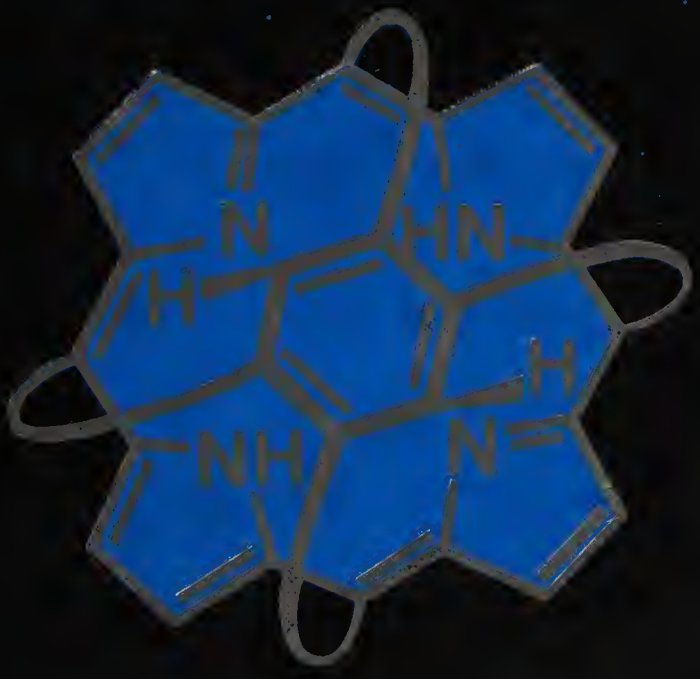
NITYA ANAND
JASJIT S. BINDRA
SUBRAMANIA RANGANATHAN

ART IN ORGANIC SYNTHESIS

Second Edition



Art in Organic Synthesis

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Second Edition

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To

Soniya, Naveen, Neeraj, and Swarn
Ratna, Ranjit, and Ranjna
Anand and Darshan

Preface

Art in Organic Synthesis, originally published in 1970, was conceived as a novel method of presenting the great achievements of synthetic organic chemistry, mainly in the form of flow charts. It was hoped that this type of uninterrupted graphic presentation—new at the time—would have a better impact on the reader and would facilitate the understanding of strategies for synthesis of complex structures. The flow chart presentation is particularly suited to illustrating the dissection of complex structures into smaller building blocks or synthons, which can then be joined together by appropriate reactions, as was first verbalised by E. J. Corey in his formal retrosynthetic analysis approach. We are happy that our expectations for *Art in Organic Synthesis* were fulfilled and that the volume was welcomed enthusiastically by practitioners of the art and, much to our delight, served for many years as an important teaching tool.

The art of organic synthesis resides in the optimum and coordinated utilisation of each element of the complete ensemble of conception of strategy, and in the selection of appropriate reactions and reagents. The potential and capabilities of each element are best illustrated by a total synthesis, which provides a clear comprehension of the integrated construction and rupture of bonds. A total synthesis is like a symphony orchestra, where each instrument plays its own and important role but the combined effect transcends the sum of the contributions of all.

In the 17 years since the publication of the first edition, major developments have taken place in the art of organic synthesis which underline the shifting focus of attention on different facets of the art. Some of the new facets relate to the use of chiral synthons and chiral reagents, strategies for greater steric control, selective functional group transforms, and yield optimisation. Another important facet of the art is the delineation and use of synthetic pathways that simulate those encountered in nature. The challenges posed by total synthesis have led to the development of many new reagents and the discovery of new reactions. These developments have generated a new confidence in organic chemists in their ability to design and construct complex molecular structures at will.

The need for revision of the volume to include these newer developments is, therefore, obvious. In the planning of this second edition, our uppermost concern has been to make it as illustrative as the earlier volume. This attempt is manifested in the choice and analysis of syntheses from the numerous

excellent ones available in the literature. Some of the classic examples in the earlier volume have been retained with little change, several syntheses have been completely revised or updated, and a large number of new syntheses have been added to reflect the changing emphasis in the area. In every case the art work and the text have been completely redone.

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December 1987

Preface to the First Edition

Art is associated with the creation of new concepts and ideas and their expression in different perceptible forms, and this facet of human endeavour has contributed much to our civilization. In the area of organic synthesis, art has found expression in the synthesis of a wide variety of molecular structures. The earliest striking example of this art was Robinson's elegant synthesis of tropine using simple bond-forming reactions. The middle of this century saw the art of organic synthesis in full bloom, and many outstanding syntheses have been achieved of which special mention may be made of Woodward's chlorophyll synthesis. More than any other branch of organic chemistry, synthesis has led to a better understanding of the principles of bond-making and bond-breaking, the consequences of dissymetry, the preferred conformation of molecules and the stereoelectronic features that govern their transition state in reactions. An appreciation of these factors and the availability of sophisticated tools coupled with human ingenuity has elevated organic synthesis to a highly challenging intellectual adventure where imagination, inspiration, design, and experimental skill all converge for the achievement of the objective. "Art in Organic Synthesis" attempts to illustrate these various aspects of organic synthesis. In a hundred or so examples we have tried to highlight synthetic achievements in terms of ingenuity in design, extent of stereochemical control, new reactions and new reagents. The examples chosen describe the synthesis of a natural product or of an unusual or strained molecule prepared to check certain predicted properties of the structures or simply because it presented a unique challenge to the skill and ingenuity of the organic chemist. Due to limitation on space we have had to be rather selective, but this does not in any way imply that syntheses not included in this book are any less important. In the presentation the emphasis has been on economy of words and liberal use of flow sheets and perspective structural formulae to illustrate the force of arguments predicting the stereochemical outcome of important steps. Obscure or unusual reactions have been discussed at greater length in the footnotes. In addition to other indices, a type-transformation index is included to highlight some of the less common or new reactions. The literature coverage is up to the early part of 1969.

The authors hope that this small volume, which illustrates the creativity of organic synthesis, the tools available to it, its potentiality and predictive capacity, will provide an insight into the basic philosophy and strategy employed in the design and execution of an organic synthesis.

We wish to acknowledge the many helpful comments by Dr. P. C. Dutta, who read the entire manuscript, and by Drs. M. L. Dhar and M. M. Dhar, who read parts of it. We are also grateful to Dr. B. Singh and Mr. H. Raman for some reference work, and to Dr. (Miss) Ranjna Saxena who shared the burden of checking all references and greatly assisted in proof reading and in preparation of the indices.

All the perspective formulae have been drawn by one of us (J.S.B.). The formidable task of lettering in the formulae and typing the entire text suitable for direct reproduction of the manuscript was skillfully executed by Mr. H. C. Chhabra, who kept his patience and composure under very trying conditions: the authors would like to express their deep sense of gratitude to him.

One of us (N.A.) would like to record his profound appreciation to Swarn, his wife, for her understanding and for sparing him the time, which truly belonged to her, that went into the completion of this work.

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Acknowledgments

First and foremost our thanks are due to Mr. Ali Kausar who drew all the formulae and perspective diagrams, which are a distinctive feature of this book. The formidable task of accommodating and adjusting the text to the diagrams/graphics has been admirably carried out by Mr. M. K. Thapar, for which we thank him sincerely. The computerised preparation of Author and Reagent Indices has been done very efficiently by Mr. Ahsan Jamal and Dr. R. K. Sharma, and we are most grateful to them.

Dr. D. K. Dikshit went through the entire manuscript meticulously during the various stages of its preparation. His suggestions helped to improve the quality of the presentation, and for this we are grateful to him. We would also like to thank Dr. Naveen N. Anand for his help in structuring the chapter on Gene Synthesis.

Nitya Anand is grateful to the Indian National Science Academy for the award of a Senior Scientist position during the tenure of which this manuscript was prepared. He also thanks the Director, Central Drug Research Institute, Dr. M. M. Dhar for helpful discussions, Dr. S. S. Iyer for use of Library facilities, and the Library staff for their most forthcoming assistance. He expresses his gratitude to Ranbaxy Laboratories for their invaluable support. Above all he acknowledges his profound appreciation to Swarn, his wife, for her understanding, unstinted cooperation, and encouragement for the completion of this work.

NITYA ANAND
J. S. BINDRA
S. RANGANATHAN

Contents

Abbreviations

Ac	acetyl
Am	amyl
Ar	aryl, substituted phenyl
Aq	aqueous
BBN	9-borabicyclo[3.3.1]nonane
BOC	*t*-butoxycarbonyl
BPCOCl	4-phenylbenzoyl chloride
Bs	benzenesulfonyl
Bu	butyl
Bz	benzoyl
Bzl	benzyl
ca	about
CE	-cyanoethyl
Chf	chloroform
CSA	camphorsulfonic acid
CSC	camphorsulfonyl chloride
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,5-diazabicyclo[5.4.0]undec-5-ene
DCB	*o*-dichlorobenzene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEA	N,N-diethylaniline
$CpCo(CO)_2$	Cyclopentadienyl cobalt carbonyl
DEG	diethylene glycol
DHF	dihydrofuran
DHP	dihydropyran
DIBAL	diisobutylaluminum-hydride
DIC	diisopropylcarbodimide
Diox	dioxane
DMA	N,N-dimethylaniline
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane, glyme
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
DMT	4,4′-dimethoxytriphenyl-methyl, 4,4′-dimethoxytrityl
EAA	ethyl acetoacetate
Et	ethyl
FPh	9-phenylfluorenyl
HMDS	hexamethyldisilazane
HMPT	hexamethylphosphoric triamide, hexamethylphosphoramide
H_3O^+	aqueous acid
Imid	imidazole
Imid-co-imid	1,1′-carbonyldiimidazole
INOC	isonitrileoxide cycloaddition
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide

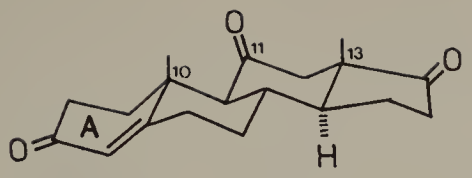
Liq	liquid
LTA	lead tetraacetate
Lindlar catalyst	deactivated palladium on carbon/$BaSO_4$
Lut	lutidine
Me	methyl
MCPBA	*m*-chloroperbenzoic acid
MeBmt	(4R)-4[(E)-2-butoxyl]-4-N-dimethyl-1-threonine
MEM	β-methoxyethoxymethyl chloride
MIRC	Michael initated ring closure
MOM	methoxymethyl
MSNT	1-(mesitylenesulfonyl)-3-nitro-1,2,4-triazole
Ms	mesyl, methanesulfonyl
MsOH	methanesulfonic acid
MTM	methylthiomethyl
MVK	methyl vinyl ketone
n	normal
NBA	N-bromacetamide
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NHBT	N-hydroxybenzotriazole
NHS	N-hydroxysuccinimide
NMMNO	N-methylmorpholine-N-oxide
NPS	*o*-nitrophenylsulfenyl
ODCB	*o*-dichlorobenzene
ONP	*p*-nitrophenyl ester
PBPCO	4-phenylbenzoyl
PCC	pyridinium chlorochromate
PCP	pentachlorophenol
pCP	*p*-chlorophenol
PDC	pyridinium dichromate
PDS	dipyridyl disulfide
Ph	phenyl
Phth	phthaloyl
PNB	*p*-nitrobenzyl
PP	4-pyrrolidylpyridine
PPA	polyphosphoric acid
Pr	propyl
Py	pyridine
RT	room temperature
SEM	-trimethylsilylethoxymethyl
s	secondary
t	tertiary
TBDMS	*t*-butyldimethylsilyl
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
TBSOTf	*t*-butyldimethylsilyloxyl triflate
TCAA	trichloroacetic anhydride
Tce	1,1,1-trichloroethyl
TEA	triethylamine
TfA	trifluoromethanesulfonic acid
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran, tetrahydrofuranyl
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TMB	1,3,5-trimethoxybenzoyl
TMEDA	N,N,N′,N′-tetramethylethylenediamine
TMS	trimethylsilyl
Tol	toluene
TPST	1-(1,3,5-triisopropyl)-phenylsulfonyl-1,2,3,4-tetrazole

Triflate	trifluoromethane-sulfonate	TsOH	*p*-toluenesulfonic acid
tRNA	transfer ribonucleic acid	Xy	xylene
		Z	benzyloxycarbonyl
Ts	*p*-toluenesulfonyl	Δ	reflux or heat

Although only one enantiomer is depicted in structural formulae, all compounds are racemates, unless otherwise stated. The following conventions have been followed:

1. A short line without a letter at the end denotes a CH_3 group.
2. A solid thick line indicates β-configuration.
3. A broken line indicates α-configuration.
4. A wavy or straight line indicates either unknown or unspecified configuration.
5. Commonly accepted amino acid abbreviations have been used.

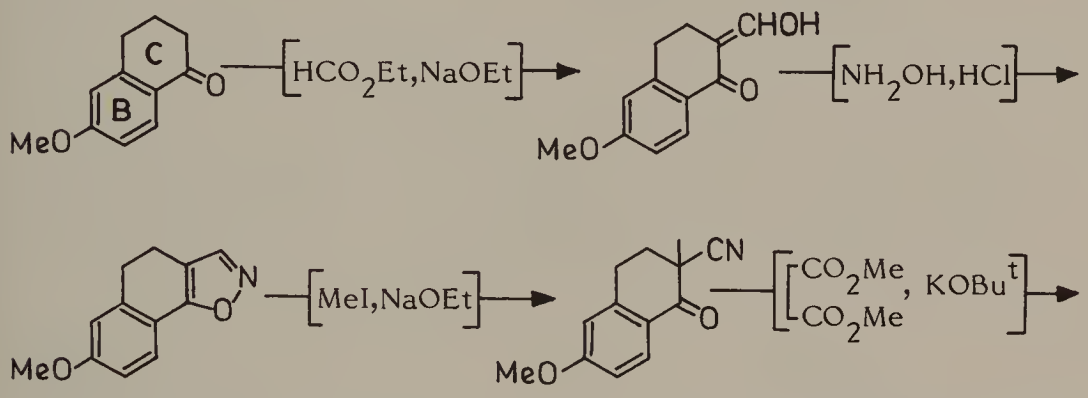
1



ADRENOSTERONE

The first synthesis of adrenosterone illustrates the application of a versatile steroid synthesis developed by Leon Velluz and his colleagues at Roussel-Uclaf, Paris, for the direct preparation of optically active steroids on an industrial scale(1-3).

The linear version of this Scheme(4), outlined below, is based on construction of a B-C-D tricyclic compound already possessing the five-membered D-ring and the methyl group at C-13. Introduction of the asymmetric centre at C-10 has been accomplished by reaction with 1,3-dichlorobutene-2 followed by stereoselective introduction of the angular 19-methyl group [transformation B→C].



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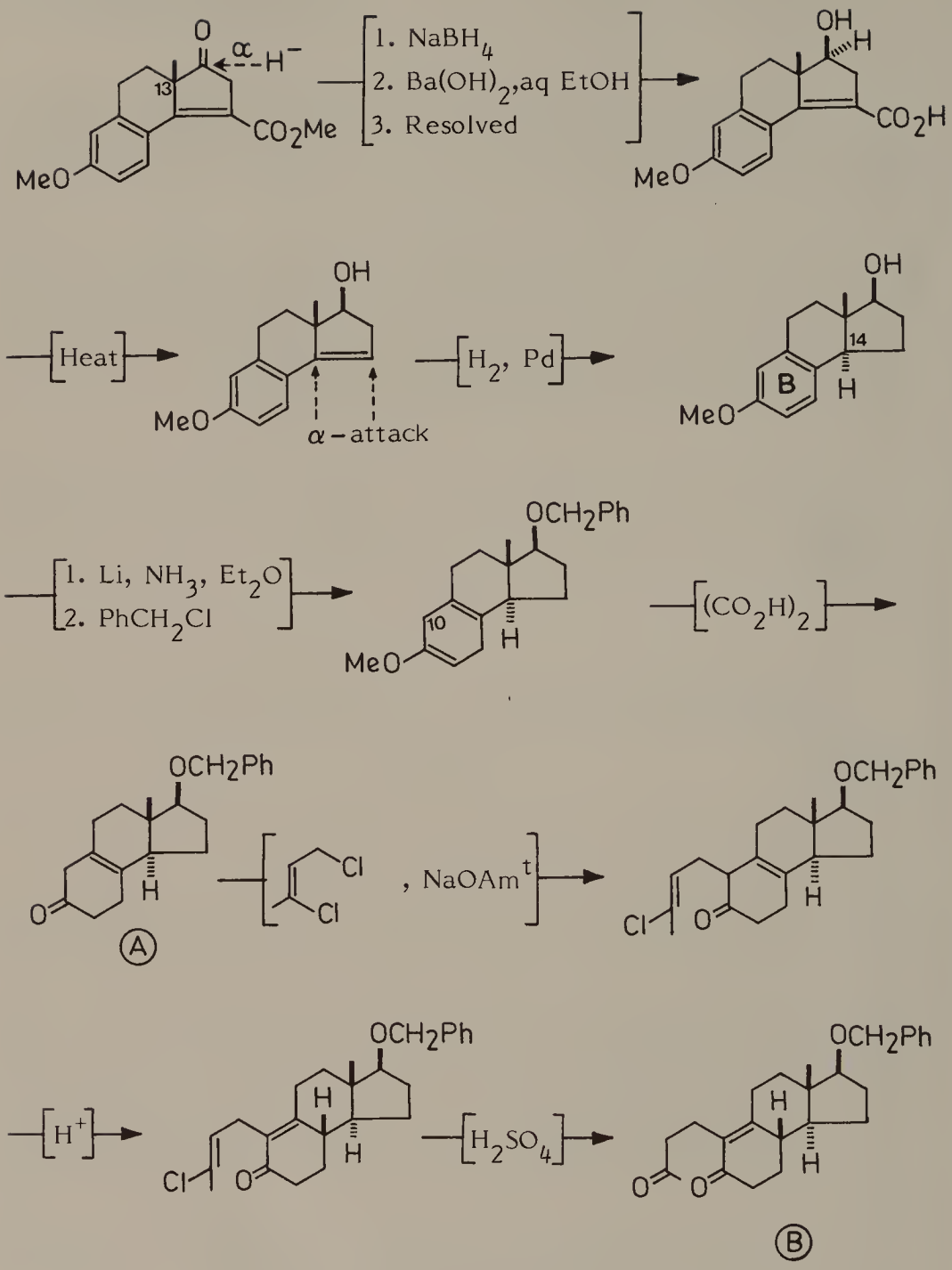
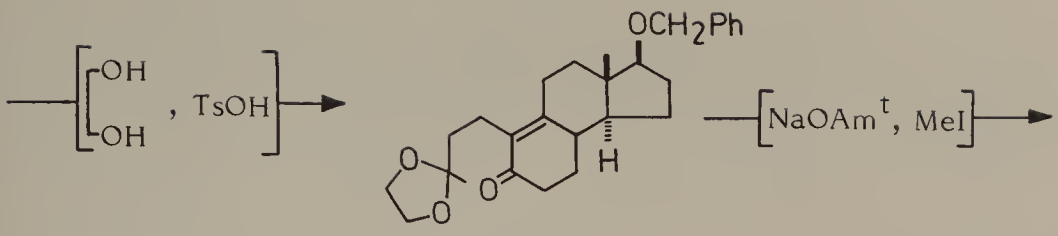
1. Velluz, L., Nominé, G., Mathieu, J. Angew. Chem., 1960, 72, 725.

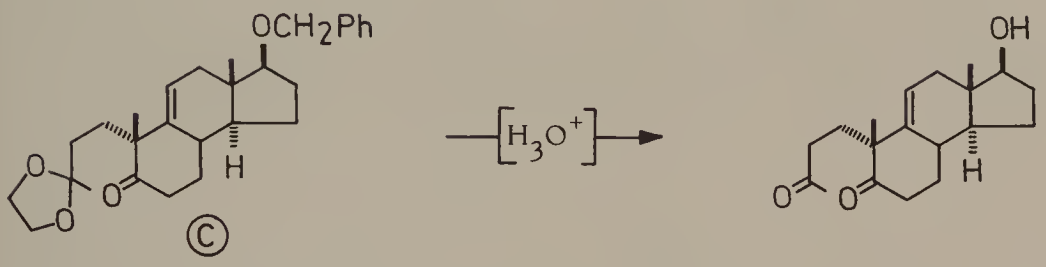
2. This route is quite general for the synthesis of both aromatic and non-aromatic steroids. Suitable modifications of the reaction scheme from the key tricyclic ketone(A) permit the preparation of either estradiol, 19-norsteroids or adrenosterone and cortisone.

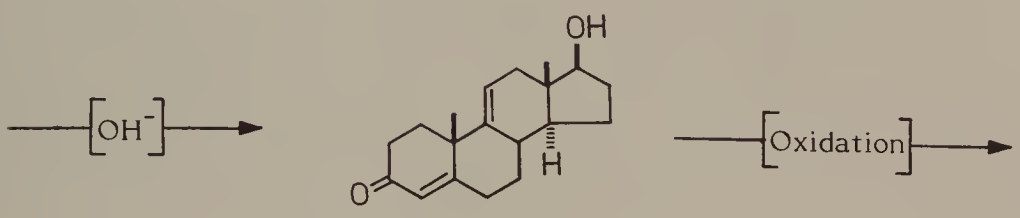
3. Unlike other syntheses which are generally carried out with racemates and in which optical resolution is attempted only at the end of the synthesis, this approach involves resolution of the intermediates at the earliest possible opportunity. Unwanted optical isomers are thus excluded quite early from the reaction mixture, avoiding the expense of processing material which has anyhow to be discarded at the end of the sythesis. Such a strategy was adopted earlier in the synthesis of cortisone by Barkley, L.B., Farrar, M.W., Knowles, W.S., Raffelson, H., Thompson, Q.E. J. Am. Chem. Soc., 1954, 76, 5014.

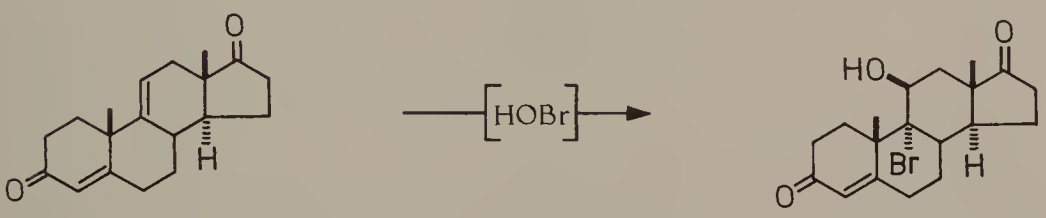
4. Velluz, L., Nominé, G., Mathieu, G., Toromanoff, E., Bertin, D., Tessier,J., Pierdet,A. Compt. Rend. 1960, 250, 1084; Velluz, L., Nominé, G., Mathieu, J., Toromanoff, E., Bertin, D., Bucourt, R., Tessier, J. Compt. Rend. 1960, 250, 1293.

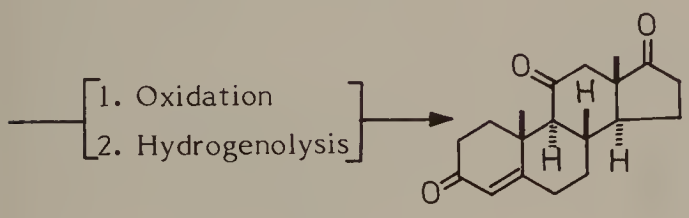

1. $NaBH_4$
2. $Ba(OH)_2$,aq EtOH
3. Resolved
Heat
H_2, Pd
α–attack
1. Li, NH_3, Et_2O
2. $PhCH_2Cl$
$(CO_2H)_2$
, $NaOAm^t$
H^+
H_2SO_4
MeO
OH
OCH_2Ph
CO_2Me
CO_2H
Cl
A
B





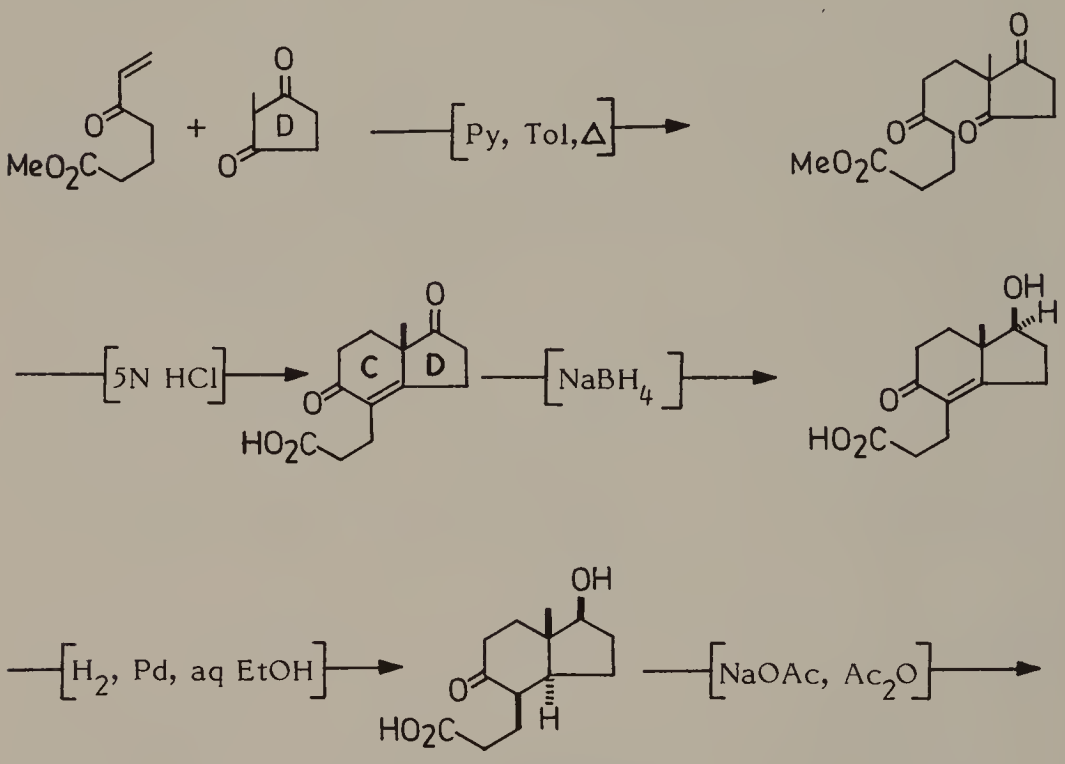






Adrenosterone

In the converging version(5) of this synthesis the asymmetric centre at C-13 has been established by joining ring C onto a pre-methylated ring D, followed by stereoselective reduction of the resulting hydroindene(6).



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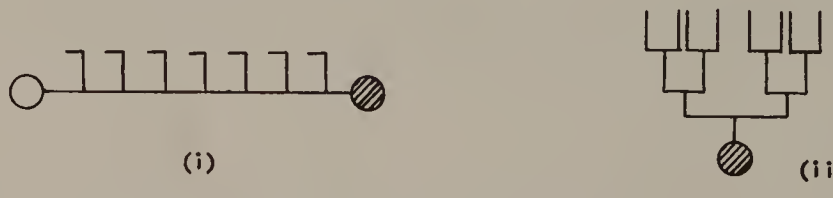
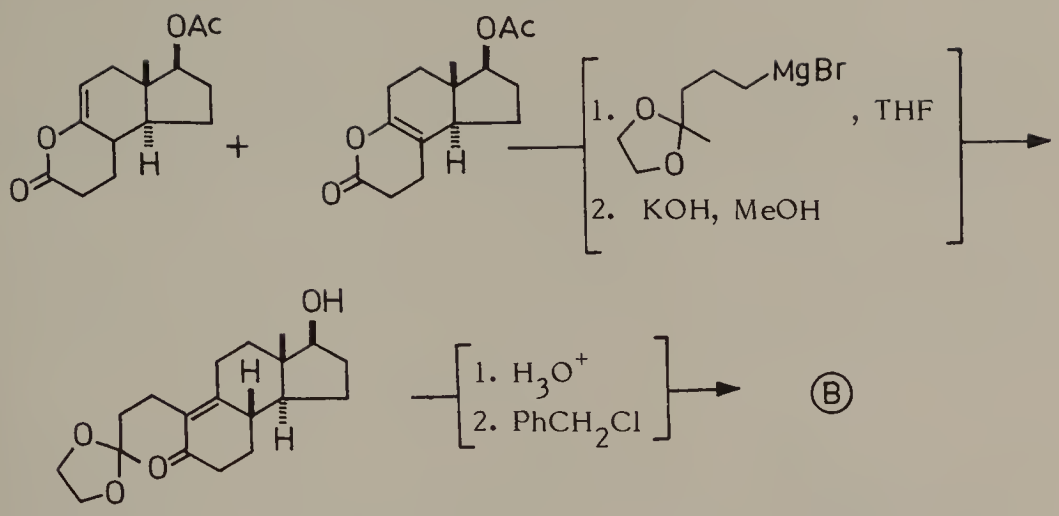
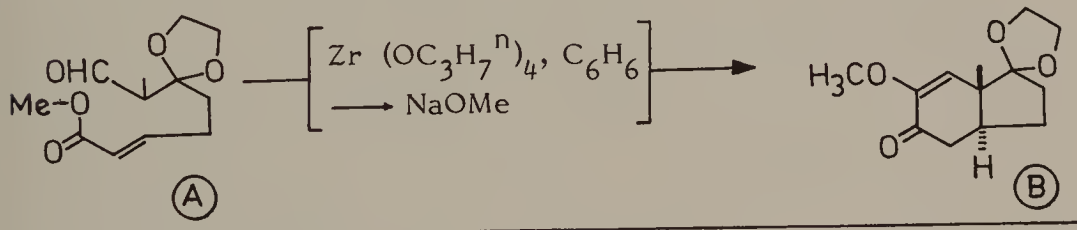
5. In a multistep synthesis the overall yield drops rapidly with the number of successive steps. This results in loss of increasingly expensive intermediates (i). A converging synthesis, on the other hand, is more economical of material in the sense that each product of the reaction sequence is obtained by combination of two precursors delaying the formation of expensive intermediates until a late stage of the synthesis, Velluz,L. Valls,J.; Mathieu,J. Angew. Chem. Int. Ed., 1967, 6, 778.



6. Velluz,L.; Nomine,G.; Amiard,G.; Torelli,V.; Cerede,J. Compt. Rend., 1963, 257, 3086.



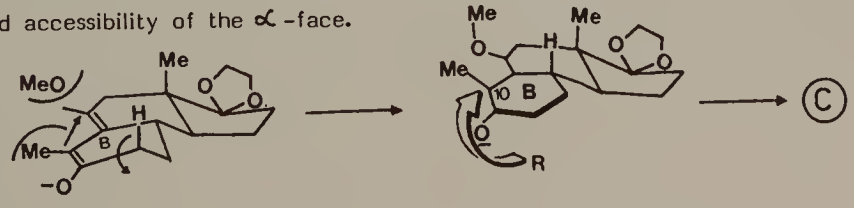
Recently, Stork et al.(7) have described a short and highly stereoselective synthesis of adrenosterone which is based on: (i) the construction of a trans-fused hydrindan by intramolecular Michael addition to control vicinal stereochemistry [transformation A→B] (8); (ii) obtaining the required stereochemistry at C-10 by construction of ring A on B-C-D tricyclic system carrying the C-10 Me and C-11 carbonyl (as enol ether) which direct the alkylation from the ∝-face (9).

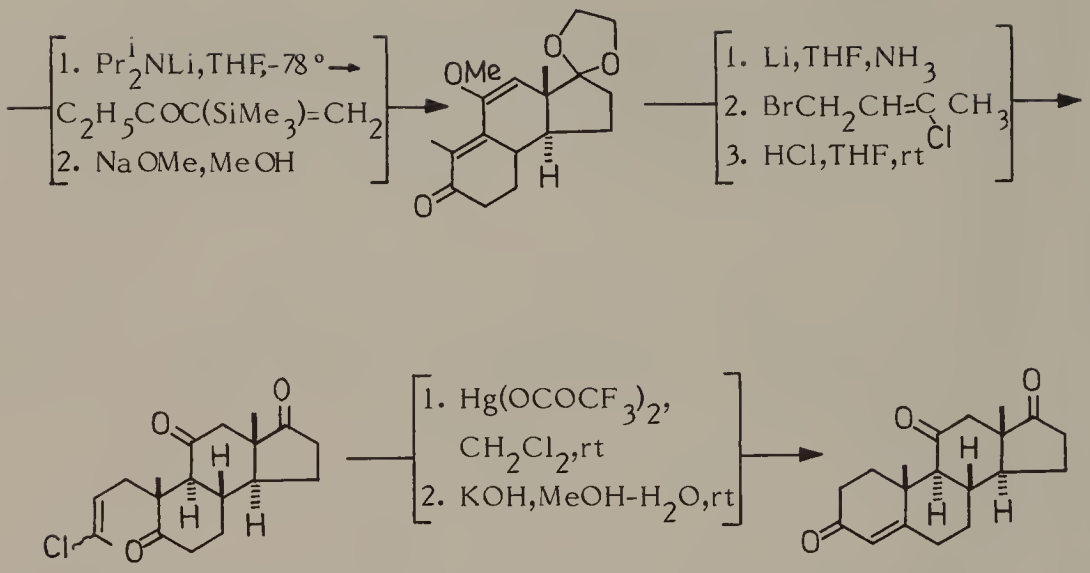


7. Stork, G., Winkler, J.D., Shiner, C.S.; J. Am. Chem. Soc., 1982 , 104, 3767.

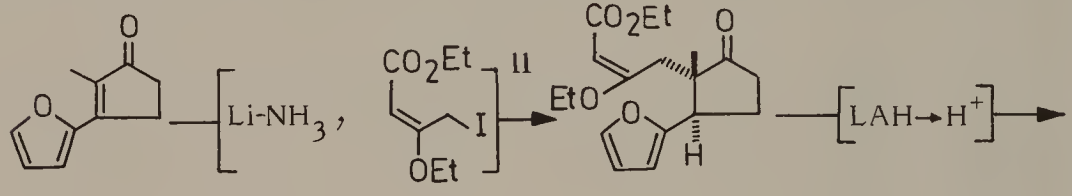
8. Stork, G., Shiner, C.S. and Winkler, J., J. Am. Chem. Soc., 1982 , 104, 310.

9. Previous work (Stork, G. & Logusch, E. J. Am. Chem. Soc., 1980 , 102, 1218, 1219) suggested that the ring B must be twisted into a half-boat conformation to alleviate the severe interaction between the C-10 methyl and the methoxyl group at C-11, with increased accessibility of the ∝-face.





A novel D→BCD→ABCD route to 11-keto steroids described below, has been reported recently (10) which involves a high yield stereoselective intramolecular Diels-Alder reaction of furan-diene [A] as a key step.



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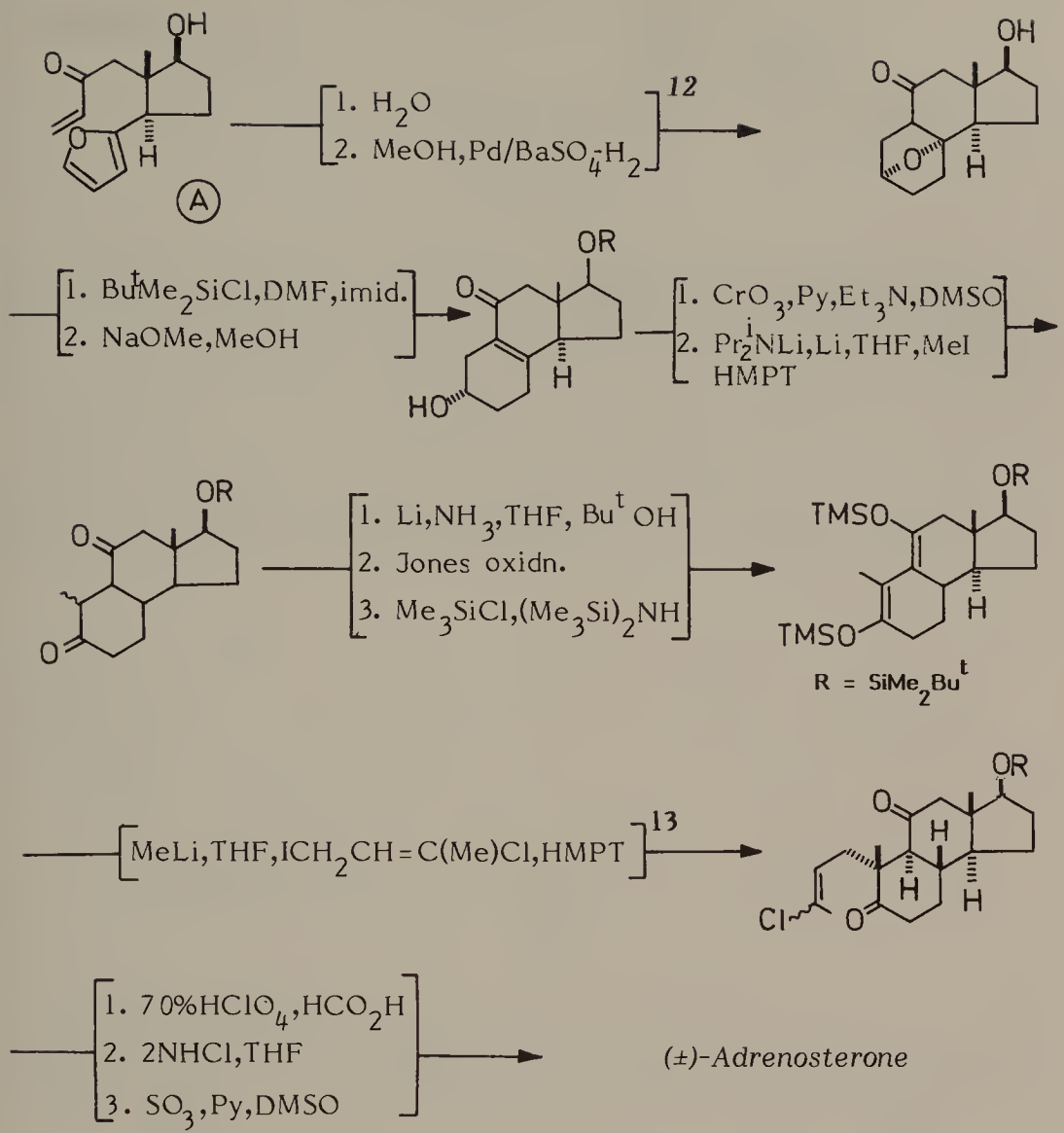
10. Van Royen, L.A., Mijngheer, R.; DeClarcq,P.J.; J. Tetrahedron, 1985, 41, 4667; and earlier references cited therein.

11. The product was obtained in 34% yield after HPLC purification along with 7% of 2,5-dialkylated product.



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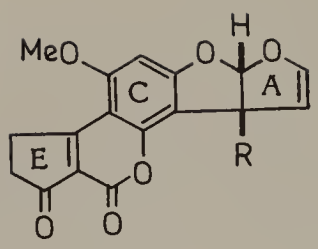
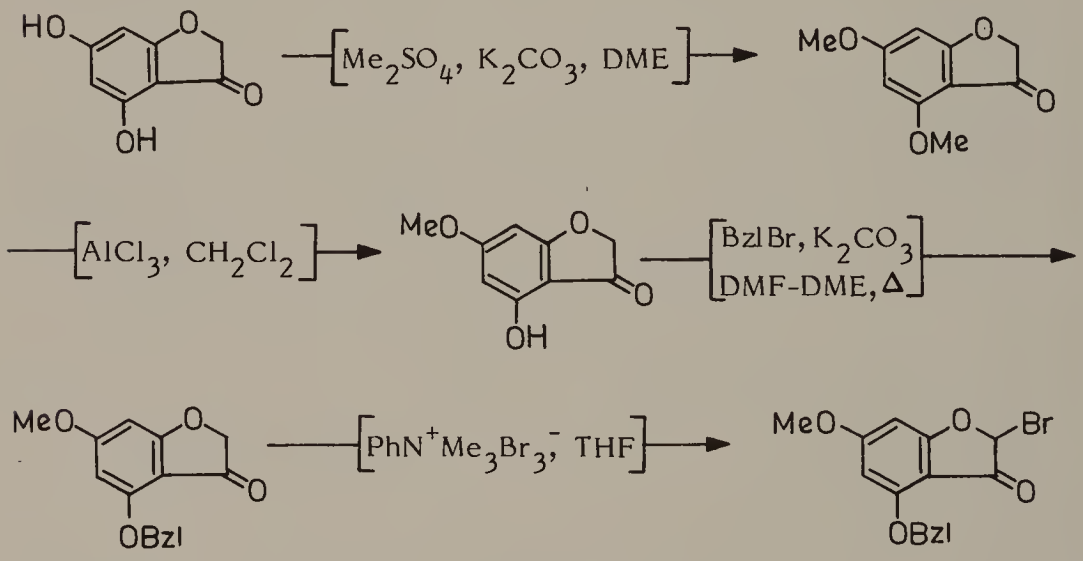
12. The cycloaddition did not proceed in non-polar solvents, presumably due to hydrogen bonding between the hydroxy group and the dienophilic side chain. The addition unexpectedly proceeded at a very fast rate in H_2O [c.f. Rideout, D.C. and Breslow,R. J. Amer. Chem. Soc., 1980, 102, 7816]. The adduct could easily revert back on isolation into organic phase, and it was found expedient to hydrogenate the aqueous emulsion of the adduct dissolved in methanol.

13. Stork *et al* had in their synthesis shown that 11-substituent because of steric bulk directs the introduction of the electrophile from the α-face (9).



AFLATOXINS

The aflatoxins are a group of highly toxic and carcinogenic secondary metabolites produced by a number of strains of Aspergillus and Penicillium species; aflatoxin B and the corresponding oxa homolog Aflatoxin G are the major mycotoxins. Lactating cattle fed on sublethal doses of aflatoxins excrete a hydroxylated metabolite named aflatoxin M (milktoxin). The first chemical synthesis of an aflatoxin reported in 1966 by Büchi & his associates(1) was accomplished in rather low overall yield. Subsequently, Büchi & Weinreb(2) developed an improved route to aflatoxins based on a mild new coumarin synthesis, specially applicable to acid-sensitive phenols, and synthesised aflatoxins M , B & G .



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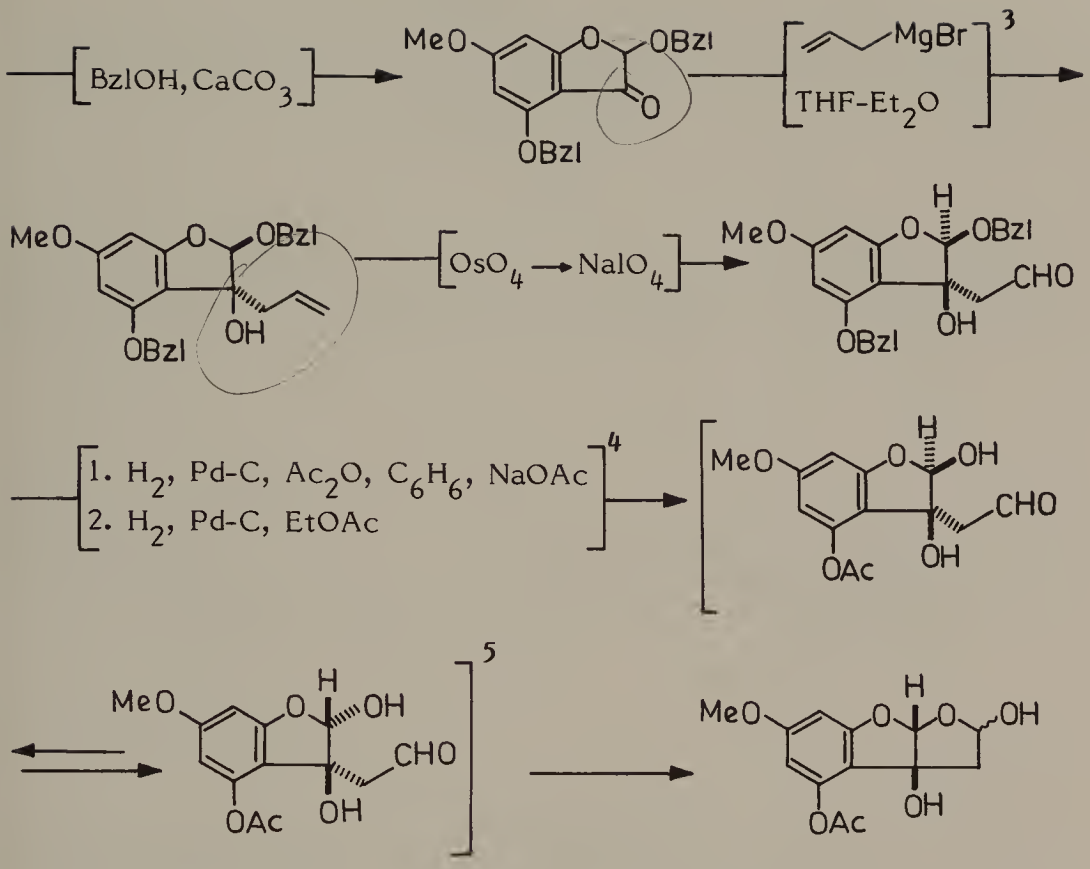
1. Büchi, G., Foulkes, D.M., Kurono, M., Mitchell, G.F., Schneider, R.S. J. Am. Chem. Soc., 1966, 88, 4534; 1967, 89, 6745.

2. Büchi, G., Weinreb, S.M. J. Am. Chem. Soc., 1969, 91, 5408; 1971, 93, 746.



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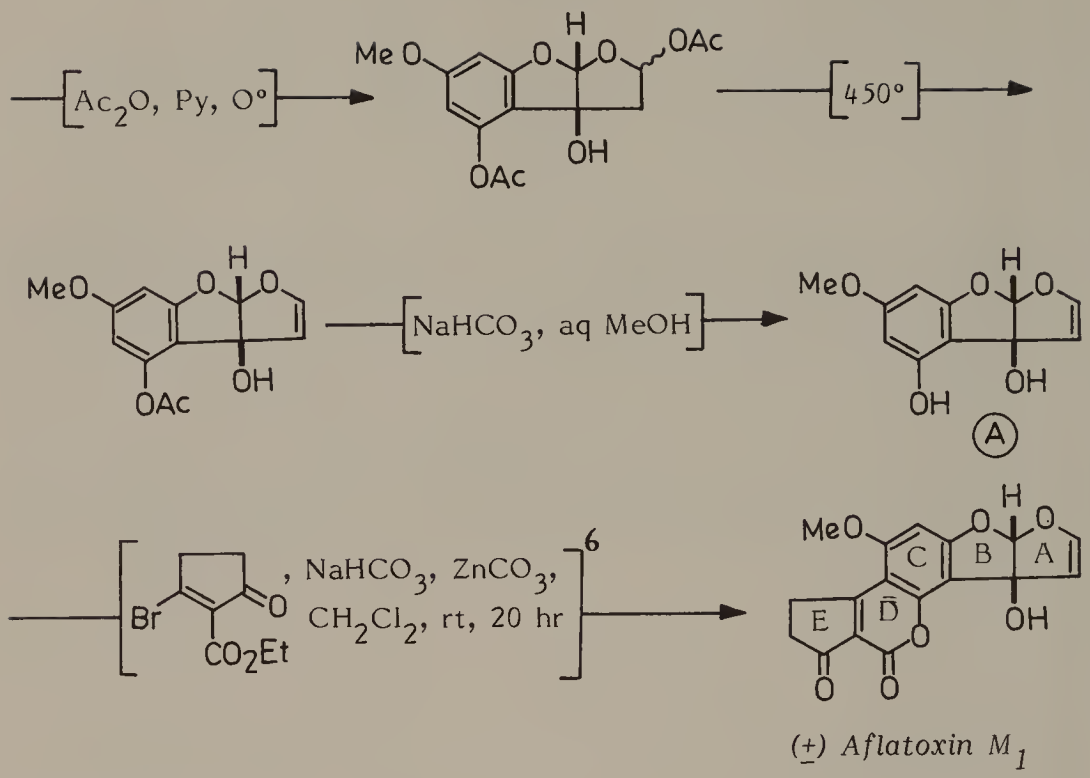
3. The Grignard reagent presumably attacks from the side opposite to that of the bulky benzyloxy group resulting in predominant formation of the trans isomer; see Cram, D.J., Wilson, D.R. J. Amer. Chem. Soc., 1963, 85, 1245, and the two isomers could be separated by chromatography. As both the isomers yielded the same tricyclic product, although the reaction is depicted with one isomer, it was found more practical to use the mixture of epimeric aldehydes for further transformations.

4. The first hydrogenation cleaves the benzyl group on the aromatic ring to give a monoacetate, which is further hydrogenated in a different solvent for removal of the second benzyl group.

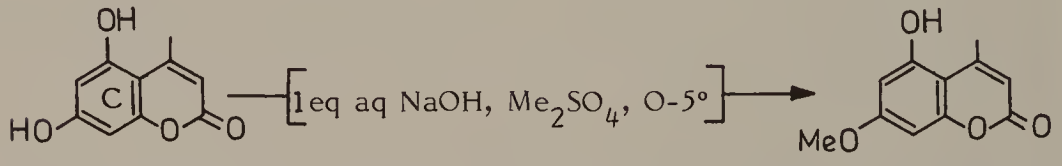
5. The more stable cis-ring fused furobenzofuran is favored over the trans-fused system.



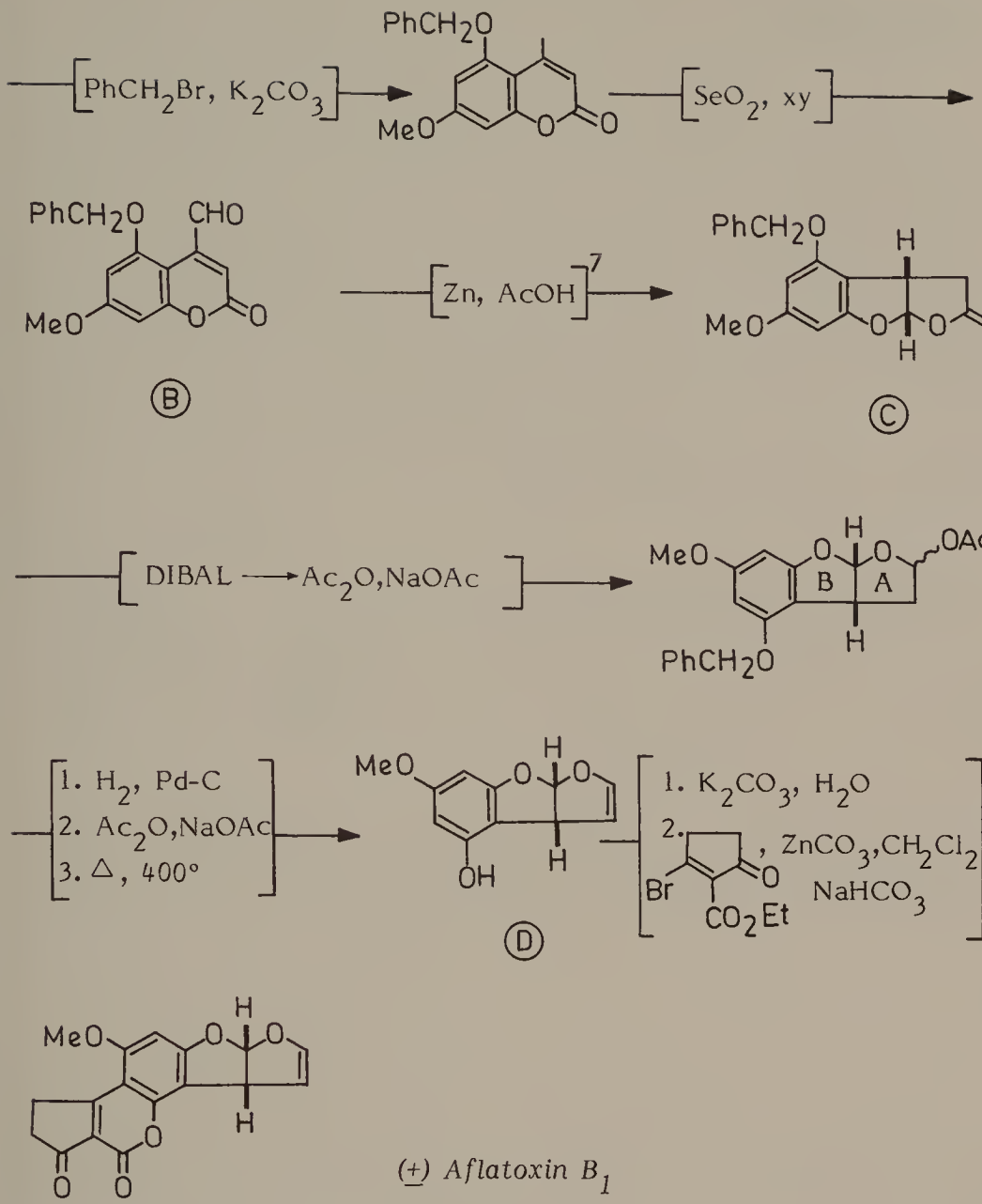
(±) Aflatoxin M_1

Aflatoxin B_1

For the synthesis of aflatoxin B_1 the key intermediate furo[2,3-b] benzofuran (C) was obtained by β-acyl lactone rearrangement of the 4-formylcoumarin (B) (1).



6. Owing to exceptional sensitivity of the tricyclic phenol (A) to acidic reagents, direct condensation with 2-carbethoxycyclopentane-1,3-dione under von Pechmann coumarin synthesis conditions proved impossible. However, 3-bromo-2-carbethoxycyclopent 2-enone readily underwent condensation to give the desired coumarin ring D when zinc carbonate was used both as catalyst and acid scavenger.



(±) *Aflatoxin* B_1

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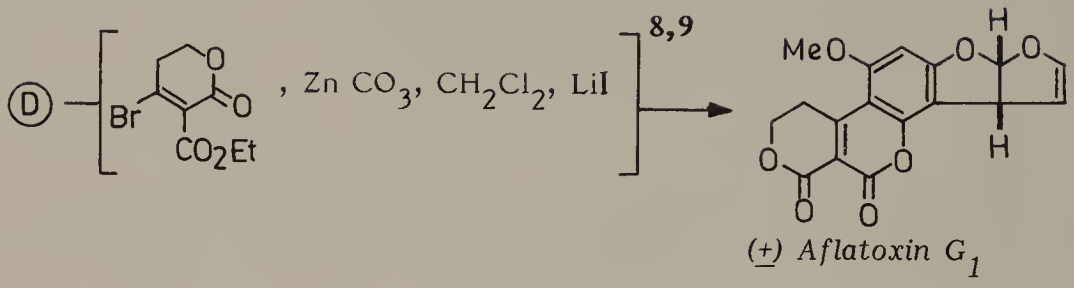
7. This rearrangement involves opening of the δ-lactone and formation of a new ring through the hydroxyl and the enolized carbonyl of the β-acyl group, Lawson, A. J. Chem. Soc., 1957, 144; Lange, C., Wamhoff, H., Korte, F. Ber. 1967, 100, 2312.

Aflatoxin G_1



(±) Aflatoxin G_1

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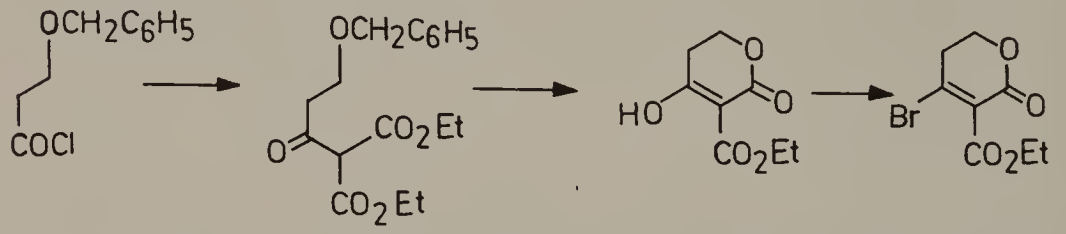
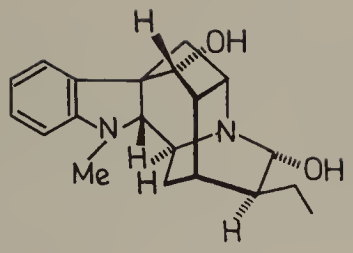
8. The bromo-lactone was prepared as follows :

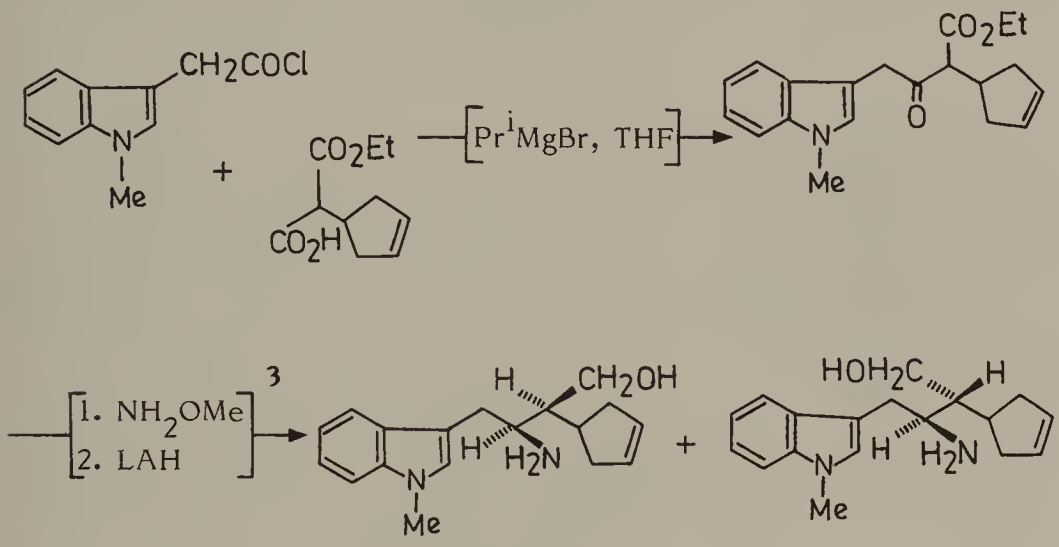


9. The bromolactone had low reactivity, and the addition of finely powdered anhydrous LiI improved the yield significantly.



AJMALINE

Possessing six rings and nine asymmetric centres, ajmaline(1) presented a big challenge for total synthesis. In the first synthesis by Masamune et al(2) the characteristic quinuclidine ring of ajmaline was obtained by an oxidative scission of a cyclopentene-containing precursor [A] and cationoid cyclization of the resulting dialdehyde to give the key tetracyclic aldehyde [B].



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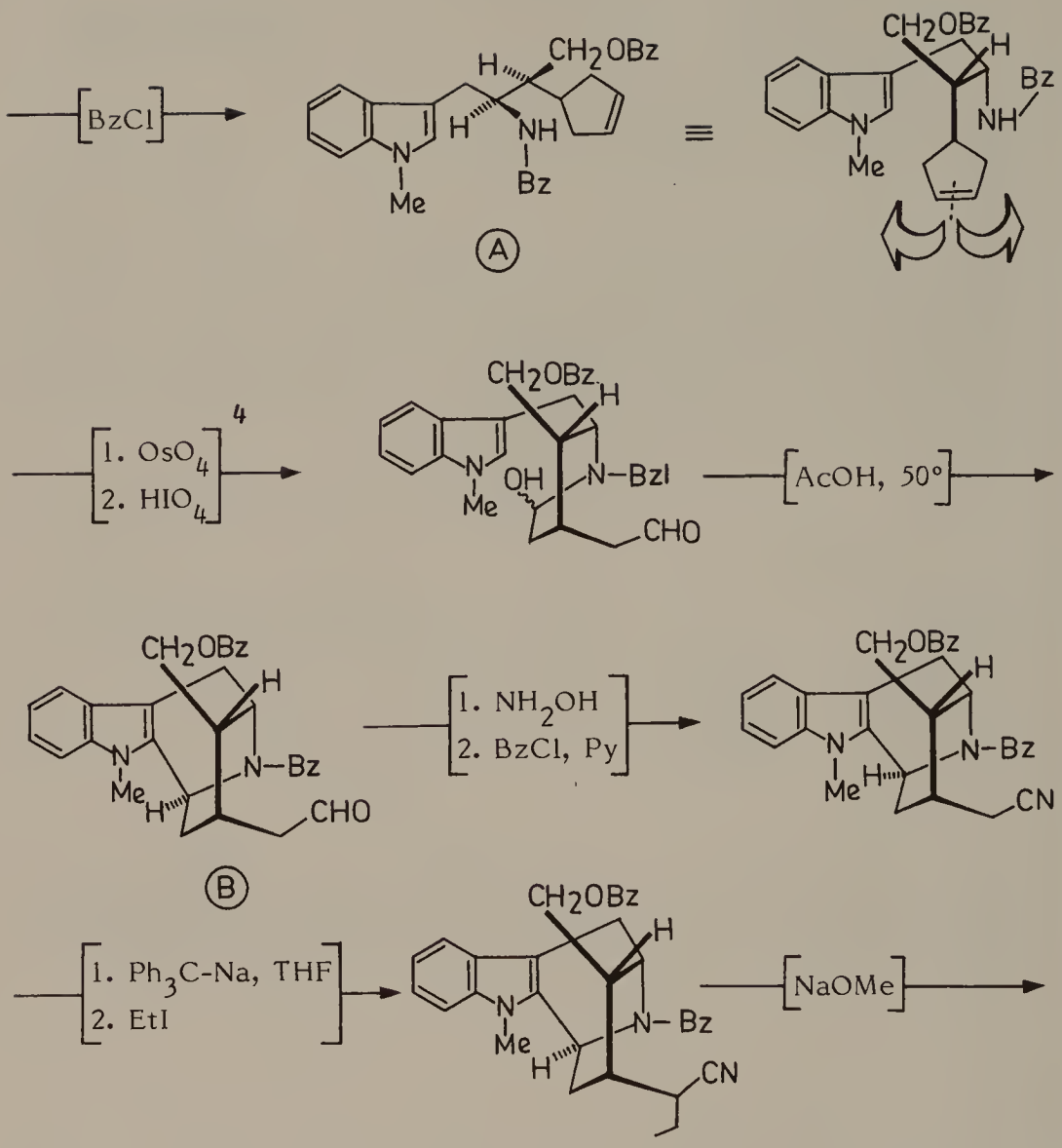
1. Named in memory of Hakim Ajmal Khan, a great physician of the Unani system in India in early this century; Siddiqui, S., Siddique, R.H. J. Ind. Chem. Soc., 1931, 8, 667.

2. Masamune, S., Ang, S.K., Egli, C., Nakatsuka, N., Sarkar, S.K., Yasunari, Y. J. Am. Chem. Soc., 1967, 89, 2506.

3. A 2:1 mixture of epimeric alcohols is produced in the reaction. However, both epimeric series are useful for synthesis, and are interconvertible at a later stage. The reaction sequence with only one epimeric amino alcohol is shown.



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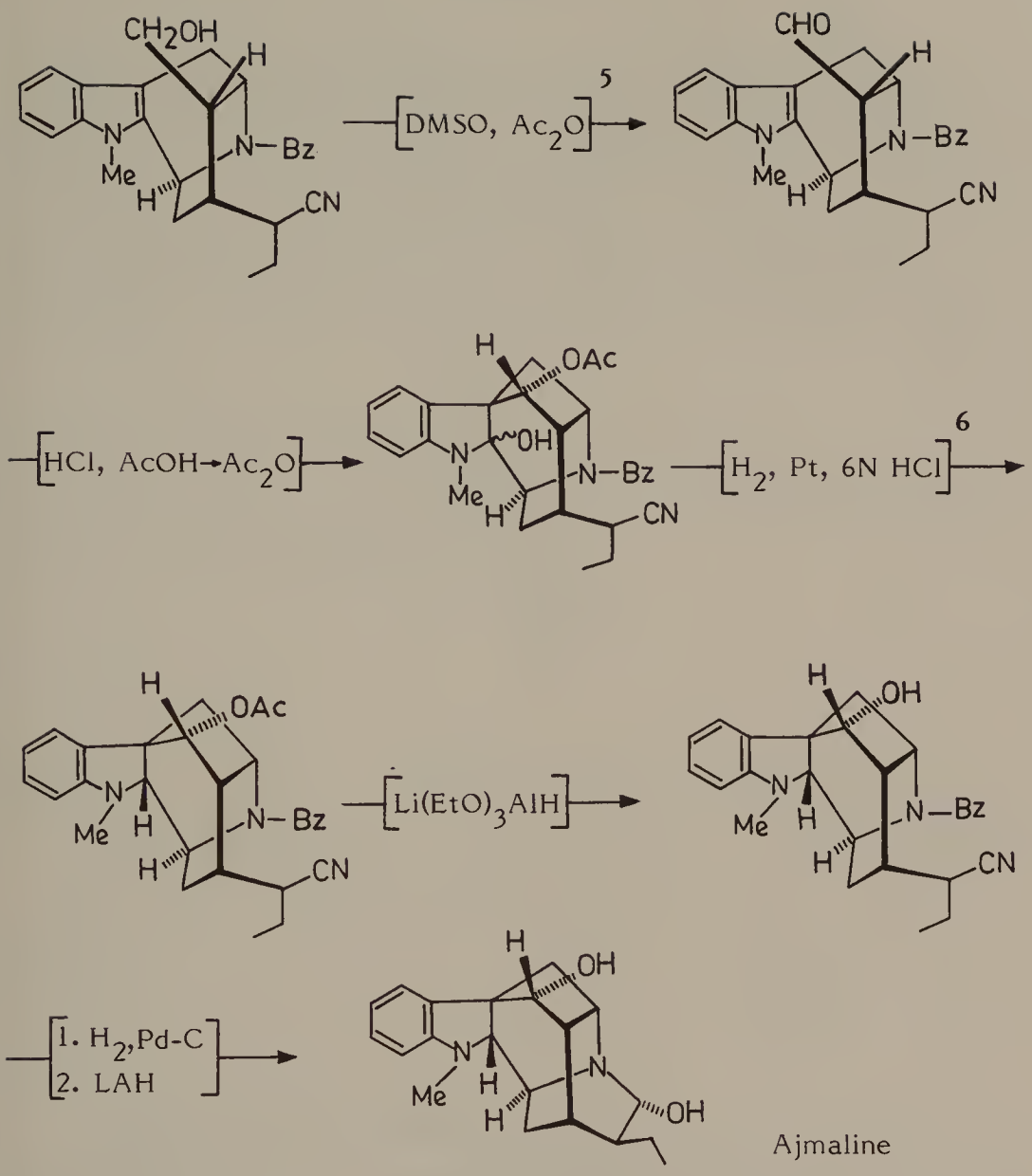
4. The preparation of dialdehydes by this procedure was utilised in earlier indole alkaloid synthesis: (a) van Tamelen, E.E., Shamma, M., Burgstahler, A.W., Wolinsky, J., Tamm, R., Aldrich, P.E. J. Am. Chem. Soc., 1958, 80, 5006; van Tamelen, E.E.,Dolby,L.J., Lawton, R.G. Tet. Letters, 1960, 19, 30.



Ajmaline

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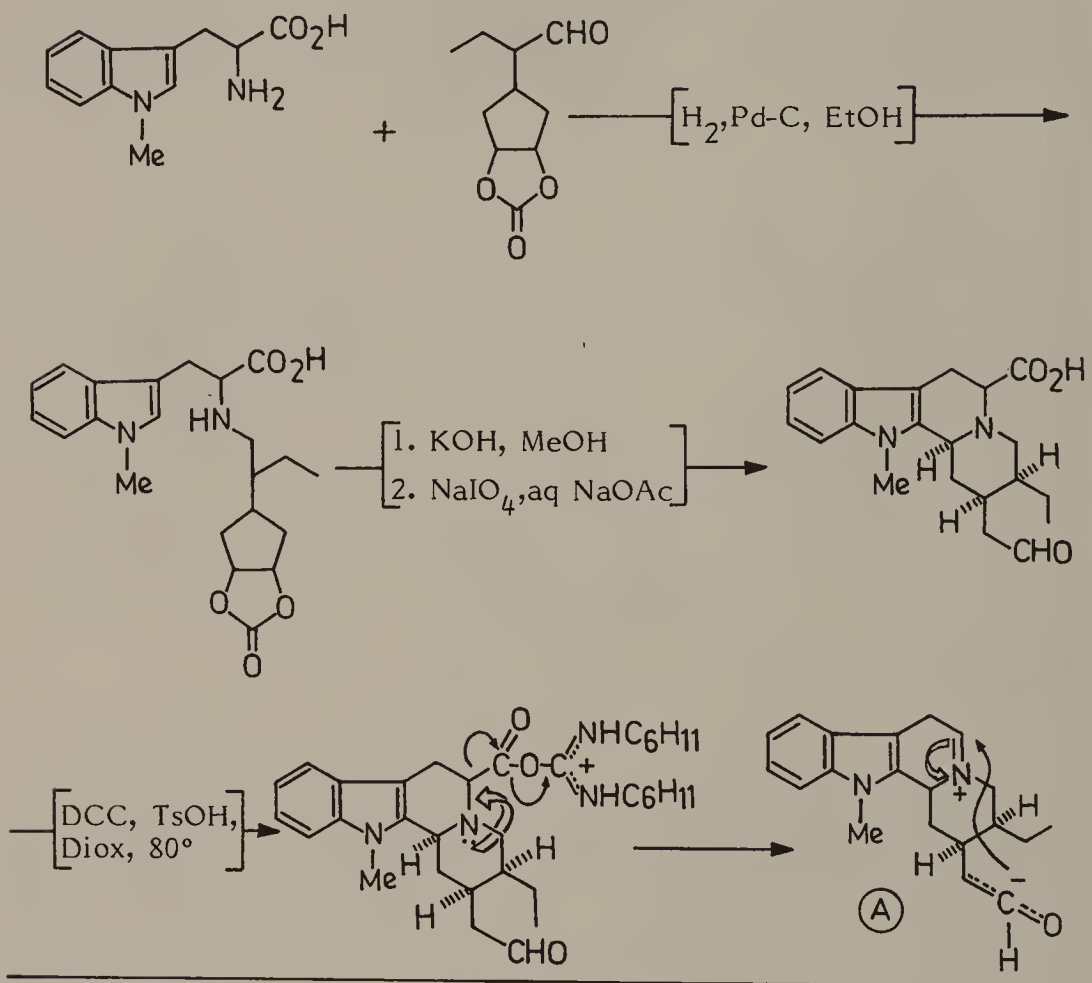
5. Fenselau, A.H., Moffat, J.G. J. Am. Chem. Soc., 1966, 88, 1762.

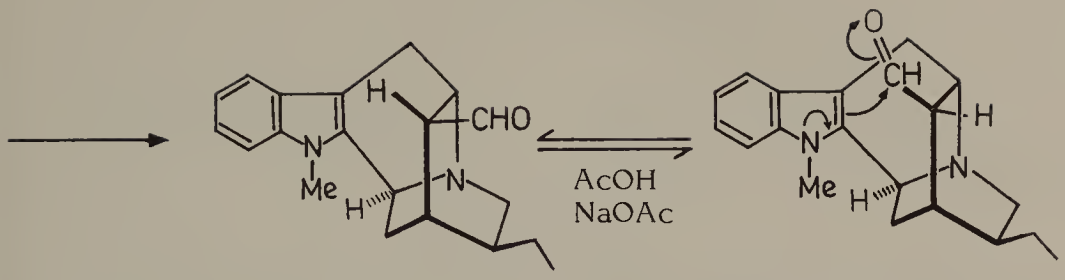
6. Since there is very little difference in steric hindrance between α and β sides of the molecule towards catalytic hydrogenation, reduction proceeds mainly from the α-side if the nitrogen is not protected (presence of a protonated nitrogen on α-side) giving the 2-epi series of ajmaline-type compounds. In order to encourage β-attack, therefore, reduction was carried out on the benzoylated amine, and this resulted in the exclusive formation of a compound of the normal series.

The biogenetic-type synthesis by van Tamelen & Oliver(7) commences from N-methyltryptophan and a suitable "C9" precursor, incorporating a dihydroxycyclopentene nucleus which serves as a latent dialdehyde functionality. The iminium salt [A] required for the critical C-5, C-16 bond formation was generated by an ingenious decarbonylation reaction(8) of β-carboline-carboxylic acid. Final stages of the synthesis utilise the known deoxyajmalal-A → 21-deoxyajmaline transformation(9), and functionalisation of the latter at C-21 by a phenyl chloroformate ring opening-oxidative ring closure sequence(10)

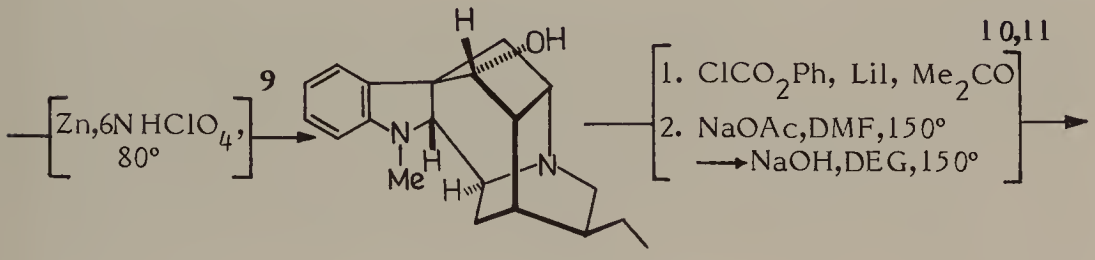


7. Van Tamelen,E.E., Oliver,L.K., J. Amer. Chem. Soc., 1970, 92, 2136; Bioorganic Chemistry, 1976, 5, 309.

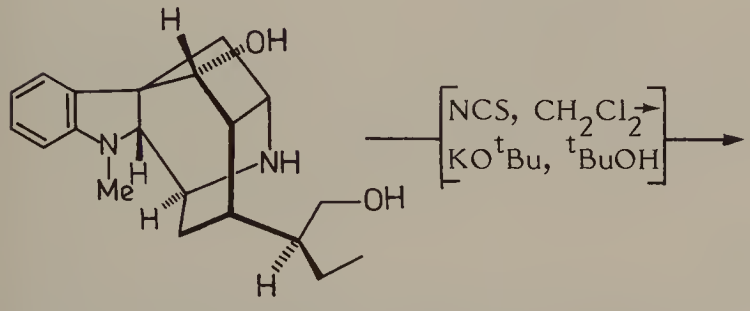
8. Maksimov,V.I., Tetrahedron, 1965, 21, 687.



Deoxyajmalal-B *Deoxyajmalal-A*



21-Deoxyajmaline



Ajmaline

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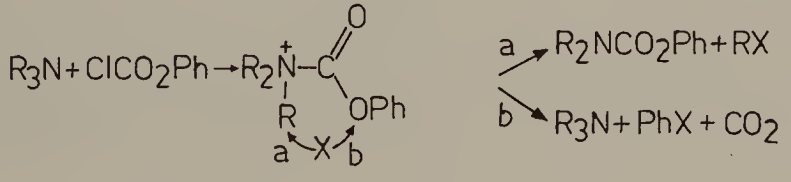
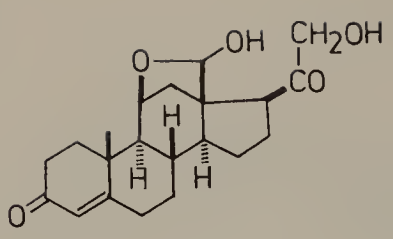
9. Bartlett, M.F., Lambert, B.F., Werblood, H.M., Taylor, W.I. J. Amer. Chem. Soc., 1963, 85, 475.

10. Hobson, J.D., McCluskey, J.G. J. Chem. Soc., 1967, 2015.

11. The reaction of phenyl chloroformate with tertiary aliphatic and alicyclic amines to give the corresponding N-carboxylates (pathway a) is an efficient general procedure for cleavage of tertiary amines under mild conditions, and provides a convenient alternative to the well-known von Braun cyanogen bromide cleavage. The choice of phenyl chloroformate over alkyl esters in this reaction probably results in suppression of the undesired competitive reaction pathway b.

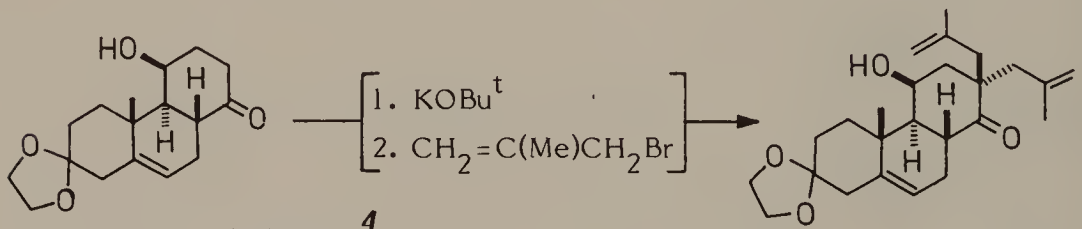




ALDOSTERONE

Aldosterone occurs in such minute quantities in natural sources that supplies of this highly active material have relied heavily upon the development of total and partial synthesis of the hormone (1,2).

The synthesis by Heusler, Wieland and Wettstein (3), outlined below, is based on a key intermediate from Sarett's cortisone synthesis representing ring A, B and C, and upon this the rings D and E of aldosterone have been built. Introduction of the asymmetric centres at C-13, C-14 and C-17 has been carried out by an extension of the asymmetry at C-11 to C-13 (A), stereospecific hydrogenation of the 14,15-double bond (B) and a kinetically controlled ketonization of the $\Delta^{17(20)}$ -enol (C) for obtaining the β -oriented hydroxy-acetone side chain at C-17.



Sarett's tricyclic ketone[4]

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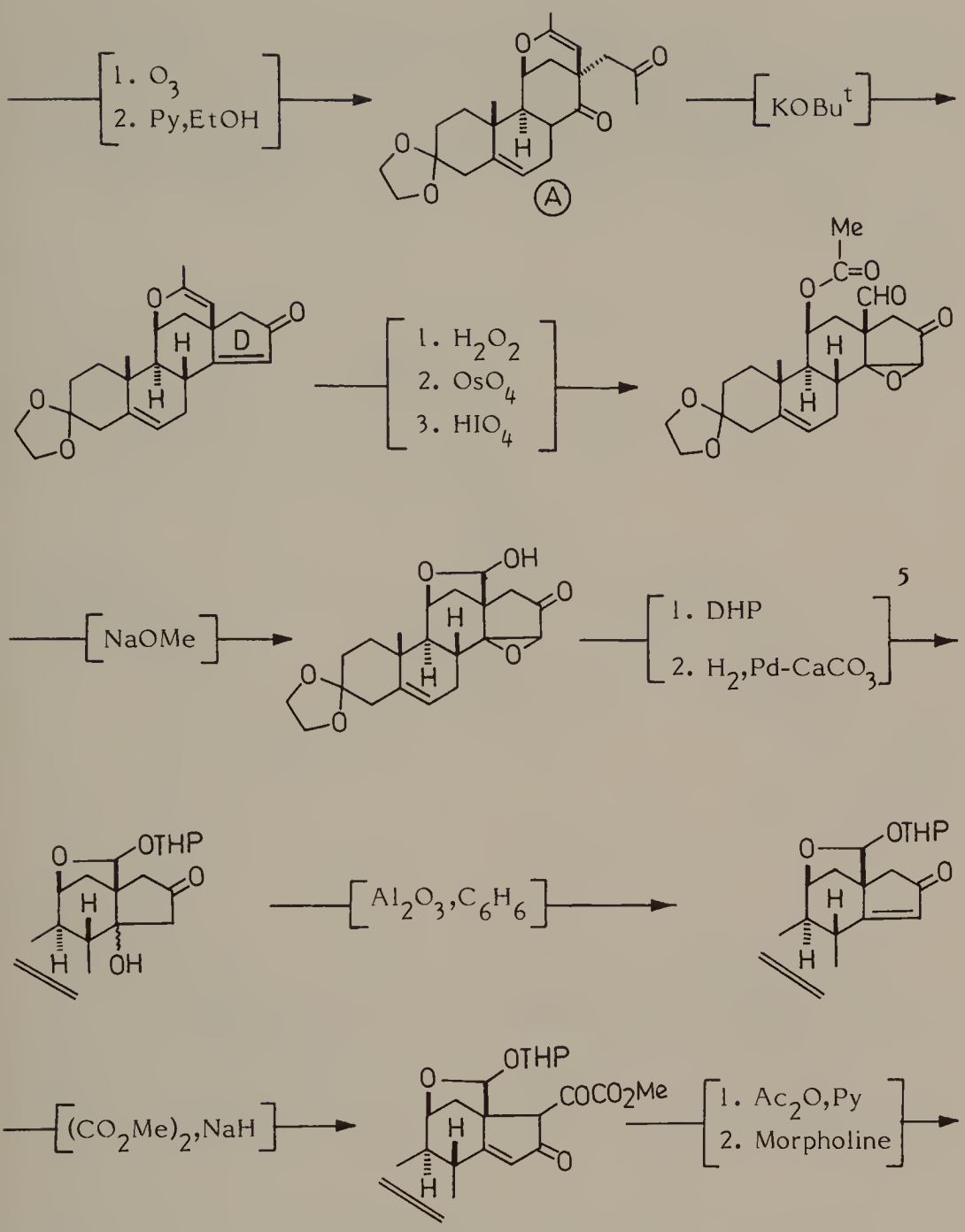
1. Indeed, so urgent was the problem that aldosterone by total synthesis became the objective of a joint effort of no less than four notable group of workers of Basel, Zurich and Oss. The first synthesis was achieved by Wettstein,A.et al.at Ciba; the synthesis outlined above is a modification of the original sequence announced by these workers in 1955. For an engrossing account of the early history of aldosterone synthesis, see: Fieser,L.F.; Fieser,M. in "Steroids", Reinhold, New York (1959), p.713. Amongst other synthesis of aldosterone may be mentioned the synthesis of D-homoaldosterone, which could be converted to aldosterone; Szpilfogel,S.A.; Van Der Burg,W.J.; Siegmann,C.M.; Van Dorp,D.A. Rec. Trav. Chim., 1958, 77, 157, 171.

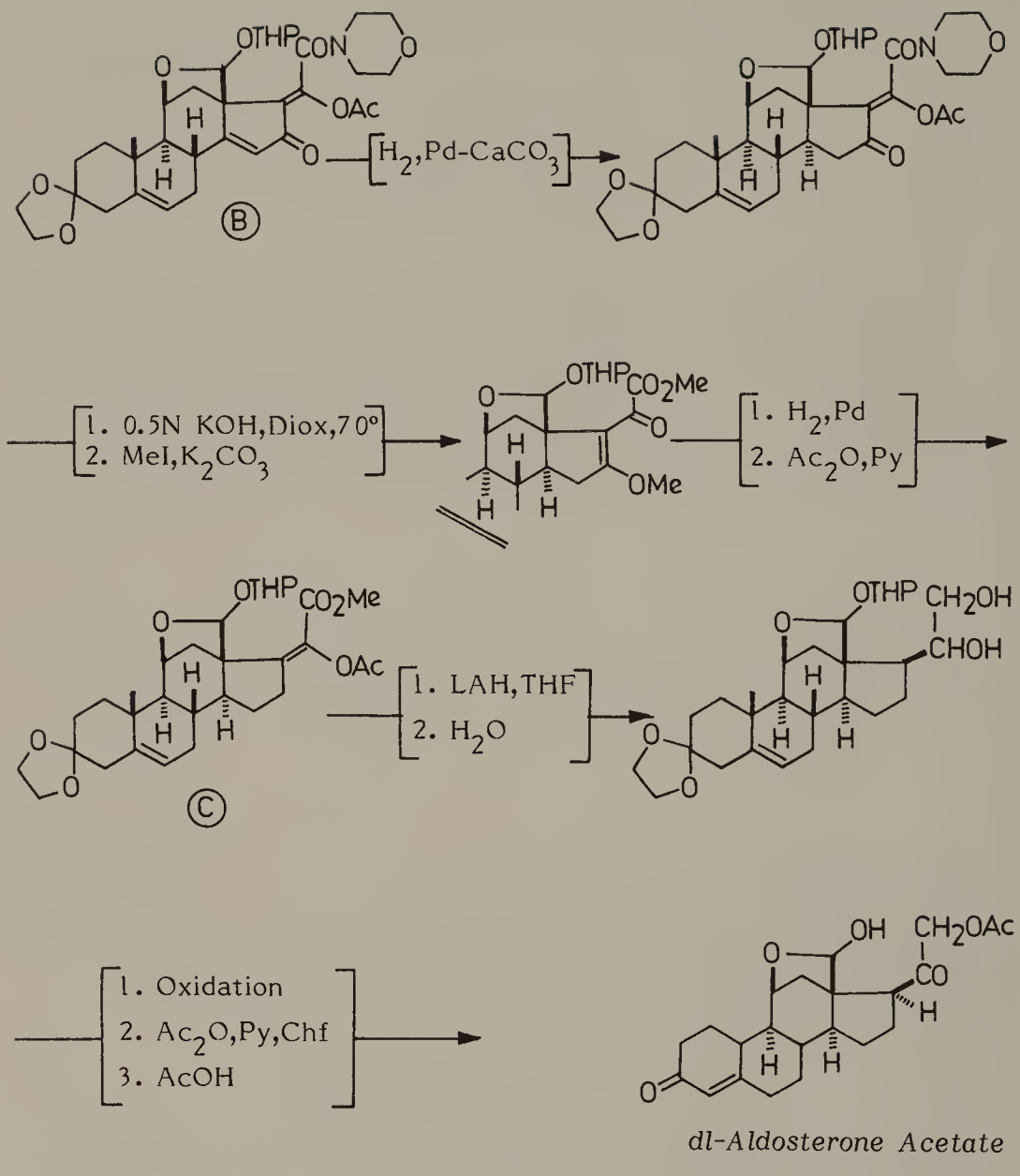
2. Aldosterone is one of those rare examples in which the partial practical synthesis of a complex natural product was realized long after the successful execution of a total synthesis. Since the partial synthesis of aldosterone from steroid precursors entails the functionalizing of an unactivated angular methyl group, many new and ingenious methods have been developed for selectively functionalizing the C-18 methyl group by intramolecular transfer substitution procedures such as of nitrile transfer (12); for a review of the earlier work see: Schaffner,K.; Arigoni,D.; Jeger,O. Experientia, 1960, 16, 169.

3. Heusler,K.; Wieland,P.; Wettstein,A. Helv. Chim. Acta, 1959, 42, 1586.

4. See under synthesis of cortisone.

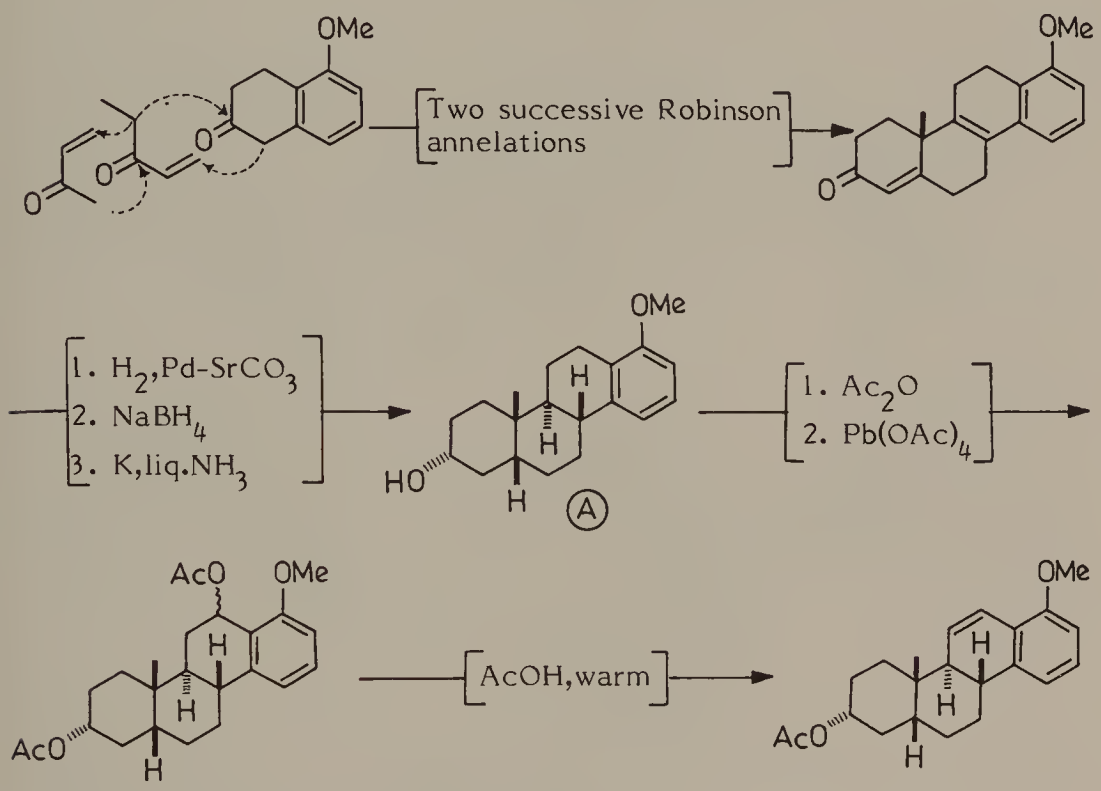


5. The 18,11ß-cyclohemiacetal was preserved throughout the synthesis as a tetrahydropyranyl ether.



dl-Aldosterone Acetate

Johnson and his colleagues(6-10)described a highly stereoselective total synthesis of aldosterone using the "hydrochrysene approach". Introduction of the 11β-hydroxyl in (A) is based on a method developed earlier at Wisconsin for the production of 11-oxygenated steroids (10). Material for completing the hemiacetal ring has been obtained by an oxidative fission of ring D in the homosteroid (B).



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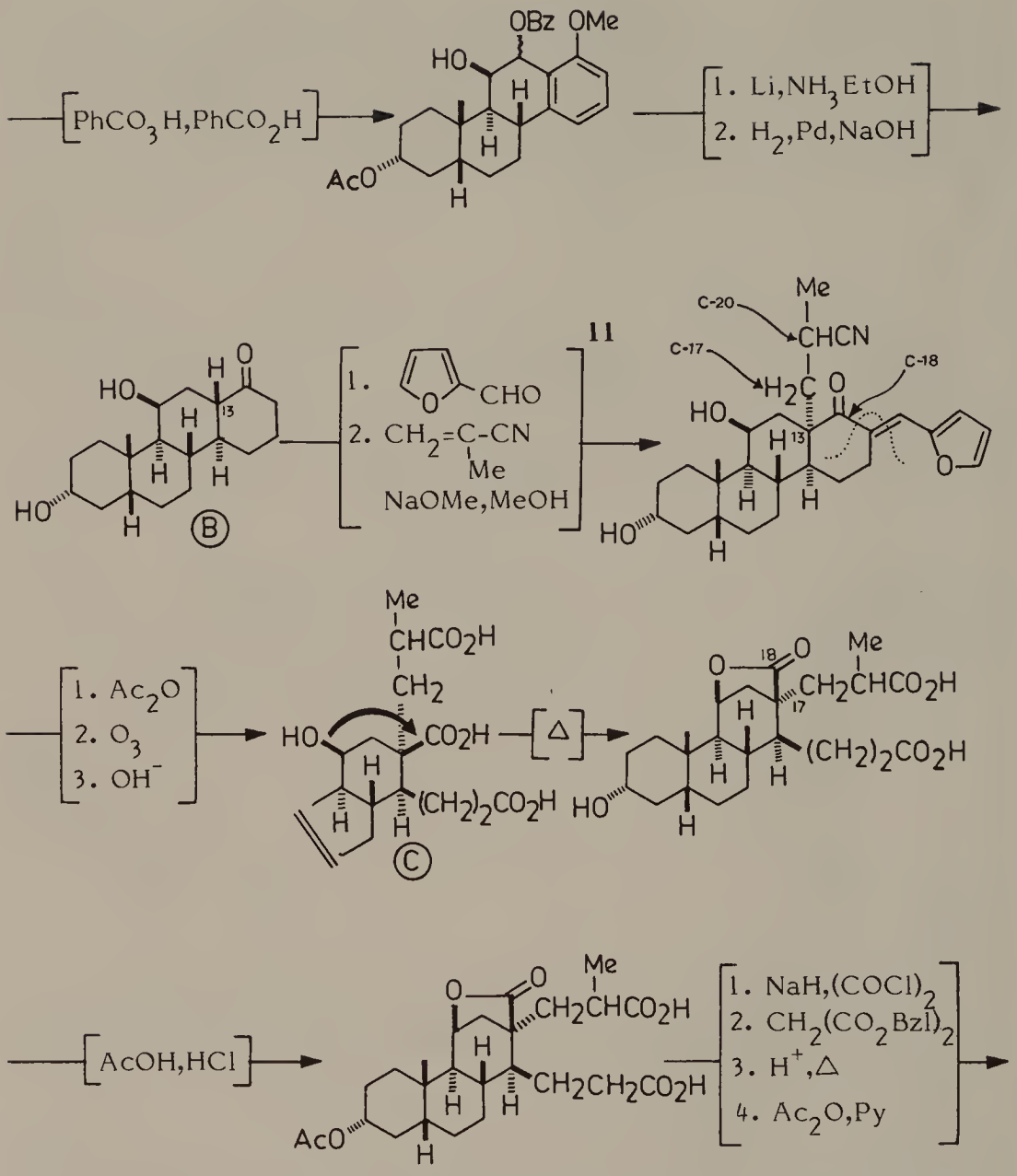
6. Johnson,W.S.; Collins,J.C.; Pappo,R.; Rubin,M.B. J. Am. Chem. Soc., 1958, 80, 2585; Johnson,W.S.; Collins,J.C.; Pappo,R.; Rubin,M.B.; Kropp,P.J.; Johns,W.F.; Pike,J.E.; Bartmann,W. ibid, 1963, 85, 1409.

7. Johnson,W.S.; Szmuszkovicz,J.; Rogier,E.R.; Hadler,H.I.; Wynberg,H. J. Am. Chem. Soc., 1956, 78, 6285.

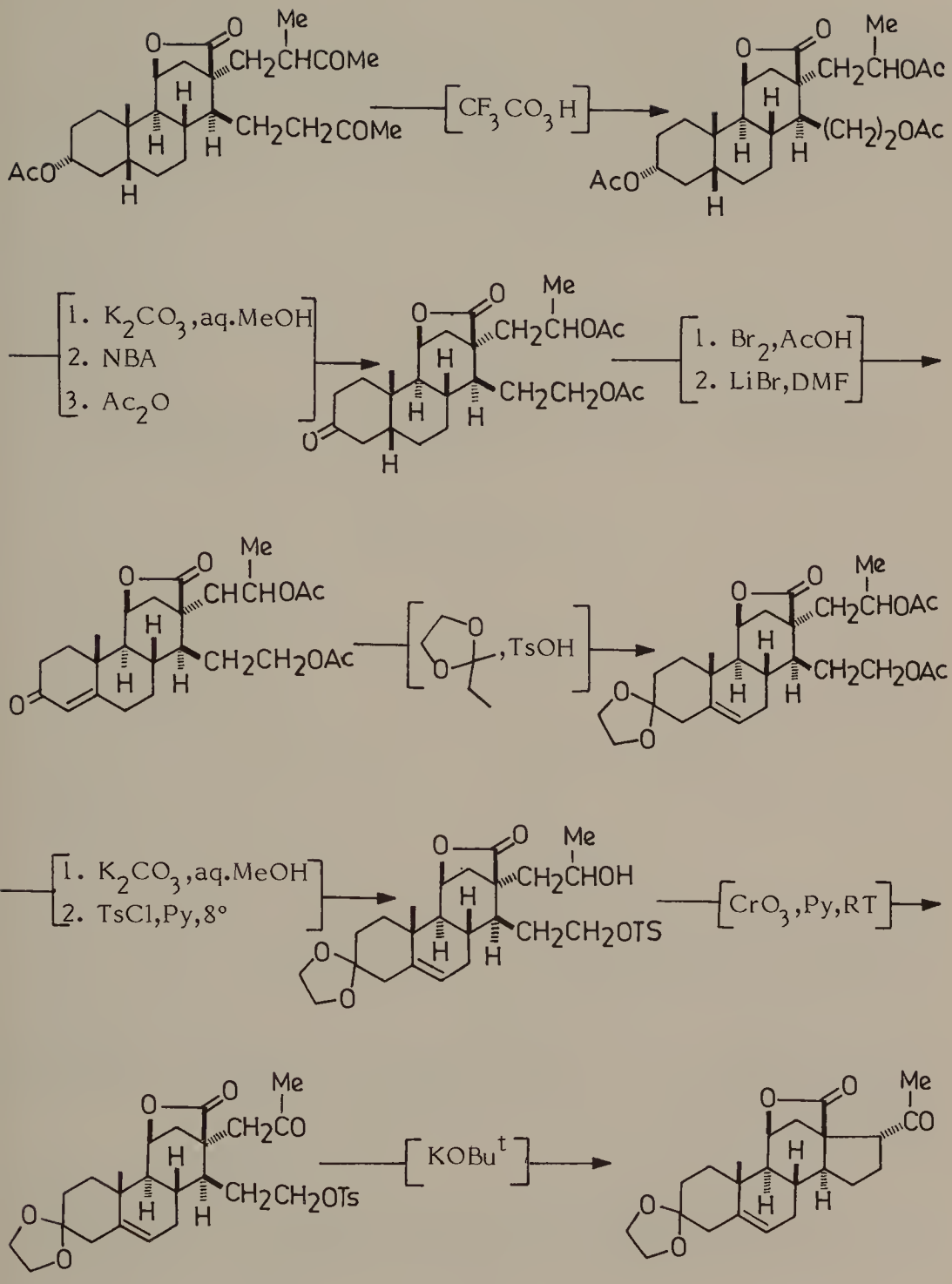
8. Johnson,W.S.; Rogier,E.R.; Szmuszkovicz,J.; Hadler,H.I.; Ackerman,J.; Bhattacharyya,B.K.; Bloom,B.M.; Stalmann,L.; Clement,R.A.: Bannister,B.; Wynberg,H. J. Am. Chem. Soc., 1956, 78, 6289.

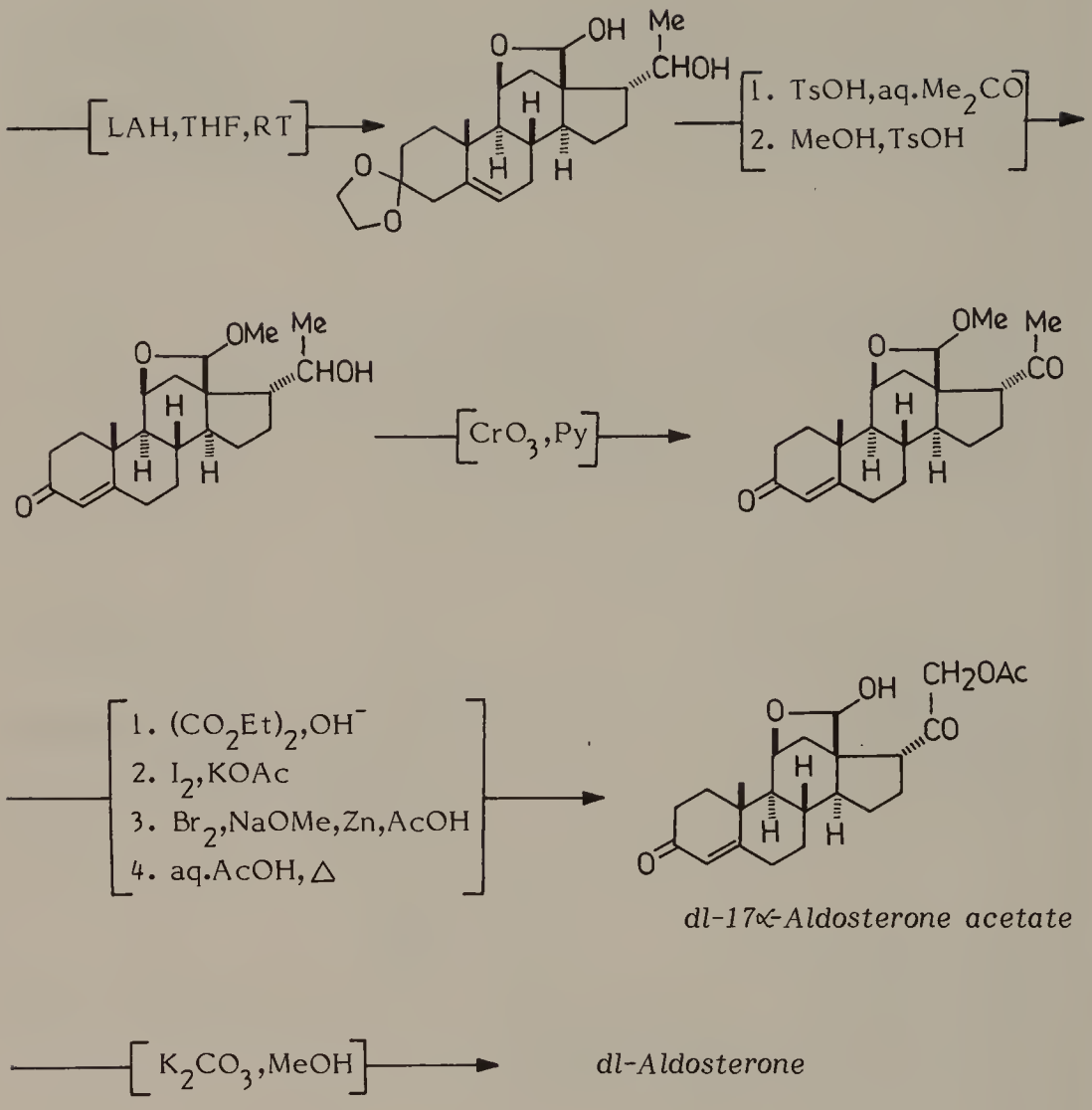
9. Johnson,W.S.; Kemp,A.D.; Pappo,R.; Ackermann,J.; Johns,W.F. J. Am. Chem. Soc., 1956, 78, 6312.

10. Johnson,W.S.; Pappo,R.; Johns,W.F. J. Am. Chem. Soc., 1956, 78, 6339.



11. Introduction of the angular substituent in the tetracyclic D-homosteroid (B) results in a C/D-cis ring fusion with the alkylating group attached to C-13 in an α-orientation, thus totally unsuited for incorporation as the 11,13α-oriented ring E. The incoming α-alkylating group was therefore destined to serve as the C-17 hydroxyacetone side chain and it befell the newly formed β-oriented C-13 carboxyl group, obtained during oxidative fission of ring D, to serve as C-18 of aldosterone.


Me
CH2CHCOMe
CH2CH2COMe
AcO
CF3CO3H
CH2CHOAc
(CH2)2OAc
1. K2CO3,aq.MeOH
2. NBA
3. Ac2O
1. Br2,AcOH
2. LiBr,DMF
CHCHOAc
,TsOH
1. K2CO3,aq.MeOH
2. TsCl,Py,8°
CH2CHOH
CH2CH2OTS
CrO3,Py,RT
CH2CO
CH2CH2OTs
KOBut
CO



dl-17α-Aldosterone acetate

dl-Aldosterone

Barton and Beaton (12,13) reported a three step synthesis of aldosterone acetate from cortisone acetate by functionalisation of 18-CH_3 by photolytic transfer of a nitrite group (2).

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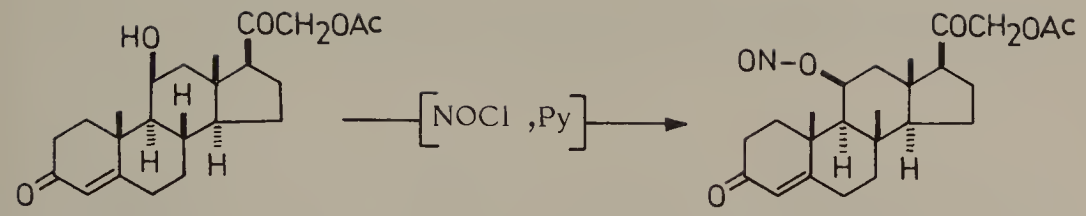
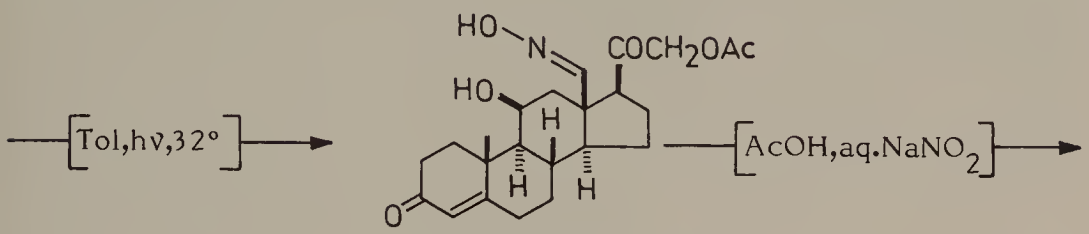
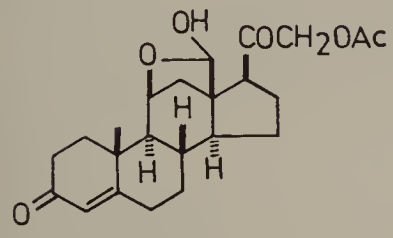
12. Barton,D.H.R.; Beaton,J.M. J. Am. Chem. Soc., 1960, 82, 2641; ibid, 1961, 83, 4083.
13. For a detailed photochemical transfer reaction see: Barton,D.H.R.; Beaton,J.M.; Geller, L.E.; Pechet,M.M. J. Am. Chem. Soc., 1960, 82, 2640; 1961, 83, 4076.



Corticosterone acetate

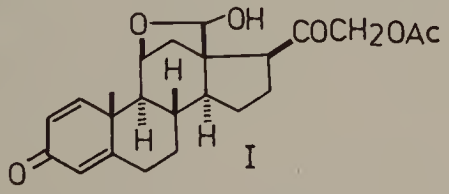


aldosterone acetate oxime



aldosterone 21-acetate

The overall yield in this reaction was rather low, on account of the competition between C-19 and C-18 functionalisation. In a further refinement of this method, it was observed that photolysis of the nitrites of the corresponding 1,2-dehydro derivatives resulted in almost exclusive C-18 functionalisation, and thus afforded greatly improved yields of aldosterone through 1,2-dehydro-(I) and of 1,2,6,7-didehydro-(II) aldosterone 21-acetates (14).



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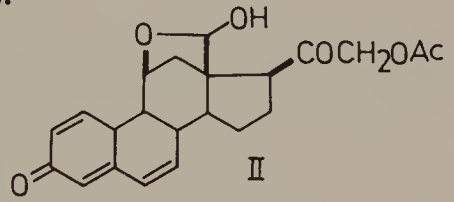

II

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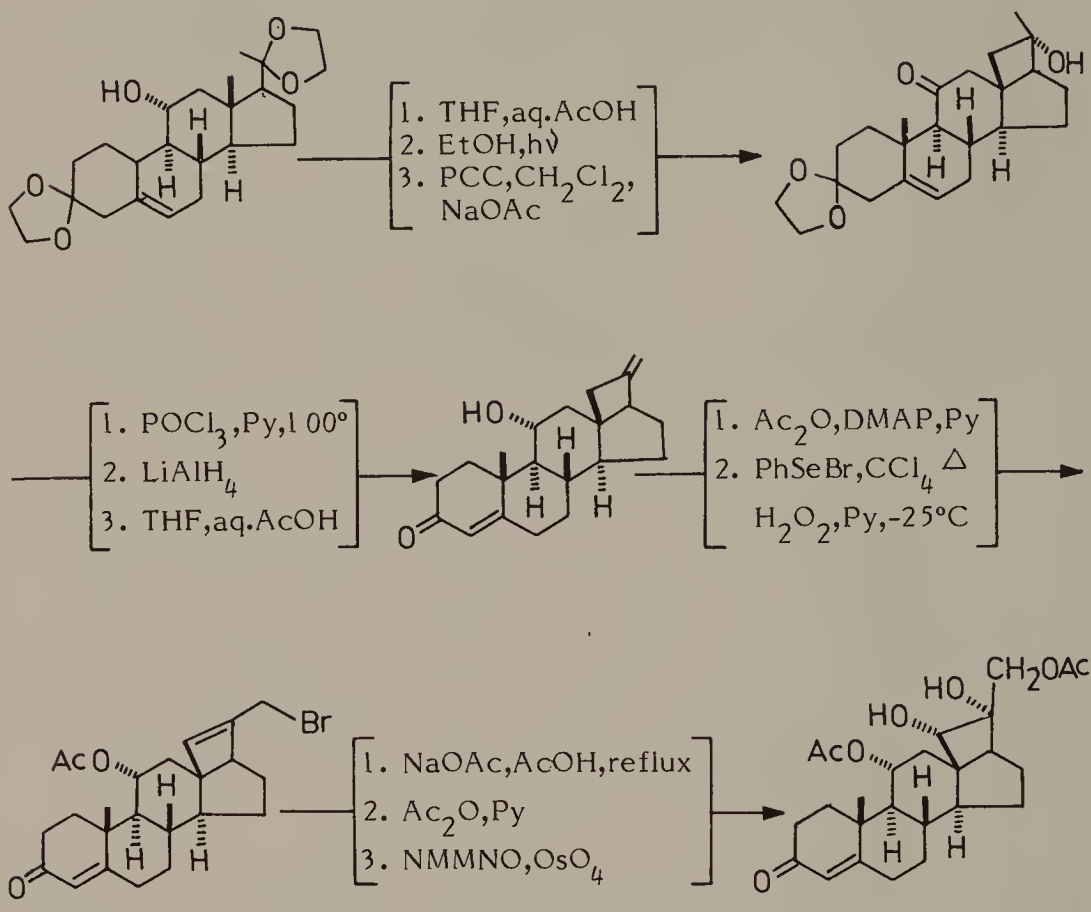
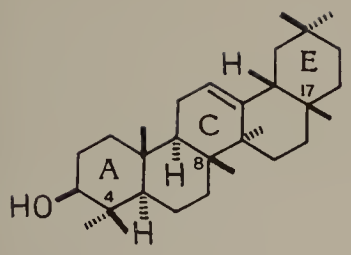
14. Barton,D.H.R.; Basu,N.K.; Day,M.J; Hesse,R.H.; Pechet,M.M.; Starratt,A.N.J. Chem. Soc. Perkin Trans., 1975, 2243.

Miyano (15) has more recently described an efficient synthesis of aldosterone. from 20-hydroxy-18,20-cyclosteroids.

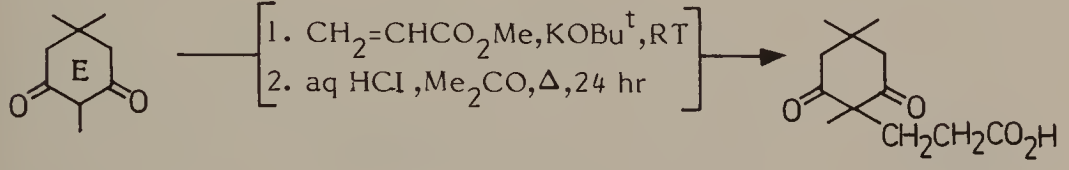


15. Miyano,M. J. Org. Chem., 1981, 46, 1846.



AMYRIN

A general approach to the oleanane skeleton has been the construction of a tetracyclic (AB-DE) system (1) in which ring C is completed by an internal cationic cyclization reaction (3-5). The synthesis of 18α-olean-12-ene (C) based on this approach is described below (2). The remaining task of introducing a β-hydrogen at C-18 and a 3β-hydroxyl into the pentacyclic system (C) has been accomplished by Barton and his colleagues (7), thus completing a total synthesis of β-amyrin. Introduction of the oxygen function in ring A has been accomplished by a novel photolytic exchange process (8) involving a functional derivative based on the ring C olefinic linkage.



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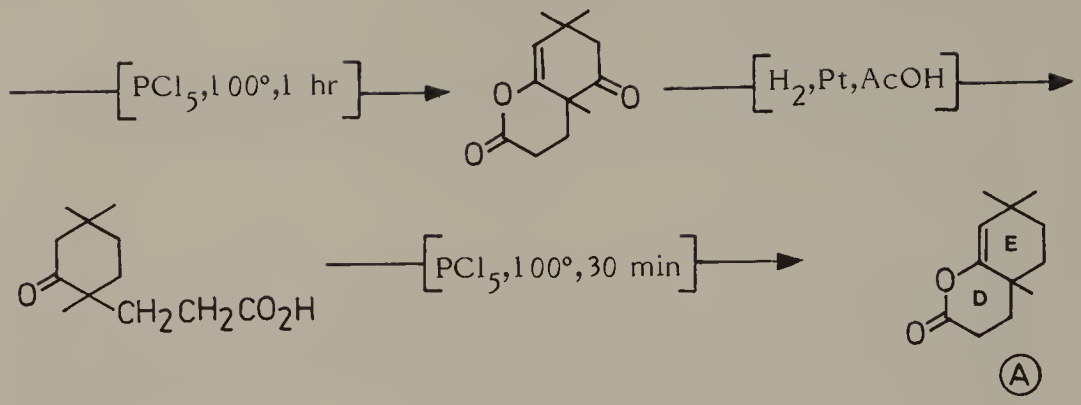
1. This approach, which was first suggested by Halsall and Thomas, provides an admirable solution to the problem of introducing the vicinal C-8 and C-14 methyl groups, an otherwise difficultly accessible feature of ring C. The desired anti-trans arrangement of rings B,C and D is obtained during cyclization when a carbonium ion is generated at C-8, Halsall,T.G.; Thomas,D.B. J. Chem. Soc., 1956, 2431.

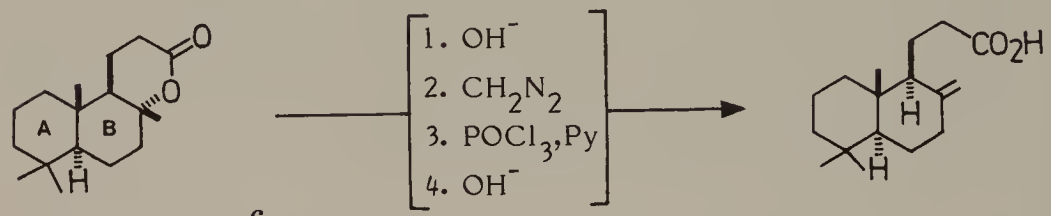
2. The outlined synthesis is a composite of the efforts of groups of workers; the steps leading to the key tetracyclic ketone (B) are taken from Corey's synthesis of olean-11,12,13,18-diene (ref.3) while subsequent steps leading to the pentacyclic skeleton are from the synthesis of Barltrop et al (ref.4); Ghera and Sondheimer (5) have also synthesised this intermediate by a similar approach.

3. Corey,E.J.; Hess,H.J.; Proskow,S. J. Am. Chem. Soc., 1959, 81, 5258; 1963, 85, 3979.

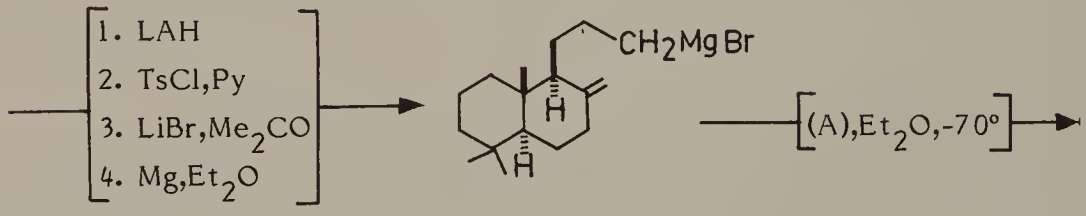
4. Barltrop,J.A.; Littlehailes,J.D.; Rushton,J.D.; Rogers,N.A.J. Tetrahedron Lett., 1962, 429.

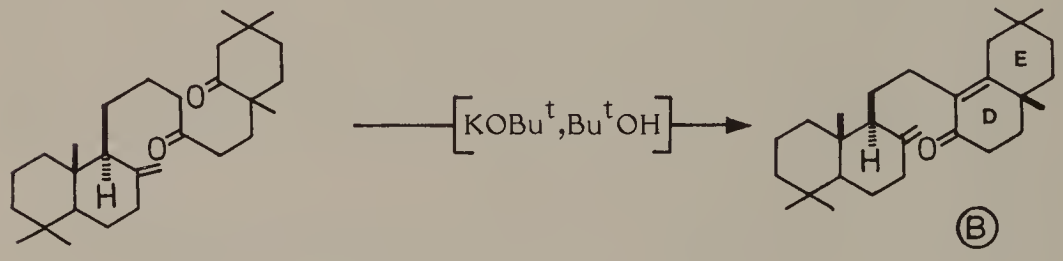
5. Ghera,E.; Sondheimer,F. Tetrahedron Lett., 1964, 3887.





(+)-Ambreinolide[6]





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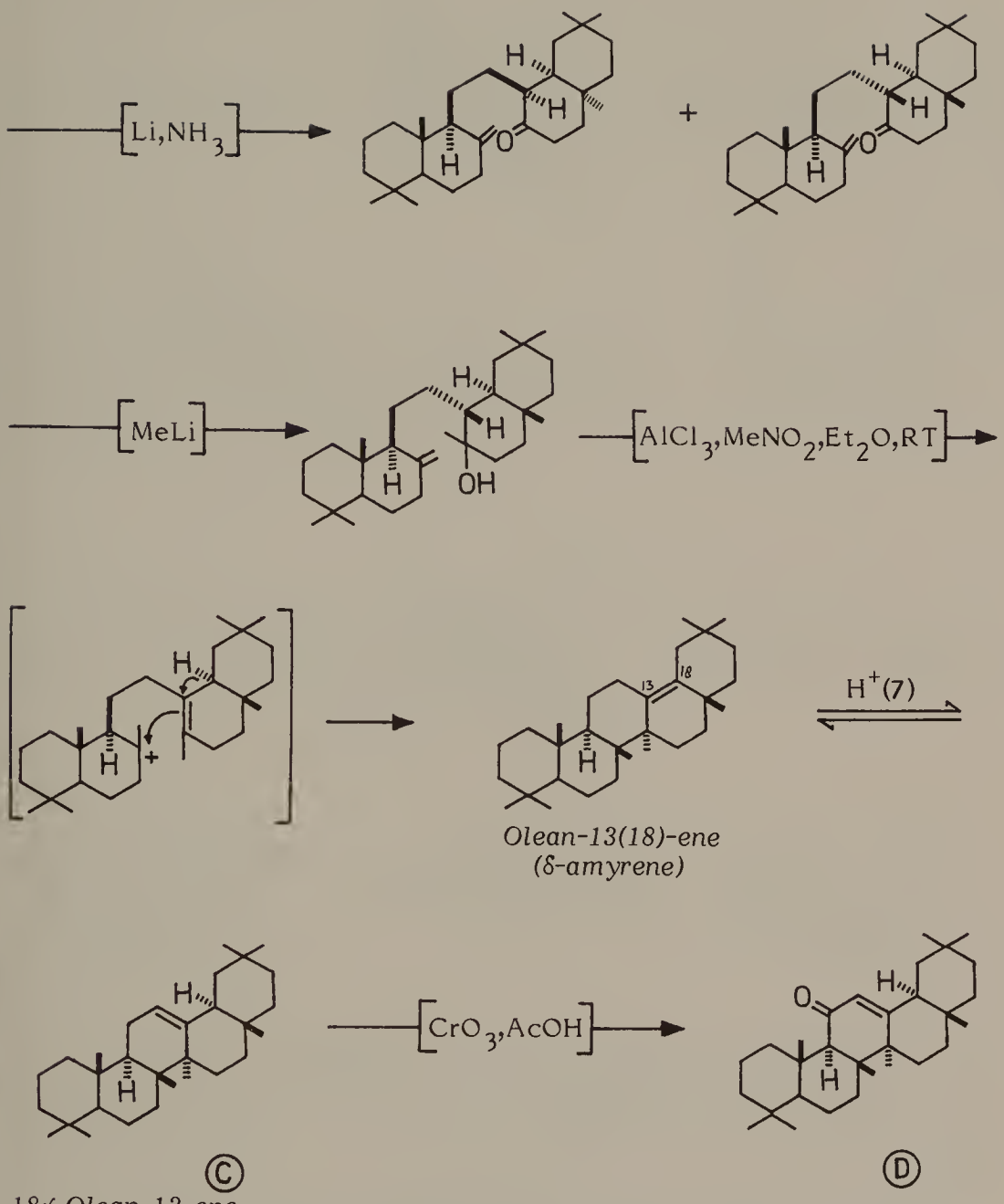
6. For a total synthesis of (±)-ambreinolide, see Dietrich,P., Lederer,E., Helv. Chim. Acta, 1952, 35, 1148.



Olean-13(18)-ene
(δ-amyrene)

Ⓒ
18α-Olean-12-ene

Ⓓ

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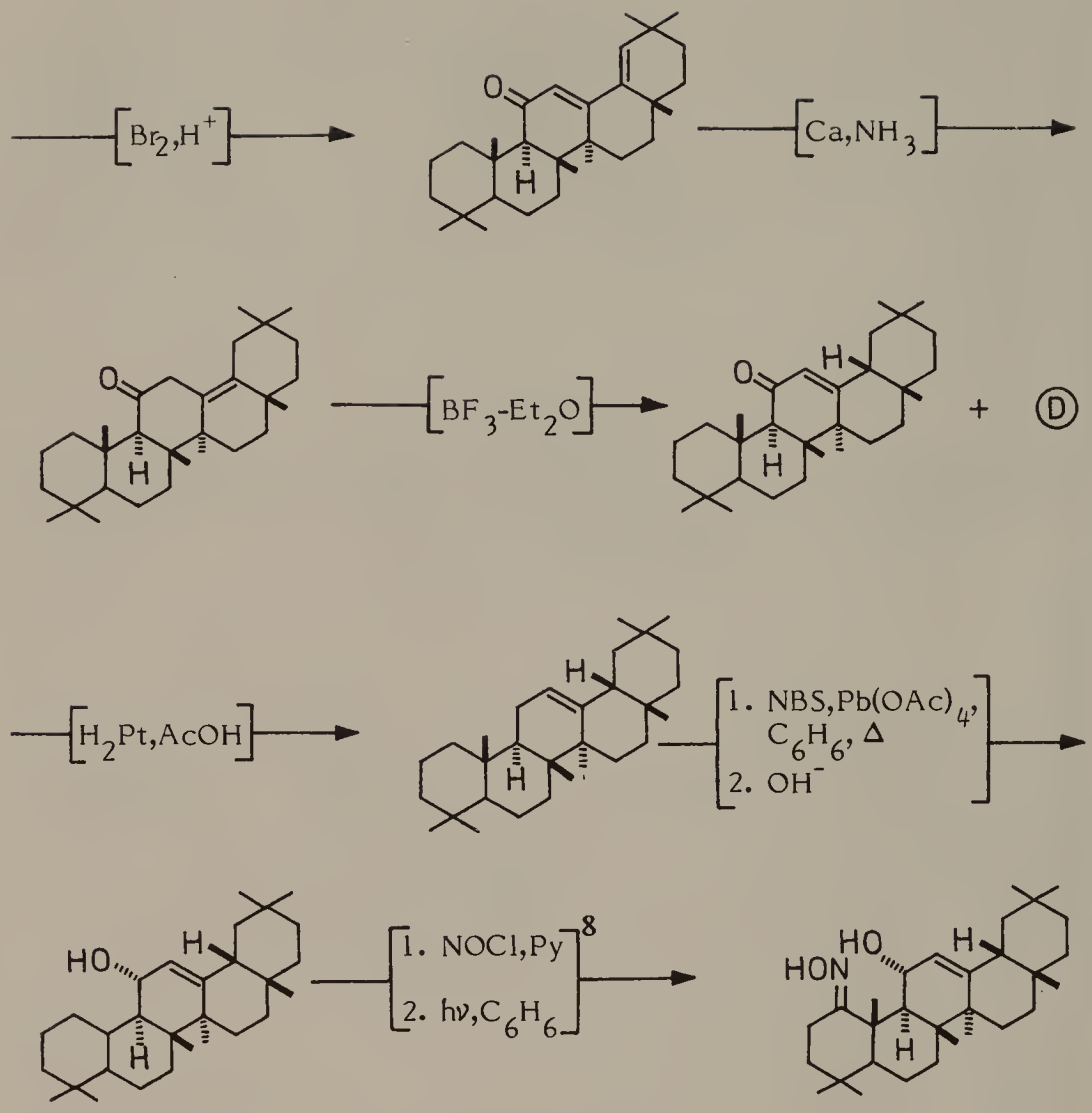
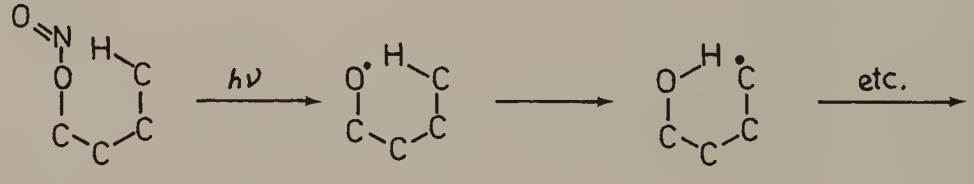
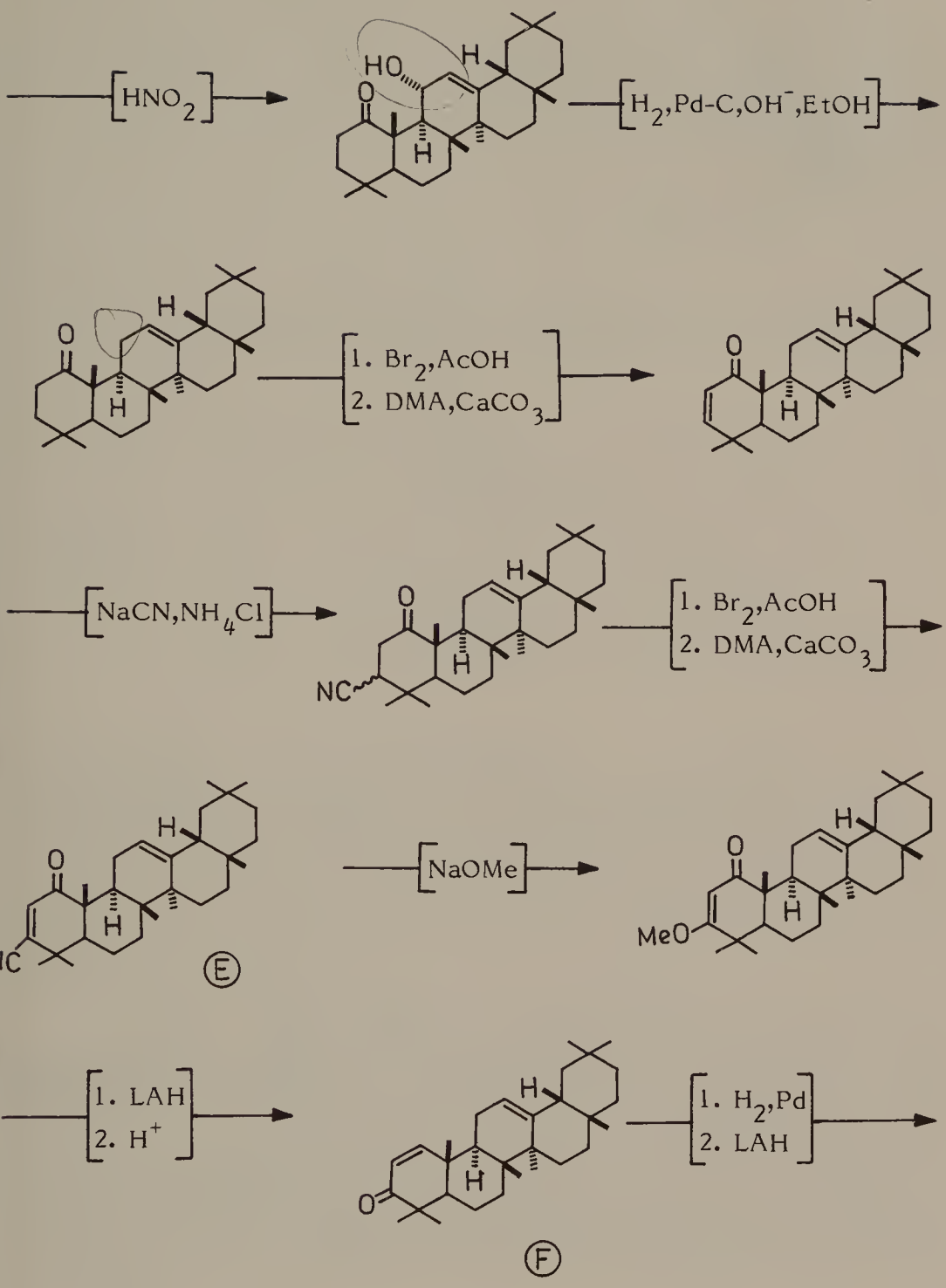
7. Barton,D.H.R., Lier,E.F., McGhie,J.F., J. Chem. Soc.(C), 1968, 1031.



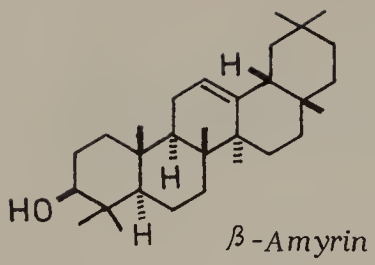
8. This photolytic exchange process involving the intramolecular transfer of the NO of the organic nitrite to a γ-carbon atom probably involves an activated alkoxy radical (i), Barton,D.H.R., Beaton,J.M., Geller,L.E., Pechet,M.M., J. Am. Chem. Soc., 1961, 83, 4076.



(i)

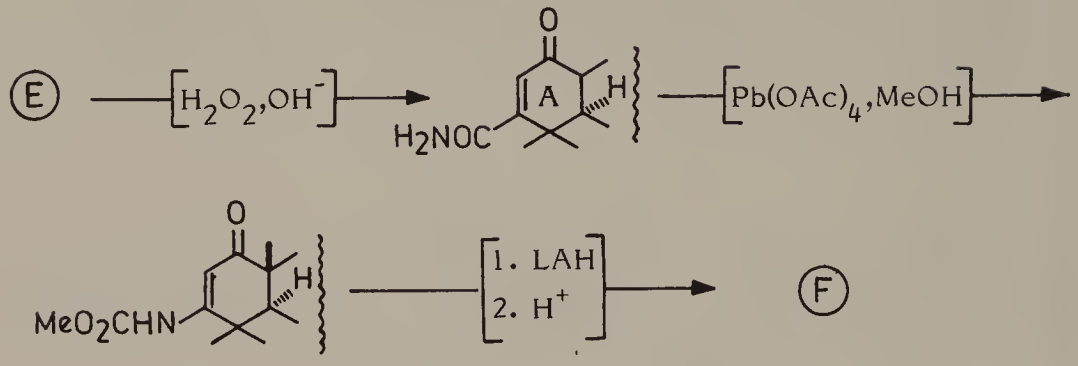

HNO2
HO
H
O
H2,Pd-C,OH⁻,EtOH
1. Br2,AcOH
2. DMA,CaCO3
NaCN,NH4Cl
NC
NaOMe
MeO
1. LAH
2. H+
1. H2,Pd
2. LAH

Ⓔ Ⓕ



β-Amyrin

An alternative route to *β*-amyrin from (E) (9) is as follows:



Van Tamelen and his associates have described a biogenetic type of synthesis of δ-amyrin featuring the stereoselective generation of five asymmetric centres during a polyolefinic cyclization of the terminal epoxide (D) (10,11). In view of the prior conversion of δ-amyrin to *β*-amyrin through *β*-amyrene (7,12) this constitutes a formal synthesis of *β*-amyrin. Presumably in nature amyrins are derived from squalene 2,3-oxide (13).

---

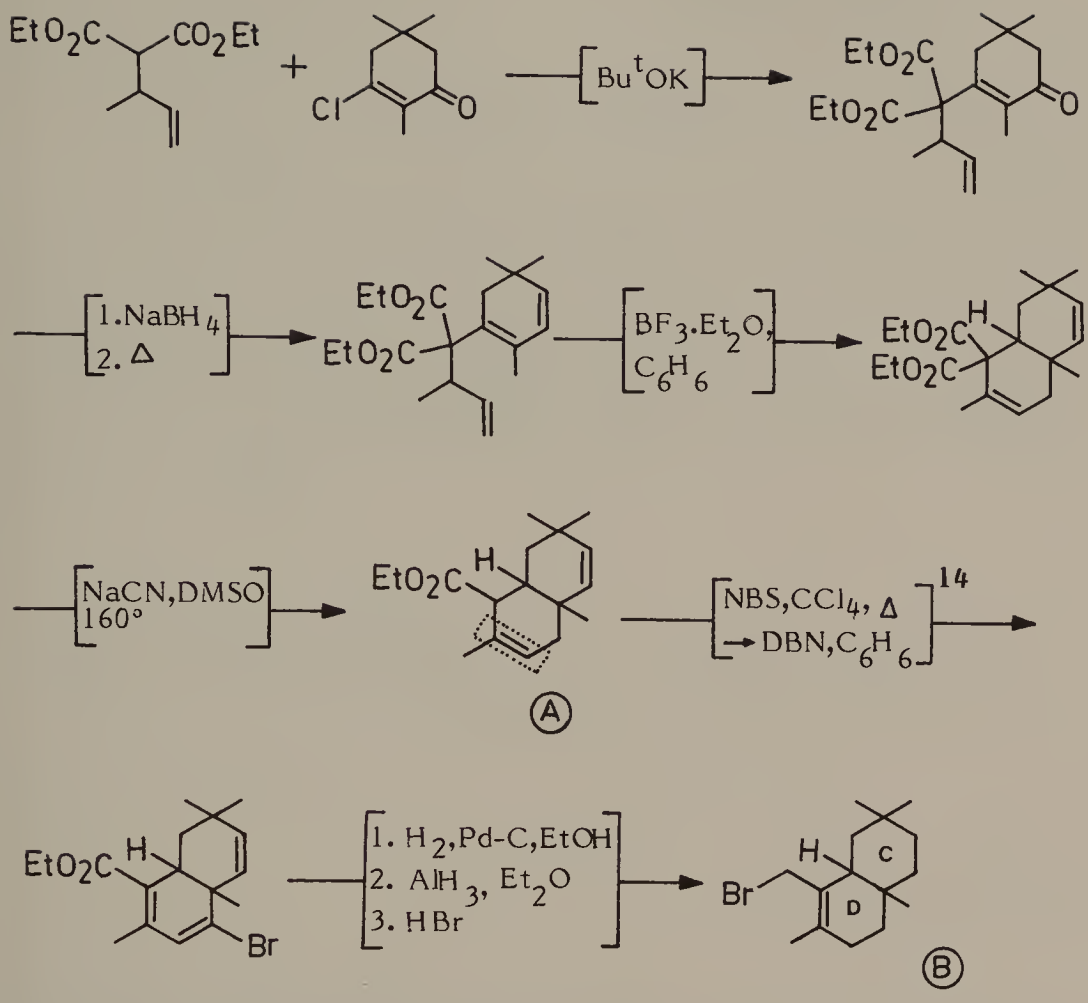
9. Involves the intermediate formation of an isocyanate.which adds on MeOH.

10. Van Tamelen,E.E.; Seiler,M.P.; Wierenga,W. J. Am. Chem. Soc., 1972, 94, 8229.

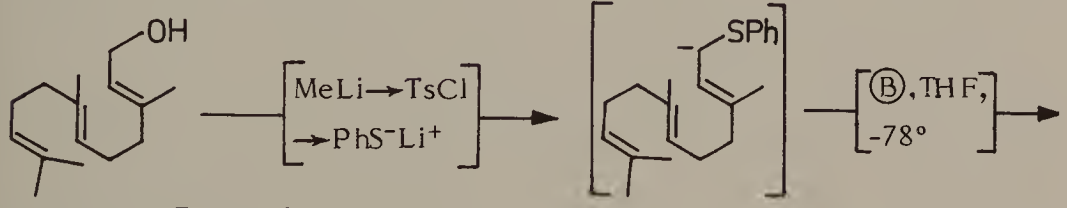
11. For related biogenetic-type total syntheses, see Van Tamelen,E.E.; Milne,G.M.; Suffness, M.I.; Rudler Chauvin,M.C.; Anderson,R.J.; Achini,R.S. J. Am. Chem. Soc., 1970, 92, 7202; van Tamelen,E.E.; Anderson,R.J. J. Am. Chem. Soc., 1972, 94, 8225; van Tamelen,E.E.; Holton,R.A.; Hopla,R.E.; Konz,W.E. J. Am. Chem. Soc., 1972, 94, 8229.

12. Brownlie,G.; Fayez,M.B.E.; Spring,F.S.; Stevenson,R.; Strachan,W.S.J.Chem.Soc,1956,1377.

13. Subsequently (S)-squalene-2,3-oxide was shown to be the exclusive precursor of *β*-amyrin in plant system: Barton,D.H.R. et al, Chem. Commun., 1974, 861; for biosynthesis from squalene see:Suga,K.et al, Chem. Letters, 1972, 129, 313.



Preparation of δ-amyrin:



trans, trans-Farnesol

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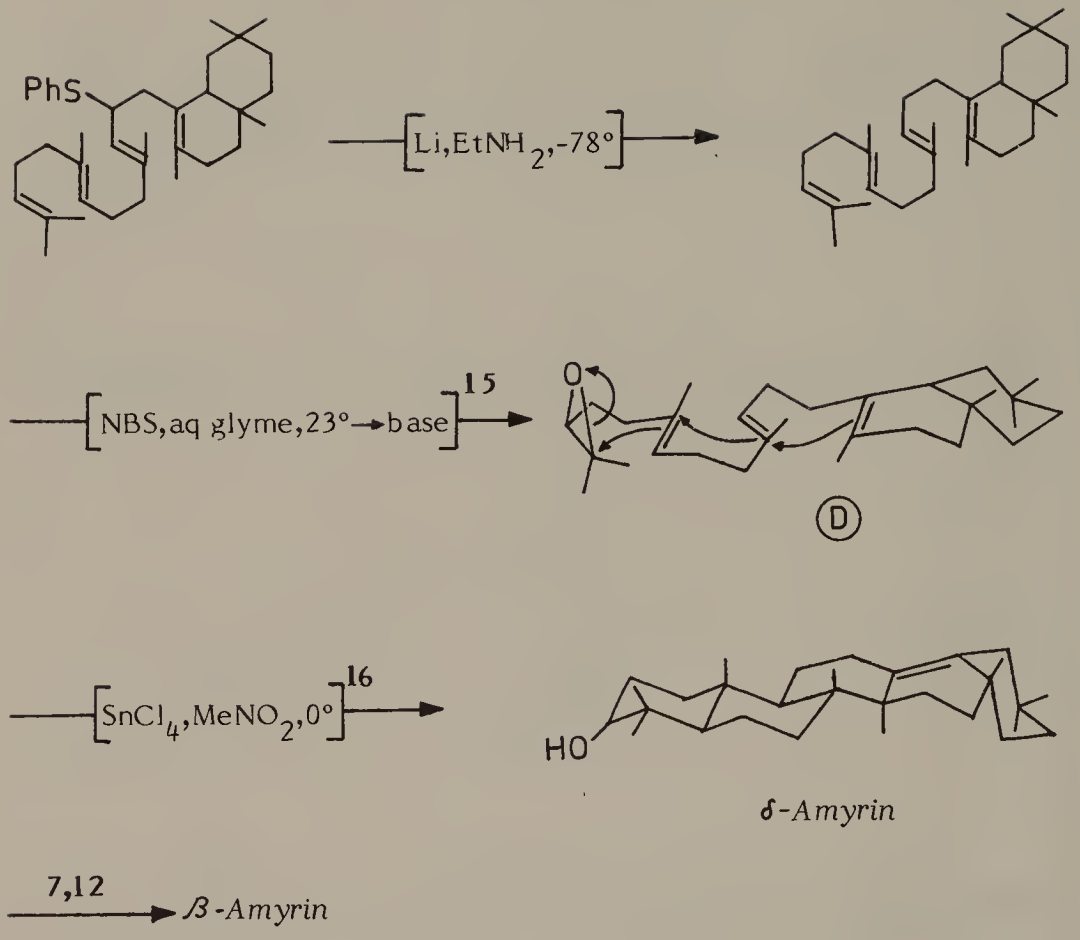
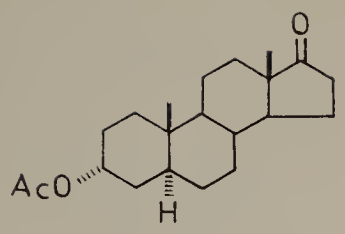
14. The β,γ-unsaturated ester (A) could not be converted directly by base or acid to the α,β isomer.



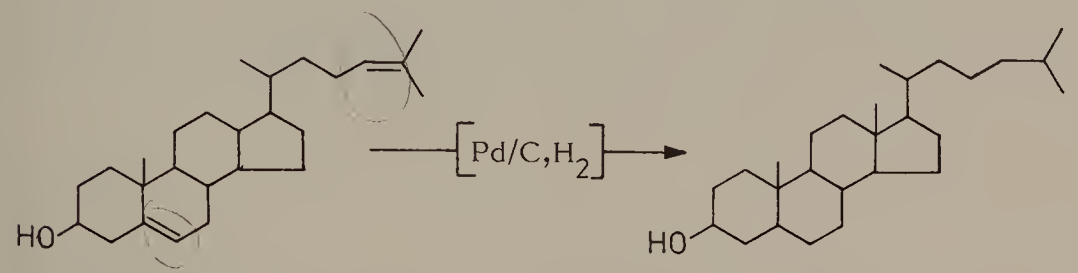
15. Selective oxidation of the terminal double bond in the starting hydrocarbon should not be possible in a solvent of low polarity because the molecule would exist in an uncoiled, fully extended state, with all of the double bonds equally vulnerable to attack by the oxidizing agent. However, in a more polar medium the molecule is expected to assume a highly coiled, compact conformation such that the system of internal hydrogen bonds would be disrupted as little as possible. Under these circumstances the internal double bonds would be sterically shielded and therefore chemically less reactive, while the terminal olefinic links would remain exposed and available for reaction.

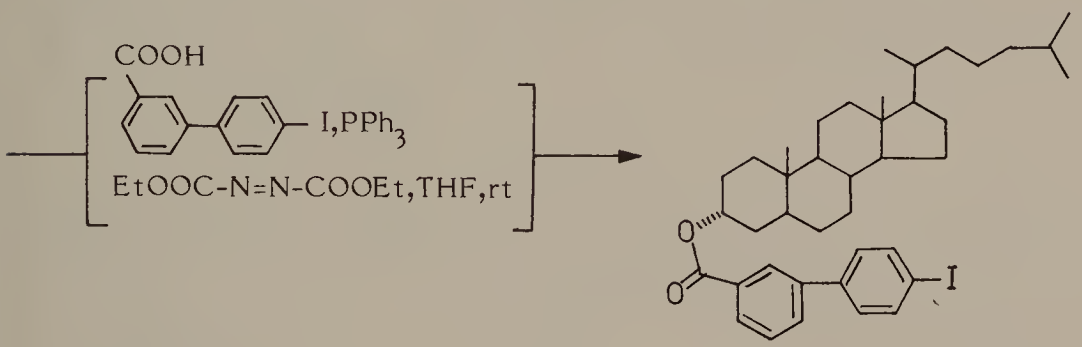
16. For papers on definitive stereochemistry of polyene cyclization, see Stork,G.; Burgstahler,A.W.J. Am. Chem. Soc., 1955, 77, 5068; Eschenmoser,A.; Ruzicka,L.; Jeger,O.; Arigoni,D. Helv. Chim. Acta, 1955, 38, 1890.



ANDROSTERONE

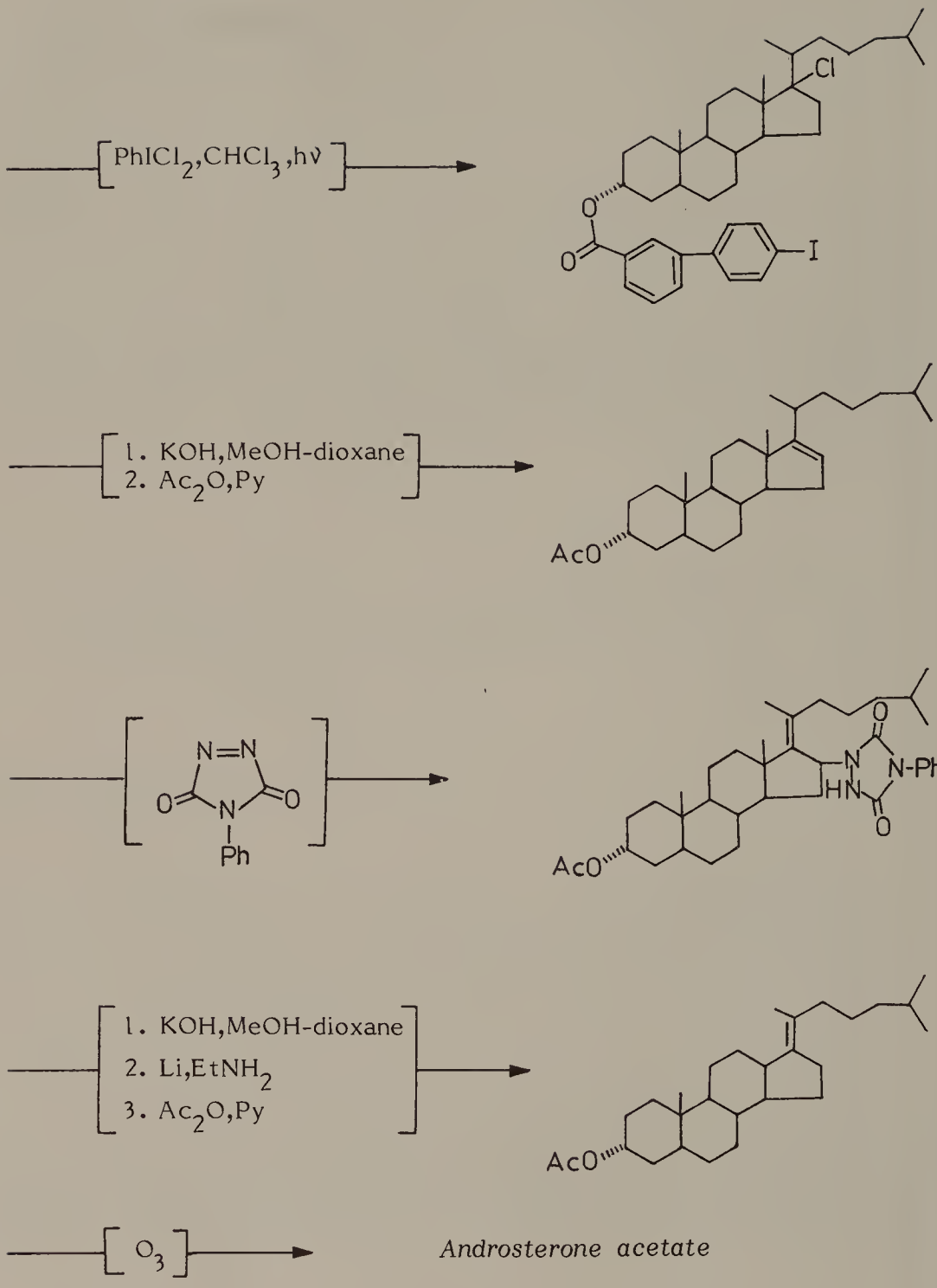
An emerging and useful facet of the art in organic synthesis is the deployment of distal control elements to effect the functionalisation of unactivated locations, at will, at prespecified sites. This approach would enable the realization of seemingly impossible transformations and also lead to a better understanding as to how similar changes may be carried out by enzymes in diverse biologically important processes. The pioneering work of Breslow in this domain can best be illustrated with the transformation of the readily available cholesterol to androsterone (1), a transformation earlier carried out by classical methods (2).



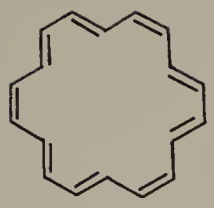


1. Breslow,R.; Corcoran,R.J.; Snider,B.B.; Doll,R.J.; Khanna,P.L.; Kaleya,R. J. Am. Chem. Soc., 1977, 99, 905.

2. Ruzicka,L.; Goldberg,M.W.; Brunger,H. Helv. Chem. Acta, 1934, 17, 1389; Ruzicka,L. Wirz,H.; Meyer,J. ibid, 1935, 18, 998; Marker,R.E.J. Am. Chem. Soc., 1935, 57, 1755.



Androsterone acetate

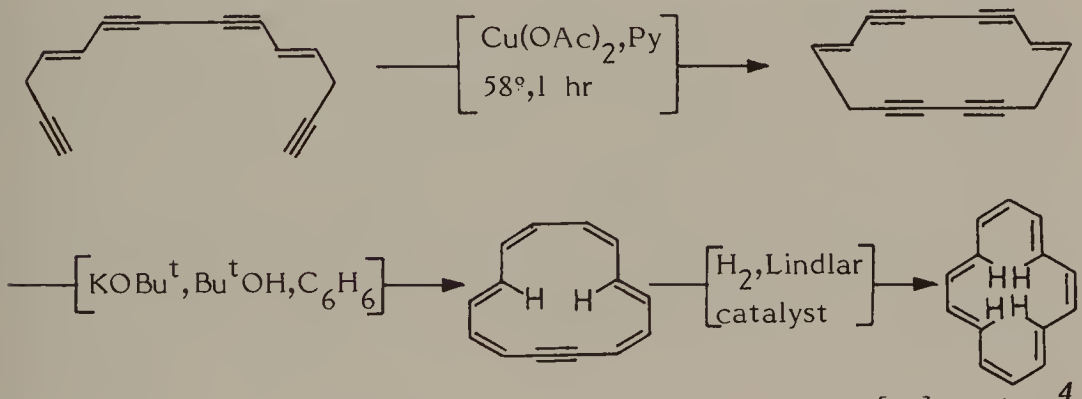


ANNULENES

Annulenes (1) are systems that are circumscribed by a periphery. The resulting annular space can be either void or contain a variety of atoms or substructures to provide viability for the π array, without becoming part of the aromatic system. There is evidence from NMR spectroscopy that annulenes having $4n+2$ π electrons do possess a ring current whilst in $4n$ π electron systems there is no ring current (2).

Sondheimer and co-workers made a series of annulenes, from [14]-annulene onwards, and examined their properties in the light of Huckel rule (2,3). The general principle followed in the synthesis of these compounds was the cyclization of 1,ω-acetylenes by oxidative coupling, followed by base catalyzed prototropic rearrangement of the linear 1,5-enynes to conjugated ene-ynes, and catalytic reduction of the latter over Lindlar catalyst to the annulenes. In general these compounds were found to be unstable to prolonged keeping.

[14]Annulene



[14]Annulene[4]

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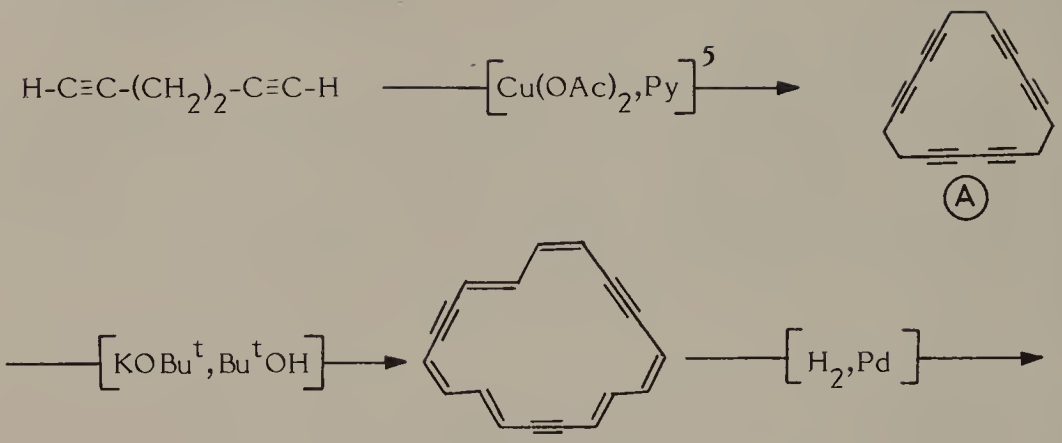
1. The name annulenes has been given to completely conjugated cyclic polyolefins. Individual compounds are described by adding a number in square brackets indicating the number of atoms in the ring.

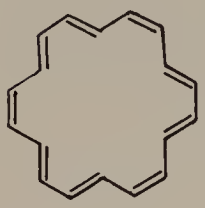
2. Sondheimer,F. Pure & Applied Chem., 1963, 7, 3639.

3. Sondheimer,F.; Calder,I.C.; Elix,J.A.; Gaoni,Y.; Garratte,P.J.; Grohmann,K.; DiMaio,G.; Mayer,J.; Sargent,M.V.; Wolovsky,R. Chem. Soc. Spl. Publn., 1967, 21, 75.

4. Sondheimer,F.; Gaoni,Y. J. Am. Chem. Soc., 1960, 82, 5765.

[18]Annulene





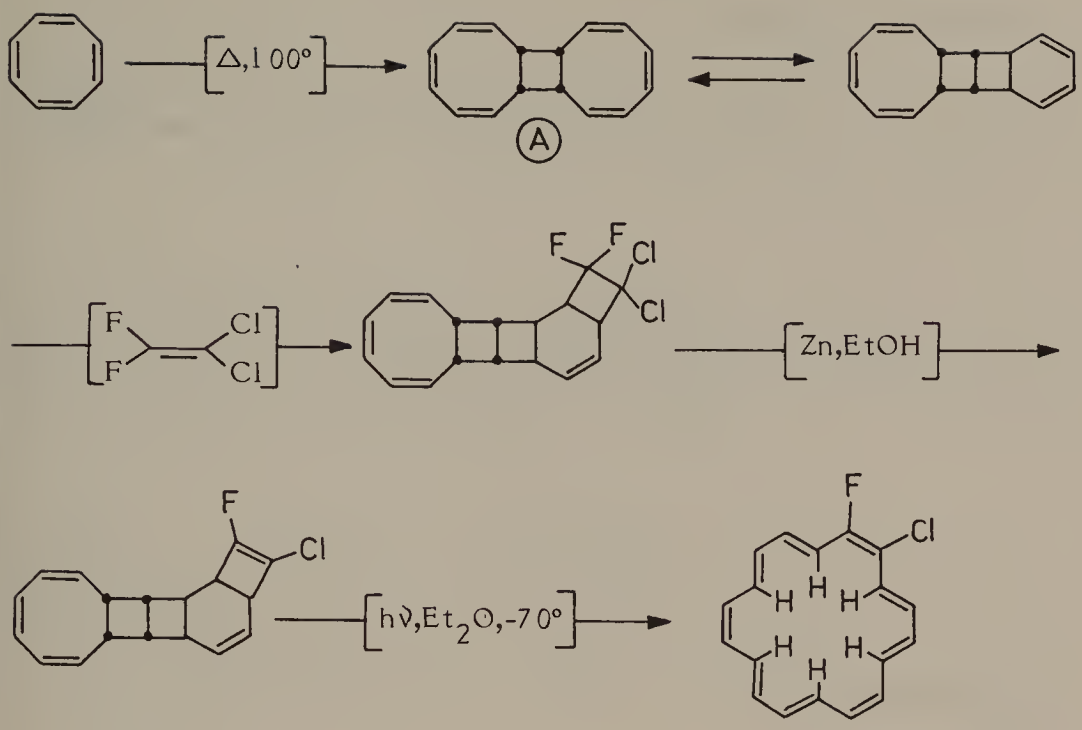
[18]Annulene

In [18]annulenes there exists a dynamic process involving the in-out change of the 18 protons as 3 degenerate sets of 6. In the case of substituted annulenes, the substituent being necessarily larger than hydrogen, would opt to stay out. In the case of a 1,2-disubstituted annulenes, it can be shown that in order to keep the substituent out, the same set of 6 protons has to be in and consequently the nmr would be temperature independent. The synthesis of such a system has been accomplished in a novel and ingenious manner from the cyclooctatetraene dimer (A) (6). Cyclooctatetraene when heated at 100° gives a mixture of two dimers formed in almost equal quantity one of which is the required dimer (A).

---

5. In this oxidative coupling of 1,5-hexadiynes, in addition to the trimer (A), tetramer, pentamer, hexamer and heptamer were also formed and could be made to undergo the same reactions to form the corresponding higher annulenes.

6. Schroder,G.; Neuberg,R.; Oth,J.F.M. Angew. Int., 1972, 11, 51.



Bridged annulenes

Severe H-H interactions prevent the immediate 4n+2 homologs of benzene, starting from cyclodecapentaene, assuming coplanarity, a condition that is essential for gainful overlap and therefore aromaticity. Investigation of the possibility that the replacement of these hydrogens by bridging would alleviate the unfavourable interactions has led to the preparation of bridged annulenes; where the bridge could be CH_2/O/NH/CO, although apparently violating the "Bredt rule" by possessing double bonds at the bridge-head, these have been shown to be truly aromatic compounds on the basis of physical and chemical probes. The syntheses are based on the increased susceptibility of the central bond in 1,4,6,8-tetrahydronaphthalene to electrophilic reactions; the remaining double bonds are converted to a tetraene by sequence of bromine addition and dehydrohalogenation (7-10).

---

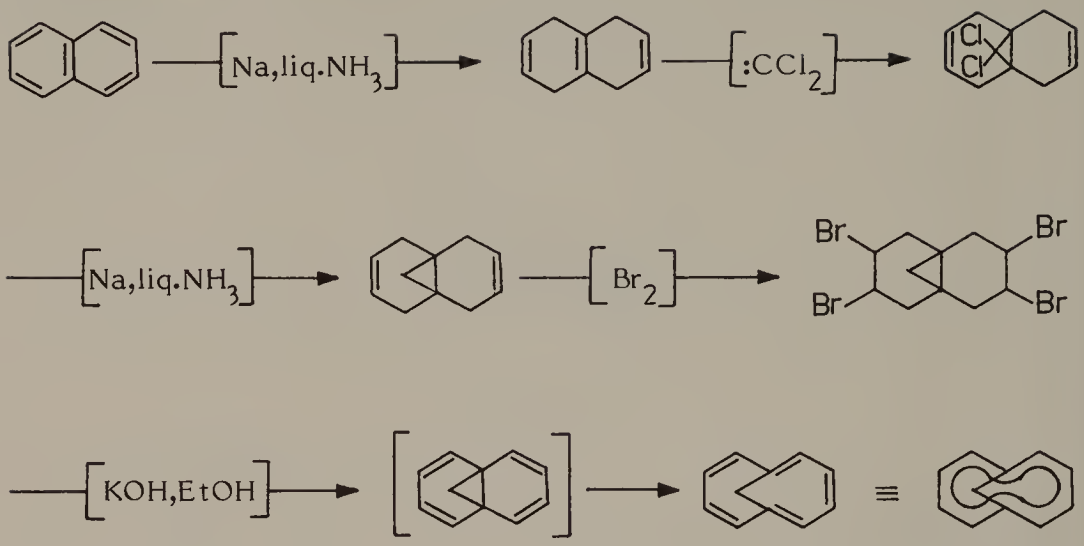
7. Vogel,E.; Roth,H.D. Angew. Chem. Int.Ed, 1964, 3, 228; Vogel,E.; Boll,W.A. ibid, 1964, 3, 642.

8. Vogel,E.; Biskup,M.; Pretzer,W.; Boll.W.A. Angew. Chem. Int., 1964, 3, 642; Sondheimer,F. Shani,A. J. Am. Chem. Soc., 1964, 86, 3168.

9. Vogel,E.; Pretzer,W.; Boll,W.A. Tetrahedron Lett., 1965, 3613.

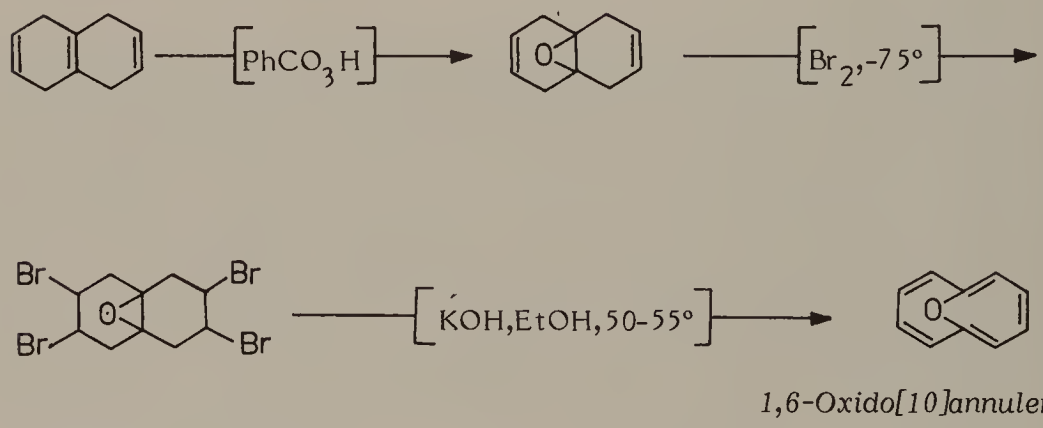
10. Homologs corresponding to cyclopentadiene anion and tropylium cation have been made; for an extensive and illuminating review of the subject, see: Vogel,E. Aromaticity, Chem. Soc. Spl. Publn., 1967, 21, 113.

1,6-Methano[10]annulene



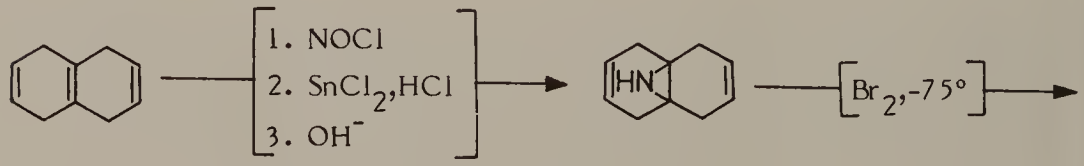
1,6-Methano[10]annulene

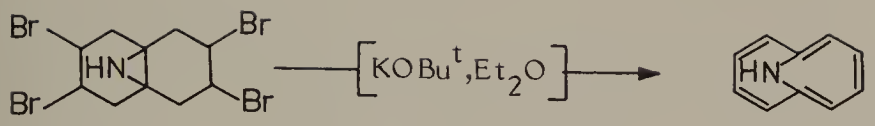
1,6-Oxido[10]annulene



1,6-Oxido[10]annulene

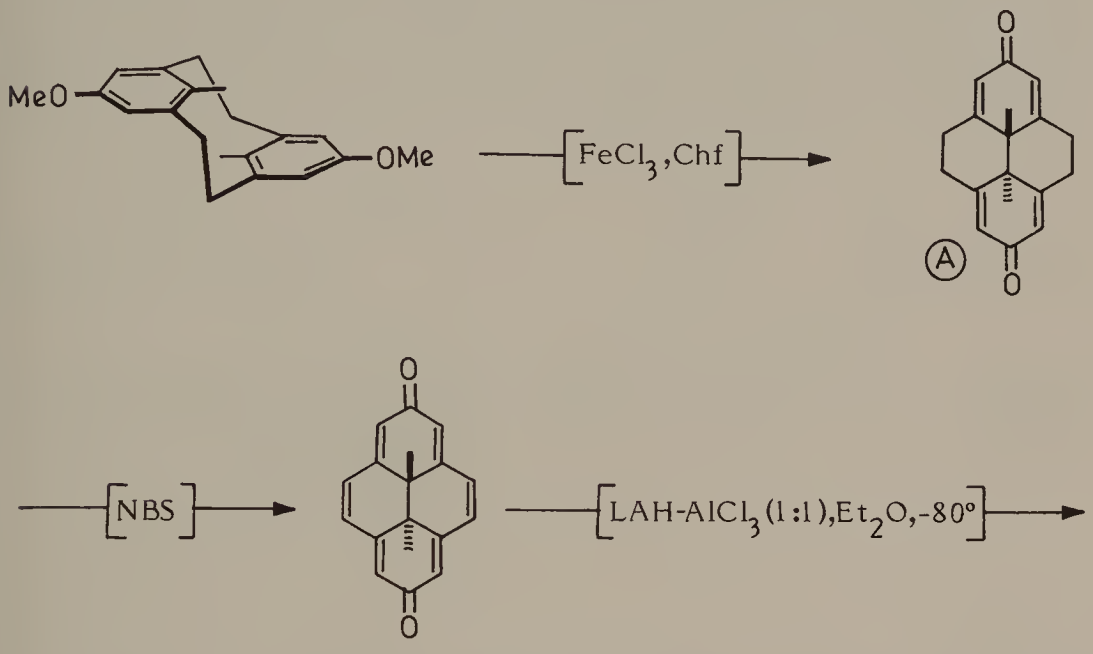
1,6-Imino[10]annulene





1,6-Imino[10]annulene

In another approach, the unfavourable H-H interactions are overcome by means of an ethane bridge. Molecular models show that in this two-carbon bridged annulene the peripheral atoms lie in a plane (11). The crucial tetracyclic intermediate (A) was synthesized by an elegant intramolecular oxidative coupling of a dimethoxymetacyclophane (12).



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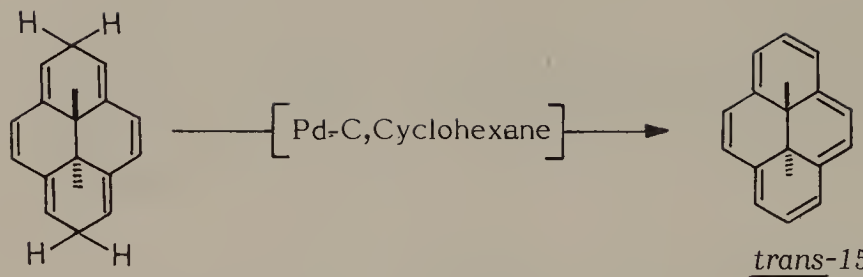
11. The molecule fulfills the criteria for aromaticity in terms of ring current and reactivity, thus showing that systems with cavities in the middle and having 4n+2 electrons in the periphery can be truly aromatic. The existence of ring current has been dramatically shown by the heavy shielding of the methyl groups (δ = -4.25) by the ring current. In accordance with predictions based on Woodward-Hoffman rule, the molecule undergoes conrotatory photolytic opening.

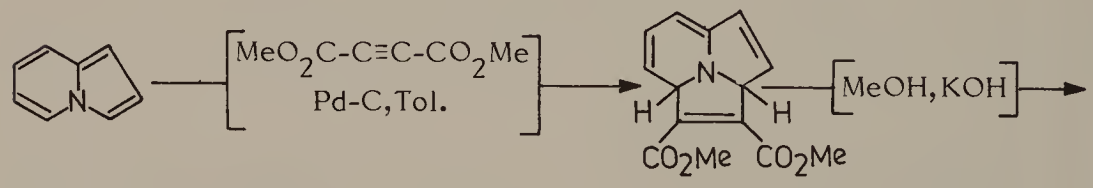
12. Boekelheide,V.; Phillips,J.B. J. Am. Chem. Soc., 1963, 85, 1545; idem, Proc. Natl. Acad. Sci. (U.S.A.), 1964, 51, 550.

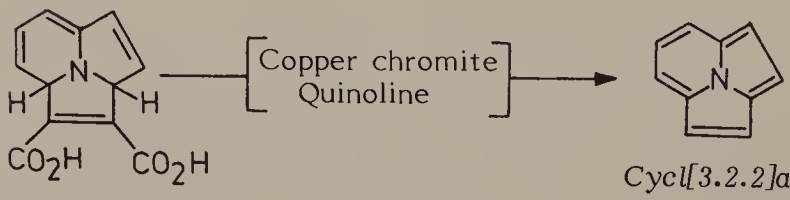


trans-15,16-Dimethyl-15,16-dihydropyrene

A particularly interesting case is where a single nitrogen serves as the bridge, without the lone pair being a part of the periphery. Accordingly, cycl[3.2.2]azine (I) having 10 π e in the periphery has been made (13) is stable and truly aromatic. The corresponding cycl-[3.3.3]azine (II) having a 12 π e in the periphery is a highly sensitive compound and is non aromatic. In the later case the nitrogen lone pair shields the peripheral protons (14).

Cycl[3.2.2]azine





Cycl[3.2.2]azine (I)

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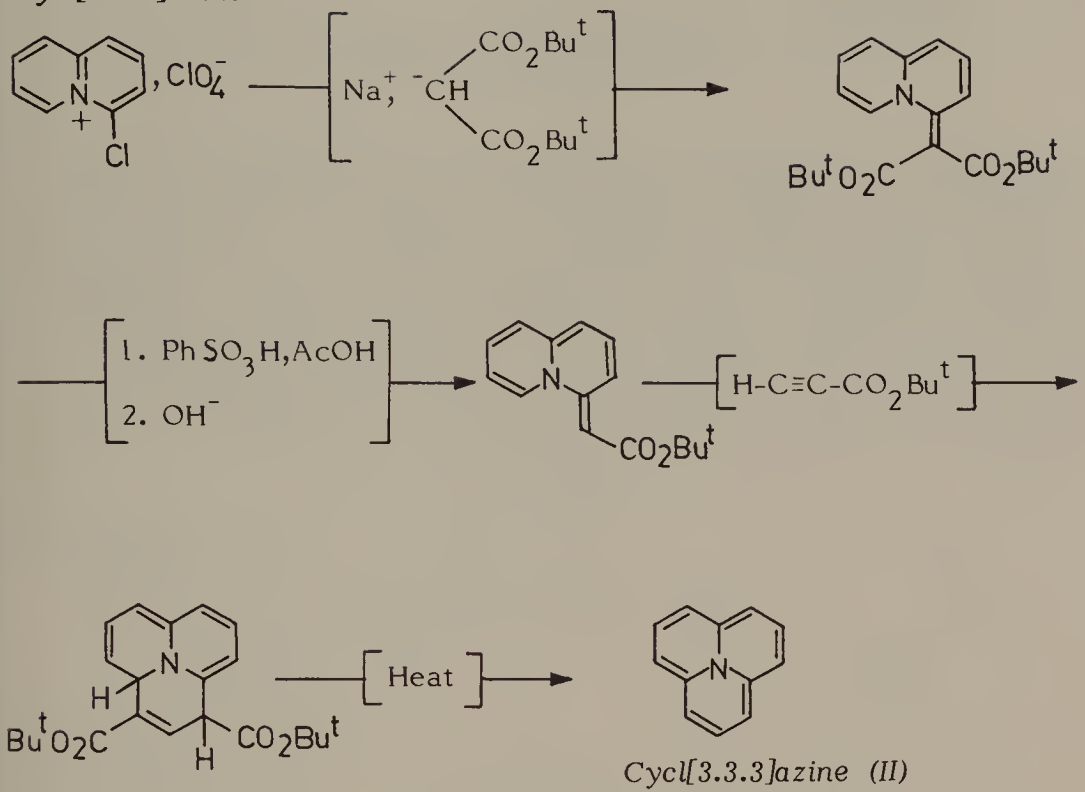
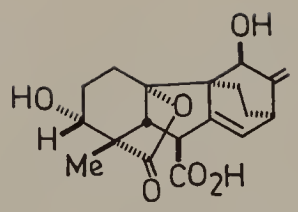
13. Galbraith,A.; Small,T.; Barnes,R.A.; Boekelheide,V. J. Am. Chem. Soc., 1961, 83, 453.
14. Farquhar,D.; Leaver,D. Chem. Commun., 1969, 24.

Cycl[3.3.3]azine

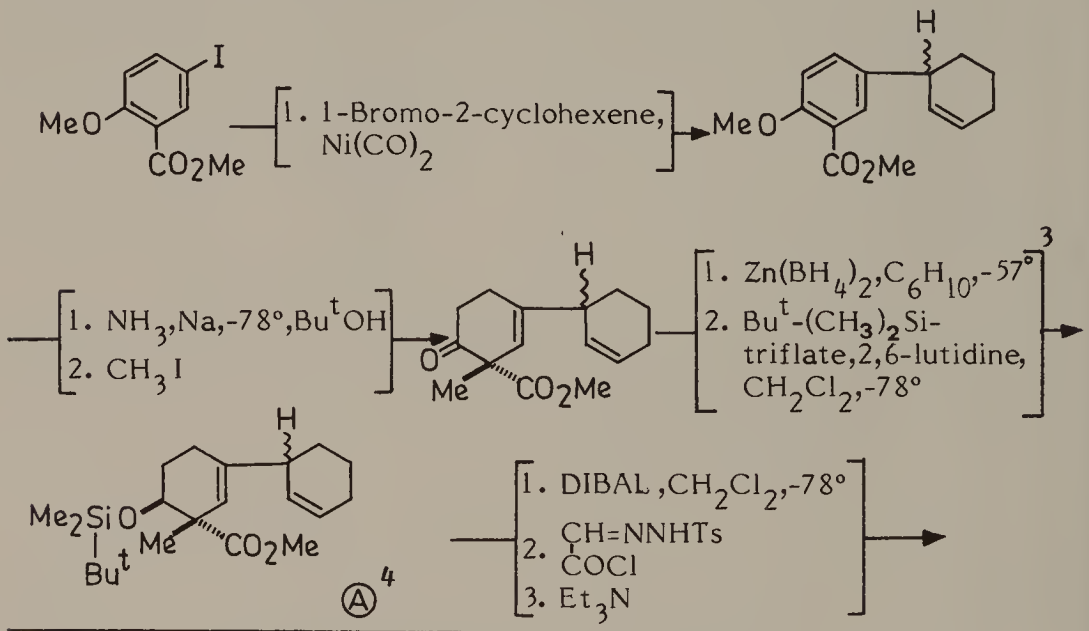


Cycl[3.3.3]azine (II)



ANTHERIDIOGEN

Antheridiogen An (Aan) is a recently discovered plant hormone(1), with a novel gibberellin-related structure(2). Interesting use is made in the present synthesis(3) of glyoxal chloride hydrazone to make a diazo-acetoxy derivative to generate a suitably disposed carbene to form cyclopropylactone, which is followed by a novel vinylcyclopropane-cyclopentene rearrangement to form the required hydrogenated ring system. Another interesting set of transformations are the conversion of B to C with ruthenium tetroxide involving simultaneous oxidation of CH_2OH to CHO and oxidative conversion of nitronate to ketone carbonyl.

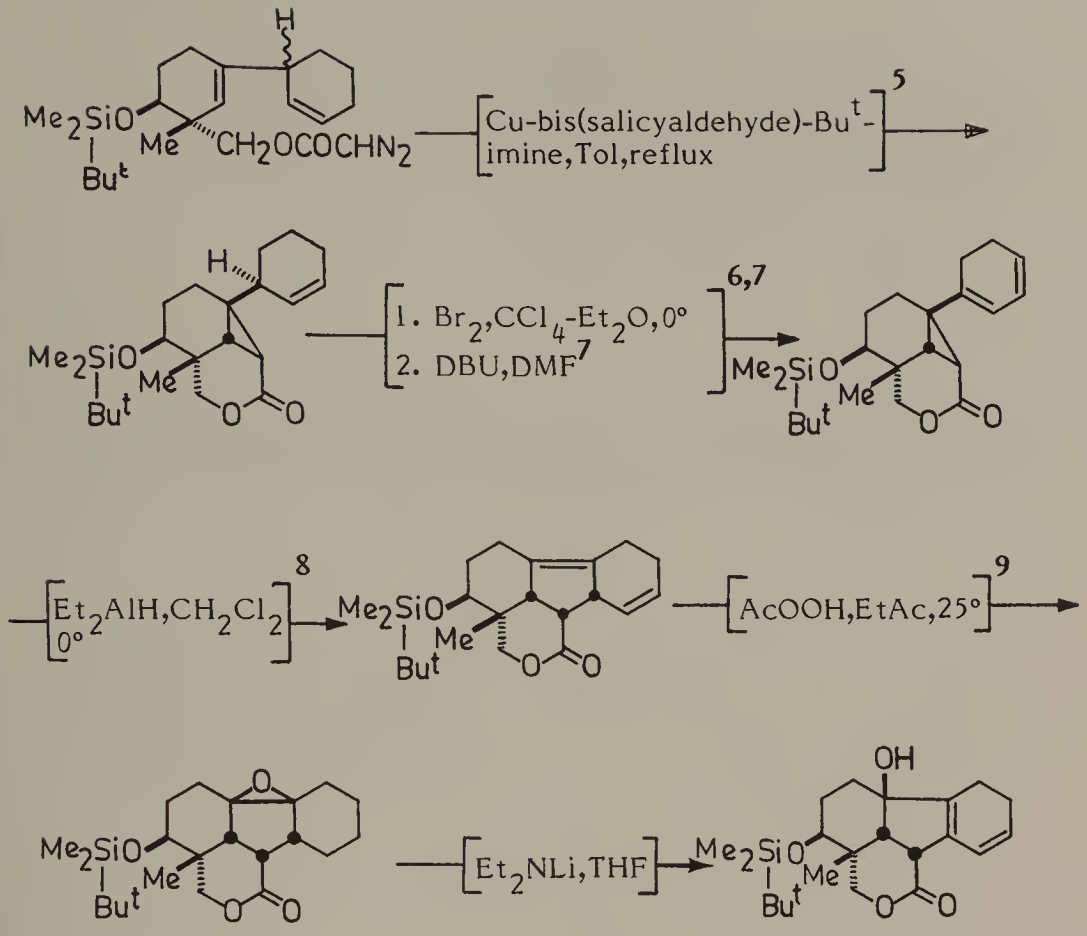


1. Naf,U,Nakanishi,K.,Endo,M.;Bot.Rev., 1975, 41, 315.

2. Nakanishi,K.,Endo,M.,Naf,U.,Johnson,L.F.,J.Am.Chem.Soc., 1971, 93, 5579.

3. Corey,E.J. and Myers,A.G.,J.Am.Chem.Soc., 1985, 107, 5574-5576.

4. Relative stereochemistry at the adjacent stereocenters in (A) is indicated by expected hydride attack at the less-screened face of the Keto group in a Zn-related β-Keto ester.



