Uses of Silicon-Containing Compounds in the Synthesis of Natural Products

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I. Introduction

The stereoselective synthesis of natural products is one of the major interests in organic synthesis today. Especially the use of flexible routes using simple reagents under mild conditions is of great importance. Most of the biologically active molecules contain quite complex ring skeletons therefore selective syntheses of cyclic systems are required.

Recently, the use of organosilicon compounds as reagents and synthons directed toward the construction of natural products has become a powerful tool in organic synthesis.[1] This article will focus on the use of these intermediates; in particular allyl-, propargyl-, and vinylsilanes will be discussed. These compounds can be described as highly nucleophilic π-systems, so-called terminators, which are stable toward a wide range of reagents and most of the common functional group manipulations (saponifications, reductions, oxidations). On the other hand, they can be activated by so-called initiators (electrophiles) which are generated *in situ* by addition of a Lewis acid. The review will mainly focus on the synthetic methodology and not on mechanistic or stereochemical details of the silicon-mediated cyclizations.

In the first section, we will consider the important factors that make these terminators such useful functionalities in cyclization reactions. They react with electrophiles in the presence of a Lewis acid via selective attack of the electrophile at that carbon, that forms a cation β to the silyl group (Scheme 1).

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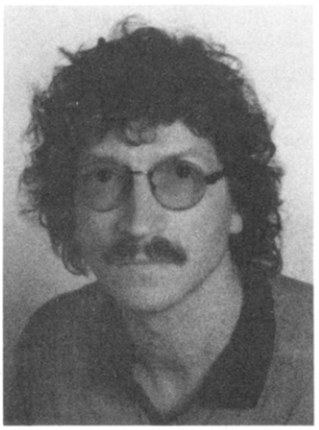
Elke Langkopf was born in Hildesheim in 1967. She studied chemistry at the Technical University of Braunschweig, Germany, where she received her diploma in 1991. Since 1991 she has been working under the supervision of Professor Schinzer on tandem reactions (Beckmann rearrangement followed by allylsilane cyclization) funded by a fellowship from the Fonds der Chemischen Industrie and received her Ph.D. in 1994. At present she is a postdoctoral fellow at the Department of Chemistry, Stanford University, Stanford, CA, with Professor P. A. Wender, funded by a Feodor–Lynen fellowship from the Humboldt foundation.

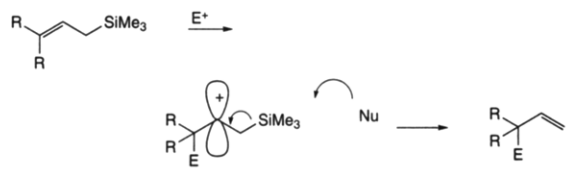


Dieter Schinzer was born in Gudensberg, Germany, in 1953. He received his doctoral degree from the University of Bonn in 1980 under the direction of Professor M. T. Reetz and completed his Habilitation, funded by a Liebig fellowship from the Fonds der Chemischen Industrie, in 1986 under the guidance of Professor E. Winterfeldt at the University of Hannover. He spent two years as a postdoctoral fellow at the department of chemistry, University of California, Berkeley (1980–1982) with Professor C. H. Heathcock, funded by a Feodor-Lynen fellowship from the Humboldt-foundation. In 1990 he joined the Institute of Organic Chemistry at the University of Braunschweig where he is currently Professor of Chemistry. His research interests are uses and applications of organosilicon compounds in synthesis, in particular development of new methods and applications in the total synthesis of natural products. In 1985 he received the Werner-von-Siemens medal from the Werner-von-Siemens-ring foundation, and in 1986 he received a Heisenberg fellowship from the Deutsche Forschungsgemeinschaft (DFG) and, in 1988, a Dozenten-Stipendium from the Fonds der Chemischen Industrie.

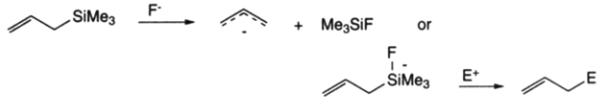
This cation is stabilized by the highly polarized C–Si bond via σ–π-conjugation (the so-called β-effect).[2]

On the other hand, allylic silanes can be attacked by fluoride ion to form allylic anions (Scheme 2) due

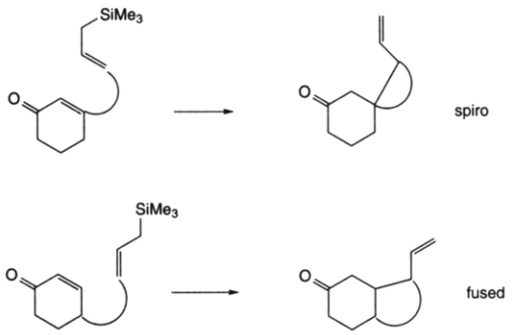
Scheme 1



Scheme 2



Scheme 3



to the strong Si–F bond, one of the strongest bonds in organic chemistry (135 kcal/mol).[3]

Of more interest are intramolecular reactions which lead to cyclized structures. Several general cyclization modes can be envisioned.

1. Allylsilanes

Allylsilanes are mostly attacked by electrophiles at the γ-carbon (there are also a few examples of α-attack, e.g. ref 4) to form the β-cation relative to the silyl group (β-effect). As a result of this feature in all cases allylic inversion is observed. Again, several cyclization modes are possible and well studied to construct many different types of 1,2-, 1,3-, and spiro-annulated systems (Scheme 3).

2. Propargylsilanes

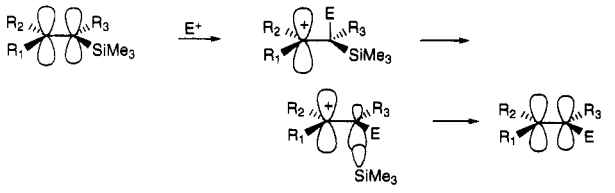
The same principles can be applied for propargyl silanes, which, as expected, react a little bit more slowly than the allylic analogs. Again, γ-attack occurs, leading to terminal allenes via inversion of the π-system.[5]

3. Vinylsilanes

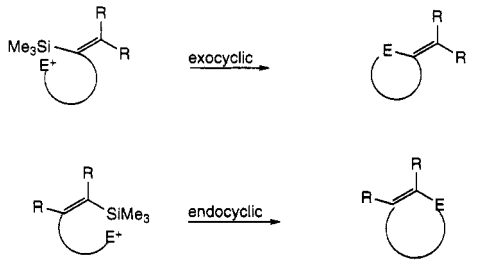
The same general principles discussed before hold also for vinylsilanes. In addition, two important factors can be added. First, the regiochemistry in electrophilic substitution reactions takes place only at the silicon-bearing carbon.[6] Even more important, electrophilic substitution reactions occur in most cases under retention of configuration, because the β-silyl cation formed is maximally stabilized where the carbon–silicon σ-bond is coplanar with the adjacent vacant π-orbital. Therefore, a rotation around the carbon–carbon single bond takes place. A rotation in the alternate sense would be disfavored (no good overlap). The overall result of the reaction is retention of configuration at the double bond[7] (Scheme 4).

Two distinct modes of cyclization are possible with this particular terminator: cyclizations can occur in an exocyclic and endocyclic way with respect to the vinyl silane terminator. In all cyclizations the silyl group controls the regiochemistry of the double bond in the product. In addition, in the exocyclic mode the stereochemistry of the double bond in the product is controlled (Scheme 5).

Scheme 4



Scheme 5



II. Allylsilanes in Natural Product Synthesis

1. Intermolecular Allylsilane Additions

1.1. Total Synthesis of (+)-Tetronomycin

An intermolecular allylsilane coupling reaction was used in the convergent total synthesis of the tetronic acid ionophore antibiotic (+)-tetronomycin (**1**) to construct the C14–C28 polyether fragment.[8] The retrosynthetic analysis of the complex structure of tetronomycin developed by Yoshii and co-workers is outlined in Scheme 6.

Synthesis of the polyether fragment **2** was achieved via a Lewis acid-catalyzed coupling of the tetrahydrofuran subunit **13** and the allylsilane **10**, containing a tetrahydropyran moiety. The more expedient route to the tetrahydopyran subunit utilizes (*R*)-3-hydroxy-2-methylpropionate **5** as starting material. Ester reduction of **5** followed by O-tosylation and subsequent treatment of the tosylate with allylmagnesium bromide in the presence of copper(I) iodide afforded 2-methyl-5-hexenol (**6**) after removal of the ethoxy ester moiety (Scheme 7).

Compound **6** was subjected to one-pot Swern oxidation/stabilized ylide Wittig olefination[9] and ester reduction with diisobutylaluminum hydride to yield the allyl alcohol, which was transformed into the epoxide **7** via Sharpless asymmetric epoxidation using L-(+)-tartrate. Epoxide opening followed by selective pivaloylation of the resulting diol, and internal alkoxymercuration afforded the desired 2,6-*cis*-tetrahydropyran **8** in 62% overall yield. Compound **8** was converted into the corresponding alcohol using Whitesides' method,[10] which was transformed to the aldehyde **9**. Transformation of the aldehyde **9** into allylsilane **10** was achieved according to the method of Smith.[11]

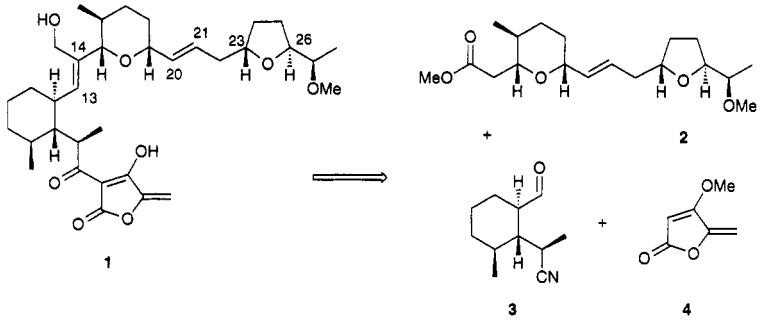
Starting material for the preparation of the tetrahydrofuran subunit **13** was L-rhamnal diacetate **11**, which has the requisite five-carbon chain. Hydrolysis[12] of **11**, followed by O-mesylation afforded aldehyde **12** in 82% yield. Catalytic hydrogenation and subsequent methoxide-induced cyclization provided, via an (4*R*,5*R*)-epoxide intermediate, 2-methoxytetrahydrofuran **13** after protection of the hydroxy group (Scheme 8).

Coupling of **13** with the allylsilane **10** proceeded in the presence of boron trifluoride etherate in dichloromethane at 0 °C, whereby the *trans* geometry of the C20–C21 double bond could be secured in one step as well as the C23–C26 *trans* stereochemistry in the tetrahydrofuran ring. The reaction product **14** was converted into the desired polyether fragment **2** by means of standard transformations.

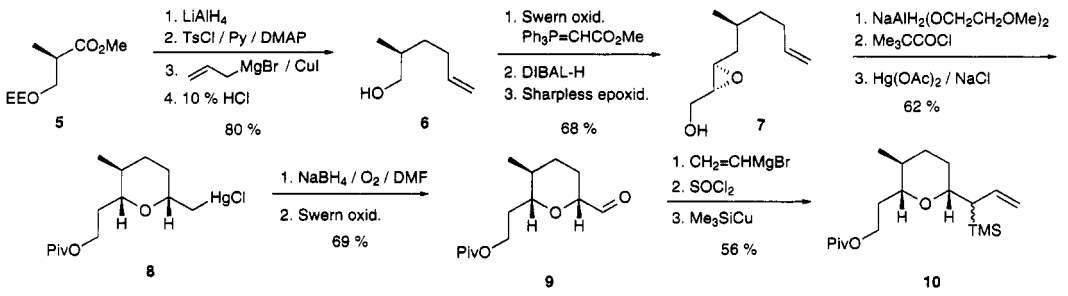
1.2. Synthesis of (±)-Lycopodine

The stereoselective addition of an allylsilane to a functionalized enone was used to control the relative C3–C5 configuration in Heathcock's total synthesis of (±)-lycopodine.[13] Thus, Sakurai reaction of the known cyano enone **15**[14] and methallyltrimethylsi-

