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Stereochemical studies on radical spirocyclization related to fredericamycin A, and studies on radical allylation.

by

Christine Chua Paul

A thesis submitted to the faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

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UNIVERSITY OF ALBERTA

FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled **STEREOCHEMICAL STUDIES ON RADICAL SPIROCYCLIZATION RELATED TO FREDERICAMYCIN A, AND STUDIES ON RADICAL ALLYLATION** submitted by **CHRISTINE CHUA PAUL** in partial fulfillment of the requirements for the degree of **DOCTOR OF PHILOSOPHY**.

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(External Examiner)

Date: April 18, 1996

To my parents, my brothers, and my husband.

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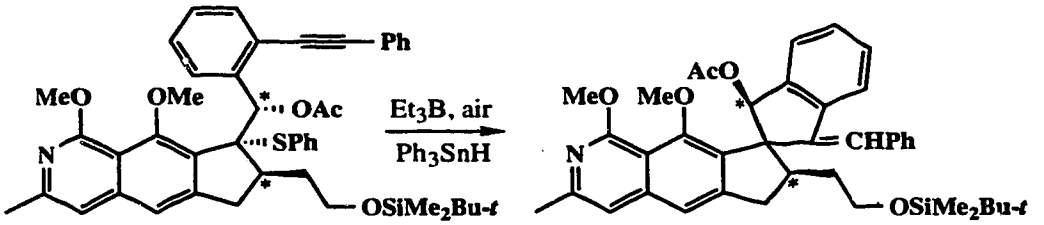
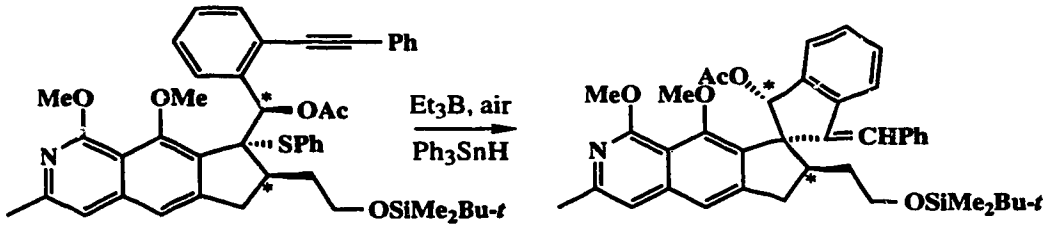
I thank my husband for the sacrifices he has made for me, for his patience and constant encouragement during the long period we have been apart.

ABSTRACT

The first chapter of this thesis describes a study on the sensitivity to steric effects of the key radical spirocyclization step in a synthesis of fredericamycin A, previously reported from this laboratory. The aim of the work was to establish if the radical spirocyclization could be used for an asymmetric synthesis. The study employed the model compounds **211a** and **211b** shown in **Scheme A-1**. Spirocyclization of **211a** afforded the cyclization product **212a** as a mixture of four isomers while spirocyclization of **211b** afforded **212b** as a single isomer. Consideration of possible transition states that account for these observations show that a single preferred mode of cyclization is likely only for **211b**. We conclude that radical spirocyclization is very sensitive to steric factors, but the method is not ideal for asymmetric construction of compounds with the fredericamycin skeleton, because of difficulties in cleaving the exocyclic double bond in the cyclization products.



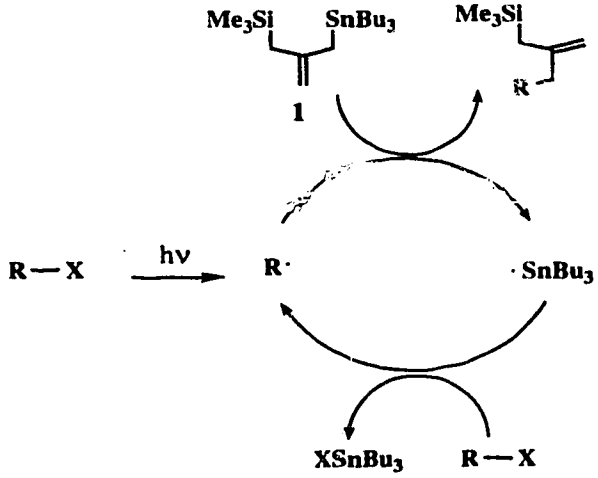
211a **212a** four isomers



211b **212b** one isomer

Scheme A-1

The second chapter of this thesis describes our studies on the application of 3-(tributylstannyl)-2-(trimethylsilylmethyl)-1-propene (**1**) as an allylating agent in radical chemistry. Under photoinitiated free radical chain reaction conditions (**Scheme A-2**), the compound was found to react with primary and secondary alkyl iodides having a β-oxygen substituent. Primary alkyl iodides without a β-oxygen were also found to react. Primary and secondary α-bromoketones react well but not tertiary α-bromoketones. In addition, while acceptable yields of allylated products could be obtained with both electrophilic and nucleophilic radicals, it was observed that electrophilic radicals generally react faster. The allylation of radicals with reagent **1** serves as a link between radical processes and the extensive chemistry of allylsilanes.



Scheme A-2

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LIST OF ABBREVIATIONS

acac.....acetylacetonate

AIBN.....2,2'-azobisisobutyronitrile

Bn.....benzyl

t-Bu.....*tert*-butyl

m-CPBA.....*m*-chloroperoxybenzoic acid

CAN.....cerium (IV) ammonium nitrate

CM.....complex mixture

DEAD.....diethylazodicarboxylate

DIBAL.....diisobutylaluminum hydride

DMAP.....4-(dimethylamino)pyridine

DMF.....dimethylformamide

DMP.....3,5-dimethylpyrazole

DMSO.....dimethyl sulfoxide

h.....hours

HMPA.....hexamethylphosphoric triamide

KHMDS.....potassium hexamethyldisilazide

LAH.....lithium aluminum hydride

LDA.....lithium diisopropylamide

LHMDS.....lithium hexamethyldisilazide

NOE.....nuclear Overhauser effect

PCC.....pyridinium chlorochromate

Ph.....phenyl

PhH.....benzene

PhMe.....toluene

pyr.....pyridine

SM.....starting material

TBAF.....tetrabutylammonium fluoride

TBDMS.....*tert*-butyldimethylsilyl

TBDPS.....*tert*-butyldiphenylsilyl

THF.....tetrahydrofuran

TMEDA.....tetramethylethylenediamine

TMS.....trimethylsilyl

p-TsOH·H_2O.....*p*-toluenesulfonic acid monohydrate

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CHAPTER 1

INTRODUCTION:

Fredericamycin A, an antitumor antibiotic, is a natural product produced by the soil fungus *Streptomyces griseus.*[1] Discovered in 1981, with the structure elucidated a year later,[2] the compound has attracted attention from many research groups. Scientists who studied the biological activity of the compound found that the natural product possesses potent *in vitro* cytotoxic activity with modest *in vivo* tumoricidal activity against several transplantable tumors in mice.[3] Exactly how the natural product exerts its antitumor activity is still unclear. There is evidence that the biological activity of the compound lies in the inhibition of DNA processing enzymes, topoisomerases I and II, and the DNA polymerase α.[4] Free radical formation was proposed by Hilton,[5] and disputed by Dalal,[6] as being at the core of all these biological activities. The challenge provided by the unique structure of the compound (**Figure I-1**) has been of great interest to synthetic chemists. An examination of the compound reveals only one stereogenic center. This arises as a result of the methoxy group on ring F. To date however, the absolute stereochemistry of fredericamycin A is still unknown inspite of available X-ray structural data.[1]

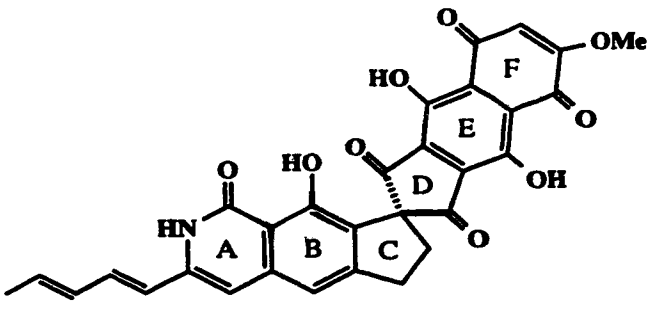


Fig. I-1. Fredericamycin A

Kelly[7] was the first to complete a total synthesis of Fredericamycin A. This was followed by Clive,[8] and later by Rao,[9] Julia,[10] Bach,[11] and Boger.[12] As none of the existing total syntheses demonstrated an asymmetric approach, we sought to develop a methodology for the enantioselective synthesis of Fredericamycin A. At the time of the completion of this project, there was still no report of an asymmetric synthesis of the spiro center in Fredericamycin A.

LITERATURE REVIEW

The following is a literature survey on the approaches developed for enantioselective construction of spiro centers. A number of them employ some form of chiral auxiliary, which is removed at a later stage. Some, on the other hand, rely on natural stereoselection, either guided solely by the anomeric effect, as in the cases involving spiroketals or simply by the vicinity of the spiro center being formed near to an existing chiral center. In order to understand the following discussion, a briefing is necessary on some of the usual ways of constructing spiro centers. This will be followed by a more detailed explanation, with examples, on how some spiro centers were constructed asymmetrically.

GENERAL STRATEGIES FOR CREATION OF SPIRO CENTER.

A. Since a spiro center is a quaternary carbon, a good number of approaches to spiro compounds start with the creation of the desired quaternary carbon[13] and this is followed by the required intramolecular bond formation elsewhere in the molecule **(Figure I-2)**.

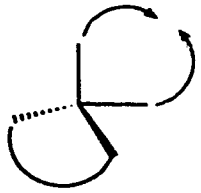


Fig. I-2 Spiro formation via a pre-formed quaternary center

B. Another common method is spirocyclization, where the center of bond formation in the cyclization process involves the incipient spirocenter. In this instance, the incipient spiro center can be nucleophilic, electrophilic or radical in nature (**Figure I-3**).

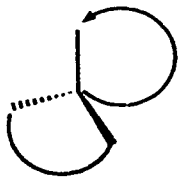


Fig. I-3 Spiro cyclization

C. Some spirocenters have been created by cycloadditions onto an exocyclic double bond (**Figure I-4**).

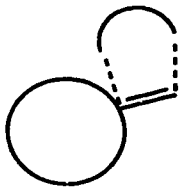


Fig. I-4 Cycloaddition

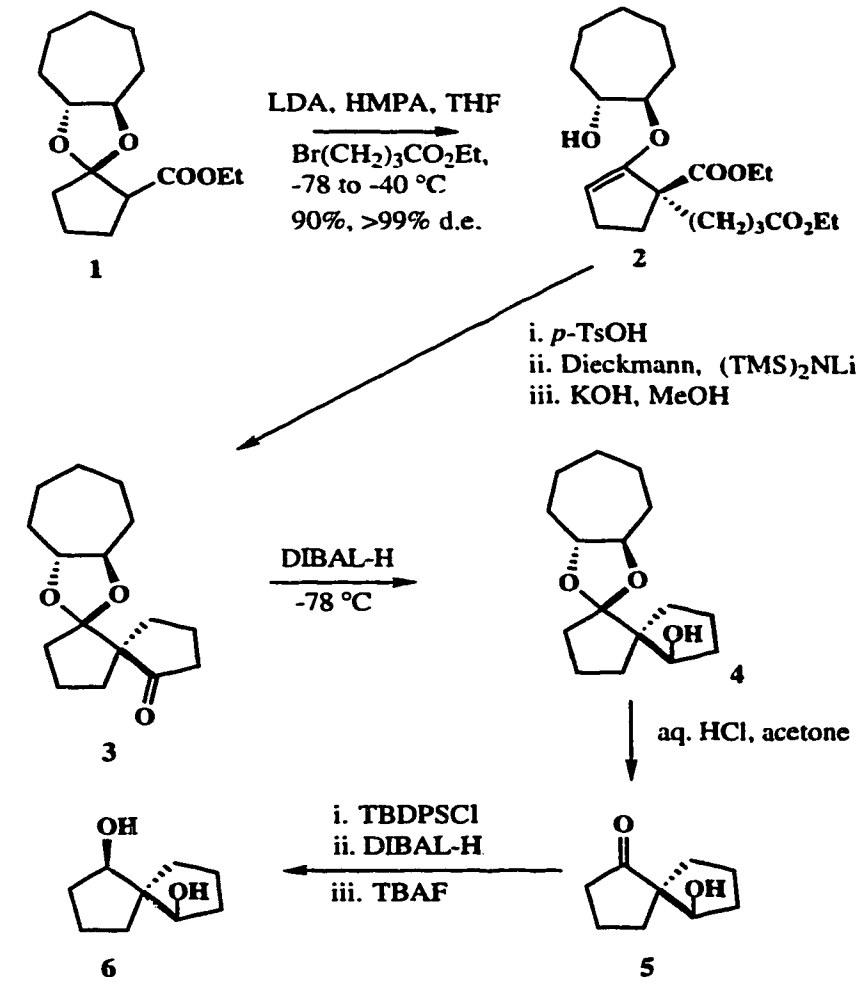
D. Other methods involve rearrangements from a non-spiro structure to a spiro structure.

Asymmetric or enantioselective approaches to spiro compounds

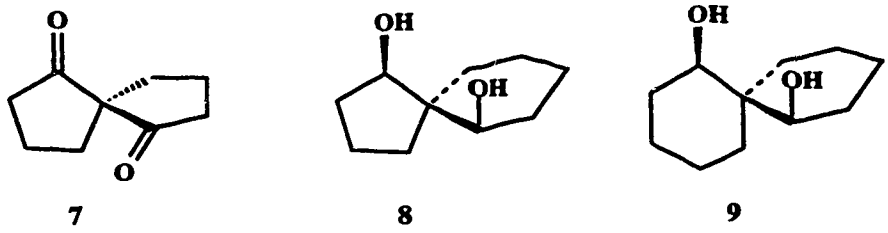
With so many examples available on the asymmetric or enantioselective construction of spiro compounds, classification (for this thesis) is done according to the general type of spiro construction outlined above.

A. Spiro formation by pre-construction of a chiral quaternary center.

The promising results obtained by Kumar and coworkers on the use of *cis,cis*-(+)-spiro[4,4]nonan-1,6-diol **6** as a chiral auxiliary for enantioselective LAH reduction of phenyl alkyl ketones[14] has spurred some interest on the efficient synthesis of chiral spiro-1,3-diols for studies related to their utility as chiral auxiliaries. Sakai and coworkers have developed a synthesis of spiro compound **6** whereby each chiral center in the molecule was generated in a highly stereoselective manner.[15] With the spiro center being the first chiral center generated, it then served as an internal guide for the stereoselective generation of the other two centers. Asymmetric alkylation of the chiral acetal **1** (**Scheme 1**), made from the corresponding 5 membered β-ketoester and (*R,R*)-cycloheptane-1,2-diol, with ethyl 4-bromobutyrate gave the enol ether **2**. Subsequent conversion to **3**, followed by DIBAL-H reduction of the latter, afforded **4**, which was deacetalized easily to **5**. Protection of **5** with the bulky *tert*-butyldiphenylsilyl group allowed for a highly stereoselective reduction of the other carbonyl functionality which, after a final treatment with TBAF, gave **6** in a high overall yield. With the successful presetting of the configuration at the spirocenter, it follows that optically active compounds like **7** can also be made easily.



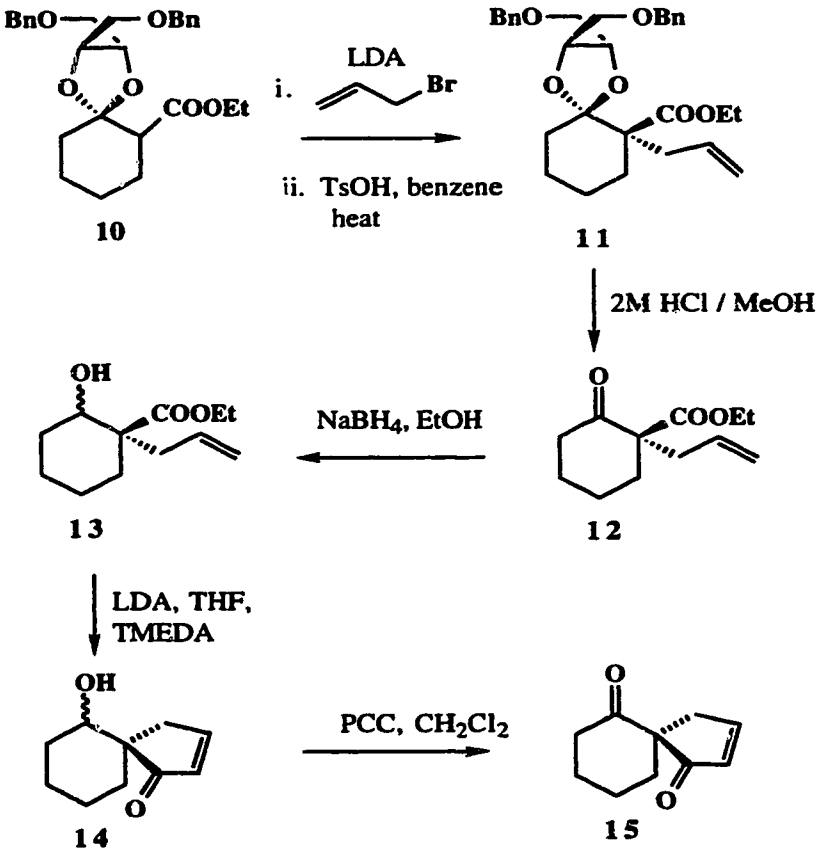
Scheme 1



The construction of diols **8** and **9** has also been reported[15] and their syntheses follow closely the same principle involved in making compound **6**.

Another approach similar to Sakai's is that of Thebtaranonth[16] (**Scheme 2**). The similarity lies in the fact that the configuration of the spirocenter was preset by

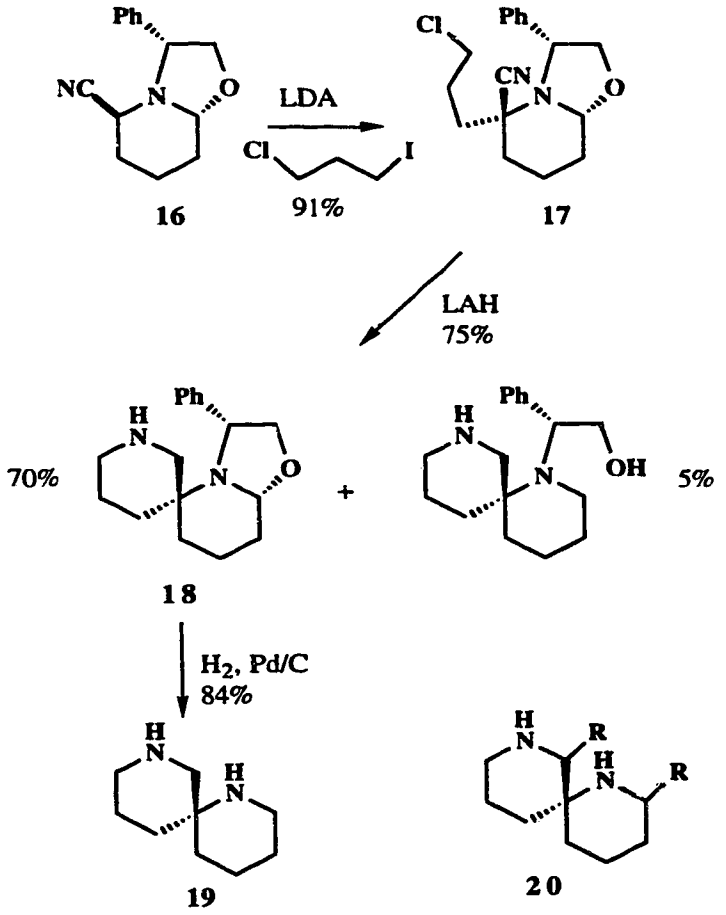
asymmetric allylation, also with the aid of an optically active diol as chiral auxiliary. This time the diol was derived from (2*R*,3*R*)-(+)-tartaric acid. (They reported trying other methods for asymmetric allylation, namely, the use of optically active enamine and menthyl ester, but found that the use of the diol derived from (2*R*,3*R*)-(+)-tartaric acid gave the best yields and selectivity.)



Scheme 2

Asymmetric allylation of **10** afforded **11** in 95% yield and 88% ee. Subsequent deacetalization to **12**, followed by $NaBH_4$ reduction, gave **13**, which was treated with LDA to generate the allyl carbanion that can cyclize onto the ester moiety to give **14**. A final oxidation step affords **15** with the spirocenter bearing the original configuration preserved all the way from **11**.

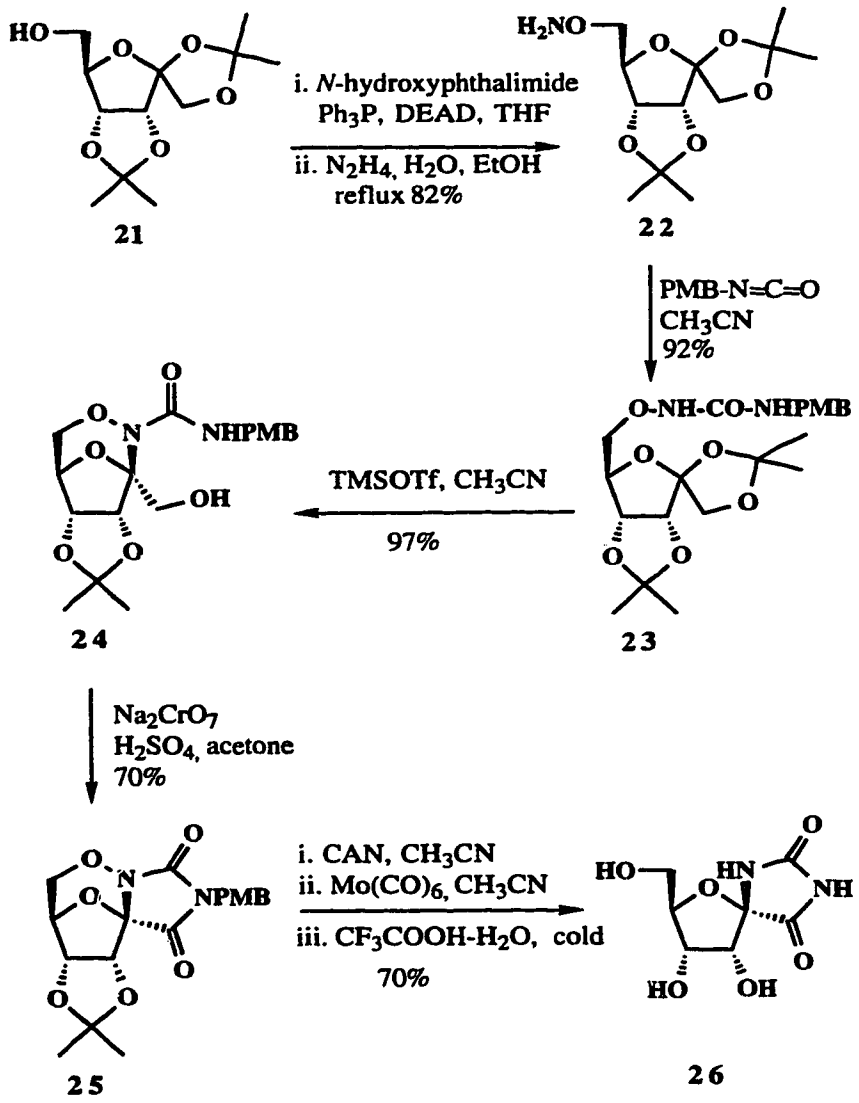
Husson[17] employed the use of chiral synthon **16** (**Scheme 3**) to construct the spiro compound 1,8- diazaspiro[5,5]undecane **19**. The stereochemistry of the



Scheme 3

spirocenter is basically a result of the stereoselective alkylation of **16** with 1-chloro-3-iodopropane to give **17** as a single isomer. With the stereochemistry of the quaternary carbon fixed, the ensuing cyclization to **18**, followed by hydrogenation, furnishes **19** bearing the spirocenter with the (*R*)-configuration. Other examples of the use of synthon **16** for making diaza spirocompounds of type **20** are reported in the literature.[17]

Chemla[18] has described a stereocontrolled synthesis of (+)-hydantocidin (**26**) (**Scheme 4**) from 1,2:3,4-di-*O*-isopropylidene-D-psicofuranose (**21**), utilizing the

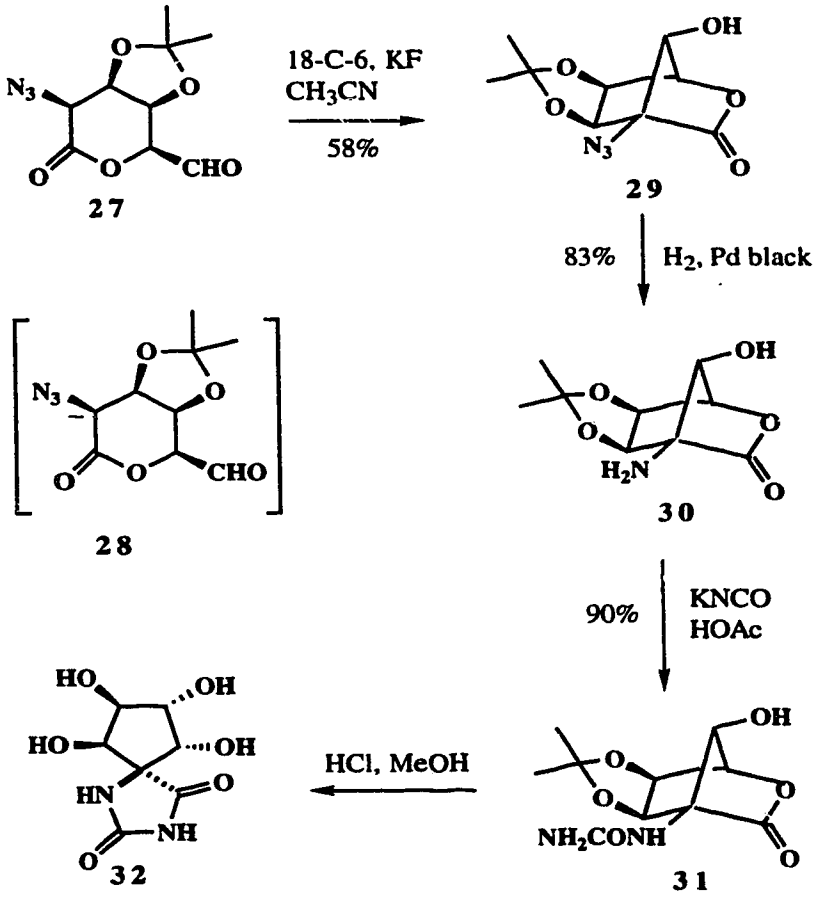


Scheme 4

intramolecular oxygen-bridged Vorbruggen coupling to generate exclusively the desired configuration at the spirocenter. This method overcomes the difficulty posed by the fact that the isomer with the nitrogen in the α-anomeric position is thermodynamically more stable than the one with the nitrogen β. Beginning with **21**, conversion to the hydroxylamine **22** was effected in two steps by treatment with *N*-hydroxy-phthalimide followed by cleavage with hydrazine. Subsequent conversion to the corresponding *p*-methoxybenzylurea **23**, followed by treatment at room temperature with a catalytic amount of trimethylsilyltriflate, led to the formation of **24**, with the configuration at C-1

fixed, thus eliminating any risk of epimerization in the subsequent synthetic manipulations (**24**→**25**→**26**).

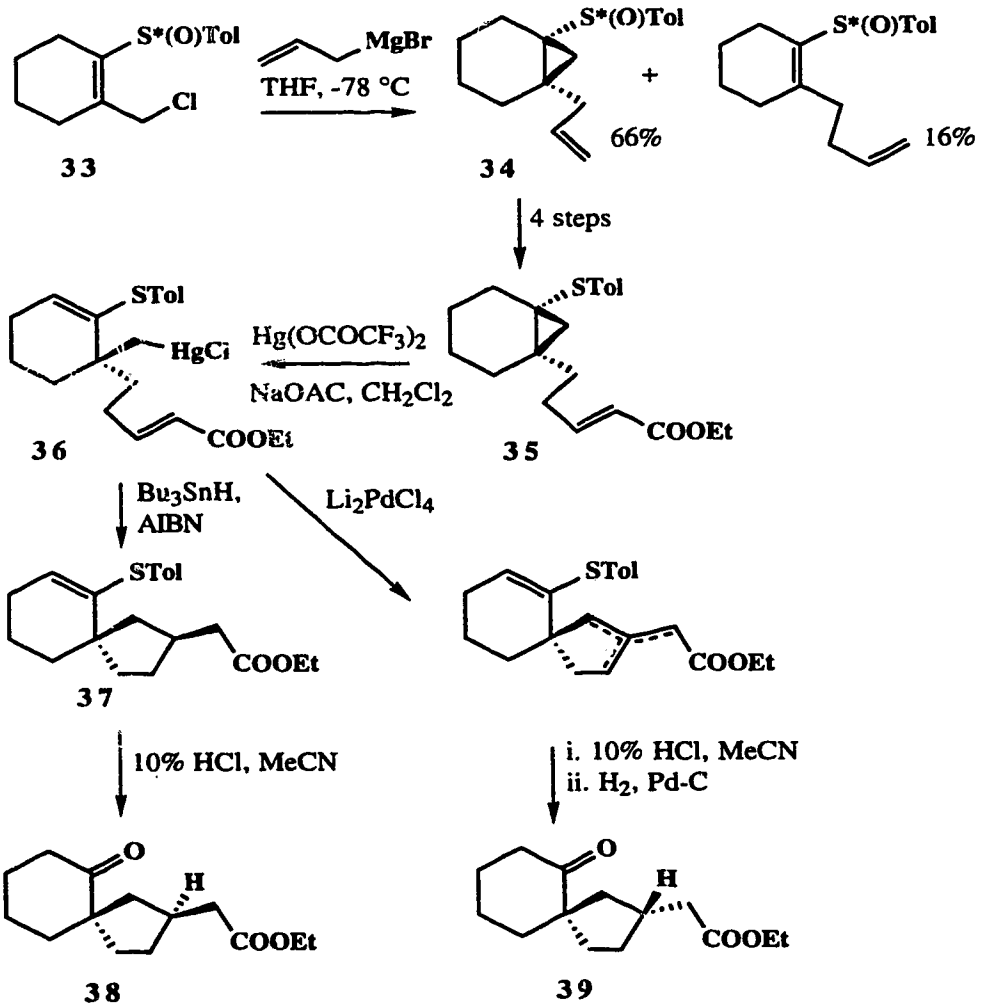
Fleet[19] and coworkers were able to make the optically active spirohydantoin **32** by presetting the configuration of the incipient spirocenter via initial formation of the



Scheme 5

bicyclic azidolactones **29**. Beginning from the optically active aldehyde **27**[20,21] (**Scheme 5**), treatment with potassium fluoride in acetonitrile at -6 °C in the presence of 18-crown-6 gave **29** as the major product by way of an intramolecular closure of anion **28**. Subsequent hydrogenation, followed by conversion to urea **31** and finally, treatment with methanolic hydrogen chloride, gave the spirohydantoin **32**, whose spirocenter bears the original stereochemistry of the quaternary center attached to the azido group in **29**.

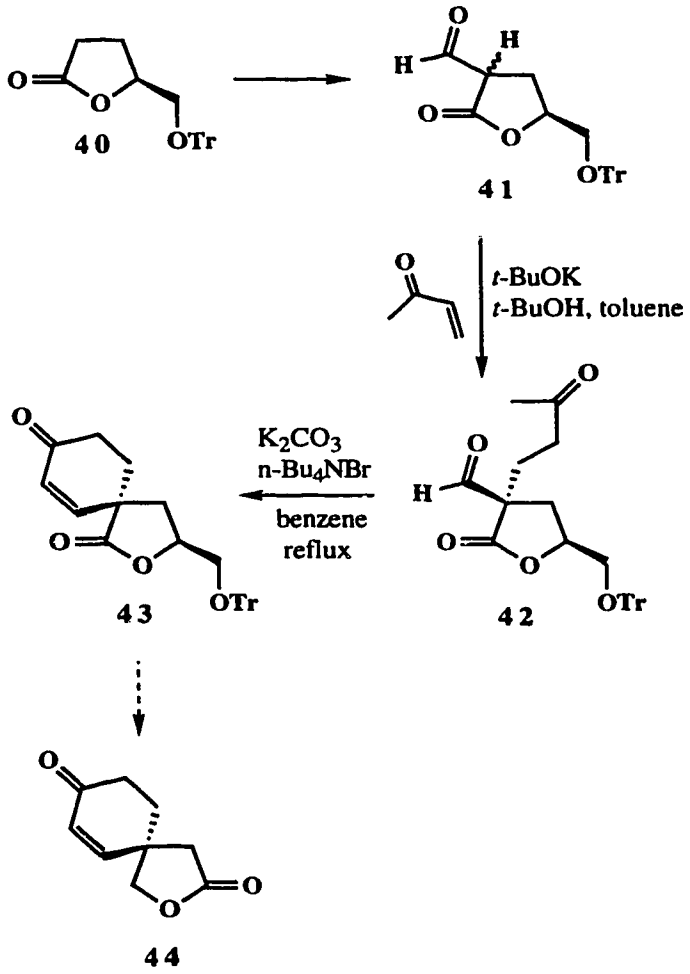
Iwata[22] has described a regioselective ring opening procedure for converting **35** to **36** (**Scheme 6**). The stereochemistry of the asymmetric centers in **35** were in turn set up by a highly diastereoselective cyclopropanation of **33** to **34** at an earlier stage. Cyclization of **36** by radical reaction with tributyltin hydride and AIBN, followed by hydrolysis of **37**, gave **38** as the major product. On the other hand, it is interesting to note that the palladium(II) assisted cyclization of **36**, followed sequentially by hydrolysis and catalytic hydrogenation, afforded **39** as the major product.



Scheme 6

Koga[23] had demonstrated the use of (S)-γ–hydroxy-methyl-γ-butyrolactone, protected in the form of its trityl ether (**40**), as a chiral synthon in the asymmetric

construction of quaternary centers. Stereoselective sequential dialkylation produces a particular configuration at the α carbon. When the opposite configuration is desired, reversing the sequence of dialkylation is all that is required. This stereoselectivity is consistent with the expectation that alkylation would preferentially take place from the face opposite to the trityloxymethyl group. Extension of this knowledge to the construction of spiro compounds is shown in the following example (**Scheme 7**).

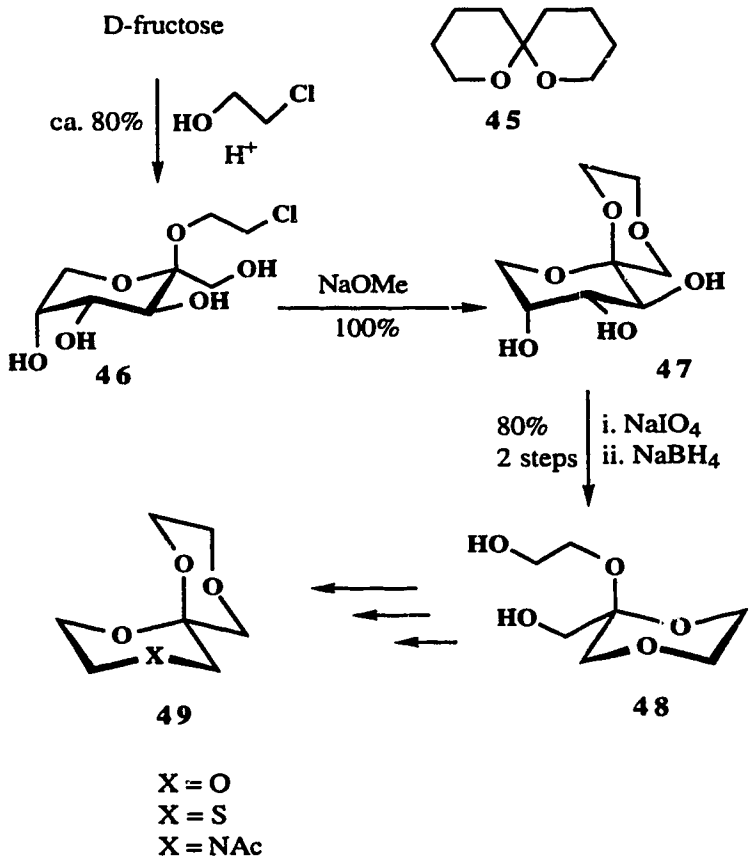


Scheme 7

Alkylation of **41** (note that this is the second alkylation) produced a diastereomeric mixture (83:17) in 86% yield, with **42** being the major product. Subsequent intramolecular aldol condensation by refluxing in benzene with potassium carbonate and tetrabutylammonium bromide afforded the optically pure spirolactone **43** in 65% yield.

Although they did not actually convert **43** into **44**, it is worth noting that in other experiments, they have established the possibility of converting compounds resembling **43** into those that resemble **44** by means of lactone carbonyl transposition.[24]

Related to their studies on the sex pheromone **45**, a sex hormone of the olive fruit fly,[25] Richardson has reported the asymmetric synthesis of compounds of the type **49**, in which the chirality of the spiro carbon is dictated by the configuration of the anomeric carbon of its glycoside precursor.[26] Starting from D-fructose (**Scheme 8**),



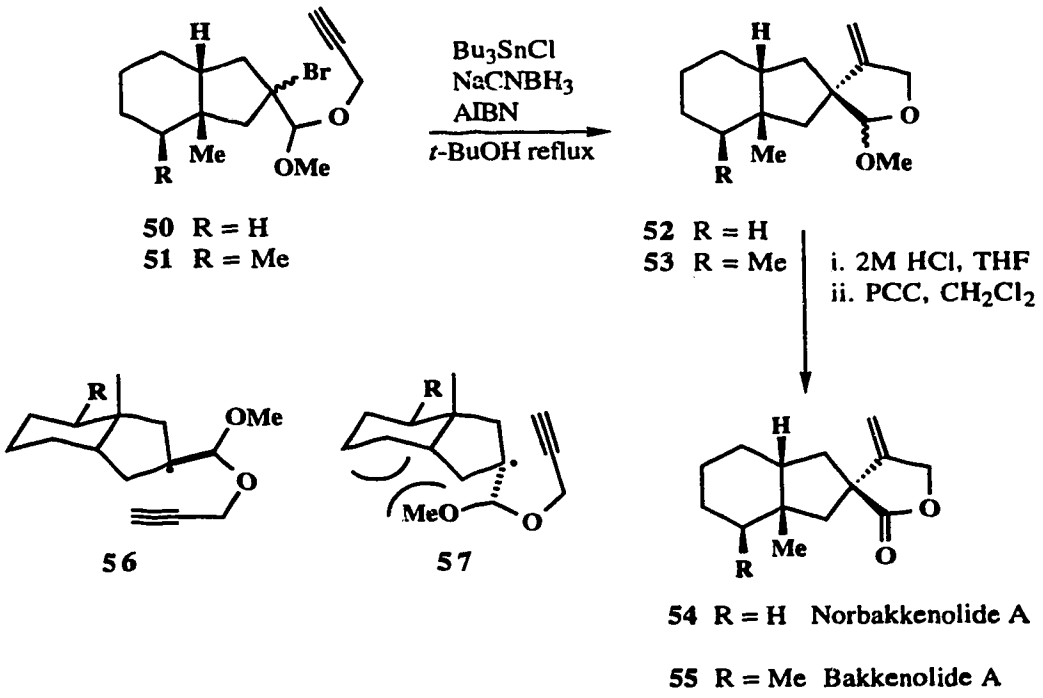
Scheme 8

reaction with 2-chloroethanol in the presence of acid afforded **46** in *ca.* 80% yield as a single isomer. Internal cyclization was effected by treatment with base to give the spiroanhydride **47**. Further treatment with sodium metaperiodate, followed by immediate borohydride reduction, afforded the diol **48**. With the quaternary center fixed

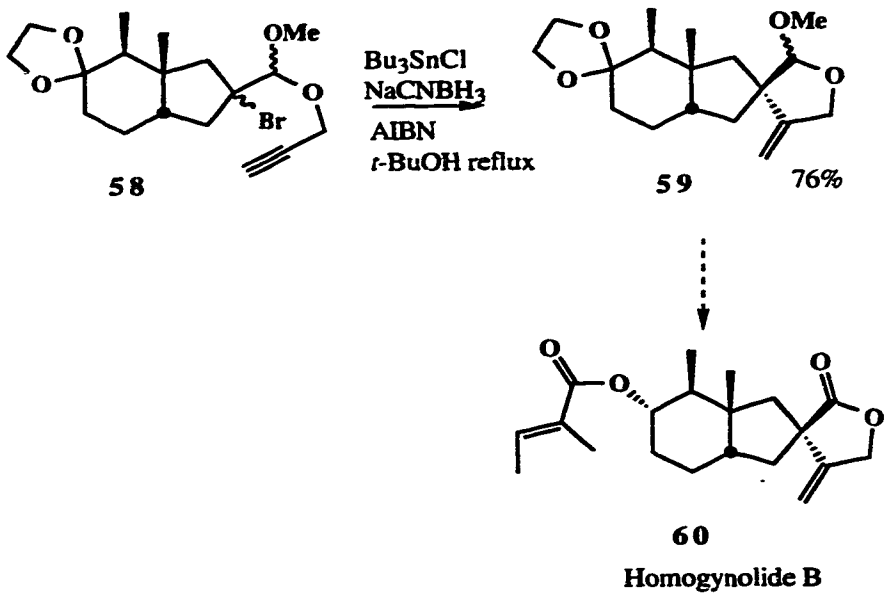
as early as the first step from D-fructose, all that is left is ring closure to give **49**, and this can be achieved in a few simple steps. The point to be made is that the configuration of the spiro center in the final product stemmed from a quaternary center, the chirality of which resulted naturally from anomeric stereoselection.

B. Spiro formation by stereoselective spirocyclization:

Srikrishna has reported several works related to the stereoselective synthesis of the sesquiterpenes bakkenolide A (**55**),[27] norbakkenolide A (**54**),[28] and homogynolide B (**60**).[29] At the heart of all these syntheses is a stereoselective radical spiroannulation producing one diastereomer preferentially over another. Thus, when **50** and **51** (**Scheme 9**) were subjected to radical cyclization conditions, **52** and **53** were obtained highly diastereoselectively (*ca.* 75% yield for each case). The rationale behind the diastereoselectivity is the preference for cyclization to occur via the less crowded endo radical **56** as opposed to the more crowded exo radical **57**. The same principle operates



Scheme 9



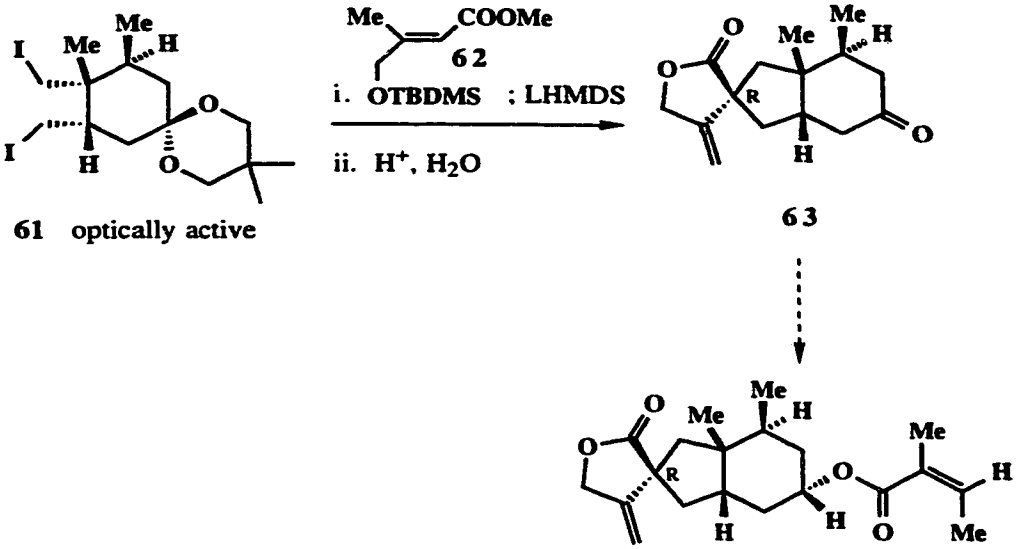
58 59 60

Homogynolide B

Scheme 10

in the spiroannulation of **58** to **59**, (**Scheme 10**) an essential precursor to homogynolide B (**60**).

Greene[30] has reported a stereocontrolled synthesis of a related sesquiterpene, (-)-homogynolide A (**64**). In their strategy (**Scheme 11**), they observed that the cyclo-alkylation between **61** and **62** occurred with a stereo-selectivity of *ca.* 3:1 in favor of the *R* configuration at C-7 of **63**. No rationalization was provided, however, for the observed stereoselectivity.



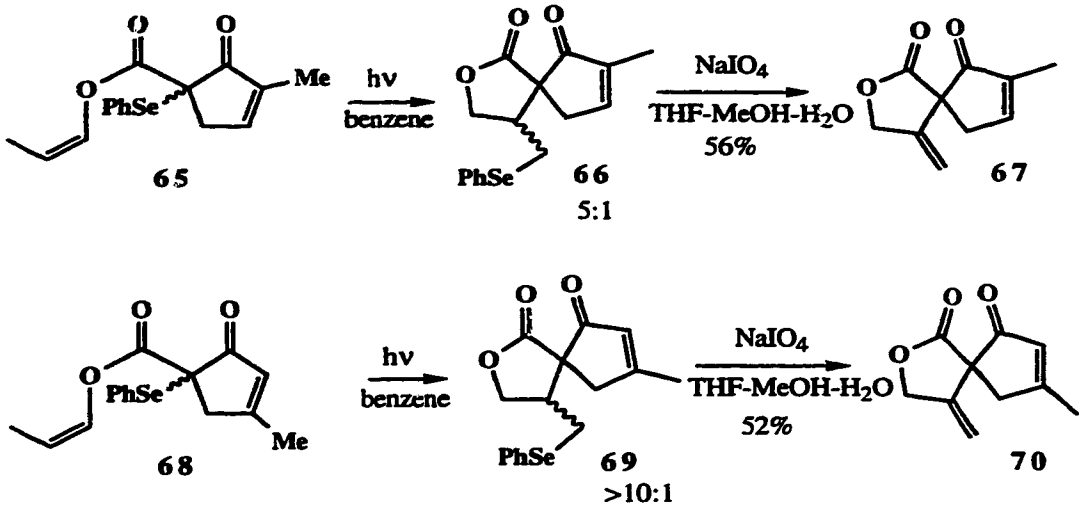
61 optically active

63

64 (-)-Homogynolide A

Scheme 11

Back and coworkers[31] have prepared the spirolactones **67** and **70**, related to the spiro ring system in bakkenolides. They employed a photochemically induced free radical cyclization (**Scheme 12**) of allyl-1-(phenylseleno)-3-methyl-2-oxo-3-cyclopentene carboxylates **65** and **68**, giving **66** and **69**, both as a mixture of diastereomers in 5:1 and 10:1 ratios, respectively. It is important to note, however, that although acceptable diastereoselectivities were observed in each case of spiro-cyclization, the fact that the intermediate radical is not chiral, and therefore has no inherent guiding factor to take it along an asymmetric path, means that this route yields racemic material.