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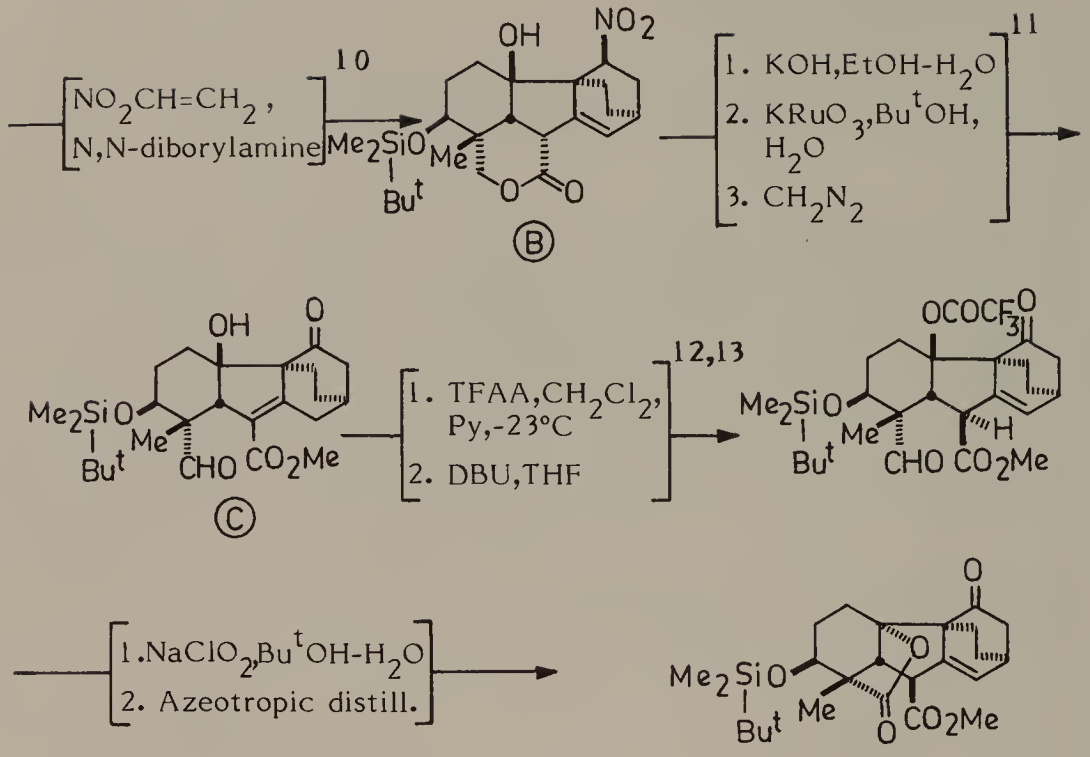
5. This internal carbenoid addition generates the cyclopropyl lactone stereospecifically.

6. This reaction formed the four isomeric trans-dibromides, and the mixture was used for next reaction.

7. DBU converted two of the dibromides to diene and left the others unchanged, which could be converted to the starting material by Zn-AcOH.

8. This is a novel version of the vinyl cyclopropane-cyclopentene rearrangement.

9. Epoxidation takes place from the less screened face of the double bond.



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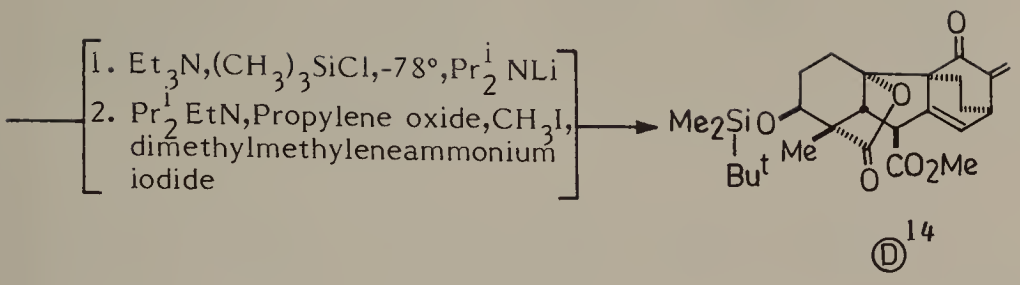
10. This reaction proceeds with orientational- and stereo-specificity.

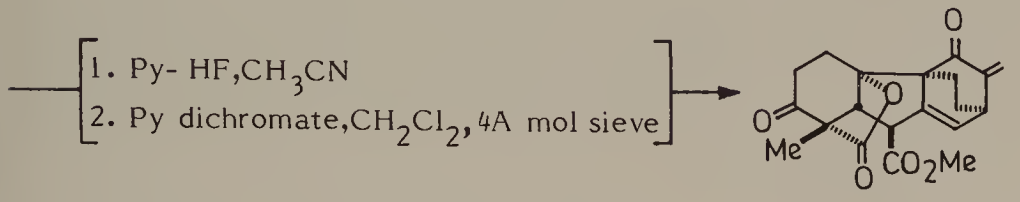
11. This conversion was unusual for the number of structural changes which included olefinic transposition, δ-lactone hydrolysis, RuO_4 oxidation of CH_2OH to CHO and oxidative Nef conversion by Ru(VI) oxidation.

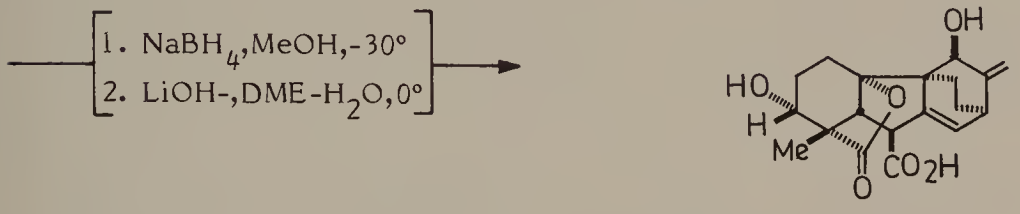
12. In addition to trifluoracetylation of angular hydroxyl concomitant $\alpha,\beta \rightarrow \beta,\gamma$ migration of the double bond.

13. This led to isomerisation to the more stable β-(methoxycarbonyl)epimer.



Ⓓ[14]





(±)-Antheridiogen

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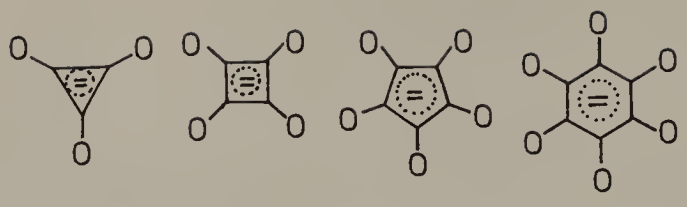
14. Reduction of Ⓓ with $NaBH_4$ in MeOH gave stereo-selectively the β-alcohol, which on desilylation yielded the product with stereochemistry assigned to antheridiogen, but its nmr spectrum proved to be very different from that reported for the latter and therefore its 3-epimer was then synthesised.

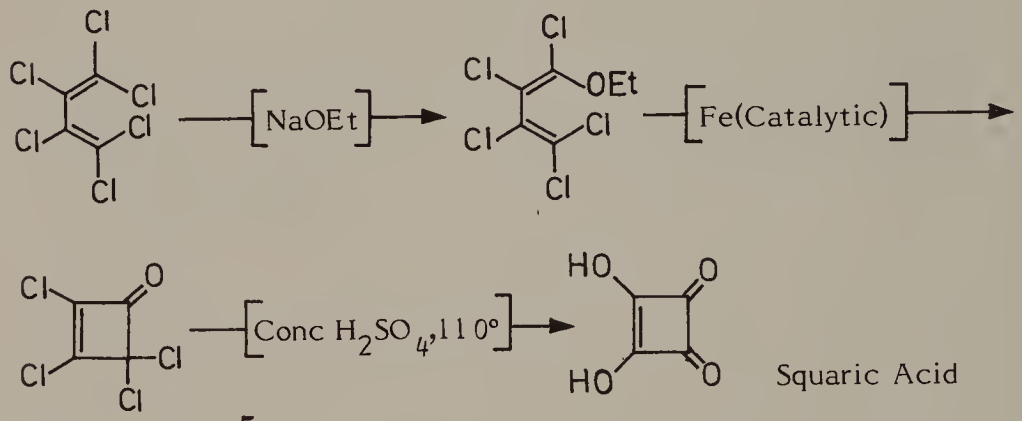


I II III IV

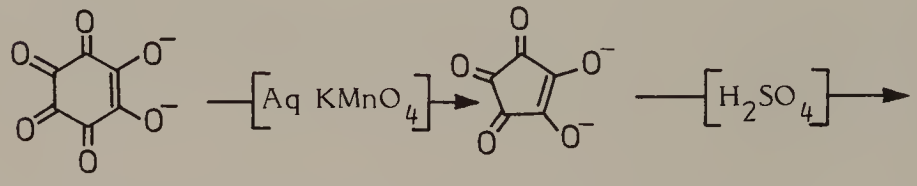
AROMATIC ANIONS

The aromatic nature of these anions was realized from studies on squaric acid (1,2). This compound, which is almost as strong as sulfuric acid, readily forms a truly delocalized planar dianion [II]. Simple LCAO-MO calculations predict that dianions having a wide range of n values should be aromatic (2,3). The lowest member of this series, $C_3O_3^{-2}$, although predicted to have unusually high delocalization energy, is not known; in contrast the two immediate higher homologs of II, croconic acid [III] and rhodizonic acid [IV], have been known for nearly a century.

Squaric Acid[4]



Croconic Acid[5]



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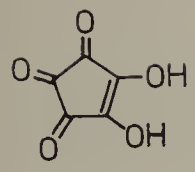
1. Maahs,G, Hegenberg,P., Angew. Chem. Internat. Ed., 1966, 5, 888.

2. West,R., Powell,D.L., J. Am. Chem. Soc., 1963, 85, 2577.

3. LCAO-MO calculations show that at least in the case of small rings the -2 ions are more stable than those having smaller or larger charge.

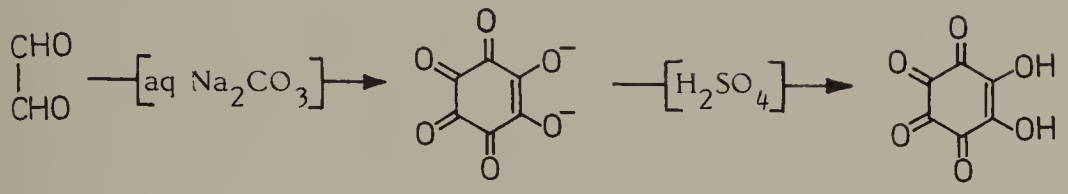
4. Maahs,G., Annalen, 1965, 686, 55.

5. Yamada,K., Hirata,Y., Bull. Chem. Soc. (Japan), 1958, 31, 551.



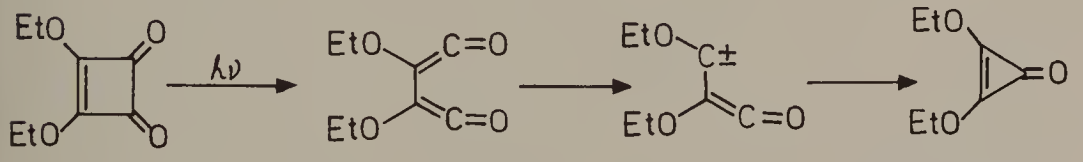
Croconic Acid

Rhodizonic Acid[6]



Rhodizonic Acid

An ingenious transformation of diethyl squarate to diethyl dreieck-saure (diethyl three cornered acid) has been accomplished, although its further transformation to free acid could not be achieved (7).



Diethyl dreieck-saure

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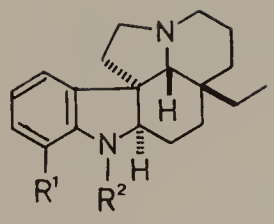
6. Homolka,B., Ber., 1921, 54, 1393.

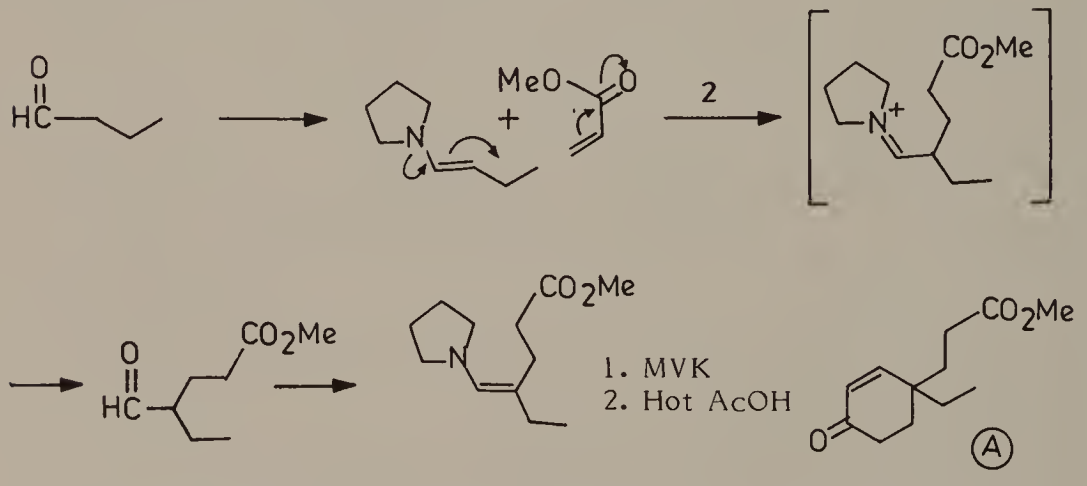
7. Dehmlow,E.V., Tetrahedron Lett., 1972, 1271.



ASPIDOSPERMINE
ASPIDOSPERMIDINE

The Aspidosperma alkaloids have attracted much attention for many years on account of the marked physiological activity exhibited by many of them and the central place they occupy in the biosynthesis of monoterpene alkaloids. A number of ingenious strategies have been developed to construct the Aspidosperma skeleton, from the first synthesis of (±)-**aspidospermine** by Stork and Dolfini utilising the classical Fischer-indole synthesis (1) to the most recent quinodimethane cyclisation to construct the core tetracyclic skeleton (12).

Stork and Dolfini (1) in their synthesis of aspidospermine, utilized the arylhydrazone-carbazolenine rearrangement on a ring C-D-E tricyclic ketone (B) for construction of the characteristic pentacyclic indoline nucleus of aspidospermine.



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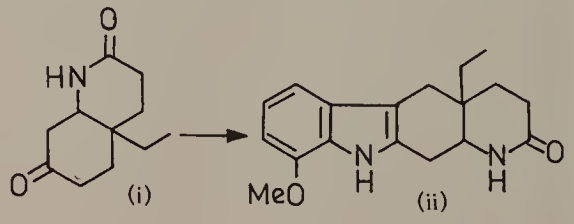
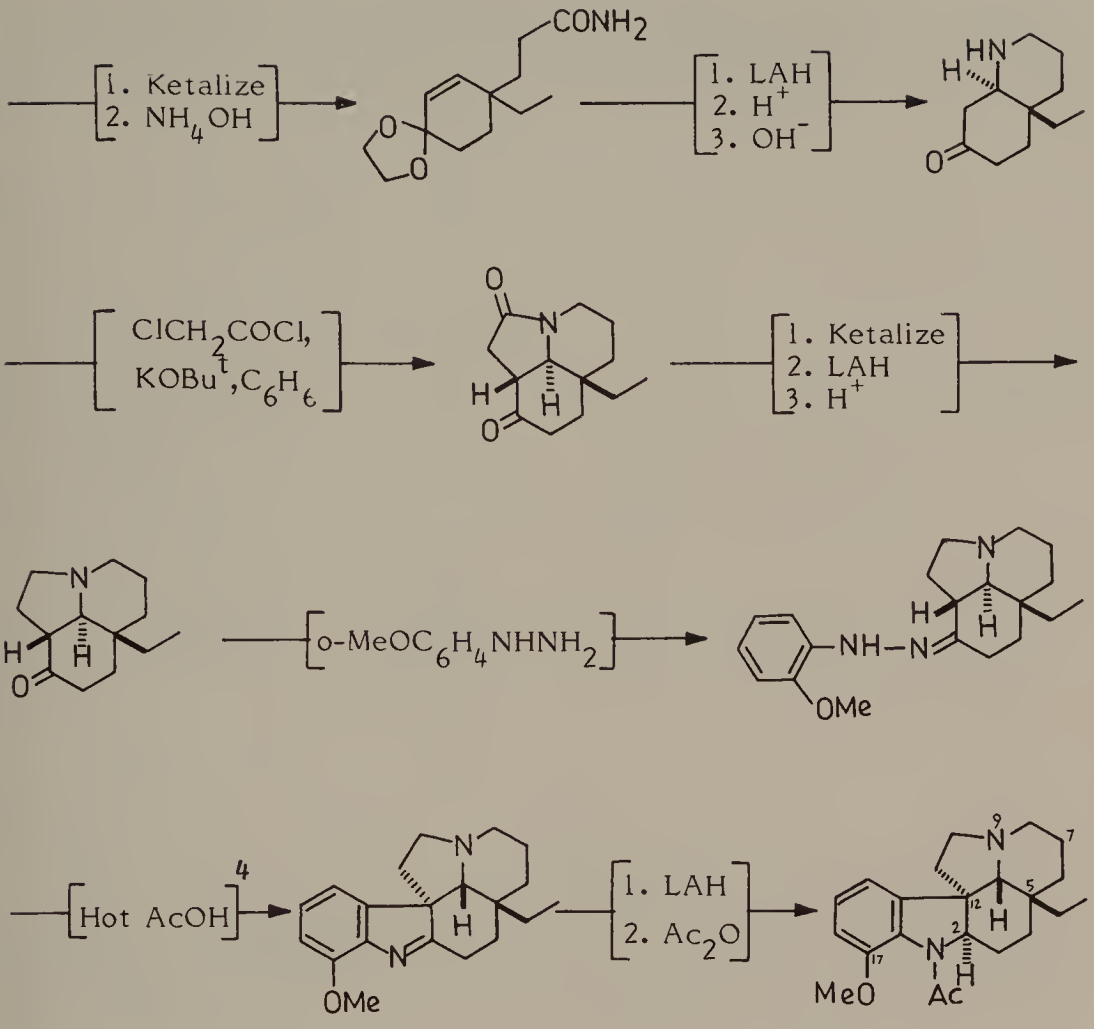
1. Stork,G.; Dolfini,J.E. J. Am. Chem. Soc., 1963, 85, 2872.
2. Enamine alkylation procedure, Stork,G.; Brizzolara,A.; Landesman,H.; Szmuszkovicz,J.; Terrell,R. J. Am. Chem. Soc., 1963, 85, 207.
3. Reaction of (A) with ammonia gave a mixture of cis and trans keto lactams (i) which formed the unwanted linear system (ii) on Fischer indole synthesis, indicating that enolization at C-2 occurs away from the ring junction. Construction of ring E was therefore undertaken at this stage in order to induce enolization in the desired direction.





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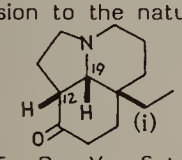
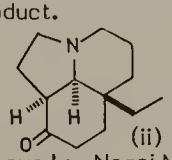
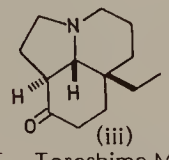
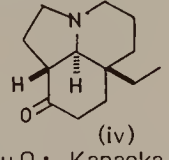
4. Although all four stereoisomers of (B) have been synthesized (refs.1,5 and 6) and Stork's tricyclic ketone has been shown to possess the stereochemistry depicted in (iv), the stereochemistry of these intermediates has little effect on final outcome of the synthesis. During the Fischer cyclization there is equilibration at C-12 and C-19 asymmetric centres involving a retro-Mannich reaction which results in the formation of the most stable relative arrangement of the three asymmetric centres in rings C,D and E. Therefore, in principle, all the four isomers [(i)-(iv)] are capable of conversion to the natural product.


(i)


(ii)

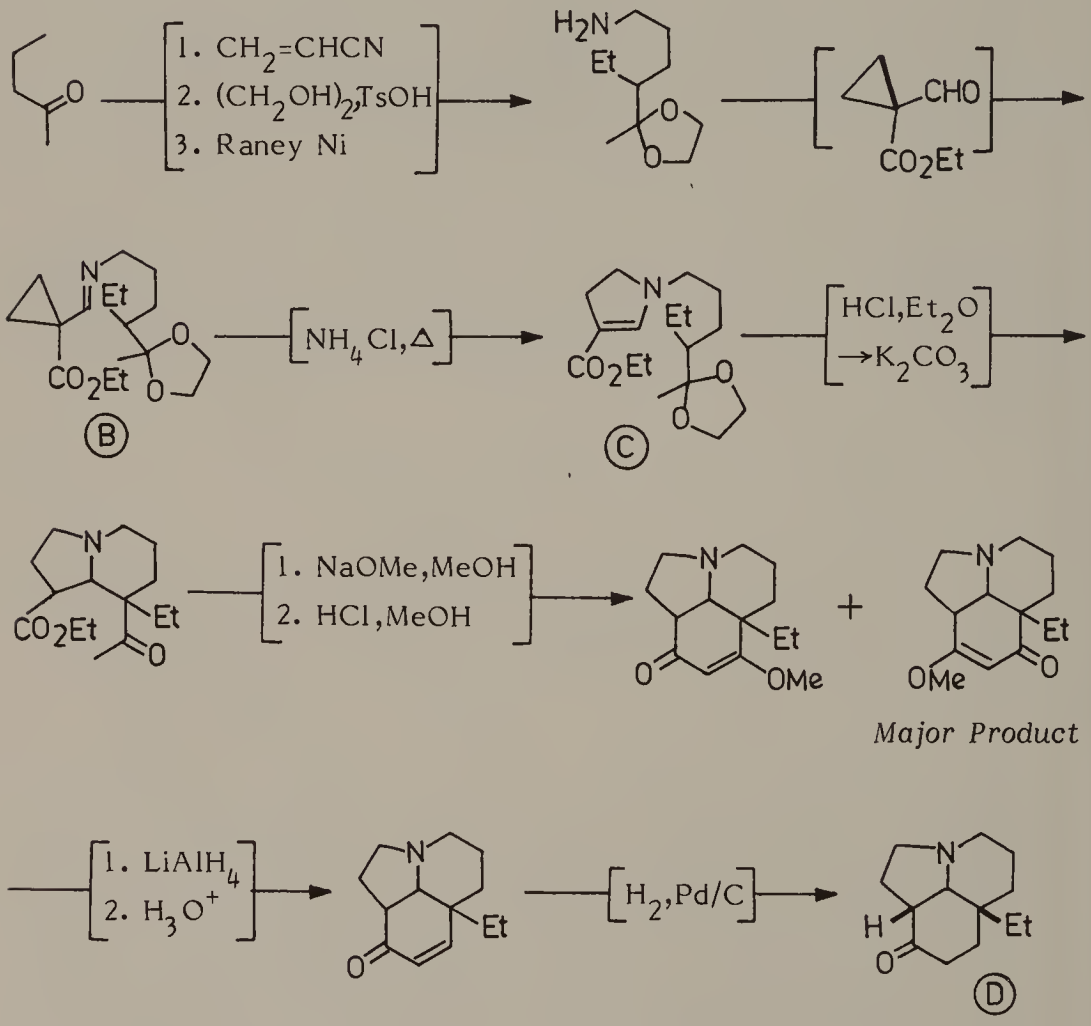

(iii)


(iv)

5. Ban,Y.; Sato,Y.; Inoue,I.; Nagai,M.; Oishi,T. Terashima,M.; Yonemitsu,O.; Kanaoka,Y.; Tetrahedron Lett., 1965, 2261.

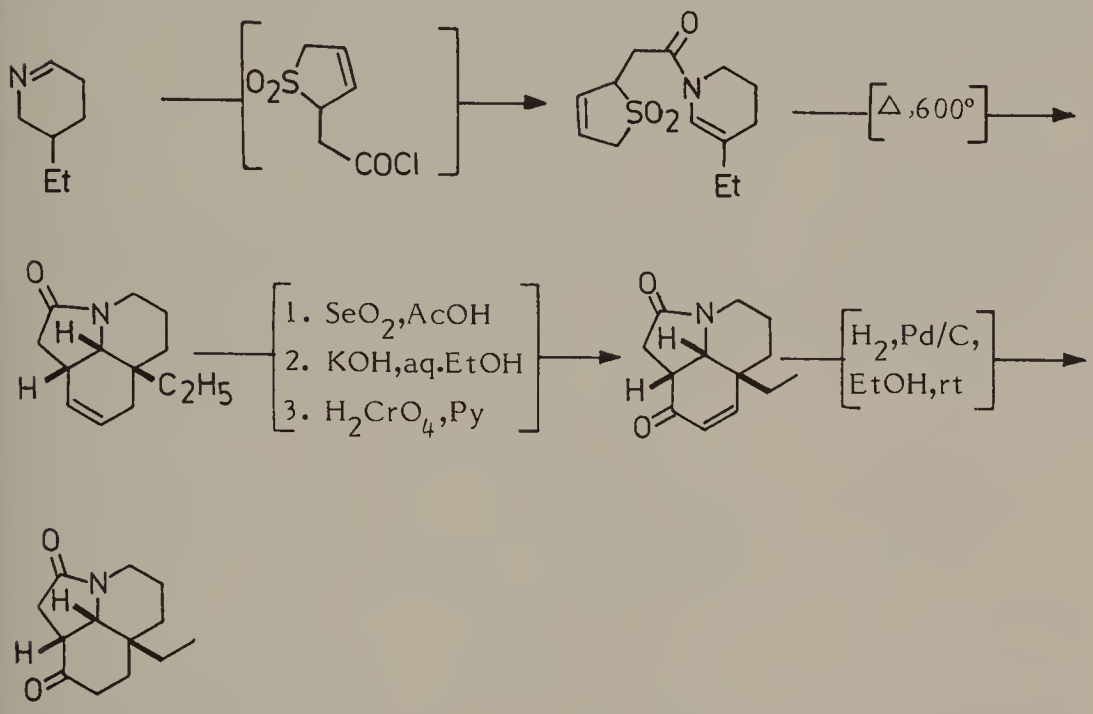
6.Kuehne,M.E; Baylia,C. Tetrahedron Lett., 1966, 1311.

Stevens et al. described the synthesis of the hydrolulidone (D) of Stork and Dolfini by a fundamentally different approach which involves acid-catalysed thermal rearrangement of a cyclopropylimine, (B) to an appropriately substituted 2-pyrroline, (C), as a key step (7).

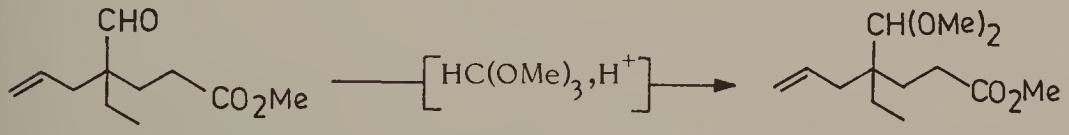


7. Stevens,R.V.; Fitzpatrick,J.M.; Kapla,M.; Zimmerman,R.L. Chem. Comm., 1971, 857.

Martin et al. have used yet another approach to the synthesis of the key hydrolulidone system by an intramolecular [4+2] cycloaddition reaction of enamides (8,9).



In the synthesis by Harley-Mason and Kaplan the pentacyclic system with the correct stereochemistry was obtained through a deep seated rearrangement of the octahydro-pyridocarboline intermediate Ⓔ (10,11).



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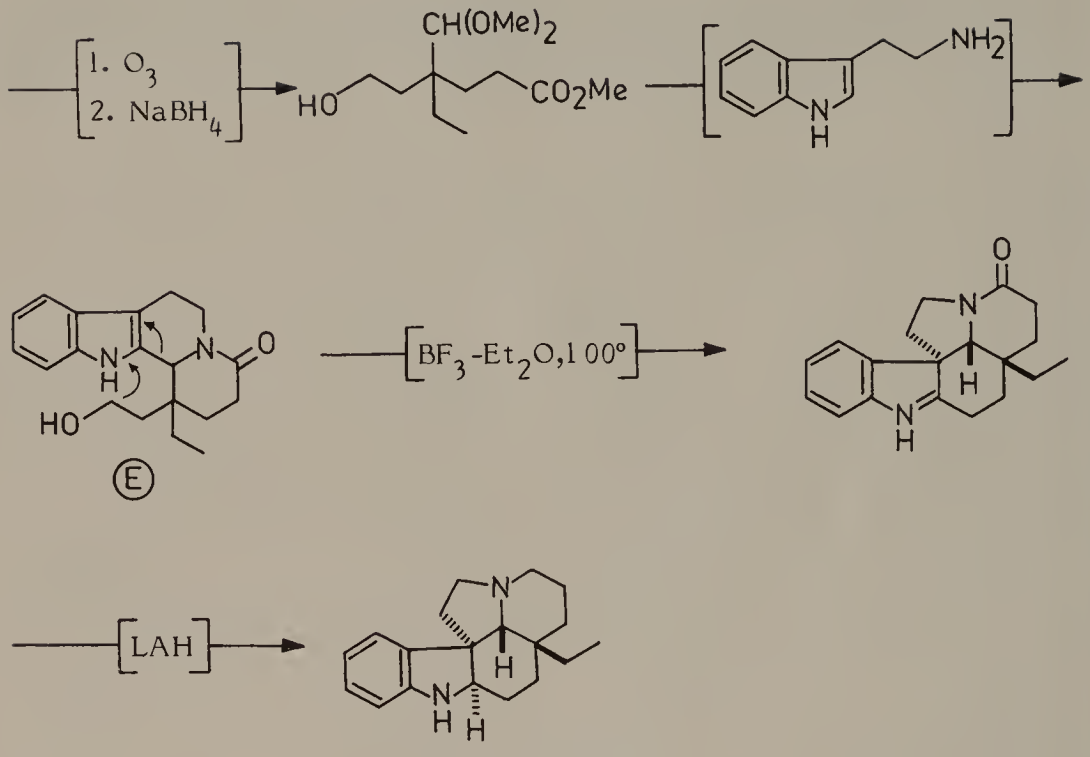
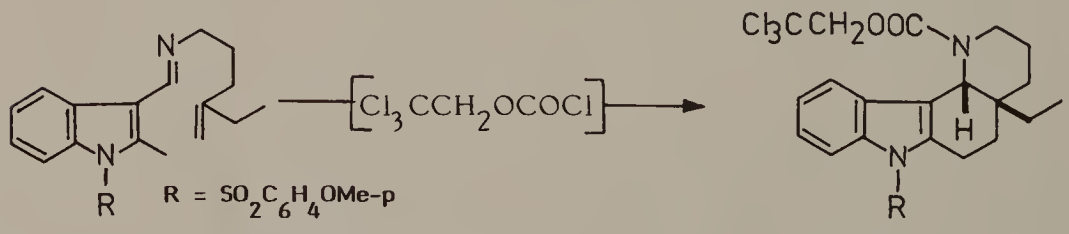
8. Martin,S.F.; Desai,S.R.; Phillips,G.W.; Miller,A.C. J. Am. Chem. Soc., 1980, 102, 3294.
9. For some of the other synthesis of the hydrolulidone; see: Ban,Y.; Akagi,M.; Oishi,T.; Tetrahedron Lett., 1969, 2057; Ban,Y.; Lijima,I.; Inone,I.; Akagi,M.; Oishi,T. ibid, 1969, 2067; Klioze,S.S.; Darmory,F.P. J. Org. Chem., 1975, 40, 1588.
10. Harley-Mason,J.; Kaplan,M. Chem. Comm., 1967, 915.
11. It appears that this remarkable stereospecific skeletal rearrangement is initiated by the formation of a carbonium ion at C-16 of the tetracyclic lactam (E).



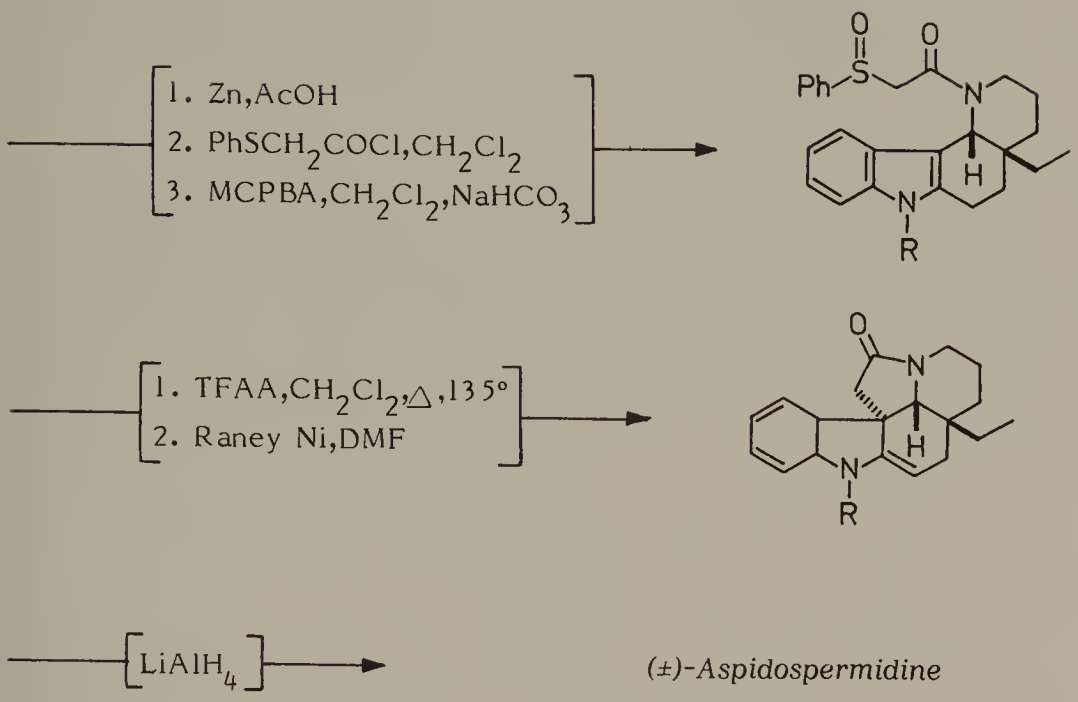
dl-Aspidospermidine

Gallagher et al. have described two versions of a highly convergent and stereospecific synthesis of (±)-aspidospermidine, based on the utility of 2,3-quinodimethane systems to construct polycyclic systems by [4+2] cycloaddition with defined stereochemistry at a number of contiguous asymmetric centres (12).

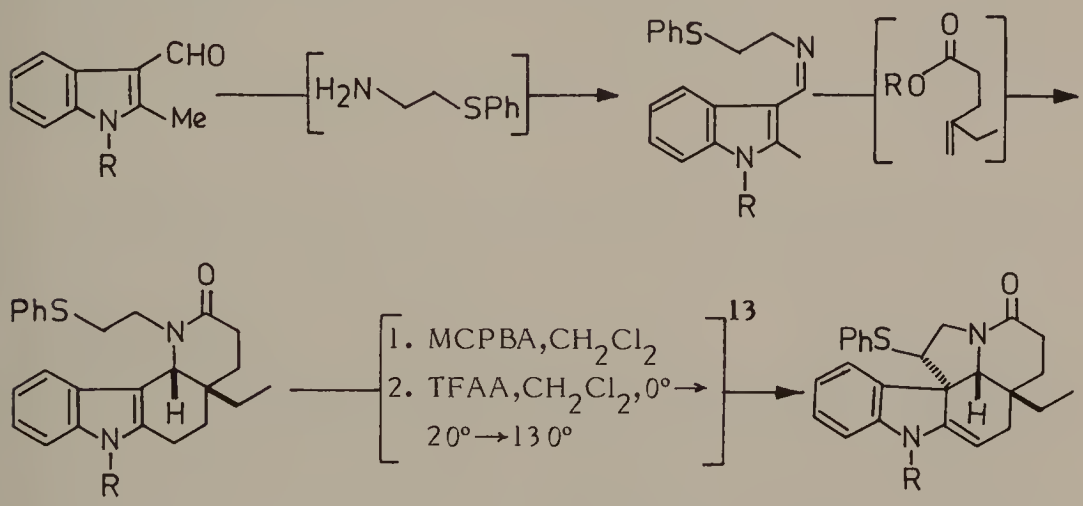
Carbamate route



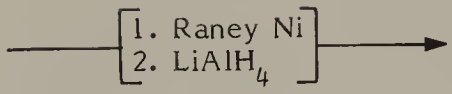
12. Gallagher,T.; Magnus,P.; Huffman,J.C. J. Am. Chem. Soc., 1982, 104, 1140; 1983, 105, 4750.



Endocyclic amide route

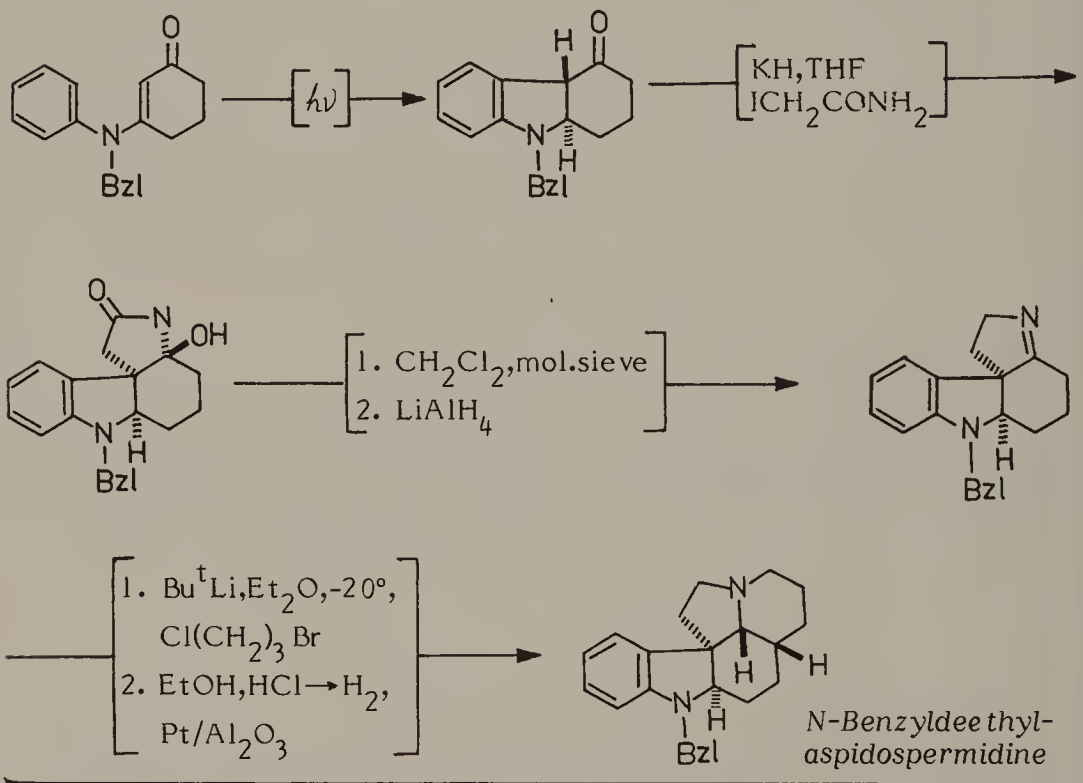


13. The assignment of stereochemistry at C-12 is based upon mechanistic consideration that align the sulfonium ion trans to the indole 2,3-double bond as shown below, and confirmed by obtaining the same product from Vincadiffermine; Gallagher,T.; Magnus,P.; Huffman,J.C. J. Am. Chem. Soc., 1983, 105, 4750.



(±)-Aspidospermidine

Gramain et al. have recently described a novel, short and efficient synthesis of Aspidosperma ring system (14), which is based on their photochemical approach for the formation of C-4a-substituted carbazol-4-one (15), which was followed by alkylation of the enolate with iodoacetamide to produce the key ABCE tetracyclic skeleton.

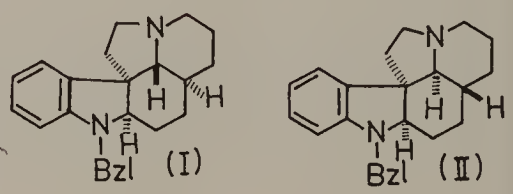


N-Benzyldeethyl-aspidospermidine

14. Gramain,J.C.; Husson,H.P.; Troin,Y. J. Org. Chem., 1985, 50, 5517.

15. Gramain,J.C.; Husson,H.P.; Troin,Y. Tetrahedron Lett., 1985, 26, 2323.

16. Hydrogenation led to the formation of three of the four possible diastereomers with the desired isomer as the major product, which were separated easily by column chromatography; the other two isomers were assigned the stereochemistry shown below on the basis of spectroscopic data.

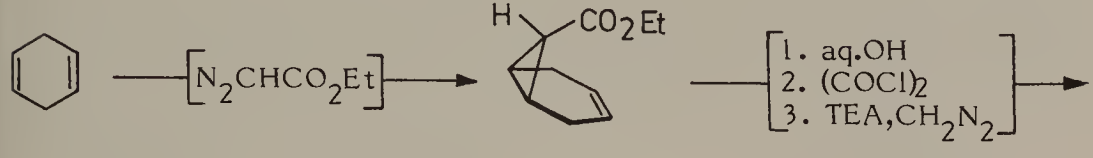


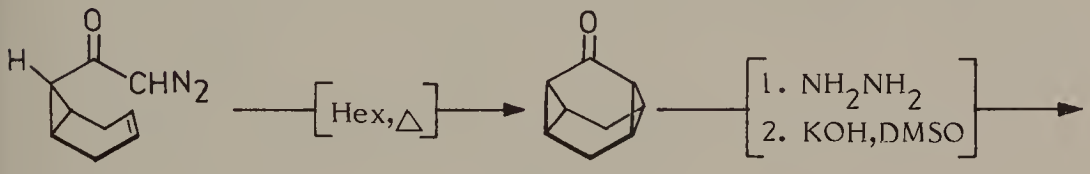
I

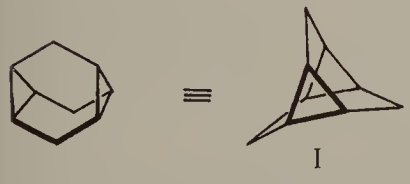
II

ASTERANES

Methylene bridging of parallelly stacked cyclic duplexes results in a periphery of rigidly held cyclohexane boats with a pleasing design that has been appropriately named as asteranes. The tri-asterane (I) has been prepared from cyclohexa[1,4]diene (1).

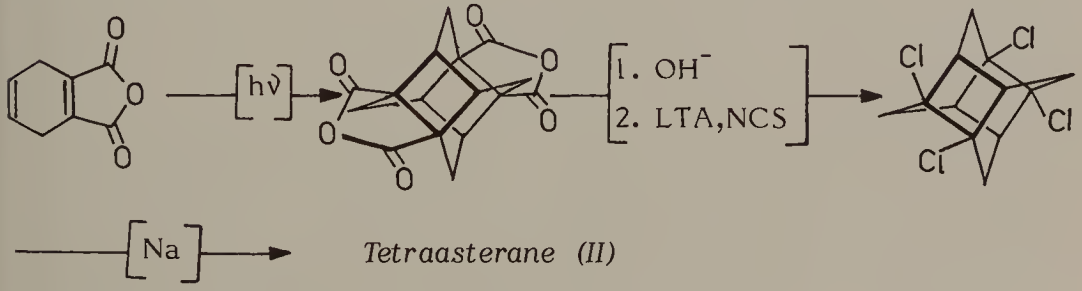






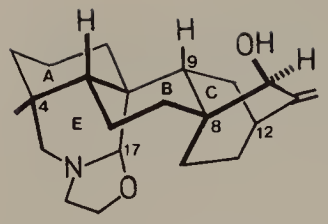
I

Tetra-asterane (II) has been prepared involving a key 4+4 photo-cyclo addition (2).



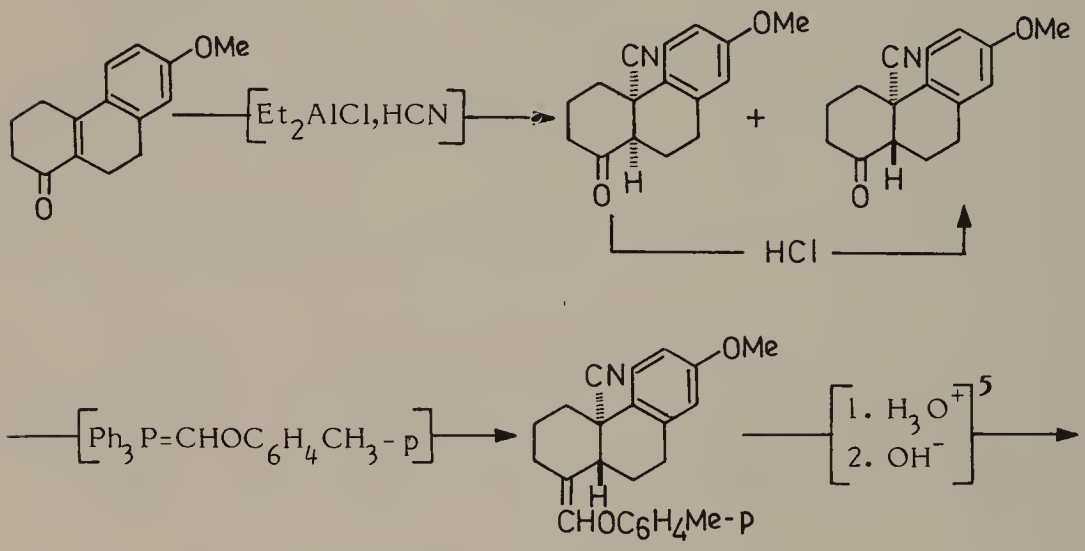
Tetraasterane (II)

1. Biethan,U.; Gizycki,U.; Musso,H. Tetrahedron Lett., 1965, 1477.
2. Musso,H. Angew. Chem. Int. Ed., 1975, 14, 180.



ATISINE

A major obstacle in the synthesis of diterpene alkaloids is the problem of constructing the A-E and C-D bridge ring systems, each of which have one end located at an angular position. The key to the first successful synthesis of atisine (1) was the application of a versatile new hydrocyanation procedure (2) for functionalizing the otherwise inaccessible C-10 and C-8 angular positions on the ABC tricyclic system. The angular cyano groups thus introduced have provided the necessary handle for building the desired bridged rings (3,4).



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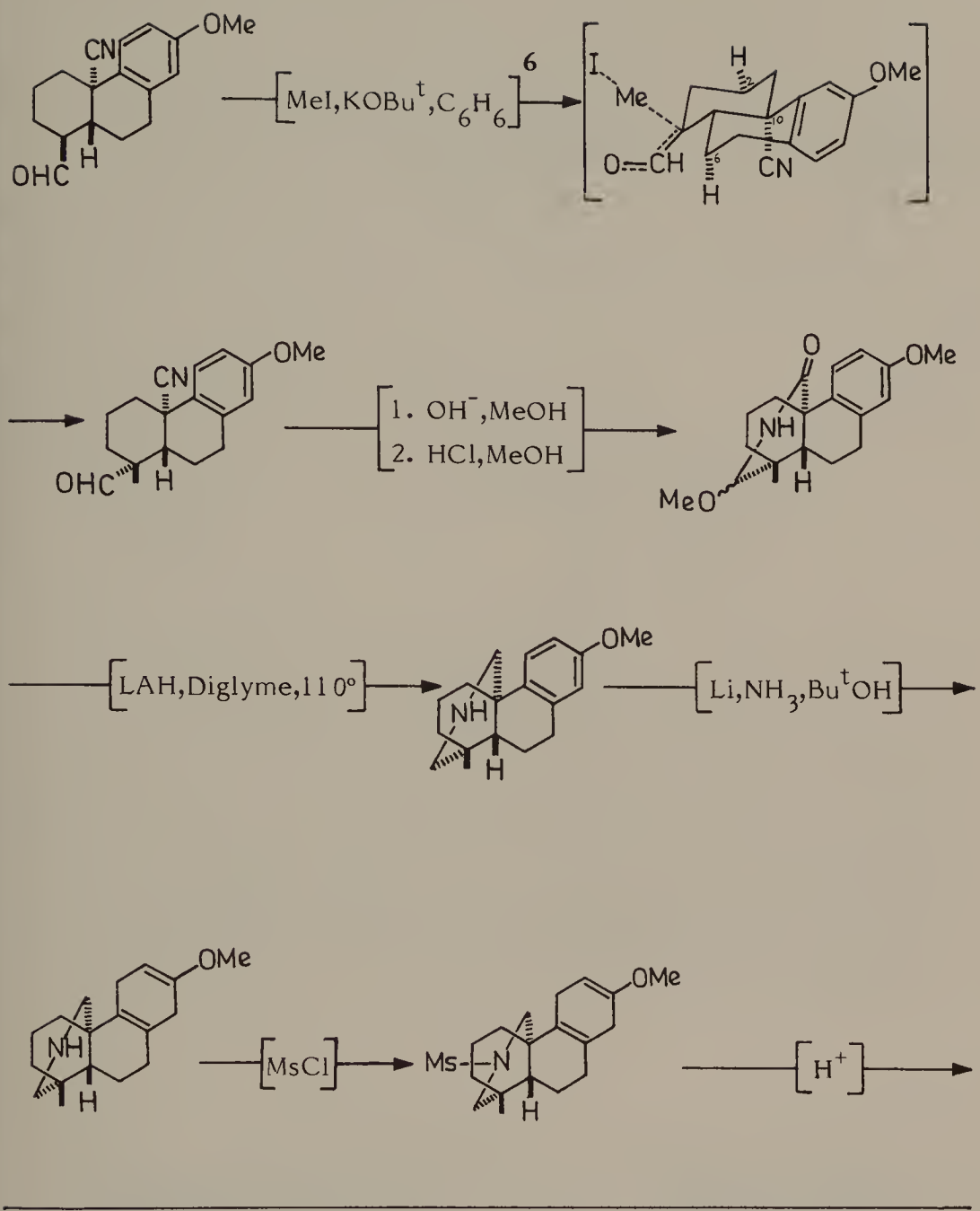
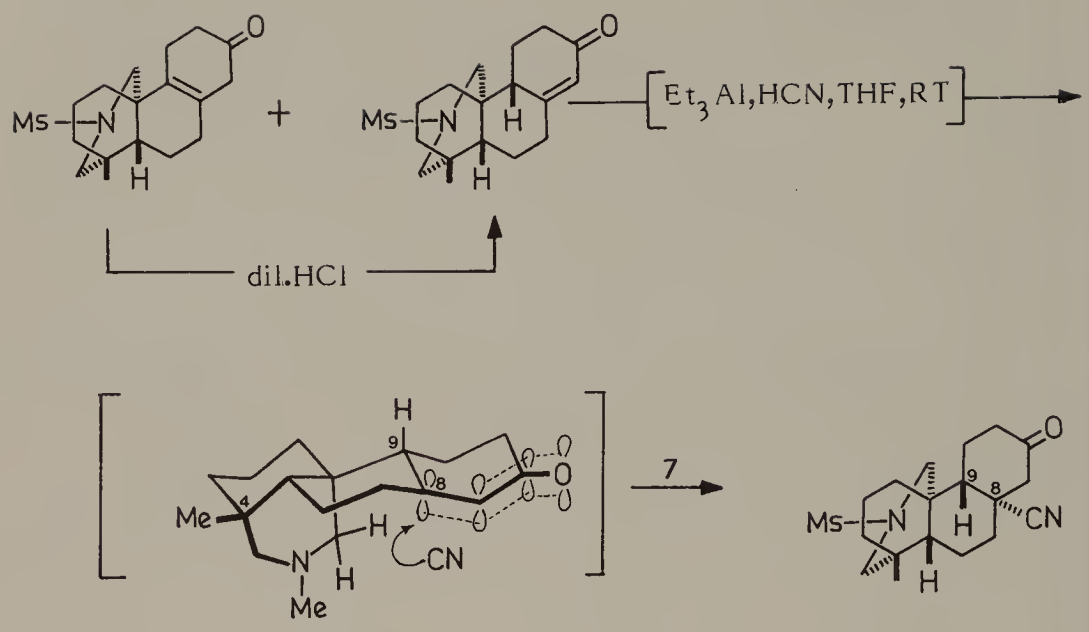
1. Nagata,W.; Sugasawa,T.; Narisada,M.; Wakabayashi,T.; Hayase,Y. J. Am. Chem. Soc., 1963, 85, 2342; 1967, 89, 1499.
2. For the use of alkylaluminium cyanides for hydrocyanation, see: Nagata,W.; Yoshioka,M. Tetrahedron Lett., 1966, 1913 and references cited therein.
3. An interesting account of the earlier work on the synthesis of atisine has been given by Ireland,R.E. Record Chem. Progr., 1963, 24, 225.
4. References to numerous other approaches towards the diterpene alkaloids are given in a recent review by Pelletier,S.W. Quart. Revs., 1967, 21, 525; successful syntheses of atisine have been reported by Masamune,S. J. Am. Chem. Soc., 1964, 86, 291 and Guthrie,R.W., Valenta,Z.; Wiesner,K. Tetrahedron Lett., 1966, 4645.
5. In Wittig reaction a mixture of geometrical isomers was formed, both of which on mild acid treatment gave the 9α-aldehyde which on base treatment was transformed to the 9β-epimer.



6. The approaching electrophile enters equatorially, avoiding axial substituents at C-2, C-6 and C-10.



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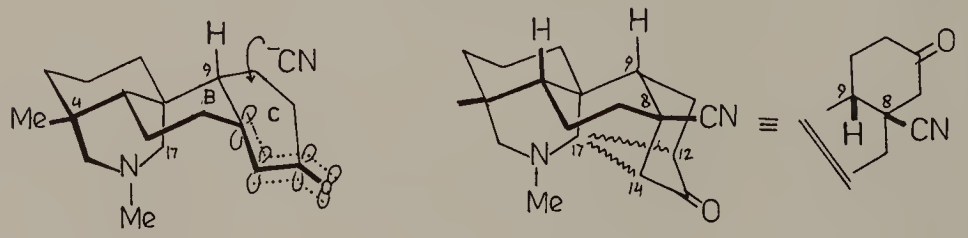
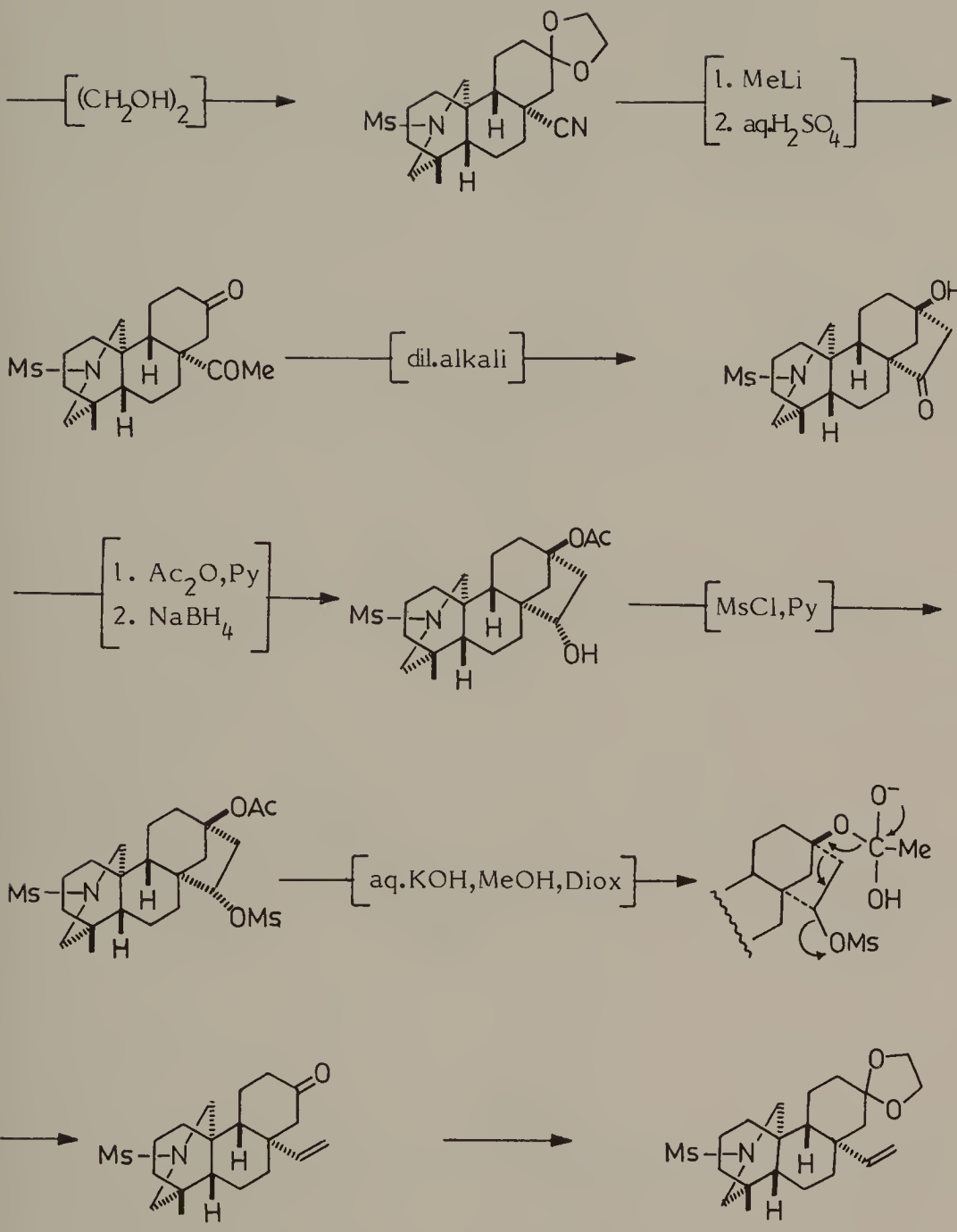
7. At the first sight it may appear that attack of the cyanide anion at the C-8 trigonal C-atom would occur relatively unhindered from the β-face [cf.(i)]resulting in a preferential formation of the B/C-cis fused product (ii). However, since we are dealing with transition states in which there must be a maximum overlap between the cyanide anion and the developing p-orbital at C-8 (i.e., C-8 is more nearly tetragonal), geometry of the transition state will resemble more the final product. In such an event two factors serve to militate against (i) as the more probable transition state: (a) ring C is in the energetically less favoured half-boat conformation, and (b) there is 1,3-diaxial interaction between the C-17 methylene and the protons at C-14 and C-12.



(i) (ii)



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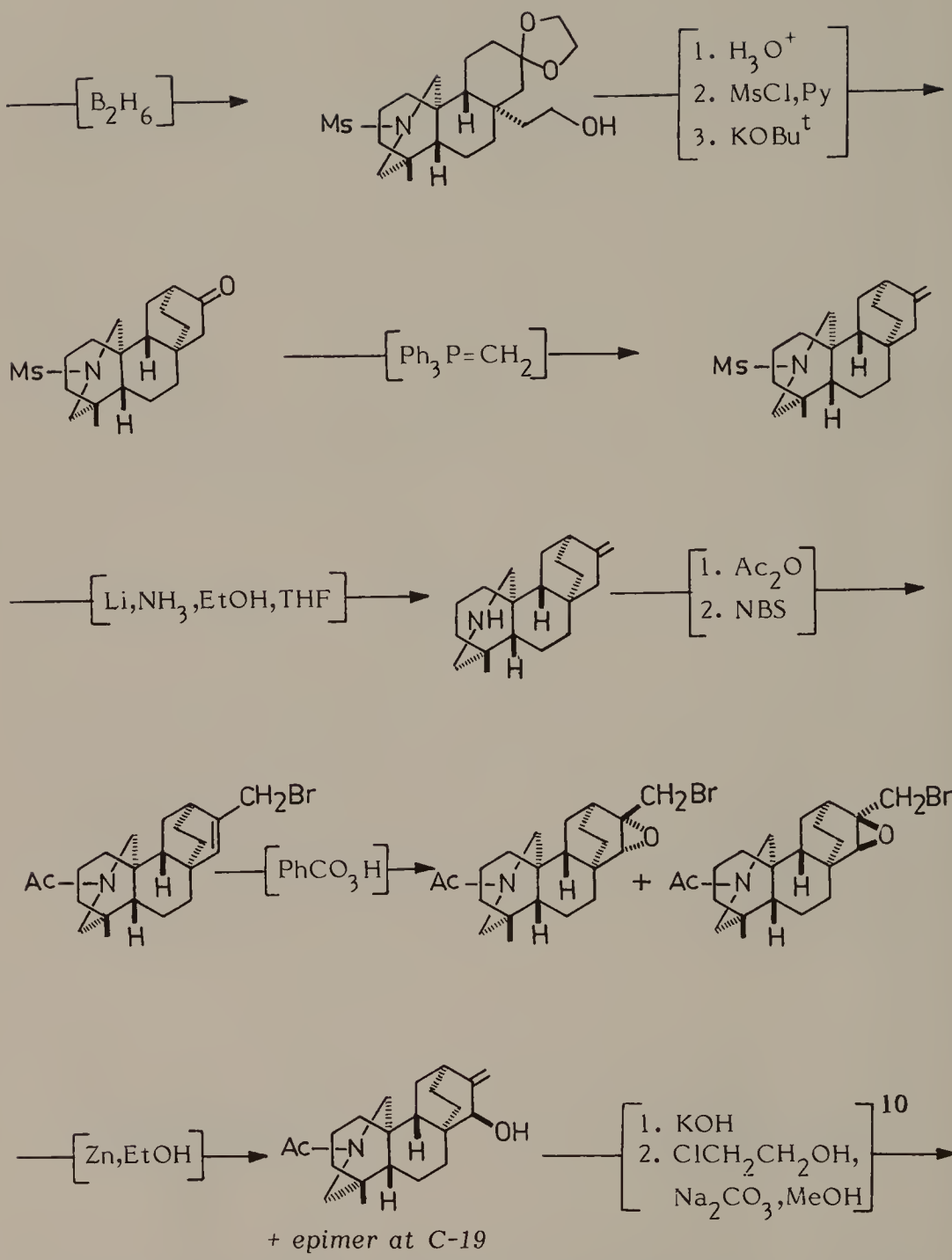
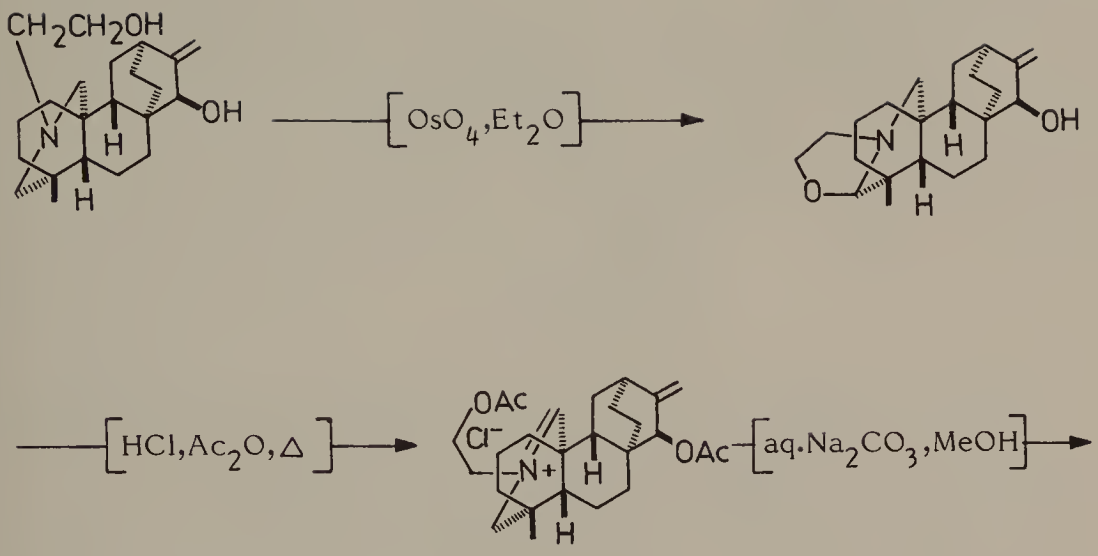
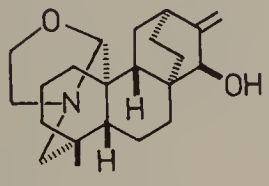
8. cf. Grob,C.A.; Schiess,P. Angew. Chem. Internat. Ed., 1967, 6, 1.

9. Employing this intermediate Nagata et al.(1) have also carried out the synthesis of dl-Veatchine and dl-garryine using approaches similar to that employed for atisine.

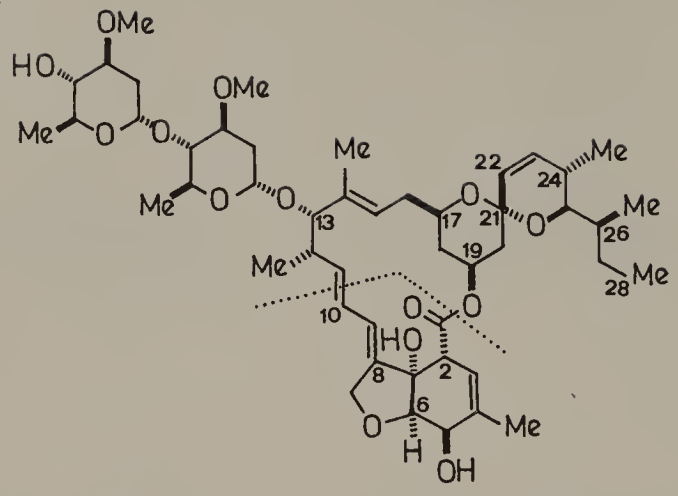


10. At this point the synthetic scheme intersects the partial synthesis of atisine reported by Pelletier,S.W.; Jacobs,W.A. J. Am. Chem. Soc., 1956, 78, 4144.


CH2CH2OH
OH
N
H
H
[OsO4,Et2O]
OH
N
H
O
H
[HCl,Ac2O,Δ]
OAc
Cl⁻
N+
H
H
OAc
[aq.Na2CO3,MeOH]


O
OH
N
H
H

dl-Atisine

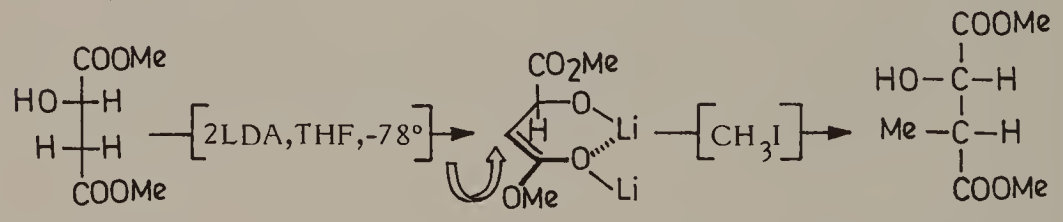


AVERMECTIN

The avermectins are a group of 16-membered macrocyclic lactones isolated from Streptomyces avermitilis with a high order of anthelmintic and insecticidal activities and seem to act by interfering with neurotransmission (1-3). These molecules with 12 asymmetric atoms in the aglycone part and 8 in the disaccharide residue with delicate functionalities offered a veritable challenge for synthesis. The first synthesis of avermectin B_{1a} described below is based on the strategy of constructing the molecule in two units, the "northern" segment (C_{11} -C_{28}) utilising chirons derived from (S)-malic acid and L-isoleucine, and the "southern" segment (C_1 -C_{10}), followed by coupling the two, macrolactonisation, stereocontrolled glycosylation and adjustment of functionalities (4).

"Northern" Segment (C_{11}-C_{28} fragment)

C_{11}-C_{14} Unit :



(S)-(-)malate

(S,S)-2-hydroxy-3-methylsuccinate

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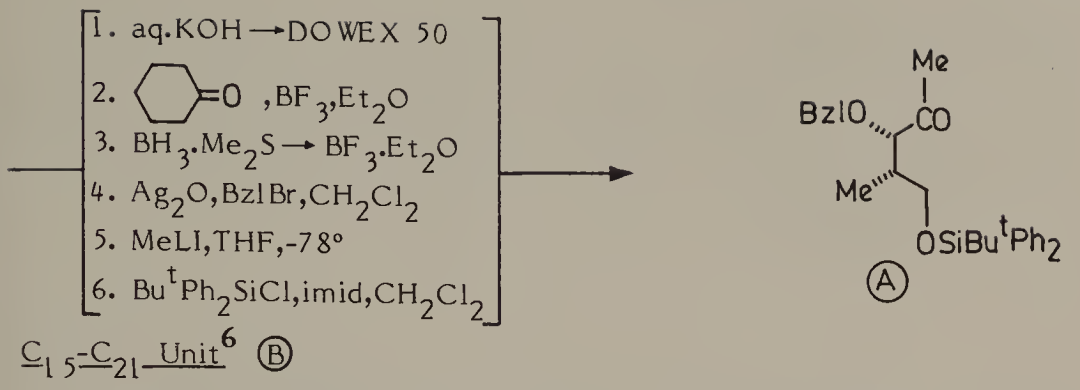
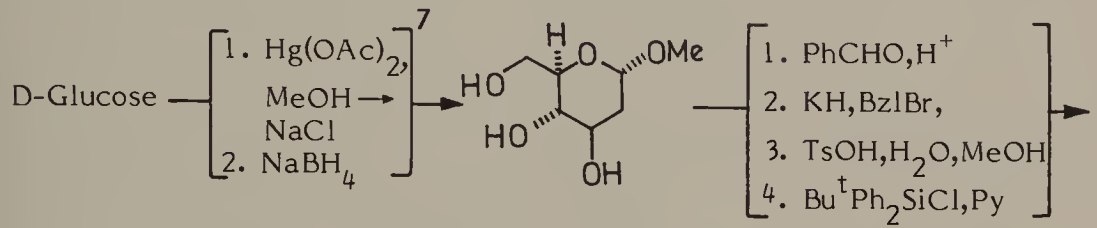
1. Burg,R.W.; Miller,B.M.; Baker,E.E. Antimicrob. Agents & Chemother., 1979, 15,361.
2. Miller,T.W.; Chaiet,L.; Cole,D.J. Antimicrob. Agents & Chemother., 1979, 15, 368.
3. Chabbale,J.C.; Mrozik,H.; Tolman,R.L. et al, J. Med. Chem., 1980, 23, 1134.
4. Hanessian,S.; Ugolini,A.; Dube,D.; Hodges Paul,J.; Andre,C. J. Am. Chem. Soc., 1986, 108, 2776, and references cited therein of their earlier work on the synthesis of some fragments.
5. Seebach,D.; Wasmuth,D. Helv. Chim. Acta, 1980, 63, 197.

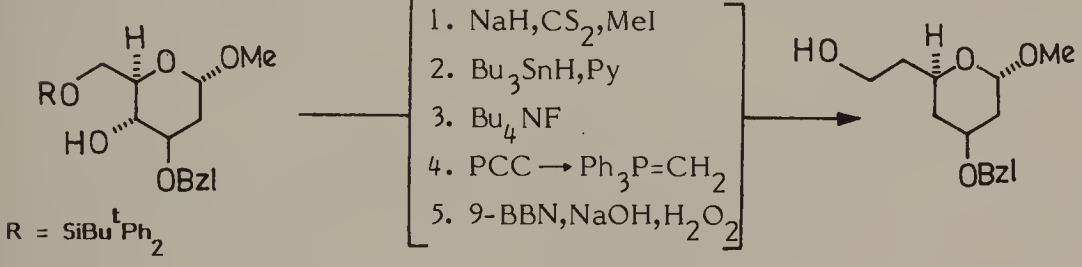


$\underline{C_{15}\text{-}C_{21}}$ $\underline{\text{Unit}}^6$ (B)

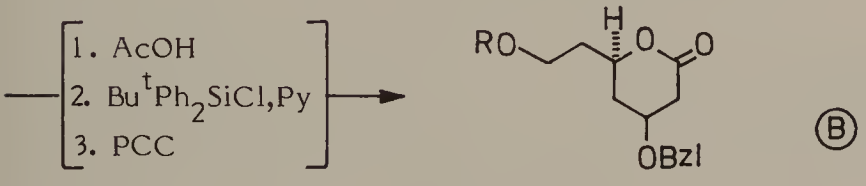
This was synthesised both from D-glucose and (S)-(-)-malic acid as follows:

From D-Glucose





R = $SiBu^tPh_2$



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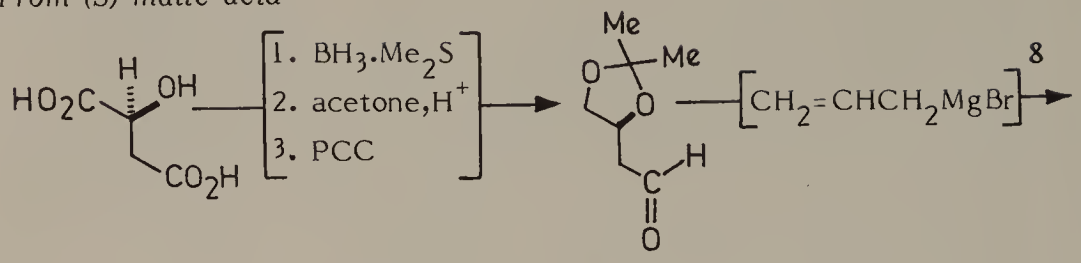
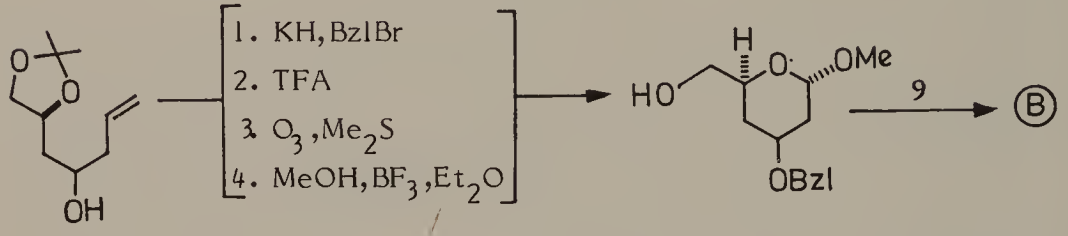
6. Hanessian,S.; Ugolini,A.; Therien,M. J. Org. Chem., 1983, 48, 4427.

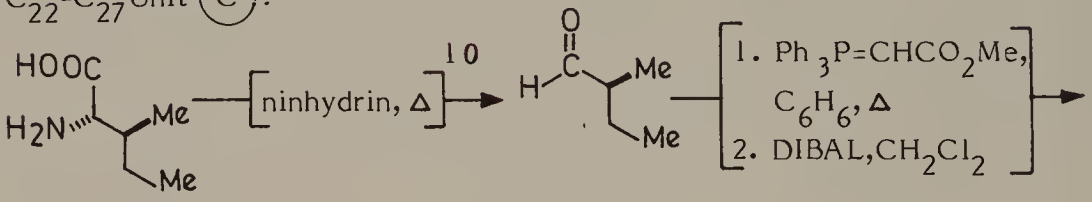
7. Corey,E.J.; Fuchs,P.L. Tetrahedron Lett., 1972, 3769.

From (S)-malic acid

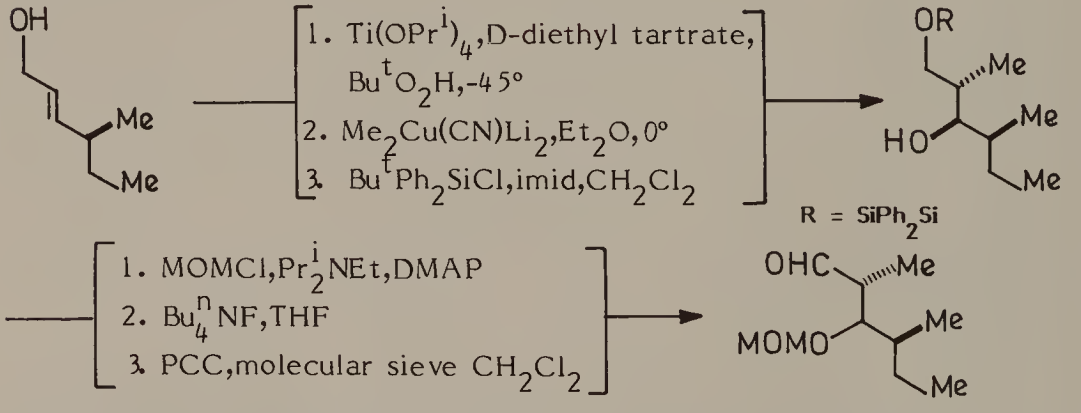




C_{22}-C_{27} Unit (C):



L-isoleucine



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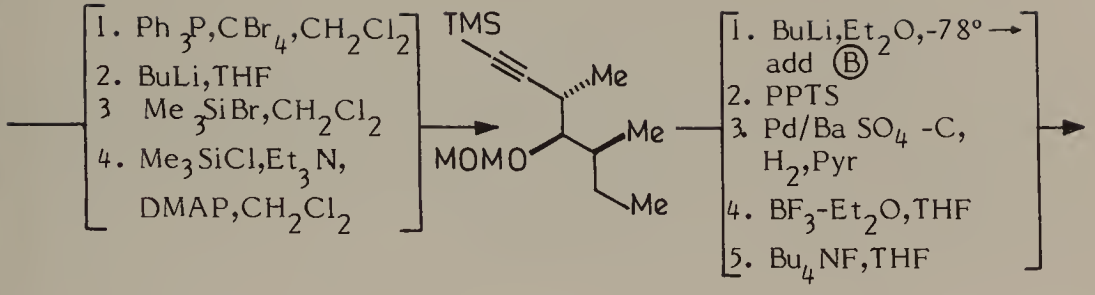
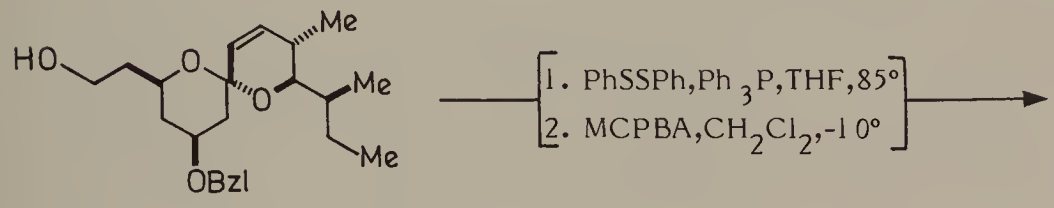
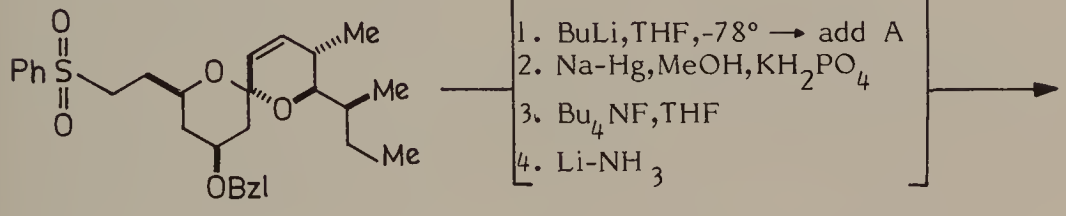
8. The product was obtained as a 1:1 mixture of homoallylic alcohols, which could be separated by chromatography.

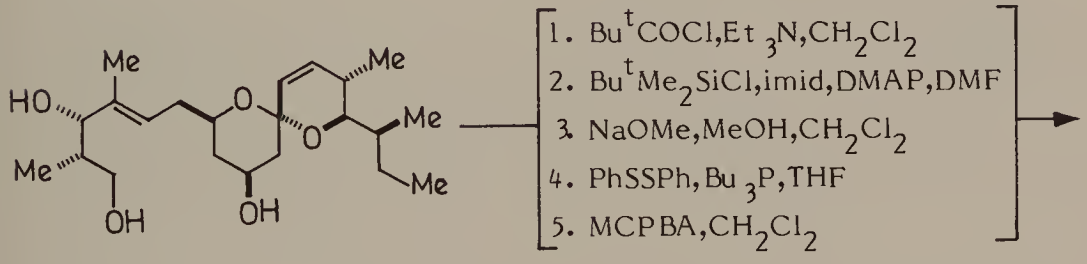
9. Chain was extended and (B) obtained as in the case of (D)-glucose.

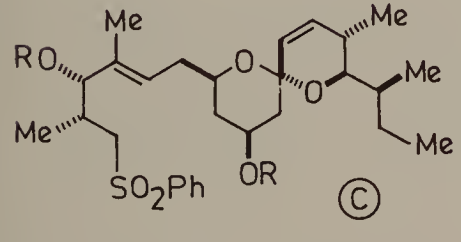
10. Fores,W.S. J. Am. Chem. Soc., 1954, 76, 1377.


1. Ph_3P,CBr_4,CH_2Cl_2
2. BuLi,THF
3. Me_3SiBr,CH_2Cl_2
4. Me_3SiCl,Et_3N, DMAP,CH_2Cl_2
TMS
MOMO
Me
Me
Me
1. BuLi,Et_2O,-78° → add Ⓑ
2. PPTS
3. Pd/Ba SO_4 -C, H_2,Pyr
4. BF_3-Et_2O,THF
5. Bu_4NF,THF


HO
Me
Me
Me
OBzl
1. PhSSPh,Ph_3P,THF,85°
2. MCPBA,CH_2Cl_2,-10°


O
Ph S
O
Me
Me
Me
OBzl
1. BuLi,THF,-78° → add A
2. Na-Hg,MeOH,KH_2PO_4
3. Bu_4NF,THF
4. Li-NH_3

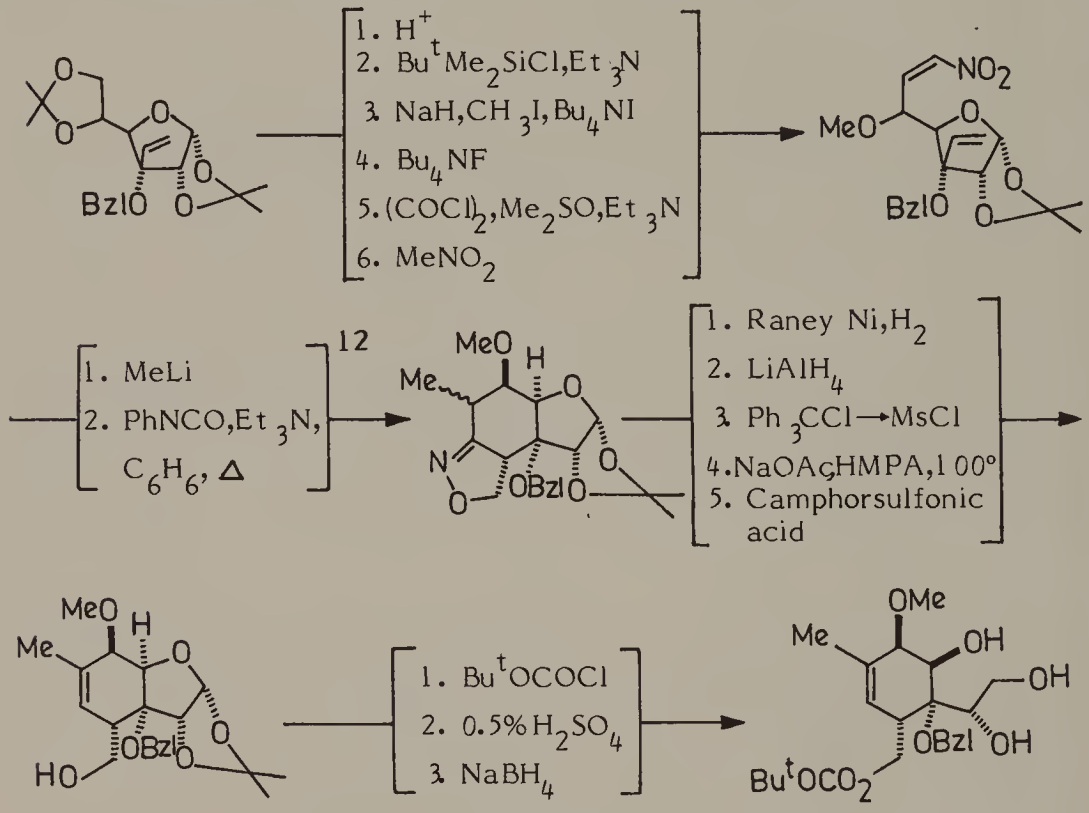

HO
Me
Me
Me
Me
Me
OH
OH
1. Bu^tCOCl,Et_3N,CH_2Cl_2
2. Bu^tMe_2SiCl,imid,DMAP,DMF
3. NaOMe,MeOH,CH_2Cl_2
4. PhSSPh,Bu_3P,THF
5. MCPBA,CH_2Cl_2


RO
Me
Me
Me
Me
Me
SO_2Ph
OR
Ⓒ

R = Bu^tMe_2Si

"Southern" Segment (C_1-C_{10} fragment)

This segment has been obtained by controlled ozonolysis of avermectin B seco-ester by Hanesian et al (4). Its synthesis by Prashad & Fraser-Reid (11) described below starts with diacetone glucose as the core chiron and the additional chiral centres are created by an intramolecular nitrile oxide-vinyl group (3+2) cycloaddition reaction (INOC) (12), leading to oxahydrindene.



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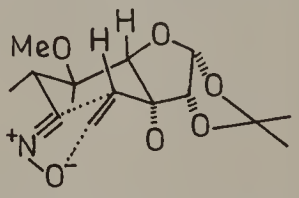
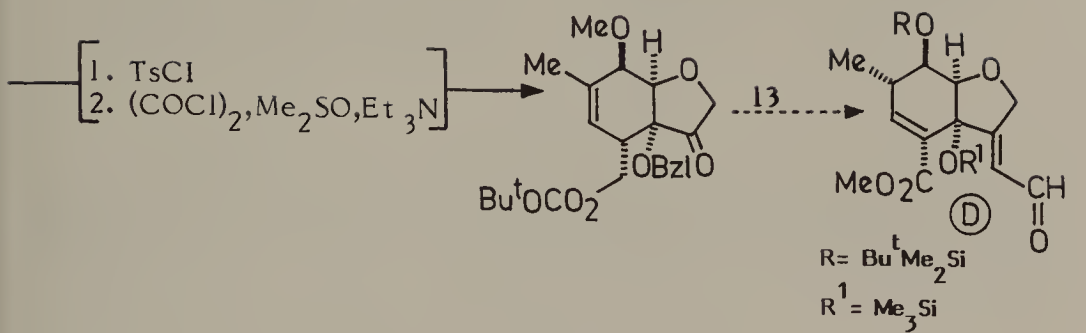
11. Prashad,M.; Fraser-Reid,B. J. Org. Chem., 1985, 50, 1564.

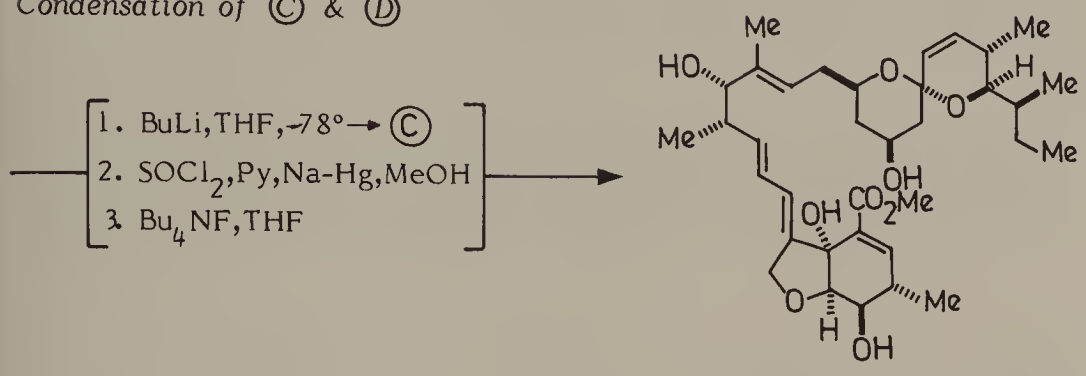
12. The INOC reaction and the configuration thus generated at C_2 was central to the whole strategy; of the possible modes of cyclisation the one which proceeds through the chair transition state shown below seemed more likely and only one product was obtained in this reaction. The stereochemistry of the product was supported by the H1-H2 relationship determined by the 250 MHz PMR of the benzylidene derivative of the olefin obtained in the next step.

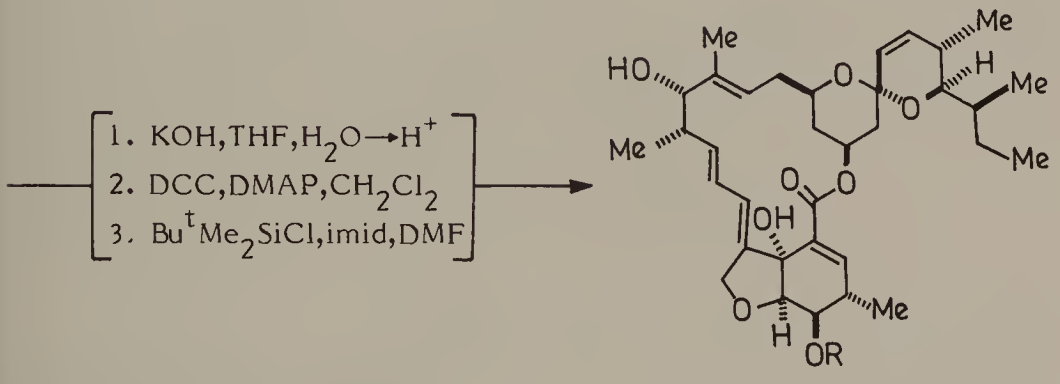


13. Prashad and Fraser-Reid have described this synthesis upto the primary alcohol, while Hanessian, et al (4) have stated that the synthesis of (D) will be reported later.



Condensation of © & Ⓓ





1. 2-Pyridyl-thioglycoside of disaccharide (**14**),CH_2Cl_2→AgOTf
2. Me_3SiCl,Et_3N,DMAP,CH_2Cl_2
3. LDA,Me_3SiCl,THF,-78°→AcOH
4. Bu_4NF,THF

→ *Avermectin (+)-B_{1a}*

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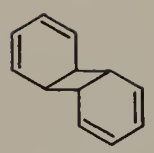
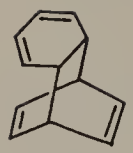
14. The disaccharide subunit was obtained from avermectin B_{1a} (4).



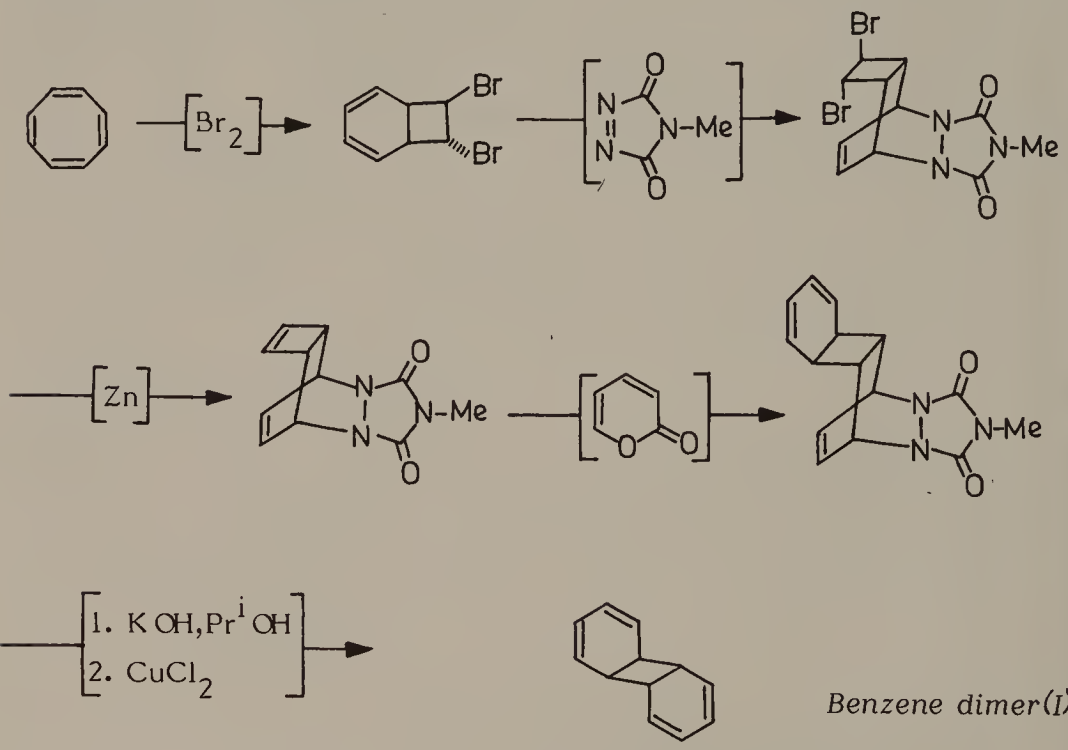
I



II

BENZENE DIMER

Benzene dimers are important members of the $C_{12}H_{12}$ family. As in the case of Dewar benzene, their reversal to the aromatic benzene could be restrained by imposing orbital symmetry constraints. For example, of the two possible benzene dimers I and II, thermal reversion to benzene is allowed only for II. Consequently the energetics related to I and II reversal could provide information about the magnitude of the orbital symmetry control. Compound I has been prepared in a very elegant manner (1).



Benzene dimer(I)

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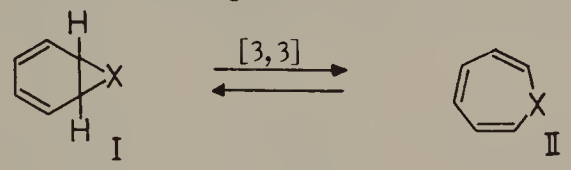
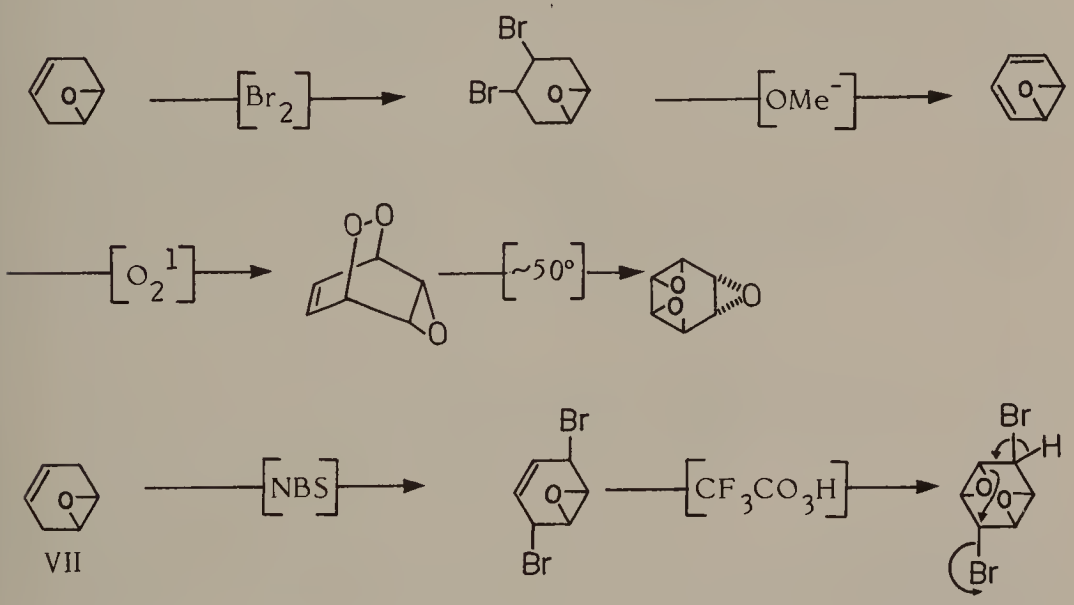
1. Berson, J.A., Davis, R.F. J. Am. Chem. Soc., 1972, 94, 3658.

BENZENE OXIDES

The exploitation of fragile sigma bonds in pericyclic reactions have led to many novel systems, the most notable being Doering's bullvalene (1). The inspiration for bullvalene came from the understanding of the facile I--II change. Thus, benzene oxide (I,X=O) gives



oxepin (II,X=O) and it could be predicted that Z,Z benzene dioxide [III] should give 1,4-dioxocin [IV] and finally that all Z benzene trioxide [V] should give VI. These expectations have been realized (2). The interrelationships that exist in the benzene oxide series is illustrated below:



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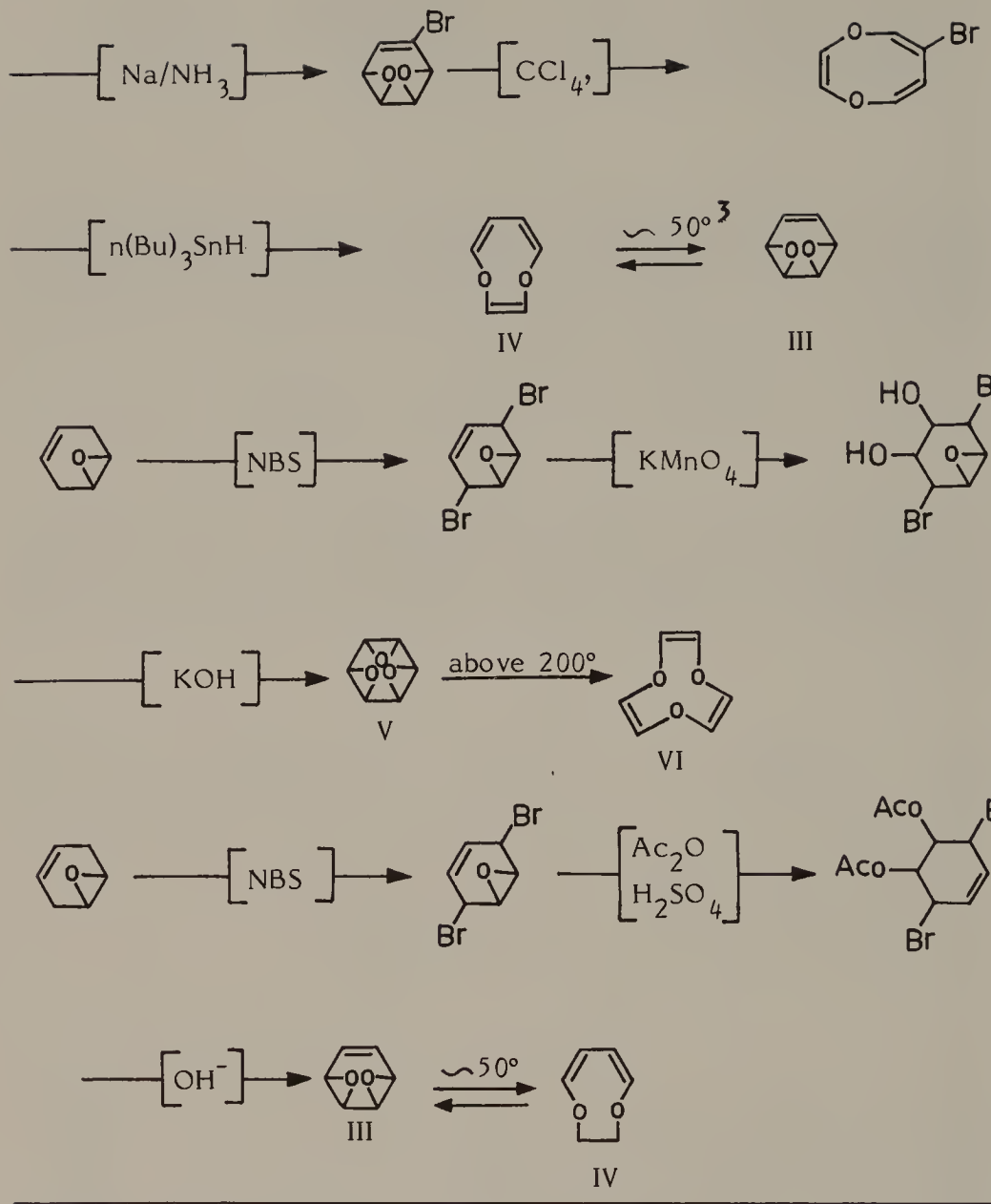
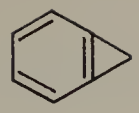
1. Von Doering, W., Ferrier, B.M., Fossel, E.T., Hartenstein, J.H., Jones Jr., M., Klumpp, G., Rubin, R.M., Saunders, M., Tetrahedron, 1967, 23, 3943.

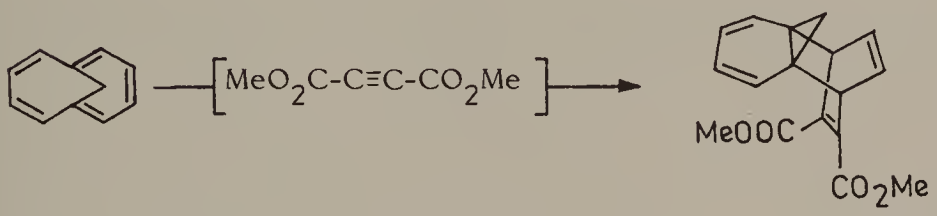


2. Vogel,E.; Altenbach,H.J.; Cremer,D. Angew. Int., 1972, 11, 935; Altenbach,H.J.; Vogel,E. Angew. Int., 1972, 11, 937.
3. At 50°, III:IV::5:95; Ea = 27 kcal/mole; A = 7.1×10^{13}.



BENZOCYCLOPROPENE

Benzocyclopropene is an intriguing compound in which two of the sigma bonds of benzene are bent to form a three membered ring(1). The compound, prepared(2) in an ingenious manner by a retro Diels-Alder reaction, was found to be a reasonably stable one and spectral data showed no noteworthy disturbance of delocalization of the π system(3).



Benzocyclopropene

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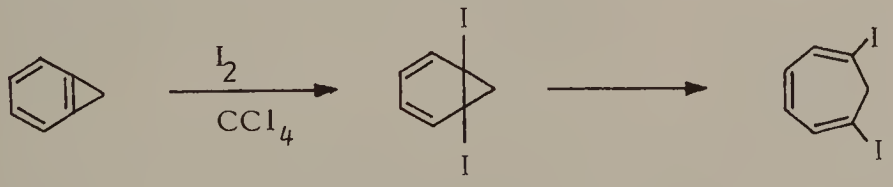
1. E. Fullman and E. Buncel, J. Am. Chem. Soc., 85, 2106 (1963).

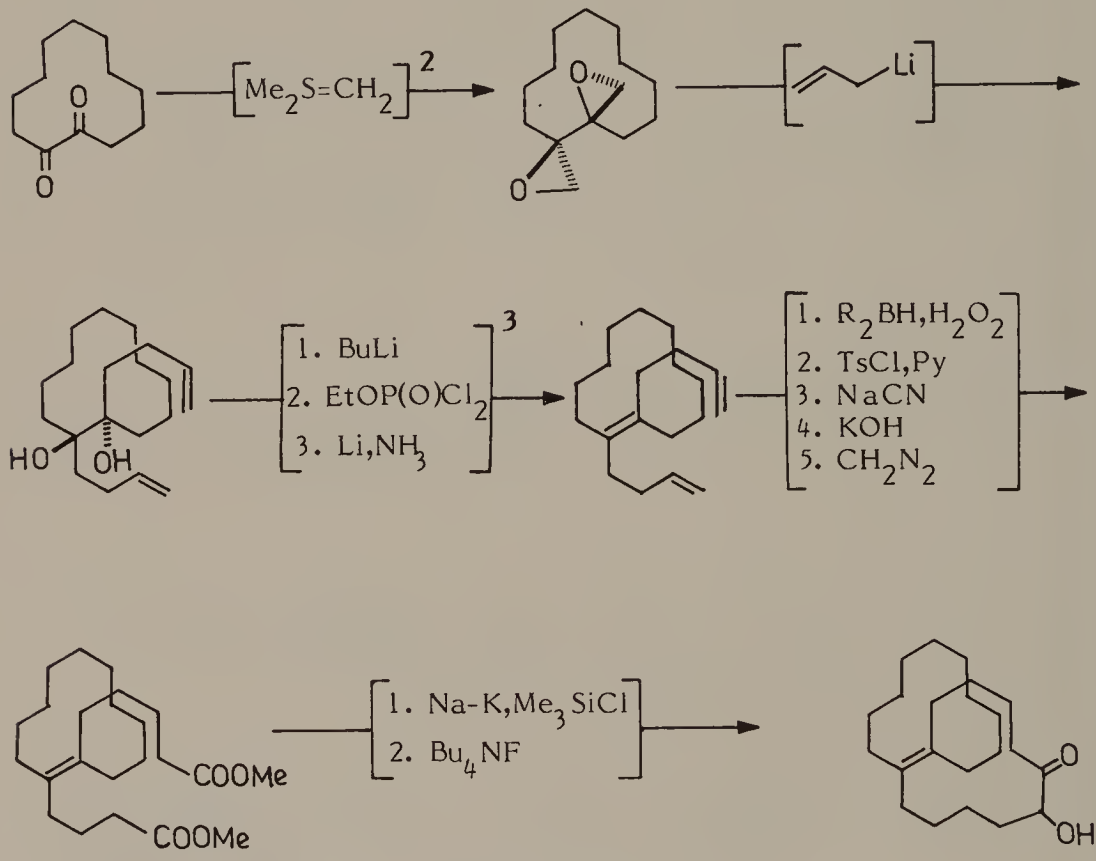
2. E. Vogel, W. Grimme and S. Korte, Tetrahedron Letters, 3625 (1965).

3. The bridge double bond, however, is highly reactive:



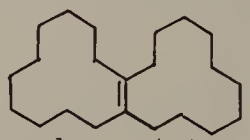
BETWEENANENES

Betweenanenes represent a particularly aesthetically pleasing carbon constellation. These chiral compounds are π systems, necessarily sandwiched "between" the alkyl chains. The first ingenious and selective synthesis of [1 0,1 0]betweenanene was accomplished from cyclododecane-1,2-dione (1).

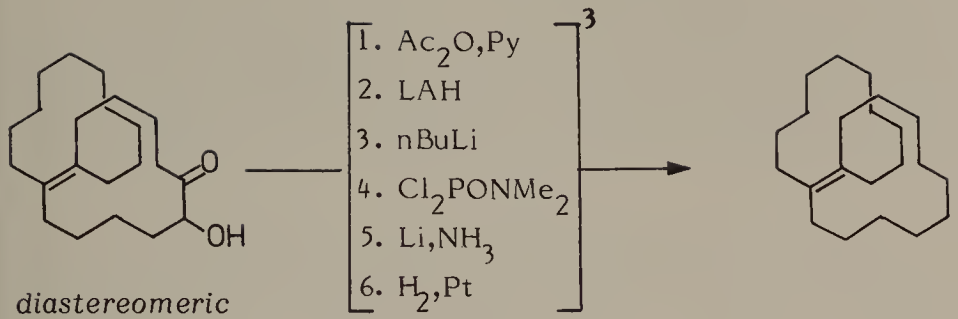


1. Marshall,J.A.; Lewellyn,M.E.J. Am. Chem. Soc., 1977, 99, 3508.

2. A mixture of trans and cis bisepoxides formed in a ratio of 1.5:1 was obtained, separable by column chromatography. The subsequent reaction sequence when carried out on the cis bisepoxide afforded bicyclo [10.10.0]docos-1(12)-ene.

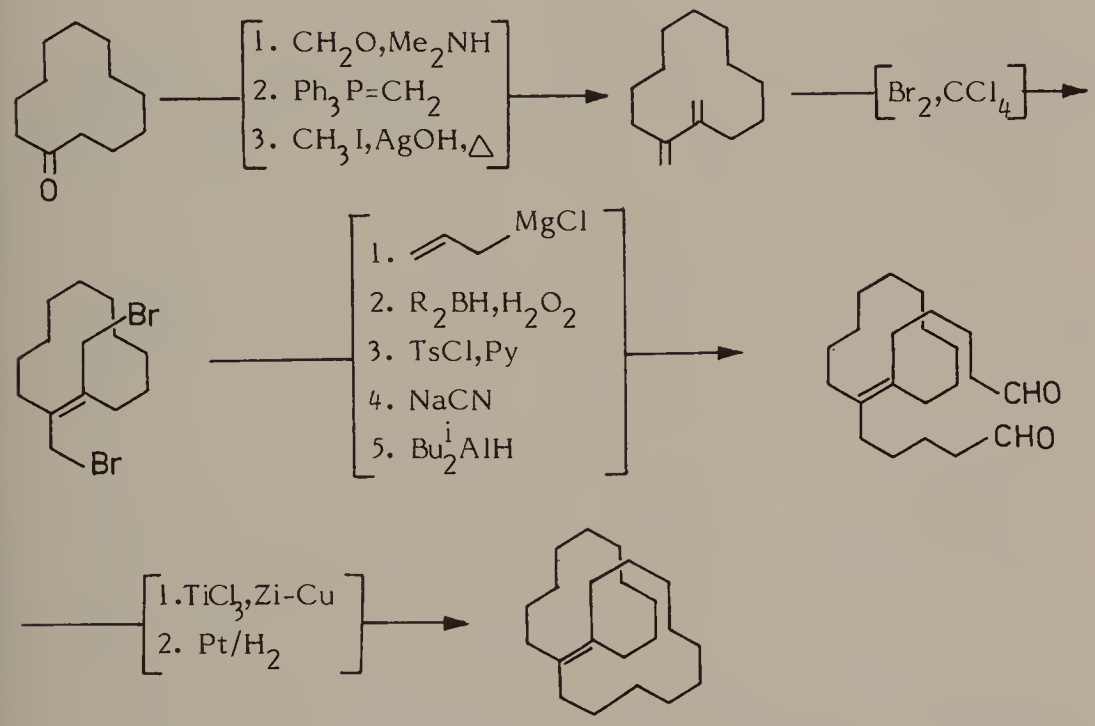


Bicyclo[10.10.0]docos-1(12)-ene



diastereomeric mixture of 60:40

A variant of the above strategy was to start with cyclododecanone (4).



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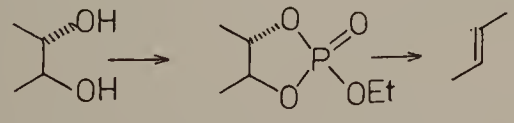
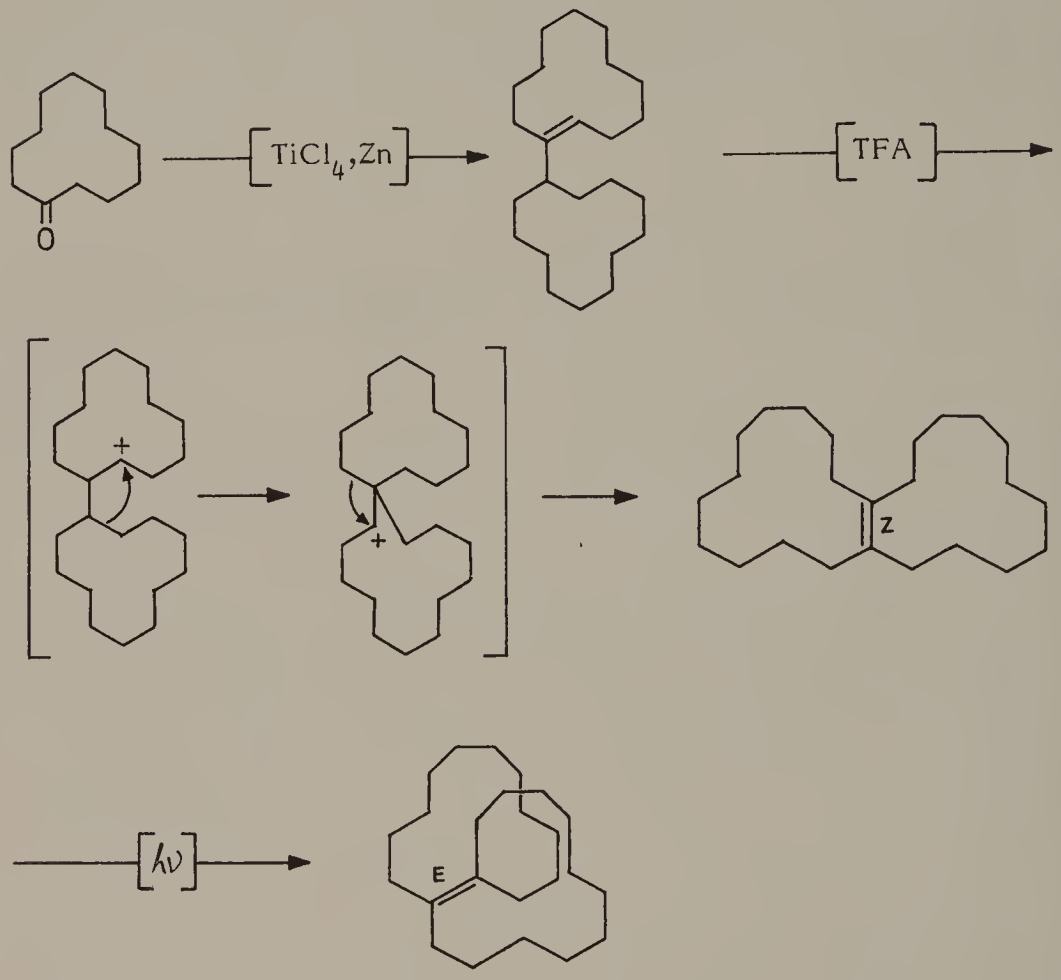
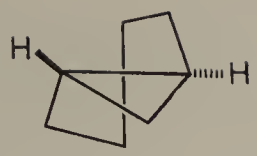
3. 

4. Marshall,J.A.; Chung,Kyoo-Hyun, J. Org. Chem., 1979, 44, 1566.

The photochemical E→Z isomerization of systems has been taken advantage of towards the synthesis of [11,11]betweenanene, in 3 steps from cyclododecanone, the most attractive feature of which is the creation of the bicyclic system by carbocation reorganization (5).

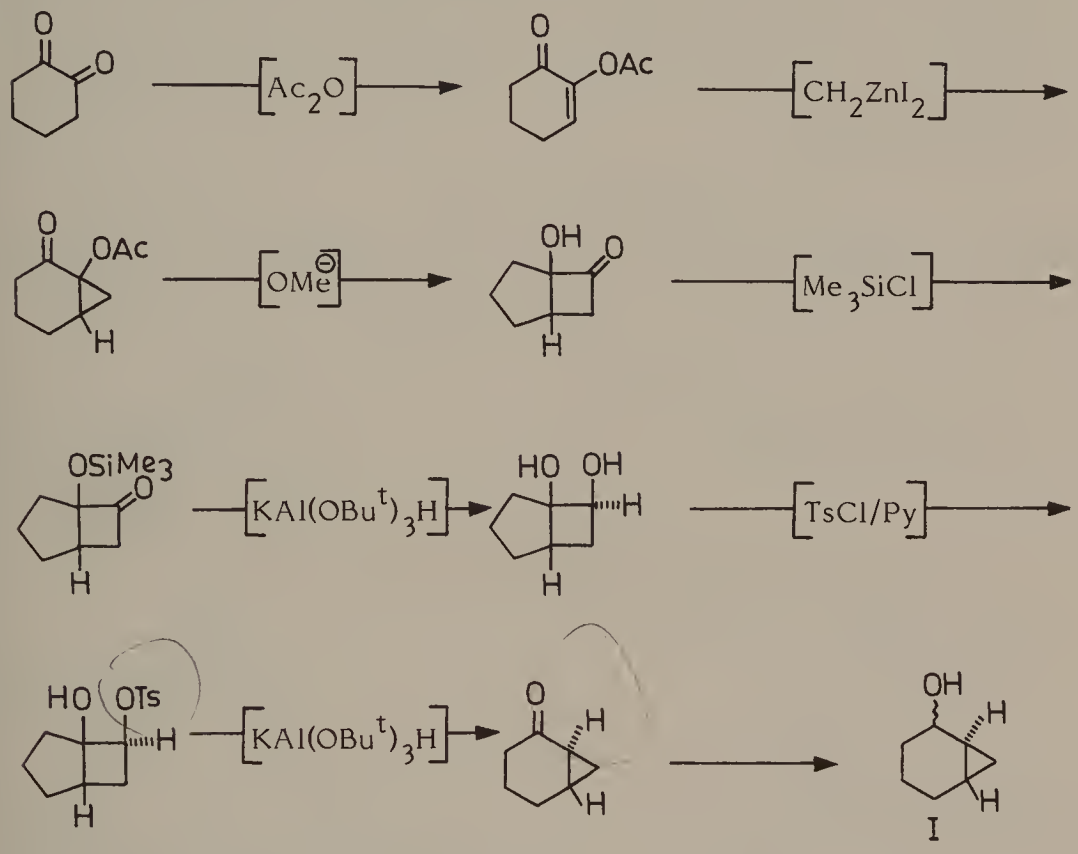


5. Nickon,A.; Zurer,P.St.J.Tetrahedron Lett., 1980, 3527.

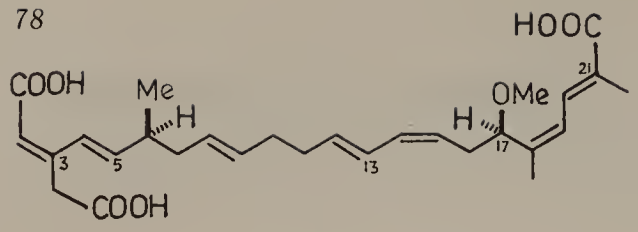


E-BICYCLO(4,1,0)HEPTANE

A cyclopropane unit would considerably enhance the strain relative to the corresponding olefins in alicyclic systems. On this basis, E-bicyclo(4,1,0)heptane [I] should be considerably more strained than E-cyclohexene. Yet, such systems have been made involving a highly stereospecific ring contraction step (1).



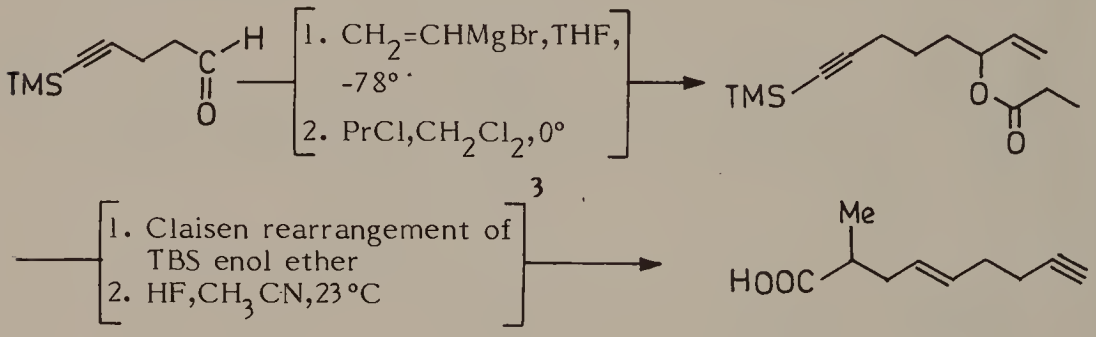
1. Paukstelis, J.V., Kao, J. J. Am. Chem. Soc., 1972, 94, 4783.

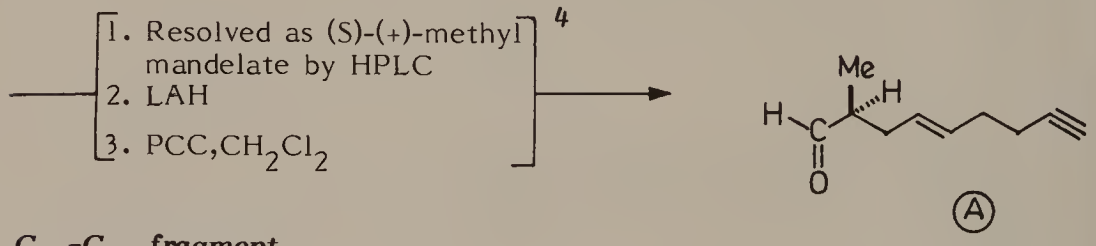


BONGKREKIC ACID

Bongkrekic acid, a toxin produced by Pseudomonas cocovenenans, has a high affinity for the mitochondrial translocator protein necessary for ATP function in eukaryotic cells (1). Its synthesis by Corey and his associates (2) is based on a retrosynthetic recognition of two β-methyl glutaconate units in two end segments of the molecule, which led to the design of a stereocontrolled converging synthesis from three fragments, C_1-C_4, C_5-C_{13} and C_{14}-C_{22} with required absolute stereochemistry, and this allowed for good stereocontrol.

C_5-C_{13} *Fragment*





C_{14}-C_{22} *fragment*

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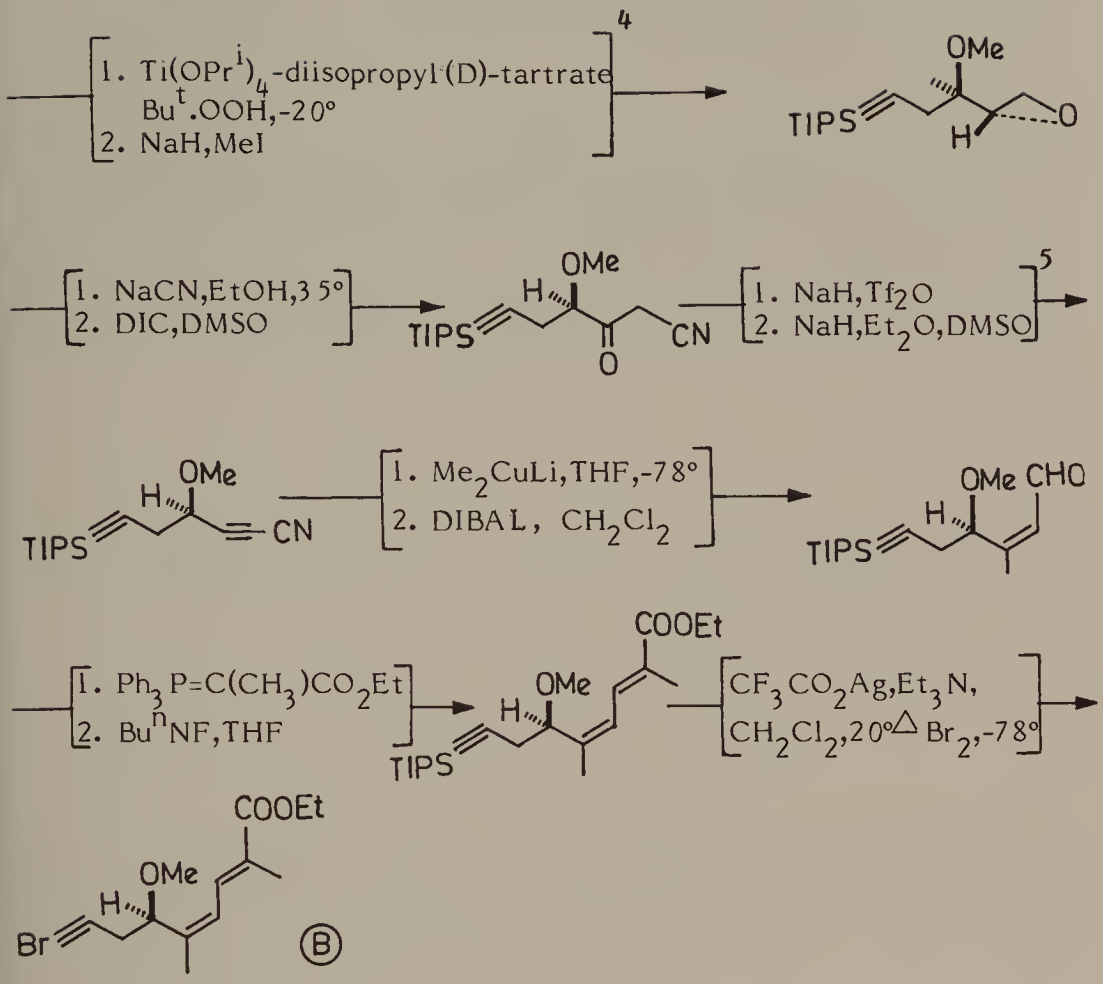
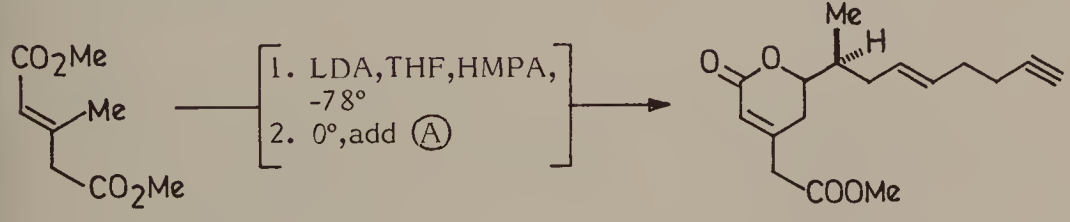
1. Khugensberg,M. Trends Biochem. Sci., 1979, 4, 249, and references cited therein.
2. Corey,E.J.; Tromantano,A. J. Am. Chem. Soc., 1984, 106, 462.
3. Ireland,R.E.; Mueller,R.H.; Willart,A.K. J. Am. Chem. Soc., 1976, 98, 2868.
4. The product was obtained as a mixture of (S,S) and (R,S) diastereomers.



C_1-C_{13} fragment



mixture of R,S & S,S diastereomers

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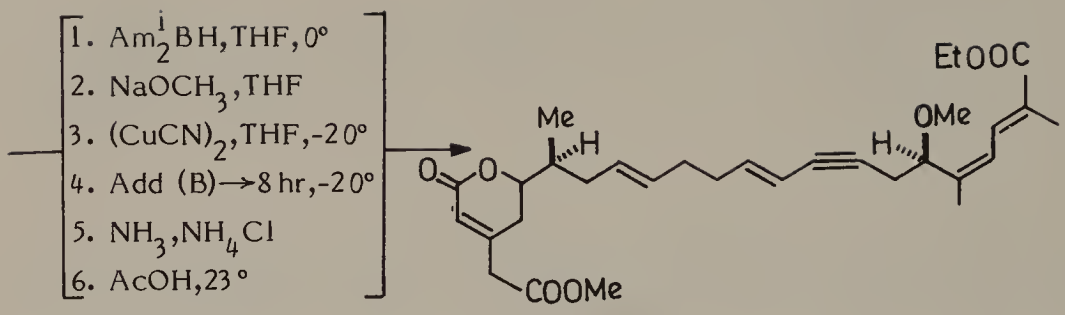
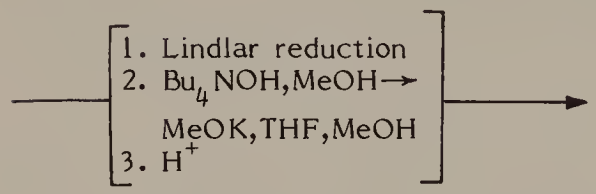
5. This is a novel method of enyne generation through enol-triflate.





Bongkrekic acid[6]

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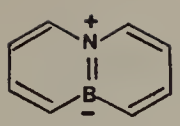
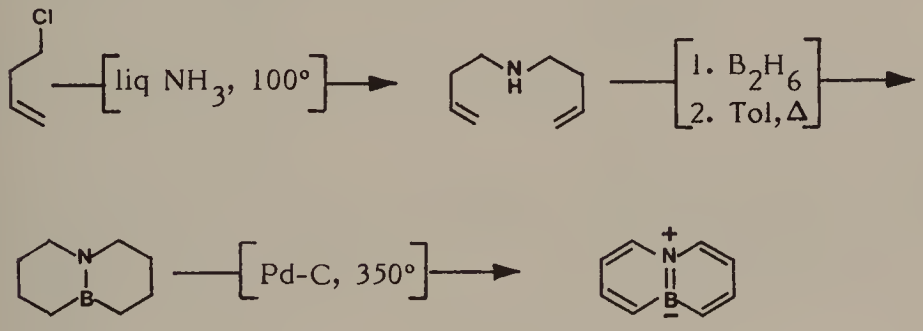
6. Free acid in neat form is unstable, and it was better characterised by conversion to trimethyl ester by treatment with etherial diazomethane.



10,9-BORAZARONAPHTHALENE

Dewar's extensive work on heterocyclic compounds containing boron and nitrogen has demonstrated that an aromatic C-C bond could effectively be replaced by a B-N bond. In the synthesis of 10, 9-borazaronaphthalene (1) the final step involved Pd/C dehydrogenation of a perhydro precursor! The compound looks and smells like naphthalene and nuclear magnetic resonance studies show that it is truly aromatic.



10,9-Borazaronaphthalene[2]

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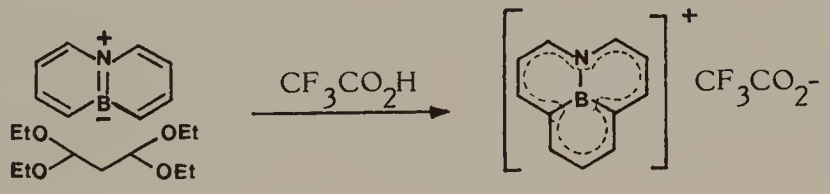
1. M.J.S. Dewar, G.J. Gleicher and B.P. Robinson, J. Am. Chem. Soc., 86, 5098 (1964); M.J.S.Dewar and R. Jones, J. Am. Chem. Soc., 90, 2137 (1968); F.A. Davis, M.J.S. Dewar, R. Jones and S.D. Worley, J.Am. Chem. Soc., 91, 2094 (1969).

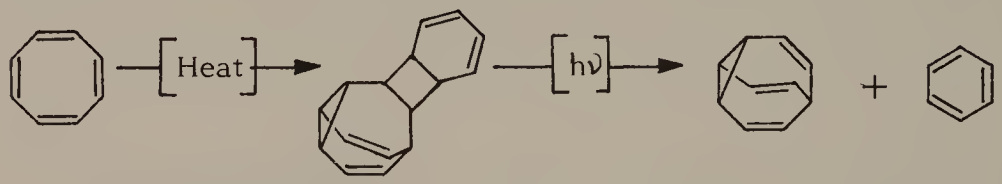
2. The most interesting reaction of this compound thus far reported is the one leading to another B-N aromatic system on treatment with 1,1,3,3-tetraethoxypropane and CF_3CO_2H: M.J.S. Dewar and R. Jones, Tetrahedron Letters, 2707 (1968).



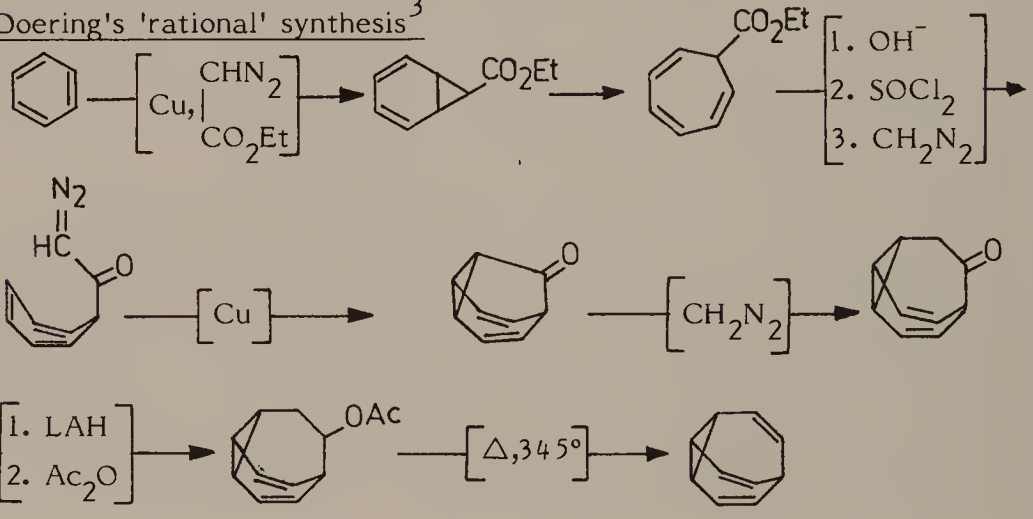
BULLVALENE

The synthesis of bullvalene(1-3), which undergoes rapidly reversible and structurally degenerate isomerization, demonstrated in a remarkable manner the predictive powers of organic chemistry.

Schroder's 'spectacular' synthesis[2]



Doering's 'rational' synthesis[3]



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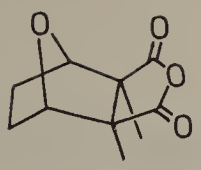
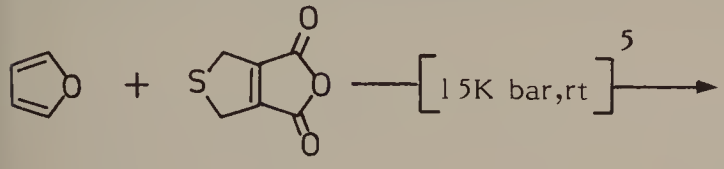
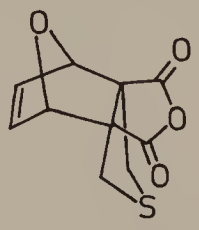
1. For a recent review, see: Schroder,G.; Oth,J.F.M. Angew. Chem. Internat. Ed., 1967, 6, 414.
2. Schroder,G. Angew. Chem. Internat. Ed., 1963, 2, 481.
3. Von Doering,W.; Ferrier,B.M.; Fossel,E.T.; Hartenstein,J.H.; Jones,M.Jr.; Klumpp,G.; Rubin, R.M.; Saunders,M. Tetrahedron, 1967, 23, 3943.



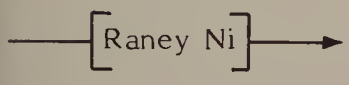
CANTHARIDIN

Although the possibility of introducing the structural features of cantharidin, virtually all in one step, by a diene addition attracted the attention of many workers, much of the earlier efforts directed along these lines were infructuous (1). The earlier stereospecific synthesis by Stork and his associates (2) which involved two successive diene reactions, and that by Schenk & Wirtz (3) which involved a diene-type photochemical peroxidation, were based on classical lines. It is only recently that Dauben, Kessel and Takemura achieved a short and efficient synthesis based on Diels-Alder reaction by carrying out the reaction under high pressure (4).





85:15 mixture of this and the endo-anhydride



Cantharidin

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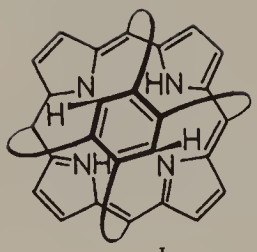
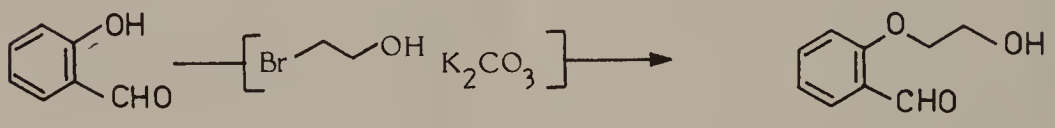
1. For a review of the previous synthetic efforts, see: Alder,K.; Schumacher,M. Fortschr. Chem. Org. Naturstoffe, 1953, 10, 87.
2. Stork,G.; van Tamelen,E.E.; Friedman,L.J.; Burgstahler,A.W. J. Am. Chem. Soc., 1951, 73, 4501; 1953, 75, 384.
3. Schenck,G.O.; Wirtz,R. Naturwiss, 1953, 40, 581.
4. Dauben,W.G.; Kessel,C.R.; Takemura,K.H. J. Am. Chem. Soc., 1980, 102, 6893
5. Furan, on account of its aromaticity is a poor diene, and high temperature could not be used due to thermal cycloreversion; however, pressure in the range of 10-20K bars facilitates Diels-Alder reaction of furan. Dimethylmaleic anhydride is a poor dienophile on account of unfavourable electronic (electron donation by Me group) and steric factors (crowding by Me groups). It was anticipated that a sulfur-containing methylene bridge in place of the Me groups would reduce the electron donating character of the Me groups and also reduce the steric demands of the disubstituted maleic anhydride.



I

CAPPED PORPHYRINS

The "Capped" porphyrin I has been made in a very elegant manner by condensing a suitably substituted tetraldehyde with four molecules of pyrrole to provide stereoselectively the tetrasubstituted meso-porphyrin. It not only forms complexes with oxygen which are indefinitely stable at -20°C, but in the presence of imidazole it effectively carries oxygen (2,3).



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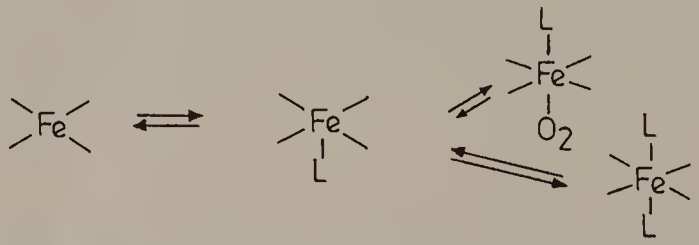
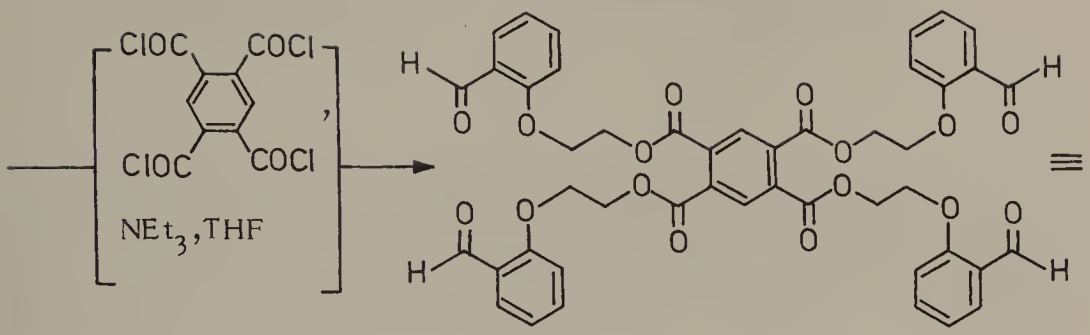
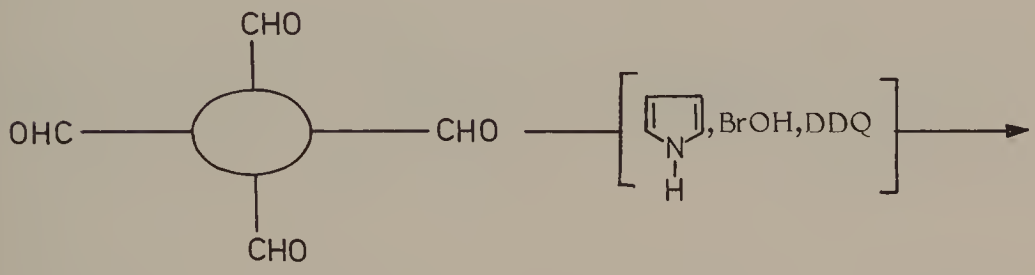
1. Almog,J.; Baldwin,J.E.; Dyer,R.L.; Peters,M. J. Am. Chem. Soc., 1975, 97, 226.

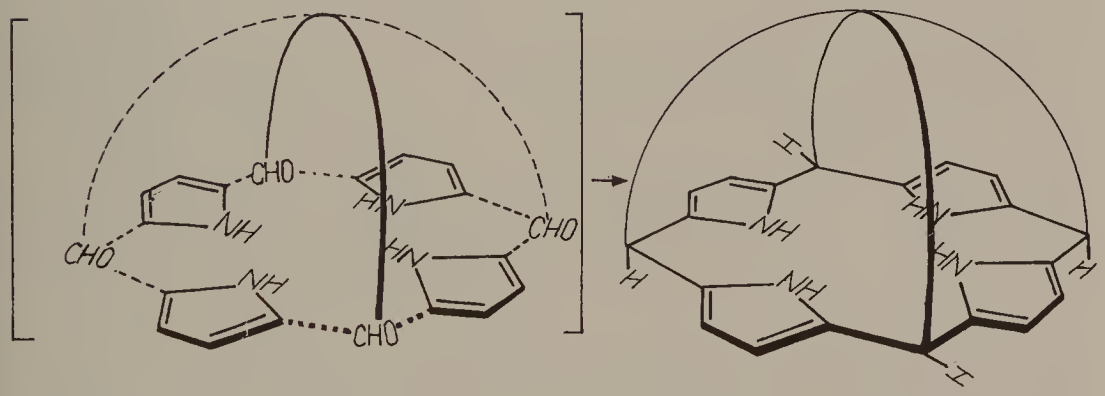
2. The porphyrin group in haemoglobin is remarkably different from the unencumbered parent system in the sense that the haemoglobin-oxygen complex is more stable and does not exhibit tendency to oxidize to the Fe^{3+} system. Further, most fascinating is the observation that the Fe^{2+} in haemoglobin can be replaced by Co^{2+} without significantly affecting its oxygen carrying properties; in contrast, the parent Co^{2+}-porphyrin shows no tendency to bind oxygen. Evidentally, the protein plays a dominant role in stabilizing the oxygen complexes and this could be achieved by shielding one of the porphyrin faces, thus making the formation of the stable octahedral bi-liganded complexes impossible, whilst permitting the oxygen coordination. The stability of the dioxygen adduct is largely dependent on the nature and concentration of the coordinating base.



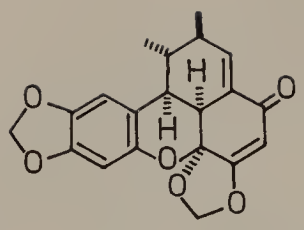
3. Baldwin,J. J. Am. Chem. Soc., 1975, 97, 227; for a recent review relating to blood substitutes, see: Riess,J.G.; LeBlanc,M. Angew. Chem. Int. Ed., 1978, 17, 621.





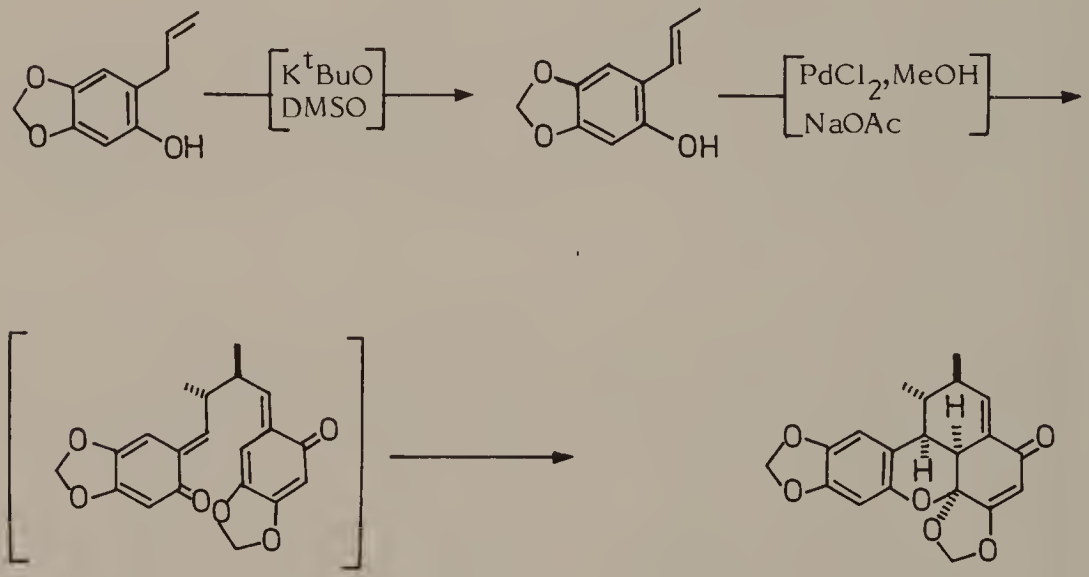


$$\xrightarrow{[FeCl_3, THF, 2.Cr^{II}]} \textit{Capped Porphyrin}$$



CARPANONE

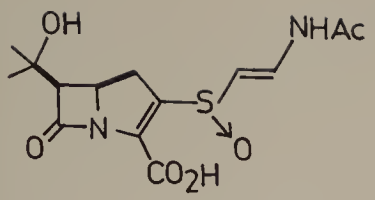
The synthesis of carpanone by Chapman et al is based on the cycloaddition of o-quinonemethides and nucleophilic olefins which generated contiguous multiple assymetric centres in one step, in this case five. The required o-quinonemethide (A) was generated in situ by phenolic coupling of two molecules of 2-(trans-1-propenyl)-4,5-methylenedioxyphenol.



Carpanone

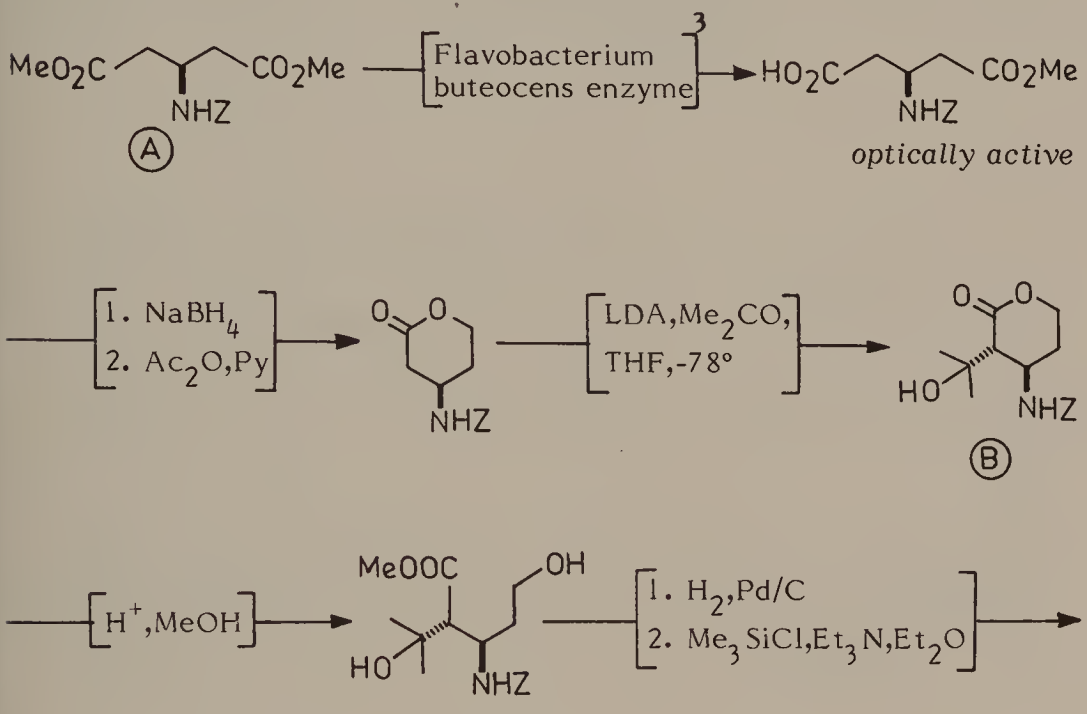
1. Chapman,O.L., Engel,M.R., Springer,J.P., Clardy,J.C.;J. Am. Chem. Soc., 1971, 93, 6696.

2. Chapman,O.L., McIntosh,C.L., Chem. Commun., 1971, 383.



CARPETIMYCIN A

Carpetimycin is an important representative of cis-substituted carbapenem antibiotics. Although a number of synthesis of trans-substituted carbapenems have been reported (1), this is the first chiral synthesis of a cis-substituted carbapenem antibiotic (2). The synthesis involves the enzymatic conversion of prochiral diester (A) to a chiral acid-ester and an efficient novel conversion of a trans-substituted δ-lactone (B) to a cis-substituted β-lactam.



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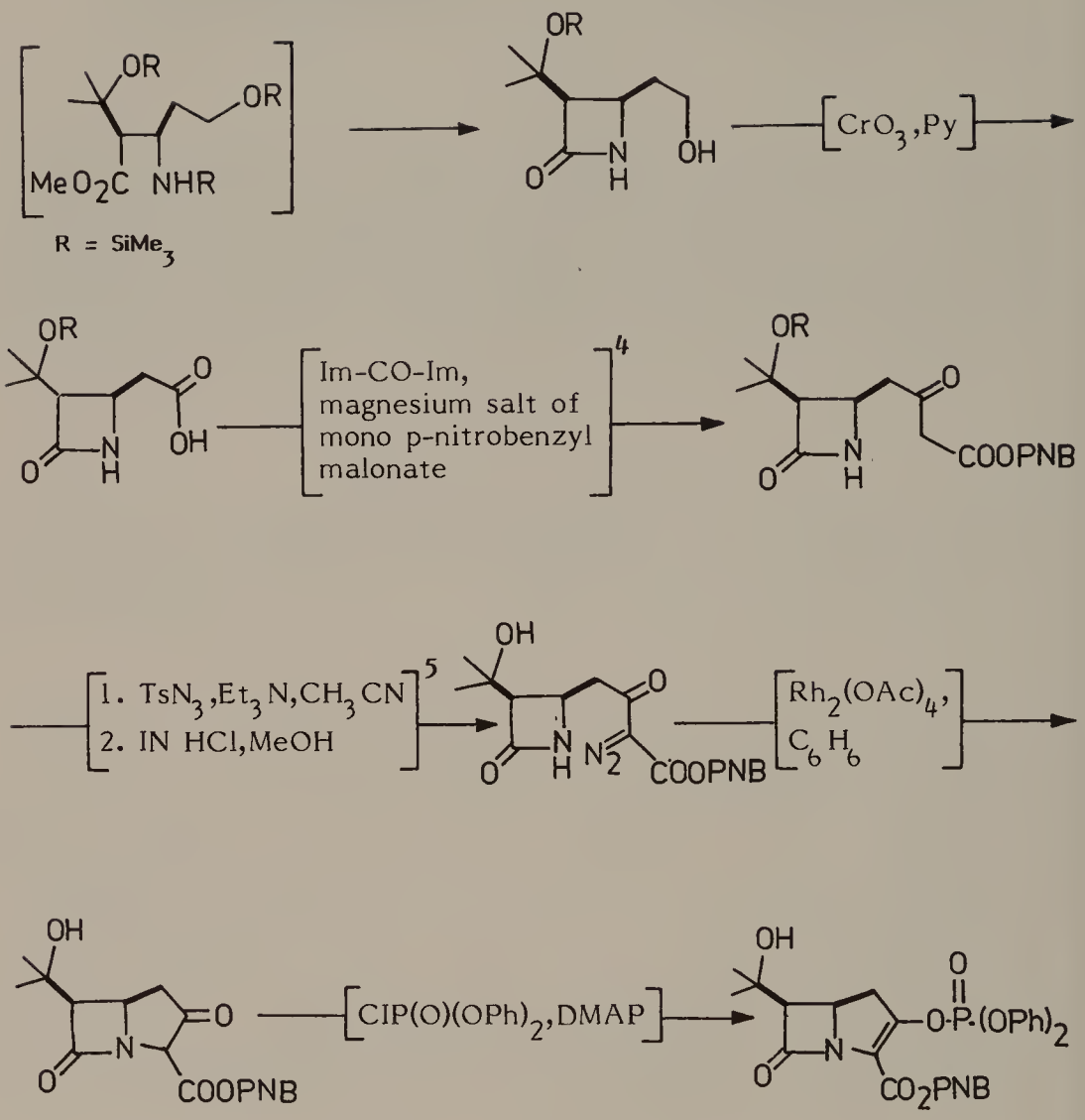
1. see Thienomycin, p. 351.

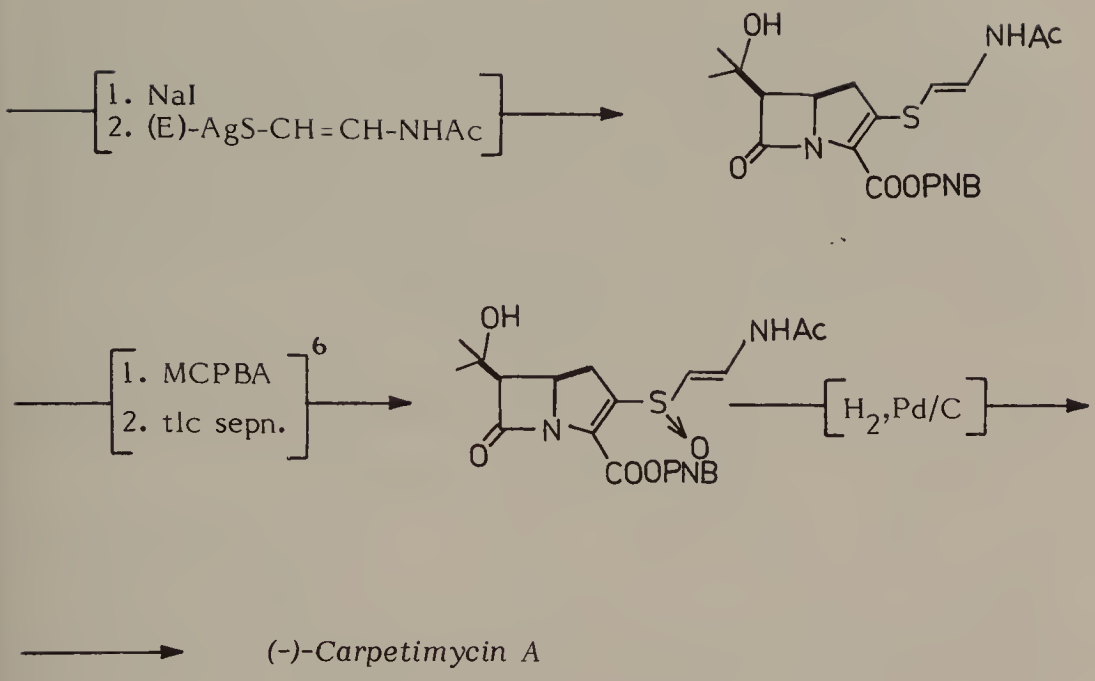
2. Limori,T.; Takahashi,Y.; Izawa,T.; Kobayashi,S.; Ohno,M. J. Am. Chem. Soc., 1983, 105, 1659.

3. Ohno,M.; Kobayashi,S.; Limori,T.; Wang,Y.F.; Izawa,T. J. Am. Chem. Soc., 1981, 103, 2405.



4. Brooks,D.W.; Lu,L.D.L.; Masamune,S. Angew. Chem. Int. Edn.,1979, 18, 72.

5. Salzmann,T.N.; Ratcliffe,R.W.; Christensen,B.G.; Bouffard,F.A. J. Am. Chem. Soc., 1980, 102, 6161.



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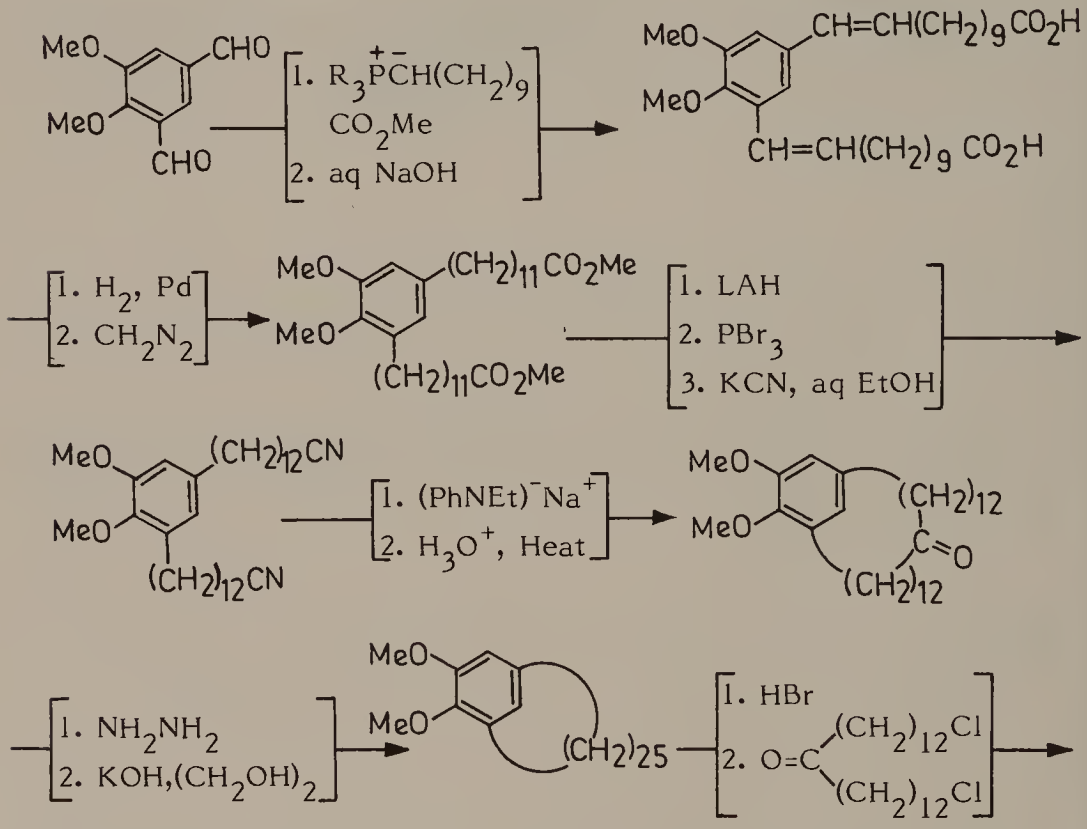
6. In oxidation a mixture of (R)- and (S)-sulfoxides was obtained, which were separated by preparative tlc in 45 and 47% yield respectively; hydrogenolysis of (R)-sulfoxide yielded (-)-carpetimycin A.

CATENANES

The possibility of creating an interlocked system has captured the imagination of many investigators and a variety of ingenious methods have been tried to achieve this objective(1). Lüttringhaus and Schill(2) were the first to effect the synthesis of a catenane employing essentially a non-statistical approach. The key intermediate in this synthesis, (A), was prepared by an intramolecular N-dialkylation across the benzene ring of a bis-ω -haloalkyl acetal (B), which on hydrolysis easily generated the required ketone.



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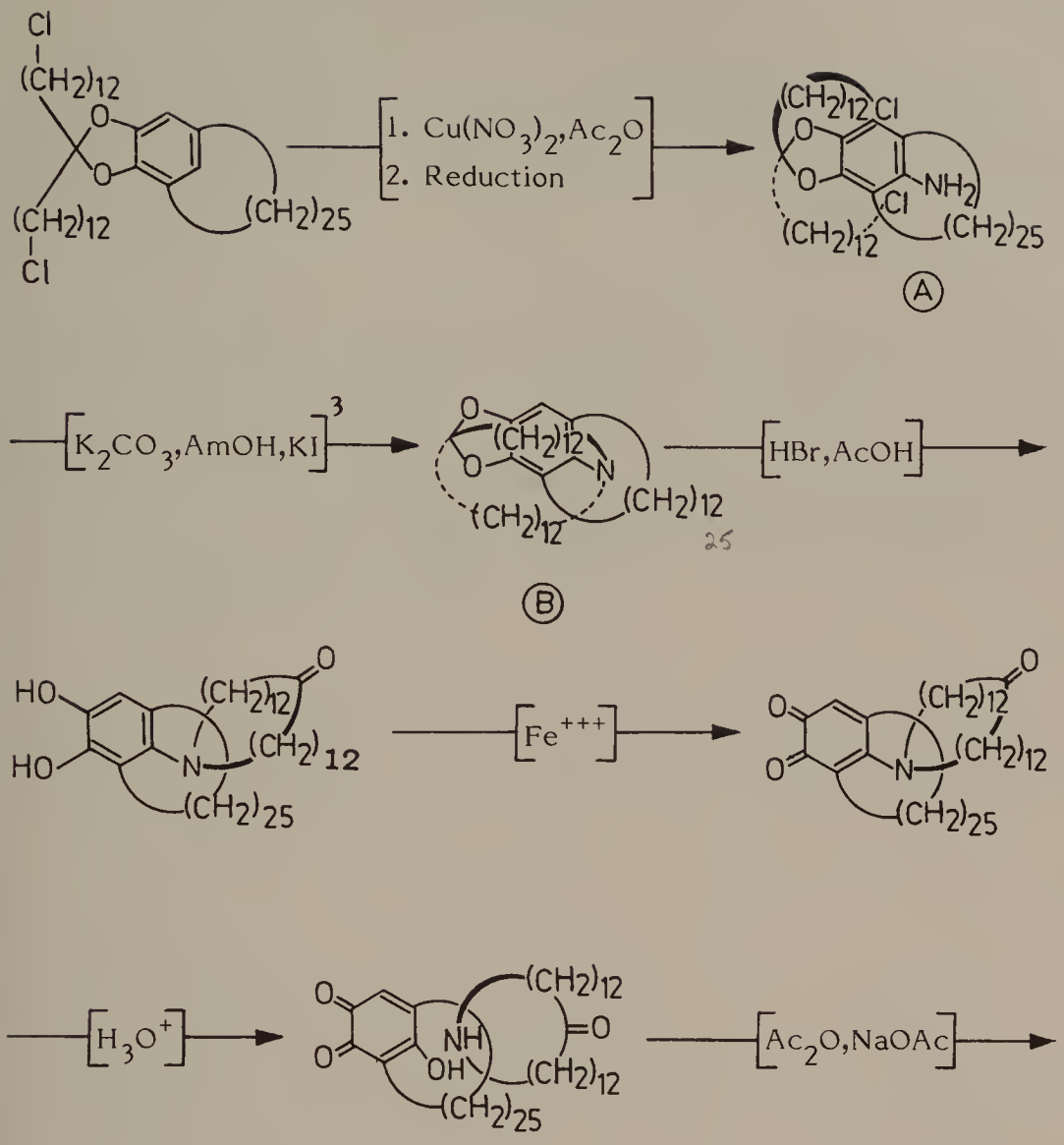
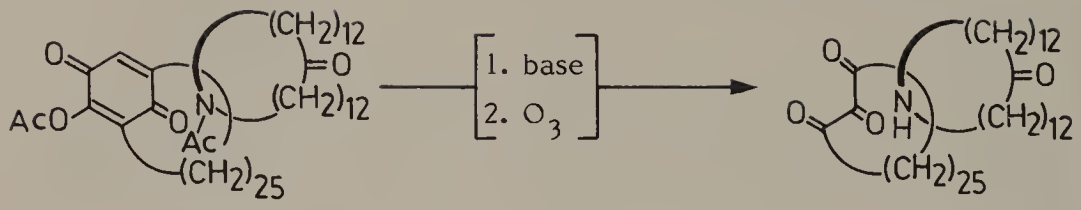
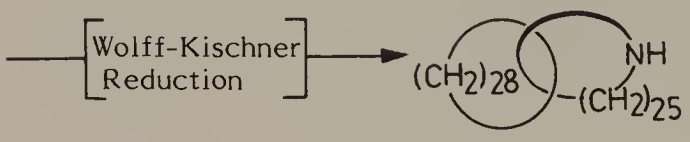
1. Frisch, H.D., Wasserman, E. [J. Am. Chem. Soc., 1961, 83, 3789], have dealt with chemical topology, examining in some detail several model systems and also possible ways by which interlocked systems could be created.

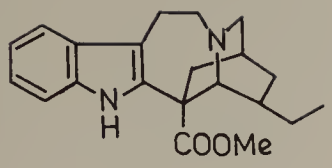
2. Schill, G., Lüttringhaus, A. Angew. Chem. Internat. Ed., 1964, 3, 546; Lüttringhaus,A., Isele, G. ibid, 1967, 6, 956; Schill, G. Ber. 1967, 100, 2021. Schill, C., Logemann, E., Zurcher, C. Angew. Int., 1972, 11, 1089; Schill, G., Logemann, E., Vetter, W. Angew Int., 1972, 11, 1089.



3. The possible alternative mode of cyclization of the "ansa" compound (not involving interlocking) is not sterically favoured.

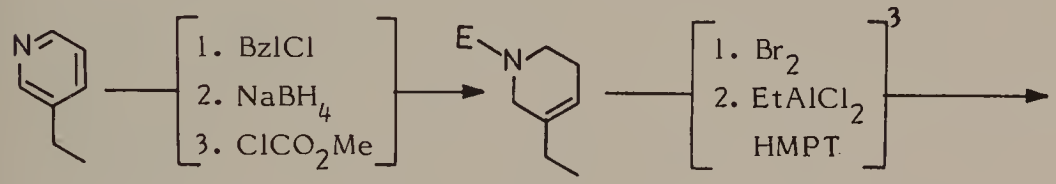

AcO
O
N
Ac
(CH2)12
=O
(CH2)12
(CH2)25
1. base
2. O3
O
O
N
H
(CH2)12
=O
(CH2)12
(CH2)25

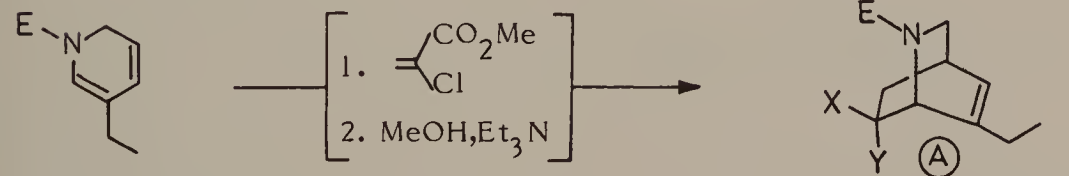

Wolff-Kischner
Reduction
(CH2)28
NH
(CH2)25



CATHARANTHINE

Catharanthine is only a minor constituent of the alkaloids of Catharanthus roseus, and therefore its practical synthesis is of critical importance for the preparation of semisynthetic vinblastine, vincristine and related dimeric alkaloids. A number of syntheses have been described for (±)-catharanthine (1). Raucher and his associates have very recently described an efficient total synthesis of (±)-catharanthine which employs a Diels-Alder reaction between a dihydropyridine and α-chloroacryloyl chloride to assemble the appropriately substituted isoquinuclidine intermediate (A).





E = CO_2Me

1:1.4 , endo:exo

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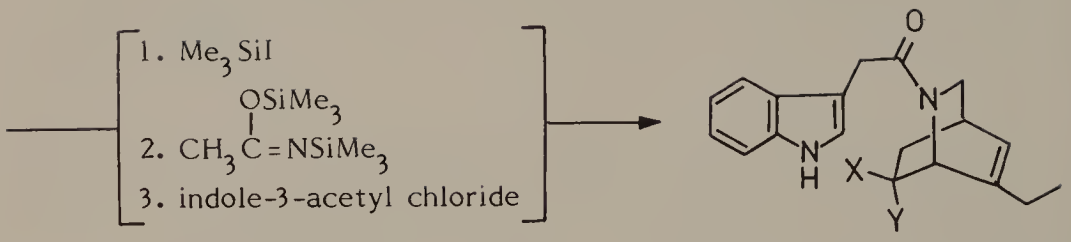
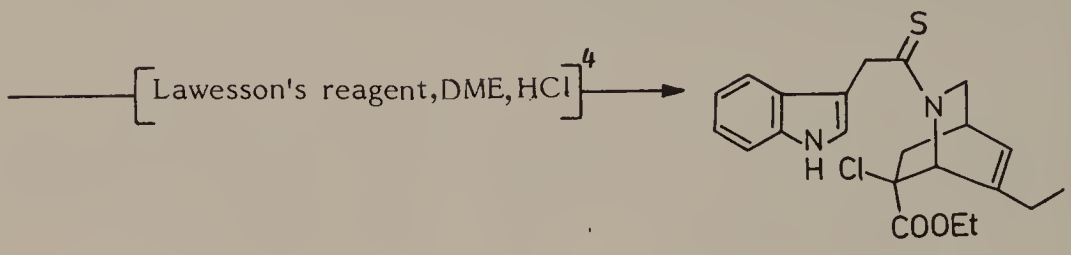
1. (a) Buchi,G.; Kulsa,P.; Ogasawara,K.; Rosati,R. J. Am. Chem. Soc., 1969, 92, 999; (b) Marazano,C.; LeGoff,M.T.; Fourrey,J.L.; Das,B. J. Chem. Soc., Chem. Commun., 1981, 389; (c) Keuhne,M.E.; Bornmann,W.G.; Earley,W.G.; Mark,I. J. Org. Chem., 1986, 51, 2913.
2. Raucher,S.; Bray,B.L. J. Org. Chem., 1985, 50, 3236; Raucher,S.; Bray,B.L.; Lawrence,R.F. J. Am. Chem. Soc., 1987, 109, 442.
3. This dehydrobromination procedure is crucial for this preparation since other reagents such as DBU, DBN, quinoline were not successful.

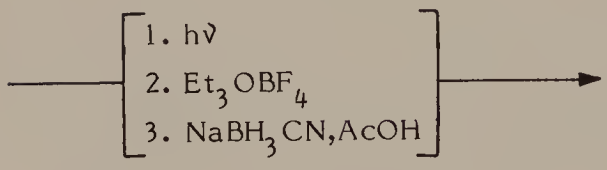


1:1.4 mixture of a&b isomers

a; X = Cl, Y = CO_2Me

b; X = CO_2Me, Y = Cl





(±)-Catharanthine

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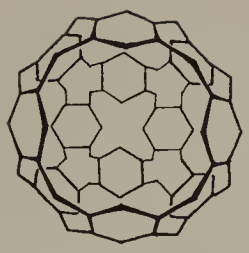
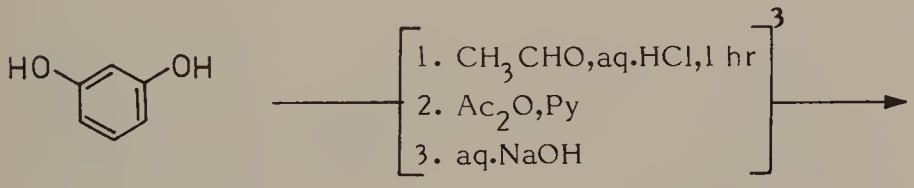
4. This thioamide formation did not proceed well without catalytic amount of anhydrous HCl, which presumably causes isomerisation of isomer b to a, which undergoes thionation readily.



CAVITANDS

An emerging facet in the art of organic synthesis is the creation of tailor made cavities on a rigid frame. Such structures, called cavitands, are molecular vessels which can harbor substrates and reagents. They could be used to simulate biological processes, since, in such enzyme controlled changes the acceptor sites possess rigid cavities whose internal surface are compatible with that of the substrates and reagents. A range of cavitands have been made (1) and cavitands II and III, arising from the resorcinol-acetaldehyde tetramer I, would be a good illustration. Molecular models show that the cavity dimensions of II can accommodate single molecule of CH_2Cl_2, $CHCl_3$, THF or 4 molecules of water. In III the void is big enough to engulf one molecule of [2.2]paracyclophane or 10 of water (2).



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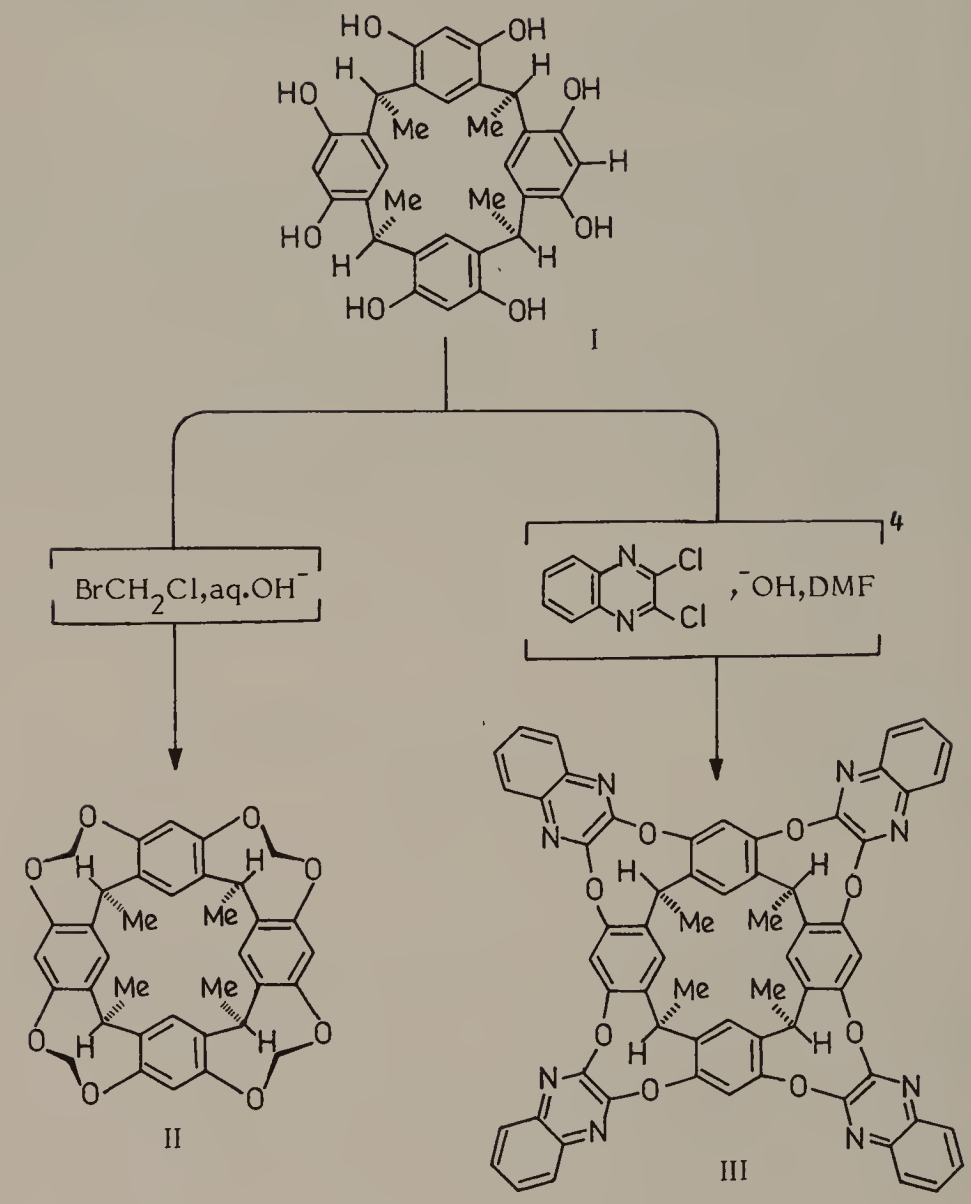
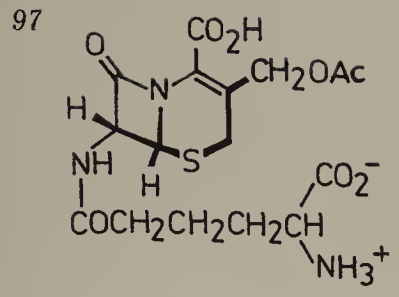
1. Cram,D.J. Science, 1983, 219, 1177; Cram,D.J. Trueblood Top. Curr. Chem., 1981, 98, 43.

2. Moran,J.R.; Karbach,S.; Cram,D.J. J. Am. Chem. Soc., 1982, 104, 5826.

3. The reaction gave, in addition to the all cis 1, the cis, trans, cis isomer in smaller amounts, which could be separated by acetylation.