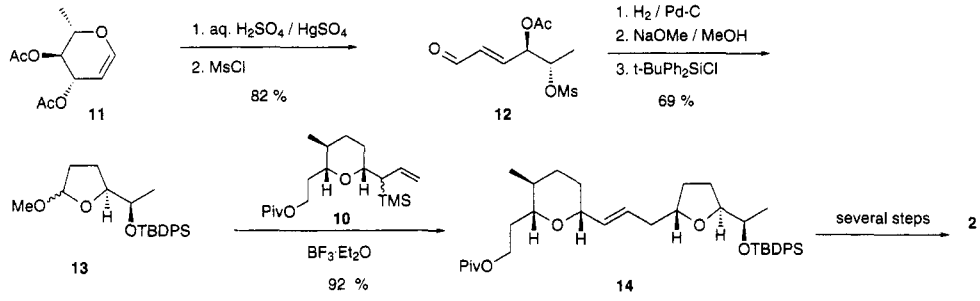
Scheme 6



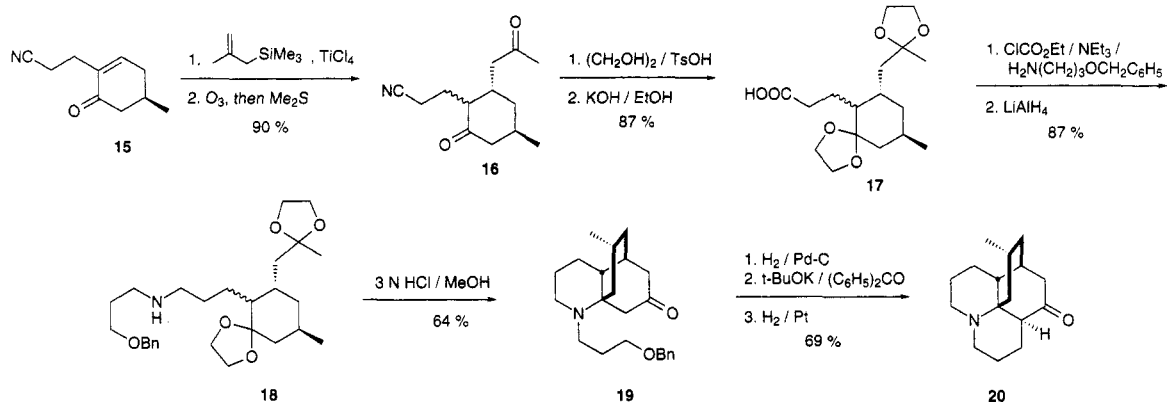
Scheme 7



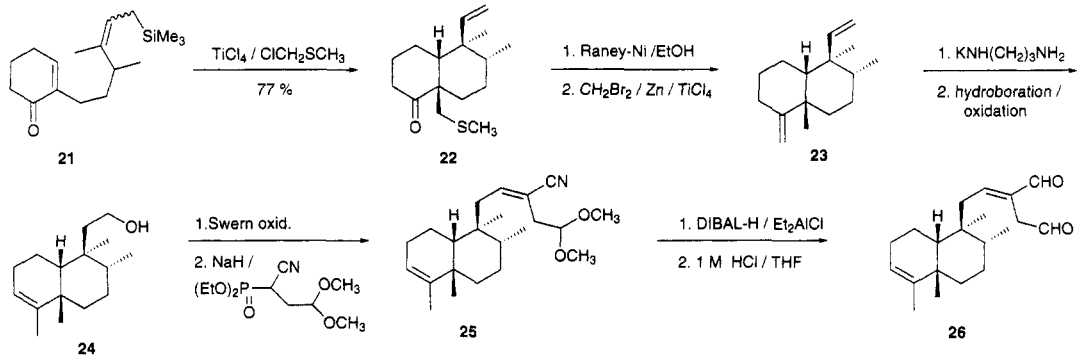
Scheme 8



Scheme 9



Scheme 10



lane in the presence of titanium tetrachloride provided the alkylation product as an approximately equimolar mixture of C2-epimers, possessing the desired *trans* C3–C5 stereochemistry. Introduction of the side chain could also be accomplished by way of lithium dimethallyl cuprate addition or the Corey–Enders method.[15] The Sakurai method gave the best overall yields of cyano dione **16** after ozonolysis. Protection of the two carbonyl groups and hydrolysis of the nitrile afforded the acid **17**, which was converted, via the amide intermediate, into amine **18** (Scheme 9).

Upon treatment with methanolic HCl, smooth Mannich cyclization of **18** took place to provide tricyclic amino ketone **19** as a single product in 64% yield. Hydrogenolysis of the benzyl ether, followed by treatment of the resulting hydroxy ketone with potassium *tert*-butoxide and benzophenone afforded (±)-dehydrolycopodine, which was transformed into (±)-lycopodine (**20**) by catalytic hydrogenation of the enone double bond.

Lewis acid-promoted addition of an allylsilane to an enone in order to control the relative C3–C5 stereochemistry was also used in the total synthesis of fawcettimine reported by the same authors.[16]

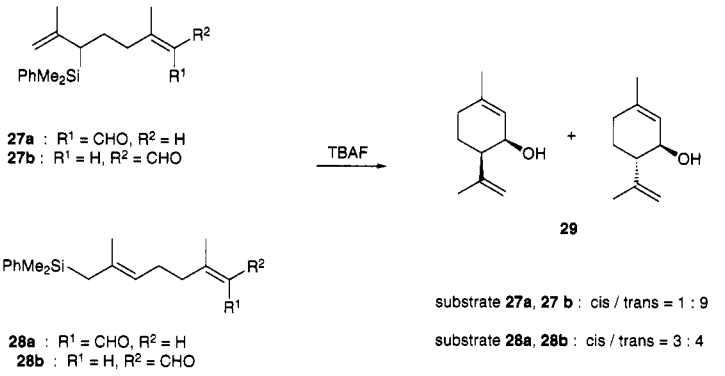
2. Intramolecular Allylsilane Additions

2.1. Allylsilane-Based 1,4-Annulations

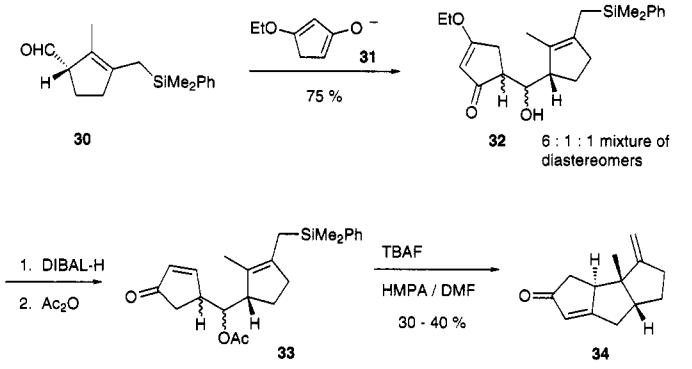
2.1.1. Total Synthesis of (±)-Linaridial. The key step in Tokoroyama's total synthesis of (±)-linaridial (**26**) is the one-pot stereospecific construction of the *cis*-clerodane skeleton by means of a doubly stereocontrolled cyclization of allylsilane derivative **21**[17] (Scheme 10). Cyclization of **21** in the presence of titanium tetrachloride followed by trapping of the intermediary enolate with $ClCH_2SCH_3$ in a one-pot manner gave decalone derivative **22**, in which all of the four contiguous diastereomeric centers of the clerodane diterpenoid skeleton have been established.

Reductive removal of the methylthio group in **22** followed by methylenation using the Nozaki procedure provided **23**. After double-bond isomerization, subsequent selective hydroboration and oxidation gave alcohol **24**, which was converted into the corresponding aldehyde using Swern conditions. Hor-

Scheme 11



Scheme 12



ner–Emmons condensation with diethyl (1-cyano-3,3-dimethoxypropyl)phosphonate gave **25** as a mixture of stereoisomers (*E*/*Z* = 1:5). Reduction of **25** proceeded smoothly and, after acidic treatment, afforded linaridial (**26**) in 73% yield.

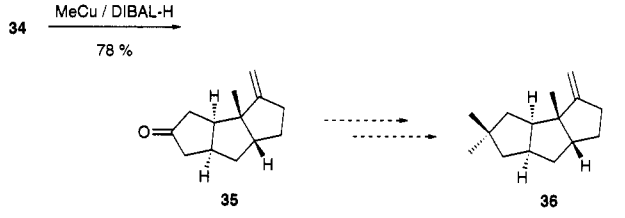
2.1.2. Synthesis of (±)-Isopiperitenol. In the presence of fluoride ion, allylsilanes react at either α- or γ-site of the allylsilane, depending upon the structure of molecules. Nakamura et al.[18] synthesized aldehydes **27** and **28** having regioisomeric allylsilane moieties and examined fluoride ion mediated cyclization reactions. Allylsilane **27a** readily cyclized in the presence of a catalytic amount of TBAF to yield a 1:9 mixture of *cis*- and *trans*-isopiperitenol (**29**) (Scheme 11). Aldehyde **27b** having *E* configuration cyclized more slowly to give a 1:9 mixture like **27a** but in lower yield.

In contrast to **27** the regioisomeric terminally substituted allylsilanes **28** reacted very slowly and required a stoichiometric amount of TBAF to complete the reaction forming isopiperitenol (**29**) as a 3:4 mixture of *cis*- and *trans*-isomers.

2.1.3. Synthetic Approach toward (±)-Hirsutene. Majetich has reported an approach toward the total synthesis of the linear triquinane (±)-hirsutene (**36**) featuring an intramolecular allylsilane cyclization of two functionalized cyclopentane rings linked by a one-carbon tether for the construction of the *cis,anti,-cis*-cyclopenta[*a*]pentalene skeleton.[19]

The cyclization precursor was prepared by aldol condensation between the two cyclopentane rings **30** and **31** in 75% yield; isomeric adducts **32** were obtained in roughly 6:1:1 ratio, respectively. Conversion of the major isomer **32** into **33** was achieved using 2 equiv of DIBAL-H, followed by mild acid hydrolysis and acetylation of the hydroxy group (Scheme 12).

Scheme 13



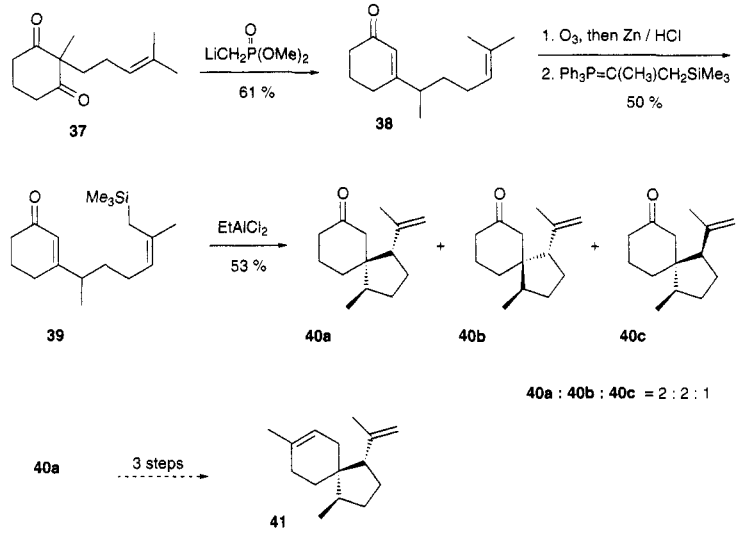
During the fluoride ion-induced cyclization of **33**, which afforded enone **34** in 30–40% yield, a dienone was generated *in situ* by fluoride-promoted elimination of an acetate ion. The relative configuration of the ring junctions was inferred from the disposition of the reacting centers. Enone **34** was converted to ketone **35** via 1,4-addition of hydride ion using Tsuda and Saegusa's procedure[20] (Scheme 13).

Unfortunately, all attempts to complete the synthesis of (±)-hirsutene (**36**) by conversion of the carbonyl group of **35** into a geminal dimethyl group failed.

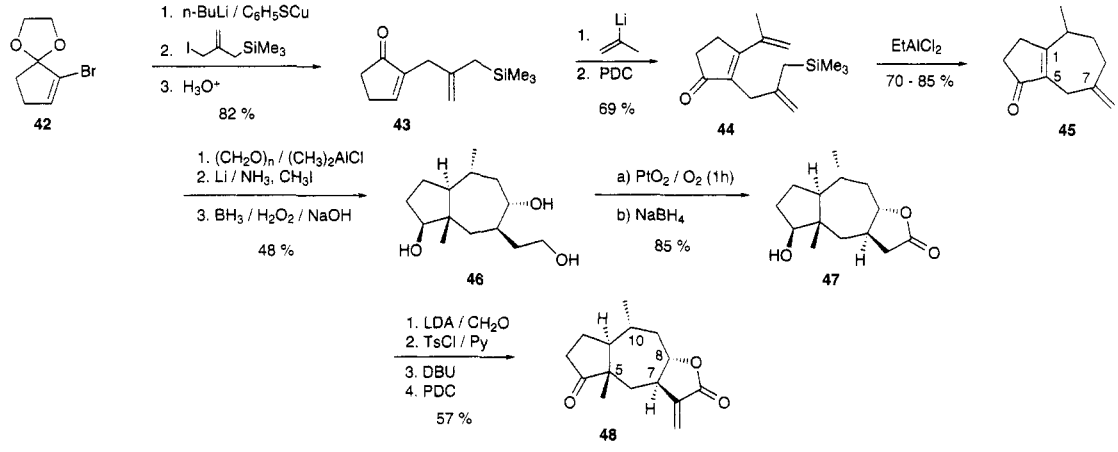
2.1.4. Synthesis of (±)-α-Acoradiene. Yamamoto and Furuta[21] have reported a short formal synthesis of the spirocyclic natural product (±)-α-acoradiene (**41**) utilizing a spiro cyclization of an allylic silane[22] to establish the α-acoradiene skeleton. 3-Substituted 2-cyclohexenone **38** was prepared via the keto phosphonate anion derived from diketone **37** and dimethyl methylphosphonate anion. The rearrangement led to cyclohexenone **38**, which was subjected to selective ozonolysis followed by reductive workup. Allylsilane **39** was prepared using the Seyferth–Fleming method[23] (Scheme 14).

Spiro cyclization of **39** in the presence of ethylaluminum dichloride[21] gave the spiroketone **40** in 53% yield as a mixture of three diastereomers (**40a/40b/**

Scheme 14



Scheme 15



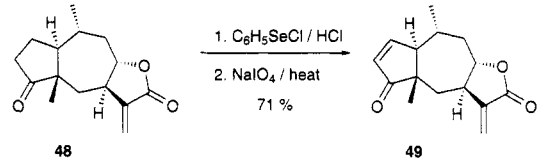
40c = 2:2:1). The desired diastereomer **40a** results from a synclinal transition state, while the other two diastereomers **40b** and **40c** are produced via antiperiplanar transition states. Synthesis of (±)-α-acoradiene (**41**) from **40a** could be performed in three steps according to the procedure reported by Oppolzer et al.[24]

2.2. Allylsilane-Based 1,6-Annulations

2.2.1. Stereoselective Syntheses of (±)-Graveolide and (±)-Aromaticin. Majetich and co-workers[25] have reported a stereoselective synthesis of the pseudoguaianolide (±)-graveolide (**48**), which features the use of an allylsilane-based 1,6-annulation to construct the functionalized perhydroazulene skeleton. Dienone **44** was prepared in 52% overall yield from ketal **42** using a four-step procedure (Scheme 15). Cyclization of the dienone **44** in the presence of 2 or more equiv of ethylaluminum dichloride afforded bicyclic enone **45** in 70 to 85% yield.

