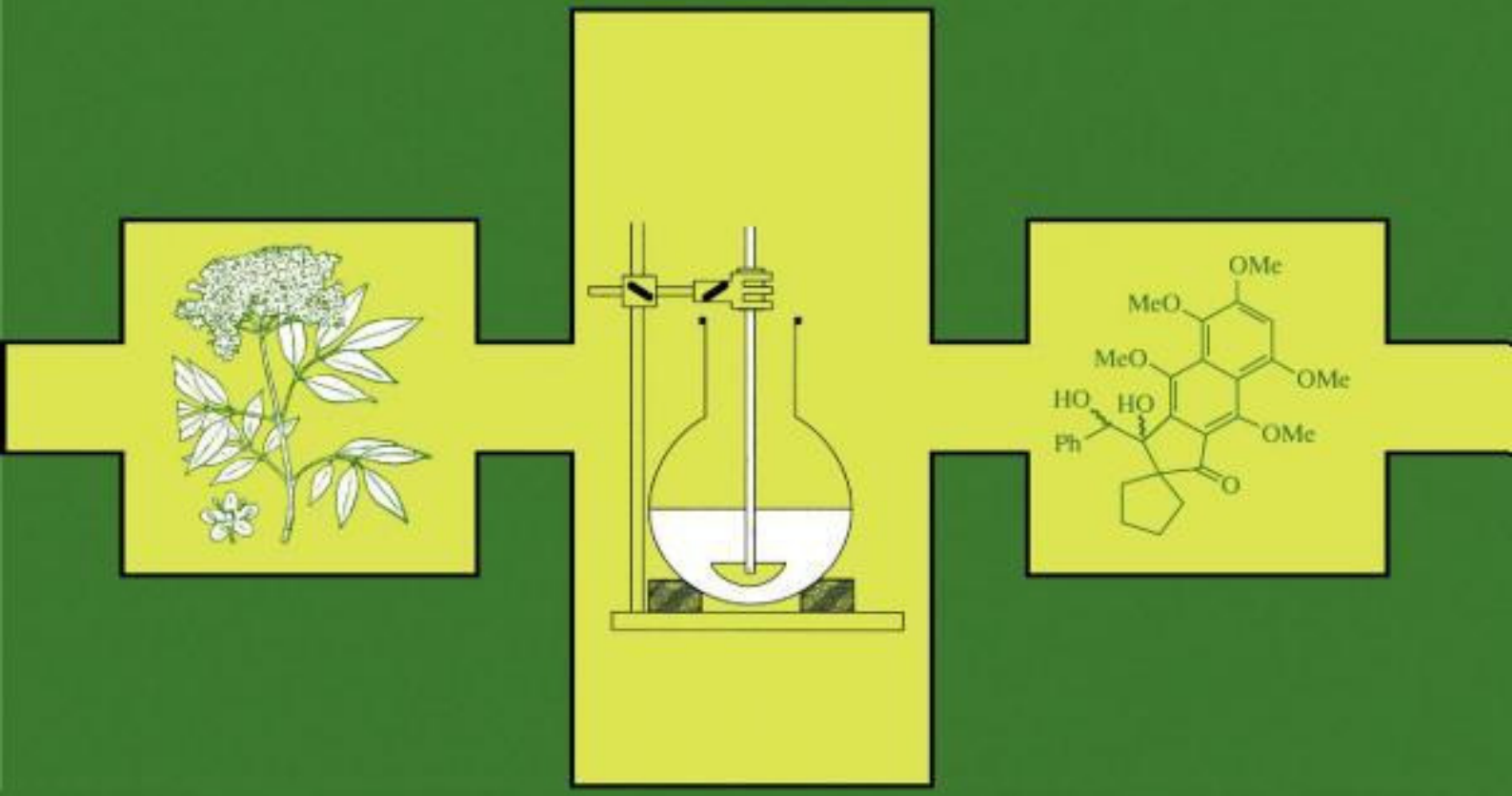
Studies in Natural Products Chemistry

Atta-ur-Rahman/Editor



Volume 16

Stereoselective Synthesis (Part J)

Elsevier

FOREWORD

Natural product chemistry continues to be a treasure-house of a growing diversity of natural products, many with interesting biological activities. The present volume, the 16th of this Series, contains comprehensive reviews on synthetic approaches to the antitumor antibiotics actinobolin and bactobolin, fredericamycin A, the glycosidase inhibitor siastatin A, enantioselective synthesis of a number of natural products starting from cyclic monoterpenoids, stereoselective synthesis of iridoids and brassinosteroids, use of organopalladium compounds in the synthesis of prostaglandins and alkaloids as well as the synthesis of amino acids using transition metal organometallic methods. Recent advances in the synthesis of piperidine and indolizidine alkaloids, aporphine alkaloids, neolignans, pterocarpans, 2-aryl-2,3-dihydrobenzoquinones, photooxygenation of 4-substituted phenols, the use of furan, γ-butyrolactones and fluoro-β-lactams in natural product synthesis, are also covered. It is hoped that the articles written by eminent experts will be enthusiastically received by the readers.

I wish to express my thanks to Mr. Ather Ata for his assistance in the preparation of the index.I am also grateful to Mr. Wasim Ahmad, Mr. Asif Khan and Mr. Shabbir Ahmad for the typing work and Mr. Mahmood Alam for secretarial assistance.

December 1994

Atta-ur-Rahman
Editor

Preface

As a natural product chemist interested in biosynthetic mechanisms and the use of enzymes in multi-step synthesis, it was indeed a pleasure to have been asked to write a preface to this volume of studies in Natural Products Chemistry, which, like its predecessors, encompasses a wide range of topics held together by the common theme of synthetic chemistry. The tools of our trade have been honed almost to perfection, and, as can be learned from the contents of this volume, progress in the synthesis of the most complex natural products continues at an exponential rate. Although the original *raison d' être* for synthesis has now been replaced with the much broader goal of molecular recognition of the synthetic target by the biological receptor, organic synthesis remains at the center of gravity of our discipline, both in academia and (for obvious reasons) in industry.

The editor of the series, Professor Atta-Ur-Rahman is to be congratulated, for once again he has gently elicited a further fifteen contributions which are at the cutting edge of Contemporary Synthetic Chemistry.

This series will surely stand as a major reference work covering all aspects of this field and is particularly timely, thanks to the global renaissance of natural product chemistry.

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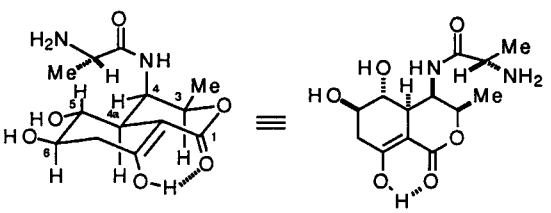
Atta-ur-Rahman (Ed.) *Studies in Natural Products Chemistry, Vol. 16*

Total Synthesis of the Microbial Antitumor Antibiotics Actinobolin and Bactobolin

Steven M. Weinreb

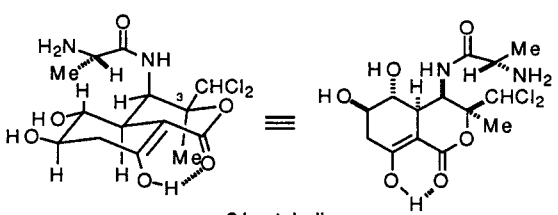
1. INTRODUCTION

Approximately twenty five years ago Haskell and Bartz at Parke, Davis and Co.[1] isolated actinobolin (**1**) from submerged aerated broth cultures of *Streptomyces griseoviridus* var. atrofaciens originating in a Georgia soil sample. This compound was found to inhibit growth of both gram-positive and gram-negative bacteria.[2] In addition, actinobolin has been reported to have weak antineoplastic activity [3] as well as dental cariostatic activity.[4] It has been found that actinobolin interferes with protein synthesis at a late stage in mammalian cells and this



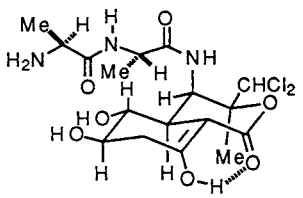
1 actinobolin

phenomenon may account for the biological activity of the metabolite.[5] More recently, actinobolin was shown to have immunosuppressive activity.[6] The structure and absolute stereochemistry of actinobolin was formulated as shown in **1** by application of an elegant combination of chemical degradation and spectroscopic methods.[7,8] Stereostructure **1** was subsequently fully confirmed by X-ray crystallography.[9]

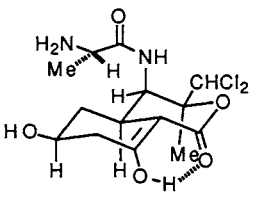


2 bactobolin

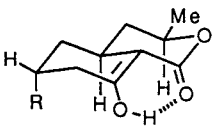
In 1979, a congener of actinobolin, bactobolin (**2**), was isolated from *Pseudomonas yoshitomiensis* Y-12278.[10,11] Bactobolin is structurally identical to actinobolin except for the unusual dichloromethyl group at C-3.[12] This metabolite was also found to have significant antibacterial activity.[10] However, bactobolin shows considerably higher potency in antitumor screens than does bactobolin.[13,14] Two closely related bactobolin analogs **3** and **4** have been isolated from *Pseudomonas* and were also found to have good antitumor activity.[15] In addition, a number of semi-synthetic analogs of bactobolin have been prepared and tested for biological activity.[16] It might be noted that two simpler but structurally similar compounds, ramulosin (**5**)[17] and 6-hydroxyramulosin (**6**),[18] have been isolated from the fungus *Pestalotia ramulosa*. These metabolites undoubtedly arise from a biogenetic pathway closely related to that for actinobolin and bactobolin.



3 Y-12896



4 Y-14556



5 R=H ramulosin
6 R=OH 6-hydroxyramulosin

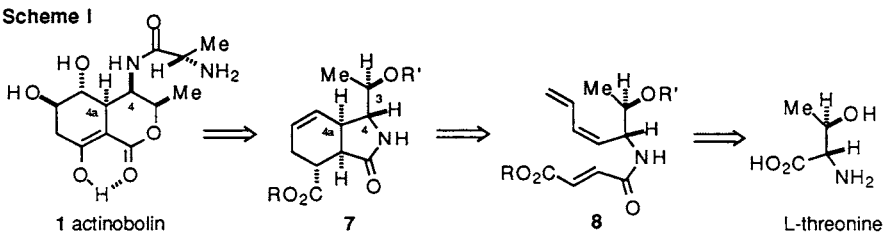
Actinobolin and bactobolin provide appealing challenges for the synthetic chemist. These relatively small natural products incorporate a high level of functionality and both contain five contiguous chiral centers. This challenge has been accepted to date by six groups, which have described approaches to actinobolin and/or bactobolin.

2. APPROACHES TO ACTINOBOLIN (1)

2a. Ohno Synthesis

In 1984, Ohno and coworkers reported the first successful routes to actinobolin.[19] This group chose to utilize a strategy involving an intramolecular Diels-Alder reaction as a key step for construction of the carbocyclic ring of **1** and for establishment of the stereochemistry at C-3,4 and 4a (**Scheme I**). Thus, it was planned to prepare a Z-diene **8**, which was expected to cyclize

Scheme I

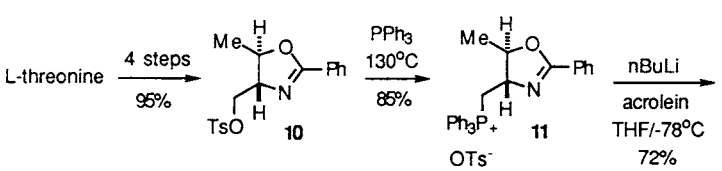


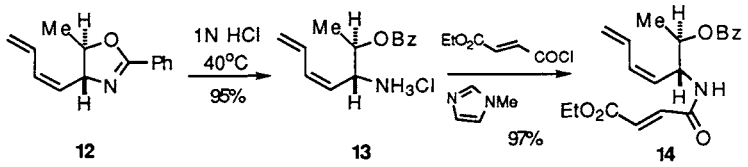
1 actinobolin — **7** — **8** — L-threonine

to **7**, thereby controlling C-3,4 vs C-4a stereochemistry. Based upon literature precedent in intramolecular Diels-Alder chemistry, the corresponding E-diene could be anticipated to show low stereoselectivity in the [4+2]-cycloaddition.[20] L-Threonine was intended to provide the correct absolute configuration at C-3,4.

Therefore, L-threonine was converted in high yield via a known sequence[21] of steps to oxazoline **10** (**Scheme II**). This compound was then transformed to phosphonium salt **11**, which underwent a Wittig reaction with acrolein to yield a 97:3 mixture of Z-diene **12** and the corresponding E-isomer. Hydrolysis of the oxazoline afforded amine salt **13** which was acylated to give the requisite Diels-Alder substrate **14**.

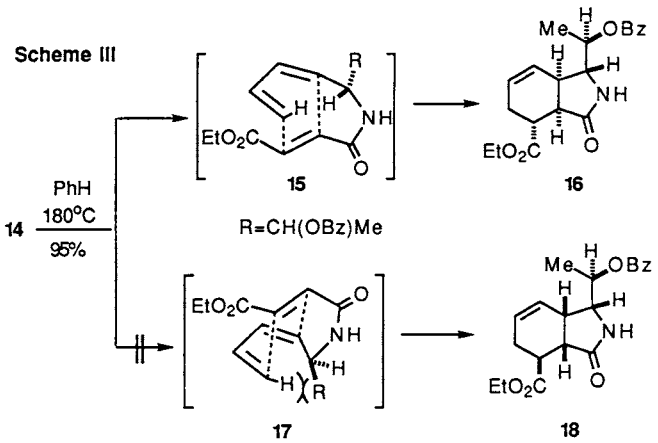
Scheme II





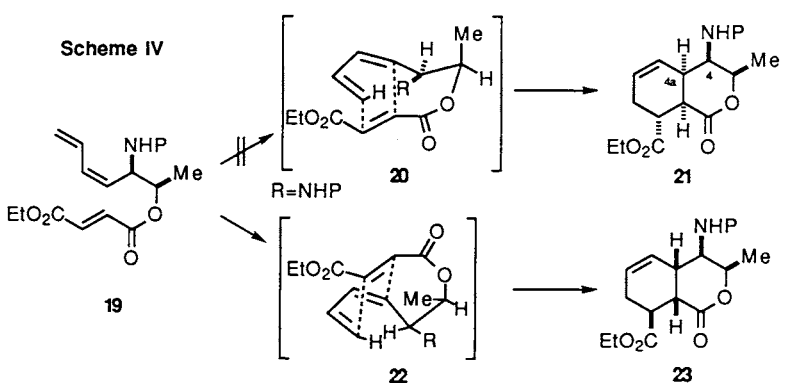
Thermolysis of **14** in benzene at 180°C afforded a high yield of the desired cycloadduct **16** along with a trace of another isomer which was not characterized (**Scheme III**). It is believed that adduct **16** arises via Diels-Alder transition state **15**. The alternative transition state **17**, which would lead to isomeric product **18**, is destabilized relative to **15** by a steric interaction between a diene vinylic hydrogen and the large benzoyloxyethyl group. Thus, this cycloaddition step stereospecifically established the correct C-4/C-4a stereochemistry of actinobolin.

Scheme III



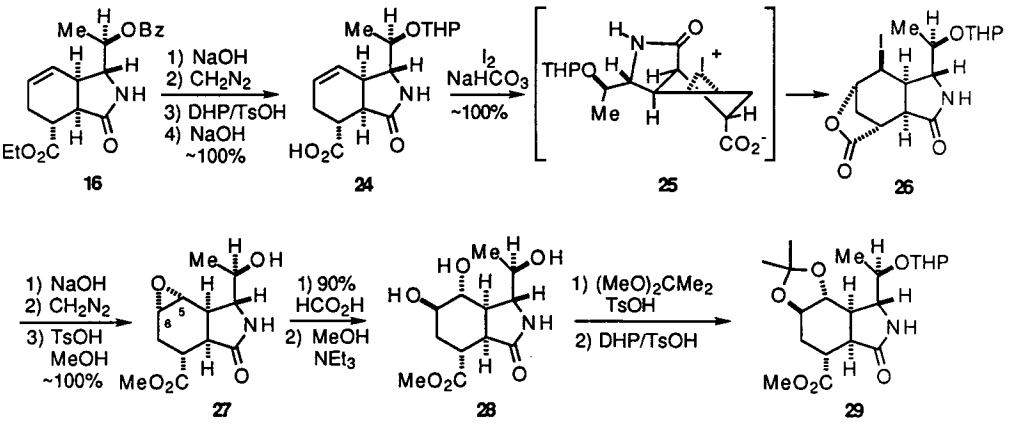
An alternative and potentially more direct strategy to the actinobolin bicyclic ring system might have, in principle, involved a Diels-Alder precursor like **19**, where the dienophile is tethered to the C-3 oxygen rather than the C-4 amino group. Such a route would not require a lactam to lactone rearrangement as needed in the case of **16** (*vide infra*). However, analysis of the transition states for cycloaddition of **19** indicated that conformation **20**, leading to the desired adduct **21**, would be destabilized relative to **22**, which would afford **23** (**Scheme IV**). Therefore, this sequence was not pursued.

Scheme IV



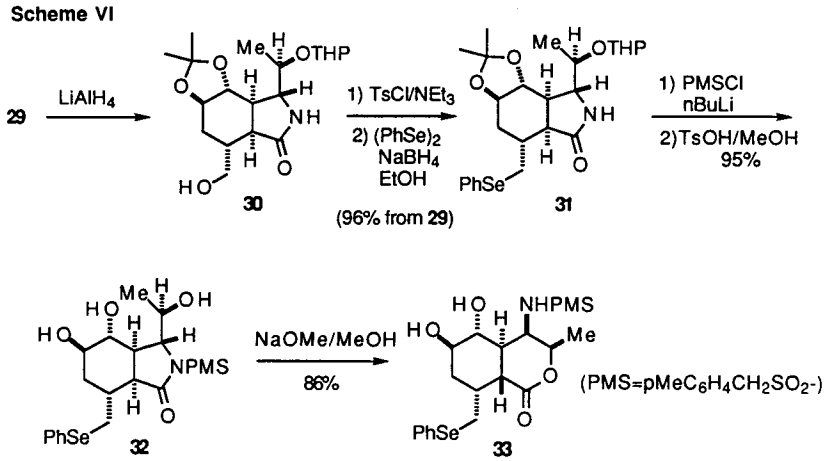
In order to continue the synthesis, cycloadduct **16** was converted in four steps in high yield to acid THP ether **24** (**Scheme V**). Functionalization of the olefinic double bond of **24** to establish the proper C-5,6 diol stereochemistry began with iodolactonization via **25** to yield **26**. Lactone opening under basic conditions led to the desired α-epoxide in the form of hydroxy ester **27**. A key step in the sequence was diaxial opening of epoxide **27** by attack at the less hindered C-6 carbon to afford trans diol **28**. This compound now possesses all five contiguous chiral centers of actinobolin (**1**). Protection of the 1,2-diol functionality as the acetonide and the secondary hydroxyl as the THP ether provided **29** in high yield from **27**.

Scheme V



The remaining stages of the total synthesis involved degradation of the carboxyl group to a ketone and rearrangement of the γ-lactam to a δ-lactone. Towards this end, ester **29** could be reduced selectively to hydroxymethyl compound **30** (**Scheme VI**), which was then converted to phenyl selenide **31**. In order to open the lactam ring in **31** it was necessary to first activate the

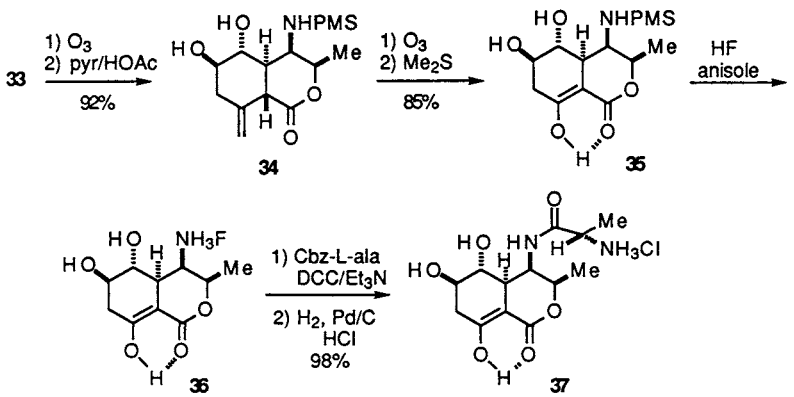
Scheme VI



system, which was effected by attaching a sulfonyl group to the lactam nitrogen. Thus, compound **31** was treated with p-methylbenzylsulfonyl chloride[22] to afford, after THP ether and acetonide removal, N-sulfonyl lactam triol **32**. Exposure of **32** to sodium methoxide gave the desired lactone **33**. The same PMS group used to facilitate this rearrangement now acts as a suitable protecting group for the actinobolin nitrogen.

Several attempts were made to next remove the PMS group, but the system appeared prone to rearrange back to a γ-lactam. Therefore, it was necessary to first elaborate the enol lactone moiety of **1**. In two successive ozonolyses, seleno ether **33** was converted to exomethylene compound **34** and then to enol δ-lactone **35 (Scheme VII)**. It was now possible to

Scheme VII

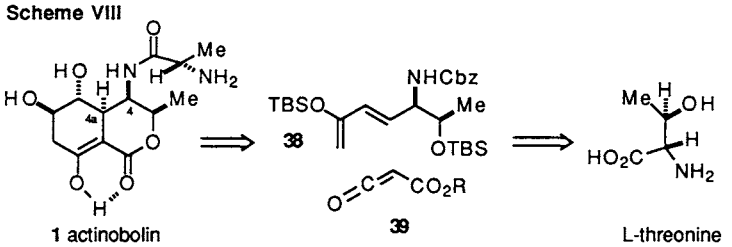


remove the PMS protecting group with liquid HF[22] to produce the amine salt **36** in high yield. Completion of the synthesis entailed installation of the alanine residue leading to (+)-actinobolin hydrochloride (**37**). This first total synthesis of scalemic actinobolin required 29 steps from L-threonine, although, despite the length of the sequence, an overall yield of 28% could be achieved.

2b. Kozikowski Synthesis

In 1986, Kozikowski and coworkers reported a total synthesis of actinobolin (**1**) which also utilized a Diels-Alder strategy, but in this case an intermolecular cycloaddition was applied.[23] As in the Ohno synthesis, L-threonine was chosen as the starting material and the

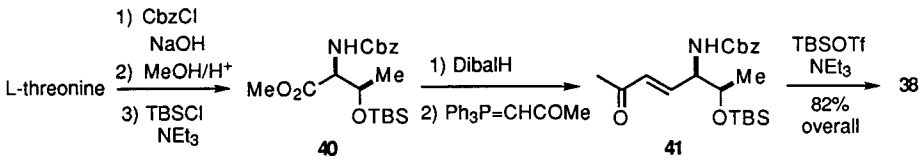
Scheme VIII



proposed strategy was to convert it to diene **38 (Scheme VIII)**. It was hoped that Diels-Alder cycloaddition of **38** with a carboxy ketene equivalent **39** would be facially selective, establishing the proper C-4/C-4a configuration of actinobolin.

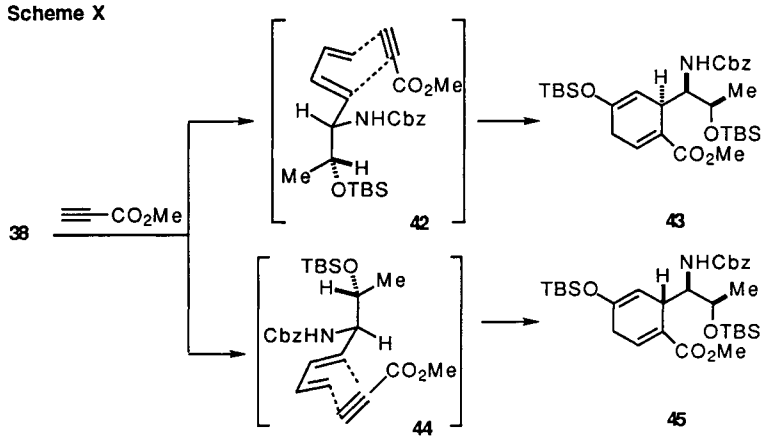
Therefore, L-threonine was protected as derivative **40** in three steps (**Scheme IX**). Reduction of the ester group of **40** to the aldehyde and subsequent Wittig reaction afforded E-enone **41**. Conversion of **41** to the enol silyl ether provided the desired 1,3-diene **38**.

Scheme IX



Several attempts were made to utilize β-substituted propiolate derivatives as equivalents of ketene **39** in Diels-Alder reactions with diene **38**. However, since none of this work was fruitful, methyl propiolate itself was of necessity explored as the dienophile (**Scheme X**). Treatment of diene **38** with this acetylene at 110°C unfortunately gave about a 3:1 mixture (85% yield) of the undesired epimeric C-4a adduct **45** and the desired product **43**. At 220°C the ratio improved somewhat to 1.7/1 of **45/43**. High pressure promoted cycloaddition at room temperature provided a 10:1 mixture, again favoring the undesired adduct.

Scheme X

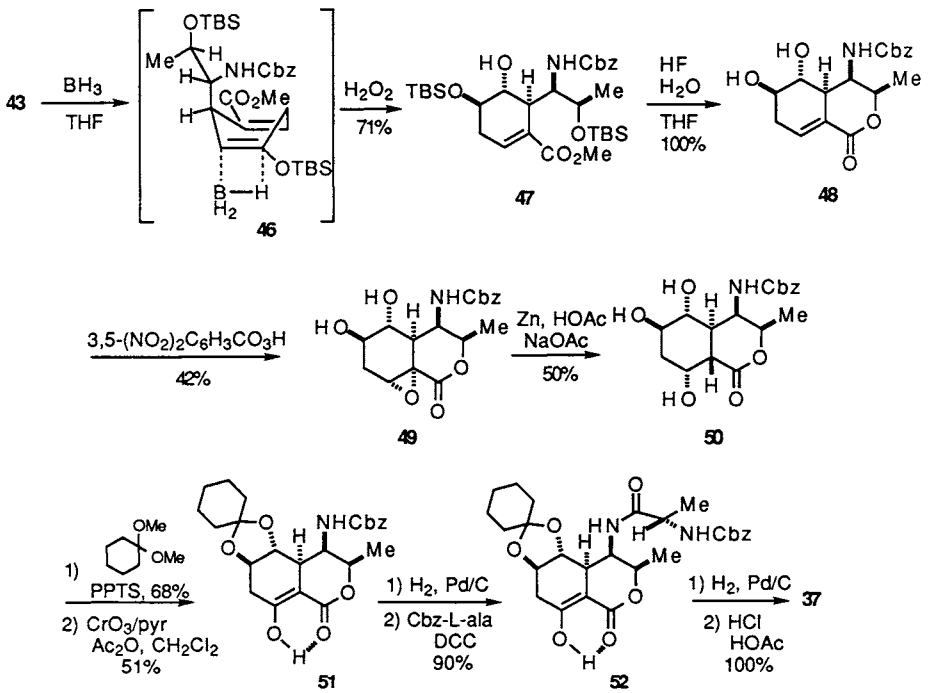


Formation of **45** as the major stereoisomeric product of cycloaddition can be rationalized by inspection of transition states **42** and **44** (**Scheme X**). It is believed that in a conformation such as **42** with the large nitrogen substituent in an "inward" position, there is a steric interaction with the carboxyl group of the linear acetylenic dienophile. In the alternative conformer shown in **44** with the nitrogen substituent in an "outward" position, this interaction is relieved and thus **45** is the principal adduct. In some studies by others of related chiral diene Diels-Alder reactions, but with olefinic dienophiles,[24] it seems that a conformation with the large α-substituent in an "inward" position is preferred. Presumably the geometric arrangement at an sp^2 center minimizes steric congestion in this diene conformation.

Although the requisite adduct **43** is the minor product of cycloaddition, it was possible to convert this compound in a relatively short sequence to actinobolin. Hydroboration of **43** could be effected in good yield to afford the trans-diol derivative **47** (**Scheme XI**). This reaction probably occurs via attack on a boat-like cyclohexadiene anti to a quasi-axial sidechain as shown

in **46**. The large nitrogen-containing chain is presumably in an axial position to minimize $A^{1,2}$-strain. Silyl ether cleavage with HF provided δ-lactone **48**. Oxidation of **48** with 3,4-dinitroperbenzoic acid gave the α-epoxide **49** in 42% yield along with 24% of recovered starting material. Zinc reduction of **49** afforded triol **50** along with 33% of α,β-unsaturated lactone **48**. Next, the 1,2-diol functionality of **50** was protected as the cyclohexylidene derivative and the remaining alcohol group was oxidized to yield enol lactone **51**. To complete the synthesis, **51**

Scheme XI

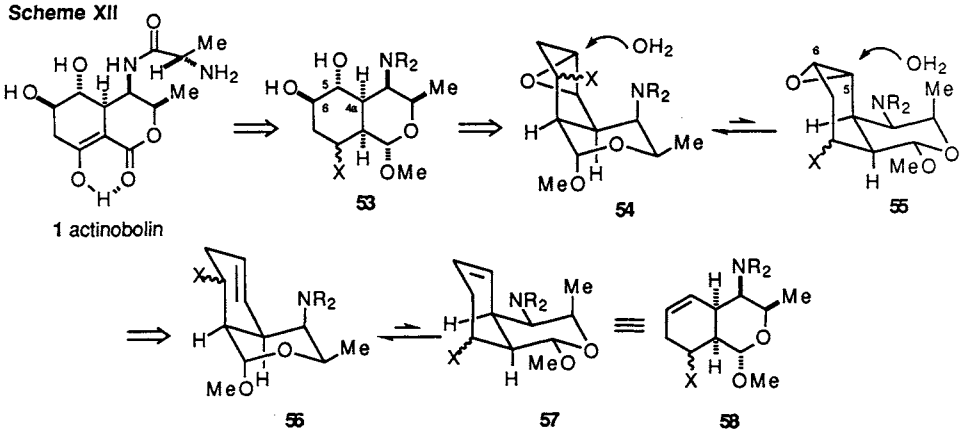


was converted to the primary amine and acylated with Cbz-L-alanine to produce **52**. Finally, Cbz and ketal protecting group removal gave (+)-actinobolin hydrochloride (**37**). This total synthesis required only 17 steps from L-threonine. However, the overall yield was not high due in large part to the formation of the desired adduct **43** as the minor product in the key Diels-Alder step.

2c. Fraser-Reid Approach

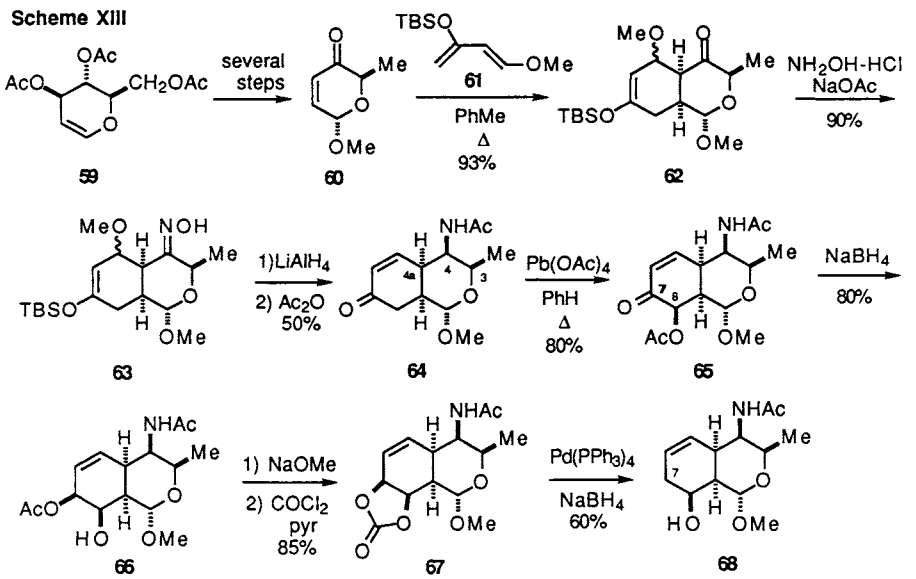
Fraser-Reid and coworkers described a carbohydrate-based route to N-acetyl-desalanylactinobolin in 1985.[25] Their strategy involved preparation of a bicyclic intermediate like **58** via Diels-Alder chemistry (**Scheme XII**). It was hoped that **58**, because of an anomeric effect, would prefer conformation **56** rather than **57**. It was anticipated that **56** would undergo epoxidation from the less hindered α-face to produce **54**, once again held in the conformation shown by an anomeric effect. Hydrolytic diaxial opening of epoxide **54** would then generate the necessary C-5,6 diol stereochemistry. The alternative α-epoxide conformer **55** would be disfavored, as would diaxial opening at the more hindered C-5 position.

Scheme XII



The starting material for this sequence was commercially available triacetyl glucal (**59**), which had previously been converted to chiral enone **60** (**Scheme XIII**).[26] Diels-Alder reaction of **60** with Danishefsky diene **61** gave adduct **62**, which was converted to oxime **63**. Reduction of this oxime with lithium aluminum hydride occurred from the less hindered α-face to afford, after N-acetylation, a 4:1 mixture of enone **64** and the corresponding allylic alcohol. The latter compound could be converted to **64** by MnO_2 oxidation. The C-8 oxygen substituent (X in **58**) could be introduced by oxidation of enone **64** with lead tetraacetate, yielding α-acetoxy enone **65**.

Scheme XIII

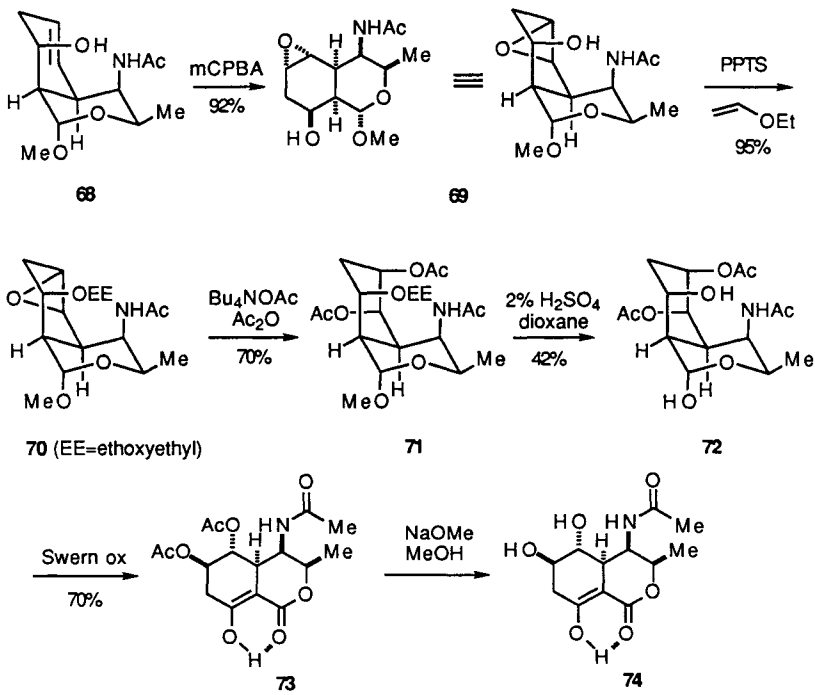


The next task in the synthesis was removal of the unneeded carbonyl oxygen at C-7. Apparently direct methods for this transformation proved unsuccessful, and thus it was necessary to apply a more circuitous route. Therefore, ketone **65** was reduced, giving alcohol **66** in which the acetyl group had migrated. Although palladium promoted deoxygenation of allylic acetate

66 failed, the derived cyclic carbonate **67** could be reduced to olefin alcohol **68**. This reaction presumably occurs via hydride reduction of an intermediate π-allylpalladium species at the less hindered C-7 position.

Epoxidation of **68** proceeded as desired (*cf* **Scheme XII**) to afford the α-epoxide **69** (**Scheme XIV**), which by ^{1}H NMR was found to have the conformation shown, as had been predicted based upon the anomeric effect. The hydroxyl group of **69** was next protected as the ethoxyethyl ether, yielding **70**. Epoxide opening of **70** with tetrabutylammonium acetate was regioselective giving the desired 1,2-diaxial diacetate **71**. Once again, it appears that diaxial attack in **70** at C-6 in the conformation shown is preferred (*cf* **Scheme XII**). Interestingly, NMR indicated that **71** has the conformation indicated despite severe 1,3-diaxial interactions. This conformational form was again attributed to maintaining an anomeric effect.

Scheme XIV



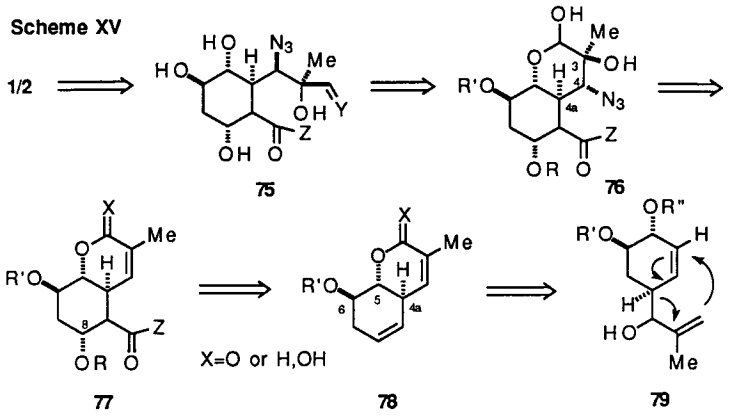
To continue the synthesis, **71** was hydrolyzed to hemiacetal alcohol **72** in moderate yield. Swern oxidation of the 1,3-diol led to enol lactone **73**. Finally, diacetate cleavage provided desalanyl-N-acetylactinobolin (**74**). The synthesis of **74** required 15 steps from the known scalemic enone **60**. However, it seems unlikely that the N-acetyl group of **74** can be removed, and thus a synthesis of actinobolin (**1**) would require repeating the sequence using a more readily removable protecting group.

2d. Danishefsky Route

Danishefsky and coworkers have described an approach to racemic desalanyl-N-acetylactinobolin.[27] Their initial plan was conceived, however, with the intent of constructing bactobolin, although this goal was never achieved. The synthetic strategy (**Scheme XV**) entailed

construction of a system like **78** via suprafacial oxy-Cope rearrangement of **79**. Compound **78** contains three of the chiral centers of the natural products (*i.e.*, C-4a, 5, 6). Functionalization of

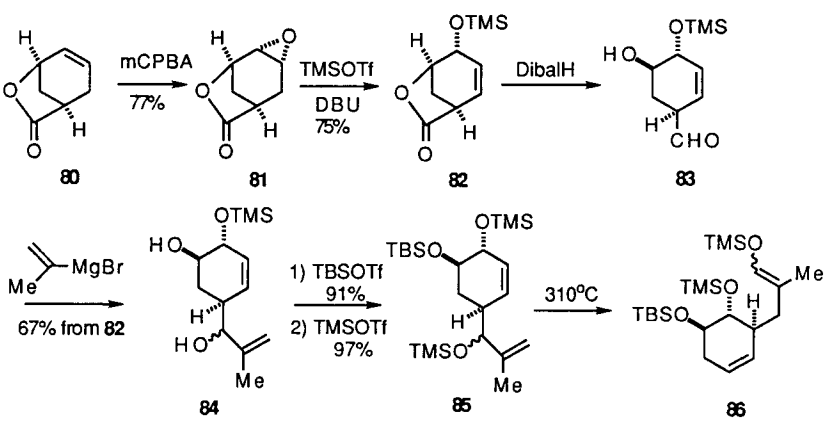
Scheme XV

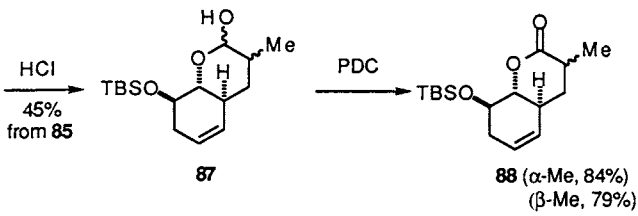


the carbocyclic double bond of **78** was intended to introduce the C-8 oxygen and eventual δ-lactone carbonyl moiety as in **77**. The remaining olefinic group in **77** was to be functionalized to hydroxy azide **76** now possessing all the chiral centers of bactobolin (**2**). Lactal opening of **76** would lead to **75** having a functional group (C=Y) transformable to the dichloromethyl group of **2**. Ring closure of **75** by acylation would give the δ-lactone ring of the natural product.

The synthetic route began with readily available racemic lactone olefin **80**, which could be oxidized to afford α-epoxide **81** along with a trace of the β-isomer (**Scheme XVI**). This epoxide could be rearranged to **82**, which was reduced to hydroxy aldehyde **83** and subjected to isopropenylmagnesium bromide to produce allylic alcohol **84** as a 1:1 mixture of isomers. The ring hydroxyl group of **84** could be selectively silylated, followed by trimethylsilylation of the allylic alcohol, yielding tris-silyl ether **85**. Thermolysis of **85** induced an oxy-Cope rearrangement, as anticipated, to give silylenol ethers **86** as a mixture of E and Z isomers. Exposure of the crude mixture to dilute HCl afforded a separable 3.2:1 mixture of lactols **87**. Each pure lactol isomer could be oxidized to the α- and β-methyl lactone epimers **88** in good yields.

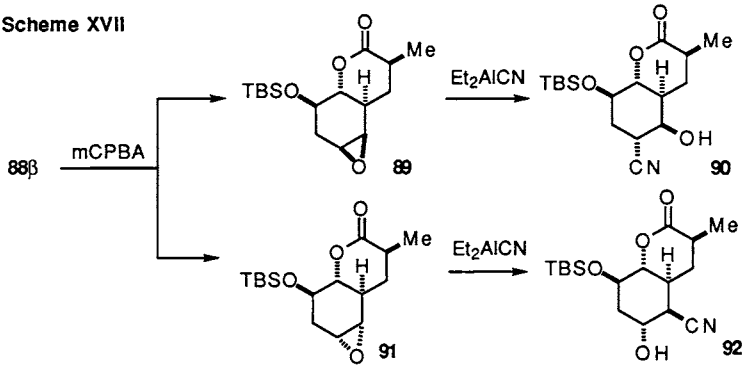
Scheme XVI





The next stage of the synthesis involved functionalization of the olefinic moiety to introduce the C-8 oxygen and the C-1 carbonyl carbon (*cf* **77**). Epoxidation of **88β** with mCPBA afforded predominantly the β-epoxide **89** and a lesser amount (1.8:1) of α-isomer **91** (**Scheme XVII**). Diaxial opening of the major epoxide **89** with Nagata's reagent gave the

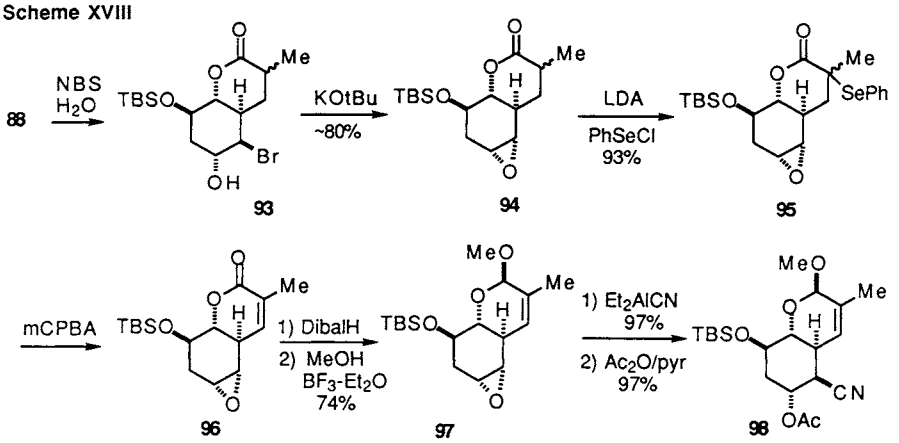
Scheme XVII



undesired regioisomeric cyanohydrin **90**. However, the minor α-epoxide **91** did open to give the requisite cyanohydrin **92**.

Fortunately, an alternative route to the α-epoxide series was found. Thus, treatment of both **88a** and **88b** with aqueous NBS afforded a single bromohydrin **93** in each case (**Scheme XVIII**), which could be cyclized to the α-epoxides **94**. It was decided to next introduce α,β-

Scheme XVIII

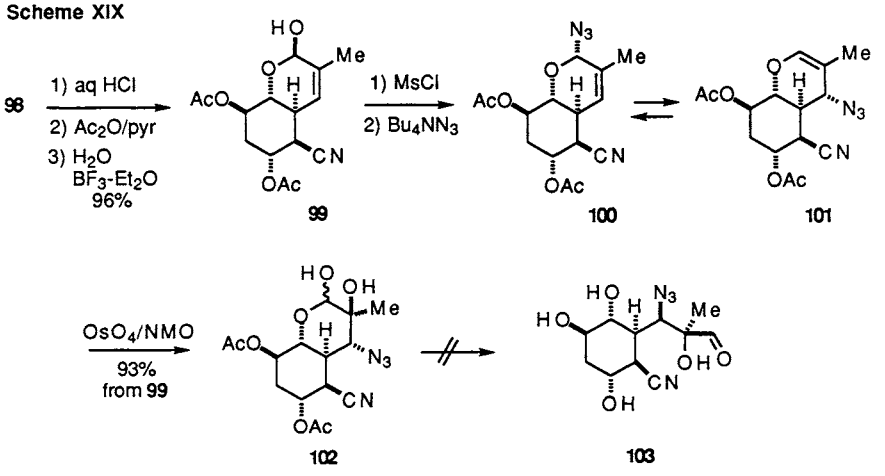


unsaturation into the δ-lactone. Therefore, deprotonation of **94** with LDA and selenation gave **95** as a mixture of isomers (~ 4:3). Oxidation of the major isomer yielded the desired endocyclic α,β-unsaturated lactone **96**. However, the minor isomer of **95** eliminated to afford a 1:1.4 mixture of the desired endocyclic product **96** and the corresponding exocyclic elimination compound.

The lactone functionality of **96** could be reduced to the lactol which could then be converted to a single methyl acetal **97**. Exposure of **97** to diethylaluminum cyanide yielded a single regioisomeric cyanohydrin, which was acetylated to afford **98**.

Studies were next initiated to introduce the C-4 nitrogen into the system. Therefore, **98** was converted in three steps into lactol diacetate **99 (Scheme XIX)**. The lactol was transformed to the corresponding mesylate which reacted with tetrabutylammonium azide to produce an equilibrating mixture of allylic azides **100** and **101**. Exposure of this mixture to osmium tetroxide gave azide alcohol **102** as a mixture of lactol anomers in excellent overall yield. At this

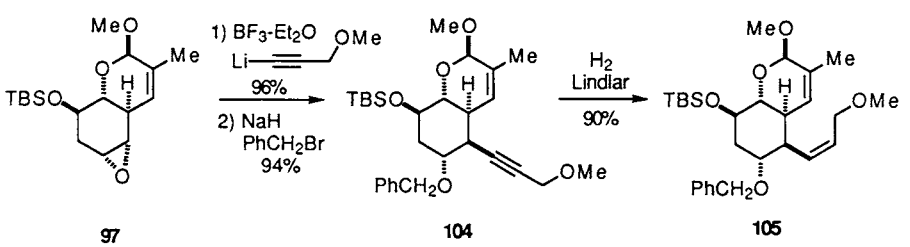
Scheme XIX

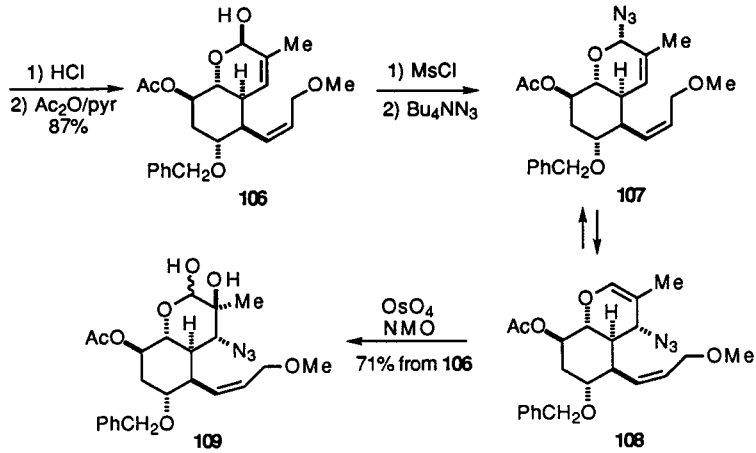


point in the synthesis some serious problems were encountered. Despite considerable effort, the lactol ring of **102** could not be opened to a system equivalent to **103** (*cf* **75**, **Scheme XV**). Moreover, the nitrile functionality could not be transformed to the carboxylic acid. It was therefore decided to back up and replace the nitrile with another carboxylate equivalent, in particular one which might be more amenable to alternative lactol ring opening conditions.

Toward this end, epoxide **97** was opened with an acetylide to give **104** after O-benzylation (**Scheme XX**). It was found best that this compound first be reduced to olefin **105**, which was converted to lactol acetate **106**; and, as done previously, to allylic azides **107** and **108**. Hydroxylation proceeded via isomer **108** to afford hydroxy azide **109**.

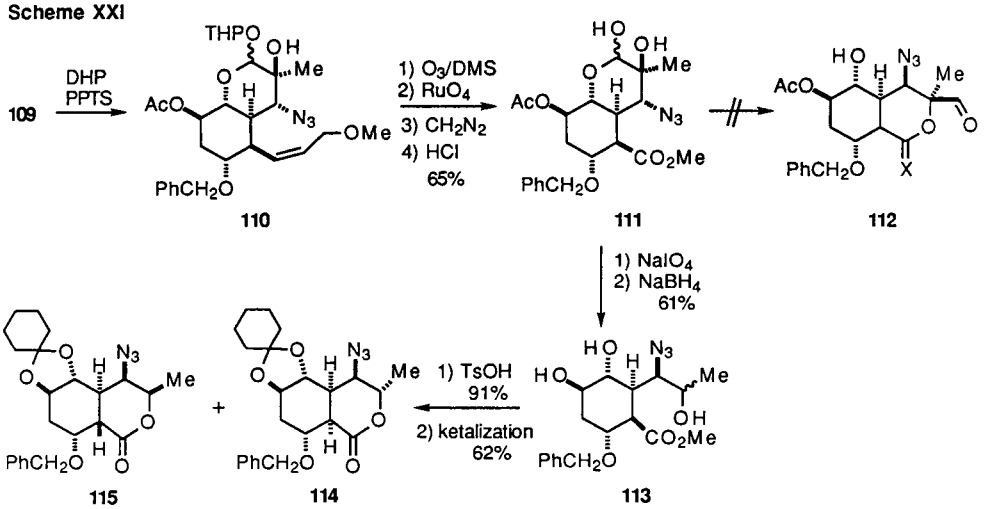
Scheme XX





This compound was next converted to THP ether **110** (**Scheme XXI**). The olefinic sidechain was then cleaved to the aldehyde which was oxidized to the acid and esterified, followed by THP ether removal yielding key intermediate **111**. Unfortunately, all attempts to rearrange lactol ester **111**, or the precursor acid and aldehyde, to a system corresponding to **112** were again unsuccessful.

Scheme XXI

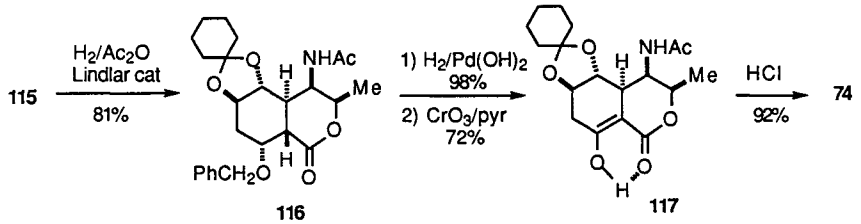


Since this strategy for total synthesis of bactobolin seemed to have run its course, it was decided to use late intermediate **111** in an approach to the actinobolin system. It was found that **111** could be oxidatively cleaved to an α-azido ketone which was reduced to a 1.25:1 mixture of alcohol **113**. This mixture could be lactonized and the resulting diol protected affording a separable mixture of isomeric lactones **114** (minor) and **115** (major). Interestingly, the desired isomer **115** had undergone epimerization to the trans-fused system, although of no consequence to the synthesis.

The requisite stereoisomer **115** was then reduced and acylated to give acetamide **116** (**Scheme XXII**). Removal of the benzyl protecting group and oxidation of the resulting alcohol

with Collin's reagent afforded enol lactone **117**, which was identical to a sample prepared by degradation of natural actinobolin. Finally, ketal removal afforded desalanyl-N-acetylactinobolin (**74**).

Scheme XXII

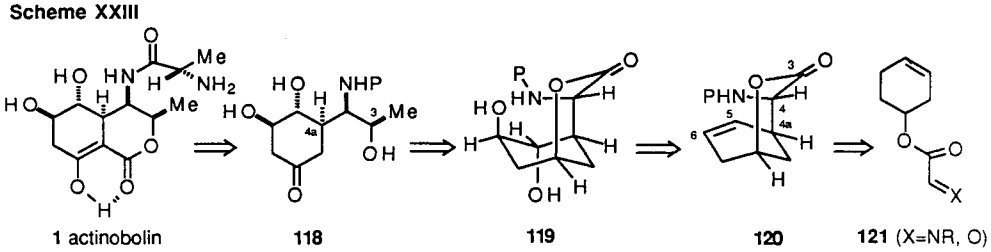


This synthesis of **74** required about 33 steps from bicyclic lactone **80**. However, it should be again noted that the synthetic strategy was directed at bactobolin, not actinobolin. Although elegant in concept, a number of unexpected problems prevented this approach from achieving its ultimate goal.

2e. Weinreb Synthesis

The Weinreb group has described an efficient total synthesis of actinobolin.[28] The strategy here was to prepare an intermediate bridged lactone like **120** via an intramolecular ene reaction of an imine or aldehyde **121** (**Scheme XXIII**). Compound **120** bears the correct C-4/C-4a stereochemistry of actinobolin and bactobolin. trans-Hydroxylation of the olefinic double

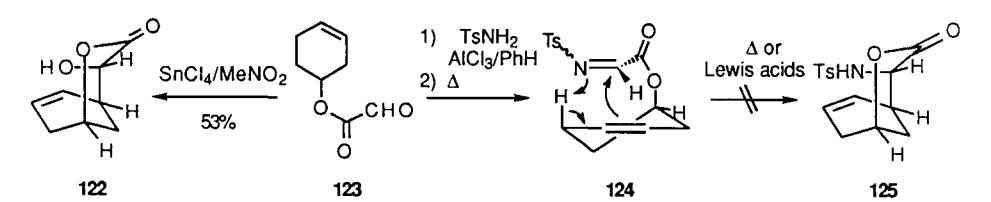
Scheme XXIII



bond of **120** would provide 1,2-diol **119**. Elaboration of the lactone carbonyl (C-3) of **119** and oxidation of the C-8 hydroxyl group would lead to an intermediate such as **118**, and carboxylation of the ketone would result in synthesis of actinobolin (**1**).

Readily prepared glyoxylate ester **123** was first converted to N-sulfonyl imine **124** (**Scheme XXIV**). However, despite extensive experimentation, intramolecular imino ene reaction of **124** to **125** could not be effected. This failure was somewhat surprising since both

Scheme XXIV

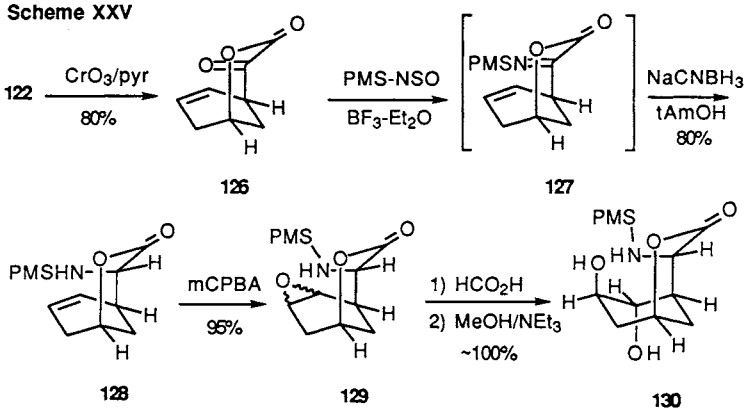


intermolecular and intramolecular ene reactions of N-sulfonyl imines have previously been successfully executed.[29] Alternatively, it was found that glyoxylate **123** itself did undergo Lewis acid catalyzed ene cyclization to afford α-hydroxylactone **122** as a single stereoisomer.

In order to introduce the C-3 nitrogen into **122**, the alcohol was oxidized, affording α-keto lactone **126** (**Scheme XXV**). A procedure was next devised to allow introduction of a nitrogen bearing suitable protection for the remainder of the synthesis. From earlier model studies it had been found that acyl protection of the C-3 nitrogen was not amenable to functionalization of the olefin. Based upon these observations, and the success of the Ohno group in using PMS protection, this group was therefore chosen.

It was found that the N-sulfinyl compound prepared from p-methyl benzylsulfonamide reacts with keto lactone **126** to generate N-sulfonyl imine **127**, which without isolation was reduced from the less hindered face to PMS-protected compound **128** (**Scheme XXV**). Epoxidation of **128** gave a 1.5:1 mixture of α-and β-epoxides **129** in high yield. That a mixture

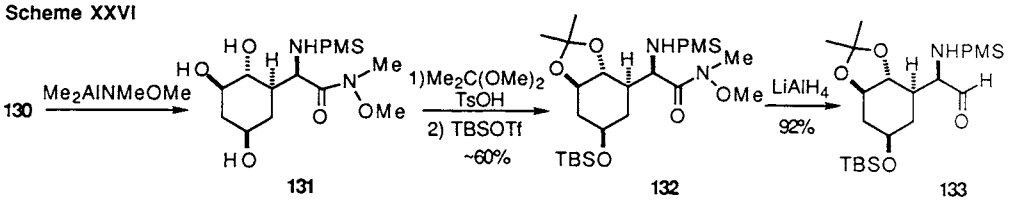
Scheme XXV

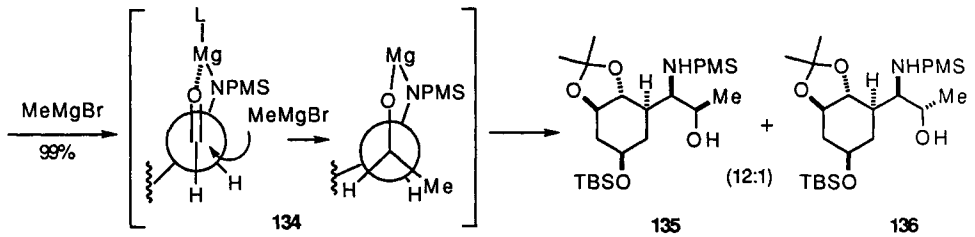


is formed here is of no consequence, since a critical feature of this strategy is that diaxial opening of either lactone bridged epoxide affords the same diol **130**. Thus compound **130** now bears the C-4, 4a, 5, 6 stereochemistry of both actinobolin (**1**) and bactobolin (**2**).

To continue the synthesis, lactone **130** was opened with the aluminum amide reagent derived from N,O-dimethylhydroxyl amine to give amide **131** (**Scheme XXVI**). The trans-diol was protected as the acetonide and the secondary alcohol as the TBS ether affording **132**. The amide could then be reduced to the aldehyde **133**. As anticipated, conditions could be found which promoted a Cram chelation controlled addition of methylmagnesium bromide to **133** (*cf* **134**) to afford a 12:1 mixture of the desired adduct **135** and epimeric alcohol **136**.

Scheme XXVI

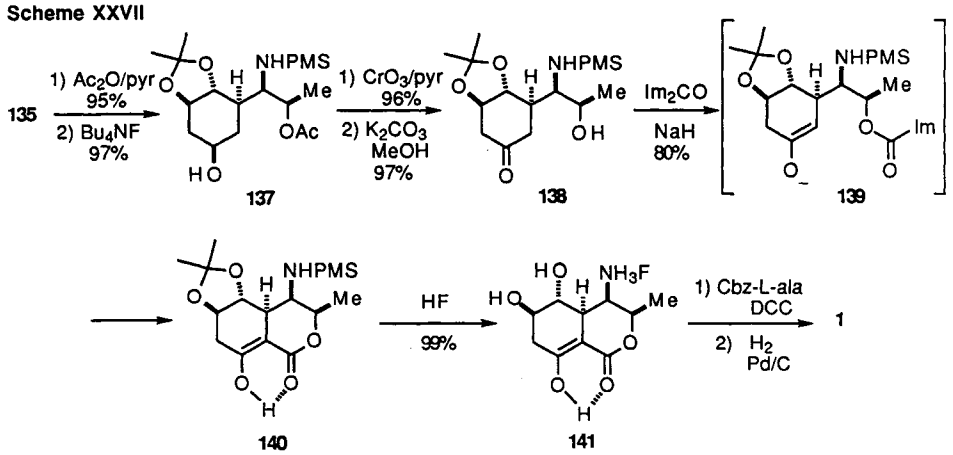




The final stages of the synthesis required introduction of the δ-lactone carbonyl functionality. In order to do this the alcohol functionality in **135** was protected as the acetate and the TBS group was removed giving cyclohexanol **137** (**Scheme XXVII**). This compound could then be oxidized to the ketone and the acetyl group removed affording **138**.

Since it was anticipated that enolization regiochemistry in **138** could not be kinetically controlled, it was decided to effect an intramolecular acylation via an equilibrating mixture of ketone enolates. Only one of the enolates would be capable of undergoing the desired intramolecular acylation. To effect this transformation, keto alcohol **138** was treated with

Scheme XXVII



diimidazole carbonyl and sodium hydride, presumably giving **139**, which in fact cyclized cleanly to the desired enol lactone **140**. The PMS protecting group could be cleaved with liquid HF[22] to afford racemic amine salt **141**. Acylation of **141** with Cbz-L-alanine gave a separable mixture of diastereomers, one of which on deprotection yielded (+)-actinobolin (**1**).

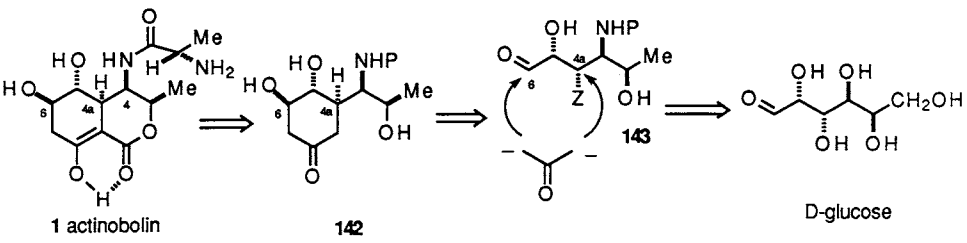
This route to actinobolin required approximately 18 steps from glyoxylate ester **123**, and in general yields were high. One drawback of the synthesis is the fact that racemic compounds were used and a resolution was required at a late stage. However, in principle, starting ester **123** might be prepared optically pure by a number of schemes.

2f. Ward Synthesis

Recently, Ward and Kaller described an interesting total synthesis of actinobolin starting from D-glucose utilizing the strategy outlined in **Scheme XXVIII**.[30] The plan was to prepare chiral aldehyde **143** from glucose, and to then append a three carbon unit. Thus, alkylation of **143** with an acetone anion equivalent via chelation controlled addition to the aldehyde and eventual second alkylation by replacement of Z with net inversion would provide a

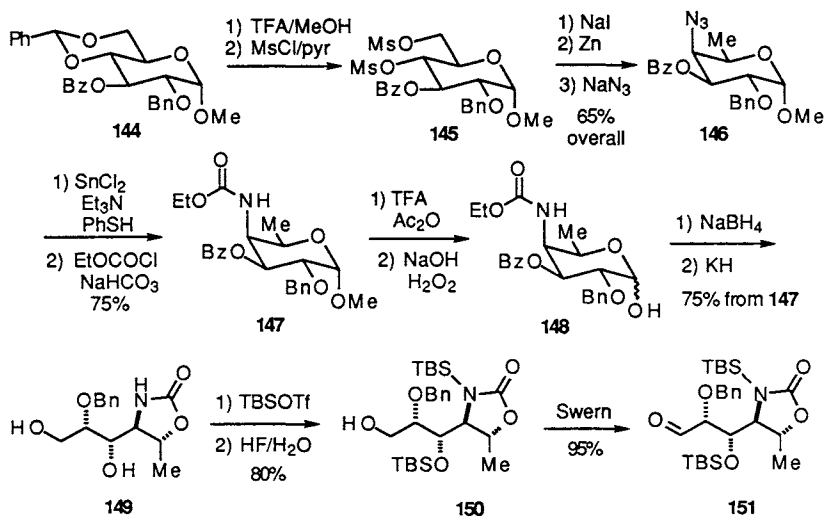
cyclohexanone intermediate **142**. Carboxylation of this intermediate as done in the Weinreb synthesis[28] would yield actinobolin.

Scheme XXVIII



Compound **144**, which can be readily prepared from D-glucose, was converted to dimesylate **145** (**Scheme XXIX**). Reduction of the primary mesylate via the corresponding iodide to a methyl group, followed by azide displacement of the secondary mesylate afforded **146**. Reduction of the azide and acylation with ethyl chloroformate led to carbamate **147**.

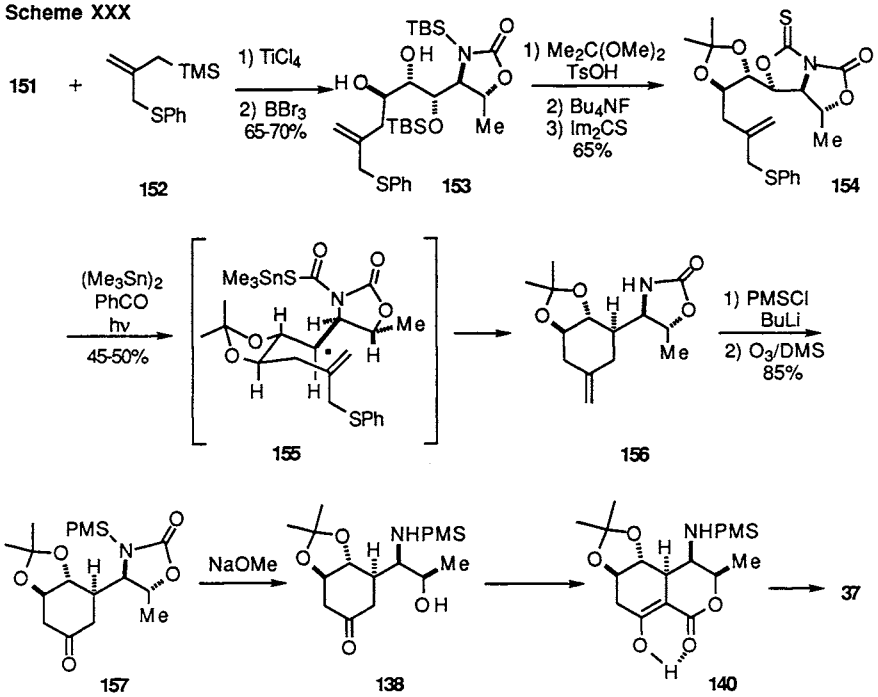
Scheme XXIX



Acetolysis of **147** and anomeric acetate cleavage yielded **148**, which was reduced to an acyclic triol and the carbamate cyclized to provide **149**. The diol and carbamate were silylated and the primary TBS ether was selectively cleaved to yield alcohol **150**. Swern oxidation of **150** provided the key aldehyde **151**.

Formation of the cyclohexyl system was cleverly patterned after previous studies by this group[31] utilizing **152** as a bifunctional alkylating reagent. Thus, treatment of allylic silane **152** with aldehyde **151** using $TiCl_4$ as catalyst as anticipated afforded a single diol via a Cram chelation controlled addition (**Scheme XXX**). Debenzylation of the crude product provided **153**.

Scheme XXX



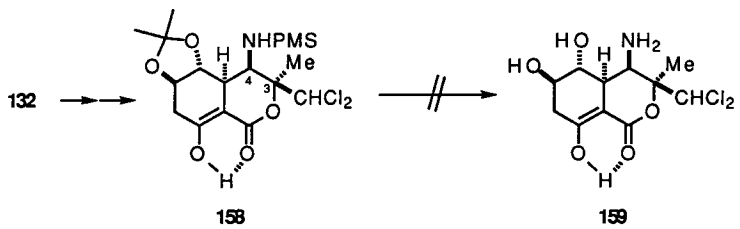
To prepare the system for the second alkylation, **153** was converted in three steps to thiocarbamate **154**. Ring closure was then effected by a 6-endo radical addition to the allylic sulfide, followed by phenylthio radical expulsion affording **156** as a single stereoisomer. This transformation probably occurs via radical **155** in the conformation indicated. The carbamate was next protected as the PMS derivative and the exocyclic olefin was ozonized to produce ketone **157**. Cleavage of the carbamate gave a keto alcohol **138** prepared in the Weinreb synthesis.[28a] This compound was processed as previously described via **140** into (+)-actinobolin hydrochloride (**37**). This approach to actinobolin required about 26 steps from D-glucose derivative **144.**

3. APPROACHES TO BACTOBOLIN (2)

3a. Weinreb Synthesis

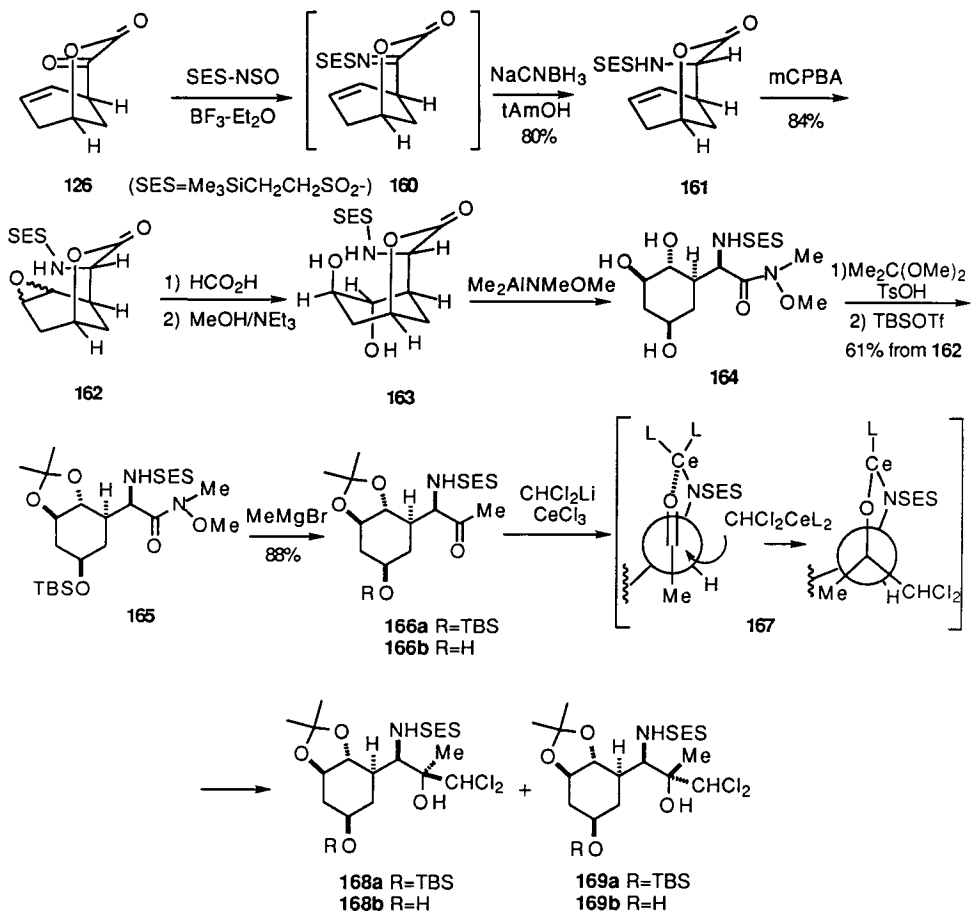
To date only one successful total synthesis of bactobolin (**2**) has been reported. Weinreb and coworkers have utilized a modification of their actinobolin strategy to construct **2**.[28a,32] The basic plan was to use an advanced actinobolin intermediate and modify functionality at C-3 in order to introduce the dichloromethyl group. The synthesis was found to hinge on finding a suitable nitrogen protecting group. The PMS group used in the actinobolin synthesis proved to be a problem in the bactobolin work. It was possible using the chemical sequence outlined below to convert actinobolin intermediate **132** to bicyclic compound **158 (Scheme XXXI)**. However, it was not possible to remove the PMS group to get to amine **159** despite considerable effort.

Scheme XXXI



A successful route to bactobolin was in fact finally executed using the β-trimethylsilylethylsulfonyl (SES) protecting group.[33] α-Keto lactone **126** could be converted to N-sulfonyl imine **160** and reduced to **161** (**Scheme XXXII**). Oxidation of **161** afforded a mixture of α- and β-epoxides **162** which, as previously could both be opened to trans 1,2-diol **163**. Ring opening of the lactone provided amide **164** which was protected as **165**. Addition of methylmagnesium bromide to amide **165** gave methyl lactone **166a** in high yield.

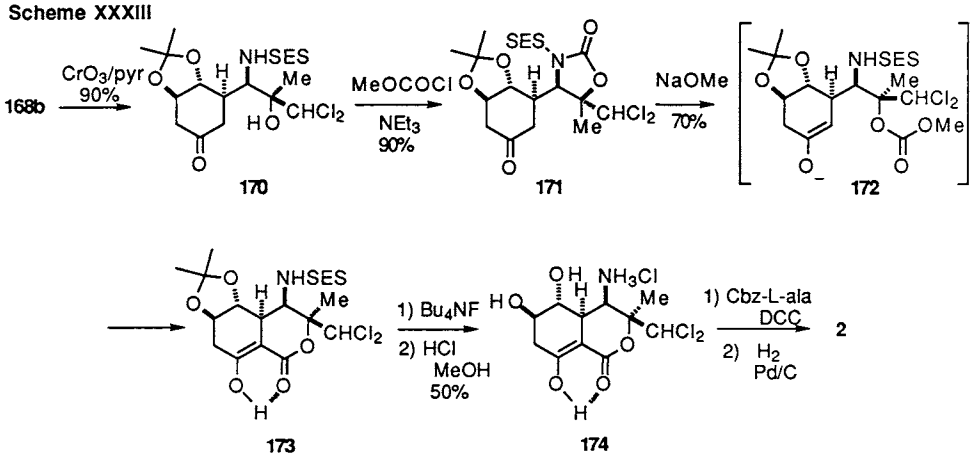
Scheme XXXII



Addition of a dichloromethyl group to this ketone was then explored. Lithio dichloromethane addition to **166a** provided only intractable material. However, the corresponding cerium reagent gave a 3:1 mixture of adducts **168a:169a**. Despite numerous attempts, desilylation of the desired compound **168a** could not be effected. Therefore, it was necessary to remove the silyl group from **166a** before addition to the ketone, providing **166b**. Inexplicably, addition of the cerium reagent to **166b** afforded **168b** as the only adduct. None of epimeric compound **169b** was produced. This fortuitous result set the stage for the final steps of the synthesis.

Alcohol **168b** could be oxidized to ketone **170** (**Scheme XXXIII**). However, since the remaining sidechain alcohol is tertiary, an activated carbonate derivative like **139** (*cf* **Scheme XXVII**) could not be generated. Under forcing conditions, **170** could be converted to cyclic N-sulfonyl carbamate **171**. However, it is evident from models that direct enolate acylation of **171** is precluded for stereoelectronic reasons. On the other hand, **171** was susceptible to ring opening, and treatment with sodium methoxide presumably generated carbonate enolate **172**, which cyclized to afford enol lactone **173**. Completion of the total synthesis entailed cleavage of the SES protecting group with fluoride to yield, after ketal hydrolysis, amine salt **174**. Finally, N-acylation of **174** with Cbz-L-alanine led to a separable mixture of diastereomers. One of these isomers upon Cbz-protecting group removal provided (-)-bactobolin (**2**). The successful sequence outlined here only required about 17 steps from glyoxylate ester **123**. The route was totally stereoselective and the steps involved were generally high yielding.

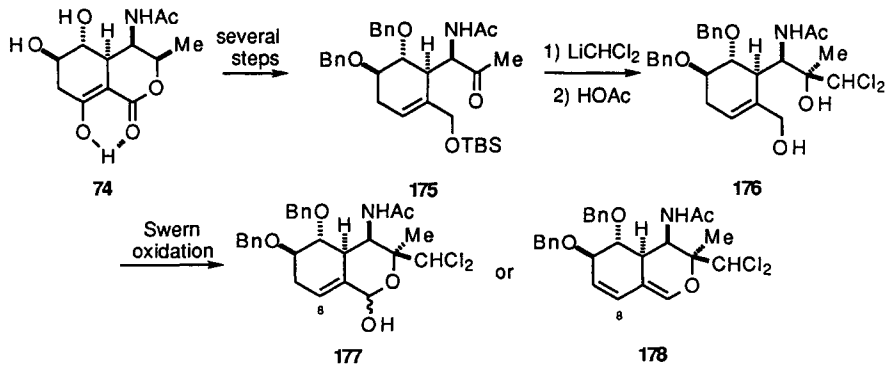
Scheme XXXIII



3b. Fraser-Reid Model Studies

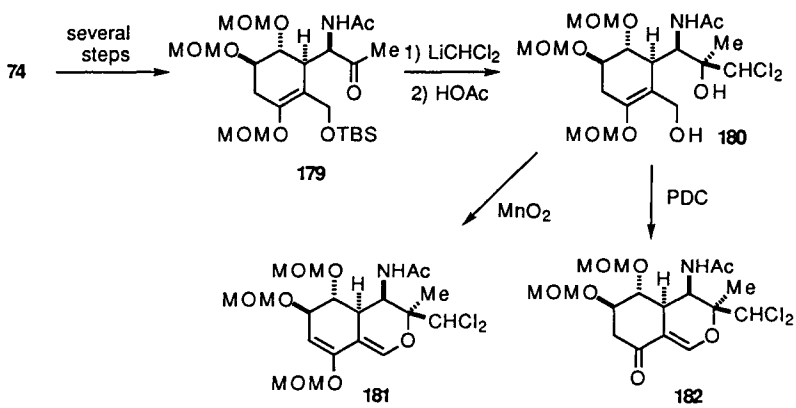
Fraser-Reid and Underwood have reported some studies aimed at modifying their actinobolin synthesis to prepare bactobolin.[34] Thus, desalanyl-N-acetylactinobolin (**74**) was converted in a few simple steps to ketone **175** (**Scheme XXXIV**). Treatment of **175** with dichloromethyl lithium at -100°C gave a single adduct having stereochemistry as shown in **176**, presumably via a Cram chelation controlled addition (*cf* **167**, **Scheme XXXII**). Swern oxidation of **176** was temperature dependent, at -30°C giving hemiacetal **177** and at -10°C diene **178**. Several attempts were made to reintroduce the C-8 oxygen into **177** and **178** via hydroboration, but these experiments were unsuccessful.

Scheme XXXIV



An alternative series of compounds retaining the oxygen was therefore prepared as shown in **Scheme XXXV**. Compound **74** was degraded to enol ether methyl ketone **179**. This ketone also underwent successful addition of dichloromethyl lithium to provide a single adduct **180**. PDC oxidation of **180** then afforded **182**, whereas manganese dioxide led to diene **181**. It is intended that these studies will eventually be used in completing a total synthesis of bactobolin.

Scheme XXXV



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Atta-ur-Rahman (Ed.) *Studies in Natural Products Chemistry, Vol. 16*

Total Synthesis of Crystalline (±)-Fredericamycin A

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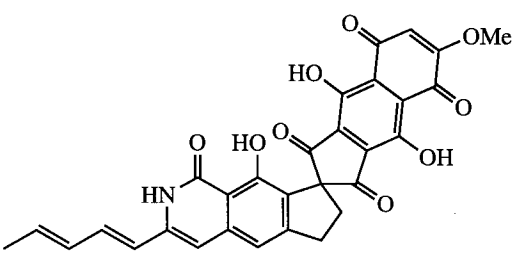
INTRODUCTION

Fredericamycin A (**1**)[1-3] is an antitumor antibiotic[4] of unusual structure.[5] The compound has attracted a great deal of attention, especially from synthetic chemists,[6-9] and there are, of course, a number of reasons for this interest. The substance is a powerful antitumor agent, but that in itself is not a sufficiently important

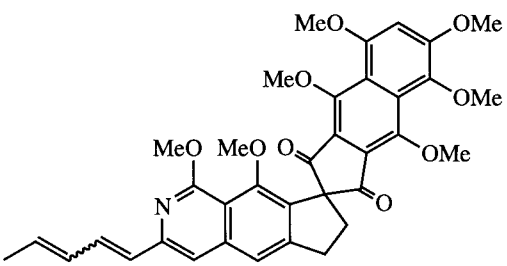


1

reason. What makes this antitumor agent special is the fact that its structure type is unique; consequently, the identification of structure-activity relationships might reveal new mechanisms for destroying cancer cells. At present little is known[4] about how fredericamycin A works except for the fact that it inhibits topoisomerases I and II.[4d]

The other characteristic of fredericamycin A is that the structure is complicated, and so, if the biological implications of synthetic work — the possibility of finding useful structure-activity correlations — are not fruitful, then, at least, the chemical experiments would probably lead to something new.

When we began, no synthesis of fredericamycin A had been reported, but during our work Kelly and his collaborators described[7] the first synthesis. More recently, the isomer mixture **2**, which is an intermediate in our route, was made by an independent method, and also converted into the natural product.[9]



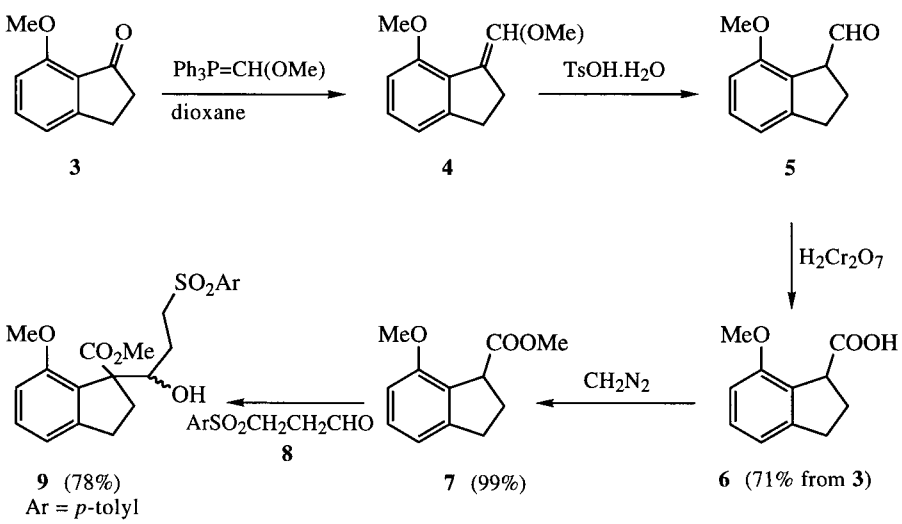
2

MODEL STUDIES

Development of Radical Spirocyclization

We took as our starting point the spiro center, and we quickly found out that that structural feature is not so easy to generate. We tried, in simple model experiments, a number of standard approaches,[10] and one of these[11] (see Scheme 1), with slight modification, did eventually provide the spiro diketone **12**.[6i] However, this turned out to be an unprofitable start because enedione **12** did not behave satisfactorily in Diels-Alder reactions that would have

Scheme 1 (first part)



3 **4** **5**

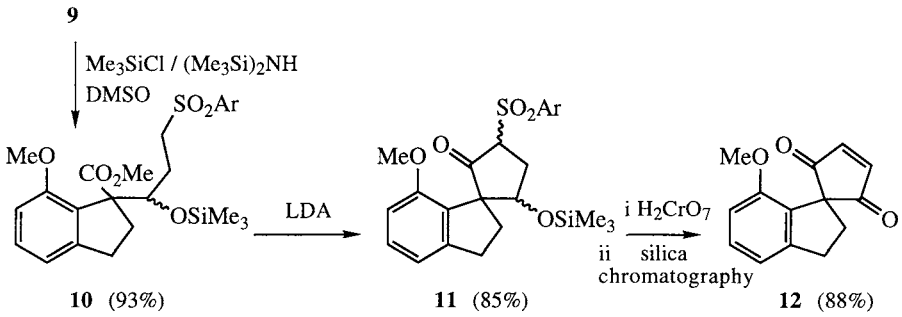
6 (71% from **3**)

7 (99%)

8

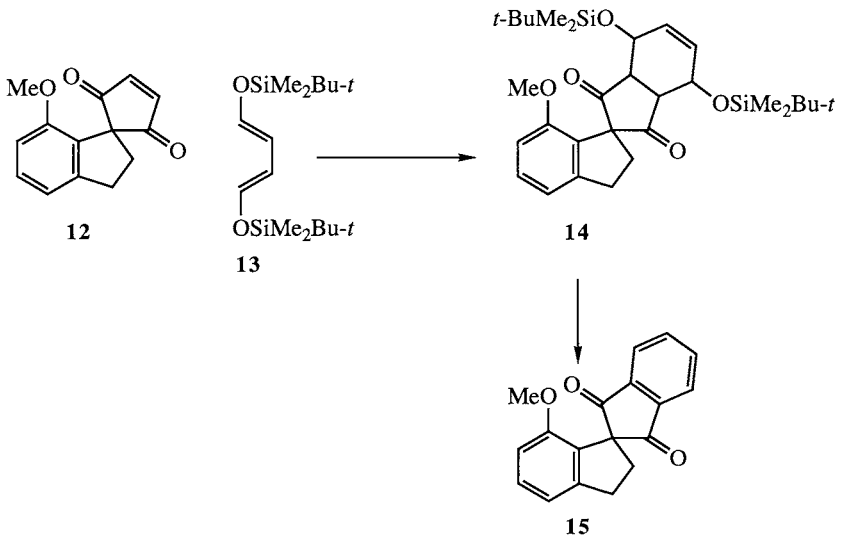
9 (78%)
Ar = *p*-tolyl

Scheme 1 (continued)

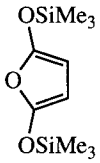


taken the route to a more advanced point. Compound **12** is a rather unreactive dienophile, probably for steric reasons,[12] and cycloaddition with **13**[13] (Scheme 2) required very long reaction

Scheme 2



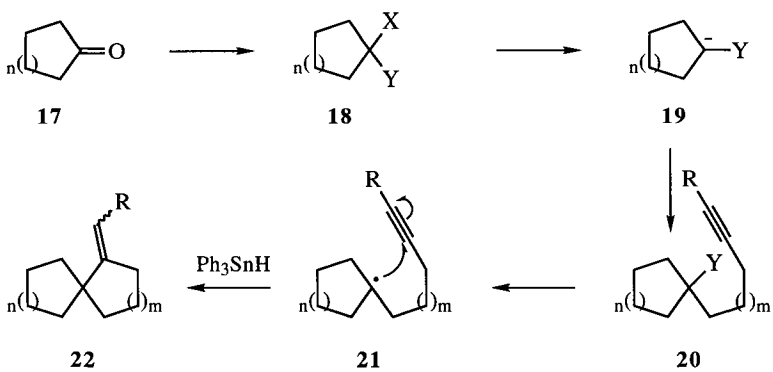
times at 140°C, the product (9% yield) being the aromatized material **15**. In order to isolate the initial adduct (**14**) very high pressure (for which we had only make-shift equipment) was required, and even then the yield was poor (48%). The diene **16**[14] was equally unsuitable and it did not react at all under purely thermal conditions. We did not try the application of extreme pressure.



16

These problems and a number of others related to the generation of the quaternary center from compound **6** (see Scheme 1) caused us to become concerned — perhaps overly concerned — with steric factors. Be that as it may, we asked ourselves the general question "What is a good way of making sterically congested molecules?" One answer, clearly, is to use reactions that have an early transition state, and that approach made us think in terms of radical chemistry. Addition of a carbon radical to a multiple bond does have an early transition state, and radical reactions are also less sensitive to steric factors than ionic processes. The idea of adding a radical to a π system therefore became the basis of our approach, and Scheme 3 shows the principle of the method.

Scheme 3



17 **18** **19**

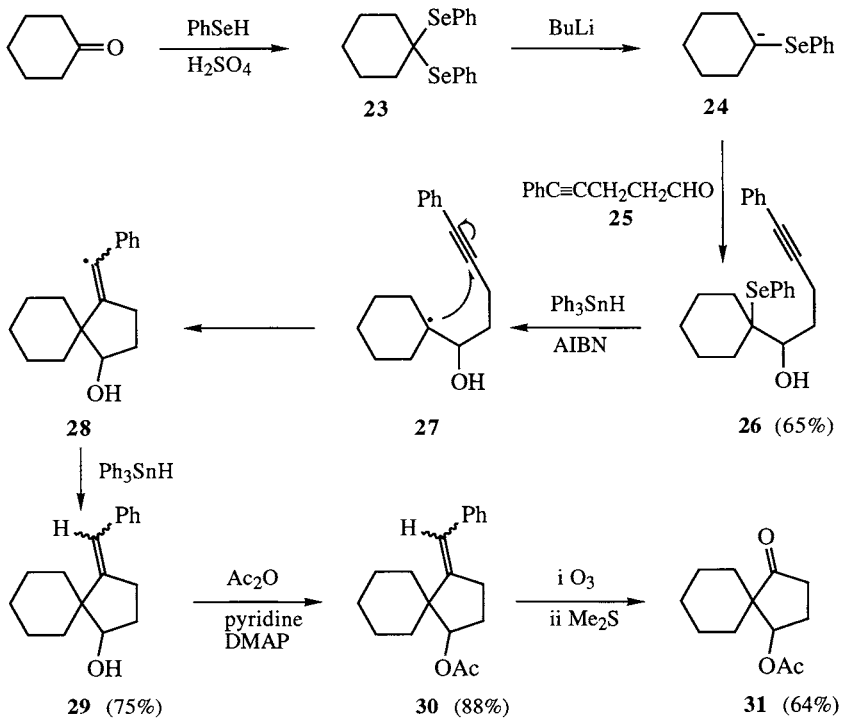
22 **21** **20**

We start with a ketone and we convert the carbonyl carbon first of all into a carbanion (**17→19**). The carbanion is then used to attach a chain that carries a suitably located triple bond, and we then convert what was the carbonyl carbon into a radical (**20→21**). At that stage the radical closes onto the π system so as to generate a spiro structure (**22**). The groups X and Y have to be chosen so that bond C—X can be broken ionically and bond C—Y by homolysis. These requirements are easily met by using

benzeneseleno groups for both X and Y.

To test our plan we converted cyclohexanone into its selenoacetal **23** (Scheme 4).[15] There are a number of ways of doing

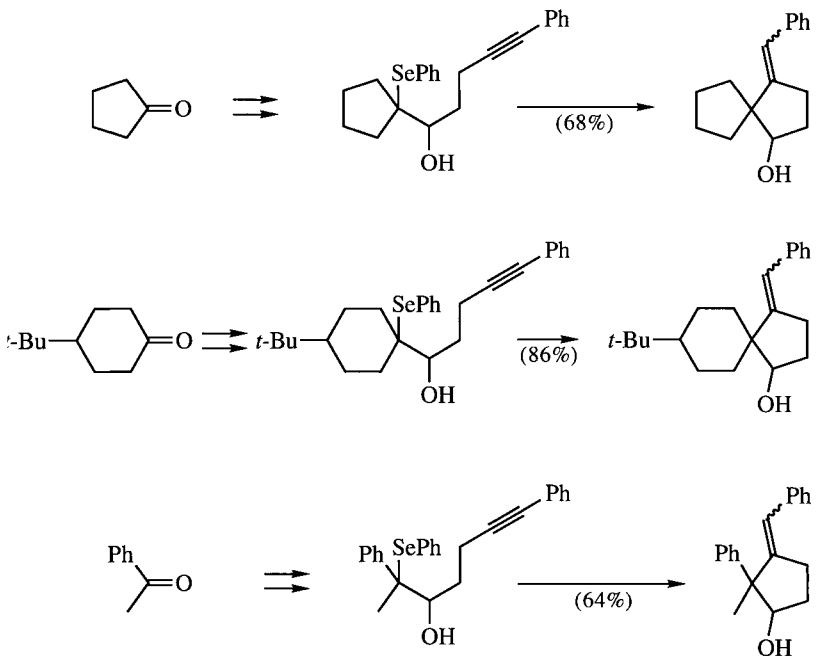
Scheme 4



that and it was convenient for us to use benzeneselenol in the presence of sulfuric acid. Formation of selenium-stabilized carbanions from selenoacetals (*cf.* **23→24**) by treatment with butyllithium is very well-known[16] and, just as a matter of convenience, we took aldehyde **25**[17] as our acetylene unit. The hydroxy selenide **26** was formed easily, and we then generated the carbon radical by a standard method.[18] The radical behaved as shown in the Scheme, the structure of the product (**29**) being easily proved by acetylation and ozonolysis (**29→30→31**).

We have studied a number of related examples, and some of these are shown in Scheme 5.[15] In each case the appropriate ketone was converted into its selenoacetal and then into the selenium-

Scheme 5

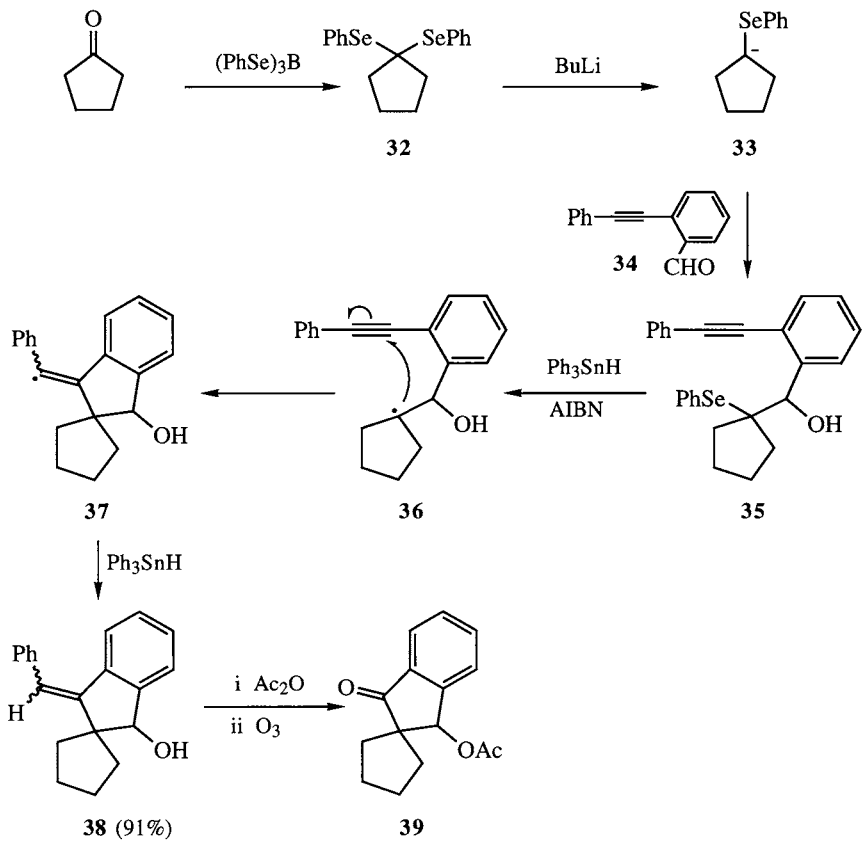


stabilized carbanion. That, in turn was condensed with our acetylenic aldehyde **25** to produce the desired hydroxy selenide. The last step is the radical cyclization, which worked quite well — as shown.

We then studied one example (Scheme 6)[15] that serves as an extremely simple model for fredericamycin A. We converted cyclopentanone, via its selenoacetal **32**, into the stabilized carbanion **33**. The carbanion, as expected, reacted smoothly with aldehyde **34**, which is a known compound and easy to prepare.[19] That brought us to the hydroxy selenide **35**, and we then generated the radical by our usual method. The radical does exactly what we want: it closes in a 5-*exo* manner to afford the desired spiro compound (**36**→**37**→**38**). And, after cleavage of the resulting double bond, we obtained the spiro ketone **39**, which resembles the central part of fredericamycin A, but does not have the proper oxygenation pattern.

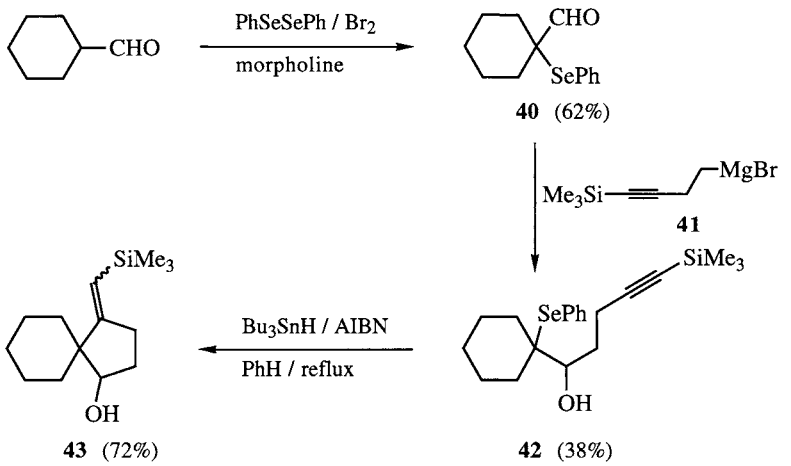
Our method for making spiro compounds is general. It does not depend on the ring size of the ketone and it does not require the presence of a rigid unit, such as the benzene ring of **34**, in the carbon chain.

Scheme 6



Another feature of the radical spirocyclization is that it is versatile, because the method does not have to be based on selenoacetal chemistry. All one has to do is to select a carbon atom, attach a chain with a properly located triple bond, and then convert the original carbon into a radical. Scheme 7, for example, shows another (but non-optimized) variation of the theme.[21] In this case, cyclohexanecarboxaldehyde was selenenylated by a standard method[22] and we attached the acetylenic unit using Grignard reagent **41**.[23] The spirocyclization (**42**→**43**) works quite well.

Scheme 7

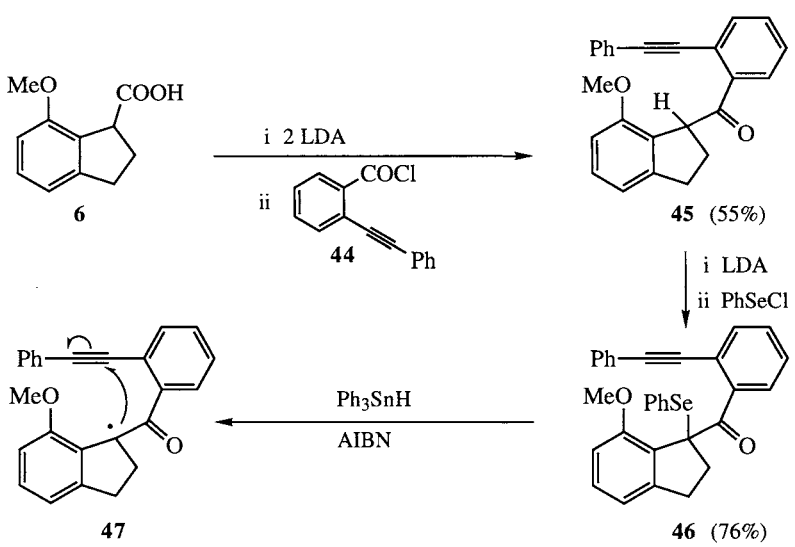


Studies on Radical Spirocyclization

With the above experience to guide us, we decided to make a number of informative models of the fredericamycin A spiro unit, and we chose first the simple case of **15**, which we had previously obtained in very low yield by a Diels-Alder reaction.

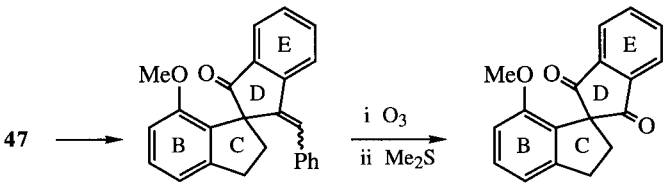
Our new approach[6i] to this compound is summarized in Scheme 8, and the experiments served the additional purpose of giving us some

Scheme 8 (first part)



practice in combining the radical precursor (the eventual BC rings) with the radical acceptor (the DE ring unit). Even in this simple

Scheme 8 (continued)

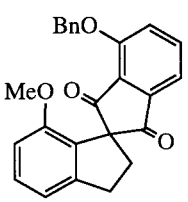


48 (85%) **15** (84%)

study that operation was not initially straightforward and the method of Scheme 8 represents the result of a fair number of orienting experiments.

The dianion derived from acid **6** condensed with acid chloride **44** to yield directly ketone **45**, the product of *in situ* decarboxylation. This material was selenenylated in the usual way and the radical spirocyclization (**46**→**48**) was effected in high yield, the product being easily converted into spiro diketone **15**.

Our next planned step was to make a compound corresponding to **15** but having two oxygen substituents on ring E. However, initial difficulties in preparing the ring E precursor caused us to aim instead for the simpler model **49**. The requisite ring E unit **51**

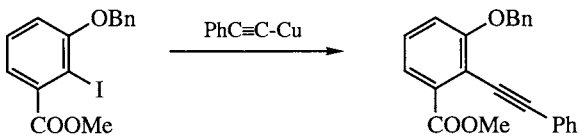


49

was made,[6i] as shown in Scheme 9, from the iodo ester **50** by coupling with copper phenylacetylide.[20] Ester **50** was easily prepared from the parent acid, which is a known compound.[24] We had intended to use the acid chloride corresponding to **51**, but hydrolysis of the ester was inefficient and so we decide to use the ester directly.

Condensation of the dianion derived from acid **6** with ester **51**, in the presence of HMPA, which was an essential additive, gave

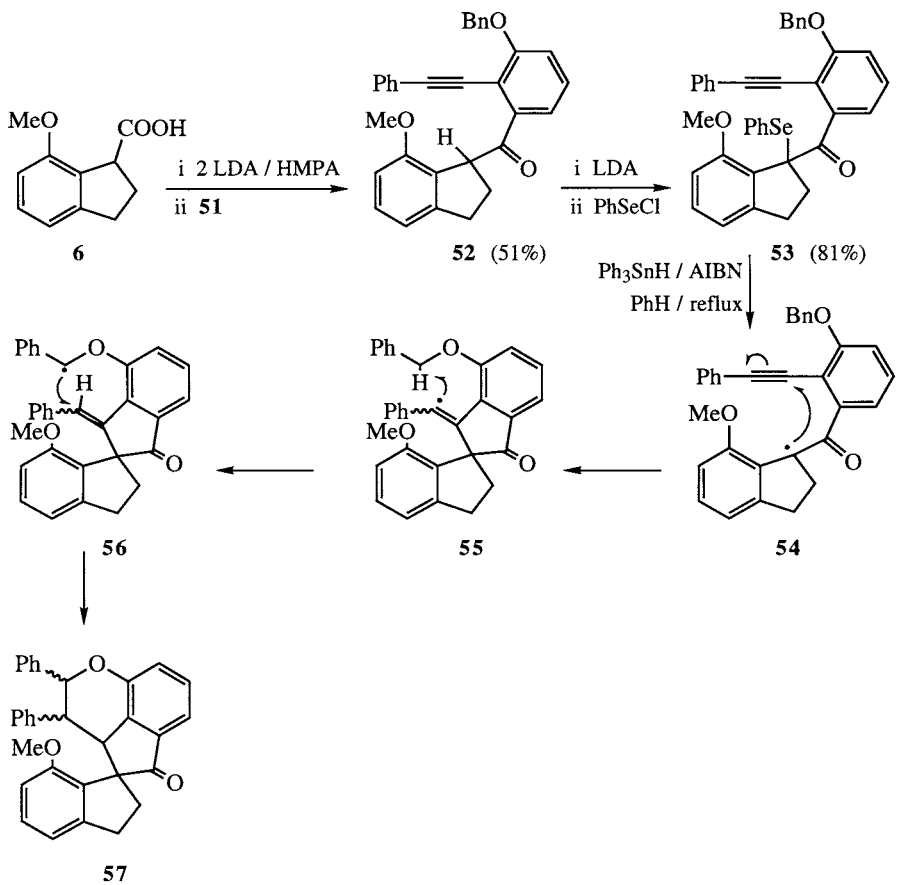
Scheme 9



50 **51**

ketone **52**, decarboxylation having again taken place *in situ* under our reaction conditions (50°C).[6i] Selenenylation by the standard

Scheme 10



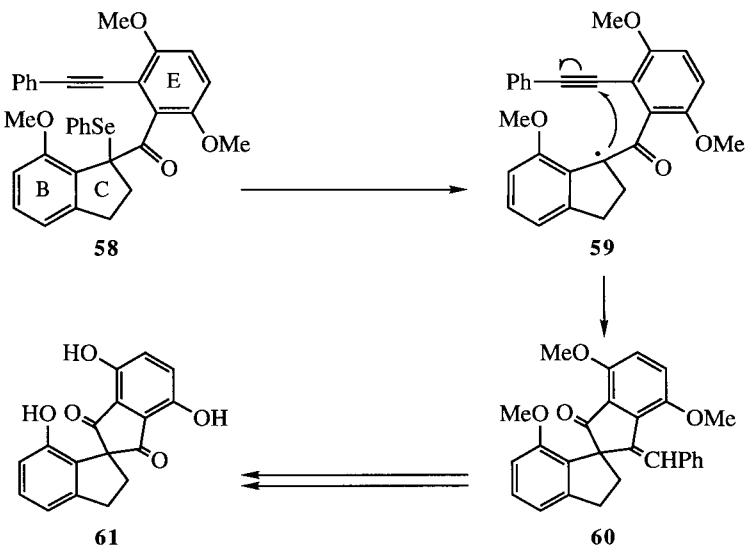
6 **52** (51%) **53** (81%) **54** **55** **56** **57**

method afforded the radical precursor **53**, from which radical **54** was then generated. Cyclization occurs normally (**54**→**55**), but the resulting vinyl radical undergoes intramolecular hydrogen transfer

(**55**→**56**) to form a new radical that then closes by a 6-*endo* pathway, so that the final product is the polycyclic compound **57** (as an isomer mixture). The intramolecular hydrogen transfer takes place easily, and even when the stannane was added in one portion, rather than by slow addition, the yield of **57** exceeded 90%.

Intramolecular hydrogen transfer has, of course, been developed into a useful technique in radical-based methodology,[25] but when these experiments were done — which was a few years ago — the phenomenon was not well known in such a context, and for us it was a nuisance. However, the experiment did at least show what ought to be done: any protecting group adjacent to the acetylene should not carry a readily abstractable hydrogen. On that basis then, we could redefine the model study in the following terms (Scheme 11).

Scheme 11

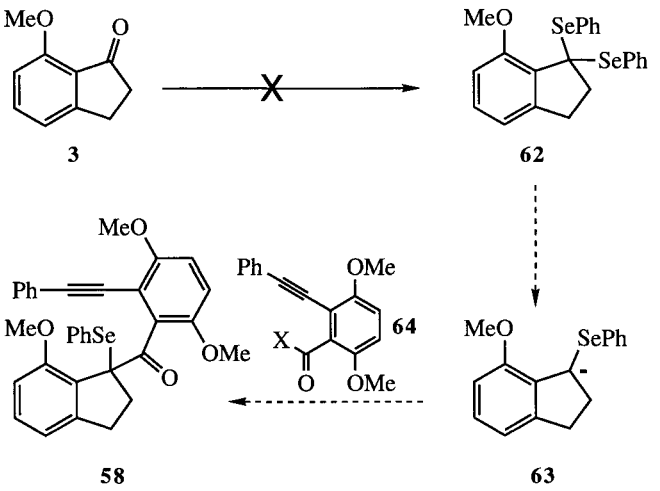


We would try to make compound **58** and the derived spiro ketones **60** and **61.** In the structure of **58** a methoxy group is present instead of a benzyloxy unit and, since the carbon hydrogen bonds of a methoxy group are stronger, we hoped that hydrogen abstraction would not be a problem. We also took the opportunity to include an additional oxygen atom; consequently ring E in this series carries two oxygen functions.

Our initial plan of approach to **58** was based on selenoacetal

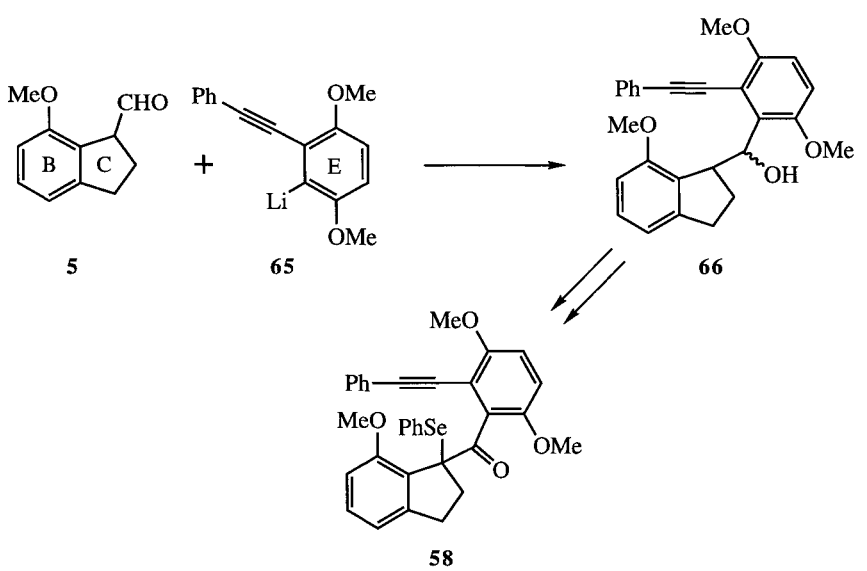
chemistry (Scheme 12) but, to our surprise, we were unable to make

Scheme 12



the required selenoacetal **62**. However, in retrospect, it is possible that we just did not try hard enough. In any event, we looked at another route (Scheme 13) in which aldehyde **5** would be combined with the organolithium **65**. This is the route that works and it should be noted that it differs from the earlier model

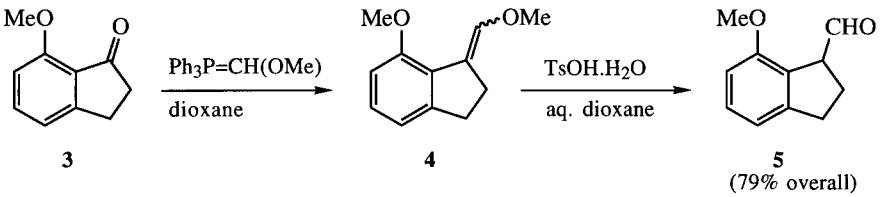
Scheme 13



studies of Schemes 8 and 10 in that the BC ring system is now the electrophilic unit while the ring E portion is the nucleophile. In the earlier studies the polarity of the two ring systems was reversed and, since that coupling reaction was not very efficient (51-55% yield), we adopted the approach of Scheme 13.

Aldehyde **5**, that we now needed, was very easy to make (Scheme 14) using a Wittig reaction, followed by acid hydrolysis.[6u] In fact the compound had actually been prepared earlier (see Scheme 1).

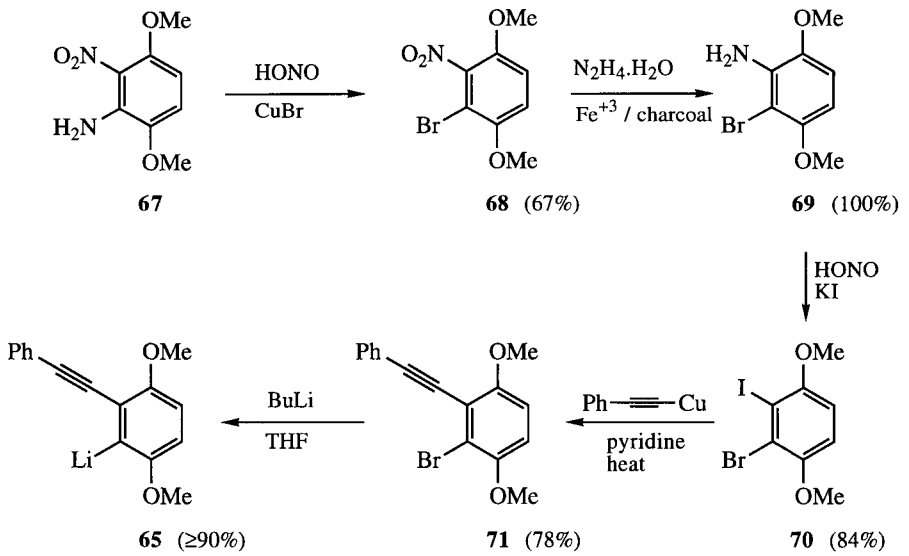
Scheme 14



3 **4** **5** (79% overall)

Making the other component — the acetylenic organolithium **65** — was not quite so easy and our route, which is by no means the first that we tried, is shown in Scheme 15.[6u]

Scheme 15



67 **68** (67%) **69** (100%)

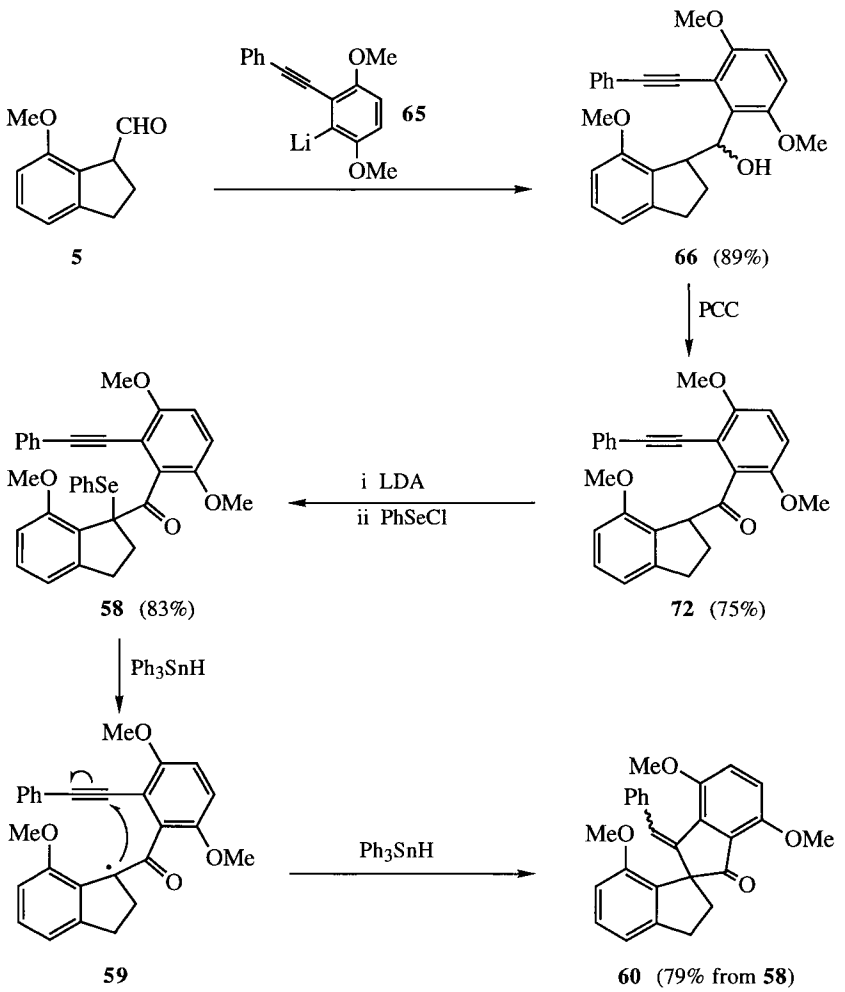
65 (≥90%) **71** (78%) **70** (84%)

The nitro amine **67** is a known substance and it is readily accessible in large quantities.[26] We used a Sandmeyer reaction to

replace the amino group by bromine (**67**→**68**) and then, after reduction with hydrazine, another Sandmeyer reaction to introduce an iodine atom (**68**→**69**→**70**). The next step, reaction with copper phenylacetylide, worked well, and finally, halogen-metal exchange generated the organolithium (**71**→**65**).

We now had both of the required subunits and it was a simple matter to join them together (Scheme 16). Oxidation of the resulting alcohols (**66**) gave ketone **72**, which was selenenylated in the standard way (**72**→**58**).

Scheme 16



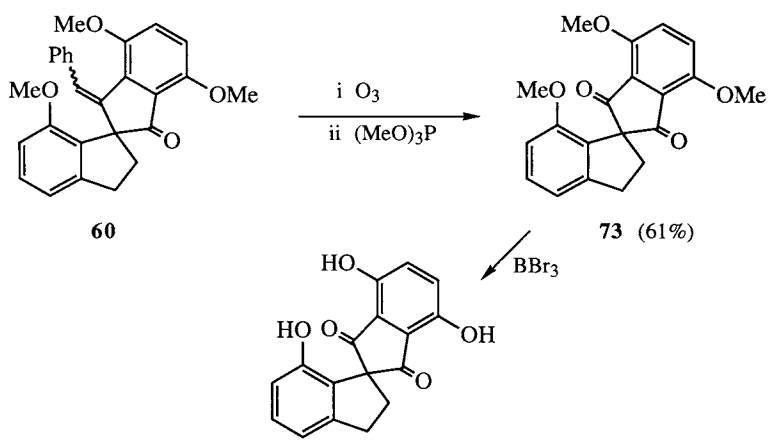
Treatment of selenide **58** with triphenyltin hydride proceeded exactly according to plan: the desired radical was formed, and it closed efficiently by a 5-*exo* pathway (**58**→**59**→**60**). From the rather high yield it is clear that intramolecular hydrogen abstraction occurs to a slight extent only, if at all.

Normally, when one carries out a thermal radical cyclization the tin hydride and the initiator — in our case AIBN — are added slowly to a refluxing benzene solution of the radical precursor, but for this reaction (**58**→**60**), the yield was highest when the stannane and the initiator were added in one portion at the beginning of the experiment.

Radical **59** (as well as **54** of Scheme 10, which we had made earlier) is an α-keto radical, and these species have the very useful property of always closing through carbon.[27] Their behavior was not known at the time we did these experiments, and so we were well pleased to find that cyclization occurred in a way that is essential for our purposes.

With the product of radical spirocyclization (**60**) in hand, we cleaved the double bond and then removed the phenol protecting groups (Scheme 17). That gave us the phenolic diketone **61**, which represents completely the four central rings of fredericamycin A.

Scheme 17



60

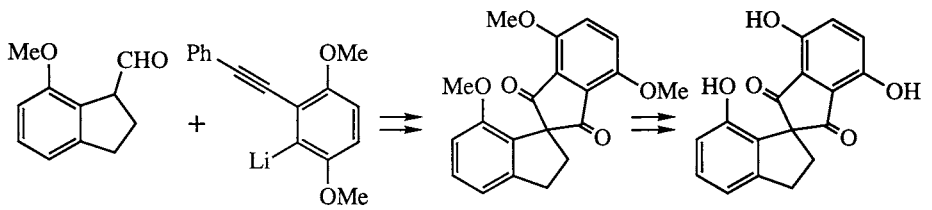
73 (61%)

61 (85%)

FORMULATION OF THE SYNTHETIC PLAN

At this point we felt that we were in a position to define a realistic synthetic route to fredericamycin A. What we had achieved so far was to combine the two subunits **5** and **65** in order to make first the model **73**, and then the deprotected compound **61** (Scheme 18). If that series of reactions was to guide our approach

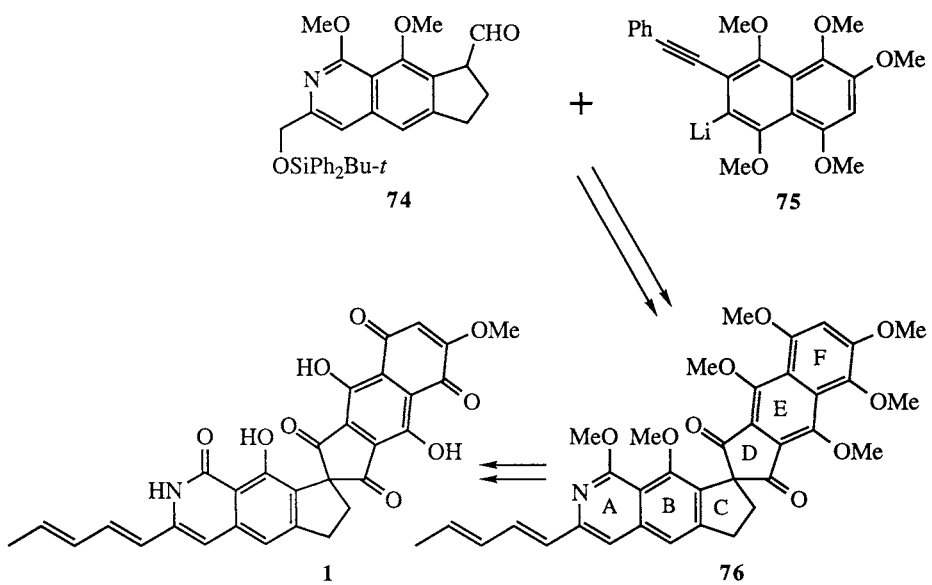
Scheme 18



5 **65** **73** **61**

to the natural product itself, then, instead of an indanyl aldehyde and a lithiated benzene, we would need the isoquinoline-derived aldehyde **74** (Scheme 19) and the lithiated naphthalene **75**. However, extrapolation from the first series to the second one is a very big extension that disguises a number of problems.

Scheme 19



74 **75**

1 **76**

The first point to make is that fredericamycin A has *one* methoxy group but the intermediate **76** has *seven*, and so we are faced with the problem of selectively removing six *O*-methyl groups. If this could not be achieved then, of course, a different choice of protecting groups would become necessary. Exclusive reliance on *O*-methyl groups was considered first for a number of reasons: there was the analogy with the model work already done, the fact that intramolecular hydrogen transfer would probably be avoided, and our belief that construction of the required subunits — in this case **74** and **75** — would be simplified. Naturally, this approach could be considered only because it was possible to recognize a number of ways (see later) for tackling the problem of selective deprotection, although the prospects for demethylation of ring B (see **76**) were a source of worry for a long time.

The business of selective demethylation is not the only obstacle that is hidden in summary Scheme 19, for there is also the task of controlling the stereochemistry of the pentadienyl unit. We did not give this aspect of the synthesis much attention at this stage because, at least in principle, a number of powerful methods were available to handle the task. When we actually came to this part of the work we found that the problem was not at all straightforward but, fortunately, the problem was unexpectedly bypassed.

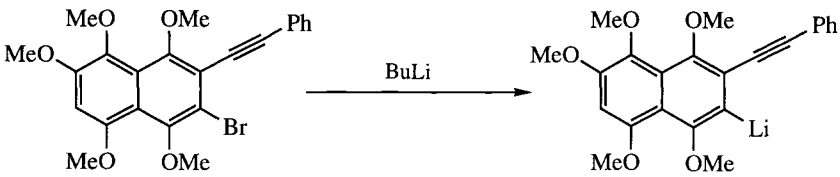
So much for the more obvious difficulties that can be anticipated; there remained the fundamental problem of making the subunits **74** and **75**. To our surprise, the naphthalene was much more difficult and its preparation was the most time-consuming part of the whole synthesis.

CONSTRUCTION OF THE EF RING SUBUNIT

Preliminary Considerations

From the start we planned to generate the lithiated naphthalene **75** from the corresponding bromide **77** (Scheme 20).[28] It should be noted that the regioisomer of **77** with the bromine and acetylenic substituents interchanged would also have been suitable and, in fact, we could even have used a mixture of the two. We worked out several routes to the bromide, but we had to mount a very determined effort before we were successful in finding a practical method.

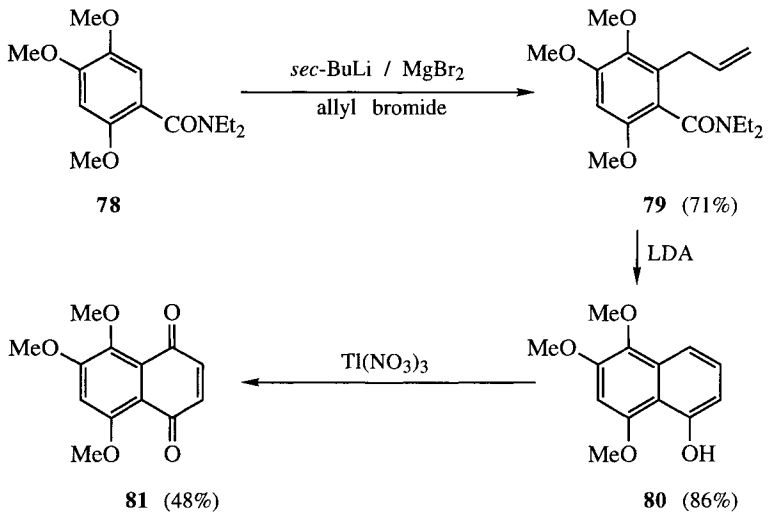
Scheme 20



EF Ring System by Directed Lithiation

All of our initial approaches involved quinone **81** (Scheme 21) as an intermediate.[28] We made several attempts to prepare the quinone and our first successful effort relied on the methodology of directed lithiation. Amide **78** is readily made from the corres-

Scheme 21

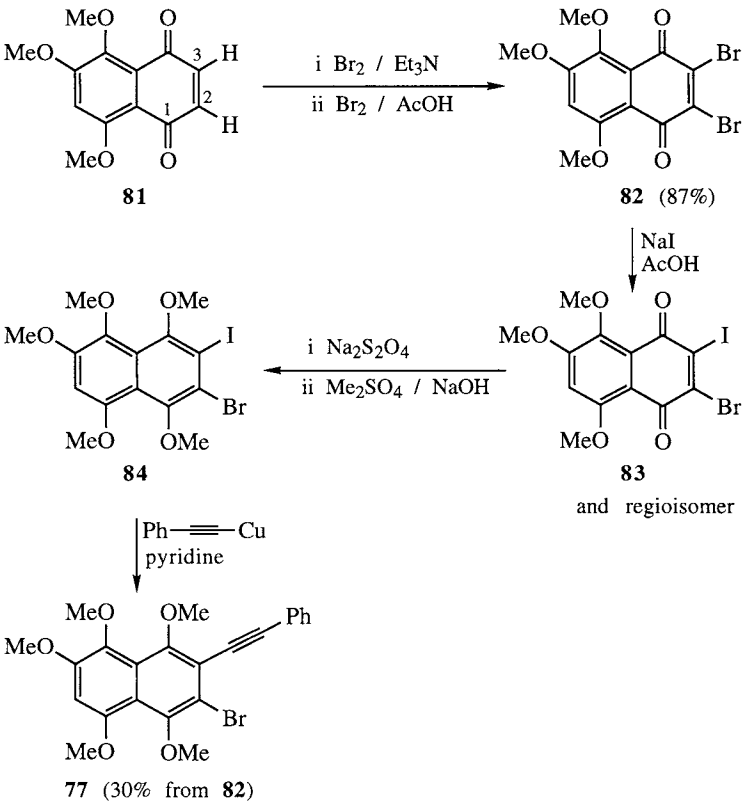


ponding acid, and the acid is commercially available. Standard conditions for allylation ortho to an amide group[29] were very effective, and then cyclization[30] with LDA gave naphthol **80**. Now, however, we encountered a problem, because it was difficult to oxidize the naphthol to the quinone. We had to evaluate several reagents, and eventually we settled on thallium trinitrate,[31] which led to quinone **81** in about 50% yield. Thallium trinitrate is a rather expensive chemical and, obviously, this route was a stopgap measure. We used it on a number of occasions, but we were later

able to replace it by a much more convenient method.

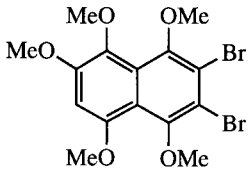
With the quinone in hand, our main effort was then directed to the problem of converting it into bromo acetylene **77** (or its regioisomer, with the bromine and acetylene units again interchanged).

Scheme 22



81 **82** (87%) **83** and regioisomer **84** **77** (30% from **82**)

We adopted in our early work the route shown in Scheme 22. Reaction of quinone **81** with molecular bromine and then with triethylamine served to introduce a bromine atom at C(3), the hydrogen simply being replaced by the halogen. Further reaction with bromine in acetic acid then gave the dibromo quinone **82**. Although two steps are involved the overall yield is good, even when done on a large scale. From this point, the pentamethoxy bromide **85** (see below) was easily prepared by reduction with sodium dithionite and methylation. However, all attempts to replace[32] one



85

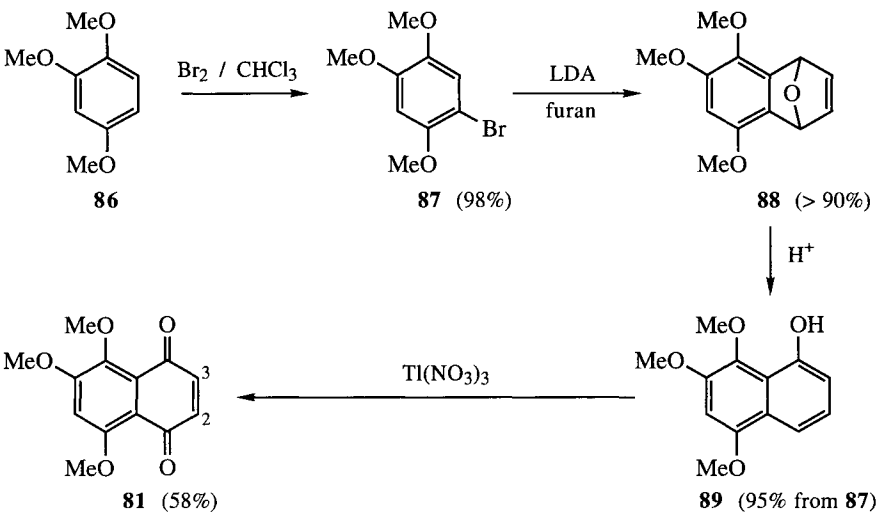
of the bromines in **85** by an acetylene group were unsuccessful. For this reason, we converted the dibromo quinone into a mixture of bromo iodo quinones (**82**→**83**, Scheme 22). (The Scheme shows only the major isomer.) This halogen exchange can be done in several ways. The nature of the solvent appears to be important and we find that warm acetic acid is best. The mixture of dihalo quinones also contains some of the starting dibromide, but we do not attempt any separation. The crude product is reduced with sodium dithionite to the corresponding hydroquinones, and that mixture is methylated in the usual way (**83**→**84**). Finally, the material is treated with the copper salt of phenylacetylene. The iodine is replaced by the acetylene unit, but the dibromo ether corresponding to **84**, and arising from dibromide that did not react with sodium iodide (*cf.* **82**→**83**), is unchanged, and this is the stage at which we purify our product. The yield of bromo acetylene **77** is 30% from dibromo quinone **82** and the material contains about 10% of the regioisomer (with the bromine and acetylene interchanged). The presence of the isomeric contaminant is of no consequence because both substances would eventually give the same spiro compound. Experimentally it also turned out that the minor component was removable after the next step.

The reactions shown in Scheme 22 provided enough of the bromo acetylene **77** to continue further experiments on a modest scale, but it was clearly necessary to improve the synthesis of this subunit, and we realized that the approach would probably have to be redesigned; it was not going to be a question of finding superior reagents.

At this point, we made the first of the major improvements that were called for, and this was done by developing a method based on benzyne chemistry. The new approach greatly facilitated preparation of the key intermediate **81** in batches of 10 to 20 g.

EF Ring System by Benzyne Reaction

Scheme 23



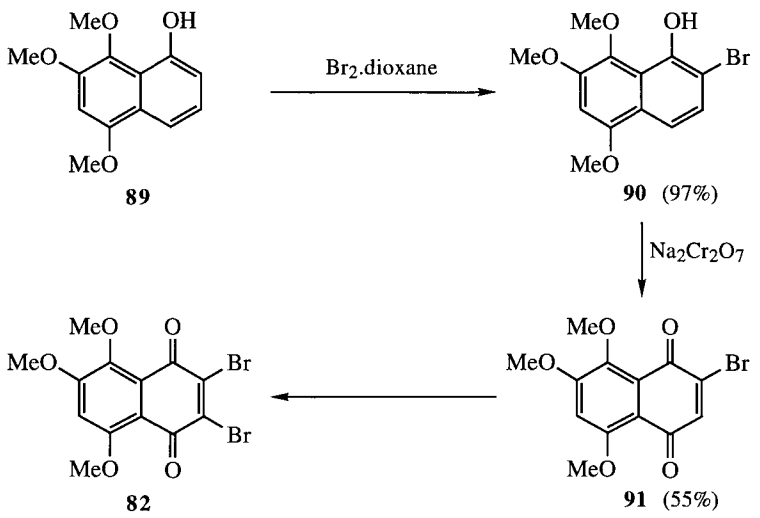
86 **87** (98%) **88** (> 90%)

81 (58%) **89** (95% from **87**)

The trimethoxybenzene **86** is commercially available and it is a simple business to brominate it in the manner shown in the Scheme.[28] When the trimethoxy bromide is exposed to the action of LDA in the presence of a large excess of furan then a benzyne is generated and trapped by cycloaddition to the furan. The yield of the adduct **88** is well above 90% and it is not necessary to purify the adduct. The crude material is simply treated with a small amount of perchloric acid, and that experiment affords naphthol **89** in excellent yield. At the time we developed this benzyne route we still had to rely on thallium trinitrate for the final oxidation and, based on our earlier experience with this reagent (when applied to the isomeric naphthol **80**), we were not surprised that the yield is quite modest (**89**→**81**, 58%). We accepted this result for a short time but it is not the last word on the generation of a suitable quinone (see later).

When we had first prepared quinone **81** we had treated the material with bromine in two steps in order to replace the C(3) and C(2) hydrogens sequentially with bromine. We now found that we could improve the synthesis by introducing one of the bromines *before* oxidation to the quinone level (Scheme 24).

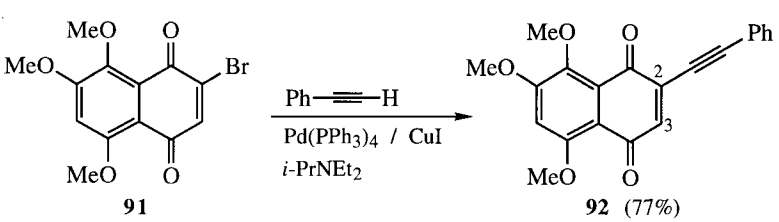
Scheme 24



Naphthol **89**, produced by the benzyne route, can be brominated in good yield (**89**→**90**), and simple oxidation of the bromo naphthol with Jones' reagent gave the same bromo quinone **91** that was an intermediate in our previous route to the dibromo compound **82**.

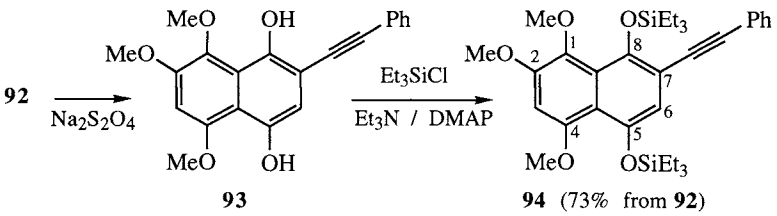
Now it was all very well for us to get our hands easily on a large amount of dibromo quinone **82**, but there still remained a problem because conversion of the dibromo quinone into the bromo iodo quinone (see **84**, Scheme 22) was a difficult and poor-yielding step. Here, clearly, was the place to make another significant improvement, and that we were able to achieve. This improvement was effected by introducing the phenylacetylene unit at the stage of monobromide **91** (Scheme 25).

Scheme 25 (first part)



We took the monobromo quinone and condensed it with phenylacetylene (**91**→**92**). The process[33] is mediated by palladium and copper catalysts in the presence of an amine, and the yield is

Scheme 25 (continued)



good.

It was now necessary to introduce bromine at C(3) of **92** because eventually we need a naphthalene with bromine in that position for halogen-metal exchange (*cf.* Scheme 20). To prepare for the bromination, quinone **92** was reduced, and the resulting hydroquinone was silylated (**92**→**93**→**94**). This sequence was dictated by the fact that the hydroquinone is very sensitive to bromine; it is oxidized back to the quinone (**93**→**92**). The silylated material, however, behaves in an acceptable way. Of course, silicon is not very electronegative and so C(6) of **94** is still a highly activated position.

Reaction with pyridinium bromide perbromide (Scheme 26) took the route as far as bromo naphthol **95**, and the other simple operations summarized in the Scheme completed the task of methylating the two oxygen substituents on ring E (**95**→**96**→**77**).

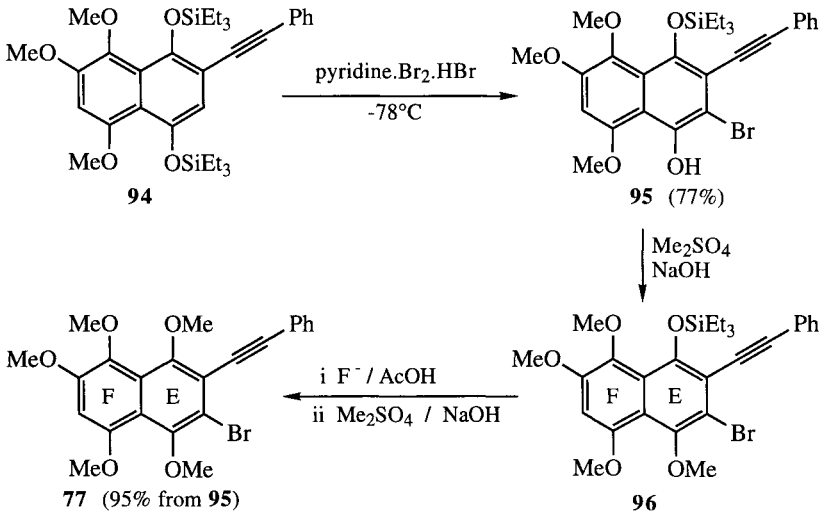
It *is* possible to prepare the pentamethoxy naphthalene **77** without isolating the intermediate **96**, but we generally prefer to isolate the partially methylated material, although we do not purify it. In removal of the silicon group of **96** the presence of acetic acid is essential; in its absence the intermediate phenoxide slowly attacks the acetylene side chain to produce a furan[34] that is not separable from the desired final product **77**.

A special feature of this route is that the oxygen substituents on ring E are protected sequentially, and it was later possible to take advantage of this fact in order to deal with the problem of intramolecular hydrogen transfer (see later).

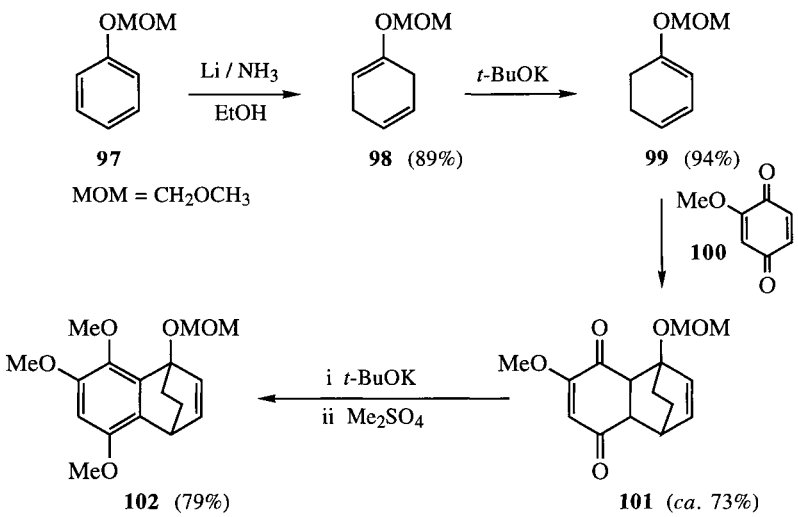
EF Ring System by a Diels-Alder Route

While the benzyne route to the EF ring system was being developed we also examined an approach, summarized in Scheme 27, based on a Diels-Alder reaction.[35-37] However, the benzyne route to the intermediate naphthol **89** is easier and was the method we

Scheme 26



Scheme 27 (first part)



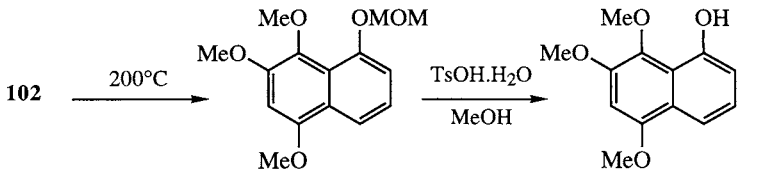
regularly used for large scale work.

FURTHER MODEL STUDIES

Deprotection of Oxygenated Naphthalenes

During the course of synthesizing the pentamethoxy naphthalene **77** we also made some related compounds, and with such materials we were able to explore ways of selectively deprotecting polyoxygen-

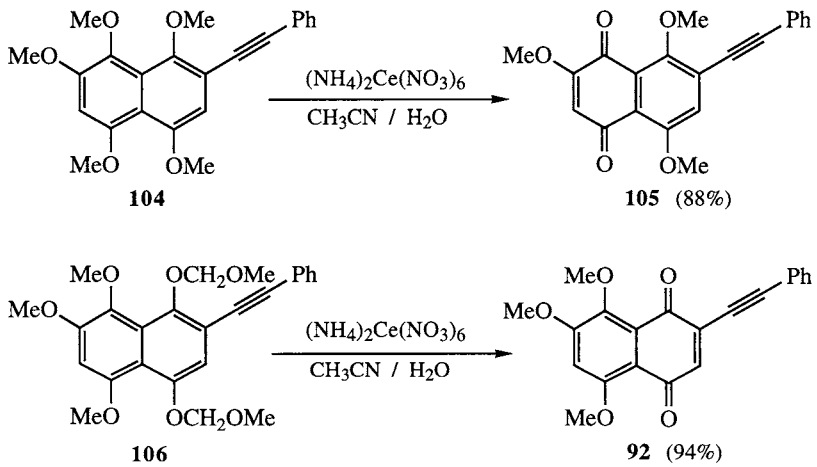
Scheme 27 (continued)



ated naphthalenes.

In one study (Scheme 28),[6hh] for example, we examined the response of the naphthalenes **104** and **106** to ceric ammonium nitrate. Where there are only methoxy groups, then the more highly

Scheme 28



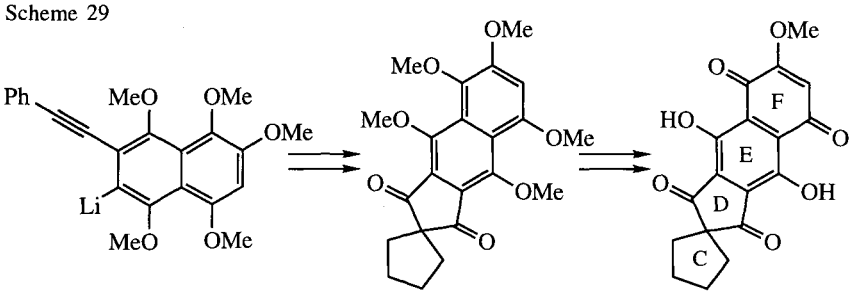
oxygenated ring is the one that is converted into a quinone, in accordance with prior literature.[6v] However, the regiochemistry can be altered by using methoxymethyl instead of methyl ethers. The effect of the methoxymethyl group is a general phenomenon but, in the event, we did not have to use this technique, and in any case methoxymethyl groups would probably have been incompatible with the radical spirocyclization because of the intervention of intramolecular hydrogen transfer.

Deprotection of CDEF Ring Models

We also carried out a more advanced model study to look at

other ways of deprotection. Our plan (Scheme 29) was to make the spiro diketone **107** and to convert it into the quinone system **108**.

Scheme 29

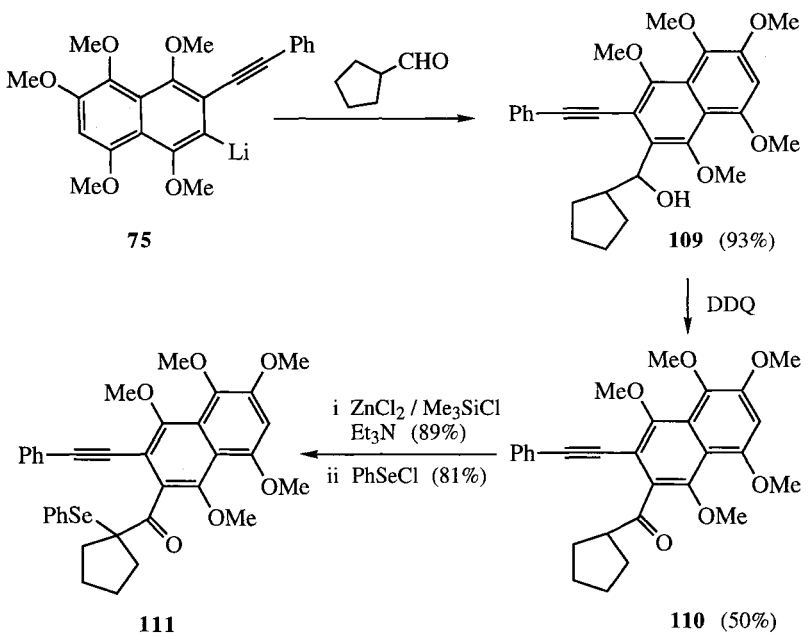


75 **107** **108**

Such an exercise would give us practice in assembly of the C—F rings of fredericamycin A.

Condensation of the lithiated naphthalene **75** (which we generated from the bromide by halogen/metal exchange) with cyclo-

Scheme 30



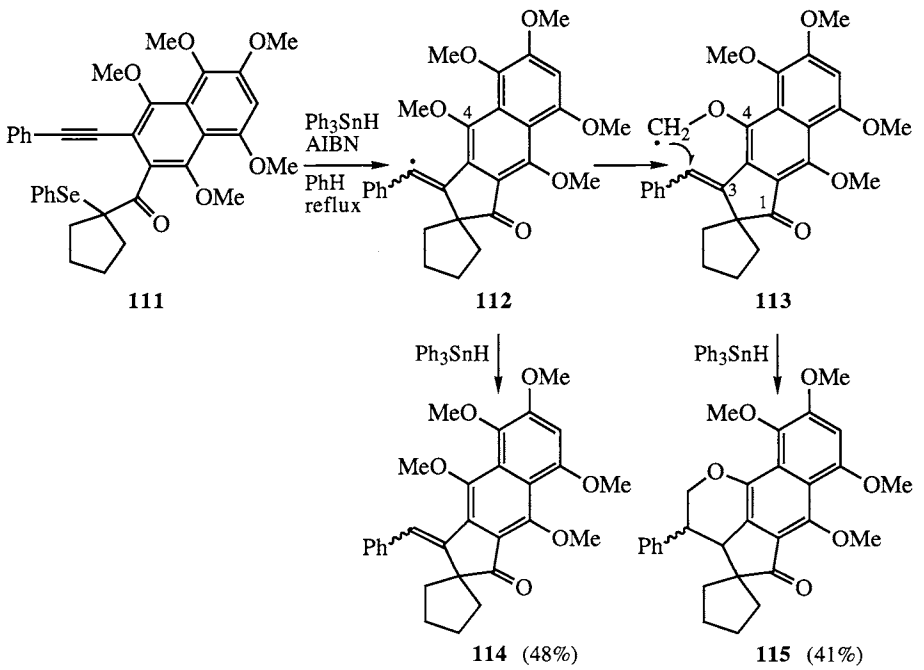
111 **110** (50%) **109** (93%)

pentanecarboxaldehyde proceeded without incident (Scheme 30), and the resulting alcohol could be oxidized to the ketone (**109**→**110**).

From that point we formed the corresponding silyl enol ether, and then introduced selenium in the normal way (**110→111**). The intermediate silyl enol ether has a rather unusual property in that it can be chromatographed on silica gel. Unlike normal trimethylsilyl enol ethers (as a general class), it does not decompose on ordinary silica.[38] Also the selenenylation was rather slow.

When we treated the selenide with triphenyltin hydride, the result was not very encouraging, because two products were formed

Scheme 31



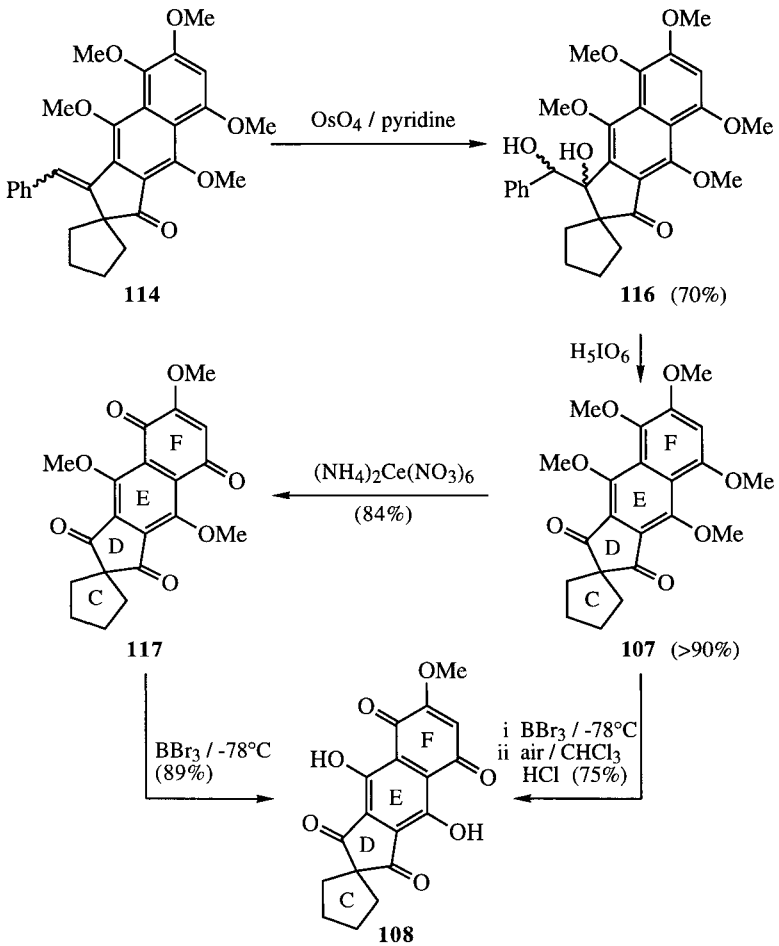
(Scheme 31). The mass balance is very good but the yield of the desired compound (**114**) is less than 50%. In this reaction, as in our earlier model study on radical spirocyclization (Scheme 16), we obtained best results when the stannane was introduced in one lot rather than by slow addition. However, if the concentration of the tin hydride is too high in the present case, then a number of stannylated byproducts are formed.

The undesired material **115** arises by intramolecular attack of vinyl radical **112** on the adjacent methyl group, so as to generate a new radical (**112→113**) which closes back onto the double bond

(**113→115**). The problem was dealt with at a later date (see below), but at this point we had accumulated enough of the desired spiro ketone **114** to see if the double bond could be cleaved and the appropriate oxygens deprotected.

Vicinal hydroxylation (Scheme 32) gave a mixture of diols (**114→116**), and the diols responded to periodic acid in the usual

Scheme 32



way. The final product was the spiro diketone **107**, which represents about half the structure of fredericamycin A, although in a heavily protected form.

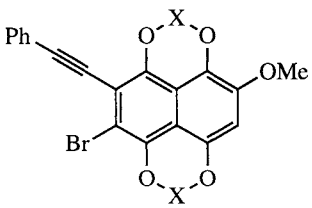
Treatment with ceric ammonium nitrate then served to convert

ring F into a quinone and, finally, exposure to boron tribromide removed two of the remaining *O*-methyl groups (**107**→**117**→**108**).

We also found that if the fully methylated compound **107** is itself treated with boron tribromide, and then exposed to air and to acid, the selective deprotection (**107**→**108**) can be accomplished directly.[39]

Suppression of Intramolecular Hydrogen Transfer

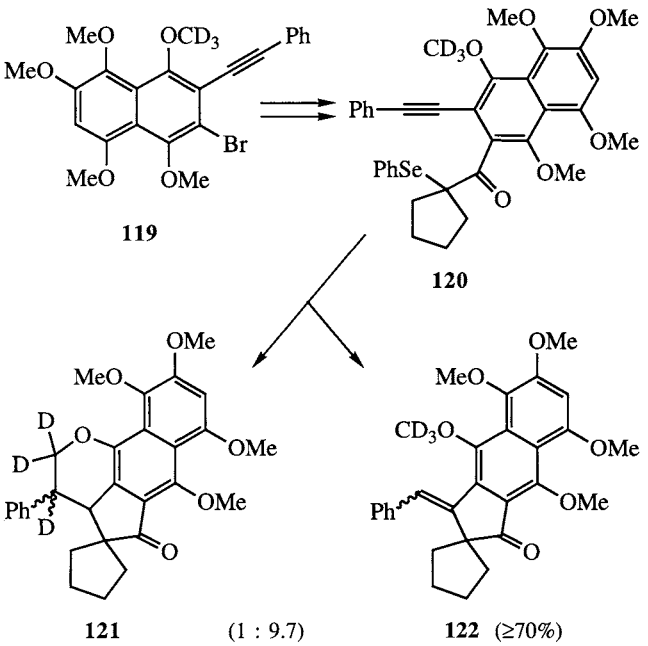
As indicated earlier (Scheme 31) the radical spirocyclization was marred by intramolecular hydrogen transfer even when *O*-methyl groups were used, so that when we had treated keto selenide **111** with triphenyltin hydride in refluxing benzene the ratio of the two products **114** and **115** was just a little better than 1:1 in favour of the desired material **114**. It is obvious that the peripheral substituents on the naphthalene force the C(4) *O*-methyl group close to the vinyl radical. Of course, we did try to improve selectivity by conducting the reaction at a low temperature[40] but we could not get it to work under such conditions. An obvious way to avoid the problem was to use as the EF subunit compounds such as **118**, but our



118 X = SiR_2; CR_2

attempts to protect the peri oxygens[41] in this way were unpromising. Consequently we examined the effect of replacing the offending *O*-methyl group by an *O*-trideuteromethyl group.[42] By chance, our route (Scheme 26) to the pentamethoxy naphthalene **77** very easily accommodated the required changes. We simply had to substitute trideuteromethyl *p*-toluenesulfonate[43] for dimethyl sulfate in the last step (*cf.* **96**→**77**) of Scheme 26 in order to obtain the deuterated naphthalene **119** (Scheme 33). This was used exactly as before (*cf.* Scheme 30) to prepare the labelled selenide **120**. Now, when we carried out the radical spirocyclization under our standard thermal conditions the operation of isotope effects changed the ratio of the two types of product (see **121** and **122**) to

Scheme 33



almost 10:1 in favour of what we wanted (compounds **122**).

Just as a precautionary measure, we now used the methods of Scheme 32 to degrade **122** into **108**, and found that all the reactions work without incident.

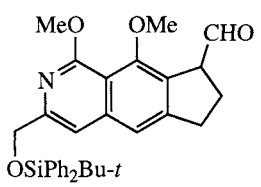
What we had achieved, then, was to improve a protecting group by isotopic substitution,[44] and this had been done without need for any detour from our main synthetic path.

Naturally, we felt at this point that our model studies for the quinone system of fredericamycin A were complete.

SYNTHESIS OF THE ABC SUBUNIT

Model Study

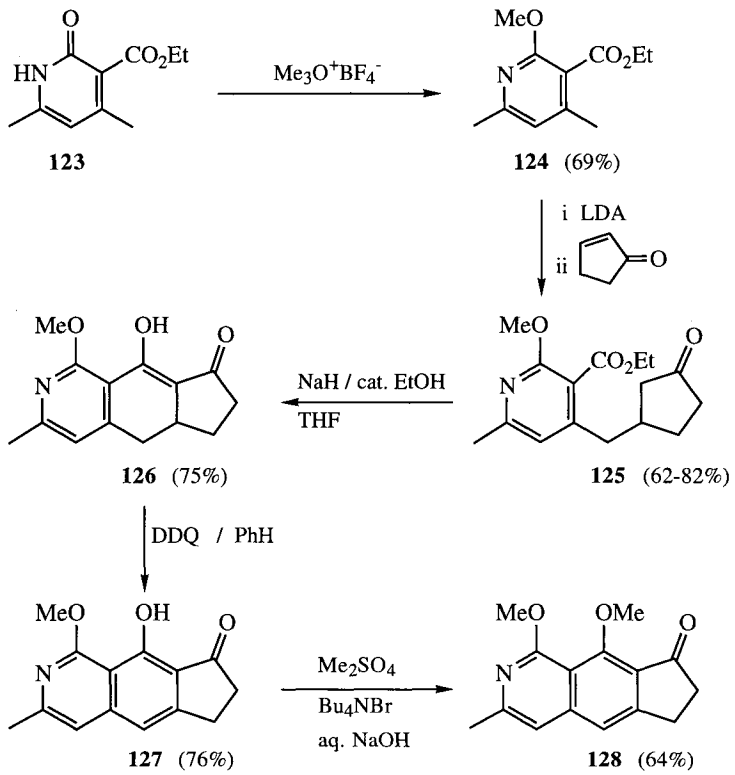
Compound **74** (see Scheme 19) represents an unusual structure



74

and, in order to gain experience in making this type of substance, we prepared the model **128**, using the route summarized in Scheme 34.

Scheme 34



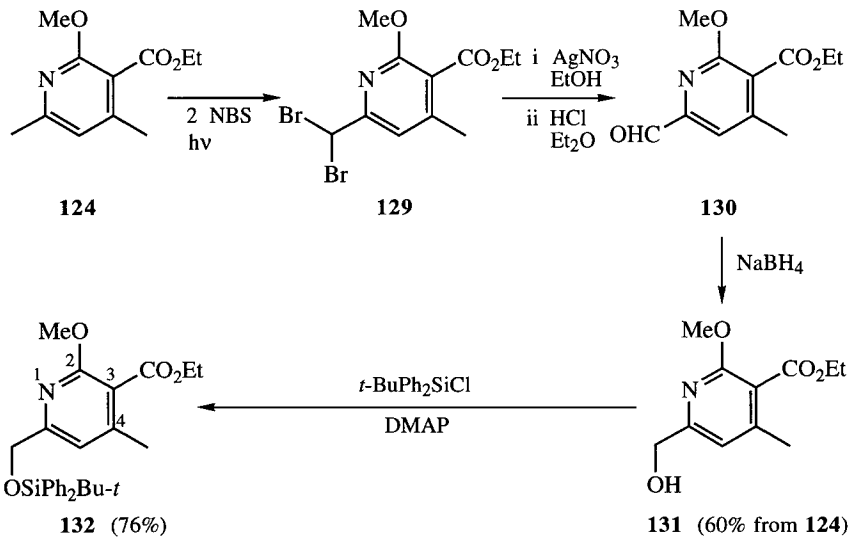
Although this approach was straightforward, making the actual ABC ring unit **74**, in which the pyridine ring carries a functionalized carbon, as opposed to the methyl group of **128**, took a great deal of time and effort. Several totally different approaches had to be examined before we found that the method of Scheme 34 could be modified for our purposes.

Synthesis of the ABC Subunit

Again, the route begins with the readily accessible[6s] pyridone **123**, which is methylated on oxygen with trimethyloxonium tetrafluoroborate (**123**→**124**, Scheme 34). Treatment (Scheme 35) of the dimethylpyridine **124** with *N*-bromosuccinimide took an unexpected but most helpful course, as the gem dibromide **129** was formed. The

result of free radical bromination of dimethylarenes is not easy to predict,[45] and we had been prepared to use a product in which each of the methyl groups of **124** was brominated; however, the actual product was much more convenient for us. Hydrolysis to an

Scheme 35

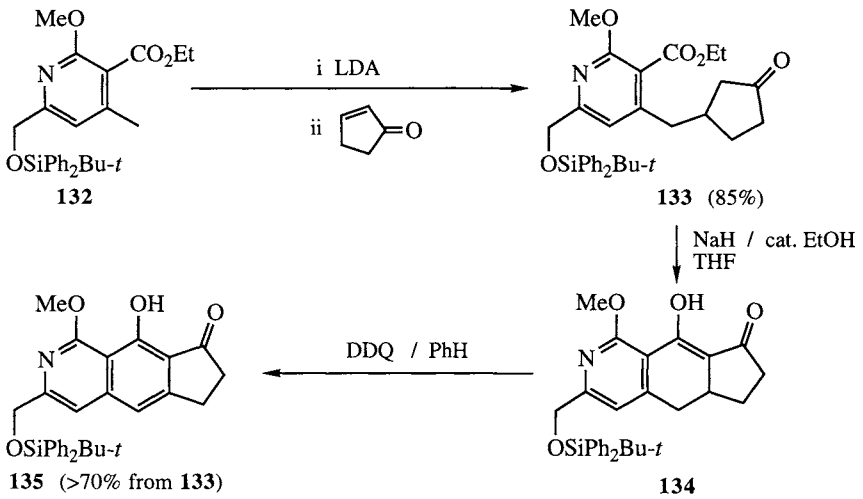


aldehyde, reduction to an alcohol, and protection (**129**→**130**→**131**→**132**), worked without much difficulty.

Just as in the model study of Scheme 34, it was possible to deprotonate the C(4) methyl group of **132**, and the resulting carbanion added smoothly in a conjugate manner to 2-cyclopentenone (**132**→**133**, Scheme 36). Base-catalyzed cyclization then gave a β-diketone (**133**→**134**), which exists in an enolized form, and dehydrogenation afforded the naphthol **135**. We experienced some difficulty in methylating the naphthol (**135**→**136**), and could obtain a satisfactory yield only by use of a Mitsunobu reaction[46] (Scheme 37) — a process not normally employed for methylation of phenols.

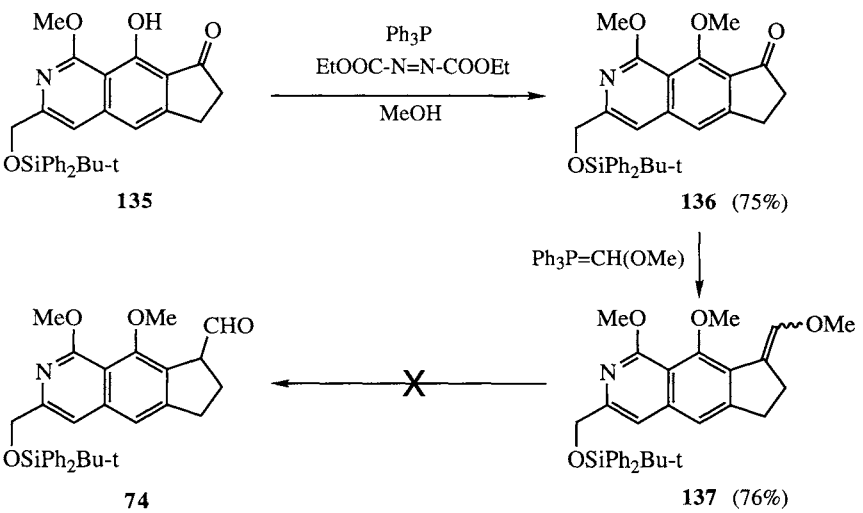
When we used benzyl alcohol or triethylsilanol in the Mitsunobu process, then we obtained compounds **138** and **139** respectively, in which the ring B oxygen is protected as a benzyl or silyl ether. These last two experiments were done at a much later date and, at about that time, we also prepared the methoxymethyl ether **140**. This compound was accessible (81%) from

Scheme 36

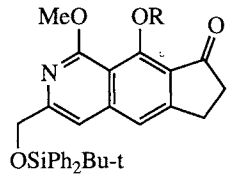


naphthol **135** by treatment with methoxymethyl chloride in the presence of diisopropylethylamine.

Scheme 37



We made compounds **138—140** because we were not at all confident of our ability to remove a ring B *O*-methyl group. However, near the end of the synthesis we were lucky enough to find a curious method for that deprotection.

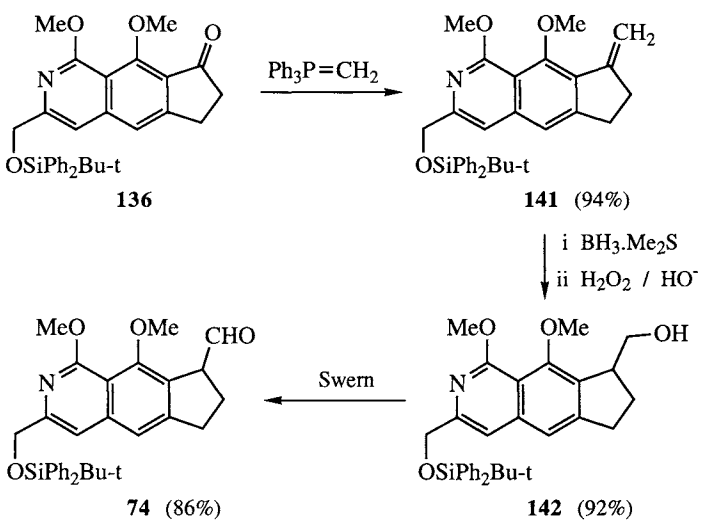


138 R = CH_2Ph
139 R = $SiEt_3$
140 R = CH_2OCH_3

The use of silanols in a Mitsunobu reaction is an unusual but general process which we have tried with a number of phenols and secondary alcohols. In the case of secondary alcohols the silylation occurs with retention and so a displacement is occurring on silicon. In the fredericamycin A work (where a number of conventional silylation techniques[47] were unsuccessful with **135**) we used triethylsilanol, but the reaction is not limited to that.[48]

To return to the methyl series: A Wittig reaction (Scheme 37) gave a mixture of enol ethers (**136**→**137**) but, unfortunately, we could not hydrolyze them without damaging other parts of the molecule. However, this problem was readily overcome, because a different Wittig reaction (**136**→**141**, Scheme 38), followed by hydroboration, gave an alcohol (**142**) that was easily oxidized to the required aldehyde **74**.

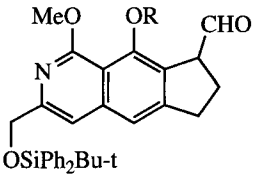
Scheme 38



136
141 (94%)
74 (86%)
142 (92%)

At a later date we used the same procedure to convert the benzyl and methoxymethyl derivatives **138** and **140** (but not the silyl ether **139**, which was too labile) into the corresponding

aldehydes **143** and **144**, and these compounds were taken forward a number of steps as a reserve that, in the event, was not actually needed (see later).



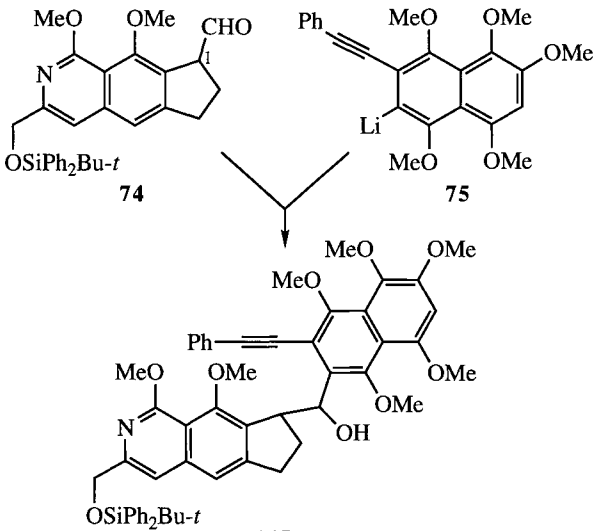
143 R = CH_2Ph
144 R = CH_2OMe

LINKING OF THE SUBUNITS AND RADICAL SPIROCYCLIZATION

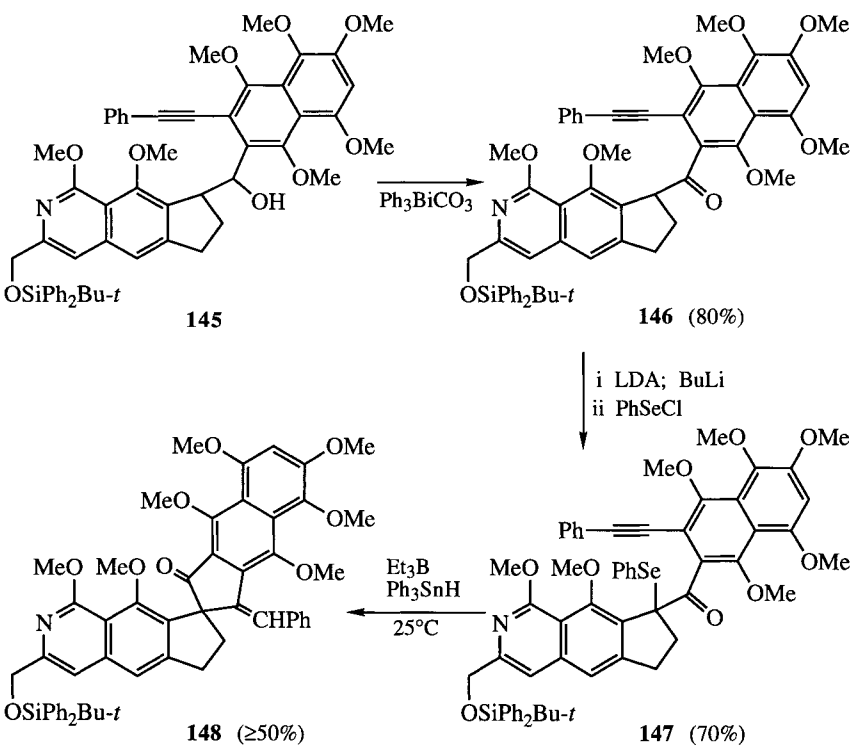
With aldehyde **74** and pentamethoxy naphthalene **77** in hand, the next step was to link the two units together. Halogen/metal exchange smoothly converted the naphthalene into the required organolithium **75**, and this species reacted very efficiently (93%) with cyclopentanecarboxaldehyde, as indicated earlier (Scheme 30). However, the response of aldehyde **74** was quite different, and in all our many early attempts little of the desired coupling product **145** (see Scheme 39) was formed. We tried a number of standard procedures to raise the yield: the C(1) hydrogen of **74** was replaced by deuterium and we also used cerium, zirconium, or titanium salts corresponding to the lithium salt **75**. At one point we even began to explore a modified route[49] that still utilized many of the reactions we had already studied, but which altered the sequence in which the rings are assembled. Eventually, though, we discovered that bromide **77**, which is the precursor to the organolithium, usually contains a trace contaminant that inhibits the desired coupling. This impurity is not apparent from 400 MHz ^1H NMR spectra but, if the bromide is chromatographed and crystallized (90% recovery in the purification process) before use, then the coupled alcohol **145** can be isolated in 68% yield (Scheme 39). We get in this coupling only one alcohol and we did not determine its stereochemistry because in the next step one of the asymmetric centers is removed by oxidation to a ketone (Scheme 40).

That oxidation was best done with triphenylbismuth carbonate[51] (**145→146**). Next we selenated the ketone (**146→147**), and here again the experimental conditions are crucial (and took some time to develop[52]). After deprotonating the ketone with LDA, an equivalent of butyllithium must be introduced, followed by benzeneselenenyl chloride. This procedure gives the required

Scheme 39

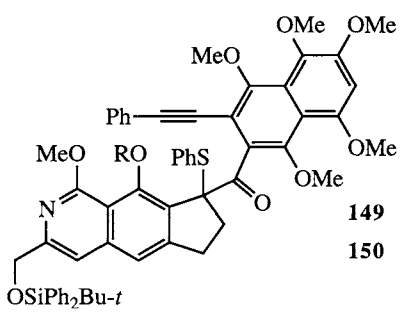


Scheme 40



selenide in good yield and, when the compound is treated at room temperature with triphenyltin hydride in the presence of triethylborane and air,[40] the required α-keto radical is formed and it cyclizes to the advanced intermediate **148**. After several trial runs, this crucial experiment was done twice, using each time over a gram of selenide, and it gave the product in more than 50% yield, as a single isomer whose stereochemistry was not established.[53] As we were not here relying on deuterium isotope effects to suppress unwanted intramolecular hydrogen transfer, we sought to optimize selectivity by performing the reaction at room temperature instead of in refluxing benzene. In an earlier model experiment (Scheme 31) we had also tried to generate the radical at room temperature (with the same purpose in mind) but had been unsuccessful. In the present case, however, the radical to be formed is both benzylic and α to a ketone, while earlier (*cf.* **111**) activation was provided only by a ketone function.

Parallel with our efforts to make selenide **147** we examined, as a precautionary measure, a similar sequence to that shown in Schemes 39 and 40, but using as the ABC unit compounds **143** and **144**, in which the ring B oxygen is protected as a benzyl or methoxymethyl ether. Introduction of selenium was not possible, but we were able to make sulfides **149** and **150**. Each of these does



149 R = CH_2Ph

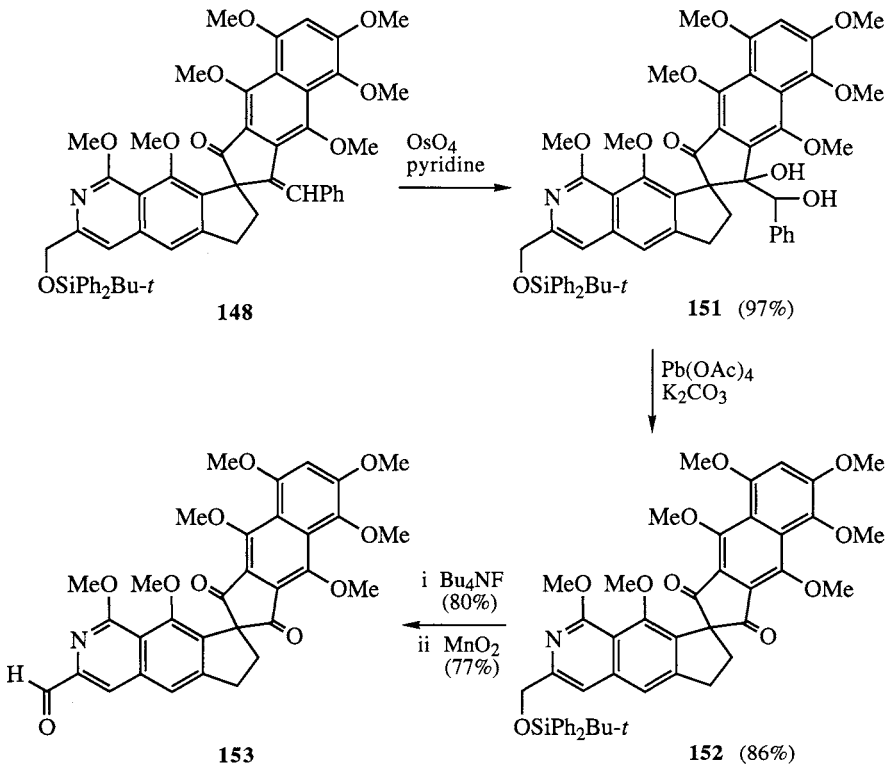
150 R = CH_2OMe

undergo the radical spirocyclization but, before we had optimized the benzyl or methoxymethyl sequences, it had become clear that our worries about deprotection of ring B were unfounded.

Completion of the Synthesis

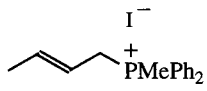
Having brought the synthesis to the point of compound **148**, the next task was to cleave the exocyclic double bond, and we planned to do that by vicinal hydroxylation followed by diol

Scheme 41



cleavage (**148**→**151**→**152**). That hydroxylation proved very troublesome until we realized that the concentration of osmium tetroxide must be high in order to increase the rate of hydroxylation relative to some undesired processes that also occur. As shown in Scheme 41, the yield is very good, when the reaction is done under the proper conditions. Cleavage of the diol with lead tetraacetate was straightforward, and we were then almost ready to build up the pentadienyl side chain. To prepare for that, the protected hydroxymethyl group on the pyridine ring was desilylated and oxidized to an aldehyde (**152**→**153**), both steps being very efficient under standard conditions.

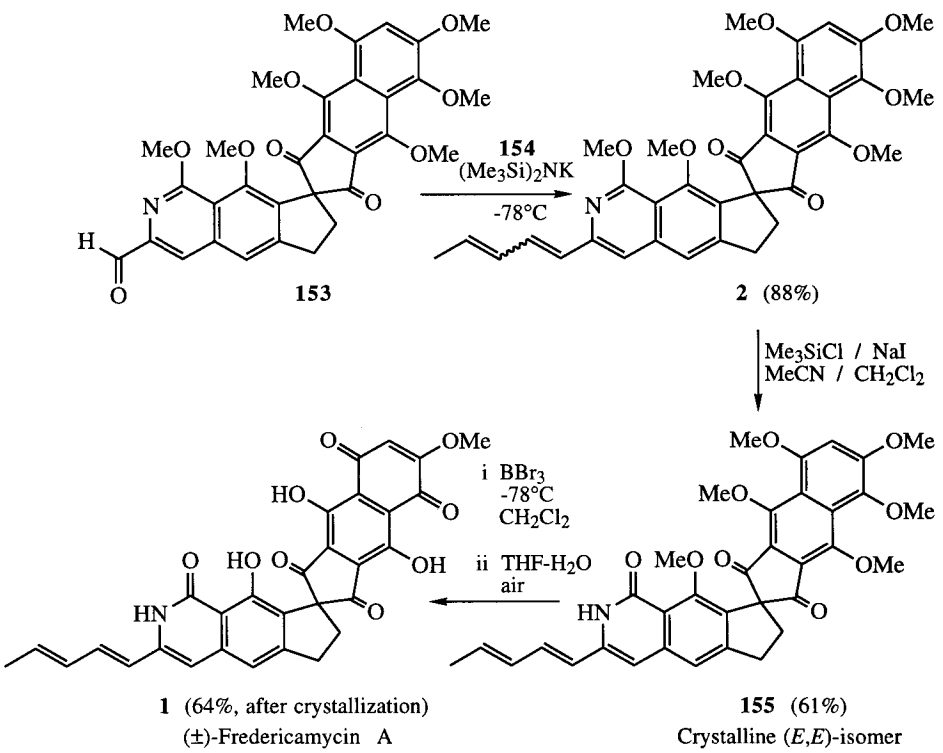
A careful examination of the literature suggested that the Wittig reagent derived from the phosphonium salt **154**[54] should be used for construction of the pentadienyl side chain. Wittig reagents with the same substitution pattern on phosphorus give *E,E*



154

dienes with aliphatic aldehydes, but much lower selectivity with benzaldehyde. The particular reagent **154** does not appear to have been used with aromatic aldehydes and, when we tried it, we obtained a mixture of two (16:84) geometrical isomers (**2**). We were unable to separate them and decided to continue, if only to gain experience with the deprotection.

Scheme 42



To our surprise, only a few orienting experiments were needed, and we quickly found that when the isomer mixture **2** is treated with an excess of trimethylsilyl chloride and sodium iodide,[55] it is possible to isolate compound **155** as a pure crystalline substance in 61% yield. This reaction has some peculiar features. First of all, only the oxygen substituent on the pyridine ring is

deprotected, even though we use an excess of reagent. Secondly, compound **155** is easily isomerized by light[56,57] and (although we have no evidence on this point[58]) it may be that a mobile equilibrium among the isomers is displaced in the mother liquors as the *E,E* material crystallizes out. The sensitivity of **155** to light (and possibly, also to acid) is such that for some days we did not realize that isomerically pure material was in hand: all our ^{1}H NMR spectra revealed the presence of isomer mixtures, but preparation of the solution in the dark, preferably using deuterated DMF, soon revealed the true situation.

Finally, exposure to boron tribromide[59] selectively deprotects[60] five of the remaining six *O*-methyl groups to give a borate ester. Aqueous hydrolysis[61] and aerial oxidation then affords synthetic fredericamycin A (**155**→**1**), which we crystallized from a mixture of chloroform, methanol and acetic acid — a solvent combination that was found totally by chance. The synthetic material was identical with a natural sample as judged by ^{1}H and ^{13}C NMR spectra and a number of chromatographic assays.

Acknowledgements. We thank the Natural Sciences and Engineering Research Council of Canada for financial support. An NSERC Postdoctoral Fellowship (YJW), an Alberta Heritage Foundation for Medical Research Graduate Fellowship (SMB), an FCAR (Quebec) Postdoctoral Fellowship (LB), an FCAR (Quebec) Graduate Fellowship (MC), an NSERC Summer Undergraduate Award (GK[62]), and AHFMR Summer Undergraduate Awards (CJN,[62] SRR[62]) are gratefully acknowledged. CNB was a High School research participant. We thank H. W. Manning (U of A) and Professor E. Vedejs for advice; D. Lucyk,[62] N. Khazanovich,[62] F. Sartorelli,[62] and Dr. C. Lowe for assistance; and Dr. S. Forenza (Bristol-Myers Squibb) and Dr. M. Suffness (NIH) for samples of natural **1** and its potassium salt, respectively.

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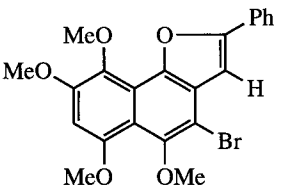

i

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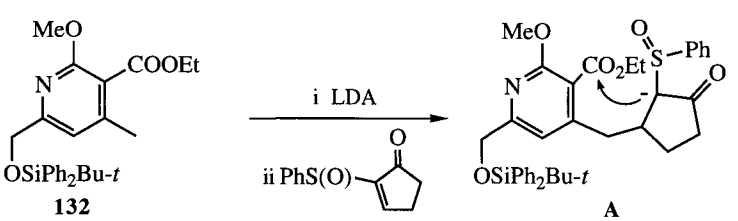
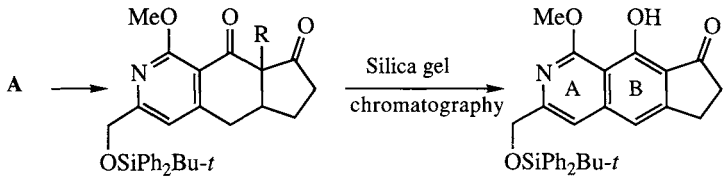
49 We first tested the possibility (see Scheme i) of adding the ring A unit late in the synthesis. The conjugate addition (**132**→**A**) worked well and afforded directly **135**, in which the B ring had been aromatized.

Scheme i (first part)



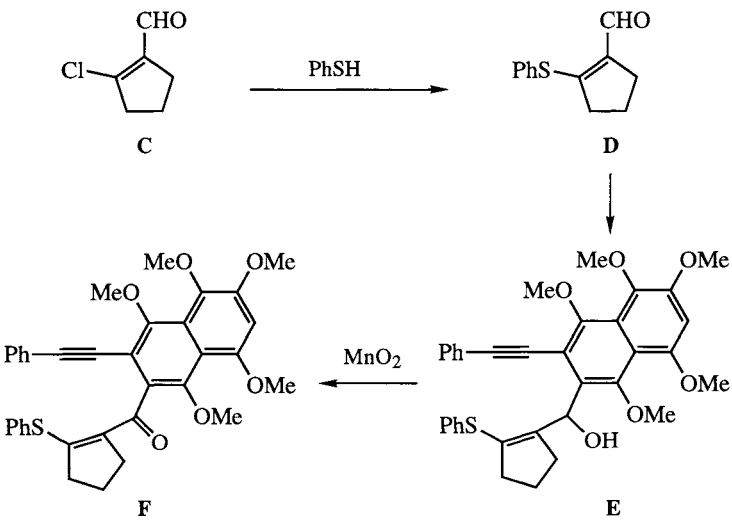
Next, we converted the known[50] chloro aldehyde **C** into the phenylthio compound **D** (Scheme ii), and condensed that material with our lithiated naphthalene (**D**→**E**). Oxidation with manganese dioxide then served to generate ketone **F**.

Scheme i (continued)



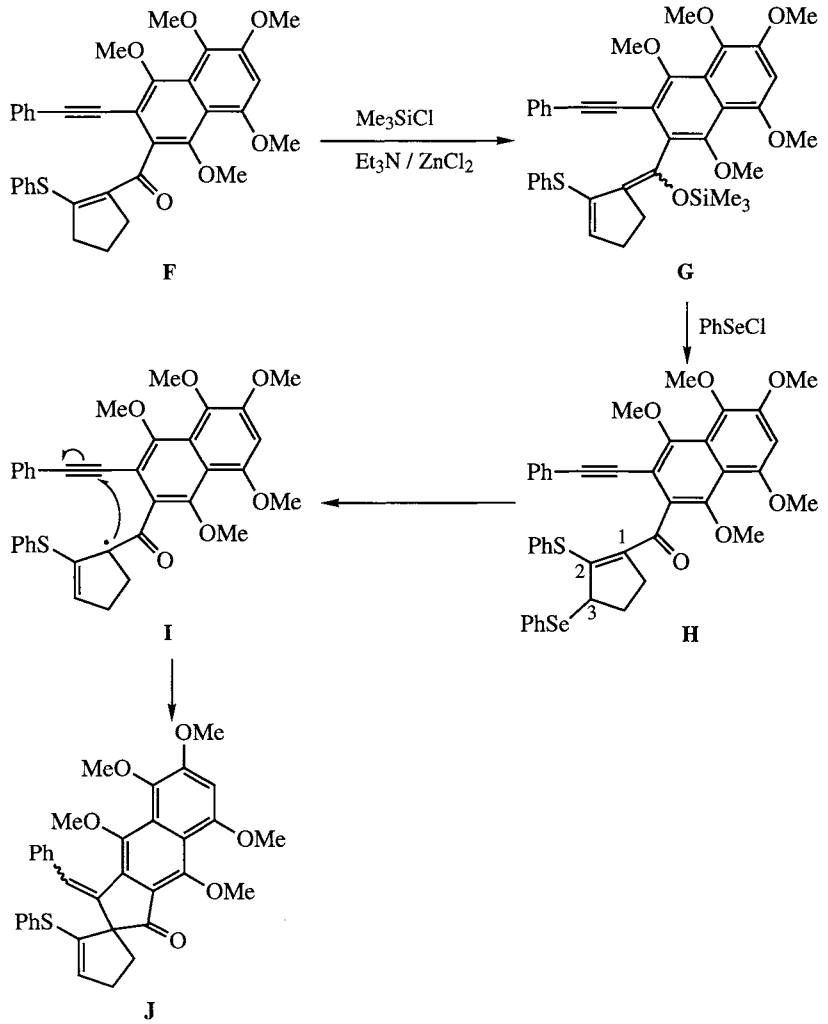
B R = S(O)Ph **135**

Scheme ii



The ketone was selenenylated in two steps (Scheme iii): formation of the trimethylsilyl enol ethers (**F**→**G**) followed by treatment with benzeneselenenyl chloride. The product of this sequence (**H**) contains a small amount of an isomer in which the benzeneseleno group is at C(1) and the double bond at C(2)–C(3), but both isomers are equally suitable as precursors to radical **I**. In the event, when selenides **H** are treated with triphenyltin hydride in refluxing benzene the desired radical is formed and it closes to afford the spiro ketones **J**. Oxidation to the corresponding sulfoxide was not easily achieved, but use of *m*-chloroperbenzoic acid gave the sulfoxides in modest yield (*ca.* 53%). Unfortunately, our attempts to carry out the conjugate addition (*cf.* Scheme i, **132**→**A**) were unsuccessful. We did not pursue this matter, however, because by this stage the problem in the main series

Scheme iii



had been solved.

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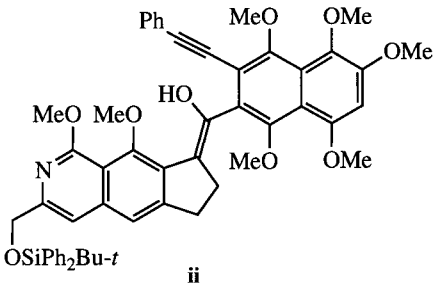
52 During attempts to selenenylate ketone **146**, we isolated what we believe to be the enol **ii** (arbitrary geometry shown for double bond).



ii

53 We did not examine the reaction mixture for the presence of another geometrical isomer. The cyclization can be done thermally in refluxing benzene but the triethylborane method is more reliable and gives a higher yield.

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56 Fortunately, this tendency is not shared, at least to such a significant degree, by fredericamycin A itself.

57 And possibly also to acid.

58 Iodine is liberated in the conversion of **2** into **155**, which is done without protection from light.

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60 When we treated the fully protected isomer mixture **2** with boron tribromide we found that under our mild conditions (-78°C) only the EF ring system is deprotected.

61 *Cf.* Fisher, M. J.; Chow, K.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 2900.

62 Summer Undergraduate research participant.

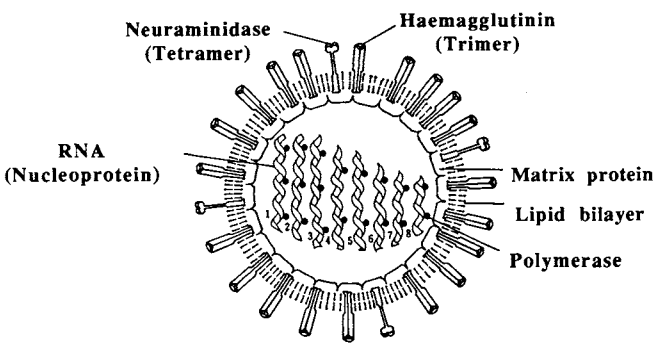
Atta-ur-Rahman (Ed.) *Studies in Natural Products Chemistry, Vol. 16*

Stereoselective Synthesis and Transformation of Siastatin B, A Novel Glycosidase Inhibitor, Directed toward New Drugs for Viral Infection and Tumor Metastasis

Yoshio Nishimura

1 INTRODUCTION

Recent studies (refs. 1-5) have proved that cell-surface carbohydrate, as glycoconjugates, are bioregulators which mediate in cell-to-cell communication, cell-cell recognition and the "social behavior" of cells. Telltale surface sugars are involved in various biological functions such as immune response, oncogenesis, metastasis of tumors, sperm penetration, differentiation of neuronal cells, and enhancement of neurite outgrowth. They can also serve as binding sites for antibodies, hormones, toxins, bacteria, drugs, lectins, fibronectins, enzymes, and viruses. New drugs aimed at such carbohydrates could stop infection, inflammation, *etc.* through a better understanding of biochemical processes.

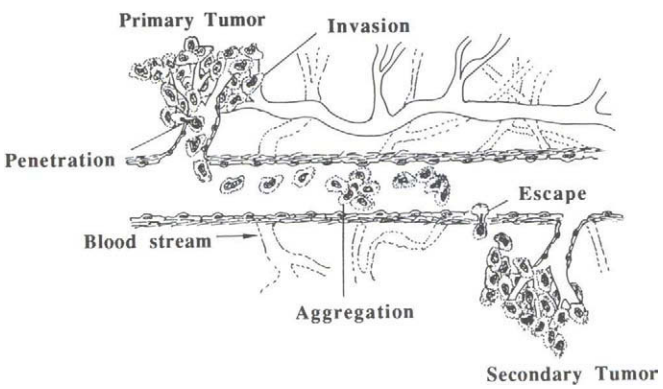


Structure of influenza A virus

Influenza virus express two integral membrane glycoproteins, haemagglutinin and neuraminidase, on the envelope. Influenza virus infection is initiated by the attachment of haemagglutinin to cell-surface receptor containing *N*-acetyl-neuraminic acid (sialic acid) and subsequent membrane fusion (refs. 6-8). The

neuraminidase (sialidase, EC 3.2.1.18) of influenza virus is involved in the elution of progeny virions from the infected cells (ref. 9) and the prevention of self-aggregation of progeny virions (ref. 10), and may facilitate transport of the virus through the mucus within the respiratory tract (ref. 11). Thus, the neuraminidase, which hydrolyzes either α(2,6)- or α(2,3)-ketosidic bonds between terminal sialic acid and adjacent carbohydrate residues on glycoconjugates, is an important factor in the spread of the infection.

The structure of carbohydrates on cancer cells is remarkably distinct from that on normal ones (refs. 12-16). Cell surface carbohydrates also change upon malignant transformation (ref. 17) and exhibit differences in the tumor cell surface properties between metastatic and nonmetastatic cells (refs. 17-19). It was proved that the total and neuraminidase-releasable neuraminic acid (sialic acid) content of tumor cell surface seems to be closely related to the metastatic potential of the tumor cells (refs. 20-25). Metastasis formation occurs *via* a complex multistage

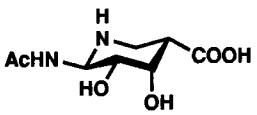


The process of tumor cell metastasis

process which includes an important step of tumor cell penetration into endothelial basement membrane. Tumor invasion through the basement membrane involves cell adhesion to various basement membrane components, degradation of extracellular matrix and basement membranes, and cell migration to the target tissue. Proteolytic enzymes secreted by metastatic tumors are capable of degrading extracellular matrix and basement membrane components, and their activities are closely related to the metastatic potential of the tumor cells (refs. 26-31). For example, heparanase (end-β-glucuronidase) in malignant tumor cells degrades heparan sulfate proteoglycan, a major constituent of endothelial basement membranes, and correlates with the metastasis (ref. 32).

In 1974, siastatin B (*1*), an inhibitor of sialidase (neuraminidase), was isolated from *Streptomyces* culture (ref. 33). Siastatin B is a natural inhibitor for neuraminidase, cleaving sialic acid to yield terminal oligosaccharide chains of

glycoproteins or glycolipids. Siastatin B inhibits neuraminidases isolated from various microorganisms and animal tissues as well as β-D-glucuronidase and *N*-acetyl-β-D-glucosaminidase. Chemical, biochemical and pharmacological studies on siastatin B can have practical applications to the prevention and treatment of viral infection and cancer. The present article describes our recent progress in the chemistry, biochemistry and pharmacology of siastatin B focused on new drugs for antiviral and cancer chemotherapy.



Siastatin B

2 THE TOTAL SYNTHESIS AND ABSOLUTE CONFIGURATION OF SIASTATIN B

The relative configuration of siastatin B was determined as 6(*R*/*S*)-acetamido-4(*S*/*R*)-5(*R*/*S*)-dihydroxypiperidine-3(*S*/*R*)-carboxylic acid by ^{1}H NMR and X-ray crystallographic studies (ref. 33). The absolute configuration of siastatin B was speculated from its biological activity to be that shown in *1* by analogy with *N*-acetylneuraminic acid (*2*) and glucuronic acid (*3*). Compound *1* has an unusual

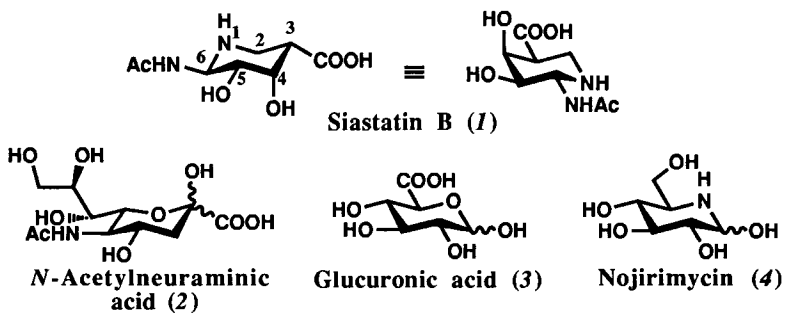
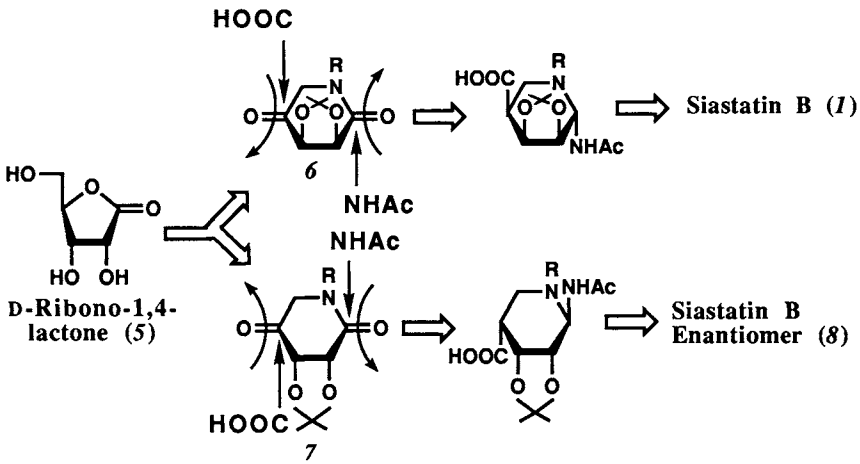


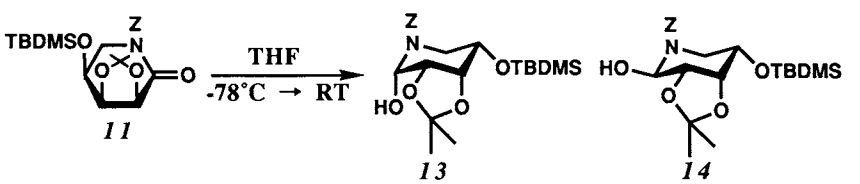
Fig. 1

structure possessing the continuous -CH(NHAc)-NH-CH_2-CH(COOH)- constituent in a frame work. It is distinct from general glycohydrolase inhibitors belonging to the sugar analogues having a piperidine ring such as nojirimycin (*4*) (ref. 34). The strategy for total synthesis (refs. 35-38) is based on an enantiodivergent method employing D-ribono-1,4-lactone (*5*) as a chiral source *via* stereospecific introduction of *N*-acetyl and carboxyl substituents into the key intermediate-lactams (*6* and *7*) (Scheme 1). The method is applicable to a wide range of siastatin B analogues.



Scheme 1

As shown in Scheme 2, the synthesis of the key intermediate, lactam ***10***, began with L-ribose (ref. 39), enantiodivergently prepared from ***5***. L-Ribose was transformed to 5-azido-5-deoxy-2,3-*O*-isopropylidene-L-ribonolactone (***9***) by protection of the 2,3-diol, azido formation, and oxidation (ref. 40). Hydrogenation of the azide group of ***9*** and ring expansion by catalytic hydrogenation afforded crystalline ***10***. Stereospecific introduction of the hydroxyl group at C-2 was best achieved by hydride reduction of the protected lactam ***11*** to ***12***, and Swern oxidation (ref. 41) to give the axial aminal ***13***. Remarkably, a single stereoisomer controlled by an anomeric effect (ref. 42) results from this oxidation, whereas oxidation with CrO_3 in pyridine gives a 2:1 mixture of ***13*** and its epimer, equatorial



		Yield
i-Bu_2AlH (1.2 eq)	trace	87%
LiB*sec*-Bu_3H (1.2 eq)	88%	trace

Fig. 2

aminal ***14***. One-step stereospecific transformation from the lactam ***11*** into ***13*** was also best achieved by L-selectride reduction in tetrahydrofuran (THF) in excellent yield. On the other hand, diisobutylaluminum hydride (DIBAH) reduction in THF gave predominantly ***14*** in excellent yield (Fig. 2). Stereoselectivity in L-selectride reduction was caused by hydride attack from the less sterically hindered, upper side,

whereas in DIBAH reduction it was controlled by metal chelation between aluminum and oxygen atoms of the isopropylidene group. Displacement of the axial hydroxyl group in ***13*** to the equatorial amino group proved troublesome until the Mitsunobu reaction (ref. 43), using phthalimide in *N,N*-dimethylformamide as a solvent, was uncovered to give quantitatively the equatorial phthalimido ***15***. Replacement of the amino substituent from phthaloyl in ***15*** to acetyl, removal of *t*-butyldimethylsilyl group and oxidation furnished the acetamido ketone ***18***. Condensation of ***18*** with nitromethane was found to proceed smoothly to give the

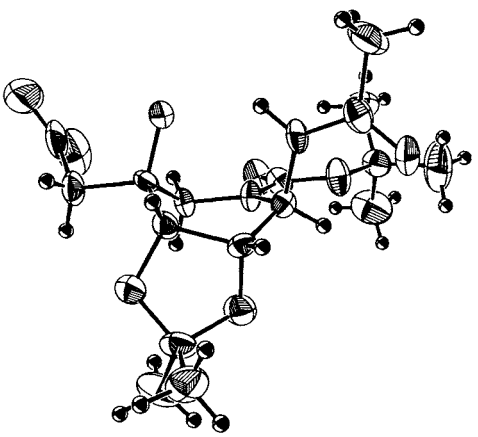
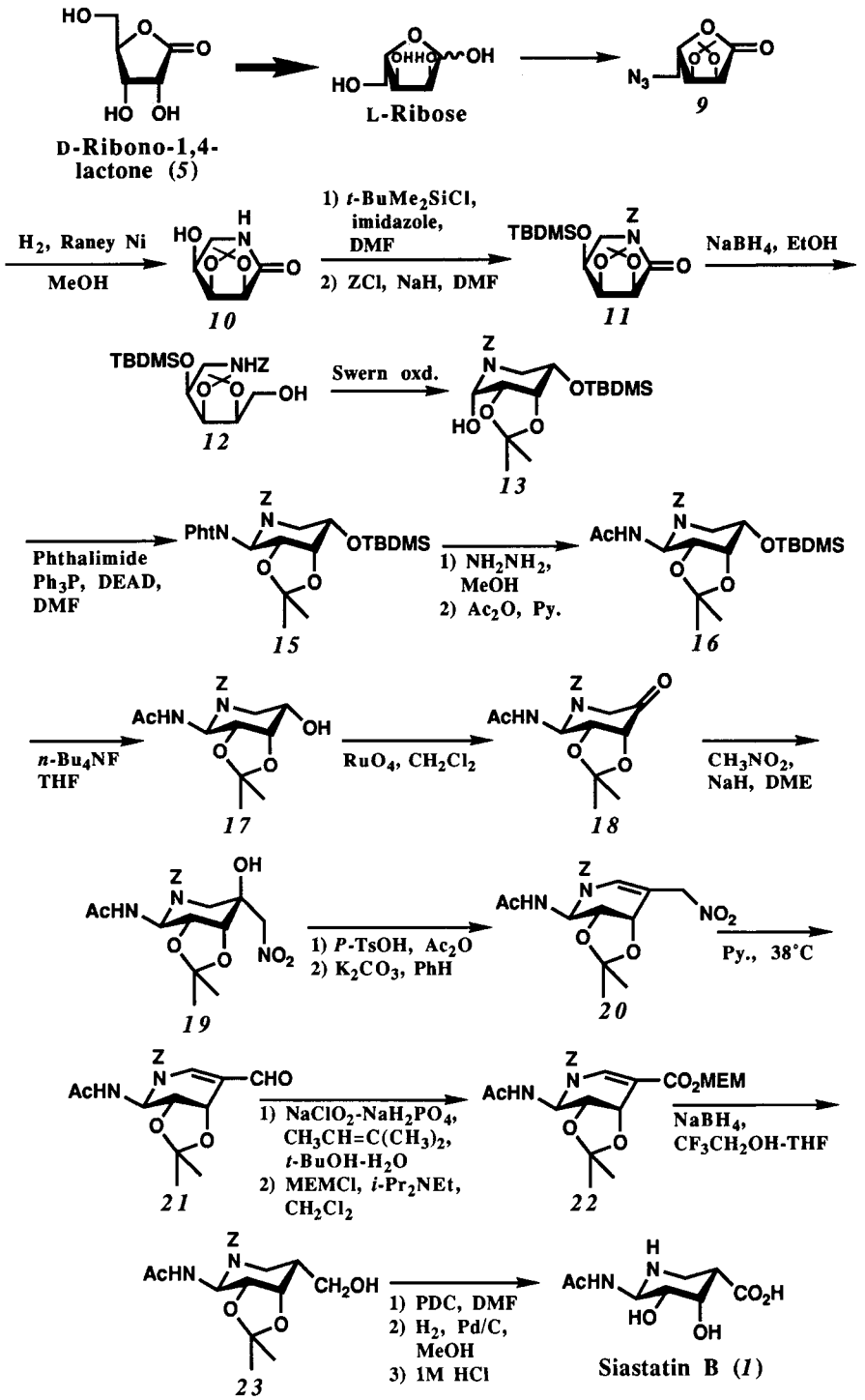


Fig. 3. X-Ray molecular structure of *24*

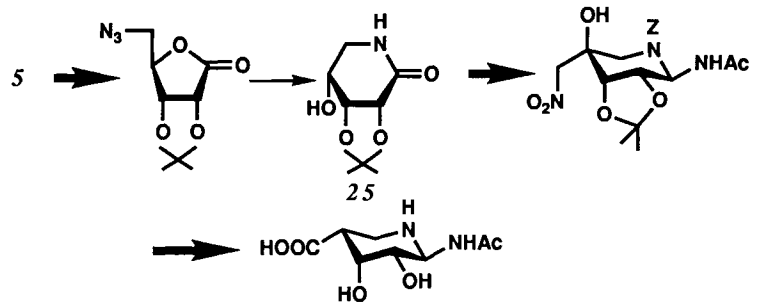
nitromethyl adduct ***19***. The stereochemistry at C-5 was deduced to be *S*-configuration by analogy with the stereochemistry of synthetic *N*-(*t*-butoxycarbonyl) antipode ***24*** determined by X-ray crystallographic anlaysis (Fig. 3, ref. 44, see section 3.1). The boat conformation caused by the fused isopropylidene and bulky *t*-butoxycarbonyl groups leads to an axial orientation of the *N*-acetyl group, and consequently the nucleophile attacks from the less sterically hindered, lower side. The structure of ***19*** was also supported by the smooth base-catalyzed β-elimination of the acetoxyl group of the acetate of ***19***. Acetylation of ***19*** followed by base-catalyzed elimination of the acetoxyl group afforded exclusively the endocyclic nitro olefin ***20***. The compound ***20***, upon simply warming in pyridine, afforded the α,β-unsaturated aldehyde ***21***, which was converted to the carboxylate ***22*** by a subsequent oxidation and protection. Catalytic reduction (ref. 45) of the double bond in ***22*** accompanied by elimination of the hydroxyl group at C-4, and hydride reduction (ref. 46) of the double bond with or without combination of a transition metal also proceeded unfavorably and without chemoselectivity. To circumvent this problem, ***22*** was stereoselectively hydrogenated to the α,β-saturated hydroxymethyl compound ***23*** by sodium borohydride in 1:10 mixture of 2,2,2-trifluoroethanol and THF. The carboxylic acid formed upon oxidation of ***23*** was converted by removal of the protecting groups to crystalline ***1***. Its spectral


D-Ribono-1,4-lactone (5)
L-Ribose
9
10
11
12
13
15
16
17
18
19
20
21
22
23
Siastatin B (1)
H2, Raney Ni
MeOH
1) t-BuMe2SiCl, imidazole, DMF
2) ZCl, NaH, DMF
NaBH4, EtOH
Swern oxd.
Phthalimide
Ph3P, DEAD,
DMF
1) NH2NH2,
MeOH
2) Ac2O, Py.
n-Bu4NF
THF
RuO4, CH2Cl2
CH3NO2,
NaH, DME
1) P-TsOH, Ac2O
2) K2CO3, PhH
Py., 38°C
1) NaClO2-NaH2PO4,
CH3CH=C(CH3)2,
t-BuOH-H2O
2) MEMCl, i-Pr2NEt,
CH2Cl2
NaBH4,
CF3CH2OH-THF
1) PDC, DMF
2) H2, Pd/C,
MeOH
3) 1M HCl

Scheme 2

properties (IR, ^1H NMR, ^{13}C NMR, mass spectrum) and specific rotation were identical with those of the natural specimen.

The enantiomer *7* was also prepared in a straightforward manner by the same sequences mentioned above from 5-amino-5-deoxy-2,3-*O*-isopropylidene-D-ribono-lactam (*25*) (ref. 40), readily available from *5*. Compound *7* was identical in all respects with the synthetic and the natural *1* except for the sign of the specific rotation.



Siastatin B Enantiomer (*7*)

Scheme 3

Thus, the absolute configuration of siastatin B has been elucidated as the (3*S*,4*S*,5*R*,6*R*)-isomer *1* (refs. 35-38). Synthetic *1* shows the same inhibitory effects as the natural one against neuraminidases (*Clostridium perfringens*, *Streptomyces*, chorioallantoic membrane), β-D-glucuronidase and *N*-acetyl-β-D-glucosaminidase, whereas *7* demonstrates weak activity against only β-D-glucuronidase (IC_{50}=50 μg/ml).

3 CHEMICALLY SYNTHESIZED ANALOGUES OF SIASTATIN B FOR ANTIMETASTATIC ACTIVITIES

The sialic acid content or sialyltransferase activity of tumor cell surface were found to be positively correlated to the metastatic potential of tumor cells (refs. 20-25, 47-49). In addition, recent studies (refs. 32, 50-54) have provided considerable evidence of the increase of β-glucuronidase activity in human tumors and suggested that β-glucuronidase play a role in the metastatic process of tumor cells. Thus, since sialic acid metabolism on the cell surface as well as β-glucuronic acid metabolism of the extracellular matrix play crucial roles in tumor metastasis, modification of their metabolism with drugs becomes very interesting. Chemically synthesized analogues of siastatin B were therefore rationally designed to be able to mimic sialic acid in the metabolism of glycoproteins or glycolipids or to mimic β-glucuronic acid in the metabolism peptidoglycans, and were evaluated for their antimetastatic activity in tumor cells. The sites chosen for modification in the synthesis of siastatin B analogues is shown in Fig. 4.

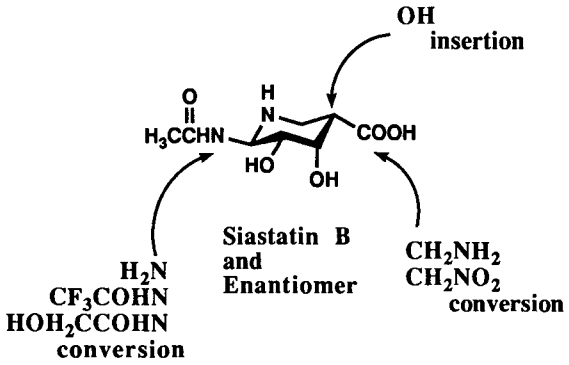


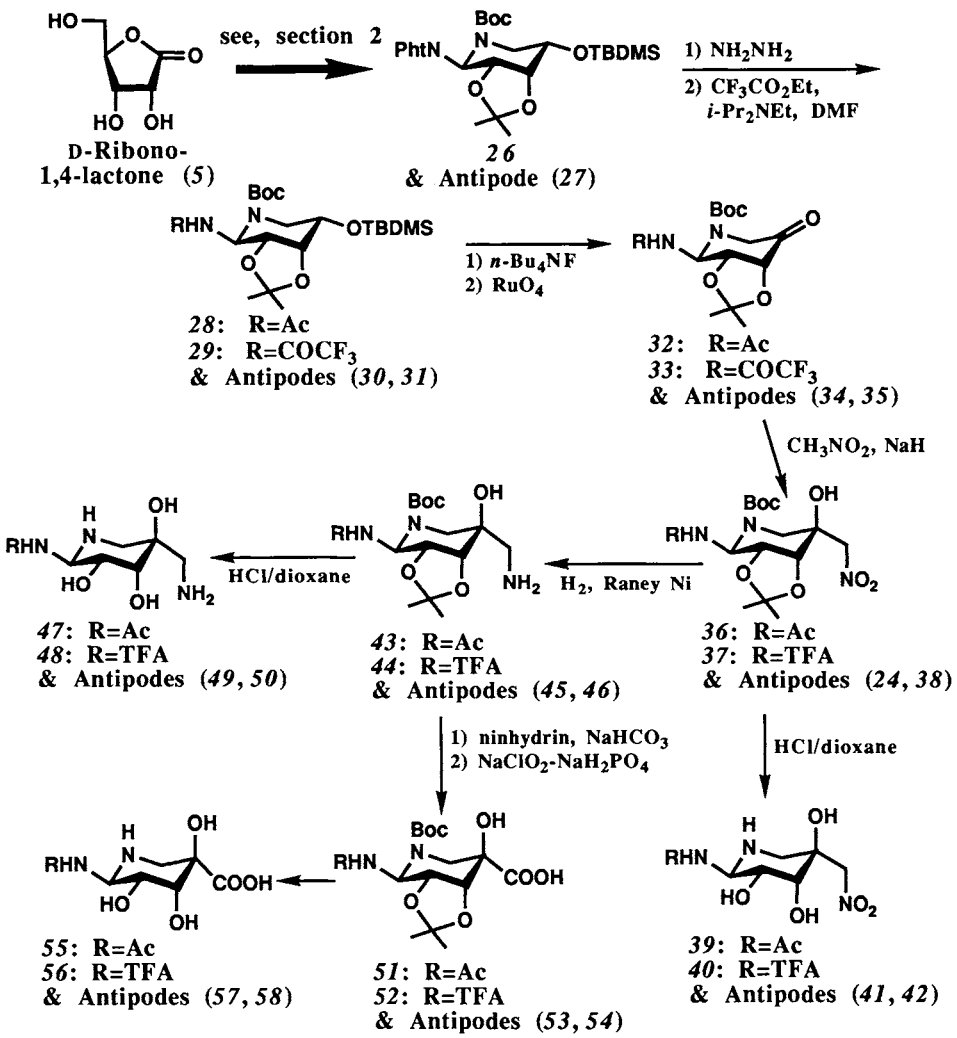
Fig. 4. The sites in siastatin B chosen for modification in the preparation of chemically synthesized analogues

3.1 Synthesis of optically active 2-acetamido-, trifluoroacetamido- and glycolamido-3,4,5-trihydroxypiperidines having 3-nitromethyl, aminomethyl and carboxyl branched groups

Siastatin B analogues, optically active 2-acetamido-, trifluoroacetamido- and glycolamido-3,4,5-trihydroxypiperidines having nitromethyl, aminomethyl and carboxyl branched groups at C-3 have been obtained by total synthesis from D-ribono-1,4-lactone by the enantiodivergent, stereospecific convergent method (refs. 55, 56). The hydroxyl group was introduced at C-3 by analogy with an anomeric center of sialic acid (*2*). The carboxyl group was replaced by nitromethyl and aminomethyl groups to examine the effect of acidic, neutral and basic substituents on affinity for sialyltransferase, neuraminidase or β-glucuronidase. The *N*-acetyl group was also substituted for trifluoroacetyl and glycolyl groups, thereby altering the function of the ring-imino group which probably interacts with the glycopyranosyl binding site to inhibit the enzymatic process. Since *N*-glycolylneuraminic acid is not found in human cells but in tumor cells, and *N*-glycolyl type ganglioside GM3 acts on suppression of tumor-cell growth, the possibility of altering tumor-cell growth by modification of sialic acid metabolism with *N*-glycolyl analogues becomes very interesting.

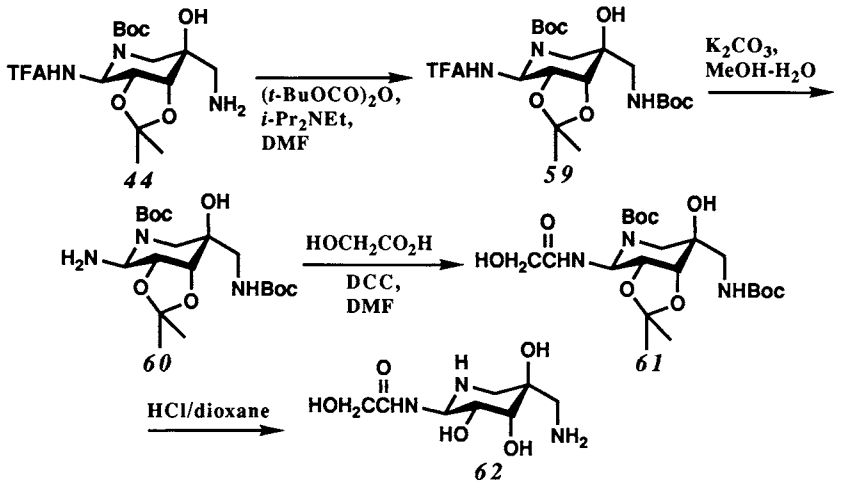
A strategy related to the total synthesis (refs. 35-38) of *1* and its antipode *7* was effectively applied to these syntheses (Scheme 4). The acid labile *t*-butoxycarbonyl (Boc) group was employed as the protecting group of the ring-imino group, thereby differentiating it from the benzyloxycarbonyl group in the total synthesis. The trifluoroacetamide analogue *29* and its antipode *31* were prepared from the key intermediate *26* and its antipode *27*, respectively, by hydrazinolysis followed by treatment with ethyl trifluoroacetate. The crucial compounds (*36*, *37*) and their antipodes (*24*, *38*) were derived from *28*, *29*, *30* and *31*, respectively, in similar, straightforward manners as that used in the total synthesis. The absolute configurations of *36*, *37*, *24* and *38* were determined by X-

ray crystallographic analysis of ***24*** discussed in the previous section (Fig. 3). Catalytic reduction of ***36***, ***37*** and their antipodes (***24***, ***38***) with Raney Ni gave the corresponding aminomethyl compounds (***43***, ***44***, ***45*** and ***46***) which were converted to the corresponding carboxylic acids (***51***, ***52***, ***53*** and ***54***) by ninhydrin oxidation (ref. 57) of the aminomethyl groups to the aldehyde groups and subsequent oxidation with sodium chlorite. The final desired nitromethyl (***39***, ***40***, ***41***, ***42***) aminomethyl (***47***, ***48***, ***49***, ***50***) and carboxyl (***55***, ***56***, ***57***, ***58***) compounds were obtained upon removal of the protecting groups with acid from the corresponding precursors.



Scheme 4

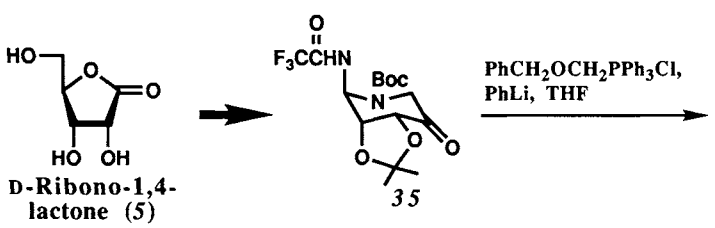
On the other hand, *N*-glycolyl analouge ***62*** was prepared in a straightforward manner from the intermediate ***44*** (Scheme 5). Protection of the aminomethyl group in ***44*** with *t*-butoxycarbonyl group followed by removal of the *N*-trifluoroacetyl group afforded ***60***. Coupling ***60*** with glycolic acid gave the glycolamide ***61***, which was transformed into ***62*** upon treatment with acid.

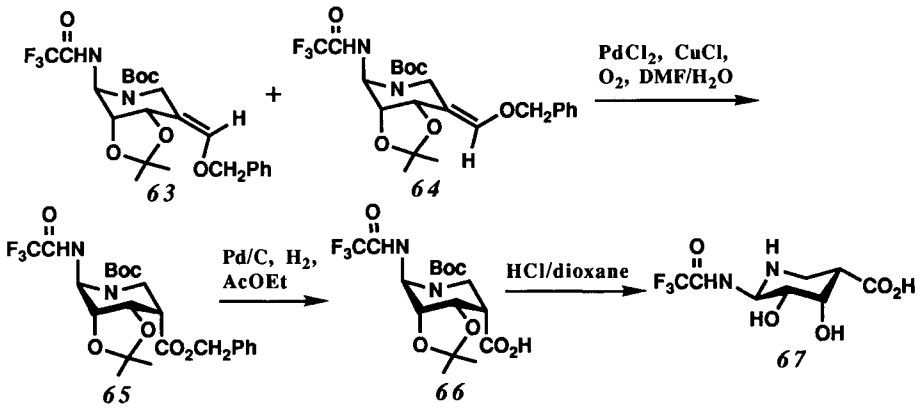


Scheme 5

3.2 Synthesis of trifluoroacetamide analogue of siastatin B, (3*S*,4*S*,5*R*,6*R*)-6-trifluoroacetamido-4,5-dihydroxypiperidine-3-carboxylic acid

In the course of a study to investigate the relationships between structure and biological activity of analogues of siastatin B (***1***), it was proved that (3*R*,4*R*,5*R*,6*R*)-6-(trifluoroacetamido)-3,4,5-trihydroxypiperidine-3-carboxylic acid (***56***) shows a marked inhibition for β-glucuronidase (see section 3.3). This suggested that an analogue of ***56*** lacking a 3-hydroxy branched group, which resembles β-glucuronic acid (***3***) closely, should affect β-glucuronidase as strongly as ***56***. Thus, (3*S*,4*S*,5*R*,6*R*)-6-trifluoroacetamido-4,5-dihydroxypiperidine-3-carboxylic acid (***67***) has been prepared by total synthesis from D-ribono-1,4-lactone (***5***) *via* the key intermediate ***35*** (see section 3.1) by a stereospecific convergent route (ref. 58) (Scheme 6).





Scheme 6

The stereospecific introduction of the carboxyl group was successfully carried out by a one-carbon homologation of the ketone ***35*** using a Wittig reaction, followed by the oxidation of the resulting enol ether ***63*** and ***64*** employing the Wacker process (ref. 59). Reaction of ***35*** with benzyloxymethylenetriphenylphosphorane afforded the (*Z*)-benzyloxyvinyl ether ***63*** and the (*E*)-isomer ***64*** in a ratio of 1:1. Oxidation of ***63*** and ***64*** by the Wacker process using palladium chloride and cuprous chloride in *N,N*-dimethylformamide-water gave the ester ***65*** as a single stereoisomer. Fig. 5 shows a possible reaction mechanism *via* the Wacker process. The boat conformation in ***63*** and ***64*** should be predictable from the boat conformation of ***24*** determined by X-ray crystallographic analysis (see section 2). The π-complex ***68*** is formed by attack of the palladium reagent from the less-sterically hindered side. The unstable σ-alkyl intermediate ***69***, formed by subsequent addition of water to the double bond, is transformed into the benzyl ester ***65*** by a 1,2-hydride shift and reductive elimination of the palladium. Catalytic hydrogenolysis of ***65*** afforded ***66***, which was converted into ***67*** by removal of protecting groups with acid.

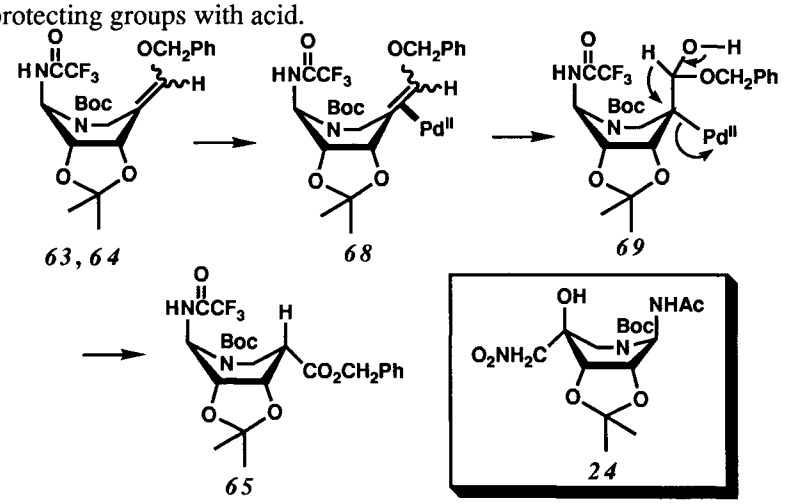
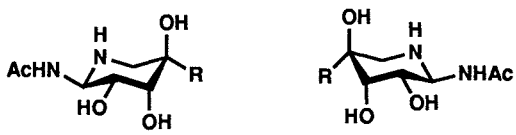


Fig. 5. A possible reaction mechanism *via* the Wacker process

3.3 Biological activities of chemically synthesized analogues of siastatin B

As shown in Table 1, 3-hydroxy-3-nitromethyl compound ***39*** and its antipode ***41*** showed inhibitory activity against yeast α-glucosidase, and ***41*** also showed a weak effect on the inhibition of almond β-glucosidase. 5-Hydroxysiastatin B (***55***) as well as siastatin B (***1***) affected β-glucuronidase isolated from bovine liver, but the antipode ***57*** had no affect. All the analogues did not inhibit either the other glycosidases (α-mannosidase from soybean, α-amylase from porcine pancreas, β-amylase from sweet potato) or the sialidases isolated from microorganisms (*Streptococcus* sp., *Anthrobacter ureafaciens* and *Clostridium perfringens*) and A/Aichi/2/68 (H3N2) strain of influenza virus. Siastatin B (***1***) itself had no inhibitory activity on these glycosidases and sialidases isolated from *A. ureafaciens* and A/Aichi/2/68 (H3N2) strain of influenza virus, whereas ***1*** demonstrated activity for sialidases isolated from *Streptococcus* sp. and *C. perfringens* (IC_{50} 7.40 and 50 μg/ml, respectively). In addition, ***39*** showed weak inhibition of human-platelet aggregation induced with collagen (IC_{50} 1 mM).

Table 1. Inhibitory activity against glycosidases



R=CH_2NO_2; CH_2NH_2; COOH

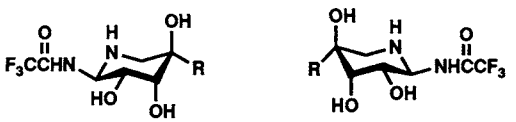
Compound	Inhibition % at 100 μg/ml α-Glucosidase (Yeast)	β-Glucosidase (Almond)	β-Glucuronidase (Bovine liver)	Inhibition % Sialidases at 100 μM (*Streptococcus*)	at 100 μg/ml (Influenza v. A/Aichi/2/68)
Siastatin B (*1*)	3	24	85 (15.5)	40.9 (7.40)	20
39	89 (2.5)	3	3	5.6	—
41	76 (2.0)	56 (70.0)	8	0	—
47	23	32	38	0	8.1
49	0	3	24	0	14.7
55	7	8	77 (28.5)	0	16.2
57	7	6	2	0	10.8

( ): IC_{50} μg/ml

The inhibitory activity of 3-hydroxy-*N*-trifluoroacetyl analogues against glycosidases is shown in Table 2. All analogues inhibited the α-glucosidase from yeast, and some of them also inhibited the β-amylase from sweet potato. Strikingly, 3*R*-hydroxy-*N*-trifluoroacetyl siastatin B (***56***) strongly inhibited the β-glucuronidase from bovine liver. The analogues did not show inhibition against the other glycosidases (α-mannosidase from soybean, α-amylase from porcine pancreas) or

sialidases isolated from microorganisms (*Streptococcus* sp., *A. ureafaciens* and *C. perfringens*) and A/Aichi/2/68 (H3N2) strain of influenza virus. In addition, the nitromethyl analogue ***40*** weakly affected human-platelet aggregation induced with ADP (IC_{50} 1 mM).

Table 2. Inhibitory activity against glycosidases



Compound	Inhibition % at 100 μg/ml			Inhibition % Sialidases	
	α-Glucosidase (Yeast)	β-Glucuronidase (Bovine liver)	β-Amylase (Sweet potato)	at 100 μM (*Streptococcus*)	at 100 μg/ml (Influenza v. A/Aichi/2/68)
Siastatin B (*1*)	3	85 (15.5)	6	40.9 (7.40)	20
40	88 (2.2)	14	77 (16.8)	0	—
48	90 (1.9)	13	73 (10.0)	0	12.0
50	90 (1.6)	43	70 (16.5)	0	11.7
56	87 (7.7)	100 (0.02)	19	1.6	14.7
58	81 (5.3)	74 (37.0)	15	0	5.7

( ): IC_{50} μg/ml

Interestingly, both enantiomers in the series of 3-hydroxy-*N*-trifluoroacetyl analogues possess inhibitory activity against α-glucosidases. It is possible that both enantiomers (siastatin B type and siastatin B-antipode type) structurally resemble α-glucoside and mimic it in the ground-state binding to α-glucosidase, inhibiting the enzymatic reaction (Fig. 6).

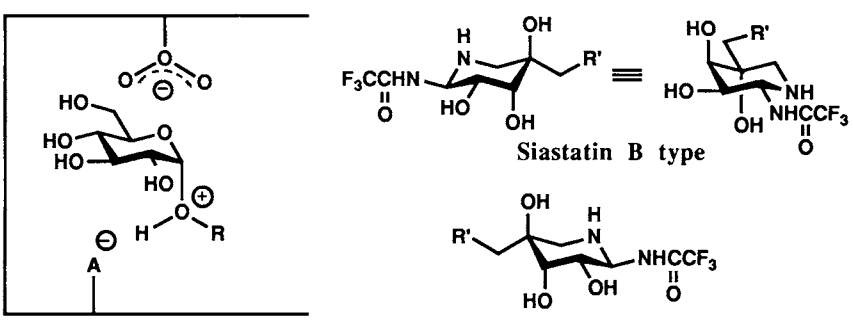
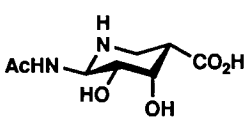


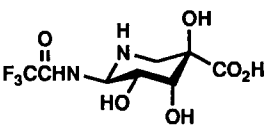
Fig. 6. Structural resemblance of α-glucoside and analogues of siastatin B type and its antipode type

Table 3 shows the inhibitory activity of the trifluoroacetamide analogue ***67***, siastatin B (*1*) and 5-hydroxy-*N*-trifluoroacetyl analogue ***56*** against glycosidases. As was expected, ***67*** affected more strongly the β-glucuronidase from bovine liver than ***56***. It is possible that, as shown in Fig. 7, ***56*** and ***67*** have the same topographical orientation of the functional groups as glucuronic acid (*3*) and mimic *3* in the ground-state binding to β-glucuronidase, inhibiting the enzymatic process. Compound ***67*** also showed weak inhibition against α-glucosidase (yeast) and showed no inhibition against sialidases isolated from *Streptococcus* sp. and the A/Aichi/2/68 (H3N2) strain of influenza virus.

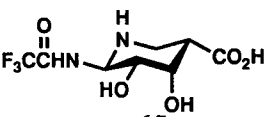
Table 3. Inhibition (%) of siastatin B (*1*), *56* and *67* at 100 μg/ml against glycosidases



1



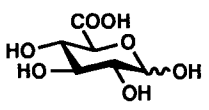
56



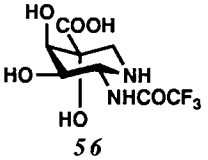
67

Compound	α-Glucosidase (Yeast)	β-Glucosidase (Almond)	β-Glucuronidase (Bovine liver)	Sialidases (*Streptococcus*)	Sialidases (Influenza v. A/Aichi/2/68)
Siastatin B (*1*)	3	24	85 (15.5)	40.9 (7.40)	20
56	87 (7.7)	22	100 (0.02)	1.6	14.7
67	69.5 (40)	85.4 (19)	100 (0.0080)	0	1.7

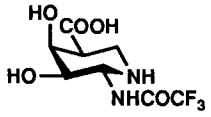
( ): IC_{50} μg/ml



Glucuronic acid (*3*)



56



67

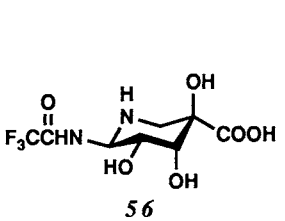
Fig. 7

Table 4 shows the inhibitory effect of ***56*** on [^{14}C]NeuAc incorporation into lactosylceramide using mouse mammary carcinoma mutant cell line (ref. 60). Compound ***56*** as well as cytidine 5'-diphosphate (CDP), a well-known sialyltransferase inhibitor, inhibit the transfer of sialic acid to lactosylceramide [Galβ1→ 4Glcβ1 → 1Cer], and the resulting ganglioside GM3 [NeuAcα2 → 3Galβ1 → 4Glcβ1 → 1Cer].

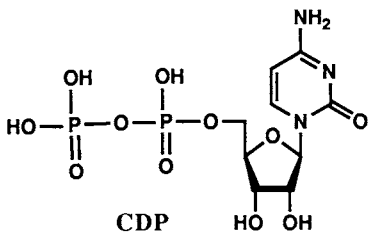
Table 4. Effects of *56* and CDP on [^{14}C]NeuAc incorporation into lactosylceramide (LacCer) as an exogenous acceptor

Treatment		[^{14}C]NeuAc incorporated into GM3 cpm/mg lipid added	%
None		850	100
56	1.3 mM	961	110
	4.3 mM	659	78
	13 mM	13	1.5
CDP	13 mM	7	0.82

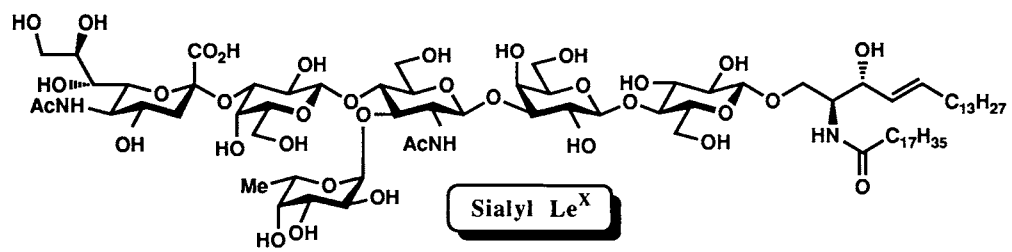
The sialyltransferase activity was determined according to the method of Hakomori *et al.* (ref. 60) using mouse mammary carcinoma mutant cell line (FUA169) which shows high activity of CMP-sialic acid:LacCer 2,3-sialosyltransferase.



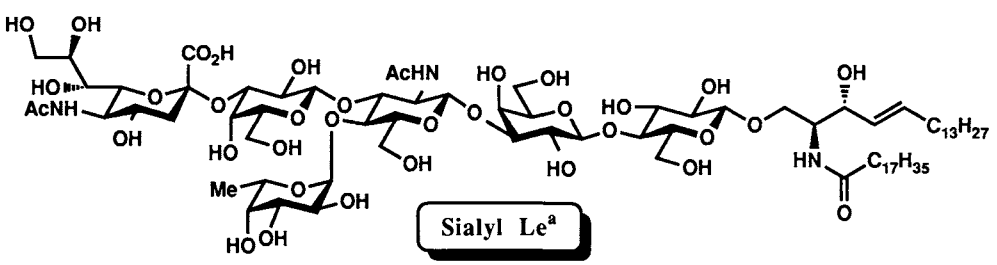
56



CDP



Sialyl Le^X



Sialyl Le^a

Fig. 8. Structures of sialyl Lewis X and sialyl Lewis A

A number of studies (refs. 20-25, 47-49) indicate the dose correlation of the sialic acid content or the sialyltransferase activity of tumor cell membranes with the metastatic potential. In addition, recent studies (refs. 61-64) have proved that a group of cell adhesion molecules (selectins or LECCAMs) expressed on the surface of vascular endothelium recognize the carbohydrate structure on the glycoprotein and/or glycolipid such as sialyl Lewis A (sLe^a) or sialyl Lewis X (sLe^x) (Fig. 8) antigen expressed in human cancer cells, leading to promotion of tumor extravasation and metastasis. Furthermore, a sialic acid:nucleoside conjugate (KI-8110) (ref. 65) having sialyltransferase inhibiting activity inhibits experimental pulmonary metastasis of mouse colon adenocarcinoma 26 sublines.

On the other hand, heparanase (end-β-glucuronidase) degrades heparan sulfate proteoglycan, a major constituent of endothelial basement membranes (ref. 26). Heparanase activities in malignant cells such as melanoma (ref. 66), T-lymphoma (ref. 67), fibrosarcoma (ref. 68), rhabdomyosarcoma (ref. 69), and colon carcinoma (ref. 70) correlate with the metastatic potentials of these tumors. Furthermore, heparanase inhibitors inhibit lung colonization of B16 melanoma cells in their syngeneic host (refs. 52, 71-73). In addition, β-glucuronidase inhibitors, suramin (ref. 74) and ND2001 (ref. 75) were reported to inhibit tumor cell invasion through reconstituted basement membrane and experimental metastasis. These facts suggest that ***56*** and ***67*** as glucuronidase inhibitors are capable of inhibiting melanoma cell invasion by inhibiting melanoma cell-mediated degradation of endothelial extracellular matrix. Table 5 shows the inhibitory effect of ***67*** on the highly metastatic variants of B16 melanoma and Lewis lung carcinoma (3LL) cell invasion. Compound ***67*** was highly inhibitory against B16 variant and 3LL cell invasion in a dose-dependent manner through reconstituted basement membranes (ref. 76).

Pulmonary colonization after intravenous transplantation of the highly metastatic B16 cells (isolated by Fidler's modified method) into the tail veins of mice was significantly suppressed by *in vitro* pretreatment with ***56*** and ***67***, as shown in Table 6 (ref. 58).

As shown in Table 7, inhibition of spontaneous pulmonary metastasis was also observed on i.v. injection of ***67*** without pretreatment (ref. 76). Compound ***67*** significantly suppressed dose-dependently spontaneous lung metastasis of Lewis lung carcinoma (3LL) cells by s.c. inoculations into the hind footpad of mice with i.v. administration for five days starting on the day of the excision of primary tumor. ***67*** had no significant effects on cell growth at the concentrations used in this study.

Table 5. Inhibitory effect of *67* on tumor cell invasion

Treatment	Concentration (μM)	Incubation time (hr) B16	Incubation time (hr) 3LL	No. of invaded cells B16	No. of invaded cells 3LL	Average percent inhibition of invasion B16	Average percent inhibition of invasion 3LL
None	—	3	4	10.3 ± 6.1	35.3 ± 25.4	0	0
67	370	3	4	7.3 ± 3.7	9.3 ± 2.3	29.1	73.7
	740	—	4	—	3.0 ± 1.0	—	91.5
	1100	3	4	3.7 ± 3.8	7.3 ± 2.1	64.1	79.3
None	—	5	6	54.3 ± 16.3	38.7 ± 20.8	0	0
67	370	5	6	51.3 ± 8.1	10.7 ± 2.1	5.5	72.4
	740	—	6	—	7.7 ± 0.6	—	80.1
	1100	5	6	37.7 ± 31.6	7.7 ± 2.5	30.6	80.1

Metastatic B16 melanoma or 3LL carcinoma cells were cultured with or without *67* for 72 hours, and then B16 melanoma or 3LL carcinoma cells (5.0×10^4/well) were seeded on the Matrigel/Laminin-coated filters in the upper Transwell chamber. After 3 and 5-h or 4 and 6-h incubations, the invaded cells on the lower surface (the mean ± standard deviation/0.3 mm^2 of 3 determinations) were counted.

Table 6. Effect of *56* and *67* on the experimental metastasis of the highly metastatic B16 cells in mice

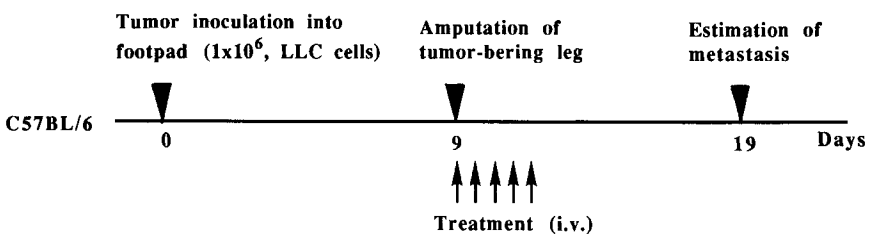
Experiment No.	Treatment	Dose (μg/ml)	No. of cells (ml)	Pulmonary metastasis (No. of colonies) Means ± SD	Range	T/C (%)
1	None	—	1.98×10^7	108.3 ± 29.7	78-138	100
1	*67*	10	2.08×10^7	55.8 ± 26.2	32-84	51.5
1	*67*	30	1.98×10^7	41.3 ± 18.4	16-58	38.1
1	*67*	50	2.09×10^7	10.0 ± 5.4	6-18	9.2
2	None	—	7.1×10^6	84.0 ± 23.0	69-119	100
2	*56*	10	6.2×10^6	74.0 ± 39.1	60-93	88.1
2	*56*	30	5.4×10^6	21.0 ± 9.8	10-29	25.0
3	None	—	7.4×10^6	114.3 ± 15.3	97-126	100
3	*56*	50	8.1×10^6	22.3 ± 6.7	18-30	19.5
3	*56*	100	9.8×10^6	11.0 ± 1.0	10-12	9.6

The highly metastatic melanoma B16 cells were incubated with or without *56* and *67* in Dulbecco's modified Eagle's medium supplemented with fetal bovine serum for 72 hours. The cell suspension (7.1 or 7.4×10^5 and 1.98×10^6 in 0.1 ml, respectively) were injected i.v. into the tail vein of mice. Fourteen days later, the mice were autopsied and the number of pulmonary tumor nodules were counted. Inhibition (%) of metastasis was calculated from the ratio of tumor nodules in treated and control experiments.

Table 7. Inhibitory effect of *67* on the spontaneous lung metastasis

Sample	Administered dose (mg/kg)	No. of lung metastasis (Mean ± SD)	(Range)	Inhibition of metastasis (%)
Saline (0.9%)	x 5	43.4 ± 16.3	35-52	0
67	10 x 5	41.2 ± 9.3	27-53	5.1
	50 x 5	33.2 ± 10.4	19-41	23.5
	100 x 5	18.6 ± 6.2	9-26	57.1
Lentinan	2 x 5	17.4 ± 10.4	9-35	59.9

Five female C57BL/6 mice per group inoculated with 3LL cells (1×10^6) by intrafootpad injection were administered i.v. with *67* for 5 days starting on the day of the surgical excision of primary tumors on day 9. Mice were killed 10 days after tumor excision.



These results suggest that the antimetastatic effect of ***67*** may be due to its antiinvasive rather than antiproliferative activities, and that these potent antimetastatic effects on experimental metastasis may be due to inhibition of extracellular matrix degradation and/or modification of tumor cell surface properties, affecting inhibition of tumor cell adhesion to vascular endothelium and of tumor cell invasion. On the one hand the analogues related to ***56*** and ***67*** may contribute to the study of the metastatic process through a better understanding of the mechanism of action of proteolytic enzymes secreted by tumors, while on the other hand they may be of pharmaceutical interest in the treatment of cancer.

4 CHEMICALLY MODIFIED ANALOGUES OF SIASTATIN B FOR ANTI-INFLUENZA VIRUS ACTIVITIES

Two integral membrane glycoproteins, haemagglutinin and neuraminidase, envelope the viral surface of influenza A and B. Infection by the influenza virus begins with the binding of haemagglutinin to terminal sialic acid residues of glycoproteins and glycolipids on the surface of the host cell and subsequent fusion of viral and host cell membranes (refs. 6-8). Neuraminidase cleaves the α2,3- and α2,6-glycosidic linkages between terminal sialic acid and adjacent sugar residues of glycoproteins and glycolipids (refs. 77, 78). Neuraminidase is thought to facilitate the elution of progeny virus particles from the infected cells (ref. 9) and the maintenance of mobility of progeny virus by prevention of self-aggregation, and thus to play an important role in the spread of the infection (refs. 10, 11). This suggests that tight-binding inhibitors of haemagglutination and influenza virus neuraminidase could prevent or limit influenza infection. The proposal mechanism of hydrolysis by influenza virus neuraminidase (ref. 79) and the crystal structure of haemagglutinin (refs. 8, 80) and sialidase (refs. 81, 82) of influenza virus have provided useful informations for the design of new, specific and potent inhibitors for influenza virus. Siastatin B (***1***) itself does not inhibit haemagglutination and hydrolysis of influenza virus neuraminidase, though it affects microbial neuraminidases. Thus, chemically modified analogues of siastatin B were rationally designed to be able to mimic sialic acid in haemagglutination and hydrolysis by influenza virus neuraminidase, and were evaluated for anti-influenza virus activity. The mode of chemical modification is shown in Fig. 9.

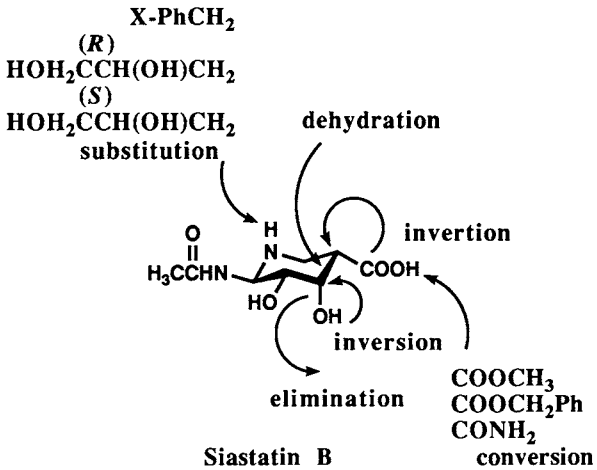
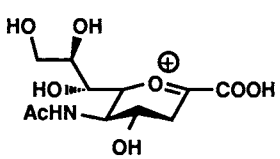


Fig. 9. The mode of chemically modified analogues of siastatin B

4.1 Synthesis of siastatin B analogues as mimics of a sialosyl cation transition-state complex in the reaction of influenza virus sialidase

The mode of action of neuraminidase should be predictable from the mechanism of action envisaged on a generally accepted catalytic mechanism (ref. 38) for glucosidase and mannosidase which hydrolyze with retention of configuration. The enzyme splits the glycosidic bond *via* formation of an oxocarbenium ion (***70***) formed by protonation of the glycosidic oxygen by a proton donor group followed by liberation of the aglycone. Thus, the generated oxocarbenium ion is stabilized temporarily by a neighboring carboxyl group of the enzyme. The kinetic isotope, NMR, and molecular dynamics studies of the enzyme-substrate complex have led to the proposal of a mechanism of the solvent-mediated hydrolysis by influenza virus neuraminidase which involves the same endocyclic sialosyl cation transition-state complex (ref. 79) as mentioned above (Fig. 11).



Oxocarbenium ion of *N*-acetylneuraminic acid (*70*)

Fig. 10

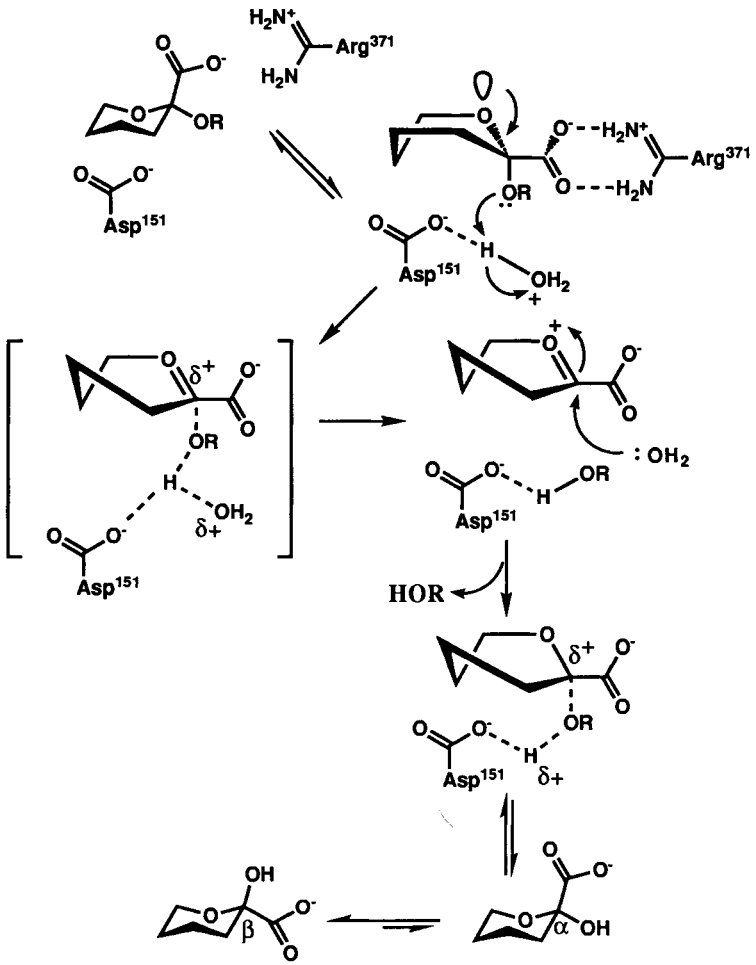


Fig. 11. The proposed mechanism for sialidase catalysis (ref. 79)

Siastatin B (*1*) probably mimics the oxocarbenium ion of *N*-acetylneuraminic acid (*70*). In fact, however, *1* does not resemble the flattered chair conformation of cation (*70*) particularly well. Oxocarbenium ion of *N*-acetylneuraminic acid (*70*) also has no hydroxy group at the C-3 position. Thus, in order to determine whether the structures of inhibitors of neuraminidase more closely resemble that of oxocarbenium ion (*70*), attempts were made to superimpose siastatin B (*1*), 3,4-didehydro-4-deoxysiastatin B (*71*), 4-deoxysiastatin B (*72*) and their derivatives onto the cation (*70*). Fig. 12 (ref. 83) shows a stereo drawing of the superposition of *1* and *71* on *70* by molecular modeling using MOPAC/AM1 (molecualr orbital calculations by the AM1 method, refs. 84, 85). The major functional groups such

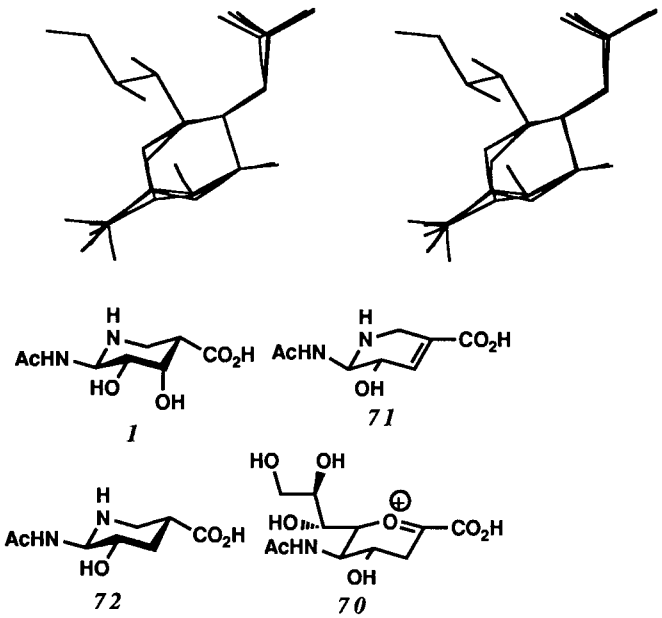


Fig. 12. Superimposition of *1* and *71* on the oxocarbenium ion of *N*-acetylneuraminic acid (*70*). Hydrogen atoms have been omitted for clarity.

as the hydroxyl, carboxyl and amide functions in *71* and *72* superimpose well in the same region of space as those of *70*. *N*-Acetylneuraminic acid also has a glycerol side chain at the C-6 position. Further attempts were then made to superimpose analogues of siastatin B (*1*), 3,4-didehydro-4-deoxysiastatin B (*71*) and 4-deoxysiastatin B (*72*) having the corresponding *S*- or *R*-configurational side chain onto *70* by molecular modeling using MOPAC/AM1 (Fig. 13) (ref. 86). Compounds *73* and *75*, which are analogues of *1* and *72* having *S*-configurational side chain, superpose well on *70*. The electronegative atoms such as hydroxyl oxygen in the ring and the side chain, carboxyl oxygen, amido nitrogen and amido-carbonyl oxygen atoms superimpose very well in the same region of space as those of *70*. The corresponding analogues having *R*-configurational side chain (*74* and *76*) are also able to be superposed onto *70*, in a similar manner to analogues *73* and *74*, but the fit is not as good in this case. In these analogues, it is not possible for the hydroxyl group at C-8 on the side chain to coincide with the hydroxyl group at C-8 of *70*. The analogues of *71* having *S*- and *R*-configurational side chains (*77* and *78*) are no longer able to superpose onto *70*. The superimposition is very poor as the conformation of the six-membered ring of the analogues does not allow optimum overlap of the amido or the carboxyl group with those of *70*.

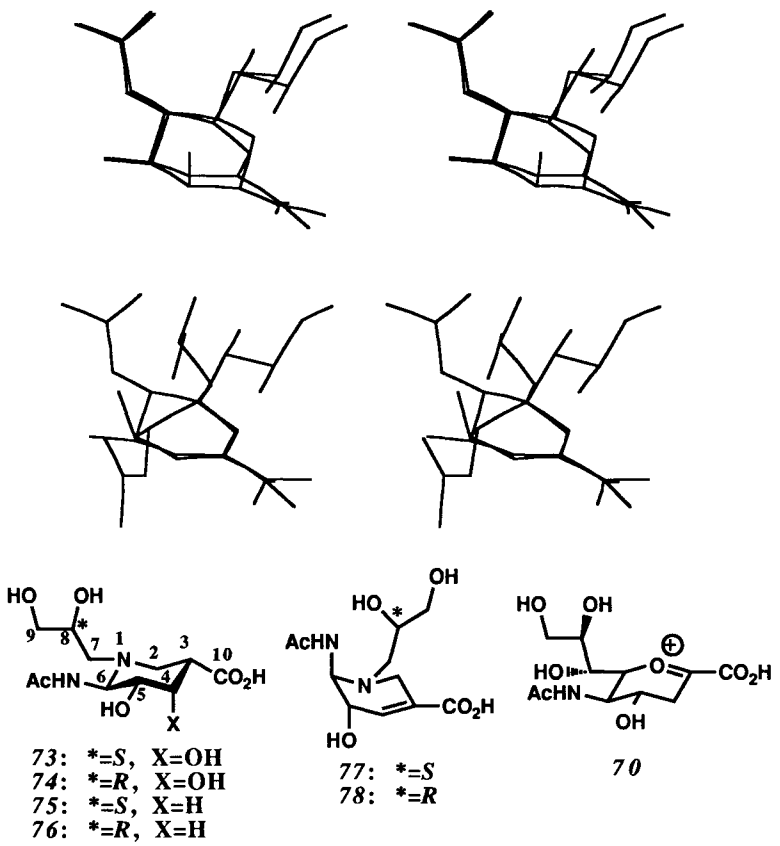
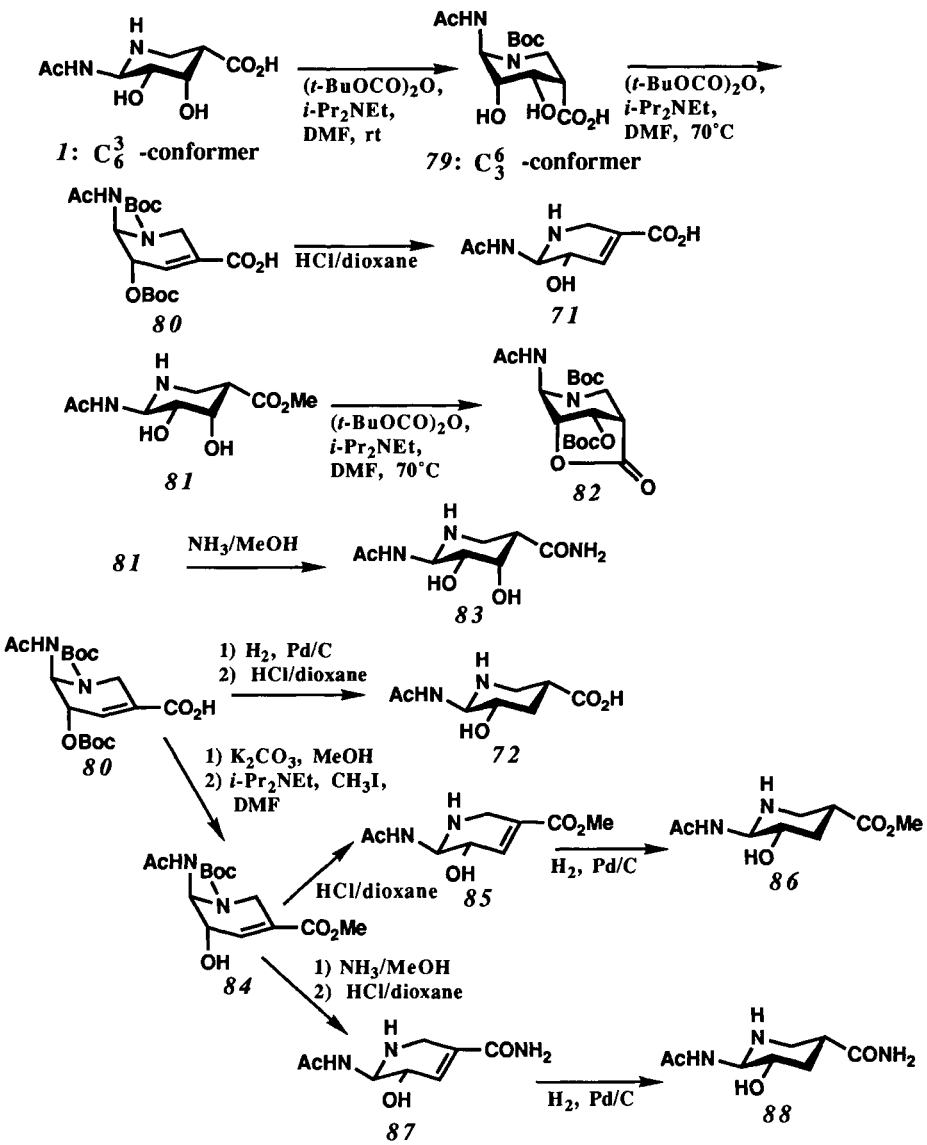


Fig. 13. Superimposition of *73* on *70* (upper) and *77* on *70* (lower). Hydrogen atoms have been omitted for clarity.

Based on these molecular-graphic studies chemically modified analogues of siastatin B (*1*), potential inhibitors of neuraminidases, were synthesized (Scheme 7) (refs. 83, 86, 87).

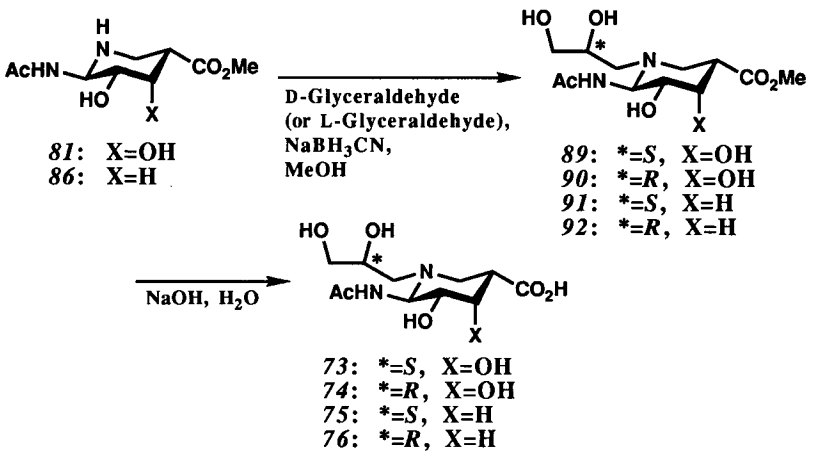
Treatment of *1* with di-*tert*-butyl dicarbonate (Boc-dimer) at room temperature (*i*-Pr2NEt, DMF) gave *N*-*tert*-butoxycarbonylsiastatin B (*79*) with conformational flip from C_6^3-conformer to C_3^6-conformer. Upon treatment of *1* at 70°C, β-elimination of the hydroxyl group at C-4 easily proceeded to afford the 3-ene-compound *80*. Presumably protection of the hydroxyl group with a Boc group occurs at C-4, with subsequent base-catalized elimination of *tert*-butylcarbonate forming *80*. Removal of the protecting groups of *80* with acid gave 3,4-didehydro-4-deoxysiastatin B (*71*). Interestingly, under the same reaction conditions, siastatin B methyl ester (*81*) yielded the lactone compound *82* with conformational flip. On the other hand, ammonolysis of *81* with ammoniacal methanol gave siastatin B

amide (*83*). 4-Deoxysiastatin B (*72*) was successfully obtained by hydrogenation of *80* followed by removal of the Boc-groups with acid. Selective removal of the *O*-Boc group of *80* with potassium carbonate followed by esterification with methyl iodide gave *84*, which was converted into 3,4-didehydro-4-deoxysiastatin B methyl ester (*85*). Ammonolysis of *84* with ammoniacal methanol and subsequent removal of the Boc-group furnished 3,4-didehydro-4-deoxysiastatin B amide (*87*). Reduction of *85* and *87* gave 4-deoxysiastatin B methyl ester (*86*) and 4-deoxysiastatin B amide (*88*), respectively.



