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# Studies directed towards total synthesis of taxol. [I] An approach to the C-ring of taxol. [II] Studies on the synthesis of the A-ring of taxol

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City University of New York, 1990

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# STUDIES DIRECTED TOWARDS TOTAL SYNTHESIS OF TAXOL. [I] AN APPROACH TO THE C-RING OF TAXOL. [II] STUDIES ON THE SYNTHESIS OF THE A-RING OF TAXOL.

BY

KAMANI R. SUBASINGHE

A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

1990

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirements for the degree of Doctor of Philosophy.

January 31, 1990

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Supervisory Committee.

January 31, 1990

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Date

Executive Officer.

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## ABSTRACT

STUDIES DIRECTED TOWARDS THE TOTAL SYNTHESIS OF TAXOL.

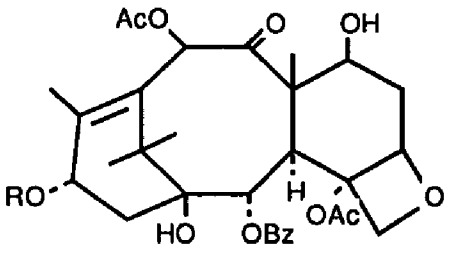
[I] AN APPROACH TO THE C-RING OF TAXOL.
[II] STUDIES ON THE SYNTHESIS OF THE A-RING OF TAXOL.

BY

KAMANI R. SUBASINGHE

Advisor: Professor William F. Berkowitz

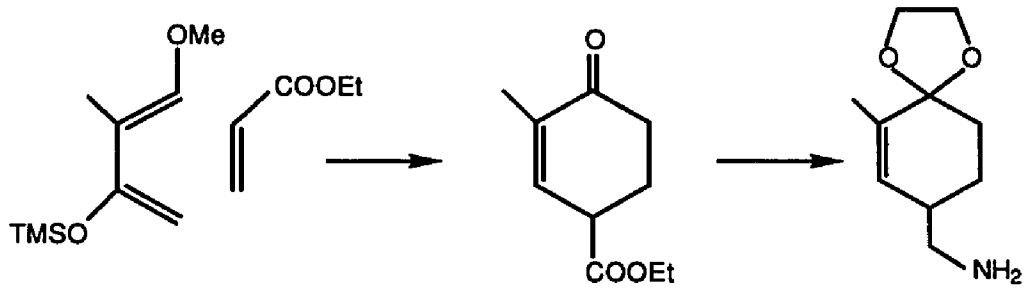
Taxol is a highly oxygenated tricyclic diterpenoid isolated from Taxus species. It exhibits unique biological activity.




$R = C_6H_5CONHCH(C_6H_5)-CHCO-OH$

Taxol

Two key aspects in the synthesis of taxol have been investigated. In the first phase a C-ring synthon of taxol was constructed by a Diels-Alder reaction.




In the second phase cyclization studies have been carried out in development of an approach to construction of the A-ring of taxol.

## ACKNOWLEDGEMENTS

I would like to thank professor William F. Berkowitz for the intellectual and financial support which made completion of this work possible. His guidance during the course of my study was indispensible. I also gratefully acknowledge professors R. W. Franck and K. G. Grohmann for their valuble discussions and encouragements. My thanks go to all of the staff and fellow graduate students who helped me to grow along this way. In particular, I would like to thank Dr. Hoe-Sup Byun. Lastly, of course not leastly I gratefully acknowledge the patience of my husband.

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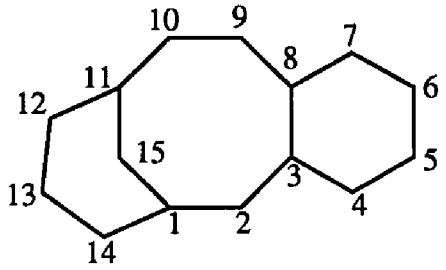
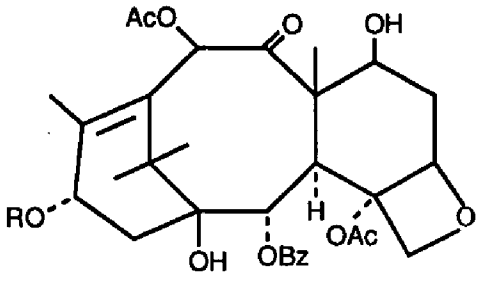
Chapter 1 INTRODUCTION

Taxanes[1-5] are a class of diterpenoids isolated from several species of yew (genus Taxus, family taxaceae). All these compounds have a highly oxygenated tricyclo[9,3,1,0]pentadecane[3] skeleton 1 known as the Taxane skeleton.




1

Representative members of this class of compounds are shown below.



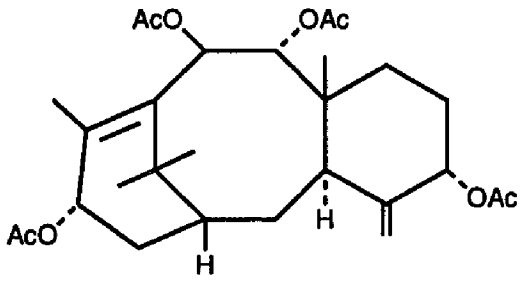

2 R = $C_6H_5CONHCH(C_6H_5)-CHCO-$ (OH)

Taxol

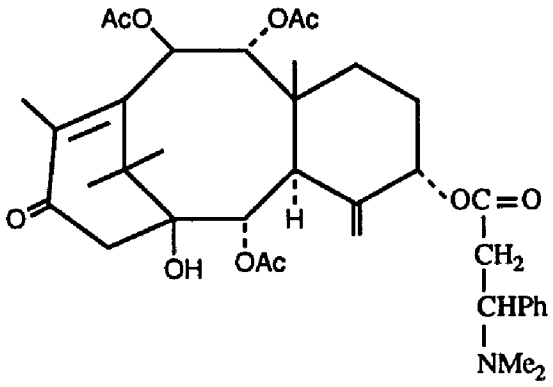
3 R = $CH_3CH=C(CH_3)CONHCH(C_6H_5)-CHCO-$ (OH)

Cephalomannine

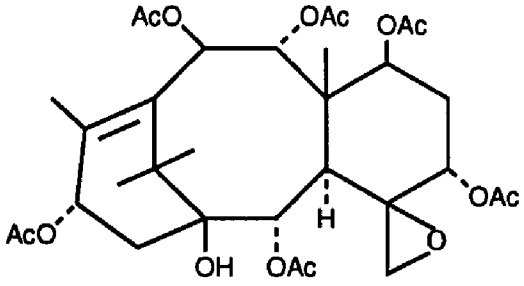
4 R = H— Baccatin III



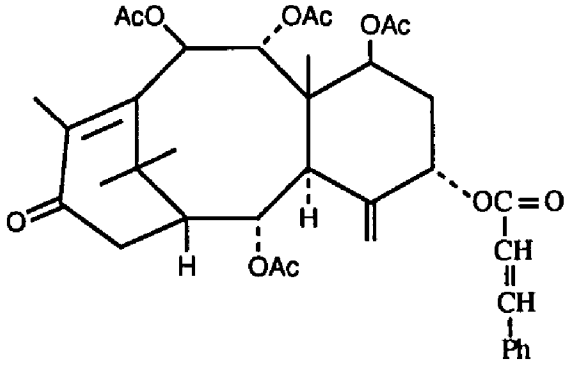

5 Taxusin




6 Taxine - 1




7 1β - Hydroxybaccatin




8 Taxinin B

The common features of this class of compounds are

1. The angular methyl group at C-8
2. The methyl group at C-12
3. The gem-dimethyl group on the bridge C-15
4. The bridgehead double bond at C-11,12
5. The trans stereochemistry at the B/C ring junction
6. The oxygen funtionalities at C-2, 9, 10 and 13 (the only exception is the C-2 position of Taxusin

| Compound | Plant source |
|---|---|
| 1. Cephalomanine | Taxus Wallichina Zucc and Cephalotaxus Mannii |
| 2. 1β-Hydroxybaccatin | Taxus Wallichina Zucc |
| 3. Taxinin B | Taxus Baccata L and Taxus Brevifolia |
| 4. Taxol | Taxus Brevifolia and Taxus Cuspidata |
| 5. Taxine-1 | Taxus Baccata L |
| 6. Taxusin | Taxus Baccata L |
| 7. Baccatin | Taxus Baccata L |

The chemistry of the taxane diterpenoids has attracted considerable interest during the last few years. Several members of this family (eg. Taxol (2) and Cephalomannine (3)) have been found to exhibit significant anti-leukemic and anti-tumor activities and represent exciting leads for the design of new cancer chemotherapeutic agents[2-10]. Taxol is active in vivo against P-388, L-1210 and P-1534 mouse leukemias, the B-16 melanocarcinoma, the CX-1 colon xenograft, the LX-1 lung xenograft and the MX-1 breast xenograft[6,7] and also shows strong cytotoxicity in KB cell culture[2]. Taxol is an interesting drug in that it appears to act by a mechanism that is different from other known anticancer drugs. It is an antimitotic agent, but it acts by promoting microtubule formation[11] by decreasing the lag time for microtubule assembly and shifting the equilibrium for assembly in favour of the microtubule, thereby decreasing

the critical concentration of tubulin required for assembly. Taxol is currently in phase II clinical trials in the United States.

Although taxol shows great promise as a chemotherapeutic agent there are technical difficulties which have hampered its entry into clinical testing. The bark of several species of yew[4,6], very slowly growing evergreens, is the current source of taxol. The isolation procedure is difficult and low yielding and obviously fatal to the source. The reported yields of taxol from the bark of various species of yew range from 40 to 165 mg/kg[4,6].

## ATTEMPTS TO ASSEMBLE THE TAXANE SKELETON

The skeletal and stereochemical complexity of taxol together with its exciting therapeutic potential have provided an enomous challenge toward its total synthesis. More than twenty research groups around the world are currently involved in studies on the synthesis of taxane system and a large number of synthetic approaches have been reported. Most recent studies will be reported here. These studies can be divided into different groups depending on the key reaction in the approach.

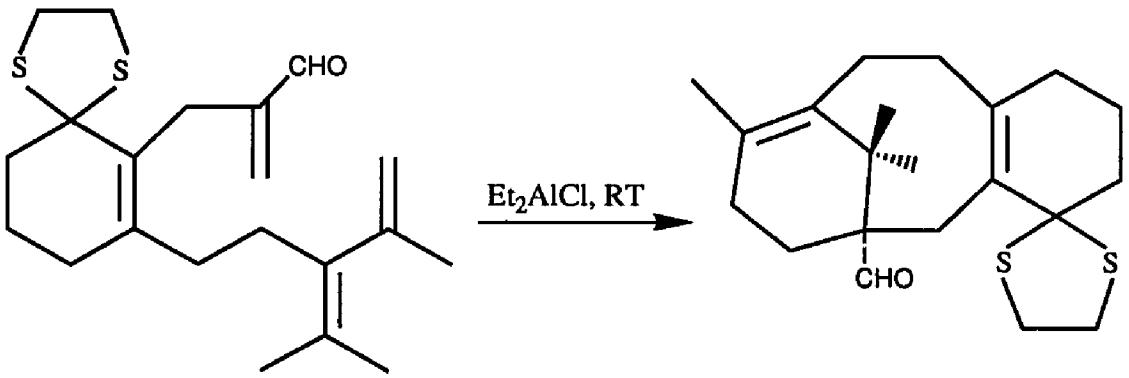
### 1. Intramolecular Diels Alder reaction

Several groups have used the Diels Alder reaction as the key step in the construction of the tricyclo[9.3.1.0]pentadecane ring system, the key substructure unit of Taxanes.

(a) K. J. Shea[12] has shown that compound 9 gave the cycloadduct 10 after Diels Alder cyclization. Compound 9 was synthesised in seven steps

starting from 1,3-cyclohexanedione.

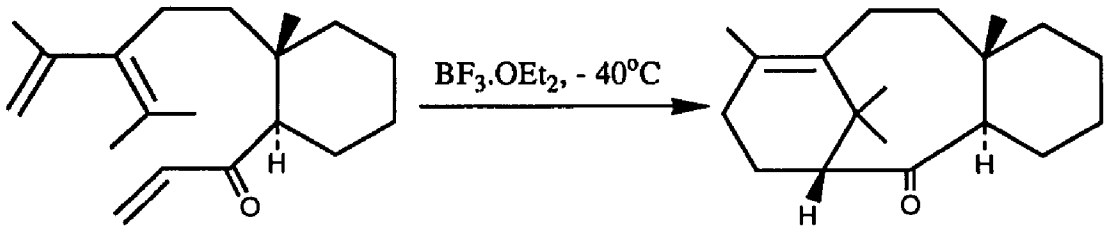
Scheme I




9 10

(b) In 1987 P. Jenkins[13] reported the same reaction on a similar system. In their studies treatment of the enone 11 with $BF_3.OEt_2$ gave the taxane model system 12. The enone 11 was prepared in 6 steps.

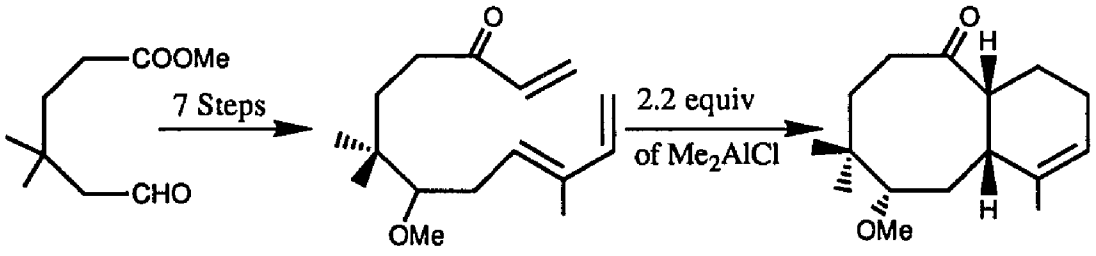
Scheme II



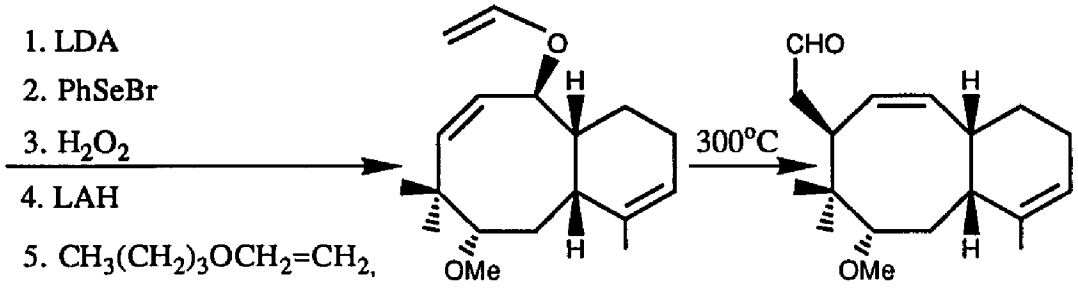

11 12

(c) S. R. Wilson and P. A. Zucker[14] have studied Lewis acid catalyzed intramolecular Diels Alder cyclization of the trienone 14 to form the 8,6 fused bicyclic ring system 15. Compound 14 was prepared from the known aldehyde ester[15] 13 in 7 steps. The bicyclic compound serves as a B/C ring synthon. They have further synthesized the intermediate 18, which is suitably substituted for construction of the tricyclic taxane skeleton via a Claisen rearrangement.

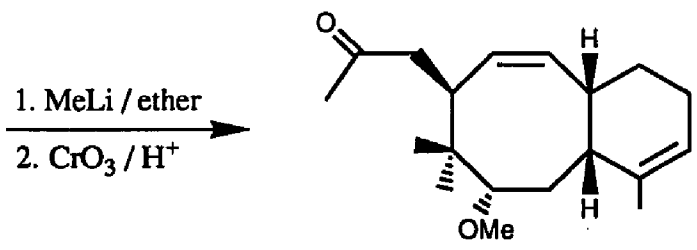
Scheme III




13 14 15




16 17

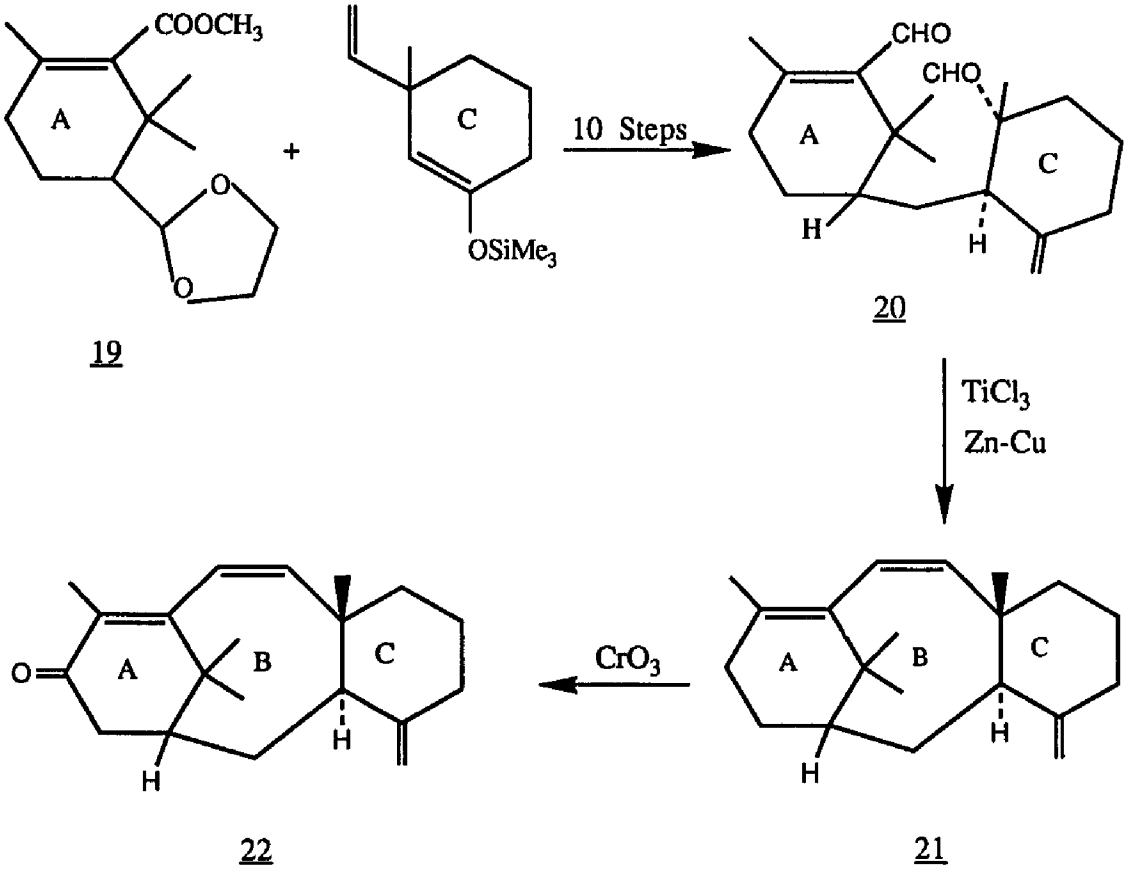



18

2. Intramolecular McMurry cyclization

In 1986 A. S. Kende et al[16] reported the synthesis of racemic taxane triene 21. This was the first total synthesis of a taxane intermediate comprising the full and stereochemically correct carbon framework of natural taxusin (5). The acetal 19 was converted in ten steps to the dialdehyde 20 which underwent McMurry cyclization[17] to form the eight membered B-ring of 21. Selective allylic oxidation of 21 using $CrO_3$/2,5-dimethylpyrazole gave the enone 22.

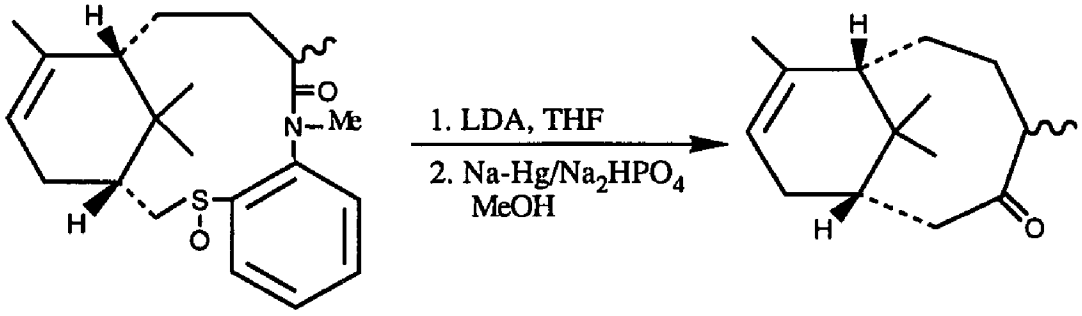
Scheme IV



3. Base induced intramolecular cyclization

Y. Ohtsuka and T. Oishi[18] reported a method for the synthesis of bicyclo[5.3.1]undecenone 24 corresponding to A and B rings of taxanes. In their synthetic approach, the eight membered B ring was constructed by a base induced intramolecular cyclization of twelve membered lactam sulfoxide 23. Compound 23 was prepared from α-ionone.