Enone **45** is an attractive pseudoguainolide precursor because the C7 exocyclic methylene unit serves as a handle for the construction of a C7,C8-α-methylene lactone, while the cyclopentenone moiety allows control of the stereochemistry of C1 and C5 chiral centers. Dimethylaluminum chloride-catalyzed ene reaction of **45** and paraformaldehyde, followed by reductive alkylation and hydroboration

Scheme 16



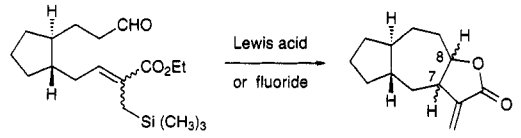
gave triol **46**, which was transformed into the hydroxy lactone **47** by selective oxidation and lactonization of the intermediate hydroxy acid. Selective reduction of "overoxidized" keto lactone was thereby achieved using sodium borohydride.

The α-methylene unit could be introduced directly on unprotected hydroxy lactone **47** using a three-step procedure described by Grieco.[26] Oxidation with PDC completed the synthesis of (±)-graveolide (**48**).

Starting from (±)-graveolide (**48**), total synthesis of a second pseudoguainolide, (±)-aromaticin (**49**), was achieved by α-phenylselenation of the cyclopentanone ring followed by oxidative elimination to establish the α,β-unsaturated ketone (Scheme 16).

Kuroda et al.[27] have demonstrated that intramolecular cyclization of ω-formyl-α-[(trimethylsilyl)-methyl]-α,β-unsaturated esters is a powerful method for the synthesis of α-methylene lactones fused to bicyclic terpenoid carbon skeletons. By using this method, carbocyclization, lactonization, and α-meth-

Scheme 17



50 *Z*-form
51 *E*-form

52 7α-H, 8α-H
53 7α-H, 8β-H
54 7β-H, 8α-H
55 7β-H, 8β-H

ylenation could be achieved in one step and several guaianolide and pseudoguaianolide derivatives have been synthesized (Scheme 17).

The stereochemistry of the cyclized lactones **52**–**55** depends on the stereochemistry of the cyclization precusor **50**, **51** (*E*- or *Z*-form) and the cyclization reagent used (Lewis acid or fluoride). Even though the yields were generally low, the desired methylenel actones with the appropriate carbon framework were obtained in one step.

2.2.2. Stereoselective Synthesis of (±)-14-Deoxyisoamijiol. Tricyclic compounds can be obtained directly by annulation on to cyclic allylsilanes, using ethylaluminum dichloride as Lewis acid.[28] The stereochemical outcome of this particular cyclization is controlled by the relative configuration of the cyclic allylsilane. The reaction follows the usual "anti" S_E2' process for reactions of allylsilanes with electrophiles. Thus, the reaction was stereospecific, which makes it very useful for stereocontrolled syntheses of complex ring systems. This strategy resulted in a direct and stereoselective synthesis of (±)-14-deoxyisoamijiol (**64**).[29]

Coupling of β-ethoxy enolate **57** with chloride **56** using the Stork–Danheiser procedure[30] gave the enol ether **58** as a mixture of diastereomers. The cyclic allylsilane **56** was prepared via a five-step synthesis in 41% overall yield (Scheme 18).

Diastereomers could be separated after conversion of vinylogous esters **58** into the conjugated dienones **59a** and **59b**. Treatment of compounds **59** with ethylaluminum dichloride afforded tricyclic dienone **60** in 93% yield, having a *trans* relationship of the C5 and C12 quaternary methyl groups (Scheme 19).

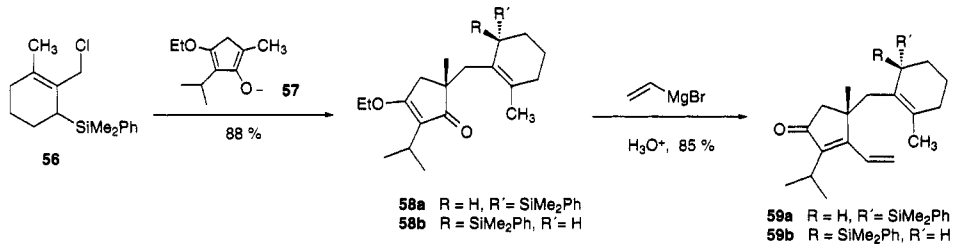
Reduction of the cycloalkenone carbonyl, followed by regioselective allylic oxidation gave the desired cyclohexenone **61**, which was transformed into diol **62**, using a three-step procedure. Selective monotosylation of the primary hydroxyl group, followed by base-promoted 1,2-elimination established the exomethylene unit. Inversion of the stereochemistry at C2 was achieved by treatment of allylic alcohol **63** with benzenesulfenyl choride. Desulfurization of the rearranged, thermodynamically favored sulfenate resulted in the correct configuration at C2 and completed the synthesis of (±)-14-deoxyisoamijiol (**64**).

2.2.3. Direct Stereoselective Syntheses of (±)-Neolemnanyl Aceteate and (±)-Neolemnane. Majetich and co-workers have demonstrated the usefulness of fluoride ion-promoted 4-butenyl dienone cyclizations for the annulation of 8-membered rings.[31] In the total synthesis of the marine sesquiterpenes neolemnanyl acetate (**72**) and neolemnane (**73**) an intramolecular allylsilane addition to a conjugated dienone was used to assemble the basic 6,8-fused skeleton.[32]

Starting material for the construction of the cyclization precursor **68** was vinylogous ester **65**, which was conveniently prepared from dihydroorcinol. The correct relative *cis* stereochemistry of the two ring methyl groups in trienone **68** was established by an alternating alkylation sequence (Scheme 20).

Cyclization of **68** under fluoride ion catalysis yielded the 6,8-fused bicyclic enone **69** in 60% via a S_E2 process.[33] Generation of the axial allylic alcohol from the cyclohexenone system in **69** was achieved using L-Selectride. After the alcohol was converted into the acetate, photooxygenation afforded enone **70** in 52% yield. Preparation of the trisubstituted enone **71** required the 1,2-addition of a methyl anion

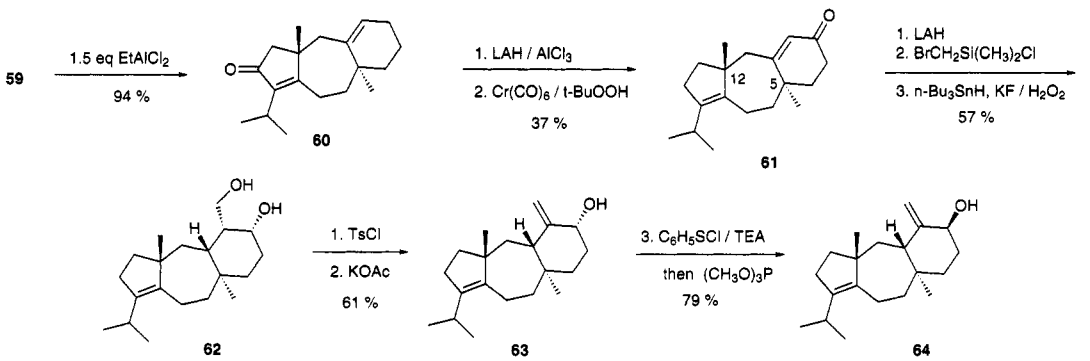
Scheme 18



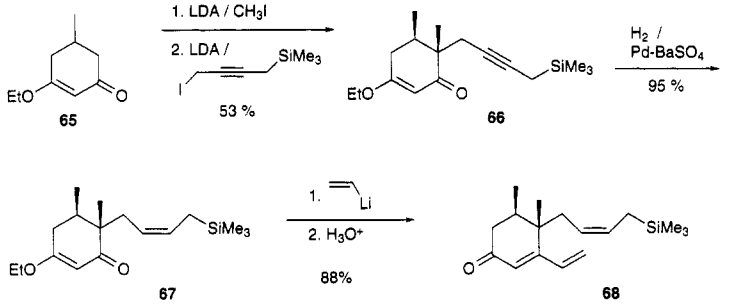
58a R = H, R' = $SiMe_2Ph$
58b R = $SiMe_2Ph$, R' = H

59a R = H, R' = $SiMe_2Ph$
59b R = $SiMe_2Ph$, R' = H

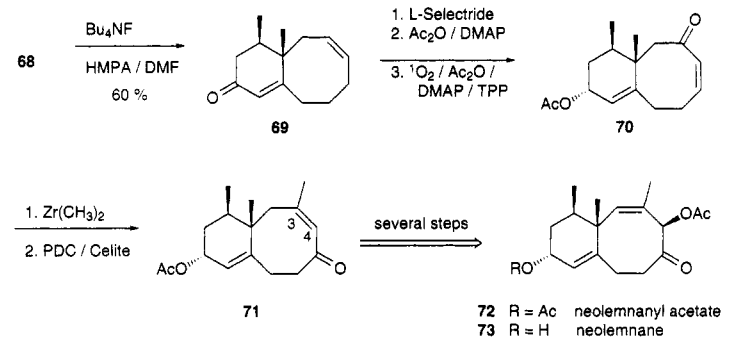
Scheme 19



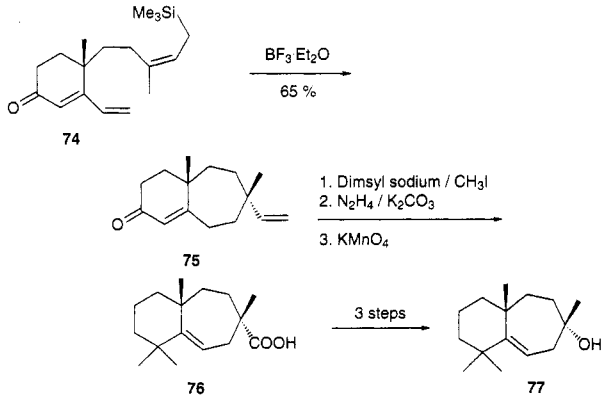
Scheme 20



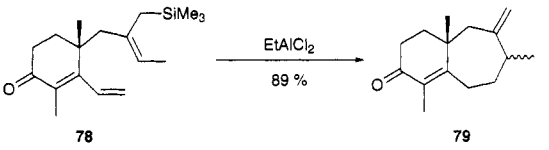
Scheme 21



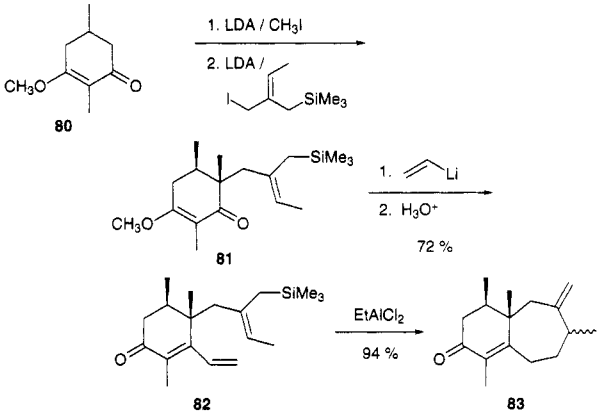
Scheme 22



Scheme 23



Scheme 24



equivalent to the C3-carbonyl in **70**, followed by oxidative rearrangement of the resulting tertiary allylic alcohol (Scheme 21).

To complete the synthesis of neolemnanyl acetate (**72**), several steps were necessary to achieve migration of the double bond, stereospecific hydroxylation of C4, and acetylation of the C4-hydroxyl group.

2.2.4. Stereospecific Total Syntheses of (±)-Epiwiddrol. Two stereospecific total syntheses of (±)-epiwiddrol (**77**) were reported by Majetich et al.[34] The first synthesis features the cyclization of dienone **74**, which possesses a (*Z*)-allylsilane moiety, to construct bicyclic adduct **75** as a single isomer (Scheme 22).

With the 6,7-bicyclic ring system assembled, **75** was converted into epiwiddrol (**77**) using conventional procedures.

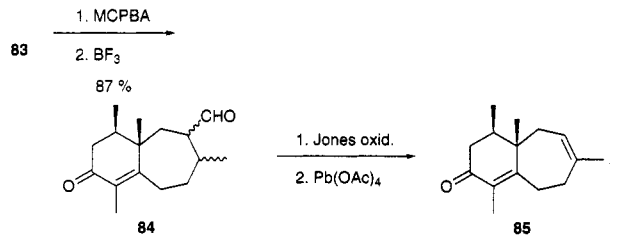
A second synthesis exploits the Lewis acid-catalyzed cyclization of dienone **78** to prepare functionalized bicyclo[5.4.0]undecene **79**, which was converted to a known epiwiddrol precursor[35] (Scheme 23).

2.2.5. Stereoselective Synthesis of (±)-Perforenone. The same basic strategy of cyclizing an allylic silane to a functionalized dienone was employed in the synthesis of the marine metabolite perforenone (**85**).[36] The cyclization precursor **82**, containing one additional methyl group at the cyclohexenone moiety, was again constructed using Stork's vinylogous ester strategy (Scheme 24).

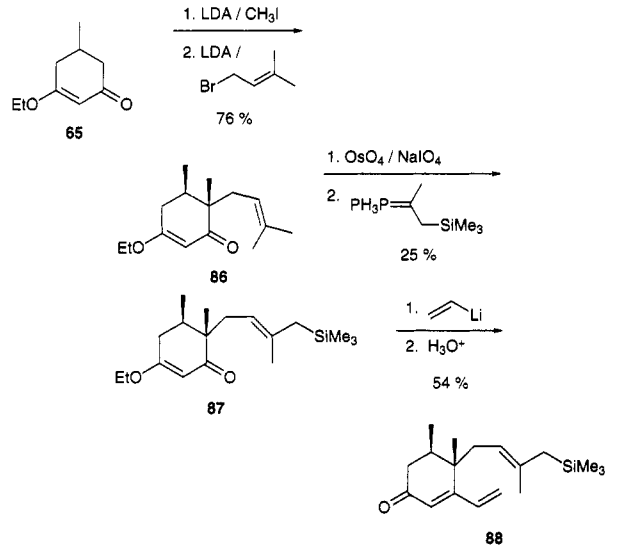
The cyclization step proceeded very smoothly in 94% yield, using ethylaluminum dichloride as the Lewis acid catalyst. Bicyclic cyclization product **83** was converted into the natural product **85** in four steps (Scheme 25).