Scheme 7

N-[(*S* and *R*)-1,2-Dihydroxypropyl] analogues of siastatin B were also successfully synthesized as shown in Schemes 8 and 9. Reductive *N*-alkylation of ***81*** with D-glyceraldehyde by sodium cyanoborohydride in methanol gave ***89***. Alkaline hydrolysis of ***89*** afforded *N*-[(*S*)-1,2-dihydroxypropyl]siastatin B (***73***). A similar reductive *N*-alkylation of ***81*** with L-glyceraldehyde furnished ***90*** which was converted into *N*-[(*R*)-1,2-dihydroxypropyl]siastatin B (***74***) upon hydrolysis. *N*-[(*S* and *R*)-1,2-Dihydroxypropyl]-4-deoxysiastatin B (***75*** and ***76***) were also obtained through their methyl esters ***91*** and ***92*** from ***86***, respectively, by a similar reductive *N*-alkylation followed by hydrolysis. *N*-[(*S*) and (*R*)-1,2-Dihydroxypropyl]-3,4-didehydro-4-deoxysiastatin B (***77*** and ***78***) were also synthesized *via* their methyl esters, ***93*** and ***94***, from ***85*** respectively, by similar reaction sequences.

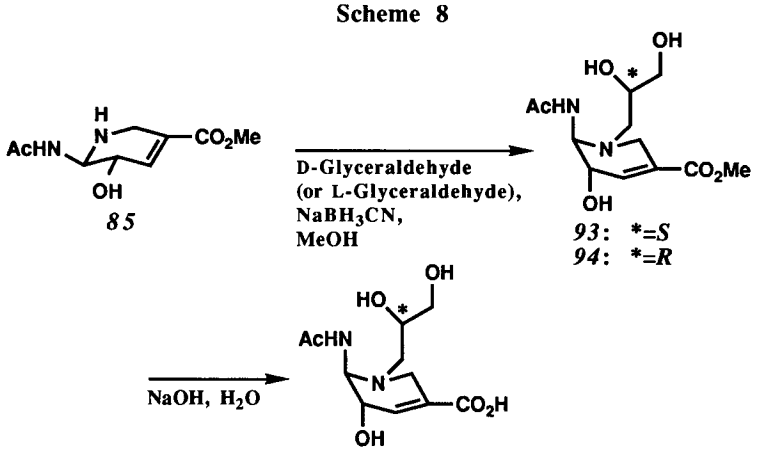


81: X=OH
86: X=H

89: *=*S*, X=OH
90: *=*R*, X=OH
91: *=*S*, X=H
92: *=*R*, X=H

73: *=*S*, X=OH
74: *=*R*, X=OH
75: *=*S*, X=H
76: *=*R*, X=H

Scheme 8



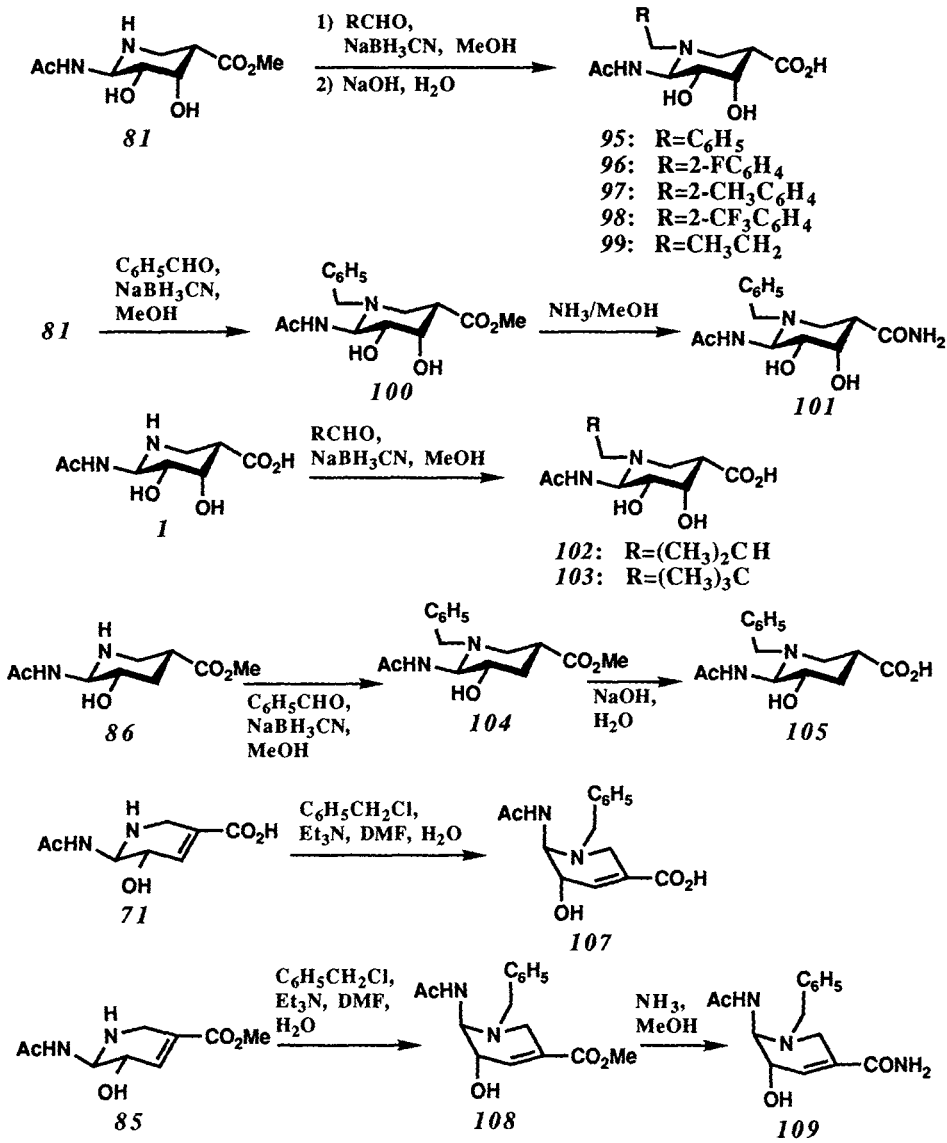
85

93: *=*S*
94: *=*R*

77: *=*S*
78: *=*R*

Scheme 9

The large coupling constants ($J_{5,6}$=~7 Hz) in the ^{1}H NMR spectra of ***71***, ***85*** and ***87*** are clearly indicative of flap down-types of half-chair conformer, while the small coupling constants ($J_{5,6}$=~3 Hz) in those of ***77***, ***78***, ***93*** and ***94*** are clearly indicative of flap up-types. These facts are consistent with the results obtained from the molecular modeling by MOPAC/AM1.



Scheme 10

In the course of the molecular graphics study of the relationship between structure and biological activity among such inhibitors, compounds ***95-109*** (ref. 88) were prepared by the substitution at the imino group of the piperidine ring which may interact with the glycopyranosyl binding site to inhibit the enzymatic process. These compounds (***95- 109***) were obtained from ***1***, ***71***, ***81***, ***85*** and ***86*** by sequences similar to those mentioned above (Scheme 10). The small coupling constants ($J_{5,6}$=~3 Hz) were also observed in the ^{1}H NMR spectra of ***107***, ***108*** and ***109***, indicative of the flap up-types of the half-chain conformer.

4.2 Synthesis of siastatin B analogues as haemagglutinin- and sialidase-based inhibitors of influenza virus replication

Siastatin B analogues can act as inhibitors (based on crystal structures) of influenza virus haemagglutinin and sialidase (*N*-acetylneuraminidase). They have been designed by computer-assisted molecular modeling.

In 1988, Weis *et al.* (ref. 8) clarified the structure of the influenza virus haemagglutinin complexed with its receptor, sialic acid (*N*-acetylneuraminic acid, ***2***). Fig. 14 and 15 show a part of the three-dimentional structures of influenza virus haemagglutinins complexed with cell receptor analogues showing sialic acids bound to a pocket of conserved amino acids surrounded by antibody-binding sites.

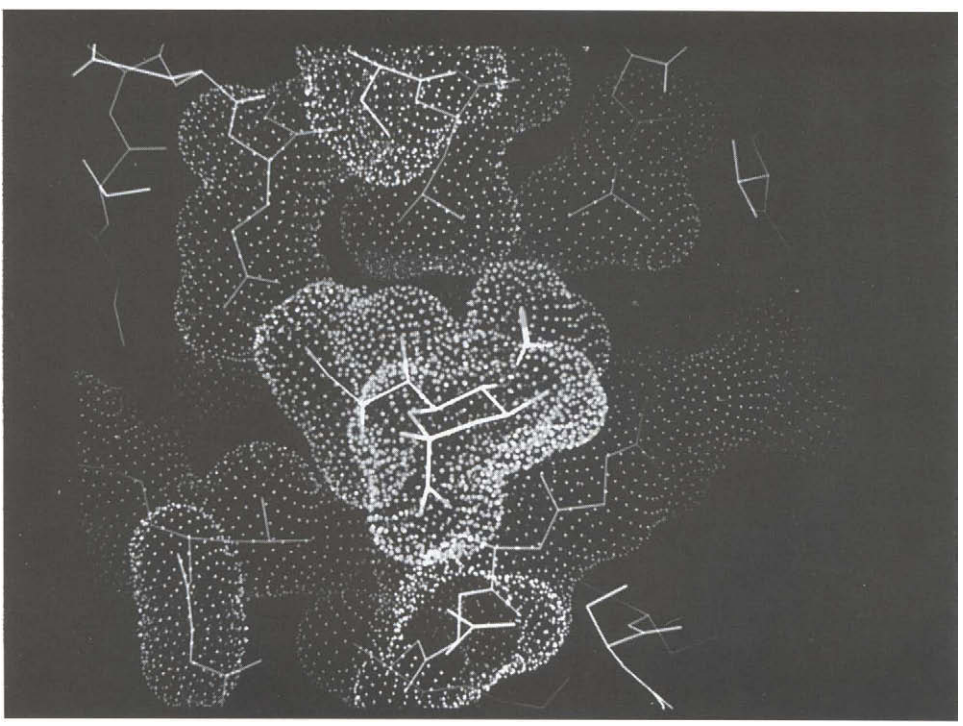


Fig. 14. A part of the three-dimentional structure (X-ray structure) of influenza virus haemagglutinin (wild-type) complexed with sialic acid (ref. 8)

It is noteworthy that the lactose part linked to sialic acid (Fig. 16) has almost no interaction with haemagglutinin, and that upon binding, apparently no conformational changes (α-chair conformer) occur in the protein. One axial-carboxylate oxygen, the acetamido nitrogen, and the 8- and 9-hydroxyl hydrogens bond with the conserved side chain and the main chain polar atoms of the protein. The 4- and 7-hydroxyls and the acetamido carbonyl oxygen face towards solution.

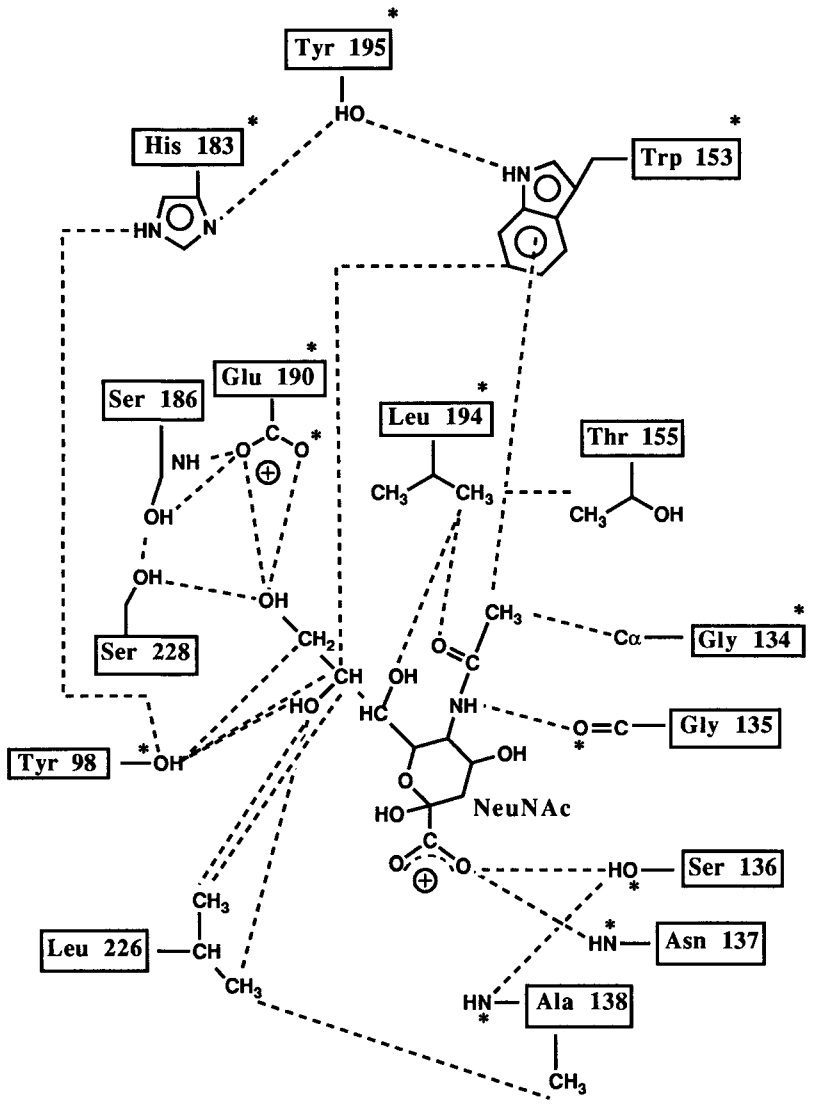


Fig. 15. Potential interactions of α-NeuAc with wild-type influenza virus haemagglutinin (ref. 8).

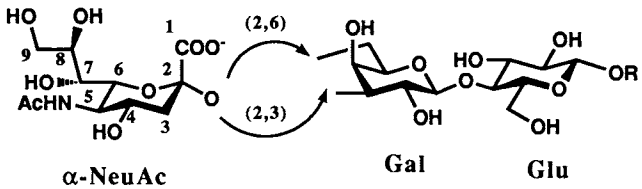


Fig. 16. Structure of α2,6(2,3)-sialyllactoside

The structures suggest approaches to the design of anti-viral drugs that could block attachment of viruses to cells. In order to analyze whether siastatin B (*1*) interacts with the enzyme active site, an examine was made to put *1* in a pocket of conserved amino acids of haemagglutinin by the aid of MOPAC/AM1 (Fig. 17), indicative of the insufficient specific-interactions of *1* with the enzyme active site. Predictions of favourable substitutions to siastatin B (*1*) were made from these analyses. The most apparent of these were the configurational change of the carboxyl group at C-3 and the alkylation with a glycerol-equivalent substituent at the ring-imino group on siastatin B (*1*).

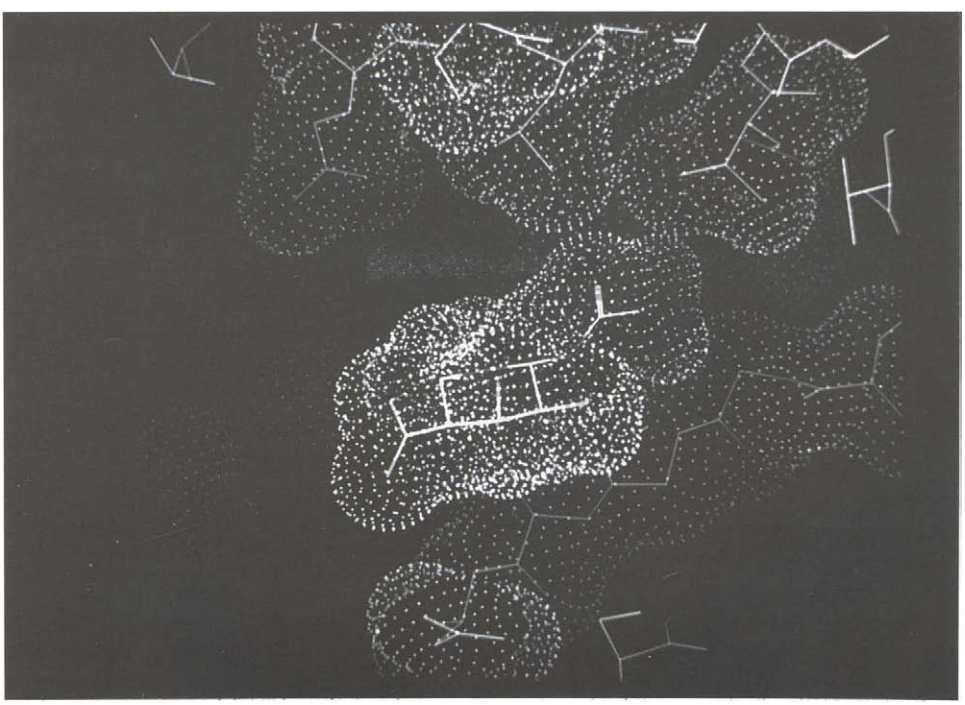
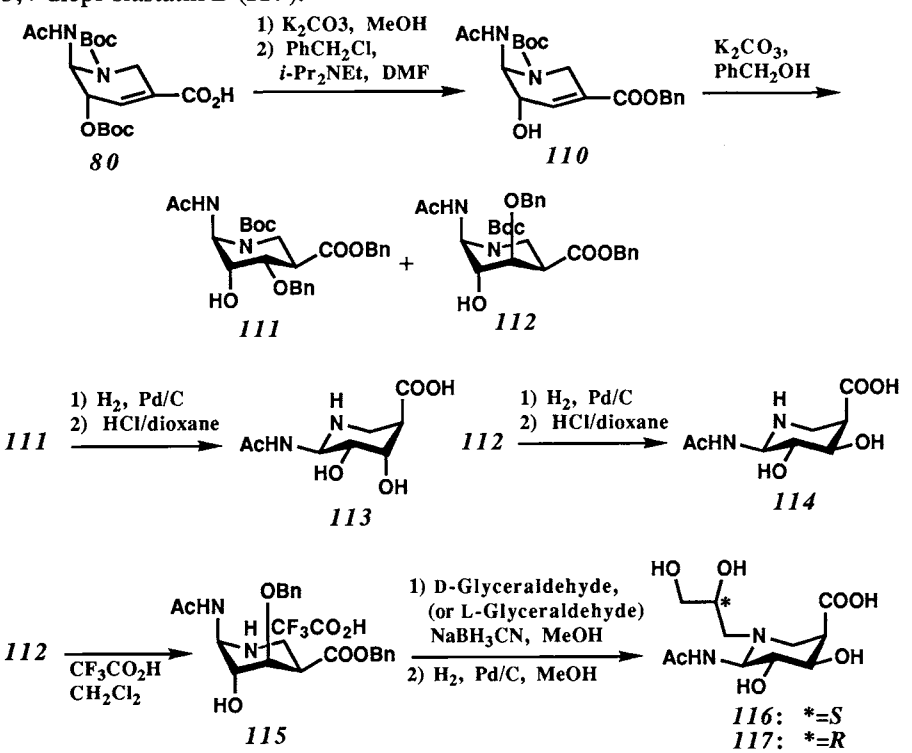


Fig. 17. A possible mode of incorporation of siastatin B into a pocket of conserved amino acids (*N*-acetylneuraminic acid binding site) of influenza virus haemagglutinin (wild-type) by MOPAC/AM1

The four target compounds (***113***, ***114***, ***116***, ***117***) (refs. 83, 85, 89) were prepared *via* the 3,4-didehydro-4-deoxysiastatin B derivative (***110***) easily obtained from ***1*** (Scheme 11). Epimerization at the C-3 position was successfully achieved by a 1,4-conjugated Michael addition of the alcohol to the α,β-unsaturated ester ***110*** with base. Thus the intermediate ***110*** was prepared by removal of the *O*-Boc group of ***80*** followed by benzyl esterification. Treatment of ***110*** with K_2CO_3 in benzyl alcohol afforded the 3-epimer (***111***) and the 3,4-diepimer (***112***) in a ratio of 1:13. The ^1H NMR spectra of ***111*** and ***112*** show the characteristic coupling-patterns indicative of C_3^6-conformers generally observed in the ring-imine protected siastatin B with benzyloxycarbonyl or *tert*-butyloxycarbonyl group. Catalytic hydrogenolysis of both ***111*** and ***112*** followed by acid hydrolysis gave ***113*** and ***114***, respectively. The large coupling constants ($J_{5,6}$=~8 Hz) in ^1H NMR spectra of ***113*** and ***114*** are clearly indicative of the existence of the C_6^3-conformer in both compounds. After deprotection of *N*-*tert*-butoxycarbonyl group of ***114*** with trifluoroacetic acid, reductive *N*-alkylation with D-glyceraldehyde by $NaBH_3CN$ and subsequent catalytic hydrogenolysis gave *N*-[(*S*)-1,2-dihydroxypropyl]-3,4-diepi-siastatin B (***116***). Similar reductive *N*-alkylation of ***115*** with L-glyceraldehyde followed by removal of protecting group resulted in *N*-[(*R*)-1,2-dihydroxypropyl]-3,4-diepi-siastatin B (***117***).



Scheme 11

On the other hand, in 1992, the crystal structures of the enzymatically active head of the *N*-acetylneuraminidases from influenza virus B/Beijing/1/87 and A/Tokyo/3/67, and their complexes with *N*-acetylneuraminic acid (***2***) have been presented in succession by Burmeister *et al.* (ref. 82) and Varghese *et al.* (ref. 81), respectively. The binding modes of *N*-acetylneuraminic acid to both neuraminidases, in which all the large side groups such as the carboxyl group are equatorial, involve the characteristic α-boat rather than the β-chair conformation. The active site residues of both structures have similar interactions with ***2*** in the B/Beijin and A/Tokyo neuraminidases. This is significantly different from the binding to influenza virus haemagglutinin where the carboxyl group is axial in the α-chair conformation (see Fig. 14, 15, ref. 8).

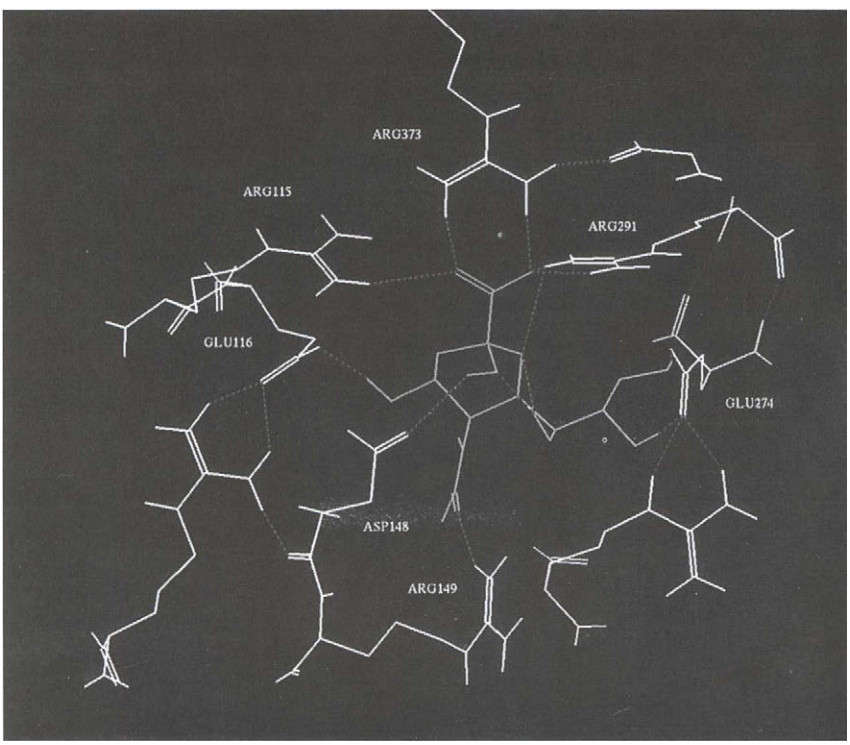


Fig. 18. Structure of active site residues and water molecules that interact with the bound sialic acid in the refined B/Beijin/1/87 neuraminidase/sialic acid model. Hydrogen bonds are shown with dotted lines.

Fig. 18 shows a part of the three-dimentional structure of influenza virus B/Beijing/1/87 neuraminidase complexed with neuraminic acid (***2***) bound to the active site residues. The carboxyl group of the *N*-acetylneuraminic acid interacts with three arginine residues, Arg 115, Arg 291 and Arg 373. Asp 148 is the only

residue to form a hydrogen bond to 2-OH and to interfere with the glycosidic linkage. This suggests that Asp 148 acts a key acid in the catalysis by protonating the glycosidic oxygen and the subsequent hydrolysis of the glycosidic bond.

In order to analyze whether compounds ***113*** and ***114*** interact with the active site residues of influenza virus B/Beijing/1/87 neuraminidase, an examination was made to get them in a pocket of active site residues of the enzyme by the aid of BIOCES[E]/AMBER (refs. 90, 91). While ^{1}H NMR spectra ($J_{5,6}$=~8 Hz) of ***113*** and ***114*** show the C_6^3-chair conformation in an aqueous solution, the most favorable conformations ***113-A*** and ***114-B*** among their boat conformations in a non-solution were empirically estimated by MOPAC/PM3 (ref. 92).

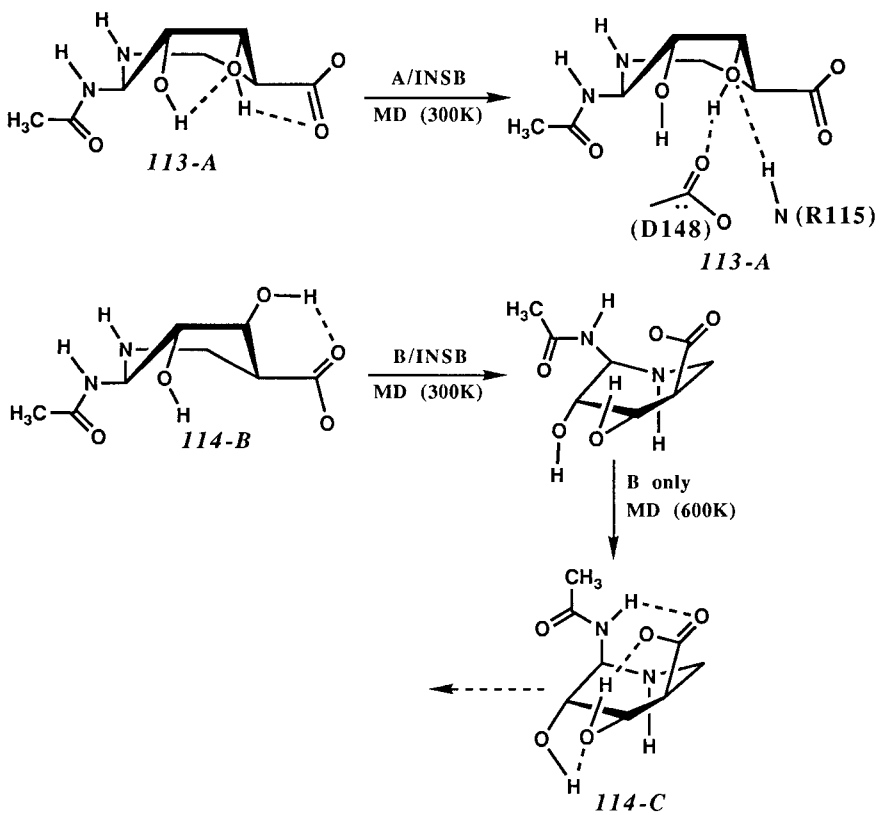


Fig. 19. BIOCES[E]/AMBER minimized structures of *113* (*113-A*) and *114* (*114-B* ⟶ *114-C* ⇢) in a pocket of active site residues of the crystal structure of influenza virus B/Beijing/1/87

These boat conformers seem to be well superposed on the α-boat conformer of *N*-acetylneuraminic acid in the crystal structure of influenza virus B/Beijing/1/87 neuraminidase. Both potential lowest energy conformers ***113-A*** and ***114-B*** were

used as the starting conformation and further minimized in a pocket of active head of crystal structure of influenza virus B/Beijing/1/87 neuraminidase complexed with *N*-acetylneuraminic acid using BIOCES[E]/AMBER. While this yielded the same minimum energy conformer ***113-A*** for compound ***113***, compound ***114*** no longer has the boat conformer ***114-B*** as the minimum energy conformer (Fig. 19).

The lowest energy conformer ***113-A*** was superimposed onto the α-boat conformer of *N*-acetylneuraminic acid in a pocket of active site residues of the crystal structure of influenza virus B/Beijing/1/87 neuraminidase complexed with *N*-acetylneuraminic acid (Fig. 20). The superimposed conformer rigidly fitted in the active head of the enzyme: the carboxyl group of ***113-A*** interacts with three arginine residues, Arg 115, Arg 291 and Arg 373, and a key acid in the hydrolysis of the glycosidic linkage, Asp 148, forming a hydrogen bond to the 3-OH of ***113-A***.

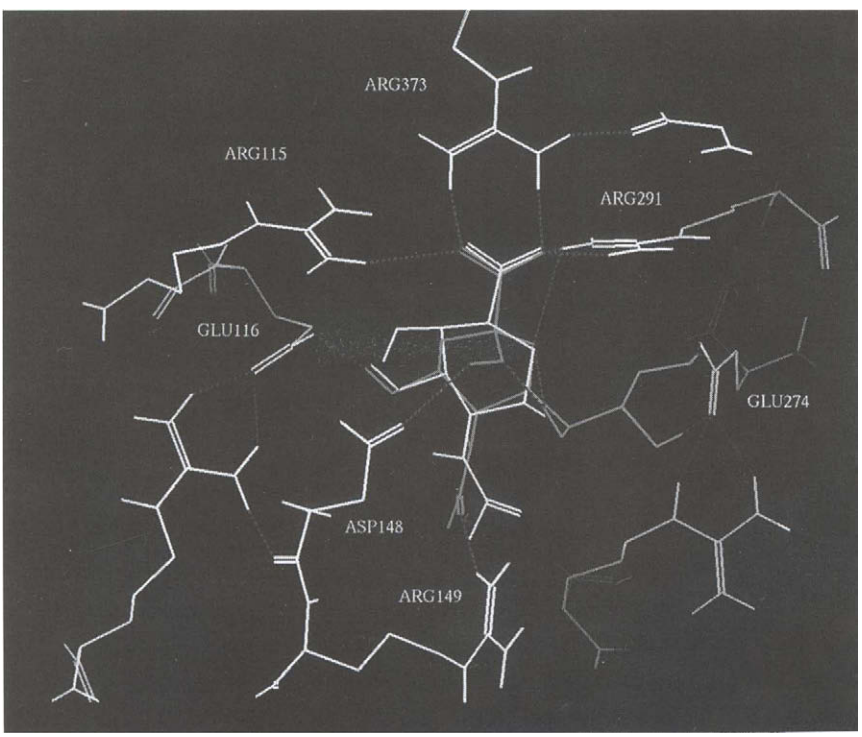
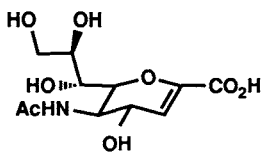


Fig. 20. BIOCES[E]/AMBER minimized structure of *113-A* superimposed on the structure of *N*-acetylneuraminic acid in the crystal structure of the enzymatically active head of influenza virus B/Beijing/1/87 neuraminidase complexed with *N*-acetylneuraminic acid

This suggests that compound ***113*** could interfere with the hydrolysis of sialoside-glycoproteins and glycolipids by neuraminidase and thus prevent or limit the influenza infection.

4.3 Biological activities of chemically modified analogues of siastatin B

As shown in Table 8, siastatin B (*1*) and analogues *71* and *72* showed inhibitory activity against *Streptococcus* sp. and *Clostridium perfringens* neuraminidases, whereas their methyl esters (*81*, *85*, *86*) and the amides (*83*, *87*, *88*) did not inhibit these enzymes. As expected by the molecular modeling studies on the transition state of the enzymatic reaction using MOPAC/AM1 (see 4.1), analogues *71* and *72* are more potent inhibitors than *1* against these neuraminidases and affected as strongly as the well-known inhibitor, 2,3-didehydro-2-deoxy-*N*-acetylneuraminic acid (DDNA, *115*) (ref. 93). Compounds *1*, *71* and *72* also showed the inhibitory activity against β-D-glucuronidase. These results suggest that the potency and specificity of inhibitors are influenced by the topographical equivalents of both carboxyl and amide groups in the oxocarbenium ion (*70*). However, all compounds had little effect on the neuraminidases isolated from influenza viruses. Besides being inhibitors of neuraminidase and glucuronidase, *71* and *72* exhibit an unexpected range of activity against yeast α-glucosidase. These findings contrast dramatically with findings for DDNA (*115*) and other known neuraminidase inhibitors derived from *N*-acetylneuraminic acid (ref. 94) which were found to have little effect on glucosidase.

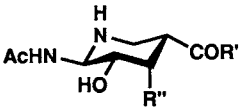


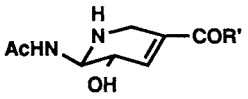
2,3-Didehydro-2-deoxy-*N*-acetylneuraminic acid (DDNA, *115*)

Fig. 21

The inhibitory activity of *N*-(1,2-dihydroxypropyl) derivatives of siastatin B and its 4-deoxy analogues is shown in Table 9. Analogues *73* and *75* were potent inhibitors of microbial neuraminidases (*Streptococcus* and *Clostridium perfringens*) with activities comparable to that of DDNA (*115*). Analogues *76* and *77* were poor inhibitors, and analogues *74* and *78* did not affect these enzymes. Their methyl esters (*89-92*, *93*, *94*) also did not inhibit these enzymes.

Table 8. Inhibitory activity against glycosidases

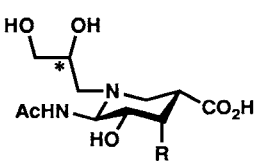


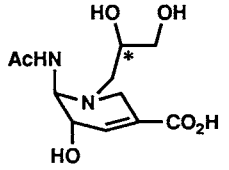


No.	R'	R"	Inhibition % at 100 μg/ml α-Glucosidase (Yeast)	β-Glucuronidase (Bovine liver)	β-Amylase (Sweet potato)	Sialidases at 100 μM (*Streptococcus*)	at 100 μg/ml (*Cl. perfr.*)
1	Siastatin B		3	85 (15.5)	6	40.9 (7.40)	(50)
81	OMe	OH	6	18	4	0	5.3
83	NH_2	OH	5	0	15	9.2	3.6
72	OH	H	91 (5.3)	90 (12.0)	49	76.5 (1.81)	(20)
86	OMe	H	0	0	0	0	31.6
88	NH_2	H	9	36	12	15.3	9.2
71	OH	—	88 (16.0)	81 (22.5)	43	69.6 (3.12)	(32)
85	OMe	—	92 (5.3)	0	79 (9.6)	0	16.6
87	NH_2	—	10	0	36	11.2	7.8
115	DDNA		—	—	—	78.1 (1.97)	(12)

( ): IC_{50} μg/ml

Table 9. Inhibitory activity against glycosidases



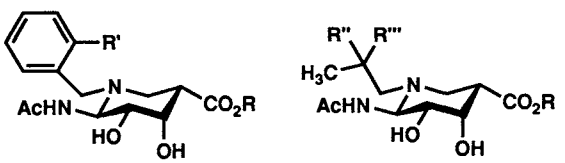


No.	*	R	Inhibition % at 100 μg/ml α-Glucosidase (Yeast)	β-Glucuronidase (Bovine liver)	β-Amylase (Sweet potato)	Sialidases at 100 μM (*Streptococcus*)	at 100 μg/ml (*Cl. perfr.*)
1	Siastatin B		3	85 (15.5)	6	40.9 (7.40)	0
73	*S*	OH	0.6	0	14.0	90.4 (3.00)	(7.8)
74	*R*	OH	2.5	0	0	35.6	(130)
75	*S*	H	65.6 (12)	2.2	73.6 (64)	98.6 (1.30)	(14)
76	*R*	H	74.9 (8.5)	2.7	16.6	69.9 (12.44)	(22)
77	*S*	—	—	—	—	80.8 (8.95)	(80)
78	*R*	—	—	—	—	21.9	36
115	DDNA		—	—	—	78.1 (1.97)	(12)

( ): IC_{50} μg/ml

These results are in fairly good agreement with predictions by molecular modeling studies on the transition state of the enzymatic reaction of neuraminidase using MOPAC/AM1 (see 4.1). These results again indicated that the potency and specificity of inhibitors are influenced by the topographical equivalents of hydroxyl, carboxyl and amide groups in the oxocarbenium ion (***70***). Any *N*-acetylneuraminic acid analogues which lack these important groups are also inactive (ref. 95). The efficient recognition and binding to the active site of neuraminidase require the proper spatial disposition of the binding groups of inhibitors. The *N*-(1,2-dihydroxypropyl) analogues also did not affect influenza virus neuraminidases.

Table 10. Inhibitory activity against glycosidases



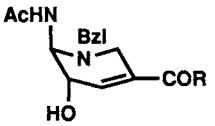
No.	R	R'	R''	R'''	Inhibition % at 100 μg/ml α-Glucosidase (Yeast)	β-Glucuronidase (Bovine liver)	at 100 μM Sialidase (*Streptococcus*)
1		Siastatin B			3	85 (15.5)	40.9 (7.40)
	Me	F	—	—	0	0	0
96	H	F	—	—	0	0	86.5 (4.93)
	Me	CH_3	—	—	0	0	0
97	H	CH_3	—	—	0	7.6	95.7 (1.39)
	Me	CF_3	—	—	0	1.1	0
98	H	CF_3	—	—	0	0	66.6 (16.82)
	Me	—	H	H	0	2.2	27.1
99	H	—	H	H	40.0	0	97.9 (0.78)
102	H	—	CH_3	H	0	1.1	87.5 (5.35)
103	H	—	CH_3	CH_3	0	0.5	77.6 (15.14)
115		DDNA			—	—	78.1 (1.97)

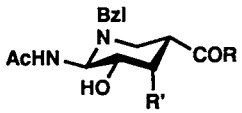
( ): IC_{50} μg/ml

As shown in Tables 10 and 11, the analogues ***95***, ***96***, ***97***, ***98***, ***99***, ***102***, ***103***, ***105*** and ***107*** showed inhibitory activity against microbial neuraminidases (*Streptococcus* sp. and *Clostridium perfringens*), whereas their methyl esters and the amides did not inhibit these enzymes. Strikingly, analogues ***99*** and ***105*** strongly affected microbial neuraminidase more effectively than DDNA (***115***). These results suggest that bacterial neuraminidase has the bulky hydrophobic pocket in the region of space around the glycerol side chain at C-6 of the oxocarbenium ion (***70***) in the

transition state. The role of the ring-imino group has not been clearly defined, but it is probably involved in the proper recognition of the inhibitor and tight binding into the active site. However, all analogues had little effect on influenza virus neuraminidases.

Table 11. Inhibitory activity against glycosidases





No.	R	R'	Inhibition % at 100 μg/ml α-Glucosidase (Yeast)	β-Glucuronidase (Bovine liver)	β-Amylase (Sweet potato)	Sialidases at 100 μM (*Streptococcus*)	at 100 μg/ml (*Cl. perfr.*)
1	Siastatin B		3	85 (15.5)	6	40.9 (7.40)	0
95	OH	OH	93 (13.0)	23	76 (18.0)	70.4 (3.96)	(3.5)
100 *	OMe	OH	93 (5.6)	22	83 (5.8)	0	42.7
101	NH_2	OH	10	0	13	7.1	9.2
104	Me	H	0	0	0	0	—
105	OH	H	0	0	0	98.2 (0.58)	(3.5)
107	OH	—	10	0	72 (84.5)	65.7 (14.55)	(50)
108	OMe	—	10	12	68 (58.0)	8.2	18.0
109	NH_2	—	10	2	62 (61.2)	0	9.6
115	DDNA		—	—	—	78.1 (1.97)	(12)

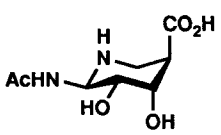
( ): IC_{50} μg/ml
* inhibits weakly the aggregation of human platelet induced by both collagen and ADP (IC50=1 mM).

In the course of studies on the design of potential neuraminidase inhibitors based on dehydration, deoxygenation and *N*-substitution of siastatin B (*1*) mentioned above, none of the analogues were found to be inhibitors for influenza virus neuraminidases even though many analogues were potent inhibitors of microbial neuraminidases. These results suggest that the binding mode of *N*-acetylneuraminic acid (*2*) and/or the transition state of the enzymatic reaction in influenza virus neuraminidase and bacterial one differ considerably. As discussed in section 4.2, *N*-acetylneuraminic acid (*2*) binds to influenza virus neuraminidase in a distorted conformation (α-boat conformation). On the other hand, *N*-acetylneuraminic acid (*2*) may bind to microbial neuraminidase in another conformation.

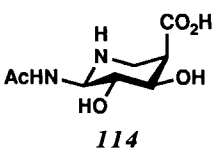
Analogues (*113*, *114*, *116* and *117*) designed as haemagglutinin- and neuraminidase-based inhibitors of influenza virus replication (see 4.2) with DDNA (*115*) as the reference compound were tested for their inhibitory effects on *N*-

acetylneuraminidases of influenza viruses, Sendai virus, Newcastle disease virus and bacterial neuraminidases, and on haemagglutination of influenza viruses. As shown in Table 12, ***113*** as well as DDNA strongly inhibited *N*-acetylneuraminidases from influenza virus (A/FM/1/47 (H1N1), A/Kayano/57 (H2N2) and B/Lee/40), whereas ***114*** showed no inhibition of these enzymes. Analogues ***116*** and ***117*** also showed no inhibiton of these enzymes. These results agree very closely with predictions of molecular modeling studies on the crystal structure of influenza virus neuraminidase complexed with *N*-acetylneuraminic acid using BIOCES[E]/AMBER (see 4.2). While DDNA also affected *N*-acetylneuraminidases from Sendai virus (HVJ)/Fusimi, Newcastle disease virus (ND)/Miyadera (47.9 and 83% inhibition, respectively, at 100 μM) and bacterial neuraminidases, ***113*** and ***114*** did not inhibit these enzymes. These facts support that the binding fashion of *N*-acetylneuraminic acid (***2***) and/or the transition state of the enzymatic reaction in influenza virus neuraminidases are different from those in bacterial ones.

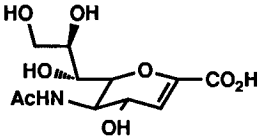
Table 12. IC_{50} (M) values of *113*, *114* and DDNA (*115*) against neuraminidases



113



114



DDNA (*115*)

Compound	Influenza virus neuraminidase A/FM/1/47		A/Kayano/57		B/Lee/40	
113	7.4×10^{-5}	(43.1)	$>1.0 \times 10^{-5}$	(25.6)	4.2×10^{-5}	(67.2)
114	—	(<0.0)	—	(2.0)	—	(19.8)
DDNA	$<1.0 \times 10^{-5}$	(95.3)	2.9×10^{-5}	(84.4)	4.9×10^{-5}	(75.6)

( ): % at 100 μM

In agreement with these findings, ***113*** as well as DDNA exhibited potent antiviral activity against influenza virus A/FM/1/47 infection in MDCK cells *in vitro* (Table 13). DDNA is essentially nonselective, inhibiting bacterial, mammalian as well as viral sialidases (refs. 94a, 96-98). In contrast, analogue ***113*** specifically affects influenza virus neuraminidases. These results indicate that analogue ***113*** should prove to be a candidate for the synthesis of useful and specific anti-viral agents inhibiting the influenza virus neuraminidase.

Table 13. Anti-influenza virus activity *in vitro* (MDCK cells) of *113* and DDNA (*115*) against influenza virus A/FM/1/47 (H1N1)

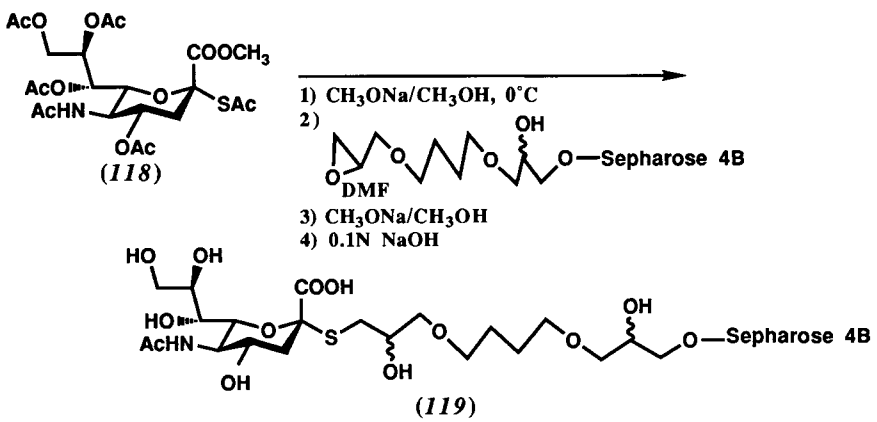
Compound	Dose (μM)	Inhibition (%) Plaque forming units (PFU)	Stained area
113	40	88.9	97.1
	20	55.5	87.2
	10	35.6	64.1
DDNA	40	100	100
	20	100	100
	10	89.6	98.7

Analogue ***113*** as well as DDNA did not affect influenza virus haemagglutinins, as predicted by the molecular modeling using BIOCES[E]/AMBER, indicating the boat conformer as being the favorable one in the enzyme (see 4.2). On the other hand, analogues ***114***, ***116*** and ***117*** also showed no inhibition at 250 μM for the influenza virus haemagglutinins, as opposed to the prediction based on the crystal structure of influenza virus haemagglutinin complexed with its receptor, *N*-acetylneuraminic acid (*2*), showing an α-chair conformer (see 4.2). A number of papers have recently demonstrated that monovalent sialosides exhibit only weak affinity to haemagglutinins, while polyvalent sialosides dramatically enhance the inhibition of viral adhesion to erythrocytes (refs. 99-107). This qualitative difference may reflects polyvalent interactions between the influenza virus and the cell surface. These facts suggest that polyvalent ligand analogues of ***114***, ***116*** and ***117*** could well inhibit haemagglutination and prevent or limit influenza infection.

5 SYNTHESIS OF AN AFFINITY ADSORBENT FOR SIALIDASE

The informations gained from the crystal structures of enzymes have provided opportunities for the design of new and specific inhibitors that might have improved potency and selectivity. While the crystal structures of sialidases derived from influenza virus B/Beijing/1/87 and A/Tokyo/3/67, and their complexes with *N*-acetylneuraminic acid (*2*) which binds in a distorted α-boat conformation have been solved (see 4.2, refs. 81, 82), little is known about those derived from microbial sources. Studies on the design of potential neuraminidase inhibitors based on analogues of siastatin B (*1*) in the preceding sections suggest that the binding mode of *2* and/or the fashion of hydrolysis in microbial neuraminidases are distinct from those of influenza virus ones. Thus, the elucidation of the three-dimensional structure of the neuraminidase of microbe, mammal *etc.* becomes very interesting. We began to examine the purification of microbial neuraminidase using an affinity adsorbent for the study of its crystal structure.

An affinity adsorbent (***119***) (ref. 108) with immobilized sialic acid through a thioglycosidic linkage was obtained by treatment of the sodium salt of methyl 5-acetamido-4,7,8,9-tetra-*O*-acetyl-3,5-dideoxy-2-thio-D-*glycero*-α-D-*galacto*-2-nonulopyranosonate (***118***) with epoxy-activated Sepharose 4B (ref. 109) (Scheme 12). The synthetic adsorbent (***119***) efficiently adsorbed the partially purified sialidase obtained from *Cl. perfringens* culture supernatant and separate it from the bulk of protein, and it was capable of repeated operation. The whole process of the purification of *Cl. perfringens* sialidase from the culture supernatant is shown in Table 14. The enzyme was purified about 8,800-fold from the culture supernatant. The protein obtained by affinity column chromatography of ***119*** showed a single protein band with an approximate molecular weight of 90,000 on SDS-polyacrylamido gel electrophoresis. *Cl. perfringens* sialidase, thus purified, should be useful for its structural elucidation. This methodology should also be applicable for purification of the receptors recognizing *N*-acetylneuraminic acid, and other sialidases including mammalian one.



Scheme 12

Table 14. Purification of *Cl. perfringens* sialidase

	mL	Total protein (mg)	Total activity (U)	Specific activity (U/mg)	Purification factor (fold)	Yield (%)
Culture supernatant	410	3,000	18,800	6.3	1	100
Precipitates with ammonium sulfate*	20	270	16,000	59.3	9.4	85
Sephadex G-75	70	75	12,600	168	26.7	67
DEAE-Cellulose	42	4.8	8,500	1,770	281	45
Affinity adsorbent	55	0.07	3,900	55,700	8,840	21

* Contaminating impurities were removed by salting-out with ammonium sulfate at 50% saturation. Subsequently sialidase was precipitated by increasing the ammonium sulfate concentation to 85% saturation.

6 CONCLUDING REMARKS

Many naturally occurring inhibitors of glycosidase and glycosyltransferase have been useful in unraveling how cell surface carbohydrates, as the primary markers for cell recognition, regulate biological functions, and they have the practical potential of the prevention and treatment of a variety of ailments, including cancer. Due to the various pharmacological and biological activities and the multifunctionalized chemical structures, these inhibitors have also attracted intensive synthetic interest.

In this chapter, our own contributions in this area have led to the synthesis of some examples of topical interest having significant biological properties, using siastatin B, a novel multifunctionalized piperidine, isolated from *Streptomyces* culture. Much work remains to be done in this fascinating field. The author has presented his progress toward the rational, computer-assisted drug design of sialic acid-based inhibitors for the influenza virus sialidase and influenza virus haemagglutination, and of sialic acid- and glucuronic acid-based inhibitors for tumor invasion, as well as indicating significant progress in the development of a new therapeutic and prophylactic treatment for influenza infection and tumor metastasis.

As the researches on the structures and biological specifities of cell surface carbohydrates progress, the day may not be far off when highly selective and extremely powerful inhibitors of cell interaction will be developed for use as new drugs to prevent and treat infections, inflammations, cancer, *etc.*

ACKNOWLEDGEMENTS

I am deeply indebted to Drs. Tomio Takeuchi and Shinichi Kondo for their encouragement in the preparation of this manuscript. I thank all my past and present co-workers whose names were cited in references for their valued and enthusiastic contributions. I am grateful to the members of the Pharmaceutical Research Center, Meiji Seika Kaisha, Ltd. for the large scale preparation of siastatin B and biological evaluation of the derivatives, and to the members of the Central Research Institute, MECT Corp. for biological evaluation of the derivatives. My thanks are due to Ms Michiko Kubota for the preparation of the camera-ready typescript.

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Atta-ur-Rahman (Ed.) *Studies in Natural Products Chemistry, Vol. 16*

The Use of Cyclic Monoterpenoids as Enantiopure Starting Materials in Natural Product Synthesis

Thomas Money and Michael K.C. Wong

INTRODUCTION

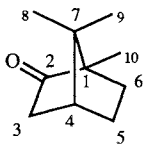
The vast majority of natural products are chiral and are biosynthesized in one of two possible enantiomeric forms. In some well-known cases (e.g. tartaric acid, α-pinene, carvone, camphor, etc.) both enantiomeric forms are recognized as natural products. The recent trend in natural product synthesis is to devise synthetic routes that will provide a specific enantiomer of the natural product; this is often accomplished by using a chiral, enantiopure starting material, and if this material is readily available in either enantiomeric form the synthesis may be described as enantiospecific. Indeed this is the most generally useful case since there may be several valid reasons[1,2a] for synthesizing both natural and "unnatural" enantiomers.

Chiral monoterpenoids are included in the fairly large number of chiral starting materials (the so-called chiral pool[2a]) used in natural product synthesis. Not all of these compounds are available in both enantiomeric forms, however, and this limits their versatility as chiral starting materials. In addition, it has been noted[2a] that the enantiomeric purity of many monoterpenoids, or for that matter, natural products[2b] in general, has not been determined. For example, it has only recently (1992) been demonstrated[3] that commercially available (+)-camphor and (–)-camphor are 99.6% and 98.3% enantiopure, respectively. It is advisable, therefore, that the enantiomeric purity of key intermediates in the synthetic route be determined by direct methods. Despite these reservations, readily

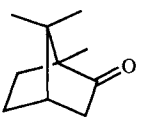
available chiral monoterpenoids are valuable and versatile starting materials for the enantiospecific synthesis of natural products* and their widespread use in this respect is illustrated by the many successful syntheses summarized in this review.

1. CAMPHOR

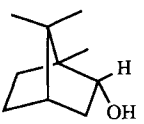
Although camphor is commercially available in both enantiomeric forms, (–)-camphor is approximately five to ten times more expensive than (+)-camphor. Fortunately, (–)-camphor can be prepared[4–6] by oxidation of commercially available (–)-borneol



(+)-camphor



(–)-camphor



(–)-borneol

with relatively inexpensive oxidizing agents. The versatility of (+)-camphor and (–)-camphor as enantiopure starting materials in natural product synthesis is due to the fact that the camphor structure can be functionalized regiospecifically at the C(4), C(5), C(6), C(8), C(9), and C(10) positions** In addition, cleavage of the C(1)–C(2), C(2)–C(3), and C(1)–C(7) bonds in camphor and camphor derivatives can be accomplished to provide a variety of synthetically useful chiral intermediates. A brief summary of the methods available for the regiospecific functionalization of camphor is given in each of the sections below. A more detailed, mechanistic account of these transformations can be found in recent reviews.[7]

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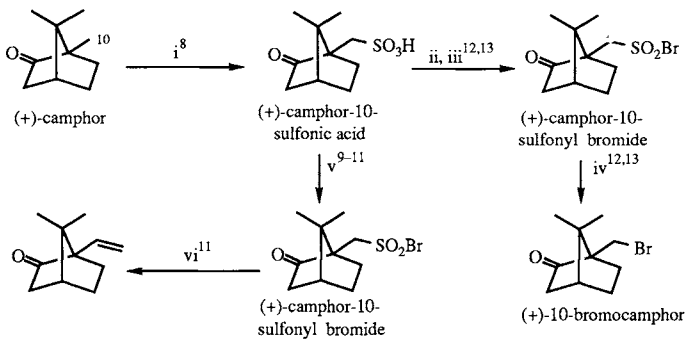
* The general use of chiral terpenes in natural products synthesis is addressed in an excellent book[354] that appeared during the preparation of this manuscript.

** The numbering system shown is the one most commonly used in the literature. However, in the IUPAC system, camphor is named bornan-2-one and positions C(8) and C(9) are reversed. In the early literature (before 1940) the C(3), C(8), C(9), and C(10) positions were designated as α, *cis*-π, *trans*-π, and ω (or β), respectively.

a. C(10)-Substitution: Camphor-10-sulfonic acid, etc.

Treatment of (+)-camphor with sulfuric acid and acetic anhydride provides (+)-camphor-10-sulfonic acid (Scheme 1),[8] and this compound is the synthetic precursor of other C(10) camphor derivatives that are important in natural product synthesis. It is interesting to note that direct C(10)-bromination of 3,3-dibromocamphor with bromine, sulfuric acid, and acetic anhydride, unlike bromination at the C(8) and C(9) positions (see below), cannot be accomplished in reasonable yield.[7] However, C(10) bromination of 3,8- and 3,9-dibromocamphor can be accomplished readily to provide valuable synthetic intermediates (*cf.* Scheme 27).

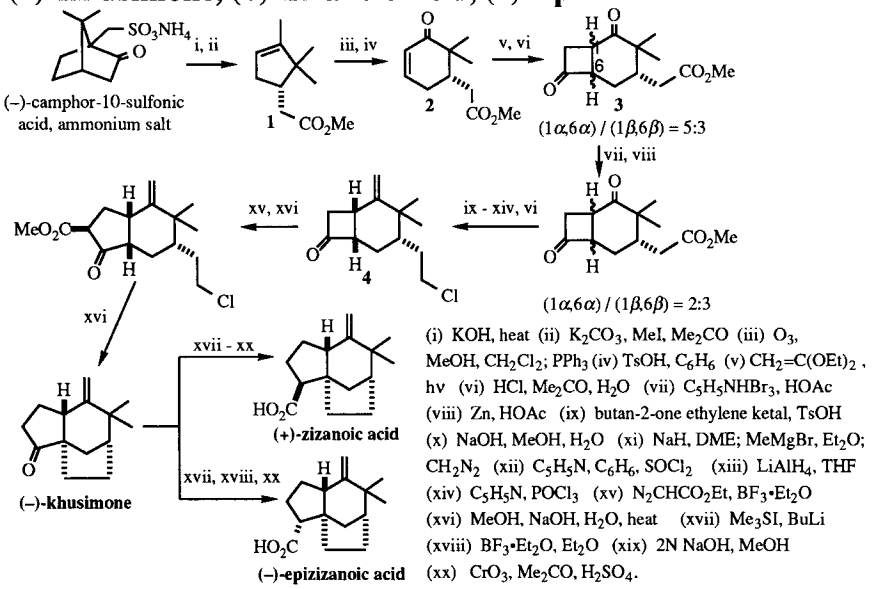


(i) H_2SO_4-Ac_2O (1:2) (ii) KOH, MeOH (iii) PBr_3 (iv) xylene, heat (v) $SOCl_2$ (vi) Et_3N, CH_2N_2, Et_2O; 95°C.

Scheme 1

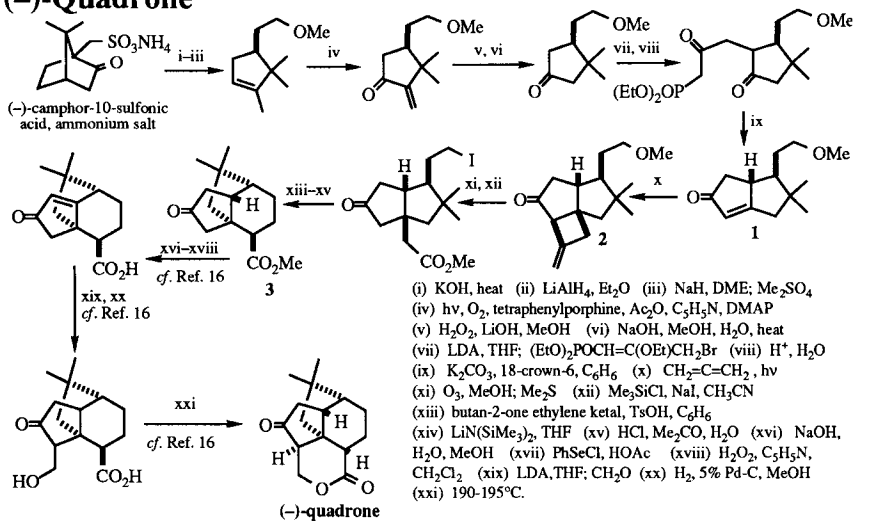
The use of C(10)-substituted camphor derivatives as intermediates in natural product synthesis is illustrated in Schemes 2 and 3. Base promoted ring cleavage of the C(1)–C(2) bond in ammonium (–)-camphor-10-sulfonate provides (–)-α-campholenic acid (Scheme 2).[14] Liu and co-workers[14] have used the corresponding methyl ester **1** to construct a cyclohexenone intermediate **2** that undergoes photochemical [2 + 2] cycloaddition to provide bicyclic diketone **3**. The typical tricyclo[6.2.1.$0^{1,5}$]undecane system that is characteristic of the zizaane sesquiterpenoids is derived from bicyclic ketone **4** by ring expansion and intramolecular alkylation.

(–)-Khusimone, (+)-Zizanoic Acid, (–)-Epizizanoic Acid[14]



Scheme 2

(–)-Quadrone[15]

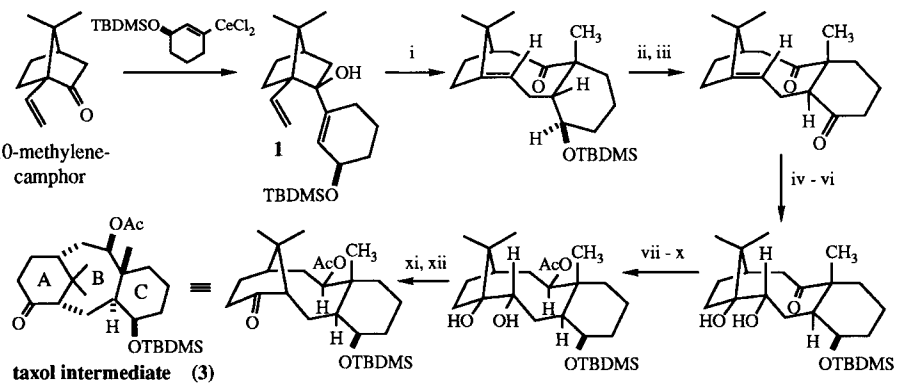


Scheme 3

Later studies by Liu and co-workers[15] have shown that α-campholenic acid (derived from camphor-10-sulfonic acid; Scheme 3) can also be used to construct a key tricyclic ketone intermediate **3** that can be elaborated to (–)-quadrone. An important feature of the synthetic route is the regioselective photochemical [2 + 2] cycloaddition of allene to enone **1** to provide the tricyclic ketone **2**.

Paquette and co-workers[17] have used 10-methylenecamphor[11] as an intermediate in a synthetic approach to the taxol structure (Scheme 4). Key features of the synthetic route are anionic oxy-Cope rearrangement of a tertiary alkoxide derived from **1** and pinacol-pinacolone rearrangement of an intermediate diol **2** to produce the typical tricyclo[9.3.1.$0^{3,8}$]pentadecane (ABC) system (**3**) of taxol.

Synthetic Approach to Taxol[17]



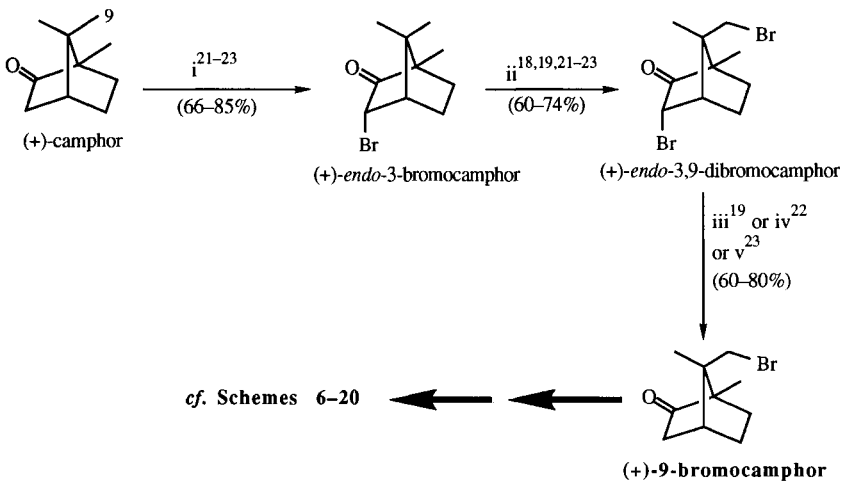
(i) KHMDS, THF, 50°C; MeI (ii) TBAF, THF (iii) PDC, NaOAc, CH_2Cl_2 (iv) NaOMe, MeOH (v) DIBAL, THF, –78°C (vi) TBDMS-Cl, Et_3N, CH_2Cl_2 (vii) OsO_4, C_5H_5N (viii) $LiAlH_4$, THF (ix) Ac_2O, C_5H_5N, DMAP (x) K_2CO_3, MeOH, H_2O (xi) MsCl, C_5H_5N (xii) Et_2AlCl, CH_2Cl_2

Scheme 4

b. C(9)-Substitution: 9-Bromocamphor, etc.

Sulfonation of commercially available *endo*-3-bromocamphor with fuming sulfuric acid or chlorosulfonic acid results in C(9)-sulfonation. By using a mixture of bromine in chlorosulfonic acid (*cf.* Scheme 5), (+)-3,9-dibromocamphor[18,19] is formed in ~50% yield and subsequent regioselective removal of the C(3)-bromo substituent with zinc in glacial

acetic acid[20] provides (+)-9-bromocamphor.* A great variety of C(9)-substituted camphor derivatives have been synthesized from 9-bromocamphor and the use of these compounds as intermediates in natural products synthesis is illustrated in Schemes 6–20.



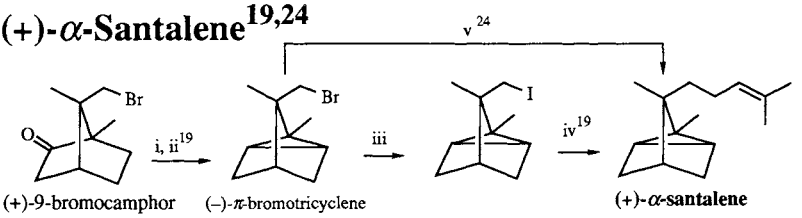
(i) Br_2, HOAc (ii) Br_2, $ClSO_3H$ (iii) Zn, HBr, CH_2Cl_2 (iv) Zn, HOAc (v) Zn, HOAc, Et_2O (vi) NaI, DMF, 110°C, 4 h (vii) NaI, HOAc (viii) NaI, HMPA, 100°C, 4 d.

Scheme 5

(–)-π-Bromotricyclene, derived from (+)-9-bromocamphor, has been used as an enantiopure intermediate in various synthetic routes to (+)-α-santalene (Schemes 6 and 7),[19,24,25] (+)-α-santalol (Schemes 8–10)[26–30], and (+)-β-santalol (Scheme 9)[29]. A key feature of one of the routes (Scheme 6)[19,24] to (+)-α-santalene is the use of a dimeric allylnickel bromide reagent[24] to construct the typical dimethylallyl terpenoid structural subunit in this compound.

* It is interesting to note that bromination of (+)-camphor under these conditions provides a mixture of (+)- and (–)-9-bromocamphor. A general mechanistic account of C(9)-bromination reactions is provided in a recent review.[7]

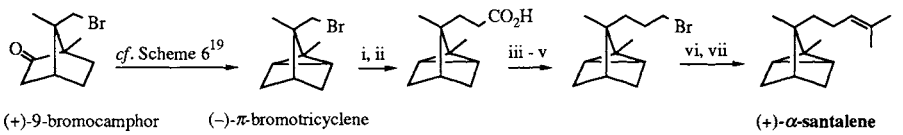
(+)-α-Santalene[19,24]



(i) NH_2NH_2, HOAc, EtOH (ii) HgO, MeOH (iii) NaI, DMSO (iv) Mg, Et_2O; γ,γ-dimethylallyl mesitoate, Et_2O (v) $(Me_2C{=}CHCH_2NiBr)_2$, DMF.

Scheme 6

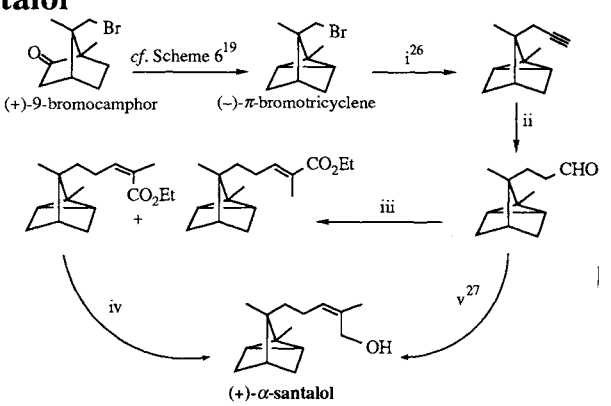
(+)-α-Santalene[25]



(i) $KH(CO_2Et)_2$, xylene (ii) 10% KOH, MeOH; dil. HCl; 180-200°C, 100 mm (iii) CH_2N_2, Et_2O (iv) $LiAlH_4$, Et_2O (v) TsCl, C_5H_5N; LiBr, Me_2CO (vi) Mg, Et_2O; Me_2CO (vii) $SOCl_2$, C_5H_5N.

Scheme 7

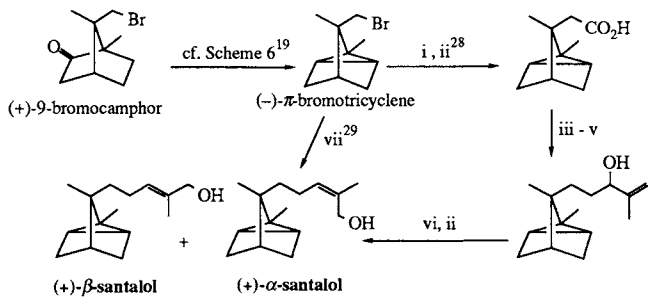
(+)-α-Santalol[26,27]



(i) $LiC{\equiv}CH$, $NH_2CH_2CH_2NH_2$, HMPA (ii) $(Me_2CHCH_2CH_2)_2BH$, THF; H_2O_2, NaOH (iii) $CH_3C(CO_2Et){=}PPh_3$, MeOH (iv) $LiAlH_4$, Et_2O (v) $CH_3CH{=}PPh_3$, THF, -78°C; n-BuLi, -78°C; CH_2O, 0°C.

Scheme 8

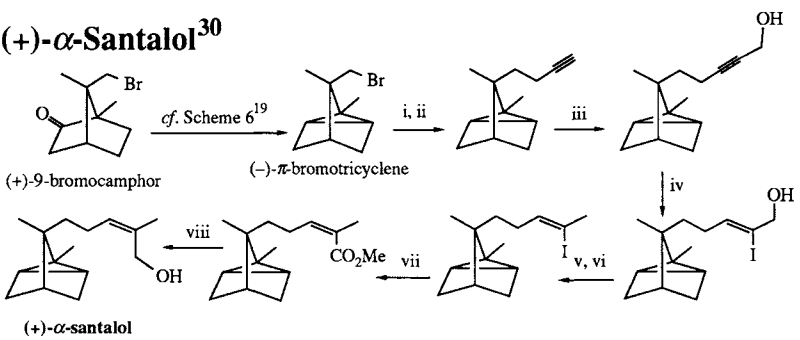
(+)-α-Santalol, (+)-β-Santalol[28,29]



(i) NaCN, DMSO (ii) K, $(CH_2OH)_2$, H_2O, heat (iii) $LiAlH_4$, Et_2O (iv) $SOCl_2$, C_5H_5N (v) Mg, Et_2O; $CH_2=C(CH_3)CHO$ (vi) PBr_3, petroleum ether, C_5H_5N (vii) Li, NEt_3, pentane; isoprene epoxide, pentane.

Scheme 9

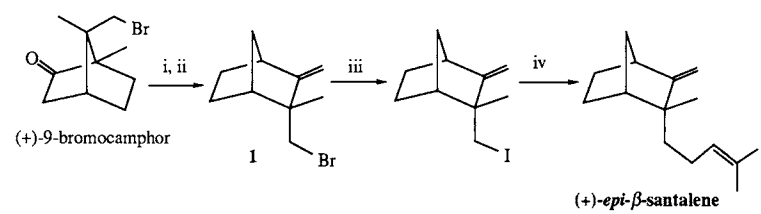
(+)-α-Santalol[30]



(i) $LiCH_2C{\equiv}CSiMe_3$, HMPA (ii) $AgNO_3$, EtOH; KCN, H_2O (iii) BuLi, THF; CH_2O (iv) DIBAL-H; I_2 (v) BuLi, MsCl, LiBr, Et_2O (vi) $NaBH_4$, DMSO (vii) $Ni(CO)_4$, NaOMe, MeOH (viii) $LiAlH_4$, Et_2O.

Scheme 10

(+)-*epi*-β-Santalene[24]

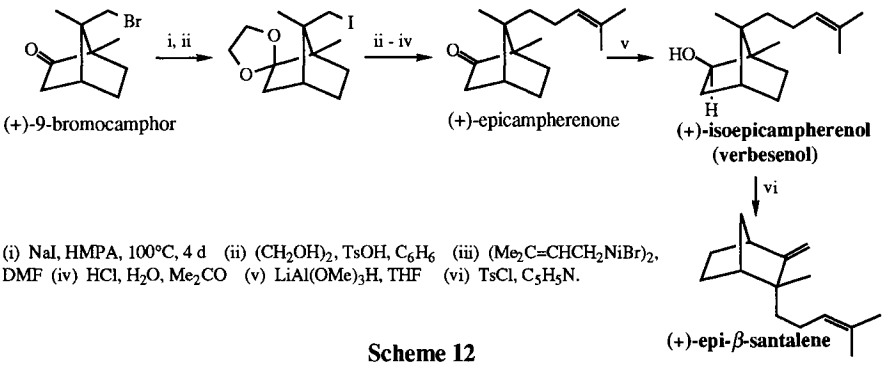


(i) $NaBH_4$ (ii) $POCl_3$, C_5H_5N (iii) Mg; $HgCl_2$; I_2 (iv) $(Me_2C{=}CHCH_2NiBr)_2$, DMF

Scheme 11

An important feature in the synthesis of (+)-*epi*-β-santalene[24] (Scheme 11) is the construction of the substituted camphene system **1** by Wagner-Meerwein rearrangement of 9-bromoisoborneol, derived from (+)-9-bromocamphor. An alternative synthesis (Scheme 12)[31] involves Wagner-Meerwein rearrangement of (+)-isoepicampherenol. The latter compound was identified as a metabolite of *Verbesina rupestris* after its synthesis had been reported.

(+)-epi-β-Santalene, (+)-Isoepicampherenol (verbesenol)[31]

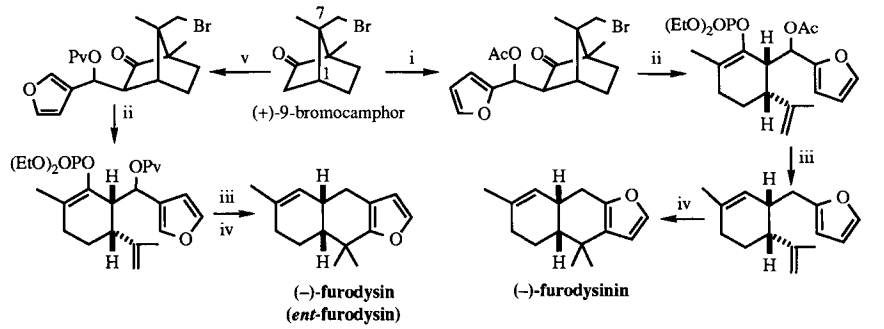


(i) NaI, HMPA, 100°C, 4 d (ii) $(CH_2OH)_2$, TsOH, C_6H_6 (iii) $(Me_2C{=}CHCH_2NiBr)_2$, DMF (iv) HCl, H_2O, Me_2CO (v) $LiAl(OMe)_3H$, THF (vi) TsCl, C_5H_5N.

Scheme 12

Albizati and co-workers[22] have used the sodium naphthalenide promoted cleavage of the C(1)–C(7) bond in 9-bromocamphor derivatives as a general theme to develop enantiospecific synthetic routes to (–)-furodysin[22], (–)-furodysinin[22] (Scheme 13), (–)-cannibidiol[32] (Scheme 14), and (+)-hapalindole Q[33] (Scheme 15).

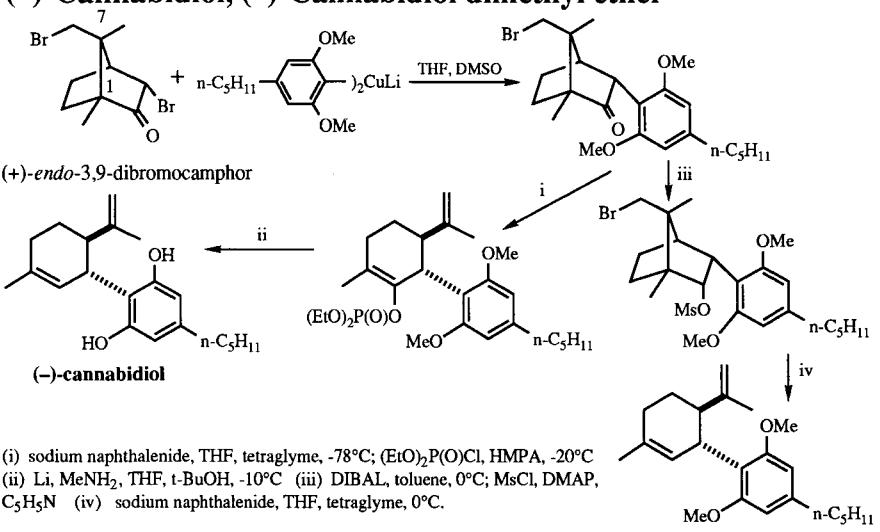
(–)-Furodysin (*ent*-furodysin), (–)-Furodysinin[22]



(i) LDA, THF, -78°C; 2-furaldehyde; AcCl (ii) sodium naphthalenide, THF, tetyraglyme; $(EtO)_2POCl$ (iii) Li, NH_3, -78°C, Me_2CHOH, THF (iv) $Hg(NO_3)_2$, CH_2Cl_2, 0—>23°C; $NaBH_4$, NaOH, H_2O, 0°C (v) LDA, THF, -78°C; 3-furaldehyde; Me_3CCOCl.

Scheme 13

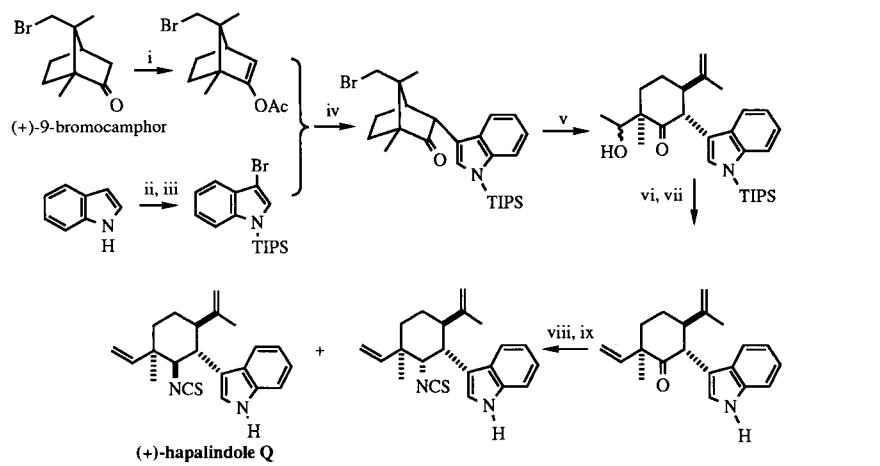
(–)-Cannabidiol, (–)-Cannabidiol dimethyl ether[32]



(i) sodium naphthalenide, THF, tetraglyme, -78°C; $(EtO)_2P(O)Cl$, HMPA, -20°C (ii) Li, $MeNH_2$, THF, t-BuOH, -10°C (iii) DIBAL, toluene, 0°C; MsCl, DMAP, C_5H_5N (iv) sodium naphthalenide, THF, tetraglyme, 0°C.

Scheme 14

(+)-Hapalindole Q[33]

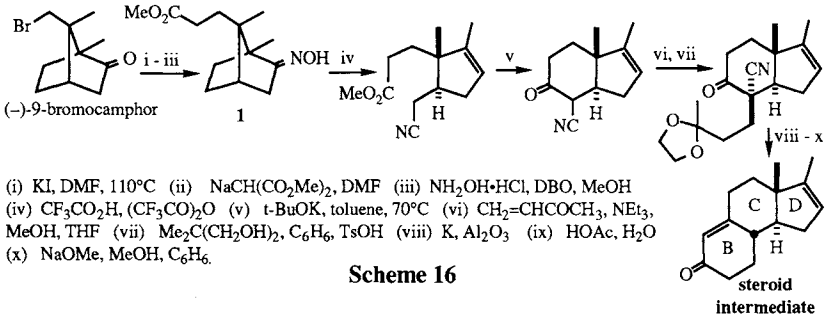


(i) LDA, THF, -78°C; Ac_2O, -78—>0°C (ii) NaH, DMF, i-Pr_3SiCl, 0°C (iii) $C_5H_5NHBr_3$, C_5H_5N, 0°C (iv) Bu_3SnOMe, $Cl_2Pd[(o\text{-tol})_3P]_2$, $PhCH_3$, 100°C (v) sodium naphthalenide, THF, tetraglyme, -78°C; CH_3CHO, -78°C (vi) MsCl, DMAP, CH_2Cl_2 (vii) NaI, HMPA, 130°C (viii) $NaBH_3CN$, NH_4OAc, MeOH, THF (ix) (imidazolyl)$_2$CS, CH_2Cl_2, 0°C

Scheme 15

Stevens and co-workers have made extensive use of 9-bromocamphor as a chiral starting material in enantiospecific routes to potentially useful intermediates for steroid[21,34] (Schemes 16 and 17) and Vitamin B_{12} synthesis[35] (Scheme 18). The key reaction in these investigations is ring cleavage of the C(1)–C(2) bond in a C(9)-substituted camphor oxime (*cf.* **1**, Scheme 16) or C(9)-substituted isoborneol intermediates (*cf.* **1**, Scheme 17; **1**, Scheme 18). Similar ring cleavage of C(9)-substituted camphor oximes (so-called "abnormal Beckmann rearrangement") was used to prepare an intermediate for helenanolide synthesis[36] (Scheme 19) and bicyclic enone **1** for steroid synthesis[37] (Scheme 20).

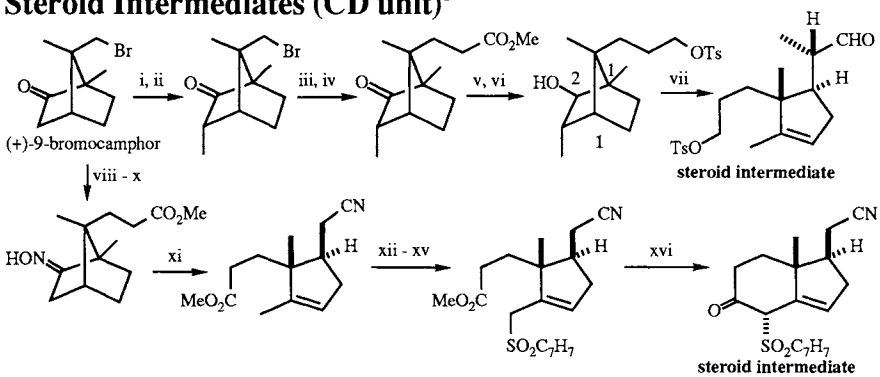
Steroid Intermediate (BCD unit)[21]



(i) KI, DMF, 110°C (ii) $NaCH(CO_2Me)_2$, DMF (iii) $NH_2OH{\cdot}HCl$, DBO, MeOH (iv) CF_3CO_2H, $(CF_3CO)_2O$ (v) t-BuOK, toluene, 70°C (vi) $CH_2{=}CHCOCH_3$, NEt_3, MeOH, THF (vii) $Me_2C(CH_2OH)_2$, C_6H_6, TsOH (viii) K, Al_2O_3 (ix) HOAc, H_2O (x) NaOMe, MeOH, C_6H_6.

Scheme 16

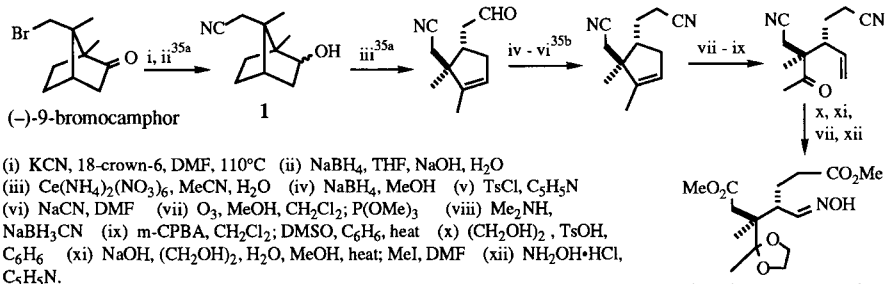
Steroid Intermediates (CD unit)[34]



(i) LDA, THF, -78°C; MeI (ii) NaOMe, MeOH (iii) KI, DMF (iv) $KH(CO_2Me)_2$, DMF (v) $LiAlH_4$, THF (vi) TsCl, C_5H_5N (vii) $Ce(NH_4)_2(NO_3)_6$, CH_3CN, H_2O (viii) KI, DMF, 110°C (ix) $NaCH(CO_2Me)_2$, DMF (x) $NH_2OH{\cdot}HCl$, DBO, MeOH (xi) CF_3CO_2H, $(CF_3CO)_2O$ (xii) SeO_2, t-BuOH (xiii) $NaBH_4$, MeOH, -30°C (xiv) $(COCl)_2$, DMF (xv) $CH_3C_6H_4SO_2Na$, DMF (xvi) NaOMe, C_6H_6.

Scheme 17

Vitamin B_{12} Intermediate[35]



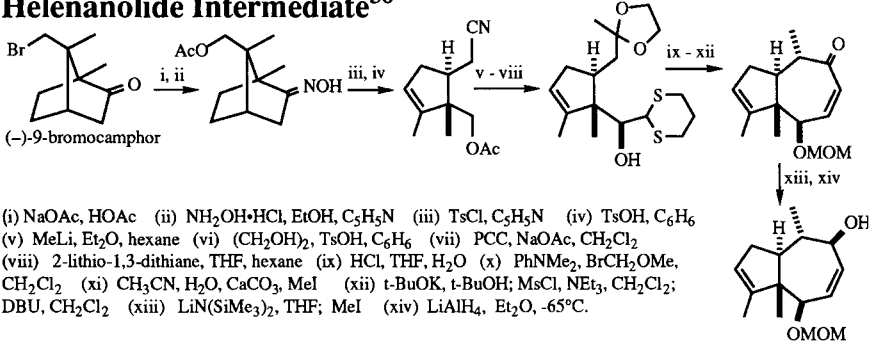
(–)-9-bromocamphor

Vitamin B_{12} intemediate

(i) KCN, 18-crown-6, DMF, 110°C (ii) $NaBH_4$, THF, NaOH, H_2O
(iii) $Ce(NH_4)_2(NO_3)_6$, MeCN, H_2O (iv) $NaBH_4$, MeOH (v) TsCl, C_5H_5N
(vi) NaCN, DMF (vii) O_3, MeOH, CH_2Cl_2; $P(OMe)_3$ (viii) Me_2NH, $NaBH_3CN$ (ix) m-CPBA, CH_2Cl_2; DMSO, C_6H_6, heat (x) $(CH_2OH)_2$, TsOH, C_6H_6 (xi) NaOH, $(CH_2OH)_2$, H_2O, MeOH, heat; MeI, DMF (xii) NH_2OH•HCl, C_5H_5N.

Scheme 18

Helenanolide Intermediate[36]



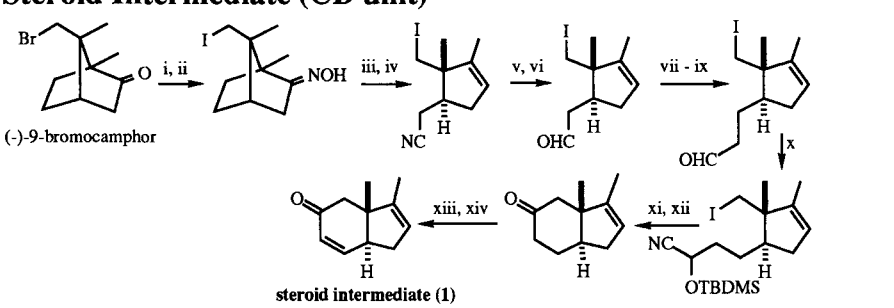
(–)-9-bromocamphor

helenanolide intermediate

(i) NaOAc, HOAc (ii) NH_2OH•HCl, EtOH, C_5H_5N (iii) TsCl, C_5H_5N (iv) TsOH, C_6H_6 (v) MeLi, Et_2O, hexane (vi) $(CH_2OH)_2$, TsOH, C_6H_6 (vii) PCC, NaOAc, CH_2Cl_2 (viii) 2-lithio-1,3-dithiane, THF, hexane (ix) HCl, THF, H_2O (x) $PhNMe_2$, $BrCH_2OMe$, CH_2Cl_2 (xi) CH_3CN, H_2O, $CaCO_3$, MeI (xii) t-BuOK, t-BuOH; MsCl, NEt_3, CH_2Cl_2; DBU, CH_2Cl_2 (xiii) $LiN(SiMe_3)_2$, THF; MeI (xiv) $LiAlH_4$, Et_2O, -65°C.

Scheme 19

Steroid Intermediate (CD unit)[37]



(-)-9-bromocamphor

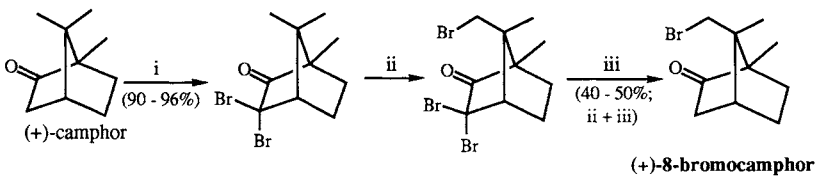
steroid intermediate (1)

(i) KI, DMF, 110°C (ii) NH_2OH•HCl, EtOH, C_5H_5N (iii) TsCl, C_5H_5N (iv) CF_3CO_2H, CH_2Cl_2 (v) DIBAL, hexane-toluene (1:1), -5°C (vi) 2N HCl (vii) Ph_2POCH_2OMe, LDA, THF, -78°C (viii) KH, THF (ix) $(CO_2H)_2$, THF (x) Me_3SiCN, KCN, 18-crown-6; HCl, H_2O; TBDMSCl, DMF, imidazole (xi) LDA, THF, HMPA, -45°C (xii) Bu_4NF, THF (xiii) LDA, THF, -78°C; PhSeCl (xiv) 30% H_2O_2, CH_2Cl_2, C_5H_5N.

Scheme 20

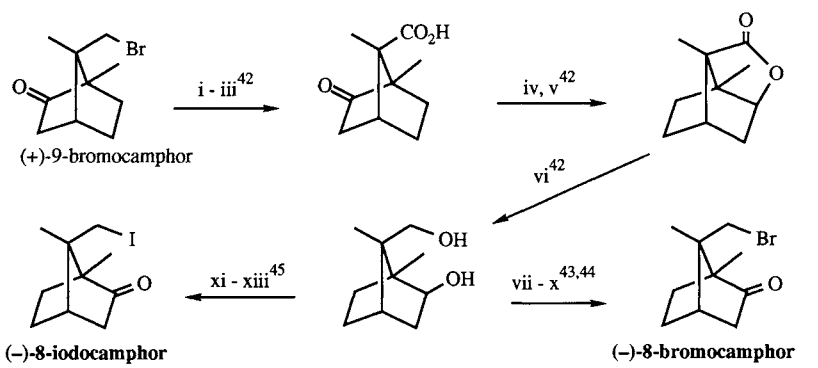
c. C(8)-Substitution: 8-Bromocamphor

A simple, three-step synthesis of 8-bromocamphor (Scheme 21)[38–41] offers obvious advantages over a previous ten-step procedure (Scheme 22),[42–45] and has provided a greater opportunity to evaluate the use of C(8)-substituted camphor derivatives as starting materials in the synthesis of natural products, as exemplified in Schemes 23–26. The mechanism proposed for the C(8)-bromination of (+)-3,3-dibromocamphor (*cf.* Scheme 21) has been elucidated[38] using deuterium-labelled substrates.



(i) Br_2, HOAc, HBr (ii) Br_2, $ClSO_3H$ (iii) Zn, HOAc, Et_2O

Scheme 21

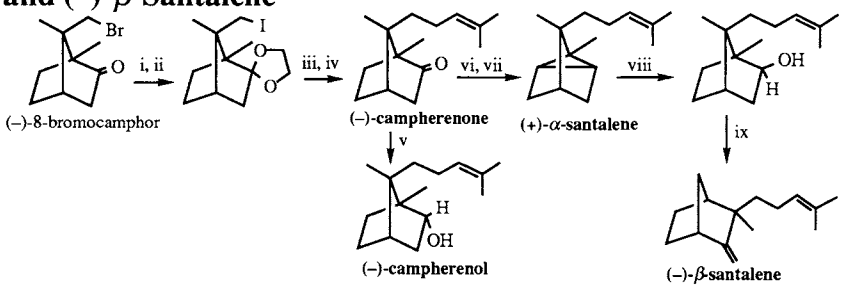


(i) KOAc, HOAc (ii) KOH, EtOH (iii) CrO_3, $MnSO_4$, H_2SO_4 (iv) $NaBH_4$, KOH, MeOH (v) CF_3CO_2H, H_2SO_4 (vi) $LiAlH_4$, Et_2O (vii) PhCOCl, C_6H_6, C_5H_5N (viii) CrO_3, Me_2CO, H_2SO_4 (ix) KOH, MeOH (x) PBr_3, PhBr, quinoline (xi) TsCl, C_5H_5N (xii) CrO_3, H_2SO_4, Me_2CO (xiii) NaI, DMSO, 120°C.

Scheme 22

The development of a short synthetic route[38–41] to (+)- or (–)-8-bromocamphor (Scheme 21) has led to the use of these compounds as chiral intermediates in the enantiospecific synthesis of campherenone[31,39] (Schemes 23 and 24), ylangocamphor[31] (Scheme 86), copacamphor[31] (Scheme 25), and longicamphor[31] (Scheme 26) and to the recognition that these "sesquicamphors" could serve as key intermediates in the synthesis of "sesquicamphenes" such as β–santalene[31] (Scheme 23), sativene[31] (Scheme 25), copacamphene[31] (Scheme 25), and longifolene[39] (Scheme 26). The conversion of the "sesquicamphors" to the "sesquicamphenes" is analogous to the well-known conversion of (+)-camphor to (+)-camphene.

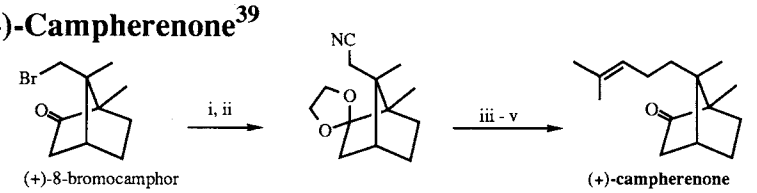
(–)-Campherenone, (–)-Campherenol, (+)-α-Santalene, and (–)-β-Santalene[31]



(i) NaI, HMPA (ii) $(CH_2OH)_2$, TsOH, C_6H_6 (iii) $(Me_2C{=}CHCH_2NiBr)_2$, DMF (iv) 6 N HCl, Me_2CO (v) Na, $CH_3CH_2CH_2OH$, reflux, 16 h (vi) NH_2NH_2, HOAc, EtOH (vii) HgO, MeOH, reflux (viii) $LiAlH(OMe)_3$, THF (ix) TsCl, C_5H_5N, 95°, 22 h.

Scheme 23

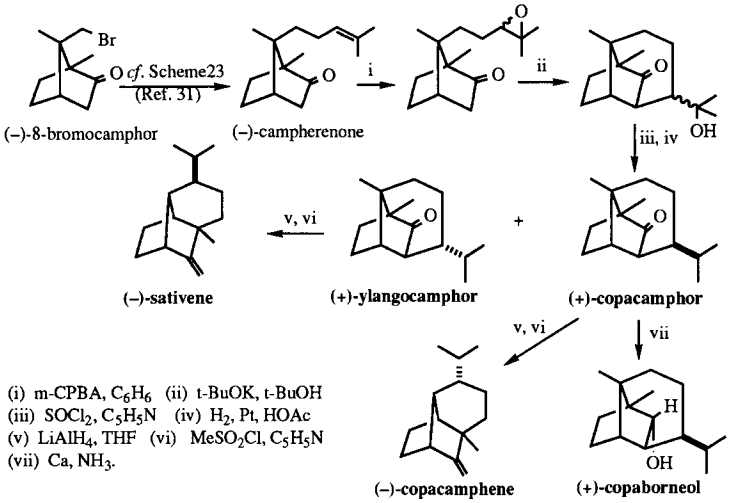
(+)-Campherenone[39]



(i) Me_3SiCl, $(CH_2OH)_2$, 23°C (ii) NaI, DMSO, 110°C (iii) NaCN, DMSO, 60°C (iv) LDA, THF, -78°C; $Me_2C{=}CHCH_2Br$ (v) K, HMPA, Et_2O, t-BuOH, 0°C (vi) HCl, Me_2CO, H_2O.

Scheme 24

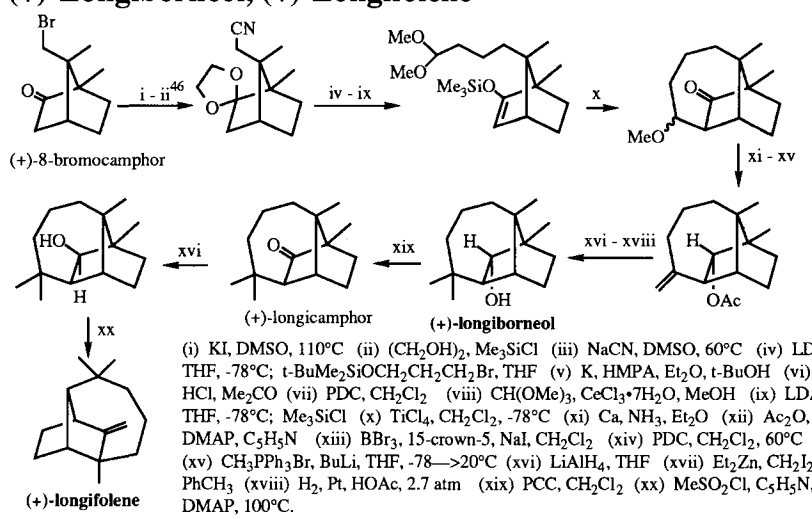
(–)-Sativene, (–)-Copacamphene, (+)-Copaborneol[31]



(i) m-CPBA, C_6H_6 (ii) t-BuOK, t-BuOH
(iii) $SOCl_2$, C_5H_5N (iv) H_2, Pt, HOAc
(v) $LiAlH_4$, THF (vi) $MeSO_2Cl$, C_5H_5N
(vii) Ca, NH_3.

Scheme 25

(+)-Longiborneol, (+)-Longifolene[39]

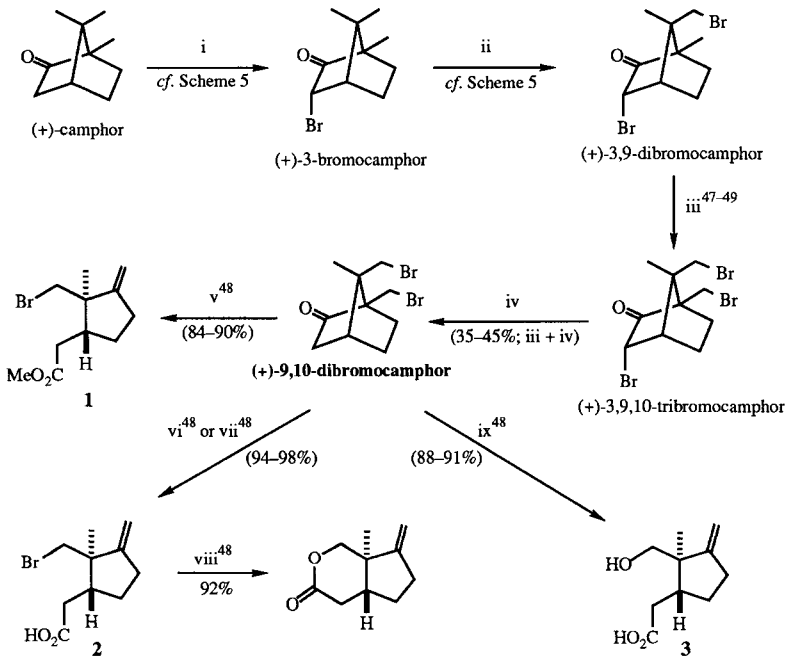


(i) KI, DMSO, 110°C (ii) $(CH_2OH)_2$, Me_3SiCl (iii) NaCN, DMSO, 60°C (iv) LDA, THF, -78°C; t-$BuMe_2SiOCH_2CH_2CH_2Br$, THF (v) K, HMPA, Et_2O, t-BuOH (vi) 1 N HCl, Me_2CO (vii) PDC, CH_2Cl_2 (viii) $CH(OMe)_3$, $CeCl_3 \cdot 7H_2O$, MeOH (ix) LDA, THF, -78°C; Me_3SiCl (x) $TiCl_4$, CH_2Cl_2, -78°C (xi) Ca, NH_3, Et_2O (xii) Ac_2O, DMAP, C_5H_5N (xiii) BBr_3, 15-crown-5, NaI, CH_2Cl_2 (xiv) PDC, CH_2Cl_2, 60°C (xv) CH_3PPh_3Br, BuLi, THF, -78—>20°C (xvi) $LiAlH_4$, THF (xvii) Et_2Zn, CH_2I_2, $PhCH_3$ (xviii) H_2, Pt, HOAc, 2.7 atm (xix) PCC, CH_2Cl_2 (xx) $MeSO_2Cl$, C_5H_5N, DMAP, 100°C.

Scheme 26

d. C(9,10)-Disubstitution: 9,10-Dibromocamphor and Ring-Cleavage Products.

Prolonged treatment of (+)-3,9-dibromocamphor with bromine in chlorosulfonic acid followed by regioselective removal of the C(3)-bromo substituent provides (+)-9,10-dibromocamphor[47–49] in ~35% overall yield (*cf.* Scheme 27). Highly efficient cleavage of the C(1)–C(2) bond then provides chiral cyclopentanoid compounds **1**–**3** (Scheme 27).[48,50]



(i) Br_2, HOAc (ii) Br_2, $ClSO_3H$, 1 h (iii) Br_2, $ClSO_3H$, 5 d (iv) Zn, HOAc, Et_2O, 0°C (v) MeONa, MeOH, 6 h (vi) KOH, DMSO-H_2O (~6:1), 65°C, 1 h (vii) 0.5 M KOH, THF, 23°C, 4.5 h (viii) KOH, DMSO-H_2O (9:1), Ag_2O, 22—>70°C, 2 h (ix) KOH, DMSO-H_2O (~6:1), 65°C, ~22 h *or* KOH, DMSO-H_2O (9:1), 90°C, 24 h.

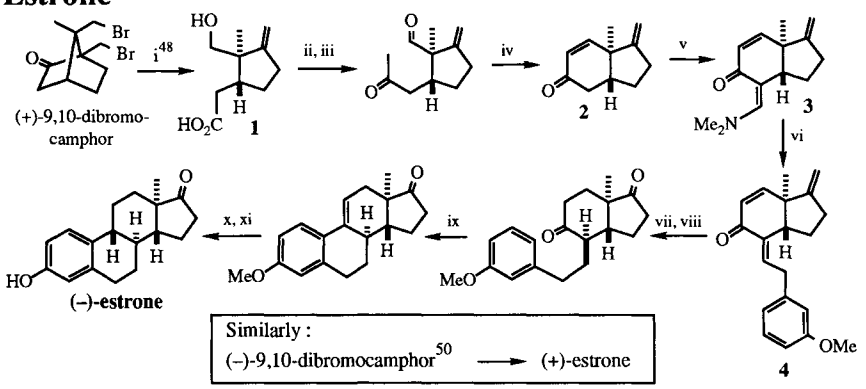
Scheme 27

The considerable potential of (+)-9,10-dibromocamphor or (–)-9,10-dibromocamphor as useful enantiopure intermediates in terpenoid and steroid synthesis has been firmly established by the use of these compounds in the synthesis of estrone[51] (Scheme 28), ophiobolin[52] (Scheme 34), California red scale pheromone[53] (Scheme 29), and in the preparation of advanced intermediates that are currently being evaluated in steroid[54–56] (Schemes 31 and 32), triterpenoid (limonoid)[57] (Scheme 33), and

helenanolide[58] (Scheme 30) synthesis. In all cases, the enantiospecific synthetic routes to steroids, triterpenoids (limonoids) and sesquiterpenoids (pseudoguaianolides) outlined above compare favourably (in terms of stereoselectivity and operational convenience) with contemporary literature routes to these compounds.

In the synthesis of estrone (Scheme 28),[51,59] hydroxy-acid **1**, derived from (+)-9,10-dibromocamphor, is converted to hydrindenone **2** and hence to the vinylogous amide **3**. Conjugate addition of a *m*-methoxybenzyl unit to this compound provides an intermediate **4** that is readily converted to unnatural (–)-estrone. By using (–)-9,10-dibromocamphor as an intermediate, the natural enantiomer, (+)-estrone, can also be prepared.

Estrone[51,59]

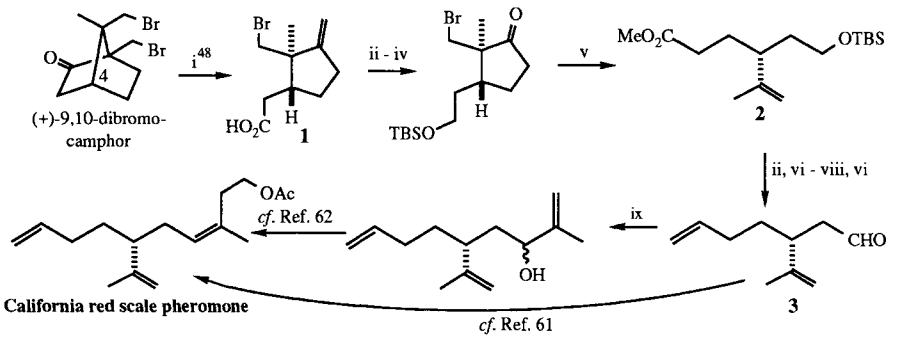


(i) KOH, DMSO, H_2O (ii) MeLi, THF; Me_3SiCl; 1 N HCl (iii) PDC, CH_2Cl_2 (iv) NaOH, MeOH, 0°C; MsCl, Et_3N, DMAP; DBU (v) t-BuOCH(NMe_2)$_2$, heat (vi) *m*-$CH_3OC_6H_4CH_2MgCl$, Et_2O (vii) Li, NH_3, Et_2O (viii) O_3, CH_2Cl_2; Me_2S (ix) HOAc-HCl (10:1), Et_2O, 0°C (x) H_2, Pd, MeOH (xi) BBr_3, CH_2Cl_2, -78°C.

Scheme 28

Ring cleavage of (+)-9,10-dibromocamphor to provide bromo-acid **1** is a reaction that is characteristic of α,α–disubstituted β-bromoketones.[60] Oxidative cleavage of the exo-methylene group in **1** (Scheme 29)[53] provides a bromoketone that can also undergo this typical cleavage reaction to provide an acyclic ester **2** in which the stereochemistry is defined by the stereochemistry at C(4) in the starting material. Ester **2** was subsequently converted to aldehyde **3** and since this compound had previously been converted to California red scale pheromone by Roelofs and co-workers (*cf.* Scheme 74),[61] the synthetic scheme outlined in Scheme 29 represents a formal enantiospecific synthesis of this compound.

California Red Scale Pheromone[53]



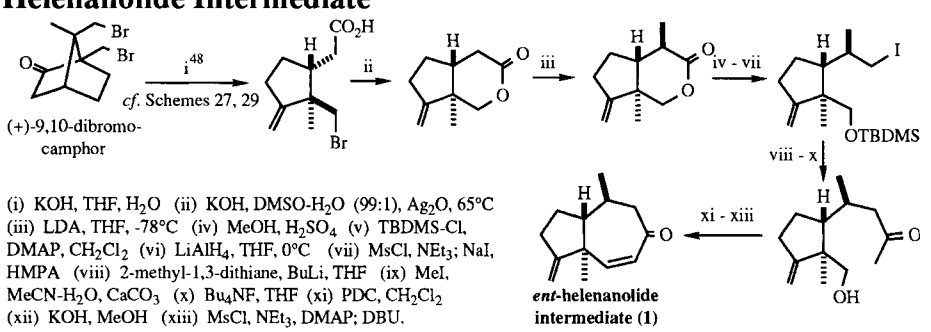
(i) KOH, DMSO, H_2O (ii) $LiAlH_4$, THF (iii) t-$BuMe_2SiCl$, DMAP, CH_2Cl_2 (iv) O_3, MeOH, –78°C; Me_2S
(v) NaOMe, MeOH (vi) PDC, CH_2Cl_2 (vii) $CH_2=PPh_3$, THF (viii) Bu_4NF, THF (ix) $CH_2=C(CH_3)MgBr$, THF.

Scheme 29

The synthesis of hydroazulenoid enone **1** shown in Scheme 30[58] represents an initial attempt to use 9,10-dibromocamphor in pseudoguaianolide synthesis. The development of a more general enantiospecific route to the ambrosanolides and helenanolides from (–)-9,10-dibromocamphor is currently in progress in our laboratories.[63]

The synthetic route outlined in Scheme 31[54,55] can provide steroid intermediates (*cf.* **2**) with the correct absolute stereochemistry at C(13), C(17), and C(20) (steroid numbering) and in which the nature of the side-chain unit is pre-determined by the electrophilic agent used for the alkylation of ketal-ester **1**.

Helenanolide Intermediate[58]



(i) KOH, THF, H_2O (ii) KOH, DMSO-H_2O (99:1), Ag_2O, 65°C
(iii) LDA, THF, -78°C (iv) MeOH, H_2SO_4 (v) TBDMS-Cl, DMAP, CH_2Cl_2 (vi) $LiAlH_4$, THF, 0°C (vii) MsCl, NEt_3; NaI, HMPA (viii) 2-methyl-1,3-dithiane, BuLi, THF (ix) MeI, MeCN-H_2O, $CaCO_3$ (x) Bu_4NF, THF (xi) PDC, CH_2Cl_2
(xii) KOH, MeOH (xiii) MsCl, NEt_3, DMAP; DBU.

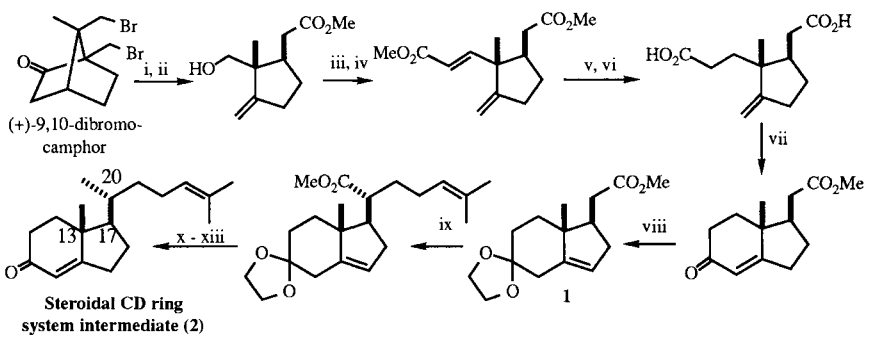
Scheme 30

The hydroxy-diene **1** (Scheme 32)[56] has considerable potential as an intermediate for the Diels-Alder route to steroids. The exo-methylene group could be converted to a 17-keto group or other steroidal side chain units by hydroboration, homologation and stereoselective alkylation at the C(20) position.

The synthesis of (+)-ophiobolin C (Scheme 34) reported by Kishi and co-workers[52] represents the most sophisticated use of 9,10-dibromocamphor in natural product synthesis. As shown in Scheme 34, hydroxy-acid **1**, derived from (+)-9,10-dibromocamphor, is used to build a major part of rings B and C and the side chain unit in (+)-ophiobolin C.

The synthesis of a potentially useful tricyclic intermediate **2** (Scheme 33)[57] for the synthesis of the limonoids, a group of complex tetranortriterpenoids, involves successive alkylation of enone **1** followed by intramolecular aldol condensation. This reaction sequence provides another example of the versatility of 9,10-dibromocamphor in natural product synthesis.

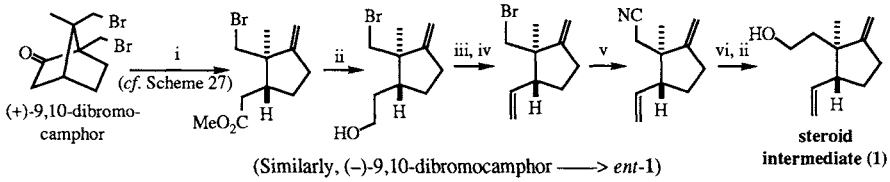
CD Ring System/Side-Chain Unit of Steroids[54,55]



(i) KOH, DMSO-H_2O (9:1), 90°C (ii) K_2CO_3, DMF, MeI (iii) $(COCl)_2$, Me_2SO, CH_2Cl_2, -60°C; NEt_3 (iv) NaH, THF, $(MeO)_2P(O)CH_2CO_2Me$ (iv) Mg, MeOH (v) KOH, MeOH, H_2O (vi) $(CF_3CO)_2O$, CH_2Cl_2; TsOH, MeOH (vii) $(CH_2OH)_2$, PPTS, C_6H_6, reflux (viii) LDA, THF, -78°C; $Me_2CH{=}CHCH_2CH_2I$, THF, -78—>25°C (ix) $LiAlH_4$, THF (x) $MeSO_2Cl$, DMAP, NEt_3, CH_2Cl_2 (xi) $LiBHEt_3$, THF (xii) HCl, Me_2CO, H_2O, reflux.

Scheme 31

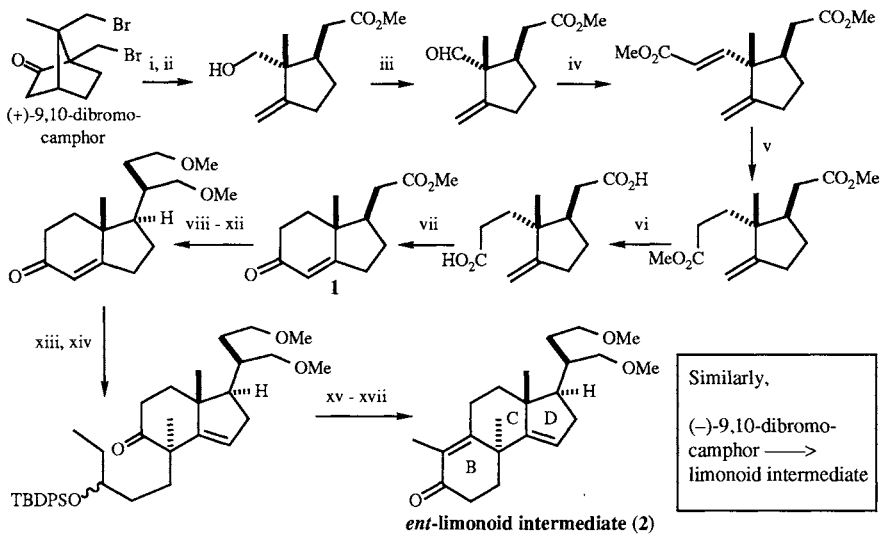
Intermediate for Intramolecular Diels-Alder Route to Steroids[56]



(i) NaOMe, MeOH, reflux (ii) DIBAL, Et_2O, 0°C (iii) *o*-$NO_2C_6H_4SeCN$, Bu_3P, THF (iv) H_2O_2, THF (v) NaCN, KI, DMSO, 110°C (vi) DIBAL, hexane, -78—>23°C; sodium potassium tartrate, 6 N HCl.

Scheme 32

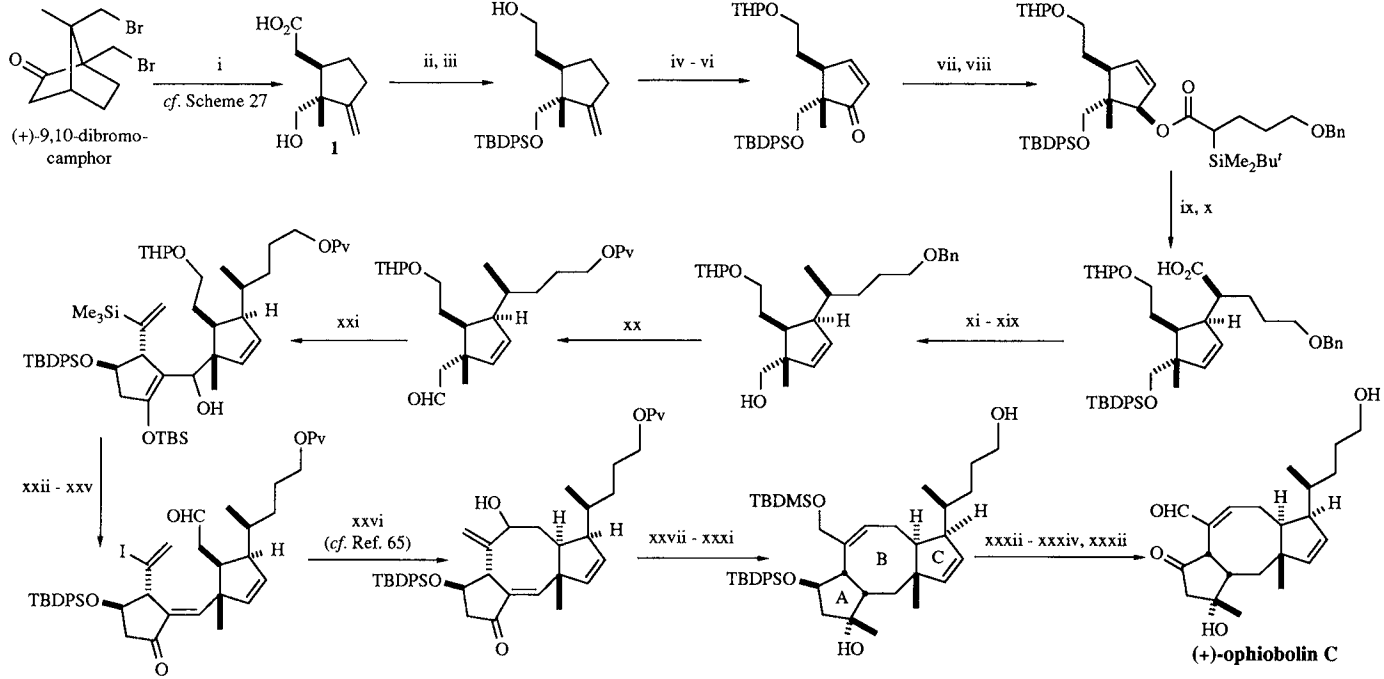
Limonoid Intermediate[57]



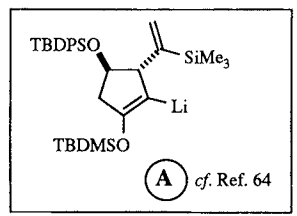
(i) KOH, DMSO-H_2O (5:1) (ii) K_2CO_3, DMF; CH_3I (iii) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; Et_3N (iv) NaH, $(MeO)_2P(O)CH_2CO_2Me$, THF (v) Mg, MeOH, 0°C (vi) KOH, MeOH (vii) $(CF_3CO)_2O$, CH_2Cl_2; p-TsOH, MeOH (viii) $(CH_2OH)_2$, PPTS, C_6H_6, reflux (ix) LDA, THF, –78°C; $BrCH_2CO_2Me$, –78°—>20°C (x) DIBAL, THF, 0°C (xi) NaH, THF; CH_3I (xii) 1 M HCl, Me_2CO (xiii) NaH, DMSO; 1-iodo-3-(*t*-butyldiphenylsilyloxy)-pentane (xiv) NaH, DMSO; CH_3I (xv) TBAF, THF (xvi) CrO_3, aq. H_2SO_4, Me_2CO, 0°C (xvii) 3 M HCl, MeOH, reflux.

Scheme 33

(+)-Ophiobolin C[52]



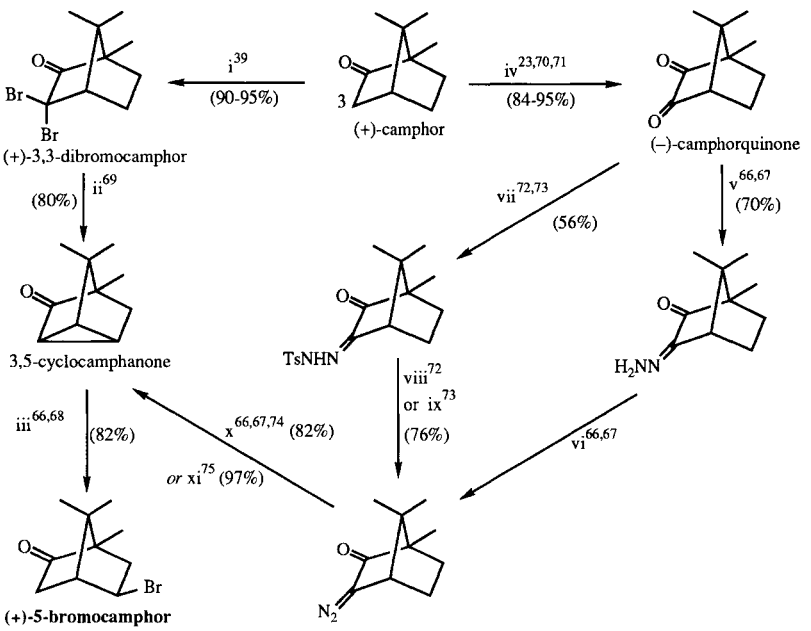
(i) KOH, DMSO-H_2O (6:1), 65°C (ii) t-$BuPh_2SiCl$, $AgNO_3$, C_5H_5N (iii) LAH, Et_2O (iv) O_3 (v) LDA, THF; Me_3SiCl, Et_3N; $Pd(OAc)_2$, MeCN (vi) DHP, PPTS, CH_2Cl_2 (vii) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, –30°C (viii) $BnO(CH_2)_3CH(TBDMS)COCl$ (ix) $KN(SiMe_3)_2$, THF, –78°C (x) 230°C, xylene (xi) 1 N HCl, MeOH, Et_2O (xii) CH_2N_2, Et_2O, 0°C (xiii) LAH, Et_2O, 0°C (xiv) MsCl, Et_3N, CH_2Cl_2, 0°C (xv) LAH, Et_2O (xvi) H_2, PtO_2, EtOAc (xvii) H_2, $Pd(OH)_2$, EtOH (xviii) Me_3CCOCl, C_5H_5N (xix) TBAF, DMF, 50°C (xx) $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N (xxi) **A**, Et_2O, –78°C (xxii) 48% HF, THF (xxiii) ICl, CH_2Cl_2, –78—>0°C; TBAF, HF, THF, 0°C, 1 min (xxiv) TsOH, MeOH, CH_2Cl_2 (xxv) Swern oxidation (xxvi) $CrCl_2$, $NiCl_2$, DMSO, Me_2S (xxvii) t-BuOOH, $VO(acac)_2$, C_6H_6 (xxviii) p-$CH_3C_6H_4OC(S)Cl$, imidazole, DMF (xxix) Bu_3SnH, AIBN, C_6H_6, reflux (xxx) TBDMSCl, imidazole, DMF (xxxi) MeMgBr, Et_2O, 0—>23°C (xxxii) Swern oxidation (xxxiii) $Me_2C{=}PPh_3$, THF, –78—>0°C (xxxiv) TBAF, THF.



Scheme 34

e. C(5)-Substitution: 5-Bromocamphor, etc.

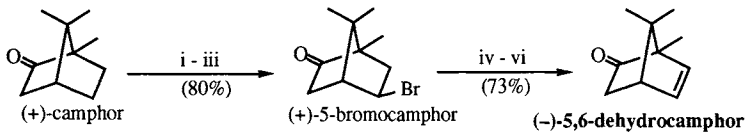
The synthesis of 5-bromocamphor normally involves treatment of 3,5-cyclocamphanone with 48% hydrobromic acid in acetic acid (Scheme 35).[66–68] Various synthetic routes to 3,5-cyclocamphanone have been reported but the one[69] involving (+)-3,3-dibromocamphor as intermediate is the most efficient and convenient.



(i) Br_2, HOAc, reflux, 5 h (ii) Et_2Zn, C_6H_6, reflux, 24 h (iii) HBr (48%), HOAc, 65°C, 3 h (iv) SeO_2, Ac_2O (v) NH_2NH_2, EtOH (vi) HgO, C_6H_6, reflux, 8 h (vii) $TsNHNH_2$, HOAc (viii) NaOH, H_2O, pentane (ix) alumina (x) Cu, $(CH_2OH)_2$ (xi) $CF_3CF_2CF_2CO_2Ag$, THF.

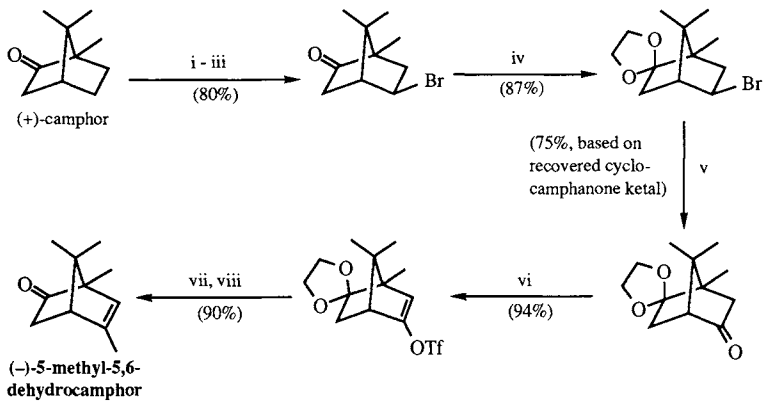
Scheme 35

As shown below (Scheme 36), (+)-5-bromocamphor is an intermediate in the synthesis of (–)-5,6-dehydrocamphor[76–78] (*cf.* synthesis from 6-bromocamphor, Scheme 43) and (–)-5-methyl-5,6-dehydrocamphor (Scheme 37).[78,88] The latter compounds have considerable potential as chiral intermediates in terpenoid synthesis (*cf.* Scheme 44).



(i) Br_2, HOAc, HBr, 110°C, 16 h (ii) Et_2Zn, C_6H_6, reflux, 22 h (iii) HBr (48%), HOAc, 65°C, 3 h (iv) $(CH_2OH)_2$, Me_3SiCl, 5 h (v) KOH, DMSO-H_2O (7:1), 100°C, 2 h (vi) 1 N HCl, Me_2CO, 1 h.

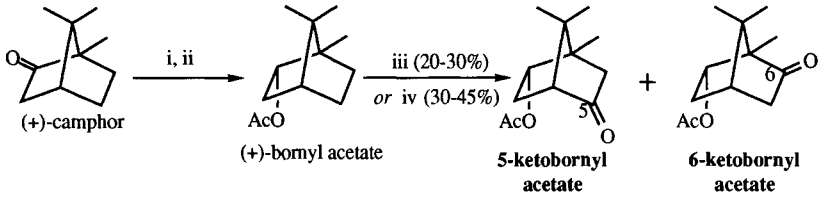
Scheme 36



(i) Br_2, HOAc, 80°C (ii) Et_2Zn, benzene, reflux (iii) HBr, Ac_2O, 65°C (iv) $(CH_2OH)_2$, Me_3SiCl (v) $AgBF_4$, DMSO; NEt_3 (vi) Tf_2O, 2,6-di-*t*-butyl-4-methylpyridine, CH_2Cl_2 (vii) Me_2CuLi, Et_2O. -20°C (viii) 1 N HCl, Me_2CO.

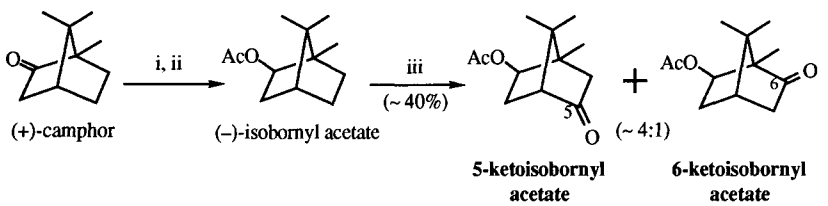
Scheme 37

The introduction of oxygen functionality into the C(5) position of camphor can be accomplished by direct oxidation of bornyl acetate[68,73,79–83,88] (Scheme 38) or isobornyl acetate[84,85] (Scheme 39). C(5)-Hydroxylation of these substrates can also be accomplished microbiologically.[7,83] The use of C(5)-substituted camphor derivatives in natural product synthesis is illustrated in Schemes 40–41. The use of 5,6-dehydrocamphor and 5-methyl-5,6-dehydrocamphor is presented later in this review.



(i) Ca, NH_3 (ii) Ac_2O, C_5H_5N (iii) CrO_3, HOAc (iv) CrO_3, Ac_2O, HOAc.

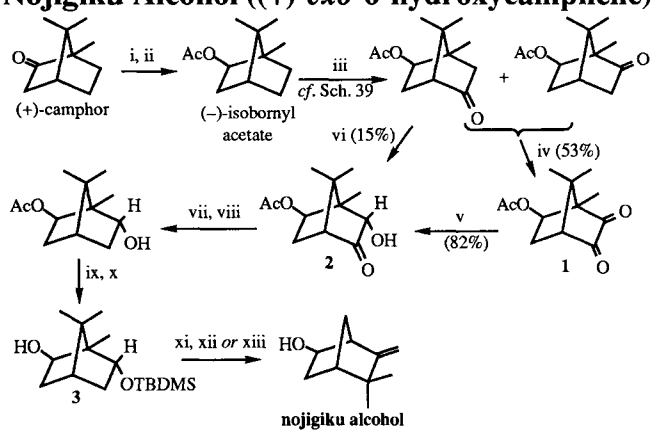
Scheme 38



(i) $LiAlH_4$, THF, 0°C (vi) Ac_2O, C_5H_5N, 100°C, 11 h (vii) CrO_3, Ac_2O, HOAc, 8 d.

Scheme 39

Nojigiku Alcohol ((+)-*exo*-6-hydroxycamphene)[85]



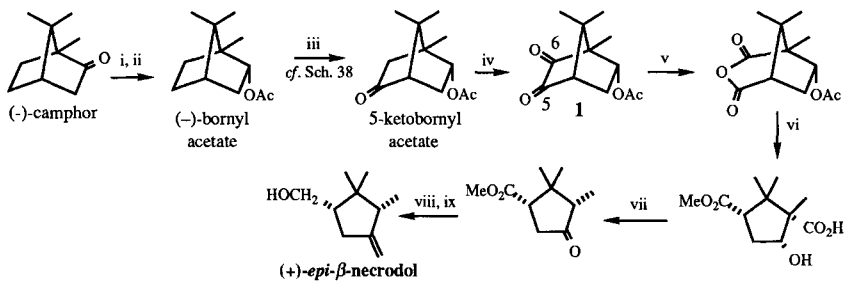
(i) $LiAlH_4$, THF, 0°C (ii) Ac_2O, C_5H_5N, 100°C, 11 h (iii) CrO_3, Ac_2O, HOAc, 8 d, 23°C (iv) SeO_2, Ac_2O (v) Zn, HOAc, H_2O (vi) LDA, THF; MoO_5•HMPA•C_5H_5N (vii) $(CH_2SH)_2$, BF_3•Et_2O (viii) Raney Ni, EtOH, reflux (ix) *t*-$BuMe_2SiCl$, imidazole, DMF, 85°C (x) KOH, EtOH, reflux (xi) MsCl, C_5H_5N, reflux (xii) Bu_4NF, THF (xiii) HOAc-H_2O-THF (3:1:1).

Scheme 40

In the synthesis of nojigiku alcohol (Scheme 40), a mixture of 5-keto- and 5-ketoisobornyl acetate, produced by remote oxidation of isobornyl acetate,[84,85] is further oxidized to 5,6-diketoisobornyl acetate, **1**. Regiospecific and stereoselective reduction then provides the key *endo*-hydroxy intermediate, **2**. The *endo*-hydroxy group in this intermediate eventually becomes the *exo*-hydroxy group in nojigiku alcohol by Wagner-Meerwein rearrangement of the derived *endo*-6-silyloxyisoborneol, **3**.

Successive oxidation of bornyl acetate leads to 5,6-diketobornyl acetate, **1** (Scheme 41),[86] and subsequent cleavage of the C(5)–C(6) bond in this compound provides entry to the typical cyclopentanoid framework of (+)-*epi*-β-necrodol.

(+)-*epi*-β-Necrodol[86] (*cf.* alternative synthesis, Scheme 51)

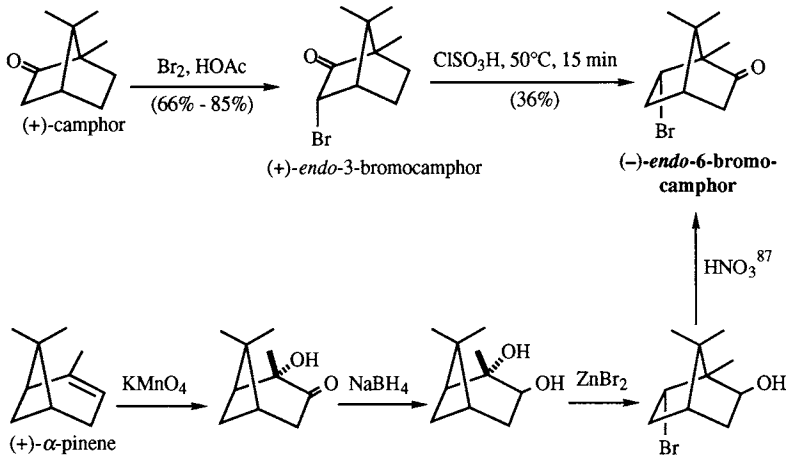


(i) Ca, NH_3 (ii) Ac_2O, C_5H_5N (iii) CrO_3, Ac_2O, HOAc, NaOAc, ~110°C (iv) Ac_2O, SeO_2, 140°C (v) H_2O_2, HOAc (vi) HCl, MeOH (vii) CrO_3, Et_2O; C_6H_6, heat (viii) Zn, $TiCl_4$, CH_2Cl_2, CH_2Br_2, THF (ix) $LiAlH_4$, THF, 0°C.

Scheme 41

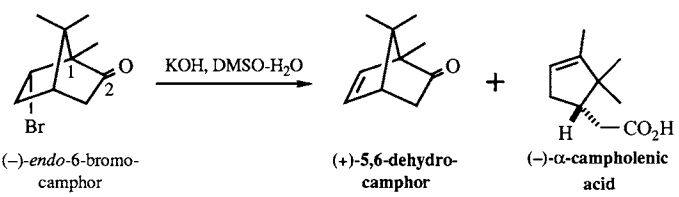
f. C(6)-Substitution: 6-Bromocamphor, etc.

The comparatively low-yielding, acid-catalyzed rearrangement[38] of (+)-*endo*-3-bromocamphor to (–)-*endo*-6-bromocamphor represents the most convenient enantiospecific access to C(6)-substituted camphor derivatives (Scheme 42). A mechanistic investigation of this fascinating rearrangement has recently been reported.[38] An alternative synthesis of (–)-*endo*-6-bromocamphor from (+)-α-pinene has also been described (Scheme 42).[87]



Scheme 42

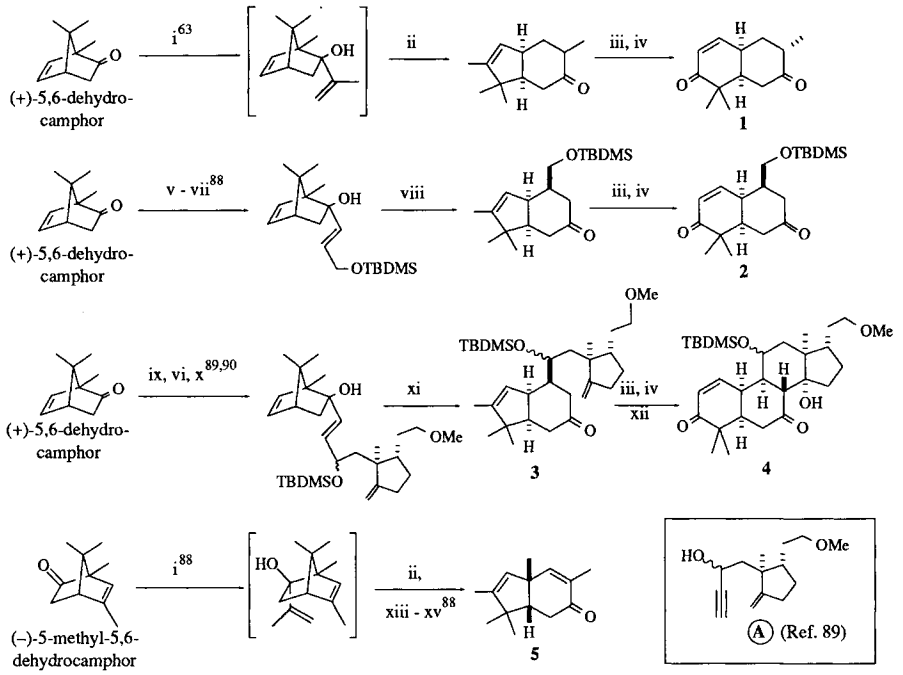
Dehydrobromination of (–)-6-bromocamphor provides a short synthetic route to (+)-5,6-dehydrocamphor[48,76,77] (Scheme 43; *cf.* Scheme 36). (–)-α-Campholenic acid, a side product in this reaction, is formed by predictable cleavage of the C(1)–C(2) bond in (–)-6-bromocamphor.



Scheme 43

The utility of (+)-5,6- and (–)-5-methyl-5,6-dehydrocamphor (*cf.* Scheme 37) lies in the fact that anionic oxy-Cope rearrangement of appropriate tertiary alkoxides derived from these two compounds provides bicyclic and tricyclic ketones **1**, **2**, **3**, and **5** (Scheme 44) that could serve as intermediates in the synthesis of sesqui-, di-, and triterpenoids.

Synthons for Terpenoid Synthesis (1,2,3, and 5)[63,88–90]

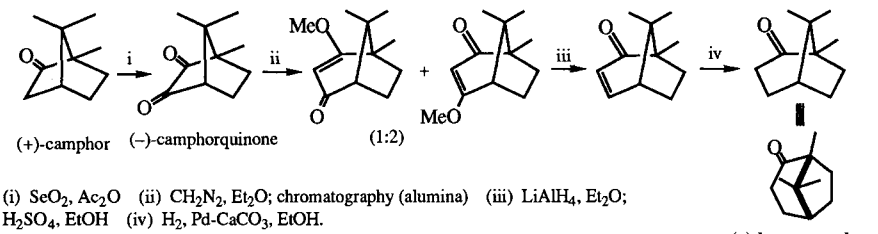


(i) CH_2=C(CH_3)MgBr, THF (ii) reflux (iii) O_3, CH_2Cl_2-MeOH (1:1), –78°C; Zn, HOAc (iv) p-TsOH, C_6H_6, reflux (v) LiC≡CCH_2OLi, THF, –78—>23° (vi) $LiAlH_4$, THF, 40°C (vii) *t*-$BuMe_2SiCl$, imidazole, DMF (viii) KH, THF, 40°C (ix) n-BuLi, **A**, THF, 0—>25°C (x) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C (xi) KH, THF, 0°C (xii) KOH, MeOH (xiii) PhSeCl, THF (xiv) H_2O_2, HOAc, H_2O (xv) 6 N HCl, Me_2CO.

Scheme 44

g. C(3)-Substitution: Camphorquinone, etc.

(–)-Camphorquinone is readily derived from (+)-camphor by selenium dioxide oxidation[23,70,71] (*cf.* Scheme 45) and is also commercially available. The use of camphorquinone as an intermediate in natural product synthesis is commonly based on the initial cleavage of the C(2)–C(3) bond (*cf.* Schemes 46–47) or on its conversion to (–)-homocamphor[91–93] (*cf.* Schemes 45, 48, and 49).

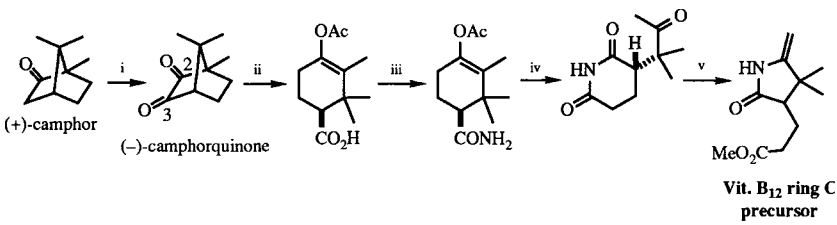


(i) SeO_2, Ac_2O (ii) CH_2N_2, Et_2O; chromatography (alumina) (iii) $LiAlH_4$, Et_2O; H_2SO_4, EtOH (iv) H_2, Pd-$CaCO_3$, EtOH.

Scheme 45

Camphorquinone rearrangement (Scheme 46) or ring cleavage (Scheme 47) has been used in an imaginative way to produce key intermediates in Vitamin B_{12} synthesis.[94,95]

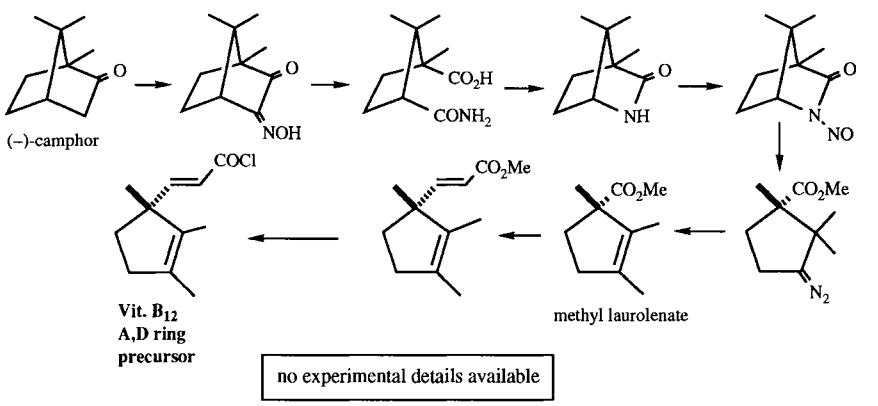
Vitamin B_{12}: Ring C[94,95]



(i) SeO_2, Ac_2O (ii) BF_3•Et_2O, Ac_2O, 0°C; NaOAc, H_2O (iii) $(COCl)_2$; NH_3 (iv) O_3, CH_2Cl_2, –70°C; Zn, HOAc (v) HCl, MeOH; 150°C.

Scheme 46

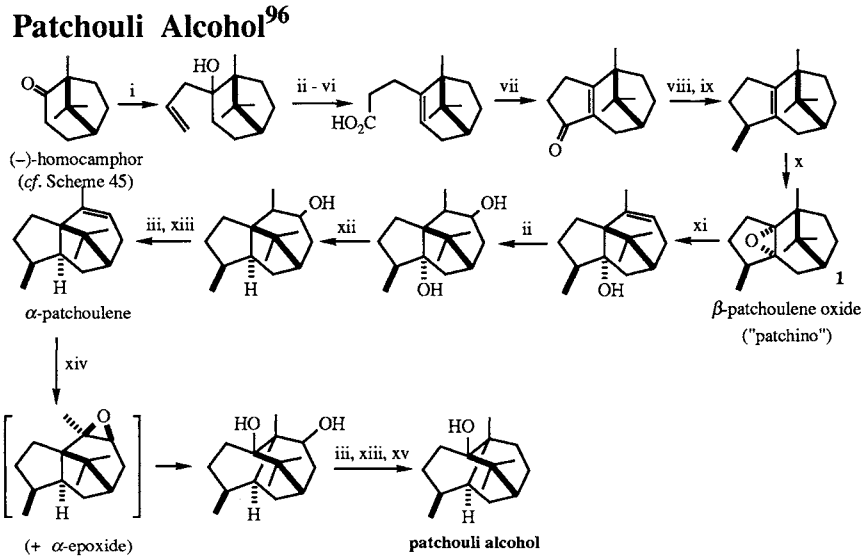
Vitamin B_{12}: A,D Ring System[94,95]



no experimental details available

Scheme 47

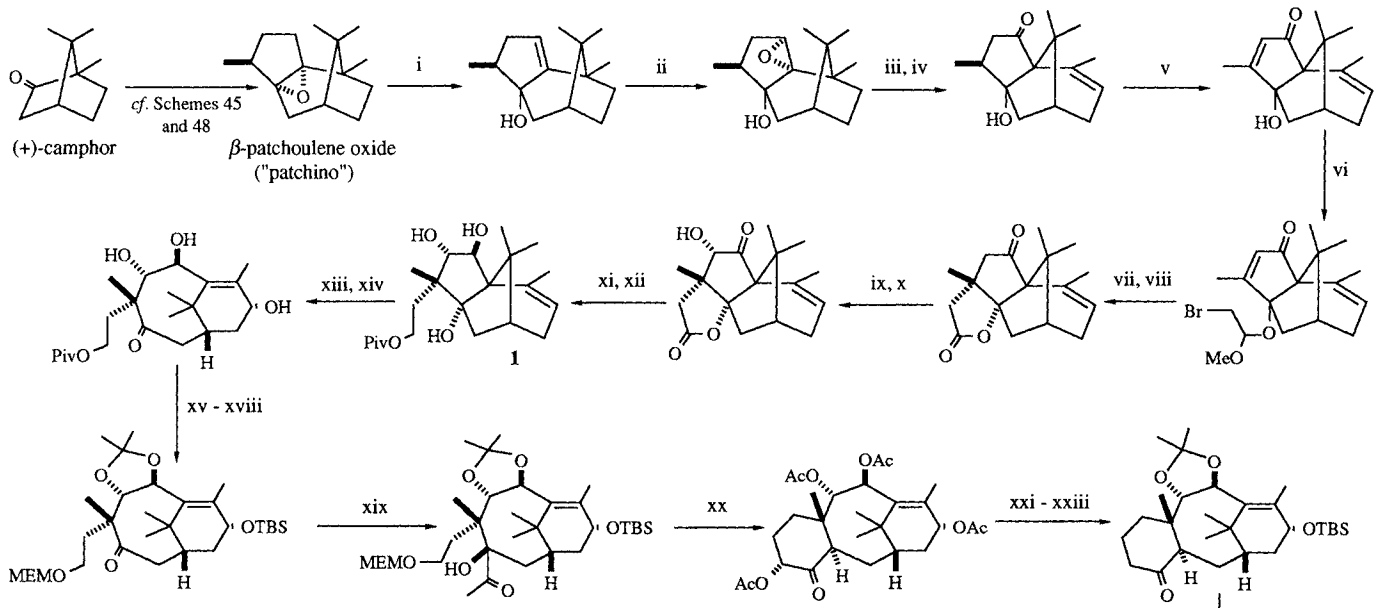
The use of homocamphor as an intermediate in natural product synthesis was first illustrated in the synthesis of patchouli alcohol (Scheme 48).[96] An interesting feature of the synthetic route is the rearrangement that occurs during "epoxidation" of α-patchoulene. β-Patchoulene oxide, **1**, an intermediate in this synthesis, is also commercially available (as "patchino") and was used as an intermediate in the first synthesis of taxusin (Scheme 49).[97] A key reaction in this route is the peracetic acid-promoted ring cleavage of a triol (**1**) derived from β-patchoulene oxide to provide the bicyclo[5.3.1]undecane (AB) ring system of the taxanes.



(i) CH_2=$CHCH_2MgCl$, Et_2O (ii) BH_3•THF; NaOH, H_2O_2 (iii) Ac_2O, C_5H_5N (iv) $POCl_3$, C_5H_5N (v) $LiAlH_4$, Et_2O (vi) CrO_3, Me_2CO, H_2SO_4 (vii) $SOCl_2$; $AlCl_3$, CS_2 (viii) Ph_3P=CH_2 (ix) H_2, Raney Ni (x) CH_3CO_3H, NaOAc (xi) BF_3•Et_2O (xii) PtO_2, H_2, HOAc, $HClO_4$ (xiii) 350°C (xiv) CH_3CO_3H, NaOAc, 0°C (xv) H_2, Pd.

Scheme 48

(–)-Taxusin[97]



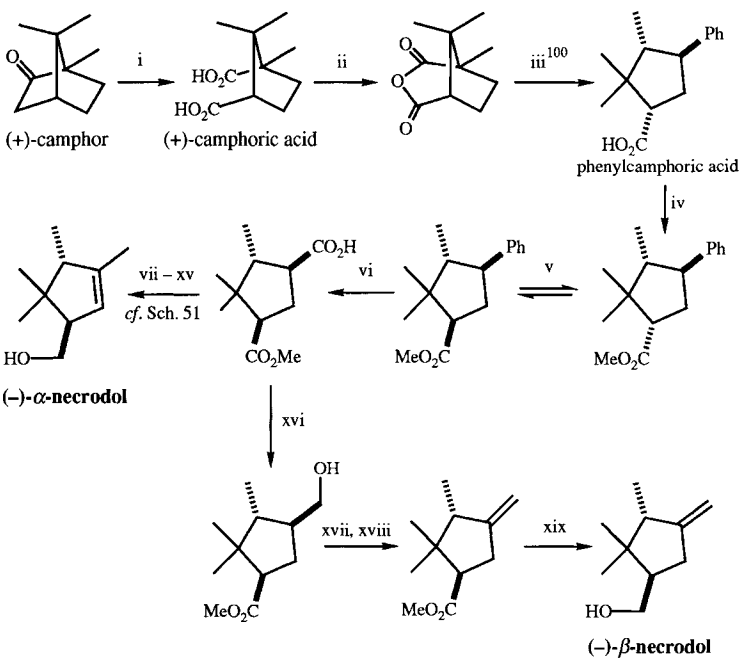
(i) t-BuLi, hexane, reflux (ii) t-BuOOH, $Ti(O\text{-}i\text{-}Pr)_4$, CH_2Cl_2 (iii) $BF_3{\cdot}Et_2O$, CF_3SO_3H, CH_2Cl_2, –80°C (iv) PDC, DMF (v) LDA, THF; Me_3SiCl; PhSeCl; H_2O_2; MeOH, K_2CO_3 (vi) $BrCH_2CH(OMe)Br$, $PhNMe_2$, CH_2Cl_2 (vii) Bu_3SnH, AIBN, C_6H_6, reflux (viii) Jones oxidation (ix) LDA, THF; Me_3SiCl (x) CH_3CO_3H, CH_2Cl_2 (xi) Red-Al, THF-C_6H_6 (1:9), reflux (xii) t-BuCOCl, C_5H_5N (xiii) CH_3CO_3H (excess), CH_2Cl_2 (xiv) $Ti(O\text{-}i\text{-}Pr)_4$, CH_2Cl_2, reflux (xv) 2,2-dimethoxypropane, TsOH (xvi) TBDMS-OTf, C_5H_5N (xvii) K_2CO_3, MeOH (xviii) $CH_3OCH_2CH_2OCH_2Cl$, $i\text{-}Pr_2NEt$, CH_2Cl_2 (xix) $CH_2{=}C(OMe)Li$, hexane, –13°C; THF, HOAc, H_2O (xx) SmI_2, THF, 0°C (xxi) $FeCl_3$, Ac_2O, –45°C; NaOMe, MeOH (xxii) Ts_2O, C_5H_5N (xxiii) t-BuONa, THF (xxiv) LDA, THF; Me_3SiCl (xxv) m-CPBA, CH_2Cl_2 (xxvi) TBAF, THF (xxvii) HCl, THF (xxviii) Ac_2O, C_5H_5N (xxix) $Ph_3P{=}CH_2$, toluene-hexane (1:1).

Scheme 49

h. Cleavage of the C(2)–C(3) Bond: Camphoric Acid

Oxidative cleavage of the C(2)–C(3) bond of (+)- and (–)-camphor with nitric acid[98,99] results in the formation of (+)- and (–)-camphoric acid, respectively. Both enantiomers are commercially available, and Meinwald's recent synthesis of the necrodols[86] (Schemes 50 and 51) involves the mechanistically interesting conversion of camphoric acid to phenylcamphoric acid.[100] The latter compound then serves as a common intermediate for the synthesis of α-necrodol, β-necrodol, *epi*-α-necrodol, and *epi*-β-necrodol.

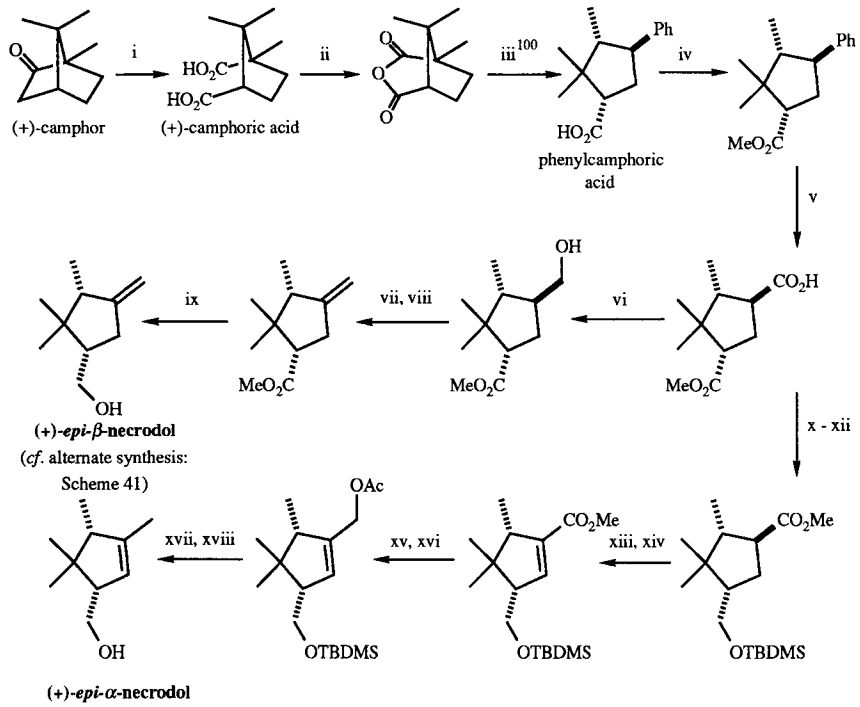
(–)-α-Necrodol, (–)-β-Necrodol[86]



(i) HNO_3, Hg_2SO_4 (ii) CH_3COCl (iii) C_6H_6, $AlCl_3$ (iv) CH_2N_2, Et_2O (v) NaOMe, MeOH (vi) $NaIO_4$, RuO_2, CCl_4–MeCN–H_2O (vii) Li, NH_3, THF, MeOH (viii) CH_2N_2, Et_2O (ix) TBDMS-Cl, imidazole, THF, DMAP (x) $(cyclohexyl)_2NLi$, THF, –23°C; PhSeCl, THF (xi) m-CPBA, CH_2Cl_2, –10°C; $(Me_2CH)_2NH$, reflux (xii) $LiAl(OEt)_3H$, THF (xiii) Ac_2O, CH_2Cl_2, Et_3N (xiv) Li, NH_3, THF (xv) TBAF, THF (xvi) BH_3, THF, 0°C (xvii) *o*-nitrophenyl selenocyanate, Bu_3P, THF (xviii) m-CPBA, CH_2Cl_2; *i*-Pr_2NH, reflux (xix) $LiAlH_4$, Et_2O.

Scheme 50

(+)-*epi*-α-Necrodol, (–)-*epi*-β-Necrodol[86]

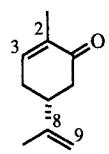


(i) HNO_3, Hg_2SO_4 (ii) CH_3COCl (iii) C_6H_6, $AlCl_3$ (iv) CH_2N_2, Et_2O (v) $NaIO_4$, RuO_2, CCl_4-MeCN-H_2O (vi) BH_3•THF, 0°C (vii) *o*-nitrophenyl selenocyanate, Bu_3P, THF (viii) m-CPBA, CH_2Cl_2; $(Me_2CH)_2NH$, reflux (ix) $LiAlH_4$, Et_2O (x) Li, NH_3, THF, MeOH (xi) CH_2N_2, Et_2O (xii) *t*-$BuMe_2SiCl$, imidazole, THF, DMAP (xiii) $(cyclohexyl)_2NLi$, THF, –23°C; Me_3SiCl; PhSeCl, THF (xiv) m-CPBA, CH_2Cl_2, –10°C; $(Me_2CH)_2NH$, reflux (xv) $LiAl(OEt)_3H$, THF (xvi) Ac_2O, CH_2Cl_2, Et_3N (xvii) Li, NH_3, THF (xviii) TBAF, THF.

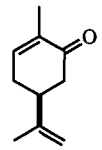
Scheme 51

2. CARVONE

(R)-(–)-Carvone and *(S)*-(+)-carvone are commercially available and together constitute the most often used monoterpenoid starting materials in natural product synthesis. In many cases (see below), regioselective reduction of the conjugated double bond to provide 2,3-dihydrocarvone is carried out as a first step in the synthesis and a wide variety of methods[101–113] are available for this purpose (Eq. 1). Regioselective reduction of the 8,9-double bond can also be achieved (by using H_2/Pt[114] or $H_2/(Ph_3P)_3RhCl/C_6H_6$[115]).



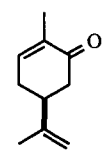
(R)-(–)-carvone



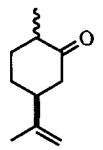
(S)-(+)-carvone

Methods for reduction of the C(2)–C(3) double bond:

1. Zn, NaOH, EtOH, H_2O (Refs. 101–104)
2. $NaBH_4$, C_5H_5N; Jones oxidation (Refs. 105,106)
3. Li, NH_3, EtOH, Et_2O; Jones oxidation (Ref. 107)
4. Li•$4NH_3$ (lithium bronze) (Ref. 108)
5. K-Selectride (Ref. 109)
6. KPh_3BH, THF (Ref. 110)
7. Bu_3SnH, $(Ph_3P)_4Pd$, HOAc-C_6H_6 *or* $ZnCl_2$, THF (Ref. 111)
8. $K_3[Co(CN)_5H]$ (Ref. 112)
9. NaTeH, EtOH (Ref. 113)



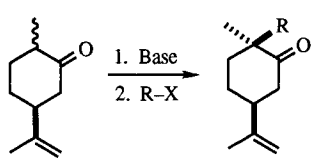
(S)-(+)-carvone



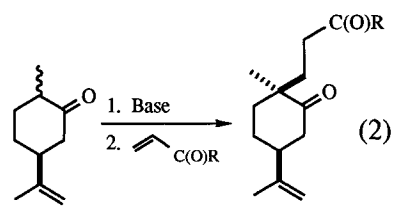
2,3-dihydrocarvone

(1)

Many synthetic routes also rely on the fact that the thermodynamic enolate derived from dihydrocarvone undergoes preferential axial alkylation or Michael addition in accordance with the rationalization proposed by House and Umen.[116] As shown below (Eq. 2), this introduces the new substituent cis to the isopropenyl group.



dihydrocarvone (major product)

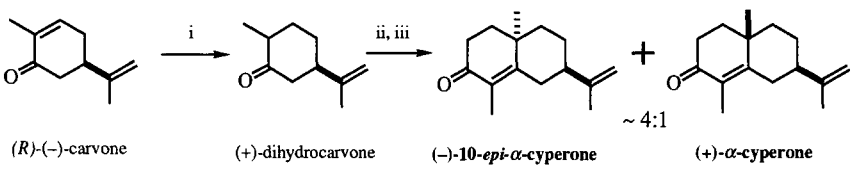


dihydrocarvone (major product)

(2)

The use of (+)- and (–)-carvone as chiral starting materials in natural product synthesis is illustrated in Schemes 52–115.

(+)-α-Cyperone[117]

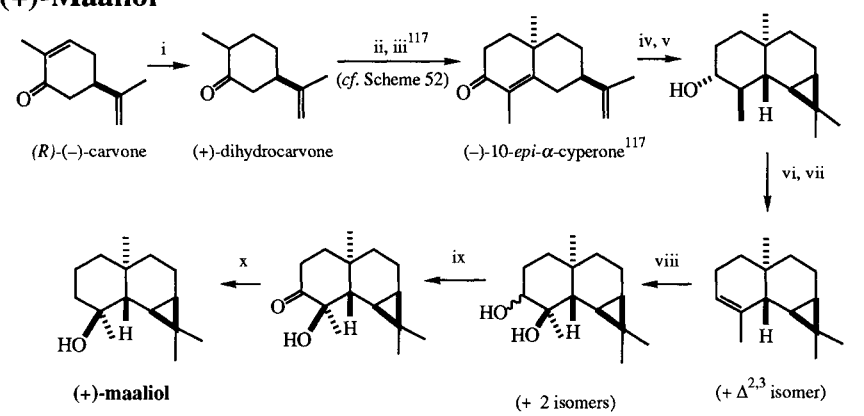


[Similarly, (–)-dihydrocarvone ⟶ ⟶ (–)-10-*epi*-α-cyperone + (–)-α-cyperone]

(i) Zn, NaOH, EtOH, reflux (ii) $NaNH_2$, Et_2O; $CH_3CH_2COCH_2CH_2NEt_2MeI$, C_5H_5N (iii) conc. HCl, EtOH or 10% KOH, EtOH, reflux.

Scheme 52

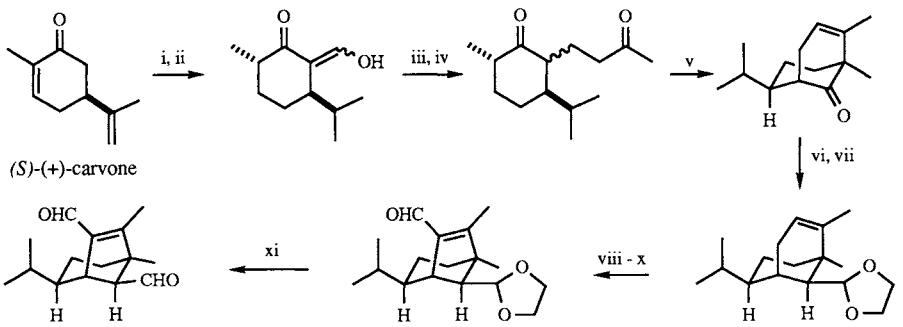
(+)-Maaliol[118]



(i) Zn, NaOH, EtOH, H_2O, reflux (ii) $NaNH_2$, Et_2O; $CH_3CH_2COCH_2CH_2NMe_2EtI$, C_5H_5N, 0°C, 12 h; reflux, 5 h (iii) KOH, EtOH, reflux (iv) HBr, HOAc; KOH, MeOH, reflux (v) Li, NH_3, EtOH, Et_2O (vi) Ac_2O, C_5H_5N (vii) C_6H_{12}, 470°C (viii) OsO_4, C_5H_5N; KOH, mannitol, H_2O, EtOH, C_6H_6, reflux (ix) $CrO_3 \cdot C_5H_5N$ (x) $NH_2NH_2 \cdot H_2O$, KOH, $HO(CH_2)_2OH$, 175°C.

Scheme 53

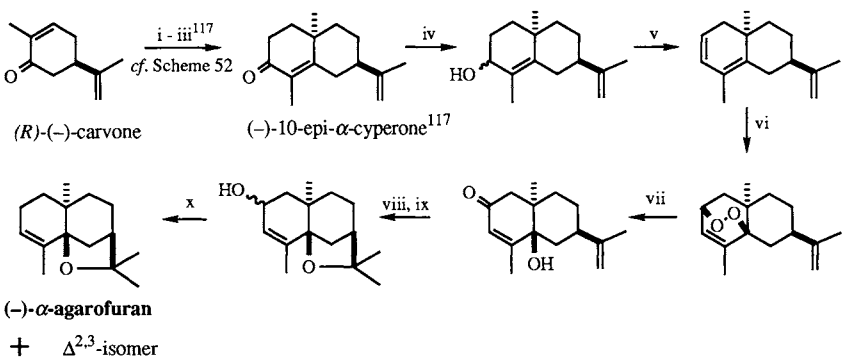
(–)-Helminthosporal[119]



(i) H_2, Pd-Al_2O_3, EtOH (ii) NaOMe, HCO_2Et, C_6H_6, reflux (iii) methyl vinyl ketone, Et_3N, 0° --> 25°C (iv) K_2CO_3, EtOH, reflux (v) BF_3, CH_2Cl_2, 0° --> 25°C (vi) $MeOCH_2PPh_3Cl$, NaH, DMSO (vii) $HOCH_2CH_2OH$, p-TsOH, C_6H_6, reflux (viii) OsO_4, C_5H_5N (ix) $Pb(OAc)_4$, HOAc, C_6H_6 (x) NaOH, EtOH (xi) 4.4% H_2SO_4, THF.

Scheme 54

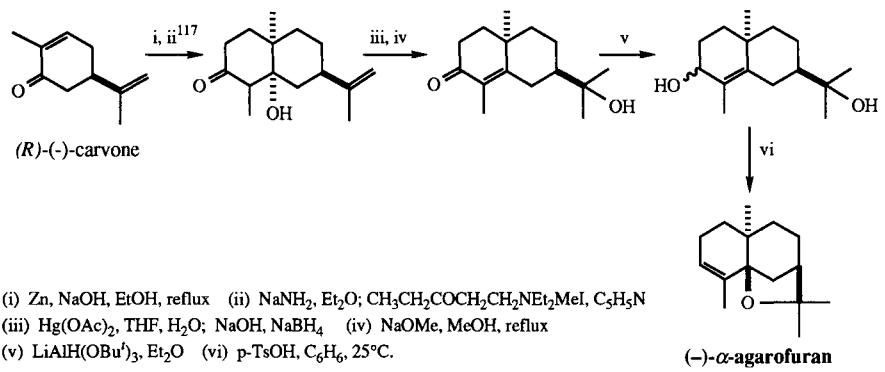
(–)-α-Agarofuran[120]



(i) Zn, NaOH, EtOH, H_2O, reflux (ii) $NaNH_2$, Et_2O; $CH_3CH_2COCH_2CH_2NMe_2EtI$, C_5H_5N, 0°C, 12 h; reflux, 5 h (iii) KOH, EtOH, reflux (iv) $LiAlH_4$, Et_2O, 0°C (v) alumina/C_5H_5N, heat (vi) O_2, eosin Y, C_6H_6, EtOH, 200 W lamp (vii) basic alumina, Et_2O (viii) acid-washed alumina, C_6H_6, 75°C (ix) $NaBH_4$, MeOH, 0°C (x) $SOCl_2$, Et_2O, 0°C; $LiAlH_4$, Et_2O.

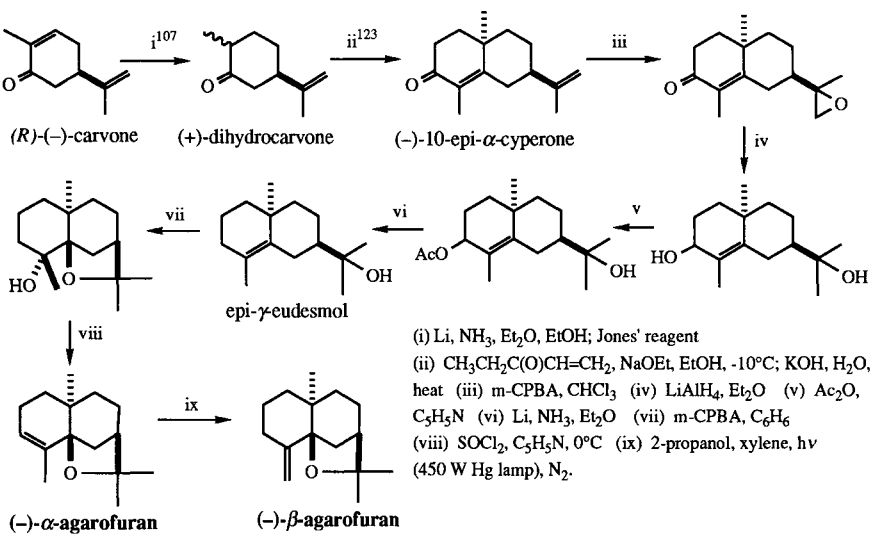
Scheme 55

(–)-α-Agarofuran[121]



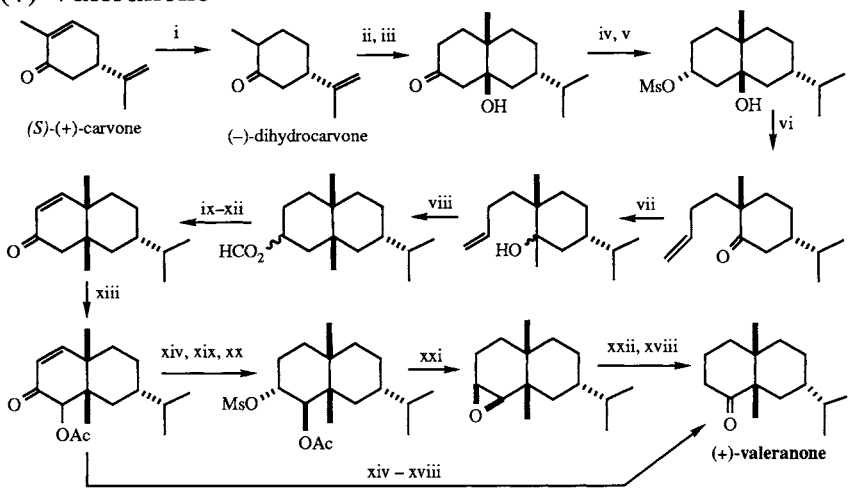
Scheme 56

(–)-α-Agarofuran, (–)-β-Agarofuran[122]



Scheme 57

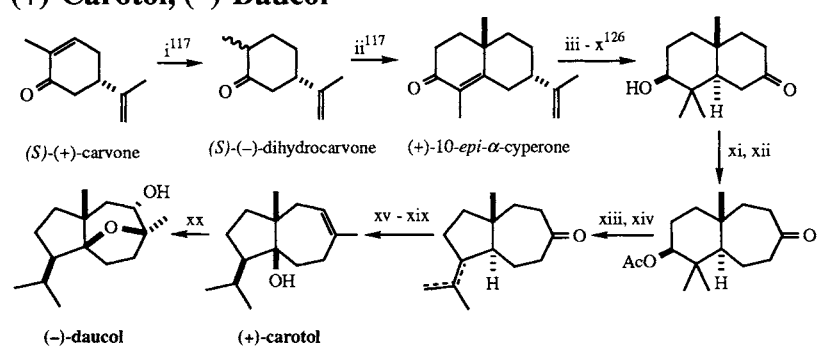
(+)-Valeranone[124]



(i) Li, NH_3, EtOH, Et_2O; Jones' reagent (ii) MVK, NaOEt, EtOH, -10°C (iii) H_2, Pt, EtOH (iv) $LiAlH_4$, Et_2O (v) MsCl, C_5H_5N (vi) t-BuOK, t-BuOH, reflux (vii) MeLi, Et_2O (viii) HCO_2H (ix) NaOH, EtOH, H_2O (x) CrO_3, H_2SO_4, H_2O, Me_2CO (xi) Br_2, HOAc (xii) $CaCO_3$, CH_3CONMe_2, reflux (xiii) $Pb(OAc)_4$, BF_3•Et_2O, C_6H_6, 50°C (xiv) H_2, Pd-C, EtOH (xv) $(CH_2SH)_2$, BF_3•Et_2O, HOAc (xvi) $LiAlH_4$, Et_2O (xvii) EtOH, W-2 Raney nickel (xviii) CrO_3, H_2SO_4, H_2O, Me_2CO (xix) $NaBH_4$, EtOH (xx) MsCl, C_5H_5N (xxi) KOH, Me_2CHOH, reflux (xxii) $LiAlH_4$, THF

Scheme 58

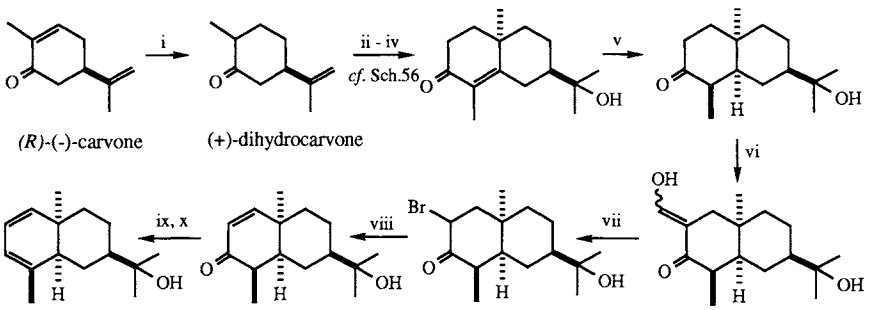
(+)-Carotol, (–)-Daucol[125]



(i) Zn, NaOH, EtOH, H_2O (ii) $NaNH_2$, Et_2O; $CH_3CH_2COCH_2CH_2NMe_2EtI$, C_5H_5N; KOH, EtOH, reflux (iii) p-$NO_2C_6H_4CO_3H$, Et_2O (iv) t-BuOK, t-BuOH, MeI (v) $LiAlH_4$, Et_2O (vi) Ac_2O, C_5H_5N (vii) $Pb(OAc)_4$, C_6H_6, reflux (viii) KOH, MeOH, reflux (ix) MnO_2, $CHCl_3$ (x) Li, NH_3, Et_2O, dioxane (xi) CH_2N_2, Et_2O (xii) Ac_2O, C_5H_5N; separation of isomers (xiii) KOH, EtOH (xiv) PCl_5, C_6H_6, toluene, -10°C (xv) $HClO_4$, $CHCl_3$ (xvi) MeMgI, Et_2O (xvii) $SOCl_2$, C_5H_5N, 0°C ; separation of isomers (xviii) p-$NO_2C_6H_4CO_3H$, $CHCl_3$ (xix) Li, $EtNH_2$, 0°C (xx) p-$NO_2C_6H_4CO_3H$, Et_2O, 0°C.

Scheme 59

(+)-Occidentalol[127]

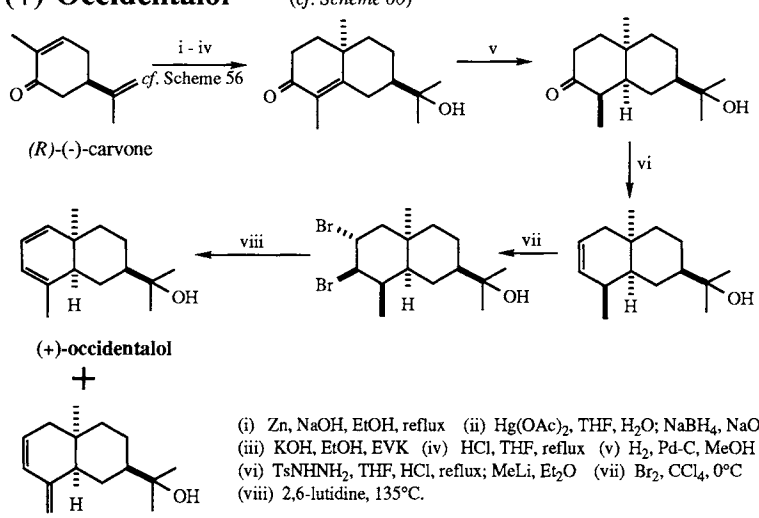


(*R*)-(-)-carvone (+)-dihydrocarvone **(+)-occidentalol**

(i) Zn, NaOH, EtOH, reflux (ii) $NaNH_2$, Et_2O; $CH_3CH_2COCH_2CH_2NEt_2MeI$, C_5H_5N (iii) $Hg(OAc)_2$, THF, H_2O; NaOH, $NaBH_4$ (iv) NaOMe, MeOH, reflux (v) H_2, Pd-C, MeOH; NaOH, MeOH (vi) $NaNH_2$, Et_2O, HCO_2Et (vii) $Ba(OH)_2$, EtOH; Br_2, EtOH (viii) LiBr, Li_2CO_3, DMF, 130°C (ix) $LiAlH_4$, Et_2O (x) TsOH, C_6H_6.

Scheme 60

(+)-Occidentalol[128] *(cf. Scheme 60)*



(*R*)-(-)-carvone **(+)-occidentalol**

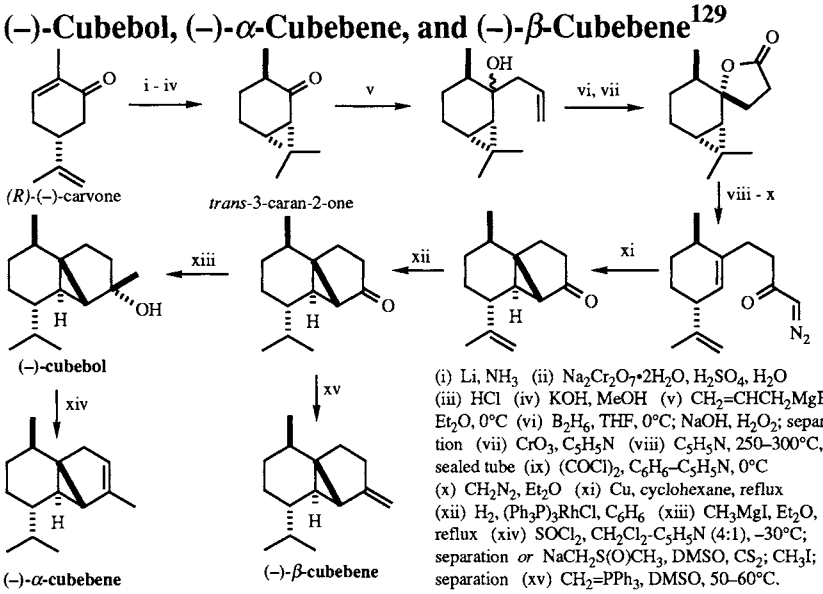
+

~ 1:1

(i) Zn, NaOH, EtOH, reflux (ii) $Hg(OAc)_2$, THF, H_2O; $NaBH_4$, NaOH (iii) KOH, EtOH, EVK (iv) HCl, THF, reflux (v) H_2, Pd-C, MeOH (vi) $TsNHNH_2$, THF, HCl, reflux; MeLi, Et_2O (vii) Br_2, CCl_4, 0°C (viii) 2,6-lutidine, 135°C.

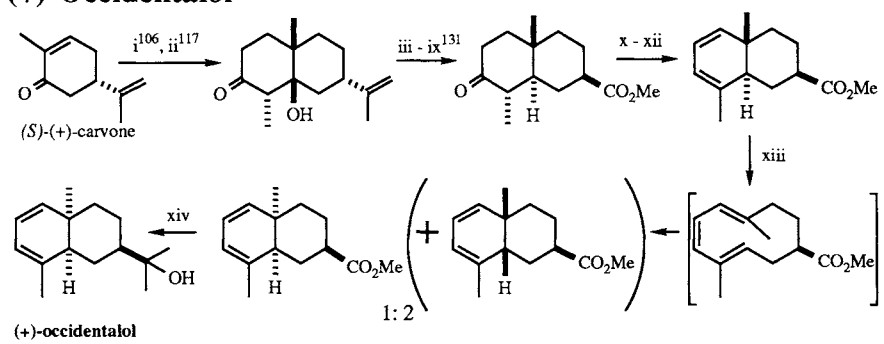
Scheme 61

(–)-Cubebol, (–)-α-Cubebene, and (–)-β-Cubebene[129]



Scheme 62

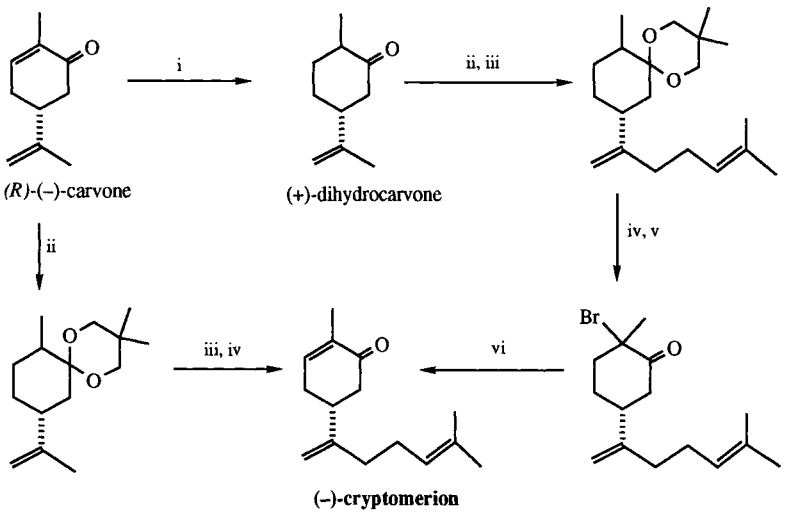
(+)-Occidentalol[130]



(i) Zn, NaOH, EtOH, reflux (ii) $CH_3CH_2COCH_2CH_2Cl$, NaH, THF, EtOH , 0°C (iii) O_3, CH_2Cl_2, MeOH, -70°C; NaI, HOAc, MeOH (iv) HCl, HOAc, CH_2Cl_2, 5°C or p-TsOH, C_6H_6, reflux (v) H_2, Pd-$SrCO_3$, EtOH; 12 N HCl, reflux (vi) $(CH_2OH)_2$, p-TsOH, C_6H_6, reflux (vii) NaOH, EtOH, furfural (viii) O_3, MeOH, CH_2Cl_2, -70°C; 30% H_2O_2, $KHCO_3$, H_2O (ix) CH_2N_2, EtOAc, Et_2O, 0°C (x) Br_2, $CHCl_3$; Li_2CO_3, LiBr, DMF, 125°C; KOH, MeOH-H_2O [4:1] (xi) Al(i-PrO)$_3$, Me_2CHOH, reflux; NaOH, MeOH, H_2O, reflux; CH_2N_2, Et_2O (xii) alumina, C_5H_5N, 220°C (xiii) hv, Et_2O, -78°C (xiv) MeLi, Et_2O, 0°C.

Scheme 63

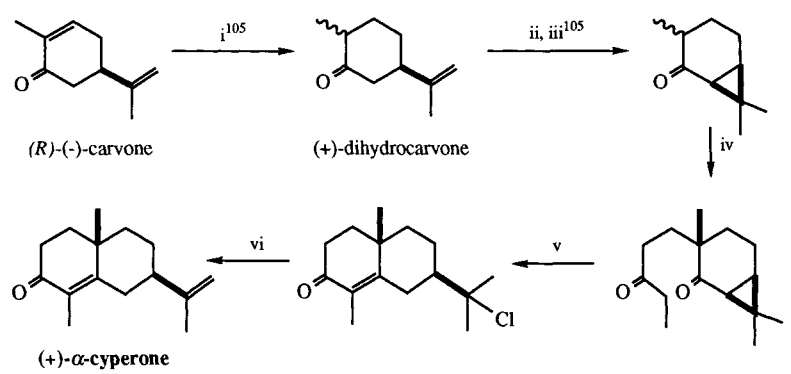
(–)-Cryptomerion[132]



(i) Zn, NaOH, EtOH, H_2O (ii) 2,2-dimethyl-1,3-propanediol, $(CO_2H)_2$, C_6H_6, reflux, 4 d
(iii) n-BuLi-TMEDA, hexane; 1-chloro-3-methyl-1,3-butene (iv) 3 N HCl, Me_2CO (v) $PhNMe_3NBr_3$, THF (vi) C_5H_5N, reflux.

Scheme 64

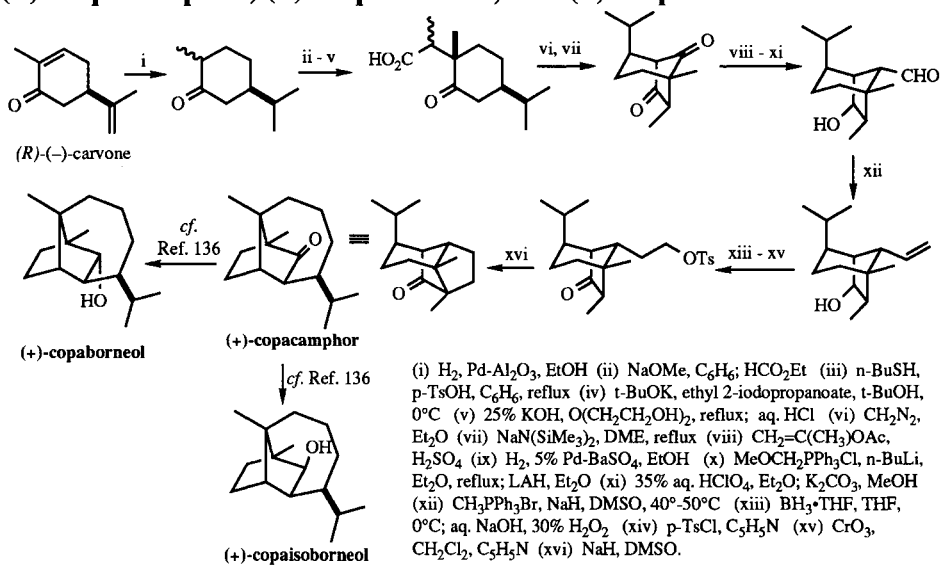
(+)-α-Cyperone[133]



(i) Zn, NaOH, MeOH, H_2O, reflux (ii) HCl, $CHCl_3$, $AlCl_3$(trace) (iii) KOH, MeOH
(iv) $CH_3CH_2COCH{=}CH_2$, KOH, EtOH, Et_2O (v) HCl, EtOH (vi) NaOAc, HOAc.

Scheme 65

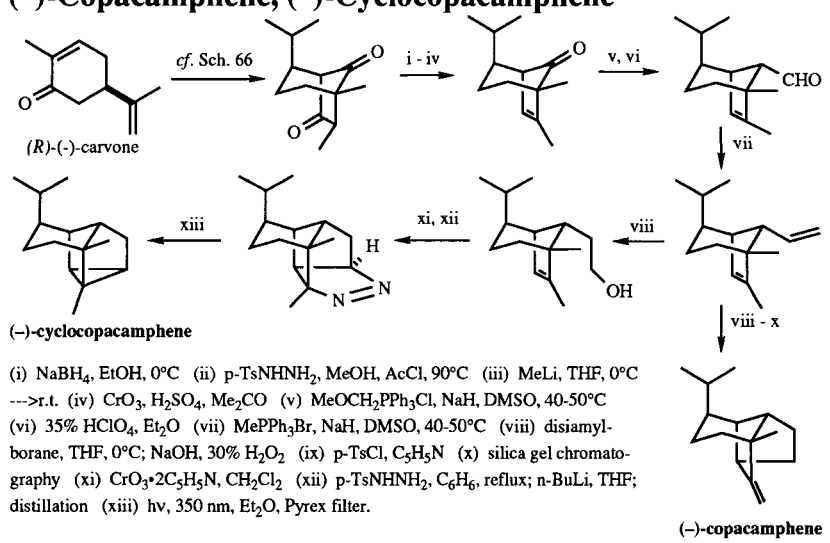
(+)-Copacamphor, (+)-Copaborneol, and (+)-Copaisoborneol[134,135]



(i) H_2, Pd-Al_2O_3, EtOH (ii) NaOMe, C_6H_6; HCO_2Et (iii) n-BuSH, p-TsOH, C_6H_6, reflux (iv) t-BuOK, ethyl 2-iodopropanoate, t-BuOH, 0°C (v) 25% KOH, $O(CH_2CH_2OH)_2$, reflux; aq. HCl (vi) CH_2N_2, Et_2O (vii) $NaN(SiMe_3)_2$, DME, reflux (viii) $CH_2=C(CH_3)OAc$, H_2SO_4 (ix) H_2, 5% Pd-$BaSO_4$, EtOH (x) $MeOCH_2PPh_3Cl$, n-BuLi, Et_2O, reflux; LAH, Et_2O (xi) 35% aq. $HClO_4$, Et_2O; K_2CO_3, MeOH (xii) CH_3PPh_3Br, NaH, DMSO, 40°-50°C (xiii) BH_3•THF, THF, 0°C; aq. NaOH, 30% H_2O_2 (xiv) p-TsCl, C_5H_5N (xv) CrO_3, CH_2Cl_2, C_5H_5N (xvi) NaH, DMSO.

Scheme 66

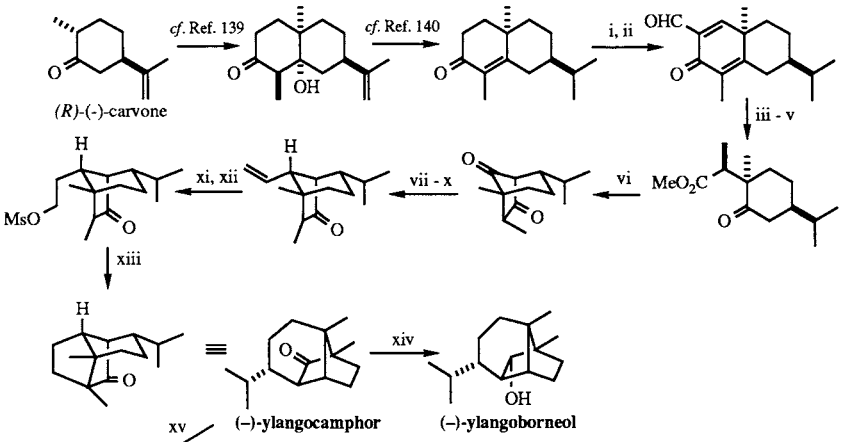
(–)-Copacamphene, (–)-Cyclocopacamphene[137,138]



(i) $NaBH_4$, EtOH, 0°C (ii) p-$TsNHNH_2$, MeOH, AcCl, 90°C (iii) MeLi, THF, 0°C --->r.t. (iv) CrO_3, H_2SO_4, Me_2CO (v) $MeOCH_2PPh_3Cl$, NaH, DMSO, 40-50°C (vi) 35% $HClO_4$, Et_2O (vii) $MePPh_3Br$, NaH, DMSO, 40-50°C (viii) disiamylborane, THF, 0°C; NaOH, 30% H_2O_2 (ix) p-TsCl, C_5H_5N (x) silica gel chromatography (xi) CrO_3•$2C_5H_5N$, CH_2Cl_2 (xii) p-$TsNHNH_2$, C_6H_6, reflux; n-BuLi, THF; distillation (xiii) hv, 350 nm, Et_2O, Pyrex filter.

Scheme 67

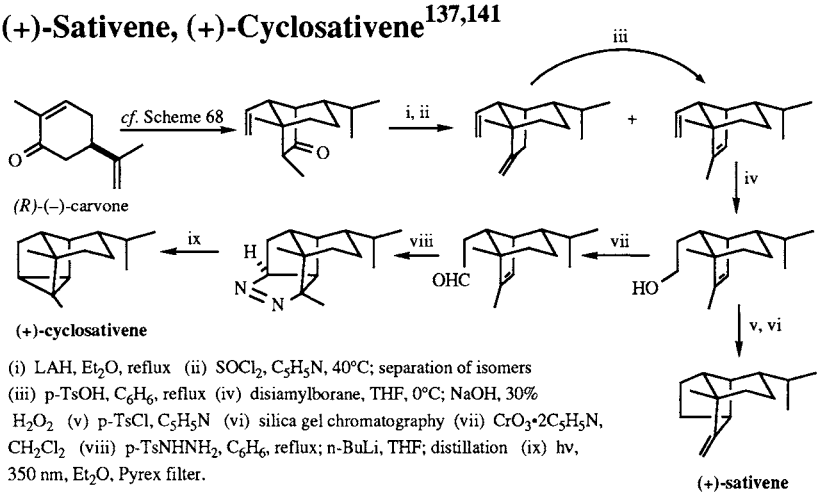
(–)-Ylangocamphor, (–)-Ylangoborneol, and (–)-Ylangoisoborneol[134,135]



(i) NaOMe, C_6H_6, HCO_2Et (ii) DDQ, dioxane (iii) Me_2CuLi, Et_2O, 0°C; AcCl, Et_2O (iv) O_3, CH_2Cl_2, -78°-->-25°C; 5% aq. NaOH, H_2O_2, MeOH, reflux; 6 M HCl (v) CH_2N_2, Et_2O (vi) $NaN(SiMe_3)_2$, C_6H_6, 80°C (vii) $NaN(SiMe_3)_2$, HMPA, Me_2CHBr, 0°--> r.t.; separation of *C*-alkylation product (viii) $MeOCH_2PPh_3Cl$, n-BuLi, Et_2O, reflux (ix) 70% $HClO_4$, Et_2O; K_2CO_3, aq. MeOH (x) CH_3PPh_3Br, NaH, DMSO (xi) disiamylborane, THF, 0°C; aq. NaOH, 30% H_2O_2 (xii) MsCl, C_5H_5N (xiii) $NaN(SiMe_3)_2$, DME (xiv) Ca, NH_3, Et_2O (xv) LAH, Et_2O, reflux.

Scheme 68

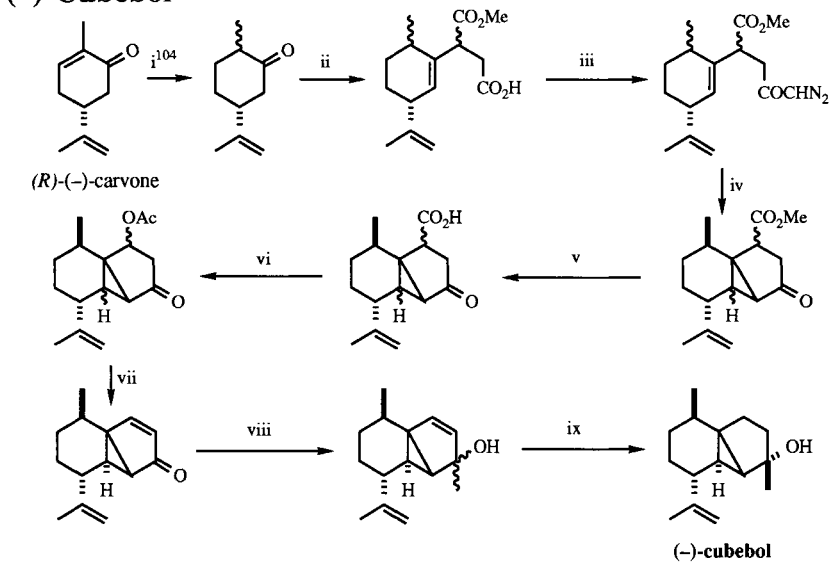
(+)-Sativene, (+)-Cyclosativene[137,141]



(i) LAH, Et_2O, reflux (ii) $SOCl_2$, C_5H_5N, 40°C; separation of isomers (iii) p-TsOH, C_6H_6, reflux (iv) disiamylborane, THF, 0°C; NaOH, 30% H_2O_2 (v) p-TsCl, C_5H_5N (vi) silica gel chromatography (vii) $CrO_3 \cdot 2C_5H_5N$, CH_2Cl_2 (viii) $p\text{-}TsNHNH_2$, C_6H_6, reflux; n-BuLi, THF; distillation (ix) hv, 350 nm, Et_2O, Pyrex filter.

Scheme 69

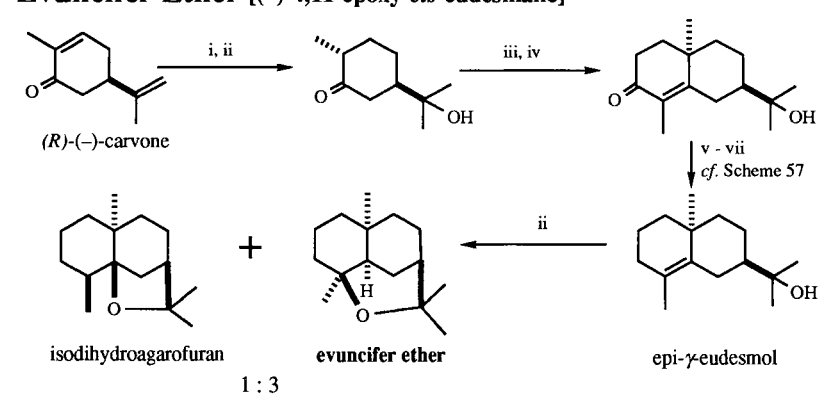
(–)-Cubebol[142]



(i) Zn, KOH, EtOH-H_2O, reflux (ii) $MeO_2CCH_2CH_2CO_2Me$, t-BuOK, t-BuOH, 90°C (iii) NaH, C_6H_6, $(COCl)_2$, 5°C; CH_2N_2, 0°C (iv) bis(*N*-propylsalicylideneaminato)copper(II), C_6H_6, 80°C; separation of diastereomers (v) KOH, 5% aq. MeOH (vi) HOAc, t-BuOH, Et_3N, electrolysis (~20 V), 10°C (vii) CH_2=PPh_3, C_6H_6, 0°C; separation of diastereomers (viii) MeMgI, Et_2O, reflux (ix) H_2, PtO_2, EtOAc; separation of diastereomers.

Scheme 70

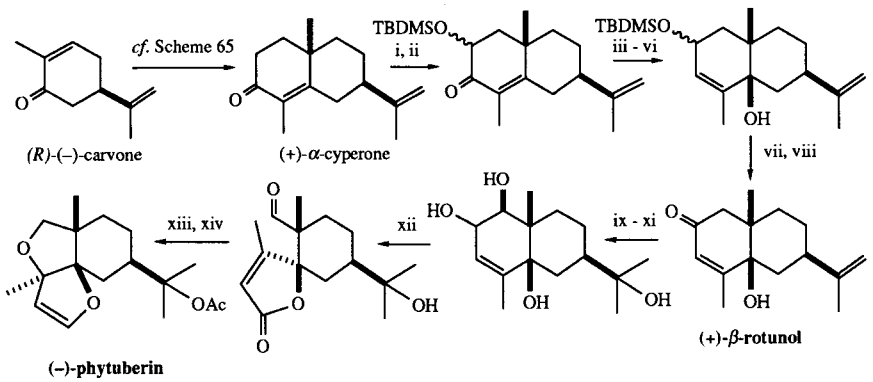
Evuncifer Ether [(–)-4,11-epoxy-*cis*-eudesmane][143]



(i) Zn, NaOH, EtOH, H_2O (ii) $Hg(OAc)_2$, THF, H_2O; $NaBH_4$, NaOH (iii) NaH, THF; $ClCH_2CH_2COCH_2Me$ (iv) HCl, EtOH (v) $LiAlH_4$, THF (vi) Ac_2O, C_5H_5N (vii) Li, NH_3

Scheme 71

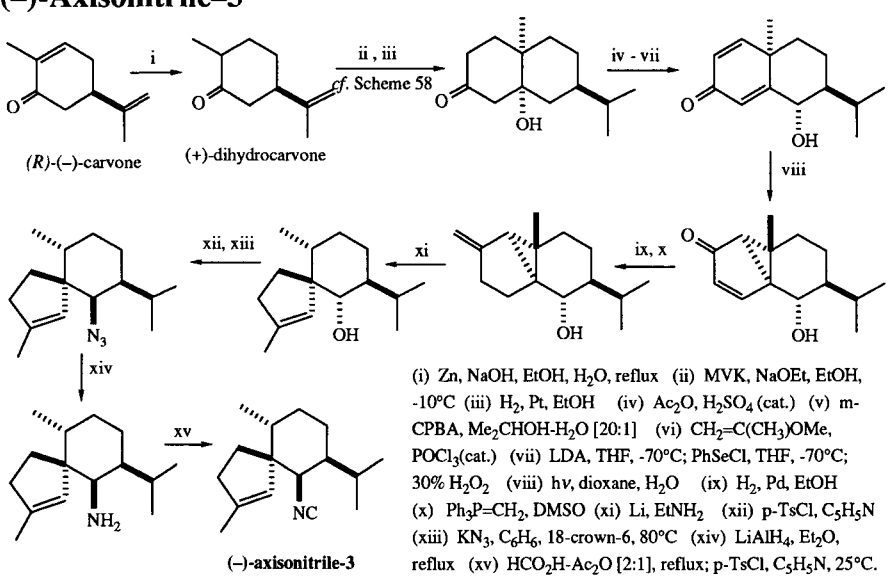
(+)-β-Rotunol, (–)-Phytuberin[144]



(i) LDA, THF; MoO_5•Py•HMPA (ii) TBDMS-Cl, imidazole, DMF (iii) Li(s-Bu)$_3$BH or $LiAlH_4$, THF (iv) *t*-BuOOH, $VO(acac)_2$ (v) MsCl, NEt_3 (vi) Li, NH_3 (vii) HOAc, H_2O, THF (viii) MnO_2 (ix) LDA, THF; MoO_5•Py•HMPA (x) m-CPBA, $NaHCO_3$, CH_2Cl_2 (xi) $LiAlH_4$, DME, THF (xii) $Pb(OAc)_4$, pyridine (xiii) DIBAL, DME (xiv) Ac_2O, DMAP, NEt_3

Scheme 72

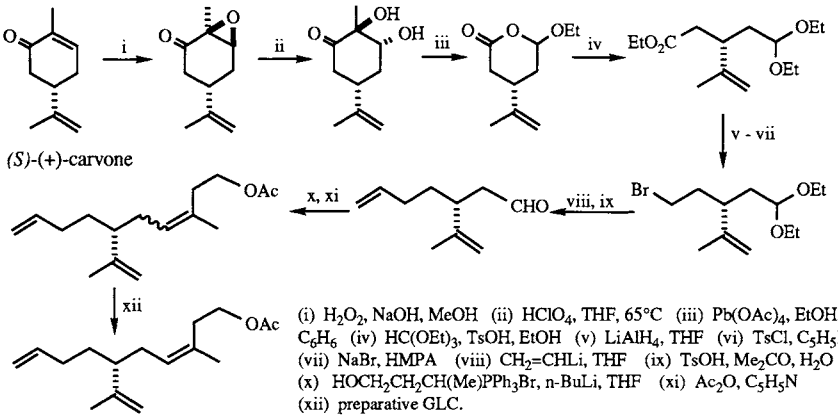
(–)-Axisonitrile-3[145]



(i) Zn, NaOH, EtOH, H_2O, reflux (ii) MVK, NaOEt, EtOH, -10°C (iii) H_2, Pt, EtOH (iv) Ac_2O, H_2SO_4 (cat.) (v) m-CPBA, Me_2CHOH-H_2O [20:1] (vi) CH_2=$C(CH_3)OMe$, $POCl_3$(cat.) (vii) LDA, THF, -70°C; PhSeCl, THF, -70°C; 30% H_2O_2 (viii) hν, dioxane, H_2O (ix) H_2, Pd, EtOH (x) Ph_3P=CH_2, DMSO (xi) Li, $EtNH_2$ (xii) p-TsCl, C_5H_5N (xiii) KN_3, C_6H_6, 18-crown-6, 80°C (xiv) $LiAlH_4$, Et_2O, reflux (xv) HCO_2H-Ac_2O [2:1], reflux; p-TsCl, C_5H_5N, 25°C.

Scheme 73

California Red Scale Pheromone[61]



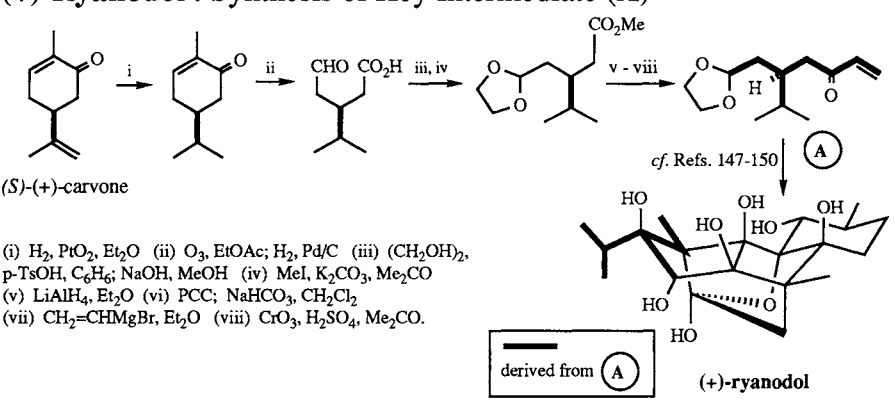
(S)-(+)-carvone

(3*Z*,6*R*)-California Red Scale pheromone

(i) H_2O_2, NaOH, MeOH (ii) $HClO_4$, THF, 65°C (iii) $Pb(OAc)_4$, EtOH, C_6H_6 (iv) $HC(OEt)_3$, TsOH, EtOH (v) $LiAlH_4$, THF (vi) TsCl, C_5H_5N (vii) NaBr, HMPA (viii) CH_2=CHLi, THF (ix) TsOH, Me_2CO, H_2O (x) $HOCH_2CH_2CH(Me)PPh_3Br$, n-BuLi, THF (xi) Ac_2O, C_5H_5N (xii) preparative GLC.

Scheme 74

(+)-Ryanodol : Synthesis of Key Intermediate (A)[146,147]



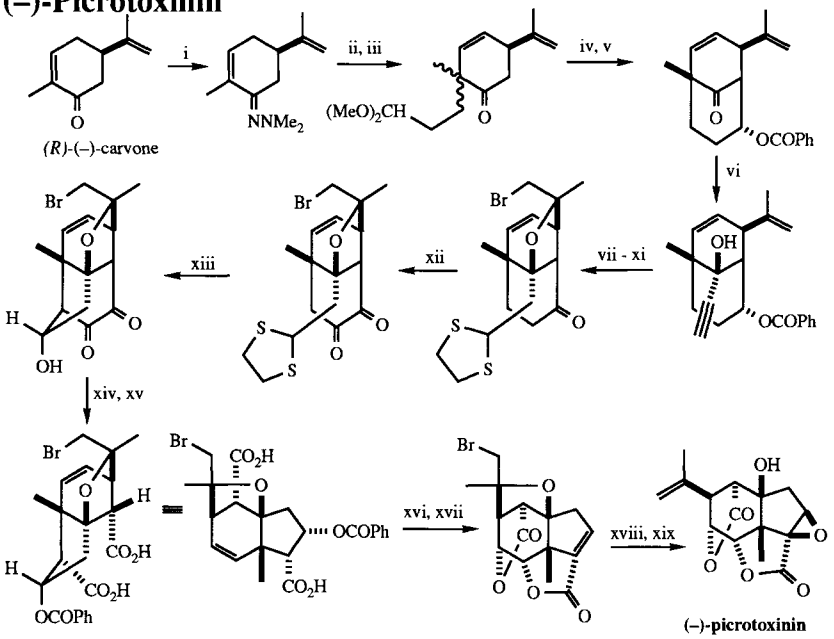
(S)-(+)-carvone

(i) H_2, PtO_2, Et_2O (ii) O_3, EtOAc; H_2, Pd/C (iii) $(CH_2OH)_2$, p-TsOH, C_6H_6; NaOH, MeOH (iv) MeI, K_2CO_3, Me_2CO (v) $LiAlH_4$, Et_2O (vi) PCC; $NaHCO_3$, CH_2Cl_2 (vii) CH_2=$CHMgBr$, Et_2O (viii) CrO_3, H_2SO_4, Me_2CO.

(+)-ryanodol

Scheme 75

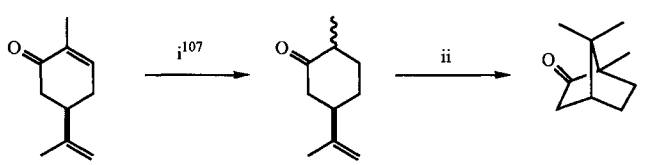
(–)-Picrotoxinin[151]



(i) Me_2NNH_2, TFA, toluene, reflux (ii) LDA, THF, DMAP; $BrCH_2CH_2CH(OMe)_2$, -60-->0°C (iii) HOAc, THF, NaOAc, H_2O (iv) HCl, H_2O, THF-DME (5:1) (v) PhCOCl, C_5H_5N; chromatography (vi) LiC≡CH, THF, -78°C (vii) NBS, THF (viii) $(C_6H_{11})_2BH$, THF, 0°C; 30% H_2O_2, $NaHCO_3$, 0-->25°C (ix) $(CH_2SH)_2$, CH_2Cl_2, BF_3•Et_2O, 0—>25°C (x) K_2CO_3, MeOH (xi) PDC, DMF, 0°C (xii) t-BuOK, t-BuOH, MeSSMe, O_2 (xiii) HgO, BF_3•Et_2O, THF-H_2O (6:1) (xiv) PhCOCl, C_5H_5N, DMAP (xv) NaOCl, H_2O-THF (2:1) (xvi) $Pb(OAc)_4$, MeCN (xvii) i-Pr_2NEt, DME, 50°C (xviii) TFA, $CHCl_3$, Na_2HPO_4 (xix) Zn, NH_4Cl, EtOH, reflux.

Scheme 76

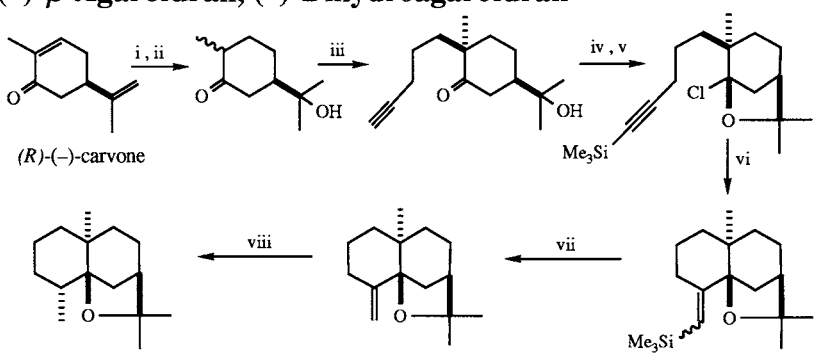
(+)-Camphor[152]



(i) Li, NH_3 (ii) thermolysis (400°C, 20 h; 55% (glc))

Scheme 77

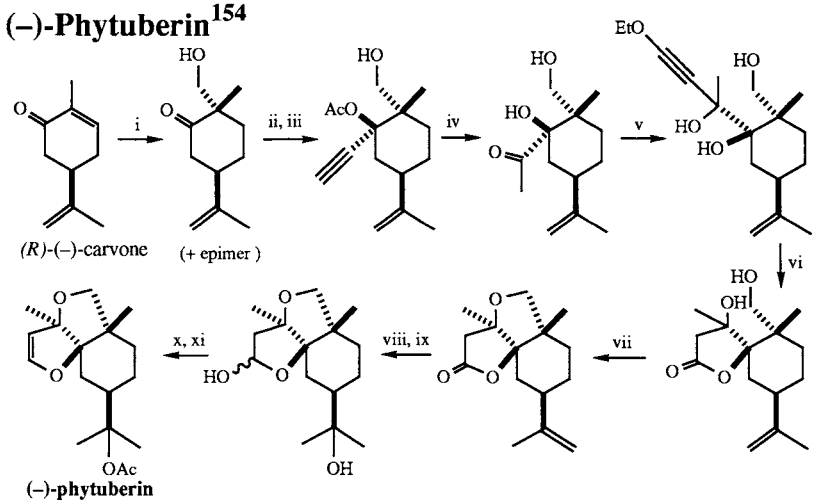
(–)-β-Agarofuran, (–)-Dihydroagarofuran[153]



(i) 50% aq. H_2SO_4 (ii) H_2, Pd-C, EtOAc (iii) KNH_2, NH_3, Et_2O, -30°C; 5-iodo-1-pentyne (iv) PCl_5, CCl_4 (v) EtMgBr, THF; Me_3SiCl (vi) Bu_3SnH, AIBN, C_6H_{12}, hv, reflux (vii) p-$CH_3C_6H_4SO_2H$, 2% H_2O, MeCN, reflux (viii) 95% NH_2NH_2, EtOH, 30% H_2O_2

Scheme 78

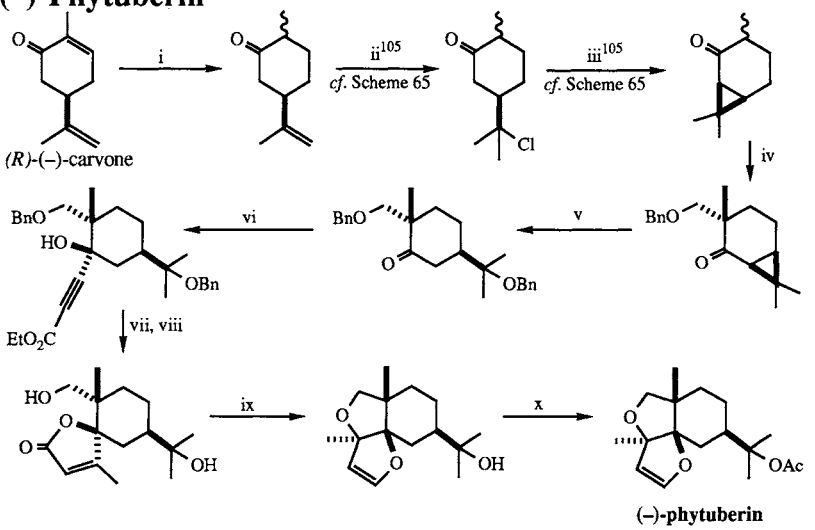
(–)-Phytuberin[154]



(i) Li, NH_3, -78°C; CH_2O (ii) LiC≡CH, THF, -78°C (iii) Ac_2O, C_5H_5N (iv) $HgSO_4$, MeOH, H_2O (v) EtOC≡CH, BuLi, THF, 0°C (vi) MeOH, H_2O, $(CO_2H)_2$ (vii) details not given (viii) m-CPBA, CH_2Cl_2 (ix) $LiAlH_4$, Et_2O (x) Ac_2O, C_5H_5N, 80°C (xi) 150°C, sealed tube.

Scheme 79

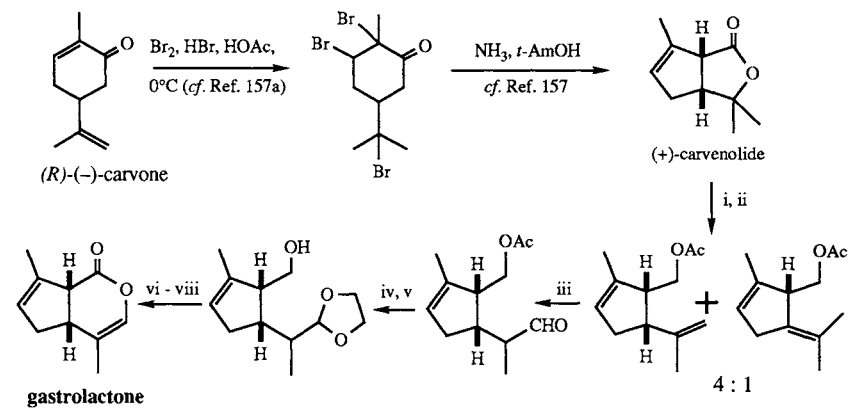
(–)-Phytuberin[155]



(i) Zn, NaOH, EtOH, H_2O (ii) HCl, Et_2O (iii) NaOEt, EtOH (iv) LDA, THF; $PhCH_2OCH_2Cl$ (v) $PhCH_2OH$, p-TsOH (vi) $LiC{\equiv}C\text{-}CO_2Et$, THF, -78°C (vii) Me_2CuLi, Et_2O, -24°C (viii) H_2, PtO_2 (ix) DIBAL, THF, -40°C; 2 N NaOH (x) Ac_2O, NEt_3, DMAP.

Scheme 80

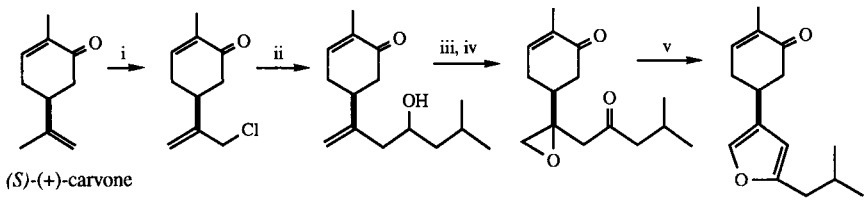
Gastrolactone[156]



(i) $LiAlH_4$, Et_2O (ii) Ac_2O, heat (iii) $(siamyl)_2BH$; PCC (iv) $(CH_2OH)_2$, p-TsOH, C_6H_6 (v) $LiAlH_4$ (vi) PDC, DMF (vii) HOAc, H_2O (viii) Ac_2O, p-TsOH, C_6H_6

Scheme 81

(+)-Bilobanone[158]



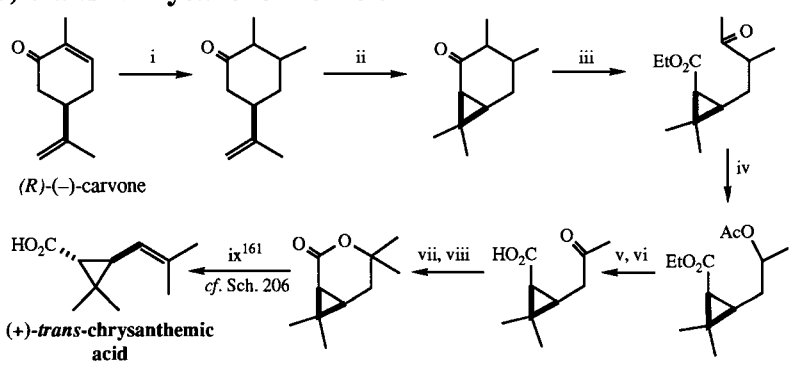
(*S*)-(+)-carvone

(+)-bilabanone

(i) $Ca(OCl)_2$, H_2O, CH_2Cl_2; distillation (ii) Zn, Me_2CHCH_2CHO, THF (iii) m-CPBA, CH_2Cl_2
(iv) $CrO_3 \cdot 2C_5H_5N$, CH_2Cl_2 (v) $BF_3 \cdot Et_2O$, THF-Et_2O [1:1]

Scheme 82

(+)-*trans*-Chrysanthemic Acid[159,160]



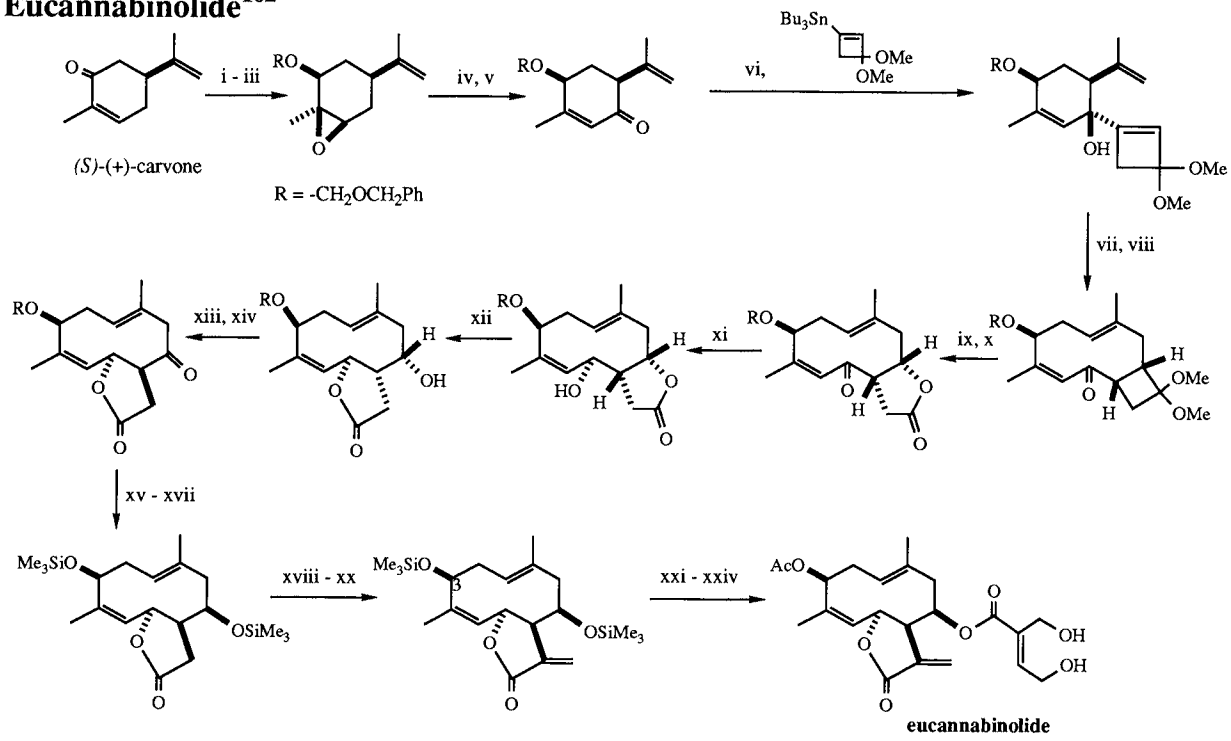
(*R*)-(–)-carvone

(+)-*trans*-chrysanthemic acid

(i) MeMgI, CuCl, THF (ii) HCl; NaOMe, MeOH (iii) NaOEt, EtONO; H_2O, H^+ (iv) CH_3CO_3H (v) NaOH, EtOH, H_2O (vi) Cl_2, C_5H_5N, CH_2Cl_2 (vii) MeMgI, Et_2O (viii) p-TsOH, toluene, reflux (ix) NaOH, $HOCH_2CH_2OH$, reflux.

Scheme 83

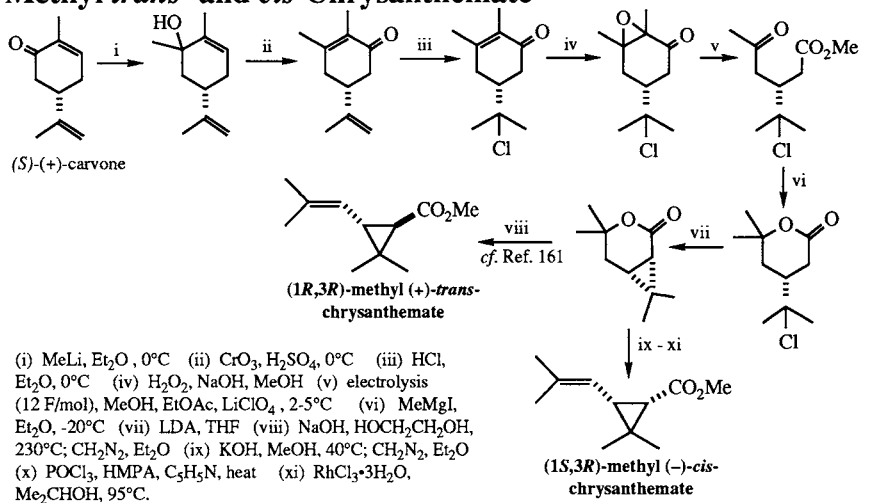
Eucannabinolide[162]



(i) $LiAlH_4$, Et_2O, 0°C (ii) m-CPBA, CH_2Cl_2 (iii) $PhCH_2OCH_2Cl$, $(i\text{-}Pr)_2NEt$ (iv) PhSeK, LiBr, THF; 30% H_2O_2, $NaHCO_3$, NaOAc, THF (v) CrO_3, H_2SO_4, Me_2CO (vi) n-BuLi, THF, -70°C (vii) $KN(SiMe_3)_2$, DME, 85°C (viii) MeOH, K_2CO_3 (ix) $(CO_2H)_2$, H_2O, silica gel, CH_2Cl_2 (x) H_2O_2, $Ti(O\text{-}i\text{-}Pr)_4$, $(i\text{-}Pr)_2NEt$, Et_2O, -30°C (xi) $NaBH_4$, MeOH, 0°C (xii) K_2CO_3 (cat.), MeOH, 25°C (xiii) CrO_3, CH_2Cl_2 (xiv) DBU, THF (xv) $NaBH_4$, MeOH (xvi) H_2, Pd-C, 22 psi, EtOH (xvii) trimethylsilyl imidazole, C_5H_5N, CH_2Cl_2 (xviii) LDA, THF; CH_2O, -70°C (xix) MsCl, Et_3N, DMAP, CH_2Cl_2 (xx) DBU, dioxane, 70°C (xxi) TBAF, THF (xxii) HOAc, DCC, 4-pyrrolidinopyridine (PDP) (xxiii) DCC, PDP, dihydroxytiglic acid acetonide (xxiv) $(CH_2OH)_2$, PPTS, MeOH.

Scheme 84

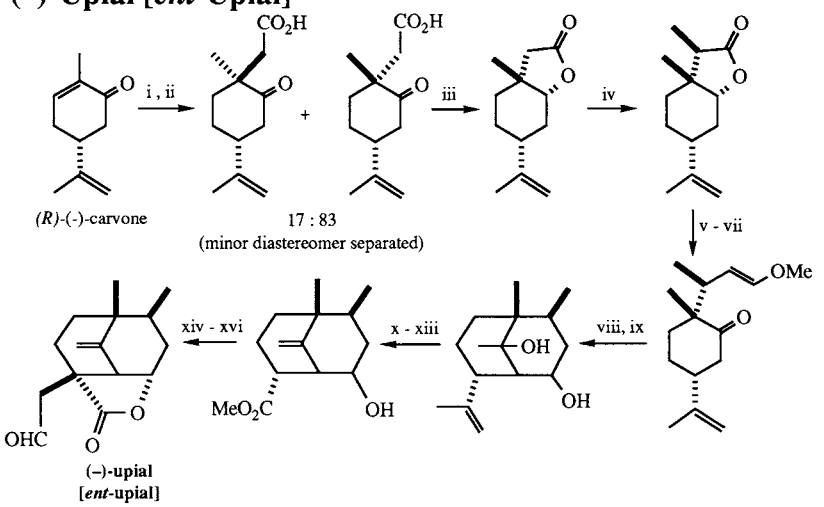
Methyl *trans*- and *cis*-Chrysanthemate[163]



(i) MeLi, Et_2O, 0°C (ii) CrO_3, H_2SO_4, 0°C (iii) HCl, Et_2O, 0°C (iv) H_2O_2, NaOH, MeOH (v) electrolysis (12 F/mol), MeOH, EtOAc, $LiClO_4$, 2-5°C (vi) MeMgI, Et_2O, -20°C (vii) LDA, THF (viii) NaOH, $HOCH_2CH_2OH$, 230°C; CH_2N_2, Et_2O (ix) KOH, MeOH, 40°C; CH_2N_2, Et_2O (x) $POCl_3$, HMPA, C_5H_5N, heat (xi) $RhCl_3{\cdot}3H_2O$, Me_2CHOH, 95°C.

Scheme 85

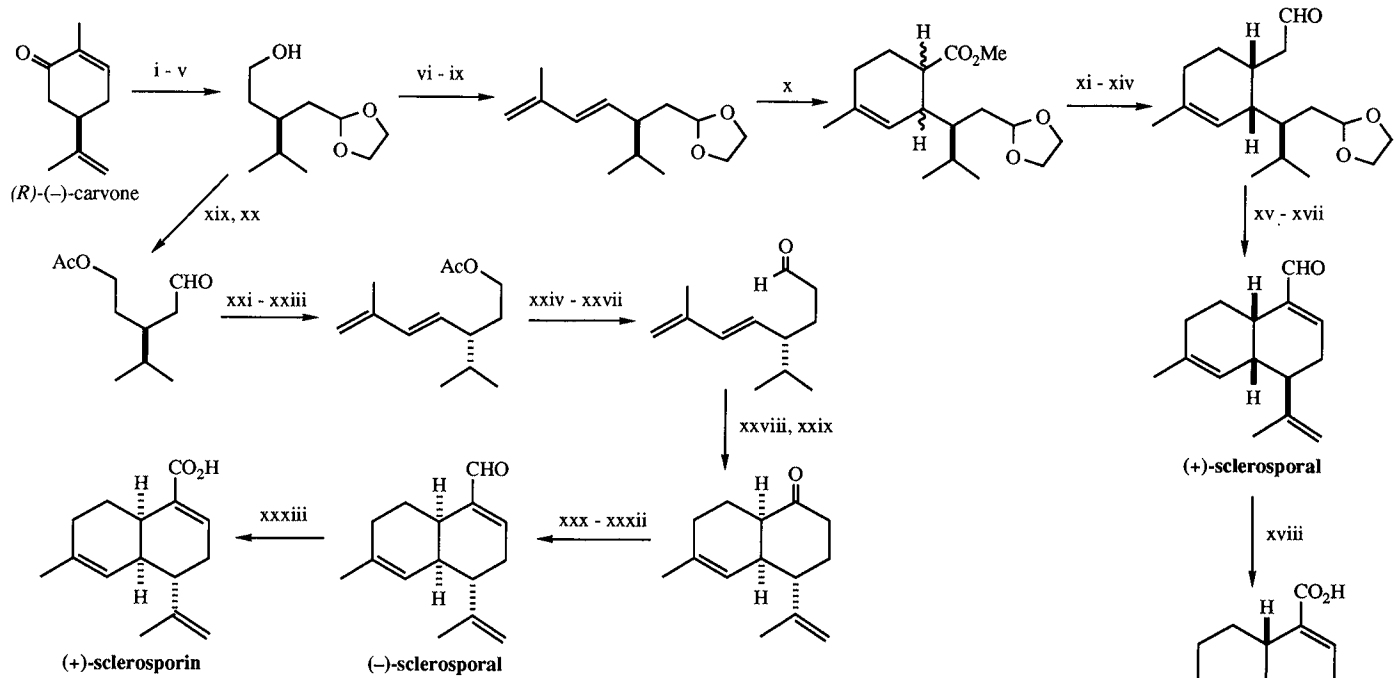
(–)-Upial [*ent*-Upial][164]



(i) Li, NH_3, t-BuOH, $BrCH_2CO_2Et$ (ii) KOH, EtOH (iii) Li, NH_3, EtOH; p-TsOH, C_6H_6 (iv) LDA, THF, MeI (v) $LiAlH_4$, Et_2O (vi) $(COCl)_2$, Me_2SO, NEt_3 (vii) Ph_3P=CHOMe, THF (viii) 10% HCl, THF-DME (5:1) (ix) MeMgBr (2.5 eq.), Et_2O, 0°C (x) OsO_4, $NaIO_4$ (xi) KOCl, MeOH, 0°C (xii) $(COCl)_2$, Me_2SO, NEt_3 (xiii) $SOCl_2$, C_5H_5N, 0°C (xiv) $NaCNBH_3$, THF, HOAc, HCl (xv) LDA, THF, HMPA, (*E*)-PhCH=$CHCH_2Br$ (xvi) OsO_4, $NaIO_4$.

Scheme 86

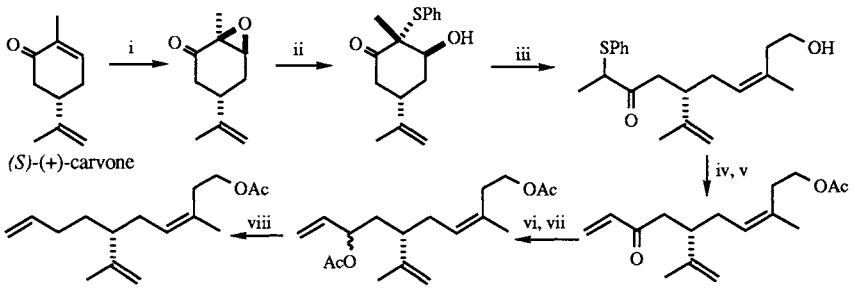
(+)-Sclerosporal, (–)-Sclerosporal, (+)-Sclerosporin, and (–)-Sclerosporin[165]



(i) H_2, PtO_2 (ii) O_3, -78°C; Me_2S, MeOH (iii) $NaIO_4$ (iv) $(CH_2OH)_2$, p-TsOH, C_6H_6 (v) NaOMe, MeOH (vi) PCC, NaOAc, CH_2Cl_2 (vii) $CH_2=C(CH_3)MgBr$, THF, 0°C (viii) MsCl, Et_3N, CH_2Cl_2, -10°C (ix) i-Pr_2NEt, HMPA, 140°C (x) $CH_2=CHCO_2Me$, 120°C (xi) $LiAlH_4$, Et_2O (xii) p-TsCl, C_5H_5N, 0°C (xiii) KCN, DMSO, 60°C (xiv) DIBAL, THF, 45°C (xv) Me_3SiCl, Et_3N, $ZnCl_2$, C_6H_6, 60°C (xvi) $TiCl_4$, Ti(O-i-Pr)$_4$, CH_2Cl_2, -70°C (xvii) 5 Å molecular sieves, p-TsOH, xylene, 140°C (xviii) CrO_3, H_2SO_4, acetone (xix) Ac_2O, C_5H_5N (xx) $HClO_4$, Et_2O, 0°C (xxi) $CH_2=C(CH_3)MgBr$, THF, 0°C (xxii) MsCl, Et_3N, CH_2Cl_2, -10°C (xxiii) PCC, NaOAc, CH_2Cl_2 (xxiv) KOH, MeOH (xxv) p-TsCl, C_5H_5N (xxvi) NaCN, DMF (xxvii) DIBAL, THF (xxviii) $CH_2=CHMgBr$, THF (xxix) $H_2Cr_2O_7$, Et_2O (xxx) LiCH(OMe)SPh (xxxi) $SOCl_2$ (xxxii) $NaIO_4$ (xxxiii) CrO_3, H_2SO_4, acetone.

Scheme 87

California Red Scale Pheromone[166]

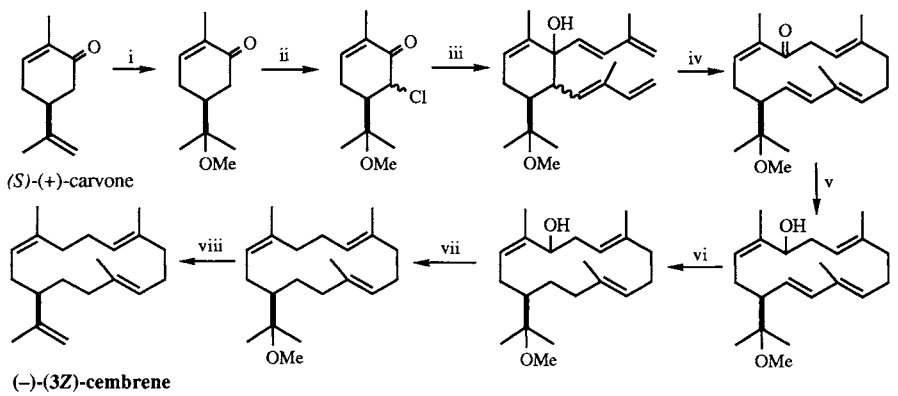


California red scale pheromone

(i) H_2O_2, NaOH, EtOH (ii) PhSH, NEt_3, MeCN (iii) $HOCH_2CH_2CH(Me)PPh_3Br$,BuLi, THF, HMPA, 0°C (iv) Ac_2O, C_5H_5N (v) m-CPBA, CH_2Cl_2, -5°C; heat (135°C) (vi) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH (vii) Ac_2O, C_5H_5N (viii) $PdCl_2(PPh_3)_2$, HCO_2NH_4, dioxane, reflux .

Scheme 88

(–)-(3Z)-Cembrene A[167]

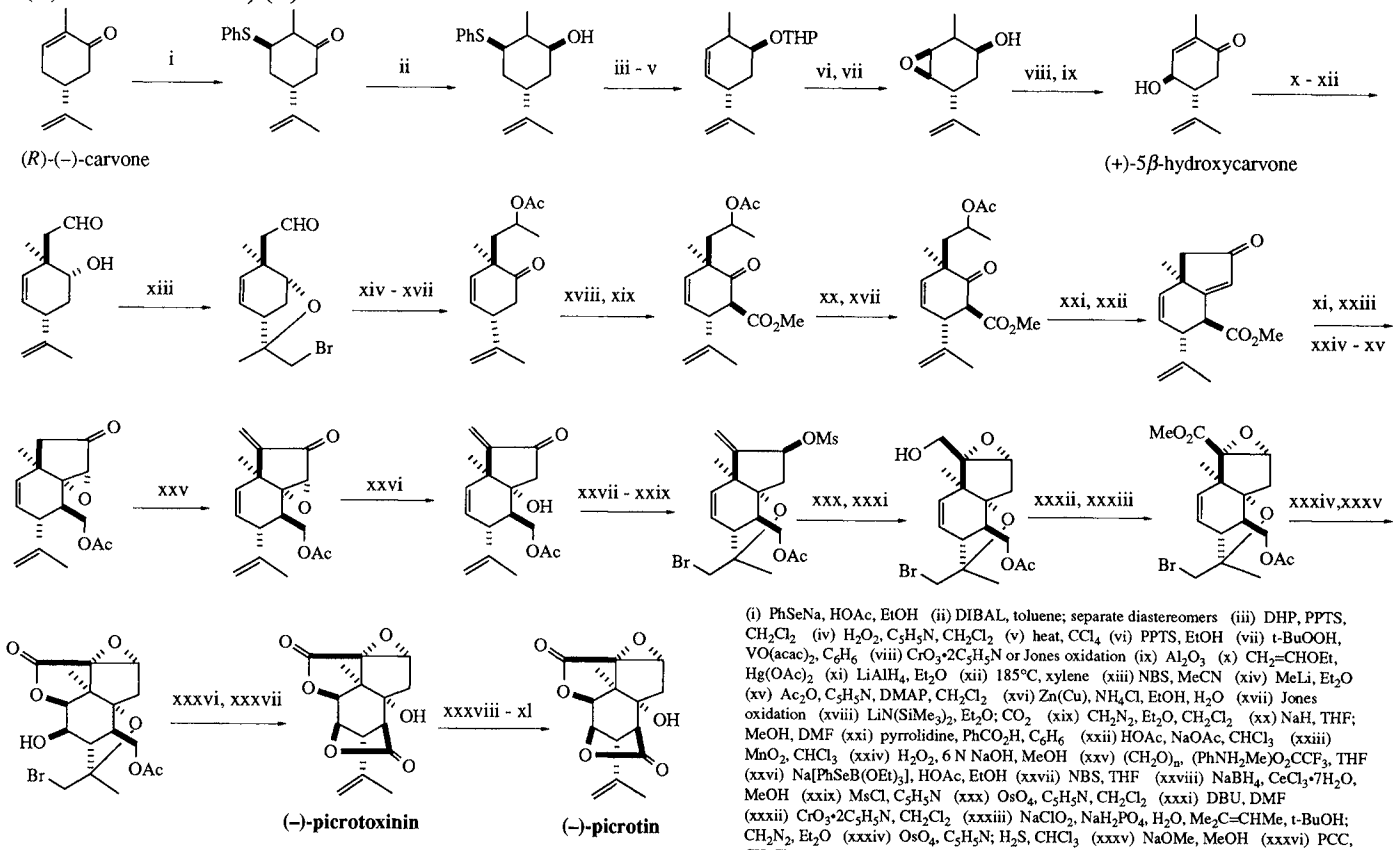


(–)-(3Z)-cembrene

(i) MeOH, H_2SO_4, 2 d (ii) LDA, THF, -78°C; CF_3SO_2Cl (iii) (*E*)-1-lithio-2-methyl-1,3-butadiene, -78°C; lithium isopropenyl acetylide (excess); heat; $LiAlH_4$, 0°C (iv) KH, 18-crown-6, THF (v) $NaBH_4$, $CeCl_3$, MeOH (vi) H_2, PtO_2, hexane, EtOAc (vii) Ac_2O, C_5H_5N; Li, $EtNH_2$, -78°C (viii) AcOMs, MeCN.

Scheme 89

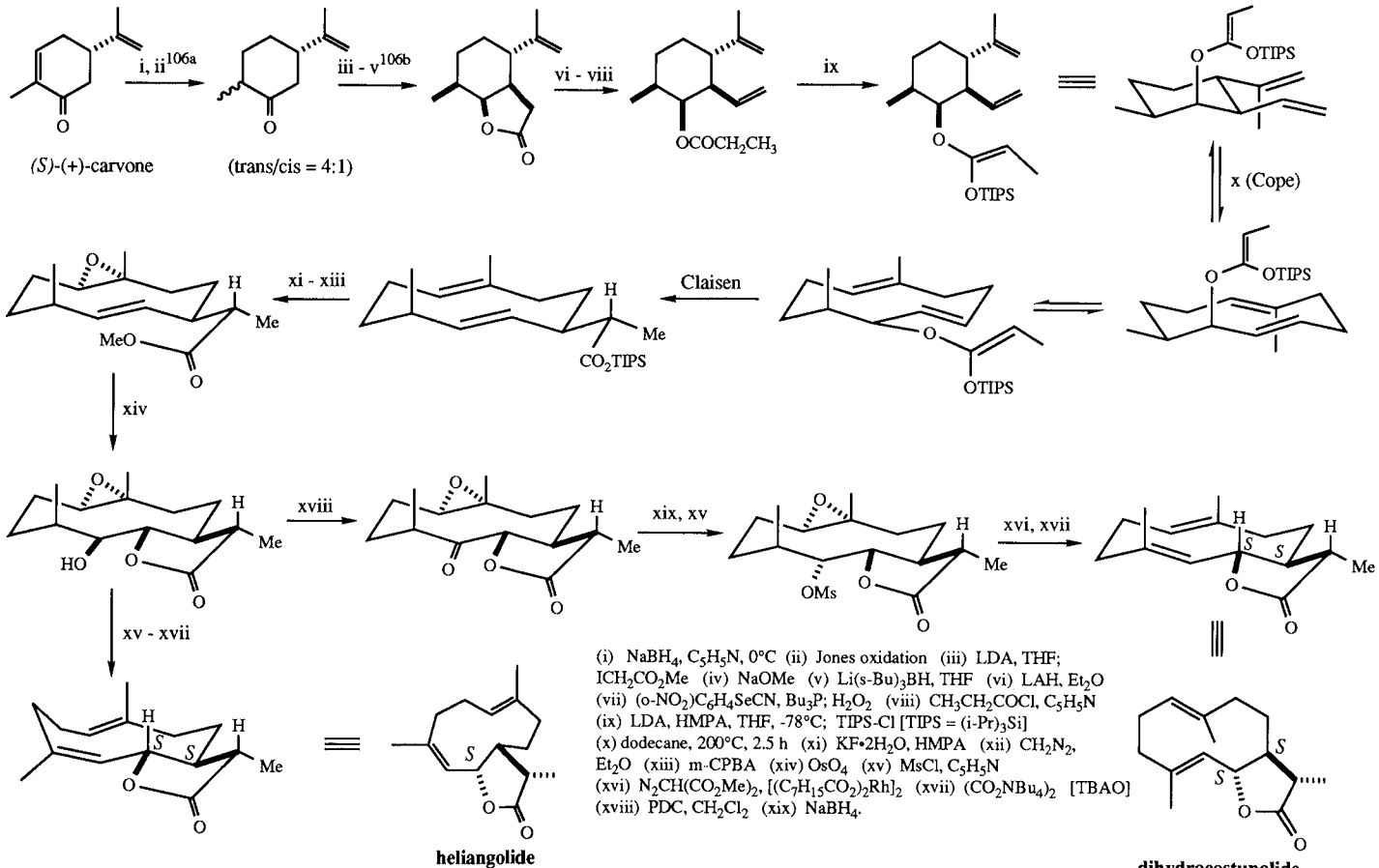
(–)-Picrotoxinin, (–)-Picrotin[168,169]



(i) PhSeNa, HOAc, EtOH (ii) DIBAL, toluene; separate diastereomers (iii) DHP, PPTS, CH_2Cl_2 (iv) H_2O_2, C_5H_5N, CH_2Cl_2 (v) heat, CCl_4 (vi) PPTS, EtOH (vii) t-BuOOH, $VO(acac)_2$, C_6H_6 (viii) $CrO_3{\cdot}2C_5H_5N$ or Jones oxidation (ix) Al_2O_3 (x) CH_2=CHOEt, $Hg(OAc)_2$ (xi) $LiAlH_4$, Et_2O (xii) 185°C, xylene (xiii) NBS, MeCN (xiv) MeLi, Et_2O (xv) Ac_2O, C_5H_5N, DMAP, CH_2Cl_2 (xvi) Zn(Cu), NH_4Cl, EtOH, H_2O (xvii) Jones oxidation (xviii) $LiN(SiMe_3)_2$, Et_2O; CO_2 (xix) CH_2N_2, Et_2O, CH_2Cl_2 (xx) NaH, THF; MeOH, DMF (xxi) pyrrolidine, $PhCO_2H$, C_6H_6 (xxii) HOAc, NaOAc, $CHCl_3$ (xxiii) MnO_2, $CHCl_3$ (xxiv) H_2O_2, 6 N NaOH, MeOH (xxv) $(CH_2O)_n$, $(PhNH_2Me)O_2CCF_3$, THF (xxvi) $Na[PhSeB(OEt)_3]$, HOAc, EtOH (xxvii) NBS, THF (xxviii) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH (xxix) MsCl, C_5H_5N (xxx) OsO_4, C_5H_5N, CH_2Cl_2 (xxxi) DBU, DMF (xxxii) $CrO_3{\cdot}2C_5H_5N$, CH_2Cl_2 (xxxiii) $NaClO_2$, NaH_2PO_4, H_2O, Me_2C=CHMe, t-BuOH; CH_2N_2, Et_2O (xxxiv) OsO_4, C_5H_5N; H_2S, $CHCl_3$ (xxxv) NaOMe, MeOH (xxxvi) PCC, CH_2Cl_2 (xxxvii) Zn(Cu), NH_4Cl, H_2O, EtOH (xxxviii) m-CPBA, CH_2Cl_2 (xxxix) $Na[PhSeB(OEt)_3]$, HOAc, EtOH (xl) Bu_3SnH, AIBN, $PhCH_3$.

Scheme 90

Heliangolide, Dihydrocostunolide[106]

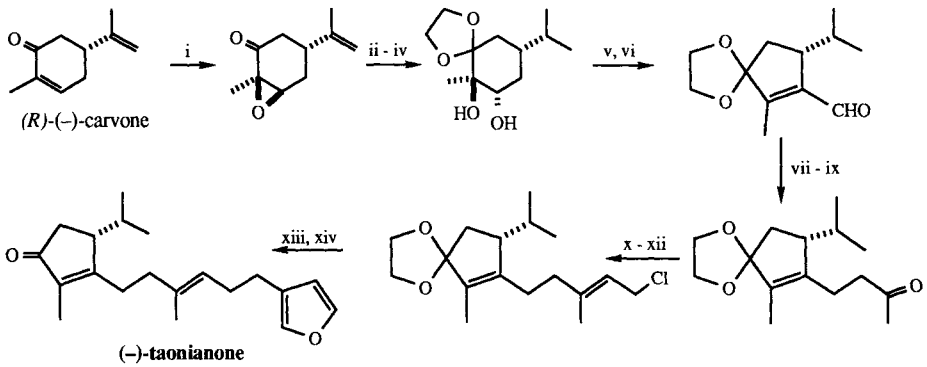


(i) $NaBH_4$, C_5H_5N, 0°C (ii) Jones oxidation (iii) LDA, THF; ICH_2CO_2Me (iv) NaOMe (v) Li(s-Bu)$_3$BH, THF (vi) LAH, Et_2O (vii) (o-NO_2)C_6H_4SeCN, Bu_3P; H_2O_2 (viii) CH_3CH_2COCl, C_5H_5N (ix) LDA, HMPA, THF, -78°C; TIPS-Cl [TIPS = (i-Pr)$_3$Si] (x) dodecane, 200°C, 2.5 h (xi) KF•2H_2O, HMPA (xii) CH_2N_2, Et_2O (xiii) m-CPBA (xiv) OsO_4 (xv) MsCl, C_5H_5N (xvi) $N_2CH(CO_2Me)_2$, [($C_7H_{15}CO_2$)$_2$Rh]$_2$ (xvii) (CO_2NBu_4)$_2$ [TBAO] (xviii) PDC, CH_2Cl_2 (xix) $NaBH_4$.

heliangolide **dihydrocostunolide**

Scheme 91

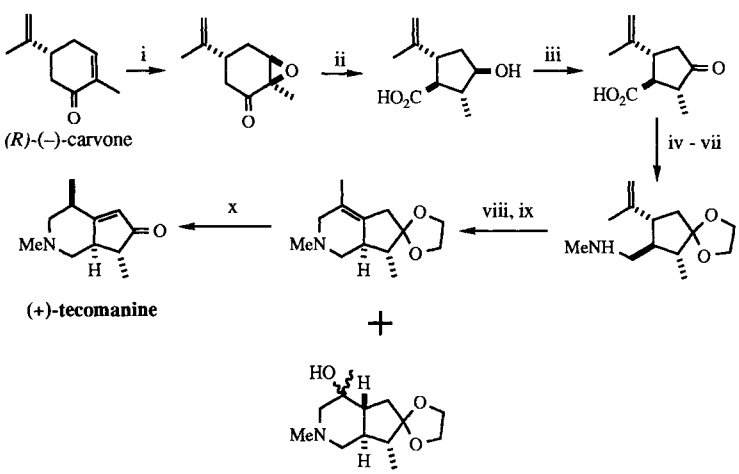
(+)-Taonianone[170]



(i) H_2O_2, NaOH (ii) $(CH_2OH)_2$, PPTS, C_6H_6 (iii) NaOH, DMSO, H_2O, 100°C (iv) H_2, Pd-C, EtOH (v) $Pb(OAc)_4$, C_6H_6 (vi) HOAc, piperidine, C_6H_6 (vii) NaOEt, EtOH, Me_2CO, 0°C (viii) $NaBH_4$, $NiCl_2{\cdot}6H_2O$, MeOH (ix) CrO_3, C_5H_5N, CH_2Cl_2 (x) $(EtO)_2P(O)CHNaCO_2Et$, DME (xi) $LiAlH_4$, Et_2O (xiii) p-TsCl, DMAP, CH_2Cl_2, 0°C (xiii) Li_2CuCl_4, (3-furyl)methylmagnesium chloride, THF (xiv) EtOH, PPTS.

Scheme 92

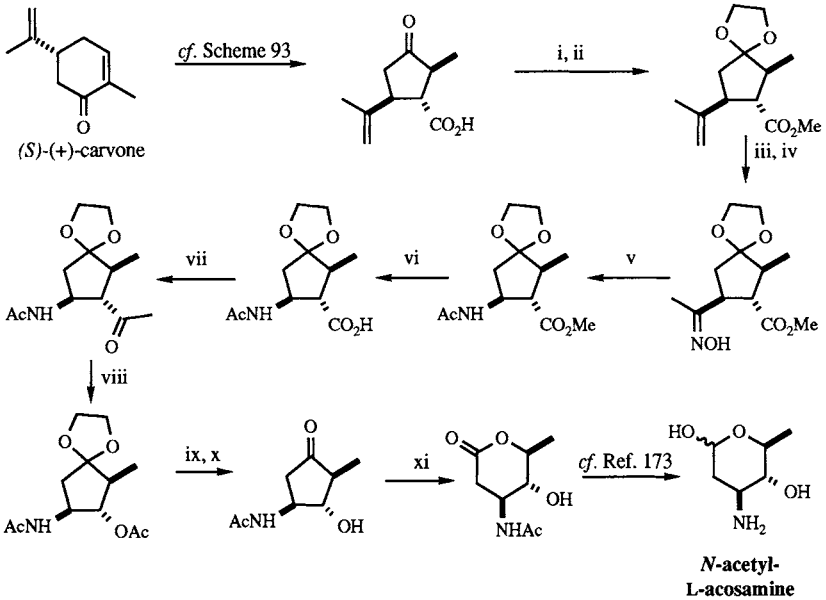
(+)-Tecomanine[171]



(i) NaOH, H_2O_2, MeOH (ii) NaOMe, MeOH; H_2O (iii) 4 N Jones reagent, acetone (iv) $HOCH_2CH_2OH$, p-TsOH, C_6H_6 (v) $LiAlH_4$, THF, 0°C (vi) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0°C (vii) 40% $MeNH_2$-MeOH, Na_2CO_3, reflux (viii) NCS, CH_2Cl_2, 0°C (ix) Ag_2O, dioxane-H_2O (2:1), reflux; separation (x) 60% $HClO_4$, acetone.

Scheme 93

N-Acetyl-L-acosamine[172]

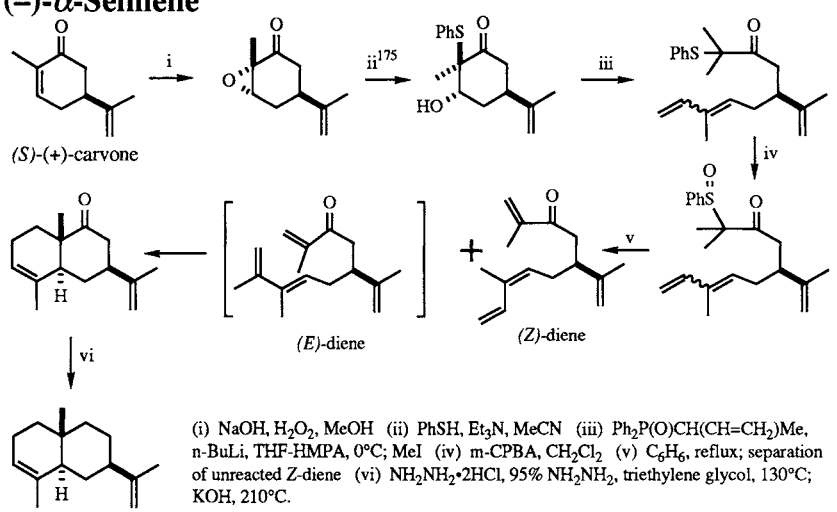


***N*-acetyl-L-acosamine**

(i) MeOH, DCC (ii) $HOCH_2CH_2OH$, p-TsOH, C_6H_6 (iii) O_3 (iv) $NH_2OH{\cdot}HCl$, C_5H_5N (v) $POCl_3$,C_5H_5N (vi) NaOH, MeOH, reflux (vii) MeLi (viii) m-CPBA, CH_2Cl_2, reflux (ix) K_2CO_3, MeOH (x) p-TsOH, acetone (xi) m-CPBA, CH_2Cl_2.

Scheme 94

(–)-α-Selinene[174]

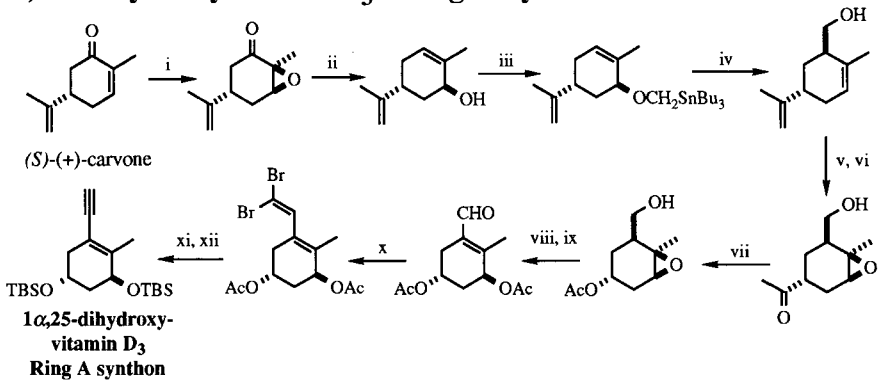


(i) NaOH, H_2O_2, MeOH (ii) PhSH, Et_3N, MeCN (iii) $Ph_2P(O)CH(CH{=}CH_2)Me$, n-BuLi, THF-HMPA, 0°C; MeI (iv) m-CPBA, CH_2Cl_2 (v) C_6H_6, reflux; separation of unreacted Z-diene (vi) $NH_2NH_2{\cdot}2HCl$, 95% NH_2NH_2, triethylene glycol, 130°C; KOH, 210°C.

(–)-α-selinene

Scheme 95

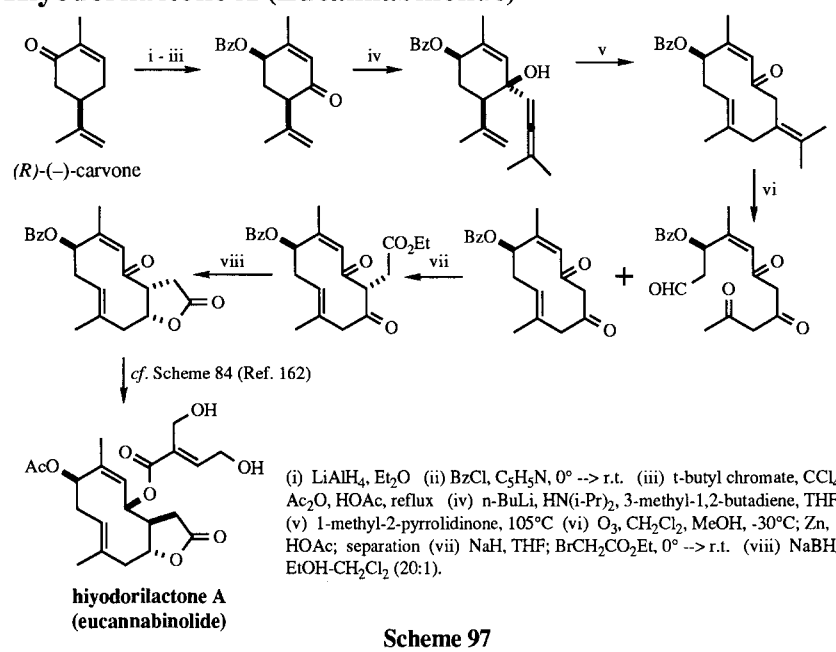
1α,25-Dihydroxyvitamin D_3: Ring A Synthon[176]



(i) 30% H_2O_2, LiOH, MeOH, 0°C (ii) $NH_2NH_2{\cdot}H_2O$, $Me_2NCH_2CH_2OH$ (iii) KH, THF; ICH_2SnBu_3, THF (iv) n-BuLi, THF (v) $VO(acac)_2$ (cat.), C_6H_6, 50°C; t-BuOOH, toluene (vi) OsO_4 (cat.), THF-H_2O (2.5:1); KIO_4 (vii) m-CPBA, $CHCl_3$ (viii) $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N (ix) Ac_2O, DMAP (cat.), C_5H_5N (x) Zn, CBr_4, Ph_3P, C_5H_5N (xi) n-BuLi, THF (xii) t-$BuMe_2SiCl$, imidazole, CH_2Cl_2.

Scheme 96

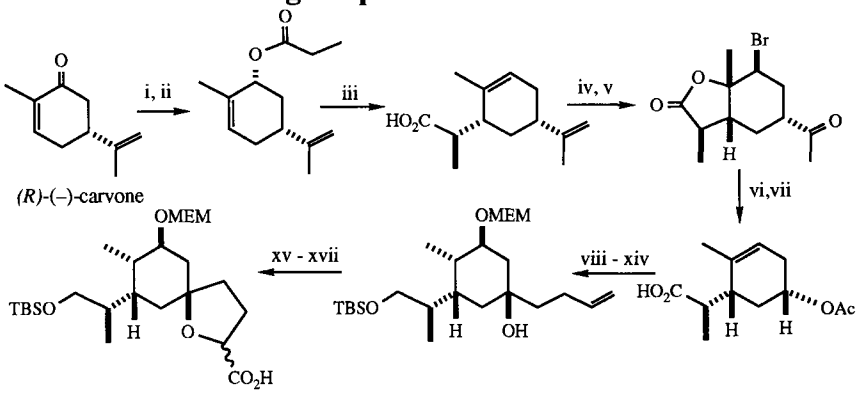
Hiyodorilactone A (Eucannabinolide)[177]



(i) $LiAlH_4$, Et_2O (ii) BzCl, C_5H_5N, 0° --> r.t. (iii) t-butyl chromate, CCl_4, Ac_2O, HOAc, reflux (iv) n-BuLi, $HN(i\text{-}Pr)_2$, 3-methyl-1,2-butadiene, THF (v) 1-methyl-2-pyrrolidinone, 105°C (vi) O_3, CH_2Cl_2, MeOH, -30°C; Zn, HOAc; separation (vii) NaH, THF; $BrCH_2CO_2Et$, 0° --> r.t. (viii) $NaBH_4$, EtOH-CH_2Cl_2 (20:1).