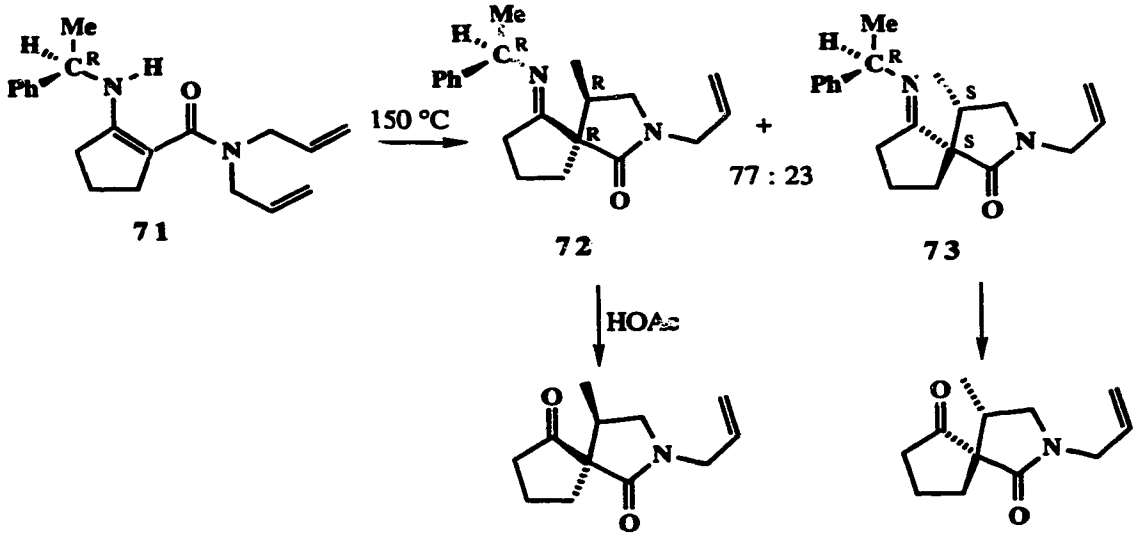


65 66 67 68 69 70

Scheme 12

A way to tap such diastereoselectivity for asym-metric spiro construction is by placing a third independent chiral center somewhere in the molecule, as done by Cossy[32] and d'Angelo.[33]

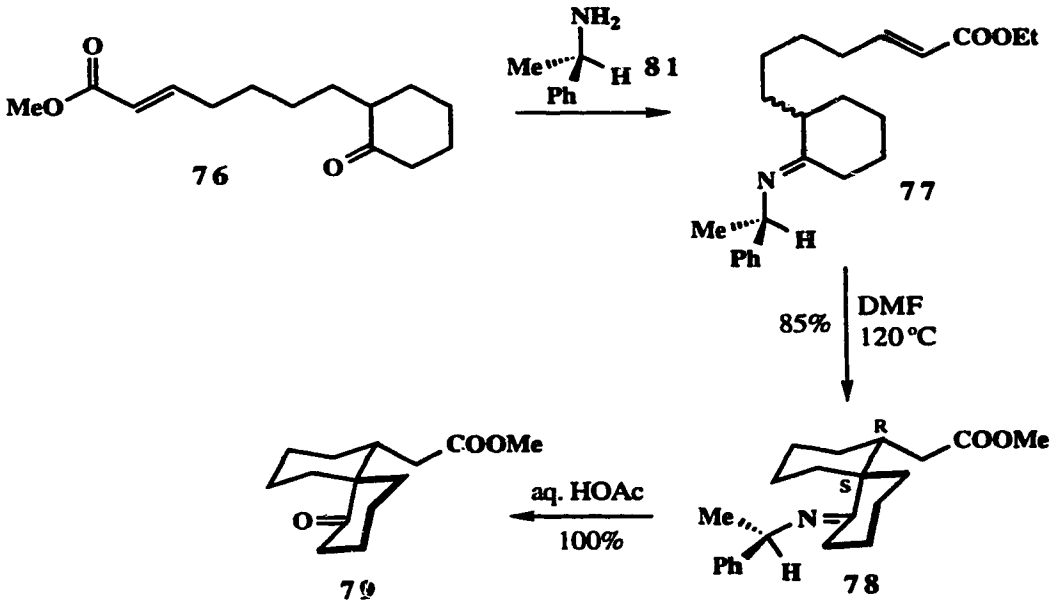
Cossy[32] has reported an asymmetric intramolecular ene-reaction to prepare the spirolactams **74** and **75**, each bearing two chiral centers formed simultaneously and dependently on one another. This process was achieved by incorporating the chiral auxiliary (*R*)-1-phenylethylamine into the common precursor. Thus, (**Scheme 13**),

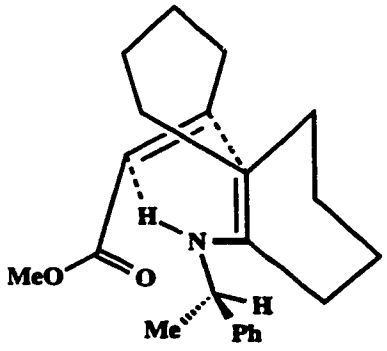


71 72 73 74 75

Scheme 13

thermolysis of optically active **71** under argon produced **72** and **73** in a 77:23 ratio with 90% overall yield. Separation by ordinary flash chromatography, followed by removal of the chiral auxiliary, furnishes the enantiomeric spiro ketoamides **74** and **75**, each as a pure single isomer. This approach by Cossy is similar to earlier work reported by d'Angelo.[33] The latter was able to achieve a high degree of regio- and stereoselectivity in the spirocyclization of **76** to **78** via the imine **77**, which was prepared from (*R*)-α-methylbenzylamine **81** and **76** (**Scheme 14**). A compact cyclic transition state **80** was



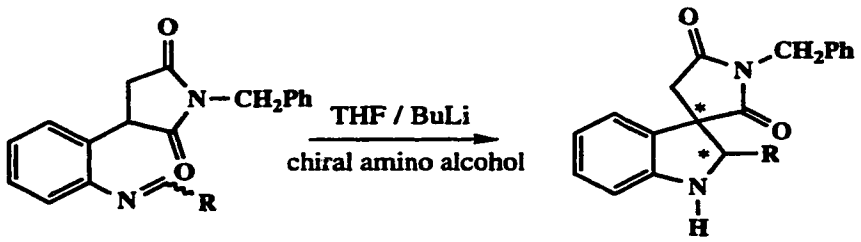


80

Scheme 14

proposed to account for the virtually complete control of the two asymmetric centers in **79**. It was suggested that the intramolecular Michael addition occurs at the more substituted α position of the imine, thus allowing for a gauche arrangement between the enamine double bond and the ethylenic ester double bond. This paves the way for a smooth transfer of a hydrogen from the enamine nitrogen to the vinyllic carbon α to the carbonyl, during the C-C bond formation.

Speckamp[34] has studied the highly diastereoselective electrocyclization of imines of the type **82**→**83** (**Scheme 15**). As the cyclization was found to be highly diastereoselective, when done in the presence of chiral amino alcohols, one enantiomer

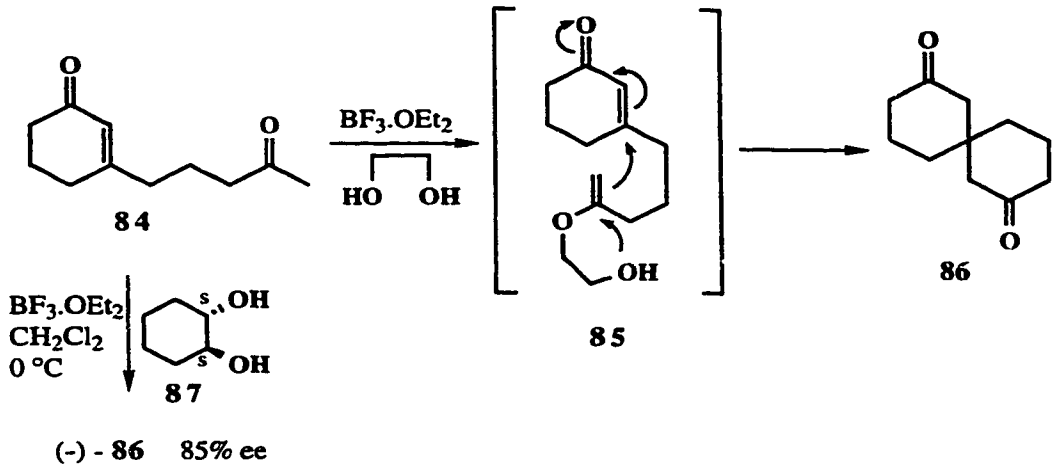


82 **83**

Scheme 15

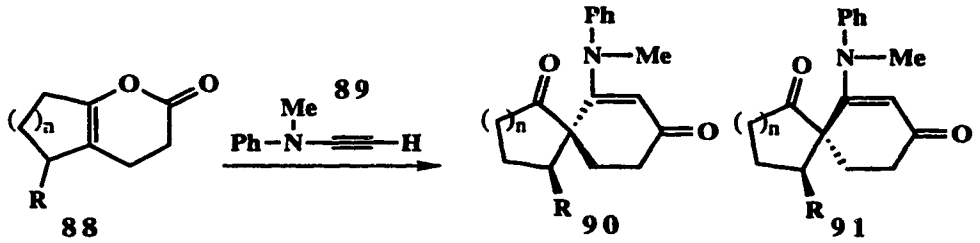
predominates over another in the product mixture. In some cases, only a single enantiomer was obtained.

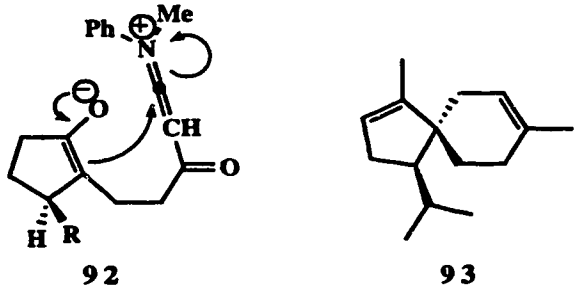
Sakai and coworkers[35] has reported an interesting preparation of the racemic spiro compound **86** (**Scheme 16**) by reaction of **84** with $BF_3 \cdot OEt_2$ in the presence of ethylene glycol. In the absence of ethylene glycol, the reaction proceeded very slowly (30% product yield, 3 days), indicating that an important role is being played by the diol. They proposed that the reaction goes via the intermediate **85**. Carrying out the same reaction in the presence of chiral diol (*S*,*S*)-cyclohexane-1,2-diol **87**, they obtained, after optimizing reaction conditions, (-)-**86** in as high as 85% ee and 86% yield.



Scheme 16

Ficini[36] has reported a highly diastereoselective anionic spirocyclization resulting from the acylation of ynamines by bicyclic enol lactones. Her group found (**Scheme 17**) that treatment of the enol lactones **88** with the ynamine *N*-methyl-*N*-



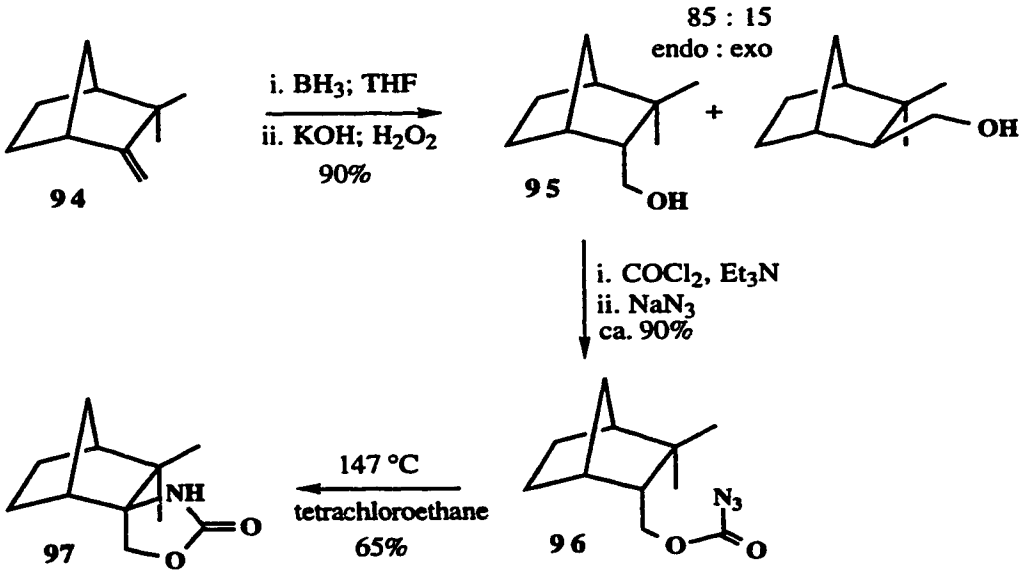


Scheme 17

phenylaminoacetylene **89** afforded, diastereoselectively, the spiro compounds **90** as the

major products. The diastereoselectivity was rationalized by assuming the presence of an intermediate of type **92**, formed after initial attack of the ynamine on the lactone carbonyl. As one face of the cyclopentene is less hindered than the other, the approach of the keteniminium ion is faster from the face opposite the alkyl group. This stereo-selective spiro annelation was extended by Ficini to the synthesis of acoradiene **93**.[37]

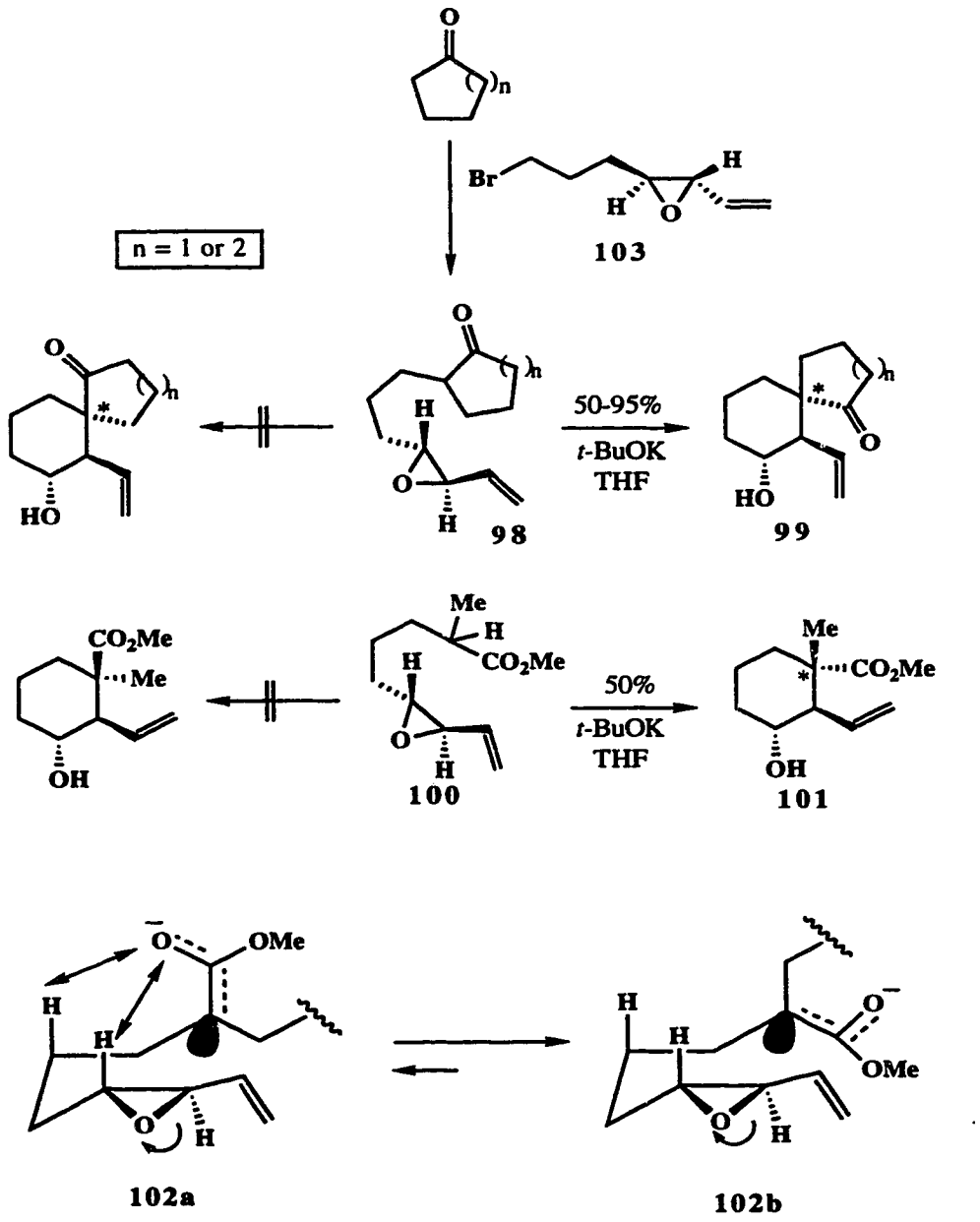
Banks has made compound **97** that was found to be a reliable chiral auxiliary for alkylation, acylation, aldol reactions and Lewis acid-mediated Diels Alder reactions.[38] Compound **97** can be made from (-)-camphene **94** (**Scheme 18**), via hydroboration of the latter to give predominantly the



Scheme 18

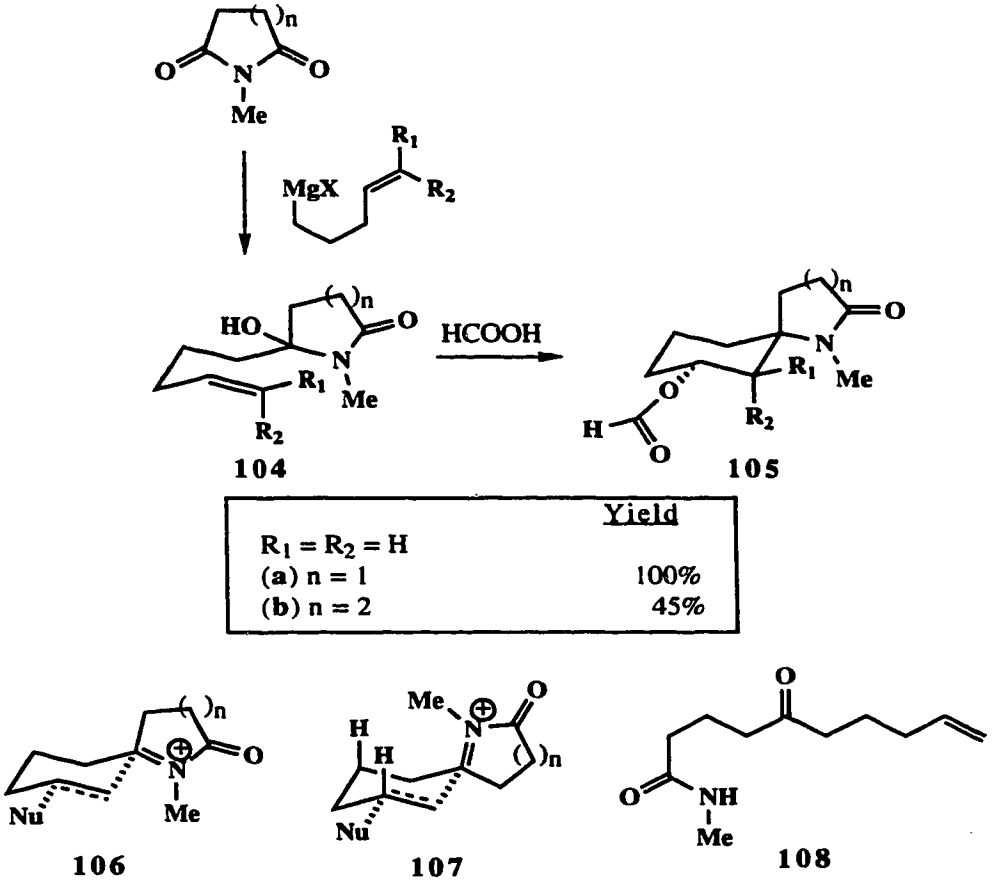
endo camphenol **95**. Conversion of this alcohol to the corresponding azidoformate **96**, followed by thermolysis of the latter, afforded **97**, bearing the spirocenter whose chirality was governed by the initial hydroboration step.

Stork[39] has reported an interesting reaction whereby the stereochemistry of a simple trans epoxide is relayed into the stereocontrolled formation of three contiguous asymmetric centers, one of which is quaternary. It was observed (**Scheme 19**) that in the intramolecular epoxide openings **98**→**99** and **100**→**101**, the attack of the carbanion occurs on the distal end of the epoxide, as opposed to the proximal end, which is a more usual phenomenon[40] when an epoxide is part of an allylic system. The stereoselectivity at the newly formed spiro center was rationalized to stem from the more stable transition state **102b** as opposed to **102a**, as the latter incurs severe 1,3-diaxial interactions. This work was easily conducted on the optically pure material as it was not difficult to obtain epoxides like **103** in enantiomerically pure form. In addition, this cyclization was found to be quite general, and is compatible with *E*- or *Z*- disubstituted homologues of the terminal vinyl groups, and could be extended to cases where an ethynyl group is in place of the vinyl group.



Scheme 19

Speckamp has reported an approach to 1-aza-[n,5]-spiranes by employing α-acylimmonium ion-initiated olefinic cyclizations.[41] His group observed (**Scheme 20**) that treatment of **104a** with formic acid afforded **105a** as a single product in quantitative

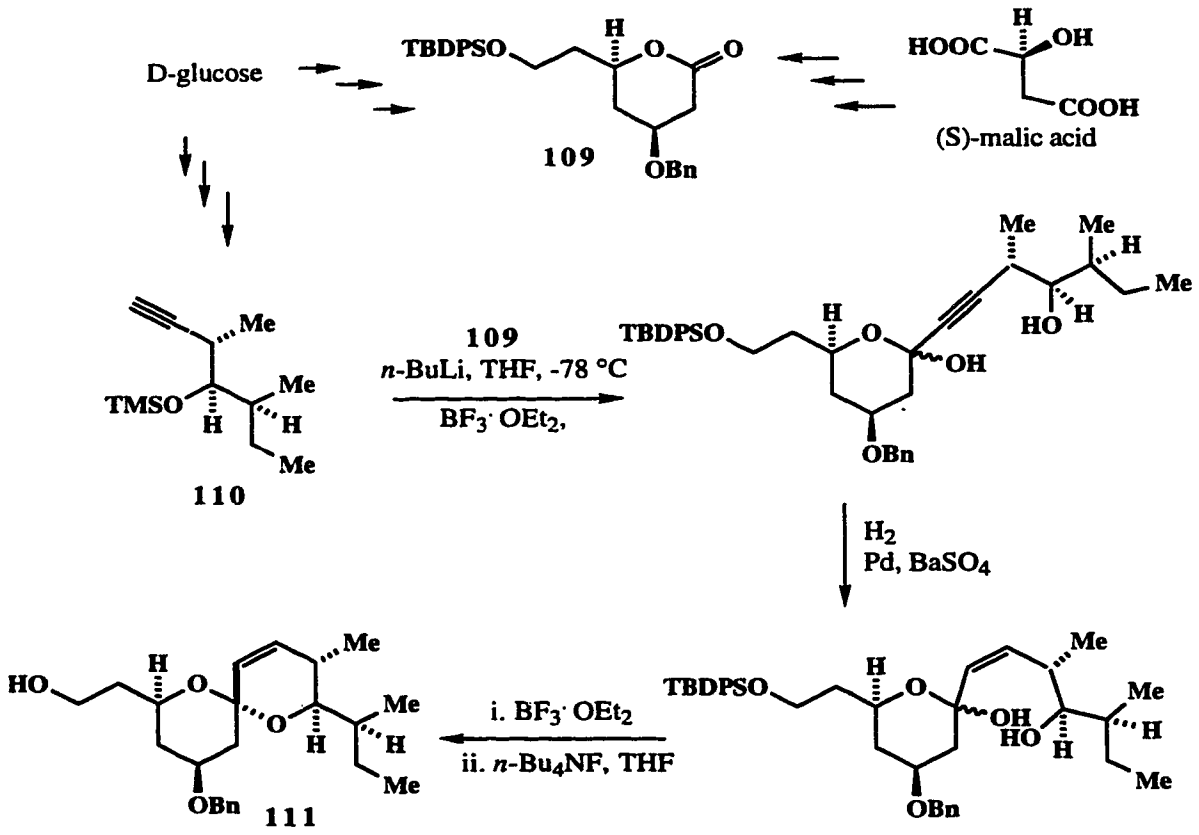


Scheme 20

yield, indicating the occurence of a highly diastereoselective cyclization. It was proposed that the desired stereochemistry was the consequence of the chair-like transition state **106**, rather than **107** where the alkyl group borne by the nitrogen cannot avoid steric interactions with the two axial hydrogens nearby. It was also found that increasing the ring size of the lactam by one methylene group, as in **104b**, led to a lower yield of the desired cyclized product **105b**. Presumably, this is the result of irreversible ring opening of **104b** to **108**, which cannot easily cyclize back. The attractiveness of this stereoselective approach lies in the fact that it allows for the controlled formation of three stereogenic centers in one step.

Hanessian[42] has reported a synthetic route to the 1,7-dioxaspiro[5.5]undecane subunit **111** of the insecticidal natural product avermectin B_{1a}

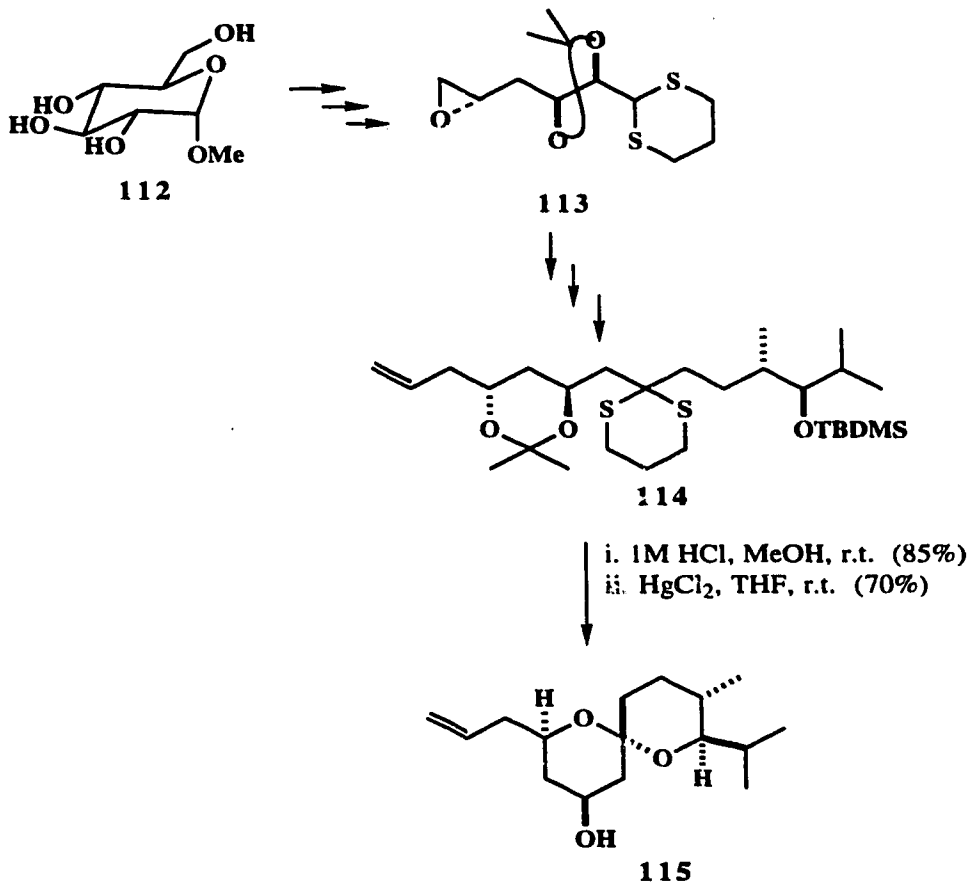
in optically pure form by utilizing readily available optically pure precursors as building blocks. Working through a convergent synthesis (**Scheme 21**) with each piece **109**



Scheme 21

and **110** coming from a series of synthetic manipulations on D-glucose (**109** can also be derived from (*S*)-malic acid), the chirality of the final stereogenic center — the spiro center — was controlled by anomeric stereoselection, giving only one detectable isomer in the final product.

Thomas[43] has reported the synthesis of the spiroacetal fragment **115** in milbemycin E, a natural product related to the avermectins. Beginning from methyl α-D-glucopyranoside **112** (**Scheme 22**), **114** was made in optically pure form via the



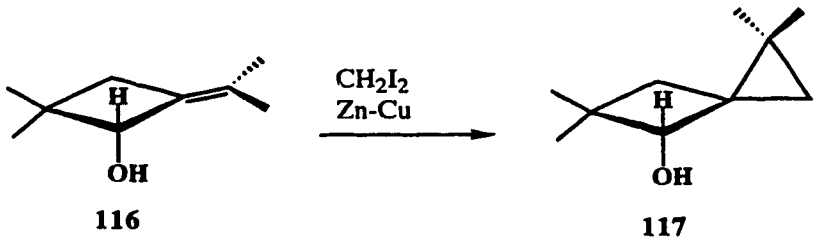
Scheme 22

versatile epoxy dithiane intermediate **113**. Deprotection of **114** led to a spontaneous cyclization to spiroacetal **115** whose spiro center adopted the configuration dictated by the anomeric effect.

C. Spiro formation by stereoselective cyclo-additions:

The asymmetric synthesis of spiro compounds by cycloaddition on an exocyclic double bond is quite uncommon and only a few examples are available in the literature. Perhaps what constitutes the simplest construction of spiranes is a Simmons-Smith methylene insertion on an exo-cyclic double bond. An established observation is

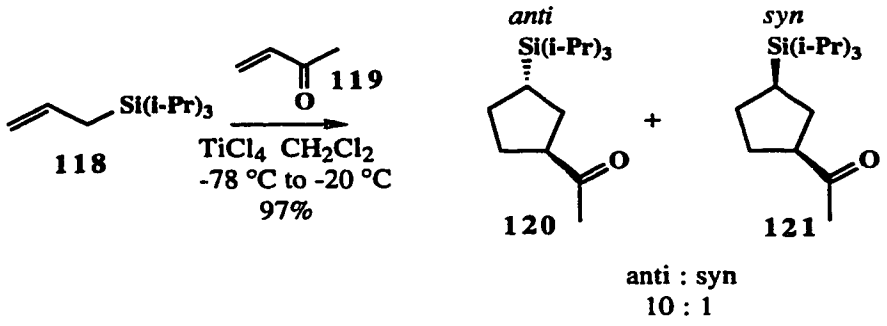
that when a hydroxyl group is allylic to an exocyclic double bond, as in structure **11o** (**Scheme 23**), Simmons-Smith reaction delivers the methylene group from the same



Scheme 23

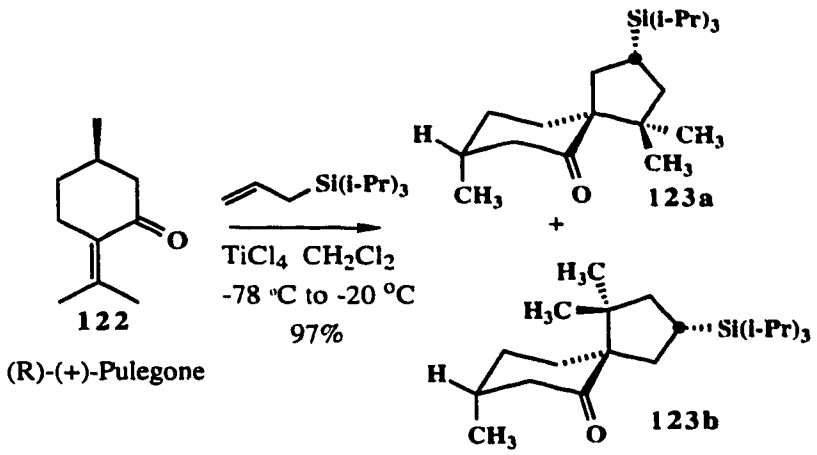
face as the hydroxyl group,[44] giving **117**. This stereospecific construction of spiranes is therefore guided by the stereochemistry of the carbon bearing the hydroxyl group. A choice on the configuration of this carbon in turn is possible by use of the appropriate chiral reducing agent on the corresponding ketone precursor of **116**.

Knölker has reported a stereoselective [3 + 2] cycloaddition of allylsilanes to enones.[45] It was observed that in such reactions, the favored diastereomer always exhibits an *anti* arrangement between the silyl group and the alkanoyl group, as shown in



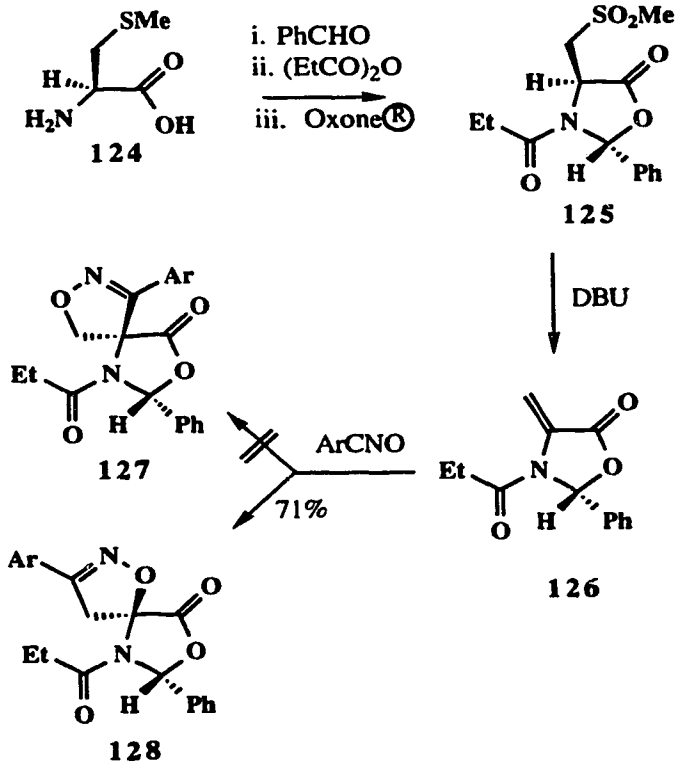
Scheme 24

Scheme 24. Thus, $TiCl_4$ mediated cycloaddition of allyltriisopropylsilane (**118**) to methyl vinyl ketone (**119**) afforded quantitatively the cyclopentanes **120** and **121** in a 10:1 ratio. This cyclo-addition was extended to the exocyclic double bond in (*R*)-(+)-pulegone (**122**) (**Scheme 25**) and two products of type **123a/b** were isolated in a 2:1



Scheme 25

ratio. The same group was able to establish the *anti* disposition of the silyl unit relative to the alkanoyl group in each case of **123** and it was clear that the two products arose from addition of the allylsilane *syn* and *anti* with respect to the methyl group of the pulegone.

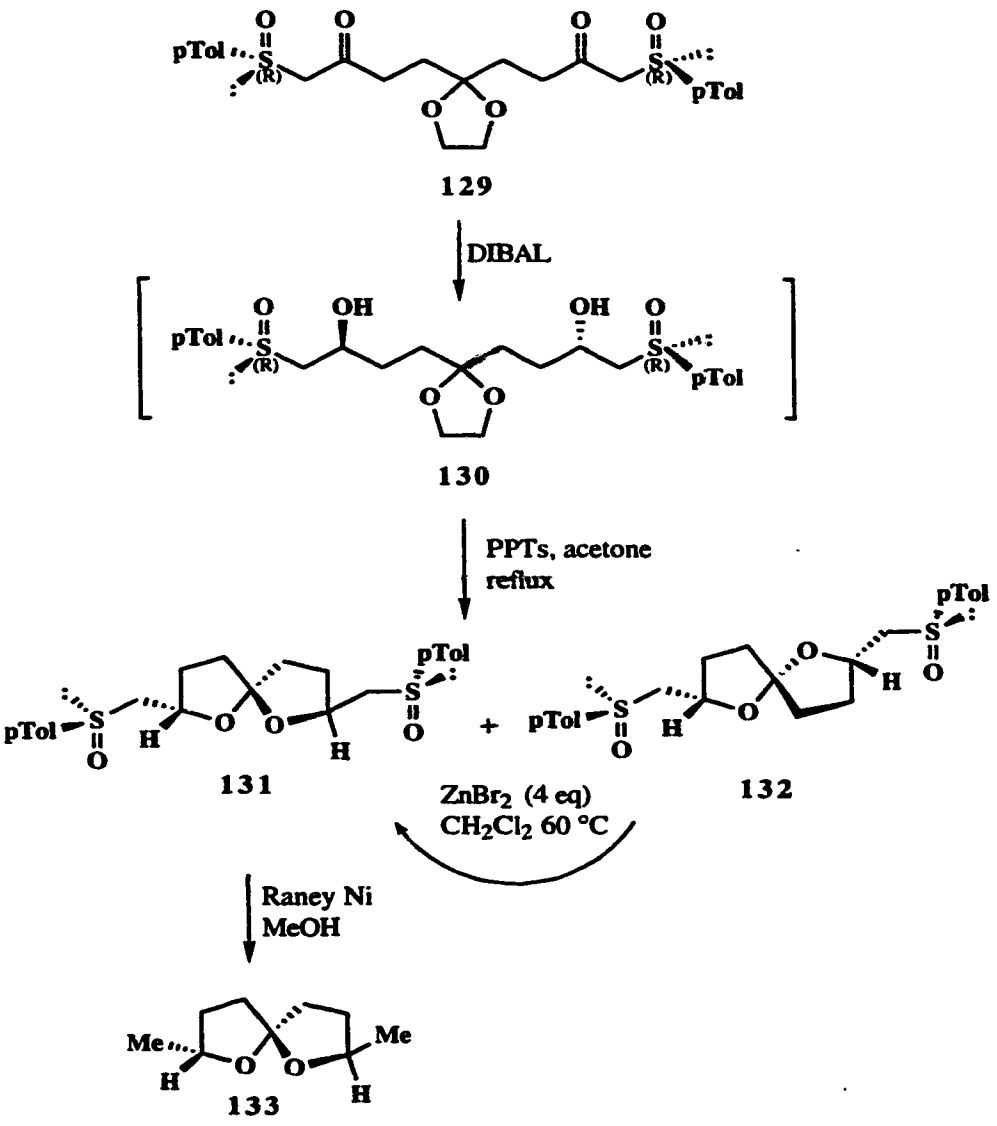


Scheme 26

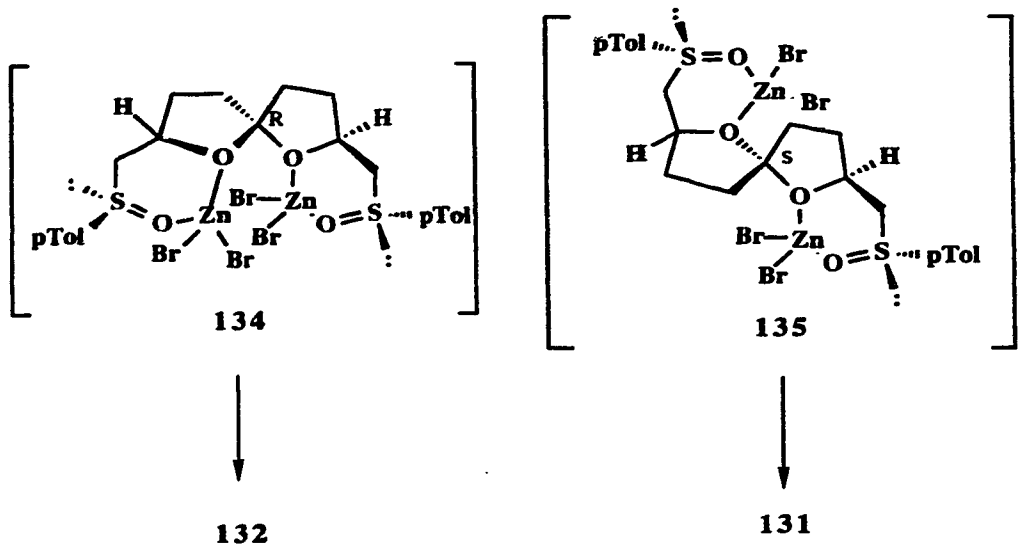
Savage and coworkers have observed a highly regiospecific and stereoselective 1,3-dipolar cycloaddition of 2,6-dichlorobenzonitrile oxide[46] (generated *in situ* by dehydrohalogenation of 2,6-dichlorobenzohydroximinoyl chloride with triethylamine) on **126** [synthesized from (2*S*)-S-methylcysteine (**124**)] giving exclusively **128** (**Scheme 26**). Of the two possible cycloaddition products **127** and **128**, **127** was not observed. This is consistent with previous observations where the nitrile oxide oxygen becomes bonded to the more hindered olefinic site, regardless of activating groups.[47] The nitrile oxide cycloaddition was postulated to have taken place from the face opposite to the phenyl substituent, leading to an *S* configuration at the spiro link. An X-ray crystallographic analysis was conducted to confirm both the regio- and stereochemistry of the cycloaddition.

D. Spiro formation resulting from rearrangements and other methods:

Recently, Solladie reported an enantioselective preparation of the spiroketal **133** by means of an interesting stereocontrolled cyclization done with the aid of zinc bromide as a chelating agent.[48] Treatment of the chiral diketodisulfoxide **129** (**Scheme 27**) with DIBAL afforded **131** and **132** as a 1:1 mixture, together with some uncyclized dihyroxydisulfoxide **130**. Cyclization was completed by refluxing the mixture in acetone with PPTS, affording in 81% yield, **131** and **132** in a 1:1 ratio. Equilibration of the 1:1 mixture of spiroacetals in CH_2Cl_2 at 60 °C in the presence of 4 equivalents of zinc bromide led to complete conversion of **132** to **131**. Thus, only **131** was isolated. It was speculated that because of the Lewis acid character of $ZnBr_2$, a dichelate was formed (**Scheme 28**) where each sulfoxide oxygen is bridged to its nearest oxygen neighbor via the metal. As **134** and **135** equilibrate via an open intermediate, the thermodynamically more stable chelate **135**, which is less hindered than **134**, accumulates over a period of time.

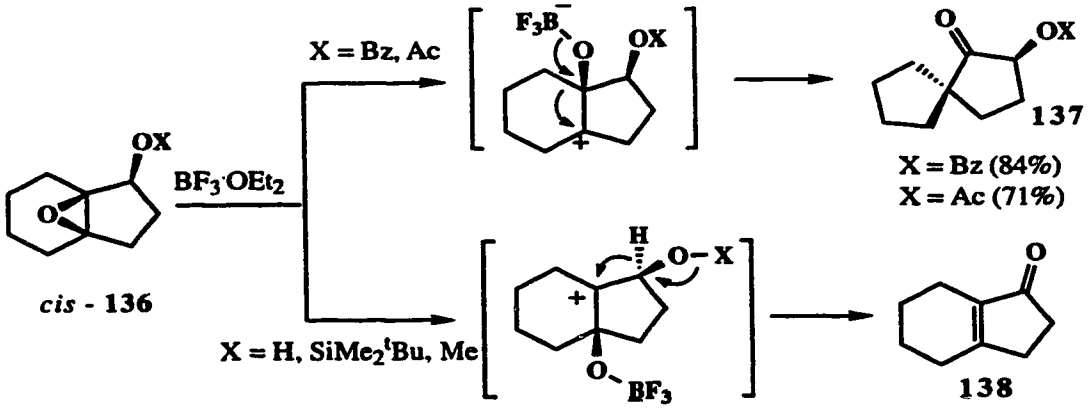

129
DIBAL
130
PPTs, acetone
reflux
131
132
+
ZnBr2 (4 eq)
CH2Cl2 60 °C
Raney Ni
MeOH
133

Scheme 27



Scheme 28

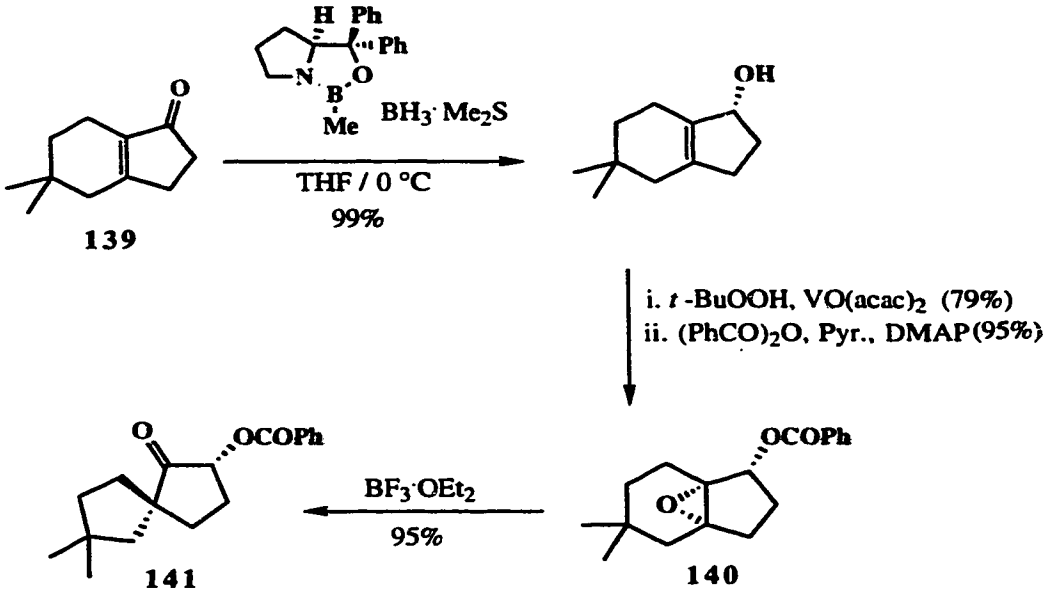
Kita has reported an interesting rearrangement of α,β-epoxyacylates in bicyclo[n.3.0]alkane systems to regioselectively and stereoselectively generate chiral spirocyclanes.[49] It was observed that in the cis-epoxy alcohol system **136** (**Scheme 29**), when X is electron deficient, as in a benzoyl or acetyl group, treatment with



Scheme 29

$BF_3 \cdot OEt_2$ results in a regioselective formation of **137**. However, when X is a hydrogen, methyl, or a *tert*-butyldimethylsilyl group, the electron donating ability of the hydroxyl derivative accelerates cleavage of the oxirane ring at the α position as well as the ensuing hydride migration, leading to the formation of **138**. Extending this finding to the

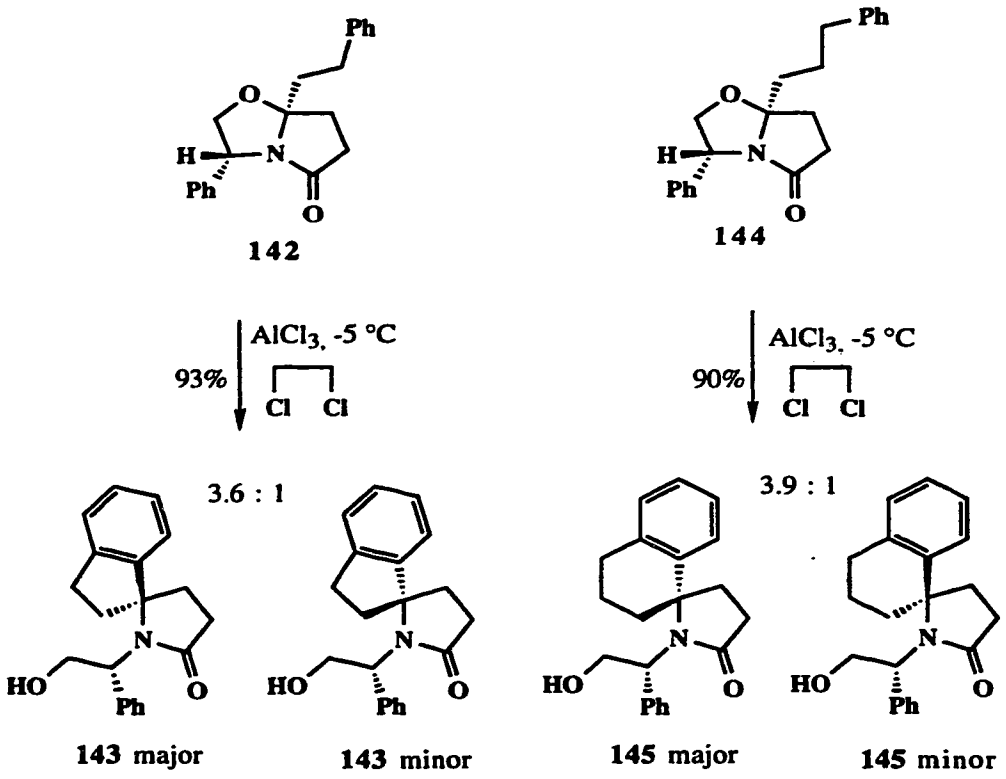
asymmetric series, Kita and coworkers made optically active **140** from **139** (**Scheme 30**). Treatment of **140** with $BF_3.OEt_2$ resulted in the optically active spiro compound



Scheme 30

141 of 91% optical purity. In the case of trans-epoxy benzoate or acetate systems, very low yields of the desired spiro compounds were obtained. Therefore no asymmetric version was carried out for the trans series.

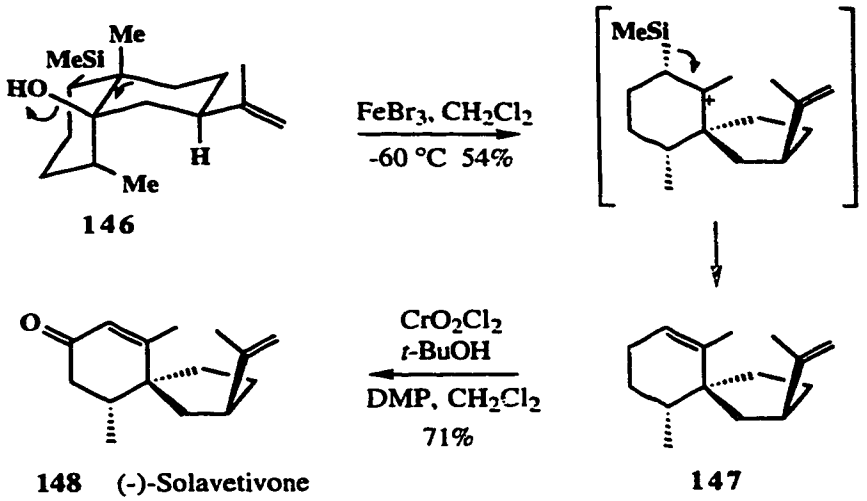
Vernon reported a way toward enantiomeric spirolactams by use of β-amino alcohols as a chiral auxiliary.[50] His group found (**Scheme 31**) that treatment of **142**[51] with 3 equivalents of $AlCl_3$ in 1,2-dichloroethane rearranges the compound into two diastereomeric spirolactams **143** in a ratio of 3.6:1. Under the same conditions, **144** gave **145** as a diastereomeric mixture in a 3.9 :1 ratio.



