C	12	84
$R_1 = R_3 = H$, $R_2 = CH_2CO_2Me$, *R*	CH_3CN	0.01M	reflux	12	82
$R_1 = R_2 = R_3 = H$	CH_3CN	0.10M	55°C	24	39
$R_1 = R_2 = R_3 = H$	CH_3CN	0.01M	reflux	4.5	80
$R_1 = R_3 = H$, $R_2 = Ph$, *RS*	CH_3CN	0.10M	55°C	4.5	34
$R_1 = R_3 = H$, $R_2 = Ph$, *RS*	CH_3CN	0.10M	reflux	4.5	60
$R_1 = R_3 = H$, $R_2 = Ph$, *RS*	CH_3CN	0.01M	reflux	4.5	97
$R_1 = R_3 = H$, $R_2 = Ph$, *RS*	DMF	0.10M	55°C	4.5	9
$R_1 = R_3 = H$, $R_2 = Ph$, *RS*	CH_2Cl_2	0.10M	reflux	4.5	trace
$R_1 = R_3 = H$, $R_2 = Ph$, *RS*	CH_3NO_2	0.10M	reflux	4.5	26
$R_1 = R_2 = H$, $R_3 = CH_2Ph$	CH_3CN	0.10M	reflux	4.5	44
$R_1 = R_2 = H$, $R_3 = CH_2Ph$	CH_3CN	0.01M	reflux	4.5	91

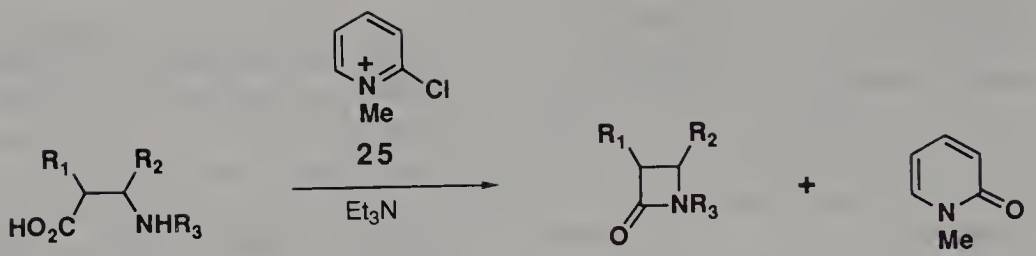
Figure 5.4 Cyclization of β-amino acids to β-lactams with triphenylphosphine–pyridine disulfide.

A number of other phosphorus-derived condensation agents have been developed. These include diphenylphosphinic chloride,[38] triphenyl phosphine/carbon tetrachloride[39,40] triphenyl phosphine/*N*-bromosuccinimide,[39] ethyl dichlorophosphate,[41] phenyl dichlorophosphate,[41,42] phenylphosphonic dichloride,[41] diphenyl chlorophosphate,[42] *N,N*-dimethylphosphoramidic dichloride,[42] bis(5′-nitro-2′-pyridyl) 2,2,2-trichloroethyl phosphate,[43] diphenyl 2-oxo-3-oxazolinylphosphonate,[44] *p*-chlorophenyl bis(2-oxo-3-oxazolinyl) phosphinate,[44] tris(2-oxo-3-oxazolinyl)phosphine oxide,[44] 4-chlorophenyl bis(2-oxo-3-benzoxazolinyl)phosphinate,[45] and tris(2-oxo-3-benzoxazolinyl)phosphine oxide.[45]

As referred to previously, 2-chloro-1-methylpyridinium iodide **25** has been effectively used as a condensation reagent.[29] High yields of β-lactams are obtained by treatment of β-amino acids with this reagent and triethylamine in methylene chloride or acetonitrile at ambient temperature (Figure 5.5). This method is noteworthy in that it occurs under mild conditions and product purification is simplified as the only by-product is 1-methyl-2-pyridone **26.**

β-Amino esters have also been used as β-lactam precursors. One of the most useful methods, first reported by Breckpot in 1923, involves the base-catalyzed cyclization of β-amino esters with Grignard reagents (Figure 5.6).[46,47] The yield of this process was found to decrease with decreasing substitution on the resultant azetidinone.[13,34,48]

Dramatic yield increases for the process were obtained by Searles and Wann, who substituted mesityl Grignard reagent for ethyl Grignard reagent.[49] Another major improvement in this process was reported by Bir-



substrate	solvent	concentration	temp	time h	yield %
$R_1 = H, R_2 = CH_3, R_3 = CH_2Ph$	CH_2Cl_2	0.02M	25°C	2	95
$R_1 = H, R_2 = nC_3H_7, R_3 = CH_2Ph$	CH_2Cl_2	0.01M	25°C	2	94
$R_1 = CH_3, R_2 = H, R_3 = CH_2Ph$	CH_2Cl_2	0.01M	25°C	2	83
$R_1 = R_2 = H, R_3 = CH_2Ph$	CH_2Cl_2	0.01M	25°C	2	60
$R_1 = R_3 = H, R_2 = Ph$	CH_3CN	0.01M	reflux	3	89
$R_1 = R_3 = H, R_2 = CH_3$	CH_3CN	0.01M	reflux	2.5	87

Figure 5.5 β-Lactam formation from β-amino acids using Mukaiyama's reagent.

kofer and Schramm.[50] These workers converted β-amino acids to their corresponding bis-silylated derivatives, which undergo Grignard-mediated cyclization to the azetidinones in good yield (Figure 5.7).

Other strong bases, such as lithium diisopropylamide and lithium bis(trimethylsilyl)amide, have also been used to cyclize β-amino esters.[51] As in the case of β-amino esters, β-amino thiol esters undergo base-catalyzed cyclization in the presence of Grignard reagents to afford β-lactams.[52] These derivatives have also been reacted with soft acids such as mercuric trifluoroacetate[53] or cuprous trifluoromethanesulfonate[54] to give good yields of azetidinone products (Figure 5.8).

The Ugi four-component condensation approach to the synthesis of β-lactams has been well known for years.[55] In a typical example, β-amino acid **27** is treated with aldehyde **28** and *t*-butyl isocyanide **30** in methanol to afford β-lactam **32** in good yield. The reaction apparently proceeds via the Schiff base **29** and the seven-membered ring product **31.** The azetidinone is formed via a facile transannular *O,N*-acyl transfer. In general, these condensation reactions proceed smoothly and in good yields. Its utility continues

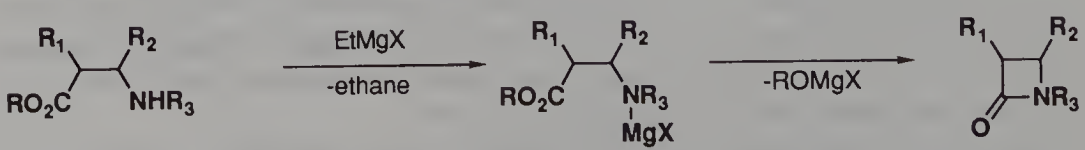


Figure 5.6 Base-catalyzed β-lactam formation from β-amino acids with Grignard reagents.

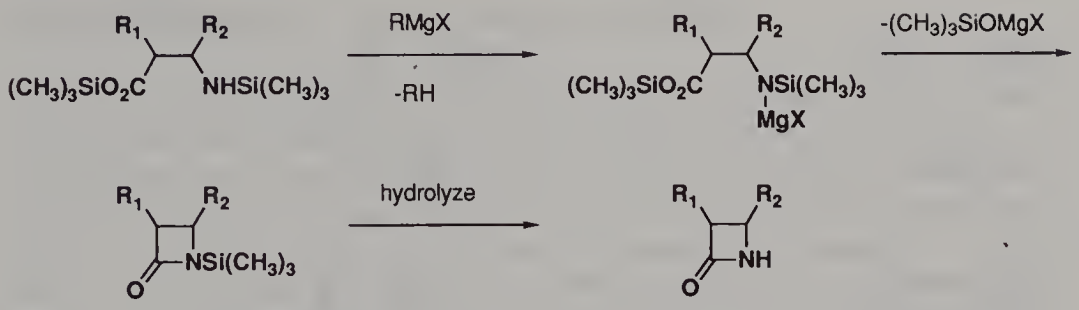


Figure 5.7 Grignard reagent-mediated β-lactam formation for β-amino acids.

to be demonstrated as more challenging azetidinone targets are addressed.[56] Thus, the application of the Ugi reaction to the preparation of **33** provides ready access to a novel precursor of the 1-carbacephalosporin nucleus **34** (Schemes 5.7 and 5.8).[57]

5.3 Formation of C_2—C_3 Bond

In contrast to amide (N_1-C_2) bond formation, azetidinone formation at the C_2—C_3 position is complicated by the inherent greater difficulty in forming a carbon–carbon bond versus an amide bond. This fact is normally compounded by the multifunctional nature of the target azetidinones. In fact, of the four single-bond retrosynthetic approaches to the preparation of the β-lactam ring, that involving union of the C_2-C_3 bond has been the least used. The most notable recent achievements with this approach are those invoking organometallic species as precursors to the azetidinone ring,[58] which are not discussed in detail in this chapter. A methodology involving a trialkylstannane-mediated closure of the C_2-C_3 bond can also be considered with the organometallic approaches. This novel method has the potential for producing chiral β-lactams from readily available β-amino acids.[59] Finally, a photochemical approach has been developed that leads to the formation of 4-keto-β-lactams such as **36**.[60] Interestingly, this reaction also falls under the C_3-C_4 bond-forming category. Conversion of these products to the 4-deoxygenated β-lactam remains a synthetic challenge (Scheme 5.9).

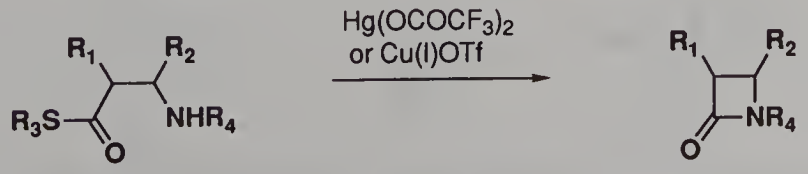
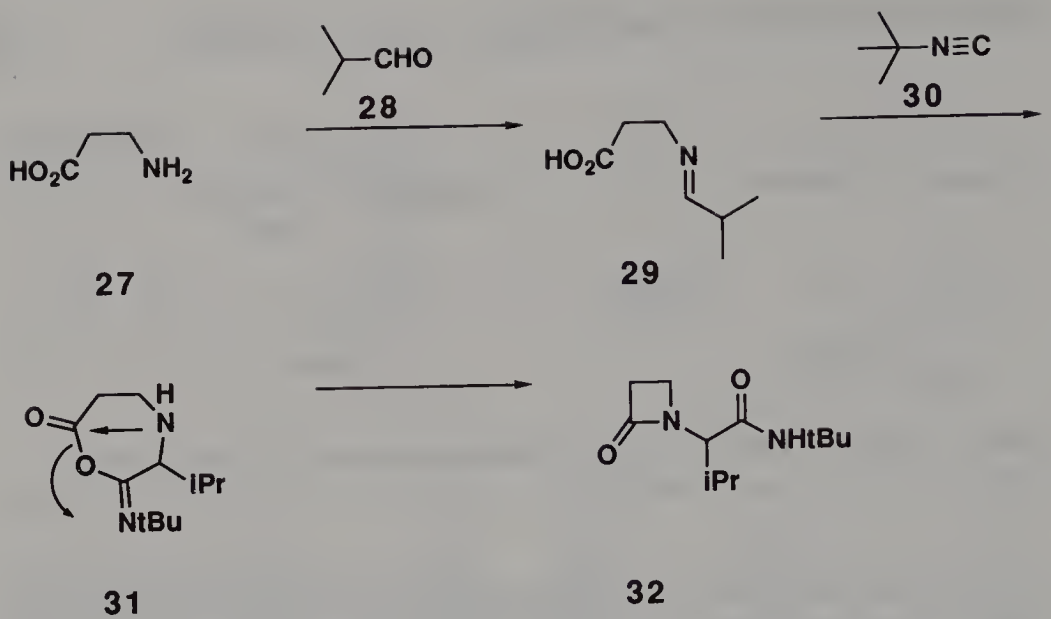
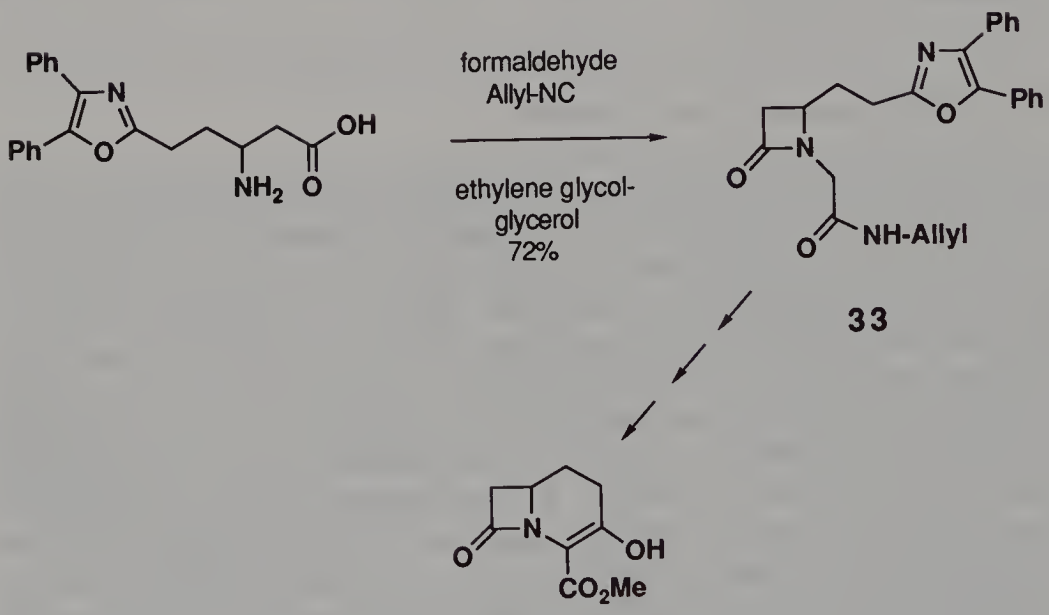


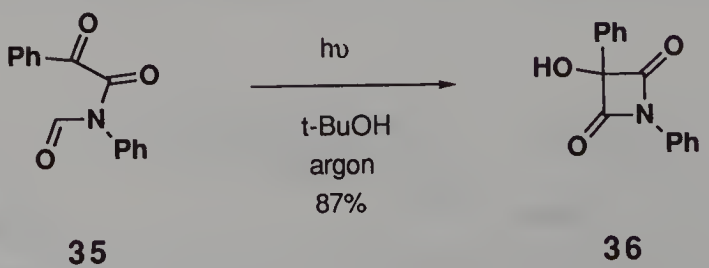
Figure 5.8 β-Lactam formation from β-amino thiol esters.



Scheme 5.7



Scheme 5.8



Scheme 5.9

5.4 Formation of C_3—C_4 Bond

As for C_2-C_3 processes discussed in the previous section, the C_3-C_4 bond-forming process is complicated because of the necessity of forming a carbon–carbon bond stereoselectively in the midst of a multifunctional array. This bond is most commonly formed as part of the enolate–imine condensation or through an electrocyclic process intermediary in the 2 + 2 cyclization. Alternatively, this bond has also been formed by organometallic carbenoid insertion methodology. These methods are described in detail in other chapters of this book. In its simplest sense, bond formation at C_3-C_4 would involve the formation of a nucleophilic center at C_3 and an electrophilic center at C_4, or vice versa. The first example of such an intramolecular nucleophilic displacement reaction was reported by Sheehan and Bose. These workers used malonate anions and halides as the nucleophilic and electrophilic components, respectively (Figure 5.9).[61]

This strategy has recently been exploited by Simig and co-workers for the synthesis of carbapenems (Scheme 5.10).[62] The arylaminomalonates **37** were reacted with diketene in refluxing acetic acid to afford the ring isomers **39** of the desired acetoacetyl derivatives **38.** Treatment of derivatives **39** with iodine in the presence of sodium ethoxide furnished the desired β-lactam products **40**. These derivatives could be further converted to the carbapenem intermediates **41.**

Malonate-activated cyclization has recently been carried out electrochemically (Scheme 5.11).[63] The malonate-stabilized anion can be formed by electrochemical reduction of a probase R—X, such as diethyl bromomalonate, in the presence of a substrate or directly on the substrate molecule **(43)** itself. The reaction is performed in dimethylformamide in the presence of tetraethylammonium perchlorate and good yields of β-lactam products are obtained. This procedure is also applicable to derivatives containing only one ester function.

The presence of a hydroxyethyl side chain in the carbapenem antibiotics has allowed a unique opportunity for these alkylation approaches. The use of an epoxide function in the alkylation process allows for a stereoselective strategy that affords this hydroxyethyl side chain directly (Figure 5.10).

Workers at Sankyo reported that bromide ester **46,** derived from threonine, was transformed to **47** by treatment with 2 equivalents of lithium bis(trimethylsilyl)amide.[64] The stereochemistry at the carbon bearing the

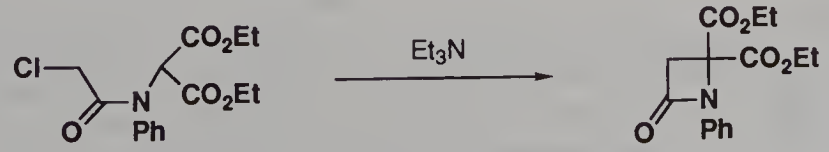
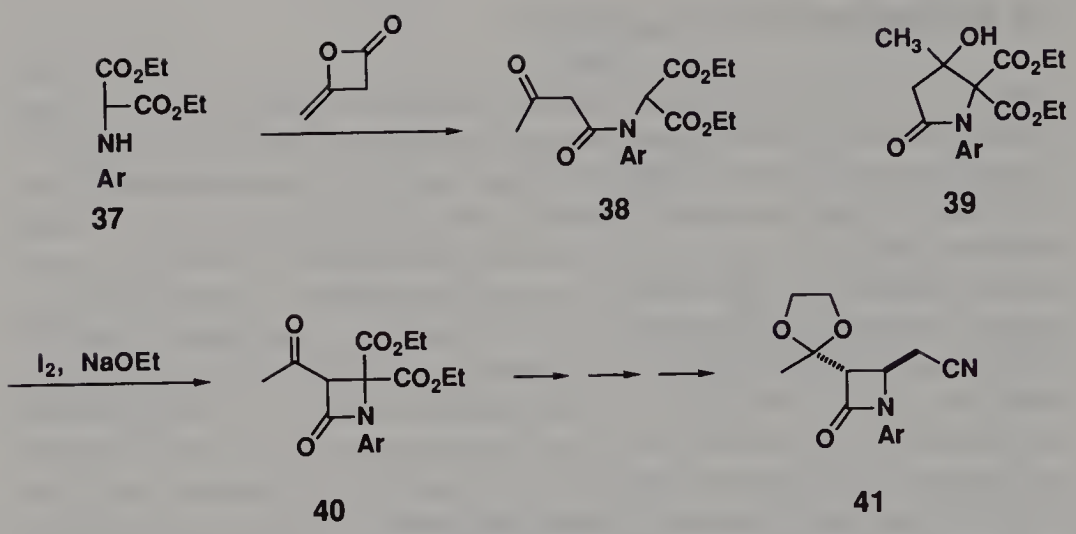
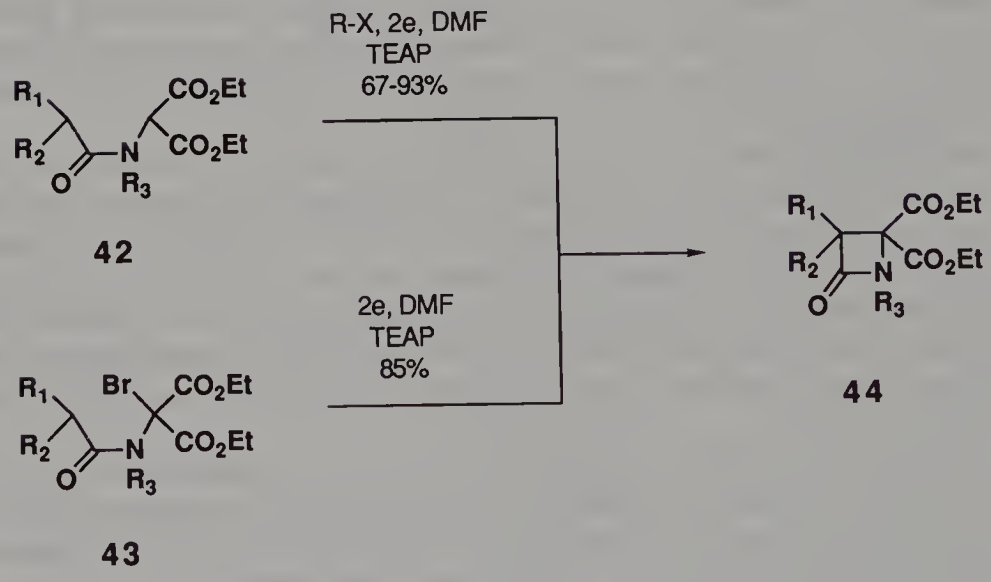


Figure 5.9 β-Lactam formation via an intramolecular nucleophilic displacement reaction.



Scheme 5.10



Scheme 5.11

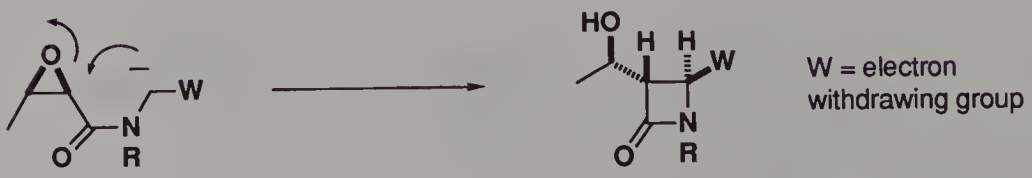


Figure 5.10 C_3—C_4 bond formation involving epoxide opening for the synthesis of 3-hydroxyethyl-2-azetidinones.

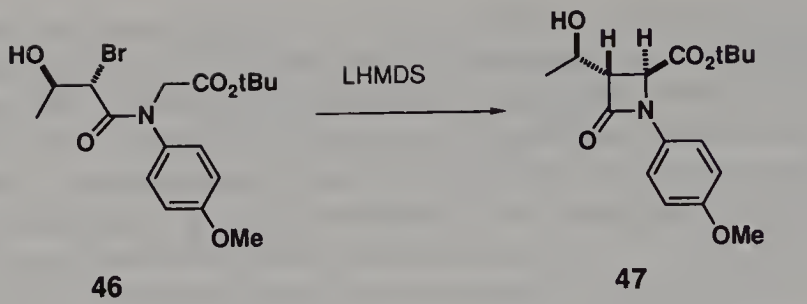
bromine was retained, indicating a double-inversion process via an epoxide intermediate. Sulfones (**48** and **49**),[65] phosphonates (**50** and **51**),[66] nitriles (**52** and **53**),[67] acetylenes (**54** and **55**),[68] and ketones (**56** and **57**)[69] have also been used as anion-stabilizing groups for this reaction (Scheme 5.12).

Hiyama and co-workers have reported a stereoselective synthesis of 3-substituted azetidinones via an oxidative coupling of dianions of acyclic amides (Figure 5.11).[70] This process is applicable to the synthesis of 3-amino derivatives which can be converted to the biologically active amido counterparts.

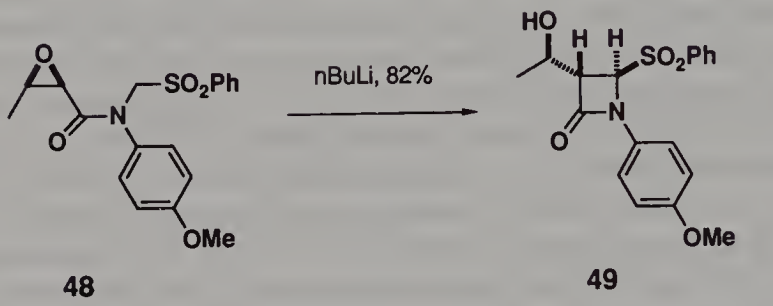
The dianions were formed with either 2 equivalents of *n*-butyllithium in the presence of 1,4-diazabicyclo[2.2.2]octane or by t-butyllithium alone in tetrahydrofuran at −78°C. These dianions were then oxidized with *N*-iodosuccinimide or copper(II) acetate. The presence of tetraphenylphosphonium bromide led to higher yields of products. High *cis* selectivity was observed with *N*-iodosuccinimide. The use of a chiral auxiliary, *(R)*-(+)-1-phenylethylamime, resulted in high enantioselectivity and diastereoselectivity as outlined in the transformation of **61** to **62**. A 90 to 10 preference for **62** over the three other isomeric products was observed. This intermediate was then used in a formal total synthesis of the monobactam antibiotic, carumonam **63** (Scheme 5.13, see page 274).

Photochemical approaches to C3—C4 bond formation have long been studied. One of the more useful methods has been the photocyclization of α-oxoamides.[71] This process has been found to be dependent on both the substituent pattern of the substrate and the photolysis solvent.[72] This approach is normally complicated by a lack of regio-, diastereo-, and enantioselectivity.[73] A number of recent studies have attempted to address these issues.[74] Toda, Kaftory, and co-workers have reported on the use of "host–guest inclusion compounds" for the preparation of optically active β-lactams from α-oxoamides.[75] For example, irradiation of the inclusion compound from oxoamide **64** and *(S)*-(−)-1,1,6,6-tetraphenylhexa-2,4-diyne-1,6-diol **65** afforded the *(S)*-(-)enantiomer of **66** in 100% optical purity (Scheme 5.14, see page 274). This same chiral host has been used for the preparation of chiral β-lactams from pyridones. Thus irradiation of the complex derived from pyridone **67** and **65** afforded the bicyclic β-lactam **68** in 97% yield (50% conversion) and 100% optical purity.[76] The photopyridone approach to β-lactams had been pioneered by Kaneko and co-workers for the preparation of useful intermediates in carbapenem synthesis.[77] A number of other photochemical approaches to C3-C4 bond formation have been recently reported (Scheme 5.15, see page 274).[60,78]

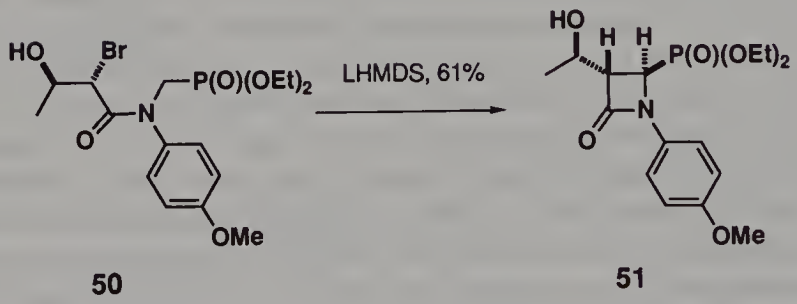
Finally, an interesting thermal ring contraction of 4-azido-2-pyrrolinones to 3-cyano-2-azetidinones has been reported by Moore and co-workers (Figure 5.12, see page 275).[79] In this process appropriately substituted pyrrolinones **69** cleave thermally to zwitterionic intermediates **70** which ring close the azetidinone products **71.** This ring contraction process can also be accomplished photochemically.



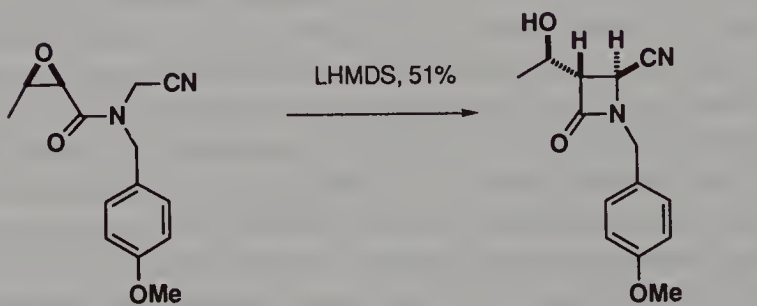
46 47



48 49

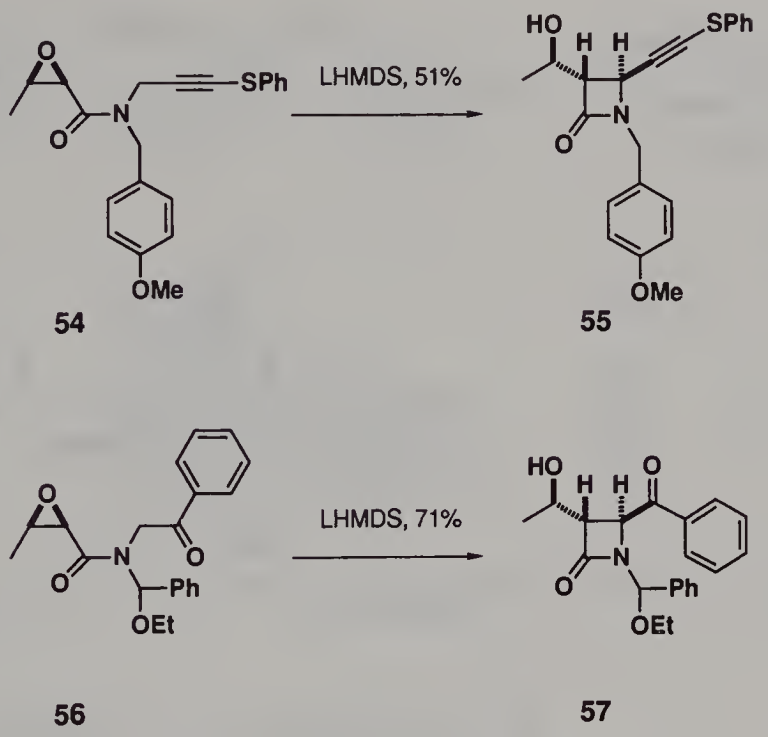


50 51

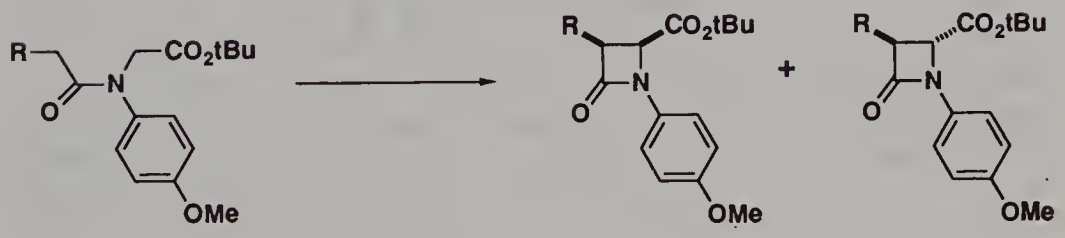


52 53

Scheme 5.12

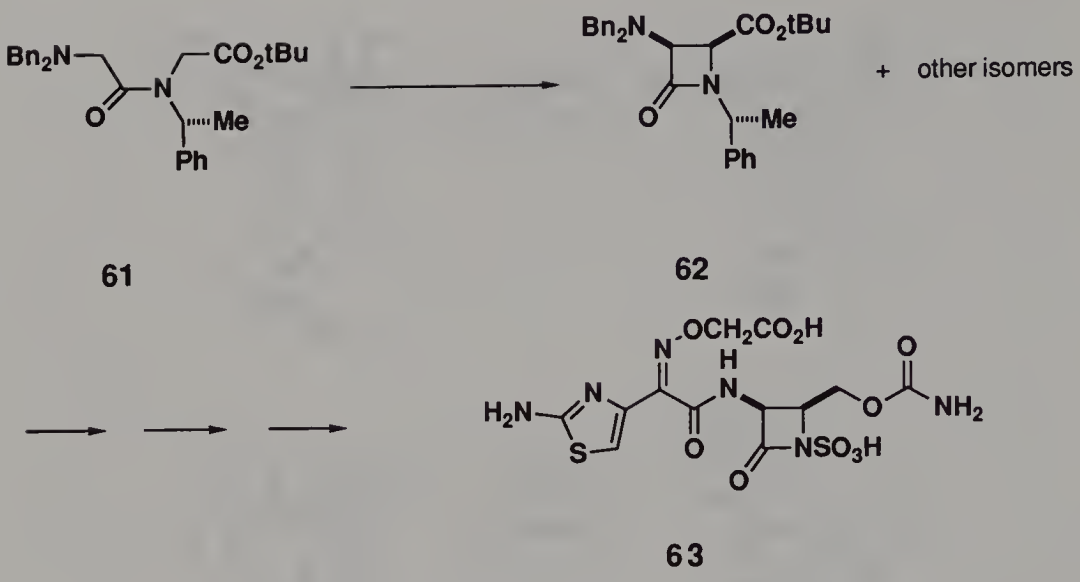


Scheme 5.12 (cont.)