Scheme V

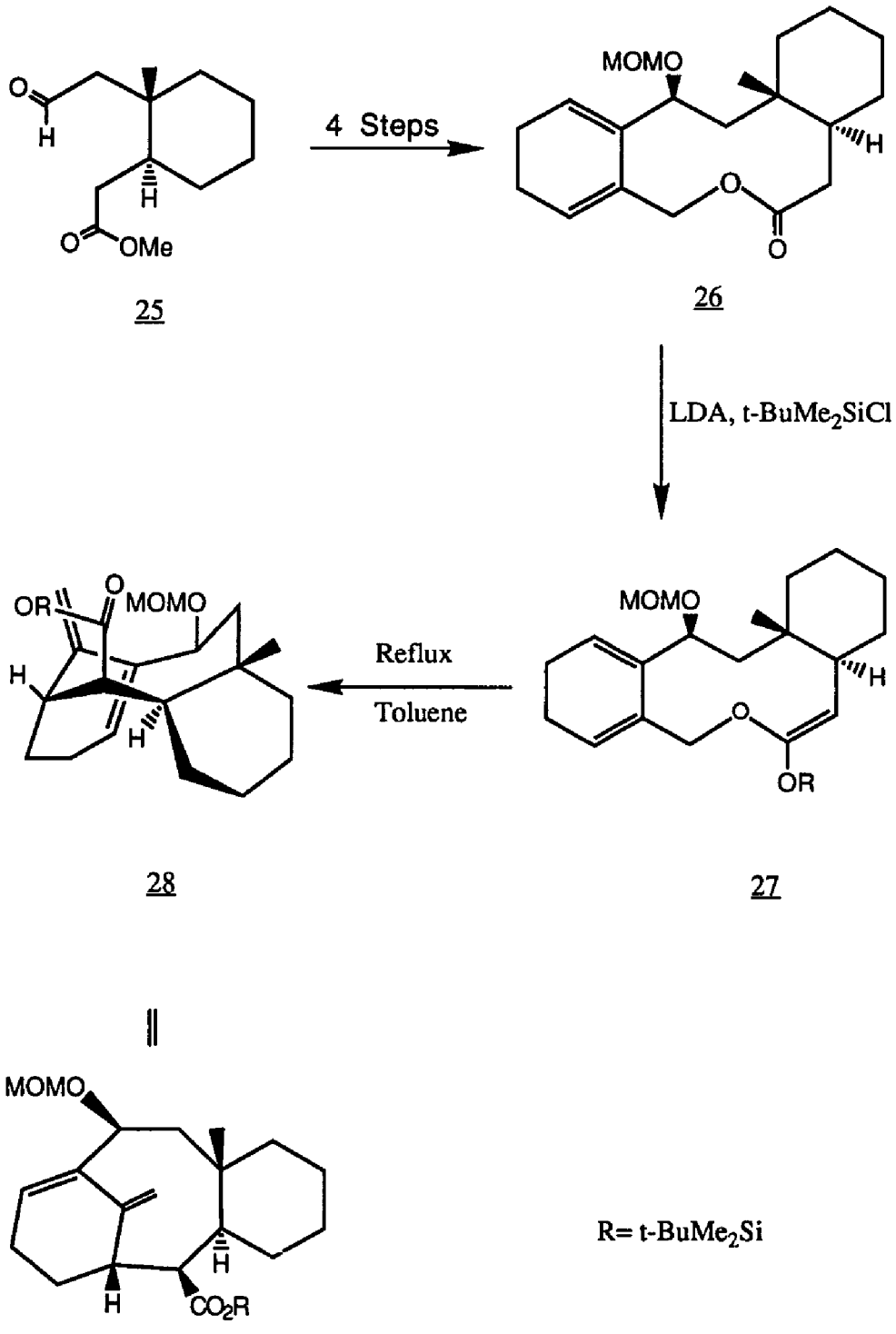



23 24

4. Claisen rearrangement mediated ring closure

R. L. Funk et al[19] synthesized the lactone 26 starting from the aldehyde 25 in four steps. Silylation of the enolate of the lactone gave rise to a single silyl ketene acetal 27. Compound 27 underwent smooth Claisen rearrangement upon thermolysis in refluxing toluene to provide the taxane intermediate 28. They have previously demonstrated the preparation of eight membered rings by Claisen rearrangement mediated ring contraction of macrocyclic lactones 20.

Scheme VI



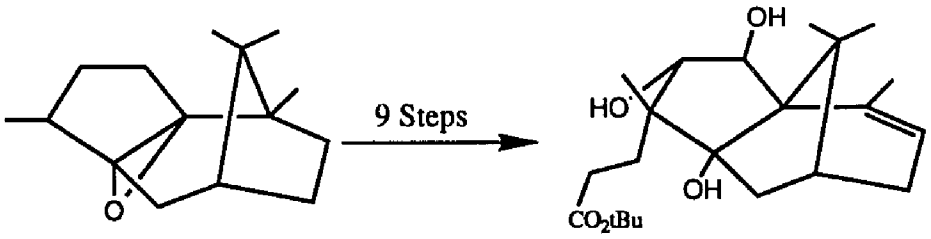

25 26 27 28

5. Carbonium ion induced fragmentation rearrangements

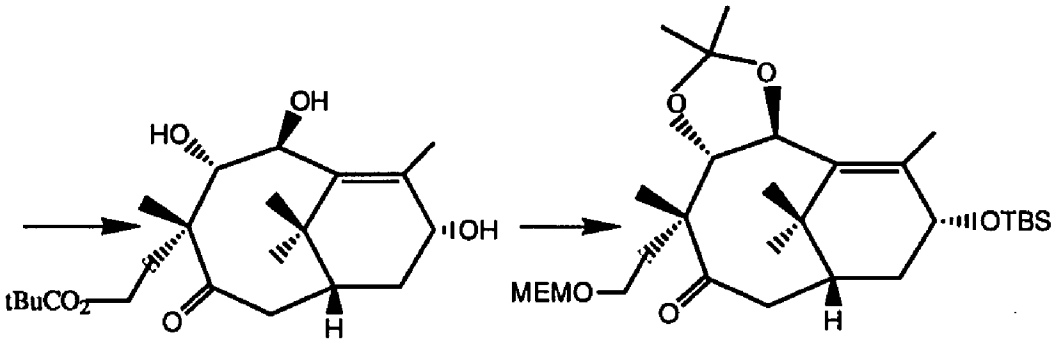
Recently R. A. Holton[21] published the first total synthesis of (-) taxusin, the enantiomer of the natural product. His starting material was β-patchoulene oxide 29, originally made by Buchi[22].

β-Patchoulene oxide was converted to compound 30 in 9 steps. Compound 30 on treatment with large excess of anhydrous peracetic acid followed by $Ti(OiPr)_4$ underwent fragmentation to provide the triol 31. The introduction of $C_4$ and $C_5$ and reduction of the OH group lead to compound 34. Cyclization, acetylation and finally conversion of the carbonyl group of 36 to an olefin gave (-) taxusin 5.

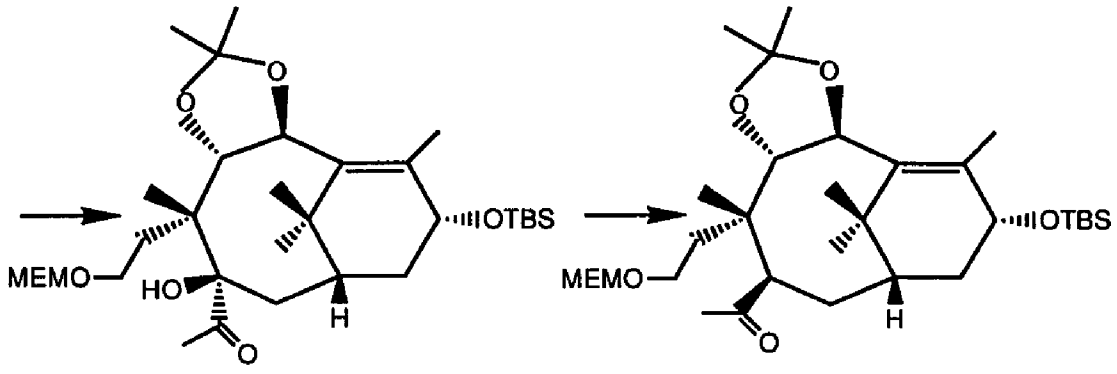
Scheme VII



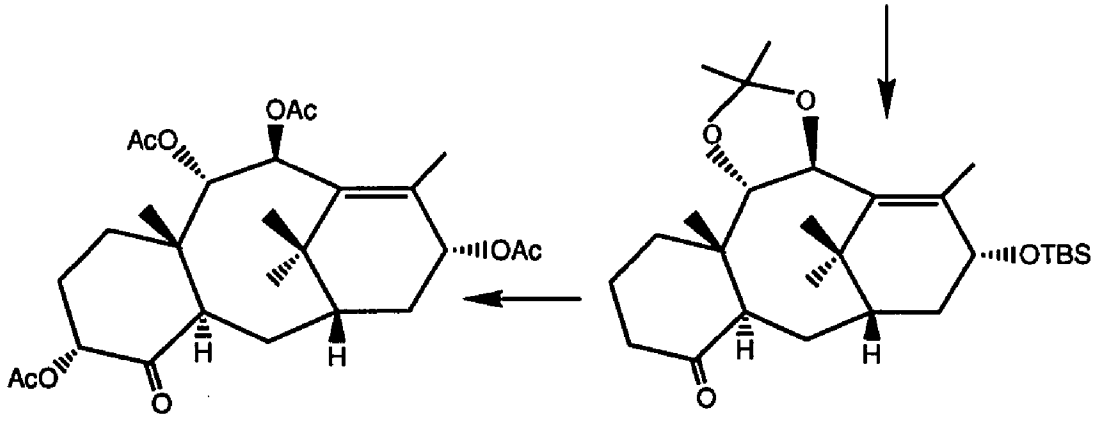

29 30




31 32




33 34

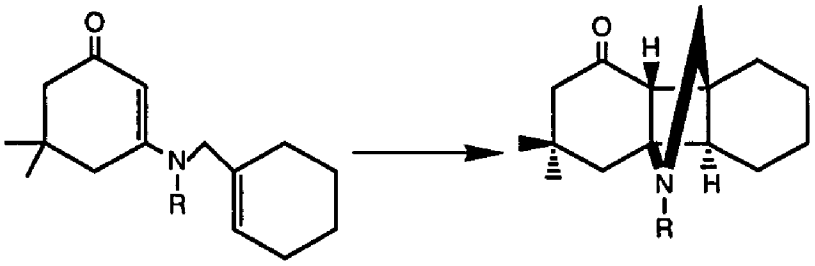



36 35

6. Photochemical methods

(a) C. S. Swindell[23] prepared the compound 38 by intramolecular photocycloaddition of vinylogous imide 37.

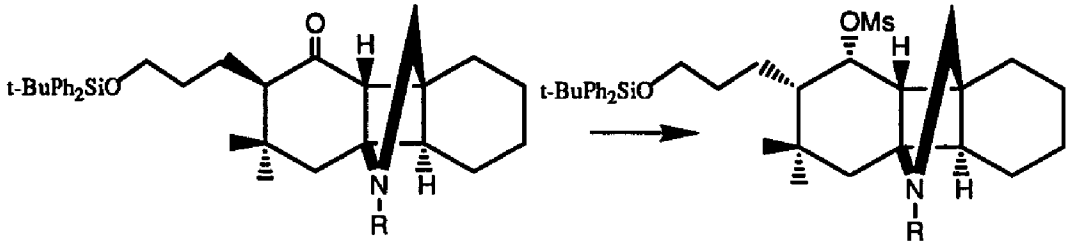
Scheme VIII



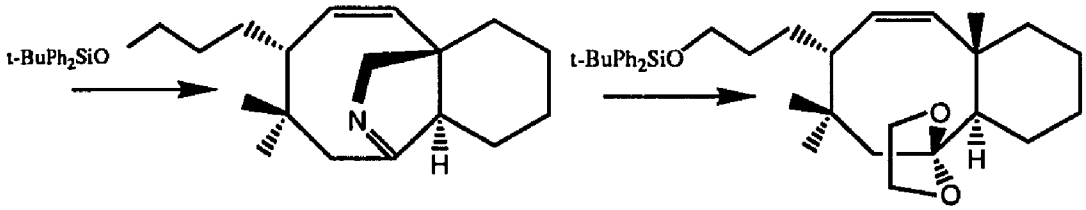

37 R = $CO_2CH_2CCl_3$ 38

Alkylation of 38 with a three carbon unit gave compound 39. Adjustment of stereochemistry at the side chain through base induced epimerization and transformation of the carbonyl group into an α-mesylate gave the intermediate 40. Fragmentation of the four membered ring by trichloroethyl urethane cleavage[24] gave the bridgehead imine 41. Hydrolytic liberation of the primary amine and its capture with acetic formic anhydride gave a formamide which led through ketalization, isocyanide formation, and reduction to the angular methyl group of 42. Taxane model 43 was formed upon ring closure of the side chain by intramolecular enolate alkylation.

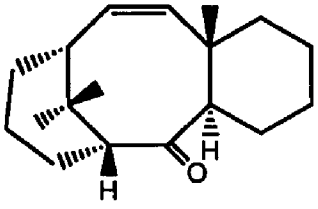
Scheme IX




39 40




41 42

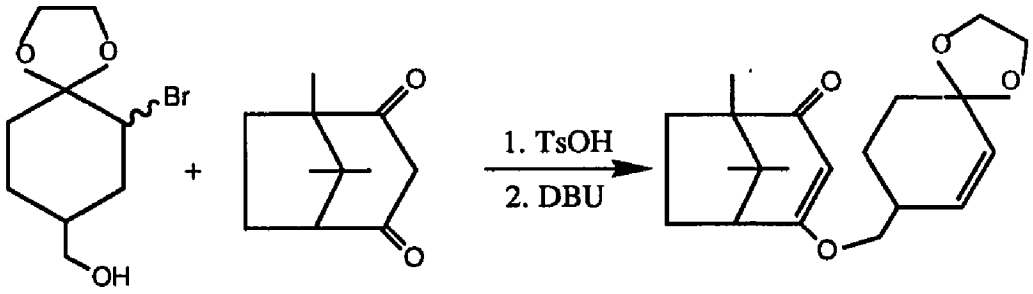



43

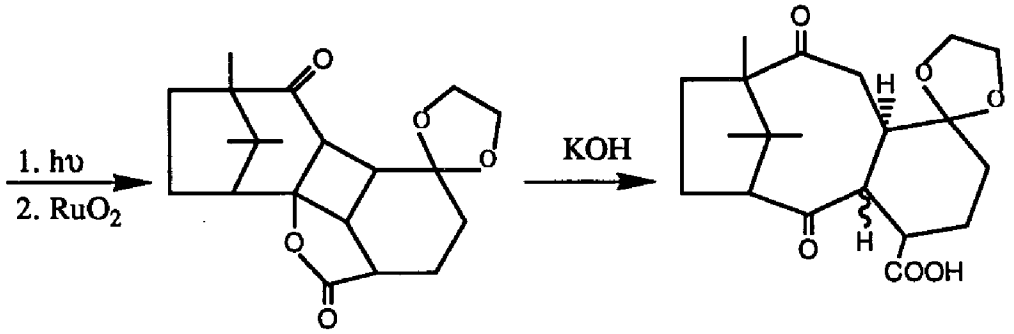
(b) W. F. Berkowitz, A. S. Amarasekara and J.J. Perumattam[25] in our laboratory have published another photochemical approach to the taxane skeleton. Their strategy was based upon the de Mayo ring closure/retroaldol sequence[24] developed by Oppolzer, Pattenden and others[27].

Bromo alcohol 44 was coupled with 45 and then dehydrohalogenated to give de Mayo precursor 46. Photocycloaddition followed by oxidation gave lactone 47 which was cleaved by base to the taxane model 48.

Scheme X




44 45 46

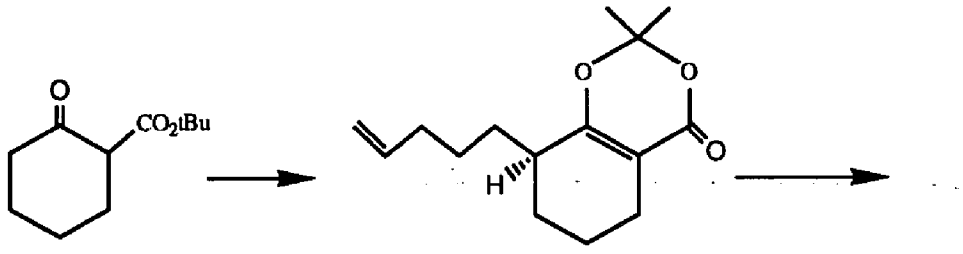



47 48

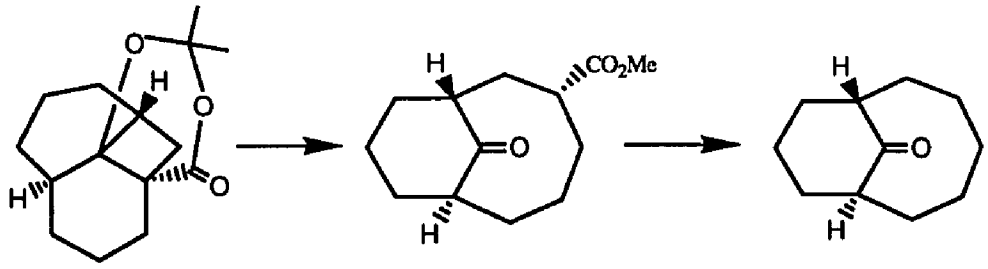
(c) J. D. Winkler et al[28] have investigated the possibility of using an intramolecular photocycloaddition of dioxolenones to prepare trans bicyclo[5.3.1]undecane ring system 53, an important structural feature of taxane diterpenes.

The photosubstrate 50 was prepared from 49 by alkylation followed by dioxolenone formation. Irridiation of 50 produced the photoadduct 51 which upon treatment with toluene-sulfonic acid underwent fragmentation to provide 52. Decarboxylation of 52 gave the bicycloundecanone 53.

Scheme XI




49 50




51 52 53

7. Intramolecular Ni catalyzed 4+4 cycloadditions

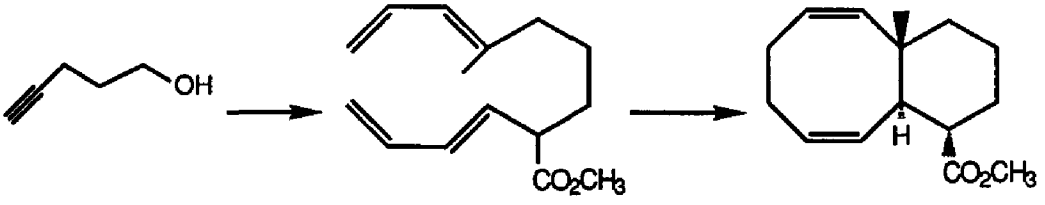
In 1987 P. A. Wender et al[29] published their results on Ni catalyzed intramolecular 4+4 cycloaddition of bis dienes in preparation of both AB and BC ring systems of taxanes. Their approach is outlined in scheme XII.

This method provided a route to angularly alkyl substituted bicyclo[6.4.0]dodecanes and to bicyclo[5.3.1]undecanes.

The cycloaddition of bis diene 54, which was prepared through an 8 step sequence starting from 4-pentyn-1-ol, gave 55. This has the basic taxane BC ring skeleton.

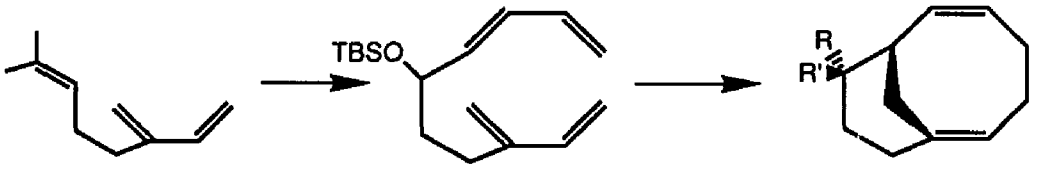
Similarly cycloaddition of 56 gave bicyclo[5.3.1]undecane 57 which has the basic taxane AB ring skeleton.

Scheme XII




54 55

Scheme XIII




56

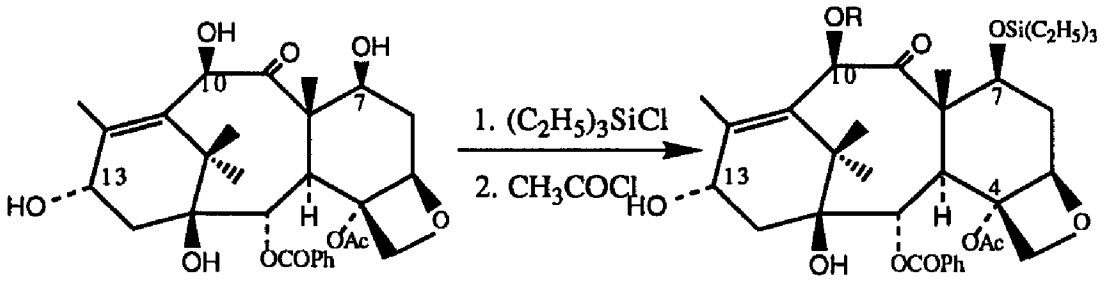
57a R'= OTBS, R= H
57b R'=H, R= OTBS

8. Conversion of 10-deacetyl baccatin III to taxol

A. E. Green[30] recently reported an approach to taxol from 10-deacetyl baccatin III (58) which can be readily extracted in high yield from the leaves of Taxus baccata L[31]. It is important that the yew leaves are quickly regenerated, hence large amounts of 58 can be continualy supplied with negligible effect on the yew population.

Triethylsilylation of 10-deacetyl baccatin III (58) under carefully optimized conditions, followed by acetylation provided 7-triethylsilyl baccatin III (59b). Esterification at C-13 of 59b was found to be exceedingly difficult. The reason was that the C-13 hydroxyl group is situated in the skeletal concavity of 59b and furthermore is able to form hydrogen bonding with C-4 acetate. They were able to esterify 59b with 6 equiv of optically pure (2R,2S)-N-benzoyl-O-(1-ethoxyethyl)-3-phenyl-iso serine (60)[32] in the presence of di-2-pyridyl carbonate (DPC) and DMAP in toluene solution at 73°C for 100 h to produce the C-2' and C-7 protected taxol derivative 61. Concomitant removal of the protecting groups at C-2' and C-7 in 61 by using 0.5% HCL in ethanol gave taxol (2).