Scheme 97

Carbamonensin Ring A Spiro Ether[178]

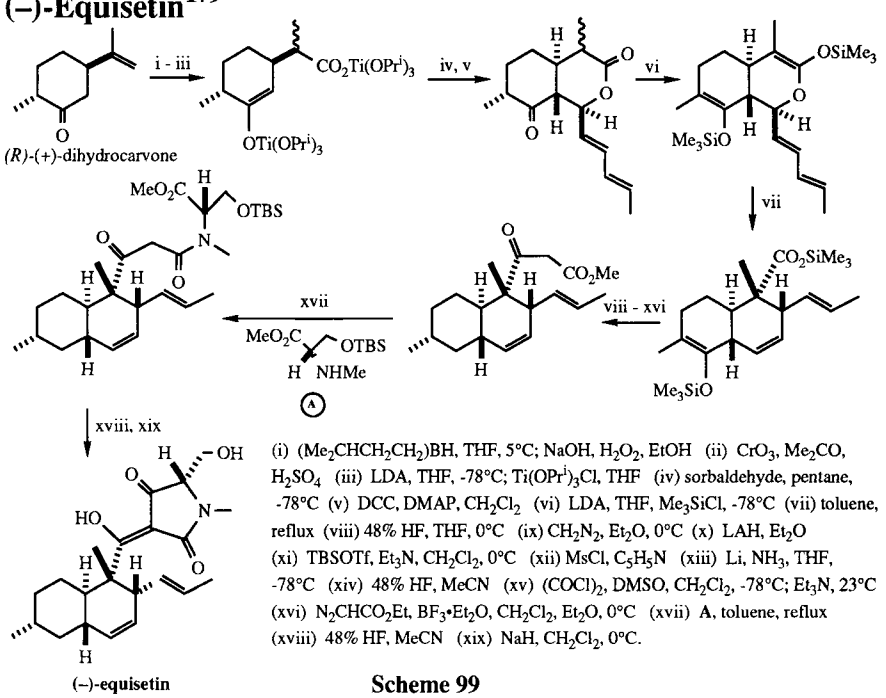


carbamonensin ring A spiro ether

(i) LAH, Et_2O, -78°C (ii) CH_3CH_2COCl, C_5H_5N, CH_2Cl_2 (iii) LDA, THF, HMPA, -78°C; TBSCl, THF, -78°C; 50°C (iv) NBS, Me_2CO, 0°C (v) OsO_4 (cat.), $NaIO_4$, THF , H_2O (vi) CF_3CO_3H, Na_2HPO_4, CH_2Cl_2 (vii) Zn, EtOH, 80°C (viii) LAH, Et_2O (ix) t-$BuMe_2SiCl$, Et_3N, DMAP, CH_2Cl_2 (x) PhCOCl, C_5H_5N, CH_2Cl_2 (xi) BH_3, THF, 0°C; 1 N NaOH, 30% H_2O_2 (xii) $MeOCH_2OCH_2Cl$, $(i\text{-}Pr)_2NEt$, CH_2Cl_2 (xiii) $(COCl)_2$, Me_2SO, CH_2Cl_2, -50°C; Et_3N, -50°C (xiv) $CH_2{=}CHCH_2CH_2MgBr$, THF , -15°C (xv) m-CPBA, NaOAc, CH_2Cl_2 (xvi) CSA, CH_2Cl_2, 0°C (xvii) PDC, DMF.

Scheme 98

(–)-Equisetin[179]

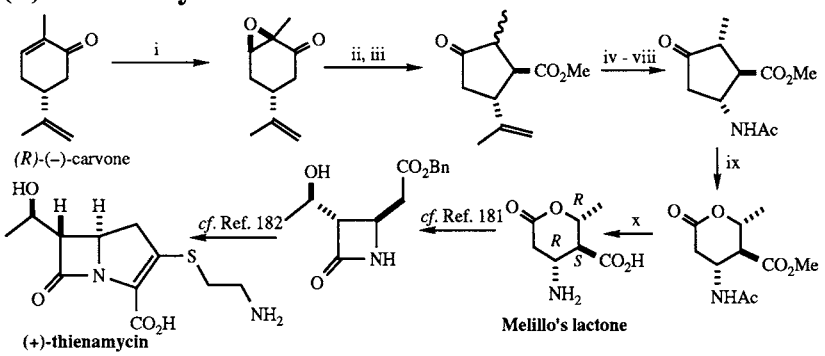


(–)-equisetin

(i) $(Me_2CHCH_2CH_2)BH$, THF, 5°C; NaOH, H_2O_2, EtOH (ii) CrO_3, Me_2CO, H_2SO_4 (iii) LDA, THF, -78°C; $Ti(OPr^i)_3Cl$, THF (iv) sorbaldehyde, pentane, -78°C (v) DCC, DMAP, CH_2Cl_2 (vi) LDA, THF, Me_3SiCl, -78°C (vii) toluene, reflux (viii) 48% HF, THF, 0°C (ix) CH_2N_2, Et_2O, 0°C (x) LAH, Et_2O (xi) TBSOTf, Et_3N, CH_2Cl_2, 0°C (xii) MsCl, C_5H_5N (xiii) Li, NH_3, THF, -78°C (xiv) 48% HF, MeCN (xv) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; Et_3N, 23°C (xvi) N_2CHCO_2Et, $BF_3{\cdot}Et_2O$, CH_2Cl_2, Et_2O, 0°C (xvii) **A**, toluene, reflux (xviii) 48% HF, MeCN (xix) NaH, CH_2Cl_2, 0°C.

Scheme 99

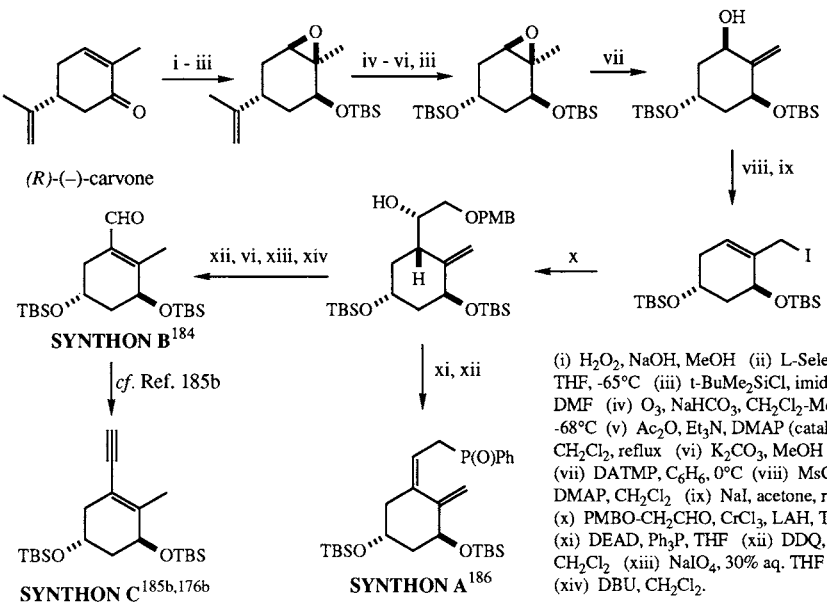
(+)-Thienamycin[180]



(i) H_2O_2, MeOH, NaOH (ii) NaOMe, MeOH (iii) Jones oxidation, -40°C (iv) $(CH_2OH)_2$, H^+, C_6H_6 (v) O_3, Me_2CO; NaI, $Na_2S_2O_3$ (vi) $NH_2OH{\cdot}HCl$, CH_2Cl_2, pyridine (vii) $POCl_3$, pyridine (viii) 60% $HClO_4$, Me_2CO (ix) m-CPBA, CH_2Cl_2, reflux (x) conc. HCl; toluene, heat.

Scheme 100

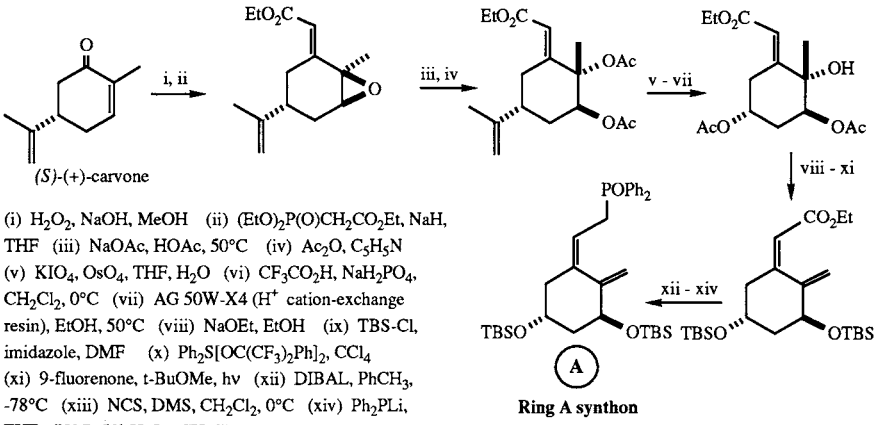
1α,25-Dihydroxyvitamin D_3: Ring A Synthons[183]



(i) H_2O_2, NaOH, MeOH (ii) L-Selectride, THF, -65°C (iii) t-$BuMe_2SiCl$, imidazole, DMF (iv) O_3, $NaHCO_3$, CH_2Cl_2-MeOH, -68°C (v) Ac_2O, Et_3N, DMAP (catalyst), CH_2Cl_2, reflux (vi) K_2CO_3, MeOH (vii) DATMP, C_6H_6, 0°C (viii) MsCl, DMAP, CH_2Cl_2 (ix) NaI, acetone, reflux (x) PMBO-CH_2CHO, $CrCl_3$, LAH, THF (xi) DEAD, Ph_3P, THF (xii) DDQ, 5% aq. CH_2Cl_2 (xiii) $NaIO_4$, 30% aq. THF (xiv) DBU, CH_2Cl_2.

Scheme 101

1α,25-Dihydroxycholecalciferol and 1α,25-Dihydroxyergocalciferol: Ring A Synthon[186]



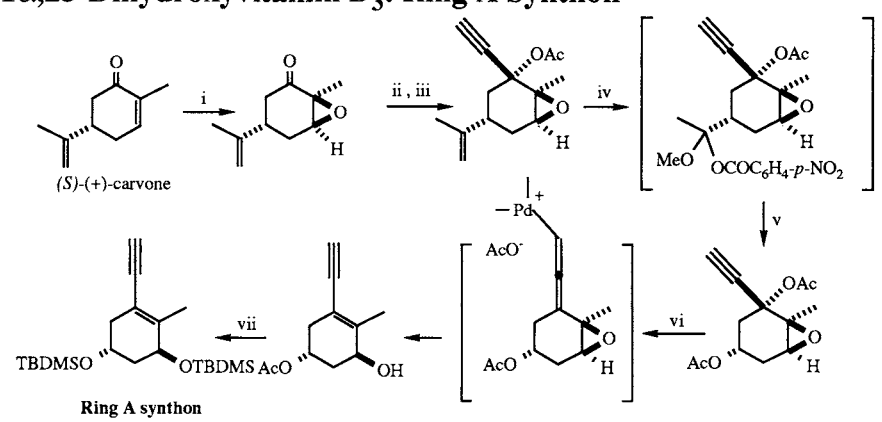
(S)-(+)-carvone

(i) H_2O_2, NaOH, MeOH (ii) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF (iii) NaOAc, HOAc, 50°C (iv) Ac_2O, C_5H_5N (v) KIO_4, OsO_4, THF, H_2O (vi) CF_3CO_2H, NaH_2PO_4, CH_2Cl_2, 0°C (vii) AG 50W-X4 (H^+ cation-exchange resin), EtOH, 50°C (viii) NaOEt, EtOH (ix) TBS-Cl, imidazole, DMF (x) $Ph_2S[OC(CF_3)_2Ph]_2$, CCl_4 (xi) 9-fluorenone, t-BuOMe, hν (xii) DIBAL, $PhCH_3$, -78°C (xiii) NCS, DMS, CH_2Cl_2, 0°C (xiv) Ph_2PLi, THF, -78°C; 5% H_2O_2, CH_2Cl_2.

Ring A synthon

Scheme 102

1α,25-Dihydroxyvitamin D_3: Ring A Synthon[185]



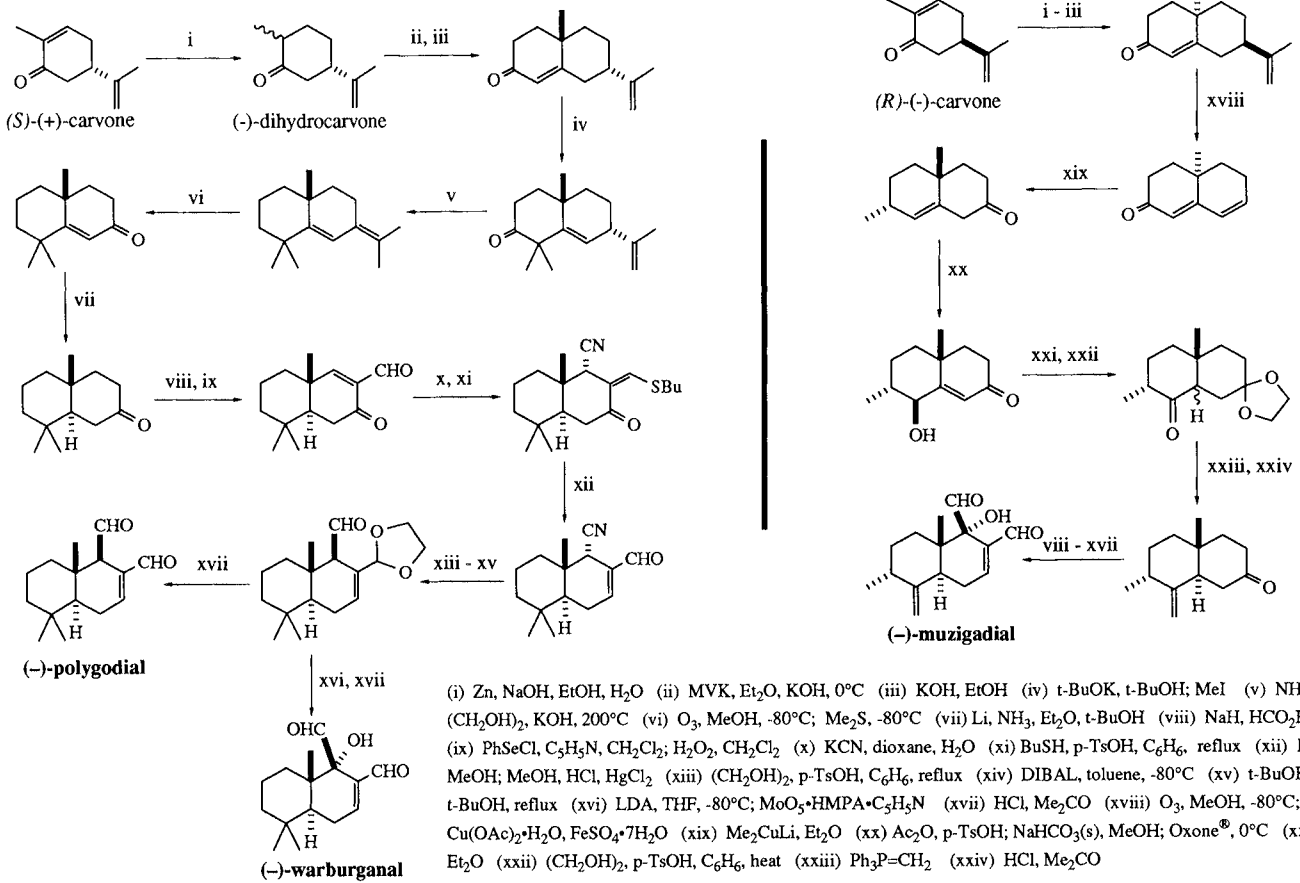
(S)-(+)-carvone

Ring A synthon

(i) H_2O_2, NaOH, MeOH, -10°C (ii) LiC≡CH, THF, -78°C (iii) Ac_2O, DMAP, Et_3N (iv) O_3, CH_2Cl_2, MeOH, -78°C; p-$NO_2C_6H_4COCl$, CH_2Cl_2, C_5H_5N (v) heat (40°C) (vi) SmI_2, $Pd(PPh_3)_4$, THF (vii) NaOMe, MeOH, 0°C; TBDMSCl, imidazole, DMF.

Scheme 103

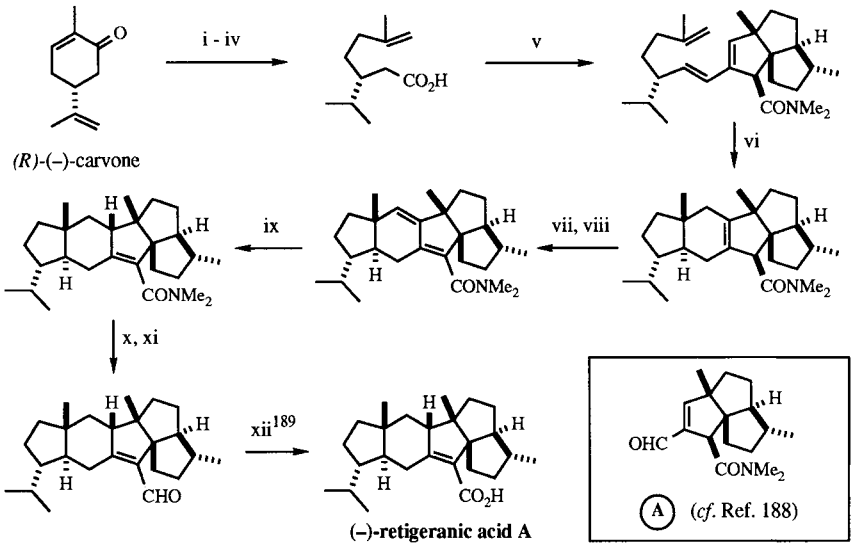
(–)-Polygodial, (–)-Warburganal, (–)-Muzigadial[187]



(i) Zn, NaOH, EtOH, H_2O (ii) MVK, Et_2O, KOH, 0°C (iii) KOH, EtOH (iv) t-BuOK, t-BuOH; MeI (v) NH_2NH_2, $(CH_2OH)_2$, KOH, 200°C (vi) O_3, MeOH, -80°C; Me_2S, -80°C (vii) Li, NH_3, Et_2O, t-BuOH (viii) NaH, HCO_2Et, Et_2O (ix) PhSeCl, C_5H_5N, CH_2Cl_2; H_2O_2, CH_2Cl_2 (x) KCN, dioxane, H_2O (xi) BuSH, p-TsOH, C_6H_6, reflux (xii) $NaBH_4$, MeOH; MeOH, HCl, $HgCl_2$ (xiii) $(CH_2OH)_2$, p-TsOH, C_6H_6, reflux (xiv) DIBAL, toluene, -80°C (xv) t-BuOK, t-BuOH, reflux (xvi) LDA, THF, -80°C; MoO_5•HMPA•C_5H_5N (xvii) HCl, Me_2CO (xviii) O_3, MeOH, -80°C; $Cu(OAc)_2$•H_2O, $FeSO_4$•$7H_2O$ (xix) Me_2CuLi, Et_2O (xx) Ac_2O, p-TsOH; $NaHCO_3$(s), MeOH; Oxone®, 0°C (xxi) HBr, Et_2O (xxii) $(CH_2OH)_2$, p-TsOH, C_6H_6, heat (xxiii) $Ph_3P{=}CH_2$ (xxiv) HCl, Me_2CO

Scheme 104

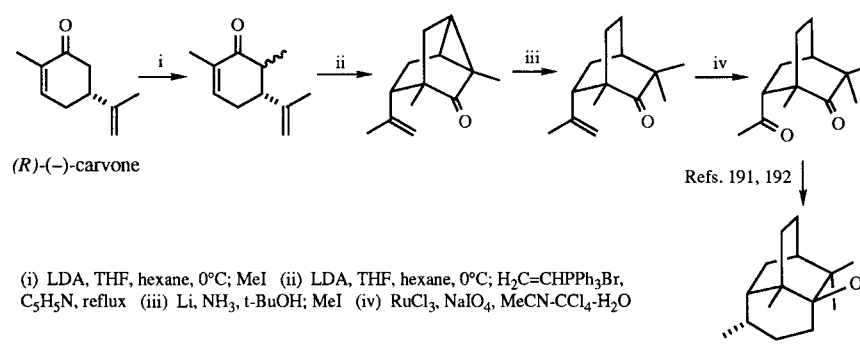
(–)-Retigeranic Acid A[188]



(i) H_2, $(Ph_3P)_3RhCl$, C_6H_6 (ii) Br_2, HOAc (iii) 2.2% KOH (iv) CH_3PPh_3Br, n-BuLi, THF (v) LDA, THF, 50°C; A, -78°--> 25°C; HOAc, $HC(OMe)_2NMe_2$, reflux (vi) 250°C, toluene (vii) m-CPBA, NaOAc, CH_2Cl_2 (viii) t-BuOK, DMSO, 100°C; 5% HCl (ix) H_2, 10% Pd-C, C_6H_6, 400 psi (x) LAH, THF, -5° --> 25°C (xi) PDC, CH_2Cl_2 (xii) $NaClO_2$, NaH_2PO_4, H_2O, t-BuOH.

Scheme 105

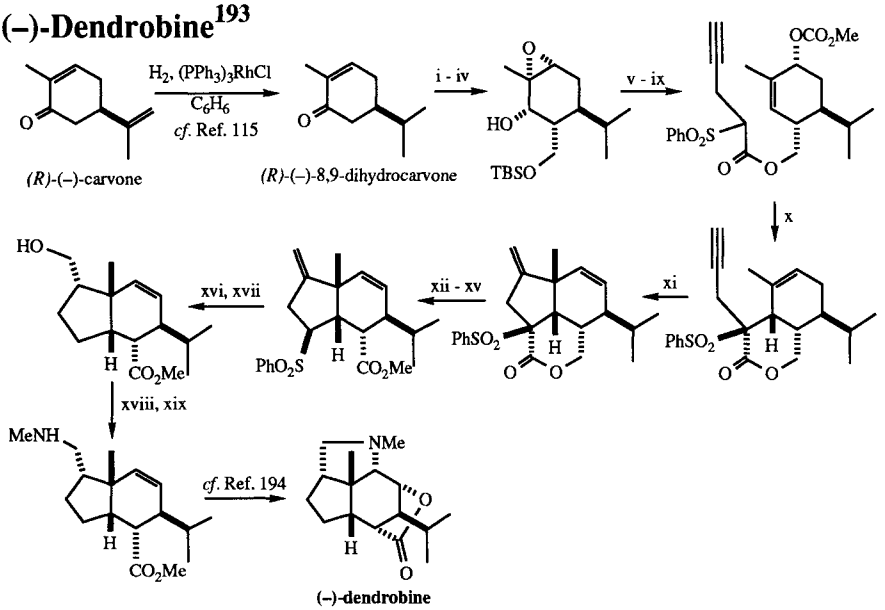
(–)-Patchouli Alcohol[190]



(i) LDA, THF, hexane, 0°C; MeI (ii) LDA, THF, hexane, 0°C; $H_2C{=}CHPPh_3Br$, C_5H_5N, reflux (iii) Li, NH_3, t-BuOH; MeI (iv) $RuCl_3$, $NaIO_4$, MeCN-CCl_4-H_2O

Scheme 106

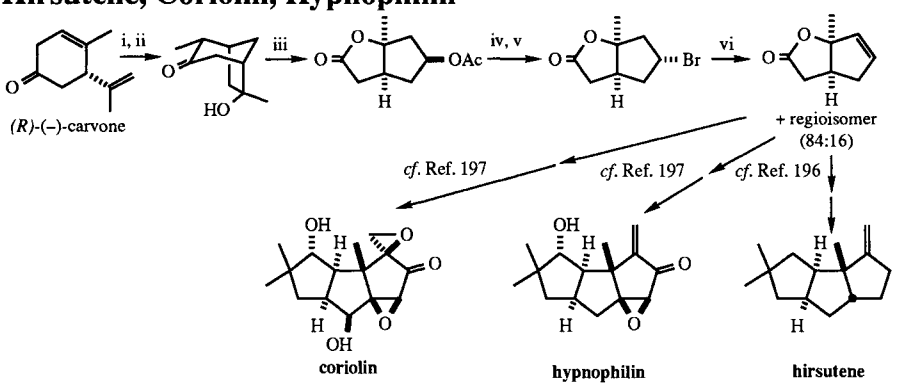
(–)-Dendrobine[193]



(i) H_2O_2, NaOH, MeOH (ii) LDA, THF, CH_2O, -78°C (iii) TBS-Cl, Et_3N, CH_2Cl_2, 0°C (iv) L-Selectride, THF, -78°C (v) MsCl, Et_3N, CH_2Cl_2, 0°C (vi) $NaC_{10}H_8$, THF (vii) BuLi, $ClCO_2Me$, hexane-Et_2O (3:7), 0°C (viii) TBAF, THF (ix) $HC{\equiv}CCH_2CH(SO_2Ph)CO_2H$, DCC, CH_2Cl_2, 0°C (x) $Pd(OAc)_2$, $(i\text{-}PrO)_3P$, THF, reflux (xi) $(dba)_3Pd_2$, $CHCl_3$, Ph_3P, HOAc, C_6H_6 (xii) KOH, EtOH, reflux (xiii) HCl, H_2O, reflux (xiv) Jones oxidation (xv) CH_2N_2, Et_2O (xvi) (thexyl)BH_2•SMe_2, CH_2Cl_2-Et_2O (1:4), 10°C; NaOH, H_2O_2 (xvii) 6% Na(Hg), Na_2HPO_4, MeOH, THF (xviii) MsCl, Et_3N, CH_2Cl_2, 0°C (xix) $MeNH_2$, DMSO.

Scheme 107

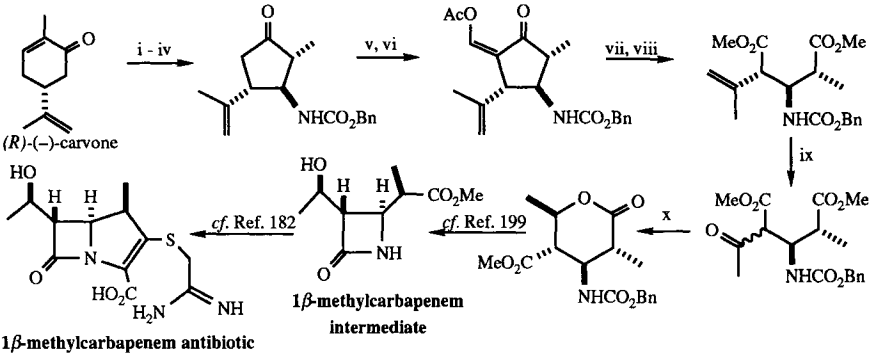
Hirsutene, Coriolin, Hypnophilin[195]



(i) $Hg(OAc)_2$, THF-H_2O (ii) $NaBH_4$, MeOH, 0°C (iii) m-CPBA, CH_2Cl_2, 40°C (iv) K_2CO_3, MeOH-H_2O (v) DEAD Ph_3P, $ZnBr_2$, THF (vi) DBU, toluene, 85°C.

Scheme 108

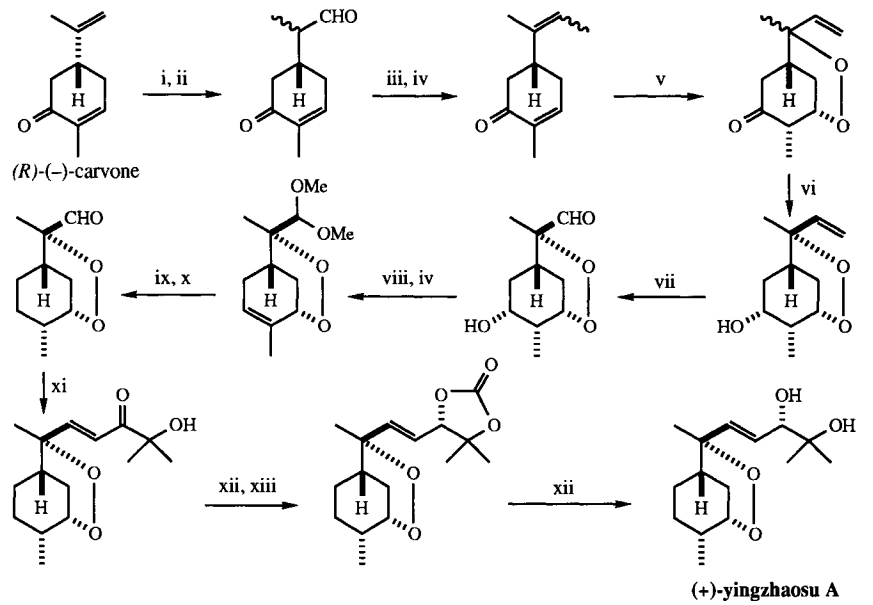
1β-Methylcarbapenem Intermediate[198]



(i) H_2O_2, NaOH, MeOH (ii) KOH, MeOH (iii) Jones oxidation (iv) $(PhO)_2PON_3$, C_6H_6, NEt_3; $PhCH_2OH$, reflux (v) NaOMe, MeOH, HCO_2Et, Et_2O (vi) Ac_2O (vii) 35% H_2O_2, MeOH, K_2CO_3 (viii) MeI, K_2CO_3 (ix) O_3, EtOAc; Ph_3P (x) Et_3SiH, TFA; MeOH.

Scheme 109

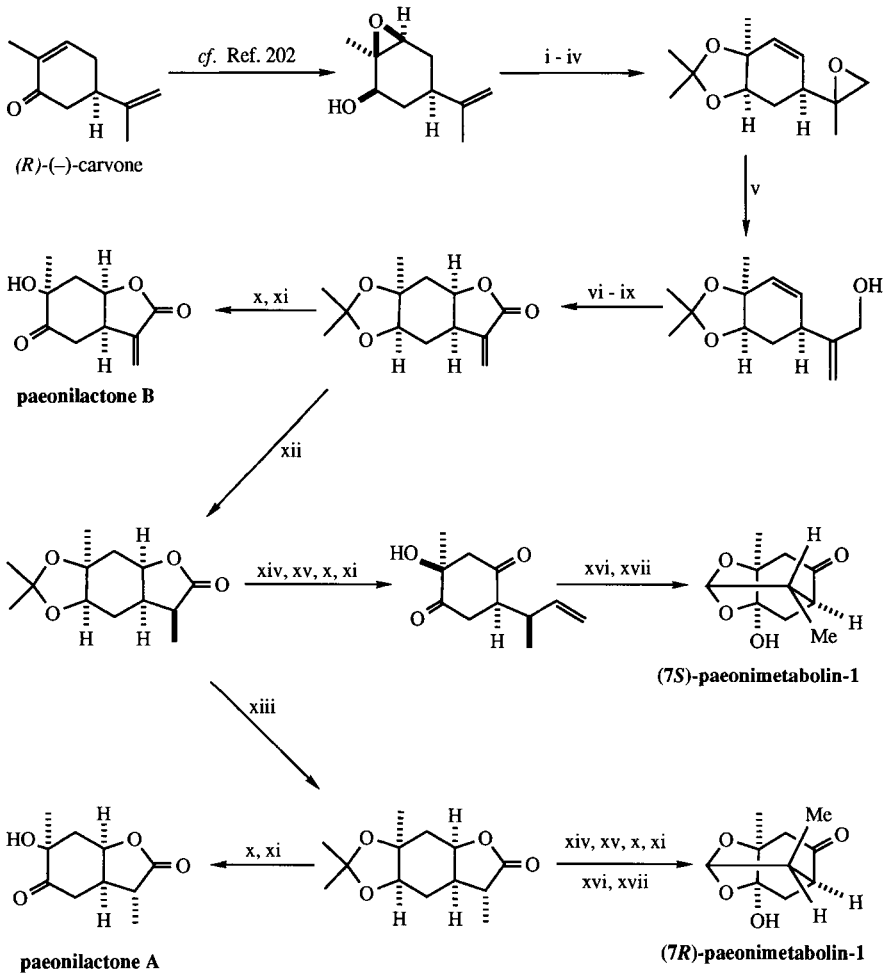
(+)-Yingzhaosu A[200]



(i) m-CPBA, CH_2Cl_2 (ii) $BF_3{\cdot}OEt_2$, C_6H_6 (iii) MeMgBr, Et_2O, -78°C (iv) $POCl_3$, C_5H_5N (v) $^1O_2$, hv, methylene blue, MeCN, p-TsOH (vi) $LiBH_4$, Et_2O; separation (vii) O_3, CH_2Cl_2-MeOH, -78°C; Me_2S (viii) $HC(OMe)_3$, MeOH, p-TsOH (ix) H_2, PtO_2, EtOAc (x) p-TsOH, Me_2CO-H_2O, 55°C (xi) $[Ph_3AsCH_2C(O)C(OH)Me_2]^+Br^-$, K_2CO_3-H_2O, CH_2Cl_2 (xii) $LiBH_4$, Et_2O (xiii) $COCl_2$, C_5H_5N; separation.

Scheme 110

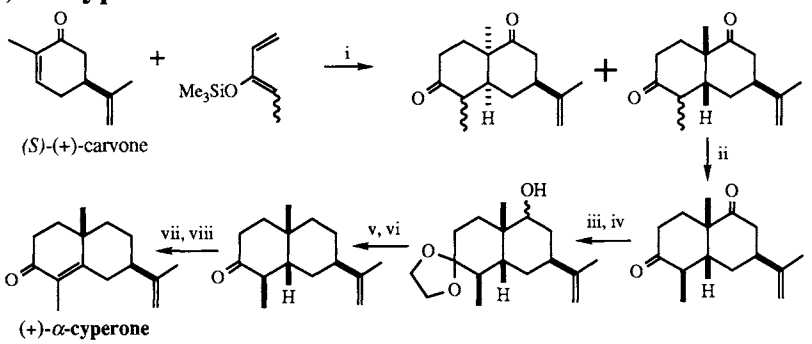
Paeonilactone A, Paeonilactone B, (7*S*)-Paeonimetabolin-1, and (7*R*)-Paeonimetabolin-1[201]



(i) $NaBH_4$, PhSeSePh, EtOH (ii) $(MeO)_2CMe_2$, TsOH, Me_2CO, reflux (iii) m-CPBA, CH_2Cl_2, 0°C (iv) C_5H_5N, C_6H_6, reflux (v) DATMP, C_6H_6, 0°C (vi) MnO_2, CH_2Cl_2 (vii) $NaClO_2$, $NaHPO_4$, 2-methyl-2-butene, t-BuOH-H_2O (4:1) (viii) I_2-KI, $NaHCO_3$ (ix) Bu_3SnH, AIBN, THF, reflux (x) 10% HCl, THF (xi) $C_5H_5N{\cdot}SO_3$, Et_3N, DMSO, CH_2Cl_2 (xii) H_2, 10% Pd-C, EtOH (xiii) NaOMe, MeOH (xiv) DIBAL, CH_2Cl_2, -78°C (xv) $Ph_3P{=}CH_2$, THF, reflux (xvi) O_3, MeOH, -78°C; Me_2S (xvii) TsOH, CH_2Cl_2.

Scheme 111

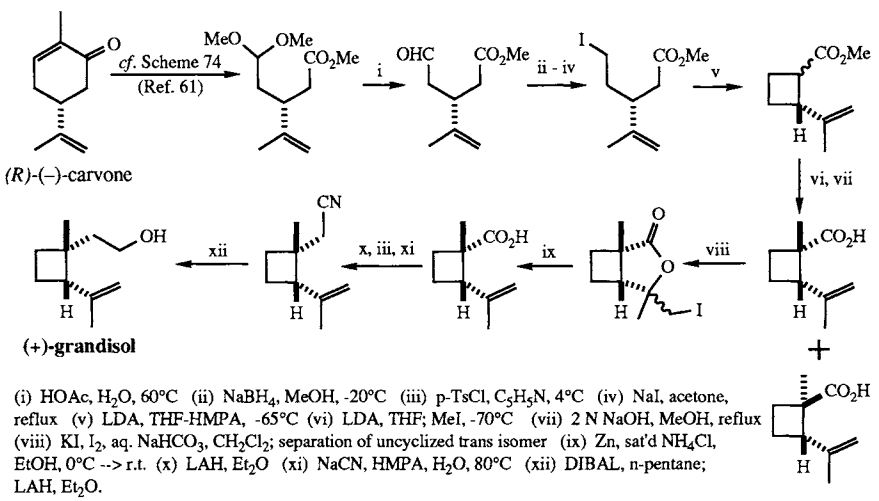
(+)-α-Cyperone[203]



(i) $EtAlCl_2$, toluene; 4 N HCl (ii) 1 M NaOMe, MeOH (iii) MED (methyl ethyl dioxolane), p-TsOH, $(CH_2OH)_2$ (iv) $LiAlH_4$, Et_2O (v) NaH, CS_2, MeI, THF, reflux; Bu_3SnH, AIBN, toluene, reflux (vi) 4 N HCl, Me_2CO, reflux (vii) Et_3N, Me_3SiCl, DMF, 130°C (viii) DDQ, benzene.

Scheme 112

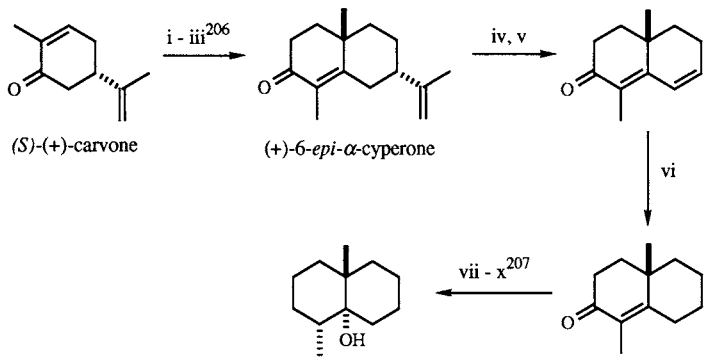
(+)-Grandisol[204]



(i) HOAc, H_2O, 60°C (ii) $NaBH_4$, MeOH, -20°C (iii) p-TsCl, C_5H_5N, 4°C (iv) NaI, acetone, reflux (v) LDA, THF-HMPA, -65°C (vi) LDA, THF; MeI, -70°C (vii) 2 N NaOH, MeOH, reflux (viii) KI, I_2, aq. $NaHCO_3$, CH_2Cl_2; separation of uncyclized trans isomer (ix) Zn, sat'd NH_4Cl, EtOH, 0°C --> r.t. (x) LAH, Et_2O (xi) NaCN, HMPA, H_2O, 80°C (xii) DIBAL, n-pentane; LAH, Et_2O.

Scheme 113

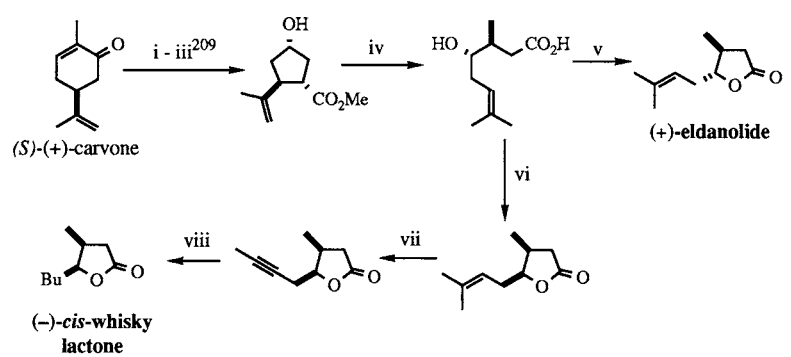
(+)-Geosmin[205]



(i) lithium bronze ($Li{\bullet}4NH_3$) (ii) LDA, THF, 20°C, 24 h; ethyl vinyl ketone, -78 --> 20°C (iii) KOH, MeOH (iv) O_3, CH_2Cl_2-MeOH (1:1), -80°C; Ac_2O, Et_3N, DMAP, 0°C (v) NaOMe, MeOH (vi) $Li(s\text{-}Bu)_3BH$, THF-DMPU, 0°C; NaOH, H_2O_2. (vii) m-CPBA, CH_2Cl_2 (viii) $NaBH_4$, MeOH (ix) p-TsCl, C_5H_5N, $CHCl_3$, 0°C (x) $LiAlH_4$, THF, reflux.

Scheme 114

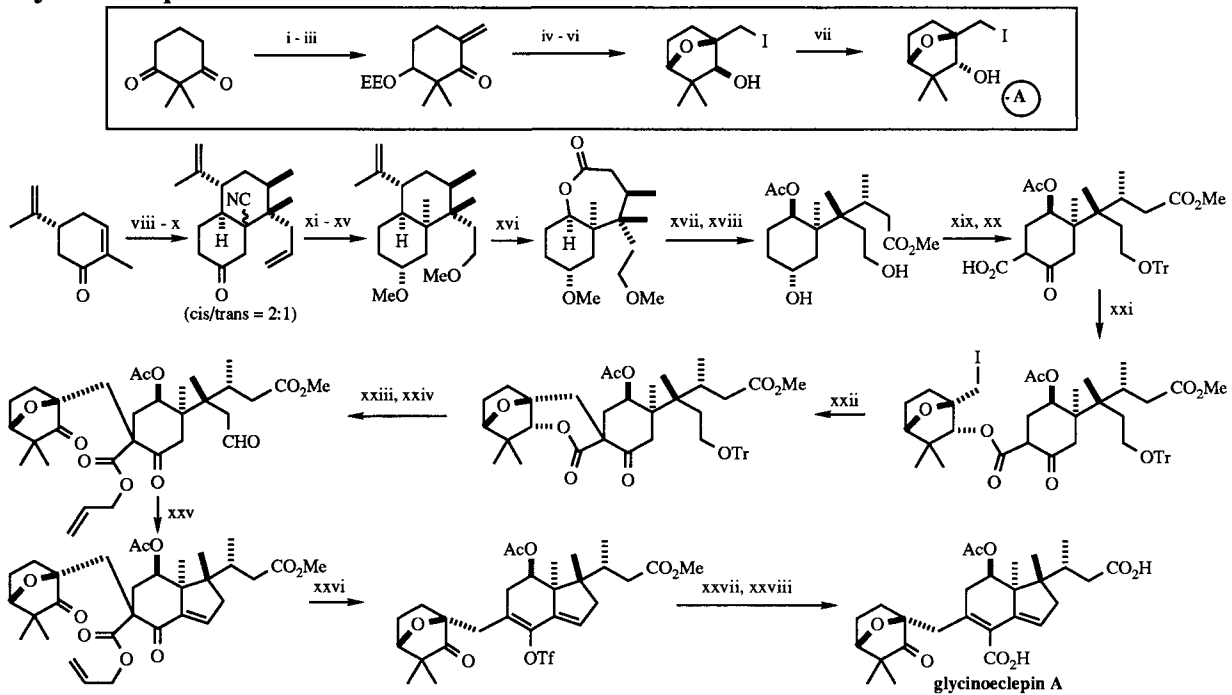
(+)-Eldanolide, (–)-*cis*-Whisky Lactone[208]



(i) NaOH, H_2O_2, MeOH (ii) 28% NaOMe, MeOH; aq. HCl (iii) CH_2N_2, Et_2O (iv) Na, HMPA; H_2O (v) Ph_3P, DEAD, EtOAc, 0°C (vi) C_6H_6, reflux (vii) $NaNO_2$, HOAc-H_2O, 0—>70°C (viii) H_2, Pd-C, EtOAc.

Scheme 115

Glycinoeclepin A[210]



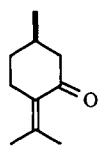
glycinoeclepin A

(i) Baker's yeast, D-glucose, KH_2PO_4, $MgSO_4$, DMF-H_2O (1:38) (ii) $EtOCH{=}CH_2$, PPTS (iii) $HC(OMe)_2NMe_2$, 110°C; DIBAL, THF; sat. NH_4Cl (iv) $NaBH(OMe)_3$ (v) HCl (vi) NIS, CH_3CN (vii) Jones oxidation; $NaBH_4$ (viii) MeLi, CuI, PBu_3, THF, -78°C; allyl bromide, HMPA, -78°C (ix) LDA, $MeCOC(SiMe_3){=}CH_2$, NaOMe (x) HCN, Et_3Al, THF (xi) OsO_4, NMO (xii) $NaIO_4$; $NaBH_4$; NaH, MeI (xiii) DIBAL; $NH_2NH_2{\cdot}H_2O$, $NH_2NH_2{\cdot}2HCl$, triethylene glycol, 120°C (xiv) O_3; Me_2S; CF_3CO_3H (xv) $LiAlH_4$; Jones oxidation (xvi) CF_3CO_3H (xvii) KOH; CH_2N_2; Ac_2O, DMAP, Et_3N (xviii) $AlCl_3$, NaI, MeCN; CH_2N_2 (xix) TrCl, DMAP, Et_3N; PDC, CH_2Cl_2 (xx) bromomagnesium thioureide–CO_2, DMF (xxi) DCC, DMAP, CH_2Cl_2; A (xxii) KF, 18-crown-6, MeCN (xxiii) $CH_2{=}CHCH_2ONa$; Swern oxidation (xxiv) TsOH; Swern oxidation (xxv) t-BuOK, DME, –78°C; 2-$FC_5H_4NMe{\cdot}OTs$, Et_3N, CH_2Cl_2 (xxvi) $Pd(OAc)_2$, PPh_3, HCO_2H, Et_3N, THF; Tf_2NPh, NaH (xxvii) CO, Bu_3N, $Pd(OAc)_2$, 1,1'-bis(diphenylphosphino)ferrocene, DMF, H_2O (xxviii) NaOMe.

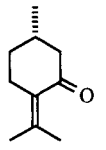
Scheme 116

3. PULEGONE

(R)-(+)-Pulegone is commercially available and its use as an enantiopure starting material in the synthesis of natural products is illustrated in Schemes 118–139. *(S)*-(–)-Pulegone can be obtained by stereospecific synthesis[211] from *(S)*-(–)-citronellol or by

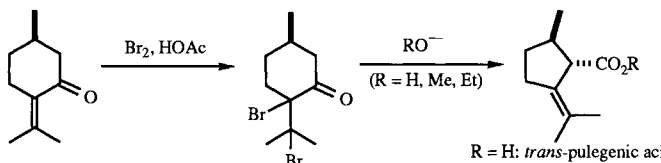


(R)-(+)-pulegone



(S)-(–)-pulegone

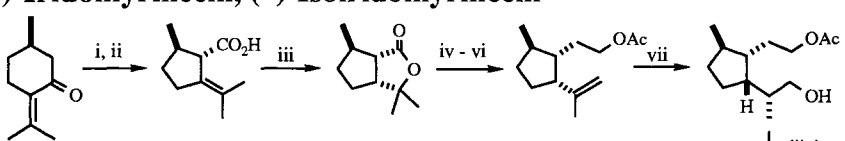
asymmetric synthesis,[212] and also from *(R)*-(+)-pulegone.[213] In many of the syntheses presented below, pulegone is converted initially to pulegone dibromide and then subjected to Favorskii rearrangement conditions to provide *trans*-pulegenic acid[157b,214–216] or the corresponding esters[216–218] (*cf.* Scheme 117). These intermediates are further elaborated into the desired natural products.



(R)-(+)-pulegone — pulegone dibromide

Scheme 117

(–)-Iridomyrmecin, (–)-Isoiridomyrmecin[219]



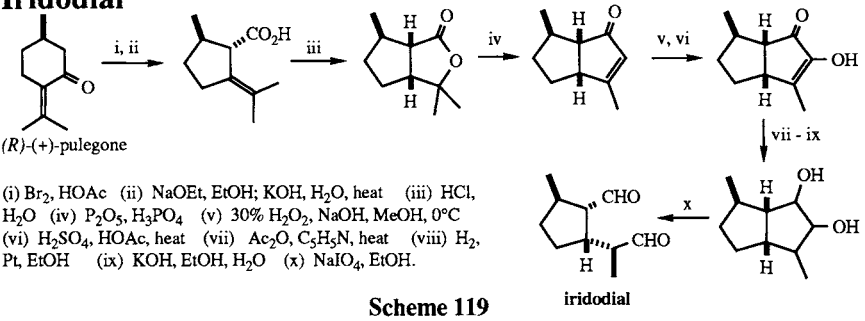
(R)-(+)-pulegone

(i) Br_2, HOAc (ii) NaOEt, EtOH; KOH, H_2O, heat (iii) HCl, H_2O (iv) $LiAlH_4$, Et_2O (v) Ac_2O, C_5H_5N (vi) Ac_2O, heat (vii) 2-methyl-2-butene, B_2H_6, THF; 30% H_2O_2, 3 N NaOH (viii) CrO_3, H_2SO_4, Me_2CO, H_2O (ix) dil. NaOH; aq. HCl (x) NaOMe, MeOH.

(+)-isoiridomyrmecin (***ent*-isoiridomyrmecin**) **(-)-iridomyrmecin** (***ent*-iridomyrmecin**)

Scheme 118

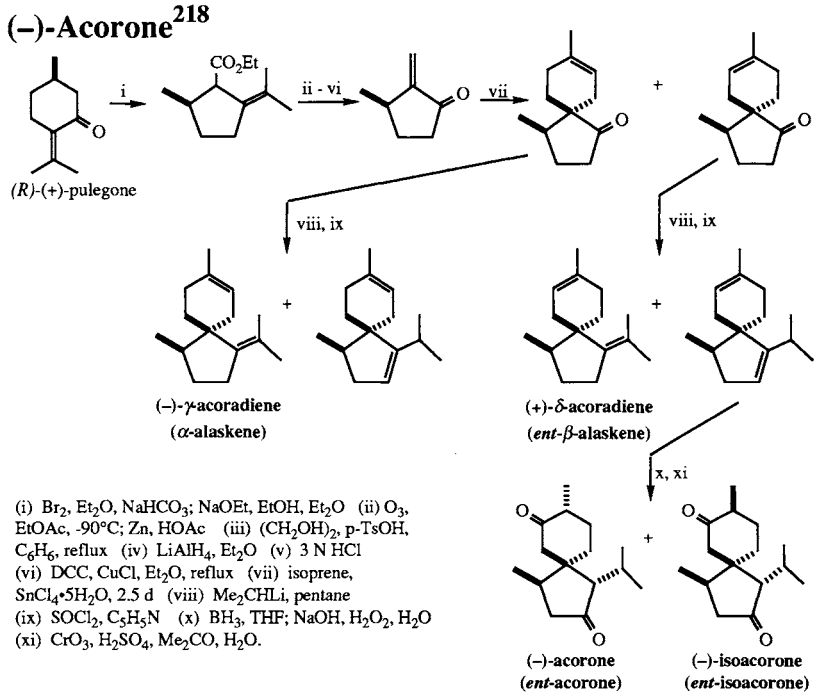
Iridodial[220]



(i) Br_2, HOAc (ii) NaOEt, EtOH; KOH, H_2O, heat (iii) HCl, H_2O (iv) P_2O_5, H_3PO_4 (v) 30% H_2O_2, NaOH, MeOH, 0°C (vi) H_2SO_4, HOAc, heat (vii) Ac_2O, C_5H_5N, heat (viii) H_2, Pt, EtOH (ix) KOH, EtOH, H_2O (x) $NaIO_4$, EtOH.

Scheme 119

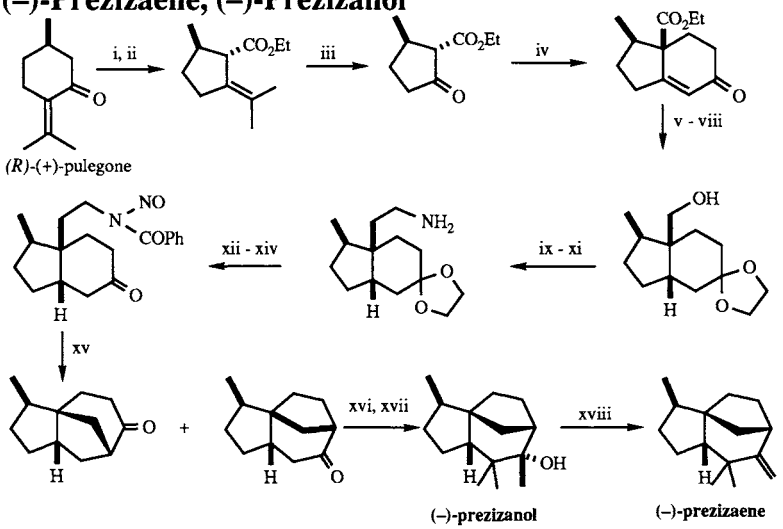
(–)-Acorone[218]



(i) Br_2, Et_2O, $NaHCO_3$; NaOEt, EtOH, Et_2O (ii) O_3, EtOAc, -90°C; Zn, HOAc (iii) $(CH_2OH)_2$, p-TsOH, C_6H_6, reflux (iv) $LiAlH_4$, Et_2O (v) 3 N HCl (vi) DCC, CuCl, Et_2O, reflux (vii) isoprene, $SnCl_4 \cdot 5H_2O$, 2.5 d (viii) Me_2CHLi, pentane (ix) $SOCl_2$, C_5H_5N (x) BH_3, THF; NaOH, H_2O_2, H_2O (xi) CrO_3, H_2SO_4, Me_2CO, H_2O.

Scheme 120

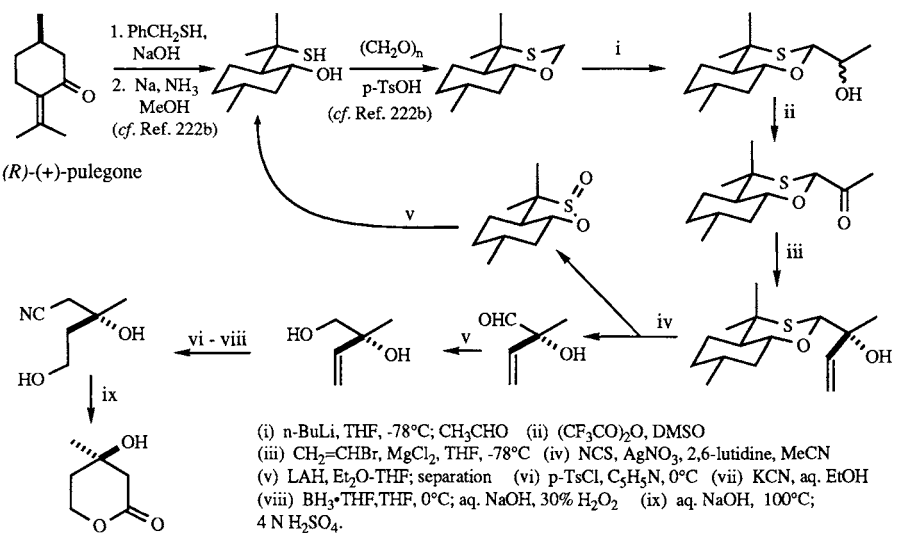
(–)-Prezizaene, (–)-Prezizanol[221]



(i) Br_2, Et_2O, $NaHCO_3$ (ii) NaOEt, EtOH, Et_2O (iii) O_3, EtOAc, -90°C; Zn, HOAc (iv) MVK, Et_3N, toluene (v) pyrrolidine, toluene, reflux; HOAc, H_2O (vi) H_2, Pd-C, EtOH (vii) $(CH_2OH)_2$, TsOH, toluene, reflux (viii) $LiAlH_4$, THF, reflux (ix) MsCl, Et_3N, CH_2Cl_2 (x) NaCN, Et_4NCl, Me_2SO, 90°C (xi) $LiAlH_4$, Et_2O (xii) PhCOCl, C_5H_5N, toluene, 70°C (xiii) HCl, Me_2CO, reflux (xiv) N_2O_4, NaOAc, CH_2Cl_2, -30°C (xv) *t*-BuOK, *t*-AmOH (xvi) KH, MeI, THF, reflux (xvii) MeLi, Et_2O (xviii) MsCl, Et_3N, CH_2Cl_2.

Scheme 121

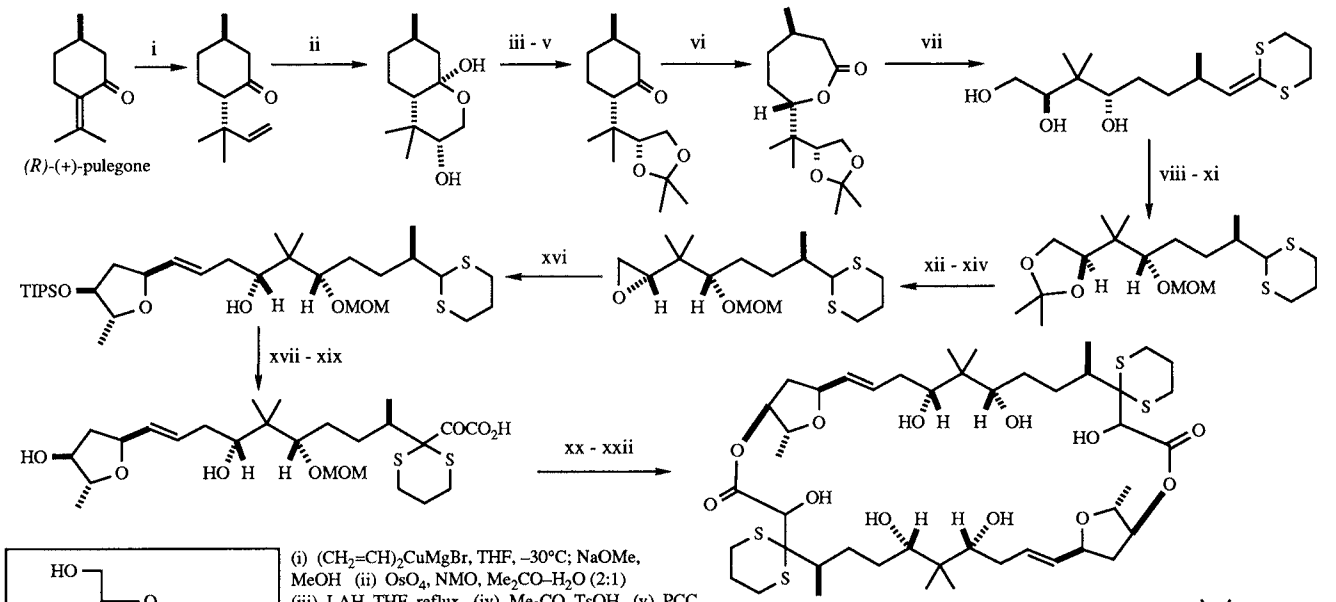
(R)-(–)-Mevalolactone[222]

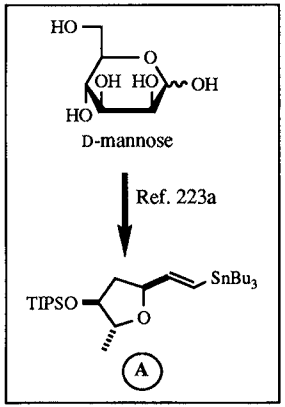


(i) n-BuLi, THF, -78°C; CH_3CHO (ii) $(CF_3CO)_2O$, DMSO
(iii) CH_2=CHBr, $MgCl_2$, THF, -78°C (iv) NCS, $AgNO_3$, 2,6-lutidine, MeCN
(v) LAH, Et_2O-THF; separation (vi) p-TsCl, C_5H_5N, 0°C (vii) KCN, aq. EtOH
(viii) BH_3•THF,THF, 0°C; aq. NaOH, 30% H_2O_2 (ix) aq. NaOH, 100°C;
4 N H_2SO_4.

Scheme 122

Aplasmomycin[223]

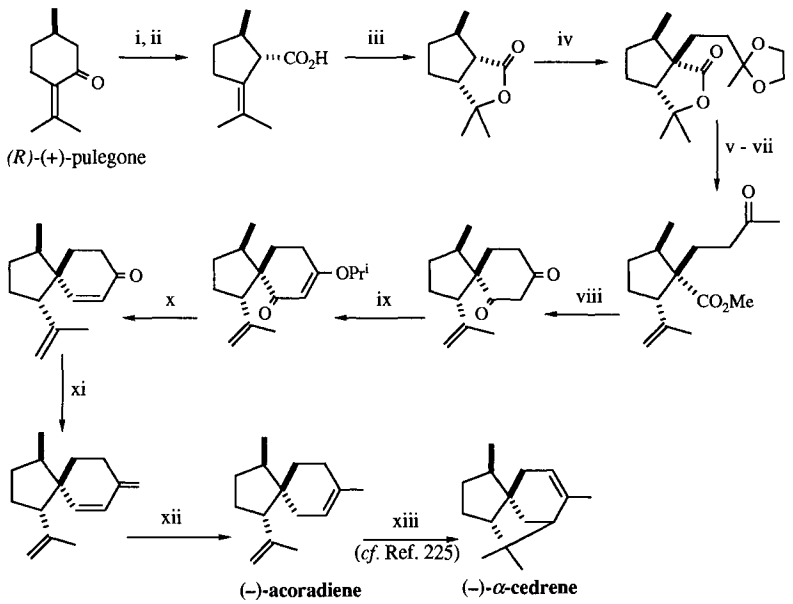




(i) $(CH_2{=}CH)_2CuMgBr$, THF, –30°C; NaOMe, MeOH (ii) OsO_4, NMO, Me_2CO–H_2O (2:1) (iii) LAH, THF, reflux (iv) Me_2CO, TsOH (v) PCC, CH_2Cl_2, 3Å molecular sieves (vi) m-CPBA, C_6H_6 (vii) Me_3Al, $HS(CH_2)_3SH$, CH_2Cl_2 (viii) O_3, MeOH, –78°C; Me_2S (ix) $HS(CH_2)_3SH$, $BF_3{\cdot}Et_2O$, CH_2Cl_2 (x) $Me_2C(OMe)_2$, TsOH, (xi) $ClCH_2OMe$, Et_3N, DMAP, DMF, 60°C (xii) HOAc–H_2O (3:1), 50°C (xiii) PhCOCN, Et_3N, MeCN, –10°C (xiv) MsCl, Et_3N, Et_2O, 0°C (xv) Bu_4NOH, Et_2O, MeOH (xvi) BuLi, THF, –78°C; A, CuCN (xvii) BuLi, $H_2N(CH_2)_4NH_2$, THF, –30°C; $(CO_2Me)_2$, HMPA, –78—>0°C (xviii) LiI, 2,6-lutidine, DMF, 75°C, 18 h (xix) TBAF, THF (xx) BOP-Cl, Et_3N, CH_2Cl_2 (xxi) $NaBH_4$, MeOH, –20°C (xxii) $(i\text{-}PrS)_2BBr$, CH_2Cl_2, –78°C (xxiii) $HgCl_2$, $CaCO_3$, MeCN-H_2O (4:1) (xxiv) $B(OMe)_3$.

Scheme 123

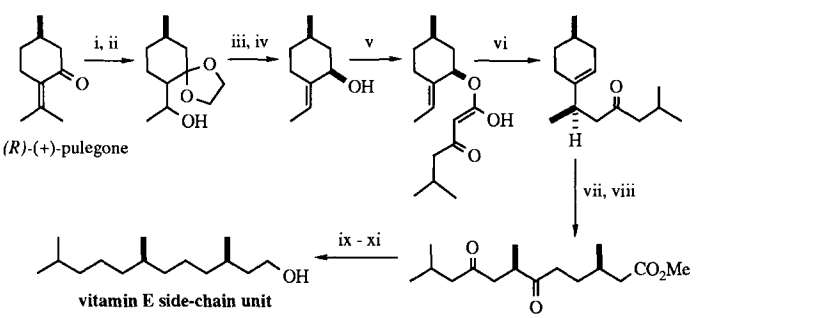
(–)-Acoradiene, (–)-α-Cedrene[224]



(i) Br_2, HOAc (ii) NaOEt, EtOH; KOH, H_2O, heat (iii) HCl, H_2O, heat (iv) LDA, THF, -78°C; 1-iodo-3,3-ethylenedioxybutane (v) t-BuOK, DMF (vi) MeI, DBU, C_6H_6 (vii) TsOH, Me_2CO, reflux (viii) t-BuOK, DMF (ix) Me_2CHN_2, Et_2O (x) $LiAlH_4$, Et_2O; H_2SO_4, H_2O (xi) $MePPh_3Br$, DMSO , $MeSOCH_2Na$ (xii) Na, NH_3, Et_2O (xiii) HCl, EtOH.

Scheme 124

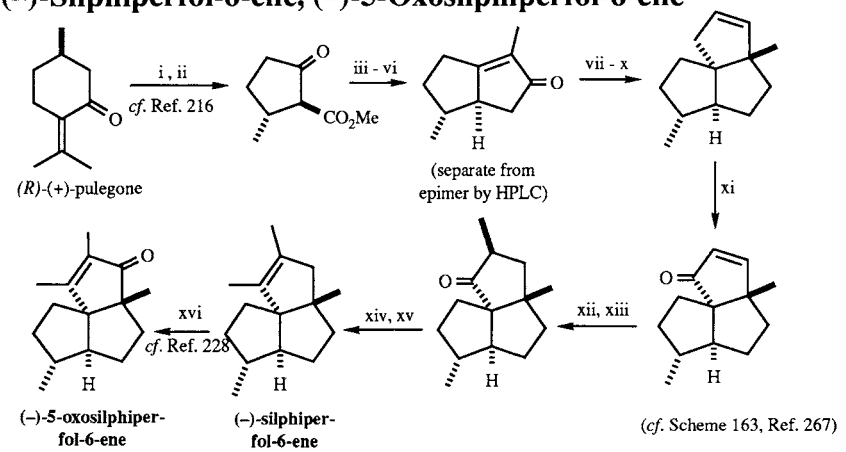
Vitamin E Side-Chain Unit[226]



(i) $(CH_2OH)_2$, $HC(OEt)_3$, TsOH, 55°C (ii) O_3, MeOH, -78°C; $NaBH_4$ (iii) PPTS, Me_2CO, H_2O, reflux (iv) $NaBH_4$, $CeCl_3$, MeOH (v) 5-isovaleryl Meldrum's acid, C_6H_6, 55°C (vi) 220°C, 2 h (vii) O_3, Me_2CO, -78°C (viii) CH_2N_2, Et_2O, 0°C (ix) $NaBH_4$, MeOH (x) MsCl, C_5H_5N (xi) $LiAlH_4$, Et_2O, 0°C.

Scheme 125

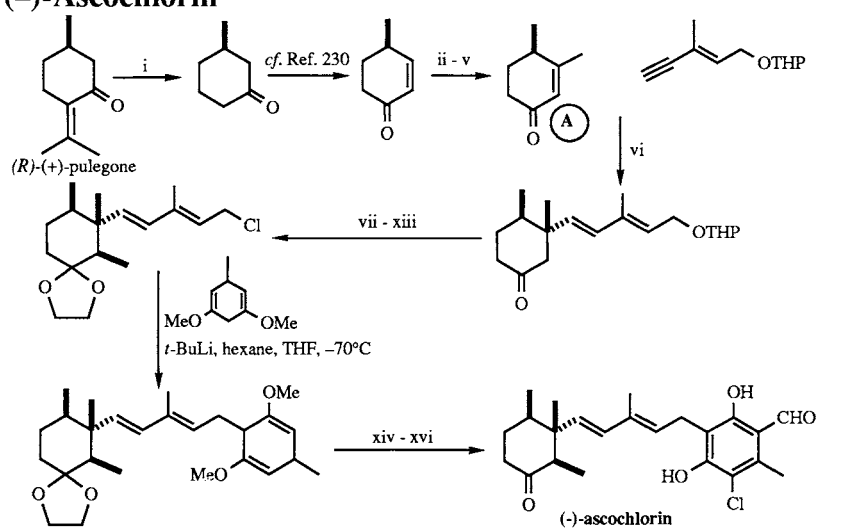
(–)-Silphiperfol-6-ene, (–)-5-Oxosilphiperfol-6-ene[227]



(i) Br_2, Et_2O; NaOMe, MeOH, Et_2O (ii) O_3, EtOAc, -90°C; Zn, HOAc (iii) NaH, KH (cat.), $CH_3CH_2C(=CH_2)CH_2OTs$, toluene, reflux (iv) O_3, MeOH, -78°C; Me_2S (v) NaH, toluene, reflux (vi) $LiI \cdot 3H_2O$, DMF, reflux (vii) 2-(2-bromoethyl)-1,3-dioxane, Mg, THF; $CuBr \cdot Me_2S$, THF, -78—>0°C (viii) HCl, H_2O, THF (ix) Ph_3PBr_2; DBU (x) K_2CO_3, $NH_2NH_2 \cdot H_2O$, $(CH_2OH)_2$, 130-200°C (xi) Na_2CrO_4, HOAc, NaOAc (xii) H_2, Pd-C, EtOH (xiii) KH, THF; Et_3B; MeI; H_2O_2, NaOH, H_2O (xiv) MeLi, Et_2O, -78°C (xv) $POCl_3$, C_5H_5N (xvi) PCC; *cf.* ref. 19.

Scheme 126

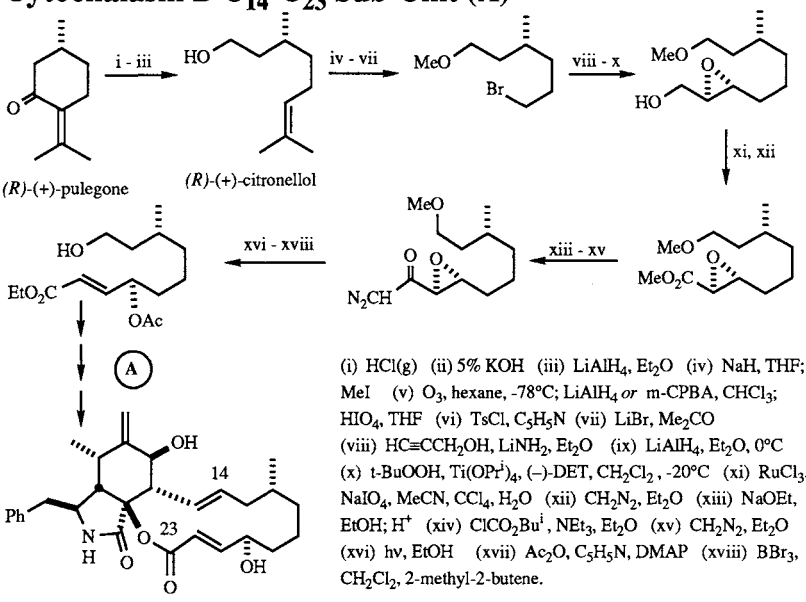
(–)-Ascochlorin[229]



(i) HCl, H_2O, reflux (ii) Me_2CuLi, Et_2O, -40°C (iii) $(PhSe)_2$, Br_2, THF (iv) O_3, CH_2Cl_2, -70°C (v) Et_2NH, CCl_4 (vi) Bu_3SnH, AIBN; BuLi; $PrC{\equiv}CCu$, $(Me_2N)_3P$; **A**, Et_2O (ii) NaH, HCO_2Et, C_6H_6, 10°C (viii) LDA, THF, -70°C; MeI, HMPA , -20°C; 2% NaOH, reflux (ix) HOAc, THF, H_2O, 40°C, 24 h (x) Ac_2O, C_5H_5N (xi) TsCl, 2-methoxy-1,3-dioxolane, C_6H_6, MeOH, 4 d (xii) K_2CO_3, MeOH, H_2O (xiii) BuLi, HMPA, Et_2O; TsCl, Et_2O, 0°C; LiCl, HMPA, 0°C (xiv) NCS, DMF, $CaCO_3$, H_2O (xv) DBU, THF, reflux (xvii) EtMgBr, Et_2O; $HC(OEt)_3$; H^+, H_2O.

Scheme 127

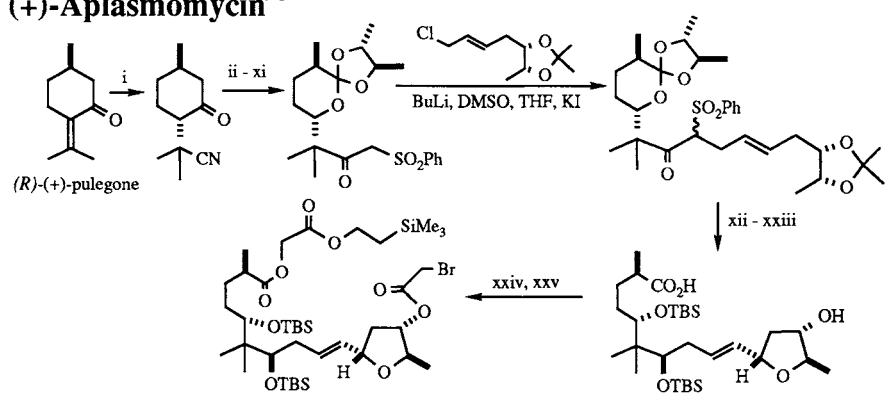
Cytochalasin B C_{14}-C_{23} Sub-Unit (A)[231]



(i) HCl(g) (ii) 5% KOH (iii) $LiAlH_4$, Et_2O (iv) NaH, THF; MeI (v) O_3, hexane, -78°C; $LiAlH_4$ *or* m-CPBA, $CHCl_3$; HIO_4, THF (vi) TsCl, C_5H_5N (vii) LiBr, Me_2CO (viii) $HC{\equiv}CCH_2OH$, $LiNH_2$, Et_2O (ix) $LiAlH_4$, Et_2O, 0°C (x) t-BuOOH, $Ti(OPr^i)_4$, (-)-DET, CH_2Cl_2, -20°C (xi) $RuCl_3$, $NaIO_4$, MeCN, CCl_4, H_2O (xii) CH_2N_2, Et_2O (xiii) NaOEt, EtOH; H^+ (xiv) $ClCO_2Bu^i$, NEt_3, Et_2O (xv) CH_2N_2, Et_2O (xvi) hv, EtOH (xvii) Ac_2O, C_5H_5N, DMAP (xviii) BBr_3, CH_2Cl_2, 2-methyl-2-butene.

Scheme 128

(+)-Aplasmomycin[231]

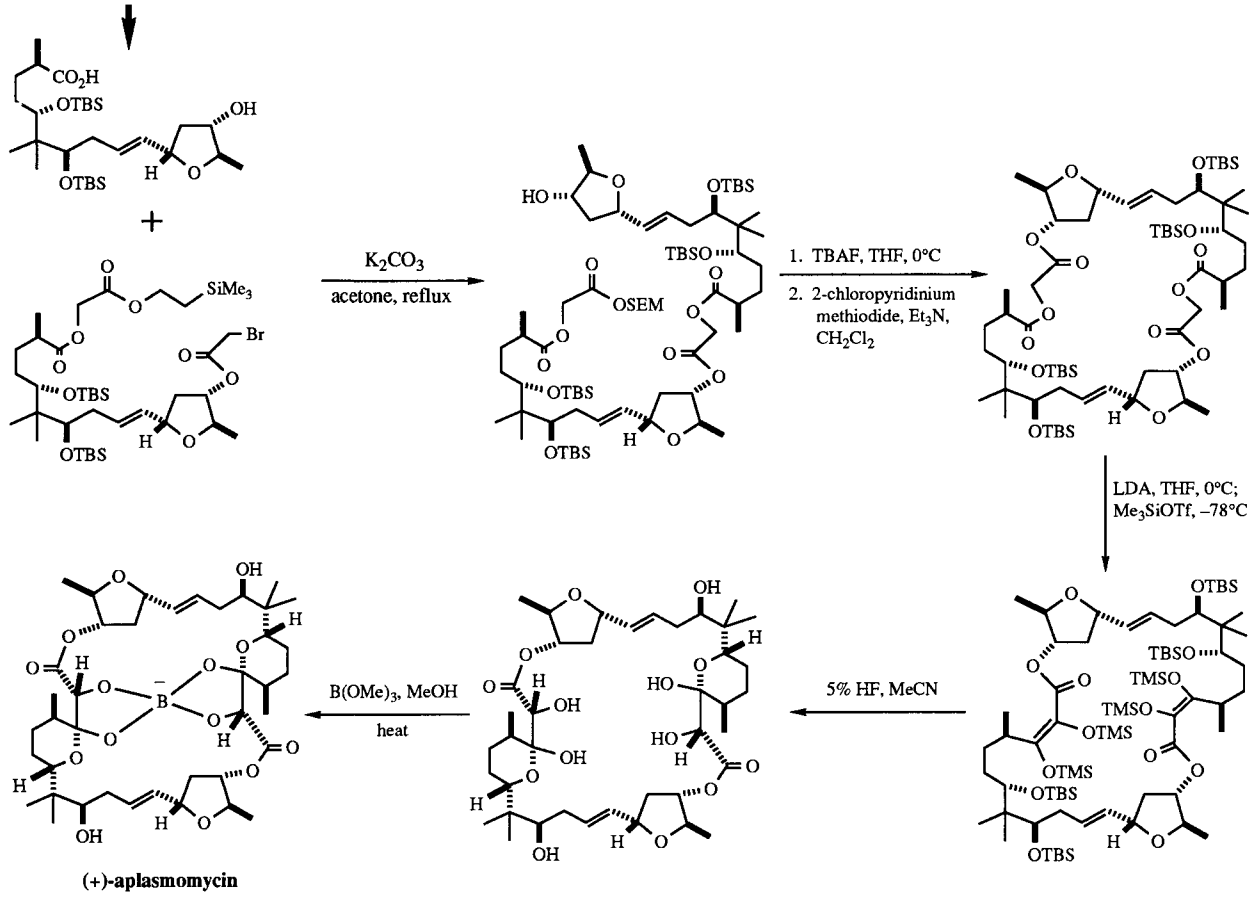


(continued on Scheme 129b)

(i) NaCN, NH_4Cl (ii) MeOH, H_2SO_4 (iii) CF_3CO_2H, CH_2Cl_2 (iv) PhMgBr, THF, 0°C (v) PPTS, C_6H_6, reflux (vi) Ac_2O, C_5H_5N, DMAP, CH_2Cl_2 (vii) $RuCl_3$, $NaIO_4$, MeCN, CCl_4, H_2O (viii) K_2CO_3, MeOH, reflux (ix) 1 N HCl, $CHCl_3$ (x) (2*R*,3*R*)-2,3-butanediol, p-TsOH (xi) $PhSO_2Me$, n-BuLi (2 equiv) (xii) Al(Hg), THF-H_2O (10:1) (xiii) $LiAlH_4$, Et_2O, -110°C (xiv) Ac_2O, DMAP (xv) TsOH, THF, H_2O (xvi) NaOH, H_2O (xvii) 5% HCl, THF (xviii) PhSeCl, CCl_4, 70°C (xix) 30% H_2O_2 (xx) *t*-$BuMe_2Si$-OTf, CH_2Cl_2, -20°C (xxi) NaOH, MeOH, H_2O (xxii) K_2CO_3, MeOH, THF, H_2O (xxiii) TBAF, THF (xxiv) $BrCH_2CO_2(CH_2)_2SiMe_3$, K_2CO_3, Me_2CO, reflux (xxv) $BrCH_2COCl$, DMAP, C_5H_5N, 0°C.

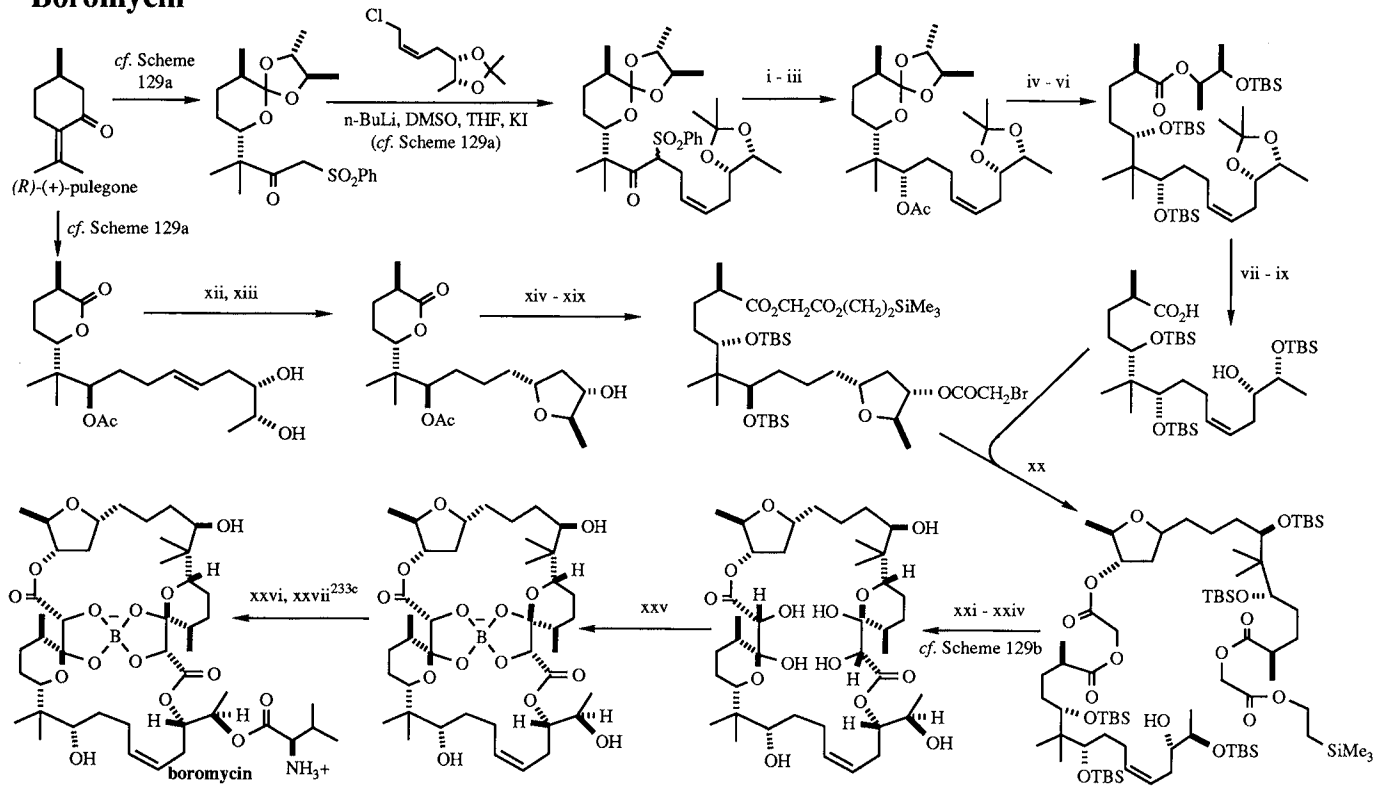
Scheme 129a

(continued from Scheme 129a)



Scheme 129b

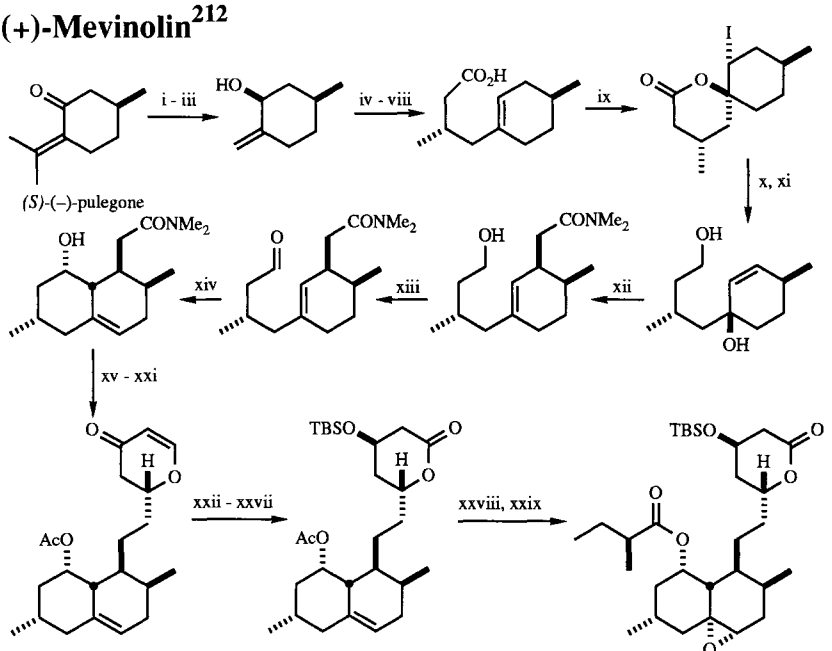
Boromycin[233]



(i) Al (Hg), THF-H_2O (10:1) (ii) L-Selectride, THF, 0°C (iii) Ac_2O, DMAP, C_5H_5N, CH_2Cl_2 (iv) $LiAlH_4$, THF, 0°C (v) p-TsOH, THF, H_2O (vi) TBDMSOTf, 2,6-lutidine, CH_2Cl_2 (vii) NaOH, MeOH, THF (viii) CH_2N_2, Et_2O (ix) PPTS, MeOH, reflux (x) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, –78°C (xi) NaOH, MeOH, THF, reflux (xii) NBS, Et_2O, MeCN, –110°C (xiii) Bu_3SnH, AIBN, C_6H_6, reflux (xiv) NaOH, MeOH (xv) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C (xvi) TsOH, hexane, EtOAc (xvii) TBAF, THF (selective desilylation) (xviii) $BrCH_2CO_2CH_2CH_2SiMe_3$, K_2CO_3, Me_2CO, reflux (xix) $BrCH_2COBr$, DMAP, C_5H_5N, 0°C (xx) K_2CO_3, Me_2CO, reflux (xxi) TBAF, THF, –23—>0°C (xxii) 2-chloropyridinium methiodide, DMAP, MeCN (xxiii) $LiN(SiMe_3)_2$, THF, 0°C; Me_3SiOTf, 0°C (xxiv) TBAF, THF; 1 N HCl (xxv) $B(OMe)_3$, MeOH, reflux (xxvi) BOC-D-valine, DCC, DMAP, CH_2Cl_2 (xxvii) CF_3CO_2H, CH_2Cl_2.

Scheme 130

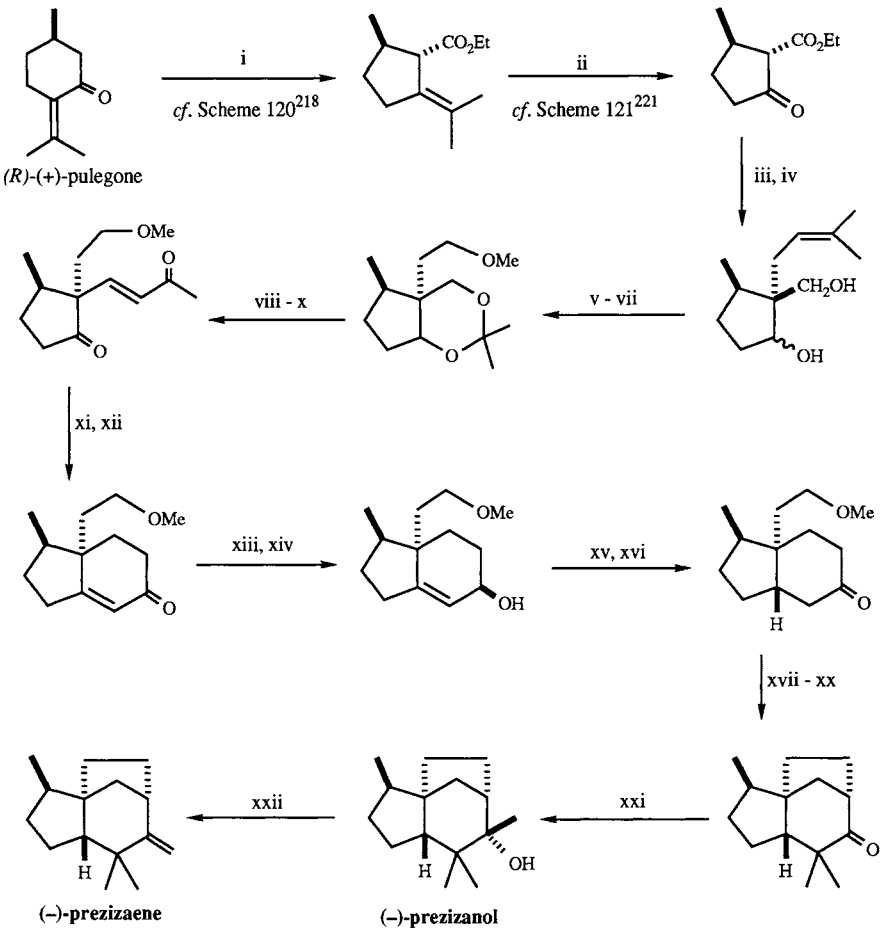
(+)-Mevinolin[212]



(i) $NaBH_4$, $CeCl_3$, MeOH (ii) O_3, CH_2Cl_2-MeOH, -78°C; Me_2S
(iii) $Ph_3P{=}CH_2$, THF (iv) $CH_3CH_2C(OEt)_3$, toluene, 90°C
(v) ester reduction (vi) p-TsCl, C_5H_5N (vii) NaCN (viii) nitrile hydrolysis (ix) I_2, $NaHCO_3$, aq. MeCN (x) DBU, toluene, 105°C
(xi) $LiAlH_4$ (xii) $HC(OMe)_2NMe_2$, xylenes, 130°C (xiii) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; Et_3N (xiv) Me_2AlCl, CH_2Cl_2, –20°C
(xv) imidazolyltrimethylsilane (xvi) $LiEt_3BH$, THF; NaOH, H_2O_2
(xvii) $(COCl)_2$, DMSO, CH_2Cl_2, -78°C; Et_3N (xviii) $Ph_3P{=}CHOMe$, THF; Bu_4NF (xix) Ac_2O, C_5H_5N (xx) H_2O, HOAc, THF
(xxi) $TiCl_4$, CH_2Cl_2, -78°C; 1-methoxy-3-trimethylsilyloxy-1,3-butadiene, -40°C (xxii) MeOH, Et_3N (xxiii) $Li(s\text{-}Bu)_3BH$, THF, -78°C
(xxiv) DIBAL, THF (xxv) HOAc, H_2O (xxvi) Ag_2CO_3, Celite
(xxvii) TBS-Cl (xxviii) $VO(acac)_2$, t-BuOOH (xxix) (*S*)-2-methyl-butanoic anhydride, C_5H_5N (xxx) TMS-OTf, toluene, 2,6-lutidine, -55°C (xxxi) Bu_4NF, THF (xxxii) $MeO_2CNSO_2NEt_3$, C_6H_6
(xxxiii) Bu_4NF, THF, HOAc.

Scheme 131

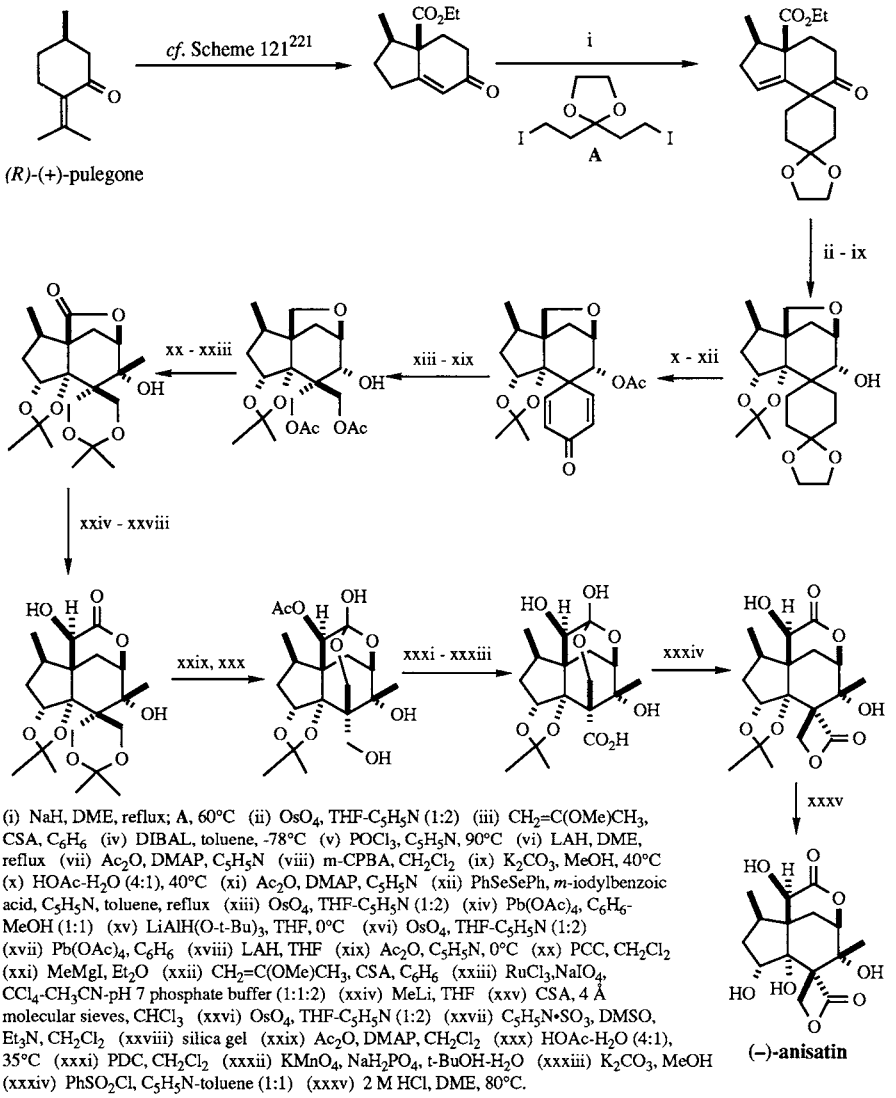
(–)-Prezizanol, (–)-Prezizaene[234]



(i) Br_2, Et_2O; NaOEt, EtOH, Et_2O (ii) O_3, EtOAc, -90°C; Zn, HOAc (iii) NaH, $Me_2CH{=}CH_2Br$, THF (iv) $LiAlH_4$, Et_2O (v) $CH_3C(OMe)_2CH_3$, TsOH (vi) O_3, MeOH; $NaBH_4$ (vii) NaH, THF, MeI (viii) 70% HOAc (ix) $(COCl)_2$, DMSO, NEt_3 (x) $Ph_3P{=}CHCOCH_2CH_3$, C_6H_6, reflux (xi) H_2, 10% Pd-C (xii) 2% KOH, MeOH, reflux (xiii) $NaBH_4$, MeOH (xiv) Ph_3P, DEAD, $PhCO_2H$, C_6H_6; K_2CO_3, MeOH (xv) [Rh(NBD)(DIPHOS-4)]ClO_4, H_2, 55 atm (xvi) Jones oxidation (xvii) BBr_3, NaI, 15-crown-5, CH_2Cl_2 (xviii) TsCl, C_5H_5N (xix) t-BuOK, THF (xx) KH, THF, MeI (xxi) MeLi, Et_2O (xxii) MsCl, Et_3N, CH_2Cl_2.

Scheme 132

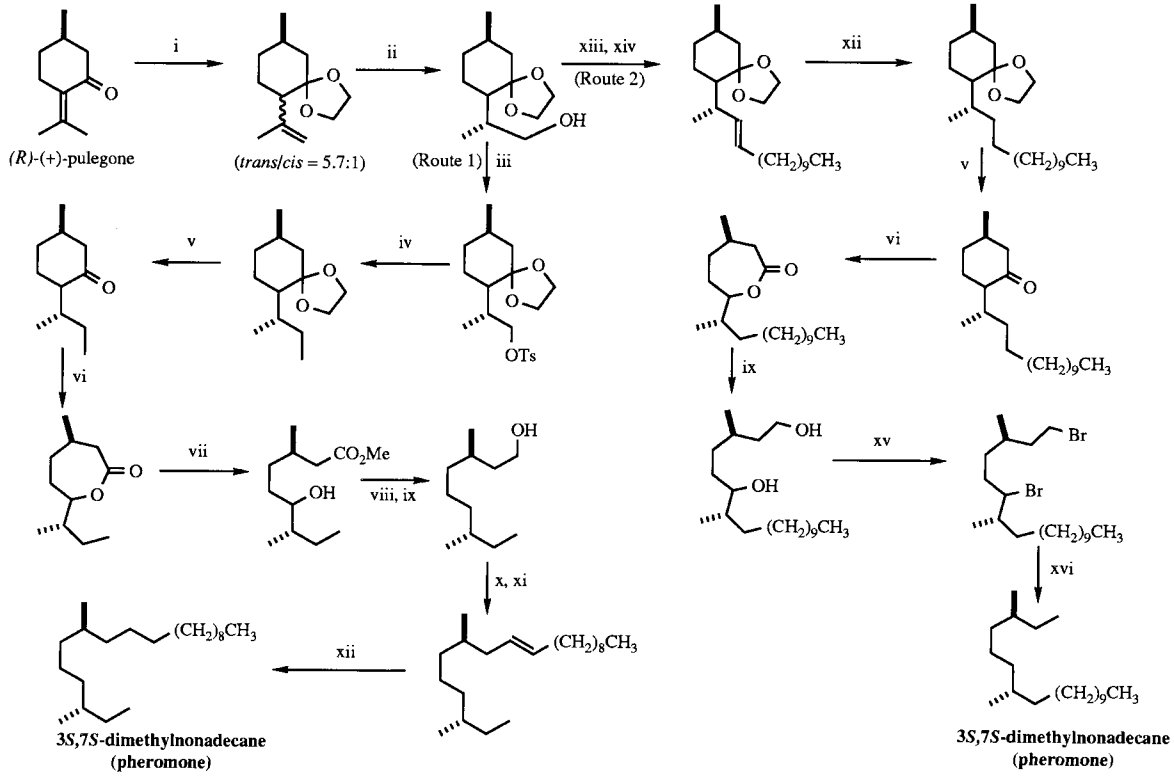
(–)-Anisatin[235]



(i) NaH, DME, reflux; **A**, 60°C (ii) OsO_4, THF-C_5H_5N (1:2) (iii) CH_2=C(OMe)CH_3, CSA, C_6H_6 (iv) DIBAL, toluene, -78°C (v) $POCl_3$, C_5H_5N, 90°C (vi) LAH, DME, reflux (vii) Ac_2O, DMAP, C_5H_5N (viii) m-CPBA, CH_2Cl_2 (ix) K_2CO_3, MeOH, 40°C (x) HOAc-H_2O (4:1), 40°C (xi) Ac_2O, DMAP, C_5H_5N (xii) PhSeSePh, *m*-iodylbenzoic acid, C_5H_5N, toluene, reflux (xiii) OsO_4, THF-C_5H_5N (1:2) (xiv) $Pb(OAc)_4$, C_6H_6-MeOH (1:1) (xv) LiAlH(O-t-Bu)$_3$, THF, 0°C (xvi) OsO_4, THF-C_5H_5N (1:2) (xvii) $Pb(OAc)_4$, C_6H_6 (xviii) LAH, THF (xix) Ac_2O, C_5H_5N, 0°C (xx) PCC, CH_2Cl_2 (xxi) MeMgI, Et_2O (xxii) CH_2=C(OMe)CH_3, CSA, C_6H_6 (xxiii) $RuCl_3$,$NaIO_4$, CCl_4-CH_3CN-pH 7 phosphate buffer (1:1:2) (xxiv) MeLi, THF (xxv) CSA, 4 Å molecular sieves, $CHCl_3$ (xxvi) OsO_4, THF-C_5H_5N (1:2) (xxvii) C_5H_5N•SO_3, DMSO, Et_3N, CH_2Cl_2 (xxviii) silica gel (xxix) Ac_2O, DMAP, CH_2Cl_2 (xxx) HOAc-H_2O (4:1), 35°C (xxxi) PDC, CH_2Cl_2 (xxxii) $KMnO_4$, NaH_2PO_4, t-BuOH-H_2O (xxxiii) K_2CO_3, MeOH (xxxiv) $PhSO_2Cl$, C_5H_5N-toluene (1:1) (xxxv) 2 M HCl, DME, 80°C.

Scheme 133

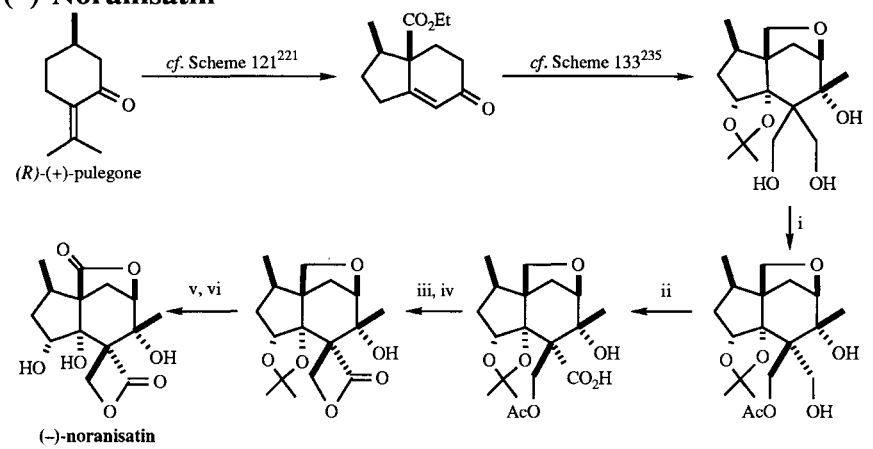
Sex Pheromone of the Alfalfa Blotch Leafminer (*Agromyza frontella* (Rondani))[236]



(i) $(CH_2OH)_2$, p-TsOH, C_6H_6, reflux (ii) BH_3•THF, THF; NaOH, H_2O_2 (iii) TsCl, C_5H_5N, 0°C (iv) Me_2CuLi, Et_2O, 0°C (v) HCl, acetone, reflux (vi) m-CPBA, CH_2Cl_2, $NaHCO_3$ (vii) H_2SO_4, MeOH (viii) TsCl, C_5H_5N, 0°C (ix) $LiAlH_4$, Et_2O (x) PCC, CH_2Cl_2 (xi) $CH_3(CH_2)_9PPh_3Br$, n-BuLi, THF, –78°C (xii) H_2, Pd-C, hexane, 35 psi (xiii) PCC, NaOAc, CH_2Cl_2 (xiv) $CH_3(CH_2)_{10}PPh_3Br$, n-BuLi, THF, –78°C (xv) Br_2, PPh_3 (xvi) $LiAlH_4$, THF, reflux.

Scheme 134

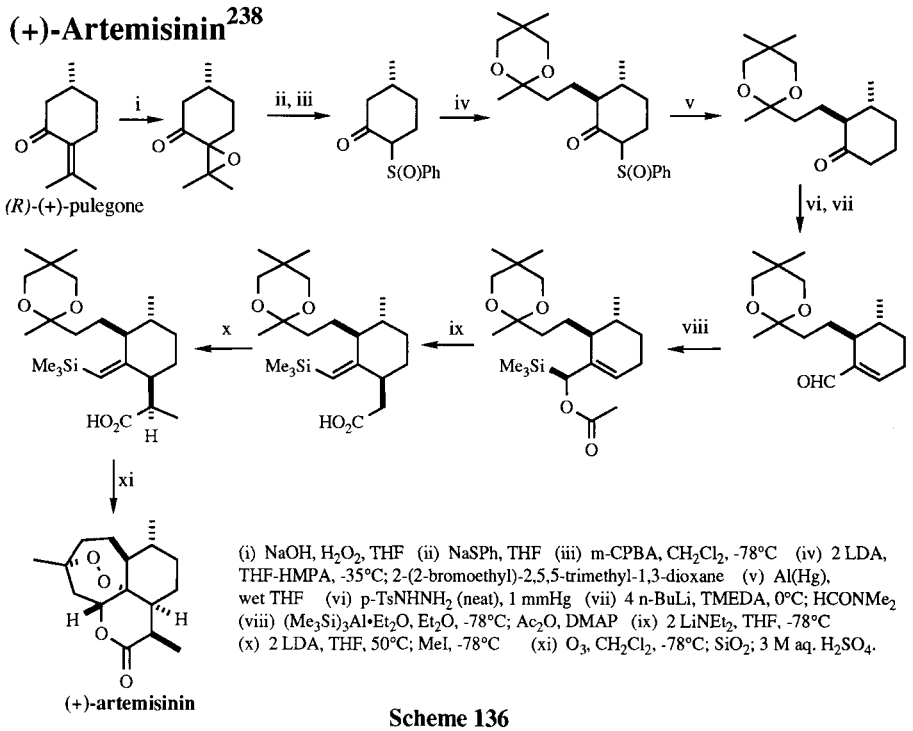
(–)-Noranisatin[237]



(i) Bu_2SnO, toluene, 4 Å molecular sieves, reflux; Ac_2O (ii) $RuCl_3$, $NaIO_4$, CCl_4-MeCN (iii) 1 M NaOH (iv) $PhSO_2Cl$, C_5H_5N, 0°C (v) $RuCl_3$, $NaIO_4$, CCl_4-MeCN (vi) 2 M HCl.

Scheme 135

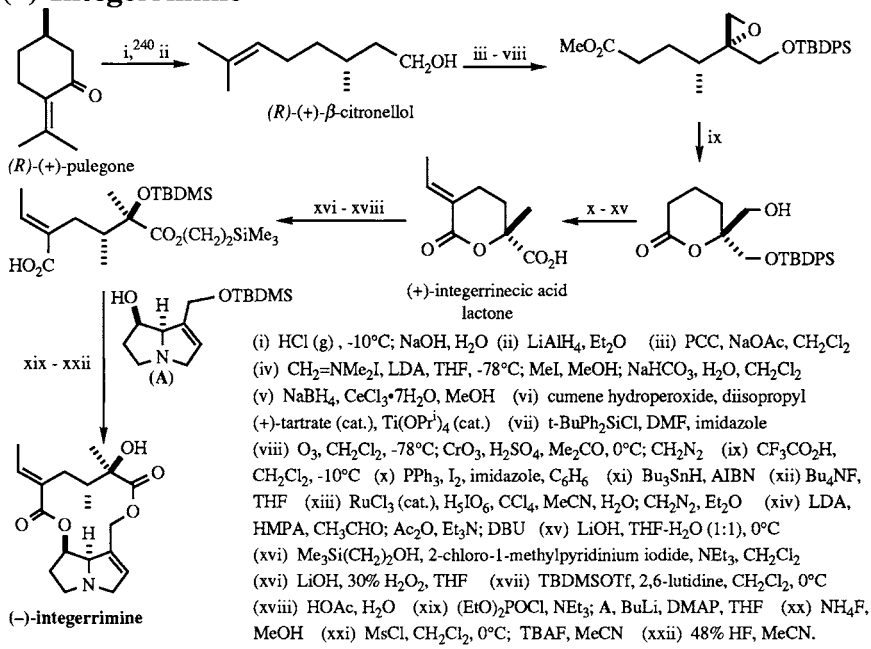
(+)-Artemisinin[238]



(i) NaOH, H_2O_2, THF (ii) NaSPh, THF (iii) m-CPBA, CH_2Cl_2, -78°C (iv) 2 LDA, THF-HMPA, -35°C; 2-(2-bromoethyl)-2,5,5-trimethyl-1,3-dioxane (v) Al(Hg), wet THF (vi) p-$TsNHNH_2$ (neat), 1 mmHg (vii) 4 n-BuLi, TMEDA, 0°C; $HCONMe_2$ (viii) $(Me_3Si)_3Al{\bullet}Et_2O$, Et_2O, -78°C; Ac_2O, DMAP (ix) 2 $LiNEt_2$, THF, -78°C (x) 2 LDA, THF, 50°C; MeI, -78°C (xi) O_3, CH_2Cl_2, -78°C; SiO_2; 3 M aq. H_2SO_4.

Scheme 136

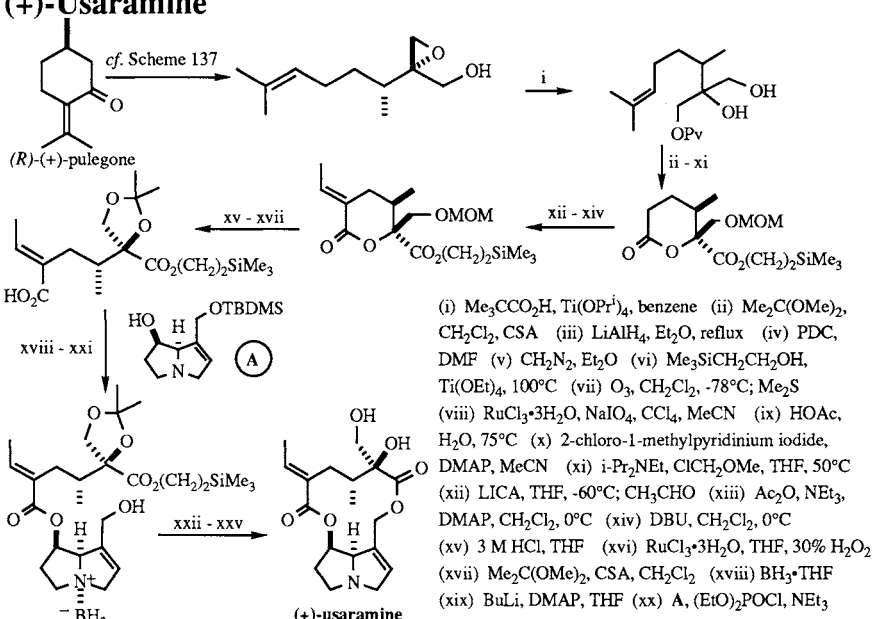
(–)-Integerrimine[239]



(i) HCl (g), -10°C; NaOH, H_2O (ii) $LiAlH_4$, Et_2O (iii) PCC, NaOAc, CH_2Cl_2 (iv) $CH_2{=}NMe_2I$, LDA, THF, -78°C; MeI, MeOH; $NaHCO_3$, H_2O, CH_2Cl_2 (v) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH (vi) cumene hydroperoxide, diisopropyl (+)-tartrate (cat.), $Ti(OPr^i)_4$ (cat.) (vii) t-$BuPh_2SiCl$, DMF, imidazole (viii) O_3, CH_2Cl_2, -78°C; CrO_3, H_2SO_4, Me_2CO, 0°C; CH_2N_2 (ix) CF_3CO_2H, CH_2Cl_2, -10°C (x) PPh_3, I_2, imidazole, C_6H_6 (xi) Bu_3SnH, AIBN (xii) Bu_4NF, THF (xiii) $RuCl_3$ (cat.), H_5IO_6, CCl_4, MeCN, H_2O; CH_2N_2, Et_2O (xiv) LDA, HMPA, CH_3CHO; Ac_2O, Et_3N; DBU (xv) LiOH, THF-H_2O (1:1), 0°C (xvi) $Me_3Si(CH_2)_2OH$, 2-chloro-1-methylpyridinium iodide, NEt_3, CH_2Cl_2 (xvi) LiOH, 30% H_2O_2, THF (xvii) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0°C (xviii) HOAc, H_2O (xix) $(EtO)_2POCl$, NEt_3; **A**, BuLi, DMAP, THF (xx) NH_4F, MeOH (xxi) MsCl, CH_2Cl_2, 0°C; TBAF, MeCN (xxii) 48% HF, MeCN.

Scheme 137

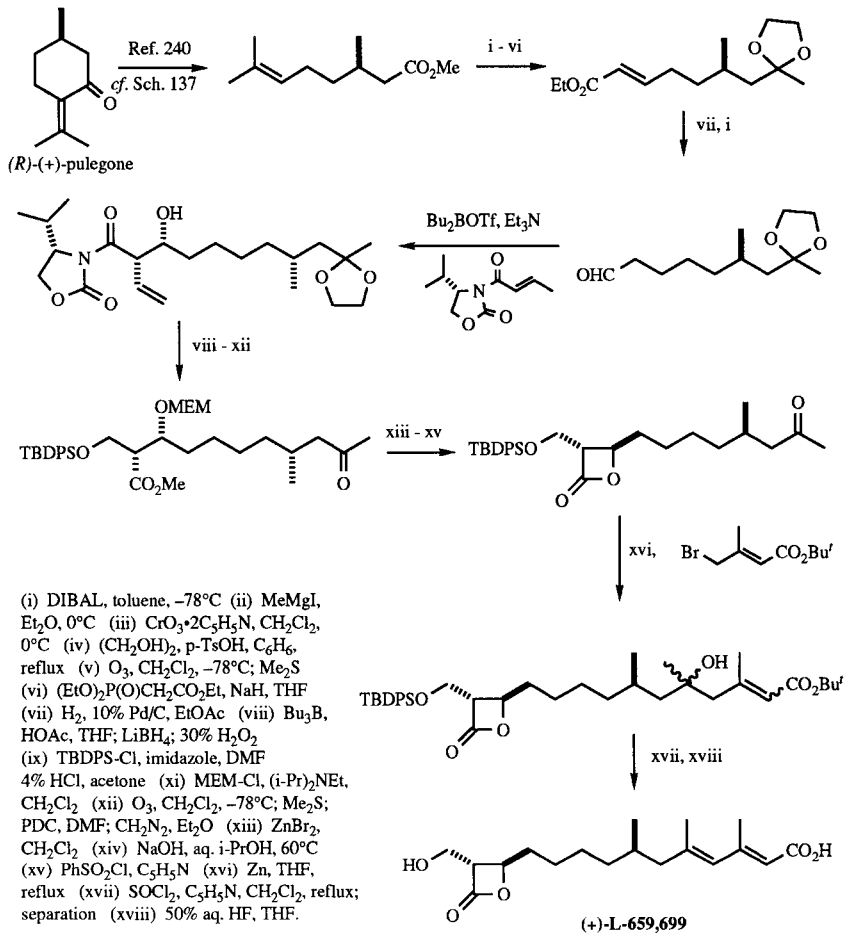
(+)-Usaramine[241]



(i) Me_3CCO_2H, $Ti(OPr^i)_4$, benzene (ii) $Me_2C(OMe)_2$, CH_2Cl_2, CSA (iii) $LiAlH_4$, Et_2O, reflux (iv) PDC, DMF (v) CH_2N_2, Et_2O (vi) $Me_3SiCH_2CH_2OH$, $Ti(OEt)_4$, 100°C (vii) O_3, CH_2Cl_2, -78°C; Me_2S (viii) $RuCl_3{\cdot}3H_2O$, $NaIO_4$, CCl_4, MeCN (ix) HOAc, H_2O, 75°C (x) 2-chloro-1-methylpyridinium iodide, DMAP, MeCN (xi) i-Pr_2NEt, $ClCH_2OMe$, THF, 50°C (xii) LICA, THF, -60°C; CH_3CHO (xiii) Ac_2O, NEt_3, DMAP, CH_2Cl_2, 0°C (xiv) DBU, CH_2Cl_2, 0°C (xv) 3 M HCl, THF (xvi) $RuCl_3{\cdot}3H_2O$, THF, 30% H_2O_2 (xvii) $Me_2C(OMe)_2$, CSA, CH_2Cl_2 (xviii) $BH_3{\cdot}THF$ (xix) BuLi, DMAP, THF (xx) **A**, $(EtO)_2POCl$, NEt_3 (xxi) NH_4F, MeOH (xxii) MsCl, NEt_3, CH_2Cl_2 (xxiii) TBAF, MeCN (xxiv) EtOH, reflux (xxv) 1 M HCl, THF

Scheme 138

(+)-L-659,699 (*syn.* 1233A)[242]

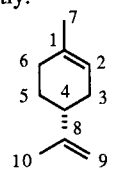


(i) DIBAL, toluene, –78°C (ii) MeMgI, Et_2O, 0°C (iii) $CrO_3 \cdot 2C_5H_5N$, CH_2Cl_2, 0°C (iv) $(CH_2OH)_2$, p-TsOH, C_6H_6, reflux (v) O_3, CH_2Cl_2, –78°C; Me_2S (vi) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF (vii) H_2, 10% Pd/C, EtOAc (viii) Bu_3B, HOAc, THF; $LiBH_4$; 30% H_2O_2 (ix) TBDPS-Cl, imidazole, DMF 4% HCl, acetone (xi) MEM-Cl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2 (xii) O_3, CH_2Cl_2, –78°C; Me_2S; PDC, DMF; CH_2N_2, Et_2O (xiii) $ZnBr_2$, CH_2Cl_2 (xiv) NaOH, aq. i-PrOH, 60°C (xv) $PhSO_2Cl$, C_5H_5N (xvi) Zn, THF, reflux (xvii) $SOCl_2$, C_5H_5N, CH_2Cl_2, reflux; separation (xviii) 50% aq. HF, THF.

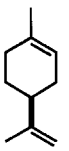
Scheme 139

4. LIMONENE

Both *(R)*-(+)-limonene and *(S)*-(–)-limonene are commercially available, although there has been a slight preference for the former as a chiral starting material in natural product synthesis. Limonene-1,2-oxide is also commercially available in both enantiomeric forms. A review of limonene reactions and microbiological transformations has been published recently.[243]

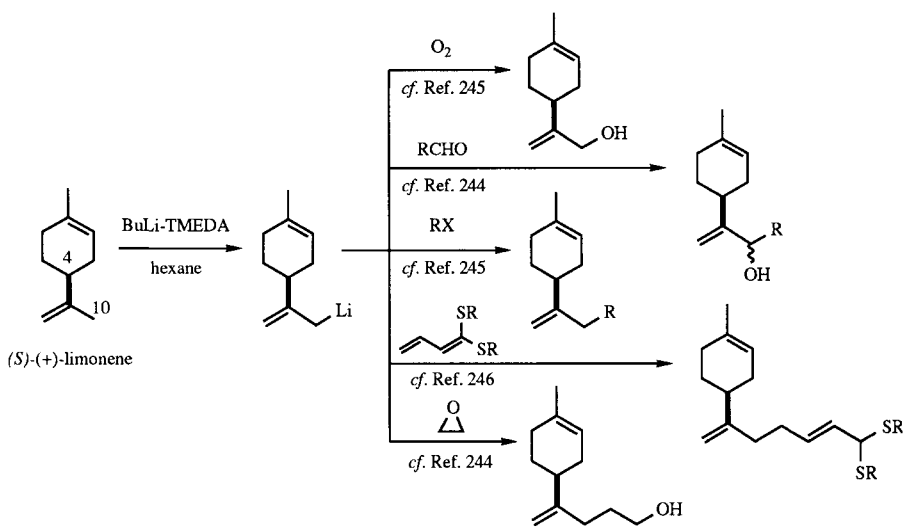


(R)-(+)-limonene



(S)-(–)-limonene

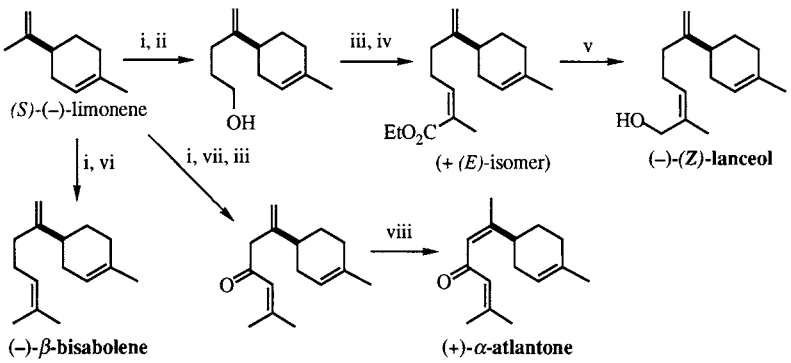
In general, three common approaches have been used in the conversion of limonene to more complex structures. Some synthetic applications of these three methods, among others, are presented in Schemes 141–174. One approach (*cf.* Scheme 140) involves initial regiospecific functionalization of the C(10) methyl group. Thus, when limonene is treated with a 1:1 complex of *n*-butyllithium[244] or *s*-butyllithium[245]



Scheme 140

and *N,N,N',N'*-tetramethylethylenediamine (TMEDA), regiospecific metalation at C(10) occurs with retention of configuration at C(4).[244] Subsequent reaction of the allyllithium intermediate with appropriate electrophiles then provides C(10)-functionalized limonene derivatives. Electrophiles that have been used in this manner include alkyl halides (Schemes 141[244] and 144[245]), aldehydes, epoxides (Scheme 141),[244] conjugated ketene dithioacetals (Scheme 142),[246] and molecular oxygen (Scheme 143).[245]

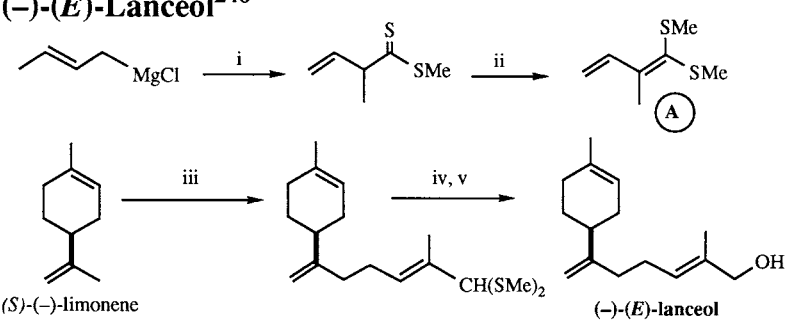
(–)-β-Bisabolene, (–)-(*Z*)-Lanceol, (+)-α-Atlantone[244]



(i) BuLi, TMEDA, hexane (ii) ethylene oxide (iii) $CrO_3 \cdot 2C_5H_5N$, CH_2Cl_2 (iv) $Ph_3P{=}CHCO_2Et$, EtOH; hν, cyclohexane; preparative glc (v) AlH_3, Et_2O, 0°C (vi) 1-bromo-3-methyl-2-butene, -60°C (vii) 3-methyl-2-butenal, -27°C (viii) alumina, Et_2O.

Scheme 141

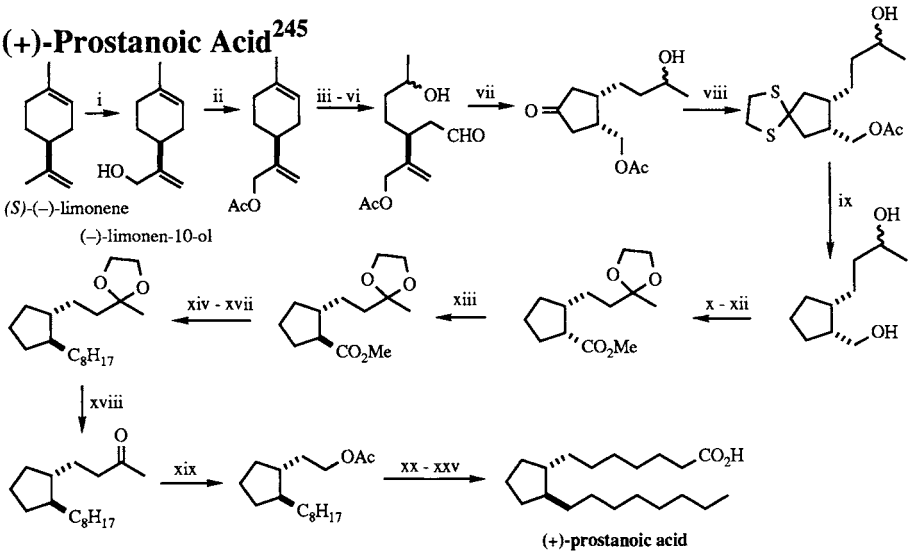
(–)-(*E*)-Lanceol[246]



(i) CS_2, Et_2O-THF, –78°C; MeI (ii) LDA, THF, –78°C; MeI (iii) BuLi, TMEDA, hexane; **A**, THF, –78°C (iv) $CuCl_2$, CuO, Me_2CO, H_2O (v) $LiAlH_4$, THF.

Scheme 142

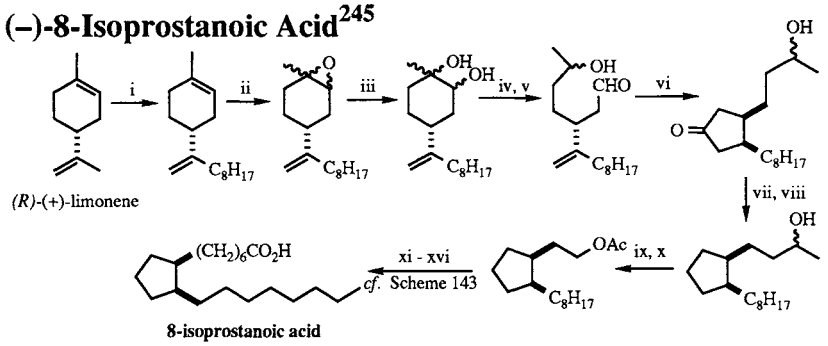
(+)-Prostanoic Acid[245]



(i) s-BuLi, TMEDA, –60°—>20°C; O_2, –60°—>0°C, t-BuOH (ii) Ac_2O, C_5H_5N (iii) m-CPBA, 5% $NaHCO_3$, CH_2Cl_2 (iv) 1% H_2SO_4, THF, 0°C (v) $NaIO_4$, H_2O-THF, 0 —> 20°C (vi) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, EtOH-H_2O, –15°C (vii) $Rh(PPh_3)_3Cl$, CH_2Cl_2 (viii) $(CH_2SH)_2$, $BF_3{\cdot}Et_2O$, CH_2Cl_2 (ix) Raney-Ni (W-4), EtOH, reflux (x) CrO_3, H_2SO_4, aq. Me_2CO (xi) CH_2N_2, Et_2O (xii) $(CH_2OH)_2$, p-TsOH, C_6H_6, reflux (xiii) NaOMe, toluene, reflux (xiv) $LiAlH_4$, Et_2O, 0°C (xv) $CrO_3{\cdot}2C_5H_5N$, CH_2Cl_2, 0°C (xvi) n-$C_7H_{15}PPh_3Br$, BuLi, THF, 5–10°C (xvii) H_2, PtO_2, MeOH, –20°C (xviii) 10% HCl, MeOH (xix) CF_3CO_3H, CH_2Cl_2, Na_2HPO_4 (xx) K_2CO_3, MeOH (xxi) PDC, CH_2Cl_2, 0°C (xxii) $HO_2C(CH_2)_4PPh_3Br$, NaH, DMSO (xxiii) CH_2N_2, Et_2O (xxiv) H_2, PtO_2, MeOH, –20°C (xxv) 5% aq. NaOH, EtOH.

Scheme 143

(–)-8-Isoprostanoic Acid[245]

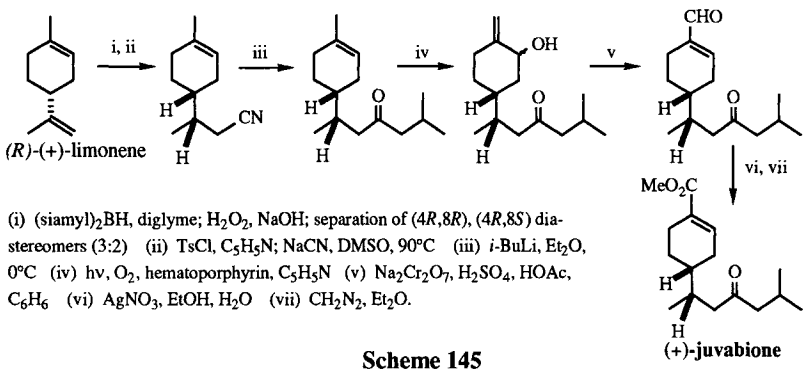


(i) s-BuLi, TMEDA, –60°C; n-$C_7H_{15}Br$, –60°C (ii) m-CPBA, 5% $NaHCO_3$, CH_2Cl_2 (iii) 1% H_2SO_4, THF, 0°C (iv) $NaIO_4$, H_2O–THF, 0 —> 20°C (v) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, EtOH-H_2O, –15°C (vi) $Rh(PPh_3)_3Cl$, CH_2Cl_2 (vii) $(CH_2SH)_2$, $BF_3{\cdot}Et_2O$, CH_2Cl_2 (viii) Raney-Ni (W-4), EtOH, reflux (ix) CrO_3, H_2SO_4, aq. Me_2CO (x) CF_3CO_3H, CH_2Cl_2, Na_2HPO_4 (xi) K_2CO_3, MeOH (xii) PDC, CH_2Cl_2, 0°C (xiii) $HO_2C(CH_2)_4PPh_3Br$, NaH, DMSO (xiv) CH_2N_2, Et_2O (xv) H_2, PtO_2, MeOH, –20°C (xvi) 5% aq. NaOH, EtOH.

Scheme 144

A second approach to the use of limonene as an enantiopure starting material in natural product synthesis involves selective functionalization of the C(9) methylene group. This is commonly accomplished by regiospecific hydroboration-oxidation using disiamylborane[247–249] or thexylborane[250] to provide 9-hydroxylimonene. Specific examples of this approach are provided in Schemes 145 through 151.

(+)-Juvabione[247]



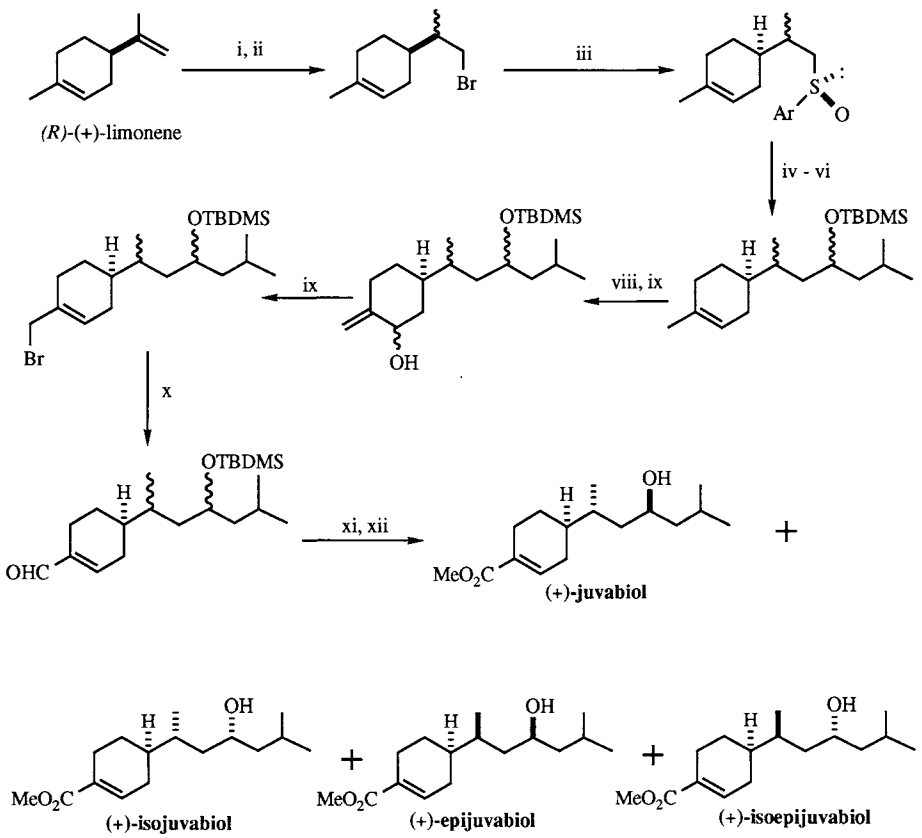
(i) (siamyl)$_2$BH, diglyme; H_2O_2, NaOH; separation of (4*R*,8*R*), (4*R*,8*S*) diastereomers (3:2) (ii) TsCl, C_5H_5N; NaCN, DMSO, 90°C (iii) *i*-BuLi, Et_2O, 0°C (iv) hν, O_2, hematoporphyrin, C_5H_5N (v) $Na_2Cr_2O_7$, H_2SO_4, HOAc, C_6H_6 (vi) $AgNO_3$, EtOH, H_2O (vii) CH_2N_2, Et_2O.

Scheme 145

In the synthesis of (+)-juvabione by Pawson and co-workers (Scheme 145),[247] C(9)-functionalization of limonene made possible the facile addition of the side chain of juvabione. The synthesis of the juvabiols (Scheme 146) by Williams and co-workers[251] follows a similar plan, and features the addition of a limonene-derived sulfoxide anion to 3-methylbutanal as a key step in the construction of the carbon skeleton of the target molecules.

In a biomimetic synthesis of (–)-isotirucallol and parkeol (Scheme 147) by van Tamelen and Anderson,[252,253] (–)-limonene serves as a precursor to the D ring of the two triterpenoids. As shown in Scheme 147, hydroboration-oxidation of the $\Delta^{8,9}$ bond of limonene provided a means of introducing the triterpenoid C(20) side chain.

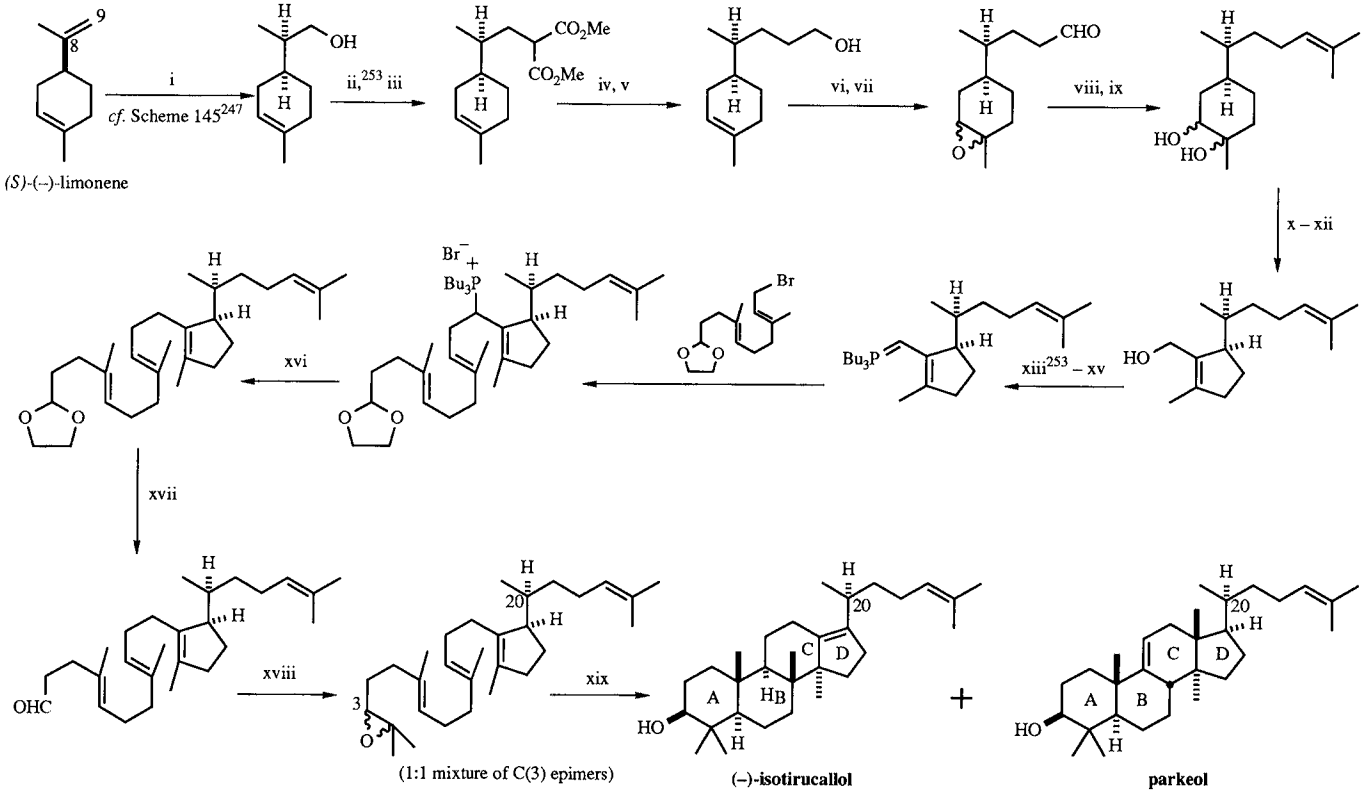
(+)-Juvabiol, (+)-Isojuvabiol, (+)-Epijuvabiol, and (+)-Isoepijuvabiol[251]



(i) (siamyl)$_2$BH, diglyme; H_2O_2, NaOH (ii) MsCl, NEt_3, CH_2Cl_2, 0°C; LiBr, THF, 60°C (iii) Mg, Et_2O; (–)-menthyl *p*-toluenesulfinate, 0°C; separation of diastereomeric sulfoxides (iv) LDA, THF, -90°C; 3-methylbutanal (v) Raney nickel, EtOH, 0°C (vi) TBDMSCl, imidazole, DMF (vii) m-CPBA, CH_2Cl_2, 0°C (viii) DATMP, benzene, 0°C (ix) PBr_3, THF, 0°C (x) Me_2CHNO_2, KOH, THF, H_2O, Me_2CHOH (xi) MnO_2, NaCN, HOAc (xii) TBAF, THF, reflux.

Scheme 146

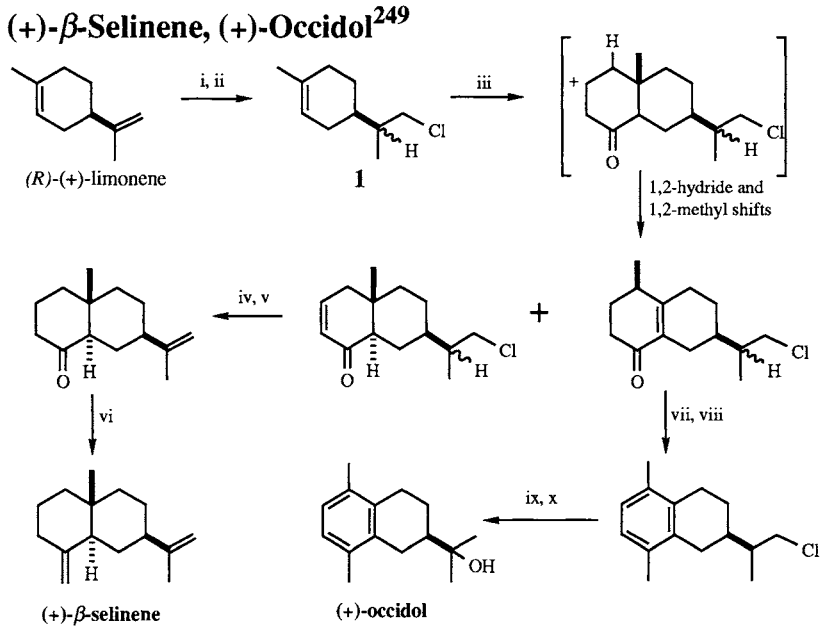
(–)-Isotirucallol, Parkeol[252,253]



(i) disiamylborane, diglyme; NaOH, H_2O_2 (ii) Ph_3P, CBr_4 (iii) $NaCH(CO_2Me)_2$, DMSO, 80°C (iv) NaCN, DMSO, 130°C (v) $LiAlH_4$, Et_2O (vi) m-CPBA, CH_2Cl_2, 0°C (vii) $CrO_3{\cdot}2C_5H_5N$, CH_2Cl_2 (viii) $Me_2C{=}PPh_3$ (ix) 3% $HClO_4$, THF (x) $NaIO_4$, THF-H_2O, 60°C (xi) HOAc, piperidine (xii) $NaBH_4$ (xiii) Ph_3P, CBr_4 (xiv) Bu_3P (xv) PhLi (xvi) Li, $EtNH_2$ (xvii) aq. $HClO_4$, THF (xviii) diphenylsulfonium isopropylide ($Ph_2S{=}CMe_2$) (xix) $SnCl_4$, CH_3NO_2, 0°C; separation of isomers by preparative TLC and preparative VPC.

Scheme 147

(+)-β-Selinene and (+)-occidol (Scheme 148) were synthesized by Wolinsky and co-workers[249] by a route which features a Lewis acid mediated acylation-cycloalkylation annulation as a key step. To prevent the participation of the limonene $\Delta^{8,9}$ bond during the annulation step, limonene was initially converted to the chloro derivative **1**.

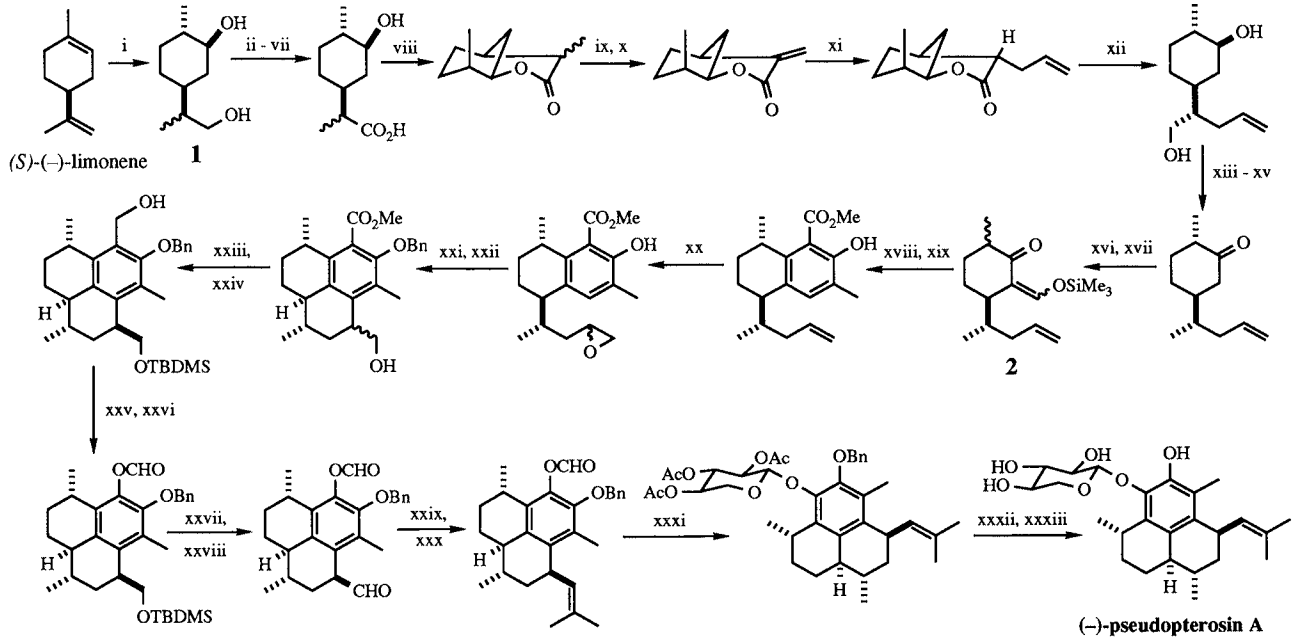


(i) (siamyl)$_2$BH, diglyme; H_2O_2, NaOH (ii) Ph_3P, CCl_4, CH_2Cl_2 (iii) CH_2=$CHCH_2COCl$, $AlCl_3$, CH_3NO_2 (iv) H_2, Pt, HOAc (v) TsOH, $(CH_2OH)_2$, C_6H_6, reflux; t-BuOK, DMSO; 5% HCl, dioxane (vi) Ph_3P=CH_2, DMSO, 80°C (vii) MeMgI, Et_2O (viii) S, 200°C (ix) t-BuOK, DMSO, 60°C (x) $Hg(OAc)_2$, THF, H_2O; $NaBH_4$, 3 N NaOH.

Scheme 148

In the synthesis of (–)-pseudopterosin A (Scheme 149) by Broka and co-workers,[250] hydroboration-oxidation of limonene yielded diol **1** which could be converted to silyloxy-ketone **2**. This latter compound was subjected to a $TiCl_4$-promoted reaction with 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-pentadiene to furnish the aromatic ring of the target molecule. The third ring was constructed by means of an intramolecular $SnCl_4$-promoted alkylation of the aromatic ring. Subsequent functional group transformations and glycosylation provided the natural product (–)-pseudopterosin A.

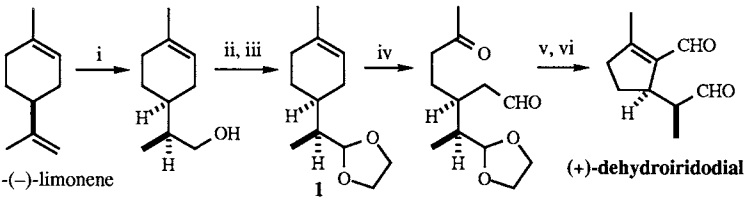
(–)-Pseudopterosin A[250]



(i) thexylborane, THF, 0°C; NaOH, H_2O_2 (ii) pivaloyl chloride, C_5H_5N (iii) DHP, PPTS, CH_2Cl_2 (iv) aq. KOH (v) PCC, NaOAc, CH_2Cl_2 (vi)$NaClO_2$, aq. t-BuOH, 2-methyl-2-butene (vii) HOAc-H_2O, 80°C (viii) p-TsOH, toluene, reflux (ix) LDA, PhSeCl, HMPA (x) H_2O_2 (xi) CH_2=CHMgBr, CuI•SMe_2, Me_3SiCl, THF, -40°C (xii) LAH, THF (xiii) $PhSO_2Cl$, NEt_3, DMAP, CH_2Cl_2 (xiv) $LiBHEt_3$, THF (xv) PCC, CH_2Cl_2 (xvi) HCO_2Et, NaH, dioxane (xvii) Me_3SiCl, NEt_3, hexane (xviii) 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-pentadiene, $TiCl_4$, CH_2Cl_2, -78°C (xix) NaOMe, MeOH; separation (xx) m-CPBA, $NaHCO_3$, $CHCl_3$, 55°C (xxi) $SnCl_4$, CH_2Cl_2 (xxii) BnBr, DMSO, K_2CO_3 (xxiii) TBDMS-Cl, imidazole, DMF, 45°C; separation (xxiv) DIBAL, CH_2Cl_2 (xxv) PCC, CH_2Cl_2 (xxvi) m-CPBA, Na_2HPO_4, $CHCl_3$ (xxvii) TBAF, HOAc, THF (xxviii) $(COCl)_2$, DMSO-CH_2Cl_2 , -60°C; NEt_3, -40°C (xxix) Me_2CLiCO_2Li, THF (xxx) (*N,N*-dimethylamino)formaldehyde dineopentyl acetal,$CHCl_3$, 4,4'-methylene-bis(2,6-di-*tert*-butylphenol), 55°C (xxxi) 1α-bromo-2,3,4-triacetyl-D-xylose, AgOTf, $(Me_2N)_2CO$, CH_2Cl_2 (xxxii) KOH, MeOH (xxxiii) Li, NH_3, THF.

Scheme 149

(+)-Dehydroiridodial[254]

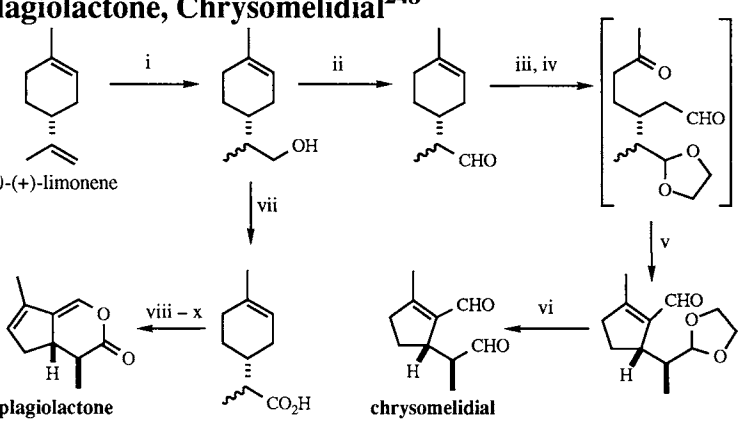


(i) disiamylborane, THF; NaOH, H_2O_2; separation (ii) PCC, CH_2Cl_2 (iii) $(CH_2OH)_2$, $(CO_2H)_2$, CH_3CN (iv) O_3; Me_2S (v) HOAc, piperidine (vi) 1 N HCl, ether.

Scheme 150

In Scheme 150,[254] the ketal **1**, derived from (–)-limonene, underwent ozonolytic ring-opening followed by acid-catalyzed intramolecular aldol condensation and deprotection to provide (+) dehydroiridodial. The natural products plagiolactone and chrysomelidial (Scheme 151)[248] were synthesized similarly.

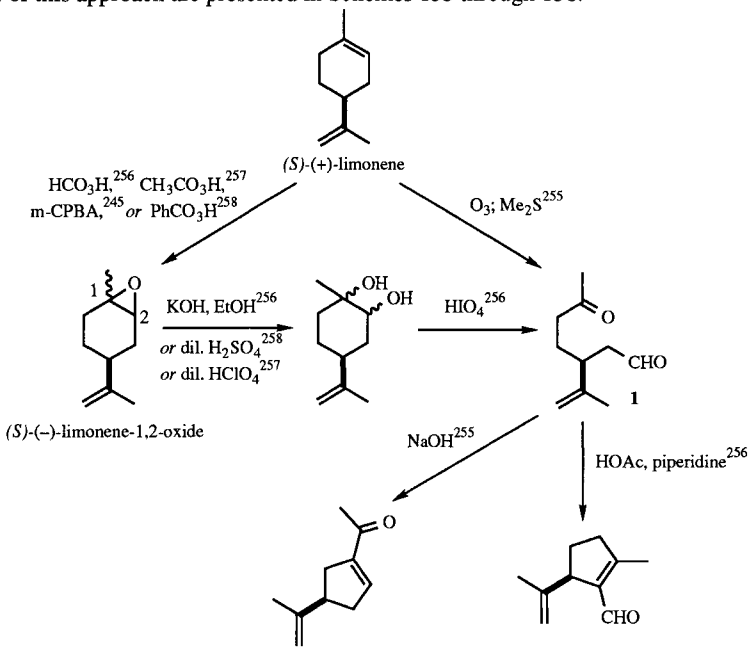
Plagiolactone, Chrysomelidial[248]



(i) disiamylborane, THF; NaOH, H_2O_2 (ii) PCC, CH_2Cl_2 (iii) $(CH_2OH)_2$, p-TsOH, C_6H_6, reflux (iv) O_3, THF, –78°C; H_2, Pd/C (v) HOAc, piperidine, C_6H_6, reflux; separation (preparative GLC) (vi) 50% aq. HOAc, reflux (vii) CrO_3, H_2SO_4, Me_2CO, 0°C (viii) O_3, THF, –78°C; H_2, Pd/C (ix) piperidine, C_6H_6, reflux (x) Ac_2O, p-TsOH, C_6H_6.

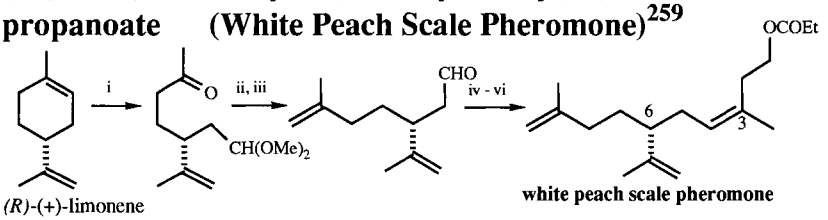
Scheme 151

A third common theme observed in the use of limonene as an enantiopure starting material is the cleavage of the $\Delta^{1,2}$ bond (Scheme 152) by ozonolysis[255] or periodic acid mediated cleavage[256] of the diol derived from limonene-1,2-oxide (Scheme 152). Examples of this approach are presented in Schemes 153 through 156.



Scheme 152

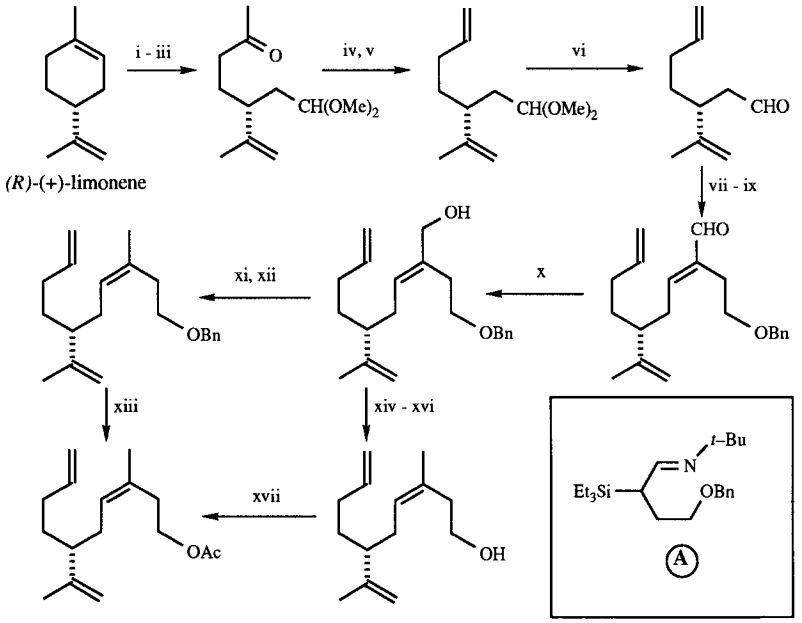
(3*Z*,6*R*)-3,9-Dimethyl-6-(1-methylethenyl)-3,9-decadien-1-ol propanoate (White Peach Scale Pheromone)[259]



(i) O_3, MeOH, –72°C; Me_2S, p-TsOH (ii) CH_2=PPh_3, THF, 0°C (iii) $HClO_4$, H_2O, THF (iv) CH_3CH=PPh_3, THF, ethylene oxide, –5°C (v) n-BuLi, THF (vi) CH_3CH_2COCl, Et_3N, Et_2O.

Scheme 153

(–)-California Red Scale Pheromone[260]



(–)-California red scale pheromone

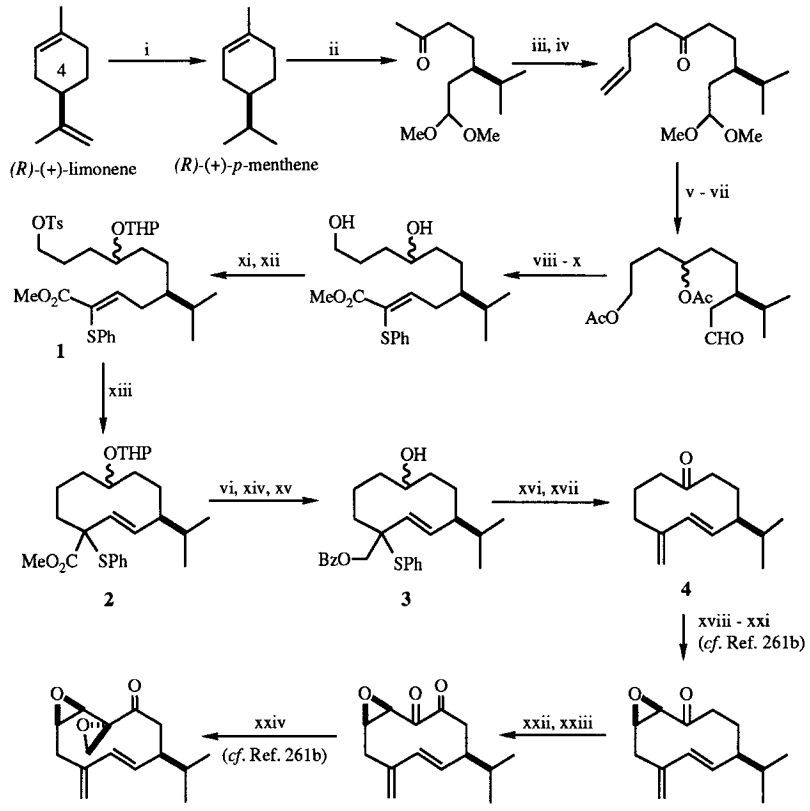
(i) O_3, MeOH (ii) thiourea, MeOH (iii) $HC(OMe)_3$, $CeCl_3 \cdot 6H_2O$, MeOH (iv) LDA, THF; $(EtO)_2P(O)Cl$, THF (v) Li, NH_3, THF (vi) $HClO_4$, H_2O-THF (vii) **A**, *s*-BuLi, THF (viii) $(CO_2H)_2$, H_2O (ix) $C_5H_5N \cdot HCl$, CH_2Cl_2 (x) $LiAlH_4$, Et_2O (xi) $C_5H_5N \cdot SO_3$, THF (xii) $LiAlH_4$, THF (xiii) Ac_2O, $HClO_4$ (xiv) Li, NH_3, Et_2O (xv) NCS, Me_2S, CH_2Cl_2 (xvi) $LiAlH_4$, Et_2O (xvii) Ac_2O, C_5H_5N.

Scheme 154

The synthesis of (–)-periplanone-B (Scheme 155)[261a] features as a key step the intramolecular alkylation of the unsaturated tosyloxy-ester **1** to provide the *(E)*-cyclodecene ester **2**. Reductive elimination of the thiophenyl-benzoate **3** with sodium naphthalenide, followed by oxidation, yielded the dienone **4**, which was then converted to the desired natural product using a modification of Schreiber's procedure.[261b]

(–)-Periplanone-B[261a]

(Sex Pheromone of the American Cockroach *Periplaneta americana*)



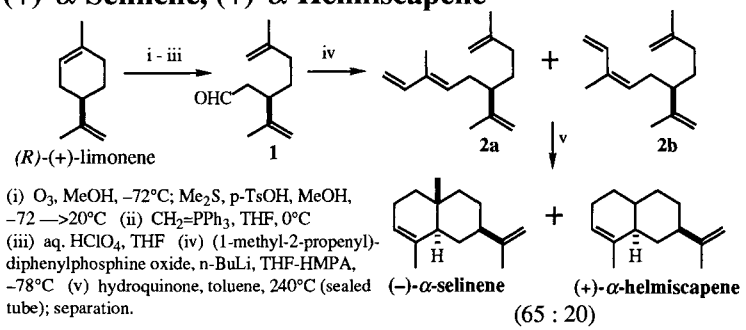
(i) H_2, PtO_2, EtOH (ii) O_3, MeOH, -60°C; Me_2S, TsOH (iii) $(MeO)_2CO$, NaH, dioxane, heat; $CH_2{=}CHCH_2Br$, heat (iv) KOH, MeOH, 90°C (v) OsO_4-$NaIO_4$, Et_2O-H_2O (vi) $LiAlH_4$, Et_2O (vii) Ac_2O, C_5H_5N; 6 N HCl (viii) LDA, $PhSCH_2CO_2Me$, THF, -78°C (ix) Ac_2O, HOAc, 130°C (x) NaOMe, MeOH, reflux (xi) TsCl, DMAP, Et_3N, CH_2Cl_2, -10°C (xii) DHP, PPTS, CH_2Cl_2 (xiii) $NaN(TMS)_2$, DME, reflux (xiv) PhCOCl, DMAP, C_5H_5N (xv) Dowex 50W (H^+), MeOH (xvi) $NaC_{10}H_8$, THF, -78°C (xvii) PCC, NaOAc, CH_2Cl_2 (xviii) $LiN(TMS)_2$, $PhSSO_2Ph$, -10°C (xix) $NaIO_4$, MeOH (xx) $CaCO_3$, $PhCH_3$, heat (xxi) t-BuOOH, KH, THF (xxii) $LiN(TMS)_2$, THF, MoO_5.HMPA.C_5H_5N, -70°C (xxiii) PCC, 3Å molecular sieves, CH_2Cl_2 (xxiv) $Me_2S{=}CH_2$, DMSO-THF, 0°C.

Scheme 155

The limonene-derived aldehyde **1** (Scheme 156) was converted to the diastereomeric tetraenes **2a** and **2b** which were not separated, but subjected to Diels-Alder

cycloaddition conditions to provide the two natural products (+)-α–selinene and (+)-α-helmiscapene.[262]

(+)-α-Selinene, (+)-α-Helmiscapene[262]



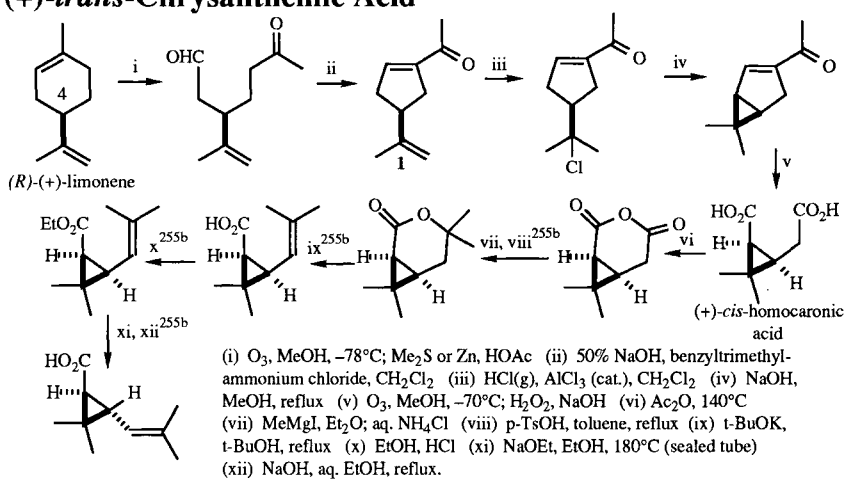
(i) O_3, MeOH, –72°C; Me_2S, p-TsOH, MeOH, –72 —>20°C (ii) CH_2=PPh_3, THF, 0°C (iii) aq. $HClO_4$, THF (iv) (1-methyl-2-propenyl)-diphenylphosphine oxide, n-BuLi, THF-HMPA, –78°C (v) hydroquinone, toluene, 240°C (sealed tube); separation.

(–)-α-selinene + (+)-α-helmiscapene (65 : 20)

Scheme 156

In many syntheses (*cf.* Schemes 157 through 166), the acyclic keto-aldehyde **1** (*cf.* Scheme 152) obtained as a result of oxidative scission of the limonene $\Delta^{1,2}$ bond is subjected to acid- or base-catalyzed intramolecular aldol condensation to provide cyclopentenoid intermediates that have potential in natural product synthesis. For example,

(+)-*trans*-Chrysanthemic Acid[255a]

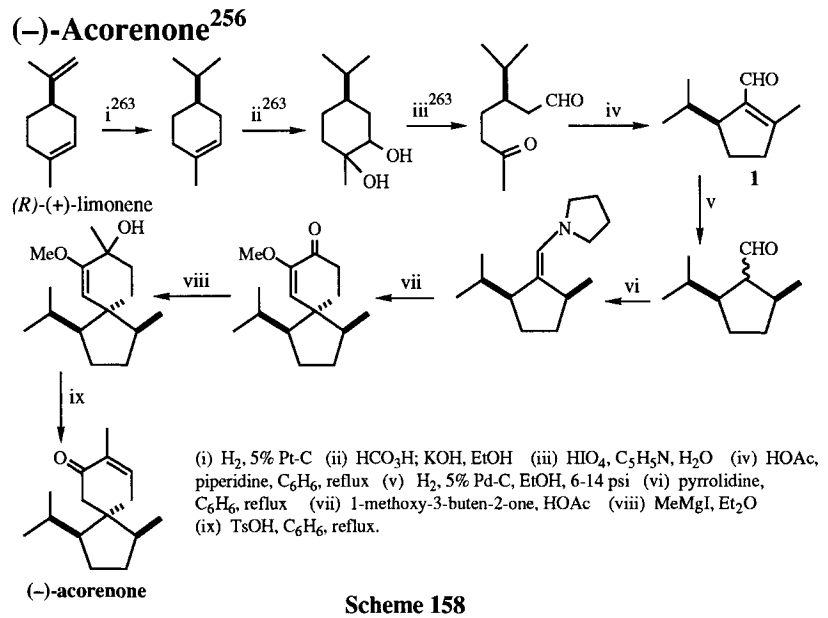


(i) O_3, MeOH, –78°C; Me_2S or Zn, HOAc (ii) 50% NaOH, benzyltrimethyl-ammonium chloride, CH_2Cl_2 (iii) HCl(g), $AlCl_3$ (cat.), CH_2Cl_2 (iv) NaOH, MeOH, reflux (v) O_3, MeOH, –70°C; H_2O_2, NaOH (vi) Ac_2O, 140°C (vii) MeMgI, Et_2O; aq. NH_4Cl (viii) p-TsOH, toluene, reflux (ix) t-BuOK, t-BuOH, reflux (x) EtOH, HCl (xi) NaOEt, EtOH, 180°C (sealed tube) (xii) NaOH, aq. EtOH, reflux.

Scheme 157

in the formal synthesis of (+)-*trans*-chrysanthemic acid (Scheme 157) by Ho and Liu,[255a] enone **1** was converted to the relay compound, (+)-*cis*-homocaronic acid,[255b] in which the stereochemistry of the chiral centres is derived from that of C(4) of limonene.

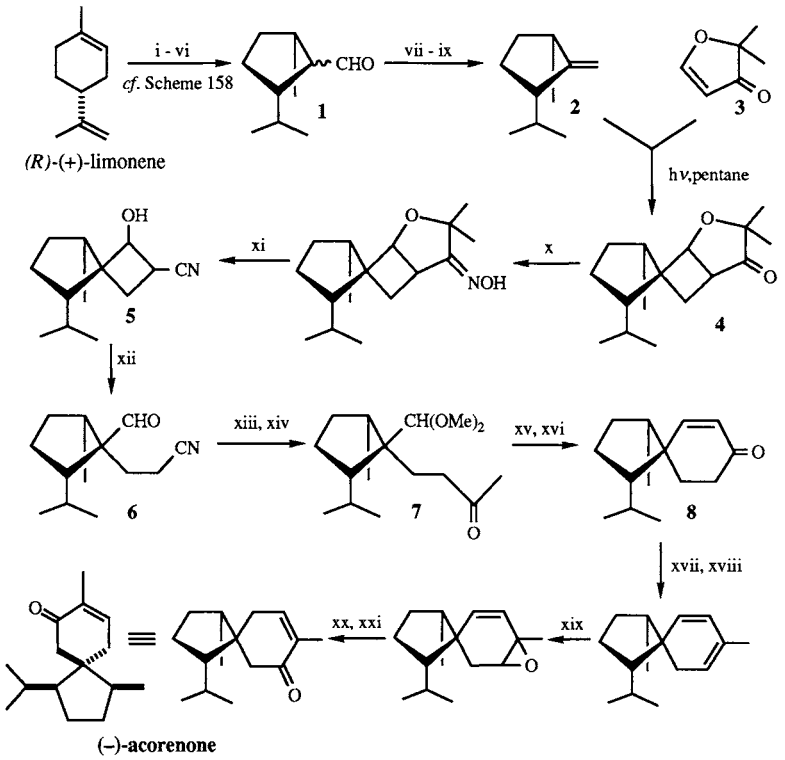
The substituted cyclopentenecarboxaldehyde **1** (Scheme 158)[256] bears structural resemblance to the natural product (–)-acorenone and construction of the spirocyclic ring in this compound was accomplished by a tandem Michael-intramolecular aldol condensation with 1-methoxy-3-buten-2-one.



Scheme 158

In another synthesis of acorenone (Scheme 159), by Baldwin and co-workers,[264] the spirocyclic system was constructed using a photoannulation method. The aldehyde **1** was converted to the exo-methylene derivative **2**. Photocycloaddition of **2** to the enone **3** yielded tricyclic ketone **4**. The oxacyclopentanone ring in **4** was opened by way of a Beckmann rearrangement to provide the spirocyclic hydroxy-nitrile **5** that underwent subsequent base-promoted fragmentation to afford the aldehydo-nitrile **6.** The desired spiro[4.5]decane ring system was obtained by intramolecular aldol condensation of the keto-aldehyde derived from **7**. Enone **8** was then converted to (–)-acorenone in a straightforward manner.

(–)-Acorenone[264]

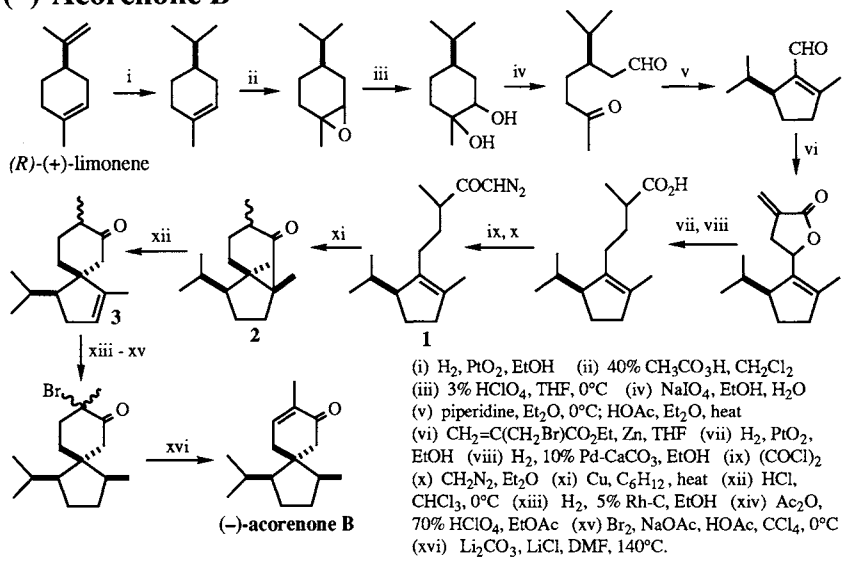


(i) H_2, PtO_2, EtOH (ii) 40% CH_3CO_3H, CH_2Cl_2 (iii) 3% $HClO_4$, THF, 0°C (iv) $NaIO_4$, EtOH, H_2O (v) piperidine, Et_2O, 0°C; HOAc, Et_2O (vi) 5% Pd-C, H_2, EtOH (vii) $LiAlH_4$, Et_2O (viii) MeC_6H_4OCOCl, C_5H_5N (ix) triethylene glycol, 250°C (x) NH_2OH (xi) $SOCl_2$, C_5H_5N (xii) NaH, Et_2O (xiii) $HC(OMe)_3$, TsOH (xiv) MeLi (xv) H_3O^+ (xvi) KOH, EtOH (xvii) MeLi (xviii) TsOH, CH_2Cl_2 (xix) m-CPBA (xx) BF_3•Et_2O (xxi) TsOH, toluene.

Scheme 159

In a third synthesis of (–)-acorenone (Scheme 160), by White and co-workers,[257] the spirocyclic ring system was constructed through an intramolecular cyclopropanation reaction involving the diazo-ketone **1**. It was observed that the cyclopropanation occurred exclusively from the face of the double bond opposite the isopropyl group. Treatment of the resulting tricyclic ketone **2** with acid provided the unsaturated spirocyclic ketone **3** which was converted to the desired natural product in four steps.

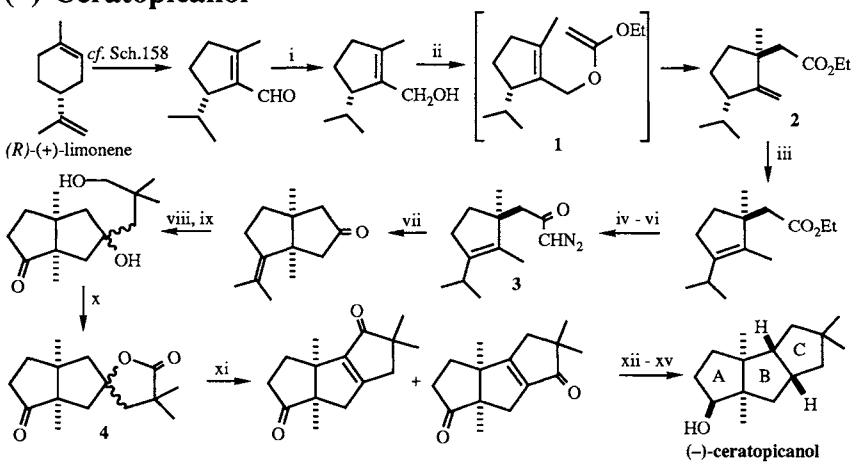
(–)-Acorenone B[257]



(i) H_2, PtO_2, EtOH (ii) 40% CH_3CO_3H, CH_2Cl_2 (iii) 3% $HClO_4$, THF, 0°C (iv) $NaIO_4$, EtOH, H_2O (v) piperidine, Et_2O, 0°C; HOAc, Et_2O, heat (vi) $CH_2=C(CH_2Br)CO_2Et$, Zn, THF (vii) H_2, PtO_2, EtOH (viii) H_2, 10% Pd-$CaCO_3$, EtOH (ix) $(COCl)_2$ (x) CH_2N_2, Et_2O (xi) Cu, C_6H_{12}, heat (xii) HCl, $CHCl_3$, 0°C (xiii) H_2, 5% Rh-C, EtOH (xiv) Ac_2O, 70% $HClO_4$, EtOAc (xv) Br_2, NaOAc, HOAc, CCl_4, 0°C (xvi) Li_2CO_3, LiCl, DMF, 140°C.

Scheme 160

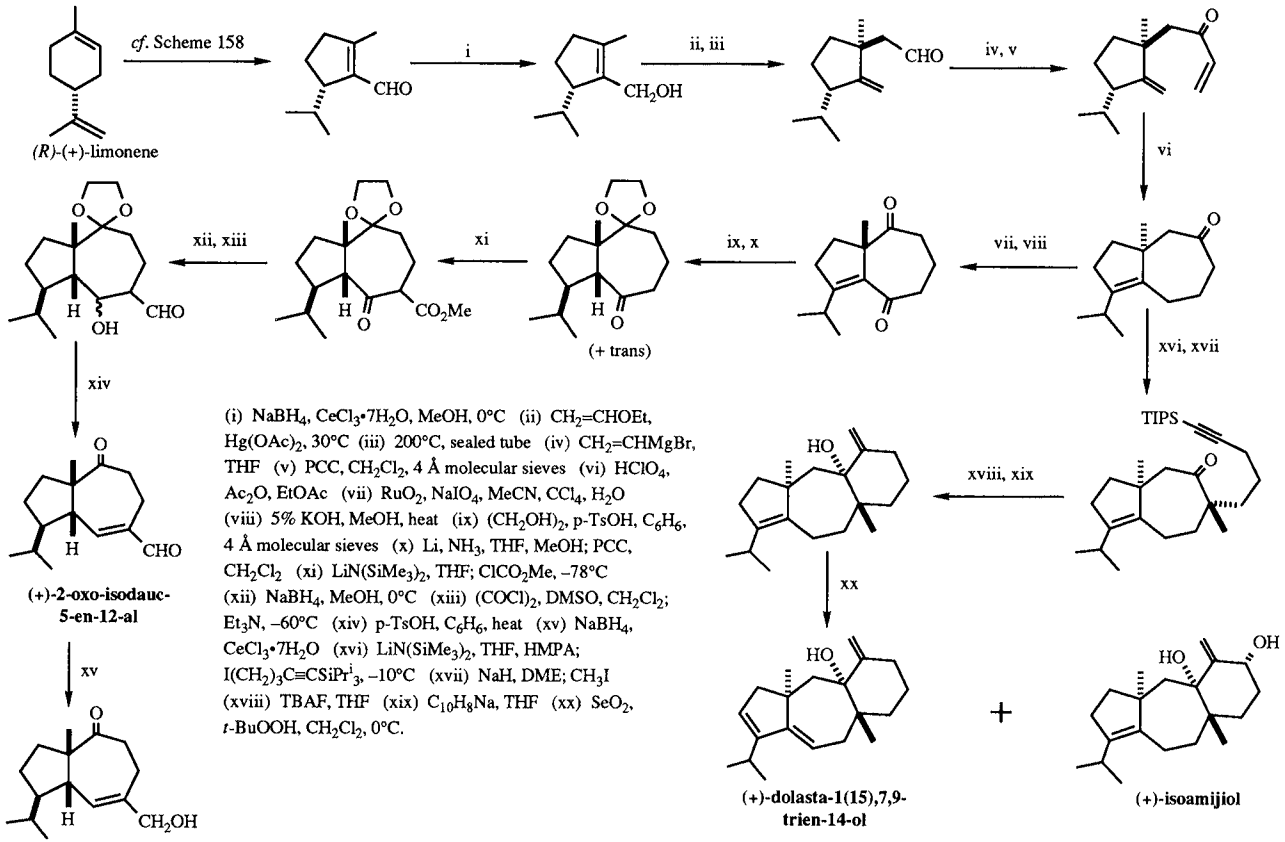
(–)-Ceratopicanol[265]



(i) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0°C (ii) $CH_3C(OEt)_3$, $Hg(OAc)_2$, $CH_3CH_2CO_2H$, 30°C; sealed tube, 200°C (iii) $BF_3 \cdot Et_2O$, CH_2Cl_2 (iv) NaOH, MeOH, 80°C (v) $(COCl)_2$, C_5H_5N, CH_2Cl_2 (vi) CH_2N_2, Et_2O (vii) $BF_3 \cdot Et_2O$, CH_2Cl_2 (viii) 3-bromo-2,2-dimethyl-1-(*t*-butyldimethylsilyl)propane, Li, Et_2O (ix) O_3, MeOH, -78°C; Me_2S; Bu_4NF (x) TPAP, NMO, MeCN, CH_2Cl_2 (xi) $MeSO_3H$, P_2O_5, 80°C (xii) $NaBH_4$, MeOH, -20°C (xiii) Li, NH_3, t-BuOH, NH_4Cl (xiv) Ac_2O, DMAP, CH_2Cl_2 (xv) Na, HMPA, t-BuOH, Et_2O.

Scheme 161

(+)-Aphanamol I, (+)-2-Oxoisodauc-5-en-12-al, (+)-Isoamijiol, (+)-Dolasta-1(15),7,9-trien-14-ol[266]

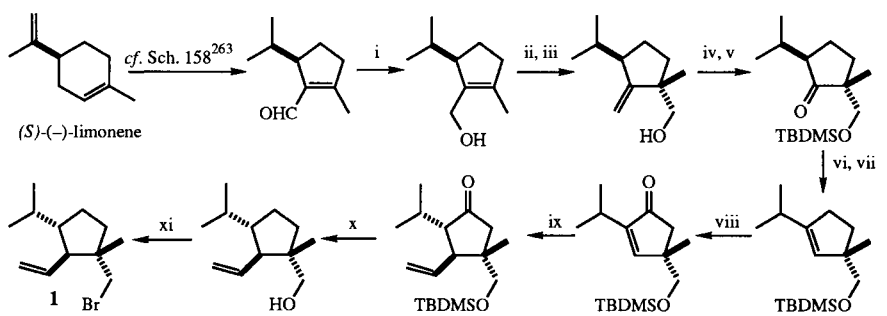


Scheme 162

In the synthesis of triquinane sesquiterpene (–)-ceratopicanol (Scheme 161) by Mehta and Karra,[265] the γ,δ–unsaturated ester **2** was prepared via an orthoester Claisen rearrangement of the substituted allyl vinyl ether **1**. The rearrangement occurred stereospecifically from the face of the endocyclic double bond opposite the isopropyl group. Ring B was constructed via a Lewis acid promoted cyclization of the α-diazo-ketone **3**, and ring C was constructed by acid-catalyzed rearrangement of the spirocyclic lactone **4**. Another application of such a directed Claisen rearrangement is presented in the synthesis of (+)-aphanamol I, (+)-2-oxoisodauc-5-en-12-al, (+)-isoamijiol, and (+)-dolasta-1(15),7,9-trien-14-ol (Scheme 162) by Mehta and co-workers.[266]

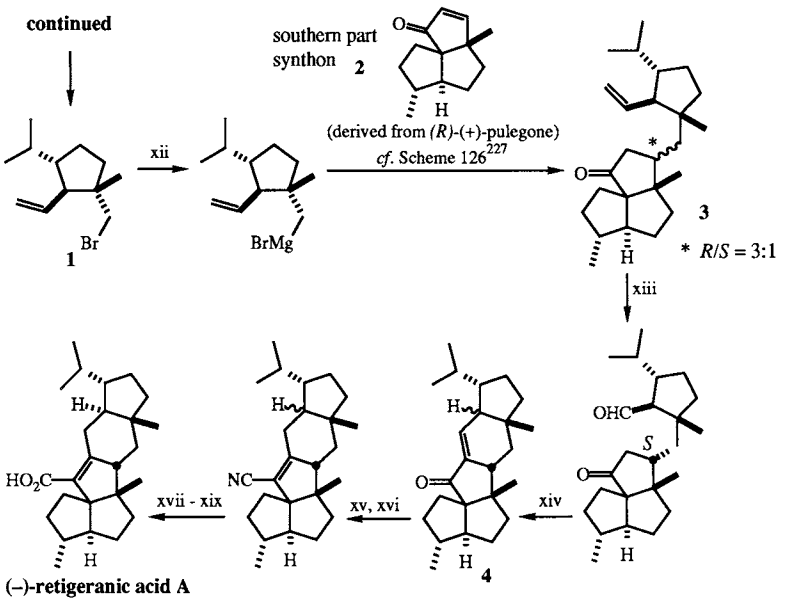
A remarkable example of the use of monoterpenoids as chiral starting materials in natural product synthesis is the convergent synthesis of (–)-retigeranic acid A (Scheme 163) by Paquette and co-workers.[267] Whereas the "southern" triquinane portion of the molecule (i.e. enone **2**) was derived from *(R)*-(+)-pulegone (*cf.* Scheme 126),[227] the "northern" portion (i.e. bromo-alkene **1**)[267] was prepared from *(S)*-(–)-limonene. Conjugate addition of the Grignard reagent derived from the bromo-alkene **1** to the triquinane enone **2** provided ketone **3** as a 3:1 mixture of diastereomers. Ozonolysis and intramolecular aldol condensation of the minor diastereomer yielded a pentacyclic enone **4** which was converted to (–)-retigeranic acid A. The major diastereomer was converted similarly to 11-*epi*-retigeranic acid.

(–)-Retigeranic Acid A[267]



(i) DIBAL, Et_2O, -78°C; 10% HCl (ii) KH, THF; Bu_3SnCH_2I (iii) n-BuLi (iv) O_3, MeOH; Me_2S
(v) TBDMS-Cl, imidazole, DMF (vi) DIBAL, Et_2O, -78°C; 1 N HCl (vii) $POCl_3$, C_5H_5N
(viii) CrO_3•3,5-dimethylpyrazole, CH_2Cl_2, -10°C (ix) CH_2=$CHMgBr$, CuBr•SMe_2, THF, -78—>25°C
(x) H_2NNH_2•H_2O, K_2CO_3, diethylene glycol, 150-190°C (xi) $(EtO_2C)_2N_2$, Ph_3P, $ZnBr_2$, THF

Scheme 163 (continued) →



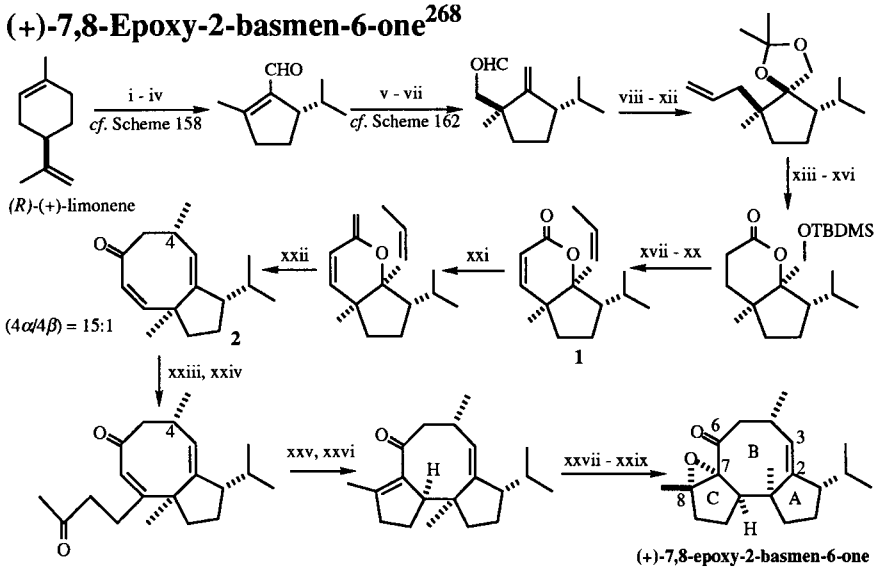
(xii) Mg, 1,2-dibromoethane, Et_2O, reflux (xiii) O_3, CH_2Cl_2-MeOH (1:1), -78°C; Zn, HOAc; separation; piperidine, HOAc, toluene, 4Å molecular sieves, reflux (xiv) H_2, PtO_2, HOAc, THF, 80 psi (xv) Me_3SiCN, KCN, 18-crown-6, 100 000 psi (xvi) $POCl_3$, DBU, C_5H_5N, reflux (xvii) DIBAL, Et_2O, -20°C; sat. aq. NH_4Cl (xviii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene (xix) separation of isomers as their methyl esters (CH_2N_2, Et_2O).

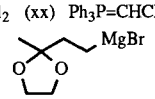
Scheme 163

Paquette and Kang also recognized that the A ring of (+)-7,8-epoxy-2-basmen-6-one (Scheme 164)[268] could be derived from *(R)*-(+)-limonene. To this end, limonene was converted to the bicyclic lactone **1** which was then methylenated using Tebbe's reagent. Subsequent Claisen rearrangement resulted in expansion of the six-membered ring to an eight-membered ring, providing the bicyclo[6.3.0]undecane system, **2**. Finally, the C ring was constructed via an intramolecular aldol condensation.

In Yamasaki's synthesis of (–)-daucene (Scheme 165),[258] *(R)*-(+)-limonene was elaborated to the hydroxy-diene **1**. Acid-catalyzed cyclization of this diene yielded a mixture of compounds from which the major component was isolated and identified as (–)-daucene.

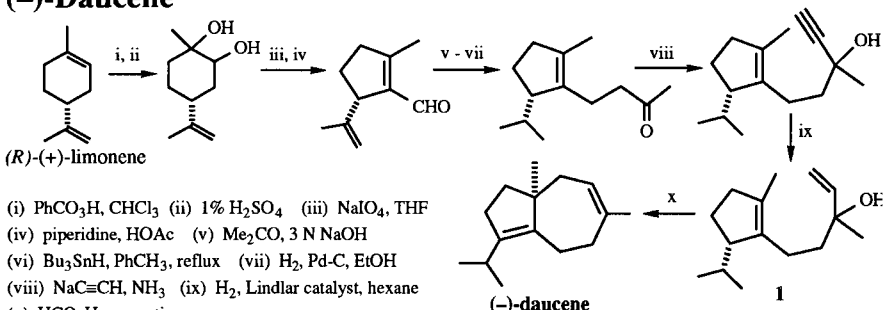
(+)-7,8-Epoxy-2-basmen-6-one[268]



(i) H_2, 5% Pt-C (ii) HCO_3H; KOH, EtOH (iii) HIO_4, C_5H_5N, H_2O (iv) HOAc, piperidine, C_6H_6, reflux (v) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0°C (vi) CH_2=CHOEt, $Hg(OAc)_2$, 30°C (vii) 200°C, sealed tube (viii) $NaBH_4$, THF, EtOH (ix) OsO_4, NMO, Me_2CO, H_2O (x) $MeC(OMe)_2$, TsOH, Me_2CO (xi) PDC, 3 Å sieves, CH_2Cl_2 (xii) Ph_3P=CH_2, THF (xiii) 9-BBN, THF; 50% NaOH, 30% H_2O_2 (xiv) PDC, DMF (xv) 10% HCl, THF (xvi) TBDMSCl, DMF, imidazole (xvii) $(PhSeO)_2O$, PhCl, heat (xviii) Bu_4NF, DMF (xix) PDC, 3 Å sieves, CH_2Cl_2 (xx) Ph_3P=$CHCH_3$, THF, 0°C (xxi) Tebbe reagent, pyridine, THF, benzene (xxii) 180°C, toluene (xxiii)  , Me_3SiCl, CuBr•SMe_2, HMPA, THF, -78°C (xxiv) PhSeCl, THF, 0°C; 30% H_2O_2, THF; 5% HCl (xxv) H_2, PtO_2, EtOH; K_2CO_3, MeOH (xxvi) $SOCl_2$, CH_2Cl_2, C_5H_5N; K_2CO_3, MeOH (xxvii) $LiAlH_4$, THF, 0°C (xxviii) m-CPBA, CH_2Cl_2, 0°C (xxix) $(COCl)_2$, DMSO, CH_2Cl_2; Et_3N.

Scheme 164

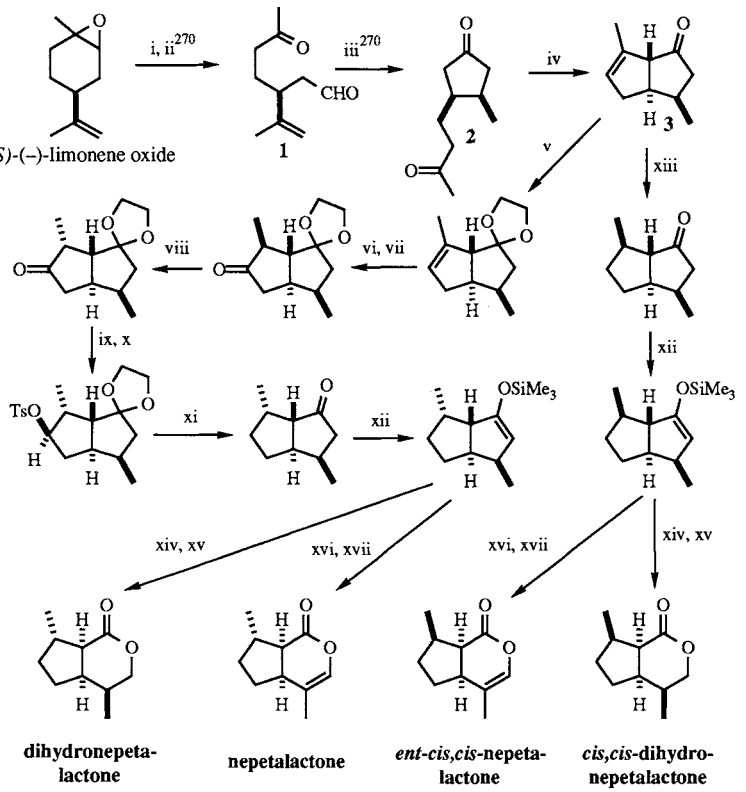
(–)-Daucene[258]



(i) $PhCO_3H$, $CHCl_3$ (ii) 1% H_2SO_4 (iii) $NaIO_4$, THF (iv) piperidine, HOAc (v) Me_2CO, 3 N NaOH (vi) Bu_3SnH, $PhCH_3$, reflux (vii) H_2, Pd-C, EtOH (viii) NaC≡CH, NH_3 (ix) H_2, Lindlar catalyst, hexane (x) HCO_2H; separation.

Scheme 165

Nepetalactones[269]



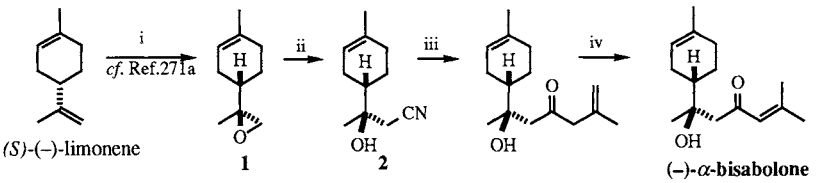
dihydronepeta-lactone | **nepetalactone** | ***ent-cis,cis*-nepeta-lactone** | ***cis,cis*-dihydro-nepetalactone**

(i) 1% H_2SO_4 (ii) $NaIO_4$, H_2O–THF, 0°C (iii) $Rh(PPh_3)_3Cl$, CH_2Cl_2 (iv) $KHSO_4$, reflux (v) $(CH_2OH)_2$, PPTS, C_6H_6, reflux (vi) BH_3•THF, THF, 0°C; NaOH, H_2O_2 (vii) $(COCl)_2$, DMSO, CH_2Cl_2, –60°C; Et_3N (viii) K_2CO_3, MeOH, 0°C (ix) $NaBH_4$, EtOH, 0°C (x) p-TsCl, C_5H_5N, 0°C (xi) $LiAlH_4$, THF, reflux; 10% HCl, THF (xii) LDA, THF, –78°C; Me_3SiCl, Et_3N (xiii) H_2, 5% Pd-C, MeOH (xiv) O_3, CH_2Cl_2–MeOH, –78°C; $NaBH_4$ (xv) p-TsOH, CH_2Cl_2 (xvi) O_3, CH_2Cl_2–MeOH, –78°C; Me_2S (xvii) p-TsOH, cyclohexane, reflux.

Scheme 166

The keto-aldehyde **1** (Scheme 166; *cf.* Scheme 152) has also been used as an intermediate in a synthesis of nepetalactone (Scheme 166).[269] Conversion of **1** to the *cis*-3,4-disubstituted cyclopentanone **2** via Rh(I)-catalyzed cyclization.[270] Subsequent intramolecular aldol condensation followed by deconjugation of the double bond provided the bicyclo[3.3.0]octenone **3** that was converted to nepetalactone and three of its isomers.

(–)-α-Bisabolone[272]



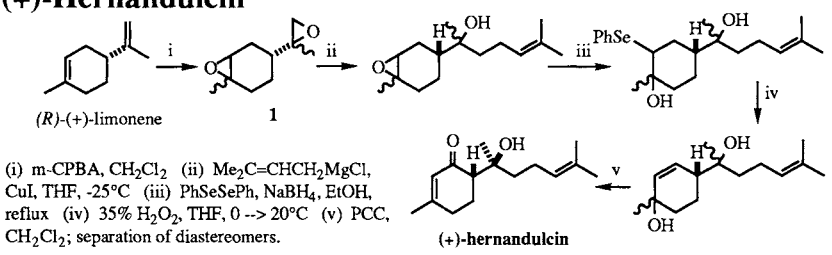
(i) PhCN, H_2O_2, $KHCO_3$, MeOH (ii) KCN, aq. EtOH (iii) $H_2C{=}C(CH_3)CH_2MgCl$, THF; 10% H_2SO_4 (iv) 4% KOH, MeOH.

Scheme 167

The epoxidation of the limonene $\Delta^{1,2}$ bond is common and straightforward (*cf.* Schemes 152, 158 – 165, and 168); moreover, limonene-1,2-oxide is also commercially available. Less common, however, is the epoxidation of the limonene $\Delta^{8,9}$ bond. Nevertheless, Payne has developed a procedure[271a] to achieve this objective* and this procedure has been employed by Kergomard and Veschambre[272] in their synthesis of (–)-α-bisabolone (Scheme 167). Limonene was treated with hydrogen peroxide in benzonitrile or acetonitrile to yield a mixture of epoxidation products from which the desired epoxide, **1**, could be separated by spinning band distillation and preparative GLC. Regiospecific opening of the oxirane ring by cyanide anion provided hydroxy-nitrile **2** which could be converted easily to (–)-α-bisabolone.

On the other hand, treatment of limonene with two equivalents of *m*-chloroperbenzoic acid yielded the bis-epoxide **1** (Scheme 168). This compound has been used as an intermediate in the synthesis of the sesquiterpene (+)-hernandulcin by Mori and Kato.[273]

(+)-Hernandulcin[273]



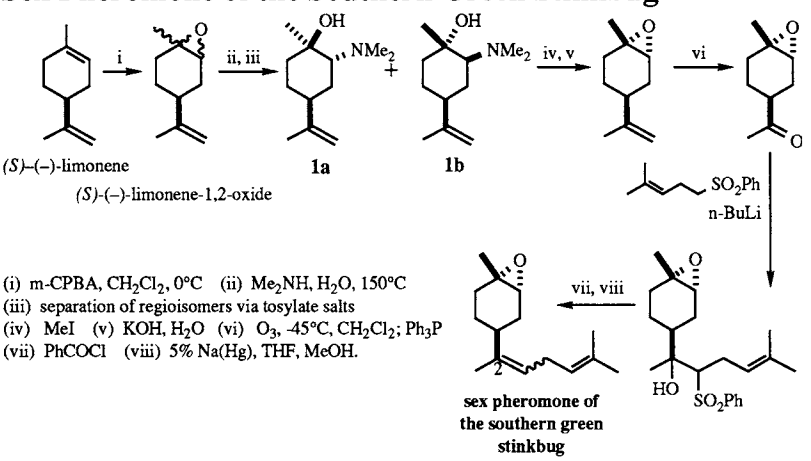
(i) m-CPBA, CH_2Cl_2 (ii) $Me_2C{=}CHCH_2MgCl$, CuI, THF, -25°C (iii) PhSeSePh, $NaBH_4$, EtOH, reflux (iv) 35% H_2O_2, THF, 0 --> 20°C (v) PCC, CH_2Cl_2; separation of diastereomers.

Scheme 168

* An alternative procedure[271b] has been reported recently by Carman and co-workers.

A method for the separation of the diastereomers of limonene-1,2-oxide is presented in the synthesis of the southern green stinkbug sex pheromone (Scheme 169) by Baker and co-workers.[274] Limonene-1,2-oxide was initially converted to the *vic*-hydroxy-amines **1a** and **1b**. The corresponding tosylate salts were separated by recrystallization, and the oxirane ring was then re-formed. The side chain of the pheromone was introduced via Julia olefination reaction which yielded a mixture of 2*E* and 2*Z* isomers.

Sex Pheromone of the Southern Green Stinkbug[274]

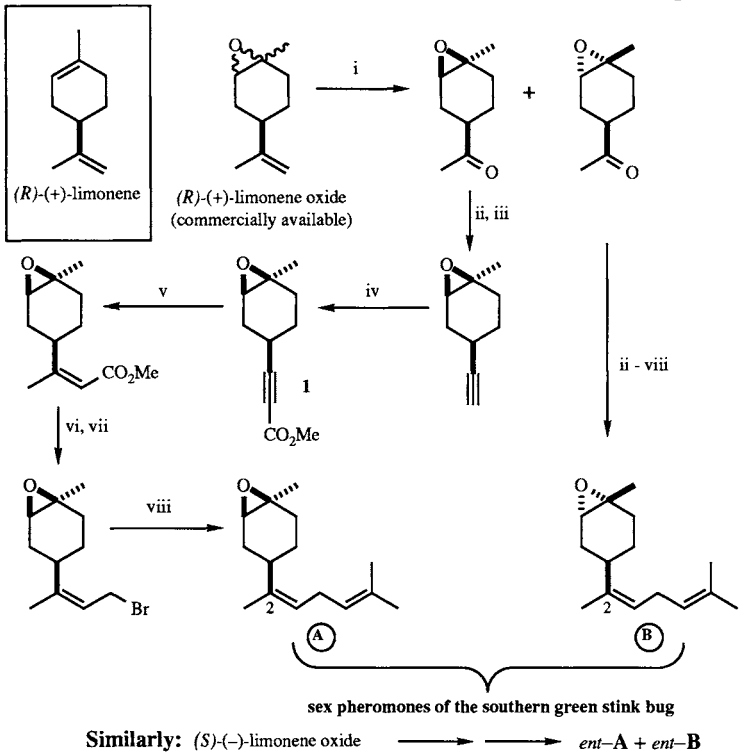


Scheme 169

Nicolaou and Marron have also synthesized the southern green stinkbug sex pheromones (Scheme 170)[275] from limonene-1,2-oxide. However, in contrast to the approach presented above, they were able to obtain the 2*Z* isomers exclusively through the conjugate addition of an organocuprate to α,β–acetylenic ester **1**.

The monoterpenoid *(S)*-(–)-perillaldehyde has been used as a chiral starting material in a number of natural product syntheses (see Section 6 of this review). On the other hand, its enantiomer, although naturally occurring, remains commercially unavailable.[276] For this reason, Tius and Kerr were prompted to develop a convenient synthetic route to *(R)*-(+)-perillaldehyde (Scheme 171)[276] from (+)-limonene oxide. Conversion of the allylic alcohol **1** to the phenylsulfenate **2** occurred with concomitant [2,3]-sigmatropic rearrangement to provide sulfoxide **3**. Subsequent Pummerer rearrangement and hydrolysis led to the desired *(R)*-(+)-perillaldehyde.

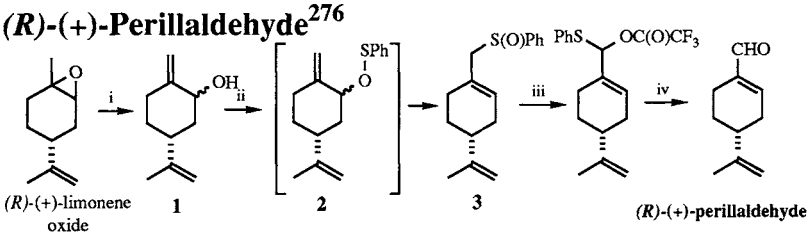
Sex Pheromones of the Southern Green Stink Bug[275]



(i) O_3, CH_2Cl_2, –78°C; PPh_3, –78°C; separation (ii) LDA, THF, –78°C; $(EtO)_2P(O)Cl$ (iii) LDA, THF, –78°C (iv) n-BuLi, THF, $ClCO_2Me$, –20 —> 0°C (v) Me_2CuLi, THF, –78°C (vi) DIBAL, THF, –78°C (vii) CBr_4, PPh_3, CH_2Cl_2, –40°C (viii) 1-bromo-2-methylpropene, t-BuLi, THF, –78°C.

Scheme 170

(R)-(+)-Perillaldehyde[276]

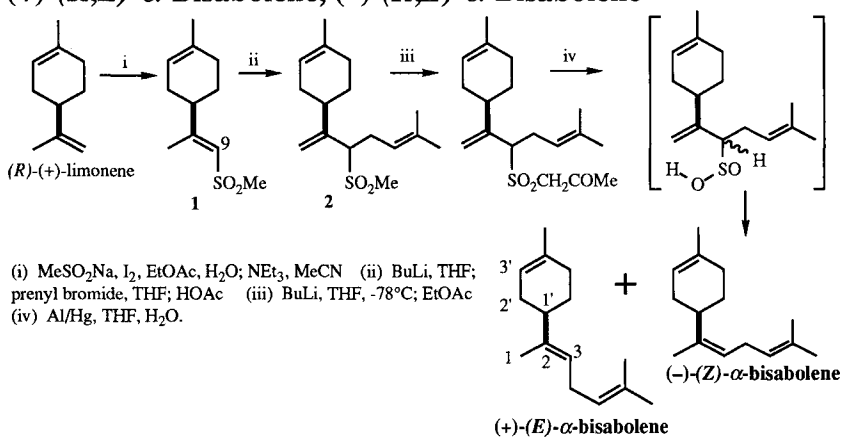


(i) methylmagnesium *N*-isopropylcyclohexylamide, toluene, 0°C (ii) PhSCl, Et_3N, CH_2Cl_2, –78°C (iii) trifluoroacetic anhydride, 2,6-lutidine, CH_4CN, –40°C (iv) $HgCl_2$, H_2O.

Scheme 171

Conversion of limonene to the 9-methylsulfonyl derivative **1** (Scheme 172)[277] has provided a means for introducing alkyl units at the C(9) position of limonene. For example, alkylation of **1** followed by acylation of the sulfone **2** and reductive desulfurization provided the 2*E* and 2*Z* isomers of *(R)*-α-bisabolene.

(+)-*(R,Z)*-α-Bisabolene, (–)-*(R,E)*-α-Bisabolene[277]

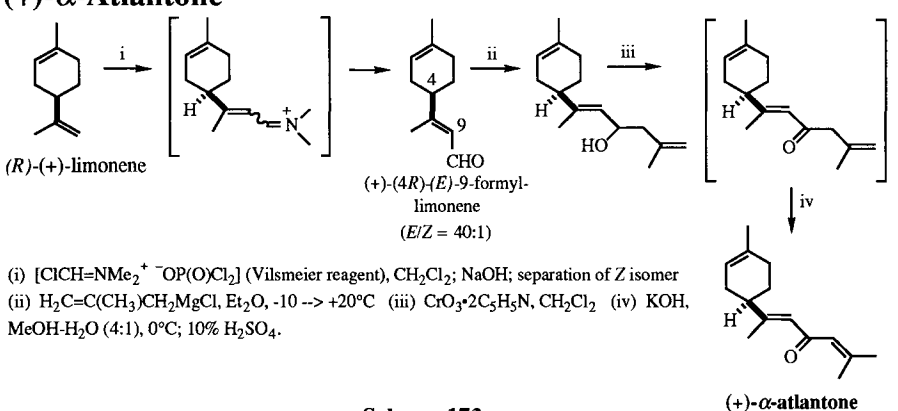


(i) $MeSO_2Na$, I_2, EtOAc, H_2O; NEt_3, MeCN (ii) BuLi, THF; prenyl bromide, THF; HOAc (iii) BuLi, THF, -78°C; EtOAc (iv) Al/Hg, THF, H_2O.

Scheme 172

(+)-(4*R*)-(*E*)-9-Formyllimonene has been prepared by Vilsmeier formylation of limonene, and has been used in a synthesis of the sesquiterpenoid (+)-α–atlantone (Scheme 173).[278]

(+)-α-Atlantone[278]

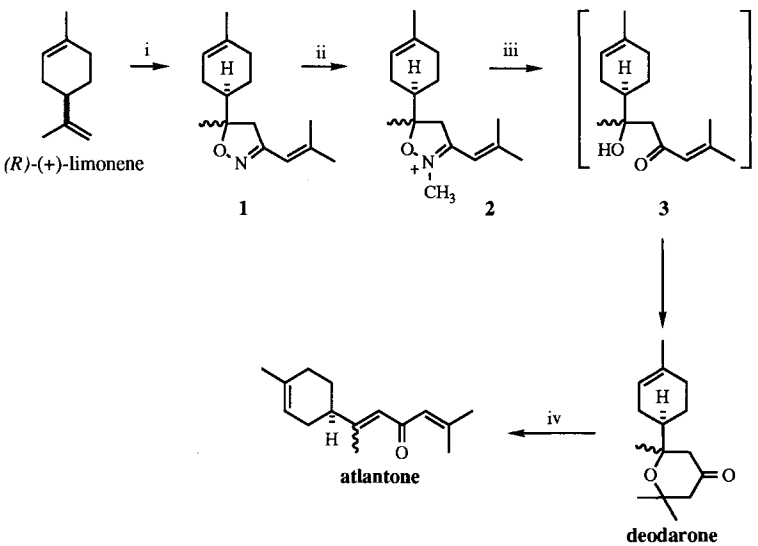


(i) $[ClCH{=}NMe_2^+\ {}^-OP(O)Cl_2]$ (Vilsmeier reagent), CH_2Cl_2; NaOH; separation of *Z* isomer (ii) $H_2C{=}C(CH_3)CH_2MgCl$, Et_2O, -10 --> +20°C (iii) $CrO_3{\cdot}2C_5H_5N$, CH_2Cl_2 (iv) KOH, MeOH-H_2O (4:1), 0°C; 10% H_2SO_4.

Scheme 173

The key step in the synthesis of deodarone (Scheme 174) by Torssell and co-workers[279] is a 1,3-dipolar nitrile oxide cycloaddition reaction with the limonene $\Delta^{8,9}$ bond. *N*-methylation of the isoxazole **1** followed by electrochemical reduction[280] of the isoxazolinium salt **2** yielded an intermediate hydroxy-ketone **3** that cyclized spontaneously to provide deodarone. In addition, acid-catalyzed opening of the tetrahydropyrone ring of deodarone furnished the sesquiterpenoid atlantone.

Deodarone, Atlantone[279]

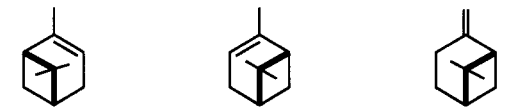


(i) 3,3-dimethylacrylonitrile *N*-oxide, $CHCl_3$ (ii) $(MeO)_2SO_2$, $NaHCO_3$, $CHCl_3$ (iii) 40% aq. EtOH, acetate buffer, pH ~ 5, –0.60 *V* (*vs.* SCE) (iv) p-TsOH, CH_2Cl_2, 30°C

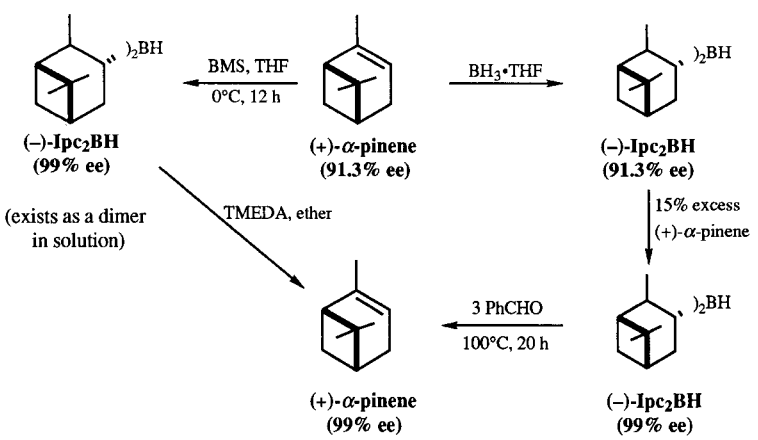
Scheme 174

5. PINENE

(+)-α-Pinene, (–)-α-pinene, and (–)-β-pinene are commercially available compounds. It has been noted,[281a] however, that the commercial samples are ~91.3%, ~81%, and ~92% enantiopure, respectively. (–)-α-Pinene of higher purity (92% ee) can readily be obtained[282] by isomerization of commercial (–)-β-pinene with potassium 3-aminopropylamide (KAPA). A simple procedure[281a] (Scheme 175) for upgrading (+)-

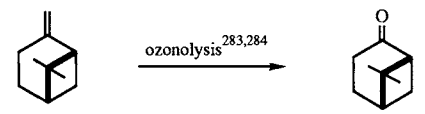


α-pinene (91.3% ee) and (–)-α-pinene (92% ee) to material of 99% enantiomeric purity involves initial conversion to crystalline diisopinocampheylborane (Ipc_2BH). Subsequent treatment of Ipc_2BH with 15% excess α-pinene causes the major enantiomer to become incorporated into the crystalline Ipc_2BH with the minor enantiomer accumulating in solution. The crystalline Ipc_2BH (99% ee) thus formed provides α-pinene (99% ee) on treatment with benzaldehyde at 100°C. A more direct, simplified procedure has also been reported.[281c] This involves hydroboration of α-pinene with borane-dimethyl sulfide complex (BMS),[281b] followed by treatment of isolated Ipc_2BH (99% ee) with TMEDA.



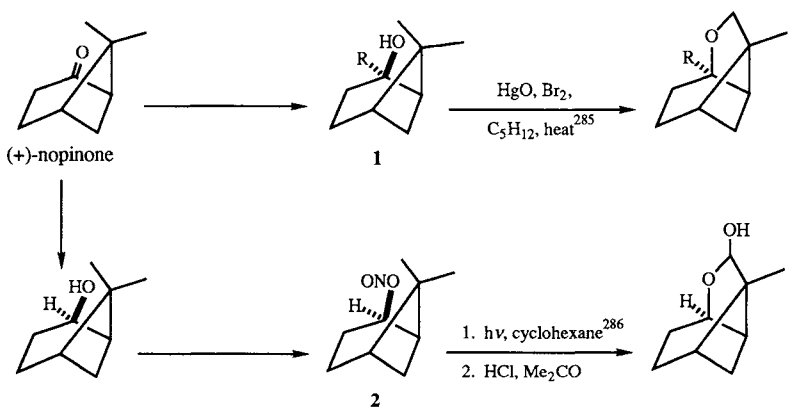
Scheme 175

The use of the pinenes and their derivatives as chiral starting materials is illustrated in Schemes 177–197. Of the commercially available pinenes, (–)-β-pinene has been the most frequently used as an enantiopure starting material in natural product synthesis. Often (*cf.* Scheme 177–185, 189, and 197), the initial step in the synthesis is the conversion[283,284] of (–)-β-pinene to (+)-nopinone, and indeed, the latter compound is



(–)-β-pinene (+)-nopinone

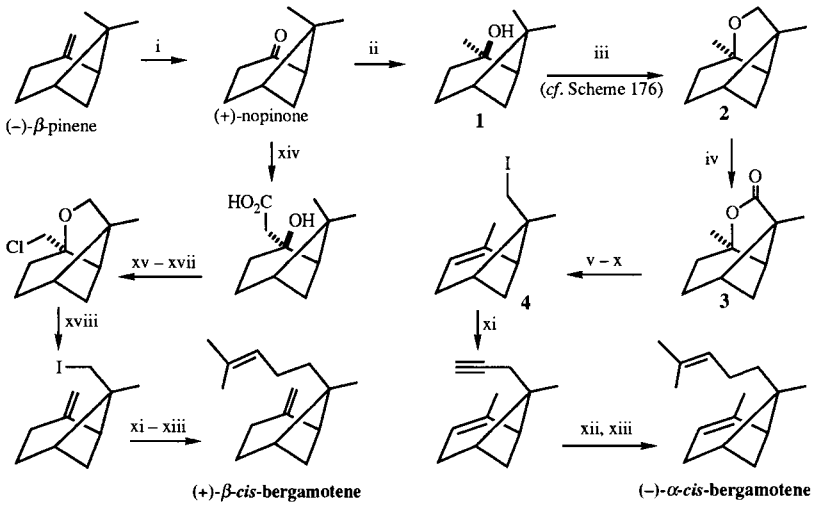
also commercially available. Another notable transformation (*cf.* Scheme 176) is the functionalization of one of the *gem*-dimethyl groups of the pinane structure by radical cyclization of a tertiary alcohol (**1**)[285] or a secondary nitrite ester (**2**)[286] derived from



Scheme 176

nopinone. This general strategy was employed by Erman and co-workers in their synthesis of (–)-α-*cis*-bergamotene (Scheme 177).[287] The tricyclic ether **2**, prepared by radical cyclization of the tertiary alcohol **1**, was oxidized to the γ-lactone, **3**. Conversion of **3** to the unsaturated iodide **4** made possible the subsequent addition of a five-carbon side chain unit to complete the synthesis of (–)-α-*cis*-bergamotene. The isomeric (+)-β-*cis*-bergamotene was prepared in a similar manner.

(–)-α-*cis*-Bergamotene, (+)-β-*cis*-Bergamotene[287]



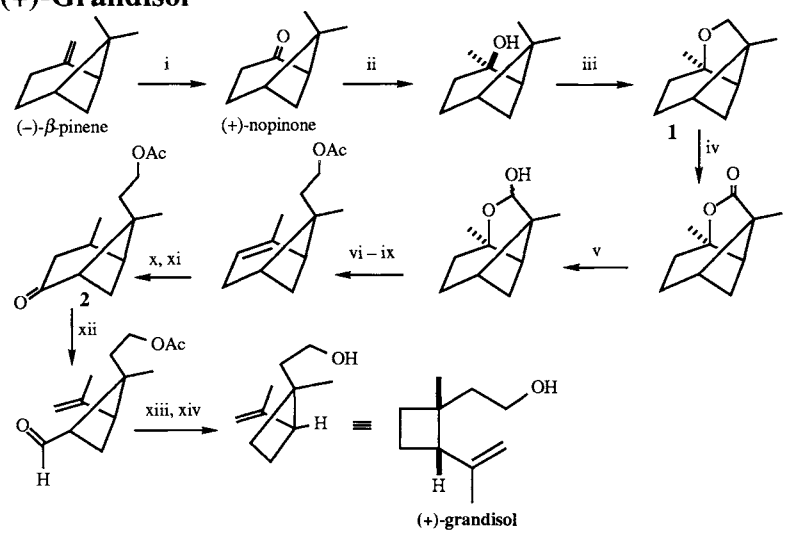
(i) O_3, CH_2Cl_2 (ii) MeLi, Et_2O (iii) HgO, Br_2, pentane, heat (iv) CrO_3, Ac_2O, HOAc (v) $LiAlH_4$, Et_2O (vi) Ac_2O, C_5H_5N (vii) $POCl_3$, C_5H_5N, 0°C (viii) $LiAlH_4$, Et_2O (ix) p-TsCl, C_5H_5N (x) NaI, Me_2CO, heat (xi) lithium acetylide ethylenediamine complex, DMSO, 0°C (xii) disiamylborane, THF; NaOH, H_2O_2 (xiii) $Ph_3P{=}CMe_2$, THF (xiv) Zn, $BrCH_2CO_2Et$ (xv) HgO, Br_2, pentane, heat (xvi) KOH, MeOH (xvii) $Pb(OAc)_4$, C_6H_6, NaCl (xviii) Na, DME; MeOH.

Scheme 177

In order to synthesize (+)-grandisol, Magnus and co-workers transformed the tricyclic ether **1** (Scheme 178)[288] into the bicyclic keto-acetate **2**. The desired cyclobutane ring is then obtained through photochemical opening of the six-membered ring of **2**.

In the synthesis of (+)-*trans*-sesquifenchene (Scheme 179) by Bessière-Chrétien and Grison,[289] treatment of tricyclic ether **1** with $BF_3{\cdot}OEt_2$ and acetic anhydride resulted in Wagner-Meerwein rearrangement and addition of acetate to provide a 90:10 mixture of the substituted bicyclo[2.2.1]heptane systems **2** and **3**. Acid-catalyzed isomerization led to a 20:80 mixture of **2** and **3**. The major alcohol **3** was subjected to another Wagner-Meerwein rearrangement to provide the unsaturated acetate **4**. Conversion of **4** to the corresponding iodide followed by nickel-mediated coupling of the prenyl unit provided (+)-*trans*-sesquifenchene. A related coupling reaction was carried out as the last step in the synthesis of (–)-α-*cis*-bergamotene (Scheme 180) by Linstrumelle and co-workers.[290]

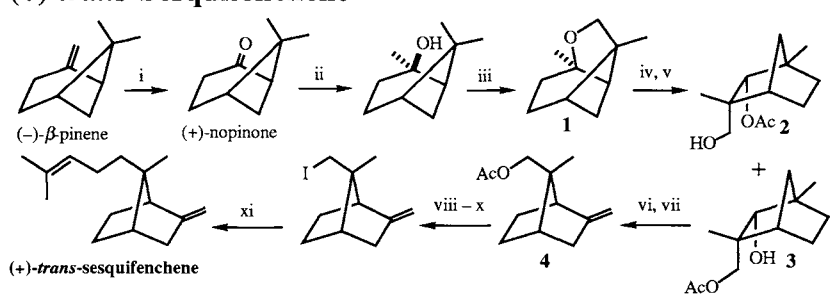
(+)-Grandisol[288]



(i) O_3, CH_2Cl_2 (ii) MeLi, Et_2O (iii) HgO, Br_2, pentane, heat (iv) RuO_2, KIO_4, CCl_4, H_2O (v) $LiAlH(OEt)_3$, Et_2O (vi) $Ph_3P{=}CH_2$, DMSO (vii) $(sia)_2BH$, THF; H_2O_2, NaOH (viii) Ac_2O, C_5H_5N (ix) $POCl_3$, C_5H_5N, 0°C (x) $CrO_3{\cdot}2C_5H_5N$, CH_2Cl_2 (xi) H_2, Pd, EtOH (xii) MeOH, $NaHCO_3$, hν (xiii) $(Ph_3P)_3RhCl$, CH_2Cl_2 (xiv) $LiAlH_4$, Et_2O.

Scheme 178

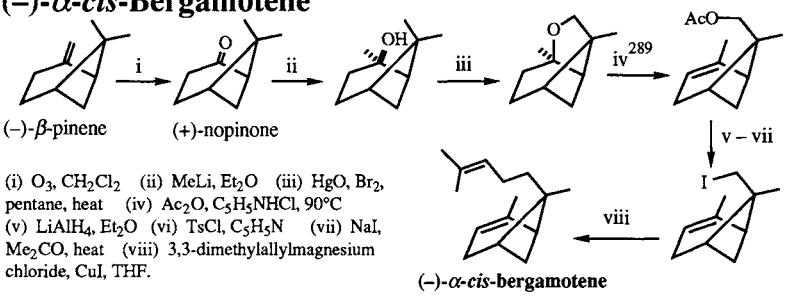
(+)-*trans*-Sesquifenchene[289]



(i) O_3, CH_2Cl_2 (ii) MeLi, Et_2O (iii) HgO, Br_2, pentane, heat (iv) $BF_3{\cdot}Et_2O$, Ac_2O, 0°C (v) CCl_4, H^+, heat (vi) TsCl, C_5H_5N (vii) NaOAc, HOAc, 90°C (viii) $LiAlH_4$, Et_2O (ix) TsCl, C_5H_5N (x) NaI, Me_2CO (xi) $(Me_2C{=}CHCH_2NiBr)_2$, DMF.

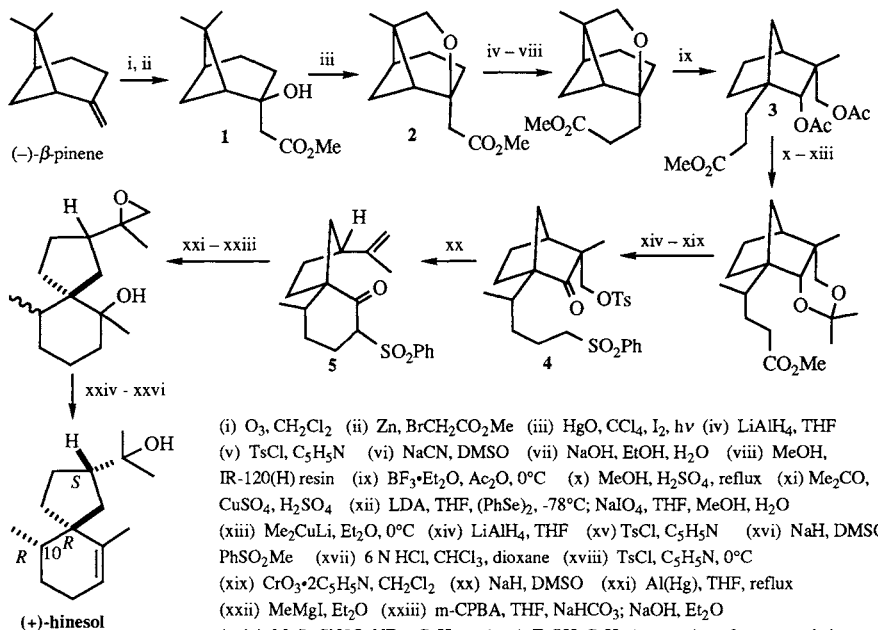
Scheme 179

(–)-α-*cis*-Bergamotene[290]



Scheme 180

(+)-Hinesol (*ent*-Hinesol)[291]



Scheme 181

Magnus and co-workers successfully carried out the radical cyclization of hydroxy-ester **1** (Scheme 181)[291] to provide the tricyclic ester **2**. Subsequent Wagner-

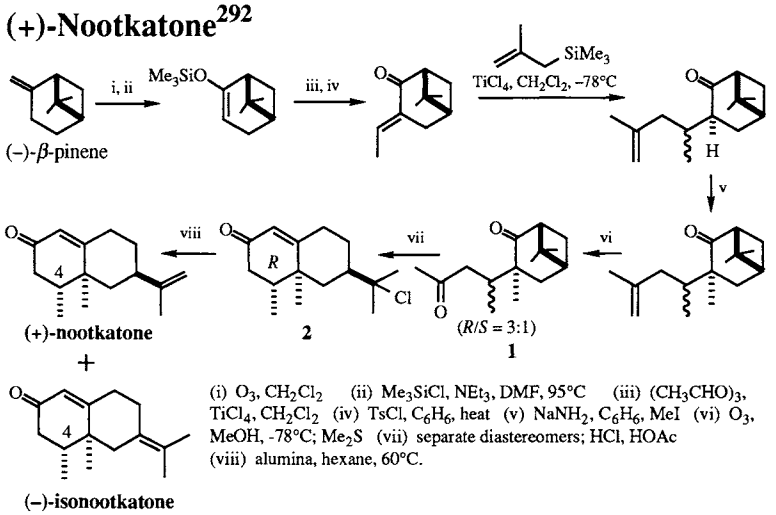
Meerwein rearrangement led to the substituted bicyclo[2.2.1]heptane system **3** that was transformed to the keto-sulfone **4** using straightforward procedures. Treatment of **4** with base resulted in cyclization with concomitant elimination of tosylate to furnish α-sulfonyl-ketone **5** which possesses the spiro[4.5]decane ring system found in (+)-hinesol.

The synthesis of (+)-nootkatone (Scheme 182) by Yoshikoshi and co-workers[292] involves acid-catalyzed aldol condensation of the dione **1** to provide chloro-enone **2**. Subsequent dehydrochlorination yielded a 95:5 mixture of (+)-nootkatone and (–)-isonootkatone.

The conversion of (–)-β-pinene to (+)-nopinone is the first step in the synthesis of (+)-nootkatone (Scheme 183) by Torii and co-workers.[293] Whereas Yoshikoshi and co-workers (*cf.* Scheme 182) obtained 3:1 mixture of diastereomers at C(4) in their synthesis of nootkatone, Torii's group was able to control the C(4) stereochemistry by performing a dissolving metal reduction of the exo-methylene group in the bicyclic enol ether **1**. The diketone **2** is the same as that prepared by Yoshikoshi's group; thus, this constitutes a formal synthesis of (+)-nootkatone.

In a third synthesis of (+)-nootkatone (Scheme 184), Takagi and co-workers[294] converted (–)-β-pinene the monocyclic ketone **1** in five steps using patented procedures.[295] Subsequent Robinson-type annulation furnished (+)-nootkatone and (–)-7-*epi*-nootkatone.

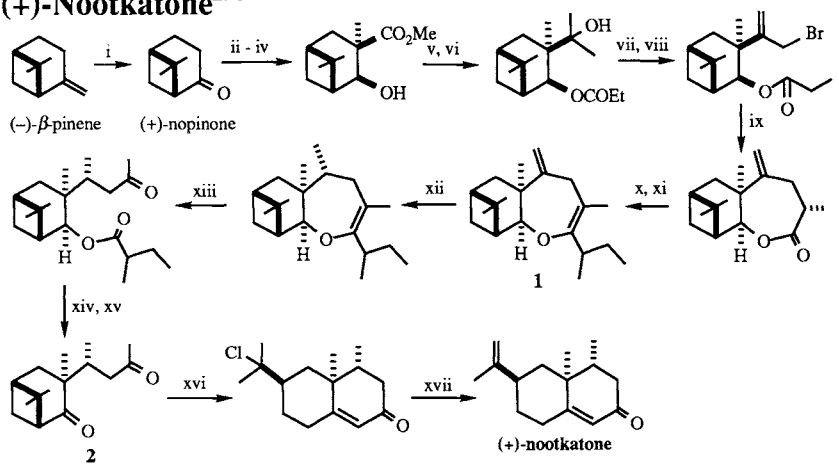
(+)-Nootkatone[292]



(i) O_3, CH_2Cl_2 (ii) Me_3SiCl, NEt_3, DMF, 95°C (iii) $(CH_3CHO)_3$, $TiCl_4$, CH_2Cl_2 (iv) TsCl, C_6H_6, heat (v) $NaNH_2$, C_6H_6, MeI (vi) O_3, MeOH, -78°C; Me_2S (vii) separate diastereomers; HCl, HOAc (viii) alumina, hexane, 60°C.

Scheme 182

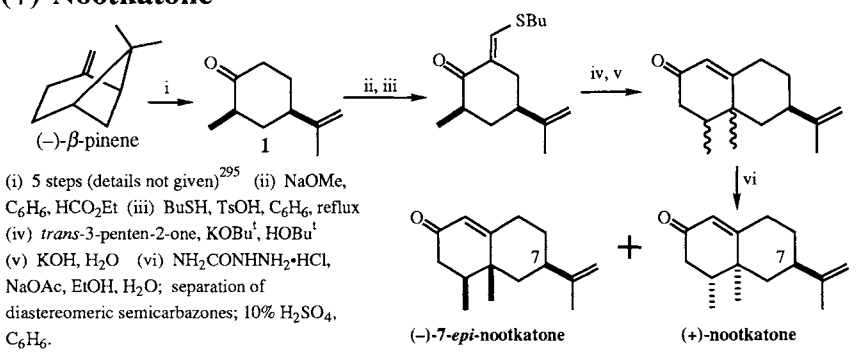
(+)-Nootkatone[293]



(i) O_3, CH_2Cl_2; MeOH, H_2O, heat (ii) NaH, $(MeO)_2CO$, heat (iii) K_2CO_3, Me_2CO; MeI (iv) $NaBH_4$, MeOH, H_2O (v) MeMgI, Et_2O, reflux (vi) $(CH_3CH_2CO)_2O$, C_5H_5N, 100°C (vii) $SOCl_2$, C_5H_5N (viii) NBS, CCl_4, heat (ix) LICA, THF, -50°C; HMPA, 20°C (x) *sec*-BuLi, THF, -78°C (xi) DHP, PPTS (xii) Li, $EtNH_2$, t-BuOH, -30°C (xiii) O_3, CH_2Cl_2, MeOH, -78°C; Me_2S (xiv) $LiAlH_4$, Et_2O (xv) PCC, NaOAc, CH_2Cl_2 (xvi) HCl, HOAc (xvii) alumina, hexane, 60°C.

Scheme 183

(+)-Nootkatone[294]



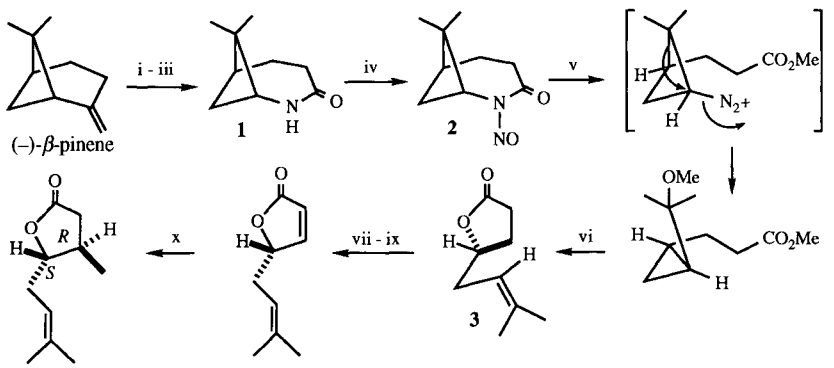
(i) 5 steps (details not given)[295] (ii) NaOMe, C_6H_6, HCO_2Et (iii) BuSH, TsOH, C_6H_6, reflux (iv) *trans*-3-penten-2-one, $KOBu^t$, $HOBu^t$ (v) KOH, H_2O (vi) $NH_2CONHNH_2$•HCl, NaOAc, EtOH, H_2O; separation of diastereomeric semicarbazones; 10% H_2SO_4, C_6H_6.

Scheme 184

An application of the cyclobutyl-cyclopropylmethyl-homoallyl cation rearrangement is seen in the synthesis of (–)-eldanolide (Scheme 185) by Yokoyama and Yunokihara.[296] The lactam **1**, prepared by Beckmann rearrangement of the oxime

derived from nopinone, was converted to the corresponding *N*-nitroso-lactam **2**. Treatment with base yielded the corresponding diazonium salt that underwent a cyclobutyl-cyclopropylmethyl cation rearrangement. Subsequent treatment with acid promoted a cyclopropyl-homoallyl cation rearrangement to provide enantiopure lactone **3** which was converted to (–)-eldanolide in four steps.

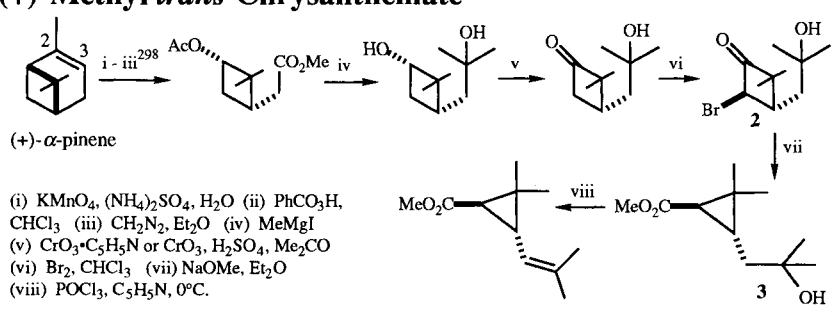
(–)-Eldanolide (*ent*-Eldanolide)[296]



(i) O_3, MeOH, -78°C (ii) $NH_2OH{\cdot}HCl$, C_5H_5N (iii) TsCl, C_5H_5N (iv) $NaNO_2$, Ac_2O (v) NaOMe (cat.), MeOH, 0°C (vi) TsOH, C_6H_6, reflux (vii) LDA, THF, -78°C; PhSSPh (viii) m-CPBA, CH_2Cl_2, - 78°C (ix) CCl_4, heat (x) Me_2CuLi, Et_2O, -78°C.

Scheme 185

(+)-Methyl *trans*-Chrysanthemate[297]



(i) $KMnO_4$, $(NH_4)_2SO_4$, H_2O (ii) $PhCO_3H$, $CHCl_3$ (iii) CH_2N_2, Et_2O (iv) MeMgI (v) $CrO_3{\cdot}C_5H_5N$ or CrO_3, H_2SO_4, Me_2CO (vi) Br_2, $CHCl_3$ (vii) NaOMe, Et_2O (viii) $POCl_3$, C_5H_5N, 0°C.

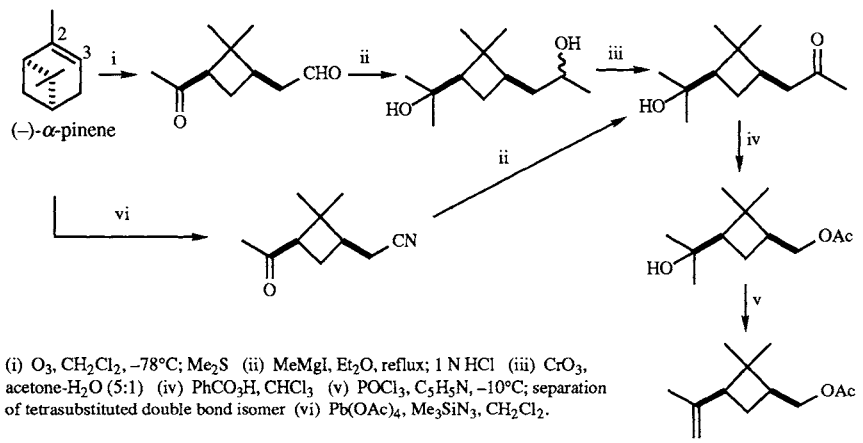
(+)-methyl *trans*-chrysanthemate

Scheme 186

The synthesis of (+)-methyl *trans*-chrysanthemate (Scheme 186) by Mitra and Khanra[297] involves initial oxidative cleavage of the C(2)–C(3) double bond of (+)-α-pinene followed by Baeyer-Villiger oxidation and esterification to provide the intermediate acetoxy-ester **1**. This was converted to the bromoketone **2** which underwent a Favorskii rearrangement to yield the ring-contracted hydroxy-ester **3**. The desired (+)-methyl *trans*-chrysanthemate was then obtained by dehydration of **3**.

Ozonolytic ring opening of (–)-α-pinene was a key step in the preparation of the sex pheromone of the grape mealy bug (Scheme 187).[299] The chirality of the two stereocentres in the final product are derived from those in (–)-α-pinene.

Sex Pheromone of the Mealy Bug *Planococcus citri*[299]



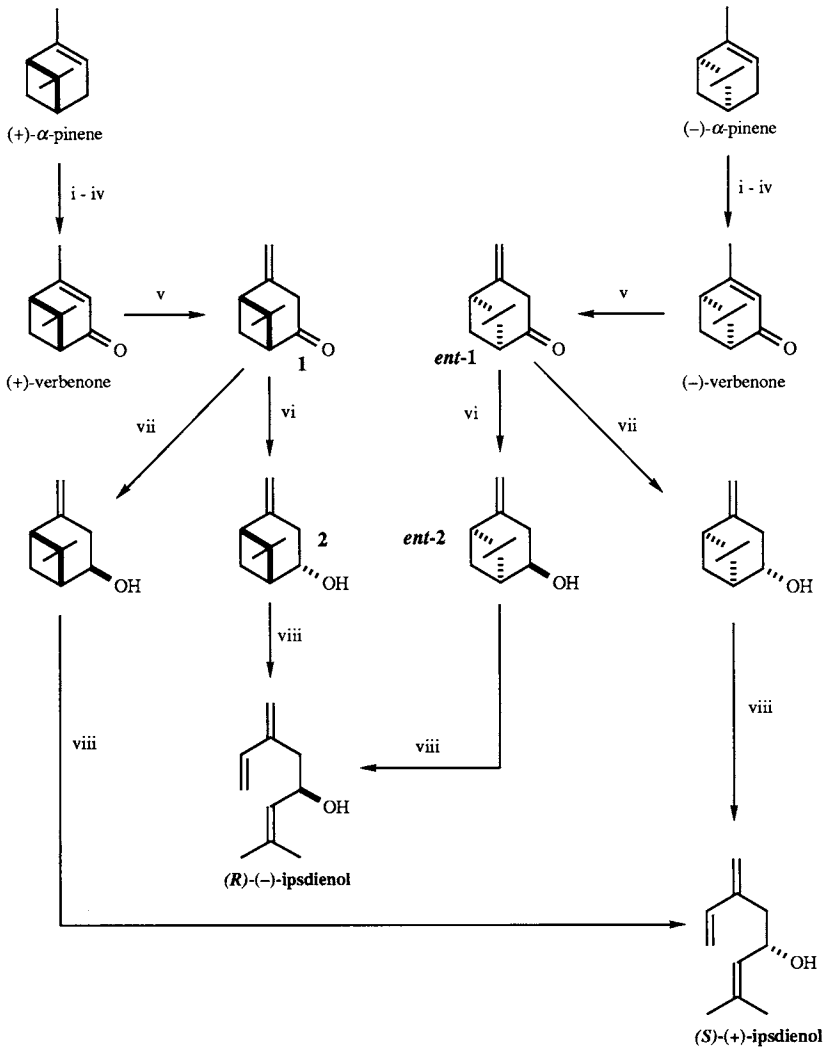
(i) O_3, CH_2Cl_2, –78°C; Me_2S (ii) MeMgI, Et_2O, reflux; 1 N HCl (iii) CrO_3, acetone-H_2O (5:1) (iv) $PhCO_3H$, $CHCl_3$ (v) $POCl_3$, C_5H_5N, –10°C; separation of tetrasubstituted double bond isomer (vi) $Pb(OAc)_4$, Me_3SiN_3, CH_2Cl_2.

sex pheromone of the mealy bug *Planococcus citri*

Scheme 187

In an enantioselective synthesis of (*R*)-(–)- and (*S*)-(+)-ipsdienol (Scheme 188),[300] (+)-α-pinene was first converted to (+)-verbenone in four steps using Whitham's procedure.[301] With oxygen functionality now in place at C(4), stereoselective reduction of the unsaturated ketones **1** and ***ent*-1** with lithium aluminum hydride or lithium-liquid ammonia yielded the alcohols **2** and ***ent*-2**, respectively. Flash vacuum pyrolysis then provided the two enantiomeric ipsdienols. An alternative sequence from (–)-α-pinene is also shown on Scheme 188.

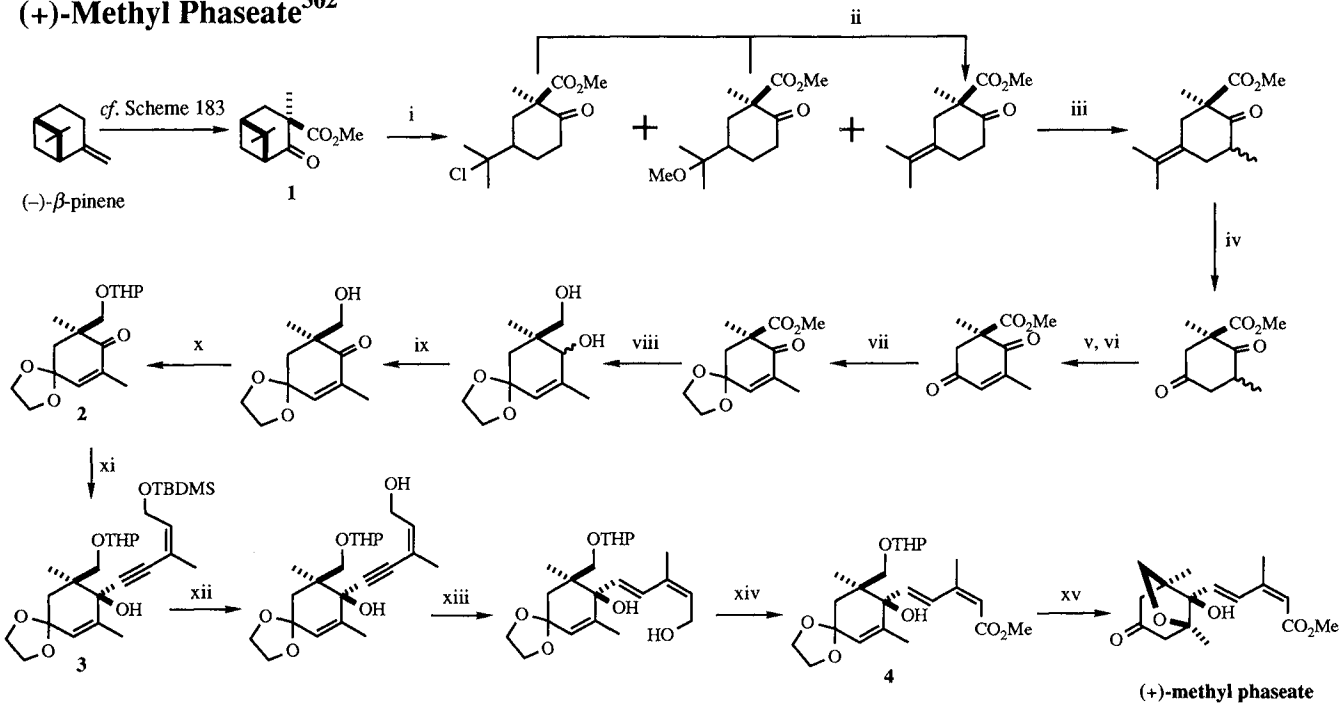
(R)-(–)-Ipsdienol, *(S)*-(–)-Ipsdienol[300]



(i) $Pb(OAc)_4$, C_6H_6, 65°C (ii) HOAc (iii) KOH, aq. MeOH (iv) MnO_2, petroleum ether (v) NaH, THF; aq. H_3BO_3 (vi) $LiAlH_4$, Et_2O, reflux (vii) Li, NH_3, t-BuOH, THF, –60°C or $(i\text{-PrO})_3Al$, i-PrOH, reflux (viii) C_5H_5N, 560°C, 0.01 mmHg, 1 s.

Scheme 188

(+)-Methyl Phaseate[302]



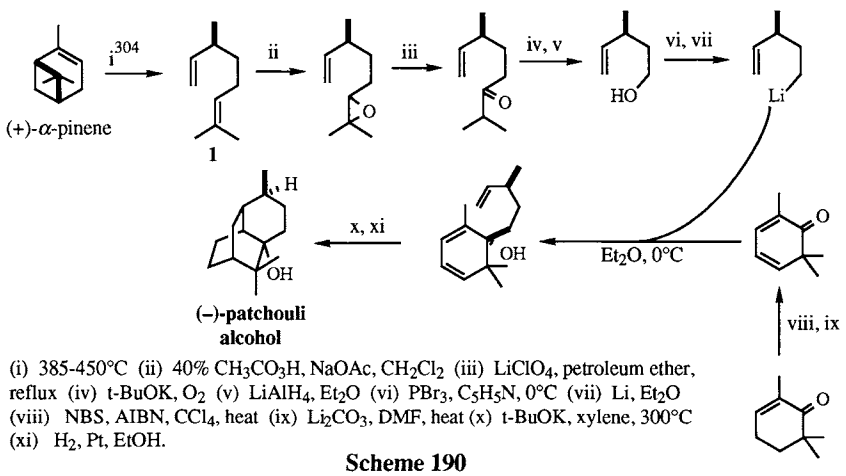
(i) HCl, MeOH (ii) SiO_2, $CHCl_3$, 65°C (iii) LDA, THF, –78°C; MeI (iv) O_3, MeOH, –78°C; Me_2S (v) PhSeCl, EtOAc (vi) H_2O_2, CH_2Cl_2-C_5H_5N, 0°C (vii) $HC(OMe)_3$, $(CH_2OH)_2$, p-TsOH, Et_2O (viii) $LiAlH_4$, Et_2O (ix) MnO_2, CH_2Cl_2 (x) DHP, PPTS, CH_2Cl_2 (xi) *trans*-1-(*t*-butyldimethylsilyloxy)-3-methylpent-2-en-4-yne, n-BuLi, THF-HMPA, –73°C; separation of diastereomers (xii) 5% NaOH, MeOH, 0°C (xiii) Red-Al, THF, 0°C; aq. NH_4Cl (xiv) MnO_2, CH_2Cl_2; MnO_2, NaCN, HOAc, MeOH (xv) 5% HCl, THF, 0—>20°C

Scheme 189

(+)-Methyl phaseate (Scheme 189) was synthesized by Takahashi and co-workers[302] who converted Torii's β-keto-ester **1**[293] to the enone **2** using standard procedures. Addition of a lithium acetylide to **2** provided a ~1:1 mixture of diastereomeric alcohols from which **3** was separated and transformed into the hydroxy-ester **4**. Acid-catalyzed hydrolysis of the protective groups in **4** resulted in cyclization to provide (+)-methyl phaseate.

The synthesis of (–)-patchouli alcohol (Scheme 190) was accomplished by Ohloff and co-workers[303] using an intramolecular Diels-Alder reaction as a key step. The dienophile component of the cycloaddition was derived from the flash pyrolytic product (**1**)[304] of (+)-α-pinene (*cf.* Scheme 188).

(–)-Patchouli Alcohol[303]

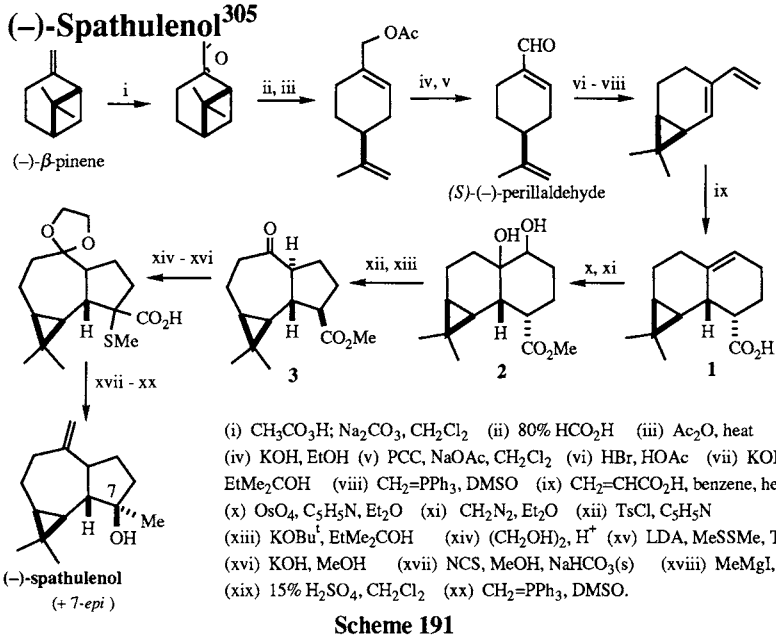


(i) 385-450°C (ii) 40% CH_3CO_3H, NaOAc, CH_2Cl_2 (iii) $LiClO_4$, petroleum ether, reflux (iv) t-BuOK, O_2 (v) $LiAlH_4$, Et_2O (vi) PBr_3, C_5H_5N, 0°C (vii) Li, Et_2O (viii) NBS, AIBN, CCl_4, heat (ix) Li_2CO_3, DMF, heat (x) t-BuOK, xylene, 300°C (xi) H_2, Pt, EtOH.

Scheme 190

The sesquiterpene (–)-spathulenol (Scheme 191) was synthesized by Mondon and Surburg[305] from (–)-β-pinene via (–)-perillaldehyde; the latter is also commercially available. The tricyclic intermediate **1** was constructed by way of a Diels-Alder cycloaddition in which the diene component was derived from (–)-perillaldehyde. Pinacol-pinacolone rearrangement of the diol **2** then provided keto-ester **3** that was converted to (–)-spathulenol by standard procedures.

(–)-Spathulenol[305]

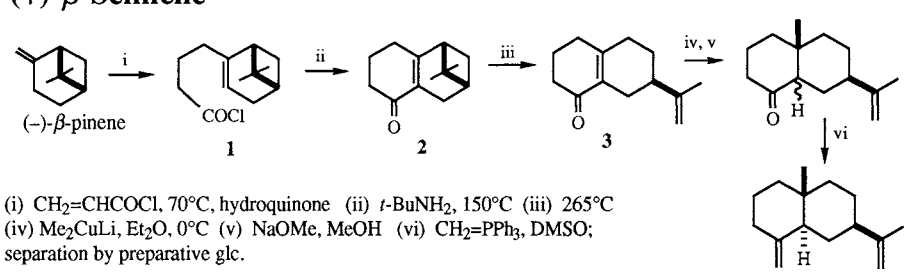


(i) CH_3CO_3H; Na_2CO_3, CH_2Cl_2 (ii) 80% HCO_2H (iii) Ac_2O, heat (iv) KOH, EtOH (v) PCC, NaOAc, CH_2Cl_2 (vi) HBr, HOAc (vii) $KOBu^t$, $EtMe_2COH$ (viii) CH_2=PPh_3, DMSO (ix) CH_2=$CHCO_2H$, benzene, heat (x) OsO_4, C_5H_5N, Et_2O (xi) CH_2N_2, Et_2O (xii) TsCl, C_5H_5N (xiii) $KOBu^t$, $EtMe_2COH$ (xiv) $(CH_2OH)_2$, H^+ (xv) LDA, MeSSMe, THF (xvi) KOH, MeOH (xvii) NCS, MeOH, $NaHCO_3$(s) (xviii) MeMgI, Et_2O (xix) 15% H_2SO_4, CH_2Cl_2 (xx) CH_2=PPh_3, DMSO.

Scheme 191

The initial step in a synthesis of (+)-β-selinene (Scheme 192)[306] is the ene reaction of acryloyl chloride with (–)-β-pinene to provide the unsaturated acyl chloride **1.** Conversion of **1** to the corresponding ketene promoted an intramolecular ene reaction with double bond isomerization to yield the enone **2.** Further heating of **2** resulted in a retro-ene reaction, again with double bond isomerization to give enone **3** that was transformed into (+)-β-selinene in three steps.

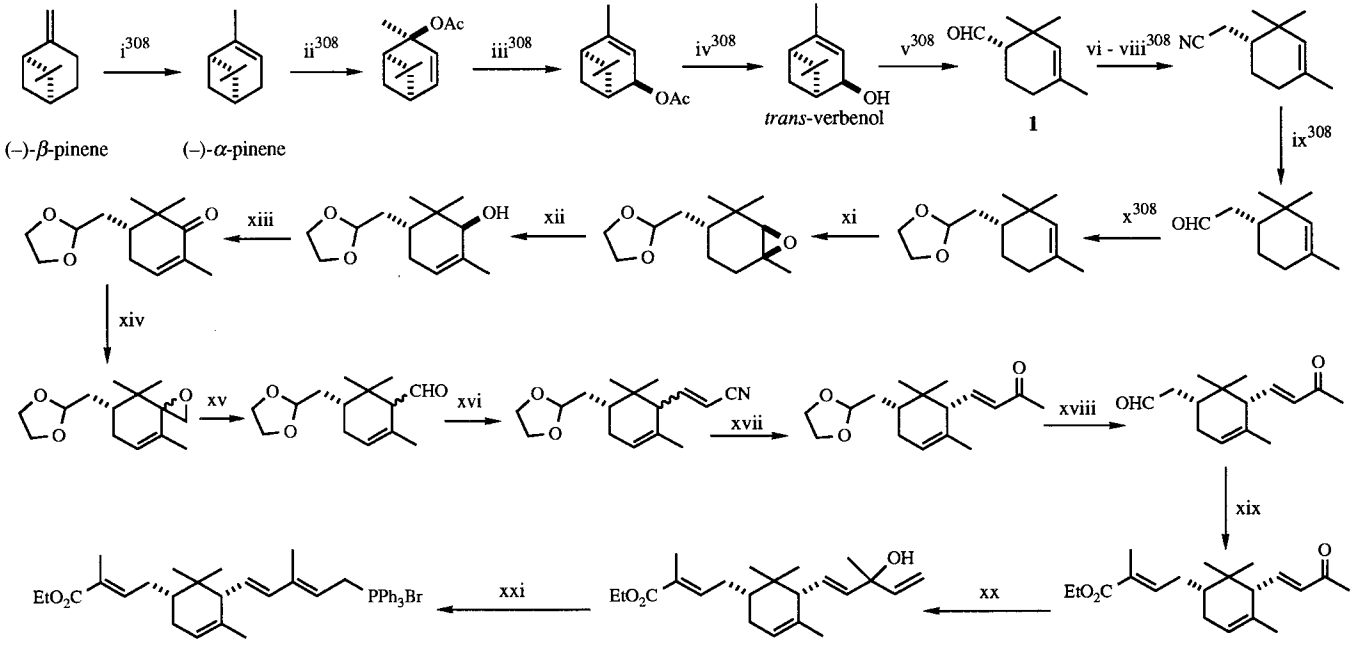
(+)-β-Selinene[306]



(i) CH_2=$CHCOCl$, 70°C, hydroquinone (ii) t-$BuNH_2$, 150°C (iii) 265°C (iv) Me_2CuLi, Et_2O, 0°C (v) NaOMe, MeOH (vi) CH_2=PPh_3, DMSO; separation by preparative glc.

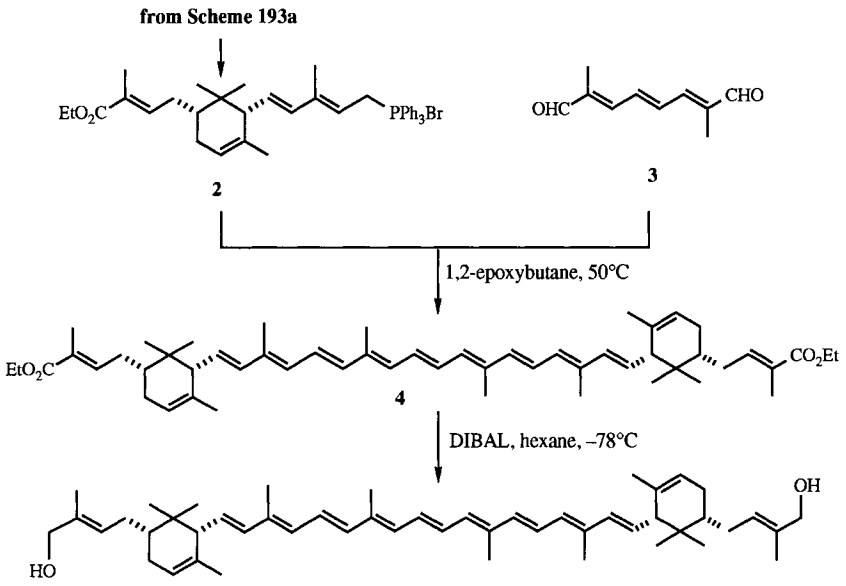
Scheme 192

Decaprenoxanthin [(2*R*,6*R*,2'*R*,6'*R*)-2,2'-Bis(4-hydroxy-3-methylbut-2-enyl)-ε,ε-carotene][307]



(i) potassium 3-aminopropylamide, 3-aminopropylamine (ii) $Pb(OAc)_4$, C_6H_6, 65°C (iii) HOAc (iv) $LiAlH_4$, Et_2O (v) 345°C (pyrolysis) (vi) $NaBH_4$, EtOH, 0°C (vii) TsCl, C_5H_5N, 0°C (viii) NaCN, DMF, 70°C (ix) DIBAL, hexane, –60°C (x) $(CH_2OH)_2$, PPTS, C_6H_6, reflux (xi) m-CPBA, CH_2Cl_2, 7% $NaHCO_3$ (xii) Filtrol®, dioxane (xiii) Cr_2O_3, H_2O, C_5H_5N (xiv) Me_3SI, n-BuLi, THF, –5°C (xv) EtMgBr, Me_2CO, toluene (xvi) $(EtO)_2P(O)CH_2CN$, NaH, THF, 0°C (xvii) MeLi, Et_2O, 0°C; separation (xviii) PPTS, Me_2CO-H_2O (9:1), reflux (xix) $(EtO)_2P(O)CH(CH_3)CO_2Et$, Na, CH_2Cl_2, 0°C (xx) CH_2=CHMgBr, THF, –78 —> 20°C (xxi) Ph_3P•HBr, MeOH

Scheme 193a



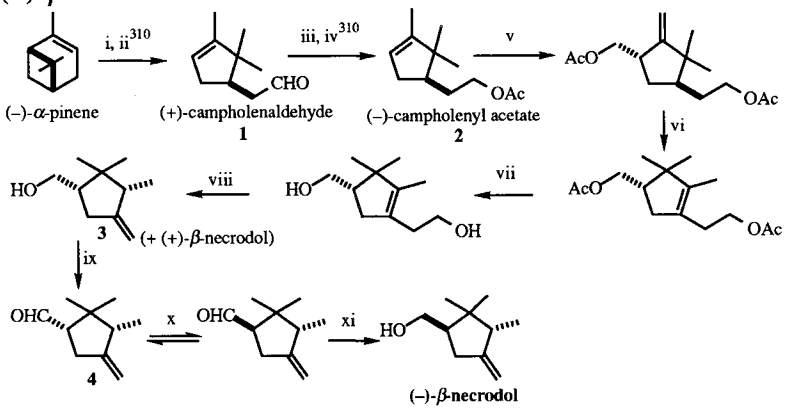
Decaprenoxanthin [(2*R*,6*R*,2'*R*,6'*R*)-2,2'-Bis(4-hydroxy-3-methylbut-2-enyl)-ε,ε-carotene]

Scheme 193b

In the synthesis of decaprenoxanthin (Scheme 193a),[307] conversion of (–)-β-pinene to (–)-α–pinene and thence to *trans*-verbenol set the stage for the pyrolytic opening of the four-membered ring to provide the substituted cyclohexenecarboxaldehyde **1**. A series of conventional transformations converted **1** to the phosphonium salt **2**. A double Wittig reaction of **2** with the dialdehyde **3** (Scheme 193b) provided the diester **4** and subsequent reduction provided the desired natural product, decaprenoxanthin.

In the synthesis of (–)-β–necrodol (Scheme 194) by Schulte-Elte and Pamingle,[309] treatment of the epoxide derived from (–)-α–pinene with $ZnBr_2$ resulted in a series of Wagner-Meerwein rearrangements to provide (+)-campholenaldehyde (**1**). Conversion of **1** to (–)-campholenyl acetate (**2**) followed by a four-step Prins—1,2-methyl shift—deprotection—retro-Prins reaction sequence yielded the exo-methylene alcohol **3**. (–)-β-necrodol was then obtained by epimerization of the hydroxymethyl substituent via the corresponding aldehyde **4**. It is noteworthy that (+)-β–necrodol was a minor co-product (1:2) during the retro-Prins reaction.

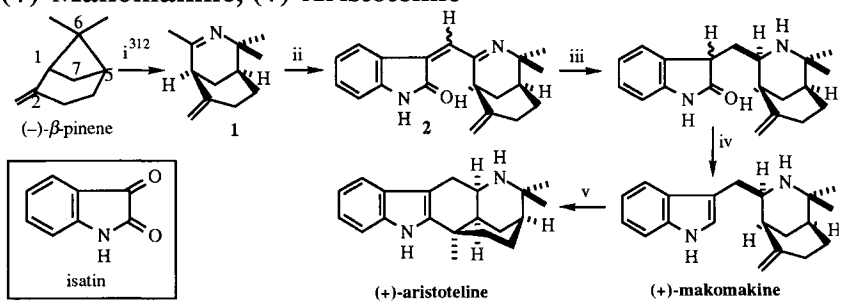
(–)-β-Necrodol[309]



(i) m-CPBA, CH_2Cl_2, aq. $NaHCO_3$ (ii) $ZnBr_2$, C_6H_6, 60°C (iii) $(i\text{-}PrO)_3Al$, i-PrOH; 50% NaOH or $LiAlH_4$, Et_2O (iv) Ac_2O, C_5H_5N (v) $(CH_2O)_n$, $BF_3{\cdot}Et_2O$, Ac_2O, CH_2Cl_2, 0°C (vi) $BF_3{\cdot}Et_2O$, toluene, 60°C (vii) $LiAlH_4$, Et_2O, 0°C (viii) 450°C, N_2, 1–5 s (ix) PCC, CH_2Cl_2, 0°C (x) NaOMe, MeOH, H_2O (xi) $LiAlH_4$, Et_2O, 0°C.