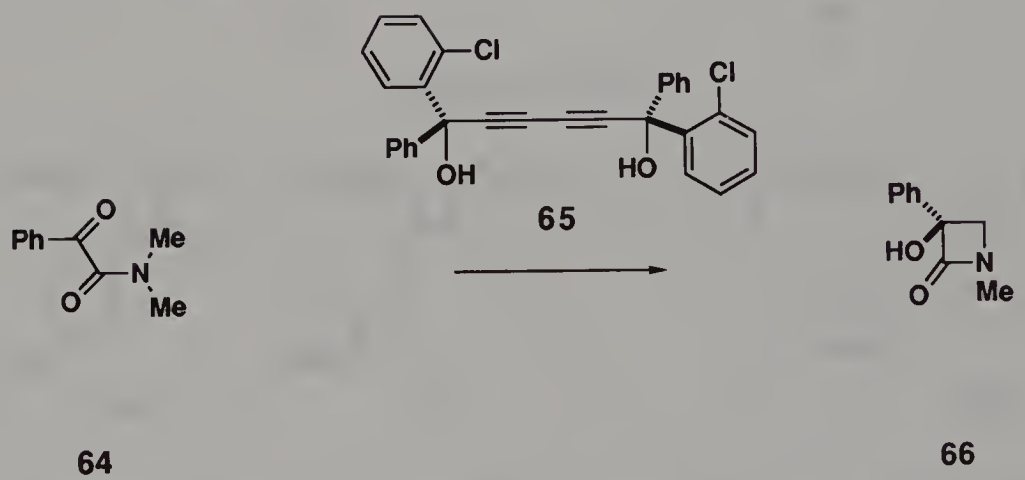


substrate	base	additive	oxidant	yield %	59:60
R = H	n-BuLi	DABCO	$Cu(OAc)_2$	40	
R = H	t- BuLi	PPh_4Br	NIS	39	
R = Et	t- BuLi		$Cu(OAc)_2$	40	3:2
R = Et	t- BuLi	PPh_4Br	NIS	51	10:0
R = MeO	t- BuLi	PPh_4Br	$Cu(OAc)_2$	43	1:2
R = MeO	t- BuLi	PPh_4Br	NIS	78	12:1
R = Bn_2N	t- BuLi	PPh_4Br	$Cu(OAc)_2$	77	1:2
R = Bn_2N	t- BuLi	PPh_4Br	NIS	48	7:1

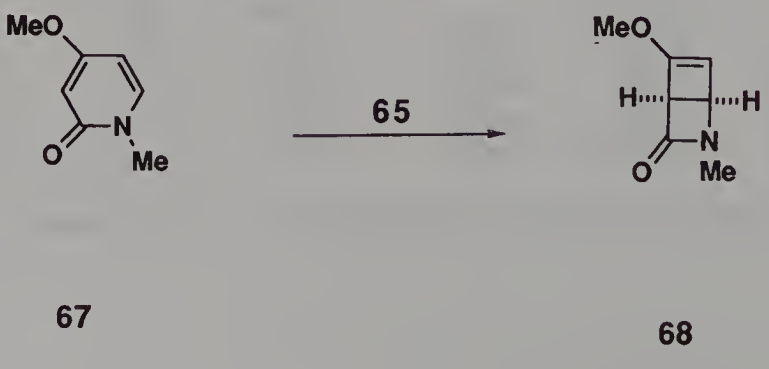
Figure 5.11 β-Lactam formation via oxidative C_3—C_4 bond formation.



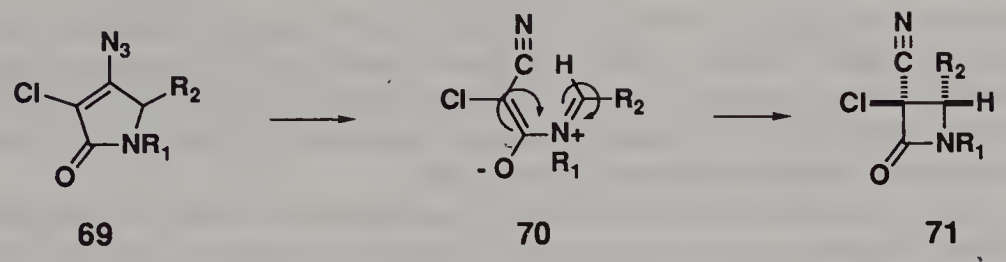
Scheme 5.13



Scheme 5.14



Scheme 5.15



substrate	yield %
$R_1 = CH_3$, $R_2 = OCH_3$	55
$R_1 = CH_3$, $R_2 = OCH_2CH_3$	60
$R_1 = CH_2CH_3$, $R_2 = OCH_2CH_3$	88
$R_1 = CH(CH_3)_2$, $R_2 = OCH_2C_6H_5$	90
$R_1 = C_6H_{11}$, $R_2 = OCH_2CH_3$	62
$R_1 = C_6H_{11}$, $R_2 = C_6H_5$	49

Figure 5.12 Thermal ring contraction of 4-azido-2-pyrrolinones to 3-cyano-2-azetidinones.

5.5 Formation of C_4—N_1 Bond

The synthesis of the β-lactam ring via formation of the C_4-N_1 bond is the synthetic route selected by nature for the biosynthesis of azetidinone-containing antibiotics (Figure 5.13).[80] For the organic chemist, retrosynthetic analysis involving cleavage of the C_4-N_1 azetidinone bond has generated a significant number of synthetic approaches to the preparation of this important heterocycle. In this section, we highlight many of these methodologies developed over the past decade for this conversion.

New methods for the preparation of the β-lactam ring through formation of the C_4-N_1 bond have been dominated by strategies involving the intramolecular displacement of a leaving group attached to carbon 4 with an appropriately activated nitrogen (Figure 5.13) In the simplest sense, this has been realized as S_N2-type displacements of primary halogens by an amide

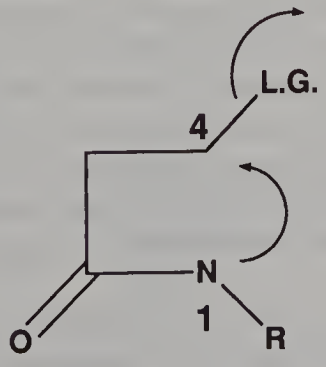


Figure 5.13 C_4—N_1 bond formation.

nitrogen under basic conditions. These straightforward cyclizations have been performed with a variety of bases under various reaction conditions.[81,94] As an example, Sebti and Foucaud reported the cyclization of **72** to **73** in 80% yield with the heterogeneous conditions of powdered potassium hydroxide in tetrahydrofuran (Scheme 5.16).[82]

These approaches are limited in that functionality at carbon 4 is typically absent. Because of the unsubstituted nature of C-4 in these examples, chirality at this center is not an issue. Chirality at other centers can, however, be preserved by such an approach[83] as demonstrated for the conversion of **74** to **75** (Scheme 5.17).[84]

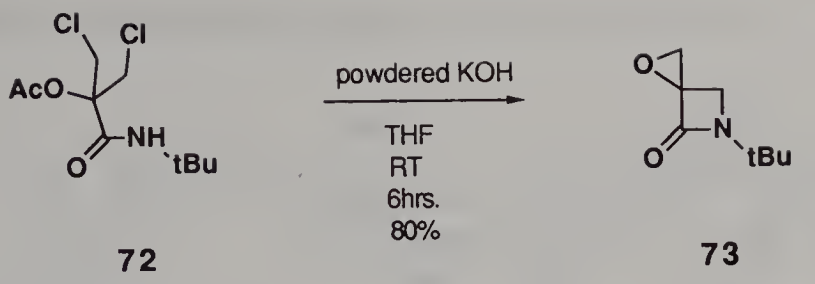
C-4 leaving groups other than halogen have also been reported for this type of transformation.[85] A novel leaving group methodology that avoids many of the problems encountered with such displacements was introduced by Hanessian et al.[86] In this process, the hydroxyl groups of *N*-substituted serine amides such as **76** are activated as the imidazolylsulfonate (imidazylate) functionality and undergo facile intramolecular displacement by the amide nitrogen, providing β-lactam products (**77**) (Scheme 5.18).

In several cases, intramolecular cyclizations of simple amides are not successful. For example, oxidative cyclization of β,γ-unsaturated amides under typical halolactonization conditions leads to the formation of lactones rather than the desired lactams.[87] Ganem and co-workers, however, were able to successfully overcome this bias by lowering the pK_a of the carboxamide functionality. Thus, the double activation of the nitrogen in **78** led to successful cyclization to the azetidinone **79** (Scheme 5.19).[88]

Successful oxidative cyclization of olefinic amides to β-lactams was also realized by Miller and Rajendra for the case of the oxygen-substituted hydroxamates. The attenuated acidity of the nitrogen in this functionality provided ready access to a number of important azetidinone intermediates. For example, **80** was converted exclusively to **81** with bromine. The exceptional selectivity for the formation of β-lactams in these examples as opposed to the alternative γ-lactam derivatives is explained by Rajendra and Miller to be due to a stereoelectronic effect (Scheme 5.20).[89]

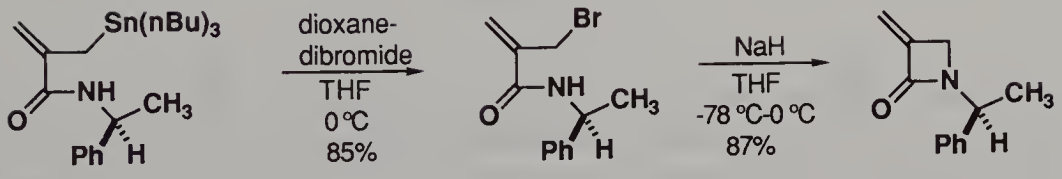
Clearly for the synthesis of more complex azetidinone-containing antibacterials, the issue of stereocontrol in the formation of the C_4—N_1 bond must be addressed. The straightforward cyclization method described so far has been shown in some cases to operate with the desired stereocontrol. Early examples used the preference for the formation of *cis*-fused bicyclic ring systems to achieve the stereocontrol at C_4.[90] Thus, cyclization of the penicillin-derived **82** under basic conditions gave rise to **83** in 81% yield as the only diastereomeric product.[91] More recently, a novel approach to stereocontrol involving the utilization of a sugar template was reported (Scheme 5.21).[92]

As discussed previously for the C_4-unsubstituted series, the intramolecular ring closure to 4-substituted azetidinones can also be accomplished using the hydroxamate functionality as activator. Thus, Evans and Sjogren



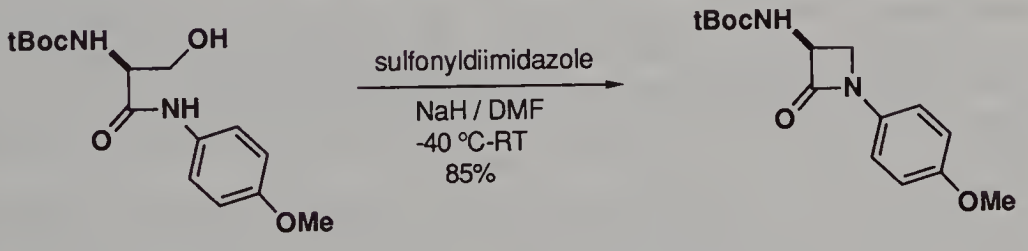
72 73

Scheme 5.16



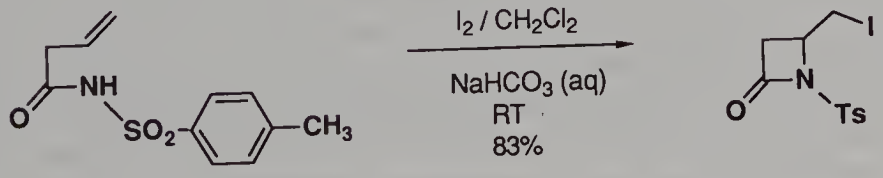
74 75

Scheme 5.17



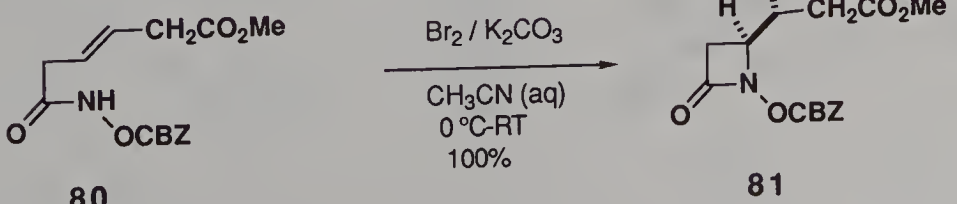
76 77

Scheme 5.18



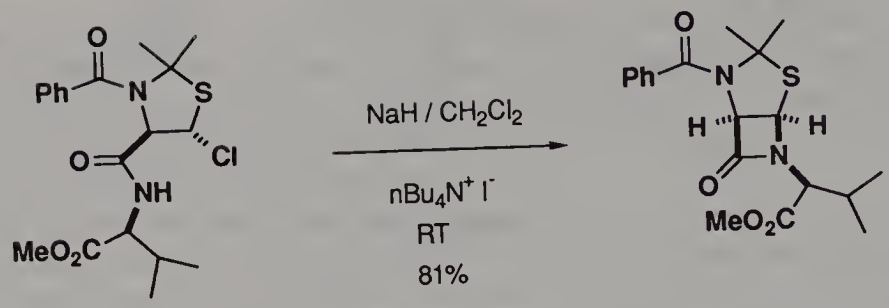
78 79

Scheme 5.19



80 81

Scheme 5.20



82 83

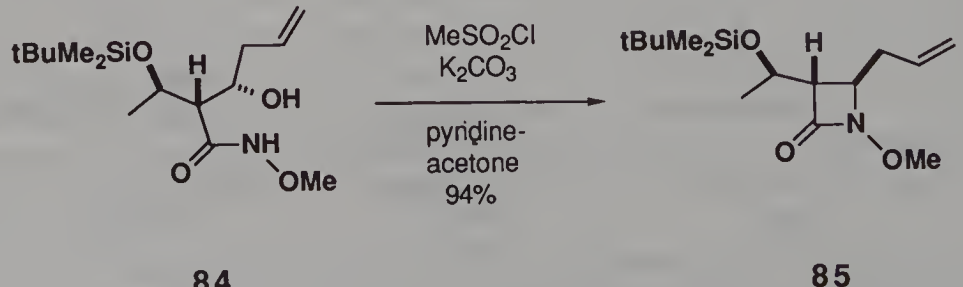
Scheme 5.21

converted **84** into **85** via base-induced ring closure of the intermediate mesylate.[93] Compound **85** served as a key intermediate in a formal total synthesis of thienamycin (Scheme 5.22).

Several other examples of hydroxamate ring closures to C_4-substituted azetidinones have been documented.[94–96] In a particularly interesting case, the hydroxamate ring closure was promoted through electrochemical means. The stereochemical outcome of these reactions (and presumably the mechanism of ring closure) is dependent on the nature of the electrogenerated base.[96]

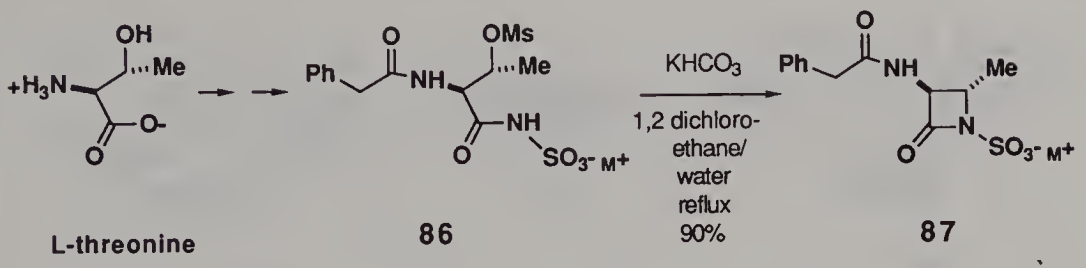
Finally, activation of the amide nitrogen and cyclization to chiral products can be realized by initial sulfonation of the amide nitrogen. This is an especially useful process, as many of the important monobactams (e.g., azetreonam) are functionalized on the azetidinone nitrogen with the sulfonic acid moiety. As an example, the Squibb group has described the conversion of L-threonine to the acyclic acyl sulfamate **86,** which in turn was readily cyclized to the azetidinone **87** in 92% yield.[97] Other cyclizations invoking this novel type of nitrogen activation have been described (Scheme 5.23).[97,98]

Another newly devised methodology for the formation of azetidinone rings via formation of the C_4—N_1 bond has been named "sulfeno-cycloamination."[99,100] In the process, developed by Kametani and co-workers, an enamide is treated with phenylsulfenyl chloride followed by base. Presumably,



84 85

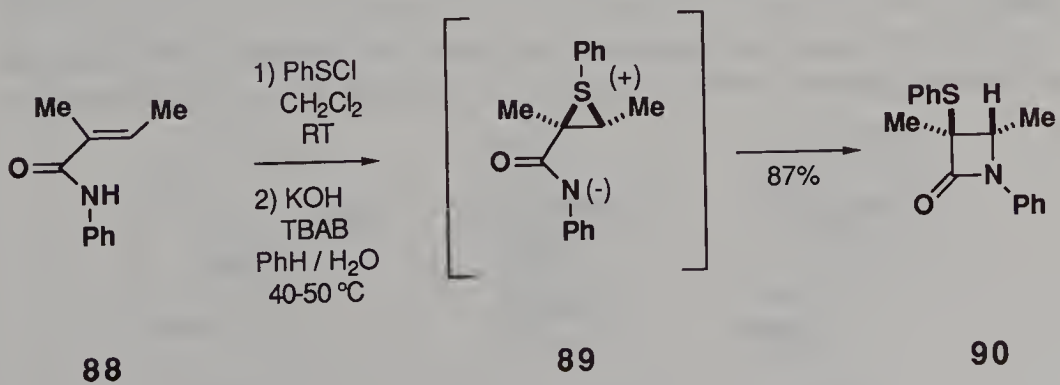
Scheme 5.22



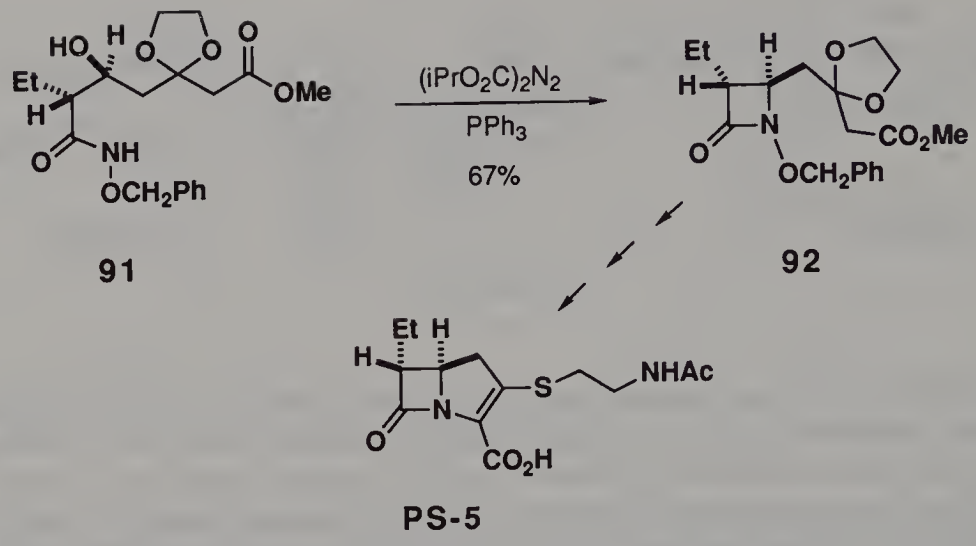
Scheme 5.23

an intermediate episulfonium intermediate forms (**89**) and then undergoes facile intramolecular cyclization to the azetidinone ring. The resulting β-lactam bears a sulfide functionality which is readily removed or used to facilitate the introduction of another useful functionality onto the ring. An example of this methodology is depicted for the conversion of **88** to **90**.[100] The sulfeno-cycloamination process has been applied to the synthesis of intermediates useful for the preparation of monobactams and carbapenems (Scheme 5.24).

Significant contributions to the synthesis of β-lactams via formation of the C_4—N_1 bond have been made by Miller and co-workers at the University of Notre Dame. A review of this work published in 1986 provides an excellent documentation of these important developments as well as their utility in the preparation of important antibacterial substances.[101] The key feature of this approach involves the intramolecular cyclization of chiral β-hydroxy hydroxamates derived from readily available chiral β-hydroxy acids under the conditions of the Mitsunobu reaction.[102] Application of these conditions (diethyl azodicarboxylate, triphenylphosphine) to such substrates provides β-lactams in which the chirality at C_3 is preserved and the configuration at C_4 is the result of clean inversion of the pro-C_4 stereocenter. The implication of these results is that any chiral β-lactam can in principle be prepared starting from an appropriate chiral β-hydroxy acid. In testimony to the success of this methodology, the challenges of β-lactam synthesis have many times



Scheme 5.24

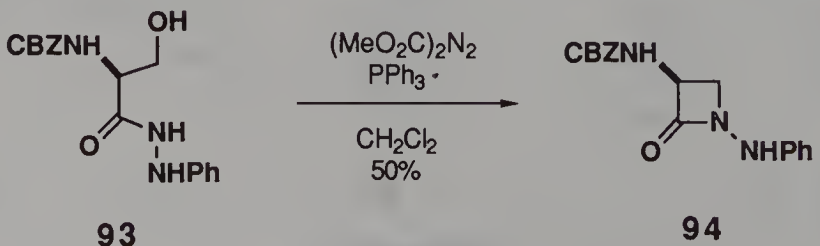


Scheme 5.25

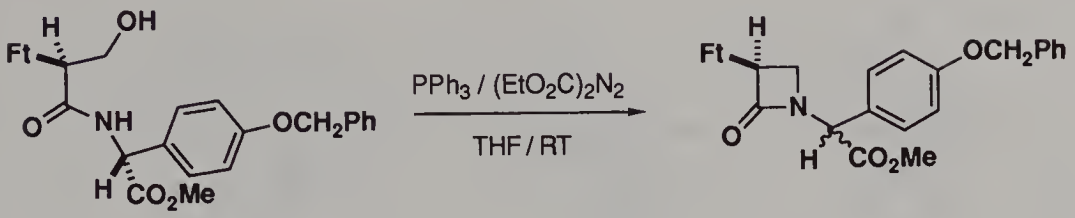
been reduced to the challenges of chiral β-hydroxy acid preparation. As an example, the β-hydroxy hydroxamate **91** was cyclized to the PS-5 precursor **92** in at least 93% enantiomeric excess and 67% yield.[103] More recently, Kolasa and Miller have extended the application of this methodology to the conversion of tartaric acid to functionalized β-lactams.[104] In addition, Kim and Sharpless have demonstrated the utility of the procedure in the conversion of optically active diols, generated by their newly described osymolation procedure, to chiral azetidinones.[105] The significance of these processes to the laboratory as well as industrial-scale preparation of important β-lactams is very apparent. Several other examples of the application of this chemistry to the formation of β-lactams have been reported (Scheme 5.25).[83,106]

Functionalities other than the nitrogen-activated hydroxamates have been shown to be suitable substrates for the formation of the C_4—N_1 azetidinone bond via intramolecular Mitsunobu coupling. Thus, the hydrazide **93** was cyclized to the *N*-aminoazetidinone derivative **94** in 50% yield (Scheme 5.26).[107]

In all of the cases referenced to this point, the nitrogen participating in the coupling reaction bears a hydrogen of sufficient acidity to facilitate the



Scheme 5.26



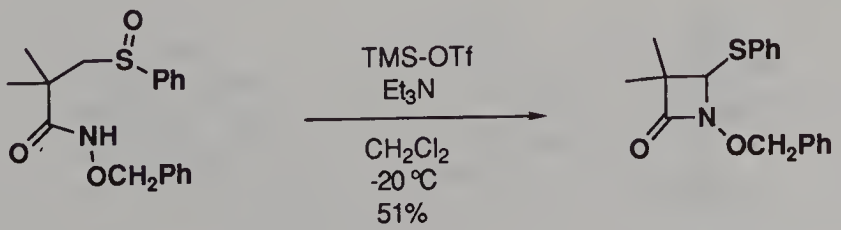
95 96

Scheme 5.27

Mitsunobu reaction according to the parameters set forth by Mitsunobu and co-workers.[102] It was found, however, that simple unactivated amides could successfully participate in this cyclization process. Thus, Townsend and Nguyen used the Mitsunobu coupling of **95** to **96** in their reported synthesis of Norcardicin.[108,109] Indeed, a careful study of the cyclization parameters gave rise to optimal conditions for the conversion.[109] In addition to Townsend's studies, Bose and co-workers have also demonstrated the utility of simple lactams in the intramolecular Mitsunobu coupling to β-lactams.[110,111] Their detailed studies of this process revealed that the acidity of the amide functionality is but one of the many factors that modulate the course of the reaction.[111] This procedure has been used for the preparation of novel *N*-tetrazole-substituted monobactams as potential antibacterial agents (Scheme 5.27).[112]

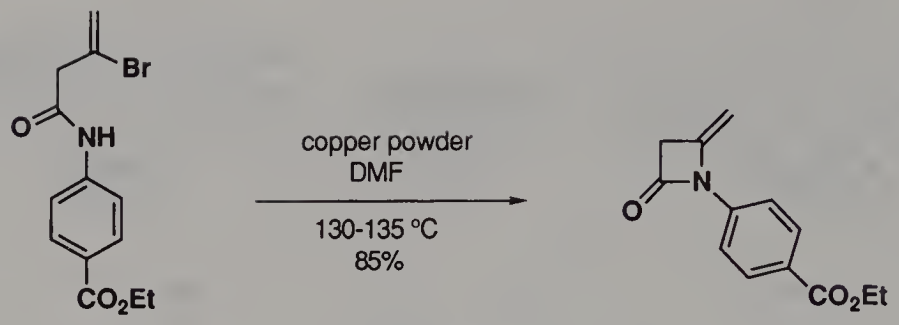
The methodologies presented thus far for the preparation of β-lactams via formation of the C_4—N_1 bond represent the major approaches that have been reported over the past decade. During this time there have been other interesting methodologies reported as well that are briefly presented in the closing paragraphs of this discussion.

One particularly novel approach involves the formation of a β-lactam ring via Pummerer rearrangement of a suitably functionalized sulfoxide. It has been proposed that this route most closely mimics the enzymatic synthesis of the β-lactams. Thus, treatment of **97** with trimethylsilyltriflate caused rearrangement to azetidinone **98** in 51% yield.[113] When the same reaction



97 98

Scheme 5.28



99 100

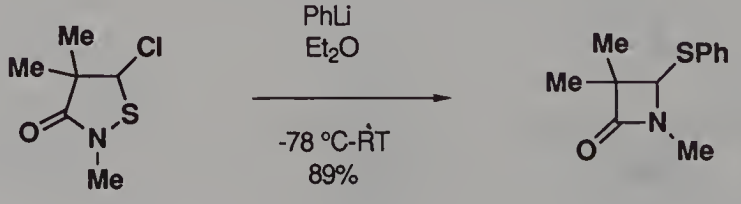
Scheme 5.29

was carried out on an enantiomerically pure sulfoxide, the product azetidinone was formed with respectable (67%) enantiomeric excess, lending further support to the biomimetic hypothesis.[114] This approach has been successfully employed in the conversion of a tripeptide to a C_3-amino-substituted azetidinone (Scheme 5.28, see page 281).[115]

The copper-mediated cyclization of a vinyl bromide (e.g., **99**) provides access to novel 4-methylene azetidinones (**100**).[116] These β-lactams are particularly reactive toward alkaline hydrolysis, presumably because of the increased strain imparted by the exomethylene functionality (Scheme 5.29).