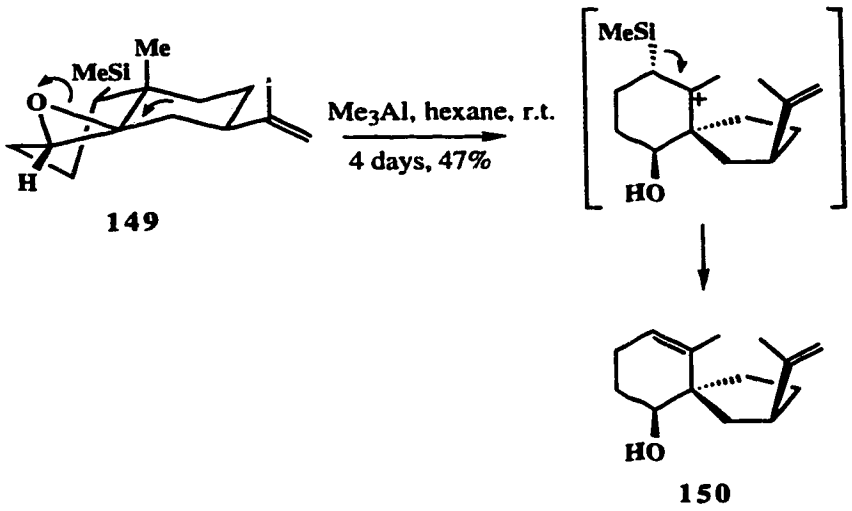
Scheme 31

It is interesting to note, though no explanation was given, that the absolute configuration of the lactam spirocarbon of the major diastereomer of **143** is the same as that in the precursor **142**, but the corresponding carbon in the major diastereomer of **145** is inverted. As the diastereomeric mixtures were chromatographically separable, subsequent removal of the chiral auxiliaries allows for the conversion of these diastereomers into single enantiomers of their corresponding spirolactams.

Another interesting rearrangement is found in the asymmetric synthesis of (-)-solavetivone **148** by Hwu and coworkers.[52] They have developed a method involving silicon promoted stereoselective ring contraction for the synthesis of carbocyclic spiro compounds. It was observed that in both cases of the optically active **146** and **149** (**Schemes 32** and **33**), silicon-promoted ring contraction occurred with a high degree of stereoselectivity, giving **147** and **150** respectively.



Scheme 32

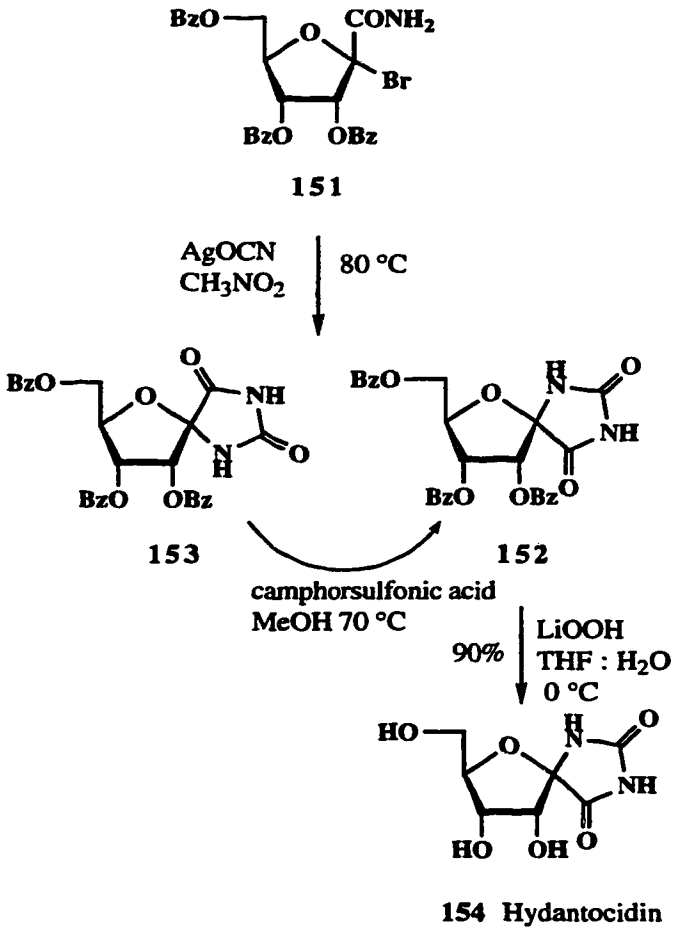


Scheme 33

The work has shown that trans coplanarity between the C-SiMe3 bond and C-leaving group bond is not a prerequisite for the formation of a positive charge on a β carbon. In addition, the facile elimination of the TMS group prevents scrambling of stereochemistry at the spiro center.

In their synthesis of hydantocidin (**154**), Harrington and Jung had observed (**Scheme 34**) that when **151** was treated with silver cyanate in anhydrous nitromethane, a 2:1 mixture of **152** and **153** was obtained.[53] As the minor isomer **153** has the wrong configuration at the spirocenter, refluxing the latter in methanol with camphorsulfonic

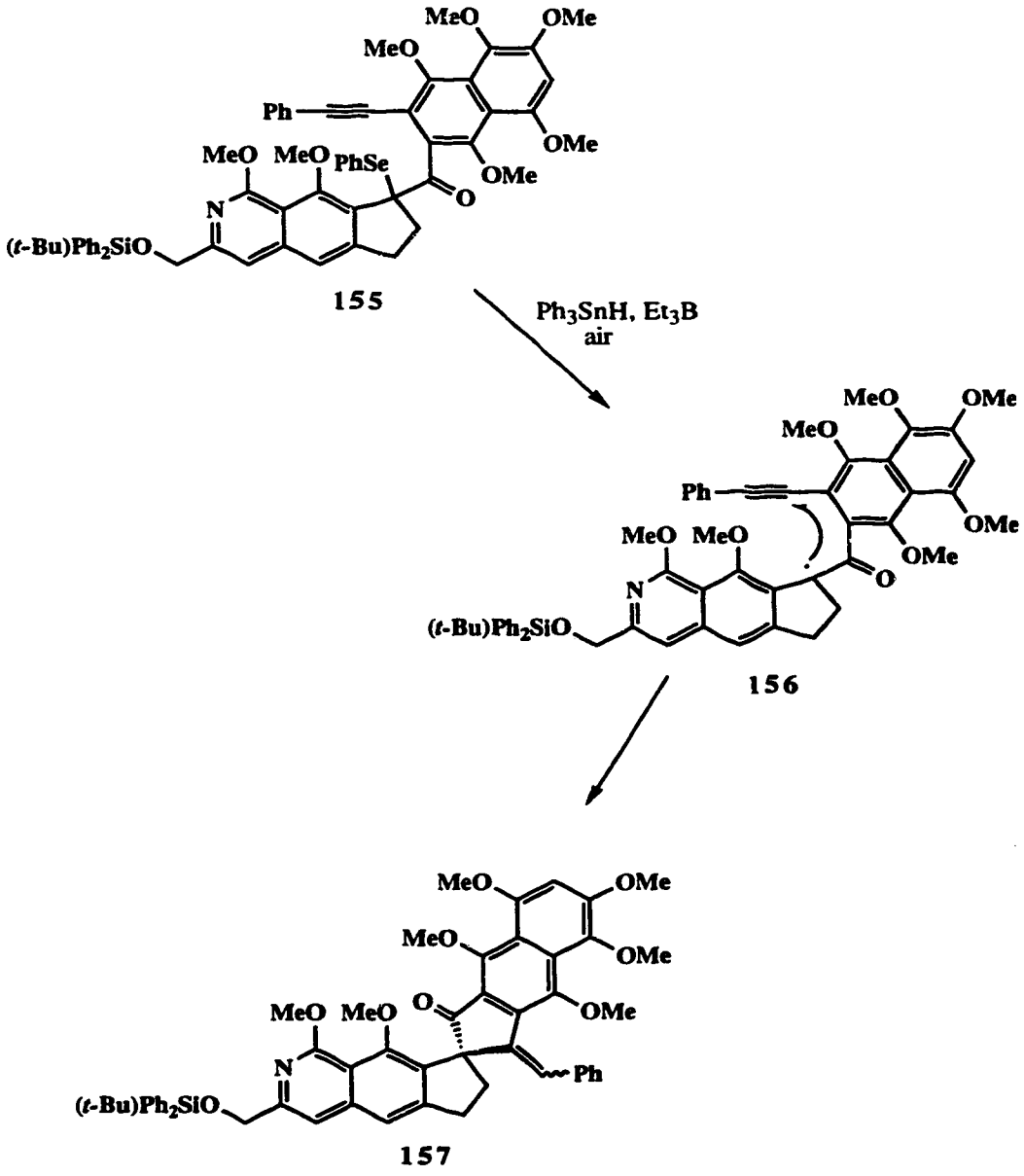
acid, after chromatographic separation from **152**, afforded a 6:1 equilibrium mixture of **152** and **153** with the rearrangement aided by anchimeric assistance of the 2-benzoate group.



Scheme 34

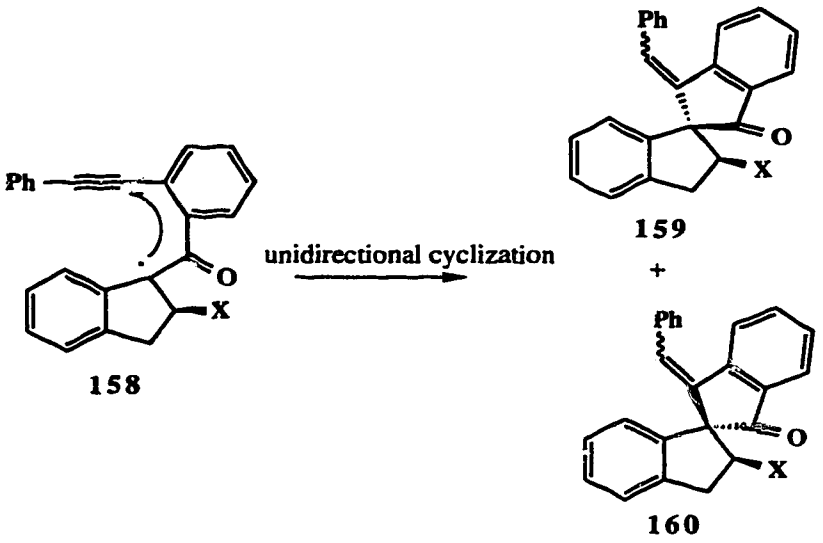
DISCUSSION:

One of the key steps in the total synthesis of fredericamycin A carried out in our group involved the 5-*exo*-dig closure of a tertiary radical **156** (**Scheme 35**), generated from **155**, to give the spirocyclized product **157**.[8] In relation to this



Scheme 35

particular step, we wondered if introduction of a certain group X in the position β to the carbonyl, as in **158** (**Scheme 36**), would lead to a diastereoselective cyclization, giving

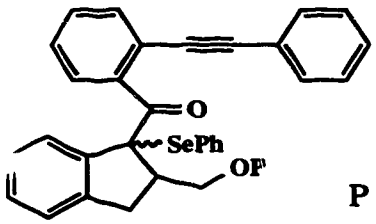


Scheme 36

unequal amounts of **159** and **160**, and preferably one of these in great excess. Should the cyclization be diastereoselective, then in the optically pure series, radical cyclization followed by removal of the X group should constitute an enantioselective methodology towards fredericamycin A.

First attempt:

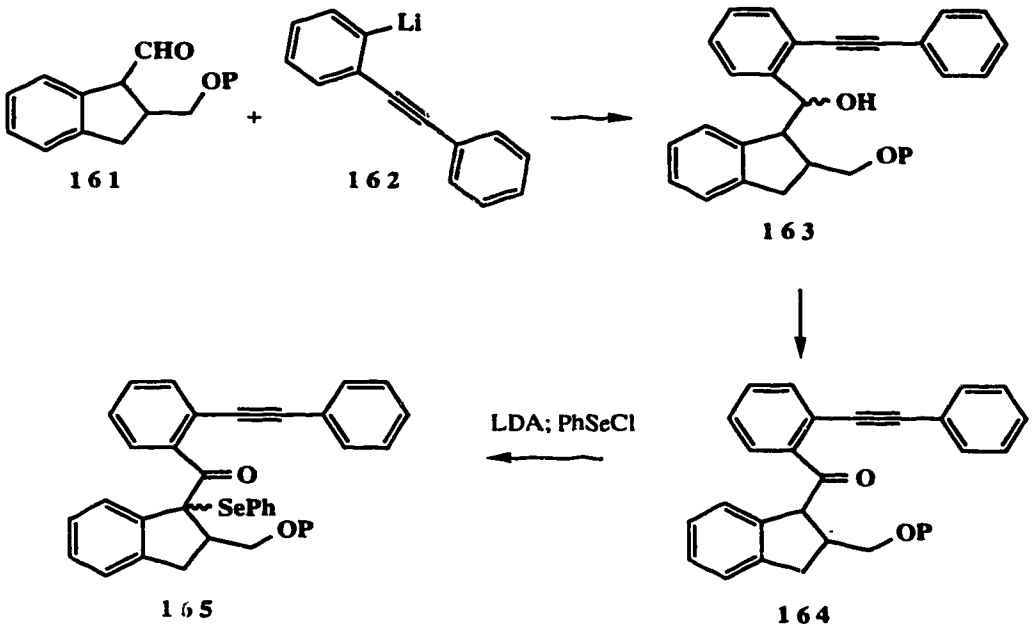
In our first attempt to develop a model to test the above idea, we envisioned building a compound such as that shown in **Figure I-5**. The model compound has all the basic features we needed; namely, a radical precursor in the benzylic position α to the



P = TBDMS or Bn

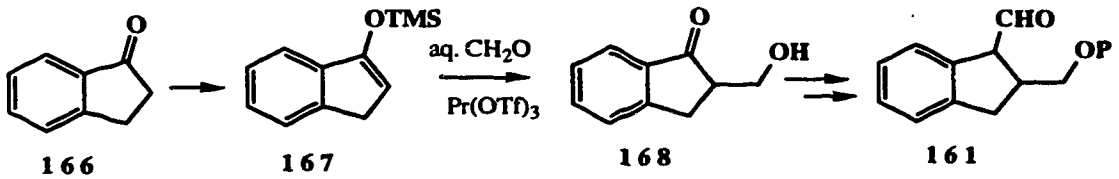
Fig. I-5 Model precursor to spiro compounds

carbonyl and a protected hydroxymethylene group in the β position, to sterically influence the mode of spirocyclization. From a retrosynthetic standpoint (**Scheme 37**), the model could be built by joining **161** and **162**,[59] giving the alcohol **163**, which



Scheme 37

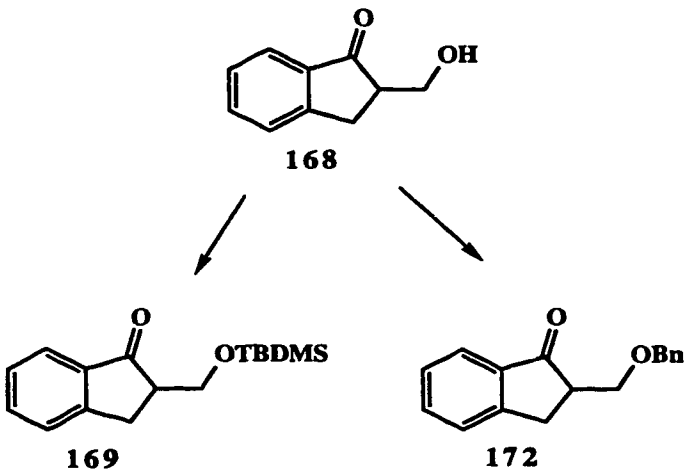
can be oxidized to **164**. Introduction of the radical precursor to **164**, by treatment with LDA and PhSeCl[8] could then provide us with the desired model **165**. However, great difficulty was encountered in synthesizing **161**. From indanone **166**, we could easily make 2-hydroxymethyl-1-indanone (**168**) via the silyl enol ether **167**, by treatment of the latter with commercial formaldehyde in the presence of $Pr(OTf)_3$ as a catalyst.[54]



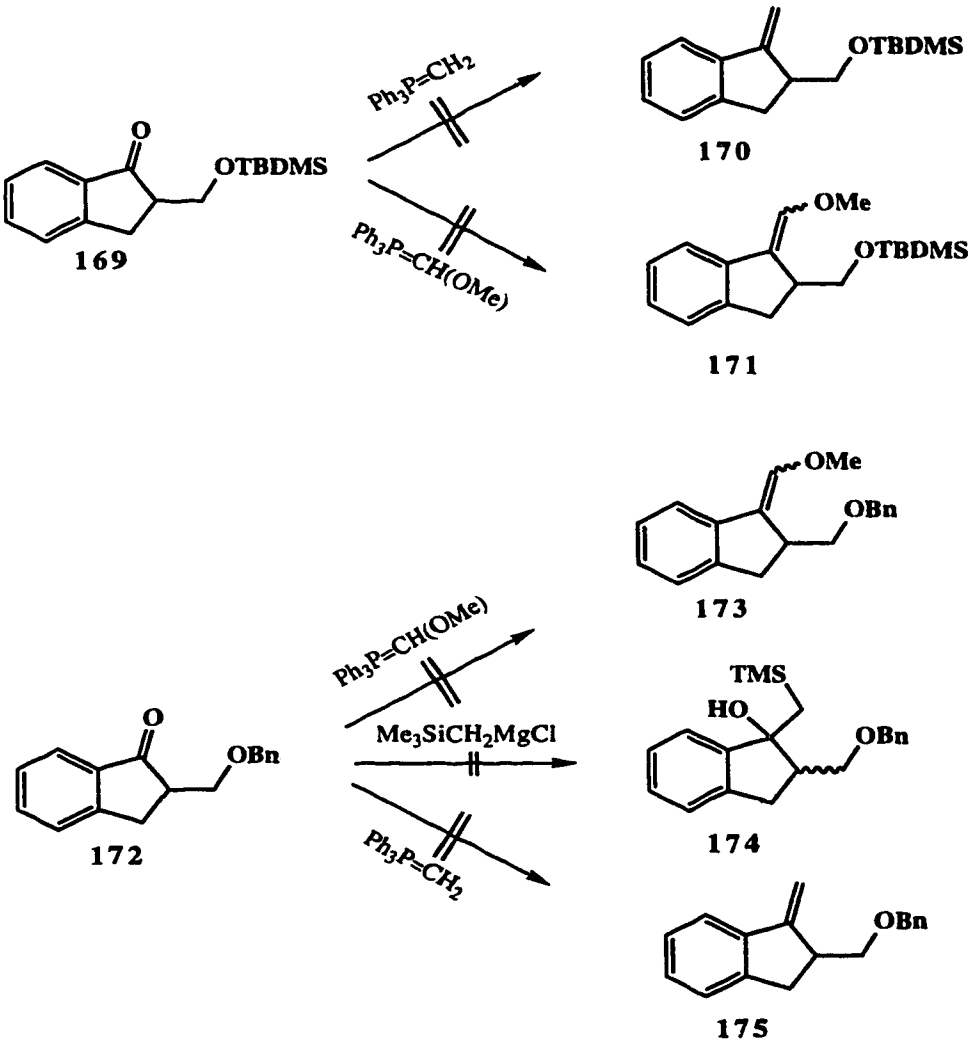
Scheme 38

Protection of the hydroxyl group did not pose any problem. However, the protecting group interfered in the homologation of the carbonyl group, a necessary step towards aldehyde **161**. As shown in the schematic sketches below (**Schemes 39 and 40**), protection of compound **168** as a *tert*-butyldimethylsilyl ether (**169**) or as a benzyl ether (**172**), led to difficulties in homologation of the carbonyl, and none of the desired

products **170**, **171**, **173**, **174**, nor **175**, which could have been taken further to aldehyde **161**, were obtained. For this reason, we decided to embark on a different strategy.



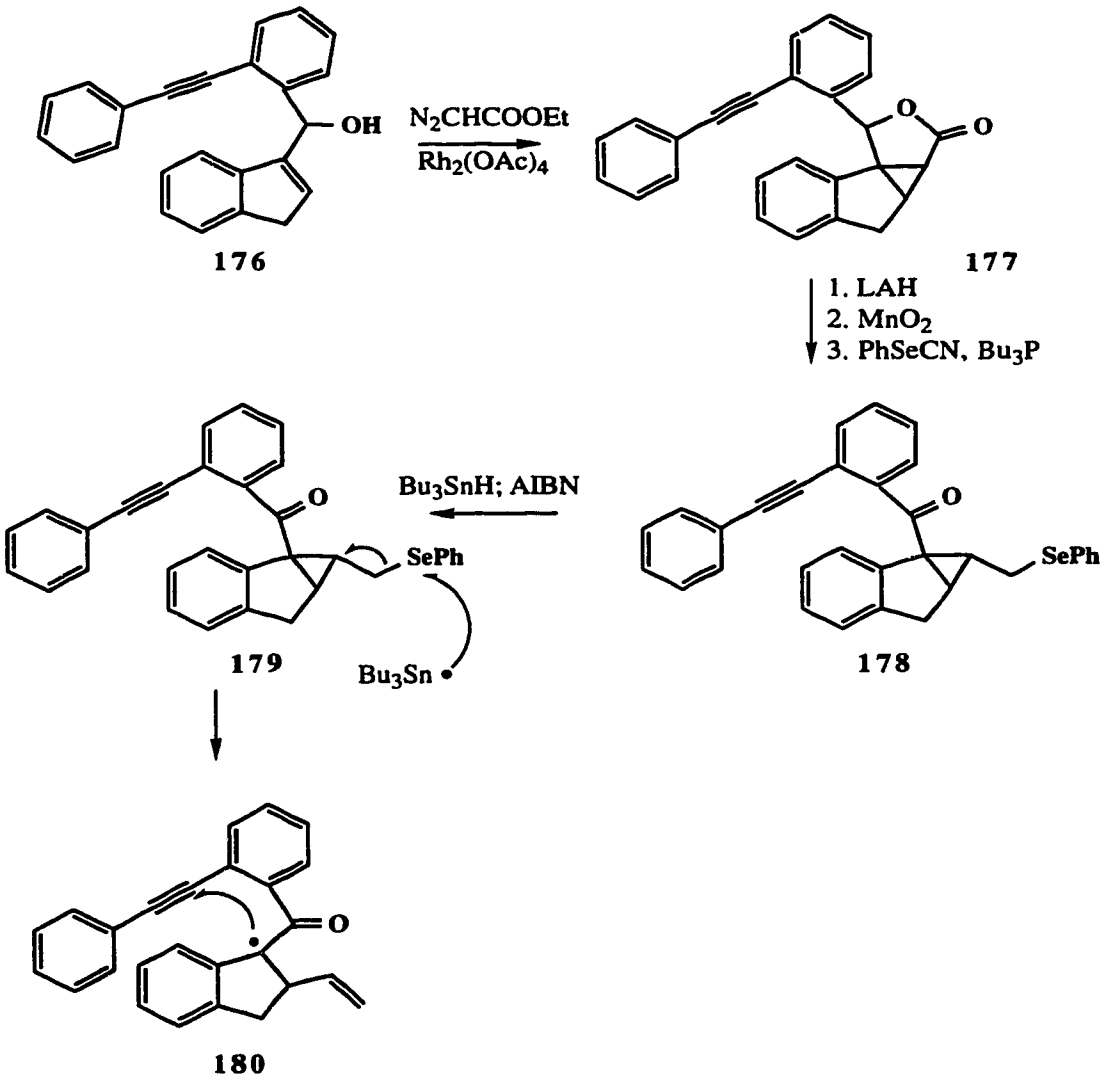
Scheme 39



Scheme 40

Second attempt:

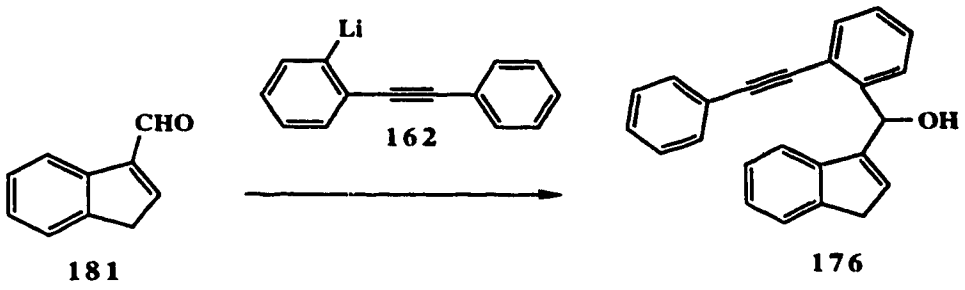
In our second attempt to develop a proper model for our spirocyclization studies, we considered introducing the necessary side chain *after* both homologation and introduction of the acetylenic unit. This strategy would require building alcohol **176**, which we planned (**Scheme 41**) to elaborate into **177** by treatment with $N_2CHCOOEt$



Scheme 41

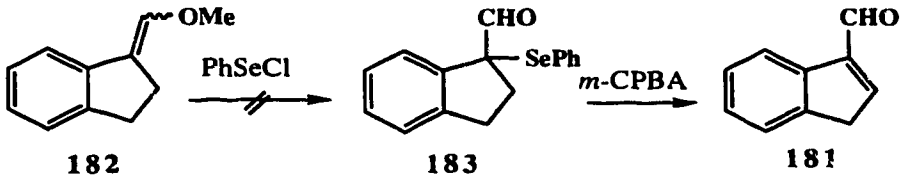
and a rhodium(II) catalyst. Reduction of the lactone, followed by oxidation of the secondary alcohol and phenylselenenylation, sets the model up for our radical spirocyclization experiment. As can be seen, the desired radical **180** is formed by a cyclopropylcarbinyl opening[55] of **179** with the side chain freed at the same time.

Two strategies were tried for the synthesis of alcohol **176**. The first one involved joining **181** to **162** (**Scheme 42**). Although compound **181** looks simple,



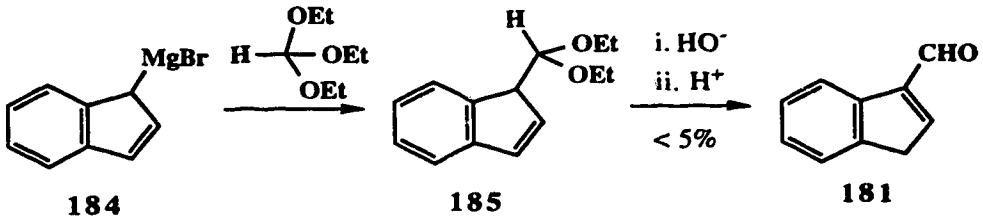
Scheme 42

our attempts to make it were not successful. We tried to make compound **181** from the enol ether **182**[56] (**Scheme 43**) by treatment with PhSeCl followed by selenoxide elimination of **183**. Unfortunately, **183** did not appear to have been generated in our experiments.



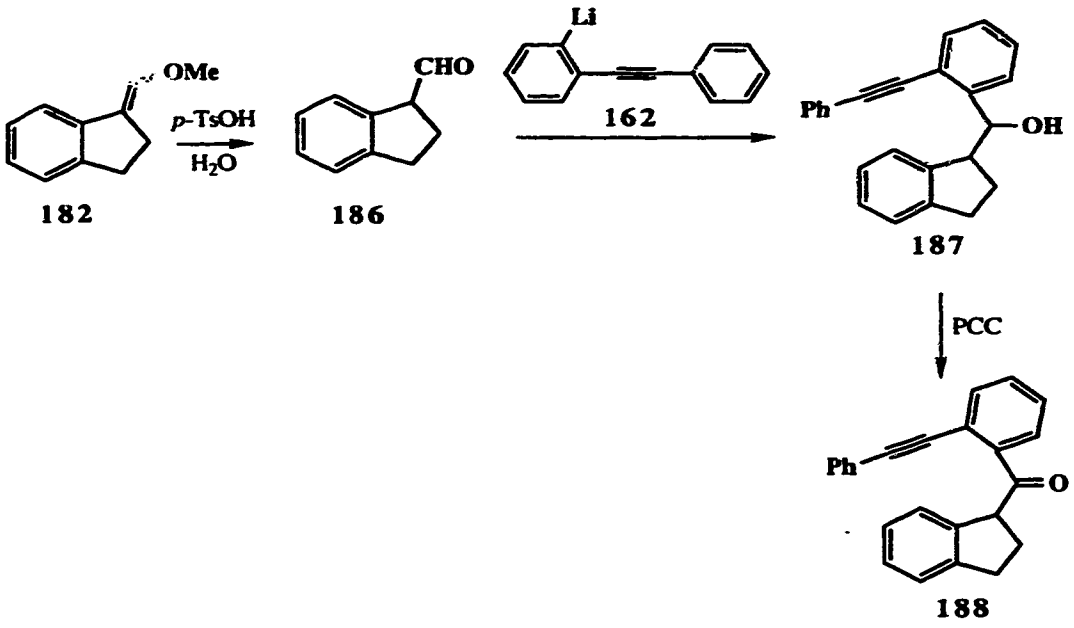
Scheme 43

Porter[57] had tried a different method towards compound **181**. The route they examined involved treating indenylmagnesium bromide **184** (**Scheme 44**) with ethyl orthoformate to give **185**. This was followed by sequential treatment of the latter



Scheme 44

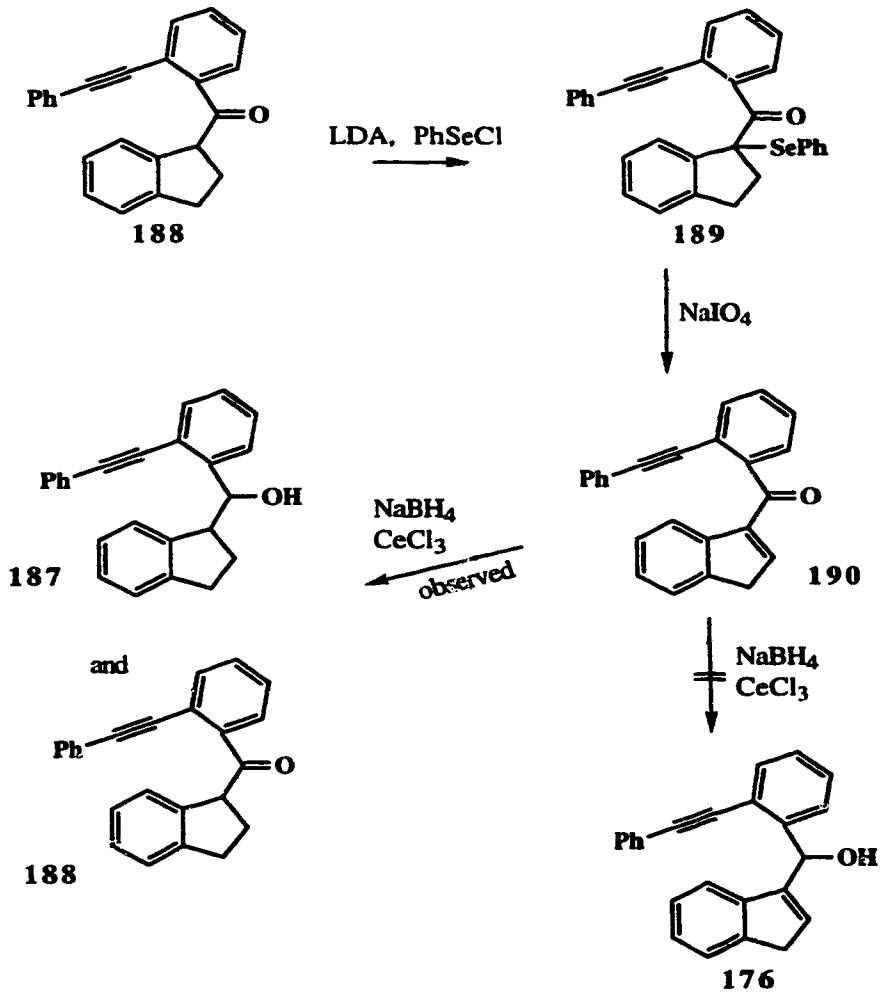
with base and acid. Unfortunately, very low yields of the desired product **181** were obtained, together with much polymer. This result may indicate that the desired aldehyde might be unstable.



Scheme 45

Instead of continuing in our attempts to make compound **181**, we tried to circumvent the problem by aiming for compound **188** first as a way to reach **176**. Compound **188** could be easily made (**Scheme 45**) by joining aldehyde **186** (made from hydrolysis of enol ether **182**) with **162**, giving alcohols **187**. These could be oxidized with PCC to **188**. Contrary to what we thought, it was not easy to convert **188** into **176**.

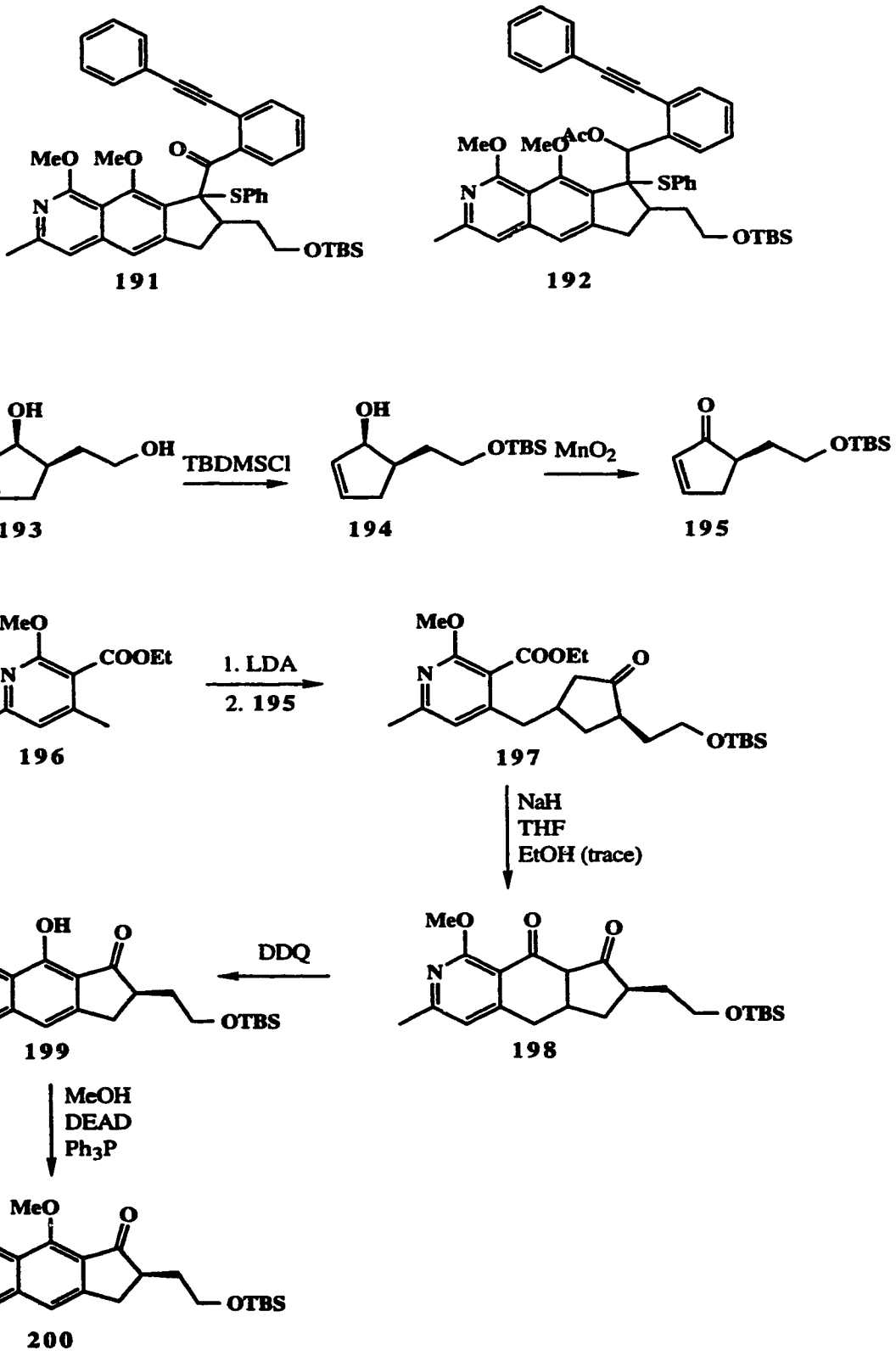
In the series of steps we employed (**Scheme 46**), ketone **188** was subjected to conditions that should have converted it into the required phenylselenoketone **189**. Without isolation,[58] the material was oxidized with sodium periodate and the product, presumed to be **190** was treated directly with sodium borohydride in the presence of cerium (III) chloride. (What we took to be **190** was difficult to purify, and was used, therefore without isolation.) The reduction gave us back ketone **188** and alcohol **187**, and none of alcohol **176** was ever obtained. We assume that the phenylselenenylation had not worked, and so we decided to focus on another model.



Scheme 46

Third attempt:

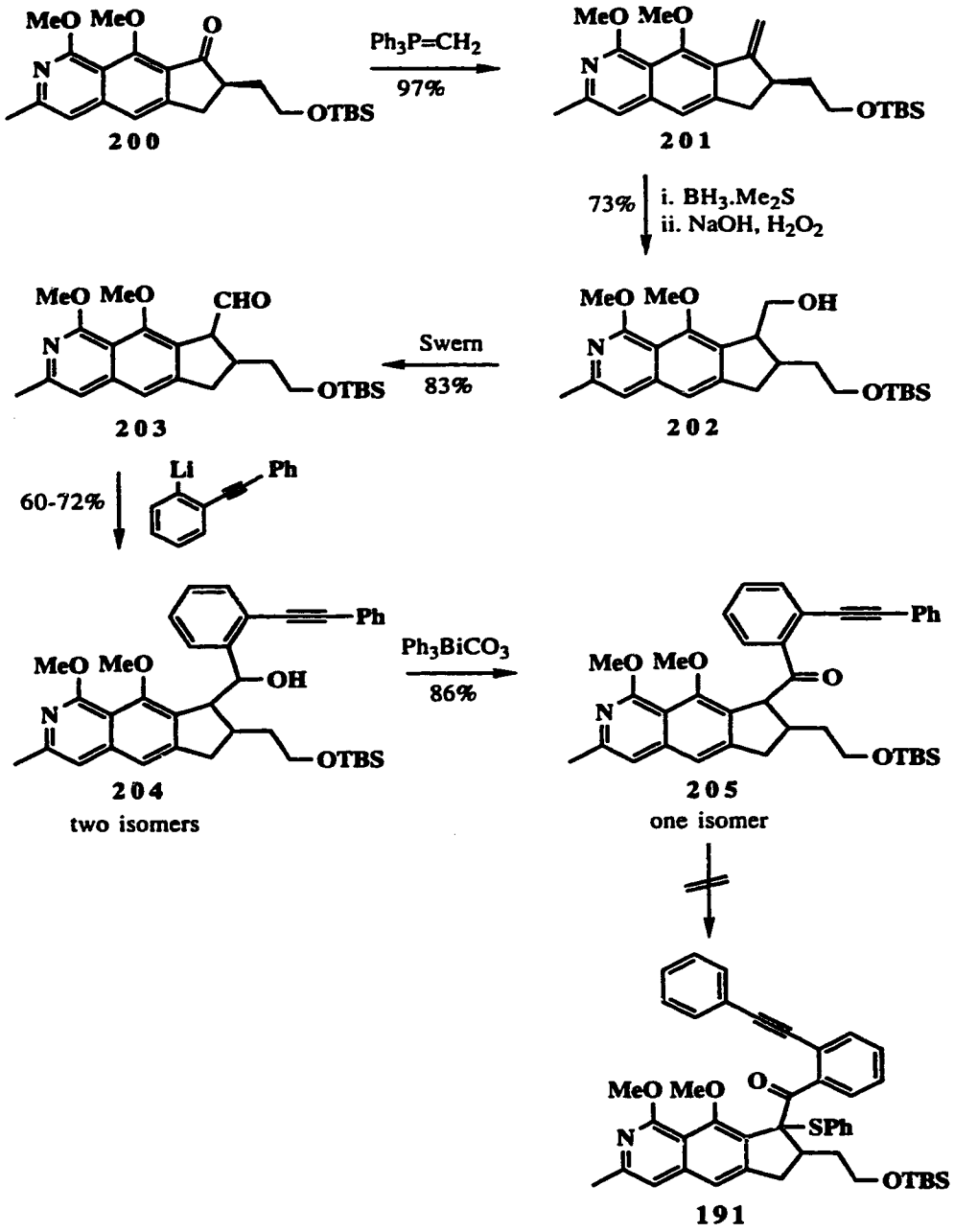
In our third attempt to find a suitable model for the methodology on radical spirocyclization, we sought to work on a compound structurally closer to that of the natural product, and the target we now had in mind was compound **191**. However, for reasons that will become evident later, we conducted the spirocyclization on the corresponding acetate **192**. Scheme 47 shows the route leading to **200**. Diol **193**[60] and pyridine ester **196**[61] were made following literature procedures. The side chain


MeO
MeO
O
SPh
N
OTBS
191
AcO
192
OH
TBDMSCl
MnO2
193
194
195
COOEt
1. LDA
2. 195
196
197
NaH
THF
EtOH (trace)
DDQ
198
199
MeOH
DEAD
Ph3P
200

Scheme 47

primary hydroxyl group in **193** was protected with a *t*-butyldimethylsilyl group giving 62% -80% yield of **194**. Allylic oxidation of **194** was accomplished with activated MnO_2 to give **195** in 45% yield. Coupling of the pyridine ester **196** with ketone **195** gave **197** in 60% yield as a mixture of two diastereomers with similar R_fs. Treatment with NaH cyclized compound **197** to **198** and, without isolation of the product, the crude material obtained after workup was treated with DDQ to afford the anticipated **199**. Again, without isolation, **199** was directly methylated giving **200** with an overall yield of 55% for the three steps. (Higher overall yields were obtained when the intermediates were not isolated.)

From **200**, two routes were tried in an effort to obtain **191**. The first approach (**Scheme 48**) involved homologation of the carbonyl group of **200** by Wittig reaction, to give **201** (in 97% yield). Hydroboration followed by treatment with hydrogen peroxide and base afforded alcohol **202** in 73% yield. Oxidation of **202** to **203** by the Swern method, followed by attachment of the acetylene unit, gave compound **204**, which was easily oxidized to **205** by refluxing in a toluene-pyridine system in the presence of triphenylbismuth carbonate.[62] It was unfortunate that we could not successfully introduce a homolyzable group on **205** so as to arrive at the desired model compound **191**.

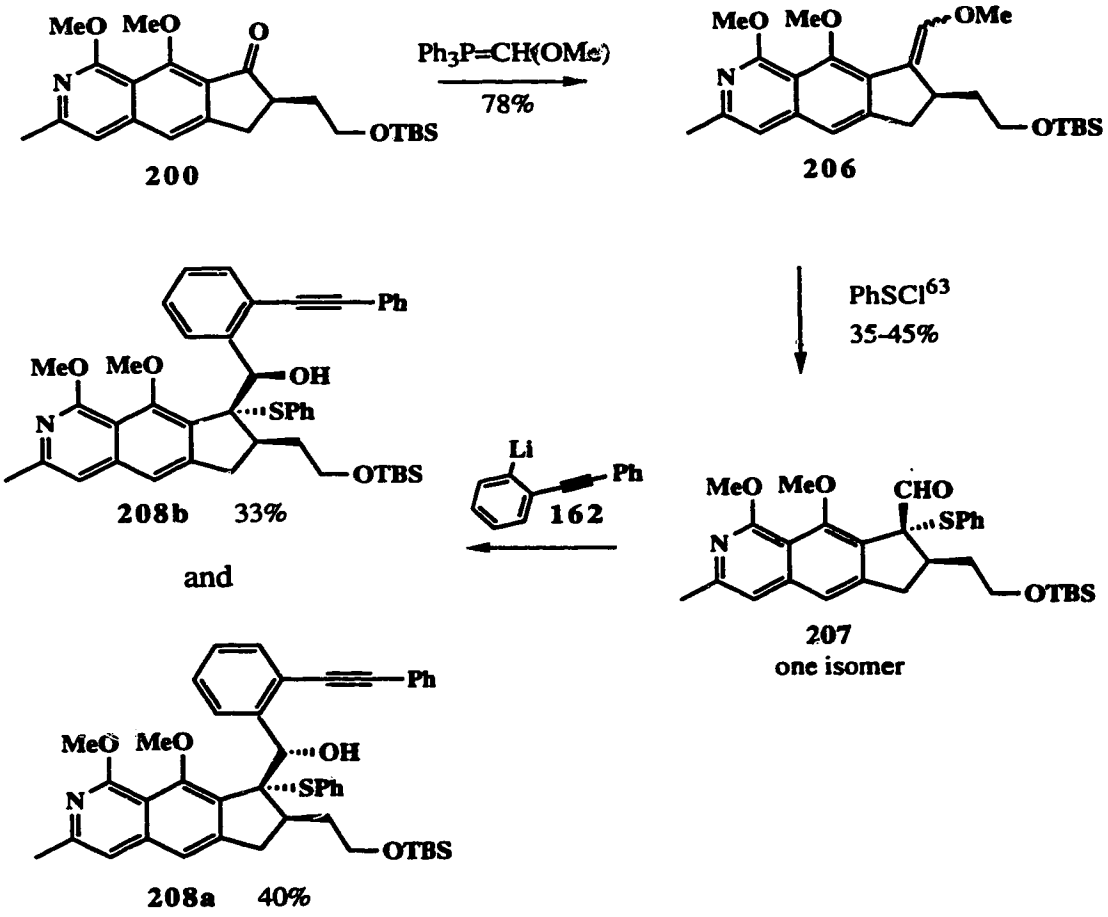


Scheme 48

We briefly enumerate here our efforts to conduct the last step in Scheme 48 **(205 → 191)**:

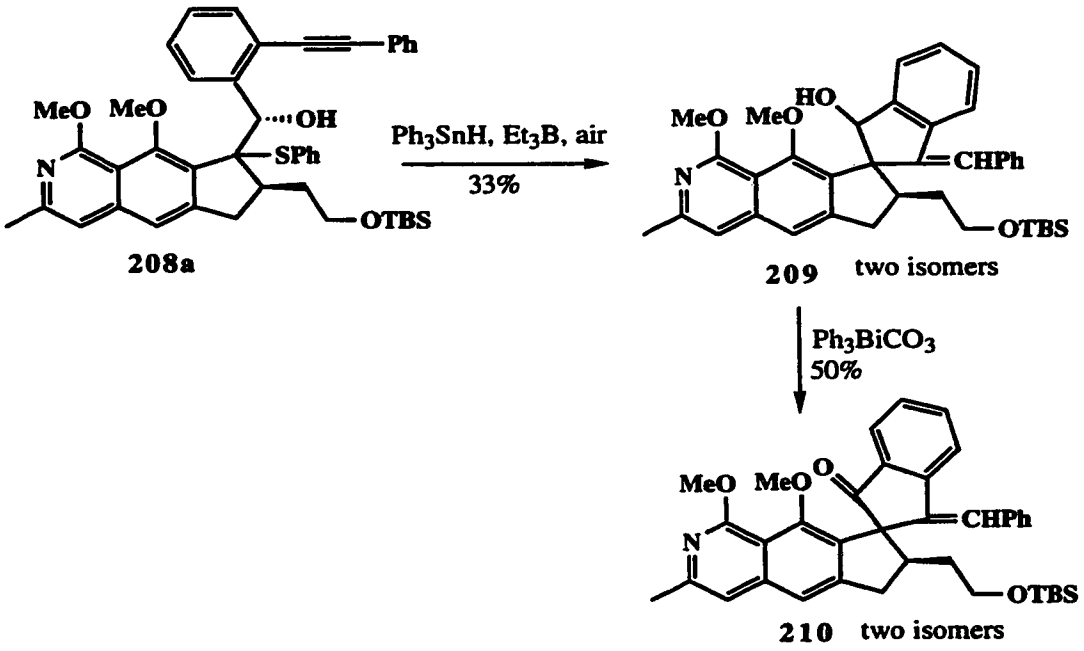
Table I-1. Conditions tried for the conversion of 205 to 191

Trial no.	Conditions	Results
1	1.5 eq. KHMDS 10 eq. PhSSPh THF -78 °C 1 h.	unstable product obtained
2	2 eq. LDA plus 1 eq. of BuLi 10 eq. PhSSPh THF -78 °C	Complex mixture
3	1.5 eq. KHMDS 10 eq. PhSSPh THF:HMPA (3.5:1)-78 °C 1 h	unstable product obtained



Scheme 49

The difficulty in this last step led us to consider introducing the homolyzable group (-**SPh**) at an earlier stage, i.e. prior to incorporation of the acetylene piece. Thus, attachment (**Scheme 49**) of a methoxymethylene group on **200** gave (78%) the enol ether **206** as a mixture of two isomers. This mixture was treated, soon after isolation and drying, with freshly made PhSCl[63] to afford **207** as a single isomer[64]. Finally, treatment of aldehyde **207** with **162** then gave the diastereomers **208a** and **208b** in 40% and 33% yield, respectively. This detour fortunately took us to just one step from **191**. From our inability to introduce a homolyzable group on compound **205**, we suspected that **191** might have been formed in those experiments, but that it was just too unstable to permit isolation. For this reason, we hesitated to oxidize **208a** and **208b** to **191**, and instead used the alcohol itself.