Scheme 194

(+)-Makomakine, (+)-Aristoteline[311]



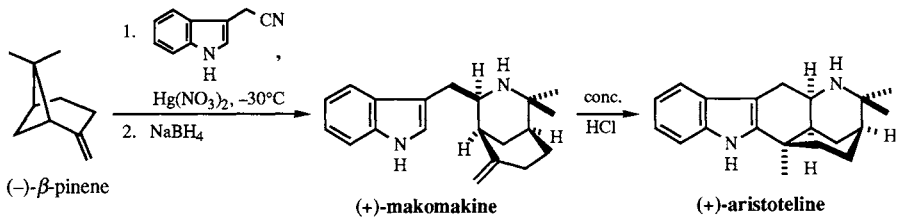
(i) $Hg(NO_3)_2$, CH_3CN (ii) isatin, piperidine, EtOH, reflux (iii) KBH_4, EtOH (iv) $LiAlH_4$, Et_2O, reflux (v) boiling concentrated HCl.

Scheme 195

The synthesis of the indole alkaloid (+)-makomakine and (+)-aristoteline (Scheme 195)[311] features a remarkable one-step conversion[312] of (–)-β–pinene to the bicyclic imine **1**. This reaction involves initial mercuration of the pinene double bond, followed by addition of acetonitrile to C(6) resulting in the fragmentation of the C(6)–C(1) bond, and finally demercuration and cyclization to provide **1**. Condensation of **1** with isatin provided the oxindole **2** that was subsequently converted to (+)-makomakine and (+)-aristoteline.

Stevens and Kenney[313] used a similar strategy (Scheme 196) to synthesize the same natural products.

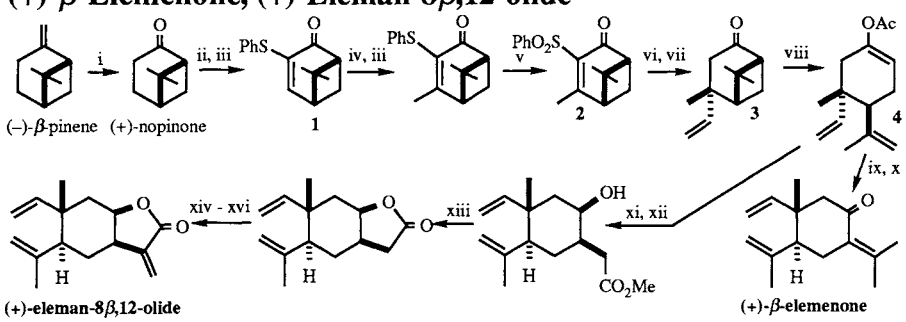
(+)-Makomakine, (+)-Aristoteline[313]



Scheme 196

In the synthesis of (+)-β-elemenone and (+)-eleman-8β,12-olide,[314] (–)-β-pinene was converted to a 4,4-disubstituted nopinone **3** by a series of conjugate addition reactions to unsaturated nopinone derivatives **1** and **2**. Cyclobutane ring opening promoted by the BF_3•OEt_2–$Zn(OAc)_2$–Ac_2O reagent combination provided the enol acetate **4** in which the stereochemistry of the isopropenyl group was retained. On the other hand, the authors noted that the use of protic acids[315] and $EtAlCl_2$[316] to effect ring opening resulted in the loss of stereochemistry at this centre. Reaction of the enol acetate with the electrophiles acetone or methyl bromoacetate provided intermediates which were converted to (+)-β-elemenone or (+)-eleman-8β,12-olide, respectively.

(+)-β-Elemenone, (+)-Eleman-8β,12-olide[314]

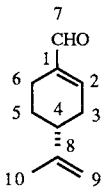


(i) O_3, CH_2Cl_2; MeOH, H_2O, heat (ii) LDA, $PhSO_2SPh$, THF, -78°C (iii) m-CPBA, CH_2Cl_2; Ac_2O, MsOH (iv) Me_2CuLi, THF, -10°C (v) m-CPBA, CH_2Cl_2 (vi) CH_2=$CHMgBr$, CuI, THF, -50°C (vii) Li, NH_3, THF (viii) BF_3•Et_2O, $Zn(OAc)_2$, Ac_2O (ix) MeLi, Et_2O, -78°C; $ZnCl_2$, Et_2O, -78°C; Me_2CO (x) $SOCl_2$, C_5H_5N; Al_2O_3, C_6H_6 (xi) MeLi, Et_2O, -78°C; $BrCH_2CO_2Me$, THF, HMPA, -78°C (xii) $LiAl(t\text{-}BuO)_3H$, THF (xiii) p-TsOH, CH_2Cl_2 (xiv) LDA, PhSeCl, THF, -78°C (xv) LDA, THF; MeI (xvi) 30% H_2O_2, C_5H_5N, THF.

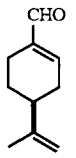
Scheme 197

6. PERILLALDEHYDE

The structures of perillaldehyde and limonene (*cf.* Section 4 of this review) are quite similar, and it is therefore not surprising that the two monoterpenoids have been used in similar fashion as starting materials in natural product synthesis. For example, C(9) functionalization can be achieved through hydroboration-oxidation of the $\Delta^{8,9}$ double bond (e.g. in Scheme 202; *cf.* Schemes 145–151), while a ring contraction sequence (e.g. in Scheme 205) comparable to that presented in the limonene section (*cf.* Scheme 152) has been employed successfully.



(S)-(–)-perillaldehyde



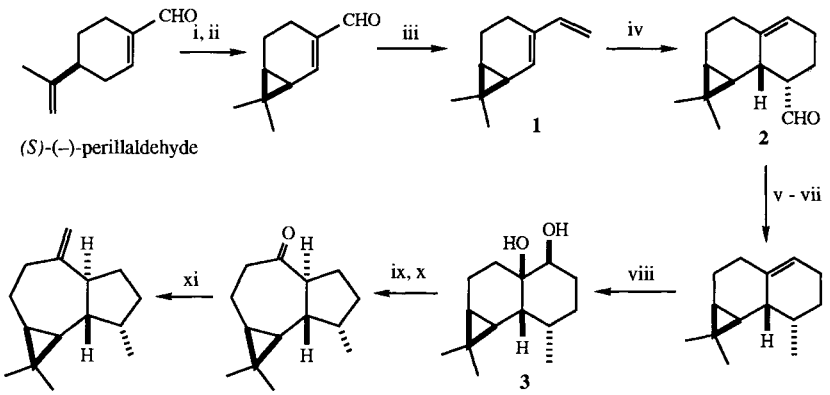
(R)-(+)-perillaldehyde

Moreover, in perillaldehyde, the aldehyde group provides oxygen functionality at C(7) and thus makes it possible for the structure to be elaborated from this part of the molecule. *(S)*-(–)-perillaldehyde is commercially available and has been used as the starting material in a number of syntheses of natural products, as exemplified in Schemes 198–205. In addition, a short synthesis of *(R)*-(+)-perillaldehyde (*cf.* Scheme 171)[276] from (+)-limonene oxide has been reported recently.

In the synthesis of (–)-aromadendrene (Scheme 198) by Büchi and co-workers,[317] *(S)*-(–)-perillaldehyde was used to prepare the diene **1** that was converted subsequently to the unsaturated tricyclic aldehyde **2** by a Diels-Alder reaction. The desired tricyclic ring system was obtained by pinacol-pinacolone rearrangement of the diol **3**.

(±)-Juvabione and (±)-epijuvabione (Scheme 199) were synthesized by Negishi, Brown, and co-workers[318] from the commercially available (±)-perillartine. The coupling of the side chain was accomplished through a hydroboration-carbonylation procedure. Of course, it should be possible to prepare either enantiomer of the above natural products using this route if enantiopure *(S)*-(–)- or *(R)*-(+)-perillaldehyde were used as starting materials.

(–)-Aromadendrene (*ent*-Aromadendrene)[317]

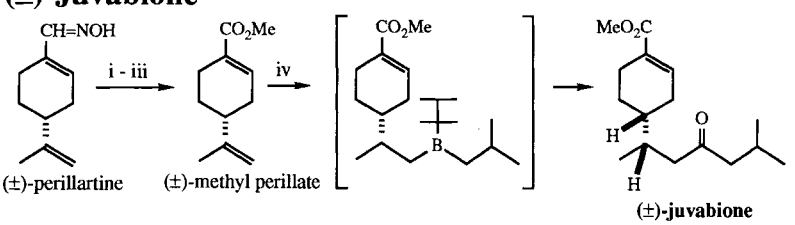


(–)-aromadendrene

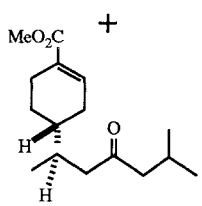
(i) HBr, HOAc (ii) t-BuOK, $EtMe_2COH$ (iii) NaH, DMSO, CH_3PPh_3Br (iv) CH_2=CHCHO, C_6H_6, 100°C (v) $LiAlH_4$, Et_2O (vi) MsCl, C_5H_5N (vii) $LiAlH_4$, Et_2O (viii) OsO_4, Et_2O, C_5H_5N (ix) TsCl, C_5H_5N (x) alumina or $EtMe_2COK$, $EtMe_2COH$ (xi) NaH, DMSO, CH_3PPh_3Br.

Scheme 198

(±)-Juvabione[318]



(i) Ac_2O (ii) KOH, EtOH (iii) CH_2N_2, Et_2O (iv) BH_3•THF, 2,3-dimethyl-2-butene, isobutylene, H_2O; CO, 70 atm, 50°C; H_2O_2, NaOAc, 50°C.

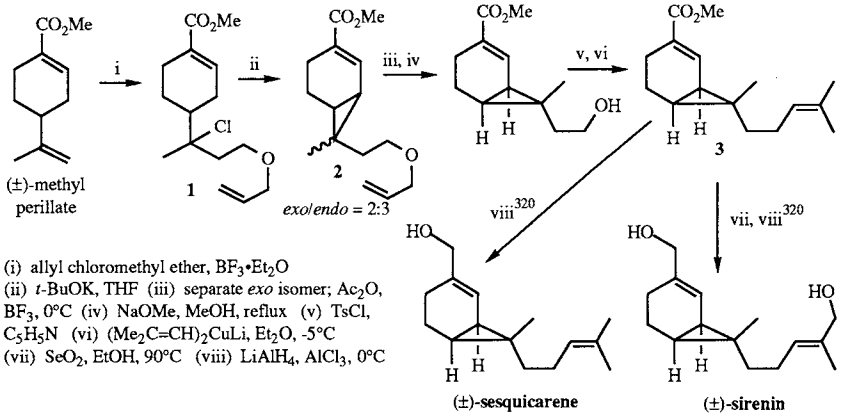


(±)-epijuvabione

Scheme 199

In the synthesis of (±)-sirenin and (±)-sesquicarene (Scheme 200),[319] the electrophilic addition of allyl chloromethyl ether to C(9) of (±)-methyl perillate provided the chloro-ester **1**. Treatment of **1** with base yielded the bicyclic ester **2** as a 2:3 mixture of exo and endo isomers. The major isomer was converted to an ester **3** that had been previously used by Plattner and co-workers[320] to prepare the same natural products. On a related note, a synthesis of (–)-sirenin from *(S)*-(–)-perillaldehyde (Scheme 201) has been reported recently by Kitahara and co-workers.[321]

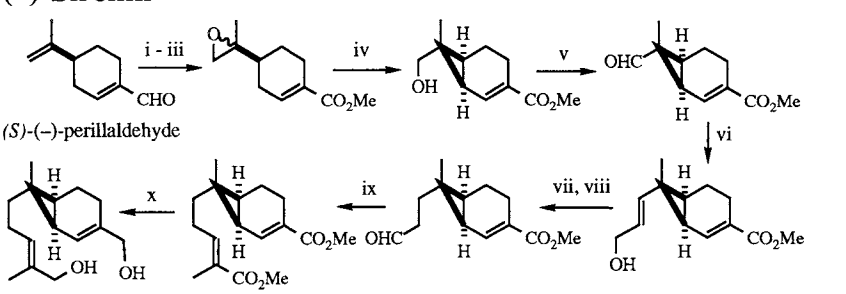
(±)-Sirenin, (±)-Sesquicarene[319]



(i) allyl chloromethyl ether, BF_3•Et_2O
(ii) *t*-BuOK, THF (iii) separate *exo* isomer; Ac_2O, BF_3, 0°C (iv) NaOMe, MeOH, reflux (v) TsCl, C_5H_5N (vi) $(Me_2C{=}CH)_2CuLi$, Et_2O, -5°C
(vii) SeO_2, EtOH, 90°C (viii) $LiAlH_4$, $AlCl_3$, 0°C

Scheme 200

(–)-Sirenin[321]

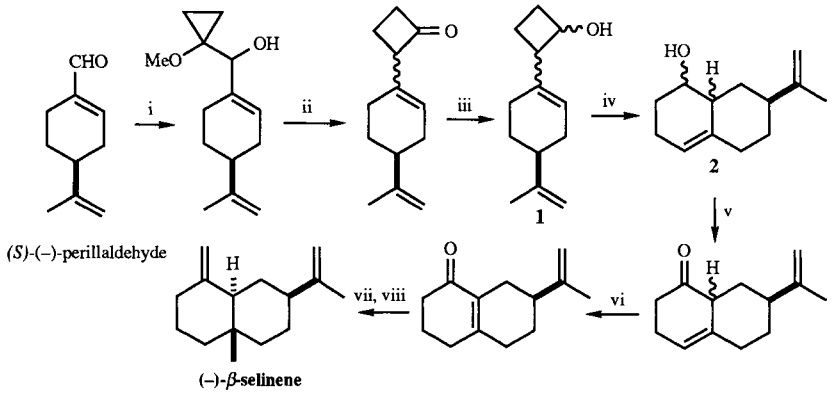


(i) $NaClO_2$, NaH_2PO_4, H_2O, 2-methyl-2-butene, t-BuOH, 0°C (ii) CH_2N_2, Et_2O (iii) m-CPBA, CH_2Cl_2 (iv) NaH, DME, reflux (v) PCC, 3Å molecular sieves, CH_2Cl_2, 0°C (vi) $HOCH_2CH_2PPh_3Br$, n-BuLi, DME, –10—>20°C (vii) H_2, PtO_2, EtOAc, 5°C (viii) PCC, 3Å molecular sieves, CH_2Cl_2, 0°C (ix) methyl 2-(diethylphosphono)propanoate, NaH, DME (x) DIBAL, toluene, –5°C.

Scheme 201

(–)-β-Selinene has been synthesized from *(S)*-(–)-perillaldehyde independently by Cohen and co-workers[322] and Harirchian and Bauld.[323] In the former synthesis (Scheme 202), *(S)*-(–)-perillaldehyde was converted to the diastereomeric alcohols **1**. The key step of this synthesis featured a [1,3]-sigmatropic vinylcyclobutane rearrangement of **1** to provide intermediate **2** which possessed the desired bicyclo[4.4.0]decane ring system of β-selinene. In the alternative synthesis[323] of (–)-β-selinene (Scheme 203), Harirchian and Bauld employed a Diels-Alder reaction of the triene **1** with phenyl vinyl sulfide to obtain the bicyclic sulfide **2** that was converted subsequently to the natural product.

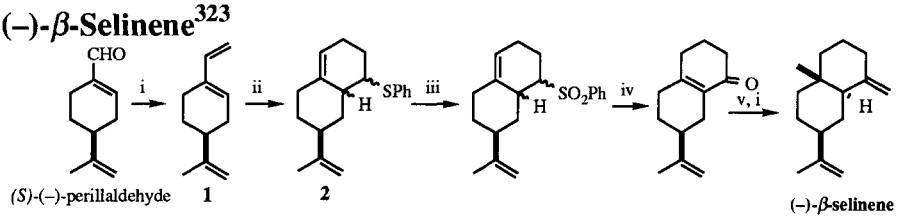
(–)-β-Selinene[322]



(i) 1-lithio-1-methoxycyclopropane, THF, –78°C (ii) 48% HBF_4, THF (iii) $LiAlH_4$, Et_2O, 0°C (iv) KH, THF, reflux (v) CrO_3, H_2SO_4, Me_2CO (vi) basic alumina (vii) $MeCuBF_3$, Et_2O, –70°C; aq. NH_4Cl (viii) $Ph_3P{=}CH_2$, DMSO, 80°C.

Scheme 202

(–)-β-Selinene[323]

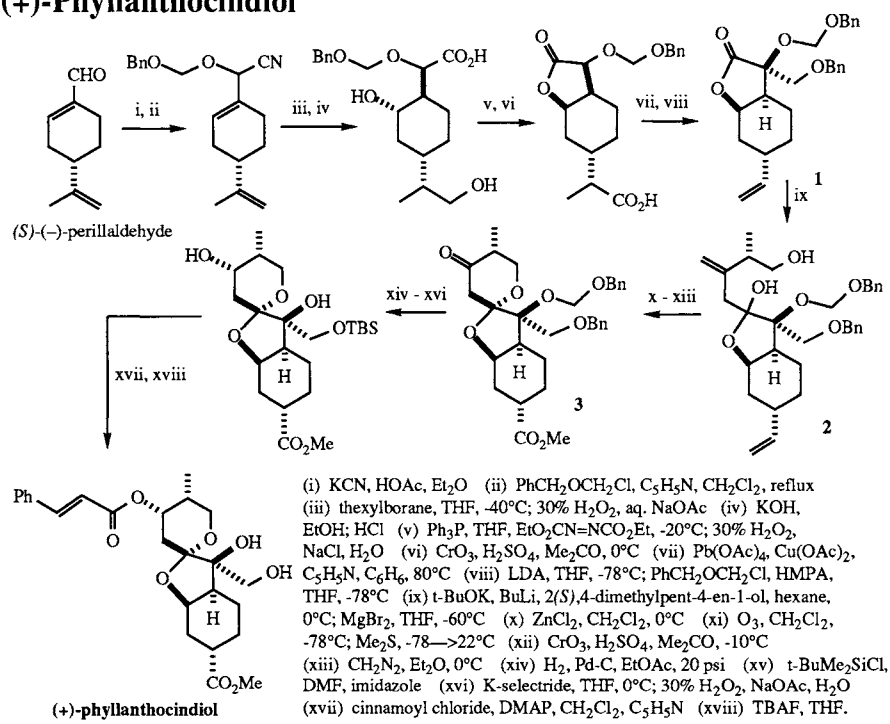


(i) $Ph_3P{=}CH_2$, THF (ii) $CH_2{=}CHSPh$, 1,4-dicyanobenzene, CH_3CN, hv (iii) m-CPBA, CH_2Cl_2, –30°C (iv) LDA, THF, –78°C; MoOPH (v) $MeCuBF_3$, Et_2O, –78°C.

Scheme 203

The synthesis of (+)-phyllanthocindiol (Scheme 204) by Collum and McGuirk[324] involves the conversion of *(S)*-(–)-perillaldehyde to the bicyclic lactone **1**. Addition of a 2*(S)*,4-dimethylpent-4-en-1-ol unit to **1** provided diol **2** that was cyclized and oxidized to furnish the tricyclic ester **3**. Straightforward functional group transformations afforded (+)-phyllanthocindiol.

(+)-Phyllanthocindiol[324]

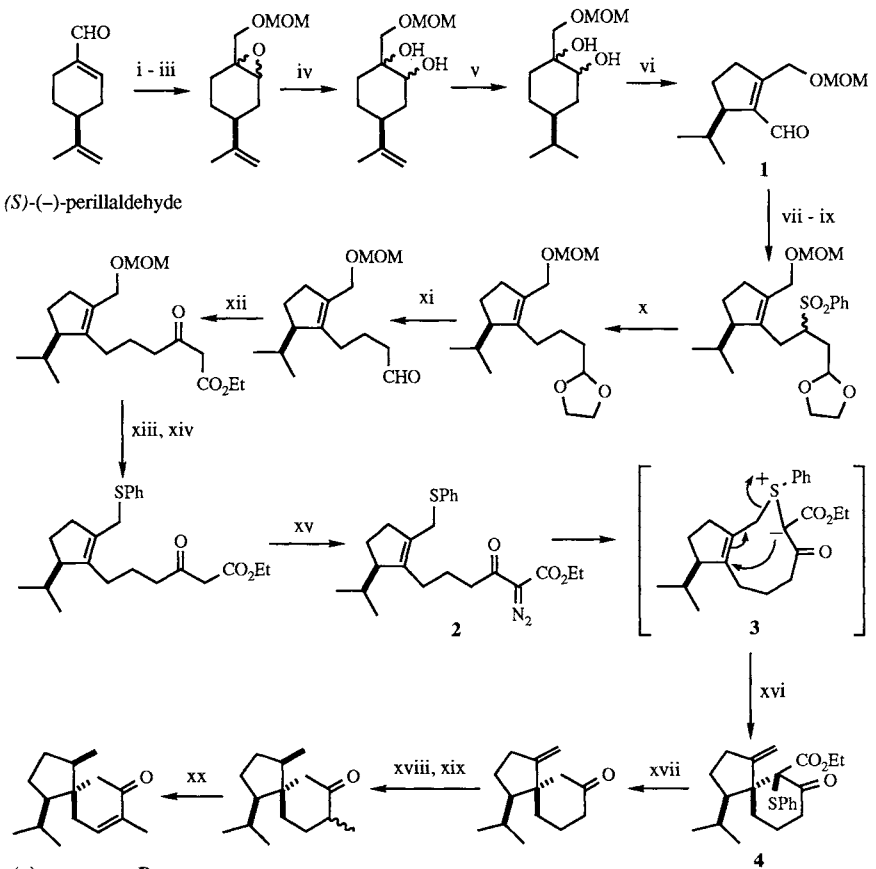


(i) KCN, HOAc, Et_2O (ii) $PhCH_2OCH_2Cl$, C_5H_5N, CH_2Cl_2, reflux (iii) thexylborane, THF, -40°C; 30% H_2O_2, aq. NaOAc (iv) KOH, EtOH; HCl (v) Ph_3P, THF, $EtO_2CN{=}NCO_2Et$, -20°C; 30% H_2O_2, NaCl, H_2O (vi) CrO_3, H_2SO_4, Me_2CO, 0°C (vii) $Pb(OAc)_4$, $Cu(OAc)_2$, C_5H_5N, C_6H_6, 80°C (viii) LDA, THF, -78°C; $PhCH_2OCH_2Cl$, HMPA, THF, -78°C (ix) t-BuOK, BuLi, 2*(S)*,4-dimethylpent-4-en-1-ol, hexane, 0°C; $MgBr_2$, THF, -60°C (x) $ZnCl_2$, CH_2Cl_2, 0°C (xi) O_3, CH_2Cl_2, -78°C; Me_2S, -78—>22°C (xii) CrO_3, H_2SO_4, Me_2CO, -10°C (xiii) CH_2N_2, Et_2O, 0°C (xiv) H_2, Pd-C, EtOAc, 20 psi (xv) t-$BuMe_2SiCl$, DMF, imidazole (xvi) K-selectride, THF, 0°C; 30% H_2O_2, NaOAc, H_2O (xvii) cinnamoyl chloride, DMAP, CH_2Cl_2, C_5H_5N (xviii) TBAF, THF.

Scheme 204

A recent synthesis of (+)-acorenone B (Scheme 205)[325] features the conversion of *(S)*-(–)-perillaldehyde to the ring-contracted aldehyde **1**. A related transformation was discussed earlier in connection with the use of limonene as an enantiopure starting material (*cf.* Scheme 152). Aldehyde **1** was then elaborated into the β-keto-α-diazo-ester **2**, setting the stage for a rhodium (II) acetate catalyzed [2,3]-sigmatropic rearrangement of an intermediate allylic sulfonium ylide[326] **3** to yield the spirocyclic α–phenylthio-ester **4**. The synthesis was completed using conventional methodology.

(+)-Acorenone B[325]

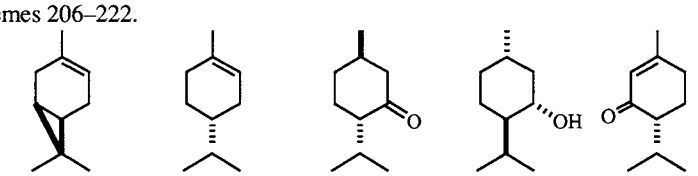


(i) 30% H_2O_2, aq. NaOH, MeOH (ii) $NaBH_4$, MeOH, 0°C (iii) MOMCl, i-Pr_2NEt, CH_2Cl_2, 0—>20°C (iv) 15% KOH, DMSO, 110°C (v) H_2, 10% Pd-C, MeOH (vi) $Pb(OAc)_4$, C_6H_6; piperidine, HOAc, 55°C (vii) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, i-PrOH–H_2O (viii) CBr_4, Ph_3P, THF, 0°C (ix) n-BuLi, 1-phenylsulfonyl-3-ethylenedioxypropane, THF-HMPA, –70°C (x) Na(Hg), NaH_2PO_4, MeOH (xi) PPTS, aq. Me_2CO, reflux (xii) N_2CHCO_2Et, $SnCl_2$, CH_2Cl_2 (xiii) Me_2BBr, CH_2Cl_2, –78°C (xiv) PhSSPh, Bu_3P, THF, 55°C (xv) TsN_3, Et_3N, MeCN, 45°C (xvi) $Rh_2(OAc)_4$, C_6H_6, reflux (xvii) Na(Hg), NaH_2PO_4, MeOH; NaCl, aq. DMSO, 130°C (xviii) H_2, PtO_2, EtOAc (xix) LDA, THF, –40°C; MeI, –50—>0°C (xx) Br_2, CH_2Cl_2, 0°C; LiBr, Li_2CO_3, DMF, 130°C.

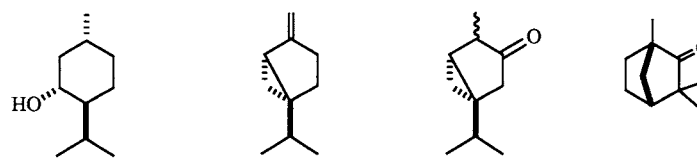
Scheme 205

7. MISCELLANEOUS CYCLIC MONOTERPENOIDS

The compounds (+)-Δ^3-carene, *(R)*-(+)-*p*-menth-1-ene, *(R)*-(–)-menthone, (+)-menthol, *(S)*-(–)-piperitone, (–)-sabinene, (–)-isopulegol, (+)-fenchone, and thujone are a group of monoterpenoids that have been used to a limited extent as chiral starting materials. Not all of these compounds are readily available in the alternative enantiomeric form. Selected examples of their use in natural product synthesis are given in Schemes 206–222.



(+)-Δ^3-carene *(R)*-(+)-*p*-menthene *(R)*-(–)-menthone (+)-menthol *(S)*-(–)-piperitone

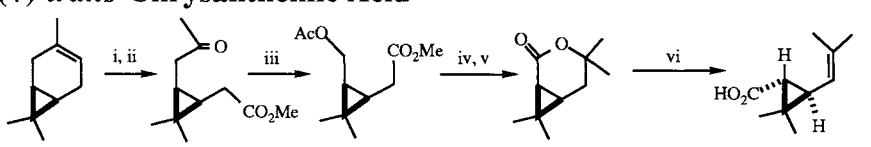


(–)-isopulegol (–)-sabinene thujone (+)-fenchone

a. (+)-Δ^3-Carene

(+)-Δ^3-Carene has been used as a chiral starting material for the synthesis of natural products that possess a cyclopropyl ring, such as (+)-*trans*-chrysanthemic acid (Scheme 206),[161] dihydrochrysanthemolactone (Schemes 206[161] and 207[327]), (–)-taylorione (Scheme 208),[328] and (+)-vitrenal (Scheme 209).[329]

(+)-*trans*-Chrysanthemic Acid[161]



(+)-Δ^3-carene (–)-dihydrochrysanthemo-lactone **(+)-*trans*-chrysan-themic acid**

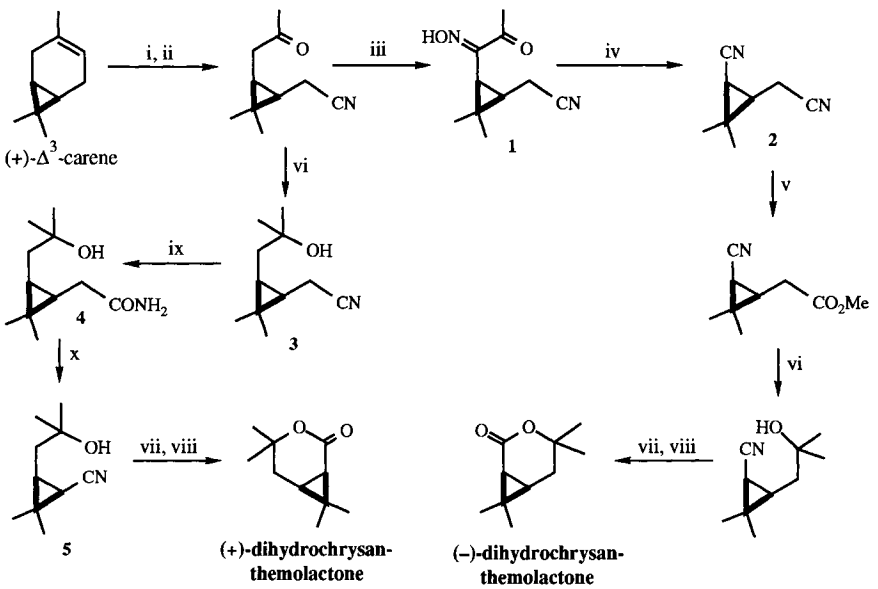
(i) O_3; Jones oxidation (ii) MeOH, HCl (iii) $MeCO_3H$, HOAc (iv) MeMgI, Et_2O (v) Jones oxidation; p-TsOH, toluene, reflux (vi) NaOH, $(CH_2OH)_2$, reflux.

Scheme 206

Straightforward ozonolytic cleavage of (+)-Δ^3-carene (Scheme 206)[161] followed by functional group manipulations yielded (+)-*trans*-chrysanthemic acid in six steps. (–)-Dihydrochrysanthemolactone is also an intermediate in this synthetic route.

An enantioselective synthesis of (+)- and (–)-dihydrochrysanthemolactone (Scheme 207) was reported recently by Tkachev and Rukavishnikov.[327] The preparation of (–)-dihydrochrysanthemolactone relied on the regiospecific hydrolysis of the dinitrile **2**, obtained by Beckmann fragmentation of the keto-oxime **1**. On the other hand, the hydroxy-nitrile **3** was converted to the hydroxy-amide **4**, and subsequent Hofmann rearrangement provided the hydroxy-nitrile **5** that was used to prepare (+)-dihydrochrysanthemolactone.

(+)- and (–)-Dihydrochrysanthemolactone[327]



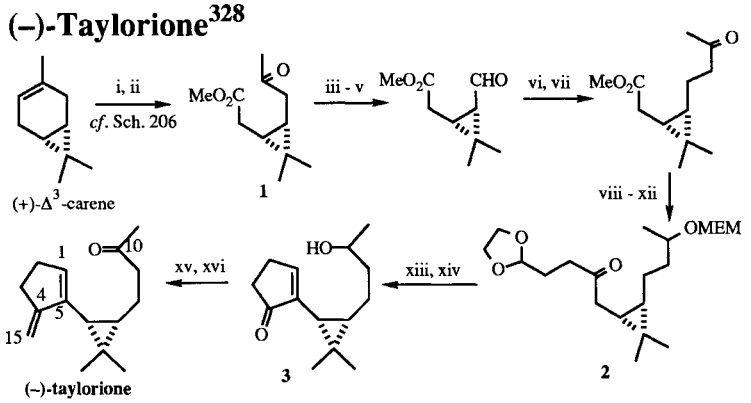
(i) $NaNO_2$, HCl; Me_2NH (ii) PCl_5, $CHCl_3$, -25°C (iii) *t*-BuONO, MeOH, NaOMe (iv) PCl_5, CH_2Cl_2 (v) HCl, MeOH (vi) MeMgI, Et_2O (vii) KOH, EtOH, H_2O (viii) TsOH, benzene, reflux (ix) KOH, MeOH, 30% H_2O_2 (x) KOH, H_2O, Br_2; $PhCH_2Et_3NCl$, CH_2Cl_2.

Scheme 207

Nakayama and co-workers used (+)-Δ^3-carene in their synthesis of (–)-taylorione (Scheme 208).[328] The keto-ester **1** was elaborated into the keto-ketal **2** by standard procedures. Acid-catalyzed hydrolysis of the protective groups resulted in an

intramolecular aldol condensation to provide the substituted cyclopentenone **3** that was subsequently methylenated and oxidized to yield (–)-taylorione (*syn. ent*-1,10-seco-aromadendra-1(5),4(15)-dien-10-one).

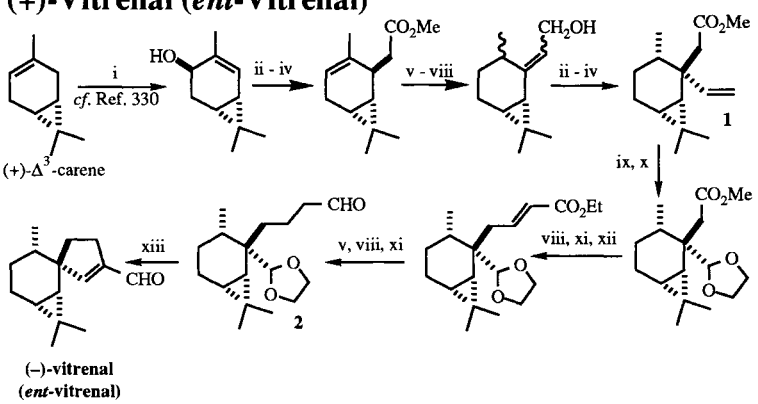
(–)-Taylorione[328]



(i) O_3; Jones oxidation (ii) MeOH, HCl (iii) $PhCO_3H$, $CHCl_3$ (iv) K_2CO_3, MeOH (v) PCC, CH_2Cl_2 (vi) $CH_3COCH{=}PPh_3$, $CHCl_3$, reflux (vii) H_2, Pt, EtOH (viii) $NaBH_4$; $CH_2(OMe)_2$, P_2O_5 (ix) $LiAlH_4$, Et_2O (x) PCC, CH_2Cl_2 (xi) 3,3-ethylenedioxy-1-propylmagnesium bromide, Et_2O (xii) PCC, CH_2Cl_2 (xiii) 5% HCl, Me_2CO (xiv) NaOH, MeOH (xv) $CH_2{=}PPh_3$, THF (xvi) DMSO, DCC, benzene, $C_5H_5NHO_2CF_3$.

Scheme 208

(+)-Vitrenal (*ent*-Vitrenal)[329]



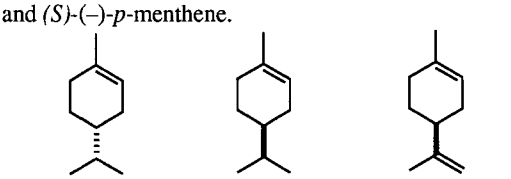
(i) O_2, hν, MeOH, rose bengal; separate from structural isomers (ii) $MeC(OEt)_3$, $EtCO_2H$, 137°C (iii) KOH, MeOH (iv) CH_2N_2, Et_2O (v) H_2, Pd-C, MeOH, 3 atm (vi) PhSeCl, LDA, -78°C (vii) $NaIO_4$ (viii) DIBAL (ix) O_3; Me_2S (x) $(CH_2OH)_2$, p-TsOH, benzene (xi) PCC, CH_2Cl_2 (xii) $Ph_3P{=}CHCO_2Et$ (xiii) HCl, THF, reflux.

Scheme 209

The synthesis of (–)-vitrenal (Scheme 209)[329] from (+)-Δ^3-carene features two successive applications of the orthoester Claisen rearrangement to yield the unsaturated ester **1**. This compound was converted to the ketal-aldehyde **2**, and subsequent intramolecular aldol condensation furnished the desired natural product.

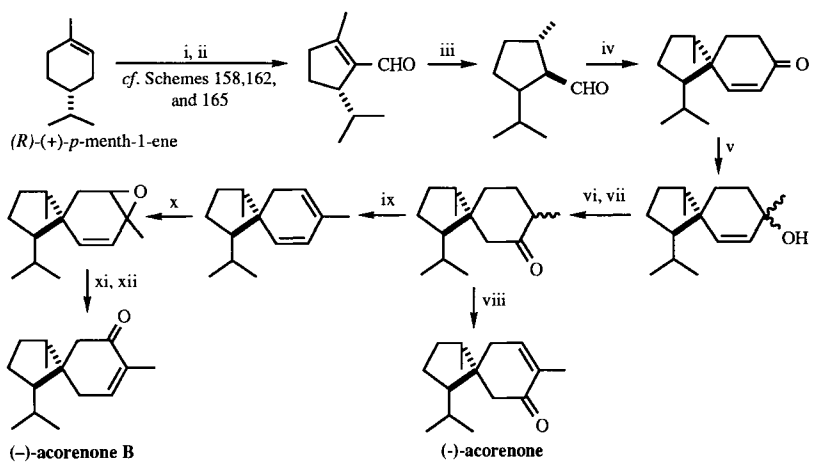
b. Menthene, Menthone, and Menthol

Due to the structural similarity of *p*-menthene and limonene, it is not surprising that there are parallels in their use as chiral starting materials for natural product synthesis (e.g. Scheme 210, *cf.* Scheme 152). Indeed, many syntheses that start with limonene (e.g. Schemes 155 and 158–164) pass through *p*-menthene as an intermediate. Moreover, the availability of both enantiomers of limonene provides ready access (H_2, PtO_2 or Pt/C, EtOH)[260] to *(R)*-(+)- and *(S)*-(–)-*p*-menthene.



(R)-(+)-*p*-menthene *(S)*-(–)-*p*-menthene *(S)*-(–)-limonene

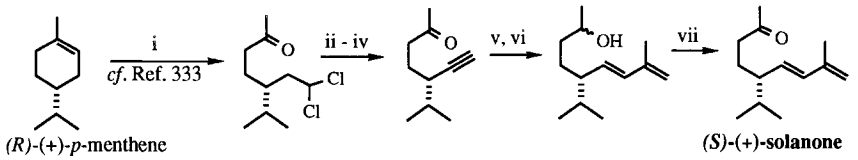
(–)-Acorenone, (–)-Acorenone B[331]



(i) O_3, MeOH; Zn, HOAc (ii) piperidine, HOAc, $CHCl_3$, reflux (iii) H_2, Pd-$CaCO_3$, K_2CO_3, MeOH, H_2O (iv) MVK, KOH, dioxane, 70°C (v) MeLi, THF (vi) BH_3•THF, THF; H_2O_2, NaOH (vii) Jones oxidation (viii) Br_2, CH_2Cl_2, 0°C; Li_2CO_3, DMF, reflux (ix) p-TsOH, C_6H_6 (x) $MeCO_3H$, CH_2Cl_2 (xi) TsOH, CH_2Cl_2 (xii) TsOH, toluene, reflux.

Scheme 210

(S)-(+)-Solanone[332]

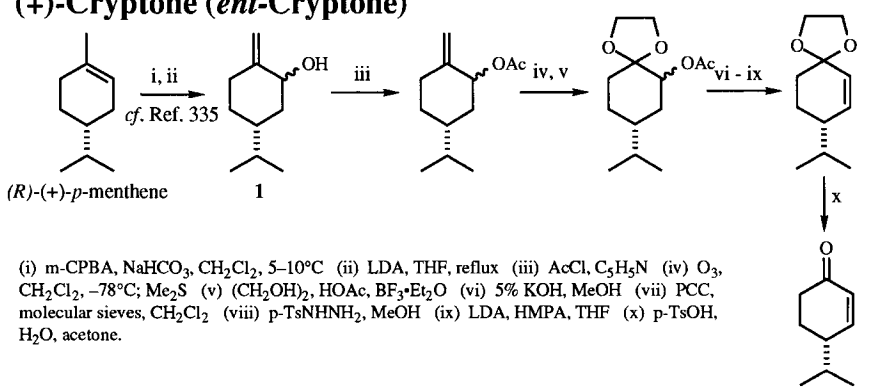


(i) $FeCl_3$, hv (ii) $(CH_2OH)_2$, TsOH, C_6H_6 (iii) LDA, THF, -10°C (iv) dil. HCl (v) catecholborane (vi) isopropenyl bromide, $Pd(Ph_3P)_4$, NaOEt (vii) Jones oxidation.

Scheme 211

Base-promoted opening of the epoxide derived from *(R)*-(+)-*p*-menthene (Scheme 212)[334] yielded the allylic alcohol **1** that was subsequently converted to (+)-cryptone.

(+)-Cryptone (*ent*-Cryptone)[334]



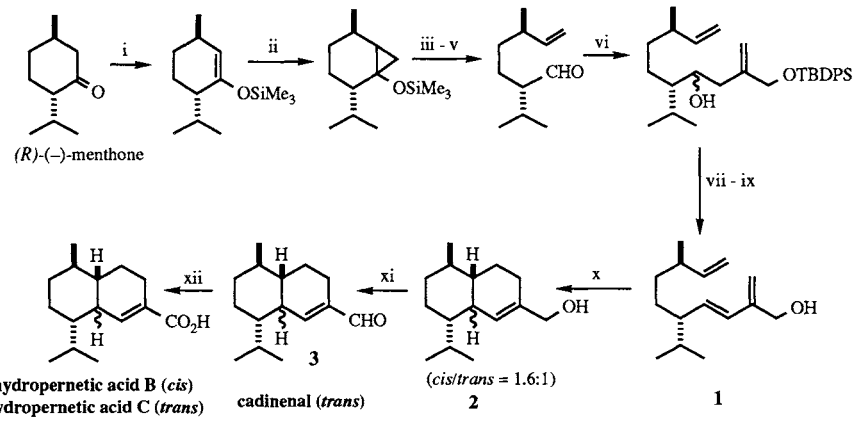
(i) m-CPBA, $NaHCO_3$, CH_2Cl_2, 5–10°C (ii) LDA, THF, reflux (iii) AcCl, C_5H_5N (iv) O_3, CH_2Cl_2, –78°C; Me_2S (v) $(CH_2OH)_2$, HOAc, BF_3•Et_2O (vi) 5% KOH, MeOH (vii) PCC, molecular sieves, CH_2Cl_2 (viii) p-$TsNHNH_2$, MeOH (ix) LDA, HMPA, THF (x) p-TsOH, H_2O, acetone.

Scheme 212

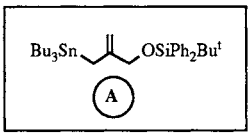
In a synthesis of dihydropernetic acids B and C (Scheme 213),[336] *(R)*-(+)-menthone was used to prepare the Diels-Alder precursor **1**. Subsequent cycloaddition, followed by Swern oxidation of the resulting allylic alcohol **2** yielded a mixture of aldehydes **3**, the trans isomer in which was the natural product cadinenal. Further oxidation of **3** yielded dihydropernetic acids B and C.

(+)-Menthol was used in an ingenious manner in the synthesis of pseudopterosin A and pseudopterosin E (Scheme 214) by Corey and Carpino.[337] Photolysis of the nitrite ester **1** resulted in the functionalization of one of the gem-dimethyl groups of menthol to yield the hydroxy-oxime **2** that was converted in several steps to the octalone **3**. γ-Alkylation of enone **3** with an acetylenic unit provided the unsaturated diketone **4** and permitted the subsequent construction of the aromatic ring by means of an intramolecular Michael addition. With the desired ring system in place, ortho-hydroxylation of **5** yielded the catechol **6**. Standard procedures were used to convert **6** to the diol **7**. Regioselective tosylation followed by glycosylation provided **8**, and subsequent removal of the acetate and tosylate protective groups furnished pseudopterosin A. On the other hand, when the dianion of **7** was allowed to react with the protected α-bromofucose **9**, the glycosylated intermediate **10** was obtained and subsequent deprotection yielded pseudopterosin E.

Cadinenal, Dihydropernetic Acid B, Dihydropernetic Acid C[336]

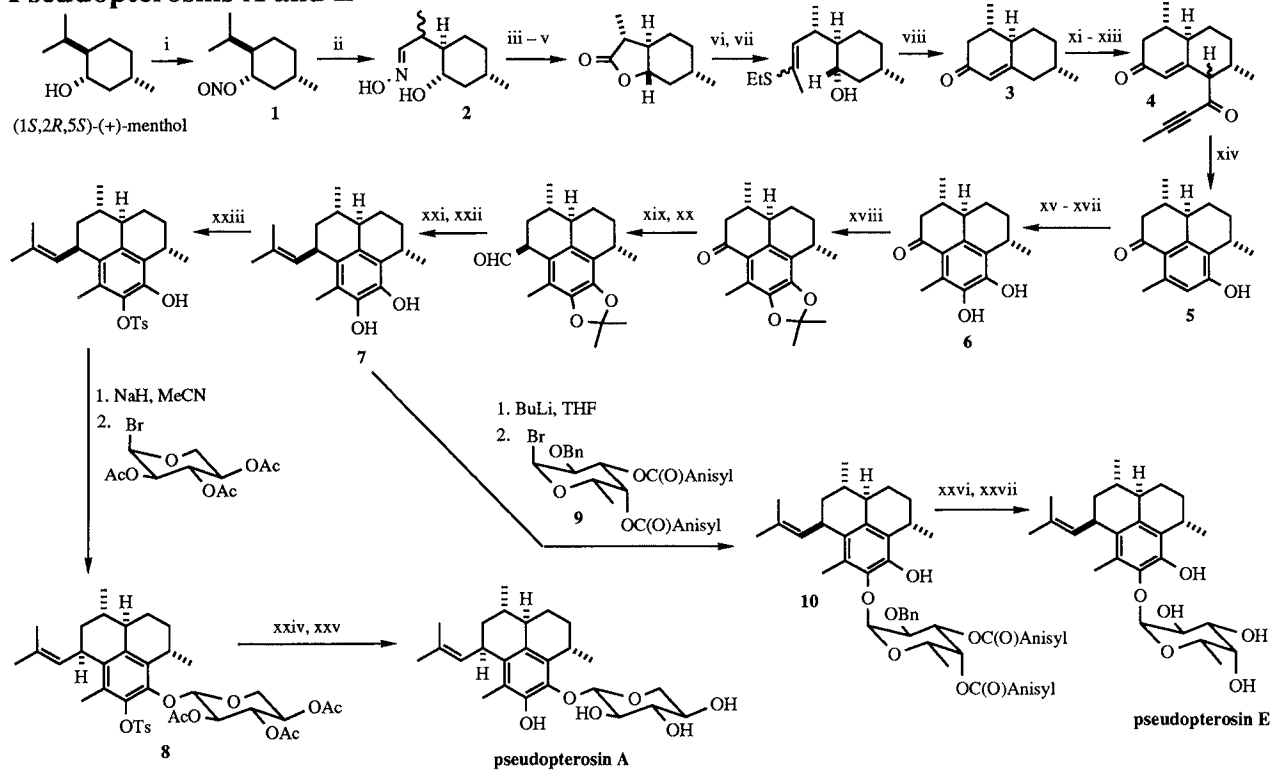


(i) LDA, THF, -78—>0°C; Me_3SiCl (ii) Et_2Zn, CH_2I_2, hexane (iii) $Pb(OAc)_4$, HOAc (iv) $LiAlH_4$, Et_2O (v) Swern oxidation (vi) A, $BF_3{\cdot}Et_2O$, CH_2Cl_2, -78°C (vii) MsCl, Et_3N, CH_2Cl_2 (viii) t-BuOK, t-BuOH, 80°C (ix) Bu_4NF, THF (x) benzene, 170°C (sealed tube) (xi) Swern oxidation (xii) NaOCl, H_2O_2, MeCN, pH 1.



Scheme 213

Pseudopterosins A and E[337]



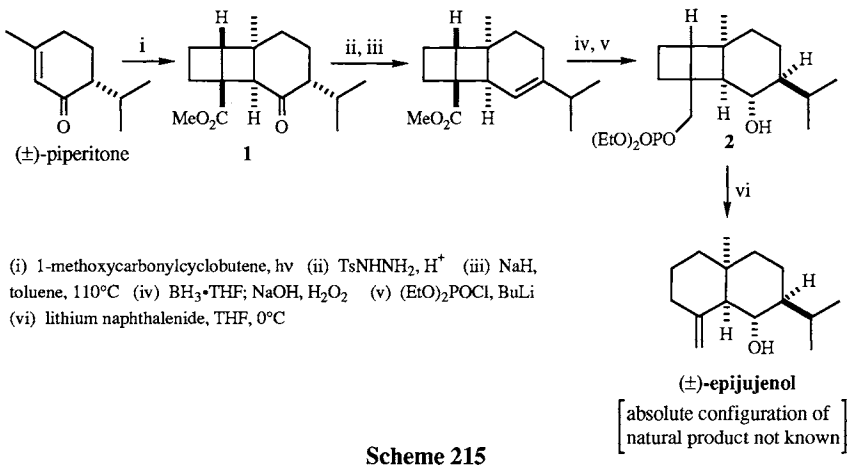
(i) $NOHSO_4$, C_5H_5N, CH_2Cl_2 (ii) hv, DABCO, $PhCH_3$, 15°C (iii) $NaHCO_3$ (5 eq.), H_2O, 50°C (iv) Br_2, $CaCO_3$, $THF-H_2O$ (v) LDA, THF, 0°C (vi) DIBAL, CH_2Cl_2, –78°C (vii) $Ph_3P{=}C(CH_3)SEt$, DMSO (viii) DMSO, $(CF_3CO)_2O$, CH_2Cl_2, –60°C; Et_3N (ix) $HgCl_2$, aq. MeCN, 50°C (x) NaOMe, MeOH (xi) KH, THF-HMPA; TBDMSCl, THF (xii) Me_3SiOTf, CH_3-≡-CHO, CH_2Cl_2, –78°C; H_2O (xiii) PCC, CH_2Cl_2 (xiv) KH, THF (xv) $(PhSeO)_2O$, $HN(SiMe_3)_2$, C_6H_6 (xvi) $HClO_4$ (cat.), aq. HOAc (xvii) aq. $NaHSO_3$, EtOH (xviii) $Me_2C(OMe)_2$, PPTS, $CHCl_3$, –70°C (xix) $Me_2S{=}CH_2$, THF (xx) $BF_3{\bullet}OEt_2$, CH_2Cl_2, –30—>23°C (xxi) $Ph_3P{=}CMe_2$, THF, 0°C (xxii) 10% HCl, 70°C, THF-MeOH (xxiii) TsCl, Et_3N, CH_2Cl_2, –30—>23°C (xxiv) KOH, aq. MeOH (xxv) Na(Hg), MeOH (xxvi) LiOH, THF, MeOH (xxvii) Li, NH_3, THF

Scheme 214

c. Piperitone

(±)-Piperitone was used as a chiral starting material in the synthesis of (±)-10-epijujenol (Scheme 215).[338] [2 + 2] Photocycloaddition of piperitone with 1-methoxycarbonylcyclobutene yielded the keto-ester **1** that was converted to the hydroxy-phosphate **2**. Finally, treatment with sodium naphthalenide resulted in reductive σ-bond cleavage to provide (±)-10-epijujenol.

(±)-10-Epijujenol[338]



(i) 1-methoxycarbonylcyclobutene, hv (ii) $TsNHNH_2$, H^+ (iii) NaH, toluene, 110°C (iv) BH_3•THF; NaOH, H_2O_2 (v) $(EtO)_2POCl$, BuLi (vi) lithium naphthalenide, THF, 0°C

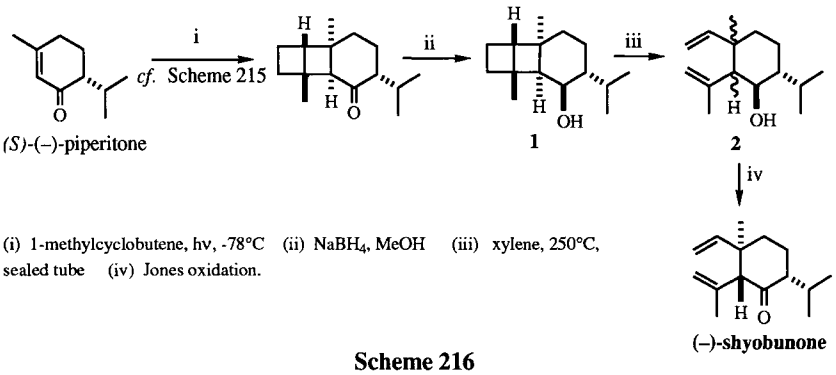
(±)-epijujenol

[absolute configuration of natural product not known]

Scheme 215

The synthesis of (–)-shyobunone (Scheme 216) by Williams and Callahan[339] featured the thermolysis of the tricyclic alcohol **1** to provide the hydroxy-diene **2**. A similar strategy was used by Lange and McCarthy (Scheme 217)[340] to prepare an intermediate **3** that has potential for the synthesis of germacrane sesquiterpenoids. Interestingly, prolonged heating of the keto-ester **1** (Scheme 217) resulted in thermolytic ring opening to provide **2**. In addition, further intramolecular ene reaction occurred to yield an intermediate **4** that could be of use for cadinane synthesis.

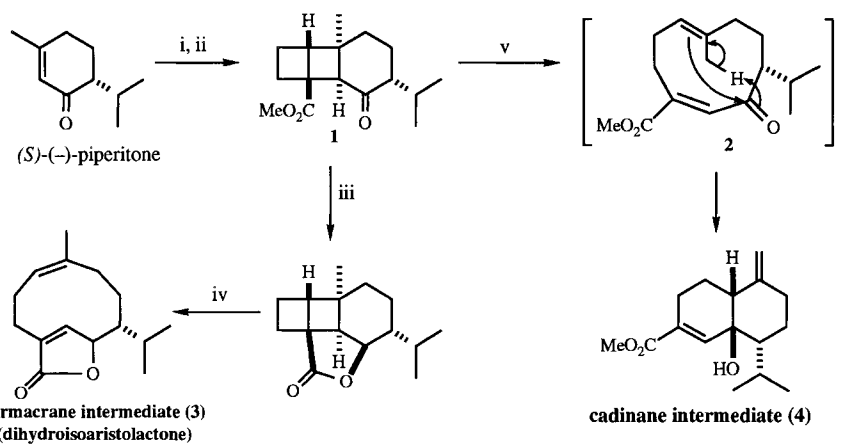
(–)-Shyobunone (*ent*-Shyobunone)[339]



(i) 1-methylcyclobutene, hv, -78°C (ii) $NaBH_4$, MeOH (iii) xylene, 250°C, sealed tube (iv) Jones oxidation.

Scheme 216

Synthetic Approach to Germacrane and Cadinane Systems[340]

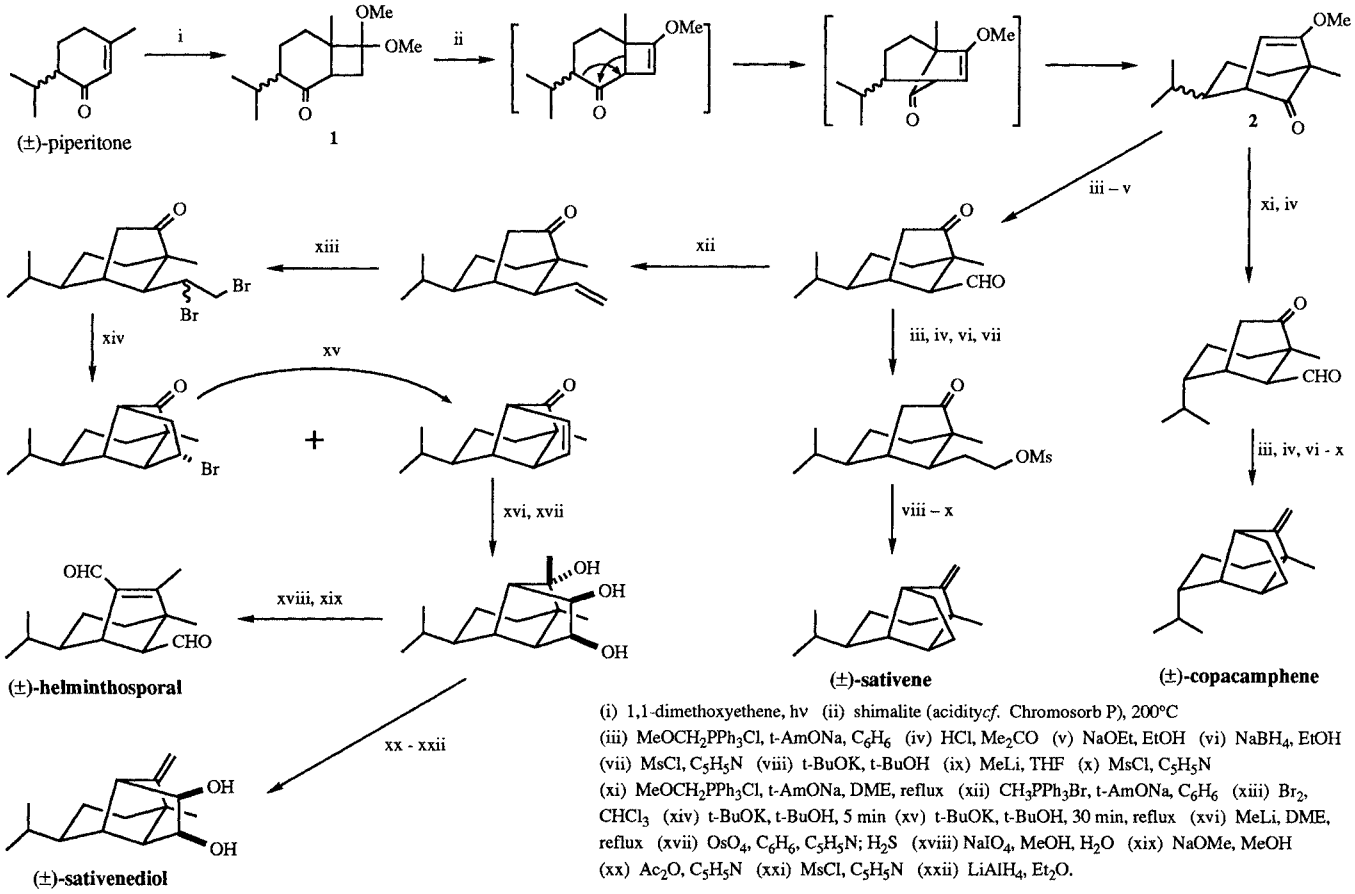


(i) cyclobutenecarboxylic acid, C_6H_6, hv (ii) CH_2N_2, Et_2O (iii) $NaBH_4$, EtOH (iv) decane, reflux (174°C) (v) decane, reflux, 10 h.

Scheme 217

The synthesis of (±)-sativene, (±)-copacamphene, (±)-*cis*-sativenediol, and (±)-helminthosporal (Scheme 218) by Yanagiya and co-workers[341] features an interesting acid-catalyzed rearrangement of the bicyclo[4.2.0]octanone **1** to the bicyclo[3.2.1]octanone **2** (an analogous rearrangement has been reported earlier by Cargill and Crawford[342]). The keto enol ether **2** was then transformed into the four natural products using standard procedures.

(±)-Sativene, (±)-Copacamphene, (±)-*cis*-Sativenediol, and (±)-Helminthosporal[341]



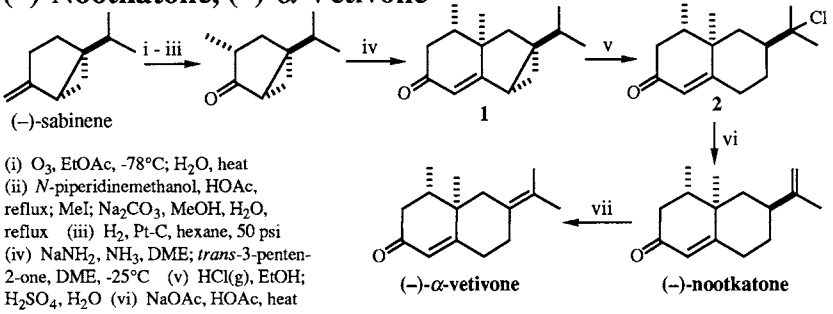
(i) 1,1-dimethoxyethene, hv (ii) shimalite (acidity*cf.* Chromosorb P), 200°C
(iii) $MeOCH_2PPh_3Cl$, t-AmONa, C_6H_6 (iv) HCl, Me_2CO (v) NaOEt, EtOH (vi) $NaBH_4$, EtOH
(vii) MsCl, C_5H_5N (viii) t-BuOK, t-BuOH (ix) MeLi, THF (x) MsCl, C_5H_5N
(xi) $MeOCH_2PPh_3Cl$, t-AmONa, DME, reflux (xii) CH_3PPh_3Br, t-AmONa, C_6H_6 (xiii) Br_2, $CHCl_3$ (xiv) t-BuOK, t-BuOH, 5 min (xv) t-BuOK, t-BuOH, 30 min, reflux (xvi) MeLi, DME, reflux (xvii) OsO_4, C_6H_6, C_5H_5N; H_2S (xviii) $NaIO_4$, MeOH, H_2O (xix) NaOMe, MeOH
(xx) Ac_2O, C_5H_5N (xxi) MsCl, C_5H_5N (xxii) $LiAlH_4$, Et_2O.

Scheme 218

d. Sabinene, isopulegol, and fenchone

The eremophilane sesquiterpenes (–)-nootkatone and (–)-α–vetivone (Scheme 219) were synthesized from (–)-sabinene by van der Gen and co-workers.[343] Acid-catalyzed ring opening of the tricyclic enone **1** yielded a bicyclic chloro-enone **2** that was dehydrochlorinated to provide (–)-nootkatone and, upon further double bond isomerization, (–)-α-vetivone.

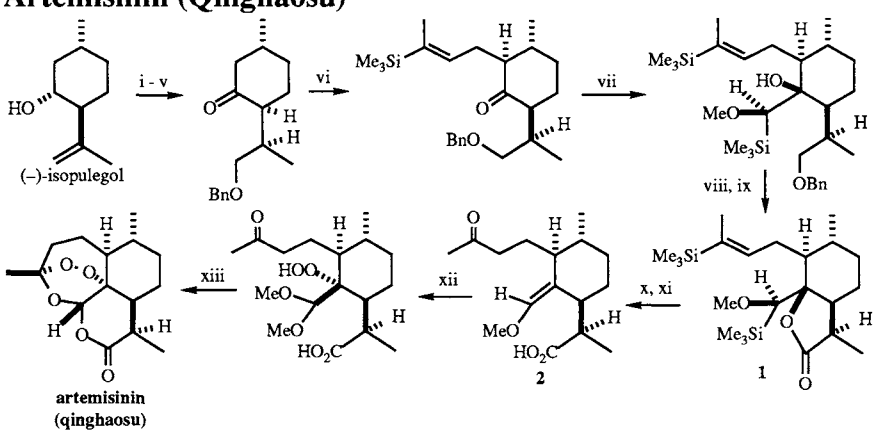
(–)-Nootkatone, (–)-α-Vetivone[343]



(i) O_3, EtOAc, -78°C; H_2O, heat (ii) *N*-piperidinemethanol, HOAc, reflux; MeI; Na_2CO_3, MeOH, H_2O, reflux (iii) H_2, Pt-C, hexane, 50 psi (iv) $NaNH_2$, NH_3, DME; *trans*-3-penten-2-one, DME, -25°C (v) HCl(g), EtOH; H_2SO_4, H_2O (vi) NaOAc, HOAc, heat (vii) p-TsOH, $CHCl_3$, reflux.

Scheme 219

Artemisinin (Qinghaosu)[344]



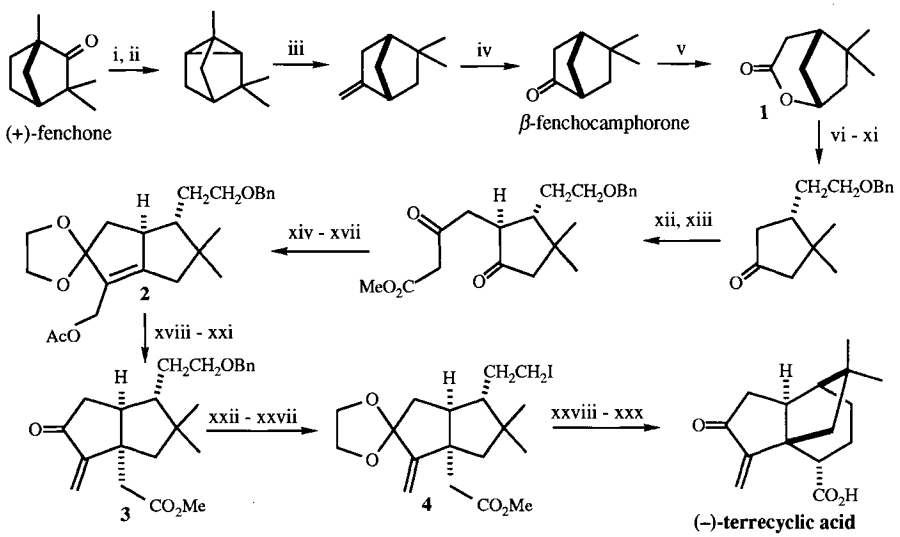
(i) $ClCH_2OMe$, $PhNMe_2$, CH_2Cl_2 (ii) B_2H_6, THF, 0°C; H_2O_2, NaOH (iii) KH, $PhCH_2Br$, THF-DMF (4:1), 0°C (iv) MeOH, HCl, 40°C (v) PCC, CH_2Cl_2 (vi) LDA, THF, 0°C; (*E*)-(3-iodo-1-methyl-1-propenyl)-trimethylsilane (vii) $LiCH(OMe)(SiMe_3)$, THF, -78°C (viii) Li, NH_3 (ix) PCC, CH_2Cl_2 (x) m-CPBA, CH_2Cl_2; TFA, CH_2Cl_2, 0°C (xi) Bu_4NF, THF (xii) $^1O_2$, methylene blue, MeOH, -78°C (on sodium salt) (xiii) HCO_2H, CH_2Cl_2, 0°C.

Scheme 220

A synthesis of the antimalarial sesquiterpene lactone artemisinin (*syn.* qinghaosu; Scheme 220) was reported by Schmid and Hofheinz[344] who employed (–)-isopulegol as the starting material. (–)-Isopulegol was initially converted to the highly functionalized lactone **1**. Epoxidation of the vinylsilane moiety in **1** followed by hydrolytic desilylation provided the keto-acid **2**, the sodium salt of which underwent an ene reaction with singlet oxygen to yield the hydroperoxide **3**. Subsequent treatment of **3** with acid furnished artemisinin.

(+)-Fenchone served as the starting material for the synthesis of (–)-terrecyclic acid (Scheme 221).[345] The intermediate β-fenchocamphorone underwent Baeyer-Villiger oxidation to yield the bicyclic lactone **1** that could be transformed into the allylic acetate **2**. Subsequent Ireland-Claisen rearrangement of **2** followed by esterification and ketal hydrolysis provided the angularly functionalized keto-ester **3**. The third ring of terrecyclic acid was constructed by intramolecular alkylation of the iodo-ester **4**.

(–)-Terrecyclic Acid[345]

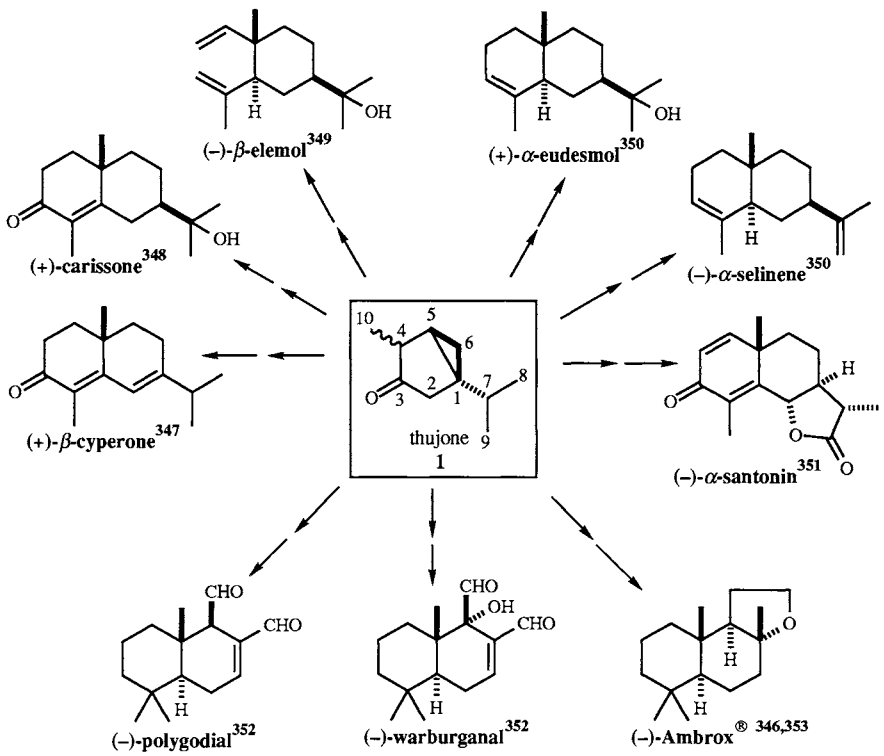


(i) NH_2NH_2 (ii) HgO (iii) $KHSO_4$ (iv) OsO_4, $NaIO_4$ (v) m-CPBA, CH_2Cl_2, Na_2HPO_4 (vi) NaOMe, MeOH, 30°C (vii) CrO_3•pyridine, CH_2Cl_2 (viii) $(CH_2OH)_2$, TsOH, C_6H_6, reflux (ix) $LiAlH_4$, Et_2O, 0°C (x) NaH, $PhCH_2Br$, DME (xi) TsOH, THF, H_2O (xii) LDA; $BrCH_2C(OMe)=CHCO_2Me$, 0°C (xiii) HCl, MeOH, H_2O (xiv) t-BuOK, t-BuOH, C_6H_6 (xv) $(CH_2OH)_2$, TsOH, C_6H_6, reflux (xvi) $LiAlH_4$, Et_2O, -20°C (xvii) Ac_2O, pyridine (xviii) LDA, THF, -78°C; t-$BuMe_2SiCl$, THF, HMPA (xix) 70-80°C (xx) KF, $KHCO_3$, HMPA; MeI (xxi) TsOH, THF, H_2O (xxi) $TiCl_4$, CH_2Cl_2, -20°C (xxiii) $(PhSe)_2$, $NaBH_4$, EtOH, 0°C (xxiv) $(CH_2OH)_2$, TsOH, C_6H_6, reflux (xxv) 30% H_2O_2, C_5H_5N, CH_2Cl_2 (xxvi) TsCl, C_5H_5N (xxvii) NaI, DMF (xxviii) $LiN(SiM_3)_2$, THF, -78°C (xxix) n-PrSLi, HMPA, 60°C (xxx) 10% H_3PO_4, THF, 0°C.

Scheme 221

e. Thujone

The bicyclic monoterpenoid thujone (**1**, Scheme 222) is commercially available and is usually supplied as a mixture of C(4) epimers.* In addition, it can be obtained in abundant quantities by steam distillation of the discarded foliage of the Western red cedar tree (*Thuja plicata* D. Don).[346] Its enantiomer, however, is not readily available. Nevertheless, the use of thujone as a chiral starting material in natural product synthesis (*cf.* Scheme 222) has been largely exploited by Kutney and co-workers. A more detailed review of this work can be found elsewhere in this series.[346]



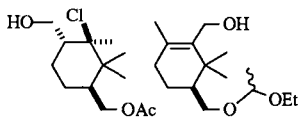
Scheme 222

* The 4α(*R*) epimer (*cf.* **1** in Scheme 222) is known as α-thujone ($[\alpha]_D^{20}$ –19.2°) while the 4β(*S*) epimer is often called β-thujone or isothujone ($[\alpha]_D^{15}$ +72.5°).

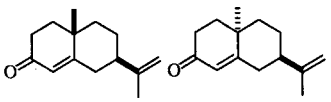
EPILOGUE

From the foregoing presentation, it is evident that natural product synthesis using monoterpenoids as enantiopure starting materials remains an active area of research. Moreover, much effort has been expended in the conversion of monoterpenoids to natural

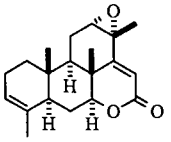
Some Intermediates and Natural Product Analogues Derived from Enantiopure Monoterpenoid Starting Materials



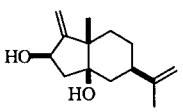
intermediates for taxane synthesis
[from (–)-camphor via (–)-camphoric acid][355]
(*cf.* Schemes 50 and 51)



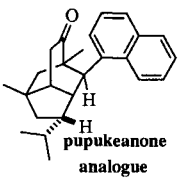
intermediates for terpenoid or steroid synthesis
[both from *(R)*-(–)-carvone][356]



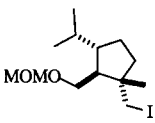
quassin intermediate
[from *(S)*-(+)-carvone][357]



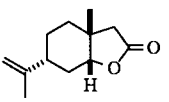
picrotoxin intermediate
[from *(R)*-(–)-carvone][358]
(*cf.* Scheme 107)



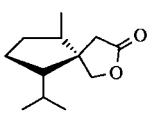
pupukeanone analogue
[from *(R)*-(–)-carvone][359]



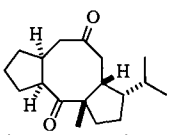
retigeranic acid A northern part synthon
[from *(R)*-(–)-carvone][360]



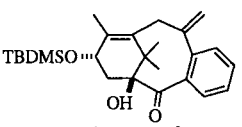
terpenoid synthon
[from *(R)*-(–)-carvone][361]



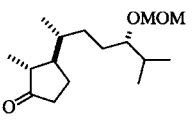
terpenoid synthon
[from *(R)*-(+)-limonene][361]



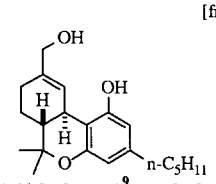
fusicoccane or ophiobolane synthon
[from *(R)*-(+)-limonene][362]



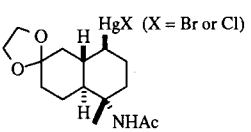
taxane analogue
[from (–)-α-pinene][363]



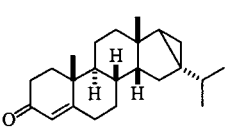
(24*S*)-24-hydroxyvitamin D_3 ring D synthon
[from (–)-menthol][364]



(–)-11-hydroxy-Δ^9-tetrahydrocannabinol
[from *(R)*-(+)-perillaldehyde][365,366]



amphilectane intermediate
[from *(S)*-(–)-perillyl alcohol][367]



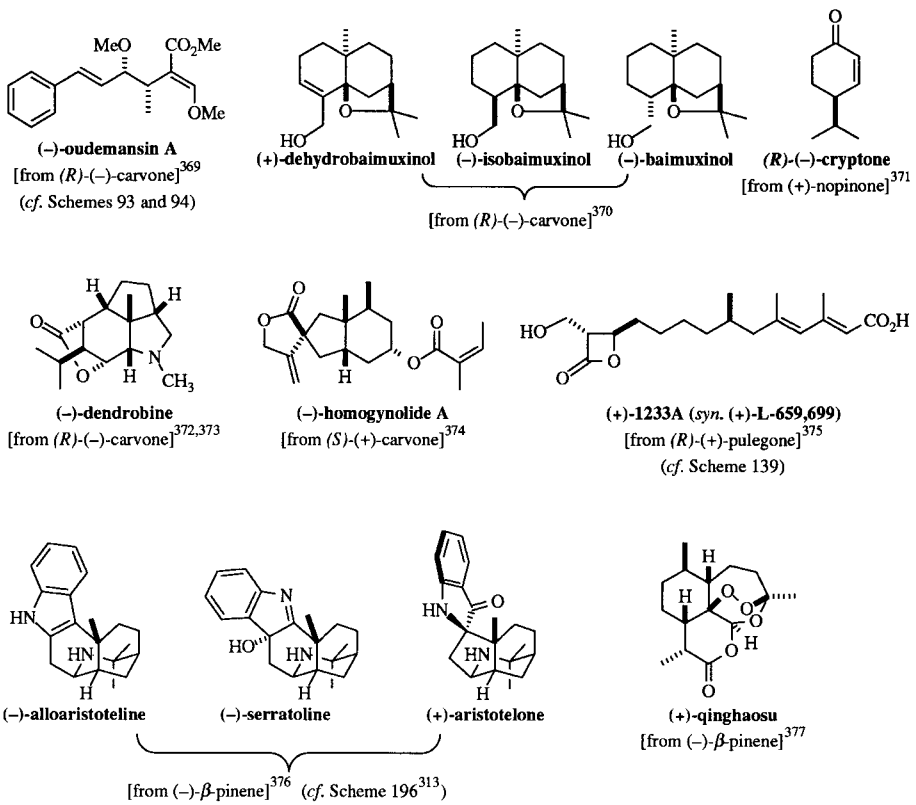
steroid analogue
[from thujone][346,368]

Scheme 223

product analogues or potential intermediates for natural product synthesis. Unfortunately, space limitations do not allow us to review this work in detail. Instead, selected examples of such analogues or intermediates are presented in Scheme 223.

In addition, several new natural product syntheses from monoterpenoid starting materials appeared in the literature during the preparation of this manuscript, and could not be incorporated into the review. These natural products are presented instead in Scheme 224.

Natural Product Synthesis from Cyclic Monoterpenoid Starting Materials: Recent Examples



Scheme 224

ACKNOWLEDGEMENTS

We thank Mr. L. Mackenzie of this department for his assistance with some of the literature searches required for this work, and Professor J.P. Kutney for making available a copy of his review[346] prior to publication. In addition, M.K.C.W. acknowledges the Natural Sciences and Engineering Council of Canada (NSERC) for financial support in the form of a graduate (PGS-3) fellowship.

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Atta-ur-Rahman (Ed.) *Studies in Natural Products Chemistry, Vol. 16*

Progress in the Synthesis of Iridoids and Related Natural Products

Sachihiko Isoe

1. INTRODUCTION

A number of iridoids and secoiridoids which possess a wide range of biological activity have been isolated from plants and insects. For example, dihydronepetalactone, isodihydronepetalactone, iridomyrmecin, isoiridomyrmecin, neoneptalactone, nepetalactone, actinidine (iridoid alkaloid) and dihydroactinidiolid (carotenoid metabolite), the mixture being a potent attractant for cat, have been isolated from *Actinidia polygama* Miq. (**Fig. 1**). Similarly neomatatabiol, isoneomatatabiol, dehydroiridodiol, iridodiol and matatabiol have been isolated from the same plant and the mixture serves as a potent attractant for lacewing (**Fig. 2**) (1-3).

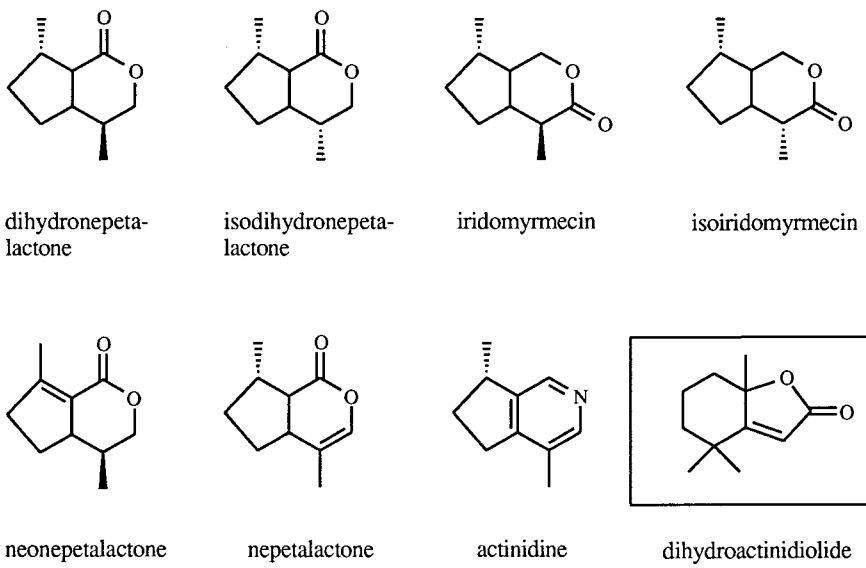


Figure. 1 Attractants for Felidae (Cat family)

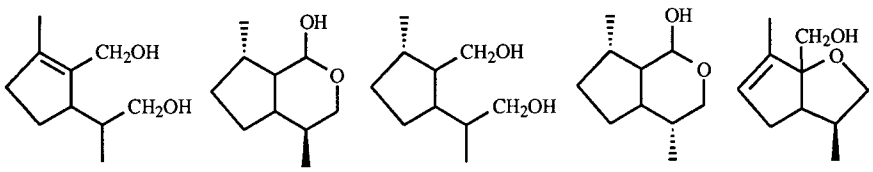
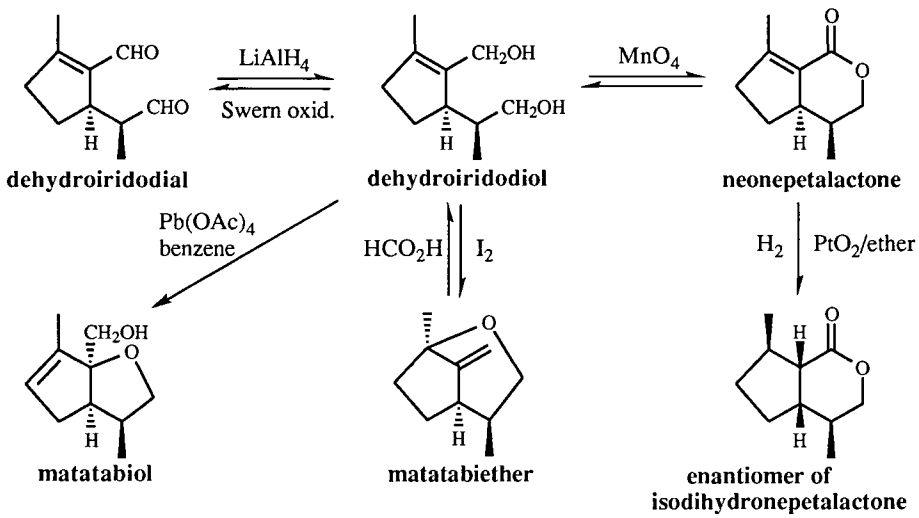


Figure. 2 Attractants for Chrysopidae (lacewing)

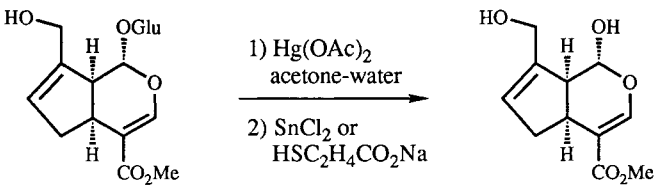
From a synthetic and biosynthetic point of view, dehydroiridodial, chrysomelidial and iridodial are considered to be the central intermediates for the biosynthesis of other iridoids from *Actinidia polygama* Miq.. The chemical interconversion of these iridoids has been demonstrated as shown in **Scheme 1**.



Scheme 1

The broad diversity of both structure and biological activity exhibited by iridoids and seco-iridoids has generated much interest in their general synthesis starting from a common intermediate. We have developed two general methodologies for the synthesis of polyfunctional iridoids and related natural products. One approach involves the effective utilization of tricyclo[3,3,0,$0^{2,8}$]octanone derivative as a building block. This methodology enabled the efficient synthesis of loganin, chrysomelidial, forthyside aglycone and other cyclopentanoid natural products. The same methodology was independently developed by Demuth *et al.* (4) and widely utilized for the synthesis of iridoids and polyquinanes. Similar methodology utilizing [3,3,0]-octane derivatives has been known and successfully applied for the synthesis of iridoids (5). The second approach is the effective utilization of (+)-genipin as a chiral building block whose functionality is quite fit for the

synthesis of polyfuntional iridoids and related natural products. Furthermore, (+)-genipin is easily obtained by the enzymatic hydrolysis of geniposide with Cellulosin AC-40 and it can be supplied from industry in Kg scale. The alternative non-enzymatic efficient method which we developed is the hydrolysis of geniposide using hydroxymercuration followed by treatment with $SnCl_2$ or sodium 3-mercaptopropionate. The second methodology enabled the efficient synthesis of loganin, penstemide, didrovaltrate, plumericin, allamandicin, plumieride, gardenoside, garjasmin, asperuloside, cerbinal, baldrinal, secologanin, sweroside, gentiopicroside, kingiside, morronoside, sarracenin, petiodial and udoteatrial in optically active form.



geniposide **genipin**

2. CHRYSOMELIDIAL, LOGANIN AND FORSYTHEIDE

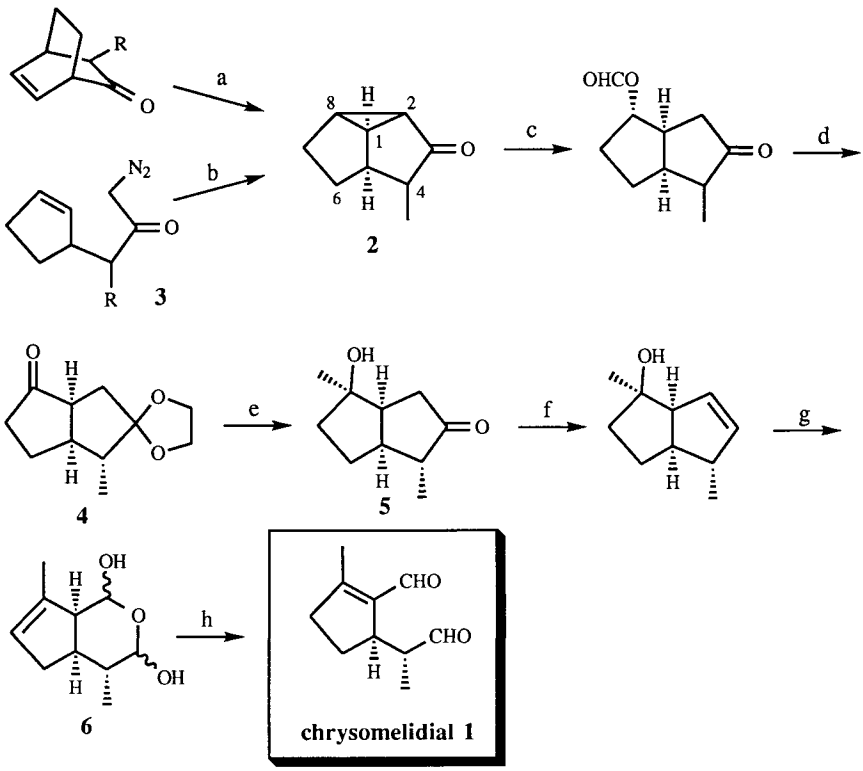
The increasing number of cyclopentanoid natural products and their interesting biological activity has stirred considerable interest into synthesis of such compounds. We have embarked upon the synthesis of polyfunctional iridoids via the same intermediate which may be easily obtained from an ordinary starting material. We selected tricyclo[3,3,0,$0^{2,8}$]octanone as the varsatile intermediate. Tricyclo-[3,3,0,$0^{2,8}$]octanone, obtained from photolysis of bicyclo[2,2,2]octenone or decomposition of 2-cyclopenten-1-yldiazomethylketone with cupric sulfate, was transformed with formic acid or p-toluenesulfonic acid into functionalized bicyclo[3,3,0]octanone, which has a distinguishable functional group in the each five membered ring and can be led into cyclopentanoid natural products via the selective conversion of the functional group. We have applied this versatile intermediate, tricyclo[3,3,0,$0^{2,8}$]octanone towards the synthesis of polyfunctional iridoids, chrysomelidial, loganin and forsythide.

2.1 Synthesis of Chrysomelidial(6) (Scheme 2)

Recently a new monoterpene dial, dehydroiridodial, was isolated as a pungent principle of *Actinidia polygama* Miq., and it was synthesized by K. Yoshihara *et al.* (7). On the other hand, chrysomelidial (**1**), the stereoisomer of dehydroiridodial, was isolated from the larval defensive secretion of a chrysomelide beetle (*Plagiodera versicolora*) in 1977, and it was synthesized in 1978 by J. Meinwald *et al.* (8). Both syntheses were non-stereospecific involving tedious separation steps.

We first attempted the stereocontrolled synthesis of chrysomelidial from 4-methyl-tricyclo[3,3,0,$0^{2,8}$]octan-3-one (**2**) which was prepared from diethyl 2-cyclopentene-1-ylmalonate by the general method of Doering. Methylation of diethyl 2-cyclopentene-1-ylmalonate with metyl iodide followed by hydrolysis and decarboxylation afforded 2-(2-cyclopentene-1yl)propionic acid in

79% yield. Conversion of this acid into its acid chloride followed by treatment with ethereal diazomethane furnished the diazo ketone **3** and the decomposition of the latter with cupric sulfate in refluxing cyclohexane yielded 4-methyl-tricyclo[3,3,0,$0^{2,8}$]octan-3-one (**2**) in 83% overall yield.



a) hν, acetone b) $CuSO_4$, heat, 88% c) HCOOH d) NaOMe; ethylene glycol, p-TsOH; CrO_3, Pyr. e) MeLi; p-TsOH, 70% from **2** f) $TsNHNH_2$; n-BuLi g) OsO_4; Ac_2O, Pyr.; $POCl_3$; $LiAlH_4$; $NaIO_4$, 64% from **5** h) 50% aq. AcOH, 99%

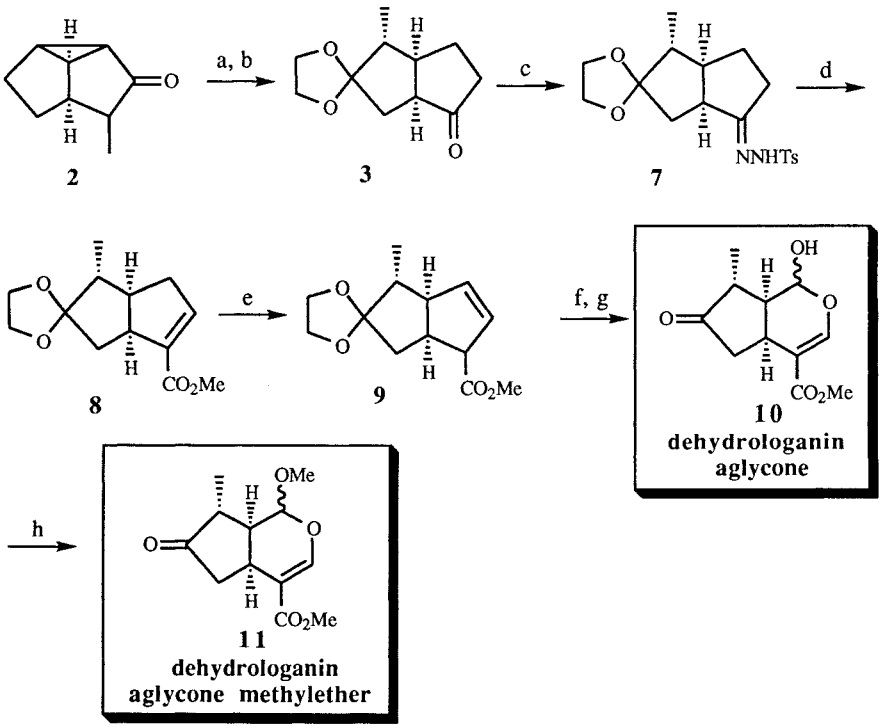
Scheme 2

Ring cleavage of **2** with 99% formic acid at 70-80 °C for 30 min followed by methanolysis and ketalization in the usual manner gave in 87% yield a mixture of the desired ketal ($C_{2\text{-}8}$ bond cleavage) and its structural isomer ($C_{1\text{-}2}$ bond cleavage) in a ratio of 4:1 by ^{1}H-NMR. The two isomers were easily separated by column chromatography. This desired ketal was oxidized with chromium trioxide-pyridine complex in methylene chloride to give the corresponding ketone **4** which, upon alkylation with methyl lithium in ether at -78 °C followed by treatment with p-toluenesulfonic acid in aqueous THF, afforded the ketoalcohol **5** in 81% yield. Refluxing of **5** with p-toluenesulfonyl hydrazine in methanol for 30 min produced the corresponding hydrazone in 93% yield. Treatment of this resulting hydrazone with excess n-butyl lithium in THF, followed by oxidation with osmium tetroxide in ether, and acetylation gave in 75% yield the stereoisomeric mixture of diacetates and

triacetate in a ratio of 83:14:3. Diacetates were treated with phosphoryl chloride in pyridine at 50 °C for 3 h to form in 97% yield a mixture of the desired tetra-substituted olefin and tri-substituted olefin in a ratio of ca. 15:85 by ^{1}H-NMR. Reduction of the tetrasubstituted olefin mixture with lithium aluminium hydride in ether followed by oxidation with sodium periodate in ether-water (1:1) at 4 °C for 24 h afforded chrysomelidial in excellent yields. The same oxidation of the trisubstituted olefin produced the hydrate **6**, which was transformed into chrysomelidial by refluxing in 50% aqueos acetic acid in 99% yield. The diacetate was also converted to chrysomelidial by the same procedure.

2.2 Synthesis of Loganin Aglycone Silylether (Scheme 3)

Loganin was first isolated from Strychnos nux vomica and it is a widely distributed secondary plant metabolite (9). It has proven to be an important monoterpene in plant biochemistry due to the role in the biosynthesis of indole alkaloids and other natural products (10). We have employed the versatile intermediate **3** in the synthesis of loganin (11-12).



a) HCO_2H; NaOMe b) ethylene glycol, p-TsOH; CrO_3, Pyr. c) $TsNHNH_2$; 89% from **2** d) n-BuLi; $ClCO_2Me$, 32% e) LDA; H^+, 96% f) OsO_4; H^+, 89% g) $NaIO_4$, 90% h) MeOH, cation exchange resin, 85%

Scheme 3

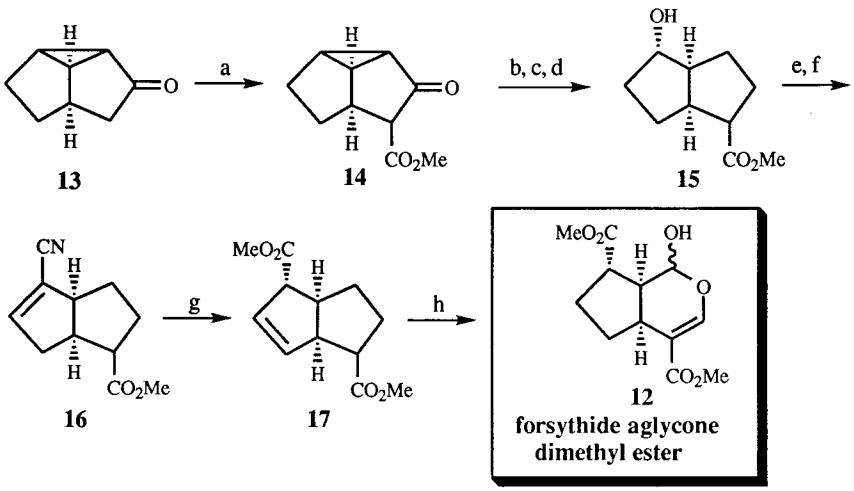
Reaction of **3** with p-toluenesulfonylhydrazine and molecular sieves (3A) in CH_3OH under reflux for 45 min gave the tosylhydrazone **7**. Treatment of **7** with butyl lithium in N,N,N',N'-

tetramethylethylenediamine, followed by trapping of the produced vinyl anion with DMF gave the α,β-unsaturated aldehyde in 36% yield. Oxidation of the aldehyde with active MnO_2 in the presence of HCN in CH_3OH at room temperature for 18 h afforded the α,β-unsaturated ester **8** in 82% yield. On the other hand, direct conversion of **7** to **8** was also accomplished in 32% overall yield by treatment of **7** with BuLi and then trapping of the produced vinyl anion with methyl chloroformate instead of DMF. Deprotonation of **8** with lithium diisopropylamide in THF at -78 °C produced the lithium enolate of **8** *in situ*, which was kinetically protonated by exposure to aqueous acetic acid at 0 °C to give the β,γ-unstaurated ester **9** in 96% yield. Oxidation of **9** with OsO_4 in ether at 25 °C for 48 h, followed by decomposition with $NaHSO_3$, and deprotection of ethylene acetal with p-toluenesulfonic acid in aqueous THF at 30 °C for 24 h gave the dihydroxy-keto derivative, which was oxidized with sodium periodate in ether/water 1:1 at 4 °C for 24 h to afford dehydrologanin aglycone **10** in 81% yield. Dehydrologanin aglycone (**10**) was transformed into the corresponding 1-O-methyl derivative (**11**) in 85% yield by treatment with cation exchange resin in CH_3OH at 25 °C for 48 h. The ^{1}H-NMR and IR spectrum of the synthetic methyl ester **11** were consistent with those of the reported methyl ether; this methyl ester **11** has already been converted into (±)-loganin by Büchi *et al.* (12a). Thus, a new synthetic route to loganin was established.

2.3 Synthesis of Forsythide Aglycone Dimethyl Ester (Scheme 4)

We have now demonstrated the potential utility of 4-methyl-tricyclo[3,3,0,$0^{2,8}$]octan-3-one **4** as a versatile intermediate in the synthesis of chrysomelidial (6) and loganin. We next describe the stereocontrolled synthesis of (±)-forsythide aglycone dimethyl ester (**12**), starting from another versatile synthon, 4-methoxycarbonyl-tricyclo[3,3,0,$0^{2,8}$]octan-3-one (**14**). Forsythide (13) is a naturally occurring iridoid glucoside isolated from the fresh leaves of *Forsythia viridissima* Lindl. The key intermediate **14** was prepared from tricyclo[3,3,0,$0^{2,8}$]octan-3-one (**13**) by methoxycarbonylation with dimethyl carbonate and sodium hydride in dimethoxyethane at reflux temperature in 84% yield (**Scheme 4**). Although the cyclopropane ring of **2** or **13** could be cleaved with 99% formic acid at 70-80 °C to afforded the corresponding formate ($C_{2\text{-}8}$ bond cleavage) and its isomer ($C_{1\text{-}2}$ bond cleavage), in the case of **14** with a methoxycarbonyl group at C_4 position, only the $C_{2\text{-}8}$ bond was selectively cleaved with 99% formic acid in the presence of conc. sulfuric acid at room temperature to afford the desired formate. Subsequent treatment with sodium methoxide afforded the hydroxyl keto ester in 88% yield from **14**. Deoxygenation of the ketone at the C_3 position was achieved by the thioketalization followed by reduction with Raney Ni (W-2). Thus, the hydroxyl keto ester gave the hydroxy ester **15** in 80% yield. Compound **15** was oxidized with Jones reagent to give the keto ester which was converted into the corresponding cyanohydrin by treatment with KCN and AcOH in EtOH at 30 °C in good yield. This was dehydrated with phosphoryl chloride in pyridine to give the α,β-unsaturated nitrile **16** in 84% yield. Compound **16** was hydrolyzed with potassium hydroxide in ethylene glycol at 160-180 °C to its dicarboxylic acid which was treated with diazomethane to give the corresponding diester in 79% yield. The diester was deprotonated with lithium diisopropyl amide-hexamethyl-phosphoramide complex in THF at -78 °C

to produce the lithium enolate of the diester *in situ*, which was quenched with acetic acid to give the β,γ-unsaturated ester **17** in 84% yield (ratio:α,β/β,γ=1.0/10.4 by ^{1}H-NMR).



a) $(MeO)_2CO$, NaH, DME, 84% b) HCO_2H, conc. H_2SO_4 c) NaOMe, 88% d) HS-CH_2CH_2SH, BF_3; Raney Ni, 80% e) Jones oxid. f) KCN, AcOH; $POCl_3$, Pyr., 84% g) KOH; CH_2N_2; LDA-HMPA, -78 °C; aq. AcOH, 0 °C, 66% h) O_3, 66%

Scheme 4

Ozonolysis of the mixture of **17** followed by reductive workup with Zn/AcOH directly led to (±)-forsythide aglycone dimethyl ester **12** after purification by preparative TLC as an oil. This was an epimeric mixture at the C_1 position and was obtained in 66% yield (ratio: α-OH/β-OH=3.5/1.0 by ^{1}H-NMR). The stereocontrolled and facile synthesis of (±)-forsythide aglycone dimethyl ester **12** was thus achieved starting from the versatile synthon **14**.

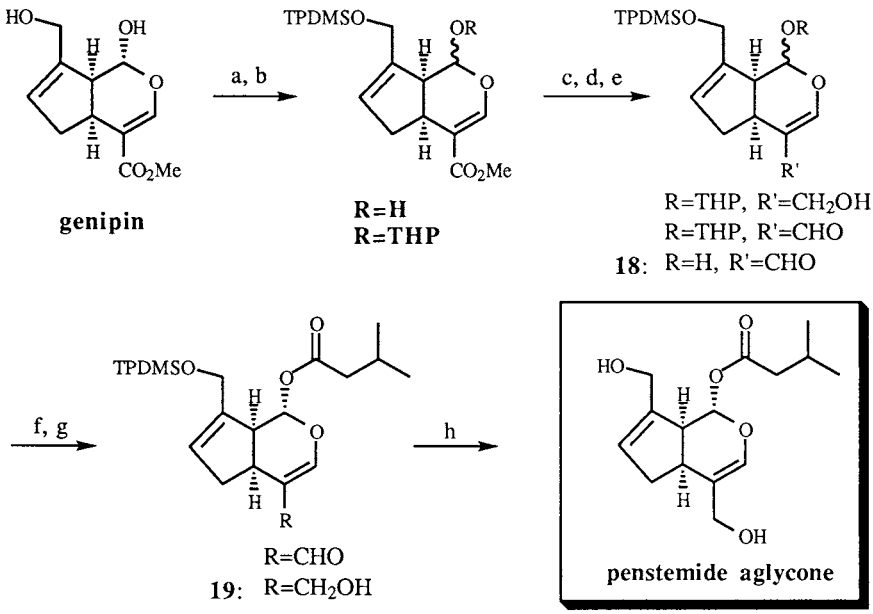
3. PENSTEMIDE AND DIDROVALTRATE

Penstemide was isolated from the methanol extracts of *Penstemon deutus* Dongl. exLindl. (Scrophulariaceae) by J. R. Cole *et al.* (14) in 1976 and its structure was revised to the present structure in 1979 (15). On the other hand, didrovaltrate was isolated from the *Valeriana Wallichii* D. C. in 1968 (16) and it's correct stereochemistry including absolute configuration was established in 1973 by Thies *et al.* (17). Penstemide was found to exhibit activity against the P-388 lymphocytic leukemia test system and didrovaltrate is a very potent cytotoxic agent for the rat hepatoma cells and induces high percent definitive remissions of the Krebs II ascitic tumors (18).

3.1 The Synthesis of Penstemide Aglycone (Scheme 5)

Selective protection of hydroxyl groups of genipin with different protective groups followed by reduction of the methoxycarbonyl groupwith DIBAL and oxidation of resulting alcohol with $BaMnO_4$ yielded the aldehyde **18**. Selective deprotection of the hemiacetal protective group followed by acylation with isovaleric acid in the presence of carbonyl diimidazole and DBU and reduction with

$NaBH_4$ furnished penstemide aglycone silylether **19** in very high yield. Glucosidation of the primary alcohol **19** followed by deprotection would lead to the synthesis of penstemide.

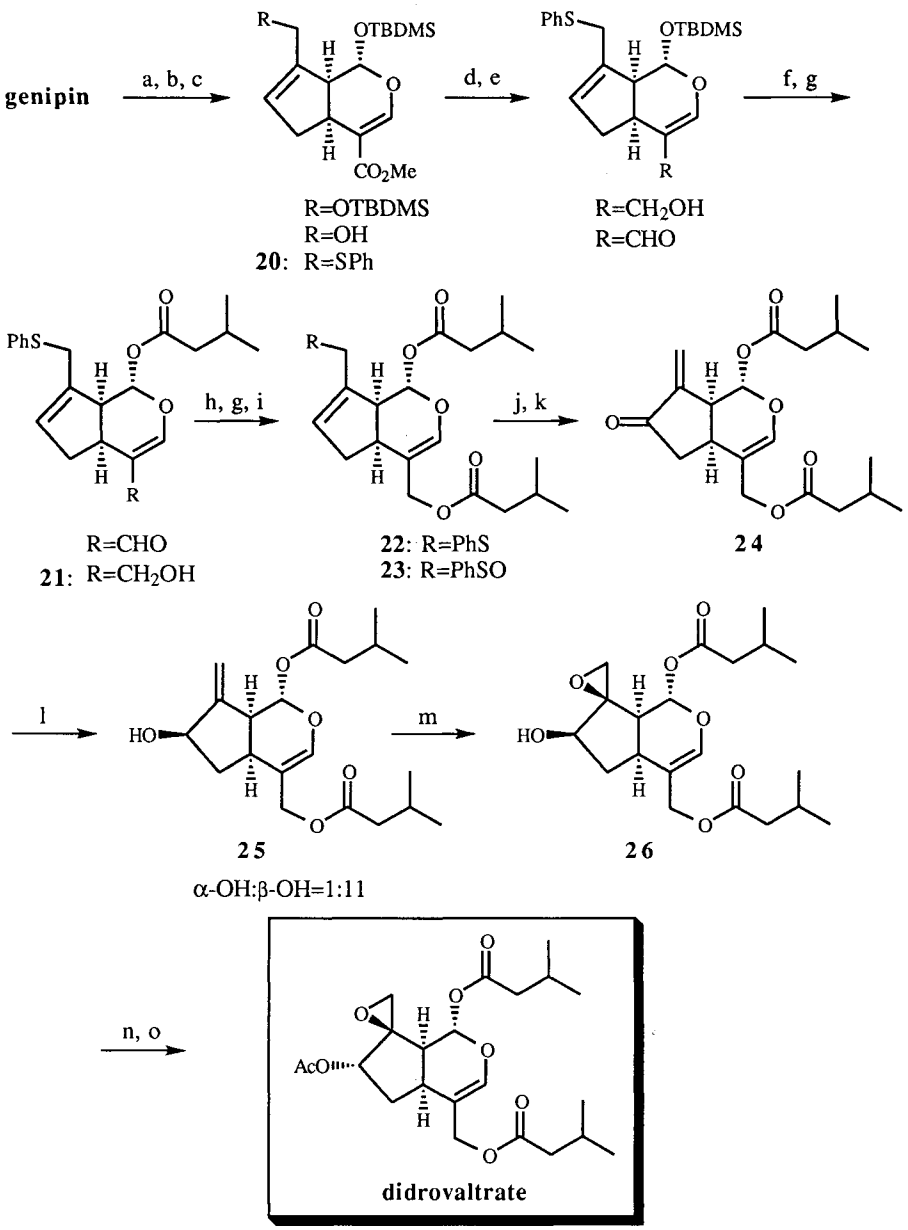


a) t-$BuPh_2SiCl$, Imidazol b) DHP, CSA, 91% from genipin c) DIBAL, 94% d) $BaMnO_4$, 91% e) PPTS, 93% f) $(Me)_2CHCH_2CO_2H$, Im_2CO, cat. DBU, 87%, α/β=9/1 g) $NaBH_4$, 89% h) n-Bu_4NF, 97%

Scheme 5

3.2 The Synthesis of Didrovaltrate (Scheme 6)

Selective protection of the hydroxyl group of the hemiacetal of genipin followed by treatment with diphenyl disufide in the presence of tri-n-butylphosphine yielded the phenyl thioether **20**. To avoid the elimination of the more reactive primary hydroxyl group at the stage of acylation, two isovaleryl groups were introduced by the following sequence. The hydroxyl group of the hemiacetal was acylated first by the same procedure used as that in the synthesis of penstemide aglycone, and then the primary alcohol was acylated to yield diisovalerate **22**. Oxidation of phenylsulfide to phenyl sulfoxide **23** followed by Evan's rearrangement and oxidation of the resulting allylic alcohol gave the exomethylene ketone **24** in high yield. Reduction of the ketone **24** to the β-hydroxy olefin **25** followed by Sharpless oxidation afforded the β-epoxy alcohol **26**. Inversion of the β-hydroxyl group to α-acetoxyl group was successfully carried out by a SN2 reaction of triflate with acetate anion in the presence of 18-Crown-6 to accomplish the synthesis of didrovaltrate.

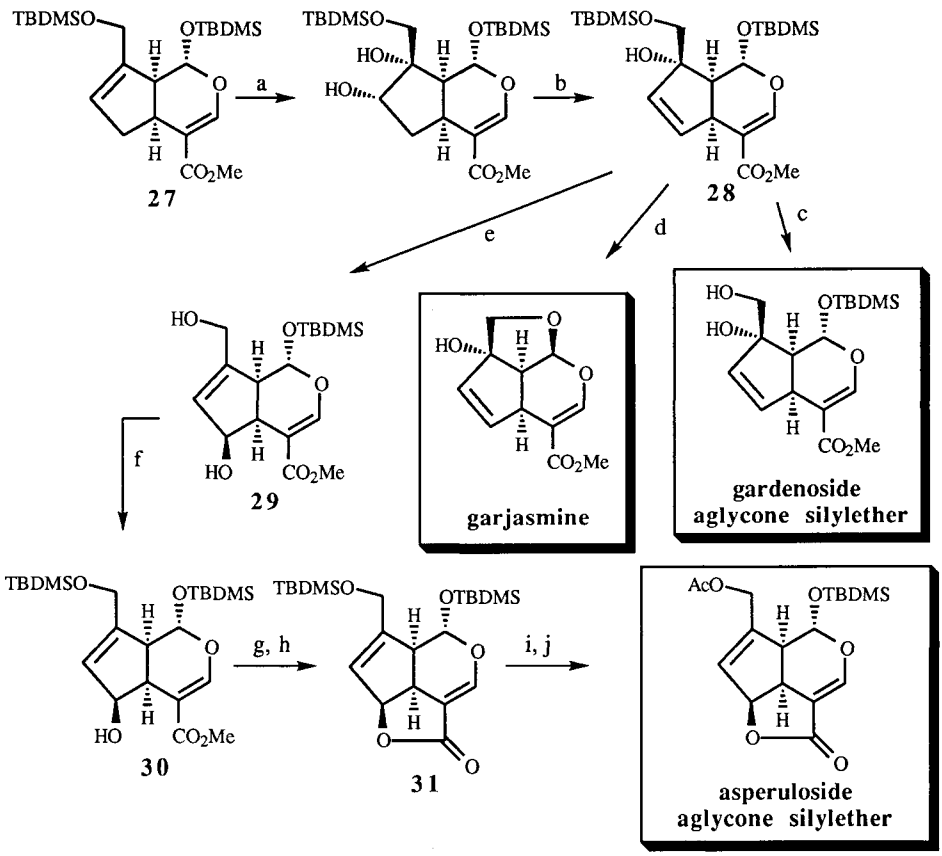


a) t-BuMe$_2$SiCl, AgNO$_3$ b) PPTS, 98% from genipin c) (PhS)$_2$, n-Bu$_3$P, 94% d) DIBAL, quant. e) BaMnO$_4$, quant. f) n-Bu$_4$NF, 94% g) (Me)$_2$CHCH$_2$CO$_2$H, Im$_2$CO, DBU, 98% for **21** and 78% for **22** h) NaBH$_4$, CeCl$_3$, 90% i) OXONE, 89% j) (MeO)$_3$P, 87% k) BaMnO$_4$, quant. l) NaBH$_4$, CeCl$_3$, 95% m) TBHP, VO(acac)$_2$, 89% n) (CF$_3$SO$_2$)$_2$O, DMAP, CH$_2$Cl$_2$, -40 °C to -20 °C o) AcOH, AcOK, 18-Crown-6, CH$_2$Cl$_2$-acetone, -20 °C to rt, 78%

Scheme 6

4. GARDENOSIDE, GAJASMIN AND ASPERULOSIDE

The fruits of *Gardenia jasminoides* Ellis are a Chinese traditional medicine used for treatment of hepatitis and hemafecia. During a screening test on antifertility agents from the flowers of this plant, J-P. Gu and R-S. Xu (19) isolated garjasmin and garjasmidin. Gardenoside (20) was isolated from *Gardenia jasminoides* f. grandiflora and other plants. Asperuloside (21) was isolated from *Asperua odorata* L..



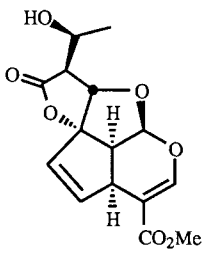
a) cat. OsO_4, NMO, t-BuOH:acetone:H_2O=10:3:1, 85% b) 1.5 eq. Tf_2O, DMAP, CH_2Cl_2; DBU, 76% c) PPTS, acetone-H_2O d) 5 eq. n-Bu_4NF; p-TsOH, 53% e) PPTS, acetone-H_2O, reflux, 50% f) TBDMSCl, Im, DMF, 93% from **28** g) 1 eq. KH, THF, 0 °C h) DCC, DMAP, CH_2Cl_2, 85% from **30** i) PPTS, acetone:H_2O=3:1, reflux j) Ac_2O, Pyr., DMAP, 54% from **31**

Scheme 7

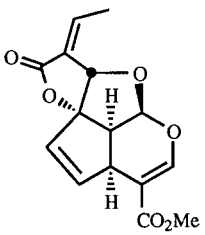
Garjasmin and asperuloside aglycone silylether were synthesized from genipin via gardenoside aglycone silylether (**Scheme 7**). Dihydroxylation of genipin disilylether (**27**) with osmium tetroxide followed by the selective elimination of the secondary alcohol via triflate gave disilylether of gardenoside aglycone (**28**) in good yield. Upon treatment of **28** with PPTS in aqueous acetone, the silyl group attached to the primary alcohol was first hydrolyzed to give gardenoside aglycone silyl ether. The prolonged reaction time, however, caused transposition of the tertiary hydroxy group to yield the desired C_6 hydroxylated compounds as a mixture of stereoisomers **29** in about 3.6 to 1 ratio. This observed hydroxy transposition was significant in that the transposition of hydroxyl group in the proposed biosynthetic pathway (22) of gardenoside from geniposide proceeded in the opposite direction. The major isomer (β-hydroxy) was converted into asperuloside aglycone silylether as shown in **Scheme 7**. Treatment of the alcohol **30**, obtained by silylation of the primary alcohol in **29**, with potassium hydride in THF cleanly afforded the hydroxy acid, which was then lactonized with DCC to give the desired lactone **31**. Finally hydrolysis of the silyl group to the primary alcohol followed by acetylation of the resulting alcohol completed the synthesis of asperuloside aglycone silylether. Garjasmin was synthesized from **28** by treatment with a large excess amount of TBAF (5 equiv.) followed by acidification with p-toluenesulfonic acid (p-TsOH) in 53% yield.

5. ALLAMANDICIN, PLUMERICIN AND PLUMIERIDE

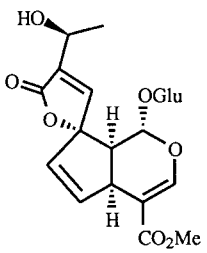
In the course of a search for tumor inhibitors of plant origin, Kupchan *et al.* (23) isolated several iridoids from *Allamanda catharica* Linn (Apocyanaceae). These are allamandin, allamandicin, allamdin, plumericin and isoplumericin. Members of this class exhibit cytotoxic, antileukemic, antifungal and antimicrobial activities.



allamandicin



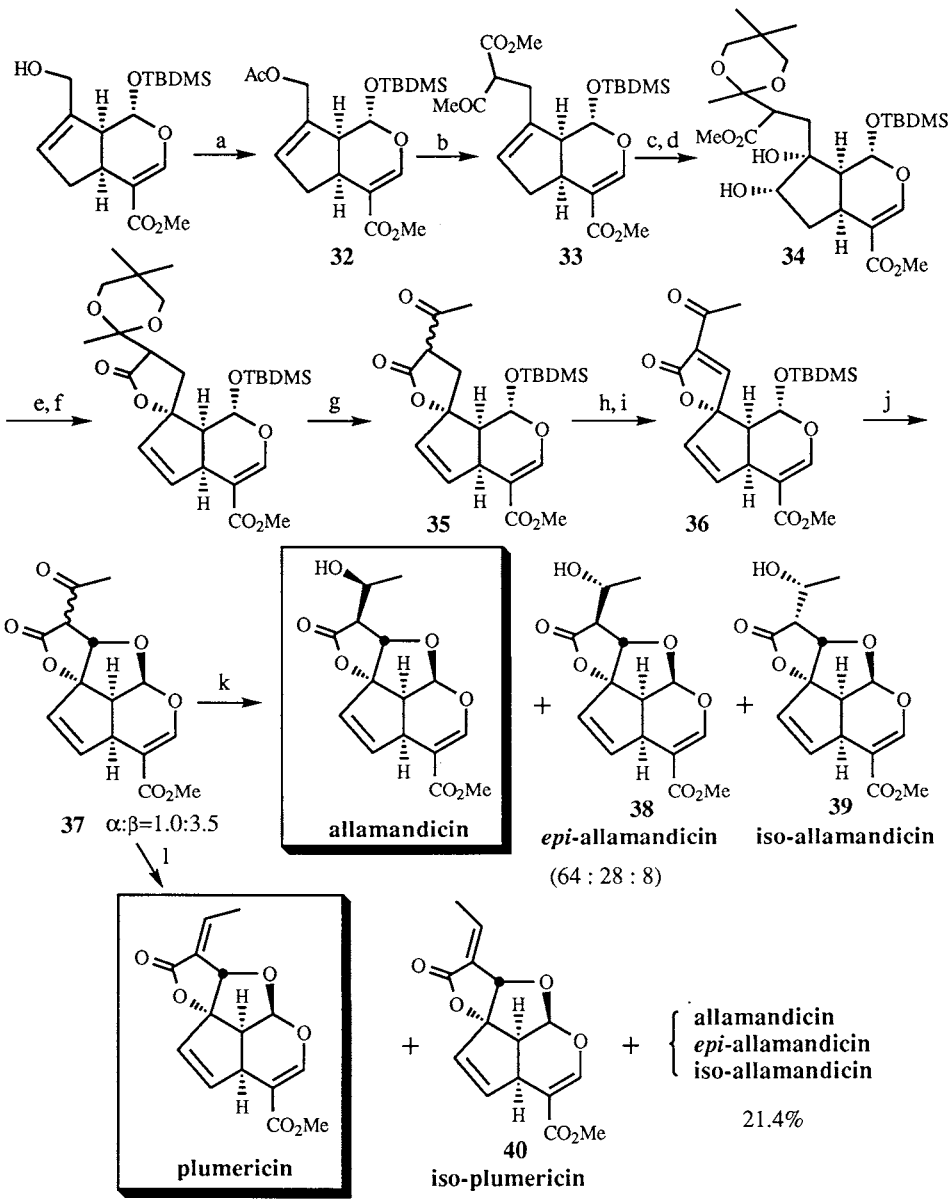
plumericin



plumieride

Synthesis of Allamandicin, Plumericin (Scheme 8), and Plumieride (Scheme 9)

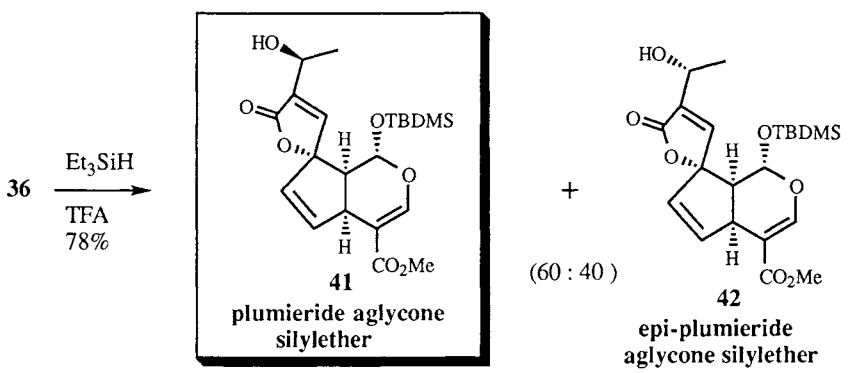
In 1983, Trost *et al.* (25) reported the synthesis of plumericin and allamandin by using the concept of substitutive spiroannulation and new carbomethoxylation of an enol ether starting from bicyclo[3,3,0]-octenone derivative. Allamcin (26), isolated from *Allamanda* sp. was synthesized by Pattenden *et al.* (27) in 1986 also starting from bicyclo[3,3,0]-octenon derivative. On the other hand,



a) Ac_2O, Pyr., CH_2Cl_2, 92% b) $Pd(PPh_3)_4$, Ph_3P, THF; $MeCOCH_2CO_2Me$, NaH,THF, quant. c) 2,2-Dimethyl-1,3-propanediol, p-TsOH, C_6H_6, 86% d) cat. OsO_4, NMO, t-BuOH-acetone-H_2O, ~50% e) NaOMe, MeOH, 94% f) $(CF_3SO_2)_2O$/DMAP/CH_2Cl_2; DBU, 90% g) Ph_3CBF_4, CH_2Cl_2, 78% h) PhSeBr or PhSeCl, DMAP, CH_2Cl_2 i) H_2O_2, CH_2Cl_2, 80% from **35** j) n-Bu_4NF, 2 eq. AcOH, THF, quant. k) Et_3SiH, TFA, 0 °C, 18 h, 40% l) Et_3SiH, TFA, rt, 20 h

Scheme 8

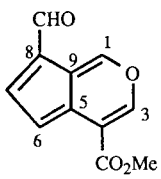
Inoue *et al.* (28) succeeded in the synthesis of plumieride (24) from 10-dehydrogardenoside tetraacetate and ethylacetoacetate by a biomimetic route in 1979. In our synthesis of plumericin and allamandicin, plumierde which was thought to be a biogenetic precursor (29) was selected as the key intermediate. We first attempted the coupling of genipin with methyl acetoacetate. Selective protection of the hydroxyl group of genipin hemiacetal followed by acetylation produced allyl acetate **32**. Palladium π allyl complex mediated coupling reaction (30) of allylacetate with sodium salt of methylacetoacetate produced the coupling product **33** in quantitative yield. Protection of the ketone as an acetal followed by reaction with osmium tetroxide yielded the dihydroxy compound **34**. Both lactonization and dehydration proceeded in high yield by the treatment of **34** with sodium methoxide followed by treatment with trifluoromethanesulfonic anhydride, 4-dimethylaminopyridine and DBU. It is noteworthy that the use of trifluoromethane sulfonyl chloride gave the chloride by substitution. Difficulty in a similar dehydration was reported in the synthesis of plumericin by Trost (31). Deprotection of the acetal protecting group proceeded well on treatment with tritylfluoroborate. The introduction of phenylselenyl group and selenoxide elimination also proceeded nicely to give an unsataurated keto lactone **36** (32). Reduction of the keto lactone **36** with triethylsilane in trifluoroacetic acid (33) furnished a mixture of plumieride aglycone silylether (**41**) and its epimer **42** (60:40) in 78% yield (**Scheme 9**). Desilylation of **36** with tetrabutylammonium flouoride (TBAF) in the presence of 2 equiv. of acetic acid followed by Michael addition of the alcohol produced the tetracyclic ether **37** in quantitative yield. The final step is the stereoselective reduction of the keto group to give allamandicin. After many fruitless attempts, it was found that this reaction was best performed by the reduction with triethylsilane in CF_3CO_2H at 0 °C to accomplish the synthesis of (+)-allamandicin. In this case (+)-*epi*-allamandicin (**38**) and (+)-iso-allamandicin (**39**) were aslo obtained. Any reductions in basic conditions gave fruitless results. When this reduction was carried out at room temperature, a mixture of (+)-plumericin and (+)-iso-plumericin (**40**) (75:25) were obtained in 50% yield. Dehydration of a mixture of allamandicin and *epi*-allamandicin (**38**) (75:25) with phosphoryl chloride afforded a mixture of (+)-plumericin and (+)-iso-plumericin (**40**) (75:25) in 83% yield.



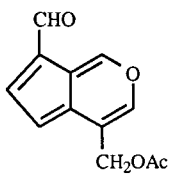
Scheme 9

6. CERBINAL AND BALDRINAL

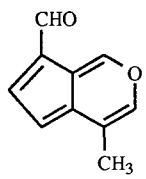
Cerbinal (**43**) (34), a yellow pigment, was isolated from the bark of *Cerbera manghas* L. in 1977. It was later isolated from *Gardenia jasminoides* Ellis again in 1986 (35). Cerbinal was reported to show antifugal activity against *Bipolaris sorokiniana, Helminthosporium, Pyricularia, Colletotrichum lagenarium* and *Puccinia* species. At concentrations of 0.75-4 μg/ml, **43** caused 100% inhibition of germination of spores of *Puccinia* species on oat, wheat, Welsh onion and white clover. The interesting thing is that both plants are used as traditional medicinal herbs. Cerbinal has been recognized by its characteristic $\Delta^{3,5,7,9}$-tetraene 10π aromatic system (a unique cyclopentadieno[c]pyran ring system). This unusual iridoid structure can also be found in baldrinal (**44**) (36), viburtinal (**45**) (37) and halitunal (**46**) (38). Baldrinal (**44**) was isolated from the roots of *Valeriana wallichii* D.C., which was recently found to exhibit potent cytotoxicity *in vitro* against HTC hepatoma cells and anti-tumor activities *in vivo* against KREBS II ascitic tumor, while viburtinal was isolated from the leaves of *Viburnum tinus* and *Viburnum opulus* (Carprifoliaceae). Its dried leaves have been traditionally used as a spasmolytic, in indigenous medicine. Halitunal (**46**), a novel diterpene aldehyde also possessing a unique cyclopentadieno[c]pyran ring system was also isolated from the marine alga *Halimeda tuna*. Halitunal was reported to show antiviral activity against murine coronavirus A59 *in vitro*.



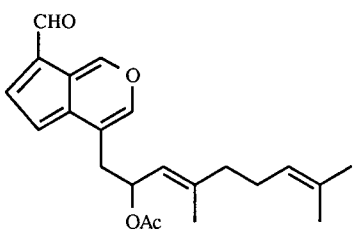
cerbinal (43)



baldrinal (44)



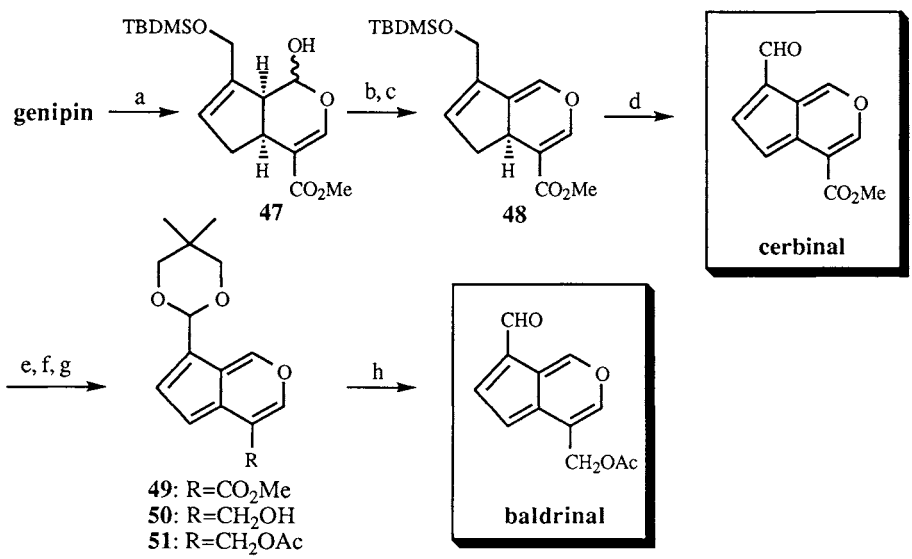
viburtinal (45)



halitunal (46)

In this section we would like to describe an efficient synthesis of **43** and **44** from (+)-genipin. It is anticipated that the introduction of the double bond at the C_1-C_9 position would make the dehydrogenation of C_5-H and C_6-H feasible to result in the formation of the desired aromatic system. We have been reported (39) the first synthesis of **43** from genipin. To approach the synthesis of other compounds involving the same aromatic system with different side chains, we needed to obtain **43** more conveniently and efficiently. We therefore tried to find a more efficient synthetic route to get this key compound.

The silylation of genipin with t-butyldimethylsilyl chloride in the presence of imidazole gave the monosilyl ether **47** quantitatively (**Scheme 10**). For the subsequent dehydration, we then tried to convert the hydroxy group of **47** into several leaving groups. However it was difficult to get compounds with leaving groups on the hemiacetal carbon, because of the instability of intermediates. We found that the thioimidazolide (40) underwent thermal decomposition smoothly to give the eliminated compound. Thus, treatment of **47** with 1,1'-thiocarbonyldiimidazole in benzene afforded the thioimidazolide. Since the product was too unstable for isolation, it was then heated up in refluxing benzene giving rise to the key intermediate **48**. Upon treatment of **48** with DDQ in benzene, the expected dehydrogenation between C_5-C_6 and oxidation of the allylic carbon occurred to give **43** as yellow needle crystals in 37% overall yield. All the experimental procedures could be carried out in a one-pot procedure and under mild conditions. Considering this successful synthetic route, the synthesis of cerbinal **43** would be hope to up to an industry scale.

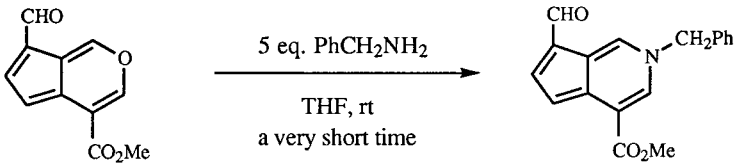


a) t-butyldimethylsilyl chloride, imidazole, CH_2Cl_2, ~100% b) 1,1'-thiocarbonyldiimidazole, benzene, rt, overnight c) AIBN, benzene, reflux, 3 h d) 1.5 eq. DDQ, benzene, rt, 1 h, 37% from genipin e) 2, 2-dimethyl-1, 3-propanediol, cat. PPTS, benzene, reflux, 2 h, 88% f) DIBAL, THF, -78 °C, 42%, recovery 23% g) Ac_2O, Pyr., 86% h) cat. PPTS, THF-H_2O, rt, 2 h, 66%

Scheme 10

Protection of the aldehyde moiety in **43** with 2,2-dimethyl-1,3-propanediol in the presence of a catalytic amount of a weaker acid PPTS was achieved to afford **49**. Treatment of **49** with DIBAL/THF at -78 °C successfully afforded the key intermediate **50** in 42% yield. Although four

equivalents of DIBAL were used, the activity of DIBAL decreased because of the use of THF as a solvent, and it led to the recovery of **49** in 23% yield. Subsequent acetylation of **50** gave **51** in good yield. Deprotection of **51** with catalytic amount of PPTS successfully afforded baldrinal in 66% yield. It seemed that this cyclopentadieno[c]pyran ring system was very unstable in the presence of nucleophiles under acidic or basic conditions. We found that in the presence of a primary amine such as benzylamine, **43** quickly reacted with 2 equivalents of amine to give unknown derivatives. However in the case of over 5 equivalents of benzylamine, an O/N exchange very quickly occurred to give a cyclopenta[c]pyridine derivative (**52**) (**Scheme 11**). This result was also found in baldrinal. (41) To our surprise, cerbinal did not show any cytotoxicity against several human carcinomas.



43 **52**

Scheme 11

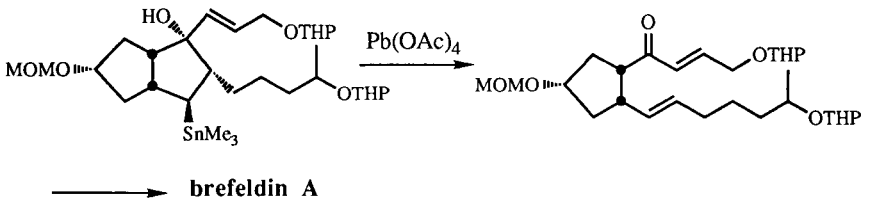
As described above we have developed a general method for the efficient synthesis of cerbinal involving a cyclopentadieno[c]pyran ring system. Using cerbinal as a building block, we have successfully achieved the synthesis of baldrinal. This synthetic scheme helped us to gain a lot of information about the chemical properties and biological activities of this unique aromatic system. This synthetic scheme may be applied to the synthesis of **45** and **46** as well as an unnatural 10 π iridoids to investigate their structure-activity relationship in their biological activities, especially their antitumor activity.

7. SECOIRIDOIDS

7.1 Secologanin, Sweroside and Gentiopicroside (Scheme 12)

Secologanin was isolated from *Lonicera morrowii* A. Gray (kingimboku) by Mitsuhashi *et al.* in 1970 (42) and has considerable biosynthetic significance, because it is the common non-nitrogenous precursor to a vast and diverse array of indole alkaloids (43). Secologanin is biosynthesized via loganin by $C_{7\text{-}8}$ cleavage of the five membered ring.

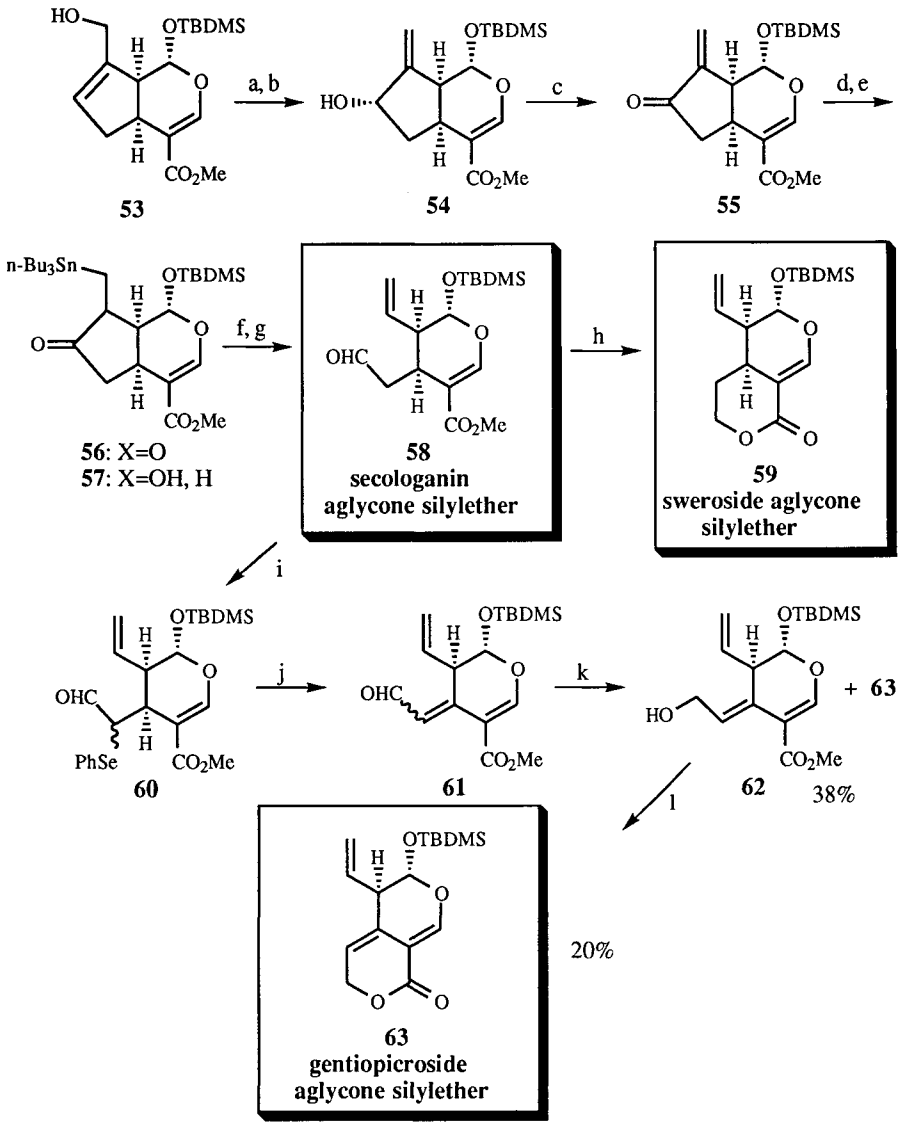
The biomimetic fragmentation approach to the synthesis of secologanin has been employed by L. F. Tietze (44) and J. J. Partridge (45). We have applied the oxidative fragmentation of γ-hydroxy alkylstannane with lead tetraacetate, which was previously developed in our laboratory, (46) to the synthesis of brefeldin A.



The monosilyl ether **53** was obtained from genipin by disilylation of the primary hydroxyl group and the hemiacetal, followed by selective desilylation of the primary hydroxyl group with PPTS in 98% yield. This simple procedure was very useful for both regioselective and stereoselective protection of the hydroxy group of the hemiacetal in genipin. Allylic rearragement of the free hydroxyl group of **55** was achieved by Evans rearrangement. (47) Thus **53** was converted to a thioether, which was oxidized to give the sulfoxide. Thermal rearrangement of the resulting sulfoxide proceeded smoothly to give the alcohol **54**, which was subjected to oxidation, yielding the exomethylene ketone **55**.

It is well known that trialkylstannyl lithium normally adds to α,β-unstaurated ketone to give the formal 1,4-adduct in excellent yield (48). However, treatment of **55** with tributylstannyl lithium gave the desired 1,4-adduct in only 23% yield along with the dimeric product. The dimer might be formed by 1,4-addition of the α-anion of **55** to the starting exomethylene ketone. Presumably tributylstannyl lithium acted as base. When triphenylstannyl lithium was allowed to react with the exomethylene ketone **55**, however, the normal 1,4-adduct **56** was obtained in 70% yield. After reduction of **56**, treatment of the resulting alcohol with lead tetraacetate did not afford any secologanin aglycone-O-methyl ether. Presumably, electron withdrawing phenyl groups decrease the electron density on the tin atom causing destabilization of the β-carbonium ion or radical intermediate. Hypercovalent bond formation of tin with γ-hydroxy group may also retard the fragmentation reaction.

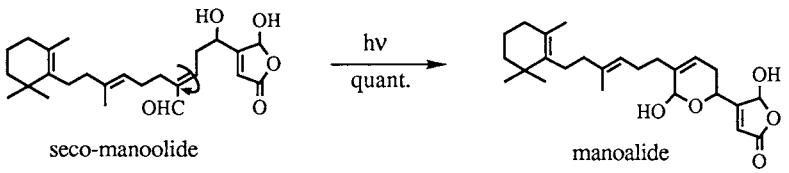
Thus, it was necessary to find an effective reagent which gives the 1,4-adduct of tributyltin to the cisoid enone such as **55**. Attempts to use ate complexes, $(PhSCuSnBu_3)^-Li^+$ and n-$Bu_3SnCu{\bullet}Me_2S$-LiBr (49) also gave the desired ketone in low yield. The dimeric product was formed as a by-product. Fortunately, it was found that (trimethylsilyl)tributylstannane was an excellent reagent for 1,4-addition of tributyltin group to cisoid enone (50). Thus, the exomethylene ketone **55** reacted cleanly with the above reagent in the presence of both a catalytic amount of KCN and 18-crown-6 to afford the desired silyl enol ether which was subjected to selective removal of trimethylsilyl group with n-Bu_4NF in the presence of acetic acid. The keto stannane **56** was obtained in high yield from **55**. Finally, the synthesis of secologanin aglycone-o-silyl ether (**58**) was achieved by reduction of **56** followed by oxidative fragmentation with lead tetraacetate. It should be noted that in contrast to Grob type fragmentation (44) this oxidative fragmentation proceeded from both cis and trans isomers in respect of the hydroxyl and tributylstannylmethyl groups of **57**. Sweroside aglycone-O-silyl ether (**59**) was obtained by the reduction of secologanin aglycone silylether (**58**) with sodium borohydride quantitatively.



a) mCPBA, CH_2Cl_2,-78 °C, 89% b) $(MeO)_3P$, MeOH, reflux, 98% c) $BaMnO_4$, CH_2Cl_2, rt, 94% d) TMS-$SnBu_3$, KCN, 18-crown-6, THF, -20 °C e) $Bu_4NF{\cdot}3H_2O$, 2 eq. AcOH,THF, 0 °C, 80% from **55** f) $NaBH_4$, MeOH, rt, 96.5% g) $Pb(OAc)_4$, $CaCO_3$, benzene, reflux, 80% h) $NaBH_4$, MeOH, rt, ~99% i) piperidine, benzene, reflux; PhSeBr, THF, -78 °C, 91% j) aq. MeOH, $NaIO_4$, rt, 72% k) $NaBH_4$, MeOH, rt l) cat. NaOMe, hν, sens., 74%

Scheme 12

Gentiopicroside, which is the principal bitter glucoside of common gentians, was isolated in 1862 (51) and has been widely used as stomachic or antidote from ancient times. The instability of the gentiopicroside made its structure elucidation extremely difficult (52). Inoue suggested that gentiopicroside could be biosynthesized via sweroside and swertiamarin (53). Secologanin aglycone silylether (**58**) was converted to its enamine with piperidine and phenyl selenyl group was introduced into the α position of the aldehyde to give **60** in 91% overall yield. Oxidation of **60** with $NaIO_4$ gave the α,β-unsaturated aldehyde **61** in 72% yield. Treatment of **61** with $NaBH_4$ in methanol resulted in the formation of gentiopicroside aglycone-O-silyl ether (**63**) (20%) contaminated with the allyl alcohol **62** (38%). We attempted the conversion of the allyl alcohol **62** into gentiopicroside aglycone silylether (**63**) by the photosensitized isomerization of the double bond in the presence of a catalytic amount of base (54). Irradiation of **62** in the presence of both catalytic amount of NaOMe as base and 2-acetonaphthone as sensitizer at 0 °C resulted in the formation of the desired gentiopicroside aglycone silylether (**63**) in good yields. Similar irreversible photoisomerization was carried out in the synthesis of manoalide as shown below (55).

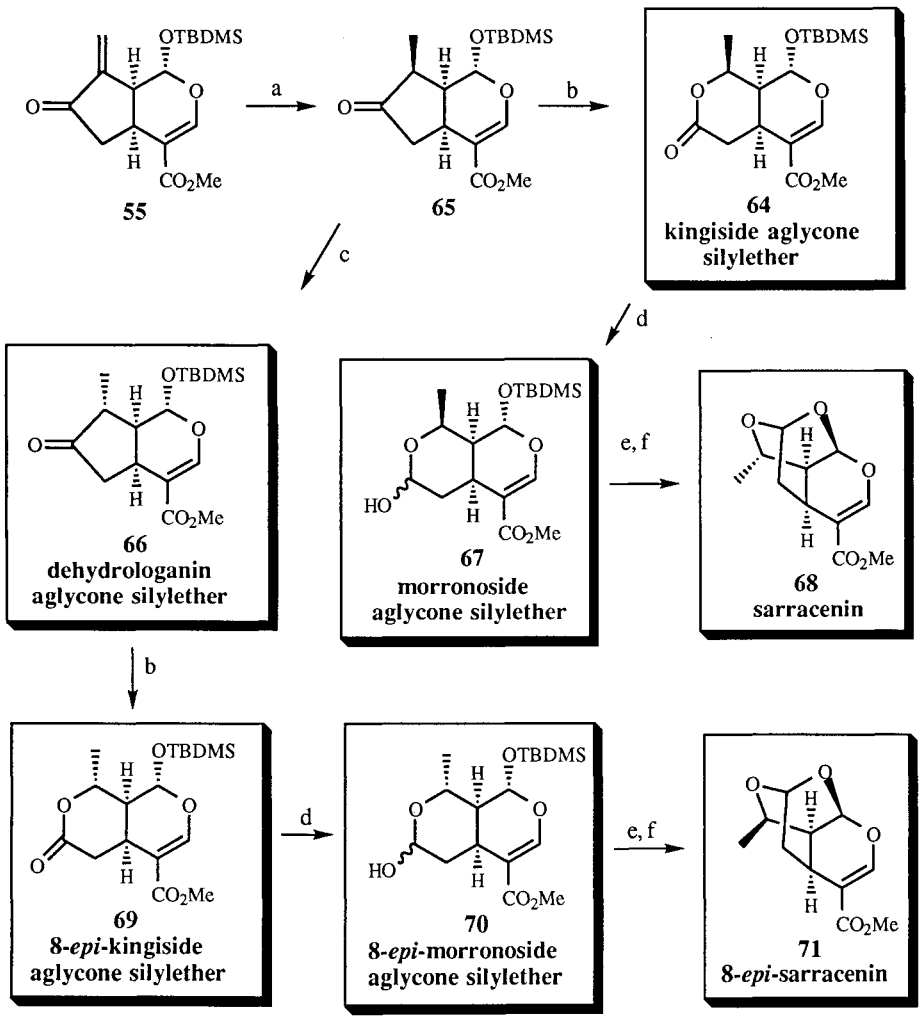


seco-manoolide manoalide

7.2 Kingiside, Morronoside and Sarracenin (Scheme 13)

Secologanin, kingiside, morronoside and sweroside have been isolated from *Lonicera morrowii* A. Gray by Souzu and Mitsuhashi (42, 56). Considering the fact that these four glucosides coexist in the same plant, these compounds are supposed to be biogenetically close congeners as suggested by Inoue (22). Since kingiside is biosynthesized via secologanin, we therefore attempted first to synthesize kingiside aglycone-O-silyl ether (**64**) from secologanin aglycone silylether (**58**). Secologanin aglycone silylether (**58**) was oxidized to give the corresponding carboxylic acid. PhSeBr was found to be an excellent reagent for lactonization. Deselenylation of the selenolactone with triphenylstannane gave a lactone, which was assigned as *epi*-kingiside aglycone silylether (**69**). Selenolactonization under equilibrium conditions ensured the formation of the thermodynamically more stable selenolactone (57). In order to control C_8 stereochemistry, we tried an alternative route. The exomethylene ketone **55**, which was also a key intermediate in the synthesis of the secologanin aglycone (**58**), was hydrogenated to give the cyclopentanone **65**. The stereochemistry was completely controlled by the approach of the catalyst from the convex face of **55**. The Baeyer-Villiger oxidation of the labile cyclopentanone **65** gave the kingiside aglycone-O-silyl ether (**64**). Morronoside aglycone-O-silyl ether (**67**) was obtained by chemoselective reduction of kingiside aglycone-O-silyl ether (**64**) with excess diborane. Reduction of **64** with 1 eq. DIBAL at -78 °C, however, afforded a mixture of the starting material and the diol. Desilylation of **67** followed by cyclization under acidic condition furnished (-)-sarracenin. 8-*Epi*-sarracenin was also synthesized

from 8-*epi*-kingiside aglycone silylether via 8-*epi*-morronoside silylether by the same procedure. Isomerization of **65** with DBU gave dehydrologanin aglycone silylether (**66**), which was also transformed to 8-*epi*-kingiside aglycone silylether (**69**), 8-*epi*-morronoside aglycone silylether (**70**) and 8-*epi*-sarracenin (**71**) by the same procedure.



a) H_2, cat. Pd-C, EtOH, rt b) mCPBA, Na_2HPO_4, CH_2Cl_2, rt, 56% from **55** c) DBU, CH_2Cl_2, 90% d) BH_3, THF, rt, 56% e) Bu_4NF, THF f) TsOH, CH_2Cl_2, 79% from **67**

Scheme 13

8. NATURAL PRODUCTS RELATED TO IRIDOIDS

Udoteal, a marine linear diterpene, is considered to be a key intermediate for the biosynthesis of petiodial , udoteatrial, halimedatrial, halimedalactone and halitunal having an iridoid framework. On the other hand, seco-manoalide, a sesterterpene having a γ-hydroxy butenolide ring, is considered to be formed from a linear sesterterpene whose functionality is very similar to udoteal. It may be possible to think that synthetic seco-manoalide analogue, which is a remarkable phospholipase A_2 inhibitor, will be isolated in the future.

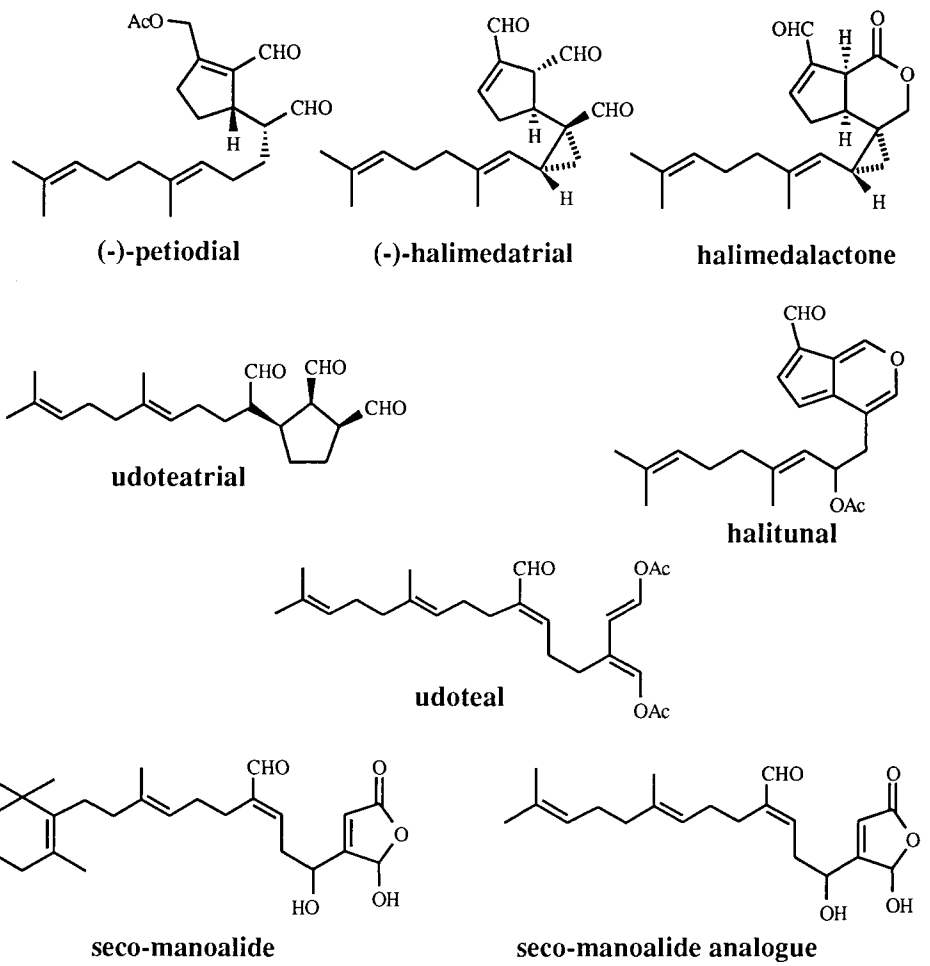
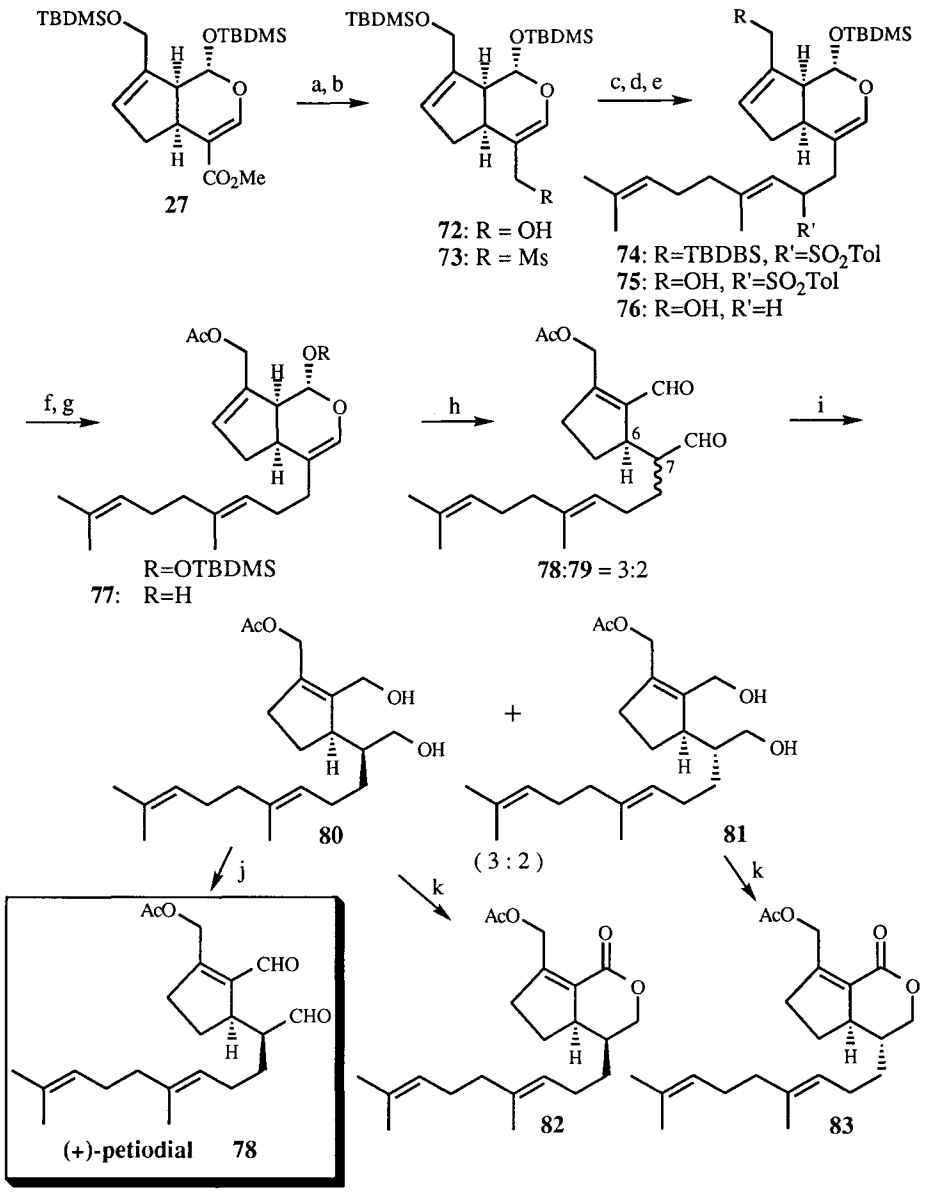


Figure 3

8.1 Petiodial (Scheme 14)

(-)-Petiodial was isolated from the marine algae, *Udotea petiolata*, collected in Naples (58) and from *Udotea Flabellum* (59) in Carribean independently. This monocyclic diterpenoid dialdehyde shows significant biological activities against several marine bacteria, inhibits of cell division in fertilized sea urchin eggs, and is toxic to herbivorous damselfish causing death within one hour. Besides petiodial, the diterpenoids udoteatrial (60) and halimedatrial (61) have been reported possessing similar structures. The absolute configuration of these compounds has not been determined, and in the case of petiodial the relative stereochemistry has also not been reported yet. In the biosynthesis of these diterpenoids, the corresponding linear diterpene udoteal, isolated from the algae, was suggested to be the biogenetic precursors (61). In this section the first efficient synthesis (62) of optically active petiodial and determination of its absolute structure (*6S, 7R*) has been described.

For the efficient synthesis of optically active petiodial, we started from the easily obtainable (+)-genipin. Silylation of genipin gave disilyl ether **27** which was subjected to reduction with DIBAL to give the alcohol **72** in 92% yield from genipin. Alkylation of the mesylate prepared *in situ* from **72** was successful at low temperature as follows. Alcohol **72** was treated with n-BuLi in THF at -78 °C followed by addition of mesyl chloride, and the lithium anion of geranyl tolyl sulfone (63) was reacted with the mesylate **73** prepared as above to give desired alkylated compound **74** in 80% yield. Attempts to detect the intermediary mesylate by thin layer chromatography was unsuccessful because of its instability at room temperature, as encountered in the corresponding chloride, and trichloroacetate. This result suggests that these type of iridoids having a good leaving group at C_{11} decompose readily at room temperature. Selective desilylation of **74** with PPTS in ethanol gave the monosilyl ether (**75**), which was subjected to reduction to afford the alcohol **76** in 64% yield. Acetylation of **76** followed by rapid treatment with n-Bu_4NF afforded the hemiacetal **77** in 93% yield. This compound was a positional isomer of the double bond in petiodial. Isomerization of the double bond in the five membered ring of **77** proved to be unexpectedly difficult and highly critical conditions were required for this isomerization. Refluxing an anhydrous benzene solution (0.05 M in substrate) of the hemiacetal **77** containing 0.5 equivalent of diazabicycloundecene (DBU) afforded the dial **78** and its stereoisomer **79** in 80% yield. More vigorous conditions or use of THF as solvent gave the desired compounds in lower yield. Treatment with other bases such as sodium hydride or sodium hydroxide under various reaction conditions gave only trace amounts of the desired compounds. From the mixture obtained above, each stereoisomer, **78** and **79** was isolated by thin layer chromatography respectively with a ratio of 3:2. ^1H- and ^{13}C-NMR spectra of the major component **78** were identical with those of the natural petiodial. The sign of optical rotations of the synthesized petiodial **78** ($[\alpha]_D^{25}$ + 32.9° (c=1.2, $CHCl_3$)) was opposite to that of the natural compound ($[\alpha]_D^{25}$ -28° (c=1.5, $CHCl_3$)), our synthetic petiodial **78** was therefore the antipode of natural one. Thus, the first synthesis of the enantiomer of natural petiodial was achieved efficiently, and the absolute stereochemistry of the stereogenic center at C_6 in natural petiodial was determined as *S* configuration.



a) DIBAL, CH_2Cl_2, -78 °C, ~99% b) BuLi, -78 °C, THF, then MsCl c) geranylsulfone, BuLi, THF, -78 °C, 30 min.; then **73**, 63% from **72** d) PPTS, EtOH, 25 °C, 20 h, 80% e) Li, $EtNH_2$, -78 °C, 79% f) Ac_2O, DMAP, Et_3N, rt, 95% g) $Bu_4NF{\cdot}3H_2O$, 0 °C, 8 min, 98% h) 0.5 eq. DBU, benzene, reflux, 2 h, 80% i) $LiAlH(t\text{-}BuO)_3$, THF, -78 °C, 71% j) Swern oxid., 80% k) $BaMnO_4$, >70%

Scheme 14

Next the absolute stereochemistry of another asymmetric center at C_7 of **78** was determined as follows. Reduction of the mixture of (+)-petiodial (**78**) and its diastereoisomer **79** obtained above with $LiAlH(t\text{-}BuO)_3$ (64) afforded the corresponding diols which were isolated respectively in a ratio of 3:2. The major alcohol **80** was reconverted into (+)-petiodial (**78**) by Swern oxidation. Each diastereoisomer of the diol **80** and **81** was subjected to oxidation with $BaMnO_4$ (65) to give the lactone **82** and its isomer **83**, respectively. The stereochemistry of **82** and **83** was elucidated respectively by comparing their ^{1}H-NMR spectra with those of neonepetalactone and iso-neonepetalactone (66). Thus the methylene protons in the lactone ring of **82**were observed at δ 4.35 and 4.24 ppm as a part of an ABX pattern (J_{AB}=11.5 Hz, J_{AX}=3.0 Hz, J_{BX}=2.0 Hz), while those of **83** were at δ 4.39 and 3.94 ppm, (J_{AB}=11.0 Hz, J_{AX}=4.0 Hz, J_{BX}=11.0 Hz). The above features of the ^{1}H-NMR spectra of both lactones **82** and **83** were in good agreement with those of the corresponding methylene protons of neonepetalactone (δ 4.34 and 4.19, dd, J_{AB}=11.0 Hz, J_{AX}=3.0 Hz, J_{BX}=3.0 Hz) and iso-neonepetalactone (δ 4.24 and 3.89, dd, J_{AB}=11.0 Hz, J_{AX}=5.0 Hz, J_{BX}=11.0 Hz), whose stereochemistry has been established. We could therefore assign the relative stereochemistry between C_6 and C_7 in (+)-petiodial **78** as (***6R***, ***7S***). The absolute structure of natural (-)-petiodial was then determined as (***6S***, ***7R***).

This syntheses also confirmed that the biogenetic precursor of petiodial is not an iridoid, but it could be a linear diterpene udoteal. The synthetic method employed here could be expanded to get various analogues involving different side chain. These compounds might show much better biological activities than those of petiodial. From this successful synthesis we can expand our research fields into more complicated diterpenes involving a cyclopentene ring system.

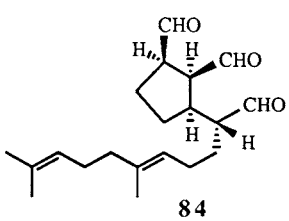
8.2 Udoteatrial Hydrate

The unique monocyclic diterpenoid trialdehyde udoteatrial (**84**) (60) isolated from marine algae *Udotea flabellum*, was reported to show antimicrobial activity against *Staphylococcus aureus* and *Candida albicans*. Since all three substituents on the cyclopentane ring are in cis relationship, udoteatrial is known to exist as a form of the mono-hydrate. Although the relative stereostructure of natural udoteatrial hydrate (**85**) was confirmed as (*2S**, *3R**, *6R**, *7R**) by synthesis of the racemic form (67), its absolute configuration has remained uncertain.

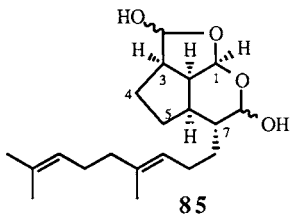
Since udoteotrial hydrate (**85**) could be considered to consist of the iridoid carbon framework and geranyl side chain, we decided to investigate the synthesis of **85** starting from genipin to demonstrate the usefulness of genipin as a chiral building block as well as to confirm the absolute configuration of **85**. In this section, the synthesis (68) of the optically active **85** and the absolute configuration of natural udoteatrial hydrate is described.

To introduce the geranyl side chain into the iridoid carbon framework, the tricyclic *exo*-methylene lactone **86** was designated to be the key intermediate. The problem upon

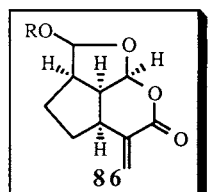
introduction of the geranyl side chain was the stereocontrol of the newly formed stereogenic center at C_7. Since it seemed, however, that the side chain in **85** occupied the thermodynamically stable α-configuration, it was considered that base catalyzed isomerization could control the stereochemistry at C_7 after introduction of the side chain into **86**. To support this assumption, semiempirical calculations (PM3) (69) of simplified analogues derived from **86** did show that the α-isomer were more stable than the β-isomer.



84



85

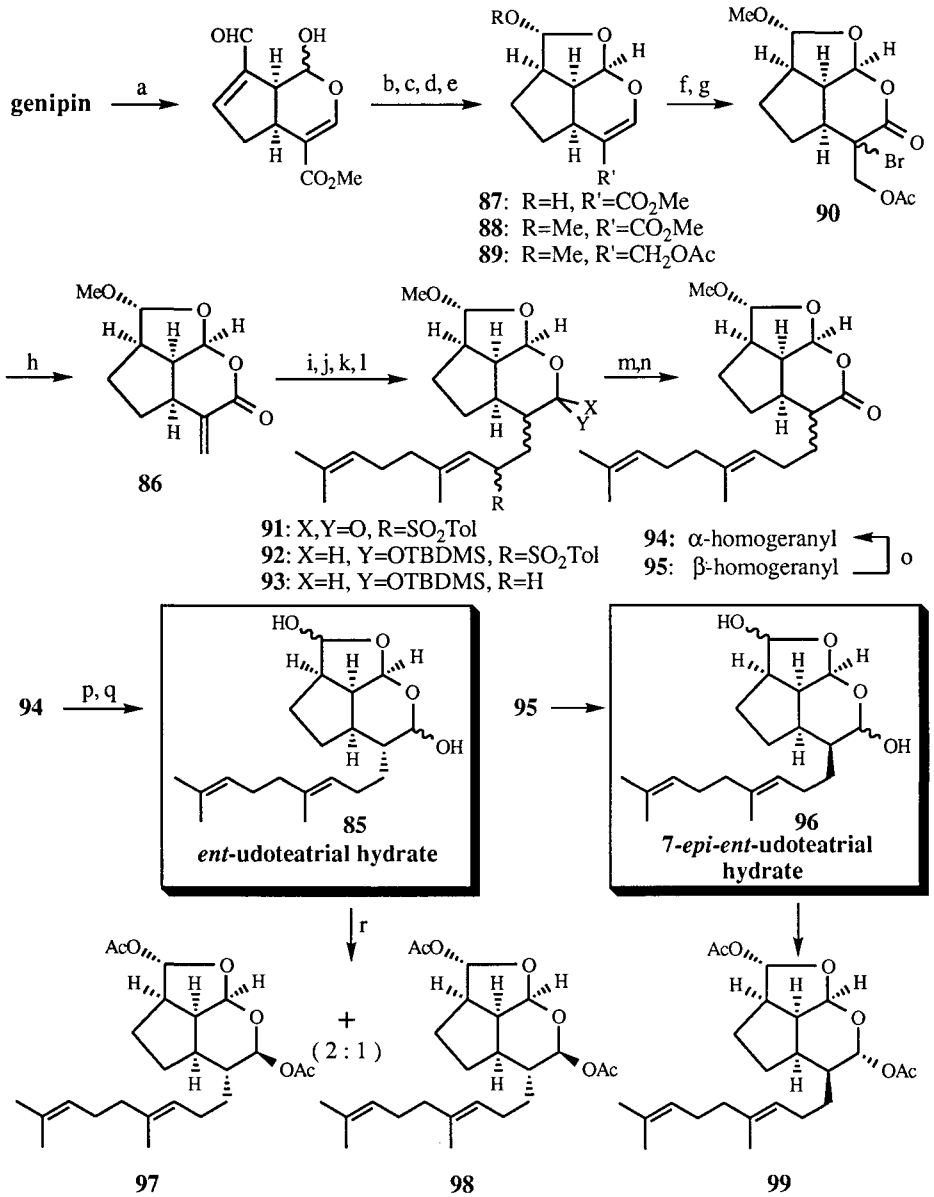


86

(Both **84** and **85** indicate tentative absolute structures of natural udoteatrial and udoteatrial hydrate)

Oxidation of genipin with barium manganate followed by hydrogenation with Rh/Al_2O_3 afforded stereoselectively the tricyclic hemiacetal **87**, which was then converted into the methylacetal **88**. Reduction of **88** followed by acetylation gave the acetate **89** in good yield. Bromohydrin formation with NBS-H_2O followed by Swern oxidation afforded the corresponding bromoacetate **90**, which was successively treated with zinc in acetic acid (70) to give the key intermediate **86**. With **86** in hand, the stereochemistry at C_7 was then considered carefully, and the stereochemistry at C_7 was confirmed by single crystal X-ray analysis of model compounds.

Thus, treatment of the lithium salt of geranyl sulfone with **86** afforded the 1,4-addition product **91**. Since the removal of the sulfone group from **91** was unsuccessful, the lactone carbonyl in **91** was temporarily reduced and protected with TBDMS to give the acetal **92**. Birch reduction (71) of the sulfone moiety in **92** afforded the compound **93**, which was deprotected and oxidized with PCC to afford homogeranyl lactone (**94** and **95**) as a mixture of diastereoisomers, of which the ratio was found to be 3:1 by ^{1}H-NMR spectroscopy. This mixture was separated by HPLC and the major isomer **94** could be isomerized into a 1:1 mixture of **94** and **95** under the influence of DBU in refluxing toluene. Reduction of the α-homogeranyl lactone **94** with DIBAL followed by acid hydrolysis of the resulting hemiacetal accomplished the synthesis of **85**. In order to determine the absolute configuration of natural udoteatrial hydrate, **85** was converted to the diacetate **97** and **98**, the spectral data of which were in good agreement with those reported previously. The signs of optical rotations of our synthetic diacetates, however, were opposite to those of natural diacetates which confirms the absolute configuration of natural udoteatrial hydrate as (***2R, 3S, 6S, 7S***) as shown in **Scheme 15**.

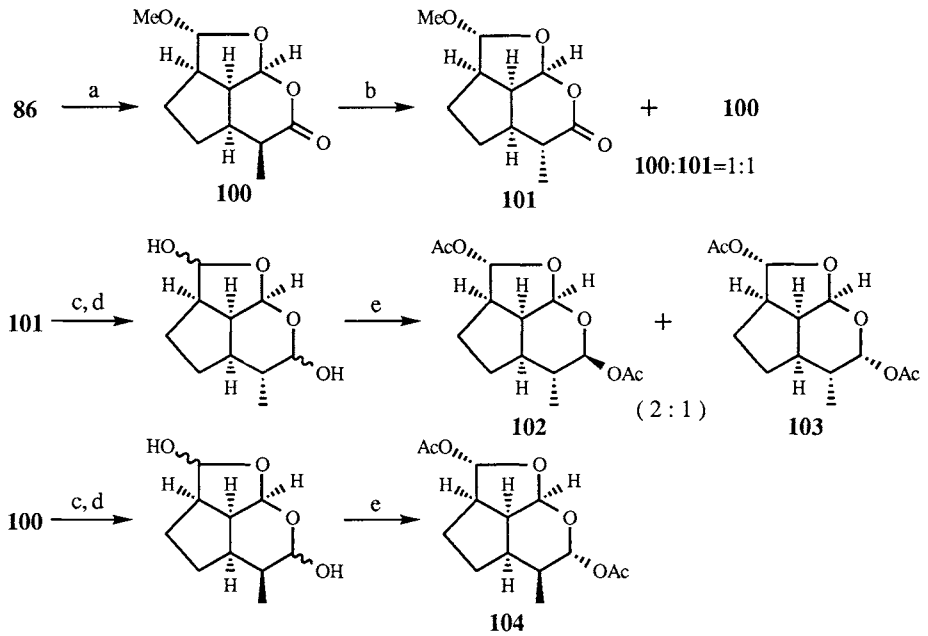


a) $BaMnO_4$, CH_2Cl_2, rt, 71% b) cat. Rh-Al_2O_3, H_2, AcOEt, rt, 56% c) BF_3•Et_2O, MeOH, 0 °C, 95% d) DIBAL, CH_2Cl_2, -78 °C, 90% e) Ac_2O, Et_3N, DMAP, rt, 94% f) NBS, H_2O, DMSO, rt g) Swern oxid. h) Zn, AcOH, ether, rt, 63% from **89** i) geranyl p-tolyl sulphone, LDA, THF, -78 °C, then **86**, 82% j) DIBAL, CH_2Cl_2, -78 °C, 93% k) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, -78 °C, 90% l) Li / $EtNH_2$, THF, -78 °C, 76% m) TBAF, THF, 0 °C, 90% n) PCC, CH_2Cl_2, rt, 80% o) DBU, toluene, reflux, 12 h, 70% p) DIBALH, CH_2Cl_2, -78 °C, 99% q) (0.1M) p-TsOH, THF:H_2O:acetone = 4:2:1, rt, 69% r) Ac_2O, Pry, rt, 66% for **97** and **98**, 52% for **96**

Scheme 15

Our synthesis, employing the tricyclic exomethylene lactone **86** as the key intermediate, was designed to obtain analogues involving a variety of side chains instead of geranyl group. Next, preliminary investigations of the structure and activity relationships of the synthetic analogues of *ent*-udoteatrial hydrate was examined. The homogeranyl lactone **95** was reduced with DIBAL followed by acid hydrolysis of the resulting hemiacetal to afford the *ent*-7-*epi*-udoteatrial hydrate (**96**). Acetylation of **96** was found to give the acetate **99** as the sole product.

To examine the effect of the side chain on the biological activities, we chose the compound bearing the methyl group as a simple side chain to compare with those involving the homogeranyl group. Thus, hydrogenation of **86** with Rh/Al_2O_3 stereoselectively afforded the β-methyl derivative **100** (**Scheme 16**). The α-methyl isomer **101** could be obtained by base catalyzed isomerization of **100**. Compounds **100** and **101** were converted into the diacetates **102**, **103** and **104**, respectively, by the same reaction sequence as that described for the preparation of **97**, **98** and **99** from **94** and **95**.



a) cat. PtO_2, H_2, AcOEt, overnight, 99% b) 3 eq. DBU, toluene, reflux, 48 h, 73% for **100** and **101** c) DIBAL, toluene, -78 °C, 1h d) (0.1M) p-TsOH, THF:H_2O:acetone = 4:2:1, rt e) Ac_2O, Pyr, rt, 50% for **102** and **103** from **101**, 75% for **104** from **100**

Scheme 16

Since the monohydrate form of the trialdehyde was not stable enough for biological tests, their diacetates were used instead. The biological properties of these analogues (**97**, **98**, **99**, **102**, **103** and **104**) were then examined. Although the natural udoteatrial hydrate was

reported to show antimicrobial activities against *Staphylococcus aureus* and *Candida albicans*, none of these analogues was active against various microogranisms. At this moment it was not clear whether protection of the two hemiacetal portions of **85** as acetate would decrease the activities of the natural product.

On the other hand, assay of *in vitro* cytotoxicity of these analogues afforded significant results. Thus, the compounds possessing the homogeranyl side chain (**97**, **98** and **99**) were found to be cytotoxic against KB human oral epidermoid carcinoma and human lung carcinoma A-549 as summarized in the **Table** (72). Compound **97** was the most toxic among the analogues examined at concentration of $4x10^{-1}$ μg/ml. The effect of side chain was apparent from the fact that the methyl derivatives were much less toxic relative to compounds **97**, **98** and **99** (73). Furthermore, **97** having the acetate in an axial orientation at C19 exhibited at least 4 fold enhanced cytotoxicity than those having equatorial acetates. From the stereoelectronic point of view, it was suggested that compounds with the better leaving ability of the acetoxy group showed stronger cytotoxicity, although the mechanism of the inhibition of cell growth of these compounds was not understood at all. This observation suggested that the generation of oxonium species by elimination of the acetoxy group might be relevant for the exhibition of cytotoxicity of these compounds. Such oxonium species may act as alkylating agents as is well known in the case of iminium species generated in the naphthyridinomycin/saframycin class of antitumor antibiotics.

Table: Cytotoxicity of analogues of *ent*-udoteatrial hydrate against human oral epidermoid carcinoma KB and human lung carcinoma A-549

compound No.	IC_{50} (μg/ml)	
	human KB cells	human A-549
97	0.4	0.5
98	1.6	1.9
99	3.4	3.9
102 and **103**	>25.0	>25.0
104	>25.0	>25.0

In conclusion, we have found that the analogues of *ent*-udoteatrial hydrate were cytotoxic against human carcinoma *in vitro*. For the exhibition of cytotoxicity the presence of the homogeranyl side chain as well as the stereochemistry of the acetoxy group at C19 seemed to be important factors. Our findings reported here may be valuable for the evaluation of new lead-compounds for cancer chemotherapy. The question we are facing is whether the diacetates of natural udoteatrial hydrate would show comparable cytotoxicity.

9 CONCLUSION

All iridoids and related natural products which are described in **Figure 4 and Figure 5** have two or three aldehydes or equivalent functionalities such as enol ether or hemiacetal groups. These functionalities may play a major role for the display of biological and pharmacological activities. We have synthesized the silyl ether of iridoid aglycones in those cases where the natural products are glucosides, because the real biological activity should be revealed by the aglycone having the aldehyde functionality, which is prepared by desilylation in nearly neutral conditions. The iridoid molecules are reminiscent of a large number of known biologically active dialdehydes such as polygodial, warburganal and manoalide.

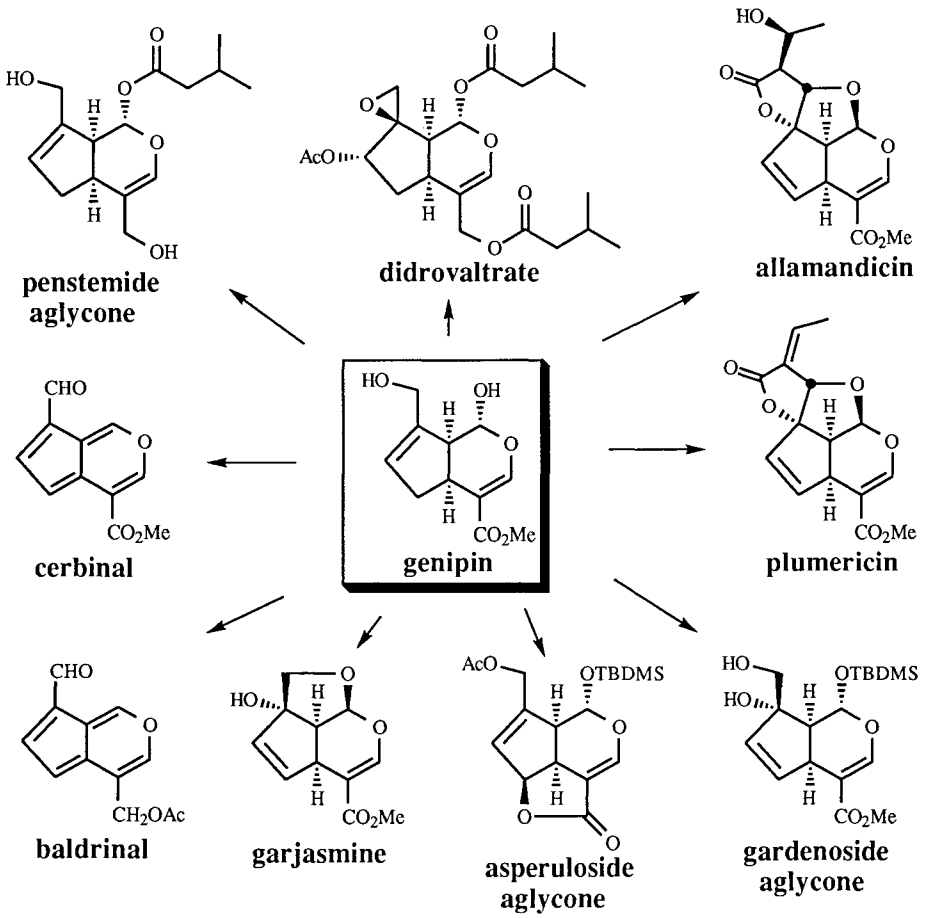


Figure. 4

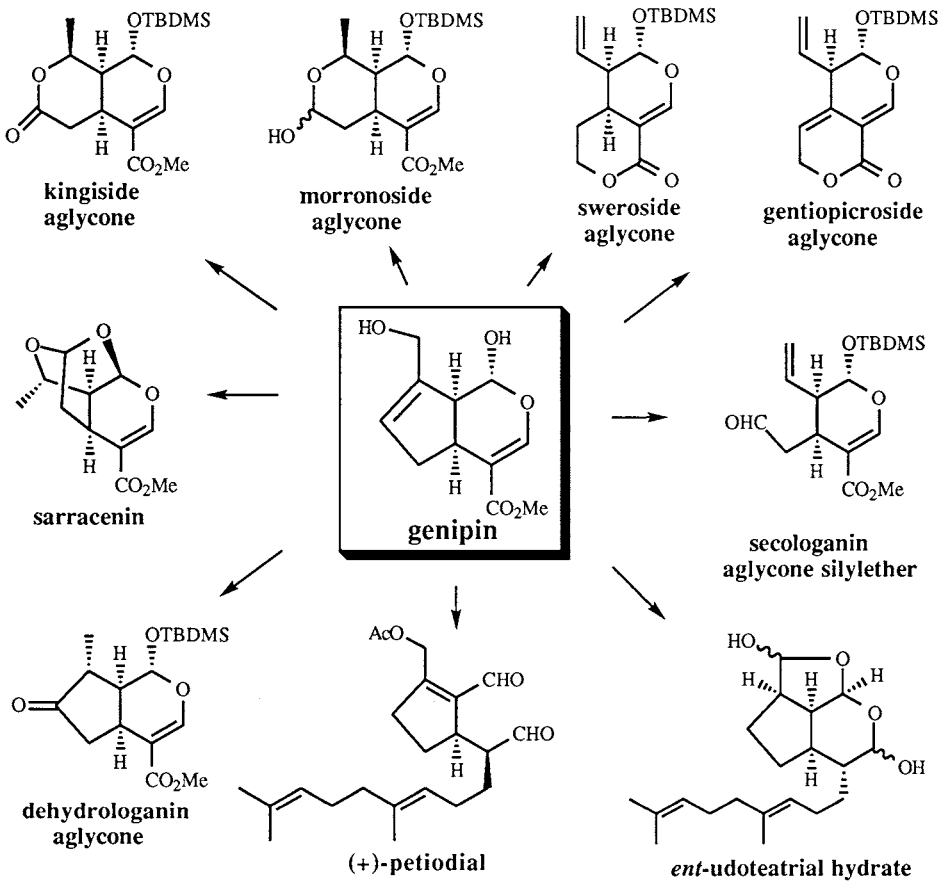


Figure. 5

10 ACKNOWLEDGEMENTS

I wish to thank my coworkers for their enthusiasm, dedication and skill in completing the research projects described here. I am particulary grateful to the late Professor T. Sakan, Osaka City University for leading my research interest into natural product chemistry and for his warmhearted encouragement.

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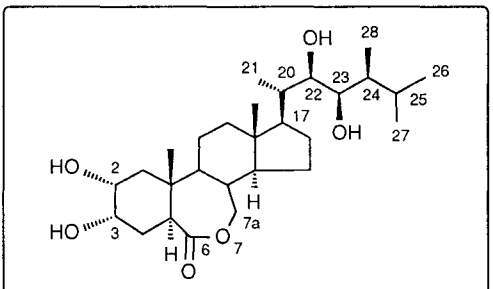
Atta-ur-Rahman (Ed.) *Studies in Natural Products Chemistry, Vol. 16*

Stereoselective Synthesis of Brassinosteroids

Thomas G. Back

1. INTRODUCTION

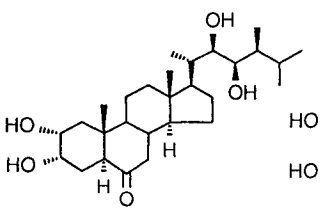
In 1979, Grove and Mandava and coworkers (1) at the U.S. Department of Agriculture reported the isolation of 4 mg of a novel plant growth promoter, which they named brassinolide, from 40 kg of *Brassica napus* pollen. The structure was determined by spectroscopic and X-ray methods to be that of 1, an unprecedented steroidal B-ring lactone. Brassinolide proved active at remarkably low concentrations, producing observable enhancement in the growth of some plant species even at the nanogram per plant level. Since then, field trials in several countries have demonstrated substantial improvements in the yields of crops as diverse as wheat, rye, corn, rice, tobacco, potatoes, peas, rapeseed, watermelon and cucumber with the applications of minute quantities of 1 or of related congeners. Moreover, brassinosteroids protect crop plants against stress from heat, cold, drought and salinity, and display antiecdysteroid activity that makes them potentially useful for insect pest control. At the same time, they are relatively harmless to other species. The low abundance of brassinolide in natural sources, its spectacular biological activity and its unusual structure have prompted considerable effort into the development of new synthetic approaches to it and related brassinosteroids. A recent monograph (2) and several reviews (3-13) have appeared on various aspects of the chemistry and biology of brassinosteroids.



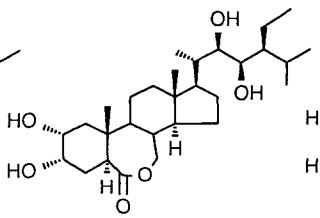
Brassinolide (1)

The structure of brassinolide poses several synthetic challenges, with attendant demand for stereochemical control. The steroid nucleus requires the introduction of the vicinal diol moiety from the α-side at C-2 and C-3, as well as the regio- and stereoselective construction of the B-ring lactone. However, the side chain at C-17, with a second vicinal diol at C-22 and

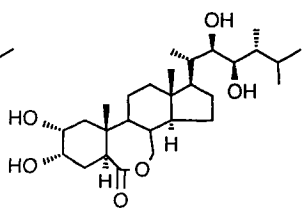
C-23, and four contiguous chiral centers at C-20, C-22, C-23 and C-24, poses the greatest obstacle to an efficient, stereoselective synthesis. A variety of ingenious solutions to these problems have appeared in recent years, although there is still a need for a concise, practical synthesis that could be performed on a commercial scale. The syntheses of castasterone (2), the B-ring ketone analogue that is frequently used as a precursor of 1, and of various epi-, homo- and norbrassinosteroids have also been reported. The latter compounds were required for structure-activity studies and in some cases also display substantial biological activity, although generally lower than that of 1 itself. The easier preparation of congeners such as 28-homobrassinolide (3) and 24-epibrassinolide (4) from stigmasterol (5) and ergosterol (6), respectively, compensates for their lower activity and consequently 3, and especially 4, have also been the subjects of field trials that have produced impressive results. However, brassinolide itself remains the main prize of synthetic endeavours and is considerably more difficult to prepare because the most readily available starting materials, such as 3 and 4, would require the difficult operation of degrading C-28 from the side chain, or inverting the configuration of C-24, respectively. Consequently, the brassinolide side chain is generally elaborated from truncated intermediates that must first be obtained from precursors like 5 or 6.



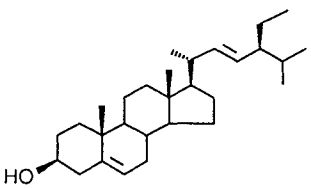
Castasterone (2)



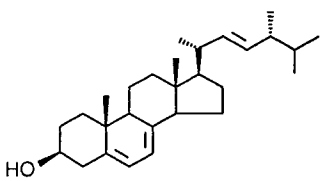
28-Homobrassinolide (3)



24-Epibrassinolide (4)



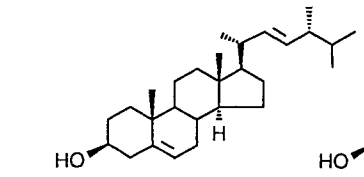
Stigmasterol (5)



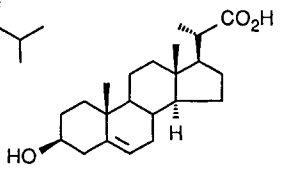
Ergosterol (6)

This review focuses on stereoselective methods for the construction of the appropriately functionalized steroid ring system and, especially, on the more difficult elaboration of the side chains of various brassinosteroids of current interest. In some cases the brassinolide or castasterone nucleus was constructed prior to the side chain, while in others, the side chain was installed first, followed by the necessary manipulation of the nucleus. Although readily available stigmasterol (5) and ergosterol (6) have served as the most popular starting materials, other steroids such as brassicasterol (7), dinorcholenic acid (8), pregnenolone (9) and its derivatives, hyodeoxycholic acid (10), crinosterol (dehydrocamposterol) (11) and

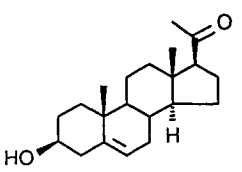
poriferasterol (12) have also been employed. The first syntheses of brassinolide were reported independently in 1980 by Fung and Siddall (14) and by Ikekawa and coworkers (15), while the first preparations of several brassinolide analogues were by Thompson and coworkers in 1979 (16), and by Mori in 1980 (17).



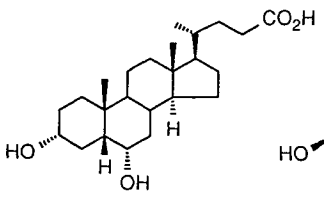
Brassicasterol (7)



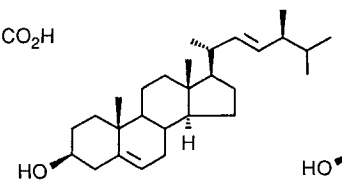
Dinorcholenic acid (8)



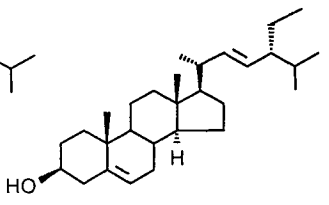
Pregnenolone (9)



Hyodeoxycholic acid (10)



Crinosterol (11)



Poriferasterol (12)

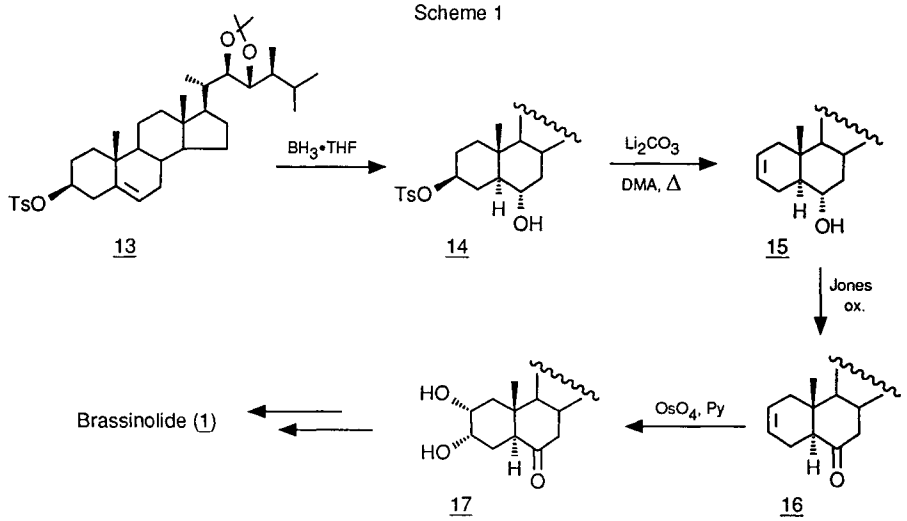
2. FUNCTIONALIZATION OF THE STEROID NUCLEUS

2.1 From 3β-hydroxy-Δ^5 Intermediates

The early syntheses of 1 by Fung and Siddall (14) and Ikekawa et al. (15,18) both employed key intermediates containing the 3β-hydroxy-Δ^5 nucleus and a fully elaborated, protected side chain, obtained from stigmasterol (5) and dinorcholenic acid (8), respectively. Since the cis-dihydroxylation of Δ^2-steroids with osmium tetroxide is known to occur with high stereoselectivity from the α-side (19,20), the problem is reduced to the conversion of available 3β-hydroxy-Δ^5-steroids to Δ^2-derivatives containing suitable oxygen functions at C-6. Thus, the former group subjected the tosylate 13 to regio- and stereoselective hydroboration to afford 14, followed by elimination to 15 and Jones oxidation of the 6α-hydroxyl group to produce the ketone 16 (Scheme 1). The conversion of 16 into the 2α,3α-diol 17 was then performed with OsO_4 and pyridine. The synthesis was completed by Baeyer-Villiger oxidation with trifluoroperoxyacetic acid (see Section 3.1). The Japanese group pursued a similar approach, except that the keto olefin 16 was produced from the mesylate analogue of 14 by oxidation with PCC, followed by elimination with LiBr-DMF. Osmylation was performed with catalytic OsO_4 and N-methylmorpholine-N-oxide (NMO) as the cooxidant. The general approach of hydroboration, oxidation, elimination and osmylation was also used subsequently for the preparation of other side chain analogues (21,22).

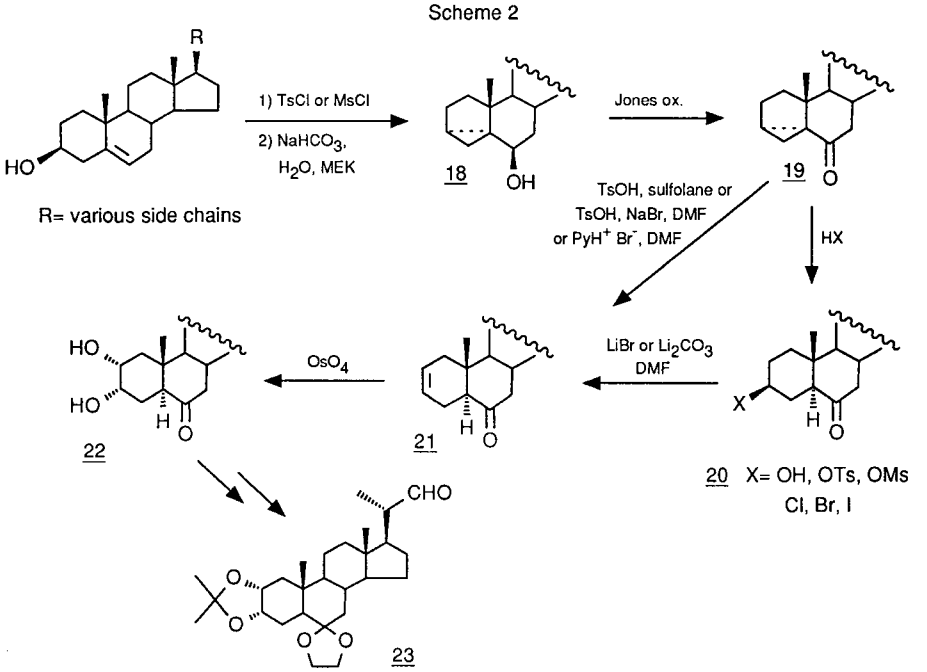
A related method developed by Mori and coworkers (17,23-25), and later employed by numerous other groups, introduces the required oxygen functions at C-2, C-3 and C-6 of

Scheme 1

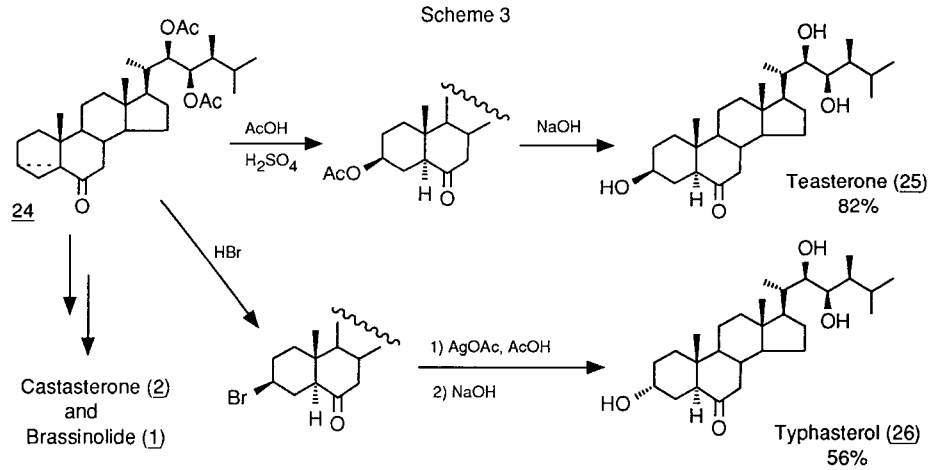


stigmasterol or other 3β-hydroxy-Δ^4-sterols, as shown in Scheme 2. The method is based on the facile formation of the cyclosterol 18 by the alkaline hydrolysis of the 3β-tosylate or mesylate of 5 (26,27), followed by Jones oxidation to give 19, isomerization to 21 with p-TsOH in sulfolane, and cis-dihydroxylation with OsO_4 to afford 22. Protection of the oxygen functions and cleavage of the stigmasterol side chain at C-22 by ozonolysis affords versatile, highly elaborated intermediates, such as 23 (23,28), that can be employed for the convenient installation of a desired side chain, as described in subsequent sections. The use of p-TsOH in sulfolane for the conversion of 19 into 21, however, produces minor amounts of the corresponding Δ^3- (29) and Δ^4-olefins (29,30) as byproducts. Osmylation of Δ^3-androstan-6-one produced a 56:44 mixture of the corresponding 3α,4α- and 3β,4β-diol, while the similar reaction of the Δ^4- analogue afforded the 4α,5α-diol as the only reported product (29). Alternative reagents for the elimination include p-TsOH and NaBr in DMF (31-33), or pyridinium hydrobromide in DMF (34). Moreover, cyclosterols 19 produce 3β-alcohols, tosylates or halides 20 when treated with H_2SO_4 (35-38), p-TsOH in benzene (30), HCl (30,39), HBr (3,40) or HI (40) respectively, usually in acetic acid. Elimination of HX from 20 (X= OTs, OMs or halide) with LiBr or Li_2CO_3 in DMF affords mainly the Δ^2-olefin, again accompanied by smaller amounts of its Δ^4-isomer (30), as well as the corresponding 3-formyl derivative when Li_2CO_3-DMF is used (41). These methods have also been applied to the functionalization of the steroid nuclei of androstanes (25,29,40), cholesterol (25), crinosterol (11) (35), poriferasterol (12) (37) and of numerous side-chain derivatives of stigmasterol. Although the latter remains the most widely utilized starting material for the method of Scheme 2, brassicasterol (7) has also been recommended recently because of its ready availability from canola oil (42) and its easy transformation into corresponding cyclosterols (42,43). Furthermore, the cyclosterol 24 was converted into teasterone (25) and typhasterol (26) (33), as shown in Scheme 3, as well as into castasterone (2) and brassinolide (1).

Scheme 2



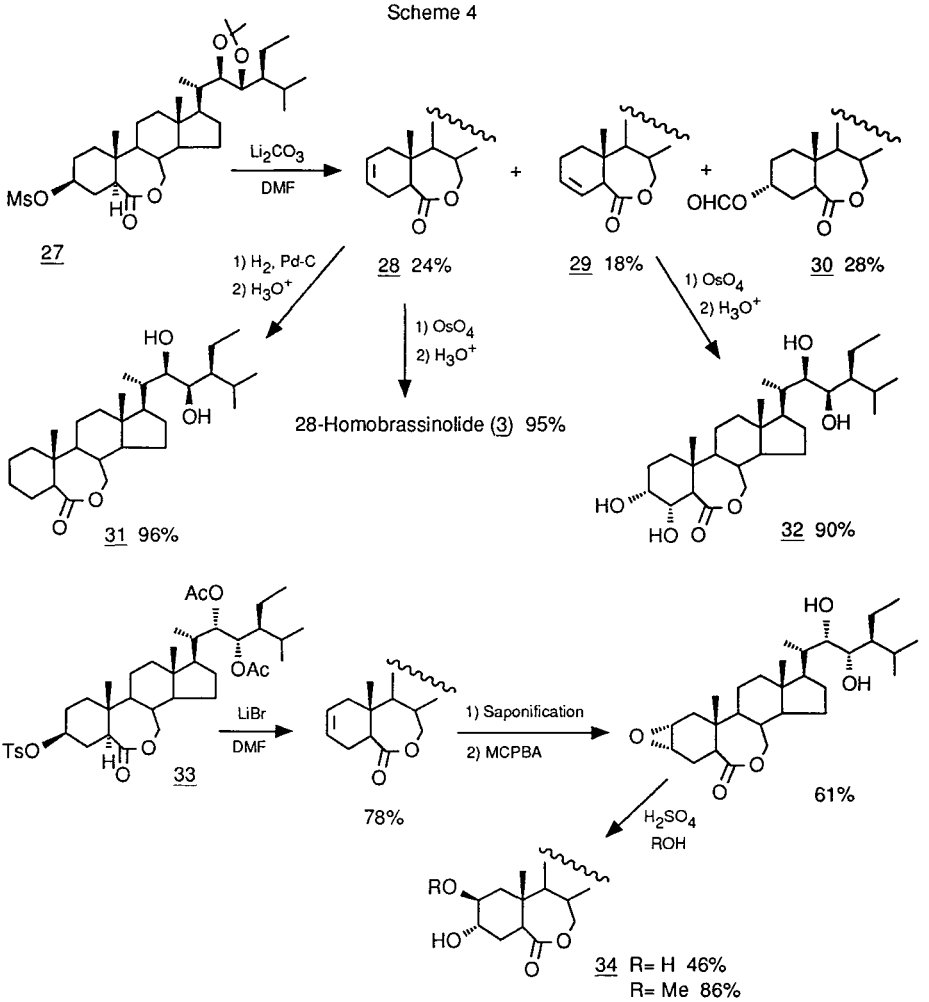
Scheme 3



Elimination of a 3β-leaving group can also be effected after lactonization, as in the examples shown in Scheme 4. Thus, mesylate 27 afforded a mixture of the Δ^2- and Δ^3-olefins 28 and 29 and the 3α-formyl derivative 30 (41). Olefin 28 was hydrogenated to the 2,3-dideoxy-28-homobrassinolide derivative 31, while cis-hydroxylation followed by removal of

the acetonide, afforded 28-homobrassinolide (3). Similarly, osmylation of 29 produced the 3α,4α-diol 32 (41), while elimination of 33, followed by epoxidation and acid-catalyzed epoxide-opening in either water or methanol, gave the 3β-epimers 34 (44).

Scheme 4

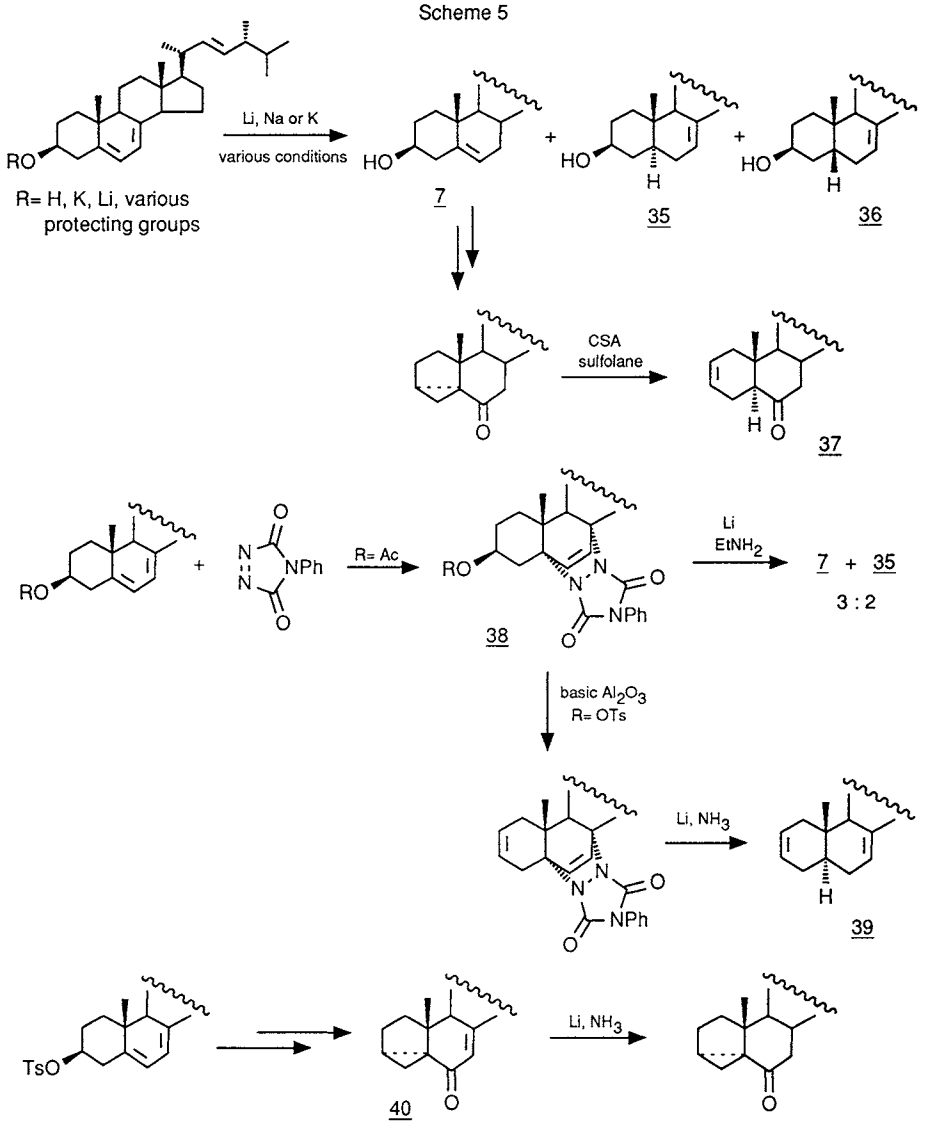


2.2 From Ergosterol

Ergosterol (6) can be employed similarly to stigmasterol (5) for the preparation of brassinosteroids with appropriately functionalized A- and B-rings, providing that reduction of the Δ^7 double bond is included at some stage of the synthesis, as shown in Scheme 5. The direct reduction of ergosterol and its 3-derivatives with alkali metals was investigated by Barton et al. (45) and afforded varying mixtures of brassicasterol 7, the Δ^7-isomer 35 and traces of its

5β-epimer 36, depending on the conditions. The further conversion of 7 into the corresponding cyclosterol and elimination to the Δ^2-6-one 37 was accomplished with camphorsulfonic acid in hot sulfolane. A similar procedure employing lithium in ethylamine was utilized by Fiecchi and coworkers (46) to afford 7 and 35 in the ratio of 3:2, either from the direct reduction of ergosterol or from that of the 1,2,4-triazoline-3,5-dione cycloadduct 38. Elimination of the 3β-tosylate of 38 with basic alumina prior to reduction also provided the triene 39 (47).

Scheme 5

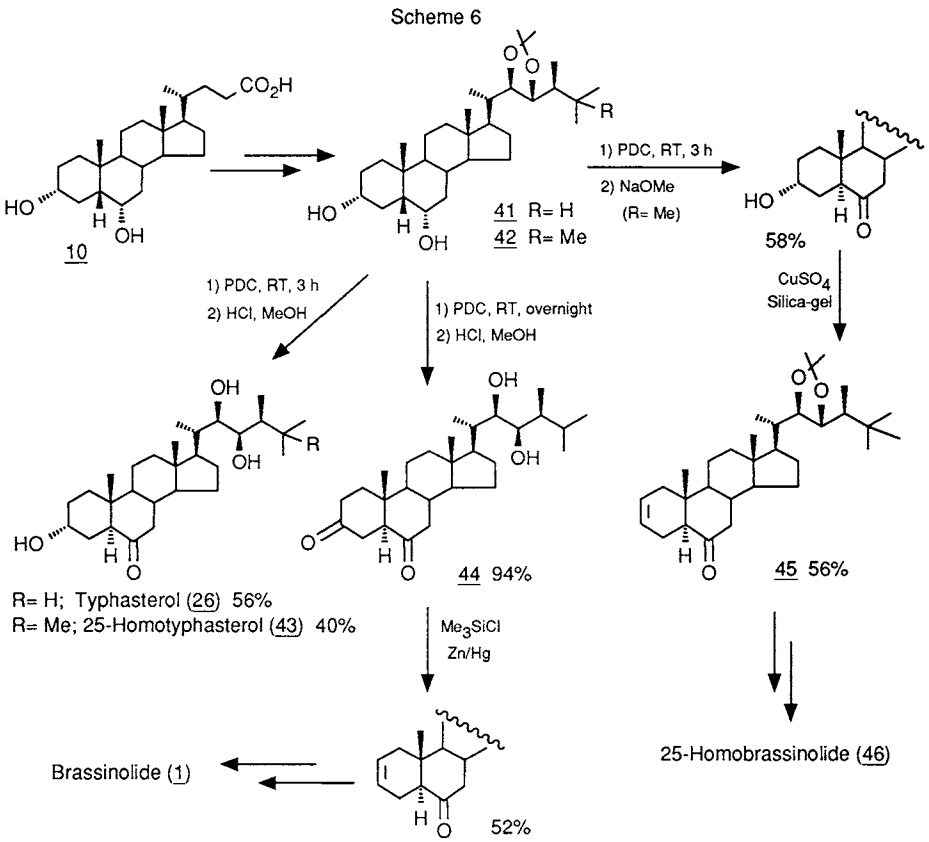


Alternatively, Thompson and coworkers (16), and later Zhou et al. (48), formed the cyclosterol first, followed by oxidation to the enone 40 and reduction of the latter with lithium in ammonia. Further transformations were carried out as in Scheme 2 (16) and Scheme 9 (*vide infra*) (48).

2.3 From Hyodeoxycholic Acid

Hyodeoxycholic acid (10) has been used as the starting material for brassinosteroid synthesis by Zhou and coworkers. The hydroxyl functions of the steroid nucleus are conveniently located at C-3 and C-6, and the 5β-hydrogen is easily equilibrated to the more stable 5α-configuration after oxidation at C-6 to the corresponding ketone (49-53).

Scheme 6



Scheme 6 shows that, after elaboration of an appropriately protected side chain, selective oxidation of the 6α-hydroxyl group of 41 or 42 with PDC afforded the corresponding 3α-hydroxy-6-one derivatives, which epimerized to their 5α-epimers under the conditions of the reaction. Removal of the acetonide protecting group from the side chain then produced typhasterol (26) (52) or its 25-homo derivative 43 (53). On the other hand, more prolonged

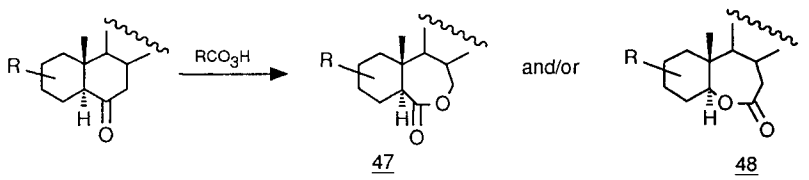
oxidation of the diol afforded the 3,6-dione 44, which underwent selective zinc amalgam-mediated conversion of the 3-keto group to the corresponding Δ^2-olefin (52). The latter was in turn converted into brassinolide (1) by the usual procedure of osmylation and Baeyer-Villiger oxidation. Selective oxidation of 42 at C-6, epimerization of C-5 under basic conditions, and elimination of the 3α-hydroxyl group with $CuSO_4$ on silica-gel gave the Δ^2-6-ketone 45, thereby providing access to 25-homobrassinolide (46) (53). This general approach was also used in the preparation of a variety of other brassinosteroids from 10 (53-57).

3. FORMATION OF THE B-RING LACTONE

3.1 Baeyer-Villiger Oxidation of 6-Ketones

The Baeyer-Villiger reaction generally results in the migration of the more substituted carbon atom with retention of configuration. This leads to the expectation that the oxidation of a 5α-6-keto-steroid would result in the stereo- and regioselective formation of the corresponding 5α-6-oxa-7-oxo isomer 48. Fortunately, the presence of certain types of substituents at the 3β-position diverts the reaction from its expected course and affords the corresponding 7-oxa-6-oxo regioisomer 47 preferentially (58), as required in the B-ring of brassinolide (Scheme 7). A more detailed study by Ikekawa and coworkers (59) demonstrated that electron-withdrawing substituents at the C-1, C-2 and C-3 positions have a marked effect upon the 6-oxa:7-oxa ratio, and can lead to the preferential formation of the desired 7-oxa isomer 47. This has been attributed to the inductive effects of such substituents upon the transition state of the migration (59), as well as upon stereoelectronic factors (60). Since the effects of the substituents are cumulative, the 2α,3α-oxygenated precursors typically used in brassinolide synthesis produce high selectivity in favour of the desired lactone regioisomer.

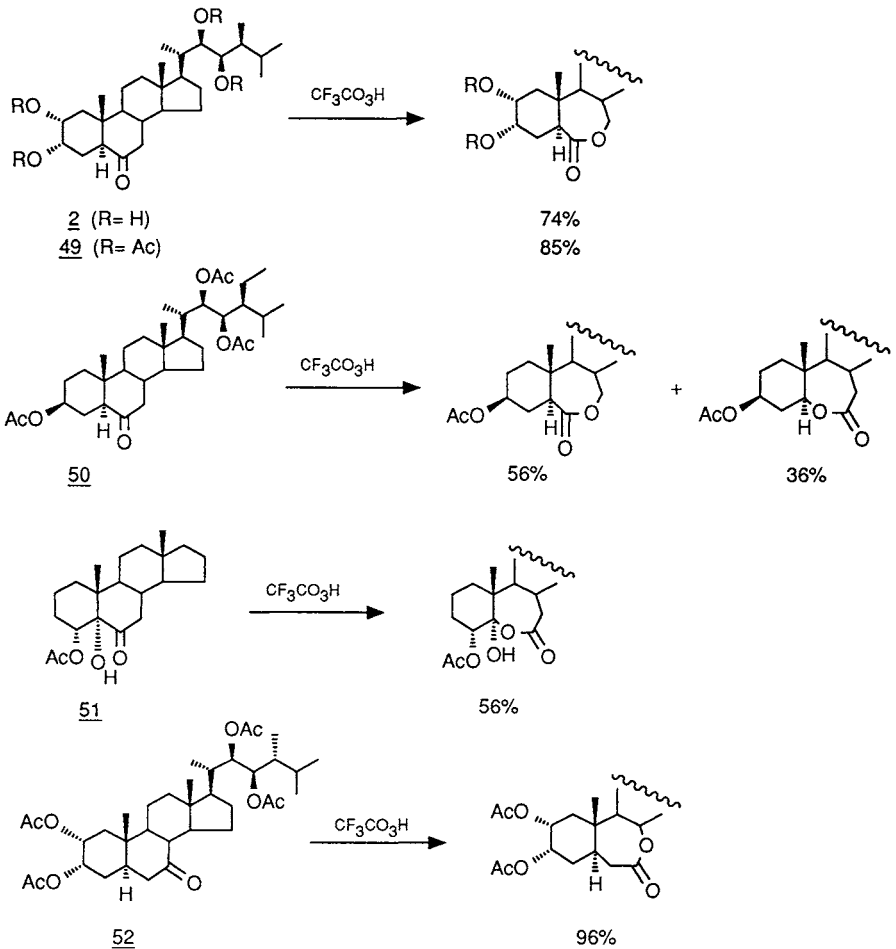
Scheme 7



47 48

Trifluoroperoxyacetic acid was employed in both of the first syntheses of brassinolide (14,15,18) and has remained the reagent of choice in most subsequent work, often in the presence of Na_2HPO_4. Brassinolide (1) was thereby produced in 74% yield from the 22,23-acetonide of castasterone (2), which underwent deprotection under the conditions of the Baeyer-Villiger reaction (14). An even higher yield of 85% of the 7-oxa isomer was reported from castasterone tetraacetate (49) (18), while the 3β-acetate (50) produced 56% and 36% of the

Scheme 8

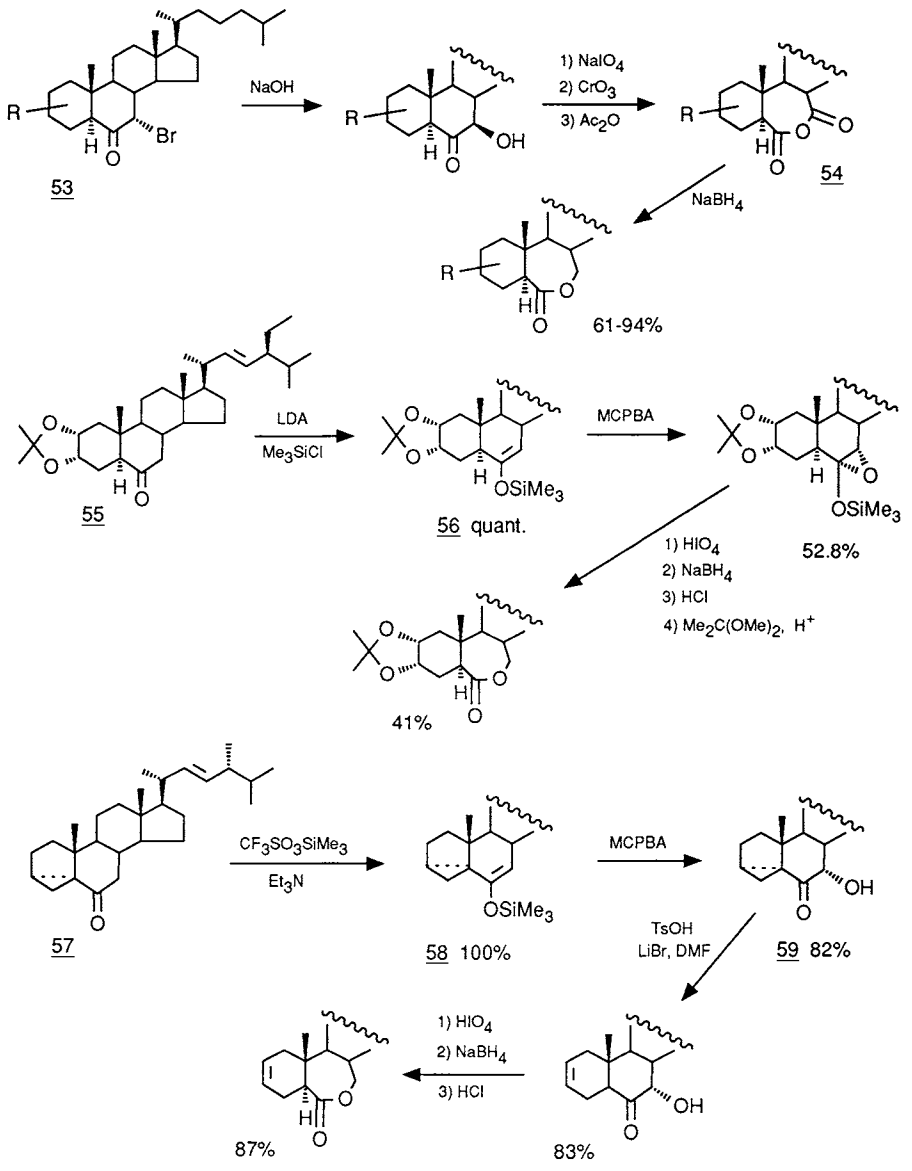


7-oxa and 6-oxa isomers, respectively (41). On the other hand, the 4α-acetoxy-5α-hydroxyketone 51 afforded chiefly the corresponding 6-oxa product (29), and the 7-ketone 52 gave the 7a-oxa-7-oxo lactone (47). These examples are shown in Scheme 8. M-Chloroperoxybenzoic acid (16,44,61-63) has occasionally been used instead of trifluoroperoxyacetic acid, but is less convenient because of its much slower reaction rate, while peroxyseleninic acids were reported (64) to give unfavourable regioisomer distributions. In contrast to the Baeyer-Villiger oxidation, the Beckmann rearrangements of oximes of variously substituted 6-keto steroids produce mainly the 6-aza regioisomer, regardless of A-ring substituents (24,65-67). The 7-aza lactam analogue of the lactone moiety of brassinosteroids has, however, been prepared in the 22,23-diepi-28-homo series by a more circuitous route (66).

3.2 Cleavage of 7-Hydroxy-6-ketones

An alternative approach to the B-ring lactone of brassinolide is via the periodate cleavage of a six-membered 7-hydroxy-6-ketone, followed by reduction and lactonization. The required 7-hydroxy-6-ketones can be prepared by bromination of the corresponding 6-ketones, e.g. as in 53, followed by substitution with hydroxide ion to furnish the 7β-hydroxy derivatives (Scheme 9).

Scheme 9



Periodate cleavage of the C-6,7 bond, further oxidation with CrO_3, and dehydration then produced the anhydrides 54. Regioselective reduction of the latter at C-7a with sodium borohydride then afforded the desired lactones (68).

Epoxidation of the enol silyl ether 56, in turn formed by silylation of the kinetic enolate of the 6-ketone precursor 55, produced an epoxy silane that was similarly cleaved. The resulting C-7 aldehyde was reduced with sodium borohydride, and lactonization occurred upon acidification of the corresponding seco-hydroxy acid (69,70). The enol silyl ether 58, obtained from the corresponding 6-keto cyclosterol 57, afforded the 7α-hydroxy ketone 59 by similar peracid oxidation. Isomerization of the cyclosterol to the Δ^2-olefin, followed by the usual sequence of steps, then produced the corresponding lactone (48). Several other examples of the conversion of 7-hydroxy-6-ketones to lactones by this approach have been reported (71), and the formation of these intermediates from enol silyl ethers can also be achieved with osmium tetroxide, with concomitant cis-hydroxylation of Δ^2- and Δ^{22}-olefins (66).

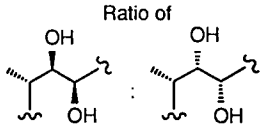
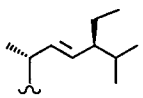
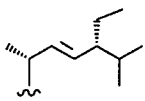
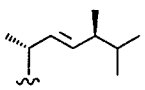
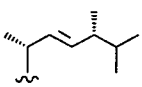
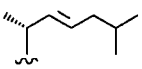
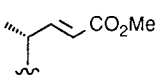
4. STEREOSELECTIVE SYNTHESIS OF THE SIDE CHAIN

4.1 Oxidation of Existing Side Chains

The stereoselective cis-dihydroxylation of the Δ^{22} double bond of stigmasterol (5), ergosterol (6) or brassicasterol (7) with osmium tetroxide provides a potential direct route to the fully elaborated side chains of 28-homobrassinolide (3) and 24-epibrassinolide (4). Similarly, the less readily available crinosterol (11) would generate the brassinolide (1) side chain. The results of these and related cis-dihydroxylation reactions are shown in Table 1. In some cases the Δ^2-double bond, which reacts more rapidly than the side chain olefin, was cis-dihydroxylated in the same step. The osmylation may be effected with a stoichiometric amount of osmium tetroxide, although it is generally more expedient to employ it catalytically in the presence of a cooxidant such as N-methylmorpholine N-oxide or potassium ferricyanide. The inclusion of pyridine is also advantageous as it accelerates the oxidation. Table 1 indicates that the side chains of both stigmasterol (5) (entry 1) and its 24-epi derivative, poriferasterol (12) (entry 2), afford predominantly the unwanted 22,23-diepi stereoisomers with the (22S,23S) configuration in the absence of chiral ligands. Crinosterol (11) also produces chiefly the (22S,23S)-diol (entry 3), as does the 24-nor side chain in entry 5. Only the ergostane side chain in entry 4 provides reasonably good yields of the required (22R,23R)-diol, formed in approximately equal amounts with the (22S,23S)-diepi isomer. This approach therefore provides a relatively convenient route to 24-epibrassinolide (4), but not to products having the brassinolide configuration at all three centers C-22,23,24. An attempt to rationalize these results by conformational analysis of the side chains and by a consideration of destabilizing steric interactions in the postulated organoosmium intermediates has been made (72). Very recently, application of the Sharpless asymmetric dihydroxylation reaction (73) to brassinosteroid side chain synthesis has proved effective in controlling the relative amounts of the two vicinal diol stereoisomers. Thus, the inclusion of dihydroquinidine 9-phenanthryl ether (DHQD-PHN) or dihydroquinidine p-chlorobenzoate (DHQD-CLB) as chiral ligands affords the desired

(22R,23R)-isomers as the principal products, whereas dihydroquinine p-chlorobenzoate (DHQ-CLB) favours the formation of the (22S,23S)-diepi derivatives.

Table 1. Cis-dihydroxylation of Brassinosteroid Side Chains With OsO_4

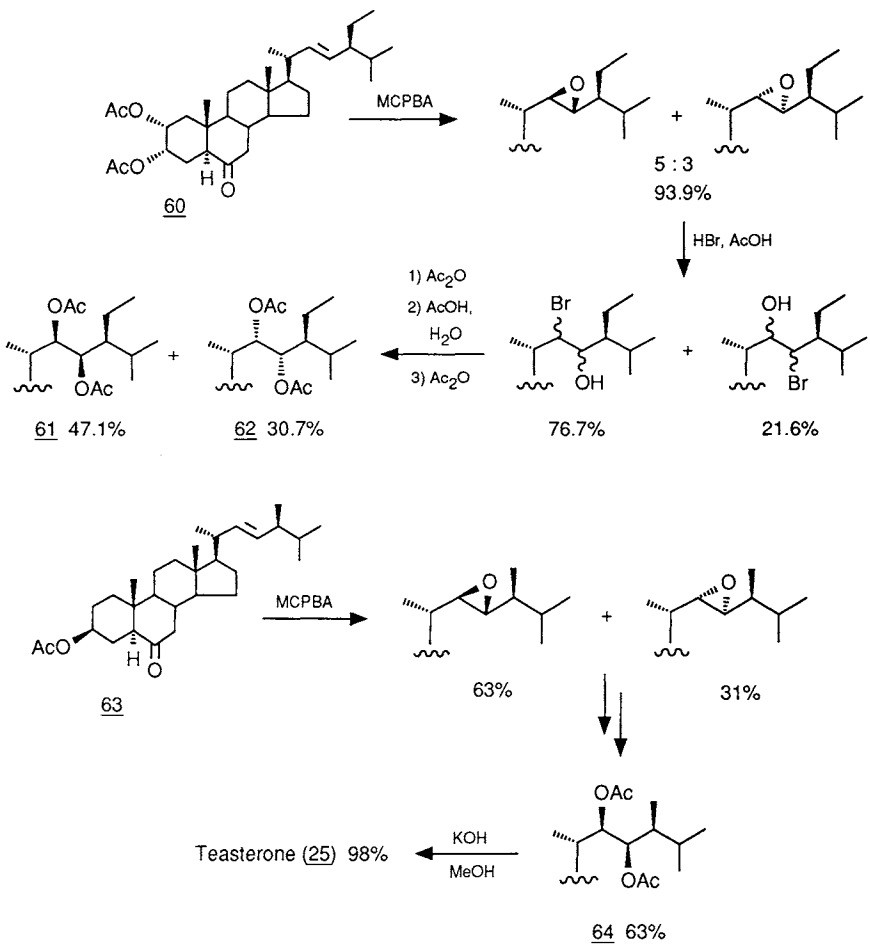
Entry	Side Chain[a]	Chiral Ligand	Ratio of  (22R,23R) : (22S,23S)	References
1		—	4 : 96	38
		—	6 : 94	44
		—	12 : 85	74
		—	minor : major	23,65,66,72
		—	1 : 24	75
		DHQD-PHN	up to 2.6 : 1	75
		DHQD-CLB	up to 1.5 : 1	76
2		—	1 : 2	37
3		—	<20 : >80	77
		—	20 : 130	39
		DHQD-CLB	8 : 1	76
		DHQ-CLB	only (22S,23S) reported	76
4		—	1 : 1	16,77
		—	78 : 75	46
		—	30 : 50	43
		—	3 : 4	48
		—	48 : 50	47
		DHQD-CLB	8 : 1	76
		DHQ-CLB	1 : 9	76
5[b]		—	2 : 5	22,78
		—	only (22S,23S) reported	24
6		—	1 : 8	79
		DHQD-CLB	4 : 1	79.80

a) Various steroid nuclei were used

b) The (Z)-isomer gave a 7:1 ratio of the (22R,23S) and (22S,23R)-isomers (ref. 22,78)

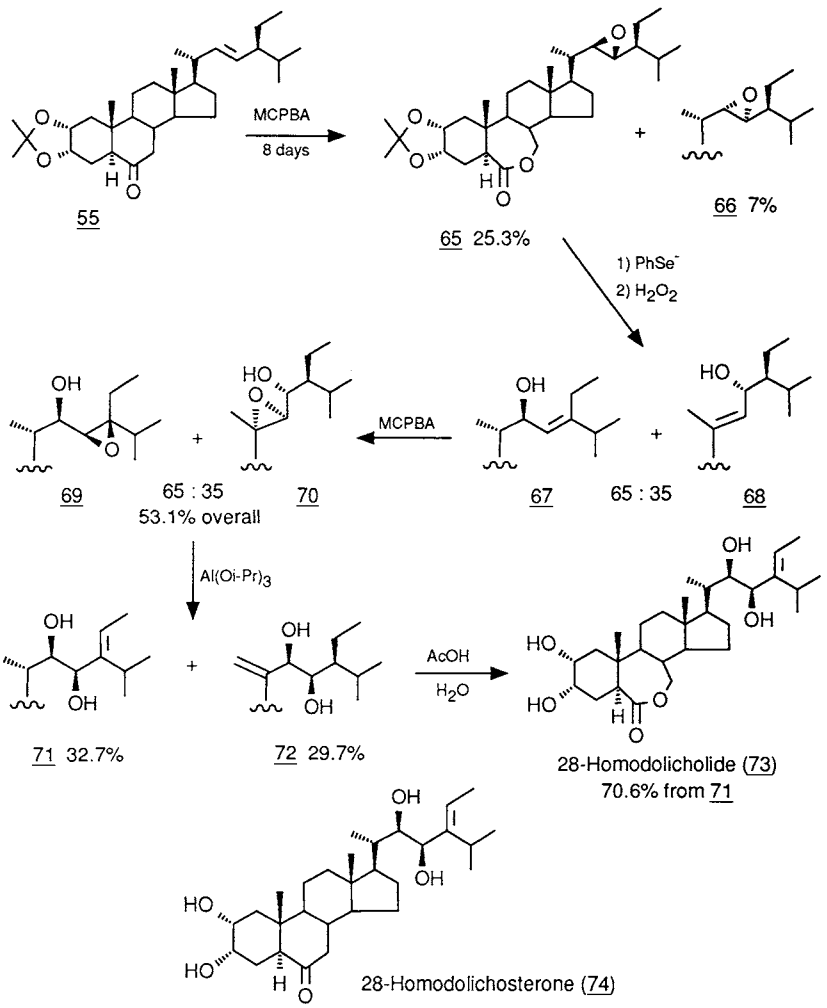
Mori (72) and Ikekawa (38,41) and their coworkers reported the epoxidation of the stigmasterol side chain en route to homobrassinolide (Scheme 10). The 5:3 mixture (38) of epoxide stereoisomers produced from 60 was converted into a mixture of regio- and stereoisomeric bromohydrins, which in turn afforded the tetraacetates 61 and 62 in reasonably good yields (72) upon acetylation, solvolysis of the bromide and further acetylation. Similarly, olefin 63, obtained from crinosterol (11), afforded the triacetate 64 when subjected to a similar sequence (35). Saponification of the latter produced teasterone (25) quantitatively. A more highly elaborated intermediate containing a synthetically derived crinosterol side chain was converted into brassinolide (1) by this approach (23), and a deuterated side chain was similarly elaborated into teasterone-d_6 and other labelled steroids (36).

Scheme 10



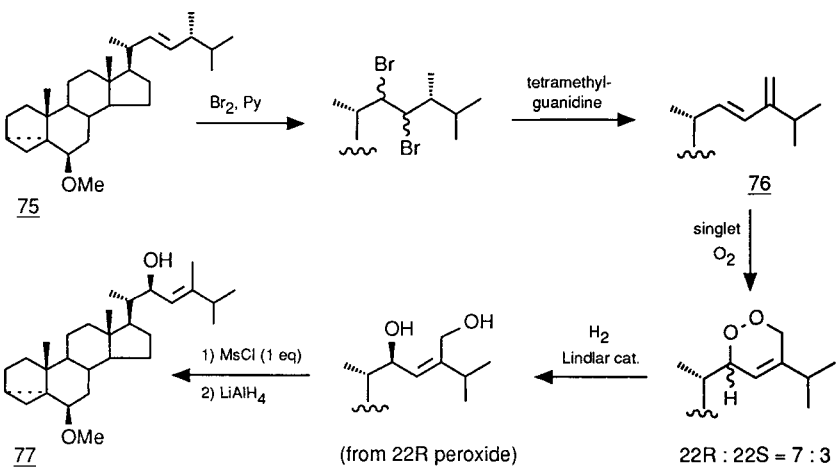
Peracid oxidation of the stigmasterol derivative 55 resulted in simultaneous epoxidation of the side chain and Baeyer-Villiger reaction as shown in Sceme 11 (62,63). The major epoxide 65 underwent a slow attack at either C-23 or C-22 with benzeneselenolate anion, with inversion of configuration. Oxidation of the mixture of corresponding hydroxy selenide regioisomers, followed by selenoxide syn-elimination, produced the allylic alcohols 67 and 68, respectively. Further epoxidation of the latter mixture and $Al(Oi\text{-}Pr)_3$ -mediated elimination afforded 71 from 69, and 72 from 70. Deprotection of 71 then produced 28-homodolicholide (73). The similar preparation of 28-homodolichosterone (74) (63) and its 6-deoxy derivative (81) was also reported.

Scheme 11



Fiecchi and coworkers (82) prepared the diene 76 by the addition of bromine to the ergosterol-type side chain of cyclosterol 75, followed by double dehydrobromination. The diene 76 was then further functionalized by cycloaddition with singlet oxygen, and the transformations shown in Scheme 12 (82). This comprises a formal synthesis of brassinolide (1) since the product allylic alcohol 77 was also a key intermediate in Fung and Siddall's original synthesis (14) of 1 (see Section 4.2.1). Other electrophilic additions, including those of peracids, halogens, PhSeCl and diborane to (E)- and (Z)-Δ^{22}-olefins lacking a 24-alkyl substituent were studied by Ikekawa et al. (78). They too occur stereoselectively and are potentially useful in the synthesis of the corresponding norbrassinosteroids.

Scheme 12

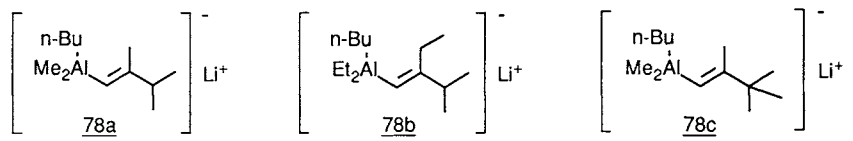


4.2 Additions to C-22 Aldehydes

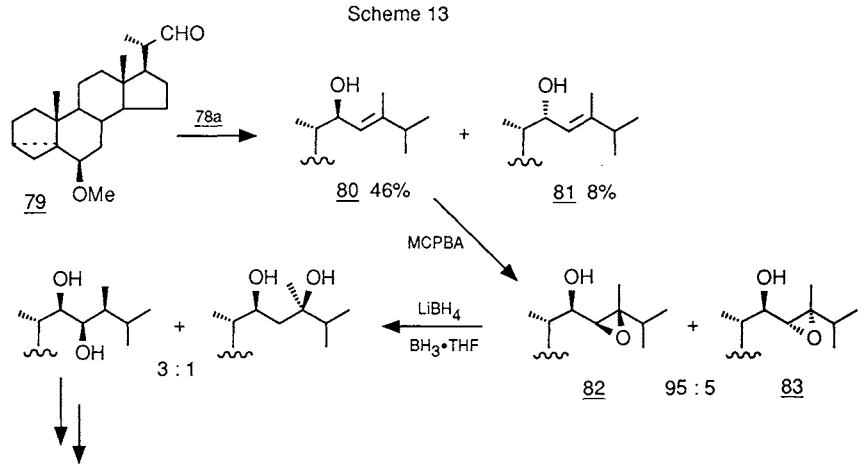
Ozonolyses of the side chains of suitably protected stigmasterol or ergosterol derivatives provide convenient access to C-22 aldehydes, which can then be employed for the elaboration of brassinosteroid side chains. The aldehydes undergo additions of various nucleophiles to give predominantly the corresponding Cram products, possessing the brassinolide configuration at C-22. This chiral center may then be used in various strategies for the diastereoselective creation of new stereocenters at C-23 and C-24. Consequently, such aldehydes are popular key intermediates in brassinosteroid synthesis. Extension of the side chain from a C-22 aldehyde has been reported with the following types of nucleophiles.

4.2.1 Alanates: Alanates 78a-c were prepared by the addition of trimethyl- or triethylaluminum to 3-methylbutyne in the presence of Cp_2ZrCl_2, or by that of the former reagent to 3,3-dimethylbutyne under similar conditions, respectively, followed in each case by treatment with n-butyllithium. Fung and Siddall's original synthesis (14) (Scheme 13) employed the addition of the alanate 78a to aldehyde 79 to afford an 85:15 mixture of the Cram and

anti-Cram allylic alcohol products 80 and 81, respectively. This was followed by a highly stereoselective hydroxyl-directed epoxidation of 80 with MCPBA, and predominantly anti-Markovnikov hydride reduction of epoxide 82 at C-24 with inversion of configuration. After appropriate functionalization of the steroid nucleus (see Scheme 1), brassinolide was obtained.

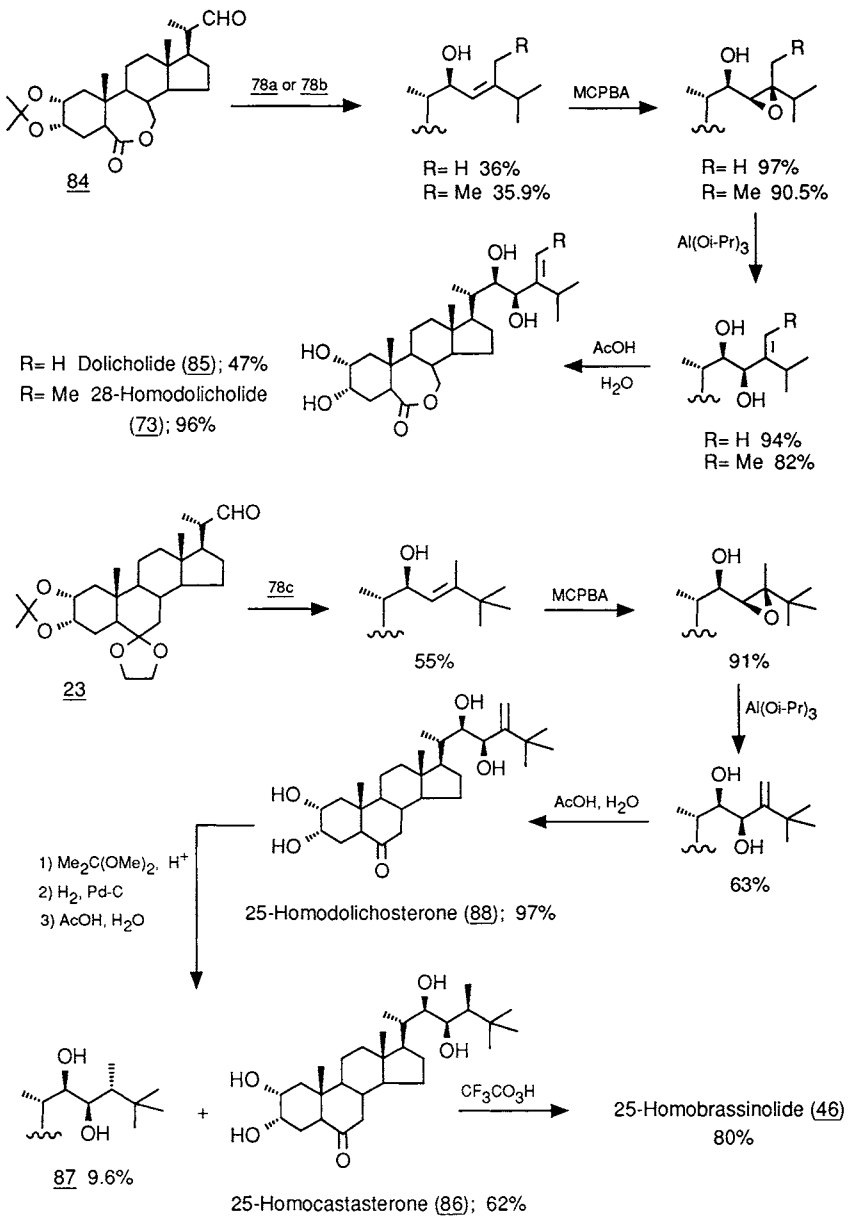


Scheme 13



A more highly elaborated aldehyde 84 was treated similarly with 78a, or its homologue 78b, by Mori and coworkers (69,83) (Scheme 14). Epoxide opening was effected by elimination with $Al(OiPr)_3$ to afford dolicholide (85) and 28-homodolicholide (73) after deprotection. The addition of alanate 78c to aldehyde 23 (Scheme 14) produced 25-homodolichosterone (88) after deprotection, and stereoselctive hydrogenation of the $\Delta^{24(28)}$ double bond of the corresponding acetonide gave 25-homocastasterone (86) and a smaller amount of the (24R)-epimer 87 (84). Ketone 86 was converted into 25-homobrassinolide (46), a synthetic brassinosteroid that is reported to display even more potent activity than brassinolide itself (84), by the usual Baeyer Villiger reaction.

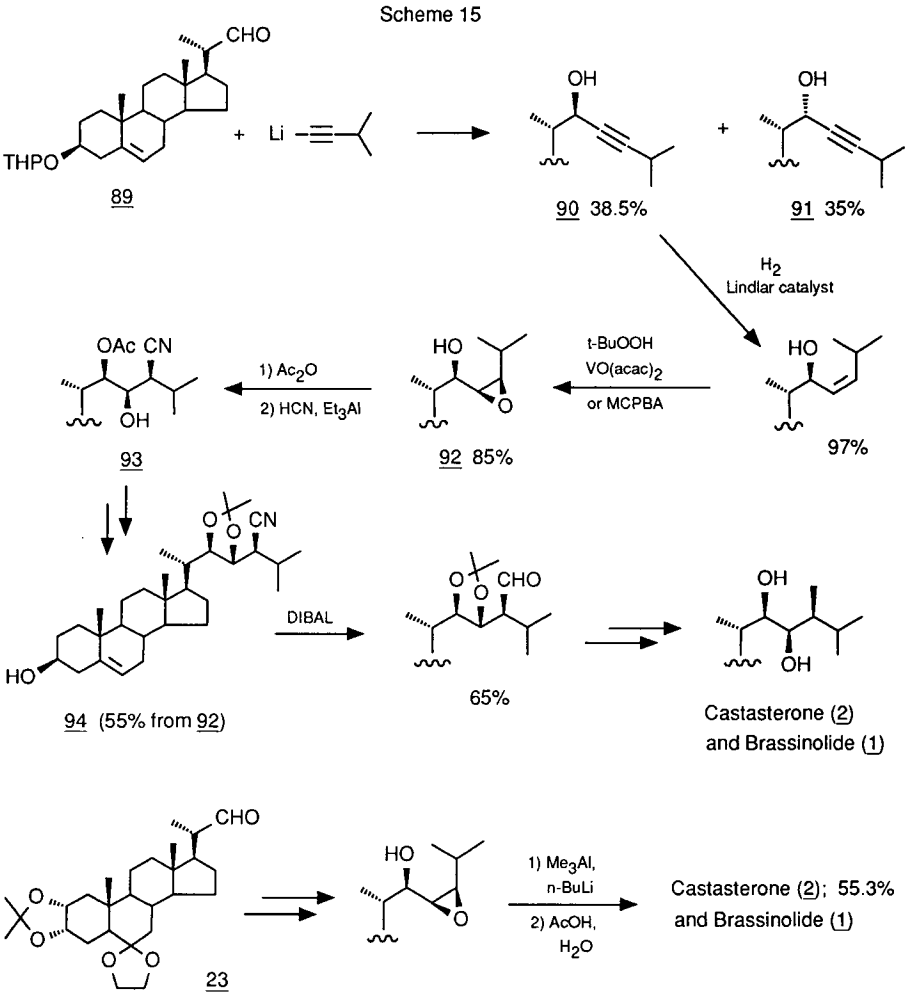
Scheme 14



4.2.2 Acetylides: Another early synthesis of brassinolide by Ikekawa et al. (15,18) employed the addition of lithium isopropylacetylide to aldehyde 89, unfortunately with essentially no stereoselectivity. The desired Cram product 90 was partially hydrogenated to the

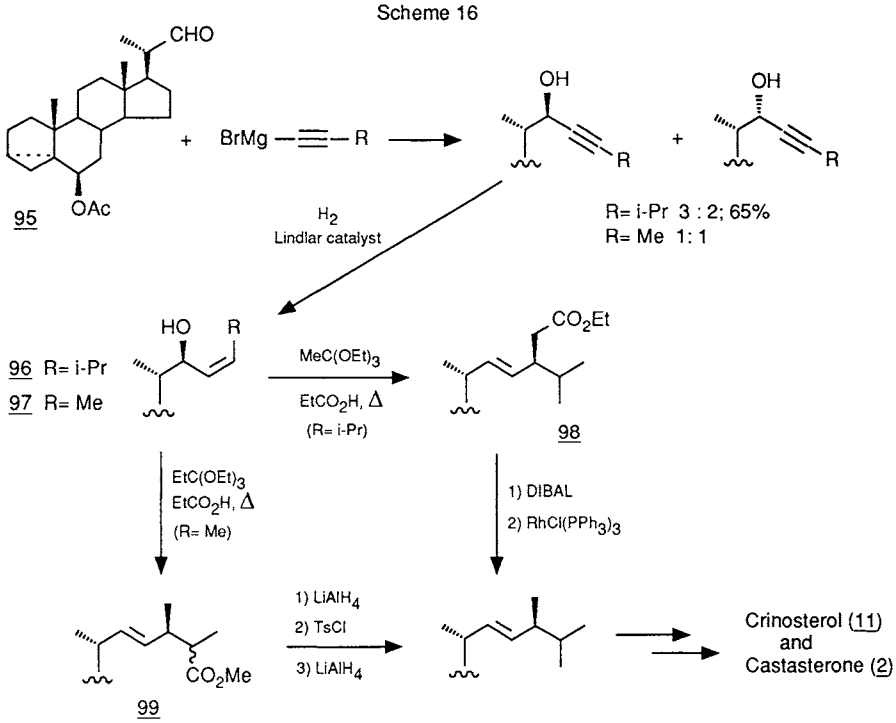
corresponding cis-olefin and converted into the single epoxide isomer 92 as shown in Scheme 15. Epoxide opening proved difficult, but was achieved by hydrocyanation, with inversion of configuration at C-24 to give 93, followed by manipulation of protecting groups to furnish 94, where the nitrile group acts as a latent C-24 methyl substituent. Reduction of the nitrile function of the latter with DIBAL, further reduction and deoxygenation of the resulting aldehyde, and functionalization of the steroid nucleus eventually afforded castasterone (2) and brassinolide (1). A shorter version of this approach was later reported (32,69,70,85), using the direct introduction of the (24S)-methyl group with trimethylaluminum into an epoxide similarly derived from aldehyde 23 (Scheme 15).

Scheme 15



The addition of magnesium acetylides to aldehyde 95 was reported by Fiecchi et al. (39,86), as shown in Scheme 16. Partial hydrogenation as in Scheme 15, followed by a Claisen rearrangement of the allylic alcohols 96 and 97 induced with triethyl orthoacetate or orthopropionate, produced esters 98 and 99, respectively. Reduction of the former ester to the aldehyde and decarbonylation with Wilkinson's catalyst provided the crinosterol side chain with the required C-24 stereochemistry, which was further converted into castasterone (2) (39). Alternatively, the ester moiety of 99 was reduced to generate the required C-27 methyl group of crinosterol (11) (86). A variation of this method was also used to prepare deuterated crinosterol analogues (36).

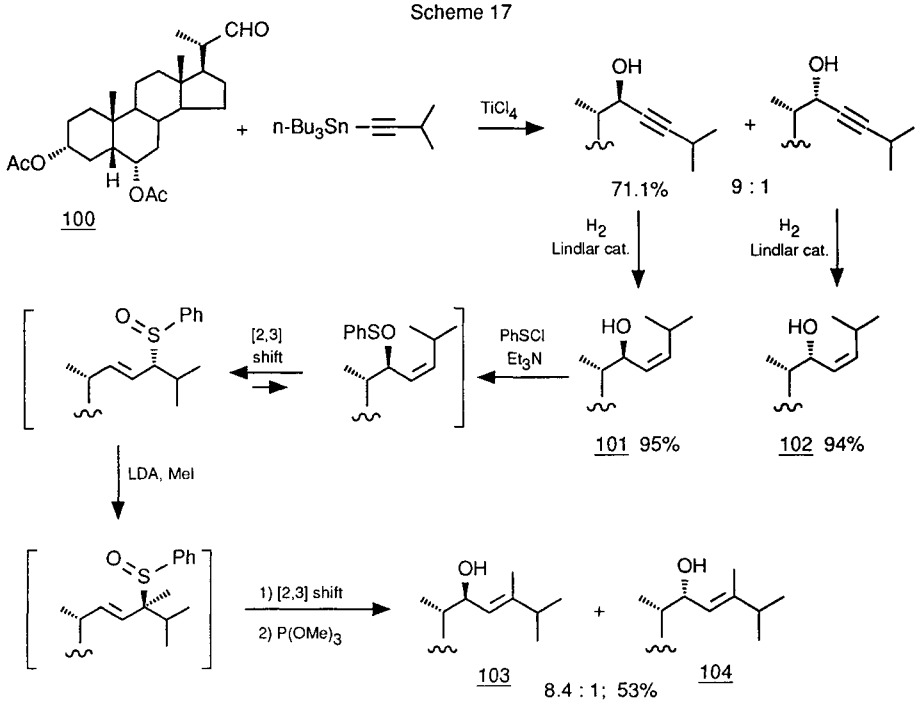
Scheme 16



The $TiCl_4$-catalyzed addition of stannylacetylenes to C-22 aldehydes provides higher Cram to anti-Cram ratios than does the use of lithium or magnesium acetylides (87). This has been exploited by Zhou et al. (88) in another brassinosteroid synthesis that uses this type of addition in conjunction with a stereoselective and reversible [2,3] sigmatropic sulfoxide-sulfenate rearrangement (Scheme 17). The aldehyde 100, obtained from hyodeoxycholic acid, thus gave 101 and 102 after hydrogenation with Lindlar catalyst. Treatment of 101 with benzenesulfenyl chloride afforded a sulfenate ester intermediate that underwent [2,3] sigmatropic rearrangement to the corresponding sulfoxide. Methylation of the

latter at C-24, followed by contrathermodynamic rearrangement back to the sulfenate ester and trapping of the latter with trimethylphosphite gave the desired allylic alcohol 103 and its 22-epimer 104 in the ratio of 8.4:1. Similar treatment of 102 produced a slightly lower ratio of 6:1. The side chain was then further elaborated by the procedure of Fung and Siddall (14) (see Scheme 13), except that the use of $Ti(Oi\text{-}Pr)_4$ instead of BH_3-THF improved the regiocontrol in the reduction of the epoxide with $LiBH_4$.

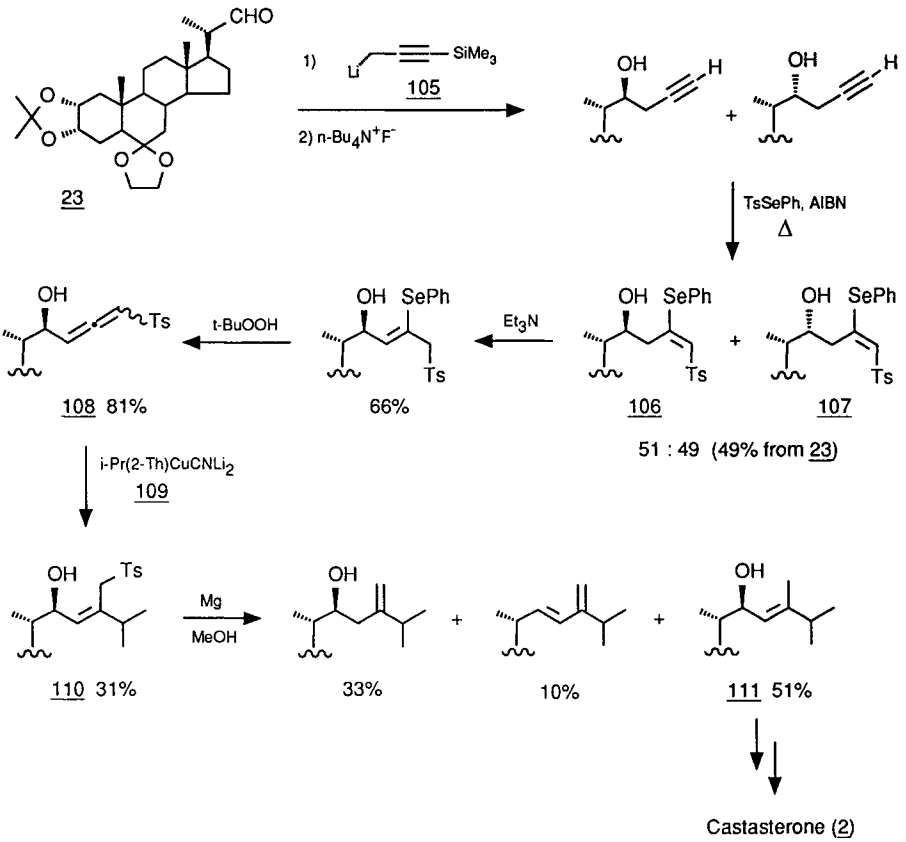
Scheme 17



4.2.3 3-Lithio-1(trimethylsilyl)propyne: Our group's first route to the brassinolide side chain (89,90) employed the addition of the propargyllithium species 105 to aldehyde 23, followed by desilylation and free-radical selenosulfonation (Scheme 18). Unfortunately, as in the case of the acetylide addition in Scheme 15, there was essentially no streoselectivity with respect to the desired Cram addition product. Presumably, the relatively long, slender and sterically undemanding structures of acetylides and propargyllithiums present too little hindrance for effective discrimination between the transition states leading to the Cram and anti-Cram products. The C-22 epimers 106 and 107 were separated and 106 was converted into the key intermediate allenic sulfone 108 by isomerization and selenoxide syn-elimination. The introduction of the isopropyl group with cuprate 109 proceeded with excellent stereoselectivity to the less hindered face of the sulfone-activated π-bond to afford 110, albeit in relatively low

yield because of competing elimination. Reductive desulfonylation then produced the allylic alcohol 111 as the principal product, which was further converted into castasterone (2) (90), essentially by the procedure of Fung and Siddall (14).

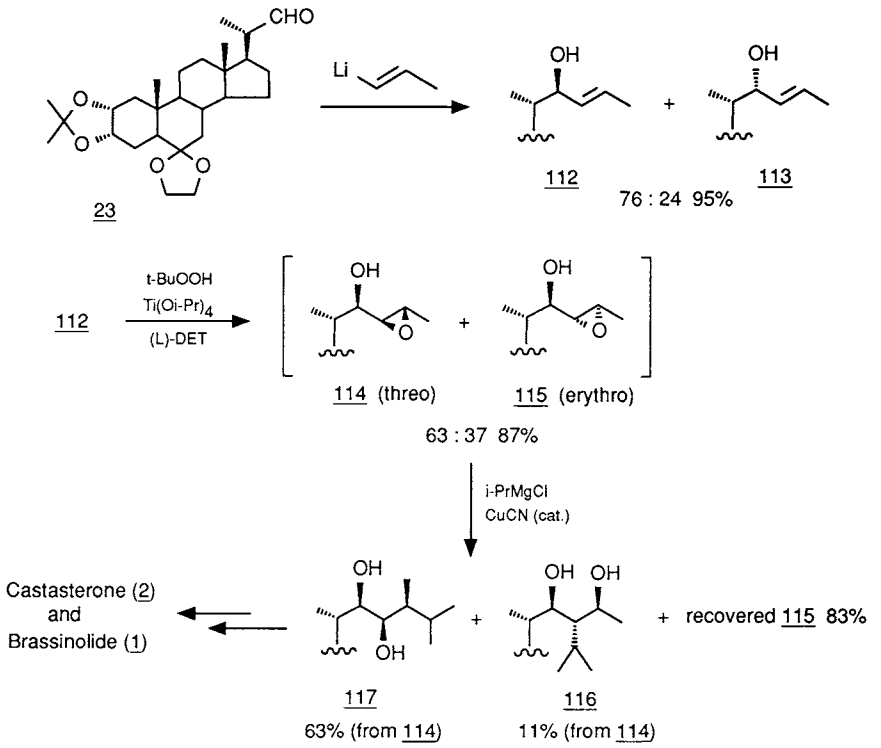
Scheme 18



4.2.4 Vinyllithiums: Further work by our group (64,91) revealed that a more stereoselective addition to aldehyde 23 was possible with (E)-propenyllithium, as shown in Scheme 19. This reagent is conveniently prepared from (trans)-1-chloropropene and lithium, and is configurationally and chemically stable in solution for extended periods. Epoxidation of the resulting major allylic alcohol 112 with peracids, or with t-BuOOH catalyzed by molybdenum or vanadium species, favoured the formation of the unwanted (erythro)-epoxy alcohol 115. However, Sharpless oxidation with diethyl L-(+)-tartrate gave predominantly the required (threo)-epoxide 114. Since the latter reacts more rapidly with nucleophiles, a kinetic separation was effected by treatment of the mixture of epoxy alcohols with isopropylmagnesium chloride and a catalytic amount of cuprous cyanide, resulting in the highly stereoselective ring-opening

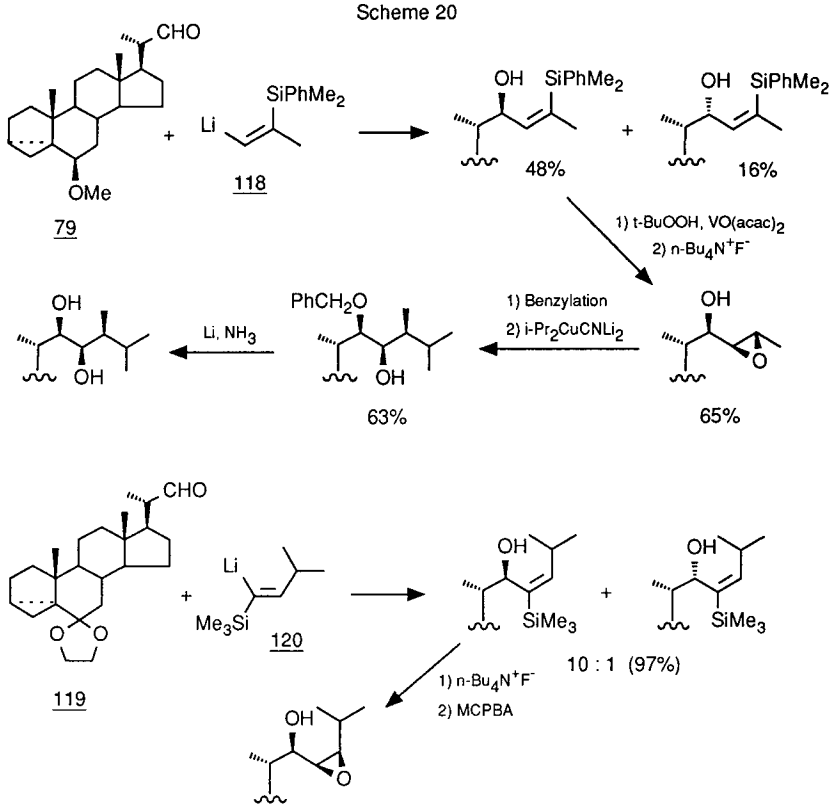
of the (threo)-epoxy alcohol 114 and recovery of the erythro isomer 115. A small amount of the regioisomer 116 accompanied the formation of the desired vicinal diol 117. This method therefore elaborates the brassinolide side chain from the C-22 aldehyde 23 in just three steps, with good stereocontrol over the chiral centers at C-22, C-23 and C-24.

Scheme 19



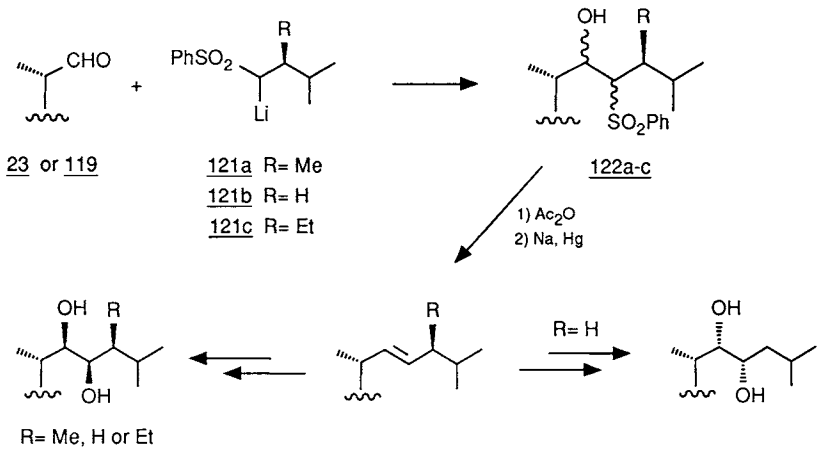
A related but longer approach that also employed a (threo)-epoxy alcohol intermediate had been reported earlier by Oshima and coworkers (92). This involved the use of the silylated vinyllithium reagent 118, as shown in Scheme 20, and necessitated a desilylation step as well as protection of the C-22 hydroxyl group. The addition of another silylated vinyllithium reagent 120 to aldehyde 119 was employed by Khripach et al. (3,93) (Scheme 20), with excellent stereoselectivity, affording an epoxy alcohol side chain similar to that of 92 in Scheme 15, reported previously by Ikekawa (15,18). This compound, in contrast to our epoxy alcohol 114 or that of Oshima, requires epoxide opening by a nucleophilic methyl group (e.g. with Me_3Al as in Scheme 15), instead of by an isopropyl group, in order to complete the synthesis of the side chain.