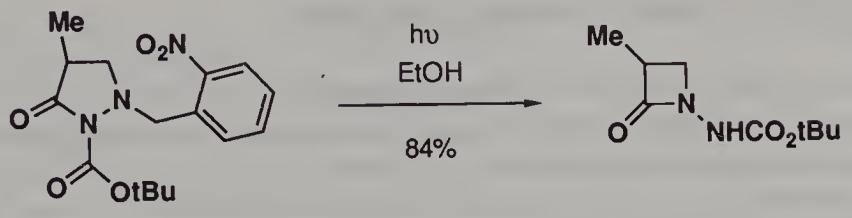
Several ring contractions resulting in the formation of the C_4—N_1 bond of a β-lactam ring have been reported. The conversion of isothiazolidinones such as **101** to azetidinones provides support to the proposal that species such as **102** may be involved in the biosynthesis of penicillin.[117] Photochemically induced ring contraction of substituted pyrazolidinones provides another unique route to *N*-aminoazetidinones (**103** to **104**) (Schemes 5.30 and 5.31).[118]

The many methods presented thus far for the synthesis of the β-lactam ring via C_4—N_1 bond formation are applicable to the preparation of a wide variety of substituted azetidinones. One exception, however, is the case of β-lactams in which C_4 exists as a quarternary carbon. Most of the methods



101 102

Scheme 5.30

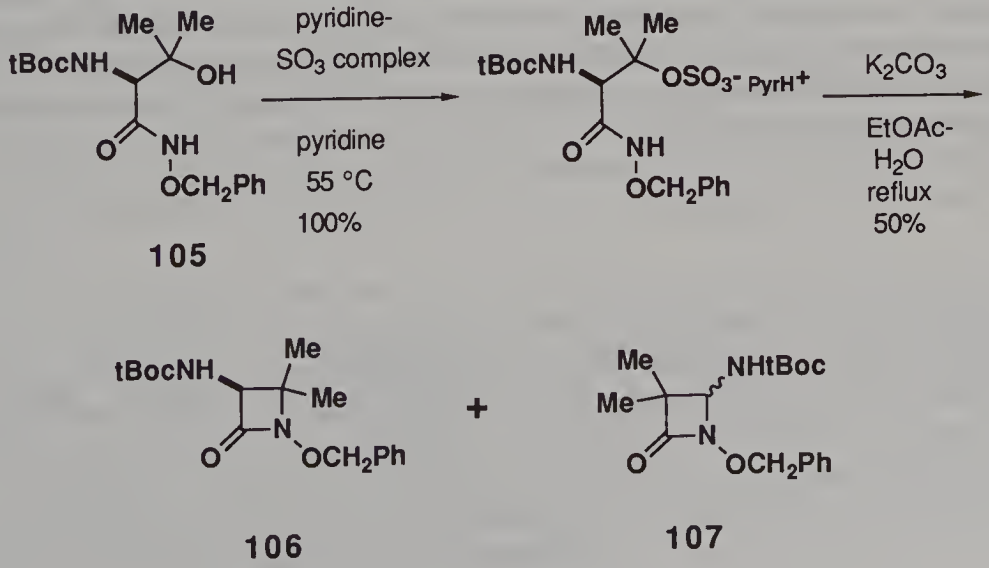


103 104

Scheme 5.31

presented thus far do not satisfactorily address this synthetic challenge. Because of the importance of C_4 dimethyl azetidinones in the development of new monobactams, methodology was developed by the Squibb group for the formation of such compounds. In this procedure, β-hydroxy hydroxamides such as **105** are sulfonated and cyclized under basic conditions. In addition to the desired product (**106**), β-lactams resulting from rearrangement processes (**107**) are also formed.[119] The azetidinone **106** serves as an important nucleus for the preparation of monobactams of clinical importance (Scheme 5.32).

It is evident from this discussion that new synthetic methods continue to be developed for the preparation of the β-lactam ring via methodology incorporating formation of the C_4—N_1 bond as the ultimate step. The utilization of these techniques for the synthesis of new antibacterial substances as well as for the large-scale preparation of β-lactams of commercial interest is testimony for the success of synthetic research in this area.



105 106 107

Scheme 5.32

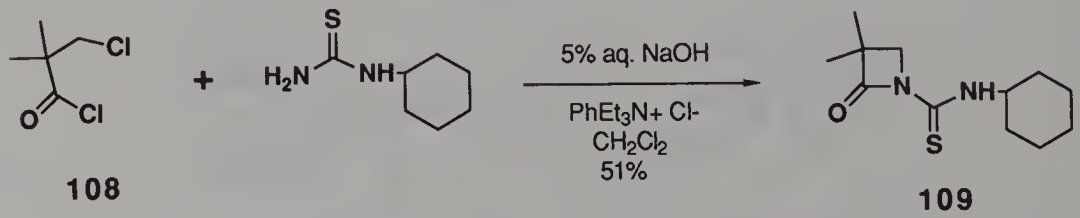
5.6 Multiple Bond-Forming Reactions

By far the most significant synthetic approaches to the formation of the β-lactam ring involving multiple-bond-forming reactions are the ketene–imine and enolate–imine methodologies discussed in other chapters of this book. Many other β-lactam preparations involving the formation of more than one bond have been reported. These methods represent a diverse array of novel approaches. It is our intent in this section to highlight those of particular interest to the practicing β-lactam chemist with a view toward their practical applicability. As has been the practice throughout this chapter, we do not include in our discussion organometallic-based methodologies, many of which involve β-lactam ring formation via carbon monoxide insertion into an appropriate substrate.

Other β-lactam-forming reactions involving multiple-bond formation are based on the simultaneous (or stepwise) formation of two bonds to the pro-N_1 center. Thus, in the most basic sense, condensation of the bis-electrophile **108** with an *N*-alkylthiourea gives rise directly to the azetidinone **109**. (Scheme 5.33).[120]

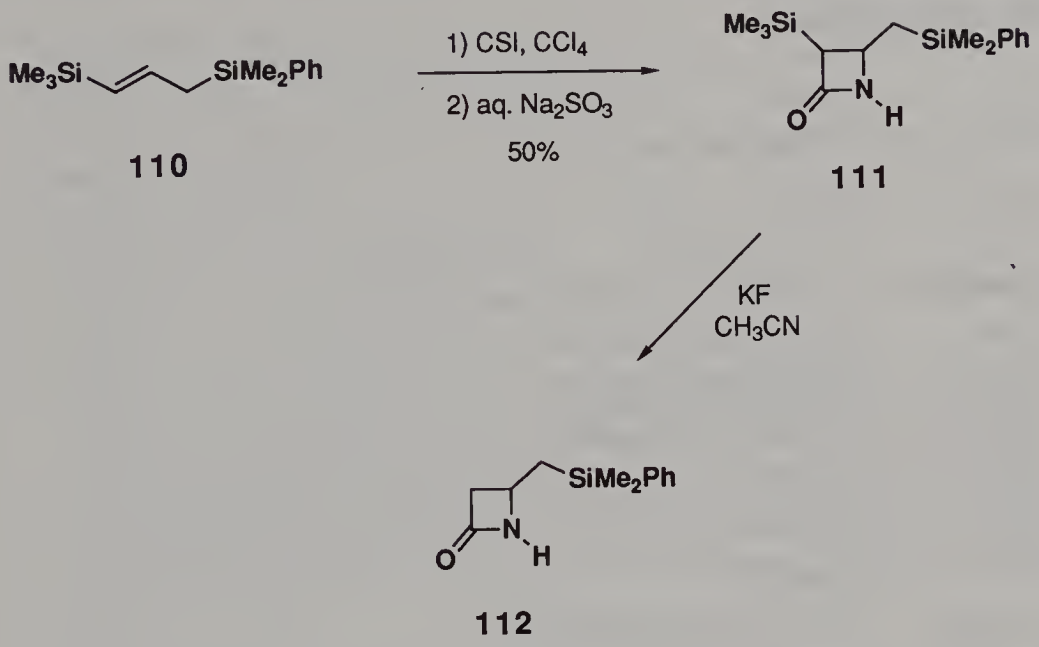
The addition of chlorosulfonyl isocyanate (CSI) to olefins is a well-established method for the construction of β-lactams.[121] Modifications and improvements to this approach continue to be made. One such development involves the addition of various allyl and allenyl silanes to chlorosulfonyl isocyanate. For example, addition of **110** to CSI provides the functionalized azetidinone **111** following removal of the chlorosulfonyl moiety. The silyl group attached to C_3 can then be selectively removed to provide **112.**[122] The potential for generating synthetically useful β-lactam intermediates with this methodology appears to be significant (Scheme 5.34).

As a final note to this section, it should be mentioned that the original report of the addition of copper acetylides to nitrones resulting in the formation of β-lactams[123] has been further studied, providing additional examples of the utility of this approach.[124] Although somewhat limited in scope, the method provides an interesting approach to the multiple-bond construction of the azetidinone ring.



108 109

Scheme 5.33



Scheme 5.34

5.7 Conclusion

It is evident from the documentation of research activities presented in this chapter that the focus on new and improved methods for the formation of the β-lactam ring remains a significant aspect of modern synthetic organic chemistry. As was pointed out in the beginning of this chapter, the clinical need for new and improved antibacterial agents as well as the continuing concern with the economic production of said entities has provided the motivation for this focus. The major single-bond-forming reactions leading to the production of the azetidine ring are those involving amide (N_1—C_2) bond formation and those invoking the biomimetic C_4—N_1 bond closure approach. Throughout the development of these approaches, the attention to stereocontrol remains an important issue which has been addressed with great efficiency.

It is likely that the next decade of research in the synthesis of the azetidinone heterocycle will be as vigorous as the last. As more structurally complex antibiotics are developed through clinical trials, the challenge to produce these materials in large scale and in an economically efficient manner will become more significant. Although many outside the area of β-lactam research may view the area as complete with no new challenges to address, those intimately involved with the science of this "enchanted ring"[17] realize that it is merely the beginning.

5.8 Abbreviations

Ac	Acetyl
Boc	*tert*-Butoxycarbonyl
Bu	Butyl
CBZ	Carbobenzyloxy
DABCO	1,4-Diazabicyclo [2·2·2] octane
DCC	Dicyclohexylcarbodiimide
DCU	1,3-Dicyclohexylorea
DMF	*N,N*-Dimethylformamide
Et	Ethyl
Ft	Phthalimide
iPr	Isopropyl
LHMDS	Lithium hexamethyldisilylamide
n-	Normal
Ph	Phenyl
PNB	*p*-Nitrobenzyl
PPY	Pyrrolidinopyridine
RT	Room temperature
Si	Silyl
t-	*tert*-
TBAB	Tetrabutylammonium bromide
TEAP	Tetraethylammonium perchlorate
Tf	Triflate
THF	Tetrahydrofuran
TMS	Trimethylsilyl
Ts	p-Toluenesulfonyl (tosyl)

5.9 Literature

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CHAPTER

6

Stereocontrolled Ketene–Imine Cycloaddition Reactions

Gunda I. Georg and Vasulinga T. Ravikumar

Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66045

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6.1 Introduction

The construction of naturally occurring or unnatural β-lactams with attendant control of functional groups and stereochemistry has been the goal of synthetic organic chemists for the past four decades. Among a multitude of synthetic methods, one of the most sought after and extensively studied is the [2 + 2] cycloaddition reactions of imines with ketenes. Broadly speaking, in the presence of base, the annulation of acid chlorides or activated carboxylic acids with imines is termed the *Staudinger reaction*. In particular, the reaction of azidoacetyl chloride with imines is called the *Bose reaction*.

In view of the recent number of publications on the chemistry of β-lactams, it has become necessary to survey and evaluate the extensive devel-

opments of this class of heterocycles. In this chapter, an attempt is made to bring up to date the various methods available for the synthesis of β-lactams using the Staudinger reaction. Cycloaddition reactions of imines with acid chlorides or with activated carboxylic acids in the presence of base have been widely used for the synthesis of β-lactams. This subject has been reviewed frequently.[1–24] Among the more recent reviews, Koppel[13] provided an excellent overview on the scope, and Holden,[12] Cooper et al.,[25] Hegedus et al.,[26] and Brady and Gu[27] reviewed mechanistic aspects, of the Staudinger reaction. Although the Staudinger reaction has been known for a long time and has been studied extensively, the mechanism and the rationale for the stereochemistry of the products obtained is still under debate. The stereochemical outcome of the reaction is sometimes difficult to predict because the reaction is dependent on many different factors such as the structures of the imine and the ketene, solvent, base, steric interactions, mode of ketene generation, reaction rates, temperature, and order of addition of reagents.[13,28]

In this chapter, we wish to provide an overview of recent results concerning the Staudinger reaction with an emphasis on stereo- and enantiocontrolled reactions. We are also providing a summary of mechanistic studies on the Staudinger reaction. Additionally, we are suggesting for the first time simple rules to predict the stereochemical outcome of the Staudinger reaction.

This review, however, does not cover in detail the reaction of transition metal carbenes with imines.[26] An excellent review on this topic by Barrett and Sturgess has appeared recently.[29]

6.2 Synthesis of β-Lactams

The first β-lactam was synthesized[30–32] by Staudinger and co-workers in 1907, but β-lactams as a class acquired importance only after it was established that penicillin contains a β-lactam unit as the unique structural feature. Since then, several other naturally occurring β-lactams have been isolated and synthesized.[8,33] More recently, β-lactams have also been recognized as useful chiral starting materials for the synthesis of other natural and unnatural products.[21] Thus, the interest in β-lactams continues unabated and several refined preparative methods have been developed, culminating in the stereospecific synthesis of the desired β-lactam with the requisite functionalities in the molecule.

Among the numerous methods for the synthesis of β-lactams, the annulation of ketenes with imines has proven to be a versatile procedure for the construction of the 2-azetidinone ring. This method is wide in scope and is useful for the synthesis of monocyclic, bicyclic,[8] tricyclic,[34] and spirocyclic β-lactams.[35,36]

6.2.1 Ketenes

The generation of ketenes can be achieved from suitable precursors in a variety of ways,[13] such as thermally,[37] photochemically from metal carbenes,[38] or from acid chlorides and related derivates in the presence of tertiary amines. Ketenes that have been used for β-lactam formation include diaryl ketenes, dialkyl ketenes, alkylaryl ketenes, haloketenes, dihaloketenes, trimethylsilylbromoketene, cyanoketenes, isocyanoketenes, halocyanoketenes, and alkylcyanoketenes.[13] Of particular interest in β-lactam chemistry are *N*-protected aminoketenes and azidoketenes, which serve as precursors for the synthesis of 3-amino-2-azetidinones. *O*-Protected hydroxyketenes serve as precursors for 3-hydroxy-2-azetidinones. 3-Hydroxy-2-azetidinones are of utility as precursors for the synthesis of penicillins,[39] cephamycins,[10] 7-methoxycephalosporins,[40] and tabtoxin.[41] They also serve as convenient precursors for the synthesis of α-hydroxy-β-amino acids,[42,43] such as (2*S*,3*R*)-3-phenylisoserine, the side chain of the potent antitumor agent taxol.[43–45] The acid chloride, from which the ketene is generated, is not always simple and easy to prepare and/or is not commercially available. An alternate synthesis of β-lactams that circumvents the use of acid chlorides involves the use of carboxyl group-activating agents.

Table 6.1 shows the various reagents that have been used for activating the carboxyl group in the Staudinger reaction. It appears that the reactions carried out with acid-activating agents generally follow the same stereochemical pattern of the resulting β-lactams as observed in the reactions with acid chlorides. Typically the yields are good to excellent.[28,46–73]

6.2.2 Imines

Imines derived from aldehydes or ketones can be used in the Staudinger reaction.[13] Often these imines possess an aromatic substituent at the nitrogen and the carbon or an aliphatic substituent at nitrogen and an aromatic group at carbon. Other imines include *N*-aryl imidates, *N*-aryl thioimidates, *N*-alkyl thioimidates,[74,75] amidines,[76] and carbodiimides.[13] Imines derived from cinnamaldehyde,[77] methyl glyoxylate,[78] phenylglyoxal,[78] diethyl ketomalonate,[79] lactic aldehyde,[80] mandelic aldehyde,[42] and others[81–83] are popular choices in the Staudinger reaction, because the C-4 substituents of the resulting β-lactams undergo facile functional group transformations. A newer study on the scope of imines in the Staudinger reaction was published recently.[84] β-Lactams have also been synthesized from cyclic imines[85,86] (which cannot tautomerize and hence are termed *fixed imines*) such as thiazolines, oxazolines,[87] imidazolines, tetra- and dihydropyrimidines,[88,89] dehydropiperidines,[90] thioimidates,[27,74,75,91–97] and 1,2-diazepines.[98,99] Utilization of cyclic imines possessing *cis*-imine geometry in the Staudinger reaction results in the formation of *trans*-β-lactams, whereas acyclic imines

possessing *trans*-imine geometry typically have a propensity toward the formation of *cis*-β-lactams. (For more details on mechanistic considerations see Section 6.4.)

6.2.3 Methods

6.2.3.1 Synthesis of 3-Amino-/3-amido-2-azetidinones: Bose Reaction

The reaction of azidoacetyl chloride (or a suitable carboxyl-activated form of azidoacetic acid) with Schiff bases or cyclic imines to form monocyclic or polycyclic α-azido-β-lactams (3-azido-2-azetidinones) has been termed the *Bose reaction*. This reaction was first described by Bose et al. in the course of their development of the total synthesis of 6-epipenicillin.[100,101] These authors were interested in the synthesis of α-amido-β-lactams; the azido group serves as a latent amino function as it is unaffected during many chemical transformations and is easily reduced to an amino group without disrupting the β-lactam ring.[86,102–107]

One serious drawback of azidoacetyl chloride and azidoacetic acid, like other azido compounds, is that they are hazardous to use and tend to decompose with explosive violence if rigorous precautions are not observed.[108,109] To overcome this problem several latent forms of amino group have been developed. One such example is phthalimidoacetyl chloride. Several groups have reported the reaction of phthalimidoacetyl chloride with imines to give β-lactams, which on treatment with hydrazine yielded 3-amino-2-azetidinones.[83,110–112]

A one-step synthesis of benzyloxycarbonyl- protected 3-amido-2-azetidinones **2** has been reported (Scheme 6.1 see page 302). The reaction of an acid chloride of type **1** with an imine in the presence of triethylamine resulted in the formation of **2**, albeit in relatively low yields (11–55%).[113,114] This procedure has also been applied to the synthesis of bicyclic β-lactams in yields of 11 to 70%.

A *t*-BOC group on the nitrogen of the amino group has also been used for the synthesis of bicyclic β-lactams (60% yield).[114] The aforementioned protecting groups could be removed from the 3-amido-β-lactams under the usual conditions without ring cleavage. 3-Amido-β-lactams (Scheme 6.2 see page 302) have also been synthesized by the cycloaddition of azlactone **3** with furan-2-aldehyde and thiophene-2-aldehyde imines.[115]

Another nonhazardous, economic, and highly *cis*-stereoselective synthesis of 3-amido-2-azetidinones was reported by several groups.[116–122] The key to this approach is the ease of formation of the "Dane salt" (Scheme 6.3) by allowing a methanol solution of the potassium salt of an α-amino acid to react with a β-dicarbonyl compound.[119,123,124] The protecting group can be

Table 6.1. REAGENTS USED FOR THE ACTIVATION OF CARBOXYLIC ACIDS

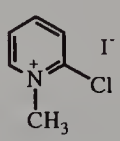
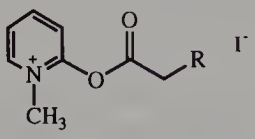
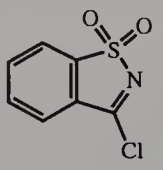
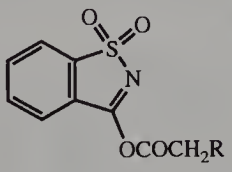
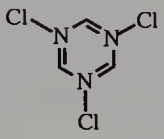
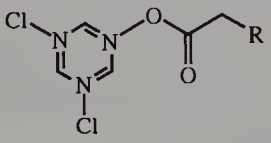
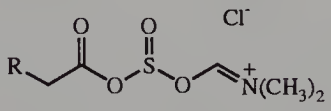
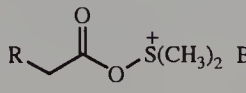
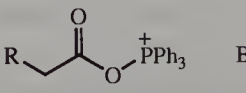
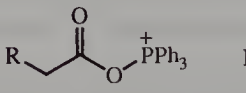
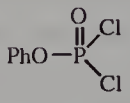
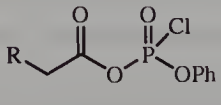
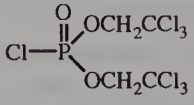
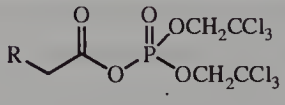
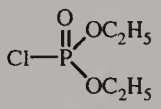
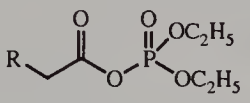
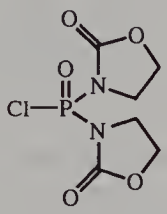
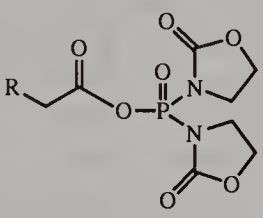
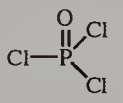
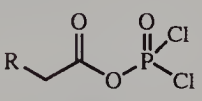
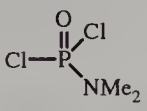
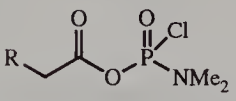
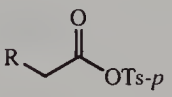
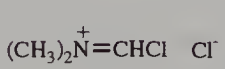
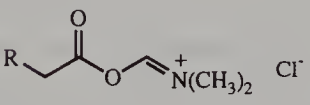
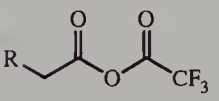
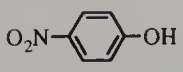
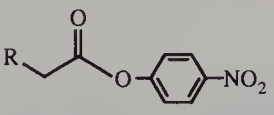
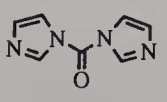
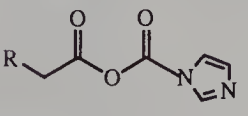
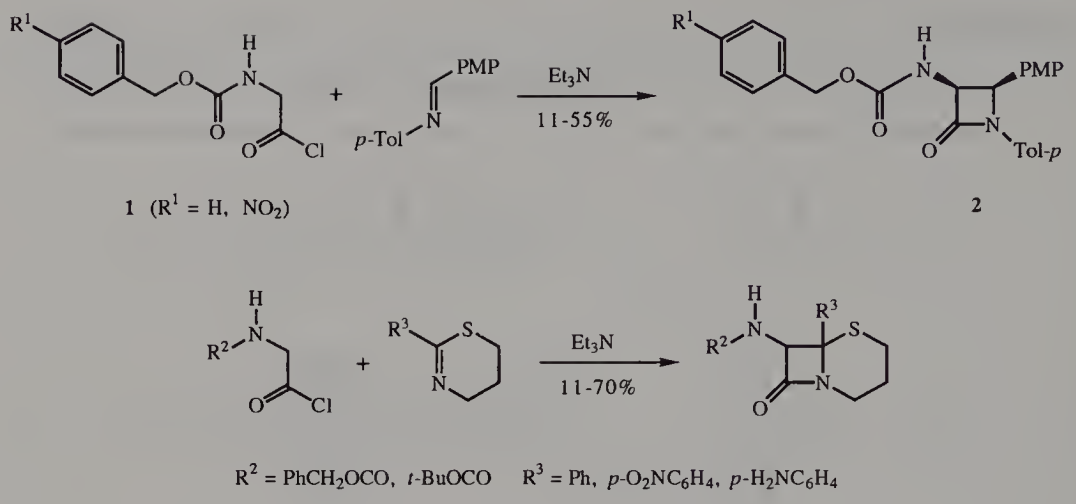
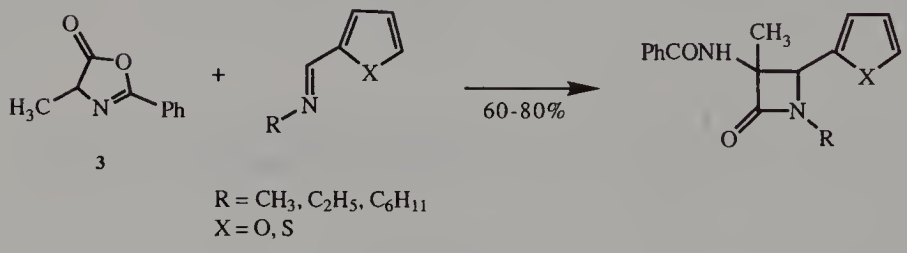
Entry	Reagent	Possible Reactive Species	References
1			46, 47
2			48, 49
3			50 - 53
4	$SOCl_2$ - DMF		54
5	$(CH_3)_2SBr_2$		55
6	Ph_3PBr_2		55
7	$Ph_3P + CBr_4$		56
8			57 - 62
9			63

Table 6.1.

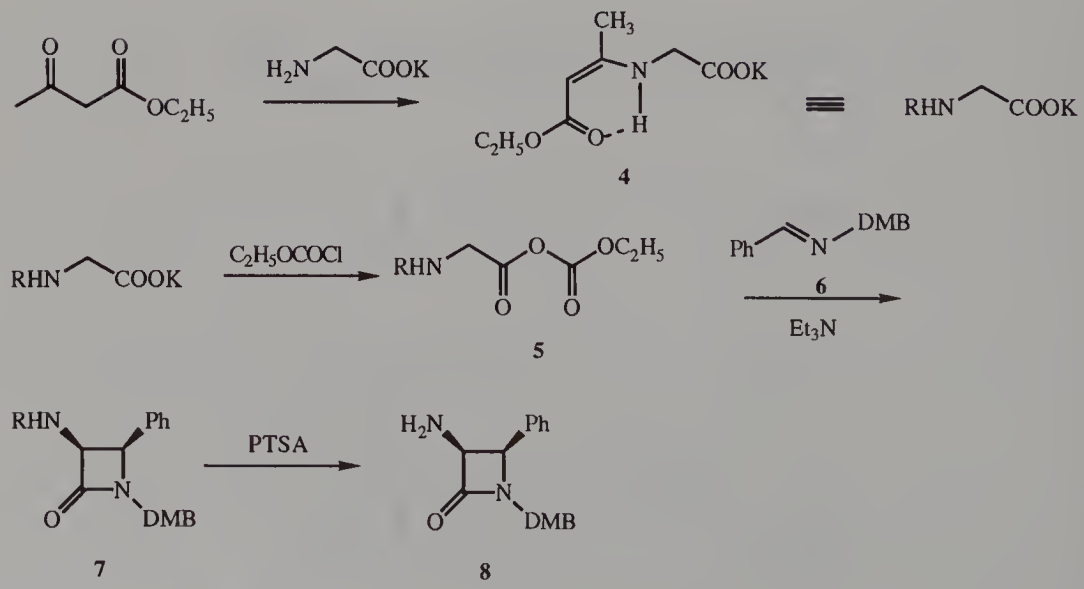
Entry	Reagent	Possible Reactive Species	References
10			64, 65
11			66
12			28, 67
13			68
14	*p*-TsCl		69
15			54
16	$(CF_3CO)_2O$		70, 71
17			72, 73
18			72



Scheme 6.1



Scheme 6.2



Scheme 6.3

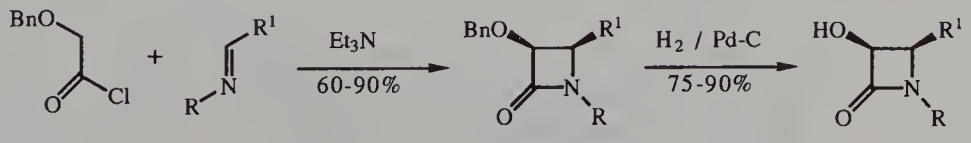
removed efficiently under very mild acid conditions (enamine hydrolysis). For example, the potassium salt of (α-methyl-β-methoxycarbonyl)-vinylaminoacetic acid (**4**) was allowed to react with ethyl chloroformate and triethylamine to form the mixed anhydride **5**. Formation of **5** in situ and subsequent reaction with Schiff base **6** afforded a single *cis*-isomer of α-vinylamino-β-lactam **7** (65% yield). The vinyl amino group of **7** was cleaved under mild acid conditions to give β-lactam **8**.

In preparing the Dane salts, several β-dicarbonyl compounds have been used.[119] It was found that the most useful dicarbonyl compounds for the preparation of the Dane salt are ethyl and methyl acetoacetate. The size of the ester group (of the keto ester) did not have any influence on β-lactam formation. Enamines derived from β-diketones, however, reacted slowly and gave low yields of β-lactams.

An efficient method of synthesizing 3-amino-β-lactams from optically active (4*S*)-phenyloxazolidylacetyl chloride was reported by Evans and Sjogren and is discussed in Section 6.3 (see Scheme 6.23).[125] Related methods were reported recently by Ikota and Hanaki (Scheme 6.27)[126,127] and Cooper (Scheme 6.25), who used heterocycles derived from L-(+)-tartaric acid, (*S*)-glutamic acid, and (*S*)-serine as crypto amino groups for the synthesis of 3-amino-2-azetidinones.

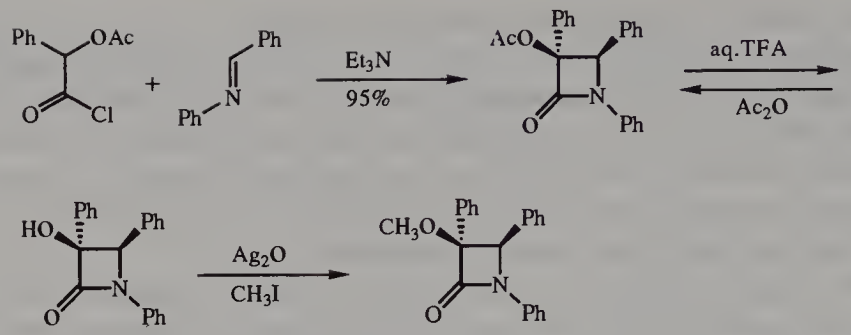
6.2.3.2 Synthesis of Hydroxy-2-Azetidinones

3-Hydroxy-β-lactams can be synthesized by reacting protected hydroxyacetyl chloride (or the activated acid) with imines in the presence of base followed by removal of the masking group. Manhas et al. have reported (Scheme 6.4) a convenient synthesis of 3-hydroxy-β-lactams involving the annulation of imines with benzyloxyacetyl chloride and triethylamine and subsequent hydrogenolysis in the presence of palladium on carbon in good yields[128]; however, when a thioimidate was used as the imino component in the annulation reaction, hydrogenolysis of the benzylated β-lactam failed. Other typical hydroxy protecting groups have been used[129,130] for the synthesis of 3-hydroxy-2-azetidinones, including the acetyl group.[131,132] Also Bose et al. have described (Scheme 6.5) a synthesis of 3-hydroxy-β-lactams in which the hydroxy group is tertiary in character.[133]



R = Ph, *p*-$CH_3C_6H_4$, R^1 = Ph, *o*-$O_2NC_6H_4$, 2-furyl

Scheme 6.4



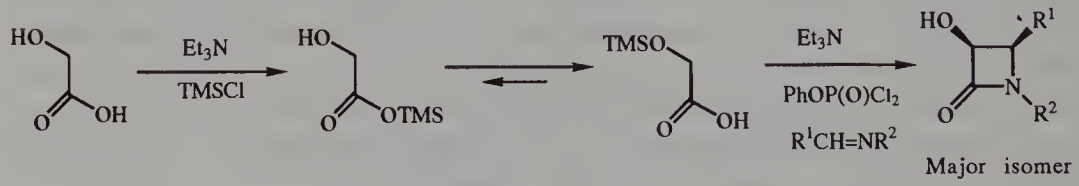
Scheme 6.5

Cassio and Palomo have communicated the synthesis of 3-hydroxy-2-azetidinones (45–65% yield) by the annulation of Schiff bases with trimethylsilyloxyacetic acids promoted by phenyldichlorophosphate (Scheme 6.6).[134] In the case of trimethylsilyloxyacetic acid, some *trans* product formation was observed, whereas the trimethylsilyl ether of mandelic acid resulted in the formation of a single isomer (55–82% yield).

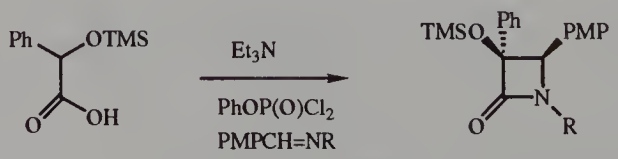
Recently, a carbohydrate was used as protecting group and chiral auxiliary in the synthesis of 3-hydroxy-2-azetidinones (see Scheme 6.28).[135] A series of 3,4-dihydroxy-2-azetidinone derivatives (Scheme 6.7) was reported by Bose and his co-workers.[136]

A stereospecific synthesis of 4-alkoxy-β-lactams was achieved (Scheme 6.8) by cycloaddition reaction between thioimidates and acid chlorides with subsequent treatment of the resulting 4-alkyl- or 4-arylthio-2-azetidinones with bromine.[137]

A highly stereoselective synthesis of 4-alkoxy β-lactams (Scheme 6.9.)