208a

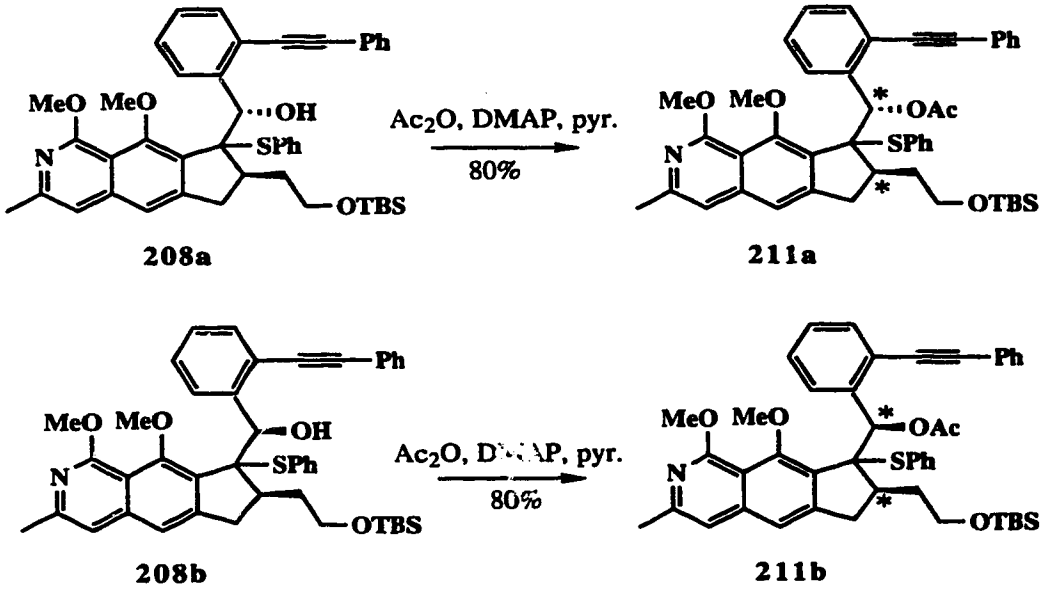
209 two isomers

210 two isomers

Scheme 50

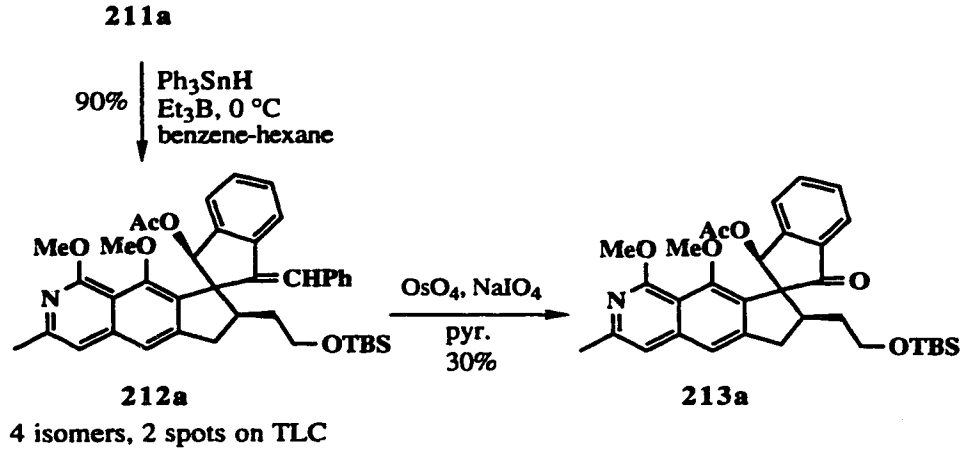
For our preliminary trial on the spirocyclization (**Scheme 50**), we used compound **208a**. Treatment with triphenyltin hydride and triethylborane in a mixture of benzene and hexane at room temperature gave **209** as a pair of isomers which we could not separate by chromatography. Whether the two isomers were due to two geometries

of the double bond or to two modes of closures, was not clear from the proton NMR spectrum of the mixture. In the hope of being able to separate the two isomers at the next stage, we decided to take the compound one step further by oxidation to **210**. Unfortunately, the two isomers were still inseparable. We realized that it should be possible to draw some conclusions about the nature of the spirocyclization, if the double bond in **209** itself was cleaved. To avoid any complications in the double bond cleavage, we decided to convert the alcohols **208a** and **208b** to the corresponding acetates, **211a** and **211b** (**Scheme 51**), respectively, prior to cyclization. When compound **211a** was subjected to our usual radical cyclization conditions at O °C



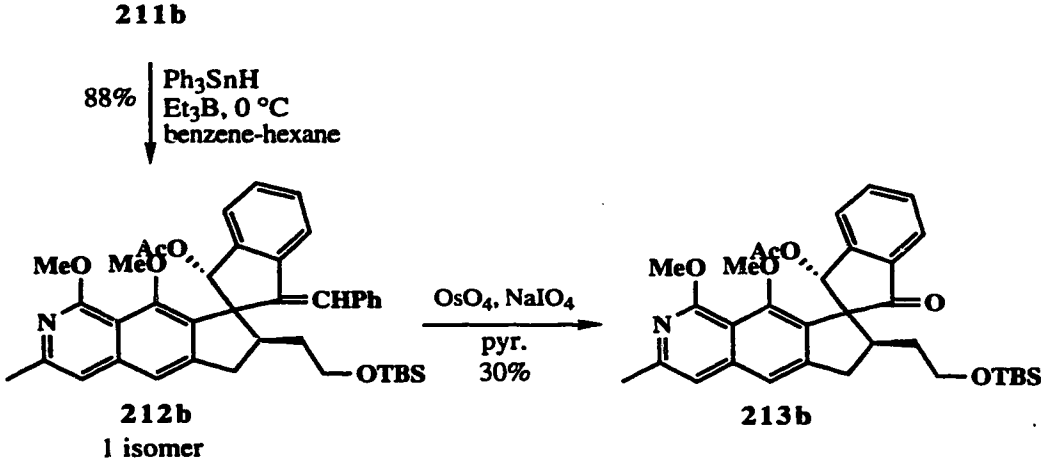
Scheme 51

(**Scheme 52**), we obtained (90%) the expected cyclization product **212a**, as a mixture of four isomers chromatographically separable into two fractions, each containing two isomers. One fraction gave a single ketone **213a** on cleavage of the exocyclic double bond by treatment with $OsO_4/NaIO_4$. Unfortunately, the yield (30%) is not high enough to let us conclude with certainty that the pair of isomers in the radical closure in the particular fraction used differ only with regard to double bond geometry. The other fraction gave no identifiable products in our attempts to cleave the double bond.



Scheme 52

Under similar radical cyclization conditions (**Scheme 53**), we obtained from acetate **211b**, a single cyclization product **212b** in 88% yield. This product gave a



Scheme 53

single ketone (**213b**) (30%), as expected, on treatment with $OsO_4/NaIO_4$, but NOE studies undertaken to establish the relative stereochemistry in the spiro product were inconclusive.

The fact that the cyclization of **211a** gave a mixture of isomers, while cyclization of **211b** gave essentially a single isomer, suggests a highly selective mode of closure.

R = OMe

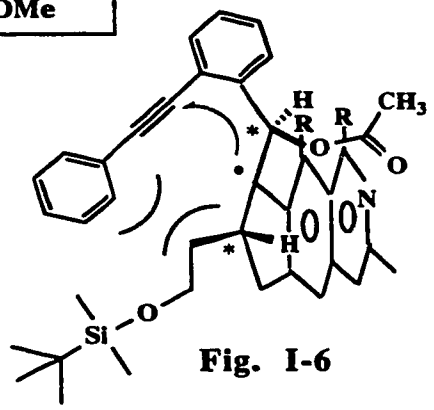


Fig. I-6

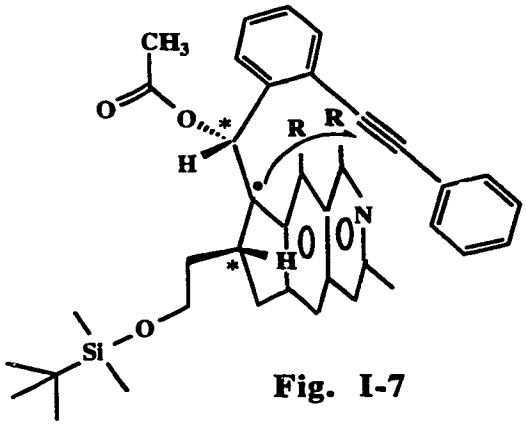


Fig. I-7

Closure of 211b

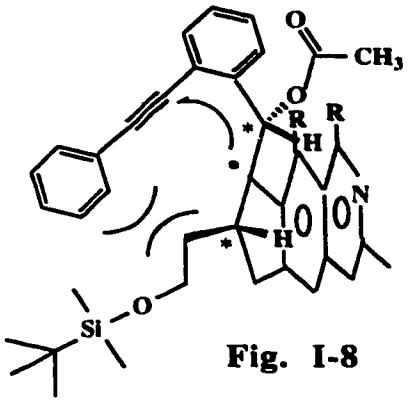


Fig. I-8

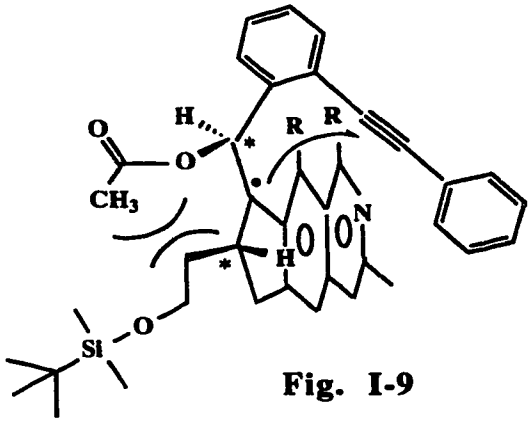
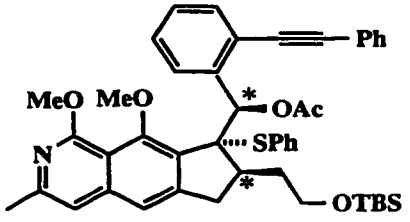


Fig. I-9

Closure of 211a

In fact, these results indicated the relative stereochemistry about the two chiral centers in compounds **211a** and **211b** to be those as shown in **Scheme 51**. The basis of this conclusion can be understood by the fact that given only two possible relative stereochemistries between the two asterisked carbons in each of **211a** and **211b** and only two modes of closures, (see **Figures I-6, I-7, I-8,** and **I-9**) only one of the four radical closures shown would not encounter severe steric interactions; that mode of closure is the one shown in **Figure I-7**. To support this interpretation, a crystal of **211b** (grown from an acetone-benzene medium) was submitted for X-ray analysis. The

results (**Figure. I-10**) confirmed our predictions. (For crystallographic experimental details, please refer to the Appendix at the end of Chapter 2.)



211b

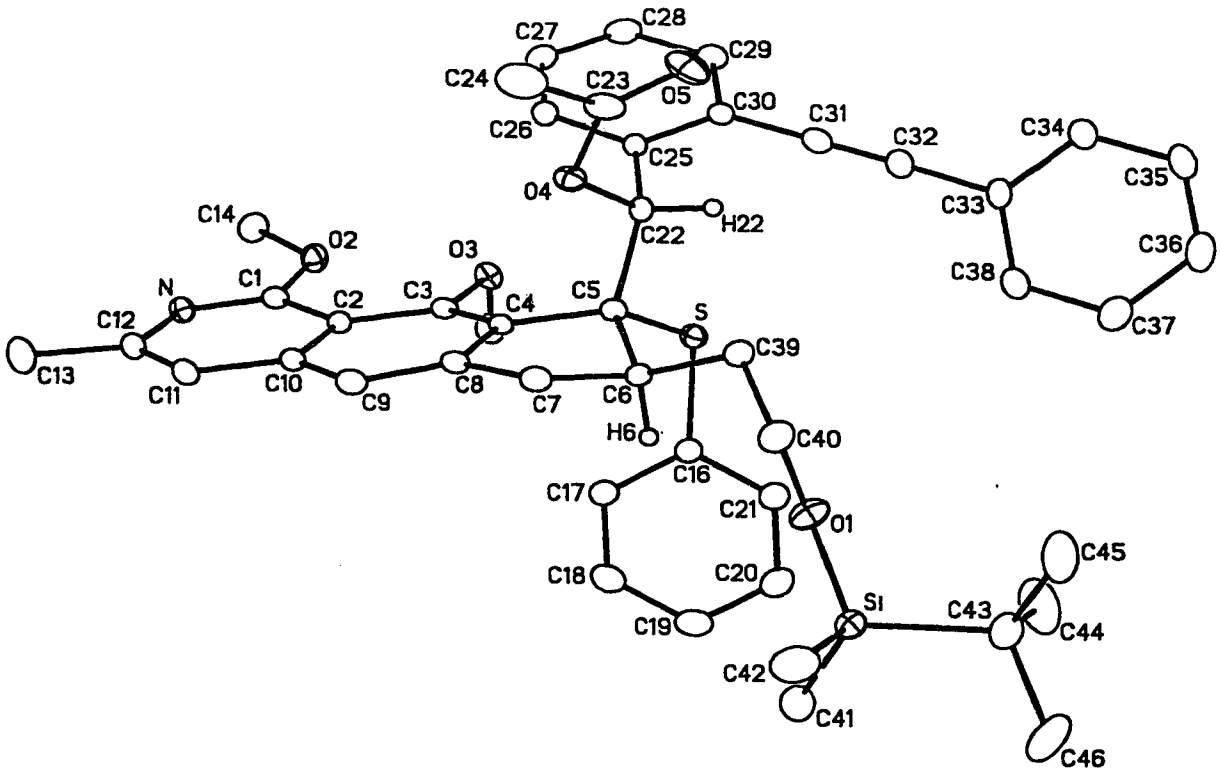


Fig. I-10 Perspective view of compound **211b**

CONCLUSION:

It is clear from our experiments that the stereochemistry of radical spirocyclization is very sensitive to steric effects, and our synthetic work also shows that cleavage of the exocyclic double bond can be very difficult in the present type of radical spirocyclization — presumably due to steric hindrance. A different radical acceptor is needed that will lead to a more easily cleaved unit than =CHPh. For these reasons, we feel that the method of radical spirocyclization is far from ideal for an asymmetric synthesis of compounds of the fredericamycin type. Potential alternatives for the ≡CPh group are (a) ≡CMe, (b) $\equiv CCH_2OPg$ (Pg = protecting group, such as $SiMe_2Bu$-*t*), (c) $\equiv CSiMe_3$. The unit ≡CMe would lead, after radical closure, to =CHMe, which should be sterically less demanding than =CHPh; the unit $\equiv CSiMe_3$, should give, after closure and desilylation, $=CH_2$; and $\equiv CCH_2OPg$ would lead to $=CHCH_2OH$. In the latter case, processes for oxidation of the double bond in allylic alcohol systems could then be tried.

EXPERIMENTAL:

General Procedures. Unless stated to the contrary, the following conditions apply. Reactions were carried out under a slight static pressure of Ar that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst and then through a similar column of Drierite. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Solvents for chromatography and extractions were distilled before use.

Products were isolated from solution by evaporation under water-aspirator vacuum at, or below, room temperature, using a rotary evaporator.

All the compounds purified by chromatography were pure as judged by TLC analysis.

Microliter syringes were washed with water and acetone, using a suction device to draw the solvents through. Then air was sucked through for 1 min. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar), not by suction.

Melting points, determined on a Kofler block melting point apparatus, were uncorrected.

Commercial thin-layer chromatography (TLC) plates (silica gel, Merck 60F–254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid, followed by charring on a hot plate, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry THF and Et_2O were distilled from Na and benzophenone ketyl. Dry PhH was distilled from sodium. Dry Et_3N, CH_2Cl_2, MeOH, MeCN, and pyridine

were distilled from CaH_2. Commercial (Aldrich) solutions of *n*–BuLi and MeLi were assumed to have the stated molarity.

FTIR measurements were made as casts on potassium bromide plates. FTIR spectra were generally obtained by depositing the compound from solution as a cast on a KBr plate.

The symbols s', d', t', and q' used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively. The assignemts made to the APT spectra are based on a consideration of the number of attached protons and the chemical shifts.

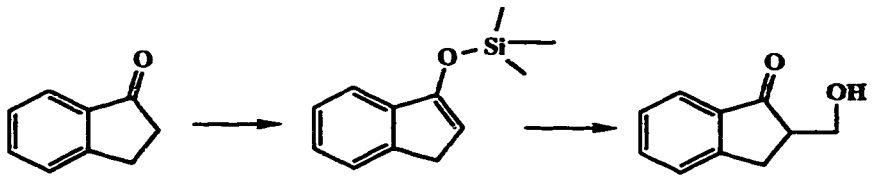
For ^{1}H NMR spectra, coupling constants are measured by assuming a first order splitting.

Mass spectra were recorded with AEI Models MS-12, MS-50, MS9 (modified), or Kratos MS50 (modified) mass spectrometers.

X-ray crystallographic experiments were performed by the Structure Determination Laboratory of this Department.

Microanalyses were performed by the Microanalytical Laboratory of this Department.

2-(Hydroxymethyl)-1-indanone (168).

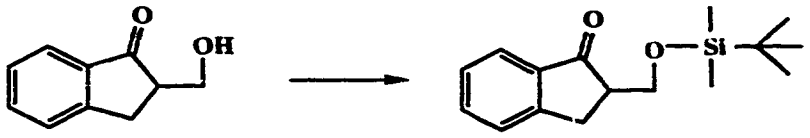


166 **167** **168**

Indanone (**166**) (4.045 g, 30.6 mmol) in dry DMF (5 mL plus 5 mL as a rinse) was added to a stirred solution of Et_3N (5.8 mL, 41.7 mmol) and Me_3SiCl (4.60 mL, 36.2 mmol) in dry DMF (50 mL) at room temperature. The resulting clear orange solution was warmed to 80 °C and stirred for 48 h. After being cooled to room temperature, the mixture was diluted with hexane (60 mL) and washed with cold saturated aqueous $NaHCO_3$ (3 x 50 mL) and brine, and then dried ($MgSO_4$). Evaporation of the solvent gave the crude product **167** (5.62 g) which, without purification, was immediately taken on to the next step.

A solution of crude silyl enol ether **167** (5.62 g) in THF (35 mL) was added by syringe to a stirred solution of commercial formaldehyde (37% aqueous solution, 34 mL, 0.45 mol) and praseodymium triflate[54] (ca. 1 g) in THF (90 mL). The resulting solution was stirred for 41 h. Water (125 mL) was added and the mixture was extracted with CH_2Cl_2 (2 x 80 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 23 cm), using 30:70 EtOAc-hexane, gave **168** (2.916 g, 58.7% over 2 steps) as colorless needle-like crystals: mp 63-65 °C; FTIR (CH_2Cl_2 cast) 3434, 1706 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 2.38 (dd, J = 9, 4.5 Hz, 1 H), 2.80-3.00 (m, 2 H), 3.32 (dd, J = 20, 9 Hz, 1 H), 3.78-3.90 (m, 1 H), 3.92-4.05 (m, 1 H), 7.35-7.43 (m, 1 H), 7.51 (d, J = 9 Hz, 1 H), 7.58-7.66 (m, 1 H), 7.72 (d, J = 9 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 29.61 (t'), 49.14 (d'), 62.85 (t'), 123.91 (d'), 126.68 (d'), 127.52 (d'), 135.16 (d'), 136.70 (s'), 154.39 (s'), 208.81 (s'); exact mass *m/z* calcd for $C_{10}H_{10}O_2$ 162.0681, found 162.0680.

2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl-1-indanone (169).



168 **169**

Imidazole (190 mg,2.79 mmol) in dry CH_2Cl_2 (2 mL) was added to a solution of **168** (180 mg, 1.11 mmol) and *t*-$BuMe_2SiCl$ (210 mg, 1.39 mmol) in dry CH_2Cl_2 (5 mL). The resulting milky suspension was stirred for 2 h at room temperature, and the mixture was diluted with water (10 mL) and extracted with Et_2O (20 mL). The organic layer was washed with water (10 mL), saturated aqueous NH_4Cl (10 mL), and water (10 mL), and then dried ($MgSO_4$). Evaporation of the solvent followed by flash chromatography of the residue over silica gel (2 x 23 cm), using 5:95 EtOAc-hexane, gave **169** (263 mg, 86%) as a clear colorless liquid: ^1H NMR ($CDCl_3$, 300 MHz) δ -0.02 (s, 3 H), 0.03 (s, 3 H), 0.75 (s, 9 H), 2.75-2.89 (m, 1 H), 3.16 (dd, *J* = 17, 4 Hz, 1 H), 3.26 (dd, *J* = 17, 7.5 Hz, 1 H), 3.90-4.05 (m, 2 H), 7.35 (br t, *J* = 7.5 Hz, 1 H), 7.47 (d, *J* = 7.5 Hz, 1 H), 7.58 (br t, *J* = 7.5 Hz, 1 H), 7.73 (d, *J* = 7.5 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 75.469 MHz) δ -5.48 (q'), -5.42 (q'), 18.39 (s'), 25.83 (q'), 30.33 (t'), 50.31 (d'), 63.27 (t'), 123.61 (d'), 126.96 (d'), 127.39 (d'), 134.88 (d'), 137.81 (s'), 155.20 (s'), 207.18 (s'); exact mass *m/z* calcd for $C_{12}H_{15}O_2Si$ (M - *t*-Bu) 219.0841, found 219.0840.

2-(Phenylmethoxy)methyl-1-indanone (172).

168 **172**

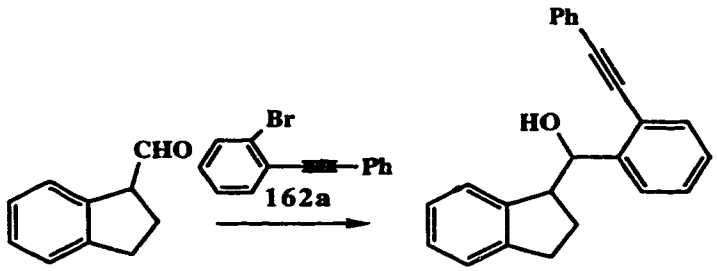
Benzyl-2,2,2-trichloroacetimidate[65] (0.79 mL, 4.23 mmol), followed by CF_3SO_3H (0.02 mL) were added to a stirred solution of **168** (504 mg, 3.11 mmol) in 2:1 cyclohexane-CH_2Cl_2 (10 mL) at room temperature. The solution was stirred under Argon for 1 h. The mixture was filtered to remove the precipitates formed and the solid was washed with CH_2Cl_2 (15 mL). The combined filtrate was washed with saturated aqueous $NaHCO_3$ (25 mL) and water (25 mL), and then dried ($MgSO_4$). Evaporation of the solvent, followed by flash chromatography of the residue over silica gel (3 x 20 cm), using 5:95 EtOAc-hexane, gave **172** (474 mg, 60%) as a clear colorless liquid: ^1H NMR ($CDCl_3$, 300 MHz) δ 2.90-3.00 (m, 1 H), 3.18 (dd, J = 17, 4 Hz, 1 H), 3.33 (dd, J = 17, 8 Hz, 1 H), 3.78 (dd, J = 9, 6.5 Hz, 1 H), 3.87 (dd, J = 9, 4 Hz, 1 H), 4.52 (s, 2 H), 7.28-7.40 (m, 6 H), 7.48 (br d, J = 7.5 Hz, 1 H), 7.59 (dt, J = 7.5, 1 Hz, 1 H), 7.76 (d, J = 7.5 Hz, 1 H); exact mass *m/z* calcd for $C_{17}H_{16}O_2$ 252.1150, found 252.1148.

2,3-Dihydro-1*H*-indene-1-carbaldehyde (186).

182 **186**

p-TsOH·H_2O (62 mg, 0.32 mmol) was added to a solution of enol ether **182**[56] (ca. 333 mg, 2.08 mmol) in 3:1 dioxane-water (28 mL) at room temperature. The resulting solution was refluxed for 11 h and then allowed to cool to room temperature. Water (15 mL) was added and the resulting solution was extracted with Et_2O (2 x 40 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), and dried ($MgSO_4$). Evaporation of the solvent, followed by flash chromatography of the residue over silica gel (3 x 23 cm), using 5:95 EtOAc-hexane, gave **186** (217.4 mg, 71%) as a rose-smelling, yellowish, clear, fairly volatile, liquid: FTIR (hexane cast) 1723 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 2.20-2.35 (m, 1 H), 2.36-2.52 (m, 1 H), 2.85-3.05 (m, 2 H), 3.90-4.05 (m, 1 H), 7.10-7.40 (m, 4 H), 9.67 (d, J = 2.2 Hz, 1 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ 25.79 (t'), 32.15 (t'), 58.46 (d'), 125.69 (d'), 125.80 (d'), 127.35 (d'), 128.53 (d'), 139.79 (s'), 145.52 (s'), 200.84 (d'); exact mass *m/z* calcd for $C_{10}H_{10}O$ 146.07317, found 146.07355.

2,3-Dihydro-1-[1-hydroxy-1-[2-(phenylethynyl)-phenyl]]methyl-1*H*-indene (187).

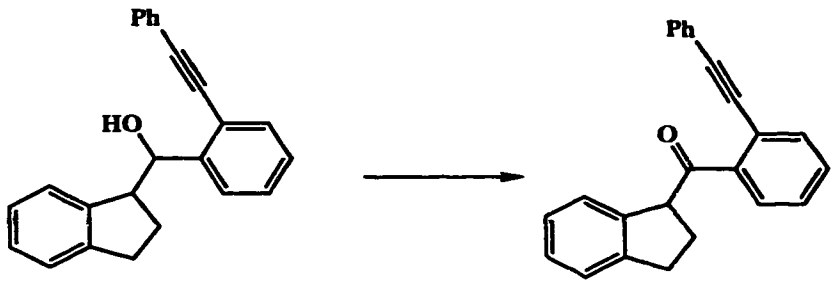


186 **187**

n-BuLi (1.6 M in hexanes, 0.75 mL, 1.20 mmol) was added to a cold (-78 °C) and stirred solution of **162a**[66] (308 mg, 1.20 mmol) in dry THF (8.0 mL). The resulting golden brown solution was stirred for 10 min and then transferred by cannula into a cold (-78 °C) and stirred solution of **186** (117 mg, 0.80 mmol) in dry THF (5 mL). Stirring was continued at -78 °C for 3 h, and the cold bath was then removed. When the mixture had warmed to room temperature, water (25 mL) was added and the mixture was extracted with Et_2O (2 x 25 mL). The combined organic extract was washed with brine and dried ($MgSO_4$). Evaporation of the solvent, followed by flash chromatography of the residue over silica gel (3 x 20 cm), using 5:95 EtOAc-hexane, gave **187** (195 mg, 75%) as a clear, colorless oil which consists of a mixture of two diastereomers in ratio of ca. 4:5: FTIR (CH_2Cl_2 cast) 3547 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.90-2.45 (m, 3 H), 2.85-3.25 (m, 2 H), 3.75-3.85 and 3.90-4.00 (both m, 1 H), 5.32 and 5.77 (both d, J = 8 and 4 Hz respectively, 1 H), 7.20-7.90 (m, 13 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 25.11 (t')*, 29.50 (t'), 31.52 (t')*, 31.64 (t'), 51.16 (d')*, 52.14 (d'), 73.25 (d')*, 75.44 (d'), 87.19 (s')*, 87.55 (s'), 94.41 (s'), 94.60(s')*, 120.65 (s')*, 121.53 (s'), 123.07 (s'), 123.10 (s')*, [the following set of peaks corresponds to the aryl doublets for both diastereomers and are not classified; some peaks must coincide: δ 123.98, 124.68, 124.79, 126.02, 126.11, 126.20, 126.38,

126.71, 127.01, 127.15, 127.36, 127.85, 128.47, 128.79, 131.49, 132.16, 132.37], 143.46 (s')*, 143.99 (s'), 144.65 (s')*, 145.12 (s'), 145.33 (s'), 145.64 (s')*; exact mass *m/z* calcd for $C_{24}H_{20}O$ 324.15143, found 324.15197.

2,3-Dihydro-1-[2-(phenylethynyl)benzoyl]-1*H*-indene (188).



187 **188**

A solution of **187** (280 mg,0.86 mmol) in dry CH_2Cl_2 (8 mL plus 1 mL as a rinse) was added by syringe to a mixture of PCC (745 mg, 3.45 mmol) and 4 Å molecular sieves (2 g) in dry CH_2Cl_2 (15 mL). The mixture was stirred for 4 h at room temperature, and then diluted with Et_2O (40 mL) and poured through a pad of Celite (3 x 3 cm). The Celite pad was washed with 1:1 Et_2O-CH_2Cl_2 (20 mL). The combined filtrates were evaporated, and flash chromatography of the residue over silica gel (2 x 25 cm), using 5:95 EtOAc-hexane, gave **188** (203.4 mg, 73%) as a pure (^{1}H NMR, 300 MHz) colorless ,clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.35-2.52 (m, 1 H), 2.53-2.65 (m, 1 H), 2.90-3.03 (m, 1 H), 3.08-3.25 (m, 1 H), 5.37 (dd, *J* = 8.5, 5.5 Hz, 1 H), 7.00-7.60 (m, 12 H), 7.66 (br d, *J* = 7.5 Hz, 1 H); exact mass *m/z* calcd for $C_{24}H_{18}O$ 322.13577, found 322.13675.

5-[2-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]ethyl]-2-cyclopenten-1-ol (194).

193 **194**

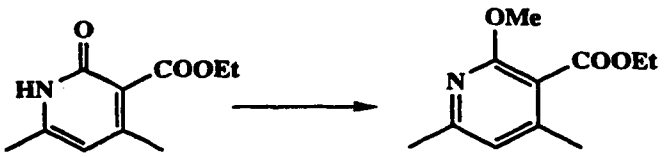
A solution of imidazole (21.27 g, 312.5 mmol) in dry CH_2Cl_2 (125 mL) was added to a cold (0 °C) and stirred solution of **193**[60] (16.0 g, 125 mmol) in dry CH_2Cl_2 (220 mL). After 5 min, *t*-$BuMe_2SiCl$ (18.84 g, 125 mmol) in dry CH_2Cl_2 (80 mL plus 25mL as a rinse) was injected over 5 min, and the resulting solution was stirred for 10 min. Saturated aqueous NH_4Cl (125 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 100 mL). The organic extract was washed with brine (350 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue in two batches, each over silica gel (5 x 23 cm), using 1:19 EtOAc-hexane, gave **194** (18.7 g, 62%) as a pure (^1H NMR, 200 MHz), clear oil: FTIR ($CHCl_3$ cast) 3404 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.09 (s, 6 H), 0.90 (s, 9 H), 1.55-1.75 (m, 1 H), 1.8-2.25 (m, 3 H), 2.25-2.5 (m, 1 H), 3.2 (br s, 1 H), 3.65 (dt, *J* = 10, 3.2 Hz, 1 H), 3.75-3.90 (m, 1 H), 4.6-4.71 (m, 1 H), 5.8-5.93 (m, 1 H), 5.93-6.5 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ -5.62 (q'), 18.15 (s'), 25.82 (q'), 31.61 (t'), 37.56 (t'), 42.01 (d'), 63.44 (t'), 75.93 (d'), 132.70 (d'), 134.72 (d'); exact mass *m/z* calcd for $C_{13}H_{26}O_2Si$ 242.17021, found 242.17040. Anal. Calcd for $C_{13}H_{26}O_2Si$: C, 64.41; H, 10.81. Found: C, 64.35; H, 10.94.

5-[2-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]ethyl]-2-cyclopenten-1-one (195).

194 **195**

Activated manganese(IV) oxide (Aldrich no. 21,764-6, 39.30 g, 452.2 mmol) and anhydrous NaOAc (2.78 g, 33.92 mmol) were added to a stirred solution of **194** (5.47 g, 22.61 mmol) in dry $CHCl_3$ (225 mL). After 24, 48, and 72 h, additional dry $CHCl_3$ (25 mL), activated manganese(IV) oxide (39 g, 448.6 mmol) and anhydrous NaOAc (2.78 g, 33.92 mmol) were added. After the last addition of reagents, stirring was continued for 12 h. The mixture was filtered through a pad of Celite (4 x 10 cm), and the pad was washed well with CH_2Cl_2 (*ca.* 1000 mL). Evaporation of the combined filtrates and flash chromatography of the residue over silica gel (5 x 23 cm), using 1:19 EtOAc-hexane, gave pure (^1H NMR, 400 MHz) **195** (2.43 g, 45%) as a thick, clear oil: FTIR ($CDCl_3$, cast) 1717 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.05 (s, 6 H), 0.88 (s, 9 H), 1.58 (m, 1 H), 1.80 (m, 1 H), 2.05 (dd, J = 19, 2.5 Hz, 1 H), 2.55 (dd, J = 18.5, 6.2 Hz, 1 H), 3.12 (m, 1 H), 3.72 (m, 2 H), 6.14 (dd, J = 6.0, 2.0 Hz, 1 H), 7.67 (dd, J = 5.8, 2.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ -3.55 (q'), 18.26 (s'), 25.93 (q'), 34.19 (t'), 36.07 (t'), 42.40 (d'), 61.49 (t'), 133.73 (d'), 163.38 (d'), 212.40 (s'); exact mass *m/z* calcd for $C_9H_{15}O_2Si$ (M - C_4H_9) 183.08414, found 183.08392.

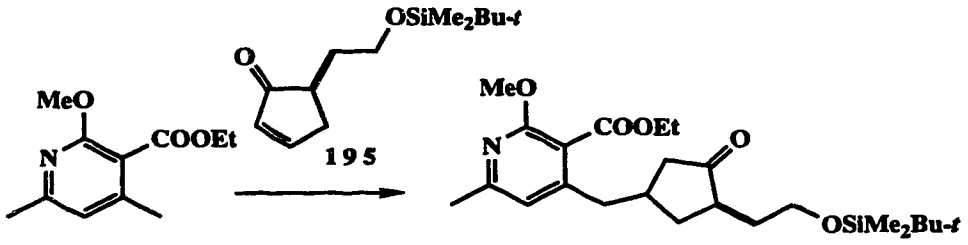
Ethyl 2-methoxy-4,6-dimethyl-3-pyridinecarboxylate (196).



196' **196**

Pyridine ester **196** was made following literature[61] procedures and had: FTIR (CH_2Cl_2 cast) 1730cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37 (t, J = 7.1 Hz, 3 H), 2.26 (s, 3 H), 2.41 (s, 3 H), 3.94 (s, 3 H), 4.37 (q, J = 7.1 Hz, 2 H), 6.57 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) δ 14.21 (q'), 18.99 (q'), 23.96 (q'), 53.68 (q'), 61.14 (t'), 114.34 (s'), 117.66 (d'), 147.51 (s'), 156.95 (s'), 160.32 (s'), 167.34 (s'); exact mass *m/z* calcd for $C_{11}H_{15}NO_3$ 209.10519, found 209.10455.

Ethyl [[4-[2-[[Dimethyl(1,1-dimethylethyl)silyl]-oxy]ethyl]-3-oxocyclopentyl]methyl]-6-methyl-2-methoxy-3-pyridinecarboxylate (197).

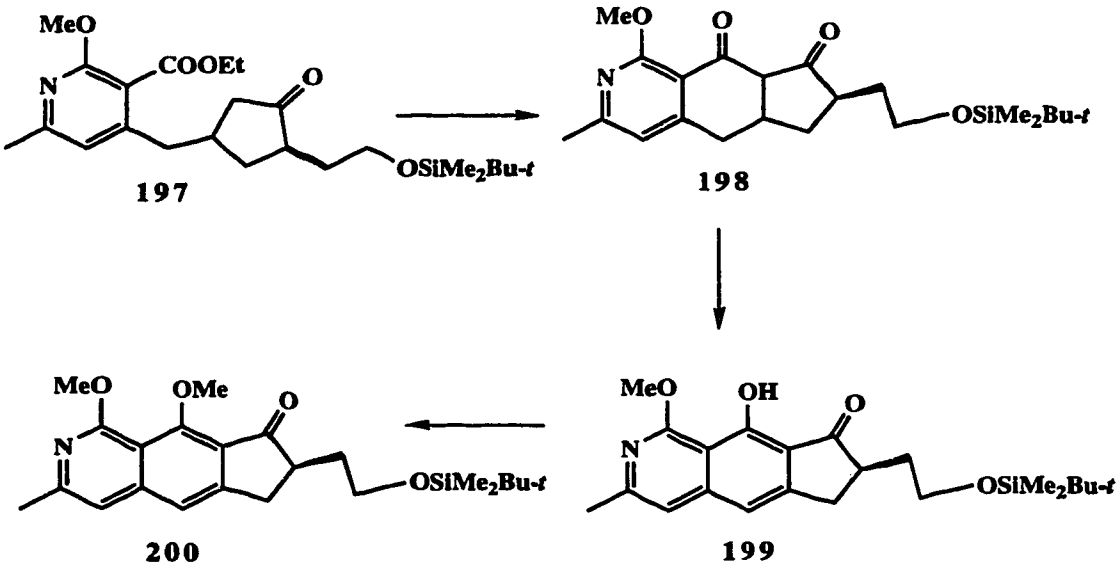


196 **197**

LDA was prepared by dropwise addition of *n*-BuLi (1.6 M in hexanes, 6.36 mL, 10.17 mmol) to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (1.43 mL, 10.34 mmol) in THF (30 mL). The solution was stirred for 10 min at 0 °C, cooled to -78 °C, and then added dropwise over 5 min by cannula to a stirred and cooled (-78 °C) solution of pyridine ester **196** (1.7 g, 8.13 mmol) in THF (82 mL). Stirring was continued for 30 min at -78 °C and then a precooled (-78 °C) solution of freshly prepared

cyclopentenone **195** (2.54 g, 10.58 mmol) in THF (55 mL plus 5 mL as a rinse) was added dropwise by cannula. Stirring at -78 °C was continued for 1 h, after which the cold bath was removed and saturated aqueous NH_4Cl (100 mL) was added immediately. Stirring was continued until the mixture had attained *ca.* 0 °C, and it was then promptly extracted with Et_2O (3 x 100 mL). The organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 x 20 cm), using 1:19 EtOAc-hexane (the mixture containing 1%$^v/_v$ Et_3N), gave pure (^1H NMR, 300 MHz) **197** (2.19 g, 60%) as a mixture of two diastereomers. The material is a thick clear oil: FTIR (CH_2Cl_2, cast) 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.03 (br s, 6 H), 0.85 (br s, 9 H), 1.35 (br t, J = 7 Hz, 3 H), 1.4-1.55 (m, 1 H), 1.7-2.1 (m, 4 H), 2.2-2.75 (m, 8 H), 3.55-3.75 (m, 2 H), 3.94 (s, 3 H), 4.30-4.45 (m, 2 H), 6.55 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75.469 MHz) (signals corresponding to the same isomer are identified by an asterisk) δ -5.44 (q'), 14.19 (q'), 18.18 (s'), 24.07 (q'), 25.85 (q'), 32.52 (t')*, 33.42 (t'), 34.47 (t'), 34.55 (d'), 35.75 (d')*, 36.50 (t')*, 37.97 (t'), 38.51 (t')*, 43.74 (d'), 44.12 (t'), 44.54 (t')*, 47.54 (d')*, 53.71 (q'), 60.75 (t'), 61.09 (t')*, 61.26 (t')*, 61.30 (t'), 114.32 (s')*, 114.52 (s'), 116.55 (d')*, 116.62 (d'), 149.33 (s'), 157.10 (s')*, 157.14 (s'), 160.43 (s'), 167.22 (s'), 167.25 (s')*, 218.83 (s')*, 220.05 (s'); exact mass *m/z* calcd for $C_{20}H_{30}NO_5Si$ (M - C_4H_9) 392.18933, found 392.18966. Anal. Calcd for $C_{24}H_{39}O_5NSi$: C, 64.11; H, 8.74; N, 3.11. Found: C, 64.22; H, 9.07; N, 3.13.

7-[2-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]ethyl]-6,7-dihydro-1,9-dimethoxy-3-methyl-8*H*-cyclopent[g]-isoquinolin-8-one (200).



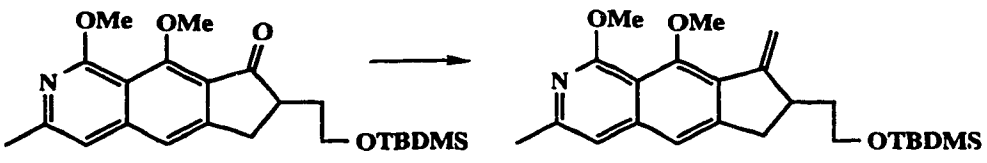
A solution of ketones **197** (2.51 g, 5.59 mmol) in dry THF (40 mL plus 2 mL as a rinse) was added to a cooled (0 °C) and stirred suspension of NaH (80% dispersion in oil, 503 mg, 16.77 mmol of NaH) in dry THF (40 mL). Absolute EtOH (0.49 mL) was then injected. Stirring at 0 °C was continued for 80 min, and then saturated aqueous NH_4Cl (50 mL) was added dropwise. The ice bath was removed after the addition, and the solution was acidified to pH 4-5 with 5%$^{v}/_{v}$ hydrochloric acid. The mixture was extracted with Et_2O (2 x 100 mL) and the organic extracts were washed with brine, and dried ($MgSO_4$). Evaporation of the solvent gave the crude diketone **198** as a yellow oil that crystallized on standing. The crude material was dried under oil pump vacuum for 30 min, and then used directly in the next step.

DDQ (1.12 g, 4.93 mmol) was added in small portions over 5 min to a stirred solution of crude **198** in dry PhH at room temperature. Stirring was continued for 1 h, and the mixture was then filtered through a pad of Celite (2 x 6 cm) that was covered with a layer of flash chromatography silica gel (1 cm thick). The pad was washed with PhH

(150 mL). Evaporation of the filtrate gave the crude naphthol **199** as a yellow-brown oil. The material was dried under oil pump vacuum for 30 min and then used directly in the next step.

Diethyl azodicarboxylate (2.40 mL, 15.24 mmol) was added dropwise to a cooled (-78 °C) and stirred solution of Ph_3P (4.30 g, 16.4 mmol) in dry THF (100 mL). Stirring at -78 °C was continued for 30 min, during which time a thick precipitate formed. Dry MeOH (19.68 mL, 485.8 mmol) was then added dropwise over 10 min, and stirring was continued at -78 °C until all precipitates had dissolved (*ca.* 20 min). As soon as a clear solution was obtained, a room temperature solution of crude naphthol **199** in dry THF (40 mL plus 2 mL as a rinse) was added by cannula over *ca.* 20 min. After the addition, stirring was continued for 12 h, the cold bath being left in place and allowed to attain room temperature. Without any workup, the solvent was evaporated, and flash chromatography of the residue over silica gel (5 x 23 cm), using 1:99 acetone-hexane (the mixture containing 1%$^{v}/_{v}$ Et_3N), gave the desired ketone **200** (1.27 g, 55% over three steps) as a pure (^{1}H NMR, 300 MHz), white solid: mp 92-94 °C; FTIR ($CDCl_3$, cast) 1710, 1617, 1349 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz) δ 0.055 (s, 3 H), 0.065 (s, 3 H), 0.87 (s, 9 H), 1.64 (m, 1 H), 2.17 (m, 1 H), 2.44 (s, 3 H), 2.83 (m, 1 H), 2.96 (ddd, J = 17, 5.3, 1.0 Hz, 1 H), 3.42 (ddd, J = 17, 8.5, 1.0 Hz, 1 H), 3.85 (m, 2 H), 4.0 (s, 3 H), 4.05 (s, 3 H), 7.07 (s, 1 H), 7.43 (s, 1 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ -5.24 (q'), -5.20 (q'), 18.78 (s'), 24.05 (q'), 26.28 (q'), 32.93 (t'), 35.14 (t'), 46.11 (d'), 54.01 (q'), 61.94 (t'), 63.02 (q'), 111.50 (s'), 113.10 (d'), 118.51 (d'), 125.54 (s'), 146.52 (s'), 152.53 (s'), 154.22 (s'), 158.9 (s'), 162.59 (s'), 204.85 (s'); exact mass *m/z* calcd for $C_{23}H_{33}NO_4Si$ 415.21790, found 415.21662. Anal. Calcd for $C_{23}H_{33}NO_4Si$: C, 66.47; H, 8.00; N, 3.37. Found: C, 66.27; H, 8.16; N, 3.33.

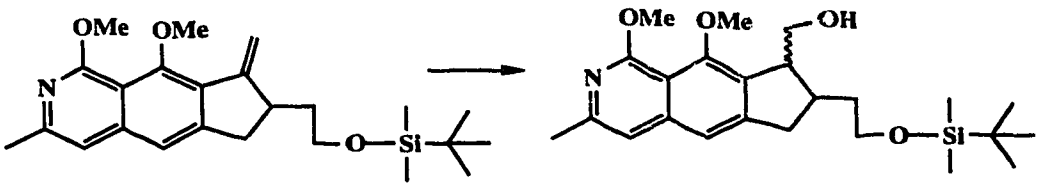
7-[2-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-ethyl]-7,8-dihydro-1,9-dimethoxy-8-methylene-6*H*-cyclopent-[g]isoquinoline (201).



200 **201**

Dry dioxane (114 mL) was added to methyl-triphenylphosphonium bromide (5.60g, 15.67mmol) and *t*-BuOK (1.76g, 15.67 mmol) and the solution was stirred for 20 min at room temperature. A bright yellow color developed. A solution of **200** (1.515g, 3.64 mmol) in dry dioxane (90mL plus 5mL as a rinse) was then added by cannula. The resulting mixture was stirred at room temperature for 2 h. Water (100 mL) was added and the mixture was extracted with Et_2O (3 x 100 mL). The organic extract was washed with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 23 cm), using 1:19 EtOAc-hexane, gave olefin **201** (1.462g, 97%) as a white solid: mp 52-53 °C; FTIR (cast) 2856, 1615cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz) δ 0.08 (s, 3 H), 0.09 (s, 3 H), 0.90 (s, 9 H), 1.55-1.70 (m, 1 H), 1.85-2.0 (m, 1 H), 2.43 (s, 3 H), 2.75-2.85 (m, 1 H), 3.05-3.15 (m, 1 H), 3.25 (ddd, J = 16, 8.5, 1.2 Hz, 1 H), 3.7-3.9 (m, 5 H), 4.5 (s, 3 H), 5.27 (t, J = 1.5 Hz, 1 H), 6.10 (br t, J = 1.5 Hz, 1 H), 7.0 (s, 1 H), 7.30 (br s, 1 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ -5.08 (q'), -5.04(q'), 18.88 (s'), 23.92 (q'), 26.40 (q'), 37.39 (t'), 39.49 (t'), 41.98 (d'), 53.82 (q'), 60.70 (q'), 61.76 (t'), 109.26 (t'), 112.88 (s'), 113.42 (d'), 118.26 (d'), 131.17 (s'), 143.47 (s'), 149.68 (s'), 150.56 (s'), 152.51 (s'), 155.79 (s'), 160.74 (s'); exact mass *m/z* calcd for $C_{24}H_{35}NO_3Si$ 413.23862, found 413.23749. Anal. calcd for $C_{24}H_{35}NO_3Si$: C, 69.69; H, 8.53; N, 3.39. Found: C, 69.58; H, 8.68; N, 3.29.

(7R*,8R*)- and (7R*,8S*)-7-[2-[[Dimethyl-(1,1-dimethylethyl)silyl]oxy]ethyl]-7,8-dihydro-8-hydroxymethyl-1,9-dimethoxy-3-methyl-6*H*-cyclopent-[g]isoquinoline (202).



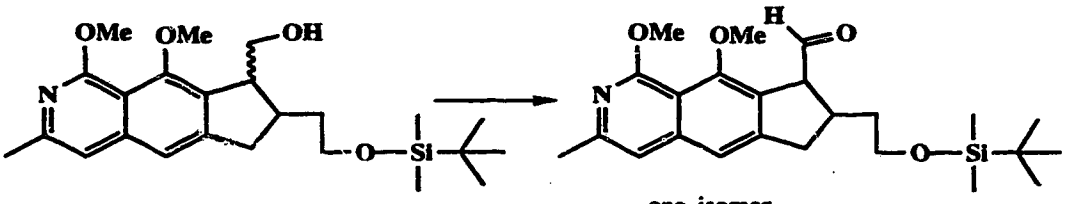
201 **202**

$BH_3.Me_2S$ (2 M in THF, 0.6 mL, 1.2 mmol) was added dropwise to a cooled (0 °C) and stirred solution of **201** (0.10 g, 0.24 mmol) in THF (10 mL). Stirring was continued for 4 h, after which aqueous NaOH (2.5M, 3.84 mL, 9.6 mmol) followed by H_2O_2 (30% aqueous solution, 3.84 mL, 37.6 mmol) were carefully added. The solution was refluxed for 1 h and allowed to cool to room temperature. Brine (25mL) was added and the mixture was extracted with Et_2O (2 x 25 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 23 cm), using 7:93 acetone-hexane (the mixture containing 1% $^v/_v$ Et_3N), gave the faster-eluting alcohol **202** (60.5 mg, 58.4%) and the slower-eluting alcohol **202** (15mg, 14.5%), both as clear, sticky, colorless liquids.