2.2.6. Stereoselective Syntheses of (±)-Nootkatone and (±)-Valencene. For the total syntheses of both nootkatone (**89**) and valencene (**90**), the same functionalized 3-ethoxy-2-cyclohexen-1-one (**65**) was used as starting material.[37] The correct relative *cis* stereochemistry of the two ring methyl groups in **86** was

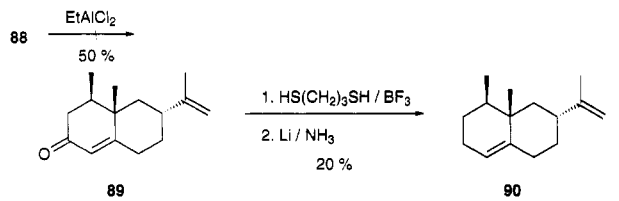
Scheme 25



Scheme 26



Scheme 27



established by an alternating alkylation sequence (Scheme 26).

Vinylogous ester **86** was transformed via oxidative cleavage of the double bond and subsequent Wittig reaction to the trienone **88**. Cyclization of **88** afforded crystalline racemic nootkatone (**89**) as the single product (Scheme 27).

The synthesis of valencene **90** was completed by removal of the carbonyl oxygen by the dithiane method.

2.2.7. Total Synthesis of (±)-Sesquiterpenoid AE 1. Schinzer and co-workers[38] have reported a total synthesis of the natural product sesquiterpenoid AE 1 (**97**) featuring a diastereoselective dienone cyclization of a functionalized allylic silane as the key step.

Alkylation of 3-ethoxy-2-cyclohexen-1-one **65**, which is easily available from 5-methylresorcinol, produced **91** in excellent 94% yield as a 4:1 mixture of diastereomers. Subsequent chemoselective ozonolysis and reductive workup led to the corresponding aldehyde, which was transformed into the functionalized allylic silane **92** by means of a Wittig reaction (Scheme 28).

Compound **92** was then treated with vinyllithium to yield after acid hydrolysis the key dienone **93**.

Cyclization with ethylaluminum dichloride as the Lewis acid catalyst afforded the bicyclic enone **94** with three defined stereogenic centers as a single diastereoisomer. Introduction of the β-methyl group was accomplished stereoselectively by employing lithium tetramethylaluminate in the presence of Ni(acac)$_2$[39] (Scheme 29).

Regioselective phenyl selenylation of **95** was achieved by deprotonation with LDA at low temperature followed by addition of phenylselenyl bromide. Subsequent oxidation yielded enone **96**, which was reduced to the natural product **97** using sodium borohydride in the presence of trifluoroacetic acid.

2.3. Cyclization of Polyene Allylsilanes

2.3.1. Synthesis of (±)-Albicanyl Acetate. An electrophilic cyclization of a polyene allylsilane was the key step in a short synthesis of the marine natural product (±)-albicanyl acetate (**103**) reported by Harris and Weiler.[40] The cyclization precursor **101** was synthesized from methyl acetoacetate **98** as shown in Scheme 30. Alkylation of the dianion of methyl acetoacetate **98** with geranyl bromide **99** gave the β-keto ester **100**.

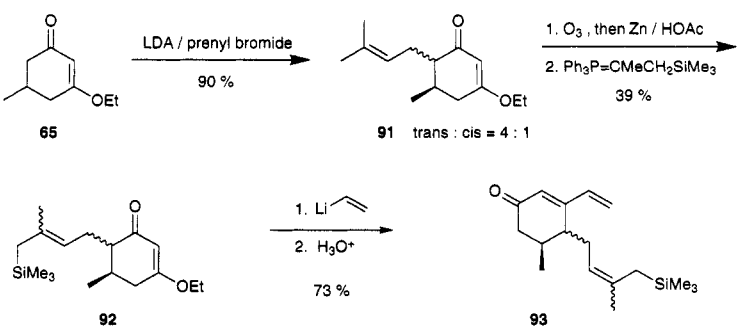
Compound **100** was converted into the (*Z*)-enol phosphate, which was treated with [(trimethylsilyl)methyl]magnesium chloride in the presence of nickel(II) bis(acetylacetonate) catalyst[41] to yield mainly the (*Z*)-allylsilane **101** (*E*/*Z* < 1:20). Cyclization of ester **101** with stannic chloride in dichloromethane gave the bicyclic product **102** in almost quantitative yield as a 4:1 mixture of diastereomers.

After reduction with lithium aluminum hydride followed by chromatographic purification the resulting alcohol was acetylated to yield pure (±)-albicanyl acetate **103** (Scheme 31).

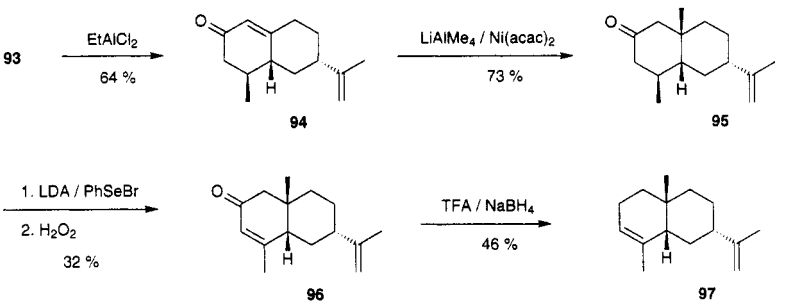
2.4. Cyclization of Epoxy Allylsilanes

2.4.1. Total Synthesis of (±)-Hirsutene. Sarkar et al.[42] described a general route to *cis*-1,2-disubstituted

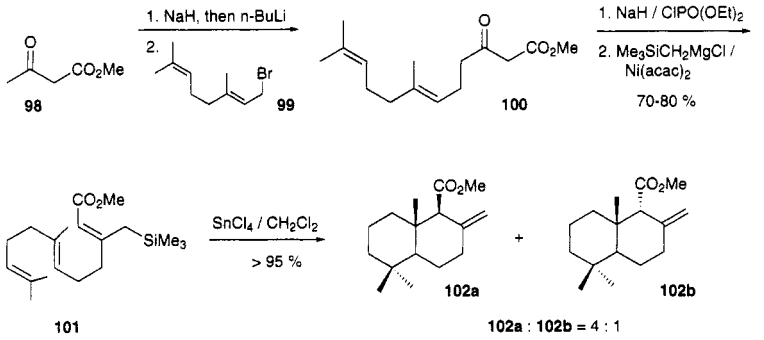
Scheme 28



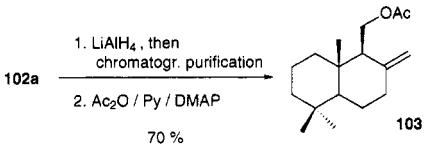
Scheme 29



Scheme 30



Scheme 31



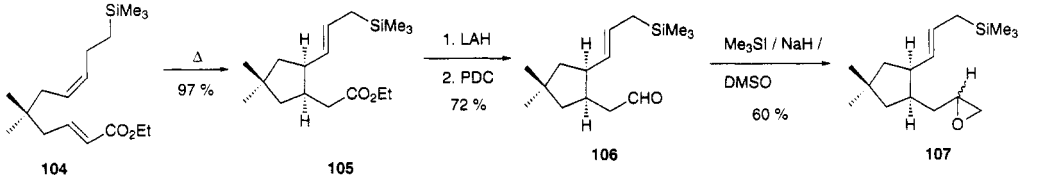
cyclopentanoid allylic silanes via intramolecular ene reaction of activated 1,6-dienes featuring a homoallylsilane unit as ene donor (Scheme 32). This strategy was used for the preparation of the funtionalized allylsilane **105**, a valuable intermediate for the total synthesis of (±)-hirsutene (**36**).[43] The exclusive formation of (*E*)-allylsilane **105** is accountable in terms of the relevant transition states.[44]

Reduction of the ester functionality in **105** and oxidation gave aldehyde **106**, which was converted to the epoxide **107** by selective addition of methylene to the carbonyl group using dimethylsulfonium methylide. Compound **107** underwent a facile Lewis acid-induced epoxy–allylsilane ring closure to give the carbinol as a mixture of stereoisomers, which was oxidized to the corresponding aldehyde **108**.

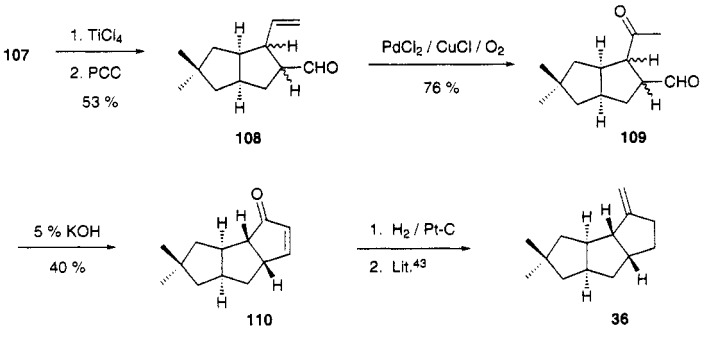
Further oxidation of **108** afforded the keto aldehyde **109** (Scheme 33). Base-catalyzed intramolecular aldolization served to channel the stereoisomeric mixture of **109** into the pure *cis,anti,cis*-triquinane (**110**). Catalytic hydrogenation of enone **110** completed the formal total synthesis, since the resulting ketone has previously been converted into (±)-hirsutene (**36**) by Little and Muller.[45]

The ene cyclization methodology[46] described above was also used in the total syntheses of the two epijasmonoids (±)-methyl curcurbate and (±)-methyl epijasmonate.[47]

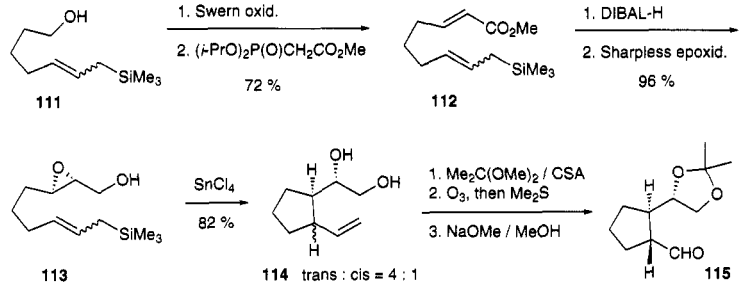
Scheme 32



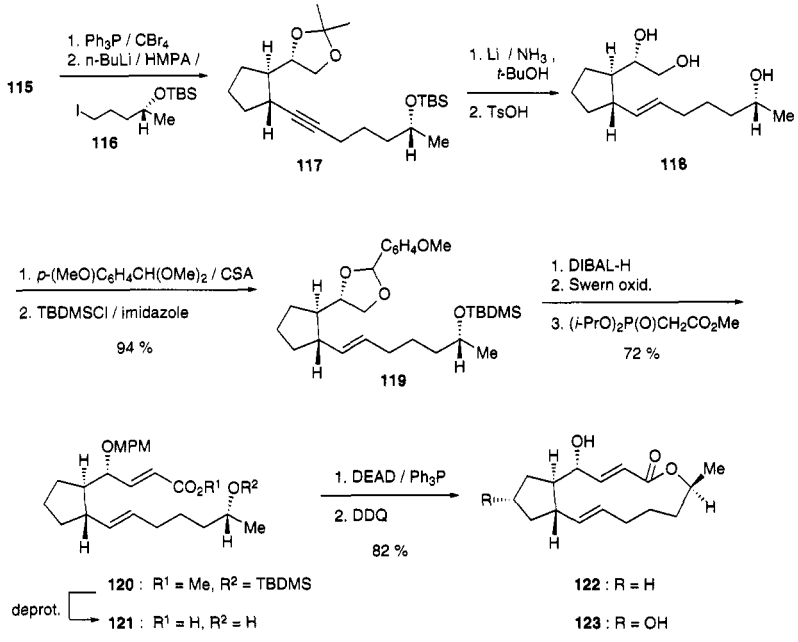
Scheme 33



Scheme 34



Scheme 35



2.4.2. Total Syntheses of (+)-Brefeldin C and (+)-Brefeldin A. An efficient method for the enantioselective preparation of functionalized chiral cyclopentanes using Lewis acid-mediated cyclizations of epoxy allylsilanes has been developed by Takano and coworkers.[48] The utility of this methodology was demonstrated in the enantioselective syntheses of the macrolide antibiotic (+)-brefeldin A (**123**) and its biosynthetic precursor, the fungal metabolite (+)-brefeldin C (**122**).[49]

The synthesis of brefeldin C started with the known allylsilane **111**,[50] which was transformed into the ester **112** by Swern oxidation followed by Horner–Emmons reaction. The ester was then converted by DIBAL-H reduction and subsequent Sharpless catalytic asymmetric epoxidation[51] to the epoxy alcohol **113**. $SnCl_4$ mediated cyclization afforded the diol **114** as an inseparable isomeric 4:1 mixture. Sequential protection, ozonolysis, and base-catalyzed epimerization led to exclusive formation of the *trans*-aldehyde **115** (Scheme 34).

Transformation of **115** into the dibromo olefin[52] and treatment with *n*-BuLi followed by *in situ* alkylation of the resulting lithium acetylide with the iodide **116** afforded the acetylene **117**. Successive reduction of the acetylenic bond and deprotection gave the triol **118**, which was converted by acetalization and subsequent silylation to the *p*-methoxybenzylidene acetal **119**. Upon sequential regioselective reductive cleavage of the acetal moiety, Swern oxidation, and Horner–Emmons reaction, **119** afforded the ester **120** in 72% overall yield (Scheme 35).

After desilylation followed by saponification, the hydroxy acid **121** was subjected to lactonization using Mitsunobu's procedure[53] to give the lactone. Finally, oxidative deprotection furnished (+)-brefeldin C (**122**).