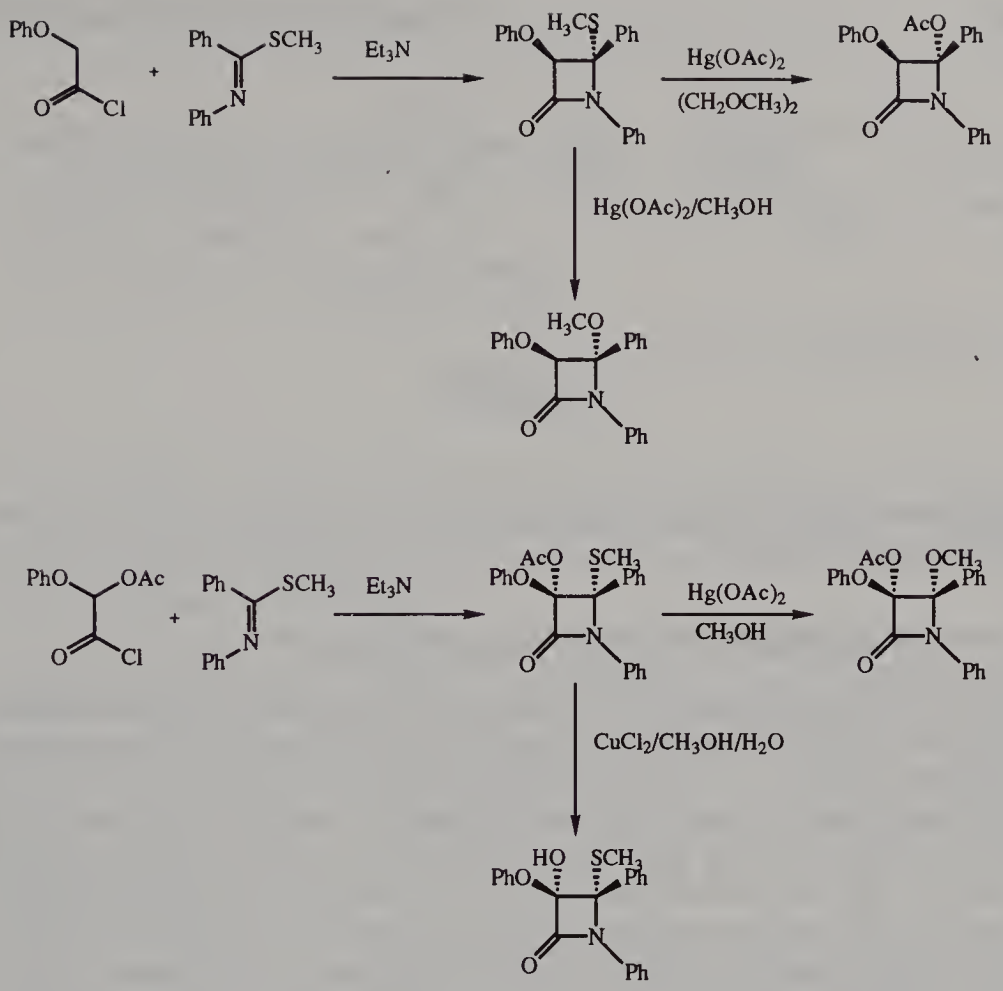


R^1 = Ph, *p*-$CH_3OC_6H_4$ R^2 = Ph, *p*-$CH_3OC_6H_4$, $CH_2CHOHC_6H_4$

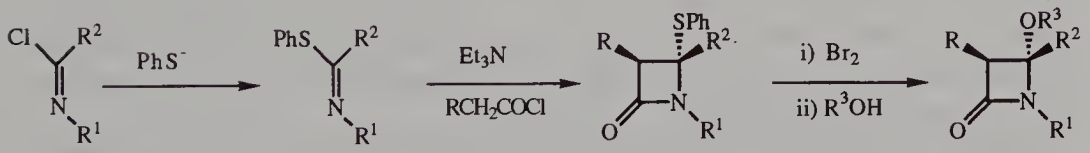


R = Ph, *p*-$CH_3OC_6H_4$, Ph_2CH

Scheme 6.6



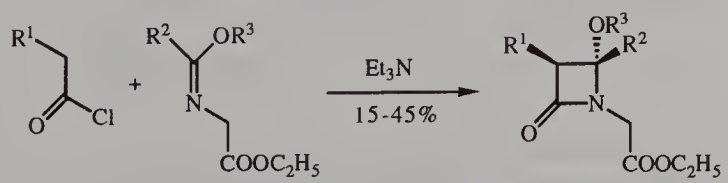
Scheme 6.7



R = CH_3O, PhO, N_3, $PhCH_2S$, $PhOCH_2CONH$ R^1 = Ph, *p*-$C_2H_5O_2CC_6H_4$

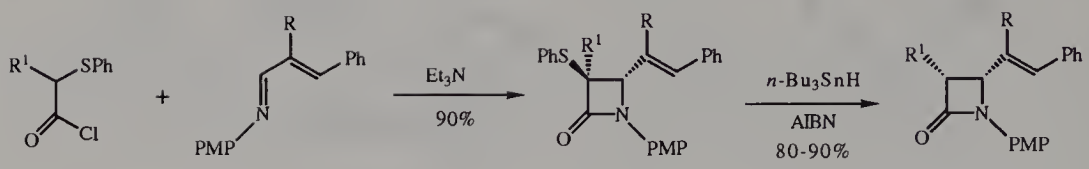
R^2 = Ph R^3 = CH_3, C_2H_5

Scheme 6.8



R^1 = OPh, Phth R^2 = H, CH_3 R^3 = C_2H_5, *i*-C_3H_7

Scheme 6.9



$R^1 = CH_3, C_2H_5, i\text{-}C_3H_7$ R = H, CH_3, Ph

Scheme 6.10

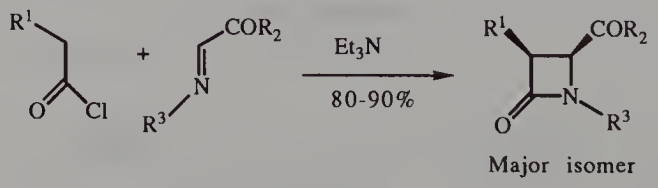
possessing an *N*-carboethoxymethyl group was reported in low to medium yields from imidates.[138]

6.2.3.3 Synthesis of 3-Alkyl-2-azetidinones

Interest in the development of synthetic methodology for 3-alkyl-2-azetidinones and related derivatives was sparked by the discovery of carbapenem antibiotics such as PS-5, PS-6, thienamycin, the olivanic acids, and the asparenomycins.[33] Direct synthesis of 3-alkyl-β-lactams from monoalkyl ketenes, generated from their corresponding acid chlorides, is often limited in scope. This fact is probably due to the inherent instability of aldoketenes.[139,140] To circumvent this problem, Palomo et al. reported (Scheme 6.10) a concise general route to 3-alkyl-β-lactams as carbapenem building blocks that involves the use of alkyl(phenylthio) ketenes as synthetic equivalents of alkyl ketenes.[141,142]

Of note is the finding in this study that the *cis* selectivity of the Staudinger reaction was enhanced using benzene as the solvent and by utilizing bulky imines (R = Ph). Reduction of the 3-alkyl-3-phenylthio-β-lactams with tributyltin hydride occurred from the least hindered face of the molecule to produce *cis*-β-lactams with high selectivity.

Contrary to earlier reports on low-yielding 3-alkyl-β-lactam syntheses, Palomo and co-workers found (Scheme 6.11) that utilization of imino esters

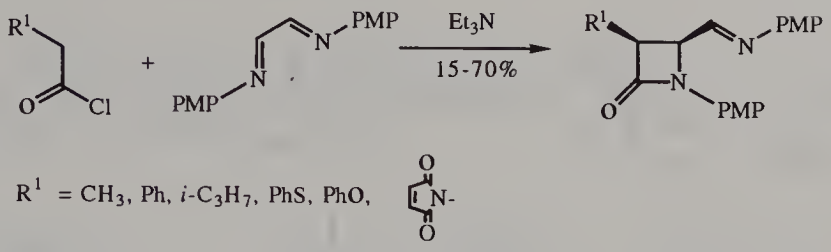


$R^1 = H, CH_3, C_2H_5, i\text{-}C_3H_7$

$R^2 = Ph, OCH_3$

$R^3 = p\text{-}CH_3OC_6H_4, CH_2{=}CHCH_2, (CH_3)_2CHCH_2$

Scheme 6.11



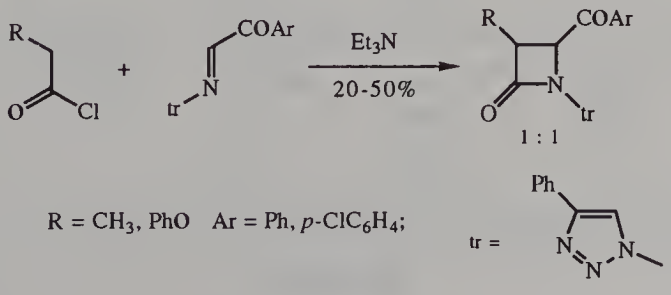
Scheme 6.12

in the Staudinger reaction with alkanoyl chlorides gave excellent yields (80–90%) and good to excellent *cis:trans* selectivity (80:20 to 100:0).[43,78] Similar results (*cis* stereospecificity) were reported by Alcaide et al. in the reaction with imines from phenylglyoxal.[143]

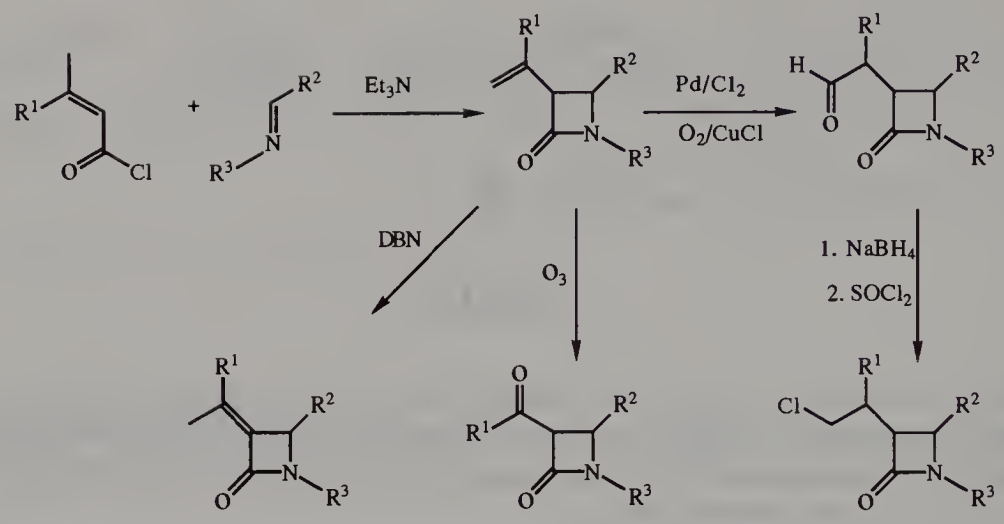
A one-flask synthesis of 3-substituted 4-formyl-*cis*-azetidin-2-ones in mostly good yields was achieved by the reaction of acid chlorides with 1,4-bis(4-methoxyphenyl)-1,4-diazabuta-1,3-diene wherein the later serves as a synthon of the corresponding 4-formylimines. The products of this reaction, the 4-imino-2-azetidinones, can by hydrolyzed to 4-formyl-2-azetidinones (Scheme 6.12).[144] A mechanistic discussion of the observed *cis* selectivity (Schemes 6.11 and 6.12) is provided later in this chapter (see also Scheme 6.88).

Recently Bojilova and Rodios have synthesized 1-(1,2,3-triazol-l-yl)-4-aroyl-2-azetidinones (Scheme 6.13) using 1-(*N*-phenacylidine)amino-1,2,3-triazoles as the imino component in the cycloaddition reactions.[145] The chemical yields ranged from 20 to 50% and typically a 1:1 mixture of *cis* and *trans* products was obtained. Attempts to remove the *N*-triazole moiety with cerium ammonium nitrate failed.

α-Vinyl-β-lactams have been synthesized (Scheme 6.14) by the cycloaddition of crotonyl chloride with imines in the presence of base.[43,46,146–148] Depending on the imine, formation of *cis* or *trans* products or a mixture of *cis* and *trans* products was observed (see also Scheme 6.79). The α-vinyl group was transformed to produce 2-azetidinones with a variety of useful substituents at C-3.



Scheme 6.13



R^1 = H, CH_3

R^2 = Ph, *p*-$CH_3OC_6H_4$, 3-pyridyl, 3-furyl, PhCO, Ph-CH=CH, $COOCH_3$

R^3 = Ph, *p*-$CH_3OC_6H_4$, $PhCH(CH_3)$, $TBDMSOCH_2CH(COOCH_3)$, $HOCH(CH_3)CH(COOPNB)$

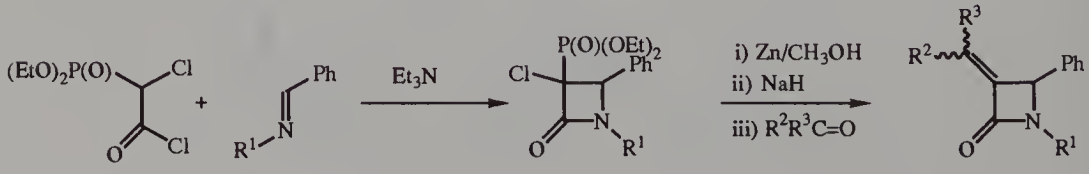
Scheme 6.14

(Diethylphosphono)ketenes were found to add to imines to give β-lactams (Scheme 6.15), which after dechlorination and Horner–Wittig reaction gave substituted 3-*exo*-methylene β-lactams.[149]

3-Hydroxyethyl-2-azetidinones were synthesized from 3-hydroxybutyric acid chloride derivatives.[150–153] Please refer to Schemes 6.31 and 6.32 in Section 6.3 in this chapter.

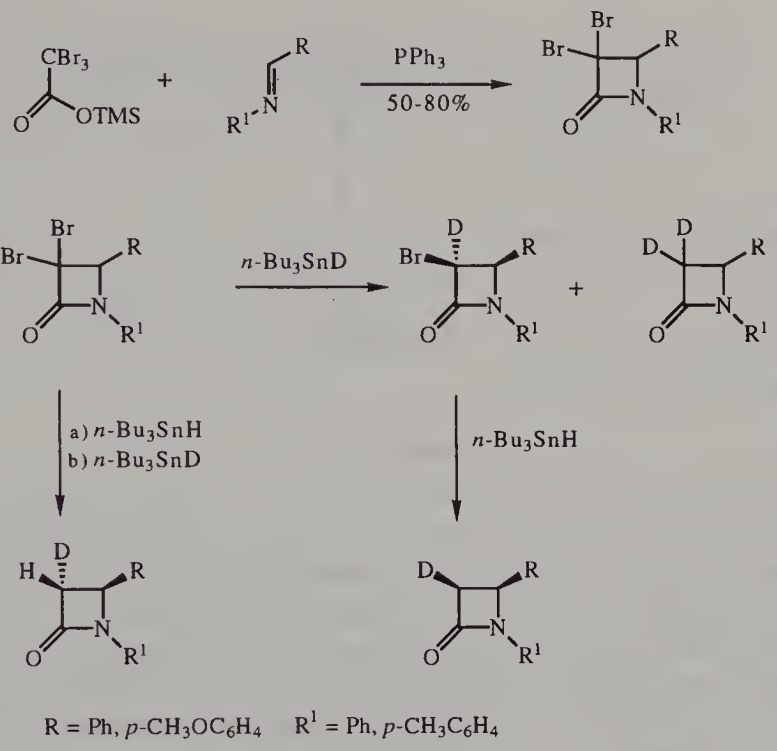
6.2.3.4 Synthesis of 3-Halo-2-azetidinones

Annulation of chloroketenes to imines has been reported to yield both [2 + 2] and [4 + 2] adducts, depending on substitution at the imine and ketene.[154–156] 3,3-Dibromo- and 3,3-dichloro-2-azetidinones were prepared by the reaction of imines with the trimethylsilyl ester of tribromoacetic acid or trichloro-



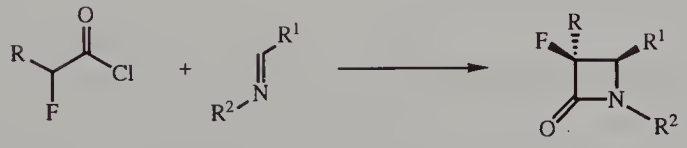
R^1 = Ph, *p*-$CH_3OC_6H_4$ R^2 = Ph, CH_3, *i*-C_3H_7 R^3 = H, CH_3

Scheme 6.15



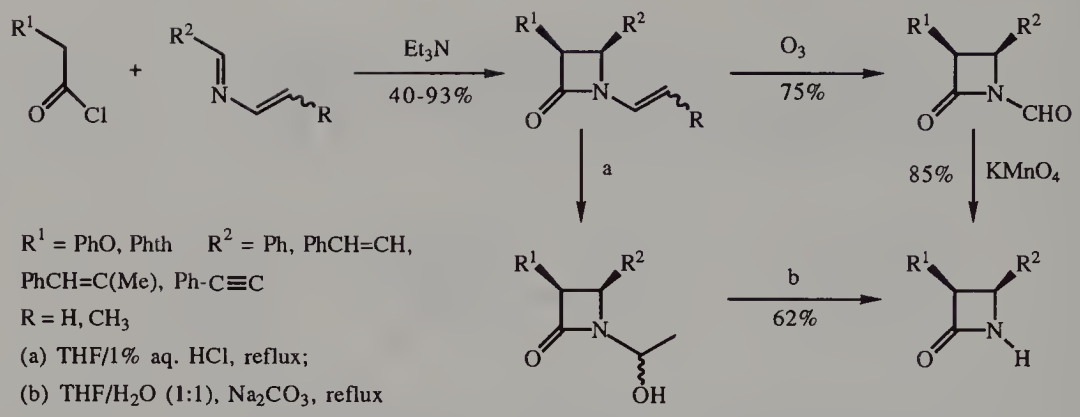
R = Ph, *p*-$CH_3OC_6H_4$ R^1 = Ph, *p*-$CH_3C_6H_4$

Scheme 6.16



Entry	R	R^1	R^2	Yield (%)	cis : trans
1	H	Ph	Ph	70	cis
2	H	Ph	PMP	70	cis
3	H	styryl	PMP	15	cis
4	H	$COOC_2H_5$	PMP	66	19:1
5	Ph	Ph	Ph	51	cis
6	Ph	Ph	PMP	16	cis
7	Ph	Ph	C_2H_5	40	cis
8	Ph	$COOC_2H_5$	PMP	48	cis

Scheme 6.17



Scheme 6.18

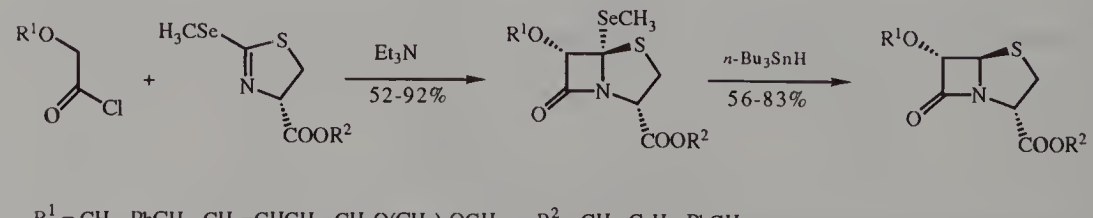
acetic acid and triphenylphosphine (Scheme 6.16 see page 309). On reduction with *n*-Bu_3SnD, 3-deuterio-β-lactams were obtained.[157]

3-Fluoro-2-azetidinones were obtained as single isomers and in mostly good yields in the reaction between fluoroacetyl chloride and imines in all but one case (Scheme 6.17 see page 309, entry 4). The high *cis* selectivity (F and the C-4 substituent in *cis* relationship) was explained as resulting from dipolar effects or secondary orbital interactions. Steric influences were ruled out because selectivity was retained in the reaction, with ketenes possessing a bulky substituent (R = Ph) at α-carbon.[158] (For a complementary interpretation of these results see Section 6.5.3.)

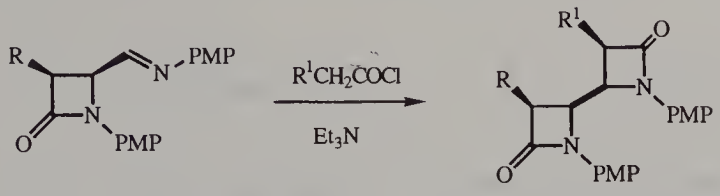
6.2.3.5 Miscellaneous Methods

Recently, Georg et al. reported a straightforward synthesis of *N*-unsubstituted β-lactams (Scheme 6.18) using 2-aza-1,3-dienes as precursors for β-lactam formation.[77,159] Good yields and very high *cis* selectivity of β-lactam formation were observed. The *N*-vinyl protecting group can be removed either oxidatively or hydrolytically to yield *N*-unsubstituted β-lactams.

A simplified synthesis of penem-type β-lactams has been accomplished



Scheme 6.19



R = PhO, $PhCH_2O$, Phth R^1 = PhO, $PhCH_2O$

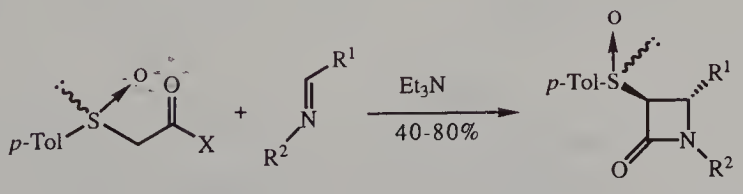
Scheme 6.20

(Scheme 6.19) by using a new methylseleno-promoted ketene–imine cycloaddition reaction and reductive elimination of the methylseleno group with tributyltin hydride. The reactions proceed in high yields and with excellent diastereoselectivity.[130,160]

Schiff bases derived from 4-formyl-2-azetidinones were reacted with acid chlorides and triethylamine to yield *bis*(β-lactams) (Scheme 6.20) as single diastereoisomers possessing *cis* stereochemistry at both β-lactam rings.[161]

Guanti et al. have condensed aryl aldimines with derivatives of 2-*p*-tolylsulfinylacetic acid to afford *trans*-β-lactams (Scheme 6.21) in diastereoselectivities ranging from 47:53 (R^1 = Ph, R^2 = CH_2Ph) to 87 : 13 (R^1 = *p*-$AcNHC_6H_4$, R^2 = Ph).[72] Similar observations were reported by Tokutake et al. as well.[73]

A newer synthetic approach to β-lactams involves the photolytic reaction of heteroatom-stabilized (Fisher) chromium–carbene complexes with imines.[26,162,163] This process is quite general and tolerates wide variations in the structure of both the carbene and the imine including cyclic imines (Scheme 6.22). The reaction proceeds in high yield under mild conditions (photolysis in the visible region; THF, ether, or CH_3CN as solvent; 25°C) and is quite stereoselective, producing a single diastereoisomer in almost all cases.

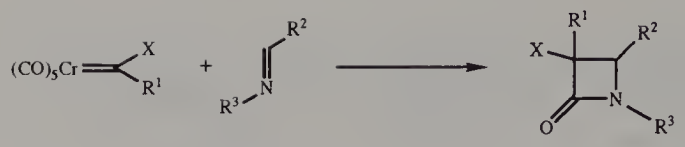


R^1 = Ph, $CH_3(CH_2)_5$, *p*-ClC_6H_4, *p*-$AcNHC_6H_4$

R^2 = Ph, *p*-$CH_3OC_6H_4$, *p*-ClC_6H_4, $PhCH_2$

X = *p*-$O_2NC_6H_4O$, imidazole

Scheme 6.21



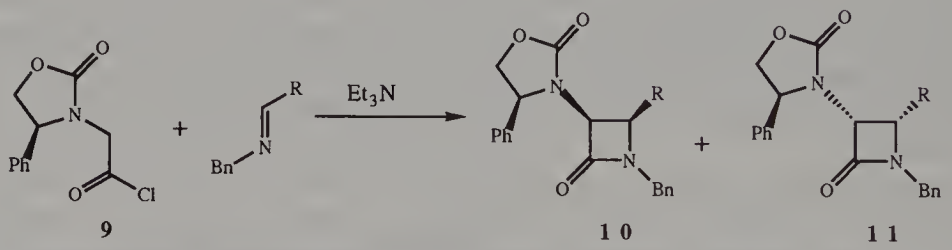
X = OR, NR_2, $N(COR)_2$, $NRCOR^1$
R^1 = H, CH_3, Ph

R^2 = H, Ph, OCH_3, CH_3, PhCH=CH
R^3 = Bn, CH_3, *t*-Bu, PMP, Ph, $CH=CH_2$

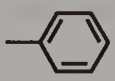
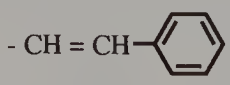
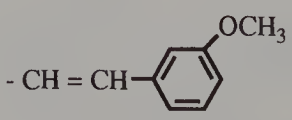
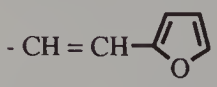
Scheme 6.22

6.3 Asymmetric Synthesis

Impressive progress has been made in the last 10 years with regard to the asymmetric synthesis of β-lactams. Chiral imines derived from chiral aldehydes or amines were investigated as were chiral acid chlorides, chiral keteneimines, and α-chloroiminium halides.



9 **10** **11**

Entry	R	Yield (%)	10 : 11
1		90	97 : 3
2		82	95 : 5
3		80	92 : 8
4		80	97 : 3

Scheme 6.23

6.3.1 Chiral Ketenes

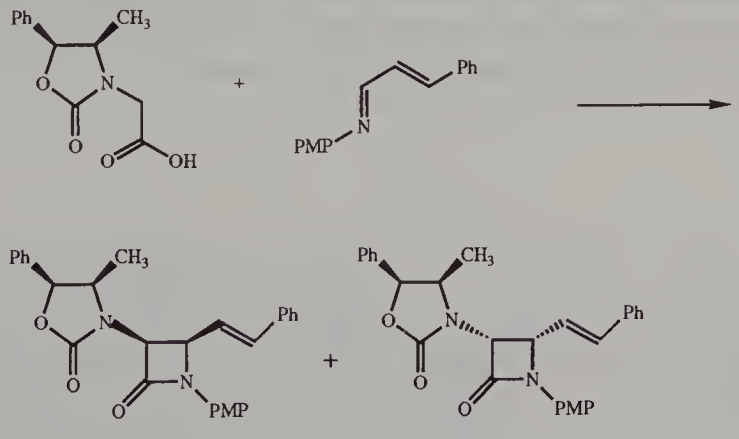
6.3.1.1 Amides and Imides

One approach to induce asymmetry to the ketene–imine reaction is to use a chiral auxiliary attached to the ketene component. Evans and Sjogren developed a chiral auxiliary that provides high diastereoselectivity.[125] In the reaction of oxazolidone **9** with *N*-benzylimines, 92 to 97% asymmetric induction within the *cis*-azetidinone product manifold (**10** and **11,** Scheme 6.23), was observed and no *trans* diastereoisomer was detected. The enantiomeric oxazolidone was employed by Boger and Myers for the synthesis of the enantiomer of β-lactam **10** (Scheme 6.23, entry 2).[164]

Cooper et al. have used a complementary chiral auxiliary (Scheme 6.24) prepared from norephedrine and found the product mixture to contain greater than 95% of one diastereoisomer.[25]

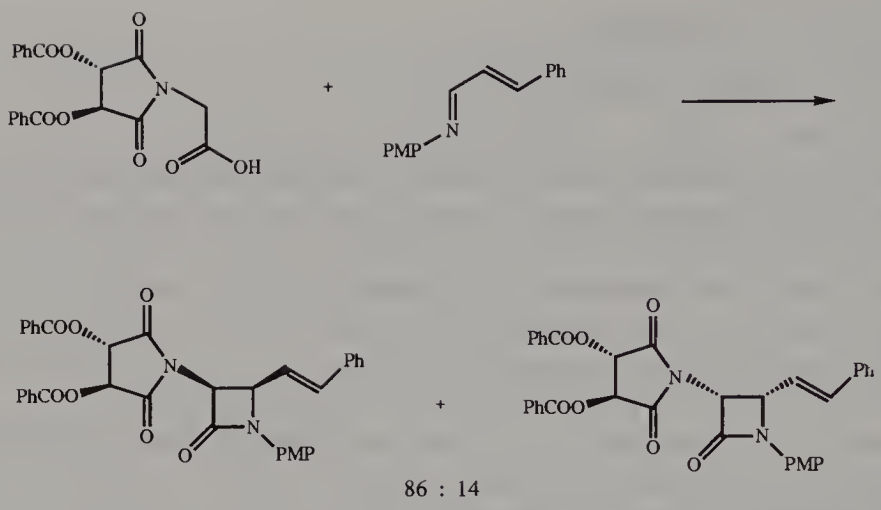
To remove the auxiliary and use it repeatedly, Cooper et al. have used a tartrimide, prepared from *S,S*-tartaric acid, as the chiral auxiliary (Scheme 6.25).[25] A key difference in this system would be that the chiral directing groups would be β to the amide nitrogen instead of α to the amide nitrogen as in the previous example and, as a consequence of being further removed, might exert less steric control. As expected, the diastereoselectivities were lower than those with a directing group α to the amide nitrogen.

Ojima and Chen observed that in the asymmetric [2+2] cycloaddition of chiral ketenes to chiral imines, the latter did not have any significant influence on the asymmetric induction (Scheme 6.26). No appreciable double-asymmetric induction was noticed and only the chiral center in the ketene played a key role in the asymmetric synthesis.[165,166] For a detailed discussion, refer to Chapter 4 by Ojima in this book.