The faster-eluting alcohol had: FTIR (cast) 3519 cm^{-1}; ^1H NMR (acetone-d_6,300 MHz) δ 0.10 (s, 6 H), 0.90 (s, 9 H), 1.8-1.95 (m, 1 H), 2.04-2.2 (m, 1 H), 2.42 (s, 3 H), 2.57-2.75 (m, 1 H), 2.86-3.05 (m, 2 H), 3.45-3.55 (m, 2 H), 3.75-4.0 (m, 7 H), 4.06 (s, 3 H), 7.0 (s, 1 H), 7.24 (s, 1 H); ^{13}C NMR (acetone-d_6,75.469 MHz) δ -5.15 (q'), 18.81 (s'), 23.75 (q'), 26.32 (q'), 34.30 (t'), 39.15 (t'), 41.09 (d'), 47.99 (d'), 53.56 (q'), 62.25 (q'), 62.59 (t'), 63.30 (t'), 112.11 (s'), 113.45 (d'), 117.33 (d'), 137.05 (s'), 143.03 (s'), 148.57 (s'), 150.36 (s'), 154.06 (s'), 159.96 (s'); exact mass *m/z* calcd for $C_{24}H_{37}NO_4Si$ 431.24918, found 431.24793. Anal. Calcd for $C_{24}H_{37}NO_4Si$: C, 66.78; H, 8.64; N, 3.24. Found: C, 67.24; H, 8.65; N, 3.19.

The slower-eluting alcohol had: FTIR (cast) 3458cm^{-1}; ^{1}H NMR (acetone-d_6,300 MHz) δ 0.08 (s, 6 H), 0.90 (s, 9 H), 1.49-1.62 (m, 1 H), 1.65-1.78 (m, 1 H), 2.41 (s, 3 H), 2.61-2.77 (m, 2 H), 3.24 - 3.35 (m, 2 H), 3.60-3.92 (m, 8 H), 4.05 (s, 3 H), 7.01 (br s, 1 H), 7.28 (s, 1 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ -5.14 (q'), 18.79 (s'), 23.73 (q'), 26.30 (q'), 38.09 (t'), 38.92 (d'), 39.53 (t'), 53.41 (d'), 53.58 (q'), 62.24 (q'), 62.30 (t'), 64.35 (t'), 112.20 (s'), 113.37 (d'), 118.00 (d'), 135.07 (s'), 143.24 (s'), 148.67 (s'), 149.93 (s'), 154.98 (s'), 159.96 (s'); exact mass *m/z* calcd for $C_{24}H_{37}NO_4Si$ 431.24918, found 431.24902. Anal. Calcd. for $C_{24}H_{37}NO_4Si$: C, 66.78; H, 8.64; N, 3.24. Found: C, 66.94; H, 8.89; N, 3.19.

7-[2-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-ethyl]-7,8-dihydro-1,9-dimethoxy-3-methyl-6*H*-cyclopent-[g]isoquinoline-8-carboxaldehyde (203).

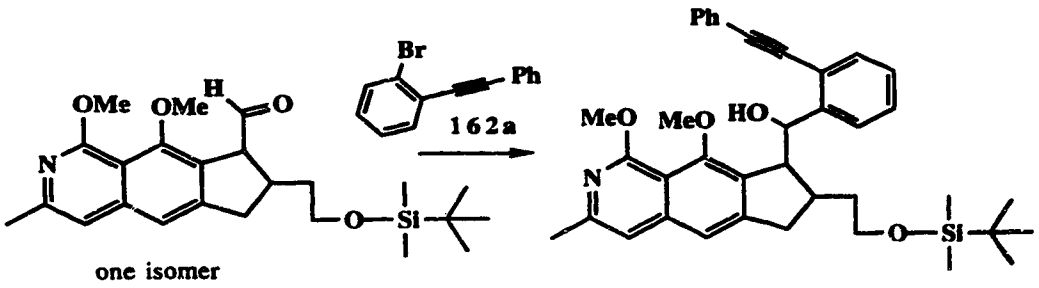


202 **203**

Dry DMSO (0.265 mL, 3.73 mmol) was added to a cooled (-78 °C) and stirred solution of $(COCl)_2$ (0.163 mL, 1.87 mmol) in CH_2Cl_2 (10 mL). The resulting solution was stirred for 10 min, and then a cold (0 °C) solution of **202** (735 mg, 1.7 mmol, mixture of both diastereomers) in CH_2Cl_2 (25 mL plus 5 mL as a rinse) was added by syringe over 2 min. Stirring was continued for another 45 min at -78 °C and Et_3N (1.18 mL, 8.5 mmol) was added. After 10 min, the cold bath was removed and stirring was continued for 30 min. Ice cold saturated aqueous NH_4Cl (45 mL) was added, and the resulting mixture was extracted with Et_2O (2 x 50 mL). The combined

organic extracts were washed with brine (50 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 23 cm), using 4:96 acetone-hexane (solvent containing 1% $^{v}/_{v}$ Et_3N), gave aldehyde **203** (610 mg, 83.5%) as a yellowish oil which crystallized under vacuum to yellowish white cry[illegible] mp 67-70 °C; ^1H NMR (acetone-d_6,300 MHz) δ 0.08 (s, 6 H), 0.90 (s, 9 H), 1.70-1[illegible] (m, 2 H), 2.43 (s, 3 H), 2.82-3.0 (m, 2 H), 3.20-3.40 (m, 1 H), 3.70-3.95 (m, 6 H), 4.04 (s, 3 H), 7.05 (s, 1 H), 7.36 (s, 1 H), 9.65 (d, J = 4 Hz, 1 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ -5.26 (q'), -5.22 (q'), 18.54 (s'), 23.79 (q'), 26.26 (q'), 37.80 (t'), 38.72 (d'), 39.28 (t'), 53.68 (q'), 61.77 (d'), 61.94 (t'), 62.09 (q'), 112.50 (s'), 113.43 (d'), 118.01 (d'), 131.76 (s'), 143.70 (s'), 149.51(s'), 155.50 (s'), 161.00 (s'), 199.71 (d'); exact mass *m/z* calcd for $C_{24}H_{37}NO_4Si$ 429.23355, found 429.23236. Anal. Calcd. for $C_{24}H_{37}NO_4Si$: C, 67.10; H, 8.21; N, 3.26. Found: C, 66.05; H, 8.00; N, 3.21.

7-[2-[[Dimethyl-(1,1-dimethylethyl)silyl]oxy]-ethyl]-7,8-dihydro-1,9-dimethoxy-3-methyl-α-[2-(phenylethynyl)benzenyl]-6*H*-cyclopent[g]iso-quinoline-8-methanol (204).



203 **204**

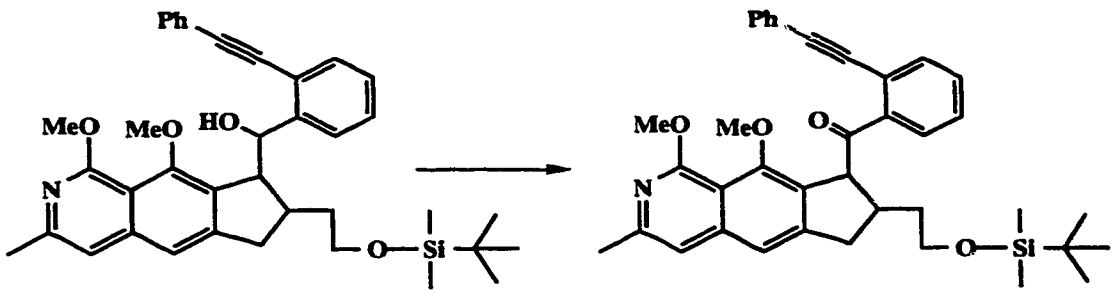
n-BuLi (1.6 M in hexanes, 2.11 mL, 3.34 mmol) was added to a cooled (-78 °C) and stirred solution of 2-bromo-1-(phenylethynyl)benzene (**162a**)[66] (867.4 mg, 3.37 mmol) in dry THF (30 mL). The resulting golden brown solution was stirred for

10 min at -78 °C and transferred by cannula to a cold (-78 °C) and stirred solution of **203** (580 mg, 1.35 mmol) in dry THF (30 mL). Stirring was continued for 1 h at -78 °C, after which the cold bath was removed and stirring was continued for 10 min. Saturated aqueous NH_4Cl (25mL) was added and the resulting mixture was extracted with Et_2O (2 x 40 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 22 cm), using 7:193 EtOAc-hexane, gave three diastereomeric alcohols with the general structure of **204** (590 mg,72%), two of which with very similar R_fs elute faster and were more stable. The other fraction is slower-eluting and was quite unstable. The ratio of faster-eluting to slower-eluting alcohols was 5:2.

The faster-eluting alcohol mixture had: FTIR (cast) 3501 cm^{-1}; ^{13}C NMR(acetone-d_6,75.469 MHz) (signals given are those of the major components only): δ -5.19 (q'), 18.73 (s'), 23.76 (q'), 26.31 (q'), 35.50 (d'), 39.62 (t'), 40.34 (t'), 53.58 (q'), 56.19 (d'), 62.00 (t'), 62.57 (q'), 73.45 (d'), 88.52 (s'), 94.74 (s'), 112.14 (s'), 113.35 (d'), 117.57 (d'), 121.25 (s'), 124.40 (s'), 127.53 (d'), 127.73 (d'), 129.03 (d'), 129.29 (d'), 129.34 (d'), 132.53 (d'), 133.42 (d'), 135.36 (s'), 143.36 (s'), 146.99 (s'), 148.55 (s'), 151.16 (s'), 155.32 (s'), 159.99 (s'); (some of the peaks coincide); exact mass *m/z* calcd for $C_{38}H_{45}NO_4Si$ 607.31177, found 607.31138. Anal. Calcd for $C_{38}H_{45}NO_4Si$: C, 75.09; H, 7.46; N, 2.30. Found: C, 75.06; H, 7.88; N, 2.23.

The slower-eluting alcohol: FTIR (cast) 3463cm^{-1}; ^1H NMR (acetone-d_6,300 MHz) δ -0.06 (s, 3 H), -0.04 (s, 3 H), 0.80 (s,9 H), 1.20-1.50 (m, 2 H), 2.40-2.75 (m, 6 H), 3.2 (dd, J = 17, 8 Hz, 1 H), 3.40-3.60 (m, 2 H), 3.97 (s, 3 H), 4.01 (s, 3 H), 4.78 (d, J = 3 Hz, 1 H), 5.30 (dd, J = 8.5, 3 Hz, 1 H), 7.05 (s, 1 H), 7.20-7.90 (m, 10 H); exact mass *m/z* calcd for $C_{38}H_{45}NO_4Si$ 607.31177, found 607.31162.

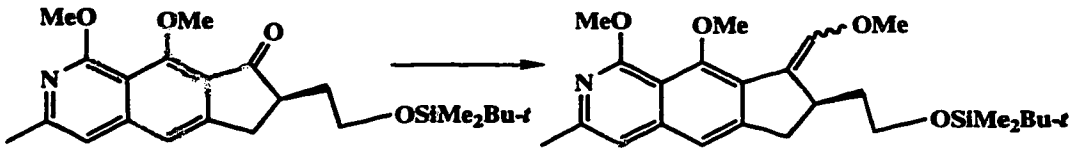
8-(2-phenylethynylbenzoyl)-7-[2-[[Dimethyl-(1,1-dimethylethyl)silyl]oxy]ethyl]-7,8-dihydro-1,9-dimethoxy-3-methyl-6*H*-cyclopent[g]isoquinoline (205).



204 **205**

Ph_3BiCO_3[62] (1.095 g, 2.19 mmol) was added to a vigorously stirred solution of **204** (295.8 mg,0.487 mmol) in PhMe (50 mL) and pyridine (4.7 mL). The resulting suspension was refluxed for 48 h and then allowed to cool to room temperature. The mixture was filtered through a pad of silica (2 x 4 cm) and the silica pad was washed with EtOAc (50 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (3 x 20 cm), using 5:95 acetone-hexane, gave **205** (254 mg, 86%) as a pure (^{1}H NMR 300 MHz), sticky, yellowish oil: FTIR (film): 1685 cm^{-1}; ^{1}H NMR (acetone-d_6,300 MHz) δ -0.06 (s, 3 H), -0.04 (s, 3 H), 0.08 (s, 9 H), 1.60-1.90 (m, 2 H), 2.45 (s, 3 H), 2.87-3.00 (m, 2 H), 3.35 (ddd, *J* = 16, 7.5, 1.5 Hz, 1 H), 3.65-3.75 (m, 5 H), 4.03 (s, 3 H), 5.22 (d, *J* = 5 Hz, 1 H), 7.08 (s, 1 H), 7.32-7.40 (m, 4 H), 7.45-7.70 (m, 4 H), 7.75(br d, *J* = 7.5 Hz, 1 H), 8.0 (br d, *J* = 7.5 Hz, 1 H); ^{13}C NMR (acetone-d_6,75.469 MHz) δ -5.33 (q'), -5.29 (q'), 18.67 (s'), 23.75 (q'), 26.23 (q'), 38.63 (t'), 38.97 (t'), 42.93 (d'), 53.61 (q'), 59.53 (d'), 61.90 (t'), 62.14 (q'), 89.29 (s'), 94.36 (s'), 112.11 (s'), 113.49 (d'), 117.77 (d'), 122.45 (s'), 124.05 (s'), 129.26 (d'), 129.36 (d'), 129.47 (d'), 129.51 (d'), 131.93 (d'), 132.37 (d'), 134.59 (s'), 134.77 (d'), 142.47 (s'), 143.60 (s'), 149.09 (s'), 149.63 (s'), 154.40 (s'), 159.99 (s'), 202.99 (s'); exact mass *m/z* calcd for $C_{38}H_{43}NO_4Si$ 605.29614, found 605.29553.

7-[2-[[Dimethyl(1,1-dimethylethyl)silyl]oxy]-ethyl]-7,8-dihydro-1,9-dimethoxy-8-(methoxy)-methylene-3-methyl-6*H*-cyclopent[g]isoquinoline (206).

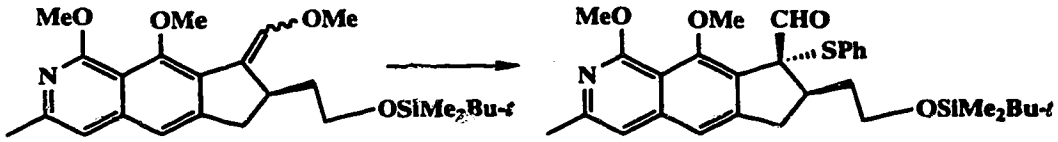


200 **206**

Dry dioxane (42 mL) was added to a mixture of (methoxymethyl)triphenylphosphonium chloride (4.09 g, 11.9 mmol) and *t*-BuOK (1.33 g, 11.9 mmol). The resulting deep orange solution was stirred at room temperature for 5 min, sonicated for 15 min [Branson, model B-12, 80 W], and stirred again for an additional 10 min. A solution of **200** (760 mg, 1.83 mmol) in dry dioxane (25 mL plus 10 mL as a rinse) was then added by syringe, over 5 min. The mixture was stirred for 1.5 h. Water (50 mL) was added and the resulting mixture was extracted with Et_2O (2 x 75 mL). The organic extract was washed with brine (100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the dark red residue over silica gel (3 x 23 cm), using 1:99 acetone-hexane (the mixture containing 1% v/v Et_3N), gave the faster-eluting enol ether (426 mg, 53%) and the slower-eluting enol ether (204 mg, 25%) both as clear yellowish liquid. The faster-eluting enol ether **206** had: FTIR (C_6D_6 cast) 1656 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 0.04 (s, 3 H), 0.05 (s, 3 H), 1.0 (s, 9 H), 1.6-1.8 (m, 1 H), 2.15-2.30 (m, 1 H), 2.50 (s, 3 H), 2.74 (ddd, J = 17, 2.3, 1.0 Hz, 1 H), 3.05 (ddd, J = 17, 8.5, 1.45 Hz, 1 H), 3.26 (s, 3 H), 3.45-3.6 (m, 1 H), 3.71 (s, 3 H), 3.71-3.80 (m, 2 H), 4.03 (s, 3 H), 6.80 (s, 1 H), 7.02 (s, 1 H), 7.41 (d, J = 2 Hz, 1 H); ^{13}C NMR (C_6D_6, 75.469 MHz) δ -5.16 (q'), -5.13 (q'), 18.49 (s'), 23.91 (q'), 26.15 (q'), 37.08 (t'), 37.14 (d'), 38.49 (t'), 53.44 (q'), 59.53 (q'), 59.70 (q'), 61.96

(t'), 112.80 (s'), 113.15 (d), 117.87 (d'), 124.08 (s'), 130.87 (s'), 141.59 (s'), 145.82 (d'), 148.07 (s'), 149.03 (s'), 152.36 (s'), 159.91 (s'); exact mass *m/z* calcd for $C_{25}H_{37}NO_4Si$ 443.24918, found 443.25062. The slower-eluting enol ether **206**: FTIR (C_6D_6 cast) 1664.96 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 0.075 (s, 3 H), 0.085 (s, 3 H), 1.0 (s, 9 H), 1.55-1.65 (m, 2 H), 2.40-2.55 (m, 4 H), 2.96-3.07 (m, 2 H), 3.30 (s, 3 H), 3.53-3.65 (m, 1 H), 3.65-3.75 (m, 1 H), 3.85 (s, 3 H), 4.06 (s, 3 H), 6.06 (s, 1 H), 6.81 (s, 1 H), 7.04 (s, 1 H); ^{13}C NMR (C_6D_6, 75.469 MHz) δ -5.17 (q'), 18.47 (s'), 23.95 (q'), 26.15 (q'), 37.77 (t'), 38.68 (t'), 40.49 (d'), 53.49 (q'), 59.85 (q'), 60.63 (q'), 61.08 (t'), 112.87 (d'), 113.07 (s'), 116.92 (d'), 119.51 (s'), 128.68 (s'), 142.37 (d'), 142.47 (s'), 148.70 (s'), 149.33 (s'), 154.98 (s'), 160.81 (s'); exact mass *m/z* calcd for $C_{25}H_{37}NO_4Si$ 443.24918, found 443.24923.

(7R*,8R*)-7-[2-[[Dimethyl(1,1-dimethylethyl)-silyl]oxy]ethyl]-7,8-dihydro-1,9-dimethoxy-3-methyl-8-phenylthio-6*H*-cyclopent[g]isoquinoline-8-carboxaldehyde (207).



206 **207**

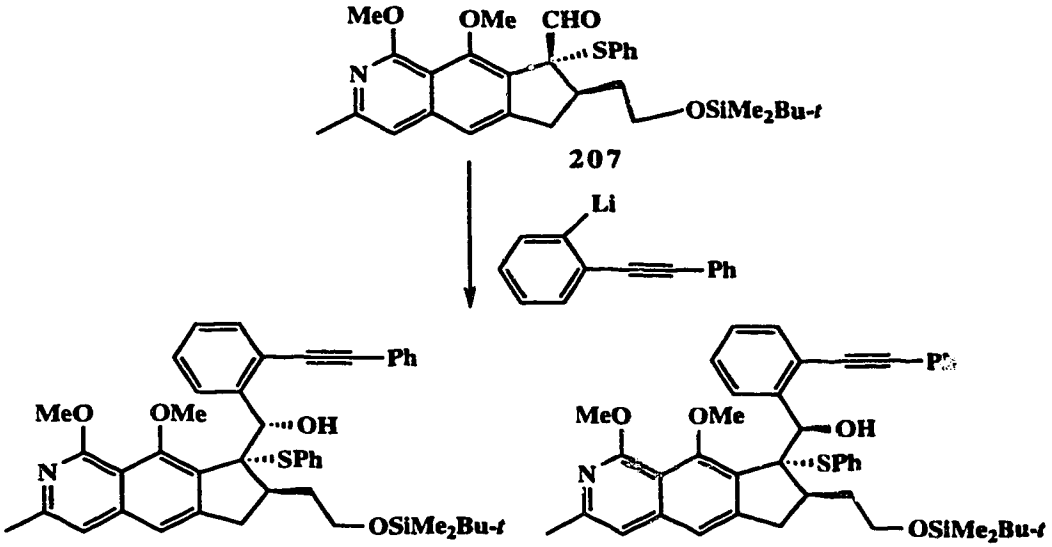
A solution of PhSCl[63] (325 mg, 2.25 mmol) in dry Et_2O (8 mL) was added dropwise over 10-15 min to a stirred and cooled (-78 °C) solution of **206** (two geometric isomers) (769 mg, 1.73 mmol) in dry Et_2O (15 mL). Stirring was continued for 3.5 h, after which the cooling bath was removed and the mixture was allowed to reach room temperature (*ca.* 30 min). Direct evaporation of the solvent, without workup, and flash chromatography of the residue over silica gel (3 x 20 cm), using 1:39 EtOAc-hexane, gave pure (^1H NMR, 300 MHz) aldehyde **207** (256.7 mg, 30%) as a thick, yellow oil:

FTIR (film) 1724 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 0.0 (s, 6 H), 0.84 (s, 9 H), 1.38 (m, 1 H), 1.8 (m, 1 H), 2.46 (s, 3 H), 2.85-3.0 (m, 2 H), 3.18 (ddd, J = 17, 8, 1.2 Hz, 1 H), 3.63 (m, 2 H), 3.93 (s, 3 H), 4.09 (s, 3 H), 7.08 (s, 1 H), 7.20-7.40 (m, 4 H), 7.45-7.60 (m, 2 H), 10.05 (s, 1 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ -5.32 (q'), -5.28 (q'), 18.69 (s'), 23.79 (q'), 26.26 (q'), 33.45 (t'), 36.56 (t'), 46.34 (d'), 53.81 (q'), 61.68 (t'), 63.84 (q'), 74.58 (s'), 112.23 (s'), 113.45 (d'), 118.70 (d'), 129.73 (d'), 130.00 (d'), 131.99 (s'), 132.45 (s'), 137.38 (d'), 144.47 (s'), 148.91 (s'), 150.30 (s'), 155.90 (s'), 160.05 (s'), 196.31 (d'); mass (HRFAB) *m/z* calcd for $C_{30}H_{40}NO_4SSi$ (M + H) 538.2447, found 538.2445.

When the experiment was done on a smaller scale (300 mg of starting material) the yield was 45%.

In other experiments, it was found that the two geometric isomers of the enol ether **206**, when separately reacted with PhSCl, each gave the same aldehyde product (**207**) in 32% and 35% yields.

(7R*,8R*,αS*)- and (7R*,8R*,αR*)-7-[2-[[Dimethyl-(1,1-dimethylethyl)silyl]oxy]ethyl]-7,8-dihydro-1,9-dimethoxy-α-[2-(phenylethynyl)benzenyl]-8-phenyl-thio-6*H*-cyclopent[g]isoquinoline-8-methanol (208a) and (208b).

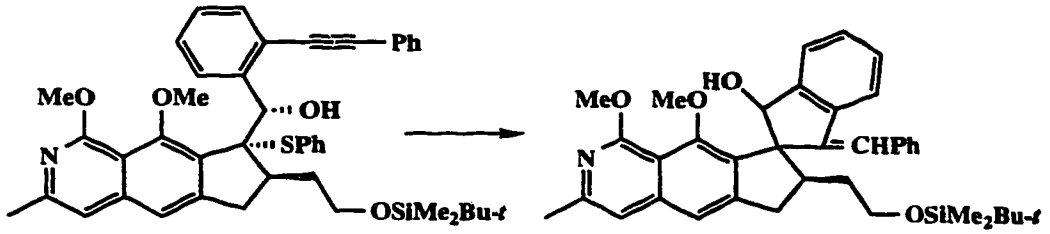


n-BuLi (1.6 M in hexanes, 1.5 mL, 2.39 mmol) was added to a stirred and cooled (-78 °C) solution of 2-bromo-1-(phenylethynyl)benzene[66] (617 mg, 2.39 mmol) in dry THF (5 mL). The resulting golden brown solution was stirred for 10 min at -78 °C and then a cold (0 °C) solution of aldehyde **207** (256.7 mg, 0.477 mmol) in dry THF (10 mL plus 2 mL as a rinse) was injected. Stirring at -78 °C was continued for 0.5 h, after which the cold bath was removed. Saturated aqueous NH_4Cl (10 mL) was added and the mixture was stirred and allowed to reach room temperature. The mixture was extracted with Et_2O (2 x 30 mL), and the organic extract was washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 23 cm), using 1:28 EtOAc-hexane, gave two diastereomeric alcohols in a 6:5 ratio, the faster-eluting isomer (**208b**) being obtained in 33% overall yield, and the slower-eluting isomer (**208a**) in 40% overall yield. For the faster-eluting isomer (**208b**) had: FTIR

($CHCl_3$ cast) 3427 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ -0.05 (s, 3 H), -0.03 (s, 3 H), 0.90 (s, 9 H), 1.60-1.80 (m, 1 H), 2.07-2.23 (m, 1 H), 2.46 (s, 3 H), 2.70-2.83 (m, 1 H), 3.12 (dd, *J* = 15.5, 6 Hz, 1 H), 3.24-3.38 (m, 2 H), 3.46 (dd, *J* = 15.5, 7 Hz, 1 H), 3.70 (s, 3 H), 3.85 (s, 3 H), 4.54 (d, *J* = 2.5 Hz, 1 H), 6.22 (d, *J* = 3 Hz, 1 H), 6.60-7.10 (m, 9 H), 7.18-7.45 (m, 5 H), 7.55 (dd, *J* = 7.8, 1 Hz, 1 H), 8.60 (d, *J* = 8 Hz, 1 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ -5.17 (q'), 18.73 (s'), 23.75 (q'), 26.31 (q'), 32.56 (t'), 38.71 (t'), 47.35 (d'), 53.62 (q'), 63.07 (t'), 63.45 (q'), 72.15 (s'), 76.26 (d'), 90.07 (s'), 94.50 (s'), 112.23 (s'), 113.30 (d'), 117.56 (d'), 123.67 (s'), 124.45 (s'), 128.13 (d'), 128.76 (d'), 129.20 (d'), 129.25 (d'), 129.40 (d'), 131.01 (d'), 132.11 (d'), 132.32 (d'), 134.85 (s'), 135.04 (d'), 135.76 (s'), 143.74 (s'), 144.48 (s'), 149.45 (s'), 149.80 (s'), 156.09 (s'), 160.17 (s'); mass (HRFAB) *m/z* calcd for $C_{44}H_{50}NO_4SSi$ (M + H) 716.3230, found 716.3221.

The slower-eluting isomer (**208a**) had: mp 171-172 °C; FTIR (CH_2Cl_2 cast) 3470, 2575 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 0.07 (s, 6 H), 1.0 (s, 9 H), 1.93 (ddd, *J* = 15.5, 11.65, 1.25 Hz, 1 H), 2.05-2.25 (m, 2 H), 2.51 (s, 3 H), 2.95 (dd, *J* = 15.5, 8 Hz, 1 H), 3.30-3.55 (m, 3 H), 4.04 (s, 3 H), 4.16 (s, 3 H), 6.05 (d, *J* = 4.8, 1 H), 6.46 (d, *J* = 4.8, 1 H), 6.5-6.6 (m, 1 H), 6.73-6.85 (m, 2 H), 6.90 (s, 1 H), 6.95-7.09 (m, 4 H), 7.10-7.20 (m, 3 H), 7.40-7.50 (m, 1 H), 7.50-7.60 (m, 2 H), 7.75-7.90 (m, 2 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ -5.18 (q'), 18.88 (s'), 23.83 (q'), 26.40 (q'), 33.74 (t'), 38.55 (t'), 49.62 (d'), 53.90 (q'), 63.35 (t'), 64.99 (q'), 73.02 (s'), 74.77 (d'), 88.84 (s'), 94.64 (s'), 112.35 (s'), 113.54 (d'), 117.97 (d'), 124.07 (s'), 124.16 (s'), 128.45 (d'), 128.73 (d'), 128.92 (d'), 129.40 (d'), 129.48 (d'), 129.73 (d'), 129.82 (d'), 132.44 (d'), 133.12 (d'), 133.35 (s'), 134.69 (s'), 136.98 (d'), 144.07 (s'), 144.18 (s'), 148.93 (s'), 150.19 (s'), 156.04 (s'), 160.01 (s'); mass (HRFAB) *m/z* calcd for $C_{44}H_{51}NO_4SSi$ (M + H) 716.3230, found 716.3198.

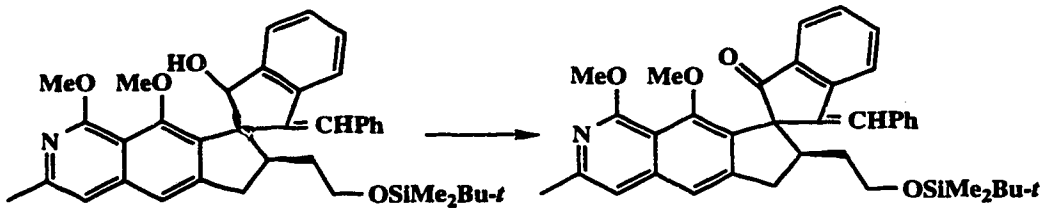
Cyclization of 208a



208a **209**

Et_3B (1 M in hexanes, 20 μL, 0.02 mmol) was added to a stirred solution of **208a** (8.0 mg, 0.011 mmol) and Ph_3SnH (75.0 mg, 0.21 mmol) in hexane (1.0 mL; ordinary distilled hexane was used) at room temperature. The mixture was left open to the atmosphere and stirred for 15 min. Without workup, evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 18 cm), using 1:19 EtOAc-hexane, gave **209** (2.2 mg, 33%): ^1H NMR (acetone-d_6, 400 MHz) (minor component indicated by asterisk) δ 0.0 - 0.05 (m, 5 H), 0.85 - 0.90 (m, 11 H), 1.2-1.4 (m, 1.6 H), 1.60-1.80 (m, 1.6 H), 1.9-2.0 (m, 0.6 H), 2.45 (s, s*, 3 H), 3.2 (s*, 0.3 H), 3.4 (s, 2.4 H), 3.5-3.7 (m, 1.3 H), 3.75 (d, J = 12 Hz, 0.74 H), 4.0 (s, s*, 3 H), 4.05 (s*, 0.25 H), 5.05 (d, J = 12 Hz, 1 H), 6.4 (d, J = 8.4 Hz, 1 H), 6.9-7.8 (m, 11 H); mass (FAB) *m/z* calcd for $C_{38}H_{47}NO_4Si$ 608.32, found 608.33.

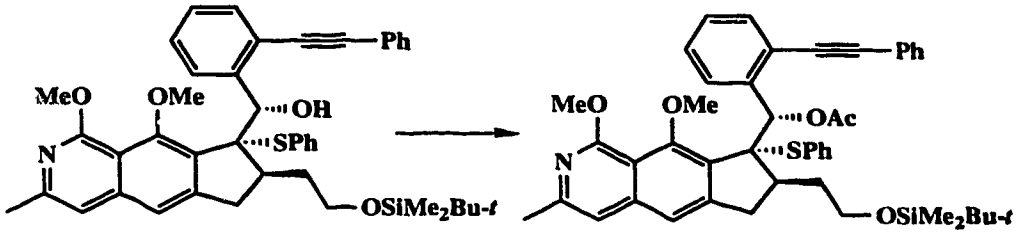
Oxidation of cyclization product from 208a.



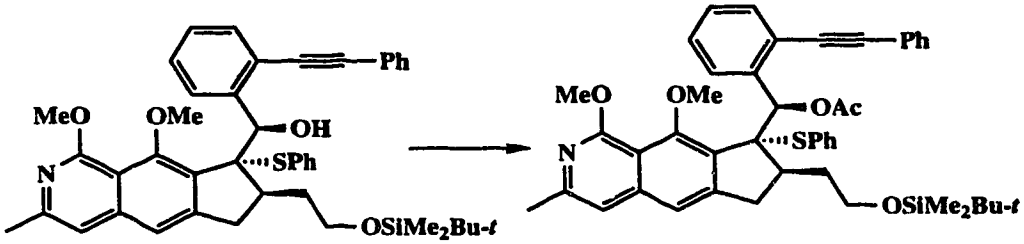
209 **210**

Ph_3BiCO_3[62] (8.2 mg, 0.016 mmol) was added to a stirred solution of **209** (2 mg, 0.003 mmol) in PhMe (1 mL) containing pyridine (70 μL). The resulting suspension was heated at 80 °C for 5 h, and then allowed to cool to room temperature. The suspension was filtered through a pad of silica gel (2 x 1 cm), and the pad was washed with EtOAc (5 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 17 cm), using 1:39 acetone-hexane, gave ketone **210** (1.0 mg, 50%) as an inseparable mixture (^{1}H NMR, 300 MHz) of two isomers: FTIR (cast) 1718 cm^{-1}; ^{1}H NMR (acetone-d_6, 300 MHz) (minor isomer indicated by asterisk) δ -0.2-0.0 (m, 6 H), 0.7-0.9 (m, 9 H), 1.3-1.7 (m, 3 H), 2.4 (s, s*, 3 H), 2.8-3.0 (m, 1 H), 3.1-3.6 (m, 6 H), 3.9 (s, s* 3 H), 6.45 (br d, J = 7 Hz, 1.5 H), 6.8-7.9 (m, 9.7 H), 8.15 (br d, J = 8 Hz, 0.7 H); mass (FAB) *m/z* calcd for $C_{38}H_{44}NO_4Si$ 606.30, found 606.73.

(7R*,8R*,αS*)- and (7R*,8R*,αR*)-7-[2-[[Dimethyl-(1,1-dimethylethyl)silyl]oxy]ethyl]-7,8-dihydro-1,9-dimethoxy-α-[2-(phenylethynyl)-benzenyl]-8-phenyl-thio-6*H*-cyclopent[g]-isoquinoline-8-methanol acetate (211a) and (211b).



208a **211a**



208b **211b**

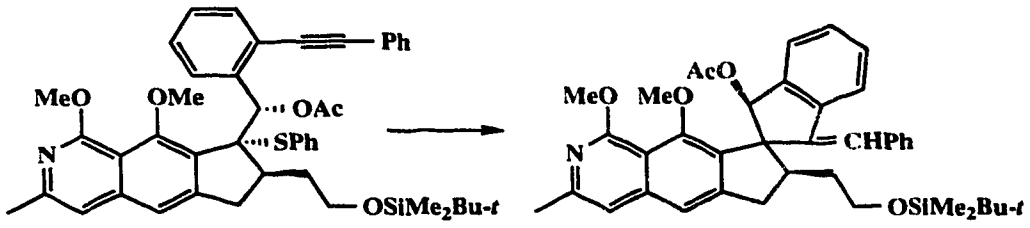
Ac_2O (0.3 mL, 3.18 mmol) and DMAP (9.8 mg, 0.08 mmol) were added to a stirred solution of the slower-eluting alcohol **208a** (110 mg, 0.154 mmol) in dry pyridine (7 mL) at room temperature. The resulting solution was stirred for 6 h, then poured into brine (25 mL) and extracted with Et_2O (3 x 25 mL). The organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:19 acetone-hexane, gave **211a** (96.7 mg, 83%) as a white solid: mp 141-143 °C; FTIR (CH_2Cl_2 cast) 1740 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ -0.05 (s, 6 H), 0.82 (s, 9 H), 1.35-1.60 (m, 2 H), 2.10 (s, 3 H), 2.34-2.48 (m, 4 H), 2.90-3.17 (m, 2 H), 3.20-3.45 (m, 2 H), 3.68 (s, 3 H), 4.0 (s, 3 H), 6.90 (s, 1 H), 6.93 (s, 1 H), 7.0 (s, 1 H), 7.10-7.35 (m, 6 H), 7.40 (s, 6 H), 7.74-7.83 (m, 2 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ -5.19 (q'), 18.71 (s'), 21.37 (q'), 23.74 (q'), 26.31

(q'), 34.01 (t'), 38.85 (t'), 50.14 (d'), 53.54 (q'), 63.14 (t'), 63.72 (q'), 69.16 (s'), 74.82 (d'), 88.06 (s'), 93.81 (s'), 112.26 (s'), 113.20 (d'), 116.64 (d'), 124.24 (s'), 124.40 (s'), 128.41 (d'), 128.65 (d'), 129.17 (d'), 129.35 (d'), 129.58 (d'), 130.05 (d'), 132.09 (d'), 132.20 (d'), 133.99 (s'), 134.08 (s'), 138.13 (d'), 140.76 (s'), 143.88 (s'), 147.89 (s'), 149.55 (s'), 157.23 (s'), 160.08 (s'), 169.80 (s') (several of the signals coincide); mass (HRFAB) *m/z* calcd for $C_{46}H_{52}NO_5SSi$ (M + H) 758.3335, found 758.3335.

Using the same procedure, the faster-eluting diastereomeric alcohol **208b** (108.3 mg, 0.151 mmol) gave **211b** (91 mg, 80%) as a white solid: mp 177-179 °C, FTIR (C_6D_6 cast) 1747 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ -0.01 (s, 3 H), 0.01 (s, 3 H), 0.93 (s, 9 H), 1.5 (s, 3 H), 1.8-2.0 (m, 1 H), 2.33-2.50 (m, 4 H), 3.05-3.23 (m, 3 H), 3.25-3.50 (m, 2 H), 3.68 (s, 3 H), 3.92 (s, 3 H), 6.73-6.85 (m, 4 H), 6.92-7.12 (m, 6 H), 7.35 (s, 1 H), 7.35-7.47 (m, 2 H), 7.50 (d, J = 7.5, 2 H), 7.55 (dd, J = 7.5, 1 Hz, 2 H), 7.73 (br d, J = 7.5 Hz, 2 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ -5.1 (q'), 18.83 (s'), 21.3 (q'), 23.8 (q'), 26.39 (q'), 32.71 (t'), 39.30 (t'), 47.35 (d'), 53.66 (q'), 63.12 (q'), 63.15 (t'), 68.76 (s'), 77.97 (d'), 90.34 (s'), 94.78 (s'), 112.54 (s'), 113.38 (d'), 116.97 (d'), 124.52 (s'), 124.87 (s'), 128.51 (d'), 128.57 (d'), 129.16 (d'), 129.40 (d'), 129.67 (d'), 130.56 (d'), 132.29 (d'), 132.50 (d'), 133.66 (s'), 135.04 (d'), 140.45 (s'), 144.07 (s'), 149.08 (s'), 149.62 (s'), 157.21 (s'), 160.41 (s'), 169.05 (s') (several of the peaks must coincide); mass (HRFAB) *m/z* calcd for $C_{46}H_{52}NO_5SSi$ (M + H) 758.3335, found 758.3298.

The assigned structure was confirmed by X-ray analysis. See Appendix at the end of Chapter 2 for experimental details.

Cyclization of 211a.



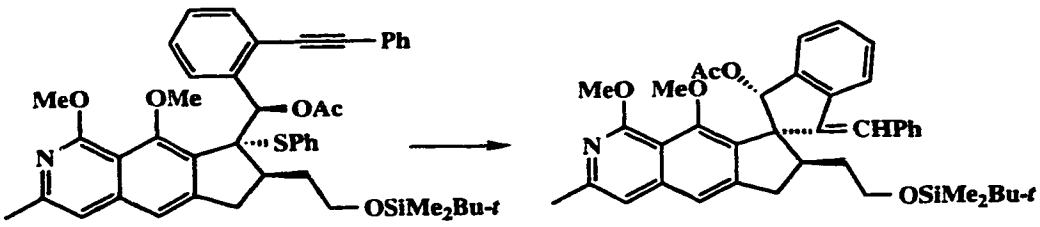
211a **212a**

Et_3B (1 M in hexanes, 0.10 mL, 0.10 mmol) was added to a cold (0 °C) and stirred solution of **211a** (71.0 mg, 0.094 mmol) and Ph_3SnH (650 mg, 1.85 mmol) in 4:1 benzene-hexane (10 mL; ordinary distilled hexane was used). Air (1.0 mL) was then bubbled into the solution over 30 sec. The mixture was stirred at 0 °C for 25 min (or until the solution turned cloudy). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:19 EtOAc-hexane, gave the faster-eluting fraction (33 mg, 0.051 mmol) and the slower-eluting fraction (17 mg, 0.026 mmol) as thick colorless oils. Each fraction contained two diastereomers (^1H NMR, 300 MHz) corresponding in structure to **212a**. The faster-eluting fraction had: FTIR (CH_2Cl_2 cast) 1741 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) (signals corresponding to the same isomer are identified by an asterisk, and proton counts are given only for non-overlapping signals of the major isomer) δ -0.84 (s)*, -0.86 (s)*, -0.91 (s, 3 H), -0.94 (s, 3 H), 0.7 (s)*, 0.80 (s, 9 H), 1.10-1.30 (m), 1.75-1.90 (m), 2.06 (s, 3 H), 2.5 (s, 3 H), 2.7-3.0 (m), 3.15-3.30 (m), 3.45-3.65 (m), 3.55 (s)*, 3.85 (s, 3 H), 3.93 (s)*, 3.98 (s, 3 H), 6.49 (s, 1 H), 6.76 (s, 1 H), 6.80-6.86 (m)*, 7.05 (s, 1 H), 7.08-7.60 (m); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ -5.17 (q'), -5.07 (q'), 18.75 (s'), 21.02 (q'), 23.69 (q'), 26.19 (q')*, 26.31 (q'), 33.49 (t'), 33.77 (t')*, 38.33 (t'), 38.50 (t')*, 47.57 (d'), 53.54 (q'), 54.28 (q'), 62.09 (q')*, 62.82 (q')*, 62.82 (t'), 67.75 (s'), 83.73 (d'), 85.72 (d')*, 112.72 (s'), 113.47 (d'), 117.24 (d'), 117.59 (d')*, 120.68 (d')*, 122.04 (d')*, 124.05 (d'), 124.09 (d'), 124.20 (d'), 127.11 (d')*, 128.00 (d'),

128.38 (d')*, 128.53 (d'), 129.29 (d'), 129.32 (d'), 129.69 (d'), 130.20 (d')*, 130.76 (d'), 138.48 (s'), 138.59 (s'), 139.40 (s'), 143.75 (s'), 144.24 (s'), 147.80 (s'), 149.05 (s'), 149.77 (s'), 154.61 (s'), 159.91 (s'), 170.83 (s'); mass (HRFAB) *m/z* calcd for $C_{40}H_{48}NO_5Si$ 650.3302, found 650.3297.

The slower-eluting fraction had: FTIR (CH_2Cl_2 cast) 1736, 1716 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) (signals corresponding to the same isomer are identified by an asterisk, and proton counts are given only for the non-overlapping signals of the major isomer) δ -0.07 (s, 3 H), -0.05 (s, 3 H), -0.02 (s)*, 0.02 (s)*, 0.82 (s, 9 H), 0.83 (s)*, 1.20-1.35 (m), 1.47 (ddd, *J* = 16, 10.5, 1.5 Hz, 1 H), 1.58 (s, 3 H), 1.60-1.8 (m), 1.67 (s)*, 2.53 (s)*, 2.55 (s, 3 H), 2.90 (br dd, *J* = 16, 9 Hz, 1 H), 3.0-3.23 (m), 3.41 (s)*, 3.43 (s, 3 H), 3.45-3.6 (m, 2 H), 3.65-3.8 (m)*, 3.98 (s)*, 3.99 (s, 3 H), 6.24 (s)*, 6.26 (s, 1 H), 6.35 (s)*, 6.45 (br d, *J* = 7.5 Hz, 2 H), 6.95 (br t, *J* = 7.5 Hz), 7.0-7.2 (m), 7.25-7.50 (m), 7.8 (br d, *J* = 7.5 Hz, 1 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) (signals corresponding to the same isomer are identified by an asterisk) δ -5.24 (q'), 17.50 (q')*, 18.72 (s'), 20.57 (q'), 20.72 (q')*, 23.75 (q'), 26.28 (q'), 35.24 (t'), 35.48 (t)*, 38.17 (t')*, 38.64 (t'), 47.36 (d')*, 47.61 (d'), 53.56 (q'), 61.39 (q'), 61.90 (q')*, 62.44 (t)*, 62.59 (t'), 66.21 (s'), 82.91 (d')*, 86.50 (d'), 111.68 (s'), 113.46 (d'), 117.09 (d')*, 117.37 (d'), 120.84 (d'), 123.42 (d'), 124.51 (d')*, 125.62 (d'), 126.36 (d')*, 127.31 (d'), 128.08 (d')*, 128.48 (d'), 128.93 (d')*, 129.17 (d')*, 129.40 (d'), 129.49 (d')*, 129.60 (d'), 130.03 (d'), 138.68 (s'), 138.94 (s'), 142.86 (s'), 143.09 (s'), 143.49 (s'), 147.17 (s'), 148.81 (s'), 150.46 (s'), 156.29 (s'), 160.07 (s'), 170.98 (s'); mass (HRFAB) *m/z* calcd for $C_{40}H_{48}NO_5Si$ (M + H) 650.3302, found 650.3306.

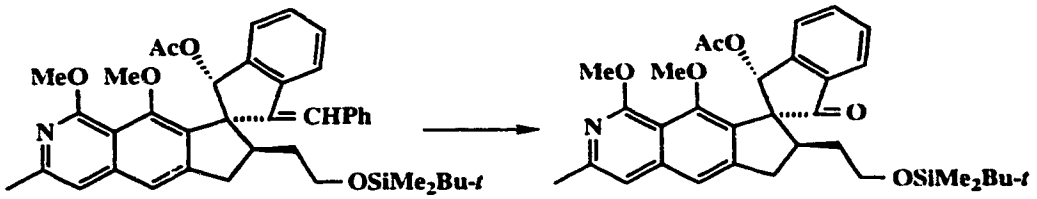
Cyclization of 211b.



211b **212b**

Et_3B (1 M in hexanes, 0.20 mL, 0.20 mmol) was added to a cold (0 °C) and stirred solution of **211b** (30 mg, 0.04 mmol) and Ph_3SnH (313 mg, 0.89 mmol) in 2:1 benzene-hexane (4.5 mL; ordinary distilled hexane was used). Air (1.0 mL) was then bubbled through the solution over 30 sec. The mixture was stirred at 0 °C for 25 min. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 18 cm), using 1:19 EtOAc-hexane, gave the cyclization product **212b** as a single isomer (23 mg, 88%): FTIR (CH_2Cl_2 cast) 1740 cm^{-1}; ^1H NMR (C_6D_6, 300 MHz) δ 0.00 (s, 6 H), 0.93 (s, 9 H), 1.67 (s, 3 H), 1.7-1.83 (ddd, J = 15, 10, 1 Hz, 1 H), 1.7-2.0 (m, 2 H), 2.48 (s, 3 H), 2.76-3.0 (m, 2 H), 3.4-3.65 (m, 5 H), 3.85 (s, 3 H), 6.52 (br d, J = 7 Hz, 2 H), 6.7-6.9 (m, 5 H), 7.23 (s, 1 H), 7.4-7.5 (m, 1 H), 7.45-7.52 (m, 1 H), 7.55 (s, 1 H), signals corresponding to 2 aromatic H overlap with the benzene solvent peak; ^1H NMR (acetone-d_6, 300 MHz) (signals for aromatic portion only) δ 6.45 (br d, J = 7 Hz, 2 H), 6.8-7.06 (m, 5 H), 7.10 (s, 1 H), 7.35-7.5 (m, 4 H), 7.8 (br d, J = 7 Hz, 1 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ 5.13 (q'), 18.85 (s'), 21.15 (q'), 23.78 (q'), 26.36 (q'), 35.36 (t'), 38.40 (t'), 41.87 (d'), 53.58 (q'), 62.06 (q'), 63.23 (t'), 64.40 (s'), 83.39 (d'), 112.28 (s'), 113.36 (d'), 117.82 (d'), 120.80 (d'), 123.38 (d'), 125.83 (d'), 127.06 (d'), 128.28 (d'), 129.39 (d'), 129.55 (d'), 129.71 (d'), 129.86 (d'), 138.40 (s'), 141.89 (s'), 142.80 (s'), 143.43 (s'), 143.79 (s'), 147.29 (s'), 148.88 (s'), 149.66 (s'), 154.45 (s'), 160.04 (s'), 170.81 (s'); mass (HRFAB) *m/z* calcd for $C_{40}H_{48}NO_5Si$ (M + H) 650.3302, found 650.3279.

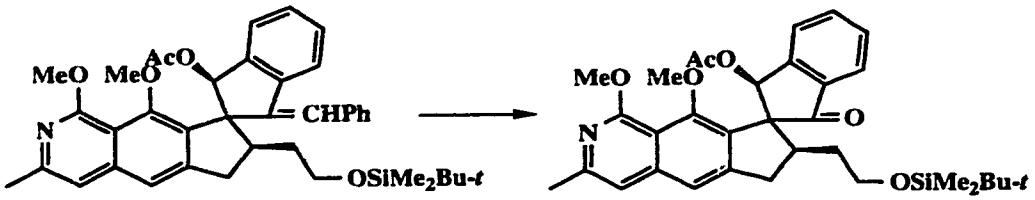
Double Bond Cleavage of Cyclization Product from 211b.