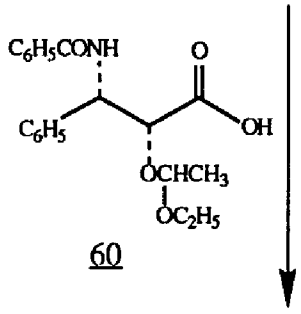
Scheme XIV



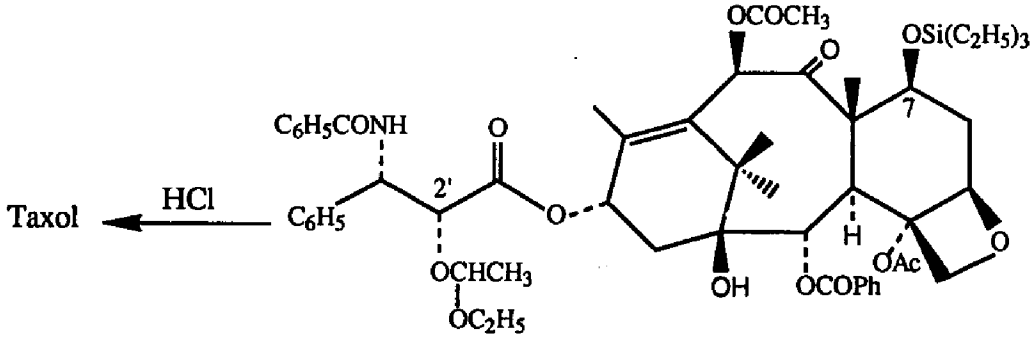

58

59 a, R = H

b, R = $COCH_3$




60

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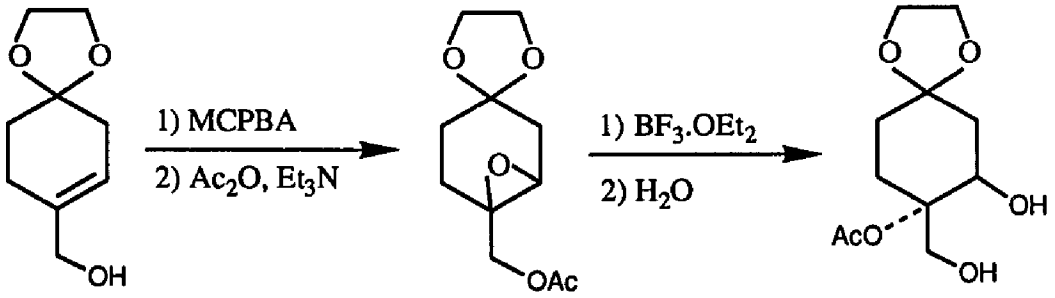
SYNTHETIC APPROACHES TO THE C/D RING SYSTEM OF TAXOL

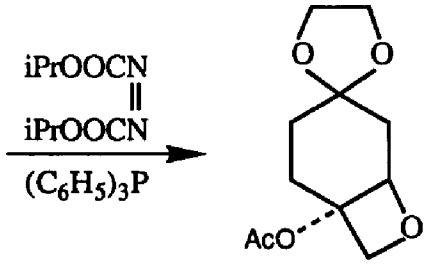
Another unusual feature found in taxol is the oxetane D-ring and the C-4 tertiary acetate. There have been several attempts published in literature recently[33,36].

(a) W. F. Berkowitz and A. S. Amarasekara[33] in our laboratory have published the first model 65 for construction of the C/D ring of taxol.

Scheme XV




62 63 64

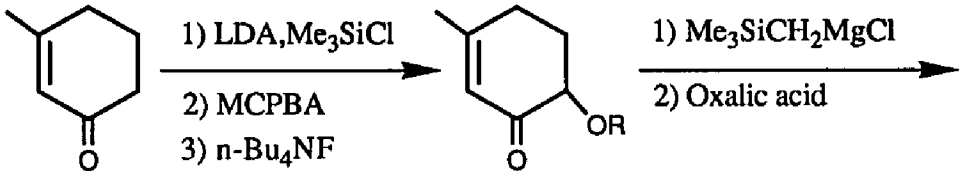



65

The known allylic alcohol[34] 62 was epoxidized and acetylated and then rearranged to give the acetoxy-cis-diol 64 which finally was closed to the oxetane 65 using the Mitsunobu procedure[35] as shown in scheme XV.

(b) G. Clark et al[36] have reported a synthesis of an another C/D ring precursor 74 using 3-methyl-2-cyclohexen-1-one as the starting material. This was converted to the ketol 67 and then to the t-butyldimethylsilyl ether 68. Olefination of 68 followed by osmylation produced a mixture of stereoisomers 70 and 71. Selective mesylation of 70 afforded the primary mesylate 72. Protection of the tertiary allylic alcohol and subsequent desilylation prodoced the oxetane 74.

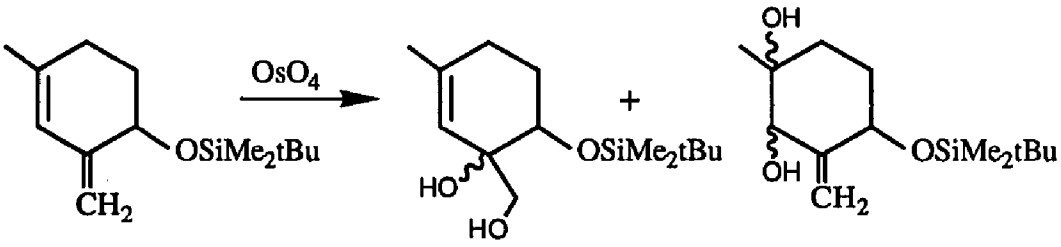
Scheme XVI



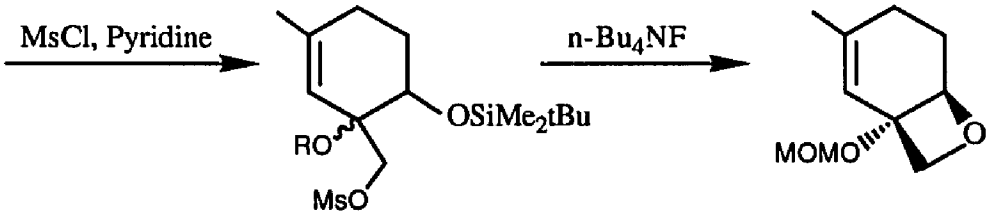

66

67 R = H

68 R = $SiMe_2tBu$




69 70 71




74

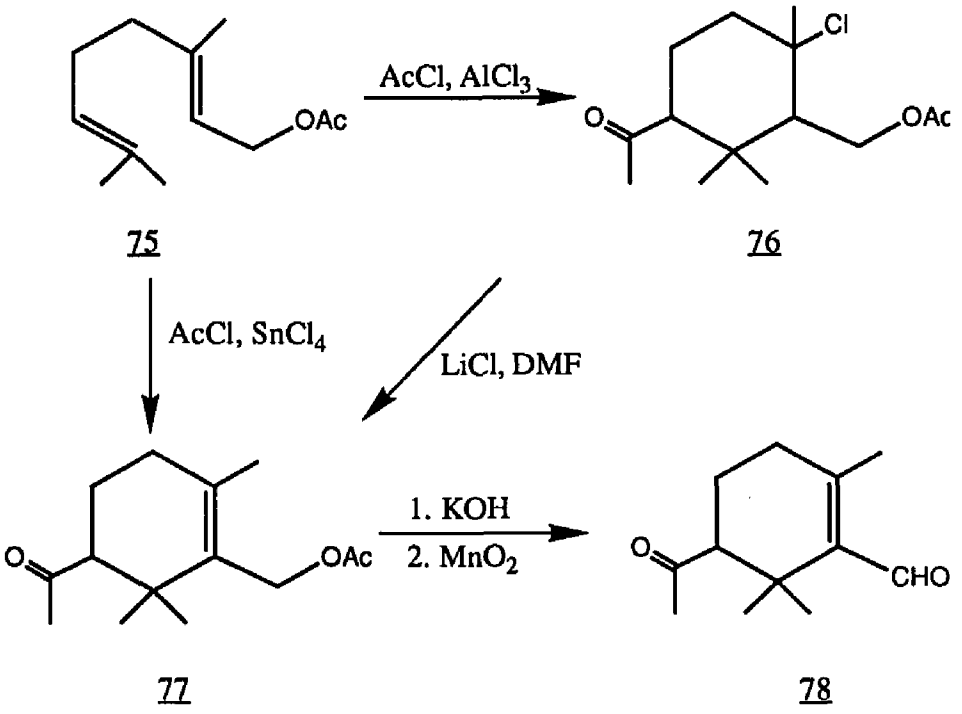
72 R = H

73 R = MOM

CYCLIZATION METHODS THAT HAVE BEEN REPORTED TO PREPARE MOLECULES SIMILAR TO TAXOL A-RING

1. In 1974 Y. Kitahara and coworkers[37] published their results on cyclization of geranyl acetate 75 using AcCl-$SnCl_4$ or AcCl-$AlCl_3$.

Scheme XVII

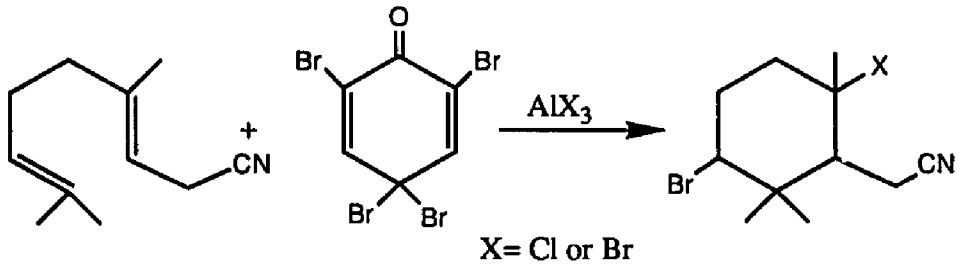



An equimolar mixture of the $AlCl_3$ complex of acetyl chloride and geranyl acetate in methylene chloride at $0^oC$ gave the acylation product 76, while the reaction of the $SnCl_4$ complex in nitromethane under the same conditions afforded the unsaturated product 77. Compound 76 was quantitatively converted to 77 with LiCl and DMF. The compound 77 was

converted to the corresponding aldehyde 78 by alkaline hydrolysis followed by $MnO_2$ oxidation.

2. Cyclization of geranyl cyanide 79 to give the compound 80 was reported by the same group in 1976[38].

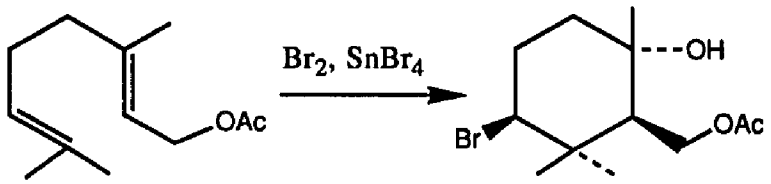
Scheme XVIII




79 80

3. J. Faulkner and coworkers[39] have investigated bromonium ion induced cyclizations on various substrates. Treatment of geranyl acetate with 1 eq each of $Br_2$ and $SnBr_4$ gave the cyclized bromoacetate 81 in 16% yield. They found that large quantities of the material underwent normal $Br_2$ additions. However by using silver fluoroborate instead of $SnBr_4$ they observed only 20% of the cyclized product 81.

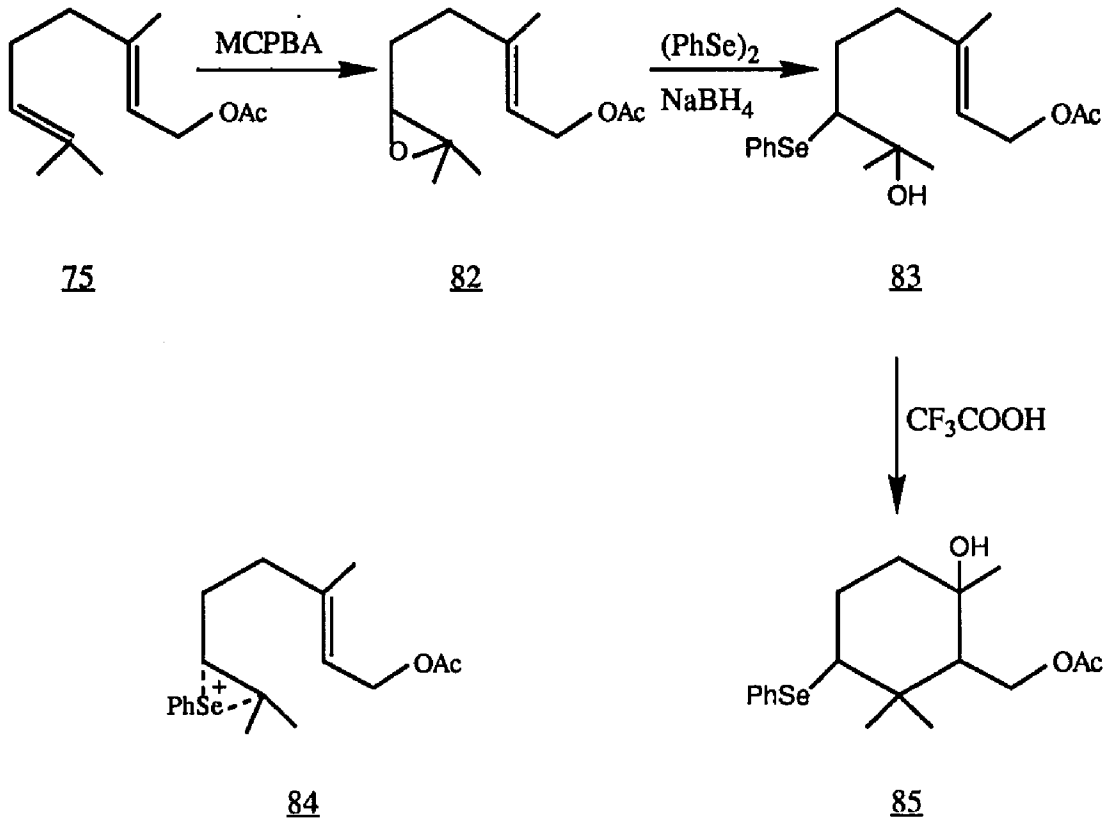
Scheme XIX




75 81

4. In 1979 T. Kametani et al[40] published a new biogenetic type selenium assisted cyclization during their synthesis of Safranal. The olefinic β-hydroxy selenide 83 was synthesized by epoxidation of geranyl acetate 75 with m-chloroperbenzoic acid, followed by ring opening of the epoxide with the phenylselenide anion. Treatment of 83 with trifluoroacetic acid at 0°C gave the cyclic phenyl selenide 85. The carbonium ion generated by the acid treatment is believed to be stabilized by the participation of the phenylselenyl group, with in situ formation of a seleniranium ion 84.

Scheme XX



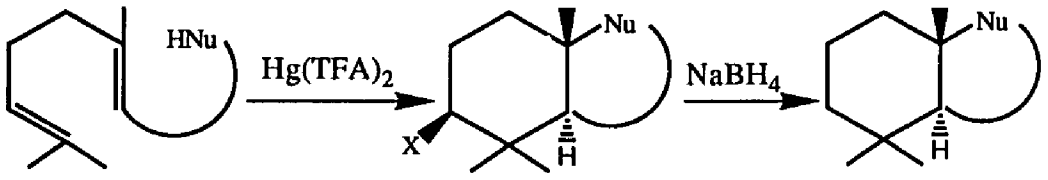

75 82 83

84 85

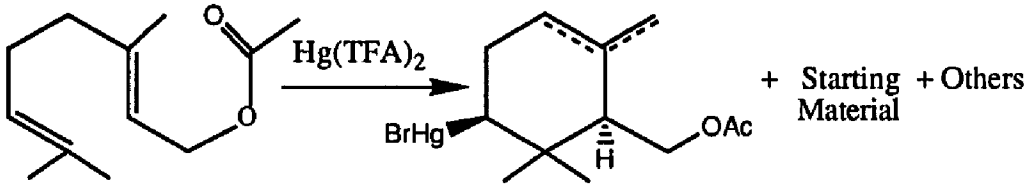
5. In 1981 T. R. Hoye[41] reported mercuric ion initiated cyclizations of simple 1,5-dienes of structure 86 where the oxygen containing functional groups such as HNu = -COOH, -OH, -C=O etc serve as terminators for cyclizations. Diene 86 was treated with mercuric trifluoroacetate following the methodology of Semenovsky[42]. The organomercury trifluoroacetates[81] were converted to the mercury bromides 89 by ligand exchange with KBr. The organomercury bromides were converted either to the bromides 89 or to the hydrocarbon 90. They found that carboxylic acids, ketones, and alcohols are effective trapping nucleophiles whereas acetate esters (eg. in geranyl acetate) are not. Geranyl

acetate 75 gave a complex mixture of products upon exposure to $Hg(TFA)_2$.

Scheme XXI




86 87 X = HgTFA 88 X = HgBr 89 X = Br 90



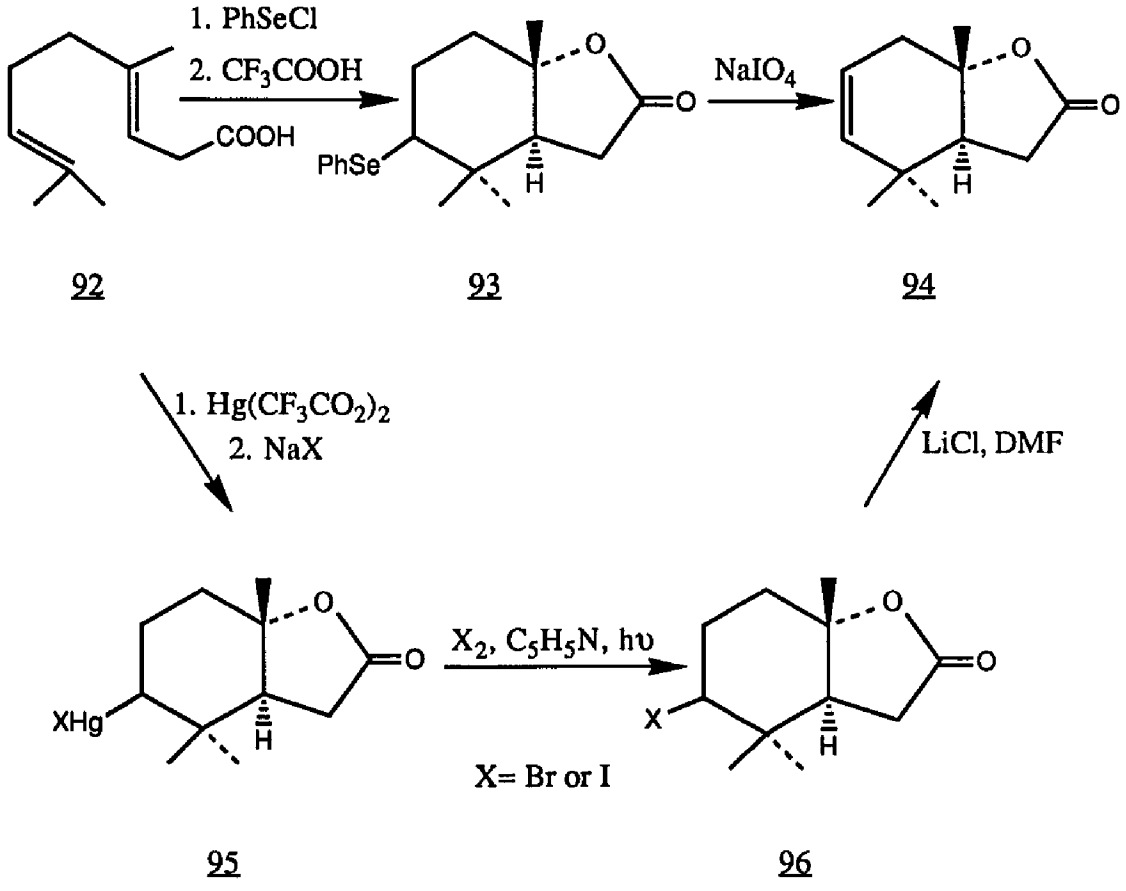

75 91

24 %

6. Preparation of the lactone 94 was reported by F. Rouessac[43] in 1983 by electrophilic cyclization of homogeranic acid 92. Their approach is outlined in the scheme XXII. Homogeranic acid 92 was cyclized on treatment with phenyl selenyl chloride followed btrifluoroacetic acid to

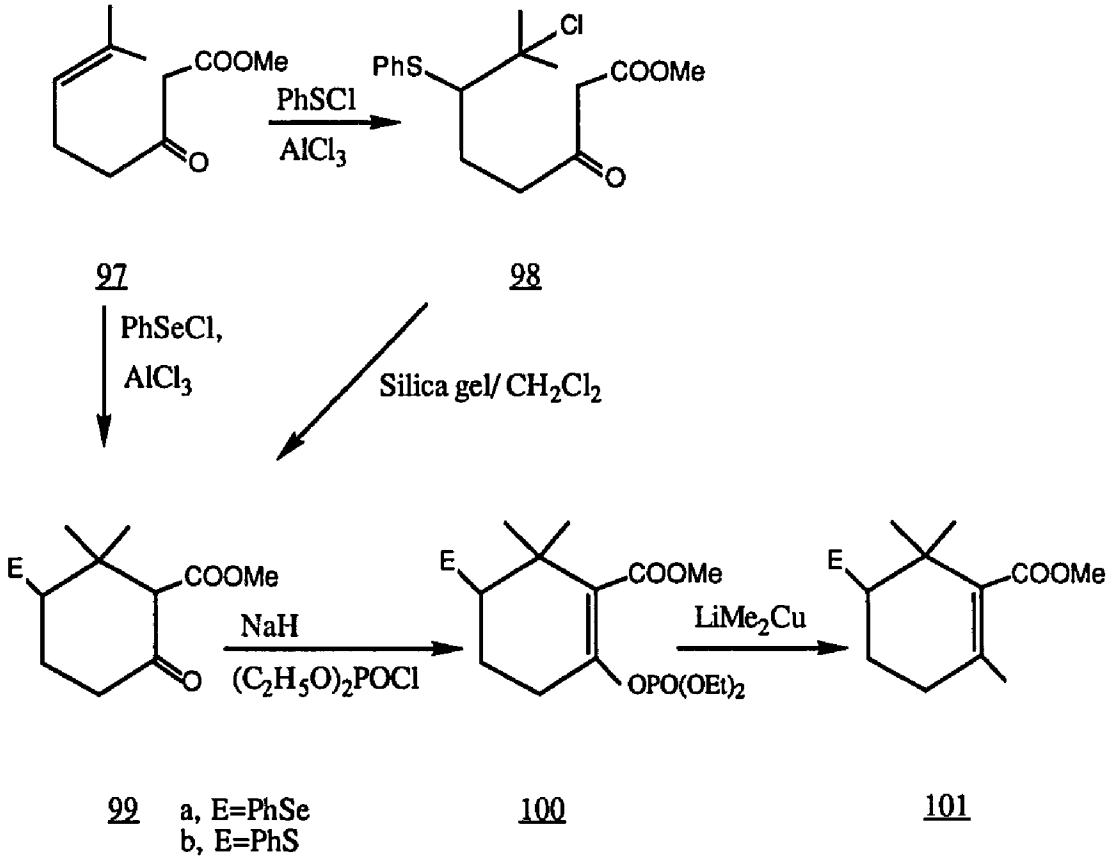
the selenolactone 93 which was transformed to the lactone 94 by oxidative elimination. Alternatively 94 was prepared via cyclization of homogeranic acid with mercuric trifluoroacetate according to T. R. Hoye et al[44]. The mercuric derivative 95 was converted to halolactone 96 by radical reaction with $I_2$ or $Br_2$ in pyridine. Treatment of 96 with LiCl/DMF gave the lactone 94.