> 95 : 5

Scheme 6.24

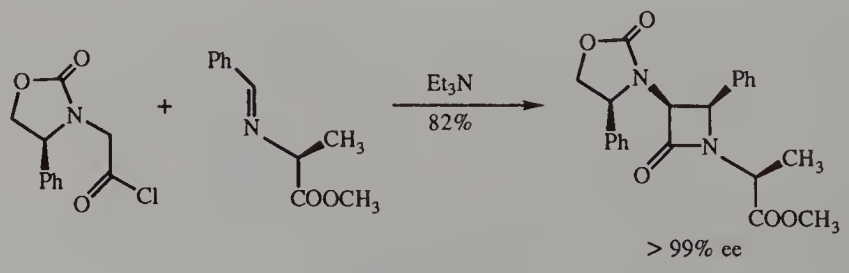


Scheme 6.25

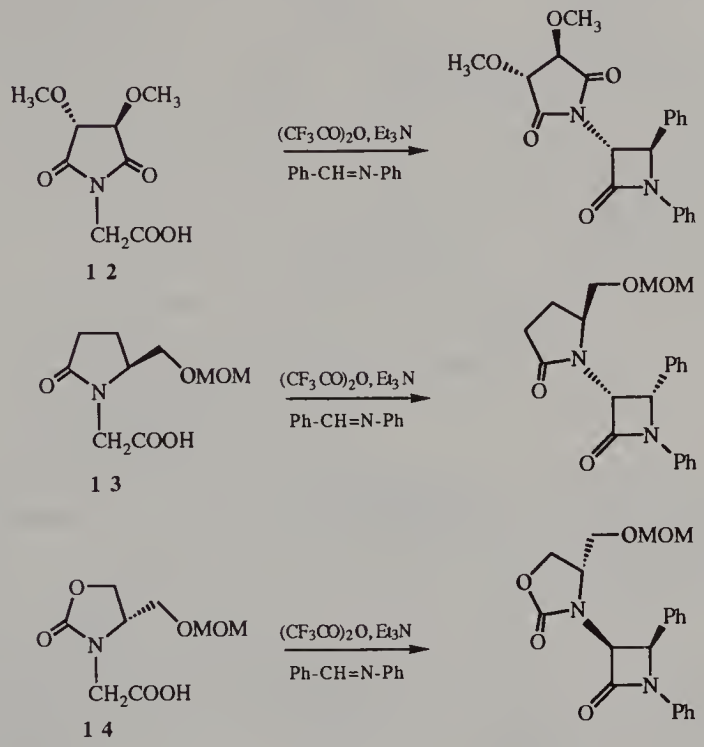
An asymmetric synthesis of β-lactams by [2+2] cyclocondensation of benzylideneaniline with mixed anhydrides of acids **12** to **14** (Scheme 6.27), bearing heterocycles derived from L-(+)-tartic acid, *(S)*-glutamic acid, or *(S)*-serine, respectively, has been reported.[126,127] The chiral auxiliaries were successfully removed (two to seven steps), leaving the β-lactam ring intact to afford the 3-amino-2-azetidinone derivatives.

6.3.1.2 Carbohydrates

Recently, Borer and Balogh have used a chiral ketene derived from a carbohydrate in the asymmetric synthesis of a *cis*-β-lactam in 52% overall yield after hydrolysis in 4 : 1 : 1 THF/H_2O/HOAc.[135] The enantiomeric excess was found to be 70% in this case (Scheme 6.28). The acid chloride **15** was synthesized in three steps from tri-*O*-acetyl-D-glucal.



Scheme 6.26



Reagent	Reaction Temp (°C)	Yield (%)	cis : trans	Ratio of diastereo-isomers	Asymmetric induction (% ee)
12	0	47	trans	84 : 16[a]	68
12	-20	40	trans	87 : 13[a]	74
13	0	71	86 : 14	97 : 3[b]	94
13	-20	62	84 : 16	98 : 2[b]	96
14	0	70	97 : 3	96 : 4[b]	92
14	-20	61	99 : 1	97 : 3[b]	94

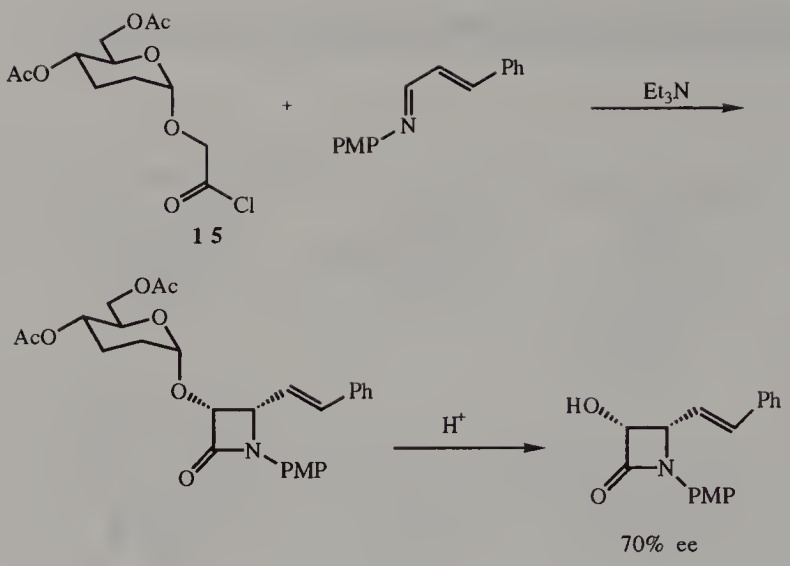
[a]Ratio of trans isomers [b]Ratio of cis isomers

Scheme 6.27

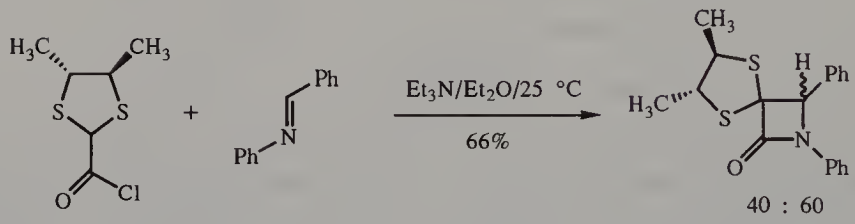
6.3.1.3 Thioketals and Ketals

Chiral ketenes derived from 1,3-dithiolane-2-carboxylic acids on cycloadditions with Schiff bases led to diastereofacial differentiation in the formation of substituted spiro-β-lactams (Scheme 6.29).[167]

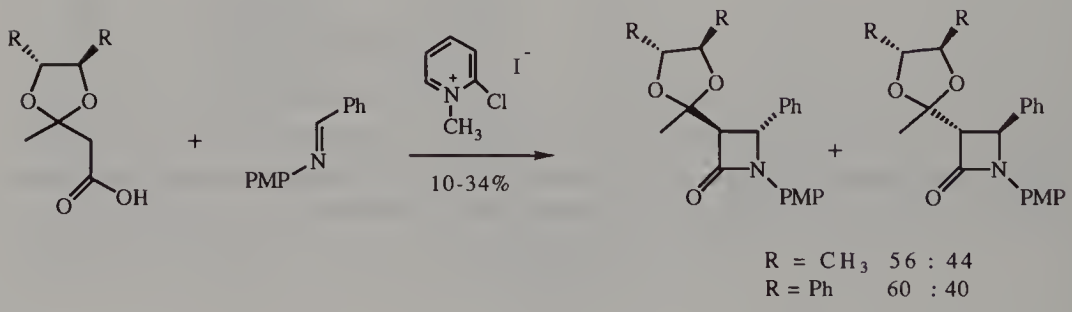
Ketenes derived from acetoacetic acid ketals produced mixtures of *trans*-diastereoisomers (Scheme 6.30) in low yields (10–34%). The relative stereochemistry of the two isomers was not assigned.[168]



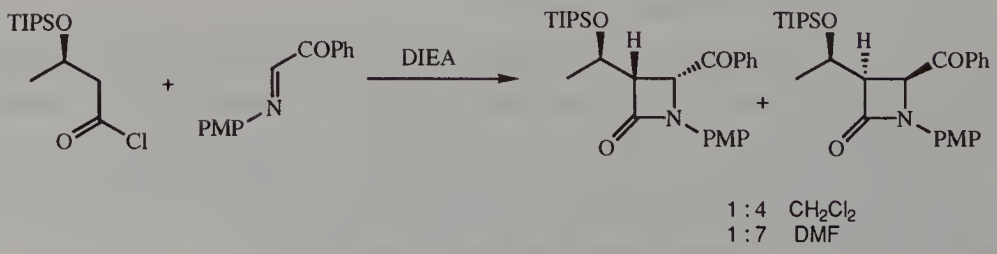
Scheme 6.28



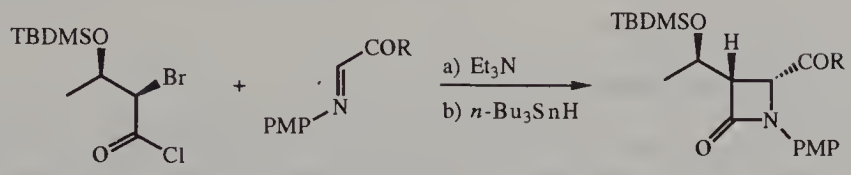
Scheme 6.29



Scheme 6.30



Scheme 6.31



R = CH_3O, *p*-ClPh

Scheme 6.32

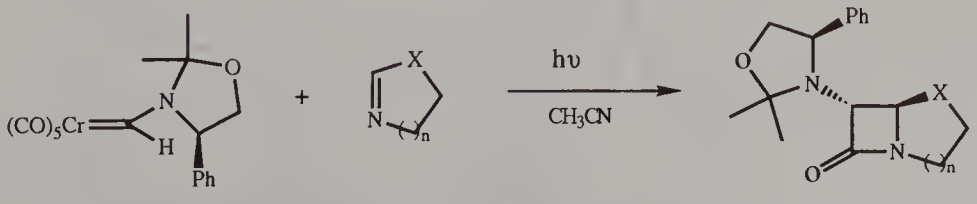
6.3.1.4 3-Hydroxybutyric Acid

Reaction between the acid chloride derived from 3-hydroxybutyric acid and an imine produced a 1 : 4 ratio of *cis*-β-lactams in methylene chloride as the solvent and a 1 : 7 mixture in DMF (Scheme 6.31). Increasing the steric bulk of the hydroxy protecting group produced better diastereoselectivity.[150,151] Related studies were reported by Ernst and Bellus.[153]

Essentially complete diastereocontrol was obtained when the 2-bromo-substituted acid chloride of 3-hydroxybutyric acid was used in the ketene–imine reactions (Scheme 6.32). Reduction of the resulting 3-bromo-2-azetidinone gave the desired *cis* product and a small amount of its related *trans* C-3 epimer.[152]

6.3.1.5 Chromium–Carbene Complexes

Photolytic reactions of cyclic imines and imidates with optically active chromium–carbene complexes were reported by Hegedus et al. to produce *trans* products (Scheme 6.33) in excellent yields (75–95%) and diastereoselectivity (> 97% de). *N*-Benzylimines of acetaldehyde gave mixtures of *cis*- and *trans*-β-lactams (major isomer), each of which was a single diastereoisomer. Excellent diastereoselectivity was obtained with chromium–carbene complexes derived from *(R)*-phenylglycinol and *(S)*-valinol.[163]



X = CH_2, O n = 2,3

> 97% de

Scheme 6.33

6.3.2 Chiral Imines

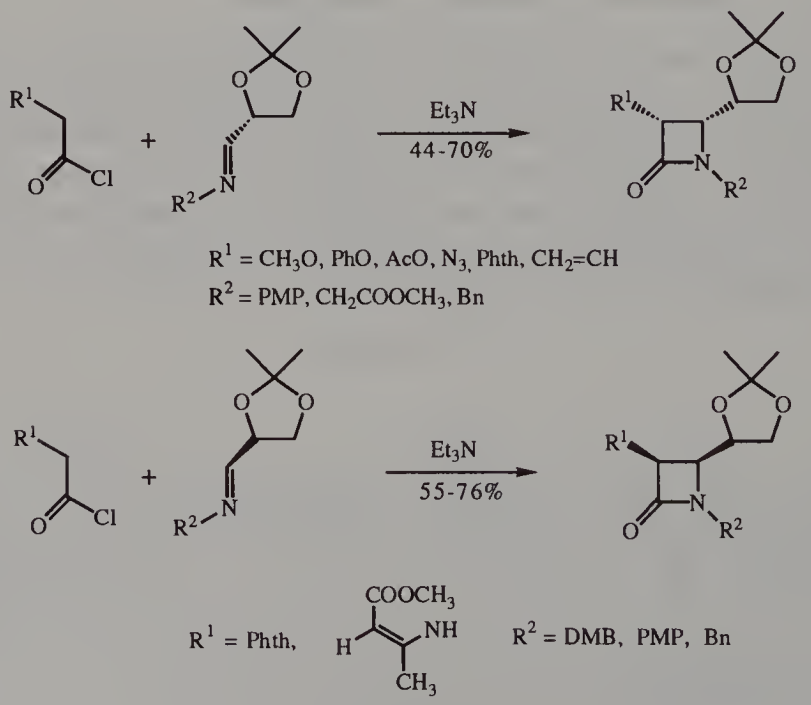
6.3.2.1 Chiral Aldehydes

Using an imine derived from an optically active aldehyde is another approach to inducing asymmetry in the Staudinger reaction. Complete *cis* diastereoselectivity was observed during the cyclocondensation of activated acids with aldimines derived from D- and L-glyceraldehyde acetonides.[82,83,131] The β-lactams were isolated in excellent optical and good chemical yields (Scheme 6.34).

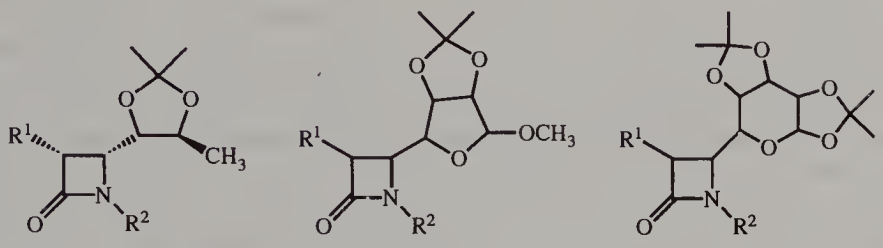
Similar observations were reported by Bose et al. They noted that imines derived from several glyceraldehyde acetonide-related chiral aldehydes (Scheme 6.35, absolute stereochemistry not given) led to a single *cis*-β-lactam in all cases.[105,131,169] This experiment demonstrated that the second chiral center in the aldehyde apparently does not exercise an influence on the stereochemical course of the annulation reaction.[104]

An imine derived from 2,3-*O*-isopropylidene-L-threitol also gave essentially complete diastereocontrol in the Staudinger reaction (Scheme 6.36.).[127]

Terashima et al. have reported a highly stereoselective addition of diketene to an imine derived from an optically active aliphatic aldehyde carrying a chiral center at the α position.[80,170,171] This aldehyde was obtained from commercially available inexpensive *(S)*-ethyl lactate. The diastereoselectivity was dependent on the solvent used (table in Scheme 6.37). The best results (90% de) were obtained with acetonitrile as the solvent (entry 5).

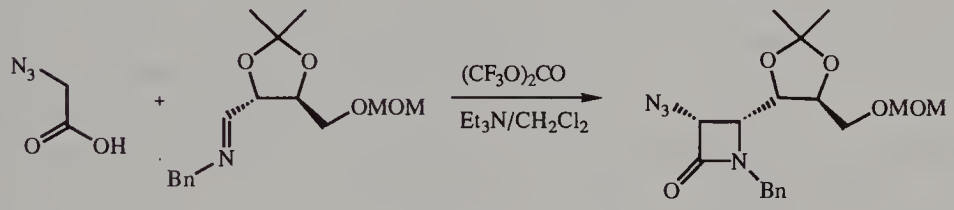


Scheme 6.34

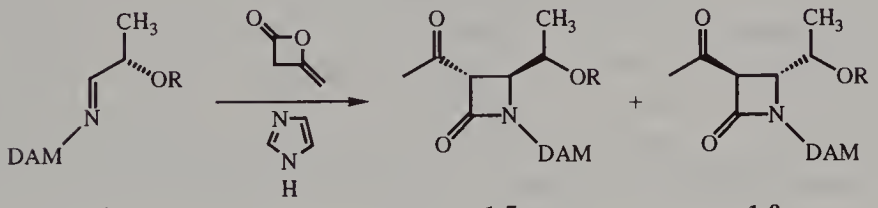


R^1 = OAc, OBn, OCH_3, OPh R^2 = PMP, Bn

Scheme 6.35



Scheme 6.36

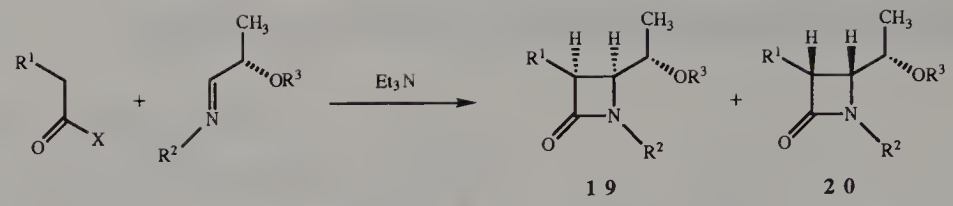


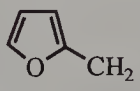
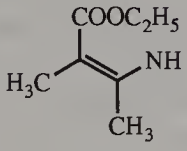
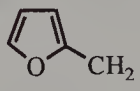
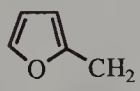
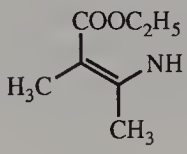
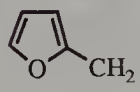
16 **17** **18**

16a R = Bn **16b** R = TBDMS **16c** R = THP **16d** R = MEM **16e** R = EE

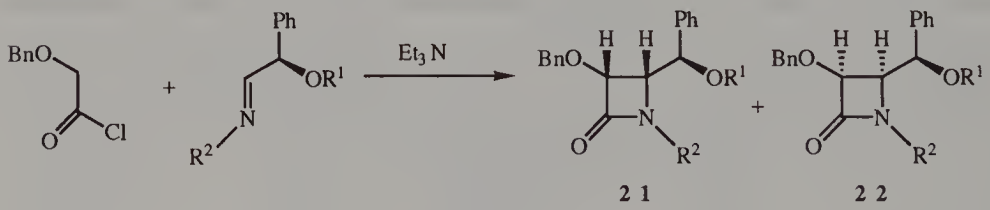
Entry	Imine	Solvent	Yield (%)	17 : 18
1	**16 a**	THF	78	8.0 : 1
2	**16 a**	CH_2Cl_2	91	7.3 : 1
3	**16 a**	CH_2Cl_2	79	4.9 :1
4	**16 a**	DMF	28	1.3 : 1
5	**16 a**	CH_3CN	67	10.0 : 1
6	**16 a**	Ether	24	3.5 : 1
7	**16 a**	Toluene	21	7.0 : 1
8	**16 b**	THF	58	2.1 : 1
9	**16 b**	CH_2Cl_2	68	5.4 : 1
10	**16 c**	THF	82	2.4 : 1
11	**16 c**	CH_2Cl_2	71	6.0 : 1
12	**16 d**	CH_2Cl_2	87	6.0 : 1
13	**16 e**	THF	76	3.0 : 1

Scheme 6.37



Entry	R^1	X	R^2	R^3	Yield(%)	**19 : 20**
1	AcO	Cl	PMP	TBDMS	61	95 : 5
2	BnO	Cl	PMP	TBDPS	70	95 : 5
3	BnO	Cl	PMP	TBDMS	75	95 : 5
4	BnO	Cl	Bn	TBDPS	60	95 : 5
5	CH_3O	Cl	PMP	TBDPS	60	95 : 5
6	PhO	OH		TBDMS	86	92 : 8
7		OK		TBDMS	86	96 : 4
8	PhO	OH		TBDPS	84	>98 : 2
9		OK		TBDPS	85	100 : 0

Scheme 6.38



Entry	R^1	R^2	Yield (%)	**21 : 22**
1	TBDMS	DAM	88	10 : 1
2	TBDMS	Bn	59	12 : 1
3	*t*-Bu	DAM	77	9 : 1
4	*t*-Bu	Bn	62	15 : 1

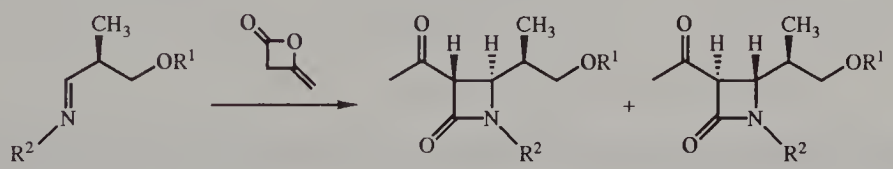
Scheme 6.39

Palomo et al.[172] and Brown and Colvin[173] used the same chiral auxiliary very effectively in the acid chloride–imine reaction in dichloromethane (Scheme 6.38). Excellent diastereocontrol was obtained by careful optimization of protecting groups. The best results by the Palomo group are shown in Scheme 6.38 entries 1 to 5, and the results by the Colvin group are detailed in entries 6 to 9. The activation of the carboxylic acids in entries 6 to 9 was achieved with phenyl dichlorophosphate.

The [2+2] cycloaddition reaction with a chiral imine derived from optically active mandelate (which is commercially available) was also reported by Terashima and co-workers (Scheme 6.39).[42]

Imines derived from *(S)*-methyl-3-hydroxy-2-methyl propionate (commercially available) were used in the synthesis of important precursors for the synthesis of 1-β-methylcarbapenems (Scheme 6.40). A careful optimization of protecting groups and reaction conditions gave a 15 : 1 ratio in favor of the desired isomer (Scheme 6.40, entry 2).[174]

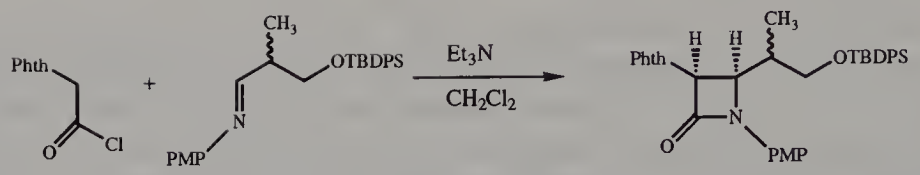
The diastereoselectivity was found to be dependent on the substituents R^1 and R^2. *N*-DAM derivatives typically gave better results than *N*-PMP imines. Particularly striking was the finding that 4-methylimidazole was a much better catalyst than imidazole for high diastereoselectivity (entries 2 and 3, Scheme 6.40). This phenomenon was explained by the increased solubility of 4-methylimidazole in toluene in comparison with imidazole. A survey of several solvents revealed that best results were obtained in toluene. Reversal of diastereoselectivity in favor of isomer **24** (R_1 = TBDMS, R_2 = PMP) was effected with THF as the solvent (entry 1). The same auxiliary was also investigated in the ketene–imine cycloaddition reaction, yielding



23 **24**

Entry	R^1	R^2	Solvent	Catalyst	Yield (%)	**23 : 24**
1	TBDMS	PMP	THF	Imidazole	10	0 : 1
2	Bn	DAM	Toluene	4-Methyl imidazole	49	15 : 1
3	Bn	DAM	Toluene	Imidazole	47	2.5 : 1

Scheme 6.40

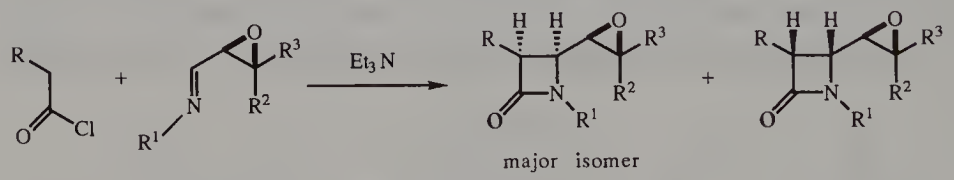


Scheme 6.41

cis-β-lactams, however as a 1 : 1 mixture of *cis*-diastereoisomers (Scheme 6.41).[111,175]

Imines derived from chiral α,β-epoxyaldehydes have been shown to be very useful chiral glyoxal imine synthons in the ketene–imine cycloaddition reaction.[81] This process, which proceeds with high levels of diastereoselectivity, affords enantiomerically pure *cis*-β-lactams in good yields (Scheme 6.42). The epoxyaldehyde can be synthesized by the Sharpless epoxidation methodology or from *S*-malic acid, (+)-tartaric acid, or sodium erythorbate.[176]

Imines prepared from chiral *N*,*O*-diprotected L-serinal on treatment with acid chlorides in the presence of base furnished β-lactams with essentially complete diastereoselection (Scheme 6.43).[132]

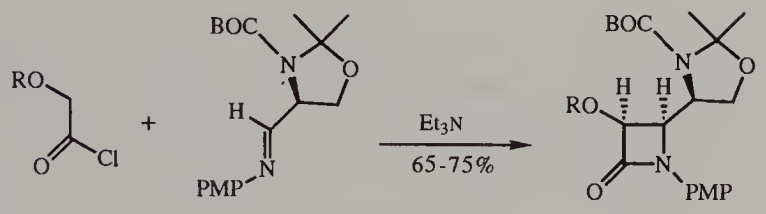


25 $R^2 = H$ R^3 = Ph **26** $R^2 = R^3 = CH_3$

Entry	Imine	R	R^1	Yield (%)	Ratio
1	**26**	Phth	Bn	84	97 : 3
2	**25**	Phth	Bn	82	93 : 7
3	**25**	Phth	2,4-DMBn	85	93 : 7
4	**25**	Ox[a]	2,4-DMBn	84	91 : 9
5	**25**	CbzNH	2,4-DMBn	60	> 95 : 5
6	**25**	Phth	CH_2COOBu-*t*	65	91 : 9
7	**25**	Phth	$CH_2(CH_3)C{=}CH_2$	88	92 : 8
8	**25**	Phth	PMP	66	90 : 10

[a]4,5-di-phenyloxazolin-2-one-3-yl

Scheme 6.42

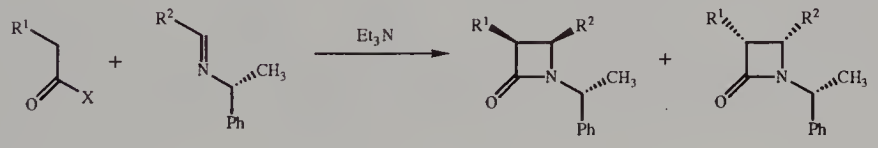


R = CH_3, $PhCH_2$, CH_3CO

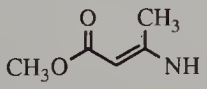
Scheme 6.43

6.3.2.2 *Chiral Amines*

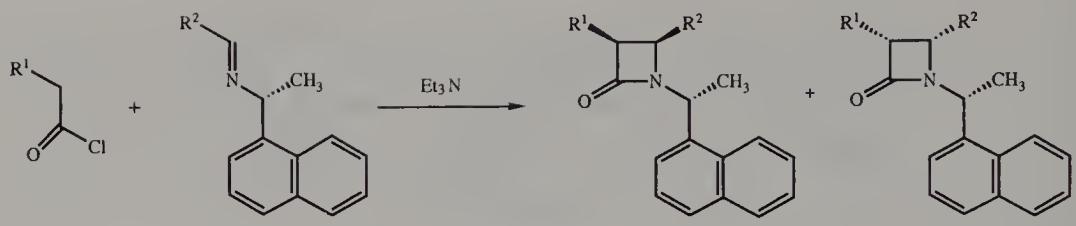
The most readily available and inexpensive optically active amine is α-methylbenzylamine. After β-lactam formation, the *N*-benzyl group can be removed either oxidatively (potassium persulfate)[120,177] or reductively by dissolving metal reduction ($Na/NH_3/THF$).[120] Several research groups reported on using imines derived from this amine in the Staudinger reaction.[120,177,178] The best results, 90 : 10 *cis*:*trans* ratio of isomers was obtained in the reaction between phthalimidoacetyl chloride and the imine derived from 3-chloroacetaldehyde (entry 3, Scheme 6.44). The isomeric ratio was found to be dependent on the solvent used (entries 3–5), chloroform giving the best results.



25 26

Entry	R^1	R^2	X	Yield (%)	25 : 26	Solvent	Ref.
1		styryl	OK	>55	75 : 25	-	120
2	Phth	CH_2F	Cl	59	80 : 20	$CHCl_3$	206,207
3	Phth	CH_2Cl	Cl	74	90 : 10	$CHCl_3$	143
4	Phth	CH_2Cl	Cl	64	65 : 35	CH_2Cl_2	143
5	Phth	CH_2Cl	Cl	53	70 : 30	Toluene	143
6	N_3	DMP	Cl	-	70 : 30	CH_2Cl_2	177

Scheme 6.44

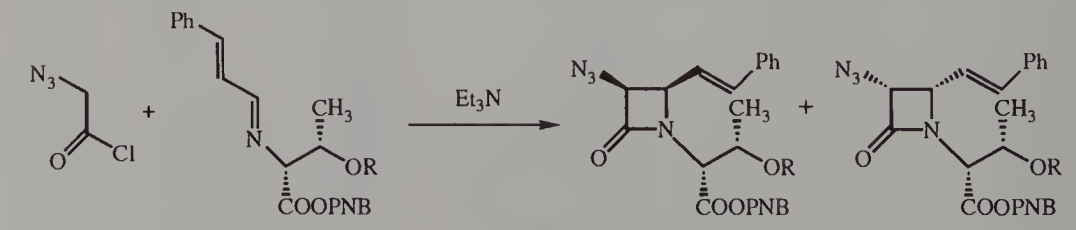


Entry	R^1	R^2	Solvent	27 : 28	Ref.
1	C_2H_5	$COOCH_3$	Benzene	50 : 50	78
2	PhO	styryl	Benzene	83 : 17	179
3	PhO	styryl	CH_2Cl_2	77 : 23	179
4	PhO	styryl	$CHCl_3$	77 : 23	179
5	PhO	styryl	DMF	60 : 40	179

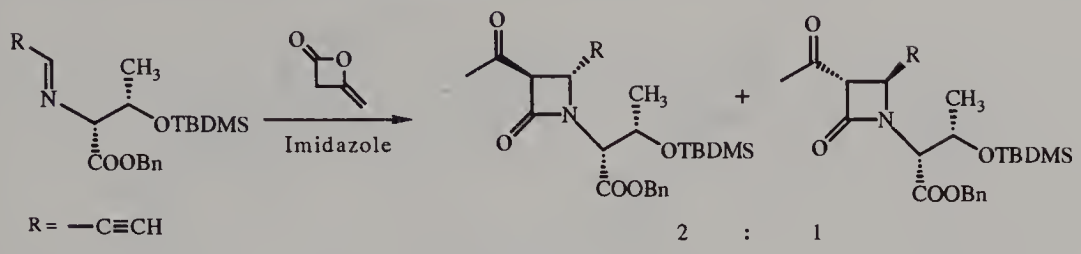
Scheme 6.45

The closely related but more expensive 1-naphthylethylamine was also investigated (Scheme 6.45) and similar results were obtained; however, benzene, toluene, and chlorobenzene were found to be the best solvents, giving a 83 : 17 ratio of diastereoisomers.[78,179]

D-Threonine has also been used as a chiral auxiliary in the Staudinger reaction to afford *cis*-β-lactams.[104,169,180] The size of the ether substituents affected the diastereoselectivities obtained (Scheme 6.46). Thus, when R was small, a 50 : 50 mixture of the two *cis*-isomers was obtained. When the size of R increased, selectivity also increased.[104,180] The imine derived from D-threonine produced the same stereochemistry at the β-lactam ring as found with imines from D-glyceraldehyde.