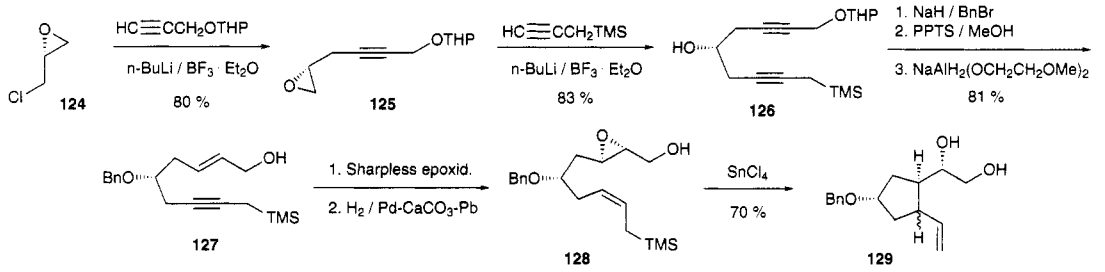
The total synthesis of (+)-brefeldin A (**123**) employs the same basic strategy to establish the 1,2-*trans*-disubstituted cyclopentane from the allylic alcohol **127**: (i) Sharpless asymmetric epoxidation, (ii) Lewis acid-mediated cyclization, (iii) ozonolysis followed by base catalyzed epimerization. Allyl alcohol **127** has been prepared in a five-step sequence starting from (*R*)-(−)-epichlorohydrin (**124**). According to Nicolaou's[54] procedure, **124** was first converted to the epoxide **125** which, upon reaction with lithiated propargyltrimethylsilane in the presence of $BF_3{\cdot}Et_2O$, gave the alcohol **126**. Alcohol **126** was then successively subjected to benzylation, acidic methanolysis, and reduction to give the (*E*)-allylic alcohol **127** (Scheme 36).

Assembly of the macro-lactone moiety followed the method established previously in the total synthesis of (+)-brefeldin C (**122**).

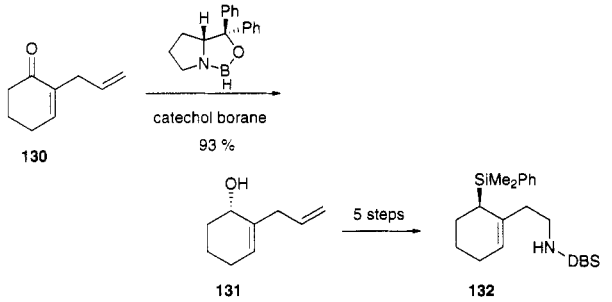
2.5. Iminium Ion–Allylsilane Cyclizations

2.5.1. Asymmetric Synthesis of (−)- and (+)-Morphine. Overman and co-workers[55] have reported asymmetric syntheses of the natural opium alkaloid

Scheme 36



Scheme 37



(−)-morphine and its enantiomer featuring an iminium ion−allylsilane cyclization and an intramolecular Heck reaction as key steps.

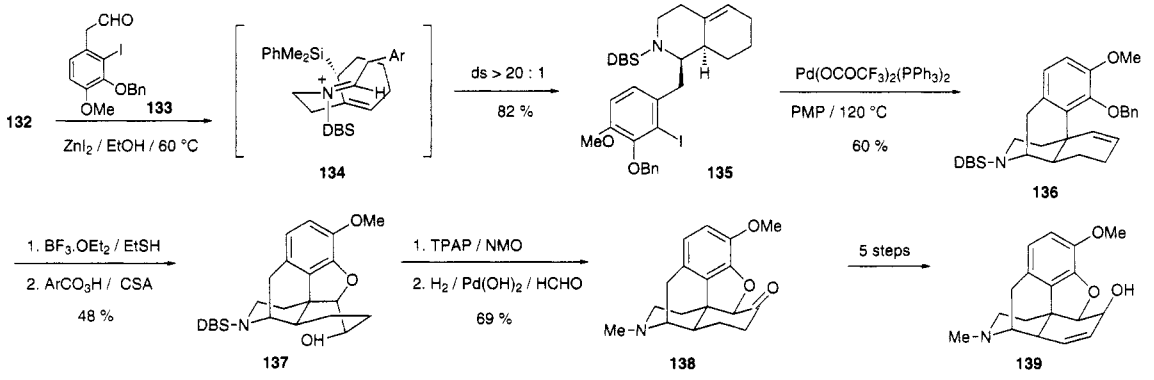
The asymmetric total synthesis of (−)-morphine (**139**) is summarized in Schemes 37 and 38. Enantioselective reduction of 2-allylcyclohex-2-en-1-one (**130**) with catecholborane in the presence of (*R*)-oxazoborolidine catalyst provided the corresponding (*S*)-cyclohexenol **131** in 93% yield and >96% ee. **131** was converted in five high-yielding steps to the enantioenriched (*R*)-allylic silane amine **132**.

Condensation−cyclization of **132** with arylacetaldehyde **133** proceeded with complete retention of absolute configuration and with high diastereoselection to provide octahydroisoquinoline **135** in 82% yield. The stereochemical outcome of the iminium ion−allylsilane cyclization is rationalized by cyclization of conformer **134**, in which the bulky dibenzosuberyl group is a critical element in stereocontrol.

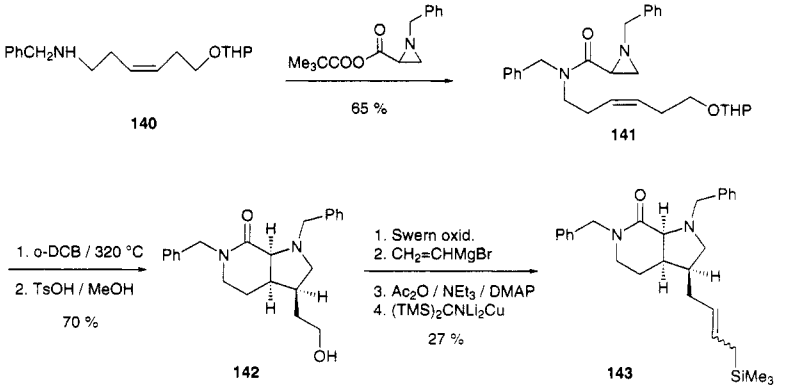
Intramolecular Heck cyclization[56] of **135**, establishing the critical quaternary center of the morphinan skeleton, afforded the unsaturated morphinan (**136**) in 60% yield. After cleavage of the benzyl ether protecting group, the final ring of the opioid skeleton was formed by reaction of the camphorsulfonate salt of **136** with 3,5-dinitroperoxybenzoic acid to provide **137**. This pentacyclic intermediate was then transformed, by way of (−)-dihydrocodeinone (**138**), into (−)-morphine (**139**) using a sequence optimized by Rice.[57] In an identical fashion, the enantiomeric (*R*)-cyclohexenol was converted to (+)-morphine.

2.5.2. Strategy for the Synthesis of (±)-Sarain A. Weinreb et al.[58] have developed an efficient route to the tricyclic nucleus of the unusual marine alkaloid sarain A (**147**) utilizing a novel intramolecular allylsilane/*N*-sulfonyliminium ion cyclization as a key step. The synthetic approach[59] outlined in Scheme

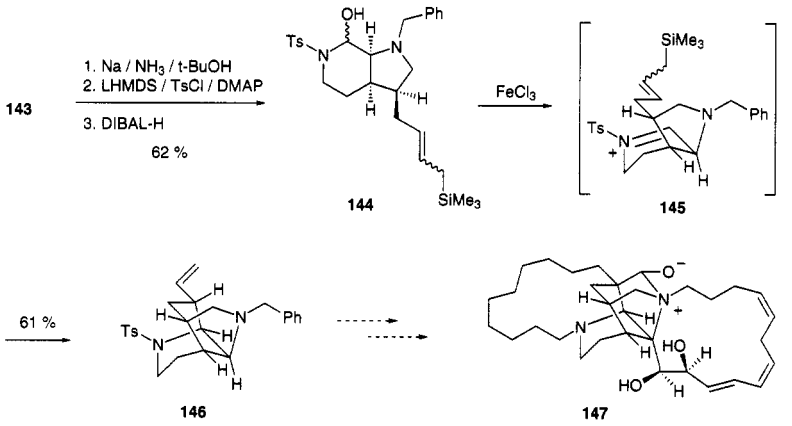
Scheme 38



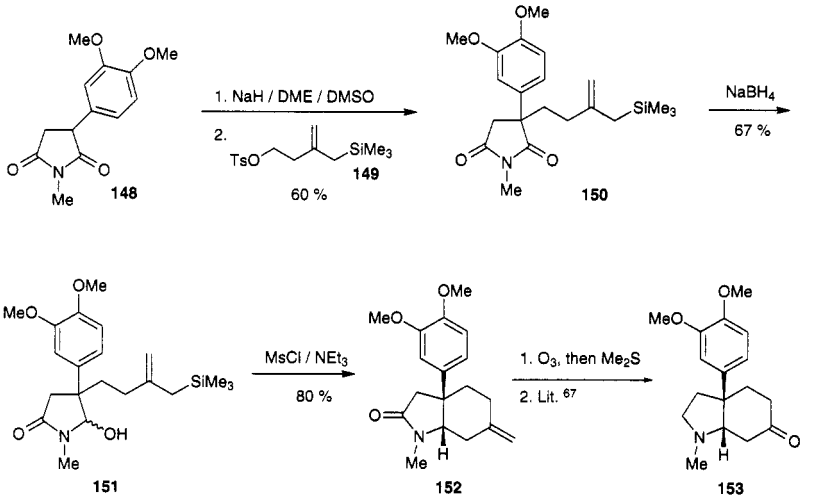
Scheme 39



Scheme 40



Scheme 41



39 began with amine **140**, which was prepared in two steps from the readily available alcohol.[60] Coupling of amine **140** with the mixed anhydride of a known *N*-benzylaziridine ester[61] afforded the amide **141**.

Thermolysis of **141** in *o*-dichlorobenzene at 320 °C gave bicyclic lactam **142** stereospecifically via an azomethine ylide/olefin [3 + 2] dipolar cycloaddition.[59,62] Alcohol **142** was oxidized to the aldehyde, which was transformed into the allylic silane **143** utilizing chemistry described by Fleming et al.[63]

Selective mono-*N*-debenzylation of **143** could be effected in high yield using Na/NH_3 in the presence of excess *t*-BuOH. *N*-Tosylation and subsequent reduction of the resulting sulfonyllactam provided hydroxy sulfonamide **144** (Scheme 40).

Cyclization of **144** was achieved by using anhydrous ferric chloride in methylene chloride to afford tricyclic compound **146** in 61% yield as a single stereoisomer. The cyclization probably occurs via *N*-sulfonyliminium intermediate **145**, which has the allylsilane group in a pseudo-equatorial position.

2.5.3. Total Synthesis of (±)-Mesembrine. An α-acyl iminium ion-initiated intramolecular allylic silane cyclization[64] was the key step in a short and highly stereoselective synthesis of the alkaloid (±)-mesembrine (**153**)[65] reported by Remuson and coworkers[66] (Scheme 41). The cyclization precursor **151** was prepared in two steps starting from *N*-methyl-3-arylsuccinimide **148**.[67] Alkylation of **148** with tosylate **149** of the known alcohol[68] gave imide **150**, which could be regioselectively reduced to afford hydroxyamide **151** as a mixture of diastereomers.

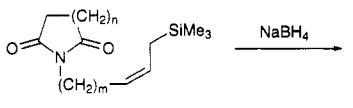
Cyclization of **151** could be effected by generating the acyliminium ion in a nonacidic medium (MsCl, NEt_3, CH_2Cl_2) to yield 7-azabicyclo[4.3.0]nonane **152** as a single isomer. Ozonolysis of **152** gave the corresponding ketone, which could be transformed into (±)-mesembrine (**153**) according to a procedure described in the literature.[69]

2.5.4. Syntheses of (±)-Isoretronecanol and (±)-Epilupinine. Hiemstra and Speckamp have studied intramolecular additions of allylic and propargylic silanes to α-acyl iminium ions.[70] Starting from ω-hydroxy lactams, reactions occur in high yields with complete regio- and stereoselectivity under mild conditions using trifluoroacetic acid (Schemes 43 and 44).[71] This methodology was used in the stereoselective syntheses of racemic isoretronecanol (**160**) and epilupinine (**163**).[72] The cyclization precursors **156** and **157** were prepared from the corresponding imides **154** and **155** via pH-controlled $NaBH_4$ reduction (Scheme 42).

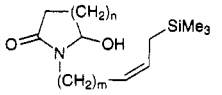
Cyclization of **156** afforded the bicyclic amide **159** as a single stereoisomer, which must have arisen from the more stable chair like π-complex **158**.

The cyclization product **159** was converted into the natural product isoretronecanol **160** by ozonolysis followed by reductive workup and subsequent reduction of the carbonyl group with lithium aluminum hydride.

Scheme 42



154 : m = 2, n = 1
155 : m = 3, n =2



156 : m = 2, n = 1
157 : m = 3, n =2

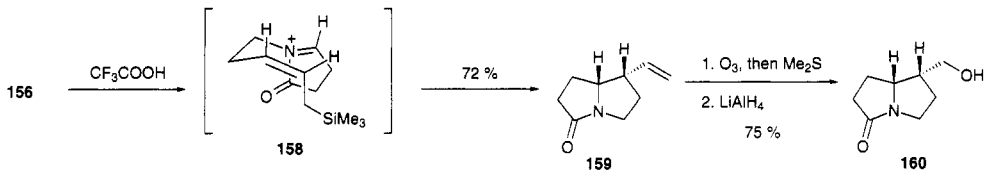
Cyclization of **157** gave the bicyclic amide **162** in 74% yield as the major product. Cyclization product **162** arises from **161** with the trimethylsilyl group in a pseudo-equatorial position. Quinolizidine **162** was transformed into epilupinine (**163**) using the two-step procedure described above.