Scheme XXII



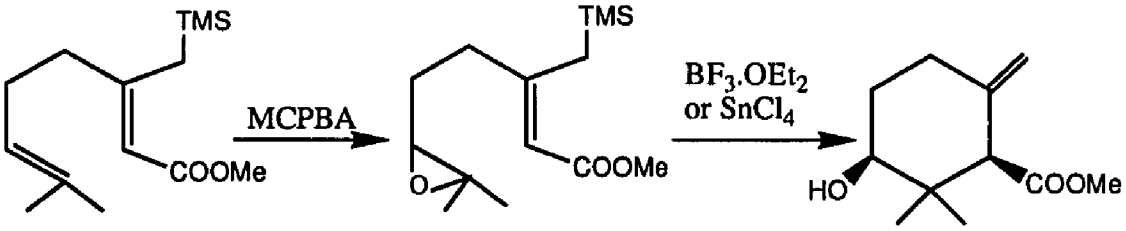
7. L. Weiler et al[45] have reported their studies on the cyclization of the olefinic β-keto ester 97 using either sulphenyl or selenyl electrophile to initiate the cyclization. When benzeneselenyl chloride was added to a suspension of $AlCl_3$ in $CH_2Cl_2$ containing 97, a smooth cyclization occured to give 99a. A similar addition of benzenesulphenyl chloride gave the addition product 98 which on refluxing in silica gel/$CH_2Cl_2$ gave the cyclic product 99b. Compound 99 was converted to the corresponding enol phosphate 100 and then to the ester 101.

Scheme XXIII



8. Recently L. Weiler and coworkers[46] published a synthesis of an interesting cyclic compound 104. The diene 102 was prepared from methyl acetoacetate in three steps. This was regioselectively epoxidized to the epoxy allylsilane 103 using m-chloroperbenzoic acid. Treatment of 103 with either stannic chloride or boron trifluoride etherate effected the facile conversion to the cyclic hydroxy ester 104.

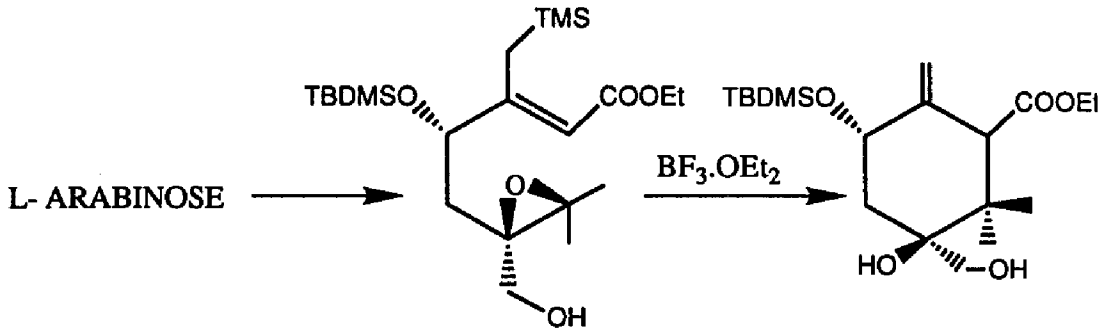
Scheme XXIV



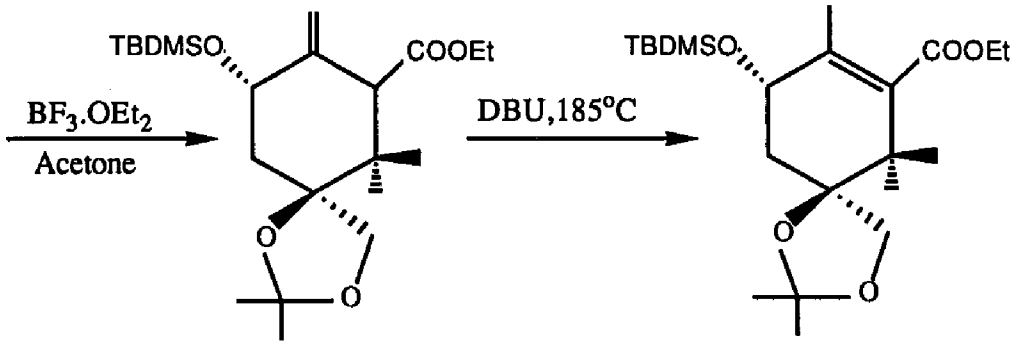

102 103 104

9. In 1987 T. Frejd and coworkers[47] reported a method for the synthesis of an optically active A-ring building block 108 for taxol. Their synthetic approach is based on an electrophilic cyclization of an epoxy allylsilane, the concept which was developed by Weiler and coworkers[46]. The epoxy allylsilane 105 was prepared from L-arabinose in twenty steps. Compound 105 on treatment with $BF_3.OEt_2$ at $0^oC$ cyclized to give the six membered ring compound 106, which formed the acetonide with acetone in the presence of $BF_3.OEt_2$. Compound 107 on heating in neat DBU resulted in isomerization into 108.

Scheme XXV




105 106




107 108

## Summary

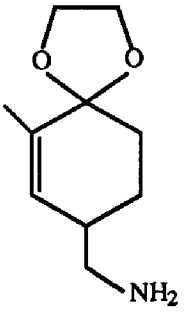
Except for the approaches of Wilson and possibly Frejd, none of the above studies were directed towards the synthesis of a taxane skeleton bearing the tertiary hydroxyl group of Taxol. Our own approach has been directed from the first with consideration of this key structural feature in mind.

Chapter II RESULTS AND DISCUSSION

This work is divided into two sections: (1) Synthesis of the C-ring synthon of Taxol, Cephalomannine and Baccatin III; (2) Studies on the A-ring synthon of Taxol, Cephalomannine and Baccatin III.

(1) Synthesis of the C-ring synthon of Taxol, Cephalomannine and Baccatin III.

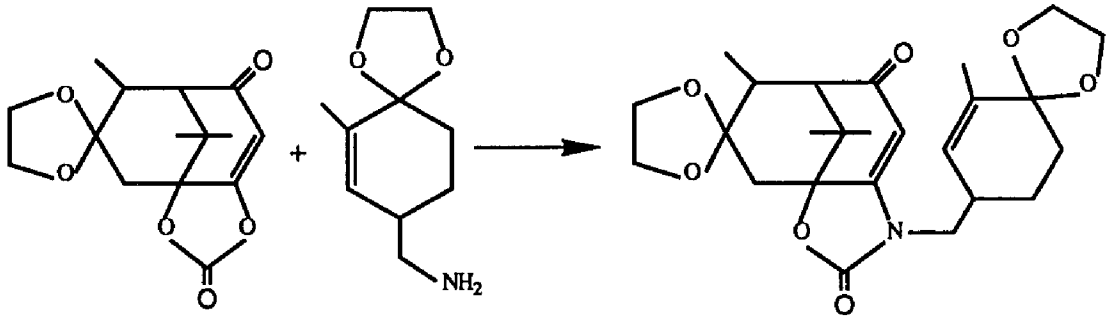
The first half of this work is directed towards the synthesis of the molecule 109.



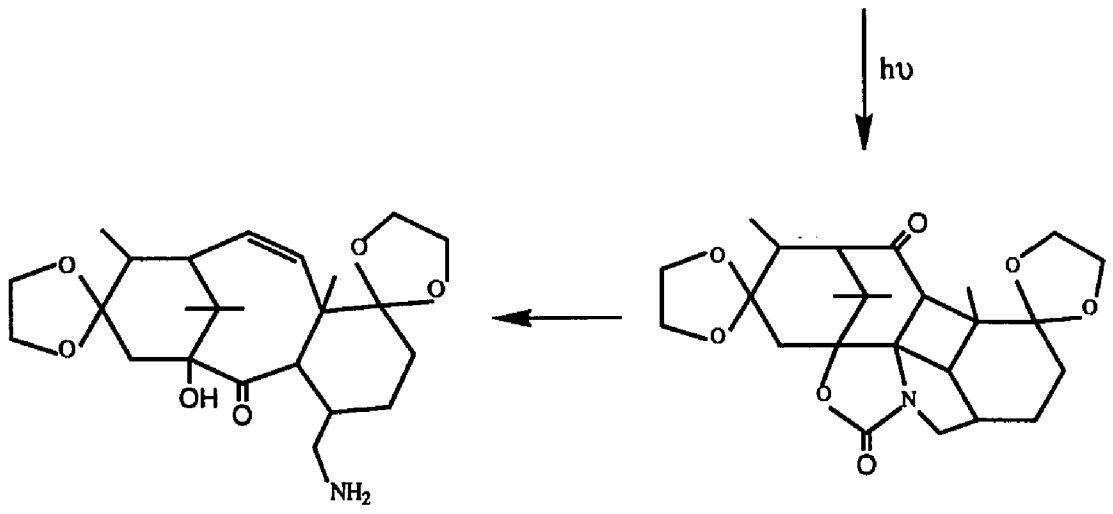

109

We expect to combine 109 with an A/B ring synthon 110 to form the cyclic carbamate 111. Intramolecular photocycloaddition would give the intermediate 112 which on hydrolysis would undergo fragmentation to provide the tricyclic carbon skeleton for taxol. Compound 113 has a C-1 hydroxyl group unlike any previous taxane model and an aminomethyl group at C-4. Subsequent elimination of the amino group would provide the exo-methylene to use as a precursor of the oxetane D-ring of taxol. The methyl group on the alkene side chain of 109 becomes the C-8 angular

methyl group with the desired stereochemistry after the photocycloaddition and ring opening. Formation of the cyclic carbamate before the photocycloaddition, would serve as an anchor for the intramolecular photocycloaddition of the alkene 109, and enolize the diketone in the correct direction.



110 109 111

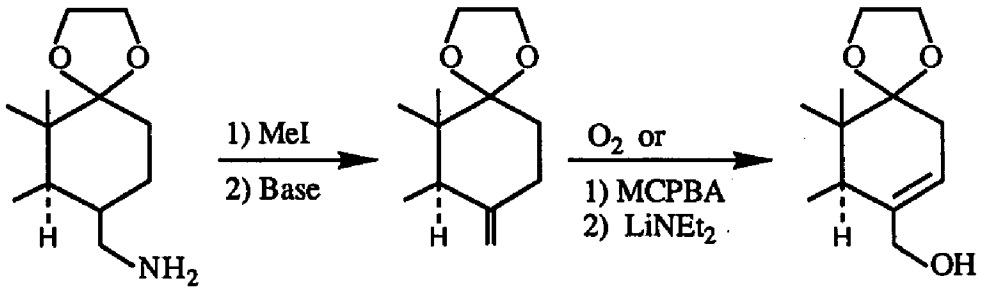


113 112

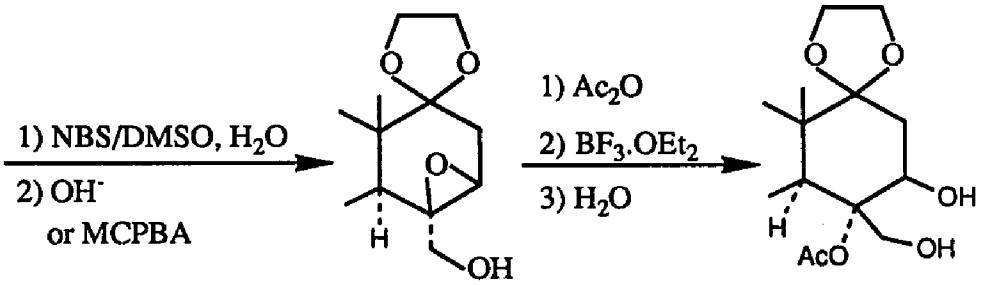
Swindell[23] has shown that the vinylogous imide function (eg. 37, scheme VIII) also succesfully participates in 2+2 photocycloaddition reactions. Blechert's[66] work leads us to believe that the cyclobutane ring will form on the side of the ring opposite to the A-ring ketal and thus syn to the gem-dimethyl, forcing the angular methyl at C-8 up.

Proposed strategy for the construction of the oxetane D-ring

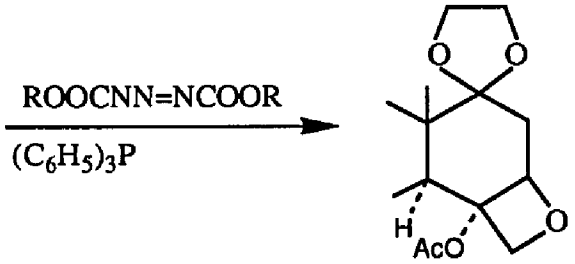
The aminomethyl group resulting from the fragmentation of the photoadduct 112 is, in effect the latent oxetane ring carbon. Elimination of the aminomethyl group should afford an exocyclic double bond, ie 114. This could be converted to an allylic alcohol 115 either (a) by treatment with singlet oxygen[48] or (b) by conversion first to an epoxide followed by base catalyzed rearrangement[49]. (It may be necessary to adjust or protect the ketone functions first; furthermore, the C-9, 10 double bond should be considerably less reactive due to the steric hindrance of both the gem-dimethyl and the C-13 ketal) The allylic alcohol 115 can be converted to the diol-acetate 117 and thus to the desired oxetane 118 according to the procedure reported by our laboratory[33] as shown in the scheme XV.




113 114 115

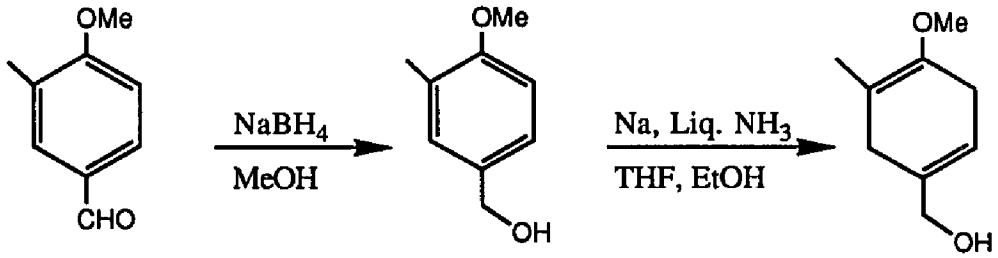



116 117

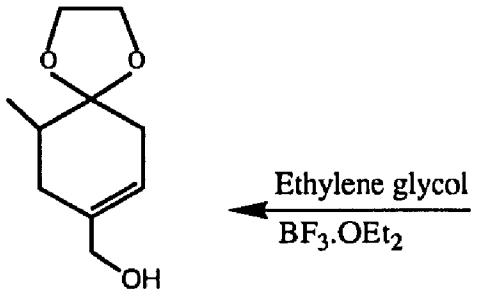



118

Preparation of the C-ring synthon was initially attempted using 3-methyl-4-methoxybenzaldehyde 119 as the starting material. This was reduced to 3-methyl-4-methoxybenzyl alcohol using sodium borohydride and then converted to 122 following the procedure of Ito and coworkers[50]. However complex mixtures of compounds (TLC and GC) were obtained when we tried to reduce the double bond using $Pd/C/H_2$ or $Rh/C/H_2$. Consequently, this procedure was abandoned.

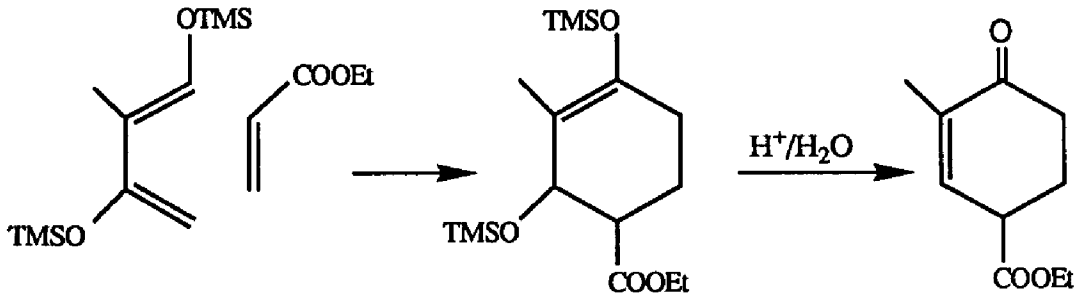



119 120 121



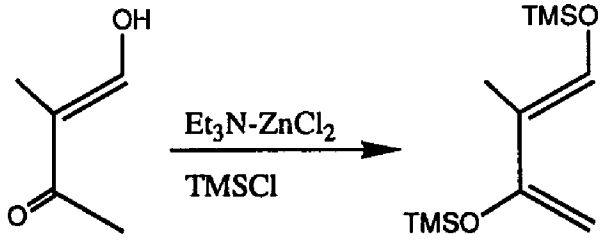

122

T. Ibuka et. al[51] have synthesized 126 by hydrolysis of the Diels-Alder adduct formed by the Danishefsky diene 123 with ethyl acrylate.



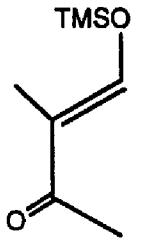

123 124 125 126

Preparation of the diene 123 was attempted by the treatment of 2-formyl-3-butanone 127[52] with trimethylsilyl chloride in the presence of $Et_3N$-$ZnCl_2$ in an ether-benzene mixture according to the procedure reported by T. Ibuka et. al[51].




127 123

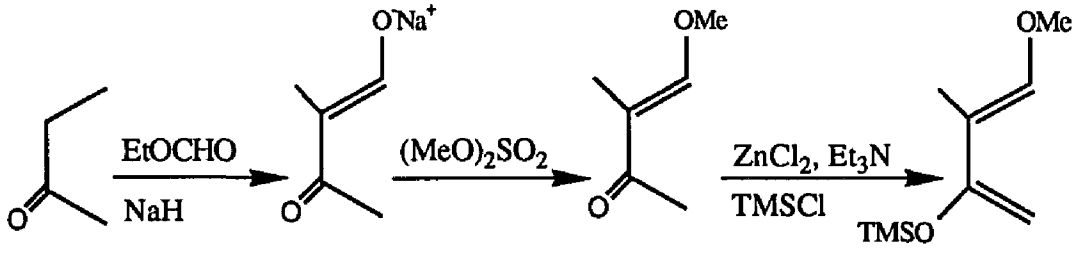
One major compound, along with small amount of 127 was isolated in 82% yield after distillation. $^1H$ NMR showed that the major product was the monosilylated compound 128.




128

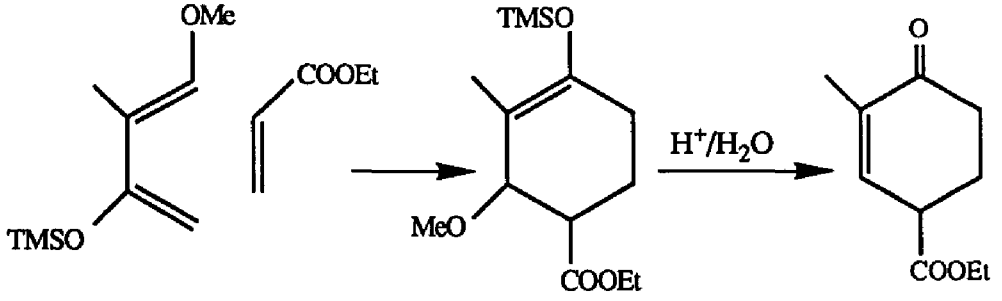
Then we turned to the preparation of the Danishefsky diene 132[53] since it would give the same enone ester 126 after hydrolysis of the Diels-Alder adduct formed with ethyl acrylate.

Compound 132 was prepared according to S. Danishefsky's procedure[53] starting from 2-butanone . Formylation of 2-butanone with ethyl formate in the presence of NaH in dry ether afforded the Na salt of hydroxy methylene butanone 130[52] in 90% yield, as a pale yellow solid. This was treated with dimethyl sulfate in water to give the enone 131[54] in 65% yield. Compound 131 was converted to the Danishefsky diene 132 in 70% yield with trimethylsilyl chloride and $Et_3N$-$ZnCl_2$ in benzene. The $^1H$ NMR of 132 was identical to that reported for the known compound[53].



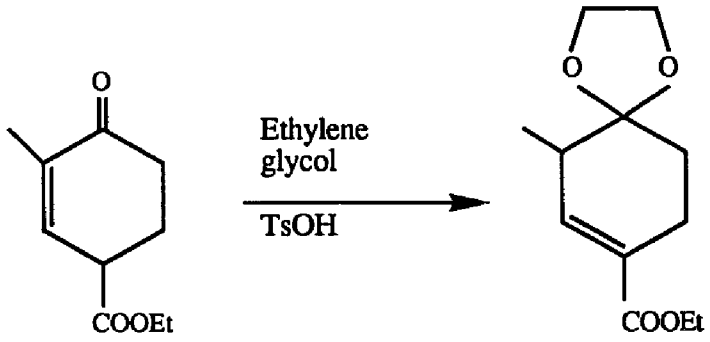

129 130 131 132

The diene 132 was then treated with ethyl acrylate in dry benzene and heated under reflux overnight[53]. The Diels-Alder adduct was directly hydrolyzed by adding 0.5M HCl in THF at room temperature[53] to provide a single product in 87% yield. This has the same boiling point as the known compound and exhibited the spectral properties ($^1$H NMR and IR) in accord with the structure 126.



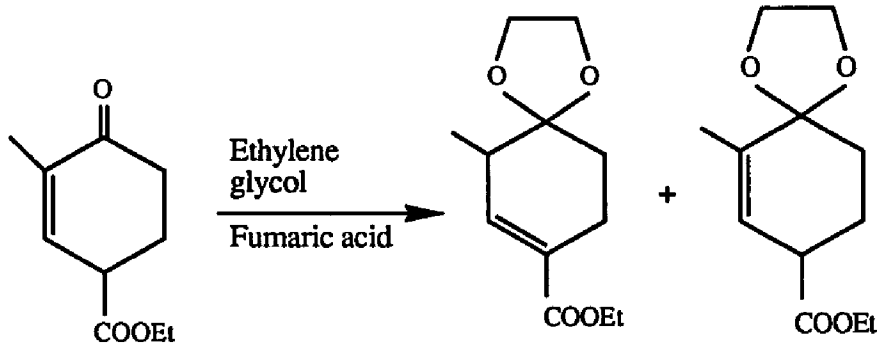

132 124 133 126

Ketalization of 126[55] with ethylene glycol and p-TsOH in benzene resulted in a single UV active compound. The IR spectrum of this compound showed a conjugated ester carbonyl at 1705 cm$^{-1}$ and the proton NMR showed a singlet at 4.1 for ketal hydrogens and a doublet at 1.0 for the methyl group consistent with structure 134. We assumed that during the ketalization, the double bond has isomerized to give the more stable isomer 134. This type of isomerization has been observed for ketalization of the Hagemann's ester[83].




126 134

Double bond isomerization could be minimized by using fumaric acid[56] as the catalyst. Compound 126 on treatment with ethylene glycol, and a catalytic amount of fumaric acid in benzene gave a mixture of two compounds in 1:7 ratio (analytical GC) in 88% yield. Separation of a small sample by preparative gas chromatography and spectral analysis showed that the major compound was the desired ketal 135 and the minor compound was 134. Compound 135 was characterized by its IR (carbonyl resonance at 1730 $cm^{-1}$, for a non conjugated ester) and $^1H$ NMR (methyl was a singlet at 1.75, for a vinylic methyl).