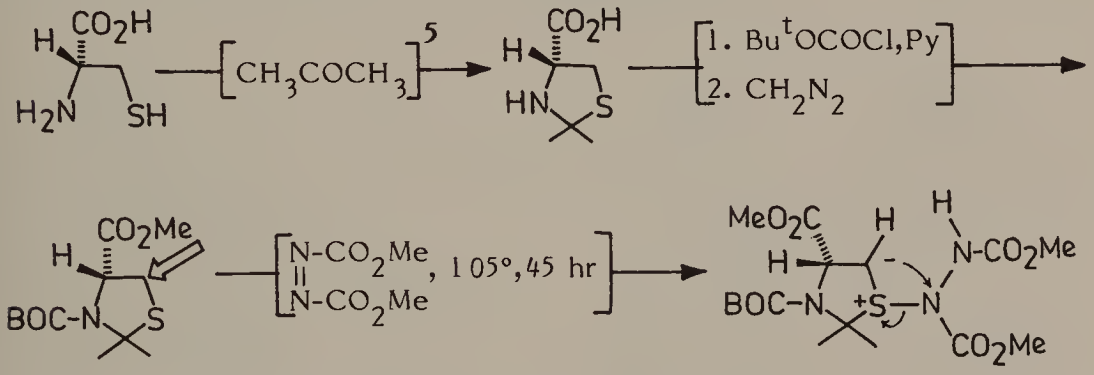


4. Compound III always crystallized with solvents ($DMF,CHCl_3$) which could not be freed even at 100°C, 10^{-5} torr.



CEPHALOSPORIN-C

Beset by the same problems that had made difficult the synthesis of penicillin, attempts for the synthesis of cephalosporin (1) projected through 7-acylaminocephalosporanic acid--the transitory dihydrothiazine counterpart of penicilloic acid--made little progress (2,3). In an ingenious solution of the synthetical problem, Woodward and his colleagues (4) have obtained the fused β-lactam-dihydrothiazine ring by Michael addition of a dialdehyde, followed by cyclization, on the key β-lactam intermediate (A) which represents the common structural feature of both penicillins and cephalosporins.



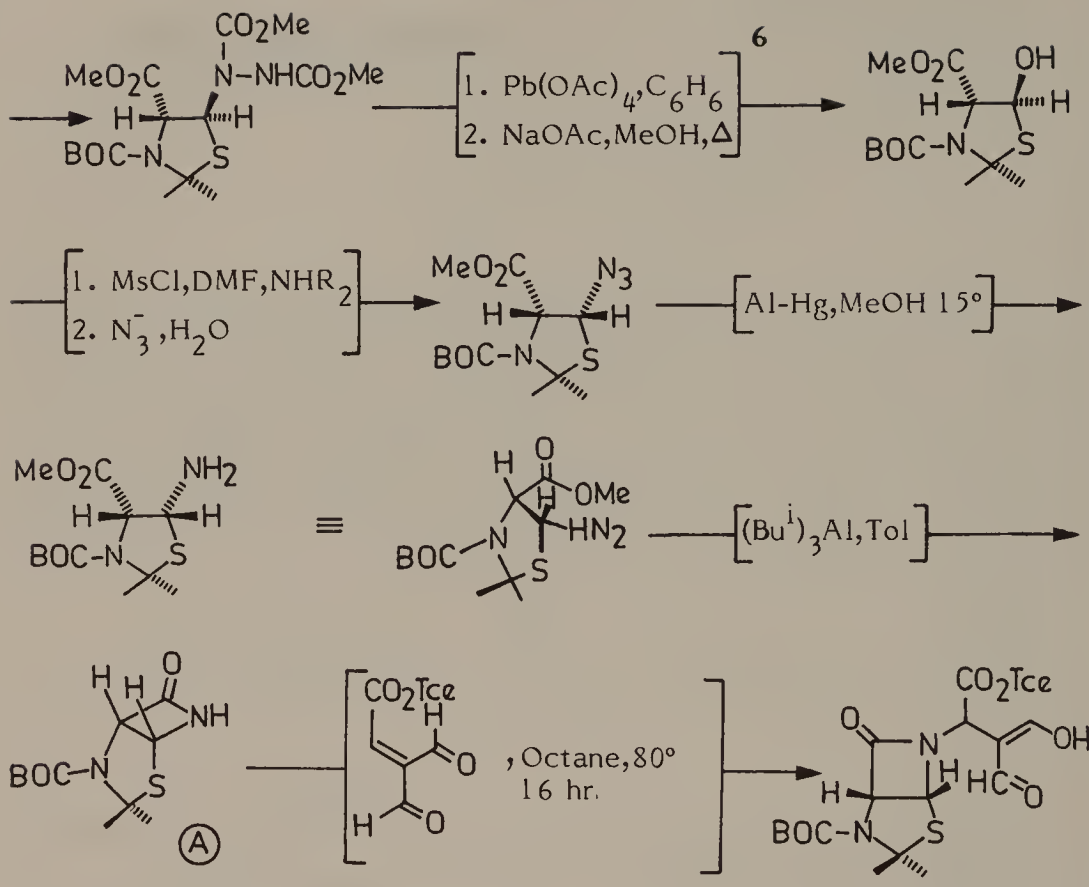
1. For a review, see Abraham,E.P., Quart. Rev., 1967, 21, 231.

2. Galantay,E., Engl,H., Szabo,A., Fried,J., J. Org. Chem., 1964, 29, 3560; Sheehan,J.C., Schneider,J.A., ibid, 1966, 31, 1635. The closest approach to cephalosporins, using a route similar to Sheehan's penicillin synthesis is the synthesis of a derivative of cephalosporin C_C by Heymes,R., Amiard,G., Nomine,G., Compt. Rend., 1966, 263, 170.

3. The interesting possibility of realizing the desired dihydrothiazine nucleus by ring expansion of thiazolidines has been explored with some success, Morin,R.B., Jackson,B.G., Mueller,R.A., Lavagnino,E.R., Scanlon,W.B., Andrews,S.L., J. Am. Chem. Soc., 1963, 85, 1896; Stork,G., Cheung,H.T., J. Am. Chem. Soc., 1965, 87, 3783.

4. Woodward,R.B., Heusler,K., Gosteli,J., Naegeli,P., Oppolzer,W., Ramage,R., Ranganathan,S., Vorburggen,H., J. Am. Chem. Soc., 1966, 88, 852; Woodward,R.B., Science, 1966, 153, 487.

5. Binding of the reactive amino and sulfhydryl groups of L(+)-cysteine into a thiazolidine ring followed by introduction of tert-butoxycarbonyl group on the nitrogen was carried out to enhance reactivity of the methylene group.



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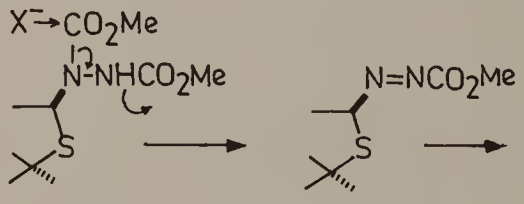
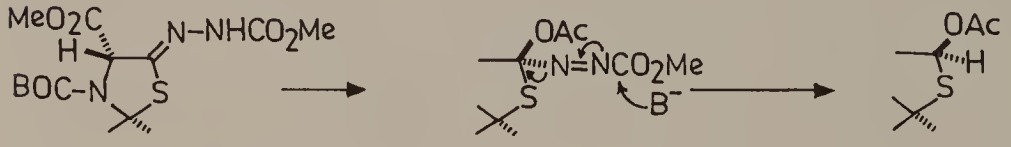
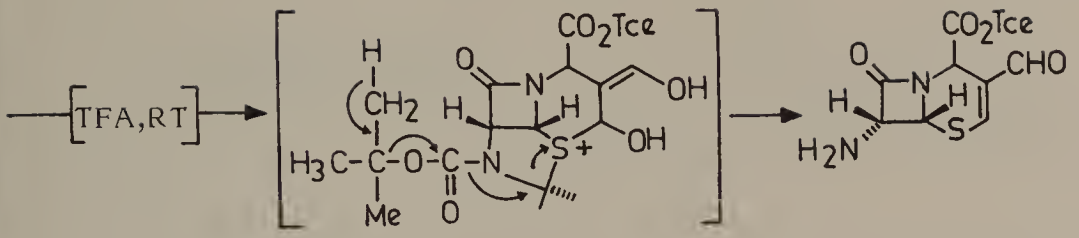
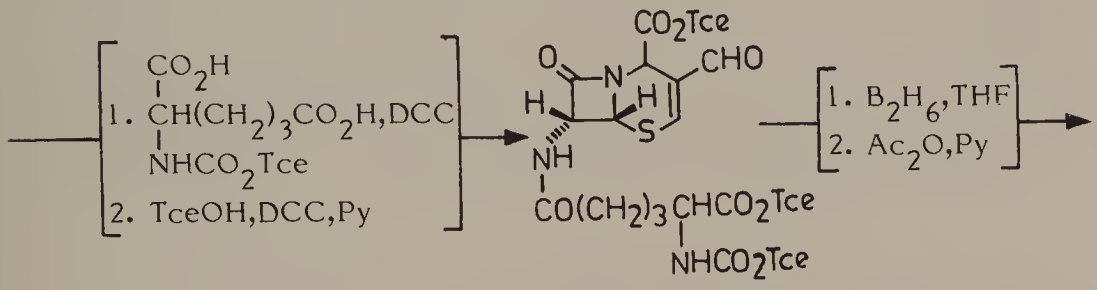
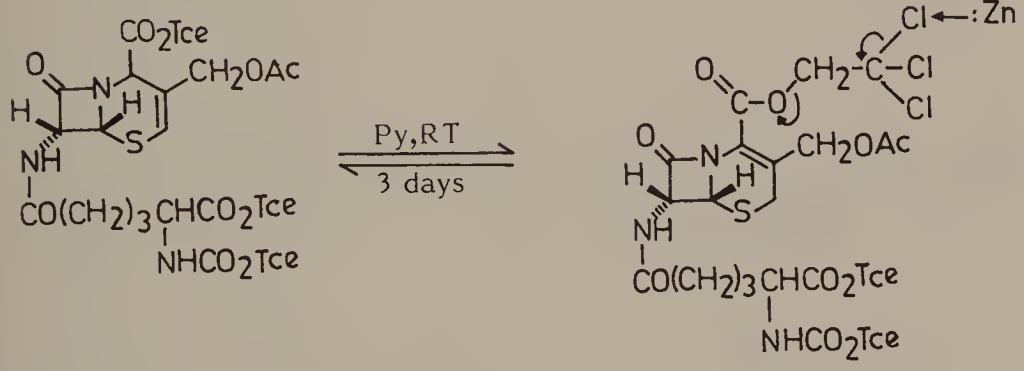
6. Introduction of the trans- acetoxy group occurs under directive influence of the bulky carbomethoxy on the adjacent carbon and is probably initiated by oxidation of the substituted hydrazine part:

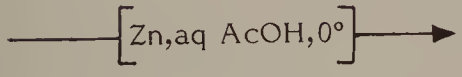




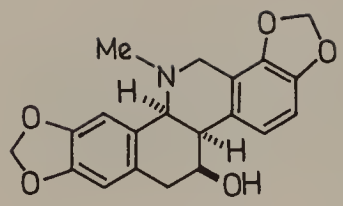






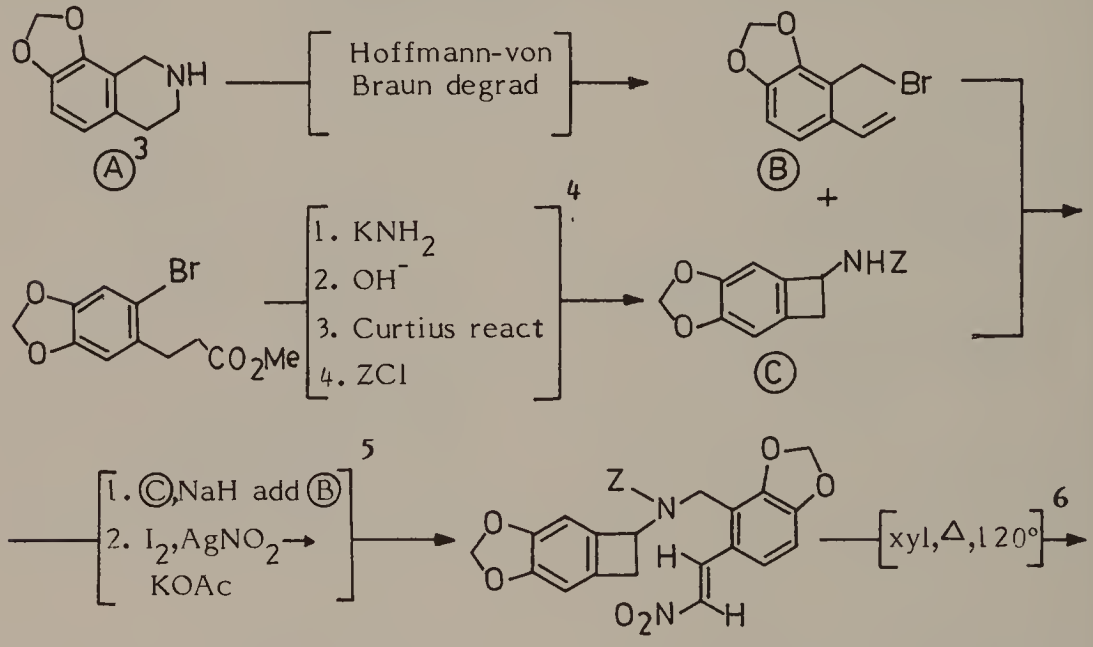


Cephalosporin-C



CHELIDONINE

The first synthesis of chelidonine by Oppolzer and Keller (1) exploited a versatile approach to annellated polycyclic heterocycles based on intramolecular cycloaddition of o-quinodimethanes, generated readily by thermolysis of benzocyclobutenes, to a suitably placed dienophile (an acetylenic residue in this case). However, the synthesis lacked steric control at the crucial step of generating ring B/C geometry. In the new synthesis described below Oppolzer & Robbiani (2) established the desired cis-B/C ring fusion by conformational control in the critical intramolecular cycloaddition step.



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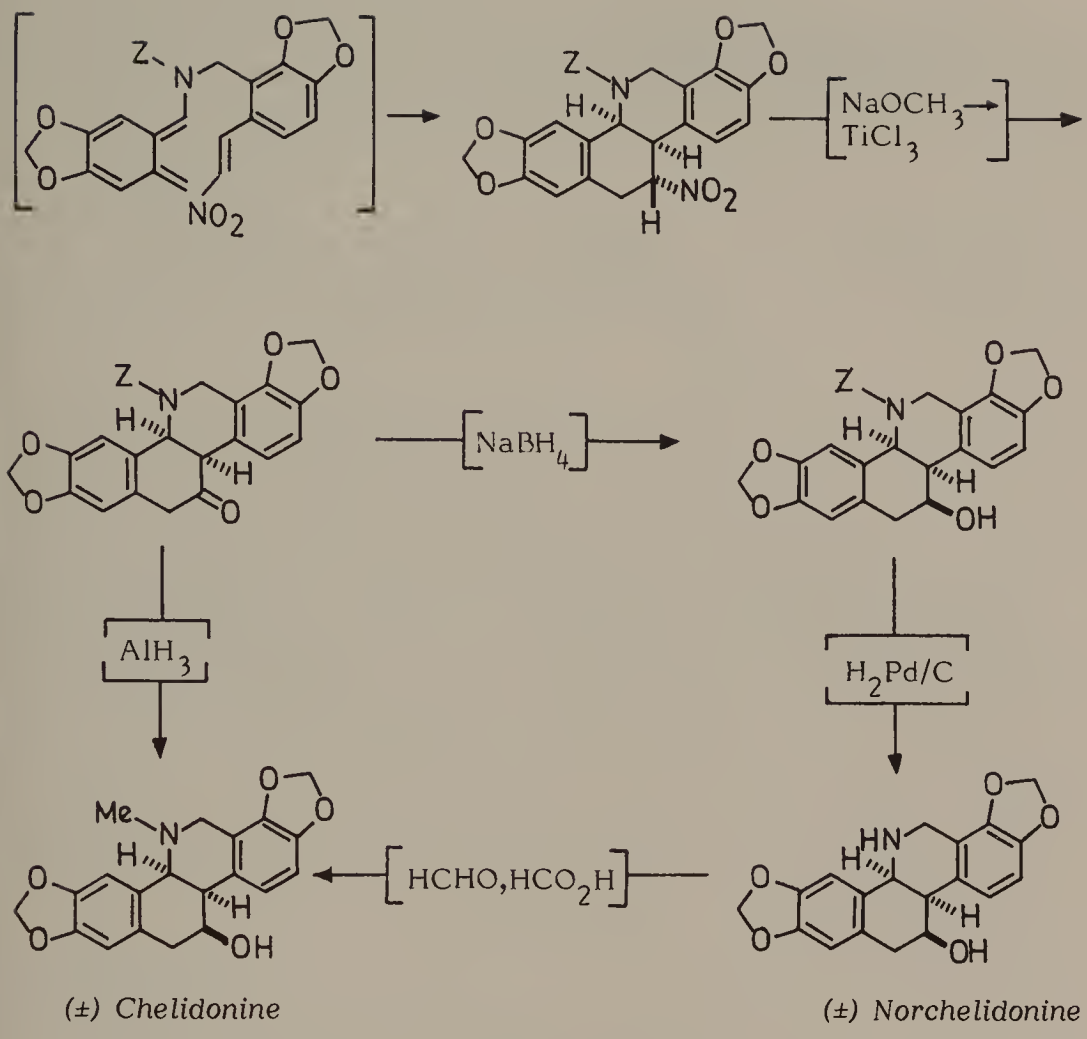
1. Oppolzer,W.; Keller,K. J. Am. Chem. Soc., 1971, 93, 3836.

2. Oppolzer,W.; Robbiani,C. Helv. Chim. Acta, 1983, 66, 1119.

3. (A) was obtained from 2,3-methylenedioxybenzaldehyde by standard reactions.

4. The cyano benzocyclobutene intermediate was also prepared by flash pyrolysis of 4,5-methylenedioxy-2-methyl-α-chlorobenzylcyanide.

5. In the nitro displacement reaction (E)-nitrostyrene was the only isolable product.



(±) Chelidonine *(±) Norchelidonine*

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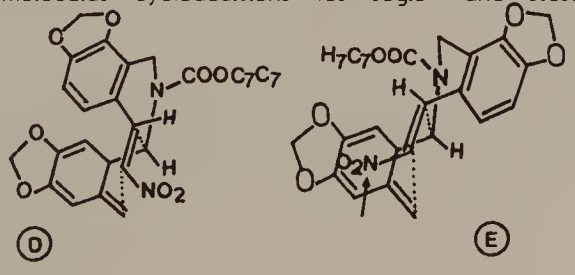
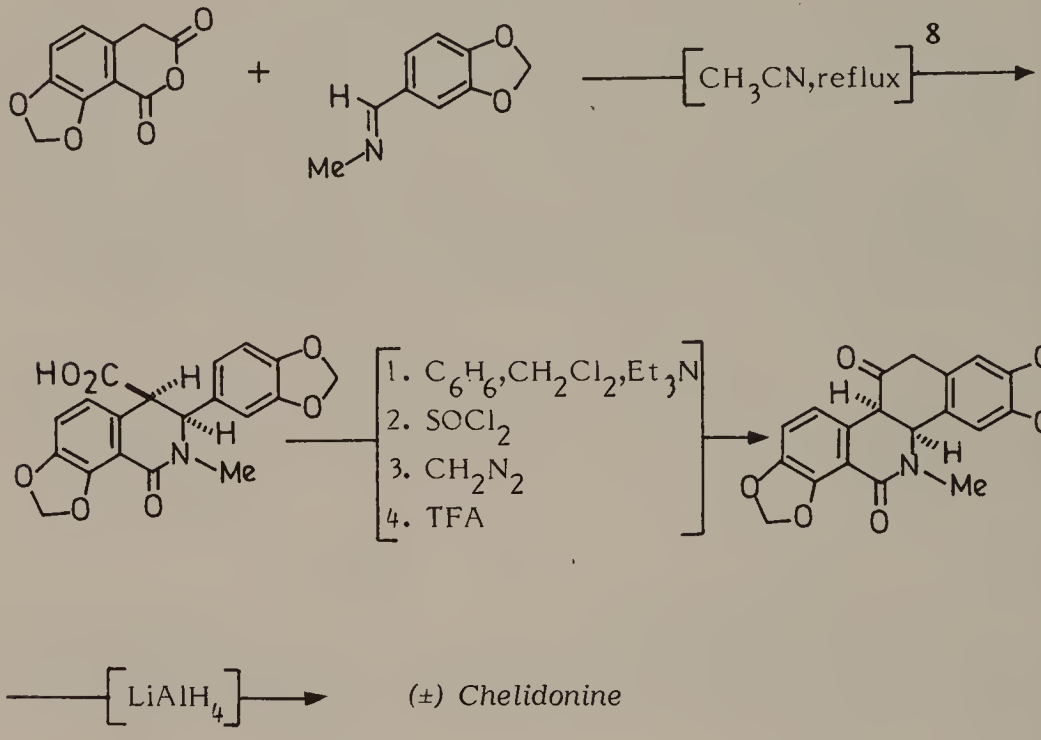
6. There would be a strong preference for exo-nitro transition state (D) over endo-nitro-transition state (E), which would explain the observed stereoselectivity. The addition of benzocyclobutene to ω-nitrostyrene took place in the opposite direction and also gave a 2:1 mixture of epimers at C-carbamate position, thus emphasising the advantages of intra- vs inter-molecular cycloadditions for regio- and stereo-chemical control.



Cushman et al (7) developed a synthesis of benzophenanthridine alkaloids, including chelidonine, based on addition of homophthallic anhydride to a Schiff's base and optimised the reaction conditions for the desired thermodynamically less stable cis-diastereoisomer.



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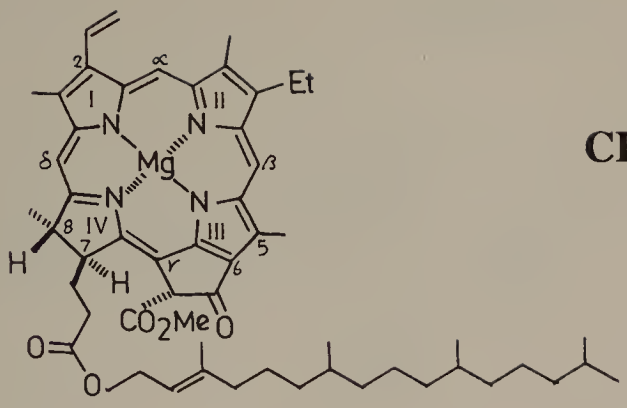
7. Cushman,M.; Choong,Tung-Chung; Valko,J.T.; Koleck,M.P. J. Org. Chem.,1980, 45, 5067; Tetrahedron Lett., 1980, 21, 3845.

8. Of a number of solvents and reaction condition tried this gave the most favourable ratio of the required cis to trans isomers, 67:33; the cis diastereomer is thermodynamically less stable.



CHLOROPHYLL

The total synthesis of so complex a substance as chlorophyll-α accomplished by Woodward and his colleagues (1) stands as a masterpiece of synthetic organic chemistry. A consideration of the stereochemical aspects and the interatomic distances in the environs of ring III and IV in chlorophyll reveals that the porphyrin→purpurin equilibration (B) is clearly a favoured transformation (conversion of trigonal C-7 and C-8 to tetrahedral configuration), resulting in release of steric compression due to molecular overcrowding along the γ-periphery (2). The creation of the isocyclic ring and selective delivery of the hydrogen at C-8 [transformation (B)] are an outcome of this understanding. Other noteworthy features ofthe synthesis are generation of the vinyl group (4) and fashioning of the $^{\gamma}$-substituent by a novel oxidation of the isocyclic ring to give chlorin e_6 from which the sequence of reactions to chlorophyll-α had already been established by Willstatter and Fischer (8).

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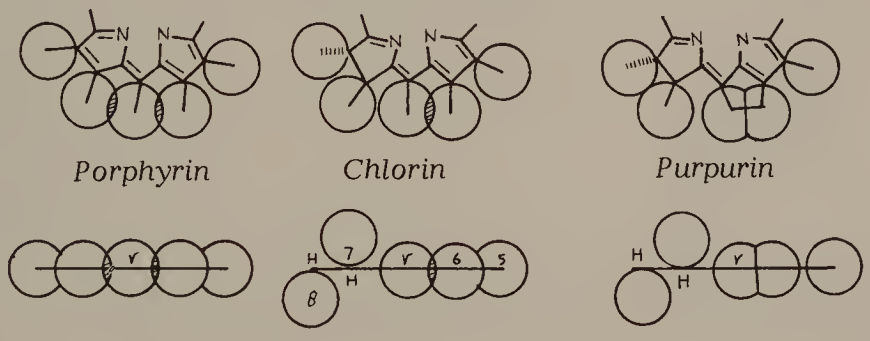
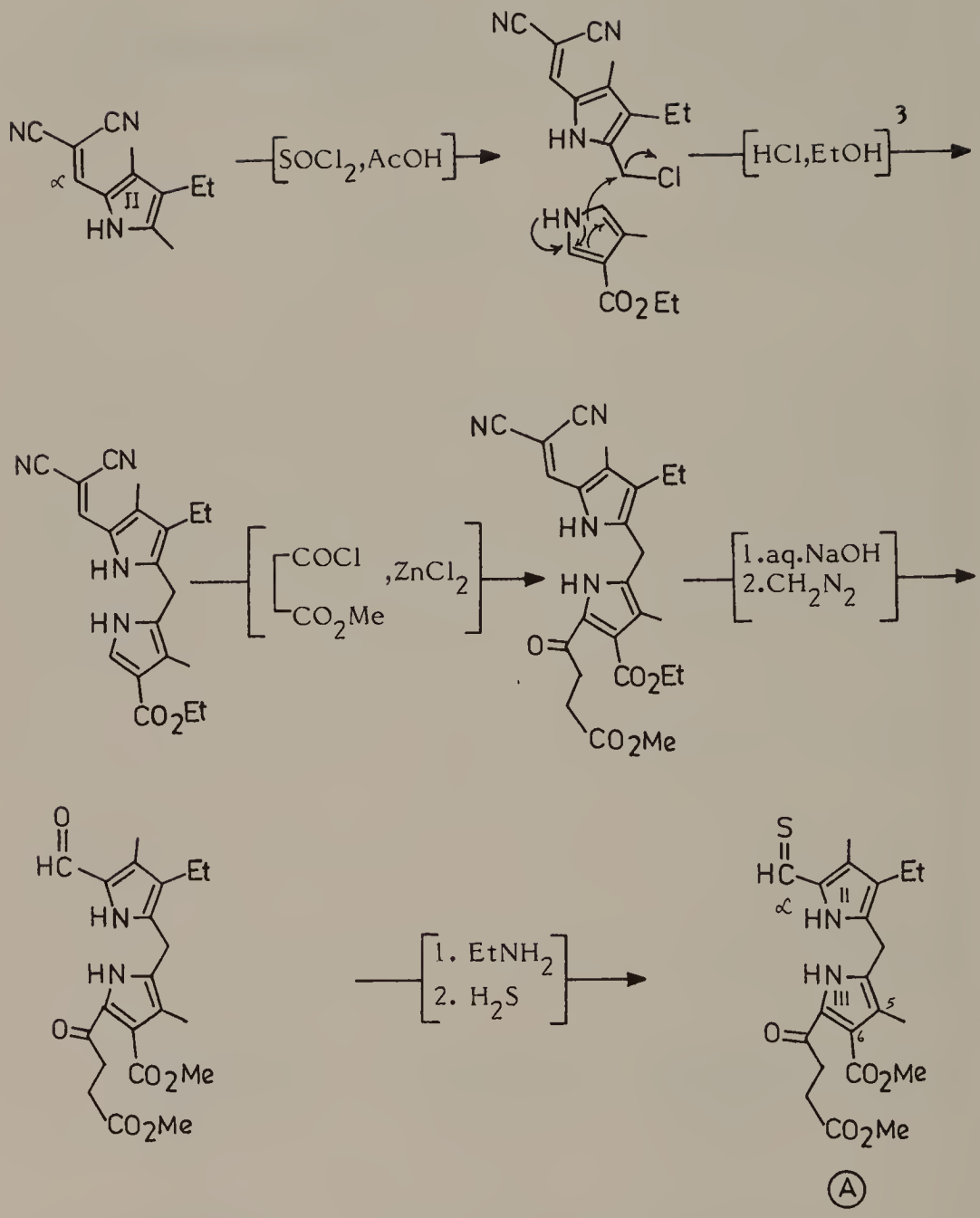
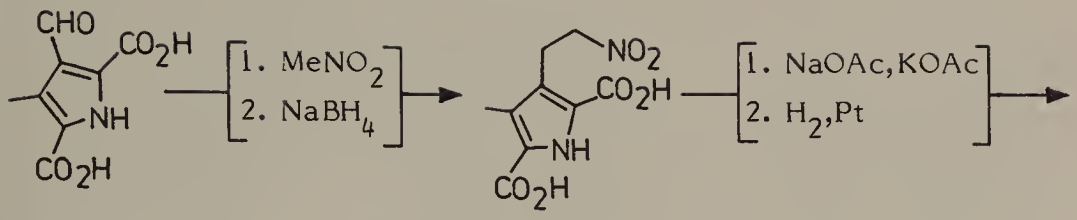
1. Woodward,R.B. et al. J. Am. Chem. Soc., 1960, 82, 3800; Woodward,R.B. Angew. Chem., 1960, 72, 651.

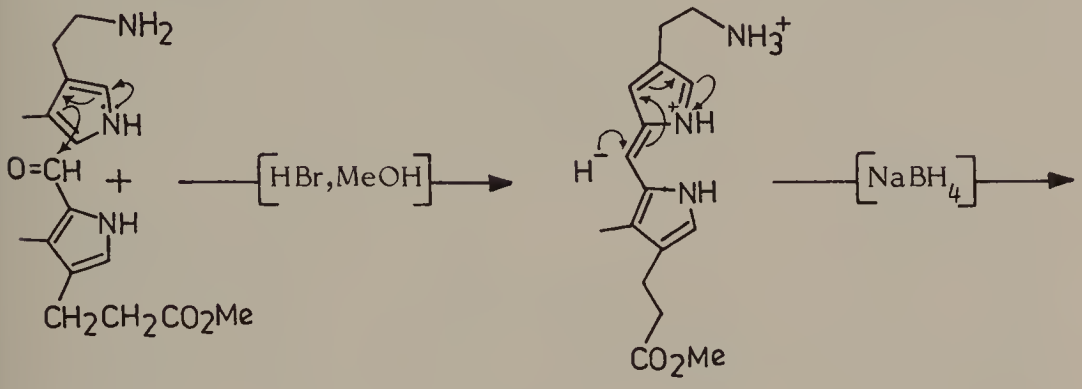
2. The release in steric compression along the crowded γ-periphery that can occur in going from a porphyrin to a purpurin structure is depicted below:

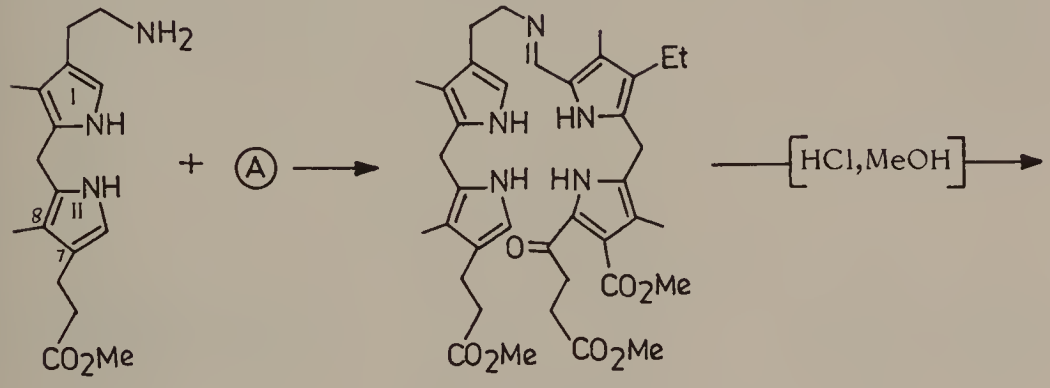


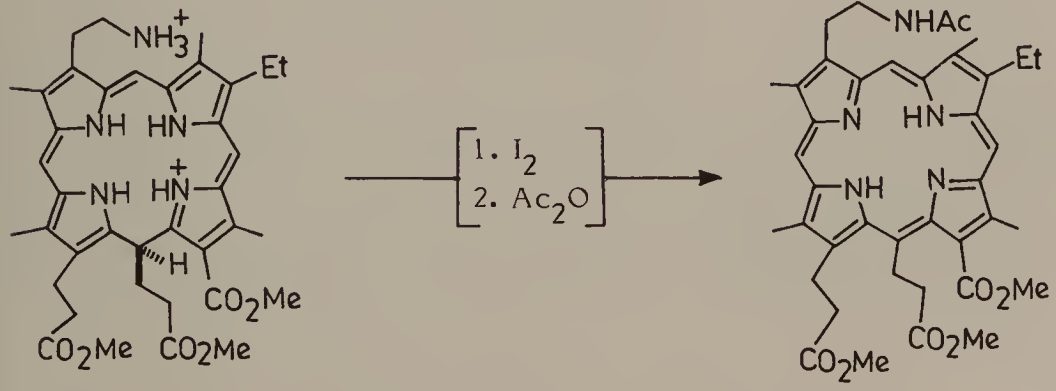


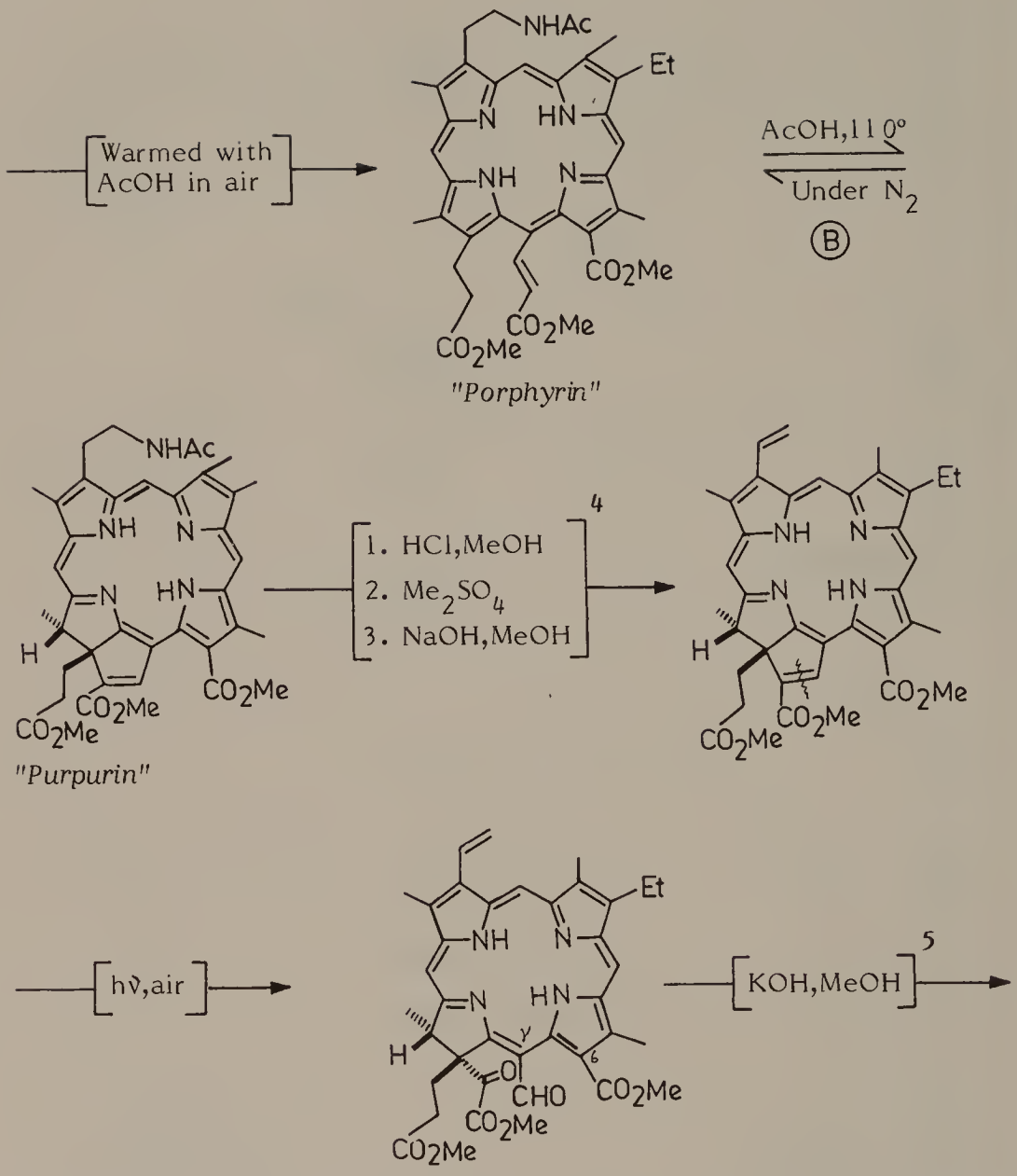
3. Malonodinitrile serves as an acid-stable aldehyde protecting group.


CHO
CO2H
NH
CO2H
1. MeNO2
2. NaBH4
NO2
CO2H
NH
CO2H
1. NaOAc,KOAc
2. H2,Pt


NH2
NH
O=CH +
NH
CH2CH2CO2Me
HBr,MeOH
NH3+
NH
H
NH
CO2Me
NaBH4


NH2
NH
NH
8
7
CO2Me
+ A
N
Et
NH HN
NH HN
O
CO2Me
CO2Me CO2Me
HCl,MeOH


NH3+
Et
NH HN
NH HN+
H
CO2Me
CO2Me CO2Me
1. I2
2. Ac2O
NHAc
Et
N HN
NH N
CO2Me
CO2Me
CO2Me



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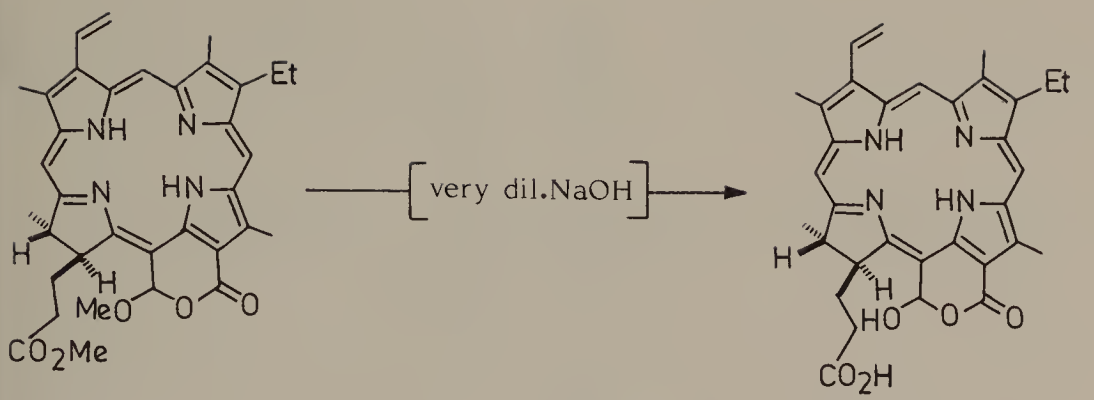
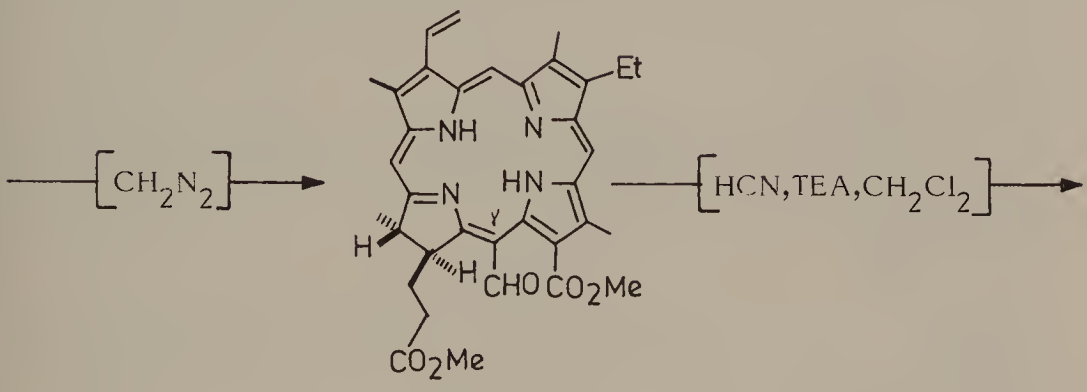
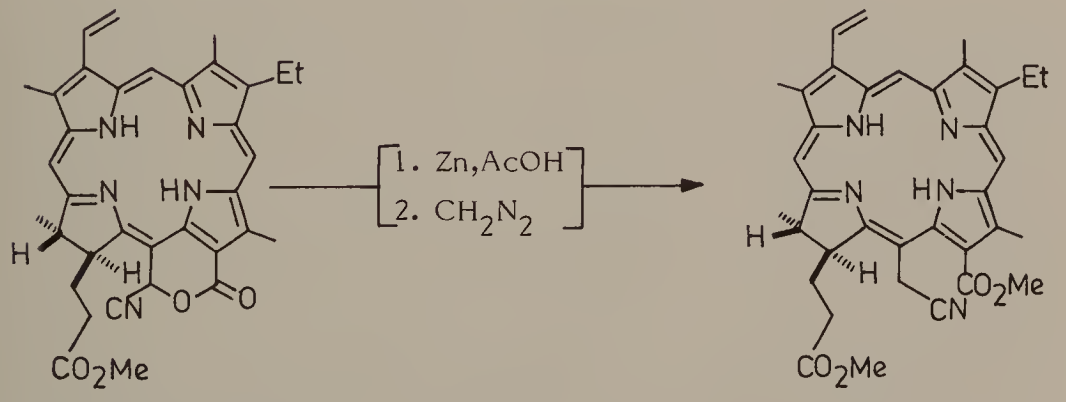
4. Introduction of the sensitive vinyl group, deferred until a late stage in the synthesis, by Hofmann degradation of a β-aminoethyl group was a strategy first evolved by Woodward in the synthesis of quinine.

5. Removal of the oxalyl group and simultaneous cyclization of formyl and 6-carbethoxy group occurs in this treatment.



(+)-Chlorin 5^{6}





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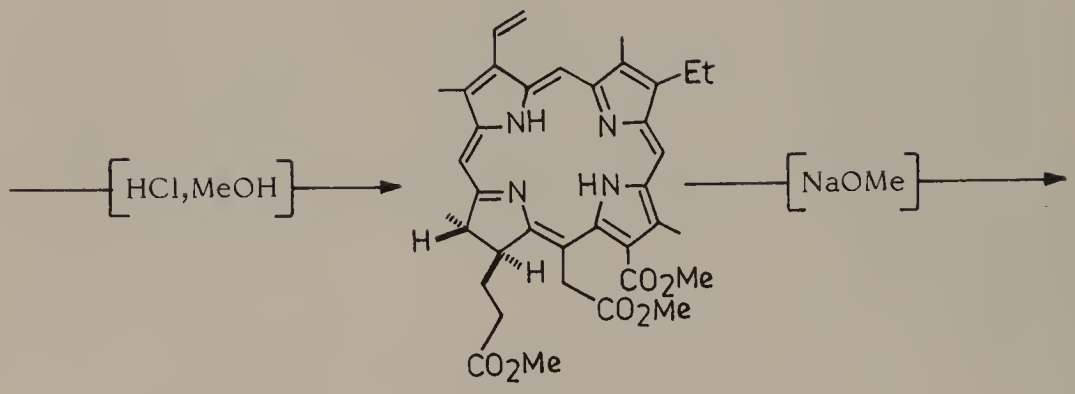
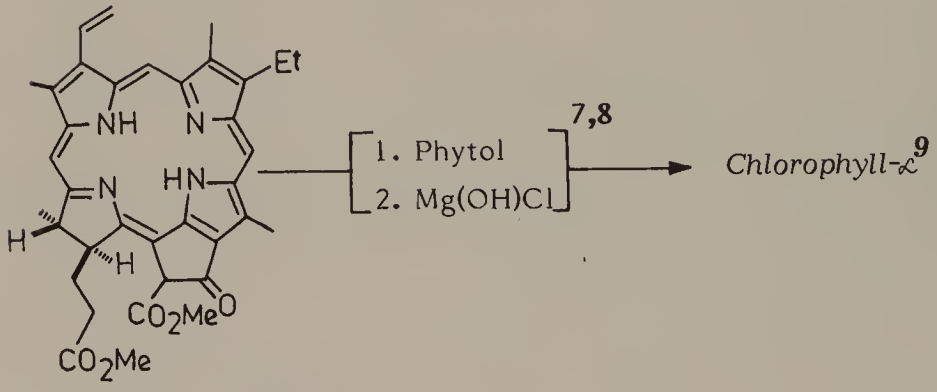
6. Resolved via quinine salt.



Chlorin e_6 Trimethyl Ester



Methyl Phaeophorbide-α

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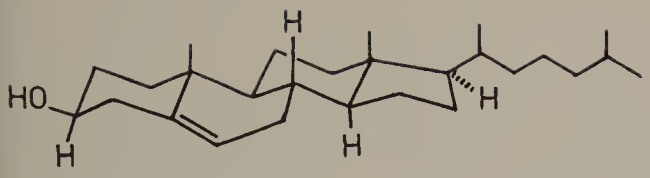
7. The total synthesis of phytol has been accomplished by Burrell,J.W.K.; Jackman,L.M.; Weedon,B.C.L. Proc. Chem. Soc., 1959, 263.

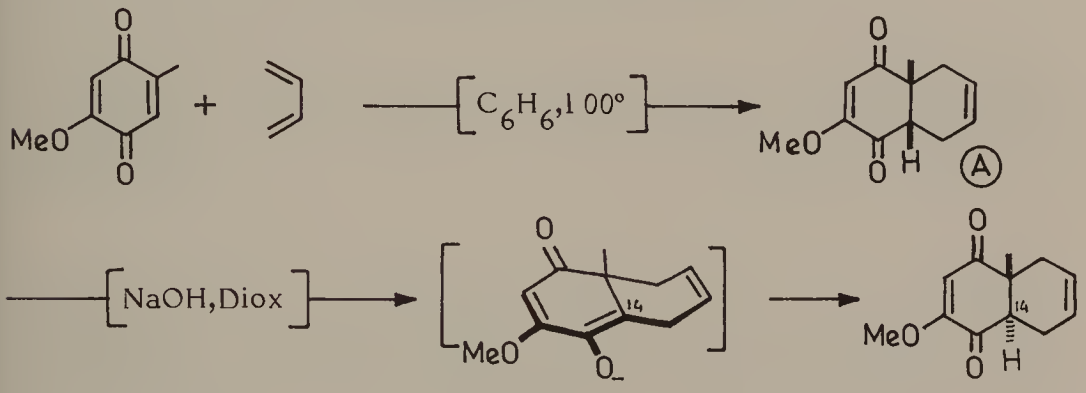
8. For introduction of the phytyl group, see: Willstater,R.; Stoll,A. Annalen, 1911, 380, 148; Fischer,H.; Stern,A. Annalen, 1935, 519, 244. For conversion of the resulting pheophytin to chlorophyll, see: Willstater,R.; Forsen,L. Annalen, 1913, 396, 188; Fischer,H.; Goebel,S. Annalen, 1936, 524, 269.

9. The closest approach to chlorophyll by Hans Fischer had been a total synthesis, of phaeporphyrin-α_5 [Fischer,H.; Stier,E.; Kanngiesser,W. Annalen, 1940, 543, 258]. Fischer's attempts, cut short by an untimely death, have been finally brought to a close in a second synthesis of the plant pigment by a German team led by Strell. The synthesis proceeds with the porphyrin → chlorin reduction using sodium and isoamyl alcohol (although there is no rigorous proof of the two hydrogens having entered the desired positions at C-7 and C-8), conversion of a γ-methyl to an acetic acid residue, introduction of a 2-acetyl as the vinyl group progenitor and conversion to pheophorbide-α, which has been previously transformed into chlorophyll, Strell,M.; Kalojanoff,A.; Koller,H. Angew. Chem., 1960, 72, 169. See also: Johnson,A.W. Science Progr., 1961, 49, 77.



CHOLESTEROL

Two total syntheses (1) of cholesterol were reported almost simultaneously in 1951 (2). The synthesis developed by Woodward and his colleagues (3) is outlined below. It commences with introduction of the future ring D as a six-membered ring in a cis-fused bicyclic adduct (A) representing the C/D ring unit. Elaboration of ring B gives the key tricyclic ketone (B) in which the desired anti-trans structure has been ensured through enol mediated equilibrations at C-8 and C-14 on two separate occasions. Completion of ring A followed by the ring contraction sequence furnishes Woodward's steroid (C) which can be transformed into cholesterol (4).



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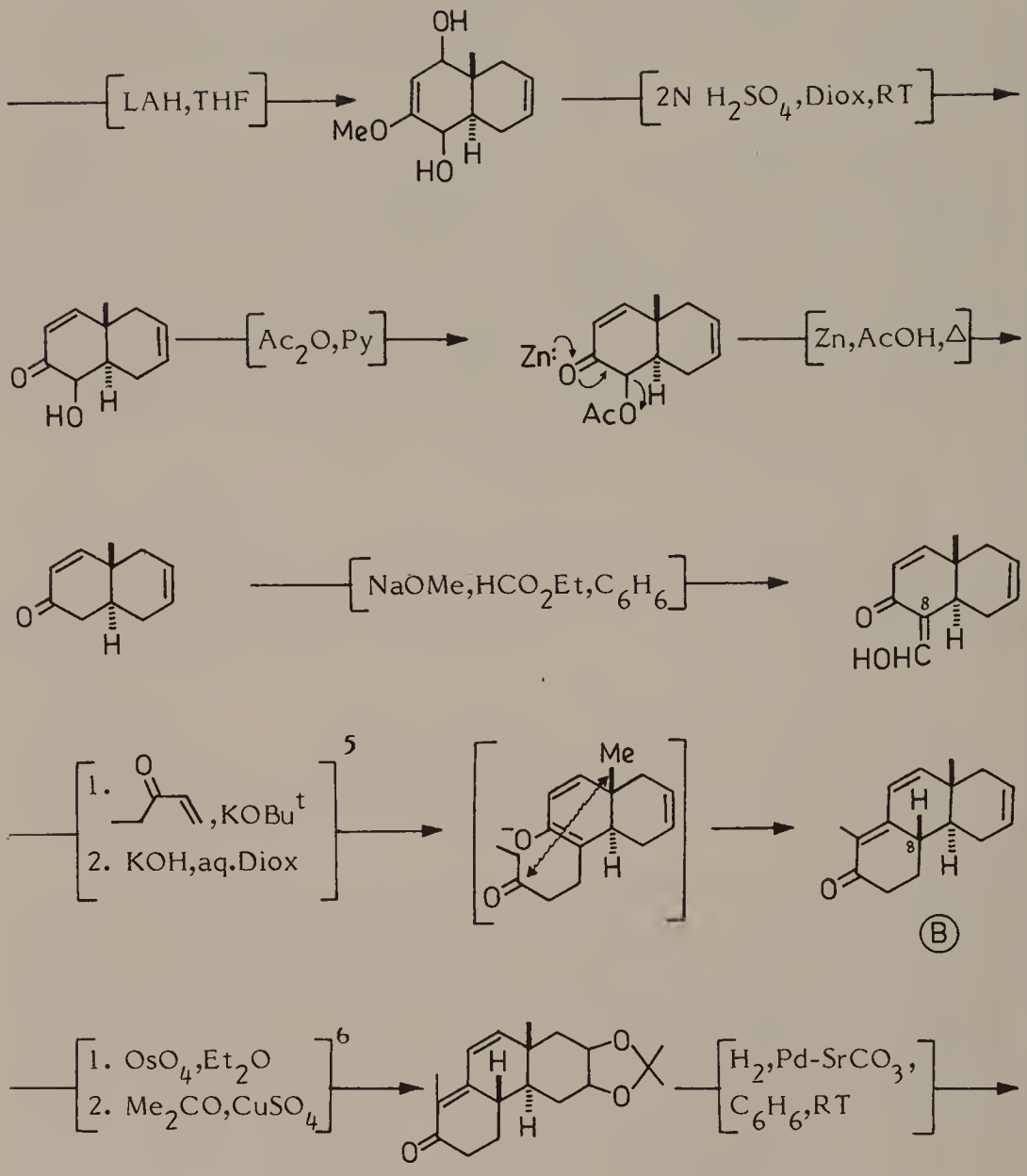
1. One of these syntheses was carried out at Harvard (ref.2) and the second in Robinson's Laboratory at Oxford. The classical approach of Robinson and his coworkers which resulted in a non-stereospecific synthesis of Reich's ketone, was based on a scheme devised as early as 1941; see: Cornforth,J.W. Prog. Org. Chem., 1955, 3, 21; it consists essentially in the addition of ring D (cf. equilenin) onto a saturated A-B-C tricyclic diketone derived from 1-methyl-5-methoxy-2-tetralone; Cardwell,H.M.E.; Cornforth,J.W.; Duff,S.R.; Holtermann,H.; Robinson,R. Chem. Ind., 1951, 389; J. Chem. Soc., 1953, 361.

2. Cholesterol has also been synthesised from dihydroprogesterone by adding the isohexyl side chain; Keana,J.F.W.; Johnson,W.S. Steroids, 1964, 4, 457.

3. Woodward,R.B.; Sondheimer,F.; Taub,D.; Heusler,K.; McLamore,W.M. J. Am. Chem. Soc., 1951, 73, 2403, 3547, 3548; 1952, 74, 4223.

4. Woodward's synthetic steroid (C) can be transformed into intermediates from which the paths to both androgenic and progestational hormones are available. If the $\Delta^{9(11)}$-double bond in (C) is utilized for introduction of the 11-oxygen function, the route to cortisone also lies open.



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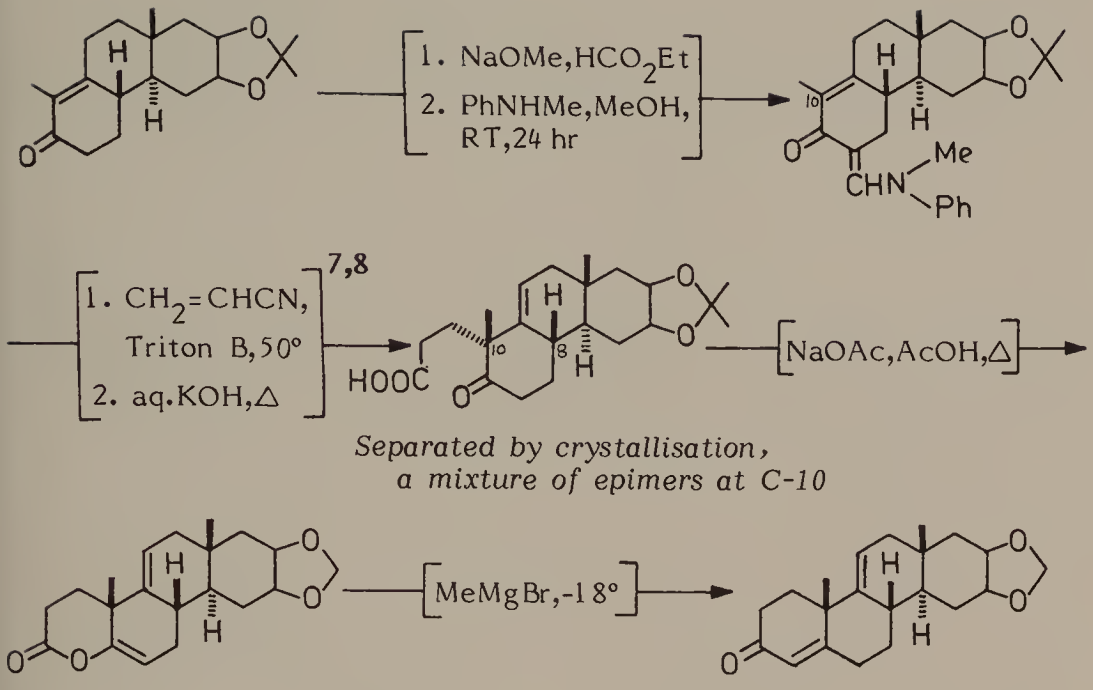
5. Modification of Robinson's annelation reaction by Shunk,C.H.; Wilds,A.L. J. Am. Chem. Soc., 1949, 71, 3946, for preparation of polycyclic cyclohexenones.

6. Iodine, silver acetate and wet acetic acid may be employed with advantage for oxidation of the double bond to a β -cis glycol; Woodword,R.B.; Brutcher,F.V. J. Am. Chem. Soc., 1958, 80, 209.



Separated by crystallisation, a mixture of epimers at C-10

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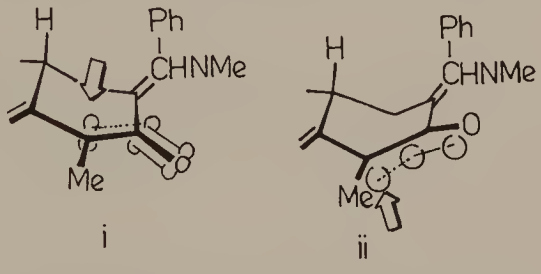
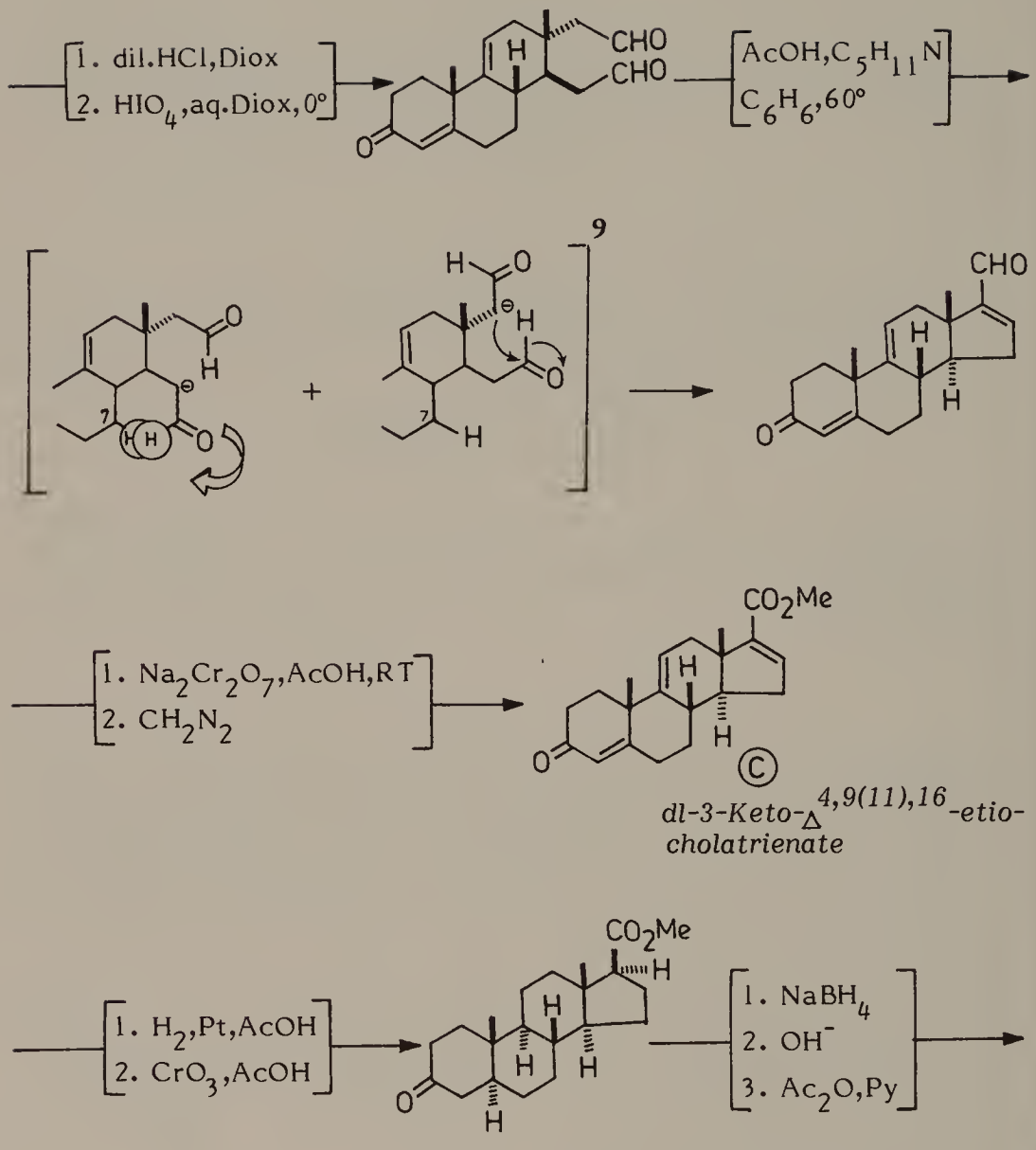
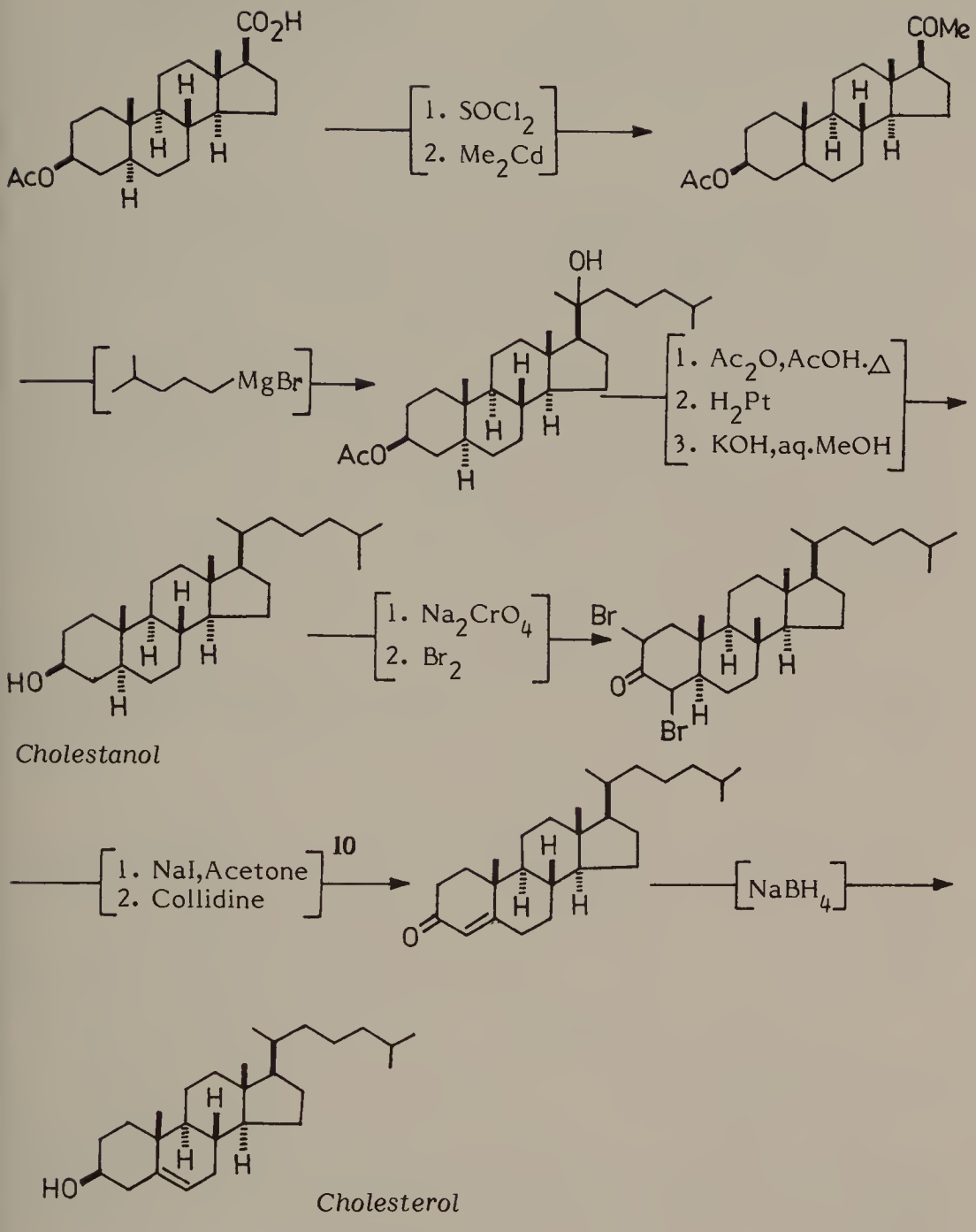
7. cf. Turner,R.B. J. Am. Chem. Soc., 1950, 72, 579; Fujimoto,G.I. ibid, 1951, 73, 1856.
8. Introduction of the asymmetric centre at C-10 results in the formation of two isomers in the ratio of 2:1, the incoming group preferentially occupying the axial position (attack from β-face). In the case at hand, where there is little difference in accessibility to the delocalized carbanion either from the α- or the β-side, the steric course of this addition appears to be determined largely by energy of the intermediate transition state. If the latter resembles the final ketonic product during rehybridization and establishment of the new C-C bond, then approach of the electrophilic attacking reagent from the β-face occurs in an intermediate resembling the pre-chair form (i). On the other hand α-attack (which results in formation of the desired 10-β-methyl isomer) occurs in an energetically less favoured pre-twist intermediate (ii). This probably explains the unfavourable stereochemical outcome of this reaction, cf. Velluz,L.; Valls,J.; Nomine,G. Angew. Chem. Internat. Ed., 1965, 4, 181.





9. Aldol condensation occurs preferentially on the upper methylene group. This is attributed to the relatively less crowded environment of the upper methylene group, whereas either the catalyst fails to gain access to the lower methylene group or the anion, if formed, cannot be restrained with sufficient facility in a suitable orientation for the cyclization to take place.



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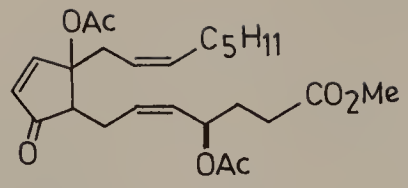
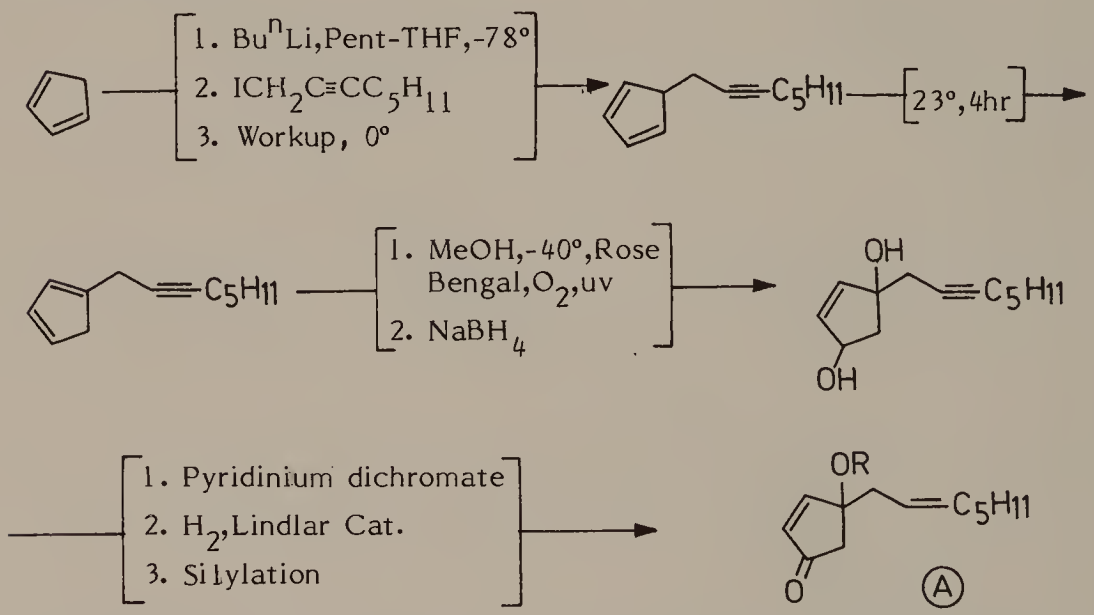
10. Collidine causes 4-dehydrobromination of the axial 4-bromo and hydrogenolysis of the presumably equatorial 2-iodo via an enolate anion in the 2-iodo-4-bromo intermediate, cf. Rosenkranz,G.; Mancera,O.; Gatica,J.; Djerassi,C. J. Am. Chem. Soc., 1950, 72, 4077.



CLAVULONES

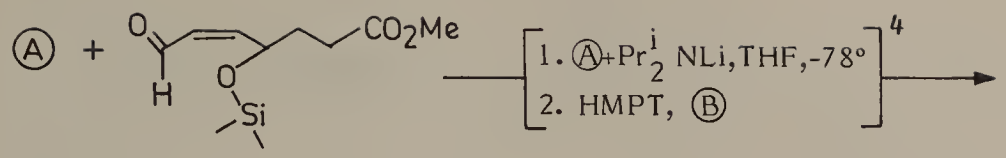
Clavulones are a newly discovered family of novel marine eicosanoids from Clavularis viridis(1), with antiinflammatory and antitumour activities(1,2). Clavulone II is the 5,6-E isomer of I, while Clavulone III is the 5,6-E, 7,8-Z isomer of I. Clavulone I can be isomerised to clavulone II & III by acid catalysis. The present synthesis of racemic clavulone I by Corey & Mehrotra (3) has as its essential synthetic strategy the attachment of ω- and then α-carbon chains to a preformed cyclopentadiene, which would be easily applicable to synthesis of chiral clavulones. The attachment of the α-side chain involves an elegant Claisen condensation taking advantage of the slowness of cyclopentadienone forming elimination. The synthesis also makes an effective use of selective temperature dependent desilylating propensity between tertiary/angular hydroxyl and secondary hydroxyl group.

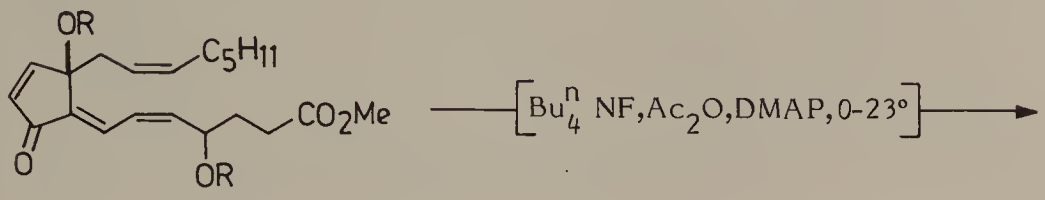


1. (a) Kikuchi,H., Tsukitani,Y., Iguchi,K., Yamada,Y., Tetrahedron Lett., 1982, 23, 5171; (b) ibid, 1983, 24, 1549.

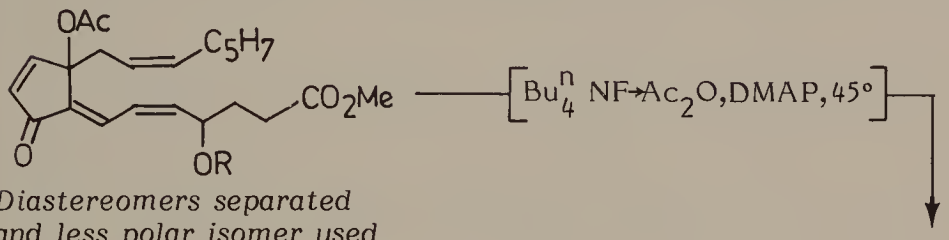
2. Kabayashi,M., et al, 26th Symp. Chem. Nat. Prod., 1983, 228.

3. Corey,E.J., Mehrotra, Mukund M., J. Am. Chem. Soc., 1984, 106, 3384.





1:1 mixture of two diastereoisomers



Diastereomers separated and less polar isomer used

Clavulone I 60%
Clavulone II 15%

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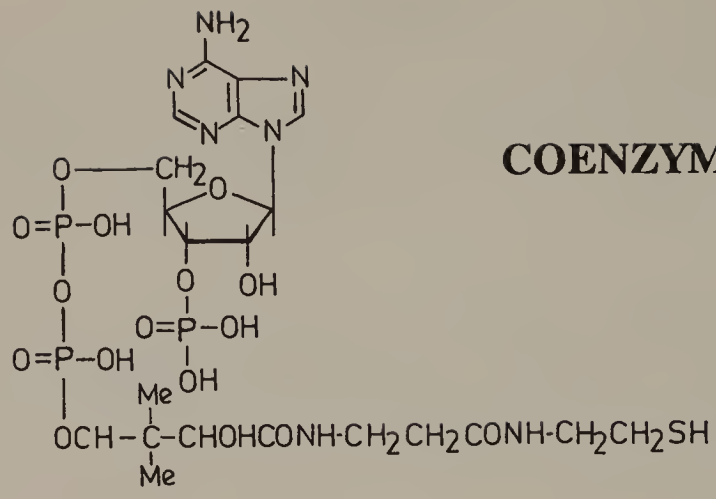
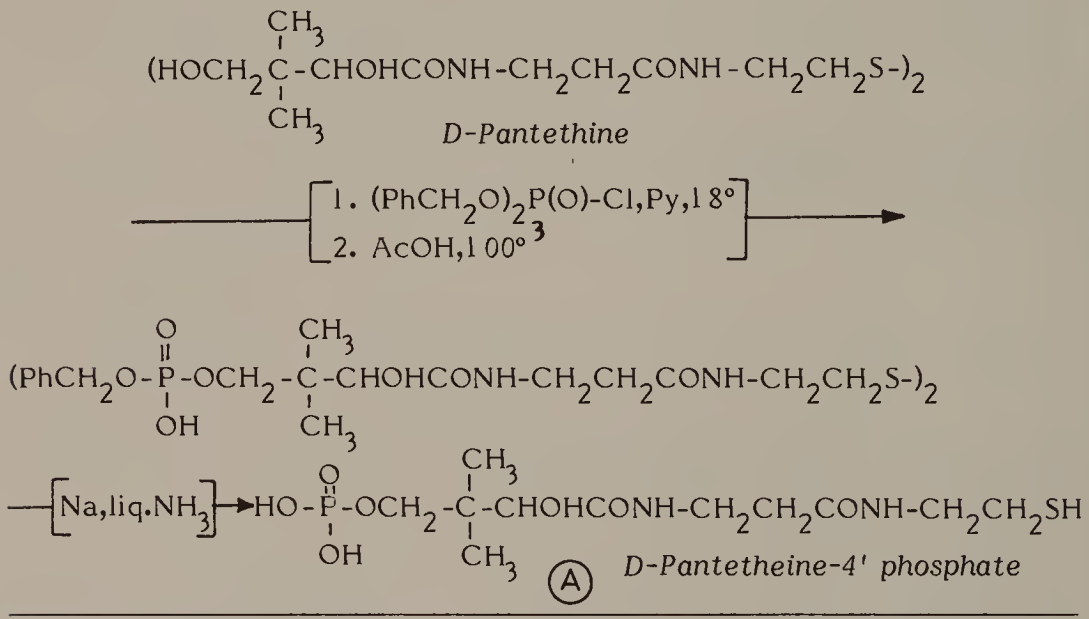
4. The success of this remarkable aldolisation has been attributed (3) to the relative slowness of cyclopentadienone forming elimination.



COENZYME A

The synthesis of coenzyme A (Co A) (1) utilizes the efficient method for the synthesis of nucleoside-5' pyrophosphates through the use of nucleoside-5' phosphoramidates (2).



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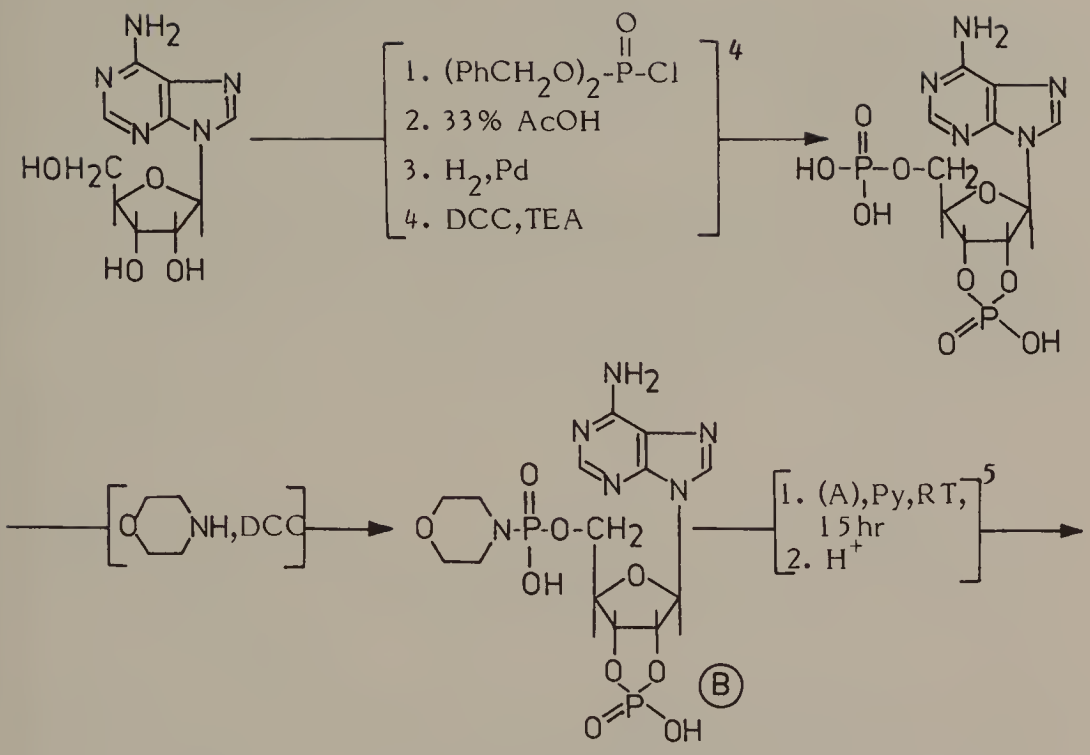
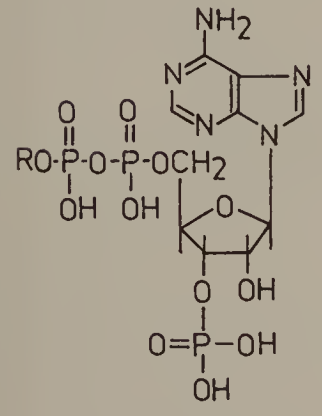
1. Moffatt,J.G.; Khorana,H.G. J. Am. Chem. Soc., 1959, 81, 1265; ibid, 1961, 83, 663.

2. Phosphoramidates are reactive intermediates and are very useful for the specific synthesis of the pyrophosphate bond, cf. Clark,V.M.; Kirby,G.W.; Todd,A.R. J. Chem. Soc., 1957, 1497; Moffatt,J.G.; Khorana,H.G. J. Am. Chem. Soc., 1958, 80, 3756; Moffatt,J.G. Khorana,H.G., ibid, 1961, 83, 649. Using this method the synthesis of a number of nucleotide coenzymes such as UDPG and FAD has been carried out, Moffatt,J.G.; Khorana,H.G. J. Am. Chem. Soc., 1958, 80, 3756; Roseman,S.; Distler,J.J.; Mofatt,J.G.; Khorana,H.G. ibid, 1961, 83, 659.

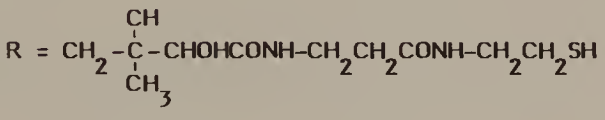
3. If AcOH treatment was omitted the product was very heavily contaminated with 2',4'-cyclic phosphate. The formation of the cyclic phosphate presumably occurred as a transesterification reaction of the tertiary phosphate; AcOH treatment presumably converts it into monophosphate, which is not a good transesterificating agent.



as bis-(4-Morpholine N,N'-bicyclo-hexyl carboxamidinium) salt



+ iso-Co A



Coenzyme A

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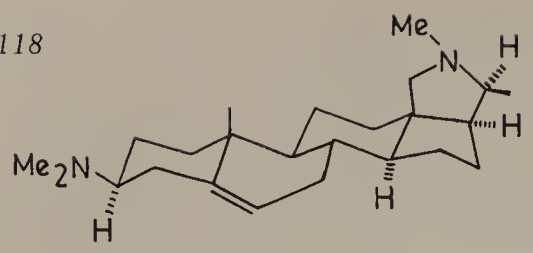
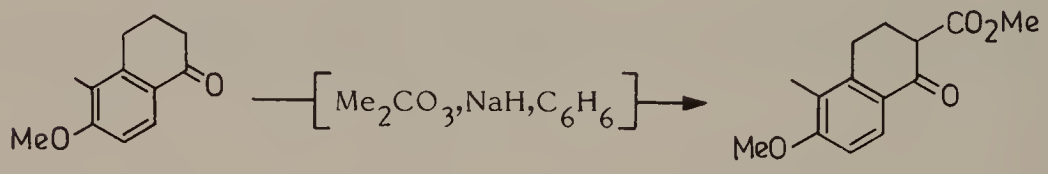
4. During phosphorylation a mixture of the 5',2'- and 5',3'-diphosphates was obtained. Treatment with AcOH caused partial debenzylation. The mixture of diphosphates thus obtained after hydrogenation could also be treated directly with morpholine and DCC, when morpholidate (B) was obtained in one step in an overall yield of 90-95%.

5. After the reaction the products were separated by chromatography on ion exchange resin and ECTEOLA column.



CONESSINE

Conessine is marked by the presence of a heterocyclic ring fused to ring D of the steroid nucleus. Stork and his colleagues (1), in their stereospecific total synthesis of conessine have chosen first to construct this nitrogen-containing ring on a B-C-D tricyclic intermediate Ⓐ (2) followed by completion of ring A.



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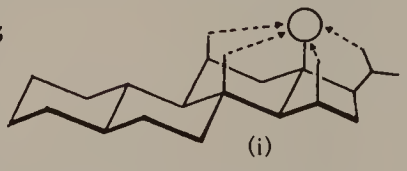
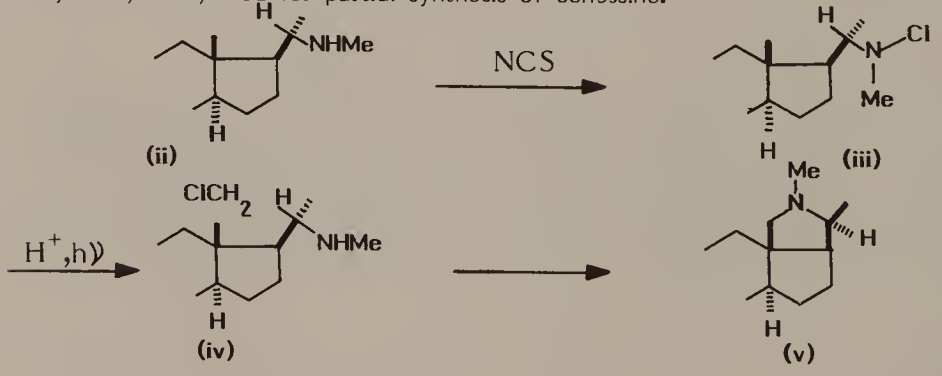
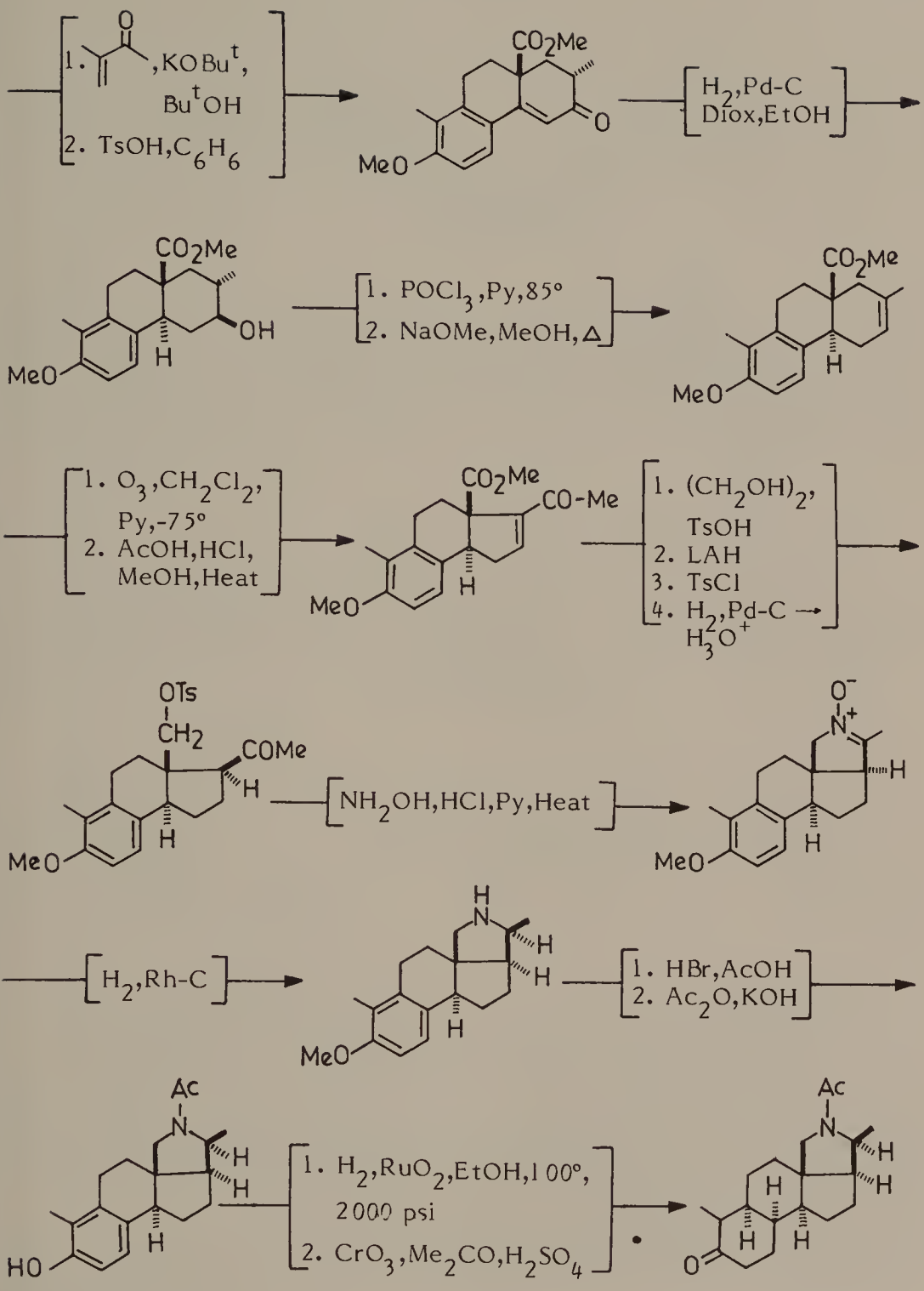
1. Stork,G.; Darling,S.D.; Harrison,I.T.; Wharton,P.S. J. Am. Chem. Soc., 1962, 84, 2018.

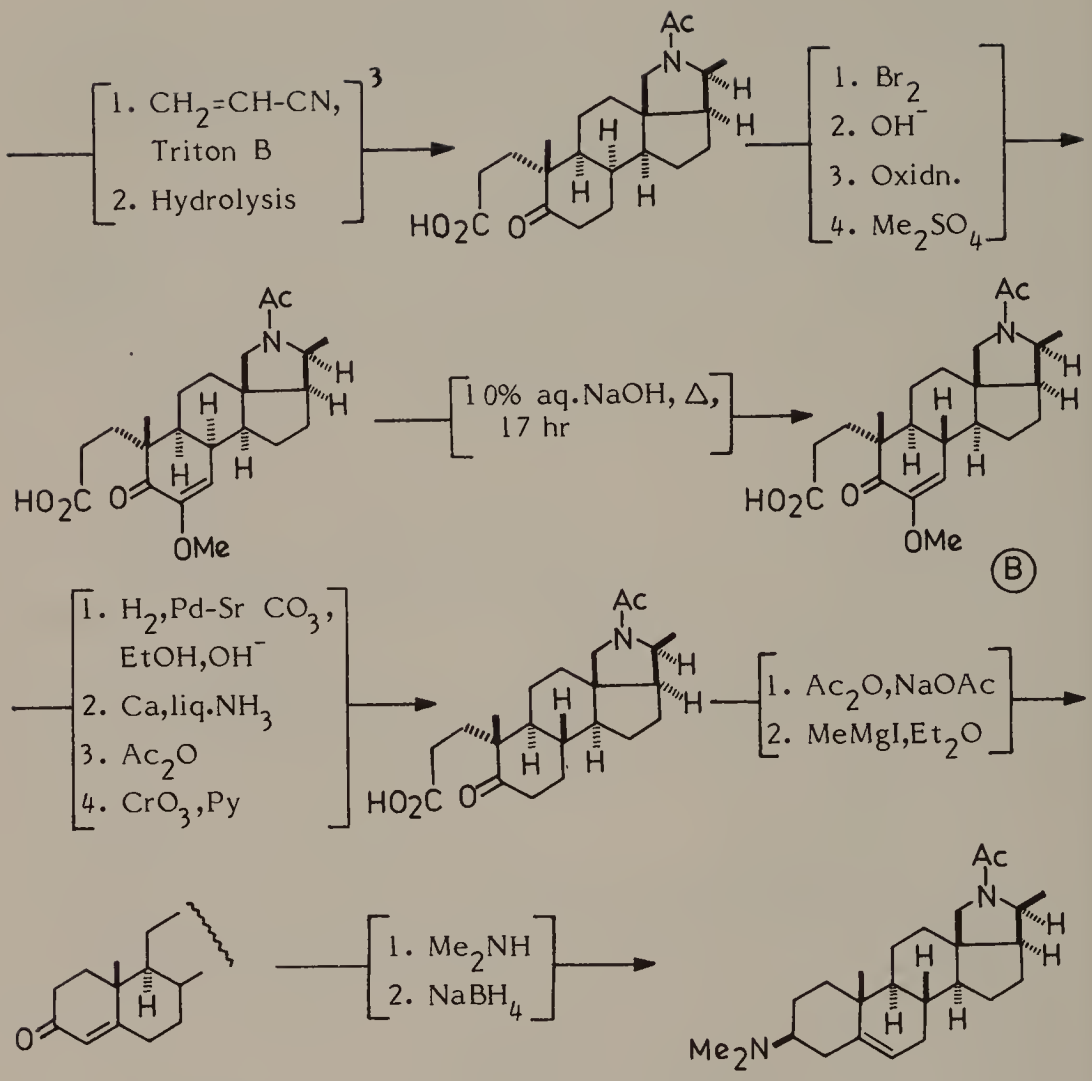
2. Synthesis of the nitrogen-containing conessine ring system from steroid precursors requires the functionalization of an unactivated C-18 angular methyl group. At this point the problems involved are shared with the related steroid hormone, aldosterone; and the ingenious use of proximity effects for selective introduction of reactive functions at C-18 [cf.(i)] are discussed by Schaffner,K.; Arigoni,D.; Jeger,O. Experientia, 1960, 16, 169. Special mention, however, must be made of the use of Hofmann-Loffler-Freytag reaction involving the free-radical chain decomposition of a C_{20}-N-chloroamine in the synthesis of dihydroconessine (ii→v) by Corey,E.J.; Hertler,W.R. J. Am.Chem. Soc., 1959, 81, 5209, and the photolytic method of Barton,D.H.R.; Starratt,A.N. J. Chem. Soc., 1965, 2444, used for partial synthesis of conessine.



(i)




1. ,KOBu^t, Bu^tOH
2. TsOH,C6H6
CO2Me
MeO
H2,Pd-C
Dioxane,EtOH
OH
1. POCl3,Py,85°
2. NaOMe,MeOH,Δ
1. O3,CH2Cl2, Py,-75°
2. AcOH,HCl, MeOH,Heat
CO-Me
1. (CH2OH)2, TsOH
2. LAH
3. TsCl
4. H2,Pd-C → H3O+
OTs
CH2
COMe
NH2OH,HCl,Py,Heat
H2,Rh-C
1. HBr,AcOH
2. Ac2O,KOH
Ac
HO
1. H2,RuO2,EtOH,100°, 2000 psi
2. CrO3,Me2CO,H2SO4



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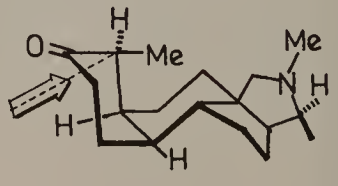
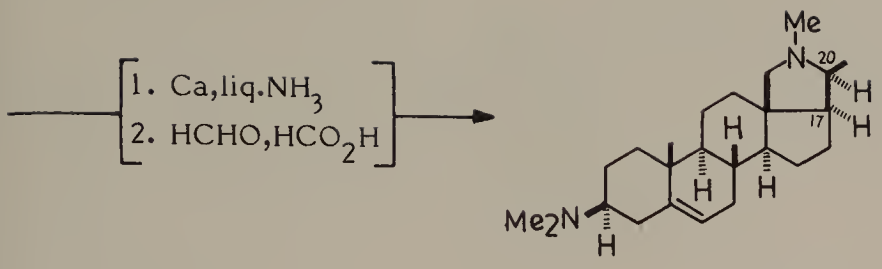
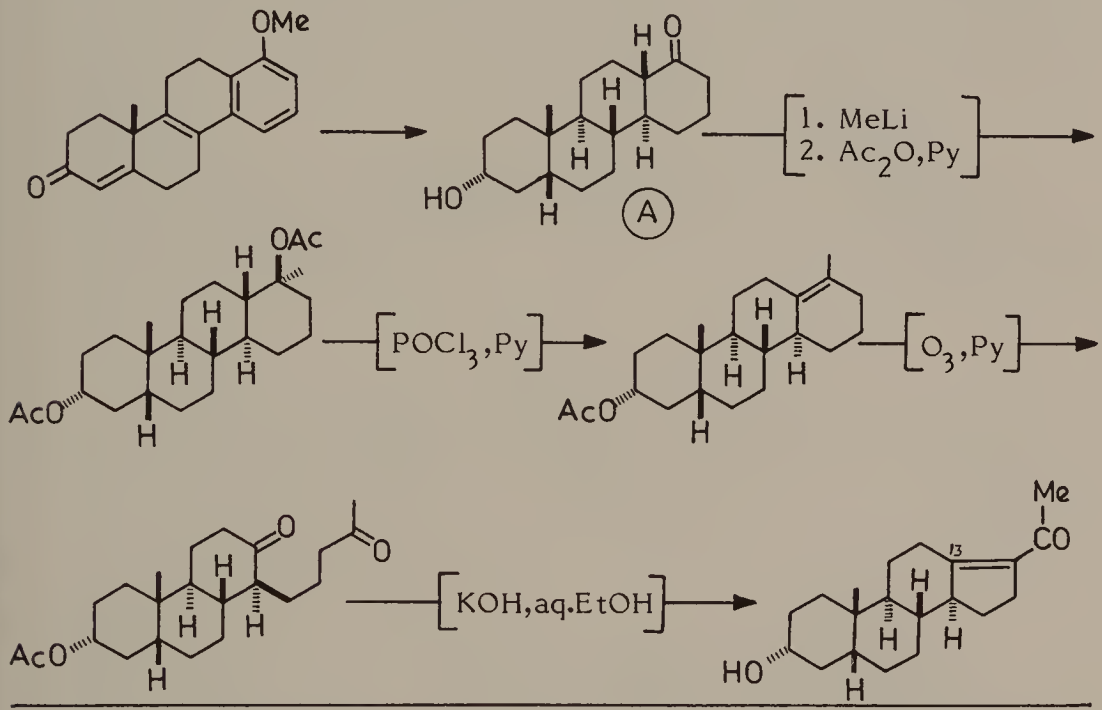
3. Control of stereochemistry at C-10 has been achieved by introducing the elements of ring A into an 8-iso intermediate having B/C rings cis. The "folded" structure of the molecule (i) now makes the position 10, already carrying the future angular methyl group, inaccessible from the α-face, thus forcing the incoming alkylating group to attack from the β-face; cf. Stork,G.; Loewenthal,H.J.E.; Mukharji,P.C. J. Am. Chem. Soc., 1956, 78, 501. The 8-iso intermediate having served its purpose, the desired trans-B/C ring fusion in the molecule is restored in an ingenious manner by introducing a double bond in conjugation with the carbonyl function which now permits inversion at C-8 by equilibration.





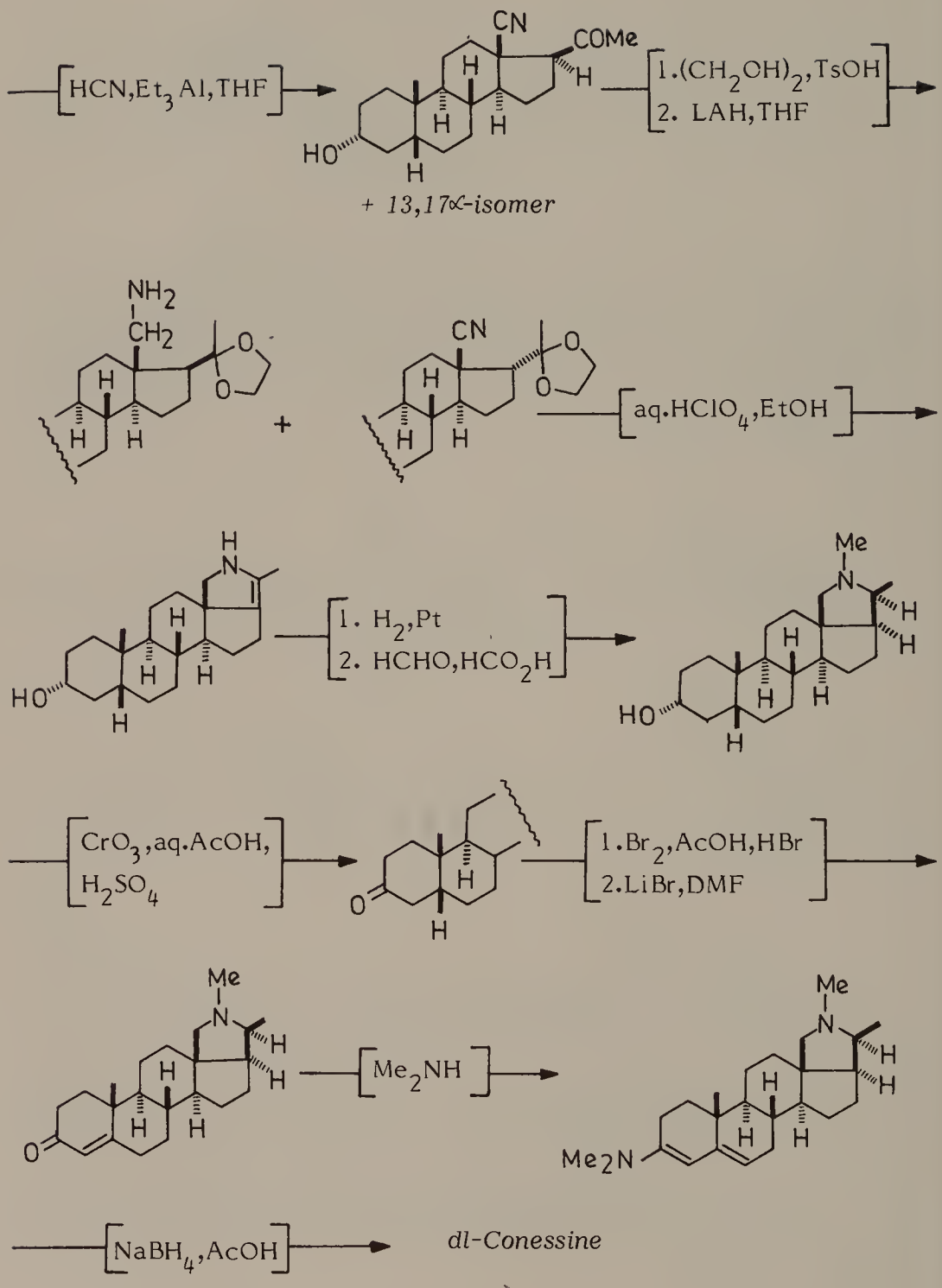
dl-Conessine

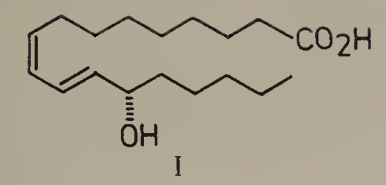
The synthesis by Johnson et al. (4) begins along lines laid down earlier in the "hydrochrysene approach" for construction of the D-ring homo-steroid (A) followed by the usual ring contraction procedure. Introduction of the C-18 group and elaboration of the heterocyclic ring E is based on the conjugate addition of cyanide ion to an α,β -unsaturated ketone system (5).



4. Marshall,J.A.; Johnson,W.S. J. Am. Chem. Soc., 1962, 84, 1485; Johnson,W.S.; Marshall,J.A.; Keana,J.F.W.; Franck,R.W.; Martin,D.G.; Bauer,V.J. Tetrahedron, Suppl.8, 1966,22, Part II, 541.

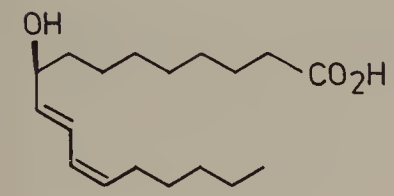
5. This hydrocyanation procedure was developed by Nagata and also used by him in his total synthesis of conessine, Nagata,W.; Terasawa,T.; Aoki,T. Tetrahedron Lett., 1963, 869.


HCN,Et3Al,THF
CN
COMe
HO
1.(CH2OH)2,TsOH
2. LAH,THF
+ 13,17α-isomer
NH2
CH2
O
O
+
CN
O
O
aq.HClO4,EtOH
HO
1. H2,Pt
2. HCHO,HCO2H
Me
HO
CrO3,aq.AcOH,
H2SO4
O
1.Br2,AcOH,HBr
2.LiBr,DMF
Me
O
Me2NH
Me
Me2N
NaBH4,AcOH
dl-Conessine



I

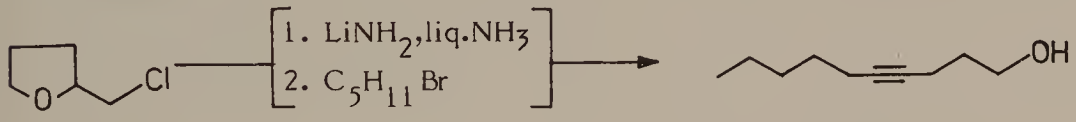
CORIOLIC ACID
DIMORPHECOLIC ACID

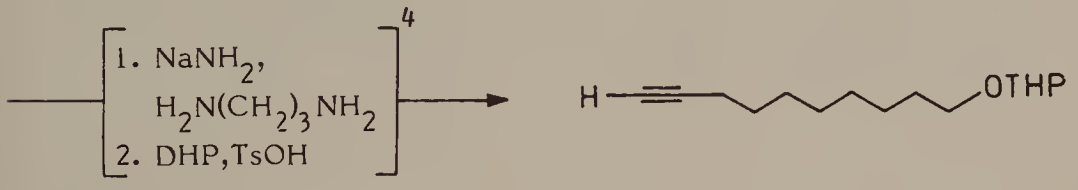


II

Unsaturated fatty acids play important roles in biological systems. Coriolic acid (I) and dimorphecolic acid (II), belonging to the family of oxyoctadecadienoates, though isolated first from bovine heart mitochondria (1), and shown to possess cation-specific ionophoric activity, have recently been isolated from rice plant Fukuyuki (2), and shown to act as self-defensive substances against rice blast disease. Rama Rao and his associates have presented a stereoselective syntheses of these acids, which have general applicability to this class of compounds (3).

Coriolic acid





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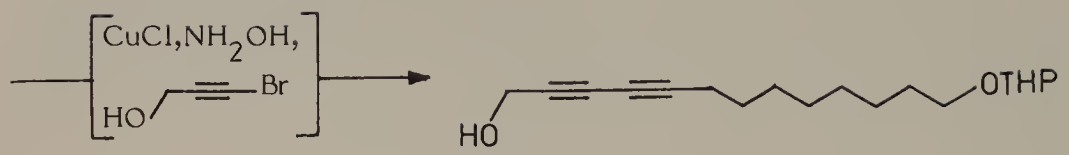
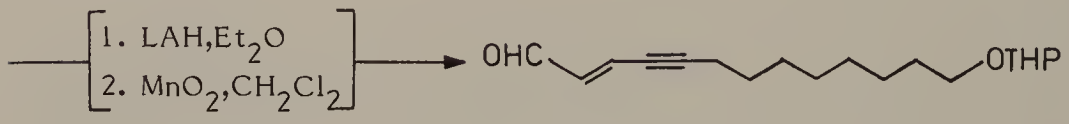
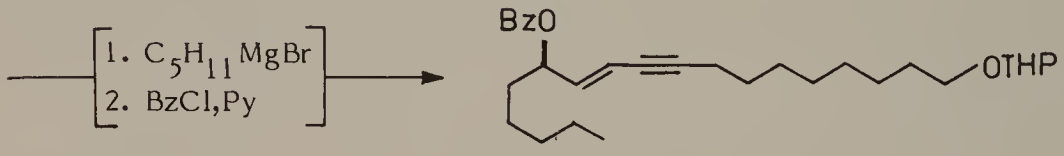
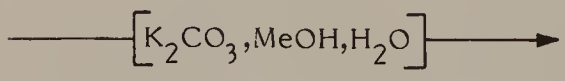
1. Blondin,G.A. Ann. N.Y. Acad. Sci., 1975, 264, 98.
2. Kato,T.; Yamaguchi,T.; Yokoyama,T.; Yyehara,T.; Namai,T.; Yamanaka,S.; Harada,N. Chem. Lett., 1984, 409.
3. Rama Rao,A.V.; Reddy,E.R.; Sharma,G.V.M.; Yadgiri,P.; Yadav,J.S. Chem. Pharm. Bull., 1985, 33, 2168; Tetrahedran, 1986, 42, 4523.
4. Brown,C.A.; Yamashita,A. J. Chem. Soc. Chem. Commun., 1976, 959.



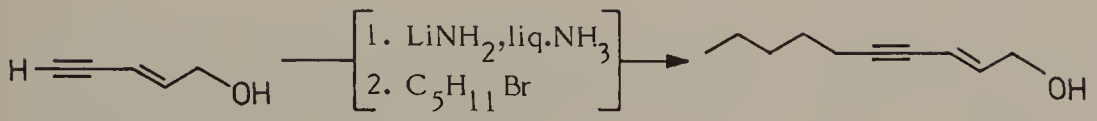


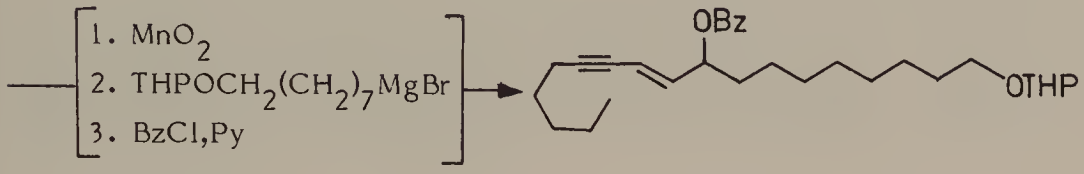


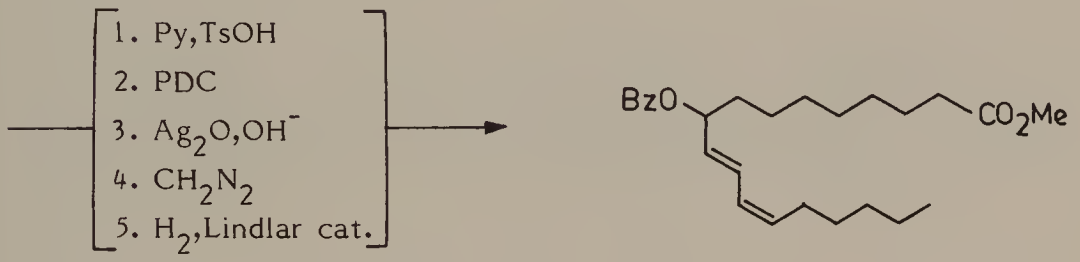


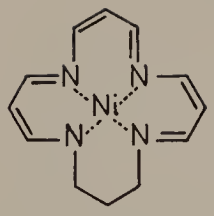
(±)-Coriolic acid

Dimorphecolic acid



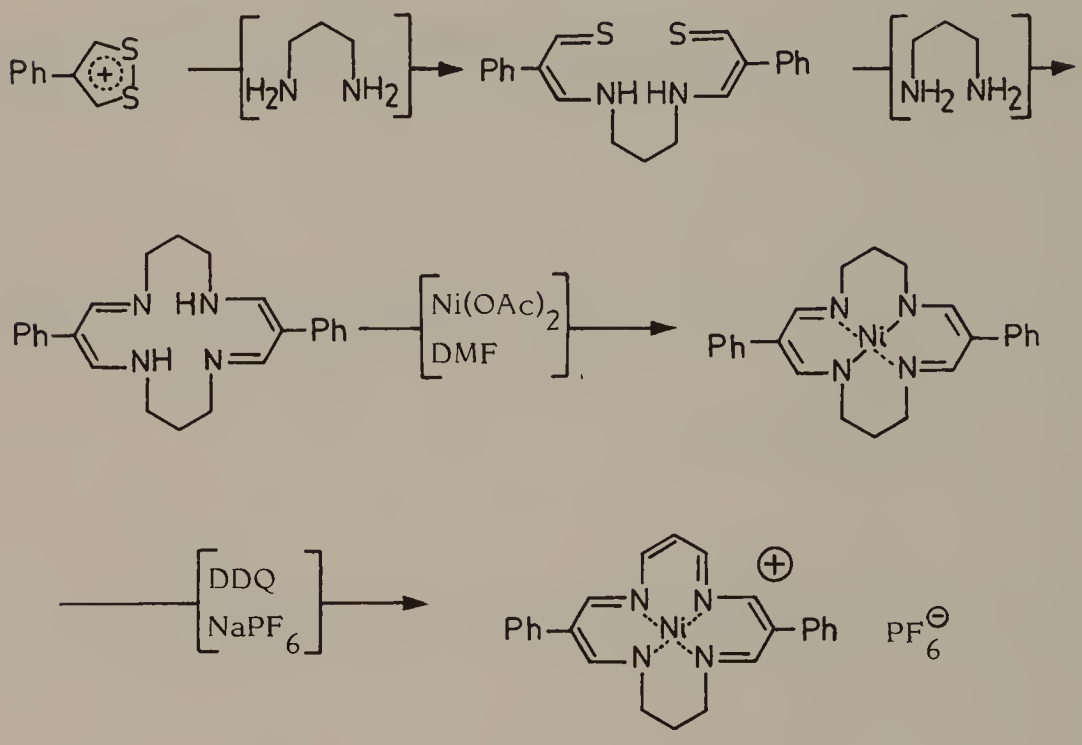






CORRIN TEMPLATE

The current interest in the function of metal complexes in biological systems has added a new facet to synthetic inorganic chemistry, namely, the creation of simple models of the biologically important systems. This aspect is best illustrated with the brilliant synthesis of the corrin template I: (1)



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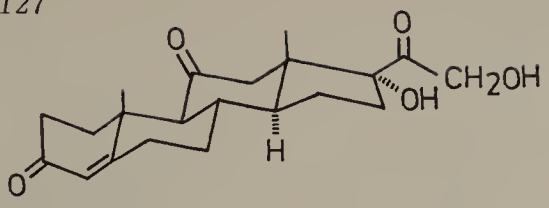
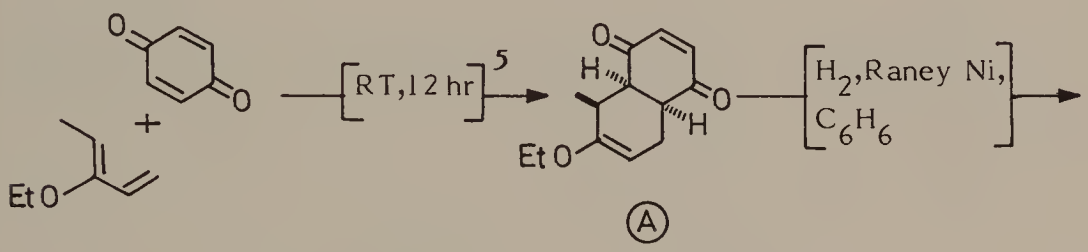
1. Tang,S.C., Weinstein,G.N., Holm,R.H., J. Am. Chem. Soc., 1973, 95, 613.



CORTISONE

The first synthesis of cortisone was reported in 1951 by Woodward and his colleagues (1). Shortly afterwards Sarett and his coworkers at Merck Laboratories (2) reported a highly stereoselective (3) route to cortisone which did not involve the use of relays (4). In this synthesis the crucial anti-trans tricyclic nucleus (D) representing rings A, B and C of cortisone has been obtained from a cis-fused bicyclic adduct (A); the cis ring junction in (A) (later equilibrated to trans) serves an important function in directing the addition of ring A from the less hindered convex α-face and in ensuring formation of the angular hydrophenanthrene derivative during the transformation (B) → (C) (7). Equilibration at C-8 during the Oppenauer oxidation furnishes the desired anti-trans ring fusion.



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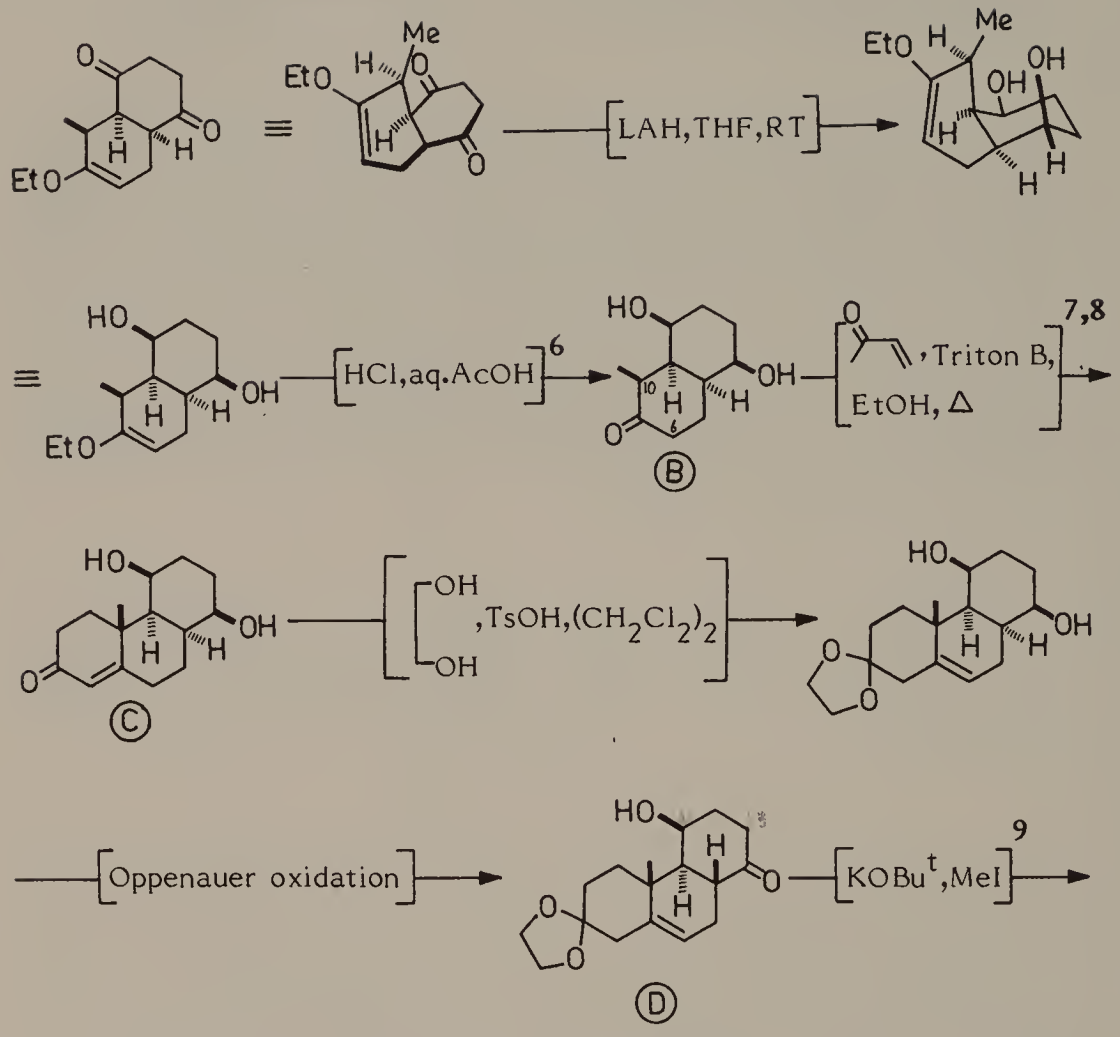
1. Woodward,R.B.; Sondheimer,F.; Taub,D.; Heusler,K.; McLamore,W.M. J. Am. Chem. Soc., 1951, 73, 4057; 1952, 74, 4223. Woodward's synthesis of $\Delta^{9(11),16}$-bis-dehydro-20-norprogesterone is described in detail under the synthesis of cholesterol, and from this point a practical route to cortisone, involving the fashioning of the cortical side-chain and addition of hypobromous acid to the 9(11)-double bond for introduction of the 11-oxygen function, is described by Barkley,L.B.; Farrar,M.W.; Knowles,W.S.; Raffelson, H. J. Am. Chem. Soc., 1954, 76, 5017.

2. Sarett,L.H.; Arth,G.E.; Lukes,R.M.; Beyler,R.E.; Poos,G.I.; Johns,W.F.; Constanin,J.M. J. Am. Chem. Soc., 1952, 74, 4974.

3. These authors use the term "stereospecific" which is taken to mean that "in each reaction producing a fixed asymmetric centre, the ratio of isomer having the same configuration as the end product to all other isomers is greater than unity" (ref.2). By this definition, ratios of 8:1 or better have been obtained at all steps in this synthesis. For use of the terms "stereospecific" and "stereoselective", see: Eliel,E.L. in "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, 1962, Chapter 15.

4. For an account of the gigantic effort that went into devising partial and totally synthetic routes to cortisone, see: Fieser,L.F.; Fieser,M. in "Steroids", Reinhold, New York, 1959, 600; Djerassi,C. Vitamins & Hormones, 1953, 11, 205.

5. Sarett,L.H.; Lukes,L.M.; Poos,G.I.; Robinson,J.M.; Beyler,R.E.; Vandergrift,J.M.; Arth,G.E. J. Am. Chem. Soc., 1952, 74, 1393.



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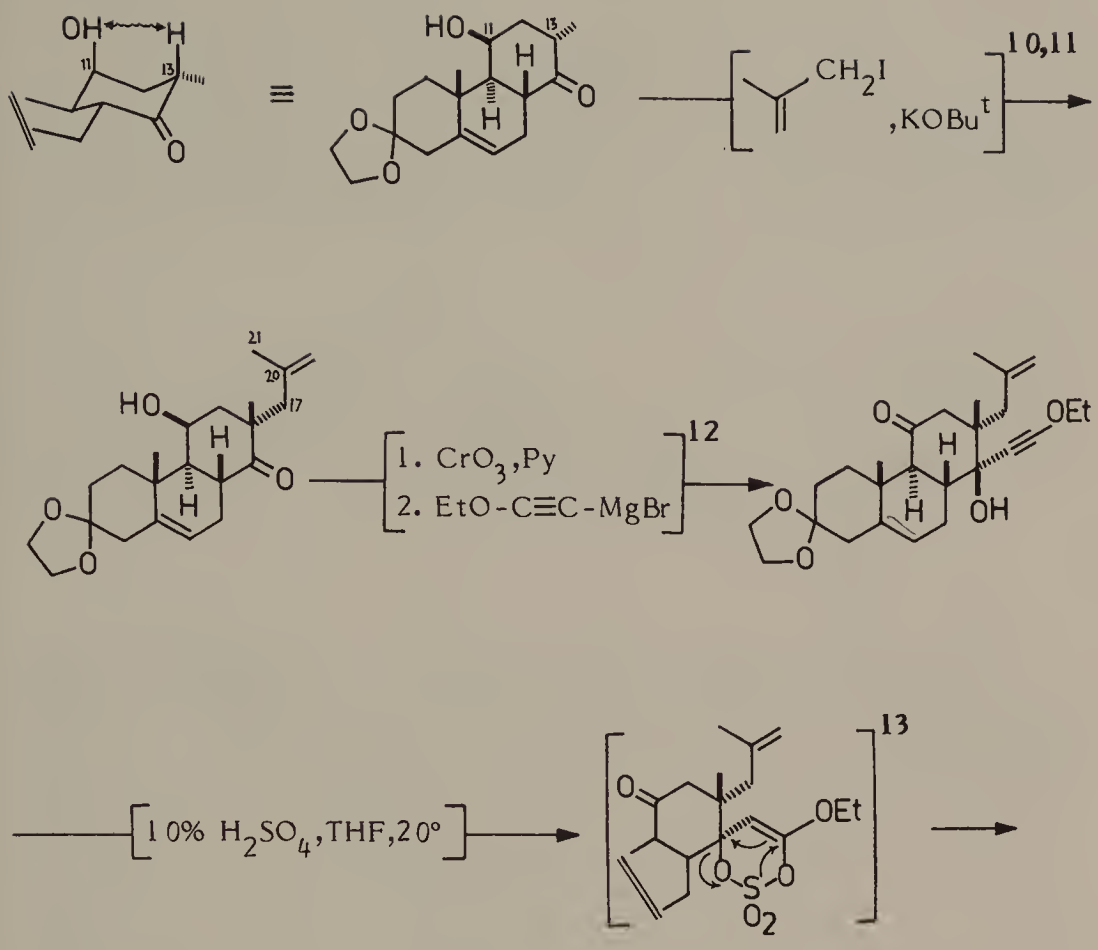
6. Beyler,R.E.; Sarett,L.H. J. Am. Chem. Soc., 1952, 74, 1406.

7. Formation of the angular hydrophenanthrene derivative instead of a linear anthracene is favoured because enolization of the carbonyl function occurs towards the ring junction in a cis-fused decalin. Addition of methyl vinyl ketone to (B) therefore occurs at C-10 rather than C-6, cf. the preferential formation of Δ^3-enols by 3-oxo-A/B cis steroids, Corey,E.J.; Sneen,R.A. J. Am. Chem. Soc., 1955, 77, 2505; Velluz,L.; Valls,J.; Nomine,G. Angew. Chem. Internat. Ed., 1965, 4, 181. The bond formation at C-10, however, occurs from both the β- and α-face, and gives a 2:1 ratio of unnatural to natural isomer.

8. Poos,G.I.; Arth,G.E.; Beyler,R.E.; Sarett,L.H. J. Am. Chem. Soc., 1953, 75, 422.

9. Lukes,R.M.; Poos,G.I.; Beyler,R.E.; Johns,W.F.; Sarett,L.H. J. Am. Chem. Soc., 1953, 75, 1707.



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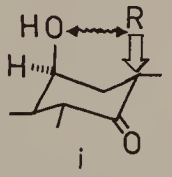
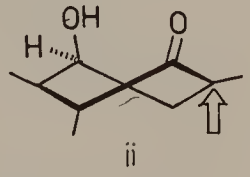
10. Sarett,L.H.; Johns,W.F.; Beyler,R.E.; Lukes,R.M.; Poos,G.I.; Arth,G.E. J. Am. Chem. Soc., 1953, 75, 2112.

11. Due to 1,3-interaction between the 11-hydroxyl group and the approaching electrophile (i), instead of the usual axial alkylation at position 13, the incoming isopropenyl group attaches itself from the α-face (ii). This is an example of "equatorial or twist-axial alkylation", see: Stork,G.; Darling,S.D. J. Am. Chem. Soc., 1964, 86, 1761.



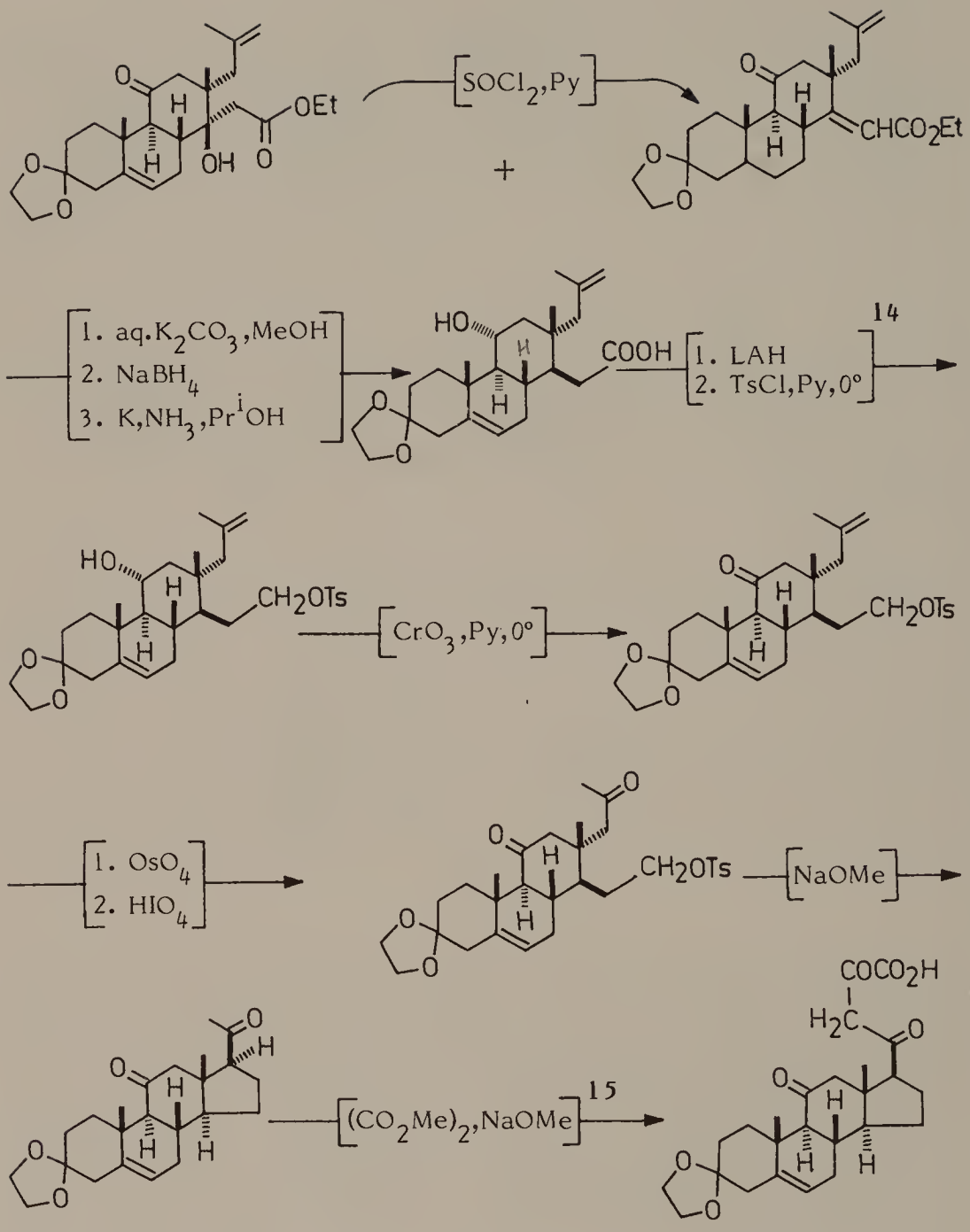
i



ii

12. Arth,G.E.; Poos,G.I.; Lukes,R.M.; Robinson,F.M.; Johns,W.F.; Feurer,M.; Sarett,L.H. J. Am. Chem. Soc., 1954, 76, 1715.

13. cf. Arens,J.F. in "Advances in Organic Chemistry", Vol.II, eds. R.A. Raphael, E.C. Taylor and Wynberg,H., Interscience, New York, 1960, 159.



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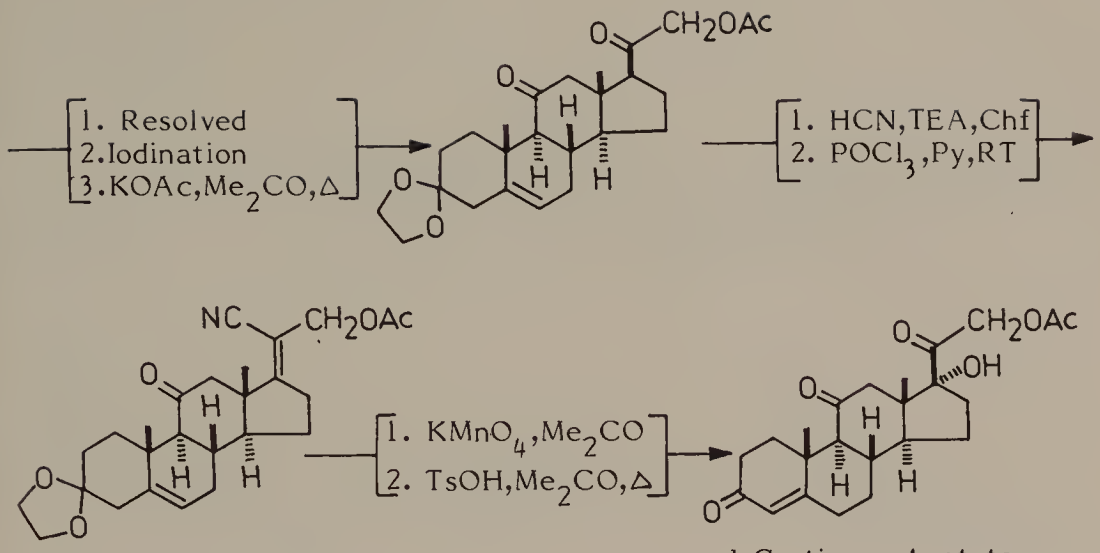
14. Johns,W.F.; Lukes,R.M.; Sarett,L.H. J. Am. Chem. Soc., 1954, 76, 5026.

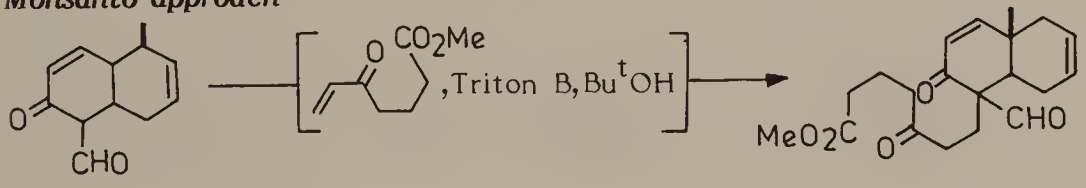
15. Poos,G.I.; Lukes,R.M.; Arth,G.E.; Sarett,L.H. J. Am. Chem. Soc., 1954, 76, 5031.



d-Cortisone Acetate

One drawback in Woodword's synthesis of cortisone (1) is the lack of stereoselectivity during construction of ring A to form the tricyclic ketone (C). The alkylating group preferentially enters from the β-face and formation of the quaternary centre at C-10 invariably results in an unfavourable 2:1 ratio of unnatural to natural isomer. The problem was resolved independently by Stork et al. (16) and a group of workers at Monsanto (17). Since it is the existing group at C-10 which finally occupies the α-configuration, these authors reversed the sequence of alkylation and introduced the methyl group last, which now entered predominantly from the β-face as desired. The Monsanto workers also found that blocking of the 6-position during introduction of ring A is unnecessary if ring D is five-membered. This route to cortisone is outlined below.

Monsanto approach



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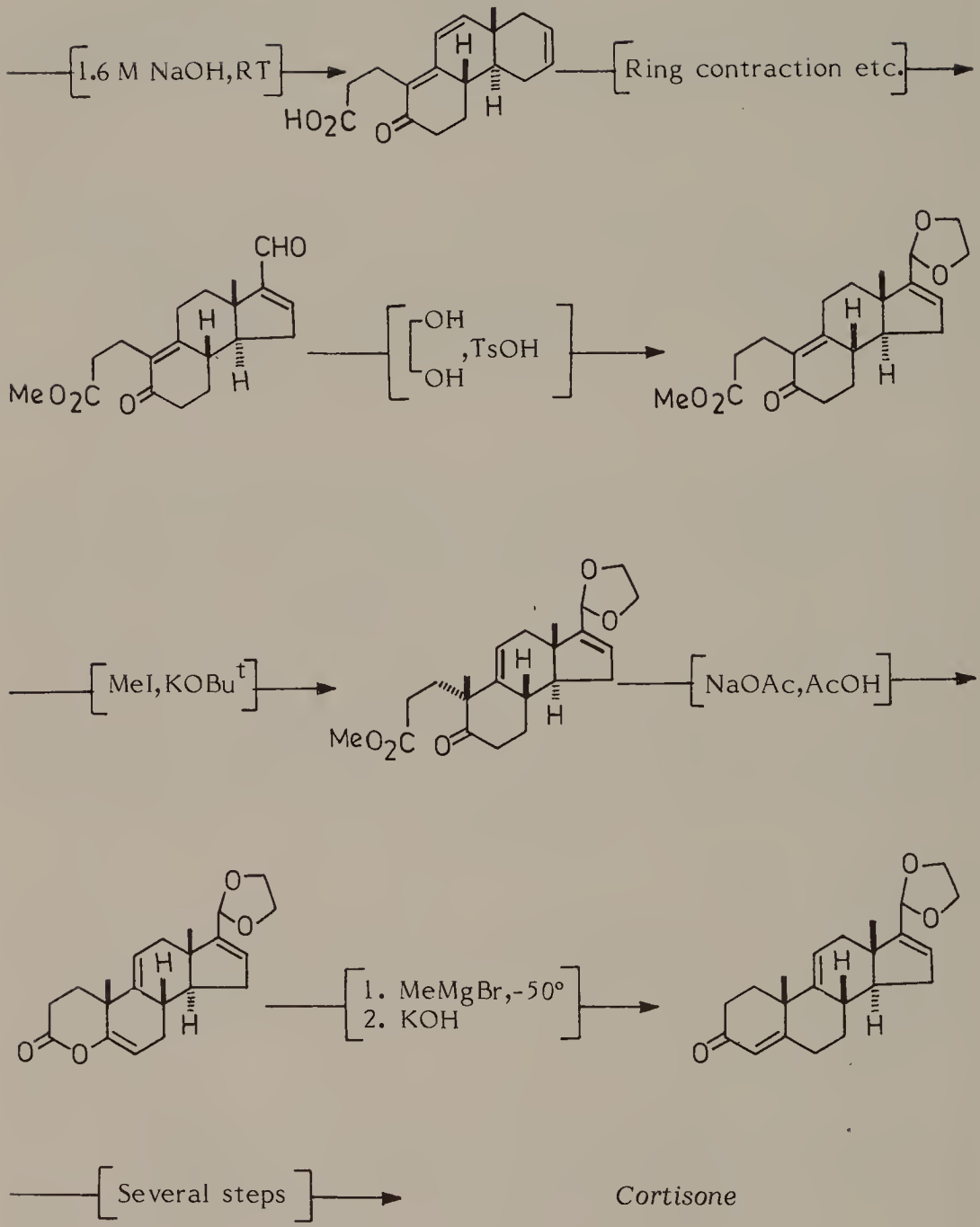
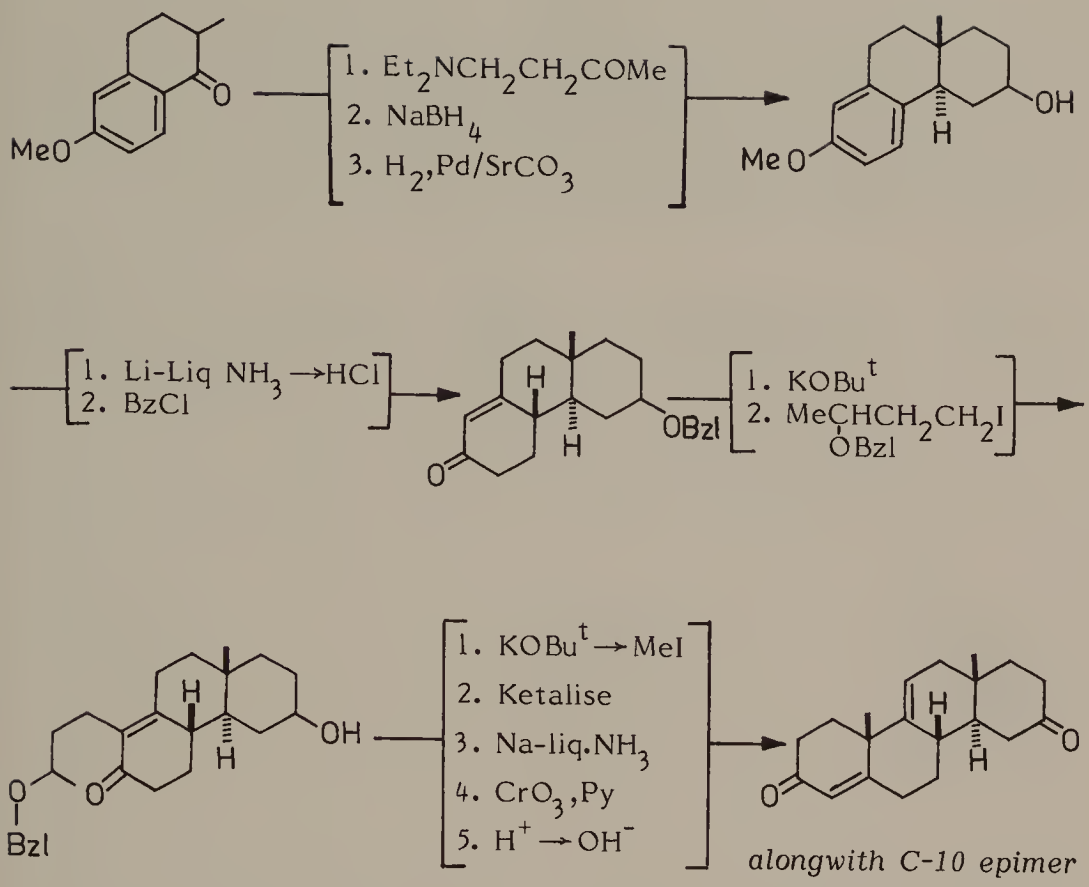
16. Stork,G.; Loewenthal,H.J.E.; Mukherji,P.C. J. Am. Chem. Soc., 1956, 78, 501.
17. Barkley,L.B.; Knowles,W.S.; Raffelson,H.; Thompson,Q.E. J. Am. Chem. Soc., 1956, 78, 4111.

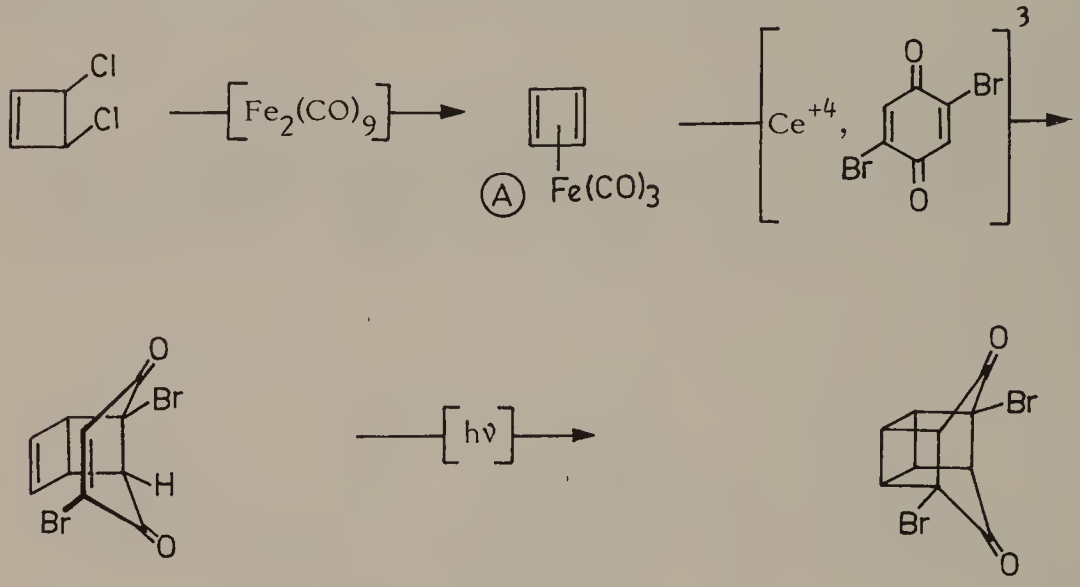

1.6 M NaOH, RT
Ring contraction etc.
CHO
OH
OH
,TsOH
MeI, KOBu^t
NaOAc, AcOH
1. MeMgBr, -50°
2. KOH
Several steps
Cortisone

Stork approach:




CYCLOBUTADIENE CUBANE

For an exceptionally long period cyclobutadiene was an enigma and the amount of work that has gone into this problem is enormous. The synthesis and characterization of cyclobutadiene (1), therefore, is a big event in organic chemistry. Perhaps the most interesting reaction involving cyclobutadiene is in the cubane synthesis (2).



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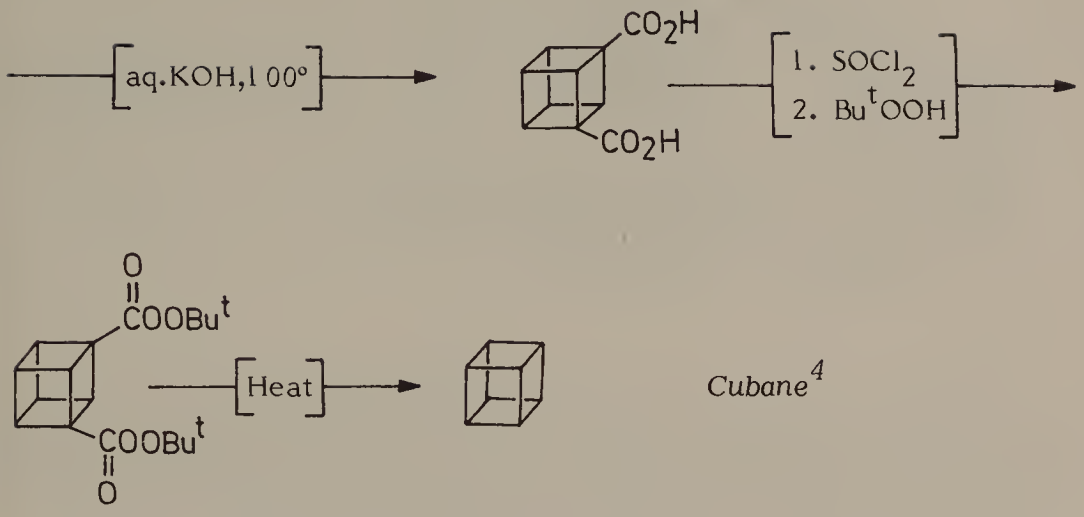
1. Cyclobutadiene, though per se unavailable for organic synthesis, because of its extreme instability, gets stabilized as an organometallic complex, cyclobutadiene tricarbonyl iron (Ⓐ), which seems to provide a useful source of the hydrocarbon, Emerson,G.F.; Watts,L.; Pettit,R. J. Am. Chem. Soc., 1965, 87, 131.

2. Barborak,J.C.; Watts,L.; Pettit,R. J. Am. Chem. Soc., 1966, 88, 1328.

3. During the course of the oxidative decomposition of (A) with ceric ion in the presence of dienophiles a molecule of cyclobutadiene can be transferred from the iron atom to the dienophile. For example, with acetylenes its oxidative decomposition gives rise to several derivatives of Dewar benzene, of Watts,L.; Fitzpatrick,J.D.; Pettit,R. J. Am. Chem. Soc., 1965, 87, 3253; Burt,G.D; Pettit,R. Chem. Commun., 1965, 517.



Cubane[4]

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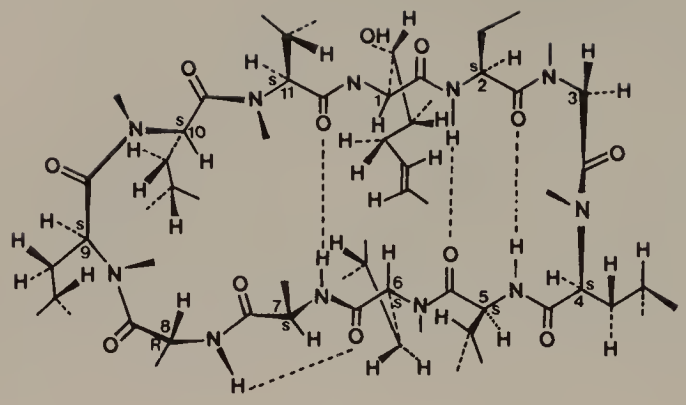
4. For an earlier synthesis of cubane, see: Eaton,P.E.; Cole,T.W.Jr. J. Am. Chem. Soc., 1964, 86, 962, 3157.



CYCLOSPORINE

Cyclosporine, a cyclic undecapeptide produced by Tolypocladium inflatum Gams, has a selective immunosuppressive action affecting mainly the T-lymphocytes, and is used successfully to prevent graft rejection following bone-marrow and organ transplantation. Its structure contains a novel amino acid, (4R)-4[(E)-2-butenyl]-4,N-dimethyl-L-threonine (MeBmt) and several known N-methylated amino acids (1); this unusual new amino acid could play a significant role in determining the pharmacological activity of cyclosporin. The new amino acid was synthesised (2) using (R,R)-(+) tartaric acid as the basic chiral building block. The strategy followed for the synthesis of cyclosporin by the Sandoz scientists (3) was to synthesise the linear peptide with 7-Ala and 8-D-Ala, the only consecutive non-N-methylated amino acids, as the carboxy and N-terminus respectively, as the bond formation between non-N-methylated amino acids would be more facile, and that the intramolecular hydrogen bonds between the amino groups of this linear peptide would operate so as to stabilise the open chain in a folded conformation approximating the cyclic structure of cyclosporin and thus assist in cyclisation. For the synthesis of the linear undecapeptide fragment-condensation technique was employed using mixed pivalic anhydride activation method as adapted for N-methylated amino acids; MeBmt was introduced at the end to reduce to the minimum the number of steps after introducing this acid. Cyclosporin was obtained in a yield of 27.5% with respect of MeBmt.

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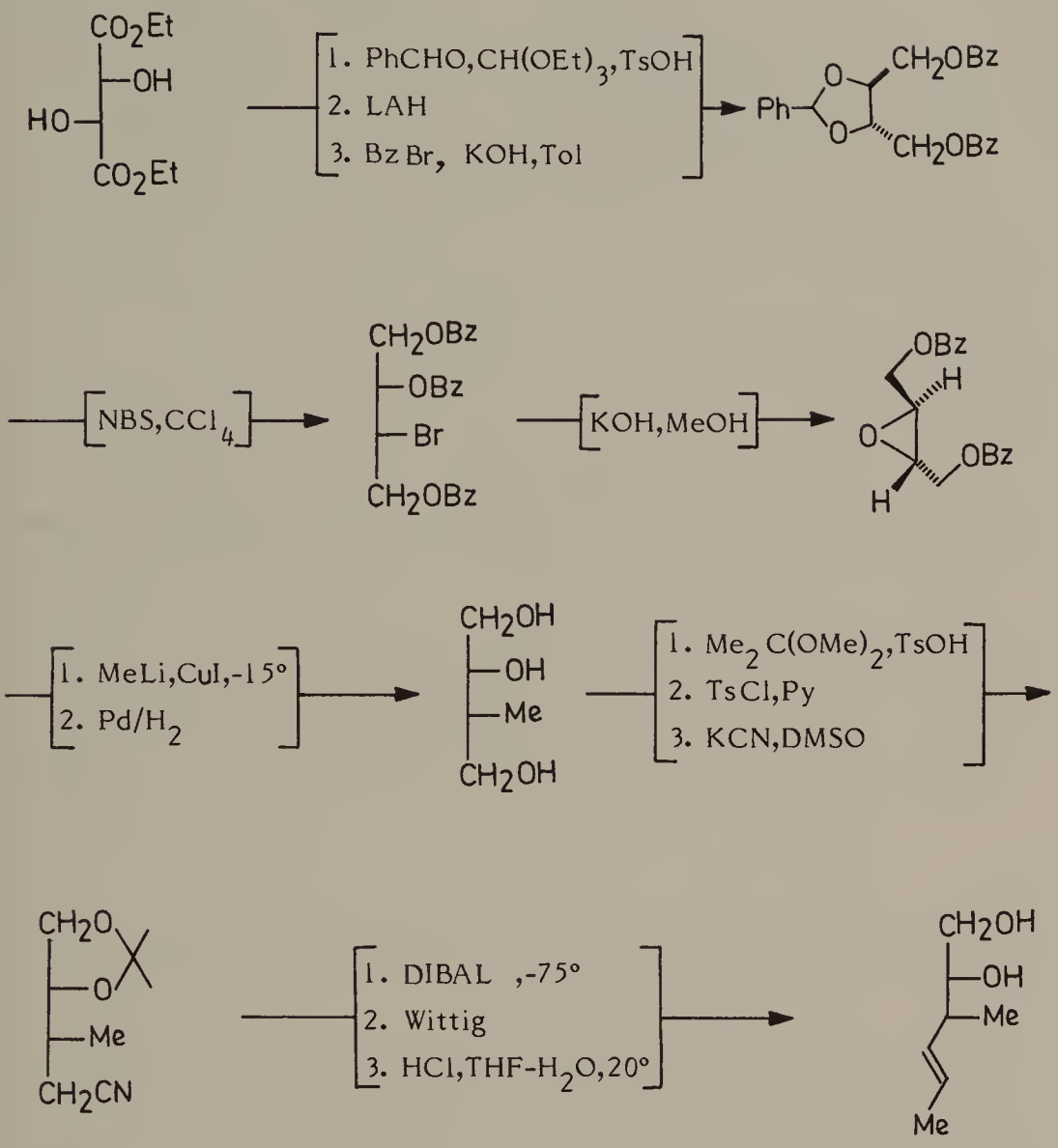
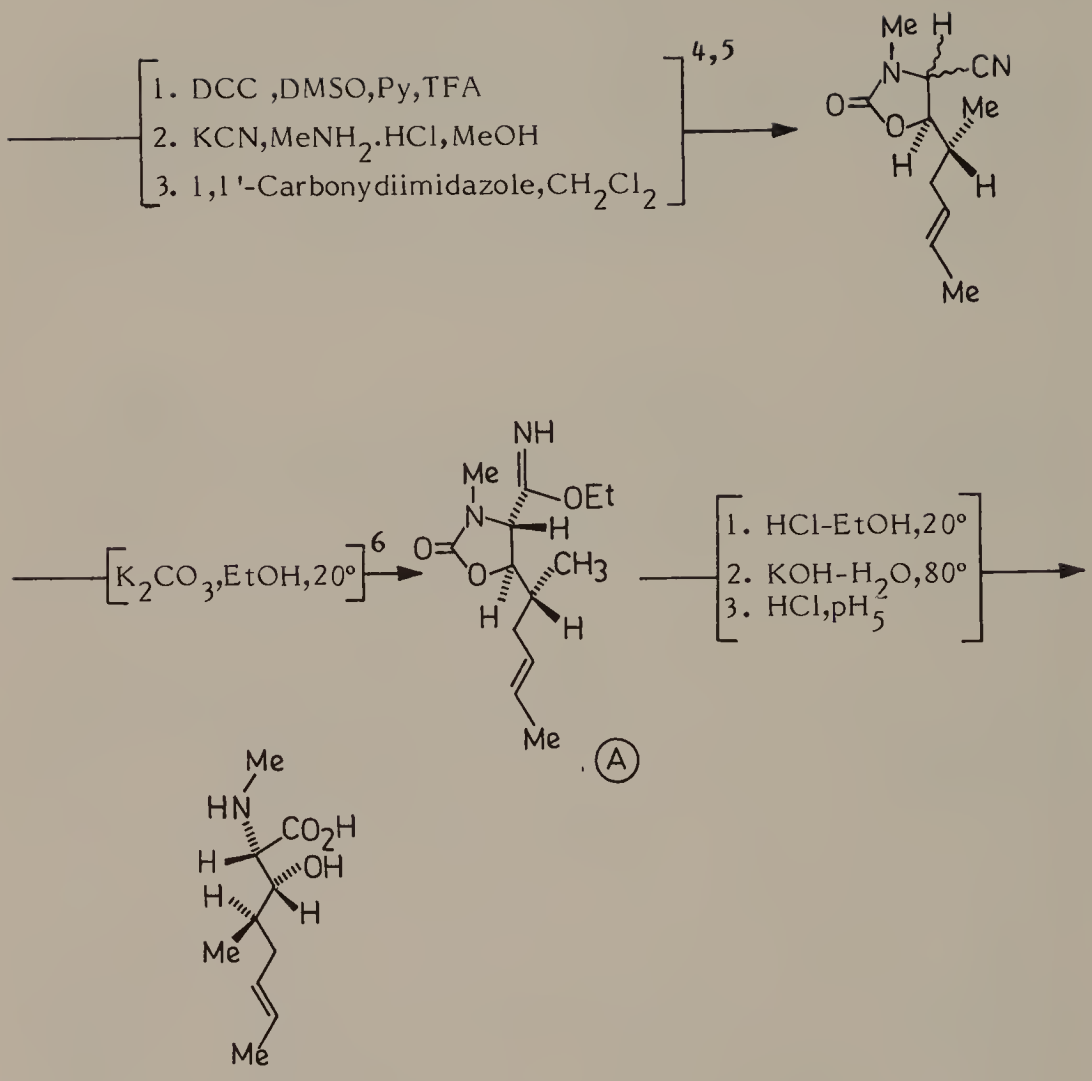
1. Ruegger,A.; Kuhn,M; Lichti,H.; Loosli,H.R.; Huguenin,R.; Quiquerez,C.; von Warburg,A. Helv. Chim. Acta, 1976, 59, 1072; Petcher,T.J.; Webber,H.P.; Ruegger,A. ibid, 1480.

2. Wenger,R.M. Helv. Chim. Acta, 1983, 66, 2308.

3. Wenger,R.M. Ang. Chem. (Int. Edn.),1985, 24, 77.

(4R)-4-[(E)-2-Butenyl]-4,N-Dimethyl-L-Threonine





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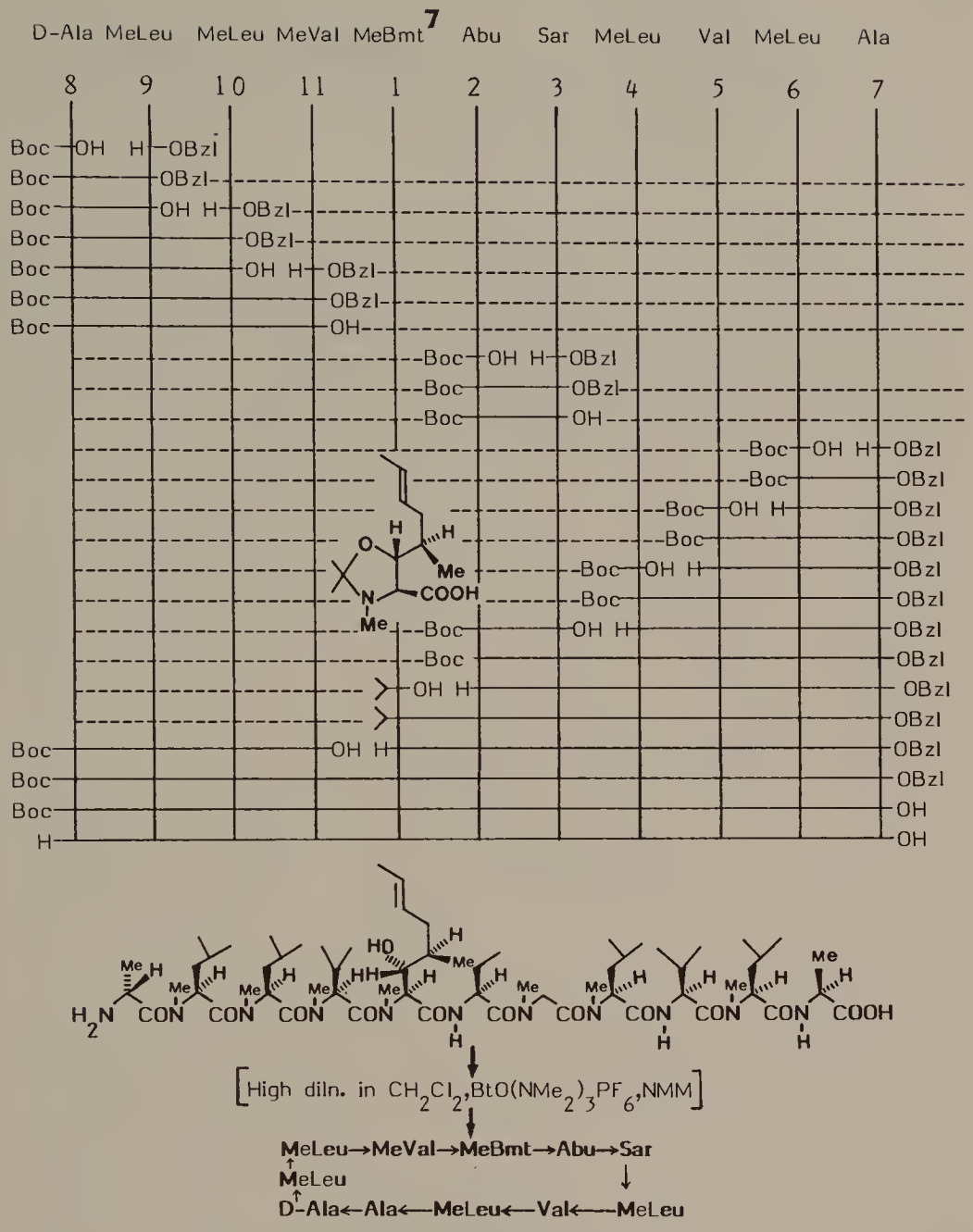
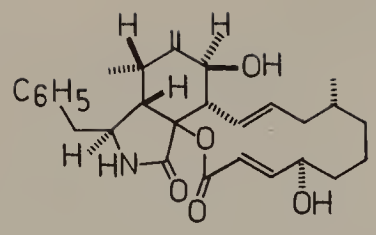
4. Direct oxidation gave low yield, but protection of secondary hydroxyl, followed by oxidation and deprotection gave the aldehyde in much higher yield.

5. The cyanhydrin was obtained as a mixture of diastereomers, and the 2-oxazolidinone as 6:1 mixture of cis: trans isomers.

6. The intermediate iminomethylene derivative reacts stereo-specifically to give the thermodynamically more stable trans-imidate (A), which on hydrolysis furnished the enantiomerically pure N-methylamino acid with the O- and N-functional groups in the desired threo- configuration.

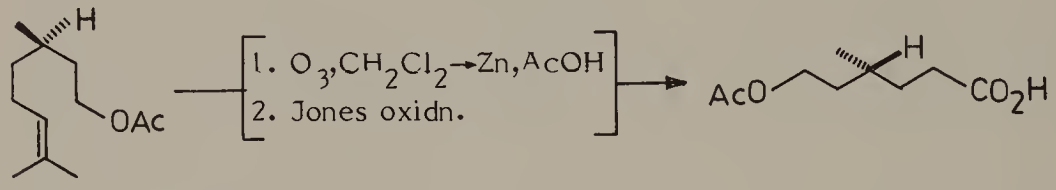


7. During incorporation of MeBmt the hydroxy and $NHCH_3$ were protected as isopropylidene derivative to avoid epimerisation and the peptide bond formed using DCC and N-hydroxybenzotriazole. The final amide bond between the tetra and hepta-peptides was made using $BtOP(NMe_2)_3^+ PF_6^-$, NMM (8).

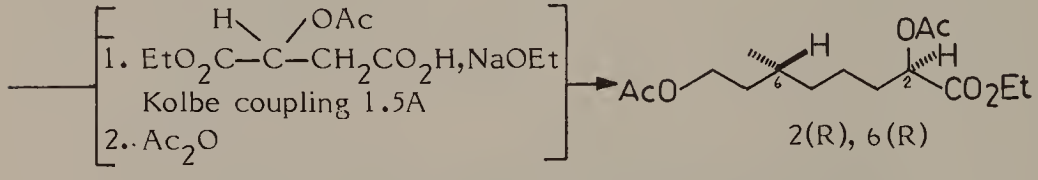


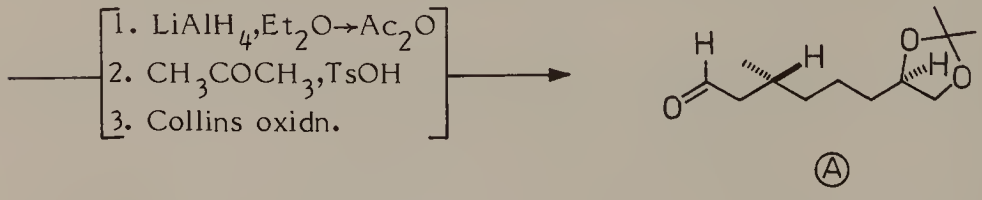
CYTOCHALASINE B

Cytochalasine B is a member of a class of fungal cytostatic substances endowed with very unusual biological activities, and have served as an important biological tool for studying cell behaviour (1). Its first synthesis by Stork and his associates involved a stereo- and regio-selective (2+4) cycloaddition between the triene (B) and the hydroxypyrrolinone (C) leading to the isoindole ring structure carrying the required side chains. This was followed by adjustment of functionalities and macro-lactonisation at the end (2).



R-(+)-β-Citronellol acetate





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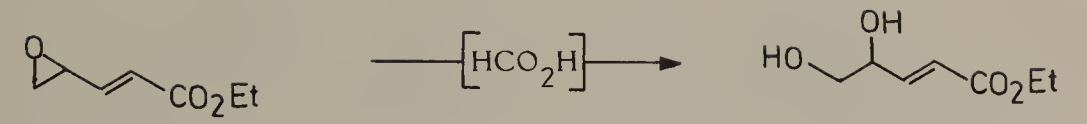
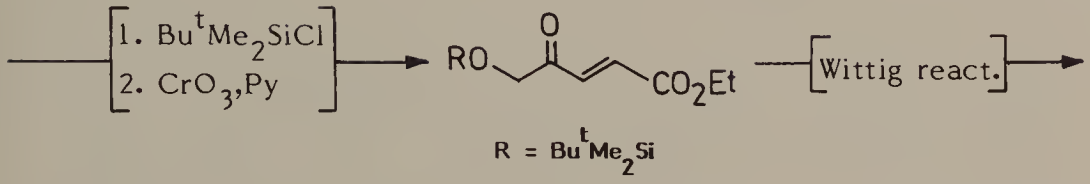
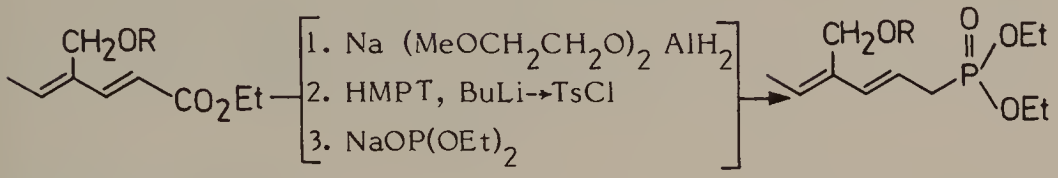
1. For a comprehensive review on Cytochalasins see: Binder, M., Tamm, Ch. Angew. Chem., Int. Ed. Engl., 1973, 12, 370.

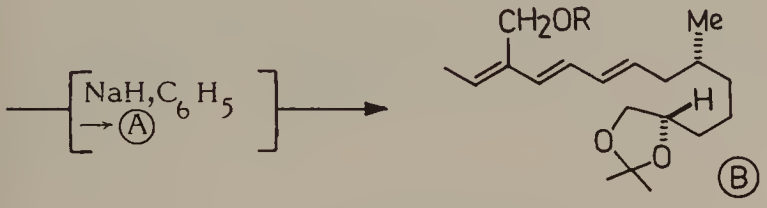
2. Stork,G.; Gilbert, Nakahara, Yoshiaki, Nakahara, Yuko, Greenlee, W.J. J. Am. Chem. Soc., 1978, 100, 7775.

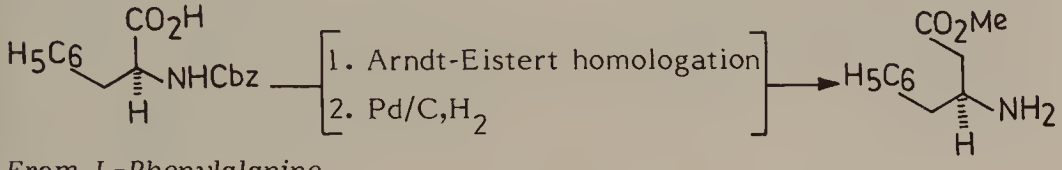




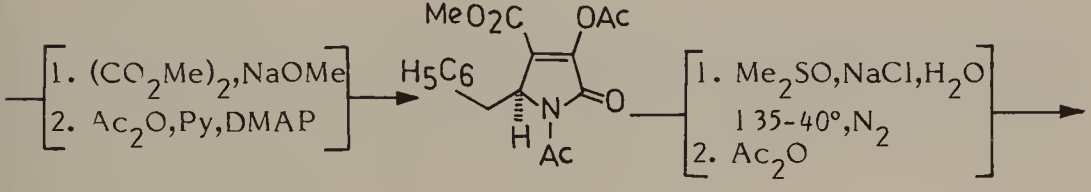


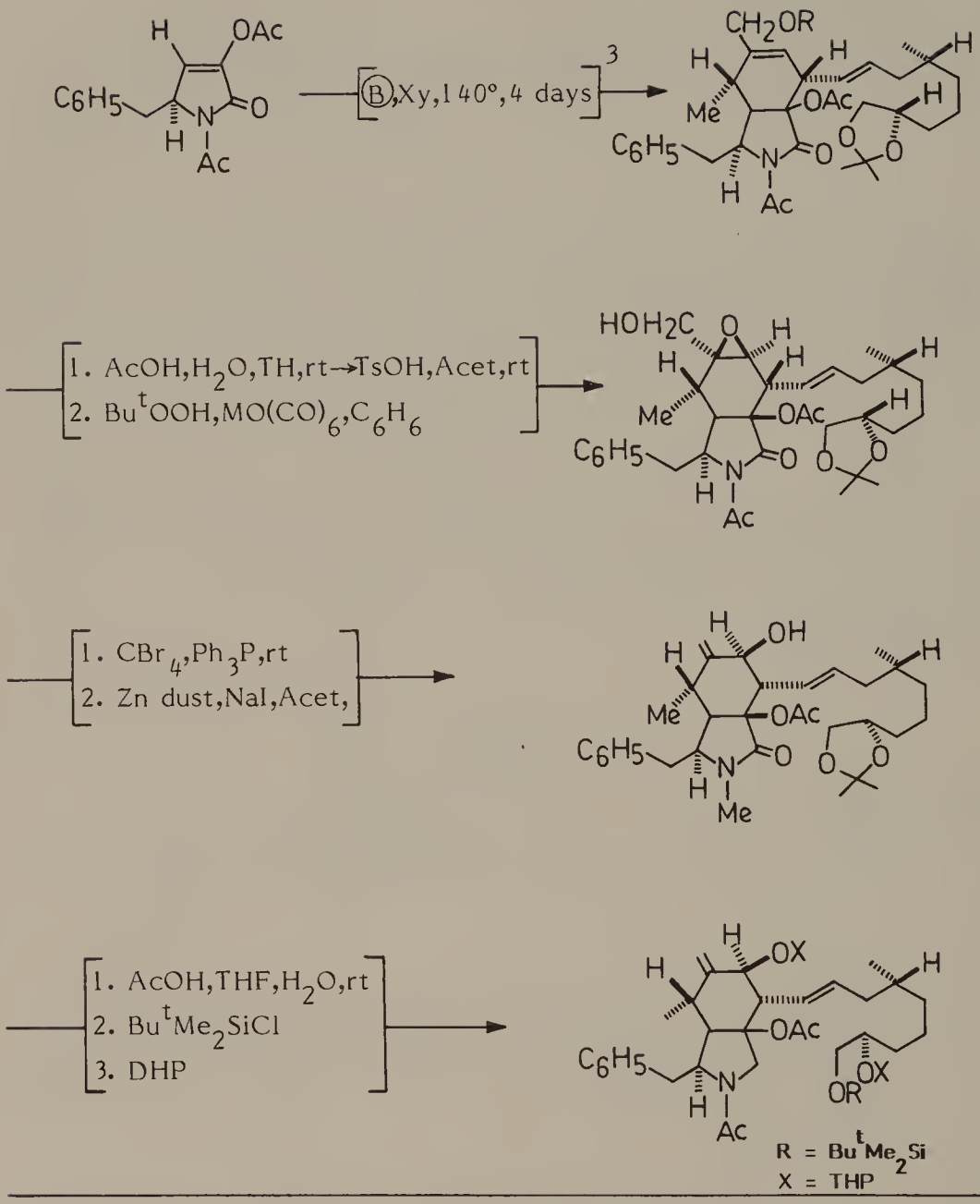
along with trans-cis isomer 5.7:1



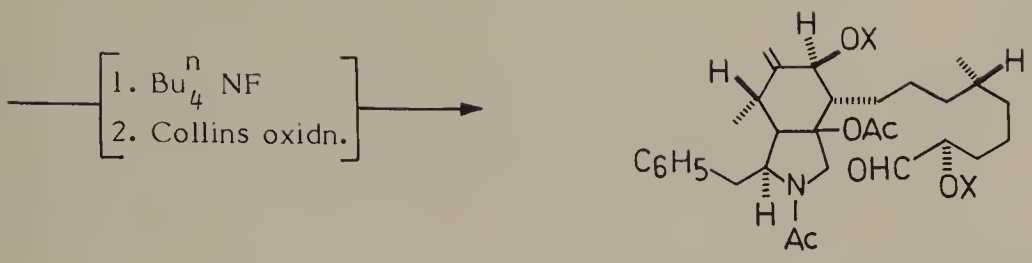


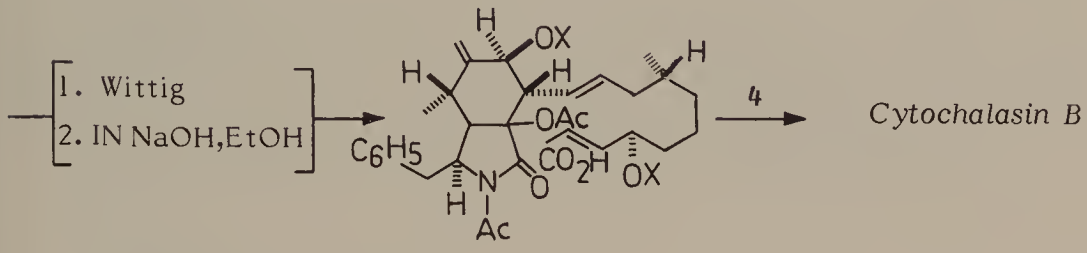
From L-Phenylalanine



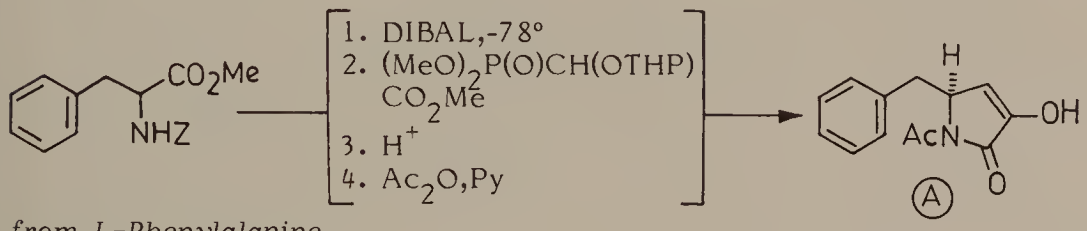


3. This addition was regio-selective and gave a 96:4 ratio of the required to the wrong regioisomer (total yield of the adduct was 40%), along with some quantity of the recovered triene and the pyrrolinone.





Stork & Nakamura in a refinement of the above synthesis constructed the macrocyclic and the hexane rings on the pyrrolone by an intramolecular Diels-Alder reaction on the tetraene (B) (5), which avoided the inefficient lactonisation at the end of the earlier synthesis (2).



from L-Phenylalanine

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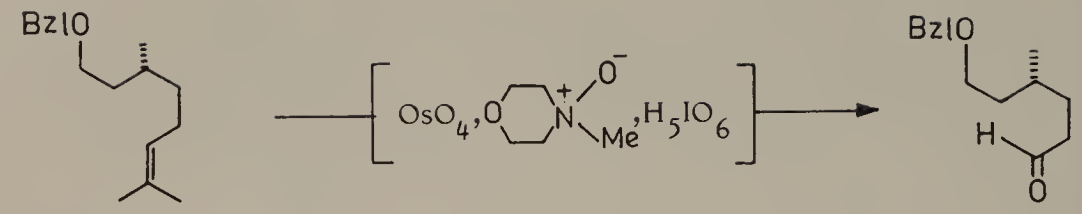
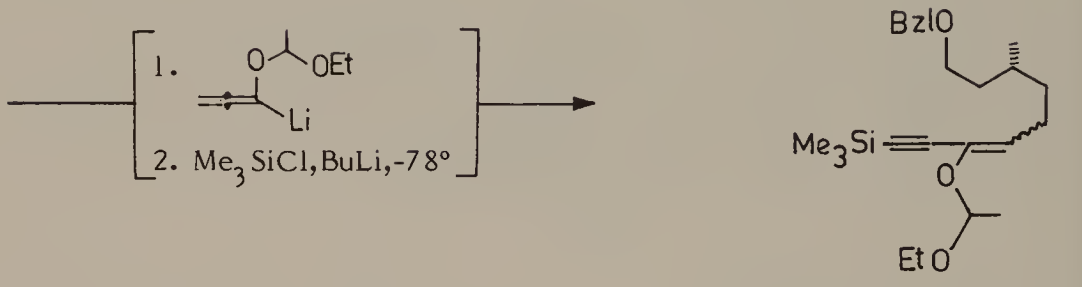
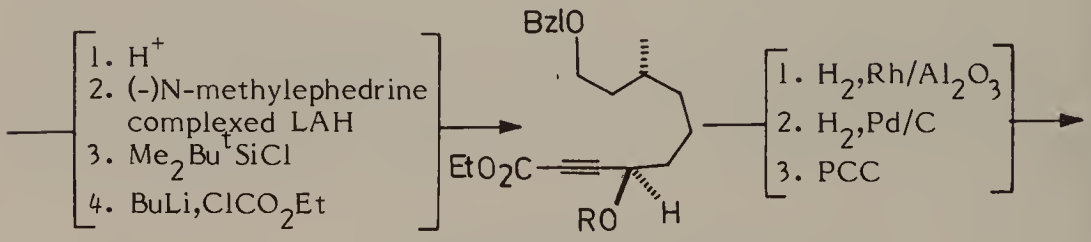
4. The cyclisation of the di-tetrahydropyranyl unsaturated acid to cytochalasin B has been accomplished previously; Massamune,S.; Hayase,Y.; Schilling,W.; Chan,W.K.; Bates,G.S. J. Am. Chem. Soc., 1977, 99, 6756.