Scheme 6.46



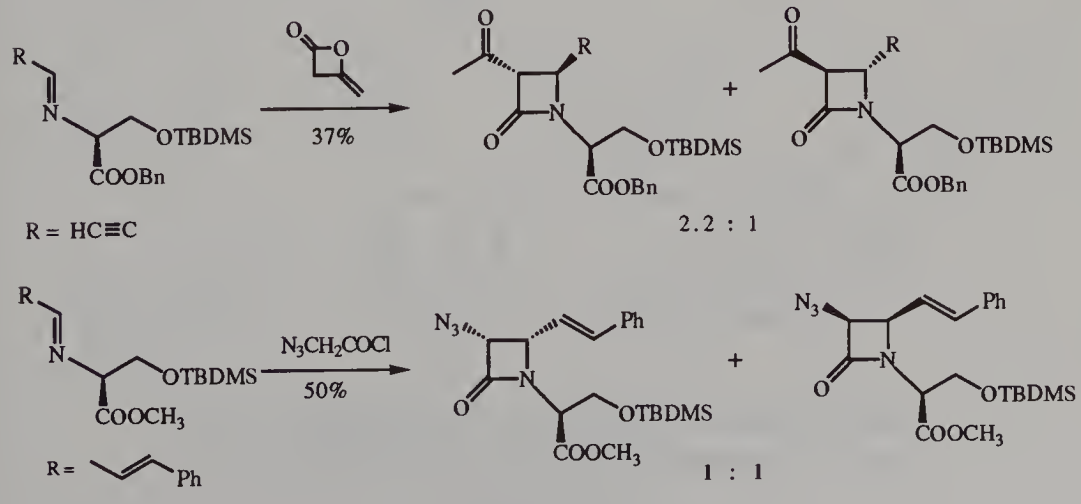
Scheme 6.47

Reaction of diketene with the imine derived from propargyl aldehyde and the TBDMS ether of D-threonine produced two *trans*-diastereoisomers in 2 : 1 ratio (Scheme 6.47). It is interesting to note that the stereochemistry at C-4 of the major isomer is the opposite stereochemistry as obtained in the acid chloride–imine reaction.[181]

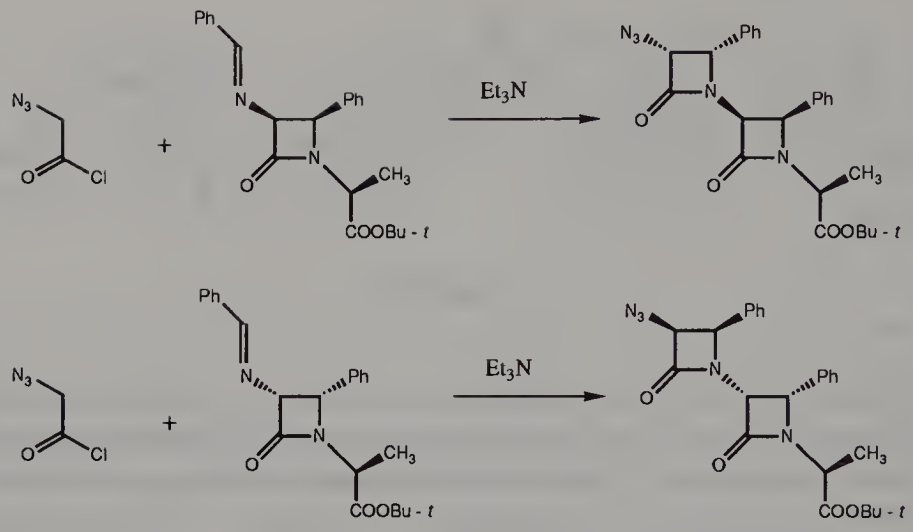
Hirai and Fujimoto observed that cycloaddition of a propargylidene Schiff base derived from L-serine with diketene gave a mixture of *trans*- and *cis*-β-lactams (Scheme 6.48) in a ratio of 2.2 : 1.[181] These results are interesting in the context of reports by Just and Liak that the chiral auxiliary of a protected L-serine cinnamylidene Schiff base racemized in the reaction with azidoacetyl chloride and triethylamine.[182]

Hatanaka and Ojima have reported a stereospecific cycloaddition of azidoketene to imines bearing a chiral β-lactam as the backbone (Scheme 6.49) which in turn was synthesized from *t*-butyl-*(S)*-alaninate.[183] For additional examples and a detailed review, see Chapter 4 by Ojima in this book.

Amino acids derived from alanine and leucinol were used by Ojima in the ketene–imine cycloaddition yielding *cis*-diastereoisomers in ratios of 55 : 45 and 56 : 44 (the major isomers are depicted in Scheme 6.50).[183,184] Thioimidates synthesized from a phenylglycine derivate and a valine methyl ester



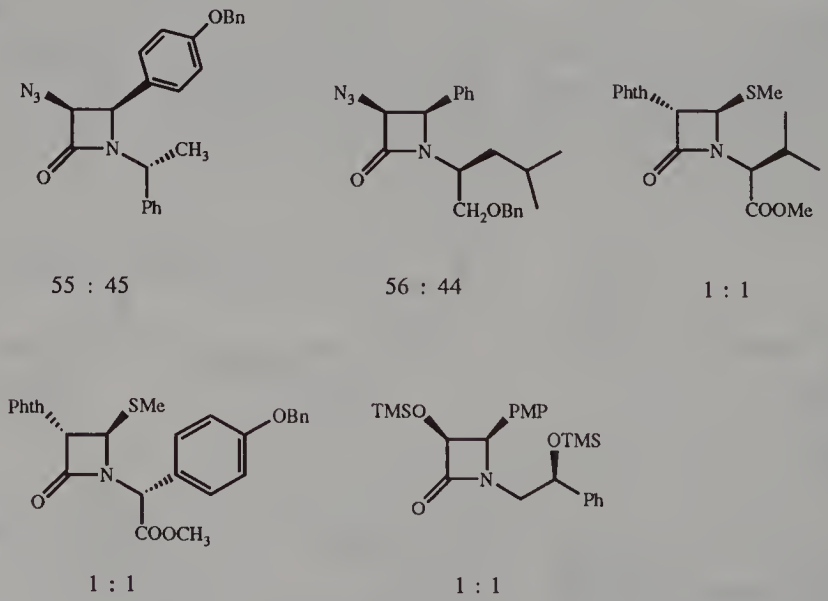
Scheme 6.48



Scheme 6.49

yielded *trans* products in a 1 : 1 ratio.[74,185] A 1 : 1 ratio of *cis*-β-lactams was also obtained from an ethanolamine (Scheme 6.50).[134]

The asymmetric synthesis of 4-unsubstituted β-lactams was accomplished from a triazine in the presence of BF_3–OEt_2.[186] Better diastereoselectivities were achieved with the bulkier phthalimidoketene than with azidoketene (entries 1 and 2 in Scheme 6.51). The best results were obtained with

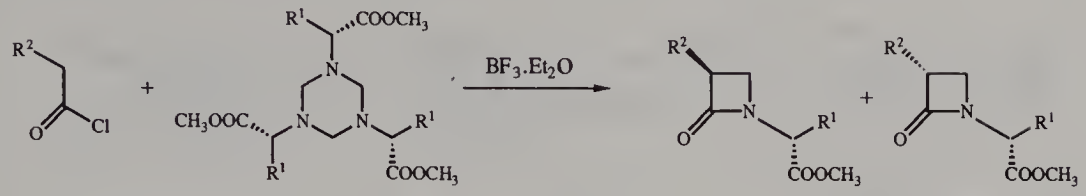


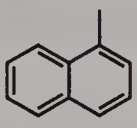
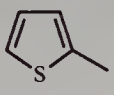
55 : 45 56 : 44 1 : 1

1 : 1 1 : 1

The major isomer is depicted. The minor diasteroisomer possesses opposite stereochemistry at C-3 and C-4 of the β-lactam ring.

Scheme 6.50

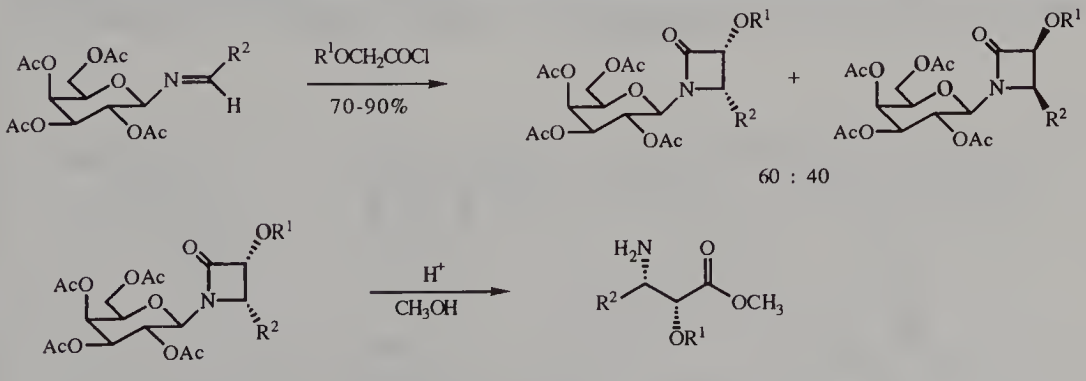


Entry	R^1	R^2	Yield (%)	29 : 30
1	Ph	Phth	80	3 : 1
2	Ph	N_3	42	3 : 2
3		Phth	51	10 : 1
4		Phth	65	7 : 2

Scheme 6.51

α-naphthylglycine, giving a 10 : 1 ratio of diastereoisomers. (Entries 1, 2, and 4 represent optically active compounds. For entry 3 relative stereochemistry is depicted.)

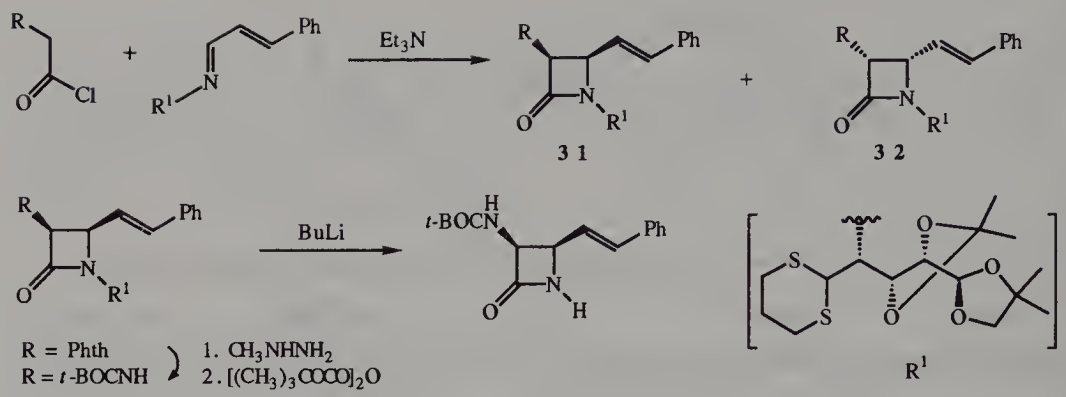
Recently a stereospecific synthesis of *cis*-β-lactams has been reported by Georg et al., using 2,3,4,6-tetra-*O*-acetyl-β-D-galactose as the chiral auxiliary (Scheme 6.52) on the nitrogen atom of the imine.[44,45] Typically a 6 : 4



R^1 = Ph, PMP, Ac

R^2 = Ph, *p*-ClPh, *p*-NO_2Ph, *p*-CH_3Ph, CH_3OPh, PhCH=CH

Scheme 6.52

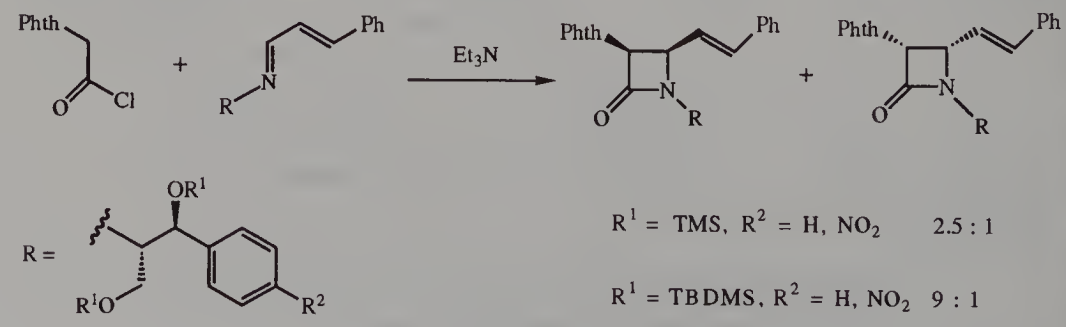


Entry	R	Yield (%)	31 : 32
1	Phth	92	100 : 0
2	CH_3O	94	65 : 35

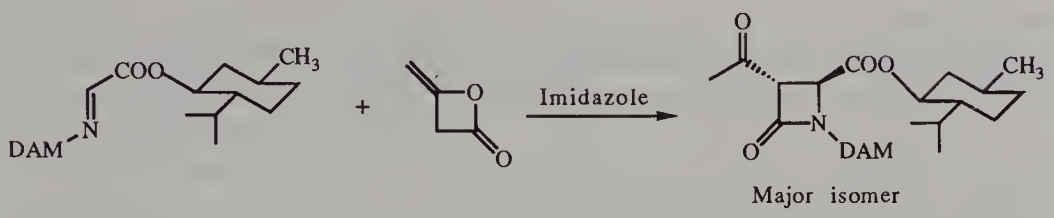
Scheme 6.53

ratio of diastereoisomers was obtained. The resulting β-lactams can be hydrolyzed to the corresponding β-amino acids.

A novel asymmetric approach to the synthesis of trisubstituted azetidin-2-ones has been reported by Barton et al.[187] The strategy relies on the use of the ketene–imine cycloadditions between ketenes generated from phthalimidoacetic and methoxyacetic acids and a chiral Schiff base derived from 3,4 : 5,6-di-*O*-isopropylidene-D-glucosamine propanedithioacetal, and cinnamaldehyde (Scheme 6.53). As the phthalimido protecting group was incompatible with the conditions for removal of the chiral auxiliary, the 3-phthalimido-2-azetidinone had to be deprotected (methylhydrazine) and then protected as the *N*-t-BOC derivative. The chiral auxiliary was removed by



Scheme 6.54



Scheme 6.55

β-elimination (35–100% yield) by taking advantage of the acidic nature of the proton at the 2′-position of the 1′,3′-dithiane ring.

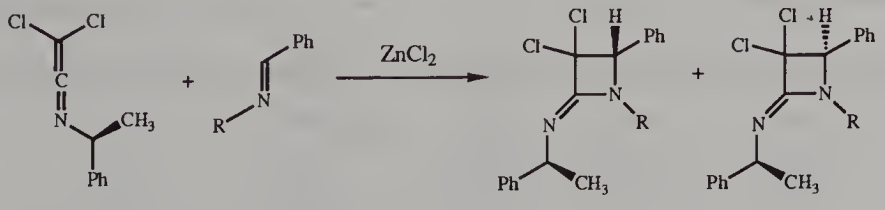
Recently Gunda et al. used aldimines derived from (1*S*,2*S*)-2-amino-1-phenyl-1,3-propandiols as chiral starting materials in the synthesis of β-lactams.[188] The size of the hydroxyl protecting groups had a pronounced influence on the diastereoselectivity of the reaction (Scheme 6.54).

Cycloaddition between diketene and an imine derived from glycolic acid (−)-menthyl ester yields the corresponding 3-acetyl-2-azetidinone, possessing the correct absolute stereochemistry at C-3 and C-4 as desired for the synthesis of thienamycin as the major isomer (Scheme 6.55).[189]

6.3.2.3 Keteneimines and α-Chloroiminium Halides

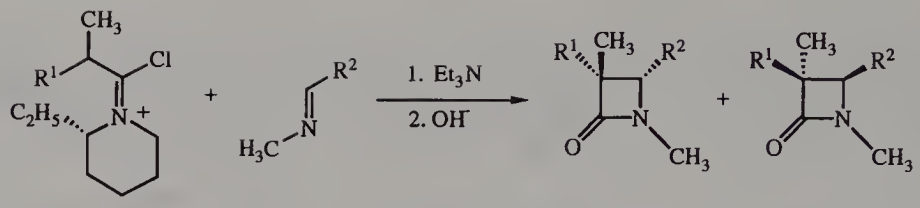
(S)-α-Methylbenzylamine was also used as a chiral auxiliary in a keteneimine–imine cycloaddition reaction with $ZnCl_2$ as the catalyst. With benzylideneaniline a single isomer was isolated (Scheme 6.56), whereas with benzylidenemethylamine a 1 : 1 mixture of diastereoisomers was obtained. The relative stereochemistry of the products was not determined.[190]

Rogalska and Belzecki have reported an interesting reaction of chiral α-chloroiminium chlorides (derivatives of 2-ethylpiperidine and *N*-methylamphetamine) with imines in the diastereoface-differentiating synthesis of substituted chiral β-lactams.[191,192] The best results are detailed in Scheme 6.57 (*cis*-isomers not depicted). Only *trans*-β-lactams were isolated in the reac-



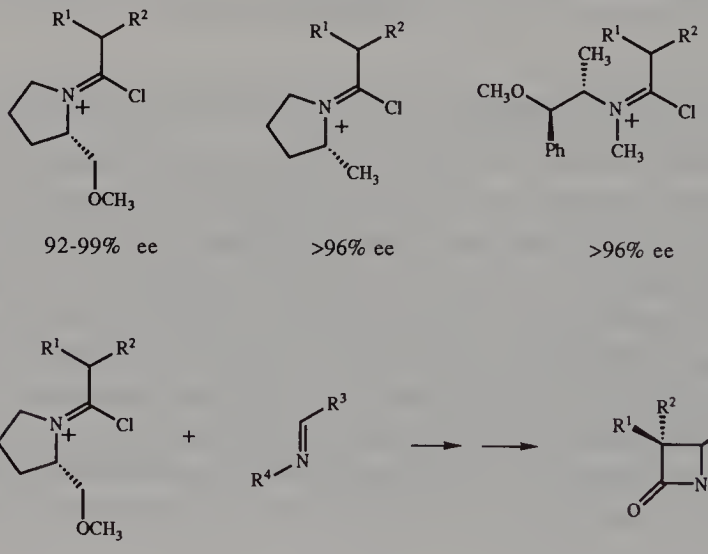
R = Ph single isomer, $[\alpha]_D$ = +123.9°, 30% yield
R = CH_3 1:1 ratio, 14% yield

Scheme 6.56



Entry	R^1	R^2	Yield (%)	trans : cis	ratio of trans isomers
1	H	*t*-Bu	54	trans	88 : 12
2	H	Ph	57	68 : 32	57 : 43
3	CH_3	Ph	60	--	88 : 12

Scheme 6.57



Entry	R^1	R^2	R^3	R^4	Yield (%)	ee (%)
1	CH_3	CH_3	Ph	CH_2=$CHCH_2$	42	98
2	CH_3	CH_3	SCH_3	Bn	65	99
3	CH_3	Ph	Ph	CH_3	29	97
4	H	H	Ph	CH_3	40	4
5	H	Phth	Ph	CH_3	-	92
6	H	Phth	Ph	Bn	-	97

Scheme 6.58

tion with the imine derived from pivaldehyde (entry 1). (The absolute stereochemistry of the products was not determined.) They also investigated imines derived from α-methylbenzylamines and obtained mixtures of the four possible diastereoisomers.

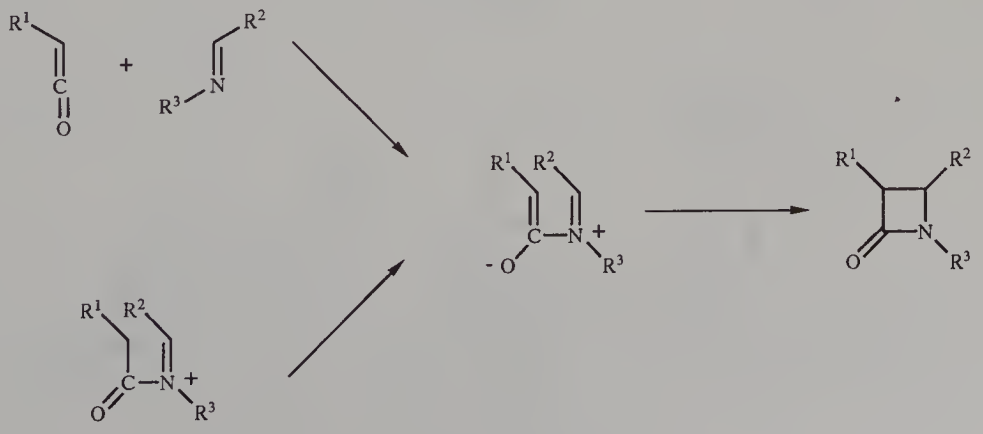
Excellent enantiomeric excesses were achieved by Ghosez et al. using α-chloroiminium chlorides derived from 2-(methoxymethyl)pyrrolidine, 2-methylpyrrolidine, and ephedrine (Scheme 6.58).[19] Of note are the *trans* selectivity of the phthalimido chloroiminium chlorides (entries 5 and 6) and the loss of diastereoselectivity for the formation of a C-3 unsubstituted 2-azetidinone (entry 4).

6.3.3 Chiral Base

Cooper et al. tried to induce chirality in the cycloaddition reaction of acid chlorides with imine by using a chiral base in the Staudinger reaction.[25] They rationalized that the acylammonium salt formed by reaction of the acid chloride and the base might react with the imine to give a chiral acyliminium salt. In the cases investigated, however, no enantioselectivity was observed under a variety of conditions.

6.4 Mechanisms

Although the reaction between ketenes and imines, and acid chlorides and imines in the presence of base leading to β-lactams has been studied extensively, the mechanism is complex and the stereochemical course of the reaction is sometimes difficult to predict. The formation of ketenes occurs thermally, photochemically, or from an acid chloride. The ketene then reacts with the imine to form a zwitterionic intermediate. Alternatively, the acid chloride acylates the imine, followed by proton abstraction to also form a zwitterionic intermediate (Scheme 6.59). The zwitterionic intermediate then



Scheme 6.59

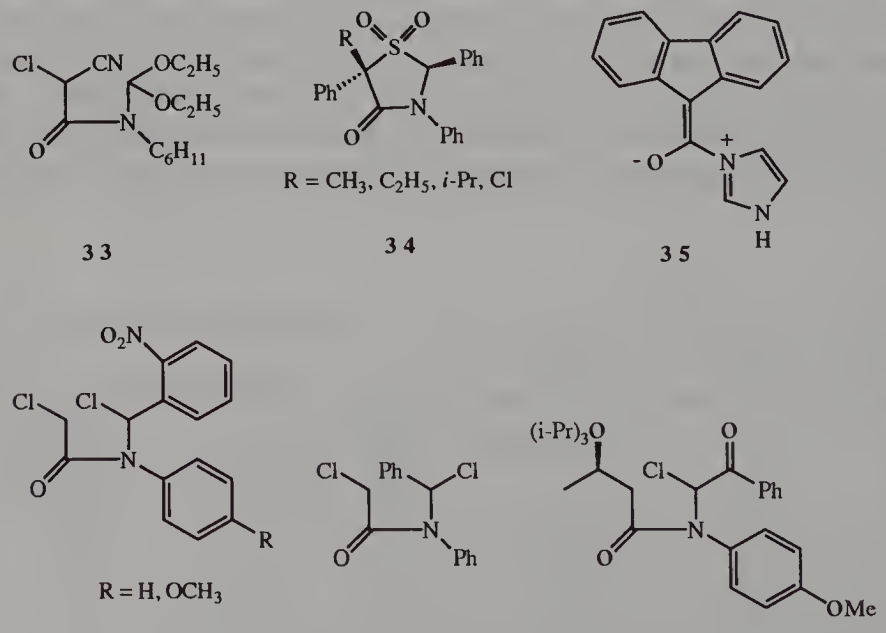
undergoes a conrotatory [2+2] cycloaddition to form the β-lactam. The reaction is believed to proceed through a two-step zwitterionic mechanism rather than a concerted [2+2] cycloaddition.

6.4.1 Zwitterion Trapping Experiments

The putative zwitterion intermediate has been trapped (Scheme 6.60) with ethanol[193] to yield *N*-(1,1-diethoxymethyl)-cyanamide **33,** and 4-oxo-1,3-thiazolidine-1,2-dioxides **34** resulted from the insertion of sulfur trioxide.[194,195] An intense purple color, which is believed to result from the zwitterionic intermediate, was observed when a toluene solution of *N*-phenylcinnamylideneamine was treated with *t*-butylcyanoketene at −78°C.[37] The color gradually fades as the reaction solution is allowed to warm to ambient temperature. The observation of both [2+2] and [2+4] products being formed in the ketene–cinnamylideneamine cycloadditions further supports the hypothesis that the Staudinger reaction is not concerted.[193,196,197] The zwitterionic intermediate **35** of a thermal ketene–imine cycloaddition has been spectroscopically characterized in a polymeric matrix.[198]

6.4.2 Ketene–Imine Mechanism

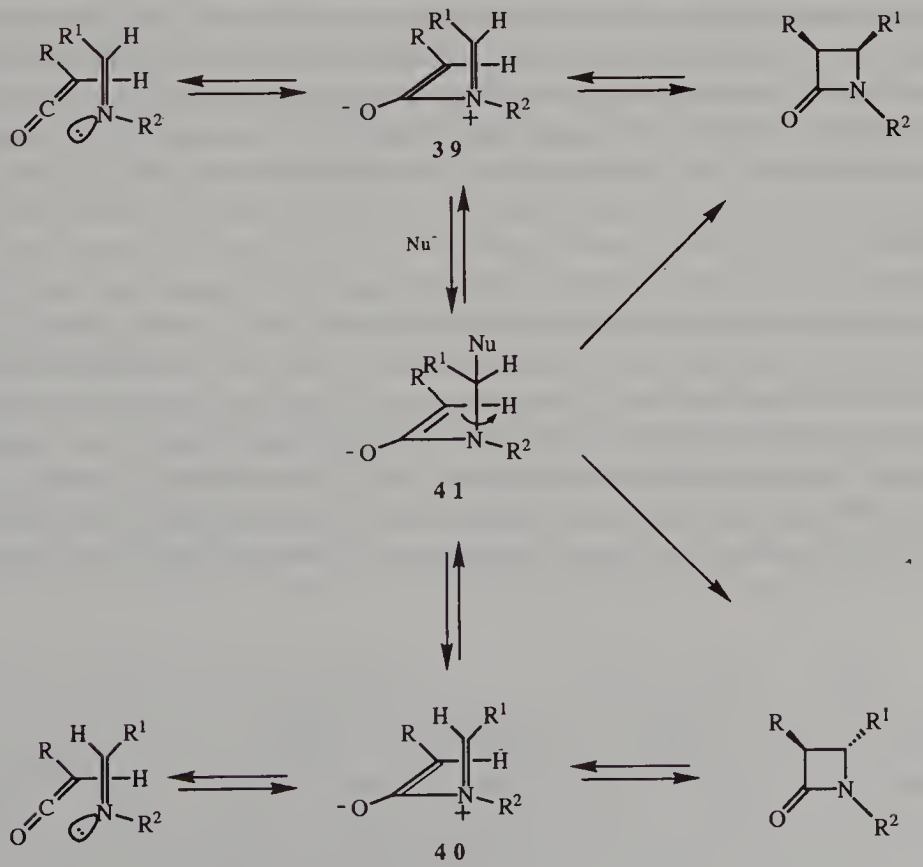
The first mechanistic pathway for β-lactam formation proceeds through a ketene generated, for example, thermally or photochemically. The ketene can also be formed by the reaction of acid chlorides and amines, which in



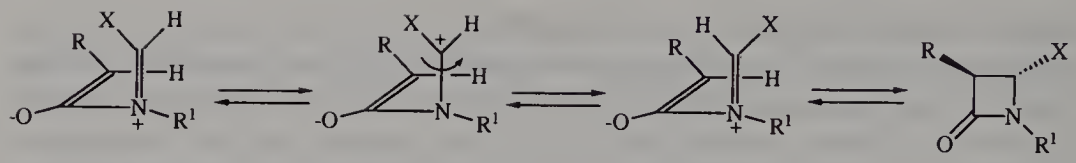
Scheme 6.60

turn react with an imine (Schemes 6.59 and 6.61). Lynch et al. have examined the reaction of a *(R)*-3-hydroxybutyric acid chloride derivative with an imine in the presence of base (Scheme 6.31) by low-temperature Fourier transform infrared spectroscopy.[150] The rate constants for the formation of the ketene from the acid chloride and base and for the subsequent reaction of this ketene with the imine were measured. From the kinetic data they concluded that the azetidinones arise completely from the ketene intermediate and not via direct acylation of the imine with the acid chloride. Treatment of the acid chloride with diisopropylamine in a Fourier transform infrared cell gave a compound exhibiting a strong band at 2120 cm^{-1}, which they assigned to the ketene. Reaction between the acid chloride and the imine in the absence of base led to the formation of α-chloroamide **38** (Scheme 6.60) and no ketene could be detected spectrophotometrically.

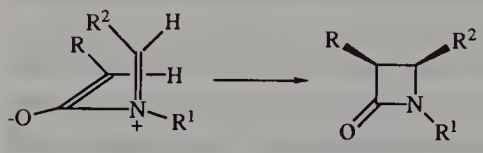
It has been postulated that the LUMO of the ketene carbonyl group, which is coplanar to the substituents of the ketene, is attacked by imines in an orthogonal approach; thus an intermediate is generated in which the planes of the imine and the enolate are perpendicular to each other (Scheme 6.61).[199] MNDO semiempirical molecular orbital calculations of a transition intermediate between methylketene and *N*-methyl-2-methylimine supported



Scheme 6.61



X = OR, SR, aryl, alkyl

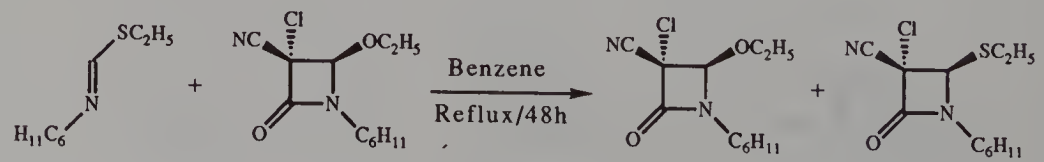


R^2= COPh, $COOCH_3$, CH_2Cl, CH_2F,

Scheme 6.62

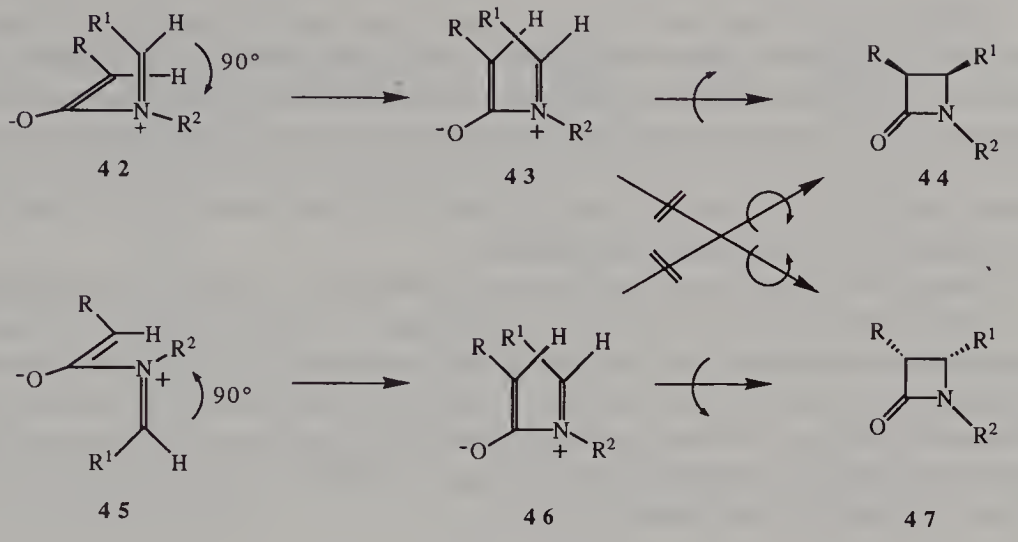
this hypothesis.[25] It is further believed that the attack of the imine occurs from the least hindered side (hydrogen or small substituent) of the ketene, generating the zwitterionic intermediate **39** (Scheme 6.61). Conrotatory ring closure will then generate the thermodynamically less stable β-lactam in which the two hydrogens (or small substituents) are *cis* to each other. These stereochemical explanations are in good agreement for the reactions of many acyclic imines and ketenes. The well-known preference for the formation of *trans* products with cyclic imines can be explained similarly. An orthogonal approach between the two reactants will produce the zwitterionic intermediate **40,** which on conrotatory electrocyclization will generate the *trans* product.