212b **213b**

OsO_4 (25 mg, 0.10 mmol) was added in one portion to a stirred solution of **212b**, (the single cyclization product from **211b**) (16 mg, 0.024 mmol) in dry pyridine (1 mL). The mixture was stirred under Ar at room temperature for 12 h. Then a suspension of $NaIO_4$ (21 mg, 0.098 mmol) in 10:1 THF-H_2O (1 mL) was added and stirring was continued for 12 h. The mixture was diluted with EtOAc (15 mL), and washed successively with brine (10 mL) and saturated aqueous $NaHSO_3$ (2 x 25 mL), and then dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 18 cm), using 2:23 acetone-hexane, gave **213b** (4 mg, 30% yield) as a clear, sticky foam: FTIR (CH_2Cl_2 cast) 1742, 1712 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz) δ 0.00 (s, 6 H), 0.84 (s, 9 H), 1.45-1.6 (m, 1 H), 1.6-1.7 (m, 1 H), 2.13 (s, 3 H), 2.39 (s, 3 H), 2.8-2.95 (m, 1 H), 3.11 (ddd, J = 16, 11, 1.5 Hz, 1 H), 3.2 (s, 3 H), 3.27 (br dd, J = 16, 8 Hz, 1 H), 3.6-3.75 (m, 2 H), 3.95 (s, 3 H), 7.02 (s, 1 H), 7.27 (s, 1 H), 7.34 (s, 1 H), 7.64 (br t, J = 7.5 Hz, 1 H), 7.75-7.8 (m, 2 H), 7.86 (dt, J = 7.5, 1 Hz, 1 H); ^{13}C NMR (acetone-d_6, 500 MHz) δ -5.23 (q'), -5.19 (q'), 18.86 (s'), 21.01 (q'), 23.74 (q'), 29.02 (q'), 34.84 (t'), 37.88 (t'), 44.01 (d'), 53.58 (q'), 62.61 (q'), 62.78 (t'), 67.36 (s'), 76.44 (d'), 111.91 (s'), 113.41 (d'), 117.49 (d'), 122.29 (s'), 123.86 (d'), 127.27 (d'), 130.85 (d'), 136.66 (d'), 137.23 (s'), 140.74 (s'), 143.68 (s'), 149.46 (s'), 149.63 (s'), 153.34 (s'), 154.23 (s'), 159.80 (s'), 170.99 (s'); exact mass *m/z* calcd for $C_{33}H_{41}NO_6Si$ 575.27032, found 575.26893.

Double bond Cleavage of the Faster-Eluting Cyclization Material from 211a.



212a **213a**

The above procedure was followed, using the faster-eluting material from the cyclization of **211a** (17 mg, 0.026 mmol), OsO_4 (28 mg, 0.11 mmol), dry pyridine (1 mL), $NaIO_4$ (23 mg, 0.11 mmol), and 10:1 THF-water (1 mL). A single ketone of general structure **213a** (4.5 mg, 30%) was obtained as a clear sticky foam: FTIR (CH_2Cl_2 cast) 1742, 1721 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ -0.05 (s, 3 H), -0.036 (s, 3 H), 0.84 (s, 9 H), 1.3-1.45 (m, 2 H), 2.15 (s, 3 H), 2.43 (s, 3 H), 2.9-3.1 (m, 2 H), 3.25-3.35 (m, 1 H), 3.45-3.6 (m, 2 H), 3.61 (s, 3 H), 4.0 (s, 3 H), 6.67 (s, 1 H), 7.06 (s, 1 H), 7.34 (s, 1 H), 7.6-7.7 (m, 2 H), 7.8-7.9 (m, 2 H); ^{13}C NMR (acetone-d_6, 125 MHz) δ -5.26 (q'), -5.21 (q'), 18.72 (s'), 21.03 (q'), 23.73 (q'), 26.26 (q'), 33.81 (t'), 39.19 (t'), 49.38 (d'), 53.54 (q'), 62.40 (q'), 62.70 (t'), 67.49 (s'), 80.72 (d'), 112.03 (s'), 113.58 (d'), 117.38 (d'), 123.77 (d'), 125.78 (d'), 127.48 (s'), 130.47 (d'), 136.34 (d'), 137.55 (s'), 137.96 (s'), 143.86 (s'), 149.24 (s'), 149.36 (s'), 151.37 (s'), 153.20 (s'), 159.74 (s'), 170.94 (s'); exact mass *m/z* calcd for $C_{29}H_{32}NO_6Si$ (M - C_4H_9) 518.19989, found 518.19722.

No identifiable products were isolated from a similar experiment using the slower-eluting fraction from the cyclization of **211a**.

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51. These bicyclic lactams were made by heating (*R*)-phenylglycinol with the appropriate oxo-acids. The resulting diastereomeric product is richer in the cis-diastereomer; i.e. both substituents carrying phenyl groups are on the convex face of the bicyclic system.

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58. Early attempts to isolate the selenoketone proved difficult as the chromatographic separation was accompanied with considerable decomposition in the column.

59. Prepared in situ by treatment of 2-bromo-1-(phenyl-ethynyl)benzene[66] with n-BuLi in THF at -78 °C.

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64. In a separate experiment, it was established that the 2 isomeric enol ethers **206**, when separately treated with PhSCl, afforded the same aldehyde product **207**, in 32% and 35% yields.

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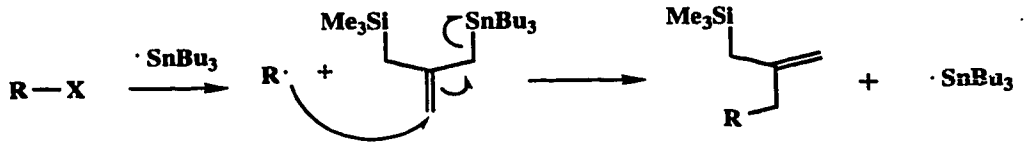
Chapter 2

INTRODUCTION:

The chemistry of allylsilanes has become very extensive since the pioneering works of Sommer,[1] Calas,[2] Corriu[3], Sakurai,[4] and Fleming.[5] Recently, an extensive review has been written on the subject of silanes,[6] and about a third of this review is devoted solely to the subject of allylsilanes; in particular, the synthetic utility of this structural unit in natural product synthesis.

Alongside the increasing interest in the synthetic usefulness of allylsilanes is a growth in the demand for various ways of introducing an allylic silane moiety into a molecule.[7] For this reason we decided to embark on a novel way of making allylsilanes by a free radical chain process. In particular, we chose to employ the bifunctional isobutylene, 3-(tributylstannyl)-2-(trimethylsilylmethyl)-propene **1**, which had been recently reported in the literature and whose synthetic utility have not been explored.[8] Our main strategy (**Scheme II-1**) involves the generation of a radical **R·** from **R-X**, which we anticipated to add to the unsubstituted end of allylic silane-stannane **1**, to afford the allylsilane **2**, as well as releasing a tributyltin radical **3**. The latter could in principle



1 **2** **3**

Scheme II-1

propagate the chain. The reaction we proposed to study involves intermolecular carbon-carbon bond formation, and the following is a brief literature survey on intermolecular C-C bond formation by free radical methods involving allylations.

Literature review:

The formation of carbon-carbon bonds by free radical chain processes is an extremely useful process in organic chemistry.[9] Intermolecular and intramolecular, free radical carbon-carbon bond-forming reactions of interest to us usually involve addition of a radical to a carbon-carbon multiple bond,[10] as this is the type of process that occurs in free radical allylations.

Allylation by a free radical chain method occupies a very important place in organic synthesis, for it is often encountered as a step in the synthesis of natural products.[11,12,13] Covering all existing references to free radical allylations is beyond the scope of this introduction, but all the studies that are related to our own allylation process are discussed.

Types of allylating agents:

Allylating agents employed in free radical chain methods have a common structural skeleton as shown in **Figure II-1**. They all have the basic framework of a propenyl system with an allylic leaving group.

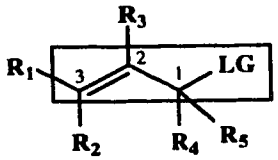


Fig. II-1. Typical framework of a radical allylating agent

The most common type of leaving groups employed are (a) tin centered radicals, e.g.. trialkyl or triarylstannyl radicals; (b) sulfur centered radicals e.g., alkyl or arylthio radicals, and sulfonyl radicals; and (c) the less common silicon centered radicals, e.g., tris(trialkylsilyl)-silyl radical.[14] However, for purposes of our discussion, it is more helpful to classify these allylating agents according to the electronic nature of the substituent in the 2-position. It turns out that the characteristics of the 2-substituent determine the type of radical that reacts best with the allylating agent. The following

classification of free radical allylating agents (**Table II-1, II-2, II-3**) is based on whether the substituent at position 2 is (a) electron-withdrawing, (b) a hydrogen, or (c) others. Under each category, there are not always examples of all the types of leaving groups mentioned above, but all the available data have been collected and comparisons will be made within and between the various classes listed in Tables II-1 to II-3.

Table II-1 (Electron-withdrawing group at C-2)

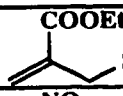
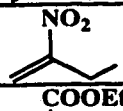
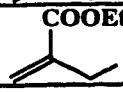
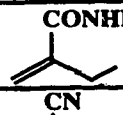
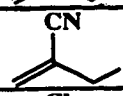
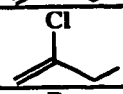
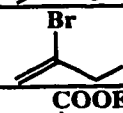
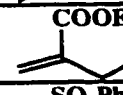
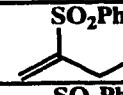
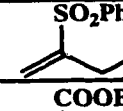
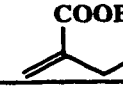
No.	Compound	Reference
6		22, 23
7		24
11		27,36
12		26, 40, 41
16		27
17		27
44		34
51		35
53		37, 38
54		37
55		39

Table II-2 (C-2 unsubstituted)

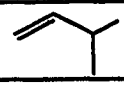
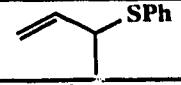
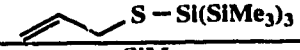
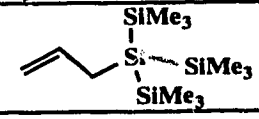
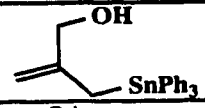
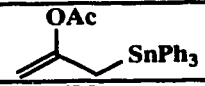
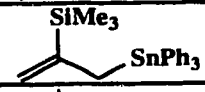
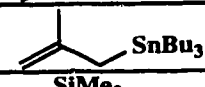
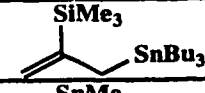
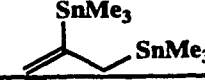
No.	Compound	Reference
4		17, 31
5		21, 42
8		26, 29
9		26
18		26
22		29
26		29
27		11, 29
46		34
50		14

Table II-3 (Miscellaneous C-2 substituents)

No.	Compound	Reference
20		28
10		26
32		30
36		31
37		31
45		34

In the following short review, it is important to bear in mind that many factors, not just the nature of the C-2 substituent, affect the success of free radical allylations. For instance, the method of radical initiation, the solvent system, the temperature, the presence or absence of radical scavengers, and the nature of the attacking radical itself all affect the course of a free radical chain reaction, so that the outcome depends on a harmonious interplay of a large number of factors.

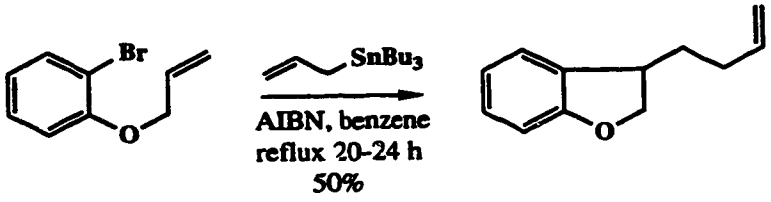
The simplest and earliest radical allylating agent to be developed was allyltributylstannane (**4**). Reported independently by a French[15] and a Japanese[16]

4

group, initial studies on the radical reactions of this compound revealed some promise for its application as an allylating agent. However, until Keck's study,[17a] the applications of compound **4** for allylation were not appreciated.

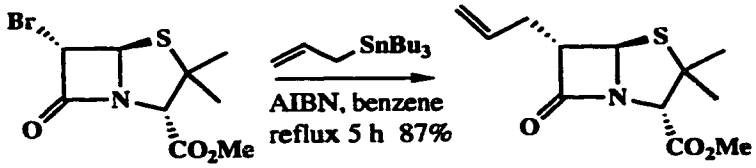
The early report by Keck[17a] on the practical application of **4** involved the now typical conditions where the radical precursor and the allylstannane are refluxed in toluene or benzene in the presence of AIBN. Sometimes the reaction can be photoinitiated at room temperature without AIBN. Since this report, many examples of the application of **4** have been described, and a few representative illustrations are given below [(a)-(c)].

(a)[18] Eq. 1



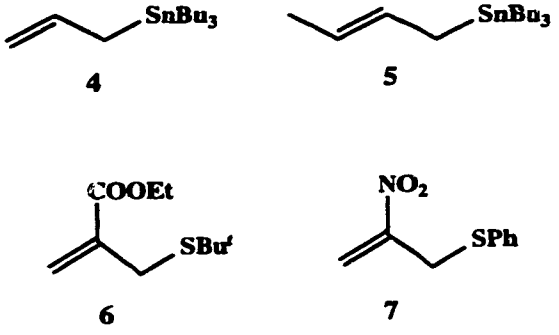
(b)[19] Eq. 2

(c)[20] Eq. 3



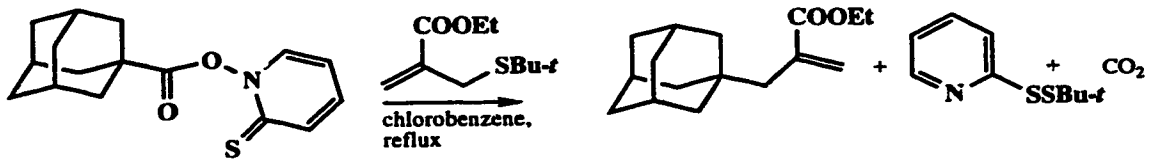
As Keck's early findings revealed that the radical allylating conditions are compatible with a wide variety of functional groups, e.g., acetals, ketals, ethers, epoxides, lactones, hydroxyl groups, esters and sulfonate esters, it was not difficult for free radical allylation to find immediate acceptance.

In order to study the scope and limitations of free radical allylations, Migita and coworkers have conducted a number of experiments in which various organic halides were subjected to reaction with the allylstannane **4** and the crotylstannane **5**.[21] Their findings revealed that under similar conditions, polyhalomethanes, α-haloesters and α-halonitriles give better yields in the reaction with allyltins, compared to aryl, benzyl and alkyl halides. Generally, compound **4** gives superior results to compound **5**, and this observation was interpreted on the basis of steric crowding at the olefinic site. However, as described by Keck,[17b] compound **5** also acts as a good hydrogen donor towards carbon radicals, and this fact also contributes to the poorer performance of **5** with respect to **4**. Later, Barton reported the allylating agents **6**[22,23] and **7**,[24] which were used to

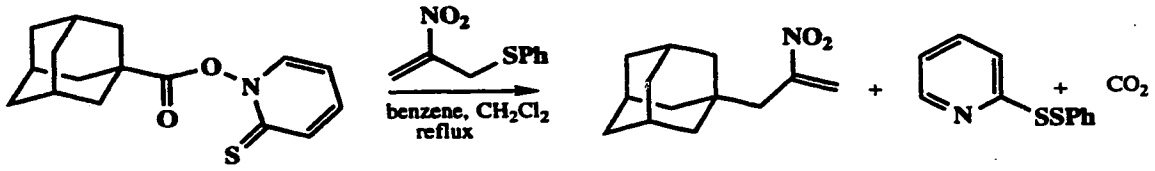


allylate radicals derived from thiohydroxamic esters,[25] and typical results are shown in equations 4 and 5.

Eq.4

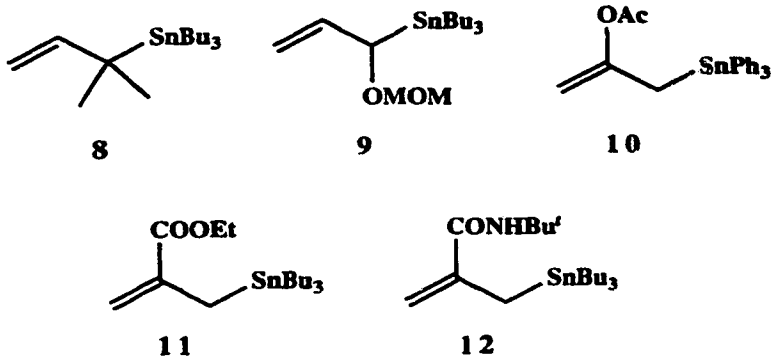


Eq.5



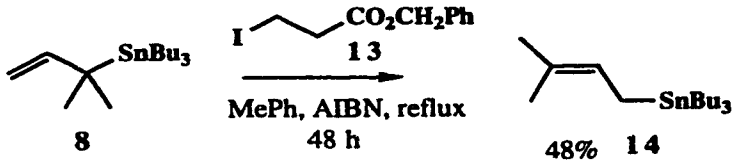
Although the use of this sulfur-based chemistry requires careful technique to contain the unpleasant smell of the sulfur compounds, these reagents offer easier purification of the reaction products from the sulfide by-products; an advantage not found with the stannanes.[22]

At around the same time, Baldwin and coworkers reported their findings with the allylstannanes **8 - 12**. While Migita[21] found that substitution at the 3-position was

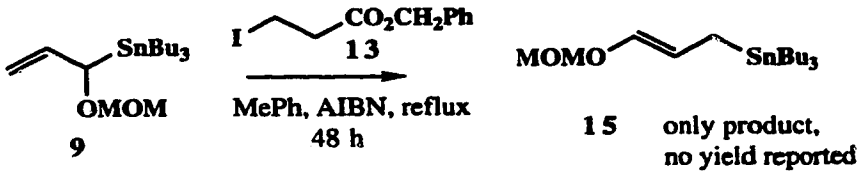


detrimental to the reactivity of an allylstannane, Baldwin found the same to be true with substitution at the 1-position (i.e., the allylic carbon carrying the tin substituent).[26] Thus, when **8** (eq. 6) or **9** (eq. 7) were treated with benzyl 3-iodopropionate (**13**) under

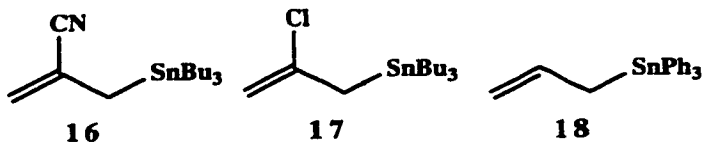
Eq. 6



Eq. 7



the standard thermal conditions, the major product obtained in each case was the rearrangement product **14** and **15**, respectively, and no addition of the carbon radical to the allylic stannane was observed. While substitution at the 2-position, as in **10**, **11** and **12**, might be thought satisfactory due to the degeneracy of the rearrangement products, Baldwin observed that only **11** and **12**, both of which have electron-withdrawing groups at C-2, reacted with alkyl halides. Compound **10** gave no useful allyl transfer. Following these findings, a few more allylating agents **16** and **17** were made[27] and

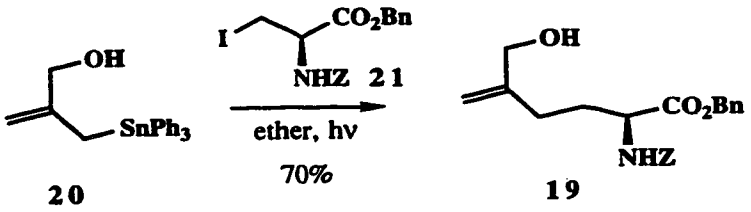


16 17 18

compared with **18**. Using 2-bromo-*N*-benzoylglycine as a carbon radical source, Baldwin found that product yields were highest with **16** (74%), followed by **18** (65%) and then **17** (50%), but no explanation was provided for the observed trend.

Recently, in their preparation of tabtoxinine β-lactam,[28] Baldwin and coworkers were able to obtain a 70% yield of **19** (eq. 8) by irradiation of a 3:1 mixture of **20** and **21** in ether with a medium pressure mercury lamp.

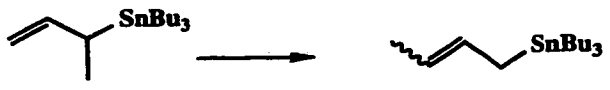
Eq.8



20 19

Referring back to Baldwin's findings on the tendency of **8** to rearrange, Keck found a solution to the problem. The allylstannanes **22** and **8** undergo facile rearrangement (eq. 9 and 10 respectively) under the usual radical allylating conditions

Eq. 9



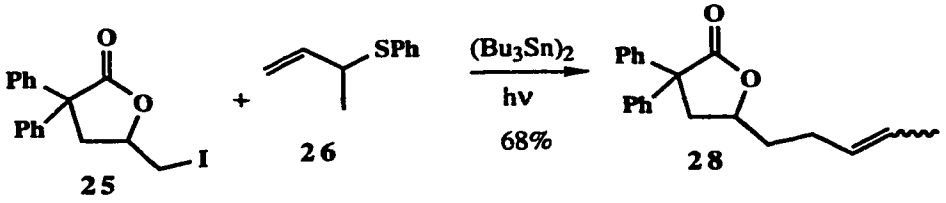
22 23

Eq. 10

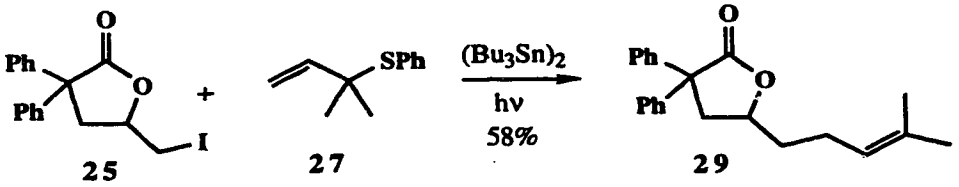
8 24

(AIBN, reflux temperature or photoinduced) to give **23** and **24**, respectively. Under the same conditions however, Keck found that the sulfide analogs can be made to undergo useful allyl transfer giving allylated products.[29] The method involves irradiation of the substrates in the presence of the required allyl phenyl sulfide and hexabutylditin. As substrates, alkyl halides were found to be better than the corresponding selenides or thionocarbonates, and best results were obtained with alkyl bromides and iodides. Thus, when lactone **25** was reacted with **26** or **27** (eq. 11 and 12, respectively), the alkylated products **28** and **29** were obtained in 68 and 58% yields,

Eq. 11

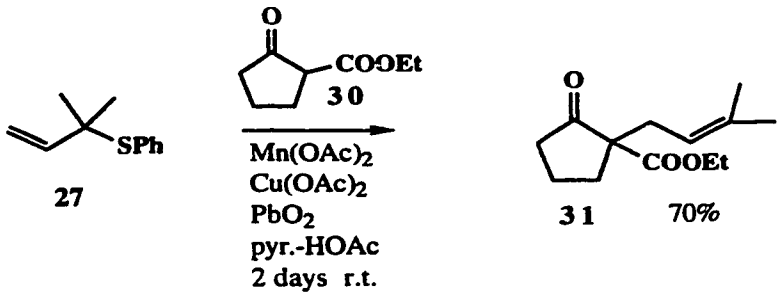


Eq. 12



respectively. To conduct the same allylations with the corresponding allylstannanes would have been fruitless, as Baldwin had demonstrated.[26] It is interesting to note that Uguen's group,[11] in their studies on radical generation utilizing manganic salts, also found compound **27** to react nicely in the prenylation of ketoester **30** (eq. 13), giving **31** in 70% yield.

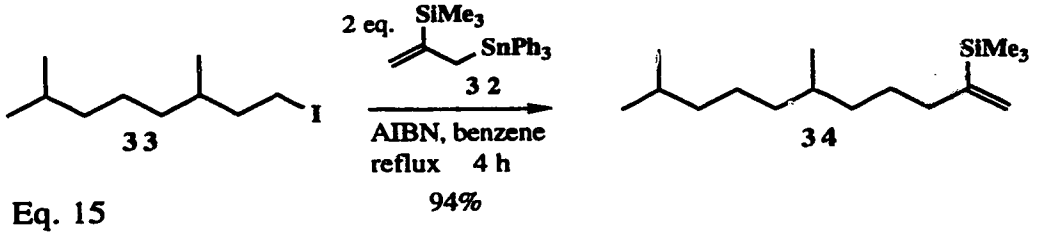
Eq. 13



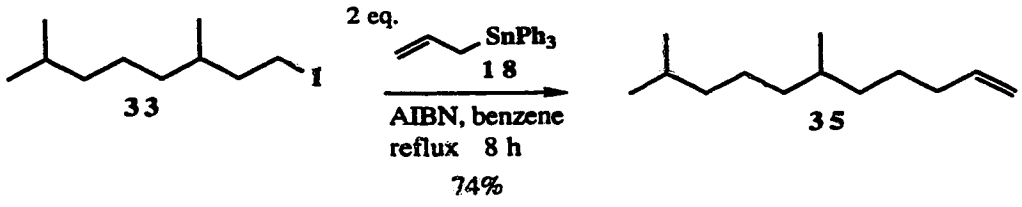
In their search to find other useful allylating agents, Lee and coworkers[30] compared the synthetic applications of **32** and **18** in radical allylations. They found that

substitution of the allylstannane at the 2-position with a trimethylsilyl group significantly enhances the reactivity towards carbon radicals, thereby necessitating only half the usual reaction time. Thus, (eq. 14 and 15) reaction of 3,7-dimethyl-1-iodooctane **33** with **32**

Eq. 14

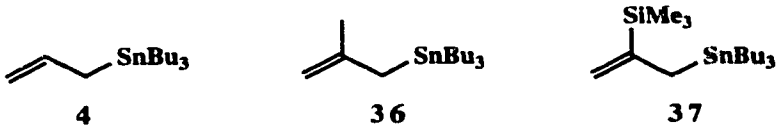


Eq. 15



for 4 hours in refluxing benzene gave the vinylsilane **34** in 94% yield, while with **18**, an 8 hour reaction time provided **35** in only 74% yield. A more detailed comparison was

conducted by Renaud and coworkers.[31] In their study, they compared the allylation rates of **4**, **36**, and **37** in reactions with nucleophilic, electrophilic and neutral radicals. The results of their measurements can be summarized as follows:



4 **36** **37**

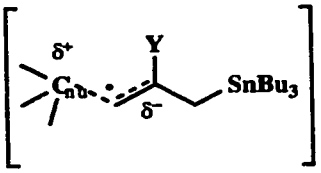
(a) Regardless of the nature of the attacking radical, the presence of the trimethylsilyl group at C-2, as in **37**, enhances the reactivity of the olefin relative to the allylstannane **4**. The degree of enhancement is greater with nucleophilic and electrophilic radicals and less when the radical is neutral in these respects, as in the case of $\cdot CH_2S(O)Ph$.

(b) With a methyl group at the C-2, a rate enhancement relative to **37** was observed only when the attacking radical is electrophilic.

Unfortunately, no direct study comparing **4** with **36** was conducted. However, based on the above results, we can deduce that with an electrophilic radical, **36** would react faster than **4**.

A partially polarized transition state was suggested to explain the above findings.

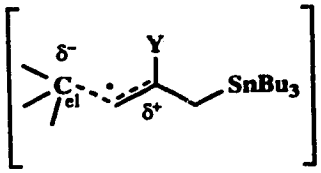
Fig. II-2



nucleophilic radicals

38 Y = $SiMe_3$
39 Y = H
40 Y = Me

Fig. II-3

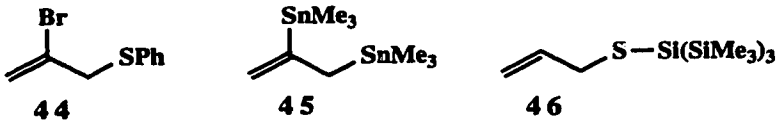


electrophilic radicals

41 Y = $SiMe_3$
42 Y = H
43 Y = Me

With a nucleophilic radical, the transition state in **Figure II-2** would be stabilized by a trimethylsilyl group at C-2 (**38**).[33] Such stabilization would not be present with a hydrogen at C-2 (see **39**) and, with a methyl group (see **40**), we would expect some destabilization. On the other hand, with an electrophilic radical, the polarized transition state in **Figure II-3** would be more stable with a methyl group (see **43**) at C-2 than with a trimethylsilyl group (see **41**) or a hydrogen (see **42**). Indeed, it has been shown that in such a situation, a methyl group is more stabilizing than a trimethylsilyl group, followed by a hydrogen whose effect was set at the baseline.[32] This study by Renaud and coworkers provides a theoretical basis for radical allylations.

Prior to Renaud's report, Curran had investigated the three allylating agents **44**, **45** and **46**.[34] With **44**, Keck's conditions shown in equations 11 and 12 were

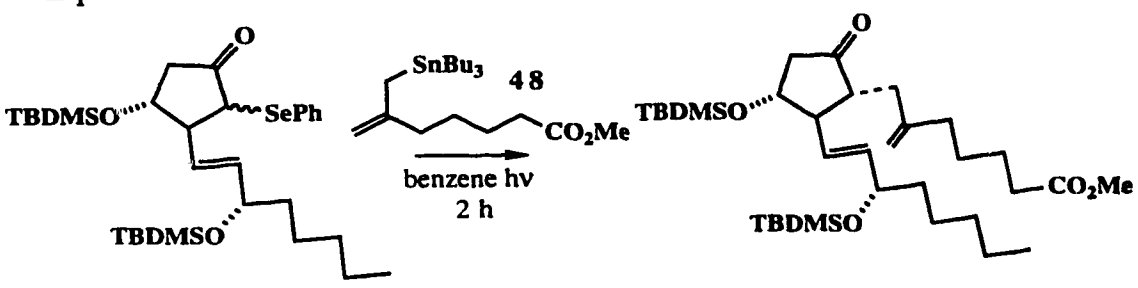


44 **45** **46**

used to identify the type of radical that would react best. The Curran group found that yields decrease as the nature of the radical is changed from tertiary to secondary to primary, and that alkyl iodides perform better than bromides, and selenides are the worst. With **45**, however, they found that electrophilic radicals generally perform better than nucleophilic radicals. With **46**, only moderate yields were achieved, and electrophilic radicals outperformed nucleophilic radicals in terms of yields.

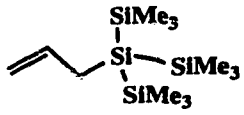
In spite of Curran's observations with **44**, phenylselenides can serve as excellent radical precursors. As an example (eq. 16), Toru and coworkers, in their construction of the skeleton for 6-oxoprostaglandin E_1,[12] were able to achieve allylation of **47** with **48**, giving **49** in 76% yield.

Eq. 16



47 49

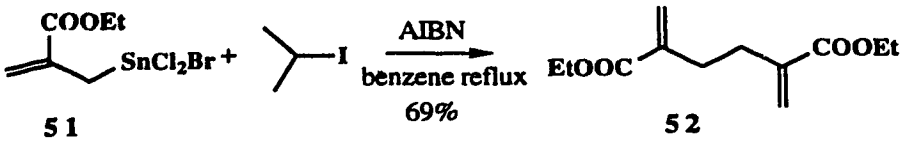
Because of the toxicity of tin species, the use of allylstannanes is restricted to areas that do not involve food or medicinal chemistry. In their efforts to achieve a tin-free allylation, Kosugi and coworkers introduced the use of allyl[(tris)trimethylsilyl]silane (**50**) as an allylating agent.[14] With an almost 1:1 ratio of **50** and a radical precursor, refluxing in benzene with AIBN afforded mostly moderate yields (36-68%) of allylated products. This result is quite respectable, nonetheless, since most allylations which give yields above 70% utilizes two equivalents of allylating agent with the excess portion usually not reported as being recovered.



50

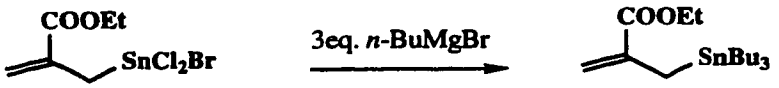
Against the background of Baldwin's report on the favorable effect of having an electron-withdrawing group at position 2 of an allylating agent,[26] Fouquet and coworkers explored the possibility of applying the easily prepared **51** (eq. 17) in radical allylations. Unfortunately, reaction with isopropyl iodide (eq. 17) under Keck's conditions, afforded nothing but the dimer **52** in 69% yield. However, **51** can easily be converted into the synthetically useful **11**[36] by treatment with 3 equivalents of *n*-BuMgBr (eq. 18). This technique constitutes a novel and convenient preparation of

Eq. 17



51 52

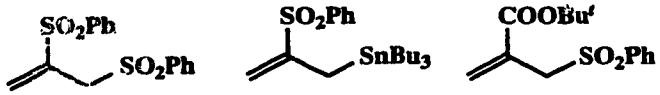
Eq. 18



51 11

allylating agents similar to **11** via allyltin trihalides.[35]

Finally, other interesting radical allylating agents are the phenylsulfonylated propenes **53** and **54**, both reported by Padwa,[37,38] and Giese's phenylsulfonyl acrylate **55**.[39] Common to both **55** and **53** is the phenylsulfonyl leaving group, a



53 54 55

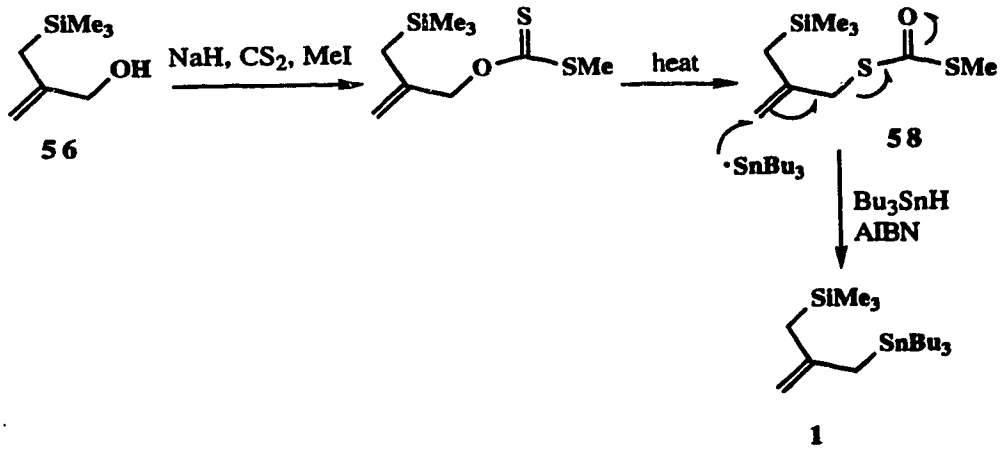
rather poor chain propagator.[37] Hence, with **53**, Padwa generated the radicals by use of Barton's thiohydroxamic esters, and obtained 80-95% yields of allylated products with alkyl halides ranging from primary to tertiary. On the other hand, Giese and coworkers employed cobalt mediated[39] generation of alkyl radicals and achieved moderate (57-80%) yields of allylated products with **55**. With **54** however, as the ejected trialkyltin radical can sustain a radical chain, it can be applied under the usual allylating conditions (AIBN/benzene, reflux or hν) giving allylated products in satisfactory yields. Padwa has also demonstrated how a sequential radical addition on allylating agents such as **53** and **54** can be applied in synthesis.[37,38]

DISCUSSION:

In the light of the above survey, we explored the synthetic utility in radical reactions of the allyl-silane-stannane reagent **1**, which had just recently been reported in the literature, in connection with ionic chemistry. Our main objectives were: (a) to find suitable conditions where compound **1** would react with carbon radicals, and (b) to explore the type of substrates that would react nicely with **1** under the established conditions. If compound **1** were found to afford allylated products of type **2** in radical reactions, then a simple link would be forged between radical chemistry and the extensively developed[6] chemistry of allylic silanes.

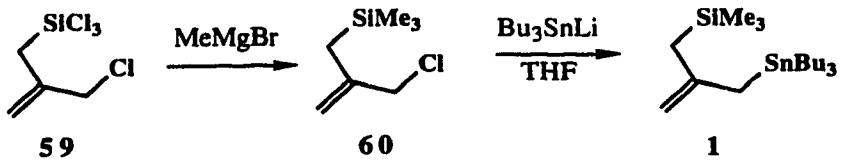
Preparation of 3-(tributylstannyl)-2-[(trimethyl-silyl)methyl]-1-propene (1):

In our preparation of compound **1**, we were guided, and misguided, by a report from Majetich and coworkers. They claimed successful preparations of compound **1** by three different methods,[43] all of which required silica gel chromatography, with hexane as eluent, as part of the procedure for product isolation. (We later found that this step actually destroys the product). Of the three methods described, the one we tried involves free radical stannylation of dithiocarbamate **58** (**Scheme II-2**), which was



Scheme II-2

made from alcohol **56**[44] following literature procedures. Unfortunately, we could not obtain compound **1** by the reported method. Later, we followed a paper by Kang and coworkers documenting their synthesis of the same compound (**Scheme II-3**).[8]

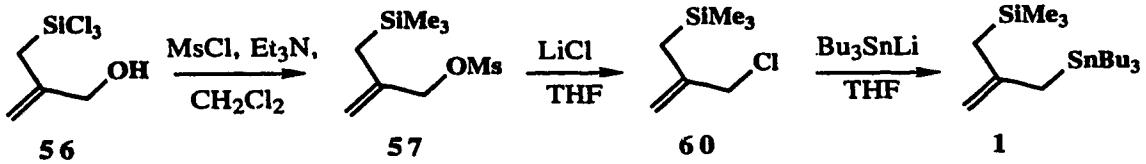


59 **60** **1**

Scheme II-3

Their method involves nucleophilic displacement on the chloride **60** (prepared from **59** by treatment with methylmagnesium bromide), by lithium tributylstannylide,[45] itself prepared from LDA and tributyltin hydride in THF. Their product isolation procedure however was by vacuum Kugelrohr distillation and NOT by silica gel chromatography. Whether Majetich and coworkers were truly able to synthesize **1** by any of the three methods they described is certainly doubtful, as attested by the different proton NMR spectra they report, which, in the same solvent system, was quite different from that of Kang's, whose data were similar to ours.

Our eventual preparation (**Scheme II-4**) of compound **1** was a result of the detour we had to take from **56**. Hence, alcohol **56** was converted into the mesylate **57**



56 **57** **60** **1**

Scheme II-4

in 81% yield, by treatment with distilled mesyl chloride in CH_2Cl_2 in the presence of triethylamine. Mesylate **57** was then stirred overnight with lithium chloride in THF to afford **60** in 75% yield. Further conversion of chloride **60** was done following Kang's procedure with minor modifications, to afford **1** in 76% yield, but with slight impurities.

We observed that even after two Kugelrohr distillations under vacuum, compound **1** remained contaminated with minor impurities. Fortunately, however, these do not seem to affect subsequent reactions. In addition, we suspect the impurities to be due to the slow decomposition of **1**, for we observed considerable gel formation to occur after keeping a freshly distilled batch of **1** in the refrigerator for one week. In such a situation, a redistillation is all that is necessary to recover the remaining intact **1**.

Radical allylations with 1:

We divided into two sets the different trials we did to study the utility of compound **1**. Table II-4 lists all trials, regardless of yield, that led to successful allylations, and Table II-5 lists all the reactions that did not work. We begin the discussion from the latter, as those experiments were done first.

Table II-4 Examples of allylations

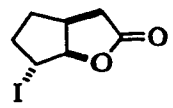
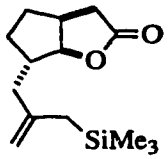
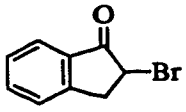
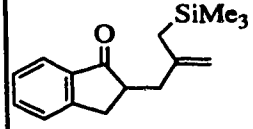
Substrate	Conditions	Product	Yield (corrected)
 **68**	2.3 eq.**1**, benzene, 5-10 °C sunlamp 15 h	 **69**	68%
 **70**	2.0 eq. **1**, benzene, 5-10 °C sunlamp 3h	 **71**	86%

Table II-4 (Continued)

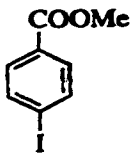
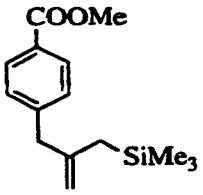
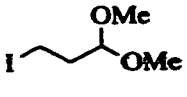
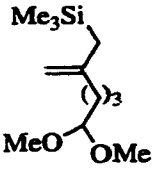
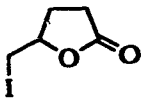
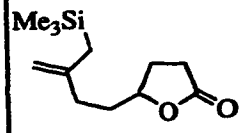
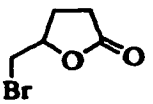
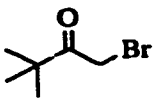
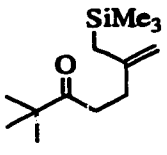
 **73**	2 eq. 1, benzene, 5-10 °C sunlamp 24h --- 4 eq. 1, benzene, 5-10 °C, Hanovia 24h	 **74**	19.6% (46%) --- 20.2%
 **77**	3 eq.1, benzene, r.t. Hanovia 20h	 **78**	50%
 **79**	2 eq. 1, benzene, 5-10 °C Hanovia 17h	 **81**	75%
 **80**	2.5 eq. 1, benzene, 5-10 °C Hanovia 21h	**81**	6%
 **83**	2.5 eq. 1, benzene, r.t. Hanovia 15h	 **84**	59%

Table II-4 (Continued)

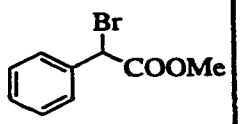
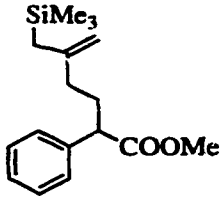
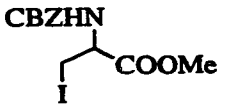
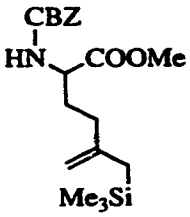
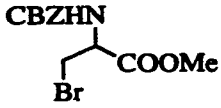
 **93**	2.5 eq. 1, benzene r.t. Hanovia 23h	 **94**	26% (51%)
 **96**	2.5 eq. **1**, benzene, r.t. Hanovia 16h	 **97**	7%
 **98**	2.5 eq.1, benzene, Hanovia 7h at 5-10 °C 13 h at r.t.	 **99**	22%

Table II-5: Examples that did not undergo allylation

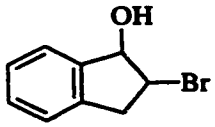
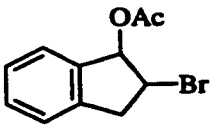
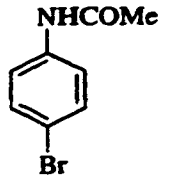
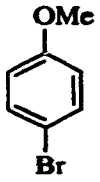
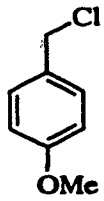
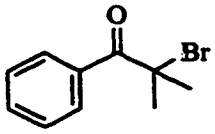
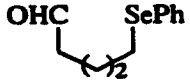
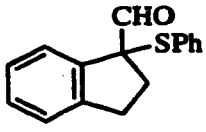
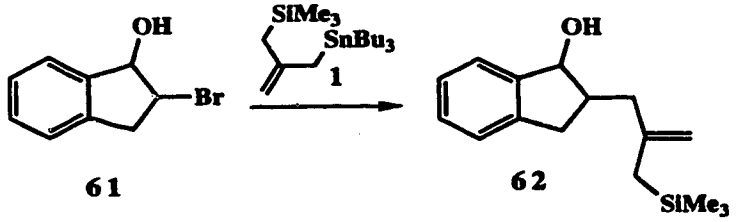
Substrate	Eq. of 1	Conditions	Result
 **61**	2.0	0.2 eq. AIBN benzene 80 °C 10 h	Complex mixture
 **63**	2.0	0.2 eq. AIBN, benzene 80 °C 8 h	Complex mixture

Table II-5 (Continued)

 **64**	2.0	0.4 eq. AIBN, benzene 80 °C 1h	Starting material is insoluble
 **65**	2.0	0.4 eq. AIBN, benzene 80 °C 10 h	Complex mixture
 **66**	2.0	0.2 eq. AIBN, benzene, reflux; $(Bu_3Sn)_2$ added 2 h later and mixture irradiated with sunlamp 15 h	Starting material remained
 **75**	2.0	benzene, 5-10 °C sunlamp 1 h Rayonet 12 h	Complex mixture
 **76**	2.0	benzene 5-10 °C sunlamp	Complex mixture
 **87**	2.6	benzene 5-10 °C Hanovia lamp	Complex mixture

The first substrate we tried was *trans*-2-bromo-1-indanol[46] **61**, using the familiar Keck's thermal conditions:[47] AIBN (~0.2 eq.) in benzene, system degassed, 80 °C, 10 h; the ratio of **1** to substrate **61** being 2:1. Under these conditions, we obtained (eq. 19) in about 20% yield an unstable material of approximately the required molecular weight of compound **62**. Careful examination of the ^{1}H NMR and mass spectra showed that the isolated material was an impure sample of the corresponding ketone. This identification was easily made by direct comparison with an authentic sample of the ketone, made as described later (see compound **71**). On further reflection we recalled that, in prior work in the fredericamycin area carried out in this laboratory, we had on several occasions observed very easy oxidation of indane aldehydes into indanones. Consequently, we realized that our choice of substrate in this case was not ideal, and no further work was done on compound **61** itself.

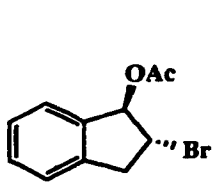
Eq. 19



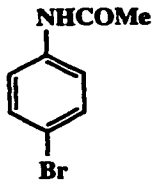
61 **62**

We next decided to acetylate the hydroxyl group in **61** to give **63**. However, on subjecting **63** to the same thermal conditions of allylation, we obtained a complex mixture. Possibly, the desired radical undergoes a 1,2-shift of the acetyl group,[48] to give a benzylic radical. (Later, we gained the impression that benzylic radicals do not react with our reagent **1**.) At this point, we turned to several readily available compounds so that we could quickly screen the reactivity of **1**. These simple test materials were: *p*-

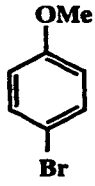
bromoacetamide **64**, *p*-bromoanisole **65**, and *p*-methoxybenzyl chloride **66**. *p*-Bromoacetamide **64** was quite insoluble in our solvent of choice (benzene), even at



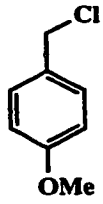
63



64



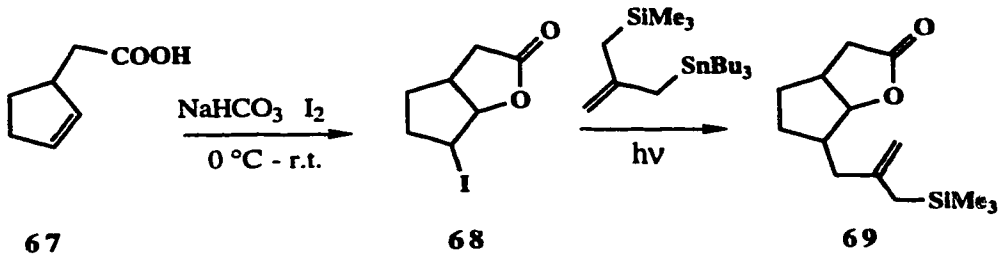
65



66

reflux. With *p*-bromoanisole **65** as substrate, a complex mixture with some starting material remaining was obtained after a 10-h reaction period at reflux. Finally, with *p*-methoxybenzyl chloride **66**, Keck's thermal conditions did not seem to lead to any reaction (TLC control), even after two hours at reflux. In this case, we also added hexabutylditin[29] and irradiated the refluxing solution with a sunlamp (275 Watt) but, again, no reaction occurred (15 h at reflux, TLC control).

We had anticipated that compound **1** would behave as nicely as allyltributylstannane itself, and we were puzzled by the apparent lack of smooth reaction between **1** and the substrates we had tried. Accordingly, we decided to change the reaction conditions from thermal to photochemical. This time, we employed irradiation of a degassed system, kept between 5 and 10 °C, the light source being a sunlamp. No AIBN was used in these experiments. Our first substrate was the bicyclic iodolactone **68**, which was made from 2-cyclopenten-1-acetic acid (**67**) (**Scheme II-5**). The compound was chosen in part because it was not volatile (and could be handled easily) and in part because iodides usually undergo radical reactions smoothly.



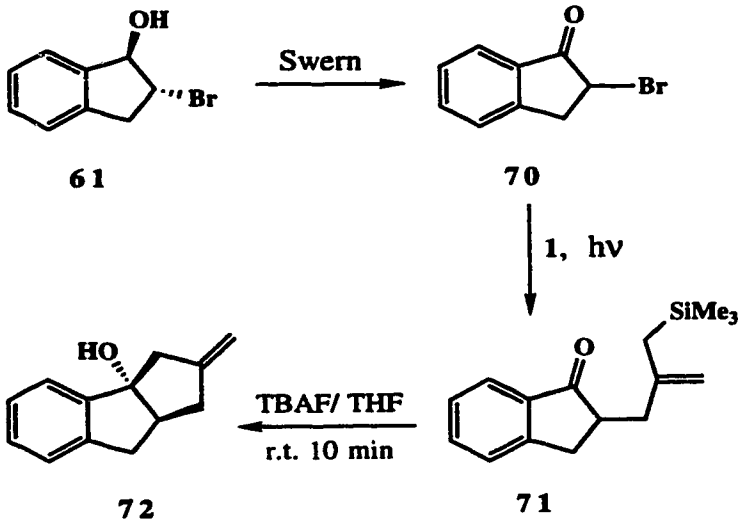
67 68 69

Scheme II-5

Using 1.4 equivalents of **1**, and a 20-h irradiation period afforded our first successfully allylated product **69** in 56% yield as a 9.3:1 mixture of two diastereomers. Some starting material was recovered. With 2.3 equivalents of **1**, **68** was essentially consumed after 15 h, and the yield improved to 68%. Having demonstrated the type of allylation we wanted, it was clear that we should now evaluate other substrates under the above photochemical conditions.