5. Stork,G.; Nakamura,E. J. Am. Chem. Soc., 1983, 105, 5510.

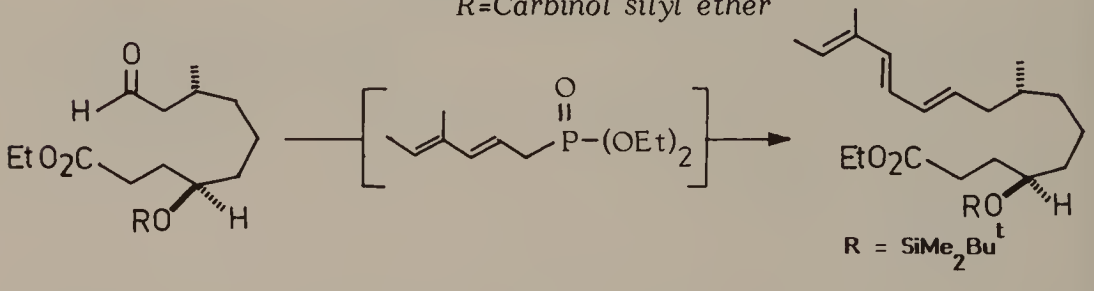


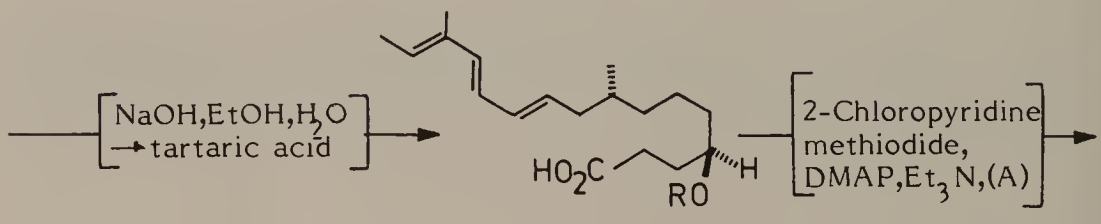
(+)-Citronellol benzyl ether

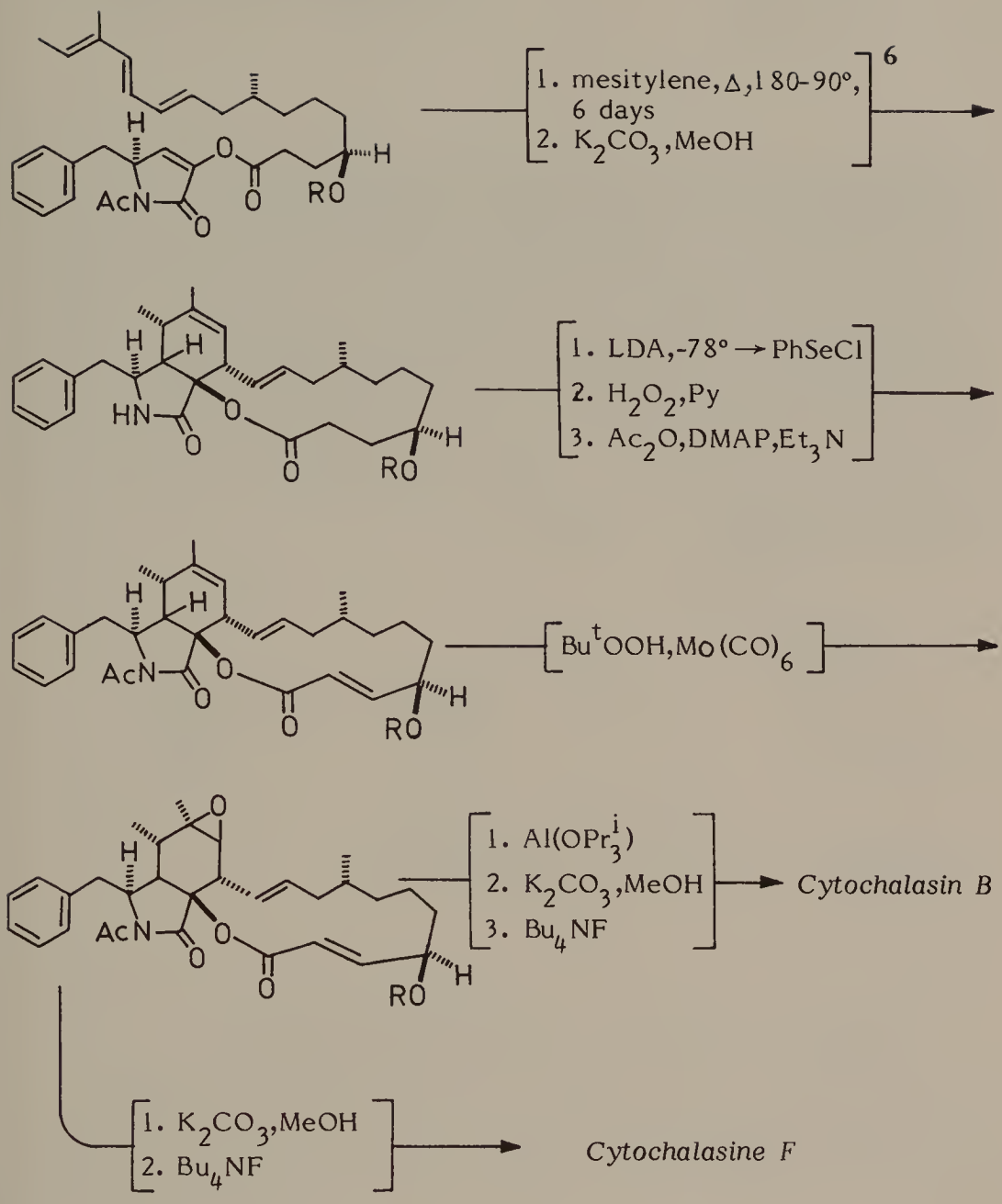




R=Carbinol silyl ether







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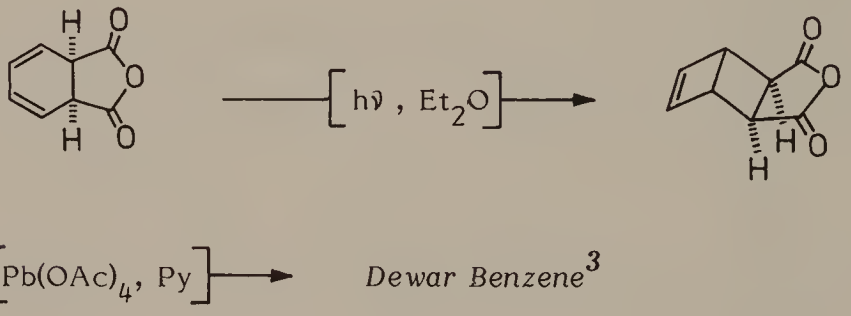
6. The required cycloaddition product was formed along with its diastereomer in a ratio of 4:1 separable on silica after deacetylation.

DEWAR BENZENE

The view is generally held that James Dewar in 1867 had proposed a para bond structure for benzene as an alternative to the Kekulé structure of 1865. This representation which visualizes a bond connecting 1-4 positions of a planar hexagon should of course be incapable of existence. However, if the para bonded structure is regarded as the classical non-planar bicyclo [2.2.0] hexa-2,5-diene, a modified version of the original 'Dewar benzene', then such a molecule should be capable of rational synthesis. Taking advantage of steric factors, van Tamelen and Pappas(1) were the first to prepare such a bicyclic system. The parent member of this class, 'Dewar benzene' was prepared by the same group(2) using an intramolecular photolytic 2+2 cycloaddition, followed by oxidative decarboxylation. This highly strained hydrocarbon is remarkably stable having a half life of two days at room temperature.

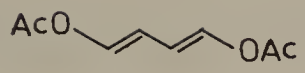


1. van Tamelen, E.E., Pappas, S.P. J. Am. Chem. Soc., 1962, 84, 3789.

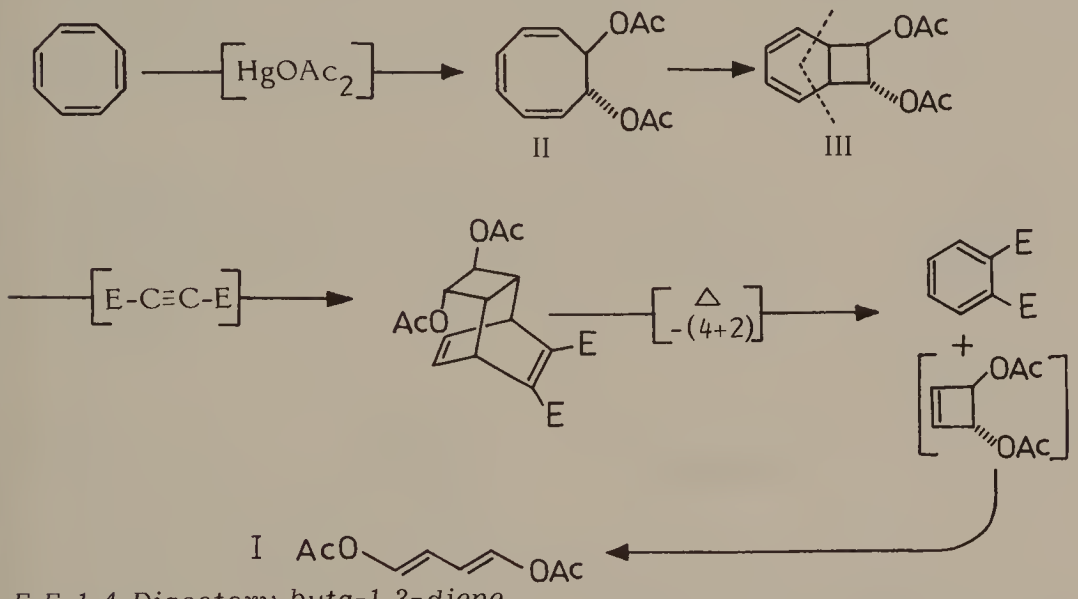
2. van Tamelen, E.E., Pappas, S.P. J. Am. Chem. Soc., 1963, 85, 3297.

3. Review: Schafer, W., Hellemann, H. Angew. Chem. Internat. Ed., 1967, 6, 518.

E,E-1,4-DIACETOXY-1,3-BUTADIENE



The Woodward-Hoffmann rules (1) have created a new dimension in the art of organic synthesis and this facet is best illustrated with the practical synthesis of E,E-1,4-diacetoxy-1,3-butadiene [I] from cyclooctatetraene (2). This transformation involves the removal of the Z,Z-1,3-butadiene unit from the intermediate III arising from a disrotatory cyclization of II. The required removal of a 1,3-butadiene has been carried out by employing a 4+2 addition followed by a 4+2 reversal sequence to give a trans-diacetoxycyclobutene, which then undergoes the expected conrotatory opening to give [I].



E,E-1,4-Diacetoxy buta-1,3-diene

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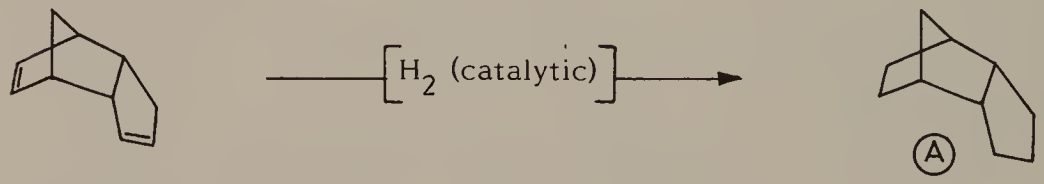
1. Woodward, R.B., Hoffmann, R. "The Conservation of Orbital Symmetry", Academic Press Inc., New York, 1970.

2. Carlson, R.M., Hill, R.Y., Org. Syn., 1970, 50, 24.

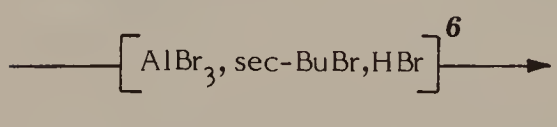
"DIAMOND" STRUCTURES

Covalent linking of carbon atoms in space and in a tetrahedral fashion gives rise to diamond. Adamantane has a "diamond" type structure in the sense that in principle its polymerization involving replacement of the C-H bonds with C-C bonds would lead to diamond (1). Adamantane occurs in coal-tar and thus gave rise to the speculation that hydrocarbons when placed under conditions where the possibility of C-H bond-forming and bond-breaking exist, could ultimately lead to a strain free "diamond" type structure. The assumption was proved correct with the transformation of a C_{10} hydrocarbon to adamantane (2). Similar methods have given rise to an "admantalogous series" The series has progressed upto triamantane, where one of the carbons is linked covalently to four neighbouring carbons as in the case of diamond (3-5).

Adamantane



Dicyclopentadiene



Adamantane

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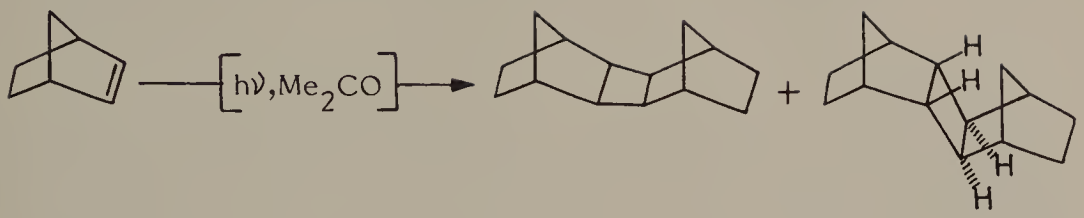
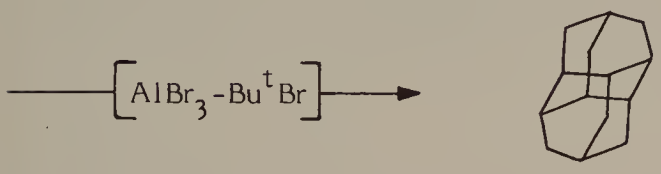
1. For a comprehensive review pertaining to adamantoid hydrocarbons, see: McKervey,M.A. Tetrahedron, 1980, 36, 971.
2. Schleyer,P.von R.; Donaldson,M.M. J. Am. Chem. Soc., 1960, 82, 4645.
3. Cupas,C.; Schleyer,P.von R.; Trecker,D.J. J. Am. Chem. Soc., 1965, 87, 917; Karle, I.L.; Karle,J. J. Am. Chem. Soc., 1965, 87, 918.
4. Williams Jr.von Z.; Schleyer,P.von R.; Gleicher,G.J.; Rodewald,C.B. J. Am. Chem. Soc., 1966, 88, 3862.
5. An attempt to synthesize tetramantane led to "Bastardane"; Schleyer,P.von R.; Osawa, E.; Drew,M.G.B. J. Am. Chem. Soc., 1968, 90, 5034.

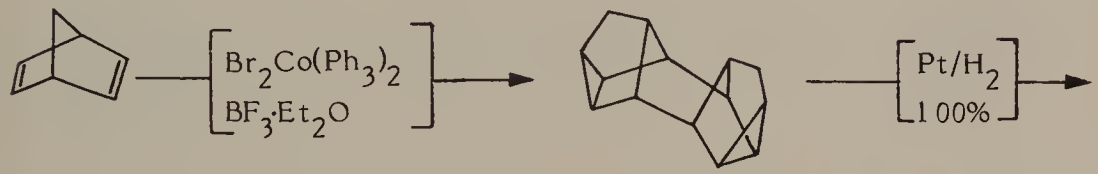
Diamantane (Congressane)

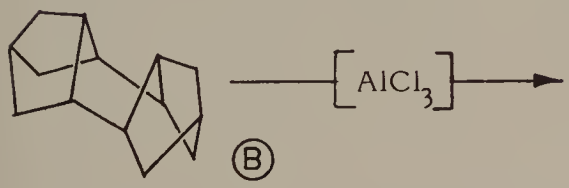




Diamantane

Congressane can now be prepared in quantities from the 4+4 dimer of bicycloheptadiene (7).





Dimantane

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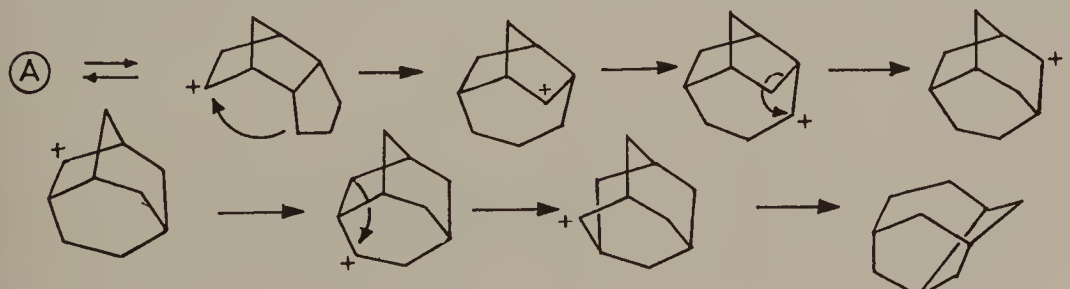
6. This profound rearrangement is pictured as proceeding by a multistage ionic process:

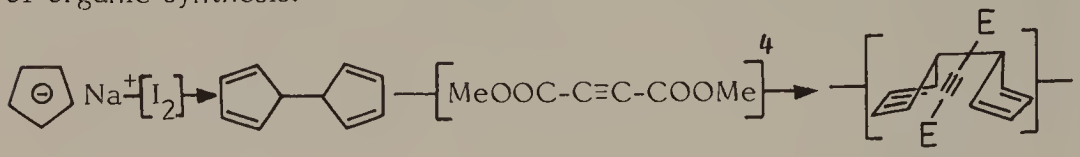


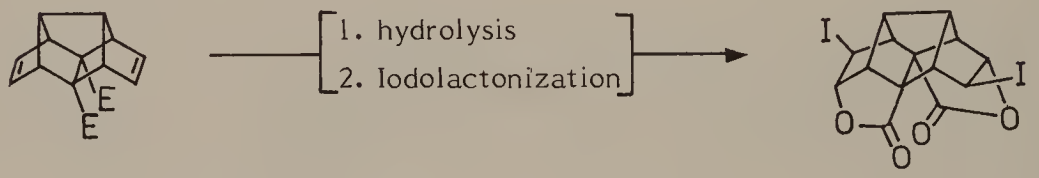
7. McKervey,M.A. J. Chem. Soc. Perkin I, 1972, 2691.

Adamantane

DODECAHEDRANE

Dodecahedrane (1) with I_h symmetry (icosahedral group), characterised by a very high torsional strain and a very small angle strain, is structurally the most complex, symmetric and aesthetically appealing member of the CnHn convex polyhedra (2). The synthesis of dodecahedrane has been intensely pursued for over two decades by several group (2b) and its recent synthesis (3,6) described below marking a culmination of years of sustained effort is a land mark in the art of organic synthesis.





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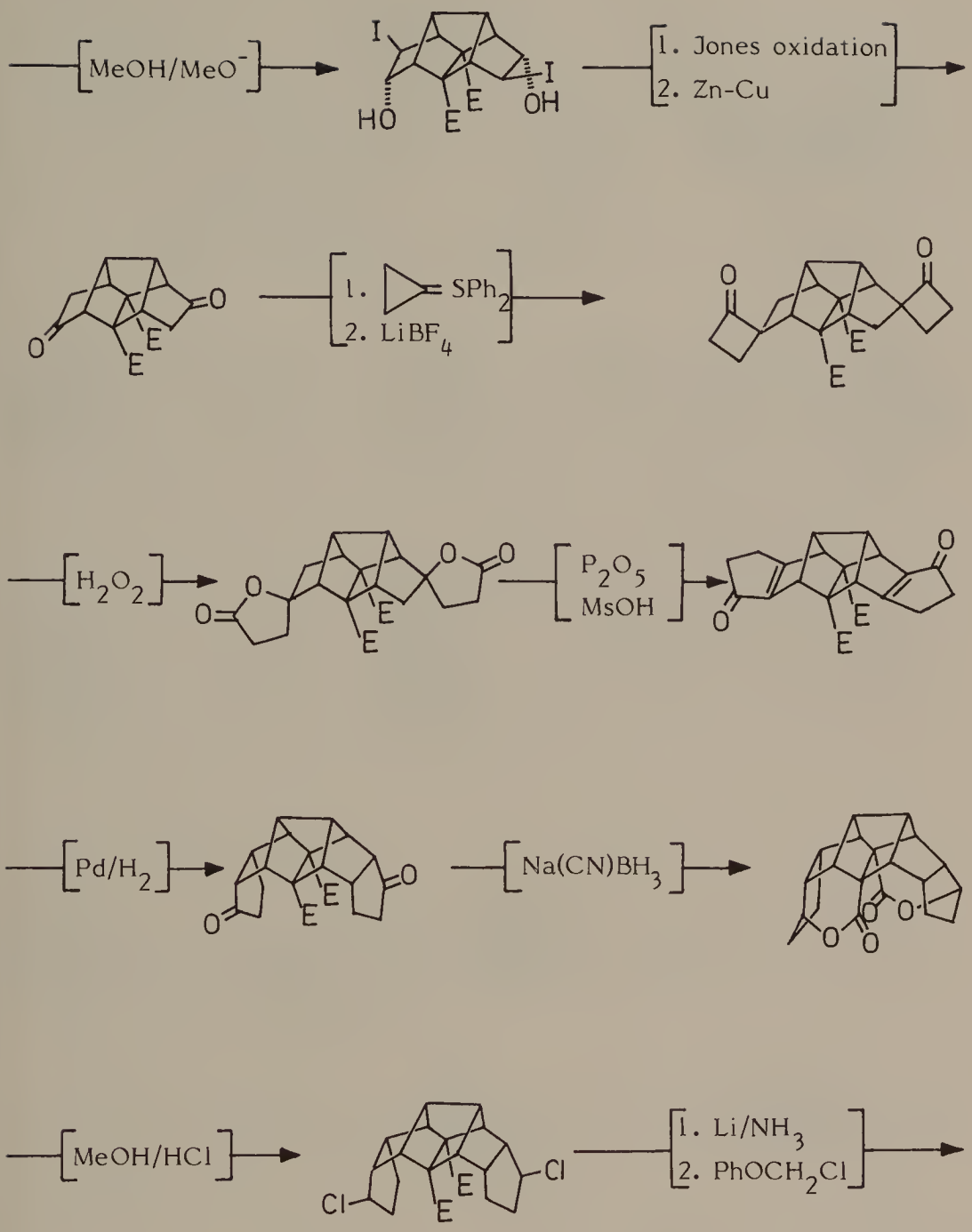
1. Plato with commendable insight limited to five the number of covex polyhedrons whose faces are congruent regular polygons forming equal dihedral angles at each edge. If 'm' number of regular 'n' sided polygons meet at each vertex they must satisfy the equation: $1/m + 1/n = 1/2 + 1/E$ where E represents the total number of edges of the polyhedron. The five fundamental solids that fulfil this requirement, called Platonic solids, are tetrahedron, cube, dodecahedron, octahedron and eicosahedron. Of these the valencies of carbon would permit the construction of only the first three and amongst these dodecahedrane holds a pre-eminent position because of its relatively strain-free array of 12 polyfused cyclopentane rings, which can generate the highest known point group symmetry (I_h), a completely closed cavity lacking solvent uptake capacity and aesthetically pleasing topology.

2. (a) Ermer,O. Angew. Chem. Int. Ed., 1977, 16, 411; (b) Eaton,P.E. Tetrahedron, 1979, 35, 2189.

3. Ternansky,R.J.; Balogh,D.W.; Paquette,L.A. J. Am. Chem. Soc., 1982, 104, 4503.

4. The term "domino Diels-Alder reaction" was coined for this inter/intra molecular addition; Paquette,L.A.; Wyvratt,M.J.; Berk,H.C.; Moerch,R.E. J. Am. Chem. Soc., 1978, 100, 5845. The compound contains many cis, syn fused 5-membered rings.

5. Paquette,L.A.; Wyvratt,M.J.; Schaldner,O.; Schneider,D.F.; Begley,W.J.Blankenship,R.M. J. Am. Chem. Soc., 1976, 98, 6744.



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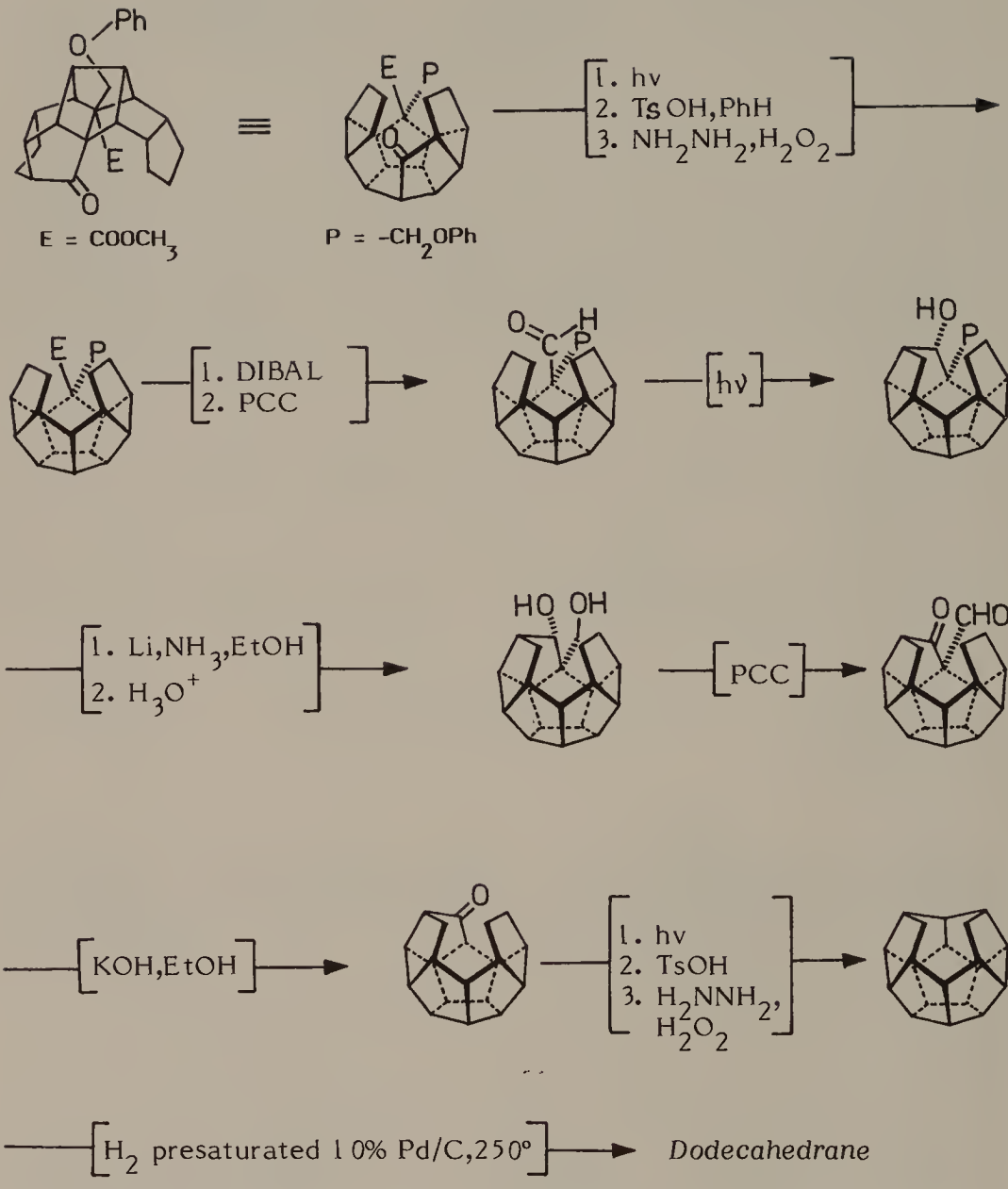
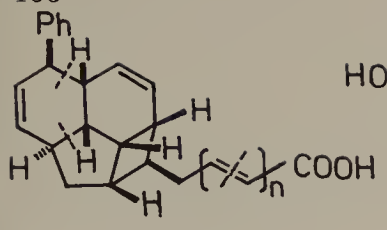
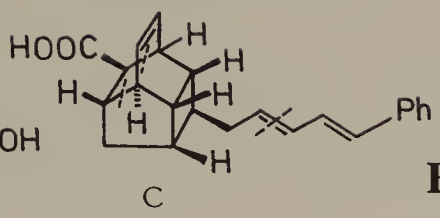
6. (a) Gallucci,J.B.; Doecke,C.W.; Paquette,L.A. J. Am. Chem. Soc., 1986, 108, 1343; (b) Paquette,L.A.; Miyahara,Y.; Doecke,C.W. ibid, 1986, 108, 1716.

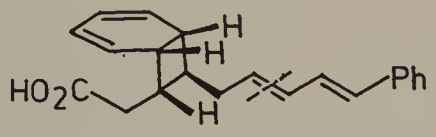

Ph
O
E
O
E = COOCH3
≡
E P
O
P = -CH2OPh
1. hv
2. TsOH,PhH
3. NH2NH2,H2O2
E P
1. DIBAL
2. PCC
O H
C
P
hν
HO
P
1. Li,NH3,EtOH
2. H3O+
HO OH
PCC
O CHO
KOH,EtOH
O
1. hv
2. TsOH
3. H2NNH2,
H2O2
H2 presaturated 10% Pd/C,250°
Dodecahedrane



A: n = 0
B: n = 1



C



D

ENDIANDRIC ACIDS

Endiandric acids A-D, isolated from Endiandra introrsa, despite the presence of eight asymmetric centres, occur in nature in racemic form (1). In view of the presence of all the possible structural types of endiandric acid cascade i.e. A,B,C and D in the same plant and in a racemic form, Black et al. (2) were led to propose that endiandric acids A-D are biosynthesised from achiral precursors by a series of electrocyclisations thermally allowed by Woodward-Hoffmann rules, namely an 8 π e conrotatory electrocyclisation, followed by a 6 π e disrotatory cyclisation, followed by an 4 π S + 2 π S intramolecular cycloaddition reaction. Nicolaou and his associates have reported both a step-wise stereocontrolled total synthesis of endiandric acids as also a biomimetic synthesis consisting of the synthesis of the polyunsaturated carboxylic acids from suitable precursors followed by one step conversion to various members of the endiandric acid cascade (4), which provide support to this hypothesis (5).

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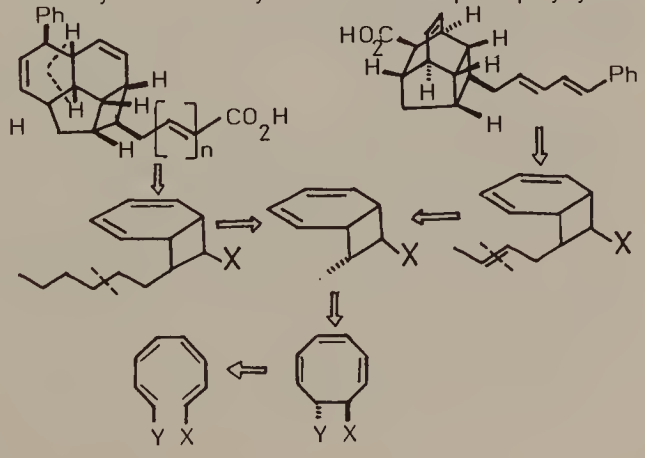
1. Bandaranayake,W.M.; Banfield,J.E.; Black,D.St.C.; Fallon,G.D.; Gatehonse,B.M. J. Chem. Soc., Chem. Commun., 1980, 162.

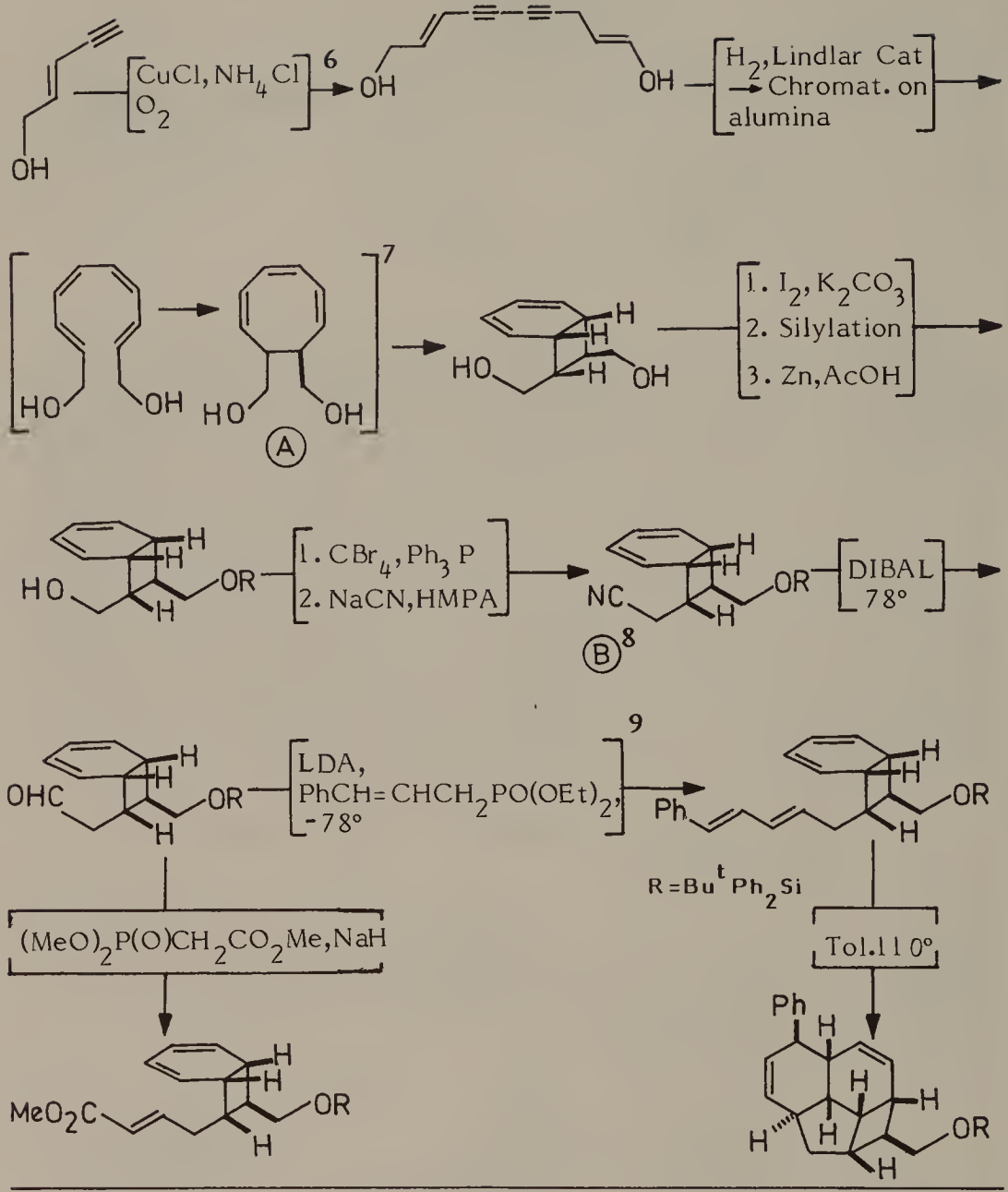
2. Bandaranayake,W.M.; Banfield,J.E.; Black,D.St.C. J. Chem. Soc., Chem. Commun., 1980, 902.

3. Nicolaou,K.C.; Petasis,N.S.; Zipkin,R.E.; Uenishi,J. J. Am. Chem. Soc., 1982, 104, 5555; Nicolaou,K.C.; Petasis,N.S.; Uenishi,J.; Zipkin,R.E. ibid, 1982, 104, 5557.

4. Nicolaou,K.C.; Zipkin,R.E.; Petasis,N.A. J. Am. Chem. Soc., 1982, 104, 5558; Nicolaou,K.C.; Petasis,N.A.; Zipkin,R.E. ibid, 1982, 104, 5560.

5. The syntheses were based on a retro-synthetic analysis of the complex polycyclic frameworks, which provides a clear picture of the endiandric acid cascade and the causal relationship of different structural types in the likely sequence of their formation in the plant.



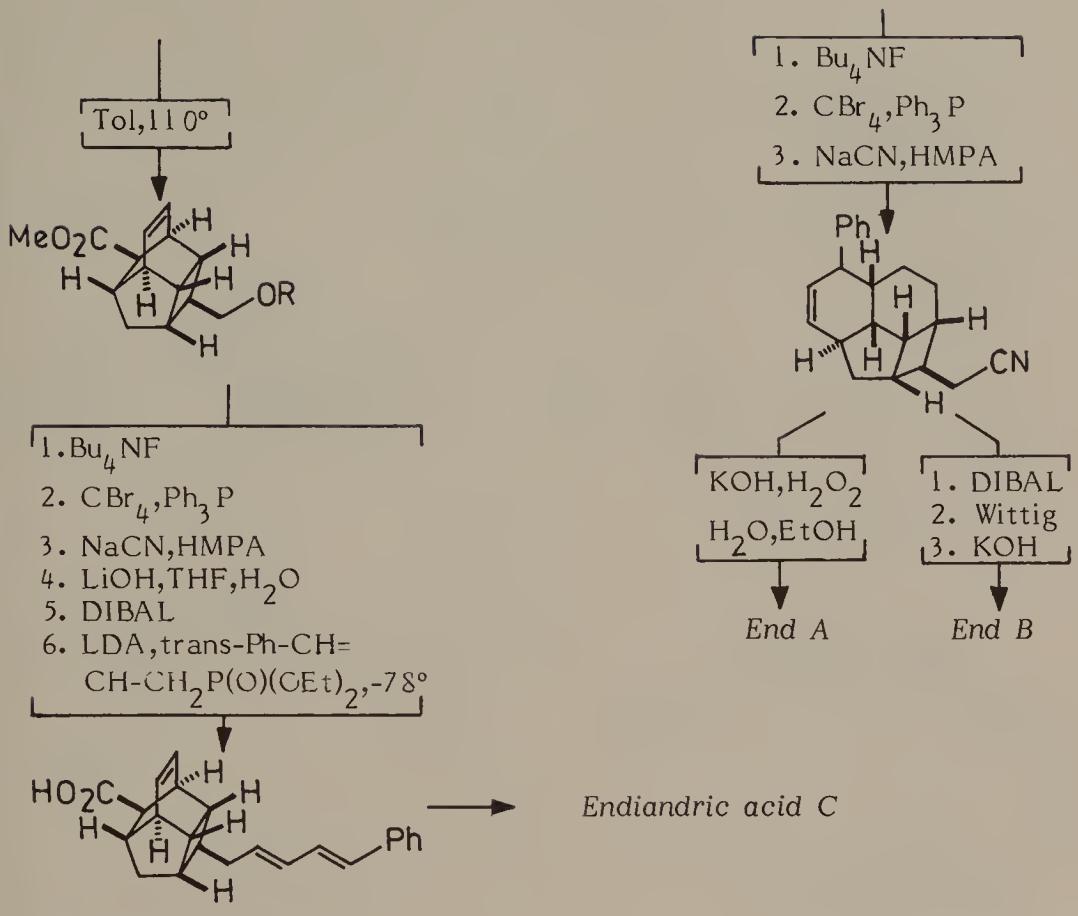


6. Haynes,L.J.; Heilbron,I.; Jones,E.R.H.; Sondheimer,F. J. Chem. Soc., 1947, 1583; Heilbron,I.; Jones,E.R.H.; Sondheimer,F. ibid, 1947, 1586.

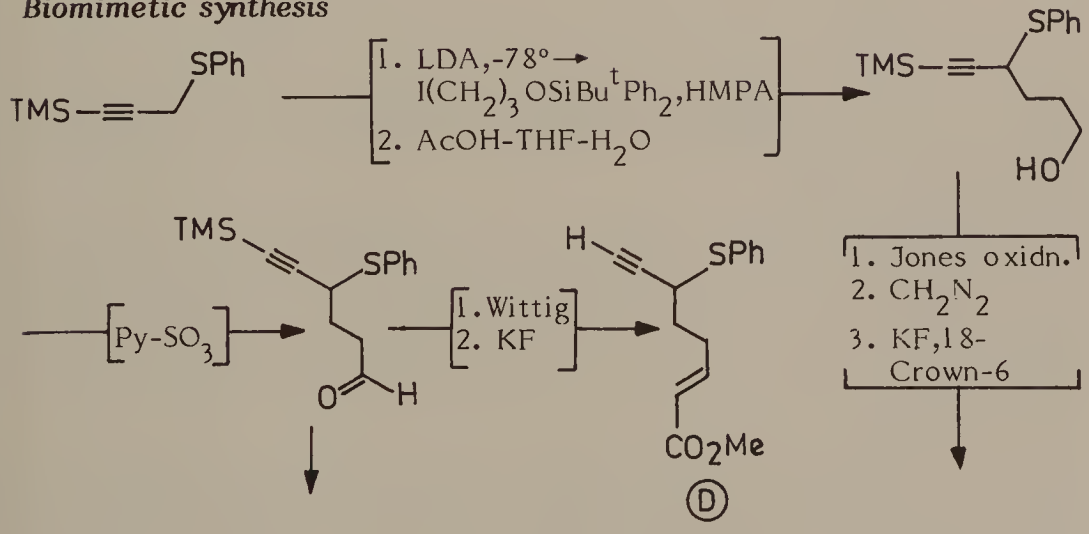
7. The bicyclic-diol (A) was obtained directly after column chromatography and the presumed intermediates were not detected under these conditions.

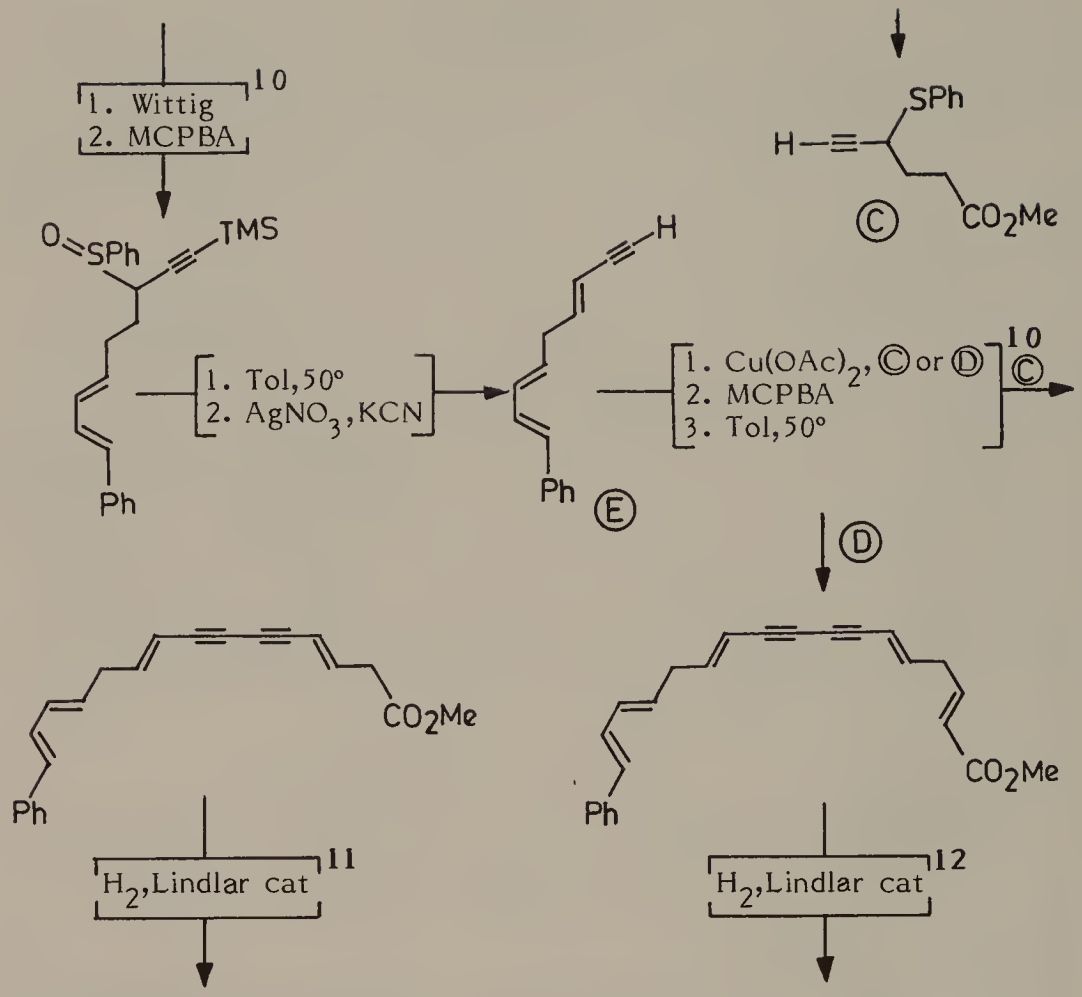
8. The cyanide (B) served as a key intermediate for the synthesis of all the endiandric acids, some of which have not even been isolated from natural sources or isolated after their synthesis.

9. This Witting reagent yielded E:Z ratio of 20:1.



Biomimetic synthesis

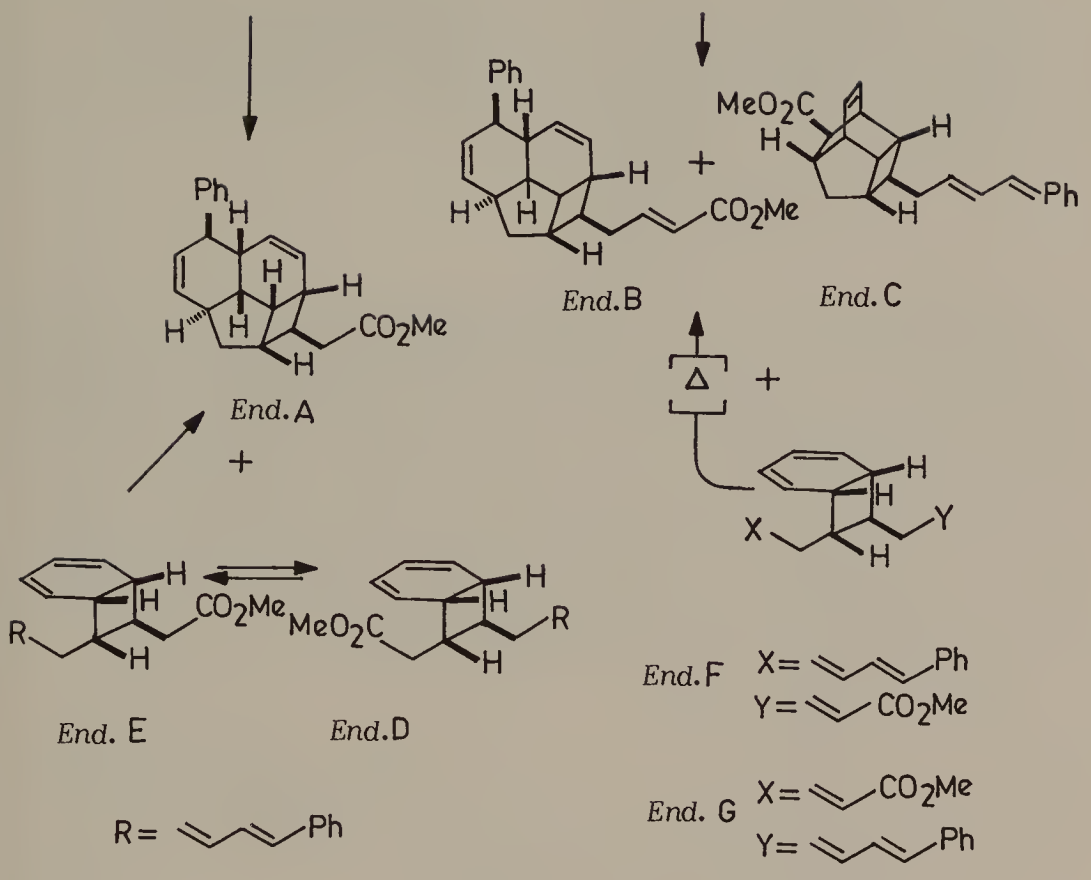


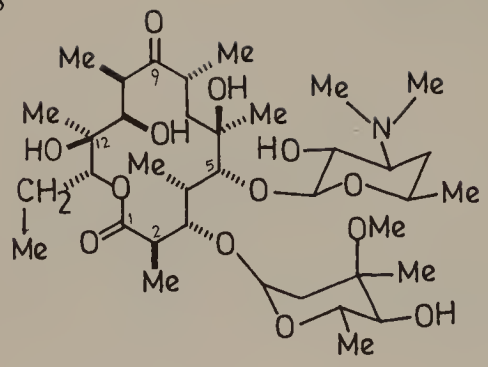


10. A 1:1 mixture of diastereomeric sulfoxides was obtained which were carried to the next step, and the mixture of E and Z olefines separated on a flash column to get the required E isomer.

11. When the hydrogenated product was heated at 100°m tolune only endiandric acid A methyl ester was isolated in Ca 30% yield after chromatography. However, if the product was worked up in the cold after chromatography Ca 12 and 10% yields of D&E endiandric acids methyl esters was obtained when pure D&E endiandric acids were heated at 70°, it was observed that while there was reversible isomerisation equilibrium between D&E, F was slowly cyclised to A and ultimately only endiandric acid A methyl ester was obtained.

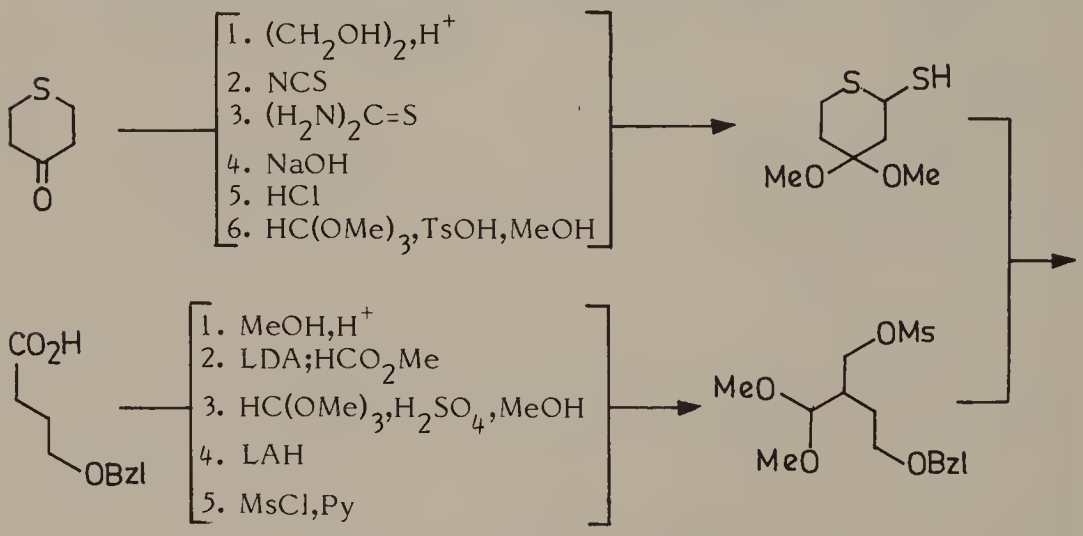
12. After hydrogenation & thermolysis only endiandric acid B&C methyl esters were obtained in a ratio of 4.5:1 (total yield 28%). However, if no heating was done during workup (25°C) a mixture of endiandric F&G methyl esters was obtained (Ca 15 & 12% yields respectively). As in the case of esters D&E, there was a reversible thermal equilibrium between esters F&G, and final conversion to B&C methyl esters.


Ph
H
H
H
H
H
H
CO2Me
End. A
+
End. E
End. D
R=
Ph
MeO2C
H
H
H
H
H
H
CO2Me
End. B
+
End. C
Δ
+
X
Y
End. F
X=
Y=
Ph
CO2Me
End. G
X=
Y=
CO2Me
Ph



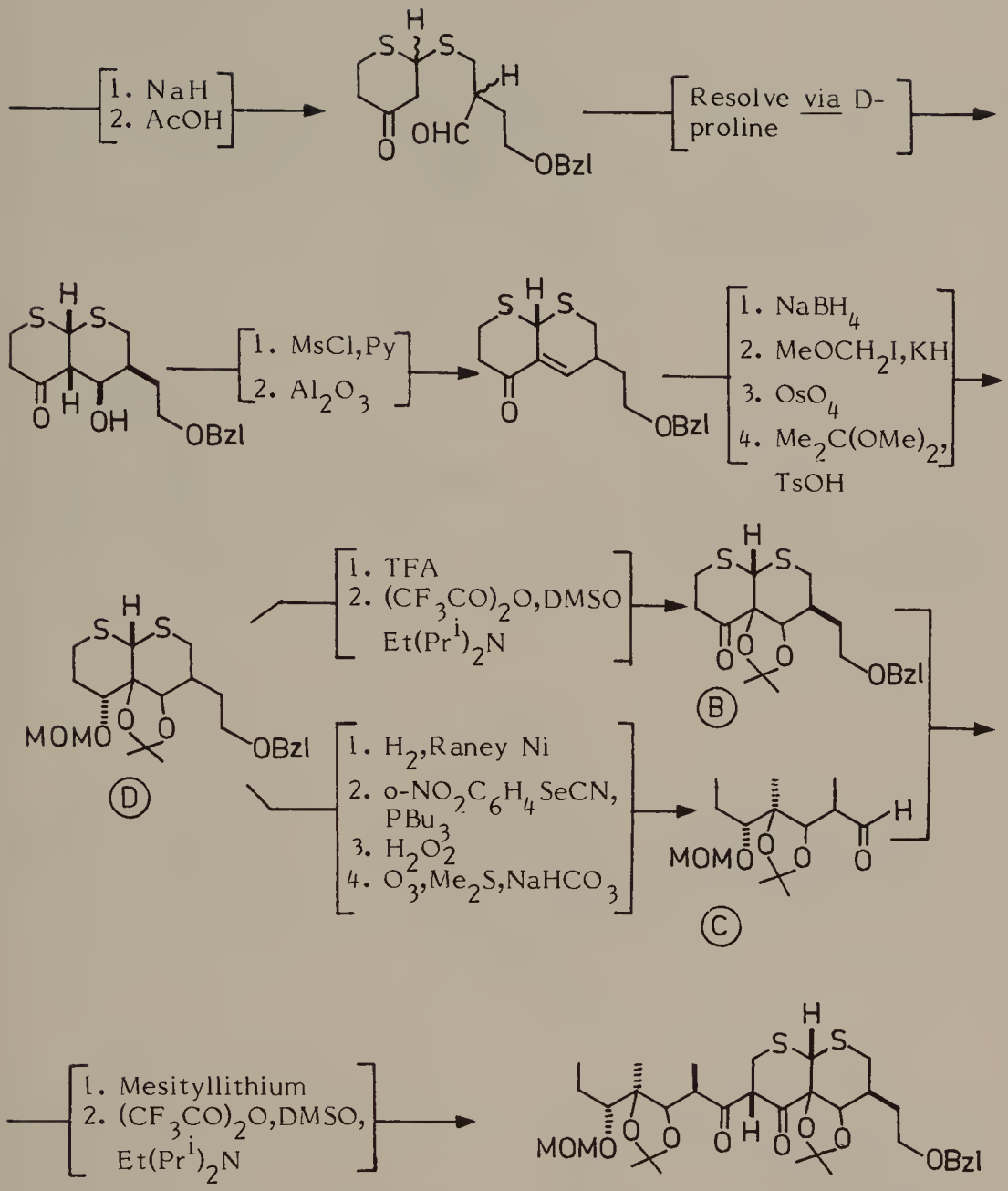
ERYTHROMYCIN

The "hopelessly complex" erythromycin molecule with "its plethora of asymmetric centers" was originally identified as a formidable synthetic challenge by Woodward in 1956 (1). Its synthesis was finally completed and published posthumously in 1981 (2), becoming Woodward's final contribution to the art of organic synthesis (3). Synthesis of the key erythronolide Ⓐ derivative proceeds via macrolactonization of the seco acid Ⓐ, which is constructed by aldol coupling of enantiomerically correct fragments Ⓑ (C3-C8) and Ⓒ (C9-C13), with subsequent introduction of the C1-C2 fragment using a thiopropionate derivative. The two fragments Ⓑ and Ⓒ, which share a hidden symmetry, are crafted from a common intermediate Ⓓ.

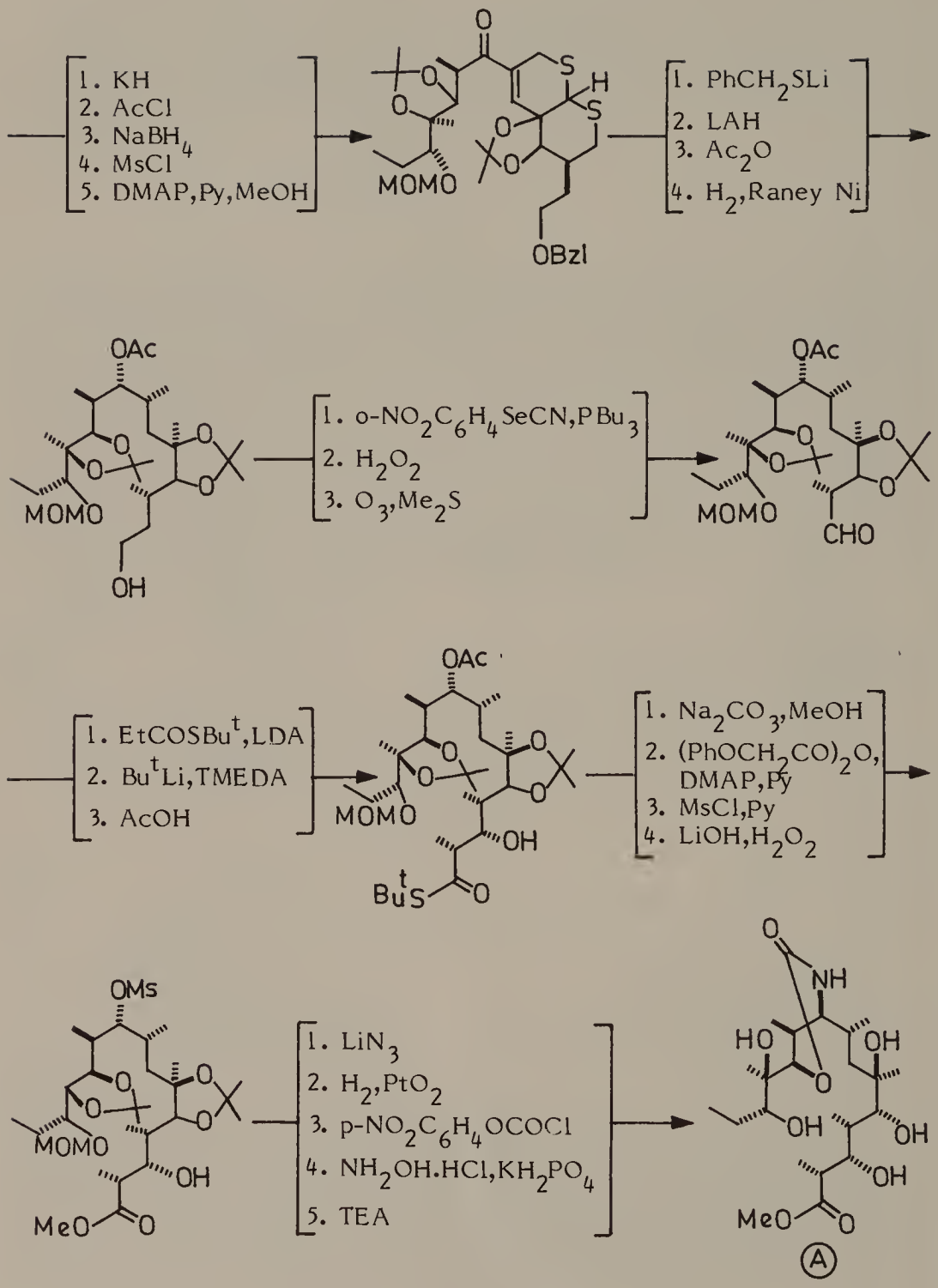


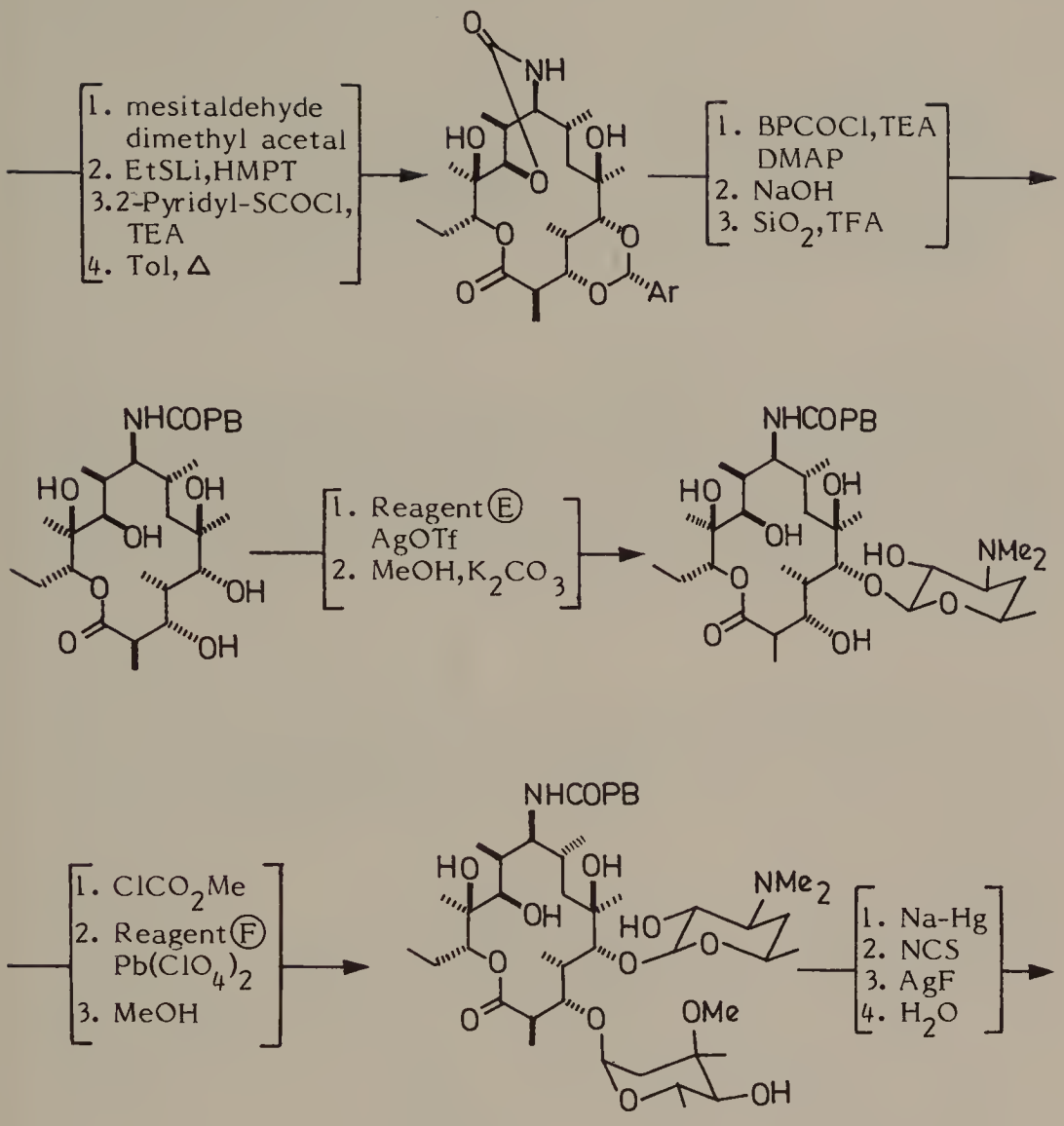
1. Woodward,R.B.; in "Perspective in Organic Chemistry, ed., A. Todd, 155, Wiley (Interscience), New York, 1956.

2. Woodward,R.B.; Logusch,E.; Nambiar,K.P.; Sakan,K.; Ward,D.E.; Au-Yeung,B.W.; Balaram,P. Browne,L.J.; Card,P.J.; Chen,C.H.; Chenevert,R.B.; Fliri,A.; Frobel,K.; Gais,H.J.; Garratt,D.G.; Hayakawa,K.; Heggie,W.; Hesson,D.P.; Hoppe,D.; Hoppe,I.; Hyatt,J.A.; Ikeda,D.; Jacobi,P.A.; Kim,K.S.; Kobuke,Y.; Kojima,K.; Krowicki,K.; Lee,V.J.; Leutert,T.; Malchenko,S.; Martens,J.; Matthews,R.S.; Ong,B.S.; Press,J.B.; Rajan Babu,T.V.; Rousseau,G.; Sauter,H.M.; Suzuki,M.; Tatsuta,K.; Tolbert,L.M.; Truesdale,E.A.; Uchida,I.; Ueda,Y.; Uyehara,T.; Vasella,A.T.; Vladuchick,W.C.; Wade,P.A.; Williams,R.M.; Wong,H.N.C. J.Am.Chem.Soc., 1981, 103, 3210,3213,3215.



3. For reviews on the strategy of macrolide synthesis, including the erythronolides, see: Masamune,S.; Bates,G.S.; Corcoran,J.W. Angew. Chem. Int. Ed. Engl., 1977, 16, 586; Nicolaou,K.C. Tetrahedron, 1977, 33, 683; Back,T.G. Tetrahedron, 1977, 33, 3041; Masamune,S; McCarthy,P.A. Macrolide Antibiotics, ed. Omura,S. p.127, Academic Press, New York, 1984; Paterson,I.; Mansuri,M.M. Tetrahedron, 1985, 41, 3569.

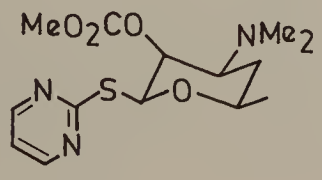

1. KH
2. AcCl
3. $NaBH_4$
4. MsCl
5. DMAP,Py,MeOH
MOMO
OBzl
1. $PhCH_2SLi$
2. LAH
3. Ac_2O
4. H_2,Raney Ni
OAc
MOMO
OH
1. o-$NO_2C_6H_4SeCN$,PBu_3
2. H_2O_2
3. O_3,Me_2S
CHO
1. $EtCOSBu^t$,LDA
2. Bu^tLi,TMEDA
3. AcOH
Bu^tS
1. Na_2CO_3,MeOH
2. $(PhOCH_2CO)_2O$, DMAP,Py
3. MsCl,Py
4. LiOH,H_2O_2
OMs
MeO
1. LiN_3
2. H_2,PtO_2
3. p-$NO_2C_6H_4OCOCl$
4. $NH_2OH.HCl$,KH_2PO_4
5. TEA
NH
HO
Ⓐ



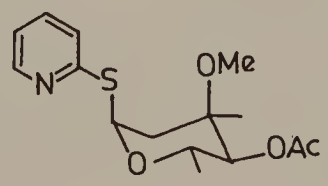
PBCO = p-phenylbenzoyl

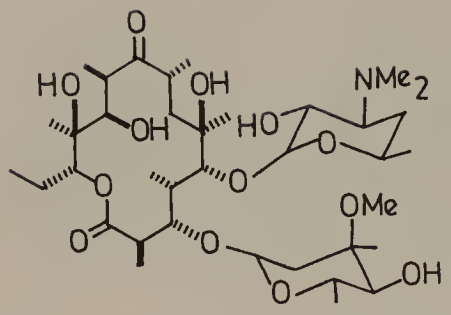
Ar = 2,4,6-trimethylphenyl

E =



F =

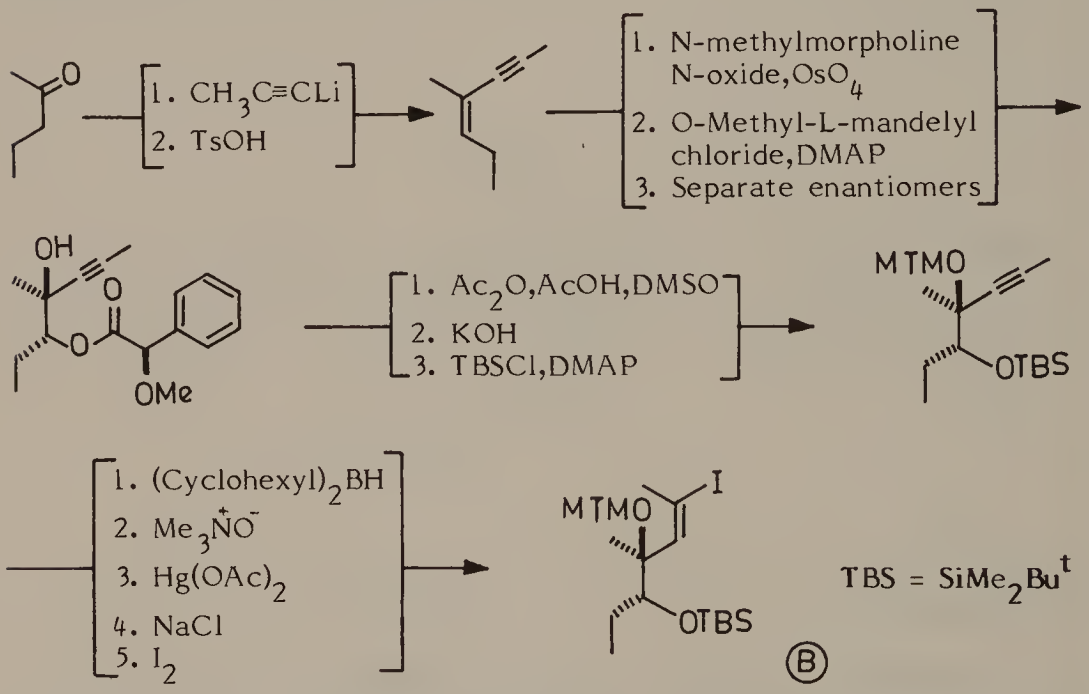




Erythromycin A

Corey synthesis of Erythronolide A

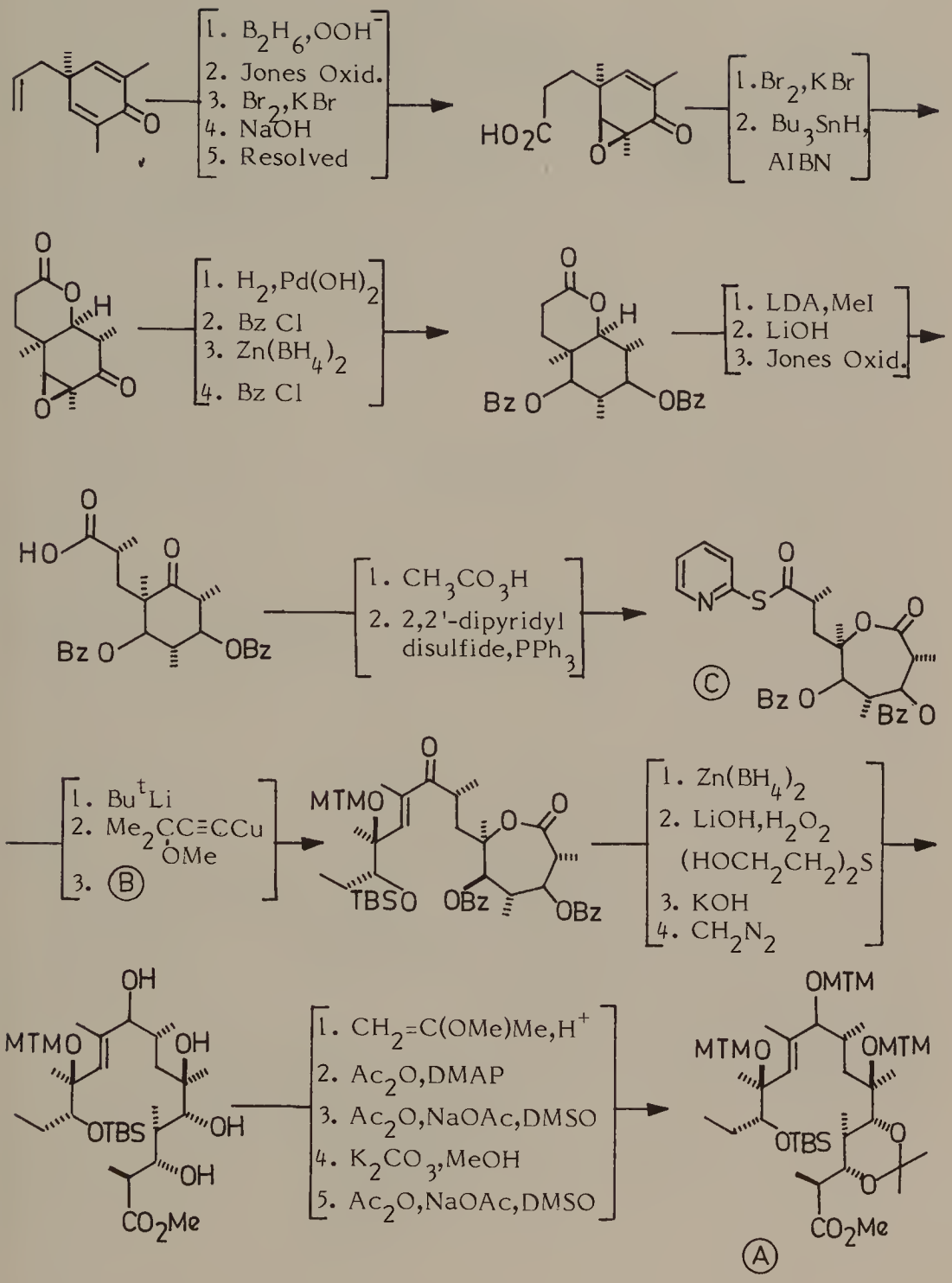
The synthesis of erythronolides Ⓑ and Ⓐ reported by Corey in 1978 (4) and 1979 (5) respectively, follow essentially parallel routes, in which the key seco-acid (A) is constructed by coupling of the two fragments Ⓑ and Ⓒ. Chiral centers at C-10 and C-11 are established following macrocyclization of Ⓐ and the stereochemistry of the C_1-C_9 fragment Ⓒ is generated from a corresponding cyclohexane precursor.

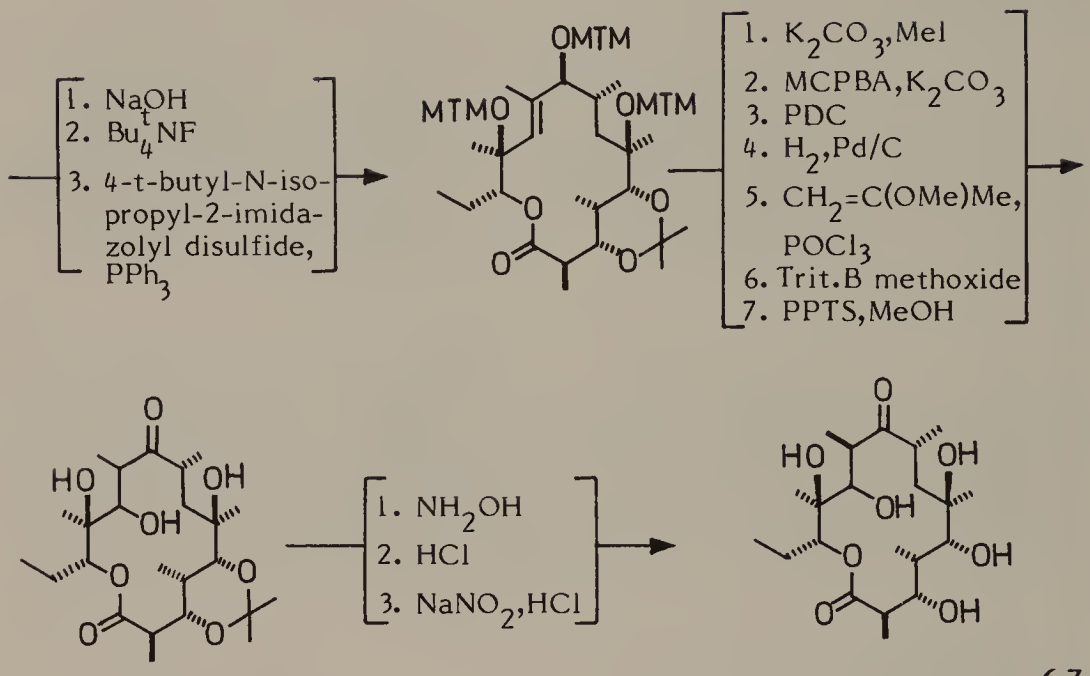


4. Corey,E.J.; Trybulski,E.J.; Melvin,L.S.Jr.; Nicolaou,K.C.; Secrist,J.A.; Lett,R.; Sheldrake,P.W.; Falck,J.R.; Brunelle,D.J.; Haslanger,M.F.; Kim,S.; Yoo,S. J. Am. Chem. Soc., 1978, 100, 4618, 4620.

5. Corey,E.J.; Hopkins,P.B.; Kim,S.; Yoo,Y.; Nambiar,K.P.; Falck,J.R. J. Am. Chem. Soc., 1979, 101, 7131.

Fragment C:


1. B_2H_6,OOH^-
2. Jones Oxid.
3. Br_2,KBr
4. NaOH
5. Resolved
HO_2C
1. Br_2,KBr
2. Bu_3SnH, AIBN
1. H_2,$Pd(OH)_2$
2. Bz Cl
3. $Zn(BH_4)_2$
4. Bz Cl
Bz O
OBz
1. LDA,MeI
2. LiOH
3. Jones Oxid.
HO
1. CH_3CO_3H
2. 2,2'-dipyridyl disulfide,PPh_3
Ⓒ
1. Bu^tLi
2. $Me_2CC{\equiv}CCu$ OMe
3. Ⓑ
MTMO
TBSO
1. $Zn(BH_4)_2$
2. $LiOH,H_2O_2$ $(HOCH_2CH_2)_2S$
3. KOH
4. CH_2N_2
OTBS
CO_2Me
1. $CH_2{=}C(OMe)Me,H^+$
2. Ac_2O,DMAP
3. Ac_2O,NaOAc,DMSO
4. K_2CO_3,MeOH
5. Ac_2O,NaOAc,DMSO
OMTM
Ⓐ



Erythronolide A[6,7]

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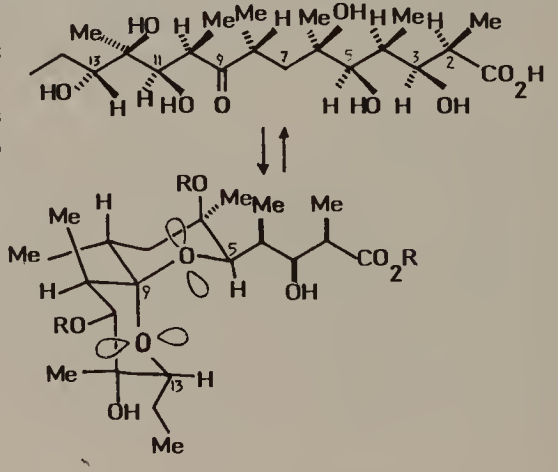
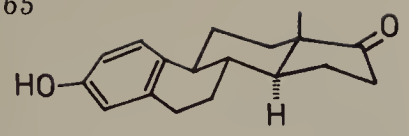
6. Masamune's synthesis of 6-deoxyerythronolide B, the biogenetic precursor of all the erythromycins, portrays the application of stereocontrolled aldol reactions using chiral enolates, for construction of the macrolide seco-ring, see: Masamune,S.; Hirama,M.; Mori,S.; Ali,S.A.; Garvey,D.S. J. Am. Chem. Soc., 1981, 103, 1568; Masamune,S.; Choy,W.; Kerdesky,F.A.J.; Imperiali,B. J. Am. Chem. Soc., 1981, 103, 1566.

7. Viewing the erythronolide A seco-acid as an appropriately substituted 1,9-dihydroxy-ketone, which can be converted to and obtained from a 1,7-dioxaspiro[5.5]undecane, (an internal acetal of the former), Deslongchamps *et al* have developed a strategy for synthesis based on using 1,7-dioxaspiro[5.5]undecane as a template to introduce several chiral centers with a high degree of stereochemical control. Sauve,G.; Schwartz,D.A.; Ruest,L.; Deschlongchamps,P. Canadian J. Chem., 1984, 62, 2929. This also shows a possible structural relationship with avermectins, which contain a 1,7-dioxaspiroundecane residue as a part of their structure.

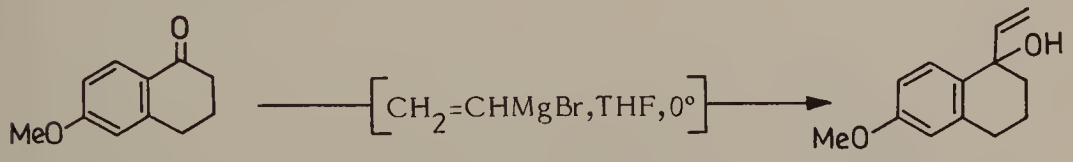




ESTRONE

The synthesis of d-estrone has been of special interest to chemists both because of its own important physiological activity and because it is a crucial intermediate in the production of 19-norsteroids in contraceptive use; it is one of the few steroids produced commercially by total synthesis (1). Its first synthesis was reported in 1948 (2), while the latest has been reported in 1986 with a number of synthesis covering varied approaches, each ingenious in its own right, appearing in between; the main thrusts of these syntheses have been stereoselectivity, brevity of path and to get optically active product, either through the use of optically active intermediates or through asymmetric induction. The syntheses described below are illustrative of the various approaches followed.

Some noteworthy features of the Johnson-Walker synthesis (3), outlined below, were the elements of stereoselectivity achieved at every step. Introduction of ring D, accomplished by a diene addition, selective removal of a carbonyl function after equilibrating the adjacent C/D ring junction to trans, followed by the usual angular methylation-ring contraction sequence applied to the D-norhomosteroids Ⓐ. The unfavourable stereochemistry at the C/D ring junction which generally results during the angular methylation step was reversed in an ingenious manner by the introduction of a 9,11-double bond (4).



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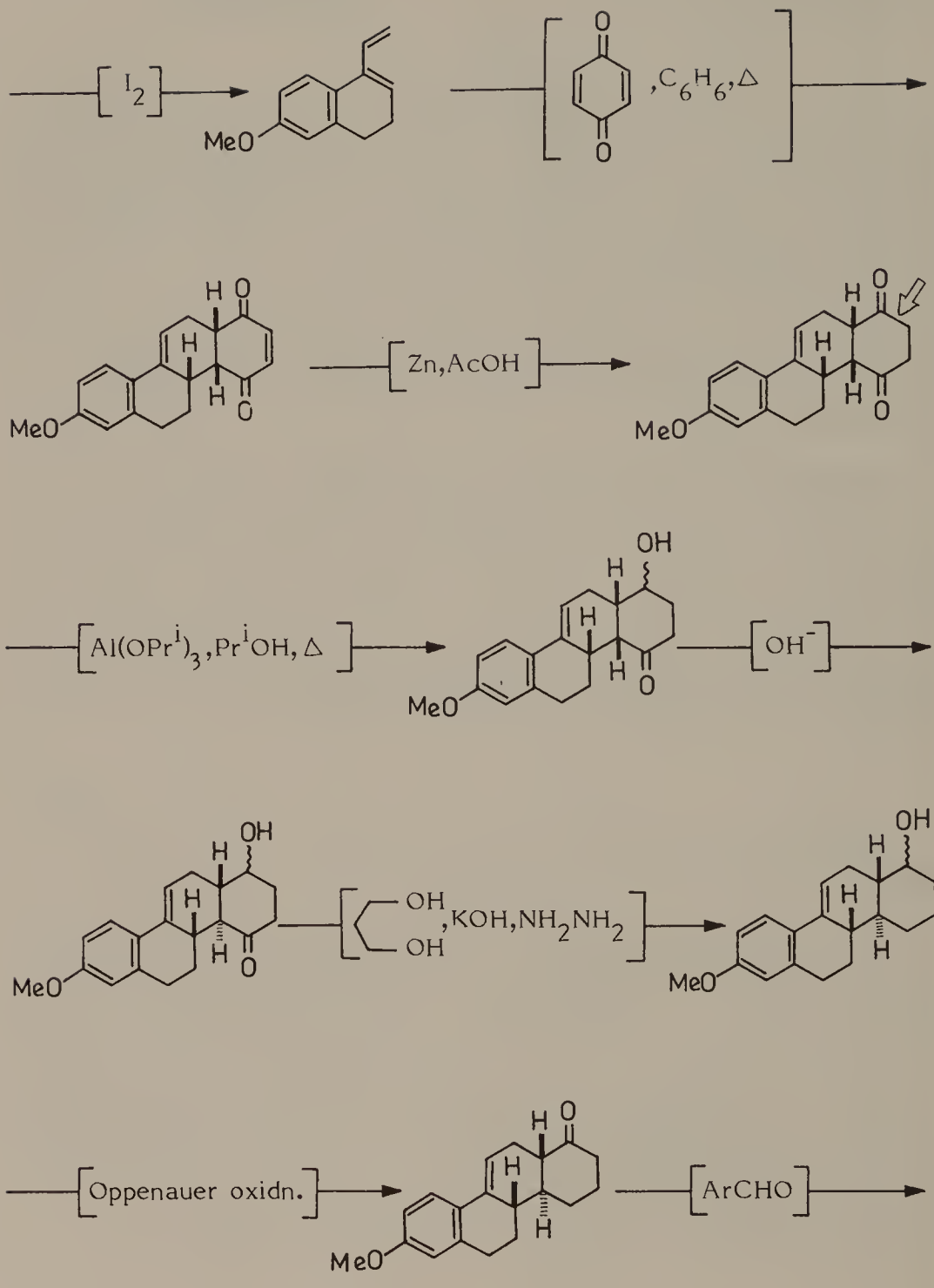
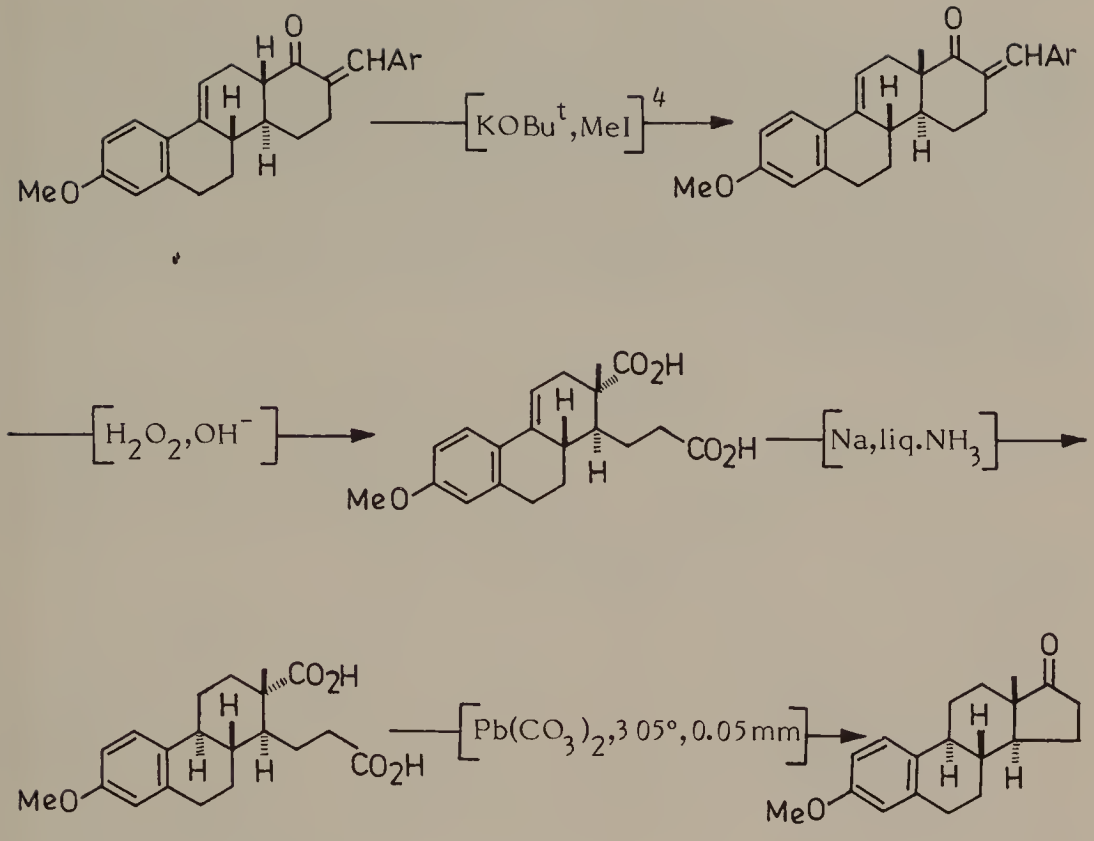
1. For two comprehensive accounts of the progress in steroid synthesis, see: Torgov,I.V. Pure Appl. Chem., 1963, 6, 525; Windholz,T.B.; Windholz,M. Angew. Chem. Internat. Ed., 1964, 3, 353. For a review of the early work on the synthesis of estrone, see: Morand,P.; Lyall,J. Chem. Revs., 1968, 68, 85.

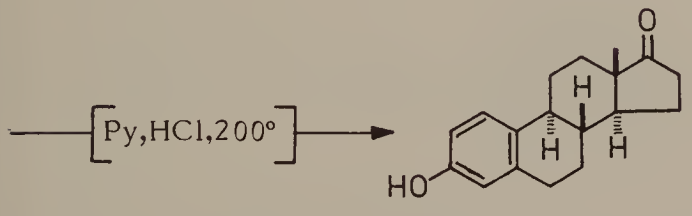
2. Anner,G.; Miescher,K. Helv. Chim. Acta, 1948, 31, 2173; 1949, 32, 1957; 1950, 33, 1379; some of the other early synthesis of estrone include: Johnson,W.S.; Banerjee,D.K.; Schneider,W.P.; Gutsche,C.D.; Shelberg,W.E.; Chinn,L.J. J. Am. Chem. Soc., 1950, 72, 1426; 1951, 73, 4987; Johnson,W.S.; Christiansen,R.G. J. Am. Chem. Soc., 1951, 73, 5511; Johnson,W.S.; Christiansen,R.G.; Ireland,R.E. ibid, 1957, 79, 1995; Banerjee,D.K.; Sivanandaiah,K.M. Tetrahedron Lett., 1960, 20; J. Ind. Chem. Soc., 1961, 38, 652.

3. Cole,J.E.; Johnson,W.S.; Robins,P.A.; Walker,J. Proc. Chem. Soc., 1958, 114; J. Chem. Soc., 1962, 244.


[I2]
MeO
,C6H6,Δ
Zn,AcOH
Al(OPr^i)3,Pr^iOH,Δ
OH
[OH^-]
KOH,NH2NH2
Oppenauer oxidn.
ArCHO



dl-Homomarrianolic acid methyl ether



d-Estrone[5]

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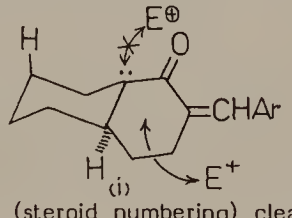
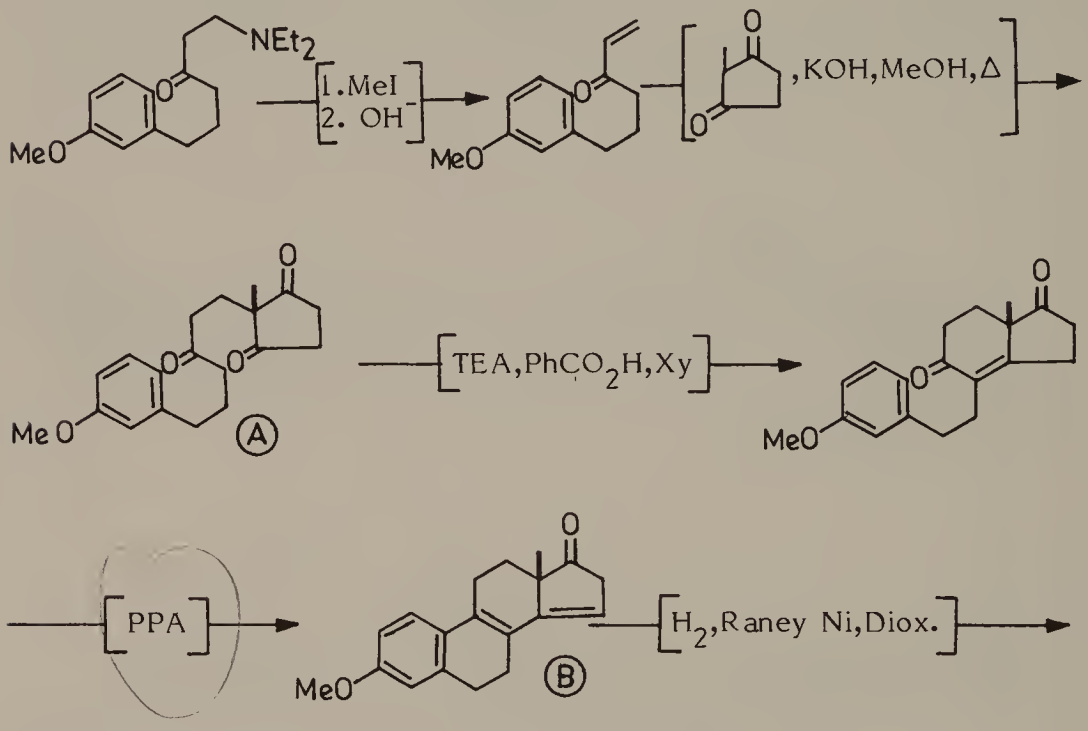
4. Methylation of 1-decalones is directed to the angular position by blocking the reactive 2-position using an arylmethylene group. However, during alkylation, an axial hydrogen at C-7 (decalone numbering) interferes with the trans-approach of an electrophile to the angular position (1,3-interaction) (i), resulting in a preponderance of the less desirable C/D cis-methylated isomer; Johnson,W.S.; Allen,D.S. J. Am. Chem. Soc., 1957, 79, 1261. Introduction of a trigonal C-11 (steroid numbering) clearly results in a removal of the offending hydrogen, permitting a free access to the anion from the β-face.



5. Resolved via 1-menthoxy acetate.

Following the improvements wrought by the versatile steroid synthesis described by Velluz et al. (BC → BCD → ABCD type) (6), a major break-through in the synthesis of estrone was achieved by the use of preformed ring D already carrying the angular methyl group. Two such closely related approaches, both proceeding through seco-estrone intermediates (ACD→ABCD and AB → ABD → ABCD type) were developed independently by Herchel Smith (7,8) and Torgov (9). The highly stereoselective synthesis of estrone by Smith et al., which involves the cyclodehydration of a trione Ⓐ to give bisdehydroestrone Ⓑ, is outlined below.

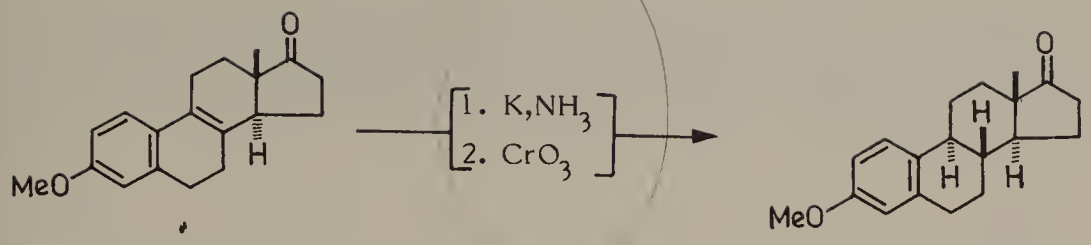


6. Velluz,L.; Nomine,G.; Mathieu,J.; Toromanoff,E.; Bertin,D.; Vignau,M.; Tessier,J. Compt. Rend., 1960, 250, 1510; Velluz,L.; Nomine,G.; Mathieu,J. Angew. Chem., 1960, 72, 725. This approach has already been illustrated by the synthesis of adrenosterone.

7. Hughes,G.A.; Smith,H. Proc. Chem. Soc., 1960, 74; Chem. Ind., 1960, 1022.

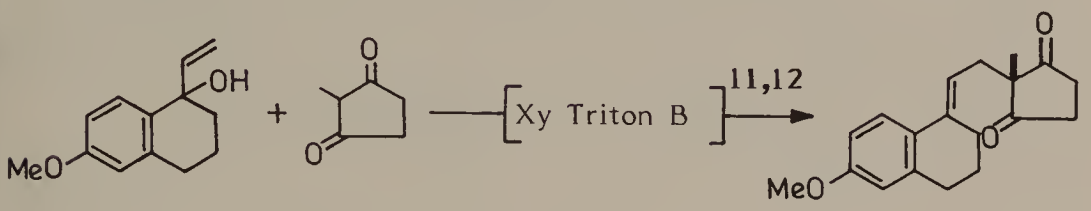
8. Douglas,G.H.; Graves,J.M.H.; Hartley,D.; Hughes,G.A.; McLoughlin,B.J.; Siddall,J.; Smith,H. J. Chem. Soc., 1963, 5072.

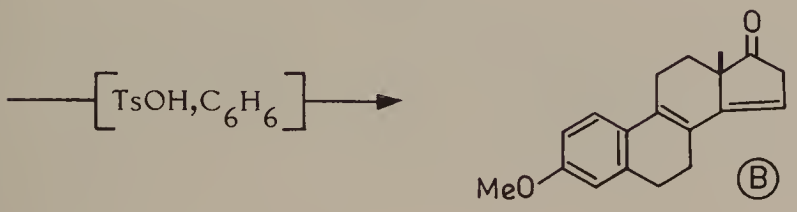
9. Ananchenko,S.N.; Leonov,V.N.; Platonora,A.V.; Torgov,I.V. Dokl. Acad. Nauk. SSSR, 1960, 135, 73; Ananchenko,S.N.; Limanov,V.Ye;Leonov,V.N.; Rzheznikov,V.N.; Torgov,I.V. Tetrahedron, 1962, 18, 1355; Ananchenko,S.N.; Torgov,I.V. Tetrahedron Lett., 1963, 1553.



dl-Estrone Methyl Ether

Torgov's novel coupling reaction between vinyl carbinols and diketones (10) provided an unusually simple route to bisdehydroestrone (B).





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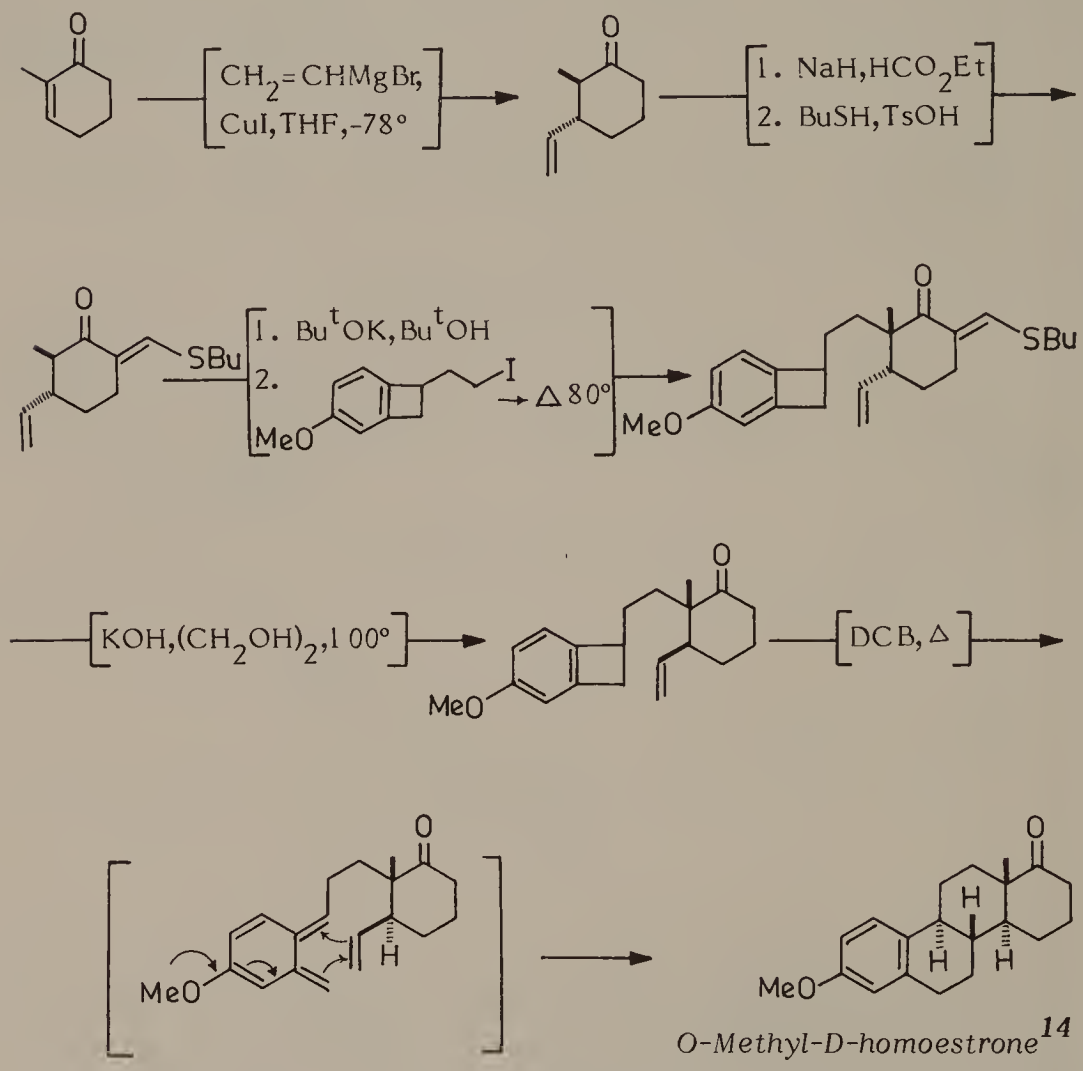
10. Ananchenko,S.N.; Torgov,I.V. Dokl. Acad. Nauk. SSSR, 1959, 127, 553.

11. Kuo,C.H.; Taub,D.; Wendler,N.L. Angew. Chem. Internat. Ed., 1965, 4, 1083; Chem. Ind., 1966, 1340; J. Org. Chem., 1968, 33, 3126.

12. The condensation was originally considered to be base-catalyzed but it has been shown since then by Wendler et al. that the condensation is in fact an acid-catalyzed reaction wherein the β-diketone functions autocatalytically. Significant improvements, including the use of isothiouronium salts to facilitate coupling, have resulted from a study of this reaction by the Merck group (11).

Kametani and his associates elaborated a stereoselective total synthesis of estrone by an intramolecular cycloaddition reaction of olefinic o-quinodimethanes, derived by thermolysis of benzocyclobutane intermediates (13).



O-Methyl-D-homoestrone[14]

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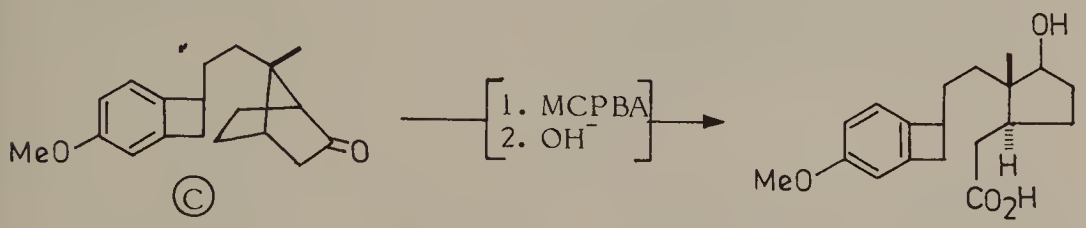
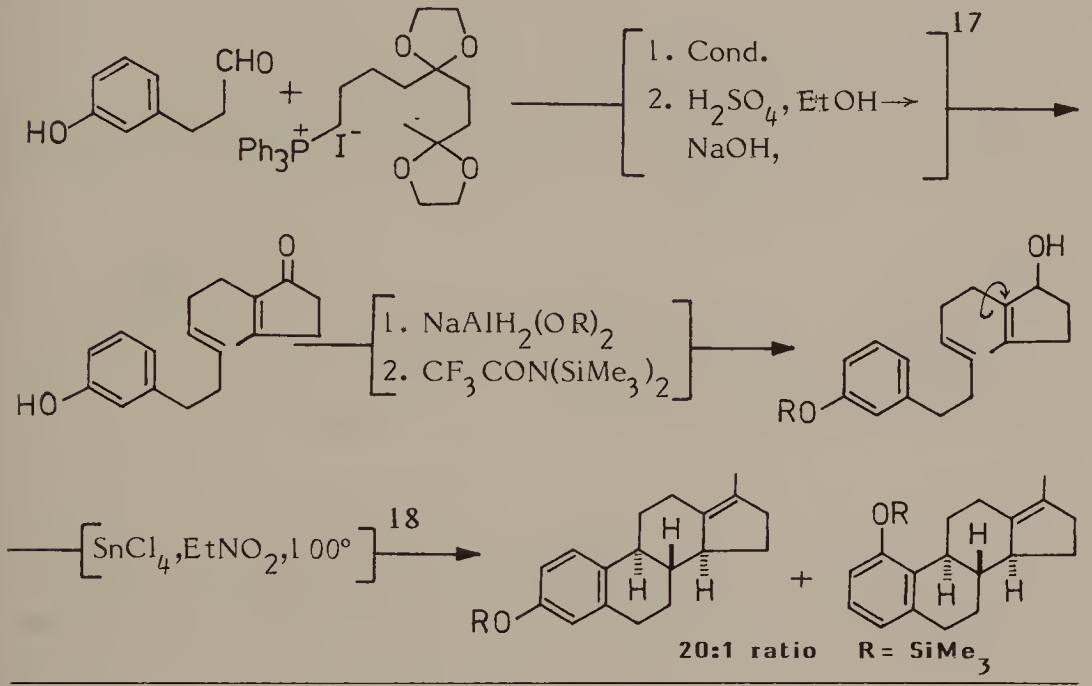
13. Kametani,T.; Nemoto,H.; Ishikawa,H.; Shiroyama,K.; Matsumoto,H.; Fukumoto,K. J. Am. Chem. Soc., 1977, 99, 3461.

14. O-Methyl-D-homoestrone has previously been converted to estrone, so this constitute a formal total synthesis of estrone.

Grieco et al. (15) also used the same approach of intramolecular cycloaddition via the corresponding o-quinodimethane to build a tetracyclic aromatic steroid structure but obtained directly estrone by going through bicyclo[2.2.1]heptane © as the key intermediate.



Bartlett & Johnson (16) described a fundamentally new approach to the synthesis of estrone through a cationic polyolefinic cyclisation.



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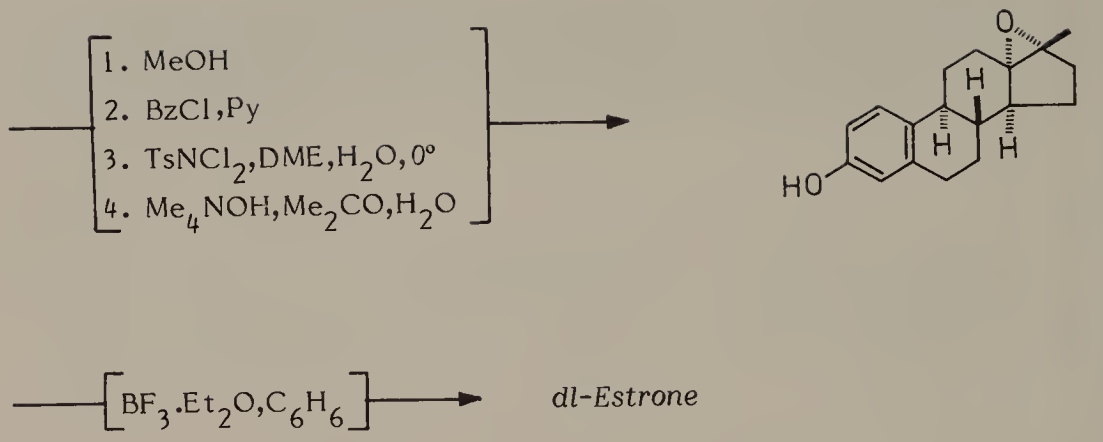
15. Grieco,P.A.; Takigawa,T.; Schillinger,W.J. J. Org. Chem., 1980, 45, 2247.

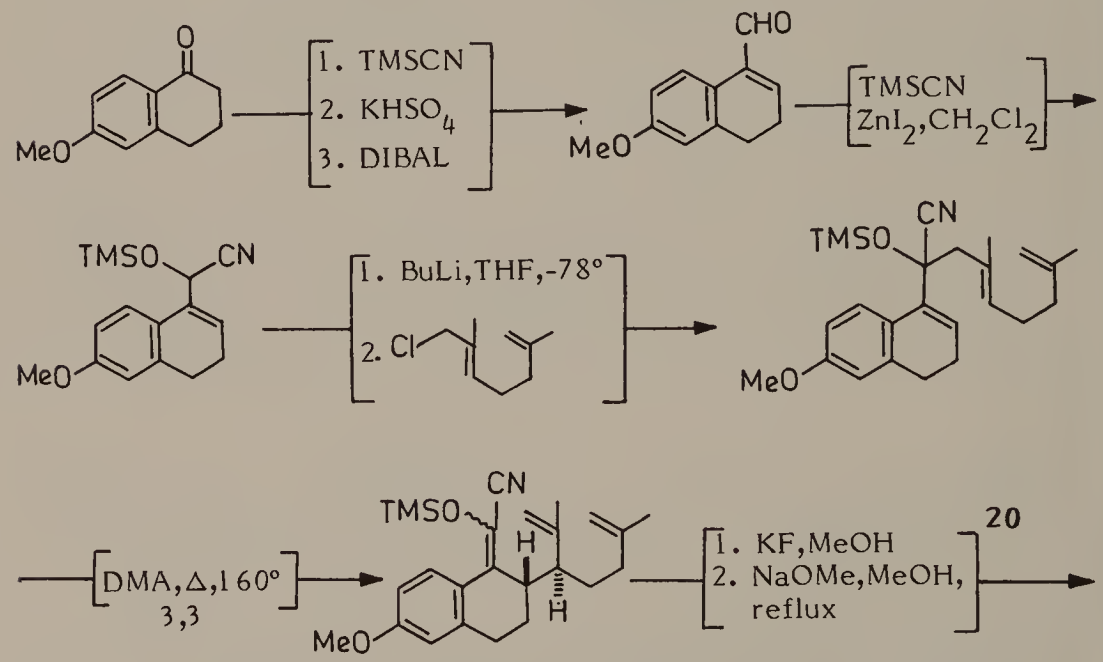
16. Bartlett,P.A.; Johnson,W.S. J. Am. Chem. Soc., 1973, 95, 7501.

17. The Wittig reaction went with greater than 98% trans-stereoselectivity.

18. With 3-methyl ether the optimum para:ortho isomers ratio obtained was 4.3:1; it was found that this ratio was strikingly dependent upon the leaving group at the substrate and suggested it to be a concerted process; Bartlett,P.A.; Brauman,J.I.; Johnson,W.S.; Volkmann,R.A. J. Am. Chem. Soc., 1973, 95, 7502.

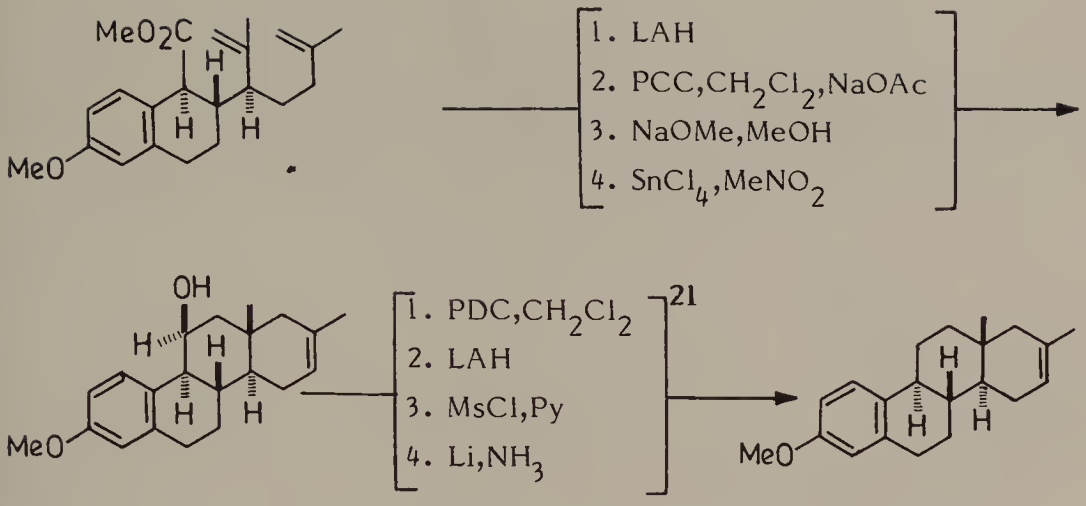


Ziegler and Wang have reported a modified polyene approach to estrone which controls the stereochemistry via a Cope arrangement (19).

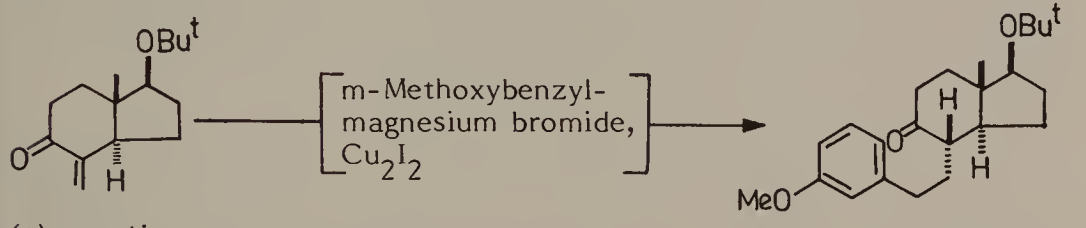


19. Ziegler,F.E.; Wang,Tein-Fu. Tetrahedron Lett., 1981, 22, 1179.

20. KF treatment gave a pair of diastereomeric esters formed in 80:20 ratio and major ester was tentatively assigned the cis stereochemistry, since NaOMe equiliberation provided the 8,9-trans:cis isomers (steroid numbering) in a ratio of 17:83; this would arise from a chair-like transition state involving pro-C_8 and pro-C_{14} atoms. The esters could be conveniently separated.



Saucy and his associates at Roche Laboratories developed a short and efficient steroid synthesis based on CD → ACD → ABCD approach and have applied it successfully to the synthesis of d-estrone (23), which involves conjugate addition of Grignard reagent destined to become ring A&B to optically active ring C-D-enone in presence of Cu^{+} salts, followed by cyclisation, hydrogenation and adjustment of functionalities (23,24).



(+)-enantiomer

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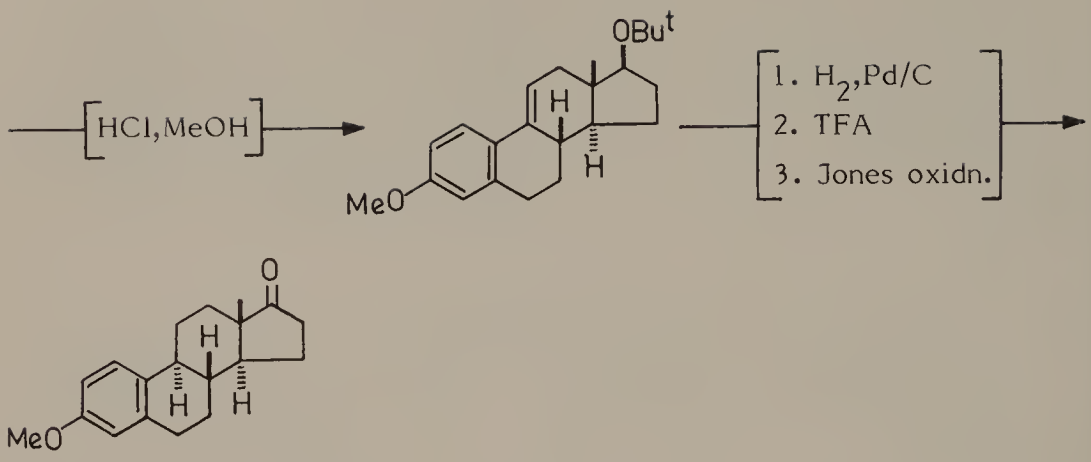
21. Attempted mesylation of the 11-axial alcohol produced a mixture of olefins arising presumably from facile trans-diaxial elimination of the expected mesylate. However, the mesylate of the equatorial alcohol as shown underwent smooth deoxygenation to provide only the tetracyclic compound. This tetracyclic compound has previously been converted to estrone by Valenta et al. (22).

22. Das,J.; Kubela,R.; MacAlpine,G.A.; Stojanac,Z.; Valenta,Z. Can. J. Chem., 1979, 57, 3308.

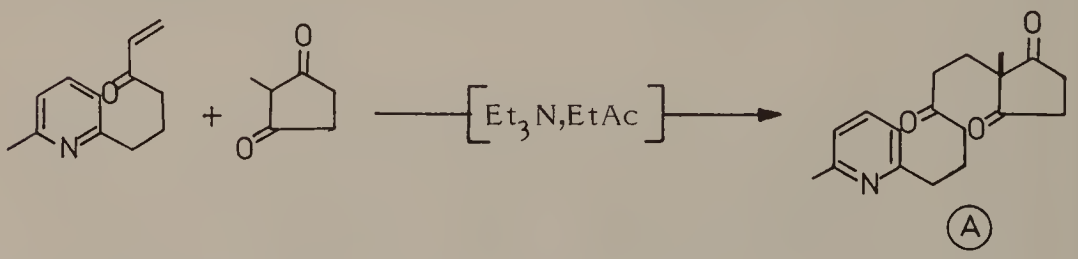
23. Cohen,N.; Banner,B.L.; Eichel,W.F.; Parrish,D.R.; Saucy,G.; Cassal,Jean-Marie; Meier,W.; Furst,A. J. Org. Chem., 1975, 40, 681.

24. This approach has also been used for the total synthesis of 19-norsteroids and androstanes; Scott,J.W.; Buchschache,P.; Lablar,L.; Meier,W.; Furst,A. Helv. Chim. Acta, 1974, 57, 1217; Micheli,R.A.; Hajos,Z.G.; Cohen,N.; Parrish,D.R.; Portland,L.A.; Sciammanna, W.; Scott,M.A.; Wehrli,P.A. J. Org. Chem., 1975, 40, 675.



(+)-Estrone 3-methyl ether

Danishefsky and his associates in some exploratory studies on annellation reactions for steroid synthesis and using α-picolines as equivalents of cyclohexenones demonstrated that bis-annellation of Wieland-Miescher ketone with 6-vinyl-α-picoline followed by Birch reduction provided a convenient synthesis of D-homoestrone (25). This approach, dovetailed with the observed optical induction in l-amino acid promoted aldolisation in hydrindenone synthesis by Hajos et al. and Eder et al. (26) was then adopted for an elegant synthesis of d-estrone (and 19-norsteroids) by inducing asymmetry by L-amino acid promoted aldolisation of the key prochiral precursor Ⓐ, achieving high chiral selectivity in the cyclisation step (27).



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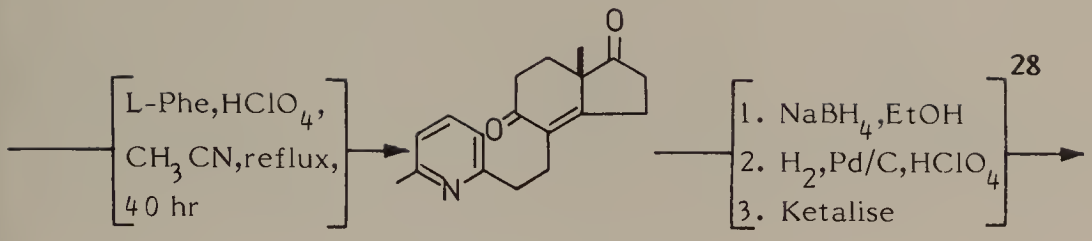
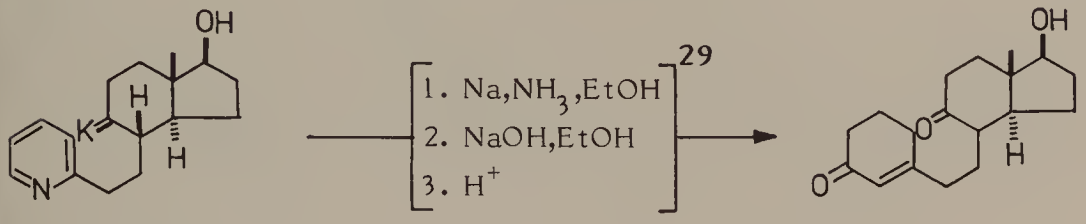
25. Danishefsky,S.; Nagel,A. J. Chem. Soc. Chem. Comm., 1972, 373; Danishefsky,S.; Cain,P.; Nagel,A. J. Am. Chem. Soc., 1975, 97, 380.

26. Hajos,Z.G.; Parrish,D.R. J. Org. Chem., 1974, 39, 1615; Eder,U.; Sauer,G.; Wiechert,R. Angew. Chem. Int. Ed., 1975, 10, 417.

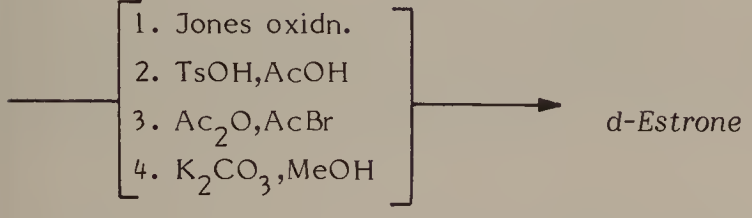
27. Danishefsky,S.; Cain,P.; J Org. Chem., 1974, 39, 2925; J. Am. Chem. Soc., 1975, 97, 5282; 1976, 98, 4975.



86% optical purity



K = Ketal



d-Estrone

Posner and his associates carried out a highly convergent synthesis of estrone in which a tandem Michael-Michael-ring closure reaction (MIMIRC) has been developed for efficient sequential formation of three C-C bonds to provide a one-pot synthesis of (±)-9,11-dehydro-estrone, which can be easily converted to estrone (30).

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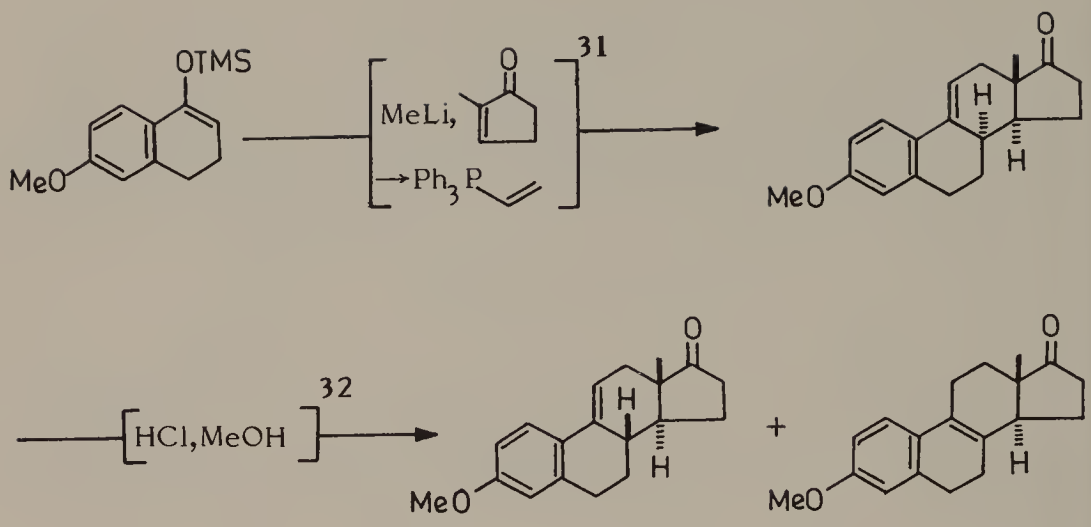
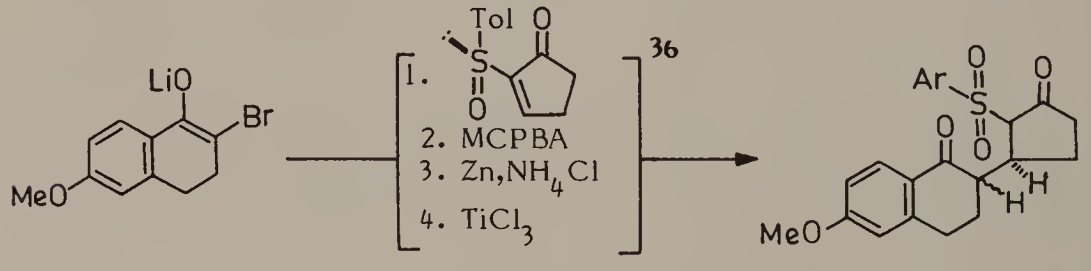
28. Along with 14 -epimer (trans:cis, 2.6:1) and hydrogenolysed product.

29. For a discussion of the conversion of 2-CH_2R-6-methylpyridines (I) to 3-CH_2R-cyclohex-2-enones (II) see: Danishefsky,S.; Cavanaugh,R. J. Am. Chem. Soc., 1968, 90, 520; Danischefsky,S.; Nagel,A.; Peterson,D. J. Chem. Soc. Chem. Comm., 1972, 374.

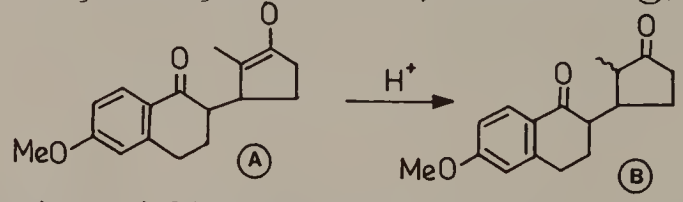
30. Posner,G.H.; Mallamo,J.P.; Black,A.Y. Tetrahedron, 1981, 37, 3921.



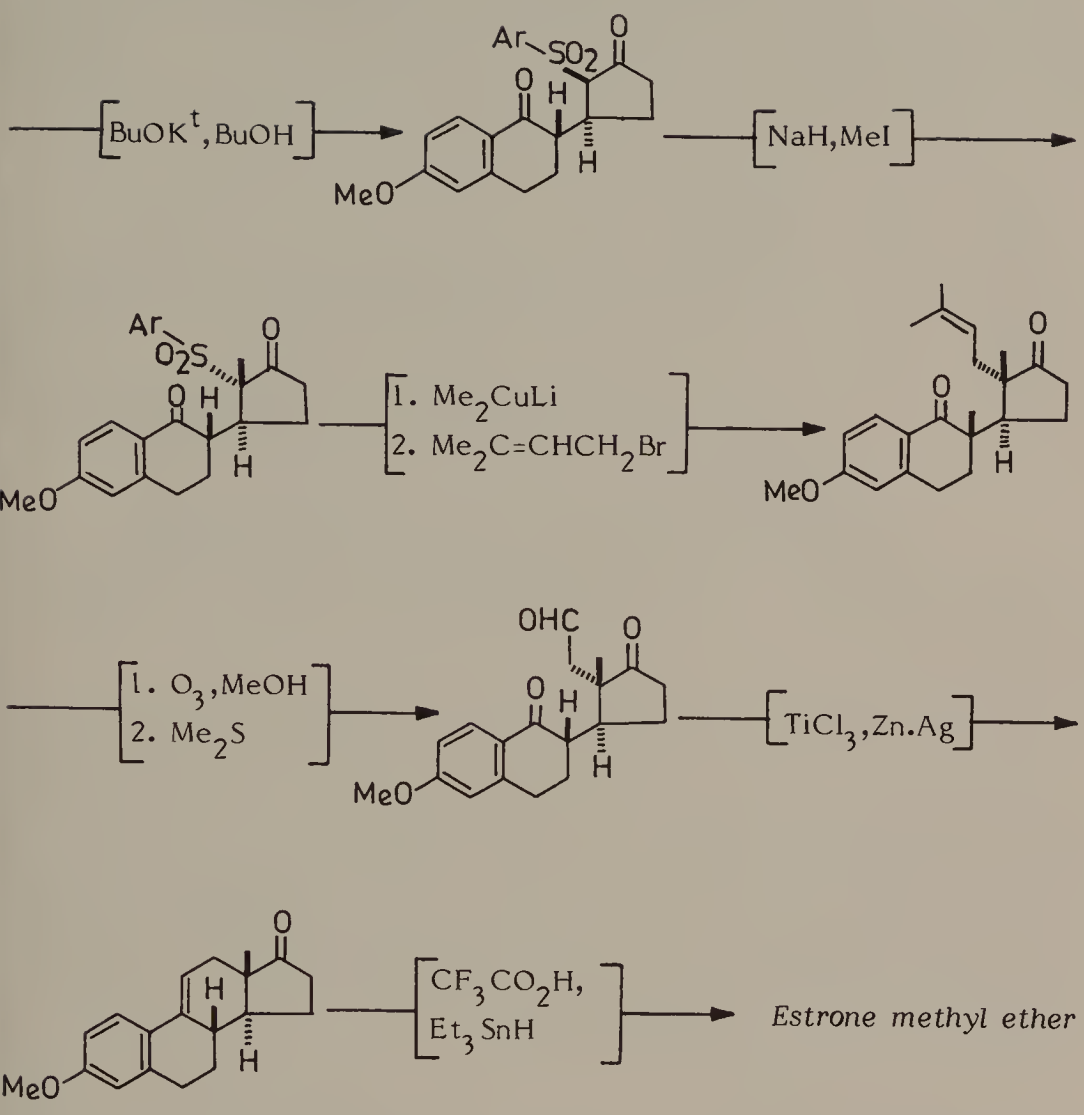
In a further refinement of this AB → ABD → ABCD approach to get optically active product, Posner and Switzer have employed a highly diastereoselective Michael addition of a ketone enolate ion to an enantiomerically pure 2-(arylsulfinyl)-2-cyclopentenone (33) as the key step in an effective asymmetric total synthesis giving esterone in over 97.3% enantiomeric purity and with natural absolute stereochemistry, which involves induction of asymmetry at the prochiral β-carbon of an enantiomerically pure α,β-ethylenic sulfoxide (34,35).



31. This reaction goes through the intermediacy of the enolate (A); (B) can be isolated.



32. Such a mixture of 9,11- and 8,9-dehydroestrones has previously been converted into estrone and into estradiol in high yield; Douglas,G.H.; Graves,J.M.H.; Hartley,D.; Hughes,G.A.; McLoughlin,J.; Siddal,J.; Smith,H. J. Chem. Soc., 1963, 5072; Quinkert,G.; Weber,W.D.; Schwartz,U.; Durner,G. Angew. Chem. Int. Ed., 1980, 19, 1027.



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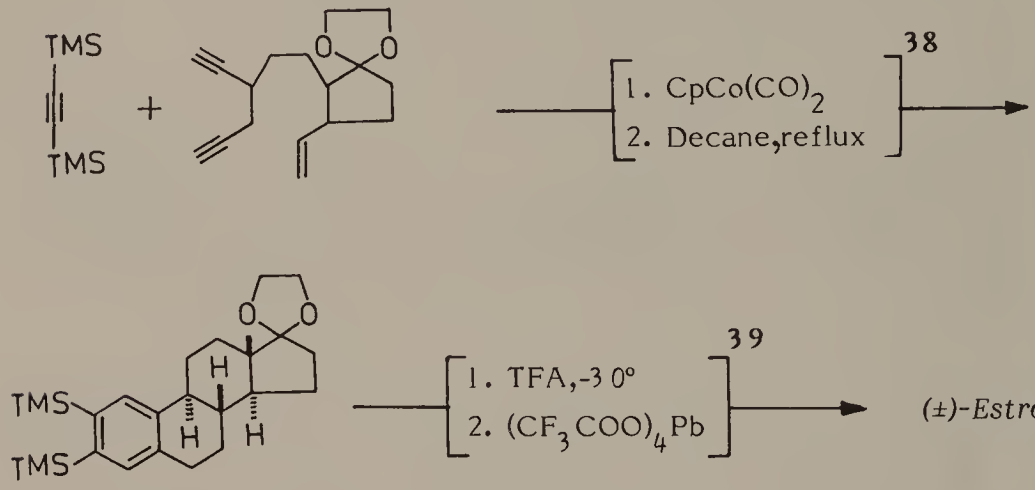
33. For R-(-)-2-(p-tolylsulfinyl)-2-cyclopentenone; see: Frye,L.L.; Kogan,T.P.; Mallamo,J.P.; Posner,G.H. Org. Synth., 1985, 64, 196.

34. Posner,G.H.; Switzer,C. J. Am. Chem. Soc., 1986, 108, 1239.

35. For review see: Posner,G.H. In "Asymmetric Synthesis"; Morrison,J.D. Ed. Academic Press, New York, 1983; Vol.2, Chapter 8, p.225.

36. When lithium enolate itself was used in Michael addition only 54% diastereomeric selectivity was achieved; however, the use of 2-bromoenolate gave a product with over 90% diastereomeric selectivity which was followed by removal of Br by Zn reduction.

Funk and Vollhardt have described yet another approach to the synthesis of A-ring aromatic steroids, which is based on construction of rings ABC constellation through cobalt-mediated cooligomerisation of bis (trimethylsilyl) acetylene with almost complete chemoregio and stereospecificity (37).



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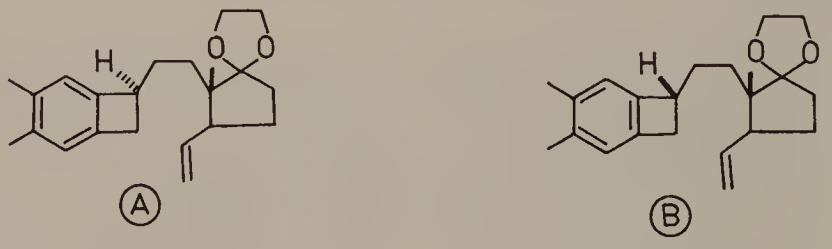
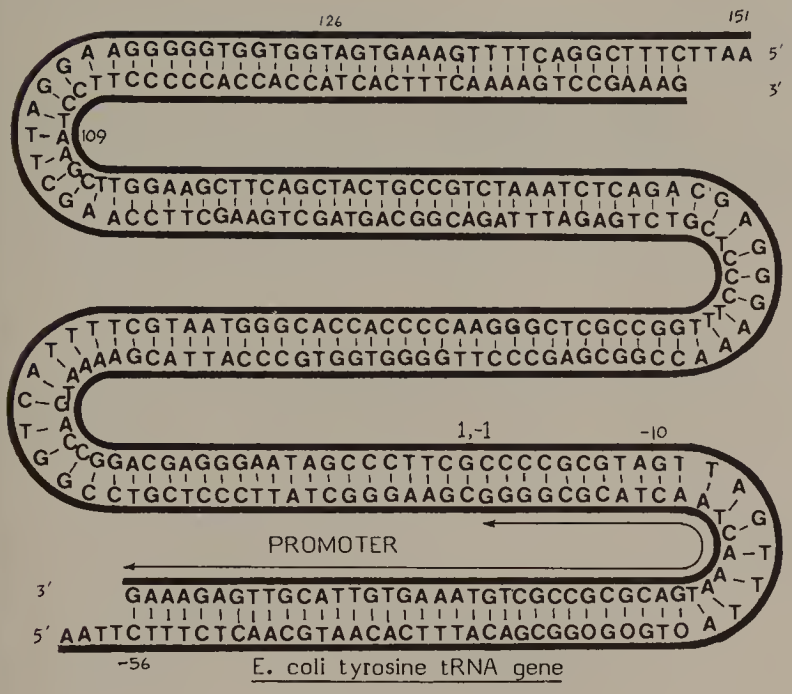
37. Funk,R.L.; Vollhardt,K.P.C. J. Am. Chem. Soc., 1979, 101, 215.

38. The cyclisation proceeds through the benzocyclobutene intermediates A&B which could be isolated by work up before heating in decalin. Both (A) and (B) on heating gave estratriene on heating, but could not be converted into each other, thus suggesting an appreciately lower barrier to intramolecular Diels-Alder reaction than to ring closure once the intermediate o-quinomethine is generated.



39. CF_3CO_2H treatment gave 3-trimethylsilylestra-1,3,5(10)-trien-17-one with 9:1 selectivity in 90% yield; oxidative aryl silicon cleavage occured almost quantitatively with lead tetrakis (trifluoracetate).

GENE SYNTHESIS



One of the great achievements of contemporary organic synthesis is the ability to construct rapidly polynucleotides of specific sequences, which has made it possible to make synthetic genes (1). This has been due primarily to dramatic improvements in the methods of polynucleotide synthesis in the last two decades (2). The relatively easy availability of DNAs of any required sequence as a result of these developments has been a big factor for the recent advances in molecular biology and biotechnology (3).

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1. For authoritative review of the earlier developments in this field see: Khorana,H.G.; Science, 1979, 203, 614; XIII Feodor Lynen Lecture, 1981.

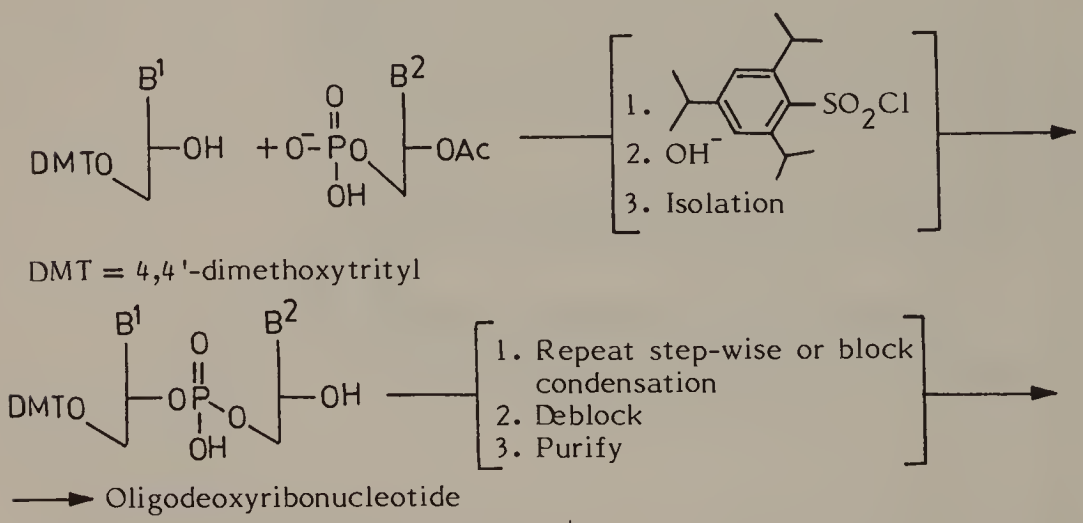
2. The major recent developments in the methods responsible for the outstanding successes in polynucleotide synthesis are: (i) switch over from phosphodiester approach to triester methodology, and from solution phase to solid support synthesis; (ii) use of DNA ligases to join oligodeoxyribonucleotide chains between juxtaposed 5'-phosphoryl and 3'-hydroxy groups and of DNA kinases to form 5'-phosphate on a preformed oligonucleotide; (iii) availability of instrumental methods for automated synthesis and for preparative separation. For some comprehensive reviews of methods of synthesis see: (a) Brown,E.L.; Belgaje,R.; Ryan,M.J.; Khorana,H.G. Meth. in Enzymology, 1979, 68, 109; (b) Narang,S.A. Tetrahedron, 1983, 39, 3; (c) Reese,C.B. Tetrahedron, 1978, 34, 3143; (d) Gassen,H.G.; Lang,A. Chemical and Enzymatic Synthesis of Gene Fragments: A Laboratory Manual, Verlag Chemie, Weinheim, 1982; also see ref.17.

3. For an appreciation of the impact of polynucleotide synthesis in genetic engineering see: (a) Itakura,K. Trends Bioch. Sci., 1982, 442; (b) Davies,J.E.; Gassen,H.G. Angew. Chem. Int. Ed., 1983, 22, 13; (c) Caruthers,M.H. Science, 1985, 231, 281.

METHODS OF SYNTHESIS

Phosphodiester method

This was the first method developed for oligonucleotide synthesis by Khorana and his associates and dominated the field for almost two decades and was employed for the first synthesis of a bihelical DNA corresponding to the major yeast Ala tRNA (1,12).



Low solubility of reactants in organic solvents, long reaction times, decreasing yields as the chain length grows and time consuming purification procedures required are the limitations of this method.

Triester methods

A solution to some of these problems was found by masking the third dissociation of the phosphate by lipophilic and easily removable blocking groups, which increased organic solvent solubility and reaction rates, reduced side product formation and simplified purification procedure (2,4). Another big advantage with triester approach is compatibility with polymer supported synthesis which is now extensively employed for oligonucleotide synthesis, and the repetitive procedures required in coupling cycles in solid phase synthesis are amenable to automation. These developments have greatly enhanced the efficiency of polynucleotide synthesis (3c,5).

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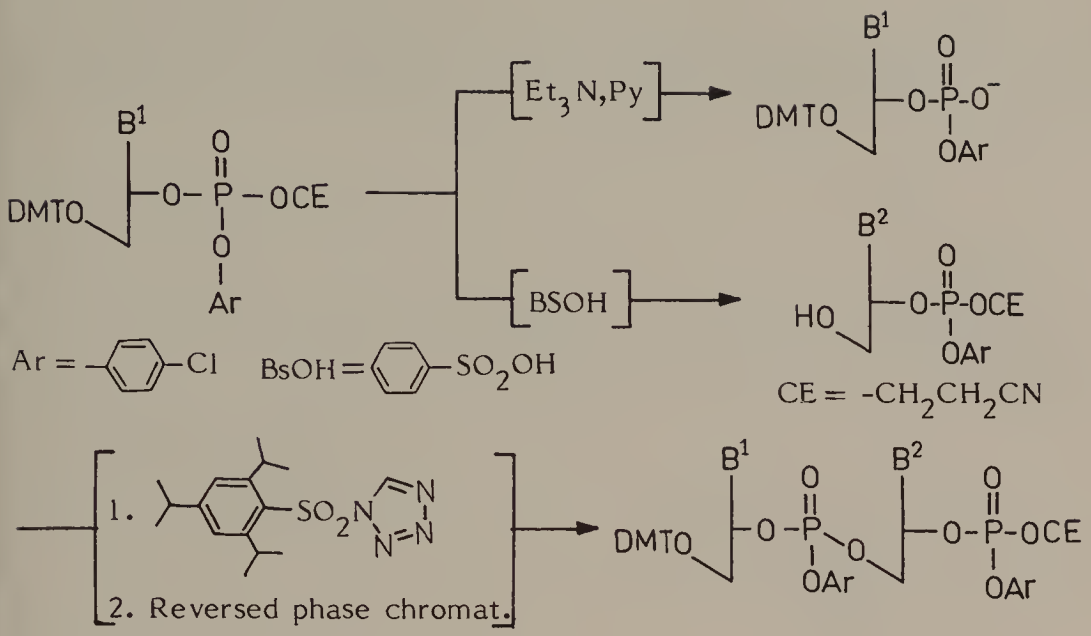
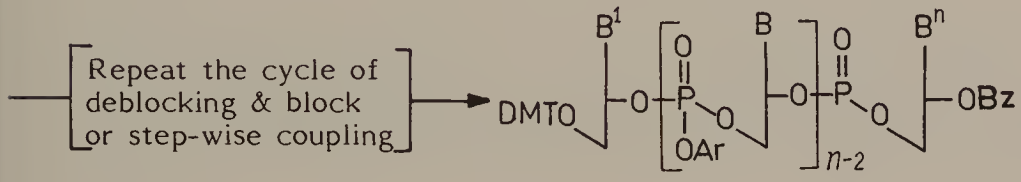
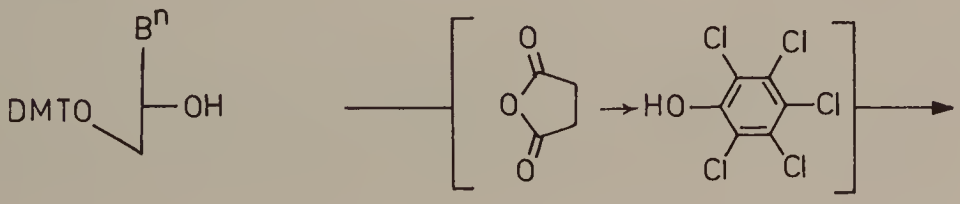
4. (a) Itakura,K.; Bahl,C.P.; Katagiri,N.; Michniewicz,J.; Wightman,R.H.; Narang,S.A. Can. J. Chem., 1973, 51, 3469; (b) Catlin,J.C.; Cramer,F. J. Org. Chem., 1973, 38, 245; Narang, S.A.; Hsiung,H.M.; Brousseau,R. Methods in Enzym., 1979, 68, 90.
5. (a) Gait,M.J.; Matthes,H.W.D.; Singh,M.; Sproat,B.S.; Titmas,R.C. in 2(c) page 1; (b) Seliger,H.; Klein,S.; Narang,Ch.K.; Seemann-Preising,B.; Eiband,J.; Hauel,H.; in 2(c) page1.

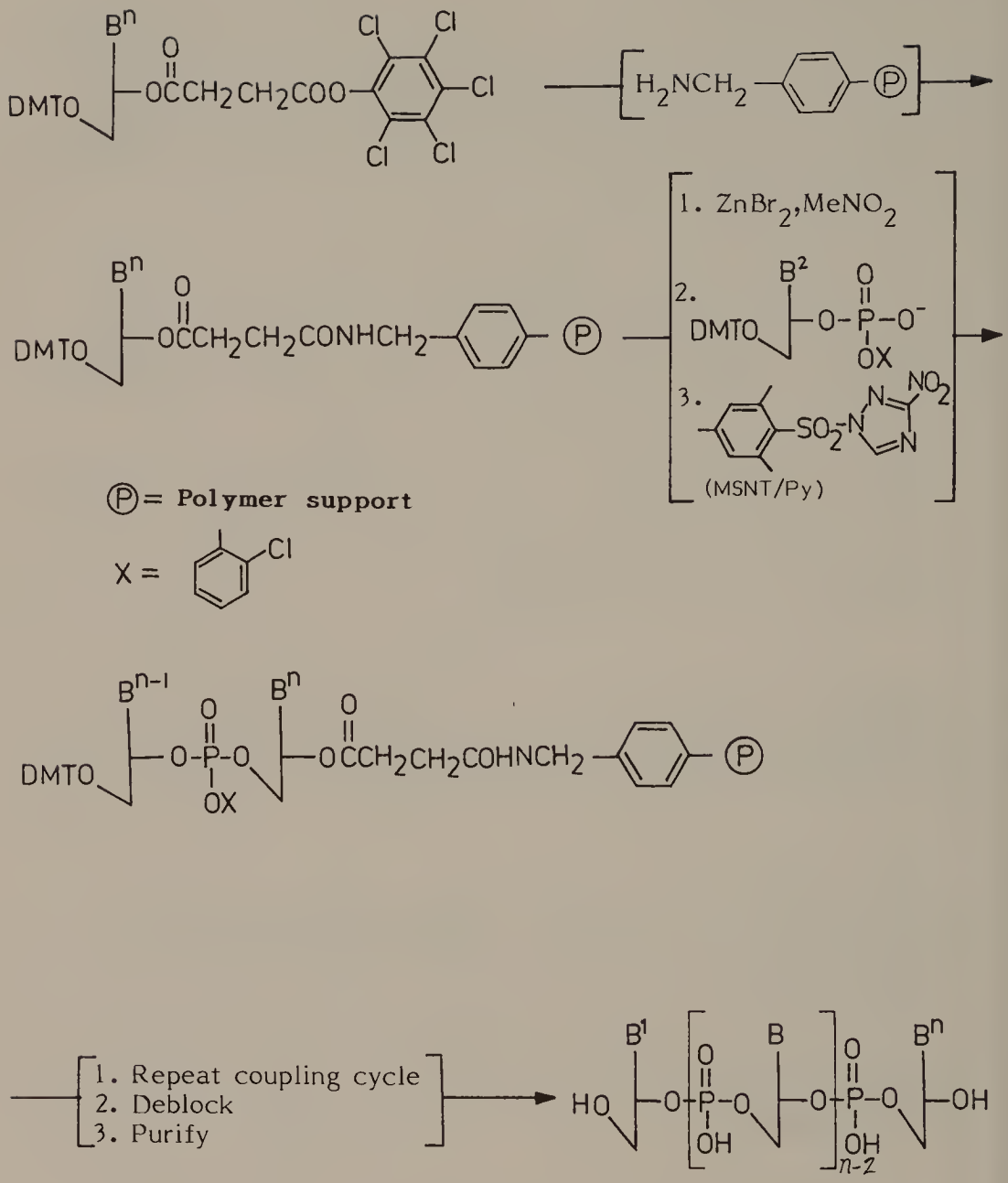
Phosphotriester method





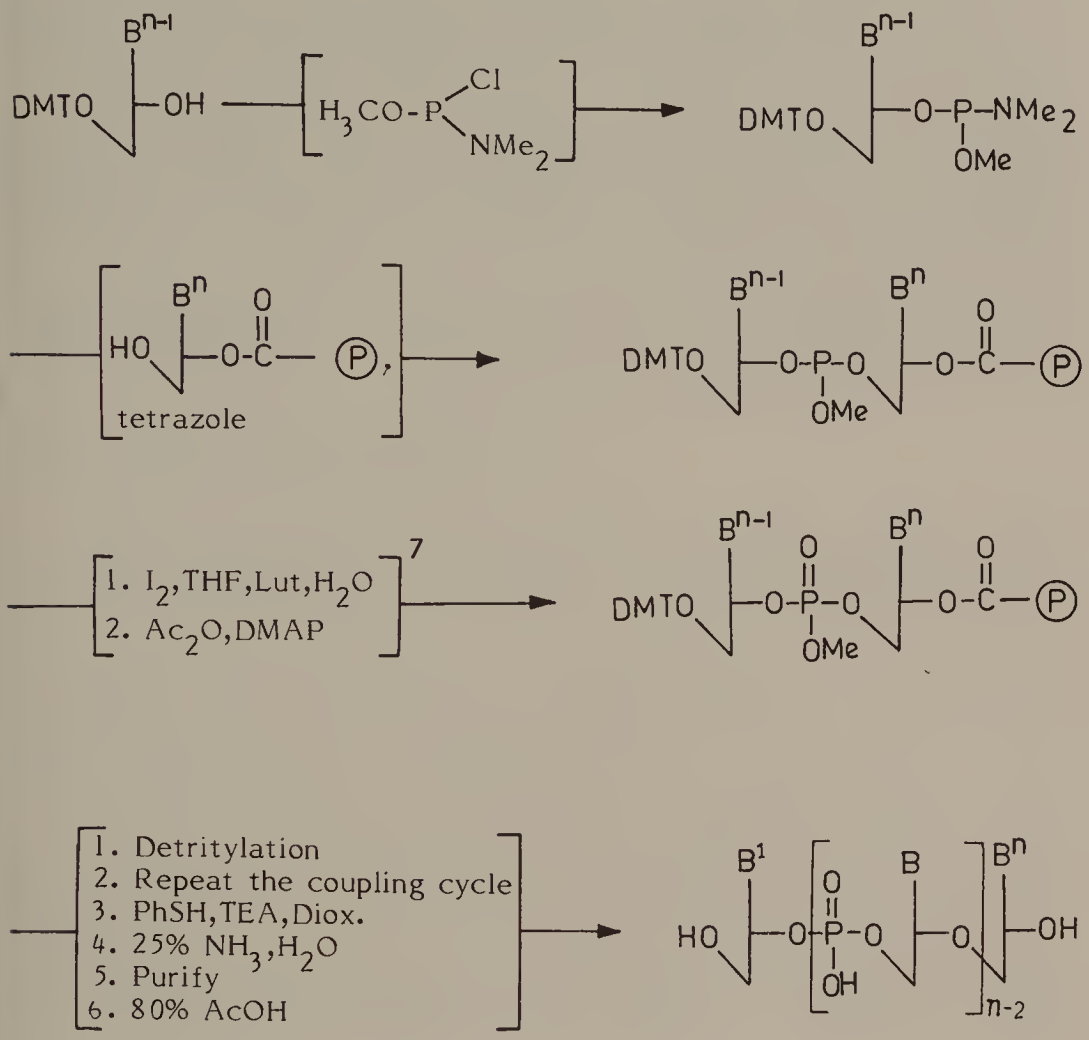
On polymer support




DMTO
OCCH2CH2COO
Cl
H2NCH2
Ⓟ
1. ZnBr2,MeNO2
2.
3.
(MSNT/Py)
Ⓟ= Polymer support
X =
OCCH2CH2CONHCH2
OCCH2CH2COHNCH2
1. Repeat coupling cycle
2. Deblock
3. Purify
HO
OH
n-2

Phosphitetriester method (5)

This method overcomes the problem of negative charge on phosphate by first preparing the dinucleotide phosphite ester, which in a second step is oxidised by iodine to a phosphate bond (2,6).



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6. (a) Beancage,S.I.; Caruthers,M.H. Tetrahedron Lett., 1981, 22, 1859; (b) Matteucci,M.D.; Caruthers,M.H. J. Am. Chem. Soc., 1981, 103, 3185.

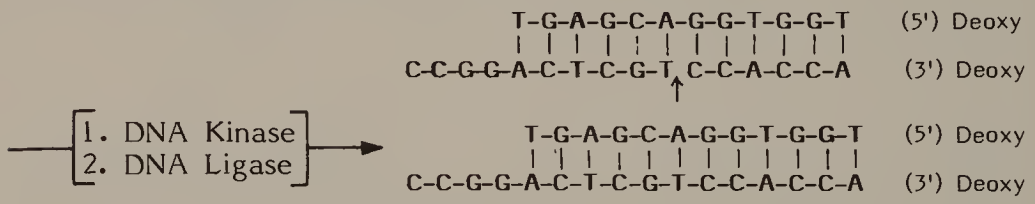
7. The product is treated with Ac_2O, Py (capping) to remove out of reaction sequence unreacted oligonucleotides attached to the polymer support.

The choice between the two methods is personal to different laboratories, but overall the phosphite–triester method does seem to offer the advantage of near quantitative yields (>98%) and much shorter reaction time (5 min at room temperature).

Enzymatic synthesis

A strategy has been developed mainly by Khorana and his group (8) whereby short synthetic oligonucleotides are joined by DNA ligase enzymes (9) in the presence of a complementary strand or template, which aligns the short segments properly; the enzyme catalyses the formation of a phosphodiester linkage between the juxtaposed 5'-phosphate and 3'-OH of two overlapping DNA chains. A minimum of four overlapping nucleotide pairs are required on each side of the junction to provide efficient template interaction for the joining of the deoxyribonucleotides with DNA ligase.

DNA kinases (10) which phosphorylate terminal 5'-hydroxyl in oligonucleotides are used to prepare the 5'-phosphorylated oligonucleotides needed for ligase catalysed coupling.



Purification

As synthesis progresses, even with 90% yield in every step, the purity of the product starts going down; the required product which comes of the column is usually 5-10% of the crude mixture relative to the first nucleoside on the solid support. Although, the materials so obtained can be used for ligation to plasmid vectors, and the correct sequence will be selected by the biological system, but for chemical characterisation, this mixture needs extensive purification which is perhaps the more time consuming step. The most commonly used methods of purification are: (1) reversed phase gel permeation chromatography; (2) HPLC, reversed phase or ion-exchange; (3) polyacrylamide gel electrophoresis.

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8. Khorana,H.G.; Aggarwal,K.L.; Besmer,P.; Buchi,H.; Caruthers,M.H.; Cashion,P.J.; Fridkin, M.; Jay,E.; Kleppe,K.; Kleppe,R.; Kumar,A.; Loewen,P.C.; Miller,R.C.; Minamoto,K.; Panet,A.; RajBhandary,U.L.; Ramamoorthy,B.; Sekiya,T.; Takeya,T.; Van de Sande,J.H. J. Biol. Chem., 1976, 251, 565.

9. For a review of DNA joining enzymes see: Higgins,N.A.; Cozzareli,N.R. Methods in Enzym., 1979, 68, 50.

10. Richardson,C.C. Proc. Nucleic Acid Res., 1971, 2, 815.

A combination of chemical synthesis and enzymatic reactions now offers the ability to synthesis bihelical DNAs of any specific sequence. The concept which is central to the whole design of synthesis is the inherent ability of polynucleotide chains having complimentary bases to form ordered bihelical complexes of sufficient stability even in aqueous solution by virtue of base pairing, and that overlapping regions of the duplex could complex with shorter chains which could then be joined end to end with parent chain by ligases.

The strategy commonly followed for DNA synthesis consists in carefully disecting the DNA in the double strand into short single stranded segments, 10-20 bases long, with suitable overlaps in the complimentary strands; the segments are chemically synthesised by solid phase method, which are phosphorylated at terminal 5'-hydroxyl using ATP and polynucleotide kinases; a few to several neighbouring oligonucleotides are then allowed to form bihelical complexes in aqueous solution, and the latter are joined end to end by polynucleotide ligases to form covalently linked duplexes; subsequent head-to-tail joining of the short duplexes leads to the total DNA synthesis.

YEAST ALANINE tRNA GENE

The synthesis of the 77 base pair (bp) structural gene corresponding to yeast alanine tRNA by Khorana and his associates is of special historical significance. This tRNA was the first to be fully sequenced (11), and DNA corresponding to this tRNA the first DNA of specific sequence to be synthesised (12). Its synthesis was the culmination of almost two decades of orchestrated development of different elements required for the total synthesis of polynucleotides, and demonstrated that genes could be synthesised.

The plan of synthesis as shown below involved: (1) chemical synthesis of such 15 polydeoxynucleotide segments shown in brackets ranging in length from 5-20 nucleotide units, with 3'- and 5'-hydroxyl end groups free representing the entire two strands of the DNA as would give overlap of 4 to 5 nucleotides in the complimentary strands; (2) phosphorylation of the 5'-hydroxyl group of these segments using T_4 polynucleotide kinase; (3) annealing and ligase-induced head to tail joining of the appropriate segments aligned properly due to bihelical complexation.

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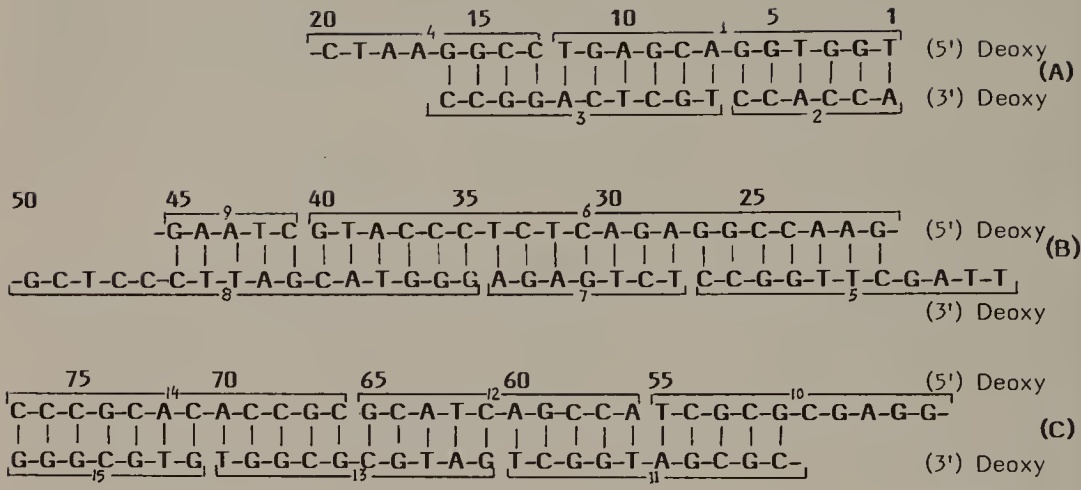
11. Holley,R.W. et al., Science, 1965, 147, 1462.

12. Khorana,H.G.; Agarwal,K.L.; Buchi,H.; Caruthers,M.H.; Gupta,N.K.; Kleppe,K.; Kumar,A.; Ohtsuka,E.; RajBhandary,U.L.; van de Sande,J.H.; Sgaramella,V.; Terao,T.; Weber,H.; Yamada, T. J. Mol. Biol., 1972, 72, 209 and twelve accompanying papers in the same issue.



Plan of Synthesis of Yeast Ala tRNA gene

This was followed by the synthesis of a biologically functional E. coli tyrosine tRNA suppressor gene by Khorana and his associates consisting of the 126 bp sequence corresponding to the tRNA, 51 bp long promoter region and a 25 nucleotide long processing signal sequence including the endonuclease specific sequence (2a,13). Many other synthetic genes, including those for human somatostatin (14), human insulin A&B chains (15) and for human leucocyte interferon (16) have since then been constructed.

HUMAN LEUKOCYTE α_1-INTERFERON GENE

It is the synthesis of 514 bp human leucocyte α_1-interferon (166 amino acid residues) gene containing initiation and termination signals plus restriction enzyme sites for plasmid insertion, by Edge et al. (16) which has demonstrated forcefully the great jump chemical oligonucleotide synthesis has made.

It involved the synthesis of 67 oligodeoxyribonucleotide units, ranging in size from 14-21 residues (one of 10) by rapid, solid phase procedures using phosphotriester coupling method, which were separately

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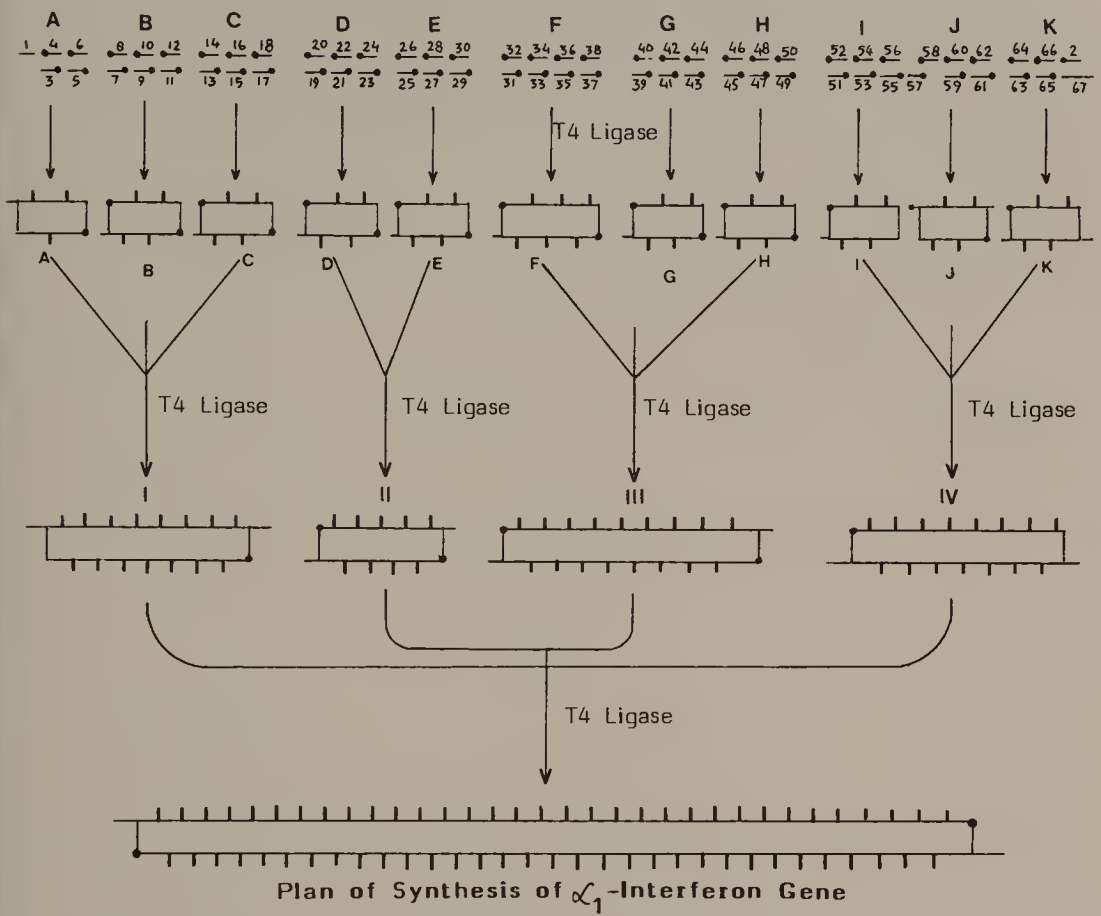
13. Belagaje,R.; Brown,E.L.; Gait,M.J.; Khorana,H.G.; Norris,K.E. J. Biol. Chem., 1979, 254, 5754; and accompanying five papers.

14. Itakura,K.; Hirose,T.; Crea,R. et al., Science, 1977, 198, 1056.

15. (a) Goeddel,D.V.; Kleid,D.G.; Bolivar,F. et al., Proc. Natl. Acad. Sci., USA, 1979, 76, 106; (b) Hsiung,H.M. et al., Nucleic Acids Res., 1979, 6, 137; (c) Narang,S.A. et al., ibid, 1980, 7, 377 and accompanying papers.

purified and 5'-phosphorylated by a kinase. This was followed by sequential enzymatic ligation of the oligonucleotides to yield a 514 base pair fragment. The synthetic gene was then ligated to a plasmid vector and cloned in Escherichia coli, and clones containing the anticipated gene sequence were obtained, and the synthetic gene charactrised by restriction enzyme digests and total sequence determination.

a



Plan of Synthesis of α_1-Interferon Gene

In planning the synthesis, the gene was divided into oligonucleotide units of ca.15 residues so as to give overlaps of at least 7 base pairs on each side of all ligation points as shown above. The phosphotriester method described above was used for synthesis of the units shown in the top portion of the diagram with arabic numerals, with

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16. Edge,M.D.; Greene,A.R.; Heathcliffe,G.R.; Meacock,P.A.; Schuch,W.; Scanlon,D.B.; Atkinson,T.C.; Newton,C.R.; Markham,A.F. Nature, 1981, 292, 756.

small changes in experimental conditions to improve the yields; mesitylene - sulfonyl-3- nitro-1,2,4-triazole was used as condensing agent which increased yield in coupling reaction and reduced coupling time. The oligonucleotides were then ligated initially in eleven groups A-K by allowing the units to anneal followed by treatment with T_4-ligase. Ligated products of the expected size were isolated by preparative polyacrylamide gel electrophoresis in denaturing conditions, aliquots of the eleven fragments combined in four blocks, annealed and again ligated with T_4-induced DNA ligase to give the four units, and the process of isolation and ligation repeated. After isolation of the final product of the expected size by polyacrylamide electrophoresis or gel permeation chromatography, the ends were phosphorylated and the product ligated to BamHI site of pM50 plasmid and introduced into E. coli strain MRC8 and the colonies screened for the presence of the synthetic oligonucleotide insert. It was found that the plasmid DNAs obtained from a number of colonies had identical 514-base pair fragment corresponding to the Ifn gene.

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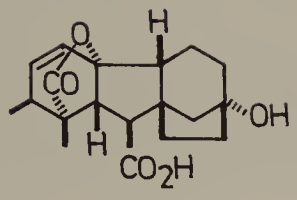
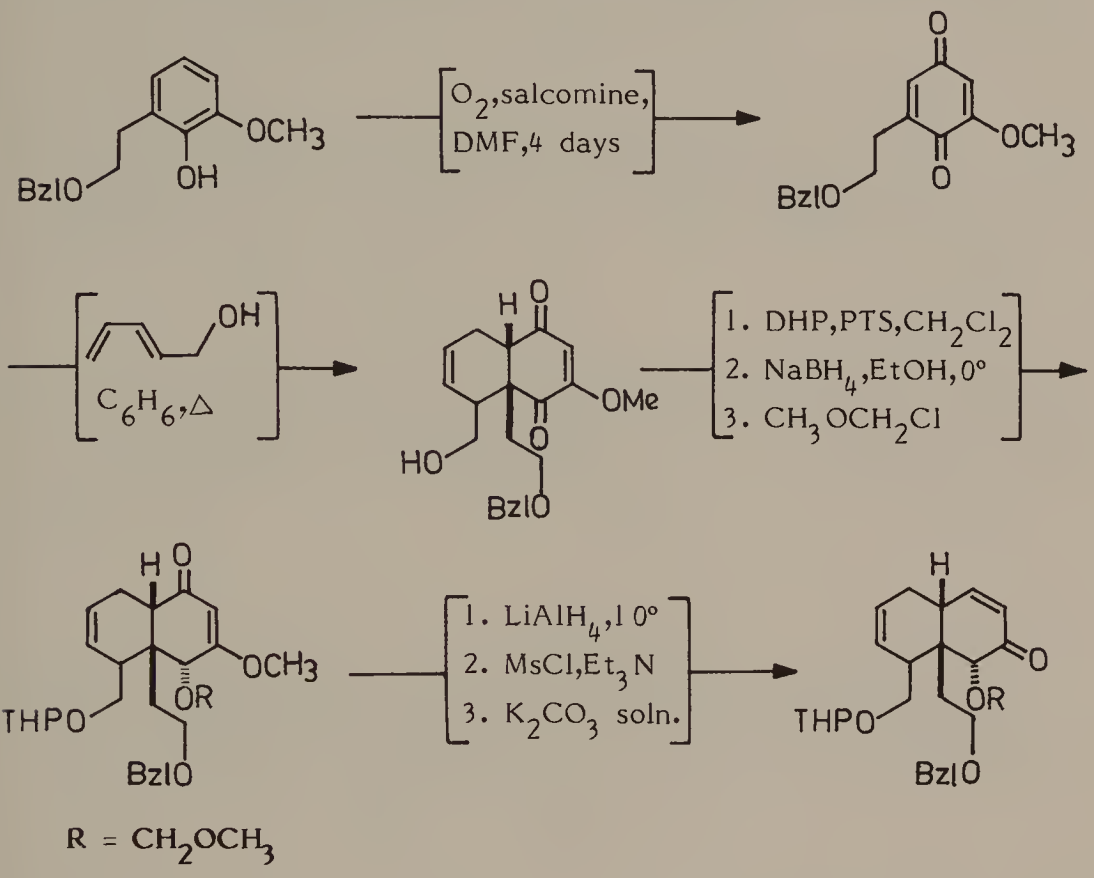
17. Oligonucleotides Synthesis, a practical approach, Gait,M.J. Ed., IRL Press, Oxford, England, 1984.



GIBBERELLIC ACID

On account of sensitivity towards reagents and high density of functionalities in some regions of the molecule, gibberellic acid remained a challenge for organic synthesis for many years and it is only relatively recently that Corey and his associates achieved its first total stereospecific synthesis (1).



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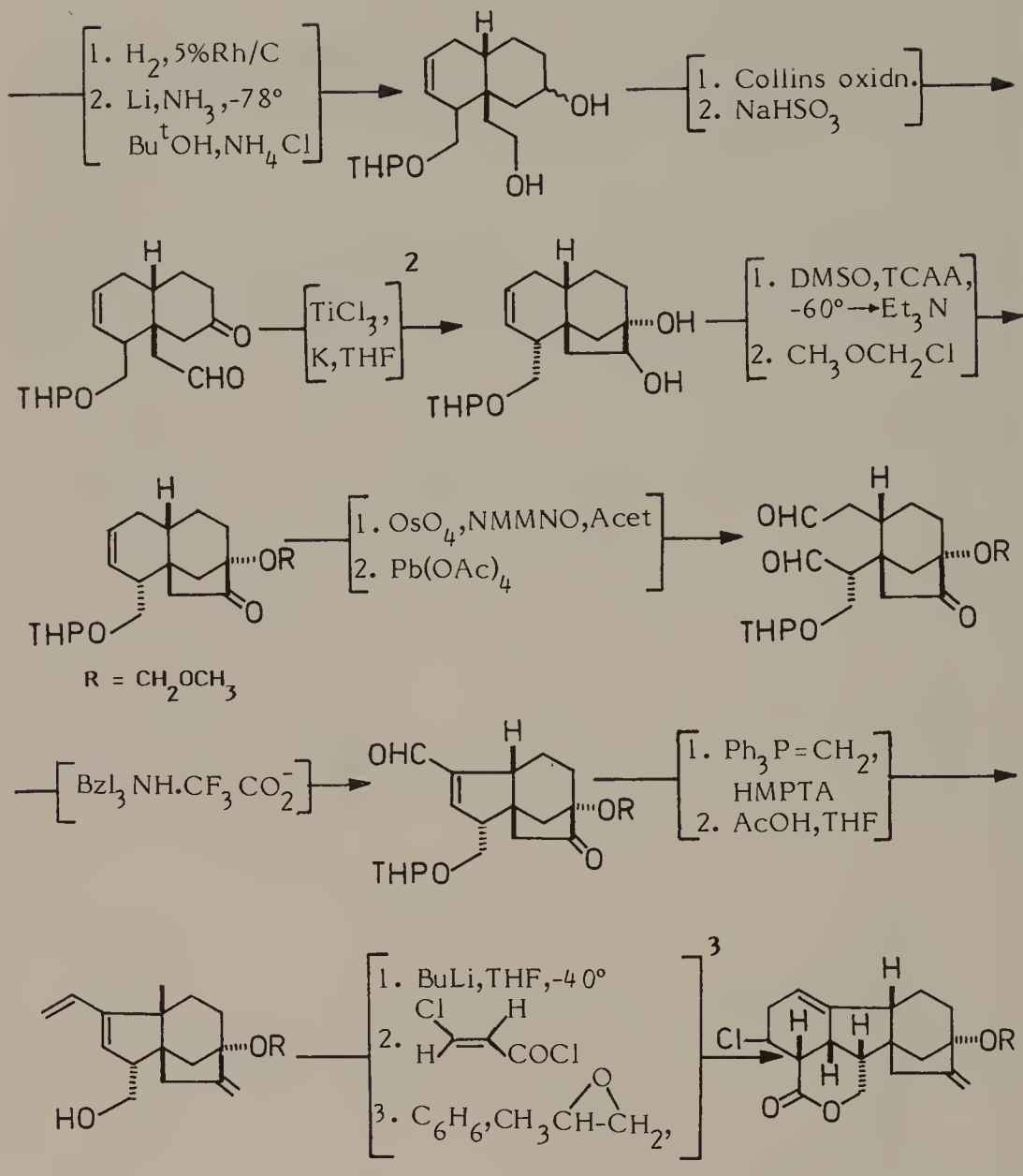
1. Corey,E.J.; Danheiser,R.L.; Chandrasekaran,S.; Siret,P.; Keck,G.E.; Gras,Jean-Louis, J. Am. Chem. Soc., 1978, 100, 8031;Corey,E.J.; Danheiser,R.L.; Chandra Sekaran,S.; Keck,G.E.; Gopalan,B.; Larsen,S.D.;Siret, P.; Gras, Jean-Louis, ibid, 1978, 100, 8034.



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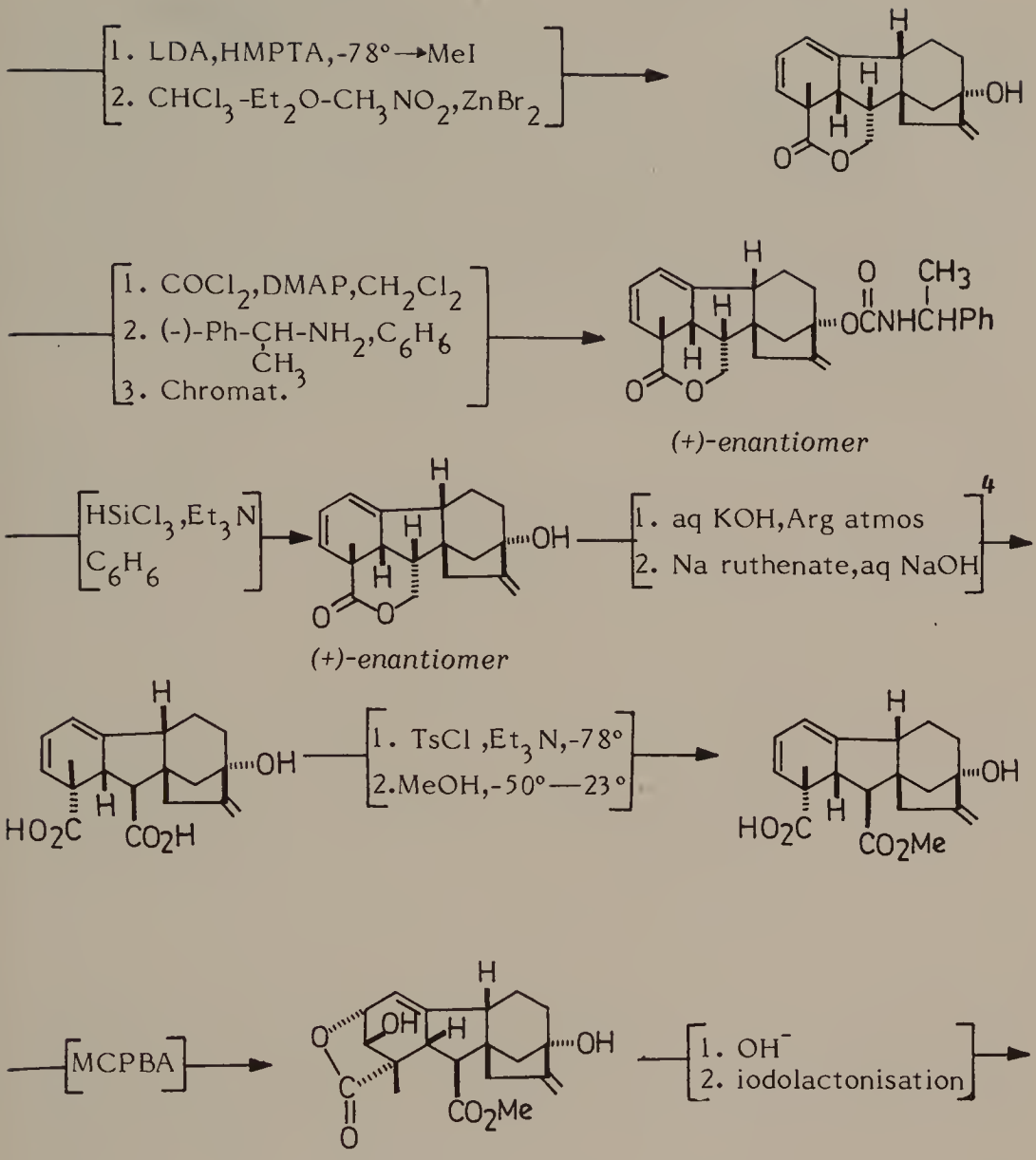
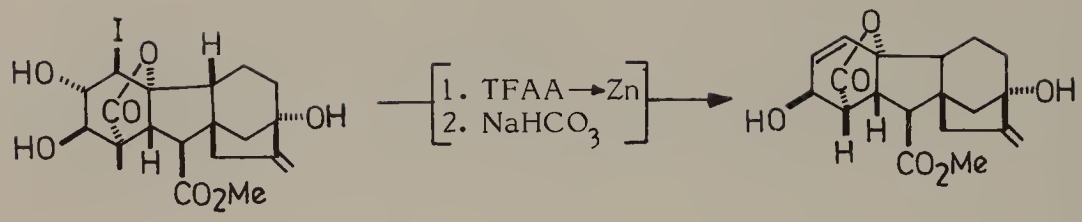
2. The reaction gave 40% of the required cis-aldol alongwith 15% of the trans isomer and 10% diol which was recycled.