2.5.5. Total Synthesis of (±)-Allokainic Acid. A total synthesis of racemic α-allokainic acid (**173**) featuring as key steps an intermolecular allylic silane *N*-acyliminium ion coupling and an intramolecular allylsilane *N*-acyliminium ion reaction has been reported by Hiemstra and Speckamp.[73] Coupling of allylsilane **165** with methoxyglycine derivative **164** induced by $BF_3{\cdot}Et_2O$ gave **166** as a 63:37 mixture of isomers. Lactonization in the presence of catalytic amounts of *p*-toluenesulfonic acid yielded a 7:3 mixture of *cis*- and *trans*-δ-lactone **167** (Scheme 45).

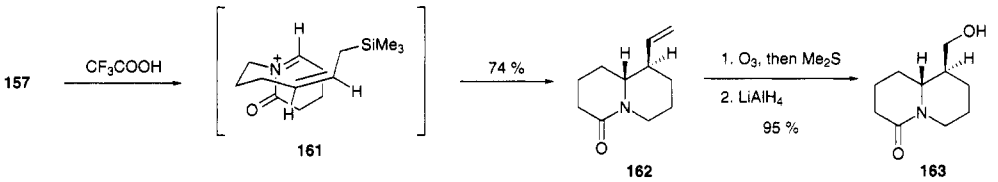
Introduction of the methoxymethyl function onto nitrogen was accomplished by treatment of **167** with sodium hydride in DMF followed by addition of chloromethyl methyl ether. Surprisingly, the alkylation product **168** was obtained as a single isomer showing *trans* stereochemistry. Ozonolysis of **168** to the aldehyde followed by Wittig-type reaction afforded allylsilane **169** as a mixture of double bond isomers.

Treatment of **169** with $BF_3{\cdot}Et_2O$ gave pyrrolidine **172** in 52% yield (Scheme 46). Compound **172** was formed from a *trans*-fused bicyclic system **171**, which

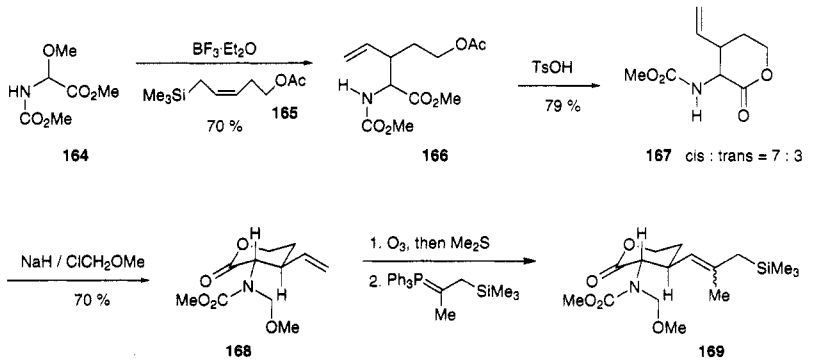
Scheme 43



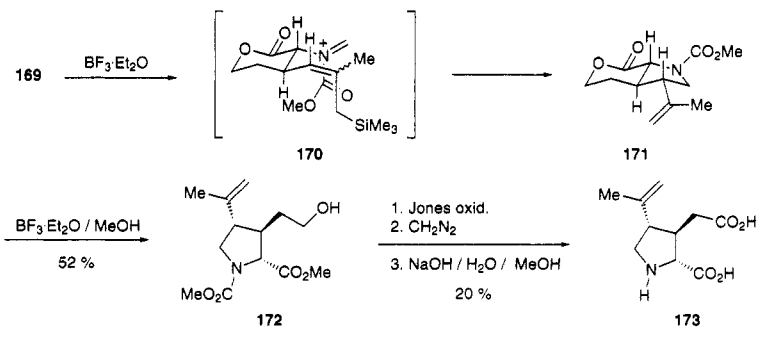
Scheme 44



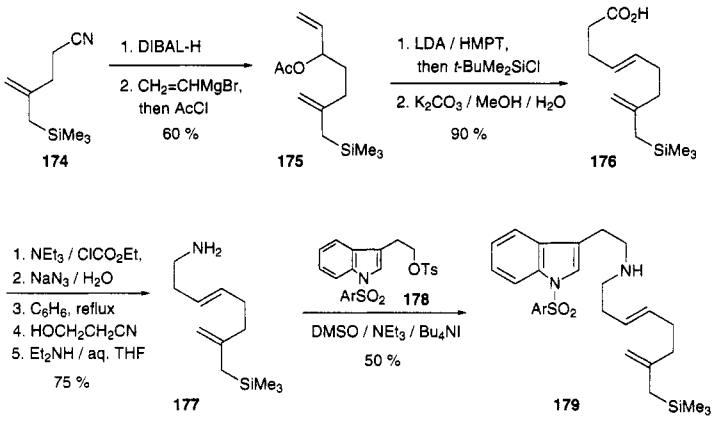
Scheme 45



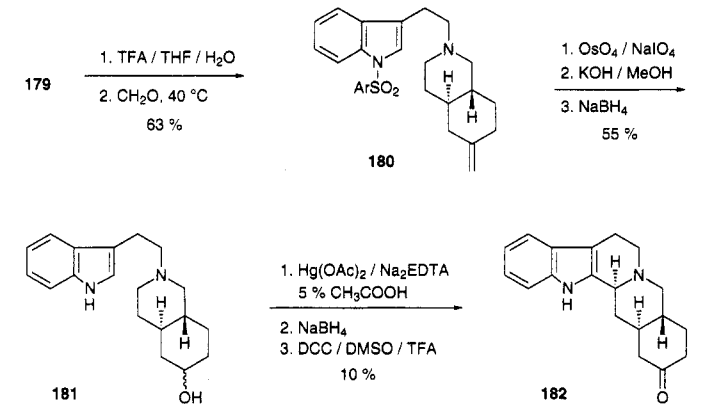
Scheme 46



Scheme 47



Scheme 48



apparently was sufficiently strained so that lactone opening readily took place. The stereochemistry of **171** is the result of a transition state conformation resembling **170**.

The final transformation of **172** into the natural product **173** was accomplished following literature precedent.[74]

2.5.6. Total Synthesis of (±)-Yohimbone. A synthesis of (±)-yohimbone (**182**) via a concerted iminium ion-induced polyolefin cyclization terminated by an allylsilane has been realized by Grieco.[75] Cyclization precursor **179** was prepared according to the procedure outlined in Scheme 47. Nitrile **174** was derived from the known homoallylic alcohol[66] via displacement of the the corresponding toluene-*p*-sulfonate by cyanide. Reduction of **174** and sequential treatment of the resultant aldehyde with vinylmagnesium bromide and acetyl chloride provided the allylic acetate **175**,which was subjected to an Ireland–Claisen ester–enolate rearrangement to afford the carboxylic acid **176**.[76]

Compound **176** was subjected to a modification of the Weinstock–Curtius reaction[77] wherein the resultant isocyanate was trapped with 3-hydroxypropionitrile giving rise to an urethane, which was transformed by treatment with diethylamine in aqueous tetrahydrofuran into the amine **177**. Alkylation of **177** with *N*-[(*p*-methoxyphenyl)sulfonyl]-tryptophyl tosylate (**178**) gave compound **179** in 50% yield. Iminium ion-induced polyolefin cyclization was achieved by treatment of the trifluoracetate of **179** with 10 equiv of formaldehyde in aqueous THF (Scheme 48).

Oxidative cleavage of the exocyclic double bond in cyclization product **180** followed by hydrolysis of the sulfonamide moiety and subsequent reduction of the ketone provided the alcohol **181**, which was cyclized by employing excess of mercury(II) acetate–ethylenediaminetetraacetic acid disodium salt in acetic acid.[78] The synthesis was completed by reduction of the crude iminium ion and subsequent oxidation of the hydroxy group to yield (±)-yohimbone (**182**).

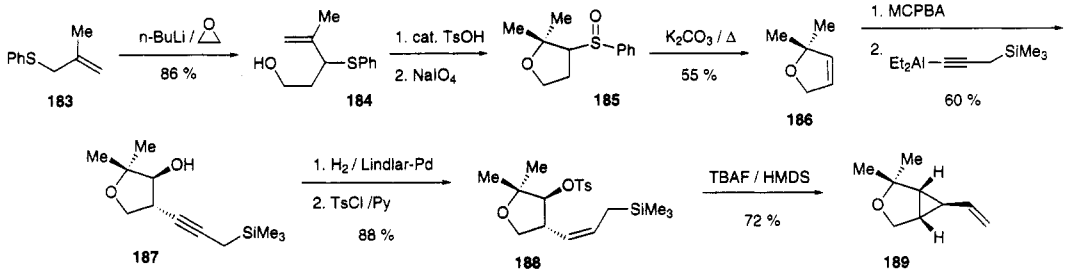
2.6. Miscellaneous Allylsilane-Mediated Reactions

2.6.1. Synthesis of (±)-Norartemeseol. The synthesis of the terpernoid (±)-norartemeseol **189** using epoxide ring opening reactions as key steps has been accomplished by Schaumann et al.[79] The vinylcyclopropane moiety in **189** was established by fluoride-induced allylsilane cyclization (Scheme 49).

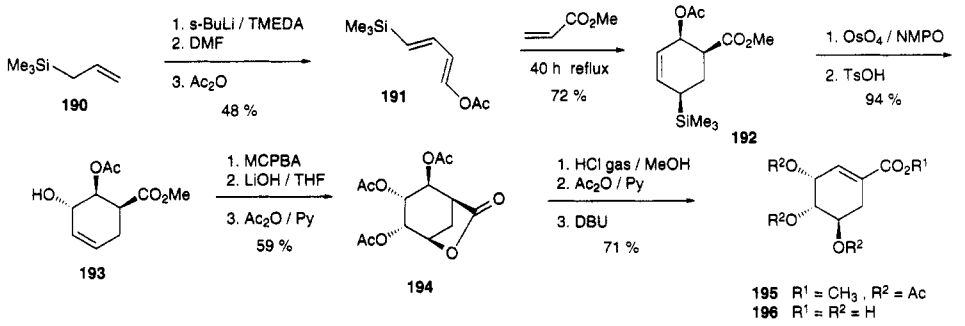
Addition of the thio-substituted allyl anion of **183** to ethylene oxide followed by proton-induced cyclization provided the tetrahydrofuran **185**. The oxirane derived from **186**, which was formed by simple functional group interconversion, was opened by the diethylaluminum salt of a propargylsilane to yield compound **187**. After catalytic hydrogenation and tosylation, fluoride-induced cyclization of the allylsilane **188** gave (±)-norartemeseol (**189**).

2.6.2. Synthesis of Shikimic Acid. A regio- and stereocontrolled total synthesis of (±)-shikimic acid (**196**) featuring a Diels–Alder reaction of (1*E*,3*E*)-4-acetoxy-1-(trimethylsilyl)-1,3-butadiene (**191**) and methyl acrylate was reported by Koreeda et al.[80] The diene **191** was synthesized from allyltrimethylsilane (**190**) via a convenient one-pot procedure. Thus,

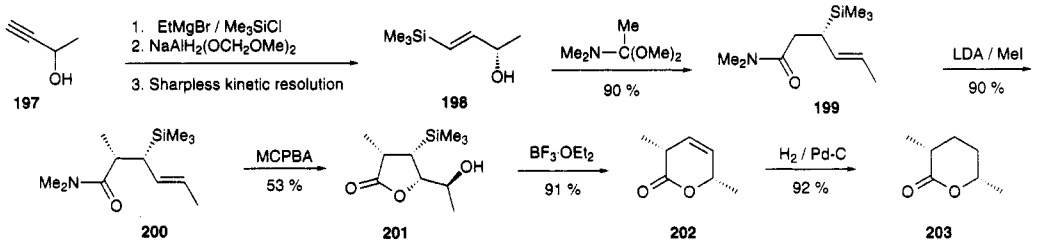
Scheme 49



Scheme 50



Scheme 51

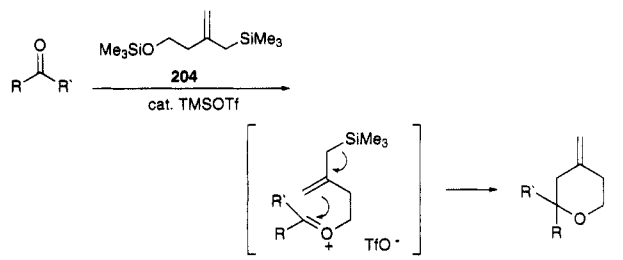


generation of the allylic carbanion using *sec*-BuLi and treatment with DMF followed by acetic anhydride afforded the diene **191** in 48% along with 12% of the 1*E*,3*Z*-isomer. Diels–Alder reaction of **191** with methyl acrylate produced the desired cycloadduct **192** in 72% yield (Scheme 50).

The most crucial step in this synthesis involves oxidative desilylation of the cyclic allylsilane **192**. Direct epoxidation–desilylation of **192** with different peracids failed. Nevertheless, stereospecific transformation of **192** into allylic alcohol **193** could be achieved by a two-step procedure via the *cis*-diol derived from **192** using the Upjohn procedure.[81] Subsequent elimination of the trimethylsilyl–hydroxy unit provided **193**. Epoxidation and treatment with lithium hydroxide followed by acetalization afforded γ-lactone triacetate **194**. (±)-Methyl triacetylshikimate (**195**) was derived from **194** via lactone ring opening with dry HCl in methanol, acetylation, and treatment with DBU. Ester **195** could be hydrolyzed under alkaline conditions to liberate (±)-shikimic acid (**196**).

2.6.3. Stereoselective Hydroxylactonization of Chiral Amide–Allylsilanes. Russel and Procter have reported a stereoselective hydroxylactonization of chiral amide–allylsilanes upon treatment with MCPBA.[82] This methodology was used in a short synthesis of the carpenter bee pheromone **203**.[83] The amide–allylsilane **199** was prepared as shown in Scheme 51. Highly stereoselective alkylation of **199** produced the amide–allylsilane **200**, which was treated with MCPBA to give the γ-lactone **201** in 53% yield. Formation of the γ-lactone took place via the corresponding epoxide, which undergoes ring-closure to a 5-membered iminium ion under the reaction conditions. Subsequent hydrolysis gave the γ-lactone **201**.