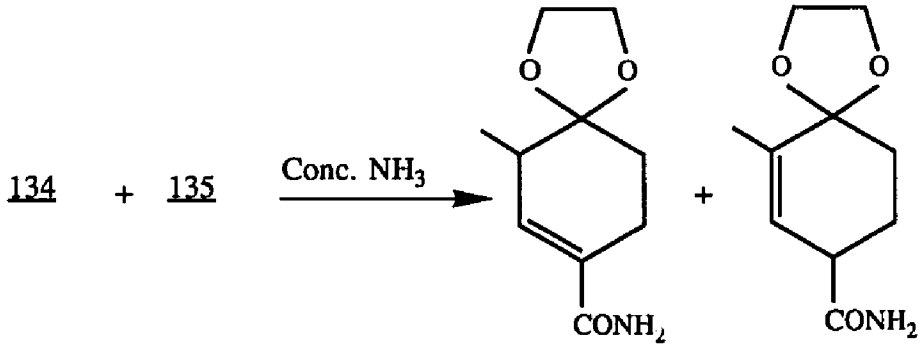



126 134 135

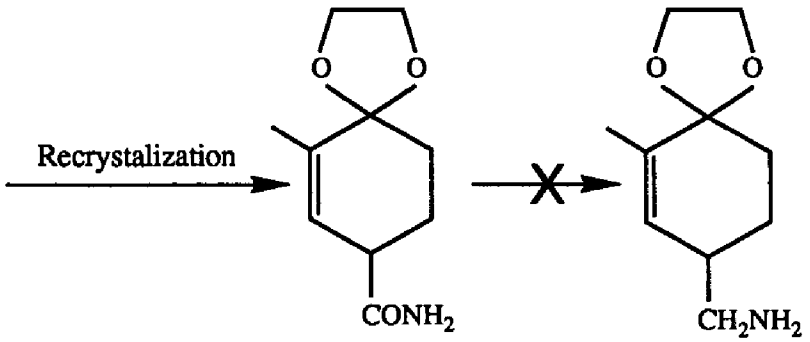
Ketalization was also attempted by Noyori's method[57] at temperatures -23°C, -42°C and -78°C. Gas chromatographic analysis showed that the products were mixtures of compounds 134 and 135 along with a large amount of the unreacted enone ester 126.

Treatment of the mixture of ketals 134 and 135 with concentrated $NH_3$[58] gave a mixture of amides which had two signals for the methyl group (a singlet at 1.7 and a doublet at 1.0). The major product was obtained in 46% yield from the ester after recrystalization with ethyl acetate/hexane and was shown to be the desired amide 137 from its $^1H$ NMR spectrum which had the methyl at 1.70 as a singlet, the ketal at 4.0 as a singlet and the amide protons at 6.2 as a broad singlet and its IR spectrum which had two absorptions at 3540 and 3410 $cm^{-1}$ characteristic for an amide. This compound also gave the correct C, H, and N analysis for structure 137.

The minor product is probably be the conjugated amide 136 resulting from 134, but it never could be purified sufficiently for spectral analysis.




136 137




137 109

The next required step was the reduction of the amide to the amine 109. The amide 137 was treated with a variety of reducing agents but none of them gave the desired amine 109.

a) Refluxing with $LiAlH_4$[58] in dry THF or ether gave a mixture of compounds on TLC.

b) Treatment with $AlH_3$ in THF at 0°C resulted in recovery of the starting material. $AlH_3$ was prepared by the addition of 100% $H_2SO_4$ to $LiAlH_4$ in THF at 0°C following the procedure reported by H. C. Brown[59].

c) Reaction with Lithium trimethoxyaluminohydride in THF at 0°C which was prepared according to H. C. Brown's procedure,[60] by adding anhydrous MeOH to $LiAlH_4$ at 0°C in THF under $N_2$ , also gave the starting material.

d) Treatment with DIBAL in THF at 0°C also resulted in recovery of the starting material.

e) Reaction with sodium borohydride and ethanedithiol[61] in boiling dry THF also gave a mixture of compounds on TLC.

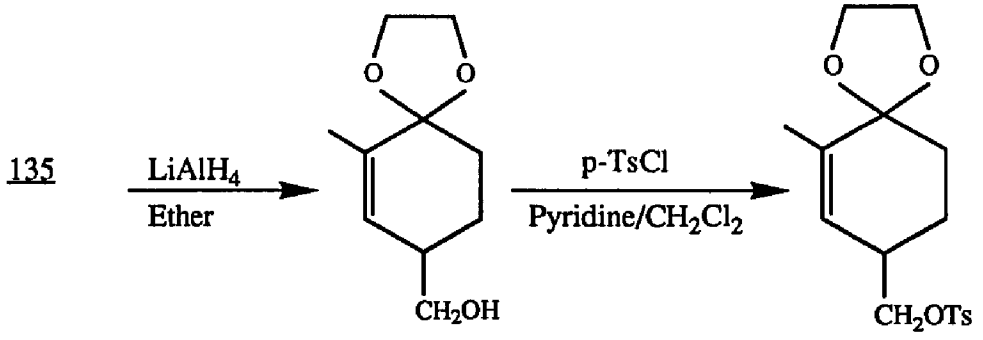
f) Reaction with excess diborane in refluxing THF[62] gave the starting material.

g) Treatment with borane-dimethyl sulfide[63] in refluxing THF resulted in recovery of the starting material.

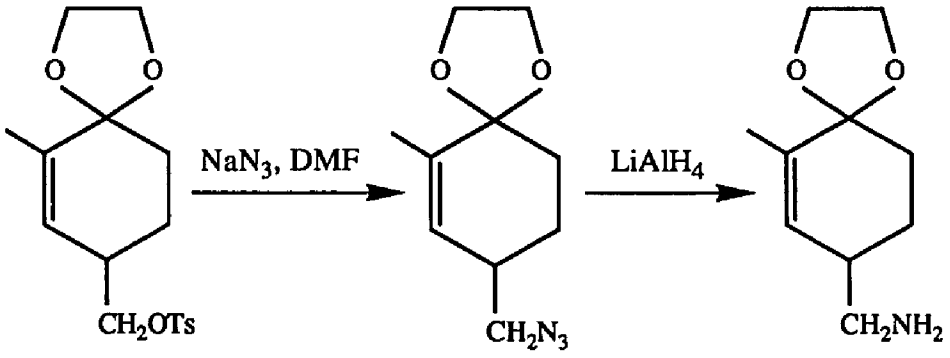
To avoid this problem we thought of using acrylonitrile instead of ethyl acrylate in the Diels-Alder reaction. But unfortunately TLC and GC showed the formation of many compounds.

At this point we decided to go through a different route starting from the mixture of ester ketals. The mixture of compounds 134 and 135 was treated with $LiAlH_4$ at $0^oC$ in dry ether to reduce the ester group to a primary alcohol. The product which was obtained in 73% yield after distillation, had hydroxyl absorption in the IR and the ketal remained unchanged at 4.0, the methyl was a vinylic singlet at 1.75 and the $CH_2$ attached to oxygen was a doublet at 3.55 in the $^1H$ NMR. Hence this compound was identified as the alcohol 138. We think that the conjugated double bond of 134 also got reduced resulting in a saturated compound which was removed during the distillation. The alcohol 138 was treated with p-TsCl in pyridine/$CH_2Cl_2$[64]. TLC of the reaction mixture showed one major product which was obtained in 77% yield after flash chromatography. $^1H$ NMR of this compound showed the presence of the phenyl and the methyl of the tosylate group. This was treated with $NaN_3$ in DMF[64] overnight at $50^oC$, and the azide was obtained in 70% yield after purification by flash chromatography. This compound had the ketal at 3.9 as a singlet, the methylene attached to $N_3$ at 3.15 as a doublet and the

olefinic proton at 5.4 in the $^1H$ NMR and an absorption 2100 $cm^{-1}$ for the azide group in the IR, and gave correct elemental analysis for the structure 140. This azide was then reduced with $LiAlH_4$ in ether[65] to obtain the amine 109 in 98% yield. The amine showed two absorptions at 3300 and 3380 $cm^{-1}$ corresponding to a primary amine and no azide absorption in the IR. The proton NMR of 109 gave a singlet for the ketal at 4.0, a doublet for the methylene attached to nitrogen at 2.6, and a singlet for the olefinic proton at 5.6. The acetyl derivative of the amine gave correct elemental analysis for C, H and N.




138 139



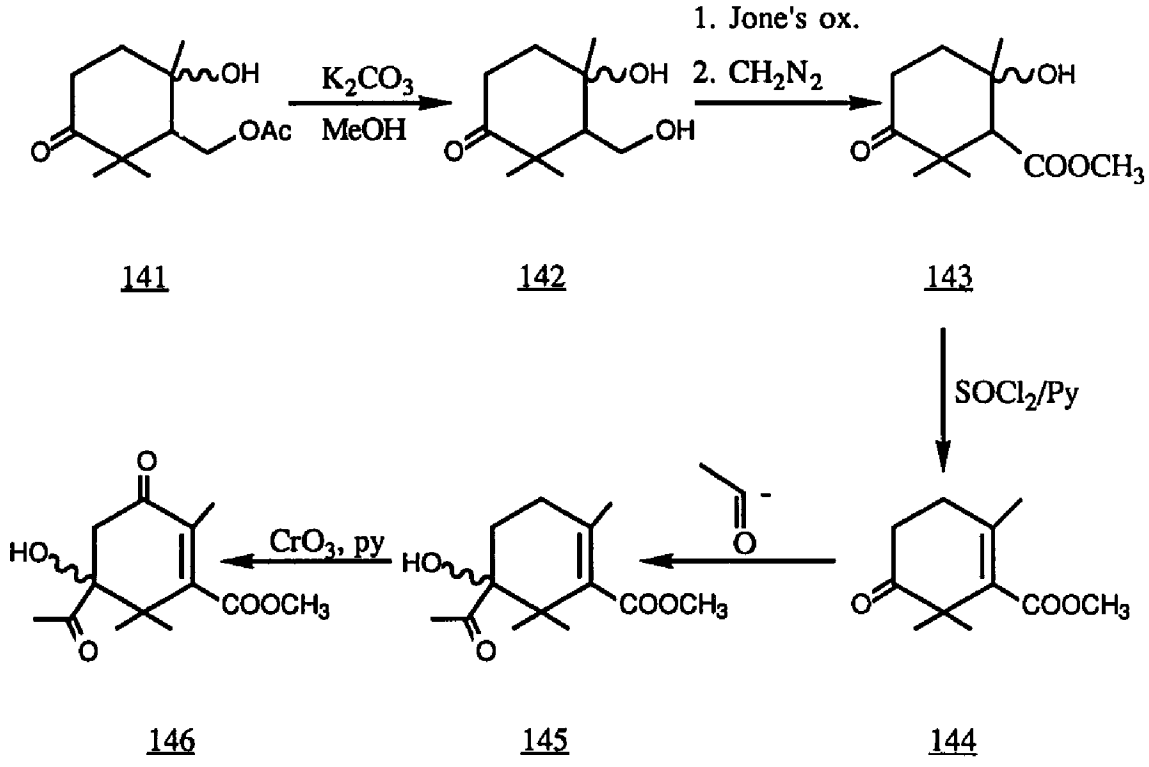

139 140 109

(2) Studies on the A-ring synthon of taxol, cephalomannine and baccatin III.

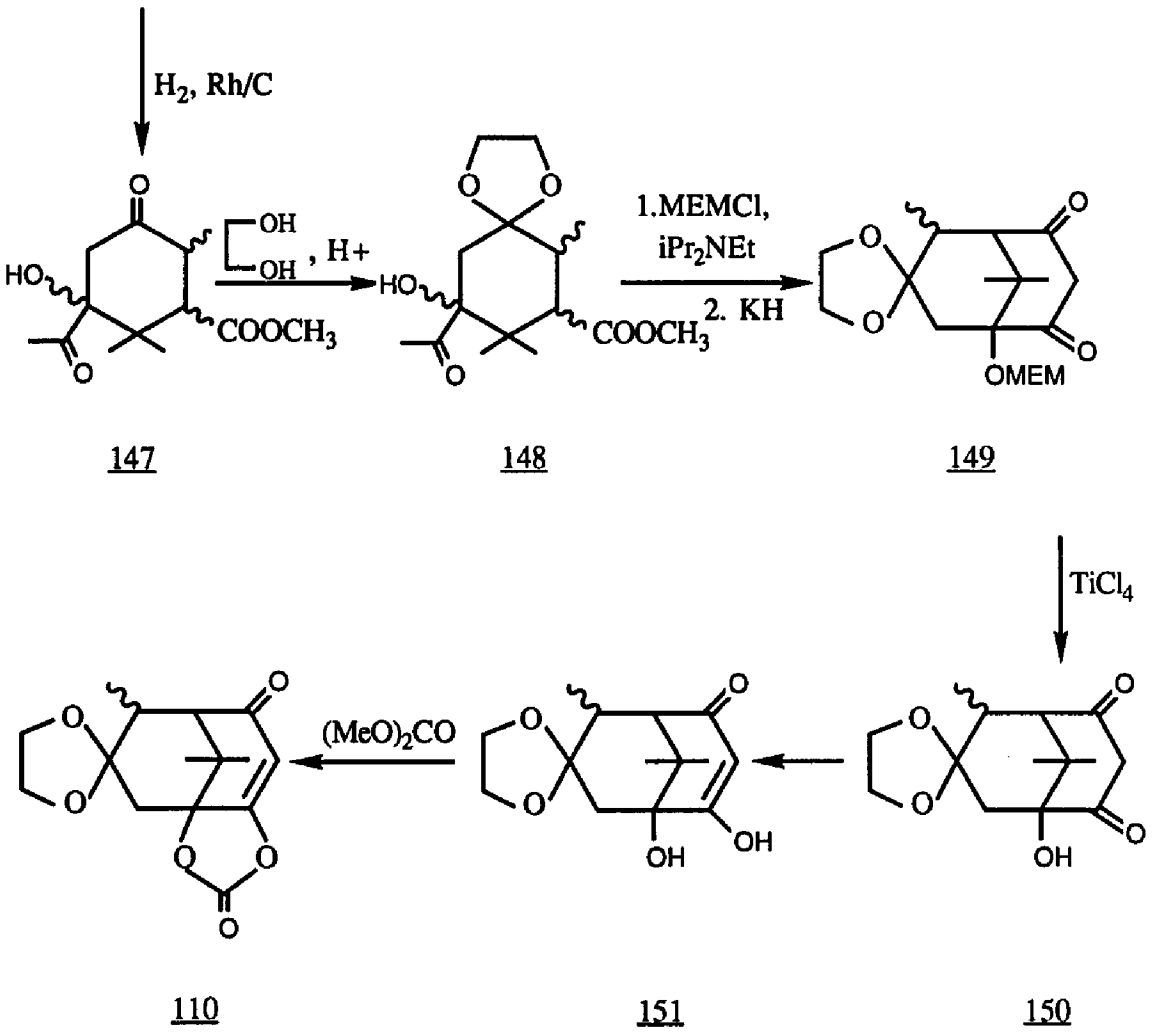
The second half of this work is directed towards the synthesis of the molecule 141, an A-ring synthon suitable for taxol, cephalomannine and baccatin III.

We expect to be able to convert ketone 141 to the A/B ring synthon 110.

Proposed strategy for the construction of taxol A/B ring synthon from 141.




141 142 143 144 145 146

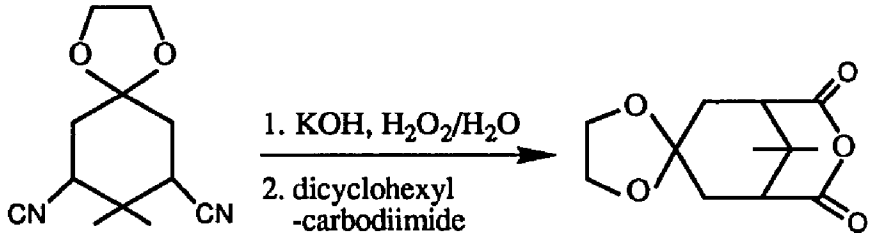



147 148 149

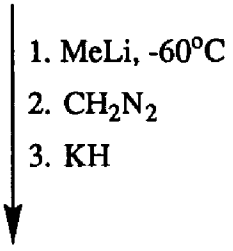
110 151 150

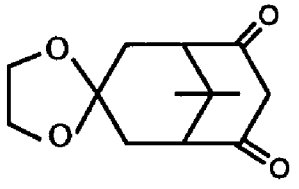
Deprotection of the acetate group of 141 followed by oxidation of the resulting primary hydroxyl group and esterification should afford the ester 143 which on treatment with thionyl chloride in pyridine would dehydrate to give 144. Addition of an acetyl anion equivalent to the carbonyl carbon of 144 should afford the α-hydroxy-keto ester 145. Allylic oxidation, followed by reduction of the double bond should provide the α-hydroxy-diketo ester 147. The stereochemistry of 147 is not important, the ester group is expected to epimerize prior to cyclization; in addition, the methyl group at (latent) C-12 will eventually be on a bouble

bond. Since the acetyl group would be hindered by the gem-dimethyl group, selective ketalization should give the ketal acid 148. Protection of the hydroxyl group as a MEM ether, base catalyzed cyclization and deprotection of the hydroxyl group should then give the desired 1-hydroxy-bicyclo(3.3.1)nonane-2,4-dione system 150. S. Blechert[66] has demonstrated this type of base catalyzed cyclization starting with compound 152 to give the bicyclo[3.3.1]nonane-dione system 154 as shown.




152 153

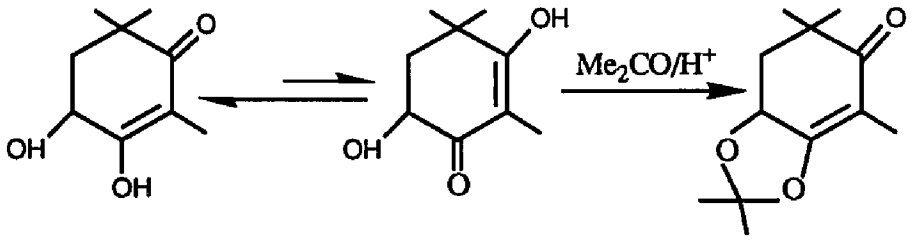



154

The hydroxyl group which is protected as a MEM ether should not interfere with the cyclization. 150 can enolize in two directions. It is conceivable that the hydroxyl group might enhance the formation of the enol 151 and the formation of the cyclic carbonate should fix the direction of the enolization. Hence 150 on treatment of $(MeO)_2CO/H^+$ should give the carbonate 110.

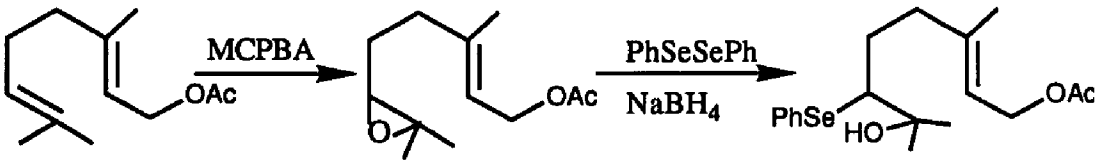
Formation of a cyclic carbonate involving a hydroxyl group on an α-carbon is supported by the known formation of the cyclic ketal 157 of the hydroxy-diketone 155 which was shown by E. Widmer et al[67].



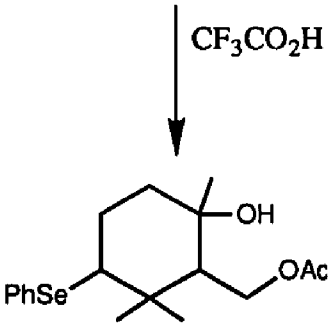

155 156 157

Geranyl acetate cyclizations

The starting material for the A-ring synthon 141 was chosen to be geranyl acetate. This was converted to the selenide 161 following the known procedure of Kametani and coworkers[40]. Geranyl acetate was selectively epoxidized with m-chloroperbenzoic acid and the resulting epoxide was treated with phenylselenide anion. Acid treatment of compound 160 gave the selenide 161. Comparison of $^1H$ NMR and IR indicated that compounds 159, 160 and 161 were same as the known compounds.

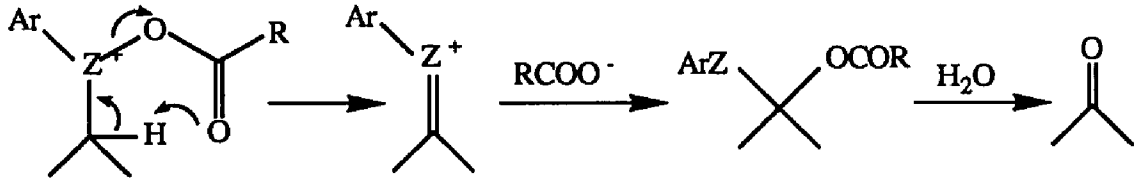



158 159 160



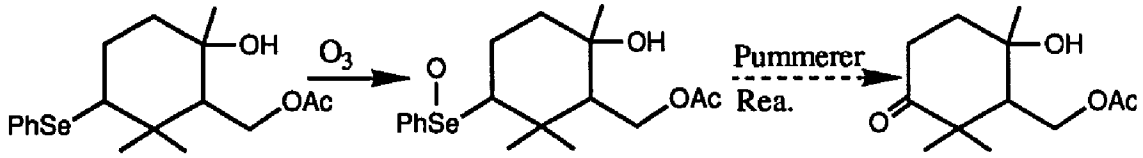

161

We expected to use the selenophenyl group as a carbonyl precursor. This transformation is well documented for sulfoxides and selenoxides as the Pummerer reaction[82]. It entails the treatment of a selenoxide/sulfoxide with an acylating agent to afford a geminal acyloxy sulfide, and subsequent hydrolysis to form a carbonyl group.



We were unable to oxidize 161 to the selenoxide by using $H_2O_2$ in MeOH according to the procedure reported by Kametani. In our hands yields were very poor because of the difficulty of isolation of the selenoxide from the aqueous layer. This reaction was also attempted with sodium metaperiodate[68] in MeOH at room temperature and with MCPBA[68] in $CH_2Cl_2$ at -78°C. However most of the selenoxide formed remained in the aqueous layer.