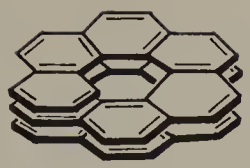
3. The stereochemistry of Diels-Alder adduct is assigned on the supposition of a concerted internal α-face, 'endo' Diels-Alder addition and only one product was isolated.



4. The formation of the di-acid very likely proceeds through an acid aldehyde intermediate which undergoes base catalysed epimerisation to the more stable 6β-formyl derivative and on further oxidation to the di-acid.

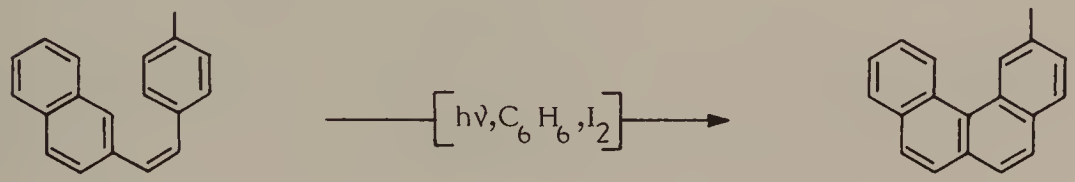


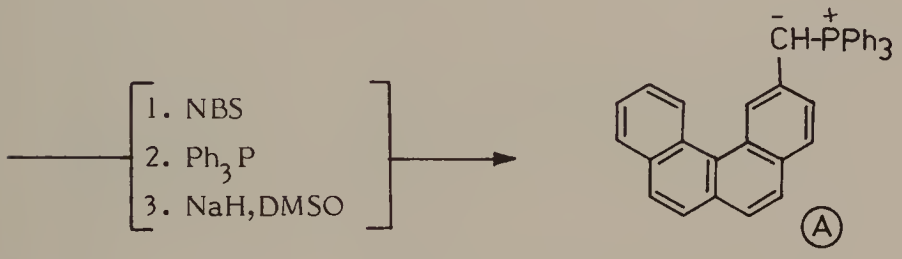
Gibberellic Acid A_3



HELICENES

Successive and appropriate angular attachment of aromatic rings would lead to a helix with every sixth ring starting a new turn and the whole system constituting a chiral π orbital chromophore (1,2). As early as 1956, Newman and Lednicer (3) effected the synthesis and resolution of hexahelicene. Members of this class upto 13 rings, [13]helicene, have been synthesized by photoinduced cyclization of suitable stilbenes (4,5).





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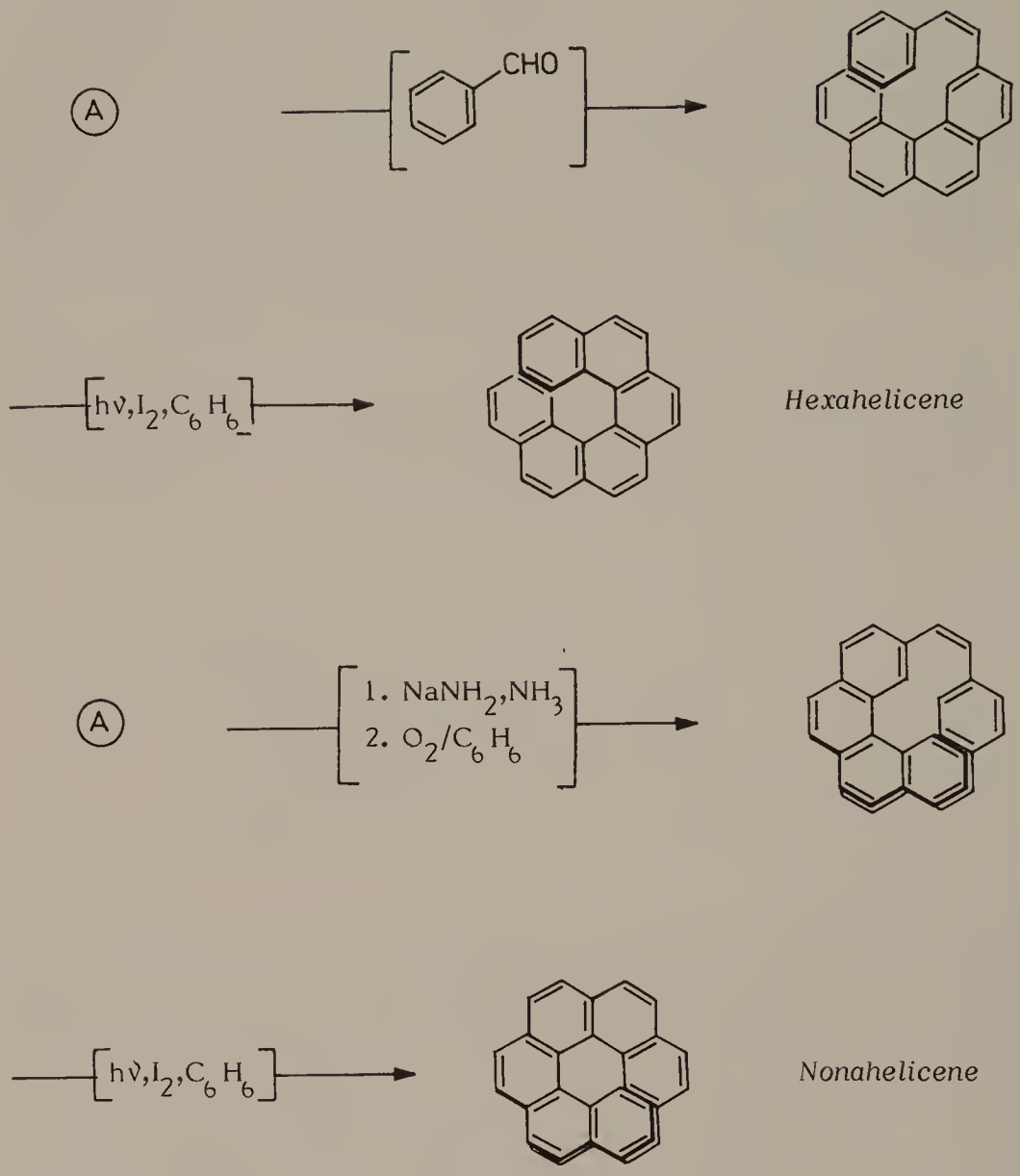
1. The NMR of these molecules show systematic changes in the ring protons as the growing end of the helix overlaps with successive rings of the previous turn; also they undergo spontaneous resolution and nonahelicene has the highest specific rotation (±15000) recorded for an organic compound.

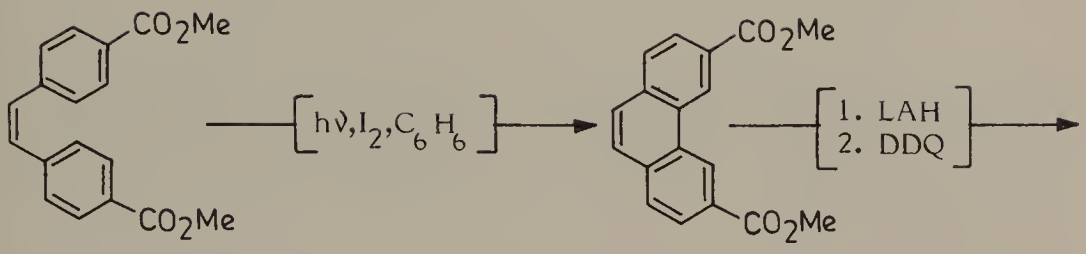
2. There is remarkablly low barrier associated with the racemization of helicenes. For example, for nonahelicene, this barrier is a mere 43.5 kcal mol^{-1}. The low value is attributed to the fact that the necessary molecular deformations are distributed on many bonds of the molecular frame: Meurer,K.P.; Vogtle,F. "Helical Molecules in Organic Chemistry: Topics in Current Chemistry, No.127, Springer-Verlag, 1985, p.1.

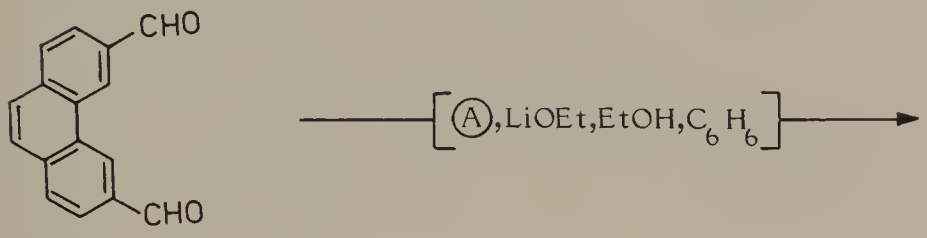
3. Newman,M.S.; Lednicer,D. J. Am. Chem. Soc., 1956, 78, 4765.

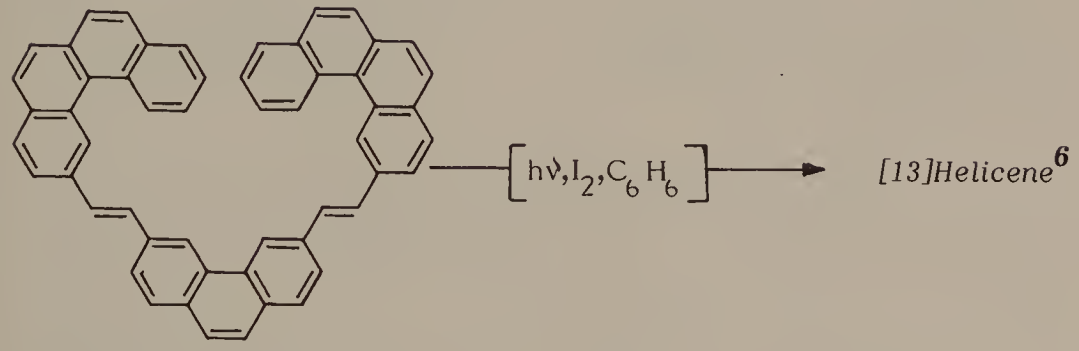
4. Martin,R.H.; Flammang-Barbieux,M.; Cosyn,J.P.; Gelbcke,M. Tetrahedron Lett., 1968, 3507.



5. Similarly, using naphthalene- and anthracene-1-carboxaldehyde, hepta- and octahelicenes have also been prepared.







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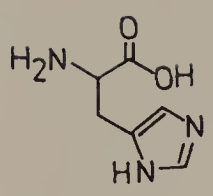
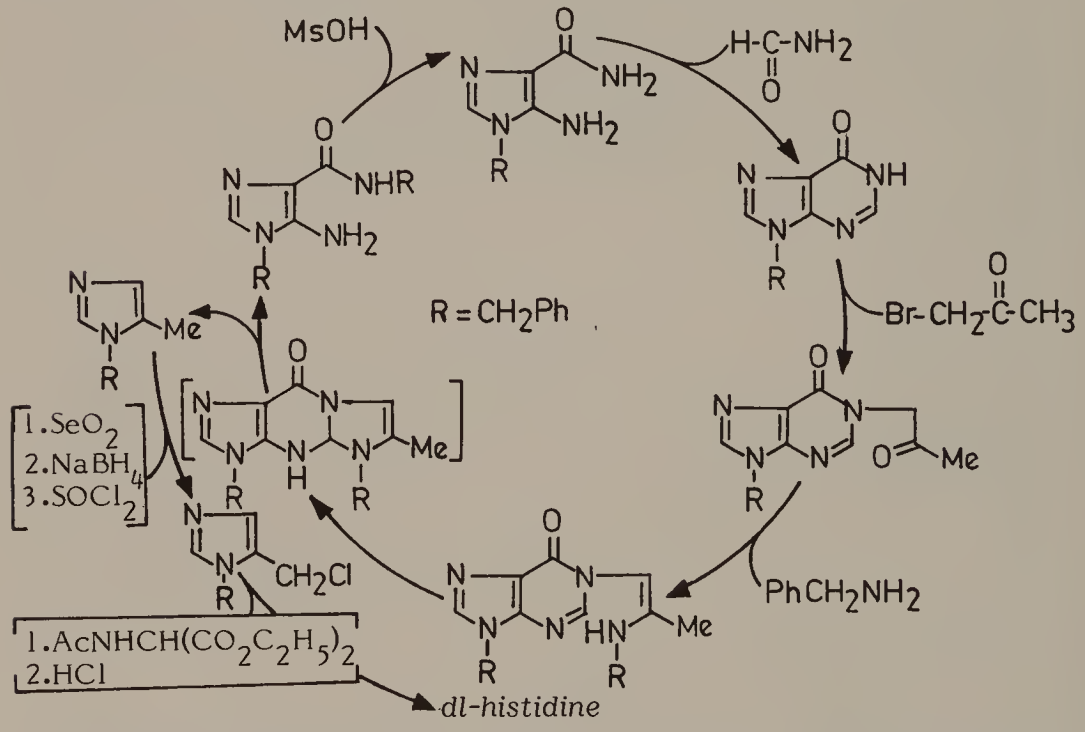
6. Martin,R.H.; Morren,G.; Schurter,J.J. Tetrahedron Lett., 1969, 3683.



HISTIDINE

The successful chemical simulation (1) of the salient features of the ATP-Imidazole cycle which is related to the biosynthesis of histidine, represents an important addition to the art of organic synthesis in the sense that it establishes that cyclic operations, so advantageously deployed by Nature (2), could be carried out in the laboratory for regenerative synthesis. Another facet of this unique cycle is the use of an imidazole parent to generate an imidazole daughter. This endeavour has led to a practical route to 5-substituted imidazoles and offers the prospects of a heterocycle synthesising machine based on template strategy (3).



1. Ranganathan,D.; Farooqui,F.; Bhattacharyya,D.; Mehrotra,S.; Kesavan,K. Tetrahedron, 1986, 42, 4481; Ranganathan,D.; Farooqui,F. Tetrahedron Lett., 1984, 5701; Ranganathan,D; Farooqui,F.; Bhattacharyya,D. Tetrahedron Lett., 1985, 2905.

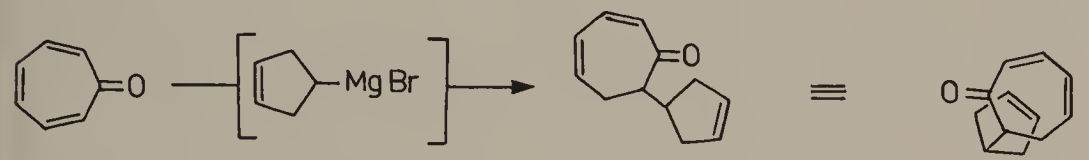
2. Metabolic pathways, vital to the sustenance of life, often proceed by cyclic pathways, as can be exemplified with the Calvin cycle, the Kreb's cycle and the Urea cycle. These pathways, undoubtedly evolved over a number of years, illustrate idyllic organic synthesis, since they represent optimization of resources with respect to yield and versatility.

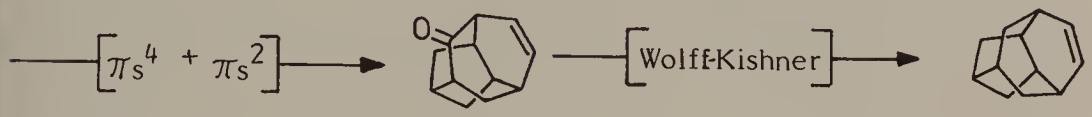
3. Ranganathan,D.; Rathi,R. Tetrahedron Lett., 1986, 2491.

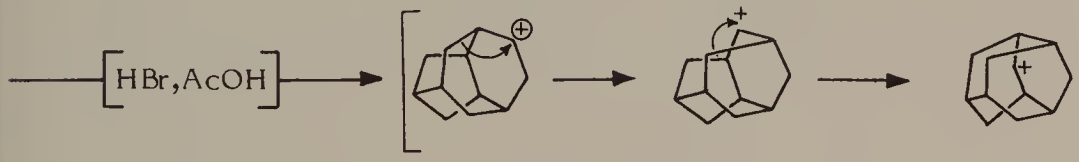
4. Albertson,N.F.; Archer,S. J.Am.Chem.Soc., 1945, 67, 308; Turner,R.A.; Huchner,C.F.; Scholz, C.R. J. Am. Chem. Soc., 1949, 71, 2801.

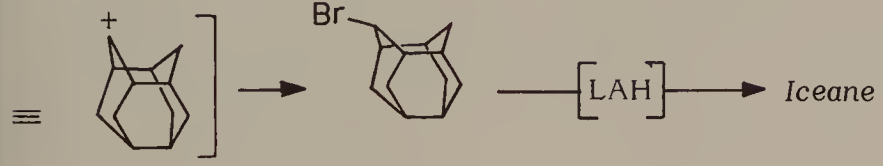
ICEANE

Iceane (tetracyclo [5.3.1.1^{2,6}O^{4,9}]dodecane) the carbon prototype of "ice" can be exhibited in any of the equivalent D_{3h} representations, as shown above. A fascinating intramolecular Diels-Alder reaction followed by a Wagner-Meerwein sequence takes tropone to iceane (1).









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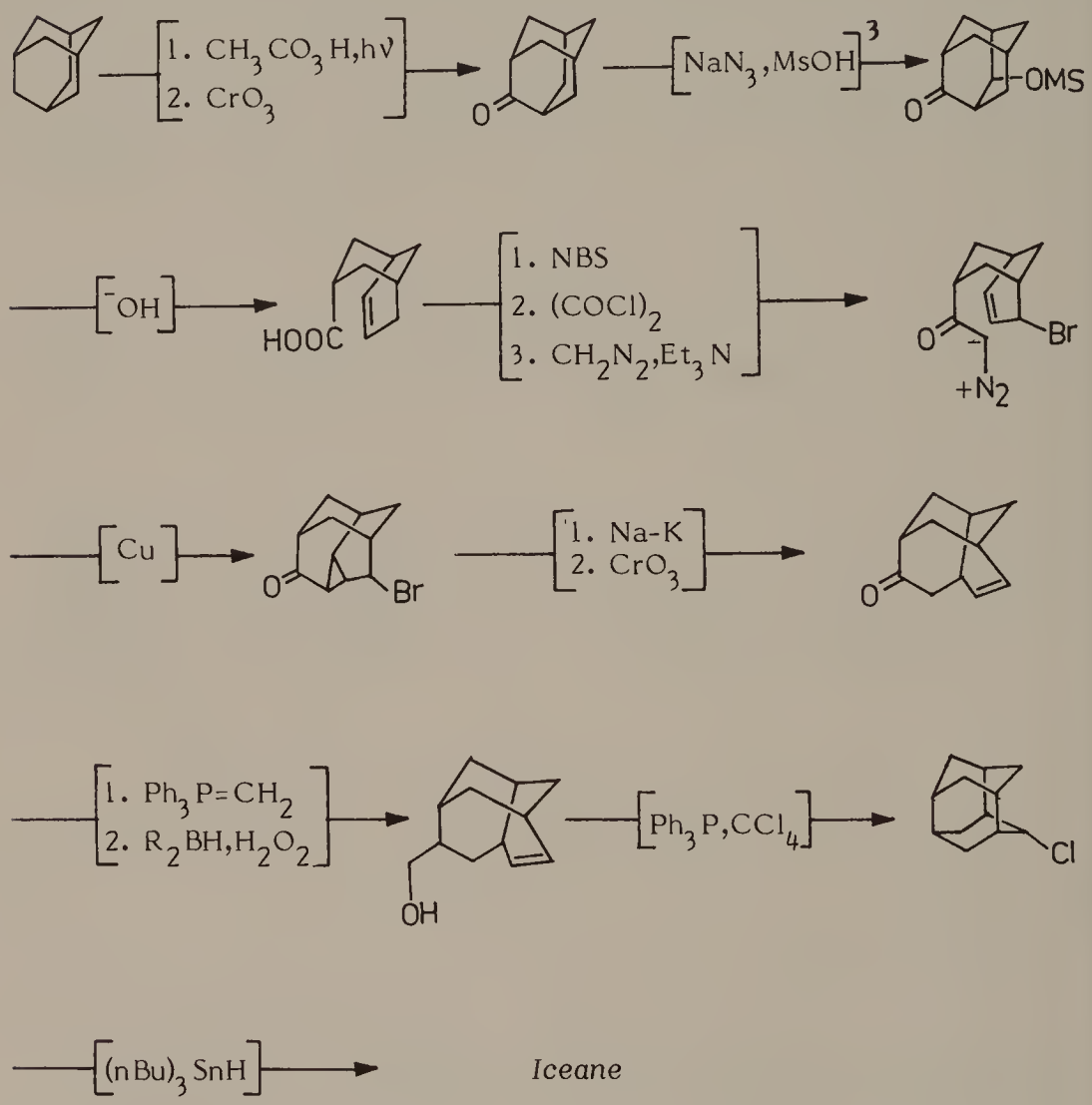
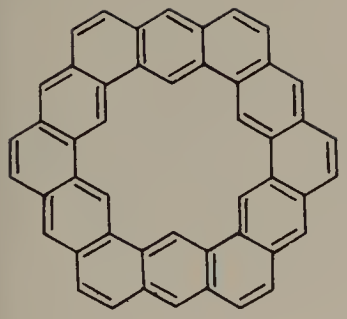
1. Cupas,C.A.; Hodakowski,L. J. Am. Chem. Soc., 1974, 96, 4668.

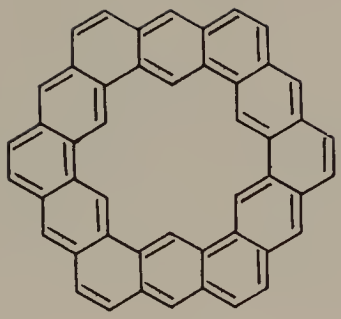
The transformation of adamantane to iceane requires precise regio-insertion of two carbons. This has been achieved in an ingenious manner taking advantage of the best of adamantane re-arrangements (2).



2. Hamon,D.P.G.; Taylor,G.F. Tetrahedron Lett., 1975, 155, 1623.
3. Sasaki,T.; Eguchi,S.; Toru,T. J. Am. Chem. Soc., 1969, 91, 3390.



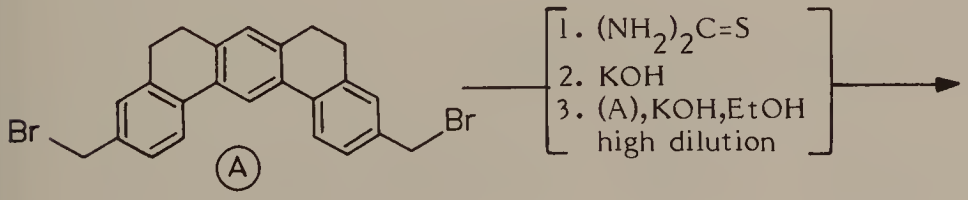
I

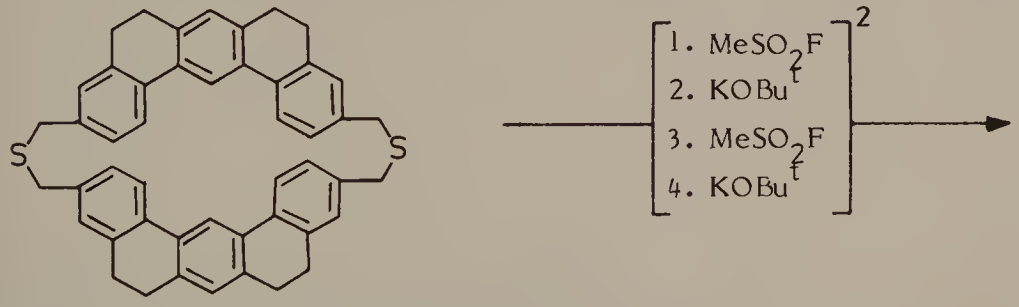


II

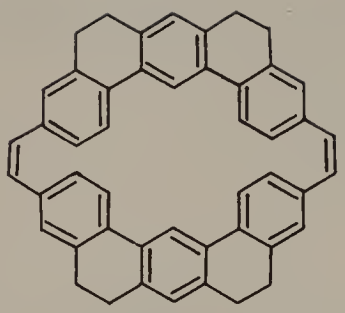
KEKULENE

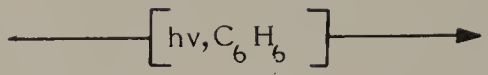
Kekulene was identified as an interesting compound as early as 1965, since it can be either 12 benzene rings sitting in a circle (I) or a split, duplex aromatic system consisting of a 30 annulene at the rim and an 18 annulene at the core, sequestered by 12 spokes. The synthesis of Kekulene was only part of the adventure. The compound did not melt till at least 620°C and was extremely insoluble in all solvents. Thus, one litre of boiling (245°C) 1-methyl-naphthalene dissolved a mere 0.03 g of Kekulene. Consequently the recording of its ^{1}HNMR, needed to distinguish I and II contributions, turned out to be an awesome task. It was accomplished eventually by making 50,000 scans of a saturated (1) solution in 1,3,5-trichlorotrideutero-benzene at 215°C. The observed lack of upfield shift was a vote in favour of I. The synthesis of Kekulene incorporates as a key feature a sulfide mediated union of two symmetrical fragments (1).

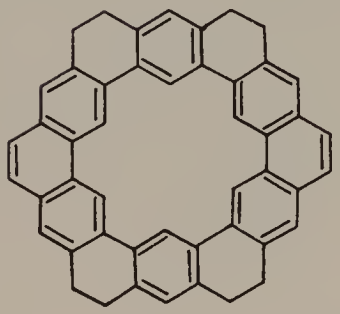


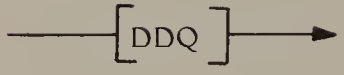


1. Diedrich,F.; Stabb,H.A. Angew. Chem. Int. Ed., 1978, 17, 372.









Kekulene (I)

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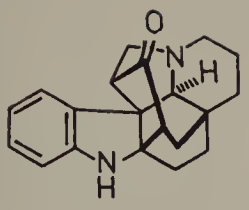
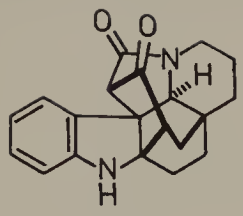
2. The overall transformation takes place as follows:



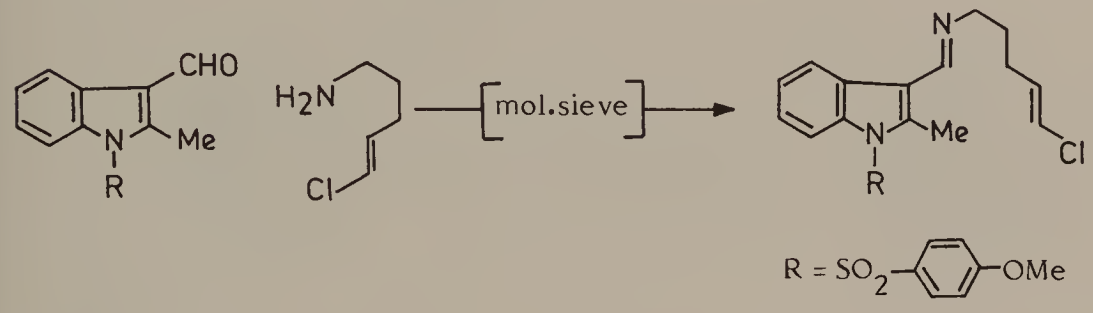
I

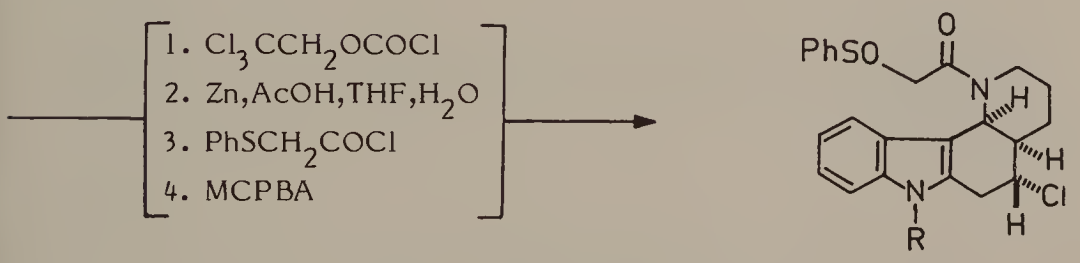


II

KOPSANONE
10,22-DIOXOKOPSANE

The heptacyclic indole alkaloids of the Kopsane class, though isolated as early as 1890 (1), yielded to structural elucidation only in 1960's when the spectroscopic and X-Ray crystallography methods had been greatly refined. The first and the only total synthesis of Kopsanone by Gallagher and Magnus employs two [4+2] cycloaddition reactions to create the extra-ordinarily complex cage-like structure of kopsane alkaloids (2).





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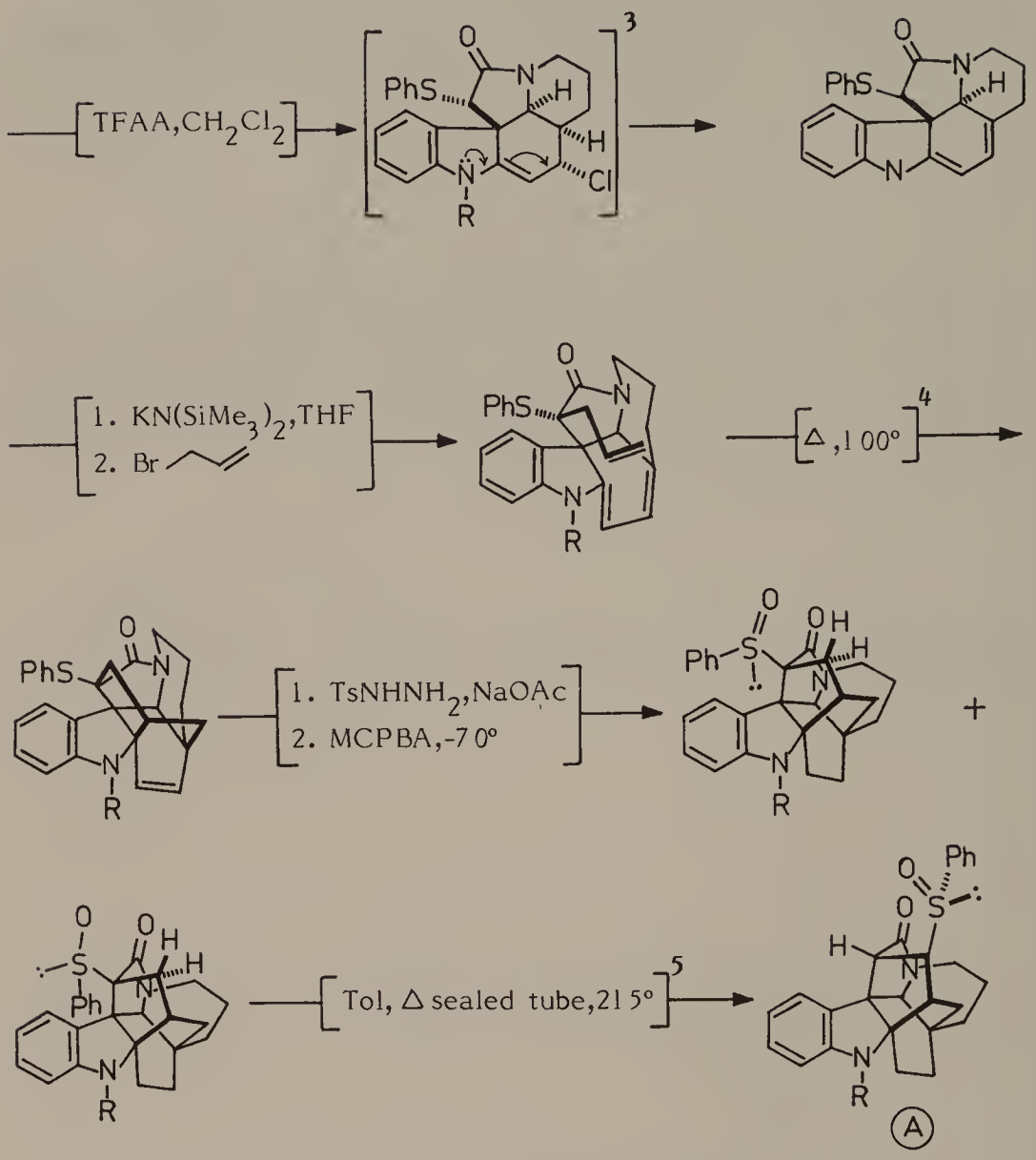
1. Greshoff,M. Ber. Dtsch. Chem. Ges., 1890, 23, 3537.

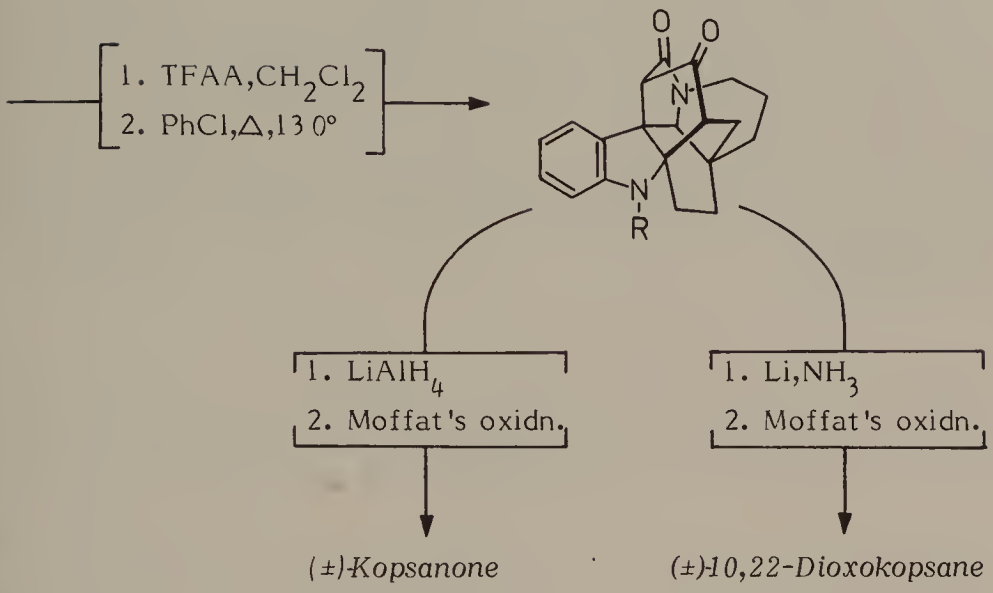
2. Gallagher,T.; Magnus,P. J. Am. Chem. Soc., 1983, 105, 2086; Magnus,P.; Gallagher,T.; Brown,P.; Huffmann,J.C. ibid, 1984, 106, 2105.

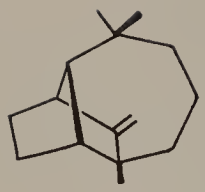


3. The indolic nitrogen is inductively deactivated, but not resonance wise; N is still able to use its lone pair of electrons. X-ray crystallographic pictures have shown that the $SO_2C_6H_4OMe$-p is not in the same plane as either of the adjacent π-systems.

4. The cycloaddition is regiospecific and none of the isomeric fruticosane structure was detected.

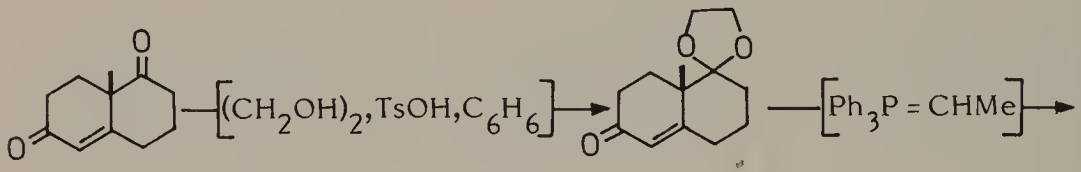
5. Only the sulfoxide (A) could undergo the syn elimination required for the Pummerer rearrangement; unreacted (B) was recovered which could be recycled by reduction and reoxidation to mixture of (A) & (B).

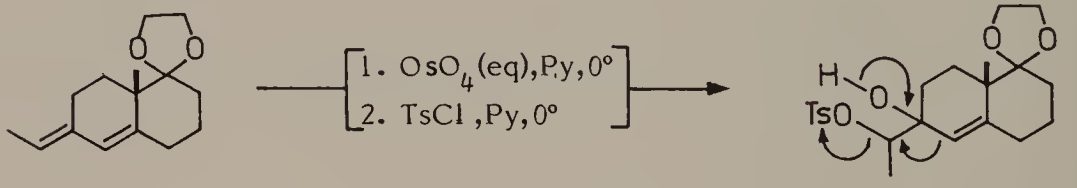

1. TFAA,CH2Cl2
2. PhCl,Δ,130°
O
O
N
N
R
1. LiAlH4
2. Moffat's oxidn.
1. Li,NH3
2. Moffat's oxidn.
(±)-Kopsanone
(±)-10,22-Dioxokopsane

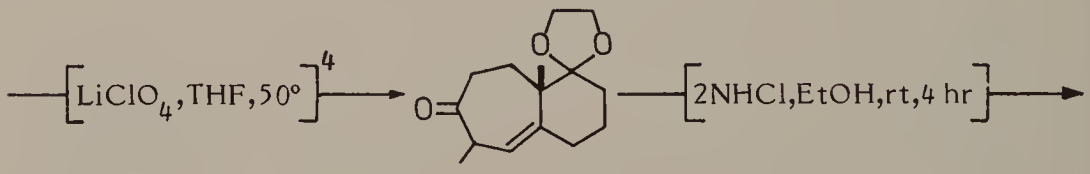


LONGIFOLENE

Longifolene, one of the very few sesquiterpenes being produced commercially in hundred ton quantities, undergoes many "unusual" reactions, which have uncovered much fascinating chemistry (1). Four syntheses, each ingenious in its own right, have been reported for longifolene. The first synthesis by Corey et al (2) involves as a key step a most ingenious intramolecular Michael addition (3), which serves to link together the six and seven membered rings of the bicyclo [5.4.0]undecane Ⓐ.







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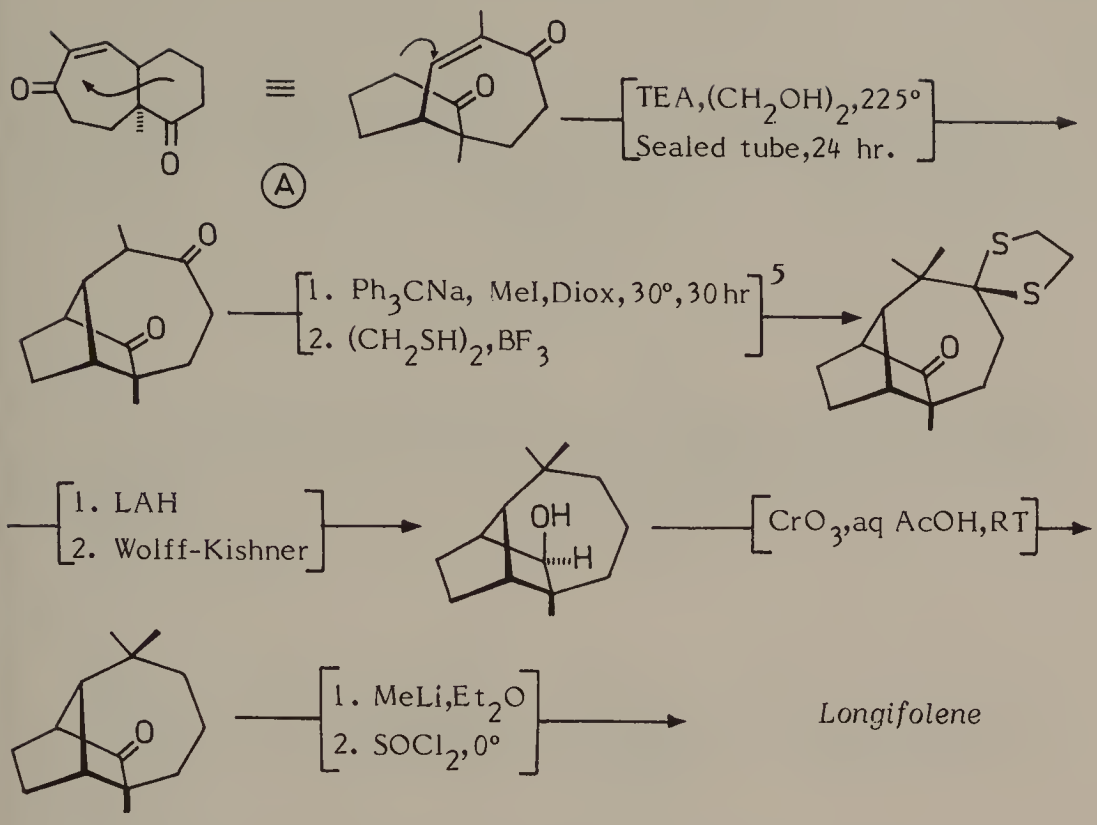
1. Dev,S. Progress in the Chemistry of Organic Natural Products, 1981, 40, 49.

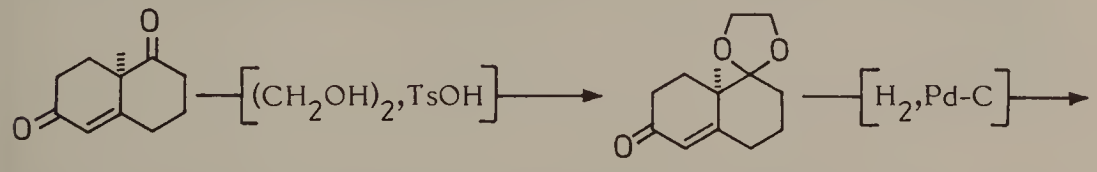
2. Corey,E.J.; Ohno,M.;Vatakencherry,P.A.; Mitra,R.B. J. Am. Chem. Soc., 1961, 83, 1251; 1964, 86, 478.

3. This novel cyclization step perhaps finds analogy in an alkali-induced santonin-santonic acid transformation, cf. Woodward,R.B.; Brutschy,F.J; Baer,H. J. Am. Chem. Soc., 1948, 70, 4216.

4. Pinacol rearrangement of the mono-p-toluenesulfonate can occur in two directions. The observed direction of ring expansion, involving C-1 as the migrating group (π-electron participation), may be anticipated to take precedence over an alternative ring expansion involving C-3 as the migrating group (less favourable alkyl rearrangement).



McMurry and Isser (6) reported a second approach for construction of the intricate carbon-network of longifolene based on the intramolecular alkylation of a bicyclic keto epoxide Ⓐ to the tricyclic compound Ⓑ. The olefin derived by dehydration of tertiary alcohol function in Ⓑ, after a dibromocarbene addition, undergoes silver ion assisted solvolytic ring enlargement to the allylic alcohol Ⓒ. Taking advantage of the potential enone system in Ⓒ, the remaining gem-methyl group has been introduced by a formal conjugate addition involving an unusual reductive process (→D) and fragmentation to generate the dimethylcycloheptane ring of the natural product.



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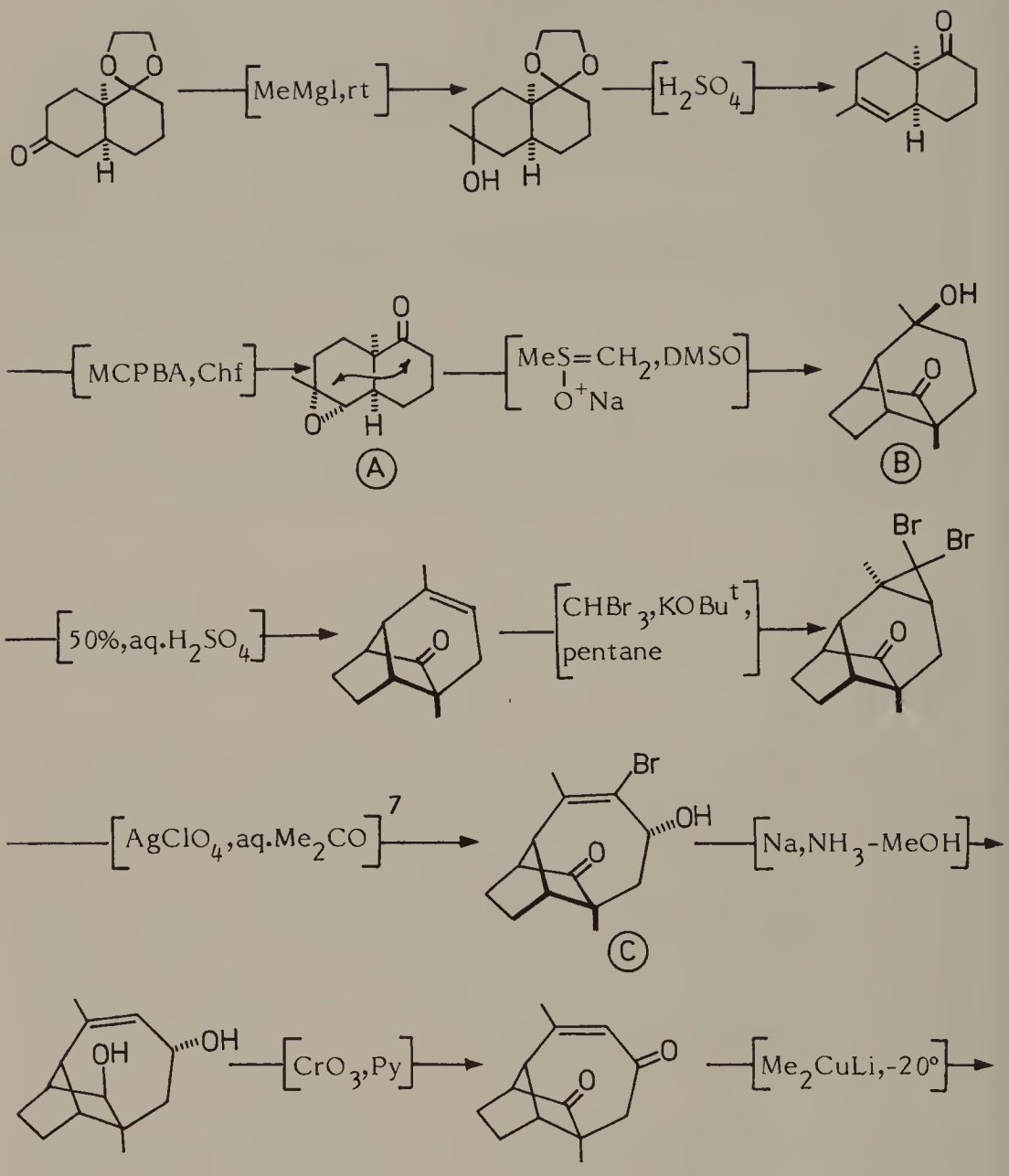
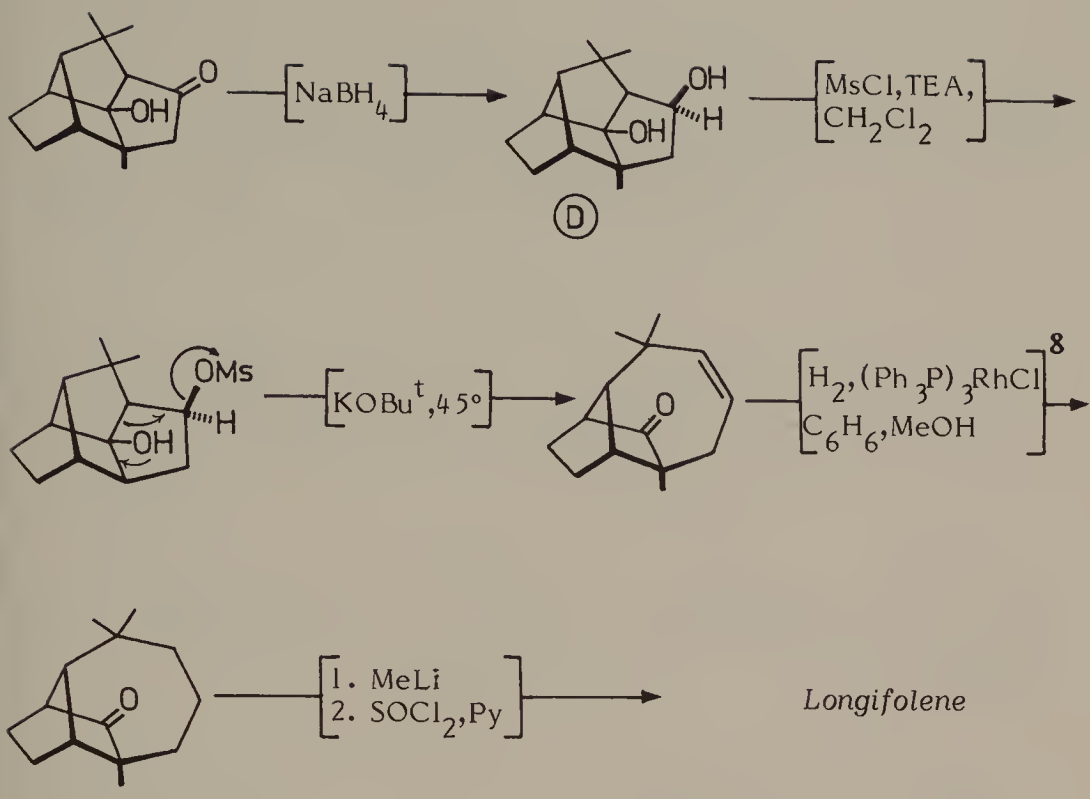
5. Resolution may be accomplished at this stage using L(+)-2,3-butane dithiol.
6. McMurry,J.E.; Isser,S.J. J. Am. Chem. Soc., 1972, 94, 7132.



7. Other methods of ring enlargement proved inadequate. However, the sequence involving addition of a dihalocarbene to an olefin followed by silver ion assisted rearrangement and oxidation proceeded smoothly.



Longicamphenilone

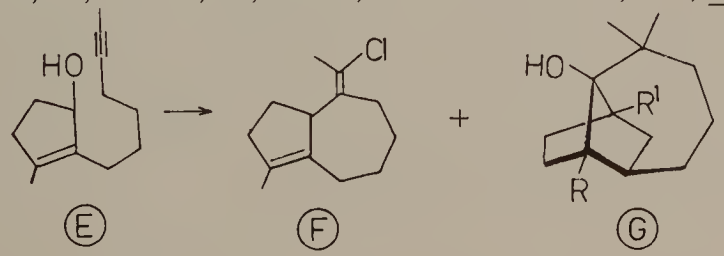
The synthesis by Volkmann, Andrews and Johnson (9) emerged as a result of their studies on Lewis acid catalysed polyolefin cyclisation for steroids. It was observed that in stannic chloride catalysed cyclisation of heptynylmethylcyclopentenol (E) in addition to the expected product (F), the tricyclic product (G) was also formed (10). The structural resemblance to longifolene was obvious, and the reaction refined and exploited for a novel synthesis of longifolene as described below.

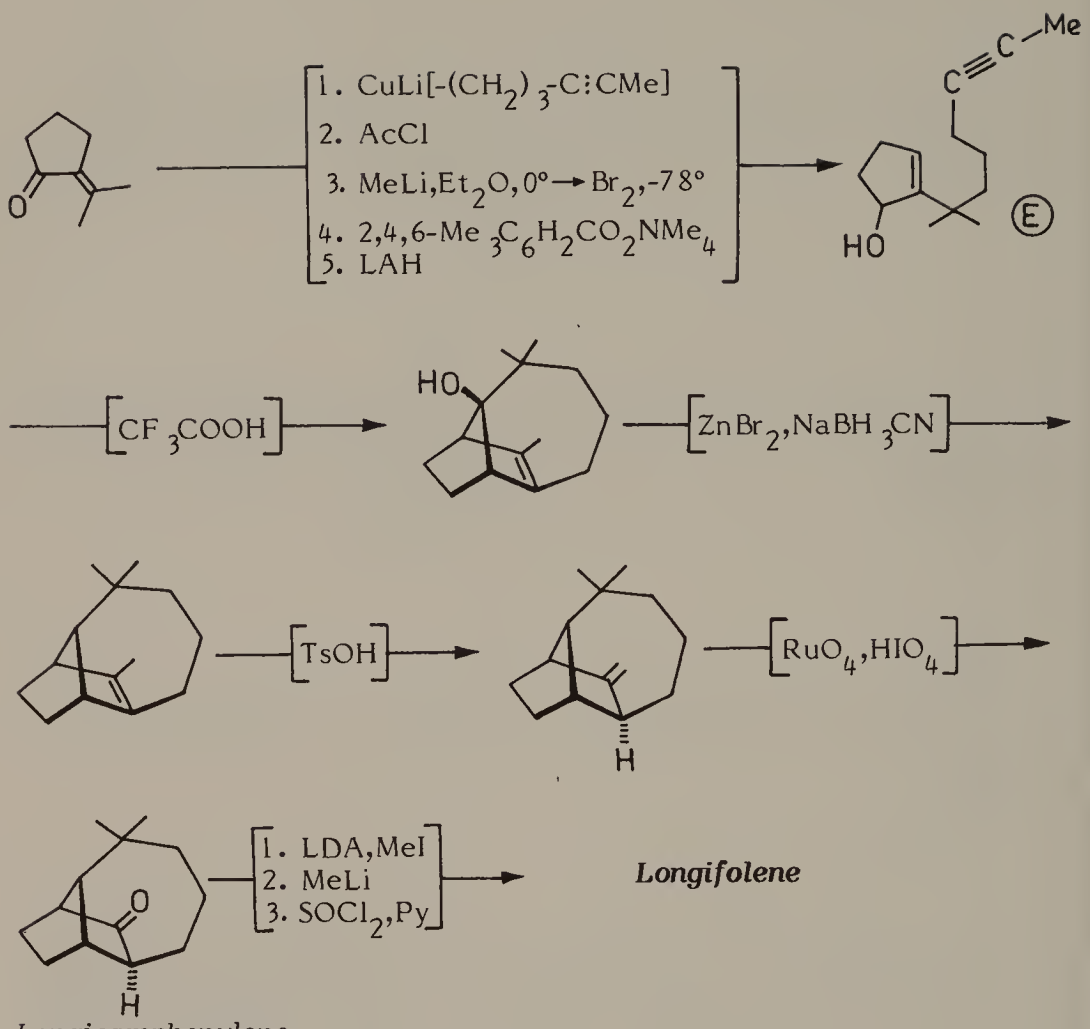
---

8. Wilkinson catalyst: Young,J.F.; Osborn,J.A.; Jardine,F.H.; Wilkinson,G. Chem. Commun. 1965, 131.

9. Volkmann,R.A.; Andrews,G.C.; Johnson,W.S. J.Am. Chem. Soc., 1975, 97, 4777.

10.

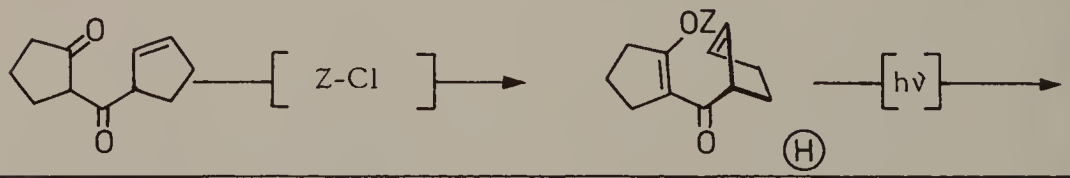




Longifolene

Longicamphenylone

The latest synthesis charted below (11) utilizes an intramolecular photoaddition-retroaldol reaction (H ⟶ I) as the key-step in the construction of the tricarbocyclic frame-work. The resulting diketone (H) could be easily transformed into the known ketone (A) which had been earlier converted into longifolene.



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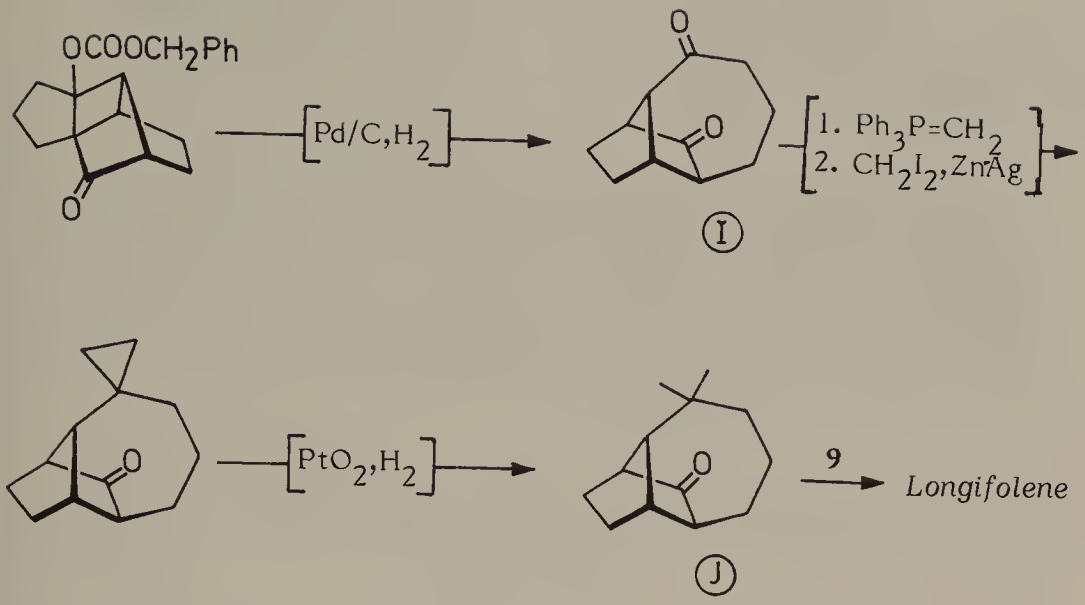
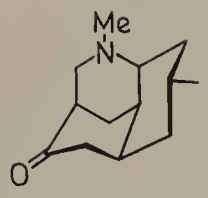
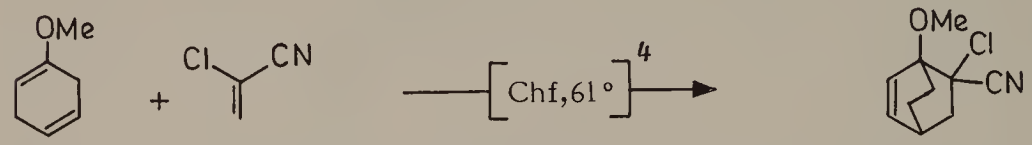
11. Oppolzer,W.; Godel,T. J. Am. Chem. Soc., 1978, 100, 2583.


OCOOCH2Ph
O
[Pd/C,H2]
O
O
1. Ph3P=CH2
2. CH2I2,ZnAg
(I)
O
[PtO2,H2]
O
9
Longifolene
(J)



LUCIDULINE

Luciduline is the simplest of Lycopodium alkaloids (1). In an elegant synthesis of this molecule, Scott and Evans (2) constructed the desired tricyclic skeleton from the key decalin ketoamine (D) by an intramolecular Mannich reaction, C-11 being derived from formaldehyde. The cis-decalin-2,6-dione suitable for construction of (D) was obtained by the oxy-Cope rearrangement (3) of a bicyclo [2.2.2]octene derivative (A) which allowed controlled introduction of the desired sites of asymmetry.



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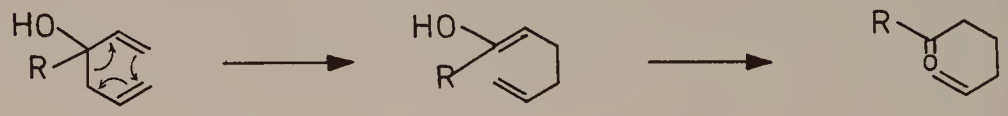
1. Reviews: Blumenkopf, T.A., Heathcock, C.H. in "Chemical and Biological Perspectives, vol.3", Ed., Pelletier, S.W., Wiley, New York, 1985, p.185; Inubushi, Y., Harayama, T. Heterocycles, 1981, 15, 611; Stevens in "The Total Synthesis of Natural Products, vol.3" Ed., ApSimon, J., Wiley, New York, 1977, p.489; Wiesner, K., Fortschr. Chem. Org. Naturstoffe, 1962, 20, 271.

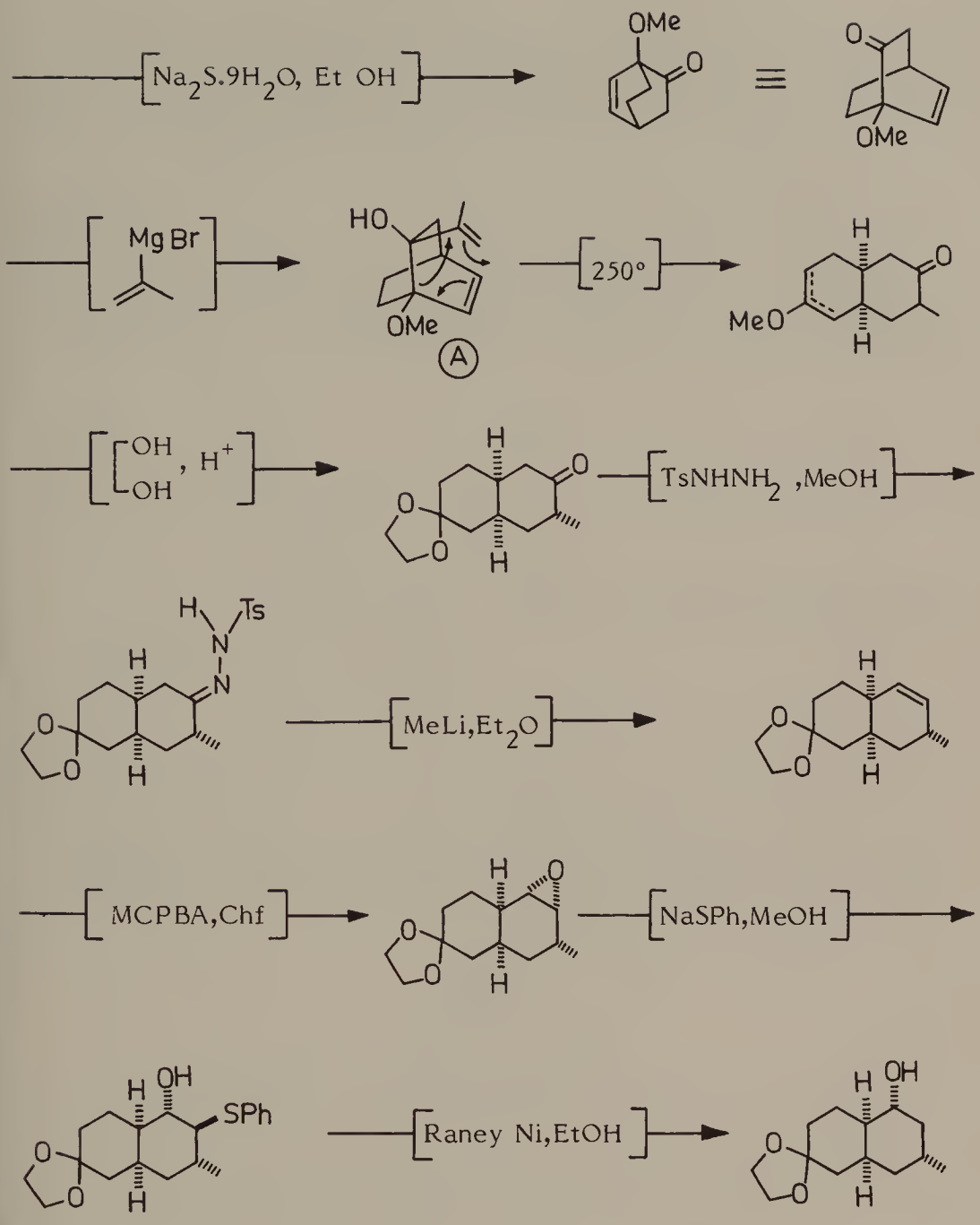
2. Scott, W.L., Evans, D.A. J. Amer. Chem. Soc., 1972, 94, 4779.

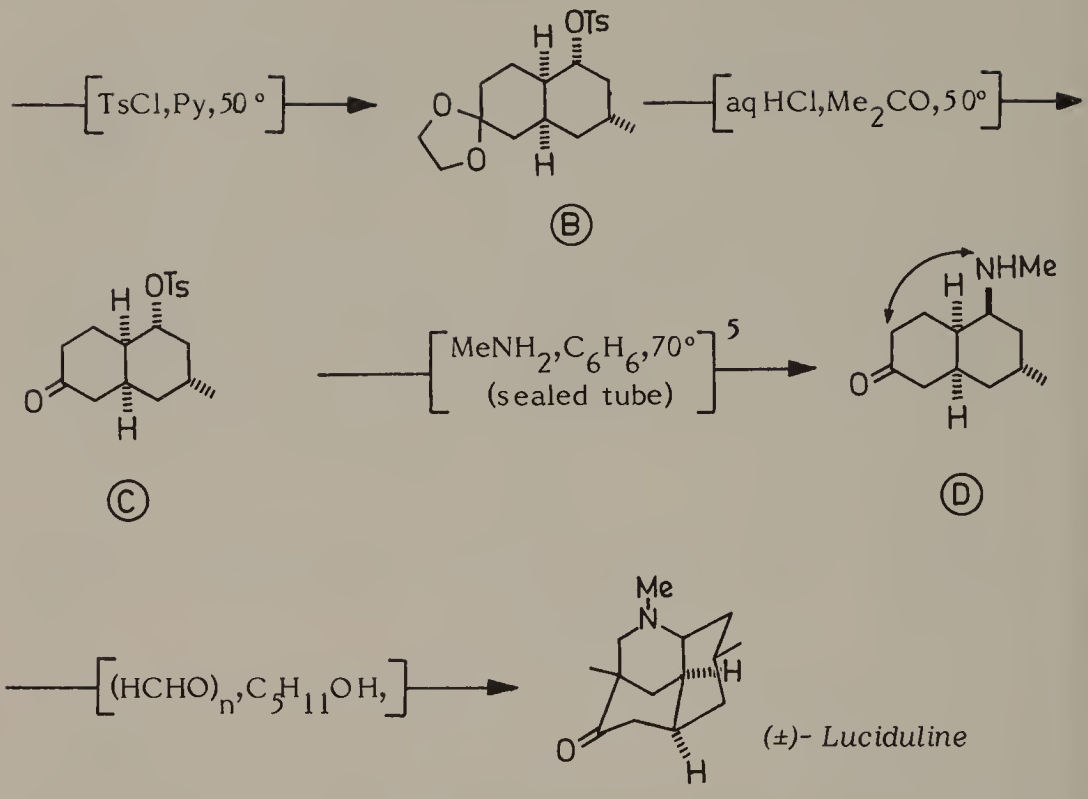
3. The oxy-Cope rearrangement involves thermal isomerization of 3-hydroxy-1,5-hexadienes (i) to enols (ii), leading to the synthesis of carbonyl compounds [Berson, J.A., Jones, M.Jr. Amer. Chem. Soc., 1964, 86, 5019; Berson, J.A., Walsh, E.J. 1968, 90, 4729]. For extension of this method to preparation of oxygenated cis-decalin carbocycles see, Evans, D.A., Scott, W.L., Truesdale, L.K. Tetrahedron Lett., 1972, 137.



(i) (ii)

4. Chloroacrylonitrile serves as a useful ketene equivalent in the Diels-Alder reaction, Freeman, P.K., Balls, D.M., Brown, D.J. J. Org. Chem., 1968, 33, 2211; Evans, D.A., Scott, W.L., Truesdale, L.K. Tetrahedron Lett., 1972, 121. Ranganathan,S.D.; Ranganathan,D.; Mehrotra,A.K. Synthesis, 1977, 289.


Na2S.9H2O, Et OH
OMe
O
OMe
Mg Br
HO
OMe
A
250°
MeO
H
O
OH
OH
, H+
TsNHNH2 ,MeOH
Ts
N
MeLi,Et2O
MCPBA,Chf
NaSPh,MeOH
SPh
Raney Ni,EtOH



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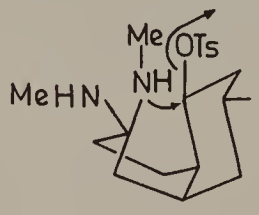
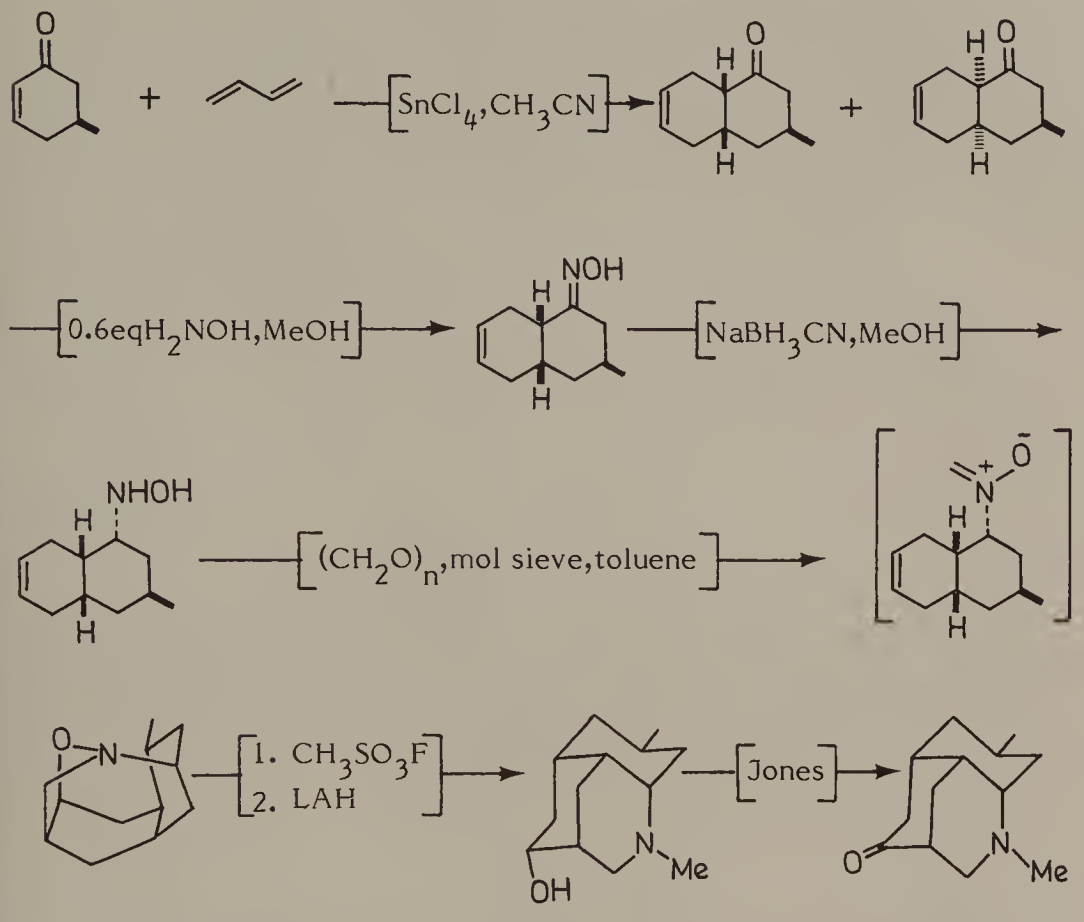
5. Smooth introduction of the N-methylamine moiety at C-6 by tosylate displacement was prevented by the sterically congested concave face of the cis decalyl system which promoted elimination in addition to substitution. However, this displacement could be smoothly effected in the ketone (C), probably through intermediacy of the aminal (i), by intramolecular delivery of nitrogen.



(i)

In the second synthesis of luciduline Oppolzer and Petrzilka (6) utilize an intramolecular 1,3-dipolar cycloaddition as the key step to assemble the heterocyclic ring and to introduce the oxygen functionality into the molecule.



Luciduline

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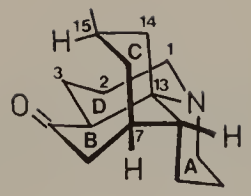
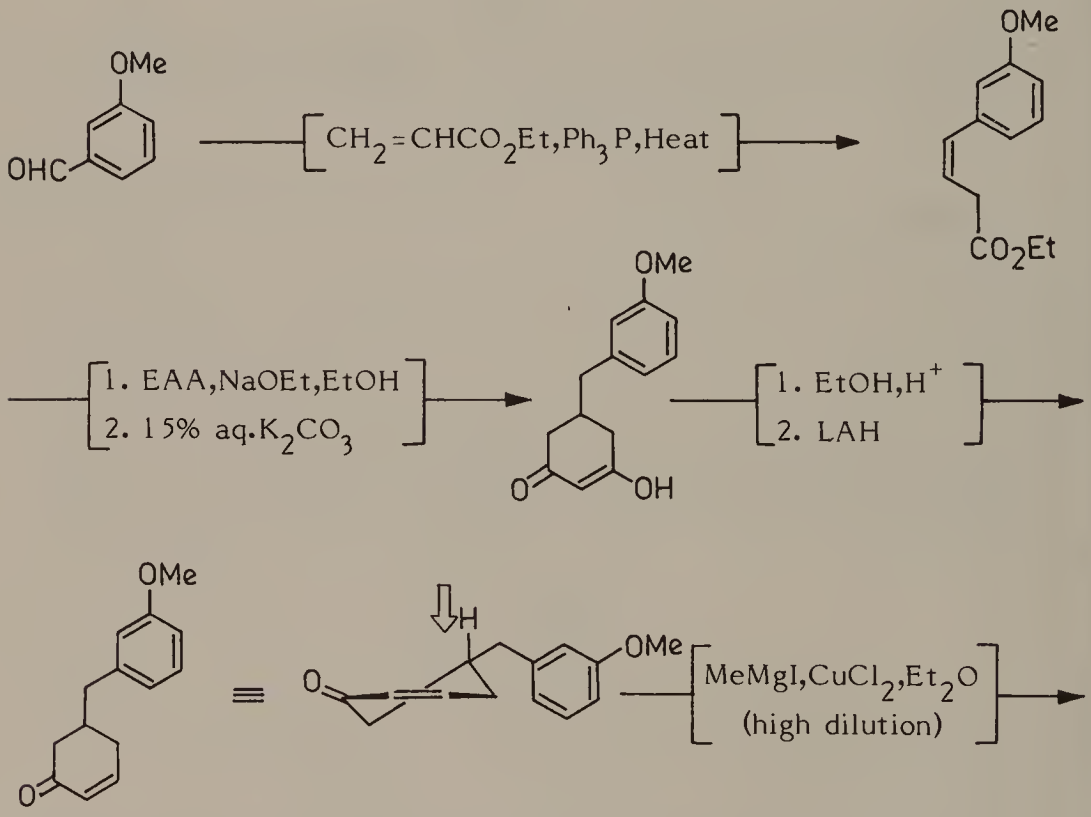
6. Oppolzer, W., Petrzilka, M. J. Amer. Chem. Soc., 1976, 98, 6722.

7. For a synthesis of luciduline patterned after the biosynthesis of Lycopodium alkaloids see, Szychowski, J., Maclean, D.B. Canad. J. Chem., 1979, 57, 1631.



LYCOPODINE

Lycopodine is characterized by the hexahydro-julolidine system (1). A number of ingenious approaches to the synthesis of lycopodine alkaloids have been reported(2).The synthesis devised by Stork and his colleagues (3), outlined below, involves an intramolecular electrophilic cyclization of the quinolone Ⓐ to give a lycodine type structure Ⓑ incorporating rings A, B and C of lycopodine. Material for construction of ring Ⓓ of lycopodine has been obtained by dismembering the aromatic ring in Ⓑ.



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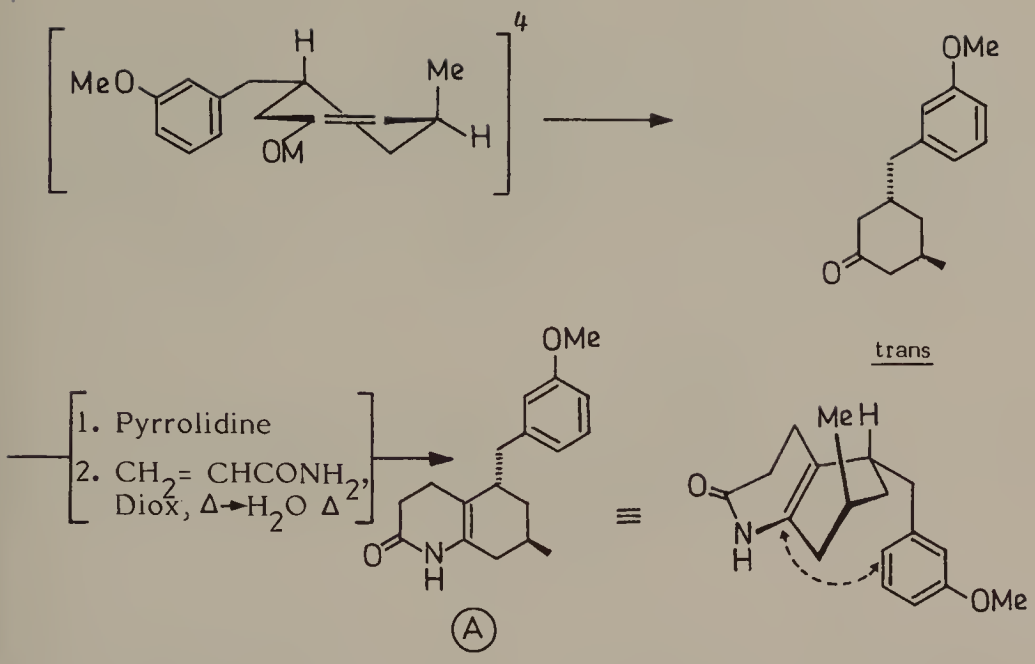
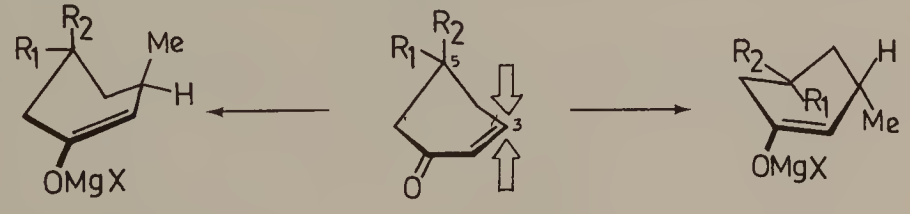
1. Review: Wiesner,K. Fortschr. Chem. Org. Naturstoffe, 1962, 20, 271.
2. For one of the earlier synthesis see: Ayer,W.A.; Rowman,W.R.; Joseph,T.C.; Smith,P. J. Am. Chem. Soc., 1968, 90, 1650.
3. Stork,G.; Kretchmer,R.A.; Schlessinger,R.H. J. Am. Chem. Soc., 1968, 90, 1647; Stork,G. Pure Appl. Chem., 1968, 17, 383.



---

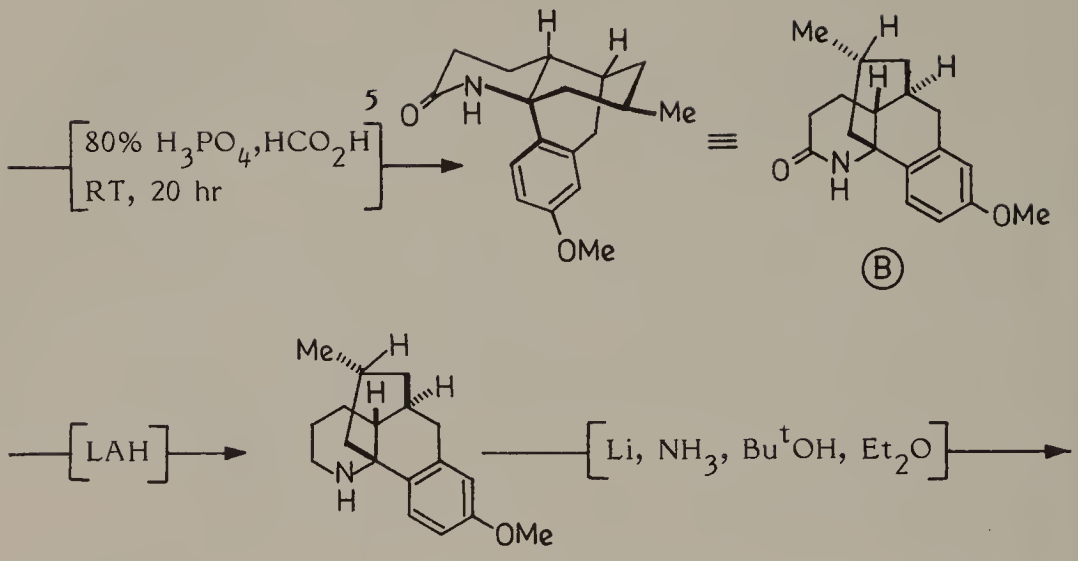
4. The 1,4-type Michael addition to the α,β-unsaturated ketone occurs in a transition state in which the incoming nucleophile approaches C-3 orthogonal to the plane of the double bond. There are thus four possible transition states which can lead to two different products, cis and trans, and the stereochemical outcome of the reaction is dictated by the relative energies of these transition states. The trans product results from a half-chair transition state in which the nucleophile approaches C-3 avoiding steric interference with the existing substituent on C-5. For a detailed analysis of a kinetically controlled Michael addition in an analogous case, see Allinger, N.L., Riew, C.K. Tetrahedron Letters, 1966, 1269.



half-chair half-boat

trans .. .. R_1 = $ArCH_2$, R_2 = H .. .. cis

cis .. .. R_1 = H, R_2 = $ArCH_2$ .. .. trans



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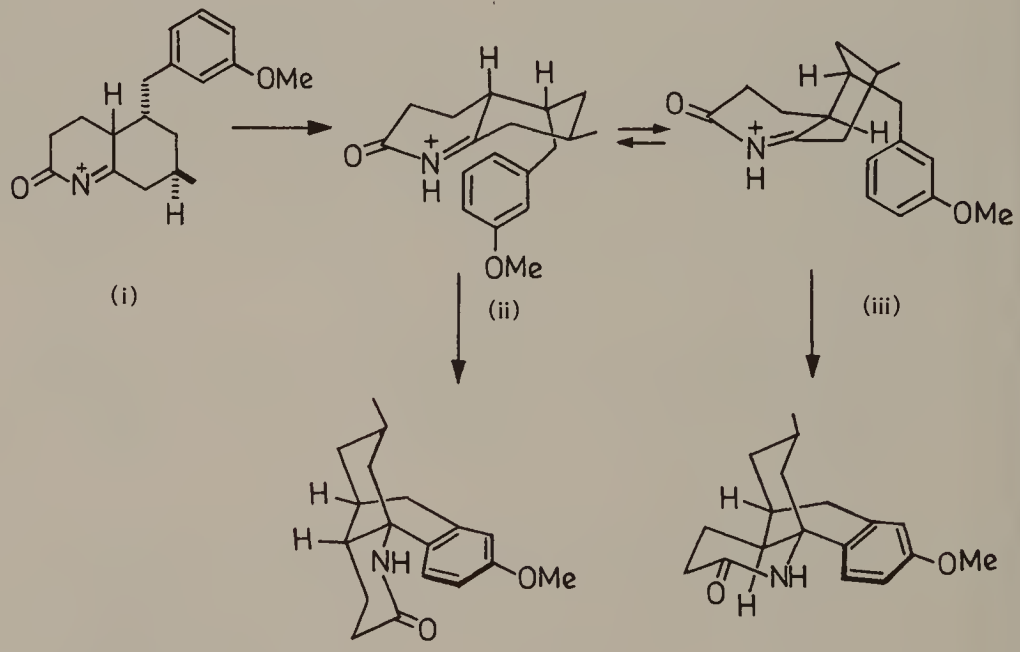
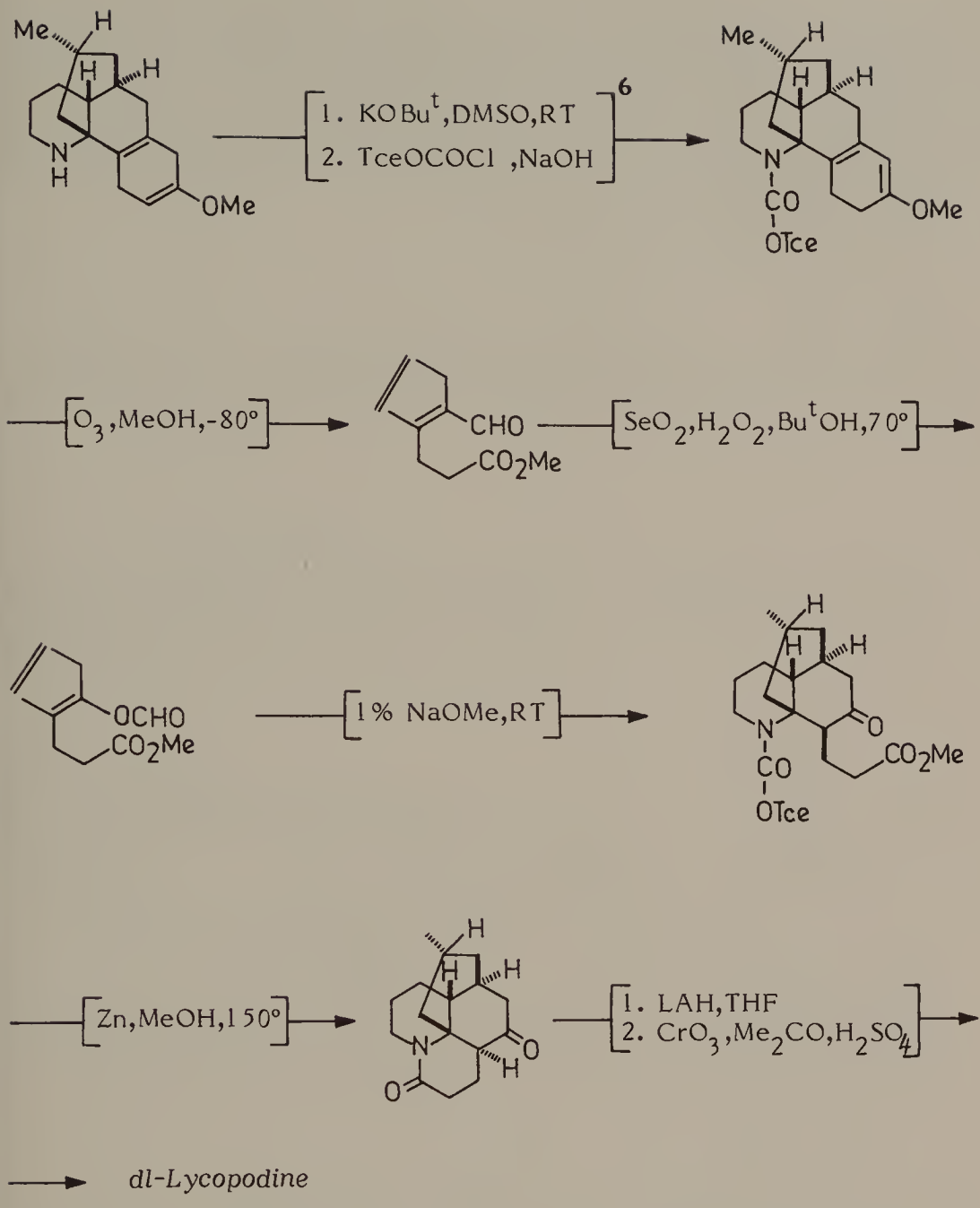
5. Protonation of the enamide double bond gives an acylimonium cation (i) which is involved in the crucial cyclization step. Generation of the desired stereochemistry at C-12 is due to the fact that of the two possible imonium ions (ii) and (iii), which could lead to the tetracyclic system, (iii) is not favoured because it involves ring B in a strained, boat-like configuration.





→ *dl-Lycopodine*

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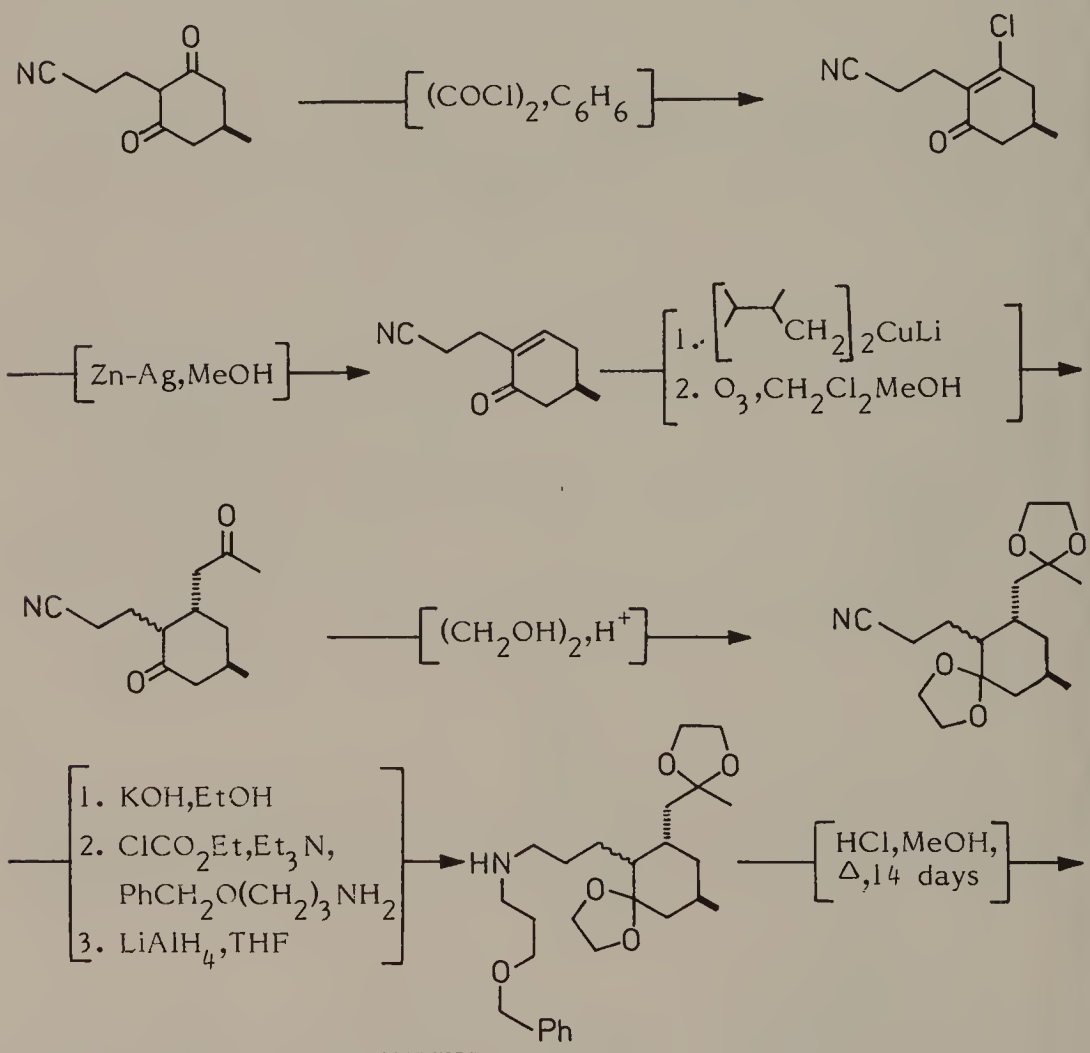
6. cf.Windholz,T.B.; Johnston,D.B.R. Tetrahedron Lett., 1967, 2555.

The synthesis of tetracyclic Lycopodium alkaloids by Heathcock, Kleinman and Binkley (7a) at **Berkeley** employs an intramolecular stereoselective Mannich cyclisation for construction of the A-B-C ring framework with the correct stereochemistry. Two versions of the **Berkeley** synthesis were subsequently developed, involving closure of ring-D bonds onto (a) the nitrogen, and (b) the C5-carbonyl by intramolecular alkylation (7b-d).

(a) The First Berkeley Synthesis:



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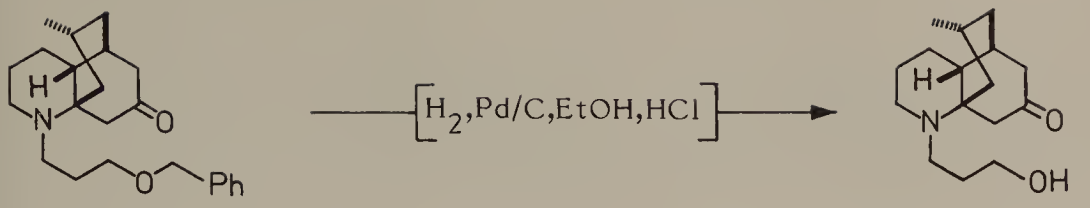
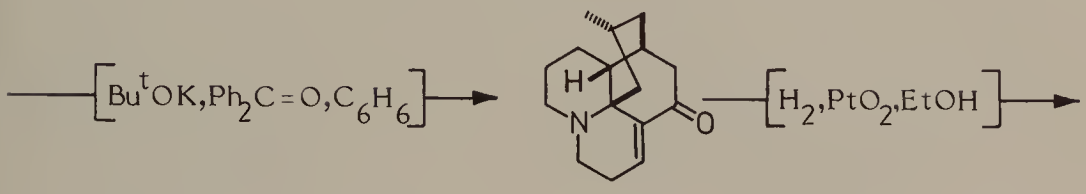
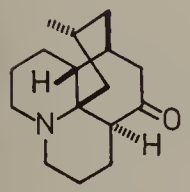
7. (a) Heathcock,C.H.; Kleinman,E.; Binkley,E.S. J. Am. Chem. Soc., 1978, 100, 8036; (b) Kleinman,E.; Heathcock,C.H. Tetrahedron Lett., 1979, 4125; (c) Heathcock,C.H.; Kleinman,E.F. J. Am. Chem. Soc., 1981, 103, 222; (d) Heathcock,C.H.; Kleinman,E.F.; Binkley,E.S. J. Am. Chem. Soc., 1982, 104, 1054.

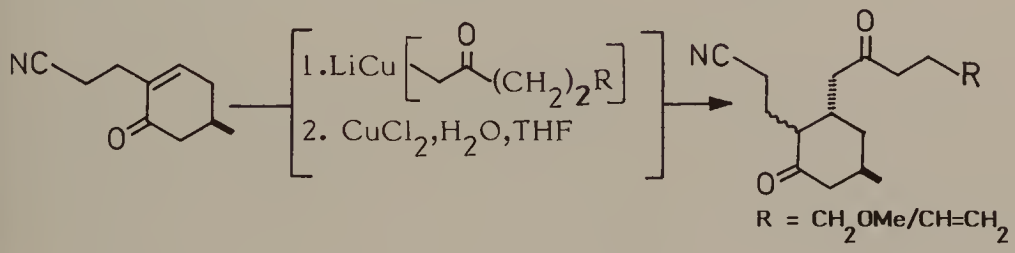


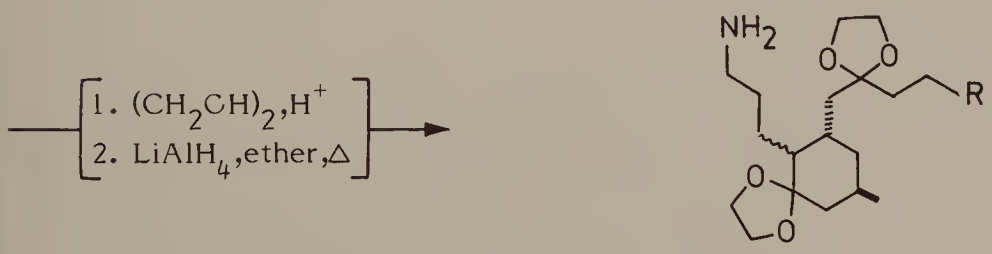


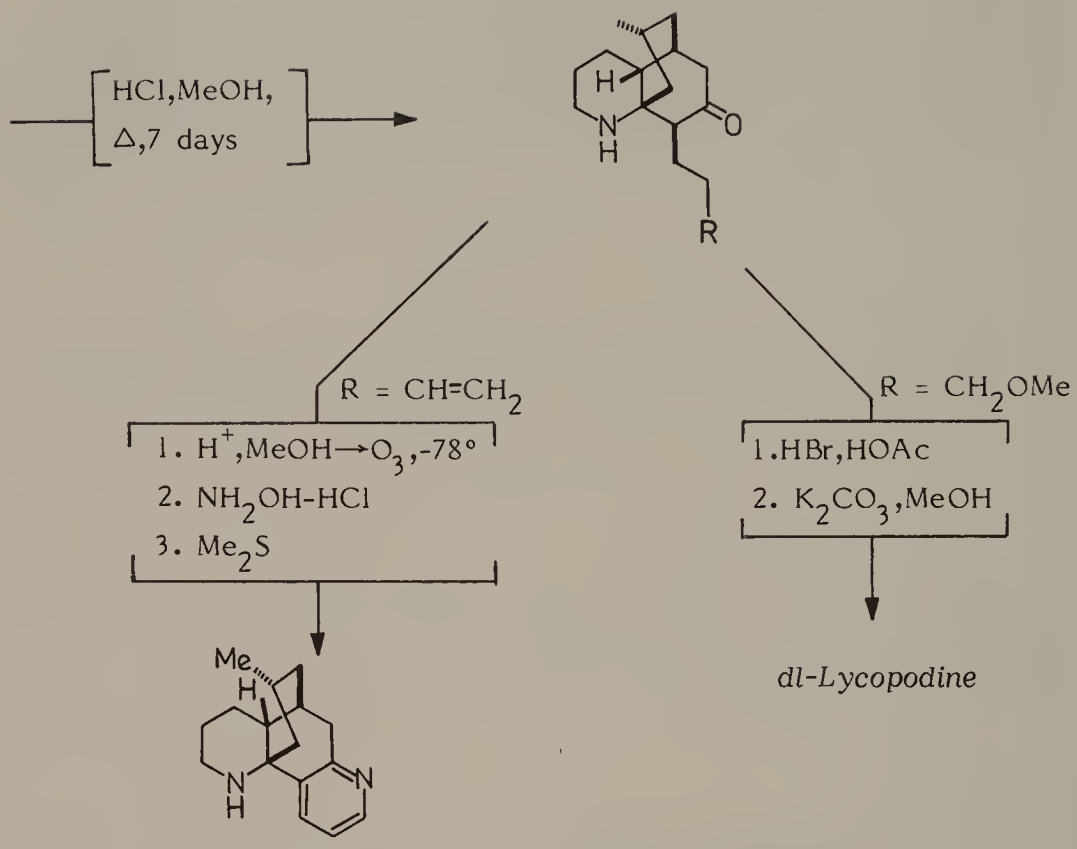


dl-Lycopodine

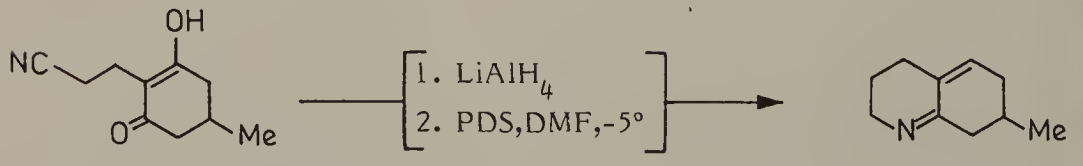
(b) The Second Berkeley Synthesis



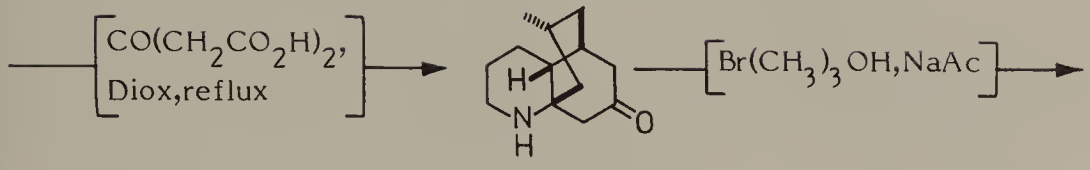


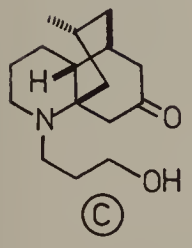


Schumann et al. (8) have described a four step synthesis of the Heathcock tricyclic ketone (C) from 2-cyanoethyl-5-methyl-1,3-cyclohexanedione, as used by Heathcock et al. (7) but following a very different strategy, which involves as an important step a stereoselective 1,3-annulation reaction of the intermediate unsaturated imine with acetone dicarboxylic acid.

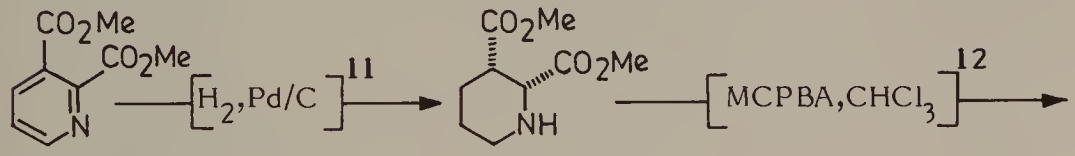


8. Schumann,D.; Muller,Hans-Jurgen; Naumann,A. Liebig Ann. Chem., 1982, 1700.

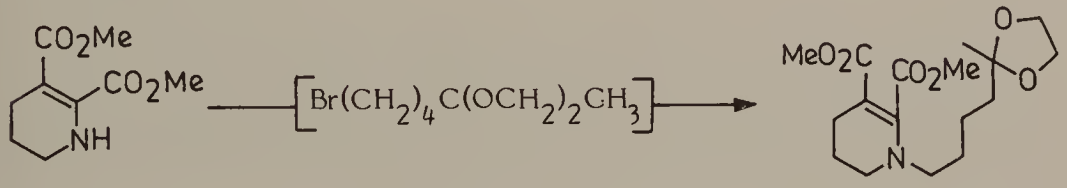




Wenkert, following his general approach to alkaloid synthesis based on partial hydrogenation of N-alkyl salts of 5-acylpyridines and acid-catalysed cyclisation of the resultant 1-alkyl-3-acyl-2-piperidines (9), has developed a new approach to the synthesis of hydrojulolidine based alkaloids including lycopodine (10); the key julolidine ring skeleton was assembled in a few steps from dimethylquinolinate. (11,12).



dimethyl quinolinate



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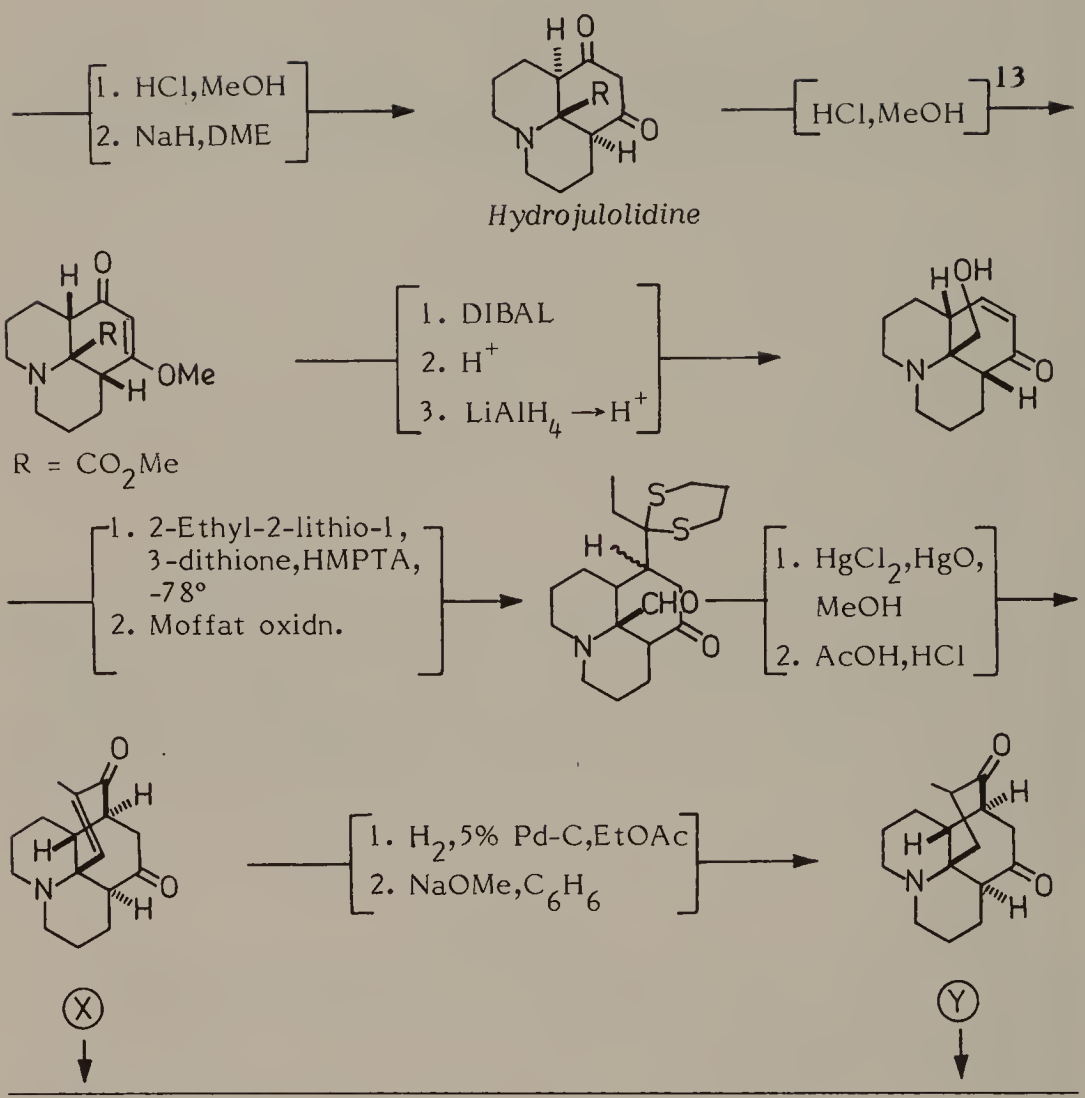
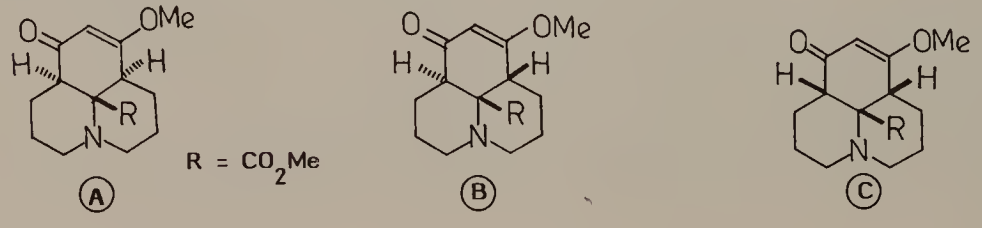
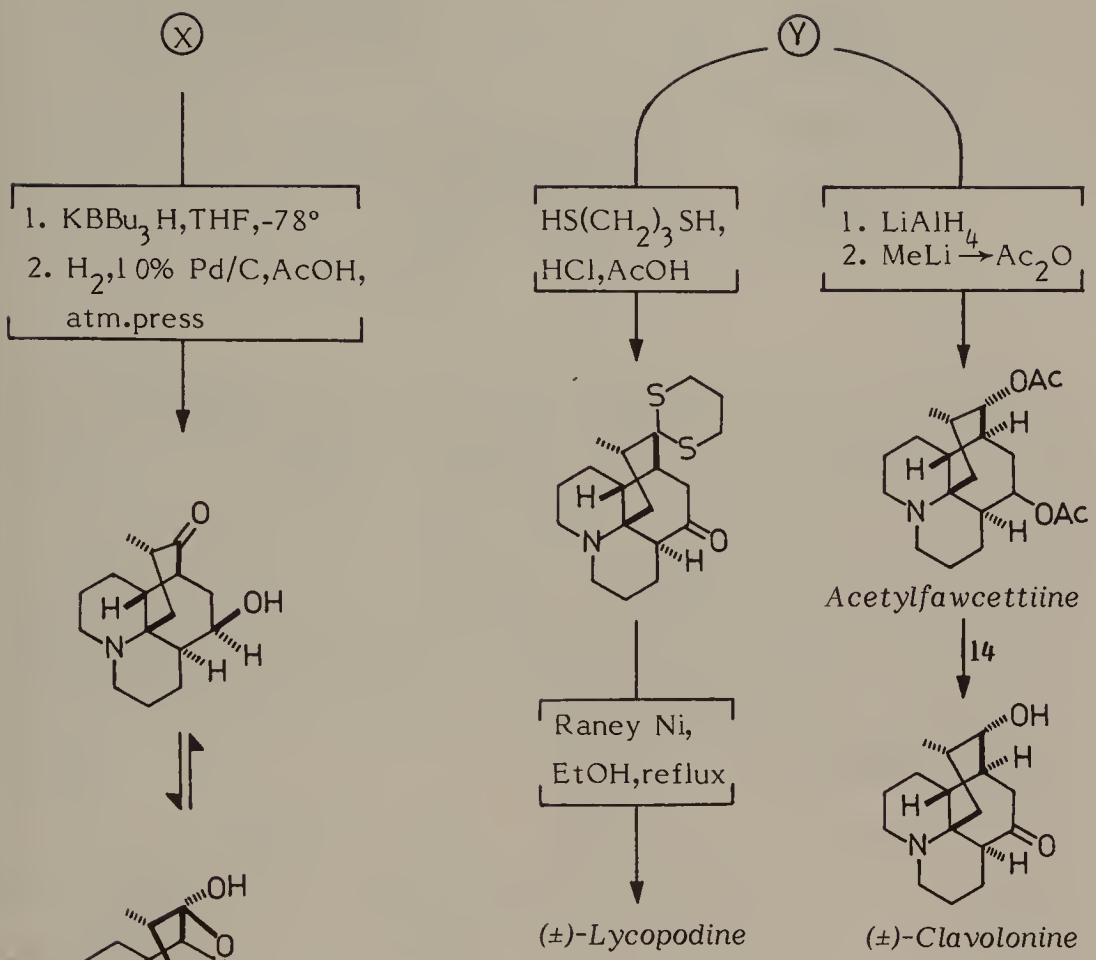
9. Wenkert,E. Accounts Chem. Res., 1968, 1, 78.
10. Wenkert,E.; Broka,C.A. J. Chem. Soc. Chem. Commun., 1984, 714.
11. Wenkert,E.; Reynolds,G.D. Aust. J. Chem., 1969, 22, 1325.
12. Wenkert,E.; Chauncy,B.; Wentland,S.H. Synth. Comm., 1973, 3, 73.



13. Treatment of diketo ester with CH_2N_2 yielded the trans enol ether (A) while exposure to methanolic HCl produced a mixture of isomers (A), (B) & (C) in a ratio of a 1:13:5, which were separated by column chromatography; this was the thermodynamic product mixture since treatment of isomer (E) with MeOH-HCl produced a mixture with same isomer ratio; the structures were assigned on the basis of ^{13}C-nmr spectroscopy. Wenkert,E. et al., J. Am. Chem. Soc., 1973, 95, 8427.





Annofoline

(±)-Lycopodine

Acetylfawcettiine

(±)-Clavolonine

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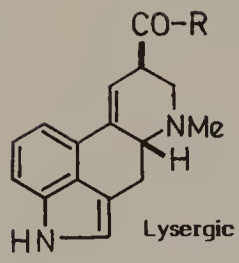
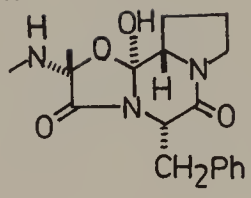
14. Nakashima,T.T.; Singer,P.P.; Brown,L.M.; Ayer,W.A. Can. J. Chem., 1975, 53, 1936.



Lysergic acid, R = OH

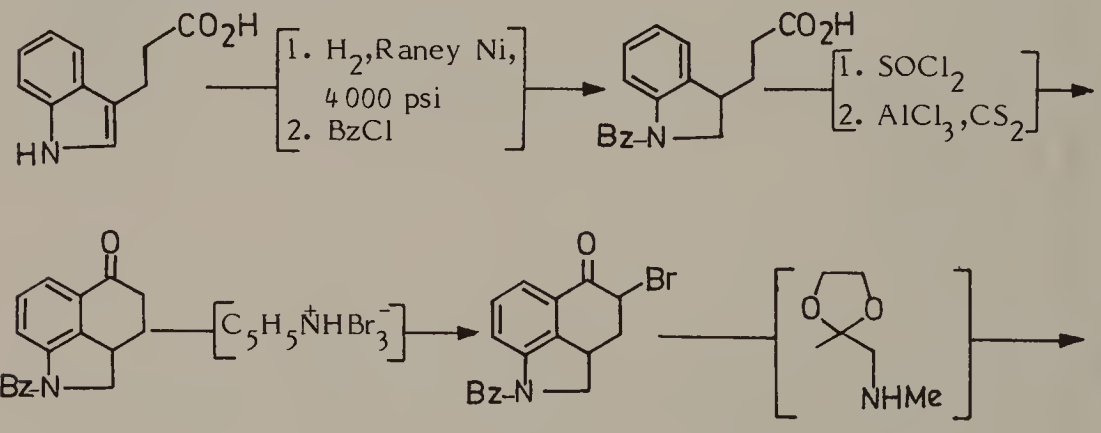
Ergotamine, R =



LYSERGIC ACID
ERGOTAMINE

Lysergic and isolysergic acids are the main alkaline hydrolysis products of the ergot alkaloids. Lysergic acid derivatives show a fascinating spectrum of pharmacodynamic actions. Five synthesis have been reported for lysergic acid, each unique in its own way. Of the many problems to be solved for any successful synthesis of lysergic acid (1), the ability of benzindoles to isomerize to naphthalenoid structures was particularly challenging. In the classical synthesis by Woodward and his colleagues (2), this problem was circumvented by using at the very outset dihydroindole derivatives and generating the indole system at the end; in three of the other four synthesis this detour has been adopted.

Woodward Synthesis (2)



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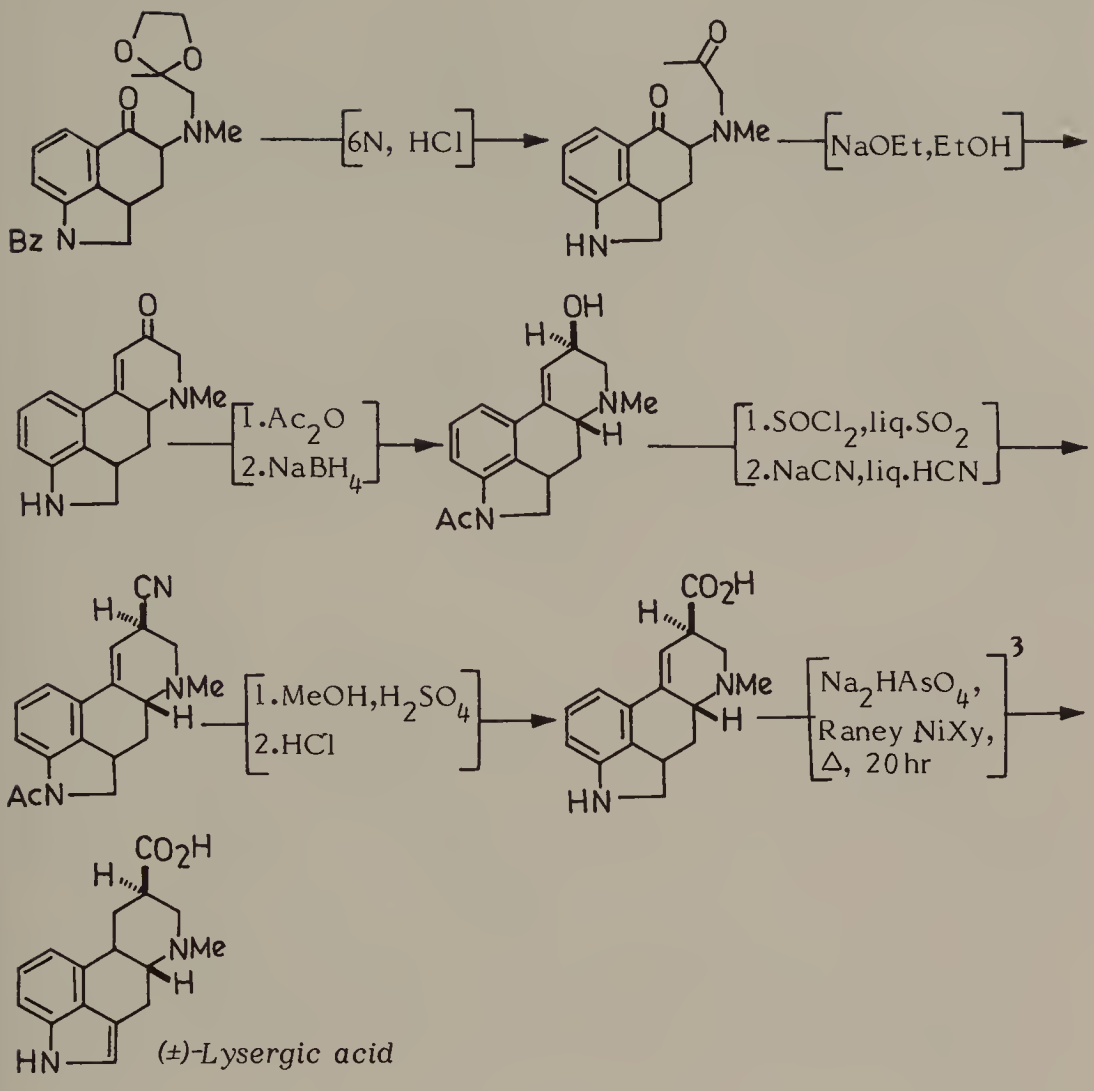
1. Review of earlier work: Stoll,A.; Hofmann,A. in "The Alkaloids", Vol.VIII, ed. R.H.F. Manske, Academic Press, New York, 1965, p.725.

2. Kornfeld,E.C.; Fornefeld,E.J.; Kline,G.B.; Mann,M.J.; Morrison,D.E.; Jones,R.G.; Woodward, R.B. J. Am. Chem. Soc., 1956, 78, 3087.



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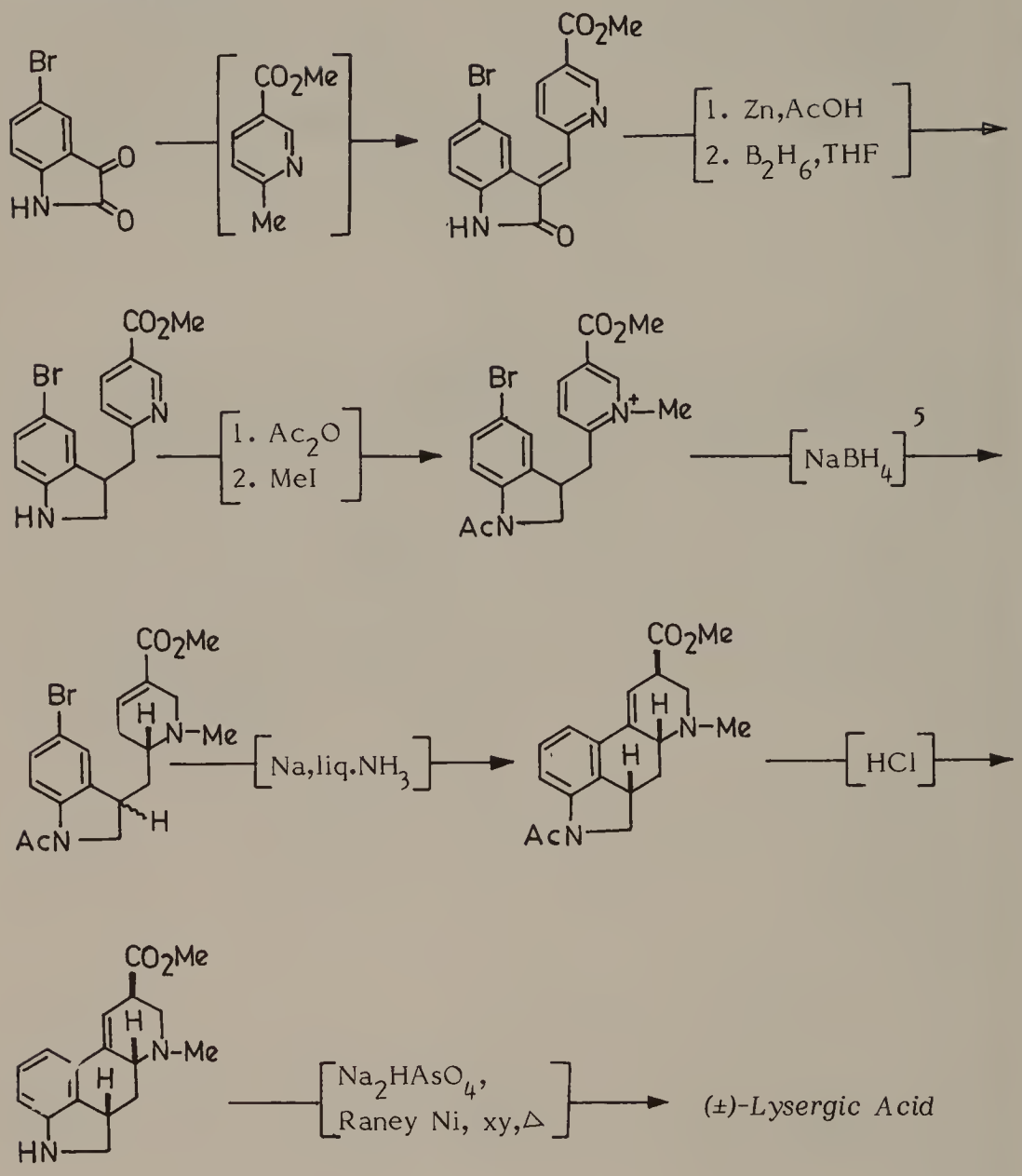
3. Recently it has been found that active MnO_2 is a more suitable reagent for dehydrogenation of indolines to indoles: Jansen,A.B.A.; Johnson,J.M.; Surtees,J.R. J. Chem. Soc., 1964, 5573.

Julia Synthesis (4)



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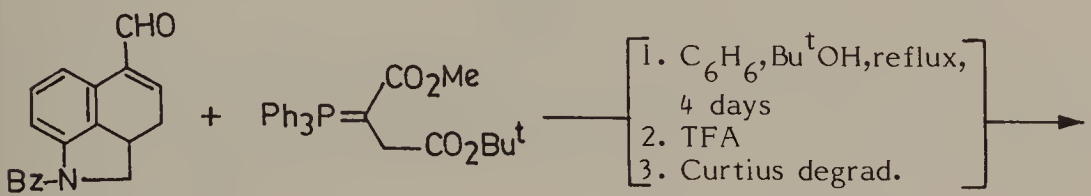
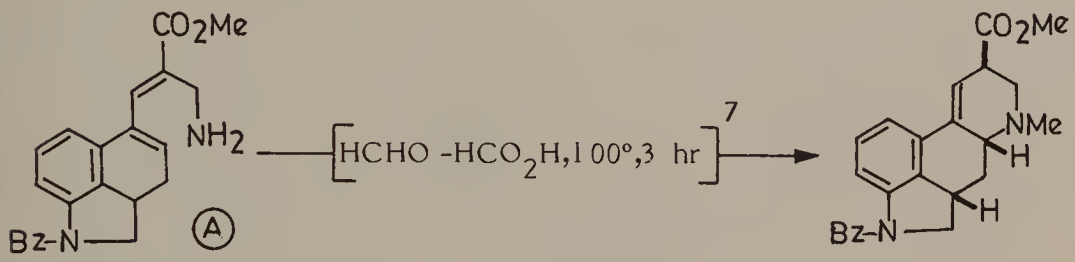
4. Julia,M.; LeGoffic,F.; Igolen,J.; Baillarge,M. Tetrahedron Lett., 1969, 20, 1569.
5. A mixture of both the isomers was formed from which the required isomer could be separated by chromatography after cyclisation.

Ramage Synthesis

The synthesis by Ramage and his associates (6) described below uses an intra-molecular Michael addition to construct the lysergic acid skeleton, which supports Woodwards hypothesis (2) that 2,3-dehydro derivatives of Ⓐ would be the intermediate in the epimerisation and racemisation of lysergic and isolysergic acids.





Oppolzer Synthesis (8)

The crucial step of constructing ring ⓒⒹ was carried out by an intramolecular imino-Diels-Alder reaction at a stationary low concentration keeping the indole nucleus intact through out the reaction sequence. The labile diene unit was kept in a protected bicyclo structure and generated insitu during the thermal cycloaddition reaction.

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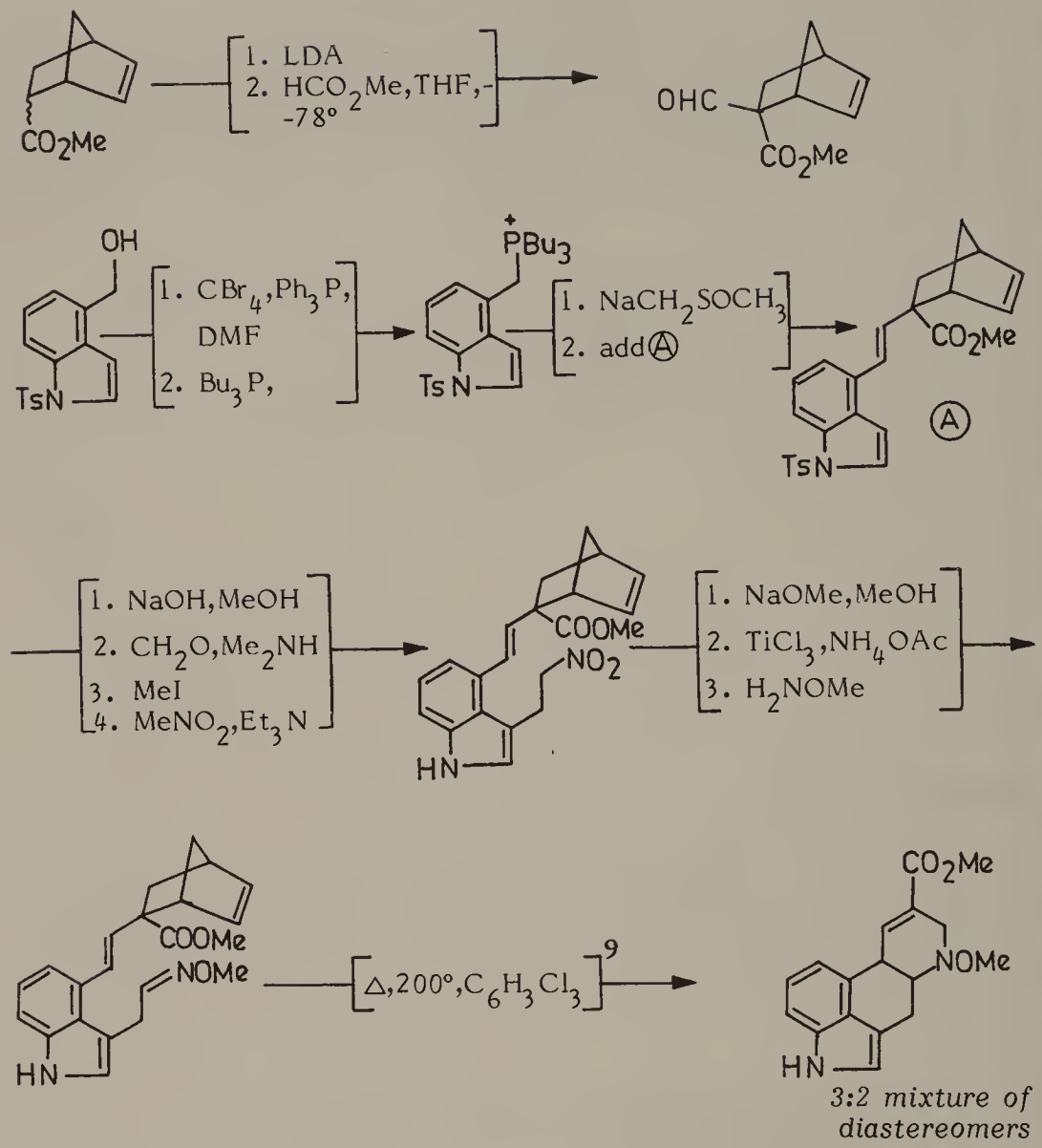
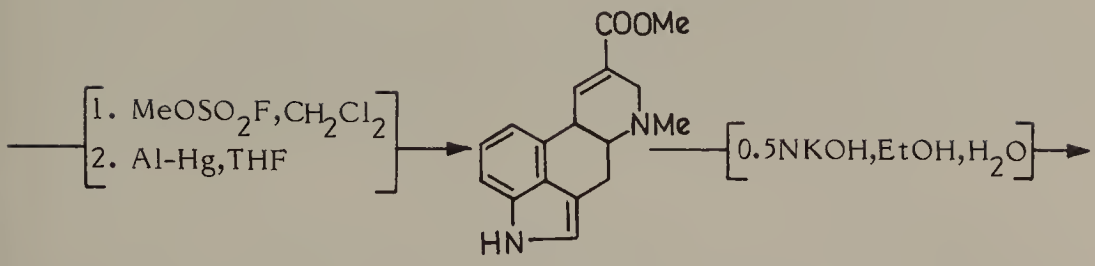
6. Armstrong,V.W.; Coulton,S.; Ramage,R. Tetrahedron Lett., 1976, 47, 4311. Ramage,R.; Armstrong,V.W.; Coulton,S. Tetrahedron, 1981, 32, Suppl., 157.

7. Clark-Eschweiler reaction did not proceed to the tertiary amine but instead the secondary amine cyclised to give the product with lysergic acid structure and stereochemistry along with isolysergic acid and 10-ene products (9:3:2); these could be separated by fractional crystallisation and tlc. Methanolysis of lysergic acid or isolysergic acid structures or the mixture gave the same mixture of debenzoylated compounds, an epimeric mixture of lysergic and isolysergic acid series formed in a ratio of 3:1.

8. Oppolzer,W.; Francotte,E.; Battig,K. Helv. Chim. Acta, 1981, 64, 478.



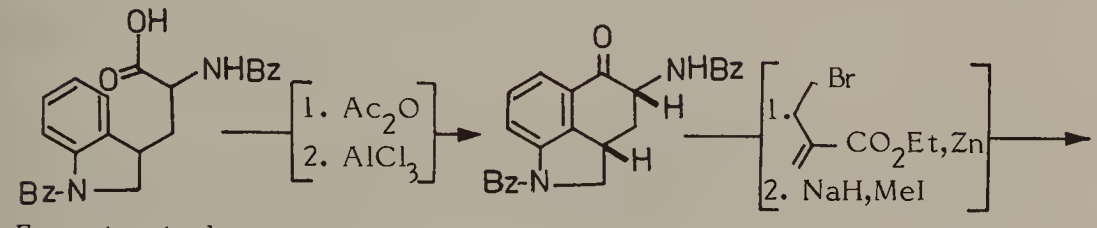
9. The reaction was forced to go intramolecularly by heating the substrate to a high temperature while keeping a stationary concentration of the transient diene as low as possible; a 1% solution of the substrate in 1,2,4-trichlorobenzene was added over 5 hr by means of a syringe drive into preheated solvent kept under argon.



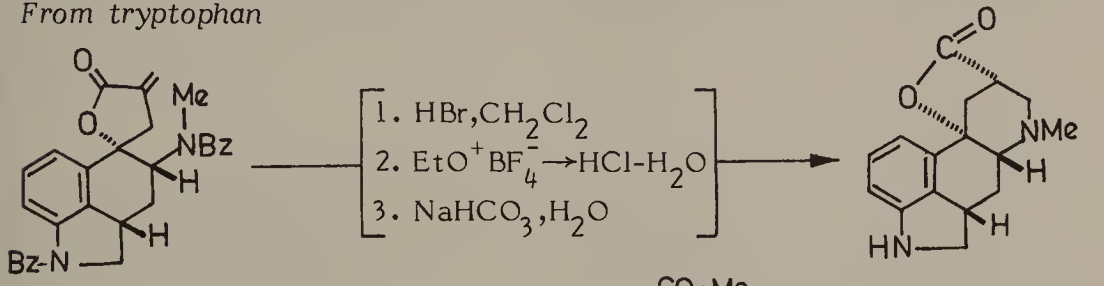
(±)-Lysergic acid

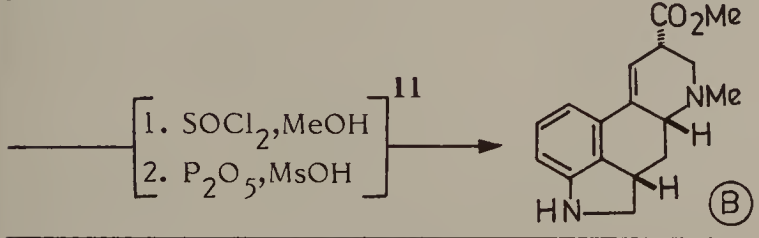
Rebek-Tai Synthesis (10)

This synthesis starts from tryptophan and can thus provide optically active lysergic acid directly.



From tryptophan



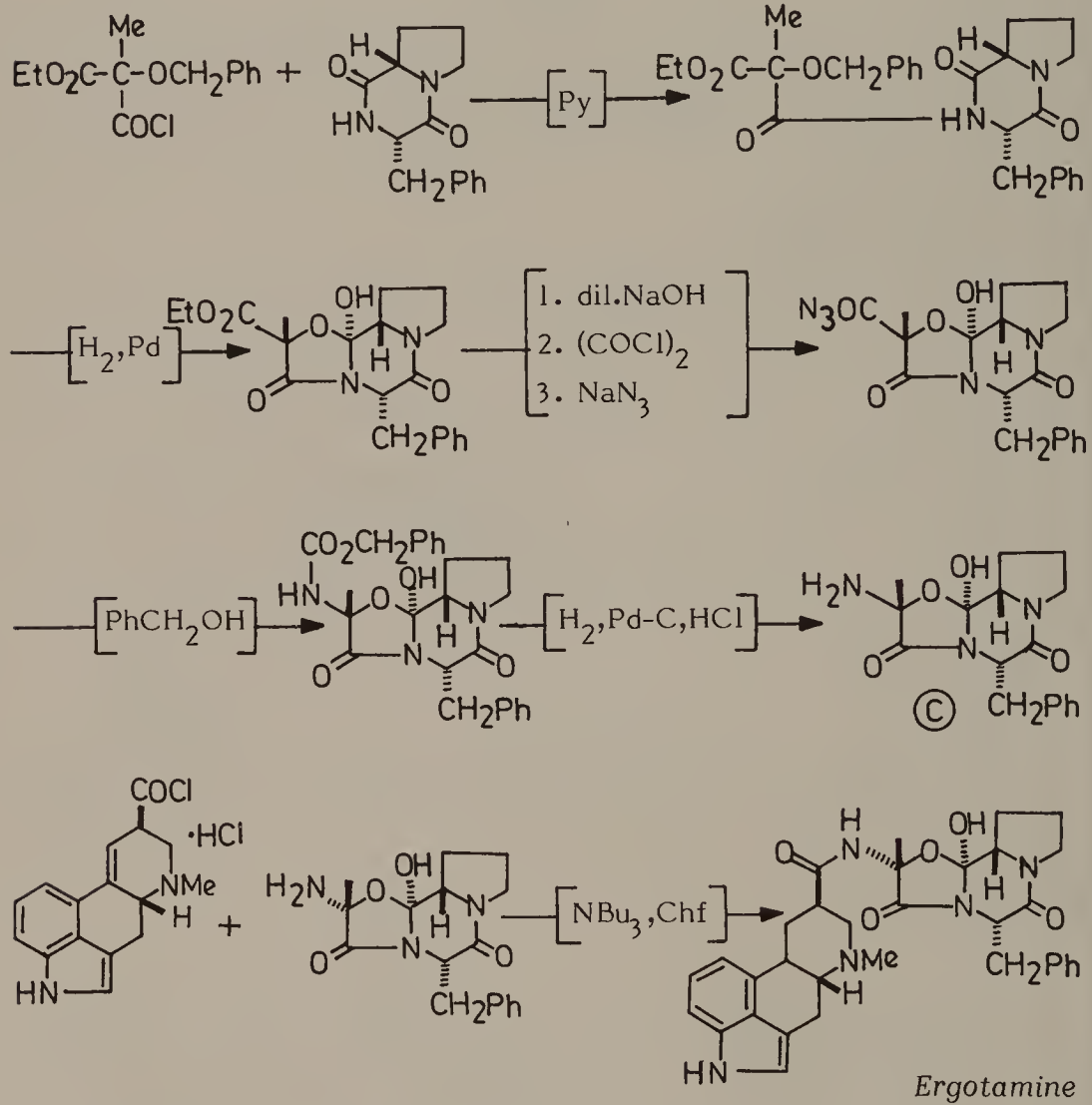


10. Rebek,Jr.J.; Tai,D.F. Tetrahedron Lett., 1983, 24, 859.

11. Substance (B) with isolysergic acid stereochemistry is known to be equilibrated to a mixture of lysergic and isolysergic acids stereochemistry by warming in MeOH (6).

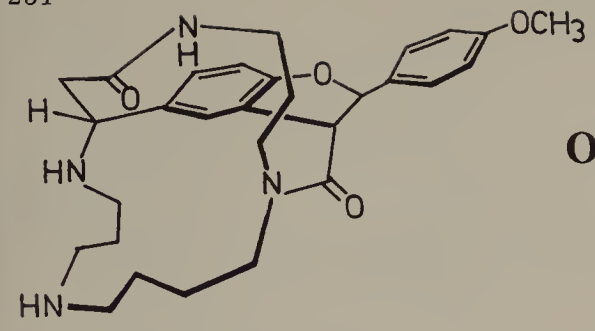
Ergotamine

Ergotamine is a peptide alkaloid of lysergic acid. The synthesis of ergotamine was carried out by Hofmann et al. (12), who synthesised the peptide portion characterized by a sensitive α-hydroxy-α-amino acid grouping, and coupled the resulting cyclol © with lysergic acid.



Ergotamine

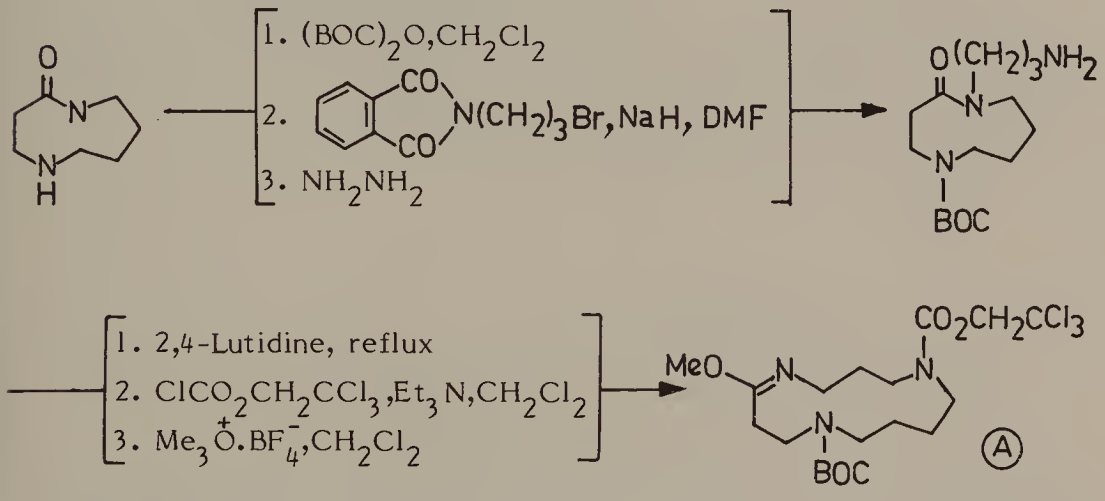
12. Hofmann,A.; Frey,A.J.; Ott,H. Experientia, 1961, 17, 206.



O-METHYLORANTINE

Orantine (ephedradine A), obtained from the roots of ephedra plants, belongs to the family of polyamine bicyclo-macrocyclic alkaloids. It is characterised by the presence of a dihydrobenzofuran nucleus bridging a 17 membered lactam ring containing a spermine nucleus (1). O-Methylorantine is obtained from species of Aphelandra (2). A number of these alkaloids have been synthesised by Wasserman et al. (3) by a convergent pathway by constructing two fragments separately and coupling them, making ingenious use of lactim ether of a 13 membered lactam intermediate both to link the two fragments andto construct the required 17-membered lactam by ring cleavage, which is followed by spanning of the bridge across the lactam by intramolecular lactam formation. The synthesis of O-methylorantine described below (4) is typical of the approach followed.

Lactim ether fragment (A) (3)



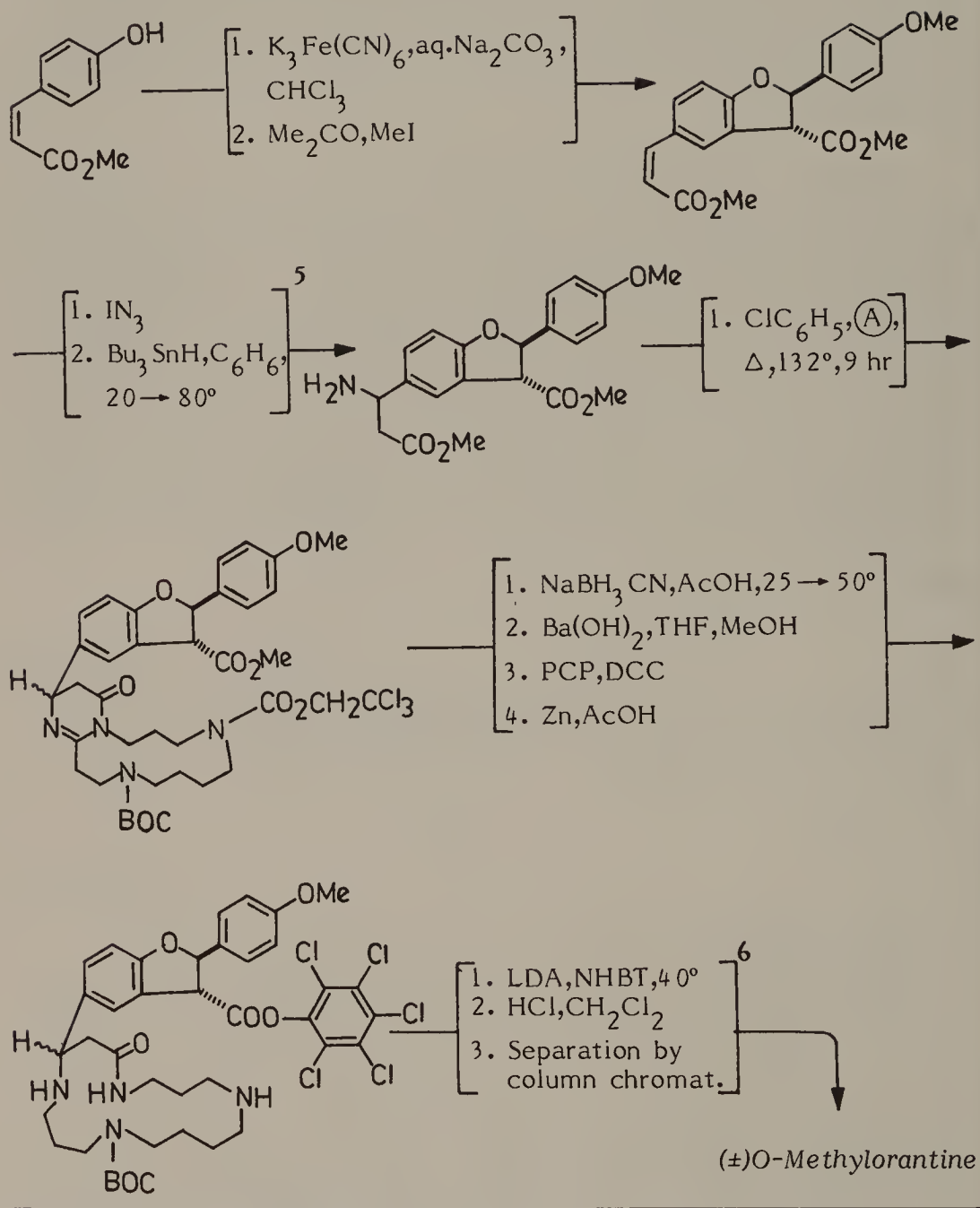
1. Hikkino,H.; Ogata,M.; Konno ,C. Heterocycles, 1982, 17, 155 and earlier references cited therein.

2. Datwyler,P.; Bosshardt,H.; Johne,S.; Hesse,M. Helv. Chim. Acta, 1979, 62, 2712; Bosshardt H.; Guggisberg,S.; John,S.; Veith,H.J.; Hesse,M.; Schmid,H. Pharm. Act. Helv., 1976, 51, 371.

3. Wasserman,H.; Robinson,R. Tetrahedron Lett., 1983, 3669; Wasserman,H.; Robinson,R.; Carter,C. J. Am. Chem. Soc., 1983, 105, 1697.

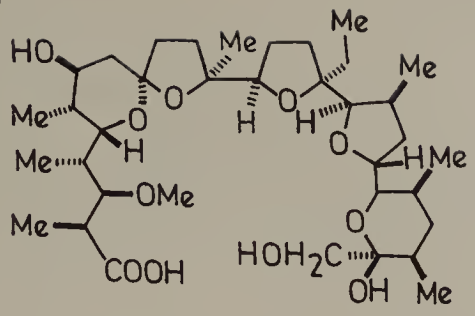
4. Wasserman,H.H.; Brunner,R.K.; Buynak,J.D.; Carter,C.G.; Oku,T.; Robinson,R.P. J. Am. Chem Soc., 1985, 107, 519.

***β*-Amino ester fragment**



5. The ratio of *β* : *α* azidoesters was favoured 5:1, and these were separated at the amino stage by flash chromatography.

6. The cyclised product was a 1:1 mixture of the two diastereomers, which were separated by column chromatography after deblocking.

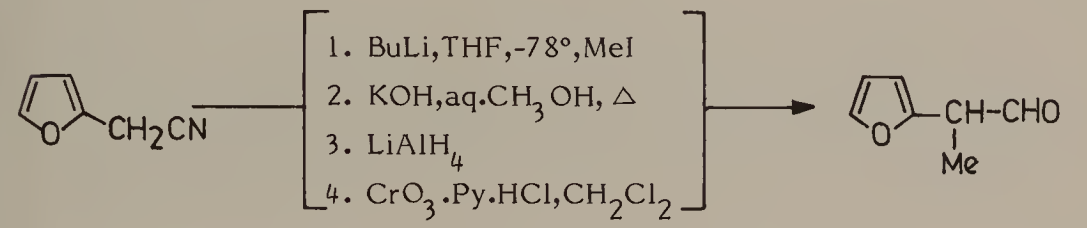


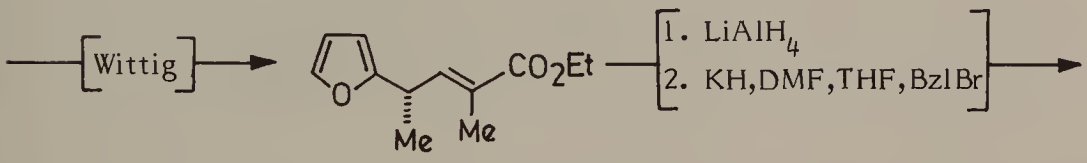
MONENSIN

Monensin, produced by a strain of Streptomyces cinnamonensis (1), is the most historic of the growing class of ionophoric polyether antibiotics, since it was the first polyether antibiotics whose structure was determined (2). Monensin presents a formidable challenge for synthesis with 17 asymmetric centers on the backbone of 26 carbon atoms. Two synthesis of monensin have been reported. Kishi and his associates reported the first total synthesis (2) and constructed the molecule from two fragments, each having the required absolute stereochemistry.

Kishi Synthesis

Left Segment (2a)





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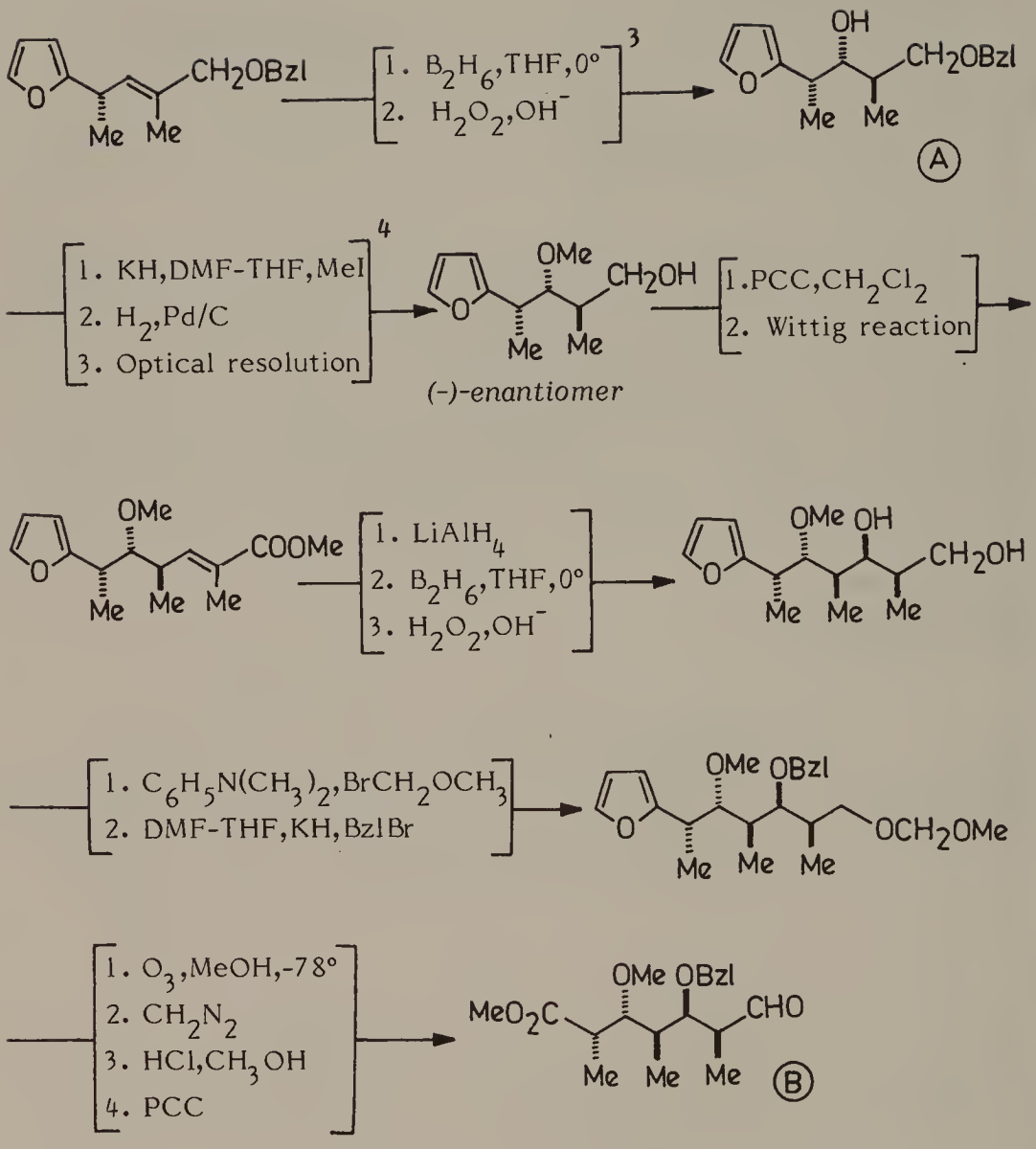
1. Agtarap,A.; Chamberlain,J.W.; Pinkerton,M.; Steinrauf,L. J. Am. Chem. Soc., 1967, 89, 5737; for reviews on polyether antibiotics see: Westley,J.W. Ann. Rept. Med. Chem., 1975, 10, 246; Adv. Applied Microbiology, 1977, 22, 177; Pressman,B.C. Ann. Rev. Biochem. 1976, 45, 501.

2. Schmid,G.; Fukuyama,T.; Akasaka,K.; Kishi,Y. J. Am. Chem. Soc., 1979, 101, 259 ; (b) Fukuyama,T.; Wang,C.L.J.; Kishi,Y. ibid, 262; (c) Fukuyama,T.; Akasaka,K.; Karanewsky, D.S.; Wang,C.L.J.; Schmid,G.; Kishi,Y. ibid, 263.



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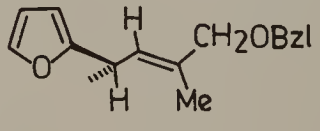
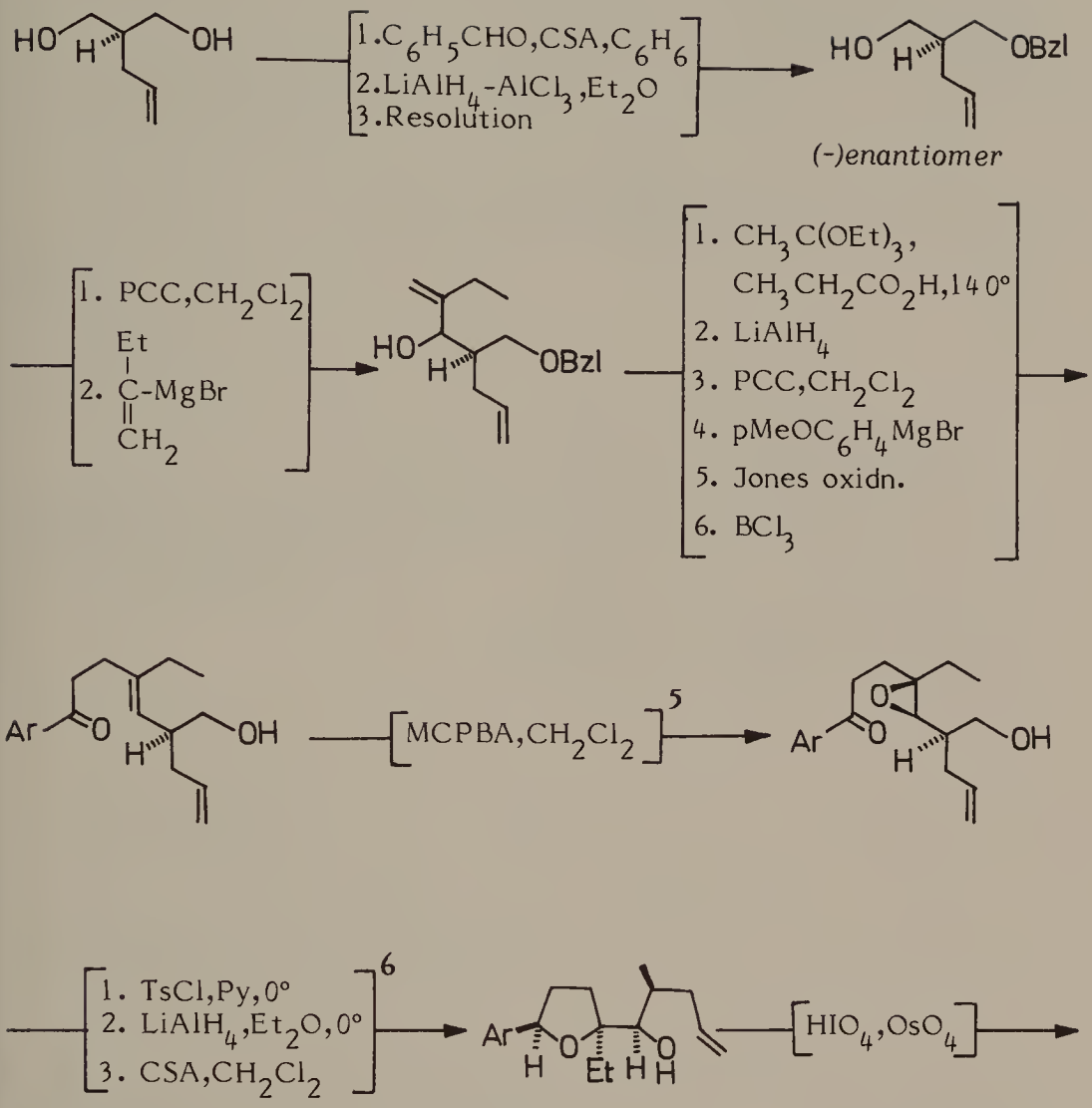
3. The ratio of (A) and its diastereoisomer was 8:1; the structure was assigned on the assumption that the preferred conformation of the olefin would be as shown and therefore the hydroboration would take place from the less sterically hindered ∝-face.



4. Optical resolution was achieved by reacting with (-)-$C_6H_5CH(CH_3)NCO$, separation of the diastereomeric urethanes by HPLC followed by $LiAlH_4$ reduction.

Right Segment (2b)



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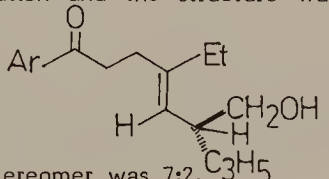
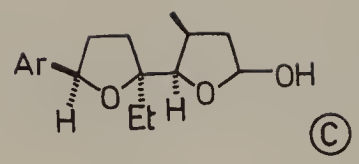
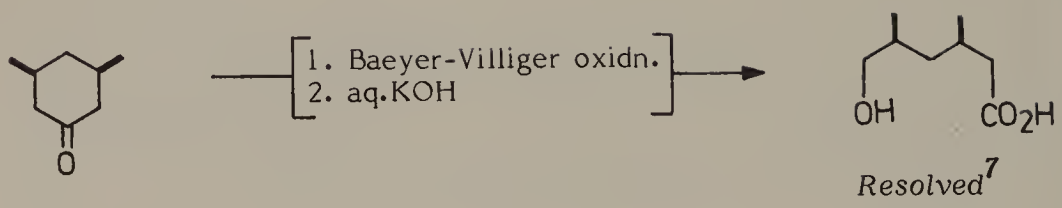
5. Only one product was obtained in this epoxidation and the structure was assigned on the consideration that the transition state shown would be preferred on account of lesser steric crowding with hydroxyl group complexed oxidant.

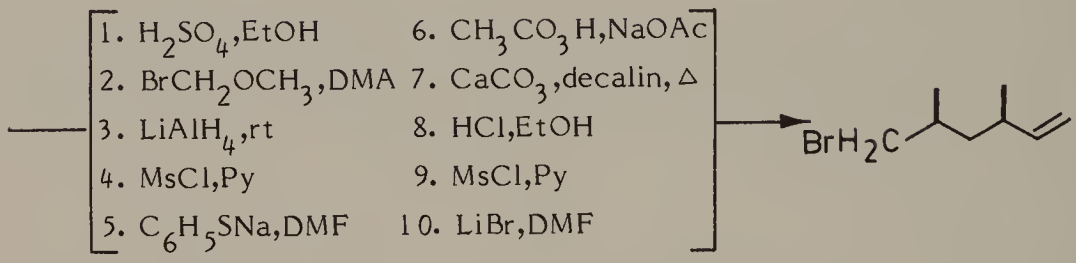


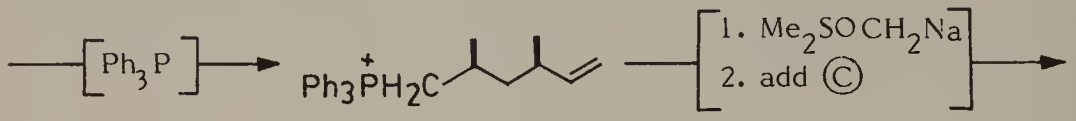
6. The best ratio of the product shown and its diastereomer was 7:2.

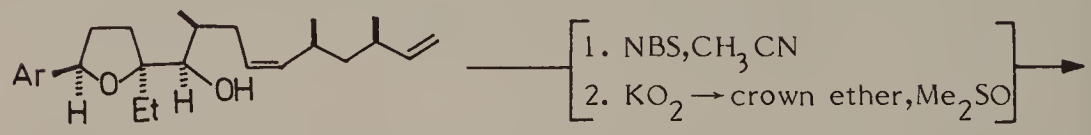




Resolved[7]







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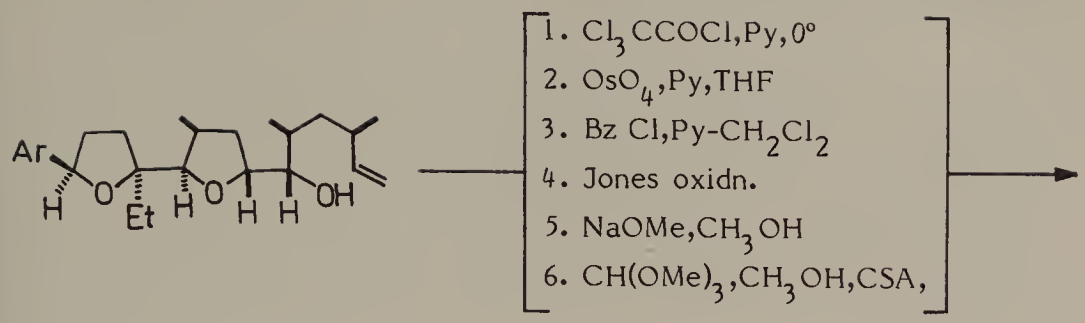
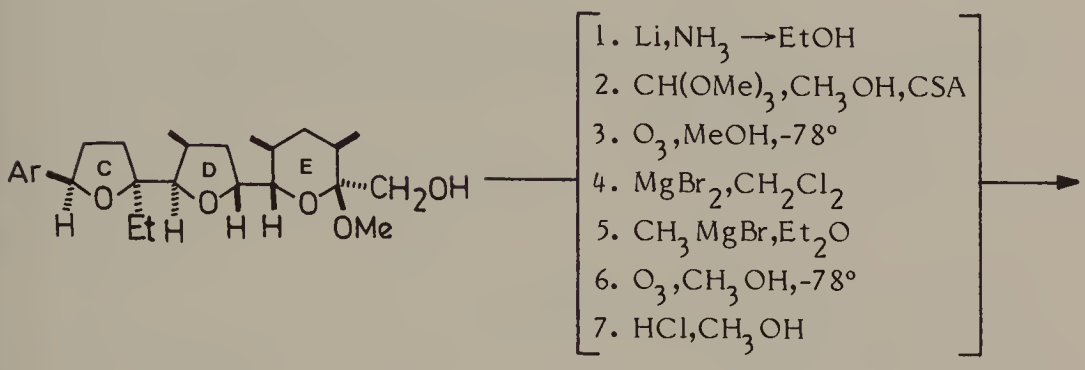
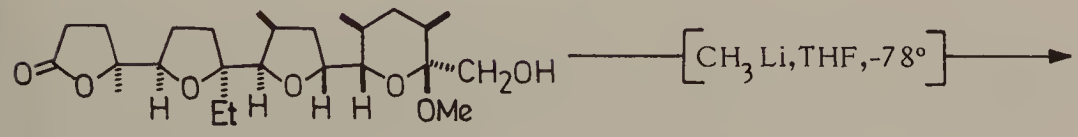
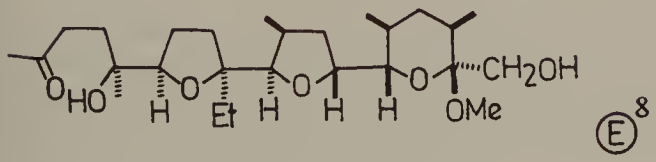
7. The optical resolution of the hydroxy acid was achieved by fractional crystallisation of the (+)- -methylbenzylamine salt, and 3R configuration assigned to the dextrorotatory isomer.



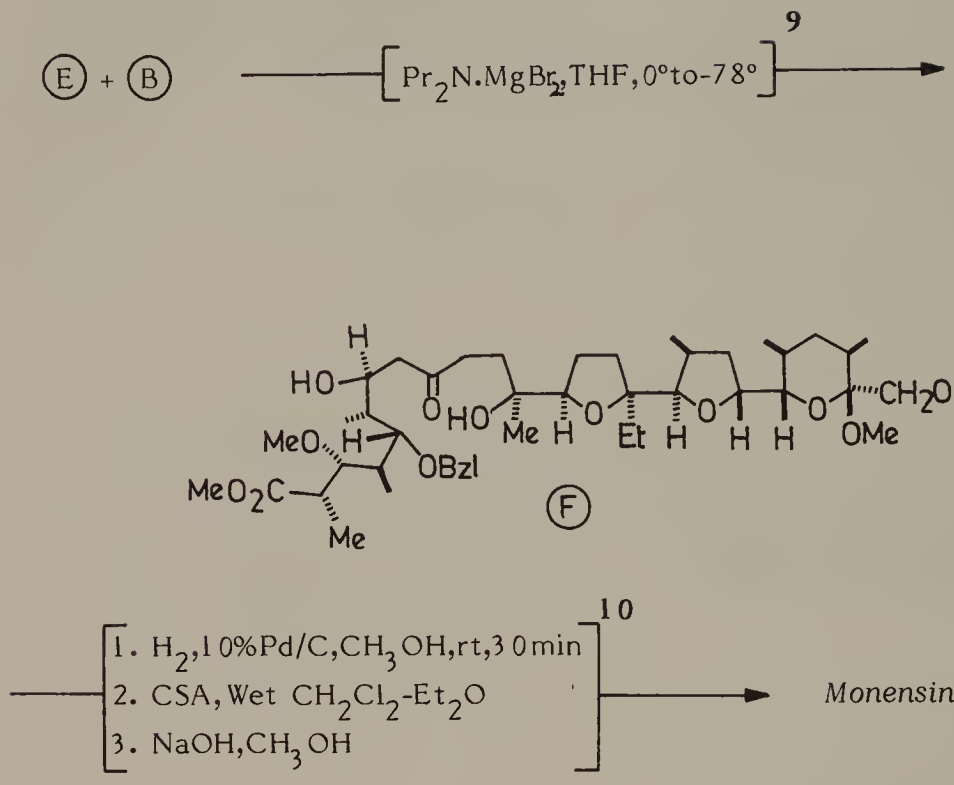






8. The structure of the product was confirmed by converting it to a ring E δ-lactone, which is obtained from monensin.

Condensation of two Segments (2c)



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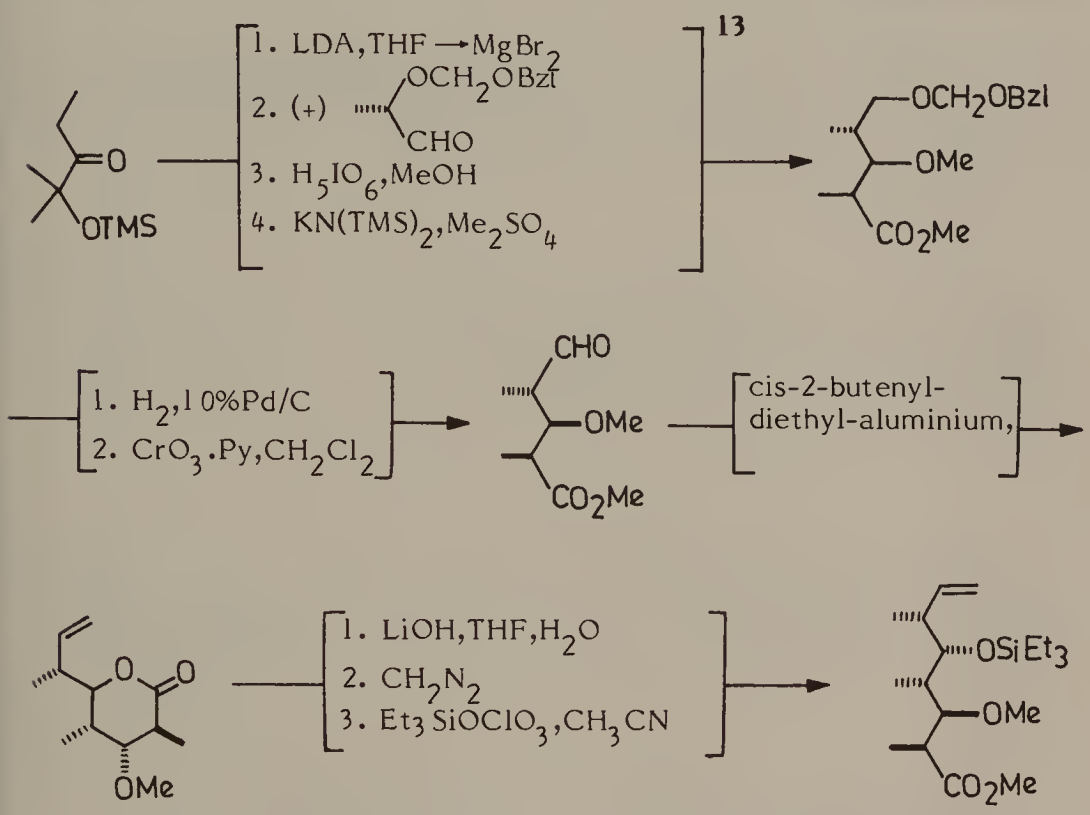
9. The yield and ratio of the two diastereomeric aldols that could be formed was found highly sensitive to reaction temperature; at 0° the yield was 70% but the products were formed in 1:1 ratio while at -78° the ratio of the required to unwanted isomer was 8:1 but the yield was only 20%. The products could be separated by preparative TLC. Based on Cram's rule the desired stereochemistry was assigned to the major product (F), which was confirmed by transformation to monensin.

10. It was anticipated that the asymmetric center at C_9 would be stereospecifically created by intramolecular ketalisation, as this configuration would be thermodynamically more stable owing to the anomeric effect. Camphor sulfonic acid treatment was required to equilibrate the spiroketal center and also to hydrolyse the tertiary methoxyl group at the C_{25} position. Pure monensin was obtained as sodium salt after preparative thin layer chromatography.

Still Synthesis

Soon after the publication of Kishi's synthesis, Still's group reported their highly convergent synthesis of monensin (11) from small fragments having the proper absolute stereochemistry (12) and the additional centers with the required stereochemistry created during coupling with control by the existing asymmetric centers. A special feature exploited for steric control is the chelation-controlled nucleophilic addition, when the stereochemistry produced may be opposite to the usual Cram's rule. The synthesis starts with (-)-malic acid and (+)- -hydroxyisobutyric acid.



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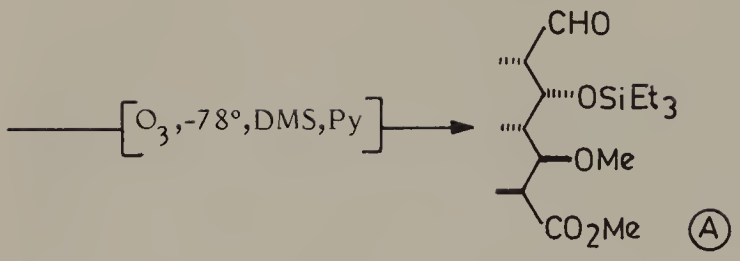
11. (a) Collum,D.B.; McDonald ,J.H.; Still,W.C. J. Am. Chem. Soc., 1980, 102, 2117; (b) idem, ibid, 1980, 102, 2118; (c) idem, ibid, 1980, 102, 2120.

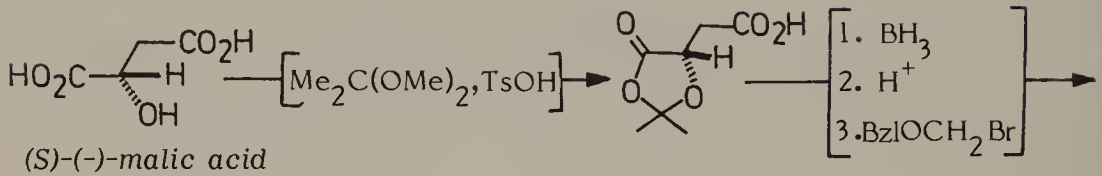
12. The stereochemical assignments of the fragments were confirmed by comparison with the authentic products obtained by degradation of natural monensin (11a).

13. The aldol condensation gave a 5:1 mixture of diastereomeric aldols, in which the major product was that predicted by chelation-controlled (anti-Cram) α-induction.

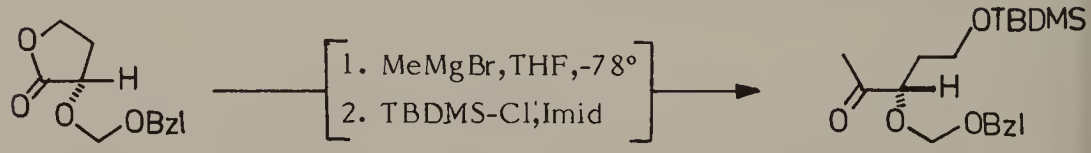
14. This condensation followed the normal Cram's rule and gave 3:1 mixture of diastereomeric aldols which were separated by flash chromatography.