The formation of *trans* and *cis–trans* product mixtures can also be explained in the context of this mechanistic explanation via the addition of a nucleophile to iminium ion intermediate **39** or **40.** α-Chloro derivatives of type **41** have been isolated as intermediates in β-lactam formation (**36–38** in Scheme 6.60).[150,155,200,201] Loss of the nucleophile from **41** after bond rotation can result in the formation of the dipolar species **40** and *trans*-β-lactam formation. Intermediate **41** can also revert back to **39** and form *cis*-β-lactam or form β-lactams via an S_N2-type displacement. Additionally, initial *cis* prod-



18 : 82

Scheme 6.63



Scheme 6.64

uct formation, followed by base-catalyzed isomerization to the *trans*-β-lactam, has also been observed.[46]

The preference of imidates, thioimidates, and sometimes *C*-arylimines and potentially *C*-alkylimines for *trans* product formation (Scheme 6.62) can be explained by the ability of these groups to stabilize the positive charge of the zwitterion intermediate (inductive or mesomeric effects). Isomerization of the *trans*-iminium ion to the sterically less congested *cis*-iminium ion is followed by ring closure to the *trans*-β-lactam.

In case of a β-lactam obtained from an imidate it was demonstrated that β-lactam formation is actually a reversible process (Scheme 6.63). Refluxing equimolar amounts of a 4-ethoxy-2-azetidinone and a thioimidate in benzene for 48 hours produced an 18 : 82% ratio of the 4-ethoxy- to 4-thioethyl-2-azetidinones.[193]

Preferential *cis* product formation, however, is observed with imines possessing α-carbonyl groups (Schemes 6.62 and 6.87) and potentially α-halomethyl substituents (Scheme 6.44). These electron-withdrawing substituents apparently have the opposite effect of the electron-donating substituents and prevent C—N bond rotation. Thus conrotatory ring closure of the initially formed zwitterionic intermediate leads to *cis* product formation.

6.4.3 Asymmetric Induction

Asymmetric induction in the ketene–imine cycloaddition reaction can be explained (Scheme 6.64) via placement of the imine on the top face (intermediate **42**) or the bottom face (intermediate **45**) of the ketene.[25,199] Conrotatory ring closure of **42** yields *cis*-β-lactam **44** and conrotatory ring closure of **45** results in the formation of the enantiomeric β-lactam **47**.

Before ring closure can occur, however, the central C—N bond has to rotate toward an eclipsed arrangement such as depicted in intermediates **43** and **46**. It is conceivable that the central bond in intermediate **42** could rotate about 270° to form intermediate **46** and intermediate **45** could also rotate that same angle to form **43.** As the rotation from **42** to **43** and from **45** to **46** is only about 90°, the principle of least motion can be invoked to explain the formation of the proposed intermediates.

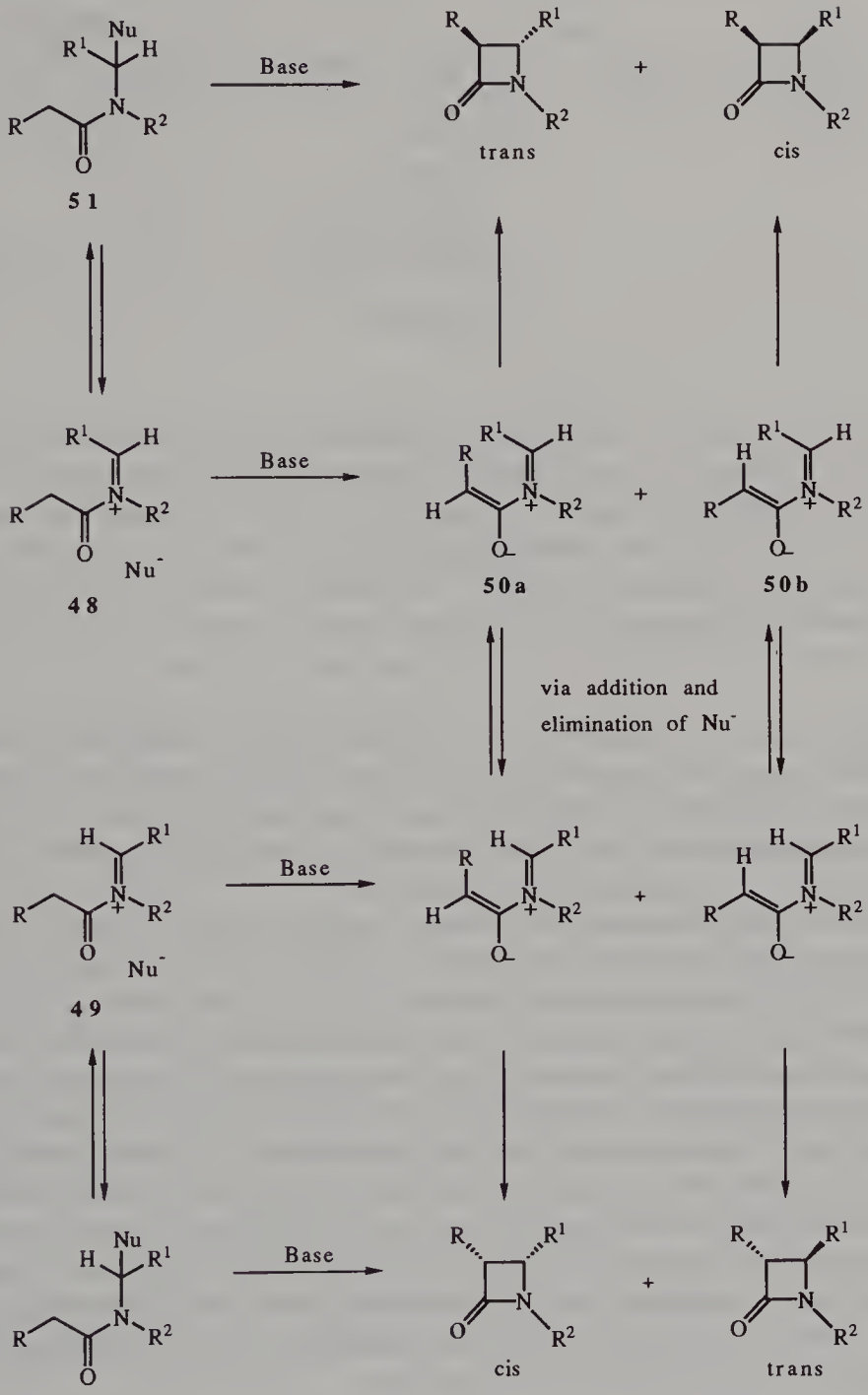
It has been pointed out by Hegedus et al. that the conrotatory ring closure of intermediate **43** can only occur clockwise.[26] Counterclockwise closure would necessitate that the hydrogen of the ketene and R^1 of the imine to pass through each other. This is of importance for chiral induction, because a counterclockwise rotation would generate the enantiomeric β-lactam. The opposite is true for intermediate **46,** which can undergo only counterclockwise conrotatory ring closure.

6.4.4 Acid Chloride–Imine Mechanism

The second postulated pathway (Scheme 6.65) involves direct acylation of the imine by the acid chloride to form *N*-acyliminium chloride **48** or **49**. The acyliminium intermediate **48** can now take two possible pathways. Proton abstraction would produce zwitterionic intermediates **50,** which could then cyclize to form the β-lactam by a [2+2] conrotatory cycloaddition reaction. Depending on enolate geometry, *trans*- or *cis*-β-lactams can be formed. Alternatively, a nucleophile could add to the zwitterion intermediate to form **51** (see Scheme 6.60, compounds 36–38), which could form β-lactams via S_N 2-type displacement. In addition, a nucleophile could add to intermediate **50** followed by nucleophile elimination (as depicted in Scheme 6.61) to result in the formation of the zwitterions, possessing the opposite *(cis)* iminium ion geometry of **50.** Intermediate **49,** generated from a *cis*-imine, could undergo similar transformations as depicted in Scheme 6.65. The rate of intermediate and product formation is likely to be dependent on substituent effects.

The second mechanistic pathway was suggested to explain the results of the inverse addition of the reactants (Scheme 6.66).[54,155,200,202] For example, addition of azidoacetyl chloride to a mixture of *N*-phenylcinnamylideneamine and triethylamine gave 85% of the corresponding *cis*-β-lactam; however, reaction of the acid chloride with the imine, followed by the addition of the base, produced a 29% yield of a 37 : 63 *cis*:*trans* ratio of β-lactams.

The propensity for better *cis* selectivity via formation of ketenes can thus be explained as a result of the stereoselective formation of the reactive zwitterion **39** (Scheme 6.61), followed by [2+2] conrotatory cycloaddition. In the case of the acylated iminium species, however, proton abstraction of either of the two α protons from the intermediate acyliminium ion **48** (Scheme 6.65) can probably occur with similar probability. The formation of the two possible enolates of the zwitterion (**50a** and **50b**, Scheme 6.65) will then result in the formation of mixtures of *cis* and *trans* products.



Scheme 6.65

Evidence in support of this mechanism comes also from NMR investigations by Bose et al.[200] They studied the NMR spectrum of a carbon tetrachloride solution containing equimolar quantities of acetyl chloride and benzylideneaniline. The NMR spectrum of the Schiff base exhibited a one-proton singlet at *d* 8.38, which is shifted to *d* 7.9 on addition of acetyl

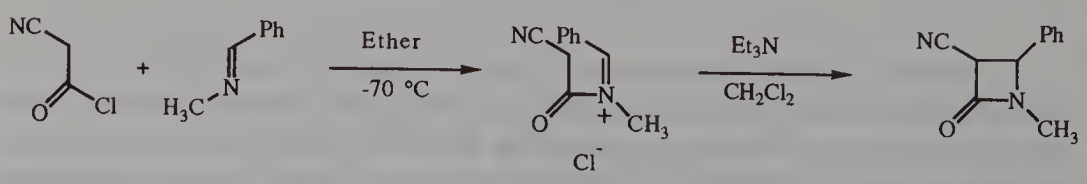
mechanism	cis:trans
ketene formation	100:0
acylation of imine	37:63

Scheme 6.66

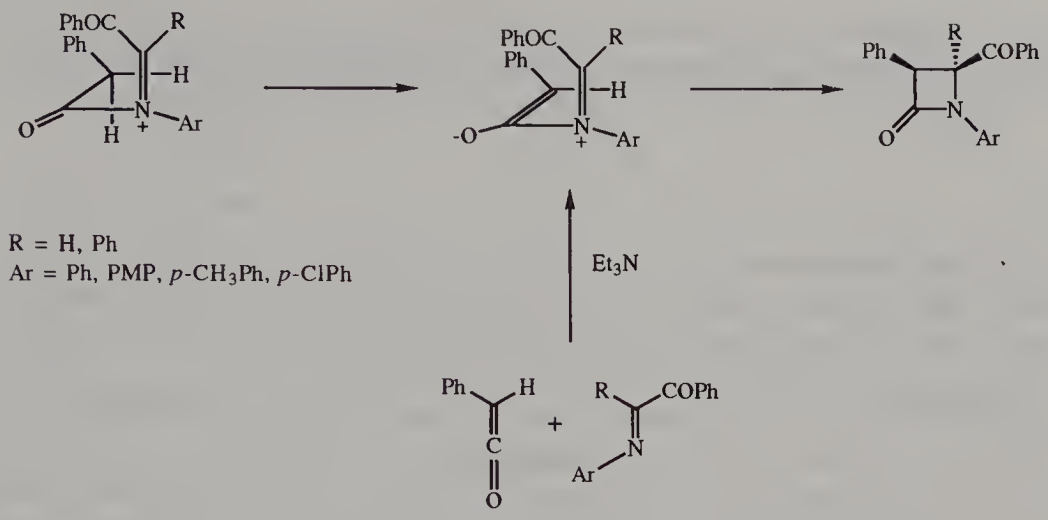
chloride. The adduct, therefore, corresponds to the covalent structure of type **51** (Scheme 6.65); the alternative acyliminium ion structure of type **48** would have shifted the signal to a much lower field.[203] Also it was observed that at 40°C, 95% of the acetyl chloride was converted to the adduct. At 65°C the corresponding proportion was reduced to about 90%. Cooling to 40°C returned the spectrum to its original form. This kind of reversible equilibrium was said to be observed with other acid chlorides and Schiff bases also.

Other evidence in support of the acylation theory comes from the work by Böhme et al., who isolated an *N*-acyliminium chloride in the reaction between cyanoacetyl chloride and imines as intermediates in the formation of β-lactams (Scheme 6.67). The structure of the *N*-acyliminium chloride was, however, not verified spectroscopically.[204]

Evidence that the second mechanistic pathway also proceeds through the formation of the zwitterionic intermediate was provided by Alcaide et al.[205] They studied the formation of β-lactams by the reaction of phenylacetyl chloride with 1,2-iminoketones in the absence of base (Scheme 6.68). (This appears to be the first instance of β-lactam formation from imines and acid chlorides in the absence of base.) Based on the observed *cis* stereochemistry (R and H *cis*) of the β-lactams derived from phenylacetyl chloride and phenylglyoxal imines, the conrotatory cyclization of the zwitterionic intermediate requires the stereochemistry as depicted (Scheme 6.68). It was also found that reaction under the same conditions but in the presence of triethylamine (ketene formation) gave similar yields and the same *cis* selectivity. Thus, it was assumed that in the case investigated, the reaction proceeded through the same zwitterionic intermediate.



Scheme 6.67

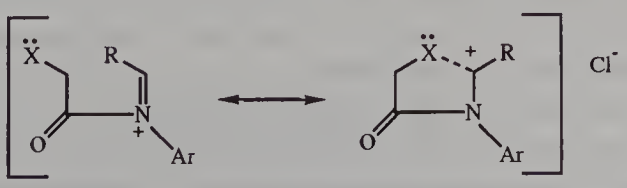


Scheme 6.68

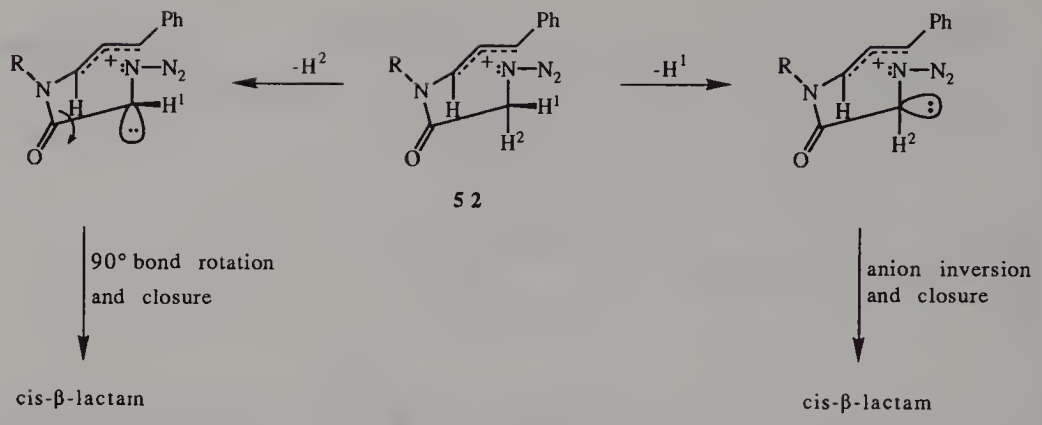
6.4.5 Zwitterion Stabilization

Bose et al. have proposed that with acid chlorides possessing a N, O, S, or Cl with a free pair of electrons at the α position, these atoms are capable of stabilizing the transition states via the formation of donor–acceptor complexes (Scheme 6.69).[129]

Doyle et al. suggested that this transition-state model is particularly attractive to explain *cis* selectivity in systems capable of extended conjugation such as with imines derived from cinnamaldehyde (Scheme 6.70).[202] Proton abstraction from complex **52** in which the carbon atoms C-3 and C-4 are held in close proximity would lead to β-lactams. Examination of Dreiding models indicated that a preferred conformation of the donor–acceptor complex, as shown in Scheme 6.70, would align the C-3/H^1 bond axis with the cationic *p* orbital at C-4. Abstraction of C-3/H^1 by base with concerted formation of the C-3/-C-4 bond would lead to a β-lactam of *cis* stereochemistry. Alternatively, abstraction of C-3/H^2 would give an anion stabilized by the carbonyl group. A 90° rotation with concomitant C-3/C-4 bond formation would also give a β-lactam of *cis* stereochemistry.



Scheme 6.69



Scheme 6.70

6.5 Stereochemical Analysis

A variety of factors such as structure and size of the substituents of the acid component and the imine, sequence of addition of reactants, and solvent play an important role in the stereochemical outcome of the Staudinger reaction. In the following we discuss the stereochemical results obtained in the Staudinger reaction as a consequence of the structure of the ketene and the imine. Based on an analysis of investigations reported in the literature, we are now suggesting that clear trends for the preference of *trans* or *cis* product formation can be observed. A recognition of these trends allows for the prediction of stereochemistry in systems not yet explored. One should recognize that not every single stereochemical outcome of the Staudinger reaction can be explained with our predictive model; however, we are of the opinion that very definite trends for the preferential formation of *cis* or *trans* product can be seen and explained in the context of the mechanistic models that have been developed. For the following discussion, we are assuming ketene formation as the first step in the Staudinger reaction rather than the acylation of the imine by an acid chloride. It should be noted that the reaction of diketene with imines and the reaction of chloroiminium chlorides with imines produce reaction products with different stereochemical patterns. These reactions potentially follow a different reaction mechanism and are therefore not discussed below.

The discussion in this part of the chapter will concentrate on steric and electronic factors exerted by the acid component and the imine on the stereochemical course of the Staudinger reaction. A summary of the results is presented first and then the supporting studies are listed in the form of tables. It should be kept in mind that the examples listed in the following schemes have been carried out under different reaction conditions (solvent, base, temperature, time, acid activating group and others); however, despite these differences, the trends for preferential *cis* or *trans* product formation seems to reside largely within the structures of the imine and the ketene.

The tables detail representative examples to underscore our hypothesis. Additional examples can typically be found in the references listed in the tables and elsewhere in the literature.

6.5.1 Ketenes

It appears that the stereochemical results (*cis* or *trans* product formation) obtained in the Staudinger reaction can be correlated well with the steric demands of the ketene in the formation of the zwitterionic intermediate. Therefore, we are now suggesting that ketenes be classified into three groups according to the size of their substituents (Scheme 6.71). From the following discussions it will become clear that ketenes in the same groups share similar preferences for *cis* or *trans* product formation with the same type of imines. We suggest that these three groups of ketenes be named after four investigators who have made significant contributions to the understanding of the Staudinger reaction.

Bose–Evans ketenes	Small-size substituents R^1
Sheehan ketenes	Medium-size substituents R^2
Moore ketenes	Large-size substituents R^3

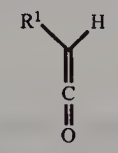
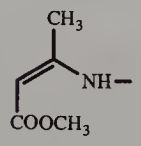
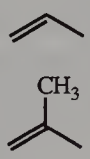
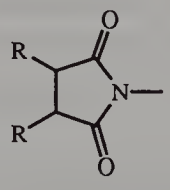
6.5.1.1 Stereochemical Rules for Ketenes

1. Bose–Evans ketenes, possessing small substituents (see Scheme 6.71) or substituents that have dipole interactions such as F, have a distinct preference for *cis*-β-lactam formation with diaryl imines and alkylaryl imines (in our discussion, alkyl groups also include vinylic substituents) (Schemes 6.73–6.78).
2. Sheehan ketenes with medium-sizes substituents (see Scheme 6.71) have a strong preference for *cis* product formation with alkylaryl imines, but diaryl imines give *trans* products (Schemes 6.79 and 6.80).
3. Moore ketenes with large substituents (see Scheme 6.71) have a preference for *trans* product formation with diaryl and alkylaryl imines (Schemes 6.81–6.87).
4. All three types of ketenes typically give (a) *trans* products with imidates and thioimidates (Schemes 6.73, 6.75, 6.76, and 6.80) and (b) *cis* products with imines derived from glyoxalic esters, phenylglyoxal, glyoxal, and related derivatives (Scheme 6.88).

6.5.2 Imines

6.5.2.1 Stereochemical Rules for Imines

1. Imidates, thioimidates, and potentially imines derived from aliphatic aldehydes will typically produce *trans*-β-lactams regardless of the ketene (Schemes 6.73, 6.75, 6.76, and 6.80).

Bose-Evans ketenes 	Sheehan ketenes 	Moore ketenes 
R^1	R^2	R^3
OCOR *O*-alkyl *O*-aryl *N*-alkylaryl NHCOR  N_3 F	 Phth 	Cl Br alkyl aryl SR SOR SO_2R $\overline{R^4}$ H CN

Scheme 6.71

2. Imines derived from glycolic acid and related derivatives (Scheme 6.88) and potentially from α-haloacetaldehydes (Scheme 6.44) will typically produce *cis* products regardless of the ketene.
3. Diaryl imines will form preferentially *cis* products with Bose–Evans ketenes (Schemes 6.73, 6.75 and 6.76) and *trans* products with Sheehan and Moore ketenes (Schemes 6.79–6.87).
4. Alkylaryl imines will yield *cis* products with Bose–Evans (Schemes 6.73–6.78) and Sheehan ketenes (Schemes 6.79 and 6.80) and *trans* products with Moore ketenes (Schemes 6.81–6.87).
5. *N*-Aryl imines possessing strongly electron-withdrawing substituents at the aryl group (amine $pK_a < 2.4$) tend to give more *trans* products than imines derived from more basic amines (pka ≥ 2.4) (Scheme 6.77).
6. In case of the Moore ketenes (preference for *trans* product formation), *ortho* substituents at the *N*-aryl group or bulky alkyl groups such as *N*-cyclohexyl and *N-tert*-butyl can induce the formation of *cis* products (Schemes 6.81–6.87).

Imines	Bose-Evans ketenes	Sheehan ketenes	Moore ketenes
Alkylaryl	cis	cis	trans
Diaryl	cis	trans	trans
Glyoxalic acid and glyoxal derivatives	cis	cis	cis
Imidates and thioimidates	trans	trans	trans

Scheme 6.72

The stereochemical rules (prediction of preferrential *cis* or *trans* product formation) for the most important ketenes and imines are displayed in Scheme 6.72.

6.5.3 Bose–Evans Ketenes

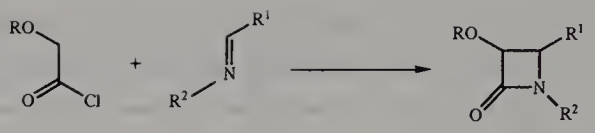
6.5.3.1 Derivatives of Hydroxyacetic Acid and N-Alkyl-N-Arylglycines

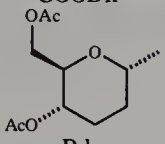
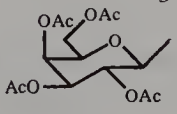
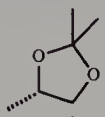
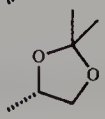
The examples listed in Scheme 6.73 demonstrate excellent to very high preference for *cis* product formation with derivatives of hydroxyacetyl acid chloride independent of the substituents at the imine or hydroxy protecting group. Similar results were obtained using hydroxyacetic acids and activating them, for example, with Mukaiyama's reagent,[46,47] triphenylphosphine/carbon tetrabromide,[56] saccharyl chloride,[50] Vilsmeier-type reagents (Table 6.1), and bis[2,2,2-trichloroethyl]phosphochloridate.[63] Tosyl chloride as activating reagent, however, showed *cis* or *trans* product formation with diaryl imines.[69]

N-Alkyl-*N*-arylglycines react analogous to the hydroxyacetic acid derivatives, producing *cis*-β-lactams with diaryl and alkylaryl imines.[27]

6.5.3.2 Amidoketenes

Amidoketenes (Scheme 6.74) share the properties of the hydroxyacetic acid-derived ketenes for high *cis* preference in the reaction with both diaryl and alkylaryl ketenes (for additional examples see Schemes 6.23 and 6.27). In particular, the *cis* selectivity in the reaction with diaryl imines (entries 1–3)



Entry	R	R^1	R^2	Yield (%)	cis : trans	Ref.
1	Ph	Ph	Ph	89	86 :14	129
2	CH_3	Ph	PMP	60	cis	208
3	CH_3	Ph	Ph	50	93:7	129
4	Ac	Ph	PMP	56	cis	208
5	Bn	PMP	*p*-Tol	55	cis	128
6	Bn	2-furyl	*p*-Tol	70	cis	128
7	COOBn	PMP	*p*-Tol	85	cis	128
8		styryl	PMP	52	cis*	135
9	Ph	Ph	$CH{=}CHCH_3$	75	cis	77,159
10	Ph	Ph		90	cis*	45
11	Ac		PMP	70	cis	131
12	Bn		PMP	69	cis	131
13	Ph	styryl	CH_2COOCH_3	--	cis	60**
14	Ph	OC_2H_5	Ph	31	trans	129
15	CH_3	OC_2H_5	Ph	18	trans	129

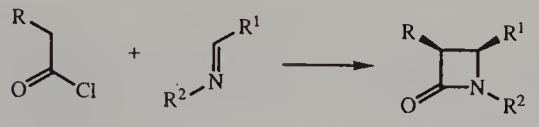
*mixture of cis diastereoisomers
**phenyldichlorophosphate as acid activating agent

Scheme 6.73

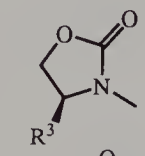
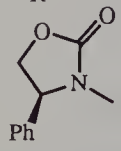
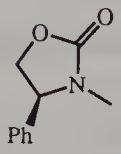
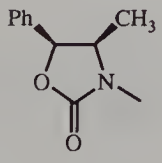
distinguishes them from the Sheehan ketenes (phthalimides and related derivatives), which give *trans* products with diaryl imines. It is of note that the cyclic amides produce higher yields than the BOC derivatives (entries 1 and 2).

6.5.3.3 Dane Salts

Excellent *cis* selectivity is found when the Dane salt is used in the Staudinger reaction (Scheme 6.75). Of particular note is the fact that even diaryl



major isomer

Entry	R	R^1	R^2	Yield (%)	Ratio of cis	Ref.
1	BnOCONH	PMP	Tol	15	cis	114
2	BnOCONH	2-furyl	PMP	22	cis	114
3		Ph	Ph	61	97:3	127
4		Ph	Bn	90	97:3	125
5		styryl	Bn	82	95:5	125
6		styryl	PMP	--	95:5	25

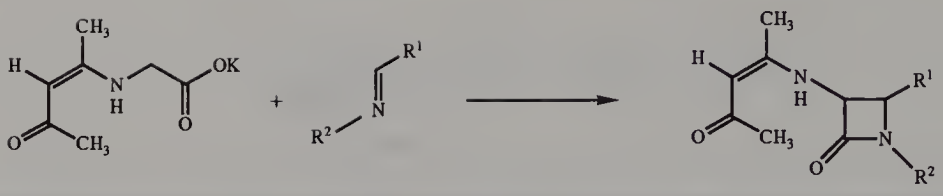
$R^3 = CH_2OMOM$

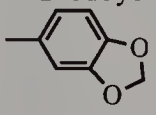
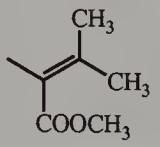
Scheme 6.74

imines (entries 1–5), which form *trans* products with phthalimidoacetyl chloride, yield exclusively *cis* products. Thioimidates, as expected, produce *trans* products (entries 10 and 11).

6.5.3.4 Azidoacetyl Chloride

The tendency of azidoacetyl chloride for formation of *cis*-β-lactams in the Staudinger reaction is exemplified by the examples in Scheme 6.76 (entries 1–6). It can be noted (entries 1 and 2) that *C*-aryl substituents of diaryl

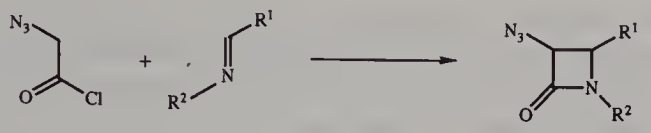


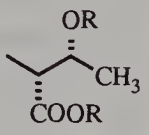
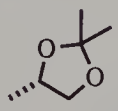
Entry	R^1	R^2	Yield (%)	cis : trans	Ref.
1	Ph	Ph	--	cis	60,119
2	Ph	DMB	65	cis	116
3	2-furyl	DMB	50	cis	119
4		*p*-Tol	--	cis	121
5	PMP	*p*-Tol	61	cis	118
6	styryl	$CHCH_3Ph$	>46	cis*	120
7	styryl	DMB	49	cis	117
8	styryl	DMB	--	cis	119
9	Ph	CH_2CH_2Cl	50	cis	41
10	SMe		--	trans	119
11	SMe	Ph	--	trans	119

*mixture of diastereoisomers

Scheme 6.75

amines can be implicated as possessing a slight tendency for *trans* product formation (see Scheme 6.62). Imines with *N*-aryl and *C*-aryl groups possessing an aliphatic or vinylic substituent at the *C* or *N* position of the imine gave *cis* products only (Scheme 6.76 entries 3–6). Dugat et al. investigated the reaction between imines synthesized from acetaldehyde and benzylic amines with azidoacetyl chloride.[84] Imines derived from α-methylbenzylamine and diphenylmethylamine give *trans* products (entries 7 and 8), which could be explained by the positive inductive effect of the *C*-methyl group. This influence could serve to stabilize the intermediate zwitterion, analogous to the stabilization described for imidates and thioimidates (Scheme 6.62) and allow for the C—N bond to rotate and form a sterically less

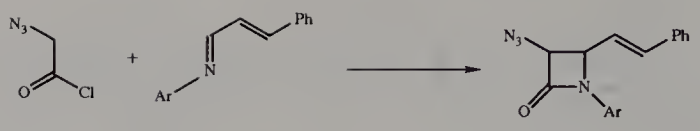


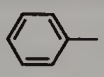
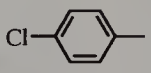
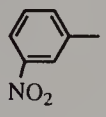
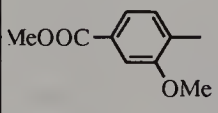
Entry	R_1	R_2	Yield (%)	cis : trans	Ref.
1	Ph	Ph	45	75 : 25	101
2	PMP	*p*-tolyl	88	90 : 10	46
3	styryl		60	cis	104,180
4		PMP	60	cis	104
5		CH_2COOCH_3	22	cis	107
6	*p*-(BnO)Ph	$CHCH_3COOBu$-*t*	80	cis*	184
7	CH_3	$CHCH_3Ph$	75	trans	84
8	CH_3	$CHPh_2$	75	trans	84
9	CH_3	$-CH(PMP)_2$	20	cis	84
10	OC_2H_5	Ph	31	trans	101
11			8	trans	102

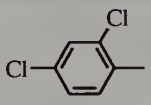
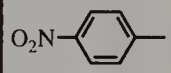
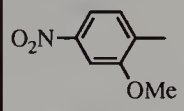
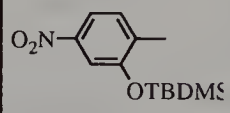
*mixture of cis diastereoisomers

Scheme 6.76

crowded reaction intermediate. Supporting evidence for this mechanism comes from the reactions of α-haloacetaldehyde-derived imines, which result in the formation of *cis* products only (Scheme 6.44, entries 2–5, and Scheme 6.80, entry 18). Thus, it appears that the negative inductive effect of the halomethyl group prevents C—N bond rotation (analogous to the carbonyl group) and yields *cis* products.