The next substrate we tried was the α-bromoketone **70**, prepared (**Scheme II-6**) by Swern oxidation of the readily available *trans*-2-bromo-1-indanol **61** which we had in hand from one of our earlier allylation experiments. Compound **70** is also quite photosensitive as judged from the fast yellowing of the compound upon exposure to light. Using 2 equivalents of **1**, we found that reaction was essentially complete in 3 h or less, giving **71** in a yield as high as 86% even after the material had been subjected twice to flash chromatography. (In some experiments, products required a second chromatographic separation to remove persistent tin impurities, and we noticed that this requirement was related to the reaction scale. Products from small scale experiments were generally easier to purify.)

At this point, simply to illustrate how compounds such as **71** could be further transformed, we treated the substance with TBAF, and obtained in 80% yield the tricyclic alcohol **72**, bearing an exocyclic double bond. Compound **72** is clearly synthetically equivalent to an α,β-unsaturated ketone, that would be available by ozonolysis and dehydration.



Scheme II-6

The noticeably short reaction time required by substrate **70**, compared with **68**, caused us to consider the differences between the derived radicals. Both radicals are secondary, with that coming from **70** being electrophilic and that from **68** being nucleophilic. Renaud has explained[31] the reactivity of substituted allylic silanes on the basis of the polarization expected in the transition state, and we can apply his arguments to the relative rates we observed. With an electrophilic radical, the transition state in **Figure II-4** is greatly stabilized through the presence of the trimethylsilyl group by virtue of the β-effect.[33] With a nucleophilic radical however (**Figure II-5**), such

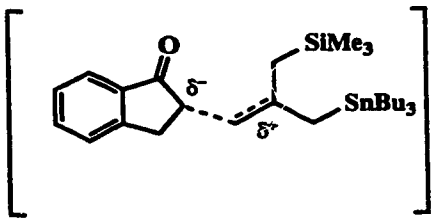


Fig. II-4

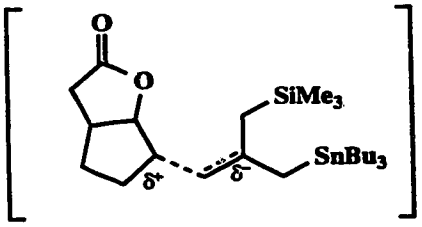


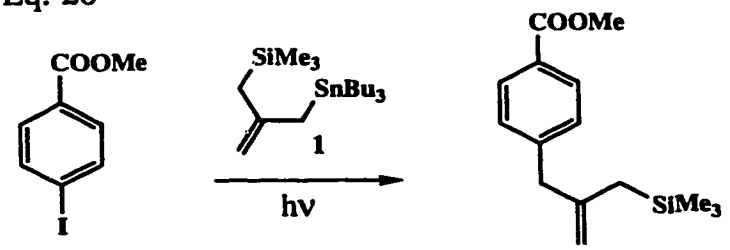
Fig. II-5

Transition state polarizations during radical addition

stabilization is not available, and this fact may explain why reactions with the radical derived from **68** are slower.

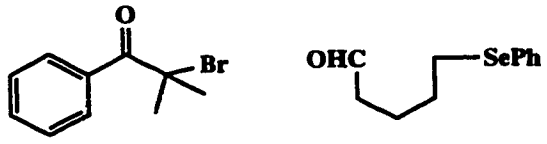
We next decided to examine methyl *p*-iodobenzoate **73** (eq. 20). Although we anticipated that **73** would produce an electrophilic radical which we expect to react rapidly with our reagent, we found that the reaction was, in fact, quite sluggish under

Eq. 20



73 **74**

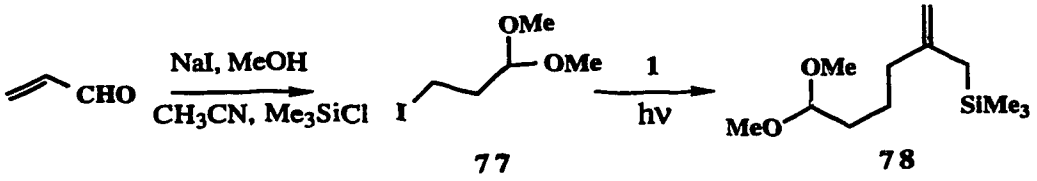
the photochemical conditions. After a 24-h period of irradiation, only 20% yield of the allylated product **74**, together with some recovered starting material was obtained. Corrected for the starting material, the yield would be 46%. There was no significant improvements in the yield when using 4 equivalents of the allylating agent **1**. The sluggishness could be due to slow generation of radicals from the substrate, and we are currently examining the use of hexabutylditin. At the time, however, we decided to explore the addition of tertiary and primary radicals, and for this purpose we employed bromoketone **75**[46] and aldehyde **76**.[49] Unfortunately, in both cases, only



75 **76**

complex mixtures were obtained under the photochemical conditions similar to those [we used a Rayonet reactor (3000 Å)[50] for **75**] that had worked well with **68**. In the case of

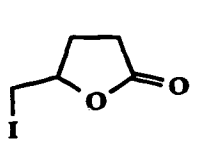
75, it was not clear why no satisfactory allylation was observed, as our secondary bromoketone (see **70**) reacts nicely. It is not at all clear why the selenide does not react, because the radical chemistry of selenides--primary, secondary, or tertiary--is well established, and many examples are known. It may be that the rate of radical formation is too low to sustain a radical chain. Homolysis of a carbon-selenium bond would be expected to be slower than that of a carbon-bromine bond.[51] At this point, our sunlamp broke and, as no immediate replacement was available, we turned to using a Hanovia UV lamp[52] (140 W, quartz) or Rayonet reactor (3000 Å).[50] As the selenide **76** had not served as a satisfactory source of primary radicals, we decided to prepare the iodoacetal **77**,[53] which can be made from acrolein (**Scheme II-7**).



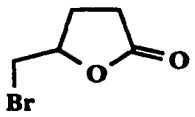
Scheme II-7

With 2 equivalents of reagent, irradiation at room temperature using the Rayonet reactor gave a 35% yield of **78**. With 3 equivalents of the allylating agent **1**, irradiation (Hanovia lamp) in Pyrex at room temperature for 20 hours gave **78** in 50% yield. The experiment was done at room temperature in order to shorten the reaction time, as we had come to the conclusion that reaction times were generally above 15 hours unless the radical was electrophilic, and long reaction times caused degradation of the reagent. However, as with substrate **77**, the reaction was still very slow.

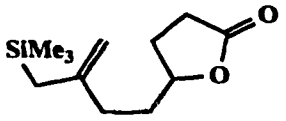
We next turned our attention to substrates **79** and **80**, prepared by halolactonization of **82**, and differing only in the halogen. With 2 equivalents of **1** and a



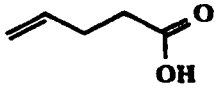
79



80



81

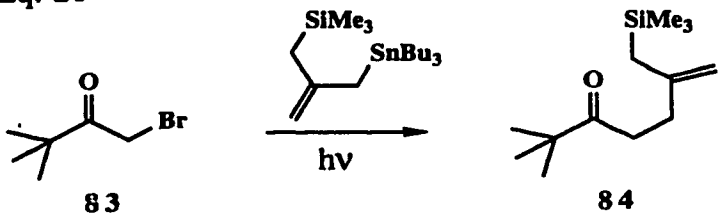


82

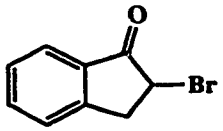
reaction temperature of 5 to 10 °C, a 75% yield of the allylated product **81** was obtained from **79** after 17 hours of irradiation. On the other hand, the bromolactone **80** reacted sluggishly, giving only 6% yield of product with 80% recovery of starting material after 21 hours of irradiation, even though more reagent had been used (2.5 equivalents of **1**). As the same radicals would be formed from **79** or **80**, clearly, the ease of homolytic cleavage of the C-halogen bond, is an important factor in the product yield. The reaction of **77**, described above, was done at room temperature and, for comparison with **79**, we are currently examining the process at 0-10 °C. Such a comparison between the two primary radical would indicate the influence, if any, of a β-oxygen effect.

We thought we should compare substrates **83** and **70**, as one of these electrophilic radicals is primary and the other is secondary. With 15 hours of irradiation at room temperature (Hanovia) and 2.5 equivalents of **1**, the allylated product **84** (eq. 21) was obtained in 59% yield from **83**. Unfortunately, the product was volatile and losses were definitely incurred when drying the compound under vacuum. (A tiny drop of the product was spotted at the base of a vial and kept under vacuum. After 10 minutes, the liquid spot had evaporated.) Hence, we suspect that both the primary and secondary radicals react quite efficiently with the reagent.

Eq. 21

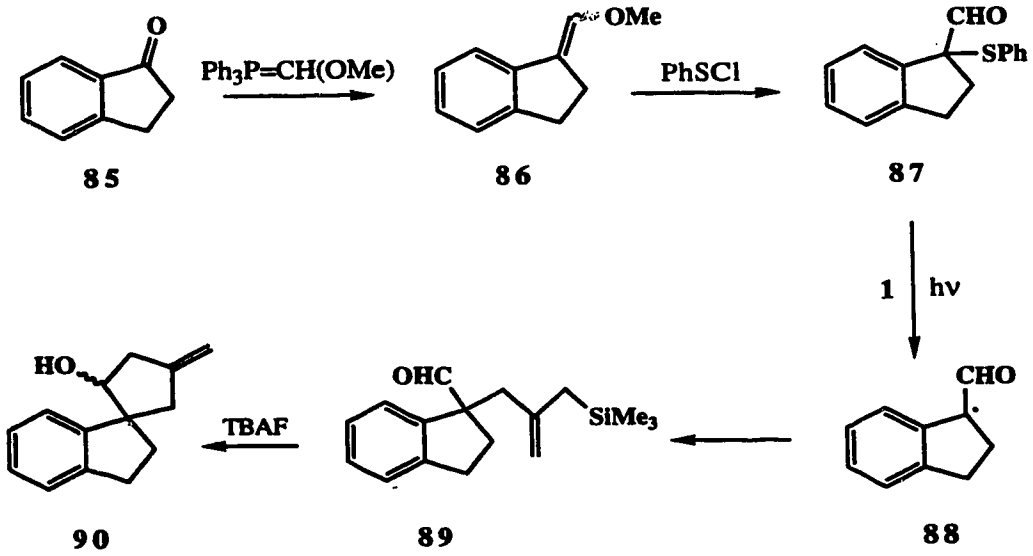


83 84



70

Although the example of compound **75**, which would have involved a tertiary radical, had not worked, we examined another case (**Scheme II-8**) because of the useful possibility that it might serve as a route to spiro compounds. We wondered if it was possible to allylate a tertiary radical like **88**, because treatment of the resulting allylated product **89** with TBAF would result in the spiro compound **90**. Aldehyde **87**, a precursor to the radical **88**, was prepared from indanone **85**. Wittig reaction of **85** with the ylide from methoxymethyltriphenylphosphonium chloride afforded the enol ether



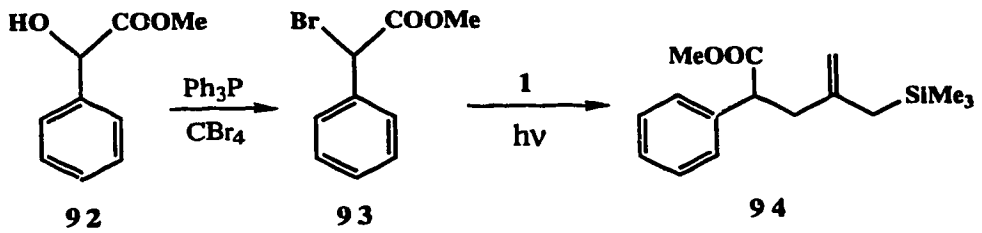
85 86 87

90 89 88

Scheme II-8

86 as a mixture of two geometric isomers containing trace impurities. Without further purification, the enol ethers were treated with freshly prepared phenylsulfenyl chloride (PhSCl)[54] to afford **87**. This compound required rapid flash chromatography and immediate recrystallization, as the dissolved form proved very unstable. Unfortunately, aldehyde **87**, when subjected to our allylating conditions (Hanovia) in the cold (5-10 °C), afforded only a complex mixture.

We also studied the substrates **93**, **96** and **98**. Substrate **93** was prepared from alcohol **92**[55] in 98% yield by bromination with triphenylphosphine and carbon tetrabromide. With 2.5 equivalents of **1**, and an irradiation period at room temperature of

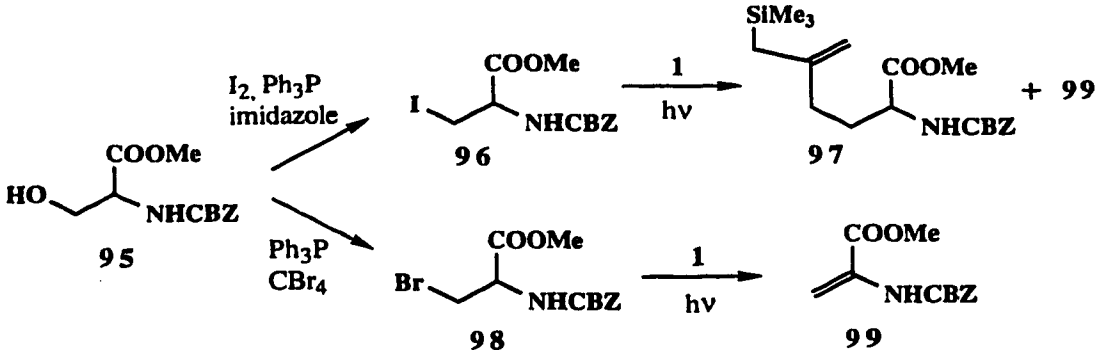


92 **93** **94**

Scheme II-9

23 hours, we obtained only 26% of the allylated product **94** and 49% recovered starting material. As the carbon-bromine bond homolysis would be expected to be very easy, we suspect that the nature of the radical — highly stabilized — is responsible for the poor yield.

Substrates **96** and **98** were both prepared from **95**, the CBZ-protected[56] methyl ester of serine. Conversion of **95** into **96** was done following a literature procedure (I_2, PPh_3, imidazole)[57] and gave the iodide in 60% yield after recrystallization. Substrate **98** was prepared[58] from **95** by treatment with carbon tetrabromide and triphenylphosphine, and was obtained in 85% yield after recrystallization. Although the bromide can be subjected to flash chromatography, the iodide does not survive unless its exposure to silica gel is very brief, as is the case when the compound is passed through a short pad of silica gel.



Scheme II-10

With substrate **98**, there was essentially no reaction after irradiation (Hanovia) with 2.5 equivalents of **1** at 10 °C for 7 hours. Removal of the cold water bath and further irradiation at room temperature for 13 hours revealed a faint new spot on TLC analysis, but isolation showed the material to be the elimination product **99** , and no allylated product was isolated. On the other hand, iodide **96**, after 16 hours of irradiation at room temperature with 2.5 equivalents of **1** afforded 7% of the allylated product **97** after a chromatographic isolation. Although TLC analysis of the reaction mixture showed this product, the elimination product, and the starting material, little of the latter was isolated, since it decomposes on silica gel. The failure of **96** to react efficiently with our reagent is surprising, since it is known[28] to be allylated efficiently (70%) by other allylating species, and we are currently examining our reaction in ether as solvent, since this was the solvent used in the allylation reported in the literature.

CONCLUSION:

The examples of photoinitiated allylation that we have surveyed indicate that nonactivated primary and secondary iodides with a β-oxygen substituent react with reagent **1**. The corresponding bromides react poorly, if at all. Primary iodides lacking a β-oxygen substituent, also react, as do α-bromoketones that are primary or secondary. Tertiary α-bromoketones do not react. Surprisingly, benzylic radicals also appear to react poorly, as judged by the behavior of compounds **87** and **93**. It seems that the reactions of reagent **1** are very sensitive indeed to the degree of stability of the attacking radical, based on the poor reactivity of **93** compared with **79**, and the reasons for this are not yet clear. In cases where the allylation proceeds in synthetically useful yields, we expect the products to be amenable to standard reactions of allylsilanes, and this possibility is illustrated by the conversion of **71** to **72**.

EXPERIMENTAL:

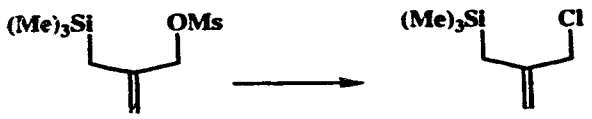
General procedures. The same procedures as in Chapter 1 apply here.

2-(Trimethylsilylmethyl)-2-propenyl methane-sulfonate (57).[59]

56 **57**

MsCl (5.35 mL, 69.12 mmol) in dry CH_2Cl_2 (50 mL) was added by cannula to a stirred and cooled (0 °C) solution of 2-(hydroxymethyl)allyltrimethylsilane[44] **56** (5.001 g, 34.7 mmol) in dry CH_2Cl_2 (100 mL) and Et_3N (14.5 mL, 104 mmol). After the addition, which took approximately 8 min, the cold bath was removed and the mixture was stirred for 1.5 h. Cold water (100 mL) was added and the mixture was extracted with CH_2Cl_2 (2 x 75 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 23 cm), using 5:95 acetone-hexane, gave **57** (6.26 g, 81.2%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR (cast) 1358, 1176, 853 cm^{-1}; ^1H NMR (acetone-d_6, 200 MHz) δ 0.05 (s, 9 H), 1.65 (s, 2 H), 3.10 (s, 3 H), 4.60 (s, 2 H), 4.85 (br s, 1 H), 5.04 (br s, 1 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ -1.43 (q'), 23.33 (t'), 37.55 (q'), 74.01 (t'), 112.19 (t'), 141.73 (s'); exact mass, *m/z* calcd for $C_8H_{18}O_3SSi$ 222.07460, found 222.07449. Anal. Calcd for $C_8H_{18}O_3SSi$: C, 43.21; H, 8.16. Found: C, 43.26; H, 8.38.

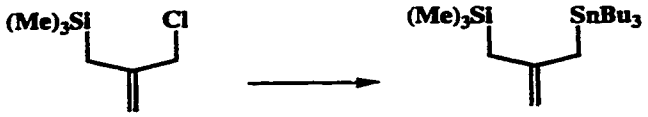
3-Chloro-2-(trimethylsilylmethyl)-1-propene (60).[8]



57 **60**

LiCl (3.6 g, 84.9 mmol, drying is not necessary) was added to a solution of **57** (6.52 g, 29.36 mmol) in dry THF (80 mL) and the mixture was stirred at 40 °C for 18 h. By this stage a white suspension had formed. The mixture was washed with brine (50 mL), and the aqueous layer was extracted with Et_2O (1 x 60 mL). The combined organic extracts were dried ($MgSO_4$), concentrated to *ca.* 15 mL, and passed through a pad of silica gel (2 x 5 cm). The pad was rinsed with hexane (80 mL) and the filtrate was concentrated. Kugelrohr distillation of the residue (85 °C, water aspirator vacuum) afforded **60** (3.56 g, 75%) as a clear, light liquid: FTIR (film) 853 cm^{-1}; ^1H NMR (benzene-d_6, 200 MHz) δ -0.10 (s, 9H), 1.53 (d, J = 1 Hz, 2H), 3.68 (d, J = 1Hz, 2H), 4.59 (br s, 1H), 4.84 (br s, 1H); ^{13}C NMR (benzene-d_6, 75.469 MHz) δ -1.55 (q'), 23.73 (t'), 49.81 (t'), 112.31 (t'), 143.33 (s'); exact mass *m/z* calcd for $C_7H_{15}Si^{35}Cl$ 162.06316, found 162.06310. Anal. Calcd for $C_7H_{15}ClSi$: C, 51.67; H, 9.29; Cl, 21.79. Found: C, 52.07; H, 9.40; Cl, 21.29.

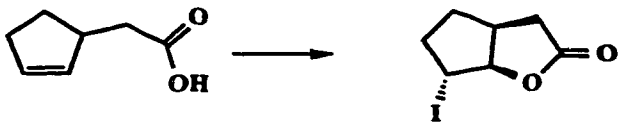
3-(Tri-*n*-butylstannyl)-2-(trimethylsilylmethyl)-1-propene (1).



60 **1**

Kang's procedure[8] for converting **60** into **1** was followed with minor modifications: *n*-BuLi (2.5 M in hexanes, 2.65 mL, 6.63 mmol) was added to a stirred and cooled (0 °C) solution of *i*-Pr_2NH (1.0 mL, 7.24 mmol) in dry THF (6.5 mL). Stirring at 0 °C was continued for 10 min, and Bu_3SnH (1.62 mL, 5.84 mmol) was added. Stirring was continued for another 30 min and the solution was then cooled to -20°C. Compound **60** (1.00 g, 6.15 mmol) was added neat by syringe. The syringe was rinsed once with dry THF (0.5 mL) and the rinsing added to the mixture. At this point, the cold bath was removed and the solution was stirred for 10 h. The mixture was poured into ice cold water (15 mL) and extracted with Et_2O (3 x 25 mL), and the organic extract was dried (Na_2SO_4). Evaporation of the solvent, followed by Kugelrohr distillation under reduced pressure, afforded **1** (1.842 g, 75.7%) as a clear oil: bp 100-105 °C (0.100 mm Hg); FTIR (film) 2956, 2925, 857 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 0.05 (s, 9 H), 0.80-0.95 (m, 15 H), 1.25-1.40 (m, 6 H), 1.42-1.65 [m including br s (2 H) at δ 1.50), 8 H], 1.80 (br s, 2 H), 4.23 (br s, 1 H), 4.40 (br s, 1 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ -1.14 (q'), 10.04 (t'), 13.96 (q'), 22.30 (t'), 28.03 (t'),29.60 (t'), 29.87 (t'), 103.49 (t'), 148.22 (s'); exact mass, *m/z* calcd for $C_{19}H_{42}Si^{120}Sn$ 418.20779, found 418.20890.

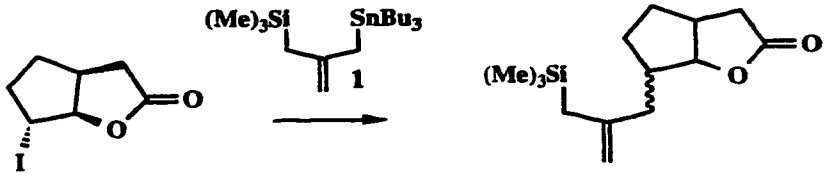
(3aα, 6α, 6aα)-Hexahydro-6-iodo-2*H*-cyclopenta[b]-furan-2-one (68).



67 **68**

Compound **68** was made following a literature procedure,[60] with some modifications. $NaHCO_3$ (6.64 g, 79 mmol) was added to a vigorously stirred and cooled (0 °C) solution of 2-cyclopentene-1-acetic acid (**67**) (2.0 g, 15.85 mmol) in 75% THF-H_2O (16 mL). I_2 (8.5 g, 33.5 mmol, divided into 5 portions) was then added carefully. The resulting dark brown solution was stirred for 15 h, the cold bath being left in place, but not recharged. The reaction mixture was diluted with Et_2O (80 mL) and washed several times with saturated aqueous $Na_2S_2O_3$ until the organic layer became colorless. The aqueous washings were extracted once with Et_2O (50 mL) and the combined organic extracts were dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 25 cm), using 1:9 EtOAc-hexane, gave **68** (3.8 g, 95%) as a clear, colorless liquid: FTIR (cast) 1782 cm^{-1}; ^1H NMR (benzene-d_6, 200 MHz) δ 1.55-1.73 (m, 1 H), 1.25-1.45 (m, 2 H), 1.47-2.20 (m, 4 H), 3.9 (br s, 1 H), 4.54 (d, J = 6 Hz, 1 H); ^{13}C NMR (benzene-d_6, 75.469 MHz) δ 30.19 (d'), 31.82 (t'), 34.63 (t'), 35.48 (t'), 35.89 (d'), 91.59 (d'), 175.13 (s'); exact mass *m/z* calcd for $C_7H_9O_2I$ 251.96474, found 251.96537.

(3aα, 6α, 6aα)- and (3aα, 6β, 6aα)-Hexahydro-6-[2-(trimethylsilylmethyl)-2-propenyl]-2*H*-cyclopenta-[b]furan-2-one (69).



68 **69**

Compounds **68** (159 mg, 0.63 mmol) and **1** (608 mg, 1.46 mmol) were weighed into a 1 x 10 cm Pyrex test tube. The test tube was stoppered with a rubber septum, kept under vacuum for 10 min and then filled with Ar. This was repeated once more, and dry PhH (1 mL) was added. The test tube was mounted in a slanted position with the base of the test tube immersed in a water bath at 5 to 10 °C. The solution was irradiated with an ultraviolet quartz lamp for 15 h, after which the reaction mixture was evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 5:95 acetone-hexane, gave **69** (108 mg, 68%) as an inseparable mixture of a major and minor isomer in a 9.3:1 ratio: FTIR (cast) 1776 cm^{-1}; ^1H NMR (benzene-d_6, 400 MHz) δ 0.0 (s, 9 H), 0.80-1.0 (m, 2 H), 1.35-1.49 (m, 3 H) 1.50-1.70 (m, 2 H), 1.71-1.90 (m, 2 H), 1.91-2.25 (m, 3 H), 4.11 (dd, J = 6.9, 2.3 Hz, 1 H), 4.63 (s, 2 H); ^{13}C NMR (benzene-d_6, 75.469 MHz) (peaks for the minor compound are indicated with an asterisk) δ -1.31 (q'), -0.97 (q')*, 26.19 (t'), 27.29 (t')*, 28.99 (t')*, 29.85 (t'), 31.62 (t'), 32.49 (t')*, 35.52 (t'), 36.34 (t')*, 37.37 (d')*, 37.65 (d'), 37.73 (t')*, 41.04 (t'), 43.93 (d'), 84.74 (d')*, 86.06 (d')*, 89.48 (d'), 108.40 (t')*, 109.41 (t'), 145.40 (s'), 146.12 (s')*, 175.83 (s') (several of the peaks coincide); exact mass, *m/z* calcd for $C_{14}H_{24}O_2Si$ 252.15456, found 252.15378.

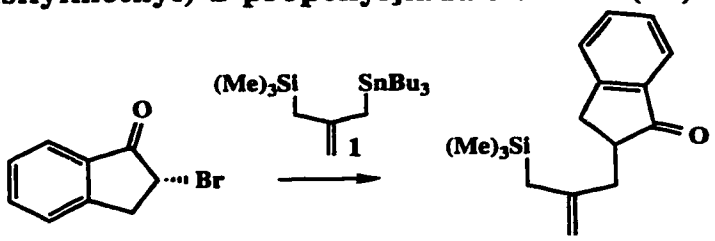
2-Bromoindan-1-one (70).

trans racemic

61 **70**

Dry DMSO (0.37 mL, 5.17 mmol) was added to a stirred solution of $(COCl)_2$ (0.23 mL, 2.59 mmol) in dry CH_2Cl_2 (15 mL) at -78°C ,and the mixture was stirred for 10 min. A cold (0 °C) solution of bromo indanol **61** (500 mg, 2.35 mmol) in dry CH_2Cl_2 (40 mL) was then added by cannula. The resulting solution was stirred at -78 °C for 30 min. Et_3N (1.64 mL, 11.75 mmol) was added and, after 10 min, the cold bath was removed and stirring was continued for 30 min. Saturated aqueous NH_4Cl (40 mL) was added and the mixture was extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were washed with brine (1 x 50 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 21 cm), using 5:95 EtOAc-hexane, gave **70** (474 mg, 95%) as a pure (^1H NMR 400 MHz), faintly yellowish oil. The compound is not very stable at room temperature. The material had: FTIR (cast) 1723 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 3.37 (dd, J = 18.2, 2.9 Hz, 1 H), 3.95 (dd, J = 18.2, 7.4 Hz, 1 H), 4.87 (dd, J = 7.4, 2.9 Hz, 1 H), 7.40-7.60 (m, 2 H), 7.65-7.80 (m, 2 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ 38.66 (t'), 45.56 (d'), 125.10 (d'), 127.65 (d'), 128.99 (d'), 134.34 (s'), 136.64 (d'), 152.30 (s'), 199.70 (s'); exact mass, *m/z* calcd for C_9H_7BrO 211.96597, found 211.96848.

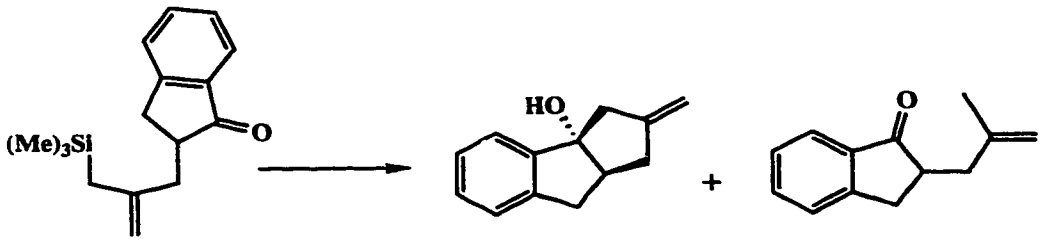
2-[2-(Trimethylsilylmethyl)-2-propenyl]indan-1-one (71).



70 **71**

2-Bromoindanone **70** (38 mg, 0.18 mmol) and allyl silyl stannane **1** (150 mg, 0.36 mmol) were weighed into a 1 x 10 cm Pyrex test tube. The test tube was stoppered with a rubber septum, kept under vacuum for 5 min, and then filled with Ar. This procedure for degassing was done three times. Dry PhH (0.5 mL) was then added and the test tube was mounted in a slanted position with the base of the test tube immersed in a water bath at 5 to 10 °C. The solution was irradiated with a sunlamp for 3 h, after which the solvent was evaporated. Flash chromatography of the residue twice over silica gel (1.5 x 25 cm), using 5:95 acetone-hexane for the first chromatography and 2.5:97.5 EtOAc-hexane for the second, gave **71** (40.1 mg, 86%) as a pure (^{1}H NMR, 400 MHz), colorless oil: FTIR (cast) 1713, 848 cm^{-1}; ^{1}H NMR (benzene-d_6, 400 MHz) δ 0.03 (s, 9 H), 1.45 (d, J = 2.1 Hz, 2 H), 1.83 (dd, J = 14.5, 10.5 Hz, 1 H), 2.45-2.60 (m, 2 H), 2.75-2.85 (m, 2 H), 4.57 (br s, 1 H), 4.62 (br s, 1 H), 6.9-7.0 (m, 2 H), 7.10-7.14 (dd, J = 7.4, 1.2 Hz, 1 H), 7.80 (d, J = 7.7 Hz, 1 H); ^{13}C NMR (benzene-d_6, 75.469 MHz) δ -1.29 (q'), 26.48 (t'), 32.87 (t'), 40.27 (t'), 45.79 (d'), 108.82 (t'), 124.03 (d'), 126.64 (d'), 127.42 (d'), 134.28 (d'), 137.40 (s'), 145.79 (s'), 153.60 (s'), 206.70 (s'); exact mass, *m/z* calcd for $C_{16}H_{22}OSi$ 258.14398, found 258.14427.

2,3,8,8a-Tetrahydro-2-methylene cyclopent[a]inden-3a(1*H*)-ol (72) and 2-(2-Methyl-2-propenyl)indan-1-one (72').

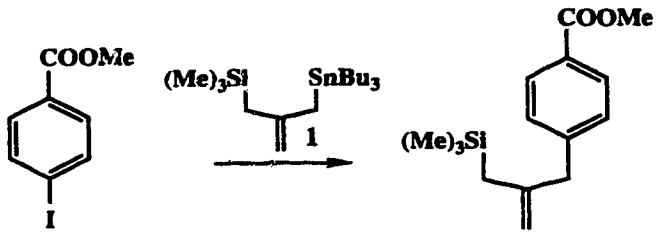


71 72 72'

Bu_4NF (1M in THF, 0.36 mL, 0.36 mmol) was added to a stirred solution of **71** (90 mg, 0.349 mmol) in dry THF (16 mL). Stirring was continued for 30 min. The mixture was then poured into a separatory funnel containing saturated NH_4Cl (30 mL), and extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 25 cm), using 6:94 EtOAc-hexane, gave **72** (48 mg, 74%) as a pure (^1H NMR, 200 MHz), white solid along with the minor product **72'** (4 mg, 5.7%). Compound **72** had: mp 67-68 °C; FTIR (cast) 3346 cm^{-1}; ^1H NMR (benzene-d_6, 200 MHz) δ 1.55 (s, 1 H), 1.9 (d, J = 15.6 Hz, 1 H), 2.3 (dd, J = 15.9, 4.8 Hz, 1 H), 2.36-253 (m, 1 H), 2.60-2.82 (m, 3 H), 2.95 (dd, J = 15.9, 7.9 Hz, 1 H), 4.75 (quintuplet, J = 1.95 Hz, 2 H), 6.90-7.13 (m, 3 H), 7.20-7.30 (m, 1 H); ^{13}C NMR (benzene-d_6, 75.469 MHz) δ 37.20 (t'), 39.48 (t'), 46.90 (t'), 52.26 (d'), 91.63 (s'), 106.83 (t'), 123.84 (d'), 125.18 (d'), 127.32 (d'), 128.46 (d'), 142.56 (s'), 147.85 (s'), 150.70 (s'); exact mass, *m/z* calcd for $C_{13}H_{14}O$ 186.10446, found 186.10383. Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.80; H, 7.49.

Compound **72'** had: ^1H NMR (benzene-d_6, 200 MHz) δ 1.52 (s, 3 H), 1.80 (dd, J = 15, 11 Hz, 1 H), 2.30-2.55 (m, 2 H), 2.58-2.85 (m, 2 H), 4.60 (s, 1 H), 4.72 (s, 1 H), 6.85-7.01 (m, 2 H), 7.10 (br d, J = 6 Hz, 1 H), 7.82 (br d, J = 8 Hz, 1 H); exact mass *m/z* calcd for $C_{13}H_{14}O$ 186.10446, found 186.10474.

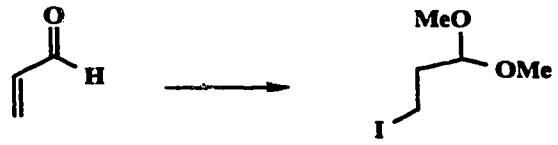
Methyl 4-[2-(Trimethylsilylmethyl)-2-propenyl]-benzoate (74).



73 **74**

p-Iodo methyl benzoate **73** (54.6 mg, 0.208 mmol) and **1** (350 mg, 0.84 mmol) were weighed into a 1 x 10 cm Pyrex test tube. The test tube was stoppered with a rubber septum, kept under vacuum for 5 min, and then filled with Ar. This procedure for degassing was done twice. PhH (0.20 mL) and THF (0.80 mL) were added and the test tube was mounted in a slanted position with the base of the test tube immersed in a water bath at 5 to 10 °C. The solution was irradiated with a UV-quartz lamp (Hanovia, 140 W) for 24 h. By this time the solution has turned cloudy white. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 25 cm), using 1.5-98.5 EtOAc-hexane (containing 0.5% Et_3N), gave **74** (11 mg, 20.2%) as a pure (^1H NMR, 400 MHz), colorless oil: FTIR (cast) 1725 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 0.05 (s, 9 H), 1.52 (s, 2 H), 3.38 (s, 2 H), 3.86 (s, 3 H), 4.60 (br s, 1 H), 4.66 (br s, 1 H), 7.34 (br d, J = 8.34 Hz, 2 H), 7.94 (br d, J = 8.34 Hz, 2 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ -1.21 (q'), 26.66 (t'), 45.44 (t'), 52.17 (q'), 110.33 (t'), 129.16 (s'), 130.13 (d'), 130.21 (d'), 146.39 (s'), 147.22 (s'), 167.18 (s'); exact mass, *m/z* calcd for $C_{15}H_{22}O_2Si$ 262.13892, found 262.13842.

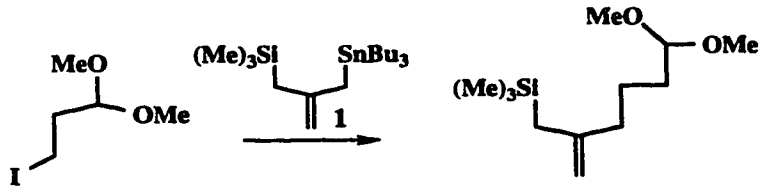
1-Iodo-3,3-dimethoxypropane (77).



77

Compound **77** was made (55%) from acrolein following exactly a literature procedure[53] and had: ^{1}H NMR (benzene-d_6, 400 MHz) δ 1.82-1.90 (m, 2 H), 2.80-2.85 (m, 2 H), 3.01 (s, 6 H), 4.24 (t, *J* = 5.5 Hz, 1 H); exact mass *m/z* calcd for $C_5H_{11}O_2I$ 229.98038, found 229.98022.

6,6-Dimethoxy-2-(trimethylsilylmethyl)-1-hexene (78).



77 78

A solution of **77** (138 mg, 0.60 mmol) and **1** (751 mg, 1.80 mmol) in dry PhH (0.9 mL) was prepared in a 1x 10 cm Pyrex test tube. The test tube was stoppered with a rubber septum and the solution was degassed by bubbling a vigorous stream of Ar through it for 6 min. The solution was irradiated with a UV-quartz lamp (Hanovia, 140 W). After 20 h the sample had become turbid. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 25 cm), using 2.5:97.5 EtOAc-hexane (containing 1% Et_3N), gave **78** (68.9 mg, 50%) as a pure (^{1}H NMR 400 MHz), colorless oil: FTIR (cast) 856 cm^{-1}; ^{1}H NMR (benzene-d_6, 400 MHz) δ 0.02 (s, 9 H), 1.49 (br s, 2 H), 1.50-1.70 (m, 4 H),.1.96 (t, *J* = 7.28 Hz, 2H), 3.15 (s, 6H), 4.33 (t, *J* = 5.5 Hz, 1H), 4.64 (br s, 1 H), 4.74 (br s, 1 H); ^{13}C NMR (benzene-d_6, 75.469 MHz) δ -1.28 (q'), 23.24 (t'), 26.75 (t'),32.52 (t'), 38.36 (t'), 52.18 (q'), 104.58 (d'),

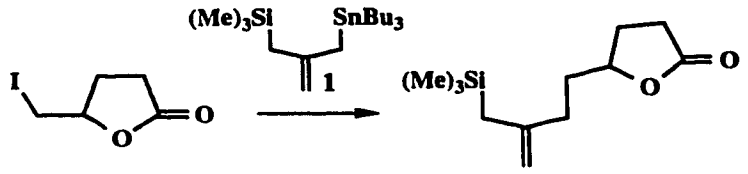
107.71 (t'), 147.32 (s'); A satisfactory mass spectrum (ei, CI, and FAB) could not be obtained.

Dihydro-5-(iodomethyl)-2(3*H*)-furanone (79).

82 **79**

$NaHCO_3$ (6.64 g, 79.0 mmol) and I_2 (8.5 g, 33.5 mmol) were added carefully to a cold (0 °C) and vigorously stirred solution of 4-pentenoic acid (**82**) (1.59 g, 15.88 mmol) in 3:1 THF-H_2O (16 mL). Stirring was continued for 16 h , the cold bath being left to attain room temperature. A solution of 10% aqueous $Na_2S_2O_3$ (70 mL) was added and the mixture was extracted with Et_2O (3 x 50 mL). The combined organic extracts, deep orange-brown in color, were washed with 10% aqueous $Na_2S_2O_3$ (50 mL) (at this point, a clear colorless organic layer was obtained) and by brine (50 mL), dried ($MgSO_4$), and evaporated. The residue was redissolved in Et_2O (50 mL) and passed through a short pad of silica gel (2 x 3 cm). The silica gel pad was washed once with Et_2O (20 mL). Evaporation of the filtrate gave **79** (3.219 g, 90%) as a clear, thick oil: FTIR (film) 1773, 1165 cm^{-1}; ^1H NMR (benzene-d_6, 400 MHz) δ 0.86-0.99 (m, 1 H), 1.20-1.31 (m, 1 H), 1.59-1.7 (m, 1 H), 1.83 (ddd, J = 17.7, 9.9, 4.7 Hz, 1 H), 2.43 (dd, J = 10.3, 6.92 Hz, 1 H), 2.55 (dd, J = 10.3, 4.78 Hz, 1 H), 3.55 (ddd, J = 14.1, 7.0, 4.8 Hz, 1 H); ^{13}C NMR (methanol-d_4, 75.469 MHz) δ 8.27 (t'), 28.88 (t'), 29.71 (t'), 80.54 (d'), 179.06 (s'); exact mass *m/z* calcd for $C_5H_7IO_2$ 225.94908, found 225.94885.

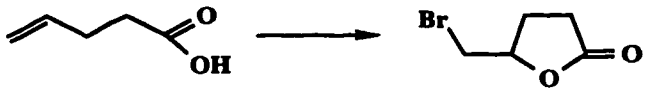
Dihydro-5-[3-(trimethylsilylmethyl)-3-butenyl]-2(3*H*)-furanone (81).



79 **81**

Iodo lactone **79** (98.7 mg, 0.436 mmol) and **1** (395.6 mg, 0.873 mmol) were weighed into a 1 x 10 cm Pyrex test tube. The test tube was stoppered with a rubber septum, and the solution was degassed for 10 min by vacuum, after which Ar was passed in. Dry PhH (1 mL) was added and the test tube was mounted in a slanted position with the base of the test tube immersed in a water bath at 5-10 °C. The solution was irradiated with a UV-quartz lamp (Hanovia, 140 W) for 17 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 23 cm), using 1:9 acetone-hexane, and again over silica gel (1 x 20 cm), using, 1:9 EtOAc-hexane, gave **81** (74.3 mg, 75.3%) as a clear, colorless oil: FTIR (cast) 1777 cm^{-1}; ^1H NMR (benzene-d_6, 400 MHz) δ 0.0 (s, 9 H), 0.92-1.05 (m, 1 H), 1.25-1.40 (m, 2 H), 1.42 (br s, 2 H), 1.48-1.60 (m, 1 H), 1.75-2.02 (m, 4 H), 3.75-3.85 (m, 1 H), 4.59-4.64 (m, 2 H); ^{13}C NMR (benzene-d_6, 75.469 MHz) δ -1.36 (q'), 26.93 (t'), 27.73 (t'), 28.52 (t'), 33.98 (t'), 34.06 (t'), 79.26 (d'), 107.80 (t'), 146.40 (s'), 175.44 (s'); exact mass *m/z* calcd for $C_{12}H_{22}O_2Si$ 226.13892, found 226.13824.

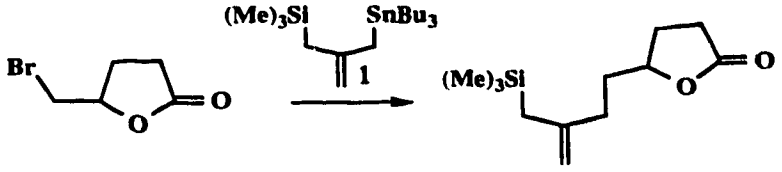
Dihydro-5-(bromomethyl)-2(3*H*)-furanone (80).



82 **80**

A similar procedure to that used for making compound **79** was followed, but with some modifications. Br_2 (5.35 g, 33.5 mmol) was added dropwise to a cold (0 °C) and vigorously stirred solution of 4-pentenoic acid (**82**) (1.59 g, 15.88 mmol) and $NaHCO_3$ (6.64 g, 79 mmol) in 3:1 THF-H_2O (16 mL). The resulting orange-red solution was stirred for 16 h, the cold bath being left in place but not recharged. Saturated aqueous $Na_2S_2O_3$ was added dropwise to the reaction mixture until the solution turned milky white (from orange red). Stirring was continued for 5 min and the mixture was diluted with water (50 mL), and extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was redissolved in Et_2O (50 mL) and passed through a short pad of silica gel (2 x 4 cm). The silica gel pad was washed once with Et_2O (30 mL). Evaporation of the combined filtrates gave **80** as a faintly yellowish, clear oil which was further purified by vacuum distillation (Kugelrohr, 85 °C, 0.1 mmHg) to give **80** (2.28 g, 80%) as a colorless, clear oil: FTIR (cast) 1774 cm^{-1}; ^1H NMR (benzene-d_6, 400 MHz) δ 1.0-1.15 (m, 1 H), 1.20-1.36 (m, 1 H), 1.65-1.78 (m, 1 H), 1.82-1.95 (m, 1 H), 2.71 (d, J = 5 Hz, 2 H), 3.70-3.80 (m, 1 H); ^{13}C NMR (benzene-d_6, 75.469 MHz) δ 25.85 (t'), 28.15 (t'), 34.64 (t'), 77.54 (d'), 175.49 (s'); exact mass *m/z* calcd for $C_5H_7O_2$ (M - Br) 99.04460, found 99.04452.

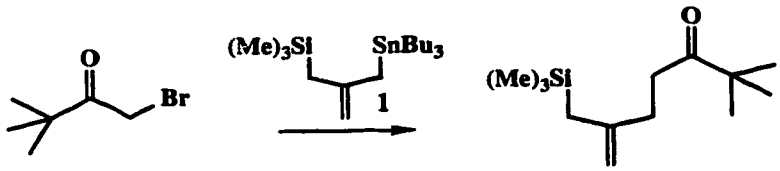
Dihydro-5-[3-(trimethylsilylmethyl)-3-butenyl]-2(3*H*)-furanone (81).



80 **81**

Bromo lactone **80** (80.0 mg, 0.45 mmol) and **1** (475 mg, 1.14 mmol) were weighed into a 1 x 10 cm Pyrex test tube. The test tube was stoppered with a rubber septum and dry PhH (0.6 mL) was added by syringe. The resulting solution was degassed by bubbling a vigorous stream of Ar through it for 5 min. The solution was irradiated with a UV-quartz lamp (Hanovia, 140 W) for 21 h at 5-10 °C. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 25 cm), using 1:9 EtOAc-hexane (containing 1% $^{v}/_{v}$ Et_3N), gave **81** (6 mg, 6%), spectroscopically identical to the material made from the iodo-analogue. In addition, starting material **80** (64.5 mg, 80.6%) was recovered.

2,2-Dimethyl-6-(trimethylsilylmethyl)-6-hepten-3-one (84).



83 **84**

Compounds **83** (153.5 mg, 0.787 mmol) and **1**(819.9 mg, 1.97 mmol) were weighed into a 1 x 10 cm Pyrex test tube. The test tube was stoppered with a rubber septum and the solution was degassed by bubbling a vigorous stream of Ar through it for 5 min. PhH (0.8 mL) was added and bubbling of Ar was resumed for another 5 min. The solution was irradiated with a UV-quartz lamp (Hanovia, 140 W) for 15 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 25

cm), using 1:99 acetone-hexane, gave **84** (105 mg, 59%) as a clear, colorless liquid: FTIR (cast) 1733 cm^{-1}; ^1H NMR (benzene-d_6, 400 MHz) δ 0.00 (s, 9 H), 1.39 (s, 9 H), 1.44 (s, 2 H), 2.25-2.40 (m, 4 H), 4.60 (br s, 1 H), 4.69 (br s, 1 H); ^{13}C NMR (benzene-d_6, 75.469 MHz) δ -1.38 (q'), 27.21 (t'), 28.10 (q'), 33.54 (t'), 34.13 (t'), 79.51 (s'), 107.37 (t'), 146.37 (s'), 172.02 (s'); exact mass *m/z* calcd for $C_9H_{17}OSi$ (M - *t*-Bu) 169.10487, found 169.10454.

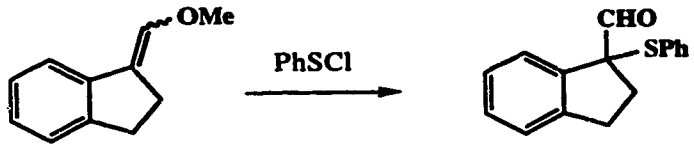
2,3-Dihydro-1-methoxymethylene-1*H*-indene (86).