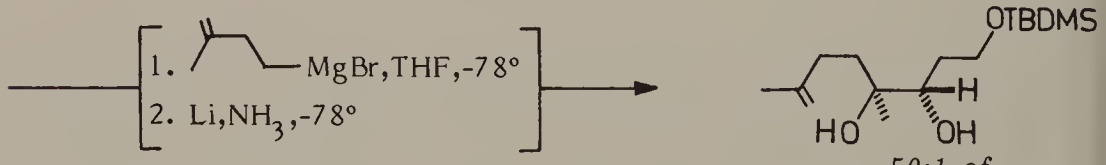


Central fragment

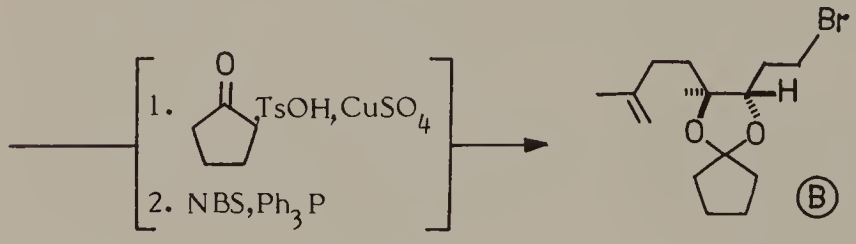


(S)-(-)-malic acid

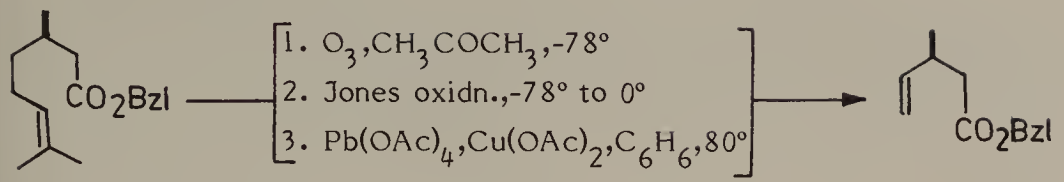




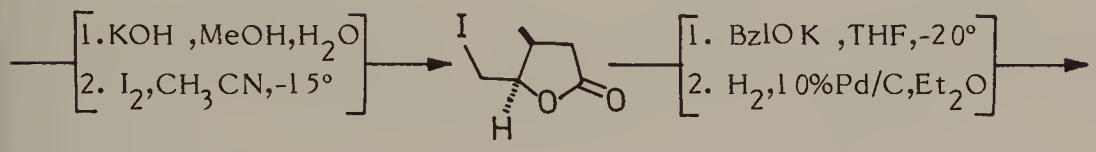
50:1 of Threo:Erythro

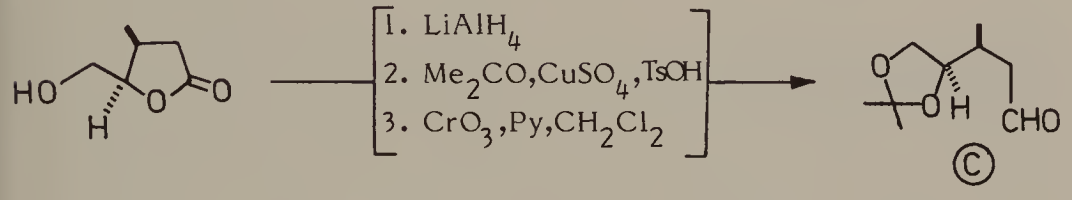


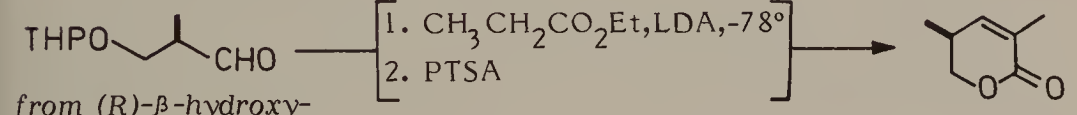
Right hand fragment



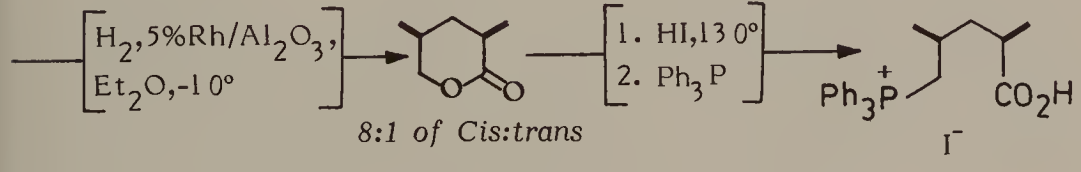
(R)-Citronellic acid



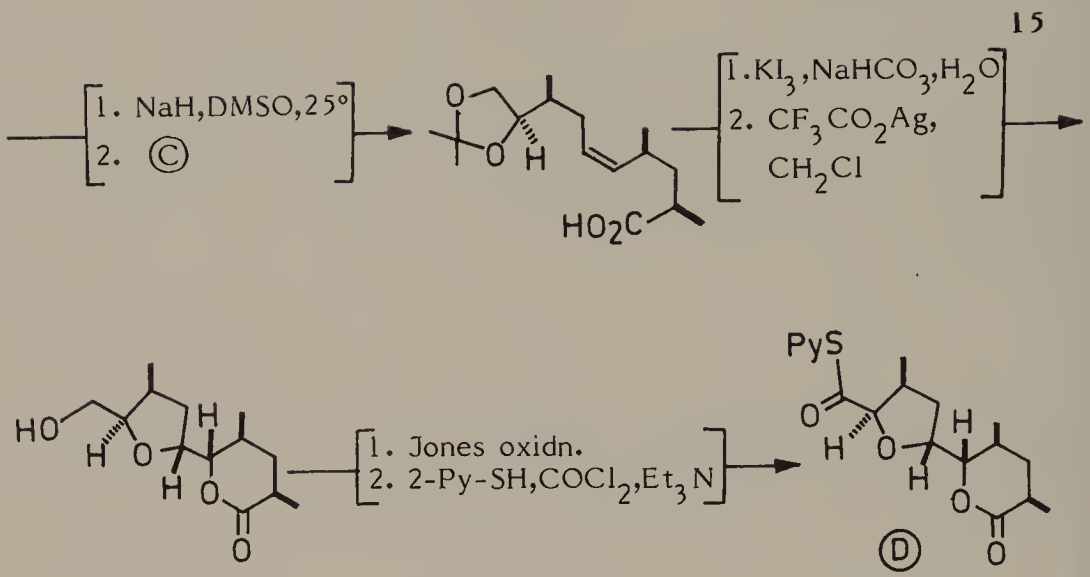




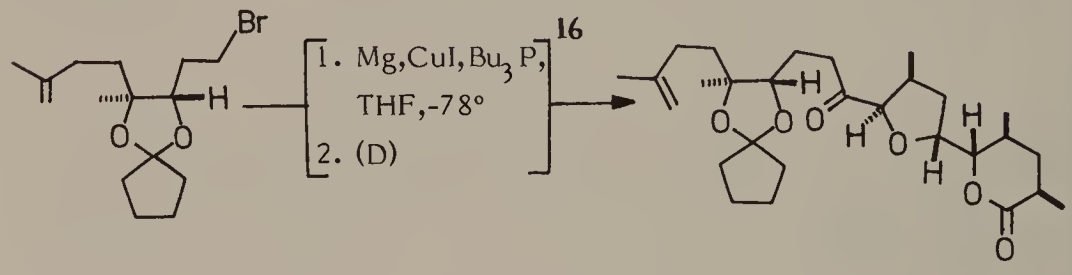
from (R)-β-hydroxy-isobutyraldehyde



8:1 of Cis:trans



Coupling of fragments



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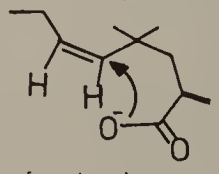
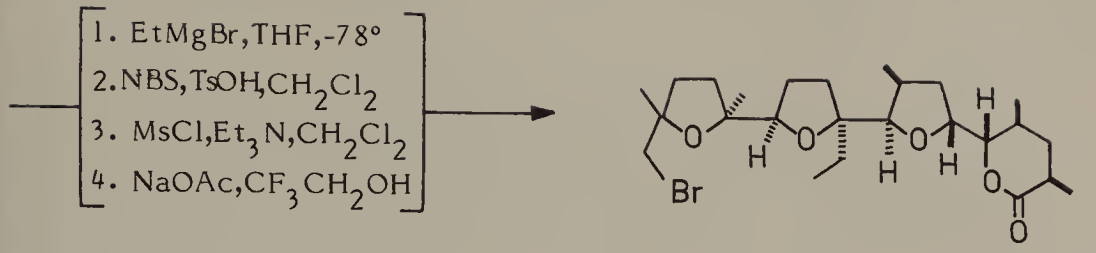
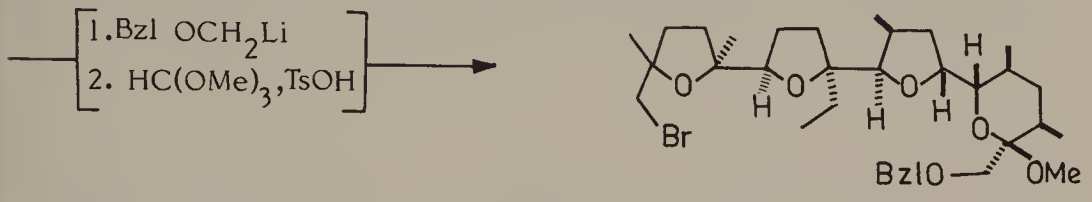
15. In iodolactonisation the required asymmetry at C_{20} and C_{21} was anticipated from steric considerations of lactonisation in which the cis-olefin and the adjacent asymmetric centre C_{22} would be expected to constrain the carboxylate-bearing appendage to the space below the olefine plane.

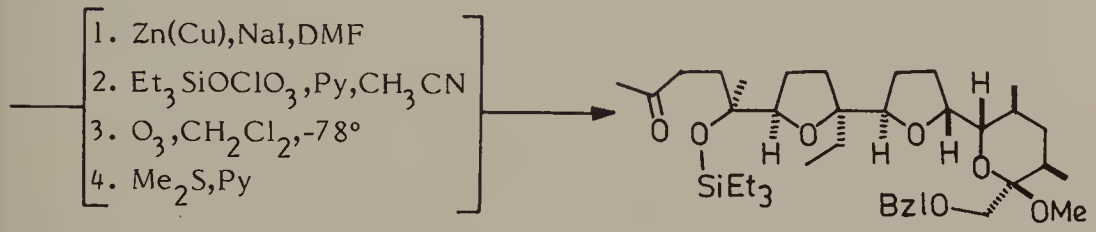


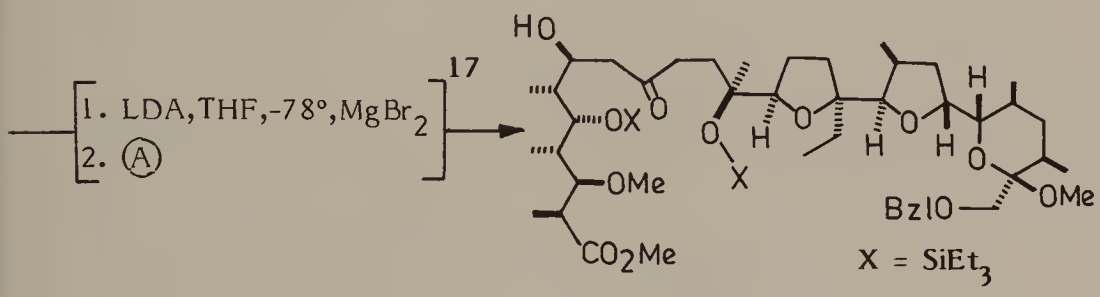
*The stereochemical assignments of the fragments were confirmed by comparison with the same products by degradation of natural monensin.

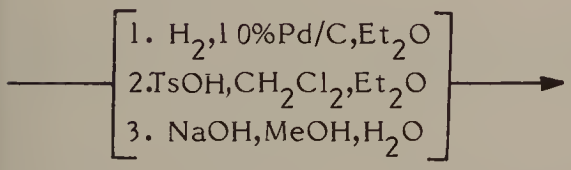
16. It was found difficult to prevent overaddition with simple Mg salt, but use of CuI with the Grignard reagent resulted in clean formation of ketolactone.











Monensin Sodium

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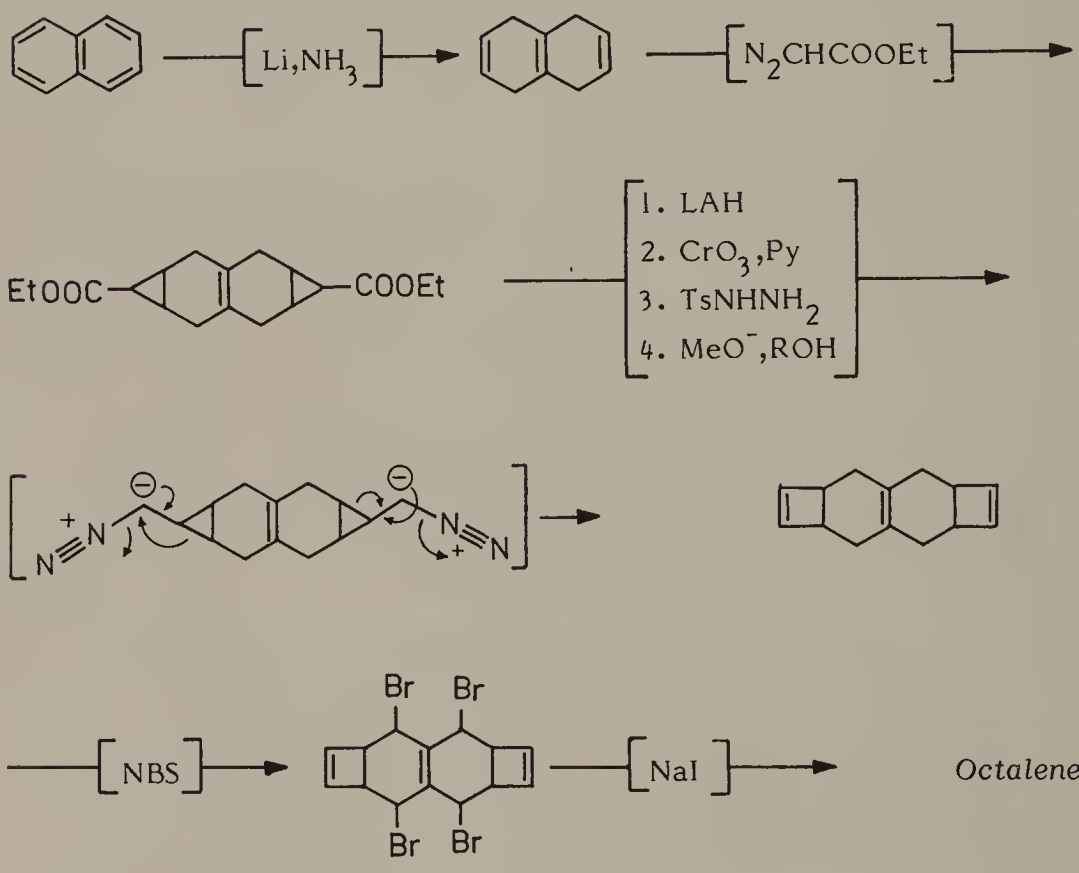
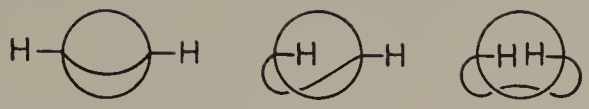
17. 3:1 mixture of the required to the unwanted aldols was produced.

OCTALENE

Octalene represents the bicyclic 14 π e^- aromatic system and in this respect is related to phenanthrene and anthracene. Indeed, all these could be reduced to the 14 π e^- pericycle by reorganising the bridging bonds. Appropriately, the synthesis of octalene starts from naphthalene, the lower homolog (1). Octalene is a lemon yellow aromatic hydrocarbon, as expected with considerable bond fixation, making above representation more appropriate.

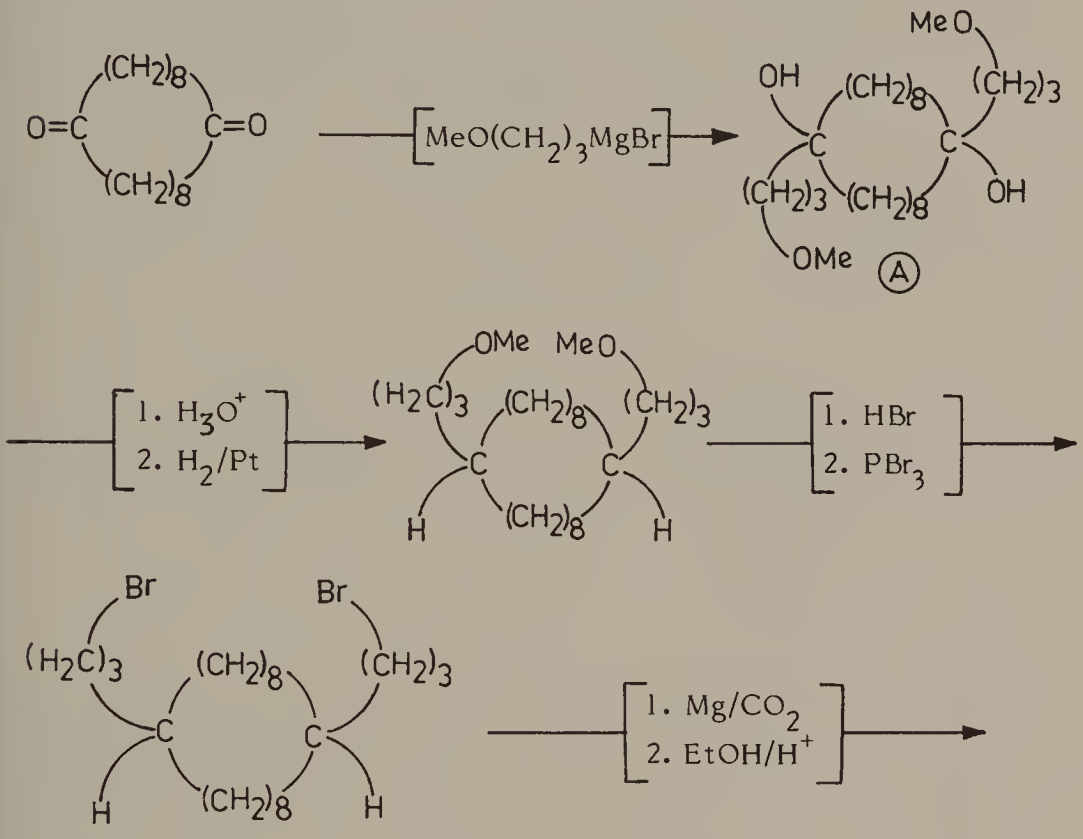


1. Vogel,E.; Runzheimer,H.V.; Hogrefe,F.; Baasner,B.; Lex,J. Angew. Chem. Int. Ed., 1977, 16, 871.



OUT-OUT, IN-IN BICYCLIC SYSTEMS

In [j.k.l]bicyclic systems, where j,k,l are small, the bridgehead hydrogens have to, necessarily, assume the out-out configuration. However, with increasing chain lengths all the three permissible configurations of the bridgehead hydrogens, namely, out-out, out-in and in-in become possible. The out-in and in-in isomers of the [8.8.8] bicyclic system have been prepared (1). The structures are established on the basis of ^{13}C-nmr and thermodynamic considerations. Interestingly, the in-in isomer, where the t-protons are not available for ready abstraction, is unreactive to bromine in contrast to the other isomers.



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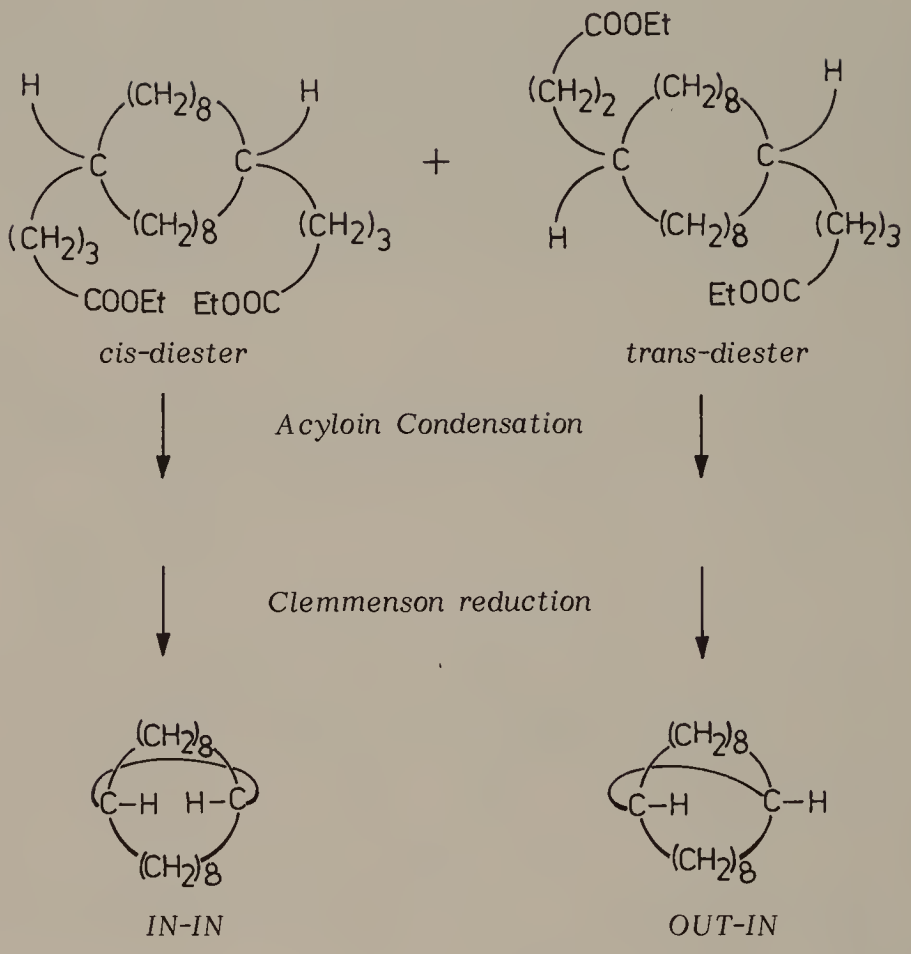
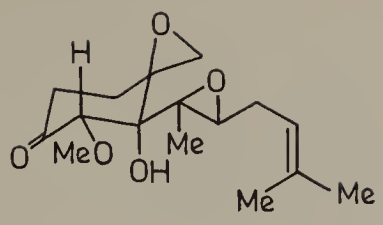
1. Park, C.H., Simmons, H.E. J. Am. Chem. Soc., 1972, 94, 7184.

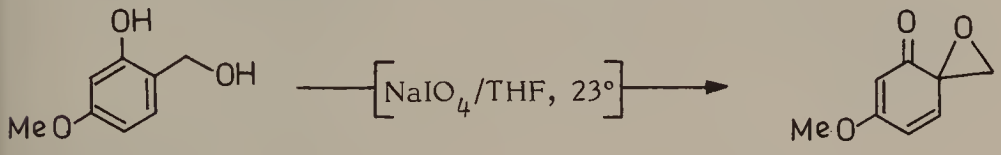
2. The intermediate hydroxy-methyl ether (A) was obtained as a mixture of cis and trans isomers, but the isomers were separated at the stage of dibromides by fractional crystallisation, which were individually converted into the cis and trans di-esters.

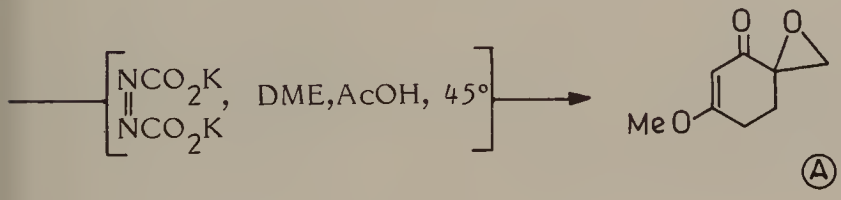

H
(CH2)8
H
C
C
(CH2)3
(CH2)8
(CH2)3
COOEt
EtOOC
+
COOEt
(CH2)2
(CH2)8
H
C
C
H
(CH2)8
(CH2)3
EtOOC
cis-diester
trans-diester
Acyloin Condensation
Clemmenson reduction
(CH2)8
C–H
H–C
(CH2)8
(CH2)8
C–H
C–H
(CH2)8
IN-IN
OUT-IN



OVALICIN

Ovalicin, a sesquiterpene diepoxide antibiotic isolated from cultures of Pseudorotum ovalis Stolk(1),exhibits antimicrobial, anticancer and immunosupressive activities(2) and has been of much chemotherapeutic interest(3). Structurally ovalicin is related to fumagillin an antiprotozoal antibiotic which has been synthesised previously by the same authors(4). The stereocontrolled synthesis reported herein(5) follows a totally different strategy and synthetic methodology. One of the crucial steps was the selective reduction of 4,5 -double bond, which was achieved by using diimide(6). The method used for the synthesis of the side chain is a new approach to a stereospecific synthesis of E-trisubstituted 1,4-dienes.





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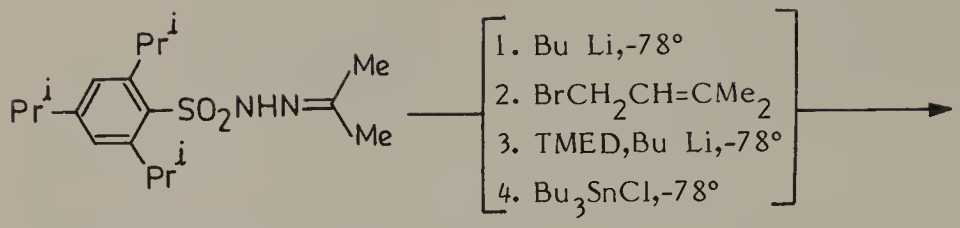
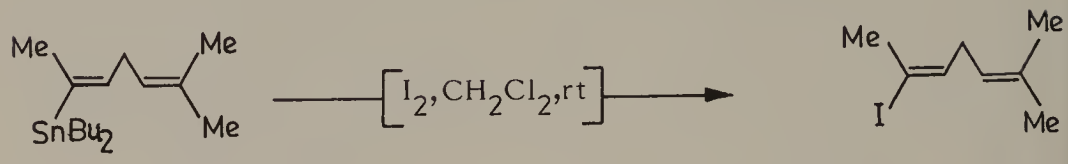
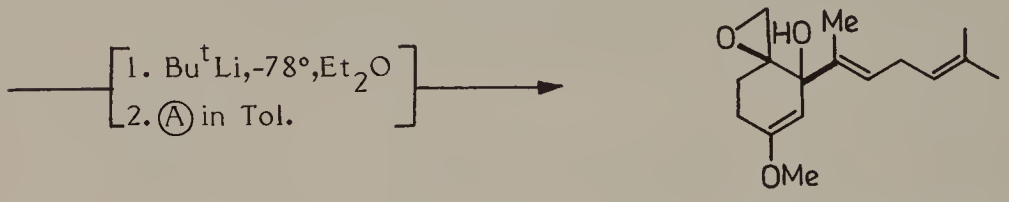
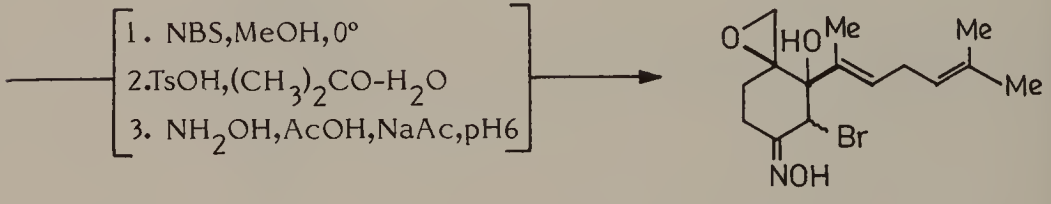
1. Sigg, H.P., Weber, H.P. Helv. Chim. Acta, 1968, 51, 1395.
2. Zimmerman, W.A., Hartman, G.R. Eur. J. Biochem., 1981, 118, 143.
3. Borel, J.F., Lazary, S., Staehelin, H. Agents & Actions, 1974, 4, 357.
4. Corey, E.J., Snider, B.B. J. Am. Chem. Soc., 1972, 94, 2549.
5. Corey, E.J., Dittami, J.P. J. Am. Chem. Soc.,1985, 107, 256-257.
6. Adam, W., Eggelte, H.J. J. Org. Chem., 1977, 42, 3987.

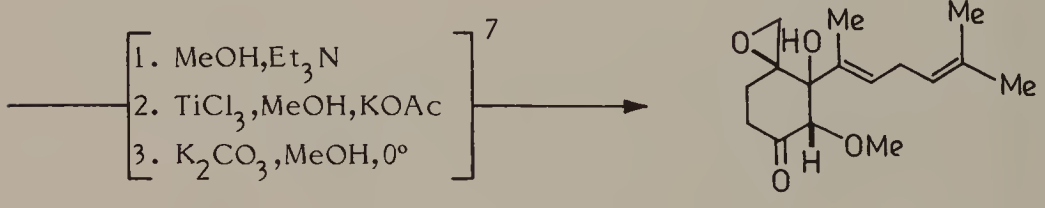


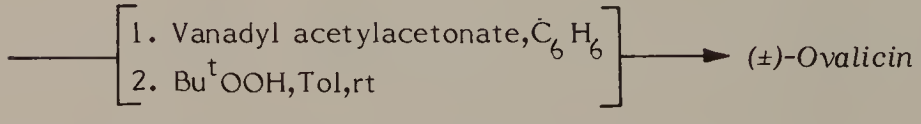




along with diasteriomer (17:1) sep. by chromatography







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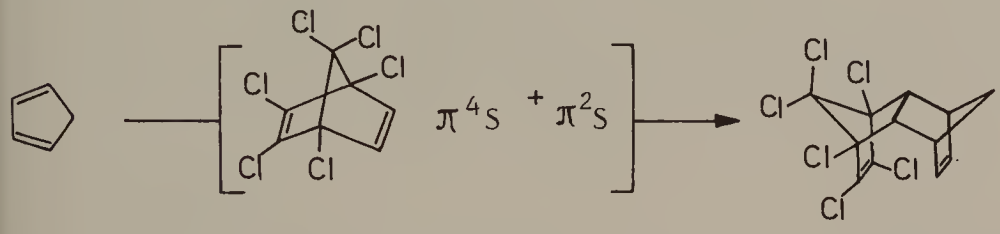
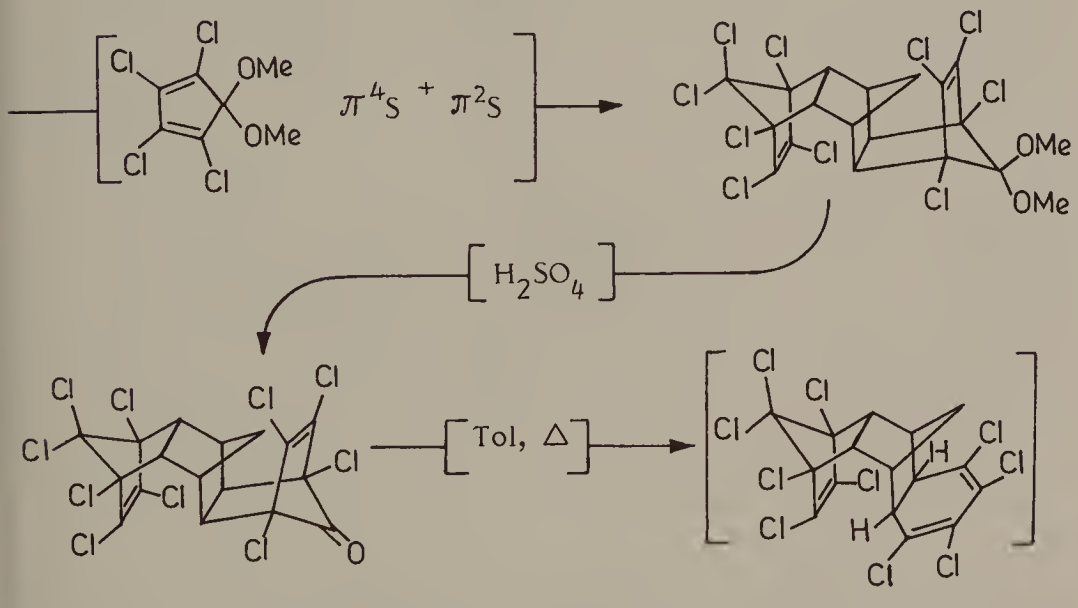
7. The above reactions gave a 1:1 mixture of diastereoisomers, which on this treatment underwent complete isomerisation to the right isomer.

PAGODANE

Eight five-membered rings radiating from a cyclobutane base generate the aesthetically pleasing pagodane constellation. Besides, the projection of the cyclobutane base outwards to pick up 4 hydrogens and the pair-wise union of the 4 peri methylenes with the loss of 4 hydrogens, would transform pagodane to dodecahedrane. Pagodane has been synthesised and its transformation to dodecahedrane demonstrated (1).





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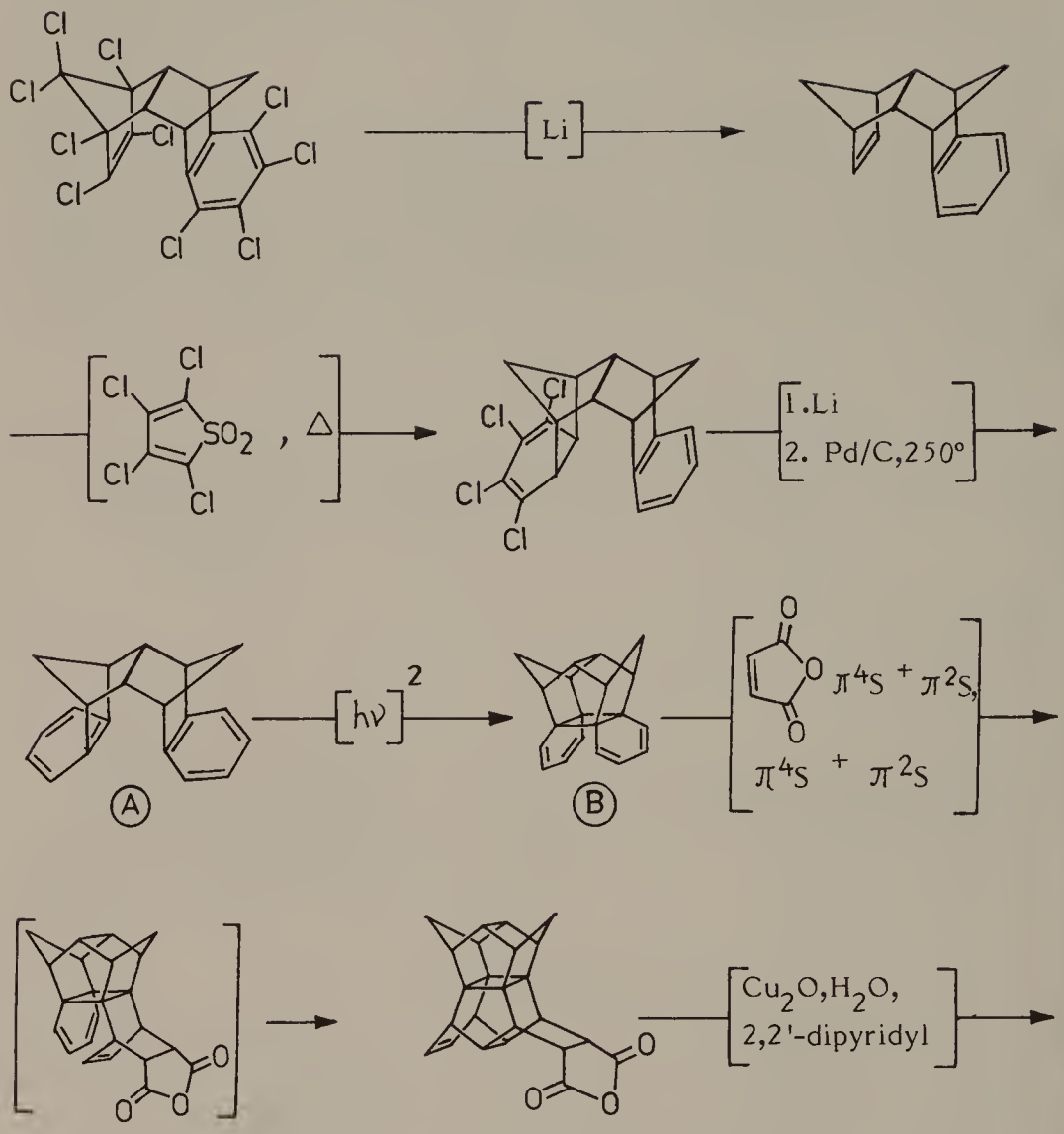
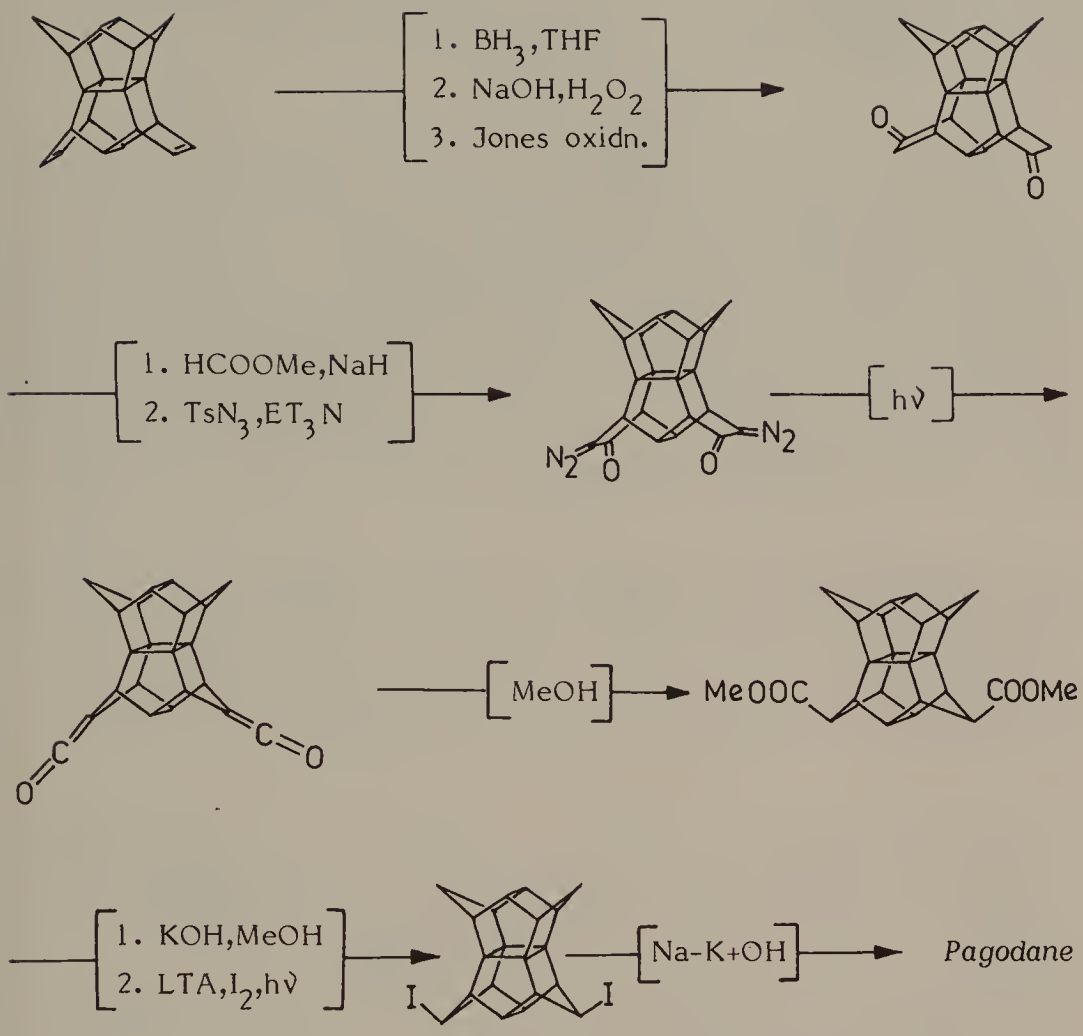
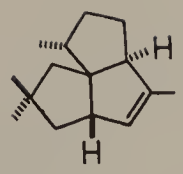
1. Fessner,W.D.; Prinzbach,H.; Rihs,G. Tetrahedron Lett., 1983, 24, 5857.



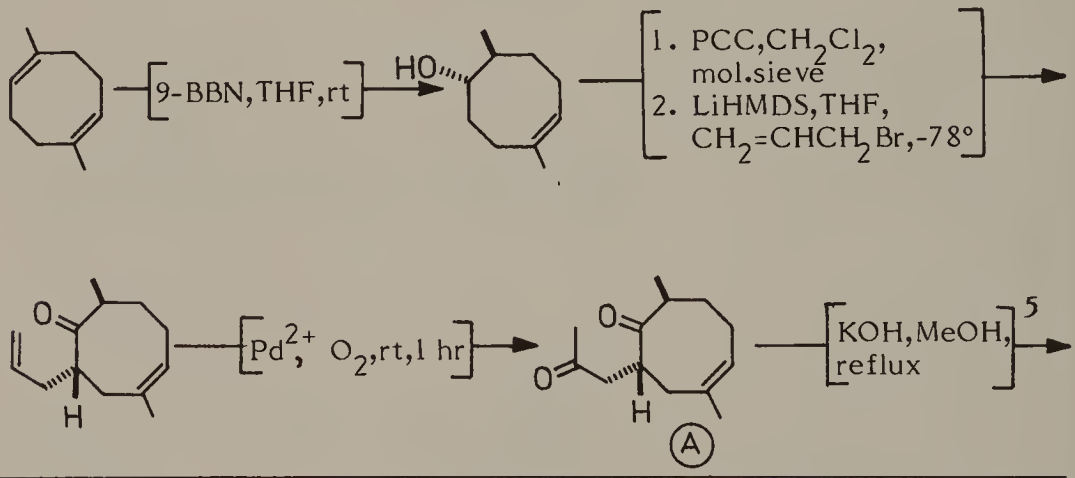
2. A photo-stationary state representing A:B::7:3 is established at 254 nm. B could be easily separated from the mixture. Thermolytic reversal is possible at 200°C in decalin.


1. BH_3,THF
2. NaOH,H_2O_2
3. Jones oxidn.
O
O
1. HCOOMe,NaH
2. TsN_3,ET_3N
N_2
O
O
N_2
hν
C=O
C=O
MeOH
MeOOC
COOMe
1. KOH,MeOH
2. LTA,I_2,hν
I
I
Na-K+OH
Pagodane



PENTALENENE

Because of the wide occurence of tricyclo [6.3.0.0]undecane skeleton (angular triquinones in a number of sesterpenes and sesquiterpenoids the synthesis of natural products based on this carbon framework has been a popular target for the development of new synthetic approaches (1). The synthesis of pentalene described here in (2) exemplifies a general and flexible approach developed by Mehta and his associates for entry into the angular triquinones via a carbonium-ion-mediated transannulation reaction in the bicyclo [6.3.0.0]undecane system (3); which is based on taking cognisance of the marked propensity of the cycloacyl derivatives towards transannular cationic cyclisations (4).

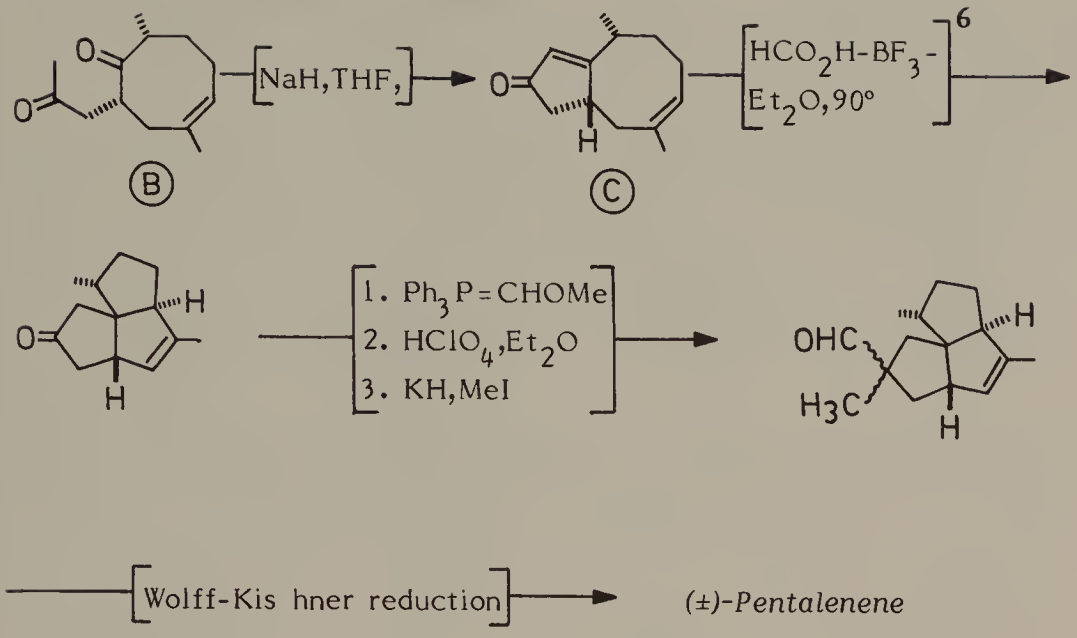


1. See references 11 & 12 of reference 2 for synthetic approches to tricyclic [6.3.0.0] undecanes and total synthesis of triquinane natural products.

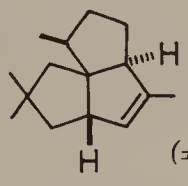
2. Mehta,G.; Rao,K.S. J. Am. Chem. Soc., 1986, 108, 8015; J. Chem. Soc.; Chem. Commun., 1985, 1464.

3. For earlier synthesis of pentalenene see: Ohfune,Y.; Shirahama,H.; Matsumoto,T. Tetrahedron Lett., 1976, 2869; Misumi,S.; Ohtsuka,T.; Ohfune,Y.; Sugita,K.; Shirahama,H.; Matsumoto,T. Tetrahedron Lett., 1979, 31; Annis,G.D.; Paquette,L.A. J. Am. Chem. Soc., 1982, 104, 4504; Piers,E.; Karunaratne,V. J. Chem. Soc.; Chem. Commun., 1984, 959; Pattenden,G. Teague,S.J. Tetrahedron Lett., 1984, 3021; Mehta,G.; Rao,K.S. J. Chem. Soc., Chem. Commun., 1985, 1464; Crimmins,M.T.; DeLoach,J.A. J. Am. Chem. Soc., 1986, 108, 800; Crimmins,M.T.; Mascarella,S.W. J. Am. Chem. Soc., 1986, 108, 3435.

4. Cope,A.C.; Martin,M.M.; Mckerrey,M.A.Q. Rev. Chem. Soc., 1986, 20, 119.



From the trans-diketone Ⓐ by the same set of reactions (±) epi-pentalenene was obtained.



(±)-epi-Pentalenene

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5. A 1:4 mixture of Ⓐ:Ⓑ was obtained in this equilibration; cf. Clark Still,W.; Galynker,I. Tetrahedron, 1981, 37, 3981.

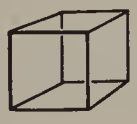
6. Ⓒ was obtained along with C-2-epimeric enone in 4:1 ratio.

(III)

PENTAPRISMANE

Annulation of cyclobutane units generates an interesting series of hydrocarbons shown below with identical methine protons. Pentaprismane (III) over a period of time earned the reputation of a rather

(I)

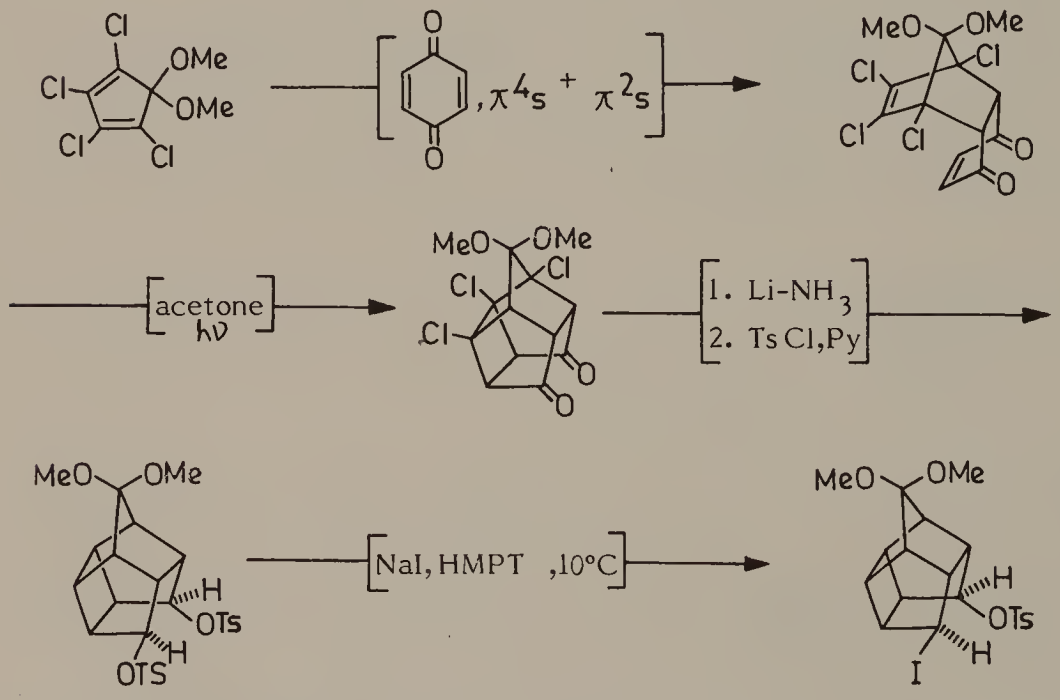


(II)

(III)

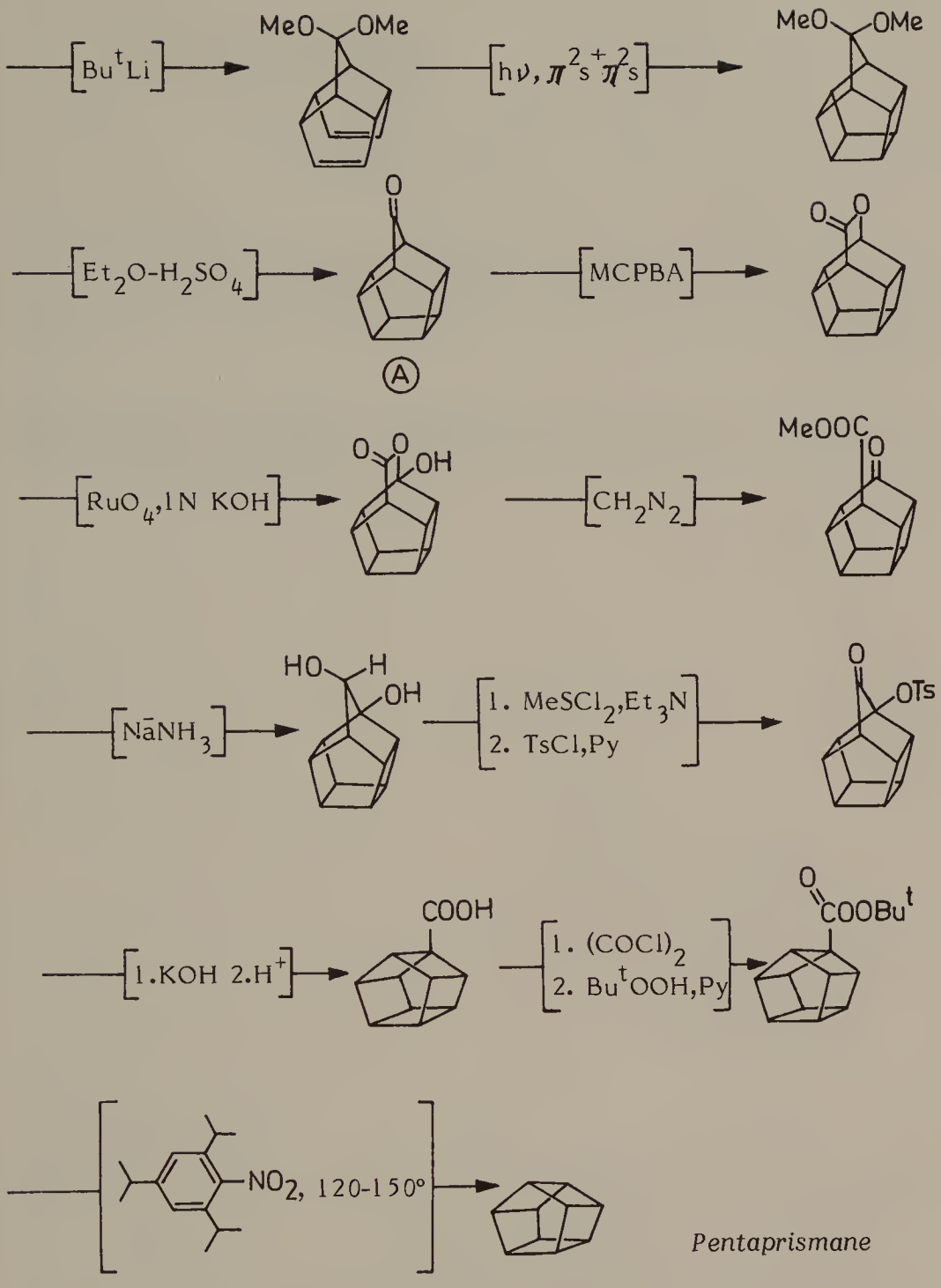
(IV)

"inaccessible" compound (1). Its synthesis (2) was achieved eventually via the key compound homopentaprismanone (A).

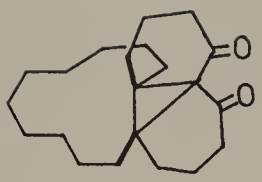


1. McKennis,J.S.; Brener,L.; Ward, J.S., Petit, R. J. Amer. Chem. Soc., 1971, 93, 4957; Paquette, L.A., Davis, R.F., James, D.R. Tetrahedron Lett., 1974, 1615.

2. Eaton, P.E., Or, Y.S., Branca, J.S. J. Amer. Chem. Soc., 1981, 103, 2134.



Pentaprismane

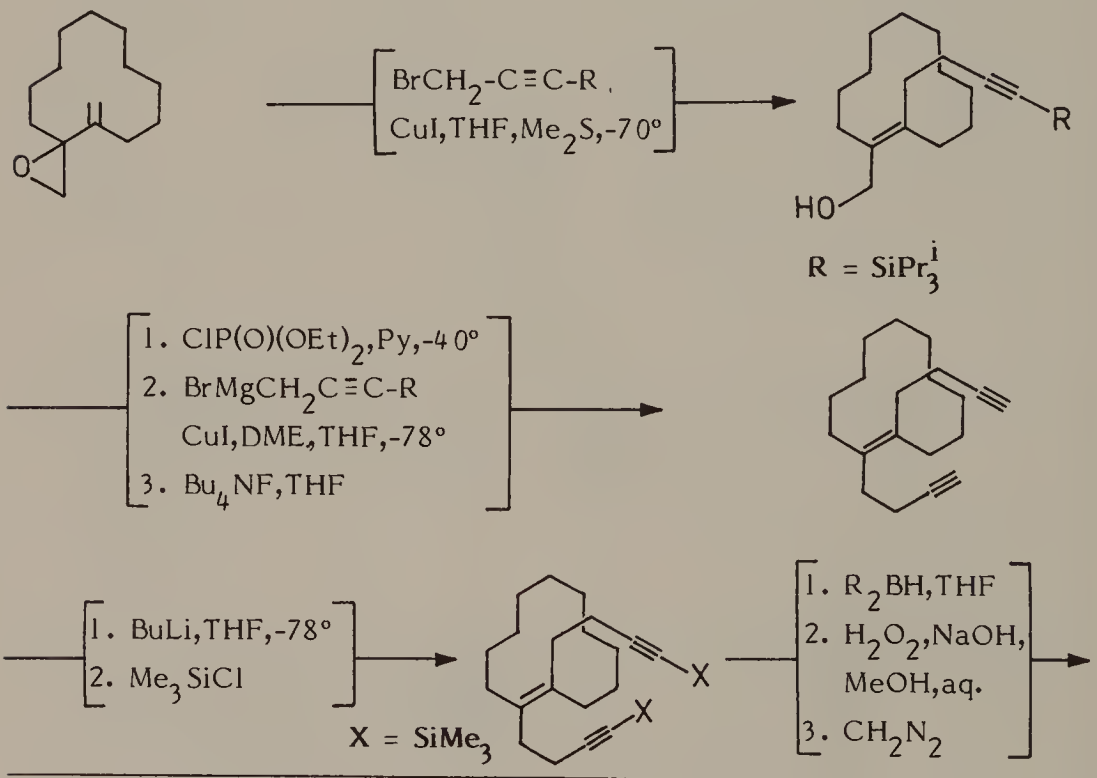


1

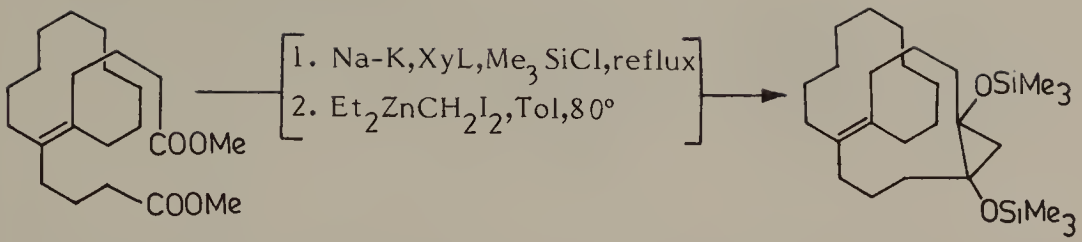
PERANNULANES

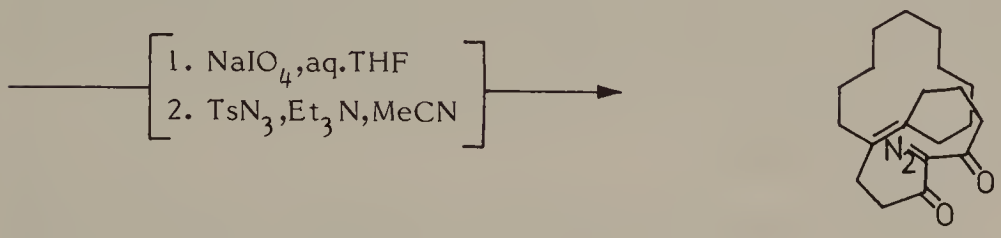
Perannulanes are perceived as fully annelated cycloalkanes in which rings of varying size are fused to each other to form a core ring. Their pleasing appearance belie complexities relating to stereochemistry and chirality, which would naturally increase with increasing perannulane size.

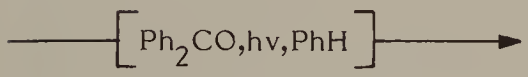
The base member of this series, namely, tri-annulane (I) has been prepared via intra-molecular carbene addition to the betweenanene bond (1). This route also illustrates improved route to betweenanenes.



1. Marshall,J.A.; Peterson,J.C.; Lebioda,L. J. Am. Chem. Soc., 1983, 105, 6515.

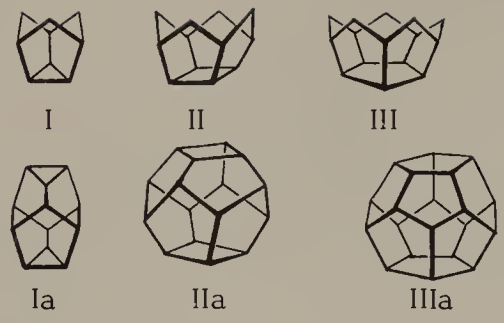






Perannulanes

trans, cis, cis-[10.4.4] tri-annulene-16,18-dione

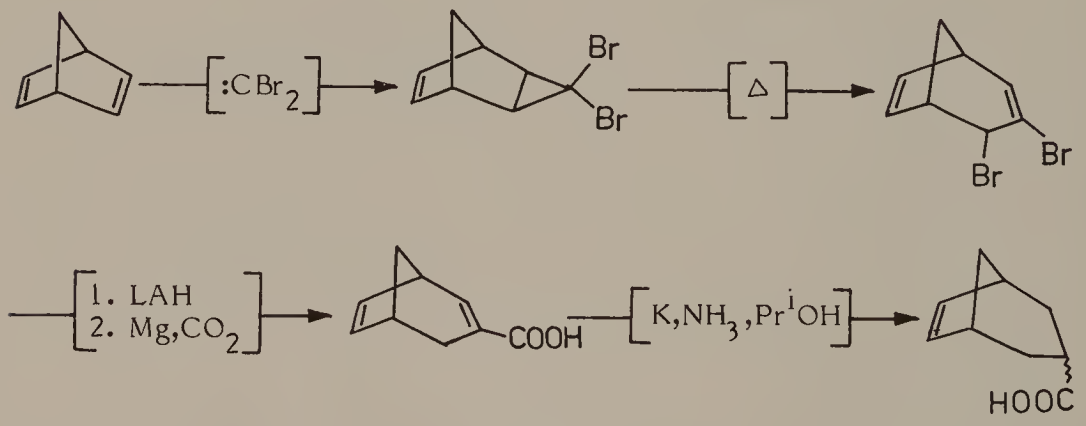


PERISTYLANES

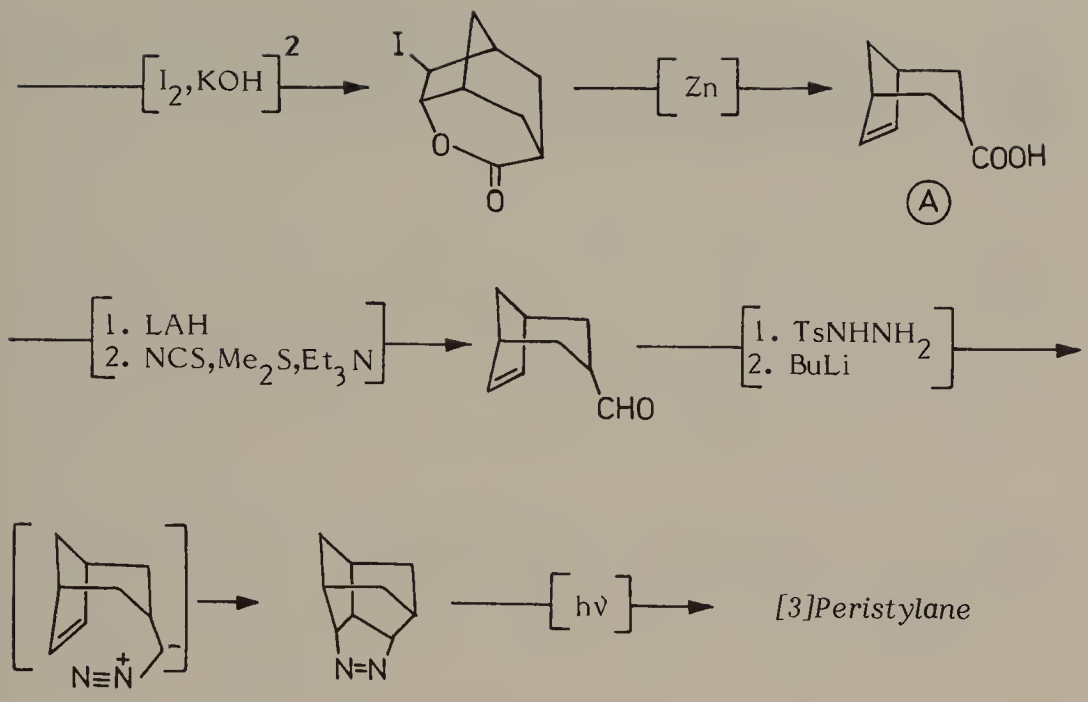
The circumscription of five membered rings around a regular polygon generates a hemi-spherical cup (peristylane) topology such that the rim to base ratio is always 2:1. Their structures are aesthetically appealing, but even more pleasing are the spherical designs hypothetically arising from their dimerization. Thus [3]-, [4]- and [5]peristylanes can be represented as I, II, III and their dimers as Ia,IIa,IIIa. The synthesis of I to III has been achieved.

[3]Peristylane [Triaxane]

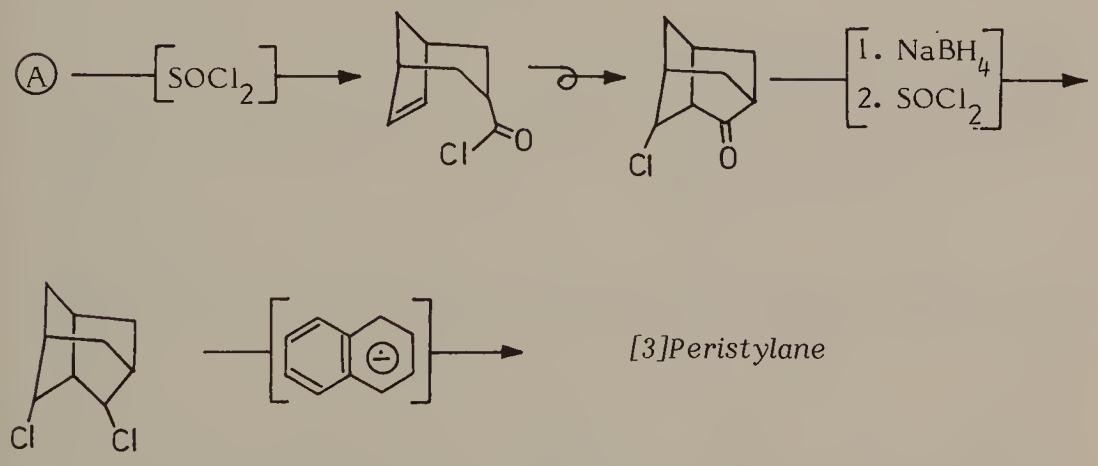
The 3 axial ligands of the chair cyclohexane describe a tripod and the union of these would result in [3]peristylane. When two of such ligands are united by a π bond a bicyclo[2.3.1]octane system is produced. The remaining axial ligands could be affixed to the π bond via cyclopropanation (1).



1. Garratt,P.J.; White,J.F. J. Org. Chem., 1977, 42, 1733.



The intermediate A was also transformed to I, by an alternate pathway involving trans annular π participation.



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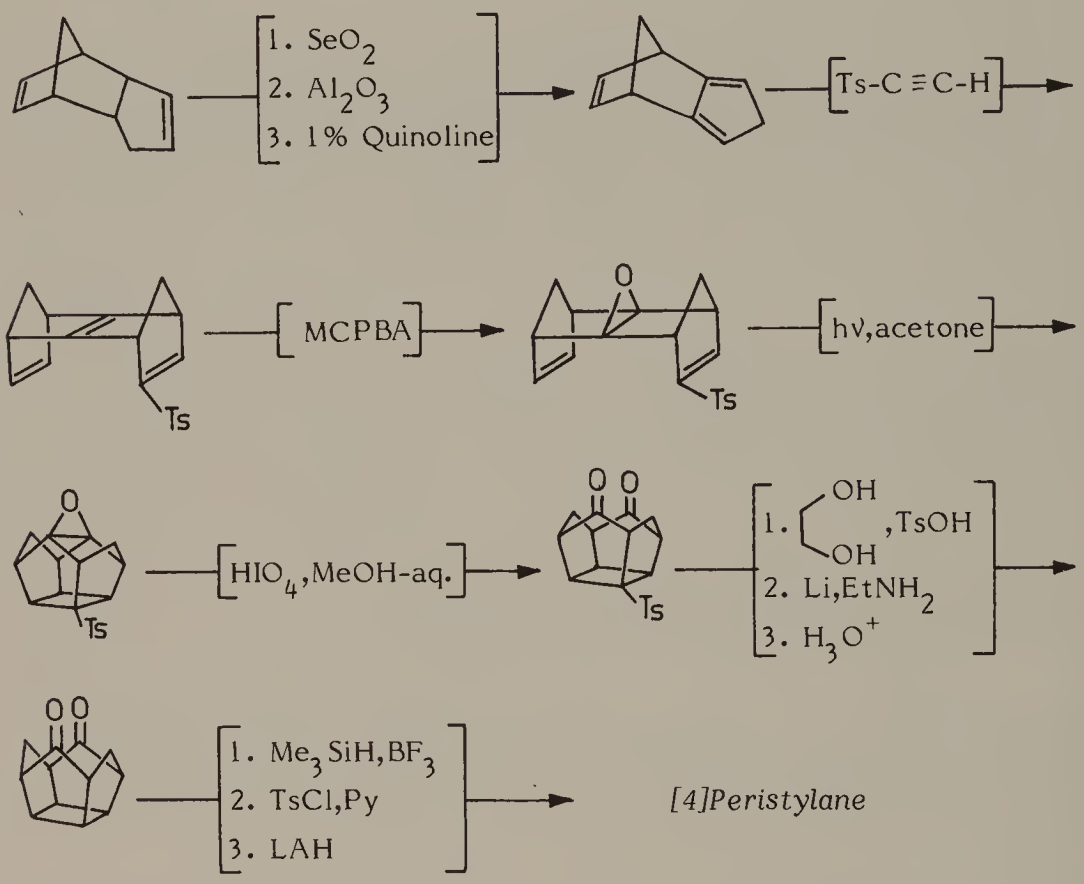
2. Iodolactonization-Zn cleavage sequence was used to separate the required endo acid.

[4]Peristylane

The core of an ingeneous synthesis of [4]peristylane is the intermediate (A), possessing a highly reactive π bond, suited for preferential epoxidation and rupture as well as a proximately aligned π pair, an ideal precursor to the base cyclobutane (3).



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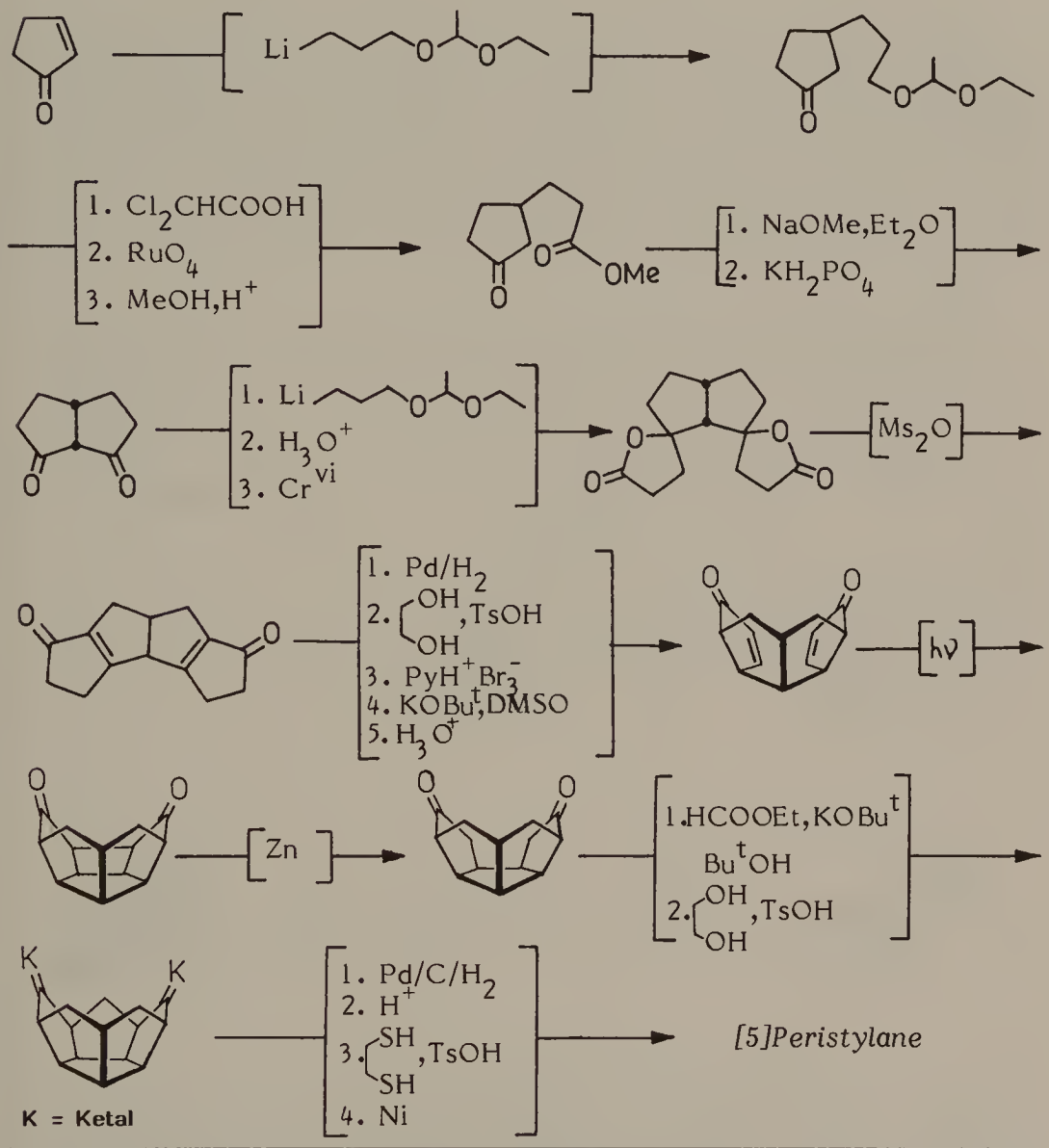
3. Paquette,L.A.; Browne,A.R.; Doecke,C.W.; Williams,R.V. J. Am. Chem. Soc., 1983, 105, 4113.

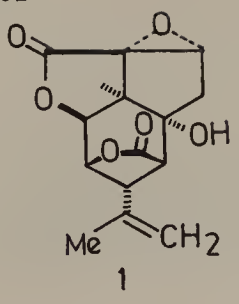
[5]Peristylane

The [5]peristylane synthesis (4) preceeded the intense endeavours to annelated cyclopentanes (5) and provided valuable methodologies in this direction. Indeed, the latest route to [5]peristylane involves the systematic cyclopentane annulation, starting from cyclopentenone.

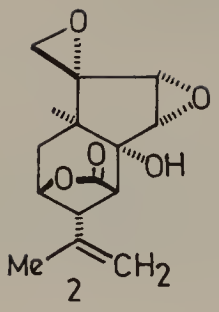


4. Eaton,P.E.; Mueller,R.H.; Carlson,G.R.; Cullison,D.A.; Copper,G.F.; Chou,T.C.; Krebs,E.P. J. Am. Chem. Soc., 1977, 99, 2751.

5. Paquette,L.A. "Recent Synthetic Developments in Polyquinane Chemistry", Springer-Verlag, 1984.



1

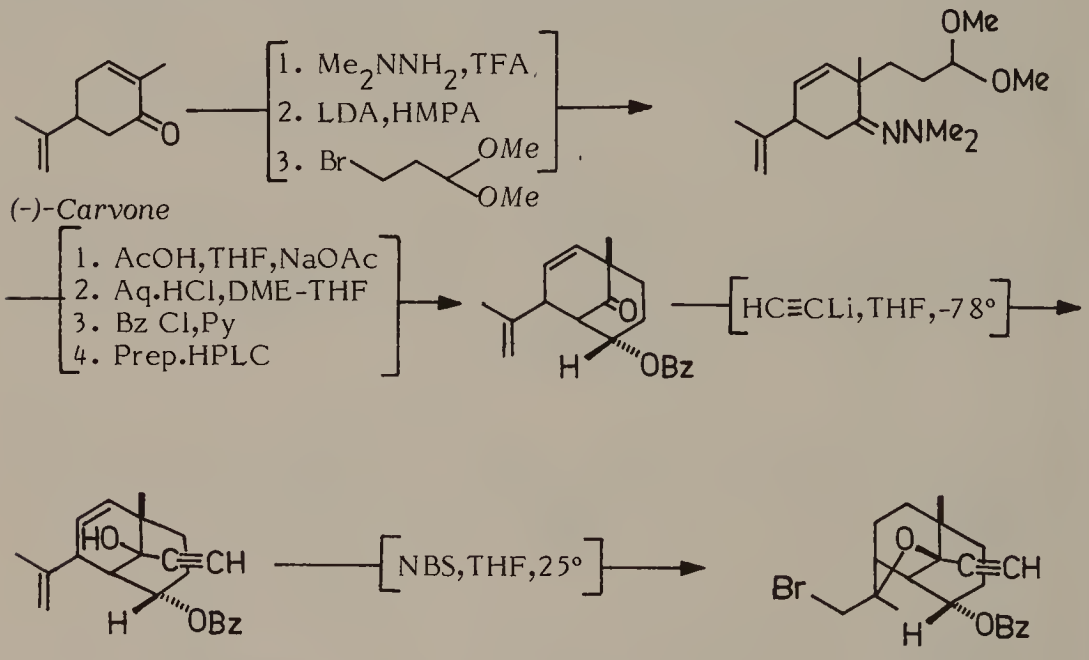


2

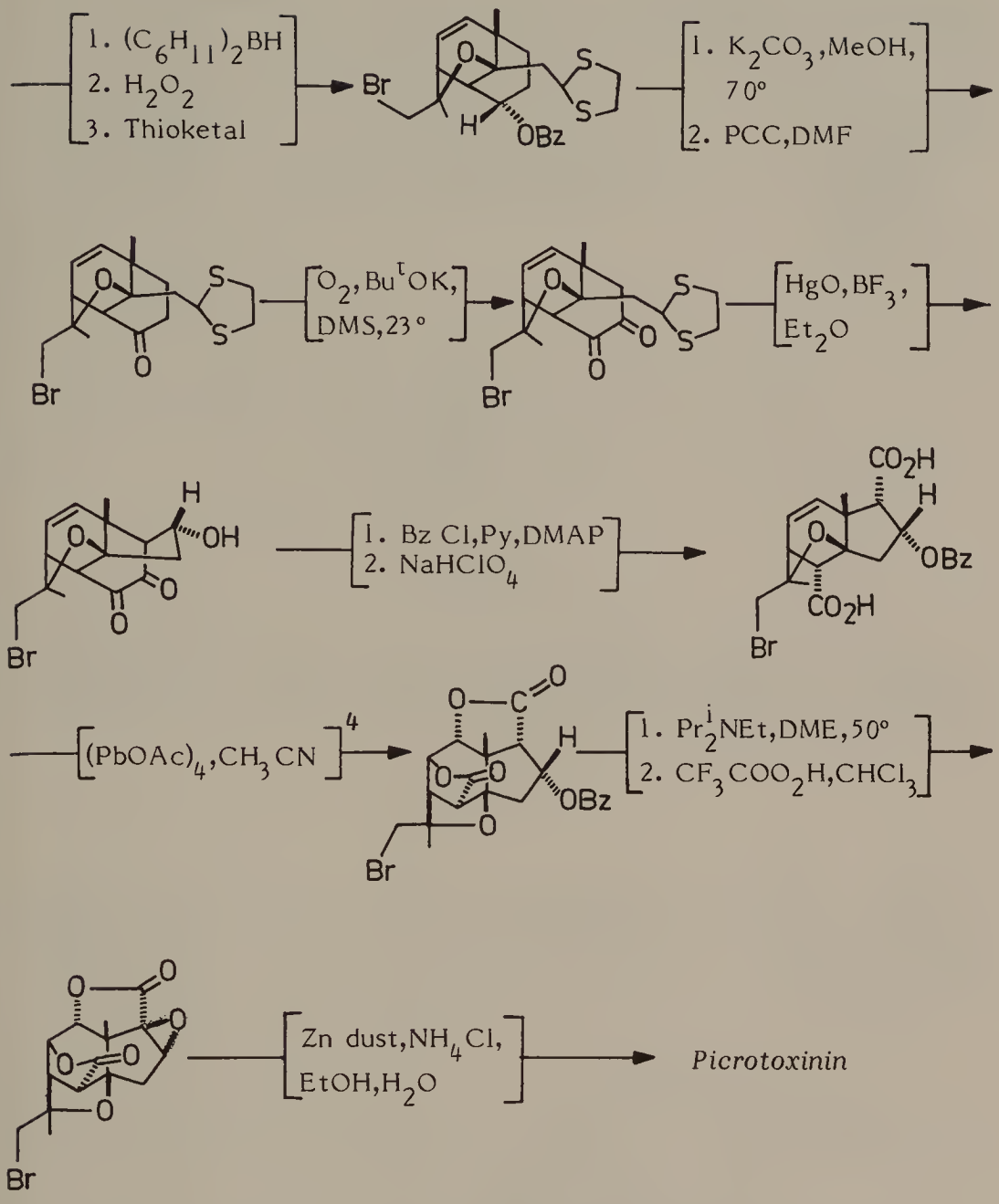
PICROTOXININ
CORIAMYRTIN

Picrotoxin, the poisonous principle from the plant Menispermum cocculus, is a molecular complex of toxic picrotoxinin and nontoxic picrotin. Coriamyrtin C, the toxin isolated from Coriaria species, also belongs to the picrotoxane group. Picrotoxinin and coriamyrtin posed a big challenge for chemical synthesis on account of delicate functionalities and high concentration of chiral centres in the molecule. Two synthesis have been reported for both picrotoxinin (1,3) and coriarmyrtin (2,3), each ingenious in its own way.

The first total synthesis for (-) picrotoxinin was reported in 1979 by Corey & Pearce (1) starting from (-) carvone.

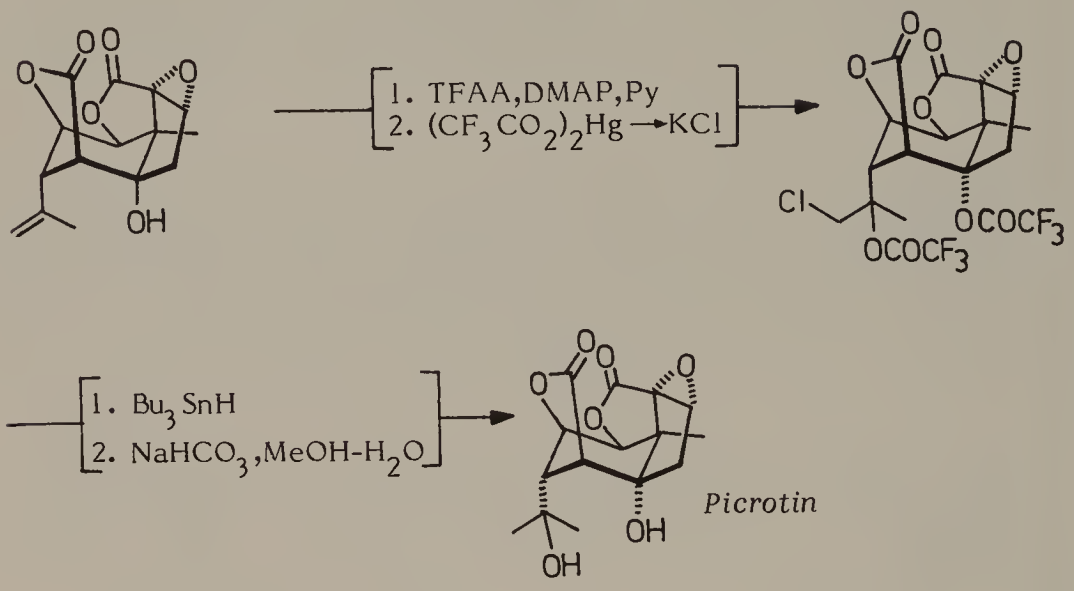


1. Corey,E.J.; Pearce,H.L. J. Am. Chem. Soc., 1979, 101, 5841.
2. Tanaka,K.; Uchiyama,F.; Sakamoto,K.; Inubishi,Y. J. Am. Chem. Soc., 1982, 104, 4965.
3. Niwa,H.; Wakamatsu,K.; Hida,T.; Niiyama,K.; Kigoshi,H.; Yamada,M.; Nagase,H.; Suzuki,M. Yamada,K. J. Am. Chem. Soc., 1984, 106, 4547.



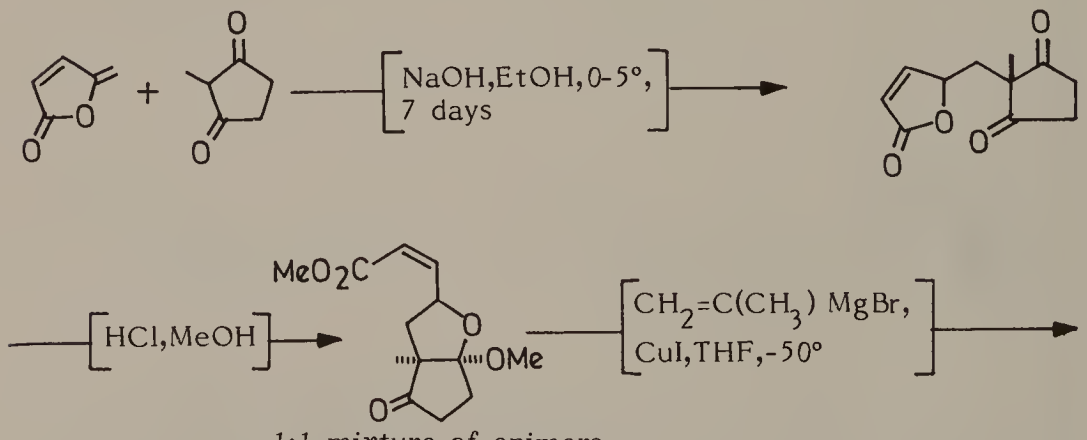
4. Halolactonisation processes to prepare the lactones under variety of reaction conditions failed, which may be due to the pronounced steric shielding of the double bond.

Corey and Pearce (5) have also reported a synthesis of picrotin starting from picrotoxinin.



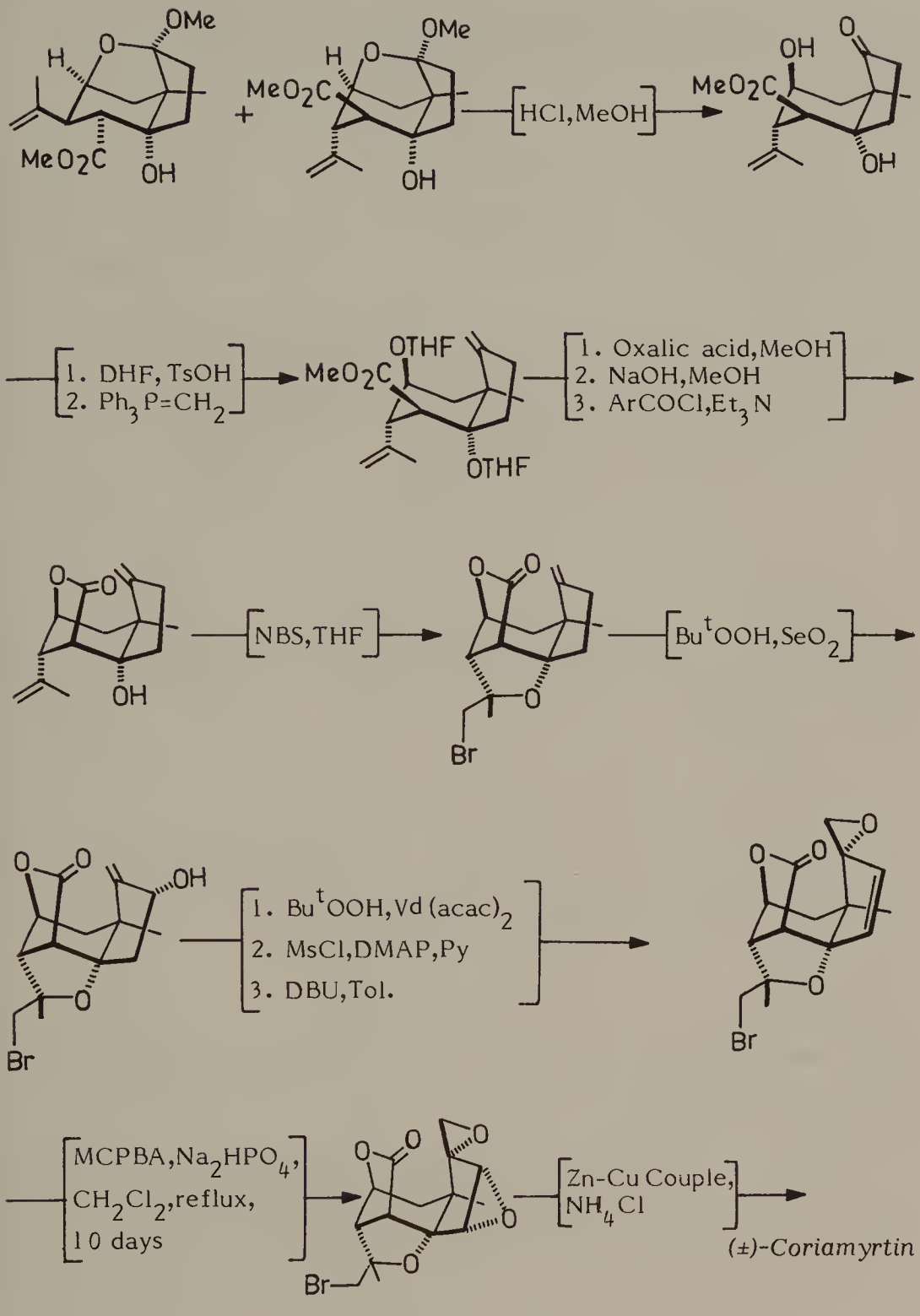
Picrotin

Tanaka et al. (2) reported the first total synthesis of racemic coriamyrtin in 1982 starting from readily available protoanemonin and 2-methylcyclopentane-1,3-dione.

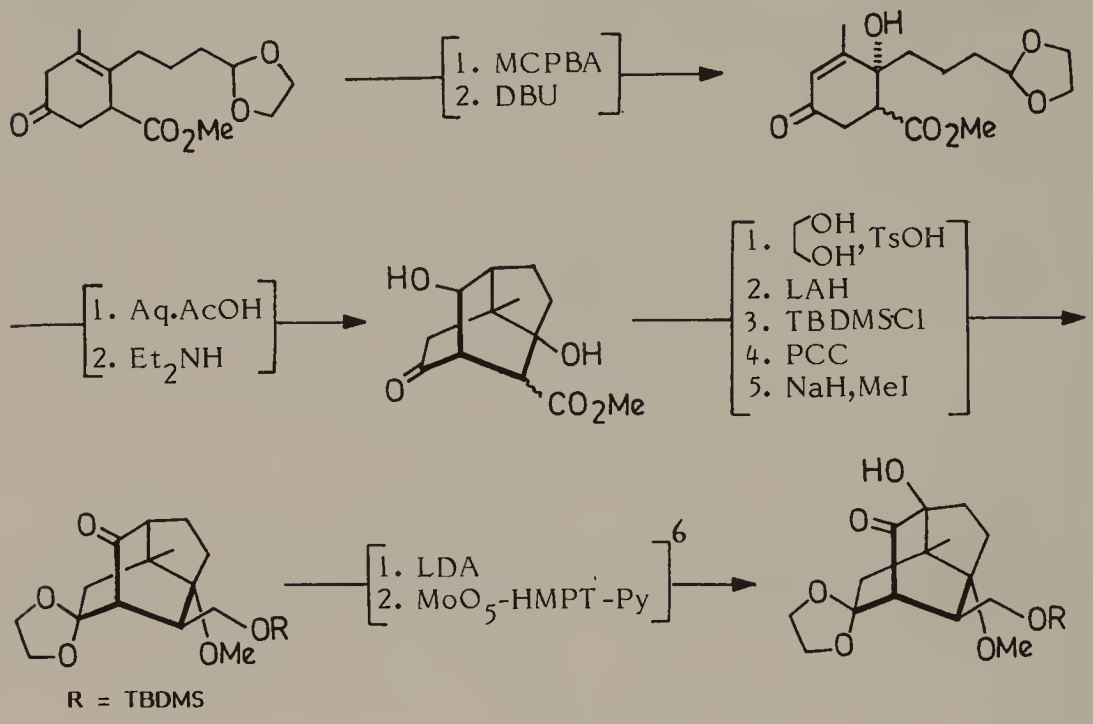


1:1 mixture of epimers

5. Corey,E.J.; Pearce,H.L. Tetrahedron Lett., 1980, 21, 1823.


OMe
H
O
MeO2C
OH
+
HCl,MeOH
1. DHF, TsOH
2. Ph3P=CH2
OTHF
1. Oxalic acid,MeOH
2. NaOH,MeOH
3. ArCOCl,Et3N
NBS,THF
Br
Bu^tOOH,SeO2
1. Bu^tOOH,Vd(acac)2
2. MsCl,DMAP,Py
3. DBU,Tol.
MCPBA,Na2HPO4,
CH2Cl2,reflux,
10 days
Zn-Cu Couple,
NH4Cl
(±)-Coriamyrtin

The second synthesis of (-)-picrotoxinin and (+)-Coriamyrtin reported by Niwa et al. (3) utilises isotwistane compounds as common and key intermediates for their synthesis.



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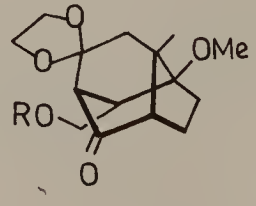
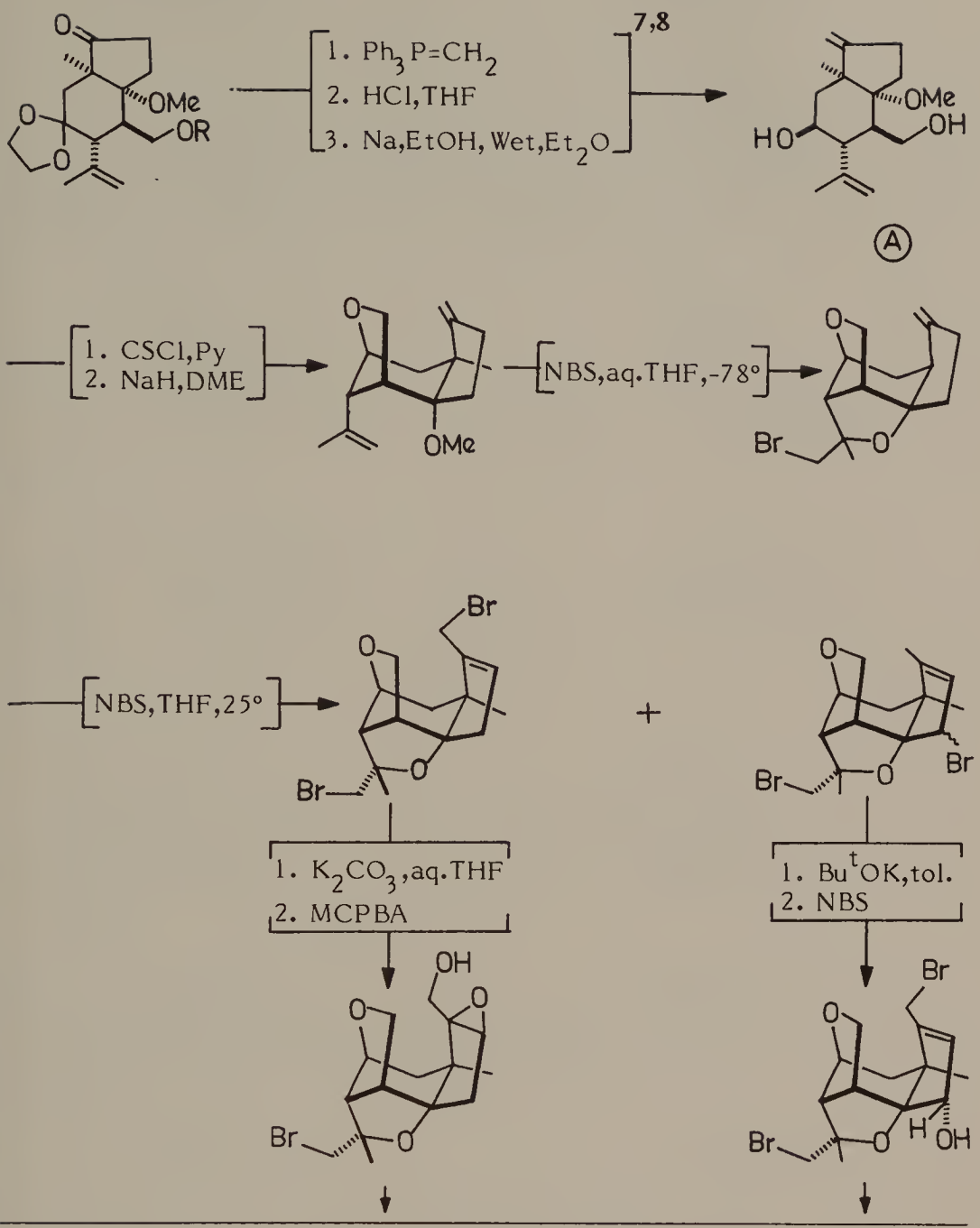
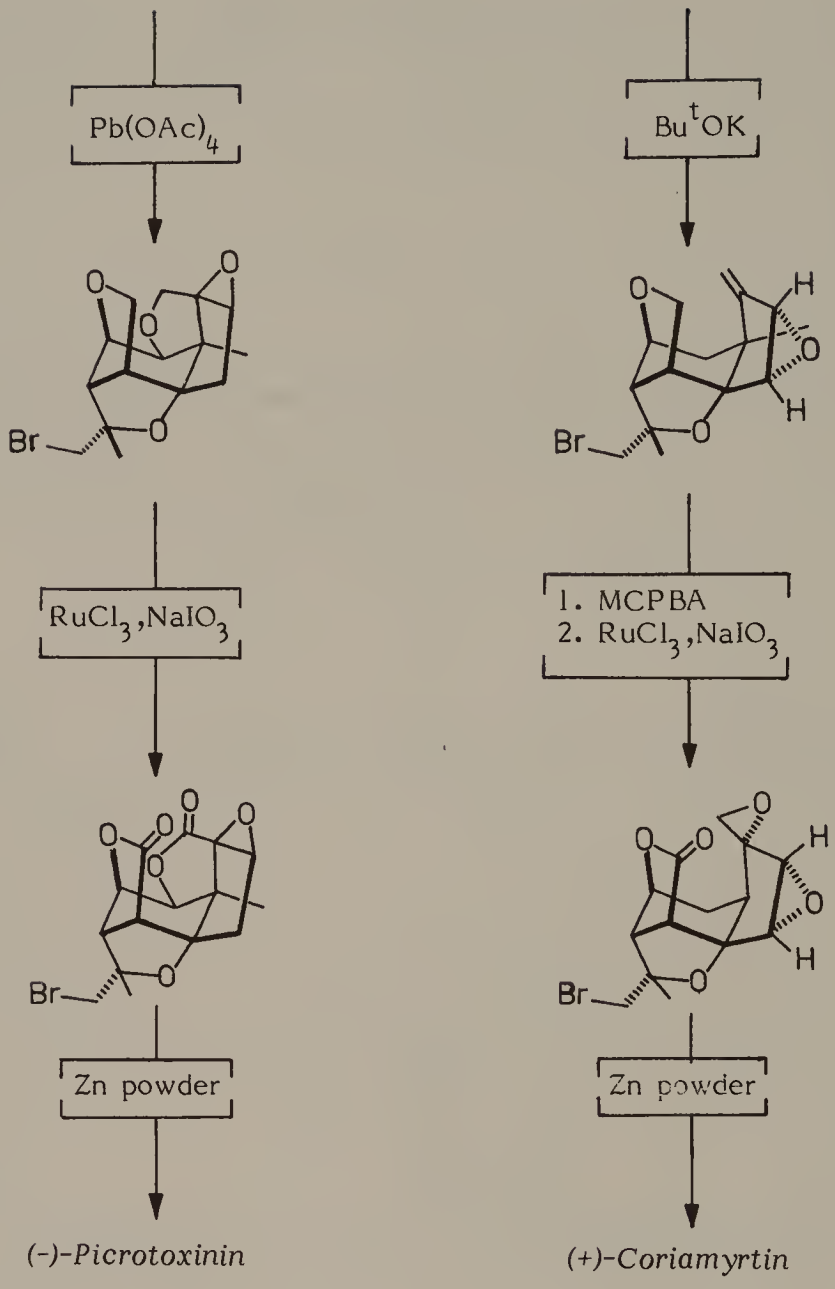
6. The success of bridgehead hydroxylation is due to the cyclohexanone ring in the bicyclo [3.2.1]octan-2-one being locked in the boat form making generation of the bridgehead enolate favourable.





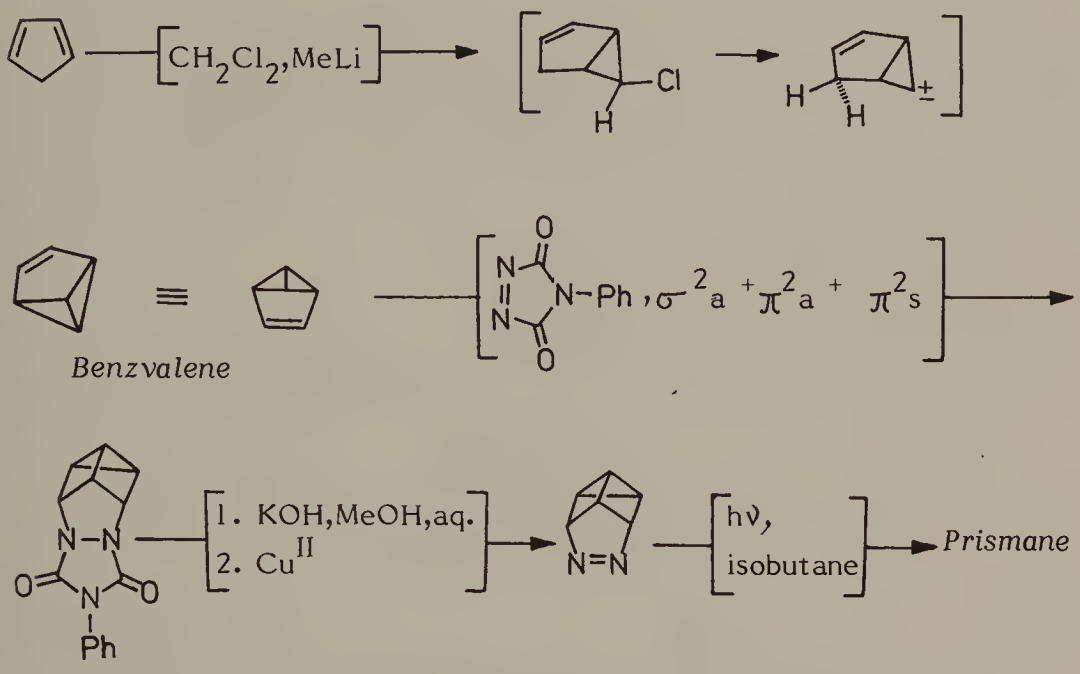
7. Reduction of the keto group after deacetylation with a variety of metal hydrides exclusively the epimer of (A) regarding the secondary hydroxyl group.

8. (A) was resolved through ∝-methoxy-∝-trifluormethyl phenylacetyl ester formation followed by chromatographic separation and LAH reduction to give (+)-(A).

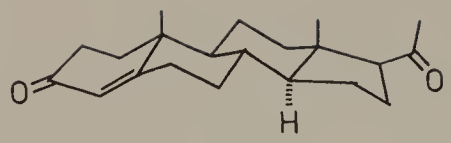

Pb(OAc)4
Bu^tOK
RuCl3,NaIO3
1. MCPBA
2. RuCl3,NaIO3
Zn powder
Zn powder
(-)-Picrotoxinin
(+)-Coriamyrtin

PRISMANE

Inspite of the fact that prismane packs an additional 130 k cal mol^{-1} over benzene, this change, being forbidden by the Woodward-Hoffman rules, is sluggish with a half-life of 11 hours at 90°C. The synthesis of prismane (1) is remarkable and proceeds through yet another isomer of benzene, namely, benzvalene (2).

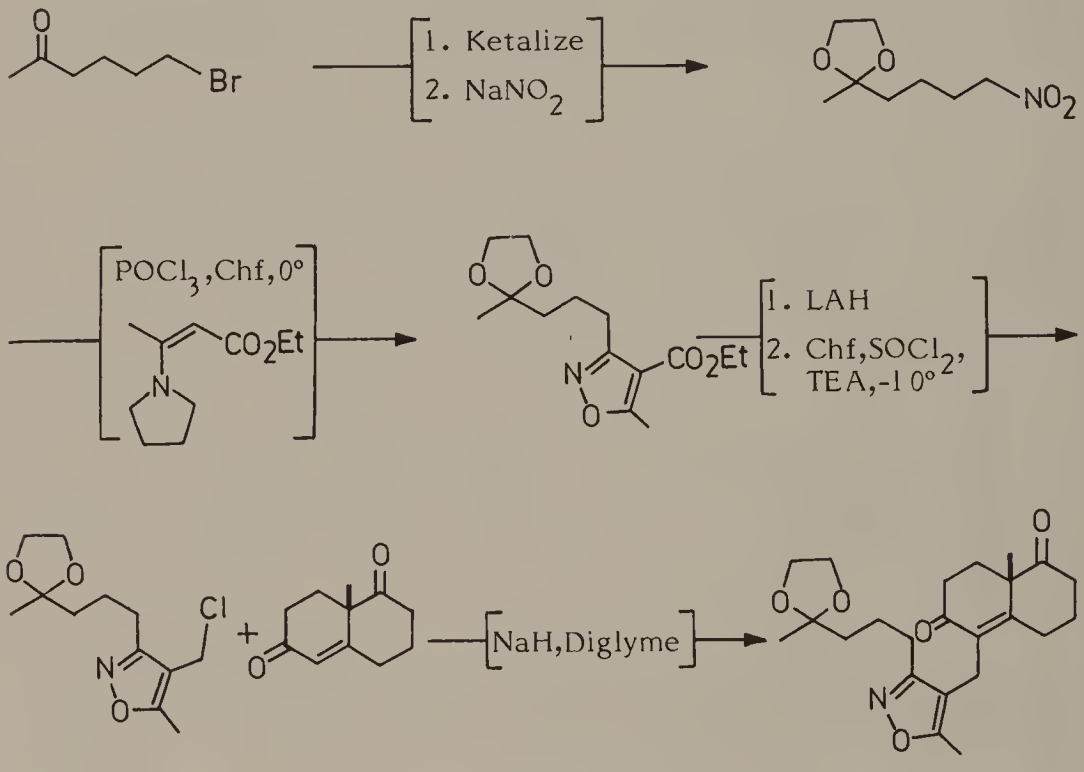


1. Katz,T.J.; Acton,N. J. Am. Chem. Soc., 1973, 95, 2738.
2. Katz,T.J.; Wang,E.J.; Acton,N. J. Am. Chem. Soc., 1971, 93, 3782.



PROGESTERONE

The annelation reaction is an indispensable tool for the construction of polycyclic systems (1). In the synthesis of progesterone outlined below, Stork and McMurry (2) have illustrated the use of a new annelation reaction in which an isoxazole serves as a masked ketoalkyl function (4).



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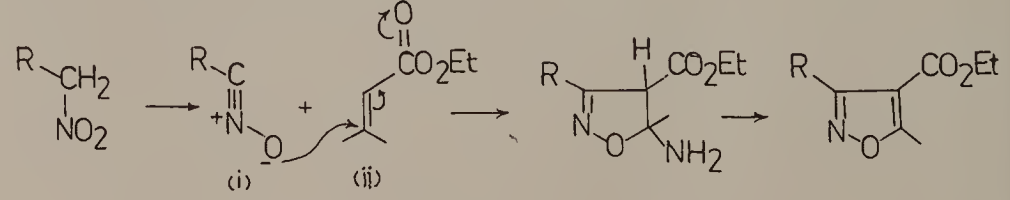
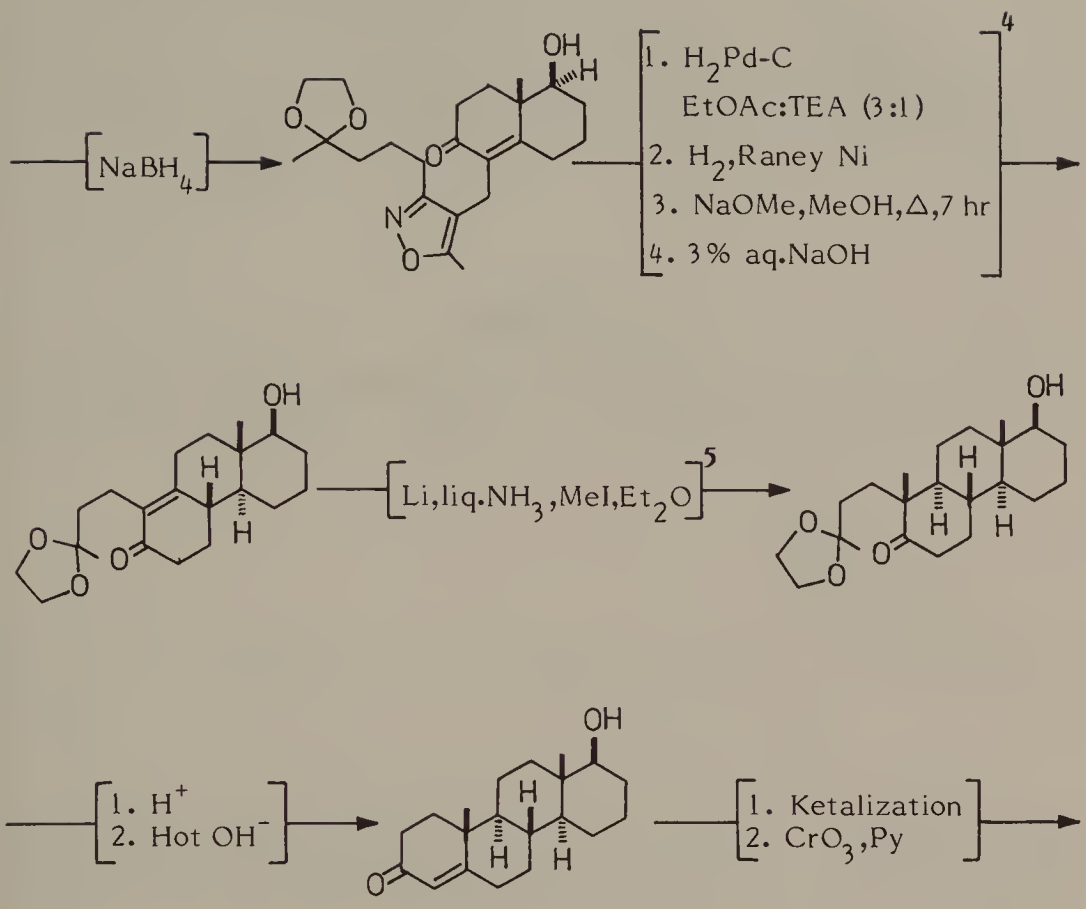
1. Stork,G. Pure Appl. Chem., 1964, 9, 931.

2. Stork,G.; McMurry,J.E. J. Am. Chem. Soc., 1967, 89, 5464.

3. This is a general synthesis of 4-isoxazolecarboxylic acids involving the addition of nitrile oxides (i) to derivatives of β-aminoacrylic esters (ii).





dl-D-Homotestosterone

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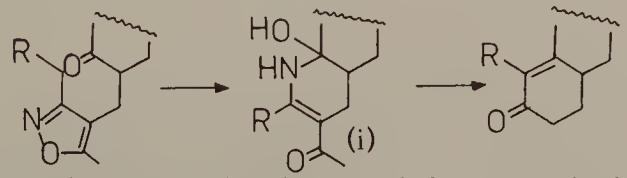
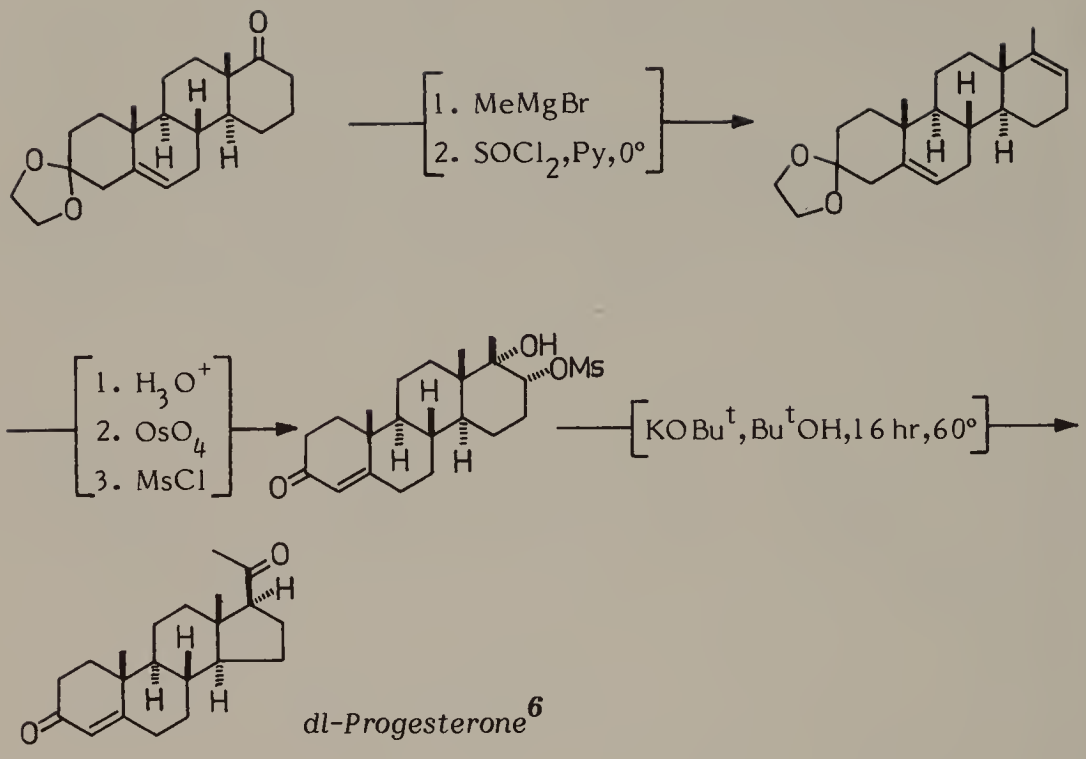
4. This reaction is based on the lability of the N-O linkage of isoxazoles under special conditions, which makes possible their use as a potential ketoalkyl group. Hydrogenolysis with Raney nickel gives rise to a cyclic carbinolamine (i), which affords the annelated ketone on refluxing with aqueous alkali, Stork,G.; Danishefsky,S.; Ohashi,M. J. Am. Chem. Soc., 1967, 89, 5459.



5. The alkylation-trapping method has been used for stereoselective introduction of the C-10 methyl group from the β-face, Stork,G.; Rosen,P.; Goldman,N.; Coombs,R.V.; Tsuji,J. J. Am. Chem. Soc., 1965, 87, 275.



dl-Progesterone[6]

The recent synthesis of 16,17-dehydroprogesterone (7) by biogenetic type polyolefenic cyclisation as the key step represents an exciting new development in steroid total synthesis. This reaction, developed by Johnson and his school (8,9), proceeds with amazing stereoselectivity, all five steric centres of the required configuration being created in one step.

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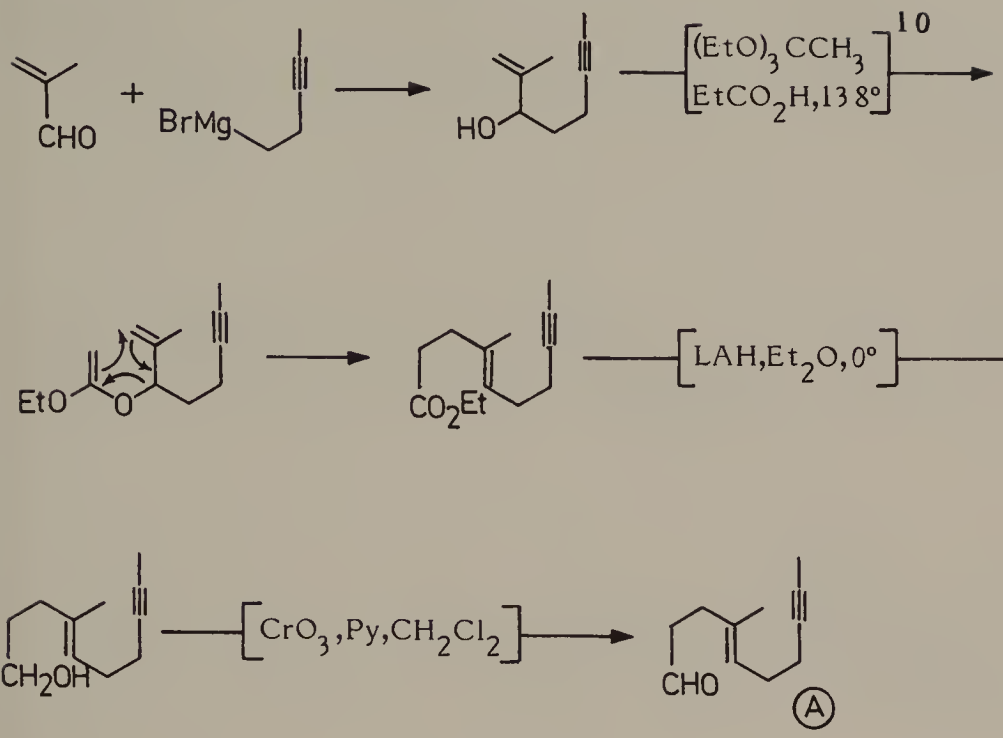
6. For a synthesis of progesterone using the "hydrochrysene approach", see: Johnson,W.S.; Marshall,J.A.; Keana,J.F.W.; Franck,R.W.; Martin,D.G.; Bauer,V.J. Tetrahedron, Supplement 8, 1966, Pt.II, 541.

7. Johnson,W.S.; Semmelhack,M.F.; Sultanbawa,M.U.S.; Dolak,L.A. J. Am. Chem. Soc., 1968, 90, 2994.

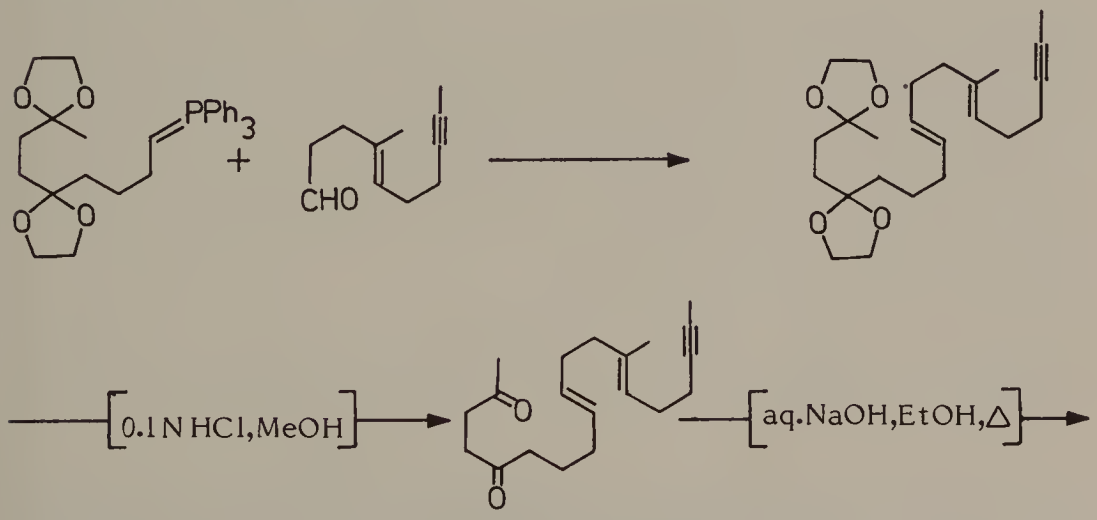
8. Johnson,W.S. Accts. Chem. Res., 1968, 1, 1; the method has already been illustrated in detail by the synthesis of Farnesol.

9. Johnson,W.S.; Gravestock,M.B.; McCarry,B.E. J. Am. Chem. Soc., 1971, 93, 4332; Johnson, W.S.; Gravestock,M.B.; Parry,R.J.; Myers,R.F.; Bryson,T.A.; Miles,D.H. J. Am. Chem. Soc., 1971, 93, 4330; Johnson,W.S.; Chen,Y.Q.; Kelogg,M.S. Biol. Act. Princ. Nat. Prod., 1984, 55; Johnson,W.S.; Chen.Y.Q.; Kellogg,M.S. Biol. Act. Princ. Nat. Prod., 1984, 55.

Preparation of Acetylenic Aldehyde (A)



Preparation of Progesterone



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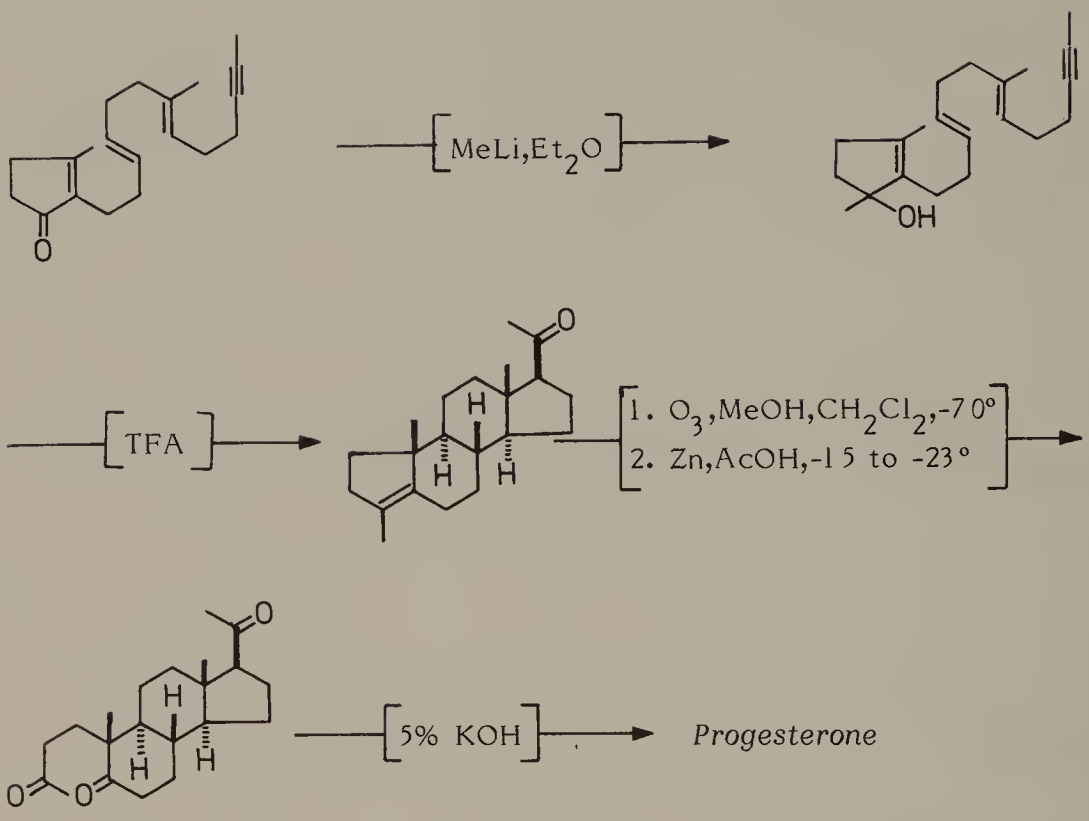
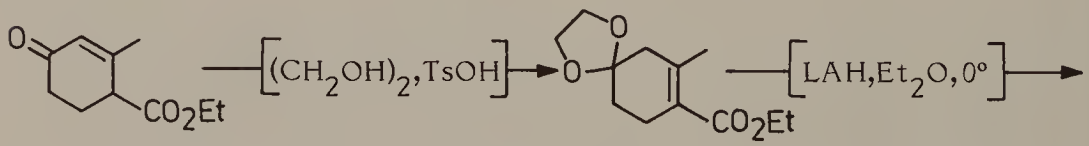
10. Ortho acetate Claisen reaction: Johnson,W.S.; Werthemann,L.; Bartlett,W.R.; Brocksom, T.J.; Li,T.; Faulkner,D.J.; Petersen,M.R. J. Am. Chem. Soc., 1970, 92, 741.



In a further refinement of this approach, Johnson and coworkers reported the direct construction of a complete steroid nucleus, in optically active form, by nonenzymic biogenetic-like cyclization (11,12). This was accomplished by incorporating, along with the terminal acetylenic residue into the key cyclization substrate, trienyol Ⓔ, a cyclohexenol moiety previously shown to be capable of initiating stereoselective cyclization to A/B cis decalin structures (13). Commencing with a substrate bearing a chiral C-5 the cyclization proceeds stereospecifically to yield an optically active tetracyclic product.

Preparation of Ring A/B Component



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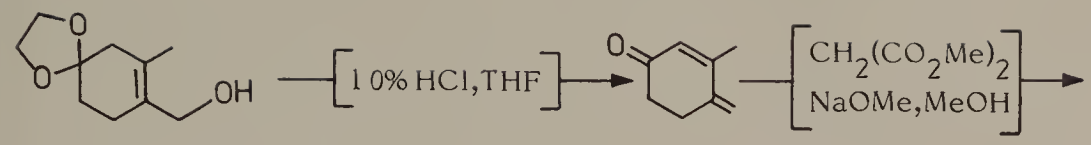
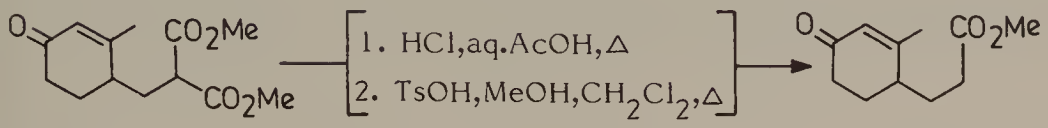
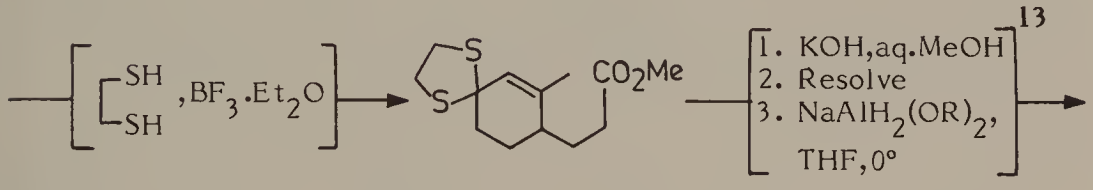
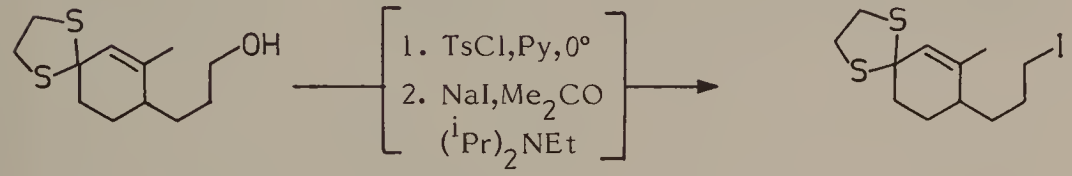
11. Markezich,R.L.; Willy,W.E.; McCarry,B.E.; Johnson,W.S. J. Am. Chem. Soc., 1973, 95, 4414.

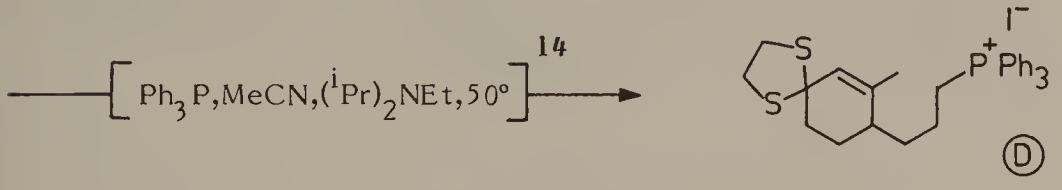
12. McCarry,B.E.; Markezich,R.L.; Johnson,W.S. J. Am. Chem. Soc., 1973, 95, 4416.











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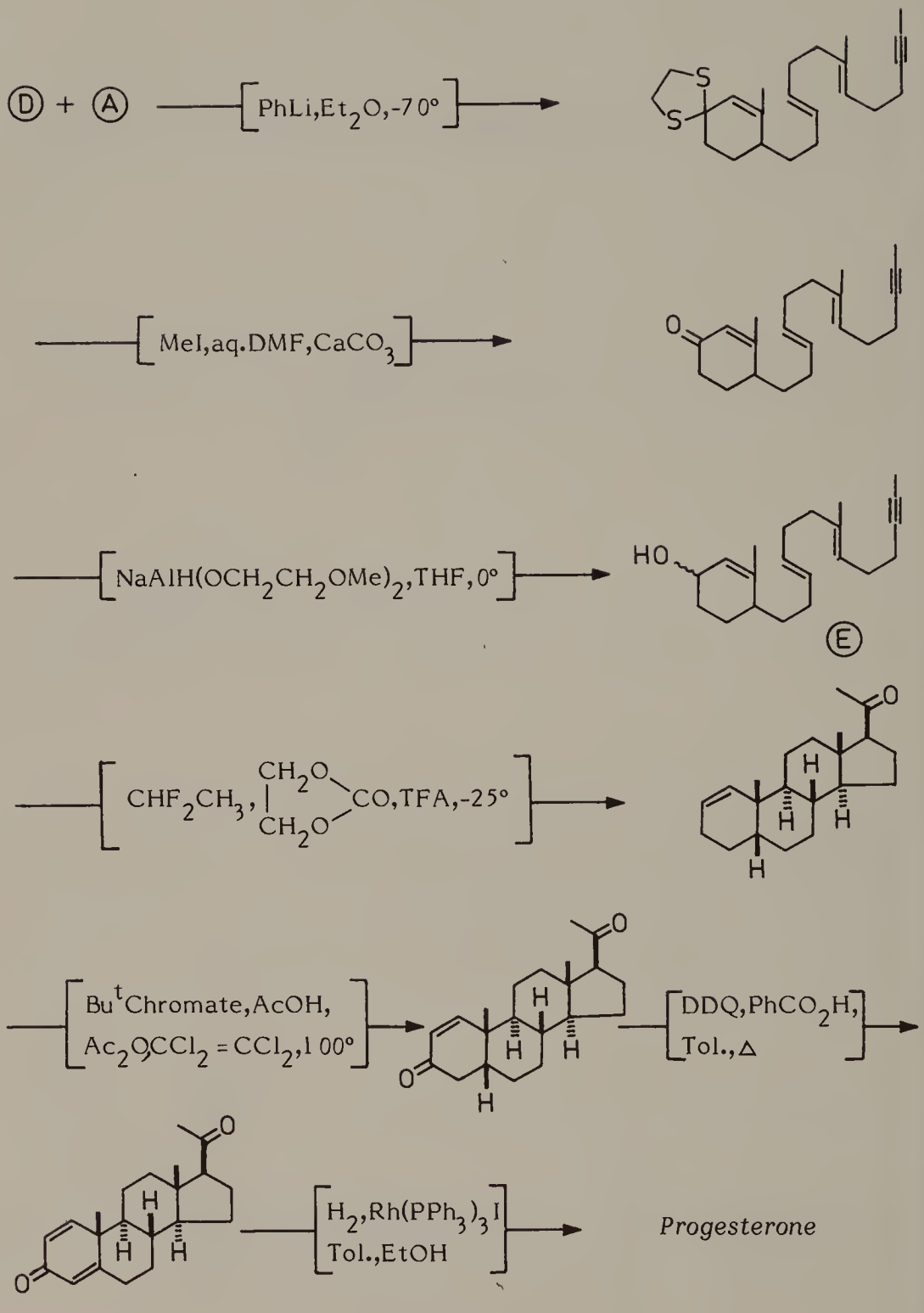
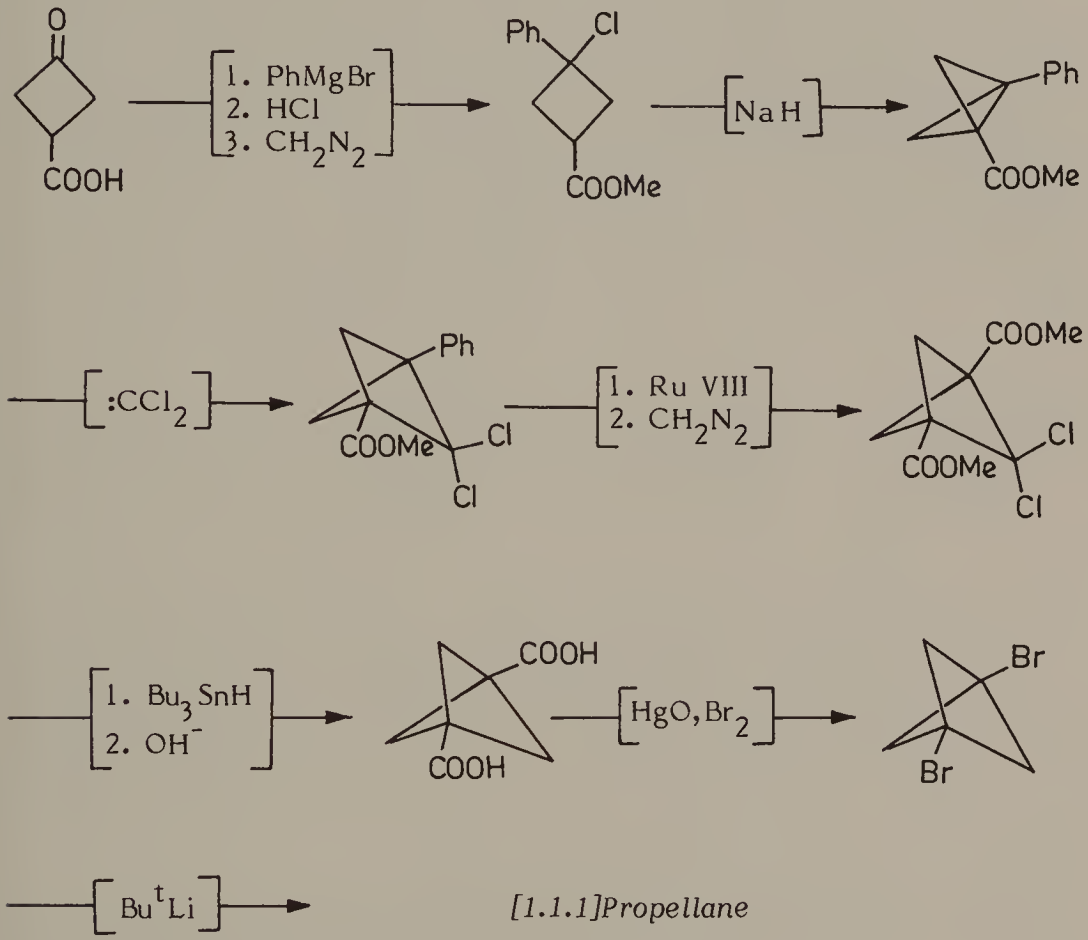
13. Johnson,W.S.; Neustaedter,P.J.; Schmiegel,K.K. J. Am. Chem. Soc., 1965, 87, 5148.
14. Diisopropylethylamine prevented migration of double bond to β,γ-position.


Ⓓ + Ⓐ
PhLi,Et2O,-70°
MeI,aq.DMF,CaCO3
NaAlH(OCH2CH2OMe)2,THF,0°
HO
Ⓔ
CHF2CH3,
CH2O
CO,TFA,-25°
CH2O
Bu^tChromate,AcOH,
Ac2O,CCl2=CCl2,100°
DDQ,PhCO2H,
Tol.,Δ
H2,Rh(PPh3)3I
Tol.,EtOH
Progesterone

[1.1.1]PROPELLANE

The tetrahedral valency distribution of saturated carbon dictates that in any representation, only 3 of the ligands can be in the same hemisphere. Bending these ligands in the direction of the 4th by an "umbrella folding" operation, would steeply increase the strain. The fact that even the ultimate in such an operation, namely, [1.1.1]-propellane can be made (1), and is found stable, provides yet another example of the remarkable flexibility permitted in carbon constellations.



[1.1.1]Propellane

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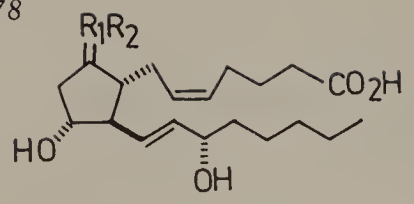
1. Wiberg,K.B. Acc. Chem. Res., 1984, 17, 379.



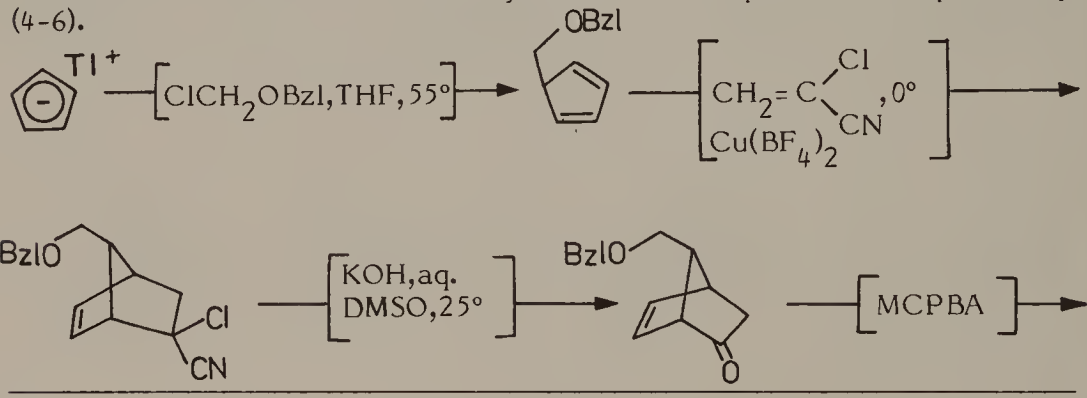
PROSTAGLANDINS

E_2, $R_1R_2 = O$

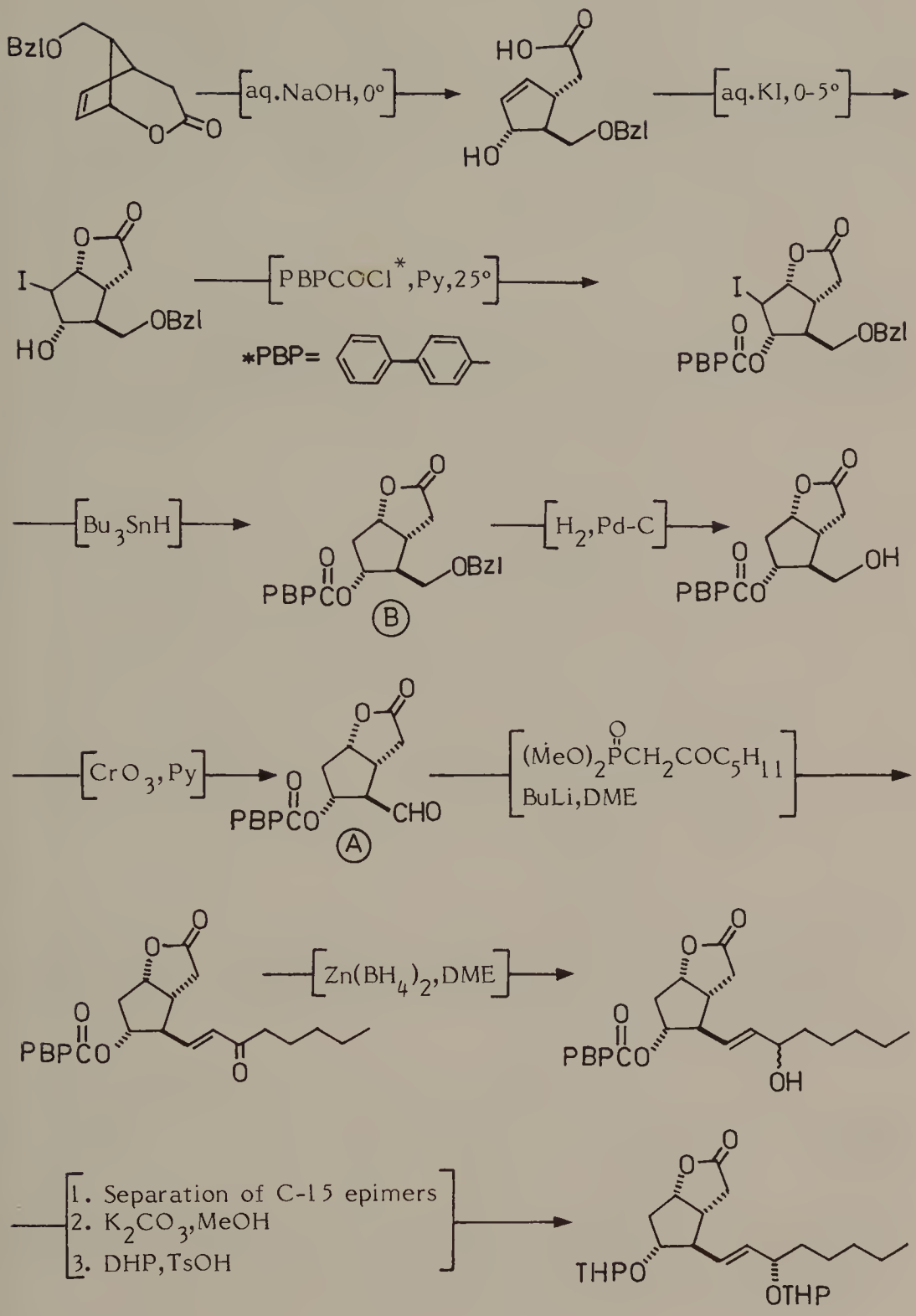
$F_2\alpha$, $R_1 = \alpha OH$, $R_2 = \beta H$

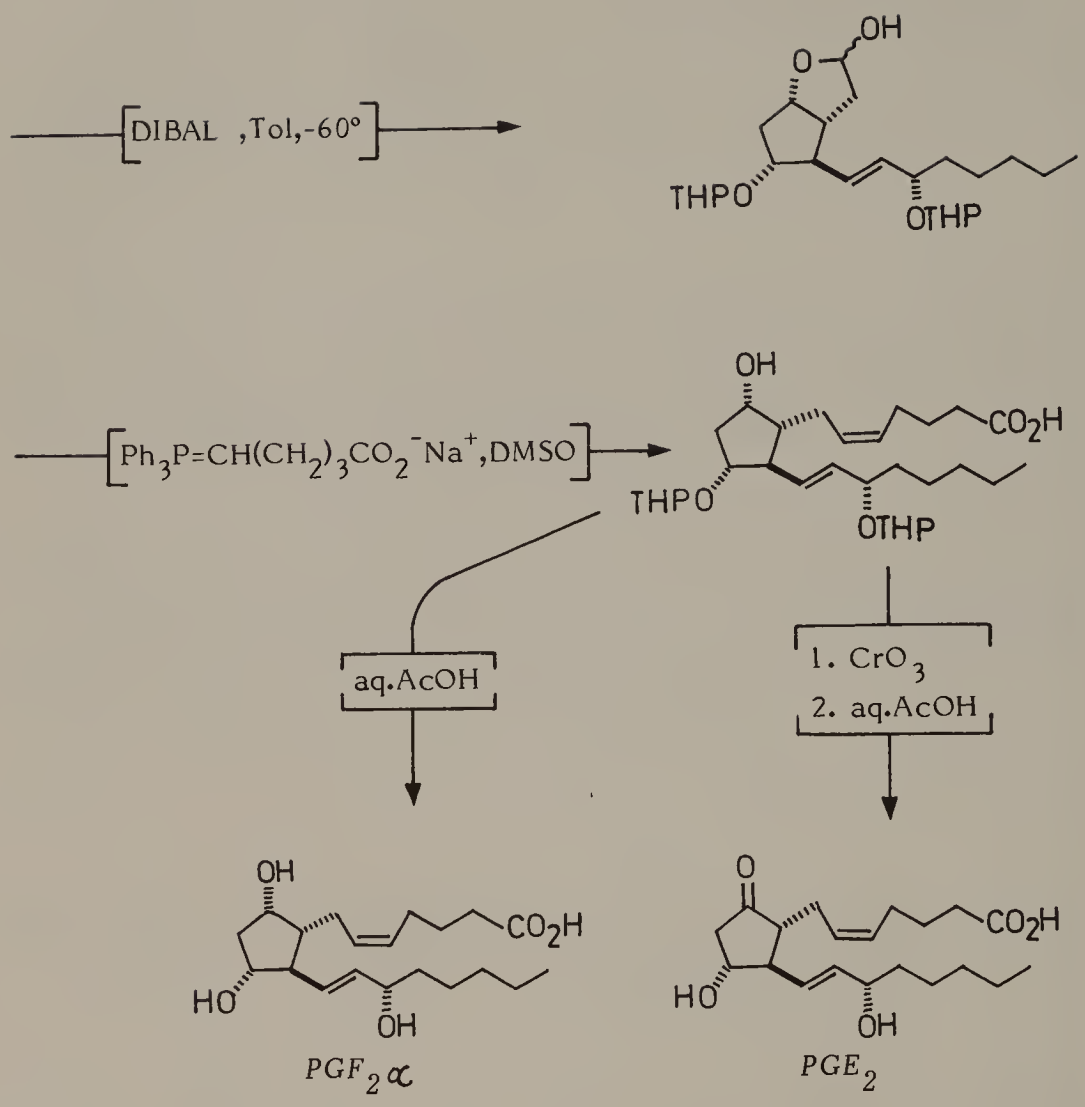
The number and variety of syntheses of these biologically important molecules which are now a legion (1,2) cover a wide span from the first almost 20 step synthesis of Just and Simonovitch (3) to the latest one pot, two step, greatly flexible synthesis of Suzuki et al. from an optically active 4-hydroxy-cyclopentenone (13).

The most successful of the earlier approaches was developed by Corey, which provided access to all of the primary prostaglandins from a single resolved precursor. It employs Diels-Alder reaction for construction of the key bicyclic intermediate in which all four of the ring appendages and stereocenters of the basic prostaglandin nucleus are established efficiently and with complete stereospecificity (4-6).

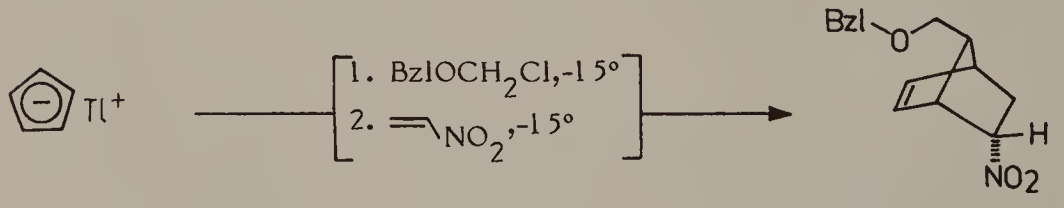


1. For a discussion of earlier synthetic strategies and classification of prostaglandins see: Bindra,J.S.; Bindra,R. Prostaglandin Synthesis, Academic Press, New York, 1977.
2. Reviews: Roberts,S.M.; Scheinmann,F. eds. "New Synthetic Routes to Prostaglandins and Thromboxanes", Academic Press, New York, 1982; Bindra,J.S. in "The Total Synthesis of Natural Products", Vol.4, ed., ApSimon,J. Wiley-Interscience, New York, 1981, p.353; Crabbe,P. ed. "Prostaglandin Research", Academic Press, New York, 1977; Caton,M.P.L.; Crowshaw,K. Progr. Med. Chem., 1978, 15, 357; Nicolaou,K.C.; Gasic,G.P.; Barnett,W. Angew. Chem. Int. Ed., 1978, 17, 293.
3. Just,G.; Simonovitch,C. Tetrahedron Lett., 1967, 2093.
4. For an excellent introduction to the strategy underlying the program of total synthesis of prostaglandins at Harvard, see: Corey,E.J. Ann. N.Y. Acad. Sci., 1971, 180, 24.
5. Corey,E.J.; Weinshenker,N.M.; Schaaf,T.K.; Huber,W. J. Am. Chem. Soc., 1969, 91, 5675.
6. Corey,E.J.; Schaaf,T.K.; Huber,W.; Koelliker,V.; Weinshenker,N.M. J. Am. Chem. Soc., 1970, 92, 397.

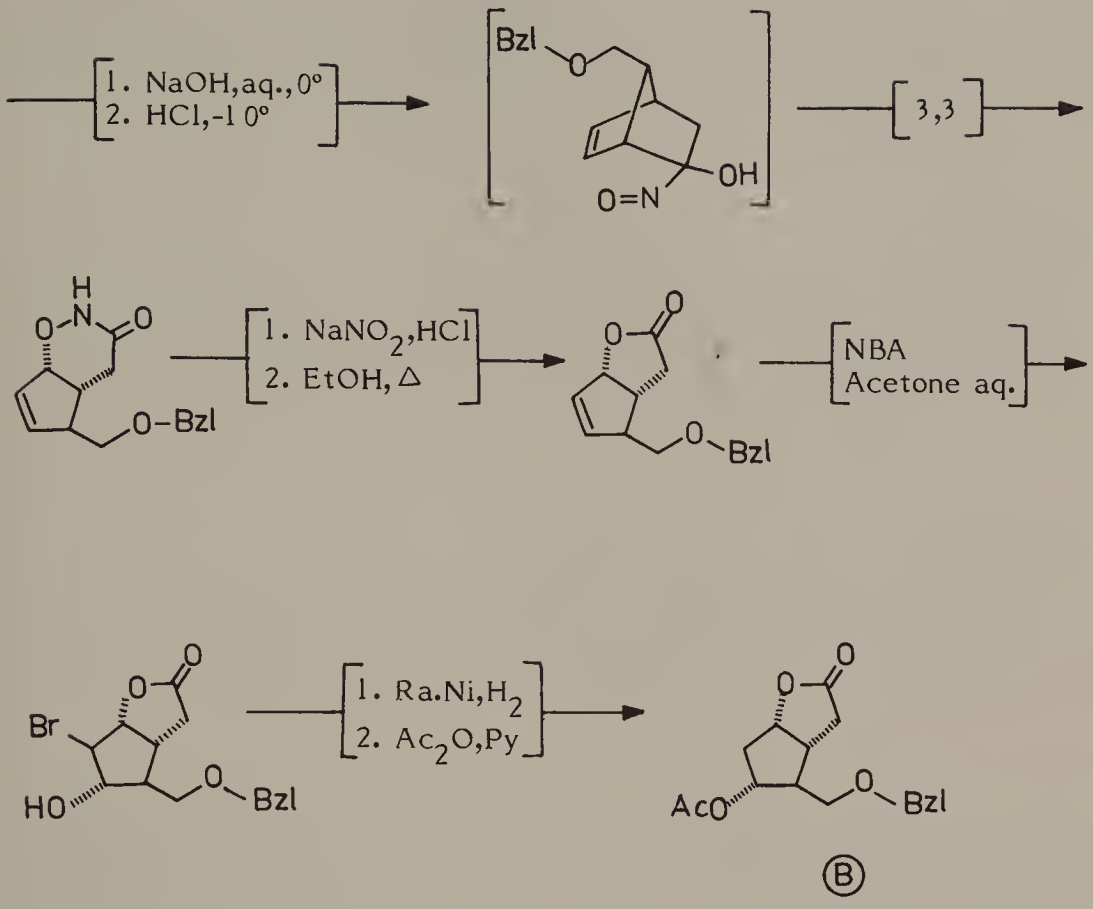

BzlO
aq.NaOH, 0°
HO
OBzl
HO
aq.KI, 0-5°
I
OBzl
HO
PBPCOCl*, Py, 25°
*PBP=
I
OBzl
PBPCO
Bu3SnH
OBzl
PBPCO
B
H2, Pd-C
OH
PBPCO
CrO3, Py
PBPCO
CHO
A
(MeO)2PCH2COC5H11
BuLi, DME
PBPCO
O
Zn(BH4)2, DME
PBPCO
OH
1. Separation of C-15 epimers
2. K2CO3, MeOH
3. DHP, TsOH
THPO
OTHP



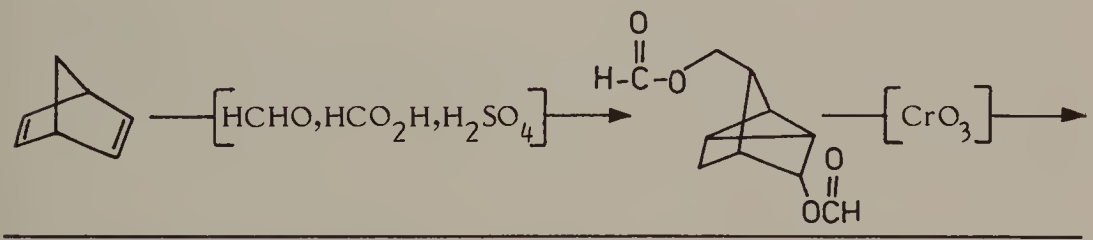
Ranganathan and his colleagues have developed a nitroethylene route to the Corey lactone B, which is short, practical and incorporates several novel features (7).



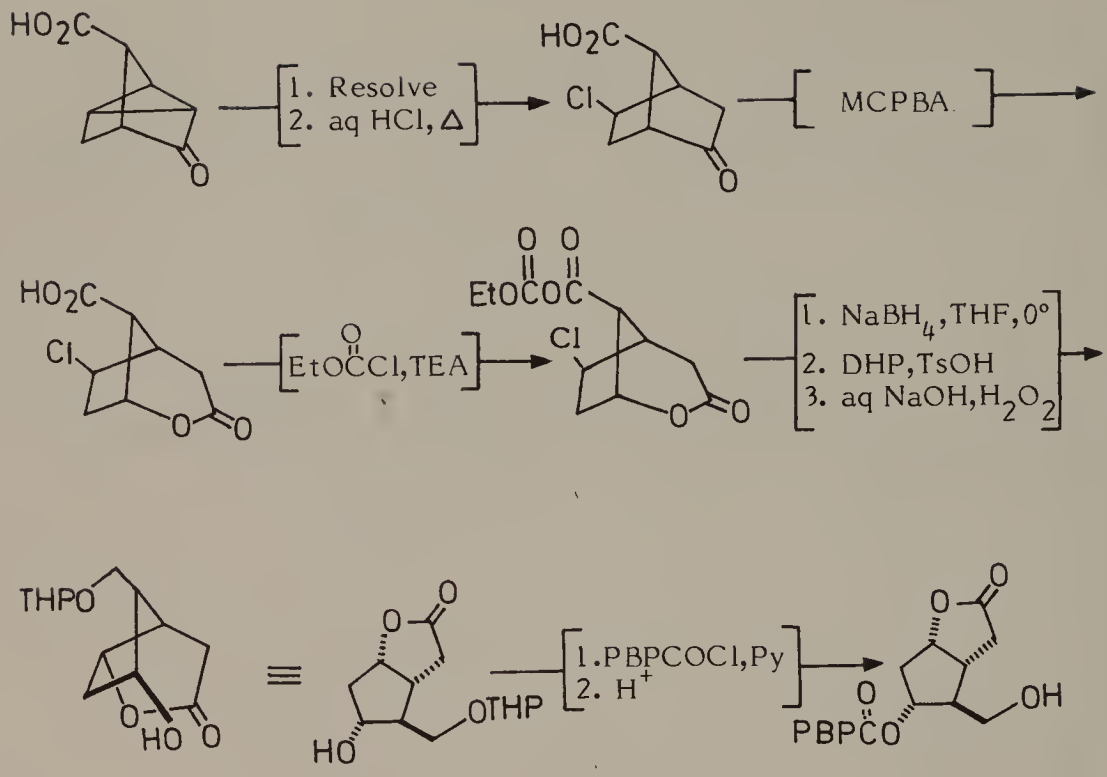
7. Ranganathan,S.; Ranganathan,D.; Mehrotra,A.K. J. Am. Chem. Soc., 1974, 96, 5261; Ranganathan,S.; Ranganathan,D.; Mehrotra,A.K. Tetrahedron Lett., 1975, 1215.



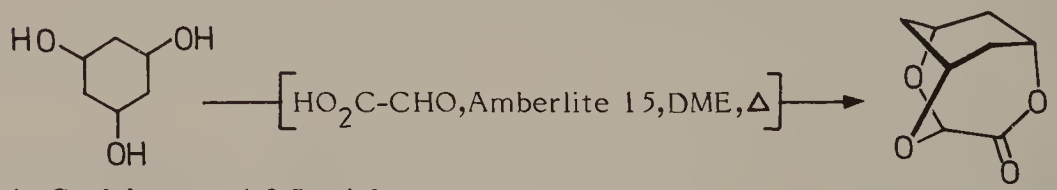
An alternative route to the Corey aldehyde (A), which was developed at Pfizer (8), utilizes an unusual Prins reaction on norbornadiene.



8. Bindra,J.S.; Grodski,A.; Schaaf,T.K.; Corey,E.J. J. Am. Chem. Soc., 1973, 95, 7522.



The stereospecific synthesis of $PGF_2\alpha$ by Woodward and his colleagues at Basel is noteworthy for its ingenious use of functional groups as internal protecting agents and their application to exert stereochemical control during synthetic operations. The synthesis commences with cyclohexane-1,3,5-triol, leading to a cyclohexyl amino diol Ⓐ which undergoes ring contraction to establish the prostanoid cyclopentane nucleus (9).



cis-Cyclohexane-1,3,5-triol

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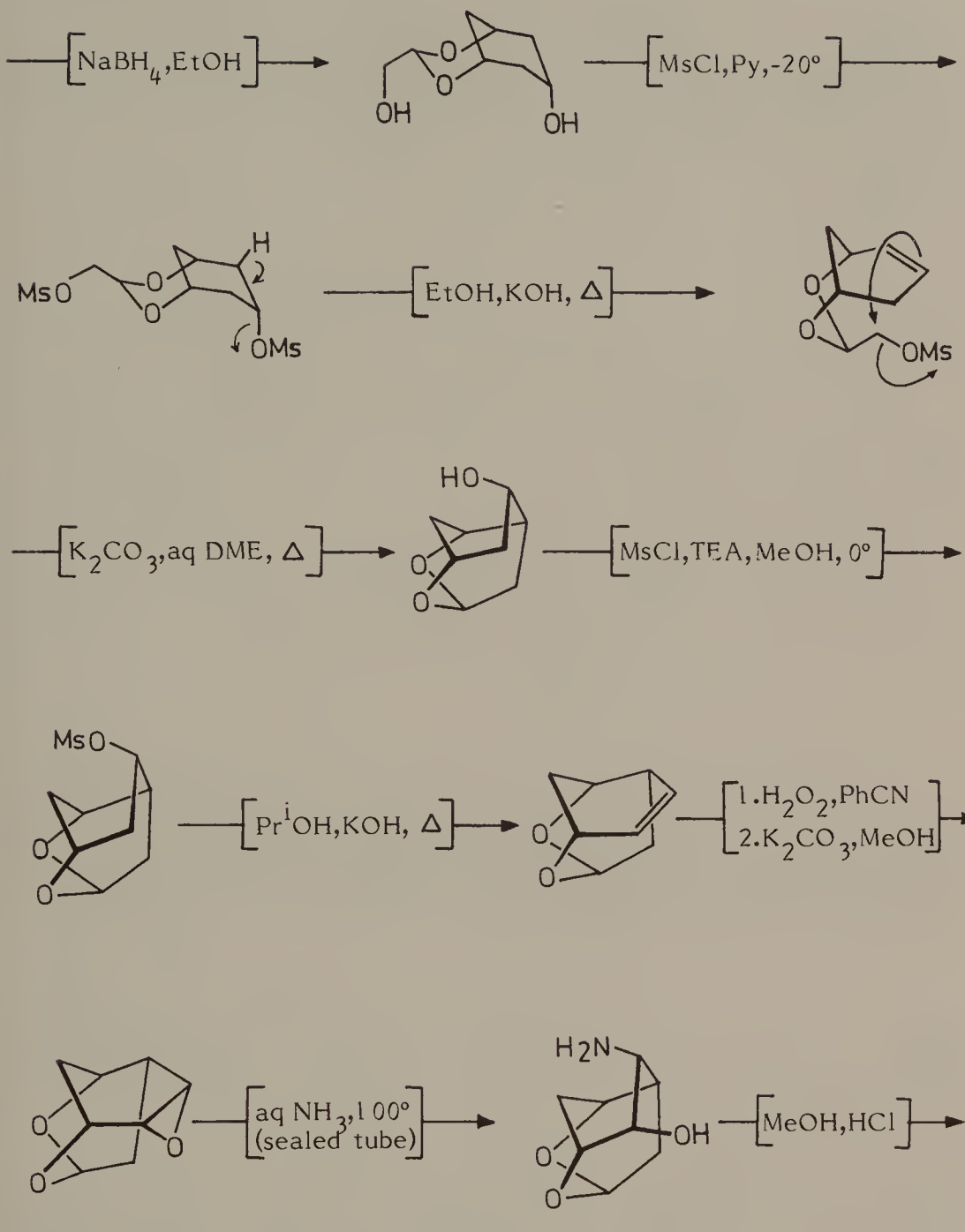
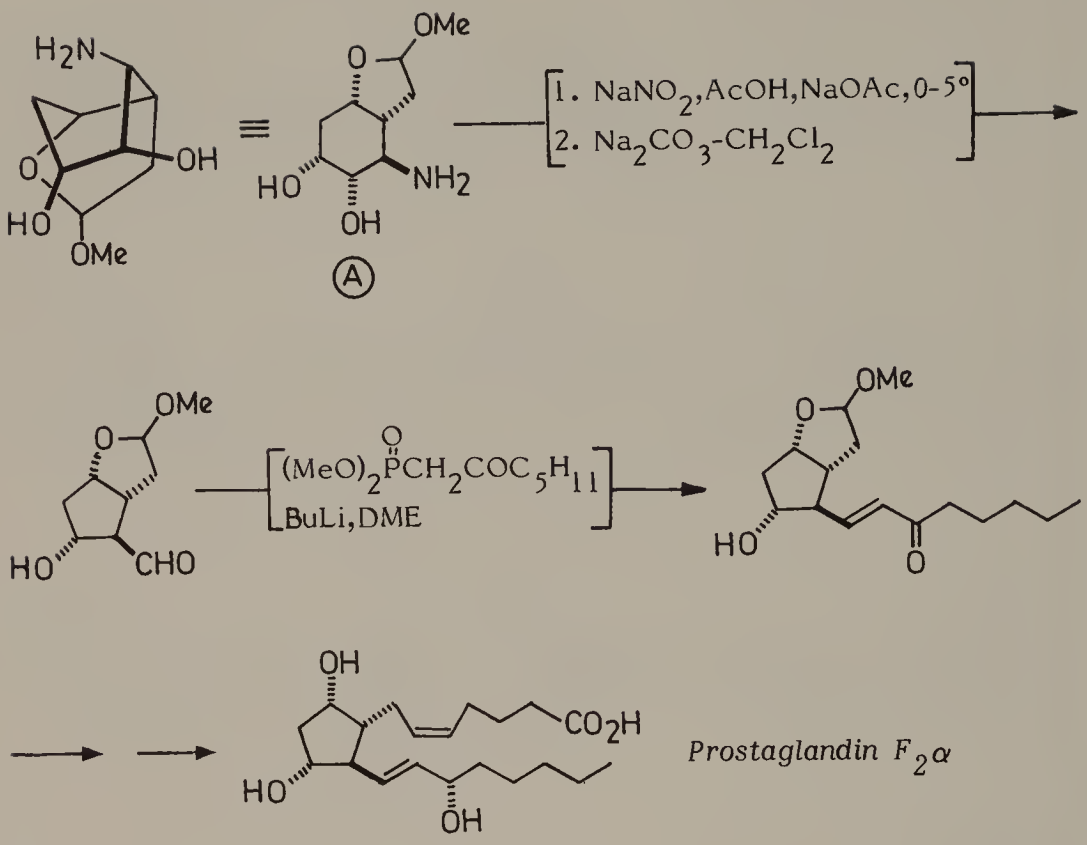
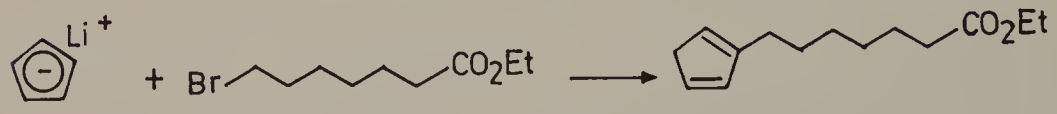
9. Woodward,R.B.; Gosteli,J.; Ernest,I.; Friary,R.J.; Nestler,G.; Raman,H.; Sitrin,R.; Suter,Ch.; Whitesell,J.K. J. Am. Chem. Soc., 1973, 95, 6853.

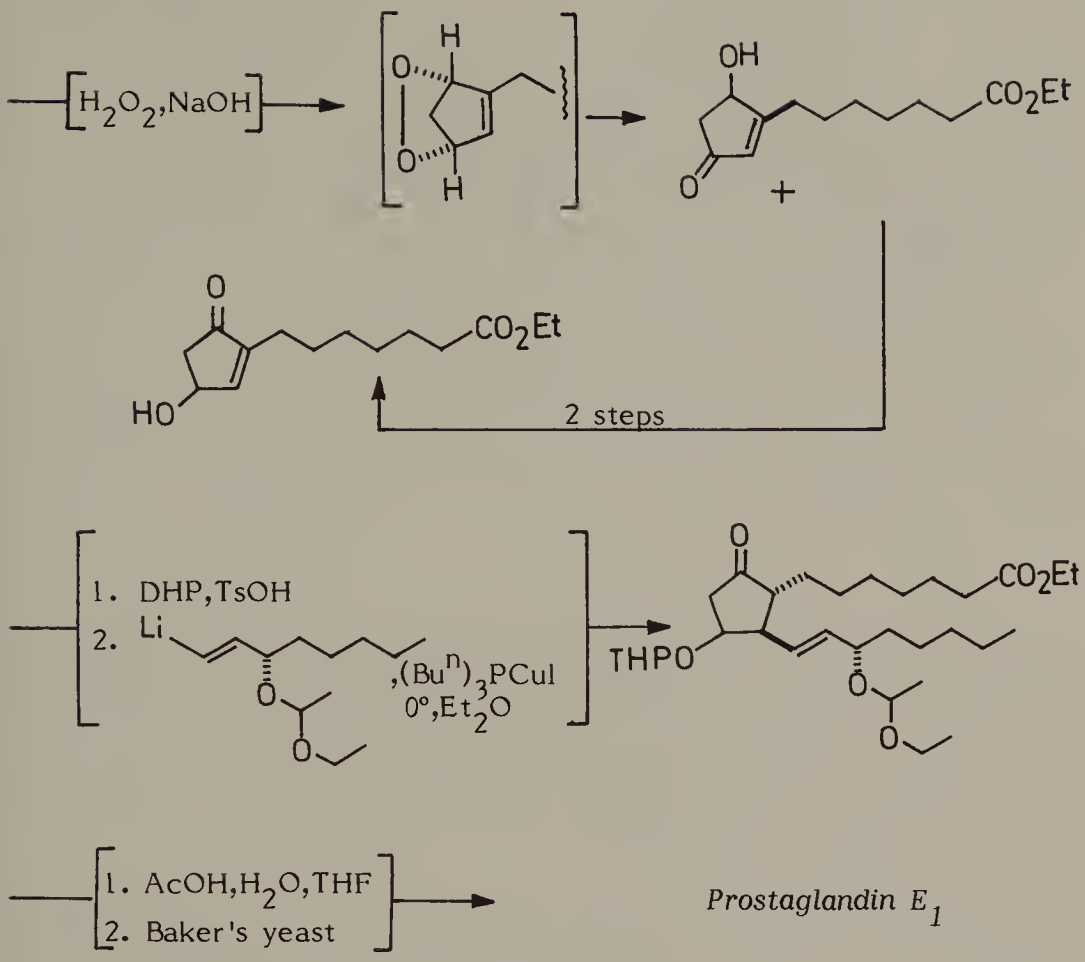

NaBH4,EtOH
MsCl,Py,-20°
MsO
OMs
EtOH,KOH, Δ
OMs
K2CO3,aq DME, Δ
HO
MsCl,TEA,MeOH, 0°
MsO
PriOH,KOH, Δ
1.H2O2,PhCN
2.K2CO3,MeOH
aq NH3,100°
(sealed tube)
H2N
OH
MeOH,HCl



Sih and his associates at the University of Wisconsin developed a short efficient synthesis of prostaglandins. The problem of introducing the asymmetric centre at C-15 in this synthesis is solved by introduction of the lower side chain, already bearing the C-15 asymmetric centre by a 1,4-addition reaction (10).



10.a) Sih,C.J.; Salomon,R.G.; Price,P.; Peruzzotti,G.; Sood,R. Chem. Commun., 1972, 240.
b) Sih,C.J.; Price,P.; Sood,R.; Salomon,R.G.; Peruzzotti,G.; Casey,M. J. Am. Chem. Soc., 1972, 94, 3643.



An 'ideal' approach to PG synthesis would be the three-component coupling process (11), conceived many years ago by the Syntex group (12) but realised only recently, which offers "an extremely short way to PG's" (13).

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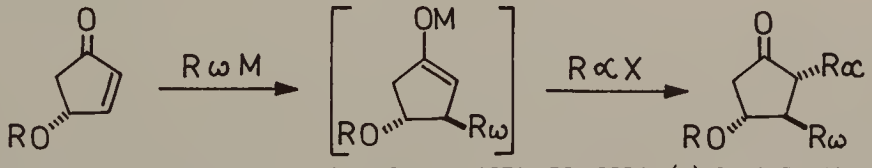
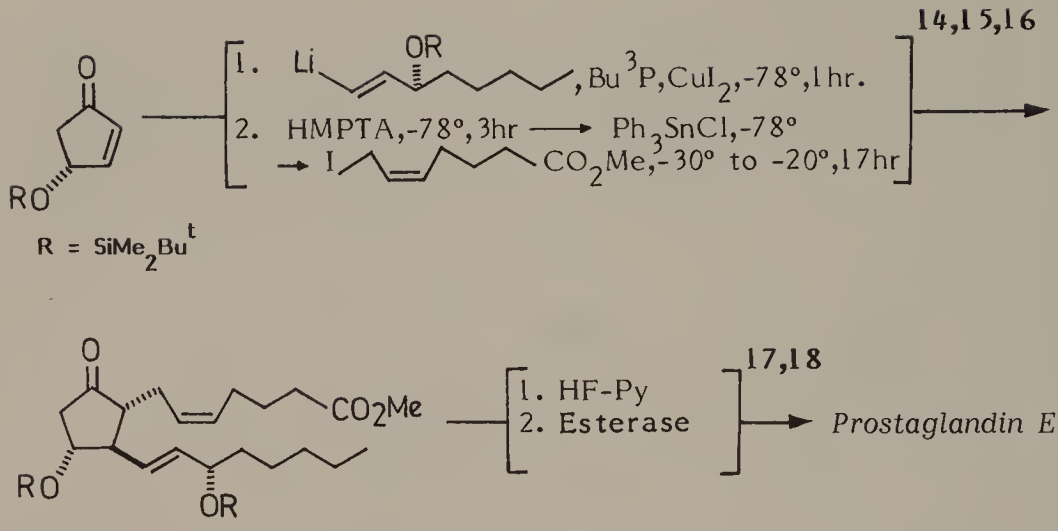
11. This was conceived as building the whole framework by coupling three units by the following strategy:



12. (a) Patterson,J.W.Jr.; Fried,J.H. J. Org. Chem., 1974, 39, 2506. (b) Davis,R.; Unich,K.G. ibid, 1979, 44, 3755.

13. Suzuki,M.; Yanagisawa,A.; Noyori,R. J. Am. Chem. Soc., 1985, 107, 3348.



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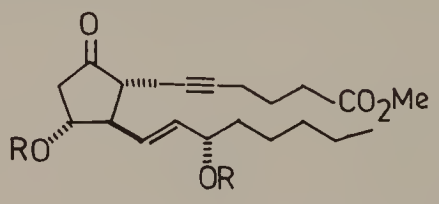
14. For optically active cyclopentenone and ω-side chain see: Noyori,R.; Suzuki,M. Angew. Chem. Intl. Ed. Engl., 1984, 23, 847; Noyori,R.; Tomino,I.; Yamada,M.; Nisizawa,M. J. Am. Chem. Soc., 1984, 106, 6717.

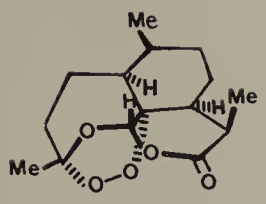
15. The conjugate addition proceeds in a completely stereoselective manner to give after quenching only the C-11/C-12 (PG numbering) trans product.

16. The success was due to the lithium (or copper) to tin transmetallation in the enolate stage: c.f. Tardella,P.A. Tetraahedron Lett., 1969, 117; Nishiyama,H.; Sakuta,K.; Itoh,K. ibid, 1984, 25, 223, 2487.

17. In a similar manner PGE, and PG's of the D&I series have also been prepared. Use of propargylic iodide as the α-side chain unit allowed the synthesis of the acetylenic compound given below in one step in 82% yield as a single stereoisomer which could serve as a common precursor of PG family.

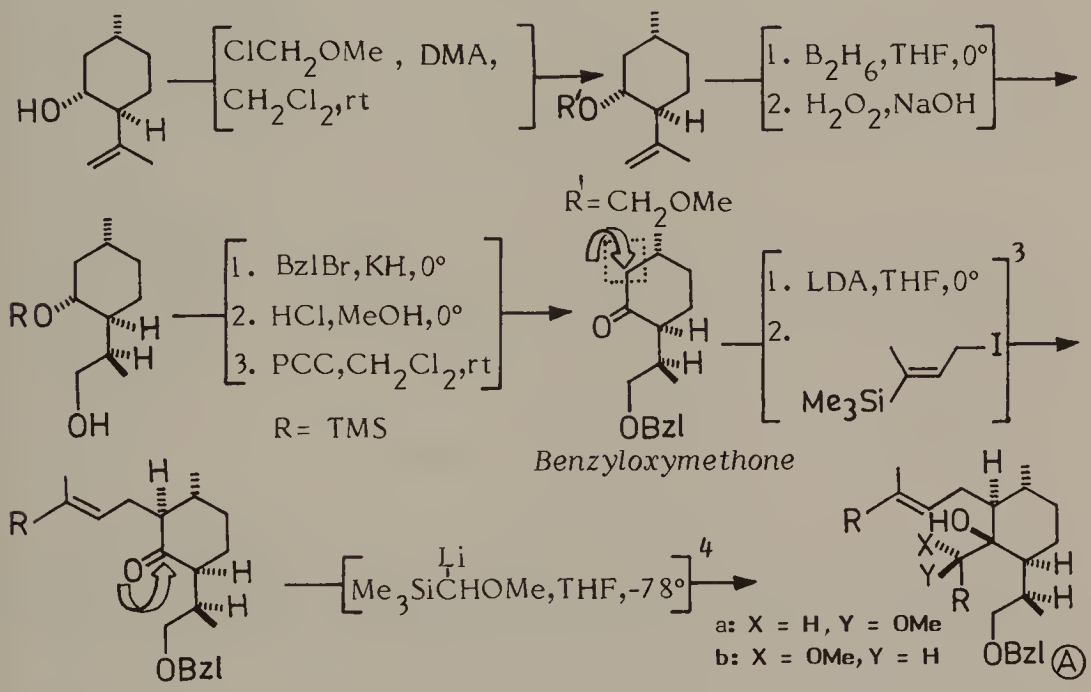


18. For other successful applications of the conjugate addition approach to the synthesis of PGF_2 , see: Stork,G.; Isobe,M. J. Am. Chem. Soc., 1975, 97, 4745, 6260; Stork,G.; Kraus,G. J. Am. Chem. Soc., 1976, 98, 6747. The Columbia synthesis of $PGF_{2\alpha}$ from D-glucose is also particularly noteworthy, see: Stork,G.; Takahashi,T.; Kawamoto,I.; Suzuki, T. J. Am. Chem. Soc., 1978, 100, 8272.



QINGHAOSU

Qinghaosu (also named artemesinin and arteannuin) isolated from Artemesia annua possessing an entirely novel structure for antimalarial activity, is perhaps the most important drug isolated in recent years from plants used in traditional systems of medicine. Its synthesis by Roche scientists (2) starts from (-)-isopulegone and the other chiral centres were generated by optical steric induction. The crucial acetal-lactone endoperoxide bridge was formed through an internal hydroperoxide cyclisation.

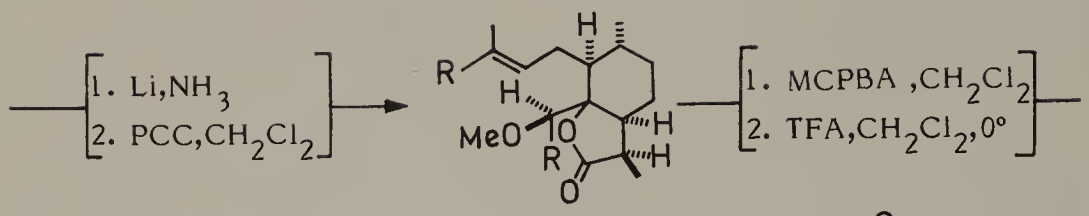


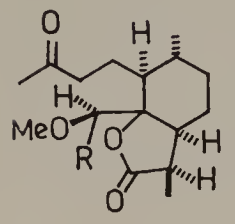
1. Liw,Jing-Ming; Ni,Mu-Yun; Yu-Fen; Tu,You-You; Wu,Zhao-Hua; Yu-Lin-Wu; Chou,Wei-Shan. Acta Chim. Sinica, 1979, 37, 129.

2. Schmid,G.; Hofheinz,W. J. Am. Chem. Soc., 1983, 105, 624.

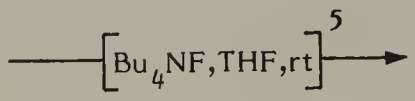
3. This reaction provided a 6:1 excess of the required epimer.

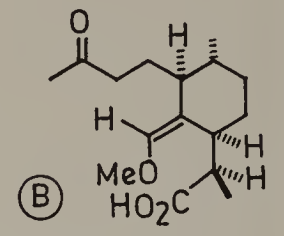
4. The stereochemistry of (A) was assigned on the considerations that large nucleophiles attack cyclohexanones preferentially from the equatorial side and therefore, both epimers a and b must have the hydroxyl group in the axial position. With equimolar quantity of the reagent a 1:1 ratio of the epimers was obtained, but with a 10-fold excess of the reagent the ratio of a to b was shifted to 8:1, and the required epimer isolated in 89% yield. This stereoselectivity was considered to be the result of kinetic resolution of the organolithium reagent by the chiral ketone. The unambiguous assignment of configuration to the epimer followed from the result of the subsequent transformations.



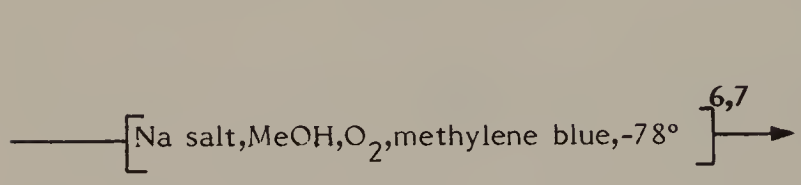


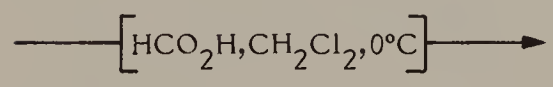
R = TMS





along with the other geometrical isomer





Qinghaosu

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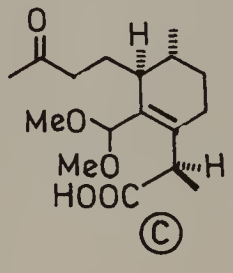
5. The fluoride ion induced ß-elimination is stereospecific; it appears to be similar to acid catalysed synchronous anti-periplanar E_2 ß-elimination of β-hydroxyalkyl silanes; Hudrlik,P.F.; Rona,R.J.; Misra,R.N.; Withers,G.P. J. Am. Chem. Soc., 1977, 99, 1993.