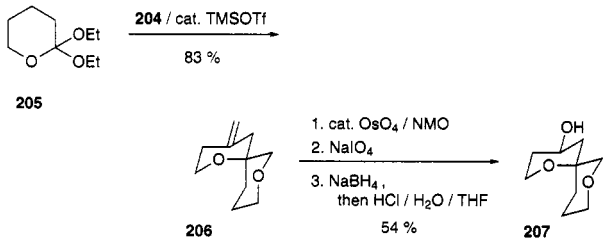
Scheme 52



Compound **201** was converted into the deconjugated δ-lactone **202** using $BF_3{\cdot}Et_2O$. Catalytic hydrogenation of **202** provided the desired natural product **203**.

2.6.4. Intramolecular Silyl-Modified Sakurai Reaction. The intramolecular silyl-modified Sakurai (ISMS) reaction is a powerful tool for the synthesis of dihydro- and tetrahydropyrans as well as spiro ketals as was recently demonstrated by Markó.[84] Thus, homoallylic ethers could be produced in one step from carbonyl compounds, allylsilanes, and trimethylsilyl ethers via ISMS reaction using trimethylsilyl triflate (TMSOTf) as catalyst. The mechanism outlined in Scheme 52 probably involves the *in situ* generation of an oxonium cation, which is intramolecularly trapped by an allylsilane.

Scheme 53



Interestingly, ketals and acetals also proved to be excellent substrates for the ISMS reaction.

The ISMS reaction was applied to a short and stereocontrolled synthesis of the simple pheromone **207**, a minor component of the rectal gland secretion of the female *Dacus oleae* fruit fly.[85] Annulation of ortholactone **205**, derived from δ-valerolactone, produced [5,5]-spiroketal system **206** in 83% yield (Scheme 53).

Oxidative cleavage of the exomethylene unit followed by sodium borohydride reduction of the resulting ketone and acidic workup afforded the desired pheromone **207** (equatorial/axial ratio ≈ 19:1) in 54% overall yield.

The same basic methodology was used to construct the spiroketal subunit **209** of milbemycin β_3 (**208**)[86] (Scheme 54).

Reaction of ortholactone **205** in the presence of catalytic amounts of TMSOTf with silyl ether **210** gave the desired spiroketal **212** in 68% yield (Scheme 55).

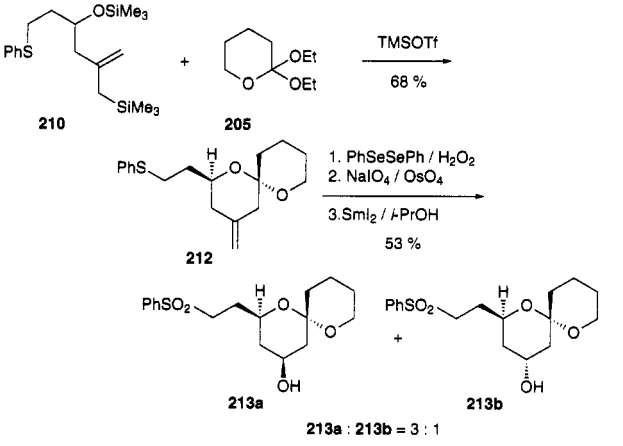
Chemoselective sulfide oxidation,[87] followed by oxidative cleavage of the exocyclic double bond, and subsequent samarium(II) iodide-mediated Meerwein–Pondorf reduction[88] of the resulting ketone afforded the desired β-hydroxy spirobicycle **213a** as the major isomer.

A modification of the ISMS protocol allowed a particularly short synthesis of a model compound for a tetrahydropyran subunit of the antifungal antibiotic ambruticine (**214**)[89] (Scheme 56).

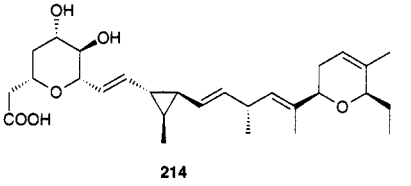
Upon treatment of an aldehyde with silyl ether **215** as the annulating agent in the presence of $BF_3{\cdot}Et_2O$, triple condensation took place to yield tetrahydropyran derivative **216** (Scheme 57).

The proposed mechanism, starting with an ene-type reaction, is outlined in Scheme 58. Condensation of the free hydroxyl function in **219** with unreacted aldehyde generates oxonium cation **220**, which undergoes intramolecular Sakurai reaction to give the exomethylene tetrahydropyran **216** with all substituents in an equatorial position.

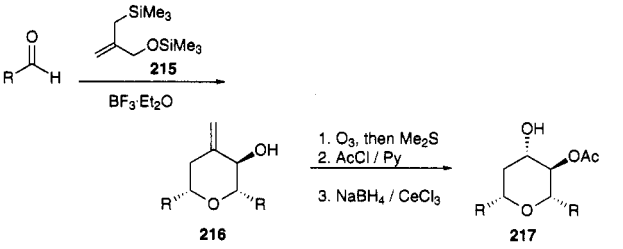
Scheme 55



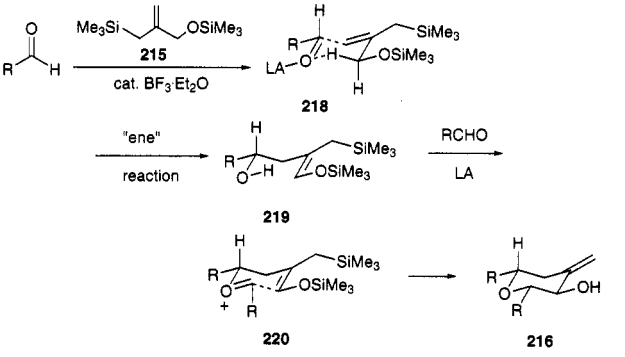
Scheme 56



Scheme 57

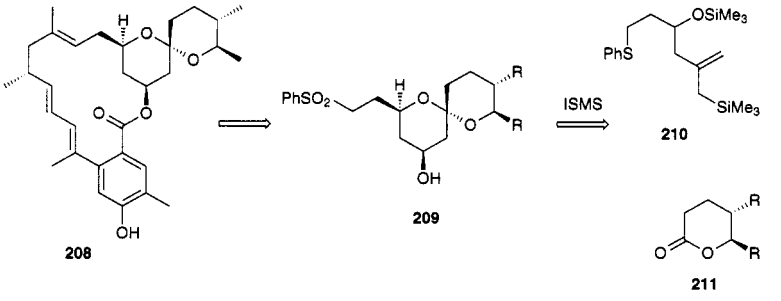


Scheme 58

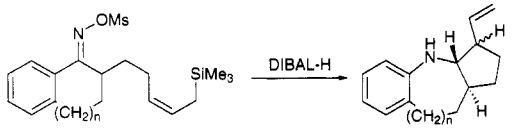


Cleavage of the exocyclic double bond followed by acetalization, and stereoselective reduction provided the pure *anti*-hydroxy acetate **217**, containing the correct functionalities and relative configurations of

Scheme 54



Scheme 59



221 : n = 1
222 : n = 2

223 : n = 1
224 : n = 2

the left-hand tetrahydropyran subunit of ambruticine (**214**). The right-hand portion of **214** has also been prepared by the same group, featuring an ISMS condensation of a functionalized vinylsilane with an aldehyde.[90]

2.6.5. Tandem Reactions: Beckmann Rearrangements/Allylsilane Cyclizations. In a recent study Schinzer et al. have shown that the Beckmann rearrangement can be combined with an allylsilane cyclization to form various heterocyclic systems by way of a tandem reaction.[91] For example, this methodology can be used in the synthesis of tricyclic 7- and 8-membered heterocyclic ring systems which are important skeletons in a number of pharmacologically important natural and unnatural products (Scheme 59).

An approach toward the pentacyclic natural product (±)-cephalotaxine (**228**) was developed utilizing the tandem sequence as a key step.[92] The starting material for the tandem reaction was synthesized in a straightforward way (Scheme 60).

Oxime mesylate derived from **226** was cyclized in the presence of 4 equiv of DIBAL-H to provide the tetracyclic azepane derivative **227**. Cyclization product **227** represents an useful intermediate toward the total synthesis of cephalotaxine **228**.

III. Propargylsilanes in Natural Product Synthesis

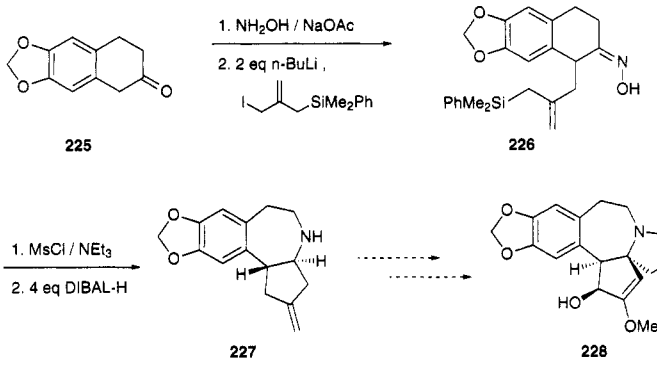
1. Propargylsilane-Terminated Biomimetic Polyene Cyclizations

1.1. Total Synthesis of (±)-β-Amyrin

A total synthesis of the racemic pentacyclic triterpenoid β-amyrin (**242**) has been reported by Johnson et al.[93] utilizing a propargylsilane-terminated cyclization of a polyolefin having a fluorine atom as the cation-stabilizing auxiliary[94] as key step. The success of this route relied upon earlier studies,[95] which showed that a fluorine atom, suitably positioned on the polyolefin, could effectively stabilize incipient cationic centers during acid-catalyzed cyclization, leading to greatly enhanced yields of tetracyclic and pentacyclic compounds.

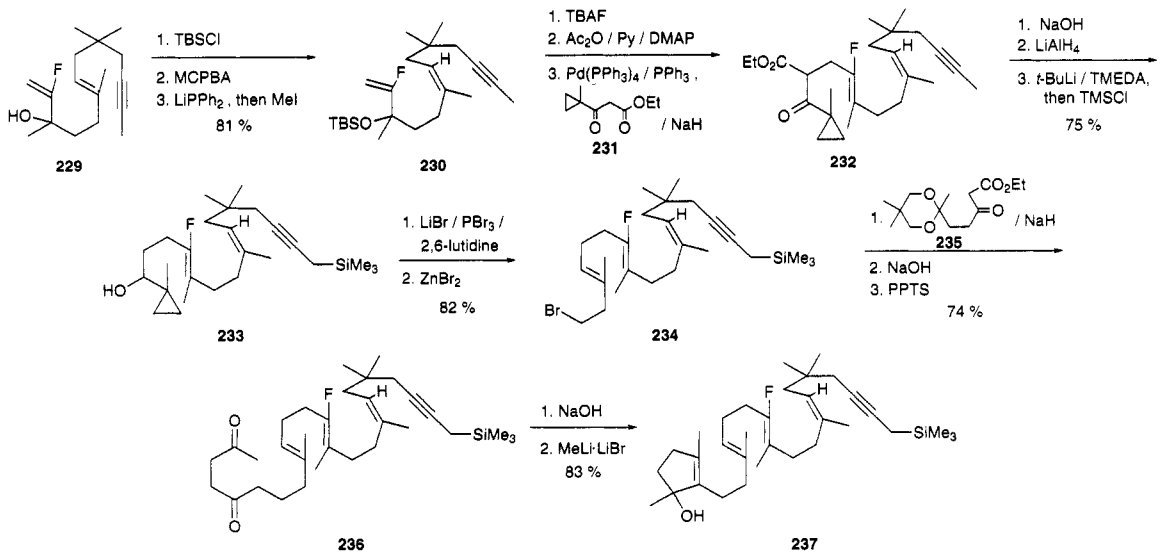
Preparation of the cyclization precursor cyclopentenenol **237** started from fluoro dienynol **229**, which was prepared in nine steps from mesityl oxide.[92] Transposition of the *trans*-trisubstituted alkene to the *cis* isomer **230**, after protection of the alcohol to

Scheme 60



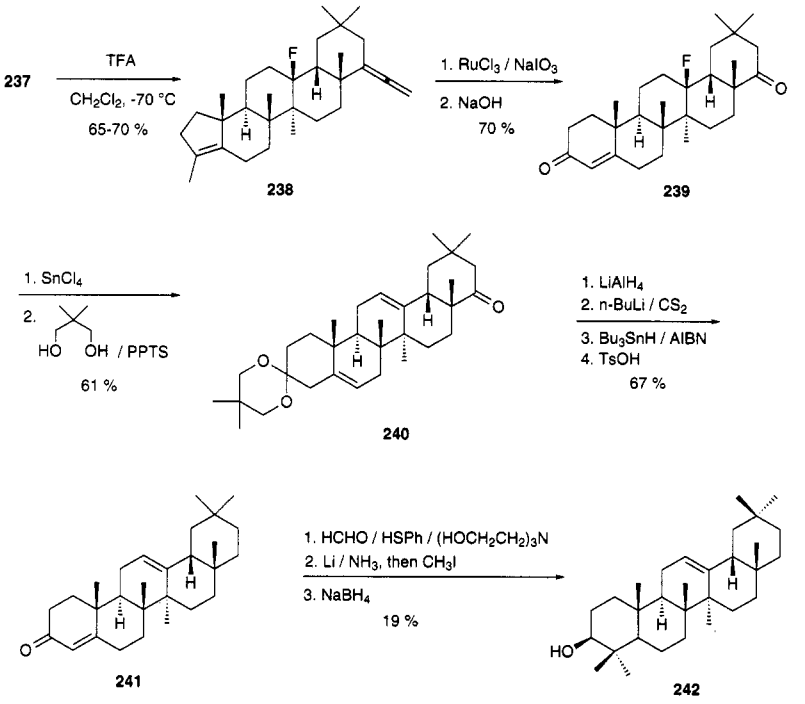
225 **226** **227** **228**

Scheme 61



229 **230** **231** **232** **233** **234** **235** **236** **237**

Scheme 62



prevent cyclic ether formation, was accomplished by the epoxidation/phosphine elimination route of Vedejs and Fuchs.[96] Removal of the alcohol protective group in **230** and acetylation provided the corresponding acetate (Scheme 61).