Scheme 20

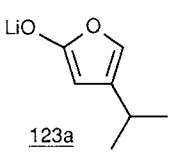


4.2.5 Sulfur-stabilized Anions: A different strategy for the synthesis of the brassinolide side chain is based on the use of a nucleophile containing the preformed chiral center at C-24 with the required configuration. An example of such a species is provided by the metalated sulfone 121a, as reported by Mori et al. (23,28). The addition of 121a to aldehyde 23 (Scheme 21) afforded a mixture of C-22 and C-23 stereoisomers of the β-hydroxy sulfone 122a, that underwent reductive elimination to afford the crinosterol side chain. Further elaboration was performed via epoxidation and bromohydrin formation as in Scheme 10. The required sulfone for the generation of 121a is available via a multistep sequence from either (R)(+)-citronellic acid (23), or from (S)-(-)-3-methyl-γ-butyrolactone (94). The sulfone-stabilized anion 121b was used in the preparation of 28-nor-22,23-diepibrassinolide from aldehyde 119 by osmium tetroxide oxidation of the Δ^{22}-olefin derived from the reductive elimination of the corresponding β-hydroxy sulfone 122b (24). Racemic 121a-c were also prepared from isovaleric acid, and then used to produce similar Δ^{22}-olefins as mixtures of C-24 epimers (3). The addition of lithiated dithiane to C-22 aldehydes provides a means for homologation of the side chain (22,95-97) that will be discussed further in Section 4.3.

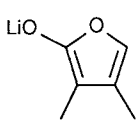
Scheme 21



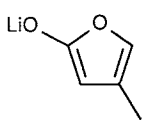
4.2.6 Lactone Enolates: The Cram additions of enolates 123a-c to C-22 aldehydes provides another avenue for the stereoselective synthesis of the brassinolide side chain. McMorris and coworkers (98) demonstrated that 123a adds to aldehyde 79 not only with control over the stereochemistry at C-22, but also at C-23 (Scheme 22). Thus, 79 afforded the (22R,23R)-adduct 124 at low temperatures, under kinetic control, with equilibration to the more stable (23S)-derivative observed at warmer temperatures. Stereoselective hydrogenation of 124 produced mainly the lactone 125, thereby regulating the remaining chiral center at C-24, and ultimately generating the brassinolide side chain by degradation of the 24-hydroxyethyl substituent of 126 to the required methyl group by means of oxidation to the corresponding aldehyde and decarbonylation with Wilkinson's catalyst. The similar use of enolates 123b by McMorris (98) and of 123c by Zhou et al. (49,57) was also reported. The former enolate afforded lactone 127 after hydrogenation, requiring only $LiAlH_4$ reduction and deoxygenation at C-27 to complete the side chain, while the latter gave lactone 128, which required methylation at C-25, as well as deoxygenation at C-27 en route to typhasterol (49). Alternatively, reduction of 128 and degradation of C-26 via a decarbonylation reaction similar to that employed with 126 provided access to 26,27-dinorbrassinolide (129) (57).



123a

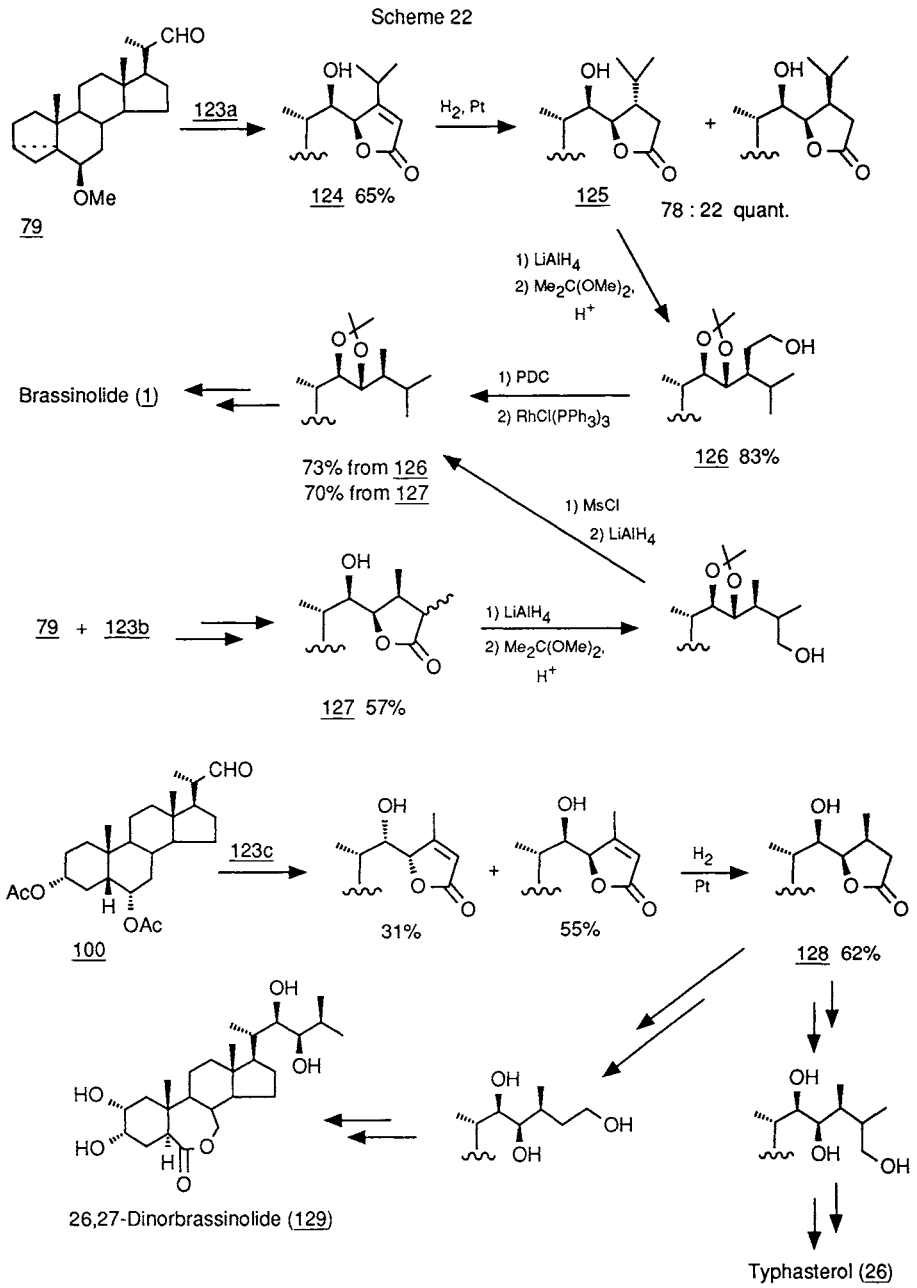


123b

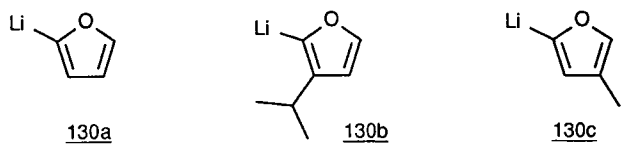


123c

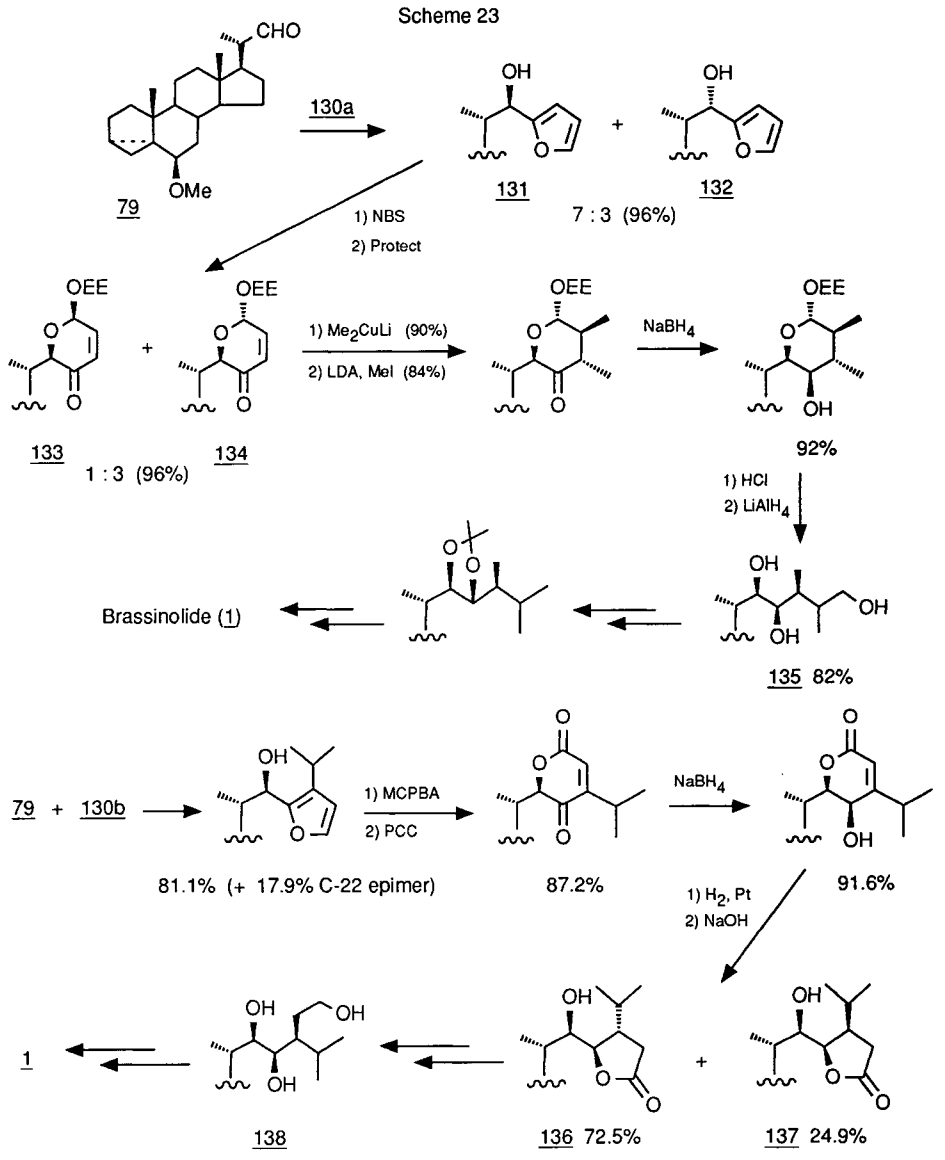
Scheme 22



4.2.7 2-Lithiofurans: More recently, the Cram additions of 2-lithiofurans 130a-c to C-22 were reported by Kametani (99,100) and Honda (101,102) and their coworkers, and are shown in Scheme 23.


Li
O
130a
Li
O
130b
Li
O
130c

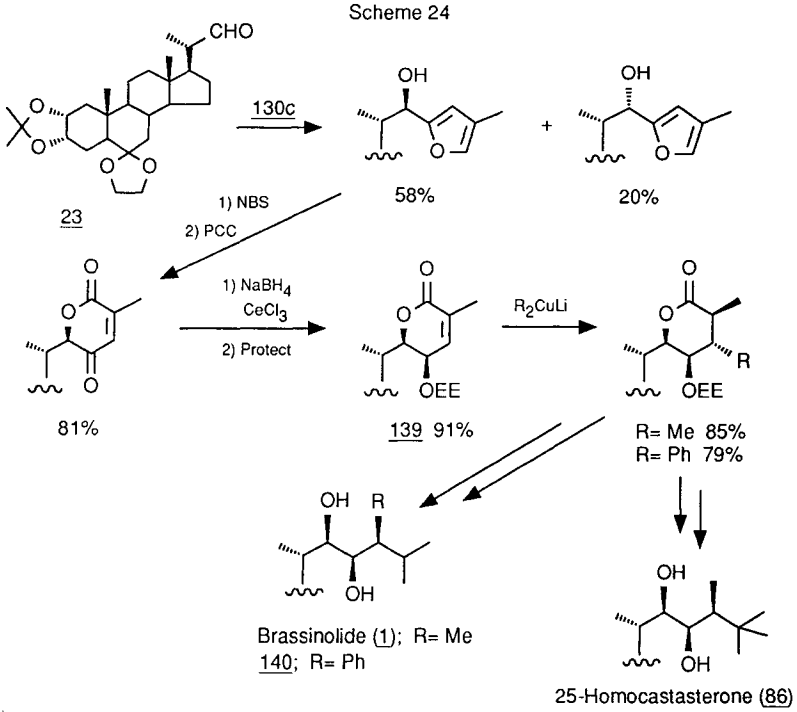
Scheme 23


CHO
OMe
79
130a
OH
O
131
+
OH
O
132
7 : 3 (96%)
1) NBS
2) Protect
OEE
O
O
133
+
OEE
O
O
134
1 : 3 (96%)
1) Me2CuLi (90%)
2) LDA, MeI (84%)
OEE
O
O
NaBH4
OEE
O
O
OH
92%
1) HCl
2) LiAlH4
OH
OH
OH
135 82%
O
O
Brassinolide (1)
79 + 130b
OH
O
1) MCPBA
2) PCC
O
O
O
81.1% (+ 17.9% C-22 epimer)
87.2%
NaBH4
O
O
OH
91.6%
1) H2, Pt
2) NaOH
1
OH
OH
OH
138
OH
O
O
136 72.5%
+
OH
O
O
137 24.9%

Rearrangement of the major adduct 131, obtained from furan 130a and aldehyde 79 was induced by NBS to afford the epimers 133 and 134 after protection of the hydroxyl group as the ethoxyethyl (OEE) ether (100). Equilibration of 133 via the unprotected lactol further enhanced the yield of 134. The stereoselective introduction of two methyl groups, comprising C-26 and C-24, to 134 was then achieved by conjugate addition and enolate alkylation respectively. Reduction of the keto group with $NaBH_4$ cleanly produced the 23-hydroxyl substituent, while deprotection and further reduction with $LiAlH_4$ afforded the 26-hydroxy derivative 135. Selective deoxygenation of the primary alcohol group of the latter then completed the synthesis of the brassinolide side chain. A variation of this approach employed the more highly substituted furan 130b, which contained the C-25 to C-27 portion of the side chain in the form of the isopropyl substituent. Reduction to the corresponding allylic alcohol, hydrogenation of the double bond and translactonization then furnished the epimeric lactones 136 and 137 (99). The major lactone 136 is a potential precursor of brassinolide via reduction to the triol side chain 138 and degradation of the hydroxyethyl substituent.

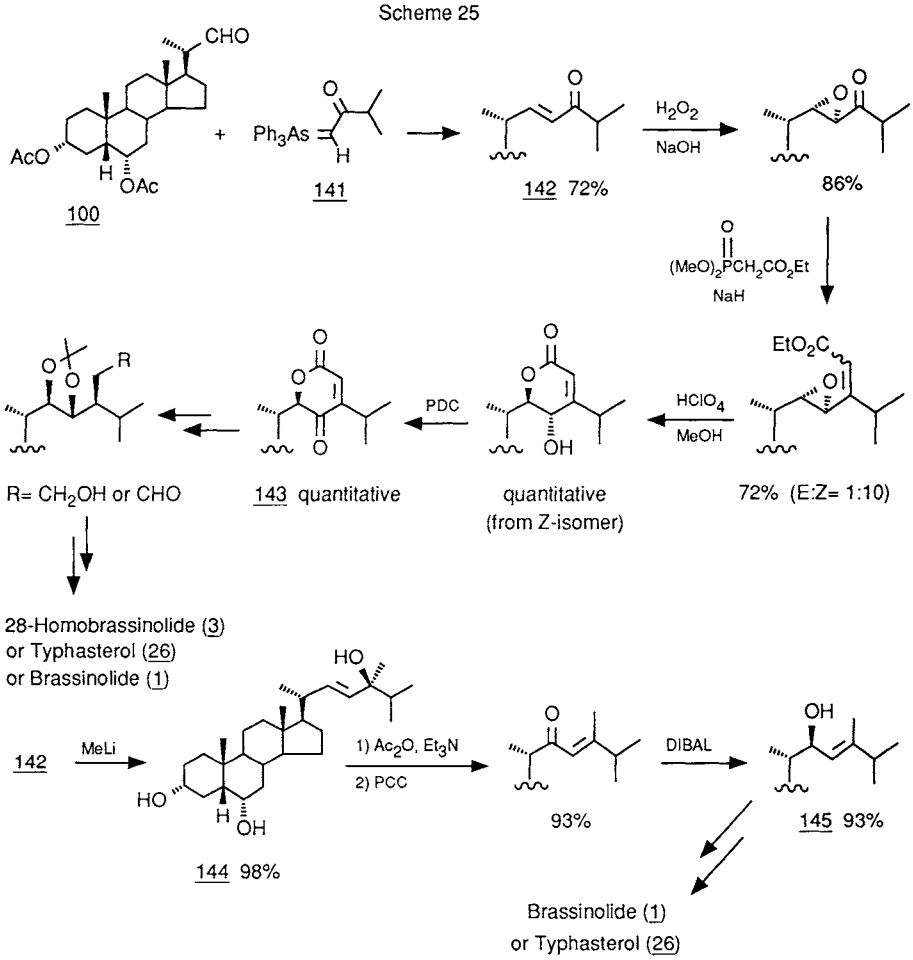
A similar addition of 130c to aldehyde 23 led to lactone 139 (101,102), where conjugate addition of either dimethyl- or diphenylcuprates permitted the preparation of brassinolide (1) or its 24-phenyl analogue 140 (Scheme 24). Moreover, dimethylcuprate addition to 139, followed by methylation of the lactone enolate, provided entry to 25-homocastasterone (86).

Scheme 24



4.2.8 Arsonium Ylides: The reaction of the C-22 aldehyde 100, derived from hyodeoxycholic acid (10), with the arsonium ylide 141 was investigated by Zhou et al. (50-52), and is shown in Scheme 25.

Scheme 25



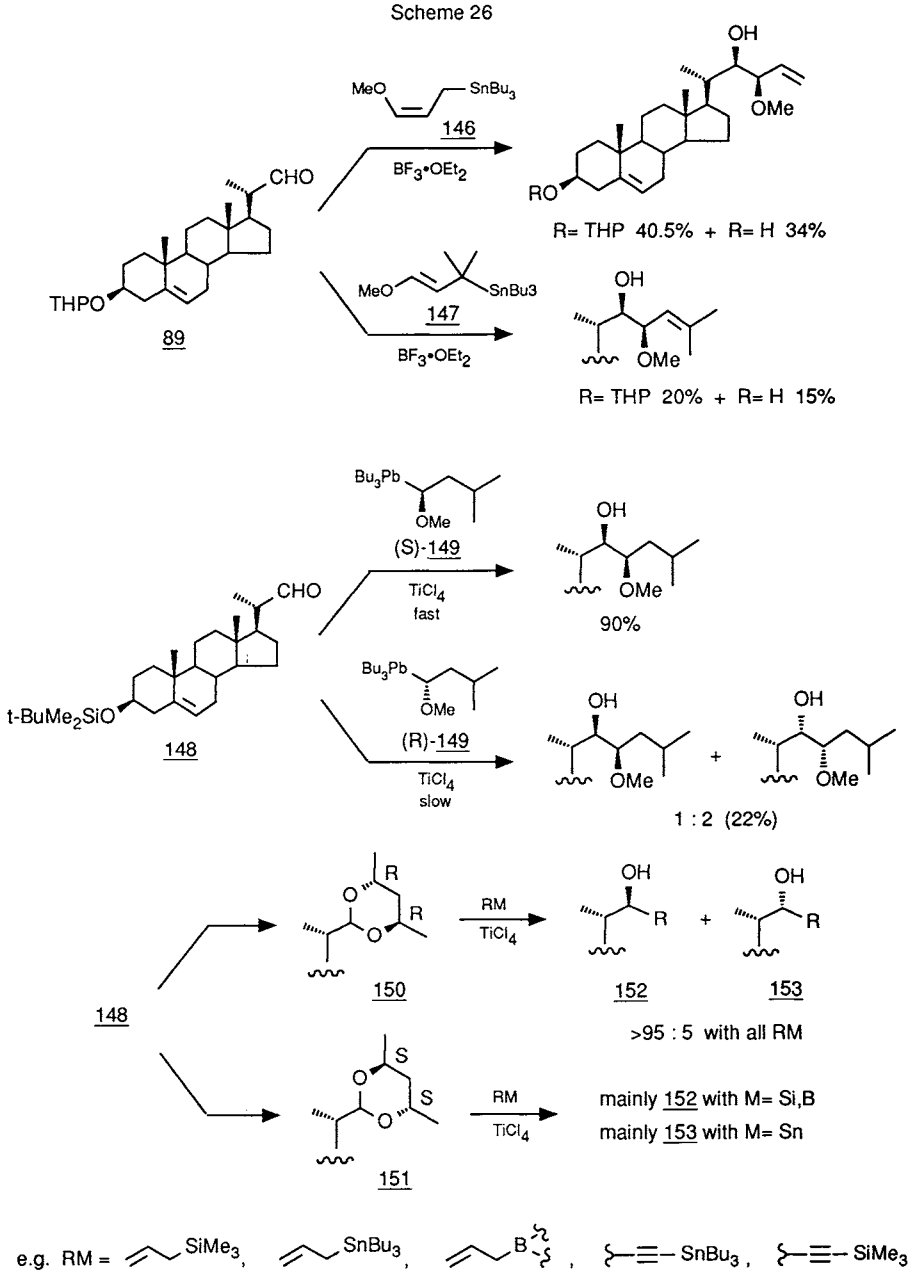
This olefination procedure provided enone 142, which in turn was subjected to a highly stereoselective epoxidation with alkaline hydrogen peroxide. Further olefination of the C-24 ketone via a Wadsworth-Emmons reaction and acid-catalyzed epoxide-opening with inversion of configuration at C-22, followed by oxidation of the free C-23 hydroxyl group with PDC, afforded the lactone 143. The latter represents the same type of side chain as prepared by Kametani (99), as depicted in Scheme 23. Lactone 143 was in turn converted into 28-homobrassinolide (3), typhasterol (26) or brassinolide (1), with the latter two compounds

requiring degradation of C-28 by decarbonylation of the corresponding aldehyde with Wilkinson's catalyst. Furthermore, the additon of excess methyllithium to the keto group of 142 produced 144 as the sole C-24 epimer (51). Allylic transposition of the oxygen function via PCC oxidation, followed by a highly stereoselective reduction of the new C-22 ketone with DIBAL, produced the allylic alcohol 145. This was converted into brassinolide (1) or typhasterol (26) by further side chain elaboration using the method of Fung and Siddall (14) (Scheme 13) and further transformation of the steroid nucleus, as in Scheme 6. The ylide Ph_3As=CHCOMe was similarly employed in the preparation of 26,27-dinorbrassinolide (129) (56).

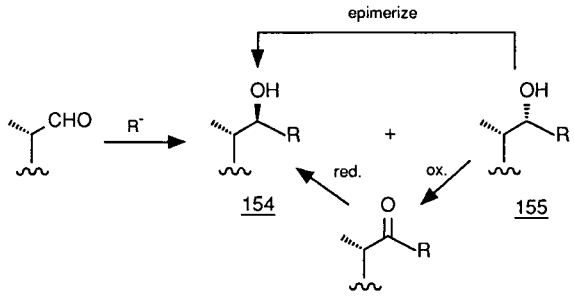
4.2.9 Tin, Lead, Boron and Silicon Compounds: The Lewis acid-catalyzed coupling of C-22 aldehydes with γ-methoxyallylstannanes 146 and 147 (103) or α-methoxyalkyl-plumbane 149 (104) produces side chains containing vicinal oxygen functions at C-22 and C-23 with the required stereochemistry at those centers (Scheme 26). Thus, 89 reacted with either 146 or 147 in the presence of BF_3•OEt_2 to afford the corresponding (22R,23R)-hydroxy ethers as unique stereoisomers. Aldehyde 148 reacted similarly with the (S)-enantiomer of plumbane 149 in the presence of $TiCl_4$ to furnish only the corresponding (22R,23R)-hydroxy ether. On the other hand, (R)-149 reacted much more slowly and less stereoselectively, favouring the (22S,23S)-epimer. The difference in the reaction rates of (R)- and (S)-149 permitted the racemic mixture to be used under conditions of kinetic resolution to afford high yields of the desired (22R,23R)-product. An alternative approach based on the different stereochemical behaviour of diastereomeric acetals of the C-22 aldehyde 148 is also shown in Scheme 26. The aldehyde 148 was first converted into either the (R,R)-acetal 150 or the (S,S)-analogue 151 (105). The former acetal reacted with various allyl- or alkynylsilanes, boranes and stannanes in the presence of $TiCl_4$ in a highly stereoselective manner to produce alcohols 152 as the principal products. It was postulated that a template effect of the Lewis acid is synergistic with the tendency towards Cram addition in this case. The acetal 151 produced chiefly 152 with M= Si or B, but with lower stereoselectivity than observed with 150. Apparently the stereochemistry here is determined largely on the basis of Cram's rule, as the template effect is less pronounced with Si or B. On the other hand, acetal 151 generally favoured the antiCram formation of 153 with M= Sn, where the template effect overrides the propensity to follow Cram's rule.

4.2.10 Epimerization of C-22: As was seen in the preceding sections, most of the methods for the elaboration of the brassinosteroid side chain by nucleophilic addition to a C-22 aldehyde generate substantial amounts of the unwanted anti-Cram C-22 alcohol 155, along with the desired adduct 154. Procedures for the inversion of configuration of the former can thus increase the yield of the required Cram isomer (Scheme 27). Epimerization techniques include mesylation of the anti-Cram alcohol, followed by S_N2 displacement with potassium superoxide (18,69), or inversion of configuration of the undesired alcohol 155 by means of the Mitsunobu reaction (32). Alternatively, oxidation of the alcohol to the 22-ketone, followed by stereoselective reduction also affords the desired epimer (69,100,106). L-Selectride reduces C-22 ketones with excellent stereoselectivity to afford 155 (106), while DIBAL is reported to favour the desired product 154 (53,106).

Scheme 26


MeO
SnBu3
146
BF3•OEt2
CHO
THPO
89
OH
OMe
RO
R= THP 40.5% + R= H 34%
MeO
SnBu3
147
BF3•OEt2
OH
OMe
R= THP 20% + R= H 15%
Bu3Pb
OMe
(S)-149
TiCl4
fast
CHO
t-BuMe2SiO
148
OH
OMe
90%
Bu3Pb
OMe
(R)-149
TiCl4
slow
OH
OMe
+
OH
OMe
1 : 2 (22%)
148
R
O
O
R
150
RM
TiCl4
OH
R
+
OH
R
152
153
>95 : 5 with all RM
S
O
O
S
151
RM
TiCl4
mainly 152 with M= Si,B
mainly 153 with M= Sn
e.g. RM =
SiMe3,
SnBu3,
B
,
SnBu3,
SiMe3

Scheme 27



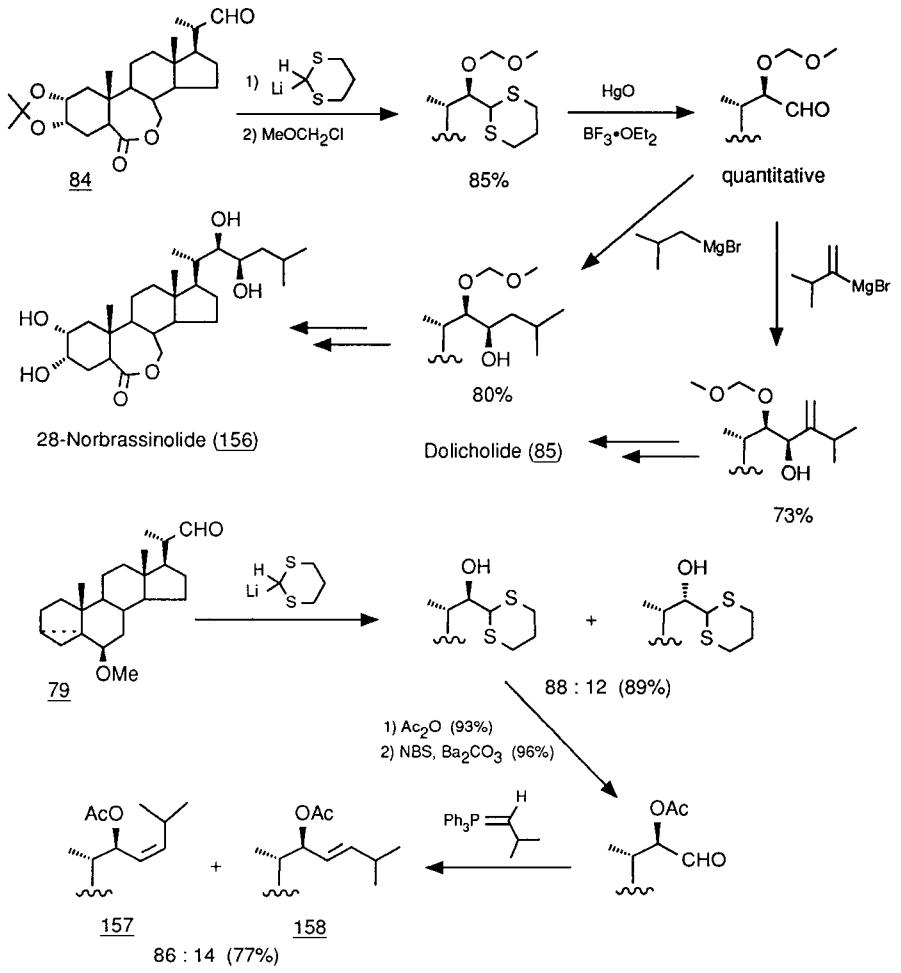
4.3 Additions to C-23 Aldehydes

Ikekawa and coworkers (22,96,97) reported that the addition of 2-lithio-1,3-dithiane to C-22 aldehydes permits their homologation to C-23 aldehydes after protection of the C-22 hydroxyl group and hydrolysis of the dithiane moiety. The further addition of Grignard reagents to C-23 produced side chains in which both oxygenated centers are formed with high stereoselectivity. The conversion of aldehyde 84 to dolicholide (85) and 28-norbrassinolide (156) (96) is shown in Scheme 28. The addition of isopropylmagnesium bromide to another C-23 aldehyde provided similar access to 26,27-dinorbrassinolide (129) (21). A variation of this method is also shown in Scheme 28, where a Wittig reaction was employed to generate the allylic acetates 157 and 158 (95). Further elaboration of 157 via Scheme 15 is then possible.

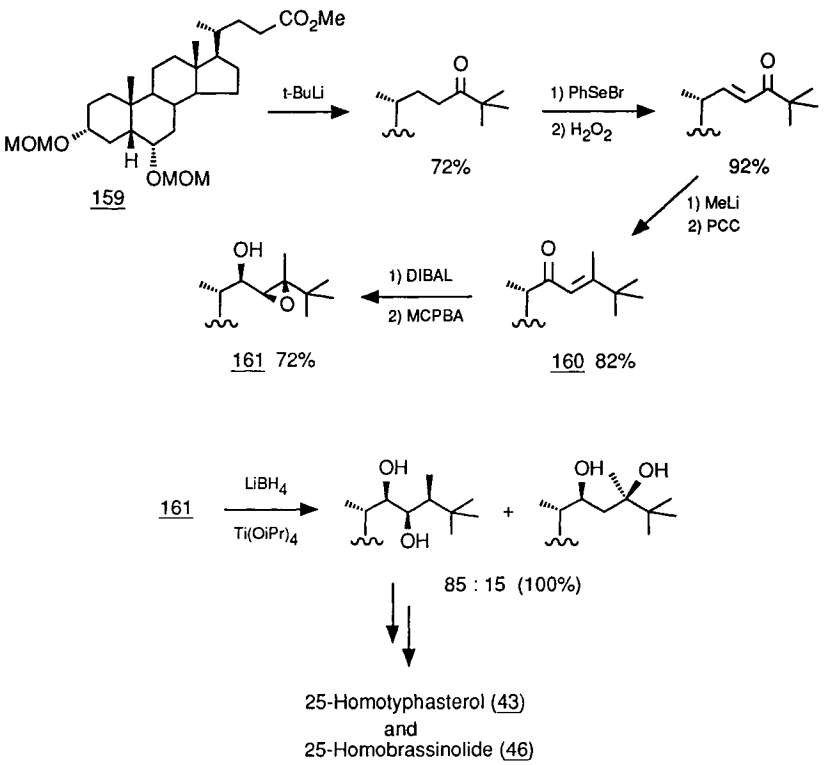
4.4 Substitution of C-24 Esters

The elaboration of C-24 esters such as 159, derived from hyodeoxycholic acid (10), comprises another method for the synthesis of the brassinosteroid side chain. Zhou et al. (53) treated 159 with t-butyllithium to afford the corresponding t-butyl ketone (Scheme 29). Dehydrogenation, addition of methyllithium to the ketone moiety and allylic transposition similar to that used in the formation of 145 in Scheme 25 furnished the 22-ketone 160. This was further elaborated to 25-homotyphasterol (43) and 25-homobrassinolide (46) via the regio- and stereoselective hydride reduction of epoxy alcohol 161 in the presence of titanium tetraisopropoxide. This procedure gave improved regioselectivity compared to the $LiBH_4$-BH_3•THF reagent employed in the similar reduction of 82 in Scheme 13. A related approach (79,80) is depicted in Scheme 30 and involves the vicinal dihydroxylation of the α,β-unsaturated C-24 ester 162 with osmium tetroxide, catalyzed by DHQD-CLB (also see Table 1). The acetonide of the principal product 163 was then further elaborated with t-butyllithium, i-propylmagnesium chloride or methyllithium to afford the side chains of 25-homotyphasterol (43) and 25-homobrassinolide (46), typhasterol (26) and brassinolide (1), and 26,27-dinortyphasterol (165) and 26,27-dinorbrassinolide (129).

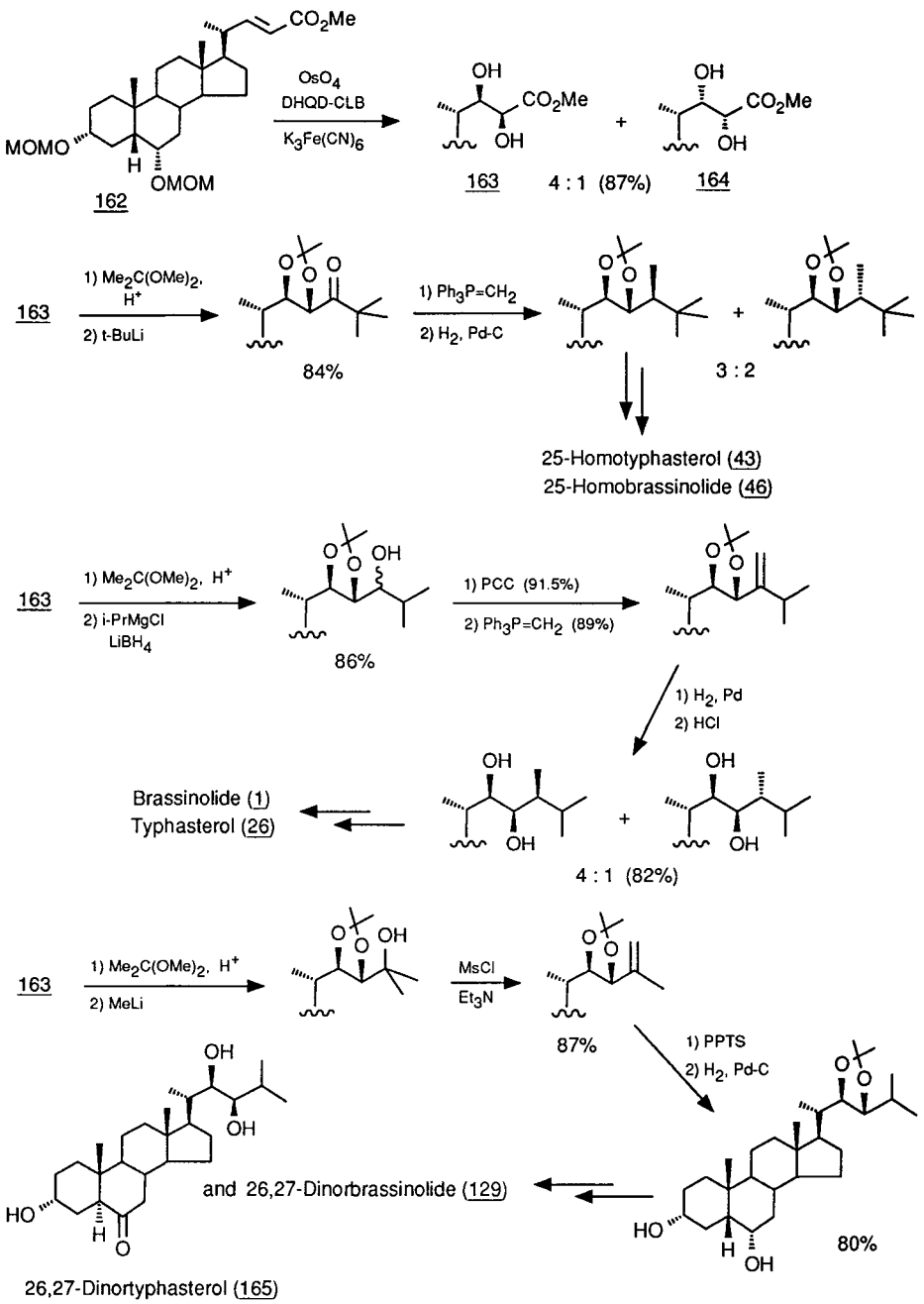
Scheme 28


CHO
1) Li
2) MeOCH2Cl
84
85%
HgO
BF3•OEt2
quantitative
MgBr
MgBr
OH
HO
HO
28-Norbrassinolide (156)
80%
Dolicholide (85)
73%
CHO
Li
OMe
79
OH
OH
88 : 12 (89%)
1) Ac2O (93%)
2) NBS, Ba2CO3 (96%)
Ph3P
H
OAc
CHO
AcO
OAc
157
158
86 : 14 (77%)

Scheme 29


CO2Me
MOMO
H
OMOM
159
t-BuLi
O
72%
1) PhSeBr
2) H2O2
O
92%
1) MeLi
2) PCC
O
160 82%
1) DIBAL
2) MCPBA
OH
O
161 72%
161
LiBH4
Ti(OiPr)4
OH
OH
+
OH
OH
85 : 15 (100%)
25-Homotyphasterol (43)
and
25-Homobrassinolide (46)

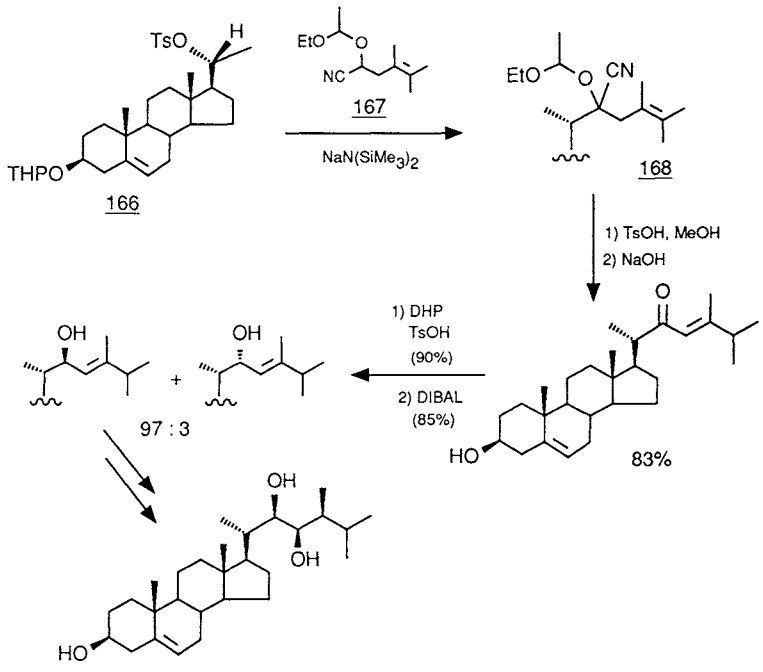
Scheme 30


CO2Me
MOMO
H
OMOM
162
OsO4
DHQD-CLB
K3Fe(CN)6
OH
CO2Me
OH
163
4 : 1 (87%)
164
1) Me2C(OMe)2, H+
2) t-BuLi
84%
1) Ph3P=CH2
2) H2, Pd-C
3 : 2
25-Homotyphasterol (43)
25-Homobrassinolide (46)
1) Me2C(OMe)2, H+
2) i-PrMgCl
LiBH4
86%
1) PCC (91.5%)
2) Ph3P=CH2 (89%)
1) H2, Pd
2) HCl
Brassinolide (1)
Typhasterol (26)
4 : 1 (82%)
1) Me2C(OMe)2, H+
2) MeLi
MsCl
Et3N
87%
1) PPTS
2) H2, Pd-C
HO
80%
and 26,27-Dinorbrassinolide (129)
26,27-Dinortyphasterol (165)

4.5 From Pregnane Derivatives

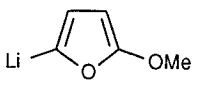
4.5.1 By Displacement of a C-20 Tosylate: Pregnanes with alcohol or ketone functions at C-20 provide another route to brassinosteroids. The tosylate 166 is available from pregnenolone and undergoes inversion of configuration at C-20 when treated with the anion of the protected cyanohydrin 167 (106) (Scheme 31). Hydrolysis of the resulting intermediate 168 generated the free C-22 ketone and moved the side chain double bond into conjugation with it. The stereoselective reduction of the ketone with DIBAL produced the desired stereochemistry at C-22 (see Section 4.2.10) and afforded an allylic alcohol which can be further elaborated by the method of Fung and Siddall (14) (see Scheme 13).

Scheme 31

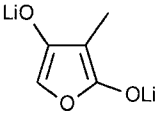


4.5.2 By Addition of Lithiated Furans and Tetronate Dianions to C-20 Ketones: The additions of the lithiated furan 169a (107) and the tetronate dianions 169b (108) and 169c (107,109) to appropriately functionalized pregnane precursors with C-20 keto groups were investigated by Kametani and coworkers. An example (109) is shown in Scheme 32, where the 20-ketone 170 was treated with dianion 169c. Although these additions proceed stereoselectively to give the (20R)-hydroxy adducts 171 and 172 as major and minor products, respectively, the stereocenters at C-20 and C-22 are subsequently lost by dehydration. Thus, syn-elimination of the trifluoroacetate of 171 afforded mainly the (Z)-olefin 173. The key step in the synthesis is a highly stereoselective double hydrogenation of 173 that creates the required configurations at C-20, C-22, C-23 and C-24 simultaneously. Reduction of 175 with lithium aluminum hydride and acetylation of the resulting diol provided 176, which in turn could be transformed into 28-hydroxybrassinolide by removal of protecting groups and the usual Baeyer-Villiger oxidation. On the other hand, deprotection, selective mesylation of the primary hydroxyl group at C-28 and further reduction with lithium aluminum hydride provided entry to castasterone (2) and thereby formally to brassinolide (1). Direct hydrogenation of 171 without prior dehydration led to 20,28-dihydroxybrassinolide (178) (109), while hydrogenation of the $\Delta^{20(21)}$-olefin obtained from dehydration of the related 20-hydroxy derivative 179 proved essentially nonstereoselective, but afforded 20-epibrassinolide (182) from the (20S)-isomer 180 (109). A similar protocol based on the dianion 169b was used to generate the corresponding 26,27-dinorbrassinosteroids (108).

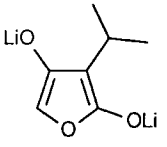
4.5.3 By 1,3-Dipolar Cycloaddition: Khripach et al. (3) added vinyl Grignard reagent or sodium acetylide to C-20 of pregnenolone acetate (183), and then performed 1,3-dipolar cycloadditions on the newly appended olefinic or acetylenic side chain with isopropyl isocyanate (Scheme 33). The intermediate 185 was obtained by either pathway, by dehydration and dehydrogenation of the olefin cycloadduct 184, or by direct dehydration of the corresponding acetylene cycloadduct. Further transformation of 185 as shown in Scheme 33 produced the enone 186, a potential intermediate for brassinosteroid synthesis (e.g. via the methods shown in Scheme 25 and 29), or the diketone 187. Enone 186 was also prepared from a similar cycloadditon to the olefin 188.



169a

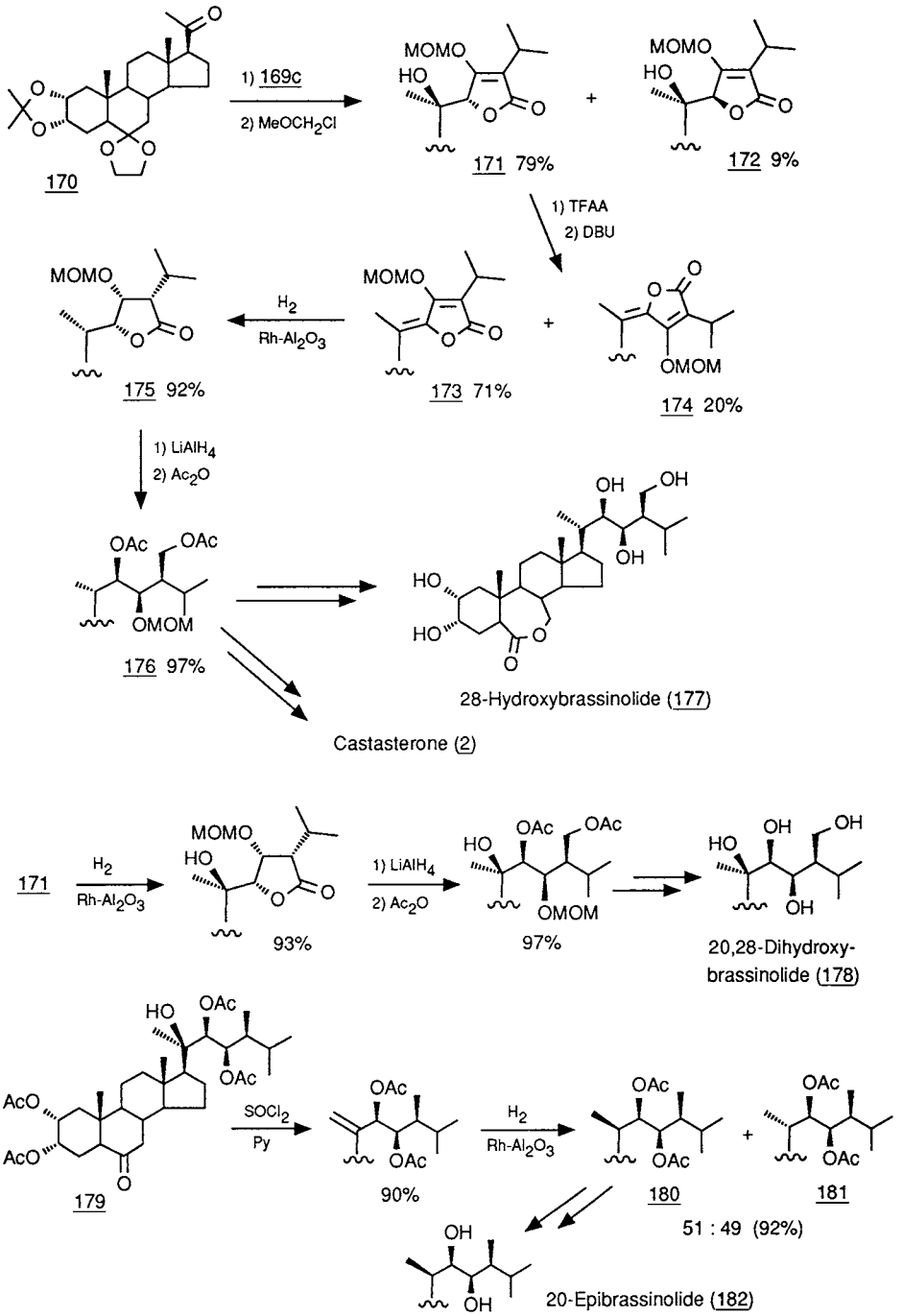


169b

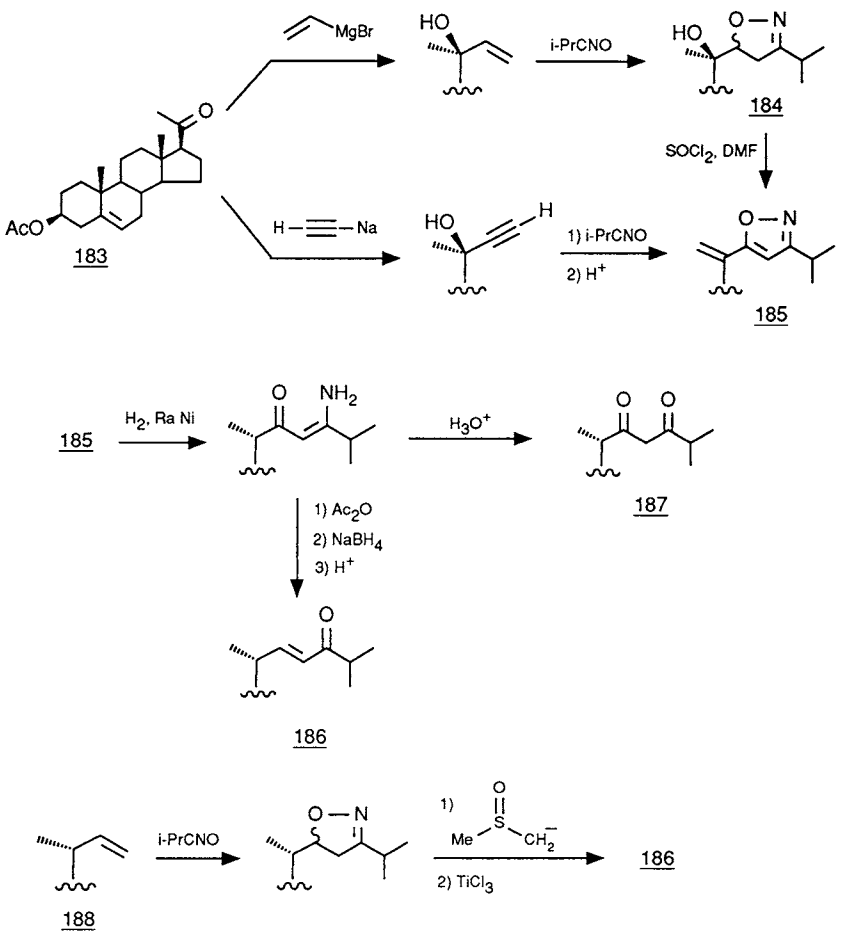


169c

Scheme 32

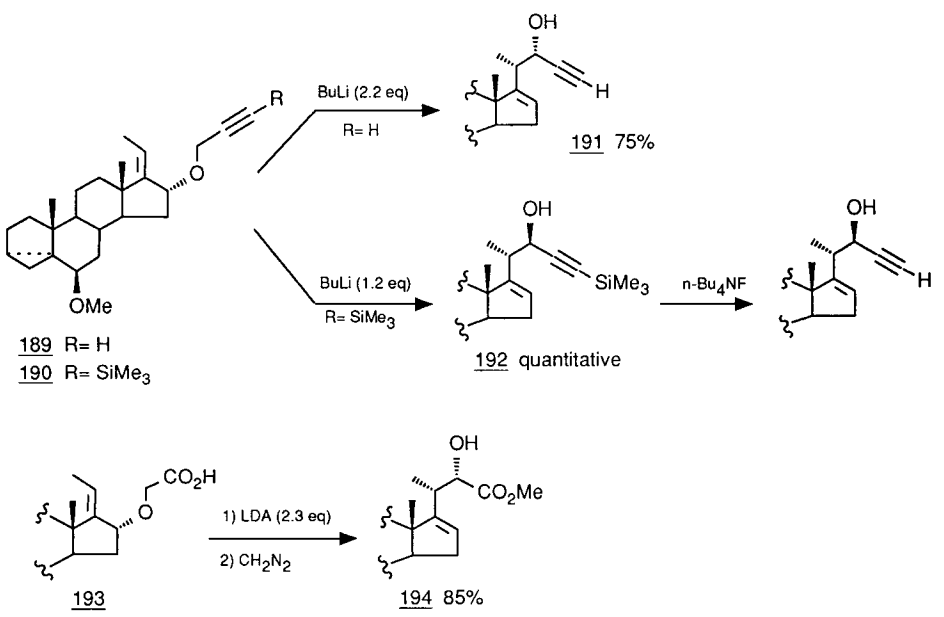

170
1) 169c
2) MeOCH2Cl
MOMO
HO
171 79%
172 9%
1) TFAA
2) DBU
MOMO
OMOM
174 20%
MOMO
173 71%
H2
Rh-Al2O3
MOMO
175 92%
1) LiAlH4
2) Ac2O
OAc
OAc
OMOM
176 97%
OH
OH
OH
HO
HO
28-Hydroxybrassinolide (177)
Castasterone (2)
171
H2
Rh-Al2O3
MOMO
HO
93%
1) LiAlH4
2) Ac2O
HO
OAc
OAc
OMOM
97%
HO
OH
OH
OH
20,28-Dihydroxy-
brassinolide (178)
HO
OAc
OAc
AcO
AcO
179
SOCl2
Py
OAc
OAc
90%
H2
Rh-Al2O3
OAc
OAc
180
OAc
OAc
181
51 : 49 (92%)
OH
OH
20-Epibrassinolide (182)

Scheme 33


MgBr
HO
i-PrCNO
O—N
HO
184
SOCl2, DMF
AcO
183
H—≡—Na
HO
H
1) i-PrCNO
2) H+
O—N
185
185
H2, Ra Ni
O
NH2
H3O+
O
O
187
1) Ac2O
2) NaBH4
3) H+
O
186
188
i-PrCNO
O—N
1)
O
Me
S
CH2−
2) TiCl3
186

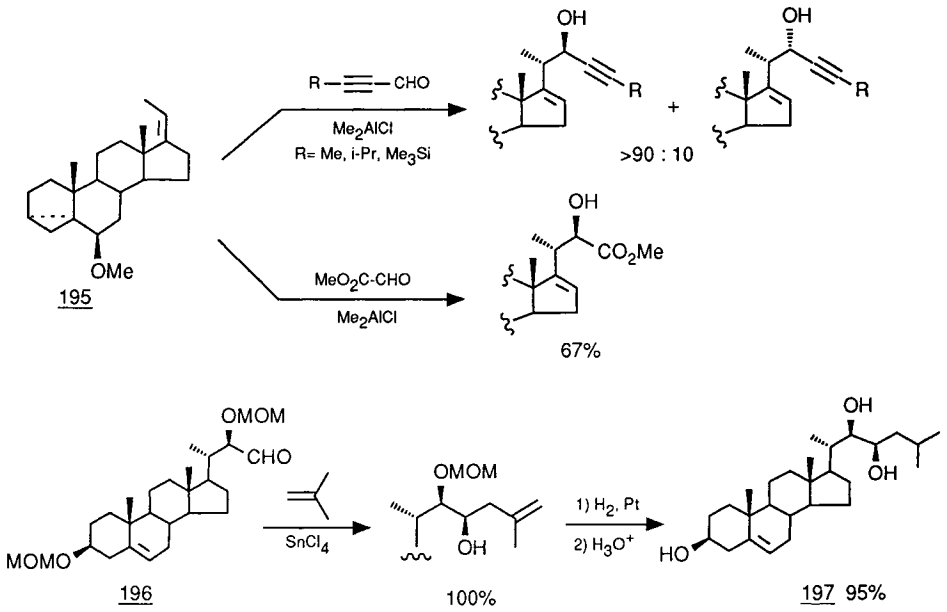
4.5.4 By [2,3] Wittig Rearrangement: The $\Delta^{17(20)}$-pregnenes 189 and 190 undergo [2,3] Wittig rearrangements with complementary stereoselectivity in the creation of the chiral center at C-22 (Scheme 34). Nakai et al. (110) have suggested that the (22S)-epimer 191 is favoured from 189 because of a destabilizing pseudo 1,3-diaxial interaction between the acetylene moiety and substituents of the cyclopentane ring in the transition state leading to the (22R)-epimer of 191. However, in 190, steric crowding between the bulky silyl group and the methyl substituent at C-20 overides the 1,3-diaxial interaction and affords the (22R)-isomer instead. Further elaboration of the products was not reported. A similar Wittig rearrangement of 193, followed by esterification with diazomethane, afforded the (22S)-hydroxy derivative of the C-23 methyl ester 194 (111).

Scheme 34



4.5.5 By Ene Reaction: Nakai has also reported that $\Delta^{17(20)}$-pregnene 195 reacts with acetylenic aldehydes (112) or with methyl glyoxylate (113) in the presence of dimethylaluminum chloride via an ene reaction that produces the corresponding acetylenic alcohol or hydroxy ester side chains (Scheme 35). The product that possesses the desired configuration at C-22 is favoured because it is formed via a less crowded endo transition state. The protected α-hydroxy aldehyde 196, available from the above glyoxylate ene reaction (114), underwent a further highly stereoselective ene reaction with isobutylene. The product was then converted into 197, which contains the 28-norbrassinosteroid side chain.

Scheme 35



5. CONCLUSIONS

The synthesis of brassinosteroids has attracted a great deal of interest since the discovery of brassinolide in 1979. This has been prompted by the challenging and unusual structures of these compounds, as well as by their potentially lucrative commercial applications, if they can be produced in sufficient amounts by a relatively inexpensive route. To date, a plethora of elegant and diverse approaches has been studied and numerous natural and unnatural analogues have been prepared. However, brassinosteroids, particularly brassinolide itself, remain scarce, even for the purpose of relatively small-scale research and field trials. There is, therefore, still an obvious need for new syntheses that would employ readily available sterol starting materials and inexpensive, easily handled reagents, and that would proceed with a minimum number of steps, each achieving high stereoselectivity. The latter point is of special importance as poor stereocontrol is not only wasteful of material, but often necessitates difficult and costly separations of complex mixtures of isomers with similar physical properties. This review demonstrates the considerable progress that has been achieved in the stereoselective synthesis of brassinosteroids in the past thirteen years. If advances continue to be made at this rate in the future, then it is possible that an increased supply of these compounds will eventually result in practical agricultural applications.

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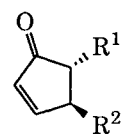
Atta-ur-Rahman (Ed.) *Studies in Natural Products Chemistry, Vol. 16*

Organopalladium Approaches to Prostaglandins

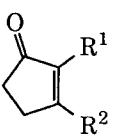
R.C. Larock

1 INTRODUCTION

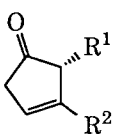
The prostaglandins (PG's) are an extremely important class of naturally-occurring substances found in mammals and marine corals, which exhibit a remarkably broad range of physiological properties. Structurally they differ in the nature of the functional groups and side chains attached to a five-membered ring and are classified as follows:



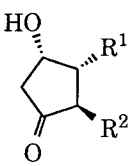
PGA



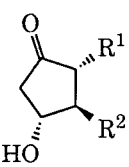
PGB



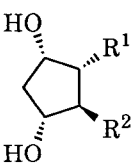
PGC



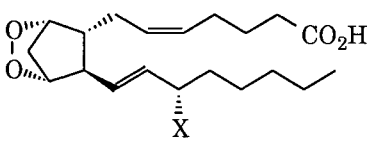
PGD



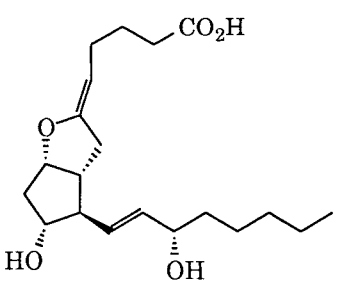
PGE



PGF



PGG_2 X = OOH
PGH_2 X = OH



PGI_2 (prostacyclin)

The most common side chains, $R^1 = CH_2CH{=}CH(CH_2)_3CO_2H$ and $R^2 = CH{=}CHCH(OH)C_5H_{11}$, are those shown above in the PGG_2 and PGH_2 structures,

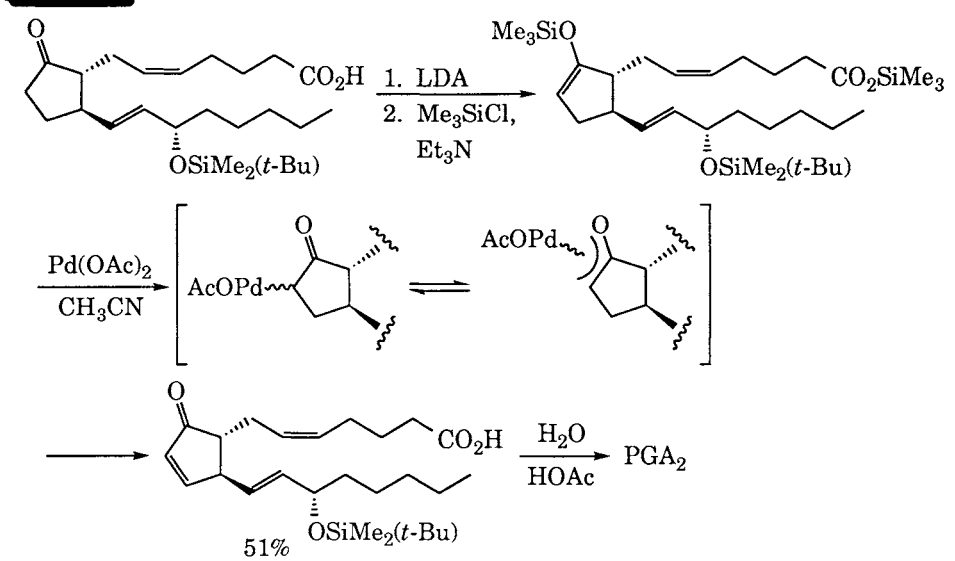
the subscript two referring in these compounds to the two carbon-carbon double bonds present in the side chains. Naturally-occurring substrates with one, two and occasionally three carbon-carbon double bonds in the side chains are known, and numerous analogues of the naturally-occurring prostaglandins have been synthesized (1-4).

Palladium has proven to be an extraordinarily useful metal in organic synthesis in recent years (5,6), and not surprisingly has found numerous applications in the synthesis of prostaglandins. Those examples reported in the literature through 1992 are hereby reviewed according to the structure of the prostaglandin.

2 A PROSTAGLANDINS

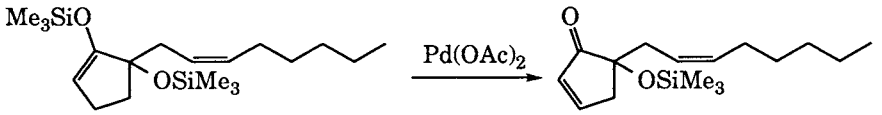
Organopalladium chemistry has proven useful for generation of the enone system present in the A prostaglandins. Palladium acetate is a very useful reagent for the conversion of enol silanes to enones (7). This reaction has been employed in the conversion of 11-deoxy-PGE_2 to PGA_2 [Scheme 1] (8). This process proceeds by

Scheme 1



electrophilic attack on the enol silane to produce a palladium-substituted ketone or oxa-π-allylpalladium intermediate which undergoes rapid β-hydride elimination to the enone.

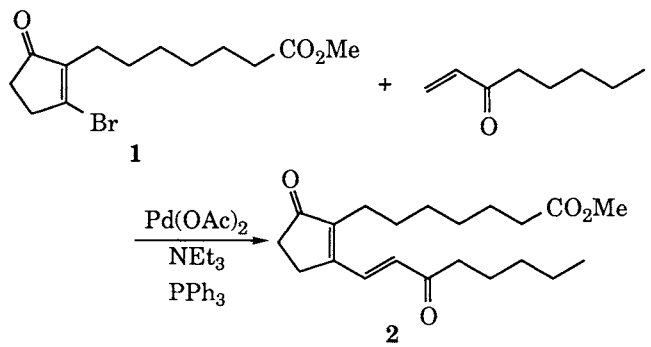
This chemistry has been employed in the synthesis of numerous natural products, including the prostaglandin-like anticancer clavulones [Eq. 1] (9).



[1]

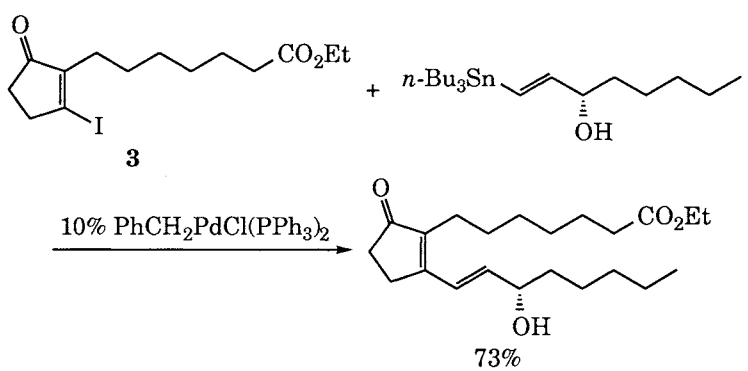
3 B PROSTAGLANDINS

B Prostaglandins are readily prepared using two of the synthetically most important of all organopalladium reactions, the Heck reaction (10) and a Stille coupling (11). Thus, the palladium-promoted reaction of vinylic bromide **1** with 1-octen-3-one produces the B prostaglandin **2** [Eq. 2] (12).



[2]

This type of coupling can also be efficiently carried out by the palladium--catalyzed Stille coupling of the analogous vinylic iodide **3** and an appropriate vinylic stannane to produce the ethyl ester of PGB_1 in 73% yield [Eq. 3] (13, 14).

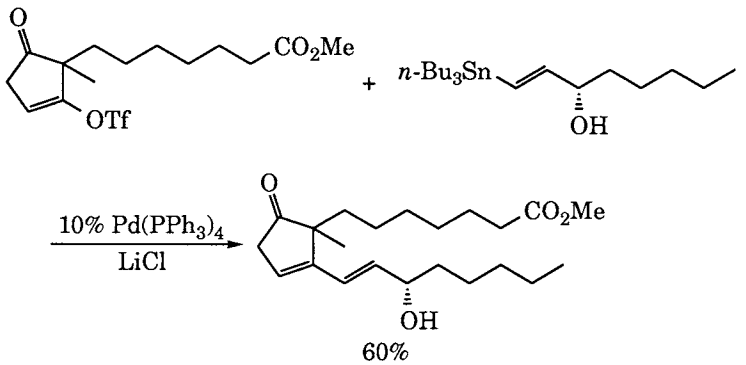


[3]

4 C PROSTAGLANDINS

C Prostaglandins can also be prepared by the Stille coupling of vinylic triflates and vinylic stannanes as illustrated by the synthesis of the methyl ester of

8-methyl-PGC$_1$ [Eq. 4] (14).

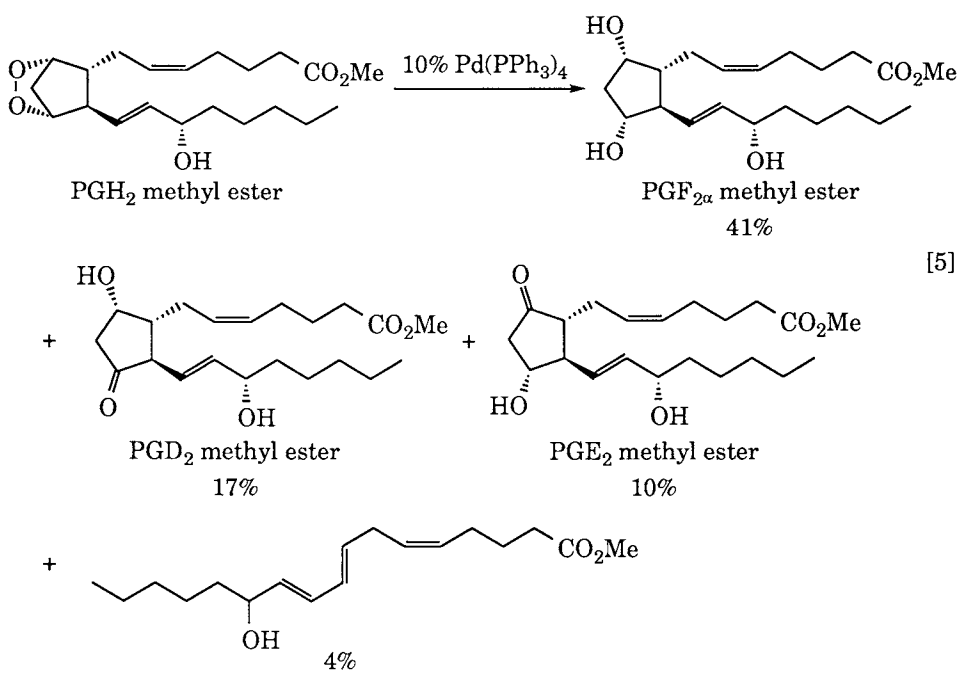


[4]

The palladium-promoted synthesis of an intermediate potentially useful for the synthesis of C prostaglandins will be discussed later in the section on the F prostaglandins.

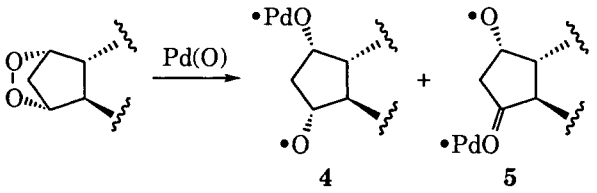
5 D PROSTAGLANDINS

D Prostaglandins have not been produced efficiently using palladium methodology, but they are generated as one of the products of the palladium-catalyzed ring opening of PGH$_2$ methyl ester [Eq. 5] (15, 16). It has been



[5]

postulated that this reaction proceeds by a Pd(O)/Pd(I) redox mechanism involving intermediates such as **4** and **5** [Eq. 6].



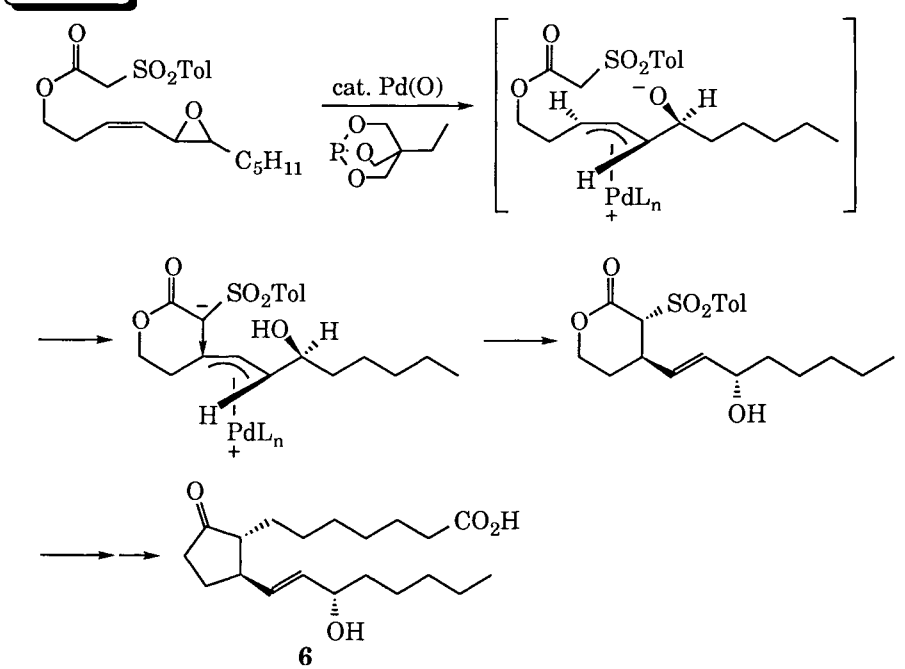
4 **5** [6]

6 E PROSTAGLANDINS

Besides the above-mentioned approach to a mixture of prostaglandins containing PGE_2, E prostaglandins can be prepared by a variety of organopalladium methodologies. π-Allylpalladium chemistry has found widespread utility in organic synthesis (17, 18), and can be employed in several ways to prepare E prostaglandins.

A useful intermediate for the synthesis of 11-deoxy-PGE_1 (**6**) has been prepared (19) by intramolecular attack on a π-allylpalladium intermediate generated by the reaction of a palladium(O) catalyst with a 1,3-diene monoepoxide (20, 21) [Scheme 2]. This reaction proceeds with overall retention of the epoxide stereochemistry by

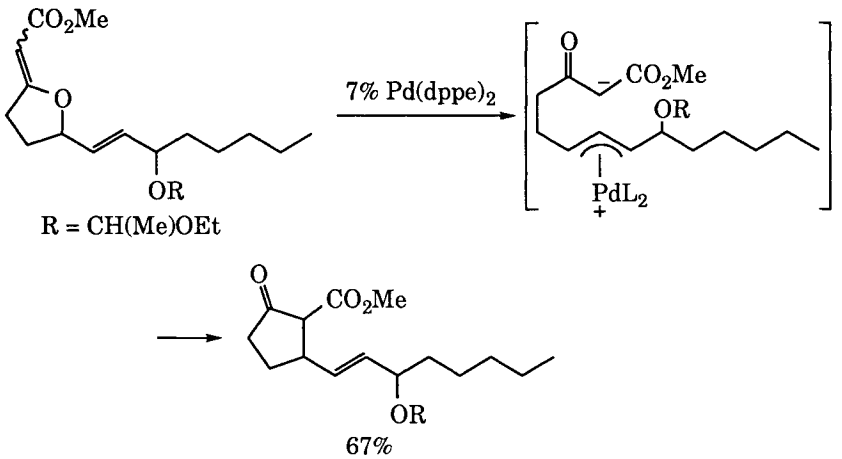
Scheme 2



6

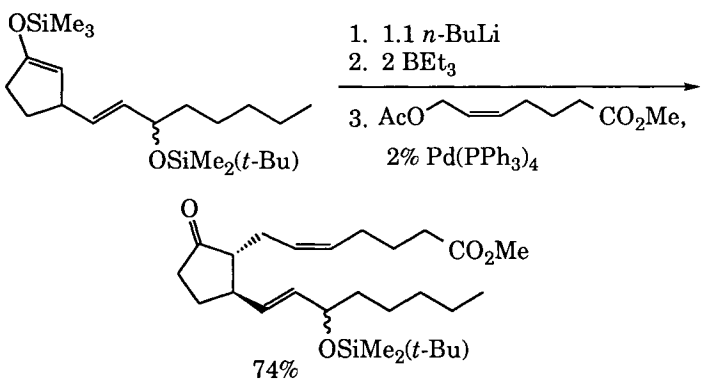
inversion of the epoxide configuration during ring opening and subsequent backside displacement of the palladium from the π-allylpalladium intermediate.

The 11-deoxy-PGE system can also be prepared by a palladium-catalyzed 1,3-oxygen-to-carbon rearrangement, which also proceeds through an intermediate π-allylpalladium species [Eq. 7] (22, 23).



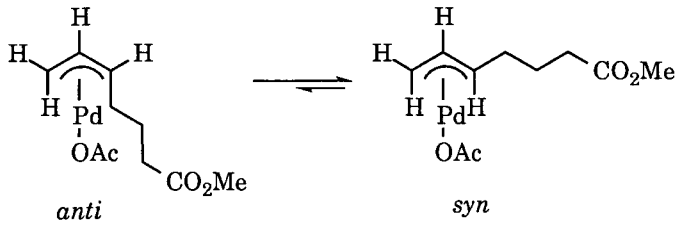
[7]

The ester side chain of 11-deoxy-PGE_2 methyl ester has also been introduced through the coupling of an enol boron intermediate and a π-allylpalladium species derived *in situ* from an allylic acetate and catalytic amounts of $Pd(PPh_3)_4$ [Eq. 8] (24).



[8]

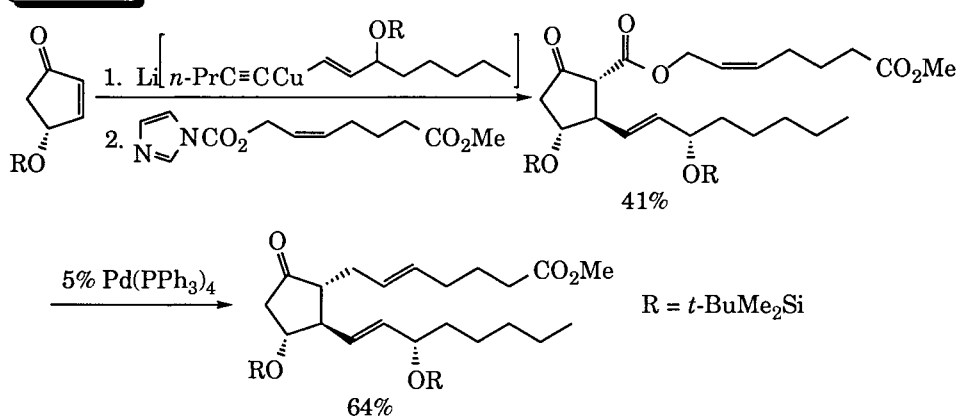
This approach is noteworthy for its high stereo- and regioselectivity. Apparently the intermediate π-allylpalladium species retains its *anti*-stereochemistry throughout this process, resulting in the 5 *Z*-stereochemistry, although such compounds are prone to rapid isomerization to the more stable *syn*-adduct, which would be expected to produce the 5 *E*-isomer [Eq. 9].



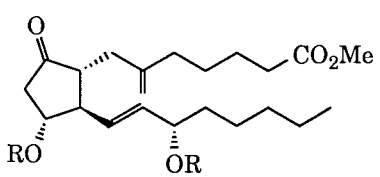
[9]

Related π-allylpalladium intermediates have been utilized to produce (5E)-PGE_2 by palladium-catalyzed decarboxylation of a β-keto ester [Scheme 3] (25,

Scheme 3



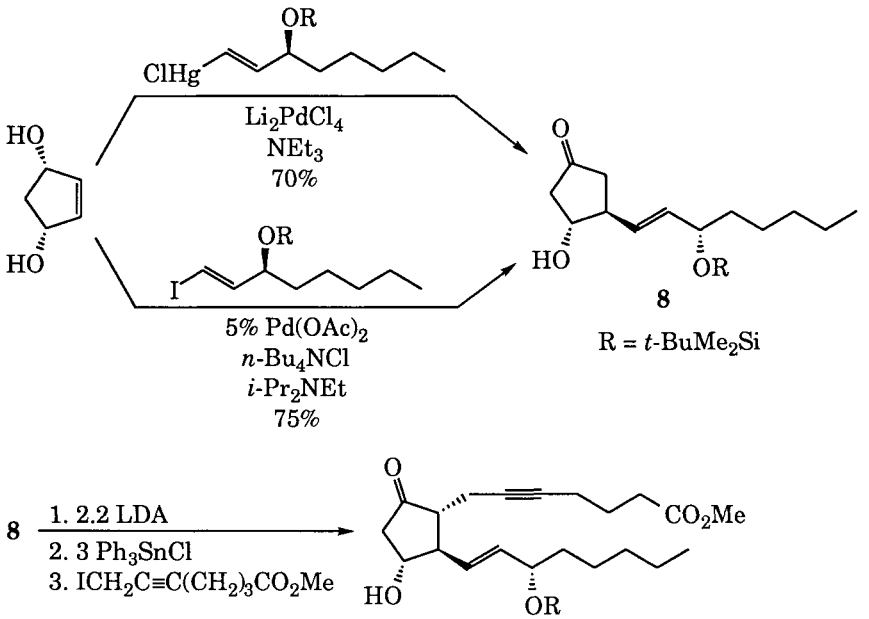
26). Note that in this case complete isomerization of the C5 carbon-carbon double bond is observed. The related 6-methylene PGE_2 ester **7** has been prepared in an analogous manner by this decarboxylative coupling process (26).



7

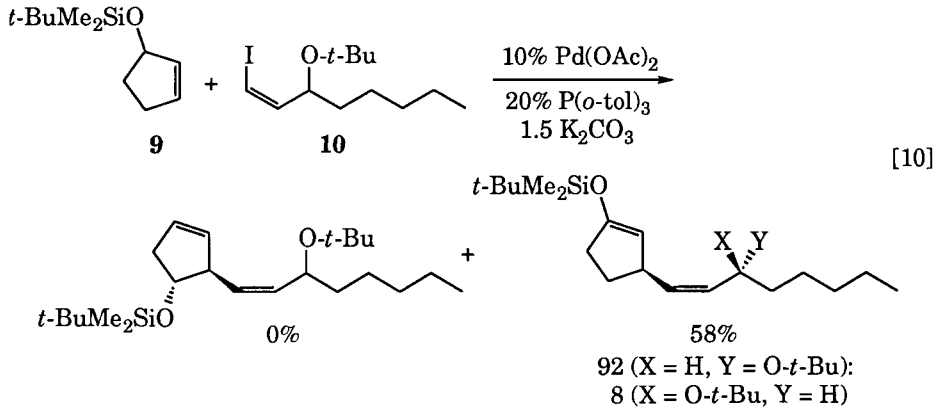
We have very efficiently synthesized PGE_2 by a two step sequence involving (1) vinylpalladation of 4-cyclopentene-1,3-diol, and (2) subsequent regio- and stereoselective alkylation via sequential dianion generation, tin enolate formation, and alkyl halide addition [Scheme 4] (27). Vinylpalladation can be effected using

Scheme 4



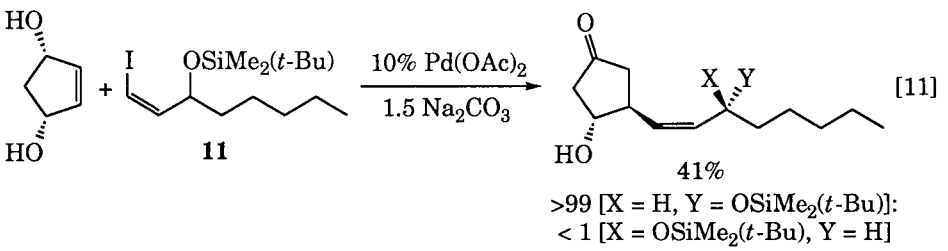
either a vinylic mercurial and stoichiometric amounts of Li_2PdCl_4 or a vinylic iodide and catalytic amounts of $Pd(OAc)_2$. This reaction proceeds by vinylic palladium addition to the less hindered face of the cyclic alkene, followed by palladium hydride beta elimination to an enol, which tautomerizes to the ketol. Unfortunately, this vinylpalladation process using the *E*-vinylic iodide produces a mixture of diastereomers. Subsequent initial alkoxide formation from the β-hydroxyl group of the ketol directs enolate formation and subsequent alkylation in the desired direction to produce an intermediate easily carried on to PGE_2.

The diastereoselectivity of this vinylpalladation process can be dramatically improved by employing the corresponding *Z*-alkenyl iodide (28). Thus, the palladium-catalyzed coupling of cycloalkene **9** and vinylic iodide **10** proceeds with excellent regio- and diastereoselectivity [Eq. 10]. Using 4-cyclopentene-1,3-diol and



[10]

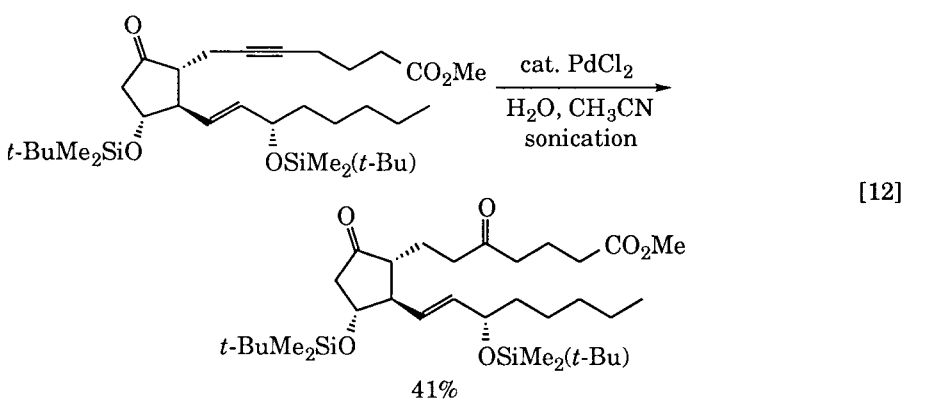
the silyl-protected vinylic iodide **11**, the diastereoselectivity can be increased to greater than 99% [Eq. 11]. When employing an appropriately monoprotected chiral



[11]

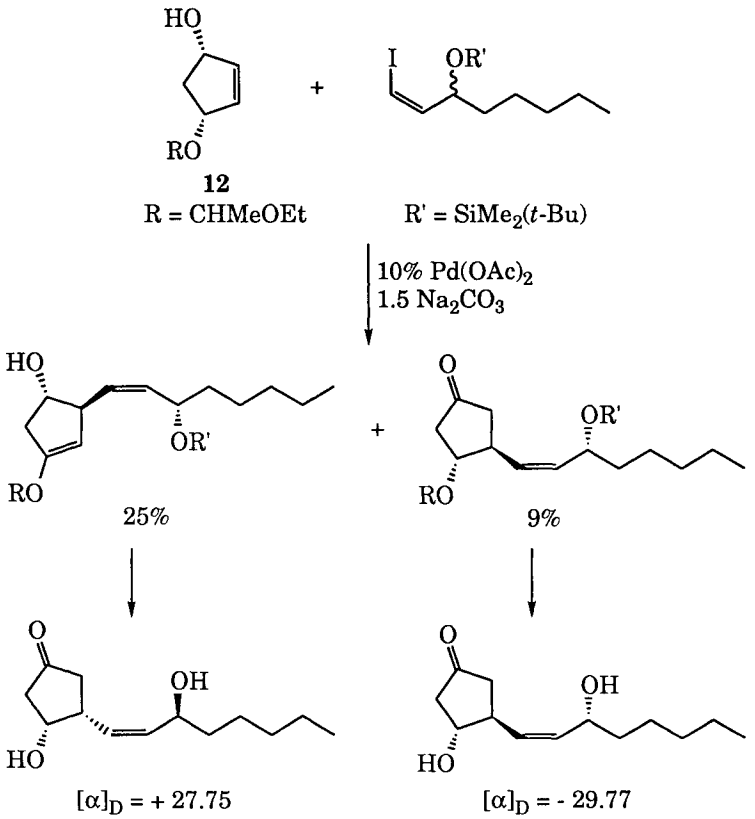
cycloalkenol **12**, the high regio- and diastereoselectivity of this process produces a mixture of products readily hydrolyzed to the two possible antipodes [Scheme 5] (29).

Finally, 5-oxo-PGE_1 derivatives useful as blood platelet aggregation inhibitors have been prepared from the corresponding 5-alkynes by palladium-catalyzed hydration [Eq. 12] (30).



[12]

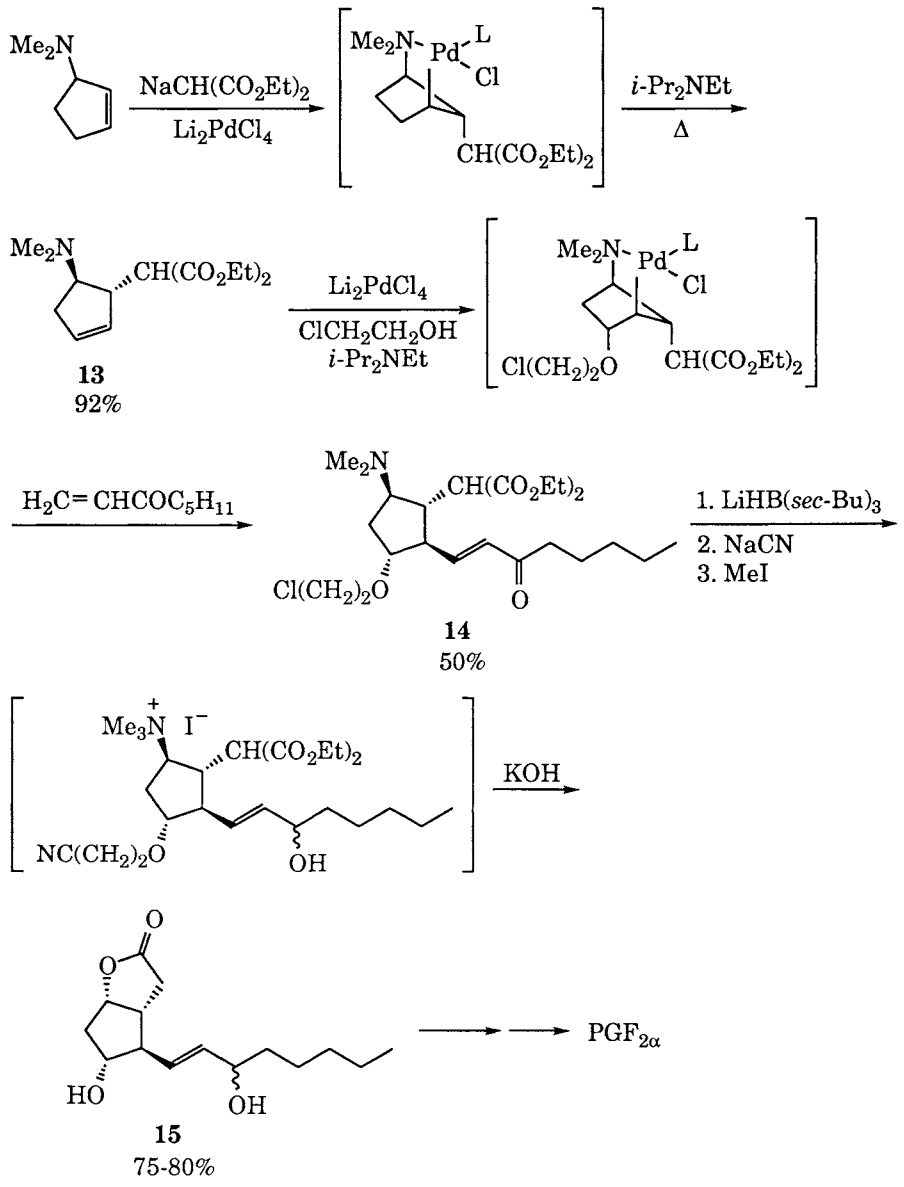
Scheme 5



7 F PROSTAGLANDINS

Several different palladium-based approaches to the F prostaglandins have been reported. One of the earliest and most elegant prostaglandin syntheses employing organopalladium chemistry involved the synthesis of $PGF_{2\alpha}$ via carbopalladation [Scheme 6] (31). Carbopalladation of the allylic amine proceeds in

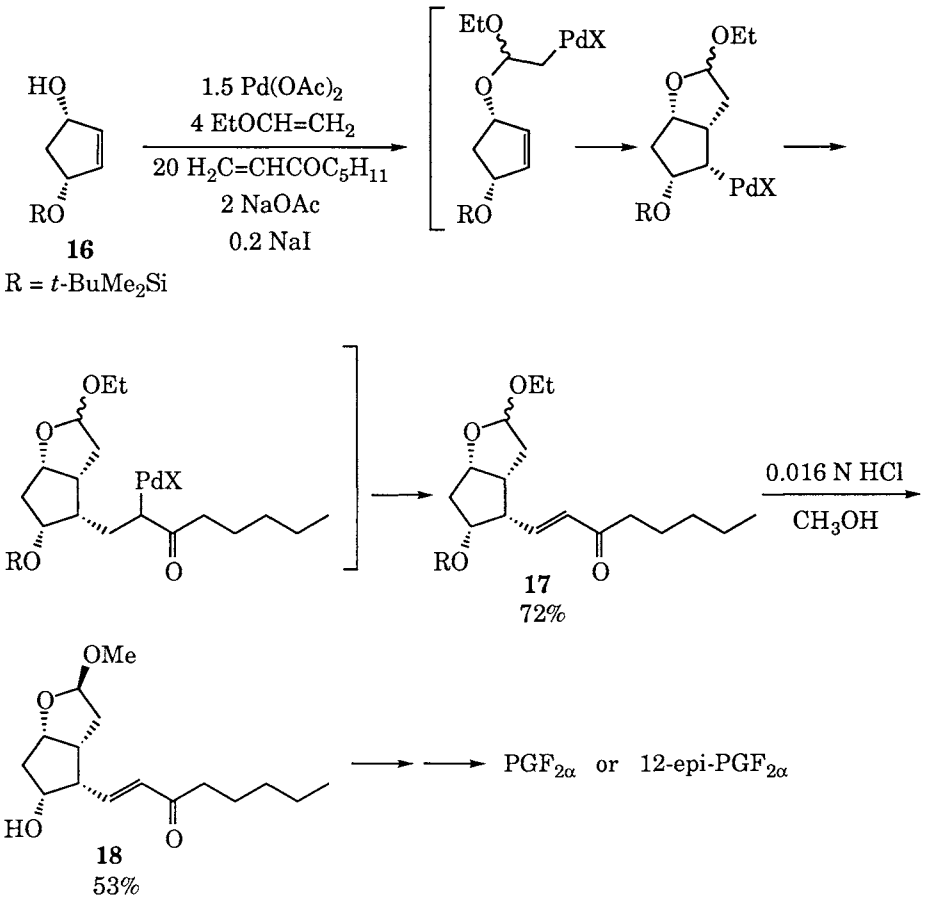
Scheme 6



a *trans* fashion to form an amine-coordinated alkylpalladium intermediate, which can be directed to β-hydride eliminate to alkene **13** by refluxing with *i*-Pr2NEt. Subsequent *trans*-alkoxypalladation and *in situ* coupling with 1-octen-3-one produced the highly functionalized intermediate **14**, which was elaborated to lactone **15**, which is easily converted to $PGF_{2\alpha}$ in two steps and 80% overall yield.

We have recently reported an expeditious synthesis of $PGF_{2\alpha}$ and its 12-epi analogue by a remarkable multiple alkene coupling process [Scheme 7] (32).

Scheme 7

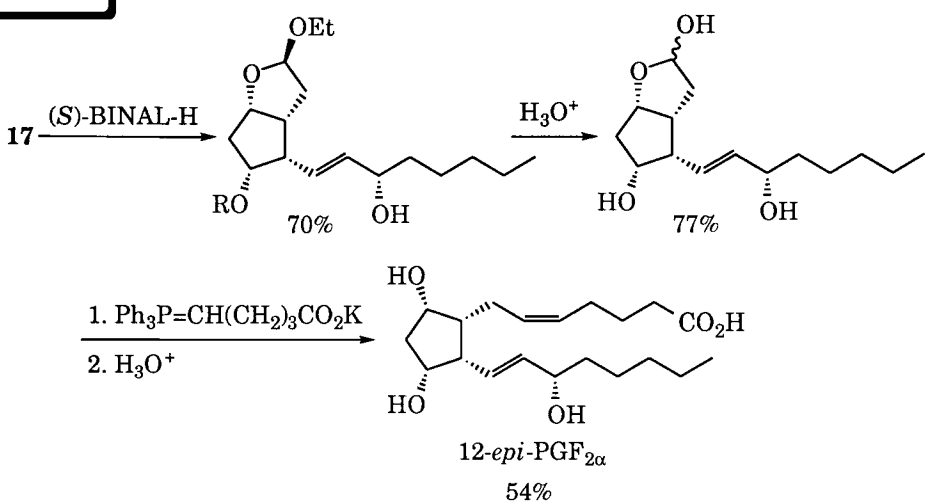


Palladium acetate reacts with the chiral cyclopentenol **16** and the electron-rich alkene ethyl vinyl ether via alkoxypalladation to produce an intermediate organopalladium species which undergoes intramolecular alkene insertion. The resulting bicyclic product is blocked from β-hydride elimination by the neighboring silyloxy group, but undergoes addition to the electron-poor double bond of 1-octen-3-one to generate an intermediate capable of β-hydride elimination. This remarkable, controlled, one-step coupling of three different alkenes produces the versatile prostaglandin intermediate **17** in high yield.

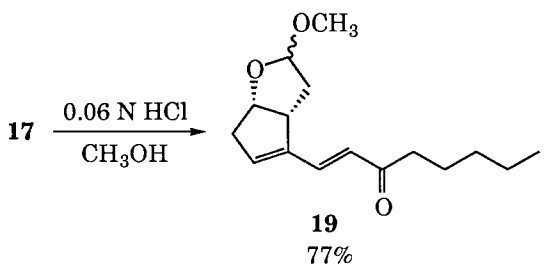
Mild acid *trans*-acetalization produces pure *exo*-acetal **18** which had been prepared previously by a biosynthetic approach and subsequently epimerized and carried on to $PGF_{2\alpha}$ in three routine subsequent steps.

Pure *exo*-enone **17** has also been converted to 12-*epi*-$PGF_{2\alpha}$ by reduction with (*S*)-BINAL-H, acid hydrolysis and Wittig olefination [Scheme 8].

Scheme 8



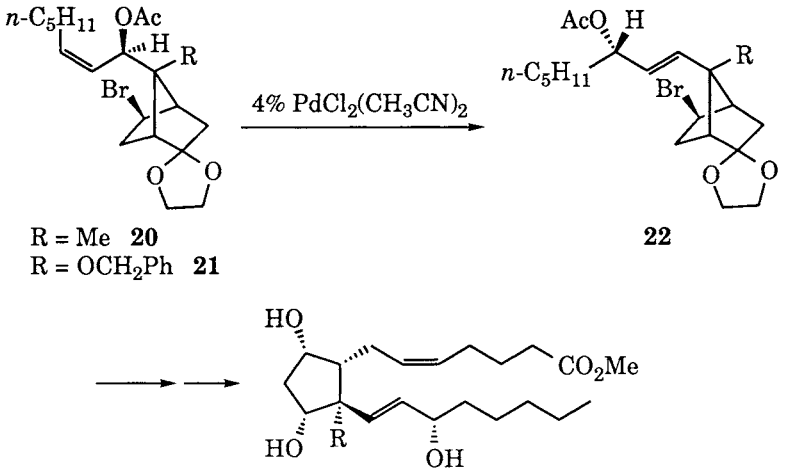
Enone **17** can also be readily converted to dienone **19**, a potentially valuable intermediate for the synthesis of C prostaglandins [Eq. 13].



[13]

The synthesis of 12-substituted $PGF_{2\alpha}$ analogues has taken advantage of another useful palladium-catalyzed reaction, the rearrangement of allylic acetates. The bicyclic derivatives **20** and **21** have been efficiently isomerized to the corresponding allylic acetates **22** upon treatment with 4 mol % $PdCl_2(CH_3CN)_2$ [Scheme 9] (33, 34). This 3,3-sigmatropic rearrangement proceeds with complete

Scheme 9



R = Me **20**
R = OCH_2Ph **21**

22

transfer of chirality and the equilibrium is driven towards **22** by relief of the steric strain present in the bicyclic system due to the bromide and R groups.

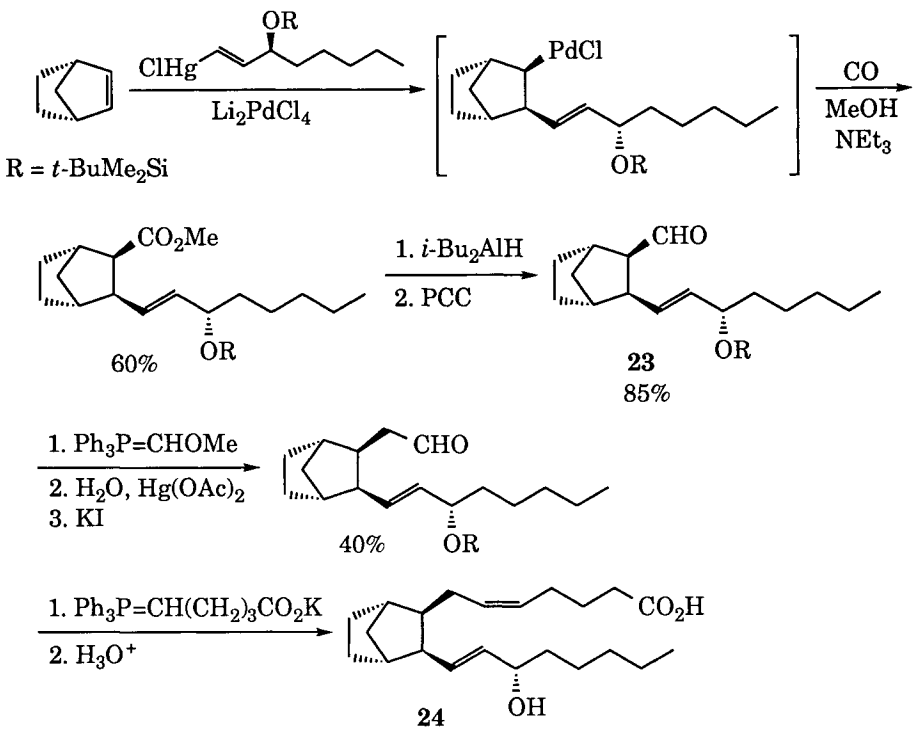
8 H PROSTAGLANDINS

The G and H prostaglandins are relatively unstable due to the presence of the peroxide moiety. It has therefore been attractive to prepare analogues of this system in which the peroxide linkage has been replaced by a more stable group. Organopalladium methodology has been especially useful in preparing a wide variety of PGH analogues, particularly those containing a carbon-carbon single bond or double bond in place of the bicyclic peroxide moiety.

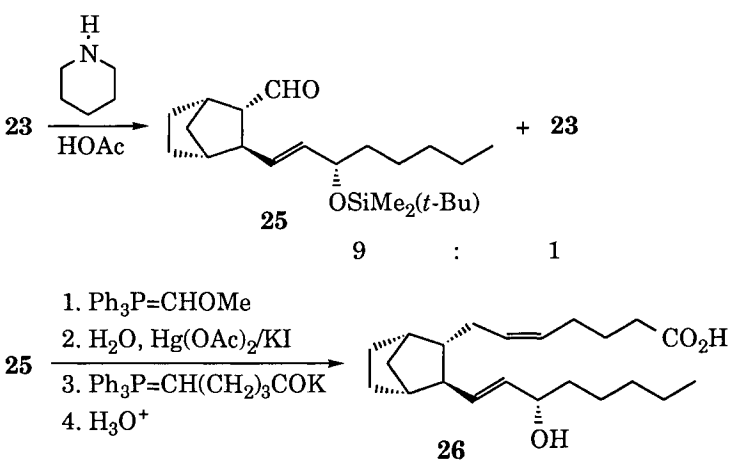
Vinylic palladium addition to norbornene provides a particularly convenient route to PGH analogues [Scheme 10] (35). The *cis-exo* aldehyde **23** can be prepared in good overall yield by (1) vinylpalladation of norbornene, (2) carbonylation, and (3) reduction. Carbonyl homologation and Wittig olefination affords the *cis-exo* PGH analogue **24**.

The key intermediate aldehyde **23** is also useful for the synthesis of a PGH analogue containing the natural stereochemistry [Scheme 11] (35). Epimerization

Scheme 10



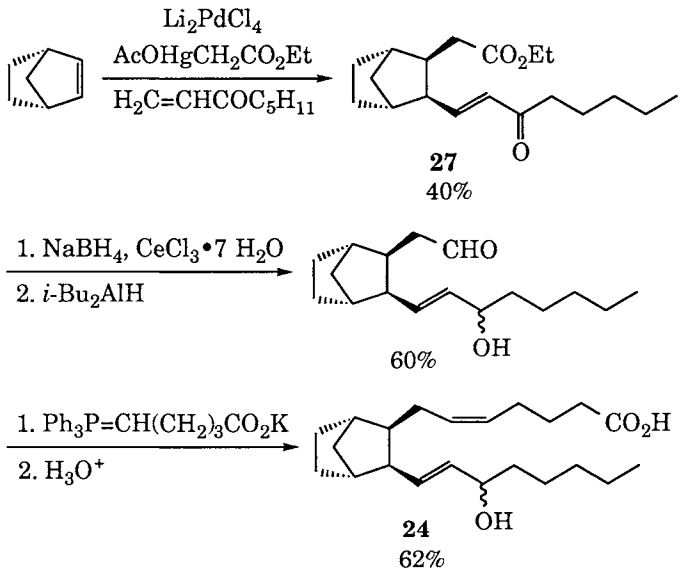
Scheme 11



of aldehyde **23** afforded predominantly *endo*-aldehyde **25**, which was elaborated to PGH analogue **26** in exactly the same fashion as described for aldehyde **23**.

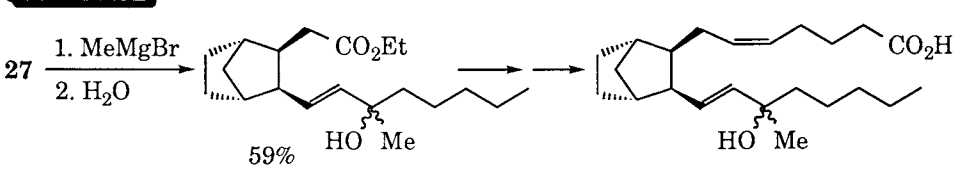
The majority of PGH analogues prepared by organopalladium chemistry have been prepared by introducing the carboxylic acid chain first. For example, compounds such as **24**, can be prepared by the reaction of norbornene, ethyl (acetoxymercurio)acetate, 1-octen-3-one and Li_2PdCl_4 and subsequent elaboration [Scheme 12] (36). This intriguing process for the preparation of **27** obviously

Scheme 12



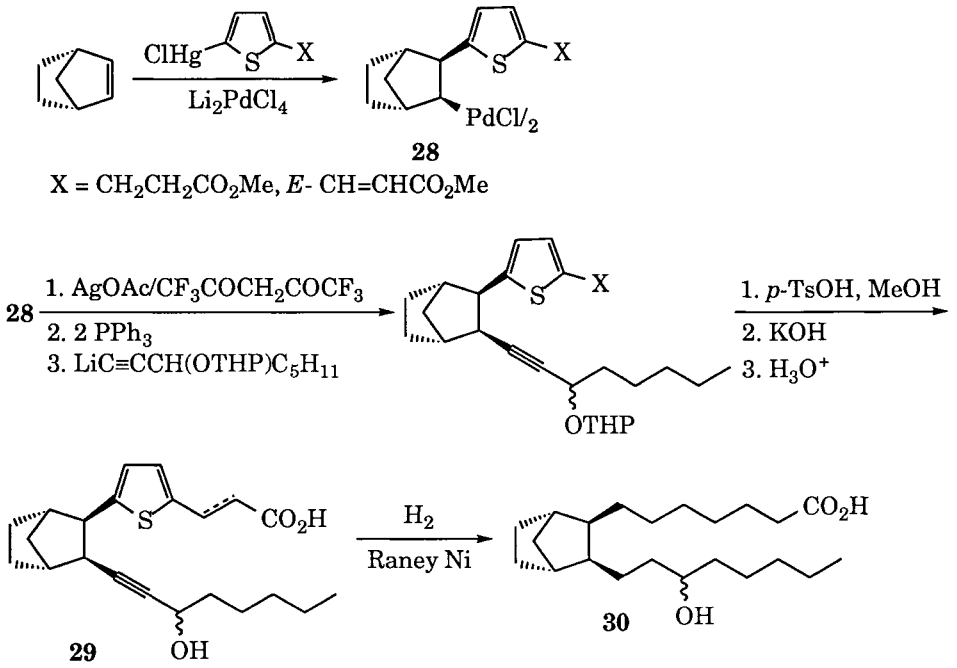
requires sequential insertion of two quite different alkenes. Reduction and Wittig olefination of **27** produced **24**, or alternatively methyl Grignard addition to the enone, plus elaboration as shown below, produced a 15-methyl analogue [Scheme 13].

Scheme 13



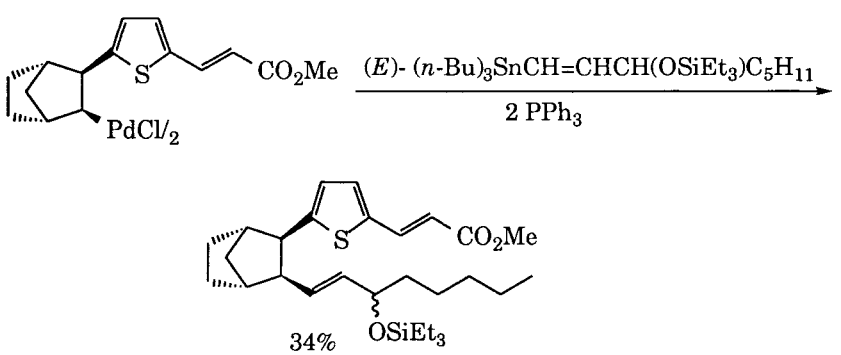
Thienylpalladium intermediates have also been employed to prepare PGH analogues [Scheme 14] (37, 38). The addition of thienylpalladium intermediates to

Scheme 14

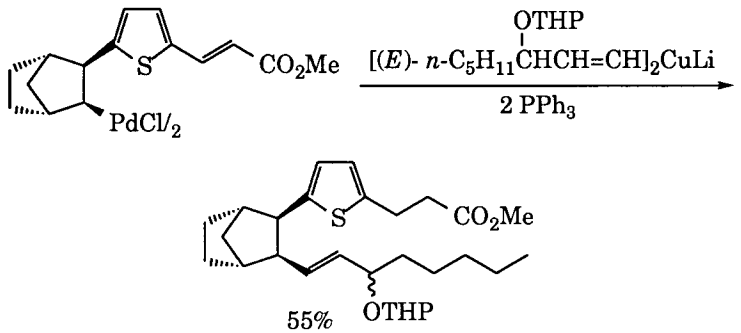


norbornene provides stable adducts **28** in which the palladium moiety is easily displaced by an acetylide. Deprotection of the alcohol group and saponification provides the interesting PGH analogues **29**, the olefinic analogue of which has been hydrogenated over Raney nickel to produce the saturated PGH analogue **30**.

PGH analogues bearing an allylic alcohol moiety, rather than the alkynol functionality, can be prepared by cross-coupling the bicyclic palladium intermediates with vinylic stannanes [Eq. 14] or cuprates [Eq. 15]. Since the yields



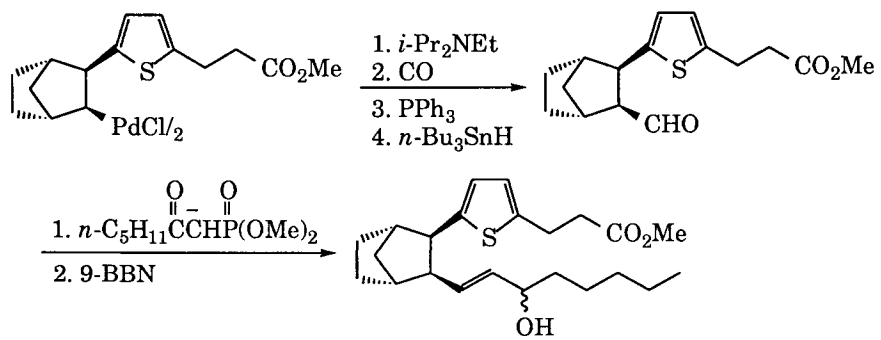
[14]



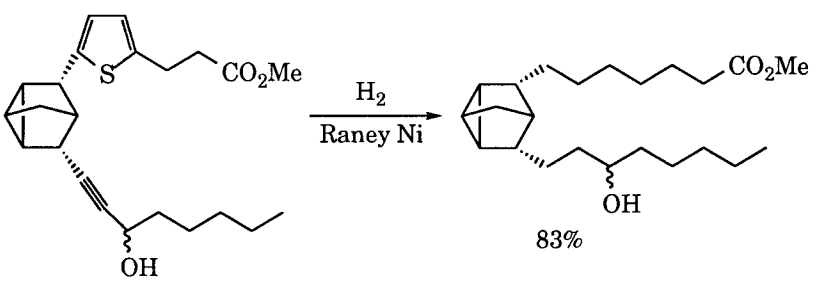
[15]

are relatively low, however, an alternative carbonylation approach has been developed [Scheme 15]. The overall yield of this sequence is 82%.

Scheme 15

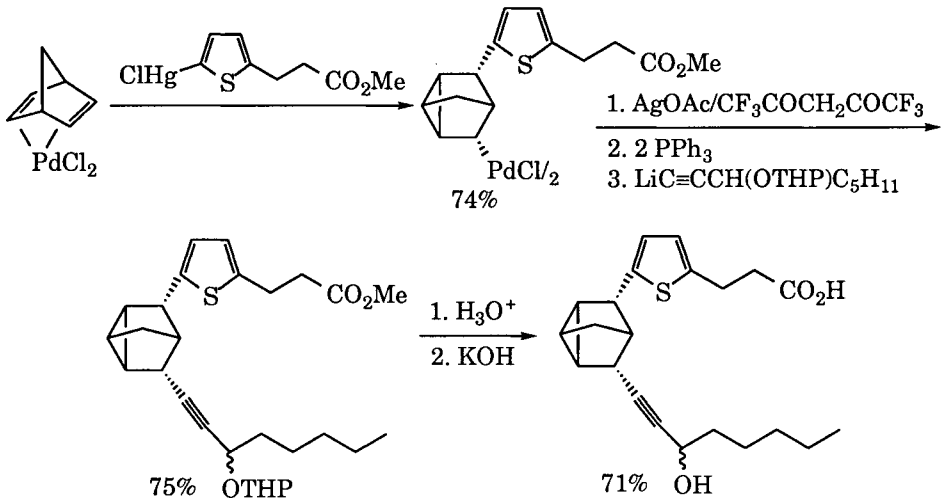


Analogous chemistry carried out on norbornadiene produces tricyclic PGH analogues [Scheme 16] (37, 38). Hydrogenation over Raney nickel produced the first tricyclic prostanoic acid derivative [Eq. 16].

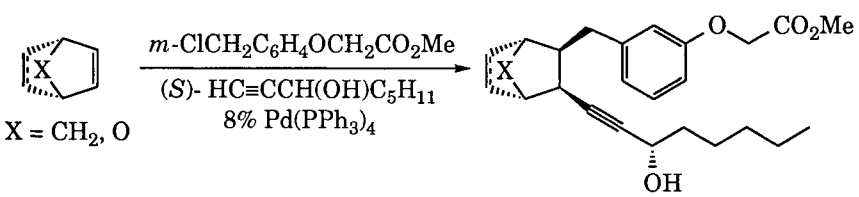


[16]

Scheme 16



Interphenylene analogues of PGH have been prepared by benzylpalladation of bicyclic alkenes [Eq. 17] (39, 40). By directly reacting norbornene, 7-oxanorbornene

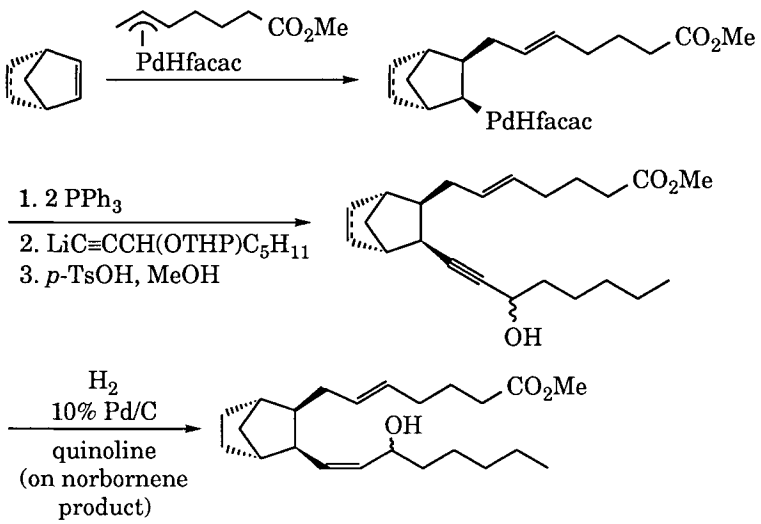


[17]

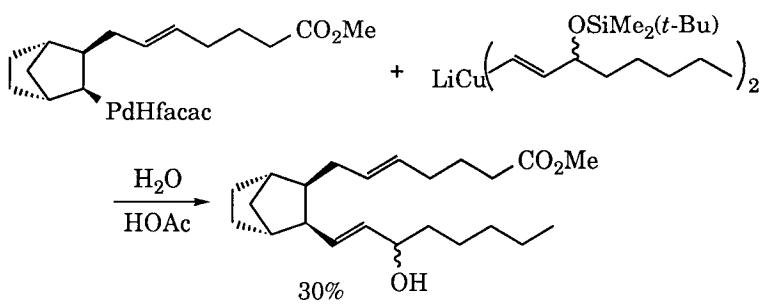
or norbornadiene with the appropriate benzylic chloride, alkynol and palladium(O) catalyst, one can prepare in one step in 58%, 34% and 37% yields, respectively, the desired *cis-exo* bicyclic products, as mixtures of the two possible diastereomers.

π-Allylpalladium compounds will also add to norbornene and norbornadiene to produce bicyclic palladium compounds easily elaborated to PGH analogues [Scheme 17] (41). π-Allylpalladium chlorides do not react directly with these bicyclic alkenes,

Scheme 17



but the corresponding hexafluoroacetylacetonate derivatives are easily prepared and add readily in a *cis-exo* manner to both norbornene and norbornadiene. Acetylide displacement as discussed previously provides an expeditious route to PGH analogues bearing a *trans* double bond in the 5 position. Subsequent hydrogenation of the alkyne moiety produces the corresponding *Z*-allylic alcohol. The *E*-allylic alcohol can be prepared by direct reaction of the bicyclic palladium intermediate with a vinylic cuprate, although the yield is low [Eq. 18].

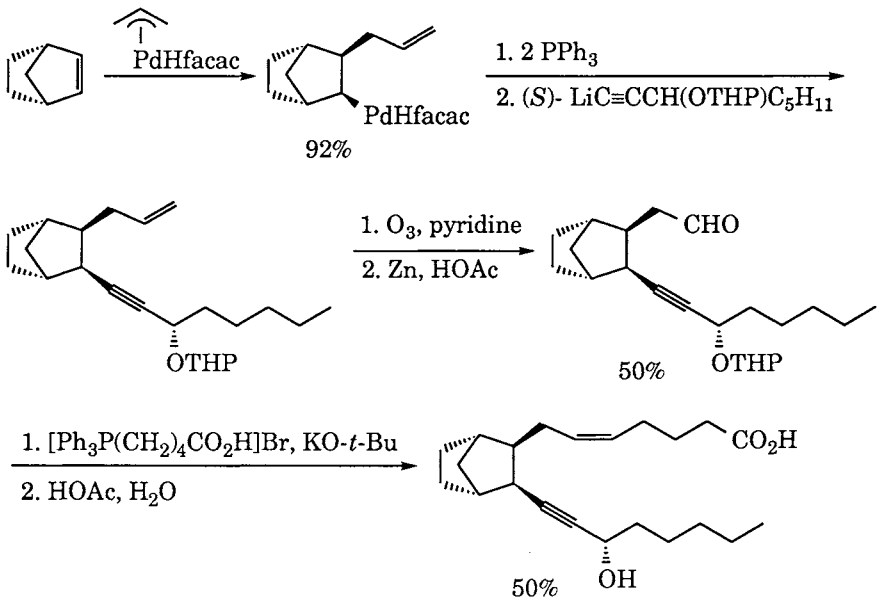


[18]

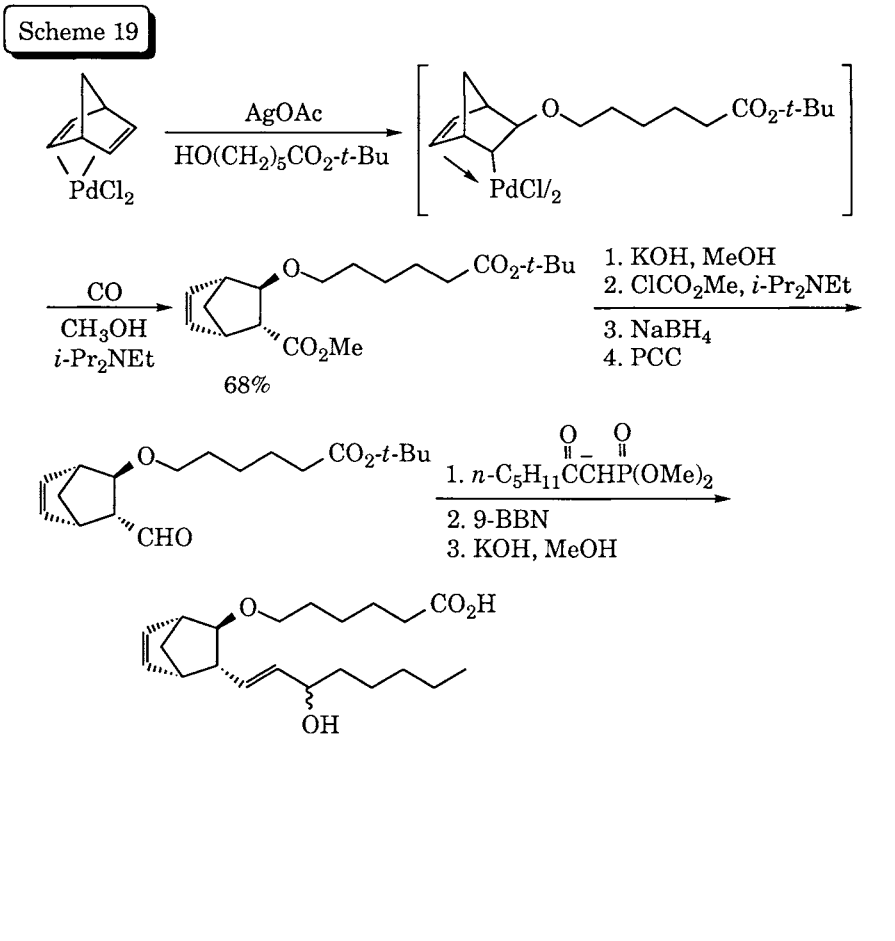
If one desires PGH analogues with a *cis* double bond in the carboxylic acid side chain, one can modify the above π-allylpalladium approach [Scheme 18] (42). The key reaction here is the selective ozonolysis of the enyne.

Bicyclic 7-oxa-PGH analogues have also been prepared by alkoxypalladation of norbornadiene [Scheme 19] (43). The norbornadiene adduct of palladium chloride is

Scheme 18



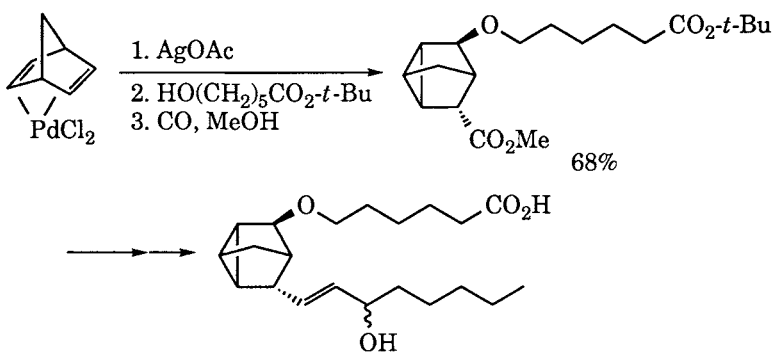
Scheme 19



activated to alkoxypalladation by treatment with silver acetate producing a relatively unstable bicyclic palladium intermediate which undergoes carbonylation *in the presence of an organic amine* to generate a bicyclic diester. Selective saponification, reduction to an alcohol, oxidation to an aldehyde, phosphonate coupling and enone reduction produces the 7-oxa bicyclic PGH analogue.

If the organic amine is omitted from the carbonylation step, a tricyclic intermediate is produced, which can be similarly elaborated to a tricyclic 7-oxa-PGH analogue in 24% overall yield [Scheme 20].

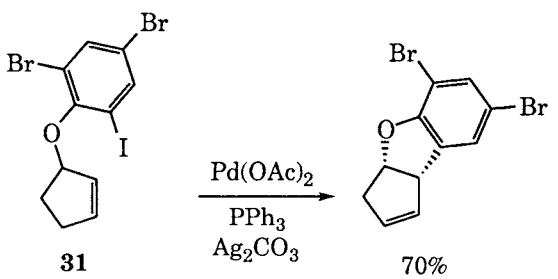
Scheme 20



9 I PROSTAGLANDINS

The I prostaglandins, otherwise known as prostacyclins, can also be prepared via organopalladium methodology. Analogues of PGI_2 (prostacyclin) in which the relatively unstable vinylic ether group is substituted by more stable functionality are pharmacologically very attractive.

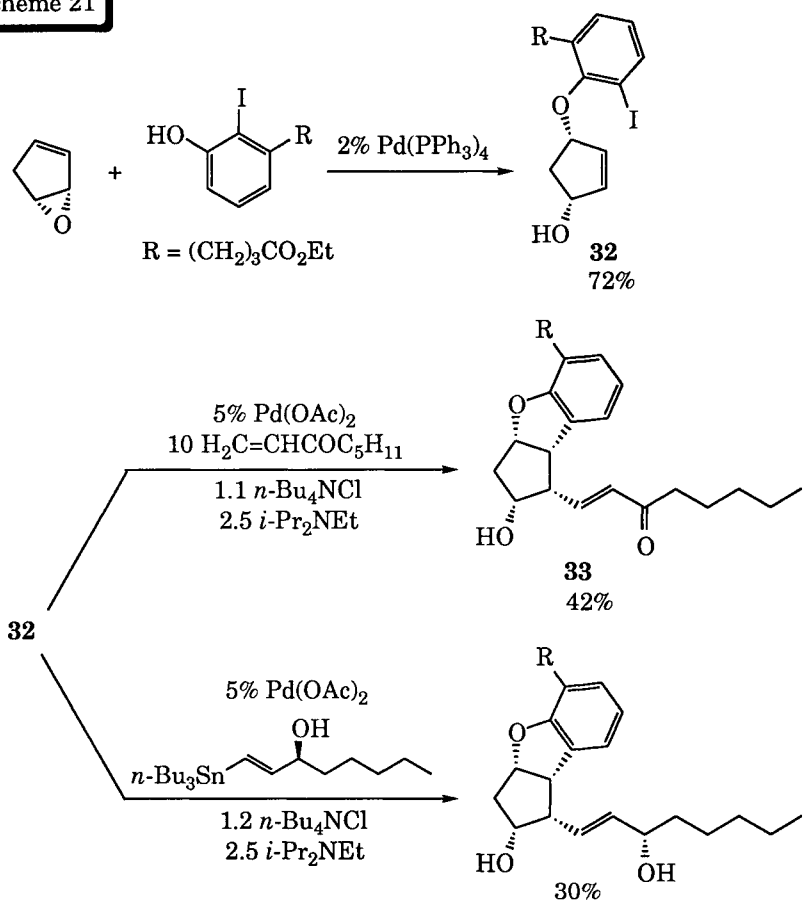
The parent ring system of benzoprostacyclins has been prepared by palladium-catalyzed cyclization of aryl iodide **31** [Eq. 19] (44).



[19]

We have developed a very efficient synthesis of benzoprostacyclins employing organopalladium methodology [Scheme 21] (45). The key intermediate **32** is

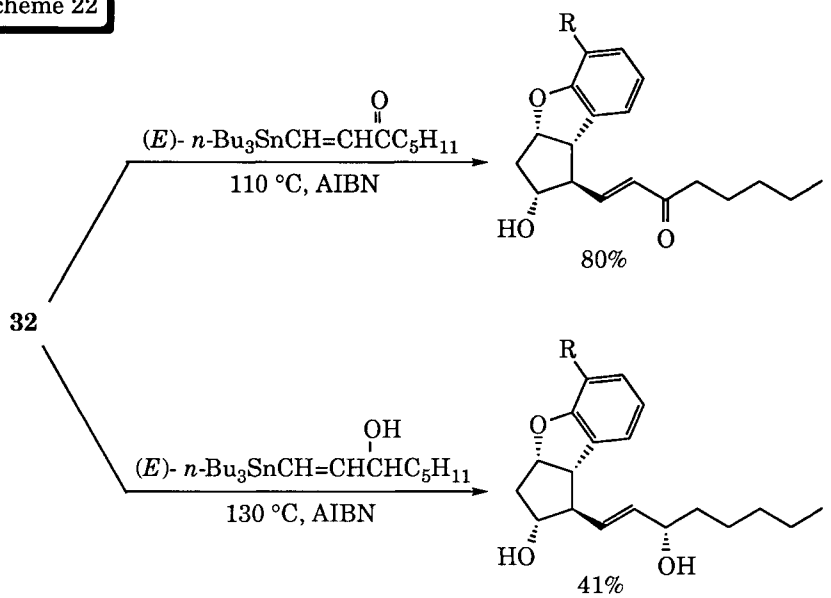
Scheme 21



efficiently prepared by the palladium(O)-catalyzed ring-opening of cyclopentadiene monoepoxide (20, 21). Palladium(O)-catalyzed tandem alkene insertion of compound **32** with 1-octen-3-one produces the all-*cis* enone benzoprostacyclin analogue **33**. Subsequent reduction of **33** with (*S*)-BINAL-H proved surprisingly unselective, affording a 1:1 mixture of diastereomers. Alternatively, the stereochemical problem can be solved by employing a chiral vinylic stannane, although the yield is low [Scheme 21].

This approach to benzoprostacyclins is very versatile. Free-radical cyclization of intermediate **32** in the presence of an appropriate vinylic stannane produces benzoprostacyclins with the stereochemistry present in PGI_2 itself [Scheme 22].

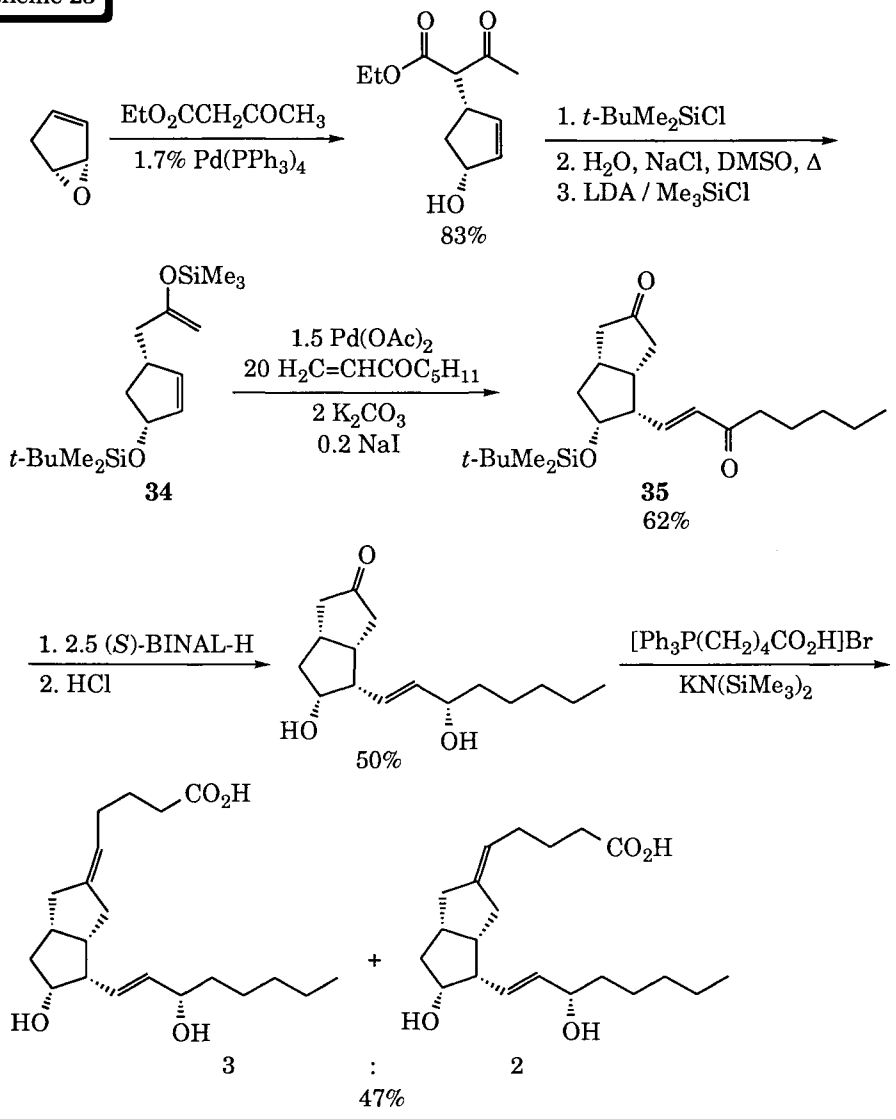
Scheme 22



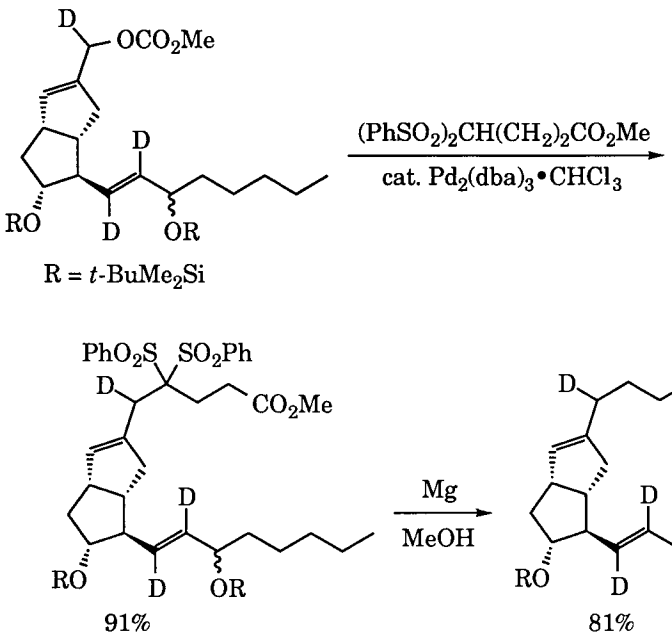
Carbon analogues of prostacyclin, known as carbacyclins, can also be prepared by organopalladium methodology similar to that just described [Scheme 23] (46). The key intermediate **34** is once again synthesized by the palladium-catalyzed opening of cyclopentadiene monoepoxide, followed by silylation, decarboalkoxylation, and enol silane formation. Sequential coupling of three different double bonds is effected in one step using an excess of palladium acetate. The all-*cis* diketone **35** is produced in 62% yield. The two different carbonyl groups could be differentiated (9:1 chemoselectivity) by chiral reduction using an excess of (*S*)-BINAL-H. Wittig olefination produced a 3:2 mixture of C-5 stereoisomeric all-*cis* carbacyclins.

π-Allylpalladium intermediates have been employed in the synthesis of isocarbacyclins. The carbonyl-containing side chain of an isocarbacyclin has been introduced by the palladium-catalyzed cross-coupling of an allylic carbonate and a disulfone [Scheme 24] (47). Isocarbacyclins can also be prepared by analogous

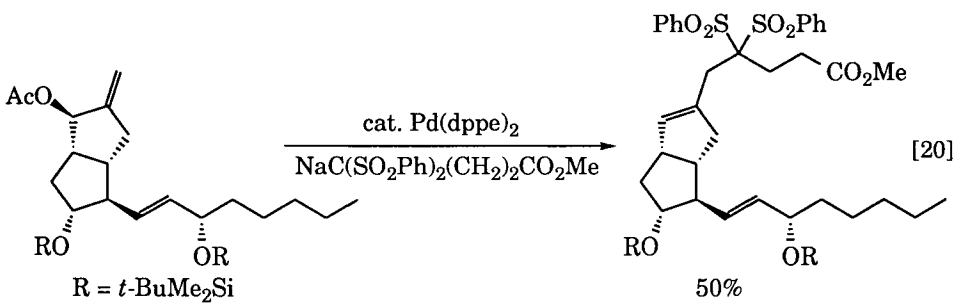
Scheme 23


EtO2CCH2COCH3
1.7% Pd(PPh3)4
1. t-BuMe2SiCl
2. H2O, NaCl, DMSO, Δ
3. LDA / Me3SiCl
83%
1.5 Pd(OAc)2
20 H2C=CHCOC5H11
2 K2CO3
0.2 NaI
34
35
62%
1. 2.5 (S)-BINAL-H
2. HCl
50%
[Ph3P(CH2)4CO2H]Br
KN(SiMe3)2
3 : 2
47%

Scheme 24

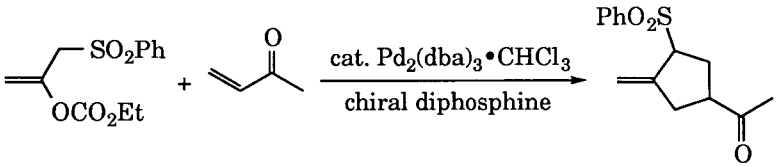


chemistry using an isomeric allylic acetate and the sodium salt of a disulfone [Eq. 20] (48).



10 MISCELLANEOUS PROSTAGLANDINS

Organopalladium methodology has been suggested to be useful in several other aspects of prostaglandin chemistry. Optically active cyclopentane derivatives of potential utility for prostaglandin synthesis have been prepared by asymmetric palladium-catalyzed cycloaddition [Eq. 21] (49).

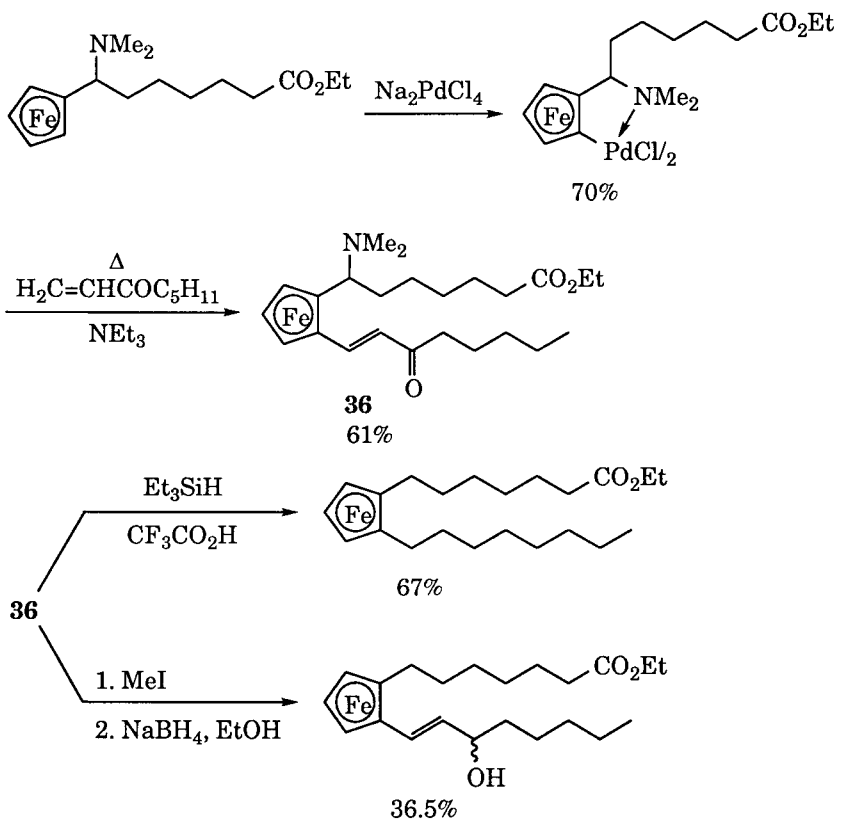


[21]

1*R*, 3*S* (75% ee)
plus 1 *R*, 3*R* (78% ee)

Finally, a ferrocene analogue **36** of prostaglandins has been prepared by *ortho*-palladation of an aminoferrocene and a subsequent Heck reaction with 1-octen-3-one [Scheme 25] (50, 51). Hydrogenolysis or reduction affords further derivatives.

Scheme 25



11 CONCLUSION

Prostaglandins or analogues of prostaglandins A, B, C, D, E, F, H and I have been prepared via organopalladium intermediates. Most useful of the palladium reactions are (1) the carbopalladation of cyclic, monocyclic and bicyclic alkenes, (2) the Heck reaction of vinylic halides or orthopalladation products and enones, (3) the Stille coupling of vinylic halides or triflates and vinylic stannanes, (4) the nucleophilic displacement of π-allylpalladium intermediates, and (5) the opening of epoxides and peroxides by palladium(O).

ACKNOWLEDGMENTS

The author would like to thank all the students in his research group over the years who have contributed to our efforts in developing new organopalladium approaches to prostaglandins. Most of them are cited in the references to our work which follow. We would also like to thank the National Institutes of Health and the American Heart Association - Iowa Affiliate for financially supporting our prostaglandin work and Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. for generous gifts of palladium salts.

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Atta-ur-Rahman (Ed.) *Studies in Natural Products Chemistry, Vol. 16*

Transition Metal Organometallic Methods for the Synthesis of Amino Acids

G. Richard Stephenson

1. INTRODUCTION

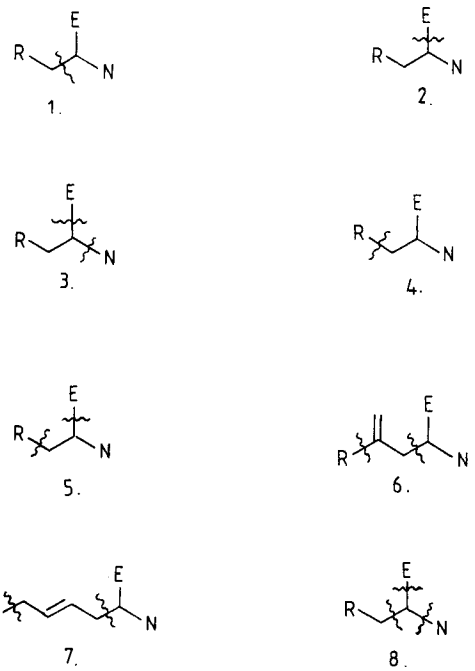
1.1 Synthetic Strategies Using Transition Metals

Transition metals impart unusual reactivity properties on organic ligands, and so can offer a wide selection of bond-forming methodologies for use in organic synthesis. Because the transition metal provides activation, these reactions are often complementary to conventional organic procedures, and so give useful alternatives in synthesis design. The principles are straight forward. An organic building block (the *working ligand*) is attached to a transition metal which typically also carries other ligands (*auxiliary ligands*) on which the stability and reactivity properties of the complex depends. Variation of auxiliary ligands thus provides a way to fine-tune the reactivity of the system, without compromising on the structure of the organic building block in the working ligand. Different classes of working ligand offer different types of bond-forming processes, depending on the nature of attachment of the ligand to the transition metal centre. Some structures can provide exceptionally powerful electrophiles, while others offer opportunities for carbonyl insertion or related coupling (ligand transfer) reactions. Transition metals can also stabilise negative charge, so nucleophilic reagents are also possible.

1.2 Organometallic Disconnections for Amino Acid Synthesis

In the context of amino acid synthesis, consideration of these possibilities reveals a variety of classes of disconnections, ranging from conceptually simple approaches (e.g. **1**) in which a pre-formed amino acid head-group is incorporated into the target structure, to more complicated systems (**2**,**3**) where metal-mediated reactions form one or both of the bonds that connect the carboxylic acid and amine units to the α carbon of the amino acid. Homologues (e.g. **4**) to the pre-formed head-group unit, are also available. Combinations of these strategies can provide versatile bond-formation sequences. Examples include **5**

which combines substitution at the β carbon with the introduction of the ester, **6** (and **7**), in which a head-group unit is combined in a two (and four) atom chain extension with addition of a substituent at the γ carbon, and **8** where all three bonds within the head group are formed by organotransition metal chemistry. These possibilities provide a wide selection of bond-forming processes which are summarised in Scheme 1 and Table 1.



Scheme 1

The most direct strategy is the introduction of pre-formed head-group units. Head-groups can be nucleophiles in reactions with organometallic electrophiles (see Section 2), or, in a less common alternative system, the head-group is bound to a metal centre as the working ligand for use as the electrophile in reaction with nucleophiles (see Section 3). Palladium catalysed coupling can also be used. When the head-group is built during the transition metal mediated sequence, carbonylation reactions offer good strategy. In some cases, the carbon-nitrogen bond attaching the amine unit can also be introduced in the same process. The Hedgedus approach using carbene complexes (see Section 4), and the Wakamatsu/Ojima/Izawa amidocarbonylation (see Section 5) are particularly versatile in this regard.

Combinations of metal-mediated steps offer synthetic routes where transition metal chemistry takes on a central role in the design process.

TABLE 1
Organotransition metal reactions corresponding to disconnections shown in Scheme 1

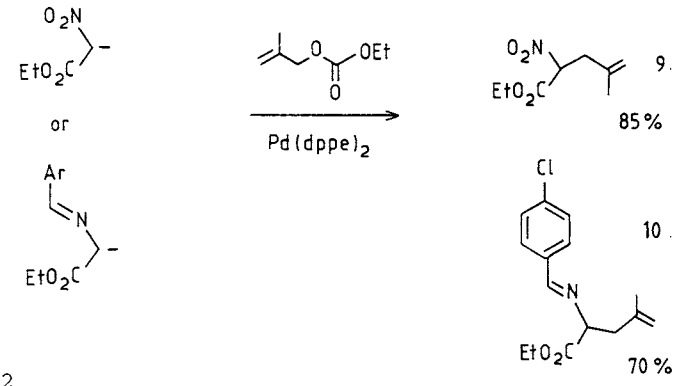
Disconnection	Examples of bond-formation process
1	Scheme 2, 4, 5[a], 6[a], 7, 9, 14, 17, 18, 19[a], 20[a], 21[a], 22[a], 23, 27
2	Scheme 29, 31, 35
3	Scheme 32, 34
4	Scheme 11, 13, 15, 16, 28, 41
5	Scheme 30
6	Scheme 8
7	Scheme 10
8	Scheme 33, 36

a: Denotes enantioselective example

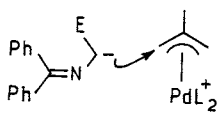
2. HEAD-GROUP ANIONS WITH ORGANOMETALLIC ELECTROPHILES

2.1 Nitroester and Schiff base nucleophiles

Nitroester enolates and Schiff base nucleophiles are typical head-group anions, though recently, homologous serine-derived zinc-copper reagents have extended the scope of the head-group anion approach with organometallic electrophiles. Much work at first has been done with palladium π-allyl complexes as intermediates in palladium catalysed allylic displacement reactions. Both nitroester enolates (1) and the Schiff base nucleophiles (2) are known to work well in these allylic displacements (Scheme 2). The products **9** and **10** are typical adducts. A key step is reaction of the enolate as a nucleophile with the electrophilic allyl complex **11** which arises by displacement of the allylic leaving group by palladium (Scheme 3). Recent examples (3) from the Genet group illustrate allylation routes to amino acids, and related phosphonic acid analogues **12** (Scheme 4).

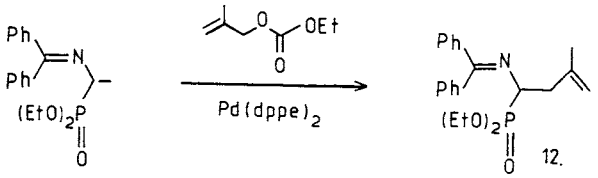


Scheme 2



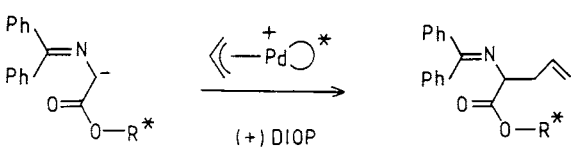
11.

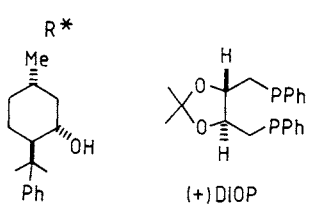
Scheme 3



12.

Scheme 4

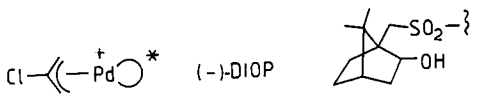




13. (+) DIOP 14.

Scheme 5

Palladium catalysed processes show the greatest advantage in the search for enantioselective routes. The chiral centre in the head-group is formed from a prochiral moiety in the nucleophile. Asymmetric induction can be approached by the use of chiral auxiliaries in the nucleophile, or chiral auxiliary ligands at palladium. Taken together (Scheme 5), this allows double stereodifferentiation to be brought into play to optimise the process by seeking out matched interactions between **13** and **14** (4). In a similar way, the chloroallyl complex (15) and the matched pair of auxiliaries (16) and (17) afford an adduct in 99% d.e. and 80% yield (Scheme 6).

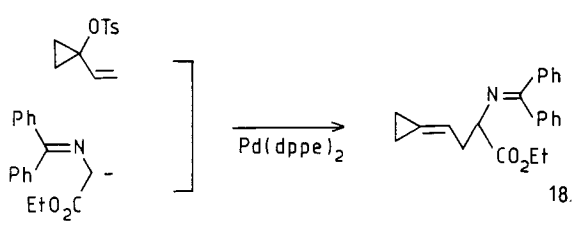


15. 16. 17.

Scheme 6

2.2 Other Types of Nucleophile

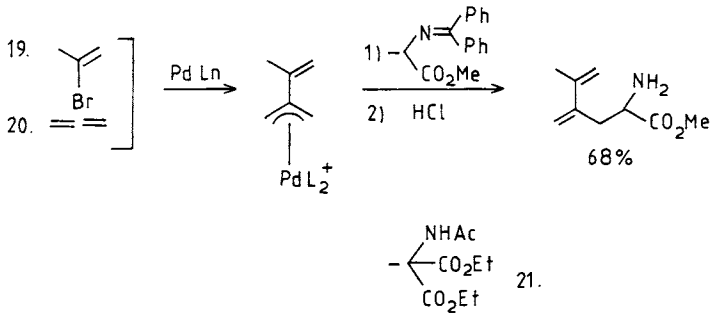
A further attraction to this route to amino acids is the possibility to build unusual functionalised systems (Schemes 7, 8). A nice example (5) gives access to interesting alkylidenylcyclopropane-substituted amino acids **18**, by reorganisation of the position of the alkene in vinyl-substituted cyclopropyl alcohols **17.**



18.

Scheme 7

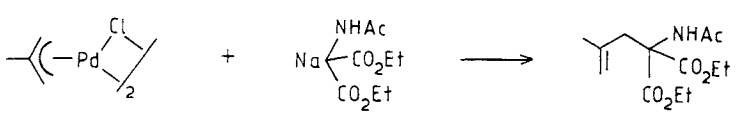
Combination of Schiff base nucleophile addition with another palladium-mediated process can offer a more extensive disconnection (6). Coupling of a vinyl or aryl halide **19** to an allene **20** is an interesting starting point. In this work, an amine-substituted diester enolate **21** has been employed. Nucleophiles of this type have also been used with stoichiometric



21.

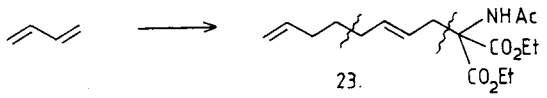
Scheme 8

palladium allyl complexes **22** (Scheme 9) and in a second palladium-catalysed two step process (Scheme 10) in which butadiene oligomerisation is combined with nucleophile addition to form the 2-aminodecanoate derivative **23** (7). Palladium catalysed Heck-type coupling offers the chance (Scheme 11) to introduce a head-group homologue in the form of a methylene derivative of a protected amino acid (8). Aryl halides are typical coupling partners, being easily activated by the transition metal by oxidative addition. π-Coordination to the C-C double bond to the methylene group is then followed by aryl transfer and loss of the metal by reductive elimination, re-forming the alkene linkage. Compared to conventional conjugate addition, the advantage of Heck coupling is that the alkene is retained in the product **24** for use in subsequent synthetic steps. The substitution pattern in the substrates is not crucial to the success of the palladium catalysed bond-formation; cross coupling in the case of **15** (9) gives precursors to β amino acids (Scheme 12). Chiral head-group homologue building blocks can also be introduced by means of serine-derived nucleophiles **26** developed by Jackson's group. These can be combined with electrophiles such as acid chlorides and allyl halides by palladium catalysis (Scheme 13) to give optically pure products (10).

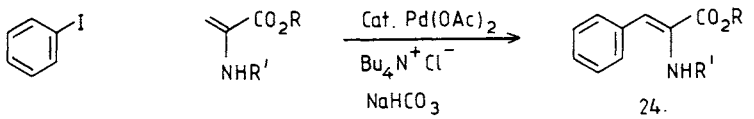


22.

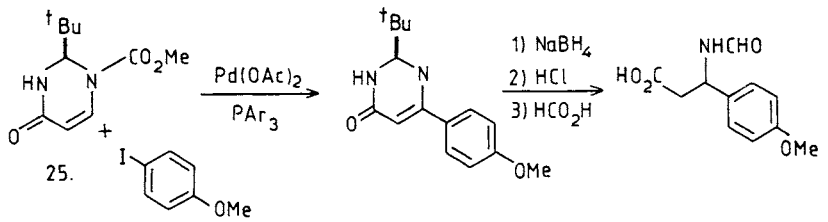
Scheme 9



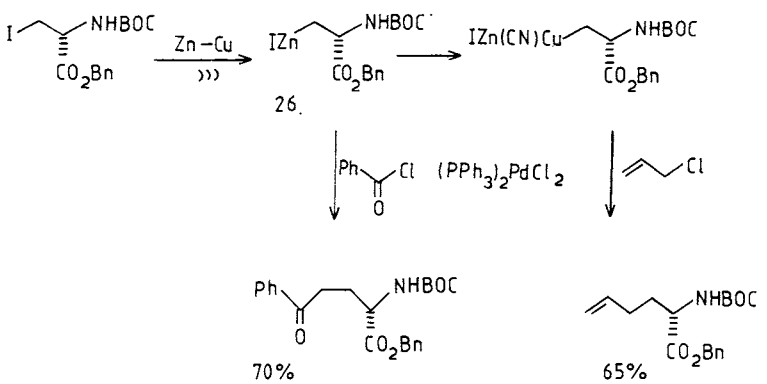
Scheme 10



Scheme 11



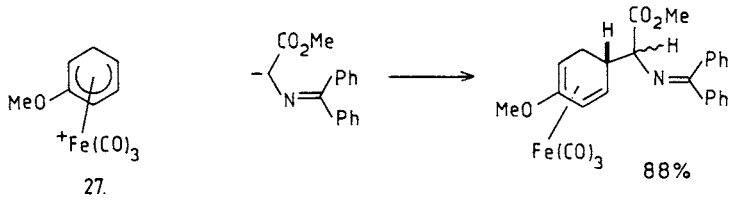
Scheme 12



Scheme 13

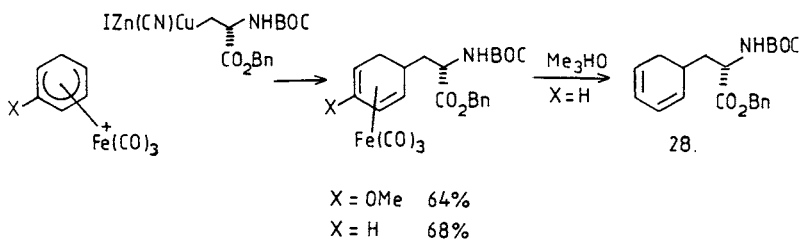
2.3 Examples Using Large Stoichiometric π-Bound Ligands

The Schiff base nucleophiles have been employed in reactions with larger stoichiometric electrophilic π-complexes. Dienyl complexes of the tricarbonyliron group (e.g. **27**) are effective for this purpose (11) (Scheme 14).

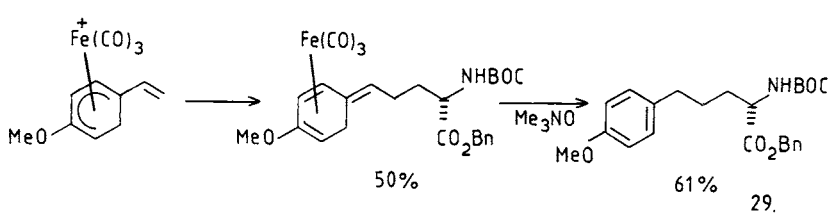


Scheme 14

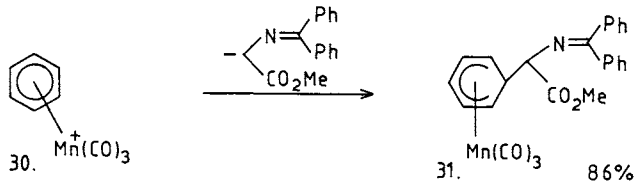
Similar additions suit the Jackson serine-derived nucleophiles (12). With the organoiron electrophiles, activation by palladium catalysis is unnecessary. The zinc/copper reagent itself is sufficiently nucleophilic, providing the homologue to the Schiff base product (Scheme 15). A further variant (Scheme 16) uses a vinyl-extended electrophile to introduce a three atom spacer. In these cases, removal of the metal has been shown to afford diene **28** and arene **29** products. Cationic electrophilic manganese arene complexes **30** (Scheme 17) react well with Schiff base nucleophiles to form neutral η^5 dienyl complexes **31** (13).



Scheme 15

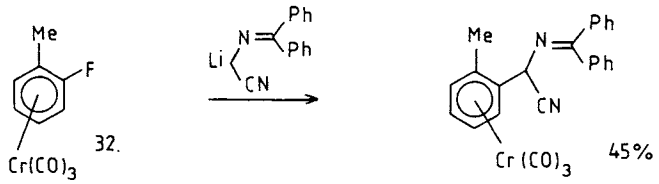


Scheme 16

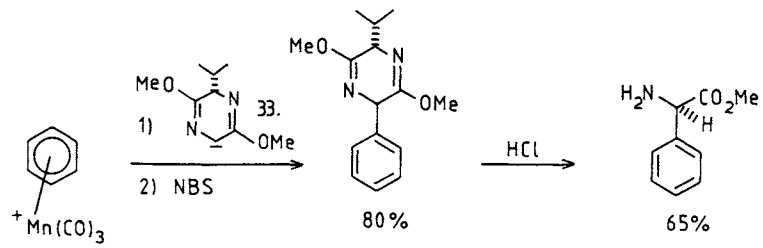


Scheme 17

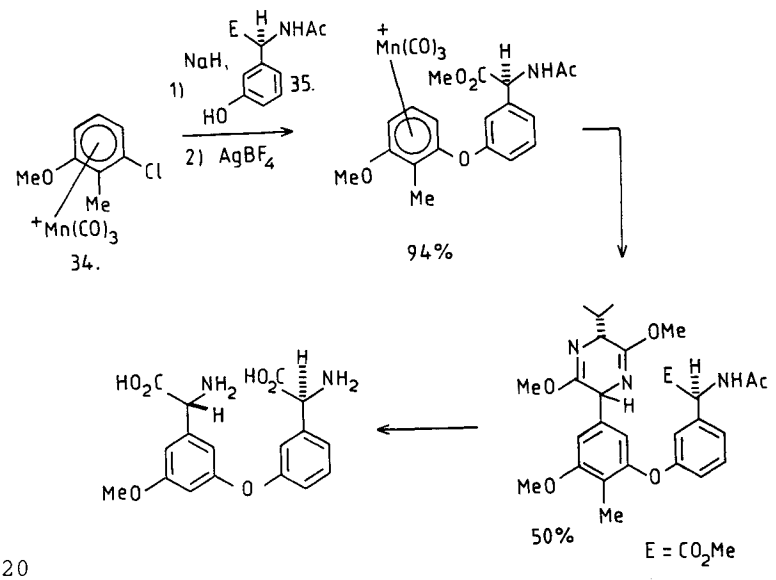
It is not always necessary for organometallic π-complexes to be cationic to serve as good electrophiles. Complexation of aromatic rings by the neutral tricarbonylchromium group is well known to promote electrophilicity and nucleophile addition/elimination processes. This has been applied (Scheme 18) to the synthesis of α-aryl amino acids by use of the Schiff base nucleophiles to displace fluorine from fluoroarene complexes **32** (14). Cationic complexes do sometimes offer advantages. In particular, they are usually compatible with a wider range of nucleophiles. Pearson's group has used a (Scheme 19) Schollkopf-type nucleophile **33** in combination with the organomanganese electrophile **30** (15). A more elaborate example makes use of two leaving groups on the aromatic ring, first by displacement of Cl^- from **34** by the anion of a protected hydroxyaryl amino acid **35**, and then with the Schollkopf system to form a di-amino acid based on a diphenyl ether nucleus (Scheme 20). Derivatives of deoxyristomycinic acid have been prepared in this way (16).



Scheme 18

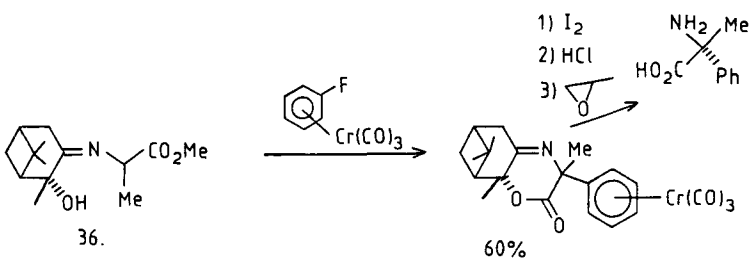


Scheme 19

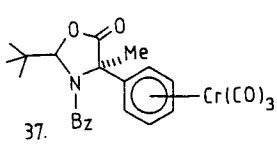


Scheme 20

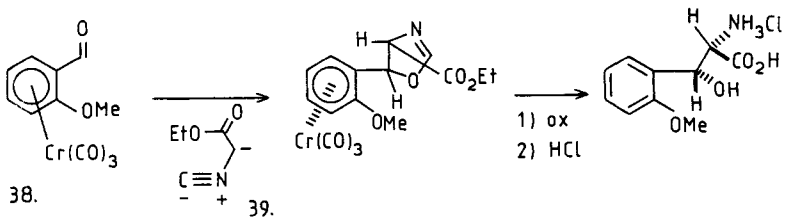
Chiral nucleophiles have been employed with the organochromium electrophiles (Scheme 21). The complex (**37**) has been obtained in a similar way (Scheme 22). Both Schiff base (e.g. **36**), and amine-substituted enolates (leading to **37**) have been used (17). Another variant (Scheme 23) uses a chiral chromium complex **38** to impose asymmetry in reactions of a prochiral aldehyde group. In this case, the nucleophile **39** was based on an isocyanide (18). Chiral benzyl anions are also available by the organochromium modification. These have been used (19) in reactions with conventional electrophilic head-groups. e.g. **40** (Scheme 24).



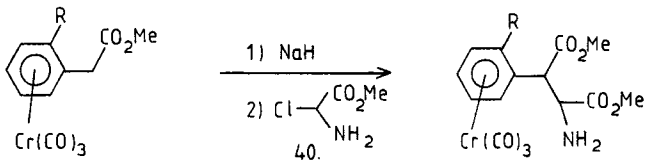
Scheme 21



Scheme 22

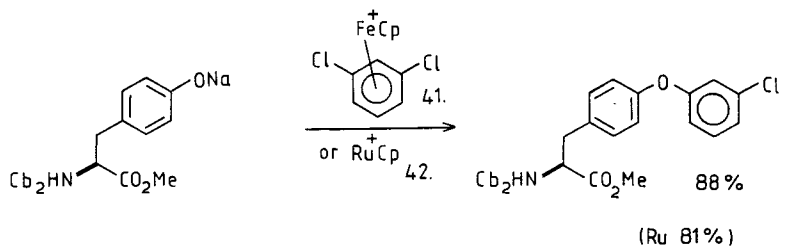


Scheme 23



Scheme 24

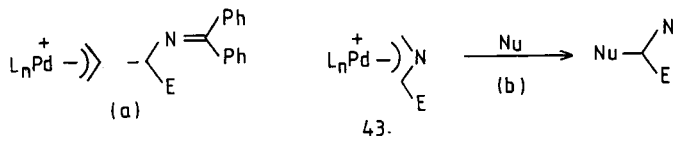
Pearson's investigations of phenolic nucleophiles that carry amino acid head-groups have recently extended the range of transition metals in use in amino acid synthesis. Cyclopentadienyliron **41** and ruthenium **42** complexes of chloroarenes have given successful results (20) in addition/elimination reactions (Scheme 25).



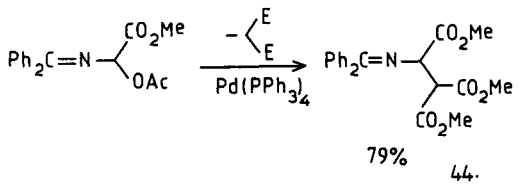
Scheme 25

3. ORGANOMETALLIC HEAD-GROUP ELECTROPHILES

O'Donnell's group at Indianapolis has turned around the normal use of π-allyl palladium complexes (Scheme 26) by binding the palladium to the amino acid head group, in an ester-substituted azaallyl complex **43** (21). Unusual regiocontrol properties allow addition of nucleophiles at the carbon bearing the ester substituent leading to the formation of **44** (Scheme 27).

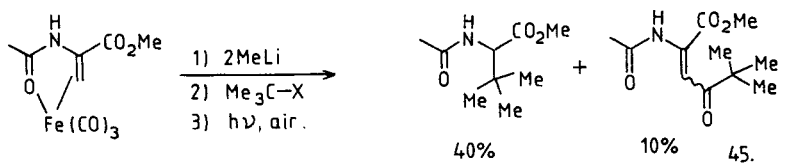


Scheme 26 a: nucleophilic head-group;
b: electrophilic head-group complex.



Scheme 27

An η^2 coordination of a head-group moiety has been explored in $Fe(CO)_3$ complexes stabilised by interaction with the oxygen atom of an adjacent organic carbonyl group (Scheme 28). As well as conjugate addition, reaction of nucleophiles at a metal carbonyl, followed by acyl transfer to form **45**, has been reported (22).

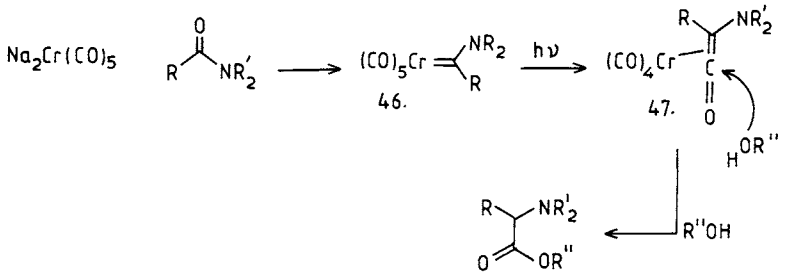


Scheme 28

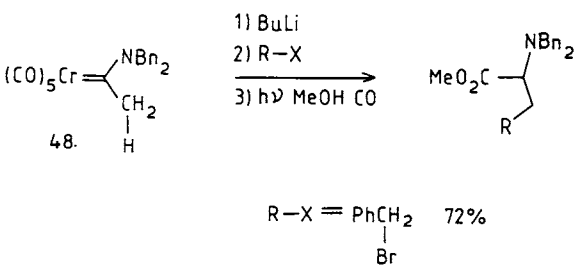
4. CARBENE COMPLEXES IN AMINO ACID SYNTHESIS

Carbene complexes **46** provide the means to elaborate amides into amino acids by carbonyl insertion. Development of a convenient route to the carbene complex, prepares for a photolytic conversion into a ketene complex **47**, which the picks up an alcohol to complete the carboxylic ester portion of the amino acid (Scheme 29). At the aminocarbene stage, stable complexes allow the development of versatile intermediates. Particularly attractive, is the use of the carbene to stabilise an anion obtained by deprotonation of **48** at what will become the β carbon. Reaction

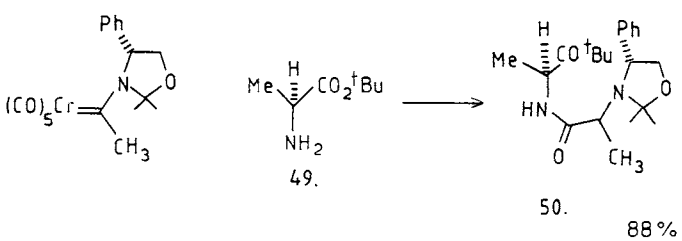
with electrophiles, followed by photolysis in methanol (Scheme 30), completes three new bonds (2 C-C bonds and a C-O bond) (23). Amines can also be used at the point where the ketene complex is trapped. The obvious amine to use is one within a protected amino acid (e.g. **49**), since this will now give access to a dipeptide. This reaction has been combined (Scheme 31) with the use of a chiral aminocarbene, so that the products can be obtained in high diastereomeric excess (24).



Scheme 29



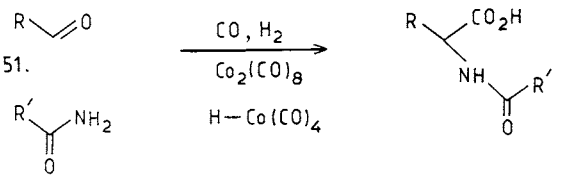
Scheme 30



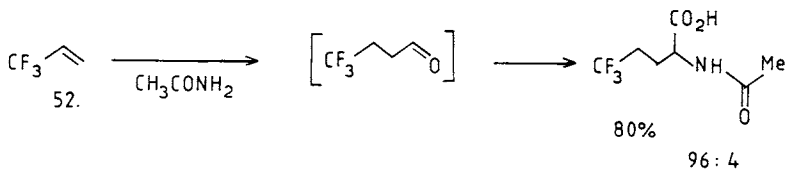
Scheme 31

5. AMIDOCARBONYLATION IN AMINO ACID SYNTHESIS

Amidocarbonylation can convert an aldehyde **51** into an amino acid in a one step process (Scheme 32) that forms both the C-C and C-N bonds required to complete the head-group (25). Since the reaction conditions are the related to those used for hydroformylation, the two processes can be combined (Scheme 33), allowing all three bonds to the α carbon to be built in a single cobalt-catalysed reaction (26). As always with hydroformylation, care must be taken to get good linear/branched ratios with unsymmetrical alkenes such as **52**.

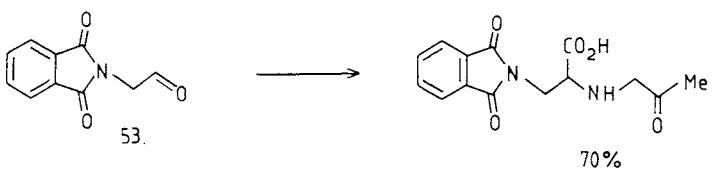


Scheme 32

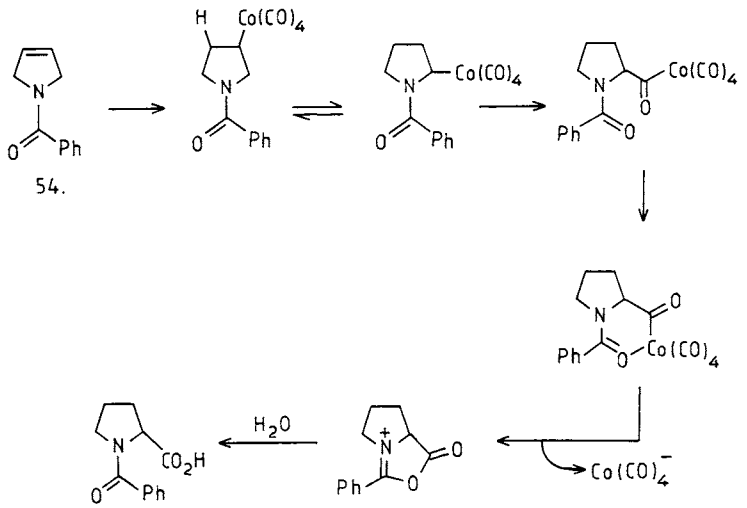


Scheme 33

Extension of these methods (Scheme 34) to functionalised aldehydes (e.g. **53**) in Izawa's group has met with considerable success. A phthaloyl moiety was used to protect the amine functionality in routes to α,ω-diamino acids such as lysine and ornithine (27). Cyclic amines **54** have been elaborated into proline (28). Scheme 35 illustrates a possible mechanism for this interconversion. Double bonds can migrate under the hydroformylation conditions, so the position of the alkene in the five-membered ring of the starting material does not determine the site of carbonyl insertion.

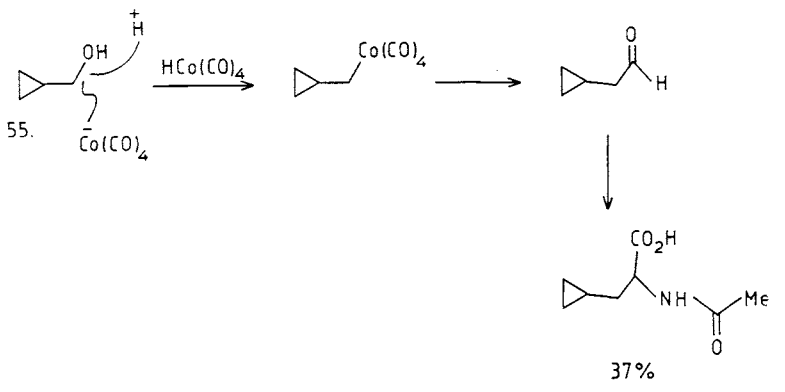


Scheme 34



Scheme 35

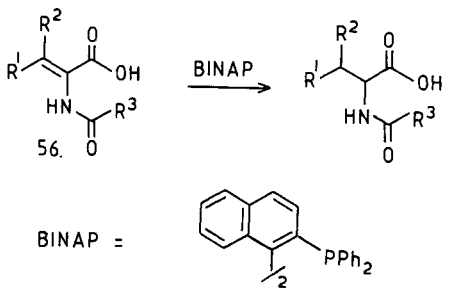
Hydroformylation is not the only means by which cobalt can become attached to the working ligand. In further studies (29) directed to cyclopropyl amino acids, $HCo(CO)_4$ was used to displace an OH group from an hydroxymethylcyclopropane **55** (Scheme 36).



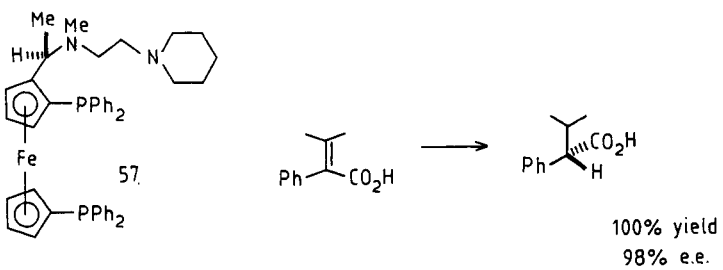
Scheme 36

6. HYDROGENATION METHODS

Homogeneous catalysis of the hydrogenation of dehydroamino acids is the classic use of organometallic chemistry in amino acid synthesis. This topic is too large to be reviewed fully within the space available, so this article will concentrate on emphasising a few recent developments. Although conceptually straight-forward, the reaction is of interest chiefly as a means to induce asymmetry by asymmetric hydrogenation. The best known example is the well established Monsanto process for the synthesis of DOPA (30). A wide variety of chelating phoshines have been used in asymmetric hydrogenation (31-6).



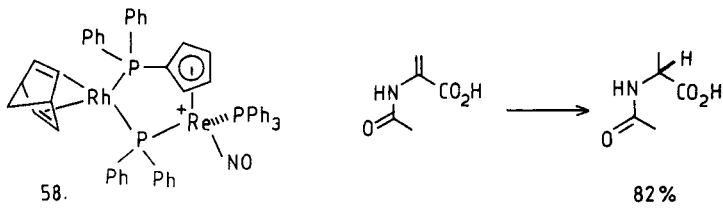
Scheme 37



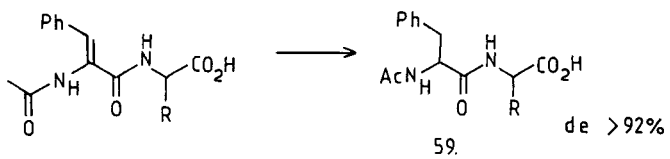
Scheme 38

More recent illustrations using ruthenium (37) and rhodium (38) in the reduction of **56** show how this type of work is developing (Scheme 37). More unusual catalysts include examples (Scheme 38) with chiral ferrocene auxiliaries e.g. **57** (39) and bimetallic catalysts (e.g. **58**) (Scheme 39) combining the catalytically active metal with a cationic π-complex (40). A

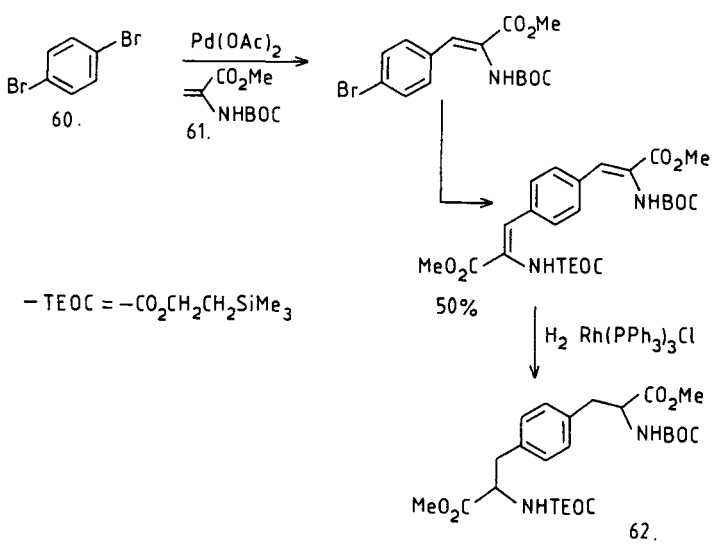
dipeptide **59** (Scheme 40) has been prepared by asymmetric hydrogenation (41). Another reaction sequence combines Heck-type coupling of **60** and **61** (see section 2) and hydrogenation (42). Methylene derivatives of head-group moieties were coupled in turn with the C-Br bonds of a dihaloarene. This afforded a substrate for hydrogenation, completing the combination of three components to form a diamino acid **62**.



Scheme 39



Scheme 40



Scheme 41

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Atta-ur-Rahman (Ed.) *Studies in Natural Products Chemistry, Vol. 16*

Palladium-Mediated Synthesis of Alkaloids

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751 21 Uppsala, Sweden

Introduction

The use of palladium in organic synthesis has undergone a remarkable expansion in recent years. Many versatile synthetic methods have been developed and palladium is now the transition metal most frequently used in organic transformations.[1,2] The reason for this rich chemistry is that palladium is highly efficient in almost all fundamental organometallic reactions,[2] particularly those involving activation of organic substrates and those leading to formation of new carbon-carbon and carbon-heteroatom bonds.

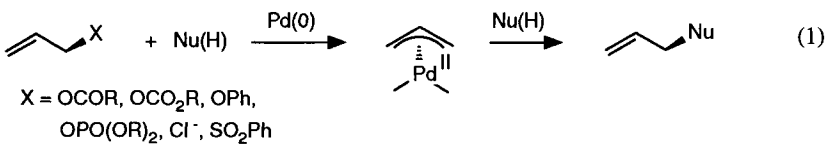
This review will deal mainly with the use of palladium-catalyzed reactions in the synthesis of alkaloids, but a few examples where palladium is used in stoichiometric amounts have also been included. We will first describe a number of palladium-catalyzed processes that are often used in organic synthesis. These techniques can be conveniently divided into palladium(0) and palladium(II)-catalyzed reactions.

A. Palladium(0)-catalyzed reactions.

In palladium(0)-catalyzed reactions the zerovalent metal is stabilized by ligands, most commonly by tertiary phosphines. Some different types of Pd(0)-catalyzed reactions are described below.

(i) Allylic substitution.

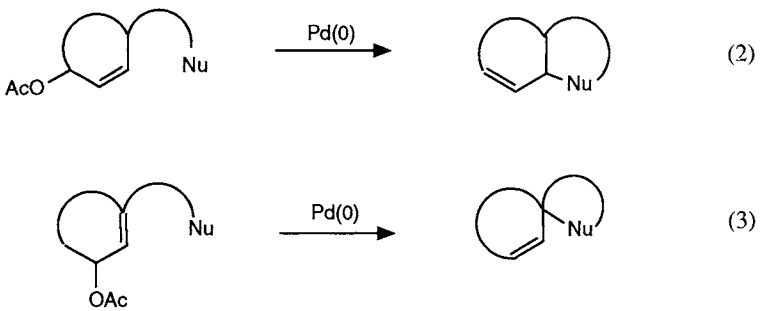
Palladium-catalyzed allylic substitution is an important process for carbon-carbon and carbon-heteroatom bond formation in inter-[3] and intra-molecular[4] reactions (eq. 1). The reactions



(1)

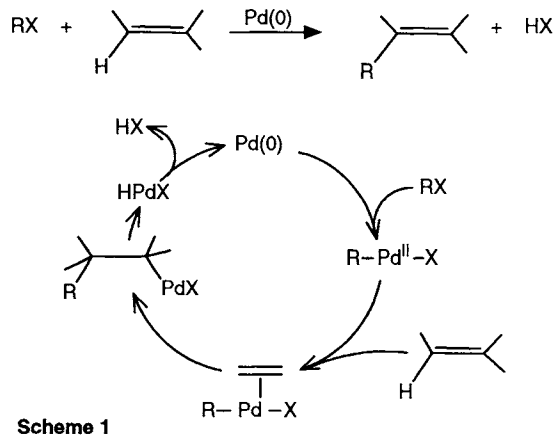
take place under mild conditions and are usually stereospecific. The overall process can be divided into two discrete reaction steps: (i) oxidative addition of the organic substrate to Pd(0) to give a (π-allyl)palladium(II) intermediate[5] and (ii) nucleophilic attack on this (π-allyl)palladium complex.[6] The overall reaction takes place with retention for typical S_N2 nucleophiles, which is a result of inversion of stereochemistry in each of the reaction steps. Some nucleophiles such as alkyl, vinyl, aryl, and hydride attack with retention which leads to an overall inversion.

The intramolecular version of this reaction is common in synthetic applications.[4] In this way annulated or bicyclic systems as well as spirocyclic systems have been synthesized (eq. 2 and 3).



(ii) Arylation and vinylation of olefins (Heck reaction)

The original version of this reaction was developed employing stoichiometric amounts of Pd(II),[7,8] the arylpalladium species required for the reaction being generated from an arylmercuric halide.[7] The reaction was later made catalytic[9] by employing an aryl- or vinyl halide as the aryl or vinylpalladium source (Scheme 1).



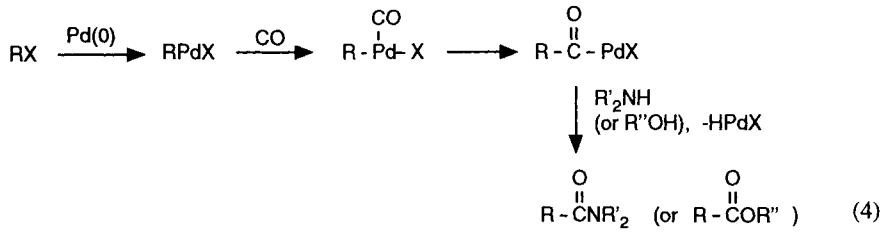
Scheme 1

In this reaction the Pd(0) catalyst activates the organic substrate by an oxidative addition. The aryl- or vinyl-palladium complex formed reacts with the olefin to produce a (σ-alkyl)palladium complex. Subsequent β-hydride elimination gives the functionalized olefin and HPdX. The latter loses HX (X is often acetate) to release Pd(0), and this closes the catalytic cycle. The reaction was later extended to aryl- and vinyl-triflates.[10]

Intramolecular versions of this process have been used to synthesize carbocyclic and heteocyclic ring systems.[11,12]

(iii) Carbonylation reactions

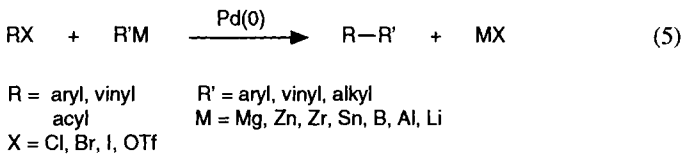
Carbonylation reactions are reminiscent of the "Heck reactions" described above but the aryl- or vinyl-palladium intermediate generated from the organohalide reacts with carbon monoxide instead of the olefin. The reaction was first described by Heck[13] and the mechanism of the reaction is shown in eq. 4. After insertion of carbon monoxide into the palladium-carbon bond the acylpalladium intermediate reacts with an amine or an alcohol to give an amide or an ester,



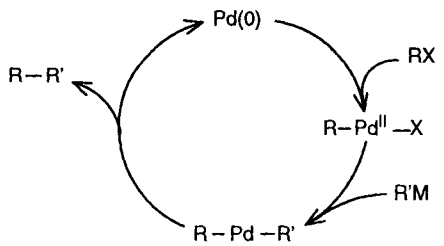
respectively.

(iv) Cross-coupling reactions

In palladium-catalyzed cross-coupling reactions an aryl, vinyl or acyl halide reacts with an aryl-, vinyl-, or alkyl-metal reagent to give a new carbon-carbon bond (eq. 5).



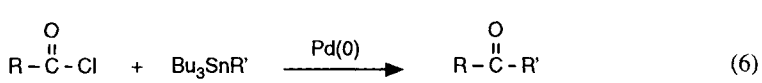
One of the first examples of this reaction was reported by Kumada,[14] who used either nickel or palladium catalysts for the reaction of aryl or vinyl halides with Grignard reagents. Later extension to other metals has increased the synthetic utility of the reaction. By using less reactive aryl- and vinyl-metal reagents such as those of Zn, Zr (Negishi[15]), Sn (Stille[16]) and B (Suzuki[17]) milder and more selective couplings are achieved. The principle and catalytic cycle of the coupling reaction is shown in Scheme 2. Oxidative addition to the catalyst produces an organopalladium intermediate,



Scheme 2

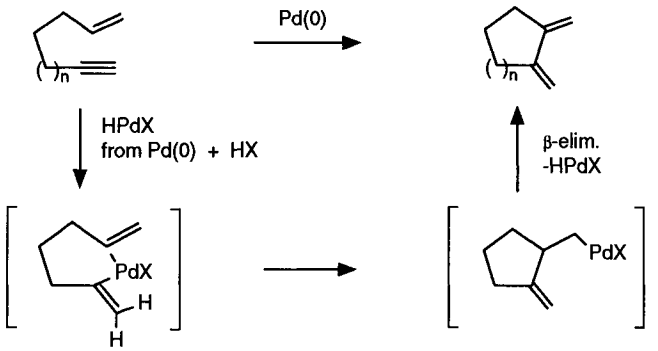
which has one palladium-carbon bond. Transmetallation exchanges the X group on palladium for R' to give a organopalladium intermediate with two palladium-carbon bonds. Reductive elimination results in carbon-carbon bond formation with concomitant production of Pd(0).

The use of an alkyltin reagent allows the alkylation of an acid chloride to a ketone (eq. 6).[16] In this case the "R" group of Scheme 2 is an acyl group.



(v) Cycloisomerization reactions.

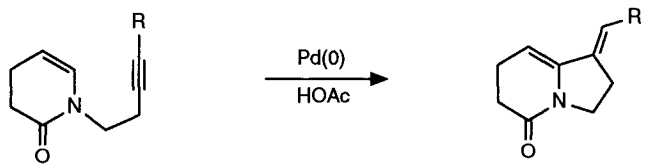
Palladium-catalyzed cycloisomerization of enynes has been developed into a useful synthetic method by Trost (eq. 7)[18] One possible mechanism suggested by Trost involves the formation of a



(7)

palladium hydride, which adds to the triple bond. The resulting vinylpalladium species would then react intramolecularly in analogy with the Heck reaction to give the product.

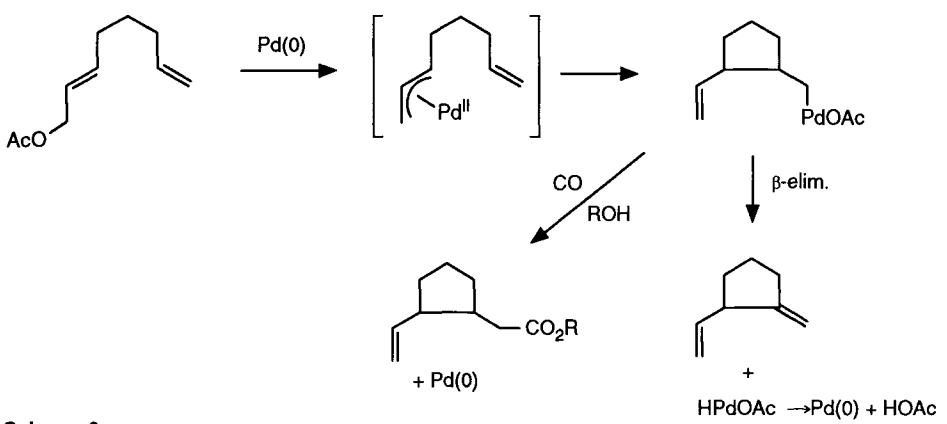
An example for the synthesis of heterocycles is shown in equation 8,[19] where the indolizidine system shown was obtained in 77% yield from the enyne substrate.



(8)

(vi) Palladium-catalyzed "metallo-ene reactions".

Intramolecular addition of a (π-allyl)palladium group to an alkene or alkyne takes place in acetic acid at elevated temperature.[20,21] The (π-allyl)palladium complex is generated from an allylic substrate and Pd(0), and it is a catalytic process (Scheme 3). The reaction has evolved into a

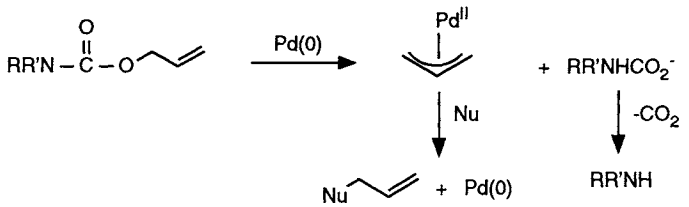


Scheme 3

powerful synthetic method. If carbon monoxide is present in the reaction, carbonylation takes place to give an acid derivative.

(vii) Deprotection

The allyloxycarbonyl group is a useful protective group for alcohols and amides[22] and it is removed under mild conditions with Pd(0)-catalysis (Scheme 4). For protected amines, oxidative



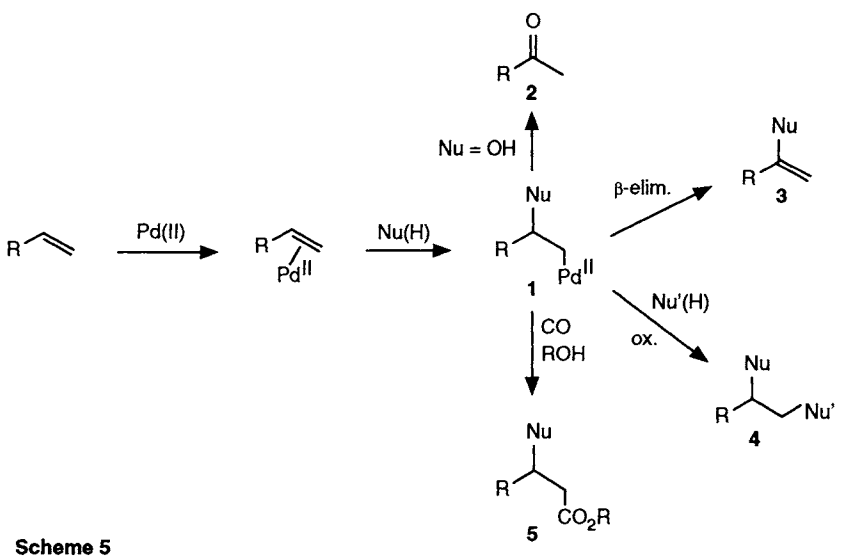
Scheme 4

addition to the allylic carbamate gives a (π-allyl)palladium complex, which is trapped by a nucleophile to regenerate Pd(0).[23] In this process the amine is released by loss of CO_2. The analogous mechanism operates for protected alcohols with an allylic carbonate as the substrate.[24]

B. Palladium(II)-catalyzed reactions.

(i) Functionalization of olefins via nucleophilic addition.

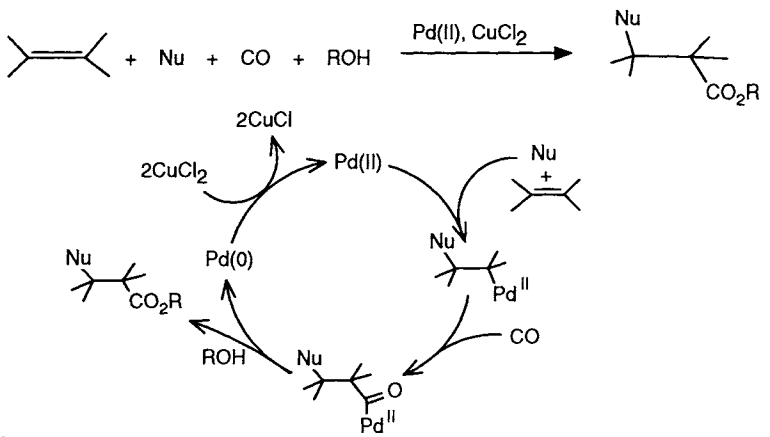
Nucleophilic addition to an alkene coordinated to palladium is an important process in organic synthesis.[25] It has been used to functionalize a double bond in four principal ways (Scheme 5). All



Scheme 5

these transformations proceed via a (σ-alkyl)palladium species **1** formed via nucleophilic addition to the (π-olefin)palladium complex. The processes shown are oxidation reactions and require the presence of an oxidant. Terminal olefins are oxidized to 2-ketones by molecular oxygen in the presence of catalytic amounts of $PdCl_2$ and $CuCl_2$.[26] An intramolecular hydride shift in **1** leads to

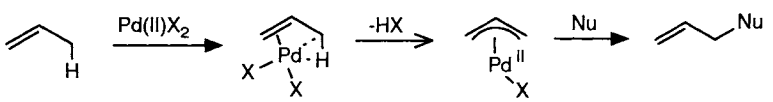
ketone **2**. A β-hydride elimination from **1** gives a vinyl functionalized olefin **3**. An oxidative cleavage of the palladium-carbon bond in **1** produces an 1,2-difunctionalized olefin **4**.[27] Finally, a carbonylation leads to a β-substituted carboxylic acid derivative **5**. A catalytic cycle for one of the processes (nucleophilic addition-carbonylation) is given in Scheme 6.



Scheme 6

(ii) Allylic oxidation.

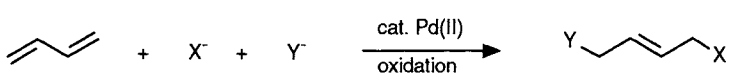
In this reaction an electrophilic activation of an allylic C-H bond by Pd(II) produces a (π-allyl)palladium complex,[28] which is subsequently attacked by a nucleophile (eq. 9).[6] Synthetic procedures for allylic acetoxylation have been developed.[29]



(9)

(iii) 1,4-Oxidation of conjugated dienes.

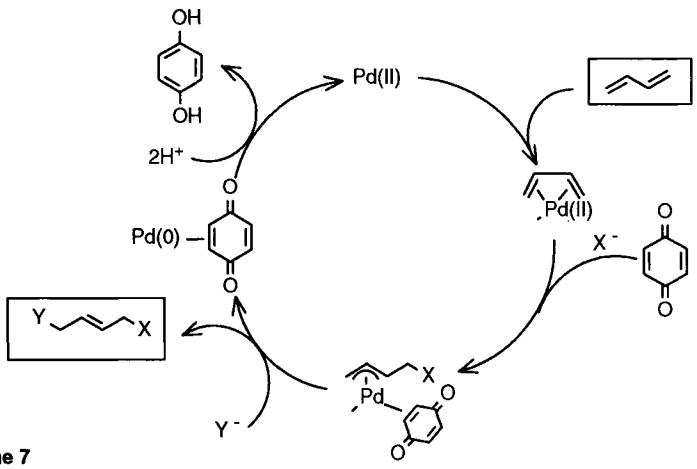
Palladium(II)-catalyzed 1,4-oxidation of conjugated dienes has evolved into a synthetically useful methodology.[30,31] In this reaction two nucleophiles are added regioselectively to the 1- and 4-positions of the 1,3-diene (eq. 10). The mechanism is given in Scheme 7. Attack on the



(10)

X = OAc, OOCR, OR
Y = Cl, OAc, OOCR, OR

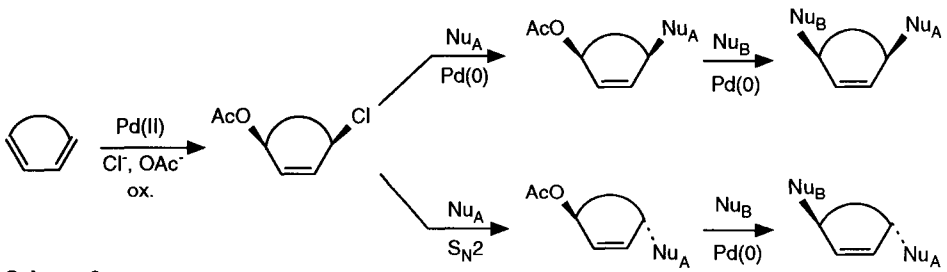
coordinated diene by the first nucleophile gives a (π-allyl)palladium complex. Activation of the latter complex by *p*-benzoquinone induces an attack by the second nucleophile. In the latter process a Pd(0)-benzoquinone complex is formed which undergoes an intramolecular redox reaction[33] to give hydroquinone and Pd(II). The first nucleophile is in most cases an electronegative atom and for this reason the attack by the second nucleophile Y^- is directed to the 4-position, which results in excellent 1,4-regioselectivity. The reaction is also highly stereoselective and, importantly, there is a



Scheme 7

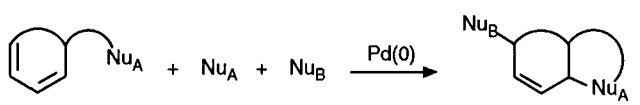
choice in stereochemistry in the 1,4-addition.

The palladium-catalyzed 1,4-chloroacetoxylation in combination with further nucleophilic substitution offers useful levels of stereocontrol. Substitution of the allylic chloride with either retention (Pd(0)-catalysis) or inversion (S_N2) results in selective formation of either of the two diastereomeric allylic acetates (Scheme 8). These allylic acetates can be further functionalized by a second nucleophile.



Scheme 8

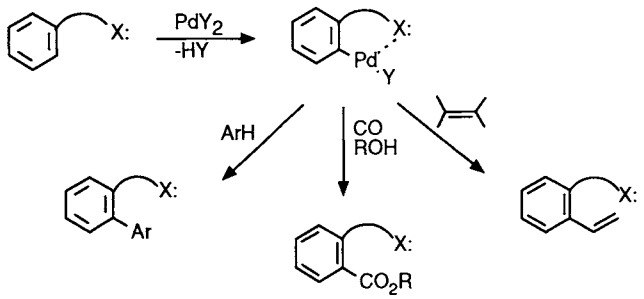
Intramolecular versions of these reactions (eq. 11)[30,32] were used in the synthesis of natural products and alkaloids (see below).



(11)

(iv) Aromatic C-H bond activation

In analogy to allylic C-H bond activation, Pd(II) can also activate aromatic C-H bonds. An *ortho*-substituent containing a heteroatom that can coordinate to the catalyst facilitates the reaction (Scheme 9). The arylpalladium species formed may undergo several different reactions such as "Heck-type" reactions and carbonylation reactions. It may also react with another aromatic ring, often via an intramolecular reaction.

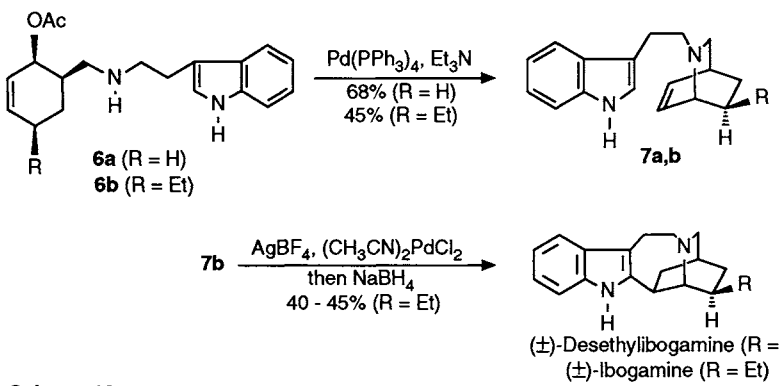


Scheme 9

C. Applications to the synthesis of alkaloids.

Reaction type A (i).

In pioneering studies on the iboga alkaloids, Trost demonstrated the power of cyclization reactions involving Pd(0)-catalyzed allylic substitution[4a]. The first targets were desethylibogamine[34] and ibogamine[35], the routes to which are shown in Scheme 10.



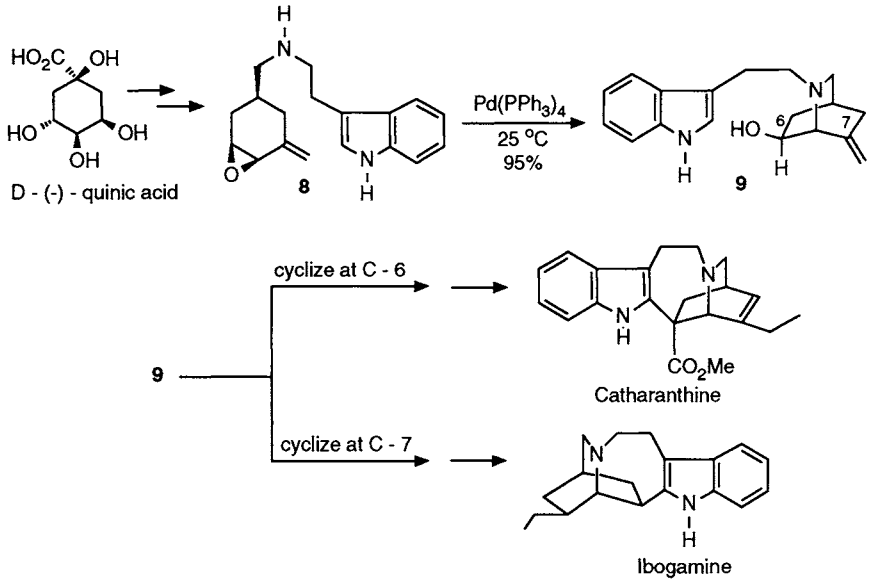
Scheme 10.

The cis stereochemistry of **6a** and **6b** (Scheme 10) was secured via Diels-Alder cycloadditions, and Pd(0) catalysis then smoothly produced isoquinuclidines **7a** and **7b**. The final cyclizations to the targets relied on Pd(II) chemistry, which will be discussed later. Use of an *O*-methylmandeloyl group instead of acetate in **6b** allowed preparation of the alkaloid in enantiomerically enriched form (60% e.e.). The related alkaloid catharanthine was also synthesized by use of the same methodology[36].

Trost later showed[37] how optically pure isoquinuclidines can be synthesized by using (-)-quinic acid to prepare the cyclization precursor, which in this case was the vinyl epoxide **8** (Scheme 11).

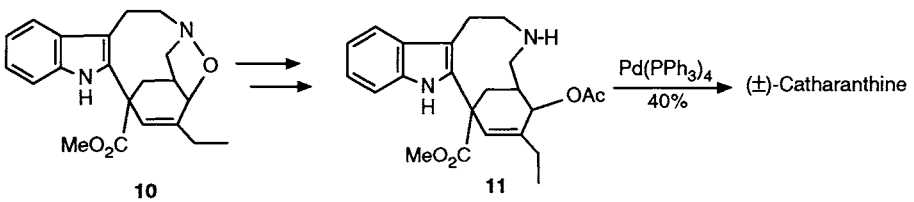
The palladium-mediated alkylation reaction proceeded in excellent yield under exceptionally mild conditions to give the optically active isoquinuclidine **9** which is suitably functionalized to allow entry to *either* the catharanthine or the ibogamine skeleton.

In an alternative palladium-catalyzed synthesis of racemic catharanthine, Langlois[38] used the



Scheme 11.

isoxazolidine **10** to prepare the allylic acetate **11** which, when subjected to the Trost cyclization conditions, furnished the target in moderate yield (Scheme 12).

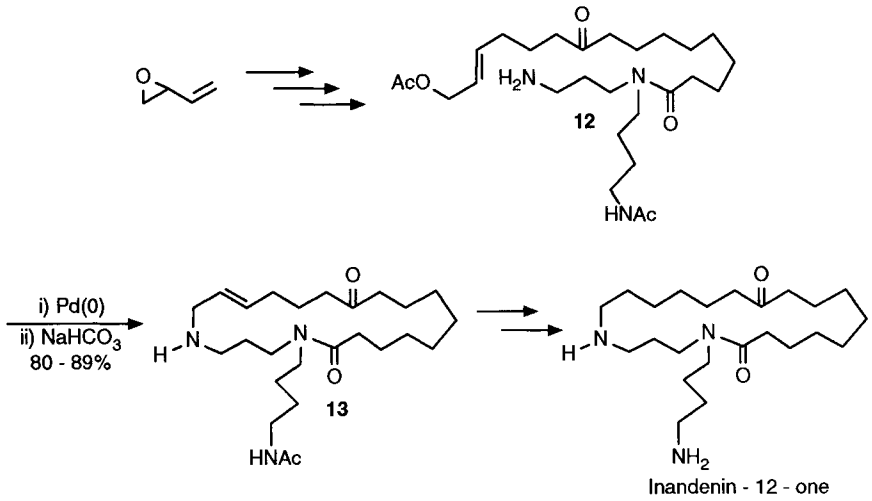


Scheme 12.

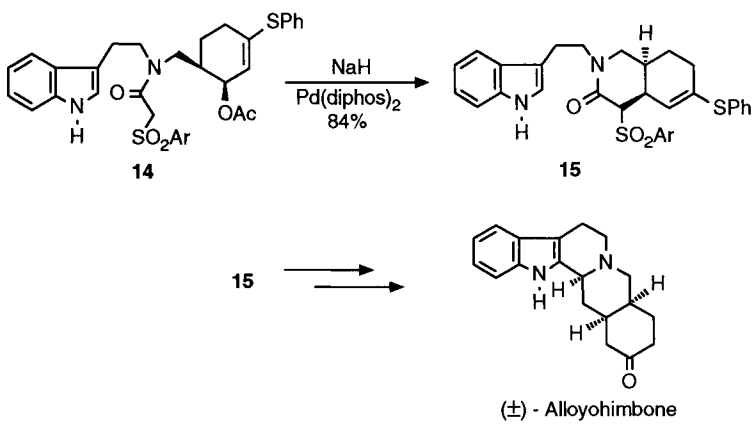
The palladium-mediated "macroheterocyclization" shown in Scheme 13 was developed by Trost and Cossy[39] for the synthesis of the spermidine alkaloid inandenin-12-one. The precursor **12** was synthesized from 1,3-butadiene monoepoxide (the first step being a Pd-catalyzed alkylation) and exposure to 10 mol% $Pd(PPh_3)_4$ and 8 mol% 1,4-bis(diphenylphosphino)butane (dppb) at high dilution in THF induced formation of the 21-membered ring of **13** in nearly quantitative crude yield.

The overall yield of inandenin-12-one from 1,3-butadiene epoxide was a remarkable 23%, the "macroheterocyclization" process being highly chemo-, regio-, and stereoselective.

A key step in Godleski's synthesis[40] of alloyohimbone (Scheme 14) was the efficient palladium-catalyzed cyclization of the enolate of **14**. The ring junction in **15** was formed exclusively as the cis-fused isomer, as expected from a reaction involving substitution of the allylic acetate via a double inversion process.



Scheme 13.

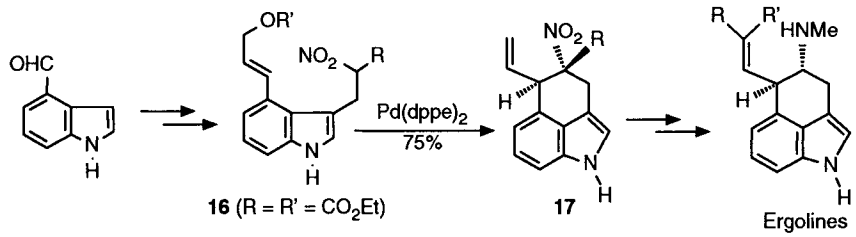


Scheme 14.

Since the vinyl sulfide moiety in **14** is a masked ketone, the palladium-mediated reaction is in effect a stereospecific equivalent of a Michael addition, which in its classical version would not have been expected to afford such high levels of stereochemical control.

Genêt[41] developed a concise route to the ergot alkaloids, based on selective Pd(0)-catalyzed allylic displacement by a nitro-stabilized anion (Scheme 15). The carbonate **16** was available in a few simple steps from indole-4-carboxaldehyde and could be cyclized to **17** in high yield under very mild conditions.

Compounds such as **17** possess the correct stereochemistry and suitable functionality for elaboration to naturally occurring ergolines. An obvious and attractive extension of such chemistry based on Pd(0) is the use of chiral phosphine ligands to induce catalytic enantioselective processes; Genêt[42] was thus able to cyclize **16** (R = H; R' = Ac) with 70% e.e. by using CHIRAPHOS as ligand



Scheme 15.

in the presence of K_2CO_3. As shown in Table 1, the enantioselectivity of this procedure could be greatly improved[43] by the use of BINAP.

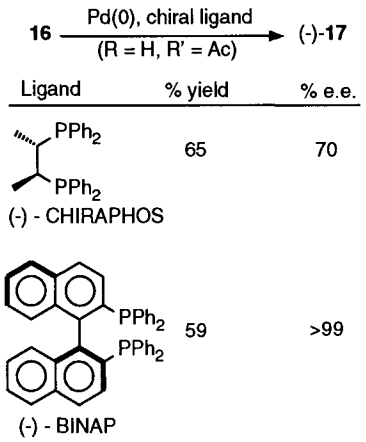
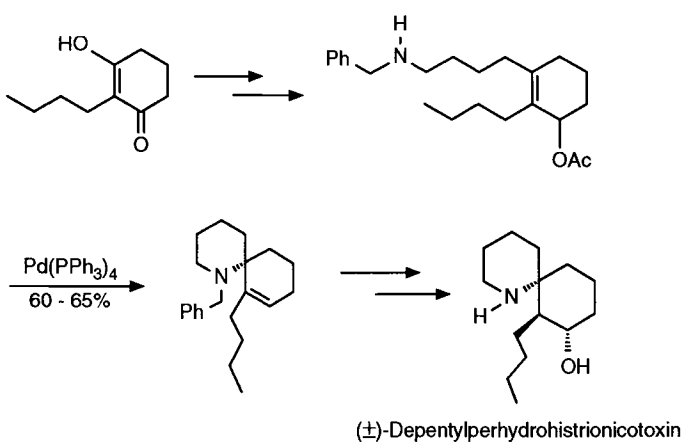


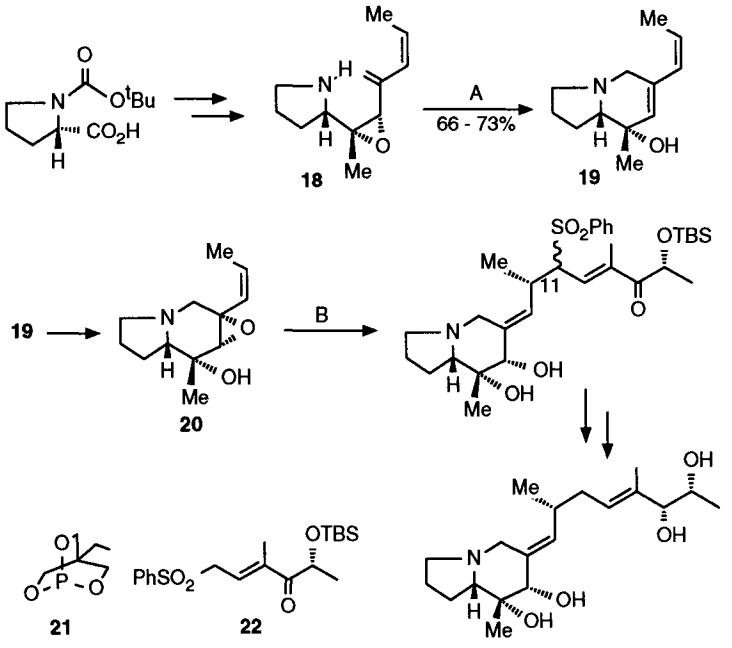
Table 1.

π-Allyl palladium chemistry also provides convenient access to spirocyclic alkaloids of the histrionicotoxin family. Godleski[44] and Carruthers[45] independently and simultaneously developed the route shown in Scheme 16.



Scheme 16.

A related family of amphibian alkaloids, the pumiliotoxins, is also synthetically accessible via the Trost vinyl epoxide methodology discussed earlier. Scheme 17 shows a route[46] to enantiomerically pure (+)-*allo*-pumiliotoxin 339B.

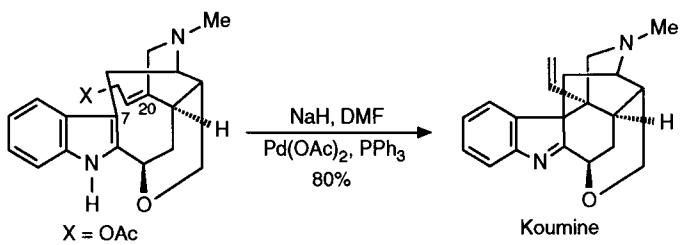


Scheme 17.

Conditions A: 1.5 mol% $(dba)_3Pd_2.CHCl_3$, 12 mol% **21**, 10 eq. H_2O, THF, 65°C.
Conditions B: 5 mol% $(dba)_3Pd_2.CHCl_3$, 20 mol% dppf, 10 eq. H_2O, THF, RT.

Ligand **21** and addition of water (as a proton source) were necessary for optimal conversion of **18** to **19**; palladium-catalyzed coupling of **20** and **22**, which neatly sets up the stereochemistry at C-11, also benefited from the addition of water.

Sakai[47] has used the Pd(0)-catalyzed chemistry of allylic acetates to mimic the hypothetical biosynthesis of the alkaloid koumine (Scheme 18). The final stage of the construction of this complex cage structure was envisaged to be formation of the C-7 to C-20 bond, and this was accomplished in excellent yield via intramolecular nucleophilic displacement of an allylic acetate by the indole anion.

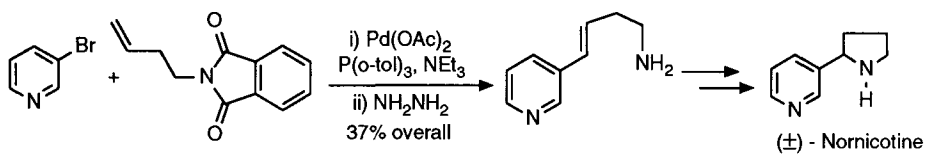


Scheme 18.

Reaction types A (ii) and A (iii).

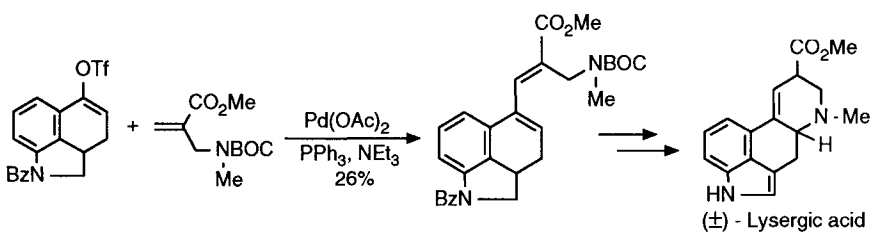
The Heck reaction[1b,7,9] is now one of the most widely used organopalladium techniques for organic synthesis; in the alkaloid field, both inter- and intramolecular versions of this reaction have been applied, and some examples are discussed below.

Heck's own very simple synthesis[48a] of nornicotine is shown in Scheme 19. The Pd-catalyzed coupling reaction gave a mixture of double bond regioisomers in near-quantitative yield. As part of an extensive study[48b] of the reactions of heteroatom-substituted olefins, Hallberg used Heck-type chemistry in a synthesis[48c] of the related tobacco alkaloid anabasine.



Scheme 19.

Vinyl triflates are also excellent substrates for Heck reactions, and Scheme 20 shows a straightforward route[49] to lysergic acid based on this method.



Scheme 20.

Although the yield of the Heck-type reaction was low, the synthesis nevertheless compared favorably with earlier routes in terms of the number of steps involved.

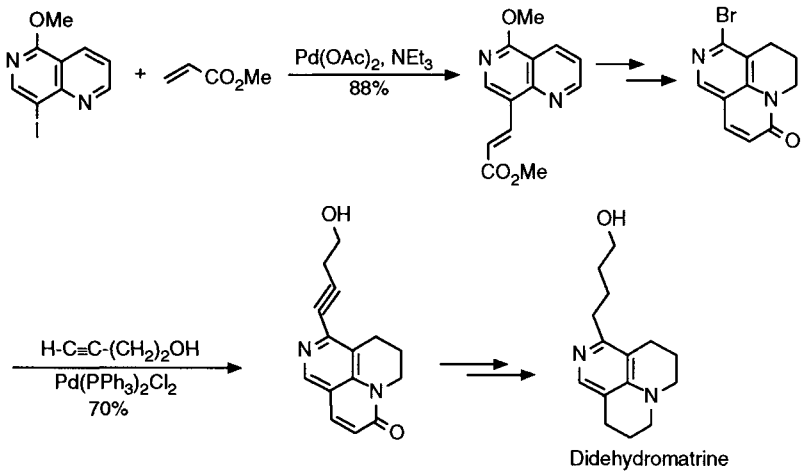
Acetylenes are also useful coupling partners, particularly if Pd/Cu catalysis is employed[50]. Yamanaka[51] has used palladium-catalyzed couplings of both alkenes and acetylenes as key steps in the synthesis of didehydromatrine (Scheme 21).

Scheme 22 shows a simple route[52] to the alkaloid dictamnine, based on the Pd/Cu-catalyzed coupling of alkynes; the initial coupling product cyclized spontaneously to the furoquinoline.

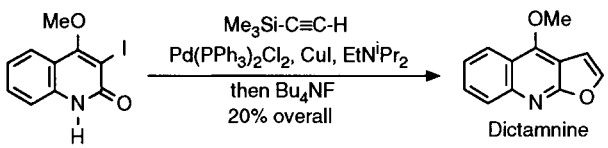
A similar palladium-mediated process was used by Grotjahn and Vollhardt[53] in a synthesis of γ-lycorane (Scheme 23). Subsequent conversion of **23** to an advanced tetracyclic intermediate relied on the very elegant organocobalt chemistry developed by the Vollhardt group.

Stork[54] performed a twofold acetylene coupling reaction in the final stages of his impressive enantioselective synthesis of (-)-histrionicotoxin (Scheme 24).

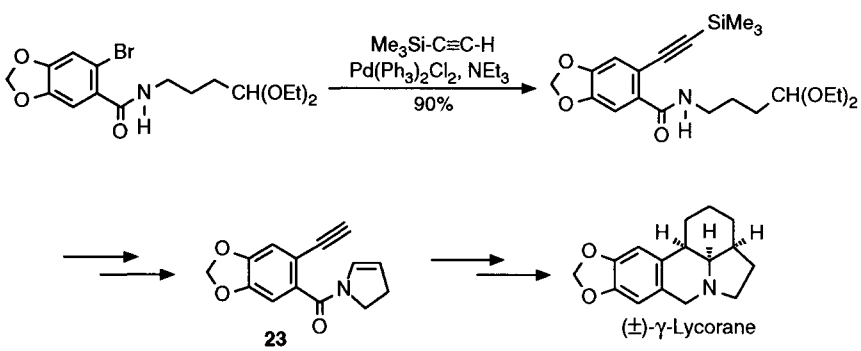
The intramolecular version of the Heck reaction[55] is a powerful tool for the rapid and efficient construction of complex polycycles. Extensive studies on nitrogenated substrates, in particular by



Scheme 21.



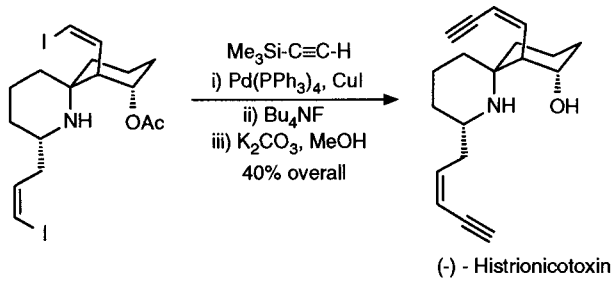
Scheme 22.



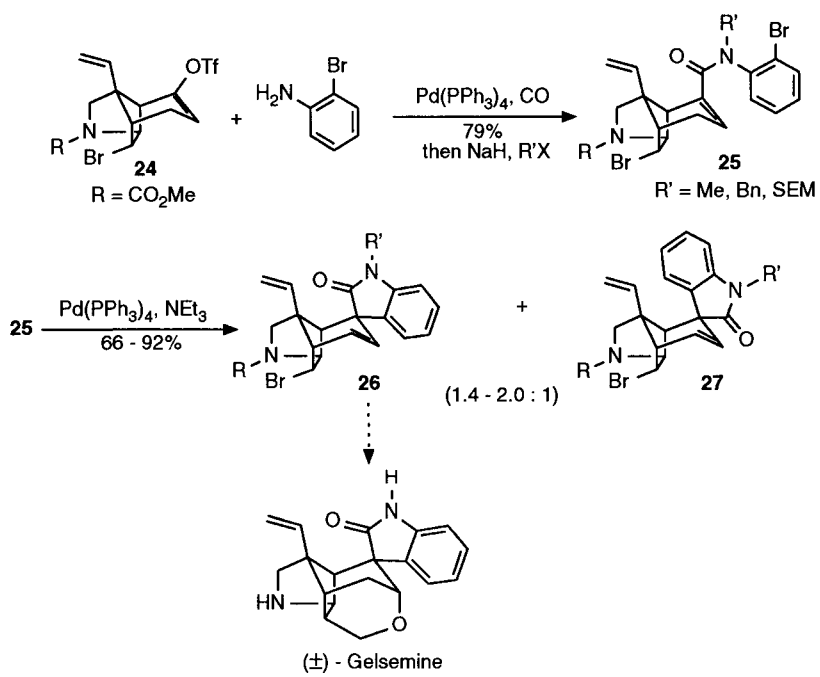
Scheme 23.

Overman[56], have defined the scope and limitations, as well as culminating in the elegant synthetic routes to alkaloids described below.

In an approach to gelsemine (Scheme 25) Overman[57] prepared the advanced pentacyclic intermediate **26** by using Pd-catalysis at two different stages (**24** to **25**; **25** to **26**). Conversion of the vinyl triflate to the amide via insertion of CO was based on the work of Cacchi et al.[58], while the intramolecular Heck reaction of **25** smoothly formed a quaternary center of the highly congested polycycle **26**.



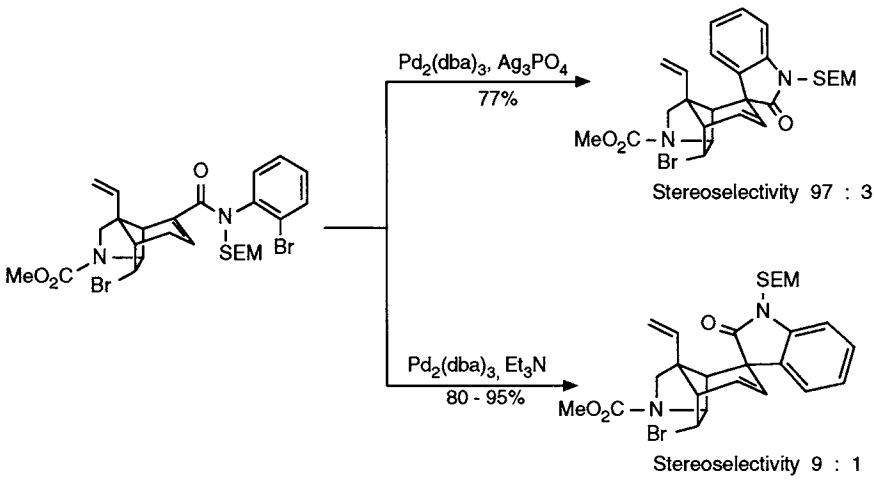
Scheme 24.



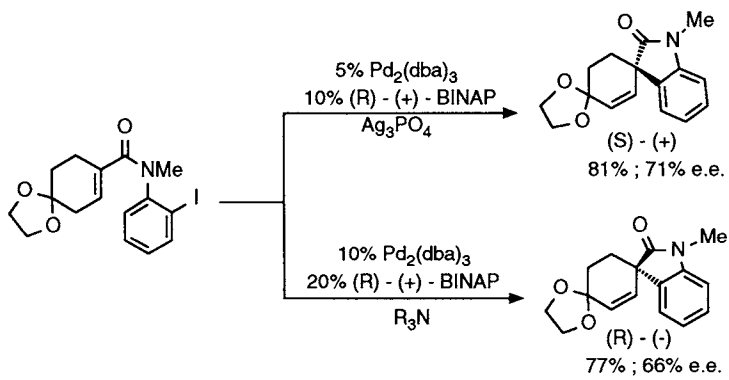
Scheme 25.

Overman later demonstrated[59] how the palladium catalyst could be "tailored" to steer the course of the Heck reaction toward *either* **26** or **27**, with impressive levels of diastereoselectivity (Scheme 26).

The effects of addition of silver salts on the rate[60] and stereochemical outcome[61] of Heck reactions had been studied earlier by Hallberg and Overman, respectively. Grigg[61c] introduced the use of thallium(I) salts as additives, and this technique has been used by both Hudlicky[61d] and Ogawa[61e] for the enantioselective total synthesis of (+)-lycoridine. Overman has also reported[62] the use of the "silver modification" of the intramolecular Heck reaction in conjunction with a chiral diphosphine. Unexpectedly, either enantiomer of the chiral azaspirocycle shown in Scheme 27 could be obtained with fairly good selectivity by using a single enantiomer of the chiral ligand.



Scheme 26.

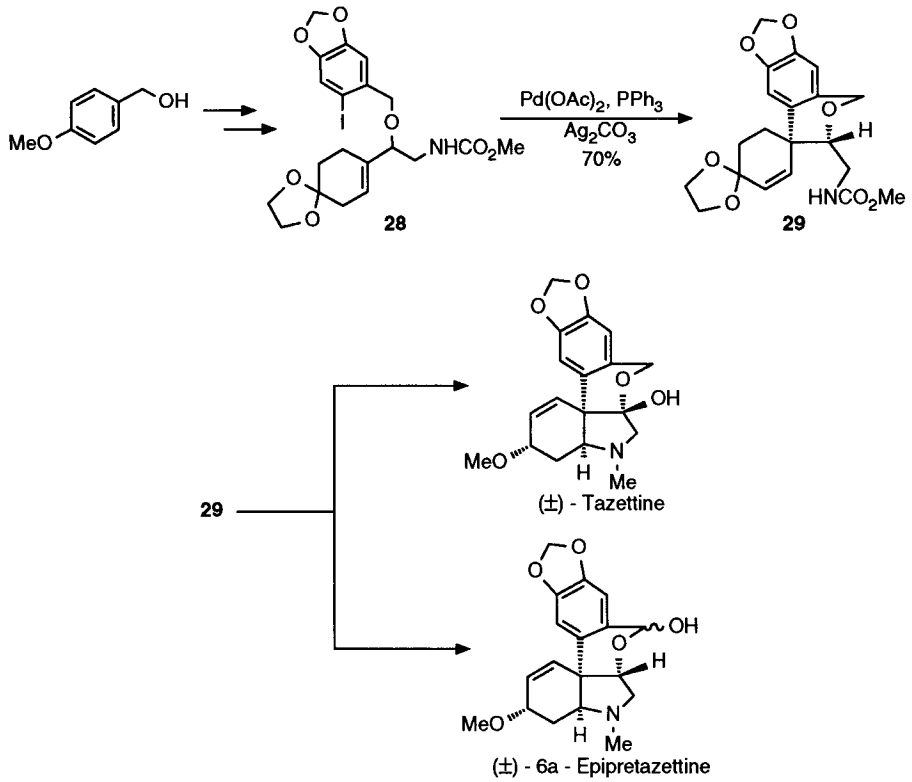


Scheme 27.

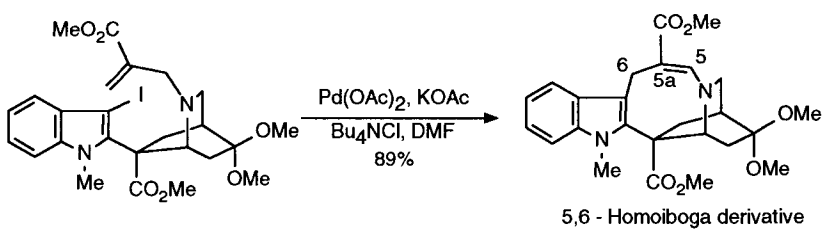
The advantages of running Heck reactions in the presence of silver salts were also exploited in the total synthesis[63] of the alkaloids tazettine and 6a-epipretazettine (Scheme 28).

The intramolecular Heck reaction of **28** delivered **29** as a single diastereomer (90% crude yield). Elaboration of **29** to the targets involved, inter alia, yet another palladium-mediated process in the form of the Saegusa oxidation reaction[64]. Overall yields of both alkaloids were ca. 4% based on *p*-methoxybenzyl alcohol.

In studies directed toward the synthesis of 5,6-homologues of the iboga alkaloids (Scheme 29) Sundberg[65] showed that the eight-membered C-ring could be closed efficiently via an intramolecular Heck reaction, but only if the indole was *N*-substituted. The Heck reaction was run under phase-transfer-catalyzed conditions[66], and proceeded in excellent yield; the initially-formed coupling product (5a,6-double bond) obviously isomerized to the 5,5a-double bond isomer, which was the only one isolated.



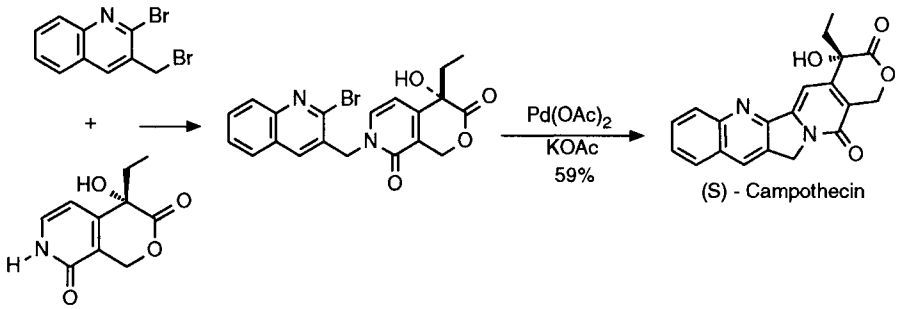
Scheme 28.



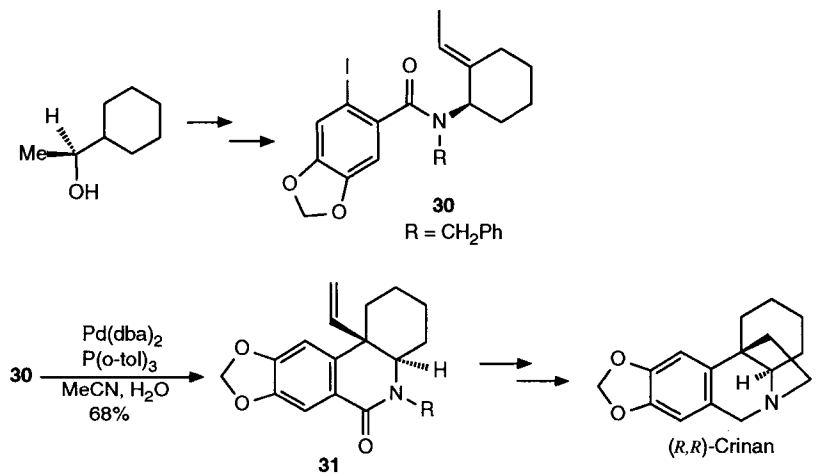
Scheme 29.

Comins[67] has described an efficient asymmetric synthesis of (*S*)-campothecin, the final stage of which is an intramolecular Heck reaction. The total synthesis required ten steps from commercially available materials and provided the enantiomerically pure target in 12% overall yield (Scheme 30).

Scheme 31 shows Grigg's enantioselective synthesis[68] of (*R,R*)-crinan. The key palladium-catalyzed step (**30** to **31**), which was sensitive to solvent, phosphine and small amounts of water, delivered a separable 20:1 mixture of **31** and the cis-fused isomer.



Scheme 30.



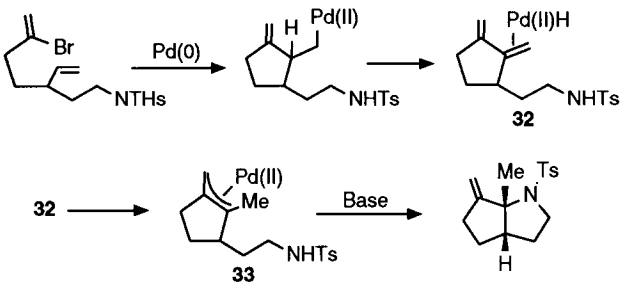
Scheme 31.

An imaginative variant of the Heck reaction for the preparation of azabicyclic systems has been reported by Weinreb[69] (Scheme 32). The strategy relies on an intramolecular Heck vinylation followed by β-elimination to form a putative η^2-diene complex (**32**) which re-adds palladium hydride to form π-allyl species **33**. Finally, the π-allyl complex is trapped intramolecularly by a suitably positioned nitrogen nucleophile.

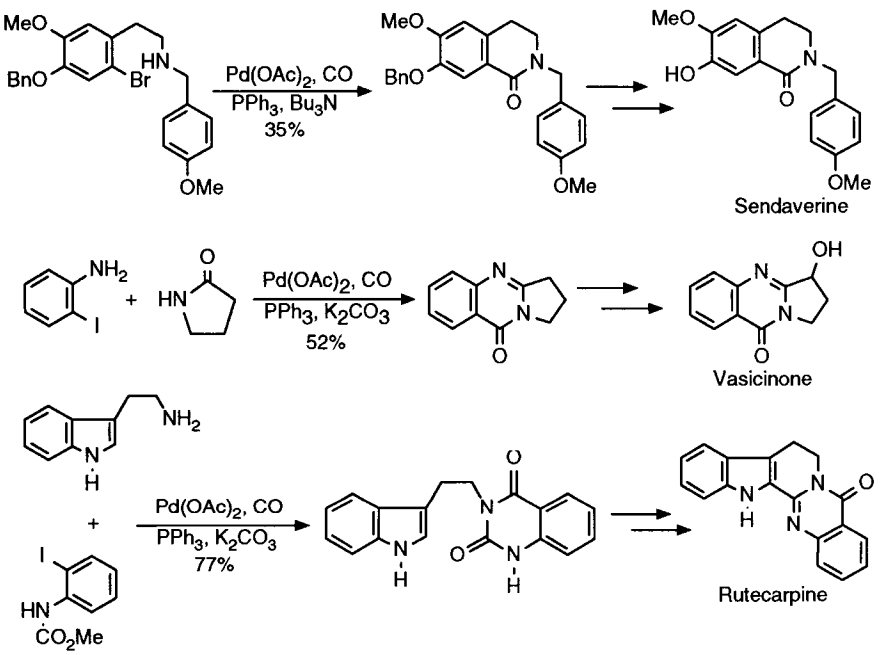
As in many of the previous examples, quaternary centers are set up with surprising ease and the chemical yields are good to excellent. The potential of this elegant chemistry for alkaloid synthesis is obvious, and Weinreb has already pointed out a possible route to the histrionicotoxins[69].

A palladium-catalyzed amidation of aryl halides via reaction with amines in the presence of carbon monoxide was developed early on by Heck[13] and extended to the synthesis of benzolactams by Ban and coworkers[70]. This intramolecular carbonylation reaction proved to be very useful for the synthesis of alkaloids such as sendaverine[71], vasicinone[72] and rutecarpine[72] (Scheme 33).

The Hokkaido group were also able to further extend the lactamization methodology to alkyl halides, in the form of α-haloamides[73] and esters[74], the putative intermediates being alkylmetal



Scheme 32.

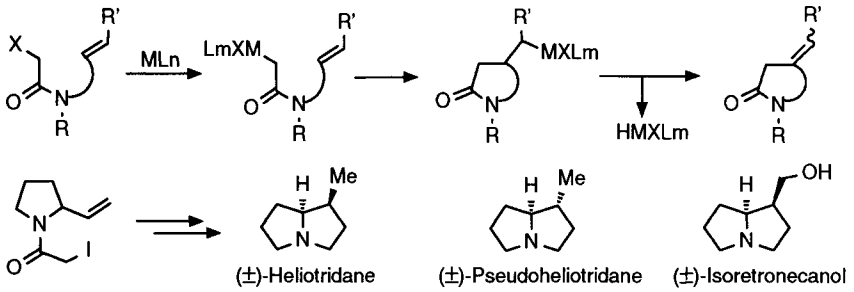


Scheme 33.

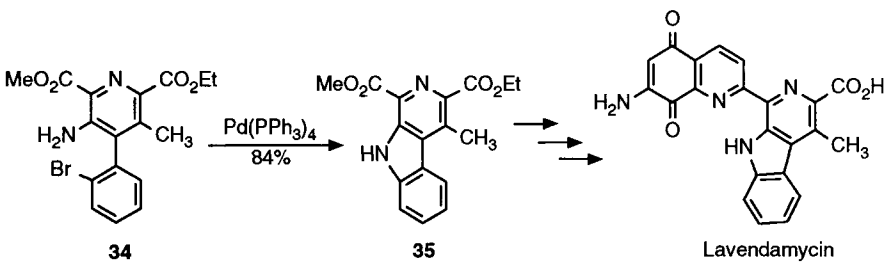
complexes; the general process is outlined in Scheme 34. In practice, yields are generally rather modest and mixtures of isomers are obtained, but some alkaloids could be synthesized by this technique.

Finally, mention is made here of an unusual Pd(0)-catalyzed synthesis of β-carbolines developed by Boger[75] en route to lavendamycin (Scheme 35).

Key intermediate **34** was prepared via the clever inverse electron demand Diels-Alder chemistry developed by the Boger group. The desired carboline **35** was not available from **34** via conventional methodology, but upon exposure of the precursor to Pd(0) smooth ring closure occurred



Scheme 34.

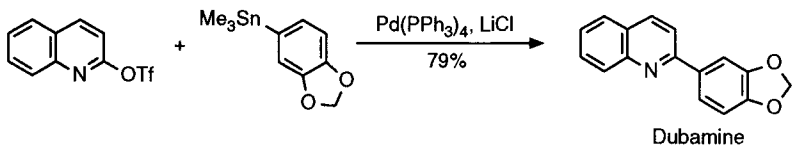


Scheme 35.

in excellent yield. The process was suggested[75] to involve oxidative addition followed by a rare case of heteroatom-Pd(II) reductive elimination.

Reaction type A (iv).

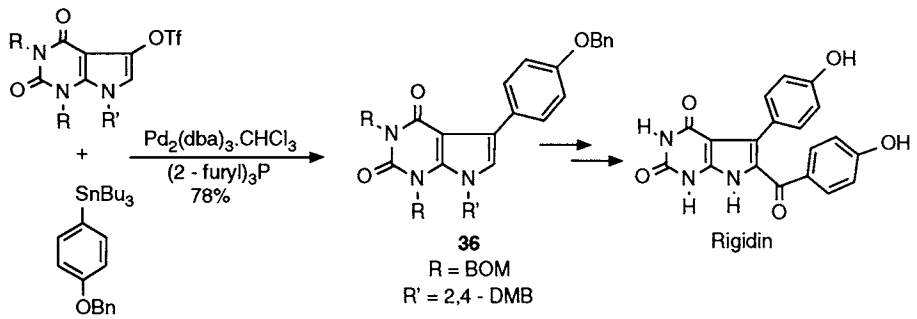
Stille[16] introduced organostannanes as partners for vinyl[76] and aryl[77] triflates in palladium-mediated coupling reactions. The reaction is a very general one, and an application to the synthesis[77] of the alkaloid dubamine is shown in Scheme 36. The power of the Pd-catalyzed reaction is underlined by comparison of this synthesis with a previous one[78] which proceeded in only 1% yield.



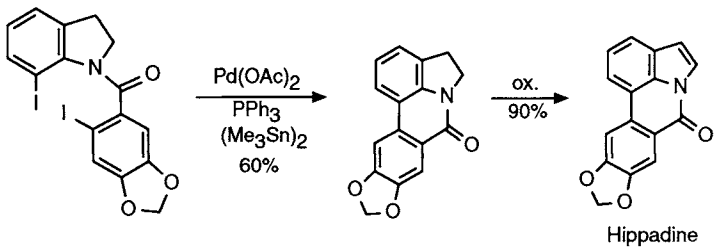
Scheme 36.

This type of palladium chemistry also performed well in the synthesis[79] of rigidin (Scheme 37). The original Stille conditions were modified, to provide coupling product **36** in good yield.

Grigg has made extensive studies of various Pd(0) coupling reactions (see, e.g., Scheme 31) and a simple alkaloid synthesis[80], involving a Pd(0)/$(R_3Sn)_2$ catalyst system (R = alkyl) for aryl-aryl coupling, is shown in Scheme 38.



Scheme 37.



Scheme 38.

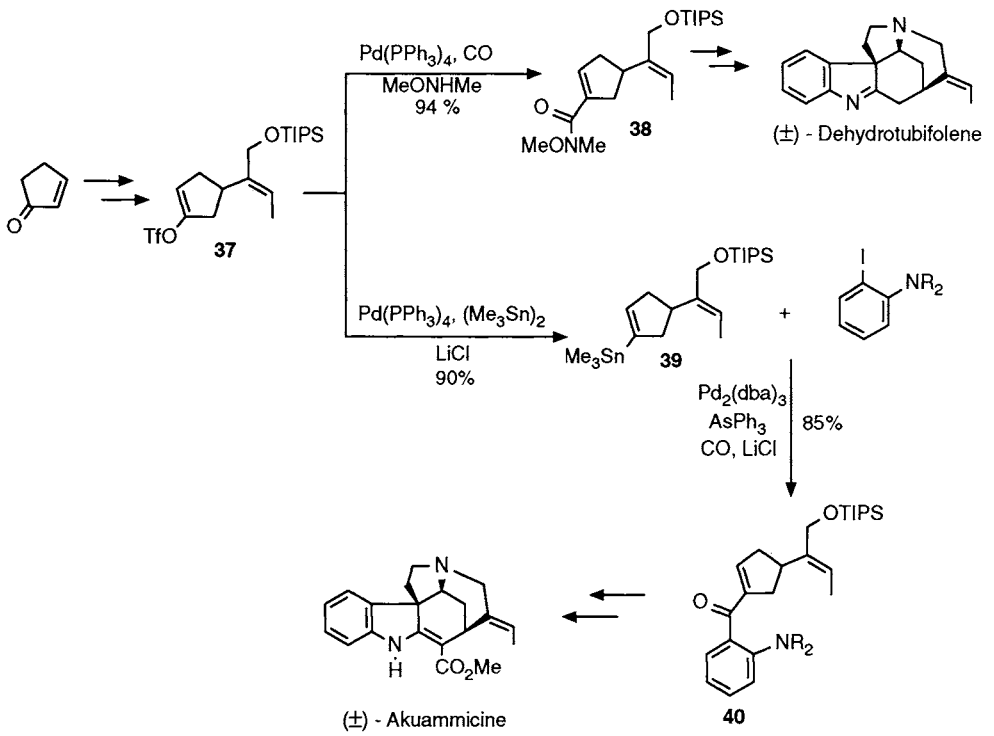
In Scheme 25, the Pd-catalyzed amidation of a vinyl triflate (via carbonyl insertion) was described. Overman[81] has also used this technique en route to the *Strychnos* alkaloid dehydrotubifolene (**37** to **38** in Scheme 39). In an efficient synthesis of the closely related akuammicine[81], he employed Stille-type Pd(0)-catalysis for two key coupling reactions (**37** to **39** and **39** to **40**, Scheme 39). The latter is noteworthy for the use of Ph_3As as ligand[82].

The two alkaloids were synthesized in 6% and 8% overall yield, respectively, from 2-cyclopentenone, the final stages featuring an intriguing aza-Cope-Mannich strategy. (It may also be noted here that Rawal[83] has used Heck-type Pd(0) chemistry in an approach to the same *Strychnos* alkaloids).

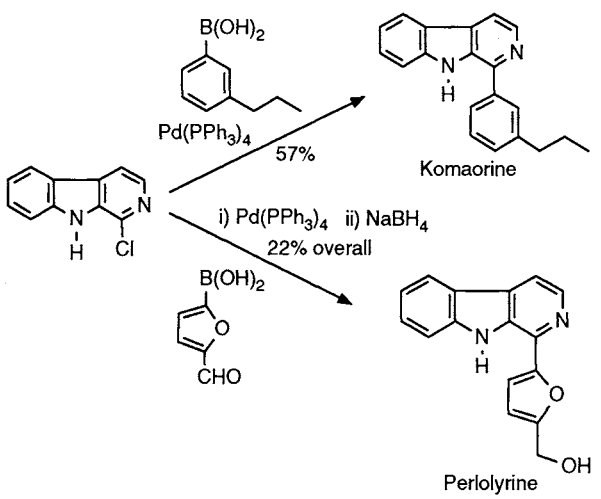
The Suzuki coupling[84] of organoboronic acids and halides provides a complement to the Stille reaction, and two recent examples[85] from the alkaloid field are shown in Scheme 40.

Reaction type A (v).

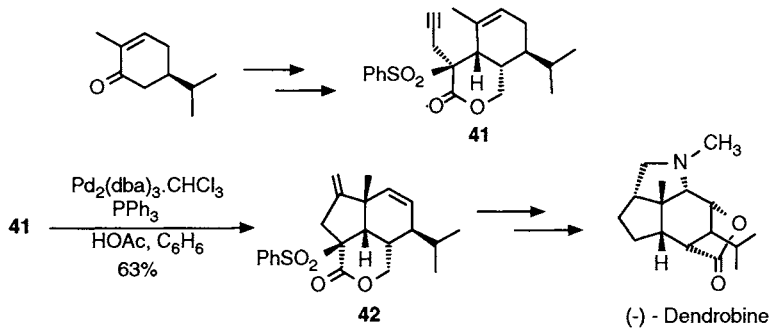
The Pd(0)-catalyzed "cycloisomerization" reaction[18] of enynes has been adapted to an enantioselective formal total synthesis[86] of (-)-dendrobine (Scheme 41). The chiral starting material was (-)-dihydrocarvone, and the final step in the preparation of substrate **41** was the type of Pd(0)-catalyzed allylic alkylation discussed earlier; the key cycloisomerization of **41** to **42** then proceeded in good yield.



Scheme 39.



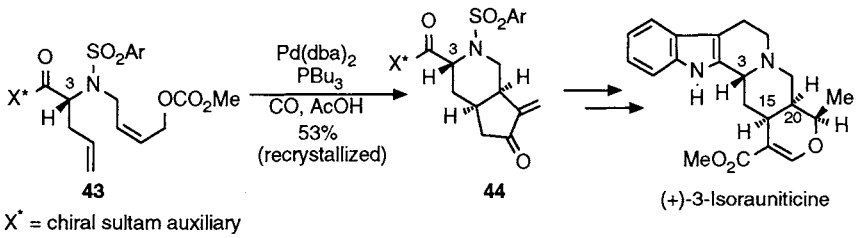
Scheme 40.



Scheme 41.

Reaction type A (vi).

Oppolzer[20,21] has pioneered the use of intramolecular catalytic metallo-ene reactions for the stereoselective construction of carbo- and heterocycles. An application[87] to the enantioselective total synthesis of (+)-3-isorauniticine, involving a catalytic tandem palladium-ene/carbonylation reaction, is shown in Scheme 42.

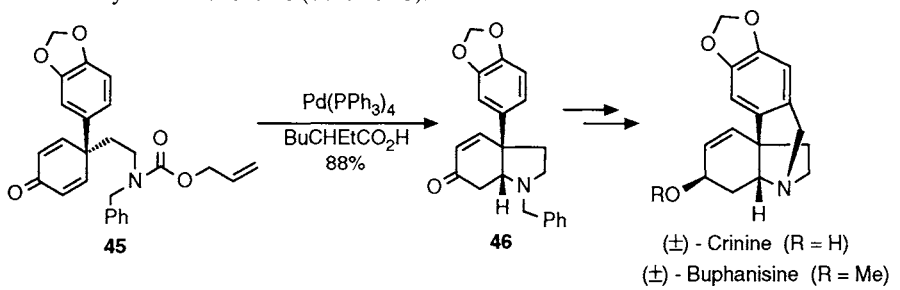


Scheme 42.

The C-3 stereochemistry, set up by Oppolzer's own chiral sultam methodology, was used to control the stereochemistry at C-15 and C-20 which was determined in the key Pd-catalyzed transformation of **43** into **44**.

Reaction type A (vii).

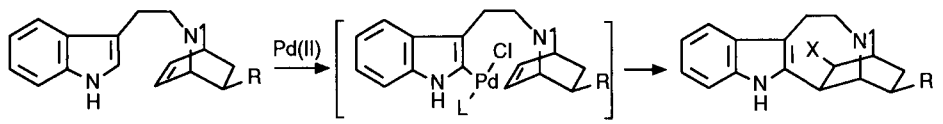
As noted in the introduction, Pd(0)-catalysis can be used for selective deprotection of allylic esters, carbonates and carbamates. Martin[88] has used this technique to good effect in total syntheses of crinine and buphanisine, the deprotection of **45** being accompanied by spontaneous Michael cyclization to hydroindolenone **46** (Scheme 43).



Scheme 43.

Reaction type B (i).

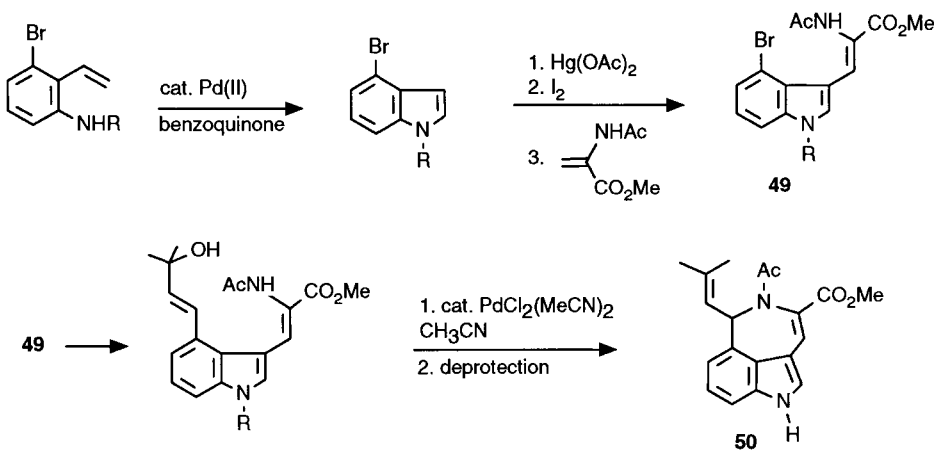
A palladium(II)-mediated intramolecular Heck reaction with stoichiometric amounts of the metal was used in the synthesis of the iboga alkaloid system (Scheme 44).[34,35] An electrophilic attack by Pd(II) on the indole would produce a 2-indolylpalladium species which can undergo a cyclization



Scheme 44

via a cis carbopalladation. The resulting organopalladium complex was treated with $NaBH_4$ to give the product **48a**. Evidence for this mechanism was provided by the use of $NaBD_4$ in the workup, which afforded **48b**.

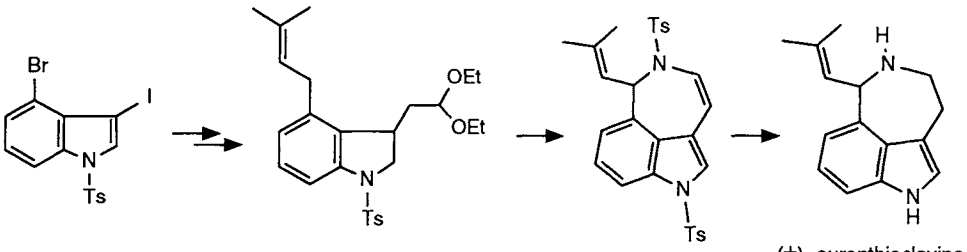
A palladium(II)-catalyzed intramolecular amination was employed for the synthesis of 4-bromoindoles.[89,90] These compounds are useful starting materials in ergot alkaloid synthesis since they are readily functionalized in the 3- and 4-position. A synthesis of the N-acetyl methyl ester of



Scheme 45

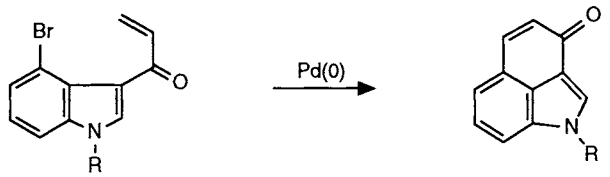
(±)-clavipictic acids **50** from these bromoindoles was developed based on several palladium-catalyzed reactions (Scheme 45).[90] The side chains in the 3- and 4-positions were introduced via Heck arylation reactions,[9] involving Pd(0)-catalyzed reactions. (cf. Reaction type A (ii)). The final cyclization was achieved by employing $PdCl_2(MeCN)_2$ as the catalyst. An amidopalladation of the olefin followed by elimination of the hydroxy group and Pd(II) furnished the product.

A similar methodology was employed for the synthesis of (±)-auranthioclavine (Scheme 46).[91] The 4-bromoindole was functionalized in the 3- and 4-position and cyclized to give the target alkaloid



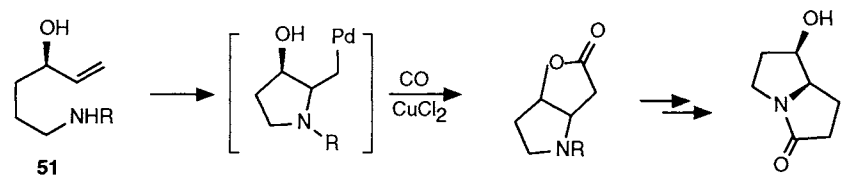
Scheme 46

In a further approach toward tetracyclic ergot alkaloids the functionalized indoles were converted to tricylic indole enones via an intramolecular Pd(0)-catalyzed Heck reaction (eq. 12).[92] However, attempted hetero-Diels-Alder reaction with 1-aza-1,3-dienes did not produce the expected tetracyclic ergot alkaloid systems.



(12)

Intramolecular nucleophilic addition to the (π-olefin)palladium(II) complex of **51** followed by oxidative carbon monoxide cleavage of the intermediate palladium-carbon bond led to the fused pyrrolidine **52** (Scheme 47).[93,94] The latter compounds are useful synthetic intermediates for further transformation to the pyrrolizidine alkaloid skeleton. In the transformation of **51** to **52** palladium(II) is used in catalytic amounts and $CuCl_2$ is employed as the oxidant.

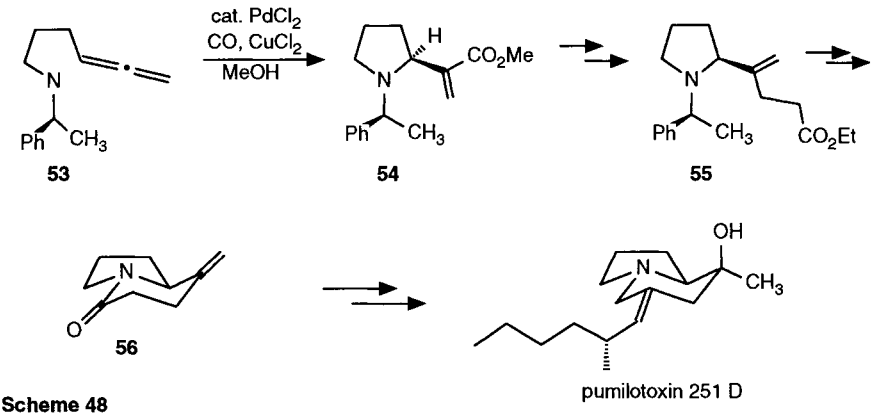


51 **52**

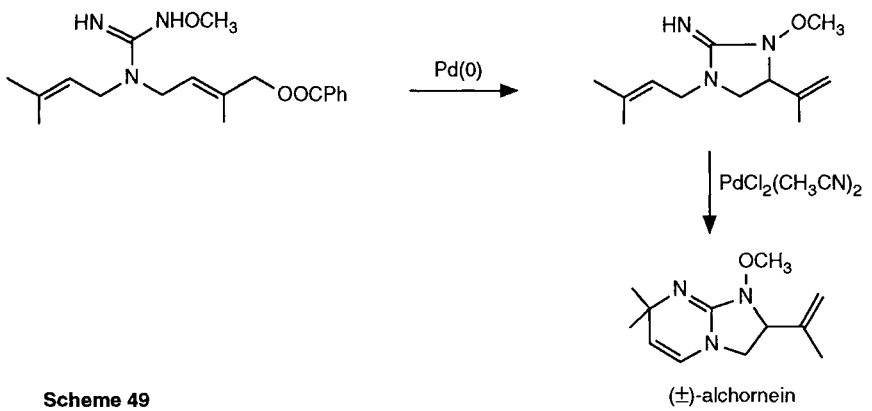
Scheme 47

A related palladium(II)-catalyzed reaction was used in the synthesis of pumiliotoxin 251D (Scheme 48).[95] Palladium(II)-catalyzed aminocarbonylation of allene **53** furnished pyrrolidine **54**. Subsequent reduction of the ester to the allylic alcohol and treatment of this intermediate under Claisen rearrangement conditions produced **55**. The latter compound was converted to lactam **56**, which subsequently was transformed to pumiliotoxin 251D.

An intramolecular aminopalladation followed by a β-hydride elimination was used in the final cyclization step to (±)-alchorneine (Scheme 49).[96] The reaction requires stoichiometric amounts of palladium. The first cyclization involves a Pd(0)-catalyzed allylic amination (cf. Reaction type A (i)).

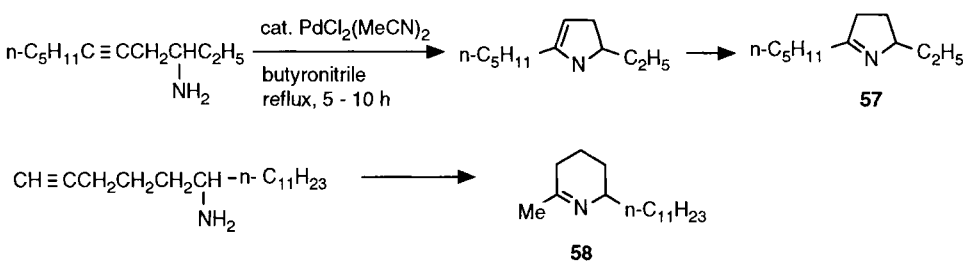


Scheme 48



Scheme 49

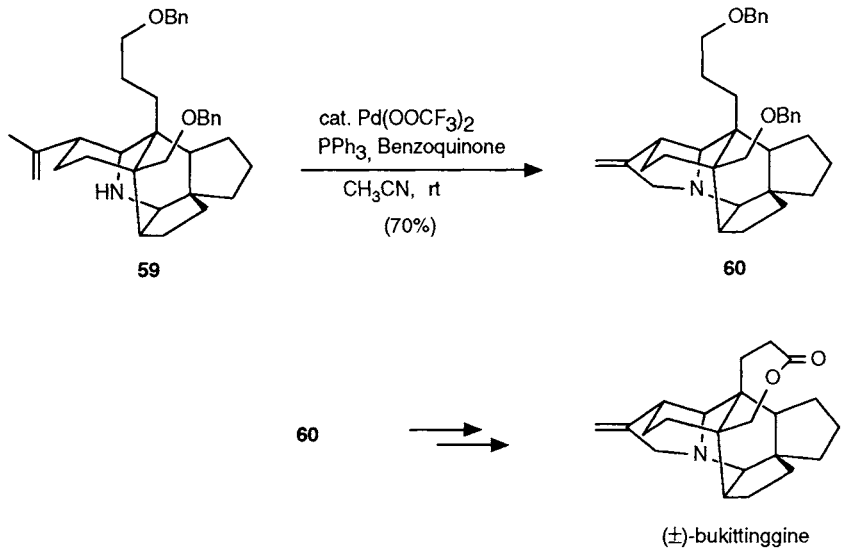
A palladium-catalyzed intramolecular addition of amines to acetylenes gave cyclic imines,[97] the reaction proceeding via an aminopalladation of the acetylene followed by hydrolysis of the palladium-carbon bond (Scheme 50). The latter step requires elevated temperature (refluxing butyronitrile). The 2-pyrroline 1,2,3,4-tetrahydropyridine initially formed in this way isomerized under the reaction conditions to the corresponding imine. By this procedure the ant venom alkaloids **57** and **58** from the South African fire ant *Solenopsis* were synthesized.