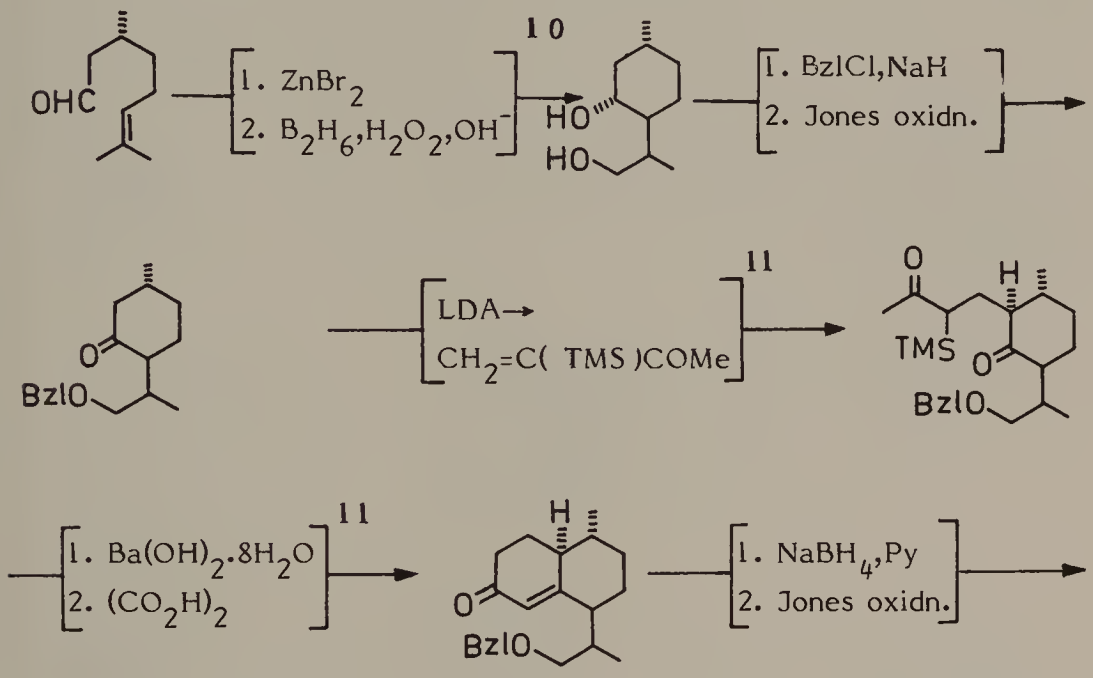
6. Asveld,E.W.S.; Kellogg,R.M. J. Am. Chem. Soc., 1980, 102, 3644.

7. A complex mixture of products was formed in this reaction; although none of the products could be identified, but from the course of the reaction of the next step which yielded qinghaosu in 30% yield the structure shown must be the main product. When this reaction was carried out at 0° in presence of methylene blue, Ⓒ shown below was formed.



Chinese synthesis

In a somewhat different approach the Chinese scientists (8) have carried out the synthesis of qinghaosu starting from R(+)-citronellal (9); the intermediate Ⓐ, corresponding to the acid Ⓑ of Schmid & Hofheinz (2) was obtained in 19 steps, which on photo-oxidation to create the peroxide bridge followed by acid treatment gave qinghaosu. Hydroxylation of Ⓐ with OsO_4 yielded the corresponding ether, deoxy-arteannuin.



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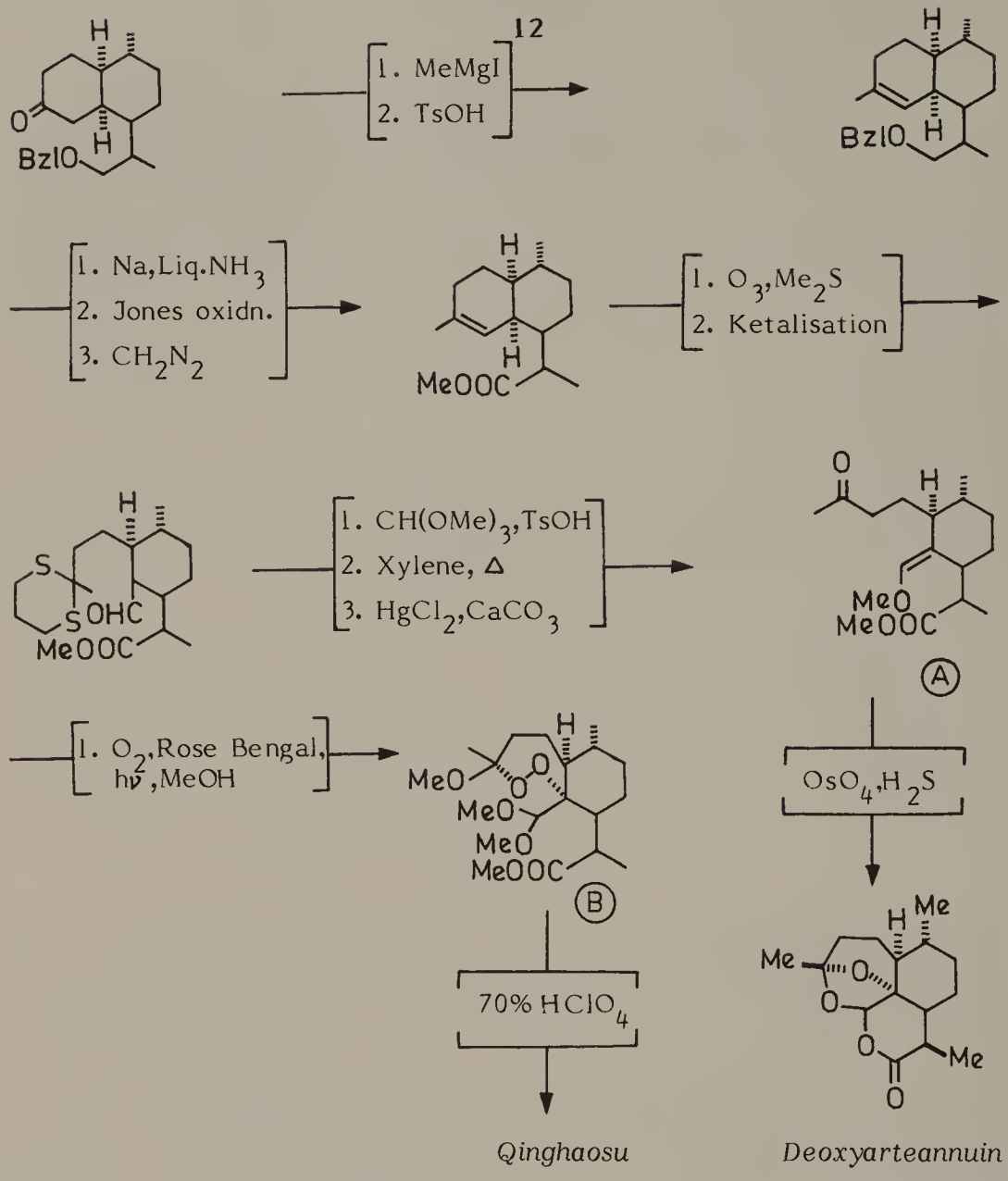
8. Xing-Xiang,Xu; Jie,Zhu; Da-Zhong,Huang; Wei-Shan,Zhou, Tetrahedron, 1986, 42, 819.

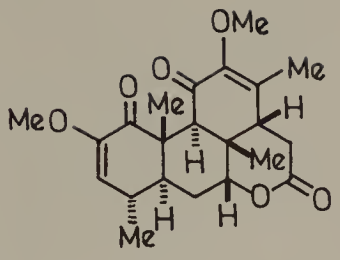
9. A review of the total synthesis of qinghaosu and related sesqinterpenes isolated from A. annua has been published; Zhou Wei-Shan, Pure & Appl. Chem., 1986, 58, 817.

10. Nakatani,Y., Kawashima,K.. Synthesis, 1978, 147; Schulte-Elte,K.H., Ohloff,G., Helv. Chim. Acta, 1967, 50, 153.

11. Use of NaOH in this cyclisation resulted in the inversion of configuration at C_7.

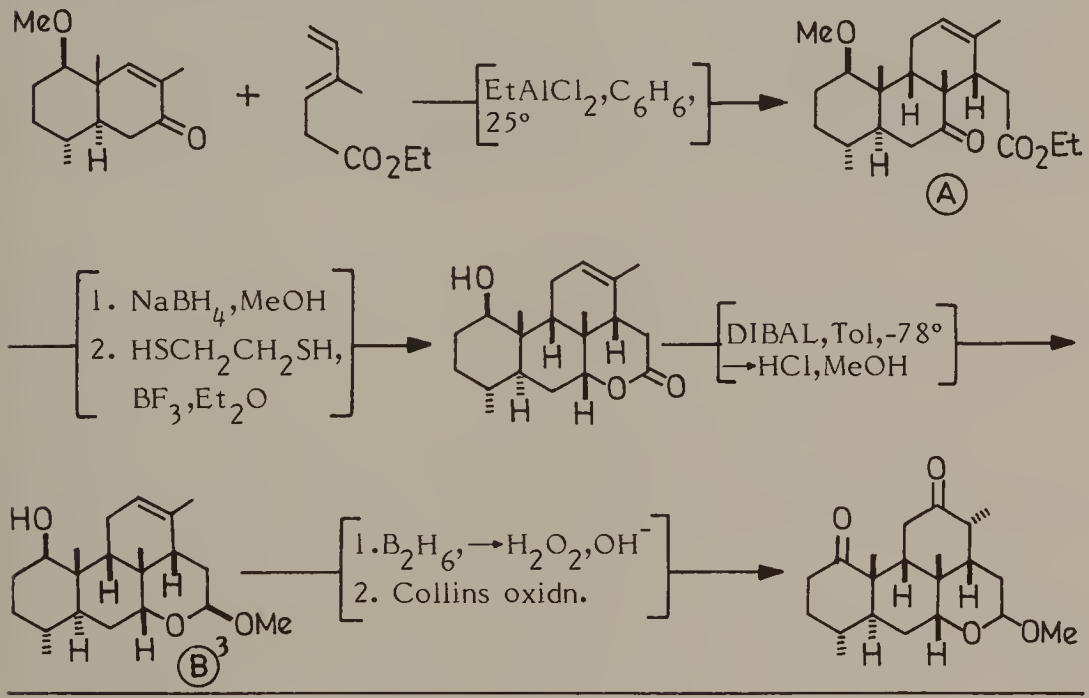


12. (A) 1:1 mixture of this and the Δ^3-isomer was obtained, which were separated by flash chromatography.

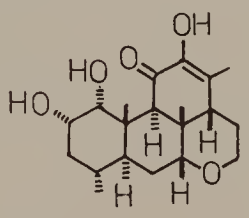


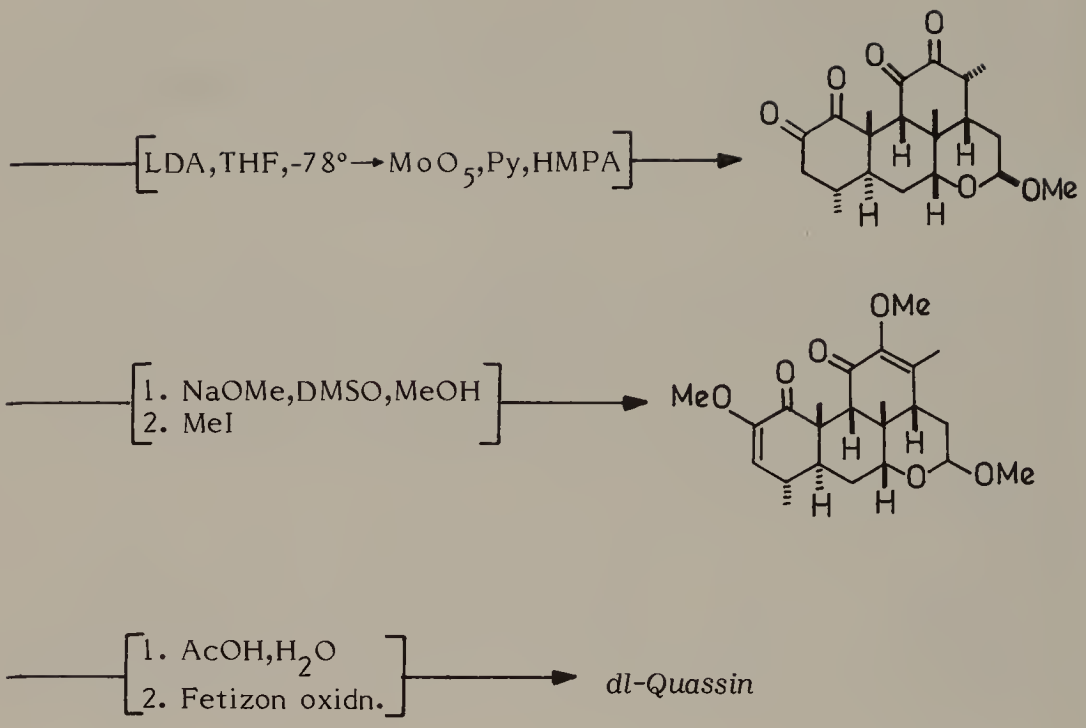
QUASSIN

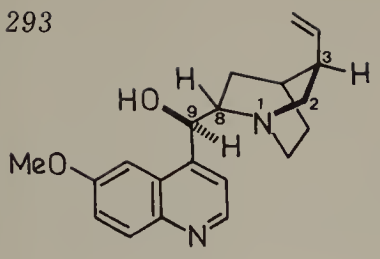
Quassinoids, the bitter principles of the Simarubaceae family have attracted much attention recently because of the wide spectrum of biological activities shown by them, which include anticancer and antiparasitic activities (1). The total synthesis described herein of dl-quassin, the parent compound of this group, assembles a key intermediate Ⓐ by a Diels-Alder reaction which six of the seven chiral centres found in quassin (2).



1. For comprehensive review of quassinoids see: Polonsky,J. in "Progress in the Chemistry of Natural Products", 1973, 30, 101; 1985, 47, 221.
2. Grieco,P.A.; Ferrino,S.; Vidari,G. J. Am. Chem. Soc., 1980, 102, 7586.
3. From the tetracyclic alcohol Ⓑ Grieco et al. have by similar synthetic reactions obtained dl-castelanolide: Grieco,P.A.; Lis,R.; Ferrino,S.; Jaw,J.Y. J. Org. Chem., 1982, 47, 601.



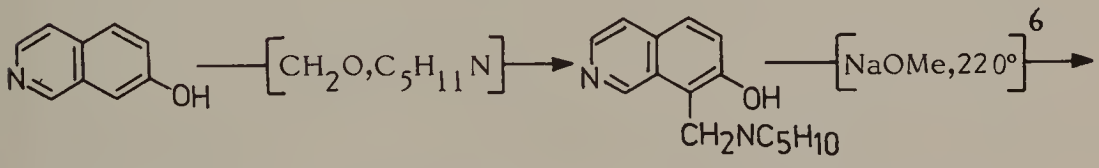

LDA,THF,-78°→MoO5,Py,HMPA
OMe
1. NaOMe,DMSO,MeOH
2. MeI
MeO
OMe
1. AcOH,H2O
2. Fetizon oxidn.
dl-Quassin



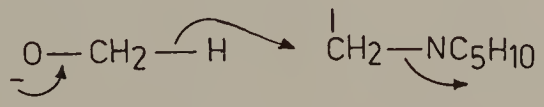
QUININE

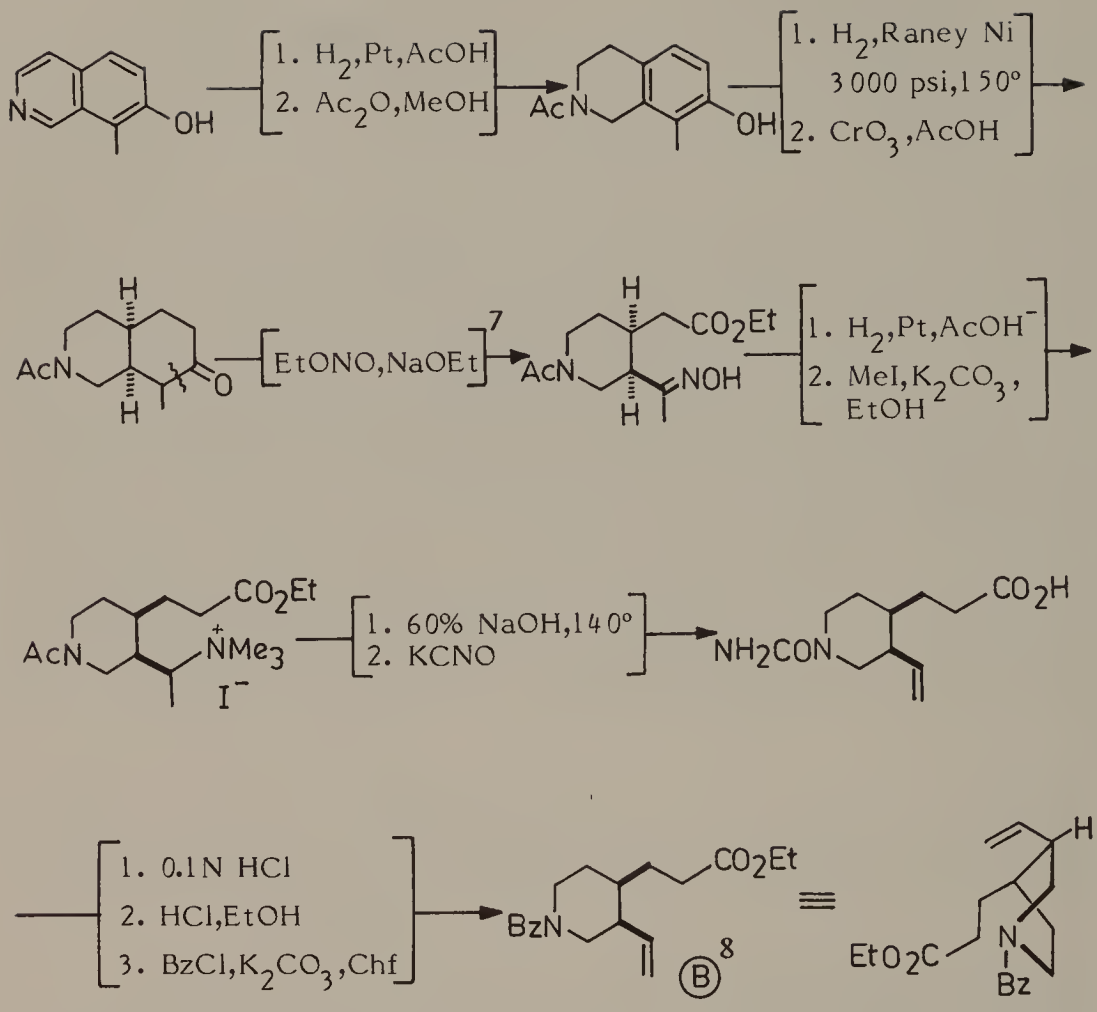
The total synthesis of quinine by Woodward & Doering in 1944 (1) unshered in the modern era of the appreciation of the art in organic synthesis, when organic synthesis started being pursued not only to prove the structure of a natural product but for the creative elements in it and for its possible practical utility (2,3).

Rabe's synthesis of dihydroquinine and partial synthesis of quinine from quinotoxine (4,5) starting in 1910s brought into proper focus the problems involved and the direction for the synthesis of quinine. The intense effort expended over some forty years along various lines of investigations (3) culminated in the ingenious synthesis of quinotoxine by Woodward and Doering (1). The noteworthy feature of this synthesis is obtention of the cis-3,4-disubstituted piperidine Ⓐ from 7-hydroxyisoquinoline, with provision for generating the vinyl group by a Hofmann elimination.

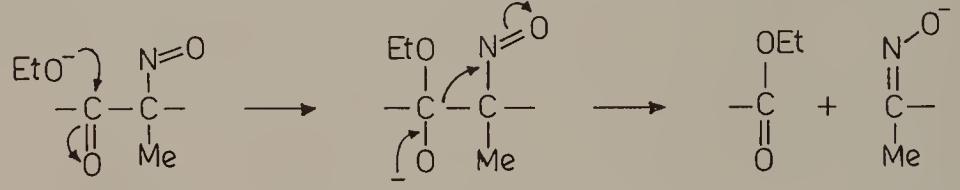


1. Woodward,R.B.; Doering,W.E. J. Am. Chem. Soc., 1944, 66, 849; 1945, 67, 860.
2. "Art in Organic Synthesis", Anand,N.; Bindra,J.S.; Ranganathan,S. Holden-Day Inc., San Francisco, 1970; "Creativity in Organic Synthesis", Bindra,J.S.; Bindra,R. Academic Press, 1975; Unique role played by physical chemistry in Chemical Sciences, Keniti,H.; Senryo to Yahukin, 1984, 29, 173.
3. For a review of the classic work on synthesis of Cinchona alkaloids, see: Turner,R.B.; Woodward,R.B. The Alkaloids, 1953, 3, 1; some of the later developments in this field have been reviewed by Uskokovic,M.R.; Grethe,G. The Alkaloids, 1973, 14, 181.
4. Rabe,P.; Kindler,K. Ber., 1918, 51, 466.
5. Rabe,P.; Huntenberg,W.; Schultze,A.; Volger,G. Ber., 1931, 64, 2487.
6. Hydride transfer from methoxide, cf. Cornforth,J.W.; Cornforth,R.; Robinson,R. J. Chem. Soc., 1942, 682.

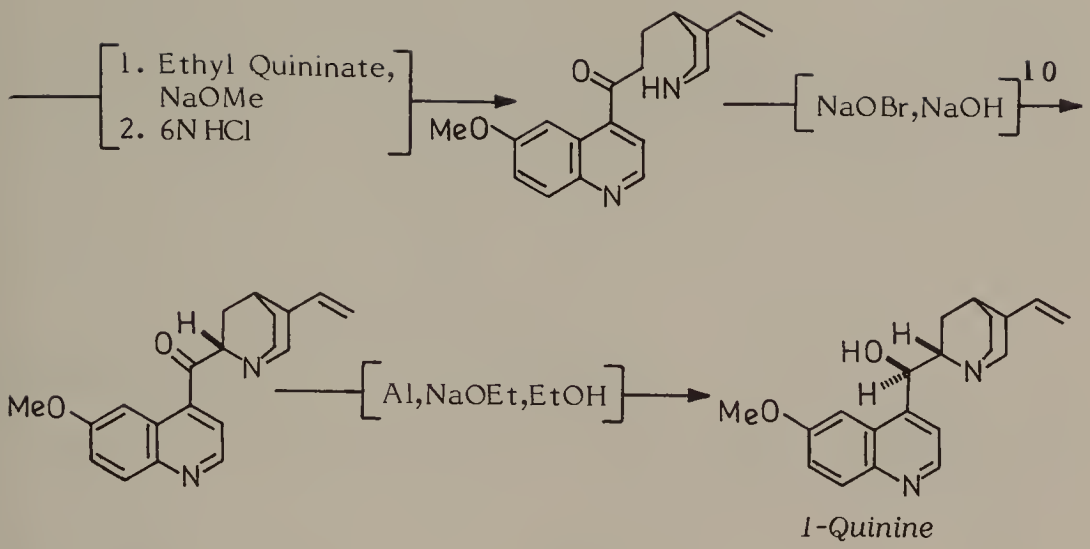




7. This reaction involves the heterolytic C-C fission in an intermediate tertiary nitroso compound (i).



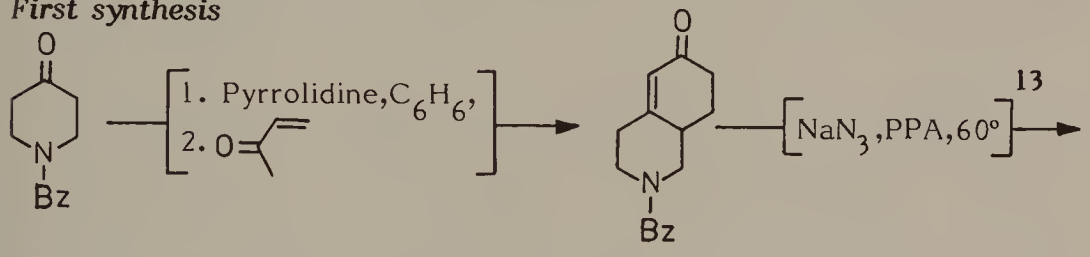
8. Uskokovic and his associates in the course of their extensive studies on the synthesis of cinchona alkaloids developed an alternative efficient synthesis for N-benzoylhomomeroquinene ethyl ester (12C) by employing Hofmann-Loffler-Freytag chlorination of side chain and formed the vinyl group by dehydrochlorination, which considerably improved the preparation of quinotoxine.



l-Quinine

After an interval of almost 25 years a number of new synthesis of quinine appeared in early 1970s (11). Uskoković and his associates developed ingenious stereoselective approaches both for the synthesis of the meroquinene component, the key intermediate whose two chiral centres are destined to become the C-3 and C-4 centres of the alkaloid, and from meroquinene to quinine (12).

N-Benzoylmeroquinene
First synthesis



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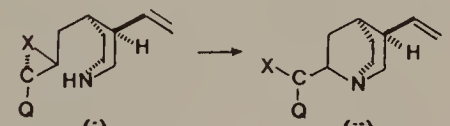
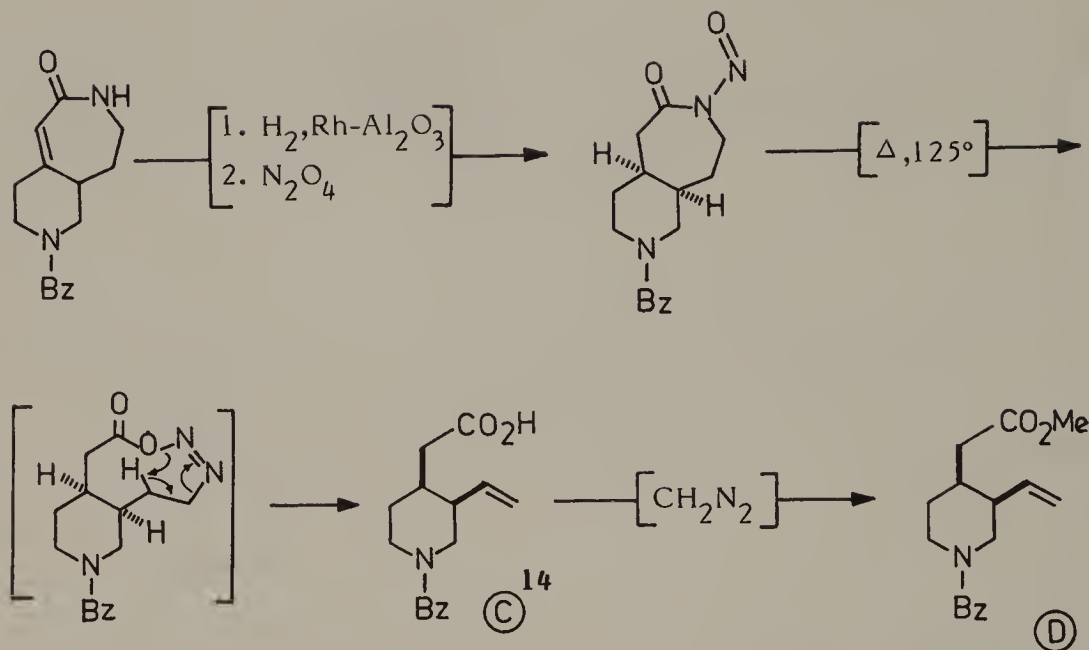
9. Resolved via dibenzoyl-d-tartrate.

10. First effected by Rabe and Kindler (5).

11. A common feature of all these syntheses is that they all proceed through meroquinene derived intermediate bearing a properly positioned functional group which facilitates the quinuclidine ring forming reaction (i→ii).

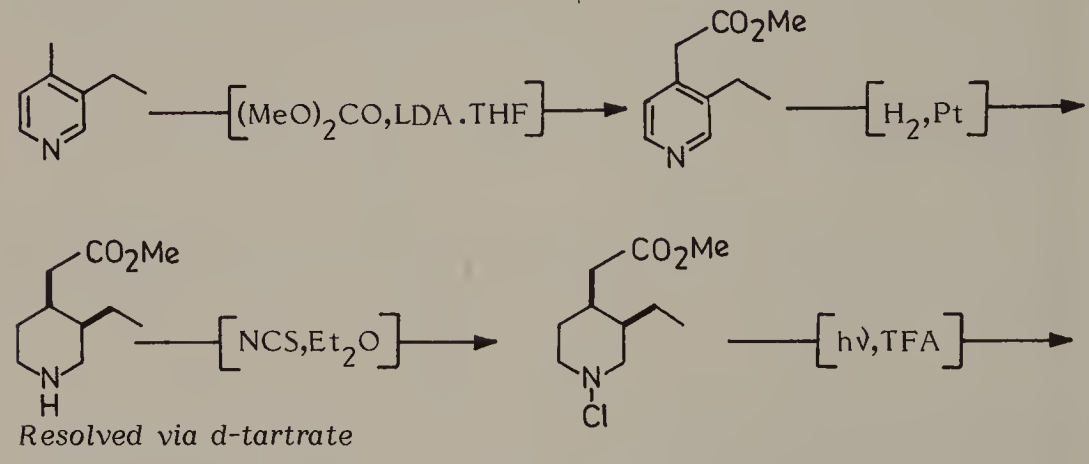


12. (a) Uskoković,M.R.; Gutzwiller,J.; Henderson,T. J. Am. Chem. Soc., 1970, 92, 203; (b) Uskoković,M.R.; Reese,C.; Lee,H.L.; Grethe,G.; Gutzwiller,J. ibid, 1971, 93, 5902; (c) Grethe,G.; Lee,H.L.; Mitt,T.; Uskoković,M.R. Helv. Chim. Acta, 1973, 56, 1485; (d) Uskoković, M.R.; Henderson,T.; Reese,C.; Lee,H.L.; Grethe,G.; Gutzwiller,J. J. Am. Chem. Soc., 1978, 100, 571; (e) Gutzwiller,J.; Uskoković,M.R. ibid, 1978, 100, 576.



N-Benzoylmeroquinene Methyl Ester

Second synthesis



Resolved via d-tartrate

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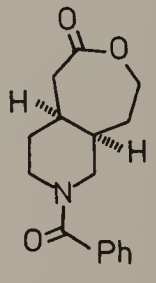
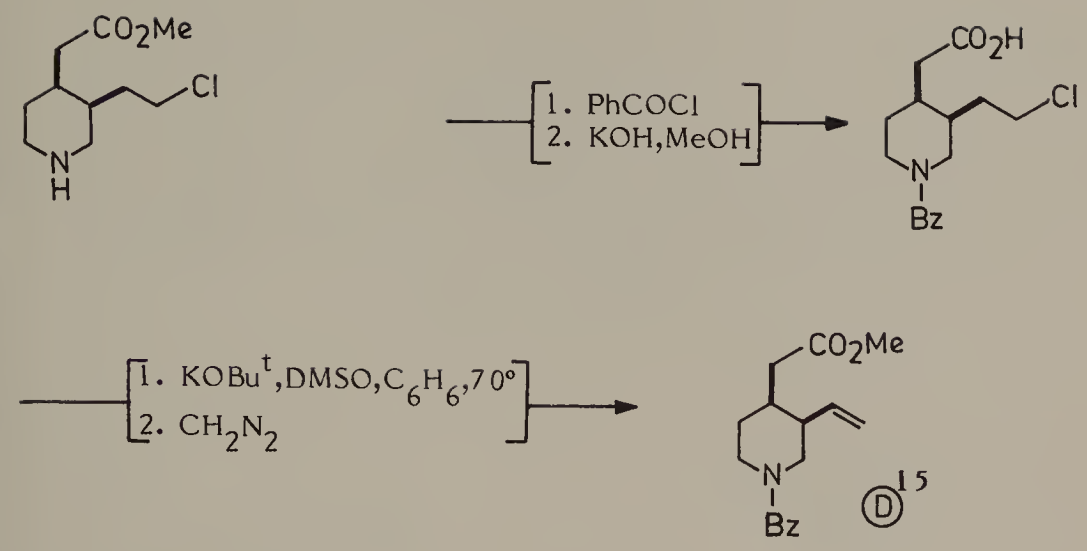
13. This lactam was obtained along with the isomeric enamine lactam in a ratio of 5:1, if the Schmidt reaction was carried out on the decahydroisoquinolone a 1:1 mixture of the two isomers.

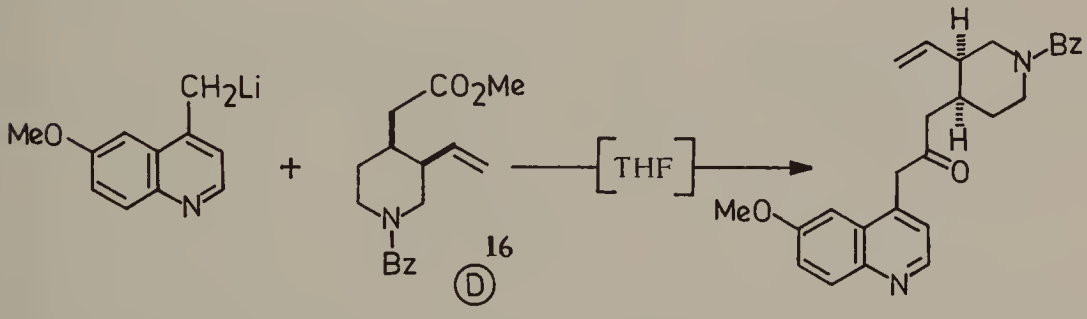
14. N-Benzoylmeroquinene Ⓒ was accompanied by the seven-membered lactone (i). The two compounds were formed in 50 and 30% yield respectively. The latter is apparently formed by nucleophilic attack of one of the ester oxygens on the C-10 carbon. Lactone (i) could be converted to Ⓓ by two different routes.





Preparation of Quinine

Uskokovic et al. explored various routes for the condensation of meroquinene component with the 6-methoxyquinoline unit (12e) and the two routes described below, though not completely stereospecific, proved relatively more efficient for stereoselectivity and yields.



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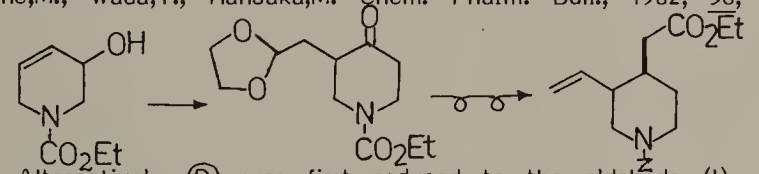
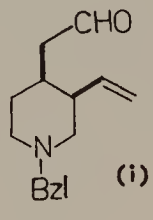
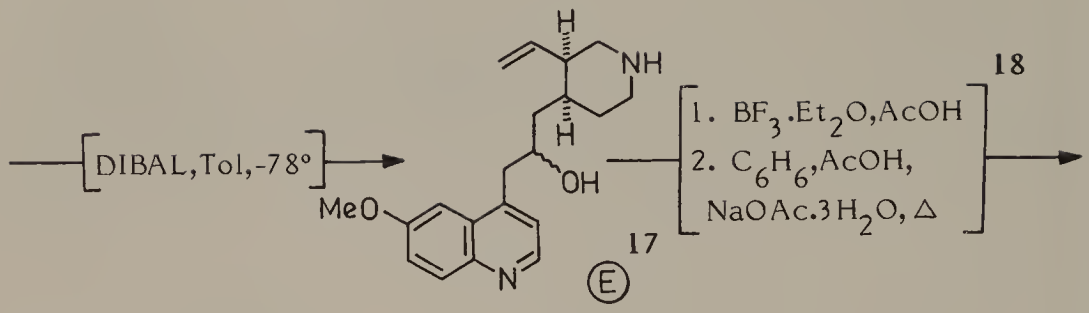
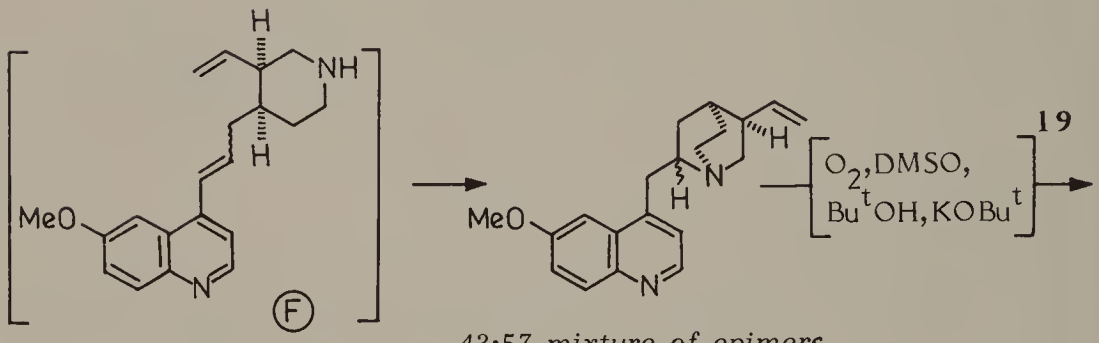
15. Imanishi et al. have described another alternative synthesis of meroquinine by a somewhat different approach starting from 3-hydroxy-Δ^4-tetrahydropyridine; Imanishi,T.; Inone,M.; Wada,Y.; Hanoaka,M. Chem. Pharm. Bull., 1982, 30, 1925; 1983, 31, 1551.



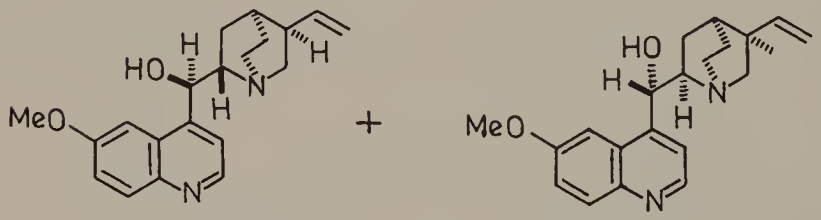
16. Alternatively (D) was first reduced to the aldehyde (I), which upon condensation with (E) followed by N-debenzoylation by reaction with LAH yielded the same mixture of epimeric alcohols (F).







43:57 mixture of epimers



Quinine (41%) *Quinidine (32%)*

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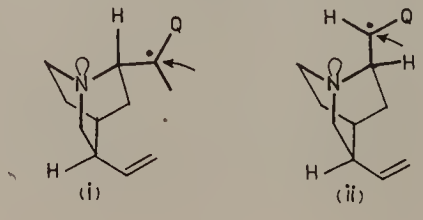
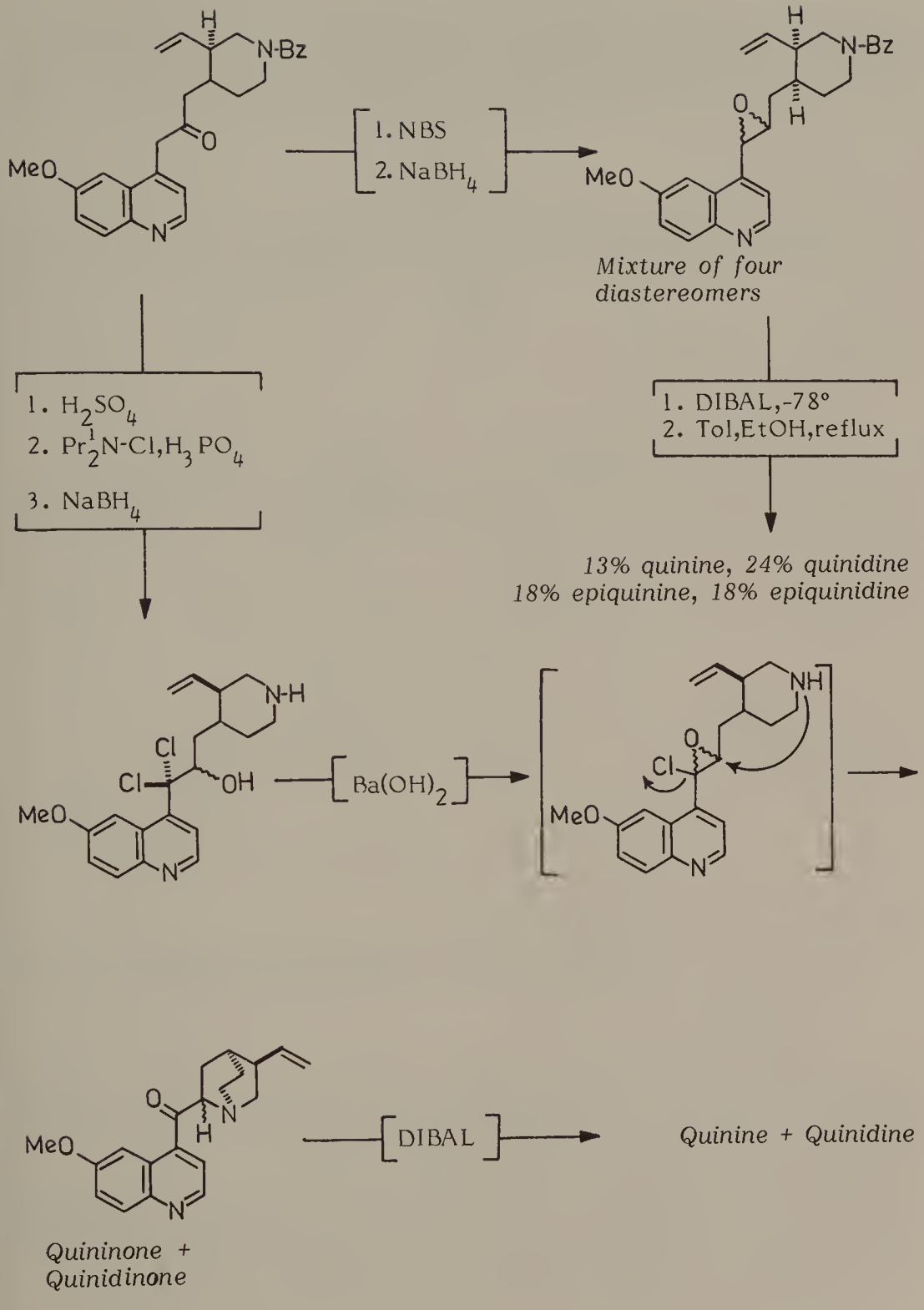
17. Resolved via dibenzoyl (+)-tartrate.

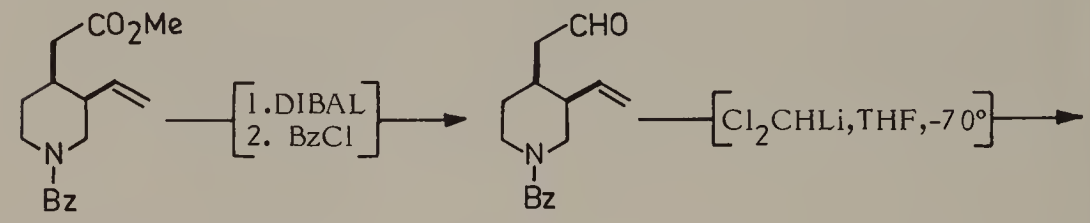
18. Pure deoxyquinine and deoxyquinidine obtained from quinine and quinidine when treated under same cyclisation conditions resulted in each case in a similar mixture of epimers, thus indicating that vinyl quinoline to → deoxyquinine + deoxyquinidine is a reversible process.

19. The high stereospecificity may be due to a preferred back side attack of the oxygen radical anion on the intermediate radicals (i) and (ii) to avoid the repulsive force of the quinuclidine nitrogen free electron pair.

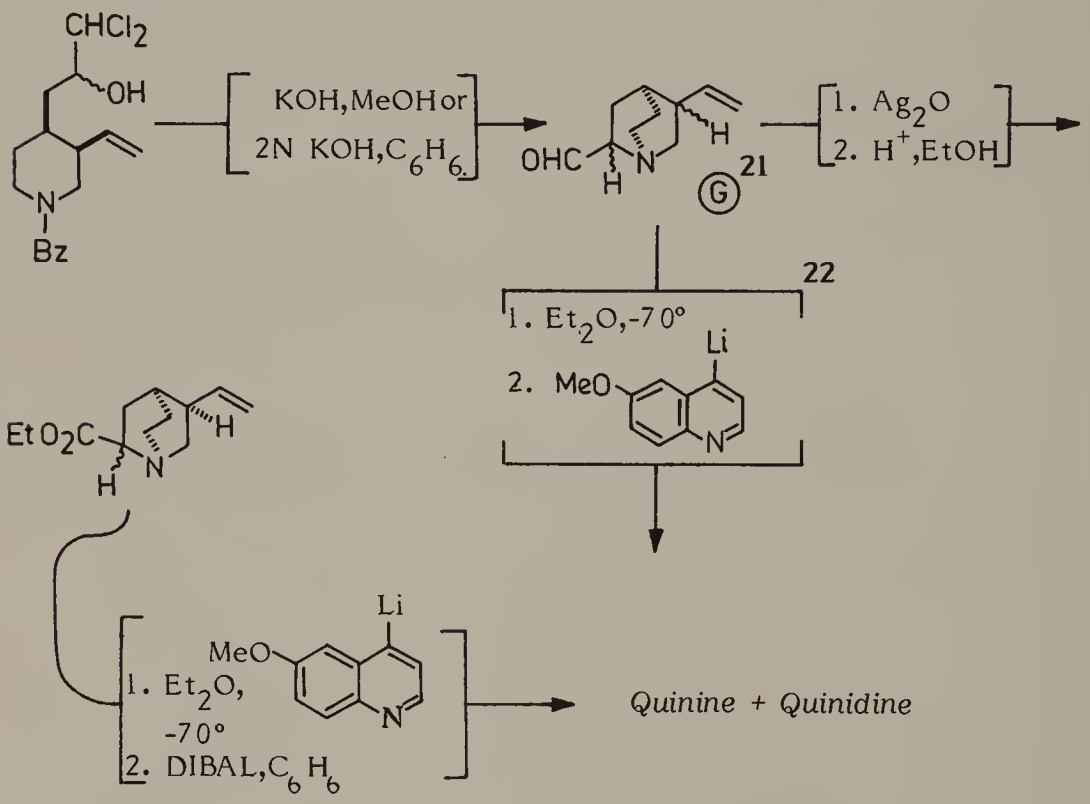



1. NBS
2. NaBH4
Mixture of four diastereomers
1. H2SO4
2. Pr2iN-Cl,H3PO4
3. NaBH4
1. DIBAL,-78°
2. Tol,EtOH,reflux
13% quinine, 24% quinidine
18% epiquinine, 18% epiquinidine
Ba(OH)2
DIBAL
Quinine + Quinidine
Quininone + Quinidinone

In yet another variation of this approach Uskoković et al. have reported a still more convergent synthesis of cinchona alkaloids which involves coupling a quinuclidine derivative of correct stereochemistry and proper functionalities with a suitably activated quinoline (20).



Meroquinene derivative



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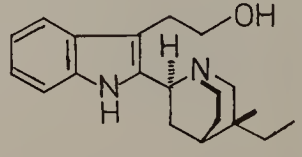
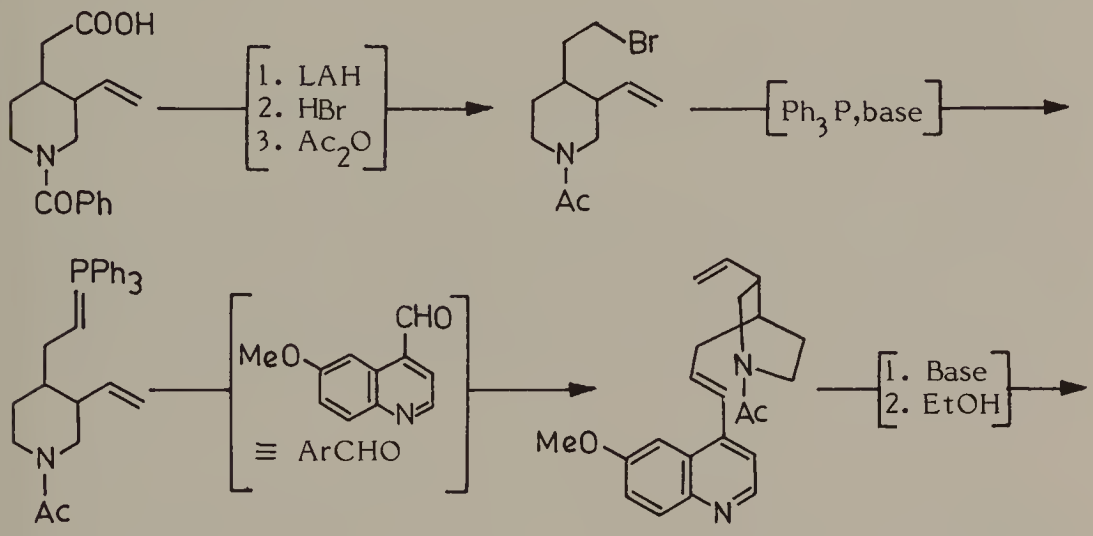
20. Grethe,G.; Lee,H.L.; Mitt,T.; Uskoković,M.R. J. Am. Chem. Soc., 1971, 93, 5904; 1978, 100, 581; 1978, 100, 589; Grethe,G.; Lee,H.L.; Uskoković,M.R. Synthetic Commun., 1972, 2, 55.

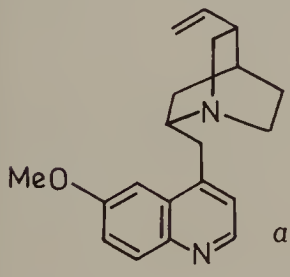
21. This reaction gave a mixture of 13% quinine, 15% quinidine, and 5% each of the two epi-isomers; the epi-isomers could be oxidised and stereoselectively reduced to the desired erythro compounds.

22. This aldehyde has also been used by Uskokovic et al. for the synthesis of dihydrocinchonamine starting from N-Li o-toluidine and quinuclidine ester.



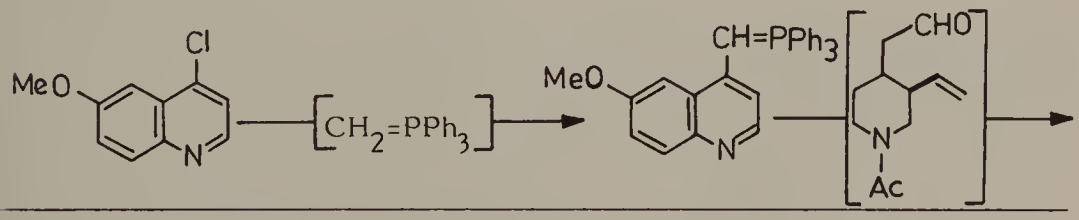
In an alternative procedure developed by Gates et al. the vinylpiperidine to quinoline union, which precedes the quinuclidine ring formation, is brought about by a Wittig reaction; the key quinuclidine cyclisation step is non-stereospecific (23).



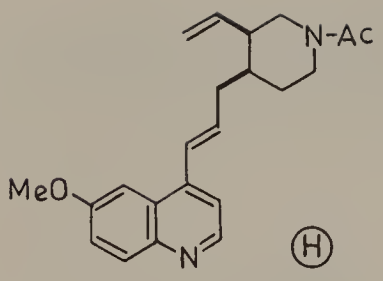


along with exo isomer

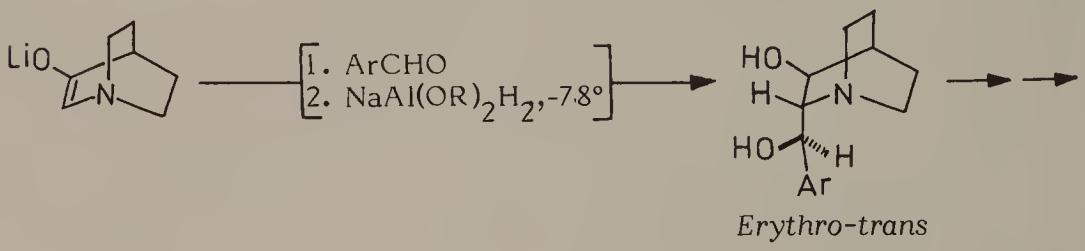
In another variation of this approach Taylor and Martin synthesised the piperidino-methylvinylquinoline Ⓗ from meroquine aldehyde and quinoline Wittig reagent (24).



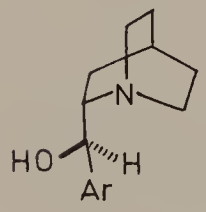
23. Gates,M.; Sugavanam,B.; Schreiber,W.L. J. Am. Chem. Soc., 1970, 92, 205.
24. Taylor,E.C.; Martin,S.F. J. Am. Chem. Soc., 1972, 94, 6218.



Stotter, Friedman & Minter have recently described, on some model compounds, conceptually a new approach to the total synthesis of quinine (25), which involves as a critical step a diastereoselective aldol condensation of a quinuclidone enolate with an aromatic aldehyde, to yield an amino-alkanol with the required erythro stereochemistry.



Erythro-trans



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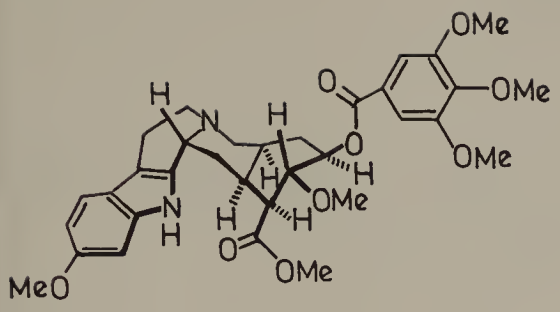
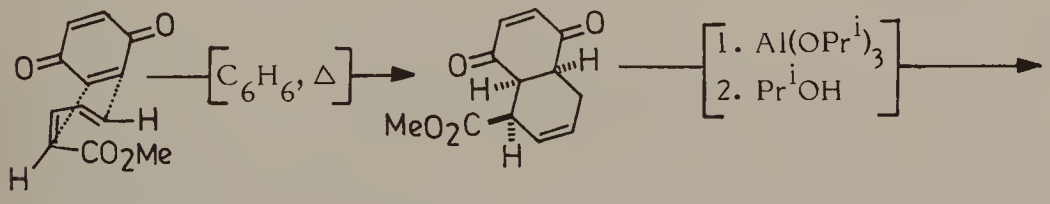
25. Stotter,P.L.; Friedman,M.D.; Minter,D.E. J. Org. Chem., 1985, 50, 29.



RESERPINE

The discovery of reserpine, pharmacologically the most important alkaloid of Rauwolfia serpentina, in 1952 was a big event in drug research as it sharply focussed attention on the possibility of finding major drugs from plants based on knowledge of the traditional systems of medicine(1)Its structure, with six chiral centres, five in one ring, and all stereochemically not in the most stable orientation offered a big challenge to synthetic ingenuity. Four synthesis have been reported all of which first constructed the essential features of D/E ring with all the five chiral centres correctly disposed but by very different synthetic strategies, each ingenious in its own way.

The synthesis by Woodward and his associates (2) reported in 1956 created all the five chiral centers of E ring in three steps in a highly stereoselective manner (3). The remaining task of completing the pentacyclic system was accomplished by an oxidative scission of the enone Ⓑ to permit insertion of N-4 and completion of the synthesis.



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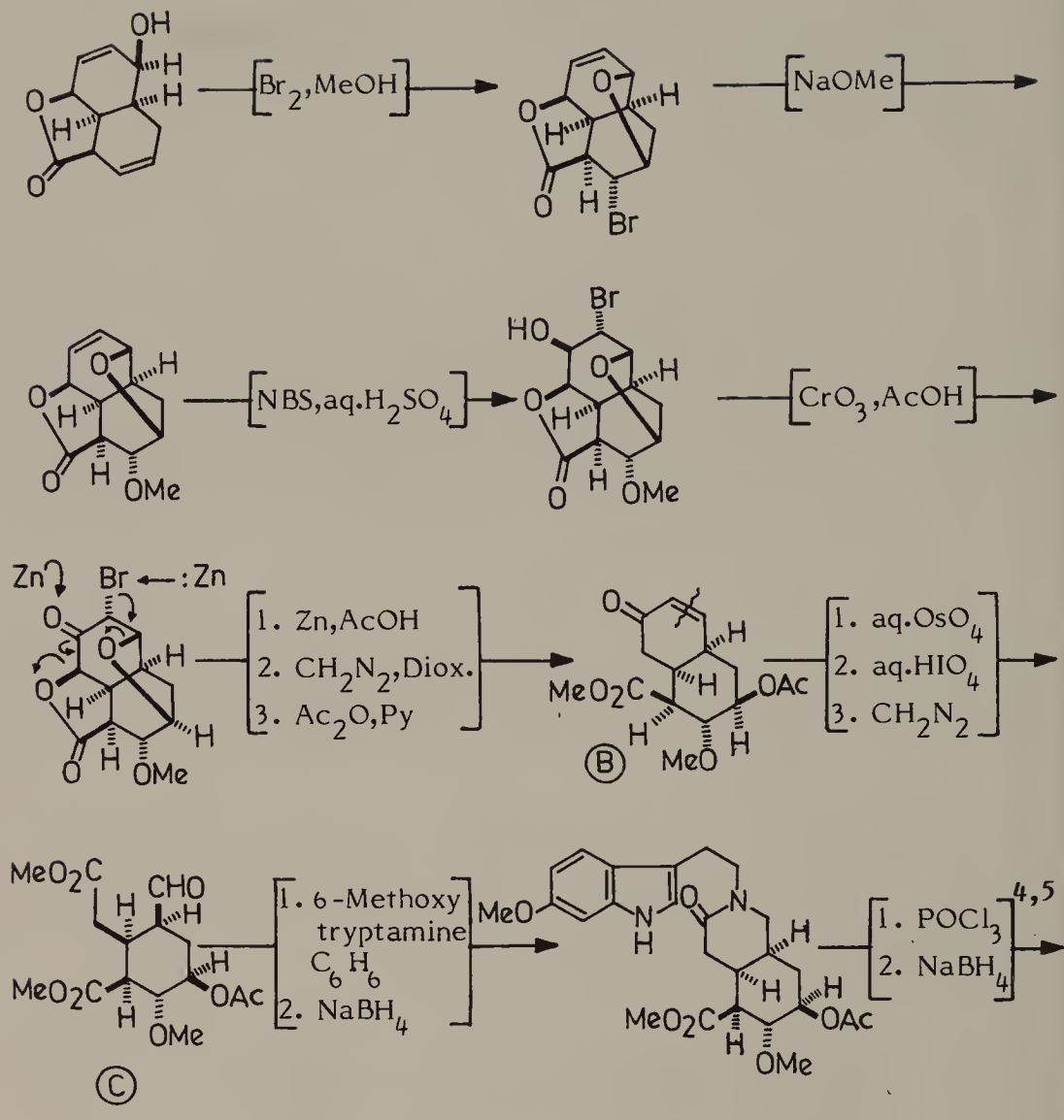
1. Woodson,R.E.; Younken,H.W.; Schlittler,E.; Schneider,J.A. "Rauwolfia: Botany, Pharmacognosy, Chemistry and Pharmacology". Little Brown & Co., Boston.

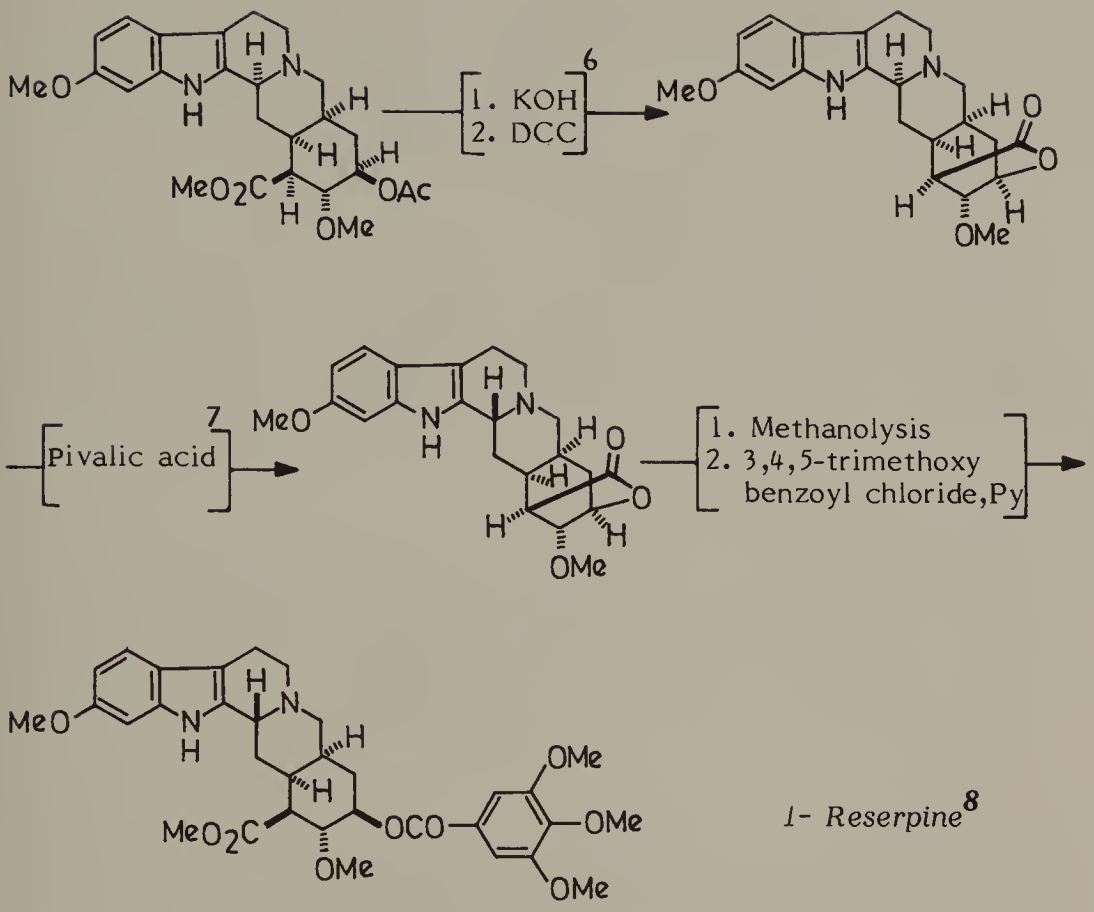
2. Woodward,R.B.; Bader,F.E.; Bickel,H.; Frey,A.J.; Kierstead,R.W. J. Am. Chem. Soc., 1956, 78, 2023, 2657; Tetrahedron, 1958, 2, 1.

3. Diels-Alder reaction gave the adduct with the cis-fused D/E ring junction and three chiral centres correctly set up as a result of the preference of endo-addition; thereafter the new centres of asymmetry were introduced stereoselectively under direction of existing centres of asymmetry. The high degree of stereochemical control evident in transformations of the cis-decalin is due to the folded structure of the molecule in which the side carrying the cis bridgehead hydrogens, the convex face of the boat-shaped molecule, is readily accessible to attacking reagents; see: Woodward,R.B. in "Pointers and Pathways in Research", Hofteizer,G. for Ciba of India Ltd., Bombay, 1963,23.



4. Reduction of the intermediate immonium salt directly to a reserpic acid derivative (C-3 hydrogen, cf.ref.5) may be accomplished with zinc and acetic acid, Weisenborn,F.L.; Diassi,P.A. J. Am. Chem. Soc., 1950, 78, 2022. Other modifications of the synthesis by later workers are all based on Woodward's intermediate carbocyclic aldehyde (C) and the synthesis is now a commercial feasibility. For a review, see: Schlittler,E. in "The Alkaloids", Vol.VIII, ed. R.H.F. Manske, Academic Press, New York, 1965, 287.

5. An isoreserpic acid derivative is obtained in which C-2,3 linkage and all large groups attached to rings D/E are equatorially disposed.



1- Reserpine[8]

Following a gap of almost 20 years the second synthesis of reserpine was reported by Pearlman (9) which uses a novel deMayo reaction with formyl acetic ester to place a vicinal carboxaldehyde and acetic ester appendages onto double bond to get the key Woodward precursor Ⓐ (10).

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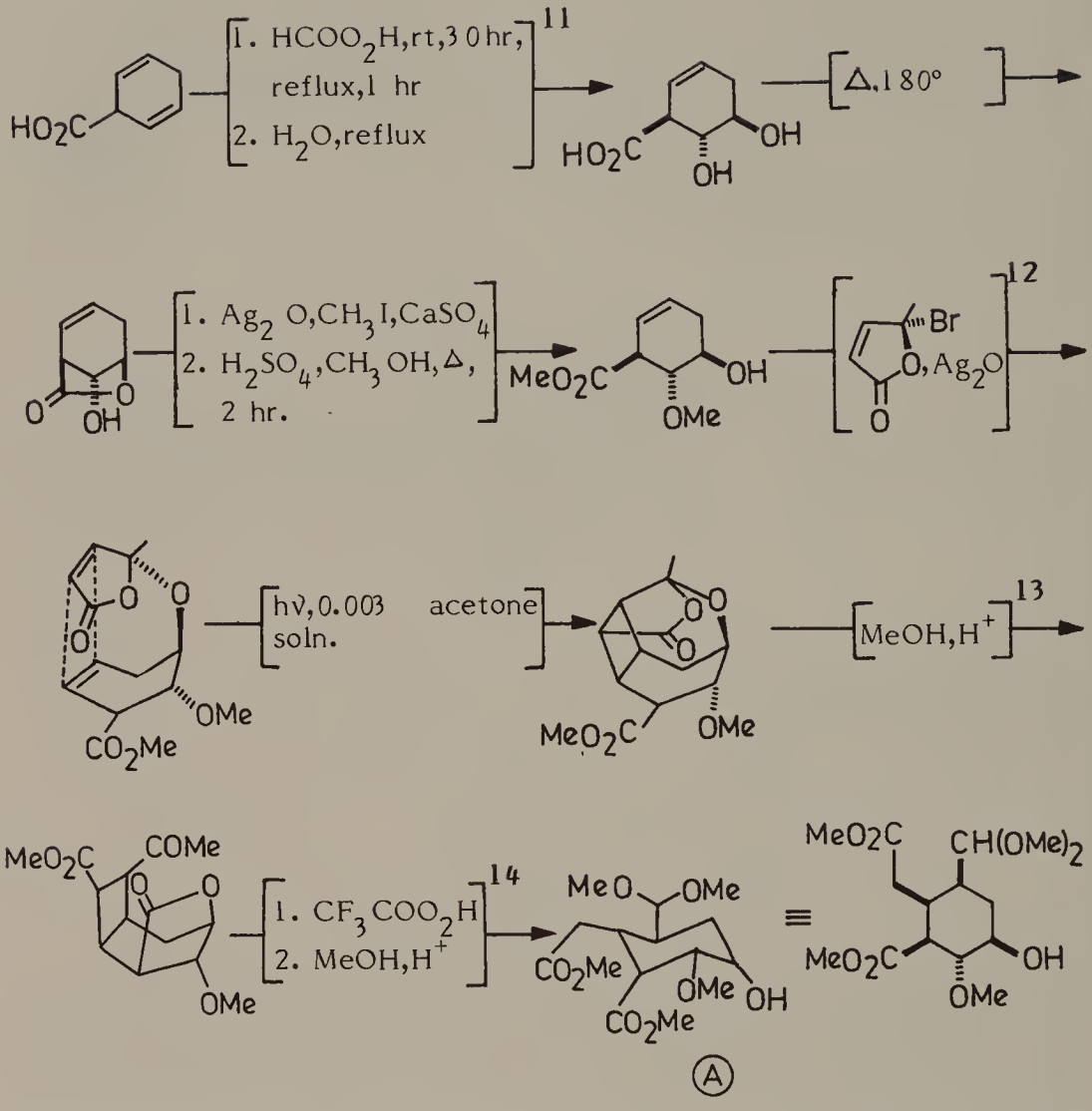
6. Lactonization forces the carboxyl at C-16 to become axial, and in the process conformation of entire substituents on the alicyclic system of iso-reserpine is inverted.

7. C-2,3 linkage which is now axial, is smoothly equilibrated to the more stable equatorial conformation; pivalic acid was chosen as the equilibrating agent because it is too weak a nucleophile to effect side-reactions such as opening of the lactone ring.

8. Resolved via d-camphor-10-sulfonate.

9. Pearlman,B.A. J. Am. Chem. Soc., 1979, 101, 6404.

10. For a discussion of the philosophy of this approach and its broad implications in natural product synthesis: see Pearlman,B.A. J. Am. Chem. Soc., 1979, 101, 6398.



Ⓐ

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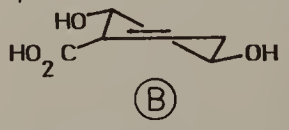
11. Presumably the undesired "diaxial" isomer Ⓑ is the major product of this reaction, but the required diequatoral diol is formed in sufficiently high yield to make the route attractive.



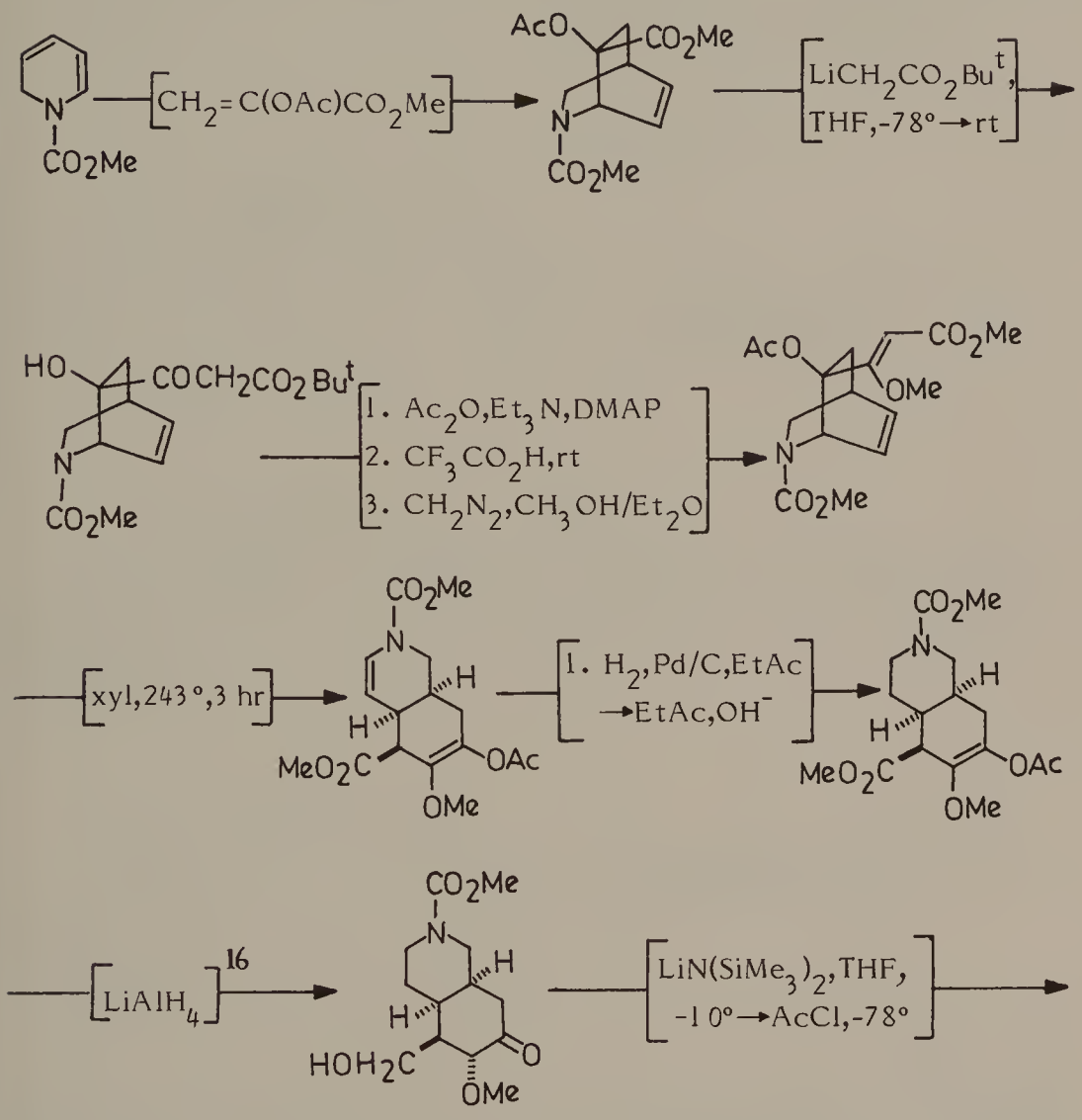
Ⓑ

12. The product was a 1:1 mixture of Ⓒ and its diastereomer, which were separated by column chromatography; the undesired isomer was converted back to the parent alcohol by methanolysis.

13. The ketal bridge underwent methanolysis, and the liberated methyl ketone epimerised to the exo configuration, and the liberated hydroxyl group formed a lactone with the carbomethoxy group of the cyclohexane ring.

14. During methanolysis the cyclobutane ring opened quantitatively by retroaldolisation, and the lactone ring underwent methanolysis by about 56%; the crude dimethyl acetal wastrimethoxybenzoylated and characterised by conversion to 3-epireserpine by known method.

The third synthesis by Wender, Schaus and White (15) is based on a general method for the synthesis of cis-hydroisoquinolines.



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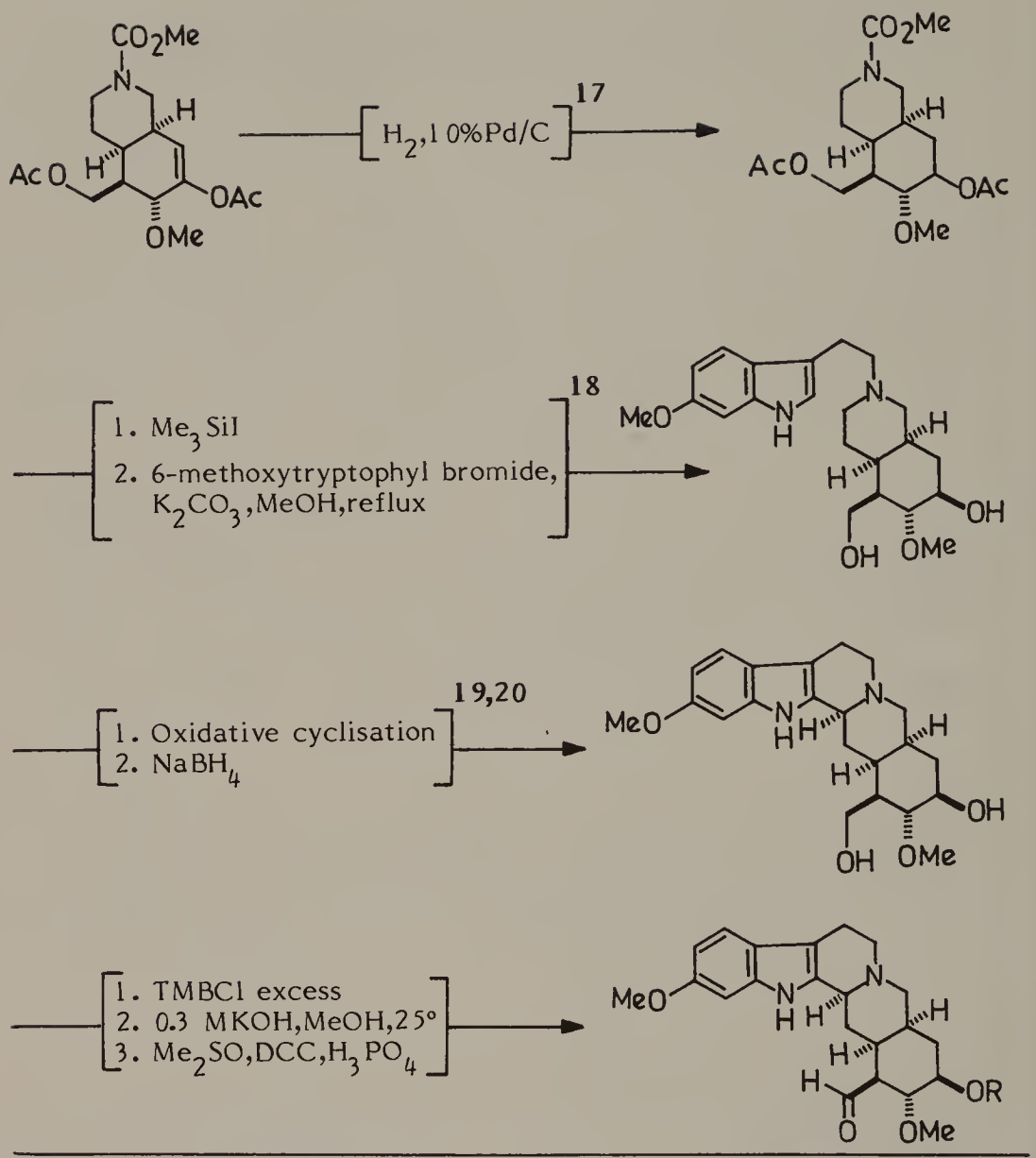
15. Wender,P.A.; Schaus,J.M.; White,A.W. J. Am. Chem. Soc., 1980, 102, 6159.

16. The ketone was obtained alongwith a small quantity of 18α & 18β-OH compounds. Since this epimerisation of (D) with $NaOCH_3$ produced a 6:1 mixture of the 17α:17β epimer, the formation of single ketone in the reaction appears to be a result of kinetic protonation of the enol aluminate intermediate.

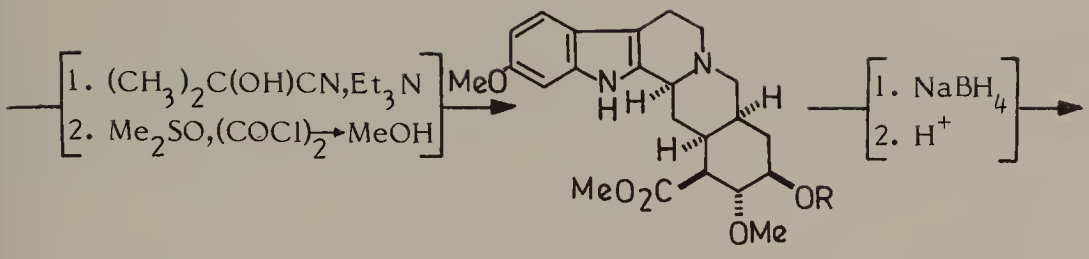


17. This reduction provided the single diacetate along with small quality of 18-hydrogenolysed product.

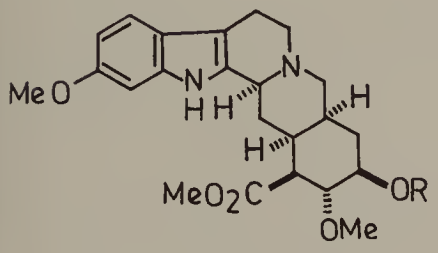
18. Alkylation also caused deacetylation.

19. (a) Wenkert,E.; Wickberg,B. J. Am. Chem. Soc., 1962, 84, 4914; (b) Morrison,G.C.; Cetenko,W.; Shavel,J.Jr. J. Org. Chem., 1967, 32, 4089; (c) Gutzwiller,J.; Pizzolato,G.; Uskokovic,M. J. Am. Chem. Soc., 1971, 93, 5908; (d) Stork,G.; Guthikonda,N. ibid, 1972, 94, 5110; (e) Aimi,N.; Yamanaka,E.; Endo,J.; Sakai,S.; Haginiwa,J. Tetrahedron Lett., 1972, 1081; (f) Tetrahedron, 1973, 29, 2015.

20. The isoreserpine diol was obtained alongwith a 4.5:3 ratio of inside reserpinediol.



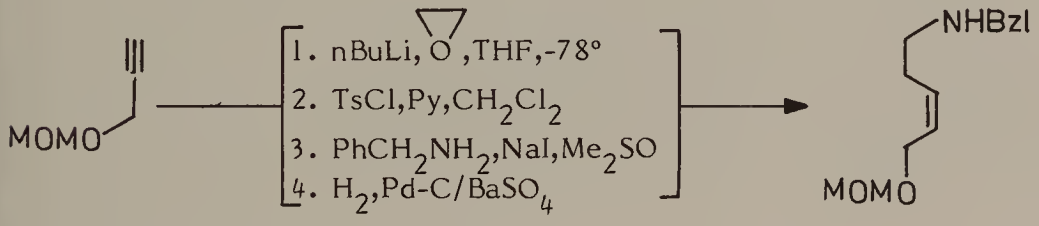
alongwith some 16 aldehyde



21 → *(±)-Reserpine*

Isoreserpine

The fourth synthesis by Martin et al (22) is based on an intramolecular Diels-Alder cycloaddition as the key step for the facile construction of the highly functionalised hydroisoquinoline component followed by catalytic hydrogenation which gave the ring D/E with all the stereocenters correct.



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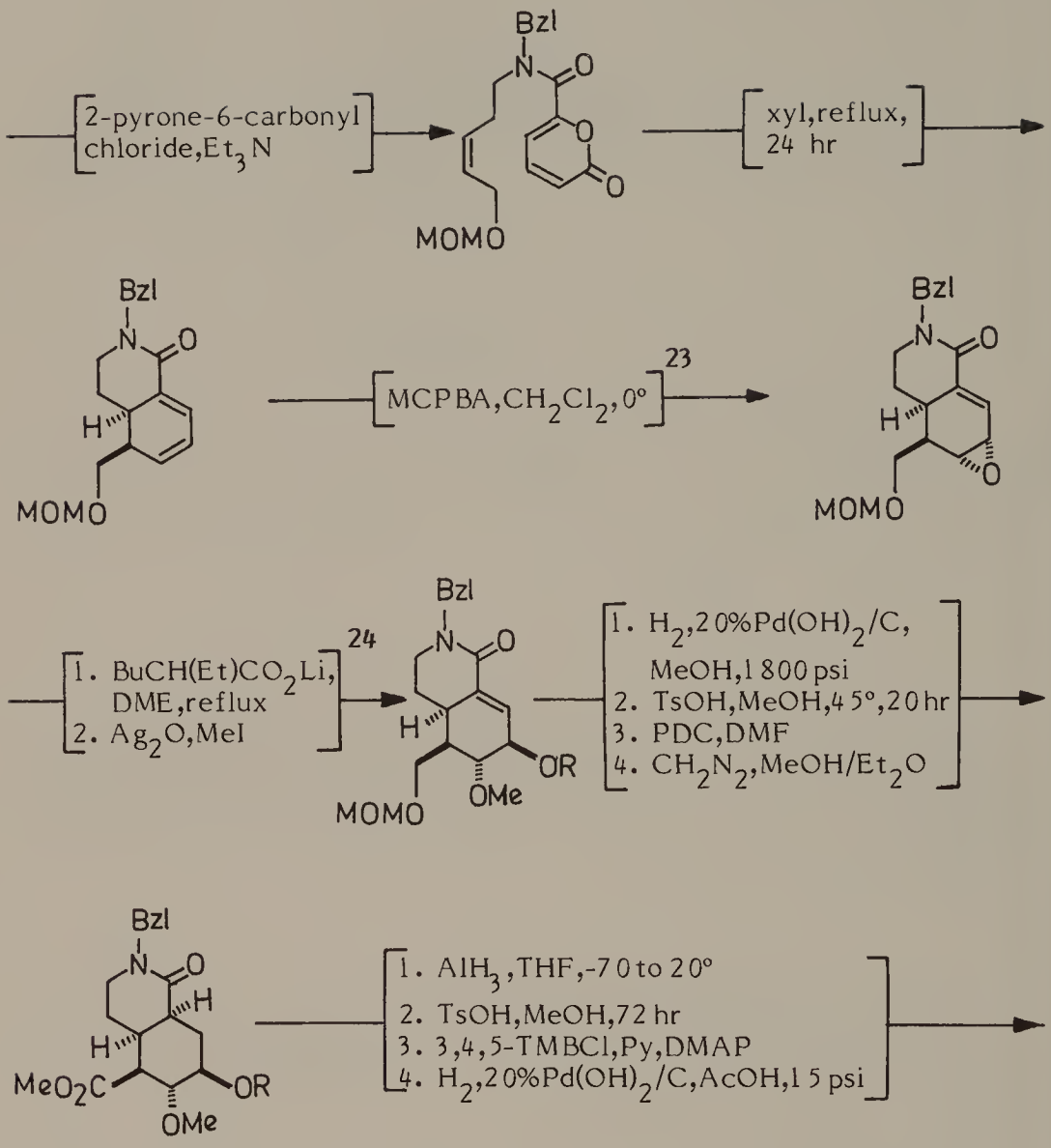
21. Huebner,C.F.; Kuehne,M.E.; Korzun,B.; Schlitter,E. Experientia, 1956, 12, 249; Weisenborn F.L.; Diassi,P.A. J. Am. Chem. Soc., 1956, 78, 2022.

22. Martin,S.F.; Grzejszczak,S.; Rueger,H.; Williamson,S.A. J. Am. Chem. Soc., 1985, 107, 4072.



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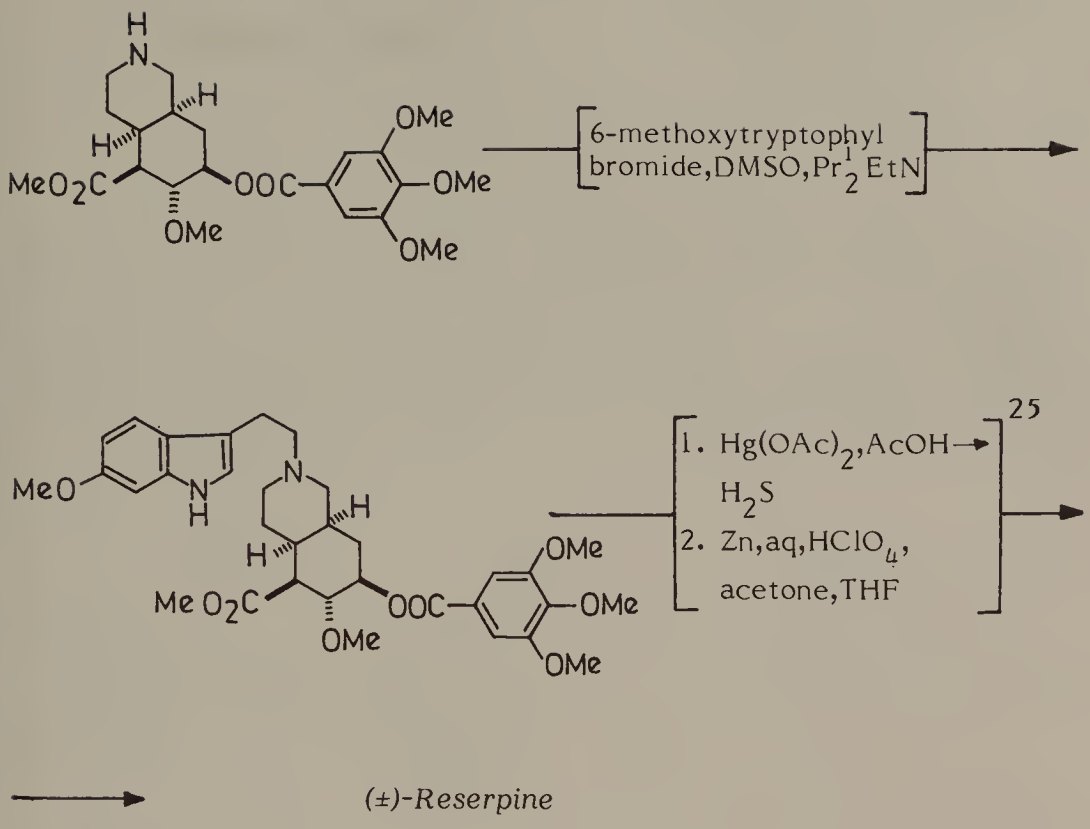
23. This epoxidation proceeded with a high degree of stereoselectivity from the less encumbered α-face.

24. The opening of the epoxide occurred exclusively at the allylic terminus.



(±)-Reserpine

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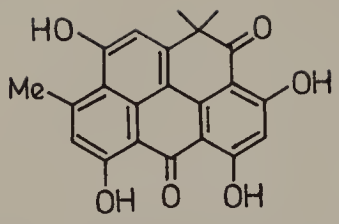
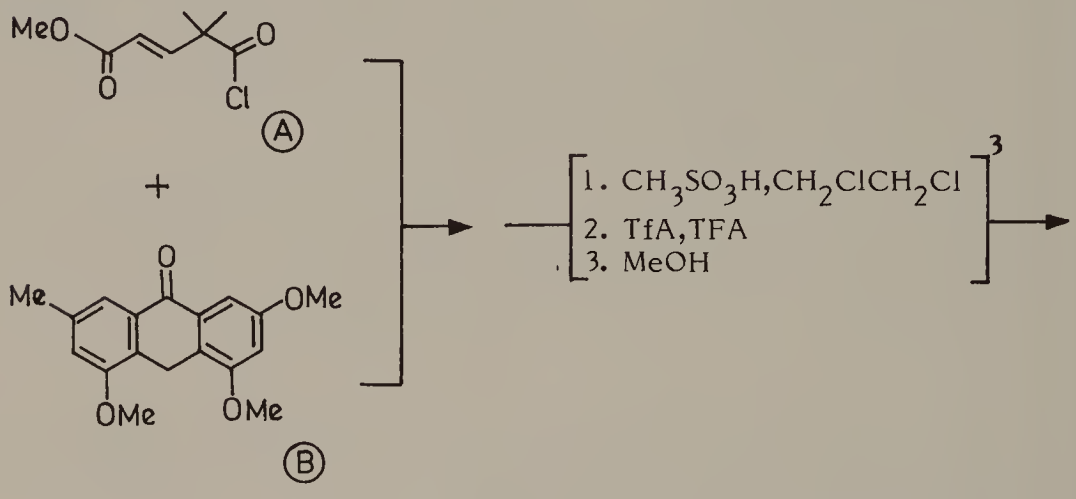
25. This conversion produced reserpine in 35% yield along with isoreserpine 8% and two corresponding inside derivatives in 18 and 4% yields.



RESISTOMYCIN

Resistomycin is one of the two natural products isolated so far which contains the benzo [cd]pyrene ring system. Recognition of the similarity between the bottom three rings of resistomycin and emodin suggested that if the three connections indicated by dotted lines (1) linking emodin to a 5 carbon unit could be constructed, an "expeditious" route to resistomycin would emerge, which has now been achieved by Kelly & Ghoshal (2).



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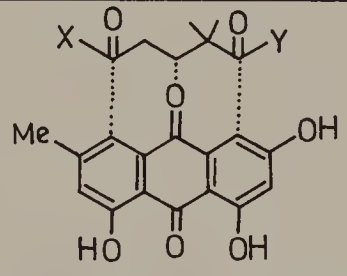
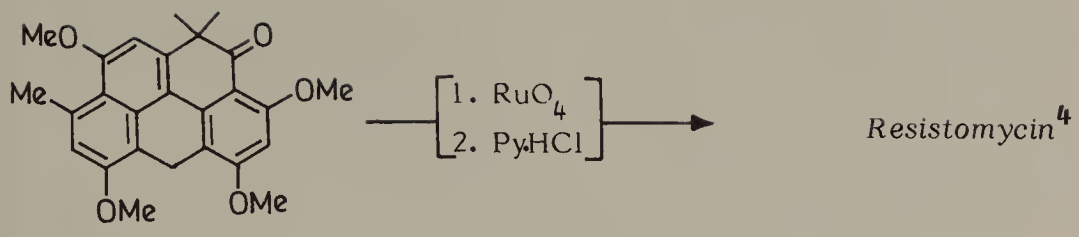
1. 

2. Kelly,T.R.; Ghoshal,M. J. Am. Chem. Soc., 1985, 107, 3879.

3. The sequence of events of the fusion of (A) & (B) has been examined by the authors in some detail and two- and three-bond formed intermediates isolated, which established that the reaction proceeded as indicated. Regio-selectivity seems to be determined by the acidity of the reaction conditions. Mechanistic details of the reaction are discussed in the paper.



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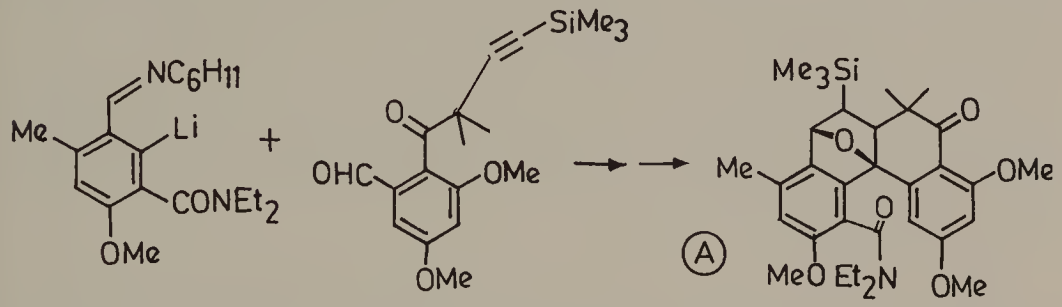
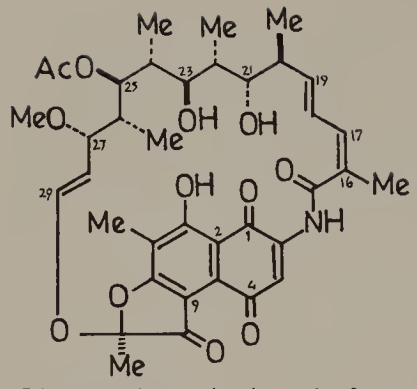
4. The only other synthesis of resistomycin was on classical lines and employed an intramolecular Diels-Alder reaction of an insitu generated isobenzofuran as the key constructive step to get Ⓐ;[Keay,B.A.; Rodrigo,R. J. Am. Chem. Soc., 1982, 104, 4725.]; Ⓐ on treatment



with pyridine hydrochloride underwent demethylation, desilylation, aromatisation and cyclisation to yield resistomycin.



RIFAMYCIN S

Rifamycins, isolated from the fermentation broth of Norcardia mediterranei, were the first examples of ansamycins (1) characterised by an aliphatic bridge linking two non-adjacent positions of an aromatic nucleus. The first and the only total synthesis of rifamycin S by Kishi and his associates (2) builds separately the aliphatic chain (the ansa bridge) and the aromatic portion, couples the two to first form the acetal link followed by macro-lactamisation and adjustment of functionalities. Other synthesis for the aliphatic chain using various acyclic approaches have also been reported; Masamune (8), Still (9) and Corey (5) developed synthetic approaches which exploited the elements of symmetry in the aliphatic chain between C_{20}-C_{26} (3), while Hanesian (7), Kinoshita (8) and Fraser-Reid (9) developed enantioselective synthesis from carbohydrate precursors.

The syntheses of the aliphatic chain by Kishi and his associates are based on the appreciation of the elements of symmetry around C_{23}, and that fragment C_{20}-C_{26} consists of four repeating structural units which led to a strategy amenable to repetitive condensation based on same synthetic operations (4). The first synthesis reported was of the racemic compound (2a); in the next modification (2d) optically pure β-benzyloxy-isobutyraldehyde was used as the starting aldehyde and the enantiomerically correct aliphatic segment prepared

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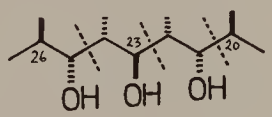
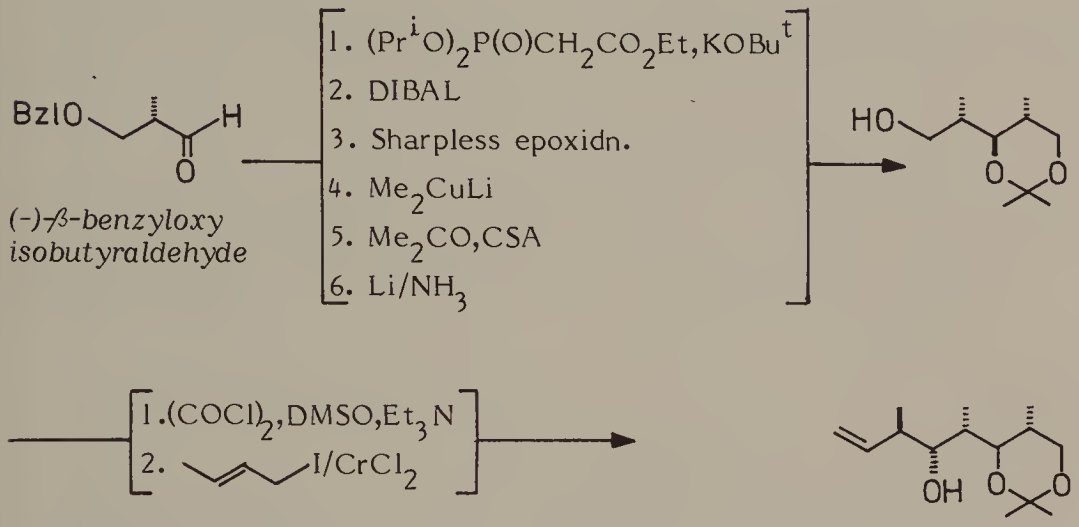
1. For reviews on rifamycins see: Prelog,V. Pure & Appl. Chem., 1963, 7, 551; Reinhart,K.L. Jr. Acc. Chem. Res., 1972, 5, 57; Sensi,P. Pure & Appl. Chem., 1975, 41, 15; Reinhart,K.L. Jr.; Shidd,L.S. Prog. Chem. Org. Nat. Prod., 1976, 33, 231; Patterson,I.; Mansuri,M.M. Tetrahedron, 1985, 41, 3569.

2. (a) Nagaoka,H.; Rutsch,W.; Schmid,G.; Lio,H.; Johnson,M.R.; Kishi,Y. J. Am. Chem.Soc., 1980, 102, 7962; (b) Lio,H.; Hagaoka,H.; Kishi,Y. J. Am. Chem. Soc., 1980, 102, 7965; (c) Nagaoka,H.; Schmid,G.; Lio,H.; Kishi,Y. Tetrahedron Lett., 1981, 22, 89; (d) Nagaoka,H.; Kishi,Y. Tetrahedron, 1981, 37, 3873; (e) Johnson,M.R.; Kishi,Y. Tetrahedron Lett., 1979, 4347.

3. 

using the previously established route (5). Further improvement in overall stereoselectivity was achieved by use of a sequence of three Sharpless asymmetric epoxidation reactions for controlling the six asymmetric centres at C_{20}-C_{23}, C_{25} and C_{26} and the stereo-selectivity at C_{27} also substantially improved by using an allyltin (II) reagent for coupling instead of the allylzinc reagent (2d). In the final and most efficient route described below the construction of the C_{19}-C_{27} segment was further simplified by conducting two of the two-carbon chain extensions with a crotyl-chromium reagent, which served to set up correctly two new asymmetric centres at the same time (2d).

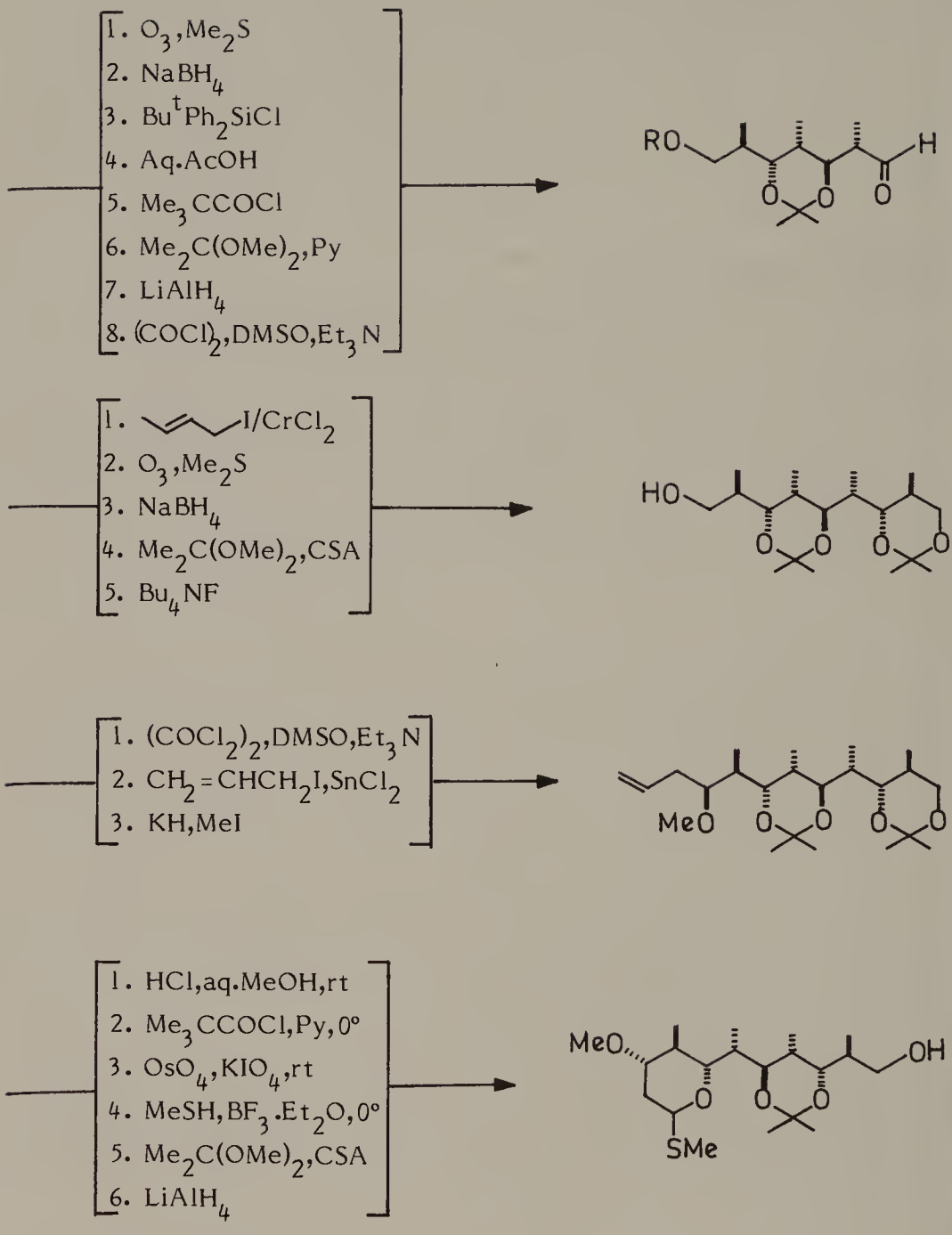
Aliphatic Segment C_{15}-C_{29}

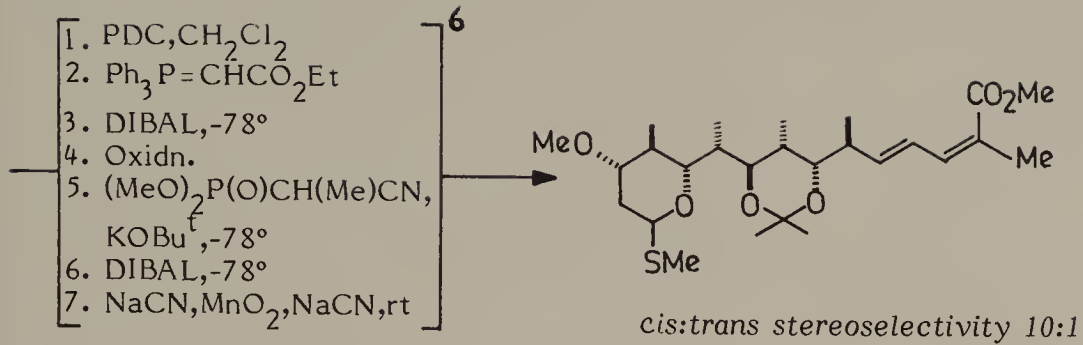


4. 

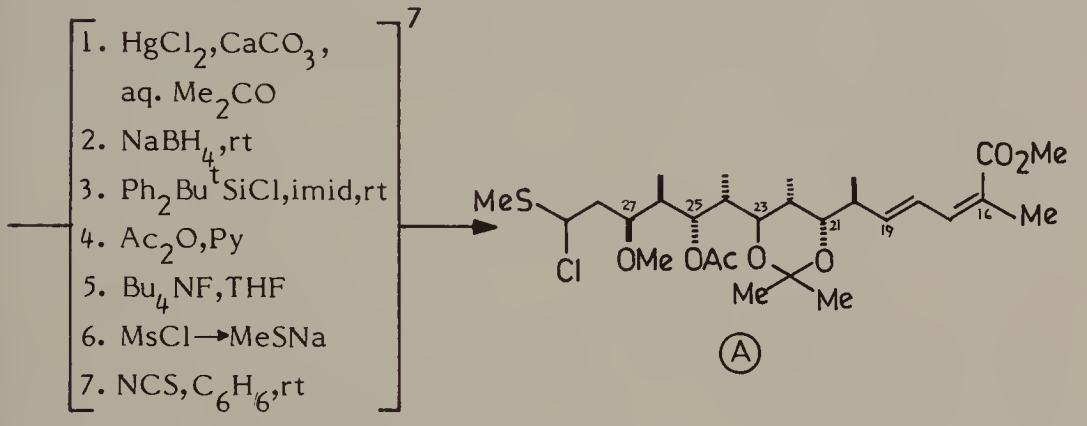
For general methods developed for stereocontrolled coupling of units see: Schmid,G.; Fukuyama,T.; Akasaka,K.; Kishi,Y.; J. Am. Chem. Soc., 1979, 101, 259; Johnson,M.R.; Nakata,J.; Kishi,Y. Tetrahedron Lett., 1979, 4343; Hasan,I.; Kishi,Y. ibid, 1980, 4229.

5. In view of the presence of the aldehyde group adjacent to the asymmetric centre the effect of different reagents and reactions on optical purity of the starting aldehyde and products has been studied in great detail and such reaction conditions selected which had minimal effect on optical purity; Nagaoka & Kishi (2d); changes of reagent were found to markedly affect the optical purity e.g. in oxidation of primary alcohol while Swern's oxidation (Mancuso,A.J.; Jung,S.L.; Swern,D. J. Org. Chem., 1978, 43, 2480) maintained optical purity in the resulting aldehyde; with pyridinium chlorochromate there was considerable loss of optical purity.


1. O_3, Me_2S
2. $NaBH_4$
3. Bu^tPh_2SiCl
4. Aq.AcOH
5. Me_3CCOCl
6. $Me_2C(OMe)_2$, Py
7. $LiAlH_4$
8. $(COCl)_2$, DMSO, Et_3N
RO
H
O
1. I/$CrCl_2$
2. O_3, Me_2S
3. $NaBH_4$
4. $Me_2C(OMe)_2$, CSA
5. Bu_4NF
HO
1. $(COCl_2)_2$, DMSO, Et_3N
2. $CH_2=CHCH_2I$, $SnCl_2$
3. KH, MeI
MeO
1. HCl, aq.MeOH, rt
2. Me_3CCOCl, Py, 0°
3. OsO_4, KIO_4, rt
4. MeSH, $BF_3.Et_2O$, 0°
5. $Me_2C(OMe)_2$, CSA
6. $LiAlH_4$
MeO
OH
SMe



cis:trans stereoselectivity 10:1



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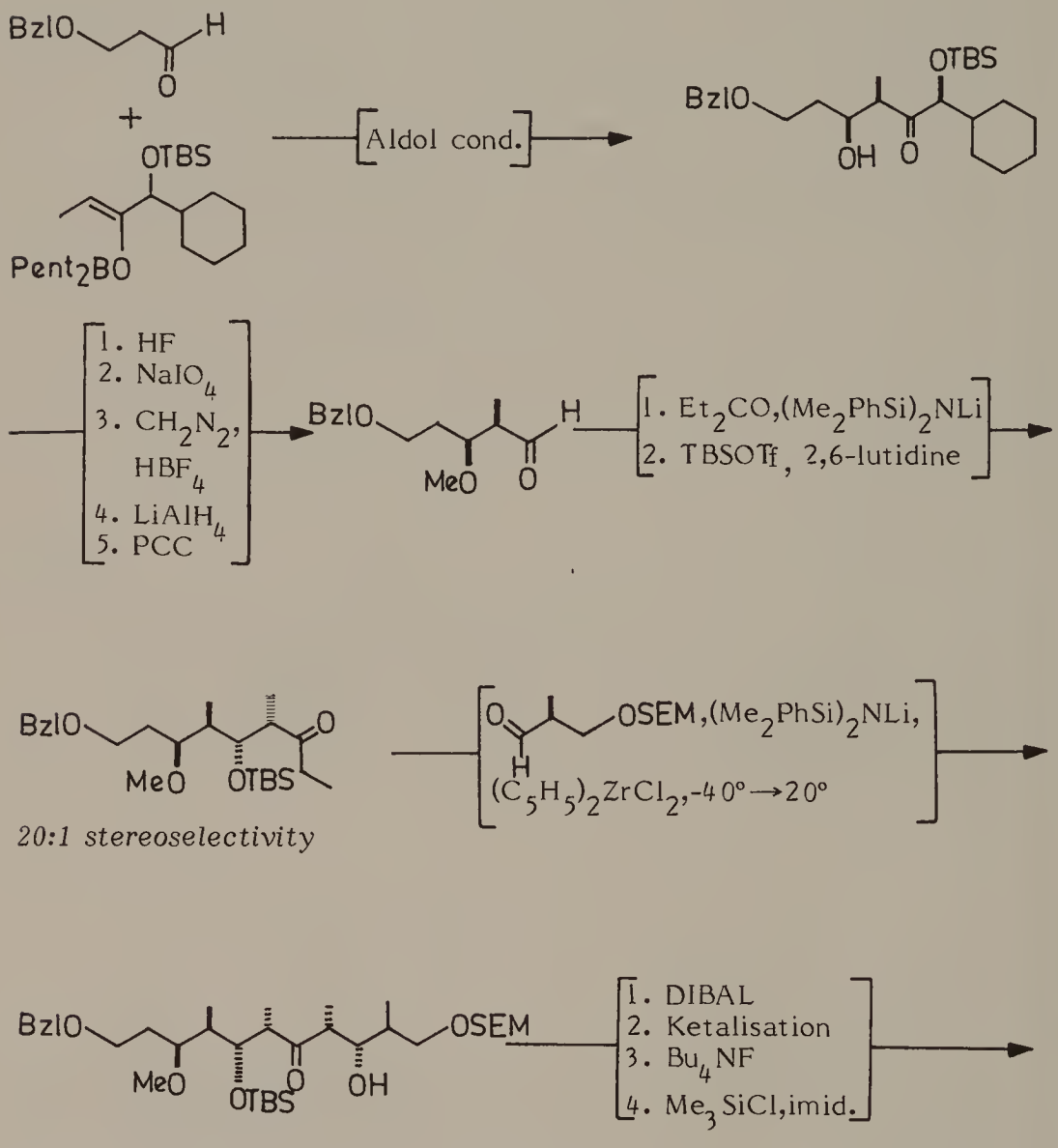
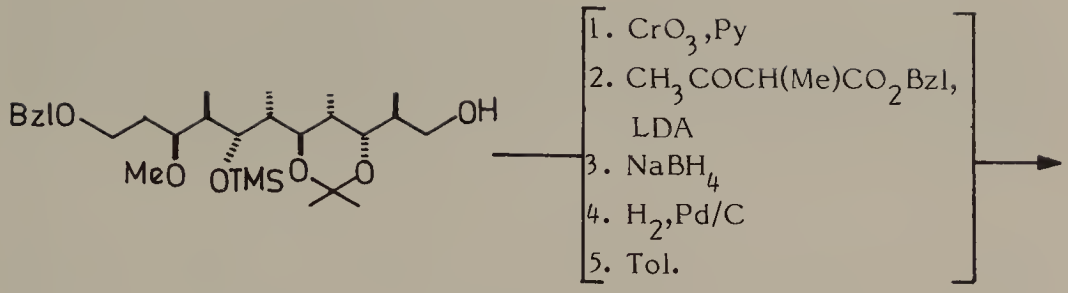
6. Use of methyl ester in the second Wittig reaction gave instead almost exclusively the trans olefine, and the best cis: trans ratio (10:1) was obtained with the cyano Wittig reagent.

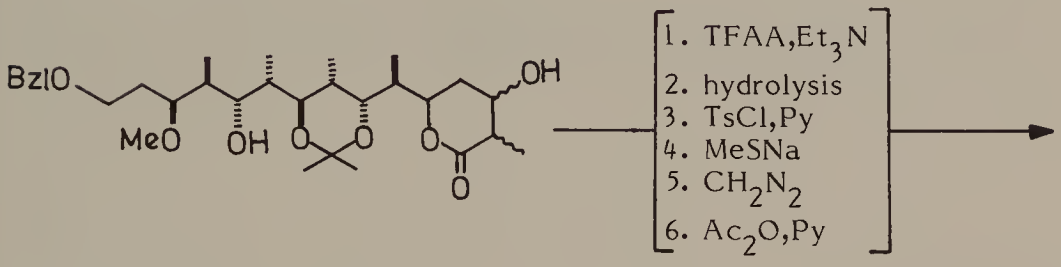
7. The N-chlorosuccimide (NCS) chlorination gave a diastereomeric mixture of ∝-chloro-sulfides.

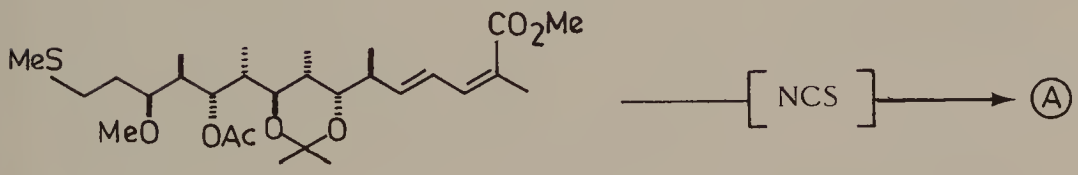
Masamune's (8) highly convergent asymmetric synthesis of the aliphatic fragment described herein assembles seven of the eight asymmetric centres by four directed aldol condensation reactions; the eighth centre, C_{23} , was created by a stereoselective reduction.



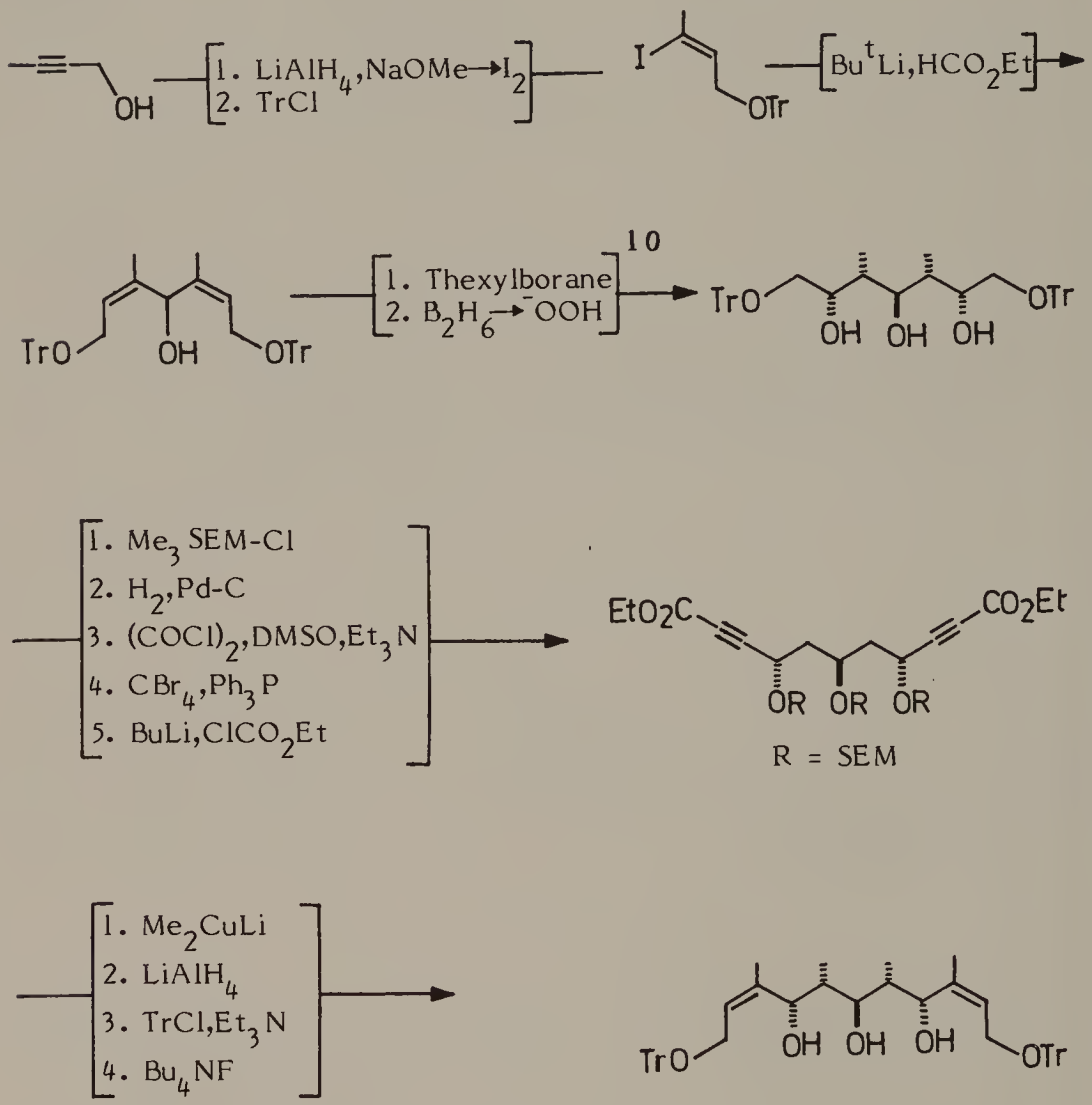
8. Masamune,S.; Imperiali,B.; Garvey,D.S. J. Am. Chem. Soc., 1982, 104, 5528.


BzlO
MeO
OTMS
OH
1. CrO_3,Py
2. $CH_3COCH(Me)CO_2Bzl$, LDA
3. $NaBH_4$
4. H_2,Pd/C
5. Tol.


BzlO
MeO
OH
OH
O
1. TFAA,Et_3N
2. hydrolysis
3. TsCl,Py
4. MeSNa
5. CH_2N_2
6. Ac_2O,Py


MeS
MeO
OAc
CO_2Me
NCS
A

Still and Barrish (9) also based their synthesis on the symmetry of the ansa chain by assembling a unit with anti-1,3-diol stereochemistry around a prochiral centre at C_{23} by stereoselective hydroboration of secondary allylic alcohols to set up first a chain of five and then nine asymmetric centres which was then converted into the C_{17}-C_{28} segment.



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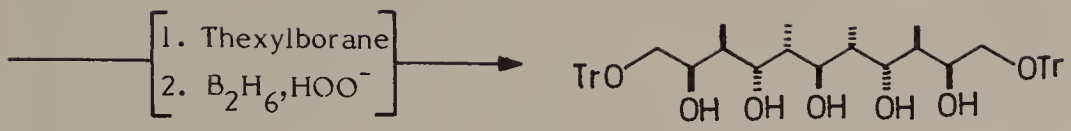
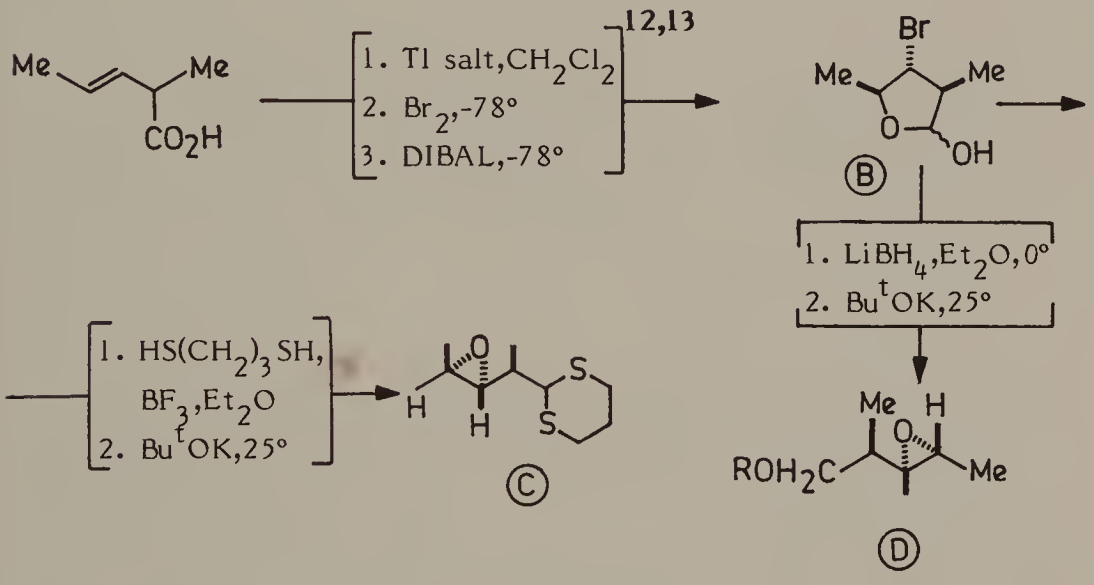
9. Still,W.C.; Barrish,J.C. J. Am. Chem. Soc., 1983, 105, 2487.

10. This reaction gave a 5:1 ratio of meso- and dl-triols.



Corey and Hase (11) noting the antipodal relationship of 5 carbon atom fragments around C_{23} developed a highly stereoselective synthesis of fragments (C) & (D) from enantiomeric but otherwise identical 6-carbon precursors (B) based on application of the halolactonisation reaction to acyclic systems. Condensation of B&C with deprotonated acetonitrile as the C_{23} nucleophilic carbonyl equivalent was used to complete the C_{19}-C_{27} fragment. Corey and Clark (11) have also developed a method for the formation of the macrolactam ring based on a relay substrate.



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11. Corey,E.J.; Hase,T. Tetrahedron Lett., 1979, 335; Corey,E.J.; Clark,D.A. Tetrahedron Lett., 1980, 2045.

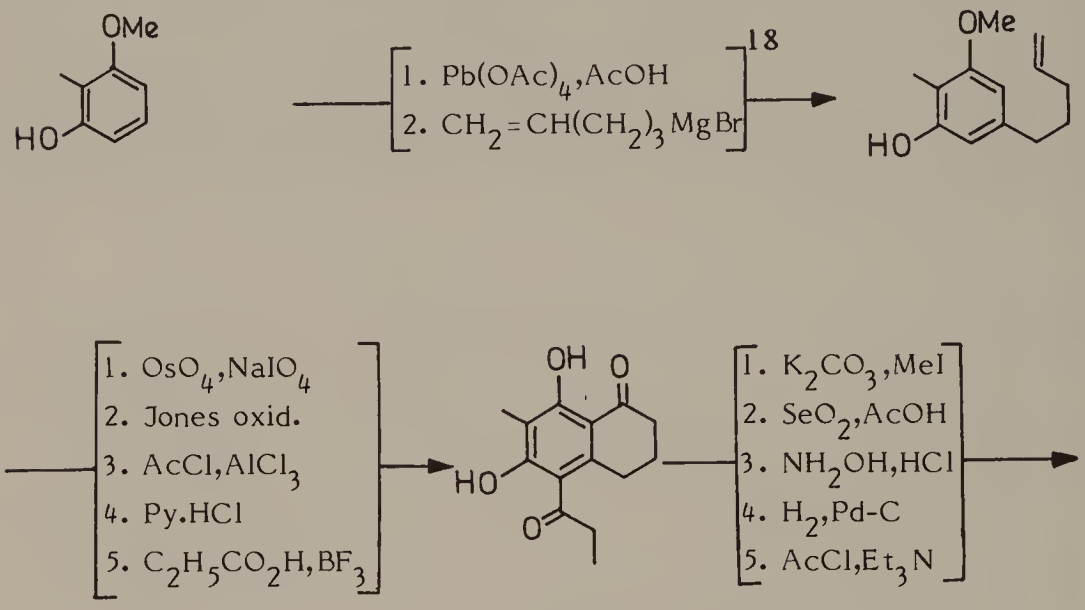
12. A trans relationship in halolactonisation is indicated by the known mode of these reactions and was supported by PMR studies; this is a result of kinetically controlled process.

13. The corresponding iodo lactal was much less stable and therefore bromo lactal was used.

Hanesian's carbohydrate approach (14) is based on constructing enantiomerically pure C_{19}-C_{24} and C_{25}-C_{29} fragments from a common D-glucose derived precursor and coupling the two by a directed aldol condensation followed by adjustment of functionalities. Kinoshita's synthesis (15) uses a similar strategy except that the disconnection is between C_{23}-C_{24}, and the two fragments are derived from epimeric pyranosides. Fraser-Reid (16) developed a novel ring cleavage approach from levoglucosan, which avoided the coupling of two sugar derived fragments, and generated the C_{19}-C_{28} chain.

Aromatic fragment

Kishi Synthesis[17]



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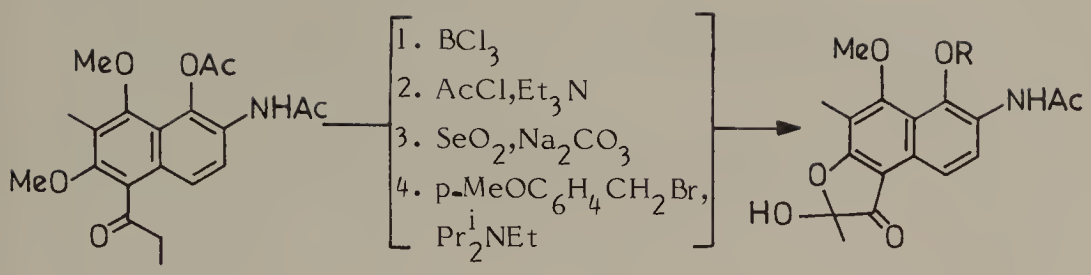
14. Hanesian,S.; Pougny,J.R.; Boessenkool,I. J. Am. Chem. Soc., 1982, 104, 6164; Tetrahedron, 1984, 40, 1289.

15. Nakata,M.; Takao,H.; Ikeyama,Y.; Sakai,T.; Tatsuta,K.; Kinoshita,M. Bull. Chem. Soc. Japan, 1981, 54, 1743, 1749.

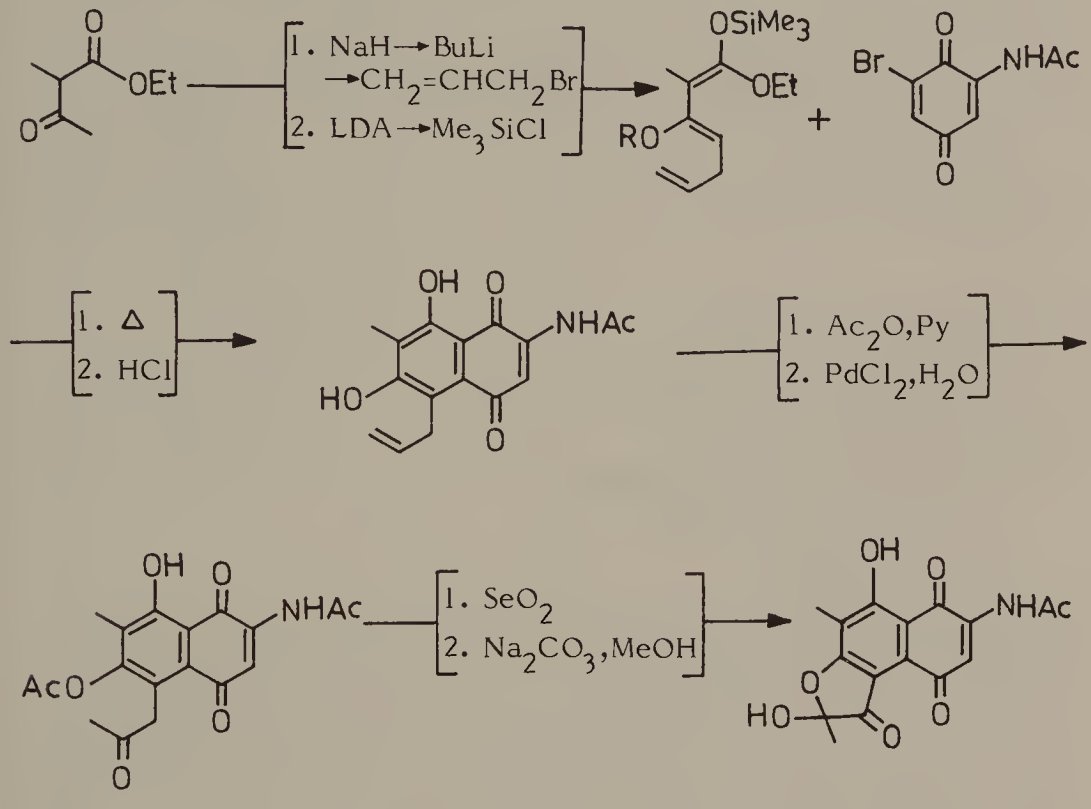
16. Fraser-Reid,B.; Magdinski,L.; Molino,B. J. Am. Chem. Soc., 1984, 106, 731.

17. The aromatic component used in the original synthesis was prepared from the aromatic fragment obtained by hydrolysis of rifamycin S (2b), and the synthesis described herein was reported subsequently; Nagaoka,H.; Schmid,G.; Lio,H.; Kishi,Y. Tetrahedron Lett., 1981, 22, 899.

18. $Pb(OAc)_4$ reaction helped to create a nucleophilic site through the intermediate.

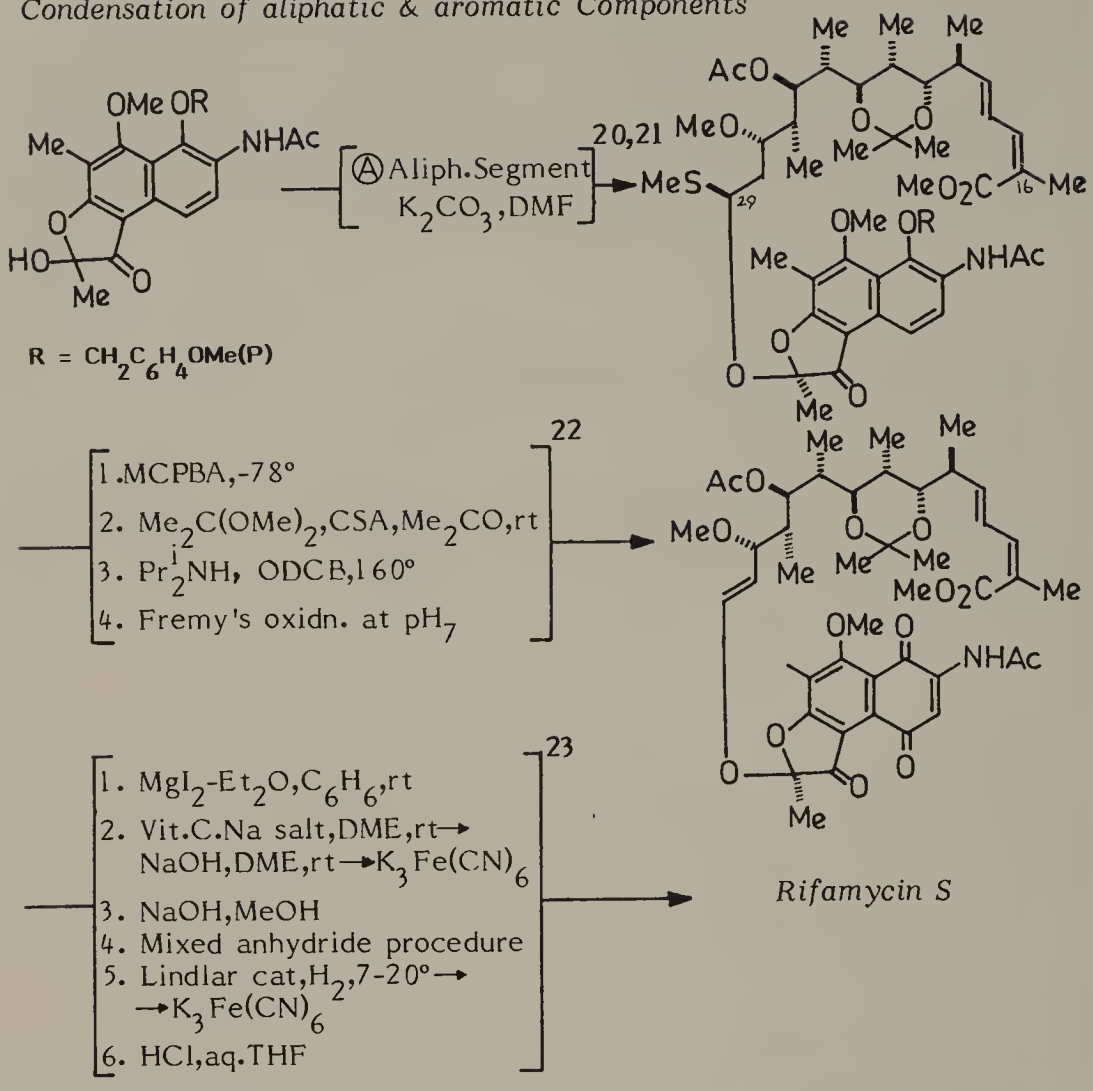


Kelly et al. (19) prepared the aromatic component with all the substituents assembled by a regiospecific Diels-Alder reaction between a suitable diene and a benzoquinone dienophile.



19. Kelly,T.R.; Behforouz,M.; Echavarren,A.; Vaga,J. Tetrahedron Lett., 1983, 23, 2331.

Condensation of aliphatic & aromatic Components



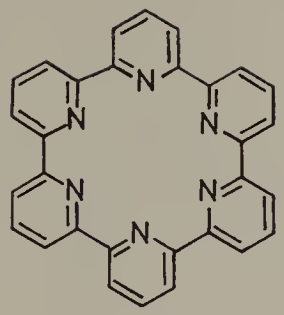
Rifamycin S

20. The p-methoxybenzyl group was chosen as this could be removed under acidic conditions without affecting the ketal group.

21. In this condensation all the four possible diastereomers with respect to C-12, C-27 and C-29 were formed in about equal proportion, of which the one having the natural relative stereochemistry with respect to the C-12 and C-27 positions could be isolated pure by preparative tlc; the mixture of these two was used for subsequent operations.

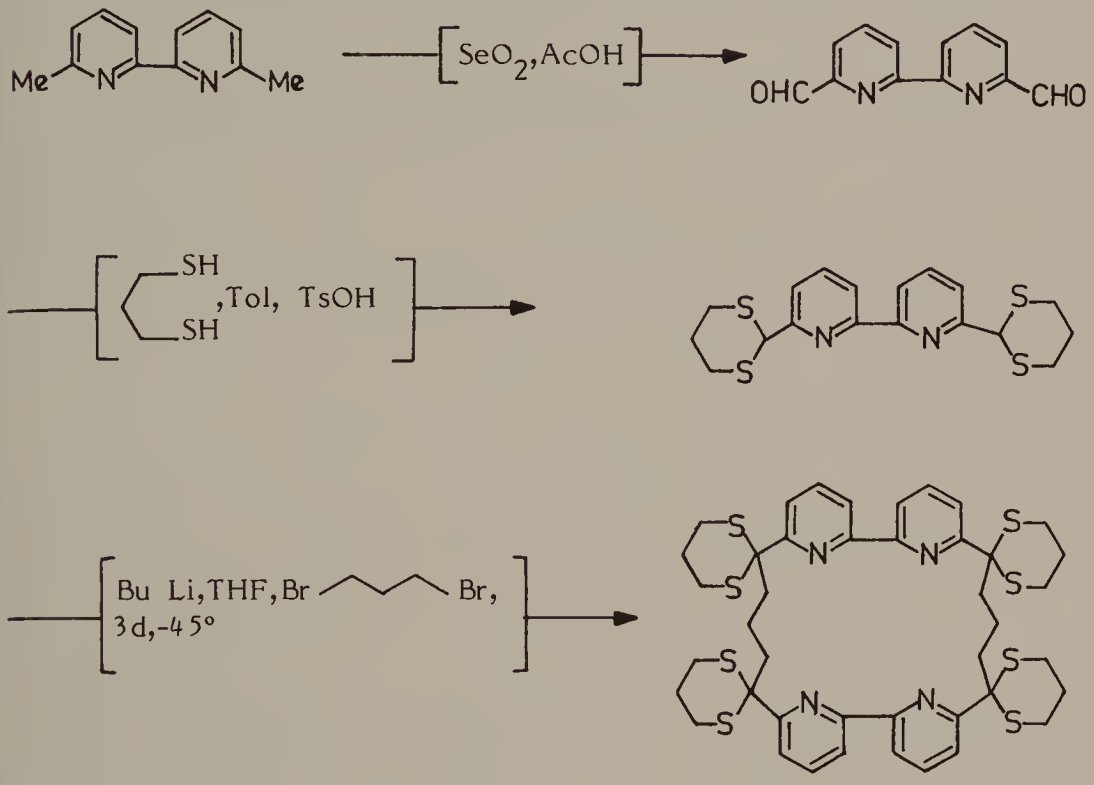
22. Olefin formed by sulfoxide elimination was a 1:1 mixture of the trans and cis olefins, which were separated at the next step after oxidation by preparative tlc, and the required trans isomer used for further conversions.

23. Lindlar catalyst at low temperature was used to reduce the naphthoquinone moiety (and in consequence to increase the nucleophilicity of the C-2 amino group in lactam formation) without affecting the olefinic bonds.

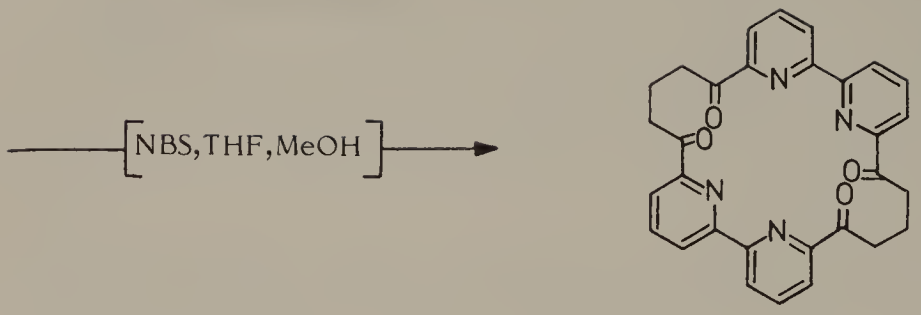


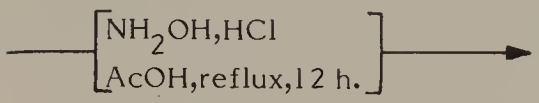
SEXIPYRIDINE

Sexipyridine offers an irresistible electron rich cavity and its synthesis has been vainly pursued since 1932. A synthetic strategy incorporating initial macrocyclization to give a flexible poly-functional intermediate which can be irreversibly rigidized to build the remaining pyridine rings, has resulted in a brilliant synthesis of sexipyridine.

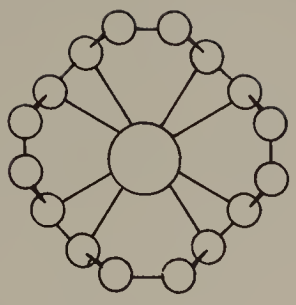


1. Newkome,G.R.; Lee,H.W. J. Am. Chem. Soc., 1983, 105, 5956.





Sexipyridine

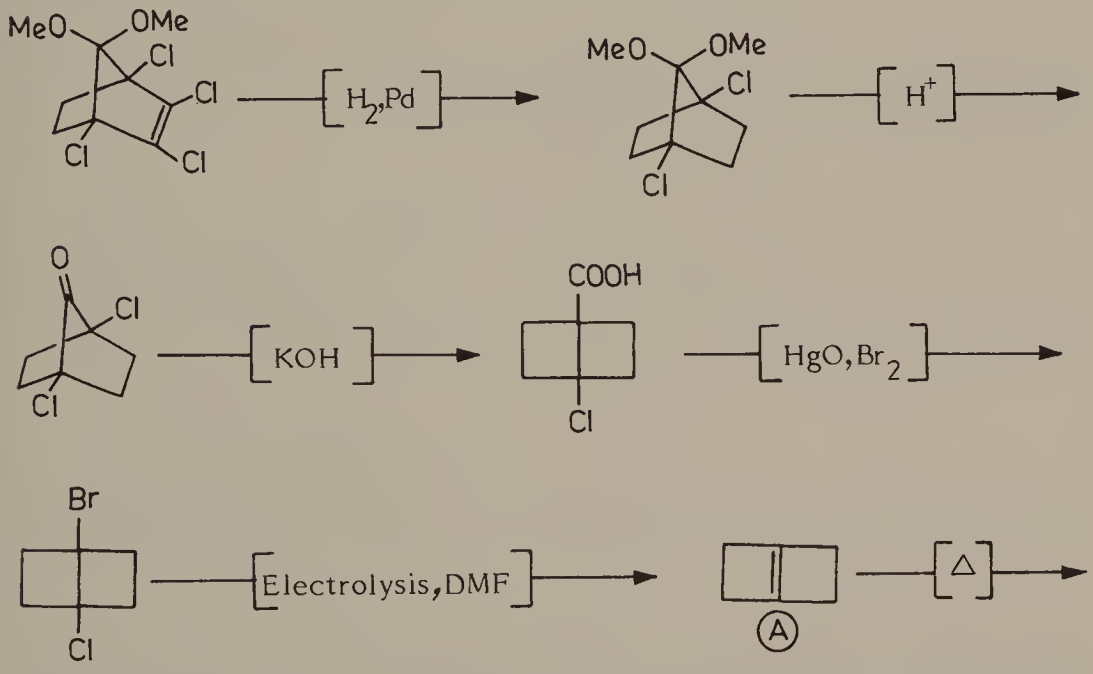


I

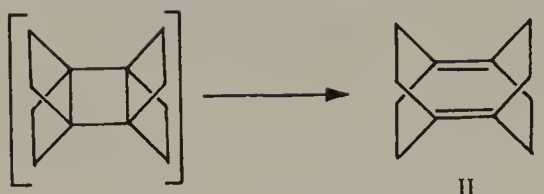
SIGMA DIRECTED pi-SYSTEMS

The reversal of the usual π-σ orientation of aromatic systems would lead to extra-ordinary structures where the π component would be directed towards the core of the molecule as illustrated with II-IV. In appropriate cases the electron rich cavity thus generated can harbor metal ions. The computer generated x-ray crystal structure of the IV-Ag^+ complex is represented by I. The strain arising from the holding back of the σ plane is, to a measure, compensated by the increase of the s character of the π bond. This is pronounced in the case of II.

Compound II arises by the dimerization of the extra-ordinarily strained compound, bicyclo [2.2.0]hex-1-ene Ⓐ (1).



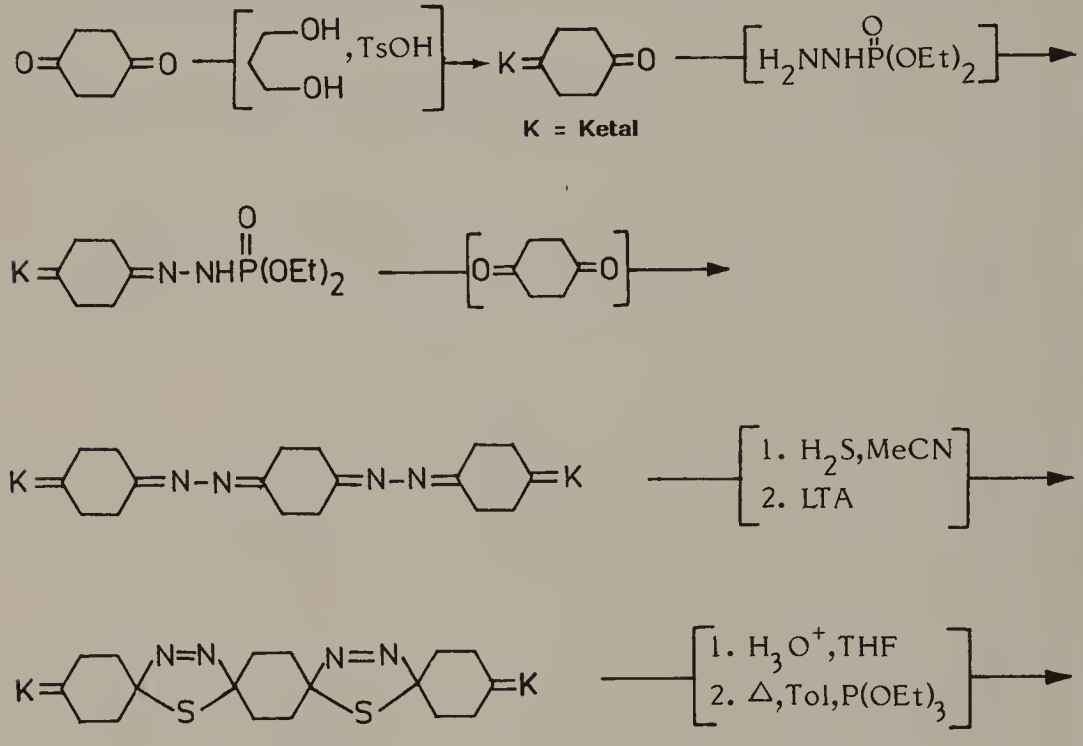
1. Wiberg,K.B.; Matturro,M.G.; Okarma,P.J.; Jason,M.E.; Dailey,W.P.; Burgmaier,G.J.; Bailey, W.F.; Warner,P. Tetrahedron, 1986, 42, 1895.



II

Synthesis of III & IV

Compounds III and IV were prepared by a generalized procedure for cyclohexane-1,4-dione unit elongation incorporating a nitrogen and sulfur extrusion sequence. The linear units are cyclized with Ti° (2).



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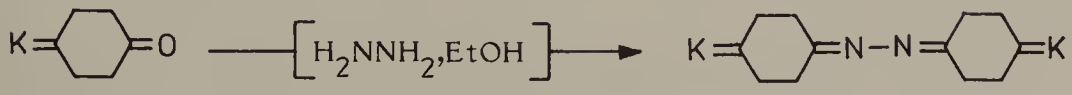
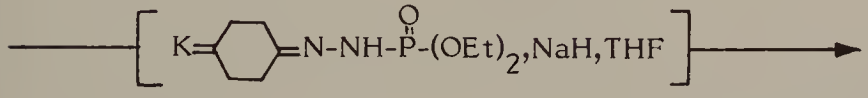
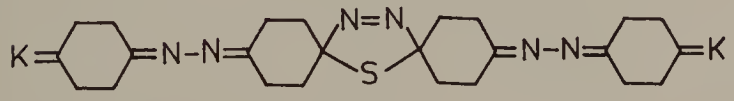
2. McMurry,J.E.; Haley,G.J.; Matz,J.R.; Clardy,J.C.; VanDuyne,G.; Gleiter,R.; Schafer,W.; White,D.H. J. Am. Chem. Soc., 1984, 106, 5018; McMurry,J.E.; Haley,G.J.; Matz,J.R.; Clardy, J.C.; Mitchell, J. J. Am. Chem. Soc., 1986, 108, 515.

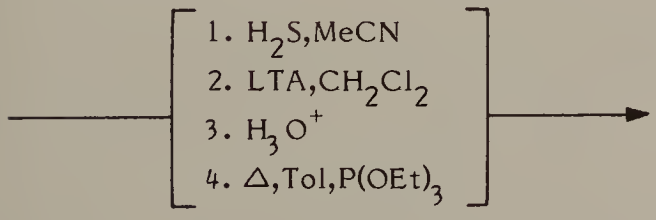
III

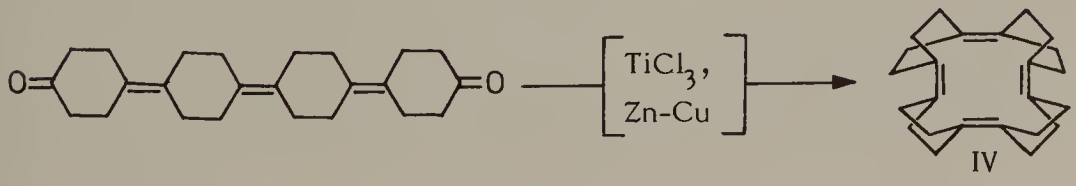
Synthesis of IV



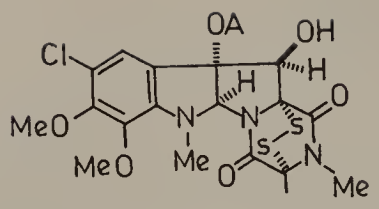








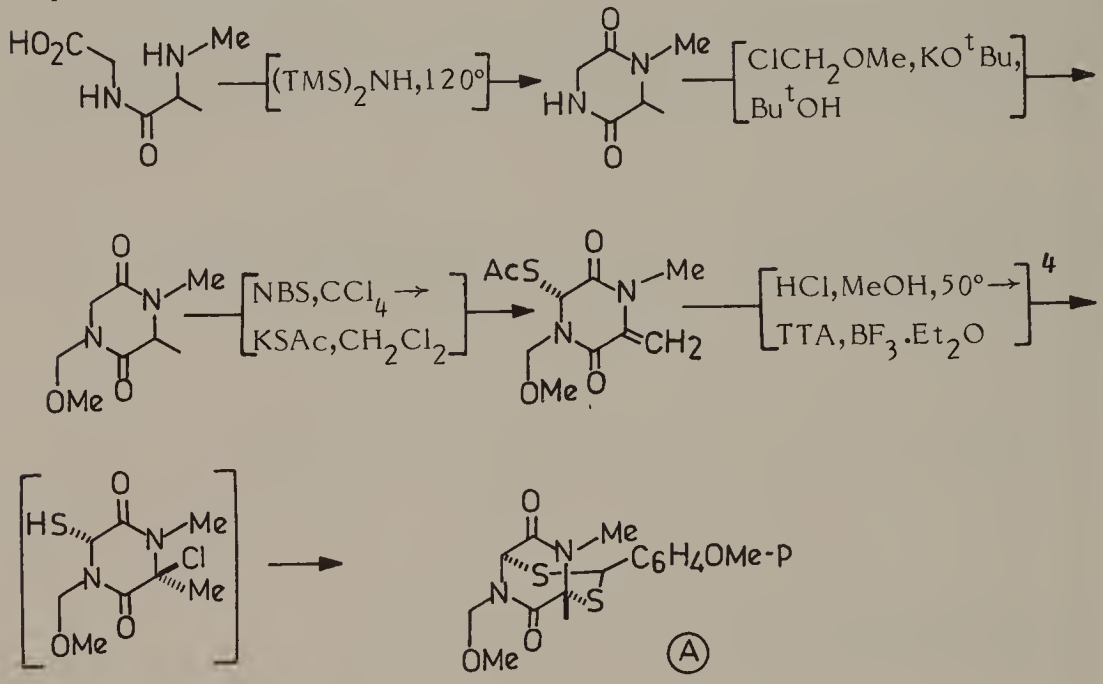
IV



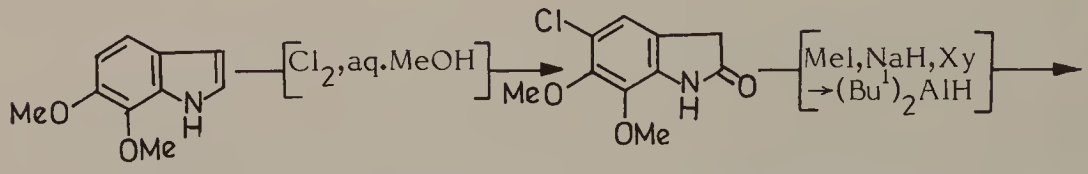
SPORIDESMIN-A

The synthesis of sporidesmin-A (1) is based on a new general method for the synthesis of epidithioketopiperazines developed by Kishi et al. (2), in which a thioacetal grouping serves as a latent episulfide bridge. Introduction of the indole part of the molecule has been carried out by acylation of the bridgehead monocarbanion derived from Ⓐ followed by oxidative ring closure of ring C Ⓒ→Ⓓ (3).

Piperazinedione part:



Indole part:



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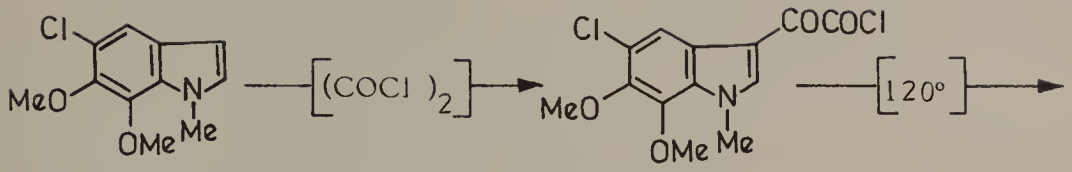
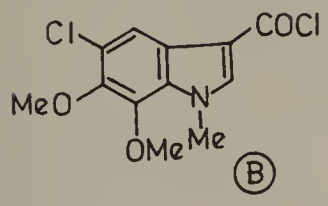
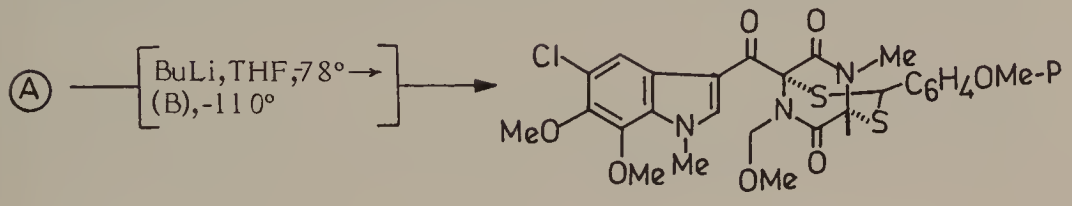
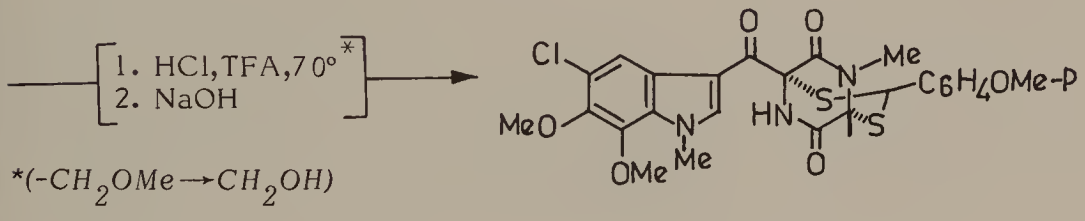
1. Sporidesmins are toxic metabolites of Pithomyces chartarum, and the cause of facial eczema and serious hepatoxic disease in sheep; Ronaldson,J.W.; Taylor,A.; White,E.P.; Abraham,R.J. J. Chem. Soc., 1963, 3172; Safe,S.; Taylor,A. J. Chem. Soc. Perkin I, 1972, 470 and references cited therein.
2. Kishi,Y.; Fukuyama,T.; Nakatsuka,S. J. Am. Chem. Soc., 1973, 95, 6491.
3. Kishi,Y.; Nakatsuka,S.; Fukuyama,T.; Havel,M. J. Am. Chem. Soc., 1973, 95, 6493.
4. TTA = Trithiane derivative of anisaldehyde.

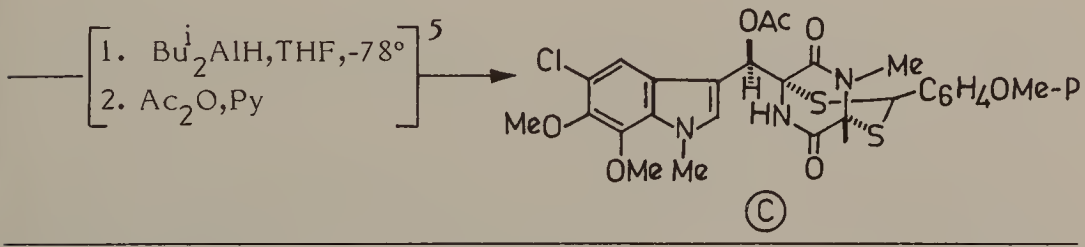




Sporidesmine-A:







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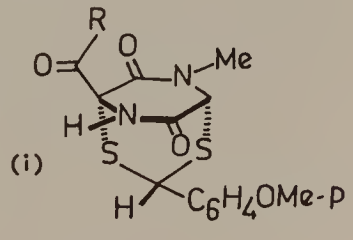
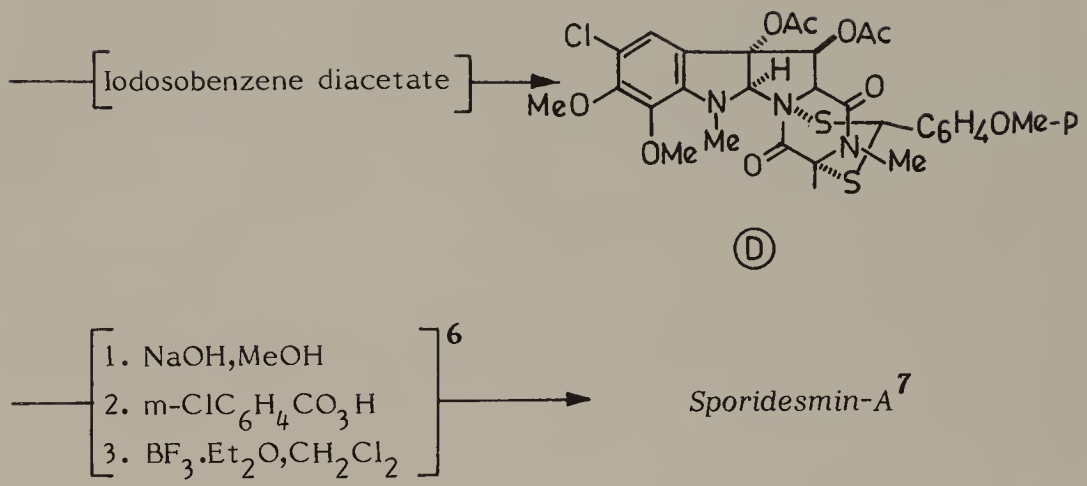
5. This reduction is rationalized as involving complex formation between the amide N-H group and the reducing agent. The crucial intramolecular hydride transfer then occurs from the α-side of the diketopiperazine which stays as far away as possible from the bulky indole unit (i).





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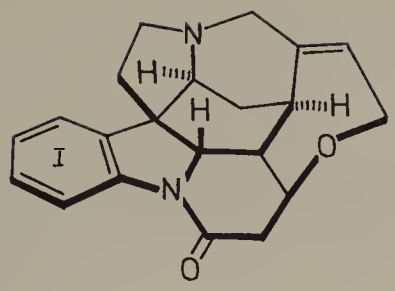
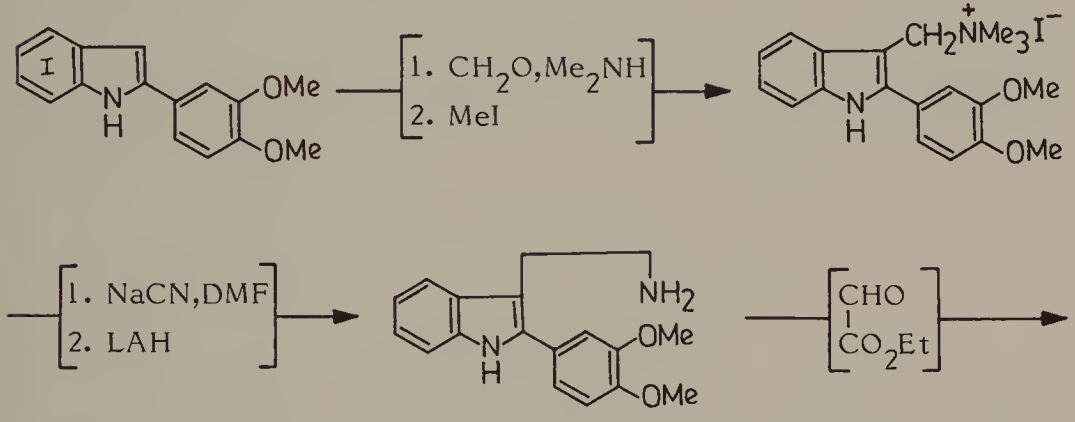
6. The dithioacetal group is readily converted to the disulfide bridge by oxidation to sulfoxide, followed by treatment with acid to effect the carbon-sulfur bond fission. The p-methoxybenzene group is essential for this cleavage and facilitates resonance stabilization of the incipient carbonium ion.

7. For the synthesis of dehydrogliotoxin, a related epidithioketopiperazine, see: Kishi,Y.; Fukuyama,T.; Nakatsuka,S. J. Am. Chem. Soc., 1973, 95, 6492.



STRYCHNINE

The synthesis of strychnine (1) illustrates how biogenetic considerations may be employed advantageously in planning the synthesis of a complex natural product (2). In cognizance of the natural process Woodward and his colleagues constructed ring V in strychnine by the condensation of an aldehyde between the β-position of a 2-veratryltryptamine (4) and the side-chain nitrogen. Another crucial step in the synthesis was the oxidative cleavage of a carbocyclic ring to provide the right structural elements for cyclizing to a pyridone Ⓐ capable of transformation to the vital intermediate pentacyclic acid Ⓑ.



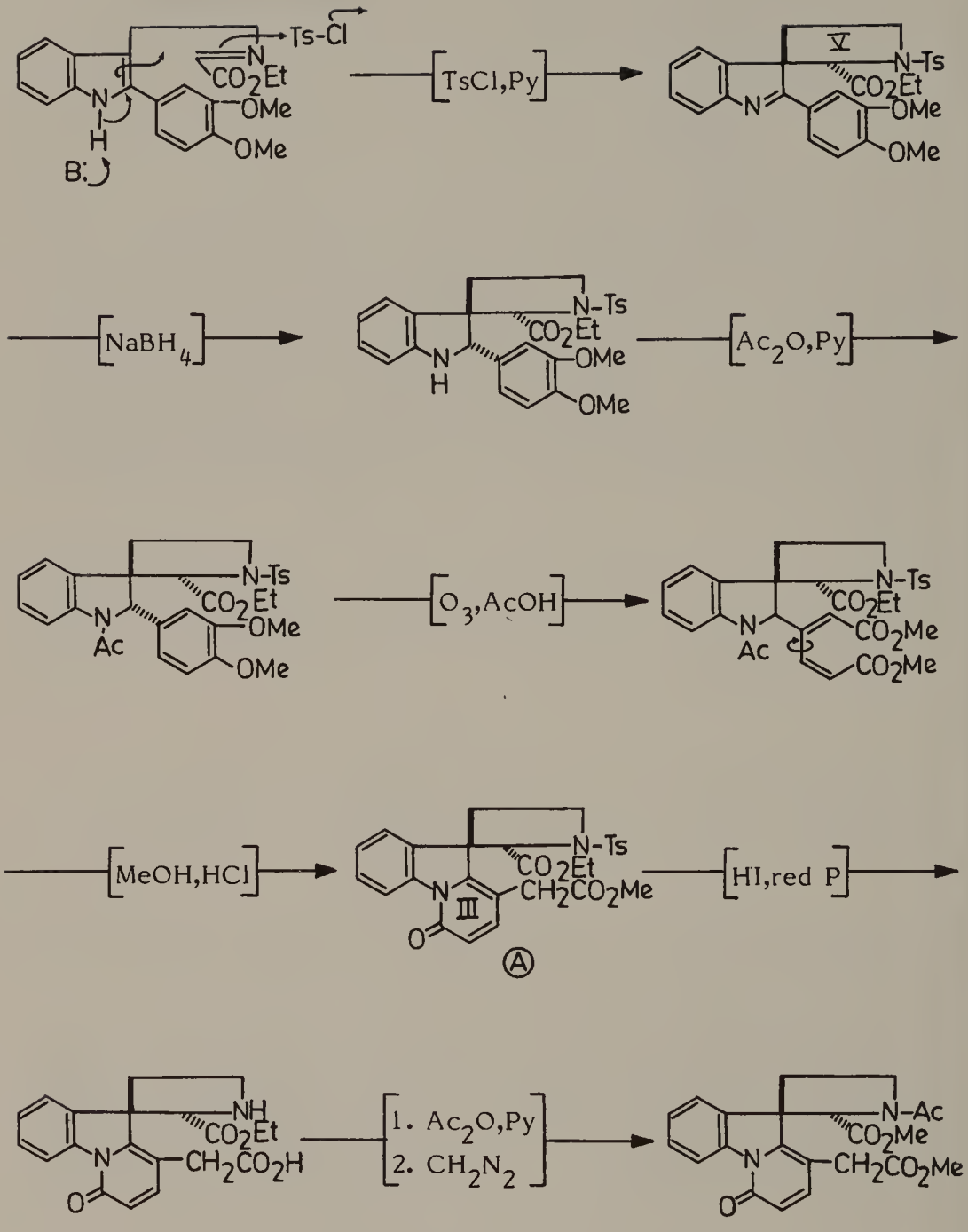
---

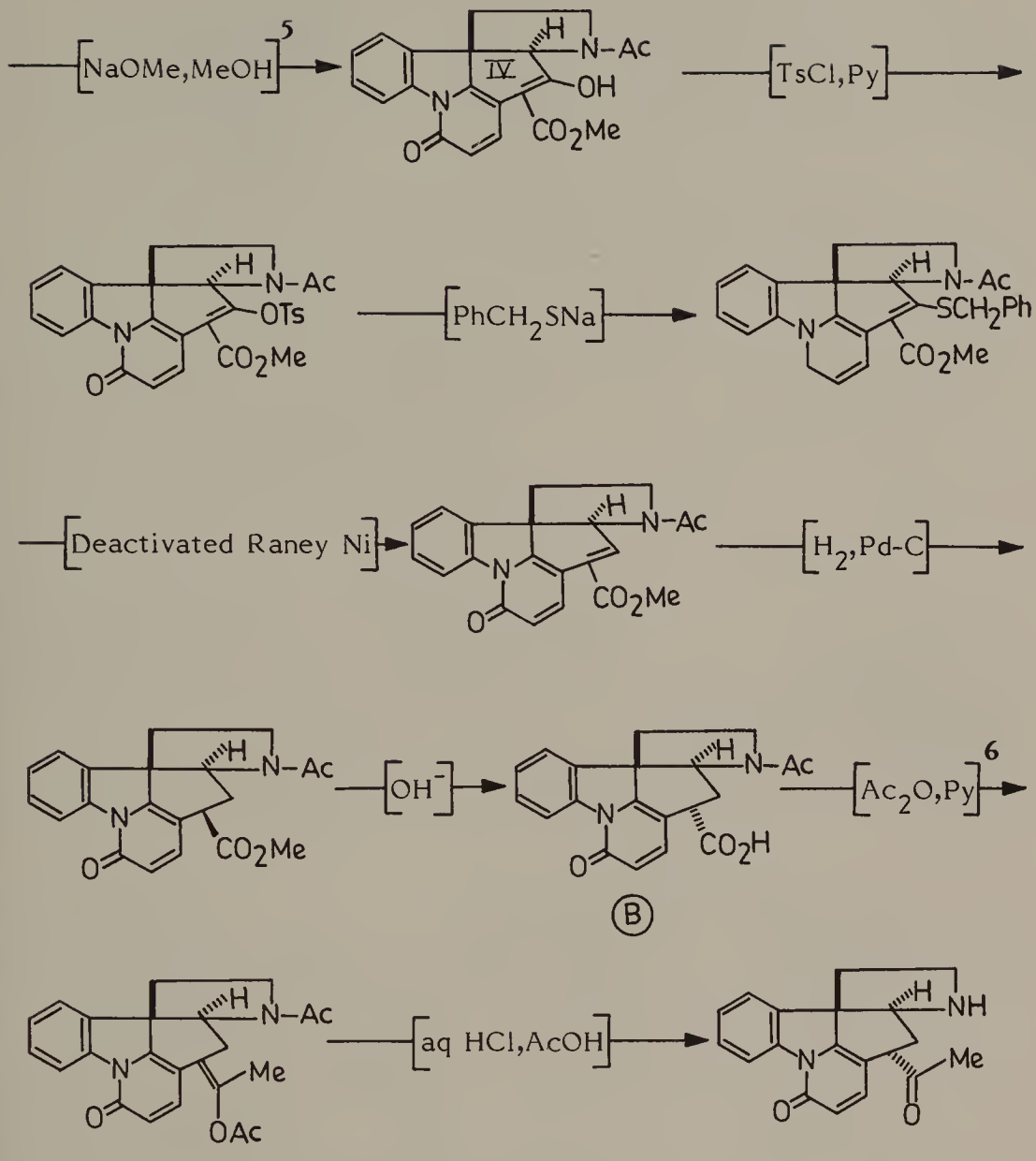
1. Woodward,R.B., Cava,M.P., Ollis,W.D., Hunger,A., Daeniker,H.U., Schenker,K. J.Am. Chem. Soc., 1954, 76, 4749; Tetrahedron, 1963, 19, 247.

2. The history of strychnine is singularly deficient in attempts directed towards its total synthesis. Apart from the synthesis by Woodward one need only mention Robinson's efforts in this connection (ref.3), notably his attempt to obtain the Wieland-Gumlich aldehyde through an ingenious biogenetically patterned intramolecular cyclization, Robinson,R., Saxton,J.E. J. Chem. Soc., 1953, 2598. See also Van Tamelen, E.E., Dolby, L.J., Lawton,R.G., Tetrahedron Lett., 1960, 30 for a more recent and successful one-step reproduction of the essential features of strychnine molecule patterned along similar lines.

3. For two excellent reviews on the synthesis of strychnine, see Hendrickson,J.B. in "The Alkaloids", Vol.VI, ed. R.H.F. Manske, Academic Press, New York, (1960), p.211; and G.F. Smith in Vol.VIII, 1965, p.591.

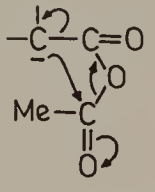
4. The veratryl group serves an additional purpose in blocking the reactive α-position of the indole nucleus.

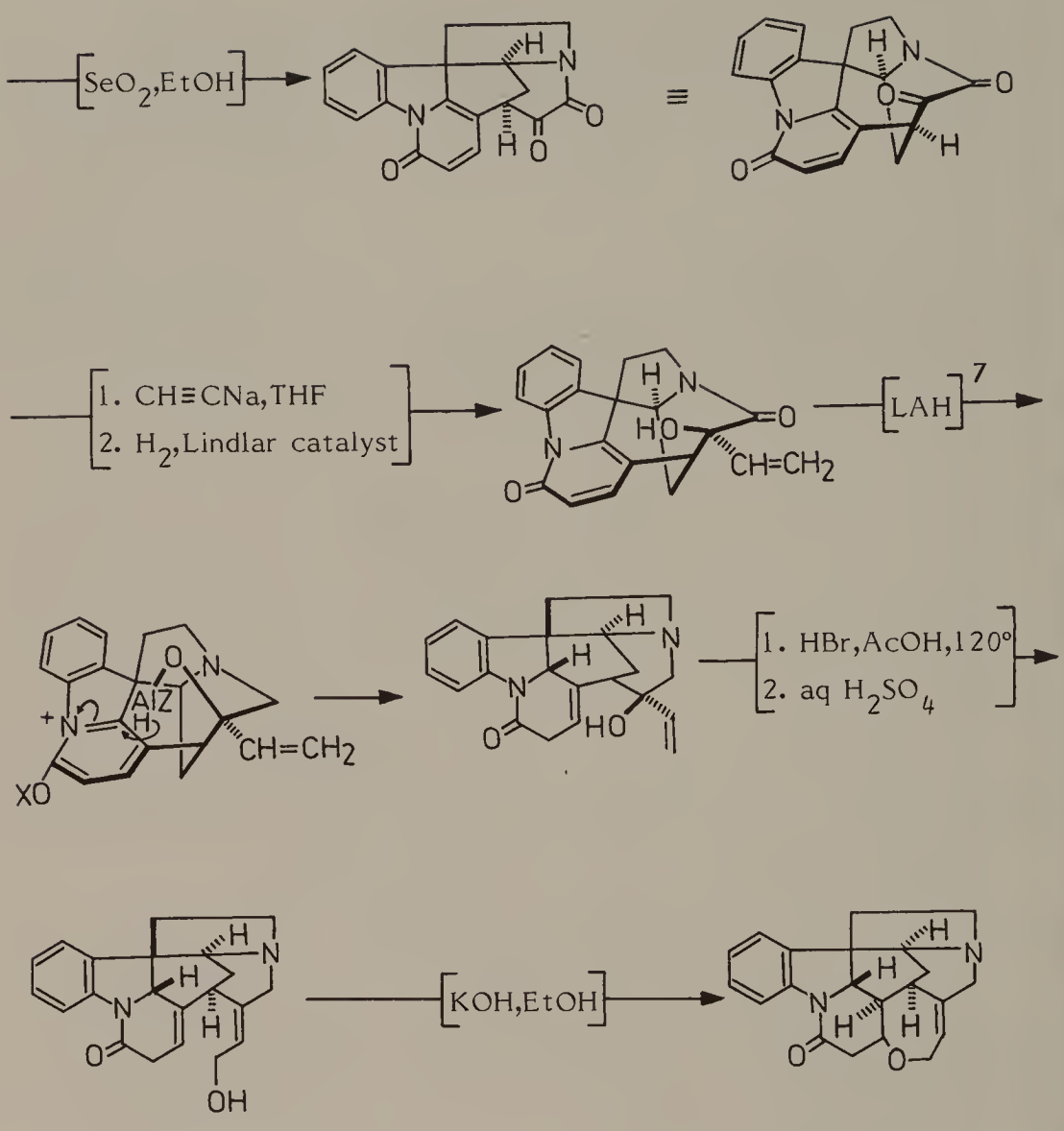

Ts-Cl
N
CO2Et
OMe
OMe
N
H
B:
[TsCl,Py]
V
N-Ts
CO2Et
OMe
OMe
N
[NaBH4]
N-Ts
CO2Et
OMe
OMe
N
H
[Ac2O,Py]
N-Ts
CO2Et
OMe
OMe
N
Ac
[O3,AcOH]
N-Ts
CO2Et
CO2Me
CO2Me
N
Ac
[MeOH,HCl]
N-Ts
CO2Et
CH2CO2Me
N
III
O
[HI,red P]
Ⓐ
NH
CO2Et
CH2CO2H
N
O
[1. Ac2O,Py
2. CH2N2]
N-Ac
CO2Me
CH2CO2Me
N
O



5. With inversion at C-16.

6. This unusual formation of a ketone is obviously due to II-14 being ionized, the steps leading to formation of ketone from the resulting ion are then easily explainable:





Isostrychnine I *Strychnine*

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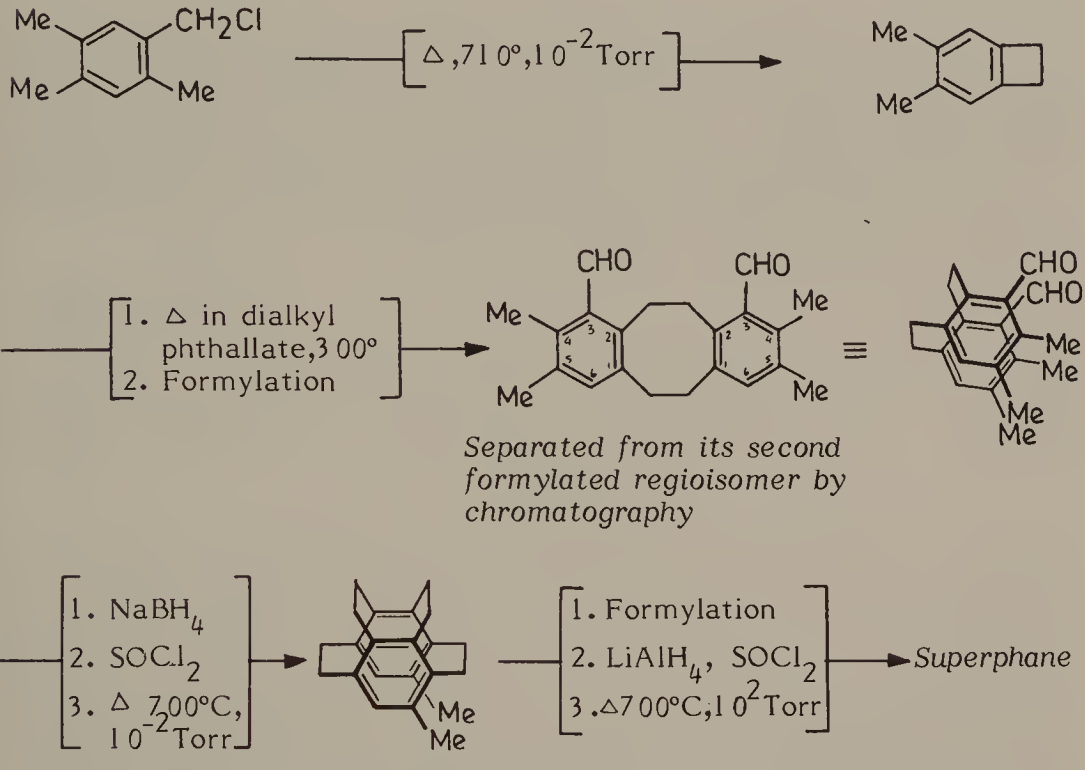
7. Concomitant reduction of the ∝-pyridone to $\Delta^{12,13}$-dihydro-∝-pyridone oxidation level occurs from the more hindered concave side and is explicable only by assembling an intermediate capable of specific intramolecular delivery of the hydride ion to C-8.

SUPERPHANE

Cyclophanes have been the subject of many studies as models to get answers to questions of bonding, strain-energy and π-π electron interaction. Superhane, which was the ultimate goal in this field, has been synthesised recently based on the ability of benzocyclobutenes to dimerise to form multibridged cyclophanes (1,2).