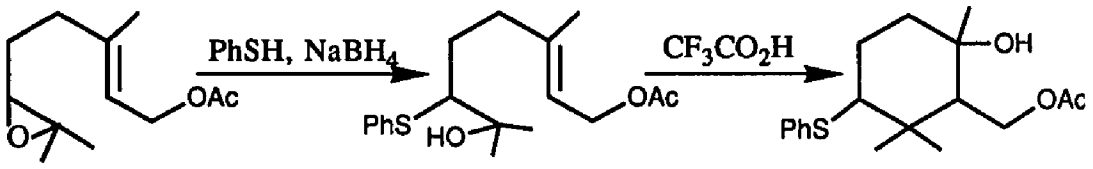
The selenide could be oxidized to the selenoxide 162 in 95% yield by passing $O_3$[69] at -78°C in dry $CH_2Cl_2$, a procedure which does not involve an aqueous phase. This compound gave the melting point and spectral properties identical to the known compound[40].




161 162 141

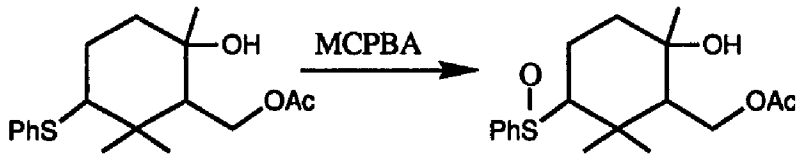
We expected the Pummerer rearrangement would convert the selenoxide to the desired ketone 141. This reaction was attempted with acetic anhydride and sodium acetate in refluxing tetrahydrofuran[70]. However the ketone could not be isolated. The results were the formation of the parent selenide or decomposition of the selenoxide. Treatment of the selenoxide with trifluoroacetic anhydride and 2,6-lutidine in acetonitrile[71] resulted in recovery of the starting material.

At this point we decided to prepare a phenyl sulfide instead of the phenyl selenide, expecting that the Pummerer rearrangement would be easier with the more stable sulfoxide.




159 163 164

Geranylacetate epoxide 159 was treated with thiophenol and sodium borohydride in ethanol to give 163 in 93% yield. The sulfide 163 gave similar IR (namely 3610 and 1720 $cm^{-1}$) and NMR (four singlets for methyls at 1.26, 1.35, 1.7 and 2.05, a doublet of doublet at 3.1 for the hydrogen attached to the carbon bearing the phenyl sulfide, a multiplet at 4.5 for the $CH_2$ group attached to the acetate, a multiplet for the olefinic hydrogen and multiplets at 7.35 and 7.55 for the phenyl hydrogens) spectra to 160, the corresponding selenide obtained using diphenyl diselenide instead of thiophenol. This was cyclized to 165 with trifluoroacetic acid in $CH_2Cl_2$ at 0°C in 75% yield. This product also showed IR (3600 and 1720 $cm^{-1}$) and NMR (four singlets for the methyls at 0.99, 1.25, 1.35 and 2.1, a doublet of doublet at 3.0 for the hydrogen attached to the carbon bearing the phenyl sulfide, a multiplet at 4.4 for the $CH_2$ group attached to the acetate, a multiplet at 7.3 for the phenyl hydrogens) spectra similar to the corresponding selenide 161. GC-mass spectrum of this gave the correct molecular weight (M+= 322) and the corresponding fragment ions such as 244 (M - $C_6H_6$), 153 (M - PhS, $CH_3CO$, OH) and 109 (PhS).



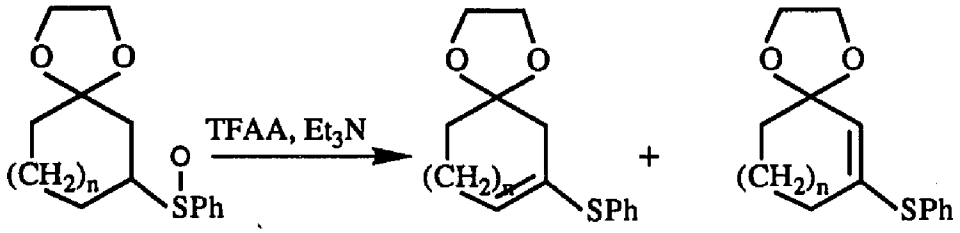

164 165

Pummerer rearrangement

The sulfide thus obtained was then oxidized using m-chloroperbenzoic acid in $CH_2Cl_2$ at -78°C[68].The product which was isolated in 92.9% yield showed a similar IR and $^1H$ NMR to the selenoxide 162 and gave correct elemental analysis for the structure 165. Pummerer rearrangement was tried on the sulfoxide 165 using a variety of reagents but the rearrangement was again unsuccessful in our system.

a) Refluxing in $Ac_2O$/NaOAc in THF[70] resulted in decomposition of the sulfoxide (formation of many spots on TLC).

b) Peter Bakuzis[72] has reported that treatment of cyclic sulfoxide 166 with trifluoroacetic anhydride in triethylamine gives vinyl sulfides 167 and 168. Varying the strength and steric size of the bases (triethyl amine, pyridine, 2,6 lutidine) or the reaction temperature (-40°C to room temperature) has not significantly influenced the product ratio.




166

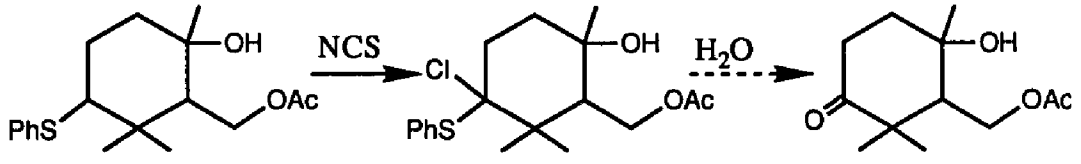
| | 167 | | 168 |
|---|---|---|---|
| n = 1 | 1.3 | : | 1 |
| n = 0 | 1 | : | 4.6 |

However when the sulfoxide 165 was treated with trifluoroacetic anhydride and 2,6 lutidine in acetonitrile the unreacted starting material was isolated.

c) Treatment of 165 with trimethylsilyl triflate in triethylamine[73] in $CH_2Cl_2$ at 0°C also resulted in recovery of the starting material.

Halogenation

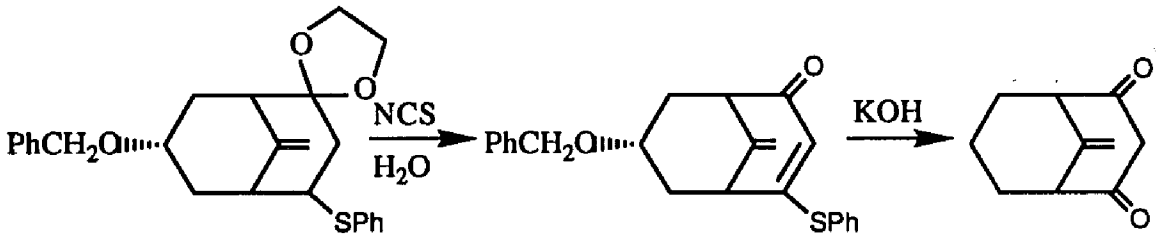
Then we turned to chlorination of the sulfide 164 expecting that the chlorination would give the compound 169 which would easily undergo hydrolysis to the ketone 141.




164 169 141

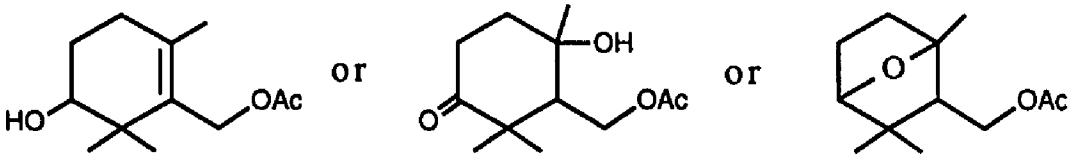
The sulfide 164 was treated with N-chlorosuccinimide in dry $CCl_4$[74]. TLC showed the formation of a new UV active compound, but this compound could not be hydrolysed either with $NaHCO_3$ or with $HgCl_2$ and $CdCO_3$ in $H_2O$ as we had planned.

H. Kakisawa and coworkers[75] have accomplished a similar rearrangement of the sulfide 170 to the ketone 172 with wet NCS.



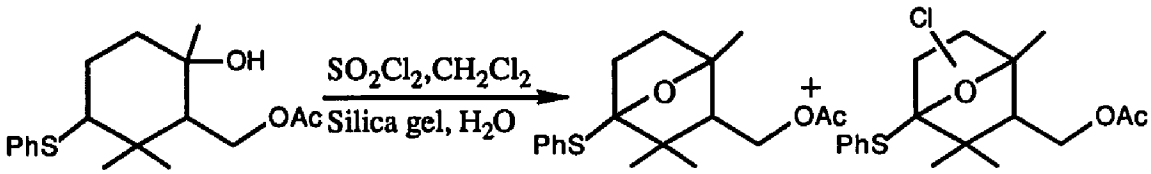

170 171 172

Consequently the sulfide 164 was treated with NCS in $CCl_4$ in the presence of water and TLC showed the formation of a new UV inactive compound. The $^1H$ NMR of this compound showed loss of the PhS group and absence of any olefinic protons, but unfortunately this reaction could not be repeated for a complete analysis of the product. The structure of this compound can be any be of the following.



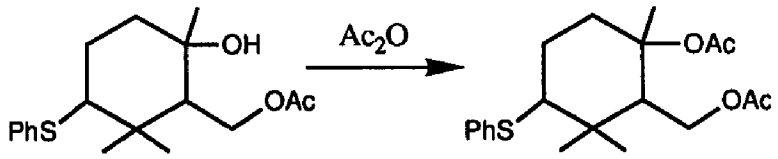
In searching for a mild procedure for converting the sulfide to the ketone 141 we came across the work of D. T. W. Chu[79] and coworkers. They have reported that sulfuryl chloride reacts with phenylsulfides to yield α-chlorophenyl sulfides which upon treatment with water in the presence of silica gel give the corresponding aldehydes and thiophenol.

This reaction was attempted using one equivalent of sulfurylchloride in $CH_2Cl_2$ at 0°C. The GC-mass spectrum of this product showed the formation of two compounds of molecular weight 320 and 354, in 6:1 ratio. A small sample of this mixture was separated by preparative HPLC and spectroscopic analysis was done. Both compounds did not have any hydroxyl absorptions (IR) or any double bonds (IR and NMR) but both had the PhS group (IR and NMR). The methylene attached to the acetate appeared as a doublet of AB quartets due to splitting by a proton on the adjacent carbon. The hydrogen atom (around 3 ppm) on the carbon bearing PhS group was no longer present. The GC mass spectrum of the minor product showed in addition, the presence of a Cl atom. Based on this spectral evidence the two compounds formed were proposed to be 173 (the major) and 174 (the minor). In addition the minor product showed a doublet of doublet at $\delta = 4.56$; consistent with Cl-CH-$CH_2$-. The major compound gave correct elemental analysis for C, H and S. The minor compound also gave correct C, H and S analysis but the Cl analysis was slightly off from the calculated value. We think that the sulfide underwent α-chlorination first, to form an 2-chlorosulfide and then the OH group displaced the Cl to form the cyclic ethers.




164 173 174

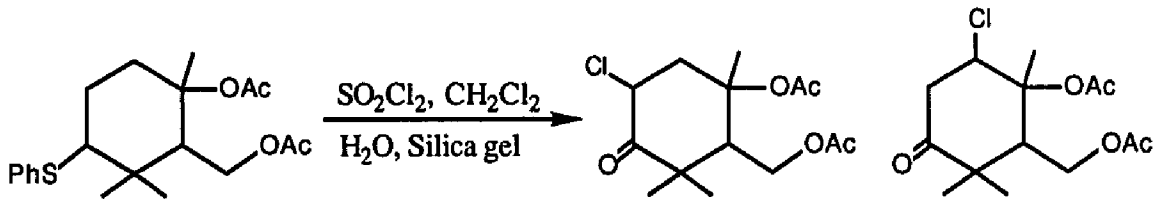
We thought that the solution to this problem would be to protect the tertiary hydroxyl group before treating with sulfuryl chloride. Thus the OH group was protected as an acetate by using acetic anhydride and triethyl amine in $CH_2Cl_2$ in the presence of a catalytic amount of DMAP[80]. NMR (singlets at $\delta$ = 1.05, 1.38, 1.50 for the three methyls, singlets at $\delta$ = 1.99 and 2.09 for the two acetate groups, doublet of doublet at 2.97 for the hydrogen on the carbon attached to PhS, an AB quartet for the $CH_2$ attached to acetate and multiplets at 7.30 and 7.45 for the phenyl group) of this product was in accord with the structure 175.




164 175

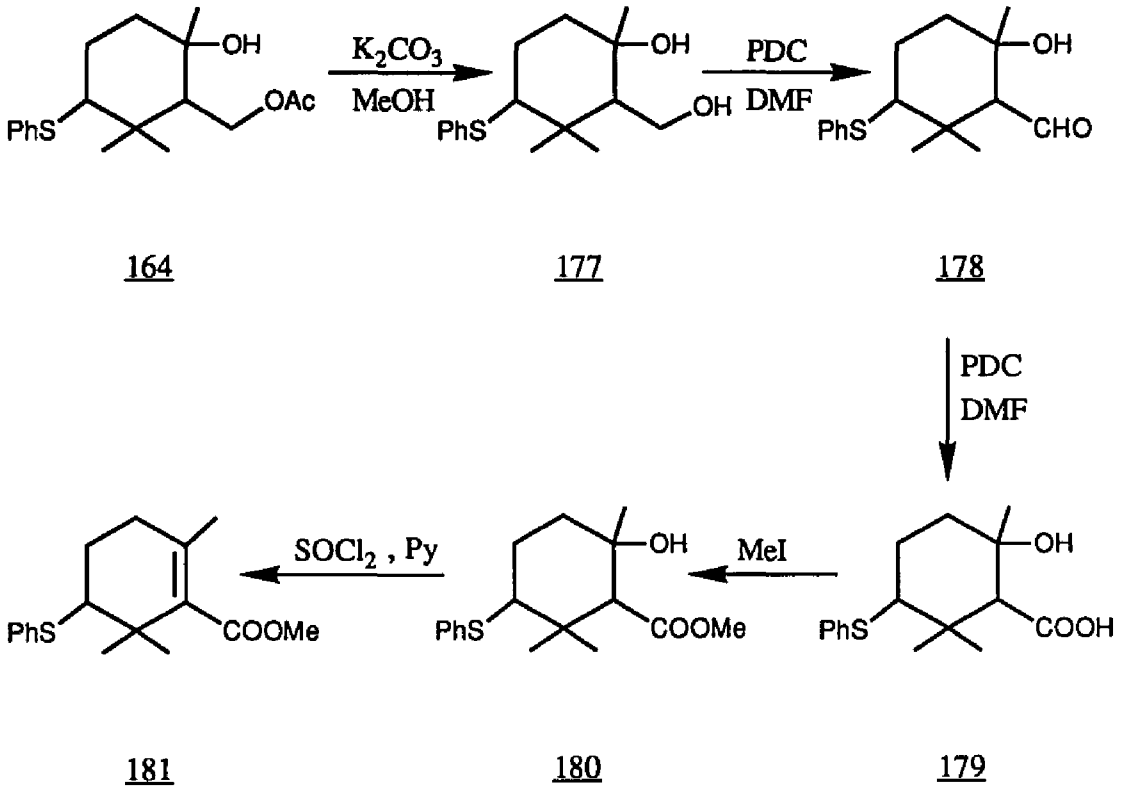
The chlorination was then repeated with the diacetate 175 under the same conditions. A new product was formed (TLC) and was hydrolysed by passing through a water deactivated silica gel column[79]. This time the product could be hydrolyzed and gave one major compound in 86% yield

after flash chromatography. $^{13}C$ NMR of this compound showed a new carbonyl group at 204.76 and loss of the PhS group. Two acetate groups remained unchanged (two singlets in the NMR at $\delta$ = 2.04 and 2.10). A doublet of a doublet for one proton appeared in the $^{1}H$ NMR at 4.78. This was considered to be a hydrogen on a carbon bearing a chlorine. After purification by HPLC, this compound gave correct elemental analysis for carbon and hydrogen for the structure 176 but the Cl analysis was slightly higher than the calculated value. The GC-mass spectrum did not give the correct molecular weight for the structure 176 probably due to decomposition at high temperature. We expected that this compound could readily be converted to 141 by treating with Zn in glacial acetic acid. However there was no change in $^{1}H$ NMR even after stirring overnight at room temperature. Consequently we think that 176a is a possibility; although any mechanism for its formation would be unusual.




175 176 176 a

Upon assumption that the tertiary hydroxyl group might be the cause of some difficulty, we decided to leave the Pummerer rearrangement to a later stage and operate on the other side of the molecule: that is eliminate the tertiary hydroxyl group to make the double bond and convert the primary acetate to an ester group. Conversion of the acetate to an ester group should in fact, ease elimination of the OH group and lead to a single product.




164 177 178

181 180 179

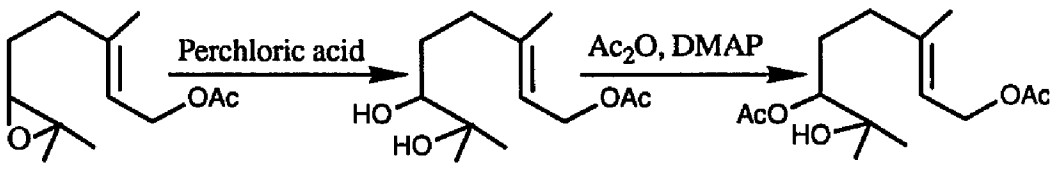
The hydroxyl group was deprotected with $K_2CO_3$ in MeOH in 92% yield to give 177 . IR and NMR of 177 showed the disapearance of the acetate group. The next problem was to oxidize the alcohol to an acid without touching the sulfide. In literature we found that PDC[76] does not oxidize sulfides. On a small scale, the alcohol 177 was treated with PDC in DMF and the aldehyde 178 was formed in 97% yield after stirring for 12 hours at room temperature. This compound had an absorption at 1700 $cm^{-1}$ in the IR spectrum and a proton at 10.0 in the $^1H$ NMR spectrum. 178 was then treated with PDC in DMF again and stirred overnight to give a new product in 47% yield. This product showed the presence of a COOH group in the IR at 3600-2000 (br) $cm^{-1}$ and was assumed to be the acid 179 . This was esterified using MeI and $NaHCO_3$ in DMF to give 180[77] in 97% yield. The structure of 180 was confirmed by its IR (3600, 2980, 1720,

1580 $cm^{-1}$) and NMR (a singlet at 1.2 for gem dimethyl, a singlet at 1.4 for the methyl, a singlet at 3.7 for the COOMe group, a doublet of doublet at 2.8 for the hydrogen attached to the carbon bearing the PhS group and a multiplet at 7.35 for the phenyl group) . A GC-mass spectrum of this gave the correct molecular weight ($M^+$ = 308). Compound 180 was dehydrated with thionyl chloride in pyridine[78] to give 181 in 68% yield which showed the correct molecular weight ($M^+$ = 290) in its GC mass spectrum. Its IR and NMR was in accord with the structure 181.

Unfortunately the acid 179 could not be prepared on large scale. Most of the compound remained in the aldehyde stage and attempts at longer reaction times and higher reagent/substrate ratio resulted in formation of complicated mixture of products.

An Alternate Cyclization Route

Since the conversion of the sulfide to a ketone gave problems, we thought of making compound 183, so that after cyclization we would have an O instead of a S. The role of S or Se in stabilizing the tertiary carbonium ion by neighbouring group participation could possibly be taken by the neighbouring acetate group.




164 182 183

The geranyl acetate epoxide 164 was opened with perchloric acid in diglyme[81] to give the diol 182 which showed a hydroxyl absorption in the IR. This was selectivelly acetylated with $Ac_2O$ in $CH_2Cl_2$ in the presence of DMAP at room temperature. The structure of 183 was confirmed by IR (absorptions at 3600 and 3500 $cm^{-1}$ for the hydroxyl group and at 1730 and 1740 $cm^{-1}$ for the two acetates) and $^1H$ NMR ( a singlet for 6H at 1.25 for the gem dimethyl, a singlet at 1.7 for the vinylic methyl, two singlets at 2.05 and 2.15 for the two acetates, a singlet for one proton at 2.6 for the hydrogen attached to the carbon bearing one of the acetate groups, a doublet at 4.6 for the $CH_2$ attached to one of the acetate groups and a triplet at 5.35 for the olefinic hydrogen). Cyclization was tried with a number of reagents but the reaction was unsuccesful.

a) Treatment of 183 with $BF_3(OEt)_2$ at $0^oC$ for 1-5 hours resulted in recovery of the starting material. Attempts at warming the reaction mixture to room temperature gave many spots on TLC .

b) Treatment of 183 with trifluoroacetic acid at $0^oC$ for 2-4 hours also resulted in recovery of the starting material.

c) Attempts at adding $SnCl_4$ to 183 at $0^oC$ resulted in formation of a brown polymer.

Work for the future

(a) The α-chloro ketone 176 which we were unable to reduce with Zn may be reduciable with $Ca/NH_3$, $SmI_2$ or $Cr^{II}$ .

(b) The compound 173 may give compound 144 by first converting the $CH_2OAc$ group to a $CO_2Me$ group and then treating with a base to open the epoxide[84].

## Chapter III EXPERIMENTAL

Melting points (uncorrected) were determined in open capillaries in a Thomas Hoover Uni melt apparatus. Routine proton spectra were obtained in the indicated solvent on a Varian EM 360 nuclear magnetic resonance (NMR) spectrometer. High field proton and $^{13}C$ spectra were determined on IBM Bruker WP 200 SY and GE-QE-300 instruments. Chemical shifts are reported in ppm downfield from tetramethylsilane (d). Splitting patterns are designed as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants are given in Hertz. Infrared spectra (IR) were recorded on a Perkin-Elmer IR 598 instrument. Gas-liquid chromatography (GC) was performed with a Varian Aerograph 920 thermal conductivity instrument on either a 10 ft by 1 in. column packed with 20% silicone oil DC 710 on Chromosob W (60-80 mesh) or a 10 ft by 1/4 in column packed with 20% Apiezon L on Chromosorb W. High performance liquid chromatography (HPLC) was conducted with a Waters Associates (Milford, MS) system consisting of two 4-mm by 30-cm m-Porasil silica columns in series, a 6000 SDS pump, U6K injector, and Model 401 differential refractometer. Flash chromatography was carried out on E. Merck silica gel (230-400 mesh) according to the Still procedure. Some separations were efficiently carried out on a Chromatotron (Harrison) apparatus with rotating plates coated with E. Merck Art. 7749 silica gel. Thin layer chromatography (TLC) was carried out on Machery-Nagel (MN) precoated Polygram Sil N/HR UV silica plates. GC-MS analyses were performed by Dr. D. C. Locke at Queens College on a Hewlett Packard 5988A GC/MS instrument. Dry solvents were used where required. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Methylene chloride, acetonitrile, triethylamine, N,N-dimethyl

formamide, benzene, dimethyl sulfoxide ($Me_2SO$) were distilled from calcium hydride. Pyridine was refluxed over potassium hydroxide. Chloroform was distilled from phosphorous pentoxide and stored over molecular sieves. Acetic anhydride, boron trifluoride etherate were distilled before use. Microanalyses were performed by Galbraith Laboratories, Knoxville, TN.