85 **86**

Dry dioxane (50 mL) was added to a mixture of (methoxymethyl)triphenylphosphonium chloride (8.38 g, 24.4 mmol) and *t*-BuOK (2.70 g, 24.1 mmol) at room temperature. The resulting deep orange solution was stirred for 5 min, sonicated for 10 min [Branson, model B-12, 80W], and stirring was then continued. After 5 min, a solution of indanone **85** (796.7 mg, 6.03 mmol) in dry dioxane (8 mL plus 2 mL as a rinse) was added by syringe over 2 min. The mixture was stirred for 10 min, water (100 mL) was added, and the mixture was extracted with Et_2O (2 x 125 mL). The combined organic extracts were washed with brine (2 x 100 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 x 25 cm), using 5:95 acetone-hexane (the mixture containing 1% $^v/_v$ Et_3N), gave **86** (945.5 mg, 98%) as a clear, yellowish oil which consists of a mixture of the two isomeric enol ethers and an unidentified impurity with a similar R_f as that of the faster-eluting enol ether. The slower-eluting enol ether had: FTIR (cast) 1676, 1125 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 2.60-2.75 (m, 2 H), 2.85-2.95 (m, 2 H), 3.68 (s, 3 H), 6.80 (t, J = 2.5 Hz, 1 H), 6.95-7.12 (m, 2 H), 7.13-7.20 (m, 1 H), 7.25-7.35 (m, 1 H);

^{13}C NMR (acetone-d_6, 75.469 MHz) δ 26.53 (t'), 30.76 (t'), 60.11 (q'), 119.27 (d'), 121.86 (s'), 125.77 (d'), 126.70 (d'), 127.09 (d'), 141.24 (d'), 141.46 (s'), 145.28 (s'); exact mass *m/z* calcd for $C_{11}H_{12}O$ 160.08882, found 160.08855. Anal. Calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.47; H, 7.62. The faster-eluting enol ether had: ^1H NMR (acetone-d_6, 300 MHz) δ 2.55-2.70 (m, 2 H), 2.86-2.97 (m, 2 H), 3.70 (s, 3 H), 6.25 (t, J = 2 Hz, 1 H), 7.00-7.20 (m, 3 H), 7.75 (d, J = 7 Hz, 1 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ 27.74 (t'), 31.02 (t'), 60.35 (q'), 125.22 (d'), 125.67 (d'), 126.90 (d'), 127.09 (d'), 138.14 (s'), 138.30 (s'), 142.22 (d'), 146.06 (s'); No satisfactory mass spectral data could be obtained.

2,3-Dihydro-1-phenylthio-1*H*-indene-1-carboxaldehyde (87).



86 **87**

A solution of PhSCl[54] (0.854 g, 5.91 mmol) in dry Et_2O (10 mL) was added by syringe over 1 h to a stirred and cooled (-78 °C) solution of enol ether **86** (two geometric isomers plus impurity) (945.5 mg, ≈ 5.9 mmol) in dry Et_2O (60 mL). Stirring was continued for 20 min, after which the cooling bath was removed and the solution was allowed to reach room temperature (*ca.* 30 min). The white precipitates was filtered off and washed with 50 mL of cold (0 °C) Et_2O to afford a clear, yellowish filtrate. Evaporation of the solvent gave a clear, yellowish oil which must be chromatographed immediately on silica gel (2.5 x 23 cm), using 1:99 acetone-hexane. Appropriate fractions were evaporated and the residue was recrystallized twice from Et_2O to give **87** (614 mg, 40% from **85**) as a pure (^1H NMR, 300 MHz), white solid: mp 61-62 °C; FTIR (cast) 1715 cm^{-1}; ^1H NMR (acetone-d_6, 300 MHz) δ 2.20-2.32 (m, 1 H), 2.59-2.70 (m, 1 H), 2.85-2.96 (m, 1 H), 3.0-3.18 (m, 1 H), 7.10-7.50 (m, 9 H), 9.8 (s, 1

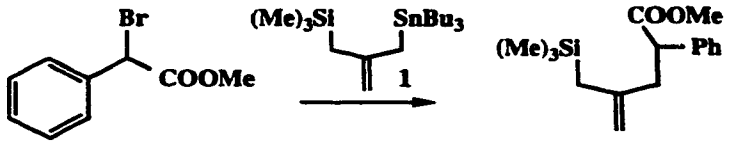
H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ 30.37 (t'), 32.46 (t'), 70.43 (s'), 125.51 (d'), 126.18 (d'), 127.52 (d'), 129.80 (d'), 129.90 (d'), 130.23 (d'), 131.70 (s'), 136.91 (d'), 139.67 (s'), 145.38 (s'), 193.27 (d'); exact mass *m/z* calcd for $C_{16}H_{14}OS$ 254.07654, found 254.07614.

Methyl 2-Bromo-2-phenylacetate (93).

92 **93**

Compound **93** was made from **92**[55] following a literature[58] procedure, but with some modifications. Ph_3P (981 mg, 3.74 mmol) in dry CH_2Cl_2 (4.5 mL) was added by syringe over 5 min to a stirred solution of **92** (518 mg, 3.12 mmol) and CBr_4 (1.45 g, 4.36 mmol) in dry CH_2Cl_2 (6.0 mL) at room temperature. Stirring was continued for an additional 1 h. Hexane (distilled, 10 mL) was added and the resulting mixture was poured through a pad of silica gel (2 x 4 cm). The pad was rinsed with 5% acetone-hexane (15 mL) and the combined filtrates were evaporated. Flash chromatography of the residue over silica gel (2 x 25 cm), using 2.5:97.5 acetone-hexane, gave **93** (699 mg, 93%) as a pure (^1H NMR 200 MHz), clear oil: FTIR (cast) 1750 cm^{-1}; ^1H NMR (acetone-d_6, 200 MHz) δ 3.75 (s, 3 H), 5.69 (s, 1 H), 7.30-7.45 (m, 3 H), 7.55-7.69 (m, 2 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ 47.28 (d') 53.54 (q'), 129.56 (d'), 129.99 (d'), 137.35 (s'), 169.30 (s'); exact mass *m/z* calcd for $C_9H_9{}^{81}BrO_2$ 229.97655, found 229.97649.

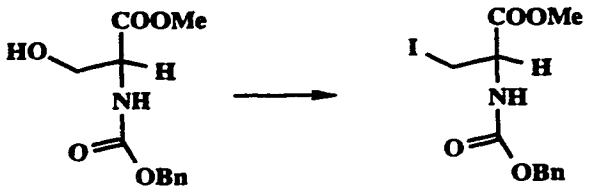
Methyl 2-Phenyl-4-(trimethylsilylmethyl)-4-pent-enoate (94).



93 **94**

Bromo ester **93** (76.5 mg, 0.33 mmol) and **1** (350 mg, 0.84 mmol) were weighed into a 1 x 10 cm Pyrex test tube. The test tube was stoppered with a rubber septum. Dry PhH (0.5 mL) was added and the resulting solution was degassed by bubbling a vigorous stream of Ar through it for 5 min. The solution was irradiated at room temperature with a UV-quartz lamp (Hanovia, 140 W) for 23 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 25 cm), using 2:98 EtOAc-hexane (containing 0.5% $^{v}/_{v}$ Et_3N), gave **94** (24 mg, 26%) as a clear, colorless oil and recovered starting material (**93**) (37.5 mg, 49%). The product **94** had: FTIR (cast) 1740 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 0.02 (s, 9 H), 1.53 and 1.60 (AB q, J = 13.4 Hz, 2 H), 2.33 (dd, J = 15, 5.8 Hz, 1 H), 2.78 (d, J = 15 Hz, 1 H), 3.6 (s, 3 H), 3.88 (dd, J = 9.4, 5.9 Hz, 1 H), 4.52 (br s, 1 H), 4.60 (br s, 1 H), 7.20-7.45 (m, 5 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ -1.29 (q'), 27.41 (t'), 42.66 (t'), 50.72 (d'), 51.99 (q'), 109.07 (t'), 127.98 (d'), 128.68 (d'), 129.36 (d'), 140.26 (s'), 145.73 (s'), 174.26 (s'); exact mass *m/z* calcd for $C_{16}H_{24}O_2Si$ 276.15457, found 276.15460.

3-Iodo-*N*-(phenylmethoxy)carbonyl-L-alanine methyl ester (96).

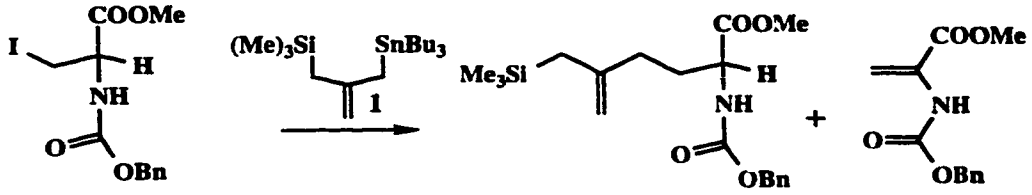


95 **96**

Compound **96** was made from **95** following a literature procedure.[57]

I_2 (555.8 mg, 2.19 mmol) was added slowly to a stirred and cooled (0 °C) solution of **95**[61] (386.7 mg, 1.53 mmol), Ph_3P (519.3 mg, 1.98 mmol) and imidazole (142.2 mg, 2.09 mmol) in MeCN (2 mL) and Et_2O (3.3 mL). A yellowish-orange suspension formed. Stirring was continued for 10 min, and the mixture was diluted with Et_2O (75 mL), washed with saturated aqueous $Na_2S_2O_3$ (50 mL), saturated aqueous $CuSO_4$ (2 x 50 mL), and brine (50 mL). The organic layer was dried ($MgSO_4$) and evaporated. The yellowish crude material was redissolved in 3:1 Et_2O-hexane (25 mL) and passed through a short pad of silica gel (2 x 3 cm). The silica pad was washed with 1:1 Et_2O-hexane (*ca.* 50 mL) and then with hexane (*ca.* 25 mL). The combined filtrates were concentrated to *ca.* 2-3 mL and cooled in an ice bath for 30 min. The resulting crystals were collected and washed with cold hexane. Evaporation and cooling of the mother liquors gave another crop of crystalline **96** (333 mg in all, 60%). The material was obtained in the form of fine short, white, needle-like crystals: mp 68-70 °C; FTIR (cast) 3333, 1747, 1723 cm^{-1}; ^1H NMR (acetone-d_6, 200 MHz) δ 3.50-3.70 (m, 2 H), 3.75 (s, 3 H), 4.40-4.60 (m, 1 H), 5.12 (s, 2 H), 6.75 (br s, 1 H), 7.20-7.50 (m, 5 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ 5.67 (t'), 52.96 (q'), 56.31 (d'), 67.08 (t'), 128.62 (d'), 128.72 (d'), 129.21 (d'), 137.87 (s'), 156.56 (s'), 170.31 (s'); exact mass *m/z* calcd for $C_{12}H_{14}INO_4$ 362.99677, found 362.99636.

Methyl (2S)-2-*N*-[(Phenylmethoxy)carbonyl]amino-5-(trimethylsilylmethyl)-5-hexenoate (97) and Methyl 2-*N*-[(Phenylmethoxy)carbonyl]amino-2-propenoate (99).

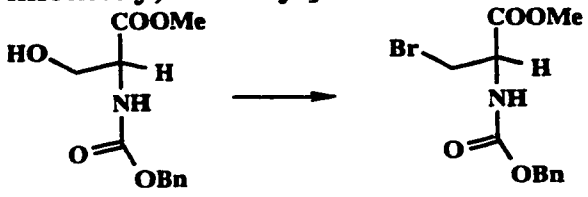


96 **97** **99**

Compounds **96** (60 mg, 0.165 mmol) and **1** (173 mg, 0.415 mmol) were weighed into a 1 x 10 cm Pyrex test tube. The test tube was stoppered with a rubber septum, kept under vacuum for 10 min, and then filled with Ar. Dry PhH (0.5 mL) was added and the resulting solution was irradiated at room temperature with a UV-quartz lamp (Hanovia, 140 W) for 16 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (1.5 x 25 cm), using 5:95 acetone-hexane, gave **97** (4.2 mg, 7%) as a colorless, clear liquid together with recovered starting material (9.10 mg, 15%) and the elimination product **99** (27 mg, 69%), which was formed during the chromatography. Compound **97** had: FTIR (cast) 3342, 1726 cm^{-1}; ^1H NMR (acetone-d_6, 400 MHz) δ 0.01 (s, 9 H), 1.57 (s, 2 H), 1.75-1.89 (m, 1 H), 1.90-2.02 (m, 1 H), 2.09 (t, J = 7.4 Hz, 2 H), 3.68 (s, 3 H), 4.24 (dt, J = 8.6, 4.7 Hz, 1 H), 4.55 (br s, 1 H), 4.61 (br s, 1 H), 5.07 (br s, 2 H), 6.67 (br s, 1 H), 7.25-7.45 (m, 5 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ -1.28 (q'), 27.22 (t'), 30.99 (t'), 34.79 (t'), 52.23 (q'), 54.70 (d'), 66.73 (t'), 108.05 (t'), 128.62 (d'), 129.19 (d'), 138.20 (s'), 147.33 (s'), 157.62 (s'), 173.60 (s'); there is an impurity peak at δ 21.325; exact mass *m/z* calcd for $C_{18}H_{26}NO_4Si$ (M - CH_3) 348.16312, found 348.16328. Compound **99** had: FTIR (cast) 3411, 3347, 1740, 1716 cm^{-1}; ^1H NMR (acetone-d_6, 200 MHz) δ 3.80 (s, 3 H), 5.15 (s, 2 H), 5.70 (s, 1 H), 6.14 (s, 1 H), 7.22-7.50 (m, 5 H), 7.82 (br s, 1 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ 53.09 (q'), 67.25 (t'), 106.14 (t'), 128.87 (d'),

129.27 (d'), 133.14 (s'), 137.46 (s'), 154.00 (s'), 164.55 (s'); exact mass *m/z* calcd for $C_{12}H_{13}NO_4$ 235.08446, found 235.08427.

3-Bromo-*N*-[(phenylmethoxy)carbonyl]-L-alanine methyl ester (98).



95 **98**

Compound **98** was made from **95**[61] following a literature[58] procedure with modifications. Ph_3P (346.2 mg, 1.32 mmol) in dry CH_2Cl_2 (1.5 mL) was added by syringe over 5 min to a stirred solution of **95** (279.5 mg, 1.10 mmol) and CBr_4 (510.7 mg, 1.54 mmol) in dry CH_2Cl_2 (2.0 mL) at room temperature. Stirring was continued for 1.5 h. Pentane (4 mL) was added and the resulting turbid solution was poured through a pad of silica gel (2 x 3 cm). The pad was rinsed with 30% EtOAc-hexane (45 mL) and the combined filtrates were evaporated. Rapid flash chromatography of the residue over silica gel (1.5 x 25 cm), using 15:85 EtOAc-hexane, gave **98** containing slight impurities (^{1}H NMR). Further purification was achieved by recrystallization from Et_2O-hexane, giving **98** (298 mg, 85%) as fine, white, hair-like crystals: mp 65-67 °C; FTIR (cast) 3332, 1750, 1723 cm^{-1}; ^{1}H NMR (acetone-d_6, 200 MHz) δ 3.74 (s, 3 H), 3.82 (d, J = 4.9 Hz, 2 H), 4.60-4.78 (m, 1 H), 5.11 (s, 2 H), 6.78 (br s, 1 H), 7.23-7.45 (m, 5 H); ^{13}C NMR (acetone-d_6, 75.469 MHz) δ 33.39 (t'), 52.89 (q'), 56.04 (d'), 67.06 (t'), 128.60 (d'), 128.69 (d'), 129.18 (d'), 137.83 (s'), 156.62 (s'), 170.17 (s'); exact mass *m/z* calcd for $C_{12}H_{14}{}^{81}BrNO_4$ 317.00858, found 317.00819.

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Appendix A

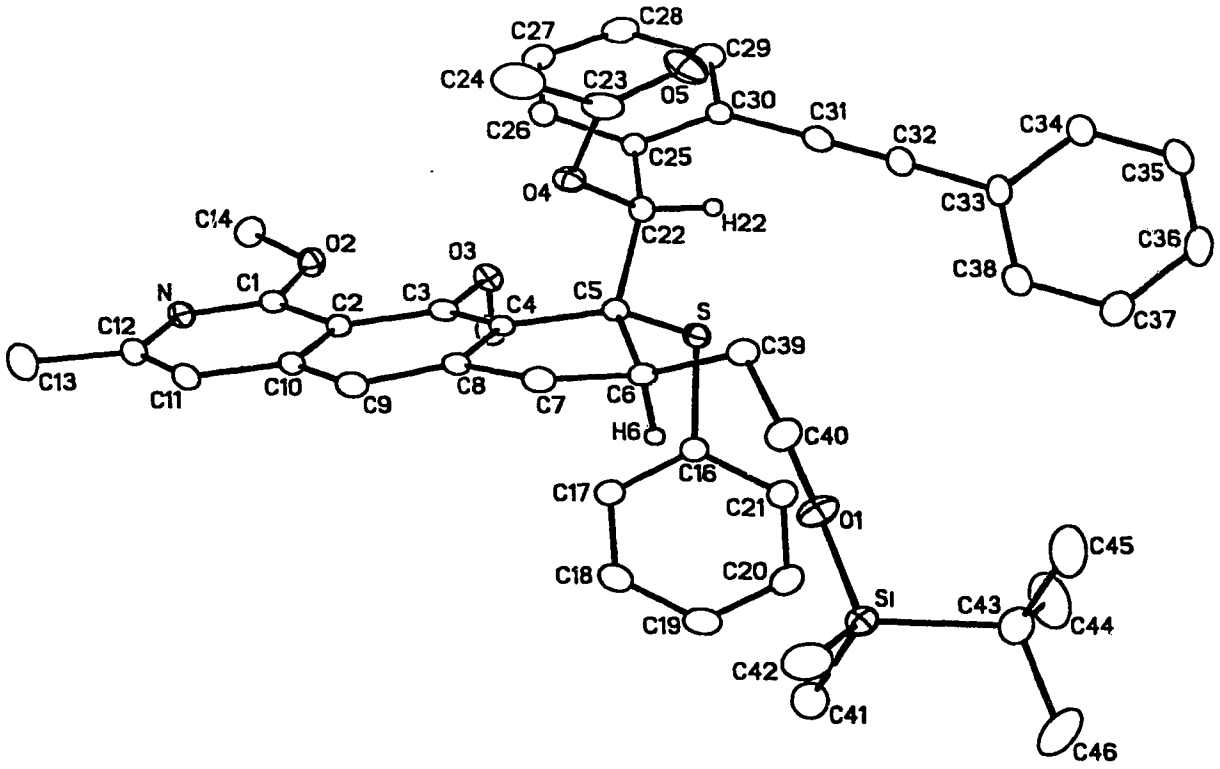

Figure A-1. Perspective view of the $C_{46}H_{51}NO_5SSi$ molecule showing the atom labelling scheme. Non-hydrogen atoms are represented by Gaussian ellipsoids at the 20% probability level. Except for those attached to chiral centers (H9 and H22), hydrogen atoms are not shown.

Table A-1. Crystallographic Experimental Details

formula	$C_{46}H_{51}NO_5SSi$
formula weight	758.03
crystal dimensions (mm)	0.53 × 0.49 × 0.16
crystal system	monoclinic
space group	$P2_1/n$ (a non-standard setting of $P2_1/c$ [No. 14])
unit cell parameters[a]	
a (Å)	14.1733 (6)
b (Å)	9.7182 (5)
c (Å)	30.520 (2)
β (deg)	98.538 (4)
V (Å^3)	4157.2 (4)
Z	4
ρ_{calcd} (g cm^{-3})	1.211
μ (mm^{-1})	1.328

B. Data Collection and Refinement Conditions

diffractometer	Siemens P4/RA[b]
radiation (λ [Å])	Cu Kα (1.54178)
monochromator	incident-beam, graphite crystal
temperature (°C)	–60
scan type	ω
data collection 2θ limit (deg)	100.0
total data collected	4934 ($-14 \le h \le 13, -9 \le k \le 9, -9 \le l \le 15$)[c]

(continued)

Table A-1. Crystallographic Experimental Details (continued)

independent reflections	4199
structure solution method	direct methods (*SHELXS–86*[d])
refinement method	full-matrix least-squares on F^2 (*SHELXL–93*[e])
absorption correction method	*DIFABS*[f]
range of absorption correction factors	1.248–0.917
data/restraints/parameters	4198 [$F_o^2 \geq -3\sigma(F_o^2)$]/0/487
goodness-of-fit (*S*)[g]	1.051 [$F_o^2 \geq -3\sigma(F_o^2)$]
final *R* indices[h]	
$F_o^2 > 2\sigma(F_o^2)$]	$R_1 = 0.0447$, $wR_2 = 0.1042$
all data	$R_1 = 0.0492$, $wR_2 = 0.1130$
largest difference peak and hole	0.494 and –0.397 e Å^{-3}

[a]Obtained from least-squares refinement of 32 reflections with $54.7° < 2\theta < 56.8°$.

[b]Programs for diffractometer operation and data collection and reduction were those of the *XSCANS* system supplied by Siemens.

[c]Data in the quadrant $+h +k \pm l$ were collected except when obstructed by the geometry of the low-temperature apparatus (Siemens LT-2), in which case Friedel equivalent reflections were obtained.

[d]Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467.

[e]Sheldrick, G. M. *J. Appl. Cryst.* , in preparation. Refinement on F_o^2 for ALL reflections except for one with $F_o^2 < -3\sigma(F_o^2)$. Weighted *R*-factors wR_2 and all goodnesses of fit *S* are based on F_o^2; conventional *R*-factors R_1 are based on F_o, with F_o set to zero for negative F_o^2. The observed criterion of $F_o^2 > 2\sigma(F_o^2)$ is used only for calculating R_1, and is not relevant to the choice of reflections for refinement. *R*-factors based on F_o^2 are statistically about twice as large as those based on F_o, and *R*-factors based on ALL data will be even larger.

Table A-1. Crystallographic Experimental Details (continued)

[f] Walker, N.; Stuart, D. *Acta Crystallogr.* **1983**, *A39*, 158.

[g] $S = [\Sigma w(F_o^2 - F_c^2)^2/(n-p)]^{1/2}$ (n = number of data; p = number of parameters varied; $w = [\sigma^2(F_o^2) + (0.0339P)^2 + 6.5378P]^{-1}$ where $P = [\text{Max}(F_o^2, 0) + 2F_c^2]/3$).

[h] $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^4)]^{1/2}$.

Table A-2. Atomic Coordinates and Equivalent Isotropic Displacement Parameters

Atom	*x*	*y*	*z*	U_{eq}, Å^2
S	0.79203(6)	0.65997(8)	0.64216(2)	0.0321(2)*
Si	0.46599(6)	0.43163(10)	0.72492(3)	0.0394(3)*
O1	0.5220(2)	0.4760(3)	0.68370(7)	0.0483(6)*
O2	1.12841(14)	0.3805(2)	0.60000(7)	0.0387(6)*
O3	0.97307(14)	0.5225(2)	0.61149(7)	0.0328(5)*
O4	0.70686(14)	0.4422(2)	0.53326(6)	0.0329(5)*
O5	0.6059(2)	0.5670(3)	0.48526(8)	0.0581(7)*
N	1.1297(2)	0.1470(3)	0.60405(9)	0.0384(7)*
C1	1.0829(2)	0.2611(3)	0.60542(10)	0.0312(8)*
C2	0.9839(2)	0.2714(3)	0.61092(9)	0.0272(8)*
C3	0.9306(2)	0.3960(3)	0.61200(9)	0.0263(7)*
C4	0.8328(2)	0.3898(3)	0.61099(9)	0.0238(7)*
C5	0.7580(2)	0.5040(3)	0.60880(9)	0.0271(7)*
C6	0.6729(2)	0.4289(3)	0.62567(10)	0.0278(7)*
C7	0.6820(2)	0.2784(3)	0.61211(10)	0.0321(8)*
C8	0.7870(2)	0.2606(3)	0.61200(9)	0.0266(7)*
C9	0.8368(2)	0.1408(3)	0.61356(10)	0.0315(8)*
C10	0.9362(2)	0.1431(3)	0.61215(10)	0.0300(8)*
C11	0.9888(2)	0.0203(3)	0.61015(10)	0.0377(9)*
C12	1.0829(2)	0.0242(4)	0.60608(11)	0.0398(9)*
C13	1.1409(3)	-0.1030(4)	0.60253(15)	0.0637(12)*
C14	1.2238(2)	0.3715(4)	0.58953(12)	0.0460(9)*
C15	1.0384(2)	0.5616(4)	0.64993(11)	0.0427(9)*
C16	0.7989(2)	0.6049(3)	0.69798(10)	0.0298(8)*
C17	0.8648(2)	0.5085(3)	0.71714(11)	0.0385(9)*
C18	0.8744(3)	0.4836(4)	0.76206(11)	0.0468(10)*
C19	0.8200(3)	0.5529(4)	0.78825(12)	0.0534(11)*
C20	0.7549(3)	0.6480(4)	0.76965(12)	0.0565(11)*
C21	0.7442(3)	0.6721(4)	0.72440(11)	0.0444(9)*
C22	0.7277(2)	0.5629(3)	0.56132(10)	0.0277(7)*
C23	0.6423(3)	0.4594(4)	0.49621(11)	0.0421(9)*
C24	0.6245(3)	0.3272(4)	0.47180(13)	0.0697(13)*
C25	0.7970(2)	0.6546(3)	0.54215(9)	0.0264(7)*

Table A-2. Atomic Coordinates and Displacement Parameters (continued)

Atom	*x*	*y*	*z*	U_{eq}, Å^2
C26	0.8758(2)	0.6005(4)	0.52609(10)	0.0347(8)*
C27	0.9390(2)	0.6843(4)	0.50803(11)	0.0418(9)*
C28	0.9232(3)	0.8225(4)	0.50494(11)	0.0449(9)*
C29	0.8443(2)	0.8802(4)	0.51941(10)	0.0402(9)*
C30	0.7806(2)	0.7972(3)	0.53810(10)	0.0304(8)*
C31	0.6978(3)	0.8575(3)	0.55231(10)	0.0350(8)*
C32	0.6273(3)	0.9064(3)	0.56405(11)	0.0369(8)*
C33	0.5429(2)	0.9586(3)	0.57826(10)	0.0335(8)*
C34	0.4897(2)	1.0617(3)	0.55456(11)	0.0404(9)*
C35	0.4072(3)	1.1093(4)	0.56743(13)	0.0502(10)*
C36	0.3755(3)	1.0556(4)	0.60425(14)	0.0546(11)*
C37	0.4275(3)	0.9537(4)	0.62851(13)	0.0553(10)*
C38	0.5111(2)	0.9056(4)	0.61574(12)	0.0446(9)*
C39	0.5742(2)	0.4917(4)	0.61242(10)	0.0350(8)*
C40	0.5003(2)	0.4343(4)	0.63867(11)	0.0437(9)*
C41	0.5561(3)	0.4137(5)	0.77455(13)	0.0677(12)*
C42	0.4047(3)	0.2647(4)	0.71337(15)	0.0746(13)*
C43	0.3784(3)	0.5704(4)	0.73431(12)	0.0527(10)*
C44	0.4314(4)	0.7034(5)	0.7465(2)	0.104(2)*
C45	0.3071(3)	0.5947(6)	0.6926(2)	0.091(2)*
C46	0.3253(4)	0.5280(7)	0.7724(2)	0.104(2)*

Anisotropically-refined atoms are marked with an asterisk (*). The form of the anisotropic displacement parameter is: $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$.

Table A-3. Selected Interatomic Distances (Å)

Atom1	Atom2	Distance	Atom1	Atom2	Distance
S	C5	1.849(3)	C11	C12	1.358(5)
S	C16	1.775(3)	C12	C13	1.497(5)
Si	O1	1.642(2)	C16	C17	1.390(4)
Si	C41	1.839(4)	C16	C21	1.365(4)
Si	C42	1.849(4)	C17	C18	1.379(5)
Si	C43	1.883(4)	C18	C19	1.367(5)
O1	C40	1.422(4)	C19	C20	1.368(5)
O2	C1	1.349(4)	C20	C21	1.387(5)
O2	C14	1.438(4)	C22	C25	1.508(4)
O3	C3	1.370(4)	C23	C24	1.488(5)
O3	C15	1.434(4)	C25	C26	1.387(4)
O4	C22	1.456(4)	C25	C30	1.408(4)
O4	C23	1.355(4)	C26	C27	1.384(5)
O5	C23	1.192(4)	C27	C28	1.363(5)
N	C1	1.296(4)	C28	C29	1.381(5)
N	C12	1.371(4)	C29	C30	1.394(4)
C1	C2	1.441(4)	C30	C31	1.435(5)
C2	C3	1.431(4)	C31	C32	1.208(5)
C2	C10	1.421(4)	C32	C33	1.425(5)
C3	C4	1.382(4)	C33	C34	1.391(5)
C4	C5	1.529(4)	C33	C38	1.390(5)
C4	C8	1.416(4)	C34	C35	1.368(5)
C5	C6	1.562(4)	C35	C36	1.374(5)
C5	C22	1.558(4)	C36	C37	1.382(5)
C6	C7	1.530(4)	C37	C38	1.382(5)
C6	C39	1.525(4)	C39	C40	1.516(4)
C7	C8	1.499(4)	C43	C44	1.514(6)
C8	C9	1.359(4)	C43	C45	1.523(6)
C9	C10	1.415(4)	C43	C46	1.532(6)
C10	C11	1.413(4)			

Table A-4. Selected Interatomic Angles (deg)

Atom1	Atom2	Atom3	Angle	Atom1	Atom2	Atom3	Angle
C5	S	C16	104.72(14)	C6	C7	C8	103.6(2)
O1	Si	C41	107.5(2)	C4	C8	C7	110.9(3)
O1	Si	C42	110.6(2)	C4	C8	C9	121.6(3)
O1	Si	C43	109.5(2)	C7	C8	C9	127.6(3)
C41	Si	C42	108.8(2)	C8	C9	C10	119.9(3)
C41	Si	C43	109.6(2)	C2	C10	C9	119.7(3)
C42	Si	C43	110.8(2)	C2	C10	C11	118.9(3)
Si	O1	C40	127.3(2)	C9	C10	C11	121.4(3)
C1	O2	C14	117.2(3)	C10	C11	C12	120.8(3)
C3	O3	C15	117.4(2)	N	C12	C11	121.1(3)
C22	O4	C23	116.4(3)	N	C12	C13	116.2(3)
C1	N	C12	119.4(3)	C11	C12	C13	122.7(3)
O2	C1	N	118.4(3)	S	C16	C17	123.0(2)
N	C1	C2	125.0(3)	S	C16	C21	117.9(3)
O2	C1	C2	116.5(3)	C17	C16	C21	118.7(3)
C1	C2	C3	126.6(3)	C16	C17	C18	119.8(3)
C1	C2	C10	114.7(3)	C17	C18	C19	120.9(3)
C3	C2	C10	119.1(3)	C18	C19	C20	119.6(3)
O3	C3	C2	121.6(2)	C19	C20	C21	119.7(3)
O3	C3	C4	118.7(3)	C16	C21	C20	121.3(3)
C2	C3	C4	119.6(3)	O4	C22	C5	104.8(2)
C3	C4	C5	130.9(3)	O4	C22	C25	109.5(2)
C3	C4	C8	119.9(3)	C5	C22	C25	118.2(2)
C5	C4	C8	109.1(2)	O4	C23	O5	123.6(3)
S	C5	C4	116.6(2)	O4	C23	C24	110.8(3)
S	C5	C6	110.6(2)	O5	C23	C24	125.7(3)
S	C5	C22	103.0(2)	C22	C25	C26	121.2(3)
C4	C5	C6	102.2(2)	C22	C25	C30	120.5(3)
C4	C5	C22	113.6(2)	C26	C25	C30	118.2(3)
C6	C5	C22	111.0(2)	C27	C26	C25	121.4(3)
C5	C6	C7	104.9(2)	C26	C27	C28	119.8(3)
C5	C6	C39	116.7(2)	C27	C28	C29	120.7(3)
C7	C6	C39	114.9(3)	C28	C29	C30	120.0(3)

Table A-4. Selected Interatomic Angles (continued)

Atom1	Atom2	Atom3	Angle
C25	C30	C29	119.8(3)
C25	C30	C31	120.5(3)
C29	C30	C31	119.7(3)
C30	C31	C32	179.0(4)
C31	C32	C33	177.7(3)
C32	C33	C34	120.9(3)
C32	C33	C38	120.6(3)
C34	C33	C38	118.5(3)
C33	C34	C35	121.0(3)
C34	C35	C36	120.2(3)
C35	C36	C37	119.8(3)
C36	C37	C38	120.1(4)
C33	C38	C37	120.2(3)
C6	C39	C40	113.0(3)
O1	C40	C39	109.8(3)
Si	C43	C44	109.6(3)
Si	C43	C45	110.8(3)
Si	C43	C46	109.4(3)
C44	C43	C45	108.5(4)
C44	C43	C46	108.9(4)
C45	C43	C46	109.6(4)

Table A-5. Torsional Angles (deg)

Atom 1	Atom 2	Atom 3	Atom 4	Angle
C41	Si	O1	C40	143.7(3)
C42	Si	O1	C40	25.0(3)
C43	Si	O1	C40	-97.3(3)
O1	Si	C43	C44	-61.4(3)
O1	Si	C43	C45	58.3(4)
O1	Si	C43	C46	179.3(3)
C41	Si	C43	C44	56.3(4)
C41	Si	C43	C45	175.9(3)
C41	Si	C43	C46	-63.1(4)
C42	Si	C43	C44	176.4(3)
C42	Si	C43	C45	-63.9(4)
C42	Si	C43	C46	57.1(4)
C16	S	C5	C4	-68.7(2)
C16	S	C5	C6	47.4(2)
C16	S	C5	C22	166.1(2)
C5	S	C16	C17	64.0(3)
C5	S	C16	C21	-123.7(3)
Si	O1	C40	C39	-176.2(2)
C14	O2	C1	N	4.8(4)
C14	O2	C1	C2	-173.2(3)
C15	O3	C3	C2	-68.5(3)
C15	O3	C3	C4	115.3(3)
C23	O4	C22	C5	152.3(2)
C23	O4	C22	C25	-80.0(3)
C22	O4	C23	O5	2.8(5)
C22	O4	C23	C24	-177.4(3)
C12	N	C1	O2	-175.0(3)
C12	N	C1	C2	2.8(5)
C1	N	C12	C11	-1.0(5)
C1	N	C12	C13	177.7(3)
N	C1	C2	C3	-179.2(3)
N	C1	C2	C10	-3.8(4)

Table A-5. Torsional Angles (continued)

Atom 1	Atom 2	Atom 3	Atom 4	Angle
O2	C1	C2	C10	174.1(2)
C1	C2	C3	O3	-5.6(4)
C1	C2	C3	C4	170.6(3)
C10	C2	C3	O3	179.1(3)
C10	C2	C3	C4	-4.7(4)
C1	C2	C10	C9	-174.6(3)
C1	C2	C10	C11	3.0(4)
C3	C2	C10	C9	1.2(4)
C3	C2	C10	C11	178.7(3)
O3	C3	C4	C5	0.7(5)
O3	C3	C4	C8	-179.3(2)
C2	C3	C4	C5	-175.6(3)
C2	C3	C4	C8	4.4(4)
C3	C4	C5	S	-39.6(4)
C8	C4	C5	S	140.4(2)
C3	C4	C5	C6	-160.4(3)
C3	C4	C5	C22	80.0(4)
C8	C4	C5	C6	19.6(3)
C8	C4	C5	C22	-100.0(3)
C3	C4	C8	C7	178.2(3)
C3	C4	C8	C9	-0.6(4)
C5	C4	C8	C7	-1.8(3)
C5	C4	C8	C9	179.4(3)
S	C5	C6	C7	-154.4(2)
S	C5	C6	C39	77.1(3)
C4	C5	C6	C7	-29.6(3)
C4	C5	C6	C39	-158.0(3)
C22	C5	C6	C7	91.9(3)
C22	C5	C6	C39	-36.6(4)
S	C5	C22	O4	176.0(2)
S	C5	C22	C25	53.7(3)
C4	C5	C22	O4	48.9(3)

Table A-5. Torsional Angles (continued)

Atom 1	Atom 2	Atom 3	Atom 4	Angle
C6	C5	C22	O4	-65.6(3)
C6	C5	C22	C25	172.2(2)
C5	C6	C7	C8	28.8(3)
C39	C6	C7	C8	158.3(2)
C5	C6	C39	C40	-166.2(3)
C7	C6	C39	C40	70.4(3)
C6	C7	C8	C9	161.5(3)
C6	C7	C8	C4	-17.2(3)
C4	C8	C9	C10	-2.9(4)
C7	C8	C9	C10	178.5(3)
C8	C9	C10	C2	2.5(4)
C8	C9	C10	C11	-174.9(3)
C9	C10	C11	C12	175.9(3)
C2	C10	C11	C12	-1.5(4)
C10	C11	C12	N	0.4(5)
C10	C11	C12	C13	-178.2(3)
C21	C16	C17	C18	-0.7(5)
S	C16	C17	C18	171.6(3)
S	C16	C21	C20	-171.2(3)
C17	C16	C21	C20	1.4(5)
C16	C17	C18	C19	-0.1(5)
C17	C18	C19	C20	0.2(6)
C18	C19	C20	C21	0.6(6)
C19	C20	C21	C16	-1.4(6)
O4	C22	C25	C26	-43.7(4)
O4	C22	C25	C30	133.1(3)
C5	C22	C25	C26	76.1(4)

Table A-5. Torsional Angles (continued)

Atom 1	Atom 2	Atom 3	Atom 4	Angle
C5	C22	C25	C30	-107.1(3)
C22	C25	C26	C27	179.3(3)
C30	C25	C26	C27	2.4(4)
C22	C25	C30	C29	-178.6(3)
C22	C25	C30	C31	0.2(4)
C26	C25	C30	C29	-1.7(4)
C26	C25	C30	C31	177.1(3)
C25	C26	C27	C28	-1.4(5)
C26	C27	C28	C29	-0.4(5)
C27	C28	C29	C30	1.1(5)
C28	C29	C30	C25	0.0(5)
C28	C29	C30	C31	-178.8(3)
C29	C30	C31	C32	143.4(167)
C25	C30	C31	C32	-35.4(169)
C30	C31	C32	C33	30.5(231)
C31	C32	C33	C38	42.7(84)
C31	C32	C33	C34	-136.2(82)
C38	C33	C34	C35	-0.7(5)
C32	C33	C34	C35	178.2(3)
C32	C33	C38	C37	-177.9(3)
C34	C33	C38	C37	0.9(5)
C33	C34	C35	C36	0.0(5)
C34	C35	C36	C37	0.4(6)
C35	C36	C37	C38	-0.1(6)
C36	C37	C38	C33	-0.5(6)
C6	C39	C40	O1	67.3(4)

Table A-6. Least-Squares Planes

Plane	Coefficients[a]				Defining Atoms with Deviations (Å)			
1	5.770(16)	1.274(13)	25.438(21)	19.212(7)				
					C25	0.012(2)	C26	-0.011(2)
					C27	0.001(2)	C28	0.008(2)
					C29	-0.006(2)	C30	-0.004(2)
2	6.253(18)	6.761(10)	15.110(40)	18.618(14)				
					C33	-0.005(2)	C34	0.002(2)
					C35	0.002(3)	C36	-0.003(3)
					C37	0.000(3)	C38	0.004(2)

Angle between planes 1 and 2: 38.44(14)°

[a]Coefficients are for the form $ax+by+cz = d$ where x, y and z are crystallographic coordinates.

Table A-7. Anisotropic Displacement Parameters (U_{ij}, Å^2)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
S	0.0382(5)	0.0274(5)	0.0302(5)	-0.0016(4)	0.0035(4)	-0.0003(4)
Si	0.0370(5)	0.0422(6)	0.0415(6)	0.0029(4)	0.0135(4)	0.0032(5)
O1	0.0417(14)	0.064(2)	0.0418(14)	-0.0069(12)	0.0154(11)	-0.0114(12)
O2	0.0270(13)	0.0395(15)	0.0517(14)	0.0017(11)	0.0127(10)	0.0020(11)
O3	0.0250(12)	0.0292(13)	0.0432(13)	0.0033(10)	0.0018(10)	-0.0042(10)
O4	0.0389(13)	0.0316(13)	0.0264(12)	-0.0020(10)	-0.0014(10)	-0.0050(10)
O5	0.060(2)	0.055(2)	0.051(2)	0.0099(14)	-0.0211(13)	-0.0034(15)
N	0.038(2)	0.039(2)	0.038(2)	0.0048(13)	0.0061(13)	0.012(2)
C1	0.032(2)	0.034(2)	0.027(2)	0.0027(15)	0.0033(14)	0.001(2)
C2	0.029(2)	0.027(2)	0.025(2)	0.0000(14)	0.0023(13)	0.003(2)
C3	0.029(2)	0.026(2)	0.024(2)	0.0010(14)	0.0023(13)	-0.005(2)
C4	0.025(2)	0.025(2)	0.020(2)	0.0025(13)	0.0008(13)	-0.0006(15)
C5	0.029(2)	0.027(2)	0.025(2)	0.0014(14)	0.0037(14)	-0.0002(15)
C6	0.025(2)	0.035(2)	0.024(2)	0.0021(14)	0.0047(13)	0.0003(15)
C7	0.029(2)	0.035(2)	0.031(2)	0.002(2)	0.0020(14)	-0.007(2)
C8	0.027(2)	0.028(2)	0.023(2)	0.0010(14)	0.0001(13)	-0.002(2)
C9	0.034(2)	0.028(2)	0.032(2)	0.0008(15)	0.0029(15)	-0.008(2)
C10	0.037(2)	0.028(2)	0.025(2)	0.0009(14)	0.0033(14)	0.002(2)
C11	0.049(2)	0.026(2)	0.038(2)	0.004(2)	0.008(2)	0.005(2)
C12	0.045(2)	0.036(2)	0.040(2)	0.005(2)	0.010(2)	0.013(2)
C13	0.066(3)	0.045(2)	0.084(3)	0.007(2)	0.023(2)	0.017(2)
C14	0.028(2)	0.054(2)	0.058(2)	0.000(2)	0.014(2)	-0.001(2)
C15	0.031(2)	0.040(2)	0.056(2)	-0.008(2)	0.004(2)	-0.010(2)
C16	0.031(2)	0.029(2)	0.030(2)	-0.004(2)	0.003(2)	-0.005(2)
C17	0.044(2)	0.039(2)	0.033(2)	-0.002(2)	0.007(2)	0.001(2)
C18	0.057(2)	0.040(2)	0.040(2)	0.001(2)	-0.003(2)	-0.003(2)
C19	0.086(3)	0.042(2)	0.032(2)	-0.005(2)	0.005(2)	-0.010(2)
C20	0.077(3)	0.053(3)	0.044(3)	-0.011(2)	0.020(2)	0.007(2)
C21	0.053(2)	0.043(2)	0.037(2)	-0.004(2)	0.008(2)	0.006(2)
C22	0.025(2)	0.028(2)	0.030(2)	-0.0024(15)	0.0032(14)	0.0015(14)
C23	0.047(2)	0.047(3)	0.030(2)	0.003(2)	-0.003(2)	-0.015(2)
C24	0.097(3)	0.058(3)	0.046(2)	-0.006(2)	-0.015(2)	-0.026(3)

Table A-7. Anisotropic Displacement Parameters (continued)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C26	0.033(2)	0.037(2)	0.035(2)	0.004(2)	0.009(2)	0.004(2)
C27	0.031(2)	0.059(3)	0.038(2)	0.004(2)	0.013(2)	0.000(2)
C28	0.045(2)	0.054(3)	0.037(2)	0.003(2)	0.011(2)	-0.017(2)
C29	0.050(2)	0.034(2)	0.037(2)	0.004(2)	0.008(2)	-0.003(2)
C30	0.030(2)	0.035(2)	0.026(2)	0.0026(15)	0.0032(14)	0.003(2)
C31	0.043(2)	0.027(2)	0.033(2)	0.001(2)	-0.002(2)	-0.002(2)
C32	0.039(2)	0.030(2)	0.040(2)	-0.003(2)	0.000(2)	0.002(2)
C33	0.031(2)	0.028(2)	0.039(2)	-0.011(2)	-0.003(2)	0.004(2)
C34	0.043(2)	0.034(2)	0.043(2)	-0.004(2)	0.002(2)	0.006(2)
C35	0.048(2)	0.045(2)	0.055(2)	-0.003(2)	-0.004(2)	0.017(2)
C36	0.041(2)	0.052(3)	0.072(3)	-0.012(2)	0.010(2)	0.014(2)
C37	0.057(3)	0.053(3)	0.060(3)	-0.003(2)	0.023(2)	0.007(2)
C38	0.048(2)	0.038(2)	0.046(2)	0.000(2)	0.002(2)	0.011(2)
C39	0.029(2)	0.043(2)	0.033(2)	0.002(2)	0.0056(15)	-0.001(2)
C40	0.029(2)	0.060(2)	0.043(2)	-0.002(2)	0.008(2)	-0.001(2)
C41	0.063(3)	0.080(3)	0.061(3)	0.009(2)	0.012(2)	0.024(2)
C42	0.099(4)	0.061(3)	0.070(3)	0.001(2)	0.033(3)	-0.014(3)
C43	0.043(2)	0.066(3)	0.049(2)	-0.008(2)	0.005(2)	0.009(2)
C44	0.119(5)	0.058(3)	0.128(5)	-0.023(3)	-0.006(4)	0.025(3)
C45	0.069(3)	0.120(4)	0.078(3)	-0.022(3)	-0.012(3)	0.048(3)
C46	0.075(3)	0.160(6)	0.086(4)	-0.007(4)	0.044(3)	0.033(4)

The form of the anisotropic displacement parameter is:

$$\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2hla^*c^*U_{13} + 2hka^*b^*U_{12})]$$

Table A-8. Derived Atomic Coordinates and Displacement Parameters for Hydrogen Atoms

Atom	*x*	*y*	*z*	U_{eq}, Å^2
H6	0.6860	0.4312	0.6584	0.033
H7A	0.6590	0.2162	0.6335	0.038
H7B	0.6461	0.2611	0.5826	0.038
H9	0.8054	0.0564	0.6156	0.038
H11	0.9582	-0.0651	0.6117	0.045
H13A	1.2059	-0.0774	0.5999	0.076
H13B	1.1137	-0.1550	0.5766	0.076
H13C	1.1405	-0.1590	0.6288	0.076
H14A	1.2488	0.4634	0.5865	0.055
H14B	1.2231	0.3217	0.5619	0.055
H14C	1.2641	0.3234	0.6131	0.055
H15A	1.0635	0.6526	0.6455	0.051
H15B	1.0905	0.4960	0.6547	0.051
H15C	1.0054	0.5627	0.6756	0.051
H17	0.9027	0.4603	0.6995	0.046
H18	0.9190	0.4181	0.7749	0.056
H19	0.8273	0.5353	0.8188	0.064
H20	0.7177	0.6967	0.7875	0.068
H21	0.6983	0.7360	0.7117	0.053
H22	0.6675	0.6148	0.5612	0.033
H24A	0.6629	0.2552	0.4876	0.084
H24B	0.6414	0.3369	0.4423	0.084
H24C	0.5575	0.3034	0.4696	0.084
H26	0.8864	0.5050	0.5275	0.042
H27	0.9927	0.6459	0.4979	0.050
H28	0.9665	0.8792	0.4928	0.054
H29	0.8335	0.9755	0.5167	0.048
H34	0.5107	1.0993	0.5293	0.049
H35	0.3721	1.1791	0.5510	0.060
H36	0.3186	1.0881	0.6129	0.066
H37	0.4059	0.9170	0.6538	0.066
H38	0.5465	0.8368	0.6325	0.053

Table A-8. Derived Parameters for Hydrogen Atoms (continued)

Atom	*x*	*y*	*z*	U_{eq}, Å^2
H39A	0.5784	0.5915	0.6168	0.042
H39B	0.5532	0.4745	0.5808	0.042
H40A	0.4368	0.4679	0.6261	0.052
H40B	0.4998	0.3336	0.6369	0.052
H41A	0.5887	0.5008	0.7809	0.081
H41B	0.6020	0.3437	0.7694	0.081
H41C	0.5251	0.3871	0.7996	0.081
H42A	0.3570	0.2731	0.6872	0.089
H42B	0.3741	0.2384	0.7385	0.089
H42C	0.4509	0.1950	0.7083	0.089
H44A	0.4772	0.6895	0.7731	0.125
H44B	0.3864	0.7743	0.7519	0.125
H44C	0.4647	0.7316	0.7224	0.125
H45A	0.2725	0.5102	0.6843	0.109
H45B	0.3408	0.6233	0.6627	0.109
H45C	0.2625	0.6660	0.6981	0.109
H46A	0.2911	0.4427	0.7648	0.125
H46B	0.2804	0.5995	0.7773	0.125
H46C	0.3708	0.5147	0.7991	0.125

Appendix B

After completion of this thesis, the following developments were achieved in radical allylations with compound **1** (see Chapter 2).

*Radical allylation of compound **70** with compound **1** under thermal con[illegible] (AIBN; reflux) was found to afford, cleanly, product **71** in acceptable yields (68%). The yield under the conditions used previously was 86%.

*It was observed that in the presence of 0.1 equivalents of AIBN, the usual photochemical conditions gave highly improved yields for substrates **77** and **96**, with isolated products being obtained in 72% and 74 % in yields, respectively. The corresponding yields had previously been 50% and 7%, respectively.

*The use of hexabutylditin for substrate **73**, under photochemical conditions, did not significantly improve the yield of product **74**. Under these new conditions the yield was only 22% (*cf.* 19% under the previous conditions).