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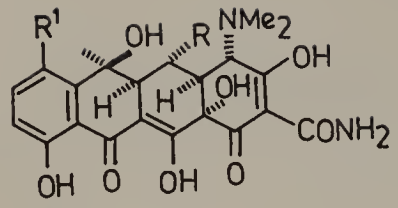
1. For review of earlier work see: Smith,B.H., "Bridged Aromatic Compounds", Academic Press, New York, 1964; Vogtle,F.; Neumann,P. Angew. Chem. Int. Ed. Engl., 1972, 11, 73; Cram,D.J.; Cram,J.M. Acc. Chem. Res., 1971, 4, 204; Misumi,S.; Otsubo,T. ibid, 1978, 11, 251; Lindner,H.J. Tetrahedron, 1976, 32, 753.

2. (a) Schirch,P.F.T.; Boekelheide,V. J. Am. Chem. Soc., 1979, 101, 3125; (b) Sekine,V.; Brown,M.; Boekelheide,V. ibid, 1979, 101, 3126.

3. Rieche,I.; Gross,H.; Hoft,E. Chem. Ber., 1960, 93, 88.

4. PMR spectrum of superhane exhibited a singlet at 2.98, while its ^{13}CNMR exhibited (proton decoupled) singlets at 144.2 and 32.3.

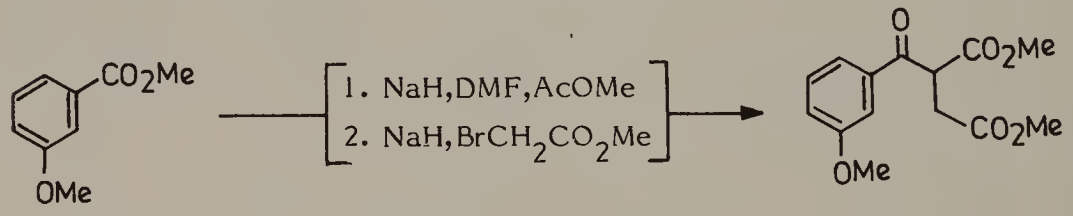


TETRACYCLINES

Tetracycline; R=R_1=H
Terramycin; R=OH, R_1=H
Aureomycin; R=H, R_1= Cl

Ever since elucidation of the structures of aureomycin and terramycin in 1952, the total synthesis of tetracyclines has engaged the attention of several groups of workers (1), culminating, almost a decade later, in the synthesis of 6-demethyl-6-deoxytetracycline by Woodward and his collaborators (2) and of terramycin by Muxfeldt et al. (5,6).

Woodward's synthesis makes use of the reactivity of the methylene group adjacent to terminal carbonyl of a key hydroanthracene triketone (A) for introduction of the N,N-dimethylglycine residue. The functionally and stereochemically complex ring A has been created from a fully substituted intermediate (B) carrying the characteristic carboxamide function by an internal Claisen condensation, followed by a Ce^{+++} oxidation to generate the required chromophore.



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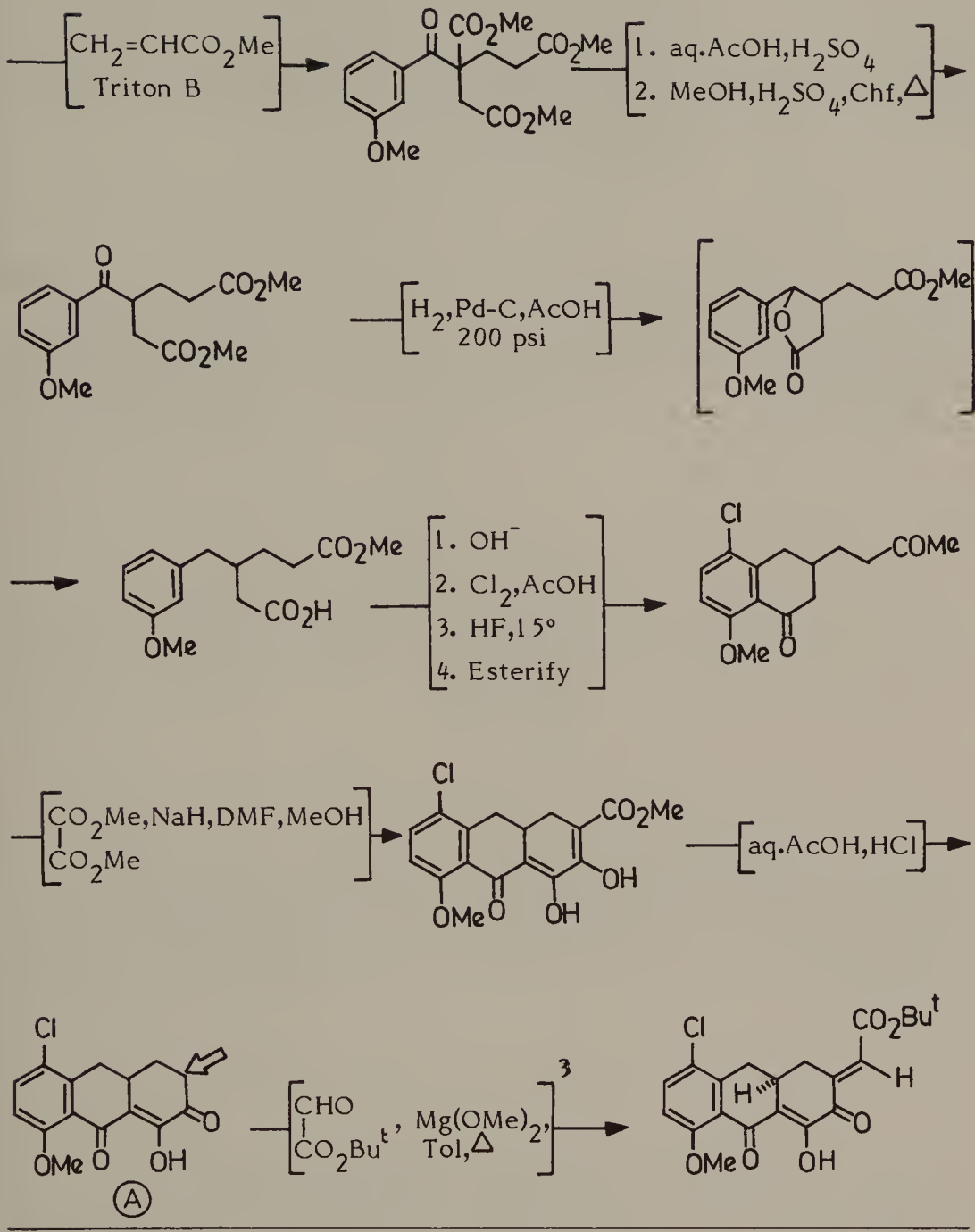
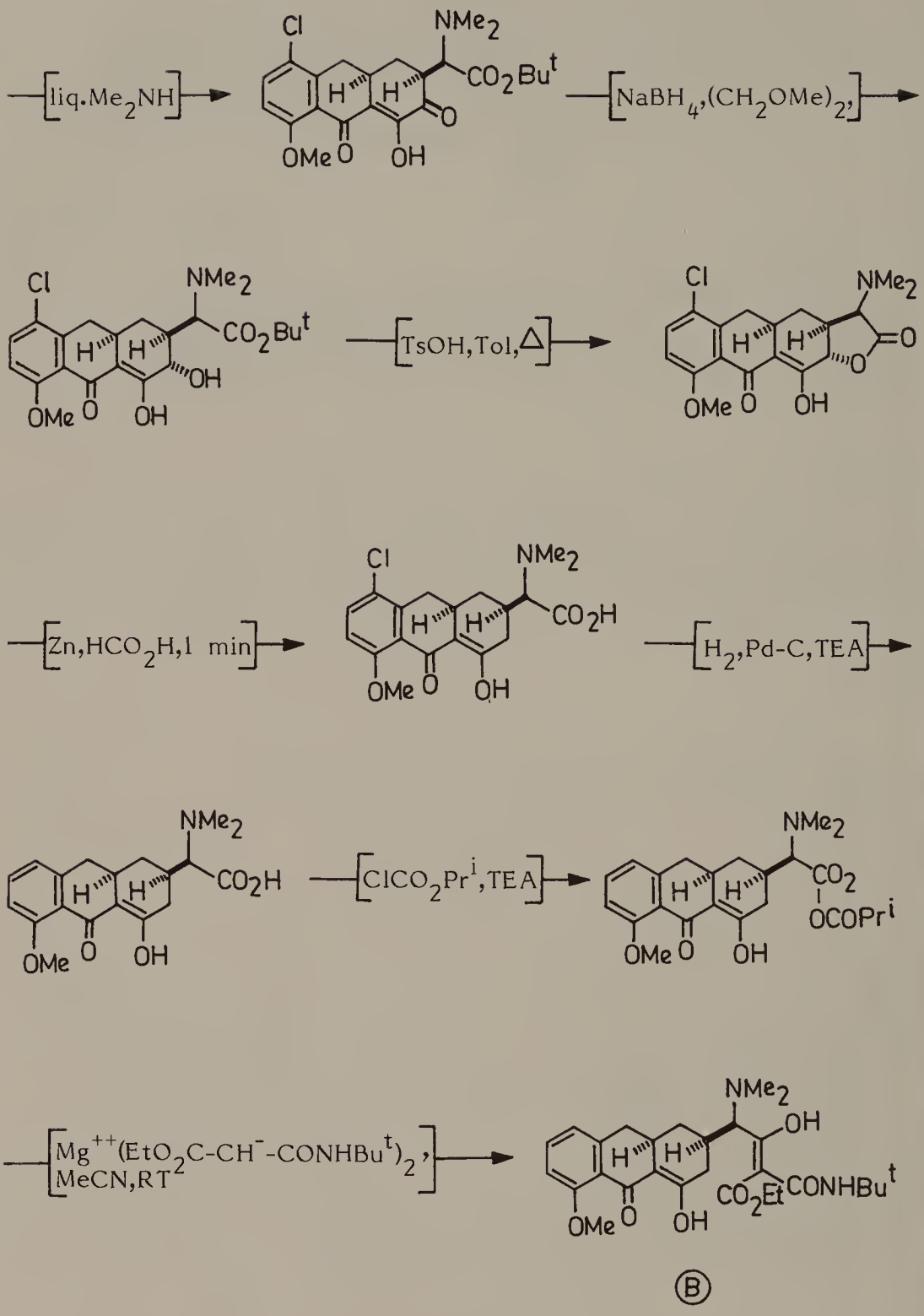
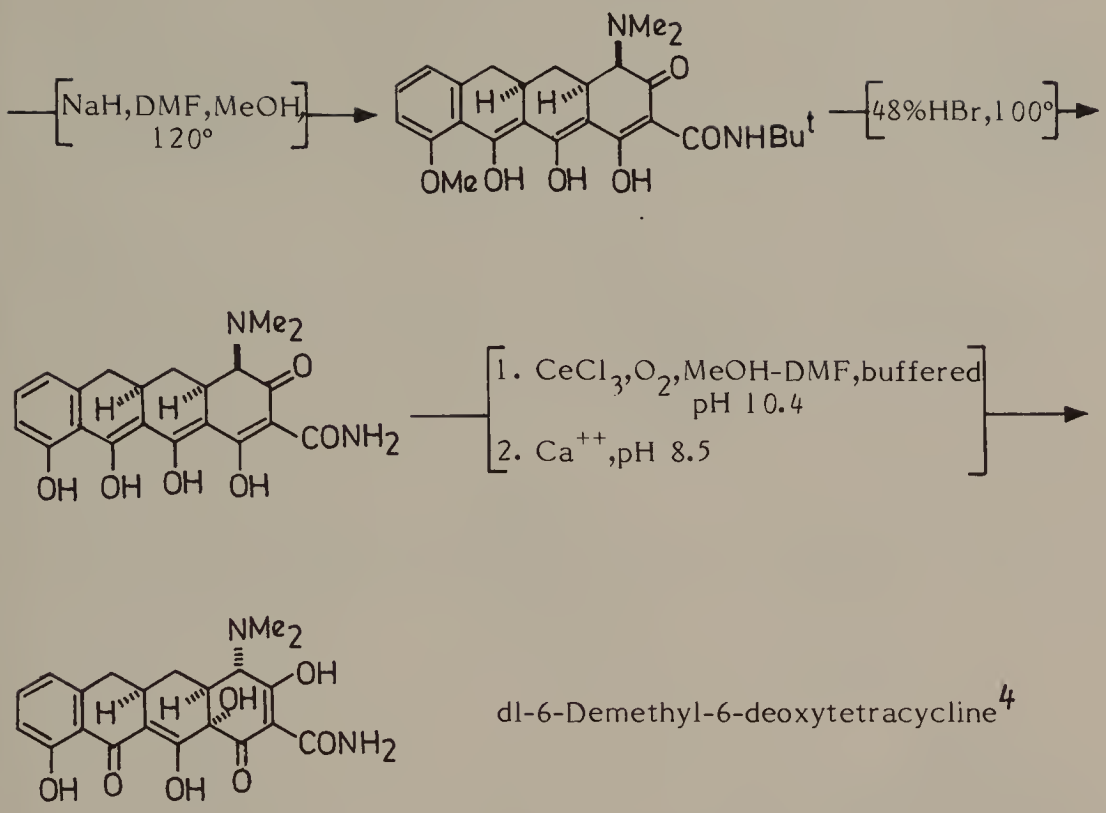
1. Apart from the notable successes wrought by the Pfizer-Harvard group (2) and Muxfeldt et al. (5,6), significant contributions towards the synthesis of tetracyclines have been made by three other groups: Shemyakin and his colleagues reported the total synthesis of 12α-deoxy-5,6-anhydrotetracycline, and since this has been converted into tetracycline, this could be construed as the first formal total synthesis of a natural tetracycline; Gurevich,A.I.; Karapetyan,M.G.; Kolosov,M.N.; Korobko,V.G.; Onoprienko,V.V.; Popravko,S.A.; Shemyakin,M.M. Tetrahedron Lett., 1967, 131; Booth et al. at the Lederle Laboratories carried out the synthesis of dediethylamino-12α-deoxy-6-demethylanhydrochlorotetracycline; Booth,A.H.; Kende,A.S.; Fields,T.L.; Wilkinson,R.G. J. Am. Chem. Soc., 1959, 81, 1006; Barton & his colleagues in a series of papers have described the synthesis of 6-methylpretetramid, a naphthacene precursor which can be microbiologically converted into tetracyclines; Barton,D.H.R.; Magnus,P.D.; Hase,T. J. Chem. Soc. (C), 1971, 2215, and accompanying series of papers for their general approach to the total synthesis of tetracyclines.

2. Conover,L.H.; Butler,K.; Johnston,J.D.; Korst,J.J.; Woodward,R.B. J. Am. Chem. Soc., 1962, 84, 3222; Woodward,R.B. Pure Appl. Chem., 1963, 6, 651; Korst,J.J.; Johnston,J.D.; Butler,K.; Bianco,E.J.; Conover,L.H.; Woodward,R.B. J. Am. Chem. Soc., 1968, 90, 439.



3. Choice of magnesium methoxide as the condensing agent was made with a view to protecting the β-dicarbonyl system against base-cleavage.


liq.Me2NH
NaBH4,(CH2OMe)2,
TsOH,Tol,Δ
Zn,HCO2H,1 min
H2,Pd-C,TEA
ClCO2Pri,TEA
Mg++(EtO2C-CH--CONHBut)2,
MeCN,RT
Cl
NMe2
CO2But
OMe
OH
CO2H
OCOPri
CO2Et
CONHBut
(B)



dl-6-Demethyl-6-deoxytetracycline[4]

Using a different approach fo the hydronaphthacene nucleus, Muxfeldt and his collaborators (5), have accomplished an elegant synthesis of terramycin (6), the first total synthesis of a natural tetracycline. Noteworthy feature of this synthesis are the stereospecific elaboration of rings C and D as the key bicyclic aldehyde Ⓐ. introduction of the 4-amino function as a thiazolidinyl group and completion of rings A and B using an oxoglutamate.

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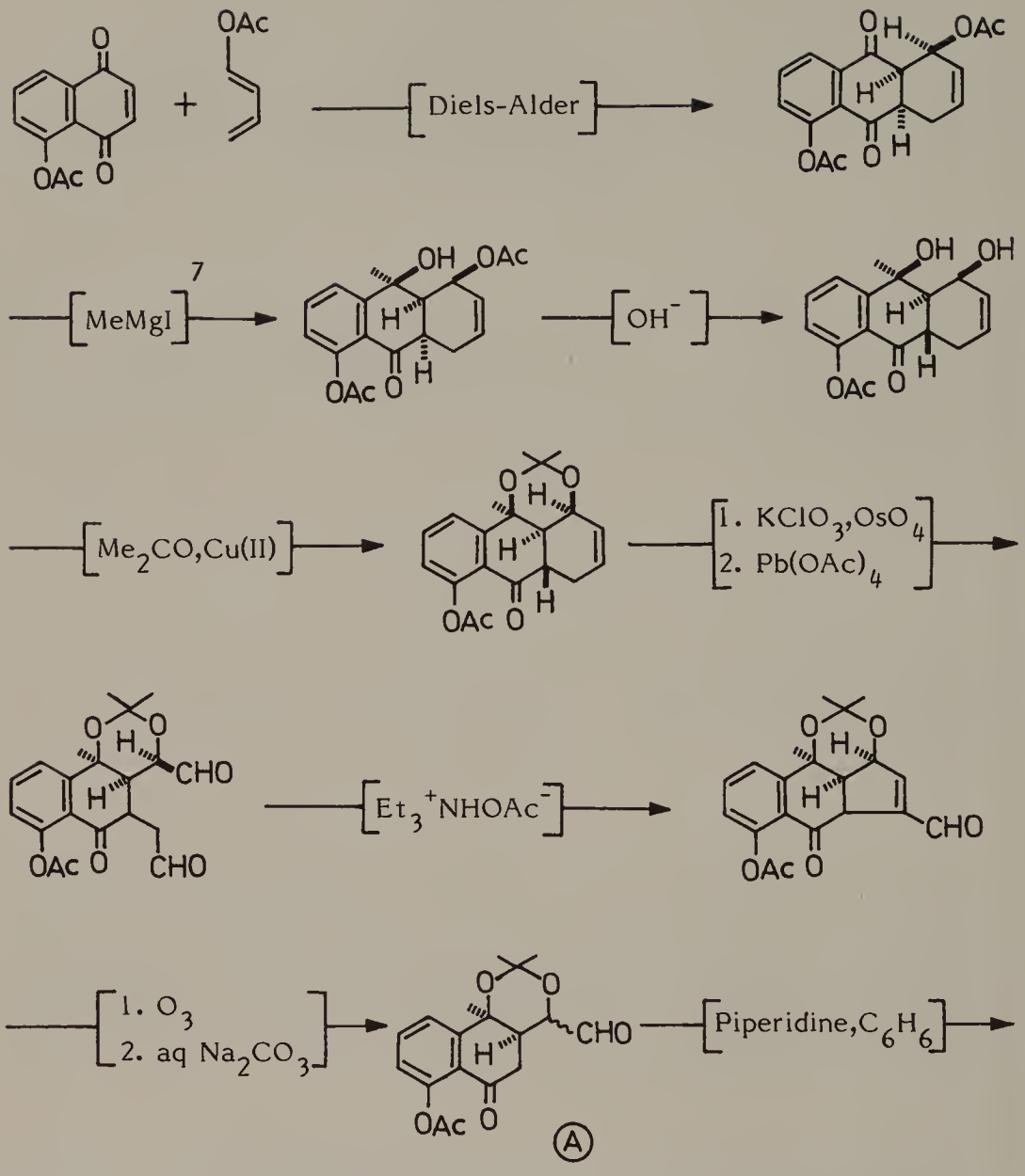
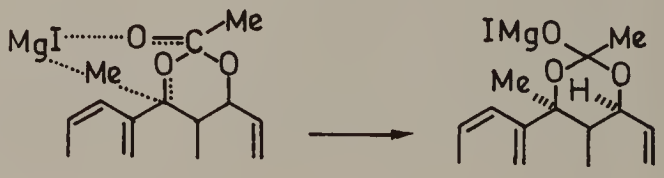
4. For another synthesis of this compound, see: Muxfeldt,H.; Rogalski,W. J. Am. Chem. Soc., 1965, 87, 933.

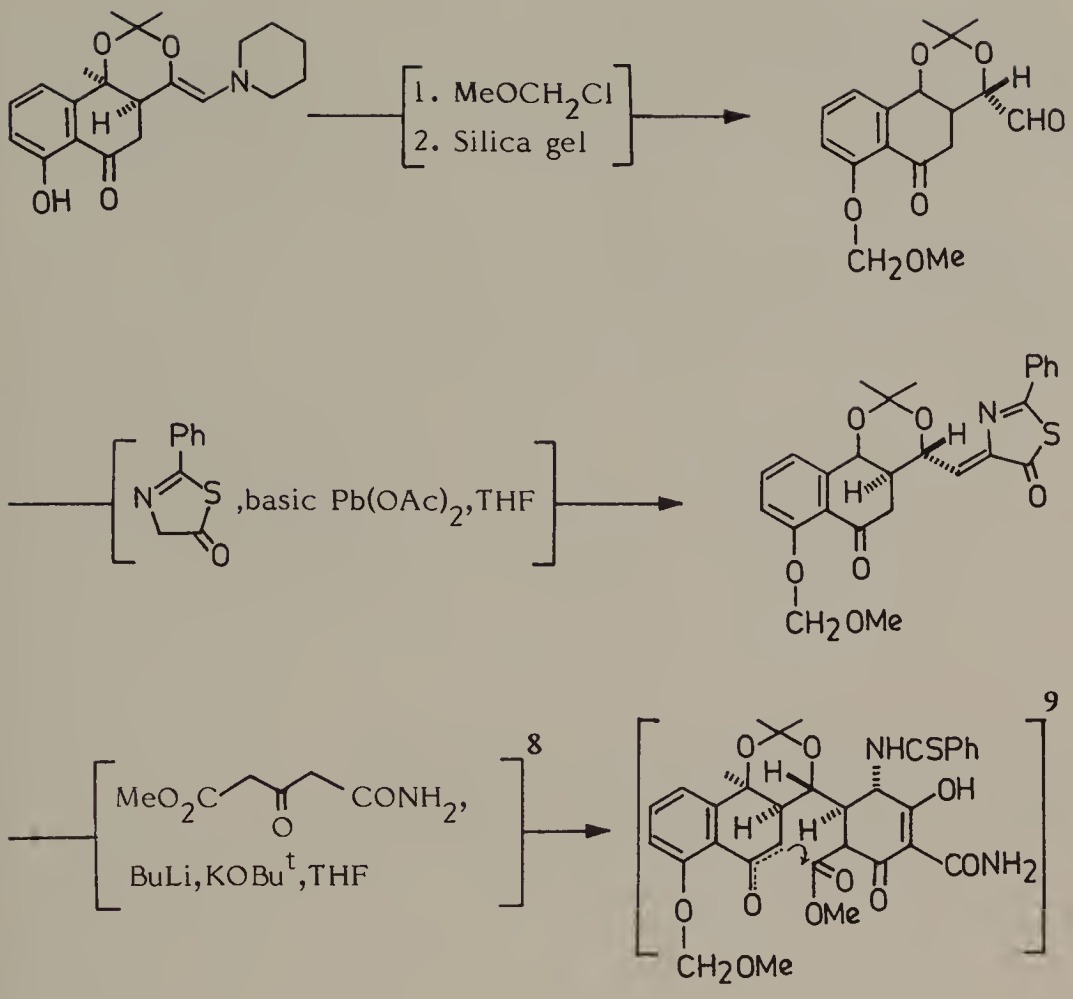
5. Muxfeldt,H. Angew. Chem., Internat. Ed., 1962, 1, 372; ibid, Angew. Chem., 1962, 74, 825; Muxfeldt,H.; Hardtmann,G. Ann., 1963, 669, 113.

6. Muxfeldt,H.; Hardtmann,G.; Kathawala,F.; Vedejs,E.; Mooberry,J.B. J. Am. Chem. Soc., 1968, 90, 6534. For an engrossing account of the total work on the chemical synthesis of terramycin by the Muxfeldt group see: Muxfeldt,H.; Haas,G.; Hardtmann,G.; Kathawala, F.; Mooberry,J.B.; Vedejs,E. J. Am. Chem. Soc., 1979, 101, 689.



7. Selective attack of the grignard reagent on the carbonyl situated adjacent to the acetoxy group can be explained if it is assumed that the acetoxy group takes part in the reaction as depicted:





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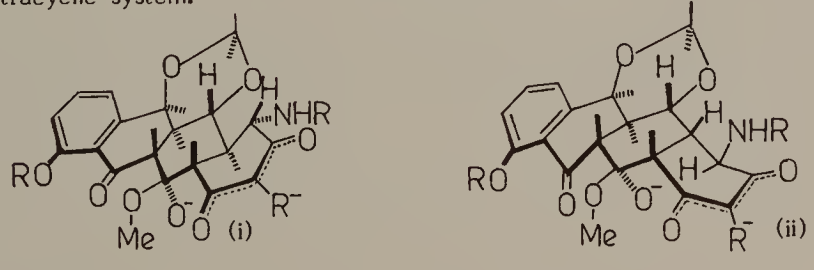
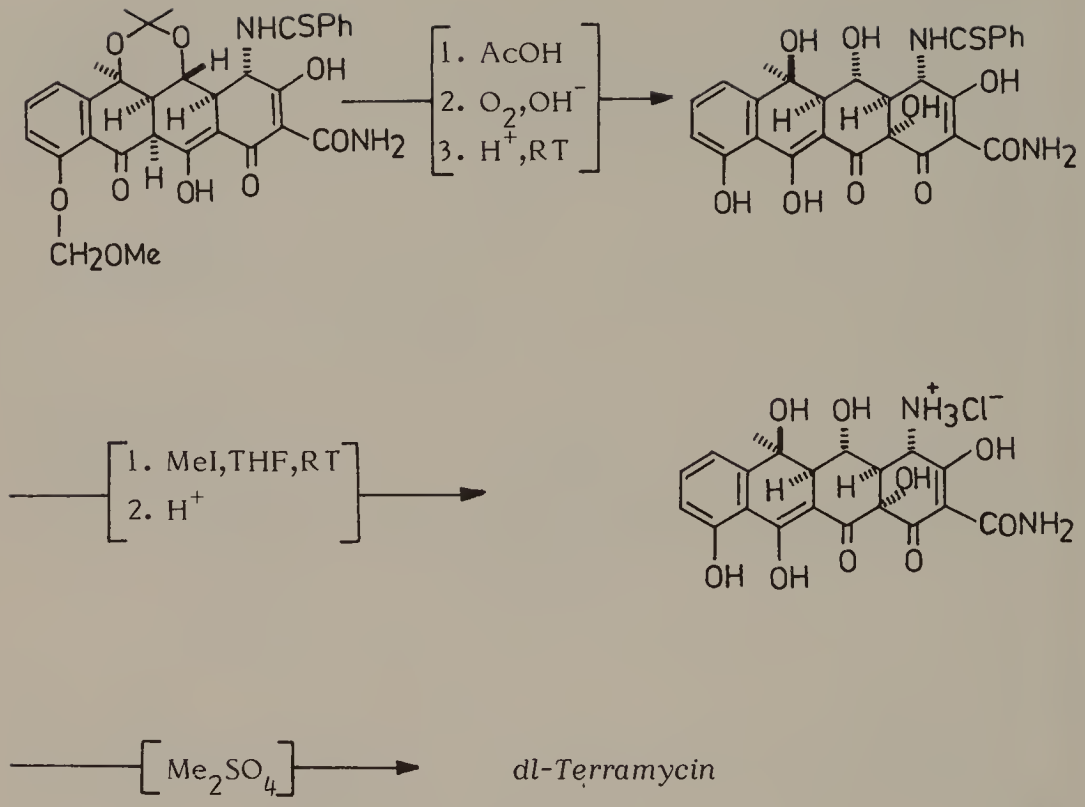
8. This is a new general reaction between azlactones and derivatives of acetonedicarboxylic esters leading to amino dihydroresorcinol derivatives.

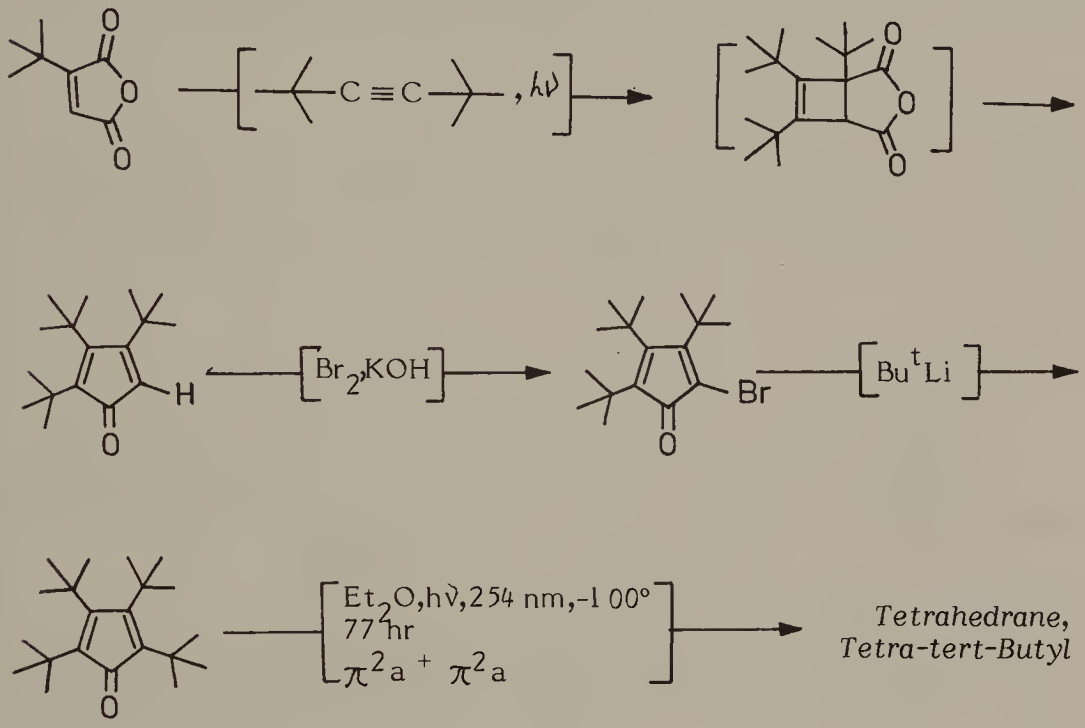
9. There are two possible modes of cyclization of the tricyclic ACD-intermediate and are shown in (i) and (ii); the final configuration at 4a is determined by the fact that conformationally (i) is the most stable intermediate (half-chair) on the pathway leading to the tetracyclic system.



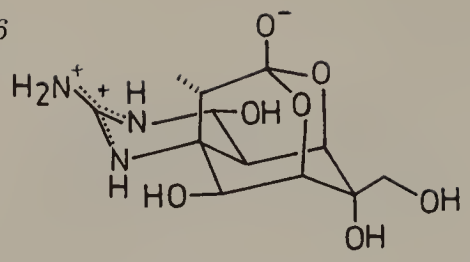

NHCSPh
OH
CONH2
CH2OMe
1. AcOH
2. O2,OH−
3. H+,RT
OH OH NHCSPh
OH
CONH2
1. MeI,THF,RT
2. H+
OH OH NH3Cl−
OH
CONH2
Me2SO4
dl-Terramycin

TETRAHEDRANE, TETRA-tert-BUTYL

Tetrahedrane represents the very ultimate in carbon angle distortion and this compound has been the synthetic objective of endeavours spanning well over five decades. The highly substituted tetrahedrane has now been made in a truly spectacular manner, inorporating, inter alia, the photochemical extrusion of carbon dioxide and carbon monoxide (1).

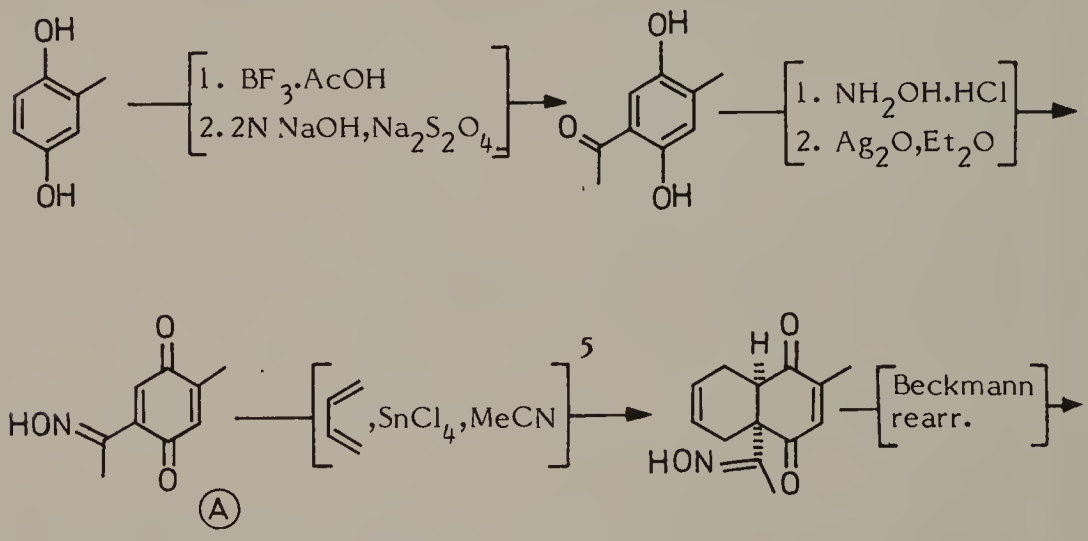


1. Maier,G.; Pfriem,S. Angew. Chem. Int. Ed., 1978, 17, 519; Maier,G.; Pfriem,S.; Shafer,U.; Matusch,R. ibid, 1978, 17, 520.



TETRODOTOXIN

Tetrodotoxin, isolated from the ovaries and liver of the puffer fish (Japanese: fugu) (1), is one of the most toxic low molecular weight poisons known. A noteworthy feature of the only synthesis of tetrodotoxin reported by Kishi's group (2-4) is the aggrandization of six chiral centers on the cyclohexane nucleus in the key tetrodamine intermediate Ⓑ by effective use of proximity effects. Other important features of the synthesis are the use of Lewis acid in Diels-Alder reaction of Ⓐ, which introduced the desired regioselectivity by enhancing the electron withdrawal of the α-oximinoalkyl substituent and the use of furan ring in Ⓓ to mask reactive functionalities during conversion of the amino group into a guanidine residue.



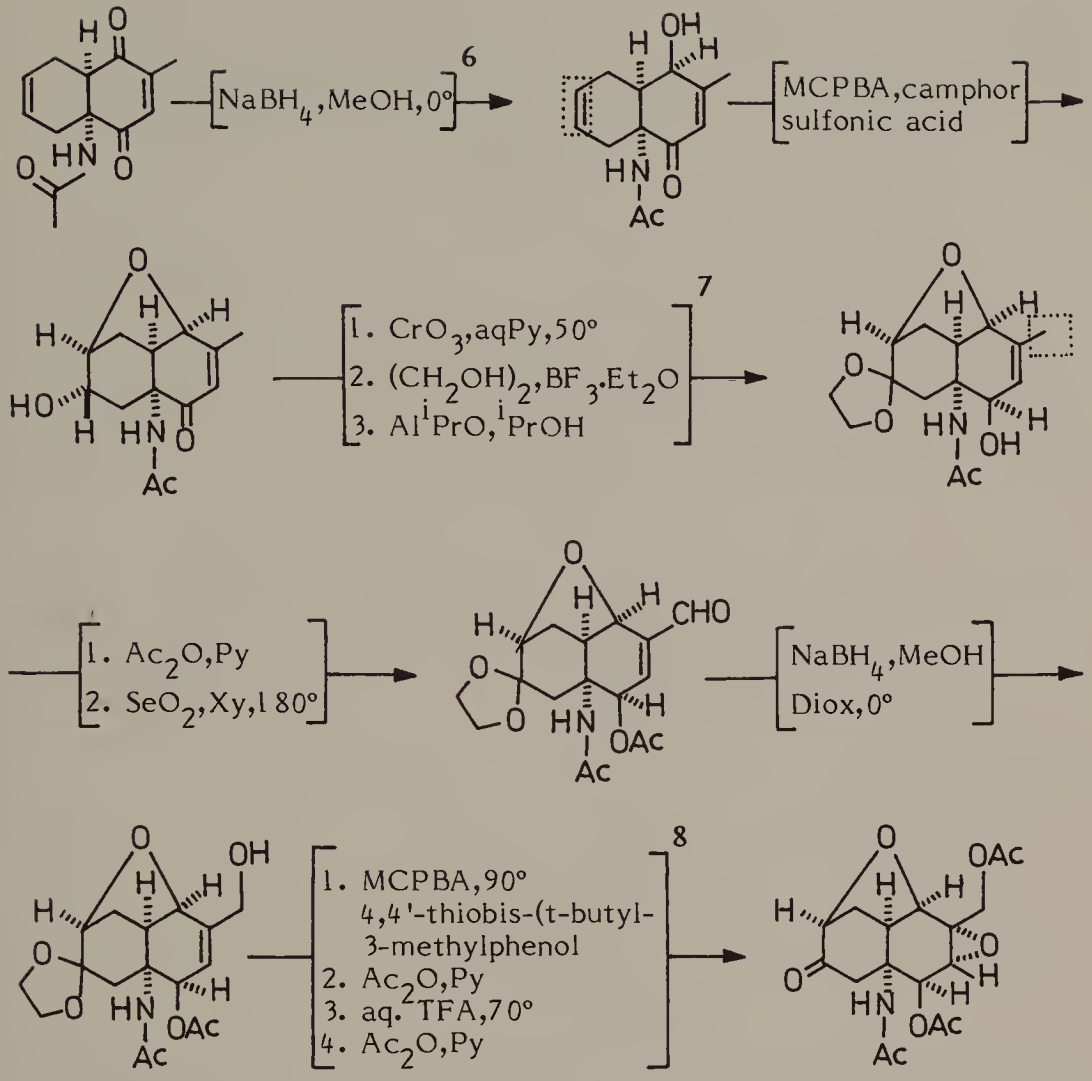
1. The complex highly oxygenated cage-like structure of tetrodotoxin was deduced in three independent studies which included X-ray crystallography as well; Goto,T.; Kishi,Y.; Takahashi,S.; Hirata,Y. Tetrahedron, 1965, 21, 2059; Tsuda,K. et al. Chem. Pharm. Bull. (Tokyo), 1964, 12, 634; Woodward,R.B. Pure Appl. Chem., 1964, 9, 49.

2. Kishi,Y.; Nakatsubo,F.; Aratani,M.; Goto,T.; Inoue,S.; Kakoi,H.; Sugiura,S. Tetrahedron Lett., 1970, 5127.

3. Kishi,Y.; Nakatsubo,F.; Aratani,M.; Goto,T.; Inoue,S.; Kakoi,H. Tetrahedron Lett., 1970, 5129.

4. Kishi,Y.; Aratani,M.; Fukuyama,T.; Nakatsubo,F.; Goto,T.; Inoue,S.; Tanino,H.; Sugiura,S.; Kakoi,H. J. Am. Chem. Soc., 1972, 94, 9217, 9219.

5. The required regioselectivity was the result of the enhanced electron withdrawal from α-oximinoalkyl substituent induced by the Lewis acid.



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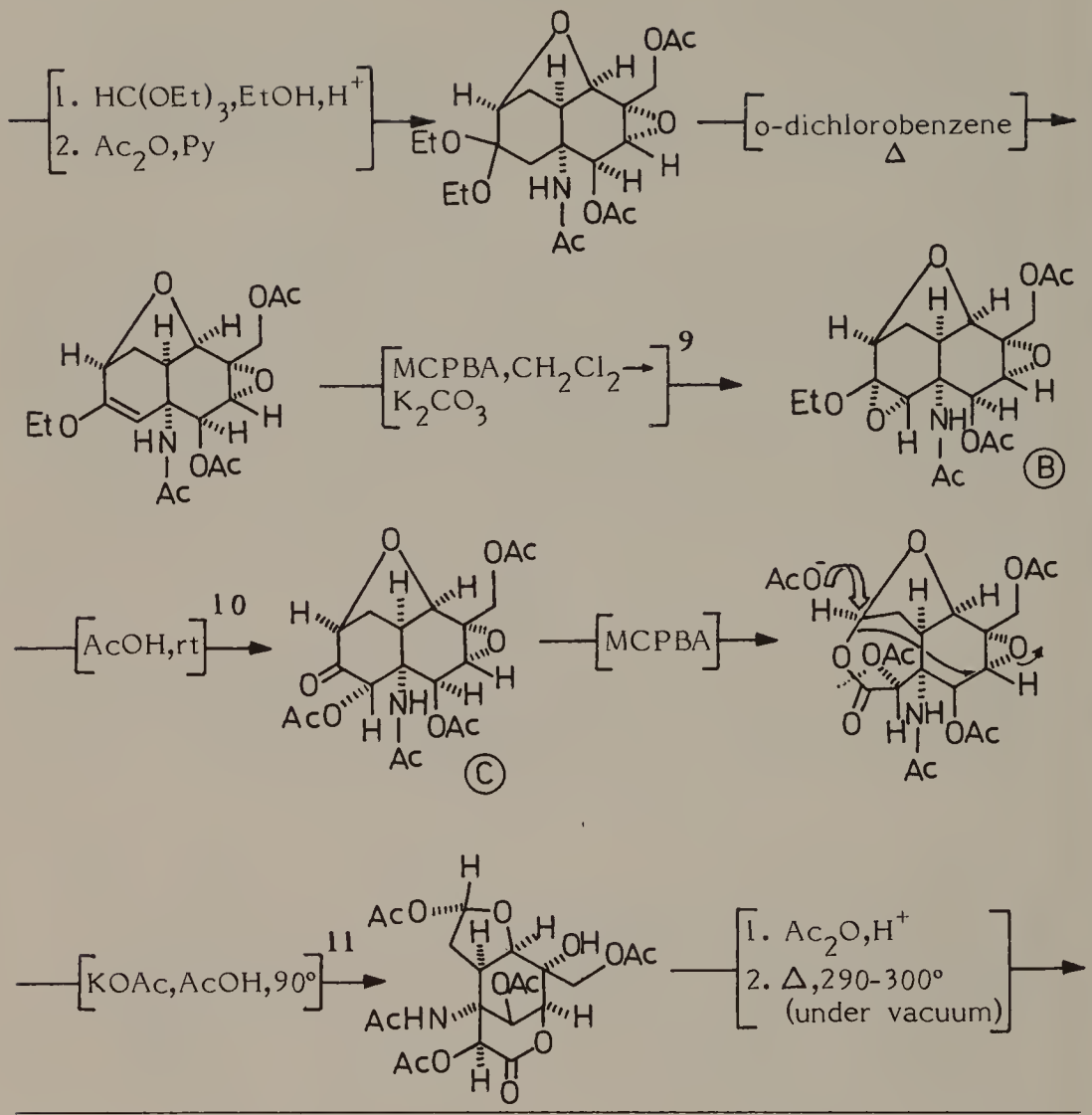
6. The reduction was highly stereoselective since the reagent could approach the carbonyl group only from the outer side of the cage-like molecule, and regiospecific since the carbonyl at C-8 was protected by presence of the vicinal axial acetamido group at C-8a.

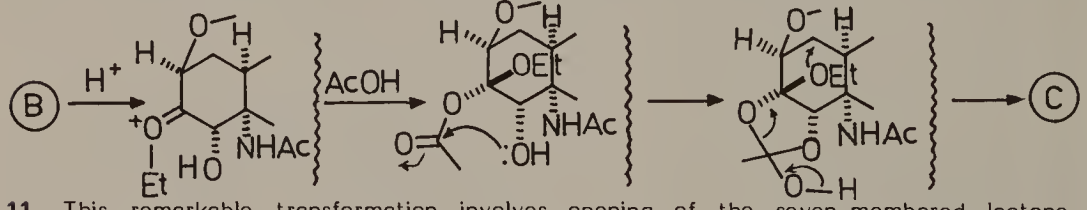
7. The reducing agent approaches from outer side of the cage-like molecule.

8. Addition of a radical inhibitor prevented thermal decomposition of the peracid, thus allowing epoxidation of the otherwise poorly reactive olefin to take place at elevated temperatures, Kishi,Y.; Aratani,M.; Tanino,H.; Fukuyama,T.; Goto,T.; Inoue,S.; Sugiura,S.; Kakoi,H. Chem. Commun., 1972, 64.

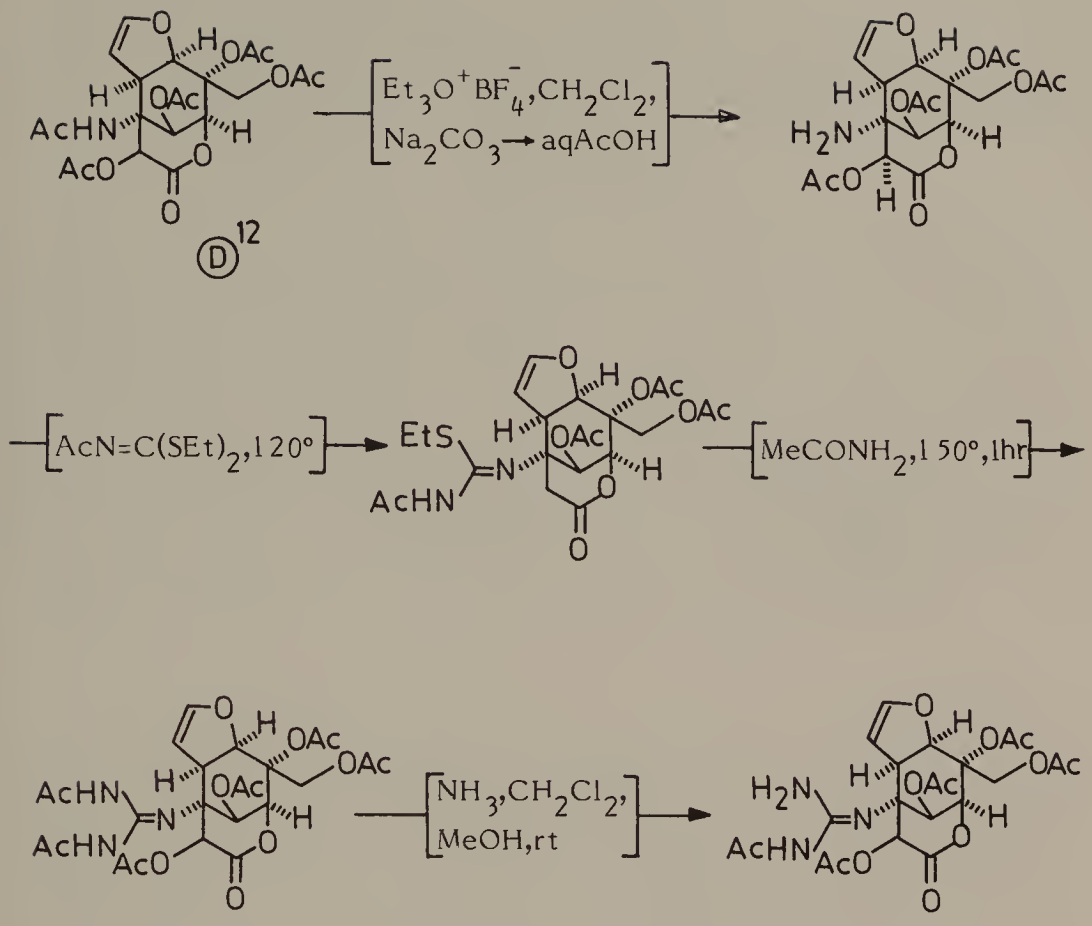


9. Addition of peracid to the double bond occurs from the α-side due to steric reasons.

10. Stereospecific opening of the epoxy ether by acetic acid may be rationalized as depicted below: (Cf. Stevens, C.L.; Dykstra, S.J. J. Am. Chem. Soc., 1953, 75, 5975)



11. This remarkable transformation involves opening of the seven-membered lactone ring, to generate at one terminus a carboxylate group which attacks the epoxide ring by an intramolecular SN2 reaction, while at the other terminus the oxonium ion is attacked by acetate ion from the less hindered side.



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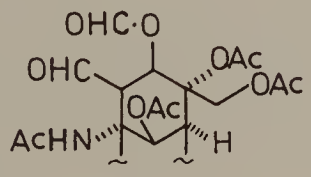
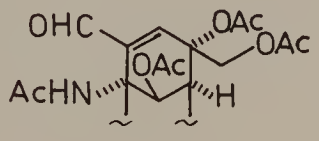
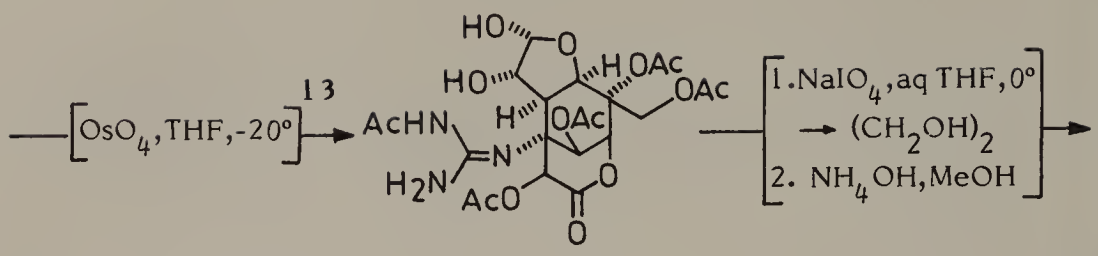
12. Because of the rather facile elimination (i→ii) generation of the aldehyde group at C-4a had to be deferred until after the guanidino group had been introduced at the C-8a position.

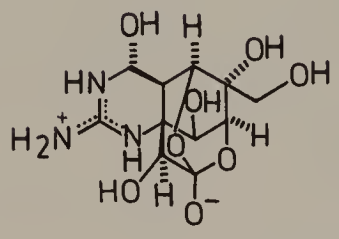


(i)



(ii)





Tetrodotoxin[13]

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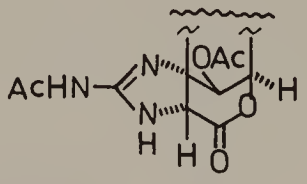
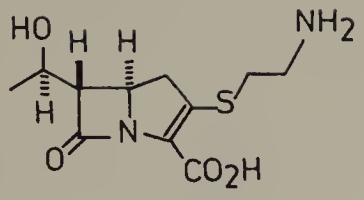
13. In an alternative route to tetrodotoxin, hydroxylation of the dihydrofuran in (D) and protection of the resulting diol as an acetonide preceded introduction of the guanidino group. However, this approach was complicated by the unwanted formation of a cyclic monoacetylguanidino group (cf i) involving the C_9-acetoxy group as the only product. This has been circumvented in later work by proceeding with the C_9-p-anisoate derivative of (D); Tanino,H.; Inoue,S.; Aratani,M.; Kishi,Y. Tetrahedron Lett., 1974, 335.

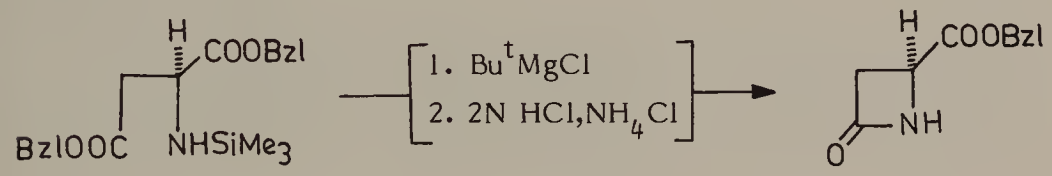


(i)



THIENAMYCIN

The discovery of carbapenem of microbial origin has been a major development in β-lactam antibiotics, as these have a novel chemical structure, exceptional potency, unusually wide antibacterial spectrum and high stability to β-lactamases (1); thienamycin, isolated in 1976 is an important member of this class. Their fermentation yields are, however, low. Their synthesis has, therefore, attracted much interest, both for structure-activity relationship studies as also to provide practical methods of total synthesis. Although a number of synthesis of thienamycin have been reported (2), the one described below by the Merck group (3) was the first stereocontrolled synthesis of (+)-thienamycin, and employ a highly efficient carbene insertion reaction to produce the bicyclic nucleus by formation of the N-C_3 bond.



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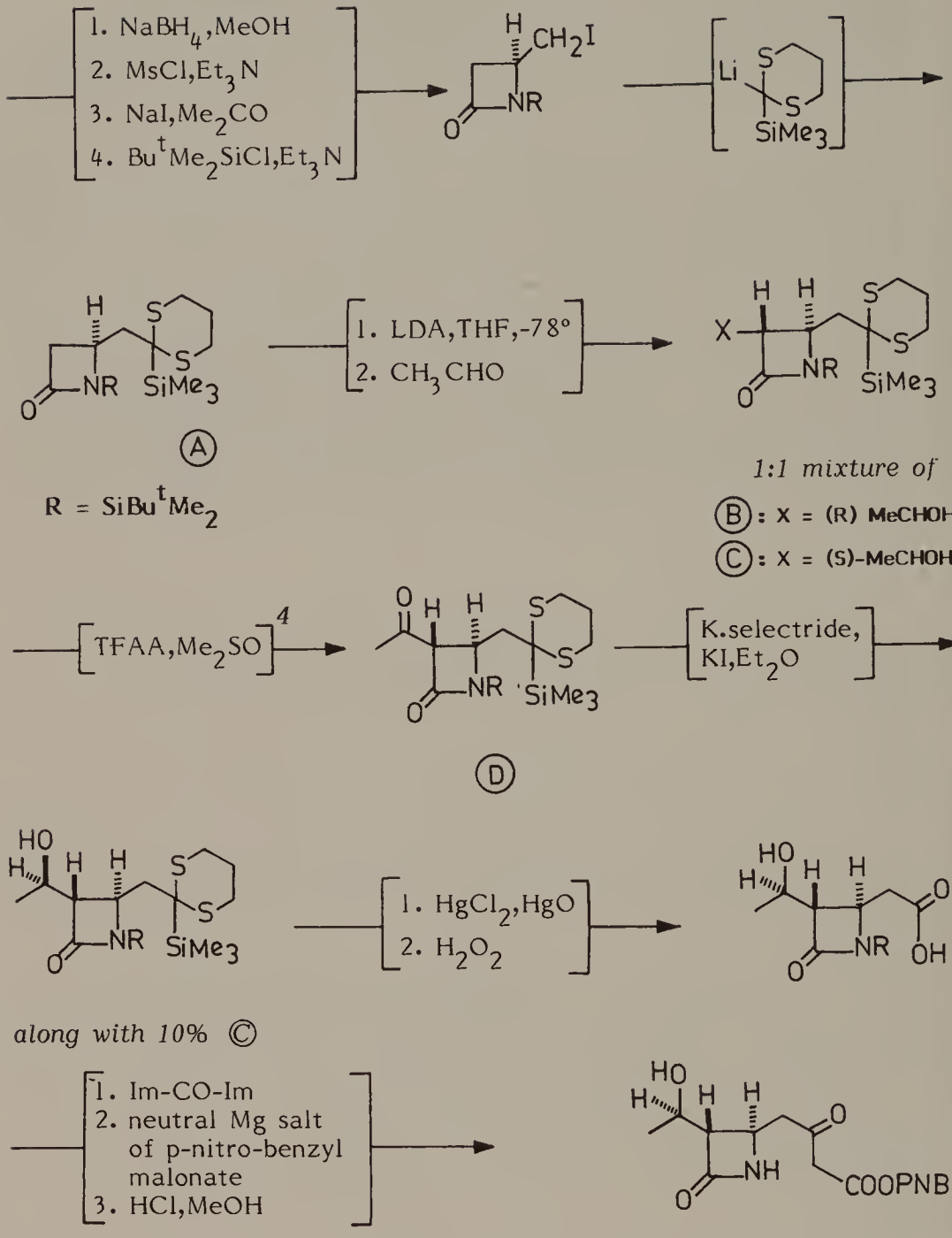
1. For recent reviews see: (a) Brown,A.G.; Roberts,S.M. Recent Advances in the Chemistry of β-lactam Antibiotics; The Royal Society of Chemistry, Burlington House, London, 1984; (b) Kametani,T. Heterocycles, 1982, 17, 463; (c) Labia,R.; Morin,C. J. Antibiot., 1984, 37, 1103.

2. For other synthetic approaches to thienamycin and related carbapenems see: (a) George,G.I.; Kant,J.; Gill,H.S. J. Am. Chem. Soc., 1987, 109, 1129; (b) From penicillin: Kerady,S.; Amats,J.S.; Reemer,R.A.; Weirstock,L.M. J. Am. Chem. Soc., 1981, 103, 6765; from 6-APA: Maruyama,H.; Hiraoka,T. J. Org. Chem., 1986, 51, 399; (c) from chiral sugar templates: Ikota,N.; Yoshino,O.; Koga,K. Chem. Pharm. Bull., 1982, 30, 1929; (d) Okano,K.; Izawa,T.; Ohno,M. Tetrahedron Lett., 1983, 24, 217.

3. Salzmann,T.N.; Ratcliffe,R.W.; Christensen,B.G.; Bouffard,F.A. J. Am. Chem. Soc., 1980, 102, 6161.



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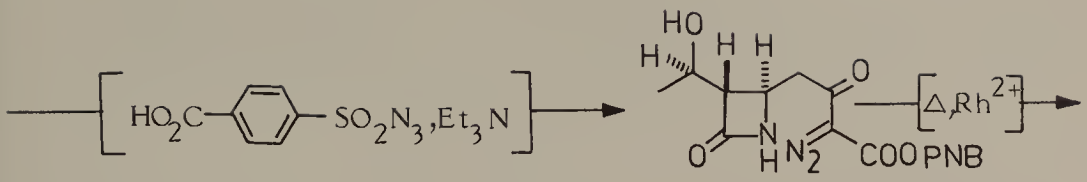
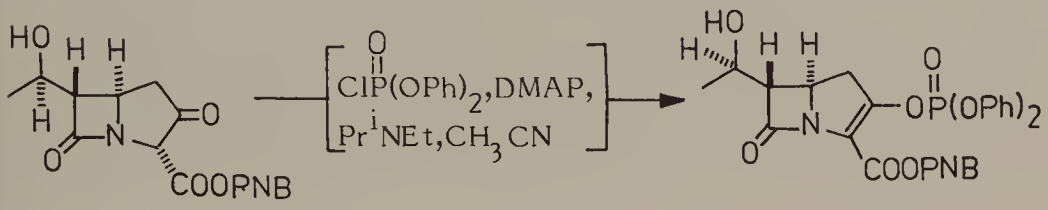
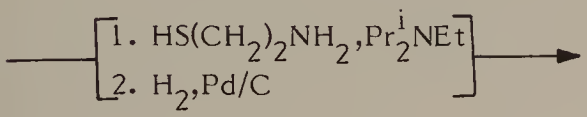
4. The acetyl derivative (D) could also be prepared directly from (A) treatment of its enolate with N-acetylimidazole.

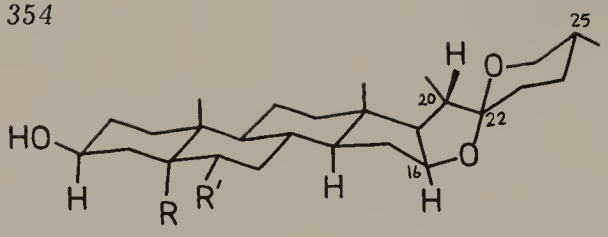
5. Brooks,D.W.; Lu,D.L.L.; Masamune,S. Angew. Chem. Int. Edn., 1979, 18, 72.





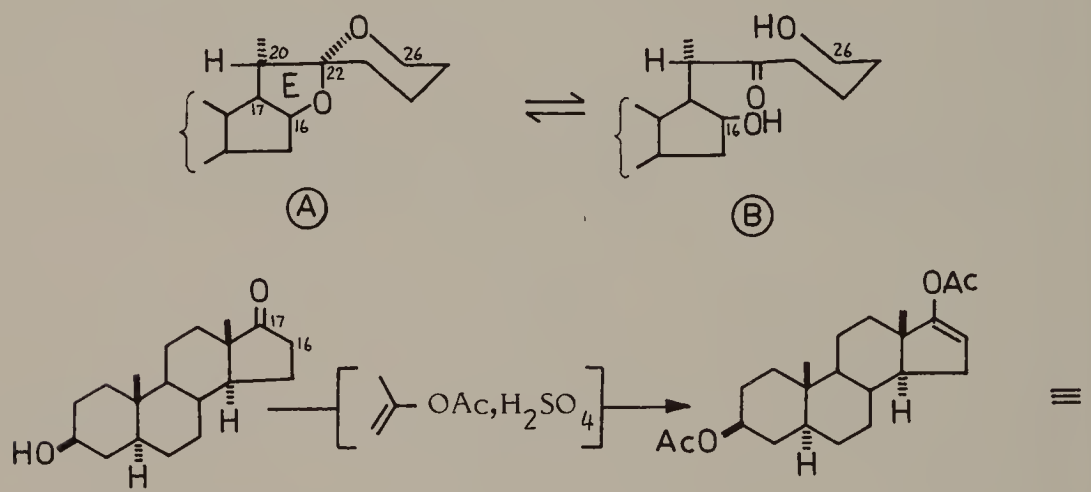


(+)-Thienamycin

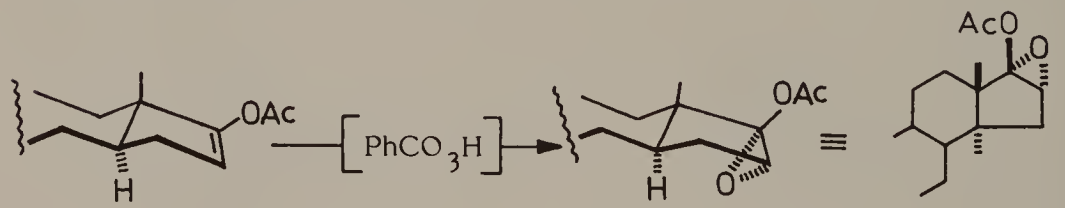


TIGOGENIN
DIOSGENIN

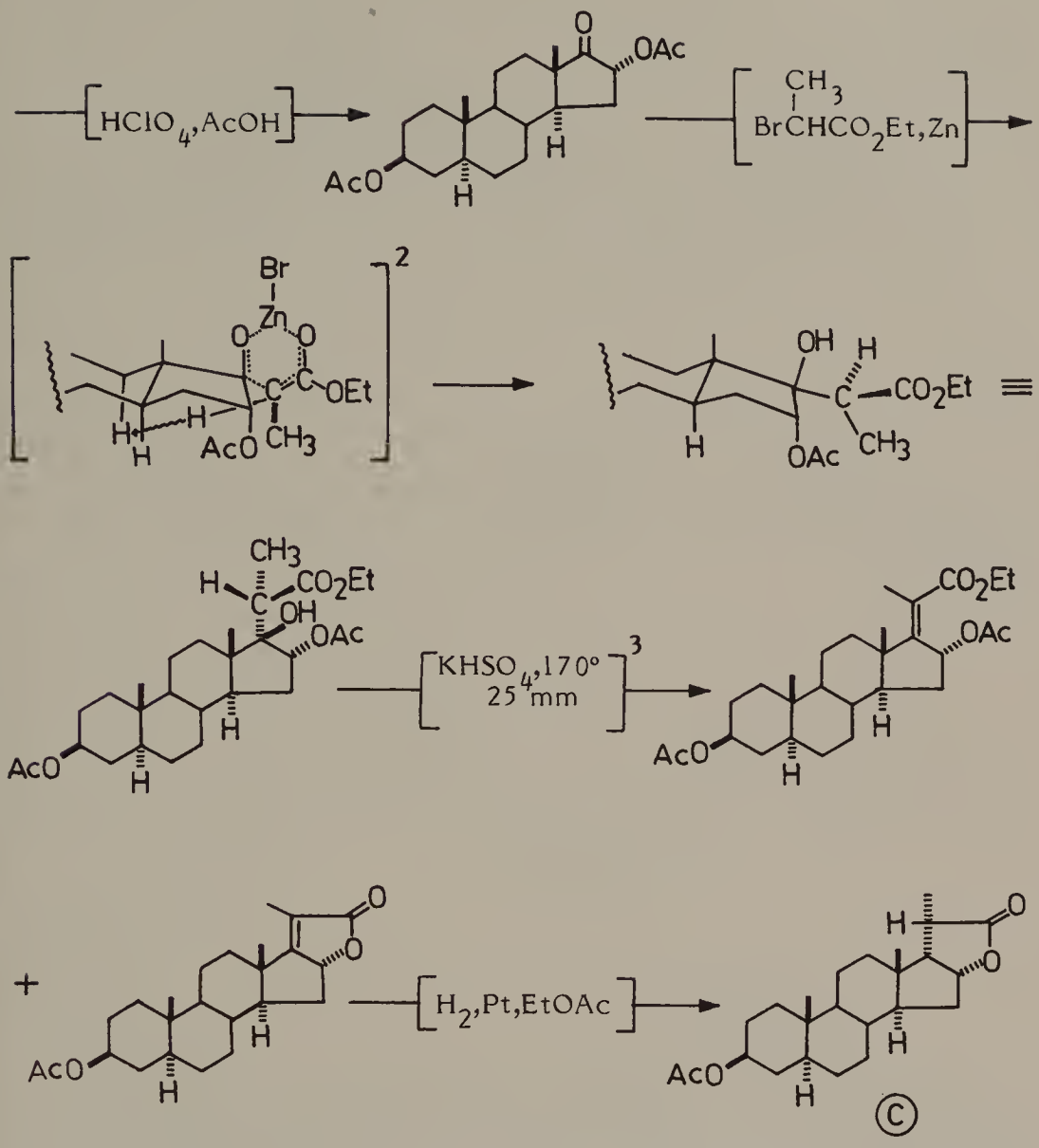
The total synthesis of steroids having been secured, steroidal sapogenins became an obvious target for synthetic attack. The route to tigogenin outlined below represents one of the earliest success wrought in this field by Sondheimer and his coworkers (1). These authors have chosen to regard the spiro ketal function Ⓐ , the characteristic feature of rings E and F, as the internal ketal of a dihydroxy-ketone Ⓑ. The required oxygen function at C-16 and the C-26 terminal oxygen, borne on an isopropyl unit, have both been introduced utilizing the 17-keto group of isoandrosterone.



3β-Hydroxyandrostan-17-one

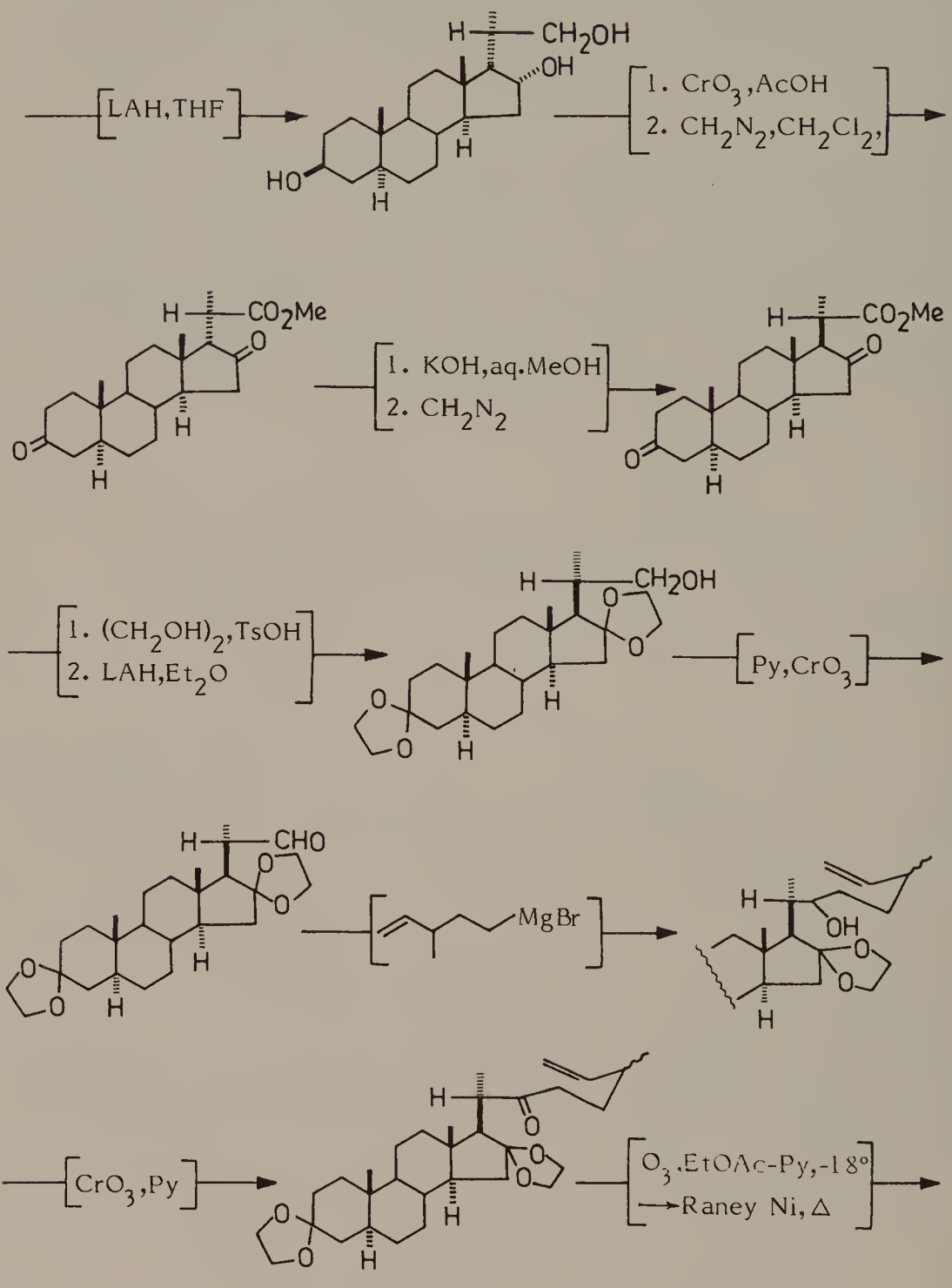


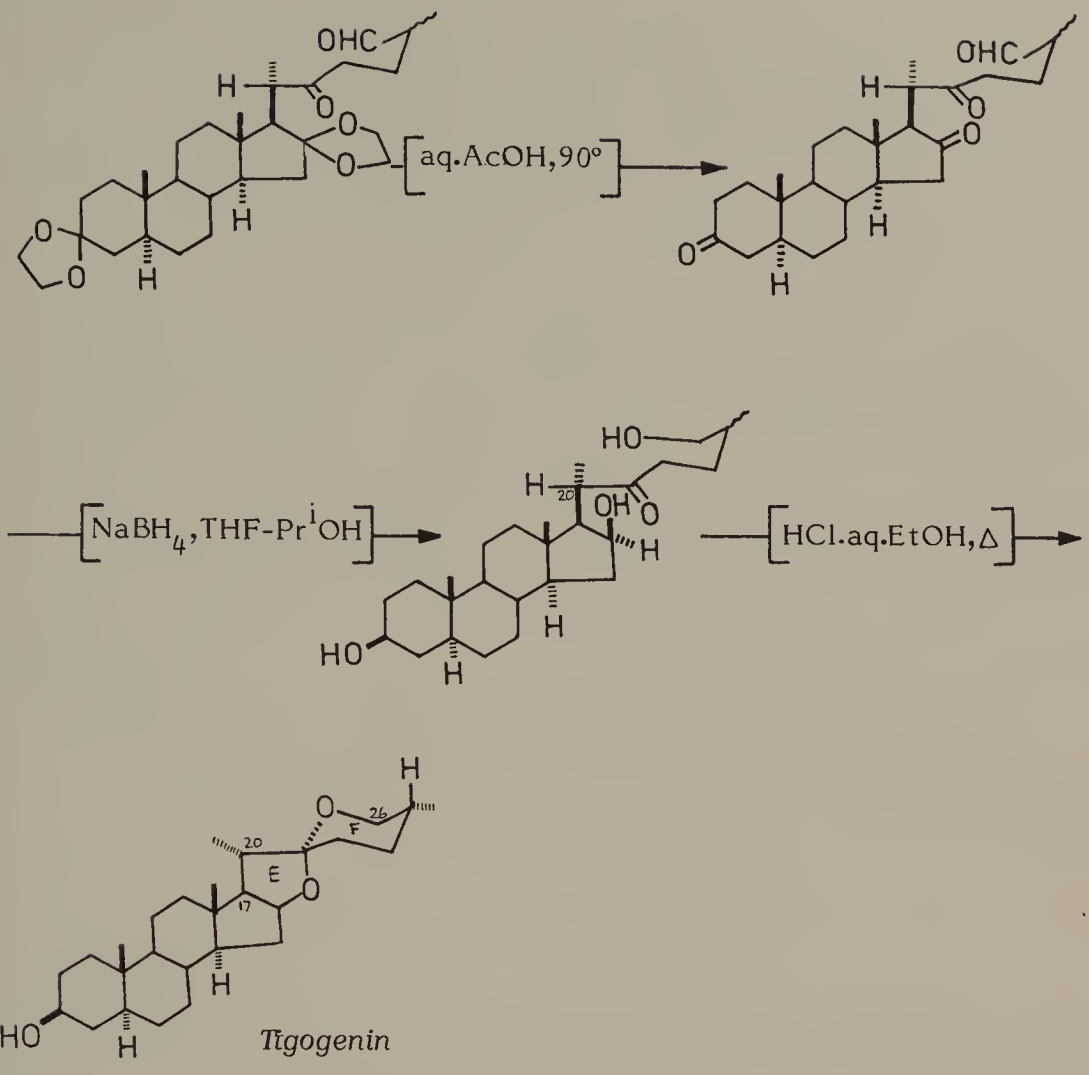
1. Mazur,Y., Danieli,N., Sondheimer,F., J. Am. Chem. Soc., 1960, 82, 5889.



2. If the opposite configuration is formulated at C-20, there is considerable interference between the 12-α-hydrogen and the 20-methyl group.

3. A mixture of two products is obtained. Each of these can be transformed independently into © using slightly different routes. The route from the α,β-unsaturated γ-lactone is only shown.


LAH,THF
1. CrO_3,AcOH
2. CH_2N_2,CH_2Cl_2,
1. KOH,aq.MeOH
2. CH_2N_2
1. $(CH_2OH)_2$,TsOH
2. LAH,Et_2O
Py,CrO_3
MgBr
CrO_3,Py
O_3,EtOAc-Py,-18°
→Raney Ni,Δ



Tigogenin

A versatile new approach to steroidal sapogenins has been developed by Kessar et al. (4) and is exemplified in the synthesis of diosgenin outlined below. The key step in this synthesis is the introduction of elements of rings E and F by Michael addition of 1-acetoxy-5-nitro-2-methylpentane Ⓐ to the α,β-unsaturated ketone Ⓑ.

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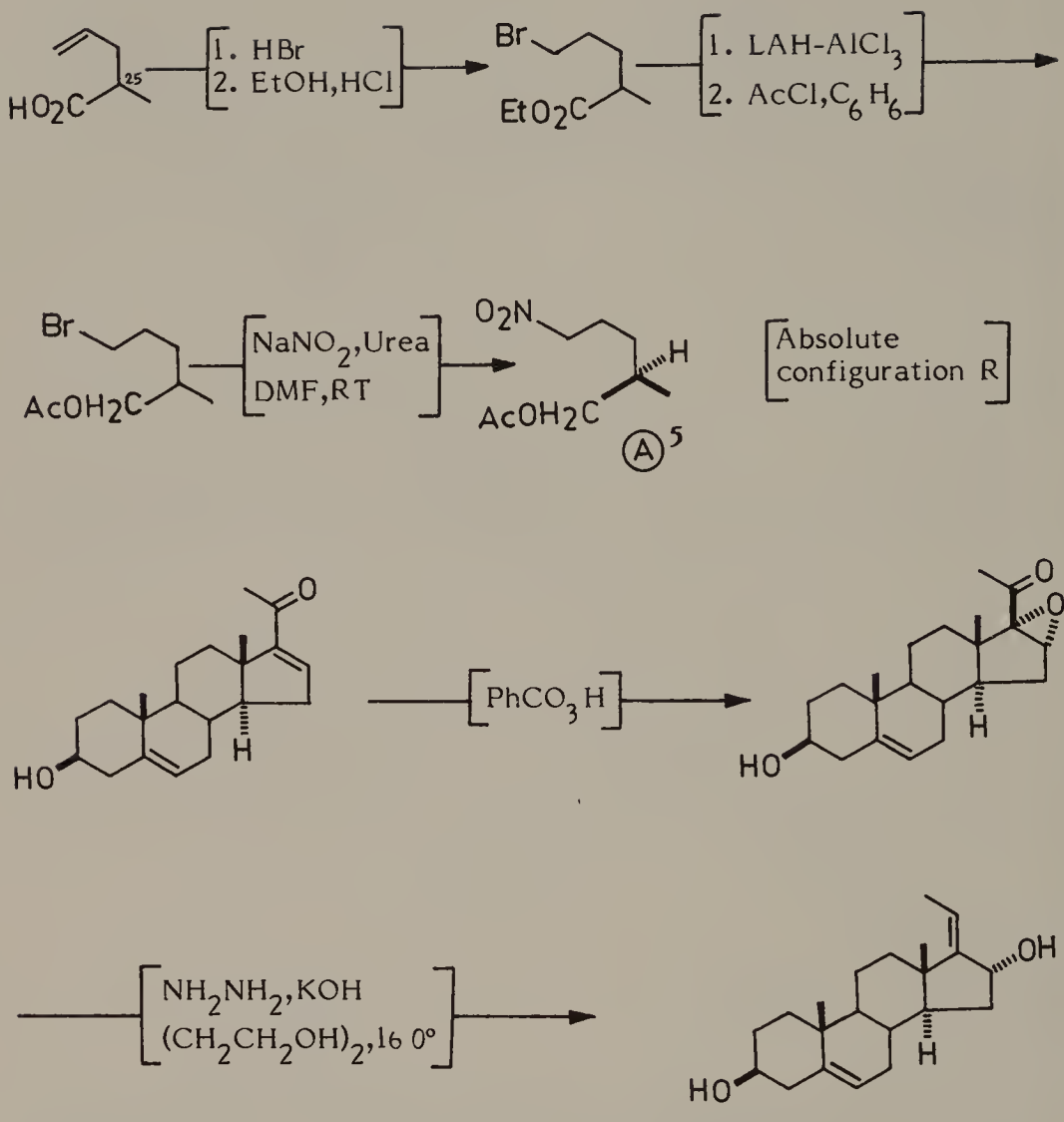
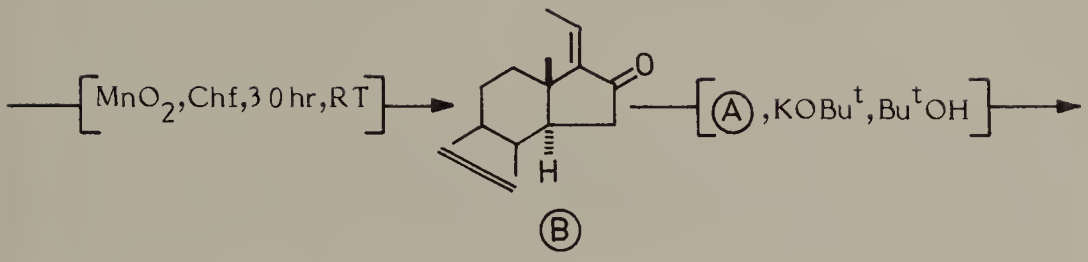
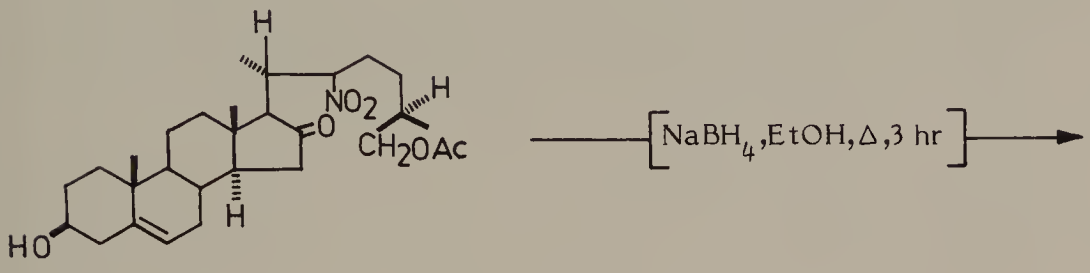
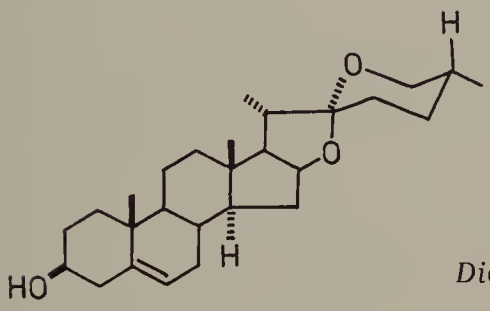
4. Kessar,S.V.; Gupta,Y.P.; Mahajan,R.K.; Joshi,G.S.; Rampal,A.L. Tetrahedron, 1968, 24, 899.



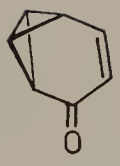
5. The stereochemistry at C-25 was controlled by selecting a nitroacetate possessing the correct configuration.


MnO2,Chf,30 hr,RT
O
H
A
,KOBu^t,Bu^tOH
B


H
NO2
H
O
CH2OAc
H
HO
NaBH4,EtOH,Δ,3 hr

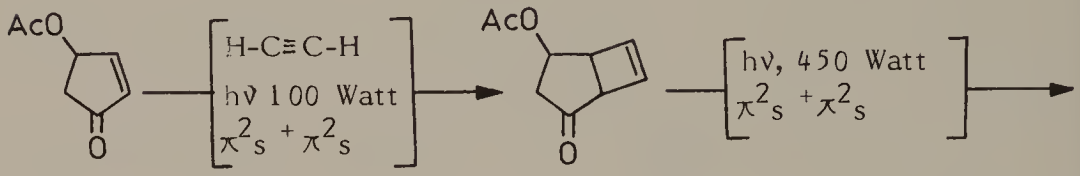

H
O
O
H
HO

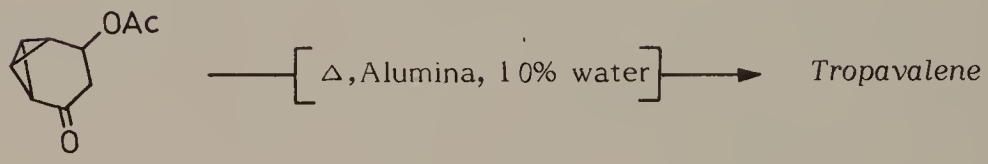
Diosgenin



TROPAVALENE

The synthesis of tropavalene (1) highlights the confidence with which the Woodward-Hoffmann rules could be used for synthesis.





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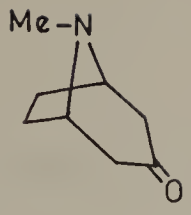
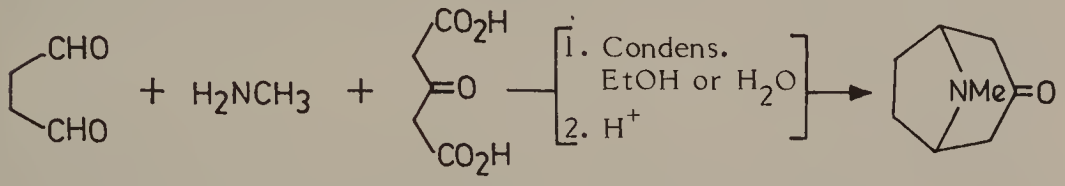
1. Sugihara,Y.; Morokoshi,N.; Murata,I. Tetrahedron Lett., 1977, 3887.



TROPINONE

Robinson's (1) synthesis of tropinone in 1917 was a landmark in the development of the art of organic synthesis. It demonstrated in a spectacular manner the power of the retro-synthetic analysis (2). The stunning simplicity and efficiency of the synthesis led Robinson to propose that plants use similar reactions for biosynthesis of this group of alkaloids, and to his general speculations about biogenesis of natural products (3). This synthesis was the fore-runner for biomimetic synthesis (although this term was not used by Robinson).



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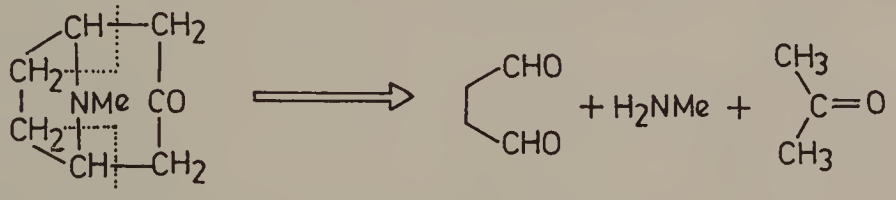
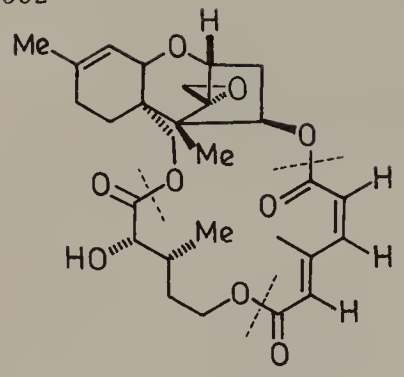
1. Robinson,R., J. Chem. Soc., 1917, 762.

2. Robinson described his thinking and his course of action thus: "By imaginary hydrolysis at the points indicated by the dotted line, the substance may be resolved into succindialdehyde, methylamine & acetone, and this observation suggested a line of attack of the problem which has resulted in a direct synthesis. It was found that tropinone was formed in small yield by condensation of succinaldehyde with acetone and methylamine in aq. solution. An improvement followed by the replacement of acetone by a salt of acetone dicarboxlic acid.



3. Robinson,R., J. Chem. Soc., 1917, 876.



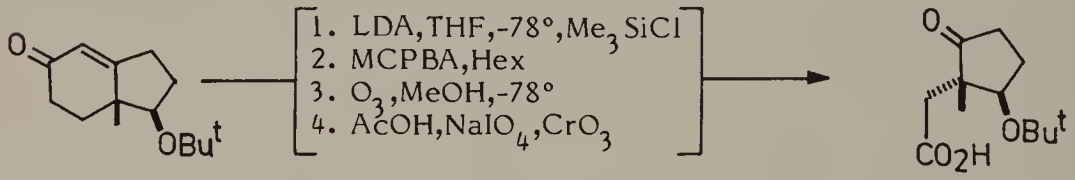
VERRUCARIN A

The trichothecenes are a group of closely related tetracyclic sesquiterpenoid epoxides produced by various species of imperfect fungi (1), and about 80 natural trichothecenes have been characterised todate. One important structural type of trichothecenes possess a macrocycle on the trichothecene skeleton, to which verrucarins belong. These have attracted much synthetic effort on account of their marked biological activity and their unusual structure, which offers much synthetic challenge (2).

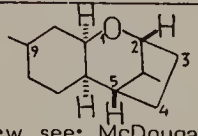
(±)-Verrucarol

Although the first synthesis of a trichothecene, the monohydroxylated trichodermin was reported in 1971 (3), the first synthesis of a polyhydroxylated trichothecene, verrucarol, on which the macrocyclic structure is built, was accomplished in 1982 by Schlessinger and Nugent (4), followed by the synthesis of Rousch and D'Ambra (5) and by Trost & McDougal (7), which are described below.

Schlessinger and Nugent synthesis followed a biomimetic approach, and starts from a hydrindenone, carrying some of the centres in the configuration in which they appear in the final molecule.



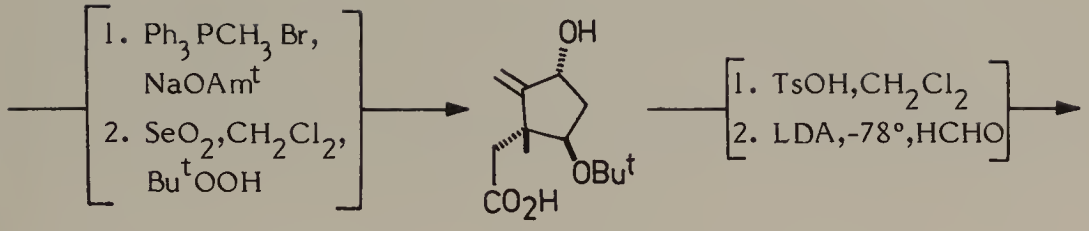
1. Trichothecane skeleton.



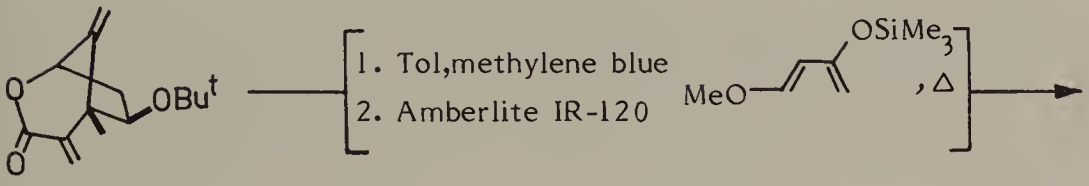
2. For a comprehensive review see: McDougal,P.G.; Schmuff,N.R. Prog. Chem. of Natural Products, 1985, 47, 153.

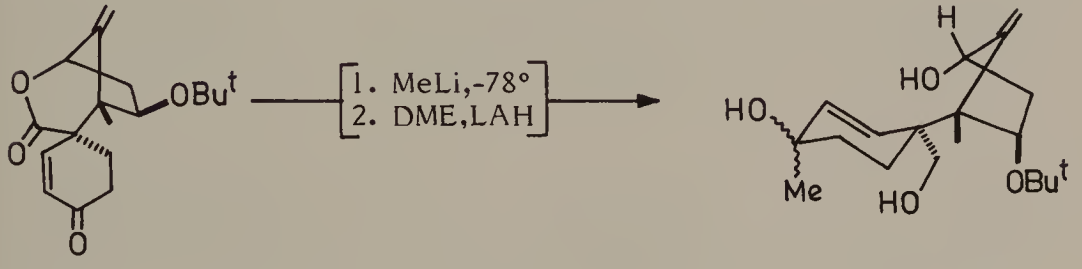
3. Colrin,E.W.; Raphael,R.A.; Roberts,J.S. Chem. Comm., 1971, 858; Colrin,E.W.; Malchenko,S.; Raphael,R.A.; Roberts,J.S. J. Chem. Soc. Perkins. Trans., 1973, 1989.

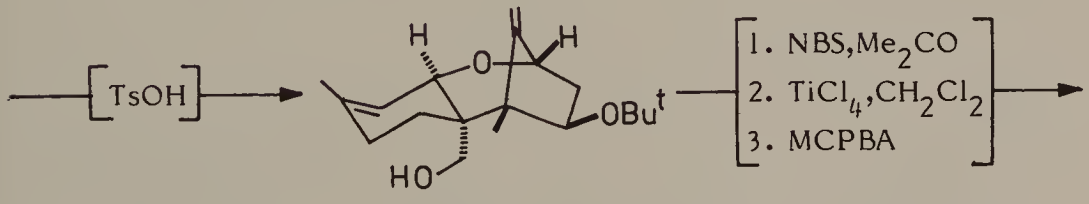
4. Schlessinger,R.H.; Nugent,R.A. J. Am. Chem. Soc., 1982, 104, 1116.

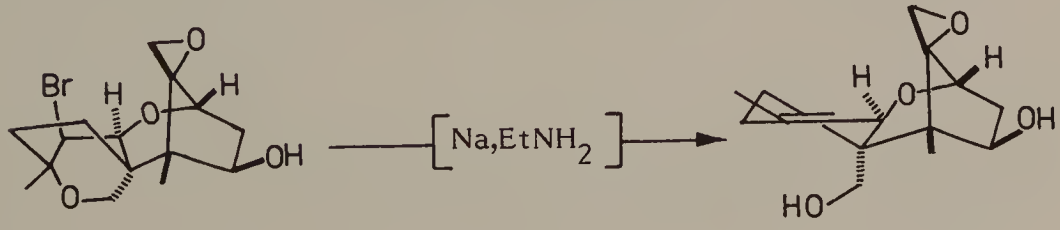


α : β alcohol, 5:1



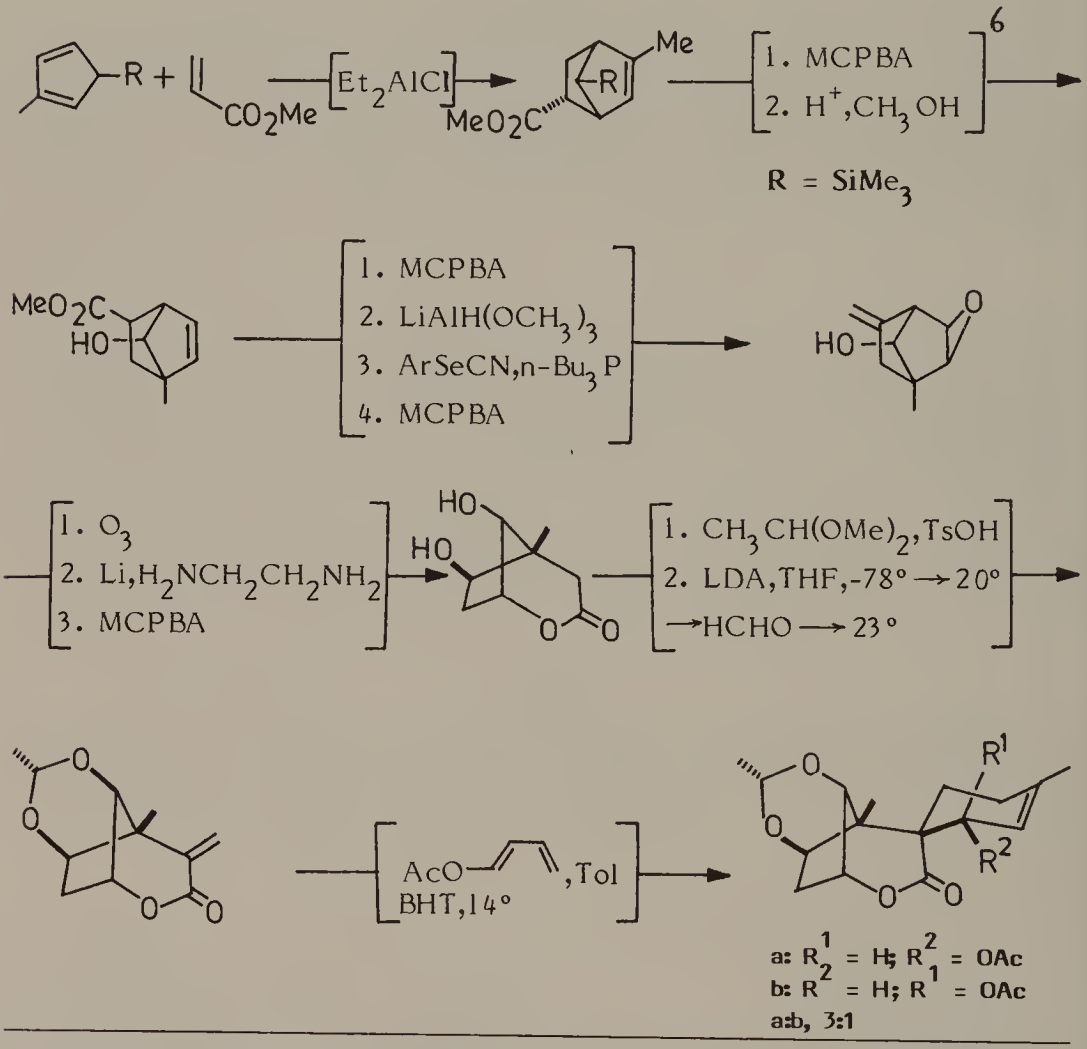






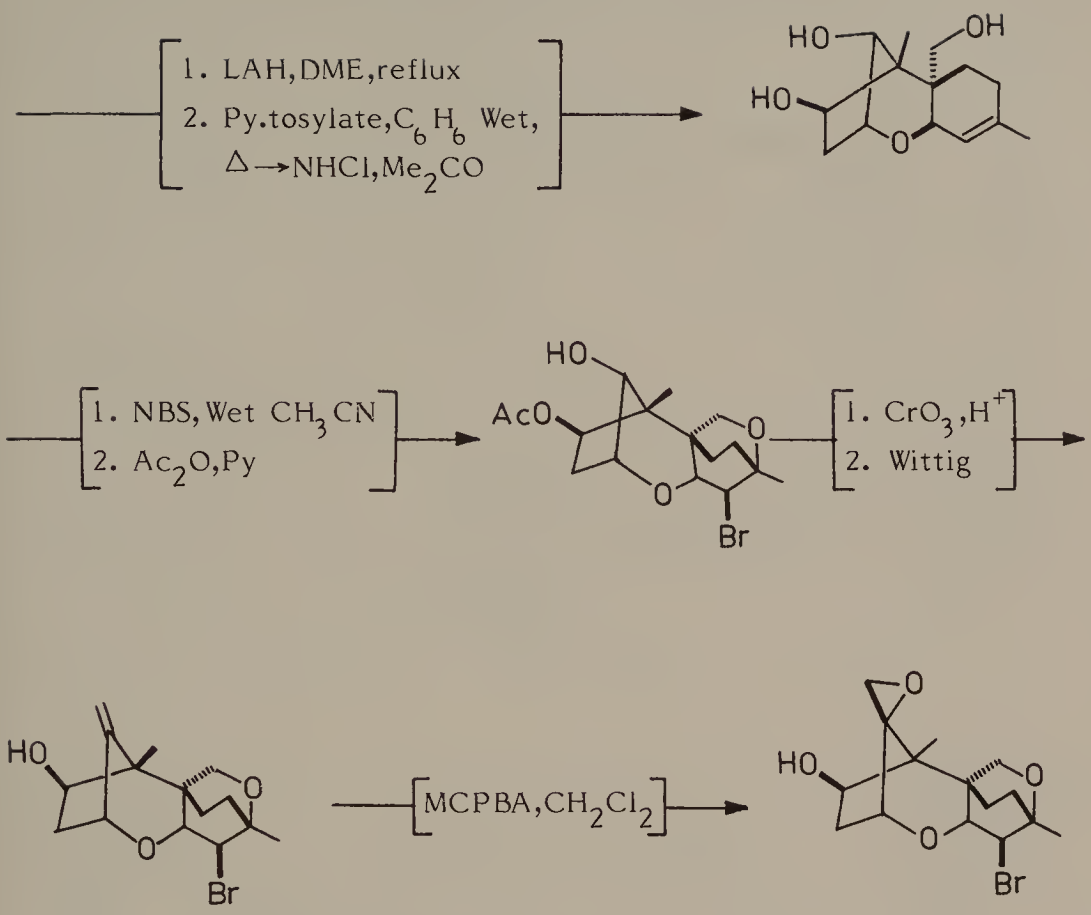
Verrucarol

Rousch and D'Ambra (5) in an alternative approach to synthesis of verrucarol constructed the critical bicyclo[2.2.1]heptene Ⓐ by a stereoselective silyl-controlled Wagner-Meerwein rearrangement; ring A was formed by a Diels-Alder reaction, and the topology of the bicyclic system directs the attack of the acetoxydiene on the α-methylene lactone to establish the required C_5,C_6 stereochemistry.

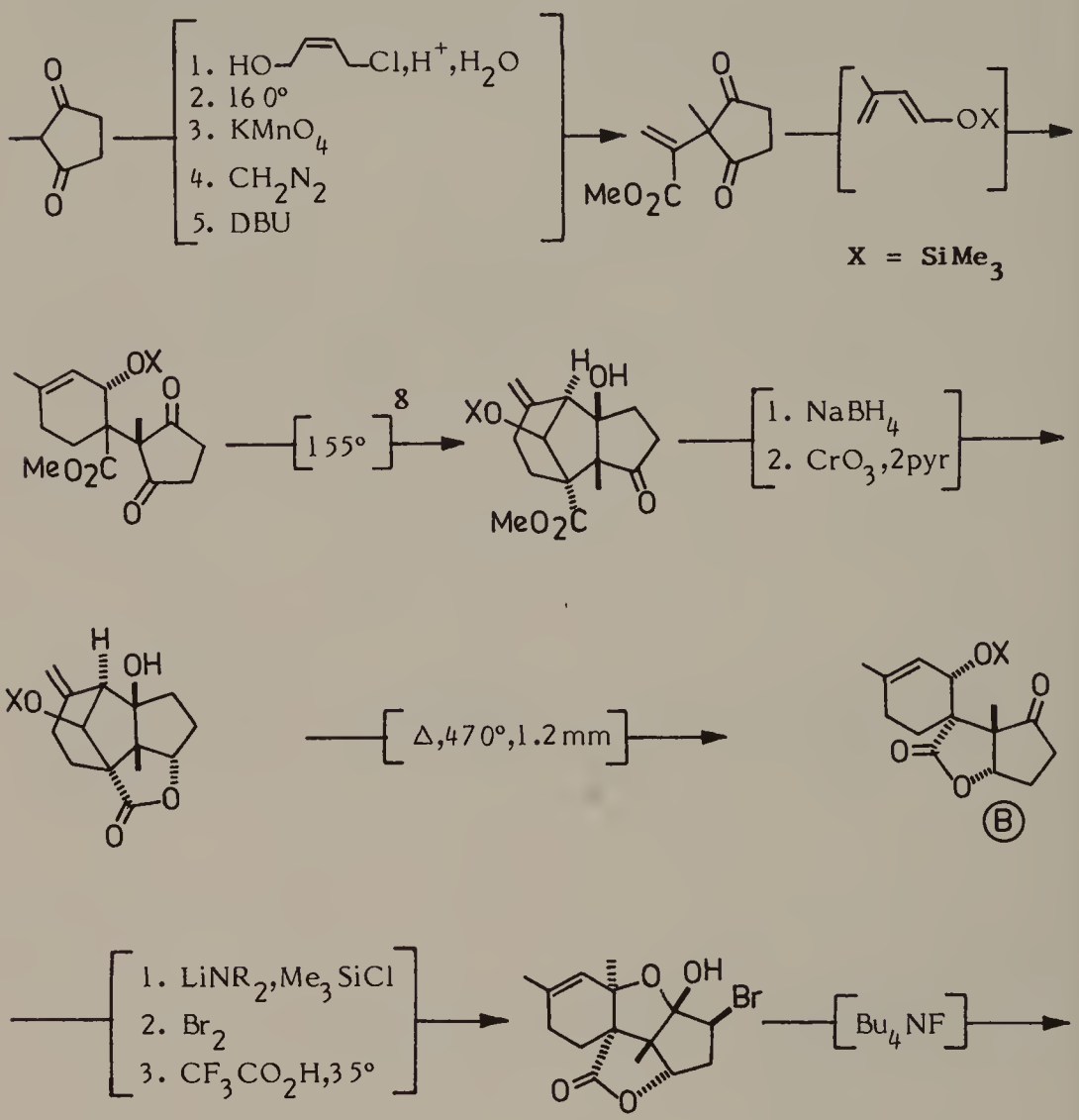


5. Rousch,W.R.; D'Ambra,T.E. (a) J. Am. Chem. Soc., 1983, 105, 1058; (b) J. Org. Chem., 1980, 45, 3927; (c) ibid, 1981, 46, 5045.

6. This results from a unique silyl-controlled Wagner-Meerwein arrangement.


1. LAH, DME, reflux
2. Py.tosylate, C_6H_6 Wet,
$\Delta \rightarrow$ NHCl, Me_2CO
HO
OH
HO
O
1. NBS, Wet CH_3CN
2. Ac_2O, Py
HO
AcO
O
O
Br
1. CrO_3, H^+
2. Wittig
HO
O
Br
MCPBA, CH_2Cl_2
HO
O
O
O
Br
≡
Br
O
O
O
OH
Zn/Ag, THF-EtOH
(±)-Verrucarol

Trost and McDougal (7) developed yet another biomimetic route to verrucarol described below starting from 2-methyl-1,3-cyclopentadione.



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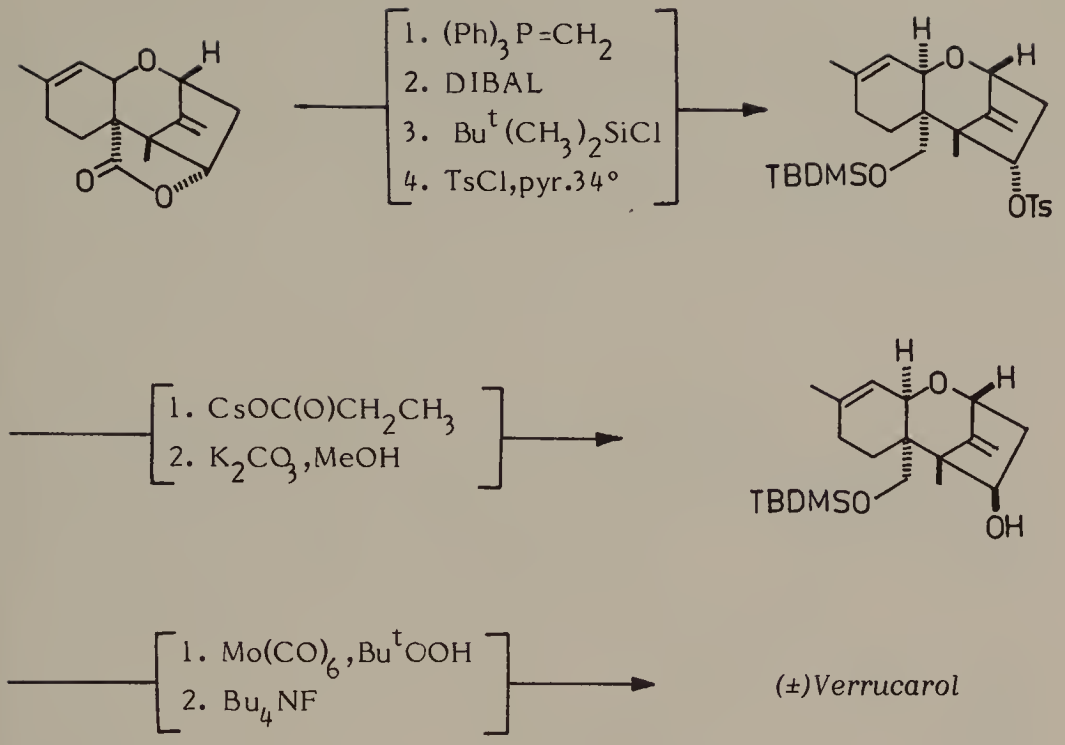
7. Trost,B.M.; McDougal,P.G. J. Am. Chem. Soc., 1982, 104, 6110.

8. Only one of the two keto groups in the dione could align itself in the right position to undergo the enone reaction, which thus serves to differentiate the two ketones; this differentiation is maintained in the subsequent step when through a retroene reaction a modified Diels-Alder adduct (B) is obtained.



Verrucarin A

Still & Ohmizu were the first to synthesise a naturally occuring macrocyclic trichothecene, verrucarin A, in 1981 (9). An alternative synthesis of verrucarin A following a similar strategy was reported soon after this by Tamm and his associates (10); the synthesis of a number of related macrocycles has since then been reported (2,11). The synthesis by Still and Ohmizu (9) described below constructs the bridge as two units, one of them obtained in optically pure form through a chiral epoxidation of an olefin precursor.

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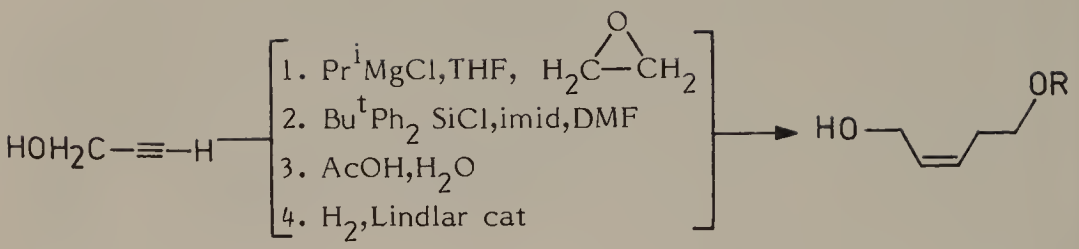
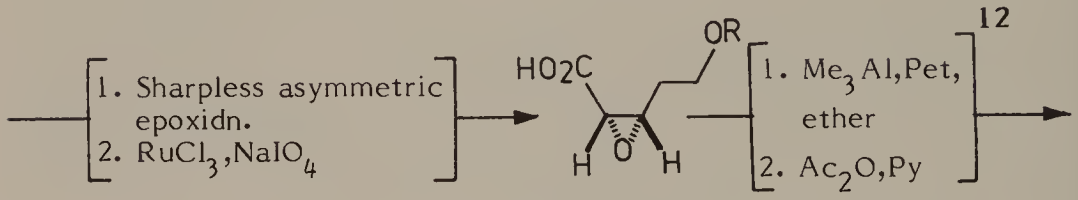
9. Still,W.C.; Ohmizu,H. J. Org. Chem., 1981, 46, 5244.

10. Mohr,P.; Tori,M.; Grossen,P.; Harold,P.; Tamm,Ch. Helv. Chim. Acta, 1982, 65, 1412.

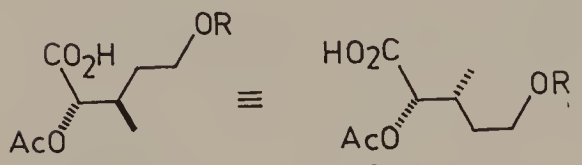
11. Most of the reported synthesis share two common strategies: (a) the syntheses are convergent, with acyclic units, mostly two, assembled prior to their attatchment to verrucarol; (b) a common retrosynthetic connection has been at the ester linkages both for the attatchment of the acyclic units and for the formation of the macrocycle, as shown by dotted lines in the formula of verrucarin A.



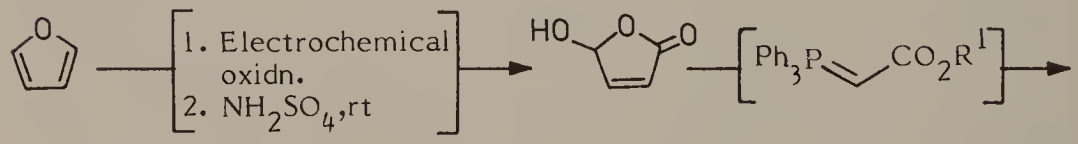


optically active

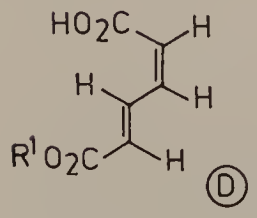
R = TBDPS



Ⓒ *Verrucarinic acid fragment*



$R^1 = CH_2CH_2SiMe_3$



Ⓓ

E,Z-muconic acid fragment

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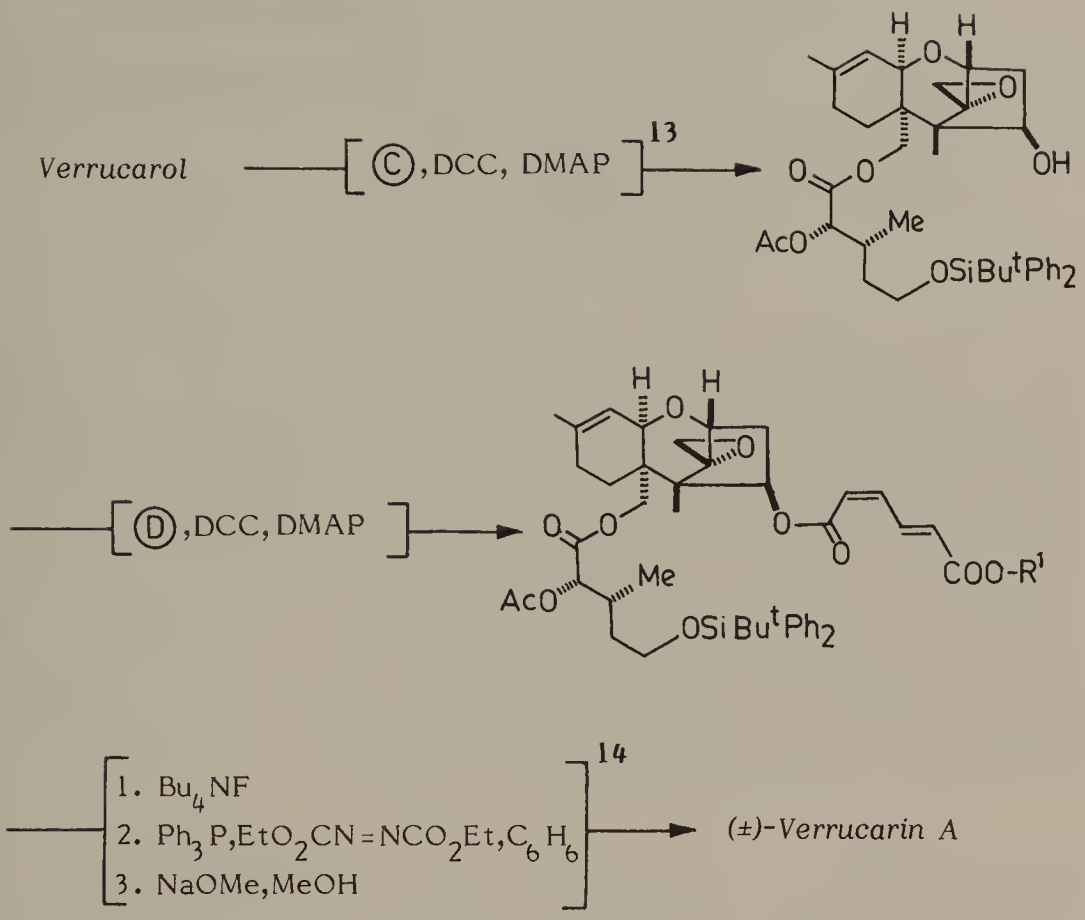
12. This reagent affected only β-addition.



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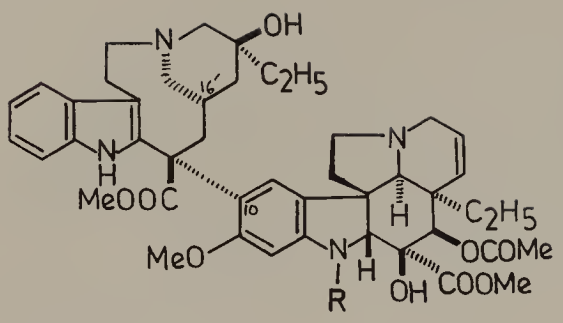
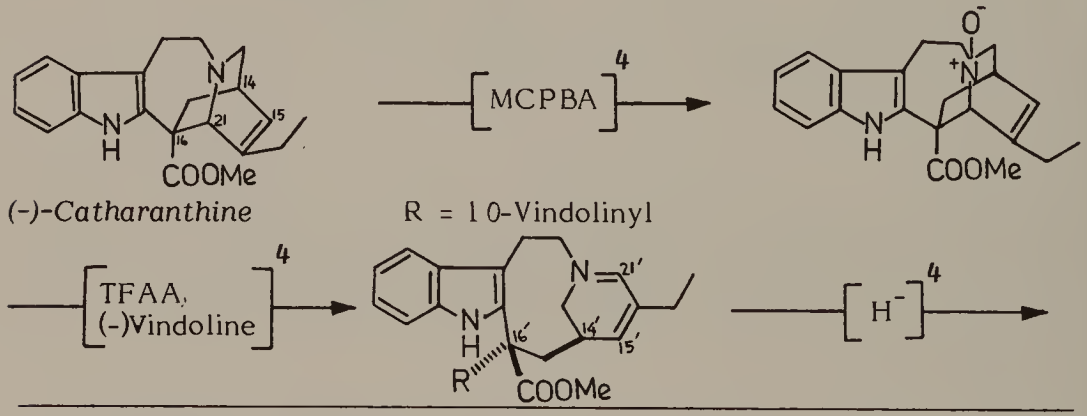
13. Hassner,A.; Alexanian,V. Tetrahedron Lett., 1978, 4475.

14. For cyclisation: Kurihara,T.; Nakajima,Y.; Mitsunobu,O. Tetrahedron Lett., 1976, 2445.



VINBLASTINE
VINCRISTINE

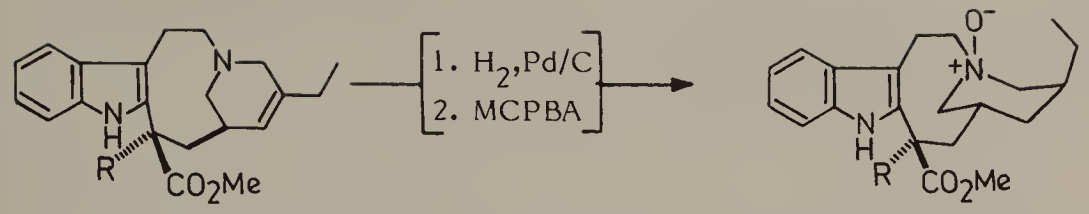
Of all the vinca alkaloids the dimeric indole alkaloids, vinblastine and vincristine (vincaleucoblastine) proved most interesting because of their anticancer activity, and are widely used in clinical practice. Their yield from natural sources is, however, very poor. Their synthesis has thus attracted much attention both to prepare analogs for structure-activity relationship studies, as also to achieve practical synthesis (1). The synthesis by Potier and his associates is based on a novel C-16', -C-21' skeletal fragmentation of (+)-catharanthine (ibogaine derivatives) induced by Polonovski fragmentation reaction, which in the presence of (-)-vindoline (aspidospermane derivatives) leads to the formation of dimeric alkaloids with the natural C-16' configuration, which seems necessary for antitumour activity (2,3). Supplies af natural catharanthine and vindoline are therefore critical for the preparation of synthetic vinblastine and vincristine.



1. For a review of the synthesis of dimeric indole alkaloids see: Kutney,J.P.; Lloydia, 1977, 41, 107; Lect. Heterocyclic Chem., 1978, 4, 59; Potier,P. J. Nat. Prod., 1980, 43, 72; Ann. Symprm., 1984, 2, 65, 67; Chem. Abst., 1984, 101, 130936z, 130937a; Rahman, A.U. Proc. of 4th Asian Symp. Med. Plants Spices, 1980, 1, 222; J. Chem. Soc. Pak., 1979, 1, 81.

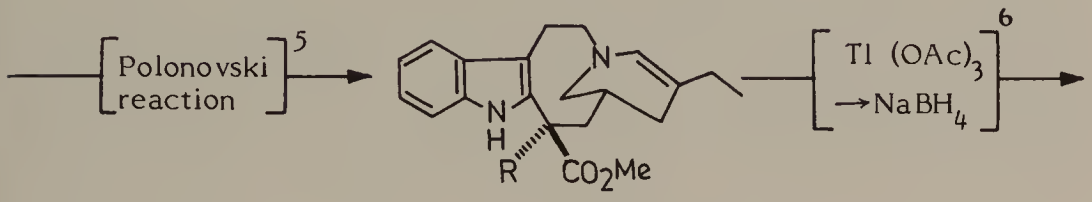
2. For earlier work leading to this synthesis see: Langlois,N.; Gueritte,F.; Langlois,Y.; Potier,P. J. Am. Chem. Soc., 1976, 98, 7017; Langlois,N.; Potier,P. J. Chem. Soc. Chem. Comm., 1978, 102.

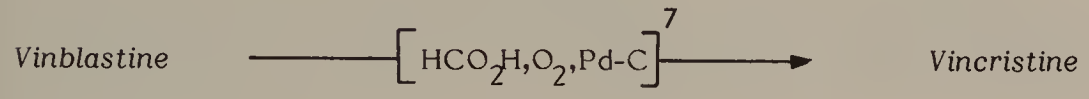
3. Mangeney,P.; Andriamialisoa,R.Z.; Langlois,N.; Langlois,Y.; Potier,P. J. Am. Chem. Soc., 1979, 101, 2243. For an earlier partial synthesis of vinblastine designed on a similar strategy see: Rehman,A.U.; Bash,A.; Gkazaia,M. Tetrahedran Lett., 1976, 27, 2351.



Anhydrovinblastine

R = 10-Vindolinyl





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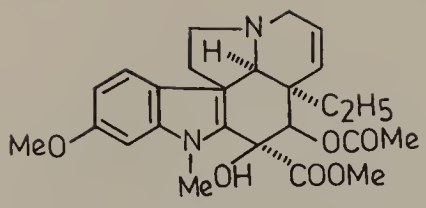
4. These three steps can be carried out as one pot reaction (5).

5. Raucher et al. have observed that the coupling of (±)-catharanthine with (-)-vindoline by the modified Polonovski reaction gave (16'S,14'R) diastereomer, (+)-anhydrovinblastine (A), which results from the coupling of (+)-catharanthine and (-)-vindoline in 46% yield based on (+)-catharanthine, along with (16'R,14'S) diastereomer, (-)-anhydrovincovaline (B), which results from the coupling of (-)-catharanthine and (-)-vindoline and was isolated in 54% yield based on catharanthine; (A) and (B) could be easily separated by flash chromatography; (±)-catharanthine can therefore be used for this synthesis: Raucher,S.; Bray,B.L.; Lawrence,R.F. J. Am. Chem. Soc., 1987, 109, 442.

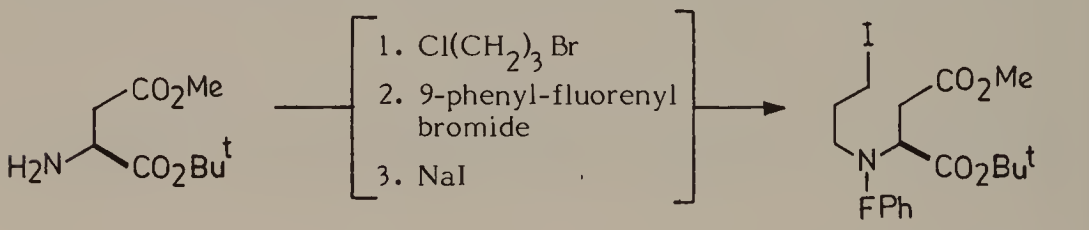
6. Use of OsO_4 as an oxidant followed by $NaBH_4$ gave instead the 21'-epimer leurosidine; this difference in stereoselectivity in oxidation may be due to the size of the oxidant, and bulky OsO_4 would attack from the less hindered -side.

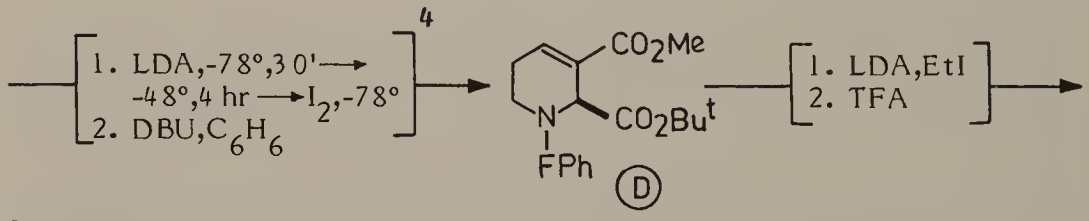
7. Gideon Richter, Belgian Patent, 823560, April 16, 1975; Chem. Abst., 1976, 84, 59835p.



VINDOLINE

Vindoline is one of the most important members of the Aspidosperma alkaloids, and is part of the potent oncolytic indole alkaloid vinblastine. A number of synthesis of (±)-vindoline have been reported all of which are linear in conception and begin with 6-methoxytryptamine or a related structure and construct on it the remaining structure (1). Feldman and Rapoport have recently reported a convergent chirospecific synthesis of (-)-vindoline (2) in which tetrahydroquinolinate, the precursor of ring E was synthesised in enantiomerically pure form from l-aspartic acid (3), followed by an enantioselective skeletal rearrangement of Ⓔ to the required aspidosperma skeleton.





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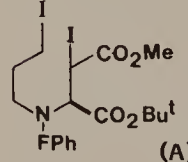
1. Total synthesis of (±)-vindoline: (a) Ando,M.; Buchi,G.; Ohnuma,T. J. Am. Chem. Soc., 1975, 97, 6880; (b) Kutney,J.P.; Bunzli-Treppo,U.; Chan,K.K.; deSouza,J.P.; Fujise,Y.; Honda,T.; Katsube,J.; Klein,F.K.; Leutwiler,A.; Morehead,S.; Rohr,M.; Worth,B.R. J. Am. Chem. Soc., 1978, 100, 4220; (c) Andriamialisoa,R.Z.; Langlois,N.; Langlois,Y. J. Org. Chem., 1985, 50, 961.

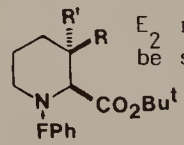
2. Feldman,P.L.; Rapoport,H. J. Am. Chem. Soc., 1987, 109, 1603.

3. Feldman,P.L.; Rapoport,H. J. Org. Chem., 1986, 51, 3382.

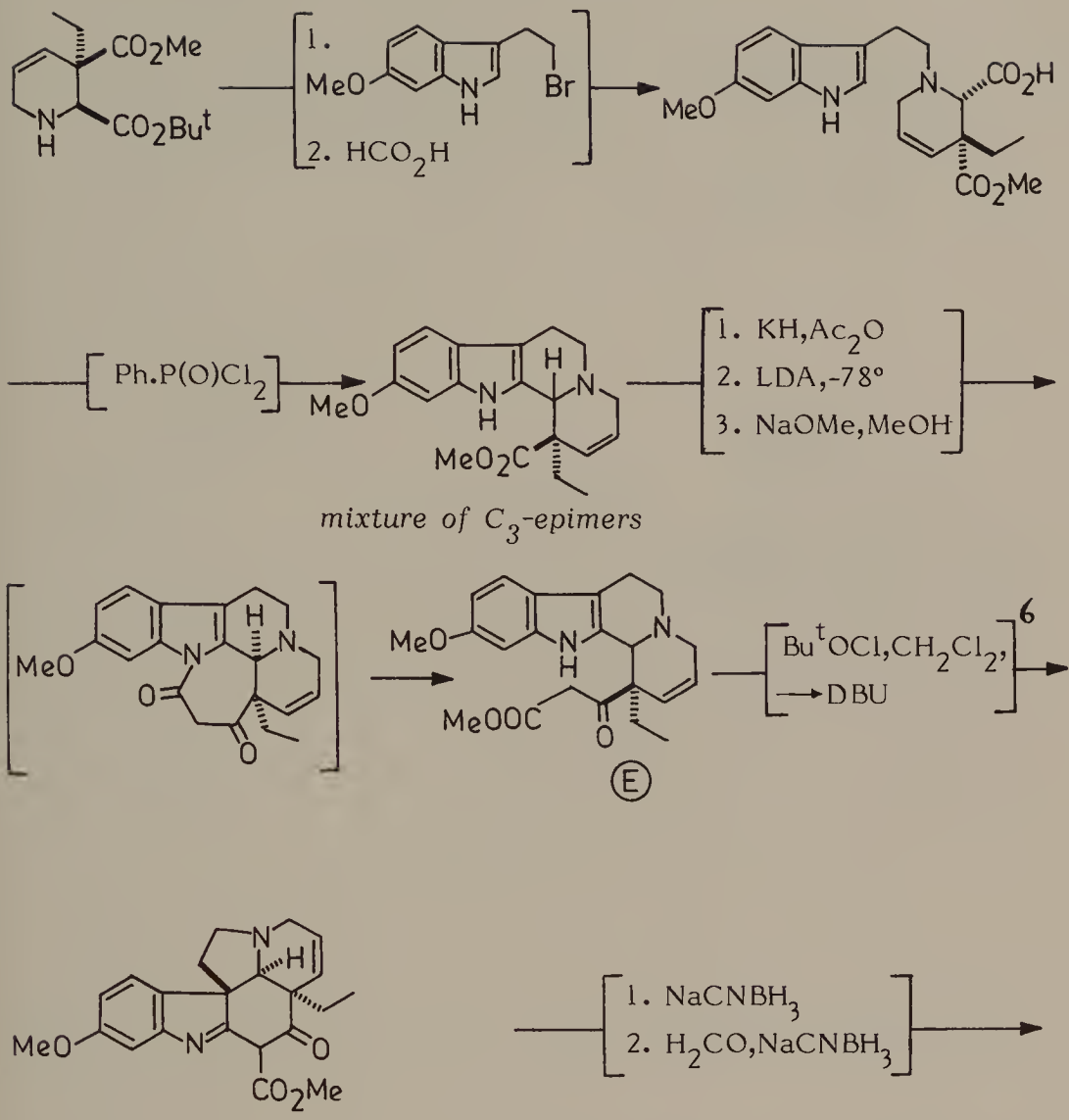
4. $LDAl_2$treatment gave a mixture of A,B&C in a ratio of 3:12:85. DBU treatment converted only isomer Ⓒ to form Ⓓ as stereoelectronic for E_2 reaction of Ⓒ was more favourable; the mixture could be separated to provide Ⓓ, while mixture of Ⓐ & Ⓑ was recycled.



(A)



(B); R'=CO_2Me; R=I (C) R' = I; R = CO_2Me



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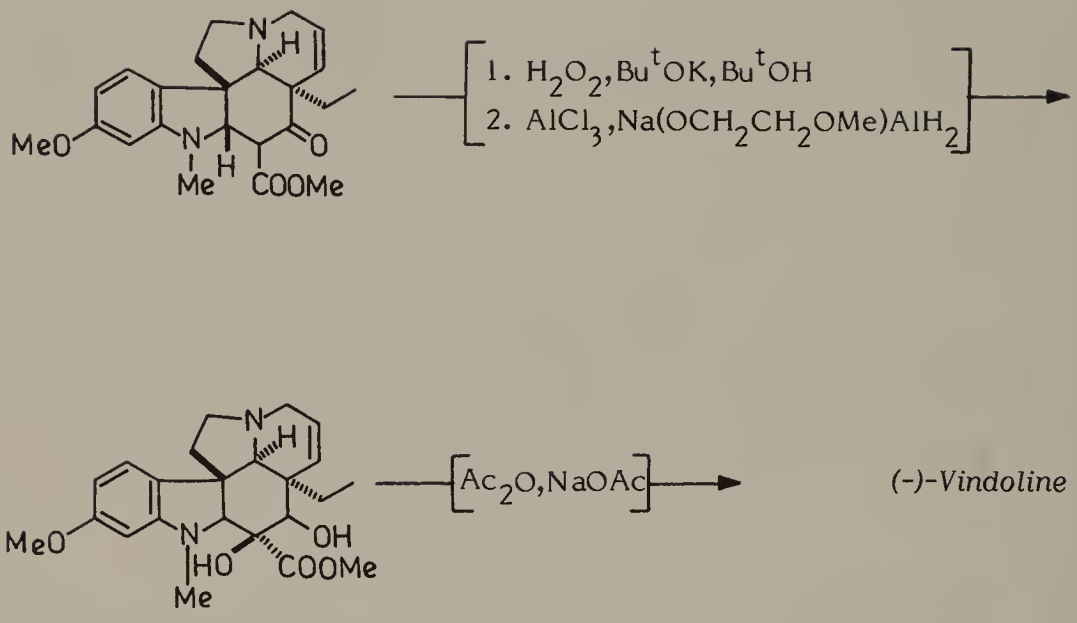
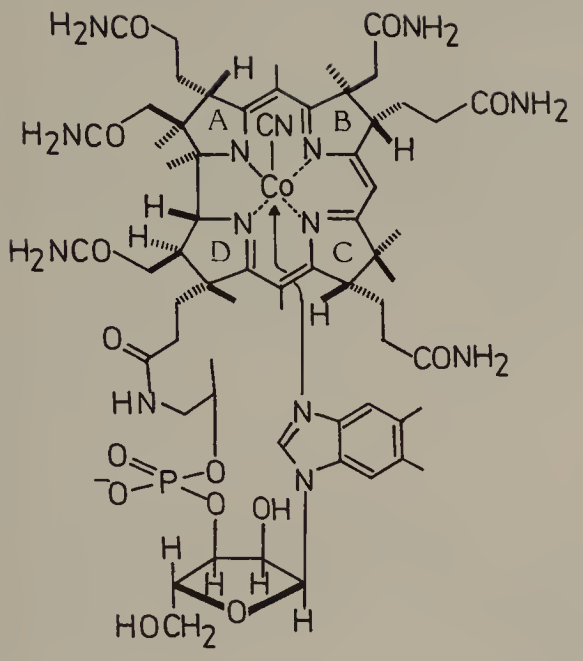
5. Feldman,P.L.; Rapoport,H. Synthesis, 1986, 735.

6. The experimental conditions for this skeletal rearrangement are critical for preserving optimal purity, as a reversible Mannich reaction is very facile in hexahydroindoloquinolizine systems with highly electrophilic carbon C-15.


MeO
N
H
N
Me
H
O
COOMe
1. H_2O_2, Bu^tOK, Bu^tOH
2. $AlCl_3$, $Na(OCH_2CH_2OMe)AlH_2$
MeO
N
H
N
HO
Me
OH
COOMe
Ac_2O, NaOAc
(-)-Vindoline



VITAMIN B_{12}

The elucidation of the structure of this complex molecule with 64 atoms and 9 asymmetric centres would stand out as one of the most significant achievements of X-ray crystallography(1) and its synthesis the most outstanding achievement of organic synthesis(2, 3). The completion of this mammoth task, which spanned over a decade, was the outcome of an intercontinental collaboration between the groups led by Woodward at Harvard University, Cambridge, and Eschenmoser at ETH, Zürich. The synthesis culminated in the preparation of Cobyric acid, the simplest of B_{12} derivatives, which had previously been converted to the vitamin by Bernhauer & associates(4), and thus constituted a formal total synthesis.

---

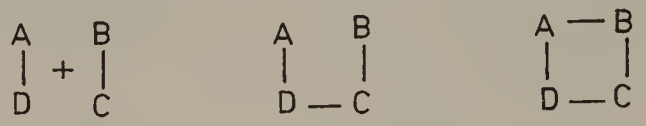
1. Hodgkin, D.C., Pickworth, J., Robertson, J.H., Trueblood, K., Prosen, R.J., White, J.G. Nature, 1956, 176, 325.

2. Woodward, R.B. Pure Appl. Chem., 1968, 17, 519; 1971, 25, 283; 1973, 33, 145; Eschenmoser, A. Proc. of the Robert A. Welch Foundation Conferences on Chemical Research XII, 1968, 9; Quart. Revs., 1970, 24, 366; XXIIIrd Int. Congress Pure Appl. Chem., 1971, 2, 69.

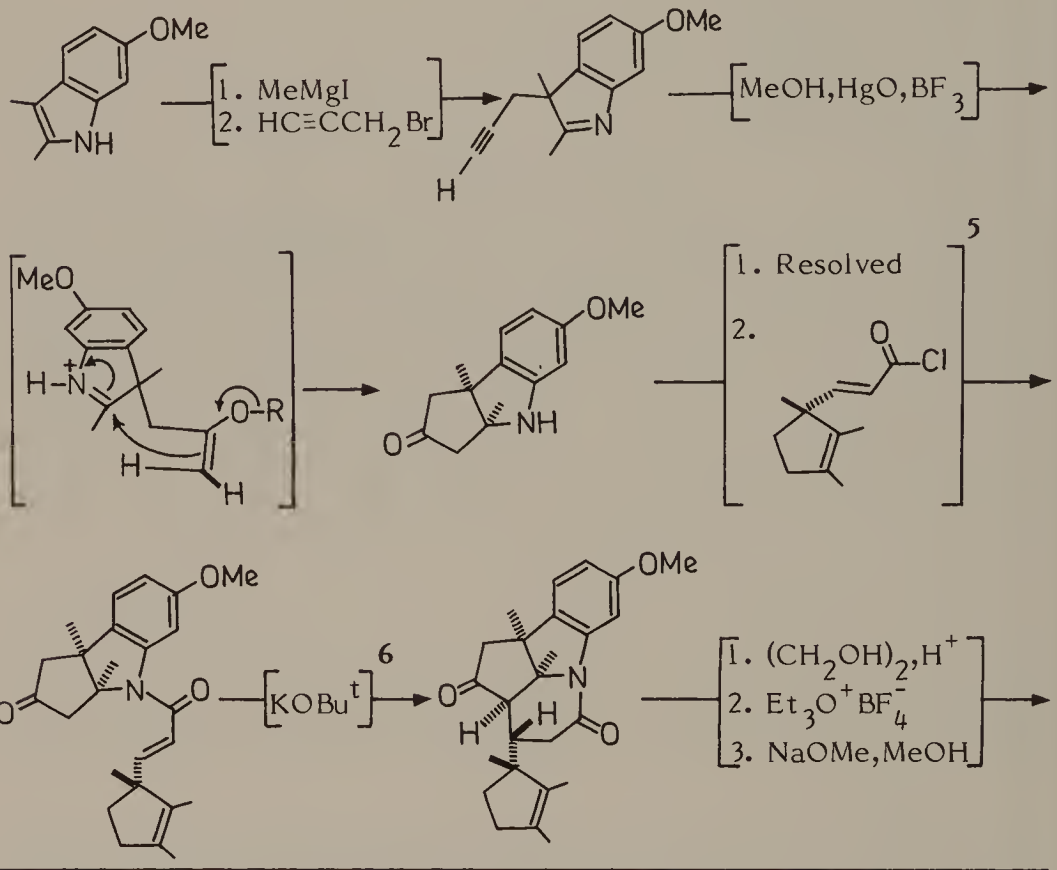
3. The synthesis of vitamin B_{12} and the related work on corrins provides a very instructive example of how a project directed towards the synthesis of a complex natural product has an impact much beyond the immediate structural boundaries of the specific synthetic problem. Innumerable synthetic methods of general applicability emerged from this monumental work, and the principle of orbital symmetry conservation (Woodward-Hoffmann rules), which is of immense consequence to chemistry as a whole, arose directly from the early studies on vitamin B_{12} synthesis. Chem. Soc. Publ. 1967, 21, 217.

4. Freidrich, W., Gross, G., Bernhauer, K., Zeller, P. Helv., 1960, 43, 704.

The overall plan of synthesis was to construct the unit structures of the molecule, designated A,B,C&D, in optically active form of the specified absolute configuration, and bring together the units to generate the needed stereochemical relations of the whole molecule.

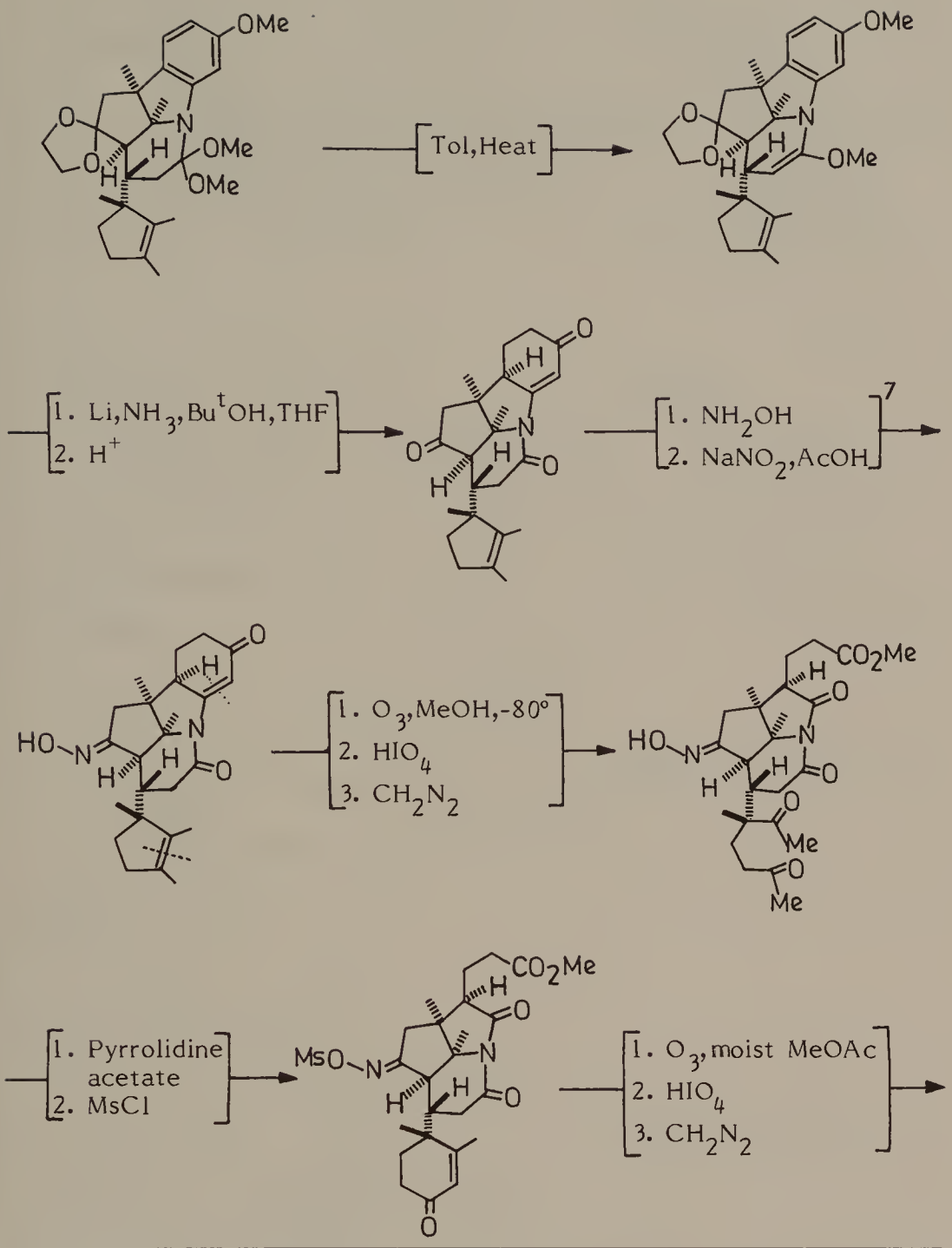


Preparation of A-D component

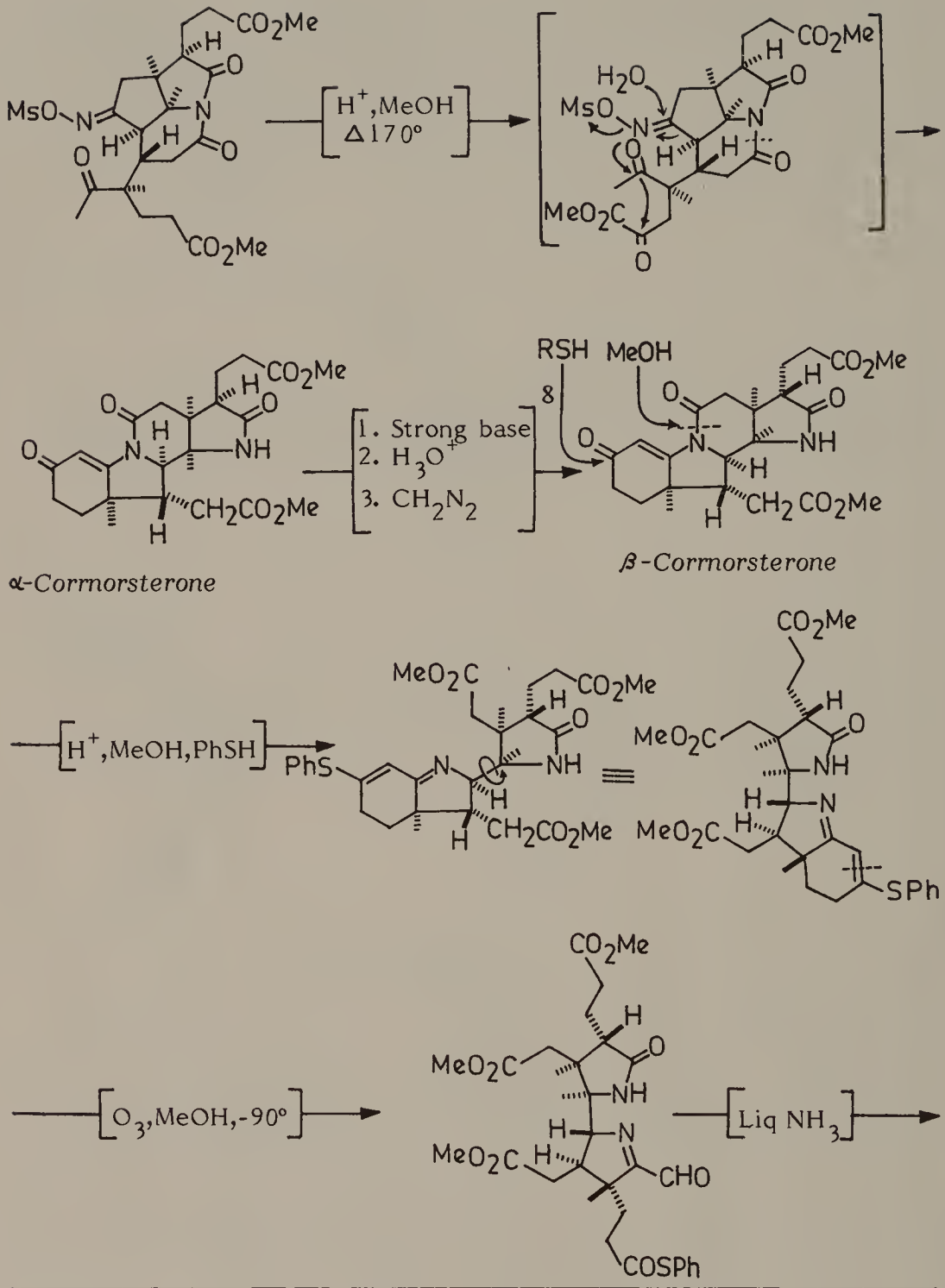


5. The resolution was carried out via the phenylethyl urea derivative. The diastereomers could easily be separated and then converted to the optically active amines by pyrolysis.

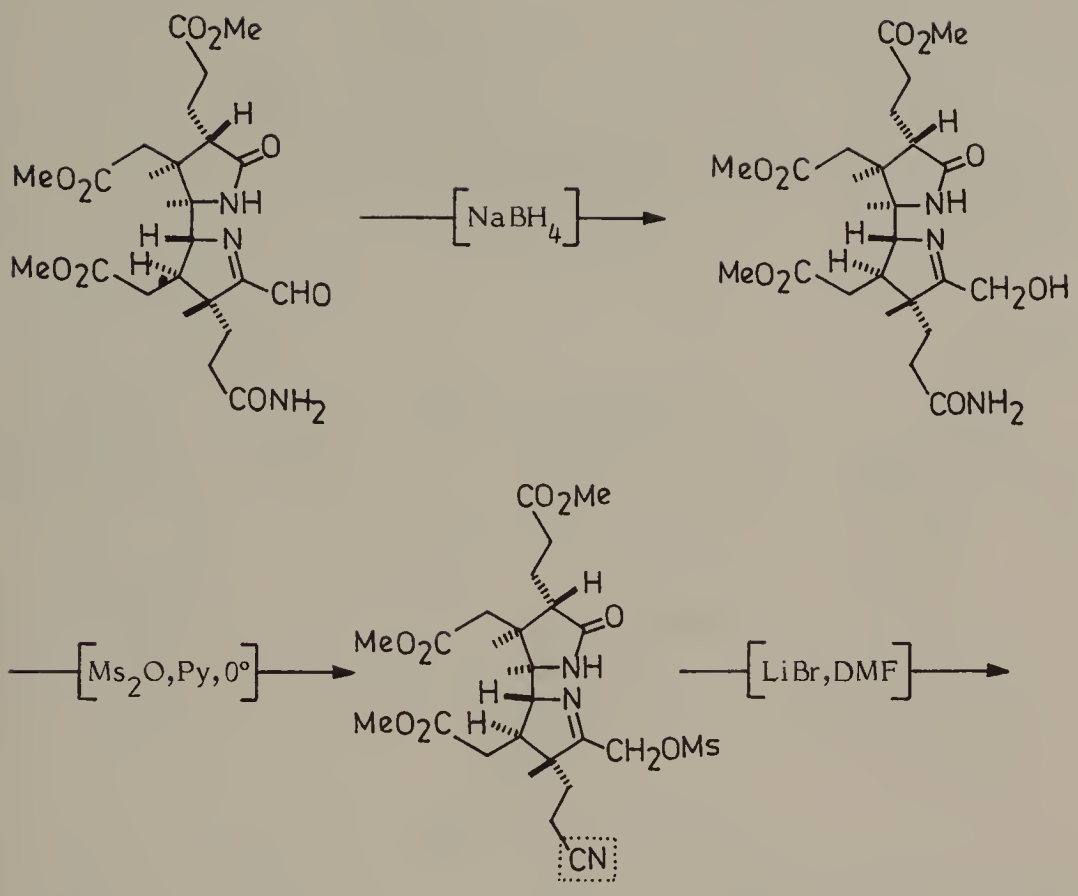
6. The alternative mode of cyclization, which would result in a β-bridgehead hydrogen is precluded on steric grounds.

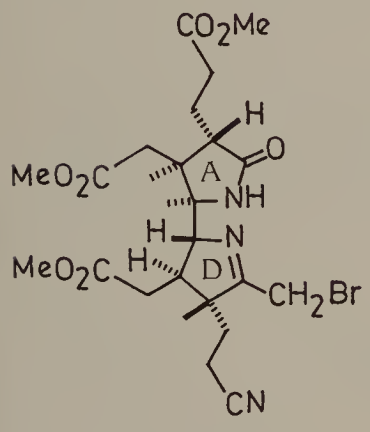


7. The less hindered oxime is selectively cleaved by nitrous acid.



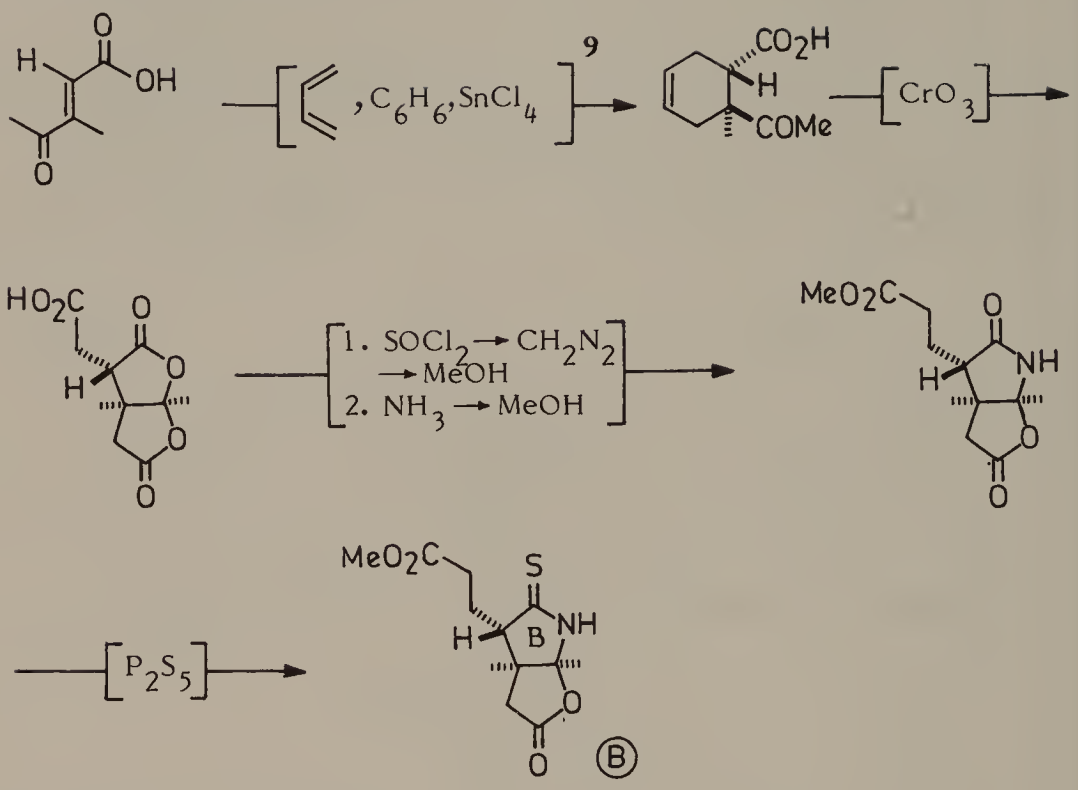
8. The β-isomers in contrast to α-isomers undergo facile ring opening.



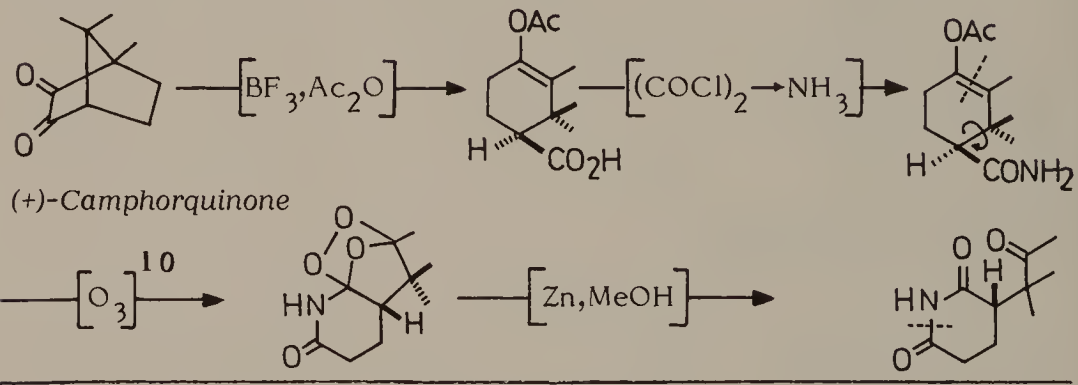


Cyanobromide

Preparation of Unit (B)



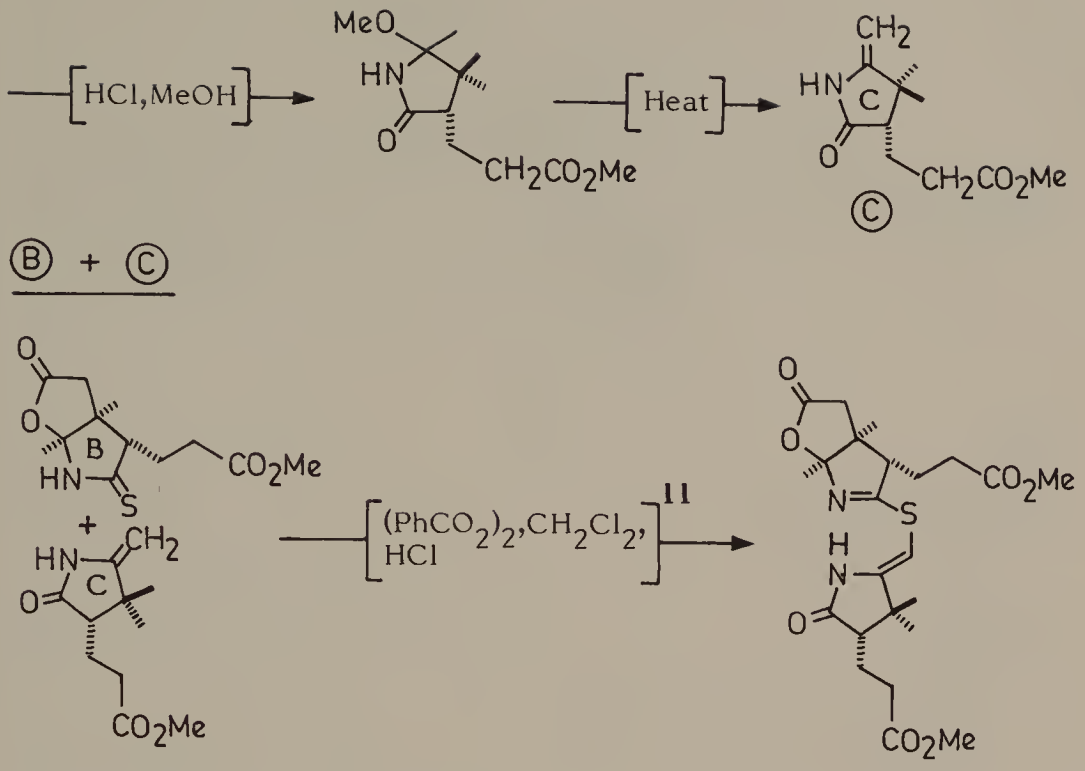
Preparation of Unit (C)



(+)-Camphorquinone

9. The adduct is resolved via ∝-phenylethylamine salt.

10. Ozone transforms the double bond to a mixed anhydride at one end and a ketone oxide at the other. Subsequent interaction of the amide group with the anhydride, results in a succinimide wherein the ketone oxide undergoes cycloaddition with one of the lactam carbonyls, to yield the 'false' ozonide.



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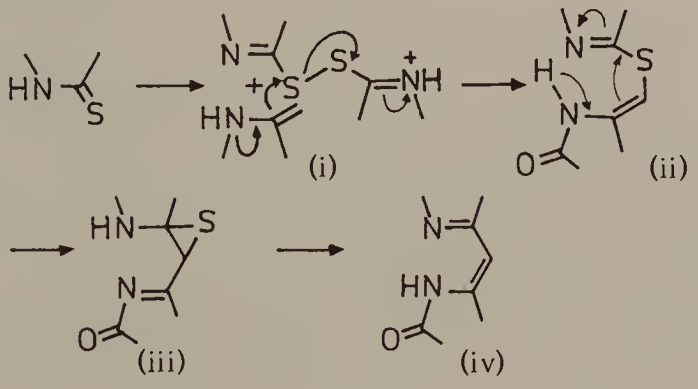
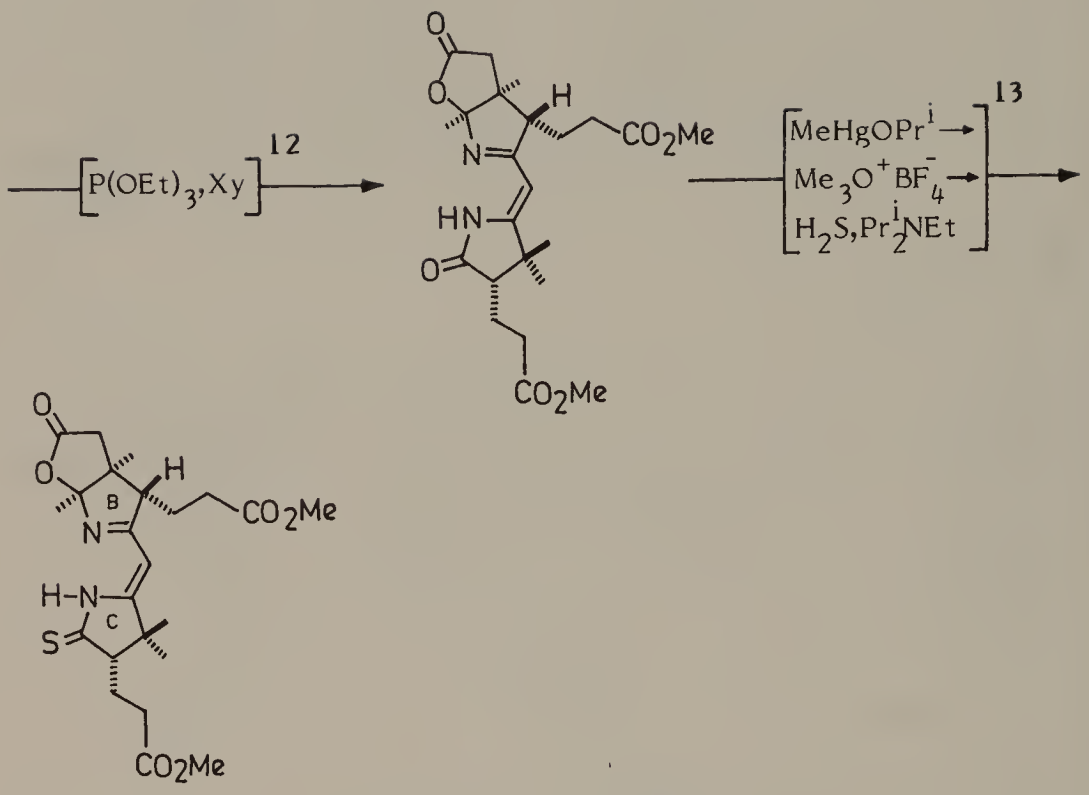
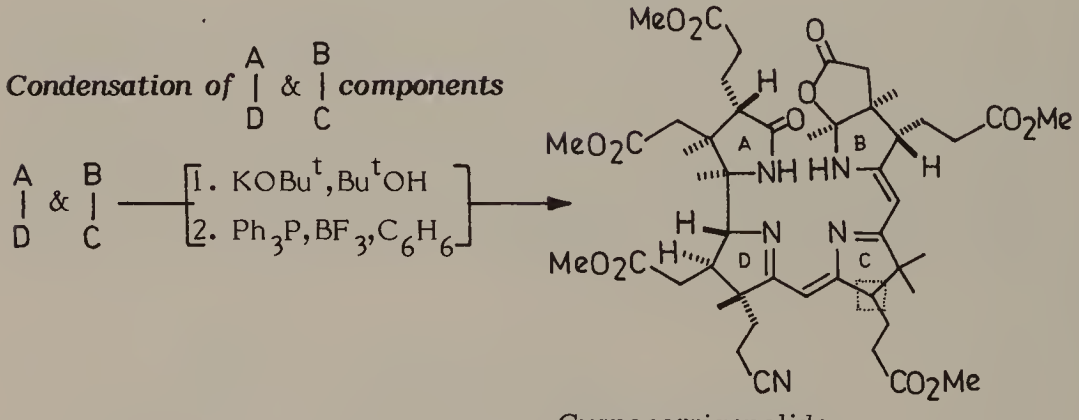
11. The central problem in construction of this component, and in corrin synthesis in general, was the production of the vinylogous amidine system, which was solved using the method of sulfide contraction via oxidative and alkylative coupling of the units B&C. The reaction involves oxidation of the thiolactam to a disulfide (i), followed by nucleophilic attack by the methylidene carbon of the enamide to form the thioiminoenamide (ii), which is suitably disposed for intramolecular enamide-imine attack to construct the critical C-C bond resulting in an episulfide formation (iii); the latter undergoes S-extrusion under the influence of a suitable sulfur acceptor e.g. phosphine or phosphite, to form the desired vinylogous amidine system (iv).





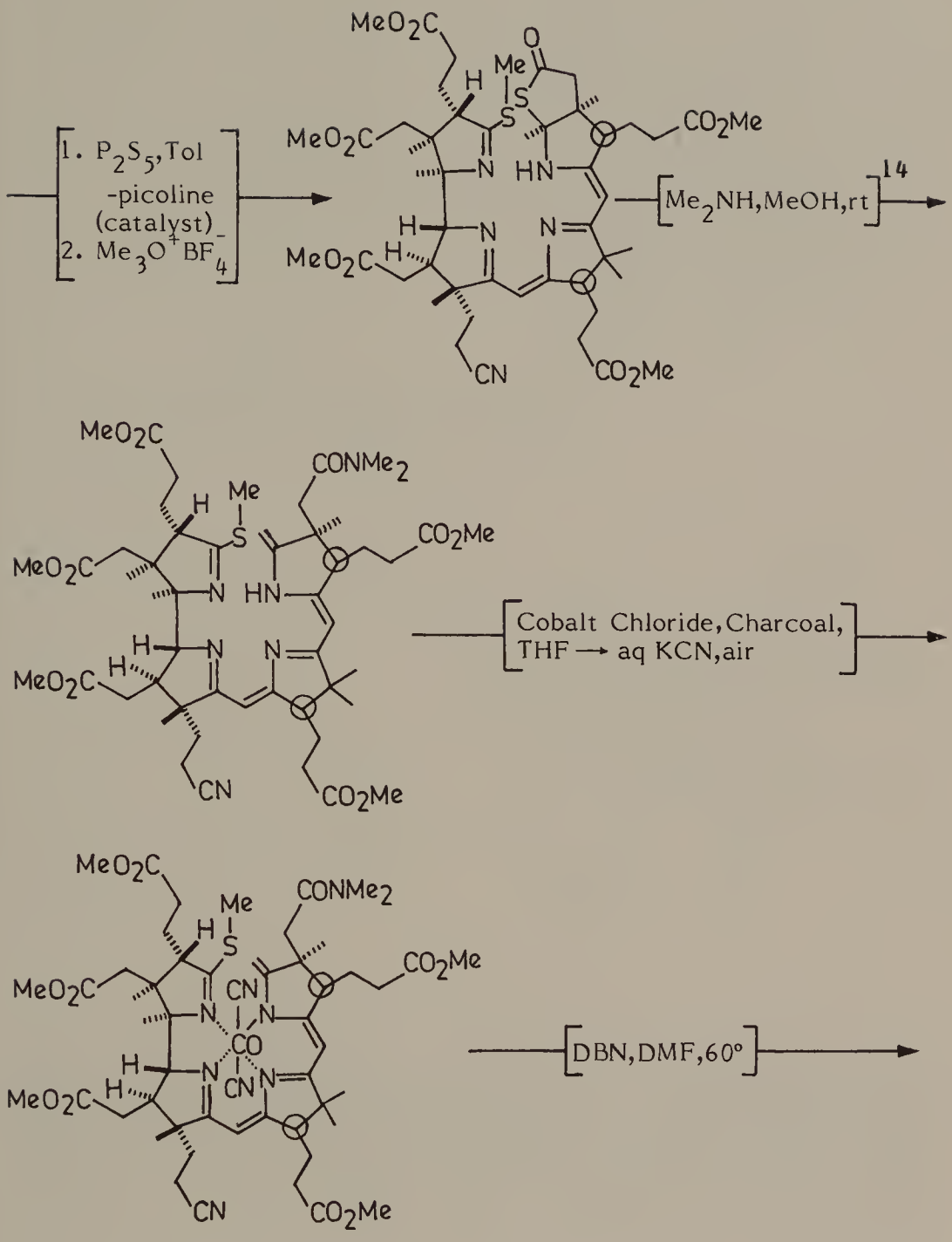
Condensation of A | D & B | C ***components***



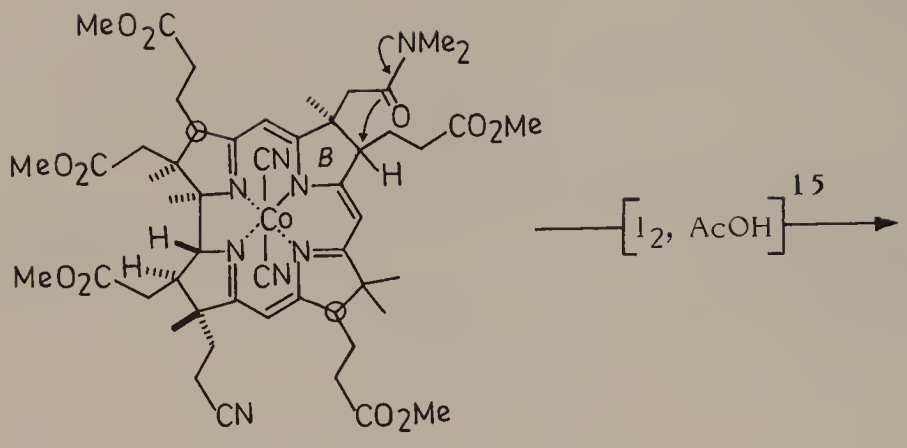
Cyanocorrigenolide

12. Since C-8 is prone to epimerization the product obtained was a mixture of C-8 epimers. This, however, did not represent a serious problem since it was known that the natural configuration at this site was more stable and restoration of correct stereochemistry at a later stage was possible.

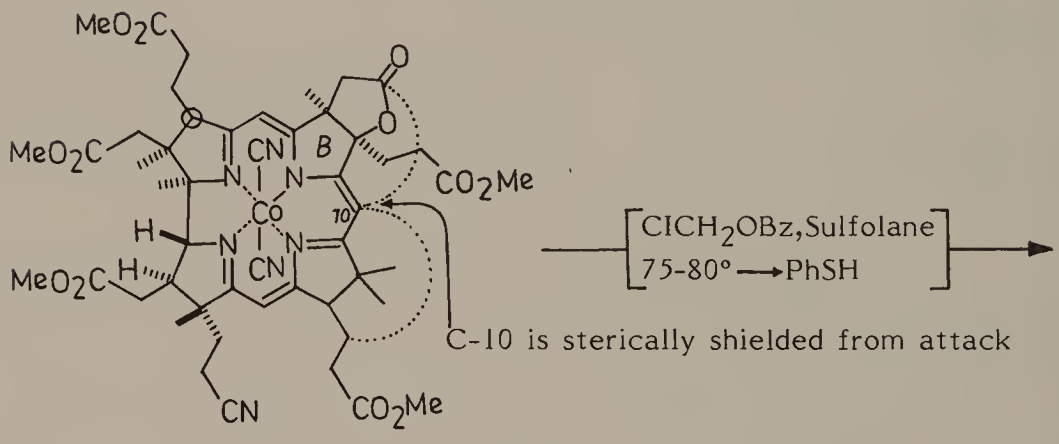
13. Since P_2S_5 attacks both the lactone and the lactam function in the B/C component with equal facility, it was necessary to resort to intermediate conversion of the free lactam to a methyl-mercury complex which allowed specific activation of the lactam oxygen towards attack by the alkylating agent, without affecting the lactone carbonyl.



14. The exocyclic ethylidene is not very stable, and under equilibrium conditions results in the undesired endocyclic compound.



Bisnorcobyrinic acid abdeg pentamethyl ester c dimethylamide f nitrile



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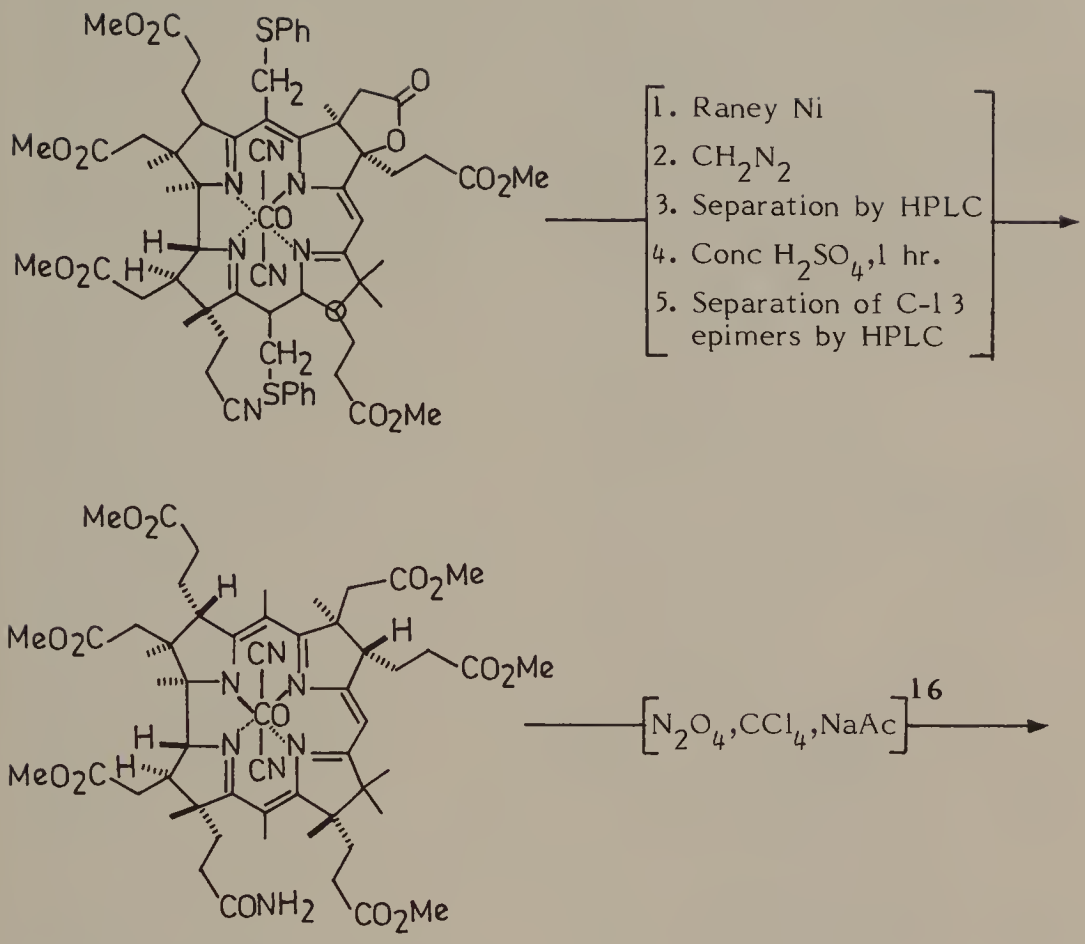
15. Alkylation procedures that worked well at unhindered meso positions of model corrin complexes failed in the more complex case in hand, presumably due to severe steric crowding around all the three meso positions. However, using the oxidative lactone formation on ring B, a procedure which finds precedence in vitamin B_{12} chemistry, it was possible to introduce an additional degree of steric hindrance around C-10 and at the same time afford greater access by alkylating reagents to the other two meso positions.



Cobyrinic acid
abcdeg hexamethyl ester f Amide

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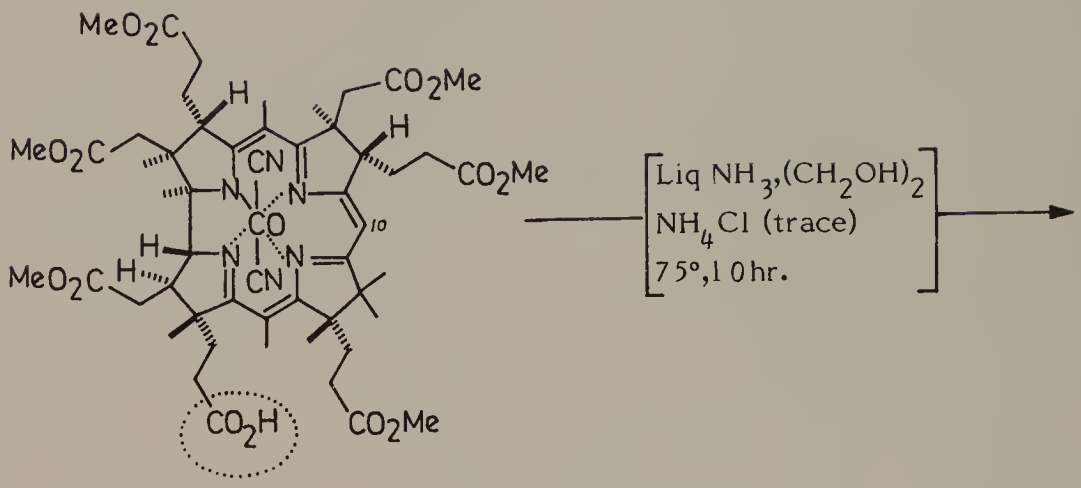
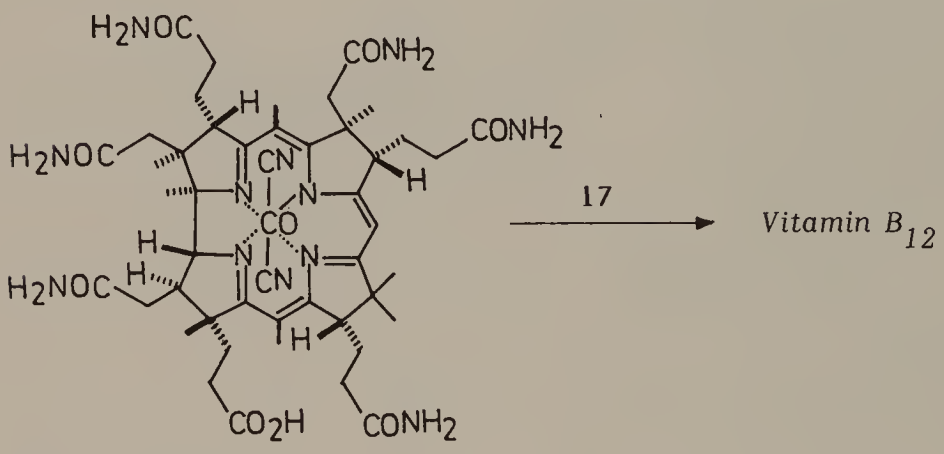
16. Transformation of the f amide to the corresponding f acid was effected conveniently by treatment with nitrogen tetroxide in carbon tetrachloride in the presence of sodium acetate. Conventional deamination of the amide using nitrous acid resulted in nitrosation at C-10.



Cobyrinic acid
abcdeg Hexamethylester
(f Acid)



Cobyric acid[17]

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17. The final stages of the synthesis leading from cobyric acid to vitamin B12 have already been accomplished by Friedrich et al (4).

The compounds synthesised having asymmetric centres were racemic products unless indicated with the appropriate sign or symbol.

The unspecified alkyl groups possess unbranched (normal,n) chains.

I. CARBON-CARBON BOND FORMING REACTIONS

IV. PROTECTING GROUPS

V. USEFUL SYNTHETIC PREPARATIONS

A. Functional Group Preparations

B. Ring Enlargement and Contraction

VI. SYNTHESIS OF HETEROCYCLES