Scheme 50

Reaction type B (ii).

A palladium(II)-catalyzed oxidative cyclization was used in the pyrrolidine forming step in a recent total synthesis of the *Daphniphyllium* alkaloid bukittinggine (Scheme 51).[98] It is likely that the palladium(II)-catalyst generates a (π-allyl)palladium complex by allylic C-H bond activation[28] of



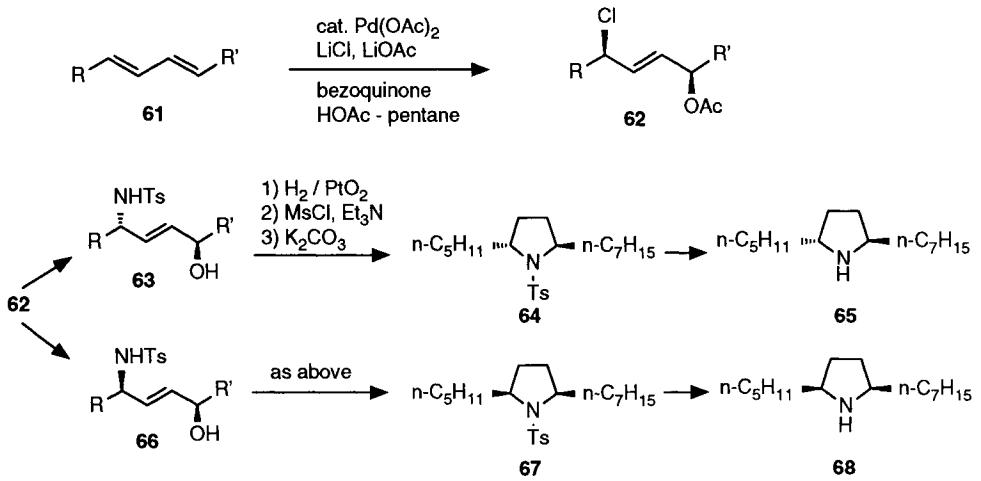
Scheme 51

the allylic CH_3 group in **59**. Intramolecular attack on the π-allyl group by the nitrogen would produce **60**. The palladium(0) complex formed would be reoxidized by quinone[29,33] which renders the process catalytic.

Reaction type B (iii).

The chloroacetoxylation approach discussed in section B (iii) offers unique opportunities for stereocontrolled functionalization of dienes with formation of new carbon-nitrogen, carbon-oxygen and carbon-carbon bonds. After a stereospecific chloroacetoxylation the chloro group can be displaced by either retention or inversion.

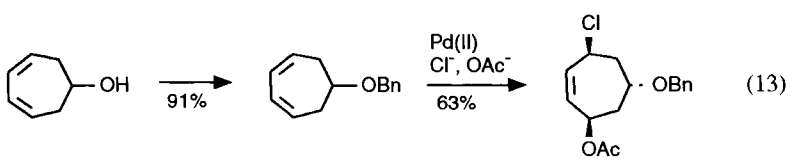
Stereoselective 1,4-functionalization in acyclic systems via the palladium-catalyzed 1,4-chloroacetoxylation was used to synthesize 2,5-disubstituted pyrrolidines,[99] many of which occur in Nature. The synthesis of ant venom alkaloid **65** (from the species *Monomorium latinode*) and its stereoisomer **68** is shown in Scheme 52. Palladium-catalyzed chloroacetoxylation of diene **61** afforded chloroacetate **62** as a mixture of regioisomers, but in a highly stereospecific fashion. Substitution of the chloride by sodium p-toluensulfonamide in an S_N2 reaction and subsequent hydrolysis afforded aminoalcohol **65**. The latter was transformed into *N*-tosylpyrrolidine **64** in a three step sequence involving hydrogenation, mesylation and cyclization. Detosylation of **64** afforded the ant venom alkaloid **65**. The *cis*-isomer of **68** was also available via the same method. Palladium-catalyzed substitution of the chloride in chloroacetate **62** and subsequent hydrolysis afforded *syn*-amidoalcohol **66**. Transformation of **66** to **68** was done employing the same methods as



Scheme 52 (Rand R' = n-C_4H_9 or n-C_7H_{15})

used for the transformation of **63** to **65**.

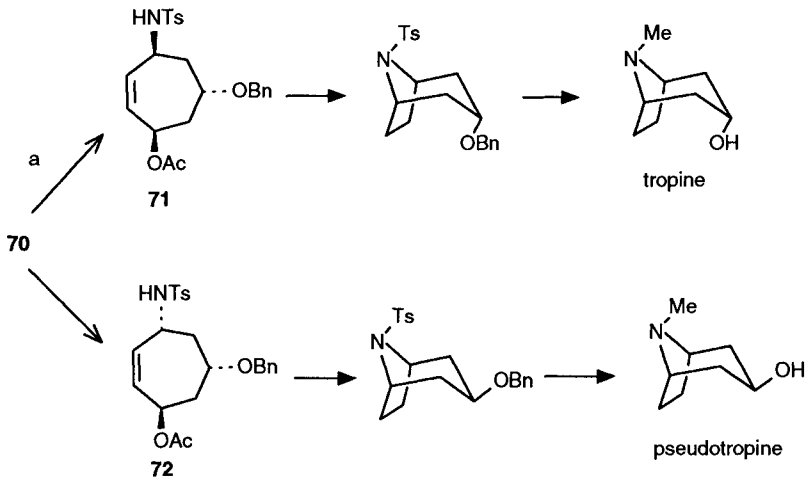
Bicyclic pyrrolidines were also available via the same type of procedure.[100,101] In this way stereocontrolled syntheses of tropane alkaloids were developed based on the Pd(II)-catalyzed chloroacetoxylation approach (Scheme 53). The key intermediate for the synthesis, chloroacetate **70** was prepared according to eq. 13. The chloroacetoxylation of diene **69** was highly stereoselective



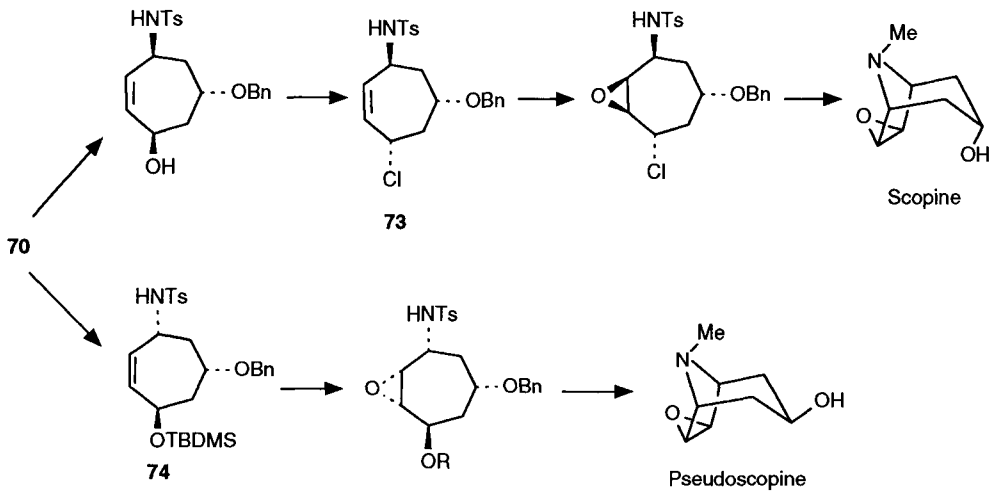
(13)

and gave chloroacetate **70** in which the chloro- and acetoxy groups have both added trans to the benzyloxy substituent. Reaction of the chloroacetate **70** with NaNHTs in CH_3CN-DMSO either at 20 °C in the presence of $Pd(PPh_3)_4$ as catalyst or in CH_3CN at 80 °C without catalyst afforded **71** and **72**, respectively. In the latter intermediates the required stereochemistry between the carbon-oxygen bond in the 6-position and the carbon-nitrogen bond in the 4-position has been established. Subsequent hydrogenation of the double bond and transformation of the acetoxy group into a leaving group allowed cyclization to the 8-aza-bicyclo[3,2.1]octane system. Deprotection and methylation afforded pseudotropine and tropine respectively.[100]

In an analogous synthesis of scopine and pseudoscopine, the double bond was epoxidized prior to cyclization (Scheme 54).[101] A syn epoxidation relative to the nitrogen is required for a synthesis of the target molecules. This was achieved by epoxidation of **73** (> 98 % syn to nitrogen) for the scopine synthesis and of **74** (> 87 % syn to nitrogen) for the pseudoscopine synthesis. The epoxides were cyclized , deprotected, and methylated to give the target molecules.

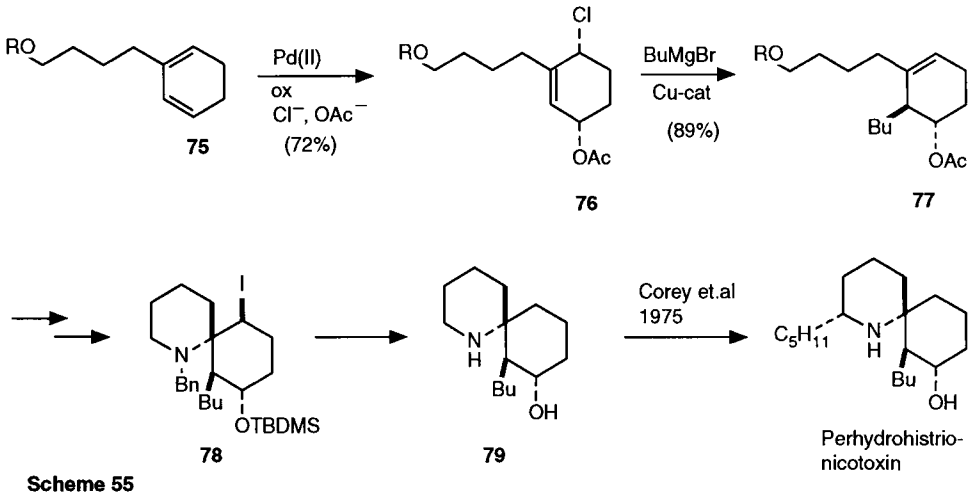


Scheme 53



Scheme 54

The palladium-catalyzed chloroacetoxylation was also applied to a stereoselective formal total synthesis of perhydrohistrionicotoxin (Scheme 55).[102] The requisite 2-substituted 1,3-cyclohexadiene **75** was readily obtained by known procedures. The present approach requires trans addition of a butyl and hydroxy function in the 3- and 4-positions, respectively, of **75**, which is offered by the chloroacetoxylation approach. Regio- and stereoselective Pd(II)-catalyzed chloroacetoxylation produced **76**, which in a subsequent copper-catalyzed Grignard cross coupling reaction afforded **77**. The latter reaction was highly anti- and γ-selective. The benzyloxy group was transformed to a benzylamino group and subsequent diastereoselective iodocyclization afforded **78**. Catalytic hydrogenation to remove the benzyl- and iodo groups and acidic workup furnished **79** and



Scheme 55

its transformation to perhydrohistrionicotoxin has previously been described.[103]

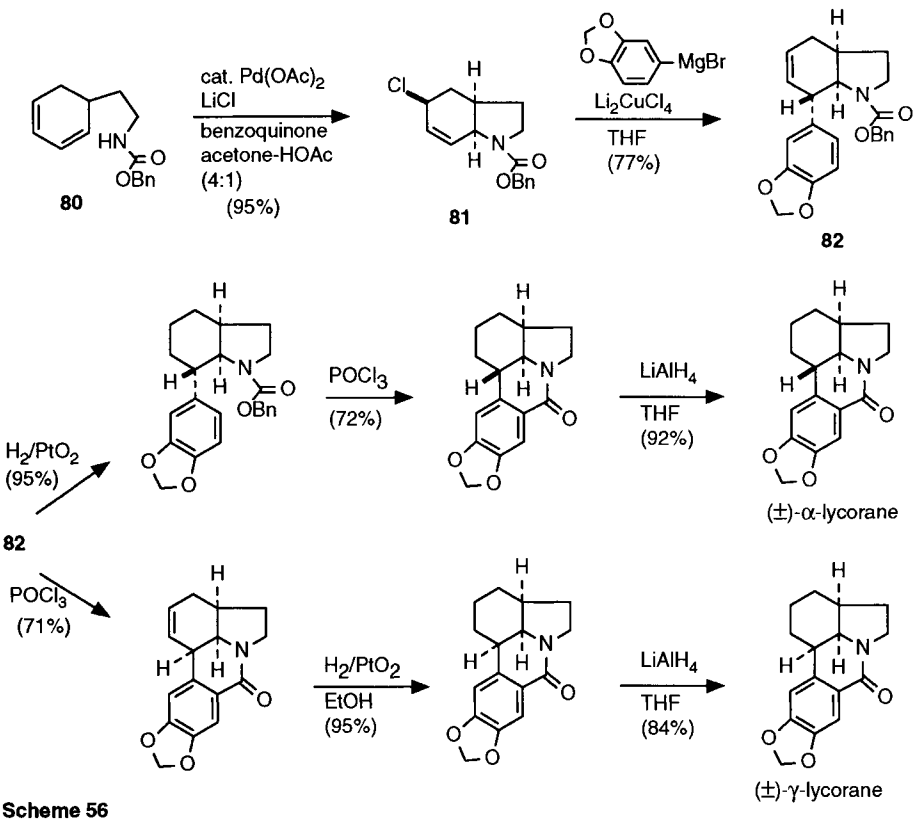
In a synthesis of α- and γ-lycorane (Scheme 56) a related combination of a Pd(II)-catalyzed 1,4-oxidation and a copper-catalyzed cross coupling was employed to obtain an intramolecular 1,2-addition of a nitrogen function and an aryl groups to a 1,3-diene.[104] Palladium-catalyzed intramolecular 1,4-chloroamidation[105] of diene **80** afforded the hexahydroindole **81** as the sole product. The nitrogen and a chloro group add to the 1- and 4-position of the diene, respectively, in a *cis*-manner. A copper-catalyzed S_N2' substitution of the chloro group by the methylenedioxyphenyl Grignard reagent similar to that described above produced **82** with good stereo- and regioselectivity. The transformation of **82** to α-lycorane was achieved by catalytic hydrogenation, Bischler-Napieralski cyclization and finally $LiAlH_4$ reduction of the amide. When the order of hydrogenation and cyclization was reversed a highly stereoselective isomerization took place in the Bischler-Napieralski cyclization. In this way transformation of **82** to γ-lycorane was realized. The method in Scheme 56 leads to α and γ-lycorane of high isomeric purity in each case (>99.8 %).

The intramolecular Pd(II)-catalyzed 1,4-oxidation was recently extended to the use of a nucleophile with the ability of making a 2-fold attack on the diene.[106] This leads to a bicyclic system and constitutes a formal [4+1] cycloaddition (Scheme 57).

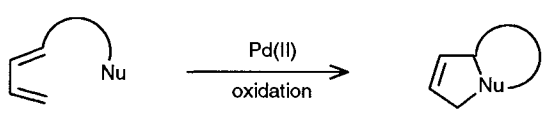
This new methodology has proved useful for the preparation of aza-bicyclic systems when an amide was employed as nucleophile. In this way a number of pyrrolizidine and indolizidine alkaloids are readily accessible. In a short synthesis of (±)-heliotridane (Scheme 58), diene amide **83** was converted to pyrrolizidinone **84** in a Pd(II)-catalyzed intramolecular 1,4-oxidation in THF with $CuCl_2/O_2$ as the oxidant.[106] Subsequent catalytic hydrogenation of the double bond, which occurred exclusively from the least hindered side, followed by $LiAlH_4$ reduction of the amide, afforded (±)-heliotridane.

Reaction type B (iv).

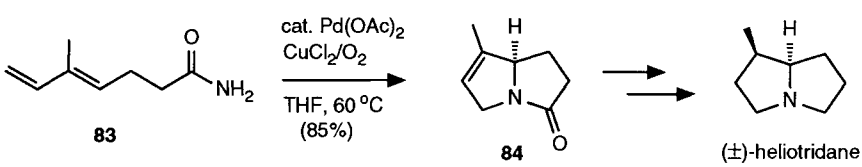
A synthesis of the *Amaryllidaceae* alkaloid narwedine via an ortho-palladation was described



Scheme 56

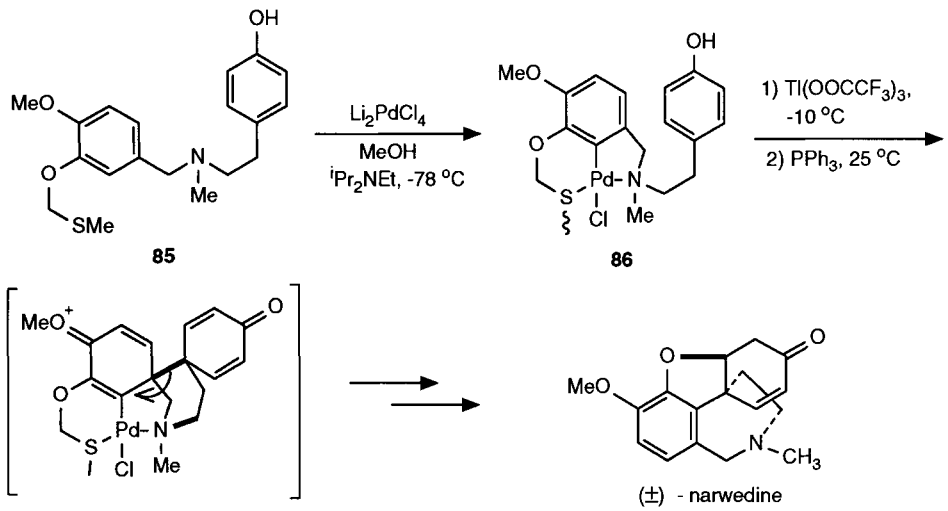


Scheme 57. Formal [4 + 1] Cycloaddition



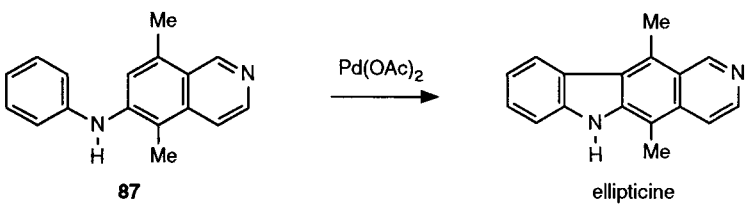
Scheme 58

by Holton (Scheme 59).[107] Reaction of **85** with stoichiometric amounts of Li_2PdCl_4 in methanol produced palladacycle **86** as an 1:1 mixture of diastereoisomers. Treatment of **86** with $Tl(OOCF_3)_3$ at -10 °C followed by addition of PPh_3 and warming the solution at room temperature for several hours afforded racemic narwedine.

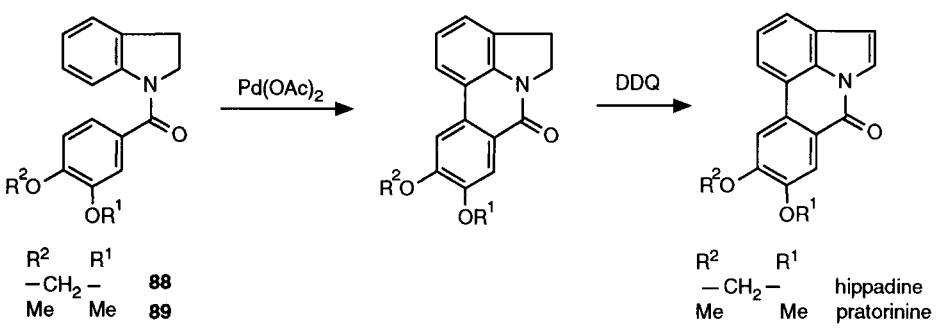


Scheme 59

Cyclization of aryl isoquinoline amine **87** to ellipticine was achieved in moderate yield by employing a $Pd(OAc)_2$-mediated C-C coupling (eq. 14).[108] The reaction most likely proceeds via an initial ortho-palladation.

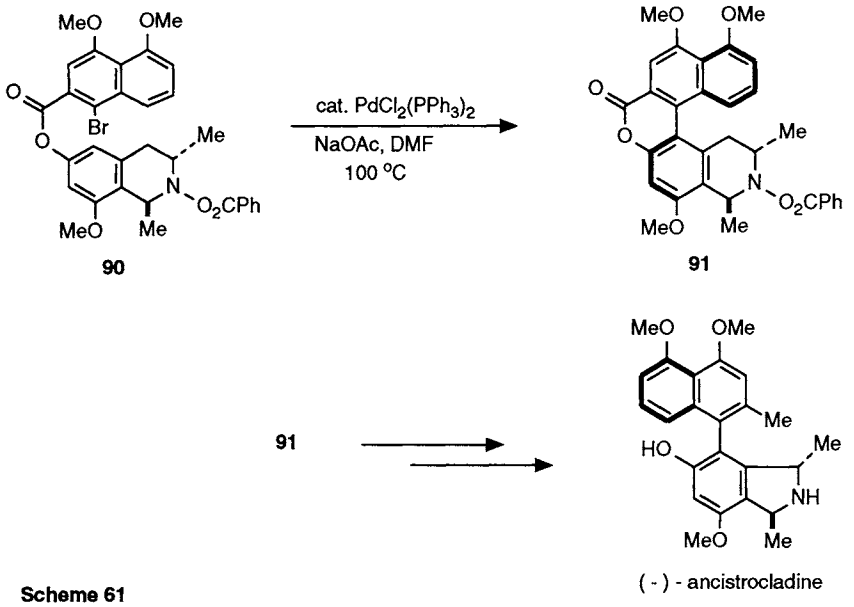


An aryl-aryl coupling based on Pd(II) activation of aromatic C-H bonds was used for the synthesis of pyrrolophenanthridone alkaloids (Scheme 60).[109] Reaction of acylindoles **88** and **89** with stoichiometric amounts of $Pd(OAc)_2$ and subsequent dehydrogenation furnished hippadine and pratorinine.



Scheme 60

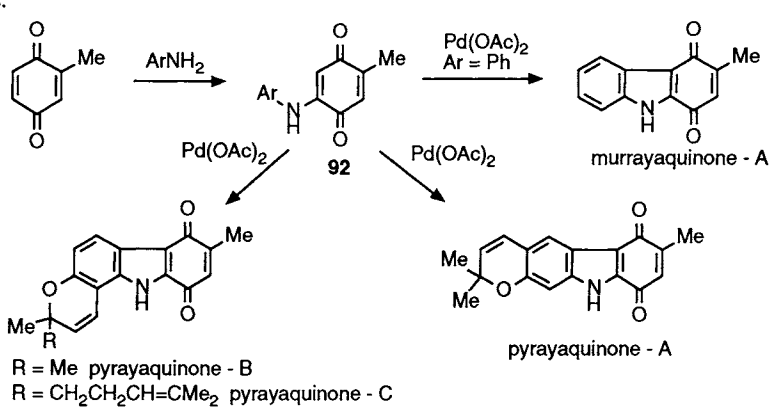
A related aryl-aryl coupling was achieved in a reaction employing $PdCl_2(PPh_3)_2$ as the catalyst in the synthesis of (-)ancistrocladine (Scheme 61).[110] Although the authors suggest that this reaction



Scheme 61

is a palladium(II)-catalyzed reaction, which then would occur via an ortho-palladation of **90**, one cannot exclude that Pd(II) is reduced in situ to Pd(0). In the latter case the reaction would begin with an oxidative addition of the C-Br bond in **90** to Pd(0) followed by an aromatic C-H bond activation by an arylpalladium(II) species.

Arylaminoquinones **92** were cyclized to carbazolequinone alkaloids via $Pd(OAc)_2$mediated carbon-carbon bond formation (Scheme 62).[111] An ortho-palladation of the aromatic compound followed by Heck type arylpalladium addition (cf. Reaction A (ii)) to the quinine would account for the products.



Scheme 62

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Atta-ur-Rahman (Ed.) *Studies in Natural Products Chemistry, Vol. 16*

Recent Progress in the Synthesis of Piperidine and Indolizidine Alkaloids

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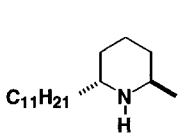
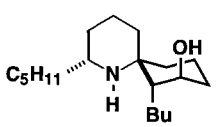
1.0 INTRODUCTION

There are many piperidine containing compounds which possess interesting biological and medicinal properties, a few of which are shown in Scheme 1.1.[1,2] The majority of piperidine based alkaloids have been isolated from plant sources. Palustrine, a macrocyclic spemidine built around a tetrahydropyridine ring, which is an isolate of the plant *Equisetum palustre,* causes disease in livestock when ingested.[3,4] Piclavine A was recently isolated from the Caribbean tunicate *Clavela picta*, and shows excellent antifungal and antibacterial activity.[5] Solenopsin A exhibits hemolytic, insecticidal, and antibiotic activity.[6]

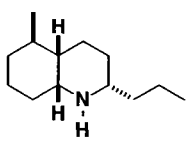
Scheme 1.1. Representative Piperdine Containing Natural Products.



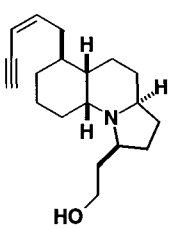
Solenopsin A



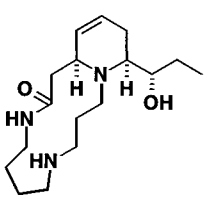
Perhydrohistrionicotoxin



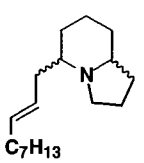
Pumiliotoxin C



Gephyrotoxin



Palustrine



Piclavine A

The secondary metabolites found in the skin secretions of the *dendrobatid* family of central American frogs have been the subject of much recent interest.[7] Among some of the important piperidine based alkaloids from this source are pumiliotoxin C, gephyrotoxin, and the histrionicotoxins. The biological activity of these alkaloids stems from their ability to effect movement of potassium and sodium ions through ion channels in nerve and muscle cells.

The varied biological activities of the piperidine and indolizidine alkaloids have resulted in a considerable number of efforts directed toward their synthesis. Two excellent reviews on the synthesis of piperidine based alkaloids, by Wang[8] and Michael,[9] cover work in this area up to 1990. This review will cover the literature from January 1990 through June 1993.

This review is divided into two sections; non-asymmetric methods, and asymmetric methods. The non-asymmetric methods section is organized by the key transformation(s) used to create the piperidine ring. The asymmetric section is divided by source of initial chirality. One important area which has been omitted is the synthesis of polyhydroxylated piperidines from carbohydrates which is the subject of a recent review by Burgess and Henderson.[121]

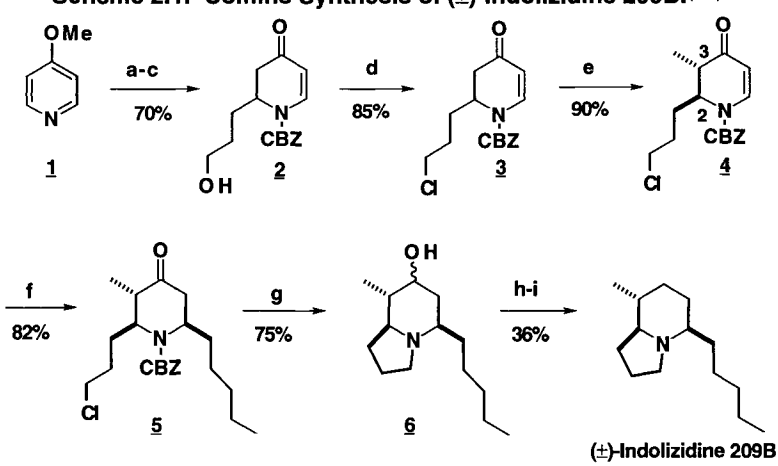
2.0 NON-ASYMMETRIC METHODS

2.1 From Pyridine Derivatives

An attractive route to the formation of piperidine and indolizidine alkaloids is through the selective functionalization of pyridine derivatives.[10] Significant recent advances in this area have been made by Comins and coworkers via selective nucleophilic addition to 4-substituted pyridines.[11-14]

The synthesis of the frog skin secretion alkaloid indolizidine 209B was accomplished in 7 steps from 4-methoxypyridine (Scheme 2.1).[12] Addition of benzyl chloroformate followed by the appropriate Grignard reagent, and acidic workup afforded enone **2**. The alcohol was converted to chloride **3** with *N*-chlorosuccinimide and triphenylphosphine.

Scheme 2.1. Comins Synthesis of (±)-Indolizidine 209B.[12]

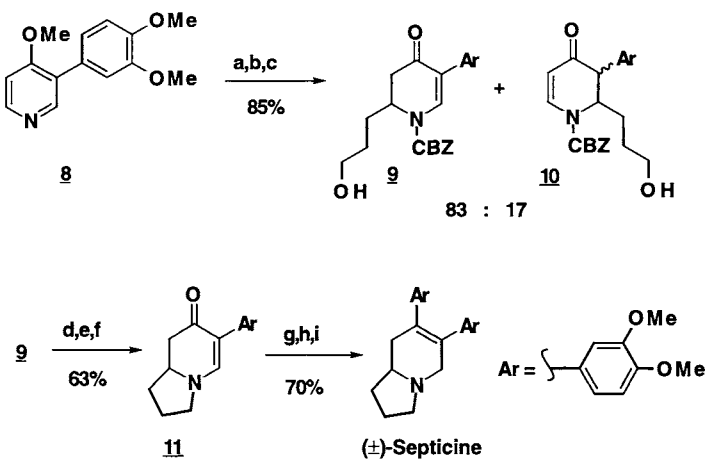


(a) CBZ-Cl; (b) $ClMgOCH_2CH_2CH_2MgCl$; (c) H_3O^+; (d) NCS, PPh_3; (e) NaHMDS, MeI; (f) $BF_3{\cdot}OEt_2$, CuBr, pentyl magnesium bromide; (g) H_2, Pd/C, Pt/C, Li_2CO_3; (h) *N,N'*-TCDI, DMAP; (i) Bu_3SnH, AIBN.

Treatment of **3** with sodium hexamethyldisilazide, followed by trapping of the enolate with methyl iodide gave a 90% yield of the desired *trans*-diastereomer **4**. A stereoselective conjugate addition was then accomplished by treatment of **4** with boron trifluoride etherate and pentyl cuprate. The stereoselectivity of addition is interesting since the C(2) substituent in **4** is in an axial orientation, due to $A^{1,3}$ strain with the carbamate. This demonstrates a strong stereoelectronic preference for axial attack of the nucleophile in the face of a significant steric interaction. Hydrogenation of the carbobenzyloxy (CBZ) protecting group in the presence of lithium carbonate resulted in cyclization and reduction to the indolizidineol **6** via a one pot reaction. Removal of the hydroxyl was accomplished by treatment with *N,N'*-thiocarbonyldimidazole, and reduction with tributyltin hydride/ azobisisobutyronitrile to provide indolizidine 209B.

A synthesis of the biaryl indolizidine alkaloid septicine was also accomplished using this methodology (Scheme 2.2).[11] Activation of **8** with benzyl chloroformate followed by addition of the Grignard reagent derived from 1-bromopropylethoxyethyl ether, and hydrolysis, provided enones **9** and **10** in a 83:17 ratio. The two regioisomers were then separated by chromatography. Conversion of the alcohol to the chloride and removal of the carbobenzyloxy protecting group from **9** afforded the secondary amine. Treatment of this amine with *n*-butyllithium resulted in intramolecular *N*-alkylation to afford the desired indolizidinone **11**. Indolizidinone **11** was then converted to the enol triflate by conjugate reduction with L-Selectride followed by trapping of the resulting enolate with *N*-phenyltrifluoromethanesulfonimide. A palladium catalyzed cross coupling with an aryl zinc reagent afforded septicine. Comins also showed that replacement of the aryl group in **8** with a bulkier triisopropylsilyl group resulted in the regiospecific addition of nucleophiles

Scheme 2.2. Comins Synthesis of (±)-Septicine.[11]

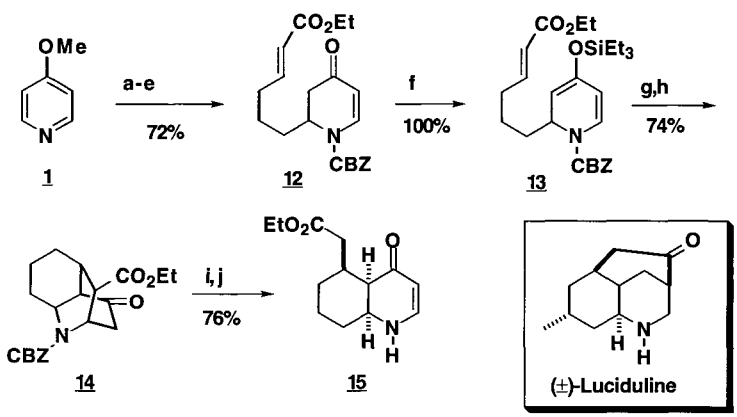


(a) CBZ-Cl; (b) $EEOCH_2CH_2CH_2MgBr$; (c) HCl; (d) PPh_3, NCS; (e) H_2, Pd/C; (f) *n*-BuLi; (g) L-Selectride; (h) $PhN(Tf)_2$; (i) ArZnBr, $(Ph_3P)_4Pd$.

to the 6-position of the pyridine ring. The resulting 3-silyl substrate was used in a second synthesis of septicine and the alkaloid tylophorine.[11]

Comins coupled the above methodology with a subsequent Diels-Alder, retro-Mannich sequence in model studies toward the synthesis of *Lycopodium* alkaloids such as luciduline (Scheme 2.3).[14] Grignard addition to **1**, followed by side chain homologation, via a Swern oxidation and Horner-Wittig olefination afforded enone **12**. Treatment of **12** with sodium hexamethyldisilazide and trapping with triethylsilyl chloride provided silyl enol ether **13**. Diene **13** underwent an intramolecular Diels-Alder reaction, upon heating to 138 °C, to give tricycle **14**. Removal of the carbobenzyloxy group followed by treatment with lithium diisopropylamide initiated a retro-Mannich ring opening to provide the bicyclic compound **15**. A formal total synthesis of the *Lycopodium* alkaloid luciduline was reported using an enantioselective version of this methodology.[14]

Scheme 2.3. Comins Model Studies Toward (±)-Luciduline.[14]



(a) $EEOCH_2CH_2CH_2MgBr$; (b) CBzCl; (c) H_3O^+; (d) Swern oxid.; (e) $(EtO)_2POCH_2CO_2Et$, t-BuOK; (f) TESCl, NaHMDS; (g) xylene reflux; (h) H_3O^+; (i) H_2, Pd/C; (j) LDA, DPA.

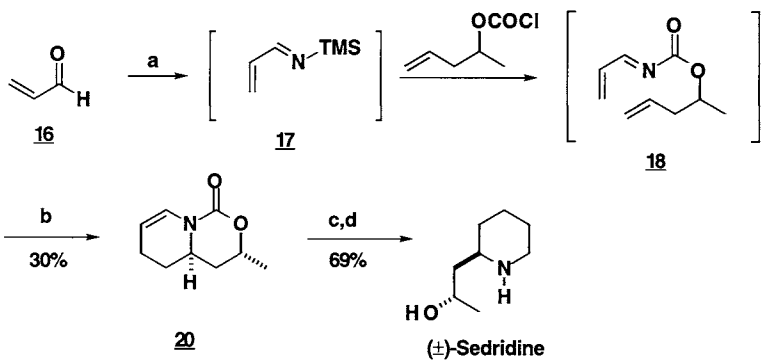
2.2 Hetero-Diels-Alder Approaches

Aza-Diels-Alder approaches to form piperidine rings have been extensively studied, and the three basic permutations; Imine + Diene, 1-azadiene + ene, and 2-azadiene + ene, have all been investigated. Major contributions to these areas have been made by the groups of Fowler,[15-17] Ghosez,[18,19] Jung,[20,21] and Weinreb.[22] However, challenges still remain in controlling the regio and stereoselectivity of these reactions.

Yamamoto and co-workers recently reported a one pot synthesis of the sedridine precursor **20** (Scheme 2.4).[23,24] Acrolein was treated with lithium hexamethyldisilazide and trimethylsilyl chloride to afford azadiene **17**. Addition of 4-pentenyl chloroformate to the reaction mixture, followed by heating, provided a single diastereomer of **20** in 30%

yield. The stereoselectivity of the cycloaddition was directed by the methyl substituent in the tether. This is a noteworthy result given that 1-azadiene Diels-Alder cycloadditions do not normally show good diastereo-selectivity.[16] Hydrogenation of **20**, followed by hydrolysis of the carbamate afforded the alkaloid sedridine in 69% yield.

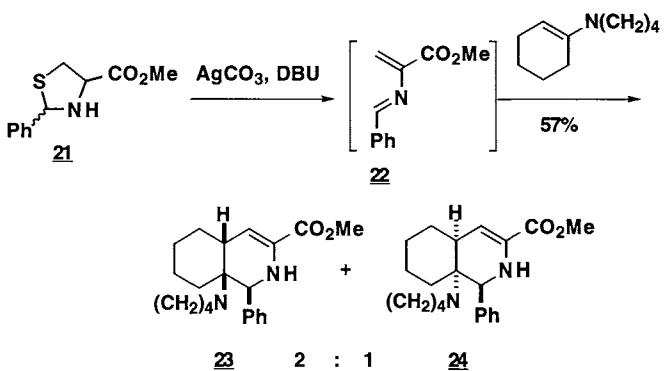
Scheme 2.4. Yamamoto Synthesis of (±)-Sedridine.[23,24]



(a) LiHMDS, TMSCl; (b) xylene reflux; (c) H_2, Pd/C; (d) KOH, H_3O^+, NaOH.

Gilchrist used the procedure of Ohler and Schmidt[25] to generate 2-azadienes from cysteine (Scheme 2.5).[26] Treatment of thiazolidine **21** with silver carbonate and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in the presence of an excess of an activated alkene provided a mixture of cycloadducts **23** and **24**. A limitation of this procedure is that the alkene must be activated with an electron donating group or dimerization of the diene is the major reaction product.

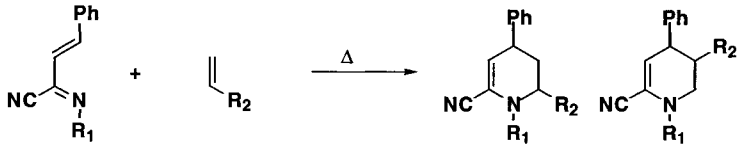
Scheme 2.5. Gilchrist Synthesis of Substituted Piperidines.[26]



Fowler reported that 2-cyano-1-azadienes were useful reagents in the synthesis of piperidine alkaloids.[15] The resulting 2-cyanopiperidines could easily be transformed into a variety of functionalized piperidines. Recent work by Fowler and Grierson examined the scope of this reaction by evaluating the stereoelectronic effects of various

substituents on the diene and dienophile (Scheme 2.6).[27] In all cases the product of endo-cycloaddition predominated (Table 1). The regiochemical course of the reactions seems to depend primarily upon the electronics of the dienophile. For example, when R_2 = CO_2Et, **28** was the sole product, and when R_2 = OEt, **27** was the sole product. This work extends the scope of the 2-cyano-azadiene Diels-Alder reaction.

Scheme 2.6. Fowler and Grierson Diels-Alder Approach to Piperidines.[27]



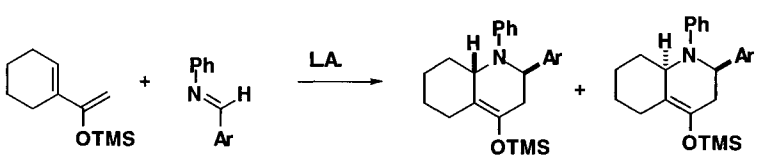
25 26 27 28

TABLE 1. Diels-Alder Cycloaddition of Aza-Dienes 25 with Dienophiles 26.

R_1	R_2	Yield	*cis*-27	*trans*-27	*cis*-28	*trans*-28
C_6H_5	C_6H_5	50%	100%	—	—	—
C_6H_5	OEt	40%	80%	20%	—	—
C_6H_5	CO_2Et	83%	—	—	85%	15%
CO_2Et	C_6H_5	92%	66%	—	30%	3%
CO_2Et	OEt	92%	95%	5%	—	—
CO_2Et	CO_2Et	91%	—	—	90%	10%

Imine Diels-Alder reactions are also useful for the formation of piperidines. These reactions require the imine to be activated by either *N*-substitution with an electron withdrawing group, or by addition of protic or Lewis acids. Ghosez has shown that the stereochemical course of the imine Diels-Alder reaction can be dramatically effected by the Lewis acid chosen for the reaction.[19] A recent example was reported by Wartski (Scheme 2.7).[28,29] Treatment of a mixture of imine **30** and diene **29** with one equivalent of aluminum chloride afforded the endo-product **32** exclusively. Alternatively, the use of a catalytic amount of *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBDMS-OTf)

Scheme 2.7. Wartski Imine Diels-Alder Reaction.[28,29]



29 30 31 32

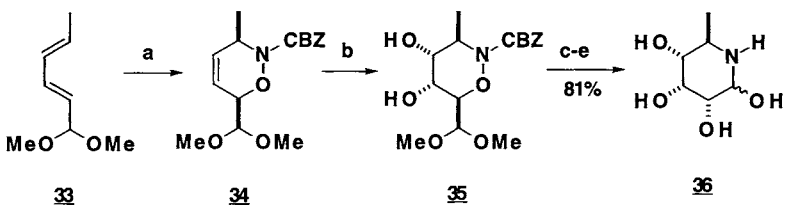
Ar= 4-$(CH_3O)C_6H_4$

L.A. =	31/32
$AlCl_3$ (1 eq)	>2:98
TBDMSOTf (cat)	>98:2

resulted in exclusive formation of the exo-product **31.** The reason for this change in selectivity is not clear; however, when the products were resubjected to the reaction conditions no change in composition was observed, arguing against equilibration of diastereomers after the cycloaddition.[19]

A unique approach to aza-sugars was reported by Defoin and co-workers (Scheme 2.8).[30] Diene **33** underwent cycloaddition with nitroso-*N*-benzyloxycarbonyl to give cycloadduct **34**. Oxidation of the alkene with osmium tetroxide occurred from the less hindered face, to provide a single diastereomer of diol **35**. Hydrogenolysis of the carbobenzyloxy group and reductive cleavage of the N-O bond was accomplished with hydrogen over palladium on carbon. Addition of sulfur dioxide resulted in formation of the imine which was converted to the 1-sulfate. This compound was then hydrolyzed with barium hydroxide to afford a mixture of α- and β-deoxyazasugars **36**.

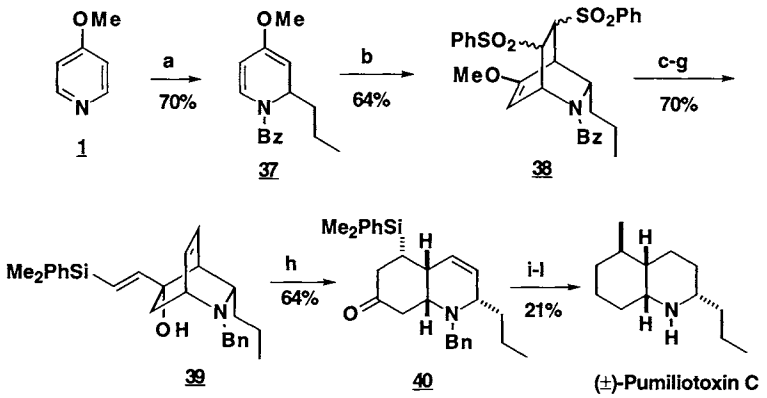
Scheme 2.8. Defoin Aza-Sugar Synthesis.[30]



(a) O=N-CO_2Bn; (b) OsO_4, NMO; (c) H_2, Pd/C; (d) SO_2, 40°C, 3 days; (e) H_2O, $Ba(OH)_2$.

Polniaszek[31a] used an approach similar to Comins' to convert 4-methoxypyridine into dihydropyridine **37** (Scheme 2.9). The resulting diene underwent a Diels-Alder cycloaddition with (*E*)-bis(phenylsulfonyl)ethylene to give bicycle **38**, where the dienophile approached exclusively from the face opposite the propyl group. The steric hindrance of the propyl group is enhanced by a pseudo-axial orientation in **37** to avoid $A^{1,3}$ strain with the amide. Hydrolysis of enol ether **38** with acid afforded the corresponding ketone. Reductive removal of the sulfate groups with sodium amalgam, followed by addition of 2-silylvinyl lithium to the exo-face of the ketone afforded alcohol **39**. Deprotonation with potassium hydride initiated an anion assisted oxy-Cope rearrangement to provide compound **40** in 64% yield. Elimination of the silyl group to form the enone, and subsequent conjugate addition with lithium dimethylcuprate introduced the required methyl group from the convex face. The enolate resulting from the conjugate addition was trapped as the enol triflate and hydrogenated providing the alkaloid pumiliotoxin C.[31b]

Scheme 2.9. Polniaszek Synthesis of (±)-Pumiliotoxin C.[31]

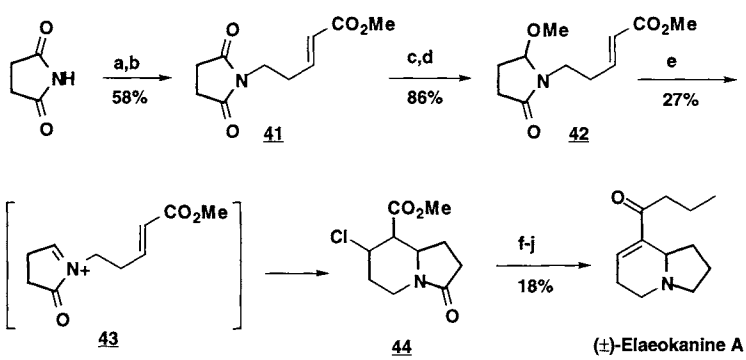


(a) PhCOCl, *n*-PrMgCl; (b) (*E*)-bis(phenylsulfonyl)ethylene, 80°C, 66h; (c) camphorsulfonic acid, CH_3OH; (d) Na(Hg); (e) $LiAlH_4$; (f) HCl; (g) (*E*)-2-(dimethylphenylsilyl)vinyl lithium; (h) KH, DME; (i) $HBF_4{\cdot}Et_2O$, H_2O_2, KF; (j) MsCl, Et_3N, DBN; (k) Me_2CuLi, $PhN(Tf)_2$; (l) Pd/C, H_2, HCl; NaOH.

2.3 Iminium Ion Cyclizations

One of the most widely used methods for the formation of piperidines is via nucleophilic addition to iminium and acyliminium ions.[32] Taber reported the use of the acyliminium ion derived from succinimide for the synthesis of elaeokanine A (Scheme 2.10).[33] Conjugate addition of succinimide to acrolein, followed by Horner-Emmons olefination of the crude aldehyde gave the cyclization precursor **41**. Reduction of **41** with sodium borohydride, and subsequent treatment with methanolic hydrochloric acid afforded methoxy lactam **42**. Acyliminium ion formation with stannic chloride and cyclization onto the alkene produced chloride **44** in 27% yield. The α-β-unsaturated

Scheme 2.10. Taber Synthesis of (±)-Elaeokanine A.[33]

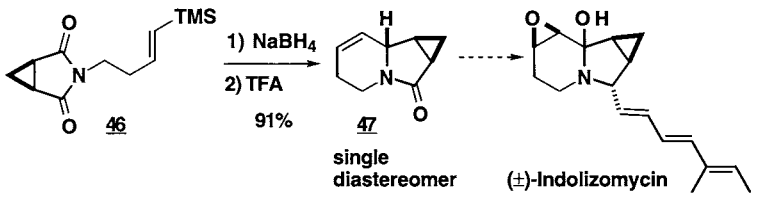


(a) Na, acrolein; (b) trimethylphosphonoacetate, NaH; (c) $NaBH_4$; (d) MeOH/HCl; (e) $SnCl_4$; (f) DBU; (g) DIBAL; (h) Swern oxid.; (i) *n*-PrMgBr; (j) PCC.

ester was used as a terminator to allow the formation of the 6-*endo* product rather than 5-*exo* product. Elimination of the chloride with 1,8-diazabicyclo[5.4.0]undec-7-ene and conversion of the ester to the butyl ketone completed the synthesis of elaeokanine A.

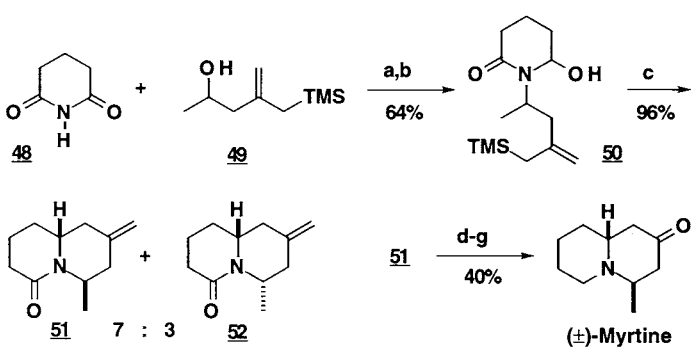
Danishefsky used an acyliminium ion/vinylsilane cyclization in a synthetic approach to the genetically engineered antibiotic indolizomycin (Scheme 2.11).[34] The succinate derived precursor **46** was reduced to the hydroxy lactam with sodium borohydride, and then treated with trifluoroacetic acid to generate the acyliminium ion. Attack of the vinylsilane onto the iminium ion occurred exclusively on the face opposite the cyclopropane ring, producing a single diastereomer of the product **47**. Although this approach was abandoned due to problems later in the synthesis, the example does demonstrate the degree of selectivity possible in this type of reaction.

Scheme 2.11. Danishefsky Approach to (±)-Indolizomycin.[34]



Remusson used an allylsilane as a terminator for an acyliminium ion cyclization in the synthesis of the quinolizidine alkaloid myrtine (Scheme 2.12).[35] Glutaramide was *N*-alkylated with alcohol **49** under Mitsunobu conditions. Subsequent reduction with sodium borohydride gave hydroxy lactam **50**. Treatment of **50** with trifluoroacetic acid resulted in the formation of the diastereomeric quinolizidines **51** and **52**. The predominance of diastereomer **51** was rationalized on the basis of developing $A^{1,3}$ strain, between the

Scheme 2.12. Remusson Synthesis of (±)-Myrtine.[35]

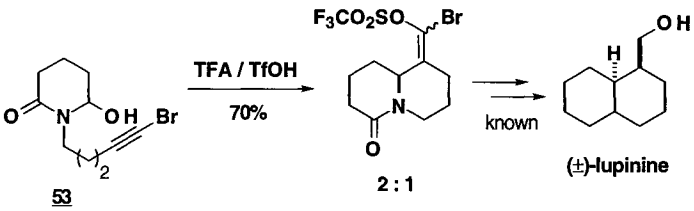


(a) DEAD, PPh_3; (b) $NaBH_4$; (c) TFA; (d) O_3, DMS; (e) 2-ethyl-2-methyl-1,3-dioxolane, *p*-TsOH; (f) $LiAlH_4$; (g) HCl; NaOH.

methyl and the lactam, in the formation of **52**. The two diastereomers were separated by flash chromatography. Compound **51** was then converted to myrtine by ozonolysis of the alkene, protection of the ketone, reduction of the amide, and deprotection.

Gesson used a 1-bromoalkyne as the terminator for the acyliminium ion cyclization of **53** to **54** (Scheme 2.13).[36] It was found that a 1:1 mixture of trifluoroacetic acid and trifluoromethanesulfonic acid was the best acid for this reaction. Trifluoroacetic acid, trifluoromethanesulfonic acid, or hydrofluoric acid alone resulted in significantly lower yields. Compound **54** had been previously converted to the quinolizidine alkaloid lupinine.[37]

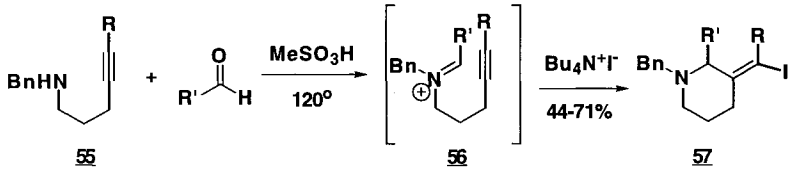
Scheme 2.13. Gesson Synthesis of (±)-Lupinine.[36]



53 **54**

Overman has worked extensively on the total synthesis of alkaloids via iminium ion cyclizations. Recently he used an activated alkyne as the cyclization terminator for an iminium ion cyclization (Scheme 2.14).[38] Formation of iminium ion **56** was accomplished through condensation of amine **55** with various aldehydes. Addition of iodide then promoted cyclization, affording vinyl iodide **57**. Overman's enantioselective work in this area is covered more extensively in Section 3.2.

Scheme 2.14. Overman Iminium Ion Cyclization Approach to Piperidines.[38]

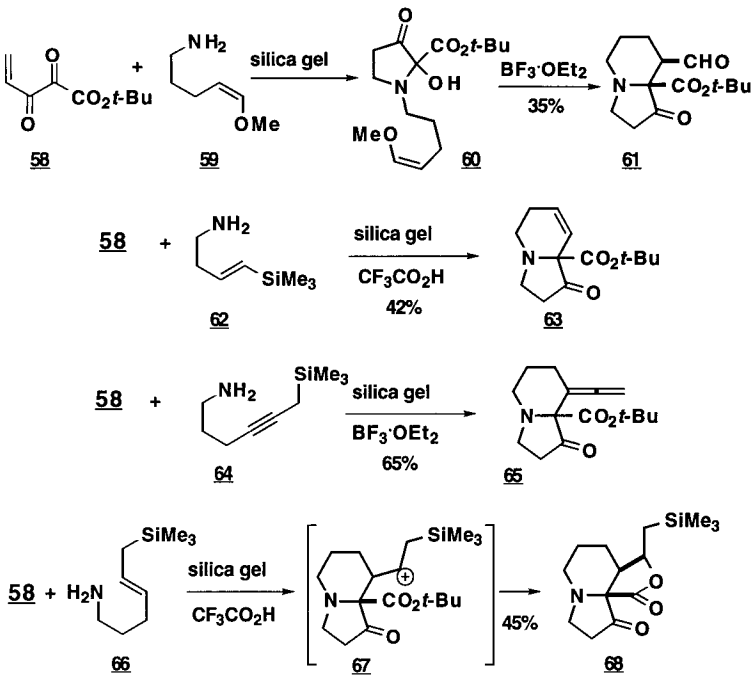


55 **56** **57**

R = H, Me; R'= Me, Et, CO_2Et

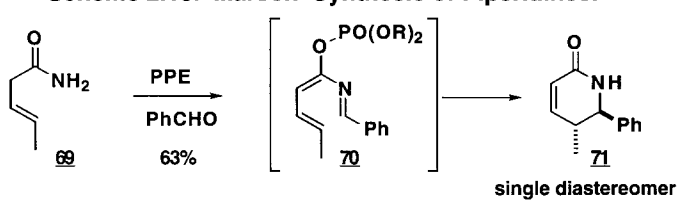
Wasserman reported the use of vicinal tricarbonyls as sources of acyliminium ions (Scheme 2.15).[39] Amines possessing tethered nucleophiles such as enol ether **59** were added to tricarbonyl **58** in the presence of mild acid. Initial conjugate addition of the amine and subsequent addition to the central carbonyl provided aminal **60**. Lewis acid mediated acyliminium ion formation and cyclization onto the pendant enol ether afforded indolizidinone **61**. The cyclization reaction was also performed with vinyl silanes (**62**) and propargyl silanes (**64**) as terminators. In the case of allylsilane **66** the β-silyl cation **67** was trapped by the *t*-butyl ester prior to elimination, resulting in the formation of lactone **68** as the major product.

Scheme 2.15. Wasserman Vicinal Tricarbonyl Approach to Piperidines.[39]



Marson[40] examined the condensation of aryl aldehydes with β-γ-unsaturated amides in the presence of polyphosphoric acid ester[41] to give enol phosphate **70** (Scheme 2.16), which then underwent subsequent cyclization to lactam **71**. The process is proposed to proceed by a disrotatory-electrocyclic ring closure to give the *cis*-isomer of **71**.[40] The *cis*-isomer then equilibrated to the *trans*-isomer via either a [1,5] hydrogen shift, or a series of prototropic shifts.

Scheme 2.16. Marson Synthesis of Piperidines.[40]

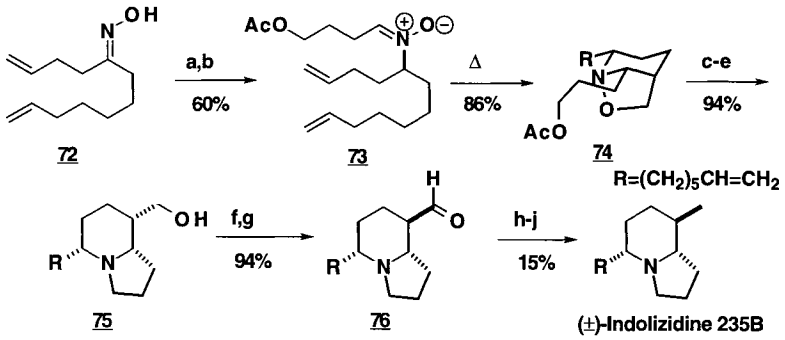


2.4 Dipolar Cycloadditions

The dipolar cycloaddition of alkenes with nitrones has proven to be a useful method for the synthesis of piperidines. Holmes recently used this strategy in the synthesis of indolizidine 235B (Scheme 2.17).[42,43] Oxime **72** was reduced to the hydroxyl amine with sodium cyanoborohydride and then immediately condensed with 4-acetoxybutanal to give nitrone **73**. Heating the nitrone in refluxing toluene afforded the dipolar

cycloaddition product **74**. The acetate was then hydrolyzed and replaced with a mesylate. Cleavage of the N-O bond with zinc in acetic acid followed by intramolecular displacement of the mesylate by the resulting amine provided indolizidine **75**. The alcohol was oxidized to the aldehyde which was then equilibrated to the all equatorial diastereomer with basic alumina. Removal of the carbonyl group in **76** by a reduction, mesylation, reduction sequence gave the frog skin secretion alkaloid indolizidine 235B.

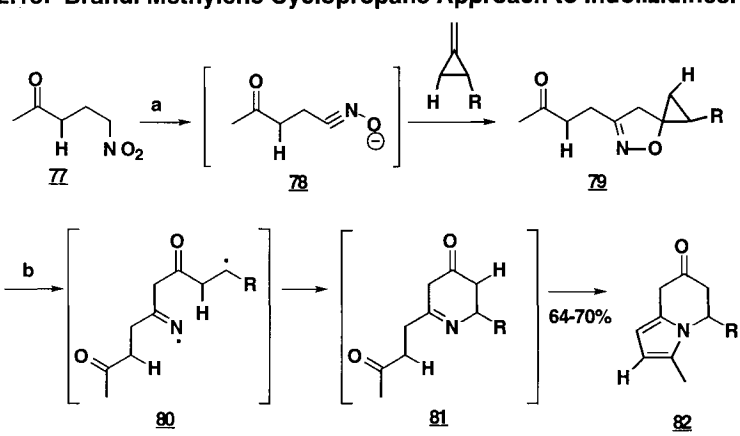
Scheme 2.17. Holmes Synthesis of (±)-Indolizidine 235B.[42,43]



(a) 4-acetoxybutanal; (b) $NaCNBH_3$, pH 3-4; (c) K_2CO_3; (d) MsCl, Et_3N; (e) Zn, AcOH, reflux; (f) Swern oxid.; (g) basic alumina; (h) $NaBH_4$; (i) MsCl, Et_3N; (j) $LiBEt_3H$.

Brandi and co-workers developed a novel approach to indolizidine and quinolizidine structures which involved the dipolar cycloaddition of a nitrile oxide[44] or a nitrone[45] with a methylene cyclopropane (Scheme 2.18). Nitrone **78** was formed in situ from nitro compound **77** using the method of Mukayama.[46] Addition of methylene cyclopropane afforded the cycloaddition product **79** (R = H). Heating a solution of **79** to 163 °C initiated homolytic cleavage of the N-O bond which resulted in cyclopropane ring opening to

Scheme 2.18. Brandi Methylene Cyclopropane Approach to Indolizidines.[44,45]

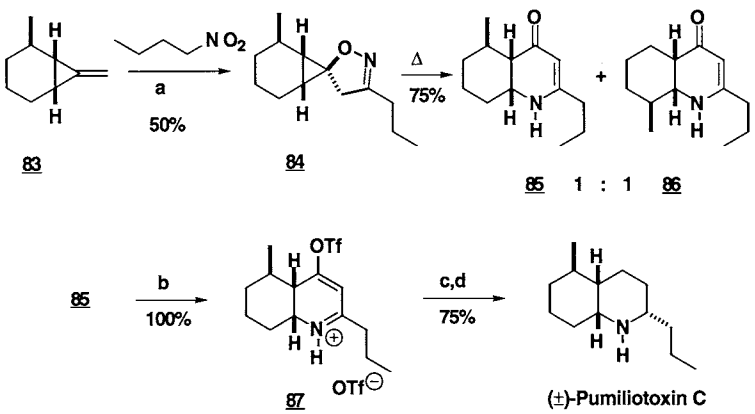


(a) 2 equiv. PhN=C=O, Et_3N; (b) refluxing mesitylene, 2 h.

afford biradical **80**. Recombination of the radicals gave piperidinone **81**. Subsequent nucleophilic attack by nitrogen on the pendent ketone followed by aromatization provided the unsaturated indolizidine **82**.

This strategy was used by Brandi for the total synthesis of pumiliotoxin C (Scheme 219).[47] Nitrobutane was converted to the nitrile oxide and reacted with methylene cyclopropane **83**. Refluxing cycloadduct **84** in xylene produced a 1:1 mixture of regioisomers **85** and **86**. The two isomers were separable by chromatography. The methyl substituent did not appear to play a role in directing the cleavage of the cyclopropane ring. Enone **85** was then treated with triflic anhydride to give the iminium salt **87**. Hydrogenation over platinum oxide provided pumiliotoxin C in 75% yield.

Scheme 2.19. Brandi Synthesis of (±)-Pumiliotoxin C.[47]

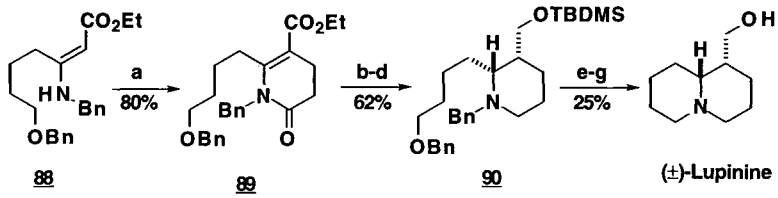


(a) PhN=C=O, Et_3N; (b) Tf_2O; (c) H_2, PtO_2; (d) Amberlite IRA-400.

2.5 Addition of an Amine to a Carbonyl Group

Cyclization of amines onto carbonyl compounds has seen broad application in the synthesis of piperidines. Stille reported the synthesis of lupinine via the annulation of an enamine with acryloyl chloride (Scheme 2.20).[48] Conjugate addition of enamine **88** onto acryloyl chloride, followed by *N*-acylation afforded lactam **89**. The regioisomer resulting from the reverse order of addition was not observed. Hydrogenation of **89** in the presence of sodium carbonate allowed reduction of the alkene without removal of the benzyl protecting groups. The ester was then reduced with lithium aluminum hydride and the resulting alcohol was protected as the *t*-butyldimethylsilyl ether to afford **90**. The benzyl protecting groups were then removed and the amine was cyclized via the alkyl bromide. Removal of the *tert*-butyldimethylsilyl protecting group with tetrabutylammonium fluoride provided the quinolizidine alkaloid lupinine.

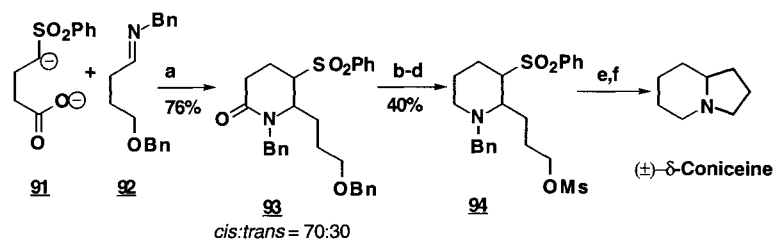
Scheme 2.20. Stille Synthesis of (±)-Lupinine.[48]



(a) acryloylchloride; (b) H_2 45 psi, Pd/C, Na_2CO_3; (c) $LiAlH_4$; (d) TBDMSCl, imidizole; (e) H_2, Pd/C; (f) Ph_3P, CBr_4, Et_3N; (g) TBAF.

Thompson treated the dianion of 4-(phenylsulfonyl)butanoic acid with imine **92** and boron trifluoride etherate to afford lactam **93** as a 70:30 mixture of diastereomers (Scheme 2.21).[49] The same process was attempted on cyclopentyl imines in an effort to provide the indolizidine skeleton directly; however, these attempts were unsuccessful. Selective removal of the benzyl ether by hydrogenation in trifluoroacetic acid followed by reduction of the lactam and mesylation of the alcohol provided piperidine **94**. Reductive cyclization by hydrogenation over palladium hydroxide and removal of the sulfone afforded δ-coniceine.

Scheme 2.21. Thompson Synthesis of (±)-δ-Coniceine.[50]

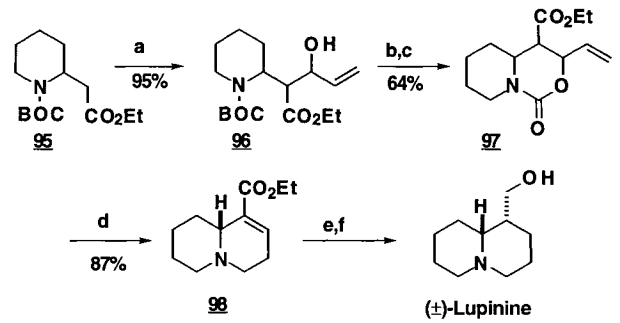


(a) $BF_3{\cdot}Et_2O$; (b) H_2, Pd/C, TFA; (c) B_2H_6; (d) MsCl, Et_3N; (e) H_2, $Pd(OH)_2$; (f) Na-Hg.

A novel synthesis of lupinine via the extrusion of carbon dioxide from cyclic carbamate **97** was reported by Kurihara and co-workers (Scheme 2.22).[50] Addition of the anion of *N*-*t*-butyloxycarbonyl-2-piperidinoacetate (**95**) to acrolein gave allyl alcohol **96**. Formation of the mesylate, followed by treatment with acid, afforded cyclic carbamate **97**. Treatment of carbamate **97** with 1,8-diazabicyclo[5.4.0]undec-7-ene initiated the elimination of carbon dioxide and formation of the amide anion. The anion then added to the δ-position of the resulting diene ester to afford quinolizidine **98**. Reduction of the ester and the alkene provided lupinine. This overall sequence provides an efficient route to quinolizidine skeletons.

Edstrom's approach to epilupinine involved the use of a zwitterionic aza-Claisen rearrangement (Scheme 2.23).[51,52] Piperidine **99** was treated with excess dichloroketene resulting in the formation of the zwitterionic intermediate **100**, which underwent an

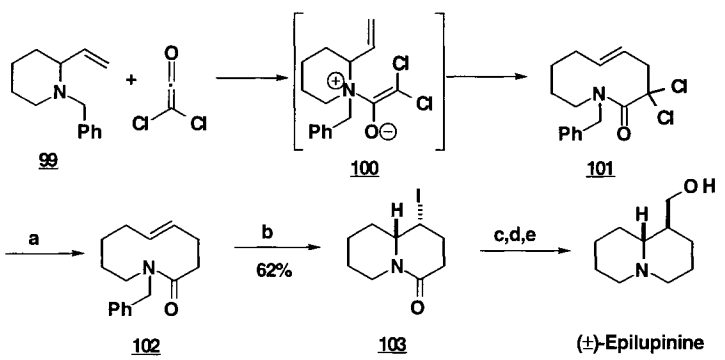
Scheme 2.22. Kurihara Synthesis of (±)-Lupinine.[50]



(a) LDA; CH_2=CHCHO; (b) MsCl, Et_3N; (c) HCl; (d) DBU, DMSO, 120°C; (e) PtO_2, H_2; (f) $LiAlH_4$.

aza-Claisen rearrangement to afford lactam **101**. Removal of the chlorines with zinc-silver amalgam followed by treatment with iodine produced a single diastereomer of theiodolactam **103**. Interestingly, if the cyclization step was performed prior to the removal of the chlorines, the opposite diastereomer was obtained with complete selectivity. Edstrom proposed that the less nucleophilic dichloroamide did not attack the iodonium species but underwent S_N2 displacement of the diiodo compound to afford the opposite diastereomer. Displacement of iodide in **103** with vinyl cuprate, ozonolysis, and reduction afforded (±)-epilupinine.

Scheme 2.23. Edstrom Synthesis of (±)-Epilupinine.[51,52]



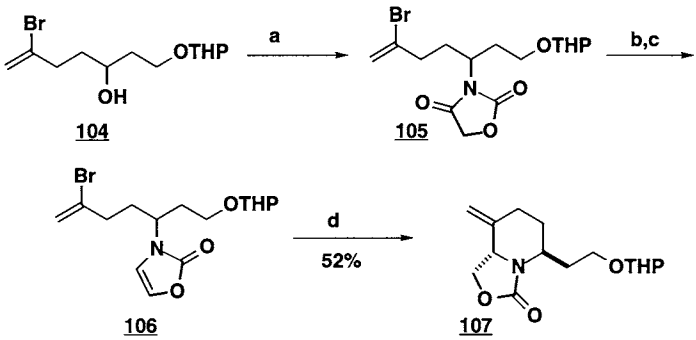
(a) Zn-Ag; (b) I_2, CH_3CN, 50°C, 8 h; (c) CH_2=CHMgBr, CuI; (d) O_3, $NaBH_4$; (e) AlH_3.

2.6 Radical and Photochemical Methods

In the past, radical cyclizations have seen little application to the synthesis of piperidine alkaloids;[53-55] however, recent interest in the utility of radical reactions in synthesis has resulted in their application to the synthesis of alkaloids.[56] Shibuya[57]

used a vinyl radical cyclization for the stereoselective preparation of substituted piperidines (Scheme 2.24). Vinyl bromide **104** was converted to oxazolidine-2,4-dione **105** by a Mitsunobu reaction. Reduction with sodium borohydride followed by treatment with methanesulfonyl chloride, and triethylamine initiated elimination to afford cyclic carbamate **106**. Refluxing **106** with tributyltin hydride and catalytic azobisisobutyronitrile generated the vinyl radical, which then cyclized to provide **107** as a single diastereomer. In general, radical cyclizations in which the stereochemistry is controlled by an acyclic stereocenter are not very selective. In this case, the high selectivity was likely due to $A^{1,3}$ strain in the carbamate which forced the side chain into a pseudo-axial orientation, resulting in the observed stereochemistry.

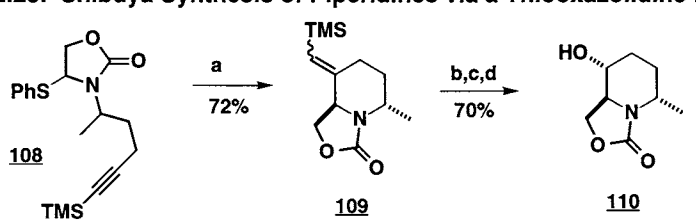
Scheme 2.24. Shibuya Synthesis of Piperidines via a Oxazolidine-2,4-dione.[57]



(a) oxazolidine-2,4-dione, diisopropyldiazodicarboxylate, Ph_3P; (b)$NaBH_4$; (c) MsCl, Et_3N; (d) *n*-Bu_3SnH, AIBN.

The reverse mode of cyclization has also been reported by Shibuya (Scheme 2.25).[58] Thiooxazolidine-2-one **108** was treated with tributyltin hydride/azobisisobutyronitrile generating the vinyl radical, which then cyclized to form piperidine **109** as a mixture of *E*- and *Z*-isomers. Again complete diastereoselectivity in the ring formation was observed. Removal of the silyl group, ozonolysis, and stereoselective reduction of the resulting ketone with sodium borohydride provided 3-hydroxy piperidine **110**.

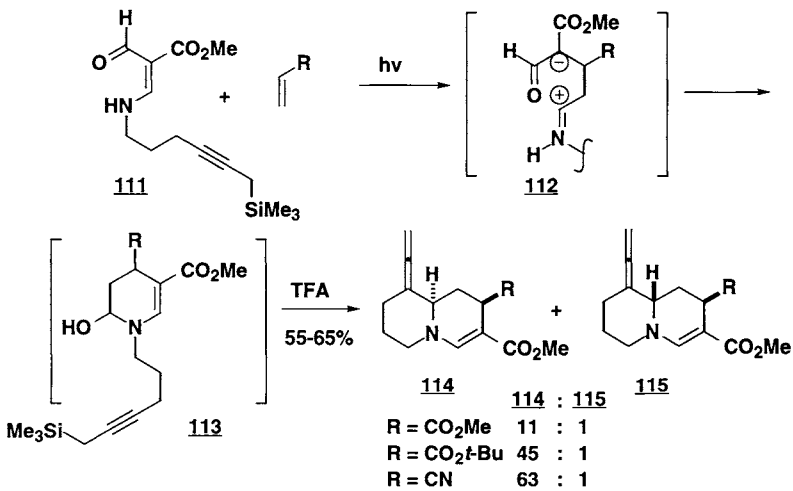
Scheme 2.25. Shibuya Synthesis of Piperidines via a Thiooxazolidine-2-one.[58]



(a) *n*-Bu_3SnH, AIBN; (b) TFA; (c) O_3, DMS; (d) $NaBH_4$.

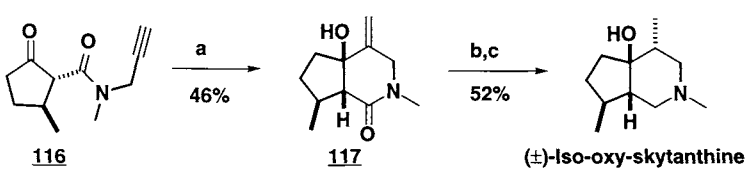
Tietze has published a number of papers on the use of photochemical cycloadditions for the synthesis of tetrahydropyridines.[59] A recent report in this area extends this methodology to the use of electron deficient alkenes (Scheme 2.26).[60] Photolysis of enamine **111** in the presence of electron deficient alkenes initiated a photochemically allowed [2+2]-cycloaddition. Cyclobutane ring opening then provided the β-keto ester enolate **112**. Proton transfer from the iminium ion to the enolate, followed by cyclization of the enamine onto the aldehyde carbonyl afforded aminal **113**. Treatment of **113** with trifluoroacetic acid provided the iminium ion which was then trapped by the propargylsilane to afford diastereomers **114** and **115**, favoring attack on the same face as the R-group. The crystal structure of **115** showed that the R-group adopts an axial orientation to avoid $A^{1,2}$ interactions with the ester. This suggests a strong stereoelectronic preference for axial attack of the nucleophile, even in the presence of steric interactions with the axial R-group.

Scheme 2.26. Tietze Synthesis of Quinolizidines.[60]



Cossy reported the photoreductive cyclization of ketone **116** to **117** which involved photochemical electron transfer from triethylamine and intramolecular radical addition (Scheme 2.27).[61] Reduction of the lactam with lithium aluminum hydride followed by reduction of the exocyclic methylene afforded the naturally occurring alkaloid iso-oxy-skytanthine.

Scheme 2.27. Cossy Synthesis of (±)-Iso-Oxy-Skytanthine.[61]



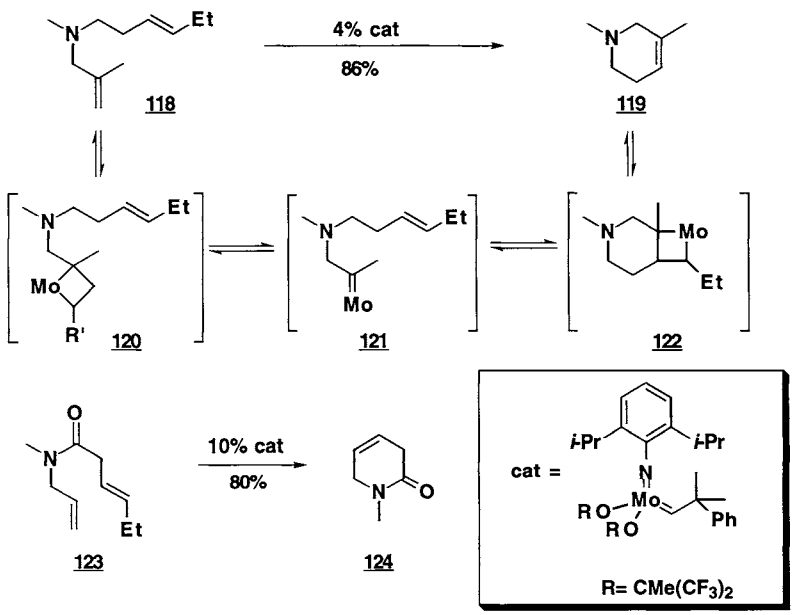
116 117 (±)-Iso-oxy-skytanthine

(a) hv, 254 nm, Et_3N; (b) $LiAlH_4$; (c)Pd/C, H_2.

2.7 Carbenoid Methods

Grubbs has made important advances in the use of catalytic olefin metathesis for the synthesis of carbocycles.[62] This methodology was recently extended to nitrogen heterocycles using the catalyst shown in Scheme 2.28.[63] The mechanism involved initial addition of the carbene to the least substituted alkene to form a metalocyclobutane. Ring opening provided the new carbene, which then cyclized onto the second alkene. Elimination of the carbene from **122** resulted in the formation of tetrahydropyridine **119**.

Scheme 2.28. Grubbs Synthesis of Piperidines.[62,63]

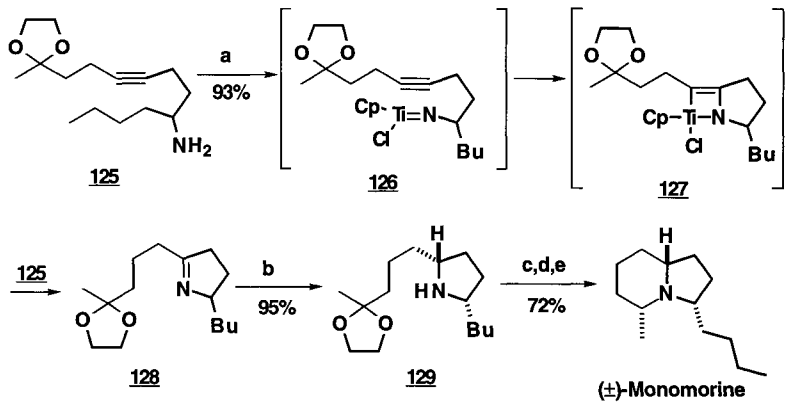


The driving force for the reaction was the loss of propene gas going from intermediate **120** to **121**. The cyclization of amide **123** was also effected using 10% catalyst to provide lactam **124**.

Livinghouse reported the synthesis of the ant trail pheromone monomorine using an imidotitanium-alkyne cyclization (Scheme 2.29).[64,65] Amine **125** was treated with 20% titanocene trichloride forming the imidotitanium complex **126**. This compound then underwent a [2+2]-cycloaddition with the alkyne to afford intermediate **127**. Ring opening and subsequent metathesis of the titanium carbene onto another molecule of **125** completed the catalytic cycle. Compound **128** was then reduced with diisobutylaluminum hydride to provide amine **129**. Deprotection and intramolecular reductive amination afforded the alkaloid monomorine.

West recently investigated the use of the Stevens rearrangement in the synthesis of piperidines.[66] This method involved the Rhodium catalyzed decomposition of diazo carbonyl compounds which contain a pendent amine (Scheme 2.30). Rhodium catalyzed

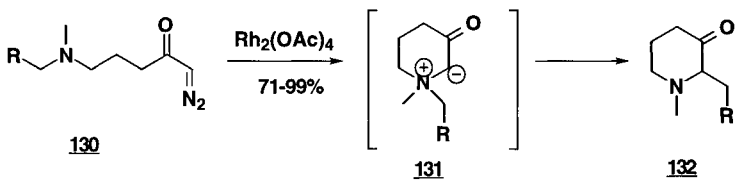
Scheme 2.29. Livinghouse Synthesis of (±)-Monomorine.[64,65]



(a) Et_3N, $CpTiCl_3$ (20% mol); (b) DIBALH; (c) HCl; (d) K_2CO_3; (e) $NaCNBH_3$.

carbene formation of **130**, followed by intramolecular attack of the amine to afford ammonium ylides **131**. Stevens rearrangement of these ylides provided piperidines **132** in excellent yields. In no case was the product resulting from methyl migration observed.

Scheme 2.30. West Synthesis of Piperidines via a Stevens Rearrangement.[66]

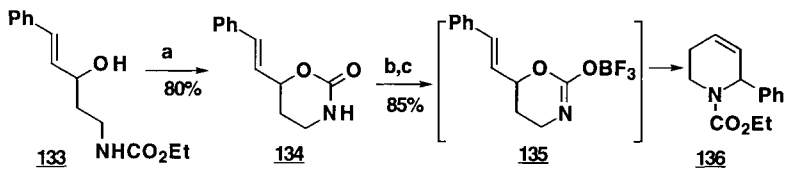


R= Ph, CO_2Et, *p*-$AcOC_6H_4$, *p*-$MeOC_6H_4$, *p*-$NO_2C_6H_4$

2.8 Miscellaneous Methods

Wang reported the synthesis of piperidines using a Claisen rearrangement of cyclic carbamates (Scheme 2.31).[67] Deprotonation of **133** with sodium hydride resulted in the formation of cyclic carbamate **134**. The Claisen rearrangement was initiated by the addition of boron trifluoride etherate. Subsequent protection of the piperidine with ethyl chloroformate provided **136** in 85% yield.

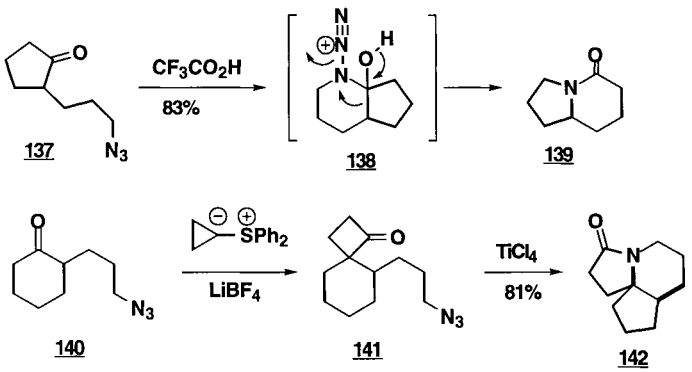
Scheme 2.31. Wang Synthesis of Piperidines via a Claisen Rearrangement.[67]



(a) NaH; (b) $BF_3{\cdot}Et_2O$; (c) $ClCO_2Et$, Et_3N.

Aube investigated the use of an intramolecular Schmidt reaction for the synthesis of indolizidines (Scheme 2.32).[68] Activation of the ketone in **137** with trifluoroacetic acid resulted in nucleophilic attack by the pendant azide to form intermediate **138**. Loss of nitrogen from **138** accompanied by bond migration afforded lactam **139**. This approach was also used to form the more complex ring system **142**. The addition of diphenylsulfonium cyclopropylide[69] to ketone **140** gave cyclobutanone **141**. Initiation of the Schmidt rearrangement with titanium tetrachloride afforded lactam **142** as a single diastereomer.

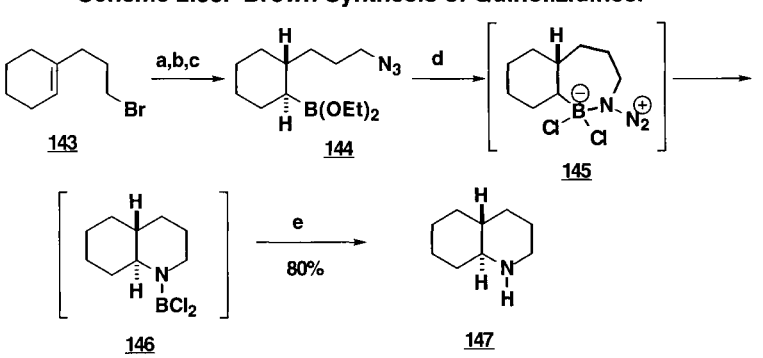
Scheme 2.32. Aube Synthesis of Indolizidines via a Schmidt Rearrangement.[68]



137 138 139 140 141 142

Brown reported a hydroboration, alkyl migration strategy to prepare piperidines (Scheme 2.33).[70] Hydroboration of the alkene in **143** followed by conversion of the bromide to an azide provided borane **144**. Exchange of the ethoxy groups for chlorides using boron trichloride enhanced the Lewis acidity of the borane resulting in the formation of cyclic intermediate **145**. Loss of nitrogen and alkyl migration to the resulting nitrene afforded intermediate **146**. Removal of boron with potassium hydroxide then provided piperidine **147**.

Scheme 2.33. Brown Synthesis of Quinolizidines.[70]

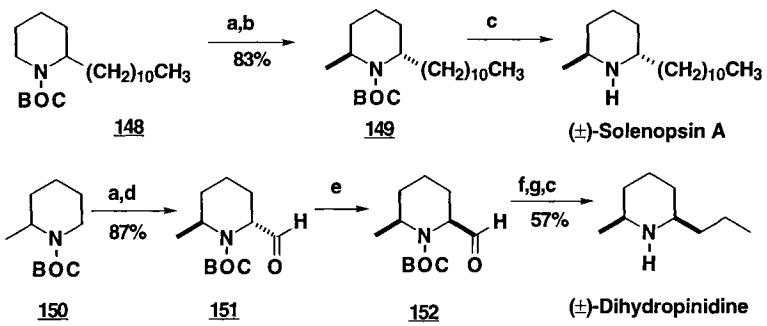


143 144 145 146 147

(a) $BHCl_2$·DMS, BCl_3; (b) H_2O; (c) NaN_3, EtOH, reflux; (d) BCl_3; (e) KOH.

Beak used a directed deprotonation of *t*-butyloxycarbonyl-protected piperidines in the synthesis of *trans*-2,6-disubstituted piperidines (Scheme 2.34).[71] Treatment of **148** with *sec*-butyllithium and tetramethylethylenediamine selectively deprotonated the less substituted 6-position of the piperidine. Addition of dimethylsulfate afforded disubstituted piperidine **149** as a single diastereomer. The stereoselectivity of the reaction was explained by the *t*-butyloxycarbonyl-directed deprotonation of the equatorial hydrogen to give the equatorial lithiated species. The C(2)-substituent adopted the axial orientation to avoid $A^{1,3}$ strain, thus attack by the equatorial anion provided the *trans*-2,6-piperidine. Deprotection of **149** with trifluoroacetic acid provided solenopsin A. In another application of this methodology, deprotonation of **150** followed by addition of dimethylformamide resulted in the formation of aldehydes **151** and **152** as an 8:1 mixturerespectively. These diastereomers were equilibrated with silica gel to provide the *cis*-isomer **152** exclusively. Wittig olefination and hydrogenation afforded the known compound dihydropinidine.

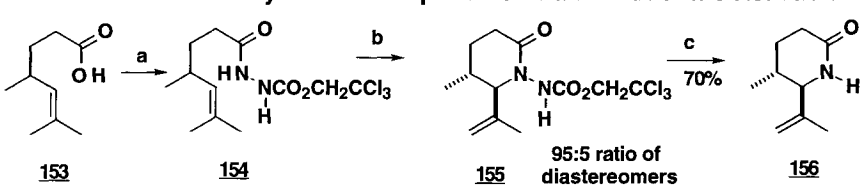
Scheme 2.34. Beak Synthesis of (±)-Solenopsin A and (±)-Dihydropinidine.[71]



(a) *s*-BuLi, TMEDA; (b) Me_2SO_4; (c) CF_3CO_2H; (d) DMF; (e) silica gel; (f)$Ph_3P{=}CHCH_3$; (g) H_2, Pd/C.

Leblanc exploited an azido-ene reaction for the synthesis of piperidines (Scheme 2.35).[72] Oxidation of hydrazide **154** with lead tetraacetate formed the corresponding azidodicarboxylate which in turn underwent an ene reaction with the tethered alkene to afford the lactam **155** as a 95:5 mixture of diastereomers. Removal of the carbamate was then accomplished by reduction with zinc in acetic acid to provide lactam **156.**

Scheme 2.35. Leblanc Synthesis of Piperidines via an Azido-Ene Reaction.[72]



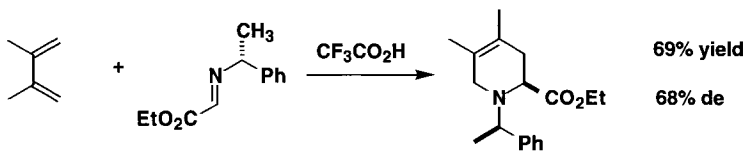
(a) 2-chloro-1-methylpyridinium iodide, Et_3N, $H_2NNHCO_2CCl_3$; (b) $Pb(OAc)_4$; (c) Zn, AcOH/acetone.

3.0 ASYMMETRIC SYNTHETIC METHODS

3.1 Use of Chiral Auxiliaries.

Bailey used an asymmetric version of the imine Diels-Alder reaction for the synthesis of chiral piperidines (Scheme 3.1).[73,74] Imine **158** was treated with trifluoroacetic acid and 2,3-dimethylbutadiene to afford tetrahydropyridine **159** in 68% diastereomeric excess. The auxiliary was easily removed by hydrogenolysis to provide optically active piperidines. 1-Methylbutadiene and 2-methylbutadiene were also used, but despite complete regioselectivity, the diastereoselectivities were low. Cyclopentadiene proved to be the most effective diene providing cycloaddition products in >98% diastereomeric excess; however, the products are not directly applicable to the synthesis of piperidines.

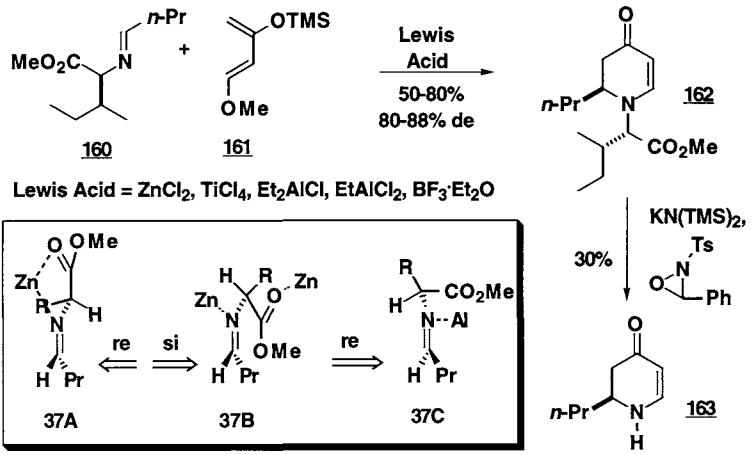
Scheme 3.1. Bailey Synthesis of Enantioenriched Piperidines.[73,74]



157 158 159

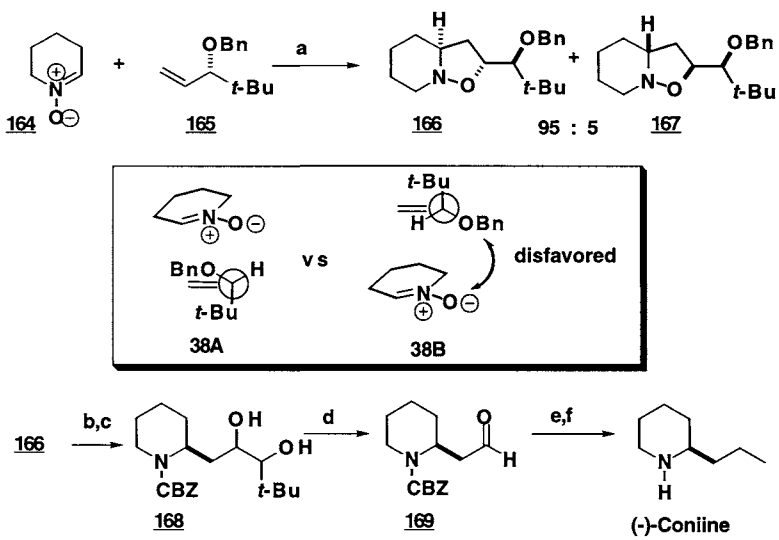
Waldmann reported asymmetric imine Diels-Alder reactions using α-amino esters as chiral auxiliaries (Scheme 3.2).[75] Addition of Danishefsky's diene to imine **160** in the presence of a variety of Lewis acids produced enone **162** in diastereomeric excesses ranging from 80 to 88%. Other α-amino esters were examined but gave consistently lower diastereomeric excess. Although all the Lewis acids used gave similar diastereomeric excess, when two equivalents of zinc chloride were used, the stereoselectivity was reversed with respect to the products obtained using other Lewis acids, providing 70% diastereomeric excess of the opposite diastereomer. Monodentate Lewis acids such as aluminum halides (AlX_3) and boron trifluoride should only complex the imine nitrogen allowing the ester group to adopt the perpendicular orientation (**37C**), preferred according to the Felkin-Ahn model,[76] which resulted in si-face attack of the diene. NMR investigations of the zinc complex of imine **160** indicated a change in the imine double bond geometry to the *E*-isomer (**37A/B**), this effect was previously observed by Ojima.[77] Bidentate complexation with one equivalent of zinc chloride (**37A**), then resulted in re-face attack. When two equivalents of zinc chloride were added the extended intermediate **37B**, resulted in si-face attack. Experiments using more than one equivalent of the mono-dentate Lewis acids were not reported. The auxiliary was removed in one step, albeit in low yields, by treatment of **162** with potassium hexamethyldisilazide and oxidation of the enolate with *N*-tosyloxaziridine to give the aminal. Hydrolysis then afforded piperidinone **163** in 30% yield.

Scheme 3.2. Waldmann Asymmetric Diels-Alder Approach to Piperidines.[75]



Asymmetric nitrone cycloadditions have also been used in the synthesis of chiral piperidines. Kibayashi synthesized (+)-coniine from chiral alkene **165**, which was prepared from commercially available (*R*)-pantolactone (Scheme 3.3).[78,79] Treatment of nitrone **164** with **165** in refluxing toluene afforded a 95:5 mixture of *N*-alkoxyamines **166** and **167**. The stereoselectivity of the cycloaddition was rationalized on the basis of transition state model **38A**. The *t*-butyl substituent should be in an orientation opposite the enophile forcing the benzyloxy group to adopt either the inner (**38A**) or outer (**38B**)

Scheme 3.3. Kibayashi Synthesis of (-)-Coniine.[78,79]

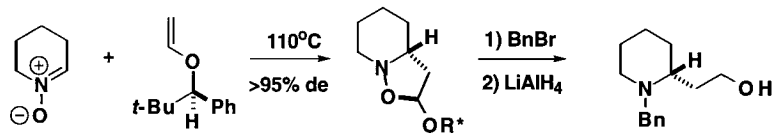


(a) toluene reflux; (b) H_2, Pd/C; (c) CBZ-Cl, Na_2CO_3; (d) HIO_4;
(e) Ph_3PCH_2Br, BuLi; (f) H_2, Pd/C.

orientation. The outer position suffers from electronic repulsion between the alkoxy group and the benzyloxy substituent, thus **38A** is the favored transition state. Reductive cleavage of the N-O bond in **166,** and treatment with benzyl chloroformate and sodium carbonate provided protected piperidine **168**. Cleavage of the glycol with periodic acid then furnished aldehyde **169**. Homologation and reduction completed the synthesis of (+)-coniine. Kibayashi also used this same general methodology in the synthesis of the indolizidine alkaloid (+)-monomorine.[79]

Coggins and co-workers reported the use of chiral vinyl ethers as nitrone cycloaddition substrates (Scheme 3.4).[80] Vinyl ether **170** was treated with nitrone **164** to provide **171** in greater than 95% diastereomeric excess. The absolute sense of selectivity was confirmed by conversion to the known alcohol **172**. Interestingly more traditional auxiliaries (i.e. menthol, 8-phenylmenthol, isopinylcamphenyl) provided very poor diastereomeric excesses (0-15%).

Scheme 3.4. Coggins Nitrone Cycloaddition Approach to Piperidines.[80]



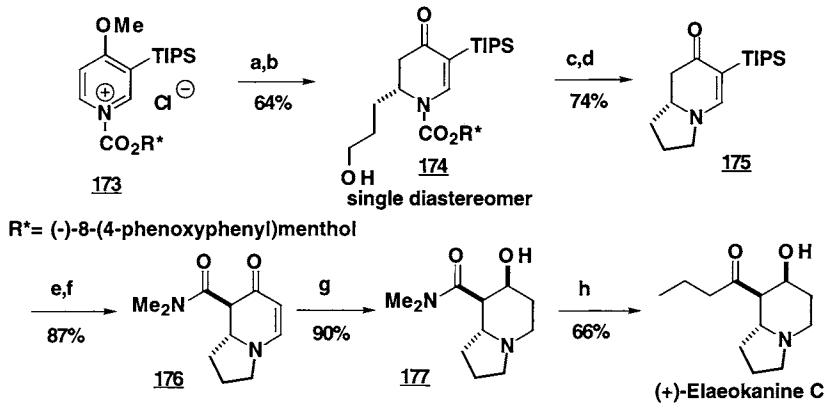
164 170 171 R* = (*R*)-*t*-BuCHPh 172

Comins has recently been successful in extending his previously described methodology (Section 2.1) to the asymmetric synthesis of piperidines.[81-83] The synthesis of (+)-elaeokanine C began with pyridinium ion **173** in which the chiral directing group was 8-(4-phenoxyphenyl)menthol (Scheme 3.5).[84] Treatment of **173** with the Grignard reagent derived from 3-bromopropylethoxyethyl ether and subsequent hydrolysis provided enone **174**. Attack of the nucleophile occurred with complete regio- and stereocontrol. Conversion of the alcohol to the chloride followed by hydrolysis of the carbamate and concomitant cyclization afforded indolizidinone **175**. The chiral auxiliary was recovered from the reaction mixture in 84% yield. Treatment of **175** with lithium diisopropylamide and dimethylcarbamoyl chloride, followed by removal of the silyl group with oxalic acid gave an 87% yield of *trans*-amide **176** along with 3% of the *cis*-diastereomer. Reduction of enone **176** to alcohol **177** was accomplished with hydrogen over platinum oxide. Treatment of **177** with cerium trichloride and propylmagnesium chloride completed the synthesis of (+)-elaeokanine C.

Comins also reported the synthesis of (+)-myrtine using the method described above (Scheme 3.6).[85] Grignard addition to **178** followed by hydrolysis gave enone **179** in 86% diastereomeric excess. The diastereomers were then separated by chromatography. Hydrolysis of the carbamate and cyclization to the quinolizidine was accomplished in a single step with potassium methoxide in dimethyl sulfoxide. Removal of the silyl group then afforded enone **180** in 90% yield from **179**. Conjugate addition to

the enone with methylmagnesium chloride then provided (+)-myrtine in 55% yield. This work constituted the first asymmetric synthesis (+)-myrtine.

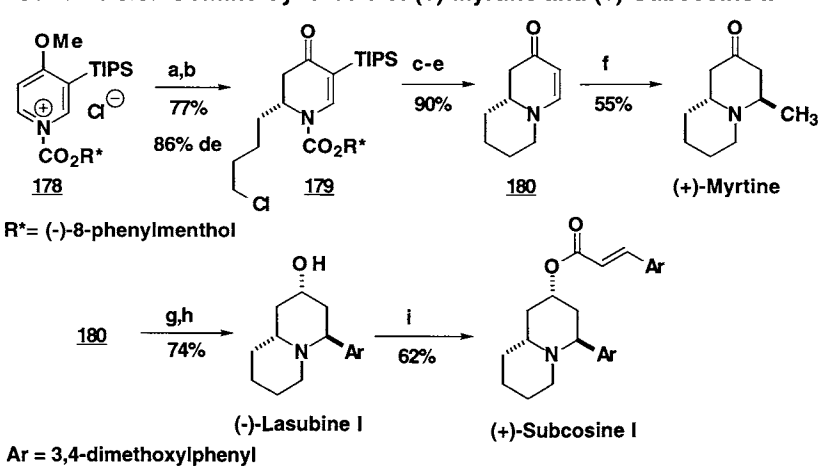
Scheme 3.5. Comins Synthesis of (+)-Elaeokanine C.(84)



(a) $EEO(CH_2)_3MgBr$; (b) H_3O^+; (c) Ph_3P, NCS; (d) NaOMe, MeOH; (e) LDA, dimethylcarbamoyl chloride; (f) oxalic acid, MeOH; (g) H_2, PtO_2; (h) PrMgCl, $CeCl_3$.

Compound **180** also served as a late intermediate in the synthesis of (-)-lasubine and (+)-subcosine I (Scheme 3.6). Addition of the 3,4-dimethoxyphenylmagnesium chloride to **180**, in the presence of cuprous bromide, followed by reduction of the ketone afforded (-)-lasubine I. Acylation of the alcohol with β-dimethoxycrotonyl chloride provided (+)-subcosine I in 62% yield.

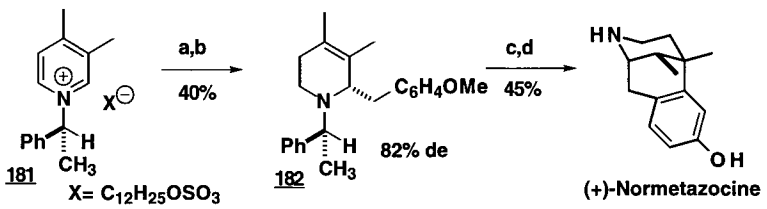
Scheme 3.6. Comins Synthesis of (+)-Myrtine and (+)-Subcosine I.(85)



(a) $Cl(CH_2)_4MgCl$; (b) H_3O^+; (c) chromatography; (d) KOMe, DMSO; (e) oxalic acid; (f) MeMgCl; (g) ArLi, CuBr, TMSCl; (h) L-Selectride; (i) $ClCO_2CH{=}CHAr$, pyr.

Marazano used pyridinium salt **181** in the synthesis of (+)-normetazocine (Scheme 3.7).[86] Initially the chloride of **181** was treated with benzylic anion equivalents; however, poor yields and selectivities were observed. The counterion was then changed to a lipophillic sulfate. Grignard addition and reduction of the enamine with sodium borohydride afforded a 40% yield of tetrahydropyridine **182** in 82% diastereomeric excess. The diastereomers were separable by chromatography. Acid mediated intramolecular electrophilic aromatic substitution followed by hydrogenolysis of the chiral auxiliary provided (+)-normetazocine in 45% yield.

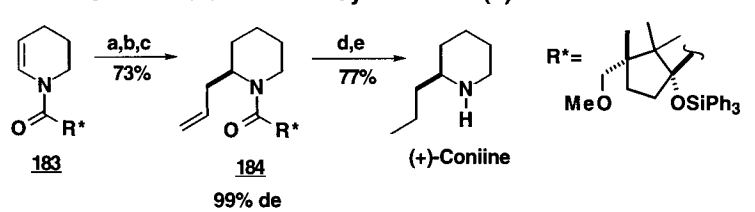
Scheme 3.7. Marazano Synthesis of (+)-Normetazocine.[86]



(a) *p*-$MeOC_6H_4CH_2MgCl$; (b) $NaBH_4$; (c) HBr; (d) H_2, Pd/C.

Wanner achieved excellent diastereoselectivities with a chiral auxiliary derived from commercially available (*S*)-camphanic acid (Scheme 3.8).[87] Treatment of *N*-acyl enamine **183** with dimethyldithiophosphoric acid followed by titanium tetrachloride generated the acyliminium ion. Addition of allyltributyltin then afforded **184** in 99% yield, as a single diastereomer. Hydrogenation of the alkene and hydrolysis of the amide provided (+)-coniine in 77% yield along with the recovered auxiliary. The steric bulk of the triphenylsilyl group in the chiral auxiliary was essential to high diastereoselectivities, when smaller protecting groups were used the diastereomeric excess was appreciably lower.

Scheme 3.8. Wanner Synthesis of (+)-Coniine .[87]



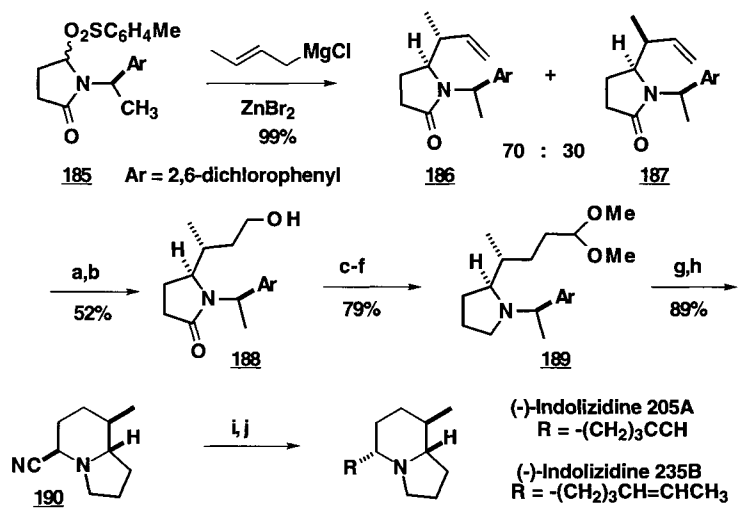
(a) $(CH_3O)_2PS_2H$; (b) $TiCl_4$; (c) $Bu_3SnCH_2CH{=}CH_2$; (d) H_2, Pd/C; (e) LiOH, 160°C.

Polniaszek reported the total synthesis of a number of indolizidine alkaloids starting with the chiral acyliminium ion precursor **185** (Scheme 3.9).[88,89] Treatment of **185** with zinc chloride followed by the addition of crotylmagnesium chloride provided a 70:30 mixture of diastereomers **186** and **187**. The facial selectivity of addition was complete; however, a diastereomeric mixture at the allylic methyl center was obtained. The mixture was hydroborated, and the resulting alcohols were separated by flash chromatography to

provide **188** in 52% yield. Homologation via a Swern/Wittig sequence and formation of the dimethyl acetal afforded **189**. Hydrogenolysis of the chiral auxiliary, followed by cyclization and trapping of the iminium ion as the cyanide adduct gave **190** as a single diastereomer.

Polniazek utilized **190** as a common precursor to two indolizidine natural products. Deprotonation/alkylation of nitrile **190**, followed by stereoselective, reductive cleavage of cyanide afforded (-)-indolizidines 205A and 235B. The stereoelectronic principles formulated by Stevens call for axial attack on the intermediate iminium ions to afford products with the stereochemistry indicated.[90] The stereochemical outcome was reversed if the nitrile in **190** was replaced directly with an alkyl group; nucleophilic attack of a carbon nucleophile on the iminium ion derived from **190** occurred from the axial orientation giving the opposite stereochemistry seen for indolizidines 205A and 235B. Polniazek used this approach for the synthesis indolizidines 167B and 209D from a similar nitrile intermediate.[89]

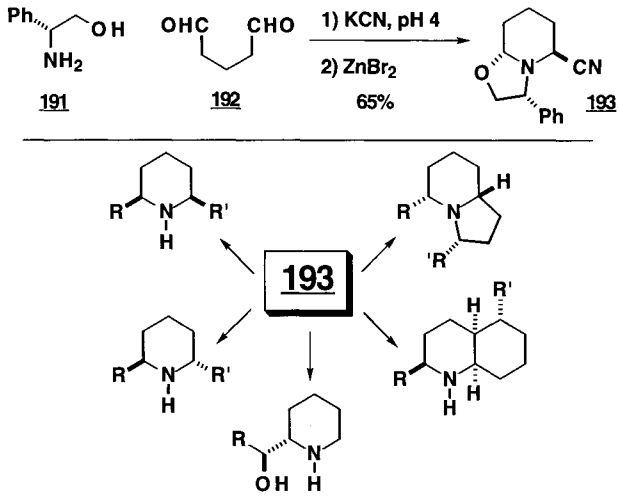
Scheme 3.9. Polniazek Synthesis of (-)-Indolizidines 205A and 235B.[88,89]



(a) $(Sia)_2BH$, H_2O_2; (b) chromatography; (c) Swern Ox.; (d) $Ph_3PCHOMe$; (e) CSA, MeOH; (f) $LiAlH_4$; (g) H_2, Pd/C, NH_4HCO_3; (h) KCN, HCl;(i) LDA, RBr; (j) $NaBH_4$.

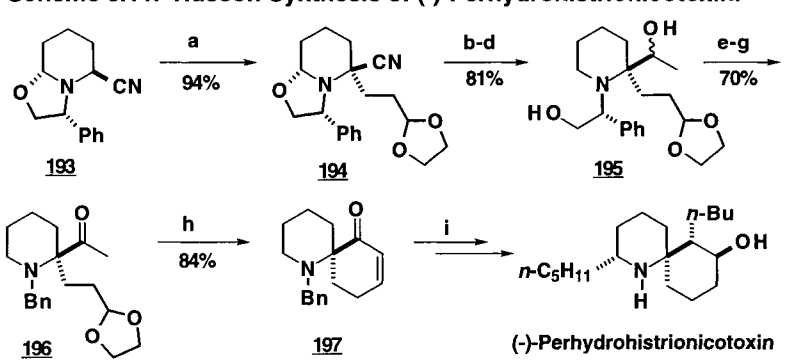
Numerous asymmetric syntheses of piperidine alkaloids have been accomplished by Husson and co-workers.[91-93] Most of these, involve the use of the versatile aminal intermediate **193**. A recent *Organic Synthesis* preparation described the large scale synthesis of this intermediate from phenylglycinol and gluteraldehyde in 65% yield (Scheme 3.10).[94] The types of compounds that have been produced from this intermediate are summarized in Scheme 3.10. The versatility of **193** is due largely to the nitrile group which can be transformed into other side chains with either the *cis*-2,6- or *trans*-2,6-orientation according to the stereoelectronic principles described above.

Scheme 3.10. Husson Synthesis of Versatile Piperdine Intermediate 193.[91-94]



Husson used intermediate **193** in the formal synthesis of (-)-perhydrohistrionicotoxin (Scheme 3.11).[95] Treatment of nitrile **193** with lithium diisopropylamide and trapping with 2-(2-bromoethyl)-1,3-dioxolane gave **194** as a single diastereomer. Addition of methyllithium generated the methyl imine which was hydrolyzed to the ketone. Reduction of the aminal and the methyl ketone with lithium aluminum hydride/aluminum chloride afforded **195**. The chiral auxiliary was then removed by hydrogenolysis and replaced with a benzyl group. Swern oxidation of the alcohol produced ketone **196** in 70% yield. Acid catalyzed aldol condensation gave the spirocyclic enone **197** which had been previously converted to the alkaloid (-)-perhydrohistrionicotoxin, constituting a formal total synthesis of this alkaloid.[96]

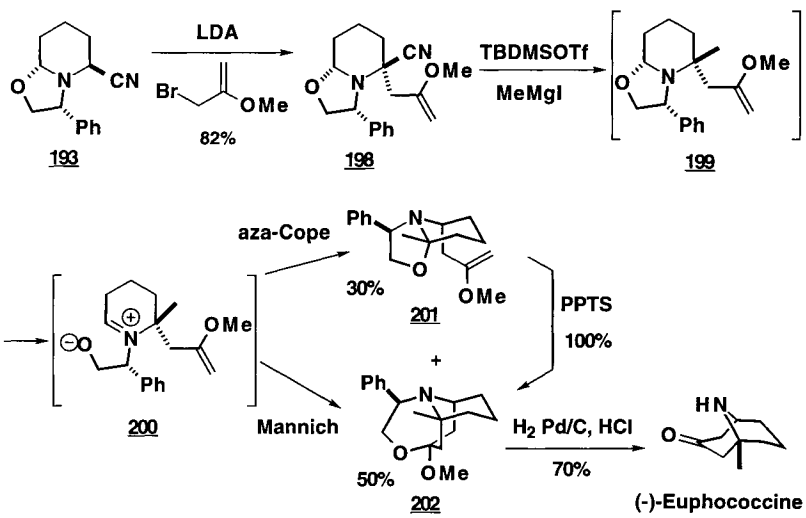
Scheme 3.11. Husson Synthesis of (-)-Perhydrohistrionicotoxin.[95]



(a) LDA, 2-(2-bromoethyl)-1,3-dioxolane; (b) MeLi; (c) citric acid, H_2O_2; (d) $LiAlH_4$, $AlCl_3$; (e) H_2, Pd/C; (f) BnBr, $NaHCO_3$; (g) Swern Ox.; (h) HCl, 100°C; (i) Ref. 96.

Royer and Husson also used intermediate **193** for the synthesis of the homotropane alkaloid (-)-euphococcine (Scheme 3.12).[97] Nitrile **193** was deprotonated with lithium diisopropylamide. Treatment of the resulting anion with 1-bromo-2-methoxy-1-propene gave **198**. Formation of the iminium ion with *tert*-butyldimethylsilyl trifluoromethanesulfonate and addition of methylmagnesium iodide generated intermediate **199**. Elimination of the nitrile occurred more rapidly than aminal opening due to the antiperiplaner relationship between the nitrile and the nitrogen lone pair. Subsequent opening of the aminal by a second equivalent of *tert*-butyldimethylsilyl trifluoromethanesulfonate generated iminium ion **200**. The iminium ion then underwent reaction via two different pathways: an aza-Cope reaction followed by trapping of the resulting iminium ion by the alkoxide, forming aminal **201**; or a Mannich reaction, in which the iminium ion was trapped by the enol ether followed by formation of the ketal **202**. These products were formed in 30% and 50% yields respectively. Fortunately, treatment of the product mixture with pyridinium *p*-toluenesulfonic acid resulted in the quantitative conversion of **201** to **202**. Hydrolysis of the ketal and hydrogenolysis of the auxiliary were accomplished in a single step to afford (-)-euphococcine.

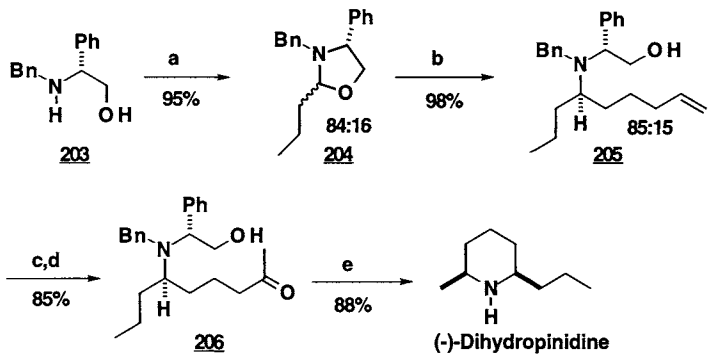
Scheme 3.12. Royer-Husson Synthesis of (-)-Euphococcine.[97]



Higashiyama used phenylglycinol as the source of chirality for the synthesis of (-)-dihydropinidine (Scheme 3.13).[98] *N* -Benzylphenylglycinol **203** was treated with propanal and magnesium sulfate to afford an 84:15 mixture of diastereomeric aminals **204**. The mixture was then alkylated with 5-pentenylmagnesium bromide which gave **205** as an 85:15 mixture of diastereomers. The nearly identical ratio of products **204** and **205** suggests a high degree of facial selectivity in the addition of the nucleophile to the activated aminal. Wacker oxidation of the mixture of diastereomers provided ketones **206** as a mixture of diastereomers, which was separated by chromatography to give pure

206 in 85% yield. Hydrogenolysis of the chiral appendage and reductive amination of the ketone was accomplished in a single step with hydrogen over palladium on carbon in dilute hydrochloric acid affording (-)-dihydropinidine.

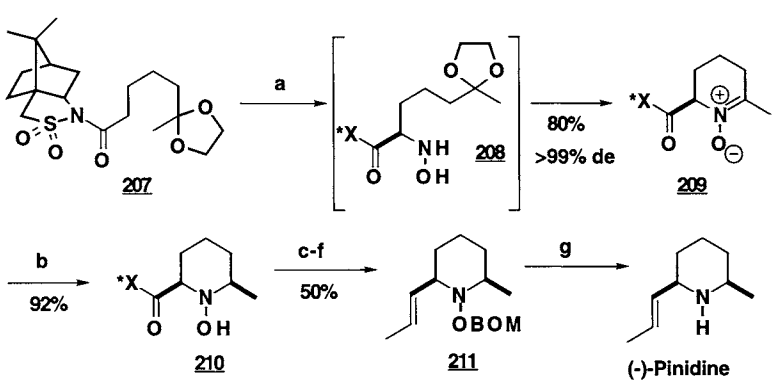
Scheme 3.13. Higashiyama Synthesis of (-)-Dihydropinidine.(98)



(a) $CH_3CH_2CH_2CHO$, $MgSO_4$; (b) $CH_2{=}CH(CH_2)_3MgBr$; (c) $PdCl_2$ $(CH_3CN)_2$, $CuCl_2$, O_2; (d) chromatography; (e) H_2, Pd/C, HCl.

Oppolzer used a chiral enolate derived from camphor sulfonic acid for the synthesis of (-)-pinidine (Scheme 3.14).(99) Successive treatment of *N*-acylsultam **207** with sodium hexamethyldisilazide and 1-chloro-1-nitrosocyclohexane generated hydroxyl amine **208**. Hydrolysis of the ketal and condensation of the resulting ketone with the amine gave nitrone **209** as a single diastereomer, in 80% yield. Hydrogenation of the nitrone from the less hindered face provided the *cis*-2,6-*N*-hydroxypiperidine **210**. The hydroxyl group was protected as the benzyloxymethyl ether. The chiral sultam was reduced to give the alcohol, which was then oxidized under Swern conditions. Attempts to synthesize **211** via Wittig or Schlosser-Wittig reactions lead to unacceptable ratios of *E*-

Scheme 3.14. Oppolzer Synthesis of (-)-Dihydropinidine.(99)

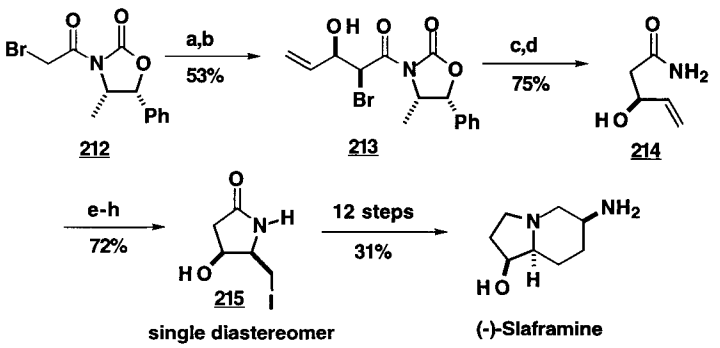


(a) NaHMDS, 1-chloro-1-nitrosocyclohexane, HCl; (b) H_2, Pd/C; (c) BOMCl, $EtN(i\text{-}Pr)_2$; (d) DIBAL; (e) Swern Ox.; (f) $CrCl_2$, CH_3CHI_2; (g) Zn, AcOH.

and *Z*-isomers. The use of Takai's procedure[100] (1,1-diiodoethane/chromous chloride) afforded a 95:5 mixture of *E*- and *Z*-alkenes, which were separable by chromatography with silver nitrate impregnated silica gel. Treatment of ***E*-211** with zinc in acetic acid provided (-)-pinidine.

Knapp[101] reported the asymmetric synthesis of (-)-slaframine in which a variation of the Evans aldol methodology[102] is used to generate the initial asymmetry. Treatment of **212** with titanium tetrachloride and Hunig's base generated the titanium enolate which then underwent a stereoselective condensation with acrolein to provide the syn-aldol product **213** (Scheme 3.15). Reductive removal of the bromide followed by hydrolysis afforded amide **214**. This strategy allows the enantioselective preparation of α-unsubstituted-β-hydroxy amides.[103] Iodolactamization of the amide gave lactam **215** as a 95:5 mixture of *cis*- and *trans*-diastereomers. The diastereomers were separated by chromatography to afford a 72% yield of ***cis*-215**. A 12 step sequence of reactions completed the synthesis of (-)-slaframine in 31% yield.

Scheme 3.15. Knapp Synthesis of (-)-Slaframine.[101]



(a) $TiCl_4$, $EtN(i\text{-}Pr)_2$, acrolein; (b) recrystallization; (c) $(TMS)_3SiH$; (d)NH_3, MeOH; (e) TBDMSOTf, Et_3N; (f) I_2; (g) Na_2SO_3; (h) chromatography.

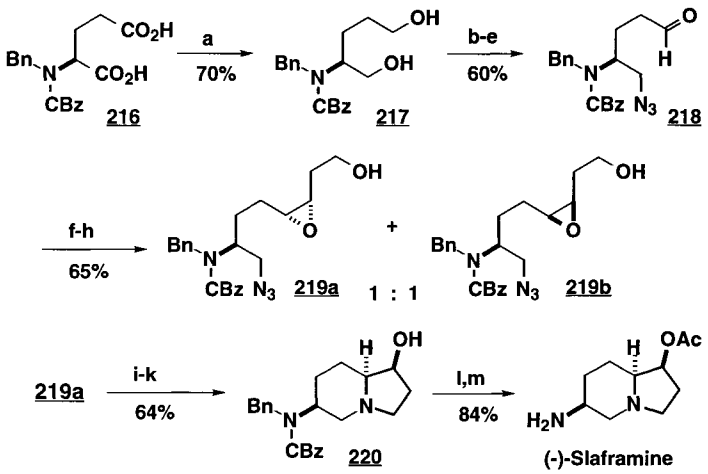
3.2 From Amino Acids

Amino acids are the most common source of chirality used for the synthesis of piperidine alkaloids. This section is devoted to those methods which incorporated the chirality of the amino acid into the final product.

Pearson converted *L*-glutamic acid to the biologically active alkaloid (-)-slaframine in a 15 step sequence (Scheme 3.16).[104] Protected *L*-glutamic acid **216** was reduced to diol **217** with borane-tetrahydrofuran. Selective protection of the δ-alcohol was accomplished using *tert*-butyldimethylsilyl chloride with pyridine and catalytic *N,N*-dimethylaminopyridine. Presumably, selective protection was possible because the alcohol closer to the benzyl and carbobenzyloxy groups was more sterically hindered. The free alcohol was then displaced with sodium azide under Mitsunobu conditions, and

the δ-alcohol was deprotected and oxidized to aldehyde **218**. Wittig olefination and deprotection of the silyl ether furnished the homoallyl alcohol with complete *Z*-selectivity. Attempts to carry out a directed epoxidation with transition metal oxidants failed to provide good yields of products; oxidation with *m*-chloroperoxybenzoic acid provided a 65% yield of **219a** and **219b** as a 1:1 mixture of diastereomers. Separation of the epoxides by HPLC afforded **219a**. The alcohol was then tosylated and the azide reduced to the amine with hydrogen and palladium on carbon. Treatment with potassium carbonate initiated the tandem intramolecular amine opening of the epoxide and displacement of the tosylate to afford indolizidine **220**. Acylation of the alcohol and hydrogenolysis of the amine protecting groups completed the synthesis of (-)-slaframine.

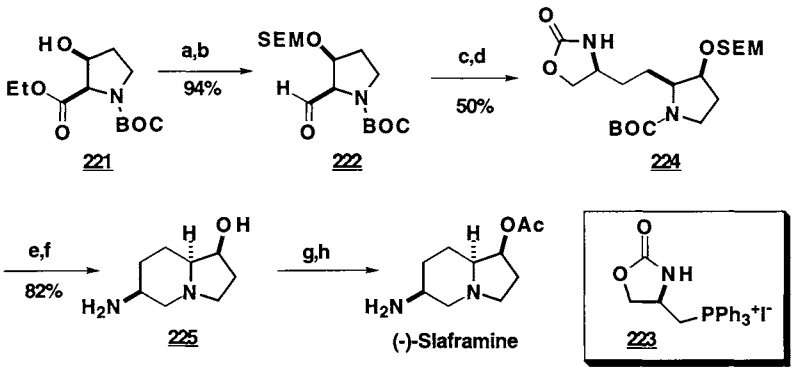
Scheme 3.16. Pearson Synthesis of (-)-Slaframine.[104]



(a) BH_3·THF; (b) TBDMSCl, pyr, DMAP; (c) DEAD, Ph_3P, NaN_3; (d) TBAF; (e) Swern Ox. (f) $Ph_3PCH(CH_2)_2OTMS$; (g) HCl; (h) *m*-CPBA; (i) TsCl, pyr.; (j) H_2, Pd/C; (k) K_2CO_3; (l) Ac_2O, pyr.; (m) H_2, Pd/C.

Another enantioselective synthesis of (-)-slaframine was reported by Sibi using proline as the source of chirality (Scheme 3.17).[105,106] *N*-*t*-Butyloxycarbonyl-3-hydroxy-proline ethyl ester **221**, available from baker's yeast reduction of the corresponding ketone, was protected as the trimethylsilylethoxymethyl ether and reduced to aldehyde **222** with diisobutylaluminum hydride. Treatment of **222** with the chiral phosphonium iodide **223** and *n*-butyllithium followed by hydrogenation of the alkene afforded **224**. The trimethyl- silylethoxymethyl ether was then removed with tetrabutylammonium fluoride. The cyclization step was initiated by pyrolysis of the *t*-butyloxycarbonyl group and ring closure on the oxazolidone, with concomitant decarboxylation, to give indolizidine **225**. This ring closure methodology was previously unprecedented. The (-)-slaframine synthesis was completed by acylation of the alcohol.

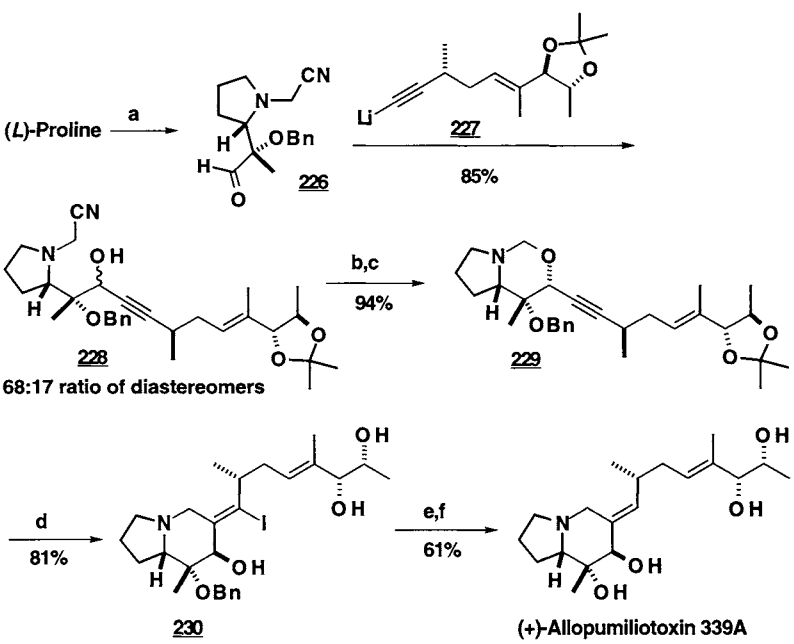
Scheme 3.17. Sibi Synthesis of (-)-Slaframine.[105,106]



(a) SEMCl, EtN(*i*-Pr)$_2$; (b) DIBAL; (c) **223**, BuLi (d) H_2, Pd/C; (e) TBAF; (f) 270°C, 5 min; (g) HCl, MeOH; (h) AcOH, 75°C.

L-Proline was also used as a source of chirality in independent syntheses of (+)-allopumiliotoxin 339A by Overman and Kibayashi. Overman's approach involved the iminium ion/alkyne cyclization described in Section 1.4 (Scheme 3.18).[107] *L*-Proline was converted to the intermediate **226** by a method previously described by Overman.[108] Alkyne anion **227** was added to aldehyde **226** to provide **228** as a 5:1

Scheme 3.18. Overman Synthesis of (+)-Allopumiliotoxin 339A.[107]

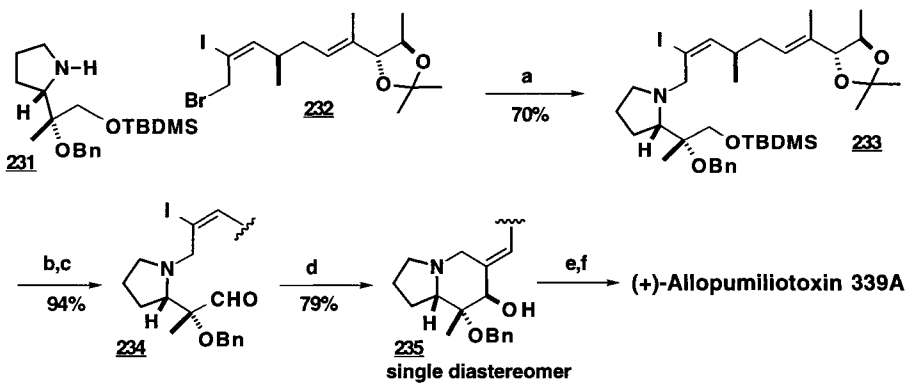


(a) Ref. 108; (b) chromatography; (c) $AgOSO_2CF_3$; (d) CSA, NaI, 100°C; (e) *n*-BuLi, MeOH; (f) Li/NH_3.

mixture of diastereomers. The alcohols were separated by chromatography. Treatment with silver triflate initiated elimination of cyanide and formation of the aminal, **229**. Iodine promoted cyclization of **229** occurred in the presence of camphorsulfonic acid to afford **230** as a single isomer in 81% yield. Reductive cleavage of the iodine and removal of the benzyl protecting group provided (+)-allopumiliotoxin 339A. This work constituted the first enantioselective synthesis of this alkaloid.

Kibayashi reported a synthesis of (+)-allopumiliotoxin 339A shortly after Overman, using the same retrosynthetic disconnection (Scheme 3.19).[109] *L*-Proline derived amine **231** was alkylated with bromide **232** in the presence of Hunig's base to afford **233**. The primary alcohol was then deprotected and oxidized to the aldehyde (**234**). The cyclization of **234** was successfully achieved by treatment with chromous chloride (5 equiv.), and nickel(II) chloride (2.5%) to form **235** with complete diastereoselectivity. The cyclization is thought to involve the formation of a vinyl chromium intermediate which then stereoselectively attacked the aldehyde to provide the correct C(7)-stereochemistry. Removal of the isopropylidine protecting group and reduction of the benzyl ether with sodium in ammonia completed the synthesis (+)-allopumiliotoxin 339A.

Scheme 3.19. Kibayashi Synthesis of (+)-Allopumiliotoxin 339A.[109]

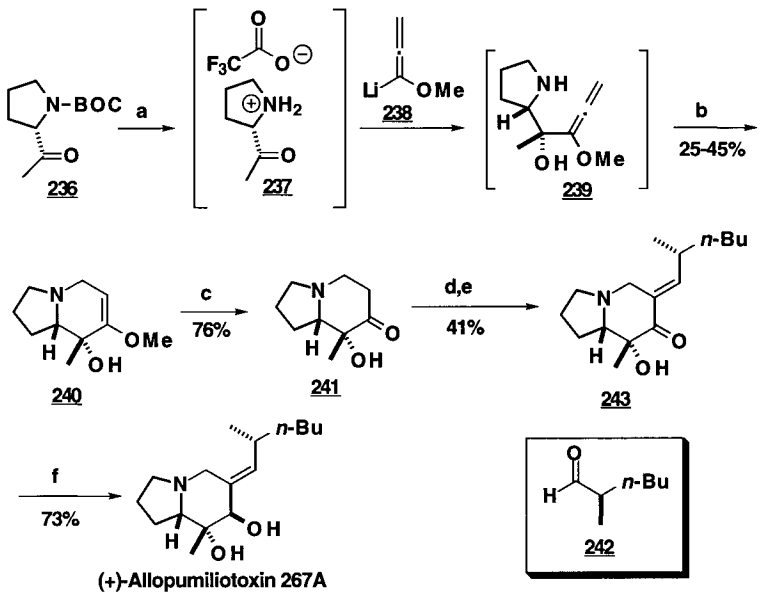


(a) EtN(*i*-Pr)$_2$; (b) TBAF; (c) Swern Ox.; (d) $CrCl_2$ (5 equiv), $NiCl_2$ cat; (e) HCl; (f) Li/NH_3

Overman used *N*-*t*-butyloxycarbonyl-*L*-proline methyl ketone **236** for the synthesis of (+)-allopumiliotoxin 267A (Scheme 3.20).[110] Initial attempts to add lithioallene **238** to the carbonyl group of **236** lead to a majority of the unwanted diastereomer resulting from Felkin-Ahn addition to the ketone. The desired chelation controlled addition product was obtained by generation of the ammonium ion **237**. Treatment of **237** with an excess of lithioallene **238** lead to the formation of allene **239** as a single diastereomer. Cyclization to the indolizidine was accomplished by treatment of the crude allene with *p*-toluenesulfonic acid to afford **240** in 25-45% yield from **236**. Hydrolysis of the enol ether with hydrochloric acid provided ketone **241**. Enolization of **241** with trityllithium and

addition of **242** afforded the β-hydroxy ketone. Elimination with trifluoroacetic anhydride and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave enone **243** stereoselectively. Reduction of the ketone with tetramethylammonium triacetoxyborohydride furnished the C(7)-alcohol with the correct stereochemistry for the natural product completing the synthesis of (+)-allopumiliotoxin 267A.

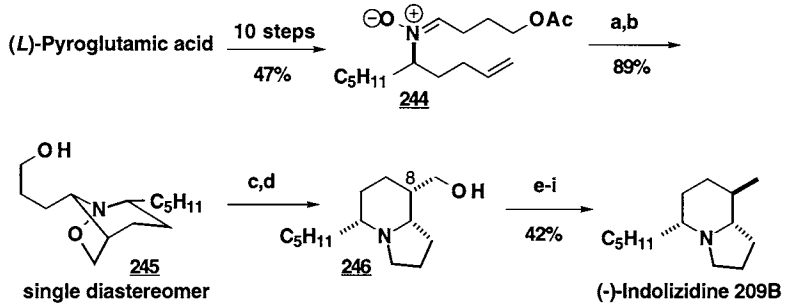
Scheme 3.20. Overman Synthesis of (+)-Allopumiliotoxin 267A.[110]



(a) CF_3CO_2H, PhOMe, (b) TsOH; (c) HCl; (d) Ph_3CLi, **242**; (e) $(CF_3O)_2CO$, DBU (f) $Me_4NBH(OAc)_3$.

Holmes and co-workers used an asymmetric nitrone cycloaddition reaction for the synthesis of (-)-indolizidine 209B (Scheme 3.21).[111] The cyclo-addition precursor **244** was synthesized from commercially available *L*-pyroglutamic acid in 10 steps and 47% yield. Refluxing **244** in toluene effected the cycloaddition reaction. Base hydrolysis of the acetate afforded **245** as a single diastereomer. The stereoselectivity of the cycloaddition was due to the preferred diequatorial orientation of the alkyl substituents in a chair-like transition state. The primary alcohol was converted to the mesylate with methanesulfonyl chloride and triethylamine. Reductive cleavage of the N-O bond, with zinc in acetic acid, and concomitant intramolecular displacement of the mesylate furnished indolizidine **246**. Epimerization of the C(8)-stereocenter was accomplished by oxidation to the aldehyde followed by treatment with basic alumina. The aldehyde was then reduced, and the hydroxyl group removed by reduction of the mesylate providing (-)-indolizidine 209B.

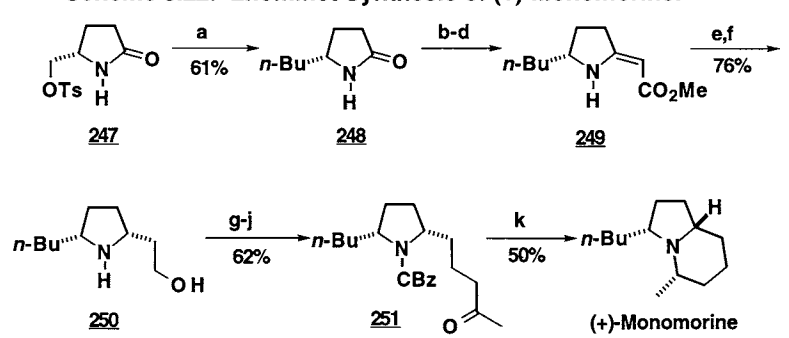
Scheme 3.21. Holmes Synthesis of (-)-Indolizidine 209B.[111]



(a) toluene reflux; (b) K_2CO_3; (c) MsCl, Et_3N; (d)Zn, AcOH; (e) Swern Ox.; (f) basic alumina; (g) $NaBH_4$; (h) MsCl, Et_3N; (i) $LiEt_3BH$.

Lactam **247**, derived from *L*-pyroglutamic acid, was used in the synthesis of (+)-monomorine by Lhommet (Scheme 3.22).[112] The tosylate in **247** was displaced by propyl cuprate to afford **248** in 61% yield. Treatment of **248** with dimethylsulfate and condensation of the resulting imidate with isopropylidine malonate using nickel(II) acetylacetonate generated the isopropylidine diester. Addition of sodium methoxide in methanol initiated monodecarboxylation and transesterification of the remaining ester to give *Z*-alkene **249**. Hydrogenation of the alkene occurred preferentially on the face of the alkene opposite the butyl group to provide a 96:4 mixture of *cis/trans* diastereomers. Reduction of the ester with lithium aluminum hydride provided alcohol **250**. Formation of **251** was accomplished by an oxidation/Wittig/hydrogenation sequence. Hydrogenolysis of the carbobenzyloxy group and subsequent reductive cyclization afforded (+)-monomorine in 50% yield.

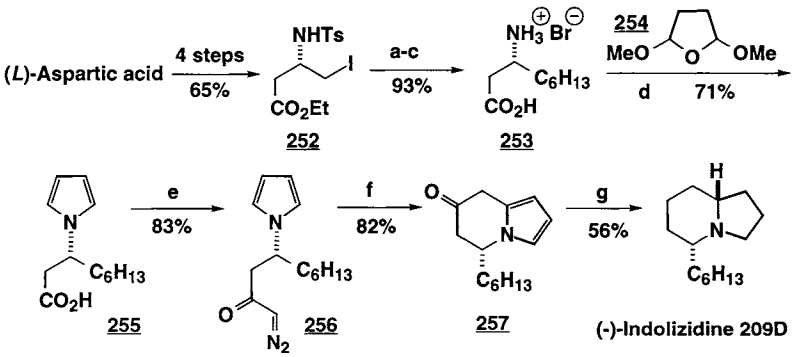
Scheme 3.22. Lhommet Synthesis of (+)-Monomorine.[112]



(a) n-Pr_2CuLi; (b) Me_2SO_4; (c) Meldrum's acid, $Ni(acac)_2$; (d) MeONa, MeOH; (e) Raney Ni, H_2, HCl; (f) $LiAlH_4$; (g) CBzCl, Et_3N; (h) PCC, CH_2Cl_2; (i) $CH_3COCHPPh_3$; (j) H_2, PtO_2; (k) H_2, Pd/C.

Jefford developed methodology for the synthesis of indolizidines from α-amino acids in which the key cyclization step was a rhodium catalyzed carbene addition to a pyrrole.[113,114] This method was recently used in the synthesis of (-)-indolizidine 209D from *L*-aspartic acid (Scheme 3.23).[115] Iodide **252** was synthesized from aspartic acid in 4 steps and 65% overall yield. The iodine was then displaced with pentyl cuprate. Base hydrolysis of the ethyl ester followed by acid hydrolysis of the tosyl group provided ammonium bromide **253**. Pyrrole **255** was obtained by treatment of **253** with 2,6-dimethoxytetrahydrofuran (**254**) and acetic acid. Treatment of **255** with *iso*-butyl chloroformate and *N*-methylmorpholine generated the mixed carbonate which was then condensed with diazomethane to afford **256** in 83% yield. The cyclization was initiated by the addition of rhodium acetate, which decomposed the diazoketone to the rhodium carbene. Trapping of the carbene by pyrrole gave a zwitterionic intermediate which then aromatized to **257**. The C(9)-stereocenter was set by hydrogenation of the pyrrole from the convex face to provide (-)-indolizidine 209D in 56% yield.

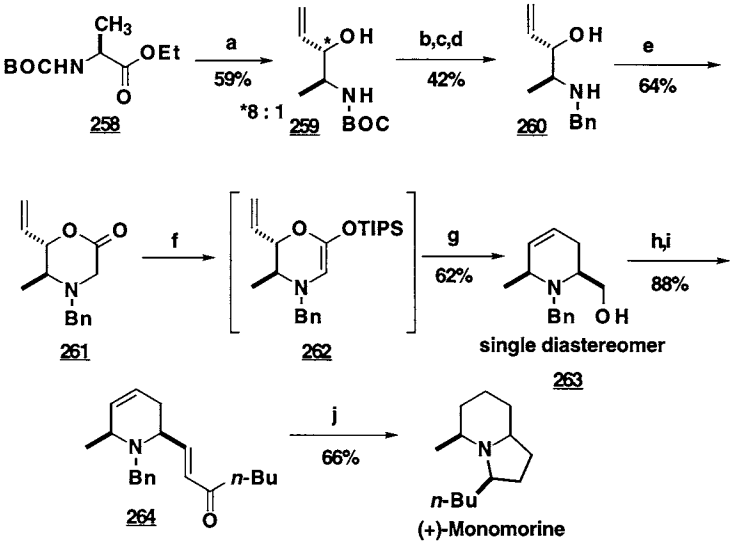
Scheme 3.23. Jefford Synthesis of (-)-Indolizidine 209D.[115]



(a) *n*-pentyllithium, CuI; (b) K_2CO_3, MeOH; (c) HBr; (d) NaOAc, AcOH;
(e) *i*-$BuCO_2Cl$, *N*-methylmorpholine, CH_2N_2; (f) $Rh(OAc)_4$; (g) H_2, Pt, HCl.

Angle and co-workers utilized a conformationally restricted Ireland-Claisen rearrangement of cyclic ketene acetals (**262**) for the enantioselective synthesis of piperidines.[116,117] Recently this approach was used for the total synthesis of (+)-monomorine (Scheme 3.24).[118] *N*-*t*-Butyloxycarbonyl-alanine ethyl ester was subjected to a one pot reduction/alkylation procedure, developed by Yamamoto,[119] to afford an 8:1 mixture of diastereomeric alcohols **259**, favoring the chelation controlled addition product. The mixture of diastereomers was treated with trifluoroacetic acid to remove the *t*-butyloxycarbonyl protecting group. The amino alcohol was then acylated with benzoyl chloride and reduced with lithium aluminum hydride to afford benzyl amine **260**. Alkylation of the amine and lactonization were accomplished in a single step by treatment of **260** with α-bromophenylacetate and Hunig's base. The use of the phenyl ester was crucial to formation of the lactone under the mildly basic conditions.

Scheme 3.24. Angle Synthesis of (+)-Monomorine.[118]

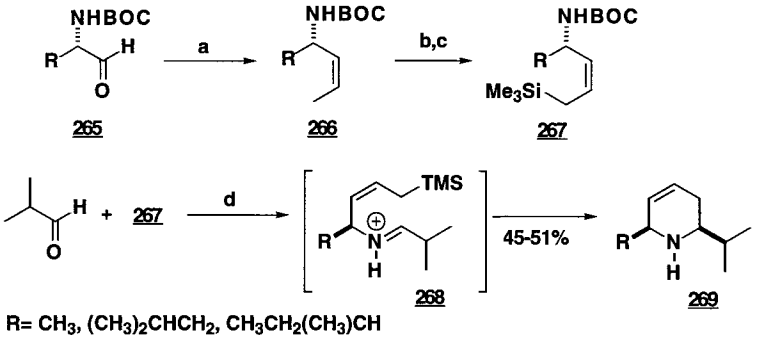


(a) DIBAL, vinylmagnesium chloride; (b) TFA; (c) PhCOCl, pyridine; (d) $LiAlH_4$; (e) $BrCH_2CO_2Ph$, $EtN(i\text{-}Pr)_2$; (f) TIPSOTf, Et_3N; (g) $LiAlH_4$; (h) Swern Ox.; (i) KH, $(EtO)_2POCH_2CO(CH_2)_3CH_3$; (j) H_2, Pd/C, HCl.

Addition of triisopropylsilyltriflate and triethylamine generated ketene acetal **262** (still an 8:1 mixture of diastereomers). Upon sitting at room temperature for 6 hours, the major *trans*-diastereomer underwent Ireland-Claisen rearrangement while the minor *cis*-diastereomer did not undergo rearrangement. The crude triisopropylsilyl ester was then treated with lithium aluminum hydride to afford alcohol **263** as a single diastereomer. Swern oxidation and Horner-Emmons olefination provided enone **264** in 88% yield. Enone **264** was then subjected to hydrogenation over palladium on carbon in methanol and 1N hydrochloric acid, resulting in the reduction of both alkenes, removal of the benzyl group, and reductive amination of the ketone, to afford (+)-monomorine in 66% yield.

Taddei synthesized 2-*iso*-propylpiperidines from amino aldehydes using a unique iminium ion/allylsilane cyclization (Scheme 3.25).[120] Wittig olefination of amino aldehyde **265** with (ethylene)triphenylphosphorane furnished *Z*-alkene **266**. Addition of Schlosser's base and trapping of the resulting allyl anion with trimethylsilyl chloride afforded allylsilane **267**. Treatment of **267** with titanium tetrachloride and 2-methylpropanal removed the *t*-butyloxycarbonyl protecting group, and the resulting amine was condensed with the aldehyde to generate iminium ion **268**. Cyclization of the iminium ion onto the allylsilane produced **269** as a single diastereomer. The stereoselectivity is probably dictated by a preference for the diequatorial conformation in the transition state.

Scheme 3.25. Taddei Iminium Ion Cyclization to Piperidines.[120]



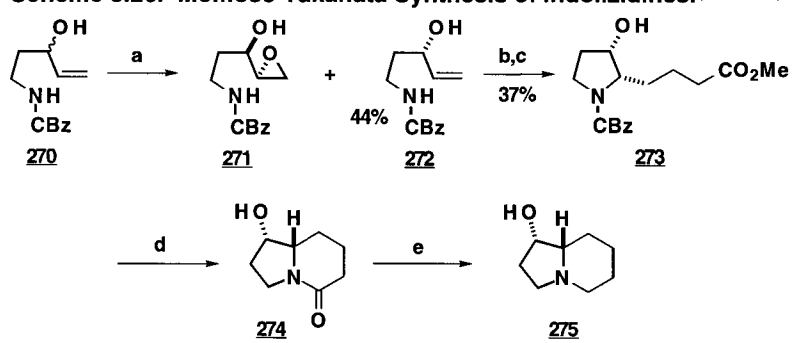
(a) $Ph_3P{=}CHCH_3$; (b) BuLi, KO*t*-Bu; (c) TMSCl; (d) $TiCl_4$.

3.3 Miscellaneous Sources of Chirality

Natural hydroxylated indolizidines such as castanospermine and swainsonine posses important biological activity. As a result, considerable effort has been directed toward the synthesis of these compounds. This work, which was recently reviewed by Burgess and Henderson,[121] is not discussed in this review.

Momose and Takahata synthesized hydroxylated indolizidines from chiral allyl alcohols. Resolution of racemic allyl alcohol **270** was accomplished through the Sharpless procedure to afford enantiomerically pure alcohol **272** along with chiral epoxide **271** (Scheme 3.26).[122,123] Intramolecular amidomercuration of **272** followed by treatment with methyl acrylate and sodium trimethoxyborohydride provided the *cis*-diastereomer **273** in 37% yield. The *trans*-diastereomer was not observed. The diastereoselectivity of the reaction arises from hydroxyl directed mercuration from the bottom face of the alkene. Attack of the carbamate nitrogen must then come from the top face.[124] Exposure of **273** to hydrogen over palladium hydroxide lead to removal of

Scheme 3.26. Momose-Takahata Synthesis of Indolizidines.[122,123]

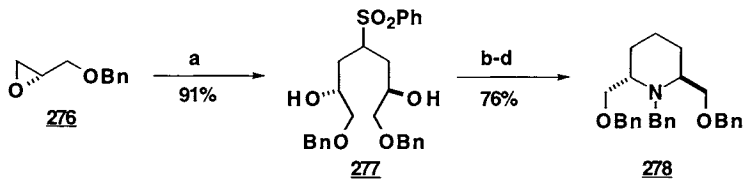


(a) *t*-BuOOH, (-)-DIPT, $Ti(OPr)_4$; (b) $Hg(CF_3CO_2)_2$; (c) methyl acrylate, $NaBH(OMe)_3$; (d) H_2, $Pd(OH)_2$; (e) $LiAlH_4$.

the *t*-butyloxycarbonyl protecting group and formation of lactam **274**. Reduction of the lactam with lithium aluminum hydride gave the hydroxylated indolizidine **275**. Momose also synthesized other hydroxylated indolizidine analogs using the same general method shown below.[123]

Kurth used chiral epoxides for his synthesis of C_2 symmetrical piperidines which were intended for use as chiral reagents (Scheme 3.27).[125] Two equivalents of chiral epoxide **276**, available through Sharpless asymmetric epoxidation, were condensed with the dianion of phenylmethyl sulfone to afford C_2 symmetrical diol **277**. Reductive cleavage of the sulfone with sodium amalgam, treatment with tosyl chloride to afford the bistosylate, followed by addition of benzylamine to sequentially displace both tosyl groups afforded 2,6-disubstituted piperidine **278**. C_2-Symmetric pyrrolidines have been used effectively as chiral auxiliaries in the formation of chiral enolates and enamines;[126] however, the piperidines have received much less attention.

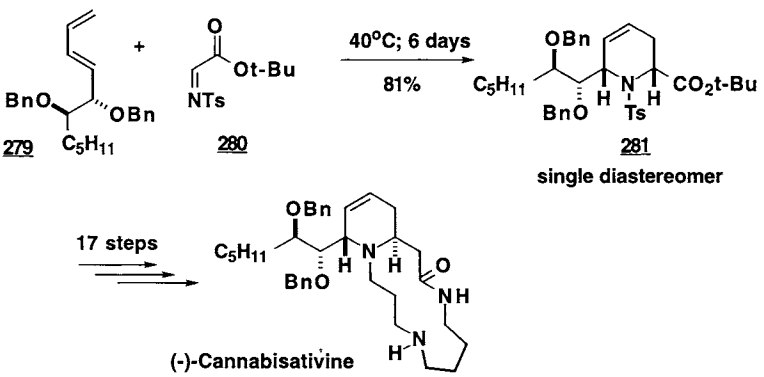
Scheme 3.27. Kurth Synthesis of C_2 Symmetrical Piperidines.[125]



(a) *n*-BuLi (2 equiv.), HMPA, $MeSO_2Ph$; (b) Na(Hg); (c) TsCl, pyr.; (d) $BnNH_2$, 85°C.

The first enantioselective synthesis of the alkaloid (-)-cannabisativine was reported by Hamada and co-workers through an imine Diels-Alder strategy (Scheme 3.28).[127] Diene **279** was synthesized in 9 steps from 2-octen-1-ol. The chirality in the diene was generated through a Sharpless asymmetric epoxidation. Addition of tosylimine **280** and heating to 40 °C for 6 days afforded tetrahydropyridine **281** as a single diastereomer. Hamada rationalized that the selectivity of the reaction depends upon stabilization of the

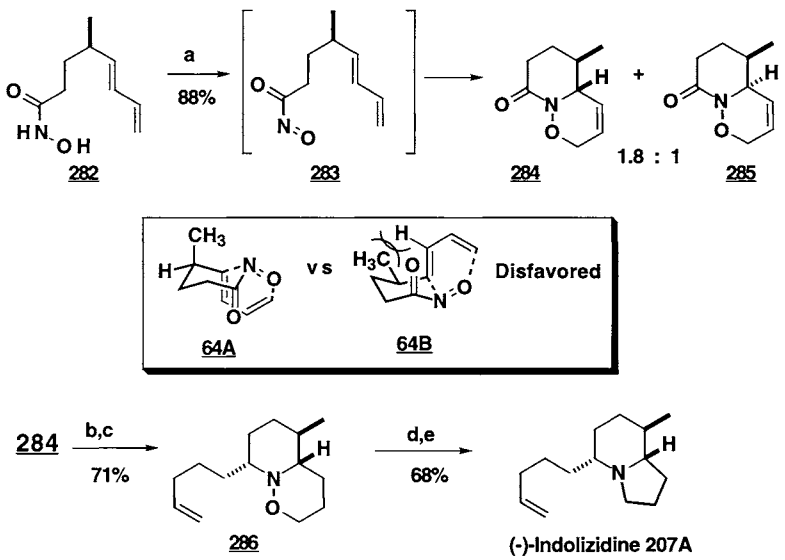
Scheme 3.28. Hamada Synthesis of (-)-Cannabisativine.[127]



developing allyl cation in the diene through homoallylic interactions with an oxygen lone pair.[128] Further elaboration of **281** resulted in the first enantioselective synthesis of (-)-cannabisativine.

Kibayashi reported the enantioselective synthesis of various 5,8-substituted indolizidines using a nitroso Diels-Alder reaction (Scheme 3.29).[129,130] The synthesis of indolizidine 207A is a representative example. (*R*)-Citronellol was converted into hydroxamide acid **282** in 7 steps and 20% overall yield. Oxidation of **282** with tetrapropylammonium periodate generated *N*-acylnitroso compound **283**. An intramolecular [4+2]-cycloaddition lead to a 1.8:1 mixture of diastereomers **284** and **285** in 88% yield. The stereochemical preference was explained by transition state **64A**, which allows for secondary orbital overlap of the diene with the carbonyl of the *N*-acylnitroso group while maintaining a chair-like conformation. $A^{1,3}$ Strain in transition state **64B** results in this conformation being disfavored. The diastereomers **284** and **285** were separated by chromatography. Treatment of **284** with hydrogen over palladium on carbon reduced the alkene. The C(8)-substituent was introduced by addition of 4-pentenylmagnesium bromide to afford an intermediate enamine. Treatment of the enamine with sodium borohydride and acetic acid resulted in stereoelectronically controlled addition[90] of hydride, affording **286** in 71% overall yield. Reductive cleavage of the N-O bond and cyclization of the aminoalcohol via the alkyl bromide afforded (-)-indolizidine 207A.

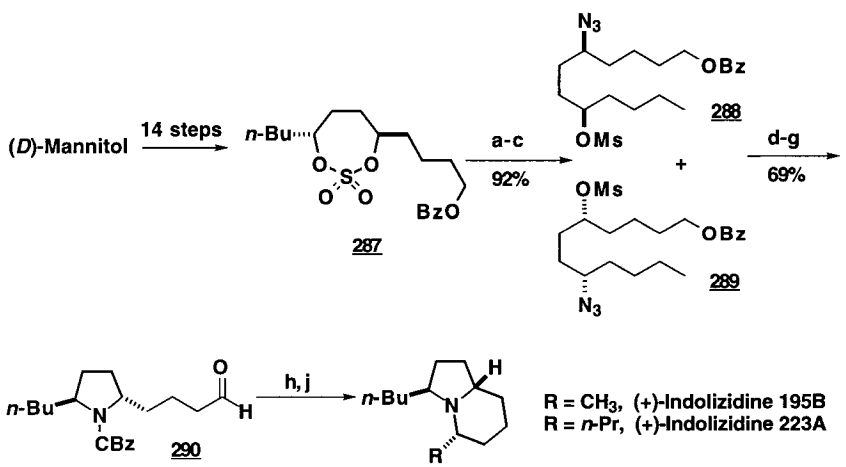
Scheme 3.29. Kibayashi Synthesis of (-)-Indolizidine 207A.[129,130]



(a) $Pr_4N^+IO_4^-$; (b) H_2, Pd/C; (c) $CH_2{=}CH(CH_2)_3MgBr$; $NaBH_4$, AcOH; (d) Zn, AcOH; (e) PPh_3, CBr_4, Et_3N.

A different approach used by Kibayashi to synthesize indolizidine alkaloids involved the synthesis of enantiopure cyclic sulfates. (*D*)-Mannitol was converted into sulfate **287** via (*S,S*)-diepoxy-1,5-hexadiene in 14 steps (Scheme 3.30).[131-133] Treatment of **287** with lithium azide resulted in a non-regioselective nucleophilic ring opening. Acid hydrolysis of the sulfate and mesylation of the resulting alcohol afforded a 1:1 mixture of diastereomers **288** and **289**. Because both of the diastereomers cyclize to the identical pyrrolidine, separation of the diastereomers at this point was not necessary. The mixture of azides **288** and **289** was reduced with hydrogen over palladium on carbon. Intramolecular displacement of the mesylate by the amine formed the pyrrolidine ring which was protected with benzyl chloroformate and potassium carbonate. Base hydrolysis of the phenyl ester and oxidation of the resulting alcohol provided aldehyde **290** as a single isomer. Addition of the appropriate Grignard reagent provided a secondary alcohol which was reoxidized to the ketone and reductively cyclized by exposure to hydrogen over palladium on carbon to afford (+)-indolizidines 195B and 223AB.

Scheme 3.30. Kibayashi Synthesis of (-)-Indolizidines 195B and 223A.[131-133]

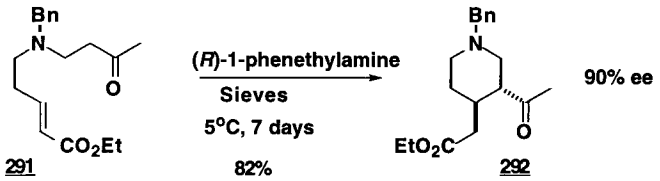


(a) LiN_3; (b) H_2SO_4; (c) MsCl, Et_3N; (d)H_2, Pd/C; (e) CBZ-Cl, K_2CO_3; (f) NaOH; (g) Swern Ox.; (h) RMgBr; (i) Swern Ox.; (j) H_2, Pd/C.

3.4 Chiral Catalysts and Reagents

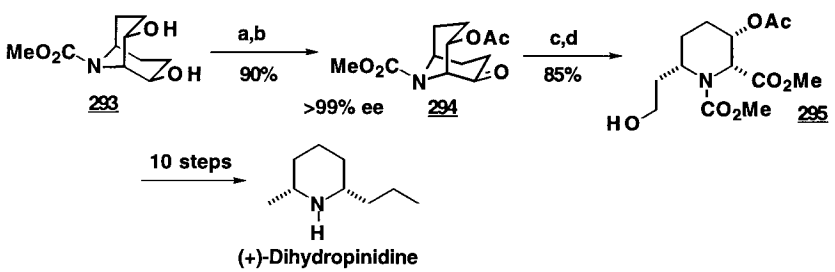
Momose explored an intramolecular Michael reaction as a means of generating chiral piperidines (Scheme 3.31).[134] Optimum results were achieved by the treatment of **291** with one equivalent of (*R*)-1-phenethylamine in tetrahydrofuran over 4Å molecular sieves. Using these conditions piperidine **292** was obtained in 82% yield and 90% enantiomeric excess. The *cis*-diastereomer was not detected. The use of chiral bases (*L*)-proline and (+)-2,6-dimethylpyrrolidine did not afford cyclization products. The stereoselectivity was explained by the formation of a transient chiral enamine.

Scheme 3.31. Momose Synthesis of Piperidines.[134]



Momose used an enzyme catalyzed desymmetrization of *meso*-diol **293** for the synthesis of (+)-dihydropinidine (Scheme 3.32).[135] The enantiospecific lipase catalyzed transesterification of **293** and vinyl acetate provided a single mono-acetate. Subsequent oxidation of the remaining alcohol afforded ketone **294** in 90% yield as a single enantiomer. Treatment with trimethyl orthoformate and sulfuric acid generated the enol ether. Ozonolysis of the enol ether provided the all *cis*-trisubstituted piperidine **295**. This intermediate was taken on to (+)-dihydropinidine in a 10 step sequence which confirmed the absolute stereoselectivity of the acylation reaction.

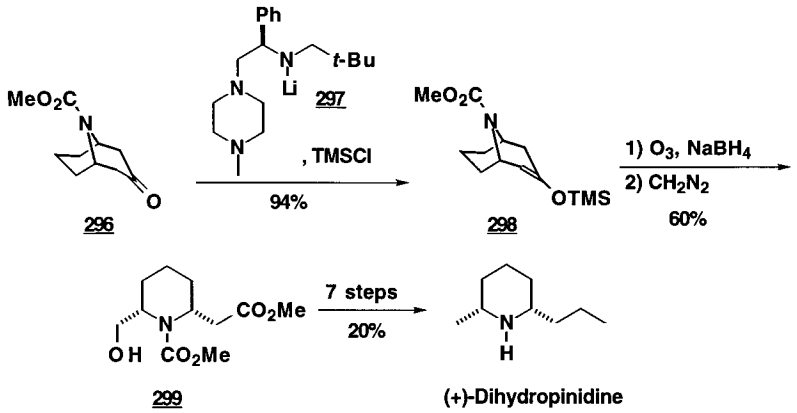
Scheme 3.32. First Momose Synthesis of (+)-Dihydropinidine.[135]



(a) lipase, vinyl acetate; (b) PCC; (c) $HC(OCH_3)_3$, H^+; (d) O_3, $NaBH_4$.

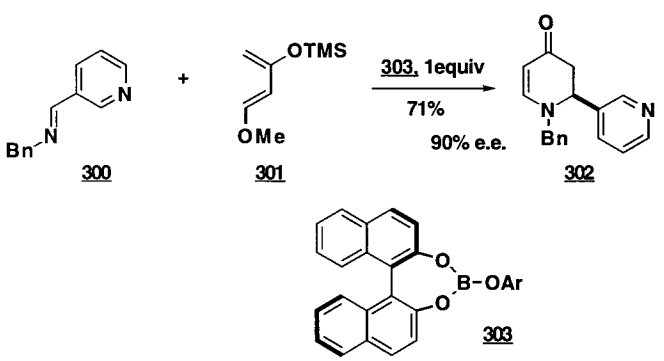
Meso-desymmetrization of the bicyclic ketone **296** was also investigated by Momose in the synthesis of (+)-dihydropinidine (Scheme 3.33).[136] The chiral base **297**, developed by Koga,[137] was added to ketone **296** at -100 °C in the presence of trimethylsilyl chloride to give trimethylsilyl enol ether **298** in 93% enantiomeric excess. Ozonolysis of the enol ether and treatment with diazomethane afforded the *cis*-2,6-disubstituted piperidine **299**. Intermediate **299** was elaborated to dihydropinidine in 7 steps and 20% overall yield.

Scheme 3.33. Second Momose Synthesis of (+)-Dihydropinidine.[136]



Yamamoto reported an efficient asymmetric imine Diels-Alder reaction mediated by chiral boron reagent **303** (Scheme 3.34).[138] The catalyst was generated in situ from triphenylborate and binaphthol. Addition of Danishefsky's diene and imine **300** at -78 °C resulted in the formation of enone **302** in 68% yield and 90% enantiomeric excess. The chiral binaphthol was recovered in quantitative yield. Other imines were also investigated with similar results.

Scheme 3.34. Yamamoto Synthesis of Piperidines with a Binapthol Catalyst.[138]



4.0 CONCLUSION

The many syntheses of piperdine and indolizidine alkaloids have resulted in the development of a wide array of methodologies. The clever, efficient approaches that have been discussed in this review, are a testament to the creativity and ability of the researchers involved. Undoubtedly, future efforts in this area will result in the development of additional methodology.

ACKNOWLEDGMENT: We thank Professor Daniel L. Comins of North Carolina State University and Dr. D. O. Arnaiz of Berlix Biosciences for carefully proofreading the manuscript.

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Atta-ur-Rahman (Ed.) *Studies in Natural Products Chemistry, Vol. 16*

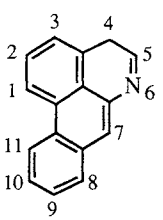
Recent Developments on the Synthesis of Aporphine Alkaloids

Osamu Hoshino

1. INTRODUCTION

Aporphine alkaloids[1] are a major group among the isoquinoline alkaloids.[2,3] Their basic skeleton is 4H-dibenzo[de,g]quinoline (**1**), 5,6,6a,7-tetrahydro-6-methyl derivatives of which are called aporphines (**2**). Isolation, structural determination and synthesis of the alkaloids have been extensively investigated by numerous organic chemists until now in order to explore both new methodology for their synthesis and their biological activity. Especially, apomorphine (**3**) and apocodeine (**4**), which are architectural aporphine-type alkaloids obtained by acid treatment of morphine (**5**) and codeine (**6**), are attractive compounds[4] for pharmacologists for searching novel biological activity. There are numerous and excellent references[1,5,6] on the aporphine alkaloids so far, in which the methodology for synthesis of the alkaloids is mainly classified in the following five categolies; 1) the Pschorr reaction,[7] 2) phenolic[8] and nonphenolic[9] coupling reaction, 3) photochemical reaction,[10] 4) benzyne reaction,[11] and 5) acid catalyzed reaction. Among them, recently, the new or modified methods have been reported. The present article reviews the syntheses of aporphine and dehydroaporphine alkaloids (except for oxoaporphine alkaloids[12] such as **7**), which have appeared in the literatures since 1982.

Homoaporphine alkaloids[13] (**8**) have been not described in this article, because they are classified as belonging to the phenethylisoquinoline group of alkaloids.



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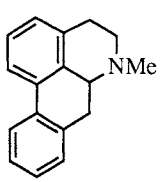

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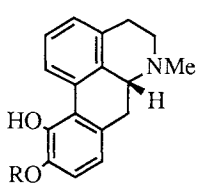
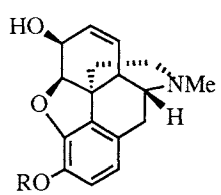


3 R = H
4 R = Me



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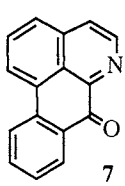
6 R = Me



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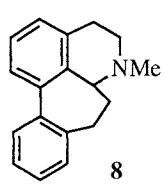
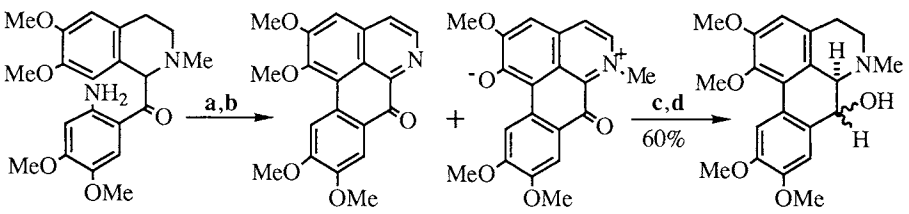


8

2. BY THE PSCHORR REACTION

Although numerous aporphine alkaloids have been synthesized by the Pschorr reaction, there is only one report[14] in which the Pschorr reaction has been attempted for the synthesis of aporphine alkaloids since 1982. Namely, 1-(*o*-aminobenzoyl)-tetrahydroisoquinoline (**9**) was treated with sodium nitrite in acetic acid (AcOH) and concentrated sulfuric acid at room temperature followed by treatment with cupper in acetone to give 7-oxotetradehydronoraporphine (**10**) and corunnine (**11**) in 22 and 8% yields, respectively. The former product (**10**) was treated with methyl iodide to give a methiodide, which was reduced with potassium borohydride in methanol (MeOH) to produce a mixture of (±)-7α- and (±)-7β-hydroxyglaucines (**12** and **13**) in 60% yield (Scheme 1).



9 **10** (22%) **11** (8%) **12** 7α-OH **13** 7β-OH

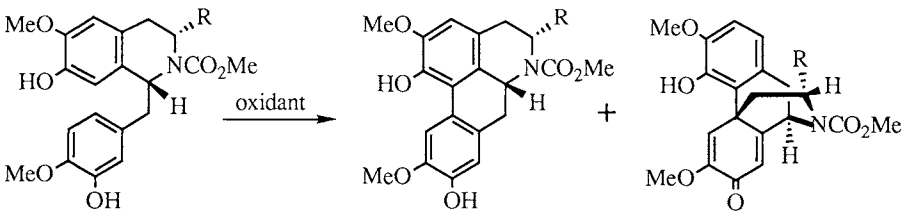
a: $NaNO_2$, AcOH, conc. H_2SO_4, room temp.; **b**: Cu, acetone, **c**: MeI, 40-45° C; **d**: KBH_4, MeOH

Scheme 1

3. BY PHENOLIC AND NONPHENOLIC COUPLING REACTION

3.1 By Phenolic Coupling Reaction

The synthesis of aporphine alkaloids by this method has been not performed exten-



14 R = CO_2Me
15 R = H

16 R = CO_2Me
17 R = H

18 R = CO_2Me
19 R = H

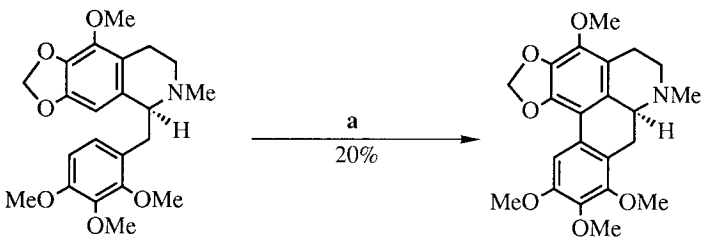
oxidant	yields (%)	
	16 (18)	**17 (19)**
$VOCl_3$	80 (70)	20 (21)
$Tl(OCOCF_3)_3$	2 (16)	33 (28)
$PhI(OAc)_2$ -TFA	21 (25)	36 (27)

Scheme 2

sively during the last decade. The synthesis of (±)-aporphine alkaloids (**16** and **17**) along with (±)-normorphinandienones (**18** and **19**) by a phenolic coupling reaction of (±)-cis-2,3-bis(methoxycarbonyl)- (**14**) and (±)-N-methoxycarbonyl-norreticulines (**15**) using some oxidants has been reported (Scheme 2).[15] Interestingly, oxidation of (R)-(-)-**14** with iodosobenzene diacetate in trifluoroacetic acid (TFA) gave only (9R)-(+)-normorphinandienone (**18**) in 25% yield.

3.2 By Nonphenolic Coupling Reaction

Since the discovery of nonphenolic coupling reaction using thallium (III) trifluoroacetate (TTFA) in 1980 by Taylor and Mckillop,[9] the synthesis of aporphine alkaloids

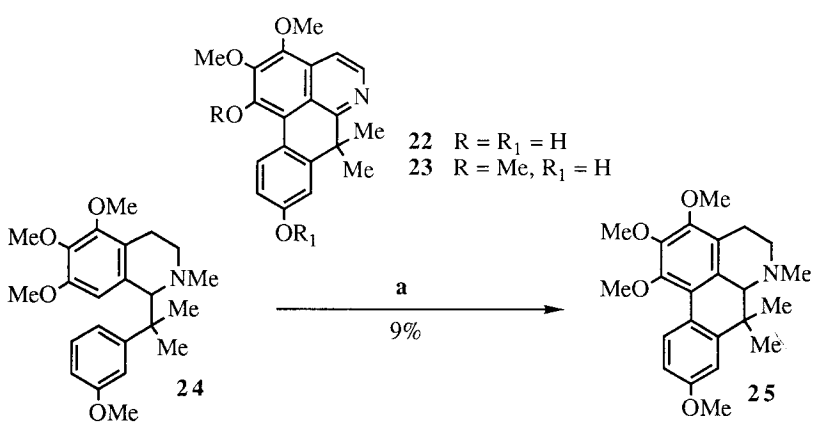


20 **21**

a: $Tl(OCOCF_3)_3$, MeCN, CCl_4, $BF_3{\cdot}Et_2O$, 0° C, then room temp.

Scheme 3

by this method has been developed. Namely, (±)-leucoxylonine (**21**) was synthesized in 20% yield by a coupling reaction of **20** using TTFA in acetonitrile-carbon tetrachloride containing boron trifluoride etherate (Scheme 3).[16] Novel 7,7-dimethyltetradehydroaporphine alkaloids, melosmine (**22**) and melosmidine (**23**) have been isolated from *Guatteria melosma*, reduction and methylation of which gave 7,7-dime-



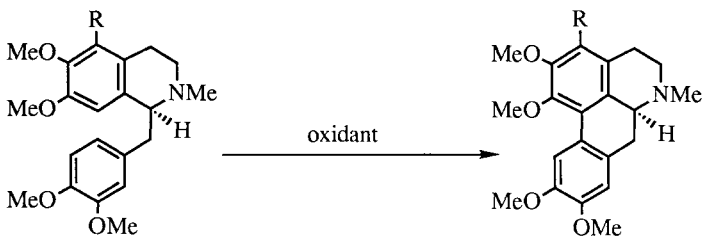
24 **25**

a: $Tl(OCOCF_3)_3$, CF_3CO_2H, CH_2Cl_2, $BF_3{\cdot}Et_2O$, -40° C

Scheme 4

thylaporphine alkaloids. One of the alkaloids, **25**, was synthesized in 9% yield from **24** in a similar manner (Scheme 4).[17]

A new oxidant, ruthenium (IV) tetrafluoroacetate[18] [$Ru(OCOCF_3)_4$] was found, oxidation with which of (±)-laudanosine (**26**) and (±)-5-methoxylaudanosine (**27**) gave (±)-glaucine (**28**) and (±)-thalicsimidine (**29**) in 76 and 68% yields. The new oxidant on comparison with TTFA and vanadium oxyfluoride showed that the former is superior to the latter two (Scheme 5).



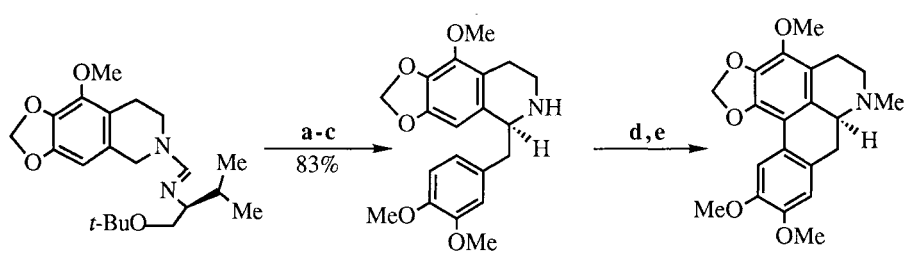
26 R = H
27 R = OMe

oxidant	yields (%)	
	28 (R= H)	**29** (R = OMe)
$Ru(OCOCF_3)_4$	76	68
$Tl(OCOCF_3)_3$	65	57
VOF_3	43[a]	---

a) From a literature; S. M. Kupchan, A. J. Liepa, V. Kameswaran, and R. F. Bryan, *J. Am. Chem. Soc.*, **1973**, *95*, 6861-6863.

Scheme 5

Recently, Meyers and Dickman[19] have reported application of this method to the synthesis of an optically active aporphine alkaloid. Namely, (S)-tetrahydroisoquinoline (**30**)(93% ee), which was prepared by asymmetric alkylation of chiral formamidine containing tetrahydroisoquinoline moiety, was oxidized according to the method[9] reported previously to give (S)-(+)-octoteine (**31**)(93% ee) without racemization during the coupling reaction (Scheme 6).

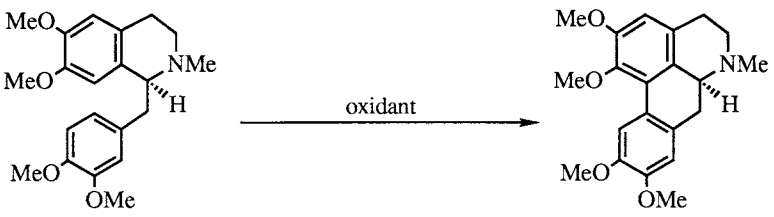


30 **31**

a: *t*-BuLi-THF, -78° C; **b**: 3,4-dimethoxybenzyl bromide; **c**: N_2H_4; **d**: N-methylation; **e**: Taylor's method[9]

Scheme 6

Similarly, (S)-laudanosine (**26**)(82% ee) gave (S)-glaucine (**28**)(83% ee) in 47% yield (Scheme 7).[20,21]



(S)-**26** (S)-**28**

oxidant	yields (%)(ee)
$Tl(OCOCF_3)_3$, TFA, BF_3•Et_2O	47 (83)[20]
$Tl(OCOCF_3)_3$, TFA, BF_3•Et_2O	40[21]
VOF_3, $(CF_3CO)_2O$, $MeSO_3H$	40 ($[\alpha]_D$ +100)[21]

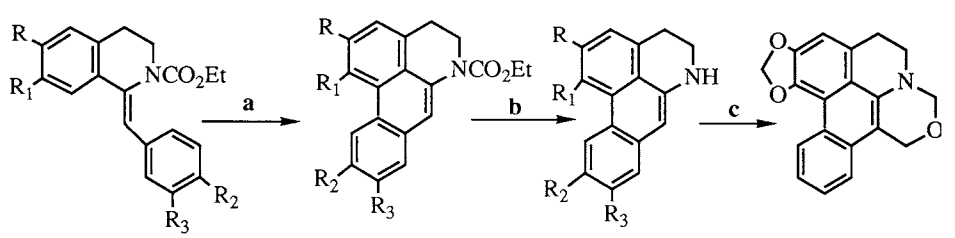
Scheme 7

4. BY PHOTOCHEMICAL REACTION

4.1 By Photochemical reaction

Photochemical reaction has been well known to be a useful method for synthesis of phenanthrene derivatives[10] and it has been also applied to synthesis of numerous aporphine alkaloids so far.

Several reports on synthesis of the alkaloids by this method have appeared. In continuation of previous investigations[22] photolysis of nonphenolic 1-(benzylidene)-tetrahydroisoquinolines was carried out. Namely, 1-(benzylidene)-N-ethoxycarbonyl-tetrahydroisoquinolines (**32-35**) were irradiated by medium-pressure mercury lamp (450-W) through a Vycor filter in the presence of iodine to produce N-ethoxycarbonyl-



32 R = R_1 = OMe, R_2 = R_3 = H
33 R + R_1 = OCH_2O, R_2 = R_3 = H
34 R = R_1 = R_2 = R_3 = OMe
35 R = R_1 = OMe, R_2+ R_3 = OCH_2O

36 56%
37 54%
38 ---
39 47%

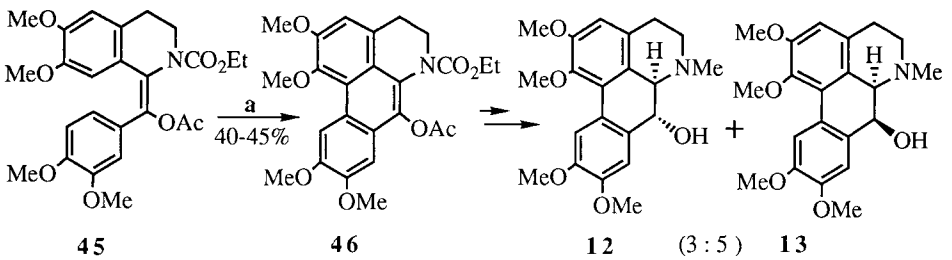
40 94%
41 97%
42 86%
43 88%

44 76%

a: *hν* (450-W), medium-pressure mercury lamp through a Vycor filter, I_2, THF, EtOH, room temp.; **b**: KOH, abs. EtOH, Δ ; **c**: 37% aq. CH_2O, dioxane, room temp.

Scheme 8

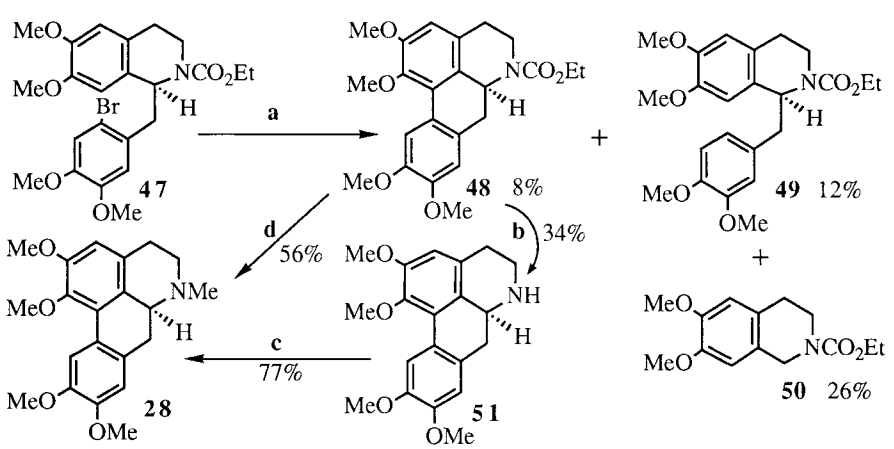
dehydronoraporphines (**36-39**) in good yields, which were converted to dehydronoraporphines (**40-43**)(Scheme 8).[23] Moreover, alkaline hydrolysis followed by treatment with aqueous formaldehyde of **41** gave highly functionalized aporphine alkaloid, duguenaine (**44**) isolated from a bark of *Duguetia calycina* Benoist. Similarly, photolysis of 1-(α-acetoxybenzylidene)-N-ethoxycarbonylnortetrahydroisoquinoline (**45**) produced 7-acetoxydehydronoraporphine (**46**),[24] which was transformed to (±)-7α- and (±)-7β-hydroxyaporphines (**12** and **13**) in a usual manner (Scheme 9).



a: *hν* (450-W), medium-pressure mercuy lamp through a Pyrex filter, C_6H_6, I_2, room temp.

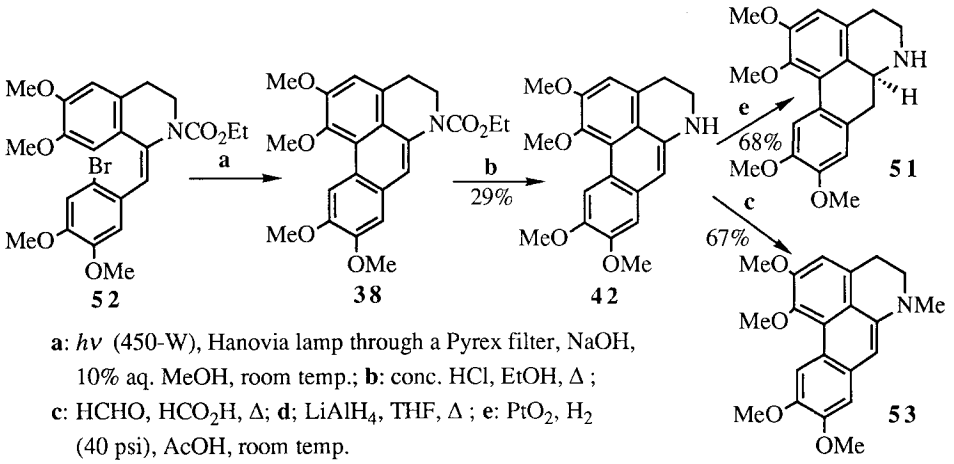
Scheme 9

Since irradiation of (±)-1-(bromobenzyl)-N-ethoxycarbonylnortetrahydroisoquinoline (**47**) in MeOH containing sodium hydroxide gave in low yield the aporphine (**48**)[24] together with the debrominated product (**49**) and the tetrahydroisoquinoline (**50**), the precursor (**47**) may be unsuitable for synthesis of norglaucine (**51**) and glaucine (**28**) using photochemical reaction (Scheme 10). However, similar attempts to convert 1-(bromobenzylidene)-tetrahydroisoquinoline (**52**) to (±)-norglaucine (**51**) was achieved



a: *hν* (450-W), Hanovia lamp through a Pyrex filter, NaOH, 10% aq. MeOH, room temp.; **b**: conc. HCl, EtOH, Δ ; **c**: aq. CH_2O, HCO_2H, Δ; **d**; $LiAlH_4$, THF, Δ

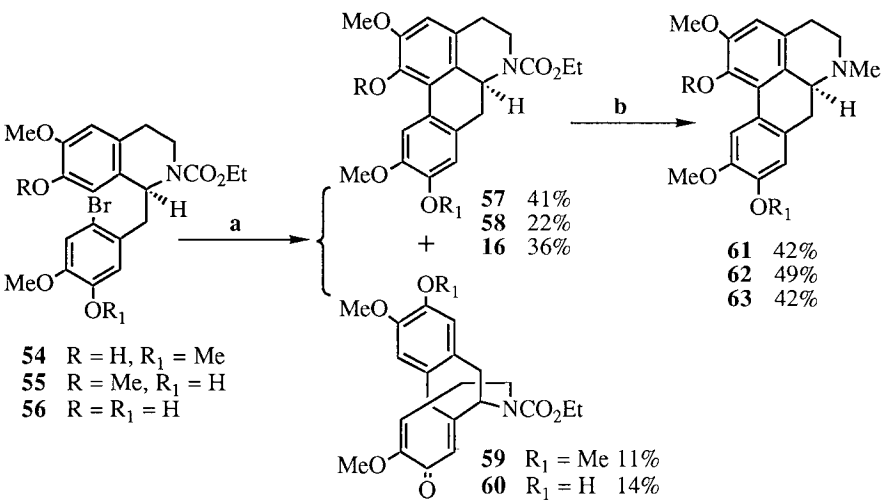
Scheme 10



a: *hν* (450-W), Hanovia lamp through a Pyrex filter, NaOH, 10% aq. MeOH, room temp.; **b**: conc. HCl, EtOH, Δ ; **c**: HCHO, HCO_2H, Δ; **d**; $LiAlH_4$, THF, Δ ; **e**: PtO_2, H_2 (40 psi), AcOH, room temp.

Scheme 11

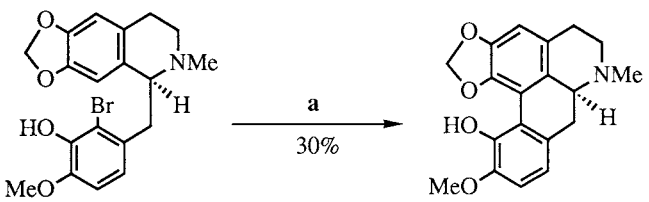
in fair yield. Namely, photolysis of **52** according to the previously reported method[26] gave N-ethoxycarbonyldehydronorglaucine (**38**).[25] Hydrolysis of **38** with concentrated hydrochloric acid gave dehydronorglaucine (**42**), which was transformed to (±)-norglaucine (**51**) or dehydroglaucine (**53**) by appropriate reduction or N-methylation (Scheme 11). These findings suggest that as expected phenolic 1-(bromobenzyl or bromobenzylidene)-tetrahydroisoquinolines may be suitable precursors for photochemical cyclization. In fact, phenolic 1-(bromobenzyl)-tetrahydroisoquinolines (**54** and



a: *hν* (450-W) Hanovia lamp through a Pyrex filter, NaOH, 10% aq. MeOH, room temp.; **b**: $LiAlH_4$, THF, Δ

Scheme 12

56) were irradiated by high-pressure mercury lamp (450-W) in basic media to afford he corresponding cyclized products (**57** and **16**) in moderate yield, though photolysis of **55** gave **58** in low yield (Scheme 12).[27] With **54** and **56**, the corresponding morphinandienones (**59** and **60**) besides noraporphines (**57** and **16**) were formed. (±)-Noraporphines (**57**, **58** and **16**) thus obtained were transformed to (±)-thaliporphine (**61**), (±)-N-methyllaurotetanine (**62**) and (±)-isoboldine (**63**), respectively, by lithium aluminium hydride reduction. On the other hand, photolysis of phenolic (±)-1-(bromobenzyl)-tetrahydroisoquinoline (**64**) gave rise to (±)-bulbocapnine (**65**) in 30% yield by photolysis in an acidic medium (Scheme 13).[27] Interestingly, irradiation of phenolic 1-(bromobenzylidene)-tetrahydroisoquinoline (**66**) in toluene containing

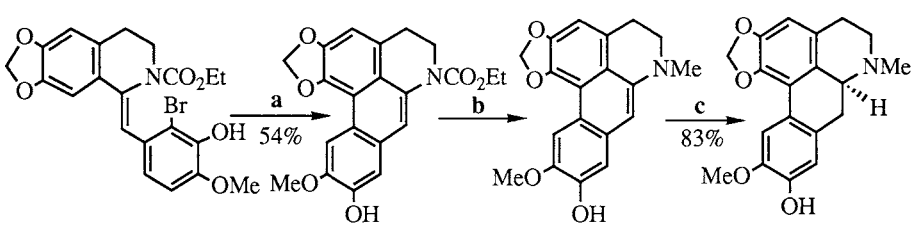


64 **65**

a: *hv* (150-W), high-pressure mercury lamp, 0.01N HCl, room temp.

Scheme 13

potassium *t*-butoxide[28] (KO*t*-Bu) gave a para-coupled dehydronoraporphine (**67**) in 54% yield, which was converted to (±)-cassythicine (**69**) via dehydroaporphine (**68**) by reduction with lithium aluminium hydride-aluminium chloride complex (Scheme 14). Analogously, phenolic 1-(bromobenzylidene)-tetra-hydroisoquinolines (**70** and **71**) produced, on photolysis in benzene in the presence of KO*t*-Bu using a Pyrex filter,

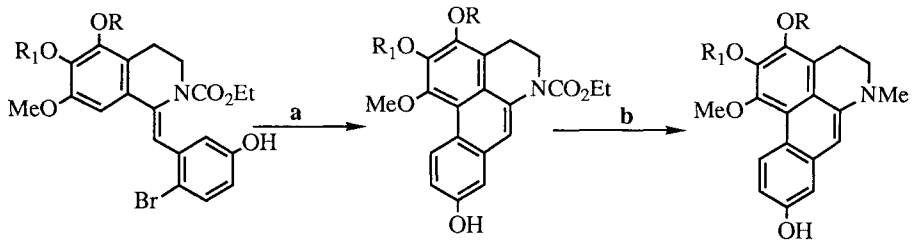


66 **67** **68** **69**

a: *hv* (500-W), high-pressure mercury lamp through a Pyrex filter, KO*t*-Bu, C_6H_5Me; room temp.; **b**: $LiAlH_4$-$AlCl_3$, THF, room temp.; **c**: PtO_2, H_2, AcOH, room temp.

Scheme 14

afforded the corresponding dehydronoraporphines (**72** and **73**) in 41 and 40% yields,[29] which were also transformed to dehydroaporphines (**74** and **75**) in good yields by aluminium hydride reduction (Scheme 15).



70 R = H, R_1 = Me
71 R = Me, R_1 = H

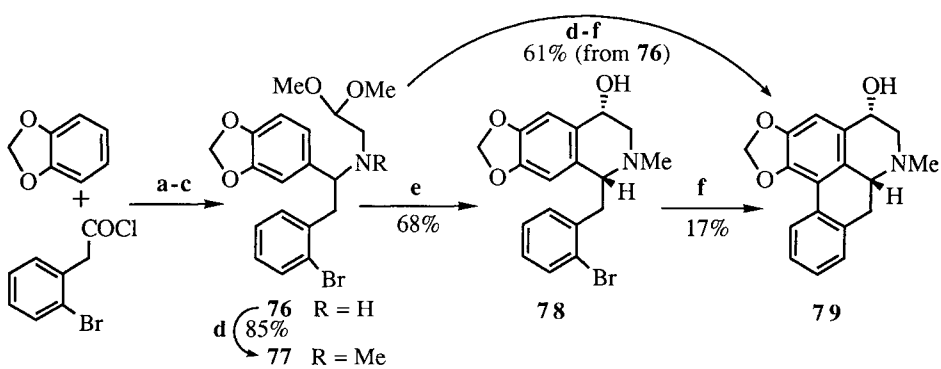
72 41%
73 40%

74 70%
75 73%

a: *hν* (450-W), Hanovia lamp through a Pyrex filter, KO*t*-Bu, *t*-BuOH, C_6H_6, room temp.; **b**: $LiAlH_4$-$AlCl_3$, Et_2O, room temp.

Scheme 15

Aporphine alkaloids possessing a hydroxyl group at 4 or 7 position have been isolated. Therefore, the synthesis of 4- and 7-hydroxyaporphines has been carried out by photolysis in acidic media.

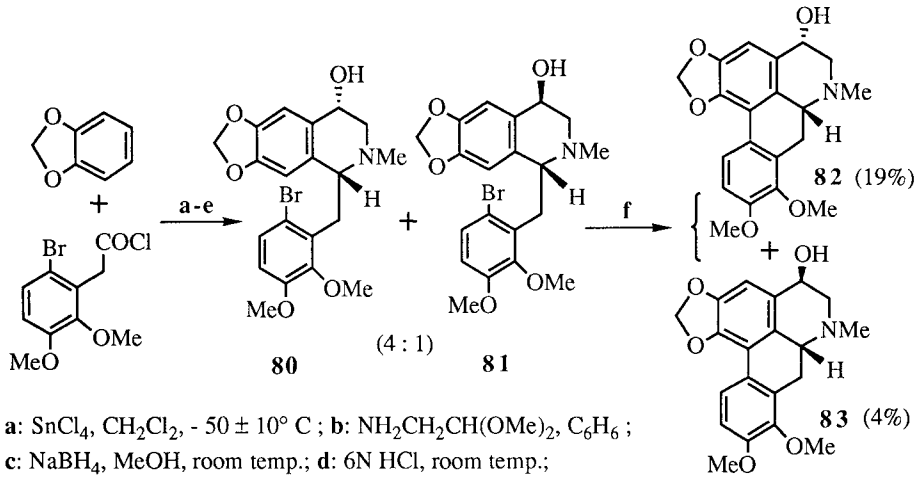


76 R = H
77 R = Me
78
79

a: $AlCl_3$, $CHCl_3$, -40 to -50° C; **b**: $NH_2CH_2CH(OMe)_2$, C_6H_6, room temp.; **c**: $NaBH_4$, MeOH, 0° C; **d**: 10% aq. HCHO, MeOH; $NaBH_4$; **e**: 6N HCl; room temp.; **f**: *hν* (100 W), high-pressure mercury lamp, 6N HCl, MeOH, room temp.

Scheme 16

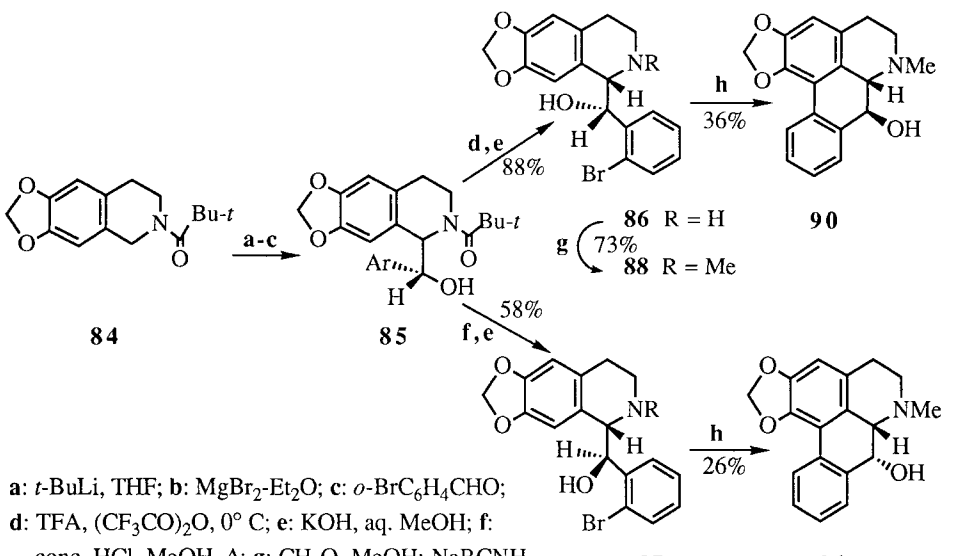
Kunitomo and coworkers[30] have reported that (±)-1-(bromobenzyl)-4-hydroxytetrahydroisoquinoline (**78**) derived from the corresponding aminoacetal (**77**) by the Pomeranz-Fritsch reaction was irradiated by high-pressure mercury lamp (100 W) in MeOH containing 6N hydrochloric acid to afford (±)-steporphine (**79**), which was also obtained in 61% yield from **76** in a manner similar to that noted for **77** (Scheme 16). Similarly, an approximately (4 : 1) diastereomeric mixture of (±)-1-(bromobenzyl)-4-hydroxytetrahydroisoquinolines (**80** and **81**) produced (±)-4-hydroxycrebanine (**82**) and its 4-epimer (**83**) in 19 and 4% yields (Scheme 17).[30]



a: $SnCl_4$, CH_2Cl_2, - 50 ± 10° C ; **b**: $NH_2CH_2CH(OMe)_2$, C_6H_6 ;
c: $NaBH_4$, MeOH, room temp.; **d**: 6N HCl, room temp.;
e: 10% HCHO, MeOH then $NaBH_4$; **f**: *hν* (100 W), high-pressure mercury lamp, 6N HCl, MeOH, H_2O, room temp.

Scheme 17

Although (±)-oliveroline (**90**) and (±)-ushinsunine (**91**) were aldready synthesized by photochemical cyclization[32] of a diastereomeric mixture of (±)-1-(α-hydroxy-*o*-bromobenzyl)-tetrahydroisoquinolines (**88** and **89**), Seebach and coworkers[33] have



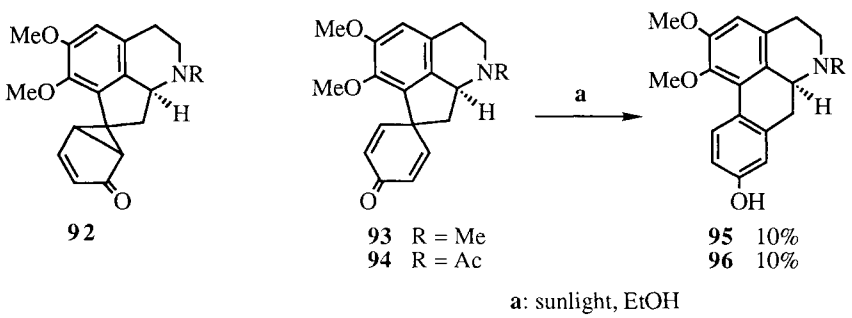
a: *t*-BuLi, THF; **b**: $MgBr_2$-Et_2O; **c**: *o*-BrC_6H_4CHO;
d: TFA, $(CF_3CO)_2O$, 0° C; **e**: KOH, aq. MeOH; **f**: conc. HCl, MeOH, Δ; **g**: CH_2O, MeOH; $NaBCNH_3$, HCl; **h**: *hν*, 3% HCl[32]

Scheme 18

reported an improved synthesis of (±)-1-(α-hydroxy-*o*-bromobenzyl)-tetrahydroisoquinolines (**88** and **89**) and the alkaloids (**90** and **91**). Namely, N-pivaroyltetrahydroisoquinol-1-ylmagnesium bromide, which was generated *in situ* by treatment of (±)-N-pivaroyltetrahydroisoquinoline (**84**) with *t*-butyllithium in tetrahydrofuran (THF), reacted with *o*-bromobenzaldehyde to furnish (±)-1-(α-hydroxy-*o*-bromobenzyl)-tetrahydroisoquinoline (**85**) in 56% yield (>97% ds). Interestingly, reaction of **85** with a (9 : 1) mixture of trifluoroacetic acid (TFA) and trifluoroacetic anhydride at 0° C and successive hydrolysis with alkali gave **86** in 88% yield, whereas that of **85** with concentrated hydrochloric acid in MeOH at reflux followed by alkaline hydrolysis afforded **87** in 58% yield. Photolysis of diastereomers (**88** and **89**), which were obtained by N-methylation of **86** and **87**, in a manner similar to that reported in the literature[32] produced (±)-oliveroline (**90**) and (±)-ushinsunine (**91**) in 36 and 26% yields (Scheme 18).

4.2 By Photorearrangement

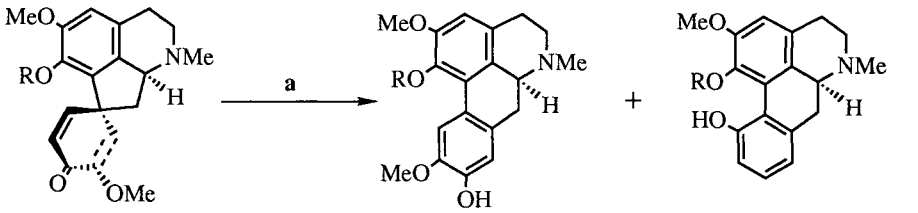
Proaporphines are known to undergo light catalyzed rearrangements, which may proceed via plausible intermediacy of a bicyclohexenone (**92**) and are dependent on a general feature of the reactivity of proaporphines, regardless of the state of aggregation of the molecule (monomer or dimer) and the degree of basicity of the



Scheme 19

nitrogen atom. Acutally, sunlight irradiation of **93** and **94** gave rearranged products (**95** and **96**) in the same yield (Scheme 19).[34]

Shamma and coworkers[35] have reported that sunlight photolysis of (-)-orientalinone (**97**) afforded (+)-isoboldine (**63**) as the major product and (+)-isothebaine (**99**) as the minor product, whereas irradiation of (-)-roemerialinone (**98**) produced mostly (+)-1-O-methylisothebaine (**100**) along with (+)-N-methyllaurotetanine (**62**). In the reaction, possible intermediates in the initial photolytic reaction of **97** and **98** are assumed to be intermediates **A** and **B**, although these intermediates can not account satisfactorily for the raitos of final aporphine products observed.



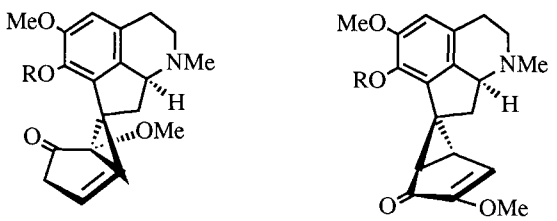
97 R = H
98 R = Me

63 R = H (major)
62 R = Me (minor)

99 R = H (minor)
100 R = Me (major)

a: sunlight, MeOH

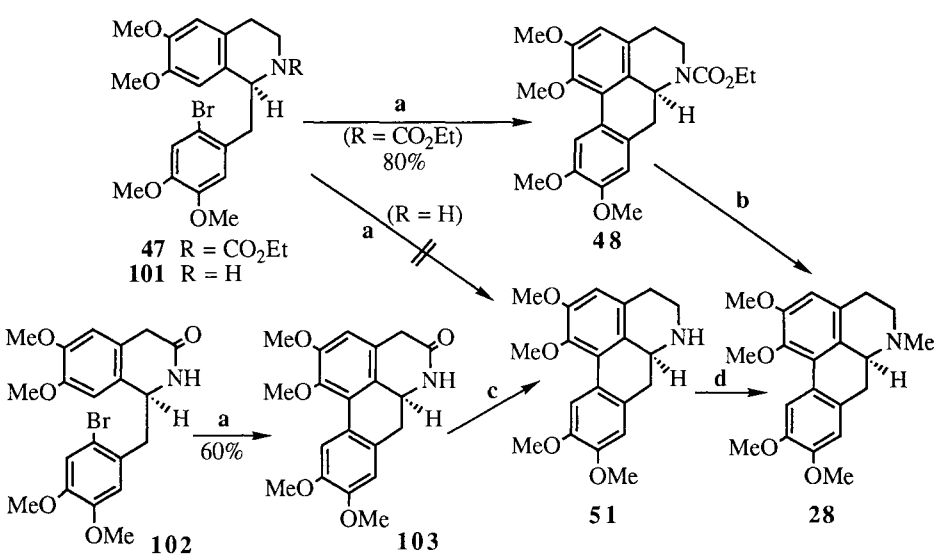
Scheme 20



A **B**

4.3 By Radical Reaction using Tributyltin Hydride

Although it is not classified as photochemical reaction, application of radical reaction[36] using tributyltin hydride (Bu_3SnH) and azobisisobutyronitrile (AIBN) has been



47 R = CO_2Et
101 R = H

48

102

103

51

28

a: Bu_3SnH, AIBN, C_6H_6, Δ ; b: $LiAlH_4$-$AlCl_3$, THF; c: B_2H_6, THF; d: MeI, NaH

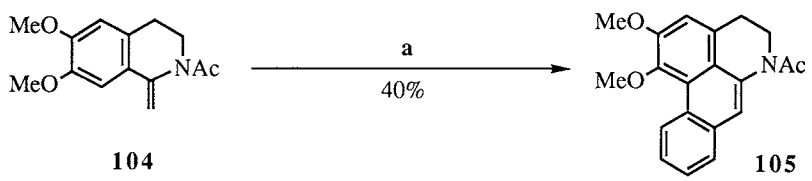
Scheme 21

reported.[37] Thus, (±)-1-(bromobenzyl)-N-ethoxycarbonyltetrahydroisoquinoline (**47**) reacted with Bu_3SnH and AIBN in boiling benzene to furnish (±)-N-ethoxycarbonyl-norglaucine (**48**) in 80% yield, which was converted to (±)-glaucine (**28**) by reduction. Although similar reaction of the corresponding secondary amine (**101**) could not be achieved, reaction of lactam (**102**) under analogous conditions proceeded smoothly to give (±)-5-oxoglaucine (**103**). These findings show that basicity of the nitrogen atom may play an important role in the cyclization reaction (Scheme 21). Furthermore, **103** was reduced with diborane in THF to afford (±)-norglaucine (**51**), which was also transformed to (±)-glaucine (**28**) by N-methylation.

5. BY BENZYNE REACTION

Synthesis of several kinds of aporphine and dehydroaporphine alkaloids by inter-molecular benzyne cycloaddition has been recently studied.

Castedo and coworkers[38] have described that N-acetyl-1-methylene-isoqunoline (**104**) reacted with benzyne, which was generated *in situ* by preformed benzenediazonium-2-carboxylate in boiling 1,2-dimethoxyethane, in the presence of trichloroacetic acid (catalytic amount) to produce N-acetyldehydronornuciferine (**105**) in 40% yield (Scheme 22). Furthermore, reaction of N-acetyl- (**104**) or N-trifluoro-

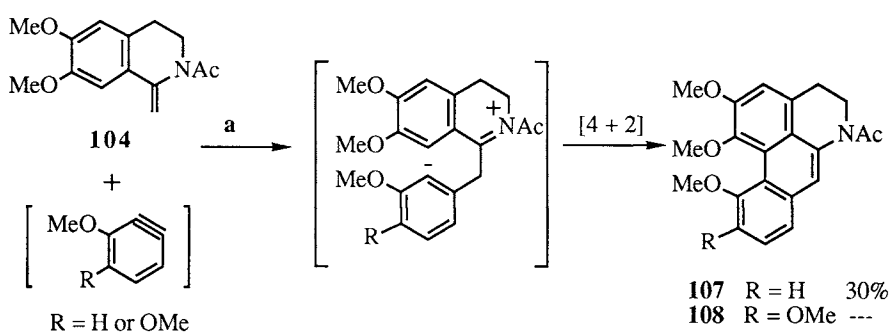


104 **105**

a: benzyne (from *o*-$N_2^+C_6H_3CO_2^-$), CCl_3COOH (cat.), 1,2-dimethoxyethane, Δ

Scheme 22

acetyl-1-methylene-isoquinolines (**106**) with appropriate benzynes under similar

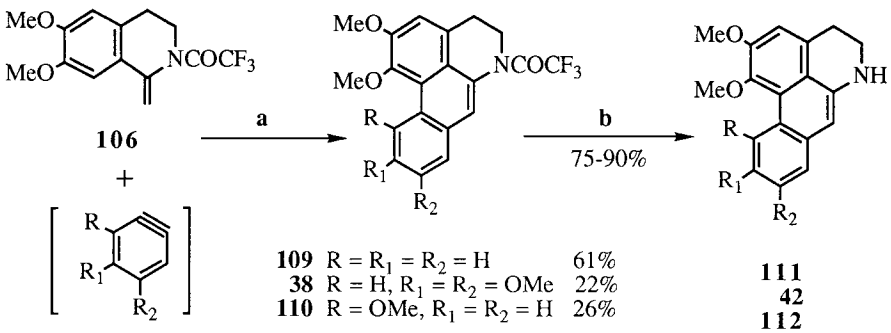


a: benzyne (from *o*-$N_2^+C_6H_2(R)(OMe)CO_2^-$), 1,2-dimethoxyethane, Δ

Scheme 23

conditions produced the corresponding dehydronoraporphines (**107** and **108** or **109**, **38**, and **110**) in moderate yields (Scheme 23 and 24).[38,39] N-Deprotection of the products (**109**, **38**, and **110**) with sodium borohydride in ethanol (EtOH) afforded dehydronoraporphines (**111**, **42**, and **112**) in 75-90% yield (Scheme 24).[39]

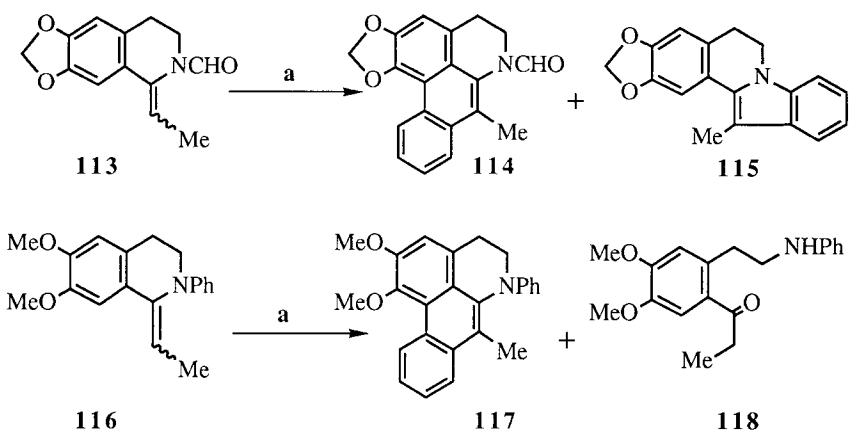
In order to confirm structure (**114**) ascribed to trichoguattine isolated from *Guatteria trichostermon*, this method was applied to the synthesis of **114** (Scheme 25).[40]



a: 1,2-dimethoxyethane, Δ ; **b**: $NaBH_4$, EtOH, room temp.

Scheme 24

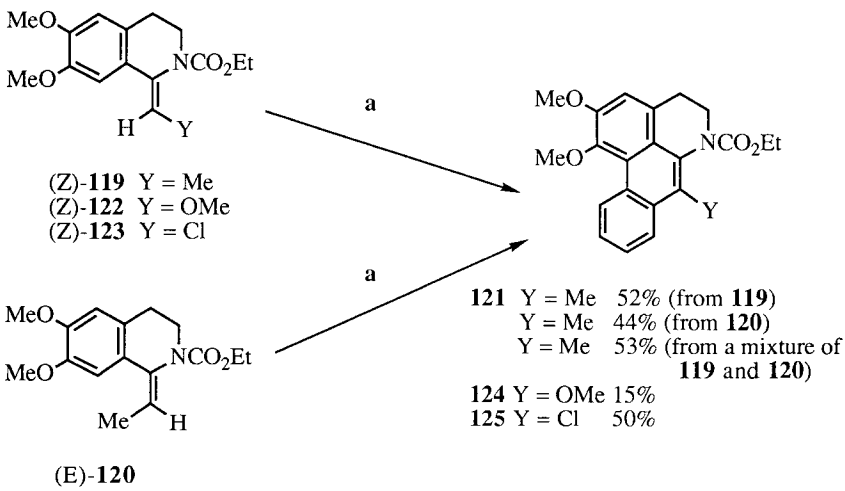
Namely, 1-ethylidene-isoquinoline (**113**) reacted with preformed benzenediazonium-2-carboxylate in boiling 1,2-dimethoxyethane to give the desired N-formyldehydronoraporphine (**114**) in 11% yield, though 12-methyldibenzoindolizine (**115**) was formed



a: benzyne (from $o\text{-}N_2^+C_6H_4CO_2^-$), 1,2-dimethoxyethane, Δ

Scheme 25

predominantly. 7-Methyldehydronoraporphine (**114**) was also synthesized in moderate yield by photochemical cyclization of N-ethoxycarbonyl-1-(α-methylbenzylidene)-6,7-methylenedioxyisoquinoline followed by hydrolysis and N-formylation.[40] However, **114** was not identical with the naturally occurring alkaloid, trichoguattine. In addition, several reports on application of the benzyne reaction of 7-substituted dehydronoraporphines have appeared. Reaction of **116** under usual conditions produced N-phenyldehydronoraporphine (**117**) along with a hydrolyzed product (**118**)(Scheme 25).[41] Analogously, (Z)-**119**, (E)-**120** and a mixture of the two, on reaction with benzyne, all afforded 7-methyldehydronoraporphine (**121**) in 52, 44, and 53% yields.[42] As 7-substituted derivatives, 7-chloro- or 7-methoxy-dehydro-noraporphine (**124** or **125**) was obtained from (Z)-**122** or (Z)-**123**. However, the mechanism for the dehydrogenation step in the reaction is uncertain (Scheme 26).



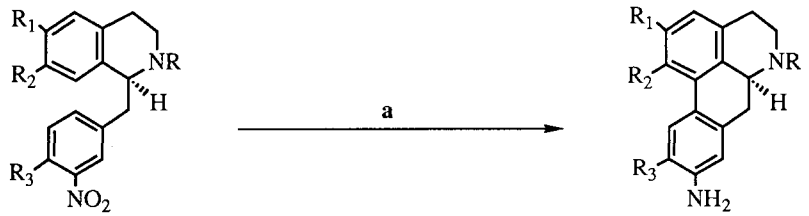
a: benzyne (from *o*-$N_2^+C_6H_4CO_2^-$), 1,2-dimethoxyethane, Δ

Scheme 26

6. BY ACID CATALYZED REACTION

6.1 By Acid Catalyzed Cyclization

Shudo and Okamoto[44] have reported that reduction of nitrobenzene with zinc in benzene in the presence of trifluoromethanesulfonic acid at 0° C afforded 4-aminobiphenyl (52%), 2-aminobiphenyl (7%), 4-aminoterphenyl (2%), and aniline (30%), respectively. This reaction was extended to intramolecular cyclization of some nitro compounds. Hence, (±)-1-(*m*-nitrobenzyl)-tetrahydroisoquinolines (**126-129**) were reduced with zinc in a (1 : 1) mixture of TFA and trifluoromethanesulfonic acid at 0° C to produce the corresponding (±)-9-aminoaporphines (**130-133**) in fair to good yields



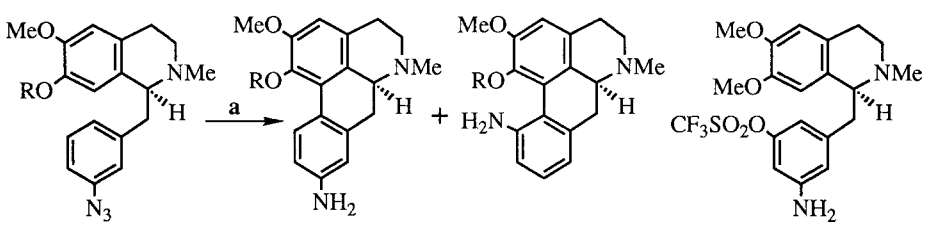
126	R = Me, $R_1 = R_2 = R_3 = OMe$	**130**	68%
127	R = H, $R_1 = R_2 = R_3 = OMe$	**131**	61%
128	R = Ac, $R_1 = R_2 = R_3 = OMe$	**132**	82%
129	R = Me, $R_1 = R_2 = OMe$, $R_3 = H$	**133**	52%

a: Zn, TFA, CF_3SO_3H, 0° C

Scheme 27

(Scheme 27). The basicity of the nitrogen atom seems to somewhat retard the reaction.

Abramovich and coworkers[45] have reported a reaction similar to that described above. Namely, the reaction of (±)-1-(*m*-nitreniobenzyl)-tetrahydroisoquinolines (**134** and **135**) in TFA containing a few drops of trifluoromethanesulfonic acid at 0° C furnished (±)-9-amino- (**133** and **137**) and (±)-11-amino-aporphines (**136** and **138**), though in low yields. With the former product (**134**), interestingly, (±)-1-(3-amino-5-trifluoromethanesulfonyloxybenzyl)-tetrahydroisoquinoline (**139**) was formed in 16% yield (Scheme 28).

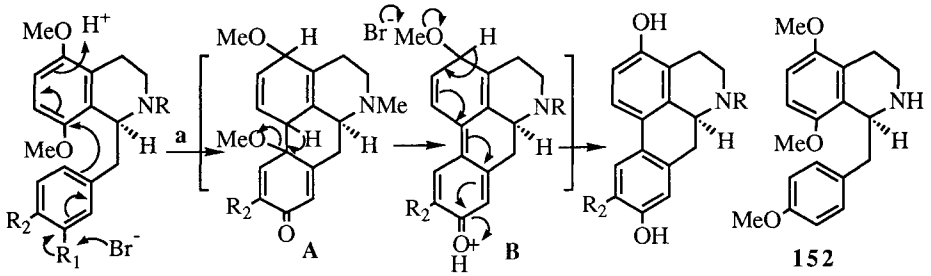


134	R = Me	**133**	R= Me	14%	**136**	R = Me	27%	**139**	16%
135	R = CH_2Ph	**137**	R = H	27%	**138**	R = H	18%		

a: CF_3SO_3H, TFA, 0° C

Scheme 28

The synthesis of aporphines by a reaction with 48% hydrobromic acid at 140° C, in which a methoxyl group in an aromatic ring serves as a leaving group, appeared as a full paper.[46] Namely, (±)-1-(*m*-alkoxybenzyl)-5,8-dimethoxytetrahydroisoquinolines (**140-145**) gave (±)-3,9-dihydroxyaporphines (**146-151**) in high yields (Scheme 29).



140 R = H, R_1 = R_2 = OMe
141 R = Me, R_1 = R_2 = OMe
142 R = H, R_1 = OMe, R_2 = H
143 R = H, R_1 = OEt, R_2 = OMe
144 R = Me, R_1 = OMe, R_2 = H
145 R = H, R_1 = OMe, R_2 = OPh

146 R = Me, R_2 = H 90%
147 R = Me, R_2 = OH 96%
148 R = R_2 = H 95%
149 R = H, R_2 = OH 86%
150 R = Me, R_2 = H 96%
151 R = H, R_2 = OPh 50%

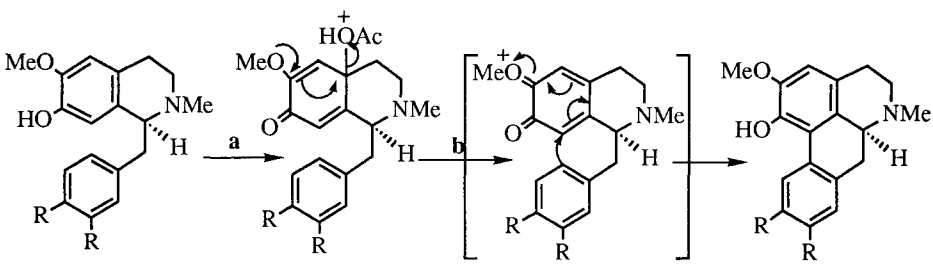
a: 48% HBr, 140° C

Scheme 29

Treatment with boron tribromide instead of hydrobromic acid did not effect aporphine cyclization. In this reaction, the presence of a methoxyl group at 4' position may not be essential for the aporphine cyclization. Actually, an analogous reaction of 5,8-dimethoxy-4'-methoxy congener (**152**) did not take place. The reaction is supposed to proceed through intermediates (**A** and **B**) as depicted in Scheme 29.

6.2 By Acid Treatment of Quinol Acetates

Application of lead tetraacetate (LTA) oxidation to the synthesis of aporphine alkaloids has been extensively studied in the author's laboratory.[47]



153 R = OMe
154 R + R = OCH_2O

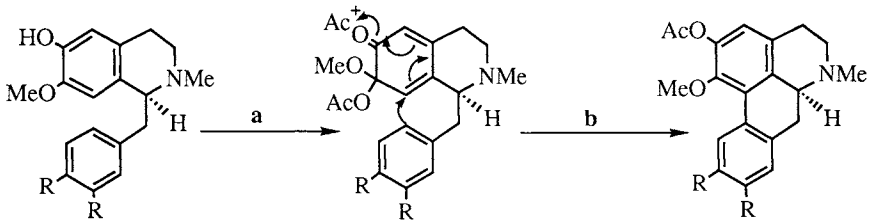
157
158

61
161

a: $Pb(OAc)_4$, AcOH, room temp.; **b**: TFA, CH_2Cl_2, room temp.

Scheme 30

Oxidation of tetrahydroisoquinolinols (**153** and **154** or **155** and **156**) with LTA in AcOH or dichloromethane (CH_2Cl_2) gave *p*- (**157** and **158**) or *o*-quinol acetates (**159** and **160**), which were treated with TFA in CH_2Cl_2 or acetic anhydride containing concentrated sulfuric acid at ambient temperature to yield aporphine alkakoids (**61** and **161** or **162** and **163**) (Scheme 30 and 31). The former compounds (**61** and **161**) can be formed through intermediates **A** (Scheme 30). On the other hand, formation of the latter compounds (**162** and **163**) was assumed as depicted in Scheme 31. This reaction is a useful method for synthesis of aporphine alkaloids, although the presence of a guaiacol-type moiety in tetrahydroisoquinolinols is crucial.



155 R = OMe
156 R + R = OCH_2O

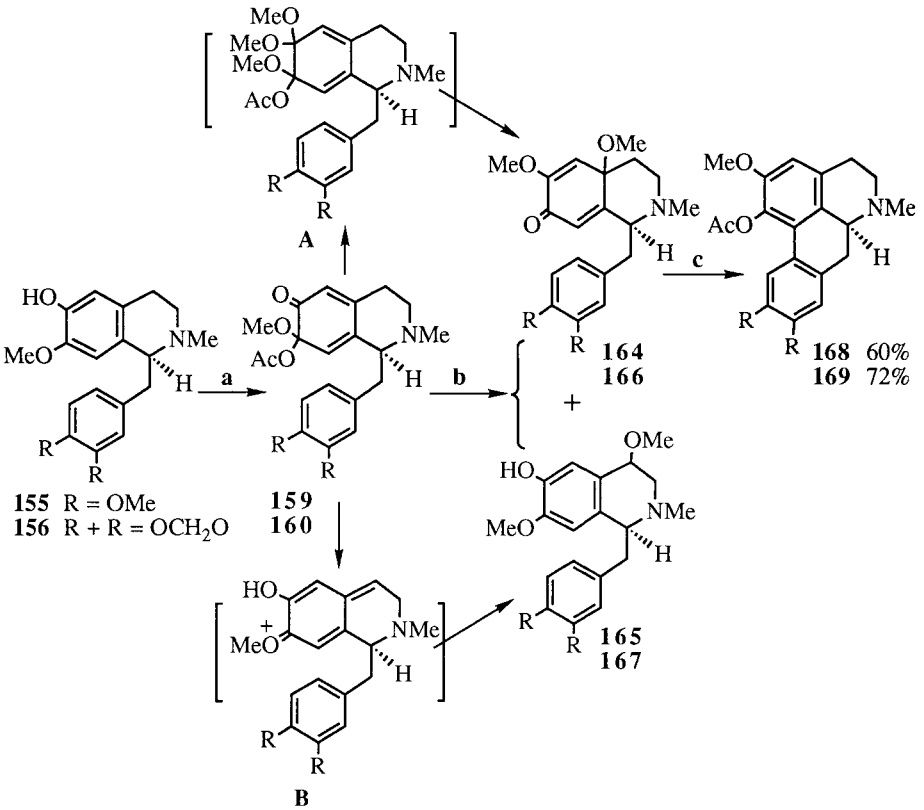
159
160

162
163

a: $Pb(OAc)_4$, CH_2Cl_2, room temp.; **b**: Ac_2O, conc. H_2SO_4, room temp.

Scheme 31

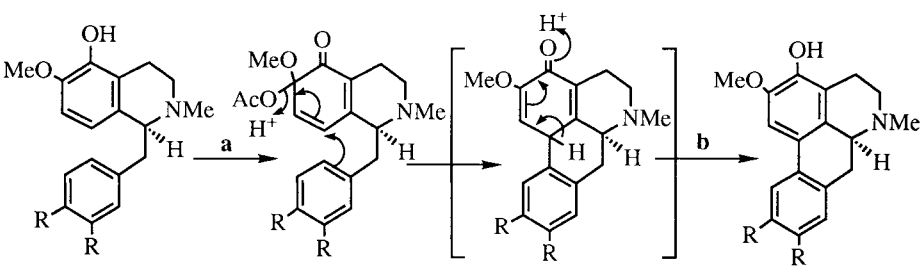
The present reaction also resulted in the formation of rearranged quinol ethers, which were applied to aporphine synthesis. Thus, (±)-1-benzyltetrahydroisoquinolin-6-ols (**155** and **156**) were oxidized under similar conditions to give *o*-quinol acetates (**159** and **160**) in quantitative yield, treatment of which, without further purification, with MeOH containing concentrated sulfuric acid at room temperature afforded rearranged *p*-quinol ethers (**164** and **166**) along with a diastereomeric mixture of 4-methoxytetrahydroisoquinolin-6-ols (**165** and **167**).[48] The rearranged *p*-quinol ethers (**164** and **166**) can be formed through intermediates **A**, whereas **165** and **167** may be formed through quinone methides **B**. The reaction of *p*-quinol ethers (**164** and **166**) thus obtained with acetic anhydride containing concentrated sulfuric acid at ambient temperature also gave rise to (±)-acetylthaliporphine (**168**) and (±)-acetyldomesticine (**169**) in 60 and 72% yields, respectively (Scheme 32).[49]



a: $Pb(OAc)_4$, CH_2Cl_2, room temp.; **b**: MeOH, conc. H_2SO_4, room temp.; **c**: Ac_2O, conc. H_2SO_4, room temp.

Scheme 32

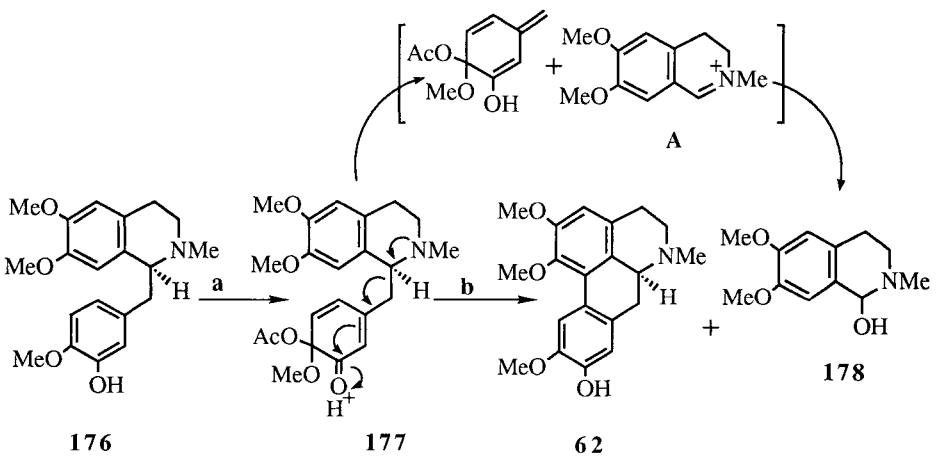
This methodology was developed for the synthesis of (±)-3-hydroxy- (**174** and



a: $Pb(OAc)_4$, CH_2Cl_2 room temp.; **b**: TFA, CH_2Cl_2, room temp.

Scheme 33

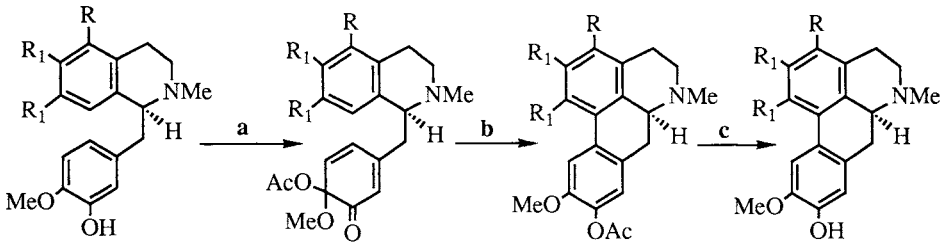
175)[50] and (±)-9-hydroxyaporphines[51] (**62**, **69**, and **186**) starting from (±)-1-benzyl-tetrahydroisoquinolin-5-ols (**170** and **171**) and (±)-1-(3-hydroxybenzyl)-tetrahydro-isoquinolines (**176**, **179**, and **180**). Thus, **170** and **171** were oxidized with LTA in CH_2Cl_2 to give the corresponding *o*-quinol acetates (**172** and **173**), which were treated with TFA in CH_2Cl_2 to afford (±)-3-hydroxyaporphines (**174** and **175**) through intermediates **A** (Scheme 33).[50] The reaction of **176** with LTA in CH_2Cl_2 followed by TFA in CH_2Cl_2 gave 1-hydroxyisoquinoline (**178**)(56%) besides (±)-N-methyl-laurotetanine (**62**)(17 %) via *o*-quinol (**177**). The former product (**178**) may be produced from 3,4-dihydroisoquinolinium salt (**A**), which was generated by vinylogous retro-Mannich reaction of *o*-quinol acetate (**177**)(Scheme 34). This assumption was supported by the following results. Namely, the reaction of *o*-quinol acetate (**177**) with concen-trated sulfuric acid in acetic anhydride instead of TFA in CH_2Cl_2 gave



a: $Pb(OAc)_4$, CH_2Cl_2, room temp. ; **b**: TFA, CH_2Cl_2, room temp.;

Scheme 34

only (±)-9-acet-oxyaporphine (**183**) in improved yield, showing that protonation of the lone pair in the nitrogen atom would prevent the fragmentation of *o*-quinol acetate (**177**) by vinylogous retro-Mannich reaction. Similarly, the reaction of **179** and **180** gave (±)-9-acetoxyaporphines (**184** and **185**) in 45 and 80% yields, respectively, through **181** and **182**. Hydrolysis of **183-185** with 5% potassium hydroxide in MeOH afforded (±)-N-methyllaurotetanine (**62**), (±)-cassythicine (**69**), and (±)-9-hydroxy-1,2,3,10-tetramethoxyaporphine (**186**) in good yields (Scheme 35).

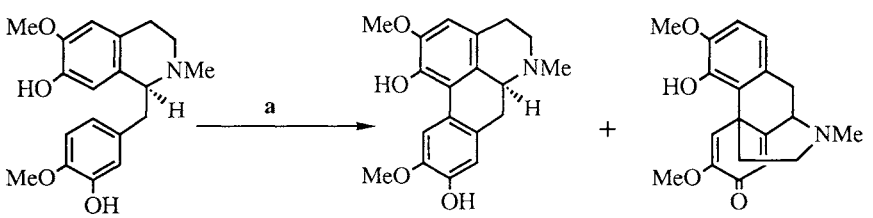


176 R = H, R_1 = OMe	**177**	**183** 37%	**62** 91%
179 R = H, $R_1 + R_1$ = OCH_2O	**181**	**184** 45%	**69** 96%
180 R = R_1 = OMe	**182**	**185** 80%	**186** 83%

a: $Pb(OAc)_4$, CH_2Cl_2, room temp.; **b**: Ac_2O, conc. H_2SO_4, room temp.; **c**: 5% KOH, MeOH, room temp.

Scheme 35

Although it is not exactly explainable as a reaction of quinol acetates, Szántay and coworkers[52] have reported that the reaction of reticuline (**187**) with LTA in CH_2Cl_2 containing trichloroacetic acid at -78° C produced isoboldine (**63**) in 14% yield along with salutaridine (**188**)(3%) and unchanged **187** (48%) (Scheme 36). LTA oxidation of **176** in CH_2Cl_2 in the presence of TFA also gave **62** and **178** in 23 and 32% yields, respectively (Scheme 34).[51]



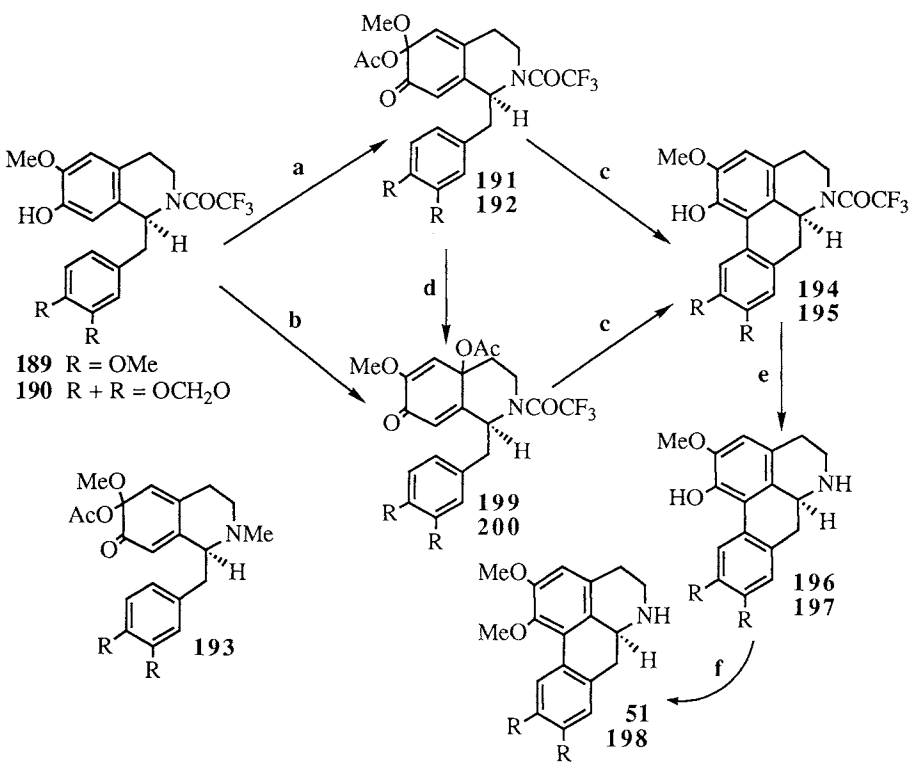
187 **63** 14% **188** 3%

a: $Pb(OAc)_4$, CCl_3CO_2H, CH_2Cl_2, -78° C

Scheme 36

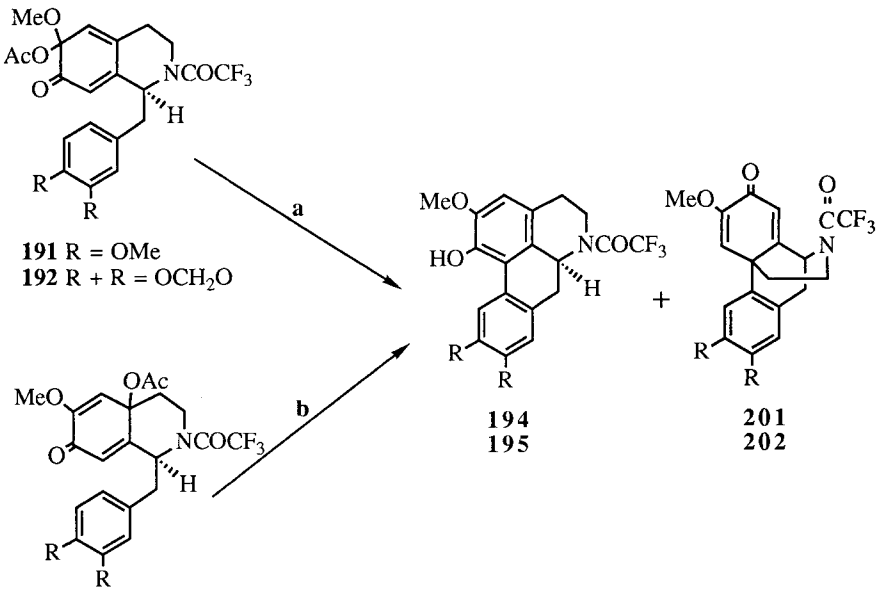
LTA oxidation of tetrahydroisoquinolinols has been extended to N-acyltetrahydroisoquinolinols and it was developed for the synthesis of noraporphines. Thus, (±)-N-trifluoroacetylnortetrahydroisoquinolin-7-ols (**189** and **190**) were oxidized with LTA in CH_2Cl_2 to give in quantitative yields *o*-quinol acetates (**191** and **192**), which were more stable at room temperature than the *o*-quinol acetate (**193**) of the N-methyl congener (**155**).

The reaction of the *o*-quinol acetates (**191** and **192**) under similar conditions afforded (±)-N-trifluroacetylwilsonirine (**194**) and (±)-N-trifluroacetylnordomesticine (**195**) in 61 and 21% yields, respectively.[53] Hydrolysis of **194** and **195** with aqueous potassium carbonate in boiling MeOH produced (±)-wilsonirine (**196**) and (±)-nordomesticine (**197**), which were also transformed by methylation with diazomethane to (±)-norglaucine (**51**) and (±)-nornantenine (**198**), respectively. Similarly, oxidation of (±)-N-trifluroacetylnortetrahydroisoquinolin-7-ols (**189** and **190**) with LTA in AcOH afforded quantitatively stable *p*-quinol acetates (**199** and **200**). The *p*-quinol acetates (**199** and **200**) were also obtained by treatment of *o*-quinol acetates (**191** and **192**) with AcOH at room temperature (Scheme 37). Recently, treatment of *o*-quinol acetates (**191** and **192**) with TFA in CH_2Cl_2 at 0 or -46°C was found to give (±)-noraporphines (**194** and **195**)(74 or 74, 59%) and (±)-morphinandienones (**201** and **202**)(16, 18 or 20, 18%)(Scheme 38).[54]



a: $Pb(OAc)_4$, CH_2Cl_2; **b**: $Pb(OAc)_4$, AcOH; **c**: TFA, CH_2Cl_2; **d**: AcOH, room temp.; **e**: aq. K_2CO_3, MeOH, Δ ; **f**: CH_2N_2, Et_2O, MeOH, room temp.

Scheme 37

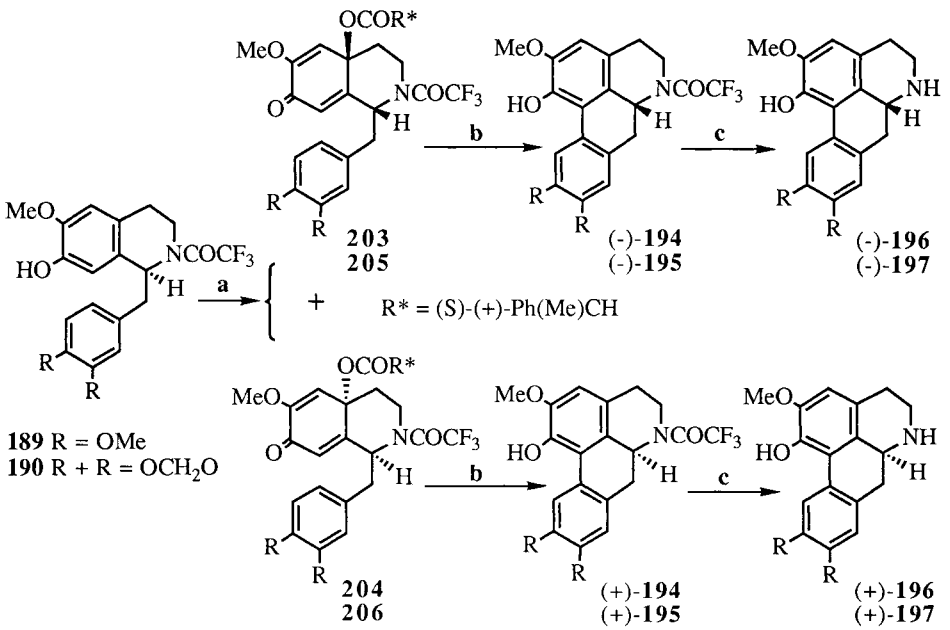


Scheme 38

Interestingly, a more careful re-examination of the reaction of *o*-quinol acetates (**191** and **192**) in acetonitrile at -25 or -30° C revealed that the yields (42, 18%) of noraporphines (**194** and **195**) decreased, whereas those (46, 52%) of (±)-morphinandienones (**201** and **202**) somewhat increased. With *p*-quinol acetates (**199** and **200**), the findings similar to those for *o*-quinol acetates (**191** and **192**) were also observed in the reaction using acetonitrile at lower temperature, although the prolonged reaction time was required (Scheme 38).[55]

Moreover, the reaction was developed for the synthesis of chiral noraporphines.[56] Thus, oxidation of (±)-**189** with LTA in (S)-(+)-2-phenylpropionic acid at room temperature gave a diastereomeric mixture of *p*-quinol acetates. In this reaction, formation of four diastereomers would be possible. Actually, N-methyl congener (**155**) afforded an inseparable mixture of four kinds of diastereomers. In this case, however, two kinds of diastereomers, (1R,4aS)-(**203**) and (1S,4aR)-*p*-quinol acetates (**204**), were obtained in 32 and 26% yields, respectively, by separation using silica gel column chromatography. The relative configuration between 4a-(S)-acyloxy and 1-benzyl groups in *p*-quinol acetates (**203** and **204**) was deduced tentatively to be *trans*, since introduction of (S)-(+)-acid to 4a position would occur from the opposite side to the quasi-axial 1-benzyl group, which was caused by allylic-like strain between 1-benzyl and N-trifluoroacetyl groups. The diastereomers (**203** and **204**) were exposed with TFA in CH_2Cl_2 at room temperature to give (-)-trifluoroacetylwilsonirine

(**194**)(64%; 100% ee estimated by HPLC using chiral column) and (+)-enantiomer (**194**)(77%; 97.7% ee estimated by the analysis similar to that described above), respectively, which were converted to (-)-(**196**)(77%; 100% ee) and (+)-wilsonirine (**196**)(78%; 95.9% ee), respectively. Similarly, (-)-(**197**) and (+)-nordomesticine



a: $Pb(OAc)_4$, (S)-(+)-1-phenylpropionic acid, room temp.; **b**: TFA, CH_2Cl_2, room temp.; **c**: K_2CO_3, aq. MeOH, room temp.

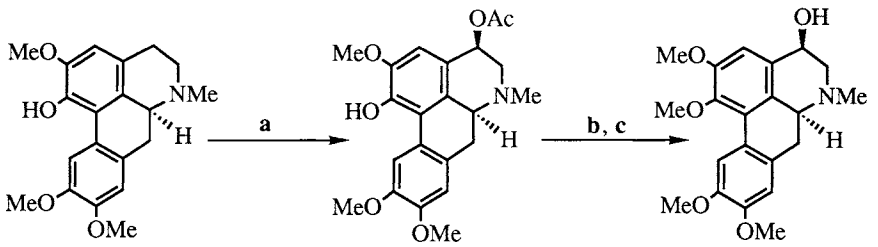
Scheme 39

(**197**) were synthesized in 62% (100% ee) and 64% (94.7% ee) yields, respectively, starting from (±)-N-trifluoroacetylnortetrahydroisoquinolin-7-ol (**190**) through chiral *p*-quinol acetates (**205**)(39%) and (**206**)(27%)(Scheme 39).

7. BY MICELLANEOUS REACTIONS

7.1 Oxidation

Previously, LTA oxidation of (±)-thaliporphine (**61**) in AcOH was discovered to give stereoselectively and quantitatively (±)-4β-acetoxythaliporphine (**207**) in the author's laboratory. Furthermore, hydrolysis of **207** with 10% hydrochloric acid followed by methylation with diazomethane in MeOH gave (±)-cataline (**208**) in good yield (Scheme 40).[57] This methodology was applied to the synthesis of (±)-srilankine

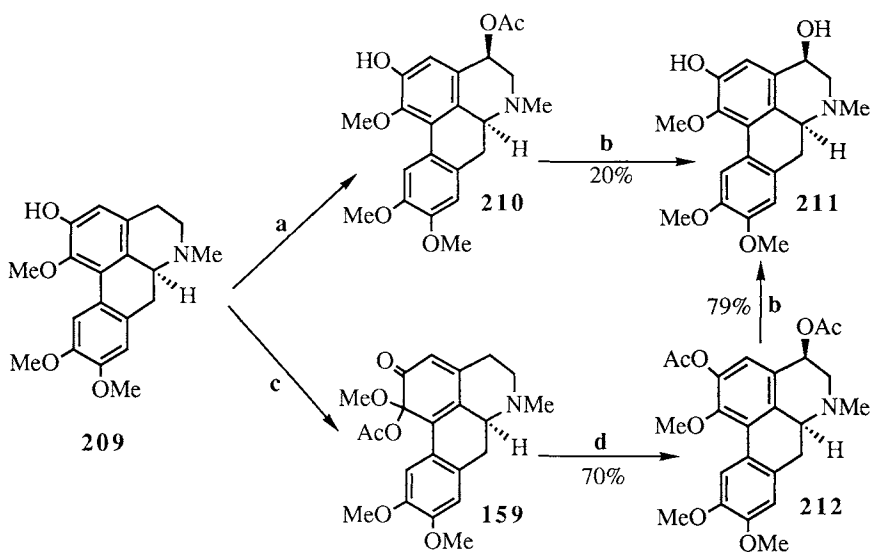


61 **207** **208**

a: $Pb(OAc)_4$, AcOH, room temp.; **b**: 10% HCl, room temp.; **c**: CH_2N_2, MeOH, room temp.

Scheme 40

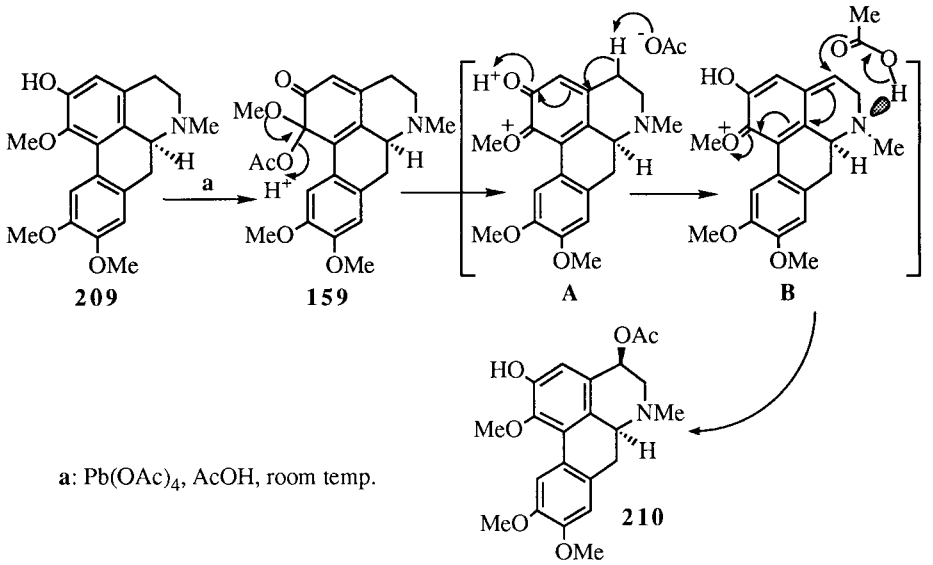
(**211**)(Scheme 41).[58] Oxidation of (±)-predicentrine (**209**) with LTA in AcOH proceeded stereoselectively to (±)-4β-acetoxypredicentrine (**210**), which was hydrolyzed in the usual manner to give (±)-srilankine (**211**), though in 20% overall yield. However, the synthesis of (±)-srilankine (**211**) was improved (Scheme 41). Thus, oxidation of **209** with LTA in CH_2Cl_2 gave as expected a diastereomeric mixture of unstable *o*-quinol acetates (**159**), treatment of which, without purification, with acetic anhydride containing concentrated sulfuric acid afforded stereoselectively (±)-4β-acetoxy-O-acetylsrilankine (**212**) in 70% yield. Hydrolysis of **212** with 10%



209 **210** **211** **159** **212**

a:$Pb(OAc)_4$, AcOH; **b**: 10% HCl; **c**: $Pb(OAc)_4$, CH_2Cl_2; **d**: Ac_2O, conc. H_2SO_4

Scheme 41

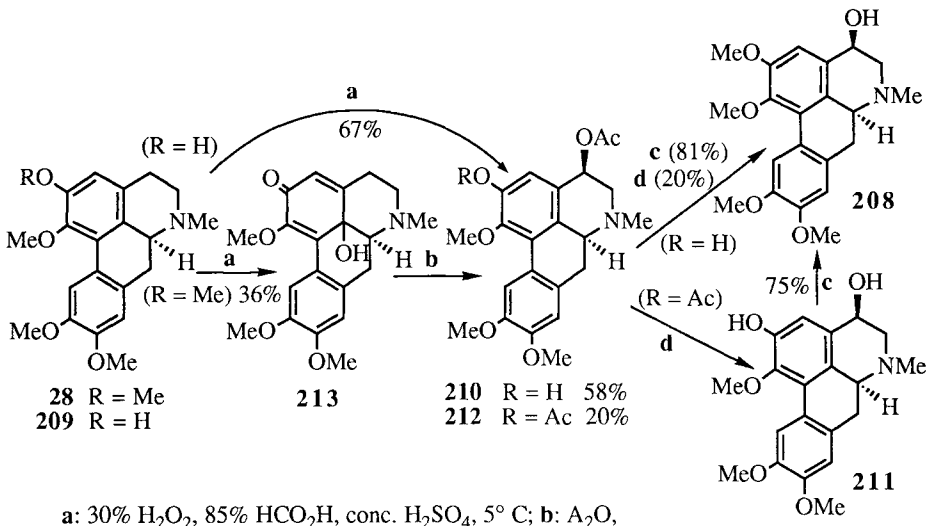


a: $Pb(OAc)_4$, AcOH, room temp.

Scheme 42

hydrochloric acid produced (±)-srilankine (**211**) in 79% yield (55% overall yield from **209**). Moreover, methylation of **211** with diazomethane in MeOH gave (±)-cataline (**208**) in 83% yield. Stereoselective formation of 4β-acetoxy product (**210**) was deduced as follows (Scheme 42). *o*-Quinol acetate (**159**), which is generated in the initial oxidation, would be transformed by removal of AcOH to *p*-quinone methide (**B**) via *o*-quinonoide (**A**). The *p*-quinone methide (**B**) may be attacked intramolecularly by AcOH, which would be linked in intermediate (**B**) by hydrogen-bonding between AcOH used as a solvent and the nitrogen atom, to give stereoselectively the 4β-acetoxy product (**210**) .

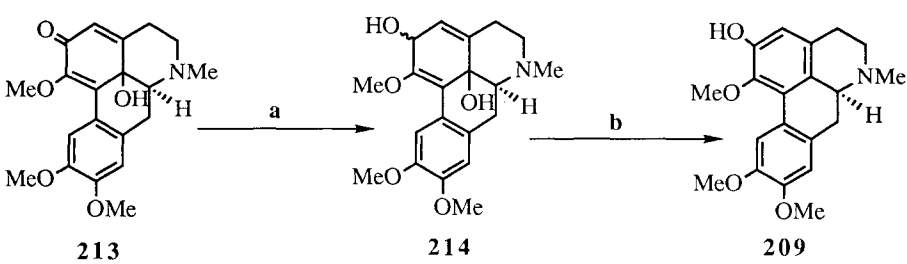
Independently, Philipov and coworkers[57] have reported synthesis of (±)-srilankine (**211**) and (±)-cataline (**208**) by oxidation of (±)-glaucine (**28**) and (±)-predicentrine (**209**). Namely, **28** was treated with 30% aqueous hydrogen peroxide (H_2O_2) in formic acid containing concentrated sulfuric acid to give *p*-quinol (**213**) in 36% yield accompanied with unchanged **28** (26%). Similarly, (±)-predicentrine (**209**) gave (±)-4β-acetylsrilankine (**210**) in 67% yield. Reaction of **213** with acetic anhydride containing concentrated sulfuric acid produced (±)-4β-acetylsrilankine (**210**) and (±)-O,O-diace-tylsrilankine (**212**) in 58 and 20% yields. Hydrolysis of **210** and **212** with potassium hydroxide in MeOH afforded (±)-srilankine (**211**) in good yield. Furthermore, methylation of **211** in the usual manner gave (±)-cataline (**208**) in 75% yield, which was also prepared from (±)-4β-acetoxypredicentrine (**210**) by methylation and subsequent hydrolysis (Scheme 43).



a: 30% H_2O_2, 85% HCO_2H, conc. H_2SO_4, 5° C; **b**: A_2O, conc. H_2SO_4; **c**: CH_2N_2, MeOH; **d**: 20% KOH, MeOH

Scheme 43

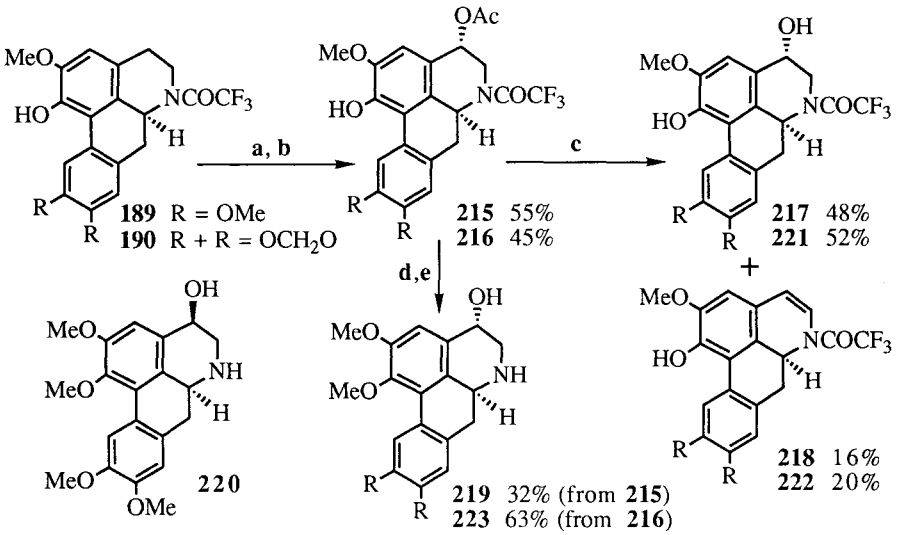
On the other hand, sodium borohydride reduction of **213** in MeOH gave the hydroxy derivative (**214**), which was exposed with 95% phosphoric acid at room temperature to afford (±)-predicentrine (**209**)(Scheme 44).[59]



a: $NaBH_4$, MeOH, room temp.; **b**: 95% H_3PO_4, room temp.

Scheme 44

In the oxidation of (±)-N-trifluoroacetylnorthaliporphine (**189**) with LTA in CH_2Cl_2, dramatically different findings from those for N-methyl congener (**62**) were observed (Scheme 45).[60] Namely, oxidation of **189** with LTA in CH_2Cl_2 followed by treatment with AcOH gave only (±)-4α-acetoxy-N-trifluoroacetylnorthaliporphine (**215**) in 55% yield. Hydrolysis of **215** with concentrated hydrochloric acid in THF at room tempe-



a: $Pb(OAc)_4$, CH_2Cl_2; **b**: AcOH, room temp.; **c**: conc. HCl, THF, room temp.; **d**: CH_2N_2, MeOH, room temp.; **e**: aq. K_2CO_3, MeOH, Δ

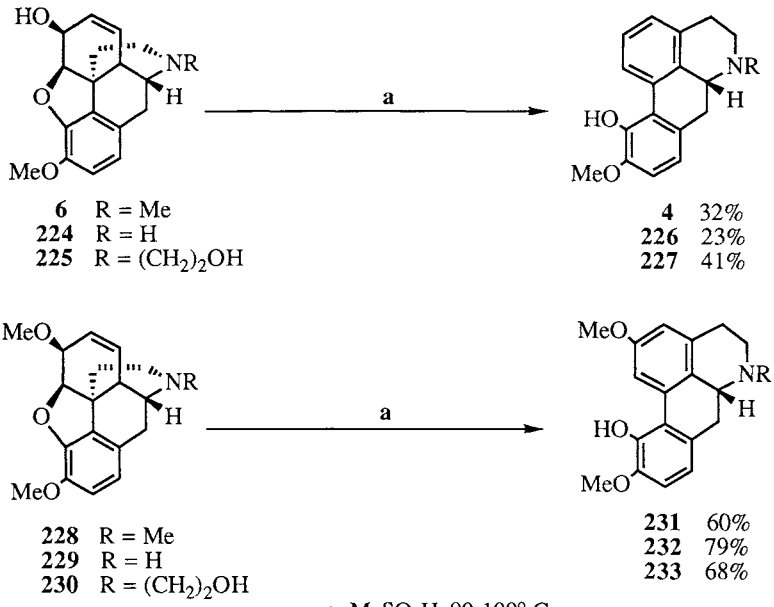
Scheme 45

rature produced in 48% yield (±)-4α-hydroxy-N-trifluoroacetylnorthaliporphine (**217**) along with N-trifluoroacetyl-3,4-dehydronorthaliporphine (**218**)(16%). Methylation of **215** with diazomethane in MeOH followed by hydrolysis with aqueous potassium carbonate in boiling MeOH gave (±)-4-epinorcataline (**219**) in 32% yield. The stereochemistry of **215** was determined by comparison of **219** with norcataline (**220**)[61] in each ^{1}H-NMR spectral data. Similar reaction of **190** gave (±)-**216** in 45% yield, which was hydrolyzed with acid to afford (±)-**221** and (±)-**222** in 52 and 20% yields. (±)-4α-Hydroxynornantenine (**223**) was obtained in 63% yield from **216** in a way similar to that described for **215**. At this stage, the mechanistic pathway for stereoselective formation of 4α-acetoxy products is obscure.

7.2 Rearrangement

Although apomorphine (**3**) and its derivatives are not naturally occurring aporphine alkaloids, attempts to prepare them starting from morphine (**5**) and its derivatives or aporphine alkaloids due to their promise of remarkable biological activity, such as dopamineric activity,[4] have been performed extensively.

In an effort to develop an improved synthesis of morphothebaine and its N-substituted derivatives, heating of codeine (**6**), norcodeine (**224**), and N-(2-hydroxyethyl)-norcodeine (**225**) with methanesulfonic acid at 90-100° C gave apocodeine (**4**), norapocodeine (**226**), and N-(2-hydroxyethyl)-norapocodeine (**227**)



6 R = Me
224 R = H
225 R = $(CH_2)_2OH$

4 32%
226 23%
227 41%

228 R = Me
229 R = H
230 R = $(CH_2)_2OH$

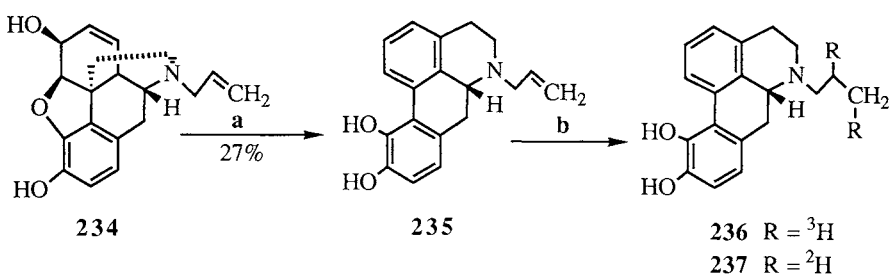
231 60%
232 79%
233 68%

a: $MeSO_3H$, 90-100° C

Scheme 46

in 32, 23, and 41% yields, respectively.[62]

Similarly, thebaine (**228**), northebaine (**229**), and N-(2-hydroxyethyl)-northebaine (**230**) afforded 2-methoxyapocodeine (**231**), 2-methoxynorapocodeine (**232**), and 2-methoxy-N-(2-hydroxyethyl)-norapocodeine (**233**) in 60, 79, and 68% yields, respectively (Scheme 46). The reaction of (-)-nalorphine (**234**) under similar conditions also produced (R)-**235**, which was transformed to (-)-N-[^{3}H- and ^{2}H]-propylnorapomorphines (**236** and **237**)(Scheme 47).[63]



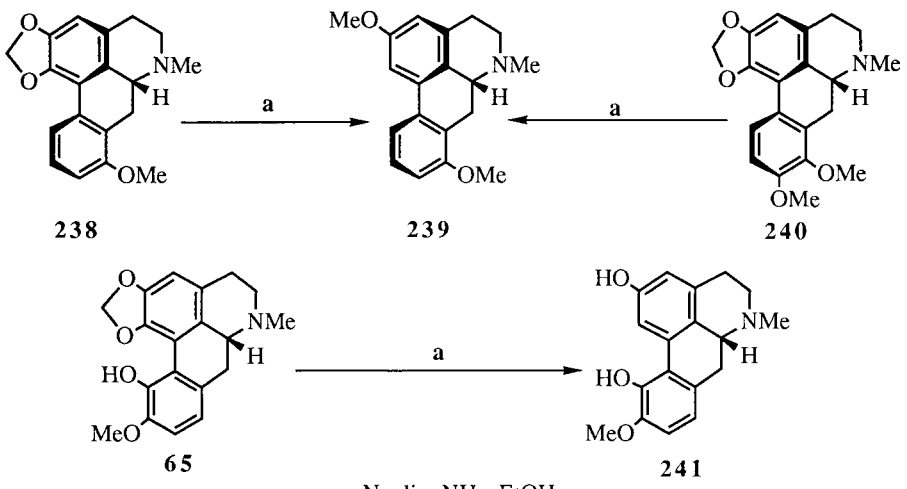
234 **235** **236** R = ^{3}H
237 R = ^{2}H

a: $MeSO_3H$, 90° C; **b**: 10% Pd-C, $^3H_2$ or $^2H_2$, EtOH, room temp.