Ar	pKa of amine	cis : trans
	4.6	cis
	3.98	cis
	2.46	cis
	2.4	cis

Ar	pKa of amine	cis : trans
	2.05	80 : 20
	1.0	66 : 37
	1	9 : 91
	1	0 : 100

Scheme 6.77

Unexpectedly, the acetaldehyde imine from di-*p*-anisylmethylamine (Scheme 6.76, entry 9) yielded *cis* product only. Formation of *trans* products occurs as expected with imidates and thioimidates (entries 10 and 11).

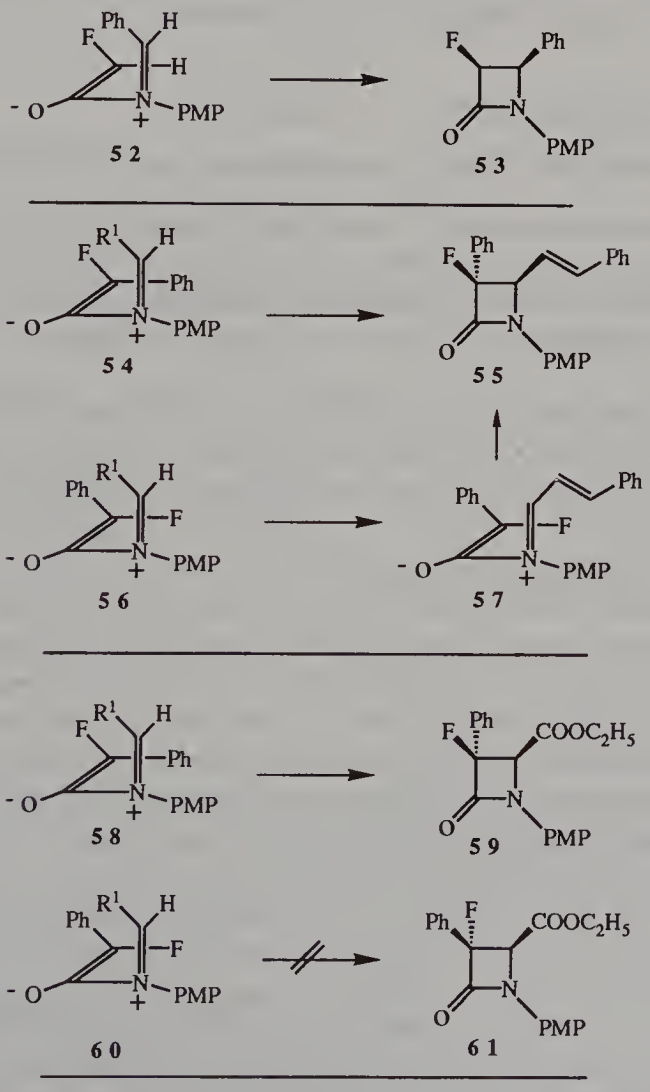
Reaction between azidoacetyl chloride and imines derived from cinnamaldehyde proceeds with excellent *cis* selectivity and Doyle et al. (Scheme 6.70) have given a mechanistic rationale for this observation.[202] An interesting study was published by Just et al. on the effect of electron-rich and electron-poor aryl groups at the nitrogen of the imine (Scheme 6.77).[106] Imines derived from relatively electron-rich amines (pK_a 4.6–2.4) gave excellent *cis* selectivity; however, aryl groups possessing one or more electron-withdrawing groups (amines $pK_a < 2.4$–1.0) gave mixtures of *cis* and *trans* products. These results suggest a change of the reaction mechanism suggested by Doyle et al. (Scheme 6.70)[202] to the mechanism depicted in Scheme 6.62. The *N*-aryl substituent possessing strongly electron-withdrawing groups can obviously effect stabilization of the positive charge of the iminium ion intermediate, allowing bond rotation and thus *trans*-β-lactam formation. Similar results were obtained by Sharma et al. in the synthesis of 3-phenoxy-2-azetidinones.[71]

6.5.3.5 Fluoroacetyl Chloride

It was shown that fluoroacetyl chloride *gave* cis products only (Scheme 6.17) in the Staudinger reaction with diaryl imines, alkylaryl imines, and

imines from cinnamaldehyde.[158] Fluoroacetic acid belongs to the group of Bose–Evans ketenes because of the small size of the fluorine substituent. The other haloacetic acids with their sterically more demanding substituents (Moore ketenes) have a tendency toward *trans* product formation. The high *cis* selectivity of the fluoroacetic acid-derived ketene (F and the substituent at C-4 of the β-lactam in *cis* relationship) is, however, due mainly to dipolar or secondary orbital effects, as discussed below (Scheme 6.78).

The formation of zwitterion **52** (Scheme 6.78) and the formation of β-lactam **53** from the reaction between fluoroketene and imines is expected, for both steric and electronic reasons. Introduction of a sterically demanding phenyl group at the fluoroketene in the reaction with diaryl or alkylaryl imines also does not provide unambiguous proof of whether steric or electronic factors play a role in determining the stereochemistry of the reaction product, β-lactam **55**. The formation of zwitterion **54** would occur for electronic



Scheme 6.78

reasons via the attack of the imine from the face opposite the fluorine and produce β-lactam **55**. If, however, initially zwitterion **56** was formed for steric reasons (attack of the imine from the face opposite the phenyl group), the formation of β-lactam **55** (relative stereochemistry) would also occur (see Scheme 6.83) via the formation of intermediate **57**. The results of the reaction of the ketene between imines derived from glyoxalic acid esters and chlorophenylketene, however, reveal that electronic factors are responsible for the observed *cis* selectivity. Imines derived from glyoxalic acid and related derivatives have a tendency toward exclusive *cis* product formation even with sterically hindered ketenes. Thus the stereochemistry of the reaction products is probably an accurate reflection of the geometry of the initially formed zwitterionic intermediate. As β-lactam **59** and not β-lactam **61** is formed in the reaction of fluorophenyl ketene with imines from glyoxalic esters, the formation of zwitterion **58** but not **60** can be assumed. It thus appears that electronic factors and not steric factors determine the stereochemistry in the initial formation of the zwitterion and the resulting formation of 3-fluoro-2-azetidinones from fluoroketenes.

6.5.4 Sheehan Ketenes

6.5.4.1 Crotonyl Chloride and Dimethylacryloyl Chloride

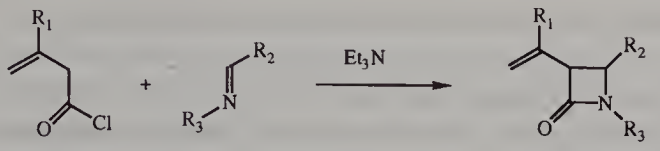
The reaction between crotonyl chloride and dimethylacryloyl chloride with imines was investigated by several research groups (Scheme 6.79).[43,46,146–148] The stereochemical results obtained can be explained on the basis of the mechanistic discussions presented in this chapter in Schemes 6.61, 6.62, and 6.70.

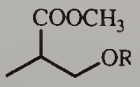
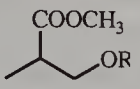
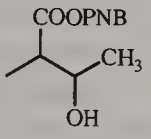
Only *trans* products were obtained in the reaction, for example, with *N*-aryl imines derived from benzaldehyde, furfural, and 3-pyridine carboxaldehyde with crotonyl chloride and dimethylacryloyl chloride (Scheme 6.79, entries 1–5).

Assuming a ketene mechanism for the formation of the zwitterionic intermediate (Scheme 6.62), both the *C*-aryl and the *N*-aryl groups are stabilizing the positive charge of the zwitterion, thus allowing rotation around the C—N bond to avoid steric interactions between the medium-size vinyl groups and the *C*-aryl group of the iminium ion. Formation of the *cis*-iminium ion intermediate is followed by *trans* product formation. Introduction of electron-withdrawing substituents at the carbon of the imine (such as esters or ketones) prevents this stabilizing effect and results in the preferential formation of *cis* products (entries 13–15).

Substitution of the *N*-aryl group in a diaryl imine by an *N*-alkyl group demonstrates that the substituent at the nitrogen is also important in effecting the stabilization of the zwitterion. The *N*-alkyl-*C*-aryl imines investigated (derivatives of serine) yielded exclusively *cis* products (entries 7-8).

N-Alkyl and *N*-aryl imines of cinnamaldehyde both gave *cis* products with high preference (entries 9–12). These results could be explained by an



Entry	R^1	R^2	R^3	Yield (%)	trans : cis	Ref.
1	H	Ph	Ph	40	trans	146,147,148
2	H	Ph	PMP	70	trans	46,146
3	H	2-pyridyl	PMP	52	trans	146
4	H	2-furyl	Ph	70	trans	148
5	CH_3	2-furyl	Ph	70	trans	148
6	H	styryl		25	17 : 83	146,148
7	CH_3	2-furyl		30	cis	147,148
8	H	2-furyl		15	cis	146
9	CH_3	styryl	$CH_2COOC_2H_5$	50	cis	148
10	CH_3	styryl	$CH_2COOC_2H_5$	60	cis	148
11	CH_3	styryl	Ph	70	cis	148
12	H	styryl	Ph	30	17 : 83	129
13	H	$COOCH_3$	DMB	40	cis	148
14	CH_3	$COOCH_3$	DMB	30	cis	148
15	CH_3	$COOCH_3$	PMP	60	cis	43
16	H	COPh	$CHCH_3Ph$	55	cis	146

R = TBDMS

Scheme 6.79

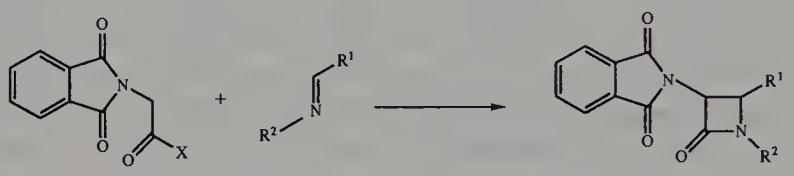
adaptation of the transition-state model suggested by Doyle et al. explaining the preference for *cis*-β-lactam formation via the capability of the *C*-styrene group of the imine to form donor–acceptor complexes (Scheme 6.70), with facilitate *cis* product formation.[202]

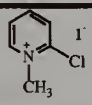
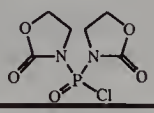
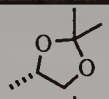
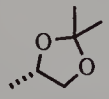
6.5.4.2 Phthalimidoacetyl Chloride

It is interesting to note that the results of the reaction of phthalimidoacetyl chloride and related derivatives with imines (Scheme 6.80) parallels the re-

sults obtained in the reaction of crotonic acid chloride with imines (Scheme 6.79).

In both cases, the reaction of ketenes with diaryl imines gives *trans* products only (Scheme 6.80, entries 1–5) and the introduction of an aliphatic or vinylic substituent as one of the imine substituents results in preferential *cis* product formation (entries 6–17). The results can again be explained by the need for both an electron-withdrawing substituent at the nitrogen and an aryl



Entry	R^1	R^2	X	Yield (%)	cis : trans	Ref.
1	PMP	*p*-Tol		81	trans	46,47
2	*p*-$O_2NC_6H_4$	*p*-Tol	PPh_3/CBr_4	70	trans	56
3	Ph	PMP	PPh_3/CBr_4	85	trans	56
4	Ph	Ph	Cl	58	trans	63,129
5	Ph	*p*-ClPh		65	trans	66
6		PMP	Cl	57	cis	131
7		DMB	Cl	76	cis	83
8	*o*-BnOPh	DMB	Cl	77	cis	109
10	PMP	$CH_2CH(OTMS)Ph$	$PhOP(O)Cl_2$	60	cis*	41
11	Ph	$CH{=}CHCH_3$	Cl	64	cis	77,159
12	styryl	PMP	Cl	80	cis	112
13	styryl	DMB	Cl	43	cis	112
14	styryl	$CH{=}CH_2$	Cl	64	cis	77,159
15	α-CH_3 styryl	*p*-TMSOPh	Cl	--	cis	210
16	styryl	*p*-TMSOPh	Cl	90	50 : 50	54,210
17	styryl	*p*-TBDMSOPh	$SOCl_2$/DMF	96	85 : 15	54
18	CH_2F	$CHCH_3Ph$	Cl	59	cis*	177
19	C_2H_5O	Ph	Cl	--	trans	101
20	CH_3S	CH(*i*-Pr)$COOCH_3$	Cl	79	trans*	131
21	CH_3S	$CH(Ar)COOCH_3$	Cl	64	trans*	185

*mixture of diasteroisomers

Scheme 6.80

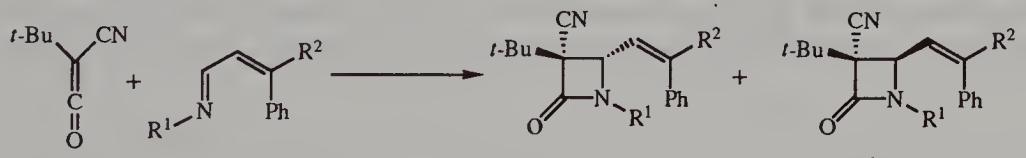
group at the C terminus of the imine to allow bond rotation and the formation of a *cis*-iminium ion intermediate. Similar results were reported on related acid chlorides by Cooper et al.[25] (Scheme 6.25.) and Ikota and Hanaki[126] (Scheme 6.27). Cooper et al. used an *N*-aryl imine derived from cinnamaldehyde and obtained *cis* products, whereas the use of a dairyl imine (benzylidineaniline) by Ikota and Hanaki produced, as expected, *trans* products. The stereochemical results detailed in Scheme 6.80 are apparently independent of the acid-activating group used. Again, imidates and thioimidates resulted in *trans* product formation (entries 18–20).

6.5.5 Moore Ketenes

6.5.5.1 Cyanoketenes

A series of very interesting studies by Moore et al. (Schemes 6.81–6.83) revealed the influence of steric factors in the ketene–imine cycloaddition reaction. *tert*-Butylcyanoketene, chlorocyanoketene, and hexynylcyanoketene were investigated in their reactions with cinnamylideneamines and benzylideneamines.[37] It was demonstrated that the *trans* product (cyano group and C-4 hydrogen in *trans* relationship) is the only reaction product with imines possessing relatively small N-substituents such as phenyl and *n*-butyl (Schemes 6.81–6.83, entries 1).

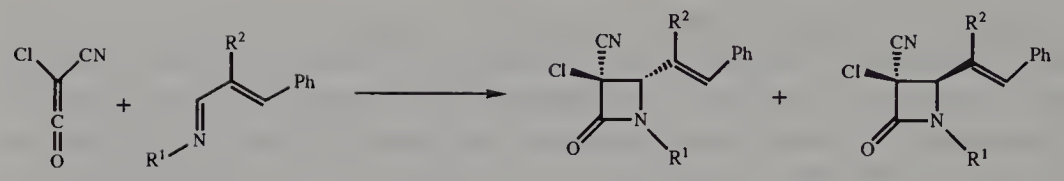
As depicted in Scheme 6.84, the initial reaction between the ketene and the imine should produce iminium ion **62.** Strong steric interactions between the large group (L) on the ketene and the vinyl group of the iminium ion favor the formation of the *cis*-iminium ion **64** via **63** and formation of *trans*-



trans cis

Entry	R^1	R^2	Yield (%)	trans : cis
1	Ph	H	82	100 : 0
2	*p*-ClPh	H	76	100 : 0
3	C_6H_{11}	H	68	93 : 7
4	*t*-Bu	H	36	44 : 56
5	Ph	Ph	77	100 : 0
6	C_6H_{11}	Ph	83	100 : 0
7	*t*-Bu	Ph	90	64 : 36

Scheme 6.81

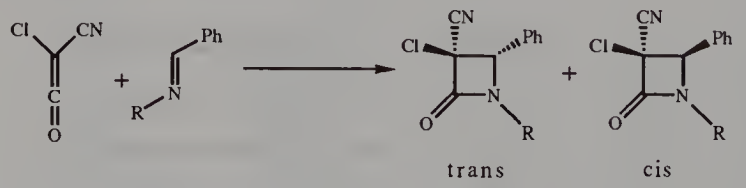


Entry	R^1	R^2	Yield (%)	trans : cis
1	Ph	Ph	82	100 : 0
2	*n*-C_4H_9	Ph	68	100 : 0
3	C_6H_{11}	Ph	58	34 : 66
4	*t*-Bu	Ph	86	0 : 100

Scheme 6.82

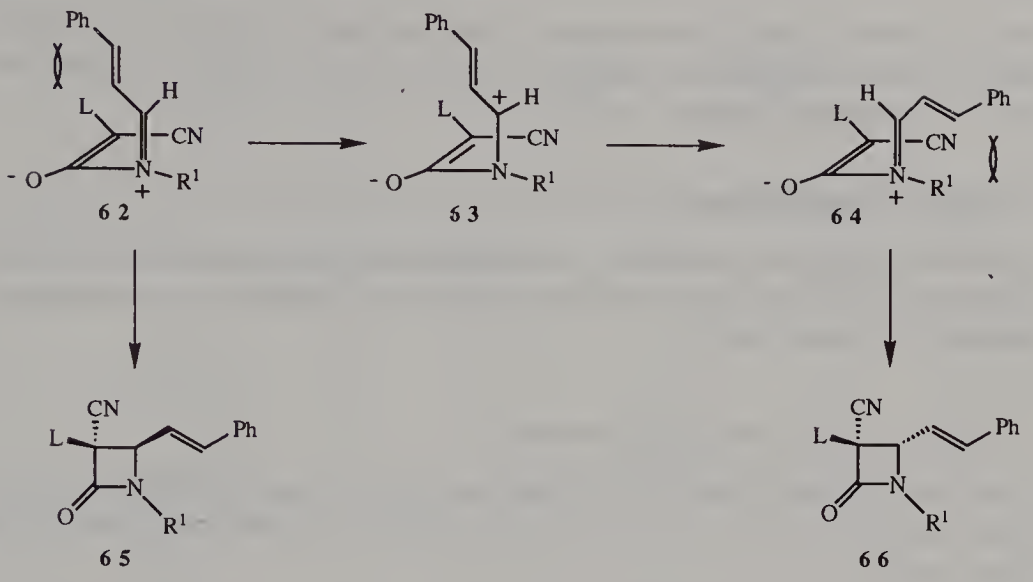
β-lactam **66.** It was also shown that the introduction of large substituents at the imine nitrogen (*tert*-butyl and cyclohexyl) gave mixtures of *cis* and *trans* products (Schemes 6.81–6.82). This can be explained (Scheme 6.84) via steric hindrance between the bulky nitrogen substituent and the styryl group in intermediate **64.** Thus, both zwitterions **62** and **64** are formed and *cis* and *trans* product formation or exclusive *cis* product formation results. (It should be noted that both [2+2] and [2+4] cycloaddition products are formed in these reactions.)

The studies by Moore et al. can also be used to explain the preferential formation of *trans* products for other ketenes (Schemes 6.85–6.87) possessing bulky ketene substituents such as alkyl, aryl, chloro, and sulfur groups



Entry	R	Yield (%)	trans : cis
1	Ph	88	100 : 0
2	C_6H_{11}	97	81 : 19
3	*t*-Bu	88	0 : 100

Scheme 6.83



Scheme 6.84

(Moore ketenes). The formation of *trans* products occurs with diaryl imines and also alkylaryl imines.

6.5.5.2 Haloketenes

All of the haloketenes (Scheme 6.85) showed strong preference for *trans* product formation. The *ortho*-substituted *N*-aryl imines, possessing *o*-nitro

Entry	L	S	R^1	R^2	Yield (%)	trans : cis	Ref.
1	Cl	H	Ph	Ph	70	trans	129,155,200
2	Br	H	Ph	Ph	50	trans	64
3	Cl	CN	Ph	Ph	88	trans	37
4	Cl	H	Ph	CH_2COOEt	4	trans	65
5	Cl	H	*o*-CH_3OPh	Ph	25	trans	156
6	Cl	H	PMP	PMP	65	trans	156
7	Cl	H	*o*-NO_2Ph	Ph	9	56 : 44	156
8	Cl	H	*o*-*t*-BuPh	PMP	10	75 : 25	156
9	Cl	CN	SC_2H_5	C_6H_{11}	36	trans	193
10	Cl	CN	OC_2H_5	C_6H_{11}	94	trans	193

Scheme 6.85

and *o-tert*-butylphenyl substituents, follow the pattern of the *N*-cyclohexyl and *tert*-butyl imines in the studies by Moore et al., and give *cis–trans* mixtures of β-lactams (entries 7 and 8).

6.5.5.3 Sulfoketenes

Not surprising, thio-, sulfoxide-, and sulfone-derived ketenes all show preference for *trans* product formation (Scheme 6.86). Additional examples can be found in Scheme 6.21.

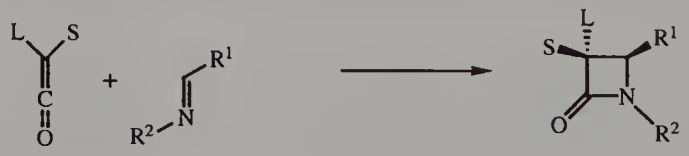
6.5.5.4 Alkyl and Aryl Ketenes

Listed in Scheme 6.87 are alkyl ketene (entries 1–3)- and aryl ketene (entries 4–11)- derived β-lactams, all of which are *trans* products regardless of the imine used.

6.5.6 Electronic Effects of Imines Precluding Steric Effects

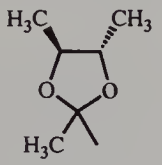
6.5.6.1 Imidates and Thioimidates

It is well recognized that imidates and thioimidates will produce *trans* products in the Staudinger reaction regardless of the size of the substituent at the ketene (see Schemes 6.62, 6.63, 6.73, 6.75, 6.76, and 6.80), because of the



Entry	L	S	R^1	R^2	Yield (%)	Ref.
1	PhS	H	Ph	Ph	55	52
2	PhS	H	Ph	PMP	--	52
3	PhS	H	styryl	CH_2CO_2Bn	30	65
4	$PhCH_2S$	H	Ph	Ph	40	129
5	TolSO	H	Ph	Ph	34	72
6	TolSO	H	Ph	PMP	38	72
7	TolSO	H	Ph	*p*-ClPh	30	72
8	$TolSO_2$	H	Ph	Ph	47	73
9	$TolSO_2$	H	*p*-ClPh	*p*-ClPh	46	73
10	$TolSO_2$	H	Ph	*p*-ClPh	43	73

Scheme 6.86

Entry	L	S	R^1	R^2	Yield (%)	Ref.
1	CH_3	H	Ph	Ph	50	129,200
2	$(CH_3)3$	H	Ph	Ph	34	200
3		H	Ph	PMP	19	168
4	Ph	H	Ph	Ph	59	129
5	PMP	H	Ph	Ph	35	206
6	Ph	OTMS	PMP	Ph	82	134
7	Ph	OTMS	PMP	PMP	71	134
8	Ph	OTMS	PMP	$CHPh_2$	55	134
9	Ph	OAc	Ph	Ph	95	133
10	Ph	H	Ph	CH_2CO_2Et	49	65
11	Ph	H	styryl	CH_2CO_2Et	70	65

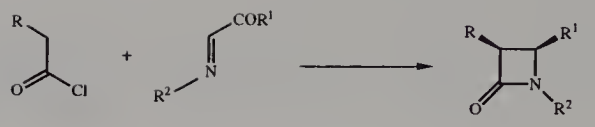
Scheme 6.87

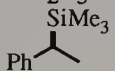
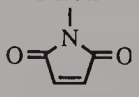
ability of sulfur or oxygen to stabilize the positive charge of the zwitterionic immediate (see Scheme 6.62).

6.5.6.2 Imino Esters and Related Derivatives

From the results presented in Scheme 6.88 it is evident that these imines have a very strong preference for *cis* product formation. (For additional examples see Schemes 6.11 to 6.13, 6.75, 6.76, and 6.79.) It is particularly striking that the Moore ketenes with bulky substituents such as halides, alkyl groups, aryl groups, and the thiophenyl group, which typically give *trans* products in the Staudinger reaction with most imines, were found to preferentially or exclusively form *cis* products.

As discussed earlier, the α-carbonyl group is apparently able to prevent addition of a nucleophile to the intermediate zwitterion (Scheme 6.62) or prevents the stabilization of the intermediate iminium ion which would be followed by bond rotation and *trans* product formation. The change from *trans* stereochemistry in the reaction of acetaldehyde-derived imines to *cis*-β-lactam stereochemistry in the reaction with α-haloacetaldehyde-derived imines (Schemes 6.44, 6.76, and 6.80) can probably be explained similarly.



Entry	R	R^1	R^2	Yield (%)	cis : trans	Ref.
1	Cl	Ph	PMP	25	cis	143
2	CH_3	Ph	PMP	75	cis	143
3	CH_3	OCH_3	PMP	86	cis	78
4	CH_3	CHNPMP	PMP	90	cis	144
5	C_2H_5	OCH_3	PMP	90	83 : 17	78
6	C_2H_5	Ph	PMP	60	cis	143
7		OCH_3	PMP	85	cis*	78
8		Ph	PMP	83	cis	150
9		Ph	PMP	68	cis	147
10	CH_2=CH	Ph	PMP	80	63 : 37	147
11	CH_2=CH	OCH_3	DMB	40	cis	147
12	Ph	Ph	PMP	60	cis	143,205
13	Ph	Ph	Ph	50	cis	205
14	Phth	Ph	PMP	75	cis	143
15		CH=NPMP	PMP	55	cis	144
16	PhS	CH=NPMP	PMP	80	cis	144
17	PhS	Ph	PMP	--	cis	52
18	PhS	Ph	C_2H_4Ph	--	cis	52

*mixture of cis diastereoisomers

Scheme 6.88

The results of the studies with imino esters also provide evidence that rotation of the C—N bond of **41** (Scheme 6.61) occurs in the formation of the *cis*-iminium ion intermediate **40** rather than a change of enolate geometry of the zwitterionic intermediate **39** as suggested by Brady and Gu.[27] Although the imino esters probably prevent C—N bond rotation or the addition of a nucleophile to the iminium ion, this would probably not cause a change in enolate geometry of the zwitterion.

6.6 Summary

A literature review on recent results concerning the Staudinger reaction and a summary of the current knowledge of the mechanism of this reaction have been provided. Additionally, we have suggested rules to predict the relative *cis* or *trans* stereochemistry of β-lactam formation in the Staudinger reaction.

6.7 Acknowledgments

The authors thank the following organizations for their support of our research program in β-lactam chemistry: National Institutes of Health (GM, AI, and NCI), American Cancer Society, American Heart Association—Kansas Affiliate, Wesley Foundation (Wichita, Kansas), Marion Merrell Dow Foundation (Kansas City, Missouri) Oread Laboratories Inc. (Lawrence, Kansas), General Research Fund at the University of Kansas, Biomedical Research Fund at the University of Kansas, J. R. and Inez Jay Fund at the University of Kansas.

6.8 Abbreviations

Ac	Acetyl
aq	Aqueous
Ar	Aryl
Bn	Benzyl
BOC, t-BOC	*tert*-Butoxycarbonyl
Bu, t-Bu	*tert*-Butyl
Cbz	Benzyloxycarbonyl
DAM	Di-(4-methoxyphenyl)methyl
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DCC	Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de	Diastereomeric excess
DMAP	4-Dimethylaminopyridine
DMB	3,4-Dimethoxybenzyl
DME	1,2-Dimethoxyethane
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxide
EE	1-Ethoxyethyl

ee	Enantiomeric excess
Et	Ethyl
Im	Imidazole
i	*iso*
m	*meta*
Me	Methyl
MEM	2-Methoxyethoxymethyl
MOM	Methoxymethyl
n	Normal
NMR	Nuclear magnetic resonance
Nu^-	Nucleophile
o	*ortho*
p	*para*
Ph	Phenyl
Ph_3P	Triphenylphosphine
Phth	Phthalimido
PMB	*p*-Methoxybenzyl
PMP	*p*-Methoxyphenyl
Pr	Propyl
PTSA	*p*-Toluenesulfonic acid
Py	Pyridine
R	An organic group
t	Tertiary, *tert*-
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TFA	Trifluoroacetyl
THF	Tetrahydrofuran
THP	2-Tetrahydropyranyl
TIPS	Triisopropylsilyl
TMS	Trimethylsilyl
p-Tol	*p*-Tolyl
p-TsCl	*p*-Toluenesulfonyl chloride

6.9 Literature

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The Organic Chemistry of β-Lactams

Edited by

Gunda I. Georg

Department of Medicinal Chemistry, University of Kansas

This book offers a comprehensive and critical review of the major advances in ß-Lactam chemistry over the past decade. Focusing on the organic chemistry of the ß-lactam regardless of their biological activity, coverage concentrates on the methodology required to synthesize ß-1actams and ß-1actam antibiotics within a broad scope of ß-lactam chemistry.

Written by chemists from industry and academia, each chapter features a brief overview of the chemistry and includes references to the literature for further research. While most chapters emphasize stereocontrol, other chapters explore such areas as novel methods for the construction of the ß-lactam ring system, the formation of bicyclic ß-lactams, the chemistry of the side-chains of ß-1actam antibiotics, functional group conversion, and the protection of group chemistry.

ISBN 1-56081-083-1 VCH Publishers, Inc.
ISBN 3-527-28188-6 VCH Verlagsgesellschaft

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