Preparation of 3-methyl-4-methoxybenzyl alcohol 120. (Ref. 50)

3-Methyl-4-methoxybenzaldehyde (10.0 g, 0.066 mol) was dissolved in 100 mL methanol and cooled to 0°C. This was mixed with a solution of sodium borohydride (3.2 g, 0.10 mol) in 50 mL of methanol during a period of 5 min, and stirring was continued for 2 h at 0°C. The reaction mixture was concentrated under reduced pressure to give a mixture of an oil and a solid. This was diluted with 50 mL of water and extracted with methylene chloride (6x25 mL). The combined organic extracts were dried over sodium sulfate and concentrated to give a colourless oil which showed only one component on TLC (silica gel, 1:1 hexane/EtOAC). This liquid was distilled at 108°C/0.7 mm Hg to afford 8.42 g (83%) of 120 as a clear liquid. IR ($CCl_4$): 3600 (br), 2950 (s), 1600 $cm^{-1}$. $^1H$ NMR (60 MHz, $CDCl_3$): 6.7-7.2 (m, 3 H), 4.55 (s, 2 H), 3.85 (s, 3 H), 2.25 (s, 3 H), 2.05 (s, 1 H).

2-Methyl-1-methoxy-4-(hydroxymethylene)cyclohexa-1,4-diene 121. (Ref. 50)

3-Methyl-4-methoxybenzyl alcohol 102 (9.0 g, 0.044 mol) was dissolved in THF (30 mL) and was added drpowise to a mixture of liquid ammonia (150 mL) and ethanol (100 mL). To this mixture was added sodium (8.0 g, 0.35 gatom) in small portions and then $NH_4Cl$ (15 g). The reaction mixture was left overnight for evaporation of ammonia, and the residual solvents were removed under reduced pressure. The residue was dissolved in methylene chloride (200 mL), and the organic layer was washed with water (2x50 mL), dried and evaporated to give the crude product. Vacuum distillation at 70°C/0.2 mm Hg afforded 4.3g (62%) of 121. IR ($CCl_4$): 3600 (br), 2808 (m), 1690 (m), 1658 (w), 1380 (s) $cm^{-1}$. $^1H$ NMR (60 MHz, $CDCl_3$): 5.65 (brs, 1 H), 4.5 (brs, 1 H), 4.05 (s, 2 H), 3.55 (s, 3 H), 2.75 (s, 4 H), 1.65 (s, 3 H).

10-Methyl-8-hydroxymethylene-1,4-dioxaspiro[4.5]dec-7-ene 122.

A mixture of enol ether 121 (3.8 g, 0.02 mol) and ethylene glycol (7.0 mL, 0.08 mol) in THF (20 mL), cooled in an ice bath, was added $BF_3.OEt_2$ (0.7 mL, 0.005 mol) via syringe under nitrogen. After stirring for 20 min at 0°C, the reaction mixture was poured into cold saturated sodium bicarbonate solution (15 mL) and extracted with methylene chloride (3x30 mL). The combined organic extracts were washed with water (50 mL), dried and concentrated to give the crude product. Vacuum distillation afforded 3.5 g (95%) of 122 at 95°C/0.25 mm Hg as a thick oil. IR ($CCl_4$):

2920, 2860, 1115, 1058 $cm^{-1}$. $^1H$ NMR (60 MHz, $CDCl_3$): 5.5 (br s, 1 H), 4.0 (s, 6 H), 3.7 (s, 1 H), 1.6-2.4 (m, 5 H), 1.0 (d, 3 H).

Preparation of Na salt of 3-hydroxymethylene-2-butanone 130.

The procedure of ref. 52 was modified by the use of NaH rather than NaOEt.
NaH (dry, 97%) (33.4 g, 1.4 mol) was covered with absolute ether (1 L) and the mixture was well cooled in an ice bath. To this was added an equally well cooled mixture of 2-butanone (100 g, 1.4 mol) and ethyl formate (102 g, 1.4 mol) with continuous stirring during 2 h. The resulting mixture was kept overnight, then filtered with suction and washed with ether. The yield of the Na salt was 160 g(90%).

Preparation of 4-methoxy-3-methyl-3-butene-2-one 131. (Ref.54)

The Na salt of 3-hydroxymethylene butanone (58.0 g, 0.47 mol) was dissolved in 120 mL of distilled water. Dimethyl sulfate (48.0 g, 0.38 mol) was added dropwise to this solution. The reaction mixture was heated at 60°C-70°C for 2 h and extracted with ether. Combined ether extracts were dried over sodium sulfate and concentrated under reduced pressure. The remaining liquid was distilled at 55°C-60°C/3.0-3.5 mm Hg to give 35.0 g (65%) of 131. IR ($CCl_4$): 2940, 2928, 1735, 1658, 1380 $cm^{-1}$. $^1H$ NMR (60 MHz, $CDCl_3$): 1.7 (s, 3H), 2.2 (s, 3H), 3.9 (s, 3H), 7.25(br s, 1H).

Preparation of 1-Methoxy-2-methyl-3-trimethylsiloxy-1-3-butadiene 132. (Ref.53)

Anhydrous $ZnCl_2$ (fused in the hood and powdered under $N_2$) (0.37 g, 2.75 mmol) was added to triethylamine (31.2 g, 0.31 mol) and the system was stirred for 1 h at room temperature under $N_2$. This was mixed with a solution of 4-methoxy-3-methyl-3-butene-2-one (10.3 g, 0.09 mol) in 22 mL of benzene followed by trimethylchlorosilane (19.52 g, 0.18 mol). The system was stirred vigorously and heated at 40°C overnight. After being cooled, the reaction mixture was poured into 250 mL of ether and the white solid was filtered. The filtrate and the combined ether washings were concentrated in vacuo to afford a brown residue. Distillation at 60°C-65°C/5 mm Hg afforded 9.33 g (70%) of 132. (Lit. bp. 45°C-49°C/5 mm Hg) $^1H$ NMR (60MHz, $CDCl_3$): 0.20(s, 9H), 1.70(s, 3H), 3.67(s, 3H), 4.17(s, 1H), 4.28(s, 1H), 6.50(br s, 1H).

Preparation of ethyl-3-methylcyclohex-2-en-4-one-1-carboxylate 126.

A solution of 132 (4.9 g, 0.026 mol) and ethyl acrylate (5.21 g, 0.052 mol) in 30 mL of benzene was heated under reflux for 24 h. The cooled solution was treated with 10 mL of 0.5 M HCl in THF (50 mL) and stirred for 3 h at room temperature, then diluted with distilled water and extracted with ether. Ether extracts were washed with water and with saturated sodium bicarbonate and dried over sodium sulfate. The ether layer was concentrated under reduced pressure and the residue was distilled at 92°C-94°C/1-1.5 mm Hg to give 1.0 g (87%) of 126. (lit. bp 117°C/2.5

mm Hg). IR ($CCl_4$): 1680, 1730 $cm^{-1}$. $^1H$ NMR (60 MHz, $CDCl_3$): 1.3 (t, 3 H), 1.75 (s, 1 H), 2.3 (4 H), 3.3 (br s, 1 H), 4.2 (q, 2H), 6.6 (br s, 1 H).

Ketalization of 126 with p-toluenesulfonic acid

Compound 126 (1.0 g, 5.0 mmol) in 20 mL of benzene was added ethylene glycol (1.84 g, 27.0 mmol) followed by p-toluenesulfonic acid (0.095 g, 0.50 mmol). The reaction mixture was refluxed overnight with azeotropic removal of water. After cooling to room temperature the reaction mixture was poured onto anhydrous potassium carbonate and filtered and then concentrated in vacuo. Compound 134 (1.0 g, 88%) was obtained as a thick oil. $^1H$ NMR (60 MHz, $CDCl_3$): 1.0 (d, 3H), 1.3 (t, 3H), 1.9 (4 H), 2.3 (br s, 1 H), 4.1 (s, 4 H), 4.2 (q, 2 H), 6.7 (s, 1 H). IR ($CCl_4$): 1705 $cm^{-1}$.

Ketalization of 126. (Ref. 56)

A mixture consisting of 126 (1.0 g, 5.0 mmol), 20 mL benzene, ethylene glycol (1.84 g, 27.0 mmol) and fumaric acid (0.058 g, 0.5 mmol) was refluxed with azeotropic removal of water for 3 days. After cooling to room temperature the reaction mixture was poured onto anhydrous potassium carbonate and filtered and then concentrated in vacuo. Distillation at 115°C/1.5 mm Hg gave 1.0 g of 134 and 135 in 1:7 ratio (Anal. GC). 134. $^1H$ NMR (60 MHz, $CDCl_3$): 1.0 (d, 3H), 1.3 (t, 3H), 1.9 (4 H), 2.3 (br s, 1 H), 4.1 (s, 4 H), 4.2 (q, 2 H), 6.7 (s, 1 H). IR ($CCl_4$):

1705 $cm^{-1}$. 135. $^1H$ NMR (60 MHz, $CDCl_3$): 1.3 (t, 3 H), 1.75 (s, 3 H), 1.9 (4 H), 3.15 (br s, 1 H), 4.1 (s, 4 H), 4.2 (q, 2 H), 5.8 (s, 1 H). IR ($CCl_4$): 1730 $cm^{-1}$.

Reaction of 134 and 135 with conc. ammonia.

A suspension of the mixture containing 134 and 135 (0.5 g, 2.21 mmol) in concentrated ammonia (2 mL) was rapidly stirred overnight at room temperature. The solution was extracted with methylene chloride and the combined extracts were dried over potassium carbonate and concentrated under reduced pressure. The resulting solid was recrystallized with ethyl acetate and hexane to give 137 as a white solid (0.2 g, 46%), mp 122°C-123°C. IR ($CCl_4$): 3540, 3410, 1670, 1590 $cm^{-1}$. $^1H$ NMR (60 MHz, $CDCl_3$): 1.7 (s, 3 H), 1.9-2.0 (br, 4 H), 3.0 (br s, 1 H), 4.0 (s, 4 H), 5.7 (s, 1 H), 6.2 (br s, 2 H). Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.89; H, 7.66; N, 7.10. Found: C, 60.79; H, 7.60; N, 7.03.

Attempts to reduce the compound 137.

All reduction experiments were carried out under a dry $N_2$ atmosphere, using hypodermic syringes to transfer solutions.

(a) With $LiAlH_4$

To a suspension of lithium aluminium hydride (95%, 0.14 g, 0.0035 mol) in 10 mL of dry THF was added slowly a solution of 137 (0.2 g, 0.0025 mol) in 1 mL of dry THF. After the addition the mixture was kept at reflux temperature for 2 h. Moist THF was added to destroy the excess lithium aluminium hydride, followed by distilled water to break up the complex. The precipitate was removed by suction filtration and the filtrate was concentrated. TLC showed the formation of a mixture of compounds.

(b) With $AlH_3$

Aluminium Hydride solution was prepared following the procedure reported by H. C. Brown[59] using 0.61 g of 95% $LiAlH_4$, 10 mL of dry THF and 0.43 mL of 100% $H_2SO_4$. The aluminium hydride solution (15 mL, 0.0067 mol) and 30 mL of dry THF were introduced into a dried flask by means of syringe under $N_2$ and the solution was brought to $0^oC$ and the compound 137 (1.0 g, 0.005 mol) in dry THF (5 mL) was injected rapidly. After stirring for 1 h at $0^oC$ distilled water was added to hydrolyze the Aluminium complex and the precipitate was filtered by suction. The filtrate and the combined washings were concentrated. TLC showed the formation of a mixture of compounds.

(c) With diborane

A solution of 2.0 mL (0.002 mol) of 1M borane in THF in a flask under $N_2$ was added (0.2 g, 0.001 mol) of compound 137 in 1 mL of THF

dropwise. The temperature was maintained at approximately 0°C during the addition. The solution was brought to reflux and maintained there for 1 hr. The flask was cooled to room temperature and 1 ml of 0.5 M HCl was added slowly. Sodium hydroxide pellets were then added to saturate the aqueous phase which was then extracted with ether. The ether layer was dried over anhydrous potassium carbonate and concentrated in vacuo. A mixture of compounds were formed as shown by TLC.

The other reactions (with Lithium trimethoxyaluminohydride, DIBAL, sodium borohydride in ethanedithiol, borane-dimethyl sulfide) were carried out using the above typical conditions. Azide 140 was succesfully reduced to amine 109 using very similar conditions to these cited above.

Reduction of 134 and 135.

A slurry of lithium aluminium hydride (1.33 g, 0.035 mol) in dry ethyl ether (30 mL) was cooled in dry ice acetone and the mixture containing 134 and 135 (4.0 g, 0.018 mol) in 10 mL of ether was added dropwise. The reaction mixture was stirred for 2 h at the same temperature and was quenched by adding 1 mL of distilled water. The resulting white precipitate was filtered by suction and was washed with dry ether. The combined organic layers were concentrated under reduced pressure to give a thick oil. Distillation at 113°C-115°C/0.9-1.0 mm Hg gave 2.43 g (73.4%) of 138. IR ($CCl_4$): 3510, 3350 $cm^{-1}$. $^1H$ NMR (60 MHz, $CDCl_3$): 1.75 (s, 3 H), 2.3 (br, 4 H), 3.55 (d, 2 H), 4.0 (s, 4 H), 5.7 (s, 1 H).

Tosylation of 138. (Ref. 64)

Compound 138 (2.5 g, 0.014 mol) was dissolved in pyridine/methylene chloride (24 mL, 1:1) and cooled in dry ice bath. p-Toluenesulfonyl chloride (2.7 g, 0.014 mol) was added and the reaction mixture was stirred for 0.5 h and then kept in the freezer overnight. The reaction mixture was allowed to warm to room temperature, diluted with ether (100 mL) and then washed with water (50 mL), 10% aqueous copper sulfate (6x50 mL), aqueous sodium bicarbonate (2x50 mL) and brine (2x50 mL). The organic layer was dried over anhydrous potassium carbonate and concentrated under reduced pressure. The residue was placed on a flash silica gel column and eluted with ethyl acetate/hexane (1:4). Solvent was removed to afford 3.0 g (77%) of 139. $^1$H NMR (60 MHz, $CDCl_3$): 1.65 (br), 2.4 (s, 3 H), 3.85 (s, 2 H), 4.0 (s, 4 H), 5.4 (s, 1 H), 7.4 (d, 2 H), 7.85 (d, 2 H).

Preparation of 140. (Ref. 64)

Compound 139 (5.0 g, 0.016 mol) was placed in a flask with sodium azide (4.09 g, 0.063 mol) and dry DMF (35.0 mL) was added. The slurry was heated to 50°C and stirred overnight. The solution was diluted with 150 mL of ether and washed with water (5x50 mL) and brine (100 ml). The organic layer was dried over anhydrous potassium carbonate and concentrated under reduced pressure. The residue was placed on a flash silica gel column and eluted with ethyl acetate/hexane (1:12). The solvent was removed to afford 2.34 g (70%) of 140. IR ($CCl_4$): 2100 $cm^{-1}$. $^1$H

NMR(60 MHz, $CDCl_3$): 1.6 (br), 3.15 (d, 2 H), 3.9 (s, 4 H), 5.4 (s, 1 H).Anal. calcd for $C_{10}H_{15}O_2N_3$: C, 57.40; H, 7.22; N, 20.08. Found: C, 57.10; H, 7.12; N, 19.86.

Reduction of 140.

To a suspension of lithium aluminium hydride (1.0 g, 0.027 mol) in anhydrous ether (200 mL) was added a solution of 140 (2.17 g, 0.013 mol) in anhydrous ether (100 mL) at such a rate that a slow reflux was maintained. After the addition the mixture was kept at reflux temperature for 2 h. Moist ether was added to destroy the excess lithium aluminium hydride followed by distilled water to break up the complex. The precipitate was removed by suction filtration and the filtrate was concentrated to isolate the amine 109. (0.88 g, 98%) IR ($CCl_4$): 3300, 3380, 1600 $cm^{-1}$. $^1H$ NMR $CDCl_3$): 1.3 (br), 1.7 (br), 2.6 (d, 2 H), 4.0 (s, 4H), 5.6 (s, 1 H).

Preparation of the acetyl derivative of 109.

A solution 109 (1.03 g, 0.0056 mol), triethylamine (0.85 g, 0.0084 mol), acetic anhydride (0.86 g, 0.0084 mol) and dimethyl aminopyridine (0.07 g, 0.00056 mol) in methylene chloride (10 mL) was stirred overnight at room temperature. The solution was diluted with distilled water and extracted with methylene chloride. The combined methylene chloride extractions

were dried over andydrous potassium carbonate and concentrated in vacuo to afford the crude product which was chromatographed on silica gel. Elution with 1:20 ethyl acetate/hexane afforded pure compound. (0.53 g, 42.8%) $^1$H NMR ($CDCl_3$): 1.4-1.7 (br, 4 H), 1.75 (br, 1 H), 1.9 (s, 6 H), 3.15 (t, 2 H), 3.95 (s, 4 H), 5.5 (br s, 1 H), 5.85 (br s, 1 H). IR ($CDCl_3$): 3450,3325, 1725, 1670 $cm^{-1}$. Anal. Calcd. for $C_{12}H_{19}O_3N$: C, 63.97; H, 8.50; N, 6.21. Found: C, 63.90; H, 8.47; N, 6.30.

Preparation of geranyl acetate 158 from geraniol

A mixture of geraniol (40.0 g, 0.25 mol) and acetic anhydride (29.0 g, 0.285 mol) was cooled in an ice bath and treated with a catalytic amount of N,N-dimethylaminopyridine (0.25 mmol). After stirring for 3 days at room temperature the reaction mixture was mixed with 50 mL of distilled water and extracted with methylene chloride. The combined methylene chloride extractions were washed with saturated sodium bicarbonate and distilled water. The organic phase was dried over anhydrous sodium sulfate and the solvent was evaporated in vacuo to afford (45.0 g, 92%) of geranyl acetate. $^1$H NMR (60 MHz, $CDCl_3$): 1.68 (s, 3 H), 1.8 (s, 6 H), 2.2 (s, 3 H), 2.8 (t, 1 H), 4.7 (d, 2 H), 5.45 (t, 1 H).

Preparation of (E)-3,7-dimethyl-6,7-epoxy-2-octen-1-ol acetate 159 from geranyl acetate. (Ref. 40)

To a mixture of a solution of geranyl acetate (5.7 g, 0.0336 mol) in $CH_2Cl_2$ (150 mL) and saturated sodium bicarbonate solution (90 mL) was added m-chloroperbenzoic acid (6.0 g, 0.0348 mol). The solution was stirred for 2 h at room temperature. The organic layer was washed with saturated sodium chloride solution and dried over anhydrous sodium sulfate. Evaporation left a residue (6.14 g, 86.2%) which was chromatographed on silica gel. Elution with 1:12 ethyl acetate-hexane afforded pure 159 . $^1H$ NMR (60 MHz, $CDCl_3$): 1.3 (s, 3 H), 1.35 (s, 3 H), 1.7 (s, 3 H), 2.05 (s, 3 H), 2.7 (t, 1 H), 4.6 (d, 2 H), 5.4 (t, 1 H).

(E)-2,6-dimethyl-3-phenylselenyl-8-acetoxy-6-octen-2-ol 160 (Ref 40)

A solution of diphenyl diselenide (2.4 g, 7.68 mmol) in absolute ethanol (50 mL) was treated with sodium borohydride (0.5 g, 14.5 mmol) at 0°C. The reaction mixture was stirred for 15 min at room temperature and a solution of 159 in ethanol (20 mL) was added. Stirring was continued for 4 h at room temperature. After removal of solvents in vacuo, distilled water (100 mL) was added to the resulting crude product and the mixture was extracted with benzene. Combined benzene extracts were washed with saturated sodium chloride. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to afford 4.8 g (99.7%) of 160 which was chromatographed on silica gel. Elution with EtOAc-hexane

(1:4) gave 2.6 g (53.6%) of 160. $^1$H NMR (60 MHz, $CDCl_3$): 1.3 (s, 3 H), 1.4 (s, 3 H), 1.7 (s, 3 H), 2.1 (s, 3 H), 3.0 (dd, 1 H), 4.5 (d, 2 H), 5.25 (t,1 H), 7.3 (m, 3 H), 7.7 (m, 2 H). IR ($CCl_4$): 3610 m, 1720 s $cm^{-1}$.

1,3,3-Trimethyl-2-acetoxymethyl-4-phenylselenocyclohexanol 161(Ref. 40)

A solution of 160 (0.65 g, 0.00175 mol) in dry $CH_2Cl_2$ (35 mL) was added to 99% trifluoroacetic acid (17 mL) dropwise under $N_2$ at 0°C. After being stirred for 1 h at the same temperature the reaction mixture was added to distilled water (150 mL). The $CH_2Cl_2$ layer was washed with saturated sodium bicarbonate, saturated sodium chloride, distilled water and dried over anhydrous sodium sulfate. Removal of solvents afforded a light yellow liquid which was chromatographed on silica gel. Elution with EtOAc-hexane (1:2) afforded 0.42 g ( 65%) of 161. $^1$H NMR (60 MHz, $CDCl_3$): 0.97 (s, 3 H), 1.18 (s, 3 H), 1.30 (s, 3 H), 2.03 (s, 3 H), 3.01 (dd, 1 H), 5.1-4.7 (m, 2 H), 7.2-7.7 (m, 5 H). IR ($CCl_4$): 3610, 1720 $cm^{-1}$.

1,3,3-Trimethyl-2-acetoxymethyl-4-phenylseleninylcyclohexanol 162.

$O_3$ was bubbled into a solution of 161 (250 mg, 0.68 mmol ) in dry $CH_2Cl_2$ (3.5 mL) at -78° C until a blue colour persisted (30 min). After being purged with $O_2$ and with $N_2$, the reaction mixture was allowed to

warm to room temprature. The solvent was removed in vacuo to give 250 mg (95%) of selenoxide as a white solid. mp 139°C-140°C. $^1$H NMR (60 MHz, $CDCl_3$): 1.2 (s,6 H), 1.4-1.6 (m for remaining H), 2.06 (s, 3 H), 3.1 (s, 1 H), 4.3 (br, 2 H), 7.6 (m, 5 H). IR ($CCl_4$): 3600-3400 m, 2950 s, 1775 m, 1730 s, 1390 w, 1360 m, 1250 m, 1150 m, 1050 m, 800 s $cm^{-1}$.