Scheme 47

7.3 Reduction

Reductive cleavage[64] of vicinal dimethoxyl and methylenedioxy groups on aromatic rings has been well known. This reaction was applied to the synthesis of several deoxyaporphine alkaloids including apomorphine (**3**) and related compounds. Kunitomo and coworkers[65] have reported that reduction of (R)-stephanine (**238**), absolute configuration of which has been determined by X-ray crystallographic anal-

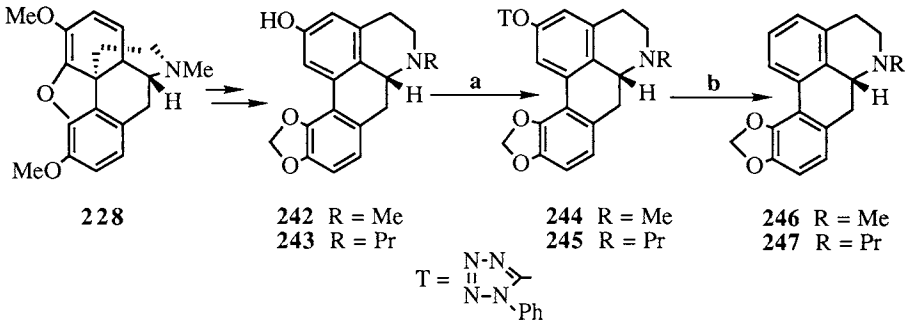


a: Na, liq. NH_3, EtOH

Scheme 48

ysis, with sodium in liquid ammonia and EtOH afforded (R)-2,8-dimethoxyaporphine (**239**). The alkaloid (**239**) was identical with the product obtained from (R)-crebanine (**240**) in a similar manner. Analogously, (+)-bulbocapnine (**65**) gave (+)-morphothebaine (**241**)(Scheme 48).[66]

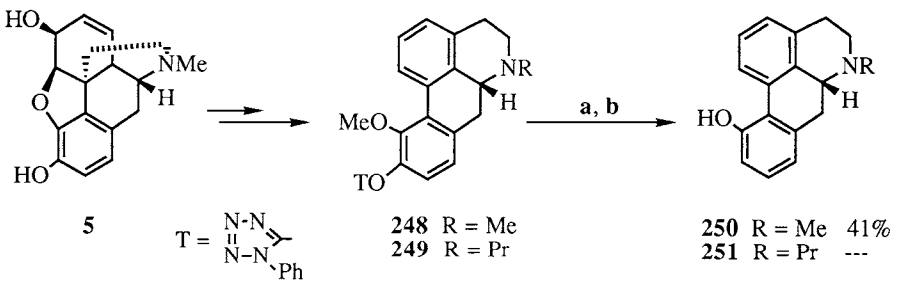
Reductive deoxygenation of phenols was carried out by Birch reduction or catalytic hydrogenation of the corresponding diethyl phosphate[67] and tetrazolyloxy[67,68] derivatives. Thus, (R)-2-tetrazoyloxy-10,11-dimethylenedioxy-aporphine (**244**) and -N-propylnoraporphine (**245**) derived from thebaine (**228**) through (R)-2-hydroxy-10,11-methylenedioxy-aporphine (**242**) and -N-propylnoraporphine (**243**) were hydrogenated over 5% palladium on charcoal in AcOH at 45° C to afford (R)-10,11-methylenedioxy-aporphine (**246**) and -N-propylnoraporphine (**247**) in good yields (Scheme 49).[63]



a: 5-chloro-1-phenyltetrazole; **b**: 5% Pd-C, H_2, AcOH, 40° C

Scheme 49

Analogously, (-)-10-deoxy-apomorphine (**250**) and -N-propylnoraporphine (**251**) were synthesized stereoselectively from morphine (**5**) via tetrazoyloxy derivatives (**248** and **249**)(Scheme 50).[69]

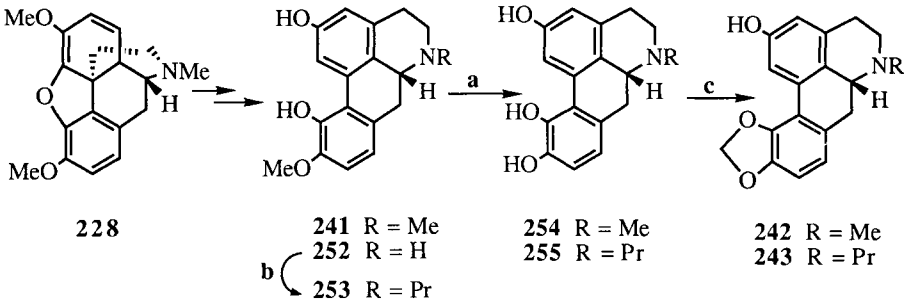


a: 5% Pd-C, H_2 (45 psi), AcOH, room temp.; 48% HBr, 115-120° C

Scheme 50

7.4 Alkylation and Dealkylation

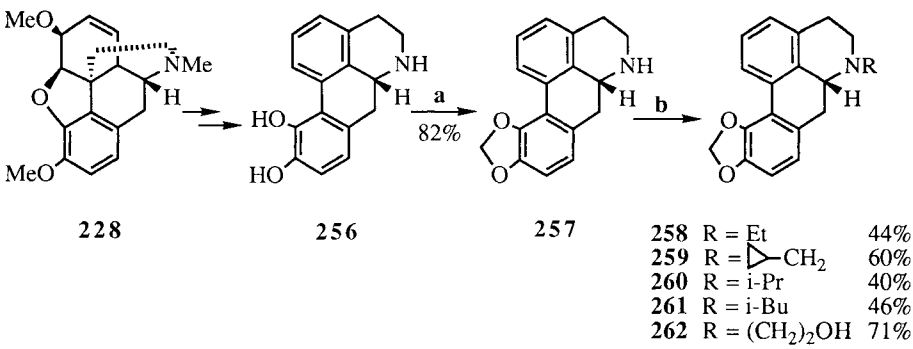
Alkylation and dealkylation are important methods in the synthesis of apomorphine derivatives. Hence, (R)-2-hydroxy-apocodeine (**241**) and -N-propylnorapocodeine (**252**) derived from thebaine (**228**) in the usual manner (**253** was prepared by N-propylation of **252**) were demethylated with hydrobromic acid to give (R)-2-hydroxy-apomorphine (**254**) and -N-propylnorapomorphine (**255**), which reacted with dibromomethane in dimethyl sulfoxide containing aqueous sodium hydroxide to afford (R)-2-hydroxy-10,11-methylenedioxy-aporphine (**242**) and -N-propylnoraporphine (**243**)(Scheme 51).[66]



a: HBr; **b**: PrI, MeCN; **c**: CH_2Br_2, NaOH, Me_2SO, H_2O

Scheme 51

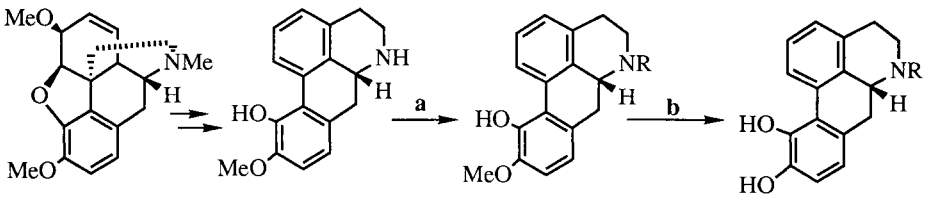
(R)-10,11-Methylenedioxynoraporphine (**257**) was obtained by methylenation of norapomorphane (**256**) derived from thebaine (**228**) For the purpose of synthesis of N-alkyl derivatives of (R)-methylenedioxyaporphine (**257**), N-alkylation of **257** with alkyl halides or ethylene oxide was carried out to leave the corresponding (R)-N-alkyl-10,11-methylenedioxynoraporphines (**258-262**) in fair to good yields (Scheme 52).[70]



a: CH_2Br_2, aq. NaOH, Me_2SO, 70-80° C; **b**: RX, aq. $NaHCO_3$, MeCN, Δ or ethylene oxide;

Scheme 52

On other hand, N-alkylation of norapocodeine (**263**) in a way similar to that noted for **257** gave the N-alkyl derivatives (**264-266** and **227**), which were further demethylated with 48% hydrobromic acid at 130° C or boron tribromide in CH_2Cl_2 to produce the corresponding (R)-N-alkylnorapomorphines (**267-270**)(Scheme 53).[70]



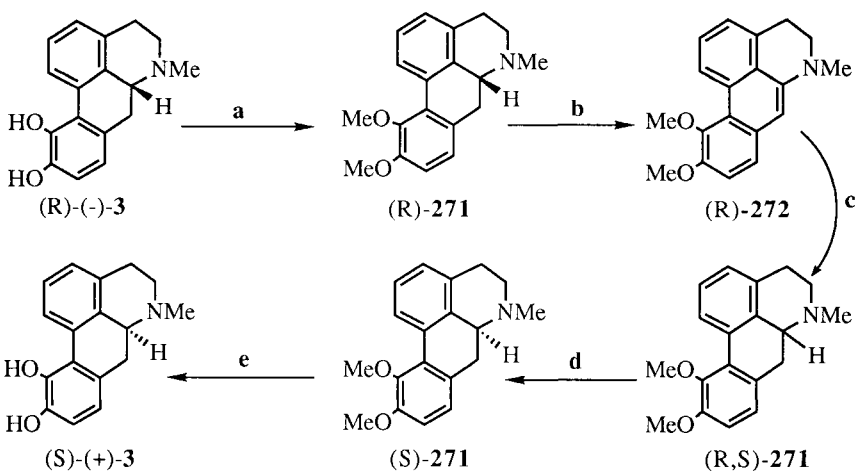
228 **263**

264	R = ▷—CH_2	51%	**267**	R = ▷—CH_2	61%
265	R = i-Pr	28%	**268**	R = i-Pr	95%
266	R = i-Bu	60%	**269**	R = i-Bu	100%
227	R = $(CH_2)_2OH$	---	**270**	R = $(CH_2)_2OH$	85%

a: RX, aq. $NaHCO_3$, MeCN, Δ or ethylene oxide; **b**: 48% HBr, 130° C or BBr_3, CH_2Cl_2

Scheme 53

Davis and coworkers[71] have reported transformation of (R)-(-)-apomorphine (**3**) to (S)-(+)-apomorphine (**3**) via dehydroapomorphine (**272**). Namely, dehy-drogenation of (R)-10,11-dimethoxyaporphine (**271**) with 10% palladium on char-coal in aceto-nitrile yielded dehydroaporphine (**272**), which was reduced with sodium cyano-borohydride in EtOH at pH 3-5 to produce (±)-10,11-dimethoxyaporphine (**271**). Optical resolution of (±)-**271** with (-)-tartaric acid led to a (-)-tartaric acid salt of (S)-

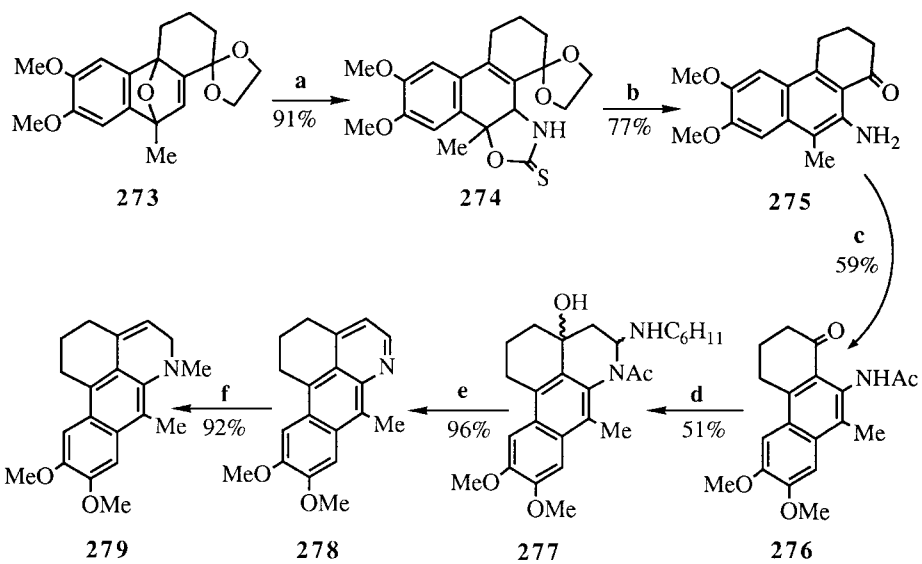


a: CH_2N_2, Et_2O; **b**: 10% Pd-C, MeCN, Δ ; **c**: $NaBCNH_3$, EtOH, pH 3-5;
d: resolution with (-)-tartaric acid in EtOH; aq. $NaHCO_3$; **e**: HI, Ac_2O, Δ

Scheme 54

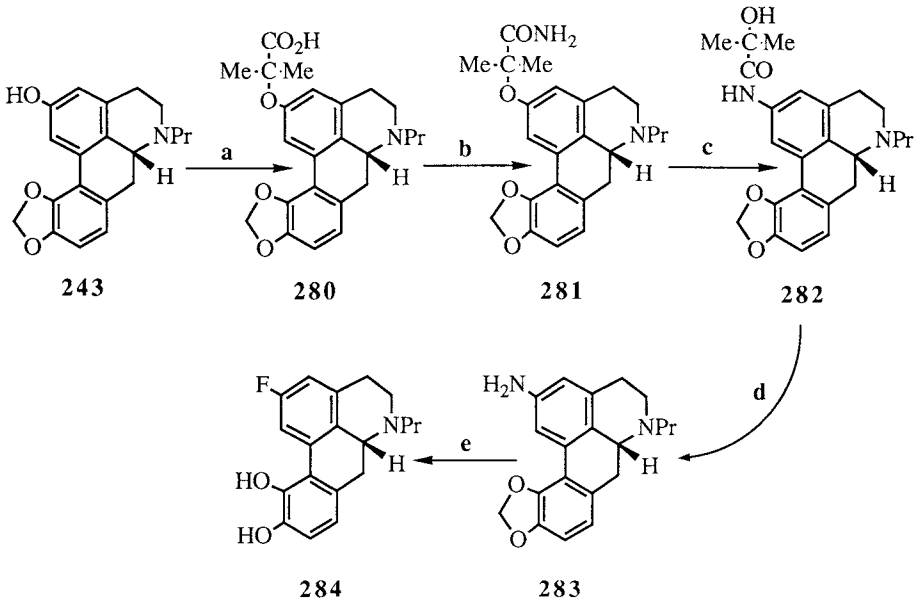
enantiomer, which was converted to (S)-(+)-apomorphine (**3**)(> 99% ee) by demethylation with hydroiodic acid in acetic anhydride at reflux (Scheme 54).

The synthesis of heterocycles (**278**, **279**) having the ring skeleton of aporphine alkaloids by introduction of a nitrogen atom using potassium thiocyanate and a direct aldol condensation has been reported.[69] The tricyclic compound (**273**) reacted with potassium thiocyanate in acetone containing 0.1N hydrochloric acid at ambient temperature to afford a cyclized product (**274**), which was treated with 0.1N hydrochloric acid to afford 10-amino-9-methyl-1,2,3,4-tetrahydrophenanthren-1-one (**275**) in 77% yield. Its acetamide (**276**) reacted with a mixture of lithium diisopropylamide and N-cyclohexylaziridine in THF at -78° C to furnish a cyclized product (**277**), further acid treatment of which gave 7-methyl-1,2,3-trihydrodehydronoraporphine (**278**) in 96% yield. Methylation of **278** followed by reduction produced 7-methyl-1,2,3,4-tetrahydrodehydroaporphine (**279**) in 92% yield (Scheme 55).



a: KSCN, 0.1N HCl, acetone, room tempt; **b**: 0.1N HCl, acetone, Δ ; **c**: Ac_2O, $CHCl_3$, Δ; **d**: LDA, N-cyclohexylaziridine, THF, -78° C, then room temp.; **e**: 5N HCl, room temp.; **f**: FSO_3Me, CH_2Cl_2 room temp.; $NaBH_4$, MeOH

Scheme 55



a: $CHCl_3$, acetone, NaOH; **b**: $SOCl_2$; NH_3, THF; **c**: NaH, HMPA; **d**: 0.17N HCl;
e: $NaNO_2$, 60% HPF_6; BBr_3, CH_2Cl_2

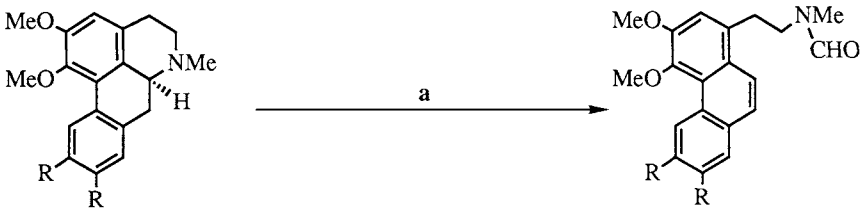
Scheme 56

For exploration of biological activity of apomorphine derivatives, Neumeyer and coworkers[73] have attempted synthesis of (R)-2-fluoro-N-propylnorapomorphine (**284**) starting from thebaine (**228**). Thus, (R)-2-hydroxy-10,11-methylenedioxynoraporphine (**243**) derived from thebaine (**228**)(see Scheme 51) was exposed with chloroform in acetone containing sodium hydroxide to leave 2-(2-oxycarbonylpropoxy)-norapor-phine (**280**), aminolysis of which gave the corresponding carbamate (**281**). Reaction of **281** with sodium hydride in hexamethylphosphoric triamide resulted in the modified Smiles rearrangement[72] with retention of the configuration at chiral 6a position to afford the corresponding 2-acylaminonorapomorphine (**282**), hydrolysis of which, without isolation, with 0.17N hydrochloric acid yielded 2-amino-N-propylnoraporphine (**283**). Finally, 2-aminonoraporphine (**283**) was transformed in the usual manner to (R)-2-fluoro-N-propylnorapomorphine (**284**)(Scheme 56).

8. REACTION

Although it may be not exactly classified as the method for the synthesis of aporphine and dehydroaporphine alkaloids, there are several interesting reports on the reactions of these alkaloids.

Treatment of nuciferine (**285**) and glaucine (**28**) with dichlorocarbene generated *in situ* from chloroform and 50% aqueous sodium hydroxide in the presence of phase transfer catalyst (tetrabutylammonium chloride) suffered ring fission to give phenanthrene formamides (**286** and **287**) in 60 and 57% yields (Scheme 57).[74]



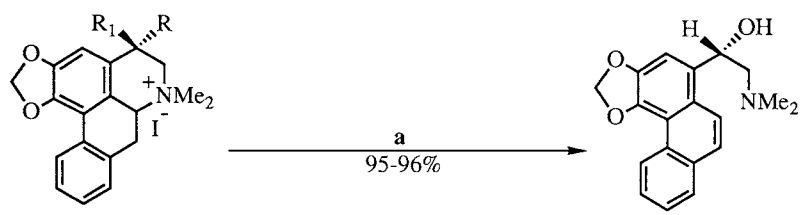
285 R = H
28 R = OMe

286 60%
287 57%

a: $CHCl_3$, 50% aq. NaOH, Bu_4NCl

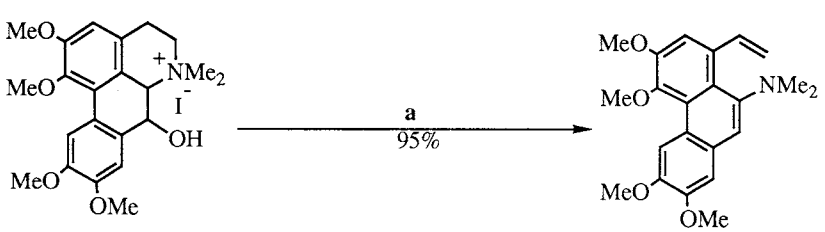
Scheme 57

Hofmann elimination of methiodides (**288** and **289**) of (±)-stephanine (**79**) and its 4-epimer under usual conditions afforded the same phenanthrene derivative (**290**) (Scheme 58).[75] A methiodide (**291**) of (±)-7-hydroxyaporphines (**12** and **13**) under similar conditions produced in 95% yield a phenanthrene (**292**), which was also formed by dehydration followed by Hofmann elimination (Scheme 58).[14]



288 R = OH, R_1 = H
289 R = H, R_1 = OH

290



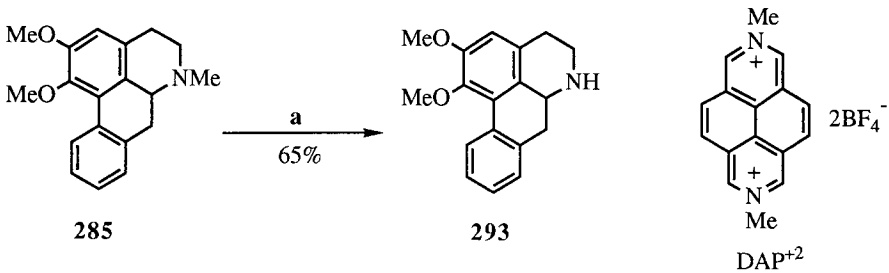
291

292

a: 10% aq. NaOH, Δ

Scheme 58

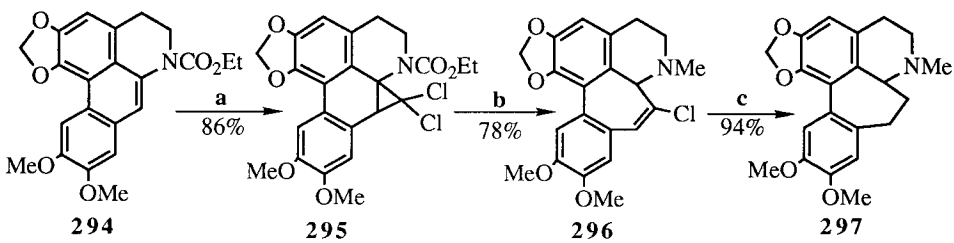
Photocleavage of N-methyl group in nuciferine (**285**) with visible light in the presence of N,N-dimethyl-2,7-diazapyrenium tetrafluoroborate (DAP^{+2})[76] and oxygen gives nornuciferine (**293**) in 65% yield (Scheme 59).[77] With glaucine (**28**), however, the reaction did not occur. Glaucine (**28**) suffered only ring fission when treated with α-chloroethyl chloroformate.[78].



a: *hν* (> 400 nm) through glass filter, O_2, DAP^{+2}, MeCN

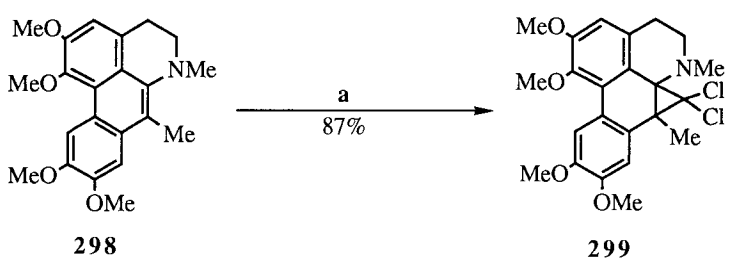
Scheme 59

Dehydroaporphine (**294**) reacted with dichlorocarbene generated as described above (Scheme 57) to result in formation of aporphine (**295**) bearing a dichlorocyclopropane ring, which was treated with lithium alminium hydride in THF to afford a ring expanded product (**296**) in 78% yield (Scheme 60).[79] This process was applied to the synthesis of (±)-homoaporphine (**297**). Similarly, 7-methyldehydroglaucine



a: $CHCl_3$, 50% aq. NaOH, Bu_4NCl; **b**: $LAlH_4$, THF; **c**: 10% Pd-C, H_2, NaOAc, EtOH

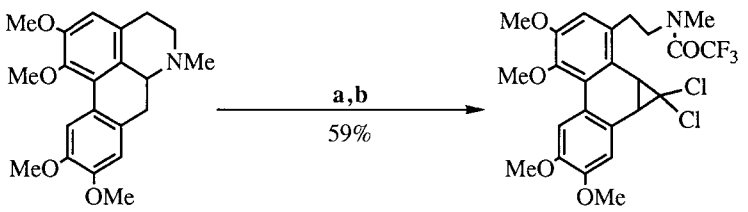
Scheme 60



a: $CHCl_3$, 50% aq. NaOH, Bu_4NCl

Scheme 61

(**298**) furnished dichlorocyclopropane (**299**)(Scheme 61).[79] Reaction of glaucine (**28**) with trifluoroacetic anhydride in pyridine followed by treatment with dichlorocarbene proceeded with ring fission to lead to phenanthrene (**300**) bearing a dichlorocyclopropane ring (Scheme 62).[79]

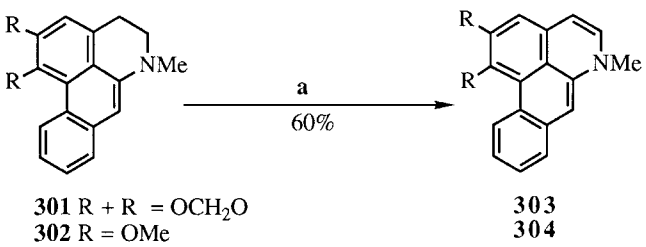


28 **300**

a: $(CF_3CO)_2O$, pyridine; **b**: $CHCl_3$, 50% aq. NaOH, Bu_4NCl

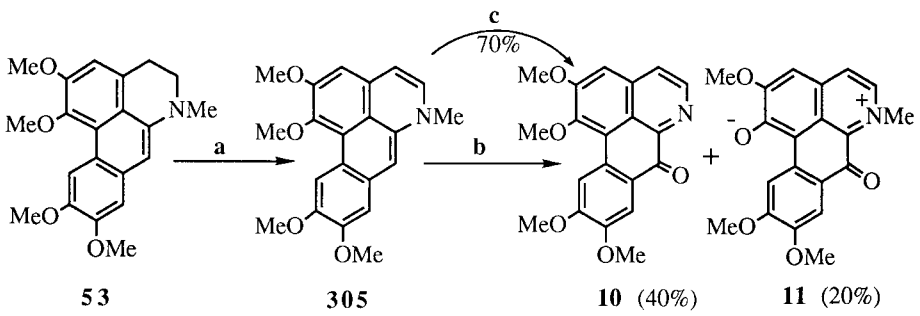
Scheme 62

Photolysis of dehydroroemerine (**301**) and dehydronuciferine (**302**) in benzene containing benzophenone produced tetradehydroaporphines (**303** and **304**), respectively. Similarly, dehydroglaucine (**53**) gave tetradehydroglaucine (**305**), which was further oxidized with Fremy's salt to yield 7-oxotetradehydroglaucine (**10**) and corunnine (**11**). On the other hand, **305** was oxidized with singlet oxygen to afford only 7-oxotetradehydroglaucine (**10**)(Scheme 63).[80]



301 R + R = OCH_2O
302 R = OMe

303
304

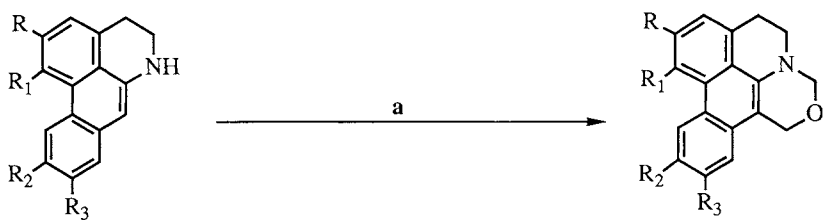


53 **305** **10** (40%) **11** (20%)

a: *hν*, C_6H_6, Ph_2CO; **b**: Fremy's salt, 4% aq. Na_2CO_3; **c**: *hν* ($^1O_2$)

Scheme 63

Dehydroaporphines when exposed to electrophiles give 7-substituted dehydroaporphines. Namely, when dehydronoraporphines (**40-43**) were treated with 37% aqueous formaldehyde in dioxane, highly substituted dehydroaporphines (**306**, **44**, **307**, and **308**) were obtained (Scheme 64).[23] In addition, formylation of acetates (**309** and **310**) of **74** and **75** with phosphoryl chloride in dimethylformamide took



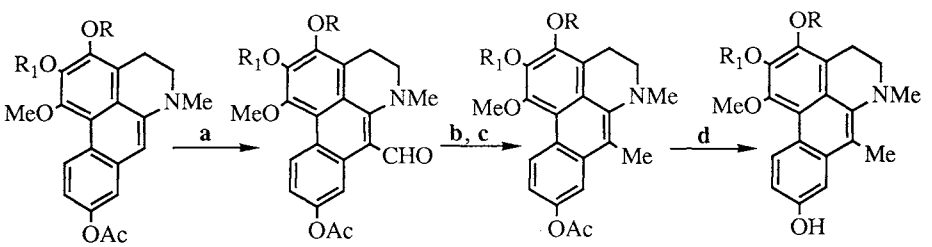
40 R = R_1 = OMe, R_2 = R_3 = H
41 R + R_1 = OCH_2O, R_2 = R_3 = H
42 R = R_1 = R_2= R_3 = OMe
43 R = R_1 = OMe, R_2 + R_3 = OCH_2O

306 91%
44 76%
307 86%
308 72%

a: 37% CH_2O, dioxane, room temp.

Scheme 64

place at 7 position to produce 7-formyldehydroaporphines (**311** and **312**) in good yields, which were converted to 7-methyldehydroaporphines (**315** and **316**) via **313** and **314** by reduction and successive hydrolysis (Scheme 65).[29]



309 R = Me, R_1 = Ac
310 R_1 = Me, R = Ac

311
312

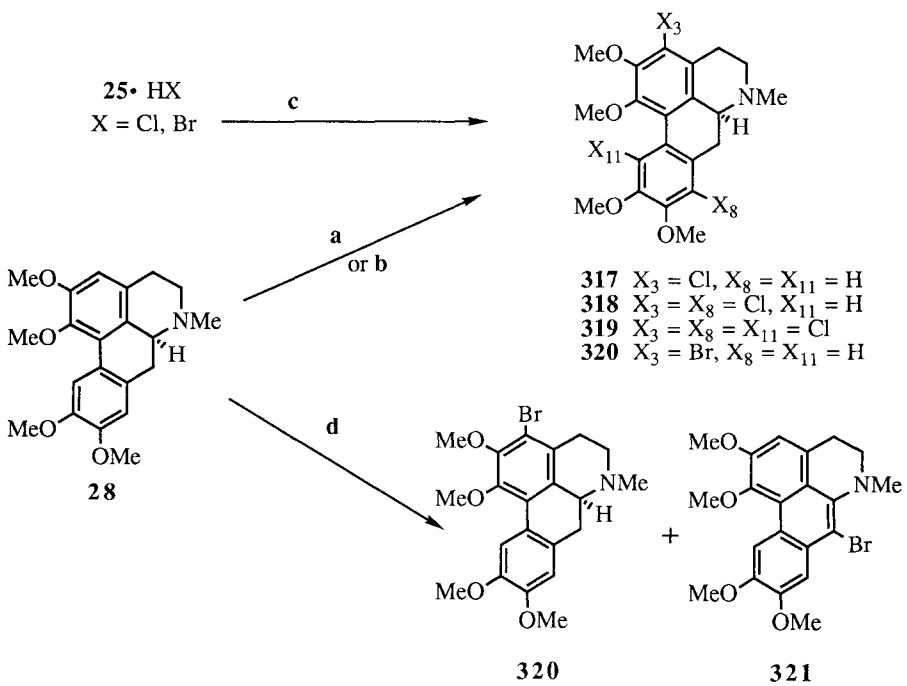
313
314

315 R= Me, R_1 = H
316 R = H, R_1 = Me

a: $POCl_3$, DMF; **b**: $NaBH_4$, EtOH, room temp.; **c**: $NaCNBH_3$, aq. EtOH, pH 3-7, room temp.; **d**: aq. $NaHCO_3$, MeOH, room temp.

Scheme 65

Halogenation of glaucine (**28**) under several conditions has been presented (Scheme 66).[81] Namely, the reaction of **28** with chloramine-T in AcOH or phosphorous pentachloride in dichloroethane led to 3-chloroglaucine (**317**) in 88 or 37% yield, which was also formed in 81% yield by reaction of glaucine hydrochloride (**28**·HCl) with 30% aueous H_2O_2 in AcOH. On the other hand, **28** on reaction with aluminium chloride and 30% aqueous H_2O_2 in AcOH afforded a mixture of 3-chloro- (**317**), 3,8-dichloro- (**318**) and 3,8,11-trichloro-glaucines (**319**) in a product ratio of 1 : 2.2 : 1. Similarly, treatment of glaucine hydrobromide (**28**·HBr) with 30% aqueous H_2O_2 gave 3-bromoglaucine (**312**) in 94% yield. However, reaction of **28** with N-bromosuccinimide in carbon tetrachloride at 10° C produced 3-bromoglaucine (**320**) and 7-bromodehydroglaucine (**321**), respectively.



a: $AlCl_3$, 30% aq. H_2O_2, AcOH, room temp.; **b**: chloramine-T, AcOH, room temp. or PCl_5, $(CH_2Cl)_2$, 50° C; **c**: 30% aq. H_2O_2, AcOH, conc. H_2SO_4, room temp.; **d**: N-bromosuccinimide, CCl_4, 10° C

Scheme 66

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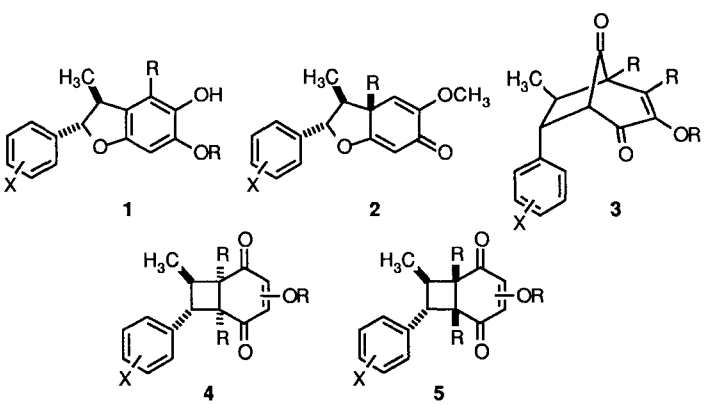
Atta-ur-Rahman (Ed.) *Studies in Natural Products Chemistry, Vol. 16*

Stereo- and Enantiospecific Reactions of 1,4-Benzoquinones with Styrenyl Systems: Stereoselective Syntheses of Neolignans, Pterocarpans and Several Naturally Occurring 2-Aryl-2,3-Dihydrobenzofuran Systems

Thomas A. Engler

1. INTRODUCTION

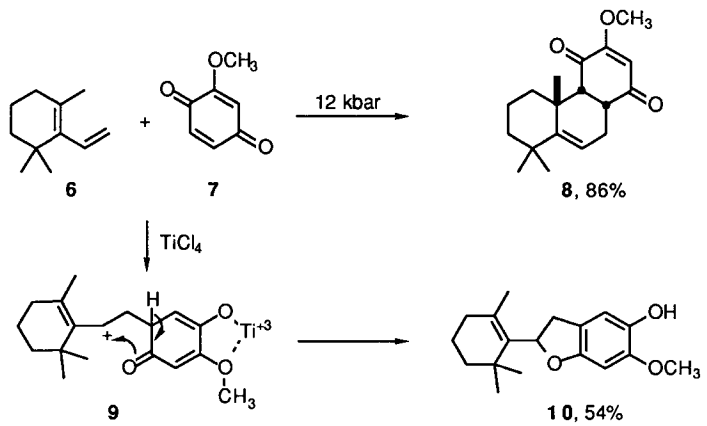
In spite of the fact that the chemistry of 1,4-benzoquinones has been explored for over 150 years, new aspects of the synthetic utility of this valuable class of compounds continue to emerge. We have been investigating the Lewis acid-promoted reactions of 2-alkoxy-1,4-benzoquinones with various styrenyl systems and have found that these reactions provide useful routes to several different structural types of cycloaddition products, i. e. **1-5**. Of particular note is that in many cases any one of the products can be formed in good yield and nearly exclusive of the others by proper control of reaction conditions and/or by proper choice of substituents on either the quinone or the styrene. In addition, utilization of chiral Lewis acids affords the products in good enantiomeric purity. Thus, the quinone-styrene reactions are extraordinarily versatile processes providing direct access to a number of classes of natural products possessing structures related to **1-3**. Products of the type **4** and **5** are also useful synthetic intermediates to others. A summary of our studies in this area is presented in this account.



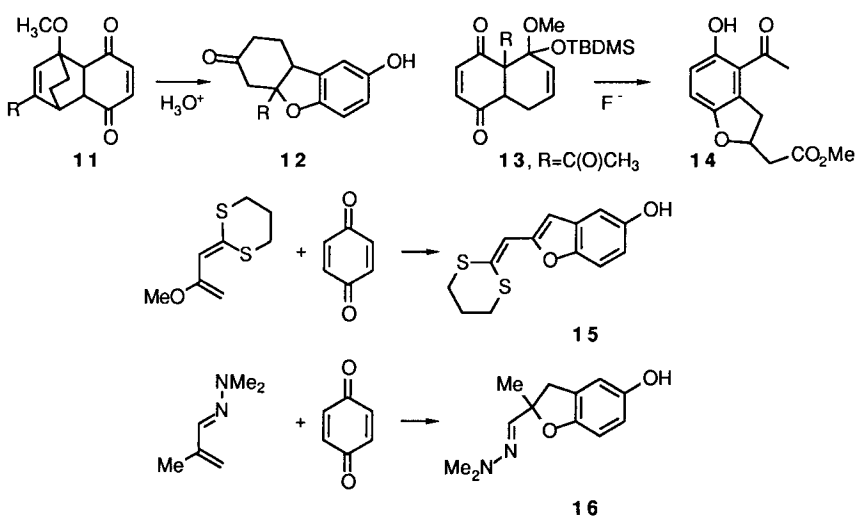
2. Lewis Acid-Promoted Reactions of Benzoquinones with Styrenyl Systems: General Aspects

2.1 Initial Studies

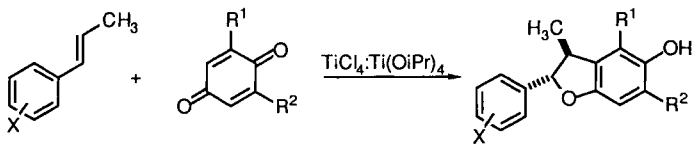
Our interest in this area originated from an observation made during the development of a new synthetic approach to various classes of diterpene systems via a Diels-Alder reaction between diene **6** and 2-methoxy-1,4-benzoquinone, **7**. Under high pressure conditions, the expected product **8** was



found in good yield (1). However, promotion of the reaction with $TiCl_4$ gave the dihydrobenzofuran **10**. The formation of **10** may have involved a Diels-Alder reaction to give **8** followed by an acid promoted ring opening to intermediate **9** which then produced the dihydrobenzofuran. Similar rearrangement reactions of quinone-Diels-Alder adducts are known. For example, the adduct **11**, from methoxycyclohexadiene and benzoquinone, gives **12** upon treatment with protic acid (2) and treatment of **13** with fluoride ion gives **14** (3). Alternatively, the formation of **10** may be rationalized via a Michael addition of the diene to the Ti(IV)-activated quinone to give **9** directly. Indeed, conjugate addition reactions of electron rich alkenes such as enamines, enol ethers or ketene acetals to benzoquinones are common (4) and mildly nucleophilic allylsilanes and -stannanes also give 1,4-addition products in Lewis acid-promoted reactions with 1,4-benzoquinones (5). Benzofuranoid products have been observed in reactions of quinones with electron rich dienes as well, for example **15** (6) and **16** (7).

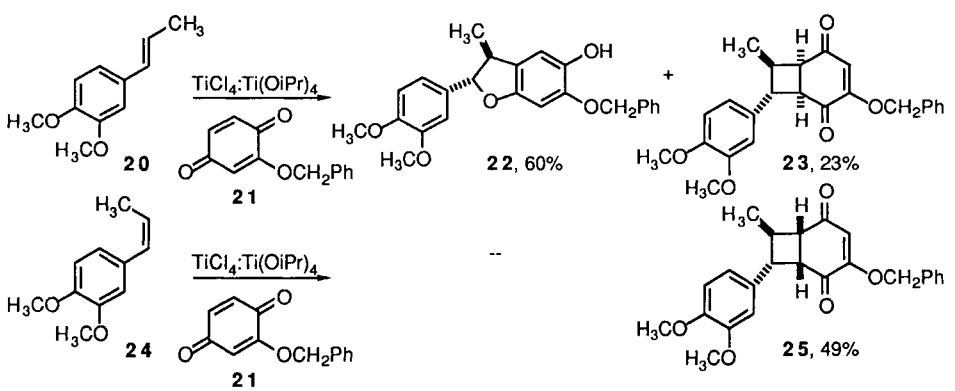


The possibility that the reaction of **6** with **7** was proceeding through a conjugate addition mechanism presented an opportunity for the development of a new, general and regioselective synthesis of dihydrobenzofurans since it indicated that with Lewis acid promoters, even simple unactivated alkenes might be induced to react regioselectively with substituted quinones. To explore this postulate, Ti(IV)-promoted reactions of quinones with various (*E*)-β-methylstyrenes **17** were explored (8). Not unexpectedly, styrenes bearing methoxy substituents gave the 2-aryl-2,3-dihydrobenzofuranols **19** in good yield. This is a noteworthy process in itself due to the large number of biologically active natural products possessing 2-aryl-2,3-dihydrobenzofuran and 2-aryl-benzofuran moieties.



17 (X)	R^1	R^2	19, % Yield
4-OCH_3	H	H	68
3,4-$(OCH_3)_2$	H	H	67
4-OCH_3	H	OCH_3	72
2-OCH_3	H	OCH_3	75
4-OCH_3	CH_3	OCH_3	75
3,4-$(OCH_3)_2$	CH_3	OCH_3	90

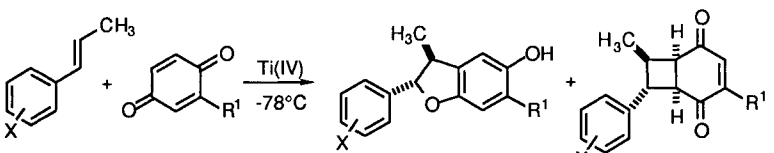
However, reaction of 2-benzyloxy-1,4-benzoquinone, **21**, with (*E*)-styrene **20** gave the dihydrobenzofuran **22** accompanied by significant quantities of the cyclobutane **23**. The isolation of the latter product was of interest in several respects. First, the formation of cyclobutanes in reactions of quinones with alkenes is not common (9). Secondly, even though four stereogenic centers are formed in the reaction, cyclobutane **23** was isolated as a single diastereomer. Because of the mechanistic implications of this finding, reaction of (*Z*)-β-methylstyrene **24** with quinone **21** was investigated and was found to give the isomeric cyclobutane **25** as the major product. Thus, **23/25**



were formed via *stereospecific* processes. This intriguing result implied that the quinone-styrene reactions were considerably more complex than anticipated and a more detailed investigation of the Lewis acid-promoted reactions of 1,4-benzoquinones with styrenyl systems was initiated.

2.2 Reactions of 1,4-Benzoquinone and 2-Methoxy-1,4-benzoquinone

Reactions of the various styrenes **17** with quinones **26a/b** were found to give dihydrobenzofurans **27** and cyclobutanes **28** as major products and the ratio of the two was dependent mainly on the nature of the substituent on the styrene and to a lesser extent on the ratio of $TiCl_4$:$Ti(OiPr)_4$ used as promoter. As previously mentioned, reactions of styrenes bearing good electron-donating substituents on the aromatic ring gave mainly dihydrobenzofurans in good yield. However, reactions of styrenes with more neutral substituents gave more of the cyclobutane products. Representative examples are shown in Table I. In many cases, the ratio of **27** to **28** could be altered by changing the $TiCl_4$:$Ti(OiPr)_4$ ratio. For example, reactions promoted by $TiCl_4$ gave

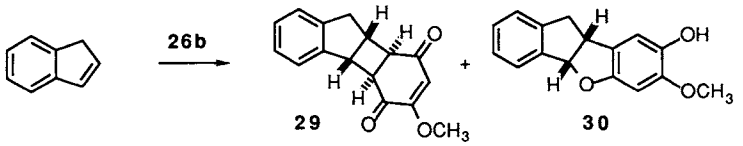


17 **26a**, R^1=H; **26b**, R^1=OCH_3 **27** **28**

Table 1

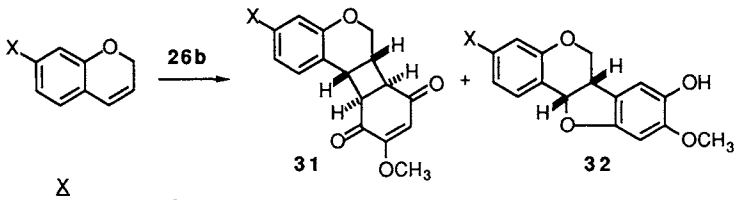
Entry	**17** (X)	Quinone	$TiCl_4$:$Ti(OiPr)_4$	**27** (% Yield)	**28** (% Yield)
1	4-CH_3	**26a**	3:1	37	20
2	3,4-$(OCH_3)_2$	**26b**	1:0	61	--
3	3,4-$(OCH_3)_2$	**26b**	1.6:1	60	23
4	4-CH_3	**26b**	1:0	64	19
5	4-CH_3	**26b**	2:1	36	49
6	2-CH_3	**26b**	1:0	27	38
7	2-CH_3	**26b**	2:1	10	60
8	H	**26b**	1:0	41	43

good yields of **27** (entries 2, 4), although reactions of the same styrenes with mixtures of $TiCl_4$:$Ti(OiPr)_4$ gave significant, and sometimes major quantities of the cyclobutanes **28** (entries 1, 3, 5, 7). Rearrangement of the cyclobutane products to the dihydrobenzofurans was effected by treatment with protic acid or in some cases by allowing the reaction mixtures to stir for extended periods or to warm to higher temperatures. Two dramatic cases of the selective formation of the 2+2 adducts by careful control of conditions were found in reactions of indene and 2H-benzopyrans with quinones to give **29** or **30** and **31** or **32**, respectively. Thus, it appears that the cyclobutanes are products of kinetic control whereas the dihydrobenzofurans are preferred under thermodynamic conditions. The Ti(IV)-Lewis acids were the best promoters of these reactions. With other Lewis acids such as BF_3·Et_2O, $SnCl_4$ or $ZrCl_4$, only the dihydrobenzofurans were found and the yields were lower than reactions promoted by Ti(IV). It should be noted that $TiCl_4$ is a powerful Lewis acid



2:1 $TiCl_4$:$Ti(OiPr)_4$ 85%

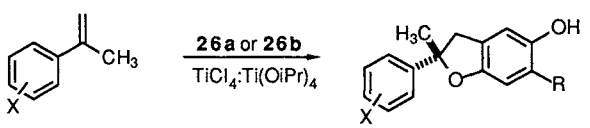
$TiCl_4$ 54%



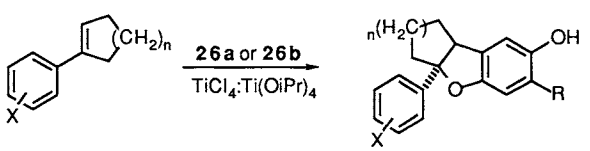
X			
H	1:1 $TiCl_4$:$Ti(OiPr)_4$, -78°C, 0.5 h	85%	--
H	1:1 $TiCl_4$:$Ti(OiPr)_4$, -78 to -30°C	--	46%
OCH_3	1:1 $TiCl_4$:$Ti(OiPr)_4$, -78°C, 0.5 h	67%	13%
OCH_3	1:1 $TiCl_4$:$Ti(OiPr)_4$, -78°C, 10 h	10%	80%
OCH_3	1:1 $TiCl_4$:$Ti(OiPr)_4$, -78 to -30°C	--	58%

and the lower yields found in reactions promoted by it are probably due to competing polymerization of the styrenes.

Reactions of quinones **26a/b** with α-methyl-styrenes and 1-arylcycloalkenes were also successful and gave dihydrobenzofurans **33** and **34**, respectively. In only a few cases were cyclobutane adducts found and the yields were low.



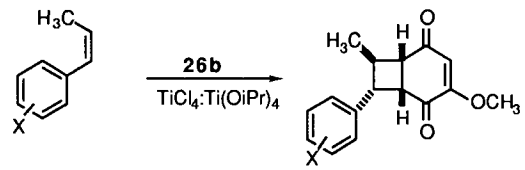
33 X=H or 4-OCH_3
R=H or OCH_3
42-60%



34 X=H or 4-OCH_3
R=H or OCH_3
n=1, 2 or 3
53-80%

The stereospecificity of the styrene-quinone reactions was of particular interest. Reactions of (*E*)-β-methylstyrenes gave significant quantities of cyclobutanes **23/28** whereas reactions of the (*Z*)-styrenes gave the isomeric cyclobutanes **25/35** as the major isolable products. Careful examination by hplc of the crude reaction mixtures obtained after aqueous quench, extraction and concentration did reveal that small amounts of **25** and **35** were present in reactions of the (*E*)-styrenes and the ratios of **23**:**25** and **28**:**35** were greater than 16:1. Similarly, small amounts of cyclobutanes **23/28**

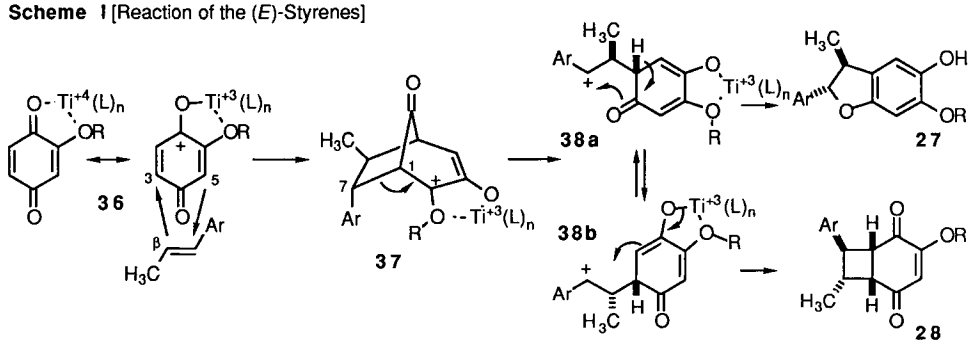
were present in the reactions of the (*Z*)-styrenes with ratios of **23**:**25** and **28**:**35** less than 1:13. Thus, although the quinone-styrene reactions were not completely stereospecific, they were highly so. These results demanded an explanation.



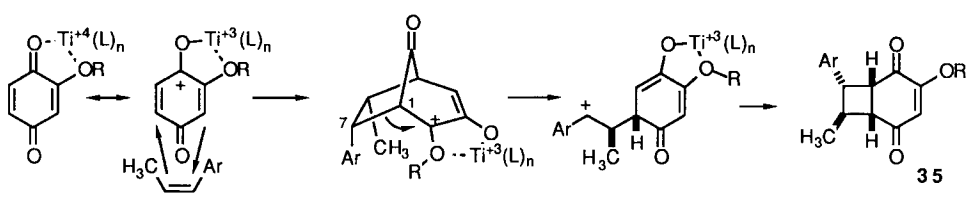
35 (X)	Yield
3,4-$(OCH_3)_2$	39%
CH_3	31%
H	39%

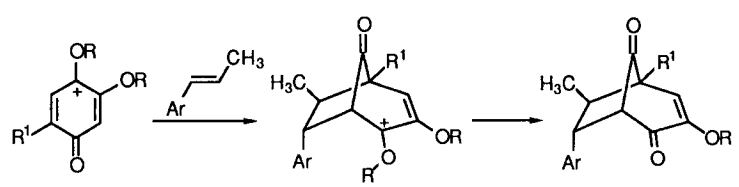
We proposed that the reactions were proceeding via a 5+2 ($4\pi+2\pi$) cycloaddition (Schemes I and II) of the styrene with the pentadienyl carbocation moiety of the quinone-Ti(IV) complex represented as **36** to give **37** which was then followed by C-1/C-7 bond cleavage to give benzylic carbocation **38** and then **27**/**28**. Several years earlier Mamont (10), Büchi (11) and Yamamura (12)

Scheme I [Reaction of the (*E*)-Styrenes]



Scheme II [Reaction of the (*Z*)-Styrenes]

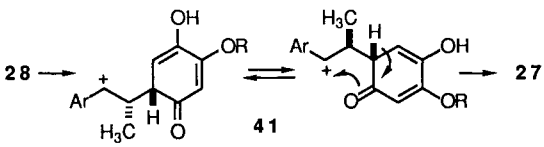




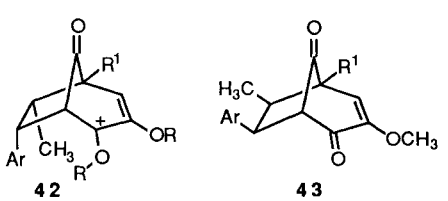
39, R=R^1=alkyl

40, R=H or alkyl

had demonstrated analogous cycloaddition reactions of styrene or of (*E*)-β-methylstyrenes with similar pentadienyl carbocations **39** (formed via a variety of techniques) to give **40** and in these reactions the aryl ring of the styrene occupied an endo orientation with respect to the pentadienyl carbocation moiety in the cycloaddition (13, 14). If the aryl rings in β-methylstyrenes similarly occupy the endo position in cycloadditions with **36**, then the stereospecificity of the reactions is readily explained as shown in the Schemes. The dependence of the ratio of **27**:**28** on the ratio of $TiCl_4$:$Ti(OiPr)_4$ used as promoter is due to the nature of the ligands on titanium in intermediates **38a/38b**. With $TiCl_4$ as promoter, L=Cl and the Ti-O bond in **38** would be expected to be strong due to the oxophilicity of titanium and results in a relatively non-nucleophilic titanium-enolate moiety; C-O bond formation to give **27** is observed in these reactions. In reactions promoted by mixtures of $TiCl_4$:$Ti(OiPr)_4$, the titanium atom in **38a/b** would possess a number of OiPr ligands and the titanium-enolate bond may be weaker resulting in a more nucleophilic enolate. In these reactions, C-C bond formation between the enolate and the carbocation is found giving **28**. The protic acid rearrangements of the cyclobutanes to the dihydrobenzofurans most likely occur via **41** and are driven by relief of ring strain and aromatization.



Unfortunately, attempts by Büchi and Yamamura to verify the stereospecific cycloaddition by isolating bicyclo[3.2.1]-adducts with endo aryl groups in reactions of cation **39** with (*Z*)-β-methylstyrenes were not successful. In these experiments, only products derived from the presumed intermediate **42** or those with with exo-aryl moieties, i.e. **43,** were found (12c). Angle reported recently that reactions of cations **39** with (*Z*)-β-methylstyrenes gave both endo- and exo-aryl bicyclic products and products derived from them (15). However, further support for the 5+2 cycloaddition/rearrangement mechanism was found in the Ti(IV)-promoted reactions of 2-methoxy-6-methyl-1,4-benzoquinone in which the bicyclo[3.2.1]-adducts could be isolated in some cases.



2.3 Reactions of 2-Methoxy-6-methyl-1,4-benzoquinone

Many of the trends observed in reaction of styrenes **17** with quinones **26a/b** were also found in reactions with quinone **26c** (Table 2). Thus, styrenes bearing good electron donating substituents gave mainly dihydrobenzofurans **44** (entries 1-3). More neutral styrenes gave more of the cyclobutanes **45**, particularly in reactions conducted at low temperatures and promoted by the milder

Lewis acids formed from mixtures of $TiCl_4$:$Ti(OiPr)_4$ (entries 4, 6). Reactions run at temperatures greater than -78°C also gave mainly the dihydrobenzofurans **44** (entries 5, 7) and rearrangement of the cyclobutanes to the dihydrobenzofurans was observed upon treatment with protic acids. The most striking difference between the reactions of quinones **26a/b** and those of **26c** was the isolation of the bicyclic adduct **46** from the latter, sometimes in good yield (entries 8, 9, ref. 16). In terms of mechanism it is particularly noteworthy that reactions of indene gave, in addition to the dihydrobenzofuran and cyclobutane products **47** and **48**, the bicyclic adduct **49** in which the aryl moiety is endo. Finally, similar to the studies outlined in the previous section, reaction of (*Z*)-β-methylstyrene with **26c** gave a cyclobutane **50** which was different from that found with the corresponding (*E*)-styrene.

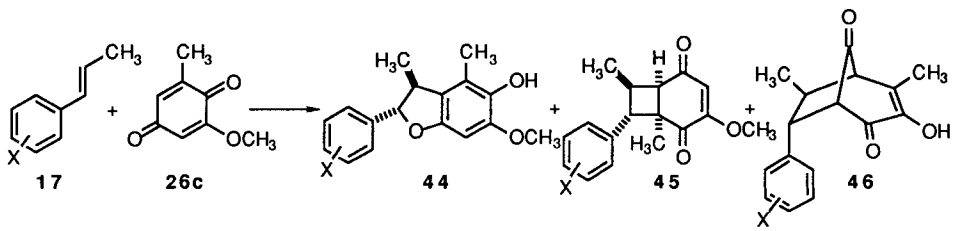
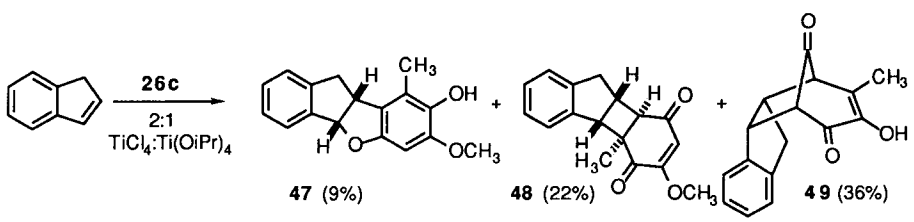
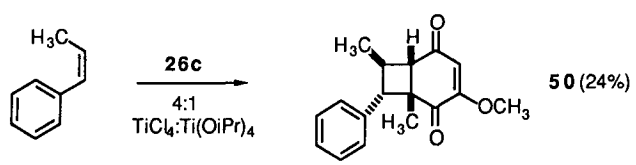


Table 2

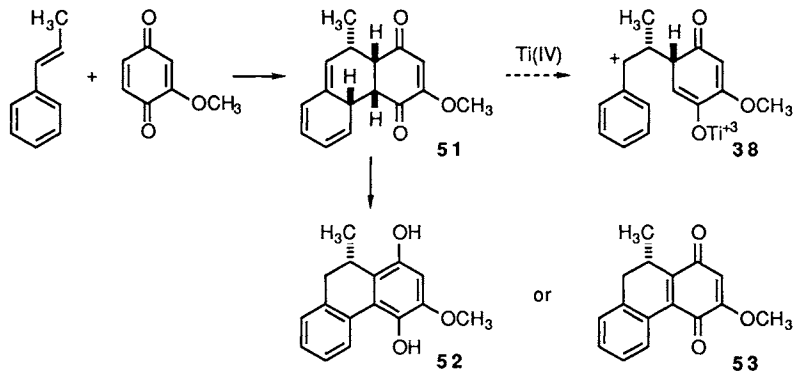
Entry	17 (X)	$TiCl_4$:$Ti(OiPr)_4$	Temp (°C)	44 (% Yield)	45 (% Yield)	46 (% Yield)
1	4-OCH_3	2:1	-78	75	--	--
2	3,4-$(OCH_3)_2$	1:1	-78	90	--	--
3	4-CH_3	1:0	-78	72	--	--
4	4-CH_3	3:1	-90	16	54	3
5	4-CH_3	3:1	-40	60	--	--
6	4-CH_3	2:1	-90	11	51	8
7	4-CH_3	2:1	-40	62	10	--
8	2-CH_3	2:1	-78	2	32	44
9	H	3:1	-78	10	18	51





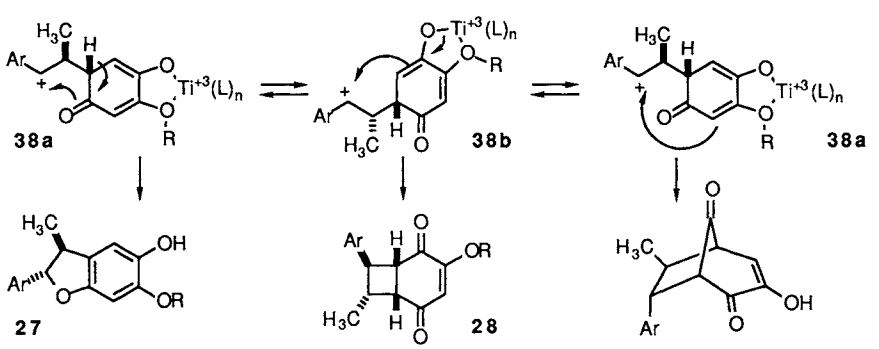
2.4 Selective Formation of the 5+2 Cycloadduct

The stereospecific formation of cyclobutanes **23/28/45** and **25/35/50** from (*E*)- and (*Z*)-β-methylstyrenes, respectively, provided reasonably good evidence for the 5+2 cycloaddition/rearrangement mechanism shown in Schemes I and II. However, it did not eliminate other possibilities. For example, the products can also be explained via a Diels-Alder reaction of the styrene with the quinone in which the quinone would be expected to adopt an endo orientation and give **51** which could then undergo Ti(IV)-mediated fragmentation to benzylic carbocation **38**. We



thought this unlikely since Diels-Alder reactions of styrenes with quinones are known to give phenanthrenediols **52** or -diones **53** (17), even with acid catalysis in which fragmentation might be expected (18). The absence of such products in the Ti(IV)-promoted reactions of quinones with styrenes argues against this mechanism. Alternatively, Swenton has suggested (19) that π-stacking interactions may be operative in nonconcerted reactions as well as concerted ones and simple alkylation of the quinone-Ti(IV) complex by the styrene may preferentially give benzylic cations **38** directly without proceeding through **37**. Intermediate **38** may then close to any one of the three products (Scheme III). There may be little difference between the cycloaddition mechanism and a simple alkylation process since in a cycloaddition process, an asynchronous transition state in which

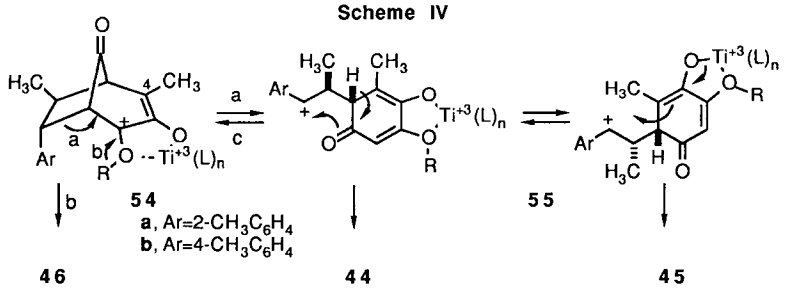
Scheme III



C-β/C-5 bond formation is further advanced than C-α/C-3 would be expected due to the higher electrophilicity of C-5 in comparison to C-3 in the complex **36**.

A comparison of the amounts of the 5+2 adducts formed in reactions of **26b** and **c** provides additional evidence that the 5+2 cycloaddition/rearrangement sequence may be operative. The formation of **46** from **26c** and our initial failure to find similar products in reactions of **26b** is likely because of greater stability of intermediate **54,** due to the C-4 methyl group, which allows dealkylation (Scheme IV, path b) to compete with fragmentation to **55** (path a). In reactions of **26c** with styrenes bearing good electron-donating substituents, little of the 5+2 adducts are found presumably because the formation of benzylic carbocation **55** from **54** via path a is fast relative to dealkylation via path b due to stabilization of the carbocation center in **55** by the ring substituent. However, reaction of (*E*)-β,2-dimethylstyrene with **26c** gave much more of the 5+2 adduct than reaction of the 4-methyl-analog (44% vs 8%, Table 2, entries 6 and 8). We interpreted this result as indicating a slower rate of path a relative to b in the case of the bicyclic intermediate **54a**, bearing an *o*-methyl substituent on the aryl ring, in comparison to the intermediate **54b** bearing a *p*-methyl group. An *o*-methyl group would inhibit resonance stabilization of the carbocation center in **55** and slow its rate of formation. In addition, in the simple alkylation mechanism to give **55** directly, introduction of an *o*-methyl group would be expected to result in less of the 5+2 adduct **46** via path c/b due to steric hindrance to C-C bond formation.

Scheme IV



With the above rationale in mind, we focussed on the postulate that the 5+2 cycloaddition/rearrangement sequence was involved in the Ti(IV)-promoted reactions of the quinones with the styrenes. We reasoned that if intermediate **54** was indeed at a divergent point in the mechanism, and the relative rates of paths a and b could be manipulated, then a selective route to the 5+2 adducts may result. To do this we chose to examine reactions of 2-(*p*-methoxybenzyl)oxy-1,4-benzoquinones **56**. If their Ti(IV)-promoted reactions with styrenes gave intermediates **57**, then dealkylation to **46/58**, either by an S_N1 or S_N2 pathway, may be faster than C-C bond cleavage. In the experiments, the 5+2 adducts were isolated as the only products in good yield (Table 3, ref. 20). In fact, the highest yield of a 5+2 product was found in the reaction involving the presumed intermediate **57a** (X=2-CH_3, entry 2) from which path a would be expected to be slow and path b fast. Whatever reality may be, the cycloaddition mechanism seems to be a useful tool for predictive purposes.

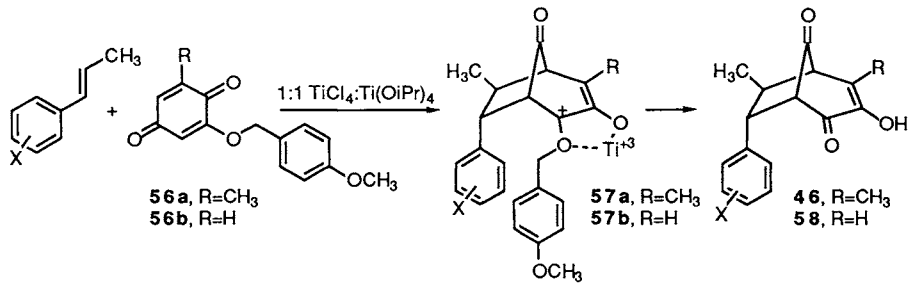
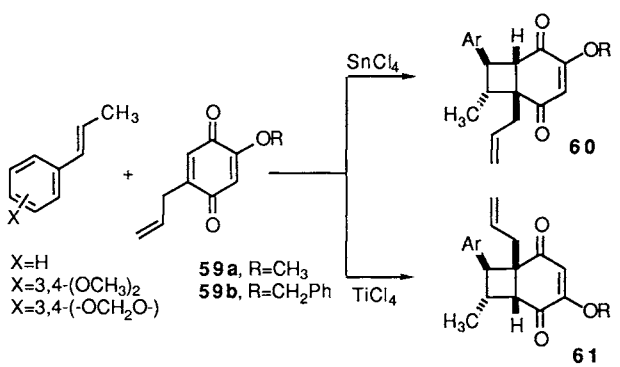


Table 3

Entry	X	Quinone	Product (X)	% Yield
1	4-CH_3	**56a**	**46** (4-CH_3)	67
2	2-CH_3	**56a**	**46** (2-CH_3)	88
3	H	**56a**	**46** (H)	76
4	4-CH_3	**56b**	**58** (4-CH_3)	44
5	2-CH_3	**56b**	**58** (2-CH_3)	46
6	H	**56b**	**58** (H)	59
7	indene	**56a**	**49**	63

2.5 Reactions of 2-Alkoxy-5-allyl-1,4-benzoquinones

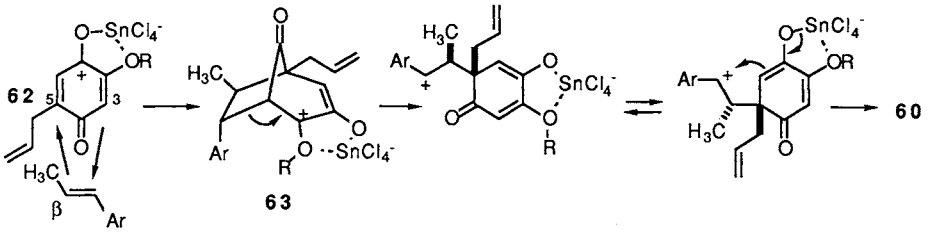
Lewis acid-promoted reactions of styrenes with 2-alkoxy-5-allyl-1,4-benzoquinones **59** provided another interesting twist: at -78°C, two cyclobutane products **60/61** were found (21). After considerable experimentation, conditions were found under which either one could be obtained selectively. Promotion of the reaction with $SnCl_4$ gave **60** (34-87%) whereas utilization of an excess of Ti(IV), as $TiCl_4$ or a reagent prepared from mixtures of $TiCl_4$:$Ti(OiPr)_4$, resulted in **61** (78-97%), exclusively in many cases.



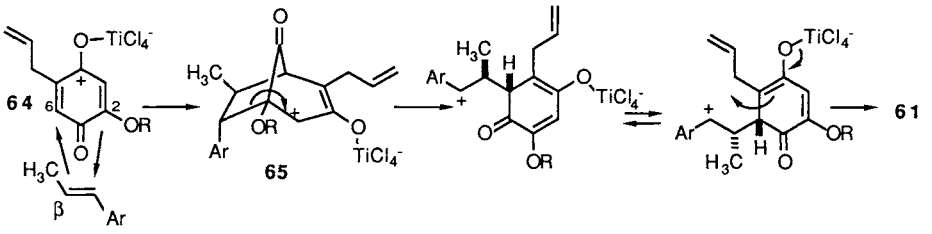
Cyclobutanes **60** and **61** are constitutional isomers, not stereoisomers, and the formation of both can be explained by cycloaddition mechanisms similar to that discussed above. Bidentate coordination of the Sn(IV) to the C-1 carbonyl oxygen and the C-2 methoxy oxygen of **59** gives a complex which can be represented as **62** (Scheme V). Reaction with the styrene then gives **63**, if the

assumption is made that the aryl ring of the styrene prefers the endo position in the cycloaddition, and **63** can then proceed on to **60** as discussed previously.

Scheme V



Scheme VI



On the other hand, the C-4 carbonyl oxygen of **59** is also a basic site, perhaps more basic than the C-1 oxygen due to resonance electron donation by the C-2 methoxy group, and coordination with Ti(IV) apparently gives complex **64** (Scheme VI). Cycloaddition of **64** with the styrene would give **65** and its rearrangement in a manner similar to **63** accounts for the production of **61**. Several possible reasons for the selective formation of **63**/**65** can be advanced. The former is likely more stable than the latter due to the carbocation stabilizing influence of the OR group. However, the formation of **63** may be expected to be slower than **65** due to steric hindrance provided by the C-5 allyl group (in an asynchronous cycloaddition transition state, steric factors associated with C-β/C-5 bond formation would be more important than those associated with C-α/C-3). It is likely that an equilibrium mixture of all possible quinone-Lewis acid complexes are present, and the formation of **63** may be thermodynamically controlled whereas the formation of **65** may be preferred kinetically. With the milder Lewis acid $SnCl_4$ as promoter, the reaction proceeds via the more stable intermediate **63**. However, with the more powerful Ti(IV)-promoter, the faster reaction via **65** is observed. A second possibility is that since more than two equivalents of Ti(IV), with respect to quinone, are required for the selective formation of **61**, the active complex may be a quinone-$[Ti(IV)]_2$ species with Ti(IV) bound to both carbonyl groups, and cycloaddition across C-2/C-6 is favored over C-3/C-5 due to steric factors imposed by the C-5 allyl group. Finally, π-complexes of Ti(IV) are known (22) and it is possible that the Ti(IV) binds to the entire π-face of the quinone activating both C-2/C-6 and C-3/C-5 to cycloaddition and reaction across the the former is again preferred.

2.6 Enantioselective Reactions

The products of the quinone-styrene reactions are chiral and the fact that these reactions are promoted by Ti(IV) suggested the possibility that utilization of chiral Ti(IV) complexes would provide a means to access the products in enantiomerically enriched form. Although on first inspection the bonds forming in the reactions may appear to be far removed from the presumed Ti(IV)-binding site(s) on the quinone, i.e. the C-1 carbonyl and C-2 methoxy oxygens, if the aryl ring of the styrene occupies an endo orientation in the transition state, it does extend toward this site. In practice, these experiments work remarkably well (23). Reactions of substituted styrenes with quinones **26b/c** promoted by a complex prepared from a 1:1:1 mixture of $TiCl_4$, $Ti(OiPr)_4$ and the chiral diol **67** at -78°C gave cyclobutane, dihydrobenzofuran and/or bicyclo[3.2.1]-adducts usually with one as the major, if not exclusive, product (Table 4). The major products were found in generally good to excellent enantiomeric purity. In all cases, recrystallization of the major products afforded enantiomerically pure material. Treatment of the enantiomerically pure cyclobutanes **28/45** thus obtained with the chiral Ti(IV)-**67** complex at -78°C and warming to room temperature effected their rearrangement to dihydrobenzofurans **27/44** without loss of enantiomeric purity. The dihydrobenzofurans were obtained as trans:cis isomers with the former predominating (>15:1). Protic acid catalysis also effected this rearrangement, although the trans:cis ratio of the dihydrobenzofuran product was lower.

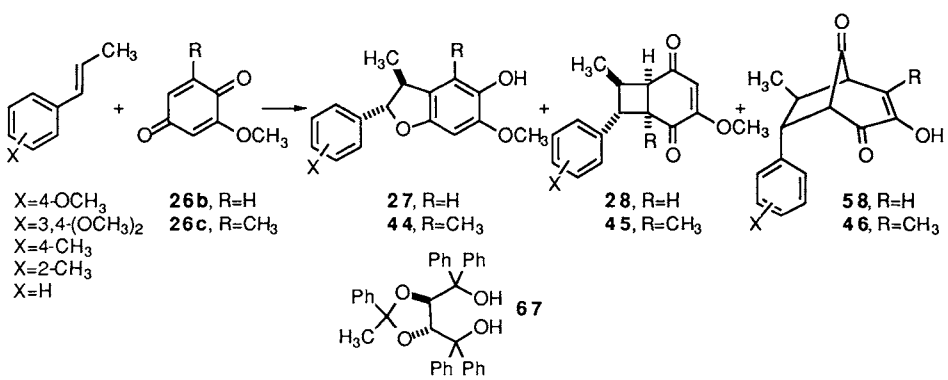
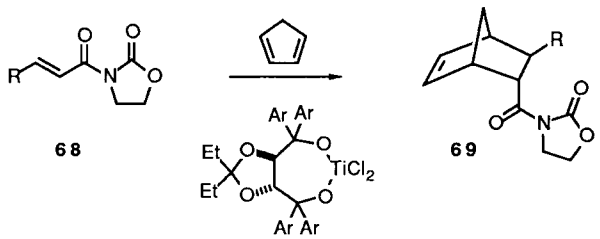


Table 4

Entry	Styrene	Quinone	Products (% Yield, % ee)		
1	X=4-OCH_3	**26b**	**27** (10, 53)	**28** (86, 90)	--
2	X=3,4-$(OCH_3)_2$	**26b**	**27** (9, n.d.)	**28** (88, 92)	--
3	X=4-CH_3	**26b**	--	**28** (70, 86)	--
4	X=2-CH_3	**26b**	--	--	**58** (64, 84)
5	X=H	**26b**	--	--	**58** (61, 90)
6	X=4-OCH_3	**26c**	**44** (15, 78)	**45** (72, 90)	--
7	X=3,4-$(OCH_3)_2$	**26c**	**44** (49, 83)	**45** (35, 88)	--
8	X=4-CH_3	**26c**	--	**45** (10, 70)	**46** (62, 92)
9	X=2-CH_3	**26c**	--	--	**46** (60, 96)

Complexes of Ti(IV) with diols similar to **67** have been used to catalyze or promote a number of asymmetric processes, including Diels-Alder reactions (24). Recently, Corey proposed a model for the transition state of the Diels Alder reaction of cyclopentadiene with oxazolidinone **68** catalyzed by a complex identified as **70** to give **69** (Fig. 1, ref. 25). A similar transition state structure can also



70, Ar=3,5-$(CH_3)_2C_6H_3$

be used to rationalize the asymmetric induction found in the quinone-styrene reactions as shown in Fig. 2a; in this structure, reaction occurs on the C-3 *si*/C-5 *re* face of the quinone. In the alternative structure Fig. 2b in which the other face of the quinone is exposed to reaction with the styrene, steric interactions develop between the axial Cl and the phenyl ring of the styrene as it approaches. However, the stoichiometry of the reaction used to prepare **70** and that used to prepare the complex that is effective in the quinone-styrene reactions is notably different. The former employed a Ti(IV)-diol ratio of 1:1 whereas in the latter studies a 2:1 Ti(IV)-diol ratio was used. Heppert has found that complexes of Ti(IV) with several chiral diols can exist in solution and in the solid state as mono-, di-, or even trinuclear complexes depending on the structure of the diol, the other ligands on Ti(IV), solvent and temperature (26). Thus, although the complex prepared in our studies may be some form of dinuclear (or higher) complex, perhaps with the titanium bridged to another titanium atom via the equatorial Cl and alkoxide moiety of the diol, the local asymmetry around the titanium bound to the diol may be similar to that in **70** (Fig. 1).

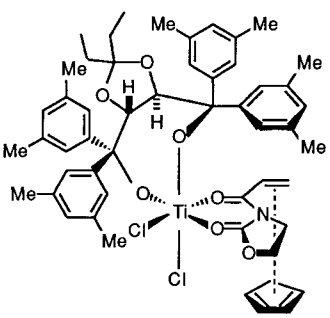


Figure 1.

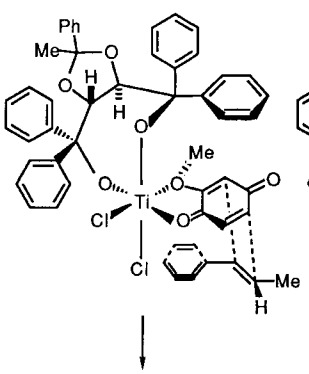


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Figure 2a.

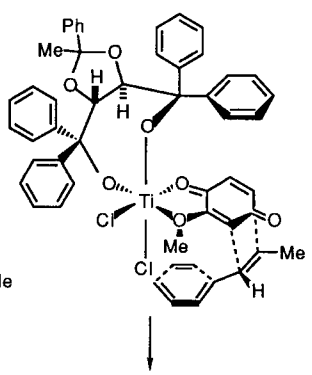

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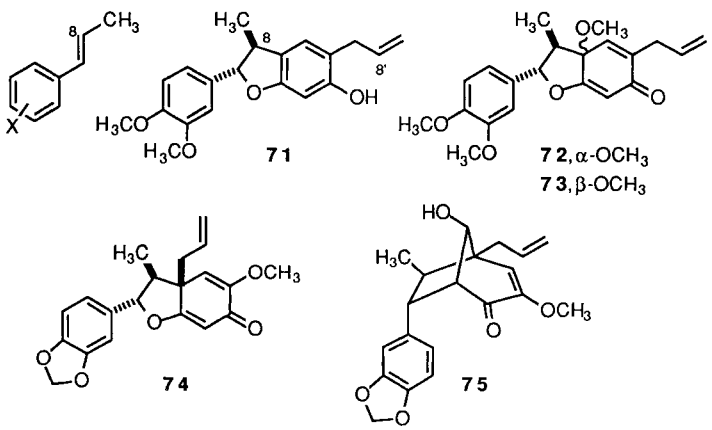
Figure 2b.

3. Synthetic Applications

3.1 Syntheses of Neolignans

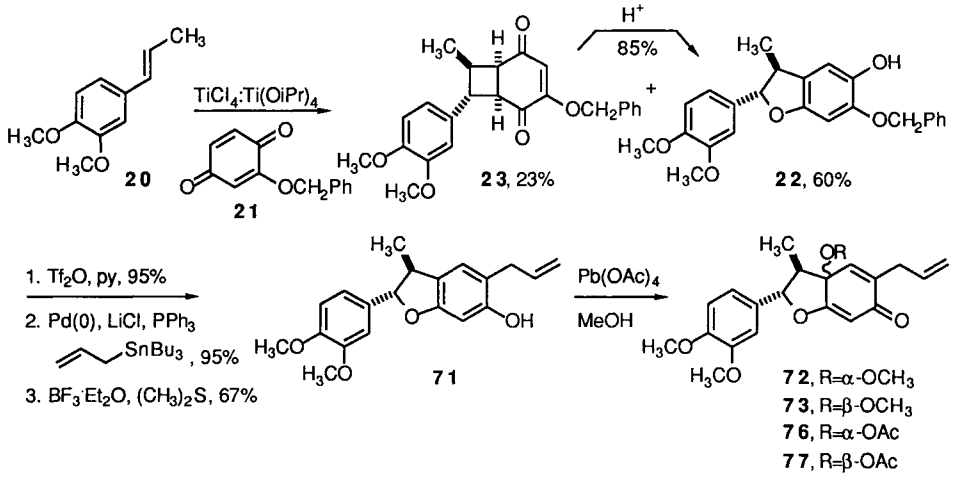
Neolignans are naturally occurring dimers of propenyl phenols in which the dimers are coupled through carbons other than C-8 and C-8'; those that are coupled through these atoms are termed lignans (27). Many neolignans are highly oxidized and the structural diversity found in these systems is impressive with more than 30 different classes characterized thus far. Liliflol B, **71**, kadsurenone, **72**, and denudatin B, **73**, are representatives of one class and burchellin, **74**, and guianin, **75**, are examples of two other classes. There has been considerable interest in synthesis of neolignans due to their powerful and varied biological activity, as enzyme and growth inhibitors (bacteria, fungi and plant), as antitumor, antileukemic, antiviral, antimitotic, and immunosuppresant agents, and as insect antifeedants, among many other activities. Kadsurenone in particular has attracted much attention as a potent, orally active platelet-activating factor (PAF) receptor antagonist (28a-c). PAF has been implicated in a variety of pathophysiological conditions and interest in PAF antagonists arises from their potential therapeutic value in allergy and immune disorders including asthma, endotoxin shock, organ transplant rejection, rheumatiod arthritis, infertility and stroke, among others (28).



Büchi (11) and Yamamura (12) originally demonstrated the utility of cycloaddition reactions of styrenes with 4-oxo-2,5-cyclohexadienyl carbocations **39** in the synthesis of a number of neolignans including **74-75**. The cations were generated via solvolysis of quinone monoketals or by anodic oxidation of *p*-alkoxyphenols. Thomas (29), Swenton (19) and Angle (15) have recently expanded on these approaches. Due to the apparent similarity of the Lewis acid-promoted quinone-styrene reactions with those of **39**, the former can also be used to prepare neolignan systems. Thus, as previously described, Ti(IV)-promoted reactions of styrene **20** with quinone **21** gave dihydrobenzofuran **22** (Scheme VII, ref. 8). Some cyclobutane **23** was also produced which was converted to **22** by treatment with protic acid. Conversion of the phenol to the corresponding triflate followed by Pd(0)-catalyzed coupling with allyltributyltin and selective debenzylation with

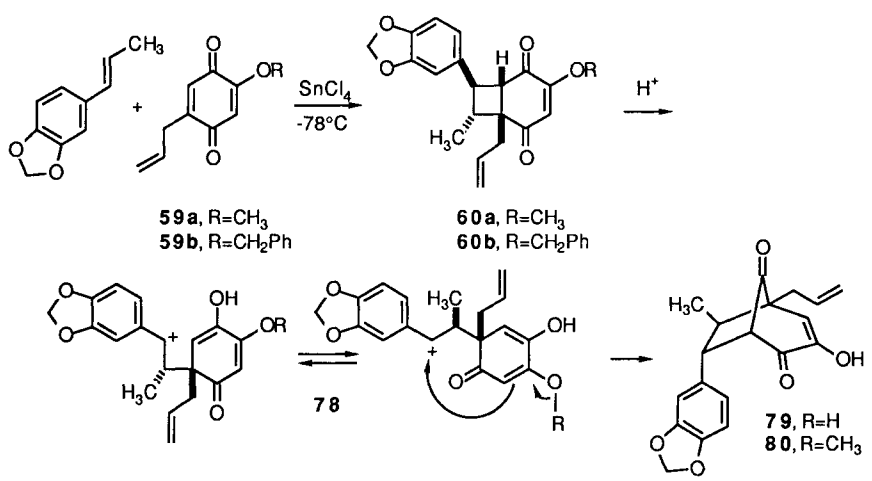
$BF_3{\cdot}Et_2O/(CH_3)_2S$ gave liliflol B, **71**, in good overall yield. Oxidation of **71** with methanolic lead tetraacetate gave kadsurenone, **72** and denudatin B, **73**, in 10% and 19% yields, respectively (28b,c). A 1:1 mixture of the epimeric acetates **76/77** was also produced in 48% yield. Although the yield of **72** formed in the last step is low, this is a very direct preparation of kadsurenone.

Scheme VII



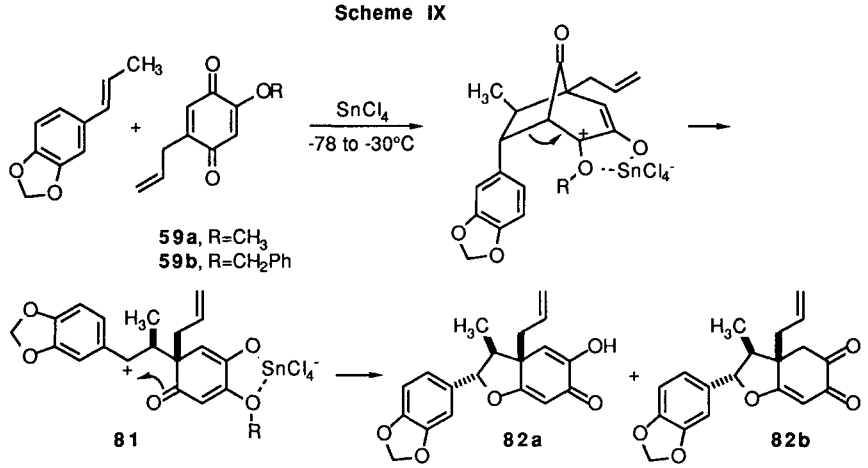
Cyclobutanes **60a/b** resulted from $SnCl_4$-promoted reactions of isosafrole with quinones **59a/b** at -78°C as described above (21). Treatment of either of these cyclobutanes with protic acids gave **79** in 48-67% yields, presumably via **78** (Scheme VIII). Methylation of **79** yielded **80** (80%) which has previously been converted to quianin, **75** (12a).

Scheme VIII

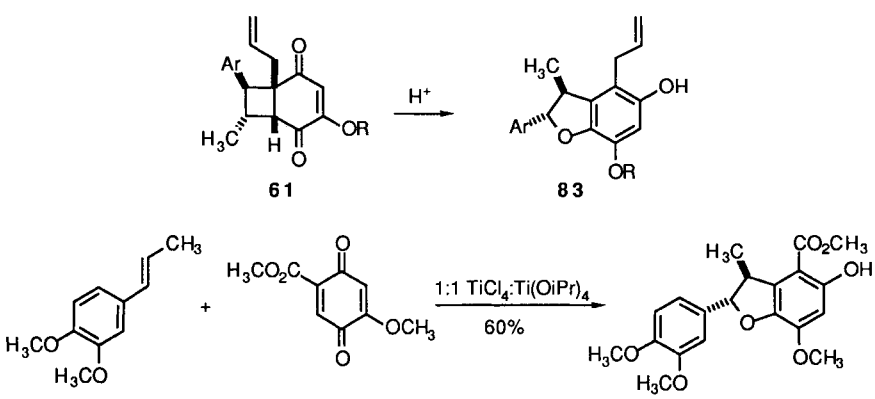


If the Sn(IV)-promoted reaction of isosafrole with quinone **59b** was allowed to warm to -30°C, a mixture of keto-enol tautomers **82** was produced in 69% yield (Scheme IX). The reaction probably proceeds as shown in the Scheme, although cyclobutane **60b** may also be an intermediate. The difference in reactivity between cations **78** and **81** is interesting. Apparently, coordination of the $SnCl_4$ to the enol ether oxygen in **81** lowers the nucleophilicty of this moiety and attack of the carbocation on the carbonyl oxygen followed by dealkylation occurs. Methylation of the mixture of **82a/b** yielded burchellin, **74** (80%).

Scheme IX



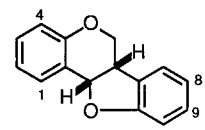
Cyclobutanes **61**, formed from the Ti(IV)-promoted reactions of styrenes with quinones **59a/b**, also undergo rearrangement upon treatment with H^+ to give dihydrobenzofurans **83** in 45-67% yield. Although the substitution pattern in **83** has not been found in a natural product to our knowledge (35), various other 7-alkoxy-2-aryl-3-methyl-2,3-dihydrobenzofurans have been found to exhibit antibacterial and immunosuppressant activity (36) and the rearrangement of **61** is noteworthy as a means to access compounds with related structures. Lewis acid-promoted reactions of styrenes with 2-carbomethoxy-5-methoxy-1,4-benzoquinone provide another approach to 7-alkoxy-2-aryl-2,3-dihydrobenzofurans.



A major advantage of the quinone-styrene reactions over other reported methods for synthesis of the neolignans is the potential for asymmetric induction in reactions promoted by chiral Ti(IV) complexes. As described above, we have already reduced this concept to practice in the context of synthesis of 2-aryl-3-methyl-2,3-dihydrobenzofurans and 7-aryl-6-methylbicyclo[3.2.1]oct-3-en-2,8-diones, frameworks present in a number of neolignan systems, and we are currently exploring the preparation of several neolignans in enantiomerically pure form. As of this writing, there have been no reported asymmetric syntheses of neolignans (27d).

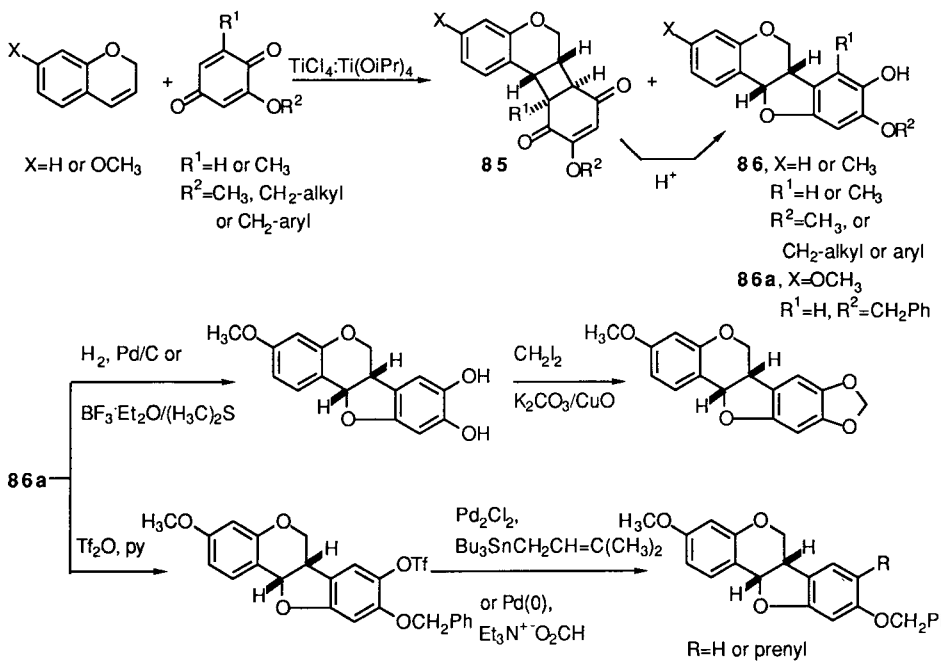
3.2 Synthesis of Pterocarpans

Pterocarpans are natural products possessing the fused benzopyrano-benzofuran structure **84**. Many are phytoalexins that display potent antimicrobial properties (30) and recently a number of pterocarpans have been found to be effective inhibitors of HIV-1 reverse transcriptase (31). The pterocarpans incorporate a 2-aryl-2,3-dihydrobenzofuran unit and these systems can be accessed directly from reactions of 2H-benzopyrans with a variety of 2-alkoxy-1,4-benzoquinones (Scheme X, ref. 30). Again, depending upon conditions, these reactions can be made to produce the



84

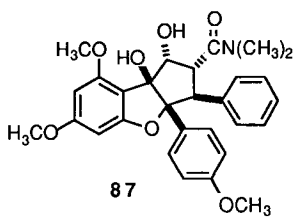
Scheme X



cyclobutanes **85** or the pterocarpans **86** and the former rearrange efficiently to the latter upon treatment with H^+. An enantioselective synthesis has been demonstrated utilizing the Ti(IV)-diol-**67** complex as a promoter which produced a number of pterocarpans **86** (X=H, OCH_3; R=H, CH_3; and R=CH_3) in greater than 60% yield and in 75-85 % ee (23). A noteworthy feature of this approach is the synthetic versatility of **86a** as an intermediate in the preparation of other pterocarpans. The C-8 phenolic and C-9 benzyloxy groups can both be selectively manipulated as shown.

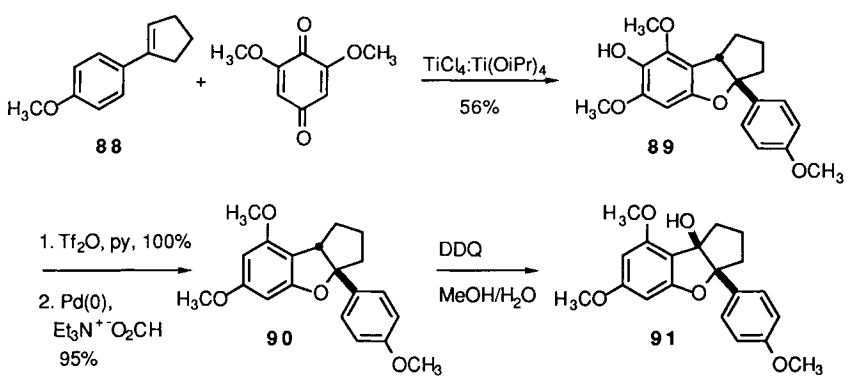
3.3 Approaches to Other Naturally Occurring 2-Aryl-2,3-dihydrobenzofurans

Rocaglamide, **87**, is a natural product that exhibits potent antileukemic activity. Several syntheses of rocaglamide have been reported (32). Our approach to its synthesis is through a Lewis acid-promoted quinone-styrene reaction. We have established the validity of the approach through the reaction of 2,6-dimethoxy-1,4-benzoquinone with 1-arylcyclopentene **88** as a model system (Scheme XI). Dihydrobenzofuran **89** was found in 56% yield and the unneccessary phenolic moiety in **89** was removed via a Pd(0)-catalyzed triethylammonium formate reduction of the triflate to give **90**. Oxidation of **90** with DDQ in aqueous methanol gave **91**. Efforts are currently underway to adapt this method to the synthesis of rocaglamide.



87

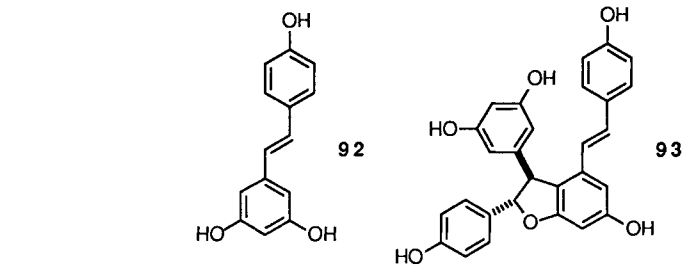
Scheme XI



88 **89** **90** **91**

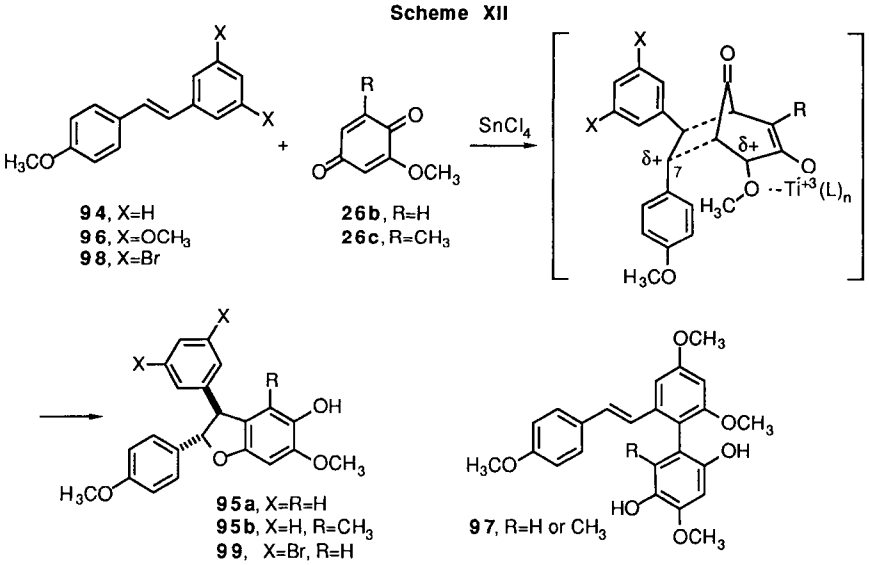
Oxidative oligomerization of resveratrol, **92**, gives rise to a number of natural products (33). One is the antifungal agent ε-viniferin, **93** (34). As a synthetic approach to ε-viniferin, and perhaps as a starting point to other resveratrol oligomers as well, we have explored reactions of quinones with stilbenes under the influence of Lewis acids (Scheme XII). The $SnCl_4$-promoted reaction of **26b/c** with **94** gave dihydrobenzofurans **95a/b** in 73 and 82% yields, respectively. The regioselectivity

follows from the mechanistic discussion presented above. In an asynchronous cycloaddition, a preference would be expected for a transition state in which the developing positive charge at C-7 is stabilized by the *p*-methoxy substituent. Unfortunately, reactions of trimethoxystilbene **96** with **26a/b** gave mainly biphenyls **97** (52 and 78% yields), apparently via an electrophilic aromatic substitution process. As a potential surrogate for **96**, reaction of the dibromo-stilbene **98** with quinone **26b** was investigated and found to give dihydrobenzofuran **99** in 90% yield. We are currently exploring the conversion of **99** to ε-viniferin.



92 **93**

Scheme XII



94, X=H
96, X=OCH_3
98, X=Br

26b, R=H
26c, R=CH_3

95a, X=R=H
95b, X=H, R=CH_3
99, X=Br, R=H

97, R=H or CH_3

4. CONCLUSION

The Lewis acid-promoted reactions of 1,4-benzoquinones with styrenyl systems provide direct access to complex structural frameworks found in several different classes of biologically important natural products in just one or two steps. Not only can the reactions be manipulated to selectively access any one of four different products of formal cycloaddition, but each of the products is obtained stereoselectively. In addition, chiral Lewis acids can be used to provide the products in nonracemic form. These versatile reactions significantly extend the synthetic utility of quinones as important and readily available starting materials.

ACKNOWLEDGEMENTS

I would like to thank the very talented group of students who are responsible for the research presented in this account. Without the dedication, hard work and insight of Mike Letavic, Keith Combrink, Jay Reddy, Donna Wei, Ken Lynch, Jim Ray, Bill Draney and Greg Gfesser, this work would not have been completed. Of course, other individuals including M. H. Ali, W. Falter, S. Naganathan, U. Sampath, S. Andruski and A. Ahmed also contributed to the well-being of the group and I wish to acknowledge their efforts as well. Finally, I acknowledge with gratitude financial support from the State of Kansas, the National Institutes of Health, the National Science Foundation, the American Chemical Society-Petroleum Research Fund, the Alfred P. Sloan Foundation and Eli Lilly and Company.

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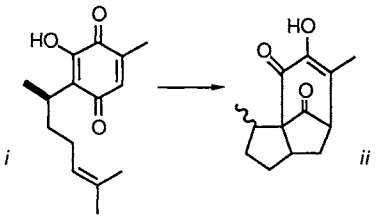

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Biogenesis-Like Transformation of 4-Substituted Phenols by Photooxygenation

K. Endo

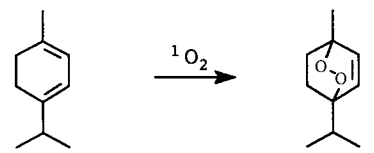
1. INTRODUCTION

Molecular oxygen constitutes about one fifth of the global atmospheric air, and hence, it is one of the most abundant and inexpensive natural resources, and can be utilized as a very useful reagent in synthetic organic chemistry. Since the electronic configuration of the oxygen molecule aquires a triplet state in the ground state [1~5], it is involved in radical type reactions such as autoxidation of benzylic positions [6~8]. In addition, by very simple modifications, it can be transformed into ozone, singlet oxygen or peroxides, all of which are excellent synthetic reagents as well. Thus, ozone adds to, by 1,3-dipolar cycloaddition, and cleaves carbon-carbon double bonds under very mild conditions [9,10]. Singlet oxygen however reacts with various olefins mostly in three modes [1~5], as shown in Scheme 1. Namely, it adds to 1,3-dienes by the Diels-Alder type mechanism, and gives such cyclic peroxides as ascaridol (**2**) (Scheme 1, a)) [11~13]. In the case of sterically hindered and electron rich olefins like **3**, a 1,2-cycloaddition reaction will take place, and unstable dioxetane **4** can be obtained (Scheme 1, b)) [14~16]. But in most cases, it participates in the ene reaction, a concerted pericyclic reaction involving six electrons, to yield allylic alcohols. Dihydromyrcene (**5**) afforded two hydoperoxides **6** and **7** by this type of reaction (Scheme 1, c)) [17~20]. Hydrogen peroxide, on the other hand, is used commonly for epoxidation of α,β-unsaturated ketones, or cleavage of α-dicarbonyl compounds to dicarboxylic acids [21~24], while organic peracids are preferentially employed in the preparation of epoxides [25], as well as in the Baeyer-Villiger reaction [26]. Chiral metal complexes of *t*-butyl hydroperoxide are known to result enantioselective epoxidation [27,28].

Despite such a wide diversity of usage, reaction mechanisms of active oxygen species are sometimes very complicated, and hence, the chemistry of these reagents is not sufficiently understood. For example, hydrogen peroxide can yield such reactive chemical species

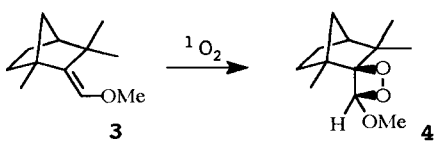
as hydroperoxide anion HOO^-, hydroperoxyl radical $HOO^{\cdot}$, hydroxyl radical $HO^{\cdot}$ and hydroxide anion HO^-, depending on the reaction conditions [1~3]. Further, they may react with substrates or solvents used, and yield the respective organic hydroperoxides or related radicals, and these secondary active species could also work as oxidants in such a reaction. Therefore, it is neither easy to interpret the reaction mechanism correctly, nor to control the reaction along the lines intended. Because of such characteristics, however, the chemistry of oxidation and oxygenation still remains interesting and challenging.

a) 1,4-Cycloaddition



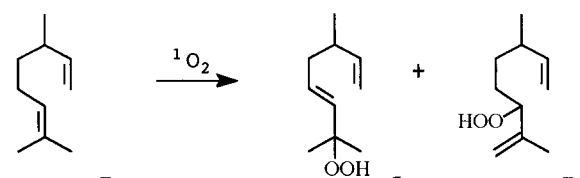
1 **2**

b) 1,2-Cycloaddition



3 **4**

c) Ene Reaction



5 **6** **7**

Scheme 1. Reaction of Singlet Oxygen and Olefins.

In addition, the term "active oxygen species" is frequently quoted in the biological field recently. The accumulated knowledge in this area illustrates the importance of these species, because they are directly related to many important physiological phenomena and diseases. For example, the active oxygens trigger the metabolic cascade of arachidonic acid, which is primarily

responsible for various physiological control mechanisms such as blood clotting, inflammation or allergy [29~31]. Generation of oxidants by polymorphous neutrophile causes cytolysis which is related to the principal defence mechanism for viral and bacterial infections [32~36]. Lipid peroxidation and related oxidative stress, due to the excessive production of oxidants or due to the shortage of antioxidants, are among the most important direct causes of various diseases such as hepatitis, arteriosclerosis or intestinal ulcers [37,38]. It is also claimed as one of the main processes of aging [39~42]. Oxidative tissue damage is pointed out as more serious problem than the injury itself, on ischemia-reperfusion [43~45]. Further, the active oxygens are involved in the initiation and propagation of tumors by oxidative damage of chromosomal DNA [46~48], while cancer therapy, with such antibiotics as bleomycin, mitomycin or adriamycin, is also dependent on the same mechanism [49~52].

It should also be borne in mind that such biochemical roles of active oxygen are not only limited to the mammalian physiochemical processes, but appear to be rather universal. Hot hydrogen peroxide is ejected by an insect for securing himself from predators [53], and cellular encapsulation caused by a phenol oxidase system seems to be the major defence mechanism of insects against their parasites [54]. The mechanism of protection in plants from their pathogens is associated with prompt induction of oxygenase systems, and depends very much upon the utilization of active oxygen for production of phytoalexins [55~58].

Although there have been significant accomplishments in the chemical investigation of the active oxygen species [1~3], it is not yet possible to write the detailed reaction mechanisms for such interesting biochemistry.

The term "active oxygen species" is referred to, in these cases, in a rather broad sense, and singlet oxygen, superoxide anion radical, hydroperoxide anion, hydroxyl radical and other related oxidizing species are included. They are listed in Table 1.

There are not many occasions in living systems, when singlet oxygen is generated by a photochemical process, but photoallergy is a related phenomenon, while chemical induction of such oxygen species by the action of cytochrome C system may be possible [59]. Superoxide anion radical may be the most common biological active oxygen, formed by one electron reduction of molecular oxygen. Usually in the living system, the superoxide anion is immediately

transformed to hydrogen peroxide and molecular oxygen by the action of superoxide dismutase, and catalase successively decomposes hydrogen peroxide to molecular oxygen and water, while a portion of the anion may be protonated to give a hydroperoxyl radical (Table 1) [1~3]. Further, the regenerated molecular oxygen may also be recycled to superoxide anion by one electron reduction, and a portion of the anion could be transformed again into a whole set of active oxygen species like hydrogen peroxide, hydroperoxyl radical, hydroperoxide anion and so on [1~3].

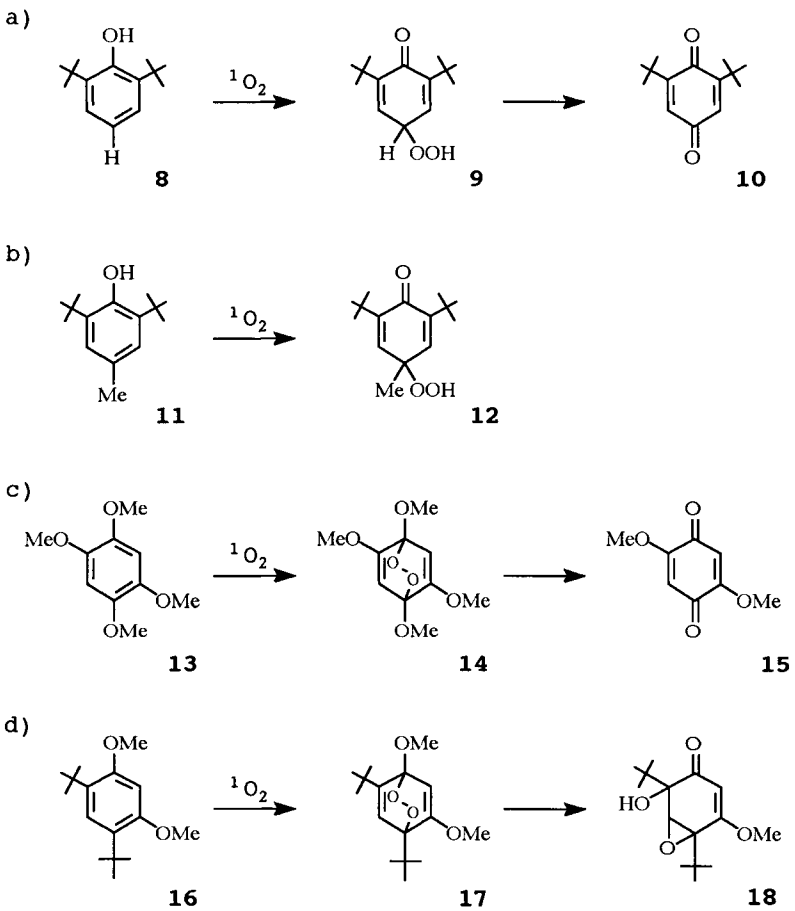
Therefore, not only is it important to determine what is the initially formed oxidant, but it is even more important to unravel the reaction which is occurring.

Table 1. Major Active Oxygen Species

molecular species	mode of formation
singlet oxygen $^1O_2$	$O_2 + Dye^* \rightarrow {}^1O_2 + Dye$
	$ROOR \rightarrow {}^1O_2 + RR$
superoxide anion radical $OO^{\cdot -}$	$O_2 + e^- \rightarrow OO^{\cdot -}$
hydroperoxide anion HOO^-	$2\ OO^{\cdot -} + H^+ \rightarrow HOO^- + O_2$
	$HOOH + OH^- \rightarrow HOO^- + H_2O$
hydroperoxyl radical $HOO^{\cdot}$	$OO^{\cdot -} + H^+ \rightarrow HOO^{\cdot}$
peroxyl radical $ROO^{\cdot}$	$ROOH + X^{\cdot} \rightarrow ROO^{\cdot} + HX$
	$R^{\cdot} + O_2 \rightarrow ROO^{\cdot}$
	$ROO^{\cdot} + RH \rightarrow ROOH + R^{\cdot}$
hydrogen peroxide HOOH	$HOO^- + H^+ \rightarrow HOOH$
hydroxyl radical $HO^{\cdot}$	$HOOH + e^- \rightarrow HO^{\cdot} + OH^-$
	$HOOH + X^{\cdot} \rightarrow HO^{\cdot} + XOH$

Aromatic hydrocarbons are stable to the usual oxidation reactions, but electron rich aromatic systems such as phenolic compounds are susceptible to electrophilic attack by active oxygen species. Owing to their aromatic stability, however, most of the initially formed charge-transfer like complexes could be stabilized and live long enough to be deactivated eventually, without participating in further transformations. Therefore, phenols act as very good quenchers of active oxygen species. α-Tocopherol and its analogs are very efficient scavengers of hydroxyl radical as well as singlet oxygen in the biological systems [60]. Flavonoids and tannins are also known to be excellent natural antioxidants [61~64].

Nevertheless, singlet oxygen adds slowly to *para* position of phenols to yield 4-hydroperoxycyclohexa-2,5-dienones such as **9** and **12**, and if the *para* position is unsubstituted like **9**, the product will be subsequently decomposed to a parabenzoquinone (**10**) (Scheme 2, a)), while in the substituted cases, such dienone hydroperoxides as **12** may remain unchanged (Scheme 2, b)) [65~67].

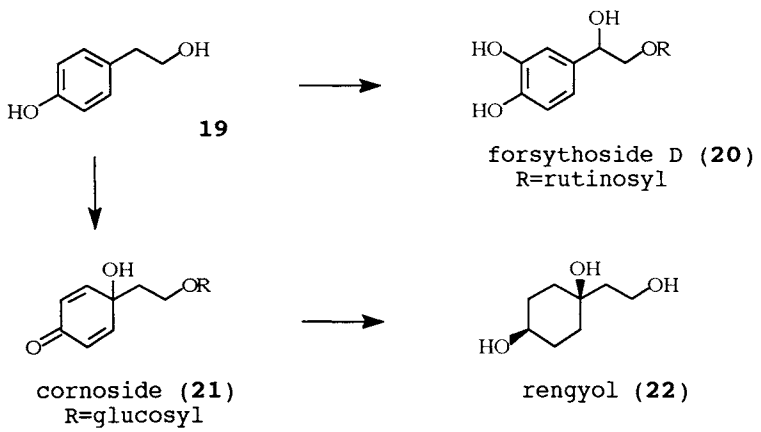


Scheme 2. Reaction of Singlet Oxygen and Phenol Derivatives.

In the case of electron rich phenyl ethers like **13** and **16**, on the other hand, endoperoxides **14** and **17** may be formed, and they are transformed further to a quinone **15**, an epoxyalcohol **18** (Scheme 2, c), d)) or diepoxides, depending on the reaction conditions as well as the nature of substituents [67].

During the course of our chemical investigation on the isolation and structure determination of the pharmacologically active constituents of traditional Chinese herbal drugs, *Forsythia suspensa* fruits afforded a number of new natural substances having C_6-C_2 type carbon skeletons with oxygeneous substituents.

It was further noted, that such systems could be derived from a common phenolic substance, 4-hydroxyphenylethanol (**19**), by sequential oxidative transformations to forsythoside D (**20**), cornoside (**21**) and rengyol (**22**), as shown in Scheme 3.



Scheme 3. Proposed biogenetic Relationship of Forsythoside D, Cornoside and Rengyol.

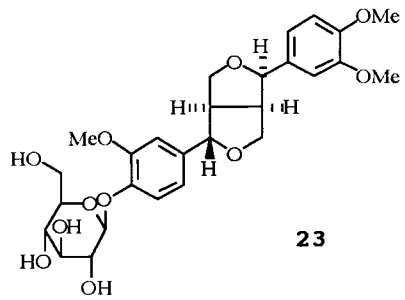
It thus appeared very attractive to follow these plausible biogenetic processes with emphasis of the reaction of phenolic compounds with active oxygen species, because it may suggest their actual biosynthetic pathways, or otherwise, provide some insights on such oxygenation reaction mechanisms.

2. BIOGENESIS-LIKE TRANSFORMATION OF THE *FORSYTHIA SUSPENSA* CONSTITUENTS AND RELATED NATURAL PRODUCTS

2.1 Constituents of *Forsythia suspensa*

The crude drug originating from the fruits of *Forsythia suspensa* (Fam. Oleaceae) is called RENGYO, and is used in the traditional Chinese medicine (KAMPO) as an antiinflammatory, a drainage or an antidote. It was also known to exhibit strong antibacterial effect, which was formerly ascribed to a lignane

glucoside, forsythin (phillyrin, **23**) [68,69]. Later, new phenol glycosides, forsythoside A (**26**) and forsythoside C (**24**), were isolated, and considered to be primarily responsible for such activity (Scheme 4) [70-72].



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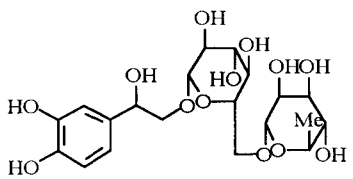

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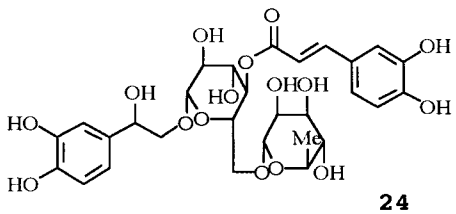

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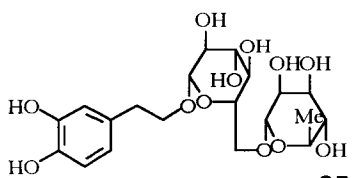

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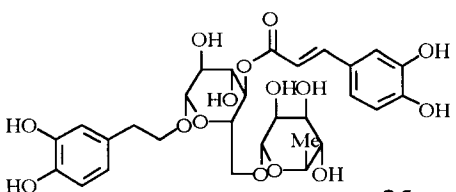

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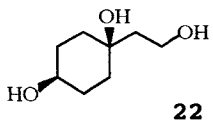
Scheme 4. Antibacterial Constituents of *Forsythia suspensa* Fruits.

Further, by more extensive surveys of the constituents in the crude drug, water soluble polar fractions of the methanol extract afforded two new related glycosides, forsythoside D (**20**) and forsythoside E (**25**) [72], five new cyclohexylethanol derivatives, rengyol (**22**), isorengyol (**27**), rengyoxide (**28**), rengyolone (**29**) [73-76] and suspenol (**30**) [77], and three new cyclohexylethyl glucosides, rengyoside A (**31**), rengyoside B (**32**) and rengyoside C (**33**) [78] in addition to two the known natural 4-hydroxyphenylethyl glucosides, salidroside (**34**) and cornoside (**21**) [73,78,79]. They

are classified, based on the structural features of the C_6-C_2 moieties, and are listed in Scheme 5.

a) Cyclohexylethanols



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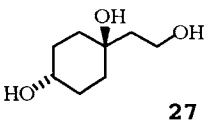

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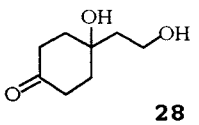

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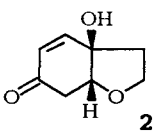

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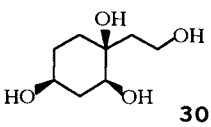

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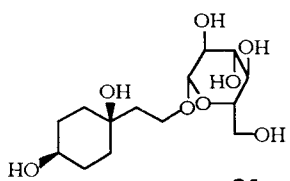
b) Cyclohexylethyl glucosides



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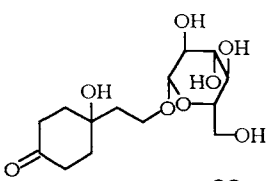

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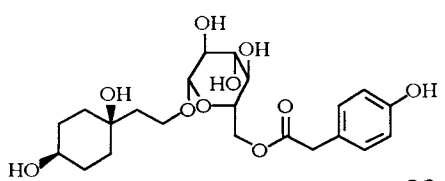

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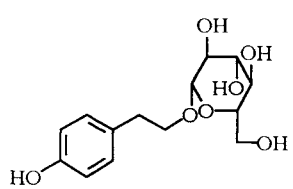
c) 4-Hydroxyphenylethyl glucosides



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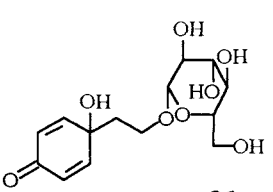

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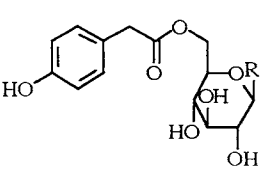

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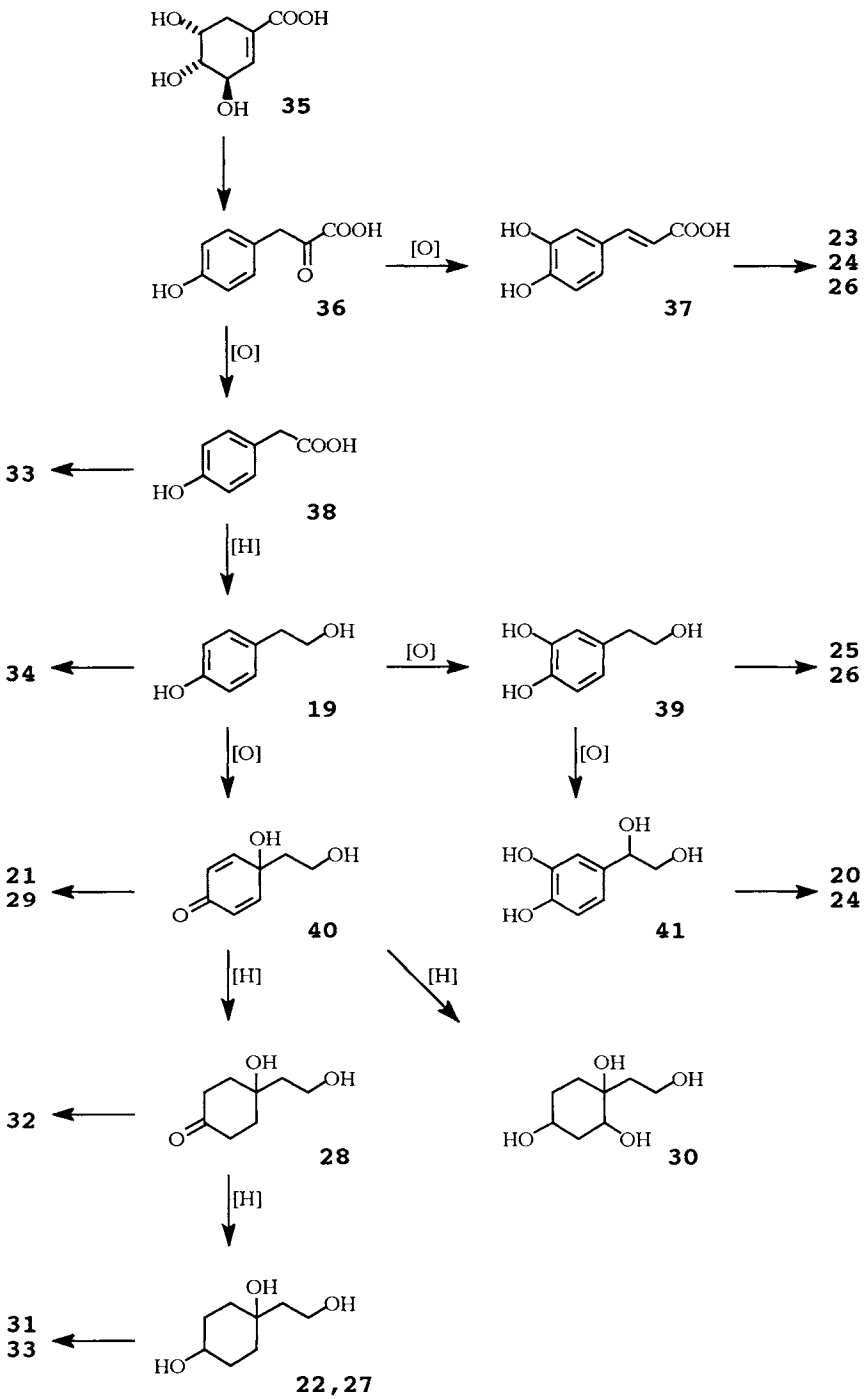
(R=22)

Scheme 5. C_6-C_2 Type Compounds of *Forsythia suspensa* Fruits.



Scheme 6. Possible biogenetic Relationship of C_6-C_3 and C_6-C_2 Moieties of *Forsythia suspensa* Constituents.

By contrasting the chemical structures of these constituents, it became very plausible that all of these natural products could belong to the metabolic group of shikimic acid (**35**) [80-82], and 4-hydroxyphenylpyruvic acid (**36**) may be assigned as the nearest common precursor of these substances. Further, these structures could be so arranged as to represent possible pathways of biological transformations as shown in Scheme 6.

Namely, by oxidative modifications of 4-hydroxyphenypyruvic acid (**36**), catechol derivatives and caffeic acid (**37**) may be obtained. The former corresponds to the lignan derivatives such as phillyrin (**23**), and the latter occurs in the antibacterial glycosides, forsythosides A (**24**) and C (**26**). Further, by oxidative decarboxylation, the precursor **36** may also be converted to 4-hydroxyphenylacetic acid (**38**), which in turn will be reduced to 4-hydroxyphenylethanol, tyrosol (**19**). This phenol **19** might be a key substance in the biosynthesis of the C_6-C_2 type carbon skeleton appearing in the crude drug constituents, since it may be oxygenated sequentially to the catechol **39** and to the benzyl alcohol **41**, both of which constitute the aglycon parts of the important antibacterial constituents, the forsythosides. In addition, by oxygenation at the *para*-position, tyrosol (**19**) may be transformed into a quinol **40**, which will be reduced successively to rengyoxide (**28**) and rengyol (**22**) (Scheme 6).

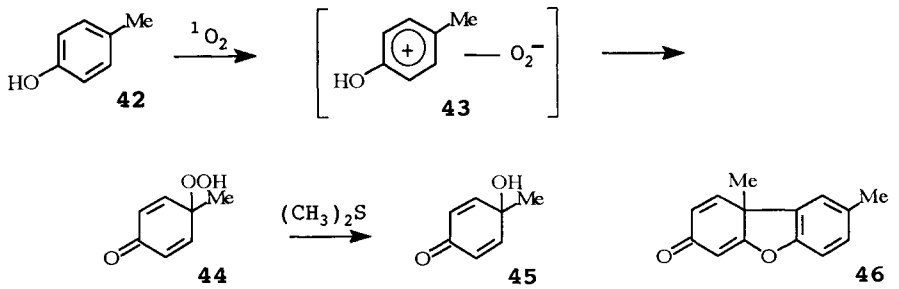
Thus, it was decided to imitate these plausible biogenetic transformations *in vitro*, in order to substantiate these processes as viable biogenetic pathways, as well as for investigation of the reaction of phenolic compounds and active oxygen species [78,83].

2.2 Oxygenation of Paracresol

Photosensitized oxygenation of paracresol (**42**) by singlet oxygen, with rose bengal as a sensitizer, yielded the expected 4-hydroperoxy-4-methylcyclohexa-2,5-dienone (**44**) in good yields [65, 83].

The reaction proceeded at reasonable rates in methanol, but went much slower in ethyl acetate (Table 2). This trend, however, is opposite to what is anticipated from the life time of singlet oxygen in these solvents. [84-86]. Since singlet oxygen has been assigned as the reactive species in this type of reactions [87], the reverse order of the reaction rate to the life time, depending on the solvent, may be attributed to the ionic nature of the crucial process. The oxygenation mechanism has already been discussed in

detail in the literatures, but in brief, the excited complex **43** having strong charge transfer character between the singlet oxygen and an electron rich phenol will be transformed into the product by a proton transfer process followed by recombination, in the type-II photooxidation [88~90].



Scheme 7. Photooxygenation of Paracresol.

A small amount of a dimeric compound **46** [91~93] was always obtained in this reaction, but its yield was not dependent on the solvent polarity (Table 2). Thus, the dimerization reaction may be mechanistically different from the para-dioxygenation.

A portion of the hydroperoxide **44** was reduced slowly and yielded the corresponding hydroxide, 4-hydroxy-4-methylcyclohexa-2,5-dienone (**45**), during the photooxygenation, by exhibiting two product spots on thin layer chromatograms. The hydroperoxide was also reduced readily with dimethyl sulfide or thiourea to give **45**

Table 2. Effects of Solvent on the Singlet Oxygen Life Time and Product Yield in Paracresol Photooxygenation

solvent	$^1O_2$ life time (sec)*	quinol (**45**) (%)**	dimer (**46**) (%)**
water	3×10^{-6}	80***	
methanol	1×10^{-5}	64	3
acetone	5×10^{-5}	32	3
ethyl acetate		6	1
chloroform	2×10^{-4}		

* life time [84]
** paracresol 1.08 g (10 mmole); rose bengal 100 mg; solvent 150 ml; oxygen bubbling under stirring below 40°C.
*** yield determined after 5 hours irradiation followed by reduction with dimethyl sulfide.

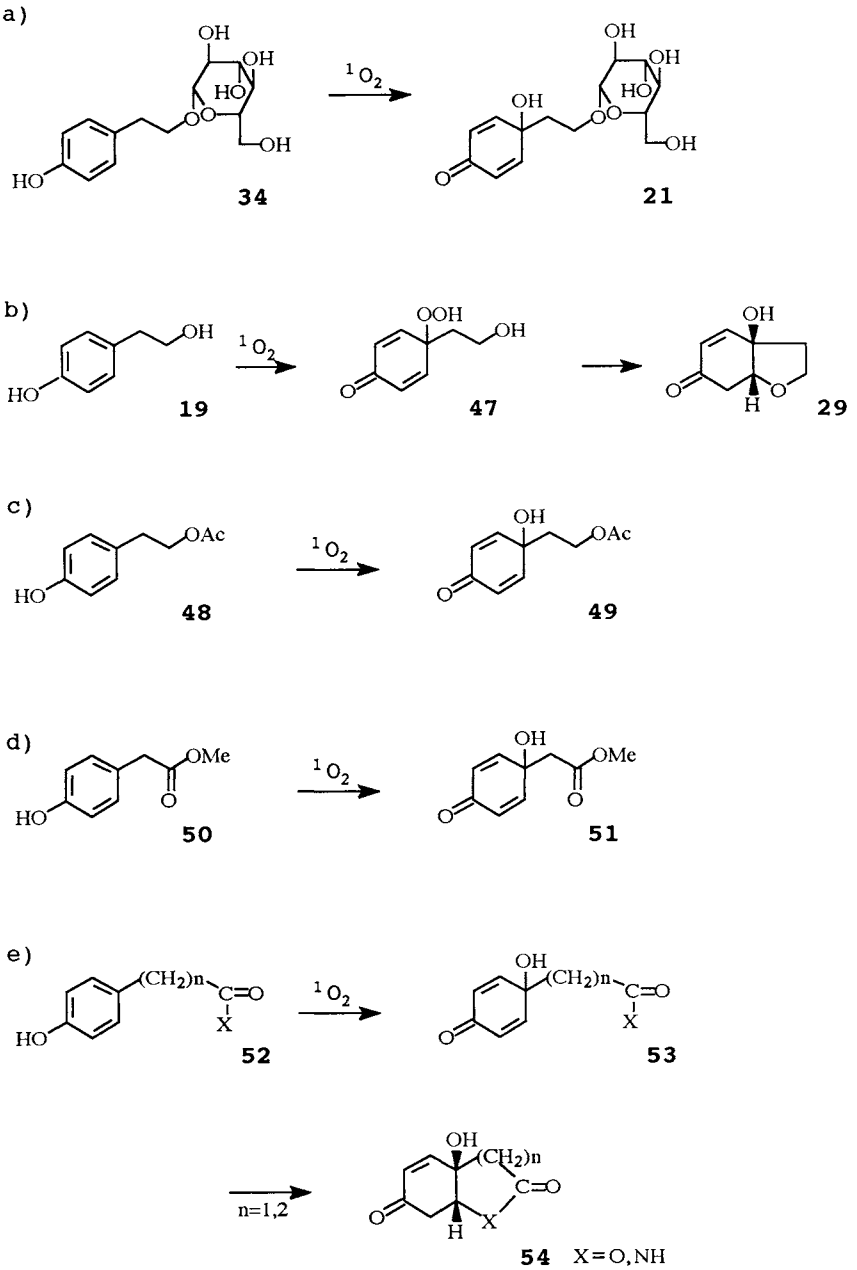
quantitatively. Both dienones **44** and **45** were found to be fairly stable, and they could be purified by recrystallization from ethyl acetate and methanol.

2.3 Photosensitized Oxygenation of Tyrosol and its Analogs

Experimental results, described in the previous section, have indicated that polar hydroxylic solvents, like water and methanol, are good reaction media for the photosensitized oxygenation of phenols, even though the life time of singlet oxygen is much shorter than in non-polar ones (Table 2). Accordingly, several natural quinol derivatives, cornoside (**21**), rengyolone (**29**), hallerone (**49**) [94] and jacaranone (**51**) [95~97], have been synthesized by this reaction in methanol, from appropriate para-substituted phenols (Scheme 8).

For example, irradiation of a methanolic solution of salidroside (**34**), with rose bengal and oxygen bubbling at room temperature, afforded cornoside (**21**) in good yields (80%) [83]. However, the reaction was found to be considerably slower, compared with the rate for paracresol (**42**), probably due to the large steric hindrance of the glucosyl group in salidroside (**34**). On the other hand, reaction of tyrosol (**19**) proceeded at reasonable rates and probably yielded a hydroperoxide **47**. The photoproduct, however, was not stable enough for isolation, nor was it even detectable by thin layer chromatography, and cyclized spontaneously, through a Michael addition, to rengyolone (**29**) [83,98~101]. Tyrosyl acetate (**48**) was similarly oxygenated to yield hallerone (**49**) [83,100,101]. The yields of these two products, **29** and **49** were not so high and hallerone (**49**) especially showed a tendency to decompose during the oxygenation reaction, or on standing in air. The phenol ester **50** was similarly oxidized to afford the corresponding para-oxygenated product, jacaranone **51** [100].

It is also worthy to note that hydroxyl groups in the glucose moiety of cornoside (**21**) did not show any indication of adding to the β-positions of the dienone system, in contrast to the isomerization of quinol **47** to rengyolone (**29**). This is in accordance to the condition that only five or six membered rings may be formed by this type of intramolecular cyclization (Scheme 8 e)) [99]. Interestingly, such a Michael type addition occurs only in the intramolecular mode. As was described in the previous section, photooxygenation of paracresol (**42**) yielded only the quinols **44** and **45**, even though the reactions were carried out in water or in



Scheme 8. Syntheses of Natural Quinol Derivatives by Photooxygenation of Parasubstitued Phenols.

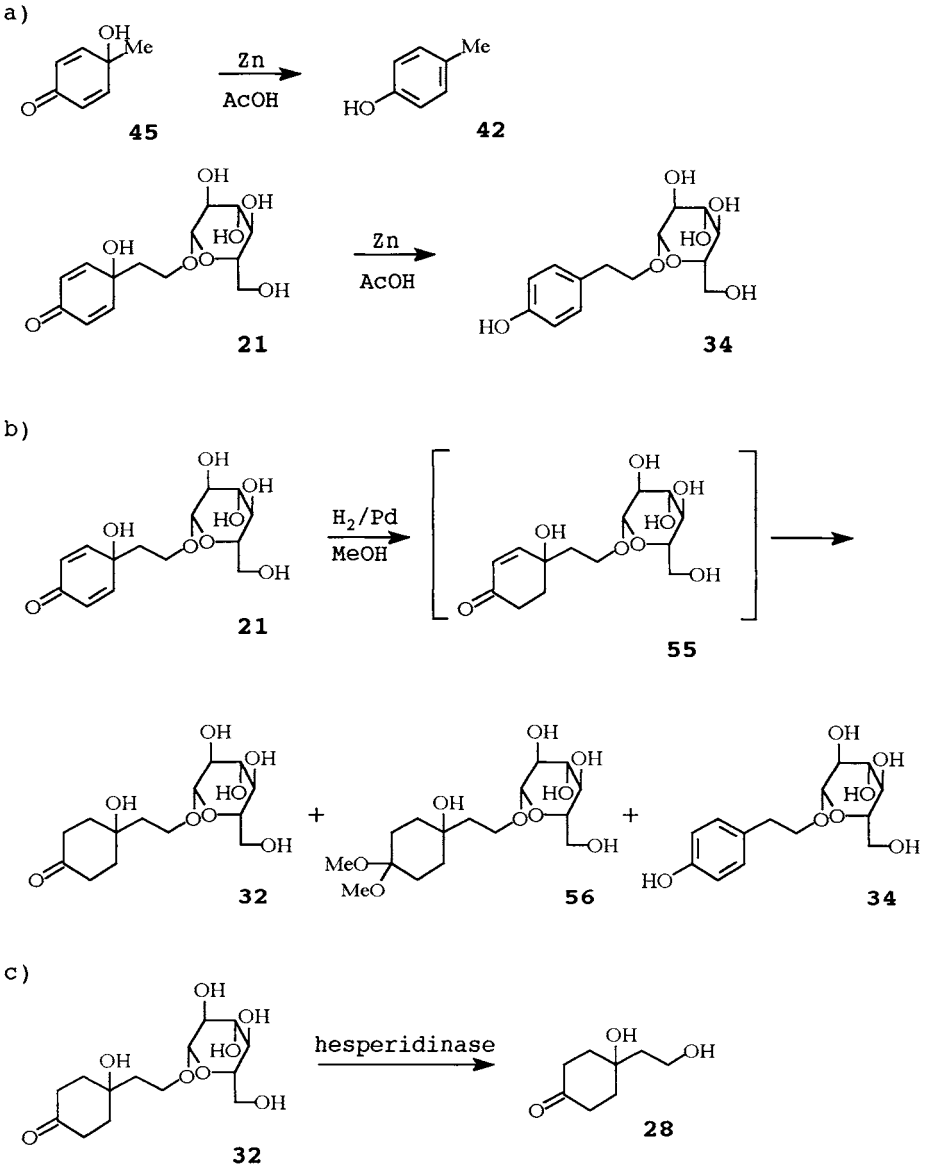
methanol. Despite full exposure of such a reactive dienone system to the polar reaction media, no intermolecular addition of such solvent molecule was observed [102].

Detailed biogenetic pathways to cornoside (**21**), rengyolone (**29**), hallerone (**49**) or jacaranone (**51**) have not been elucidated, and the reactions described in Scheme 8 suggested only a few of the various mechanistic possibilities. However, several phenol oxidase systems in plants are capable of transforming molecular oxygen to active oxygen species [59,103], and therefore, these oxidants may react with some phenols such as salidroside (**34**), tyrosol (**19**) or the acetate **48**. Among these precursors in Scheme 6, 4-hydroxyphenylethanol (**19**), and 3,4-dihydroxyphenylethanols **39** and **41** have not been identified yet in their free forms in the plant extract, probably because their contents were very low.

The CD spectrum of natural bicyclic enone **29** was examined from UV to visible range, but failed to detect any such activity [73]. This may mean that the cyclization process is not enzyme-catalyzed. Therefore, the direct biogenetic precursor of rengyolone (**29**) might also be the quinol **40** which isomerized non-enzymatically to yield a racemic product. The precursor **40** could be derived either from tyrosol (**19**) by *para*-oxygenation, or by hydrolysis of cornoside (**21**), and in fact, deglucosylation of cornoside (**21**) by acid hydrolysis or by action of hesperidinase in a citrate-phosphate buffer afforded rengyolone (**29**) exclusively and not the dienone **40** [83].

2.4 Synthesis of Rengyoside B and Rengyoxide

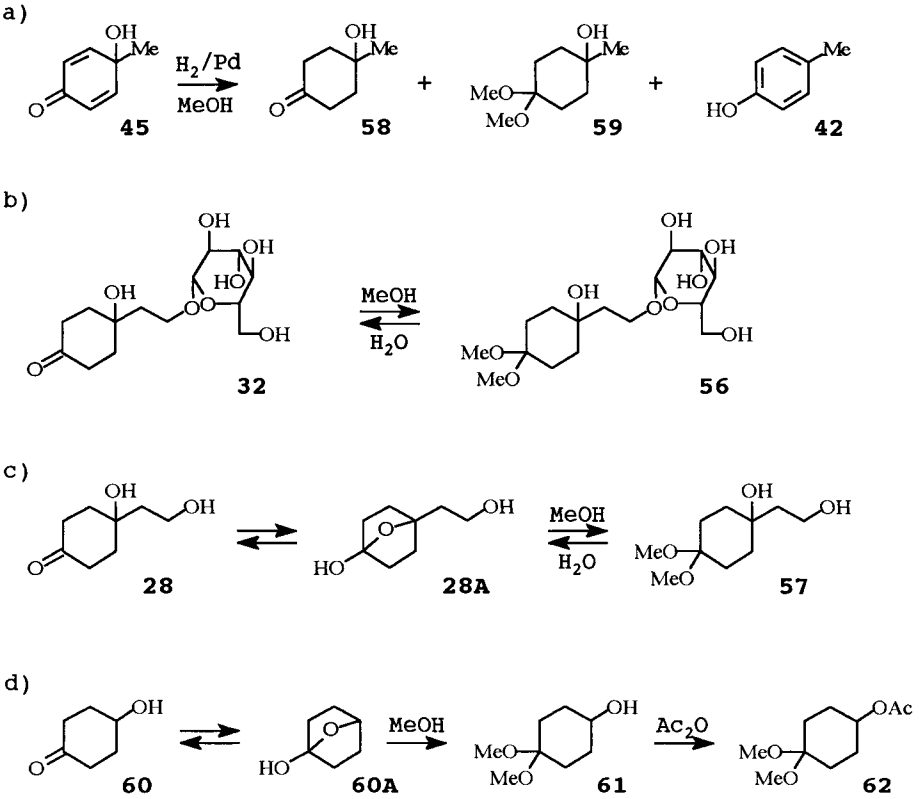
Rengyoside B (**32**) may be synthesized by reducing two olefinic double bonds of cornoside (**21**). As a test experiment, 4-methylquinol (**45**) in methanol was hydrogenated with palladium carbon as a catalyst. The reaction went easily at room temperature, and afforded the desired ketol **58** in 38 % yield, together with two by-products, a dimethyl ketal **59** (14 %) and paracresol (**42**, 40 %) (Scheme 10, a)) [83]. In the case of cornoside (**21**), however, no reaction was observed under the same conditions, probably because of severe steric hindrance of the bulky glucosyl group overhanging above the reactive dienone system. By applying a moderate pressure (10 atm) and gentle warming to 80°C, the hydrogenation proceeded slowly to give again a mixture of products, rengyoside B (**32**) and salidroside (**34**), with a ratio of 3 to 2, together with a small amount of a dimethyl ketal **56** (Scheme 9, b)) [83]. Thus the competing aromatization process of the intermedial dihydro derivative **55** was revealed to be very significant.



Scheme 9. Synthesis of Rengyoside B and Rengyoxide.

Reduction of dienone systems in cornoside (**21**) or 4-methylquinol (**45**) with zinc in acetic acid went very smoothly, but afforded the aromatization product **34** or **42**, as the sole product, respectively (Scheme 9, a)).

When the reactions were carried out in methanol, appreciable amounts of the reduction products **32** and **58** were converted to their



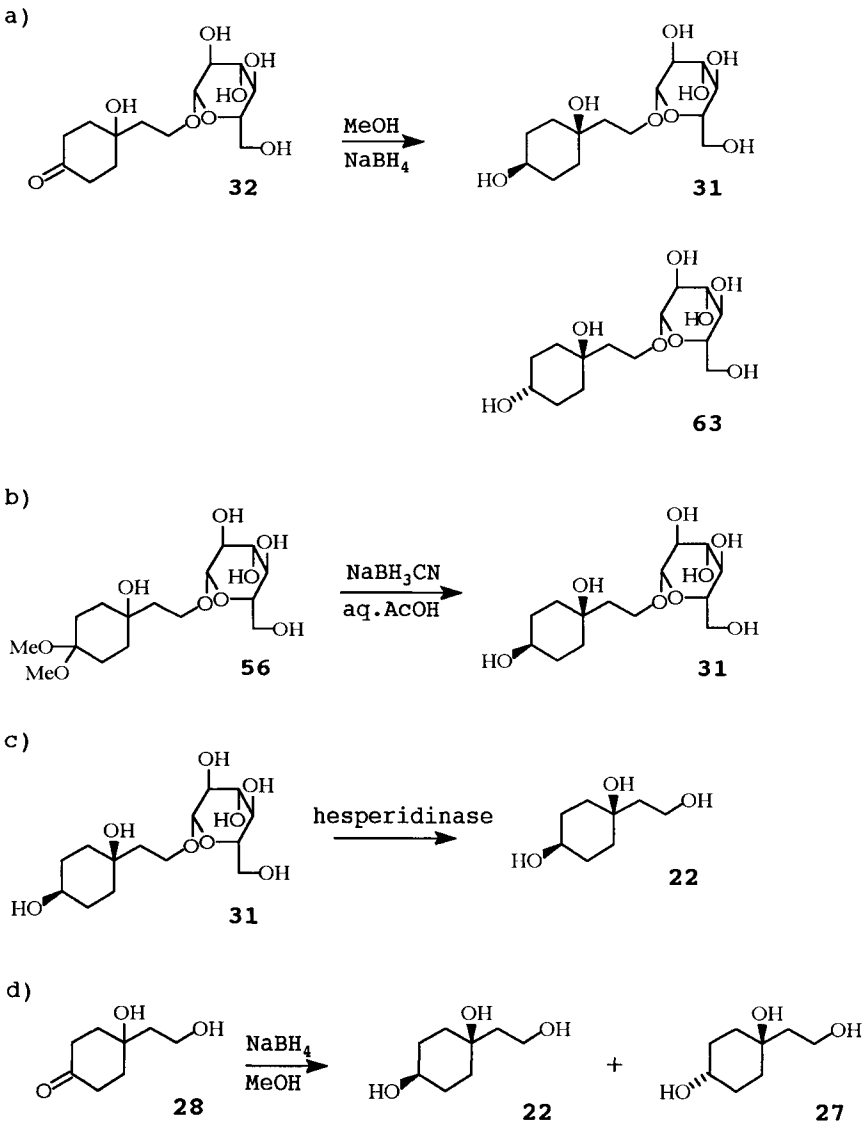
Scheme 10. Addition of Methanol to 4-Hydroxycyclohexanones.

dimethyl ketals **56** or **59**, (Scheme 10, a, b)) [83]. Under these conditions, various other ketones did not yield any detectable amount of such ketals. Previously, the carbonyl group of rengyoxide (**28**) was observed to behave abnormally to form the hemiketal **28A** [73,74], as well as to yield the dimethyl ketal **57** on handling its methanol solutions (Scheme 10, c)). Furthermore, 4-hydroxycyclohexanone (**60**) itself was similarly converted to its dimethyl ketal **61** by simple dissolving in methanol. The ketal **61** had been isolated and characterized as its acetate **62** (Scheme 10, d)) [102]. Therefore, this 4-hydroxycyclohexanone system may represent a special case where the ketal formation is unusually assisted by the transannular hydroxyl group. Such a tendency will be encountered again in a later section (Section 3.3, Scheme 18).

Rengyoxide (**28**) was obtained in quantitative yield by the treatment of rengyoside B (**32**) with crude hesperidinase in a citrate-phosphate buffer as described elsewhere [78].

2.5 Synthesis of Rengyoside A and Rengyol

Reduction of rengyoside B (**32**) with sodium borohydride in methanol proceeded stereospecifically to yield the thermodynami-



Scheme 11. Synthesis of Rengyoside A and Rengyol.

cally more stable equatorial hydroxyl group, and afforded rengyoside A (**31**), quantitatively (Scheme 11, a)). Similarly, the ketal **56** was treated with sodium cyanoborohydride in dilute aqueous acetic acid to give an alcohol **31**, with an equatorial hydroxyl group, as the sole product (Scheme 11, b)). Rengyol (**22**) was finally obtained from rengyoside B (**32**) by enzymatic cleavage of the glucosidic bond with crude hesperidinase (Scheme 11, c)) [78,83].

On reduction with sodium borohydride in methanol, rengyoxide (**28**) gave a very small amount (less than 1%) of an isomeric alcohol, isorengyol (**27**) (Scheme 11, d)) [74]. However it was unclear whether the reduction of rengyoside B (**32**) or its dimethyl ketal (**56**) did or did not yield the epimeric glucoside **63** since the epimer **63** was not present in detectable amount in the reaction mixture [78].

By these experiments, it was demonstrated as a possible metabolic pathway, that 4-substituted phenols are easily oxygenated to yield the corresponding paraquinols, which could then be reduced successively to saturated alicyclic alcohols.

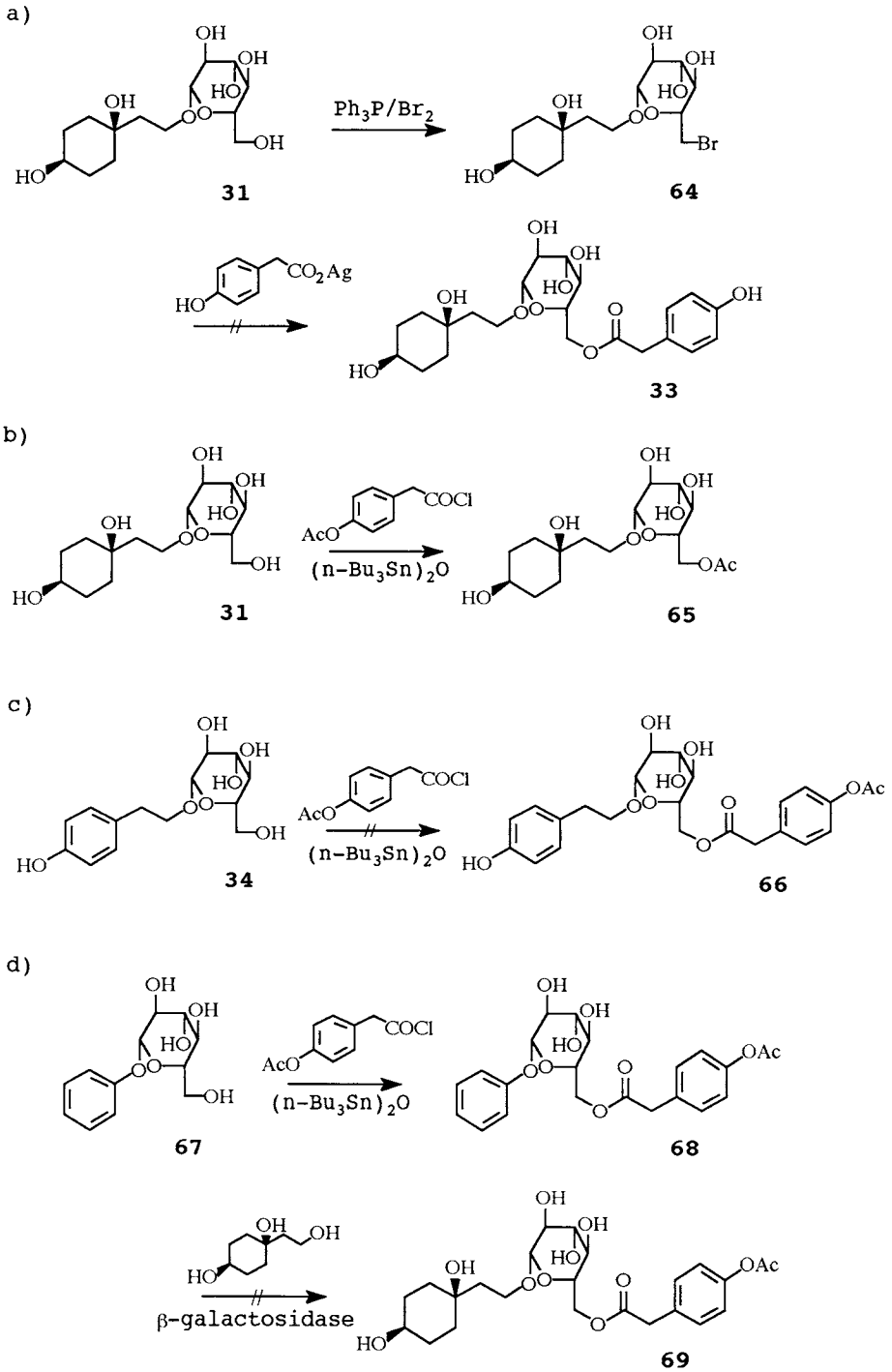
Although rengyol (**22**) exists in considerably large quantity (about 0.1% of the crude drug), its physiological role in the plant is unknown [73]. These glucosides, salidroside (**34**), cornoside (**21**) and rengyoside B (**32**) might be the metabolic intermediates leading to rengyoside A (**31**) and to rengyol (**22**). The glucosyl group would make the compounds better substrates for enzyme reactions, and would also stabilize these metabolic intermediates. Their aglycones, rengyolone (**29**) or rengyoxide (**28**), were probably liberated in small amounts from the main metabolic course by hydrolysing enzymes.

2.6 Synthesis of Rengyoside C

Finally, the synthesis of rengyoside C (**33**) was investigated [78]. It was only a matter of simple selective esterification at the primary hydroxyl group of the glucose moiety of rengyoside A (**31**), but the problem turned out to be not so easy. Coupling of the silver salt of 4-hydroxyphenylacetic acid (**38**) and 6-bromo-rengyoside A (**64**) [104,105], under various conditions, resulted in complete recovery of the starting compounds (Scheme 12, a)) [102]. Selective esterification of the glucoside **31** with 4-acetoxy-phenylacetyl chloride, catalyzed by bistributyltin oxide [106] in toluene, failed to give the coupling product, and instead, yielded

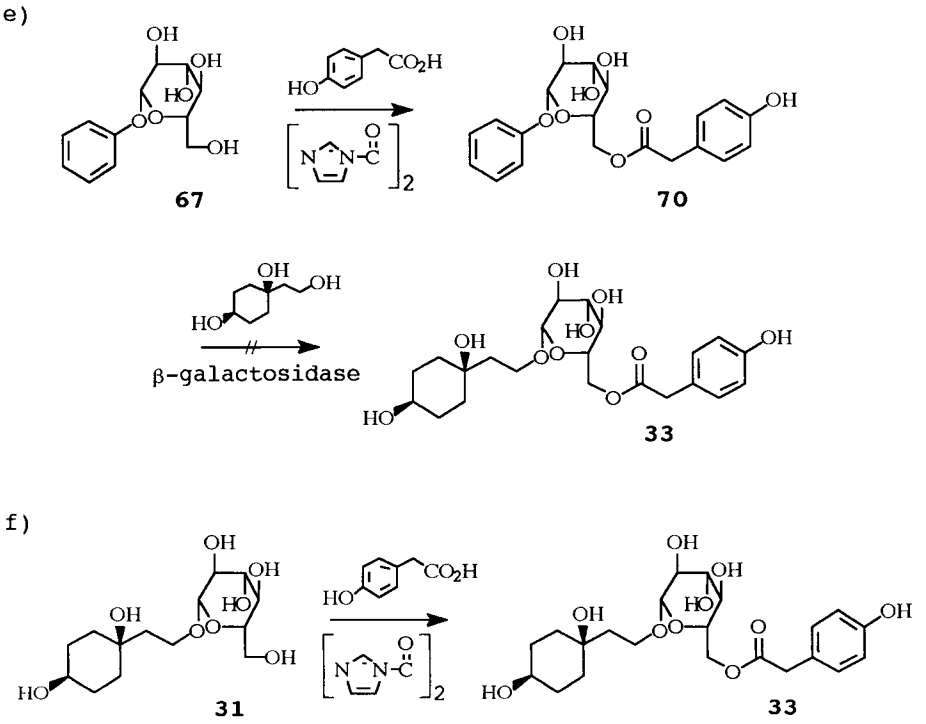
rengyoside A 6-acetate (**65**) as the only characterizable product (Scheme 12, b)) [102]. This result was very surprising because the primary hydroxyl group at the 6-position of the glucose moiety was in fact activated selectively, as expected, but a very strong acylating agent, phenylacetyl chloride, was not able to react with it, and instead, trans-esterification with the less reactive enol acetyl group in the 4-acetoxyphenylacetyl chloride took place (Scheme 12, b)). Salidroside (**34**) also failed to give the corresponding 6-phenylacetate **66** under the same conditions (Scheme 12, c)). In contrast, reaction of β-phenyl glucoside (**67**) and 4-acetoxyphenylacethyl chloride gave a fair yield of the desired ester **68** (Scheme 12, d)). Subsequent exchange of the aglycon with rengyol (**22**) by trans-glucosylation with β-galactosidase [107~109] was however unsuccessful.

Direct coupling of β-phenyl glucoside (**67**) and 4-hydroxy-phenylacetic acid (**38**), assisted by oxalyl diimidazole in dimethyl sulfoxide, also gave a good yield of the corresponding 6-ester **70**, but subseqnent trans-glucosylation was not realized at all (Scheme 12, e)). Thus, a direct esterification of rengyoside A (**31**) and 4-hydroxyphenylacetic acid (**38**) was again attempted, with oxalyl diimidazol as a co-reagent [110]. This time, a thin layer chromatogram of the reaction mixture showed a spot corresponding to the desired ester **33** in a significant amount. However, isolation of the product by silica gel column chromatography, with dichloro-methane-methanol as a solvent system, afforded rengyoside C (**33**) in only a little more than 10 %, in addition to a large amount of the starting rengyoside A (**31**), which however was not detected on a thin layer chromatogram at the end of the reaction. This meant that the ester **33** was very unstable under the isolation condition, and was easily cleaved, probably by trans-esterification, in this case, with the solvent, methanol. Since other esters do not show any such instability under the conditions, this particular occasion could only be rationalized by assuming the presence of severe steric repulsive interaction between the substituents at C-1 and C-6 positions of the glucosyl group. This destabilization may also account the difficulty of esterifying the 6-hydroxyl group, if a large substituent exists at C-1 position as in rengyoside A (**31**) or salidroside (**34**) (Scheme 12, a), b) and c)). Since β-phenyl glucoside (**67**) behaved quite normally to yield 6-esters, the steric effect of a phenyl group itself is not so significant. Consequent-



Scheme 12. Synthetic Reactions of Rengyoside C (Part 1).

ly, the combinations of rengyol (**22**) and acetic acid, or phenol and phenylacetic acid did not cause any significant steric repulsion, but such combinations of larger (longer) substituents, such as rengyol (**22**) or 4-hydroxyphenylethanol (**19**) and phenylacetic acid resulted in serious destabilization.



Scheme 12. Synthetic Reactions of Rengyoside C (Part 2).

During the course of structural determination of antibacerial constituents, forsythoside C (**24**) was noted to exist as an equilibrium mixture at the hydroxylated benzylic position, and exhibited two doublet signals for the respective methyl group of the rhamnosyl group, in its 100 MHz ^{1}H NMR spectrum [72]. Since the rest of signals were not observed in pairs, this unexpected phenomenon may be attributable only to long range steric interaction between the methyl group in the rhamnose moiety and the hydroxybenzyl group of the 3,4-dihydroxyphenylethanol moiety, located at the C-1 and C-6 positions of the glucosyl group. By appearance, they seemed to be sufficiently far apart and almost independent, but they turned out to be close enough to interact with each other.

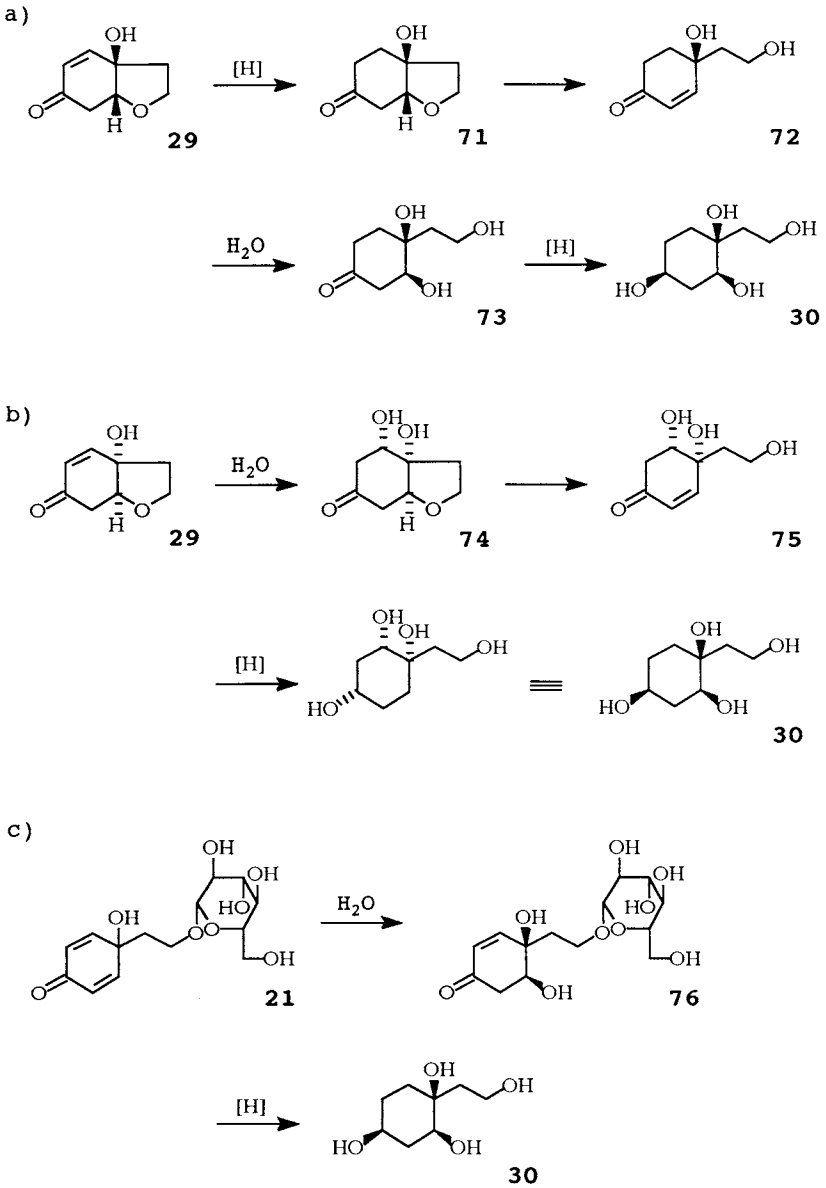
In an earlier section (Section 2.1), it was pointed out that many of the constituents of *Forsythia suspensa* may belong to the metabolic group of shikimic acid (**35**) [78], and 4-hydroxyphenylpyruvic acid (**36**) was considered as the nearest common biogenetic precursor of these constituents. Thus, by oxygenation of the aromatic ring and by side chain modification, 4-hydroxyphenylpyruvic acid (**36**) may be converted to caffeic acid (**37**) and lignan derivatives. On the ther hand, 4-hydroxyphenylethanol (**19**) could be transformed into polyhydroxylated phenylethanols **39** and **41** as well as into various cyclohexylethanol derivatives **22**, **28** and **30** [78,83]. These two metabolic groups could be linked by 4-hydroxyphenylacetic acid (**38**), generated from 4-hydroxyphenylpyruvic acid (**36**) by oxidative decarboxylation [111,112]. For the completion of the whole picture of biogenetic relationships of these constituents (Scheme 6), it is very important to note the actual existence of 4-hydroxyphenylacetic acid (**38**) in rengyoside C (**33**) [78].

3. PHOTOOXYGENATION OF TYROSINE

3.1 Stereostructure of (-) Suspenol

Suspenol, another congener of highly oxygenated cyclohexylethanol of C_6-C_2 skeleton, was isolated from the extract of *Forsythia suspensa* fruits, and its structure was assigned as all *cis* 1,2,4-trihydroxycyclohexylethanol (**30**) based on the detailed spectral analysis of its triacetate [77]. It also afforded a tribenzoate $[\alpha]_D$ +20.0° (CH_2Cl_2) exhibiting a CD maximum ([θ] +120°) at λ 235 nm. This proved it to be optically active, with the absolute configuration of its chiral centers, at C-1, C-2 and C-4, being all *S* based on the benzoate exciton theory [113,114].

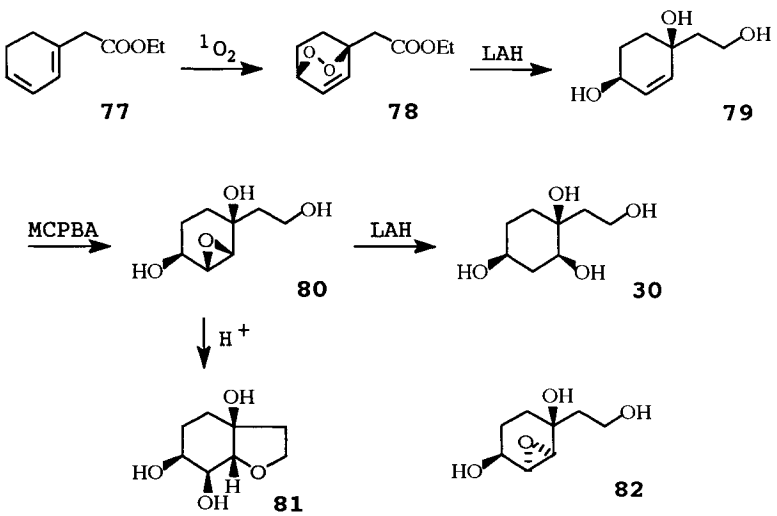
A number of possible biogenetic pathways for (-)-suspenol (**30**) could be written. However in order to account for the biosynthesis of an optically active form, such possibilities as that of enantioselective hydroxylation of rengyolone (**29**), or the biogenetically equivalent quinolethanol (**40**), (Scheme 13 a) and b)) would be less likely, because rengyolone (**29**) is in fact optically inactive [73]. One attractive alternative is the route depicted in Scheme 13 c), starting from cornoside (**21**), in which a prochiral enone system could be hydrated enantio- or diastereospecifically by virtue of the chiral glucosyl group. Thus, in order to confirm the relative stereostructure and absolute configuration of (-) suspenol, the following enantiospecific synthesis was investigated.



Scheme 13. Possible Biogenetic Routes of Suspenol.

At first, the relative stereostructure of suspenol (**30**) was confirmed by the following reactions. Photosensitized dioxygenation of ethyl cyclohexadienylacetate (**77**) in methanol afforded the corresponding endoperoxide **78** in high yield [77]. The peroxidic

bond was found to be fairly stable and resisted reductive opening by dimethyl sulfide or sodium borohydride, but was cleaved by litium aluminum hydride in tetrahydrofuran at 60°C to furnish a *cis* 1,4-diol **79** [77]. Perbenzoic acid oxidation of the allylic alcohol **79** in methylene chloride gave a single epoxide **80**, which was acetylated, followed by litium aluminum hydride reduction in refluxing tetrahydrofuran to yield a tetraol, identical to suspenol (**30**) in its spectral characteristics [77].



Scheme 14. Stereoselective Synthesis of Suspenol.

The stereochemistry of the oxirane ring was assigned to be *cis* to the 1,4-diol system, and *trans* to the hydroxyethyl group, because the epoxide **80** was easily isomerized to a bicyclic ether **81** quantitatively, by mild acid treatment. The coupling constants of the oxymethine signals in its ^{1}H NMR spectrum were also consistent with this stereostructure. In addition, a concerted S_N2 type five membered ring closure at the opening of the oxirane favors the suggested stereochemistry **80** over its epimeric structure **82**.

Based on these chemical evidences together with detailed analysis of spectroscopic data of these synthetic compounds, the stereostructure of suspenol was concluded to be all *cis* 1,2,4-trihydroxycyclohexylethanol (**30**) [77].

3.2 Product of (-) Tyrosine Photooxygenation

The relative stereostructure of suspenol (**30**) has been established rigorously by the chemical synthesis described above, and its absolute configuration was estimated from the CD spectrum of its tribenzoate [77]. However, it was felt desirable to confirm the absolute configuration, because the observed intensity of the CD spectrum was very weak, due to the limited quantity of the sample. Therefore, an enantiospecific synthesis was planned, starting from (-) tyrosine (**83**) based on the following concepts:

1) Natural amino acids are commercially available, and are very useful chiral synthons.

2) Tyrosine molecule (**83**) is close to the structure of suspenol (**30**), both in its carbon framework as well as the distribution of the oxidized carbons.

3) Tyrosine (**83**) may stand as, or very close to, the natural biosynthetic precursor of (-) suspenol (**30**).

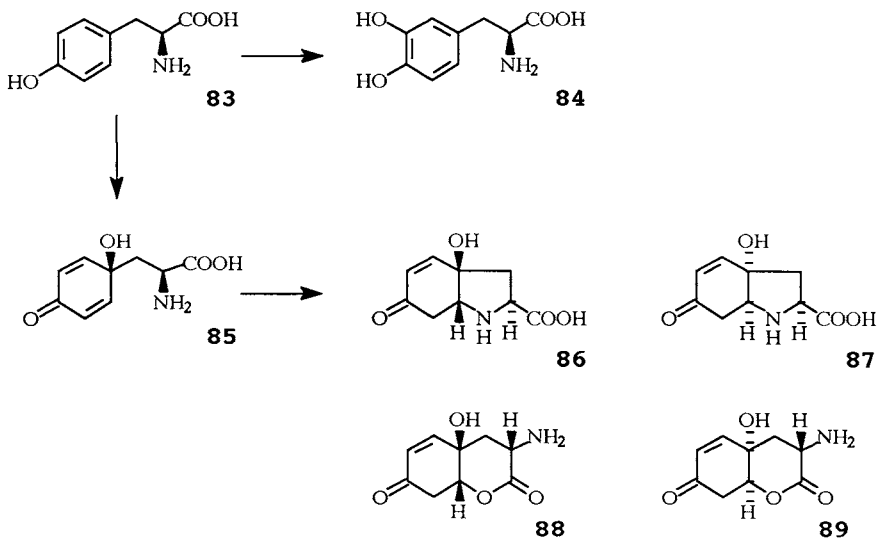
4) Photooxygenation reaction may be applicable in introducing the angular hydroxyl group to the tyrosine molecule (**83**), which may be a crucial step of this synthesis.

5) Enantiospecific Michael addition to a prochiral dienone system, assisted by remote chiral substituents, is the essential process suggested for its biogenesis (Scheme 13, e)).

There are a number of literature references concerning the photooxidation of tyrosine (**83**). However, most of them have dealt primarily with the kinetic and mechanistic measurements of photoreduction of dyes [115~118], and only one product hitherto described was not the expected quinol **85**, but rather dihydroxyphenylalanine (DOPA, **84**) (Scheme 15) [119~121]. This product **84** is, however, very attractive too, because all forsythosides (**20**, **24-26**) contain such 3,4-dihydroxyphenylethanol grouping as their aglycons (**39** and **41**). Therefore, if it is true, then photooxygenation of appropriate 4-hydroxyphenylethanols would provide these catechols, and in consequence, all the proposed metabolic routes, shown in the Scheme 6, could be substantiated.

In contrast to the formation of DOPA, there exists ample evidences (Sections 2.2 and 2.3), that simple 4-alkylphenols will give corresponding paraquinols as the first oxidation products [65,67,83], and if a good nucleophile is available within a molecule, to form a five or a six-membered ring, then intramolecular cyclization occurs to afford corresponding isomeric products [99]. In this particular case, tyrosine-derived quinol **85** has an amino

group at the β-position which will be able to form a five-membered ring, while the carboxyl group at γ-position is suitable to form a six membered lactone ring. Thus, the photoproduct **85** might well be transformed into such compounds of either of the following four possible structures **86-89** (Scheme 15).



Scheme 15. Possible Photooxygenation Products of Tyrosine.

All of these structures **86-89** would be useful to the present purpose, because whichever the photoproduct, each of them could be transformed into (-) suspenol (**30**) by chemical modifications similar to those suggested in the Scheme 13, a) and b). Thus it is an interesting question as to what is the compound obtainable by the photosensitized oxygenation of tyrosine (**83**).

Tyrosine (**83**) is practically soluble only in alkaline aqueous medium, and in addition, photobleaching of dyes is more efficient under these conditions, than in lower pH solutions [115~121]. Thus the following protocol was employed as a routine experimental conditions:

tyrosine (**83**)	500 mg (2.76 mmole), suspending
rose bengal	100 mg,
sodium carbonate	250 mg (0.125 %),
oxygen	saturation by bubbling gas
distilled water	200 ml,

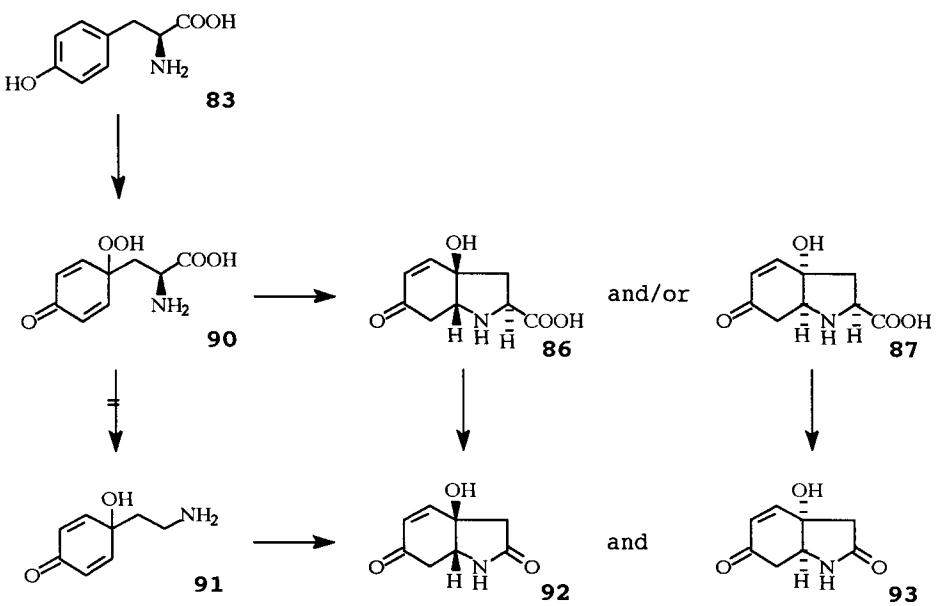
The solution of tyrosine (**83**) was irradiated with a halogen lamp (USHIO ICV 100-200 GS), cooled with running water, or ice-water if necessary, to keep the temperature below 40°C, and the reaction was followed by thin layer chromatography. The reaction proceeded very slowly, by a rate about an order of magnitude slower than the corresponding reaction of paracresol (**42**) described in the section 2.2. This probably indicates the presence of very efficient quenching of singlet oxygen by the amino group of tyrosine (**83**) [122-124].

According to the progress of the reaction, a number of product spots were detected by thin layer chromatography. None of them, however, corresponded to DOPA (**84**). A large spot slightly below that of tyrosine (**83**) was assigned as a hydroperoxide, since it was transformed into the next lower spot by reduction with dimethyl sulfide. Despite various attempts, direct isolation and characterization of these substances was unsuccessful. But their structures were estimated to be the pyrrolidinecarboxylic acid hydroperoxide (**127**) and its reduced form (**86**) [77]. Details will be presented in Section 3.5 (Scheme 26).

Next, less polar products were examined. Towards the end of reaction, another spot of lower intensity was detected by thin layer chromatography. Chromatographic fractionation of the product mixture afforded a crystalline substance in about 15 % yield. Analysis of spectroscopic data suggested its structure to be a ketolactam with only eight carbon atoms [125]. This indicated that one carbon atom of tyrosine (**83**) had been lost during the reaction. Configuration of the lactam ring juncture was assigned *cis* based on the observation of a W-type long range coupling, in the ^{1}H NMR spectrum, between the azomethine hydrogen and the β-hydrogen of the conjugated enone system with a coupling constant of 1 Hz, resembling the case of rengyolone (**29**) [73]. The *cis* configuration was also favored by mechanistic easiness of the intramolecular cyclization to yield a five-membered ring.

At this stage, we are able to answer the earlier questions, as the photooxygenation of tyrosine (**83**) will give a quinol **85** and not DOPA (**84**), and the quinol **85** cyclizes to pyrrolidine derivatives (**86** and **87**) and not to δ-lactones **88** or **89** (Scheme 15) [125].

The ketolactam **92** and/or **93** was found to be optically active, $[\alpha]_D$ -138° (c 0.71, MeOH), which indicated the Michael type addition of the amino group occurred regiospecifically, prior to the loss of the chiral center in the side chain by decarboxylation. Namely, the quinolethylamine (**91**) was not involved in this transformation, and instead, the quinolamino acid hydroperoxide **90** or the reduced hydroxide **85** cyclized immediately to pyrrolidinecarboxylic acids **86** and/or **87**, which then suffered oxidative decarboxylation to furnish



Scheme 16. Reaction Pathway of Tyrosine Photooxygenation.

non-equivalent amounts of ketolactams **92** and **93**. The ketolactam exhibited a strong Cotton effect at λ 228 nm ([θ] -58800) in its CD spectrum. This suggested that the enone chromophore in the major enantiomer to have a negative chirality. Consequently, the absolute configuration of two chiral centers, the angular hydroxyl group and the azomethine group, in the major component, are both assigned to be R [125].

In order to assess the regioselectivity in the addition reaction of the amino group to one of the two prochiral enone systems, the optical purity of the ketolactam was examined by the

500 MHz ^{1}H NMR spectra of its (-) camphanic acid esters. As a control experiment, (±) tyrosine was photooxygenated under the iden-

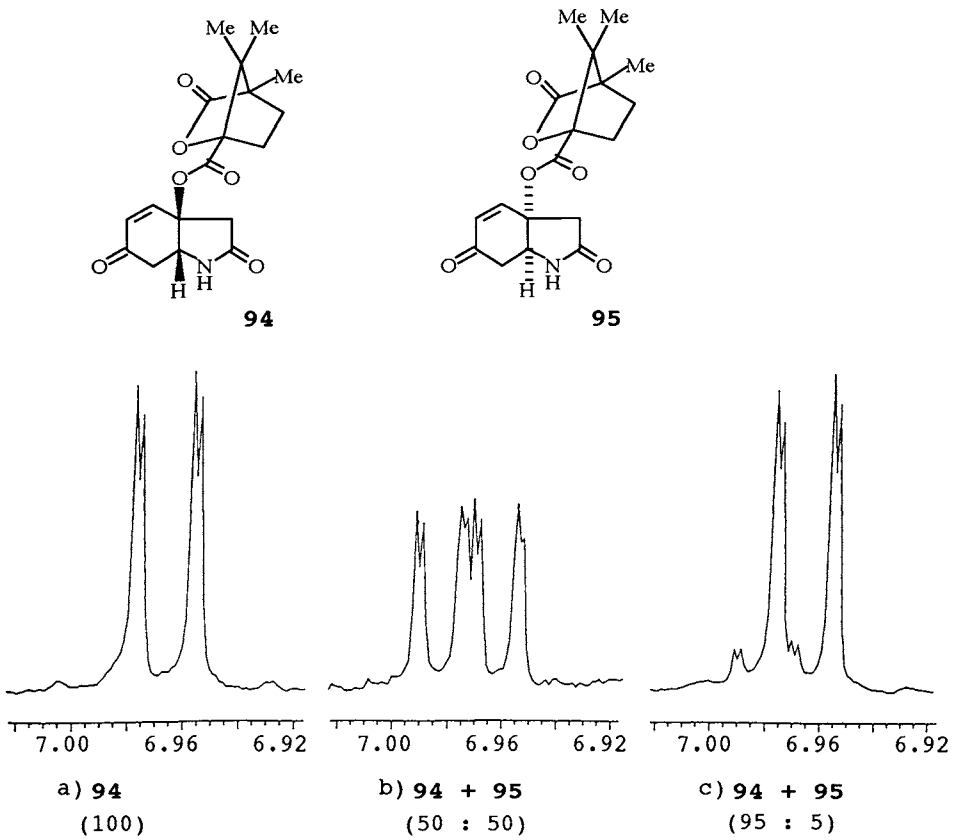
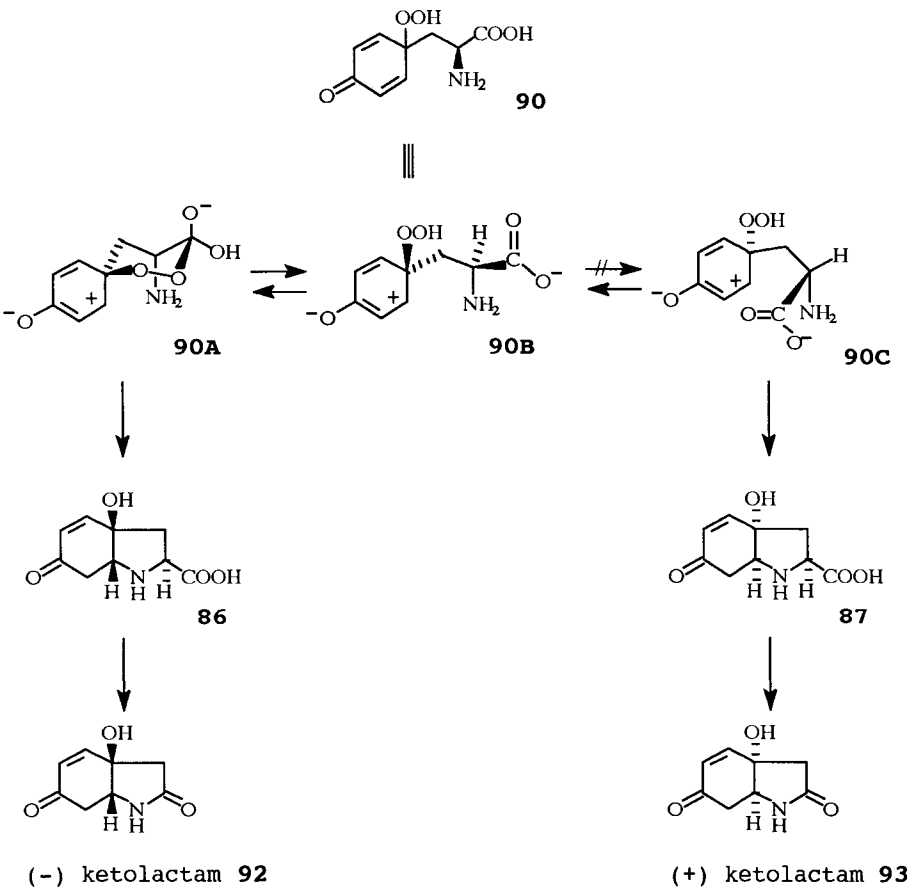


Fig 1. ^{1}H NMR Spectra (500 MHz) of (-) Camphanic Acid Esters of (+) and (-) Ketolactams.

tical conditions, and an equimolar mixture of (-) lactam **92** and (+) lactam **93** was obtained. The racemic lactam mixture was then esterified with a large excess of (-) camphanic acid chloride to yield an equimolar mixture of diastereoisomeric esters **94** and **95**. Although these diastereoisomers were indistinguishable by thin layer chromatography, they exhibited different sets of resonance peaks in the ^{1}H NMR spectra (Fig. 1). Among them, β-hydrogen signals of α,β-unsaturated ketones at δ 6.965 for the (-) lactam camphanylate **94**, and δ 6.980 for the (+) lactam camphanylate **95** have been chosen for diagnostic purpose. In the NMR spectrum of ester **94**, derived from

(-) tyrosine, the β-hydrogen signal was observed as a clean double doublet at δ 6.965 (Fig. 1, a)), and no peaks corresponding to the isomer **95** could be seen. In order to check the peak resolution of



Scheme 17. Enatiospecific Formation of (-) Ketolactam.

these spectra, 10 molar percent of the racemate ester was added, (final diastereomeric ratio became 95.0 to 5.0), and the spectrum examined again. As was shown in Figure 1, c), another pair of double doublet at δ 6.980, attributable to the isomer **95**, was clearly recognized.

It became clear then, that the existence of even one percent of such diastereoisomer could be detected by this method, and

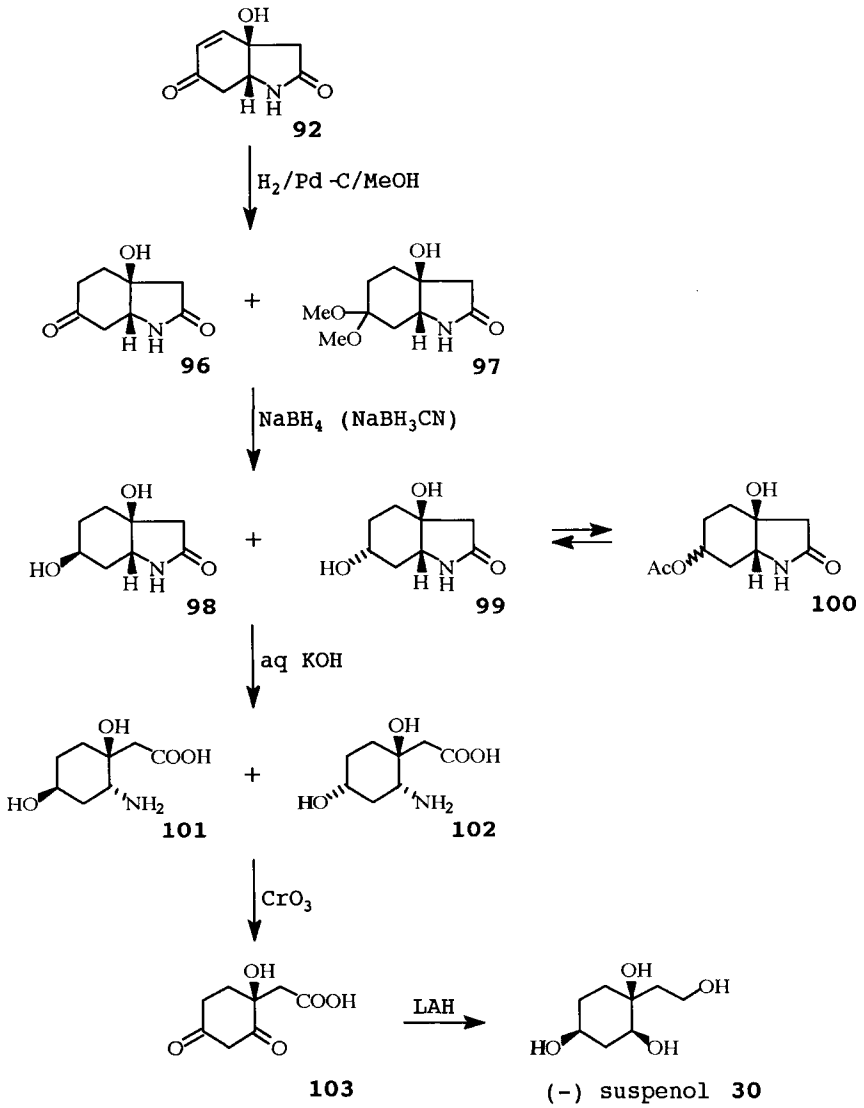
consequently, the ketolactam **92**, obtained by the photooxygenation of (-) tyrosine (**83**), was concluded to be optically pure [125].

It was very surprising to find that the cyclization reaction was revealed to be highly regiospecific. In this reaction, the aminomethylene group of quinolamino acid **90** is the sole chiral center in this molecule, and this functionality is somewhat distant from the point where the new chirality is induced. There appears to be no obvious difference in steric circumstance during the transformation of the quinolamino acid **90** to the pyrrolidinecarboxylic acids **86** and **87**. Thus, the most important directing factor for such high regiospecificity might be the electrostatic repulsion between the negatively polarized carbonyl group and the carboxylate anion, and conformation **90C** leading to the isomer (**87**) was disfavored.

In contrast, conformation **90B** could be stabilized further by formation of a fixed stable orthoester **90A**. The amino group in the conformation **90A** is located right above the pro-R enone system, affording the pyrrolidinecarboxylic acid **86** (Scheme 17) as the sole product [77].

3.3 Enantiospecific Synthesis of (-) Suspenol

For the purpose of synthesizing (-) suspenol (**30**), it was very fortunate to have the (-) ketolactam **92**, because it had already lost an excess carbon atom in tyrosine molecule (**83**), and in addition, the carbon skeleton as well as the distribution of oxygenated (or nitrogenated) carbons and their absolute configuration almost coincided with the final structure **30**. Therefore it was necessary only to reduce the double bond and hydrolyze the lactam ring. Subsequent modification of functionalities could be done as follows. The carboxyl group could be reduced easily to a primary hydroxyl group. Stereoselectivity of reduction of 4-substituted cyclohexanones are expected to give the thermodynamically more stable β-oriented equatorial hydroxyl group exclusively, as was demonstrated in the case of rengyoxide (**28**) to rengyol (**22**) (ref. Sec. 2.5). Hence, the remaining problem was to convert the α-axial amino group to a β-equatorial hydroxyl group, which could be realized either by S_N2 type substitution, or oxidative deamination followed by reduction. In order to avoid complications by the enone system during hydrolysis of the lactam ring with strong alkali, the following route (Scheme 18) was employed for the subsequent transformations.



Scheme 18. Enantiospecific Synthesis of (-) Suspenol.

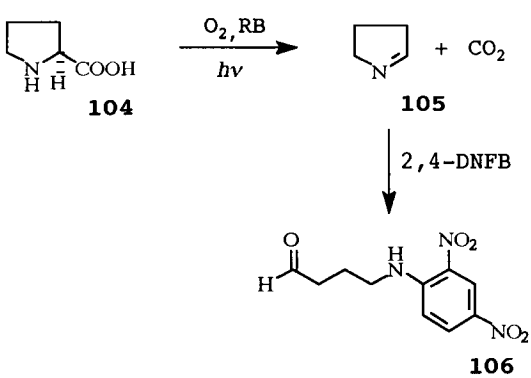
The ketolactam **92** was hydrogenated in methanol with palladium carbon to furnish the dihydro derivative **96**. The reaction went normally, but again the dimethyl ketal **97** was isolated in an appreciable amount. This indicated once more that in the 4-hydroxycyclohexanone system, the carbonyl carbon has a tendency to adopt an sp^3 form rather than an sp^2 structure (ref. Section 2.4).

Sodium borohydride reduction of **96**, or sodium cyanoborohydride on **97**, yielded an epimeric mixture of dihydroxylactams **98** and **99** in

about 4 to 1 ratio. The configuration of the secondary hydroxyl group in the major product **98** was assigned as β and equatorial, based on the chemical shift of a carbinyl methine hydrogen at δ 3.83 (multiplet) in its ^{1}H NMR spectrum. In this reaction, the α side was sterically more hindered by the lactam ring, but still, attack of the reagent from this side predominated to yield thermodynamically the more stable β-equatorial hydroxyl group. Each of the epimeric diols **98** and **99** could be purified, by fractional crystallization or silica gel column chromatography of their acetates **100**, but for the suspenol synthesis, the diol mixture was directly hydrolysed with 40% aqueous sodium hydroxide to the corresponding amino acid mixture **101** and **102**. These amino acids were then oxidized with 1% aqueous solution of chromic acid at room temperature to a diketo acid **103**, which was finally reduced with litium aluminum hydride in tetrahydrofuran to enantiomerically pure (-) suspenol (**30**), exhibiting an optical rotation of $[\alpha]_D$ -1.8° (Scheme 18) [77]. The synthetic tetraol **30** gave, on benzoylation, a tribenzoate, $[\alpha]_D$ +21.3°, and showed identical spectroscopic properties in the IR and ^{1}H NMR spectra as well as identical chromatographic behavior in comparison to natural suspenol tribenzoate [77].

3.4 Photooxidation of Proline

It was shown in Section 3.2, that tyrosine (**83**) was oxygenated to the quinolamino acid **90**, which subsequently cyclized spontaneously to afford the pyrrolidinecarboxylic acid **86** stereospecifically. However, as a matter of fact, the reaction did not stop at this



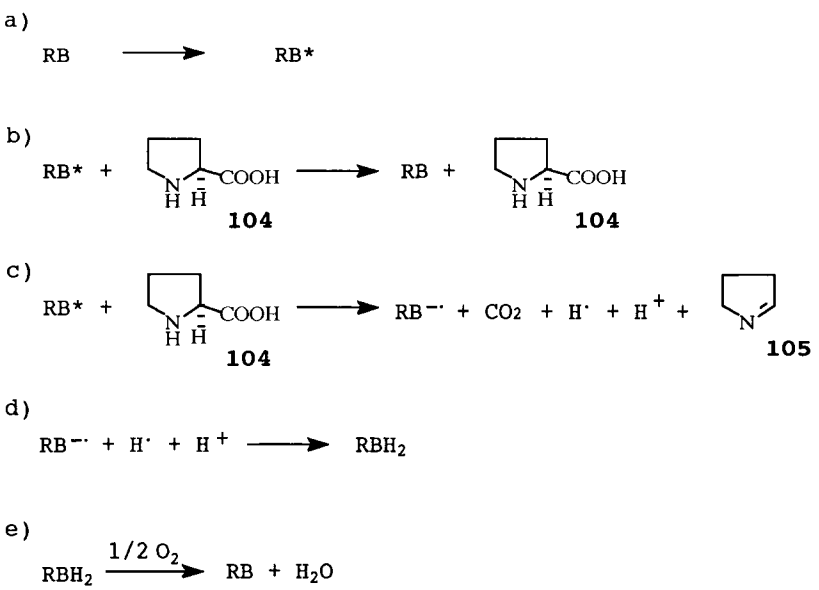
Scheme 19. Photosensitized Oxidation of Proline.

stage, but went much further and ended up by yielding the ketolactam **92**. Thus, an extended investigation was carried out to elucidate the mechanism for the later stage of this transformation. Since the presumed intermediate, pyrrolidinecarboxylic acid **90**, has the partial structure corresponding to proline (**104**), photooxidation of the amino acid **104** with rose bengal was investigated in detail.

Photosensitized oxidation of amines has been studied in only a few cases, and an electron transfer process from an amino nitrogen to an oxidant, a photoactivated sensitizer for example, was indicated [126-128]. It was also pointed out, that the oxidation potentials of primary amino groups are very high, and hence, they could inhibit the photooxidation reactions [129,130].

However, by irradiating a solution of proline (**104**) and rose bengal in aqueous sodium carbonate under bubbling of oxygen, slow but clean decarboxylation did take place, as expected, and yielded Δ^1-pyrroline (**105**) as the sole product, which was characterized as its 2,4-dinitrofluorobenzene condensate **106** (Scheme 19) [131].

The reaction was therefore examined in more detail under various conditions, and the results are summarized in Table 3 and Scheme 20.



Scheme 20. Processes of Proline Photooxidation.

As the results demonstrate, proline (**104**) was not decarboxylated under darkness or in the absence of a sensitizer (Table 3, b), d)). Therefore, this oxidative decarboxylation was really photochemical, and the photoactivated sensitizer was involved as the reacting species. Namely, the reaction was mechanistically a Type I photooxidation (Scheme 20, c)) [126~128]. Further, when the supply of oxygen was stopped, the reaction was slowed down considerably, but it did not stop fully (Table 3, c)). Preliminary kinetic studies gave the rate of this reaction to be about 2.5×10^{-3} for anaerobic condition, while oxygen saturation by bubbling of gas enhanced the rate by approximately two fold [131].

Table 3. Photosensitized Oxidation of Proline.

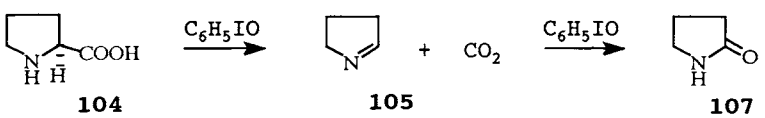
104 **105** **107**

		Δ¹-pyrroline (**105**)	2-pyrrolidone (**107**)
a)	RB + O_2 + *hν*	+++	-
b)	RB + O_2	-	-
c)	RB + *hν*	+	-
d)	O_2 + *hν*	-	-
e)	RB + O_2 + *hν* + H_2O_2	+++	(+)
f)	RB + O_2 + *hν* + *t*-BuOOH	+++	++

Oxygen may, therefore, be required only to regenerate the active oxidized form of the sensitizer from the photobleached state (Scheme 20, e)). In fact, the decarboxylation of proline (**104**) was not completed under such anaerobic conditions, and the extent of the amino acid **104** consumed was practically dependent on the amount of rose bengal employed [132]. Contrary to the case of tyrosine (**83**), no lactam, 2-pyrrolidone (**107**), was detected in the reaction mixture. Since the lactam **107** was obtained only when some peroxide was applied (Table 3, e and f)), it was considered to be a secondary photooxidation product.

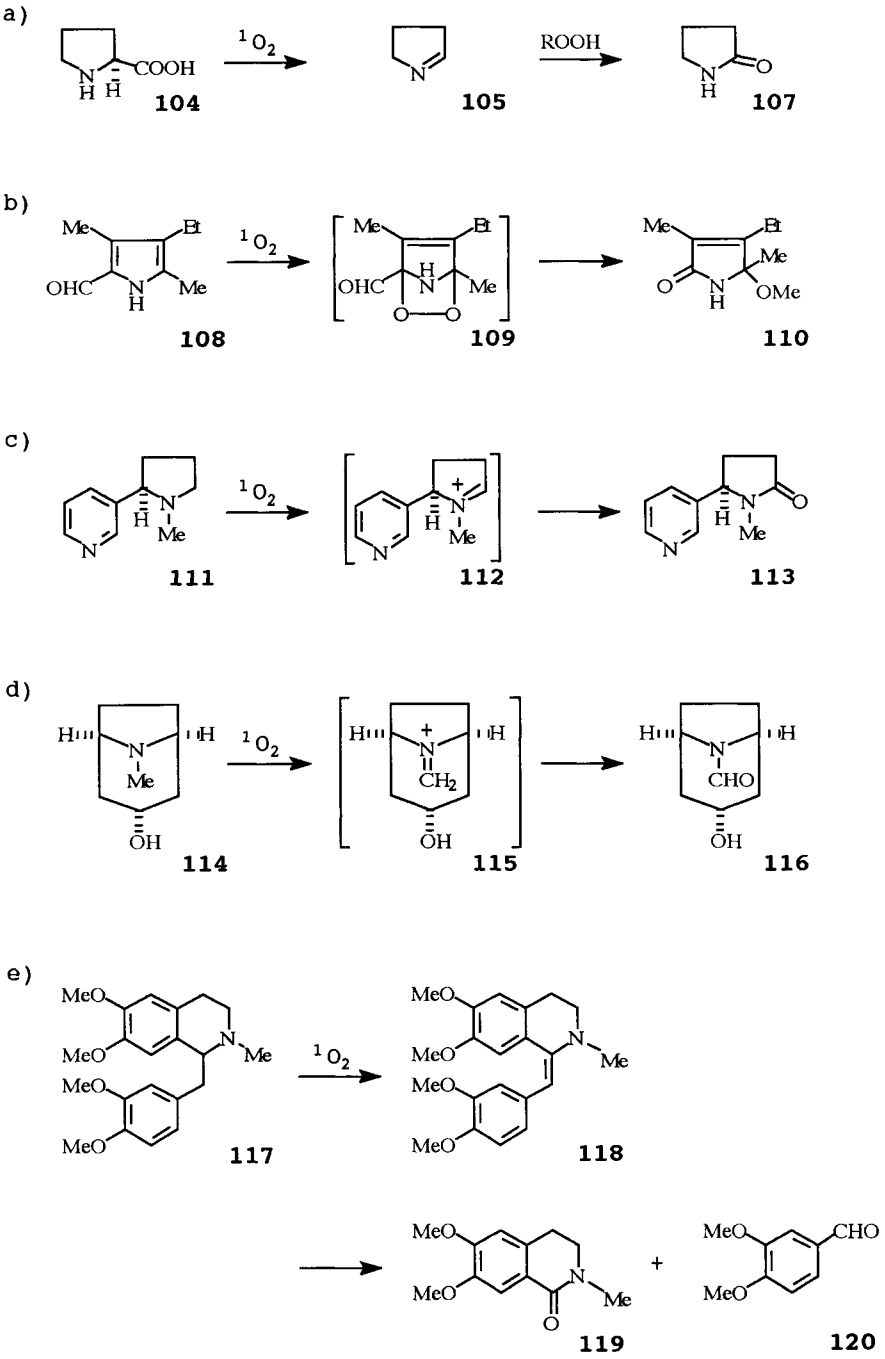
Iodosobenzene was reported to oxidize proline (**104**) just like the photooxidation described above, by reacting with the nitrogen atom by abstraction of an electron, to give Δ^1-pyrroline (**105**) in good yields (Scheme 21) [133]. The lactam, 2-pyrrolidone (**107**), was also obtained in this case when excess reagent was used [132, 133].

It has been reported that photosensitized reaction of a pyrrole derivative **108** with singlet oxygen yielded a lactam **110** by oxidative deformylation [134~136]. In this case, singlet oxygen might have reacted with the pyrrole **108** in the mode of 1,4-cycloaddition to yield a cyclic endoperoxide **109**, which was subsequently isomerized and decomposed to afford the lactam **110** (Scheme 22, b)) [134~136]. While, tertiary amines, like nicotine (**111**) and tropanol (**114**), yielded quaternary immonium intermediates **112** and **115** respectively, as the primary photoproducts by the type I process. These intermediates were then oxidized further by, for example, uptaking hydroperoxides followed by fragmentation to yield lactams **113**, **116** as the final products (Scheme 22, c), d)) [20,137~140]. Although this mechanism is supported by the fact that sodium pyruvate completely inhibited the lactam formation [141~143], it was not clarified whether such peroxides were formed in these reaction conditions.



Scheme 21. Reaction of Proline and Iodosodenzene.

Photosensitized oxidation of laudanosine (**117**) also suffered from electron abstraction at the amino nitrogen to yield, in this case, a stable enamine **118**. Subsequent oxidative cleavage by singlet oxygen afforded the lactam **119** and veratraldehyde (**120**) (Scheme 22, e)) [144,145]. This reaction resembled the oxidation of proline (**104**) to 2-pyrrolidone (**107**), in the sense that the azomethine group bearing a substituent was transformed into an amide carbonyl group by expulsion of the substituent. However, the conversion of the imine **118** to the lactam **119** could also be interpreted by a



Scheme 22. Photooxidation of Amines to Amides.

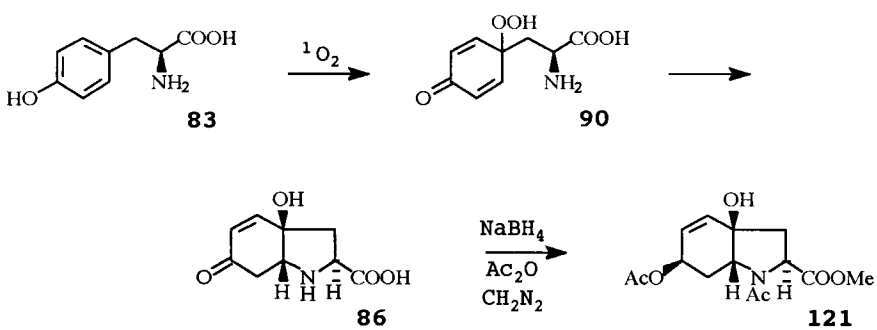
mechanism of dioxetane formation followed by carbon-carbon bond cleavage (Scheme 1, b)) [14~16].

Experiments e) and f) of Table 3 establish that proline (**104**) was oxidized to afford the lactam (**107**), only in the presence of hydrogen peroxide or, more preferably, an organic hydroperoxide. However, simple mixing of pyrroline (**105**) and t-butyl hydroperoxide did not yield any detectable amount of 2-pyrrolidone (**107**). Therefore, this process should also be photochemical, and oxidation by a hydroxyl radical, generated by photodecomposition of organic hydroperoxides, is presumed as a tentative mechanism.

3.5 Mechanism of Tyrosine Photooxygenation

Based on the analogies of such oxidation of many phenolic compounds, as well as our own result of obtaining the C_8 ketolactam **92**, the first step of photooxygenation of tyrosine (**83**) is concluded to be the formation of a quinol hydroperoxide **90** by the Type II process [88~90], followed by spontaneous intramolecular cyclization to afford an optically pure pyrrolidinecarboxylic acid **86**.

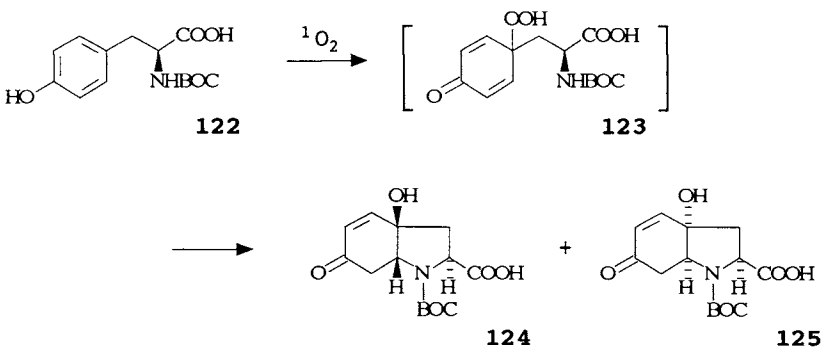
Although it was not possible to isolate and characterize the expected quinolamino acid **90** or the bicyclic pyrrolidinecarboxylic acid **86**, a stable methyl ester **121** was obtained by treating the reaction mixture with sodium borohydride followed by acetylation with acetic anhydride and methylation with diazomethane (Scheme 23).



Scheme 23. Characterization of Pyrrolidinecarboxylic Acid.

The methyl ester **121** showed the molecular ion peak at *m/z* 297.1233, in the high resolution mass spectrum, corresponding to the elemental composition of $C_{14}H_{19}O_6N$, in addition to having three methyl singlets at δ 2.07, 2.16 and 3.80 and two vinylic hydrogen multiplets at δ 5.74 and 5.82 in the ^1H NMR spectrum, all of which are consistent with the expected structure **121** [77].

Furthermore, a similar photooxygenation of N-BOC-tyrosine (**122**) afforded two diastereomeric pyrrolidinecarboxylic acids **124** and **125** in a 3 to 2 ratio, without accompanying oxidative decarboxylation (Scheme 24). The BOC group in this case protected the amino groups of **124** and **125** from subsequent oxidation by the Type I process, and also affected the regiospecificity of the intramolecular Michael addition of the BOC amino group to the dienone system in the intermedial quinolamino acid **123** [77].



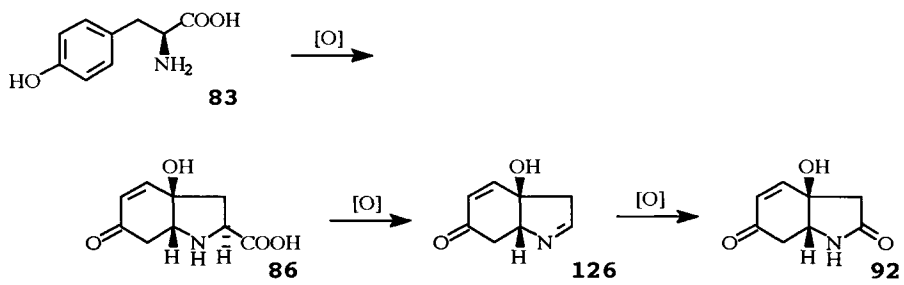
Scheme 24. Photooxygenation of N-BOC-Tyrosine.

In the case of tyrosine (**83**) itself, the photo product, pyrrolidine hydroperoxide **127** or its hydroxide **86**, was oxidized again by the Type I process, just like proline (**104**), and gave the decarboxylation product **126**, followed by further oxidation by a hydroxyl radical or a related oxidant to yield the ketolactam **92** as the end product.

In order to obtain more detailed information about these processes, from tyrosine (**83**) to ketolactam **92**, the oxygenation reaction under various conditions was analyzed by thin layer chromatography, and the results are given in Table 4.

These preliminary experiments indicated that tyrosine requires for the photosensitized oxygenation as a necessity, a sensitizer, molecular oxygen and light (Table 4, a)). Lack of any one of these factors completely suppressed the reaction (Table 4, b), c) and d)). Addition of sodium pyruvate, which eliminates peroxides [141-143], did not inhibit formation of the pyrrolidinecarboxylic acid **86**, but reduced drastically the yield of the ketolactam **92** and led to another compound **126**, which was detected at a slightly lower position than a spot of **92** on thin layer chromatograms (Table 4, e)). Structure of this minor product was assigned as an imine **126**, on analogy to the reaction of proline (**104**) (*vide supra*, Section 3.4). On the other hand, the addition of hydrogen peroxide or t-butyl hydroperoxide to the reaction system, at a time when most tyrosine had been consumed, led to improve the yield of the ketolactam **92** significantly (Table 4, g)) [77].

Table 4. Photosensitized Oxidation of Tyrosine.



								pyrrolidine **86**	imine **126**	lactam **92**
a)	RB	+	O_2	+	*hν*			+++	(+)	+
b)			O_2	+	*hν*			-	-	-
c)	RB	+	O_2					-	-	-
d)	RB			+	*hν*			-	-	-
e)	RB	+	O_2	+	*hν*	+	NaOPv	+++	+	-
f)	RB	+	O_2	+	*hν*	+	H_2O_2	+++	-	+
g)	RB	+	O_2	+	*hν*	+	BuOOH	++	-	++

These results have shown that the photosensitized oxygenation of tyrosine (**83**) is a very complex multi-step reaction, consisting of at least sixteen unit processes as shown in Scheme 25.

Namely, rose bengal is first photo-activated (Scheme 25, a)) and reacts with molecular oxygen to give singlet oxygen (Scheme 25, b)). Both the excited rose bengal and the singlet oxygen are, however, quenched very efficiently by the substrate, tyrosine (**83**) (Scheme 25, c-e)). Phenoxyl groups are excellent quenchers of various active oxygen species such as hydroperoxyl radical and superoxide anion radical, and also deactivate singlet oxygen [61~64]. The rate of quenching of singlet oxygen is proportional to the barrier height of proton transfer in the charge transfer interaction [130,146~148]. A primary amino group also quenches a photo-activated sensitizer, as has been discussed in the previous section (Section 3.4), and deactivates singlet oxygen as well by a charge

a) RB + $h\nu$ → RB*

b) RB* + $^3O_2$ → $^1O_2$ + RB

c) Tyrosine + RB* → Tyrosine* + RB

d) Tyrosine + $^1O_2$ → Tyrosine* + $^3O_2$

e) Tyrosine* → Tyrosine + $h\nu$

f) Tyrosine + $^1O_2$ → Quinol-OOH

g) Quinol-OOH → Pyrrolidine-OOH

h) Pyrrolidine-OOH → Pyrrolidine-OH

i) Pyrrolidine-OH + RB* → Pyrrolidine-OH* + RB

j) Pyrrolidine-OH + RB* → Pyrrolidine-$OH^{+\cdot}$ + $RB^{-\cdot}$

k) Pyrrolidine-$OH^{+\cdot}$ → Imine + CO_2 + $H^\cdot$ + H^+

l) $RB^{-\cdot}$ + $H^\cdot$ + H^+ → RBH_2

m) ROOH + RB* → $RO^\cdot$ + $OH^\cdot$

n) $Imine^+$ + $OH^\cdot$ → Imine-$OH^\cdot$

o) Imine-$OH^\cdot$ → Ketolactam + $H^\cdot$

p) RBH_2 + $^3O_2$ → RB + H_2O

Scheme 25. Processes of Tyrosine Photooxygenation Reaction.

transfer interaction [149~151]. Therefore, only a small flux of singlet oxygen goes into the actual reaction with tyrosine (**83**) to give a quinol hydroperoxide **90**, which immediately isomerizes to the bicyclic pyrrolidinecarboxylic acid hydroperoxide **127** (Scheme 25, f) and g)). During the reaction, a spot corresponding to the hydroperoxide **127** could be detected by thin layer chromatography.

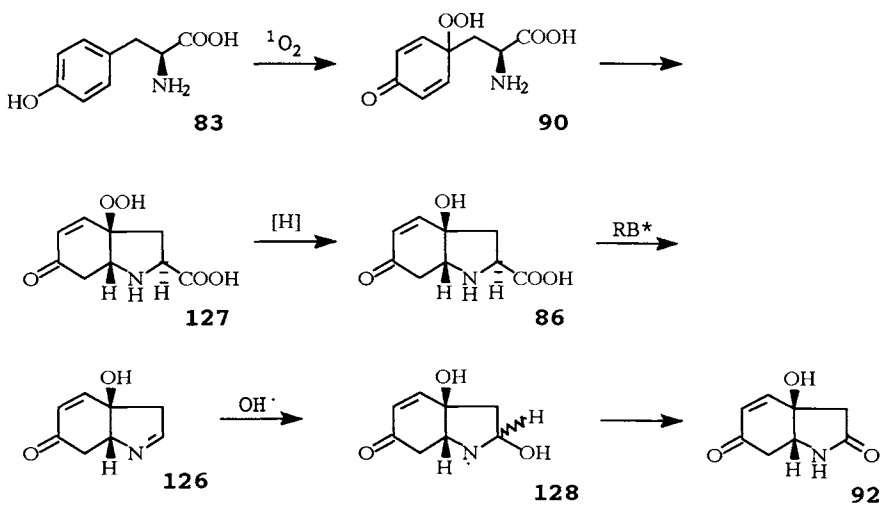
The product was reduced, gradually, to a hydroxide **86**, and exhibited a new spot slightly below that of **127**, while most of the hydroperoxide **127** lasted long after the end of the reaction. Therefore, the reduction of the peroxide could occur at any time after the cyclization (Scheme 25, h)). The pyrrolidinecarboxylic acid **86** has a partial structure of proline (**104**), and therefore, **86** can be involved in a similar photochemical processes as **104**, namely, the quenching of photoactivated rose bengal (Scheme 25, i)) as well as the Type-I oxidation with concomitant decarboxylation (Scheme 25, j)-k)) [152~154]. The imine derivative **126** was detected in the reaction mixture by thin layer chromatography in only a small amount. This was probably because **126** was oxidized relatively faster to the end product **92** (Scheme 25, n) and o)). An intermedial pyrrolidine hydroxide **128** is proposed tentatively, based on the experimental results, described before.

The starting compound, tyrosine (**83**), was not soluble in neutral water and it was necessary to make the solution alkaline to increase its solubility sufficiently for a preparative quantity. The oxidation also proceeded much faster in a solution of higher pH [121]. This conditioning made the amino group unprotonated, and hence, allowed it to work as a good quencher of both the photoexcited rose bengal as well as singlet oxygen. In these conditions, the oxidation potential of the primary amino group is not sufficiently low enough to transfer its electron to the photoactivated sensitizer, and so, the amino group may only retard the reaction. However, when the phenoxyl group is oxygenated to yield the quinol **90**, the amino group attacks a β-position of the dienone system. The oxidation potential of the resulting secondary amino group then became low enough to be a better substrate of photosensitized oxidation by rose bengal [130].

Although optimization has not yet been accomplished, in the best preparative conditions so far realized, the yield of the ketolactam **92** was increased to 48% overall, by addition of *t*-butyl hydroperoxide near the end of the first phenol dioxygenation. This amount is surprisingly high if one considers the complexity and the number of processes involved in the transformation from tyrosine (**83**) to the ketolactam **92** (Scheme 25) [77].

We are now able to draw the whole scene of photosensitized oxygenation of tyrosine (**83**) as shown in the Scheme 26.

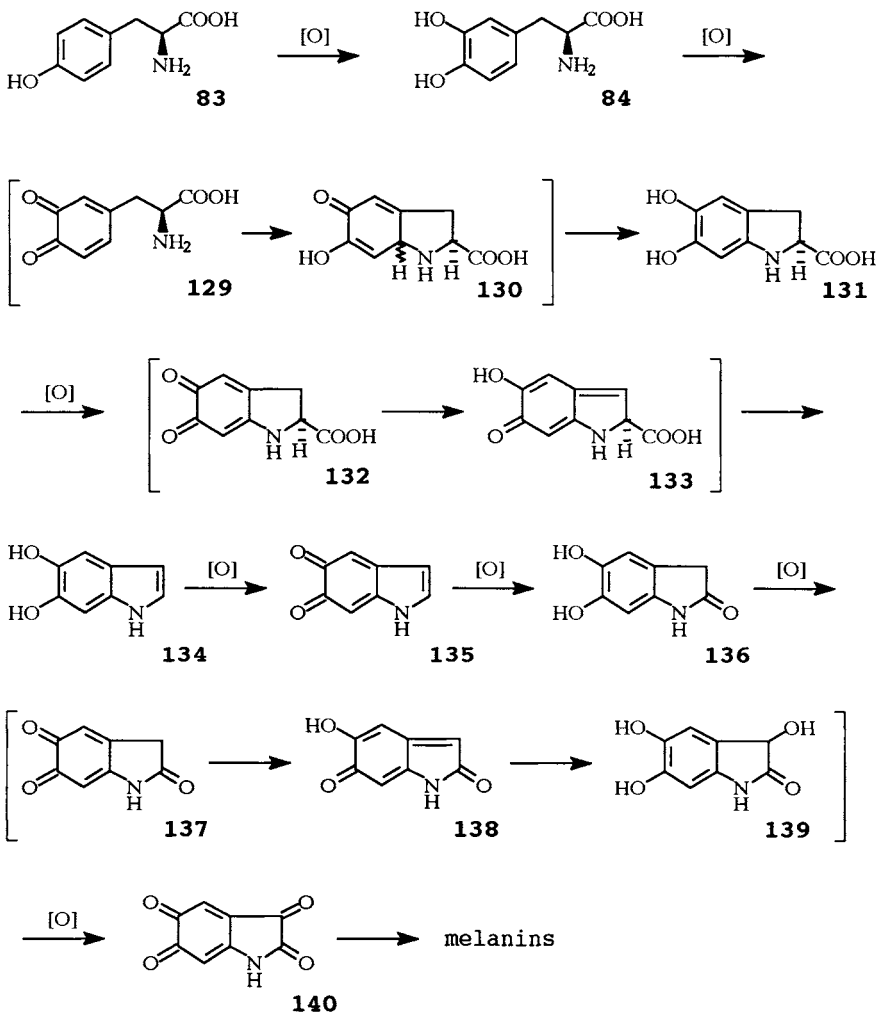
It is very interesting to note that this over all process resembles the enzymatic transformation of tyrosine (**83**) to melanochrome pigments [155~163], as outlined in Scheme 27. Thus, tyrosine (**83**) in this metabolism, is not oxygenated to the quinolamino acid **90** but to DOPA (**84**). Interestingly, the latter substance **84** was claimed as the photooxygenation product of tyrosine (**83**) as mentioned before [119~121]. It was not possible to detect DOPA (**84**) in the present photooxygenation experiments, but since it is isomeric to the quinolamino acid (**85**) with respect only to the location of a hydroxyl group, the possibility of yielding DOPA (**84**) in a photosensitized oxidation should not be completely excluded (Scheme 15). Such isomerization of a quinol to a catechol will be discussed in the next chapter (ref. Scheme 29).



Scheme 26. Over-all Reaction Pathway of Tyrosine Photooxygenation.

In the melanine biosysnthesis, DOPA (**84**) is oxidized to a quinone **129** followed by an intramolecular Michael addition to give a bicyclic pyrrolidinecarboxylic acid **130** [155,156], just like the transformation of **90** to **86** (Scheme 26). The pyrrolidinecarboxylic acid **131** is again oxidized to a quinone **132**, which spontaneously loses carbon dioxide to yield an indole **134** [160], also paralleling the case of the oxidative decarboxylation of **86** to **126** by the Type-

I photooxidation (Scheme 26). There is not sufficient data to elucidate the detailed mechanism of oxidative cyclization from DOPA



Scheme 27. Biosynthetic Pathway of Melanin Pigments.

(**84**) to leucodopachrome (**131**), but one electron oxidation of DOPA (**84**) by flash photolysis with sodium azide resulted in a semiquinone intermediate which spontaneously cyclized, followed by disproportionation to yield leucodopachrome (**131**) and dopachrome (**132**) [161~163]. Since a catechol group present in a molecule may be oxidized easily to an orthoquinone form like **132**, **135** or **137**,

subsequent isomerization to a catechol form will effect the other part of the molecule, to allow facile oxidative decarboxylation, oxidation to a pyrrolidone **136**, and to dopaquinone (**140**) under very mild conditions.

The physiological roles of the melanin pigment are not completely understood, but since the pigment occurs at very important places such as the brain and the nervous system, in addition to malignant melanoma, it could have some important biochemical roles. Therefore, the chemical aspects presented in this section on the photo-induced cascade of tyrosine degradation may provide some interesting scope for further work in this field.

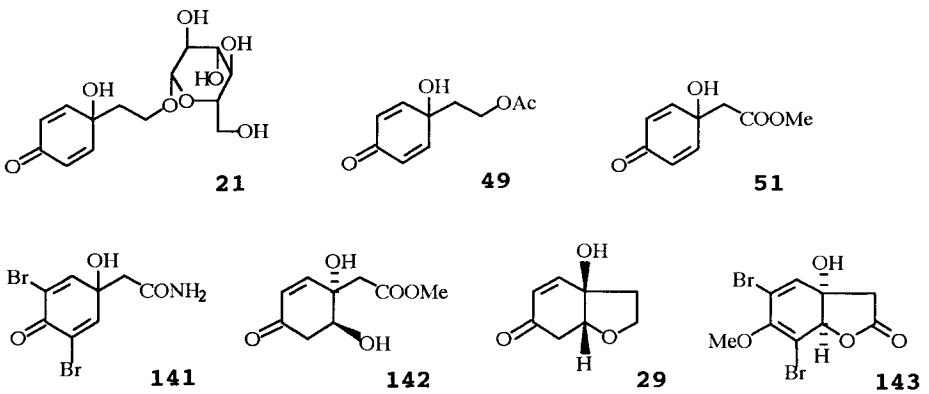
This extraordinary complex mechanism in the transformation of tyrosine (**83**) to lactam **92** is a consequence of the overlap of several unexpected conditions, by chance. Namely, the starting compound **83** was not soluble enough in water, and therefore, the reaction was run as a suspension, which required the reaction time long enough to allow a series of subsequent processes to occur. Efficient quenching of singlet oxygen as well as photoactivated rose bengal, by both the phenoxyl group and the primary amino group also slowed down the reaction extensively. Further, the primary photoproduct **90** automatically cyclized to an isomeric amino acid **86** with a secondary amino group, and by this process, the ionization potential of the corresponding nitrogen atom was lowered from 9 eV to 8 eV [130], resulting in the product **86** being a better substrate for the subsequent electron transfer process. A higher pH medium to increase the solubility of tyrosine (**83**) was also favored for this photooxidation by making the nitrogen atoms unprotonated. And finally, this reaction system yielded sufficient hydroperoxides which were just appropriate for oxidizing the imine **126** to the lactam **92**. It would be almost impossible to design such a complicated system, beforehand, from purely theoretical considerations.

4. THERMAL DIENONE-PHENOL REARRANGEMENTS

4.1 Biogenetical Interest

In the earlier chapters, it has been demonstrated that 4-alkylphenols will afford corresponding quinol hydroperoxides in good yields as the primary products on reaction with singlet oxygen (Sections 2.2, 2.3). However, it appears rather inconsistent that even though there are an abundance of phenolic compounds in nature, quinolic substances are not so common, and only a few examples could

be quoted, such as cornoside (**21**) [73,79], hallerone (**49**) [94], jacaranone (**51**) [95~97], a brominated antibacterial ketone **141** [164,165] and a ketoester **142** [166,167], in addition to isomerization products, rengyolone (**29**) [73] and a lactone **143** [166~169] (Scheme 28).



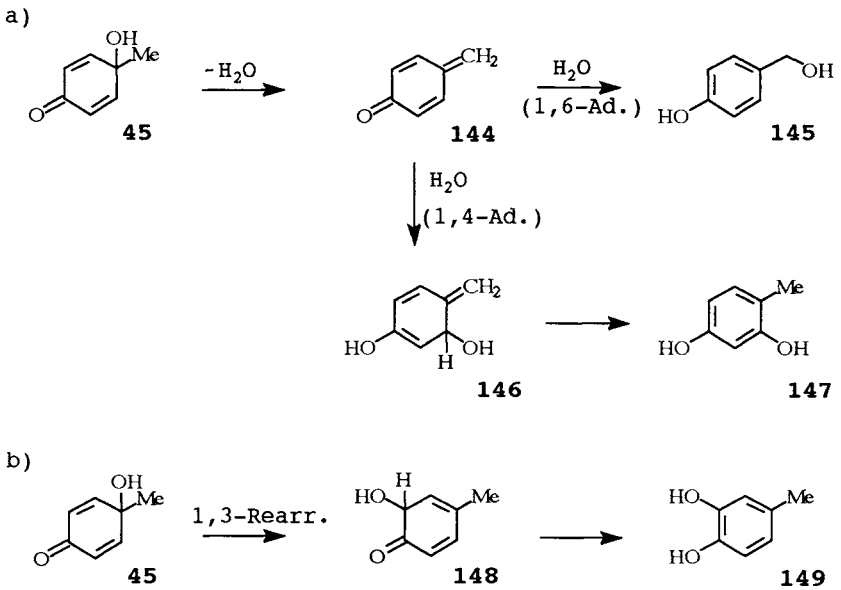
Scheme 28. Some Natural Quinols and Related Compounds.

In contrast, catechols and benzyl alcohols are the most common polyoxygenated substances found in nature, and they may be derived very likely from monophenolic substances. This trend is also followed by the constituents of *Forsythia suspensa* (Scheme 6), and the major congeners with C_6-C_2 moieties are 3,4-dihydroxyphenylethanol (**39**) occurring in frosythosides A (**26**) and D (**25**), and the benzylic hydroxylated substance **41** appearing in forsythosides C (**24**) and D (**20**) (Scheme 4). These aglycons are probably biosynthesized from 4-hydroxyphenylethanol (**19**) by oxygenation (Scheme 6).

Then, a possibility arises as to whether paraquinols could, at least in some *in vitro* conditions, be transformed into catechols and/or benzyl alcohols, by such processes as tentatively outlined in Scheme 29. It is not intended to debate with the established metabolic pathway of the transformation of monophenolic precursors to catechol derivatives by the ortho-hydroxylation mechanism [170~173], but to indicate an alternative chemical possibility, which could be utilized in some biological systems.

Namely, if quinone methide (**144**), a very unstable non-aromatic substance [174~176], is formed on dehydration of 4-methylparaquinol (**45**), the olefin will react with water, or any other available nucleophile, to resume an aromatic structure 4-methylresorcinol (**147**) by a 1,4-addition, or 4-hydroxybenzyl alcohol (**145**) by a more direct 1,6-addition [177,178].

Further, if one intentionally ignores an enone system in a quinol structure like **45**, then there is an allylic hydroxyl group capable of isomerizing to a γ position, by an allylic rearrangement (1,3-sigmatropic rearrangement [179,180]), and results in the formation of a catechol system as **149** (Scheme 29).



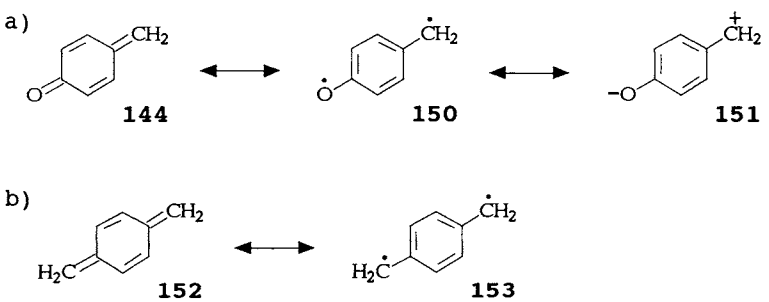
Scheme 29. Proposed Courses of Quinol Isomerization.

Catechols, resorcinols and benzyl alcohols are very popular structural features found in the natural products, and all of them could now be obtained from a single common quinol precursor, by a few isomerization processes. Certainly, it may be more appropriate to consider that the majority of resorcinols are biosynthesized from the so called β-polyketones [181~183], but there could be some resorcinols originating from monophenol precursors.

On account of such interests, the dehydration of quinol derivatives have been investigated, and following are some preliminary results obtained on the reaction of 4-methylquinol (**45**).

4.2 Reaction of 4-Methylquinol and Thionyl Chloride

A tertiary hydroxyl group could be dehydrated easily under mild acidic conditions, but in the case of 4-methylquinol (**45**), the hydroxyl group is located next to the electropositive β-carbon of an α,β-unsaturated carbonyl group. Thus it disfavors the formation of a carbocation at the γ position. On the other hand, the product **144** is a parabenzoquinone analog, and it may have a very unstable biradical form **150**, since paraxylylene (**152**) is also said to have a significant biradical character **153** (Scheme 30, b)) [184~186].



Scheme 30. Resonance Forms of Quinone Methide and Quinodimethane.

In fact, it would be very interesting to see whether the trienone will exist in the parabenzoquinone form **144** or the biradical form **150**. Further, an oxygen atom is much more electronegative than a carbon, and hence, the trienone **144** may have a significant contribution of the zwitter ion structure **151**, which could be more stable than the biradical form **150** (Scheme 30, a)). In this case, the uptake of a nucleophile should occur exclusively on the terminal carbon atom, and afford benzylic substituted phenols.

Based on these considerations, dehydration of quinols with thionyl chloride was investigated. Upon treatment of 4-methylquinol (**45**) with thionyl chloride at room temperature followed by gentle warming to about 60°C, two phenolic products **161** and **162** were obtained. The mass spectrum of the major product **161** indicated the presence of a chlorine atom in the molecule. In

addition, the ^{1}H NMR spectrum of **161** exhibited three ABX type aromatic hydrogen signals. The chemical shifts of these resonance peaks, together with ^{13}C NMR spectrum (Table 5), have enabled us to assign its structure as 2-chloro-4-methylphenol (**161**). Similarly, the structure of the minor compound was determined to be 2,6-dichloro-4-methylphenol (**162**).

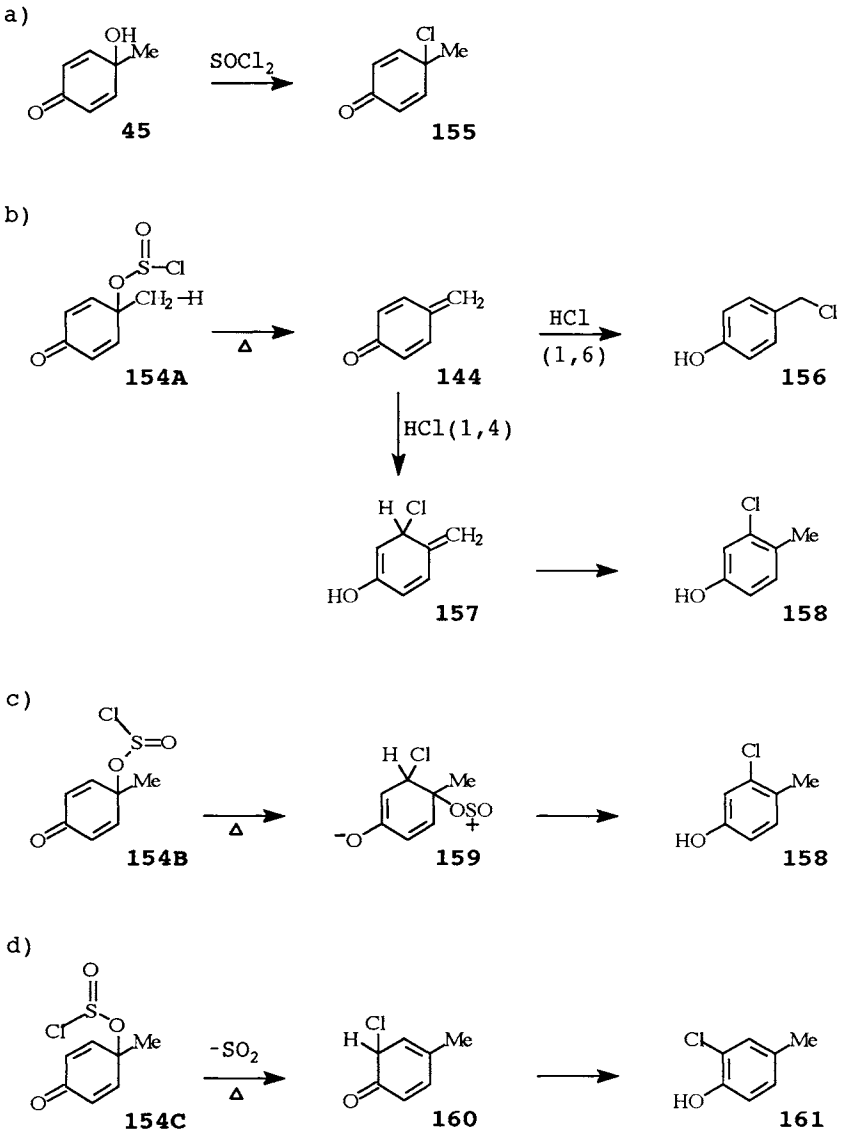
Table 5. NMR Data of Chlorinated Paracresols.

	paracresol (**42**)	2-chloride (**161**)	2,6-dichloride (**162**)
C-1	152.6 s	149.1 s	151.3 s
C-2	6.65 d; 115.3 d	119.3 s	125.9 s
C-3	6.95 d; 130.2 d	7.09 s; 130.9 d	7.06 s; 128.6 d
C-4	130.5 s	129.1 s	131.1 s
C-5	6.96 d; 130.2 d	6.95 d; 128.9 d	7.06 s; 128.6 d
C-6	6.65 d; 115.3 d	6.86 d; 115.9 d	125.9 s
C-7	20.6 s	2.26 s; 20.3 q	2.26 s; 20.3 q

This result indicated that the reaction did not proceed in the expected direction to yield the 4-chloro derivative **155** by simple substitution of the hydroxyl group with a chlorine atom (Scheme 31, a)), nor to give the quinone methide (**144**) by dehydration (Scheme 31, b)). The possibility of a Michael type addition through an intramolecular mode (**154B**) leading to the 3-chloro derivative **158** (Scheme 31, c)) was also excluded. In order to introduce a chlorine atom specifically to an α-position of the carbonyl group, an intramolecular mechanism with a transition state like **154C** is suggested (Scheme 31, d)). Namely, the major course of this reaction turned out to be an extraordinary 3,3-sigmatropic rearrangement in which two S-Cl sigma electrons were involved in the concerted [2σ + 2σ + 2π] type pericyclic reaction to afford the product **160**. The product isomerized to a stable aromatic structure **161** by subsequent enolization.

The reaction is isoelectronic with the Claisen rearrangement (ref. Scheme 37), but since there is only one double bond in **154**, the other 2π electrons are replaced by two electrons in the S-Cl sigma bond. It is also possible to accommodate two lone pair electrons on the chlorine atom to this reaction, and in this case,

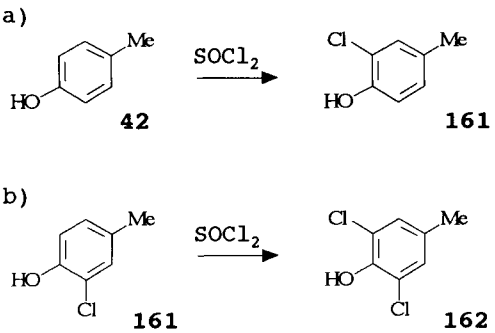
the reaction is isoelectronic to a carbanion rearrangement, which will be discussed in the next paragraph.



Scheme 31. Possible Reaction Pathway of Dehydration of 4-Methylquinol with Thionyl Chloride.

The reaction mechanism of the second chlorination to give the 2,6-dichloro derivative **162** was not obvious. Paracresol (**42**) was

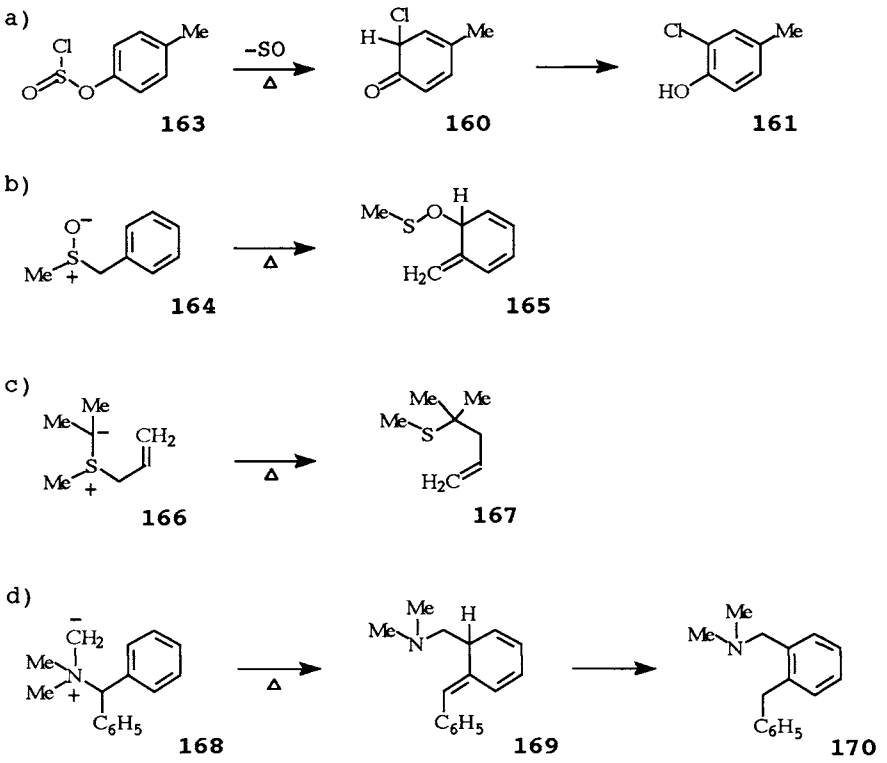
found to be chlorinated with thionyl chloride under the same conditions to yield the 2-chloride **161** (Scheme 32, a). Therefore, the monochloro derivative **161** was probably chlorinated again, by the reagent presented in excess to furnish the 2,6-dichloro derivative **162** (Scheme 32, b)). The reaction may be described by a 2,3-sigmatropic rearrangement with participation of two S-Cl sigma electrons, i.e., a new [2σ + 2σ + 2π] pericyclic reaction again.



Scheme 32. Chlorination of Phenols by Thionylchloride.

Although these two chlorination reactions are mechanistically similar, they are not identical, because the former reaction (Scheme 31, d)) should yield a molecule of sulfur dioxide, while the latter reaction (Scheme 33, a)) will yield one molecule of sulfur monoxide.

It is very unusual, and even without precedence, to have two S-Cl bonding electrons involved in a pericyclic reaction. But close analogies could be seen, if it is assumed to have the two lone pair electrons on the chlorine atom taking part in such a reaction. Namely, the two lone pair electrons and two pi electrons constitute a system isoelectronic to an enophile part in a 1,3-dipolar cycloaddition [179,180]. But a closer analogy may be the Sommelet rearrangement, in which a benzyl ammonium ylid **168** is transformed thermally to an amine **169** by a 2,3-sigmatropic rearrangement (Scheme 33, d)) [187~189]. Similar isomerizations have also been encountered in a benzyl sulfoxide **164**, as well as an allyl sulfonium ylid **166**, yielding a sulfenate **165** and a sulfide **167** respectively, by 2,3-sigmatropic rearrangements (Scheme 33, b) and c)) [190~199]. The most important difference between these isomerizations and the reactions demonstrated by chlorosufinates **154** and **163** is that latter reactions are accompanied by fragmentation processes.



Scheme 33. 2,3-Sigmatropic Rearrangemnts.

Direct electrophilic chlorination of the phenyl group may not be important in a pyridine solution, because chlorine atom is least electrophilic, and in addition, esterification of a phenoxyl group to yield a thionyl ester like **163** should predominate under such condition, and deactivate the phenyl group.

4.3 Pyrolysis of 4-Methylquinyl Acetate

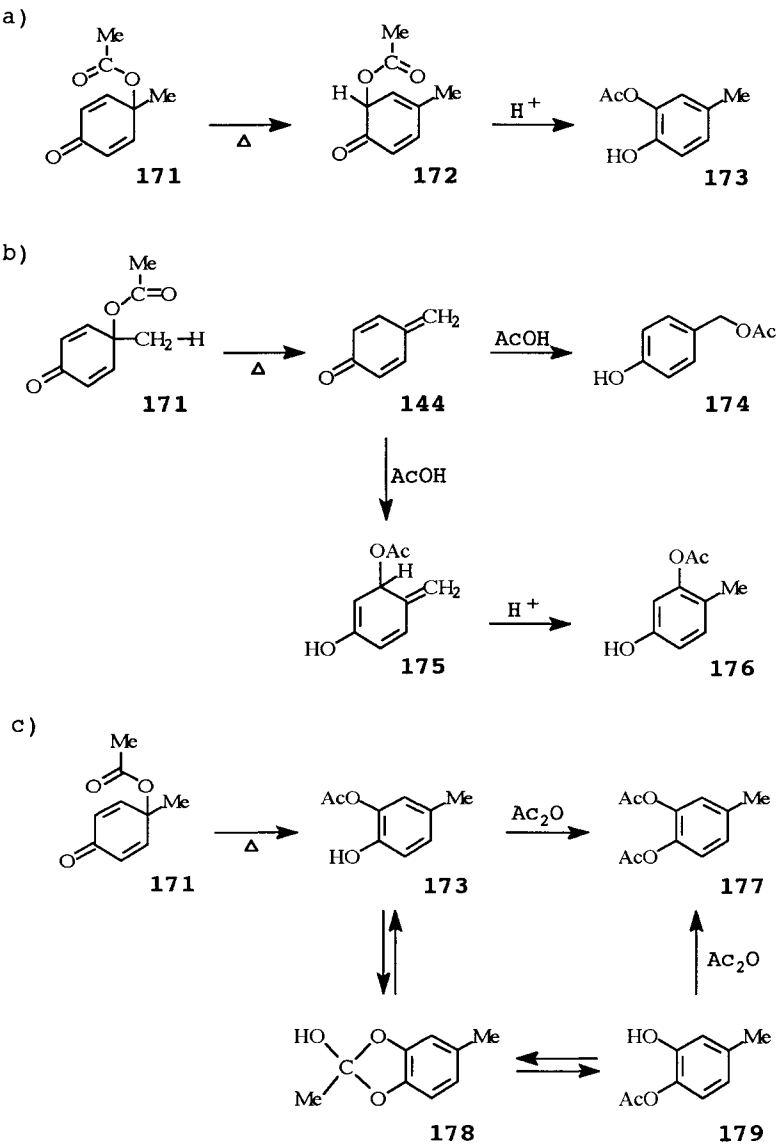
The thermal decomposition of quinol chlorosulfite **154**, presented in the previous section suggested the feasibility of similar 3,3-sigmatropic rearrangement occurring in the corresponding acetate **171**. This reaction will introduce an oxygen substitution at an α-position to the carbonyl group, and lead to a catechol derivative by subsequent enolization. Thus, if the quinol acetate **171** is pyrolyzed, the acetoxyl group should migrate from the γ-position to an α-position of the carbonyl group, through, in this

case, a genuine 3,3-sigmatropic rearrangement (or a Claisen rearrangement) (Scheme 34, a)). Another point of interest in this case is that, the pyrolysis of acetate **171** could yield an olefin, namely quinone methide **144**, by another pericyclic reaction involving six electrons. The trienone **144** may be stabilized by picking up a nucleophile, and yield the respective acetate of a benzyl alcohol **174** or a resorcinol **176** (Scheme 34, b)).

The quinol **45** was accordingly first treated with acetic anhydride in pyridine to obtain the acetate **171** in a quantitative yield. Then the ester **171** was heated in cumene to 120°C until the starting compound **171** was no longer detected by thin layer chromatography. Fractionation of the product mixture by column chromatography, followed by spectroscopic analysis, revealed that the reaction product was very complicated. The result obtained could be accounted by radical type couplings of the acetate **171** and the solvent, cumene, in a one to one ratio. It is unexpected to have radical type reactions taking place at such a low temperature. Whether this is because of the quinone methide formation or not is uncertain, since there is no further evidence regarding the formation of benzyl acetate **174** or related substances being ascribable to the quinone methide.

The reaction medium was then changed to *n*-dodecane, since it was thought to be inert under the reaction condition. The acetate **171** was again heated in the hydrocarbon until the reaction started. The reaction of chlorosulfite ester **154** occured around 60°C for the pseudo-3,3-sigmatropic rearrangement. Therefore, it was anticipated to be much easier to have the migration of the acetoxyl group by a genuine Claisen rearrangement. In cumene, a reaction did occur at 120°C, but it went in another direction. Surprisingly, no change of the acetate **171** was observed in dodecane below 160°C.

The reaction temperature was raised to 180-200°C, and at last the decomposition of the acetate **171** started, and afforded a phenolic product. In order to avoid complications involving formaiton of the isomeric acetate (**179**) by an acetyl migration (Scheme 34, c)), the product (**173**) was acetylated further with acetic anhydride and sodium acetate. The resulting ester was identified as the expected 4-methylcatechol diacetate **177**, based on the spectroscopic data (Table 6) and direct comparison with those of the authentic sample.



Scheme 34. Thermal Rearrangements of Quinol Acetate.

In this thermal isomerization, the catechol diacetate (**177**) was the only product which could be characterized, and the isolated yield was more than 80%, in addition to a small amount of insoluble polymers. Interestingly, there is no sign of the formation of such a benzylic substitution product like **174**. Therefore, in this case, a 3,3-sigmatropic rearrangement predominated, just as in the

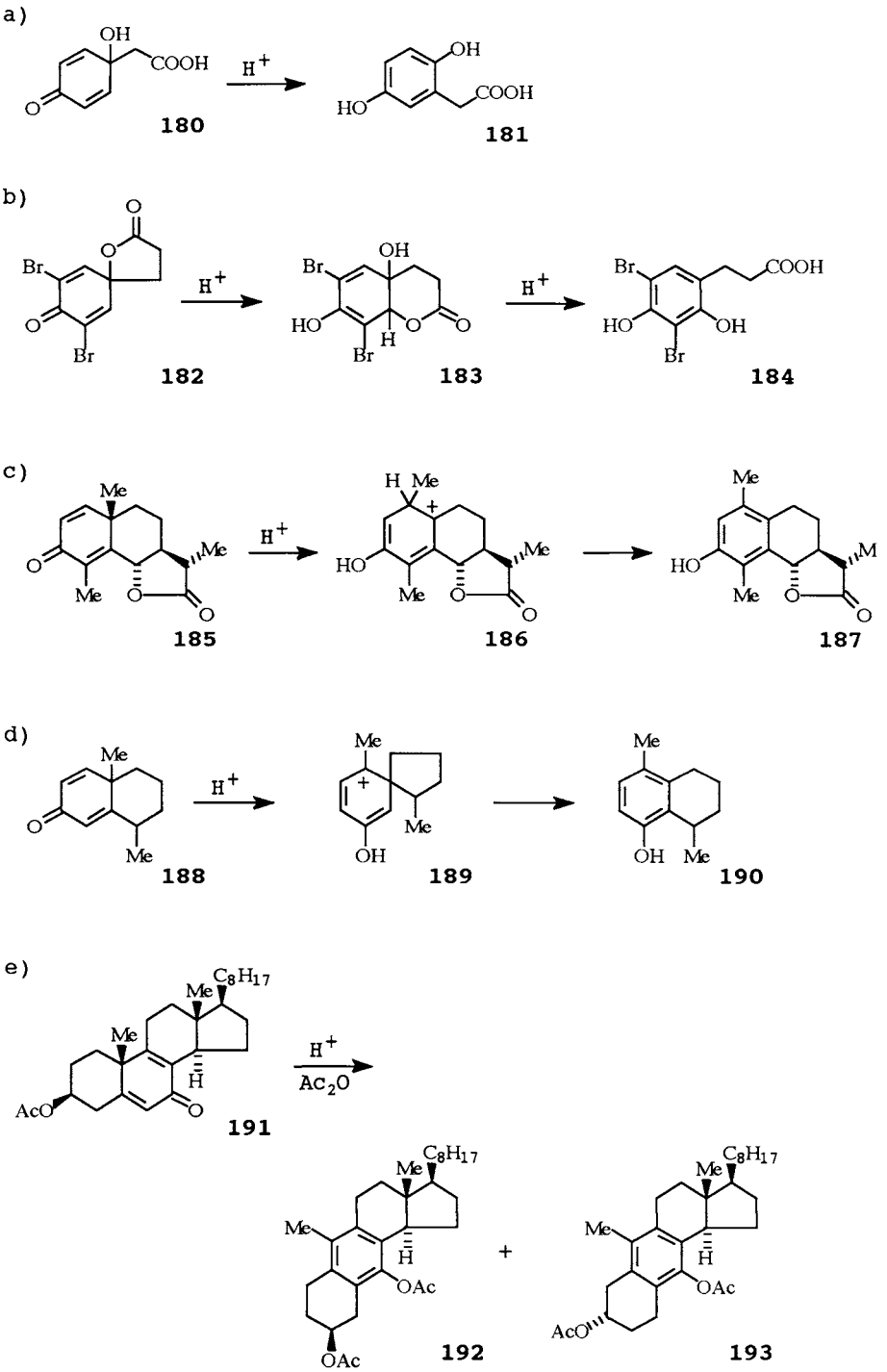
reaction of chlorosulfite ester **154** described in the preceding section. Again, no quinone methide **144** formation by a simple

Table 6. NMR Data of 4-Methylcatechol Diacetate (in $CDCl_3$).

	diacetate (**177**)		authentic	
C-1		141.7 s	141.7	
C-2		139.8 s	139.7	
C-3	7.10 (br.s)	123.0 d	122.9	
C-4		136.9 s	136.8	
C-5	7.02 (br d)	123.9 d	123.8	
C-6	6.95 (br d)	127.2 d	127.2	
C-7	2.33 (3H s)	21.0 q	20.9	
Ac	2.77 (6H s)	168.4, 168.5	168.4,	168.5
		20.7, 20.7	20.6,	20.6

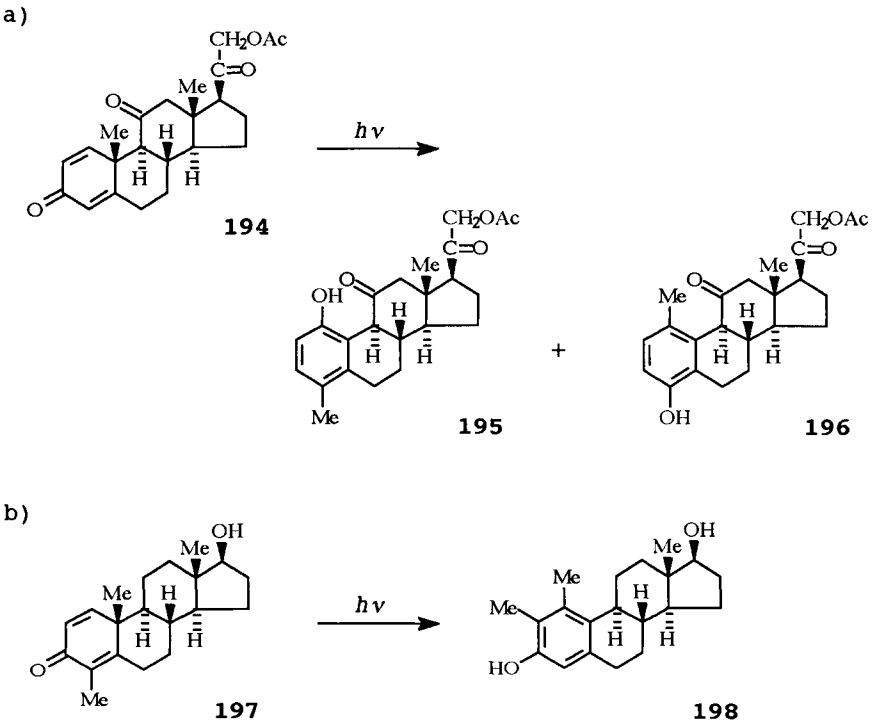
thermal deacetoxylation was indicated (Scheme 34, b)). Since it is not electronically favored to have a positive charge at the γ-position to a carbonyl group, as mentioned at the beginning of this section, a non-ionic mechanism of thermal decomposition seemed more reasonable. The fact that the pyrolysis of acetate **171** was not observed in boiling acetic anhydride (bp 138°C) at all, also ruled out ionic mechanisms. Consequently, the thermally allowed concerted 3,3-sigmatropic rearrangement [180] with a six electron system is suggested for these cases.

Transformation of a cyclohexadienone to a phenol derivative is known as the Dienone-Phenol Rearrangement. These reactions proceed to furnish the more stable aromatic systems from the unstable cross conjugated cyclohexadienones, mostly through ionic intermediates (Scheme 35). Thus quinolacetic acid **180** was converted under acidic conditions to homogentidic acid (**181**), by 1,2-migration of the carboxymethyl group (Scheme 35, a)) [200~205]. A bromo-γ-lactone **182** was similarly isomerized to a phloroglucinol **184**, although this reaction could also be interpreted by assuming the formation a δ-lactone intermediate **183** followed by its hydrolysis, rather than direct 1,2-oxygen migration (Scheme 35, b)) [205,206]. Other such examples, as santonin (**185**) and a sterol **191**, showed 1,2-alkyl migrations to occur, in which methylene shift was preferred over methyl migration (Scheme 35, c-e)) [207,208].



Scheme 35. Acidic Dienone-Phenol Rearrangements.

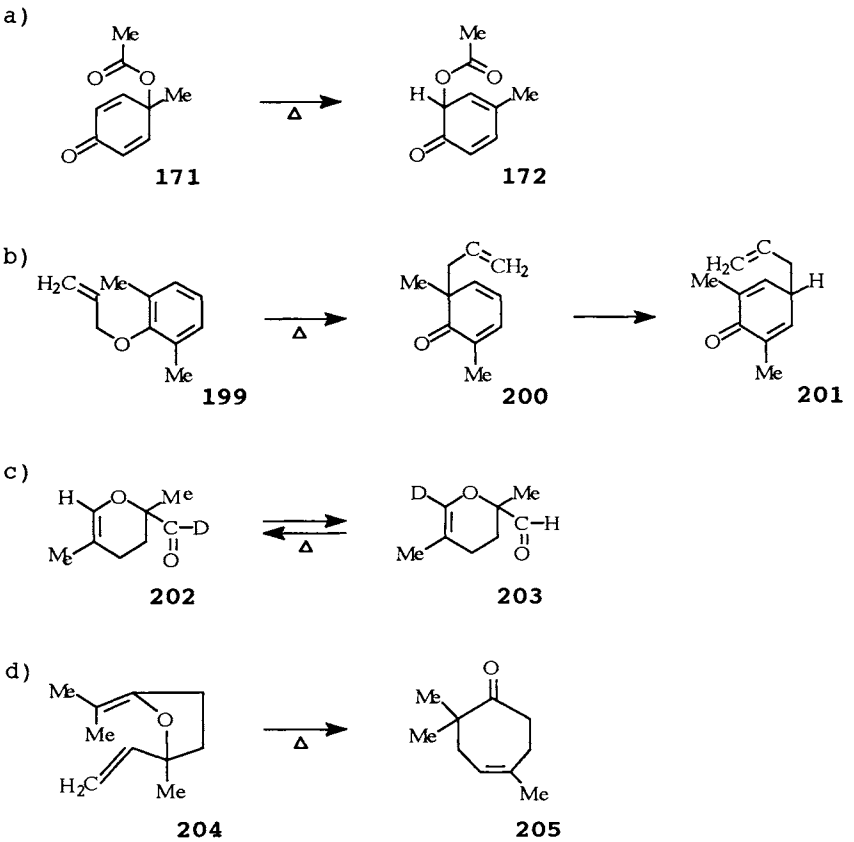
Similar rearrangements have also been encountered in photochemical processes. Steroidal dienones **194** and **197** have been transformed, by photoactivation, into phenolic products like **195**, **196** and **198** through complicated multi-step bond alternations (Scheme 36) [209~212].



Scheme 36. Photochemical Dienone-Phenol Rearrangement.

In contrast, the mode of the reaction in the rearrangement of quinol acetate **171**, by simple heating, to a derivative **172** is similar to the Claisen rearrangement (suprafacial 3,3-sigmaropic rearrangement [180]), or more specifically the Oxy-Cope rearrangement (Scheme 37, c), d)) [213~216].

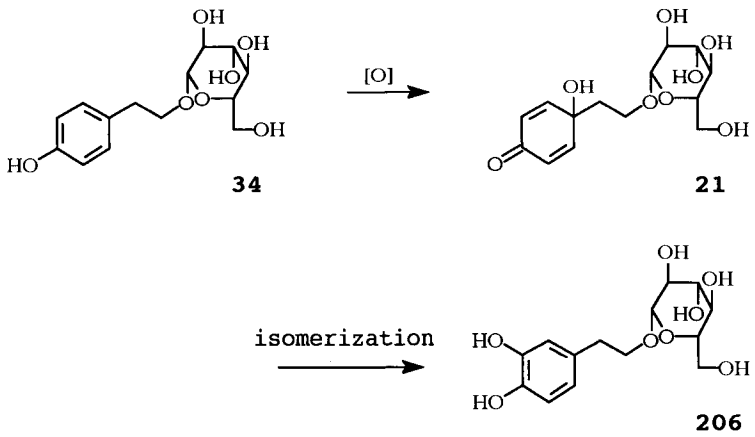
The reaction does not require an acid catalyst, nor photoactivation, but it proceeds through ground state allowed thermal bond alternations to yield carbonyl compounds. It is not mechanistically identical to those reactions induced by acid catalysis or photoactivation (scheme 35, 36). Therefore, transformation of the



Scheme 37. Claisen Rearrangements.

chlorosulfite ester and the acetate of 4-substituted quinols by thermal [2σ + 2σ + 2π] or [2π + 2σ + 2π] pericyclic reactions [180] may be classified as a new type of dienone-phenol rearrangement, or a thermal dienone-phenol rearrangement [220].

By this new "thermal dienone-phenol rearrangement", 4-hydroxyphenylethanol derivatives, such as salidroside (**34**), and 3,4-dihydroxyphenylethanol derivatives, like forsythosides A and E (**26** and **25**, Scheme 4), are now correlated in a formal sense. Therefore, these experimental results support the biogenetic pathway, from phenols (salidroside (**34**)) to quinols (cornoside, (**21**)) and then to catechols (glucoside **206**) [221~223], as represented in the form of their glucosides (Scheme 38).



Scheme 38. Formal Biomimetic Correlation of Salidroside to the Catechol Glucoside.

5. CLOSING REMARKS

The results of our chemical investigations on natural products described so far, represent presumed metabolic pathways, and experiences of some interesting chemistry. Further, we have obtained a variety of interesting compounds with respect to their structural features as well as some biological activities.

4-Hydroxycyclohexanones have a tendency to form dimethyl ketals by simply dissolving in methanol. The presence of two substituents at C-1 and C-6 positions of a glucosyl group exert very severe steric interaction, when they are sufficiently long, but not simply bulky. Further, the quinolamino acid cyclizes to pyrrolidinecarboxylic acid stereo- and regio-specifically to yield the optically pure product. The acetate and chlorosulfite of 4-methylquinol isomerize through new types of thermal dienone-phenol rearrangements to yield catechol analogs, and so on.

In addition, some of the compounds appearing in this article have been tested for their biological activities, and antibacterial, anticoccidium, cytotoxic and hypotensive effects have been recorded, and are summarized in Table 7 [77,220].

Table 7. Pharmacological Activity of Selected Compounds

substance	effect	activity (dose)
4-hydroxyphenyl-ethanol (**19**)	anticoccidium	66% (1 ppm)
rengyol (**22**)	anticoccidium	32% (10 ppm)
forsythoside A (**26**)	antibacterial (*Sta. aureus*)	++
	anticoccidium	28% (100 ppm)
	cytotoxic (P-388)	IC_{50} 5.46 μg/ml
	(HOC-21)	19.0 μg/ml
	(MKN-28)	18.4 μg/ml
rengyoxide (**28**)	anticoccidium	23% (10 ppm)
rengyolone (**29**)	antibacterial (*Sta. aureus*)	++
	cytotoxic (P-388)	IC_{50} 6.0 μg/ml
salidroside (**34**)	anticoccidium	20% (10 ppm)
4-methylquinol hydroperoxide (**44**)	antibacterial (*Sta. aureus*)	++
	anticoccidium	18% (10 ppm)
	cytotoxic (P-388)	IC_{50} 0.44 μg/ml
	(HOC-21)	1.16 μg/ml
	(MKN-28)	1.12 μg/ml
4-methylquinol (**45**)	antibacterial (*Sta. aureus*)	++
	anticoccidium	63% (1 ppm)
	cytotoxic (P-388)	IC_{50} 0.68 μg/ml
	(HOC-21)	1.04 μg/ml
	(MKN-28)	1.12 μg/ml
paracresol dimer (**46**)	antibacterial (*Sta. aureus*)	++
	anticoccidium	12% (0.1 ppm)
hallelone (**49**)	anticoccidium	96% (10 ppm)
jacaranone (**51**)	cytotoxic (P-388)	IC_{50} 32 μg/ml
ketolactam (**92**)	hypotensive (rat)	5 mg/kg
diolamino acid (**101**)	hypotensive (rat)	5 mg/kg

ACKNOWLEDGEMENTS

The author is greatly indebted to Dr. Paul de Mayo, Professor Emeritus of the University of Western Ontario, Canada, who directed my attension to the oxidation chemistry.

The work described in this article has been carried out in the Pharmaceutical Institute, Tohoku University, by most skilled and devoted colleagues, Dr. Kazuhiko Seya, presently at the Department of Medicine, Tohoku University, Miss Kaori Hirayama, presently at Mitsubishi Yuka Co. Ltd., Mr. Hirokazu Iida presently at Kyoto University and Miss Yuko Aota at Tohoku University. Some of the biological assays have been carried out at the Aburahi Laboratories of Shionogi & Co. Ltd., by Drs. Yoshiyuki Hayashi and Yasuyoshi Takeuchi, and at the Central Laboratories of Daiichi Pharmaceutical Co. Ltd., by Dr. Seiichi Yokoyama, to whom thanks are due.

The author is also very grateful, for the valuable advice and technical assistance, to Professor Yoshiharu Usui at Ibaraki University and Professors Hiroshi Horino, Keiichiro Fukumoto, Kunio Ogasawara and Masataka Ihara at Tohoku University. The drawings in schemes and this typescript have been prepared by Miss Yuko Aota and Miss Yukiko Okano.

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Atta-ur-Rahman (Ed.) *Studies in Natural Products Chemistry, Vol. 16*

Furan in the Synthesis of Natural Products

Jerzy Raczko and Janusz Jurczak

1. INTRODUCTION

The furan ring is a key element of many natural products like terpenes or alkaloids, and is also frequently found in compounds of medicinal and agricultural interest [1]. The versatility of the furan ring additionally resulted in the utilisation of this moiety in the synthesis of a range of natural products.

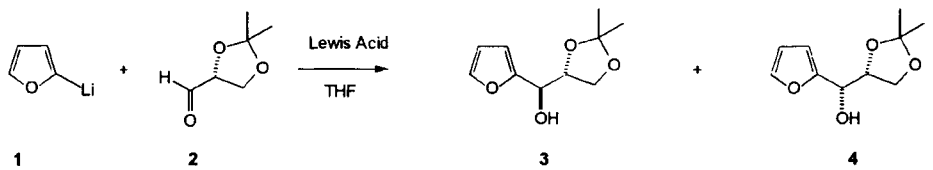
Modifications of the furan ring include its use as diene in Diels-Alder chemistry and oxidation to unsaturated carbonyl compounds, for example butenolides, 2-enopyranos-4-uloses or enediones. Since the cycloaddition processes were sufficiently reviewed in the literature [2-5], we concentrate on the above mentioned methods. This review illustrates how the furan ring may be incorporated into a synthetic scheme and describes how further modifications resulted in the synthesis of some natural products.

2. INCORPORATION OF THE FURAN RING INTO A MOLECULE

The most commonly employed method for introduction of the furan ring consists of the addition of organometallic reagents to electrophiles. Most frequently organolithium furan derivatives are used, although a variety of other organometallic reagents like the mercury [6], magnesium [7], aluminium [8], zinc [9], tin, lead [10] or copper furan [11] derivatives were described in the literature.

Addition of furyllithium to α-alkoxyaldehydes, investigated by Mukaiyama *et al.*, is the basic method for stereoselective synthesis of furylcarbinols [12]. In preliminary studies, simple addition of the 2-furyllithium **1** to 2,3-*O*-isopropylidene-**D**-glyceraldehyde **2** resulted in a mixture of diastereoisomers. However,

when carried out in the presence of metal salts (Table 1), the reaction proceeds stereoselectively to afford the *anti*-alcohol **3** predominantly (Scheme 1).

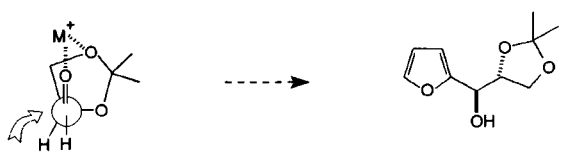


1 **2** **3** **4**

Scheme 1

Table 1. The effect of the metal salt on the stereoselectivity of the reaction of **1** with **2**

Entry	Lewis acid	Temperature	Yield (%)	**3/4**
1	-	-78°C	68	40/60
2	$MgBr_2$	0°C	49	50/50
3	$SnCl_4$	0°C	58	95/5
4	$ZnCl_2$	-78°C	10	>95/<5
5	$ZnCl_2$	0°C	60	90/10
6	$ZnBr_2$	0°C	75	95/5
7	ZnI_2	0°C	57	>95/<5



I **3**

Fig. 1

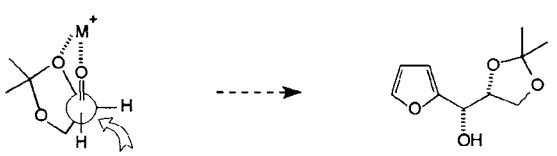
The enhancement of the *anti*-stereoselectivity by addition of ZnX_2 was explained by the coordination of the zinc(II) atom with carbonyl oxygen and 3-oxygen of the dioxolane ring, and nucleophilic attack from the less hindered side of the molecule (Fig 1). The same reaction with 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose **51** proceeds also stereoselectively, the additional substituent (CH_2OBn) being distant from the reaction site, has an only slight effect on the reaction pathway [13]. Recently,

Martin *et al.* found that replacement of the *O*-benzyl group of **51** on the γ-hydroxy function with a more bulky *tert*-butyldiphenylsilyl protecting group favors addition *via* α-chelate. In the presence of an excess of $ZnBr_2$ the *syn*-adduct originates with 13:1 stereoselectivity [14].

The reaction of 2-methylfuran with the aldehyde **2** was also studied by Jurczak and Pikul [15]. Under high pressure (10 kbar) 2-methylfuran reacts with **2** to afford **3** and **4** in poor yield and 76:24 *anti*-stereoselectivity. Addition of $ZnBr_2$ only slightly influences the yield and stereoselectivity (82:18). This result approximately reflects the differentiation between both faces of the CO double bond of **2** in the process described by Felkin model. This reaction was carried out for the lithium derivative of 2-methylfuran, with two different modes of $ZnCl_2$ addition. In mode A, $ZnCl_2$ was first stirred with the aldehyde **2**, followed by addition of the lithium derivative. In mode B, $ZnCl_2$ was mixed with the lithium derivative, followed by addition of the aldehyde **2** (Table 2).

Table 2. Effect of addition mode on stereoselectivity of the reaction of **1** with **2**

Mode of addition	Temperature	Yield (%)	**3/4**
-	0°C	80	47/53
-	-78°C	60	46/54
A	0°C	70	79/21
B	0°C	69	80/20
A	-78°C	58	57/43
B	-78°C	15	91/9

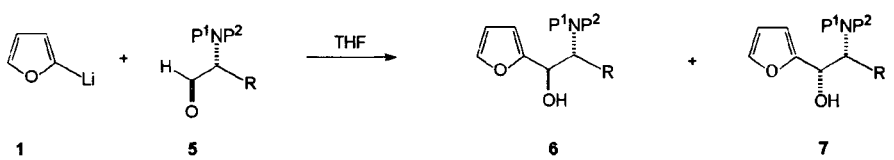


II **4**

Fig. 2

The reaction performed at 0°C with either mode of addition of $ZnCl_2$ exhibited a similar degree of *anti*-selectivity. Results obtained at -78°C were in great contrast to those found at 0°C. In mode A the predominance of the *anti*-product was only limited, while in the case of mode B the *anti*-selectivity was considerably enhanced. These facts can be rationalized by an analysis of various coordinatig interactions between the metal cation and oxygen atoms of the aldehyde **2** (Figures 1 and 2). There is an evident possibility of continuous transition of the chelating cation from its interaction with α-oxygen to that with β-oxygen, followed by changes in the conformation of **2**. The most favored conformation seems to be related to the kind of metal. For the small lithium cation, the conformation II (α-chelation) is predominant, this explaining the low *syn*-selectivity. In the case of more bulky metals (e.g. Zn) the conformation II could be expected to be preferred, this explaining the *anti*-selectivity. It seems that the active organometallic reagent has a much stronger coordination ability, as compared with the metal salt itself. The very low *anti*-selectivity found for the reaction carried out according to mode A at -78°C indicates that the organolithium reagent interacts with aldehyde much stronger than $ZnCl_2$, although the organozinc derivative is probably formed *in situ*. This latter process is much more rapid at 0°C, since there is no difference in the results of this reaction between both modes of its carrying out.

Addition of furyllithium proceeds stereoselectively also with α-amino aldehydes (Scheme 2) [16]. This reaction performed with *N,N*-diprotected alaninals [17] and threoninals [18] in THF at -78→-40°C predominantly afforded the *anti*-alcohols (Table 3).



1 **5** **6** **7**

Scheme 2

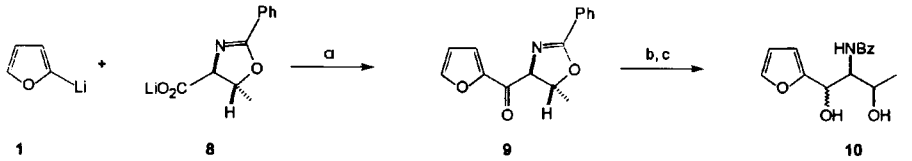
Table 3. Addition of furyllithium to α-amino aldehydes

Entry	Aldehyde	Yield %	6/7
1	*N,N*-dibenzyl-D-alaninal	90	91/9
2	*N*-Bn,*N*-BOC-D-alaninal	88	90/10
3	*N*-BOC,*N*-Me-D-alaninal	84	96/4
4	N-Bn,*N*-Ts-D-alaninal	86	92/8
5	*N*H-Ts-*O*-TBDMS-D-*allo*-threoninal	54	66/34
6	*N,N*-dibenzyl-*O*-BOM-D-*allo*-threoninal	88	94/6
7	*N*-Bn,*N*-BOC-*O*-BOM-D-*allo*-threoninal	81	>99/1
8	*N,N*-dibenzyl-*O*-TBDPS-D-*allo*-threoninal	76	62/38
9	*N,N*-dibenzyl-*O*-MEM-D-*allo*-threoninal	61	95/5
10	*N*H-Ts-*O*-TBDMS-L-threoninal	59	94/6

Nonchelation control can be explained by the Felkin-Anh model, but the high degree of stereoselectivity was rather surprising, owing to the lack of the chelation-affected limitations of the degrees of freedom. There is a noteworthy example of α-amino aldehydes bearing an additional β-alkoxy substituent. High *anti*-selectivity was achieved only in the presence of chelating protective groups like BOM or MEM (Table 3, entries 6,7,9), what suggests β-chelating interactions between aldehyde and nucleophile. An exepction is L-threoninal (entry 10) which reacts also stereoselectively. Explanation of this process remains obscure and calls for further studies.

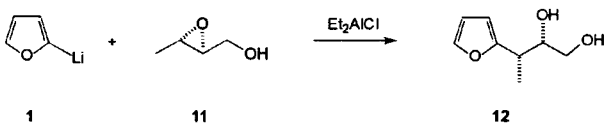
Generally, in the reactions of α-amino aldehydes chelation control is more difficult and requires application of strong Lewis acids like $SnCl_4$ or $TiCl_4$ [16]. In the case of the reaction of furan with a protected serinal, initial studies were performed by Reetz *et al.* with $MgCl_2$ and $ZnCl_2$ as additives [19]. In both cases nonchelation control increased significantly (from 81:19 to >95:<5 in the case of $ZnCl_2$); however, the percentage of conversion dropped dramatically from 87 to 31%.

2-Furyllithium was also employed by Achmatowicz and Szechner in the synthesis of sugars [20,21]. Its addition to lithium salts of α-amino acids afforded furyl ketones which were reduced with metal hydrides to the required furyl carbinols (Scheme 3). The shortcomings of this method include the moderate yield of the addition step and the lack of stereoselectivity in the reduction of furyl ketones [22].



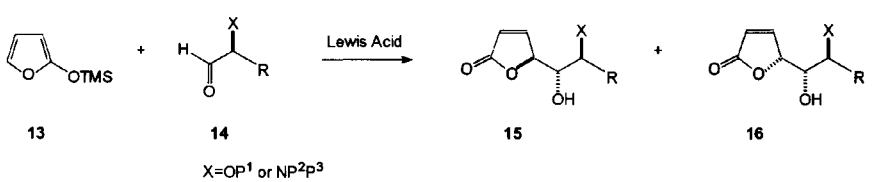
Scheme 3. (a) Et_2O, 0°C; (b) $LiAlH_4$, Et_2O; (c) HCl, THF.

Another method for incorporation of the furan ring into a synthetic framework consists of the reaction of suitable metaloorganic derivatives of furan with epoxides. This simple process can sometimes present some difficulties. In certain cases the application of special lithiation reagents like 3-methyl-phenyllithium is necessary [23], whereas in other cases only modified organometallic derivatives like organoaluminium [24] or the higher order cyanocuprates [25] ensure an acceptable yield, regio- and diastereoselectivity (Scheme 4) [26].



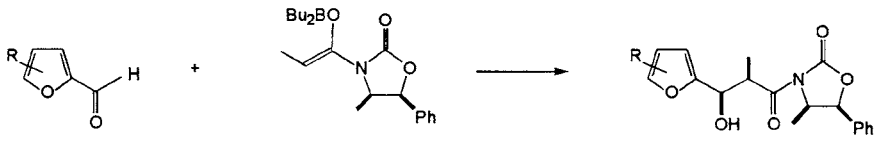
Scheme 4

2-Trimethylsilyloxyfuran **13** is another nucleophilic furan reagent used in additions to bromides [27,28], imines [29], α-alkoxy [30], α-amino [31] and sugar aldehydes [32]. This reaction catalyzed by Lewis acids ($SnCl_4$, $TiCl_4$, $BF_3{\cdot}Et_2O$) affords butenolides in very good yields and with high stereoselectivities (Scheme 5). In most cases exclusively *anti*-1,2-selectivity was observed, consistently with nonchelation controlled approach of the nucleophile to the aldehyde or imine. Likewise, for α-amino, α-alkoxy and sugar aldehydes excellent inherent diastereoselectivity was achived (>95:<5), testifying to the usefulness of this reaction in some syntheses of natural products.



Scheme 5

An alternative method for introduction of the furan ring consists of aldol condensation of furfuraldehyde with a variety of boron enolates. Aldol methodology proved to be most effective; it was developed by Evans using di-*n*-butyl boron enolates derived from chiral oxazolidinones (over 99% of *syn*-diastereoselectivity) [33] (Scheme 6); optically pure boronates like diisopinocampheyl boronates derived from (+)α-pinene were also used [34]. This methodology was frequently employed by Martin *et al.*, and resulted in some syntheses of antibiotics and their precursors.



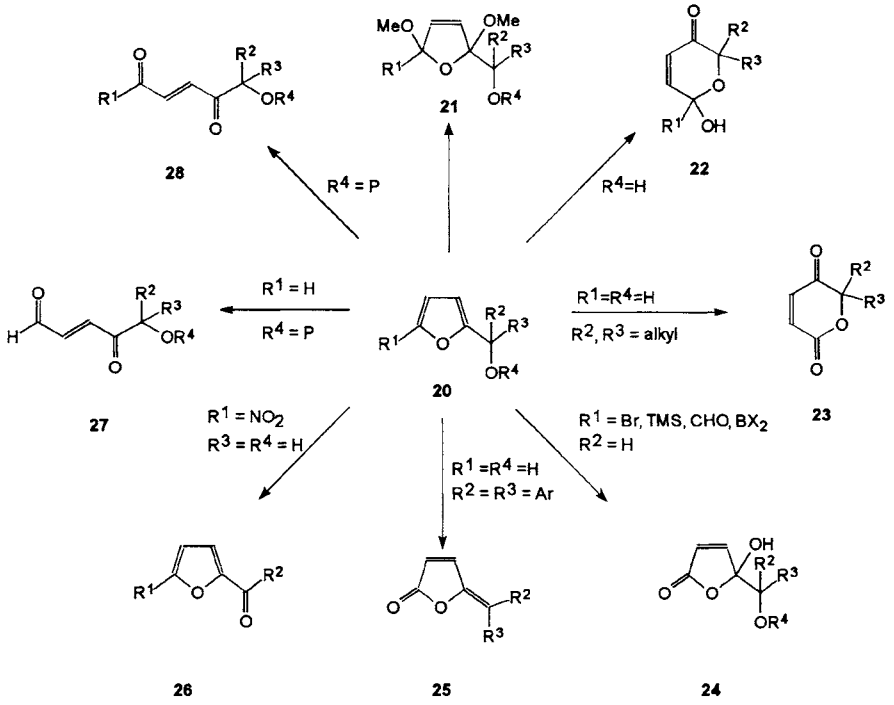
17 **18** **19**

Scheme 6

There are also many examples of other heterocyclic analogues used in total syntheses of natural products. There is the particularly noteworthy excellent method, developed by Dondoni *et al.* [35], which consists in employment of the thiazole ring as an aldehyde equivalent and in linear iterative creating of chiral centers *via* addition of a variety of thiazole derivatives to imines [36], α-alkoxy [37] and α-amino aldehydes [38]. This strategy found application in many syntheses of carbohydrates, amino and imino sugars.

3. TRANSFORMATIONS OF THE FURAN RING

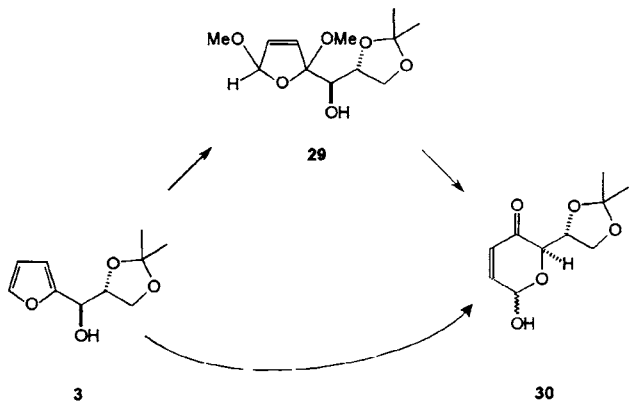
The furan ring is a very versatile C-4 building block, which can be transformed into a variety of synthons, depending on their structure and reagents used. Oxidative conversion of furyl carbinols is most commonly applied (Scheme 7). Oxidative transformation was independently elaborated by several groups. The original Clauson-Kaas method [39], consisting in 1,4-addition of bromine to the furan ring in methanol, was later modified by use of a variety of oxidants.



Scheme 7

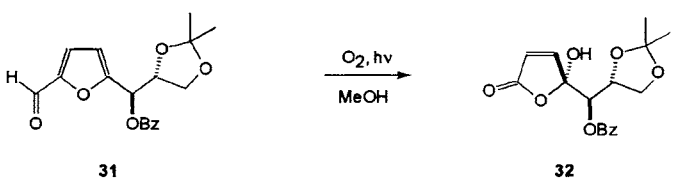
Intermediates most often applied in the synthesis of natural products are 2-enopyranos-4-uloses **22**, which were originally prepared from furyl carbinols in a two-step sequence: treatment with bromine in methanol leading to dihydrofuran hemiacetals **21** and subsequent rearrangement to uloses under acidic conditions. This procedure was simplified by application of bromine in an acetonitrile-water solution [40], chlorine in methanol-water [41], 3-chloroperoxybenzoic acid [42], pyridinium chlorochromate [43], *N*-bromosuccinimide [44], *t*-butylperoxide-VO(acac)$_2$ [45], singlet oxygen generated photochemically or chemically [46,47], and lastly by use of electrochemical methods [48] (Scheme 8). In some special cases, oxidation with pyridinium dichromate leads directly and almost quantitavely to dihydropyran-2,4-diones **23** [49].

Furan derivatives bearing substituents like TMS, Br, BX_2 or the formyl group can conveniently be used as an equivalent of butenolide [50-54]. This process is performed with oxidants like PCC or peroxyacids and also photochemically. This latter



Scheme 8

most often employed method affords stable, monomeric, unsaturated ozonides which under certain circumstances can even be isolated and characterized without subsequent rearrangement [55]. Photooxidation of the furfural derivative **31,** containing in position 5 of the furan ring a chiral chain originating from 2,3-*O*-isopropylidene-D-glyceraldehyde, proceeds stereoselectively yielding the hydroxybutenolide **32** [54]. Unfortunately, the instability of such compounds limits their usefulness for the synthesis (Scheme 9).



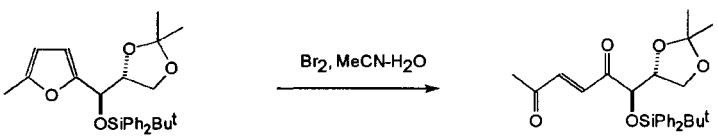
Scheme 9

Oxidation of furyl carbinols with PDC [49], generally less selective than the above-described methods, affords- apart from some by-products- butenolides **25** in a process involving a stabilized carbenium ion intermediate which subsequently undergoes nucleophilic attack by the oxidant in position 5 of the furan ring.

All previously described methods are characterized by regiospecific behavior of the reagents acting as oxidants and dienophiles with respect to the furan ring, but leaving the

alcoholic function untouched. On account of deactivation of the heteroaromatic nucleus by the NO_2 group, reagents like PCC preferentially oxidize the alcoholic function leading to 5-nitro-2-furyl ketones **26** in high yields and selectivities [56].

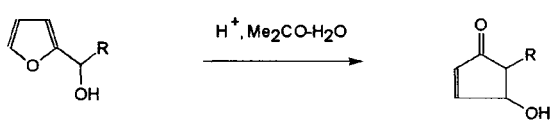
In the case of furyl carbinols with a protected hydroxy group oxidation leads to α,β-unsaturated dicarbonyl compounds (Scheme 10). The method of choice seems to be again the use of bromine in an acetonitrile-water solution [57,58], although MCPBA [59] or PCC [60,61] were also frequently used. Oxidation gives exclusively or preferentially the *Z*-enediones which isomerize to the *E*-form either upon treatment with strong acids (the method with MCPBA) or spontaneously after 1-h stirring at room temperature (for the bromine version).



33 **34**

Scheme 10

A different example of transformation of furyl carbinols under acidic conditions (TsOH, polyphosphoric acid or formic acid) consists of a rearrangement leading to substituted cyclopentenones **36** in fair yields [62]. The rearrangement proceeds stereospecifically; only the *trans*-substituted cyclopentenones were formed (Scheme 11).

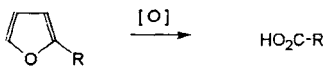


35 **36**

Scheme 11

The furan substituent itself can be applied as an equivalent of the carboxylic group. This oxidation of olefins to acids, elaborated by Sharpless *et al.* [63] involves the

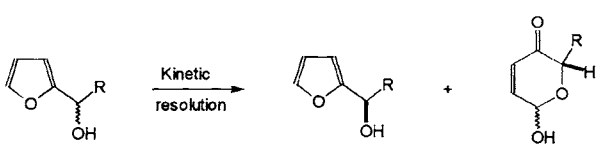
employment of sodium periodate and rutenium salts in aqueous organic solvents. Alternatively simple ozonolysis may be used [64] (Scheme 12).



37 **38**

Scheme 12

Recently two Japanese groups independently developed an efficient method for preparation of optically pure 2-furyl-carbinols based on the Sharpless kinetic resolution procedure [65,66]. In this reaction, the faster reacting enantiomer is oxidized preferentially to afford the corresponding pyranosulose **39**, and the unchanged isomer **35** is recovered in optically pure form (up to 98% ee). Therefore, either (*R*)- or (*S*)-2-furyl-carbinols are obtained depending on the configuration of the tartrate used. (*R*)-2-Furylcarbinols are obtained when diisopropyl L-(+)-tartrate is employed, whereas the use of D-(-)-DIPT leads to the formation of the (*S*)-enantiomers (Scheme 13). For carbinols bearing an allyl substituent this reaction also affords the corresponding pyranones, since the oxidation of furyl methanols is much faster than epoxidation of allylic alcohols.

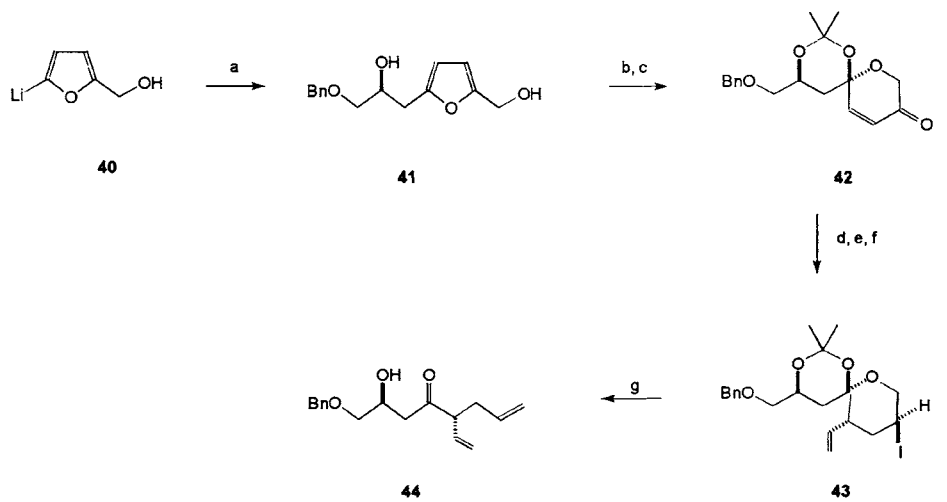


35 **(R)-35** **(S)-39**

Scheme 13

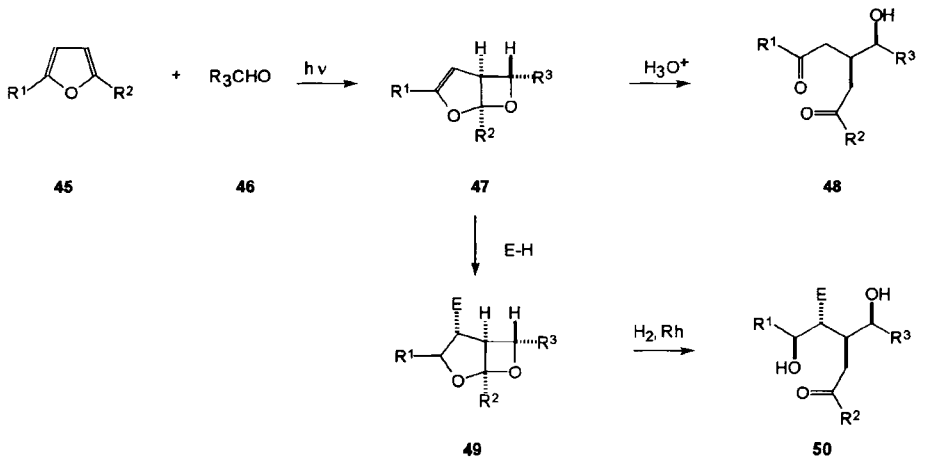
Over the past several years considerable progress was made in the development of methods for the construction of complex 1,3-dioxygenated carbon frameworks, due to their occurrence in complex polyoxygenated compounds [67]. An enantioselective synthesis of spiroketals from substituted furans is of crucial importance in the synthesis of such systems [68,69]. Thus, an

opening of epoxides like (*S*)-benzylglycidol (Scheme 14) and subsequent oxidative rearrangement of furyl alcohol **41** affords, after protection of the resulting diol, the optically pure spiroenone **42** as a result of acid-catalyzed equilibration of the spiroketal center. This system represents a masked aldol unit and is also a convenient Michael acceptor. Indeed, the conjugated addition gives in excellent yield a single stereoisomer as a result of the expected axial attack. Transformation of the resulting spiroketone to the iodide **43** and its metal-initiated fragmentation lead to the acylic aldol unit **44** without structural or stereoisomerization.



Scheme 14. (a) (*S*)-benzylglycidol, LiCl, DME, 94%; (b) MCPBA, CH_2Cl_2; (c) $CH_2C(OCH_3)CH_3$, HCl, 70%; (d) $LiCu(vinyl)_2$, Et_2O, 95%; (e) L-Selectride, THF; (f) I_2, Bu_3P, Σ 64%; (g) C_8K/Ag/Zn, 75%.

Application of furan in the synthesis can be interestingly exemplified by its photocycloaddition to aldehydes [70-74]. This reaction can serve as a photochemical version of the aldol reaction (Scheme 15). The reaction proceeds regiospecifically to afford head-to-head photoadducts and stereospecifically to yield *exo*-photoaldols **47**, exclusively. This method is, however, charged with certain drawbacks. In the case of unsymmetrically substituted furans, photocycloaddition affords two *exo*-adducts which result from addition to either one of the double bonds of furan, without selectivity. Also the chiral substituent



Scheme 15

adjacent to the aldehyde only slightly affects asymmetric induction. Only ketones undergo photocycloaddition with enhanced chemoselectivity, favoring addition to the less substituted double bond of furan. The *cis*-fused bicyclic skeleton of the photoadduct leads to a variety of functionalization schemes which can be carried out in a highly stereoselective manner. Hydrolysis of the photoadduct **47** affords *threo*-aldol of 1,4-dicarbonyl compound **48**, whereas hydrogenolysis of **49** gives the compound **50**.

Transformations of the furan compounds found many applications in the synthesis of a wide range of natural products. In the next chapter we will show some representative examples.

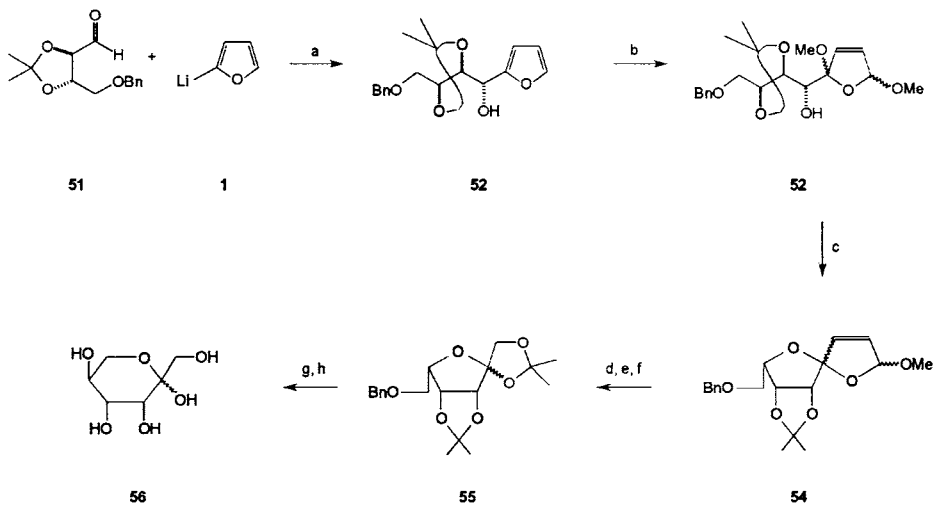
4. SYNTHESIS OF NATURAL PRODUCTS FROM FURAN PRECURSORS

4.1. SUGARS

On the turn of the eighties there appeared many reports on the syntheses of racemic sugars from furan precursors, based on the Achmatowicz oxidative rearrangement of furyl carbinols to uloses [20,21,75-81]. Development of methods for the preparation of optically pure furyl carbinols gave access to many optically pure monosaccharides.

The synthesis of L-ribulose, described by Mukaiyama *et al.* came first in this series [12], in the second synthesis performed by the same authors [13], addition of the 4-*O*-benzyl-2,3-*O*-iso-

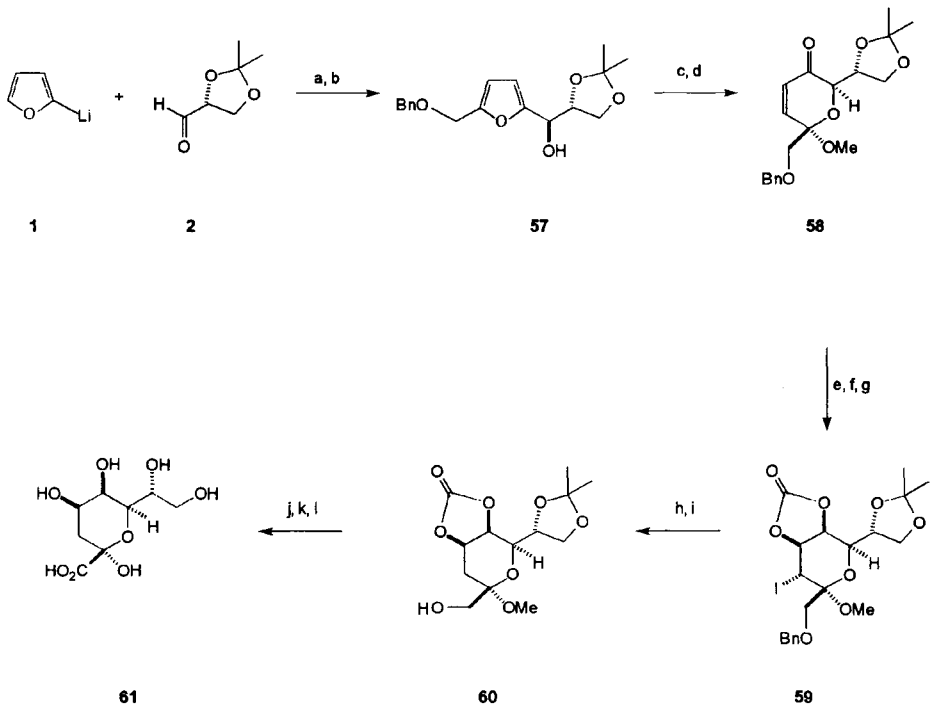
propylidene-L-threose **51** to 2-furyllithium, in the presence of an equimolar amount of $ZnBr_2$ afforded the almost pure *anti*-diastereoisomer **52** (*anti*:*syn* 98:2) (Scheme 16). Oxidative transformation of the furan ring of **52** into the dihydrofuran derivative **53** and a deprotection-protection reaction sequence gave the spiroketal **54** which after ozonolysis and a reduction-deprotection protocol was converted to L-tagatose, the enantiomer of the naturally occurring ketose of physiological and immunological interest.



Scheme 16. (a) $ZnBr_2$, THF, 97%; (b) Br_2, MeOH, 83%; (c) DMP, H_2SO_4, 56%; (d) O_3, MeOH; (e) $NaBH_4$ MeOH; (f) Me_2CO, H_2SO_4, Σ 37%; (g) H_2, Pd/C; (h) H^+, 85%.

At the same time there was reported the synthesis of D-*glycero*-D-*manno*-heptose based on the similar approach, initiated by stereoselective (85:15) reaction of furane with the 2,3-*O*-isopropylidene-D-glyceraldehyde **2** catalyzed by chloroacetic acid [82].

An excellent example for utilization of this methodology was the synthesis of (+)-KDO, a higher monosaccharide found in the outer membrane lipopolysaccharides of Gram-negative bacteria [83], reported by Martin and Zinke (Scheme 17) [84,85].

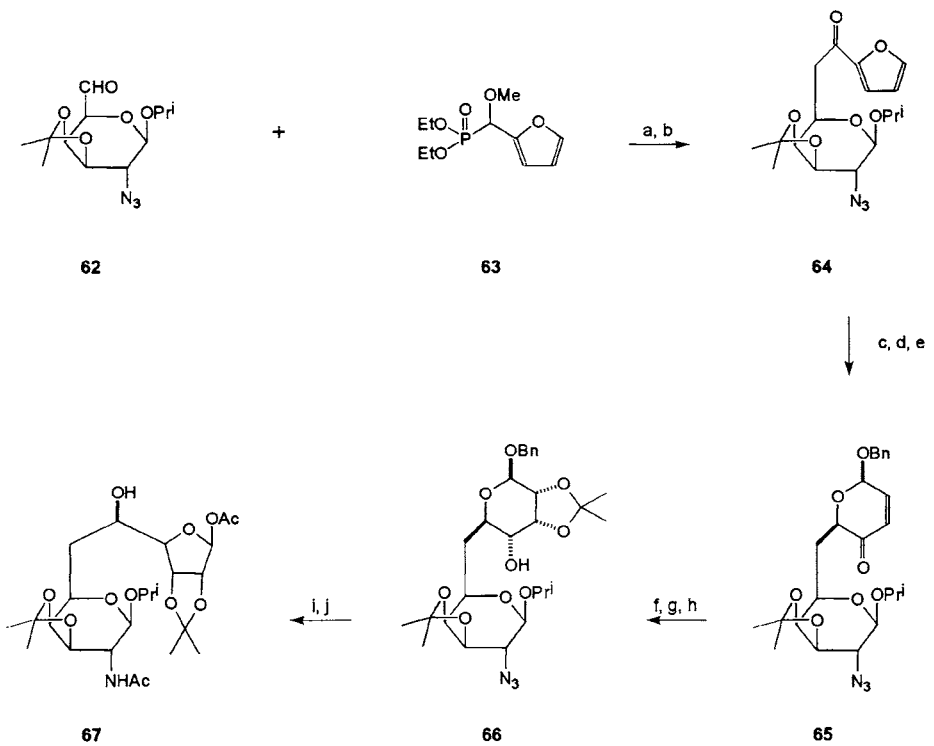


Scheme 17. (a) $ZnBr_2$, THF, then TBDMS, 53%; (b) BuLi, THF, then BOMCl, then TBAF, 92%; (c) Bu^tOOH, $VO(acac)_2$, CH_2Cl_2, 91%; (d) MeI, Ag_2O, 82%; (e) K-Selectride, THF, 88%; (f) CCl_3CONCO, CH_2Cl_2, 95%; (g) $I(collidine)_2ClO_4$, MeCN, 31%; (h) $Bu^n{}_3Sn$, AIBN, PhMe; (i) H_2(60 psi), Raney Ni, EtOH, Σ 79%; (j) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (k) Ag_2O, NaOH, EtOH, Σ 80%; (l) DOWEX 50 W (H^+), H_2O, then NH_4OH, Σ 44%.

The protected furan alcohol prepared according to the Mukaiyama procedure was alkylated in the position 5 and oxidized to the corresponding hydropyranone **58**. Stereoselective reduction of the keto group and protection of the resulting alcohol afforded the primary uretane suitable for further functionalization of the C-4 position *via* intramolecular iodonium ion-induced cyclization [86]. Unfortunately, this step crucial for the synthesis proceeded with an only moderate degree of conversion to provide the desired carbonate **59** (31%) together with 60% of the starting material. Removal of the iodide from **59** by free-radical reduction and subsequent hydrogenolysis of the benzyl group furnished the primary alcohol **60** which after a

stepwise oxidation procedure and deprotection of all hydroxy functions yielded (+)-KDO **61** isolated as its ammonium salt.

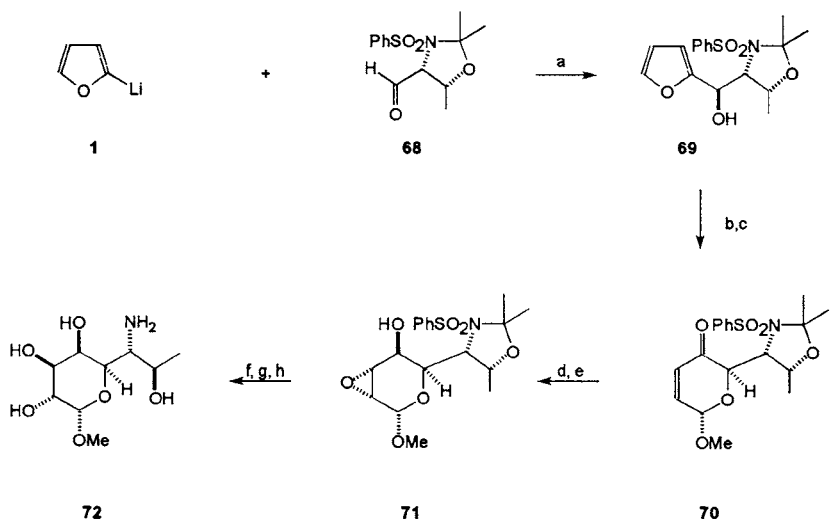
Tunicamine, an eleven-carbon atom amino sugar, the main component of the tunicamycin antibiotics [87], was the subject of studies by Zamojski and Ramza [88,89]. Two hitherto performed syntheses consisted either in the Henry nitroaldol condensation between two carbohydrate synthons [90], or in the hetero-Diels-Alder addition of the seven-carbon atom sugar aldehyde to modified Danishefsky diene [91]. According to the approach of Zamojski, the galactosamine precursor **62** was extended using the noncarbohydrate furan precursor **63** (Scheme 18).



Scheme 18. (a) LDA, THF, 59%; (b) PPTS, THF, 78%; (c) K-Selectride, THF, 75%; (d) Br_2, MeCN/H_2O, 85%; (e) Ag_2O, BnBr, CH_2Cl_2, 64%; (f) OsO_4, $AgClO_3$, THF/H_2O; (g) DMP, Me_2CO, TsOH, Σ 54%; (h) $NaBH_4$, THF, 81%; (i) H_2, Pd/C, EtOH; (j) Ac_2O, Et_3N, CH_2Cl_2, Σ 86%.

Horner-Emmons condensation and hydrolysis of the resulting enol ether afforded the ketone **64** which underwent reduction with moderate (3.3:1) selectivity. Oxidative transformation of the furyl alcohol into ulose, followed by protection of the hydroxy group formed, and *cis*-hydroxylation, gave two isomeric products in an 8:1 ratio, isolated as isopropylidene derivatives. Stereoselective reduction of the carbonyl group at C-4 and a deprotection-protection reaction sequence, combined with spontaneous isomerization to the furanose form, furnished tunicamine as its partially acetylated derivative **67**.

Lincosamine [92], another amino sugar of physiological interest, is a component of lincomycin, an antibiotic of clinical importance due to its antibacterial activity based on the inhibition of protein synthesis at the ribosomal level [93]. An addition of 2-furyllithium to the protected D-*allo*-threoninal **68** was the key step in the synthesis of this molecule (Scheme 19) [94].

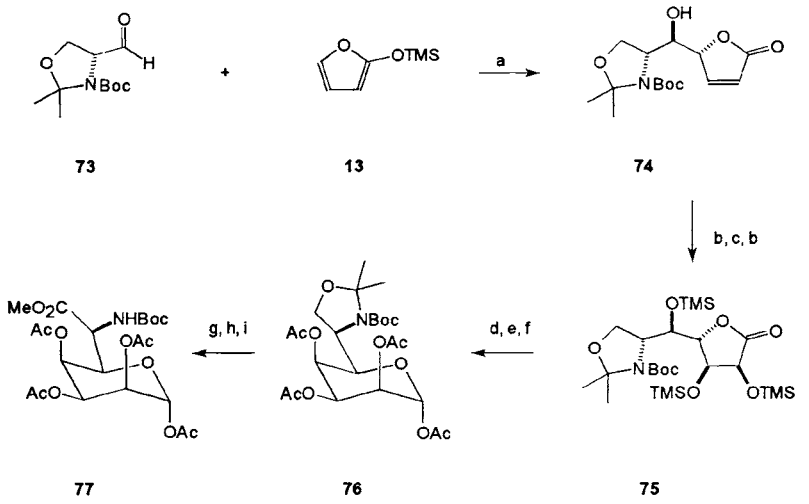


Scheme 19. (a) THF, Et_2O, 85%; (b) MCPBA, CH_2Cl_2, 98%; (c) MeI, Ag_2O, Et_2O, 79%; (d) $NaBH_4$, $CeCl_3$, MeOH, 65%; (e) H_2O_2, MeCN, 95%; (f) Ac_2O, Py, DMAP; (g) $HClO_4$, THF, H_2O; (h) Na, NH_3, Σ 89%.

Although the conditions for selective obtainment of the *syn*-adduct were successfully created by the use of Lewis acids, the desired *anti*-**69** formed was only slightly dominant (55:45), as compared with the reaction performed without additives. This result confirms our previous observations (see Table 3), concerning the influence of the β-chelating *O*-protective groups on the stereoselectivity of this addition. Oxidative rearrangement of the adduct **69** and protection of the anomeric center afforded the uloside **70** with almost exclusively the α-configuration at the C-2 position. Luche reduction of the C-4 carbonyl group rather suprisingly furnished only the *threo*-alcohol with, however, a considerable amount of the saturated alcohol being the product of 1,4-addition. Also epoxidation of the major product proceeded stereoselectively yielding the *gulo*-epoxide **71**, exclusively. Both stereochemical results were explained by steric hindrance exerted by the *N*-benzenesulfonyl group which shields the β-face of dihydropyran. Acidic opening of the epoxide ring and removal of all protecting groups led to the α-D-lincosaminide **72**.

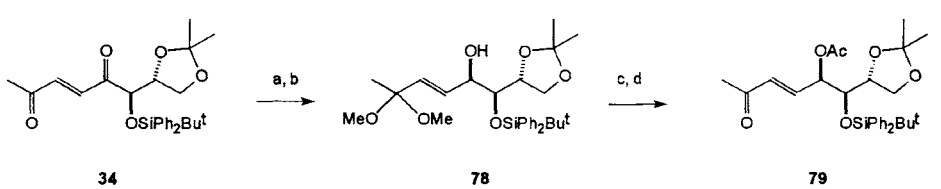
2-Trimethylsilyloxyfuran **13**, another nucleophilic four-carbon synthon, was used in the synthesis of novel 6-deoxy-6-amino-heptopyranuronic acid derivatives which are the key components of a subclass of the peptidyl nucleoside antibiotics family [95]. An aldol-type addition of **13** to the serinal **73** in the presence of BF_3 etherate provided the *arabino*-configurated butenolide **74** selectively with only traces (3-5%) of the *ribo*-diastereoisomer (Scheme 20) [96,97]. The protection and *anti*-*cis*-dihydroxylation reaction sequence afforded the lactone **75** as a sole diastereoisomer which after reduction and deprotection of the hydroxy functions isomerized to the pyranose **76**. Hydrolysis of the isopropylidene acetal, followed by oxidation-esterification of the terminal hydroxy group, furnished the 6-deoxy-6-amino-α-D-*glycero*-D-*talo*-hepto-pyranuronate **77** as its fully protected derivative.

Transformation of the 2-methylfuryl carbinols into α,β-unsaturated enediones was applied in the synthesis of multifunctional chain compounds containing pentitol fragments [58]. The principle of this approach is exemplified by the synthesis of the *arabino*-configurated diastereoisomer. Thus, the stereo-



Scheme 20. (a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, 84%; (b) TMSCl, Py; (c) $KMnO_4$, dicyclohexyl-18-c-6, CH_2Cl_2 then (b), Σ 62%; (d) DIBAL, CH_2Cl_2; (e) citric acid, MeOH; (f) Ac_2O, Py, DMAP, Σ 55%; (g) AcOH aq. (h) $NaIO_4$, RuO_2H_2O, Me_2CO/H_2O; (i) CH_2N_2, Et_2O, Σ 64%.

selective addition of 2-methylfuryllithium to the D-glyceraldehyde derivative **2** gave, after protection of the hydroxy group, the furan alcohol **33** (Scheme 10), which undergoes opening transformation into the enedione **34**. Regioselective protection of the terminal carbonyl group and subsequent stereoselective reduction of the unprotected ketone afforded, after acetalization and removal of the ketal function, the compound **79** with 20:1 selectivity on the newly created chiral center (Scheme 21). Application of the *syn*-isomer of **33**, with the use of various protective groups and reducing agents, allowed for the synthesis of acyclic fragments with the configuration specific for all pentoses.



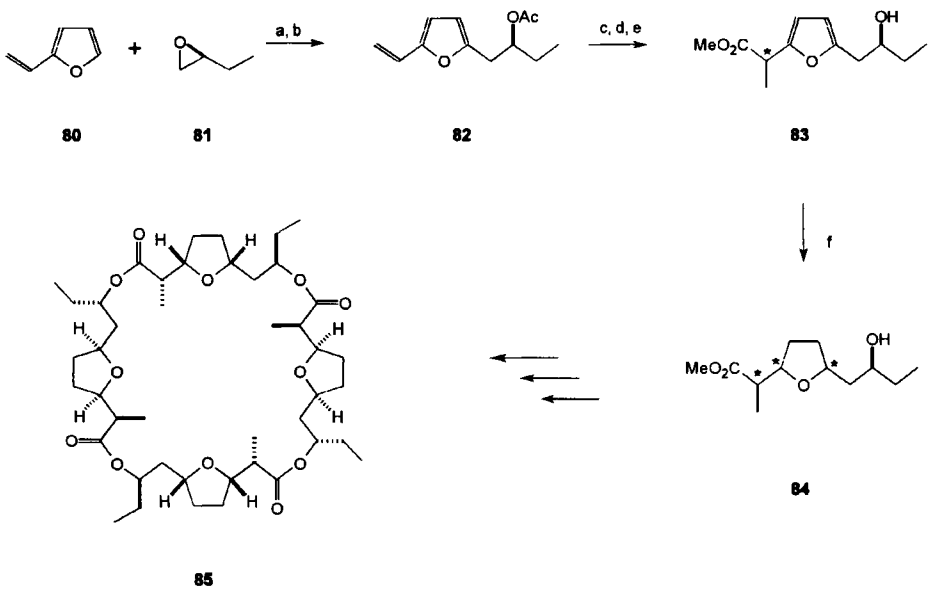
Scheme 21. (a) $MeC(OMe)_3$, CSA, MeOH, 77%; (b) DIBAL, Et_2O; (c) Ac_2O, Et_3N, CH_2Cl_2; (d) CSA, Me_2CO, H_2O, Σ 64%.

An interesting attempt at the synthesis of C-nucleosides containing ribose bound to the carbon atom of a heterocyclic aglycon was reported by Maeba *et al.* The furan ring of the 2-(D-ribofuranosyl)-furan derivative was efficiently transformed into various α,β-unsaturated analogues by the Clauson-Kaas method; this gave access, after condensation with various acyclic and heterocyclic amines, to *C*-nucleosides containing pyridazine, pyrrolinone, pyridazinone, oxazinone, quinoxaline, pyrroloquinoxaline, pyrrole, carbazone, diazepine and lumazine aglycons [98,99].

4.2. MACROLIDES

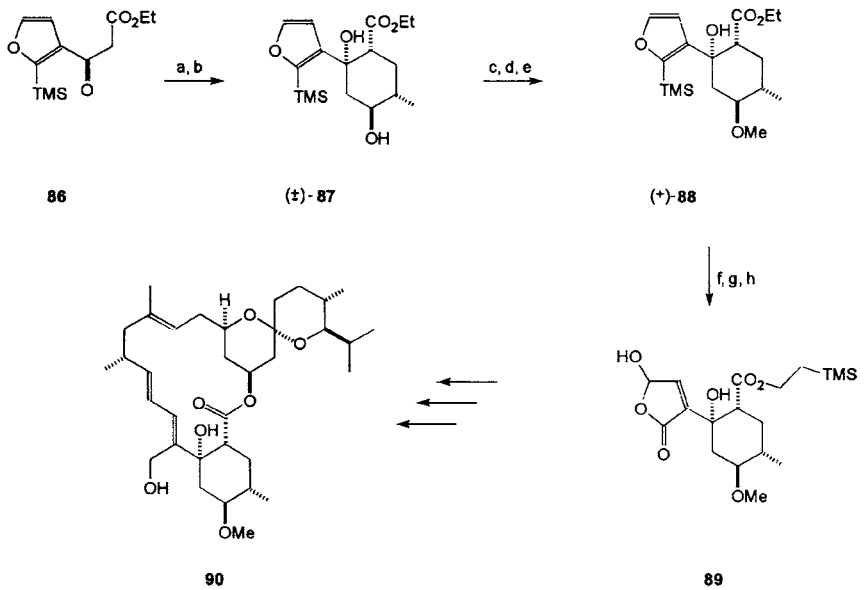
During the past 20 years the macrolide antibiotics with multiple asymmetric centers attracted considerable interest as synthetic targets, due to their stereochemical and functional complexities and broad spectrum of biological activities [100]. Furan precursors were used, among others, in these syntheses.

An elegant synthesis of tetranactin **85**, based on a strategy called "reverse coup du roi", was performed by Schmidt and Werner [23]. This expression formulated by Mislow indicates the construction of a *meso*-structure from two isometric homochiral halves [101]. In events, the addition of 2-vinylfuryllithium to the (*S*)-epoxybutane **81** leads after acetylation to the 2,5-substituted furan derivative **82**. Hydroformylation performed in the presence of the modified Wilkinson catalyst, followed by an oxidation-esterification reaction sequence, afforded the ester **83** as an equimolar mixture of both diastereoisomers (Scheme 22). Catalytic *cis*-hydrogenation of the ester **83** gave the esterified derivatives of the homononactin acid **84** as a mixture of four diastereoisomers, easily separated by medium-pressure chromatography. Since only two of the four diastereoisomers were used in the further synthesis, undersirable stereoisomers could be easily isomerized in the presence of DBU to increase the chiral efficiency of the synthesis. Further transformations consisting in appropriate protection-deprotection of the functional groups and coupling of the tetrahydrofuran containing chains afforded tetranactin **85**.



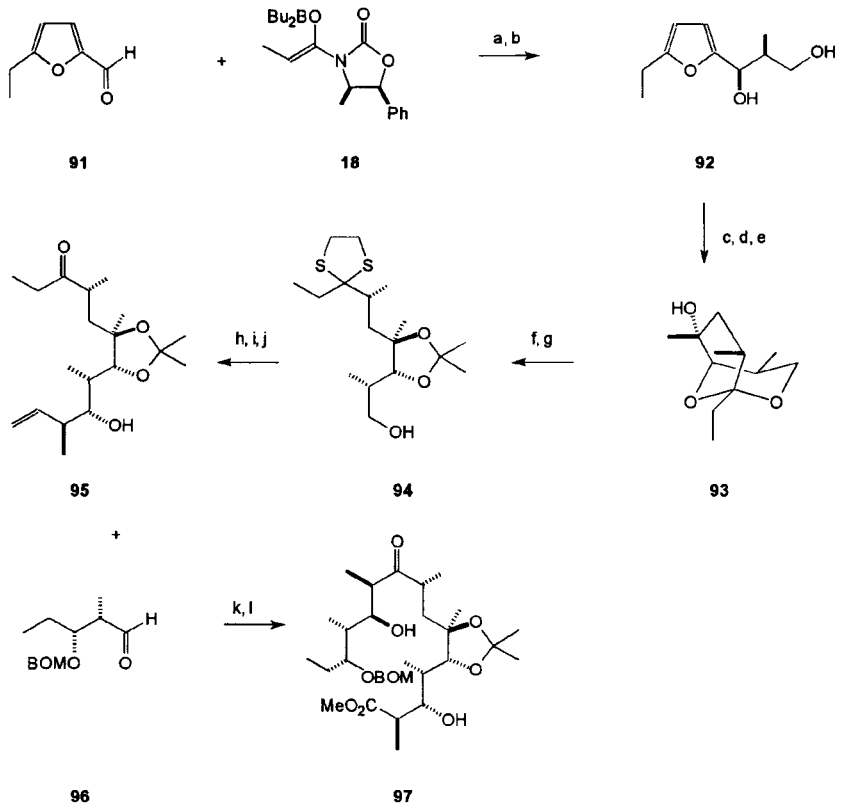
Scheme 22. (a) m-MePhLi, THF, Et_2O; (b) AcCl, THF, 81%; (c) [Rh(cycloocta-1,5-diene)Cl]$_2$, PPh_3, CO, H_2, C_6H_6, 92%; (d) $NaClO_2$, NH_2SO_3H, dioxane, H_2O; (e) KOH, MeOH; (f) CH_2N_2, Et_2O, Σ 70%; (g) H_2, Rh/Al_2O_3, MeOH, 96%.

Milbemycin E and 3,4-dihydromilbemycin E are macrolide antibiotics structurally related to avermectins isolated from certain strains of *Streptomyces* [102]. The syntheses of both macrolides were accomplished by Thomas *et al.* starting from the furan derivative **86** (Scheme 23) [103]. Robinson annelation of **86** and stereoselective reduction of the resulting ketone afforded the racemic alcohol **87** whose resolution was achieved by selective recrystallization of the diastereoisomeric (*S*)-(+)-acetoxymandelate. Transesterification of the optically pure (+)-**88**, followed by selective methylation of the hydroxy group at C-5 and photochemically induced transformation of the furan ring, gave the hydroxybutenolide **89**. The lacking C_{11}-C_{26} fragment was incorporated by the Wittig reaction with the adequate spiroketal, esterification and isomerization to the desired *E*-configurated ester which was finally converted to the goal structure, 3,4-dihydromilbemycin E **90**, by cyclization and reduction of the ester group. Generation of a double bond in **88** allowed for the synthesis of milbemycin E as well, by the same methodology.



Scheme 23. (a) methyl isopropen-2-yl ketone, NaH, EtOH, 65%; (b) $NaBH(OAc)_3$, AcOH, 98%; (c) (S)-(+)-acetoxymandelic acid, DCC, DMAP; (d) K_2CO_3, EtOH, Σ 35% of (+)-**87**; (e) Ag_2O, MeI; (f) NaOH, EtOH; (g) $TMS(CH_2)_2OH$, DCC, DMAP, CH_2Cl_2, Σ 82%; (h) O_2, hν, tetraphenylporphyrin, CH_2Cl_2, MeOH, 90%.

A remarkable, concise synthesis of the seco-acid of erythronolide B was performed by Martin *et al.* [104]. A convergent approach to this molecule was initiated from the 5-substituted furfural **90** and boron enolate **18** (Scheme 24). Evans-type aldol condensation generated, after reductive removal of the chiral oxazolidinone-auxiliary, the *syn*-alcohol **91**, exclusively [32]. Oxidation of the furan ring combined with acid-catalyzed bicycloketalization afforded the bicyclic ketal as the sole diastereoisomer. Michael addition of a methyl group, followed by 1,2-addition of a second methyl group yielded the tertiary alcohol **92**; both reactions proceeded in a highly stereoselective manner. A Lewis acid-catalyzed ketal-thioketal exchange and regioselective, thermodynamically controlled acetalization of the resulting triol gave the primary alcohol **96** which after removal of the dithiolane group and oxidation to aldehyde underwent the Lewis acid-mediated reaction with tri-*n*-butylcrotylstannane. Surprisingly, the resulting alcohol **94** was contaminated with the *anti*-epimer at C-2, according to X-Ray analysis of both molecules. Incorporation of the C_{11}-C_{15}

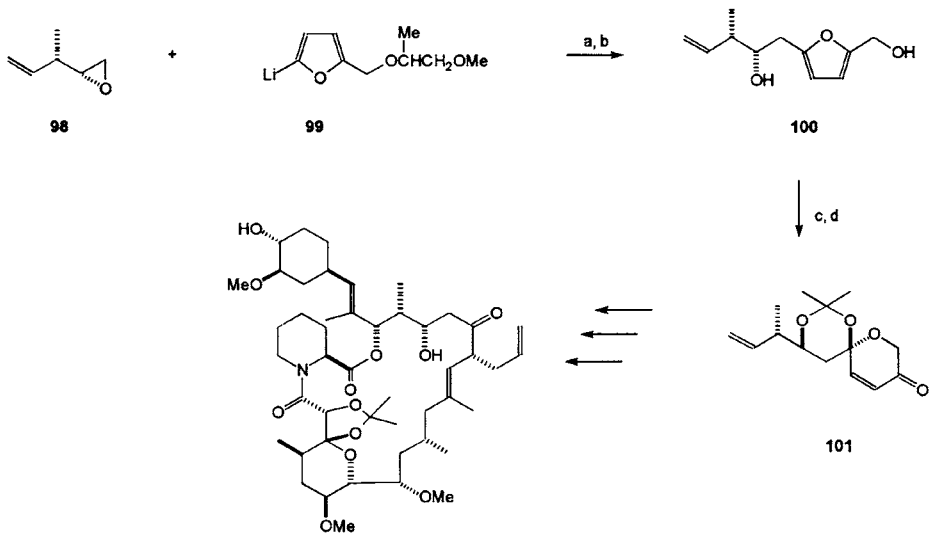


Scheme 24. (a) CH_2Cl_2, -78°→0°C, 81%; (b) $LiBH_4$, THF, 90%; (c) Br_2, MeCN, H_2O, 63%; (d) $LiCuMe_2$, Et_2O, 90%; (e) MeLi, $CeCl_3$, THF, 94%; (f) $TMSS(CH_2)_2STMS$, $TiCl_4$, CH_2Cl_2; (g)CSA, Me_2CO, CH_2Cl_2, Σ 60%; (h) NBS, Me_2CO, H_2O, 75%; (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 90%; (j) $CH_3CHCHCH_2SnBu^n_3$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 82%; (k) $LiN(TMS)_2$, 72%; (l) O_3, Sudan III, MeOH; (m) Et_3N, Ac_2O, CH_2Cl_2, Σ 61%.

fragment was realized by chelation-controlled aldol condensation using Z-enolate of **95** to obtain a mixture (6:1) of *syn*-adducts. Oxidative conversion [105] of the major diastereoisomer to the ester **96** completed the synthesis of the protected seco-acid of erythronolide B. This methodology was also applied by the same group in syntheses of other natural products like (-)-milbemycin I, (+)-tirandamycic acid, (-)-tirandamycin A and (+)-Prelog-Djerassi lactone [106-108].

In the course of work aimed at obtainmet of FK-506 [109], a potent immunosupressant isolated from *Streptomyces tsukubaensis* [110], Ireland *et al.* performed the synthesis of the closely

similar, stable analogue of this 23-membered macrolide lactone, i.e. of 9,10-acetonide of 9-dihydro FK-506 **102** [111]. One of the central features of the structure is spiroenone **100** which masks the C_{21}-C_{27} -allyl fragment of FK-506 (Scheme 25).



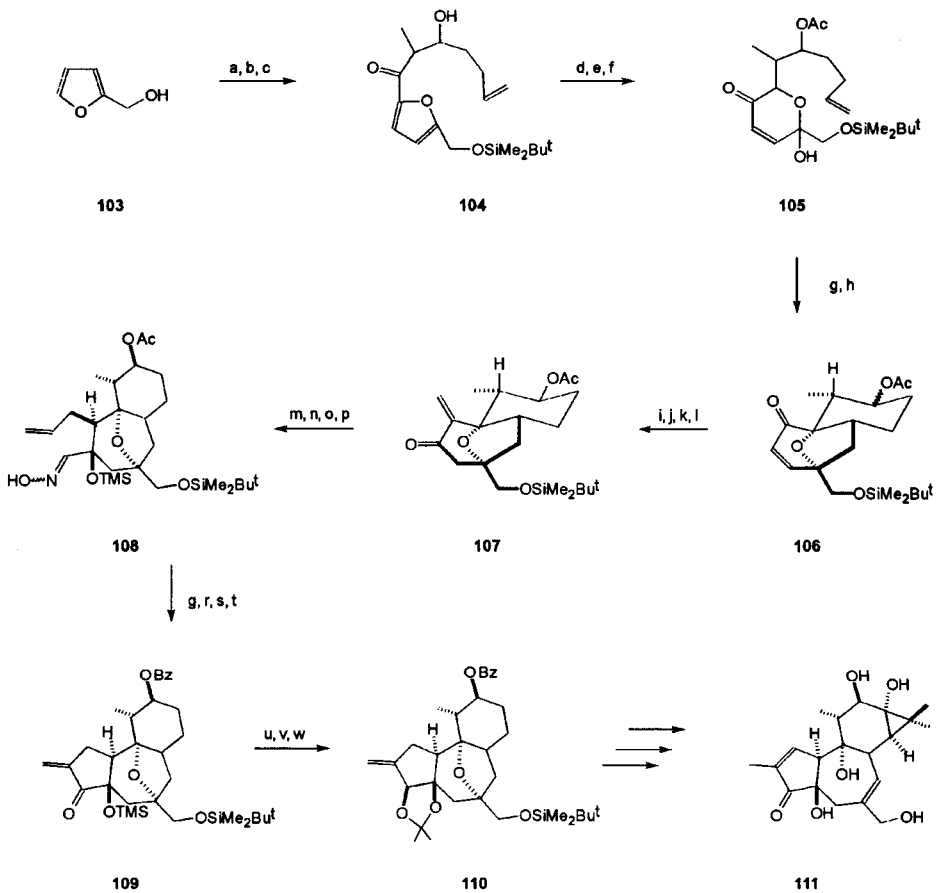
Scheme 25. (a) $BF_3 \cdot Et_2O$, THF; (b)HCl, THF, H_2O, Σ 55%; (c)MCPBA, CH_2Cl_2; (d) $CH_2C(OCH_3)CH_3$, HCl, Σ 70%.

The epoxide **97** was synthesized from benzylglycolaldehyde *via* highly stereoselective crotylation using a chiral crotylborane [112] and subsequent epoxidation of the resulting diol. Its reaction with the protected furan derivative **98** afforded, after deprotection of the furyl-substituent at C-5, the diol **99** readily transformed into the spiroenone system upon use of MCPBA. Protection of the spiroenone gave the desired synthon **100** which was further incorporated into the synthetic scheme enabling the synthesis of the FK-506-analogue.

4.3. ISOPRENOIDS

The phorbol esters are noncancerogenic compounds amplifying the effect of certain carcinogens in animals and are supposed to participate in human carcinogenesis [113-115]. In

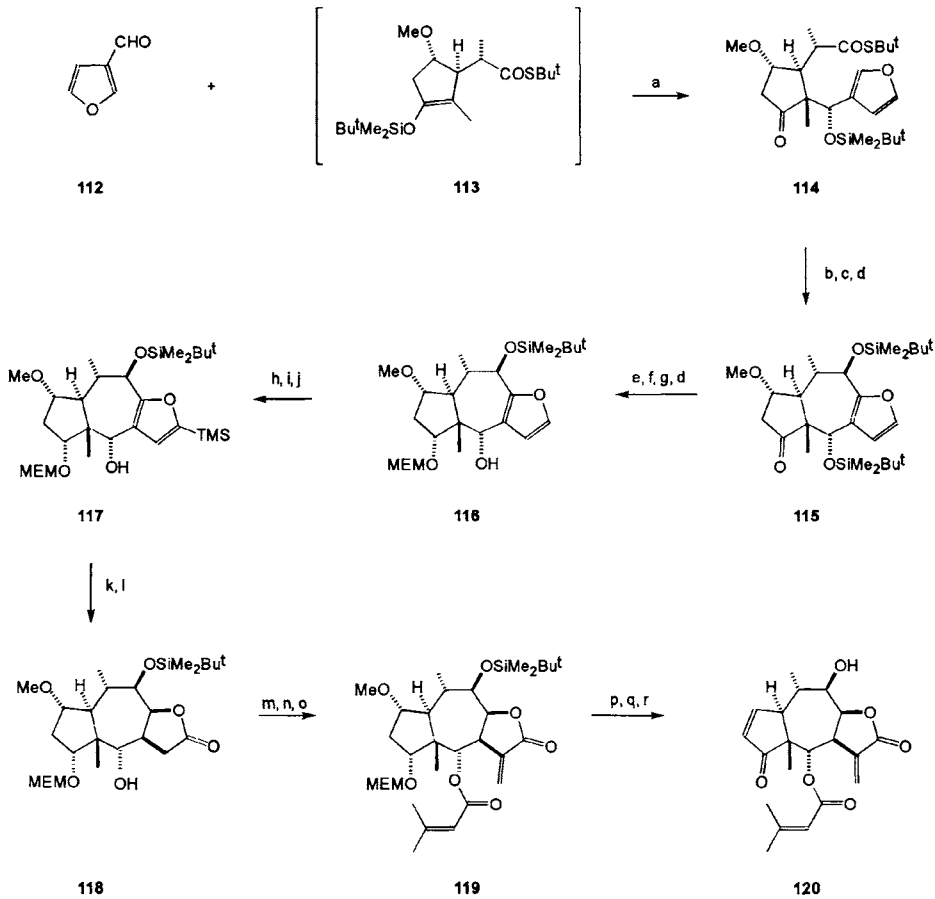
order to establish a structural basis for phorbol ester-induced activation of enzymes like protein kinase C, access to modified phorbol esters is required. Toward this end Wender *et al.* accomplished the first synthesis of phorbol **111** starting from furfuryl alcohol **103** (Scheme 26) [116,117].



Scheme 26. (a) Bu^tMe_2SiCl, DMF; (b) BuLi, THF then EtCOOLi; (c) $LiN(TMS)_2$, THF then 4-pentenal; (d) AcCl, Py, CH_2Cl_2; (e) $NaBH_4$, MeOH; (f) MCPBA, THF; (g) Ac_2O, Py, DMAP, Σ 52% from **102**; (h) DBU, CH_2Cl_2, 92%; (i) H_2, Pd/C, AcOEt; (j) Ph_3PCH_2; (k) SeO_2, Bu^tOOH, CH_2Cl_2; (l) MnO_2, CH_2Cl_2; (m) $(vinyl)_2CuCNLi_2$, THF, Σ 78% from **105**; (n) TMSCN, ZnI_2; (o) DIBAL, $PhCH_3$ p) NH_2OH, Py; (q) NaOCl, THF, Σ 46% over four steps; (r) H_2, Raney Ni, Me_2CO, H_2O; (s) Bz_2O, DMAP, CH_2Cl_2; (t) DBU, THF; (u) $NaBH_4$, $CeCl_3$, MeOH; (v) $Bu^n{}_4NF$, Et_2O; (w) $CH_2C(OCH_3)CH_3$, PPTS, CH_2Cl_2, 72% over six steps.

Protection of **103** and the sequence of two consecutive aldol condensations gave the alcohol **104** as a 2:1 mixture at C-12. Acetylation of **104** and reduction of the ketone gave after oxidation of the furan ring the pyranone **105** which underwent cycloaddition affording **106** with complete selectivity concerning the relative stereochemistry at newly creating chiral centers and also at C-11. (The C-11 methyl group occupies an equatorial position in order to minimize steric interactions with C-10 oxygen in the chair-like conformation of the transition state). Generation of the ketone **107** was achieved in a four-step reaction sequence *via* the Wittig-selenylation-oxidation protocol. Stereoselective conjugated addition of vinyl cuprate and subsequent selective transformation of the ketone into nitrile illustrate the influence of oxygen bridge on the stereochemical course of both reactions. Reduction of the nitrile and oximation of the resulting carboxaldehyde gave the oxime **108** which transformed into its nitrile oxide underwent a 1,3-dipolar cycloaddition to afford, after hydrogenolysis of the originating isoxazoline and elimination of the hydroxy group, the tricyclic ketone **109**. The reactive functionalities of the A ring were protected in the form of acetonide **110**. Construction of the cyclopropane D ring and unmasking of the functionalities in the A and B rings terminated the synthesis of this complex molecule.

Pseudoquaianolides, a group of butyrolactone-containing bicyclo[5.3.0]decanoides, belong among the most stereochemically complex sesquiterpenes. Helenanes which are members of this family exhibit diverse biological properties including cytotoxic, antileukemic and antiinflammatory activities [118,119]. The first total synthesis of (-)-fastigilin C **120**, a helenanolide first isolated from *Gaillardia fastagiata* [120], was performed by Tanis *et al.* [121]. (*S*)-(+)-4-Methoxy-2-methyl-2-cyclopentanone synthesized from the racemic compound *via* stepwise enzymatic resolution using *porcine pancreatic lipase* and methylation of the hydroxy group [122], underwent a tandem Mukaiyama-Michael-aldol condensation with 3-furfuraldehyde **112** and enol ether of *tert*-butylthiopropionate to afford adduct **114** as a sole diastereoisomer (Scheme 27).



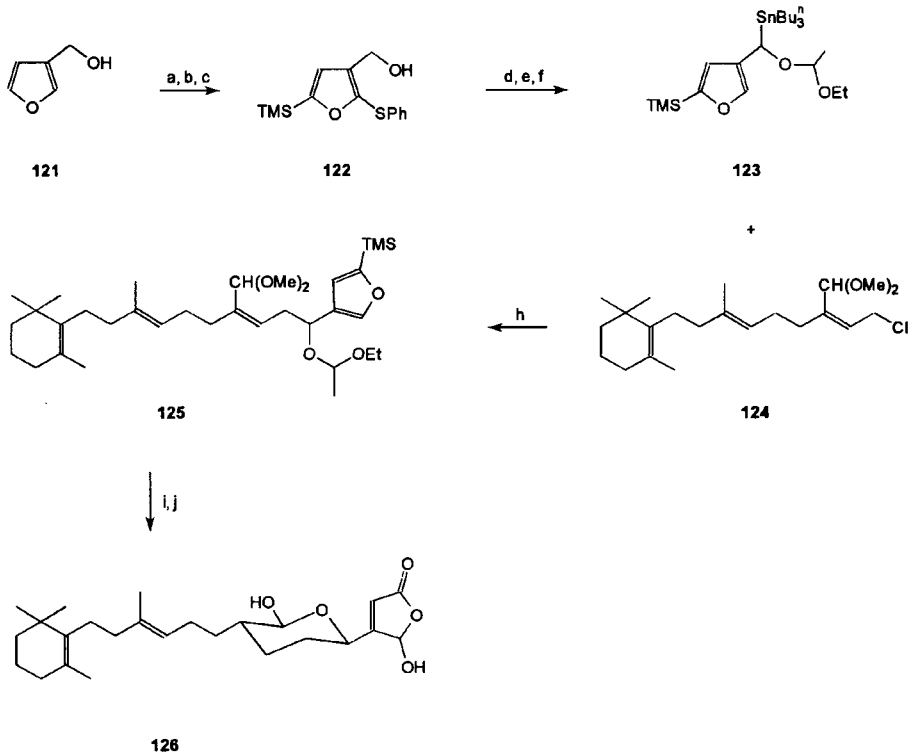
Scheme 27. (a) $Ir^+SbCl_6^-$, *O*-TBDMS-*tert*-butyl thiopropionate, CH_2Cl_2, 81%; (b) $Hg(OTf)_2PhNMe_2$, MeCN, 78%; (c) $NaBH_4$, $CeCl_3$, MeOH, 96%; (d) Bu^tMe_2SiCl, $Pr^i{}_2NEt$, DMF, 99%; (e) DIBAL, Et_2O, 96% (f) MEMCl, $Pr^i{}_2NEt$, CH_2Cl_2, 79%; (g) $Bu^n{}_4NF$, THF, 91%; (h) $CH_3CH_2OCHCH_2$, TsOH, Et_2O, 99%; (i) BuLi, THF then TMSCl; (j) TsOH, Et_2O, Σ 87%; (k) HCO_3H, NaOAc, CH_2Cl_2, 91%; (l) $[Rh(NBD)(DIPHOS\text{-}4)]BF_4$, H_2 1000 psi, CH_2Cl_2, 89%; (m) LDA then CO_2, THF; (n) CH_2NMe_2I, MeCN, Σ 77%; (o) 3-methyl-2-butenoic anhydride, Et_3N, DMAP, xylene, 88%; (p) $ZnBr_2$, CH_2Cl_2, 92%; (q) PCC, NaOAc, CH_2Cl_2, 87%; (r) Amberlyst-15, Et_2O, 85%.

Intramolecular cyclization using the Nishizawa complex [123], followed by regioselective reduction of the carbonyl group and protection of the originated hydroxy group, provided the 9-β alcohol **115** which after reduction of the carbonyl group at C-4 and selective protection-deprotection manipulations furnished the alcohol **116**. The protection-silylation reaction sequence

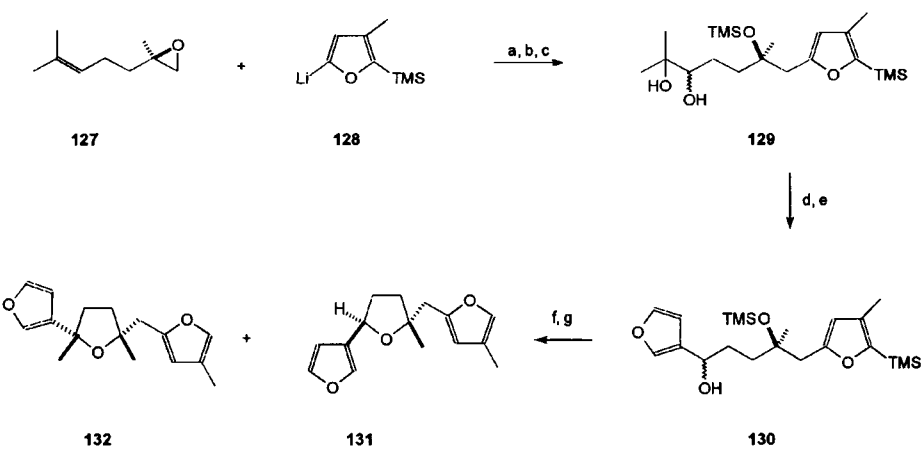
and peroxide-induced transformation of the furan ring gave the unstable butenolide immediately subjected to hydroxyl-directed hydrogenation. The catalyst of choice proved to be the cationic rhodium derivative, (bicyclo[2.2.1]hepta-2,5-diene)[1,4-bis-(diphenylphosphino-butane)]rhodium(I) tetrafluoroborate [124], furnishing the *cis*-β-fused butyrolactone **118**. Incorporation of the methylene group by means of carboxylation-Eschenmoser salt treatment and esterification of the hydroxy group at C-6 gave **119**. Finally, unmasking of the carbonyl group at C-4 and generation of the 2,3-double bond in the A ring completed the efficient and relatively brief synthesis of (-)-fastigilin C.

Manoalide **126** [125], a sesterpenoid isolated from the sponge *Luffariella variabilis*, shows a broad spectrum of antibacterial, inflammatory and inhibitory activities [126]. The first synthesis of this molecule was performed by Katsamura *et al.* applying singlet oxygen oxidation of the furan ring in the crucial step (Scheme 28) [127]. Thus, the furan derivative **123** prepared from 3-hydroxymethylfuran **121** was coupled with the chloride **124** *via* lithium anion derived from the stannane **123** to afford the intermediate **125**. Its chemoselective, photochemically-induced conversion to the γ-hydroxybutenolide and hydrolysis of both acetal functions, leading to formation of the hemiacetal ring, terminated the brief and efficient synthesis of this sesterpenoid [128].

Athanasin, a naturally occurring difuransesquiterpene isolated from certain asteraceae *Athanasia L* [129], is an excellent example of sesquiterpene containing two furan rings. Bornowski and Bojack synthesized this molecule in order to elucidate its relative and absolute configuration (Scheme 29) [130]. The oxirane **127** was synthesized from (2*S*)-*cis*-*Z*-(1,1-dimethyl-ethyl)-5-methyl-1,3-dioxolan-4-one in three steps, using the phase-transfer procedure for the epoxidation step. Addition of the furyllithium **128** to the epoxide, followed by dihydroxylation and cleavage of the resulting diol, afforded an aldehyde suitable for incorporation of the second furan ring. Addition of the 3-furyllithium to the aldehyde yielded a mixture of diastereoisomeric alcohols **130** readily cyclized to tetrahydrofuran derivatives **131** and **132**. The latter compound was proved to be the naturally occurring athanasin.



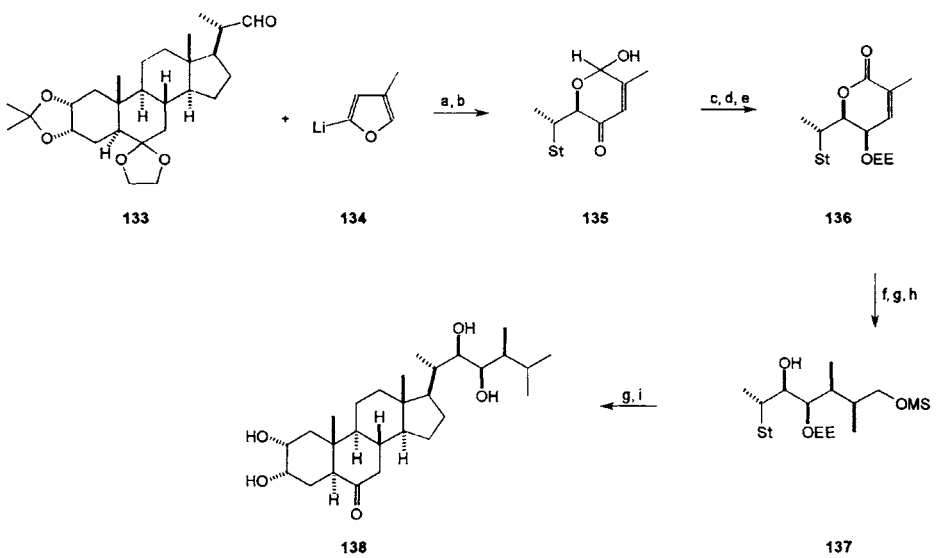
Scheme 28. (a) BuLi(2eq), PhSSPh, THF, 91%; (b) BuLi, THF then TMSCl; (c) HCl, THF; (d) Raney Ni, EtOH; (e) $Ba(MnO_4)_2$, CH_2Cl_2, Σ 41%; (f) $Bu^n{}_3SnLi$, THF; (g) $CH_3CHClOEt$, $Pr^i{}_2NEt$, CH_2Cl_2, Σ 95%; (h) BuLi, THF, 89%; (i) O_2, hν, rose Bengal, CH_2Cl_2, MeOH; (j) AcOH, THF, Σ 55%.



Scheme 29. (a) THF, RT, 41%; (b) TMS-Im, CH_2Cl_2, 88%; (c) OsO_4, NMO, Bu^tOH, Me_2CO, H_2O then Na_2SO_3aq, 79%; (d) $Pb(OAc)_4$, $CaCO_3$, CH_2Cl_2, 80%; (e) 3-furyllithium, THF, 87%; (f) citric acid, MeOH, H_2O, 53%; (g) TsCl, Py, 89%.

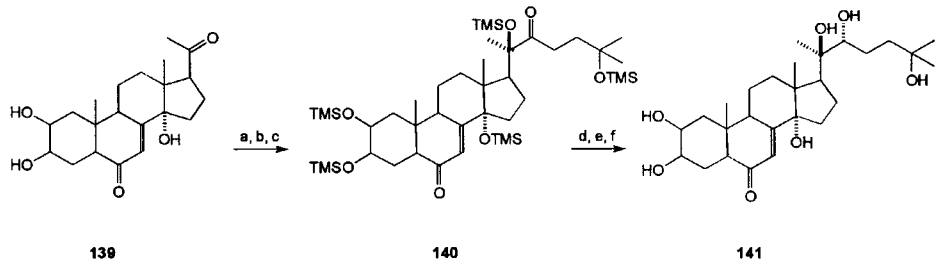
The furan methodology found application also in the syntheses of steroids, especially in the construction of the side chain homologues. Modifications of the side chain gave access to many naturally occurring and synthetic steroids.

Brassinosteroids such as castasterone **138**, isolated from the insect galls of *Castanea spp* [131], are plant growth regulators containing a side chain bearing four contiguous acyclic chiral centers, including the *syn*-diol system. The synthesis of castasteron was achieved by Honda *et al.* using the furan derivative **134** for elongation of the steroid aldehyde **133** (Scheme 30) [132]. Furan to pyran oxidation followed by three-step transformation of the latter to the lactone **136** afforded, after stereoselective 1,4-addition of a methyl group and reduction of the lactone, the primary alcohol readily converted to the mesylate **137**. Reductive elimination of the mesylate and removal of both acetals from the steroidal framework terminated the synthesis of castasterone.



Scheme 30. (a) THF, -78°C, 78%; (b) NBS, THF, H_2O; (c) PCC, AcONa, CH_2Cl_2, Σ 81%; (d) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, CH_2Cl_2, 97%; (e) $CH_2CHOCH_2CH_3$, PPTS, CH_2Cl_2, 94%; (f) Me_2CuLi, Et_2O, 85%; (g) $LiAlH_4$, Et_2O; (h) MsCl, Et_3N, CH_2Cl_2 then (g) Σ 80%; (i) HCl, THF, H_2O, 94%.

In the synthesis of 20-hydroxyecdysone **141**, performed by Welzel *et al.* [133], the side chain was modified by addition of the dihydrofuran derivative (Scheme 31).

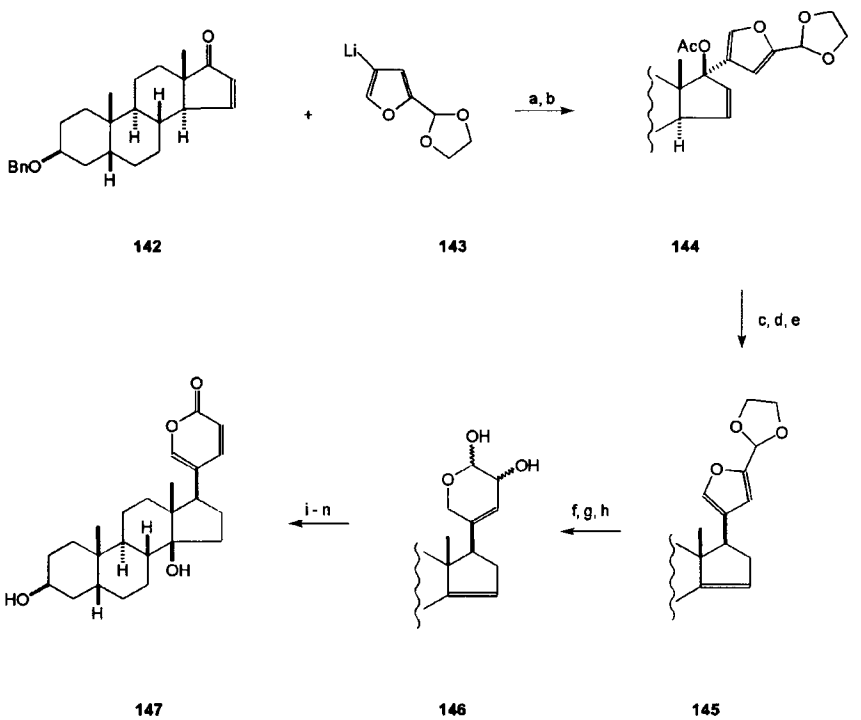


139 **140** **141**

Scheme 31. (a) dihydrolithiuofuran, THF; (b) HCl, THF, Σ 65%; (c) TMSTf, 2,6-lutidine, THF, 74%; (d) DIBAL, THF; (e) MnO_2, CH_2Cl_2, Σ 83%; (f) Bu_4^nNF, THF, 80%.

The poststerone **139** reacted with 2,3-dihydro-2,2-dimethyl-5-lithiofuran to afford, after hydrolytic cleavage of the resulting enol ether and subsequent silylation, the ketone **140**. Reduction of the keto group at C-22 with DIBAL proceeded highly stereoselectively but caused also the undesired reduction of the 6-oxo group. Allylic oxidation and removal of the silyl groups completed the synthesis.

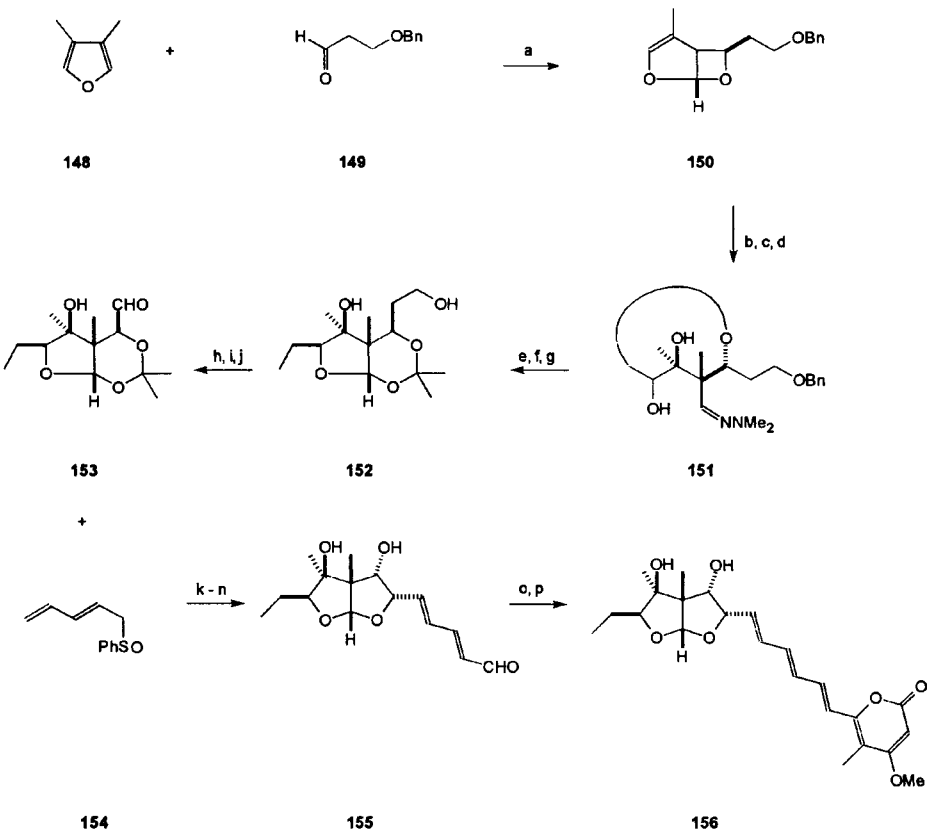
The furan strategy was extensively explored by Wiesner *et al.* in syntheses of the biologically active cardenolides [134-138]. In the synthesis of natural bufalin **147**, the side chain was constructed *via* addition of the protected furfural **143** to the derivative of testosterone **142** (Scheme 32) [139]. Allylic rearrangement of the adduct **144**, selective hydrogenation and elimination of the hydroxy group at C-15 gave **145**, which was subjected to photochemically-induced oxidation of the furan ring. Reduction of the anticipated ketoaldehyde afforded a diol readily converted *via* hydrolysis of glycol acetal to the hemiacetal **146**. Immediate oxidation of **146** followed by elimination of the hydroxy group of the lactone formed completed the construction of the α-pyrone unit. Introduction of the 14-β-OH group by the bromination-hydrolysis protocol and removal of the benzyl group furnished the bufalin **147**.



Scheme 32. (a) Et_2O, benzene, 95%; (b) Ac_2O, Py, DMAP; (c) $CaCO_3$, Me_2CO, H_2O, Σ 83%; (d) H_2, $Pd/CaCO_3$, EtOH, 93%; (e) $SOCl_2$, Py, 85%; (f) O_2, hν, tetraphenylporphyrin, CH_2Cl_2 then Me_2S; (g) $NaBH_4$, THF, H_2O, KOH, Σ 82% h) HCl, THF, 95%; (i) Ag_2CO_3/Celite, benzene, 75%; (j) MsCl, Et_3N, CH_2Cl_2; (k) DBN, benzene, Σ 85%; (l) NBS, $HClO_4$, Me_2CO, H_2O; (m) RaneyNi, AcONa, MeOH, CH_2Cl_2, Σ 70%; (n) $Pd(OH)_2/C$, EtOH, C_6H_6, C_6H_{12}, 70%.

4.4. MISCELLANEOUS

Asteltoxin **156** a trienic α-pyrone containing the bis-tetrahydrofuran moiety was isolated from toxic maize cultures of *Aspergillus stellatus* and was found to inhibit the activity of *E. coli* BF_1-ATPase [140,141]. The first total synthesis of this mycotoxin was achieved by Schreiber and Satake using photocycloaddition of furan **148** to the aldehyde **149** (Scheme 33) [142,143]. The resulting single *exo*-photoadduct **150** was transformed *via* epoxidation of the double bond and hydrolytic cleavage into an aldehyde immediately protected as the hydrazone **151**. The hydrazone occurring in the form of a monocyclic hemiacetal contains the quaternary carbon atom with the complete

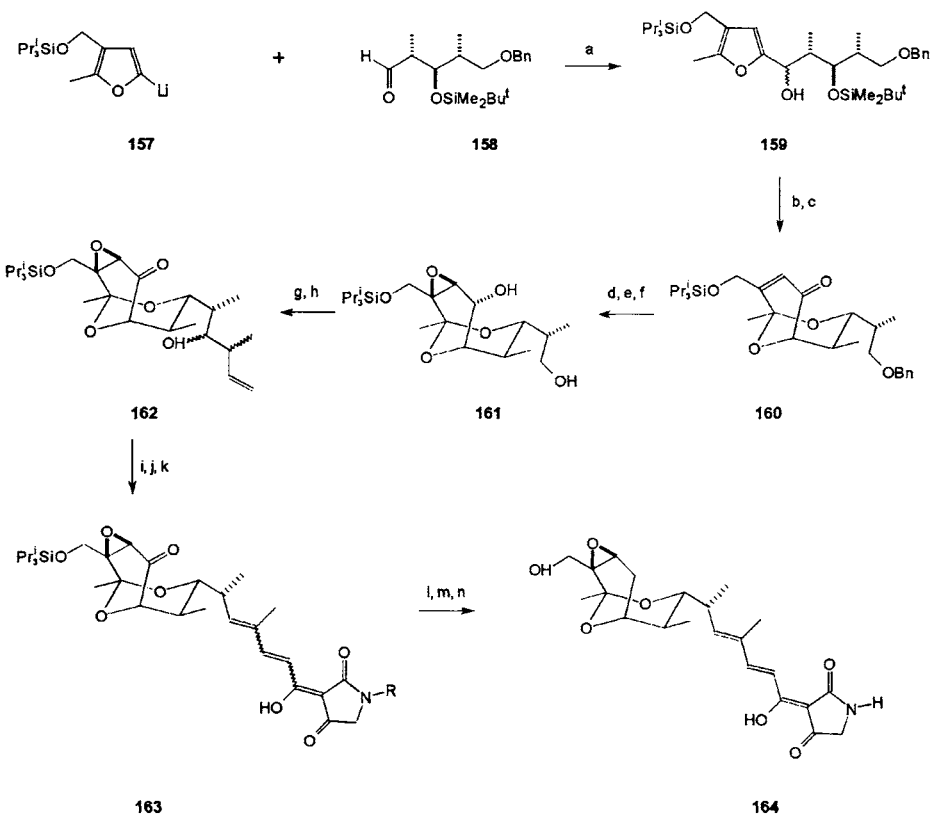


Scheme 33. (a) hν, C_6H_6, Et_2O, 63%; (b) MCPBA, $NaHCO_3$, CH_2Cl_2, 80%; (c) HCl, THF; (d) Me_2NNH_2, $MgSO_4$, CH_2Cl_2, Σ 72%; (e) EtMgBr, THF; (f) Me_2CO, $CuSO_4$, CSA, Σ 55%; (g) Li, NH_3, Et_2O, 98%; (h) o-NO_2PhSeCN, Bu_3P, THF; (i) H_2O_2, THF, Σ 81%; (j) O_3, CH_2Cl_2, Me_2S, 92%; (k) BuLi, THF; (l) CSA, CH_2Cl_2, Σ 77%; (m) $CF_3CO_2COCH_3$, 2,6-lutidine, Ac_2O; (n) $HgCl_2$, $CaCO_3$, MeCN, H_2O, Σ 60%; (o) 4-methoxy-5-methyl-α-pyrone, LDA, HMPA, THF, 80%; (p) TsCl, Et_3N, DMAP, CH_2Cl_2, 82%.

stereoconfiguration required. Chelation-controlled addition of Grignard reagent to the hemiacetal and a protection-deprotection sequence afforded the primary alcohol **152** readily transformed into the aldehyde **153** by the selenylation-ozonolyzis procedure. An addition of an anion generated from the sulfoxide **154** to the aldehyde **153** and subsequent double [2,3]sigmatropic rearrangement furnished a mixture (3:1) of easily separated alcohols. Hydrolysis of the isopropylidene acetal caused the cyclization to the bis-tetrahydrofuran derivative to give, after Pummerer rearrangement to the sulfoxide and hydrolysis, the aldehyde

155. Attachement of α-pyrone completed this convergent synthesis of racemic asteltoxin.

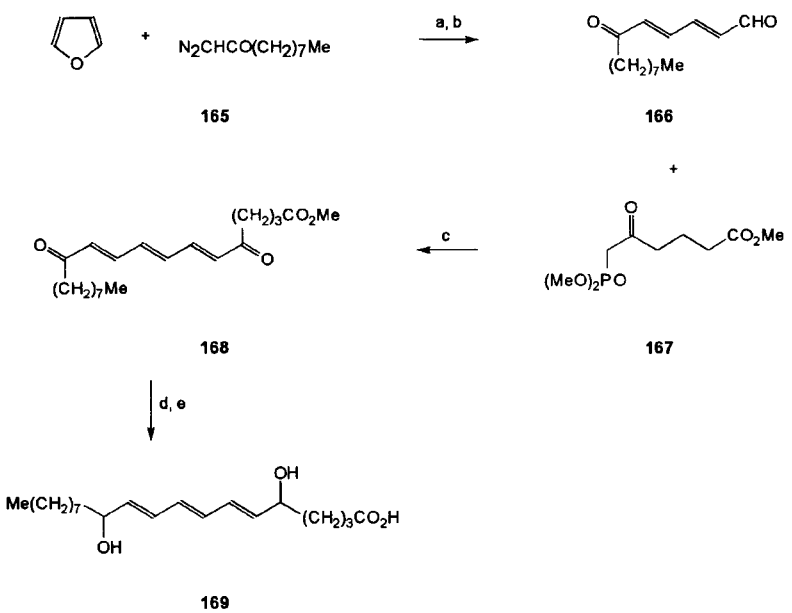
A number of research groups were involved in developing the furan strategy for the synthesis of the dienoyl tetramic acid antibiotics [34,106,144-148]. A member of this family, tirandamycin B **164,** was the subject of studies by DeShong *et al.* crowned with a total synthesis of its racemic form [149]. An addition of the furan **157** to the racemic aldehyde **158** yielded an equimolar mixture of alcohols separated by radial chromatography (Scheme 34).



Scheme 34. (a) THF, -78°C, 84%; (b) MCPBA, CH_2Cl_2, 89%; (c) HF, H_2SiF_6, MeCN, H_2O, 35%; (d) $NaBH_4$, $CeCl_3$, MeOH, 99%; (e) MCPBA, NaH_2PO_4, CH_2Cl_2, 73%; (f) Li, di-*tert*-butylbpihenyl, THF, 95%; (g) PDC, CH_2Cl_2, 85%; (h) *E*-crotyl bromide, $CrCl_3$, LAH, THF, 81%; i) OsO_4, $NaIO_4$, dioxane, H_2O, 85% j) TsOH, C_6H_6, 75%; (k) Schlessinger phosphonate, Bu^tOK, THF, 72%; (l) CF_3COOH, 98%; (m) $Bu^n{}_4NF$, THF, 99%; (n) PhMe, reflux.

The required *syn*-**159** was oxidized to anticipated pyranone whose selective desilylation under modified conditions afforded the bicyclic enone **160**. Reduction of the carbonyl group and epoxidation proceeded stereoselectively providing after removal of the benzyl group the primary alcohol **161**, subsequently oxidized and elongated using crotyl bromide to give the terminal olefin **162**. Oxidative cleavage of the alkene and dehydration gave the mixture of isomeric enals coupled with dianion of Schlessinger phosphonate [150] to afford the tetramic acid derivative **163**. Removal of the protecting groups and equilibration to the most stable *E,E*-configuration of the diene completed the synthesis of racemic tirandamycin B.

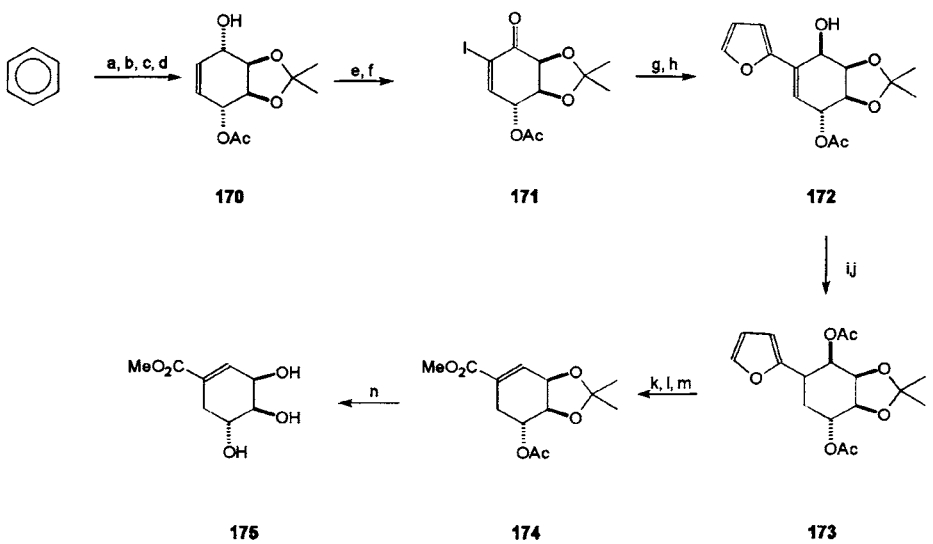
Diazocarbonyl compounds undergo rhodium-catalyzed carbene addition to furan, to give dienones or dienoates with a terminal aldehyde group suitable for further extension of conjugate by the Horner-Wittig olefination [151,152]. This strategy provides the synthesis of (±)-6(*E*)-LTB_3 **169** performed by Wenkert *et al.* 153] (Scheme 35).



Scheme 35. (a) $[Rh(OAc)_2]_2$, 79%; (b) I_2, CH_2Cl_2, 72%; (c) NaH, $(CH_2OCH_3)_2$, 70%; (d) $NaBH_4$, MeOH, H_2O, 90%; (e) LiOH, $(CH_2OCH_3)_2$, 75%.

Reaction of the diazoketone **165** with furan, catalyzed by the dirhodium tetraacetate, yielded a 7:1:1 mixture of isomeric products converted upon treatment with iodide to the all-*trans* diene **166**. Sodium salt of the phosphono ester **167**, prepared from methyl glutaryl chloride, treated with **166** to give the keto ester **168**, was readily transformed *via* reduction of the keto groups and ester hydrolysis into the racemic leukotriene **169**.

In the Johnson synthesis of both enantiomers of the methyl shikimate **175** [154], the furan ring was used as a synthetic equivalent of the carboxyl group. Microorganism-induced oxidation of benzene, photooxidation and enzymatic asymmetrization afforded the monoacetate **170** readily converted to the iodoenone **171** (Scheme 36).



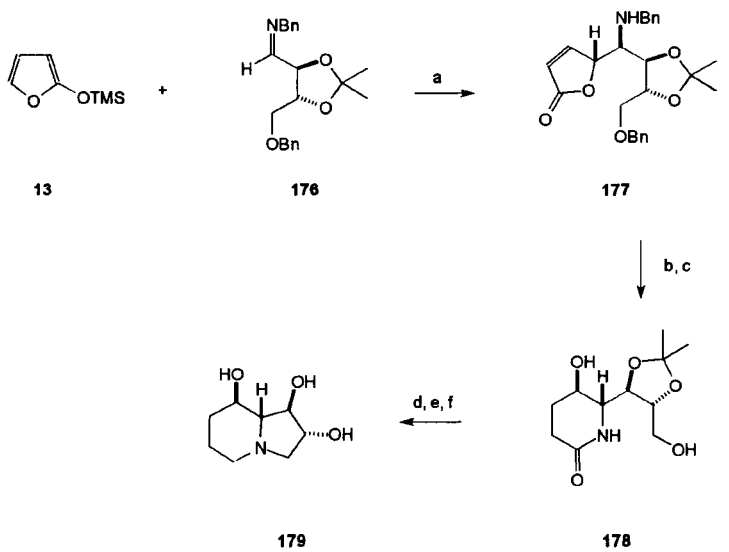
Scheme 36. (a) *Pseudomonas putida*; (b) DMP, TsOH, CH_2Cl_2, Σ 82%; (c) O_2, hν, tetramethylporphin, CH_2Cl_2, MeOH then $SC(NH_2)_2$, 65%; (d) *Amano* P-30 lipase, isopropenyl acetate, 90%; (e) PCC, CH_2Cl_2, 4Å; (f) I_2, Py, CCl_4, Σ 80%; (g) 2-($Bu^n{}_3Sn$)Fu, $Pd(PhCN)_2Cl_2$, CuI, Ph_3As, *N*-Me-pyrrolidone, 100%; (h) $NaBH_4$, $CeCl_3$, MeOH, 88%; (i) H_2, Pd/C, EtOH, 83%; (j) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 88%; (k) $RuO_2 \cdot H_2O$, $NaIO_4$, CCl_4, MeCN, H_2O; (l) CH_2N_2, Et_2O m) DBU, CH_2Cl_2, Σ 69%; (n) TsOH, MeOH, 89%.

Incorporation of the furan ring and reduction of the carbonyl group gave a 6:1 mixture of easily separated alcohols. The major β-alcohol **172** was hydrogenated stereoselectively to give **173**;

the oxidation of the furan ring according to the Sharpless method [63], followed by esterification and elimination of the acetoxy group, completed the synthesis of (-)-methyl shikimate.

Over the past 10 years the polyhydroxylated indolizidine alcaloids were frequent targets in synthetic investigations, owing to their ability of inhibition of certain glucosidases [155,156]. In order to find the substances with maximal inhibitory properties and also minimal toxicity, many analogues of naturally occurring indolizidines were synthesized.

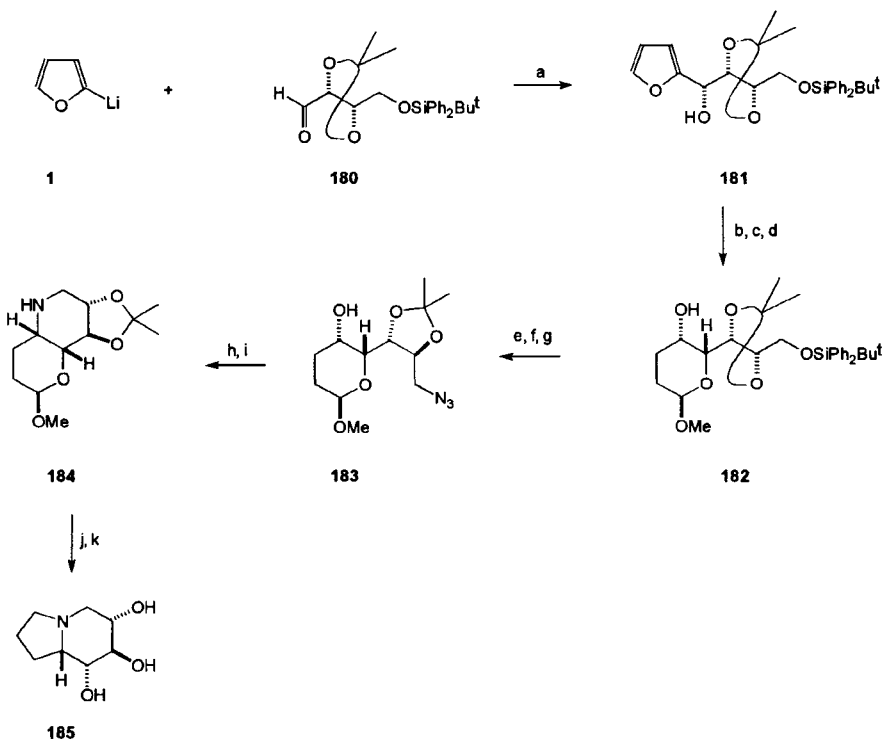
The butenolide approach was applied by Casiraghi *et al.* in the synthesis of (-)-1-*epi*-swainsonine **179** from the furan derivative **13** and imine **176** derived from D-tartaric acid (Scheme 37) [157]. The butenolide **177** was formed exlusively and then was readily transformed into the lactone **178** *via* ring expansion caused by nucleophilic attack of the deprotected amine. The carbonyl group and acetal protection were removed and second cyclization according to the Appel [158] procedure completed the brief and highly efficient synthesis.



13 176 177 178 179

Scheme 37. (a) $BF_3 \cdot Et_2O$, -85°C, CH_2Cl_2, 82%; (b) H_2, Pd/C, NaOAc, THF, 97%; (c) DBU, C_6H_6, 96%; (d) $BH_3 \cdot Me_2S$, THF; (e) TFA then DOWEX OH^-, Σ 88%; (f) PPh_3, CCl_4, Et_3N, DMF, 92%.

As concerns the crucial step of the synthesis of the hitherto unknown 1-deoxy-8a-*epi*-castanospermine **185**, Martin *et al.* developed an efficient method for obtainment of *syn*-furyl carbinols [14]. In the presence of an excess of $ZnBr_2$ the reaction of the aldehyde **180** bearing a bulky protective group, with furyllithium proceeds *via* an α-chelated transition state to afford *syn*-**181** in a highly stereoselective manner. However, the authors stated that the origin of this effect still remains obscure and requires further investigations (Scheme 38).

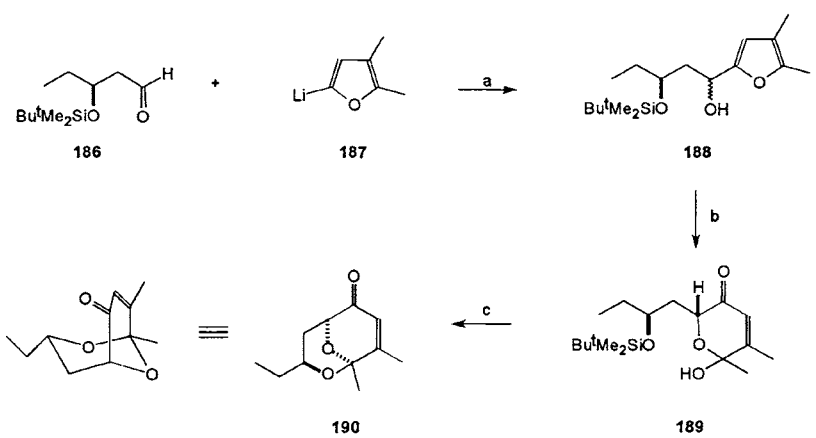


1 180 181 182 183 184 185

Scheme 38. (a) $ZnBr_2$, THF, 97%; (b) Bu^tOOH, $VO(acac)_2$, CH_2Cl_2, 81%; (c) MeI, Ag_2O, 59%; (d) K-Selectride, EtOH, THF, 92%; (e) Bu^n_4NF, THF, 91%; (f) MsCl, Et_3N, DMAP, CH_2Cl_2, 82%; (g) NaN_3, DMF, 86%; (h) $(COCl)_2$, DMSO, NMM, CH_2Cl_2, 92%; (i) H_2(70 psi), Pd/C, MeOH, 71%; (j) HCl, THF; (k) Pd/C H_2(70 psi) Σ 75%.

The alcohol **181** was transformed into an anomeric mixture of pyranones; for simplicity, only the major component was subjected to the simultaneous reduction of the carbonyl group and olefin. The resulting alcohol **182** was interconverted to the primary azide **183** *via* nucleophilic displacement of the mesylate. Re-creation of the carbonyl group at C-4 and hydrogenation of the azide brought about cyclization leading to the hydroquinoline **184** with complete stereoselectivity at the C-8a carbon atom. Hydrolysis of the hydropyran acetal and reductive amination completed the synthesis of the castanospermine analogue **185**.

Many isolated and described pheromones are characterized by the structure of spiro or bicyclic ketals easily attainable from furan precursors [159,160]. The bicyclic pyranone **190**, pheromone of the male swift moth *Hepialus hecta L.* [161], was synthesized by DeShong *et al.* in a three-step reaction sequence starting from furan **187** (Scheme 39) [162]. Its addition to the aldehyde **186**, obtained from octyl β-keto pentanoate by the biosynthetic pathway, afforded an equimolar mixture of alcohols **188**. The *anti*-diastereoisomer was oxidized to yield pyranone **189** which under treatment with diluted HF cyclized to the bicyclic ketal **190**.

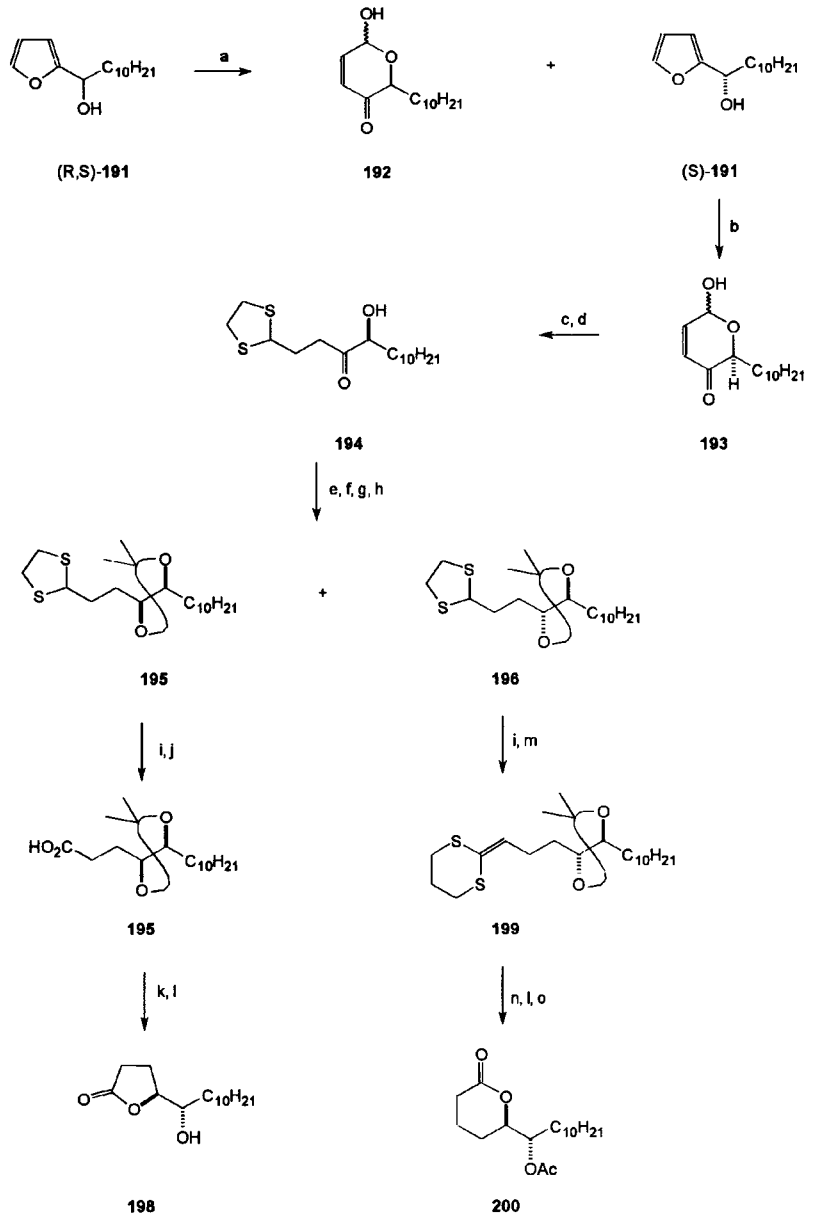


Scheme 39. (a) Et_2O, -78°C, 79%; (b) MCPBA, CH_2Cl_2, 91%; (c) HF, MeCN, H_2O, 78%.

The method of catalytic, kinetic resolution of furyl carbinols found some synthetic applications immediately after its development [65,66]. Kinetic resolution of the racemic carbinol **191** enabled Honda *et al.* to synthesize the (5*R*,6*S*)-6-acetoxy-hexadecan-5-olide **200**, an oviposition attractant pheromone of the mosquito *Celux pipens fatigans*, and of the (+)-disparlure, a pheromone of the gypsy moth *Porthetria dispar* (Scheme 40) [163,164]. The alcohol (*S*)-**191** obtained after resolution as a pure enantiomer was transformed into the ketone **194** *via* oxidation and hydrogenation-thioacetalization of the lactal **193** formed. Stereoselective reduction of the ketone **194** was achieved by choosing a proper combination of the protective group and reducing agent. Thus, application of the *tert*-bytyldiphenylsilyl group combined with L-Selectride led to the *syn*-diol, while benzyloxymethylene protection with zinc borohydride gave the *anti*-product exclusively. The *syn*-diol **195** was subjected to hydrolysis of the thioacetal and subsequent oxidation of the resulting aldehyde. Removal of the acetal followed by acid-catalyzed lactonization afforded the lactone **198**, earlier converted to (+)-disparlure by Iwaki *et al.* [165]. Alternatively, the *anti*-diol **196** was, after analogous hydrolysis of the thioacetal, elongated by one carbon to afford the ketene thioacetal **189** readily transformed into the required lactone **200**.

5. CONCLUSIONS

As can be seen from the presented survey, chiral furan derivatives are versatile synthons, widely recognized, and easily accessible *via* simple transformations of cheep, commercially available compounds. However, in some cases the degree of stereoselectivity is not satisfactory enough to meet the present requirements and thus more work has to be done to elucidate the nature of all factors responsible for asymmetric induction. Moreover, the furan ring was proved to be an excellent C-4 building block, suitable for construction of more complex structures. Finally, we feel that the near future will bring many more examples of syntheses of natural products based on the furan approach.



Scheme 40. (a) Bu^tOOH, (-)-DIPT, $Ti(OPr^i)_4$, 3Å, CH_2Cl_2, 44% calc. for (*S*)-**191**; (b) NBS, THF, H_2O, 100%; (c) H_2, Pd/C, AcOEt; (d) $(CH_2SH)_2$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 82%; (e) Bu^tPh_2SiCl, Im, DMF or BOMCl, $EtNPr^i_2$; (f) L-Selectride, THF, 42% or $Zn(BH)_4$ Et_2O, 99%; (g) Deprotection; (h) DMP, Me_2CO, TsOH; (i) HgO, $BF_3{\cdot}Et_2O$, THF, H_2O, **Σ** 87%; (j) $NaClO_2$, KH_2PO_4, 2-methylbut-2-ene, Bu^tOH, H_2O, 99%; (k) AcOH, H_2O; (l) TsOH, benzene, reflux, **Σ** 91%; (m) 2-lithio-2-TMS-1,3-dithiane, THF, **Σ** i,m 61%; (n) $HgCl_2$, MeOH, H_2O, 50% (o) Ac_2O, Py.

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Enantiomerically Pure γ-Butyrolactones in Natural Products Synthesis

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ABSTRACT

Stereochemically defined γ-butyrolactones have served as key building blocks in the syntheses of many types of natural products, including alkaloids, macrocyclic antibiotics, lignan lactones, pheromones, anti-leukemics, and flavor components. Accordingly, there are a large number of methods for the enantioselective preparation of substituted γ-butyrolactones: from simple natural products such as amino acids, tartaric acid, ascorbic acids, carbohydrates, or ribonolactones; from chiral sulfoxides, epoxides, or substituted acetylenic acids; and by various enzymatic or synthetic reductions, oxidations, and hydrolyses. This review will summarize these enantioselective methods of lactone synthesis and for each briefly show how the resultant lactone fits into the synthetic scheme for a particular natural product synthesis.

INTRODUCTION

Functionalized γ-butyrolactones have served as key components in many natural product syntheses, and the utility of these structural subunits is enhanced by the ease of construction and functionalization of this lactone ring system. For some time we have been interested in the stereoselective synthesis of substituted γ-butyrolactones for use as intermediates in natural product syntheses.[1,2] This review will cover published literature from 1982 to the present, and will be limited to γ-butyrolactones which have been instrumental in the enantioselective syntheses of natural products.[3,4] Since three thorough reviews have been published recently which detail the conversion of γ-butyrolactones into lignans,[5] this subject is excluded. The types of natural products included in this review range from fairly simple mono- and di-substituted γ-butyrolactones to more complex structures in which the γ-butyrolactone plays the role of a functional intermediate

in the total synthesis. The focus will be limited to syntheses which incorporate saturated γ-butyrolactones and will not include the use of butenolides (except as transient intermediates) since a review on advances in the chemistry of unsaturated butyrolactones has appeared.[6]

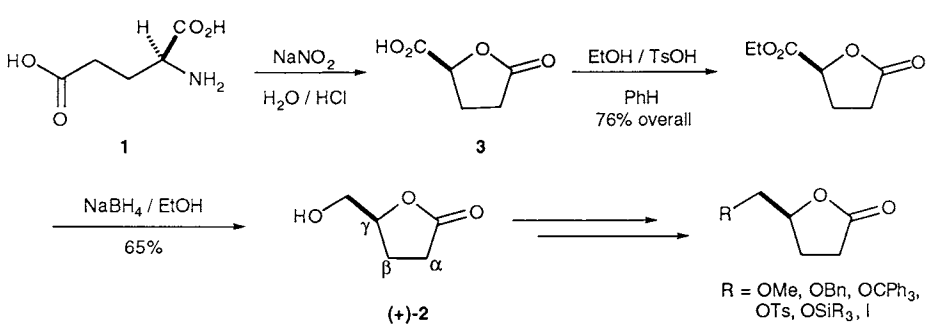
SYNTHESIS OF VERSATILE γ-BUTYROLACTONE STARTING MATERIALS

Several functionalized γ-butyrolactones have repeatedly served as intermediates in natural products synthesis, providing pivotal sources of asymmetry in many cases. The most versatile γ-butyrolactone intermediates have been derived from three natural sources: glutamic acid, ribonolactone, and malic acid. Because these sources have been tapped so often in the syntheses described in this review, the preparation of the most frequently utilized enantiomerically pure γ-butyrolactones from each is presented first.

γ-Butyrolactones Derived from Glutamic Acid

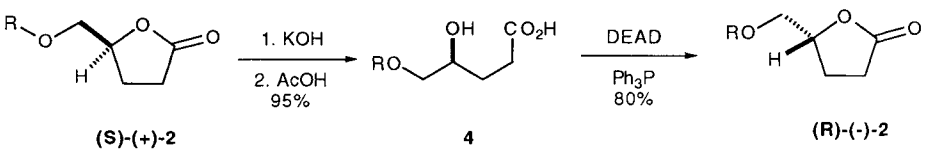
γ-Hydroxymethyl-γ-butyrolactone (**2**) has served as a versatile intermediate in natural product syntheses, and numerous examples of its utility will be given throughout this review. Koga and co-workers have reported the efficient production of (S)-(+)-γ-hydroxymethyl-γ-butyrolactone ((+)-**2**) from L-glutamic acid (**1**) (Scheme 1).[7] Glutamic acid was deaminated in aqueous nitrous acid to give the γ-carboxyl-γ-butyrolactone **3**. The carboxylic acid was esterified, and then reduced to give the (S)-(+)-γ-hydroxymethyl-γ-butyrolactone ((+)-**2**).

Scheme 1. (S)-(+)-γ-Hydroxymethyl-γ-Butyrolactone from L-Glutamic Acid

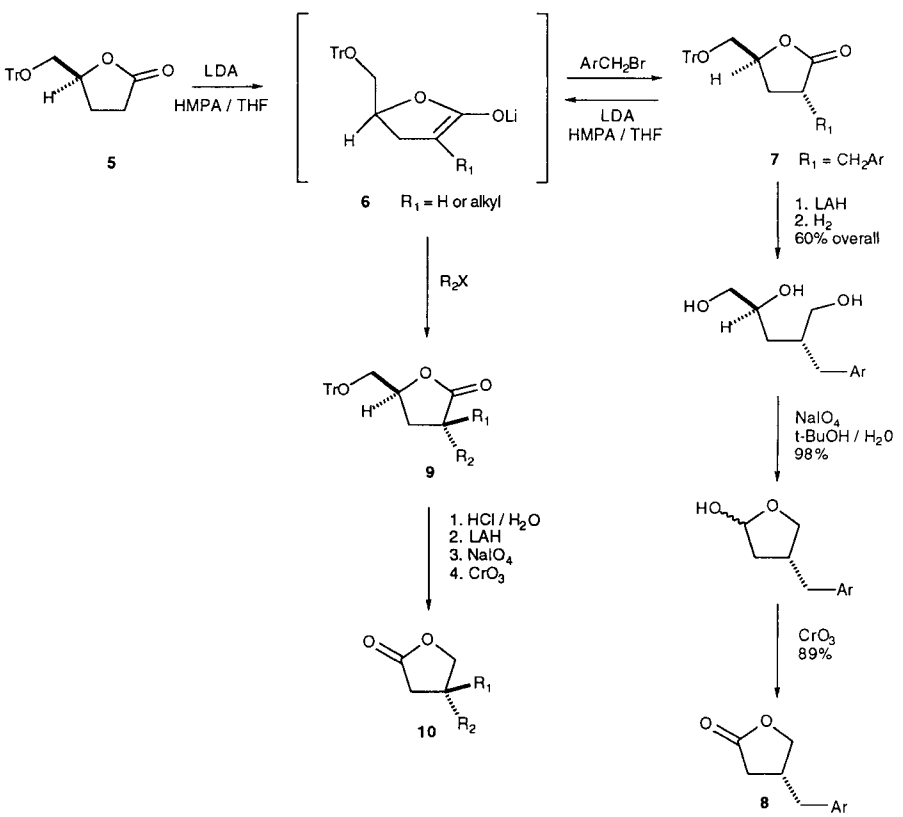


To prepare the enantiomeric (R)-(-)-γ-hydroxymethyl-γ-butyrolactone ((-)-**2**, Scheme 2), Tankano and co-workers applied a Mitsunobu inversion on the protected-acyclic hydroxyacid **4** .[8] In the role as a synthetic intermediate, the hydroxy γ-butyrolactone, (+)-**2** or (-)-**2**, has been protected as a variety of ethers (as shown in Scheme 1 and Scheme 4).[9]

Scheme 2. (R)-(-)-γ-Hydroxymethyl-γ-Butyrolactone from L-Glutamic Acid



Scheme 3. Synthesis of β-Substituted γ-Butyrolactones

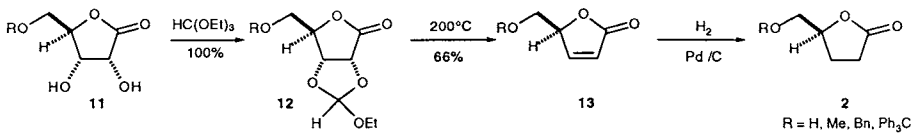


The γ-butyrolactone trityl ether **5** (Scheme 3), especially, has been instrumental as a substrate for the incorporation of additional stereogenic centers onto the ring: the trityloxy group effectively blocks one face of the butyrolactone, directing the addition of reagents from the opposite side of the ring. For example, Koga was able to prepare enantiomerically pure β-substituted and β,β-disubstituted γ-butyrolactones from the γ-trityloxymethyl γ-butyrolactone **5** (Scheme 3).[10] The enolate **6** of the trityloxy γ-butyrolactone was alkylated stereoselectively from the α-face to give the disubstituted γ-butyrolactone **7**. The following four-step sequence gave the enantiomerically pure β-alkyl-γ-butyrolactone **8**: reductive opening of the lactone to the 1,2-diol (LAH); removel of the trityloxy protecting group (H_2); oxidative cleavage of the diol and cyclization to the β-substituted lactol ($NaIO_4$); and oxidation to the lactone (Jones reagent). Two successive alkylations of the enolate **6** gave the stereoselectively tri-substituted γ-butyrolactone **9**, which was similarly transformed into the optically active β,β-disubstituted γ-butyrolactone **10**. This type of stereoselectivity and the utility of similarly substituted γ-butyrolactones will be discussed in the text of this review.

γ-Butyrolactones Derived from Ribonolactone

Ribonolactone has also served as a versatile γ-butyrolactone source. Manipulation of the three stereogenic centers of this sugar lactone has produced highly substituted γ-butyrolactone templates for incorporation into a broad range of natural product types; Joullié and Chen have written a short review on the use of D-ribonolactone in organic synthesis and discuss some of the lactone systems that are available from ribonolactone.[11] Font has described an efficient transformation of D-ribonolactone **11** into the versatile butenolide **13**,[12] which can be easily converted into substituted γ-butyrolactones, as will be apparent in many of the syntheses described later in this review.[13] The procedure of Font and co-workers starts with the cyclic orthoformate **12** of ribonolactone. Pyrolysis afforded the γ-hydroxymethyl butenolide **13**, which has served as a precursor to more highly substituted γ-butyrolactones (i.e. by stereoselective cuprate addition to the enone); several examples illustrating the utility of this butyrolactone precursor will be detailed in the text of this review. Hydrogenation of the enone produced the chiral hydroxymethyl-γ-butyrolactone **2** (Scheme 4).

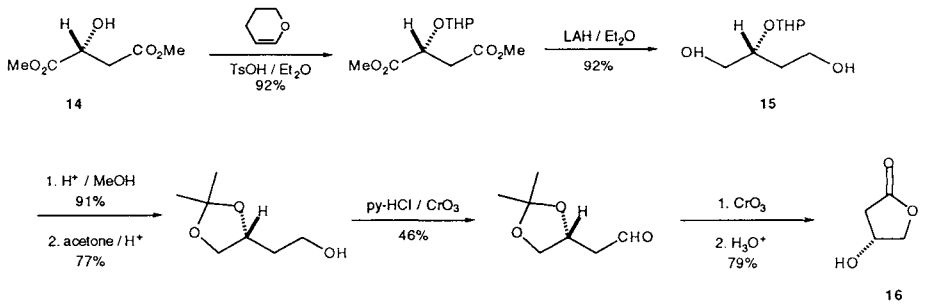
Scheme 4. (S)-(+)-γ-Hydroxymethyl-γ-Butyrolactone from D-Ribonolactone



γ-Butyrolactones Derived from Malic Acid

Mori efficiently converted (R)-(+)-malic acid (**14**) into another widely useful γ-butyrolactone, β-hydroxy-γ-butyrolactone **16** (Scheme 5).[14] Dimethyl malate was protected as the THP ether, then reduced to the diol **15**. The tetrahydropyran group was cleaved, the 1,2-diol was protected as the acetonide, then the primary hydroxyl was oxidized to the aldehyde. Further oxidation, followed by hydrolysis and lactonization afforded the enantiomerically pure β-alkoxy-γ-butyrolactone **16.** Application of this butyrolactone in natural product syntheses will be detailed later in the review.

Scheme 5. (R)-(+)-β-Hydroxy-γ-Butyrolactone from (R)-(+)-Malic Acid



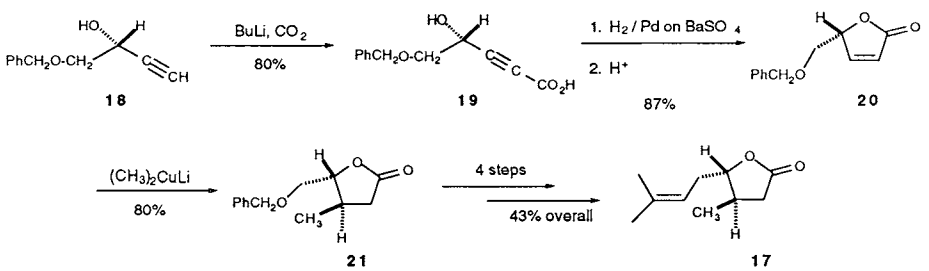
SYNTHESIS OF FUNCTIONALIZED γ-BUTYROLACTONE NATURAL PRODUCTS

Functionalized γ-butyrolactones are often themselves biologically active species. Simple γ-butyrolactones have been identified as pheromones, plant terpenoids, biosynthetic intermediates, and natural metabolites. Representative syntheses of such γ-butyrolactone natural products are shown below.

(+)- and (-)-Eldanolide (17)

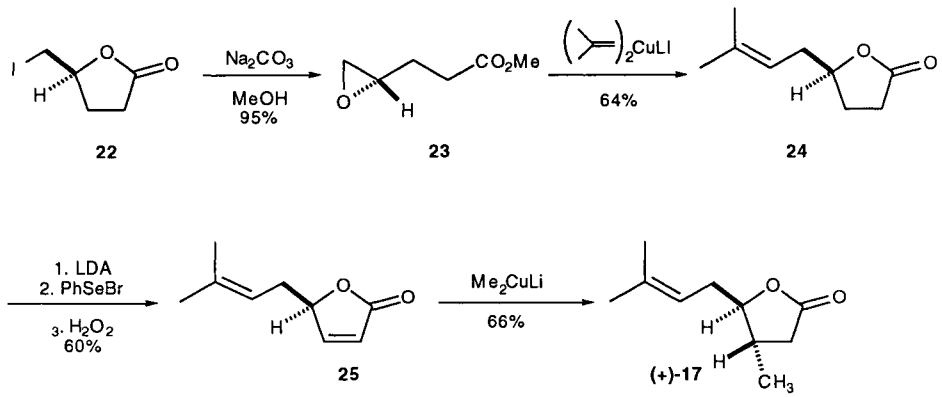
Vigneron and co-workers have prepared both enantiomers of eldanolide (**17**), the wing gland pheromone of the male African sugar cane borer.[15] The enantiomerically pure propargylic alcohol **18** was deprotonated and carboxylated to give the acid **19**; partial hydrogenation to the alkene and acid catalyzed cyclization gave the butenolide (R)-**20**. Stereospecific conjugate addition with methyl cuprate produced the β,γ-*trans*-butyrolactone, **21** (Scheme 6). This hydroxymethyl lactone was converted in four steps into the *trans*-γ-isopropylidene-β-methyl butyrolactone (-)-eldanolide ((-)-**17**). The enantiomer of eldanolide, (+)-**17**, was prepared from the

Scheme 6. Synthesis of (-)-Eldanolide ((-)-**17**)



(+)-γ-iodomethyl γ-butyrolactone **22**, an intermediate derived from glutamic acid (Scheme 7). Methanolysis (Na_2CO_3, MeOH, 95%) of the iodolactone gave the intermediate acyclic epoxy ester **23**; the epoxide was treated with lithium diisopropylidene cuprate to give the transient alkoxide carboxylate which cyclized *in situ* to give the lactone, **24**. The butenolide **25** was available in three steps, and was treated with dimethylcuprate to produce the corresponding *trans*-lactone, (+)-eldanolide, (+)-**17**.

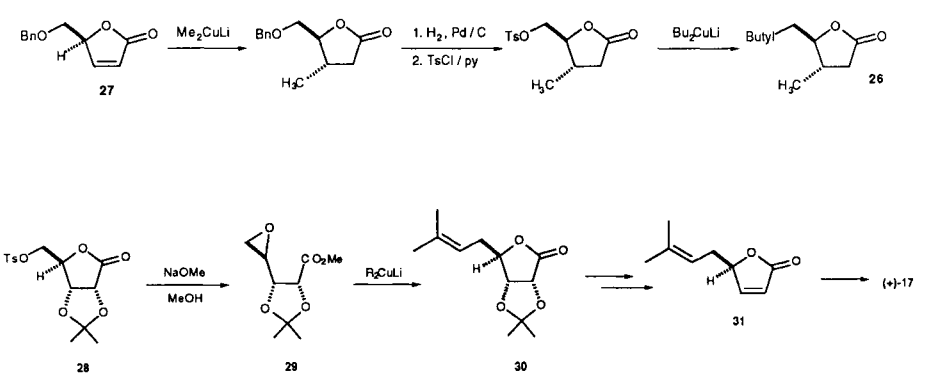
Scheme 7. Synthesis of (+)-Eldanolide ((+)-**17**)



(+)-*trans*-Cognac Lactone (26) and (+)-Eldanolide (17)

Font and co-workers synthesized (+)-*trans*-cognac lactone, **26**, and (+)-eldanolide, (+)-**17**, in sequences similar to those described above (Scheme 8).[16] In a straightforward manner, butenolide **27** (available from glutamic acid or ribonolactone) was treated with dimethylcuprate, and then the γ-alkoxymethyl substituent was transformed into a pentyl group to give **26**. To make eldanolide, the acetonide of tosylribonolactone **28** was treated with methoxide to give the epoxy acetonide **29**; the epoxide was opened with the appropriate alkylcuprate which effected cyclization to give the lactone acetonide **30**. The butenolide **31** was available in three steps and was converted into (+)-eldanolide ((+)-**17**) by stereoselective conjugate addition with dimethylcuprate.

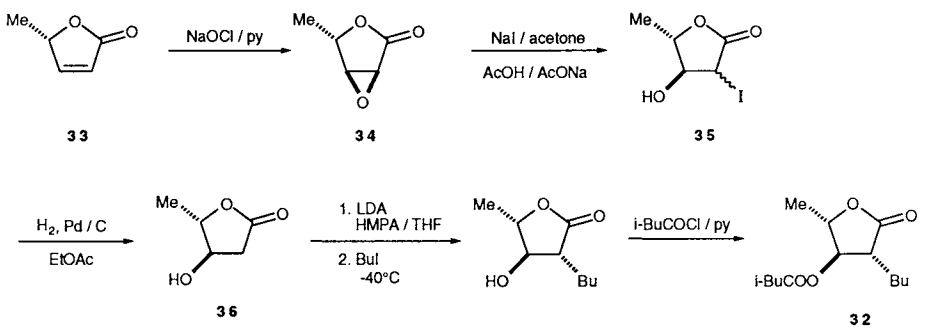
Scheme 8. Synthesis of (+)-*trans*-Cognac Lactone (**26**) and (+)-Eldanolide ((+)-**17**)



(+)-Blastmycinone (32)

Blastmycinone **32** is a metabolite derived from the antibiotic antimycine A and is an effective anti-fungal agent. Font's group has published a synthesis of this γ-butyrolactone from (+)-β-angelica lactone **33**.[17,18] The butenolide **33** was stereoselectively epoxidized with sodium hypochlorite in pyridine to give the epoxy lactone **34** (Scheme 9). Because more direct methods were not fruitful, the epoxide was opened by NaI to produce the α-iodo lactone **35**, and hydrogenolyzed to give the disubstituted γ-butyrolactone **36**. Stereoselective alkylation of the lactone enolate gave the *trans, trans*-trisubstituted hydroxy lactone, which was esterified to give the desired product, blastmycinone **32**.

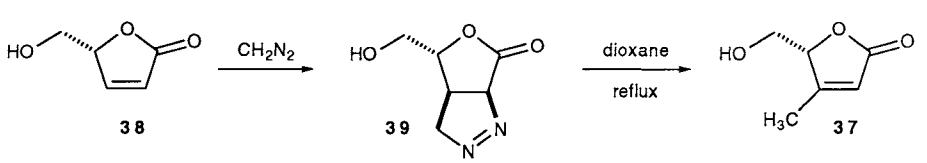
Scheme 9. Synthesis of (+)-Blastmycinone (**32**)



(+)-Umbelactone (37)

Font's group also reported the synthesis of the butenolide (+)-umbelactone, (**37**) starting from the glutamic acid derived substrate (+)-hydroxymethyl butenolide **38** (Scheme 10).[19] This butenolide underwent a facile dipolar cycloaddition with diazomethane to give pyrazoline **39**. The crude pyrazoline was heated at reflux in dioxane to give the β-methylbutenolide, **37**.

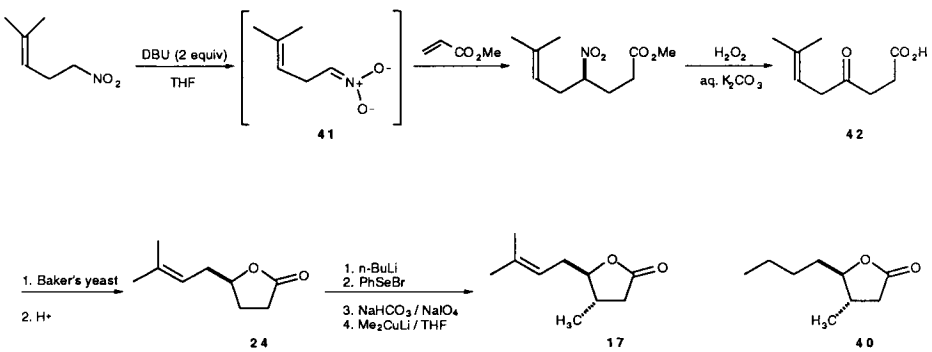
Scheme 10. Synthesis of (+)-Umbelactone (**37**)



(+)-*trans*-Whiskey Lactone (40) and (+)-Eldanolide (17)

In a recent novel approach to γ-butyrolactones, Barua and Sarmah have used an enzymatic reduction to generate (+)-*trans*-whiskey lactone (**40**) and (+)-eldanolide (**17**).[20] Michael addition of the nitroalkane dianion **41** to methyl acrylate, and subsequent hydrolysis of the nitroalkyl ester gave the γ-keto acid **42** (Scheme 11). Reduction of the ketone with baker's yeast followed by acid catalyzed cyclization gave enantiomerically pure (+)-γ-isopropylidene γ-butyrolactone (**24**). As illustrated previously (see Scheme 7), this lactone **24** was easily converted into **17**; a similar sequence led to **40**.

Scheme 11. Synthesis of (+)-Eldanolide (**17**) and (+)-*trans*-Whiskey Lactone (**40**)

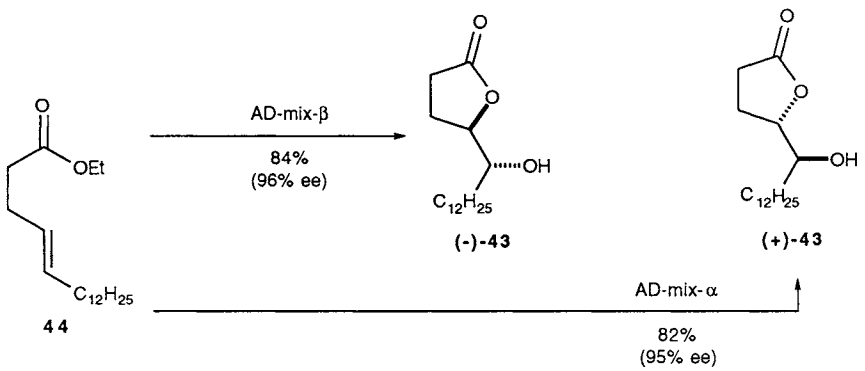


(-) and (+)-Muricatacin (43) and (+)-Disparlure (45)

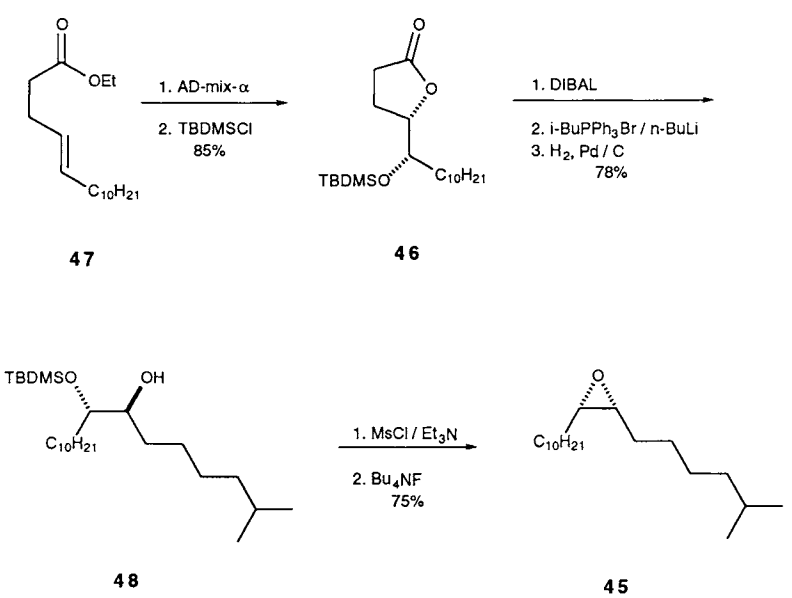
In a departure from glutamic acid and ribonolactone based syntheses of substituted γ-butyrolactones, Sharpless, Wang, and Zhang have reported an efficient synthesis of (-)- and (+)-muricatacin **43**, demonstrating the osmium-catalyzed asymmetric dihydroxylation (AD) of unsaturated esters.[21] The γ, δ-unsaturated ester **44** (prepared in two steps from acrolein) was dihydroxylated with either "AD-mix-β" or "AD-mix-α" by the prescribed method to give (-)- and (+)-muricatacin directly in 82-84% yield and 95 and 96%ee, respectively (Scheme 12). This efficient synthesis was applied to other classes of natural products as well. The sex attractant of the female gypsy moth, (+)-disparlure (**45**), was synthesized from an intermediate similar to the muricatacin lactone.[22] The necessary lactone **46** for this synthesis was available from the asymmetric dihydroxylation (AD-mix-α) of the γ,δ-unsaturated ester **47** in 86% yield and 95%ee (Scheme 13). The hydroxylactone **46** was protected as the *t*-butyldimethylsilyl ether and then was reduced to the lactol with DIBAL.

The lactol was then treated with isobutyltriphenylphosphonium ylide, and the resulting olefin was hydrogenated to give the acyclic monoprotected diol **48**. Conversion of the free hydroxyl group into a mesylate, followed by unmasking of the α-alkoxide by cleavage of the silyl protecting group with tributylammonium fluoride, afforded the *cis*-epoxide **45** (43% overall yield). The enantiomeric *cis*-epoxide and the related *trans*-epoxides were synthesized in a similar manner.

Scheme 12. Synthesis of (-)- and (+)-Muricatacin (**43**)



Scheme 13. Synthesis of (+)-Disparlure (**45**)



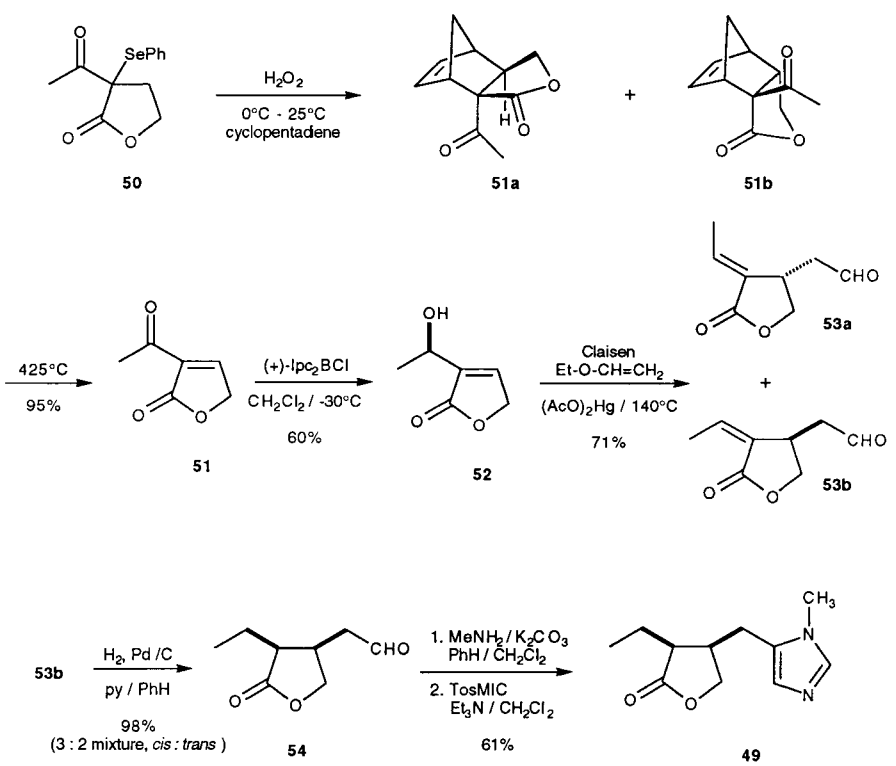
γ-BUTYROLACTONES AS INTERMEDIATES FOR THE SYNTHESIS OF COMPLEX NATURAL PRODUCTS

Butyrolactones derived from natural sources (glutamic acid, ribonolactone, or malic acid) offer pivotal stereogenic centers upon which to elaborate to various more complex structures. The synthesis of numerous natural products, including diterpenes, neolignans, steroids, macrocyclic antibiotics, and alkaloids has been accomplished with these simple γ-butyrolactones serving as synthetic intermediates.

(αS, βR)-Pilocarpine (49)

A report by Horne, Fugmann, Yakushijin, and Büchi describes the synthesis of (αS, βR)-pilocarpine (**49**), a tropical plant product which is the leading therapeutic agent for the treatment of glaucoma.[23] The synthesis begins with α-acetyl-γ-butyrolactone, which was converted into the selenolactone **50** in 94% yield (Scheme 14). The selenoxide was generated and elimination was induced in the

Scheme 14. Synthesis of (αS, βR)-Pilocarpine (**49**)

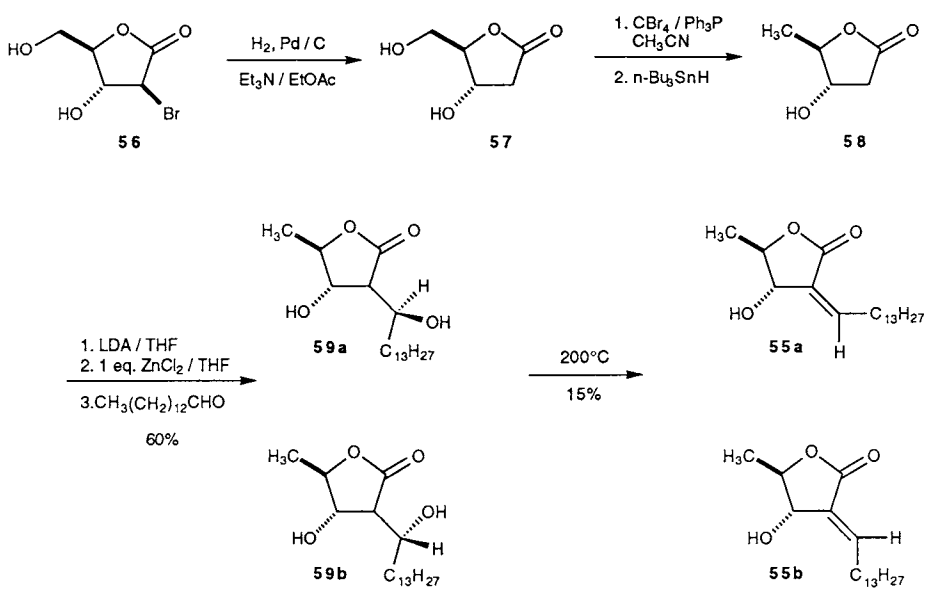


presence of excess cyclopentadiene to give a mixture of the endo- and exo-bicyclic ketones **51a** and **51b** (2.3 : 1 ratio). Flash vacuum thermolysis of the mixture produced the enone butenolide **51** as a white solid in 95% yield. This sequence avoided exposure of the labile enone to the oxidative reaction conditions. An asymmetric 1,2-reduction of the enone with (+)-β-chlorodiisopinocamphenylborane ((+)-Ipc_2BCl) proceeded without difficulty to give a 60% yield of the hydroxy enone **52** with >92% ee. To establish the β-stereogenic center on the lactone ring, the vinyl ether of the hydroxy butenolide was prepared, and, subsequent Claisen rearrangement afforded the separable mixture of the butenolide aldehydes **53a** and **53b** in a 2 : 1 ratio (71% yield). Very precise conditions were required for the reduction of the enone; expressly, hydrogenation of **53a** at 1 atm in pyridine and benzene produced the *cis*-disubstituted formyl-γ-butyrolactone **54** as a 3 : 2 mixture with the *trans* isomer. The *cis* aldehyde was then smoothly converted into the corresponding imidazole to give the natural product **49** in 61% yield.

(-)-Litsenolide C_1 (55a) and (-)-Litsenolide C_2 (55b)

Chen and Joullié utilized a γ-butyrolactone intermediate derived from ribonolactone to achieve the enantioselective synthesis of (-)-litsenolide C_1 and (-)-litsenolide C_2 (**55a** and **55b**, Scheme 15).[24] D-Ribonolactone was brominated with

Scheme 15. Synthesis of (-)-Litsenolide C_1 (**55a**) and (-)-Litsenolide C_2 (**55b**)

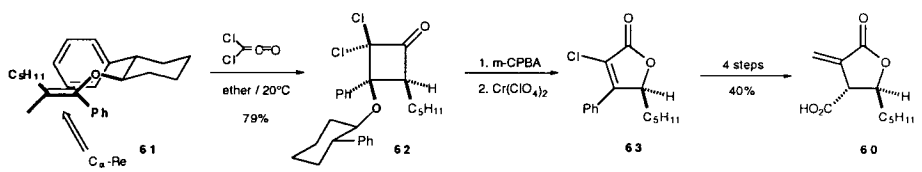


35% HBr in AcOH to give the α-bromo-γ-butyrolactone **56** and debrominated by hydrogenolysis to produce the di-substituted γ-butyrolactone **57**. The γ-hydroxymethyl substituent was selectively brominated then reduced with tributyl tin hydride to give the *trans*-γ-methyl-β-hydroxy-γ-butyrolactone **58**. Generation of the dilithium enolate of **58** and condensation with myristyl aldehyde, afforded a diastereomeric mixture of γ-butyrolactone diols **59a** and **59b**; the diol mixture was dehydrated to give the *cis*- and *trans*-α-methylene γ-butyrolactone natural products **55a** and **55b**.

(-)-Methylenolactocin (60)

Greene and co-workers reported the first synthesis of the antitumor antibiotic (-)-methylenolactocin (**60**). The synthesis, which relies on a stereoselective [2+2]-cycloaddition, illustrates a novel approach to enantiomerically pure γ-butyrolactones.[25] The cyclohexyl Z-enol ether **61**, available from common starting materials, underwent a highly stereoselective cycloaddition with dichloroketene. The cycloaddition occurred exclusively from the C_α-Re face of the enol ether, presumably because the other face is blocked by the neighboring equatorial phenyl group as shown in Scheme 16. The cycloaddition gave the diasteriomerically pure cyclobutane adduct **62** in 79% yield. The ketone was then oxidized to the γ-butyrolactone (m-CPBA) and converted into the butenolide **63** in 73% overall yield. This butenolide was efficiently converted into the α-methylene natural product **60** in four steps.

Scheme 16. Synthesis of (-)-Methylenolactocin (**60**)

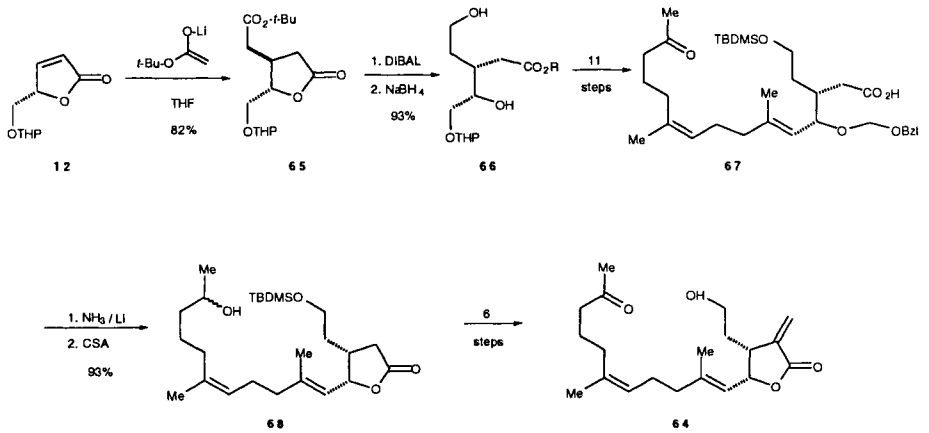


(+)-Mayolide A (64)

Yamada and co-workers elucidated the absolute configuration of the diterpene (+)-mayolide A (**64**) by an enantioselective total synthesis.[26] Elaboration of the butenolide **12** (available from D-mannitol) by asymmetric Michael addition of *t*-butylacetate lithium enolate to the enone, gave the β,γ-*trans*-disubstituted γ-butyrolactone **65** in 82% yield. This transformation established both stereogenic centers for the targeted product (Scheme 17). Selective reduction of the lactone

carbonyl with DIBAL, and sequentially with $NaBH_4$ gave the branched, alicyclic, selectively functionalized diol **66**. A series of selective protections/deprotections and chain elongation of the latent γ-position substituent (11 steps) produced the fully functionalized keto acid **67**. Removal of the benzyloxymethyl protecting group with Li/NH_3, followed by treatment with a catalytic amount of camphorsulfonic acid in ethyl acetate gave the γ-butyrolactone alcohol **68** in 93% yield. The two stereogenic centers of this penultimate lactone were set by the initial Michael addition to the mannitol-derived γ-butyrolactone; no epimerization of the C-2 position was apparent during the course of numerous transformations in this synthetic sequence. The α-methylene group was introduced without difficulty, and after some obvious adjustment of the side-chain functionality, the synthesis of the diterpene **64** was completed.

Scheme 17. Synthesis of (+)-Mayolide A (**64**)

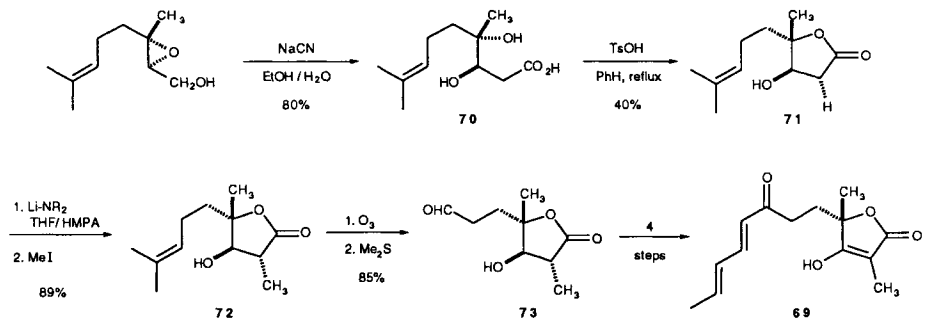


12 65 66 67 68 64

(-)-Vertinolide (69)

Ganem and Wrobel illustrate a general approach to enantiomerically pure tetronic acids with the synthesis of (-)-vertinolide (**69**, Scheme 18).[27] (2S, 3S)-geranyl oxide was heated with NaCN in $EtOH/H_2O$ to give the dihydroxy acid **70**; acid catalyzed lactonization of the crude diol acid furnished the enantiomerically pure *trans*-γ-butyrolactone **71** in 40% yield overall from the epoxide. Alkylation of the dianion of the lactone with methyl iodide gave, exclusively, the *trans, trans*-γ-butyrolactone **72**, and ozonolysis provided the lactone aldehyde **73**.[28] The aldehyde side chain was elaborated in four steps to give (-)-vertinolide **69**.

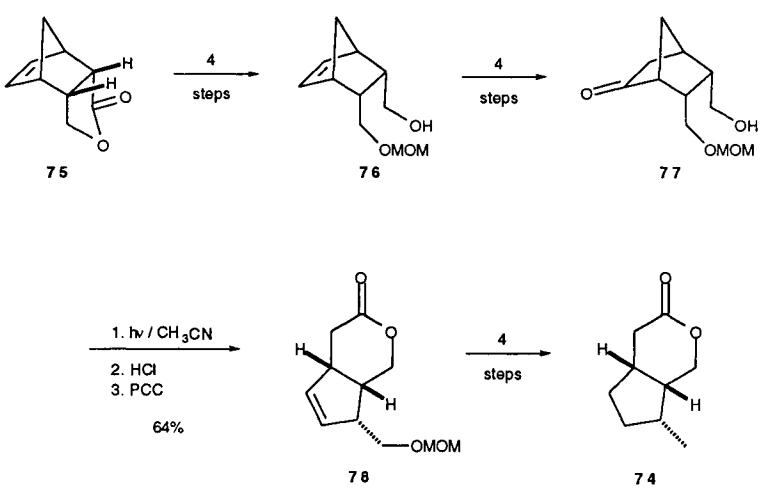
Scheme 18. Synthesis of (-)-Vertinolide (**69**)



(-)-Boschnialactone (74)

The Toyama University group of Arai, Kawanami, and Koizumi reported the total synthesis of (-)-boschnialactone (**74**) from the bridged bicyclic γ-butyrolactone **75**,[29] which was available from an asymmetric Diels-Alder reaction.[30] The γ-butyrolactone was saponified, esterified, protected, and reduced to give the monoprotected diol **76** (Scheme 19). Further manipulations to the keto alcohol **77**, followed by photolysis and oxidation gave the lactone **78**, which was transformed in three steps to the bicyclic iridoid lactone **74**.

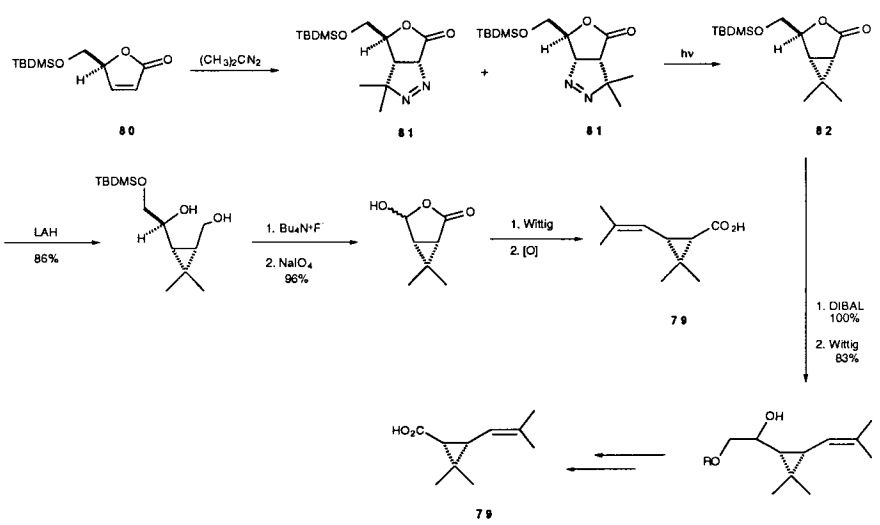
Scheme 19. Synthesis of (-)-Boschnialactone (**74**)



cis-Chrysanthemic Acid (79)

Chrysanthemic acid **79** and derivatives are members of the pyrethrin family of plant products, which exhibit potent insecticidal activity. Mann and Thomas prepared chrysanthemic acid from the butenolide **80**, illustrating another cycloaddition with a butenolide which produced highly functionalized γ-butyrolactones.[31] Addition of diazopropane to the enone produced two regioisomeric pyrazoles **81**, and subsequent photochemical elimination of nitrogen afforded the cyclopropyl lactone **82**. Reduction of the lactone to the diol (or, alternatively, to the lactol) and manipulation of the differentiated functional groups led to both *cis*-enantiomers of chrysanthemic acid (Scheme 20).

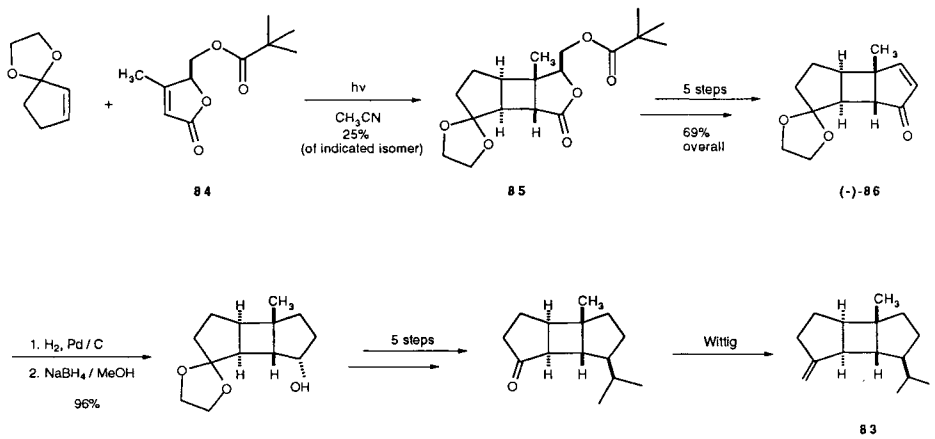
Scheme 20. Synthesis of *cis*-Chrysanthemic acid (**79**)



(-)-β-Bourbonene (83)

Tomioka, Tanaka, and Koga employed an asymmetric [2 + 2] cycloaddition to produce an enantiomerically pure tricyclic sesquiterpenoid, (-)-β-bourbonene.[32] The synthesis started from the γ-hydroxymethyl-γ-butyrolactone (available from glutamic acid), which was readily converted into the butenolide **84** (Scheme 21). Photolysis of this butenolide in the presence of the ketal of cyclopentenone produced the *cis, anti, cis*-tricycle **85** in 25% isolated yield after separation from the other diastereomer and regioisomers. This tricycle served as the backbone for elaboration into the sesquiterpene. The lactone tricycle was converted in five steps (69% overall) to the tricyclic enone **86**, and then, initially, into (-)-norbourbonone, followed by a Wittig reaction to give (-)-β-bourbonene (**83**).

Scheme 21. Synthesis of (-)-β-Bourbonene **(83)**



Acetoxycrenulide (87)

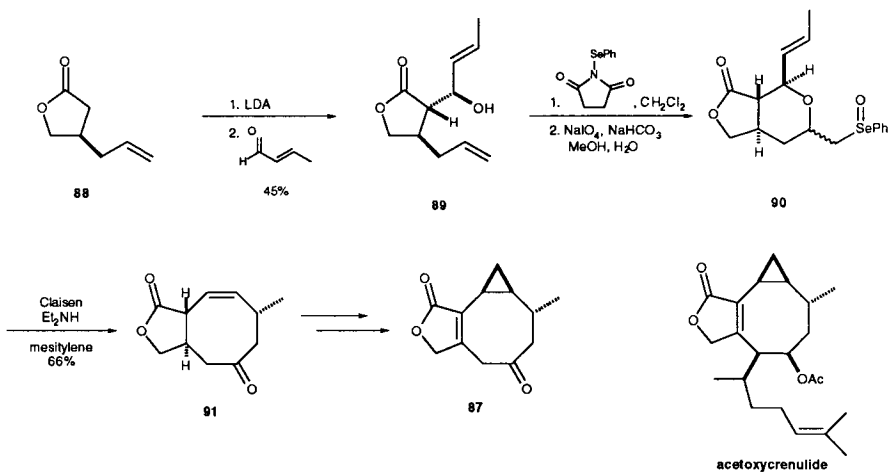
Ezquerra, He, and Paquette's synthesis of the crenulide diterpene nucleus (**87**), utilizes a stereoselective aldol alkylation with an enantiomerically pure β-substituted γ-butyrolactone (Scheme 22).[33] Thus, the γ-butyrolactone **88**, derived from glutamic acid, was deprotonated with LDA and condensed with crotonaldehyde to give a 91% yield of the diastereomeric *trans*-alcohols **89** (1 : 1 ratio), which were easily separable by chromatography; this sequence established two transient stereogenic centers. The bis-substituted γ-butyrolactone was then treated with n-(phenylseleno)phthalimide to give the bicycle tetrahydropyran, followed by oxidation to the selenoxide **90**. Elimination of the selenoxide and subsequent Claisen rearrangement of the resultant enol ether gave the *trans*-bridged bicyclic γ-enone **91**. A few further manipulations, including Simmons-Smith cyclopropanation of the B-ring, produced the bicyclic[6.1.0]-nonanyl crenulide nucleus **87**. The stereoselective Claisen and cyclopropanation reactions were essentially controlled by the stereogenic center originally contributed by the starting β-substituted-γ-butyrolactone, and these transformations ultimately established three new stereogenic centers in the final product.

6-Deoxy Sugars

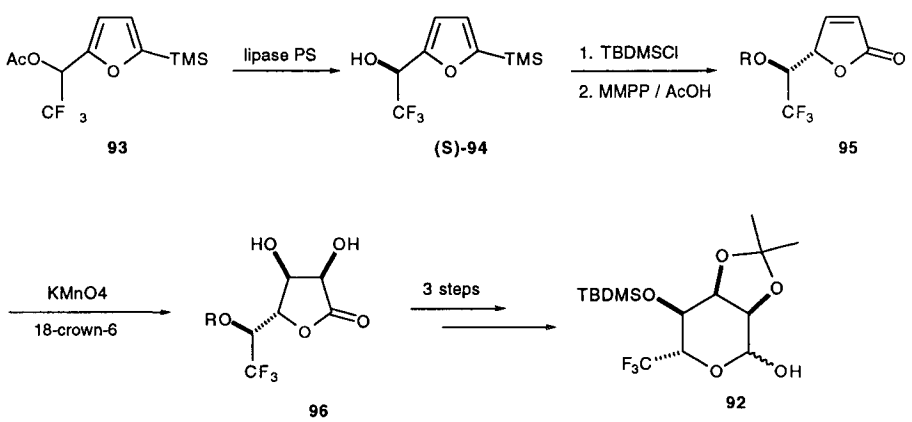
The preparation of functionalized 6-deoxy sugars was described by Yamazaki, Mizutani, and Kitazume by the enzymatic resolution of butenolides.[34] For example, the trifluoromethyl derivative of D-allose **92** was available from the enzymatic resolution of the racemic furan **93** with "lipase PS" (Amano

Pharmaceutical Co., Japan) to give the (S)-furan **94** (Scheme 23). The hydroxyl group was protected as a silyl ether, and the furan was then oxidized to furnish the 2-butenolide **195**. Dihydroxylation of the enone selectively produced the *cis, trans*-trisubstituted-γ-butyrolactone diol **96** which was protected as the acetonide during the isomerization of the γ-butyrolactone to the allose δ-lactol, **92**.

Scheme 22. Synthesis of Crenulide Diterpene Skeleton



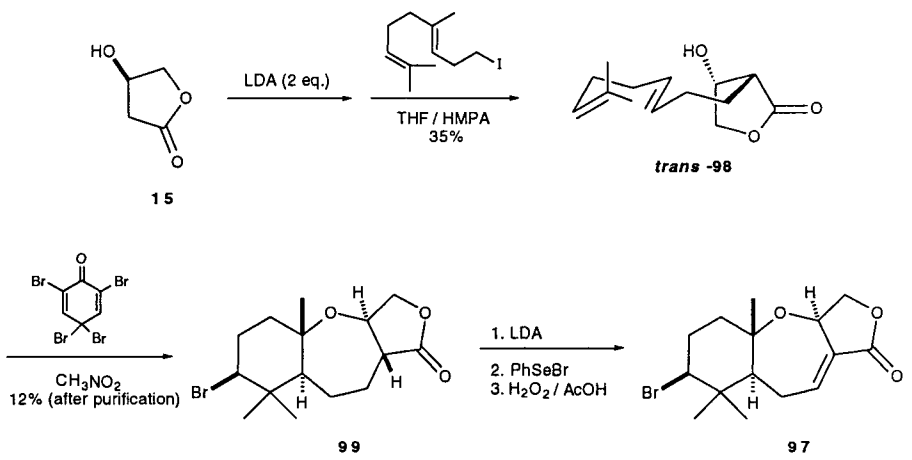
Scheme 23. Synthesis of 6-Deoxy Sugars



(-)-Aplysistatin (97)

Shieh and Prestwich reported a biomimetic total synthesis of the marine antineoplastic agent, (-)-aplysistatin (**97**), starting from (R)-β-hydroxy-γ-butyrolactone (**15**, derived from R-(+)-malic acid).[35,36] The dianion of **15** was alkylated with homogeranyl iodide to give the *trans*-substituted γ-butyrolactone **98** in 35% yield after purification. Bromocyclization via the conformation shown in Scheme 24 yielded a 1 : 5 mixture of the desired tricyclic ether **99** and the enantiomer. The mixture was carried-on for two steps (phenylselenation and oxidative elimination to give the olefin) to give (-)-aplysistatin (**97**) and (+)-12-epiaplysistatin. The diastereomeric mixture was separable by HPLC.

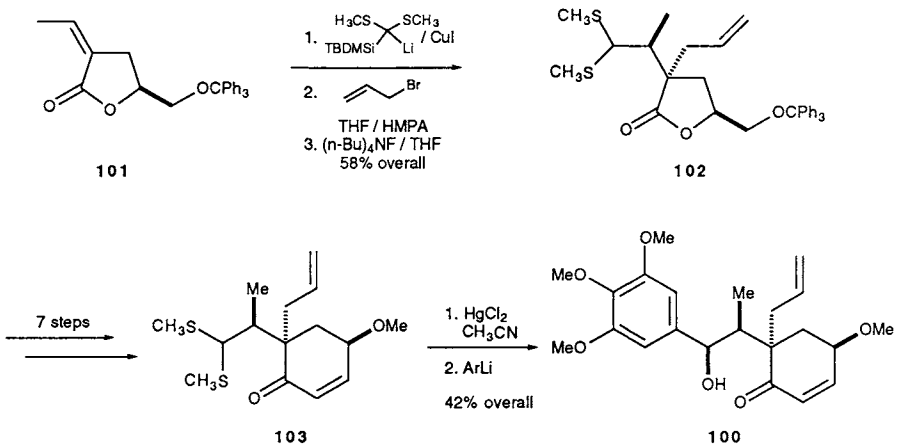
Scheme 24. Synthesis of (-)-Aplysistatin (**97**)



(-)-Megaphone (100)

The enantioselective total synthesis of (-)-megaphone was accomplished by Koga and co-workers starting from the exo-alkylidene γ-butyrolactone **101**; this enone was prepared from the glutamate derived γ-trityloxymethyl γ-butyrolactone (**5**).[37] Conjugate addition to the enone by lithiated dithiomethane followed by alkylation with allyl bromide and protodesilylation afforded the trisubstituted lactone **102** in 88% yield. As expected, both the conjugate addition and the alkylation occurred from the α-face, opposite the trityloxy substituent (Scheme 25). In seven steps, the γ-butyrolactone was converted into the enone **103**, which then was transformed into (-)-megaphone (**100**) in 42% yield.

Scheme 25. Synthesis of (-)-Megaphone (**100**)



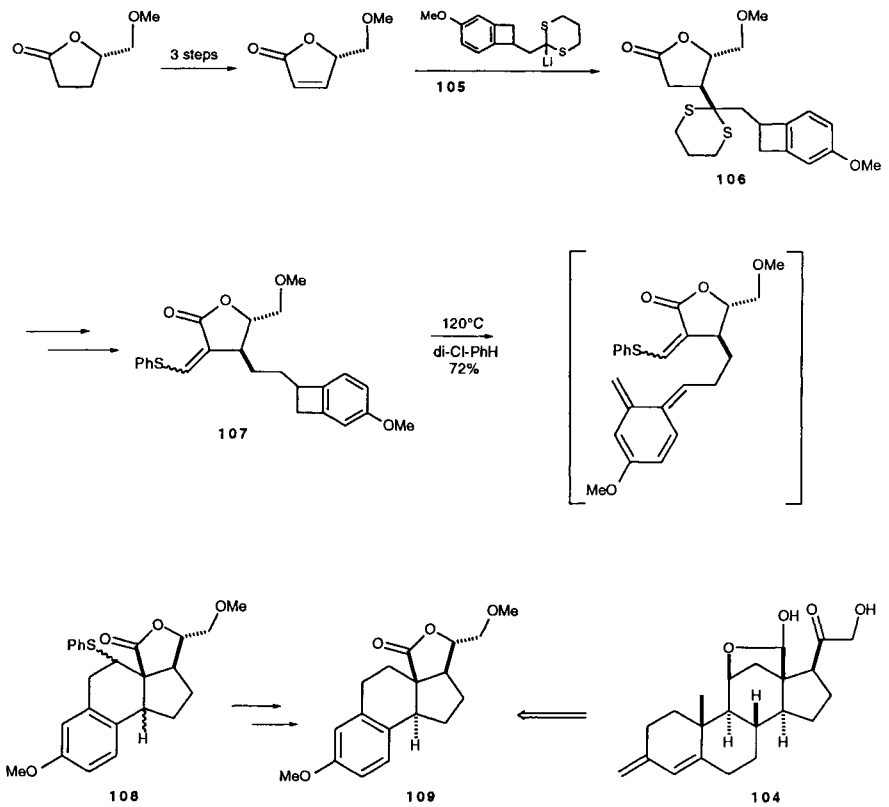
(+)-Aldosterone (104)

The enantioselective synthesis of a potential des-A-ring precursor of (+)-aldosterone (**104**) was described by Fukumoto's group, starting from (S)-γ-hydroxymethyl-γ-butyrolactone (**2**, Scheme 26).[38] The γ-butyrolactone was converted into the corresponding butenolide, and the lithiated thioacetal of the benzocyclobutene **105** was then added via a Michael addition to give the *trans*-disubstituted γ-butyrolactone **106**. This lactone was then converted into the α-methylene lactone **107**. Thermolysis to effect cyclization of this olefinic benzocyclobutene afforded in 72% yield the mixture of tetracycles **108a** and **108b** (1 : 2.3), via the proposed intermediate. The mixture was desulfurized and the products were separated to give the aldosterone precursor **109** as the minor component.

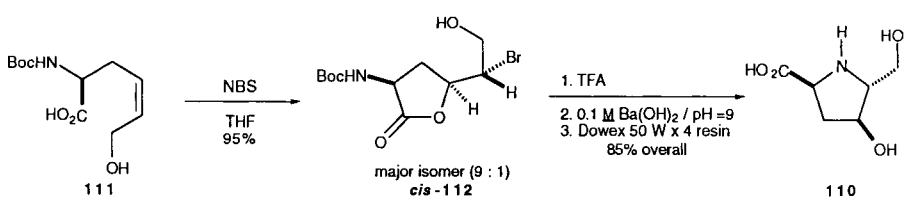
(-)-Bulgecinine (110)

Ohfune's group has reported a stereoselective bromolactonization to prepare (-)-bulgecinine (**110**).[39] The *cis*-allyl alcohol **111**, obtained from allylglycine, was treated with NBS in THF which effected the lactonization and gave a 95% yield of the γ-butyrolactones **112** in a 9 : 1 ratio (Scheme 27). The major isomer, the *cis* disubstituted lactone, could be purified by flash chromatography, and was converted into bulgecinine (**110**) in two steps.

Scheme 26. Synthesis of (+)-Aldosterone (**104**)



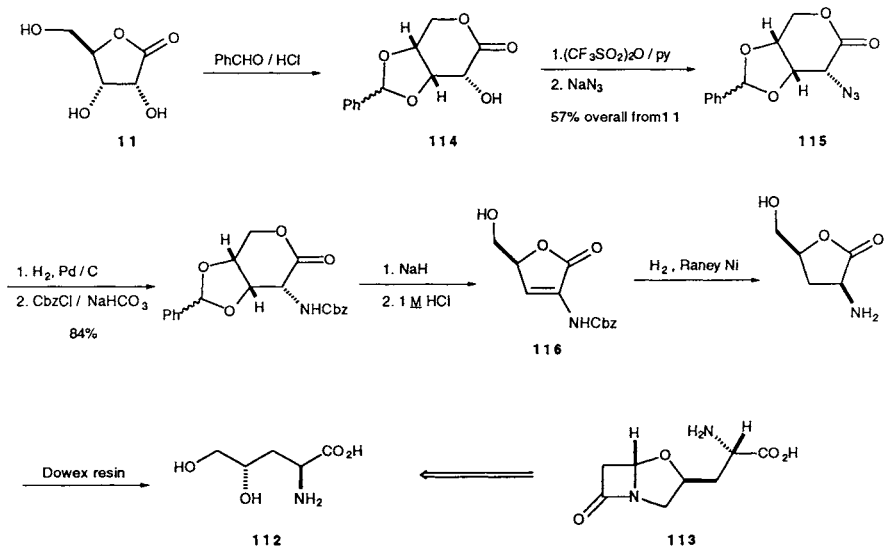
Scheme 27. Synthesis of (-)-Bulgecinine (**110**)



Clavalanine (113)

Ariza, Font, and Ortuño have introduced a strategy to induce stereogenicity at C-2 (the α-carbon) of a γ-butyrolactone through hydrogenation of a γ-substituted-butenolide derived from D-ribonolactone.[40] The approach was applied to the synthesis of the amino acid **112**, which is a formal intermediate in the total synthesis of clavalanine **113** (Scheme 28). Ribonolactone **11** was converted into the benzylidene δ-lactone in the presence of benzaldehyde and concentrated HCl, and in two steps from this hydroxylactone, the α-azido lactone **115** was easily obtained. Hydrogenation of the azido group, protection of the resultant amine as a carbamate, base induced elimination of benzaldehyde, and acid catalyzed ring rearrangement led to the butenolide **116**. Facial selective hydrogenation, followed by treatment with acidic Dowex resin afforded the target amino acid **112**, as a single stereoisomer.

Scheme 28. Synthesis of Clavalanine **(113)**

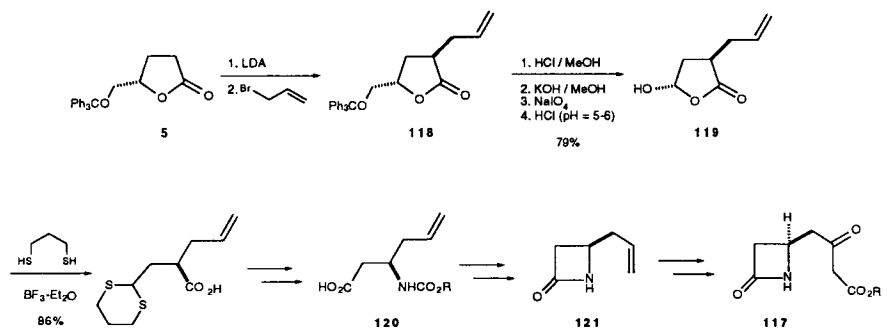


Carbapenam Alkaloids

Takano, Kasahara, and Ogasawara reported the synthesis of the β-lactam ring system **117** from a γ-butyrolactone precursor.[41] The structural units produced in this study are intermediates in the syntheses of carbapenam-type antibiotics. The γ-trityloxy-γ-butyrolactone (**5**, derived from L-glutamic acid or D-mannitol) was stereoselectively alkylated to give the α-allyl-lactone **118**, and this disubstituted γ-butyrolactone was converted into the γ-hydroxy-γ-butyrolactone **119** in 3 steps

(79% overall yield, Scheme 29). Further manipulation of the lactone gave the carbamate acid **120**; cyclization to the β-lactam ring **121** was realized after removal of the carbamate protecting group. The resultant alkyl β-lactam was further functionalized to give the β-lactam **117**, which is a formal precursor to the carbapenam alkaloids.

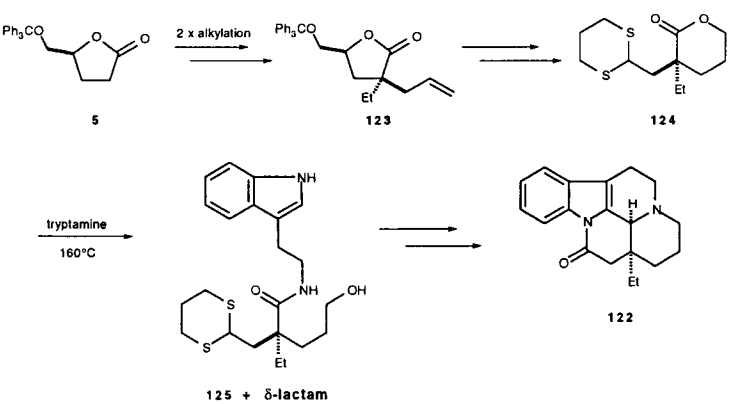
Scheme 29. Synthesis of Carbapenam Alkaloid Precursor



(-)-Eburnamonine (122)

Tankano's group has developed an enantioselective synthesis of several vincamine-eburnamine indole alkaloids.[42] For example, the synthesis of (-)-eburnamonine (**122**) starts from the familiar γ-trityloxy-γ-butyrolactone (**5**).[43] Tankano twice takes advantage of the stereoselective alkylation of substituted γ-butyrolactones to produce the tri-substituted γ-butyrolactone **123** (Scheme 30). The

Scheme 30. Synthesis of (-)-Eburnamonine (**122**)

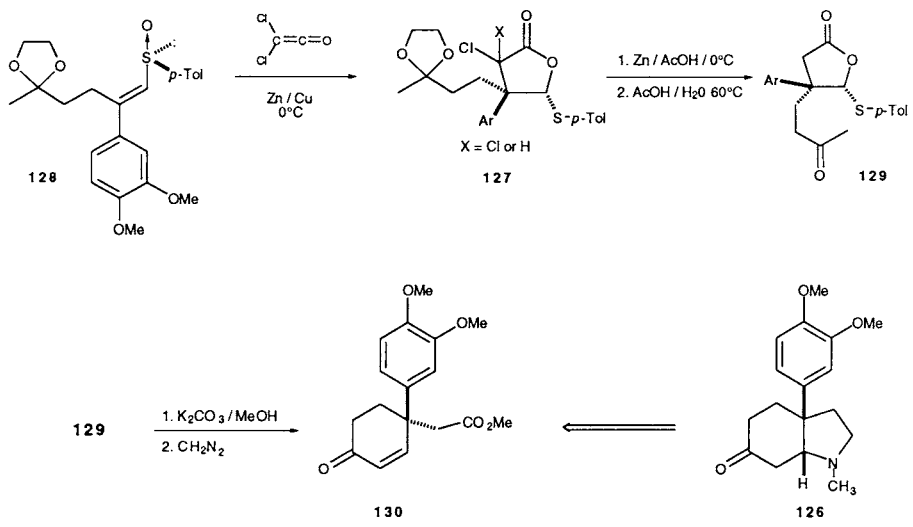


trityl group was then removed, the terminal olefin was oxidized to the primary alcohol, the lactone was hydrolyzed, and the 1,2-glycol functionality was cleaved to give the hydroxy-formyl-acid. This intermediate was trapped with propane dithiol and converted into the key dithiane-lactone **124**, which was condensed with tryptamine to give a mixture of amides. The major product, the acyclic amide **125**, was converted in 4 steps into (-)-eburnamonine (**122**). Two other eburnamine alkaloids were synthesized by modifications of this route.

(+)-Mesembrine (126)

Kosugi and co-workers described the formal synthesis of (+)-mesembrine **126** in which they apply a cycloaddition of dichloroketene with an enantiomerically pure vinyl sulfoxide to produce a β,β-disubstituted-γ-butyrolactone intermediate **127**.[44] Cycloaddition (additive Pummerer rearrangement) of the chiral sulfoxide **128** with dichloroketene furnished a mixture of dichloro- and monochloro-γ-butyrolactones **127** (Scheme 31), which was reductively dehalogenated and hydrolyzed to give the ketolactone **129**. Intramolecular condensation of the ketone enolate and concomitant desulfenylation yielded the enone carboxylate **130**. Mesembrine (**126**) was available from the lactone ester by a published procedure.[45]

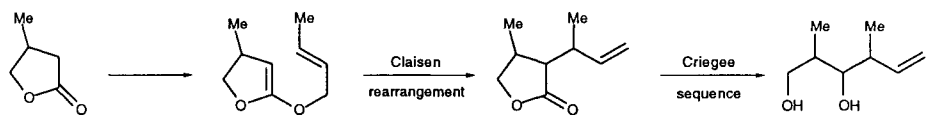
Scheme 31. Synthesis of Mesembrine (**126**)



Polypropionate Subunits from γ-Butyrolactones

In a series of papers by Ziegler and co-workers, γ-butyrolactones are extensively utilized in the syntheses of complicated natural products.[46] Ziegler translates the inherent stereogenicity of β-methyl-γ-butyrolactone[47] into polypropionate units of high enantiomeric purity, then utilizes these subunits for the syntheses of pheromones, the Prelog-Djerassi lactone, ionophores, and macrocyclic antibiotics. The stereochemically defined, disubstituted γ-butyrolactones are available by a diastereoselective Claisen rearrangement as illustrated in Scheme 32, and these structures can be converted into stereochemically diverse polypropionates by a high yielding Criegee sequence (Ziegler calls this a "formal Baeyer-Villiger"; the sequence entails the following transformations: conversion of the lactone into a hydroperoxy hemiketal, acetylation of the product mixture, thermal rearrangement to the hydroxy acetates, and saponification to the diol). The syntheses of the following natural products are included in this review to illustrate Ziegler's polypropionate methodology: ent-invictolide (**131**), (-)-calcimycin (**139**), and elaiophylin (**147**).

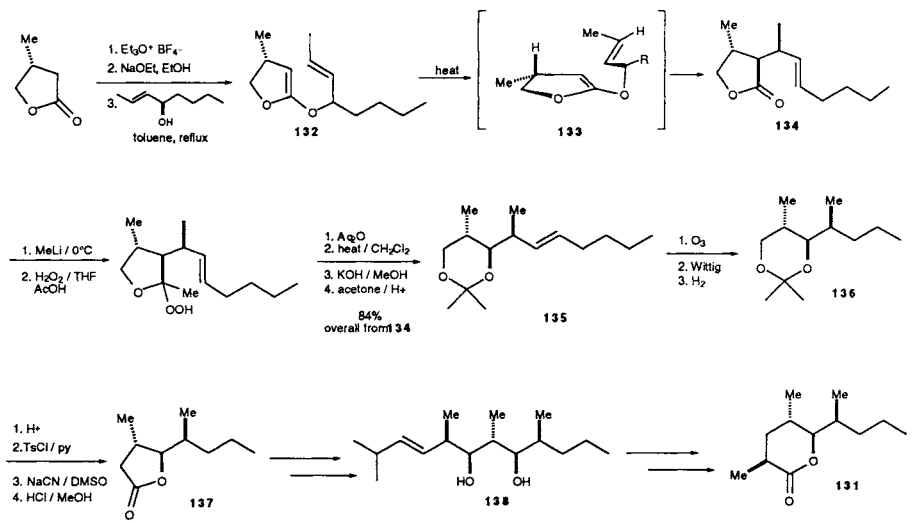
Scheme 32. γ-Butyrolactones as Polypropionate Precursors



ent-Invictolide (131)

ent-Invictolide (**131**), was synthesized by Ziegler's polypropionate route.[46c] The ketene-acetal **132** was prepared from (R)-β-methyl-γ-butyrolactone and (R)-(2E)-octen-4-ol. Claisen rearrangement of the ketene-acetal, via the indicated transition state **133,** produced the intermediate disubstituted γ-butyrolactone **134** (Scheme 33); the Criegee sequence and ketalization efficiently transformed the lactone into the acetonide **135** (84% yield). The olefinic side chain was manipulated (ozonolysis followed by a Wittig reaction of the aldehyde with ethyltriphenyl magnesium bromide, then hydrogenation of the double bond) to achieve the acetonide **136**. The acetonide was hydrolyzed and the primary alcohol was tosylated and displaced with cyanide; methanolysis of the cyanide and spontaneous cyclization gave the transposed γ-butyrolactone **137**. Further functionalization and a second Criegee sequence afforded the diol **138**. The diol was converted in four steps to *ent*-(+)-invictolide (**131**).

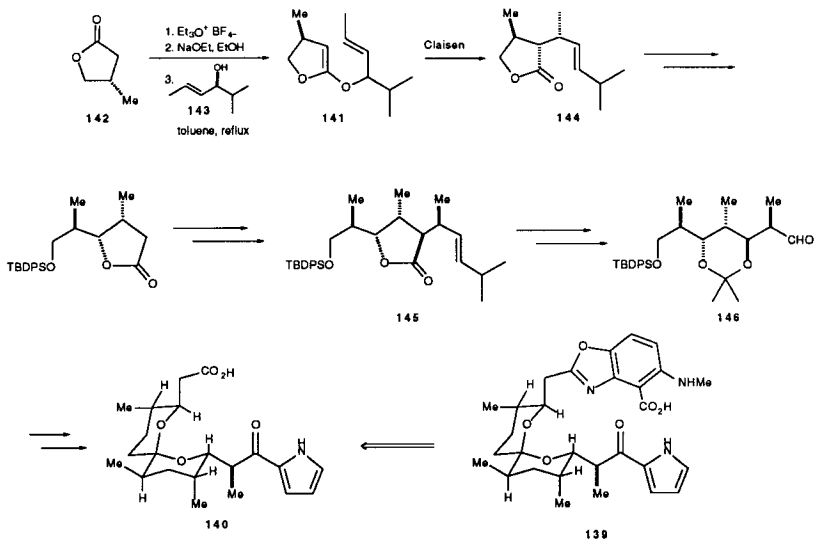
Scheme 33. Synthesis of *ent*-(+)-Invictolide (**131**)



(-)-Calcimycin (139)

Ziegler also achieved, with this polypropionate methodology, the formal total synthesis of the antibiotic (-)-calcimycin (**139**), an ionophore for intracellular calcium transport.[46d] Ziegler's approach produces the degradation product and synthetic intermediate **140**. Again, a diastereoselective Claisen rearrangement of a functionalized γ-butyrolactone was the key step in this synthesis (Scheme 34). The ketene-acetal **141**, available from the (S)-β-methyl-γ-butyrolactone **142** and the (S)-alcohol **143**, underwent Claisen rearrangement to afford the *trans*-γ-butyrolactone **144**. The Criegee sequence, ozonolysis, and lactonization, followed by a palladium-mediated alkylation, produced a mixture of trisubstituted lactones, one of which (the *trans, trans*-lactone **145**) was carried on in the synthesis. This intermediate lactone sports five contiguous stereogenic centers that were all descended from the original enantiomerically pure γ-butyrolactone **142**. The highly functionalized lactone **145** was converted in several steps to the acetonide **146**, which, in turn, through several subsequent transformations, was converted into the desired target **140**.

Scheme 34. Synthesis of (-)-Calcimycin (**139**)

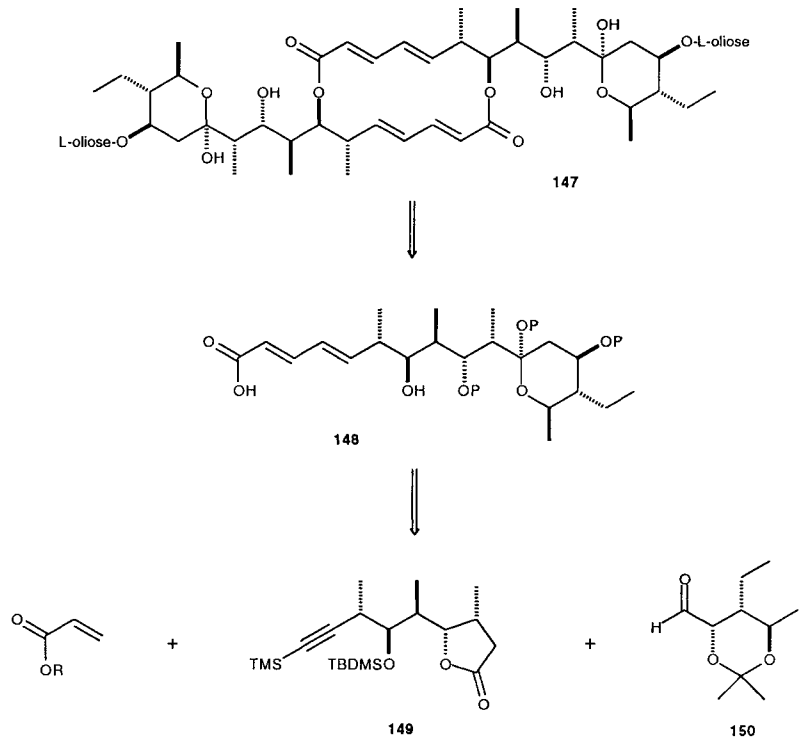


Studies on the Synthesis of Elaiophylin (147)

Most recently, Ziegler and Tung have incorporated two enantiomerically pure γ-butyrolactones in their studies of the synthesis of the macrodiolide, elaiophylin (**147**).[46e] The synthesis of this C_2-symmetric, 16-membered macrocycle was anticipated to proceed via the construction of the identical halves **148** prior to macrodiolide formation. This targeted intermediate could in turn be assembled from three components, two of which, **149** and **150**, were to be derived from γ-butyrolactones (Scheme 35). The acetonide **151** was obtained, in a sequence parallel (Claisen/Creigee/hydrolysis/diol protection) to that described above in the calcimycin synthesis, starting from (R)-β-methyl-γ-butyrolactone and (E)-2-methyl-3R-hydroxy-4-hexene. Selective functionalization of the termini of acetonide **151** produced the functionalized lactone **149**, which contained five contiguous stereogenic centers (Scheme 36).

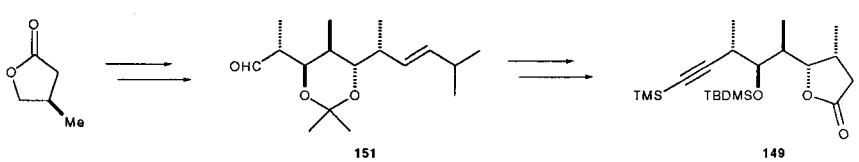
The other requisite fragment **150** for the elaiophylin synthesis, was also derived from γ-butyrolactone intermediates (Scheme 37). The butenolide **152** was selectively reduced (Red-Al/CuI) to give a 6 : 1 ratio of the *cis*- and *trans*-disubstituted-γ-butyrolactones **153**. The *cis*-lactone was recovered in 64% yield after purification, and the enolate of this lactone was methylated to give the *trans, cis*-γ-butyrolactone **154** in 90% yield as a single isomer. As Ziegler has described previously, the lactone

Scheme 35. Synthetic Components of Elaiophylin

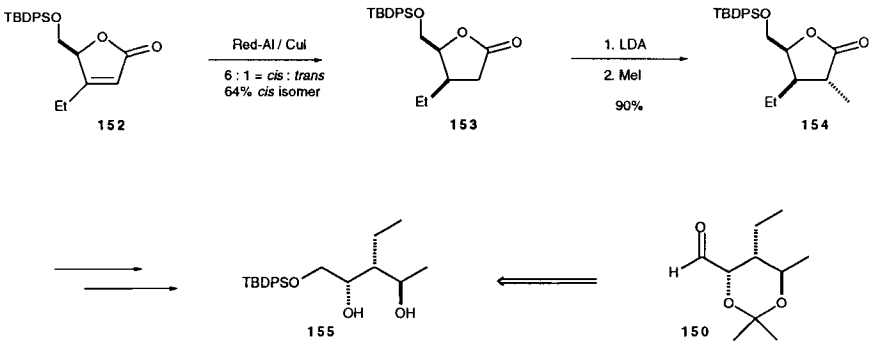


underwent the Criegee sequence to give the diol **155**, an obvious precursor of fragment **150**. The subsequent union of these fragments (**149** and **150**), or relatives of these fragments, has not yet led to a viable precursor of elaiophylin. After thorough exploration of reaction conditions, and significant manipulation of the coupling precursors **149** and **150**, a mixture of coupled-products was obtained, but the lack of selectivity precluded this sequence as a general approach to the macrodiolide.

Scheme 36. Preparation of the Key Component **149** for the Total Synthesis of Elaiophylin



Scheme 37. Preparation of the Key Component **150** for the Total Synthesis of Elaiophylin



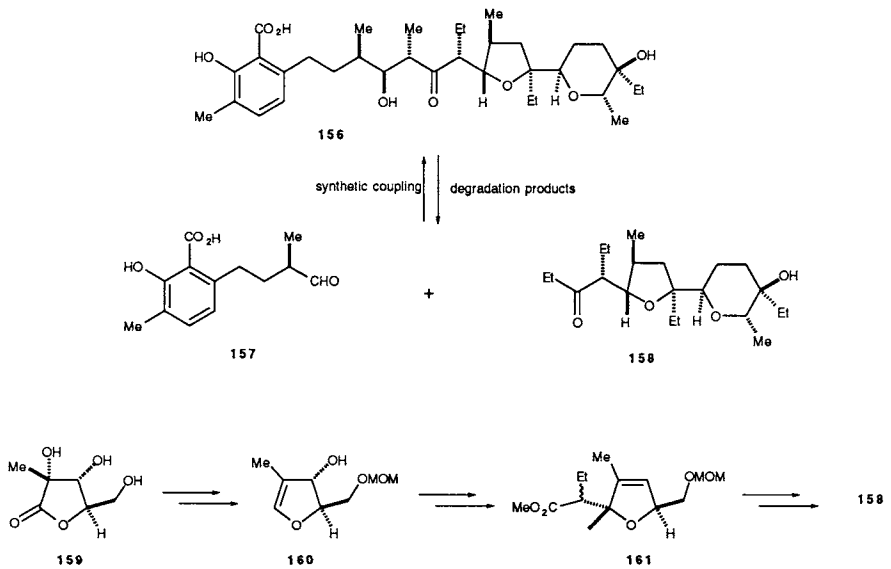
Lasalocid A (X537A, 156)

Ireland's total synthesis of lasalocid A (X537A, **156**) relies heavily on the construction of a key polyether subunit from an intermediate γ-butyrolactone.[48] The ionophore antibiotic **156** was degraded to and subsequently synthesized (through an aldol-type reaction) from the aldehyde **157** and the polyether **158** (Scheme 38). To achieve the polyether subunit **158**, the readily available, branched-chain carbohydrate triol precursor **159** was protected as the acetonide/ether, and the lactone carbonyl was reduced with DIBAL. Elimination of water and partial deprotection gave the hydroxydihydrofuran **160**. Esterification with butyryl chloride and ester enolate (TMS enol ether) Claisen rearrangement afforded the unsaturated esters **161**, with the generation of four new stereogenic centers. The stereoselectivity of the Claisen rearrangement was essentially controlled by the stereochemistry of the enol ether tether; this pivotal stereogenic center was derived from the γ-butyrolactone starting material (the β-hydroxy center). The furan **161** was further elaborated and coupled with a glycal derived from gulose to give the polyether ketone **158**.

(+)-Ionomycin (162)

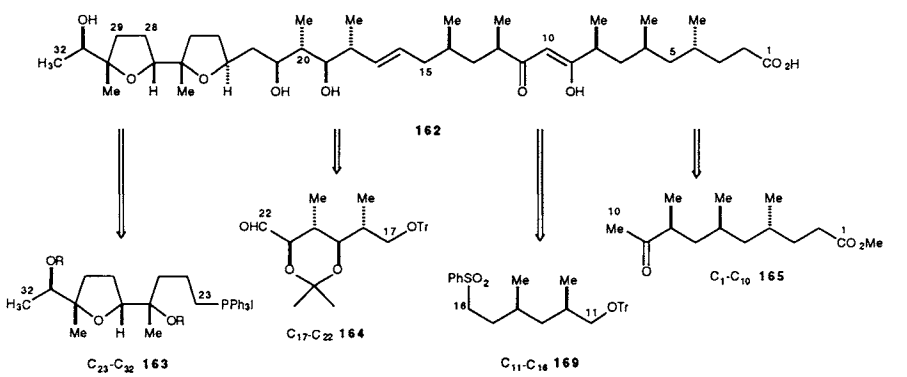
Hanessian has efficiently and repeatedly employed enantiomerically pure γ-butyrolactone templates and butenolides for natural products synthesis.[49] The so-called "chiron" approach can be illustrated with his groups' synthesis of (+)-ionomycin (**162**).[50] The 32-carbon chain of this polyether antibiotic was constructed from four subunits (**163, 164, 165, 169**, Scheme 39). The three segments which constitute C1-C22 were obtained from stereochemically-controlled elaboration of γ-butyrolactones derived from glutamic acid, while the C23-C32 fragment was available from an enantiomerically pure epoxide and geraniol.

Scheme 38. Synthesis of Lasalocid A (X537A, **156**)



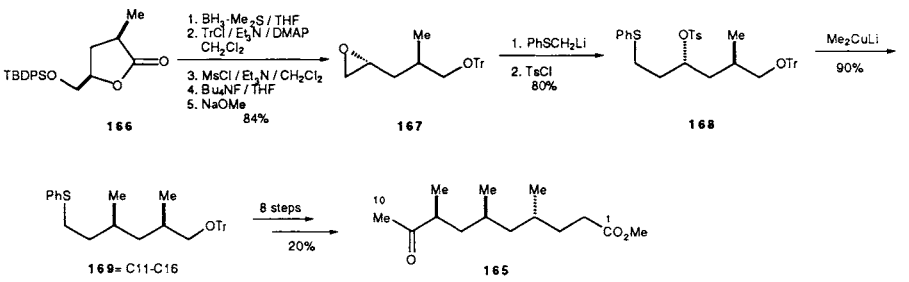
The C1-C10 fragment of ionomycin was constructed from the glutamate-derived *cis*-disubstituted γ-butyrolactone **166** (Scheme 40) The lactone was stereoselectively transformed into the trityloxy epoxide **167**. The epoxide was opened by treatment with (phenylthiomethyl)lithium to yield the corresponding alcohol which was tosylated to afford **168**. A sulfur-assisted displacement of the tosylate with lithium dimethylcuprate resulted in the formation of the *syn* 1,3-dimethyl intermediate

Scheme 39. Retrosynthetic Analysis of Ionomycin (**162**)



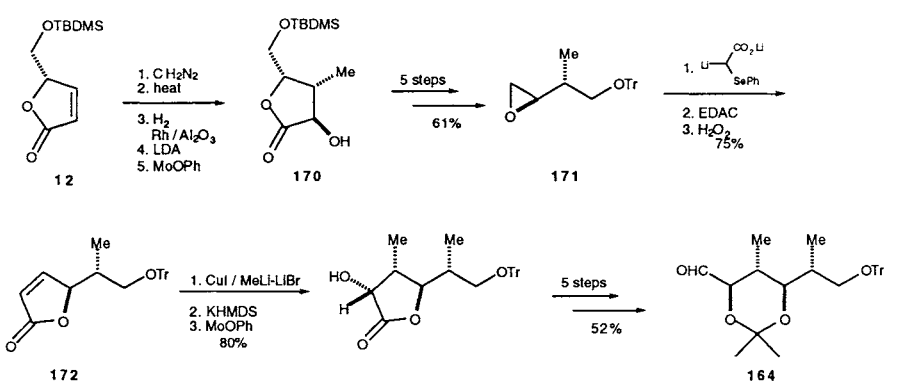
169, which was further elaborated into the 10-carbon fragment **165** in eight steps. The intermediate **169** also served as the C11-C16 fragment in the synthesis of ionomycin.

Scheme 40. Synthesis of C1-C10 Fragment of Ionomycin (**162**)



The C17-C22 fragment of ionomycin was constructed from the glutamate-derived butenolide **12** (Scheme 41). The butenolide was functionalized to the trisubstituted γ-butyrolactone **170**, then the lactone was converted into the trityloxy epoxide **171** in five steps. The conversion of the epoxide into the butenolide **172** illustrates the lactone "replication" strategy which Hanessian and co-workers designed for the synthesis of propionates and deoxypropionates.[51] The epoxide was opened with dilithio(phenylseleno)acetate followed by lactonization and selenoxide elimination to give the butenolide **172**. The butenolide was converted into the C17-C22 fragment **164** in eight steps. In a series of aldol and Julia couplings, the four subunits were successfully combined to afford (+)-ionomycin **162** .

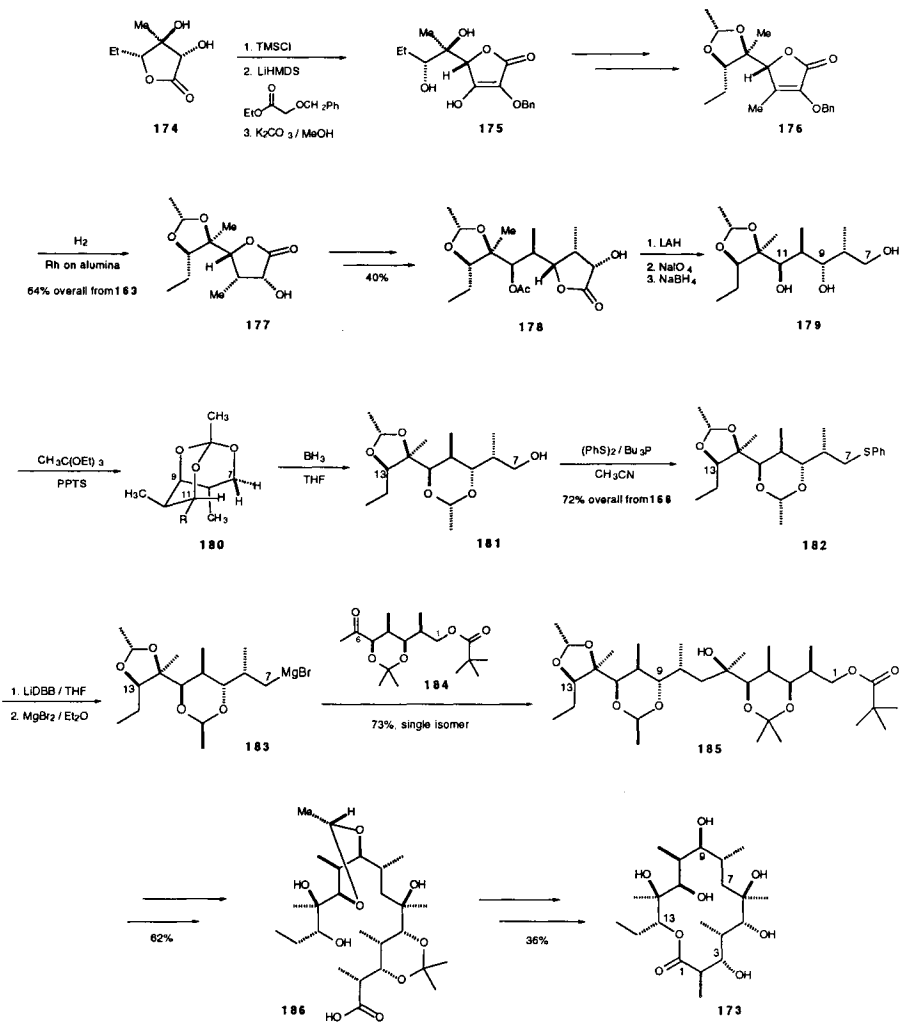
Scheme 41. Synthesis of C17-C22 Fragment of Ionomycin (**162**)



(9S)-Dihydroerythronolide A (173)

Stork and Rychnovsky have illustrated their butenolide template method for the construction of polypropionate units in the synthesis of (9S)-dihydroerythronolide A (Scheme 42, **173**).[52] The C7-C13 component of the erythronolide nucleus (containing 6 stereogenic centers) was constructed *via* two successive "hydroxybutenolide homologations". Illustrative of this iterative process, the dihydroxy γ-butyrolactone **174**, was protected *in situ* as the bis-TMS ether,

Scheme 42. Synthesis of (9S)-Dihydroerythronolide A (**173**)



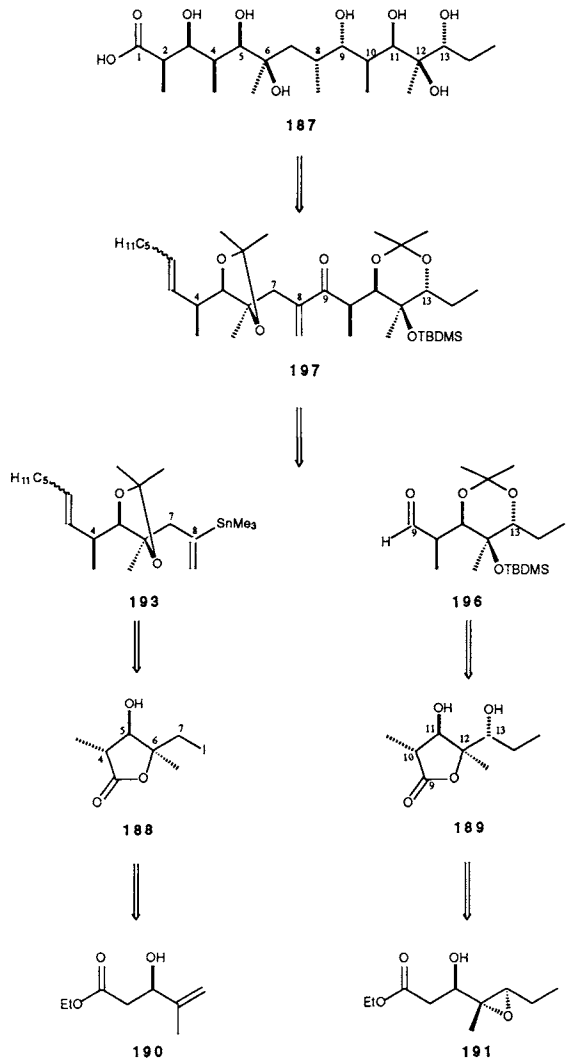
condensed with the lithium anion of ethyl(benzyloxy)acetate, and treated with basic methanol (K_2CO_3 / MeOH) to give the tetronic acid **175** (via an intermediate bicyclic hemiketal). The β-methyl group was introduced by phase-transfer phosphorylation of the ethylidene acetal of **175**, followed by nickel acetylacetonate catalyzed coupling with dimethylzinc, resulting in the formation of the butenolide **176**. Hydrogenation over rhodium of this butenolide produced the trisubstituted γ-butyrolactone **177**, and a second homologation (protection, butenolide elaboration, hydrogenation) yielded the highly functionalized γ-butyrolactone **178**. The acyclic triol **179** was easily obtained by LAH reduction, periodate cleavage of the diol, and $NaBH_4$ reduction of the resultant aldehyde. Stereospecific formation of the methyl acetal **181** was realized via reduction (diborane) of the cyclic orthoacetate **180** at the C7 oxygen-carbon bond. The primary alcohol was converted to the phenyl sulfide **182**, and, subsequently, to the corresponding grignard reagent **183**. The grignard reagent was coupled with ketone **184** to give the erythronolide precursor **185**. The coupling product was elaborated to the seco acid **186**, cyclized (64% yield) and deprotected (acid catalyzed, 56% yield) to give the desired macrocycle **173**.

(9S)-Dihydroerythronolide A Seco Acid (187)

A final example of the application of γ-butyrolactones to natural product synthesis is a concise construction of the seco acid of 9S-dihydroerythronolide A (**187**) from enantiomerically pure, highly functionalized γ-butyrolactones by our group at UC Irvine. Seven stereogenic centers of the seco acid were derived from two γ-butyrolactone building blocks (indicated in the retrosynthetic analysis, Scheme 43).[53] The functionalized lactones **188** and **189**, in turn, were derived from the enantiomerically pure β-hydroxy esters **190** and **191**, respectively, which were readily available using the kinetic resolution methodology of Sharpless et al. As shown in Scheme 44, the γ-butyrolactone **188** was prepared and then converted into the C3-C8 fragment of the seco acid. A kinetically controlled iodolactonization of the (+)-β-hydroxyester **190** afforded the chiral iodolactone **192**, and stereoselective introduction of the α-methyl group (effected by hydroxide-directed methylation of the lactone dianion) furnished the tetrasubstituted-γ-butyrolactone **188**. As was reported during the early stages of this synthetic effort,[28b] enolates of substituted butyrolactones are excellent substrates for stereoselective alkylation reactions. The enolates of secondary β-hydroxy butyrolactones react with electrophiles to give good yields of α-substituted butyrolactone products,[28] proceeding with >90% stereoselectivity favoring the *trans*-α-alkyl-β-hydroxy lactone isomer. Proceeding with the seco acid synthesis, protection of the hydroxyl group of **188** as the silyl ether (TBDMSiOTf, di-*tert*-butylpyridine, CH_2Cl_2, 93%) and purification by

chromatography gave the enantiomerically pure iodolactone; the lactone was converted into the coupling fragment, the vinyl stannane, **193** in five steps.

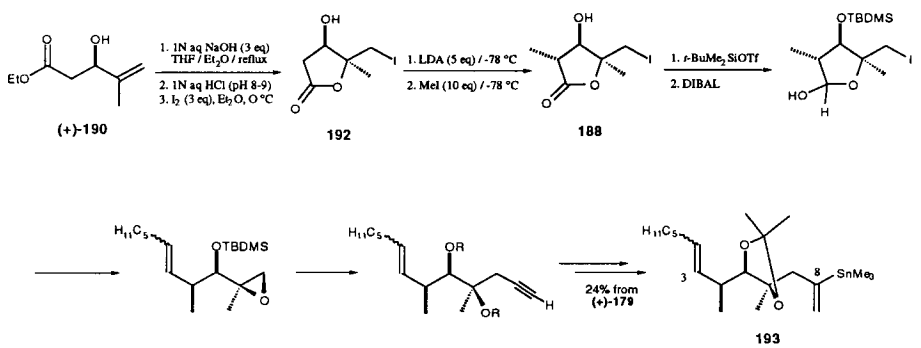
Scheme 43. Retrosynthetic Analysis of (9S)-Dihydroerythronolide A Seco Acid (**187**)



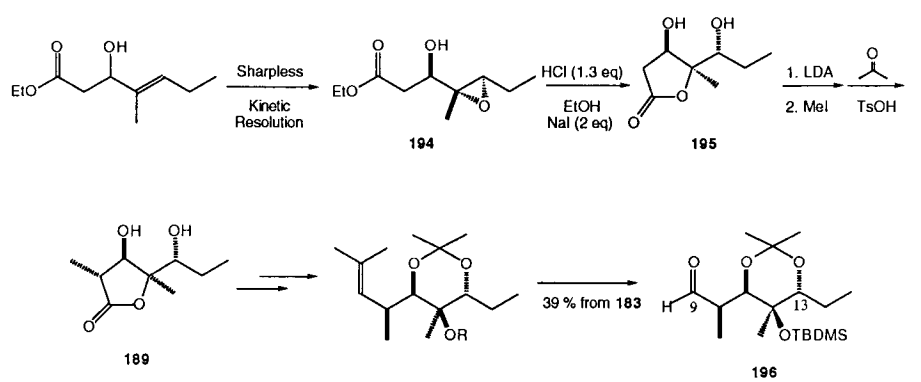
The C9-C15 fragment of the seco acid was prepared from a related intermediate, the tetrasubstituted γ-butyrolactone **189** (Scheme 45). The epoxy alcohol **194** was isolated from a kinetic resolution of ethyl 3-hydroxy-4-methyl-4-heptanoate and was

cyclized (dilute ethanolic HCl/NaI, 79%) to give the enantiomerically pure γ-butyrolactone **195**. Hydroxide-directed methylation of the lactone enolate then afforded the highly substituted lactone **189**, and acetonide formation provided the protected lactone. Purification by chromatography afforded a single diastereomer of the protected lactone, which possesses the four stereogenic centers present in the C9-C15 segment of the seco acid **187**. The coupling fragment aldehyde **196** was available from the intermediate lactone in four steps. The fragments **193** and **196** were successfully coupled by transmetalation of the vinylstannane and addition to the aldehyde to give the allylic alcohol which was oxidized to the enone **197**. A diastereoselective aldol condensation and successive stereoselective reductions established the remaining stereogenic centers on the seco acid to complete the enantioselective total synthesis of 9S-dihydroerythronolide A.

Scheme 44. Synthesis of the C3-C8 Fragment of Erythronolide A Seco Acid



Scheme 45. Synthesis of the C9-C15 Fragment of Erythronolide A Seco Acid



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3. In the text of this review, in accord with the historical name for a five-membered lactone (γ-butyrolactone), the positions of substituents on the carbon centers of the lactone ring are designated as α-, β-, and γ- starting with the carbon adjacent to the carbonyl functionality. Note that the designators α- and β- do not imply stereochemistry. Relative stereochemical designations of *trans-*, and *cis-* are used to relate substituents on the ring. Absolute stereochemical designators (R)- and (S)- are also used for specific stereogenic centers on the ring.
4. Examples of enantioselective syntheses of γ-butyrolactones which have not specifically been applied to natural products synthesis, include the following:
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49. For a review of the "chiron" approach and other examples, see: (a) Hanessian, S. *Aldrichimica Acta*, **1989**, *22*, 3; (b) Hanessian, S.; Roy, P. J.; Petrini, M.; Hodges, P. J.; Di Fabio, R.; Carganico, G. *J. Org. Chem.* **1990**, *55*, 5766.
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52. (a) Stork, G. and Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1564 and 1565; (b) Stork, G. and Rychnovsky, S. D. *Pure Appl. Chem.* **1987**, *59*, 345.
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Atta-ur-Rahman (Ed.) *Studies in Natural Products Chemistry, Vol. 16*

Fluoro-β-lactams: Synthesis and Application in Asymmetric Synthesis

John T. Welch and Robert Kawecki

Introduction

The incorporation of fluorine atom into organic molecules results in drastic changes of their properties. Especially, fluorinated natural products are of great interest due to their enhanced biological activity (1). Among them fluoro-β–lactams became recently new targets since they were proved to be effective β–lactamase and human leukocyte elastase inhibitors (2,3). Fluorinated penicillins and cephalosporins have been reviewed and their biological activity described (3). In this review we will focus on synthesis of the β–lactams with fluorine atom in the ring as well as transformations on fluoro-β–lactam molecules leading to another fluorinated materials. This approach, known as the "β–Lactam Method" (4), has been successfully used in the synthesis of aminoacids and sugars.

The fluorination of the β–lactam ring and construction of the β–lactam molecule from fluorinated building blocks represent two strategies used for the preparation of fluoroazetidinones. The fluorination procedure has been thoroughly review by Mascaretti (3). The most frequently used fluorination agents are diethylaminosulfur trifluoride (DAST), tetrabutylammonium dihydrogen trifluoride and pyridinium polyhydrogen fluoride (5). Despite the simplicity of this approach, the yields are often unsatisfactory.

Synthesis of β–lactam ring from fluorinated building blocks represents a second strategy for the construction of fluoro-β–lactams and will be covered by this review.

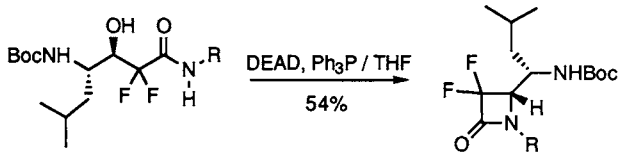
Synthesis

The preparative methods applied to the synthesis of β–lactams include cyclization of amides, ester enolate - imine condensations and [2+2] cycloadditions. The most frequently used starting materials for fluoro-β–lactam synthesis are α–fluoro substituted derivatives of carboxylic acids. They are commercially available (like mono and difluoroacetic acid derivatives) or are accessible by fluorination of α–hydroxy or α–aminoacids.

Cyclization of amides.

The cyclization of β–hydroxyamides was utilized by Thaisrivongs et al. in their synthesis of 3,3-difluoroazetidinones (6). The Reformatsky reaction of ethyl bromodifluoroacetate with optically active aldehyde derived from leucine gave single diastereoisomer of β–hydroxy ester in 60% yield (7) which was then converted to amide **1**. This material was subjected to the cyclization via a Mitsunobu reaction to give the desired difluoro-β–lactam **2** in 54% yield (Scheme 1).

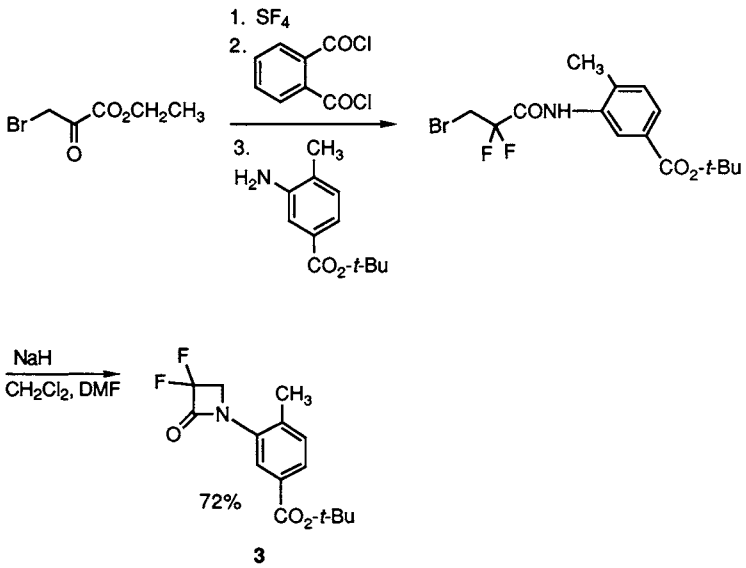
Scheme 1.



1 R = OBn (or 4-MeOPh) 2

A similar approach was used by Wakselman in the synthesis of 3,3-difluoro-β–lactams (8). The cyclization of α,α'-difluoro-β–bromopropioamides using Wasserman procedure (NaH, DMF) gave β–lactam **3** in good yield (Scheme 2).

Scheme 2.

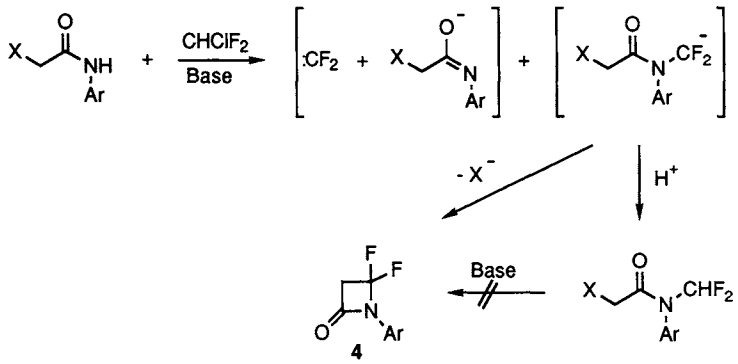


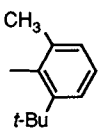
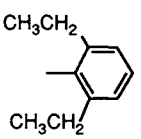
3

This procedure was also used for the preparation of the 3-bromo-3-fluoro-β–lactam derivative. Both products were inhibitors of the β–lactamase TEM-1 (8).

The reaction of α–haloacetamides with chlorodifluoromethane (Freon 22) under basic conditions gave derivatives of 4,4-difluoro-2-azetidinones **4** (Scheme 3) in low yield (9). The attack of difluorocarbene on the acetamide anion resulted in formation of N-difluoromethyl anion which subsequently cyclized to form the β–lactam **4** or after protonation gave the tertiary acetamide. The authors proved that the latter compound was not a precursor of **4**.

Scheme 3.

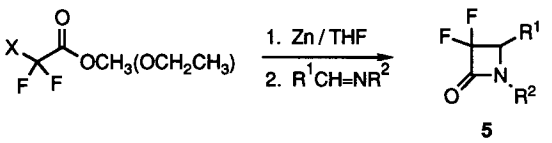


X	Ar	Base	Yield % **4**
I		50% NaOH	12
Cl		NaH	19

Ester enolate - imine condensation.

The Reformatsky reaction was used as a key step by Kobayashi in the synthesis of difluoroazetidinones (10). The zinc reagent prepared from iodo- or bromodifluoroacetates was allowed to react with a variety of imines to give 3,3-difluoro-β–lactam derivatives **5** in good yields (Scheme 4 and Table 1).

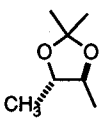
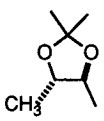
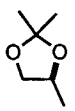
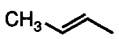
Scheme 4.



5

X = I or Br

Table 1.

Entry	R^1	R^2	Yield %	Diastereomer ratio
1		Bn	71[a]	4.3 : 1
2		Bn	67[b]	4.7 : 1
3		Bn	65[a]	3.1 : 1
4	Ph	Ph	87[b]	-
5			66[a]	-
6	Ph		79[b]	-
7		Bn	35[b]	-

a) Difluoroiodoacetate was used in this reaction
b) Bromodifluoroacetate was used in this reaction

The *syn*-stereoselectivity, established on the basis of X-ray analysis of the major product, was rather poor.

Similarly, lithium enolates of 2,4,6-trimethylphenyl fluoroacetates reacted with imines (11). Under a variety of conditions the 3-fluoro substituted β–lactams **6** and **7** were obtained in good yields but nonstereoselectively (Scheme 5 and Table 2). The addition of N,N'-dimethylpropyleneurea (DMPU) increased the yield but the stereoselectivity was diminshed.

Scheme 5

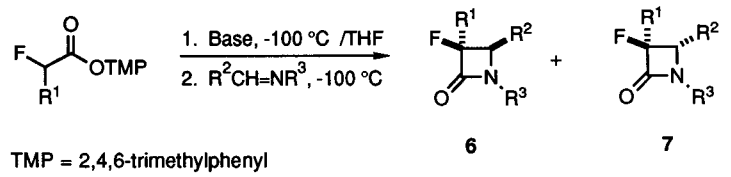


Table 2. Synthesis of 3-fluoro-β–lactams via enolate-imine condensation.

Entry	R^1	R^2	R^3	Base / Additive	Ratio **6** : **7**	Yield, %
1	Me	Ph	PMP[a]	LDA	1 : 0.9	32
2	Me	Ph	PMP	LHMDS	1 : 3.5	68
3	Et	Ph	PMP	LDA	1 : 3.0	12
4	Et	Ph	PMP	LDA / DMPU[b]	1 : 0.8	35
5	Ph	Ph	PMP	LDA	1 : 2.5	26
6	Ph	CO_2Et	PMP	LDA	1 : 3.6	48
7	Me	CO_2Et	PMP	LDA / DMPU	1 : 0.9	34
8	Me	Ph	Ph	LDA	1 : 2.1	59
9	Me	Ph	Ph	LDA / DMPU	1 : 1.8	93
10	Et	Ph	Ph	LDA	1 : 1.0	20
11	Et	Ph	Ph	LDA / DMPU	1 : 0.3	80
12	Ph	Ph	Ph	LDA	1 : 0.4	70

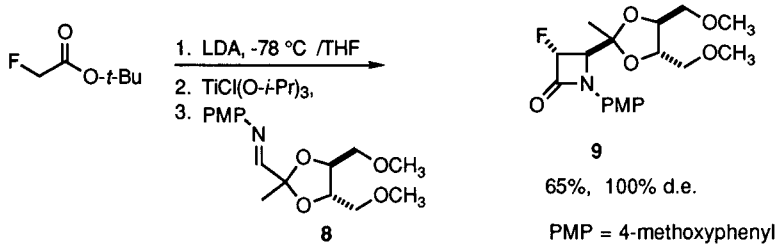
a) *Para*-methoxyphenyl

b) N,N'-Dimethylpropyleneurea (1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone).

Lithium enolates of monofluorocarboxylic acid esters have shown low stereoselectivity not only in ester enolate-imine condensation but also in alkylation and aldol reactions (12), presumably as a result of a lack of control of enolate geometry.

Titanium enolates behave in a completely different manner (13). Optically active imine **8** reacted very selectively with large excess (6-10 equivalents) of the triisopropoxytitanium enolate of *t*-butyl fluoroacetate to give solely the 3*R*,4*R* diastereoisomer of *trans*-3-fluoro-β–lactam **9** (Scheme 6).

Scheme 6.

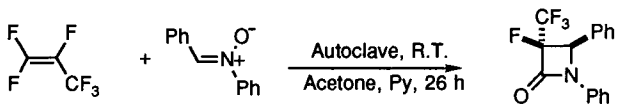


The authors assumed that this extraordinary selectivity is due to the moderate Lewis acidity of the intermediary titanium amide.

[2+2] Cycloaddition.

3-Fluoro-3-trifluoromethylazetidinone derivative **10** (Scheme 7) has been obtained by cycloaddition of hexafluoropropene to C,N-diphenylnitrone (14).

Scheme 7.

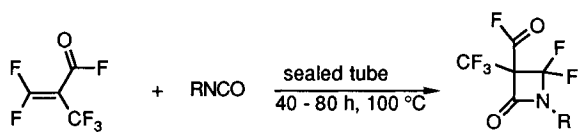


10

The yield of this reaction is rather low and is highly dependent upon the reaction time and the solvent used. The addition of a weak base like pyridine improves the yield up to 22%. The stereochemistry of the product has not been discussed by authors. However, from spectroscopic data, it seems to be obvious that resulting azetidinone has a *cis* configuration in the ring (proton at C-4 shows 3.4 Hz coupling constant to fluorine).

Cycloaddition of perfluoromethacryloyl fluoride to isocyanates (15) resulted in formation of 4,4-difluoro substituted derivatives of β–lactams **11** (Scheme 8). However, considerable amounts of [4+2] cycloadducts have been found in reaction mixture. The starting material was obtained from hexafluoroisobutyric acid in two steps (16).

Scheme 8.

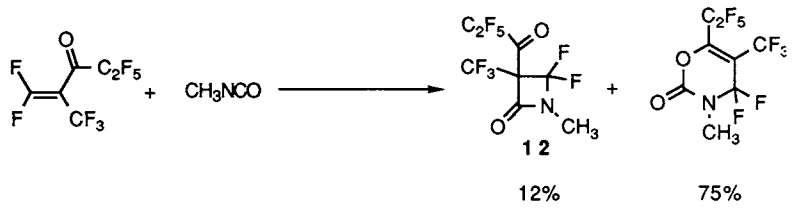


11

R	Yield, %
Me	46
n-Bu	39
	41
	37

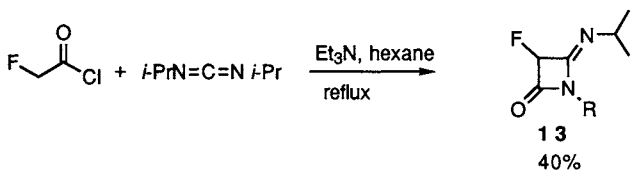
Similarly, 4,4-difluoro-β–lactam **12** (Scheme 9) was formed by cycloaddition of methyl isocyanate to the perfluoro analog of 2-methyl-1-penten-3-one (17). The latter compound was synthesized from hexafluoropropene in three steps (17). As previously, the [4+2] cycloaddition product predominated in the reaction mixture.

Scheme 9.



In 1968 Brady reported (18) reaction of fluoroacetyl chloride with diisopropylcarbodiimide in the presence of triethylamine led to formation of 3-fluoro-1-isopropyl-4-isopropylimino-2-azetidinone **13** (Scheme 10).

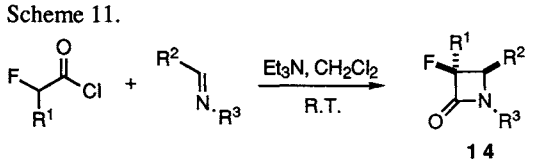
Scheme 10.



The authors postulated the involvement of fluoroketene in this reaction. However, the [2+2] cycloaddition to cyclopentadiene is the only evidence for presence of the fluoroketene (*vide infra*).

The fluoroketene-imine condensation was found to be a highly stereoselective process (11). A number of 3-fluoro-β–lactams have been synthesized with *cis* stereochemistry in the ring (Scheme 11 and Table 3).

Scheme 11.



The very high stereoselectivity of such reaction showed especially in the case of condensation with optically active imine **15** derived from (*R*)-glyceraldehyde acetonide (19). A single diastereoisomer of 3-fluoro-2-azetidinone **16** was formed in fair yield and d.e. not less than 99% (Scheme 12).

Scheme 12.

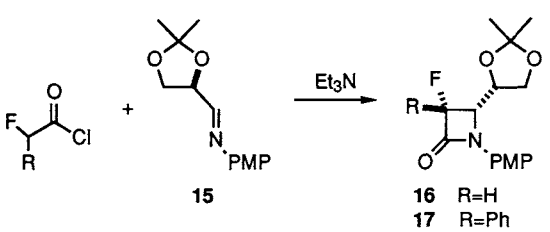


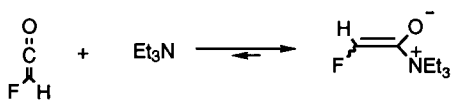
Table 3. Formation of 3-fluoro-β–lactams via ketene-imine condensation.

Entry	R^1	R^2	R^3	Yield, %
1	Ph	Ph	PMP[a]	16
2	Ph	CO_2Et	PMP	48
3	Ph	Ph	Ph	51
4	Ph	Ph	Et	40
5	Ph	Ph	Me	10
6	Ph	Ph	(*S*)-CH(Me)Ph	10
7	H	Ph	Me	33
8	H	Ph	Ph	70
9	H	Ph	PMP	70
10	H	PhCH=CH	PMP	15
11	Ph	PhCH=CH	PMP	25
12	H	CO_2Et	PMP	66[b]

a) PMP = 4-methoxyphenyl b) 19 : 1 *cis/trans* ratio was found.

The presence of fluoroketene in above mentioned reaction is not obvious. The attempts to detect free fluoroketene failed (19, 20). Low temperature ^{19}F NMR studies of a mixture of fluoroacetyl chloride and triethylamine indicated formation of a zwitterionic intermediate **19** (Scheme 13). This species may exist in equilibrium with free fluoroketene whose concentration is too low to be observable. *Ab initio* calculations on the fluoroketene molecule indicate its high reactivity is due to the destabilizing effect of fluorine (21).

Scheme 13.

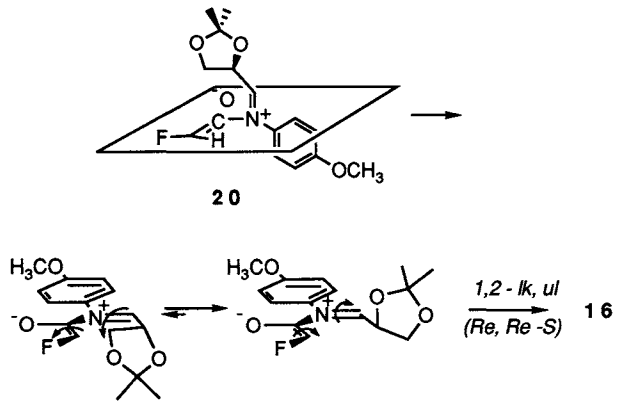


18 **19**

The outstanding stereoselectivity in the reaction of fluoroketene with imine can be explained by stereoelectronic effects. The steric control, true in the case of ketenes even with substituents like azido or methoxy but especially with bulky substitutents like phtalimido or phenoxy, is not likely for fluoroketene cycloaddition.

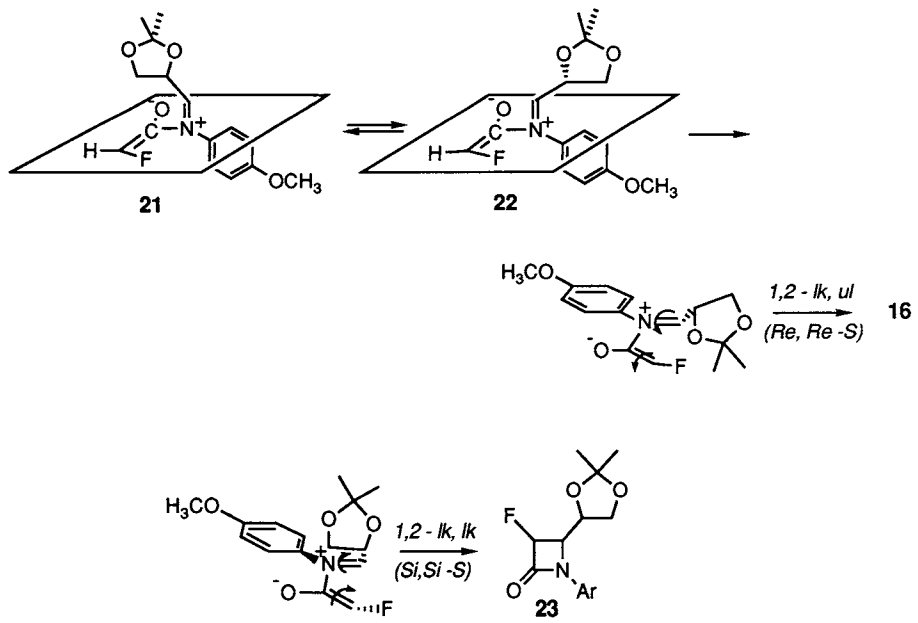
The anti addition of the imine **15** to a single face of fluoroketene **18** results in formation of zwitterionic intermediate **20** (Scheme 14).

Scheme 14.



This adduct is postulated to collapse via conrotatory ring closure with 1,2-*lk,ul* topicity, i.e. antiperiplanar to the adjacent carbon oxygen bond. The cycloaddition process with 1,2-*lk,ul* topicity is possible from the product of initial attack by the imine **15** syn to fluorine. However, in this case, the unlikely reaction of *Z*-imine or rapid isomerization of the C-N double bond in zwitterionic species **21** to form the reactive intermediate **22** would be required (Scheme 15). The latter may be stabilized by intramolecular hydrogen bonding.

Scheme 15.

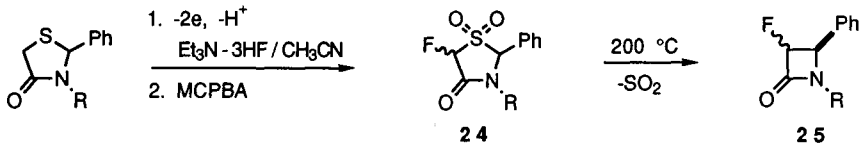


The conrotatory ring closure step can proceed from either of two equally likely conformations and both diastereoisomers **16** and **23** should be formed. The absence of **23** in reaction mixture suggests that each step of this process proceeds with excellent stereochemical control.

Other syntheses.

Fuchigami prepared 3-fluoro-2-azetidinones by thermolysis of 3-fluoro-4-thiazolidinone S,S-dioxides (22). The starting material was prepared by selective anodic fluorination of 4-thiazolidinones and subsequent oxidation to sulfone (Scheme 16).

Scheme 16.



R	Yield %	Ratio cis / trans
Me	42	36 : 65
i-Pr	59	45 : 55
Bn	65	46 : 54

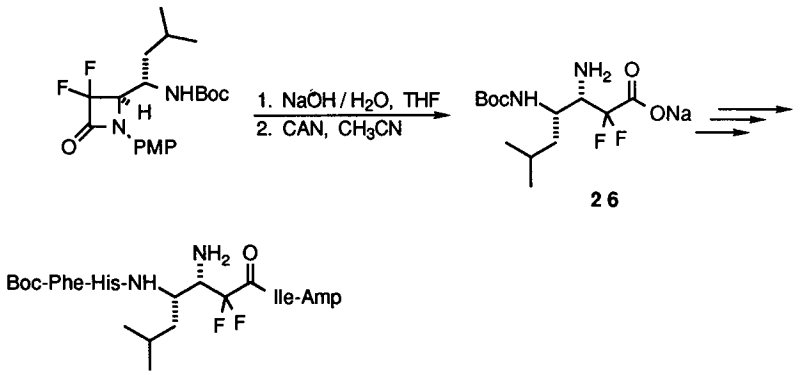
R	Yield %	Ratio cis / trans
Me	86	:100
i-Pr	80	39 : 61
Bn	84	19 : 81

Thermolysis of **24** at 200 °C with extrusion of SO_2 gave predominately the *trans* diastereoisomer of the 3-fluoro-β–lactams **25** in good yield.

Application of the Fluoro-β-lactams in Asymmetric Synthesis.

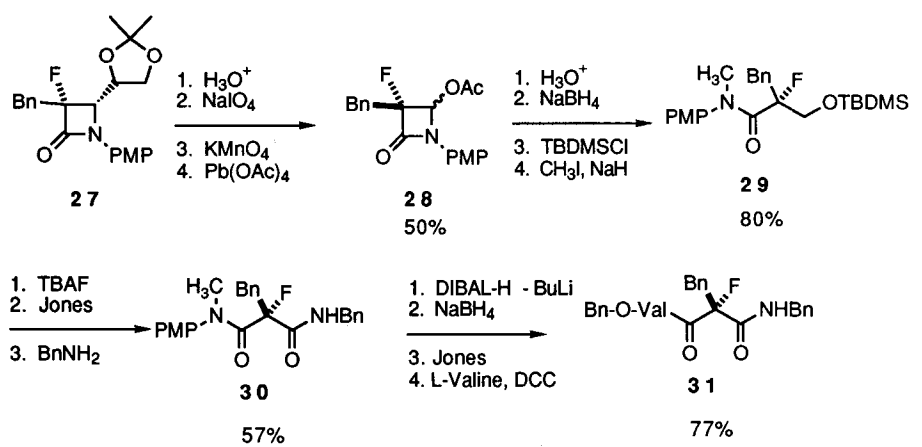
Fluoro-β–lactams serve as versatile starting materials in asymmetric synthesis. Hydrolysis of the lactam moiety leads straightforward to β–aminoacids. In this way the difluoro substituted derivative of β–aminodeoxystatine was prepared (6). Hydrolysis of the β–lactam under basic conditions and deprotection of nitrogen atom gives an analog of statine **26** that was coupled to other aminoacids (Scheme 17). Such peptide was tested as human plasma Renin inhibitor.

Scheme 17.



Optically active α–benzyl-α–fluoromalonic acid derivatives have been synthesized using fluoro-β–lactams **27** as chiral building blocks (23). Straightforward transformations (Scheme 18) led to diamide **30** which can be chemoselectively reduced to the monoamide using diisobutylaluminumhydride - *n*-butyllithium complex. The stereochemistry at α–carbon can be easily altered by change in the protection sequence, dependent upon selective conversion of the primary or secondary amide. Oxidation to an acid and coupling with *L*-valine gave retropeptide **31** that serves as potential protease inhibitor.

Scheme 18.



Functionalization of 3-fluoro-β–lactam was performed by alkylation at C-3 position (19). Optically pure β–lactam **16** as well as racemic **32** was deprotonated with LDA at -90 °C and alkylated to give exclusively *cis* substituted products (Scheme 19 and Table 4).

Scheme 19.

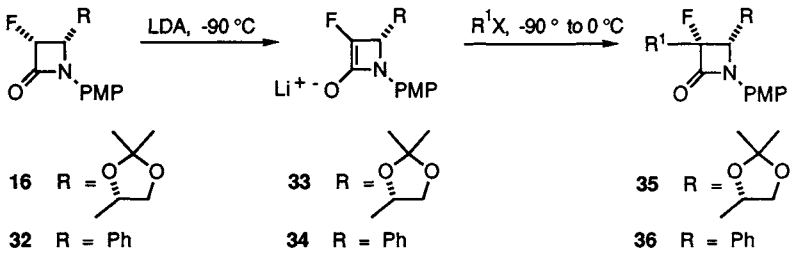


Table 4.

Entry	β–Lactam	Alkylating agent R^1X	Yield, %
1	**16**	MeI	99
2	**32**	MeI	45
3	**16**	EtI	78
4	**16**	$EtSO_3CF_3$	46
5	**32**	EtI	47
6	**16**	BnBr	57
7	**32**	BnBr	13
8	**16**	BuI	56
9	**16**	*i*-PrI	13
10	**16**	CH_2=$CHCH_2Br$	80
11	**16**	CH≡CCH_2Br	44
12	**16**	$BnOCH_2Cl$	49
13	**16**	$MeOCH_2CH_2OCH_2Cl$	38

The very high stereoselectivity of this alkylation is the result of the steric effects. The large substituent at C-4 directs electrophilic attack from the opposite face of the ring. Only with nonsterically demanding electrophiles such as D_2O or H_2O was the *cis-trans* ratio attenuated and then only to 5:1.

The 3-hydroxyalkyl side chain was introduced into 3-fluoro-β–lactam molecule by aldol reaction (19). The β–lactam enolates **33** and **34** reacted with aldehydes and ketones at -95 °C to give *cis* diastereoisomers exclusively (Scheme 20, Table 5 and 6). The stereoselectivity in the side chain was poor even with the exchange of the lithium counterion for titanium, magnesium or zinc.

Scheme 20.

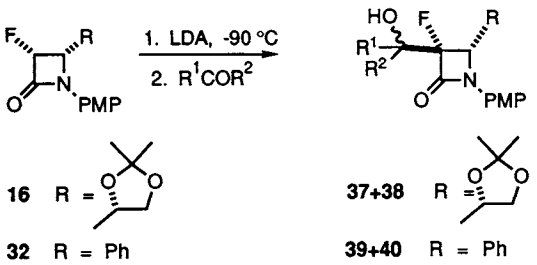


Table 5. Aldol reactions of 3-fluoro-β-lactam **16**.

Entry	R^1	R^2	Additive	Diastereo-isomer ratio **37 : 38**	Yield %
1	Me	H		1 : 1.2	64
2	Et	H		1 : 1.4	44
3	*i*-Pr	H	-	1 : 1.4	33
4	*i*-Pr	H	$TiCl_4$	1 : 1.3	30
5	*i*-Pr	H	$MgBr_2$	1 : 1.3	35
6	*i*-Pr	H	$ZnCl_2$	1 : 1.5	28
7	Ph	H	-	1 : 1.5	45
8	*t*-Bu	H	-	1 : 1.2	47
9	Me	Me	-	-	85
10	Ph	Me	-	1 : 3.7	44
11	$BuCH_2$	Me	-	1 : 1.8	51

Table 6. Aldol reaction of 3-fluoro-β-lactam **32**.

Entry	R^1	R^2	Diastereoisomer ratio **39 : 40**	Yield, %
1	Me	H	1 : 1.3	52
2	Et	H	1 : 2.0	67
3	Bu	H	1 : 1.3	61
4	*i*-Pr	H	1 : 1.1	70
5	Et_2CH	H	1 : 1.2	63
6	*t*-Bu	H	1 : 1.0	76
7	Ph	H	1 : 1.1	52
8	Me	Me	-	33
9	Et	Me	1 : 1.6	51
10	*t*-Bu	Me	1 : 57.0	73
11	$-(CH_2)_4-$		-	69

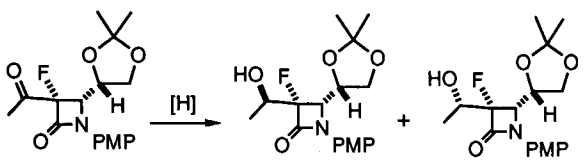
The relative stereochemistry in the fluoro-β-lactam ring can be easily determined from NMR spectra. The vicinal coupling constant of fluorine to hydrogen at C-4 in *cis* substituted compounds is

small (3-5 Hz) comparing to *trans* derivative (12 Hz). The absolute stereochemistry of compounds **16**, **17**, and 3-benzyl derivative of **35** was confirmed by X-ray analysis (19).

The alkylation and aldol reaction of α–fluoro carbonyl compounds are often troublesome (requiring very low temperatures), inefficient and nonstereoselective (12, 24). In the case of fluoro-β–lactams, the lactam enolate is stable up to -35 °C. Low temperatures ^{19}F NMR studies of **33** indicated formation of two species, possibly a dimer and tetramer, with chemical shifts δ -164 and δ -172 ppm.

The stereoselective reduction of 3-acetyl substituted β–lactams is usual route to obtain, pharmaceutically interesting, 3-hydroxyethyl derivatives (thienamycin analogs). Among many

Scheme 21.



41 (1'*R*)-**42** (1'*S*)-**42**

Table 7. Stereoselective reduction of 3-acetyl-3-fluoro-β-lactam **41**.

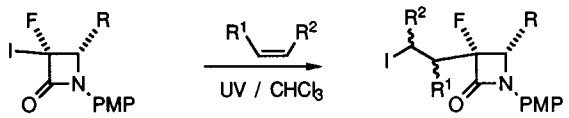
Entry	Reducing agent	Solvent	Additive	Temp. °C	Diast. ratio[a] 1'*R*:1'*S*	Yield %
1	KBH(s-Bu)$_3$	THF	-	-78	4.0 : 1	41
2	KBH(s-Bu)$_3$	Et_2O	KI	25	1.7 : 1	31
3	LiBH(s-Bu)$_3$	THF	-	-78	8.7 : 1	47
4	LiBH(s-Bu)$_3$	THF	-	-95	12.0 : 1	29
5	*i*-Pr_2NEtBH$_3$	Et_2O	$Mg(CF_3CO_2)_2$	0	1 : 1.1	84
6	*i*-Pr_2NEtBH$_3$	THF	$ZnCl_2$	0	1.6 : 1	98
7	*i*-Pr2NEtBH$_3$	THF	LiBr	0	2.9 : 1	85
8	LiBH(OEt)$_3$	THF	-	-78	6.0 : 1	85
9	LiBH(O-*s*-Bu)$_3$	THF	-	-78	6.5 : 1	77
10	LiAlH(O-*t*-Bu)$_3$	THF/Et_2O	-	-78	17.2 : 1	98
11	$PhMe_2SiH$	CH_2Cl_2	$EtAlCl_2$	25	1 : 2.5	37

a The absolute stereochemistry of the major isomer was established from X-ray analysis.

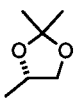
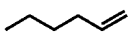
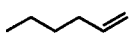
reducing agents (Scheme 21 and Table 7), lithium tri-*tert*-butoxyaluminohydride was found to be an efficient and stereoselective reagent for conversion of **41** to (*1'R*)-3-(1'-hydroxyethyl) derivative. Surprisingly, K-Selectride, the reducing agent of choice for reduction of many acetylazetidinones, was ineffective in the case of fluoro-β–lactam **41**. Interestingly the sense of stereoselectivity observed using K or L-Selectride was the same, in contrast to the variation in stereochemistry reported in the hydrocarbon series.

Radical additions to double bonds are an alternative approach to the functionalization of the fluoro-β–lactams at C-3 carbon atom. Ultraviolet light irradiation of the 3-iodo derivatives of lactam **43** in the presence of variety of olefins resulted in an iodine atom *trans*fer reaction (25). Free radical initiators like hexabutylditin were not required. The adducts were obtained in good yield with the

Scheme 22.

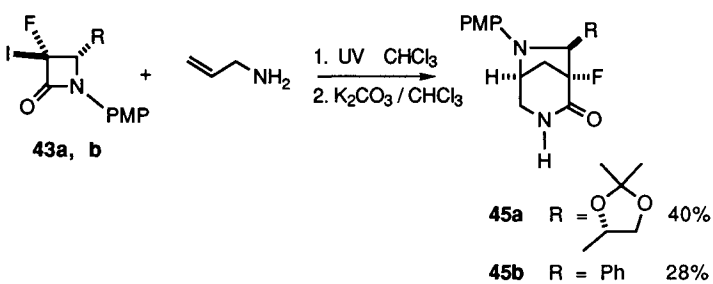


44

	R	olefin	Yield, %
43a			67
			67
			74
43b	Ph		71
43c			25

usual *cis* configuration in the ring (Scheme 22) again possibly due to the steric influence of the substituent at C-4. In the reaction with allylamine, the adduct formed in the iodine atom transfer reaction underwent an intramolecular cyclization to give bicyclic compounds **45** (Scheme 23).

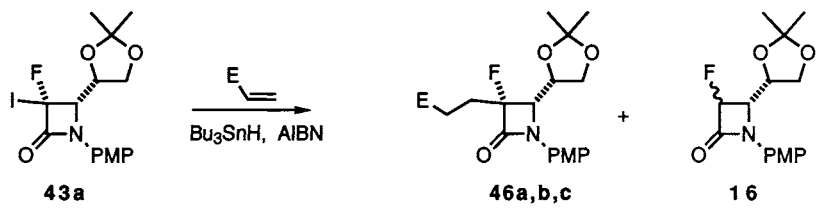
Scheme 23.



43a, b

Tributyltin hydride mediated addition to α,β–unsaturated carbonyl compounds was also used to prepare 3-substituted derivatives (Scheme 24). However, formation of the reduced β–lactam **16**

Scheme 24.



43a **46a,b,c** **16**

Table 8.

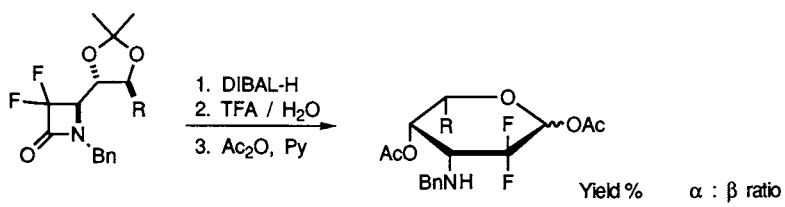
Entry	Olefin	Method[a]	Product	Yield, %	Ratio **46** : **16**
1	CH_2=CH-CN	A	**46a**	16	1 : 5.2
2	CH_2=CH-CN	B	**46a**	48	1 : 0.8
3	CH_2=CH-C(O)Me	A	**46b**	22	1 : 3.5
4	CH_2=CH-C(O)Me	B	**46b**	22	1 : 0.4
5	CH_2=CH-C(O)OMe	A	**46c**	37	1 : 1.7
6	CH_2=CH-C(O)OMe	B	**46c**	41	1 : 0.6

a) Method A: Bu_3SnH (2 eq.), AIBN (cat.), C_6H_6, reflux 6-8 h; Method B: Bu_3SnH (2 eq.) - added via syringe pump, AIBN (cat.) ,C_6H_6, reflux 6-8 h.

dominated in the reaction path. The slow addition of tributyltin hydride solution via syringe pump, improved the formation of desired adduct but the yield was generally not satisfactory. This suggests that the absolute rate constant of the abstraction of the hydrogen from the hydride by α–fluororadical must be much higher than in the case of alkyl radicals.

Fluorinated sugars have attracted significant interest since they often are useful as antiviral agents and are excellent models for probing biochemical pathways of sugar metabolism. Fluoro-β–lactams seem to be very convenient building blocks for construction such molecules. Kobayashi et al. (10) used 3,3-difluoro-β–lactam **47a** and **47b** to synthesize anomers of 2,3-dideoxy-2,2-difluoro-3-aminosugars **48a** and **48b** (Scheme 25).

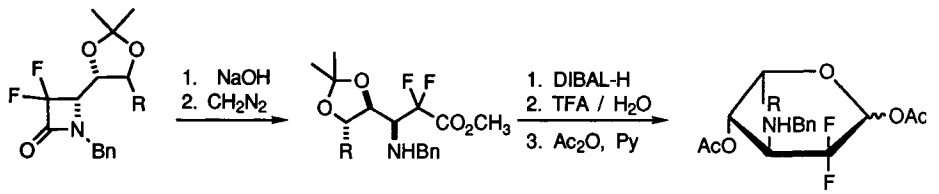
Scheme 25.



		Yield %	α : β ratio
47a R = H	**48a** R = H	45	3.0 : 1
47b R = Me	**48b** R = Me	57	3.4 : 1

Reduction of the β–lactam moiety with diisobutylaluminum hydride and deprotection of the ketol with trifluoroacetic acid gave after acetylation α– and β–1,4-O-diacetyl-N-benzyldaunosamine **48b** in 57 % yield and in a 3.4 : 1 anomeric ratio. Similarly, β–lactams **49a** and **49b** have been converted to 2,3-dideoxy-2,2-difluoro-3-aminosugars derivatives **50a** and **50b** (Scheme 26).

Scheme 26.

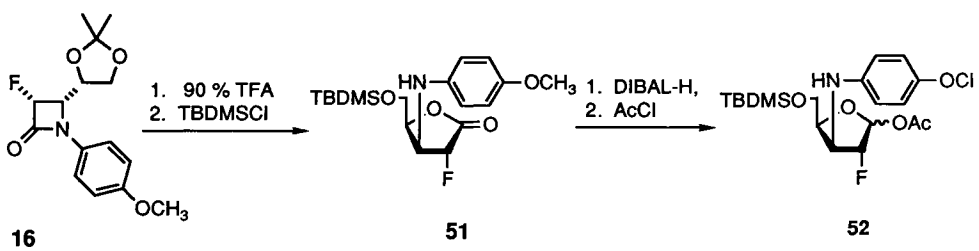


49a R = H
49b R = Me

	Yield %	α : β ratio
50a R = H	45	1.0 : 1
50b R = Me	66	2.3 : 1

3-Amino-2,3-dideoxy-2-fluoro-D-xylofuranose **52** has been prepared from 3-fluoro-β–lactam **16** (26). Deprotection of the ketal moiety and hydrolysis of the β–lactam gave lactone **51**, which was easily reduced to the lactol with diisobutylaluminum hydride. After acetylation the resultant aminosugar was obtained as a 1:3 mixture of α and β anomers respectively (Scheme 27).

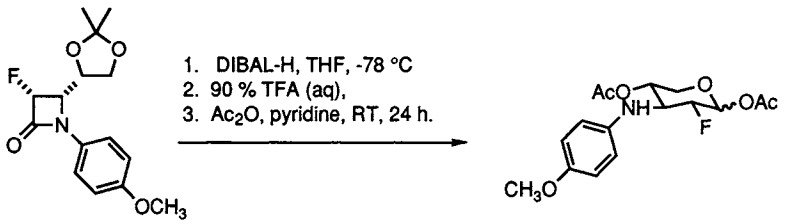
Scheme 27.



16 **51** **52**

2-Fluoro-2-deoxy-gentosamine **53** has been synthesized in optically pure form starting from β–lactam **16** (Scheme 28). The strategy was the same as in the case of difluorodaunosamine (*vide supra*).

Scheme 28.



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Subject Index