Pummerer rearrangement on 162.

(a) (Ref. 70)

A three neck flask (oven dried) was flushed with $N_2$ and was charged with 10 mL of dry $CH_2Cl_2$ and 100 mg ( 0.26 mmol) of compound 162. After 162 had dissolved acetic anhydride (0.122 g, 1.19 mmol) and anhydrous sodium acetate (0.06 g, 0.68 mmol) were added under $N_2$. The reaction mixture was refluxed overnight. After cooling to room temperature the reaction mixture was added potassium carbonate (4.0 g) in distilled water (5 mL) and methanol (20 mL) and stirred at room temperature overnight. The reaction mixture was diluted with distilled water (25 mL) and extracted with methylene chloride. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. TLC showed formation of a mixture of compounds .

(b) (Ref. 70)

A three neck flask (oven dried) was flushed with $N_2$ and was charged with 10 mL of dry THF and 100 mg (0.26 mmol) of compound 162. After 162

had dissolved andydrous sodium acetate (0.085 g, 1.04 mmol) and acetic anhydride (3 mL) were added and refluxed for 3 h. The reaction mixture was cooled to room temperature and acetic anhydride was removed under reduced pressure. The resulting mixture was dissolved in $CH_2Cl_2$ and filtered to remove sodium acetate and concentrated to give a thick oil. This thick oil was dissolved in methanol (10 mL) and treated with 10% potassium carbonate (5 mL) and stirred at room temperature. After stirring for 2 h the reaction mixture was poured into distilled water (25 mL) and extracted with $CH_2Cl_2$. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. TLC showed the formation of a complicated mixture of compounds.

(c) Compound 162 (100 mg,0.26 mmol) was placed in a three neck flask (oven dried) and was flushed with $N_2$. To this a solution of 2,6 lutidine (distilled over Barium oxide) (0.055 g, 0.52 mmol) in dry acetonitrile (5 mL) and dry $CH_2Cl_2$ (5 mL) was added via syringe. The solution was cooled to $0^oC$ and a solution of trifluoroacetic anhydride (distilled) (0.11 g, 0.52 mmol) in dry acetonitrile (2 mL) was added dropwise via syringe with stirring.. The reaction mixture was stirred for 2 h at $0^oC$. The resulting solution was mixed with 10% potassium carbonate (5 mL) and methanol (10 mL) and stirred overnight at room temperature. The reaction mixture was poured into distilled water (25 mL) and extracted with $CH_2Cl_2$. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. TLC showed the formation of a mixture of compounds.

Reaction of 159 with thiophenol.

A solution of thiophenol (0.628 g, 0.0057 mol) in absolute ethanol (50 mL) was treated with sodium (0.13 g, 0.0057 mol) at 0°C. The reaction mixture was stirred for 15 min at room temperature and a solution of 159 (1.0 g, 0.0047 mol) in ethanol (10 mL) was added dropwise and stirring was continued for 2 h at room temperature. After removal of the solvents in vacuo, distilled water (25 mL) was added and the mixture was extracted with benzene. The combined benzene extracts were washed with saturated sodium chloride. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. During the work up the acetate was hydrolysed to a primary alcohol.

(E)-2,6-dimethyl-3-phenylthio-8-acetoxyl-6-octen-2-ol 163.

A solution of thiophenol (0.31 g, 0.0028 mol) in absolute ethanol (25 mL) was treated with sodium borohydride (0.11 g, 0.0028 mol) at 0°C. The reaction mixture was stirred for 15 min at room temperature and a solution of 159 (0.5 g, 0.002 mol) in absolute ethanol (5 mL) was added and stirring was continued for 3 h at room temperature. After removal of solvents in vacuo, distilled water (50 mL) was added and the solution was extracted with benzene. The combined benzene extracts were washed with saturated sodium chloride. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to afford 0.60 g (93%) of 163. $^1$H NMR (60 MHz, $CDCl_3$): 1.26 (s, 3 H), 1.35 (s, 3 H), 1.7 (s, 3 H), 2.05 (s, 3 H), 3.1 (dd, 1 H), 4.5 (m, 2 H), 5.3 (m, 1 H), 7.35 (m, 3 H), 7.55 (m, 2 H). IR ($CCl_4$): 3610, 1720 $cm^{-1}$.

1,3,3-Trimethyl-2-acetoxymethyl-4-phenylthiocyclohexanol 164.

A solution of 163 (3.0 g, 0.0062 mol) in dry $CH_2Cl_2$ (174 mL) was added to 99% trifluoroacetic acid (86.3 mL) dropwise under $N_2$ at 0°C. After being stirred for 1 h at 0°C the reaction mixture was poured into distilled water (750 mL). The $CH_2Cl_2$ layer was washed with saturated sodium bicarbonate, saturated sodium chloride, distilled water and dried over anhydrous sodium sulfate. Removal of solvents afforded a thick light yellow liquid which was chromatographed on silica gel. Elution with EtOAc-hexane (1:2) afforded 164 (1.5 g, 75%). $^1H$ NMR (60 MHz, $CDCl_3$): 0.99 (s, 3 H), 1.25 (s, 3 H), 1.35 (s, 3 H), 1.5-2.0 (m, remaining H's), 2.1 (s, 3 H), 3.0 (dd, 1 H), 4.4 (m, 2 H), 7.3 (m, 5 H). IR ($CDCl_3$): 3600, 2960, 1720, 1440, 1360, 1250 $cm^{-1}$. GC-MS m/e: 322 ($M^+$), 244, 193, 188, 153, 135, 109.

2-Acetoxylmethyl-4-phenylsulfinyl-1,3,3-trimethylcyclohexanol (165).

To a magnetically stirred solution of 164 (340 mg, 0.00105 mol) in $CH_2Cl_2$ (5 mL) at -78 °C was added m-chloroperbenzoic acid (0.23 g, 0.00105 mol, tech. 80-85%) in small portions. After being stirred for additional 30 min at -78°C, the reaction mixture was poured into a mixture of 10 mL of $CH_2Cl_2$ and 10 mL of $Na_2CO_3$ with stirring. The aqueous layer was washed with 10 mL of $CH_2Cl_2$. The combined organic

layers were washed with saturated NaCl solution and dried over anhydrous sodium sulfate. Solvent removal gave 165 (0.33 g, 92.9%). $^1$H NMR (60 MHz, $CDCl_3$): 0.99 (s, 3 H), 1.3 (s, 6 H), 1.7 (br, remaining H's), 2.1 (s, 3 H), 2.9 (dd, 1 H), 4.35 (m, 2 H), 7.3 (m, 5 H). IR ($CCl_4$): 3600-3400 m, 2290m, 1720 s, 1400 m, 1200 m, 1100 m $cm^{-1}$. Anal. Calcd. for $C_{18}H_{26}O_4S$: C, 63.80; H, 7.74; S, 9.50. Found: C, 63.80; H, 7.70; S, 9.80.

Pummerer rearrangement of 165.

(a) Compound 165 (0.17 g, 0.0005 mol) was placed in a three neck flask (oven dried) and the flask was flushed with $N_2$. To this dry acetonitrile (3 mL) followed by 2,6 lutidine (distilled over barium oxide) (0.12 mL, 0.001 mol) was added. The solution was cooled to 0°C and a solution of trifluoroacetic anhydride (0.14 mL, 0.001 mol) in 1 mL of dry acetonitrile was added via syringe. The reaction mixture was stirred at 0°C for 1 h, then a solution of $NaHCO_3$ (5 mL) was added. The mixture was stirred at room temperature for 2 h and extracted with ether. The ether extracts were washed with dil. HCl and with saturated $NaHCO_3$ and dried over anhydrous $Na_2SO_4$. Evaporation of the solvents gave the starting material.

(b) Trifluoroacetic anhydride (0.187 g, 0.00089 mol) was dissolved in acetic anhydride (1 mL) and kept for 5 h at room temperature under $N_2$. Sulfoxide 165 (0.2 g, 0.00059 mol), and a few minutes later 2,6 lutidine

(0.13 mL, 0.0012 mol), were added to the mixture and stirred at room temperature overnight under $N_2$. After removal of acetic anhydride under reduced pressure the reaction mixture was diluted with 5N NaOH (5 mL) and stirred at room temperature for 3 h. The solution was added to distilled water (25 mL) and extracted with ether. Combined ether extracts were washed with dil. HCl , saturated $NaHCO_3$ and water. The organic layer was dried over $Na_2SO_4$ and concentrated in vacuo. The acetate group of the starting material was hydrolysed to a hydroxyl group.

(c) A three neck flask (oven dried) was flushed with $N_2$ and was charged with dry THF (5 mL) and 50 mg (0.00015 mol) of 165 . To this solution acetic anhydride (0.14 mL, 0.0015 mol) and anhydrous sodium acetate (0.12 g, 0.0015 mol) was added and refluxed for 3 h. TLC showed the formation of a mixture of compounds.

(d) Sulfoxide 165 (100 mg, 0.0003 mol) was placed in a oven dried three neck flask. After the flask was flushed with $N_2$, dry $CH_2Cl_2$ (7 mL) was added and the solution was cooled to -20°C. After 165 had dissolved trimethylsilyl triflate (0.43 mL, 0.0021 mol) followed by triethyl amine (0.3 mL, 0.0021 mol) were added via syringe and the solution was stirred at the same temperature for 20 min. The reaction mixture was mixed with 5% $NaHCO_3$ (10 mL) and stirred overnight. The reaction mixture was diluted with distilled water (10 mL) and extracted with $CH_2Cl_2$. The organic layer was dried over $Na_2SO_4$ and concentrated in vacuo. The

starting material was isolated.

Reaction of 164 with N-chlorosuccinimide.

Finely powdered NCS (0.08 g, 0.0003 mol) was added to a solution of 164 (0.10g, 0.0003 mol) in dry $CCl_4$ (10 mL) under $N_2$ at room temperature. After being stirred for 2 days at the same temperature, the reaction mixture was filtered through a pad of glass wool directly into a vigorously stirred suspension of mercuric chloride (0.26 g, 0.00096 mol) and cadmium carbonate (0.34 g, 0.00192 mol) in water under $N_2$. After being stirred overnight at room temperature, the mixture was filtered through Celite and concentrated in vacuo. The new compound formed could not be hydrolyzed.

Reaction of 164 with NCS in the presence of $H_2O$.

To a solution of 164 (0.05g, 0.00016 mol) in $CCl_4$ (10 mL) was added NCS (0.03g, 0.0023 mol) and $H_2O$ (0.03 mL, 0.0016 mol) all at once and the suspension was stirred at room temperature overnight. The reaction mixture was filtered through pad of glass wool and concentrated in vacuo to give a crude product which was chromatographed on silica gel. Elution with hexane-EtOAc (12:1) gave a new compound in 33% yield. $^1H$ NMR (200 MHz, $CDCl_3$): 0.93 (d, 3 H), 1.29 (s, 3 H), 1.41 (s, 3 H), 1.44-1.67 (br, 5 H), 4.0 (dd, 1 H), 4.12 (dd, 1 H).

Reaction of 164 with sulfuryl chloride. (Ref.79)

Sulfuryl chloride (0.023 g, 0.17 mmol) was added to a solution of 164 (50 mg, 0.15 mol) in dry $CH_2Cl_2$ (2 mL) at 0°C. The reaction mixture was stirred for 5 min at the same temperature and was then passed through a water deactivated silica gel (1 g) column (Ref. 79). The solvent was evaporated to give 45.0 mg (92%) of 173 and 174 in 6:1 ratio. This mixture was seperated using HPLC. (Silica colums, 10:1 EtOAc-hexane) Major: 173. GC-MS m/e: 320 ($M^+$), 211, 151, 109. $^1H$ NMR (300 MHz, $CDCl_3$): 1.15 (s, 3 H), 1.38 (s, 3 H), 1.47 (s, 3 H), 1.4-1.8 (m, remaining 5 H), 1.98 (s, 3 H), 4.0 (AB quartet, 2 H), 7.22 (m, 3 H), 7.50 (m, 2 H). IR ($CCl_4$): 2985 m, 1745 s, 1380 m, 1365 m, 1230 s, 740 s $cm^{-1}$. Anal. Calcd. for $C_{18}H_{24}O_3S$: C, 67.46; H, 7.54; S, 10.00. Found: C, 67.60; H, 7.53; S, 10.32. Minor: 174. GC-MS m/e: 356 (rel. intensity: 18.04), 354 (rel. intensity: 7.63), 339, 245,185,109. $^1H$ NMR (300 MHz, $CDCl_3$): 1.12 (s, 3 H), 1.43 (s, 3 H), 1.47 (s, 3 H), 1.7-1.9 (m, remaining 3 H), 1.95 (s, 3 H), 2.48 (q, 1 H), 3.9 (AB quartet, 2 H), 4.56 (dd, 1 H), 7.18 (m, 3 H), 7.66 (m, 2 H). IR ($CCl_4$): 2990 m, 1745 s, 1550 m, 1380 m, 1370 m, 1225 s, 750 s $cm^{-1}$. Anal. Calcd. for $C_{18}H_{23}O_3SCl$: C, 60.91; H, 6.53; S, 9.03; Cl, 9.99. Found: C, 60.99; H, 6.65; S, 9.21; Cl, 12.98.

Acetylation of 164.

To a solution of 164 (200 g, 0.62 mmol) in 1 mL of dry $CH_2Cl_2$ was added $Ac_2O$ (0.0076 g, 0.74 mmol), triethylamine (0.103 ml, 0.74 mmol)

and N,N-dimethylaminopyridine (0.004 g, 0.06 mmol) and the reaction mixture was stirred at 55°C overnight. The reaction mixture was cooled to room temperature and was added to distilled water (20 mL) and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ layer was washed with saturated sodium bicarbonate and dried over $Na_2SO_4$. Solvents were evaporated to give the crude diacetate which was chromatographed on silica gel. Elution with EtOAc-hexane (1:2) gave (0.14 g, 62%) of 175. $^1H$ NMR (300 MHz, $CDCl_3$): 1.05 (s, 3 H), 1.38 (s, 3 H), 1.50 (s, 3 H), 1.99 (s, 3 H), 2.09 (s, 3 H), 2.0-2.5 (m, remaining 4 H), 3.0 (dd, 1 H), 4.25 (dd, 1 H), 4.45 (dd, 1 H), 7.3 (m, 3 H), 7.43 (m, 2 H). IR ($CDCl_3$): 2970 m, 1720 s, 1365 m, 1230 m, 1255 m, 720 s $cm^{-1}$.

Reaction of 175 with N-chlorosuccinimide.

Compound 175 (0.08 g, 0.22 mmol) was dissolved in dry $CCl_4$ (2 mL) and added NCS ( 0.06 g, 0.33 mmol) and stirred overnight. The reaction mixture was concentrated in vacuo. The starting material was isolated.

Reaction of 175 with sulfuryl chloride.

Sulfuryl chloride (0.064 g, 0.46 mmol) was added to a solution of 175 (0.14 g, 0.38 mmol) in dry $CH_2Cl_2$ at 0°C. The reaction mixture was stirred at 0°C for 1 h and passed through a water deactivated silica gel

(2 g) column (Ref. 79). The solution was concentrated in vacuo and chromatographed with EtOAc-hexane (1:4) to give 176 (0.10 g, 86% ). $^1H$ NMR (300 MHz, $CDCl_3$): 1.25 (s, 3 H), 1.37 (s, 3 H), 1.77 (s, 3 H), 2.04 (s, 3 H), 2.10 (s, 3 H), 2.30 (m, 1 H), 2.78 (m , 1 H), 2.65 (m, 1 H), 3.15 (dd, 1 H), 4.40 (AB quartet, 2 H), 4.78 (dd, 1 H). $^{13}C$ NMR ($CDCl_3$): 204.76, 170.45, 170.11, 83.52, 62.38, 57.81, 50.06, 49.10, 46.96, 28.75, 25.37, 24.26, 22.84, 20.52. IR ($CCl_4$): 2990 m, 1740 s, 1385 m, 1365 m, 1230 s $cm^{-1}$. Anal. Calcd. for $C_{14}H_{21}O_5Cl$: C, 55.17; H, 6.95; Cl, 11.63. Found: C, 55.11; H, 6.98; Cl, 12.24.

Preparation of 177.

Compound 164 (200 mg, 0.62 mol) in methanol (10 mL) was mixed with 5% potassium carbonate (10 mL) at 10°C. After being stirred for 2 h at the same temperature the reaction mixture was added to water (10 mL) and extracted with $CH_2Cl_2$. The organic layer was dried over anhydrous $Na_2SO_4$ and concentrated in vacuo to give 177 (160 mg, 92%) as a white solid. $^1H$ NMR(60 MHz, $CDCl_3$): 0.9 (s, 3 H), 1.3 (s, 6 H), 1.4-2.0 (br, remaining H's), 2.9 (dd, 1 H), 3.8 (m, 2 H), 7.3(br, 5 H). IR ($CCl_4$): 3600 m, 2950 s, 1580 m, 1430 m, 1450 m $cm^{-1}$.

Preparation of 178.

Compound 177 (100 mg, 0.36 mmol) was dissolved in dry DMF (1 mL) and cooled in an ice bath. To this solution a cold solution of pyridinium dichromate (0.53g, 1.4 mmol) in DMF (7 mL) was added. After being stirred for 6 h at the same temperature the reaction mixture was added to distilled water (100 mL) and extracted with ether. Ether extractions were washed with water and concentrated in vacuo to give 178 (0.98 g, 97%). $^1$H NMR (60 MHz, $CDCl_3$): 1.15 (s, 3 H), 1.35 (s, 3 H), 1.45 (s, 3 H), 2.9 (m, 1 H), 1.8-2.2 (m, remaining H's), 7.35 (m, 5 H), 10.0 (s, 1 H). IR ($CCl_4$): 3550 m, 2950 s, 1700 s, 1580 m, 1430 m, 1450 m $cm^{-1}$. GC-MS m/e: 278 ($M^+$), 260, 234, 151, 109.

Preparation of 179.

Compound 178 (100 mg, 0.36 mmol) was dissolved in DMF (1.5 mL) and mixed with PDC (0.53 g, 1.4 mmol) in DMF (1.5 mL) and stirred overnight. The reaction mixture was poured into distilled water (100 mL) and extracted with ether. The organic layer was dried over $Na_2SO_4$ and concentrated in vacuo to give 179 (50 mg, 47%). IR ($CCl_4$): 3640 m, 3600-2000 br, 1710 s, 1580 m, 1440 m, 1400 m, 800 s $cm^{-1}$.

Preparation of 180.

Compound 179 (0.03g, 0.1 mmol) was dissolved in dry DMF and mixed with anhydrous potassium bicarbonate (0.02 g, 0.2 mmol) and stirred at room temperature until the potassium bicarbonate dissolved. To this solution MeI (0.03 g, 0.2 mmol) was added and stirring was continued overnight. The reaction mixture was added to 25 mL of distilled water and extracted with ether. The organic layer was dried over $Na_2SO_4$ and concentrated in vacuo to give 180 (40 mg, 97%). $^1H$ NMR (60 MHz, $CDCl_3$): 1.2 (s, 6 H), 1.4(s, 3 H), 1.8-2.2 (m, remaining H's), 2.8 (dd, 1 H), 3.7 (s, 3 H), 7.35 (m, 5 H). IR ($CCl_4$): 3600 m, 2980 s, 1720 s, 1580 m, 1430 m, 1255 s $cm^{-1}$. GC-MS m/e: 308 ($M^+$), 232, 121, 109.

Preparation of 181.

Compound 180 (0.03 g, 0.1 mmol) was dissolved in 1 mL of dry pyridine and cooled to 0°C in an ice bath. Thionyl chloride (0.02 g, 0.2 mmol) was mixed with dropwise and the reaction mixture was allowed to stand at 0°C for 10 min. Ice-water was then added and the product was extracted into ether. The combined ether extracts were washed with water, 5% $CuSO_4$ solution, saturated sodium bicarbonate and distilled water. The organiclayer was dried over $Na_2SO_4$ and concentrated in vacuo to give 181 (0.02 g, 68%). $^1H$ NMR (60 MHz, $CDCl_3$): 1.2 (s, 3H ), 1.3 (s, 6 H), 1.8-2.2 (m, remaining H's), 3.0 (m, 1 H), 3.75 (s, 3 H), 7.45 (m, 5 H). IR ($CCl_4$): 2950 s, 1730 s, 1580 m, 1460 m, 1430 m, 1360 m $cm^{-1}$. GC-MS

m/e: 290 ($M^+$), 259, 215, 180, 121, 109, 59.

Preparation of 182.

A solution of epoxide 164 (1.0 g, 0.0047 mol) in diglyme (10 mL) was added to 0.2 mL of 69-72 % perchloric acid in water (2.63 mL) at room temperature. After being stirred for 2 h the reaction mixture was poured into 25 mL of water and extracted with $CH_2Cl_2$. $CH_2Cl_2$ extracts were washed with saturated sodium bicarbonate and water and dried over $Na_2SO_4$. The solution was concentrated in vacuo and distilled at reduced pressure to give 182 ( 0.1 g at 45°C and 7 Hg mm). $^1H$ NMR (60 MHz, $CDCl_3$): 1.15 (s, 3 H), 1.2 (s, 3 H), 1.7 (s, 3 H), 2.05 (s, 3 H), 2.1-2.4 (br), 3.35 (dd, 1 H), 4.55 (d, 2 H), 5.4 (t, 1 H). IR ($CCl_4$): 3600 m, 2990 s, 1730 s $cm^{-1}$.

Preparation of 183.

Compound 182 (0.1 g, 0.4 mol) in 1 mL 0f dry $CH_2Cl_2$ was treated with acetic anhydride (0.09 mL, 0.47 mol) and two crystals of N,N-dimethylaminopyridine and stirred overnight at room temperature. The resulting solution was added to water and extracted with $CH_2Cl_2$. The organic layer was washed with sodium bicarbonate and dried over $Na_2SO_4$. The solution was concentrated in vacuo to give 183 (0.1 g, 91%).

$^1$H NMR (60 MHz, $CDCl_3$): 1.25 (s, 6 H), 1.7 (s, 3 H), 2.05 (s, 3 H), 2.15 (s, 3 H), 2.6 (s, 1 H), 4.6 (d, 2 H), 5.35 (t, 1 H). IR ($CCl_4$): 3600 m, 3500 m, 2990 s, 1730, 1740 s $cm^{-1}$.

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