The trisubstituted 7-*trans*-fluoroalkene bond in **232** was established via the Trost methodology utilizing palladium-catalyzed alkylation[97] of keto ester **231** with the allylic acetate. Thus, the acetate was reacted with the sodium enolate of keto ester **231** in the presence of palladium tetrakis(triphenylphosphine) to afford keto ester **232** (*trans*/*cis* = 88:12) in 59% yield. Decarbethoxylation of **232**, followed by reduction of the ketone and incorporation of the propargylsilane moiety employing the Zweifel methodology[98] provided alcohol **233** in 75% yield. The Brady–Julia rearrangement[99] of **233** was accomplished via bromination with phosphorus tribromide, followed by zinc bromide-catalyzed rearrangement to give bromide **234**. Alkylation of the keto ester **235** with bromide **234**, subsequent decarbethoxylation, and deketalization gave diketone **236**. Intramolecular aldol reaction gave rise to the cyclopentenone, which was converted via 1,2-addition of a methyl group into the cyclization precursor **237**.

Biomimetic polyene cyclization of propargylsilane **237** was achieved in the presence of trifluoroacetic acid, to yield 65–70% pentacyclic product **238** establishing six of eight chiral centers of the pentacyclic triterpene in one step (Scheme 62).

Cyclization product **238** was subjected to oxidative cleavage of the allene moiety and the cyclopentene double bond to yield a triketone, which could be transformed under basic conditions into the enone **239**. Regioselective elimination of the fluorine atom was achieved by treatment of **239** with tin tetrachloride. Protection of the C3 ketone and selective removal of the C22 ketone using Barton methodology[100] afforded, after deprotection, the deoxygenated pentacycle **241**. Introduction of the 4,4-dimethyl group into the A ring was accomplished via (phenylthio)methylation of enone **241** followed by reductive methylation, and subsequent treatment with iodomethane. The synthesis was completed by reduction of the keto group to afford racemic β-amyrin (**242**) in 0.2% overall yield.

2. Iminium Ion–Propargylsilane Cyclizations

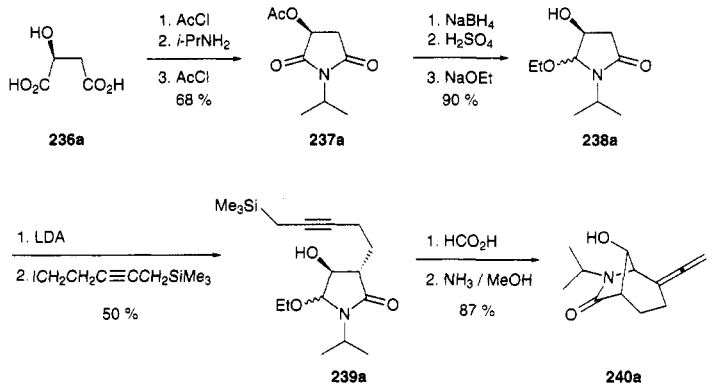
2.1. Synthesis of Peduncularine

The first total synthesis of the *Aristotelia* alkaloid peduncularine **247** featuring a propargylsilane terminated *N*-acyliminium ion cyclization to construct the azabicylo[3.2.1]octanone skeleton was described by Hiemstra and Speckamp.[101] Enantiomerically pure peduncularine **247** and its C7 epimer were prepared over 16 steps starting from (*S*)-malic acid (**236a**). Successive treatment of **236a** with acetyl chloride, isopropylamine, and again acetyl chloride resulted in the formation of enantiomerically pure imide **237a**. This was transformed upon regioselective reduction into the alcohol **238a**, followed by ethanolysis, and ethoxide-catalyzed transesterification. Deprotonation of **238a** with 2.1 equiv of LDA provided the corresponding β-hydroxy lactam dianion, which could be alkylated with 5-iodo-1-(trimethylsilyl)-2-pentyne[102] at low temperature to yield stereospecifically the 3,4-*trans*-lactam **239a** (Scheme 63).

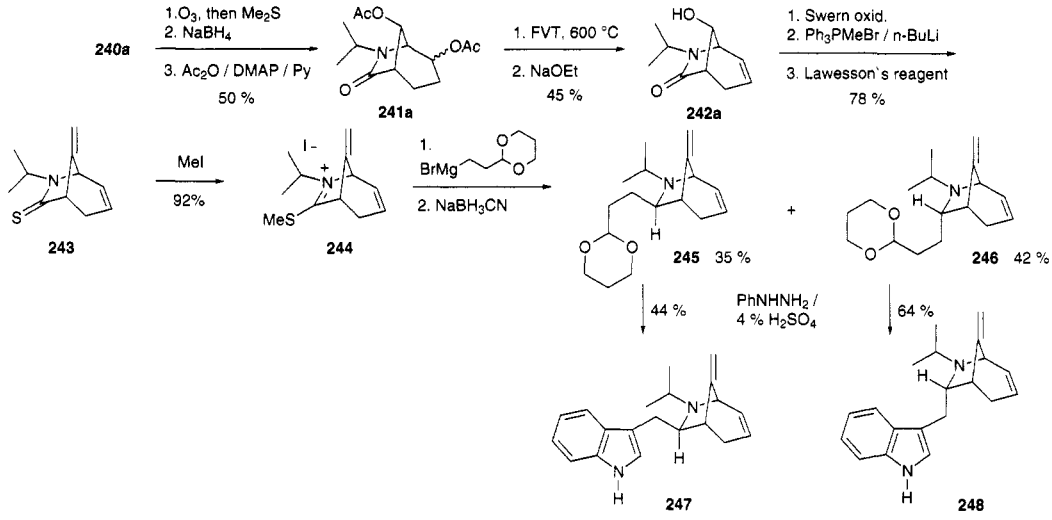
Upon treatment of **239a** with formic acid, *N*-acyliminium ion cyclization took place smoothly to afford bicyclic lactam **240a** in 87% yield after treatment of the crude product with methanolic ammonia to cleave formate esters.

Ozonolysis of the allene moiety in **240a** followed by reductive workup gave the corresponding ketone, which was converted into the diacetate **241a**. Pyro-

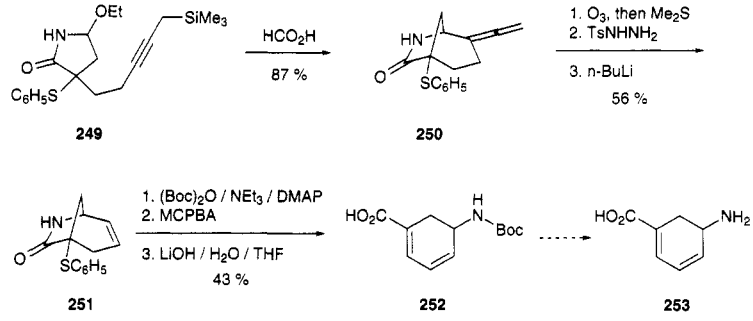
Scheme 63



Scheme 64



Scheme 65



lytic elimination of acetic acid from diacetate **241a** was achieved using flash-vacuum thermolysis (FVT) technique (600 °C) to produce the monoacetate, which was transformed to the alcohol **242a** (Scheme 64).

Oxidation of the hydroxy group under Swern conditions and Wittig olefination of the resulting ketone proceeded in high yield. Transformation into the (methylthio)methyleneiminium salt **244** was accomplished via the corresponding thiolactam **243**.[103] Iminium salt **244**, which appeared to be very reactive toward Grignard reagents, was treated with [3,3-(trimethylenedioxy)propyl]magnesium bromide and sodium cyanoborohydride to yield the alkylation products **245** and **246** in a 45:55 ratio. Chromatographic separation and Fischer indole synthesis[104] with each individual isomer provided peduncularine (**247**) and 7-epipeduncularine (**248**) in 44% and 64% yield, respectively.

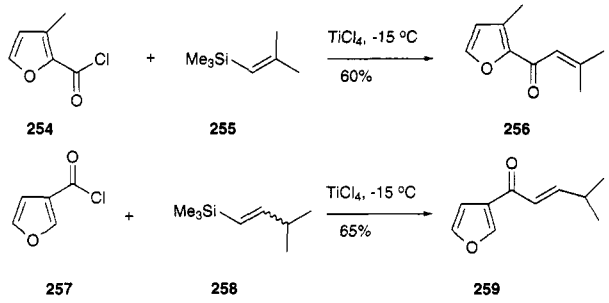
2.2. Synthesis of (±)-Gabaculine

A key step in the regioselective synthesis of (±)-gabaculine (**253**) using 5-ethoxy-pyrrolidone as dipolar bifunctional reagent is the cyclization of functionalized propargylic silane **249**.[105] Ring closure took place upon dissolution of **249** in formic acid (Scheme 65).

Ozonolysis of the allene moiety and subsequent Shapiro reaction[106] provided the desired bicyclic lactam **251**, which was hydrolyzed using Grieco's method.[107] Oxidation of sulfur and sulfoxide elimination gave *N*-(*tert*-butoxycarbonyl)gabaculine (**252**), which has been transformed to the natural product **253** by Fráter et al.[108]

A similar methodology was employed in a formal total synthesis of anatoxin A.[109]

Scheme 66



254 255 256

257 258 259

IV. Vinylsilanes in Natural Product Synthesis

1. Intermolecular Reactions of Vinylsilanes

1.1. Syntheses of Dehydroelsholtzione and Isoegomaketone

Vinylsilanes as convenient intermediates for short syntheses of dehydroelsholtzione (Naginata ketone) (**256**) and isoegomaketone (**259**) were reported by Pillot[110] (Scheme 66).

Acid chlorides **254** and **257** could be coupled in the presence of titanium tetrachloride and vinylsilanes **255** and **258** to the desired natural products **256** and **259**.

2. Vinylsilane-Terminated Cyclopentenone and -hexenone Annulations

Paquette and co-workers have developed a new cyclopentenone annulation sequence which involves Friedel–Crafts acylation of a vinylsilane with an α,β-unsaturated acid chloride followed by Nazarov cyclization.[111]

The overall concept is shown in Scheme 67. 2-Methylcyclopentanone **260** was transformed into the desired vinylsilane **261** via the Shapiro protocol. Reaction of **261** with β,β-dimethylacryloyl chloride (**262**) in the presence of aluminum trichloride provided **263** which cyclized under Nazarov conditions with tin tetrachloride.

The same authors used this concept in a total synthesis of muscone (**268**) starting with cyclic vinylsilane **265** (Scheme 68). Compound **265** and crotonyl chloride were first treated with aluminum trichloride and then with boron trifluoride etherate to yield a mixture of the desired Nazarov cyclization products **266**. Isomerization with Rh(III) catalysis provided the required enone **267** which was transformed into muscone **268** by known procedures.

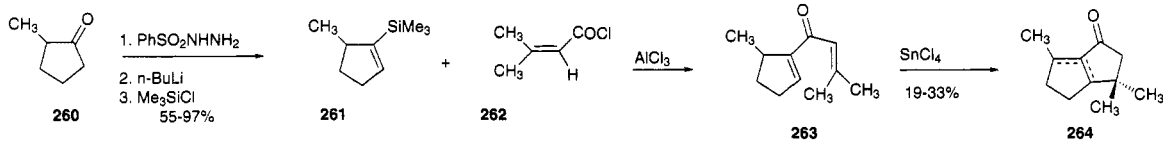
Denmark and Kuwajima have reported very similar routes to functionalized *trans*-hydrindanones via either endocyclic cyclization mode (Denmark)[112] or by exocyclic cyclization (Kuwajima)[113] using acylium ions as initiators. In a tandem sequence (copper-catalyzed addition of a Grignard reagent followed by alkylation with the required α-bromo ester) compound **270** was obtained and converted to the corresponding acid chloride. In the presence of aluminum trichloride electrophilic cyclization was accomplished to yield compound **271** (Scheme 69).

A functionalized 6-membered enone was used by Kuwajima. Deprotection of the ester with iodotrimethylsilane afforded acid **274**. Conversion to the acid chloride followed by a cyclization via the exo-mode yielded the desired alkylidene hydrindanone **275** as a single double-bond isomer (Scheme 70).

Both routes can be used for the synthesis of CD ring systems in steroid synthesis.

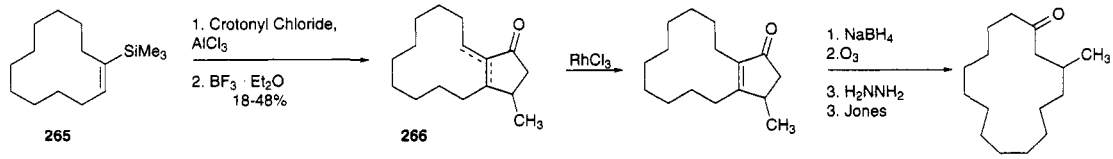
Burke reported a spiro-annulation for the preparation of spiro[4.5]decadienones.[114] Vinylogous ester **276** was treated with [β-(trimethylsilyl)vinyl]lithium to obtain dienone **277**. Reduction with LAH followed by Claisen rearrangement provided the expected aldehyde, which was oxidized with Jones reagent to carboxylic acid **278**. Conversion to the acid chloride with oxalyl chloride followed by direct cyclization with titanium tetrachloride via an acylium ion gave enone **279** in excellent yield (Scheme 71).

Scheme 67



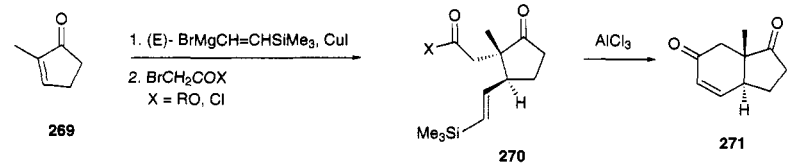
260 261 262 263 264

Scheme 68



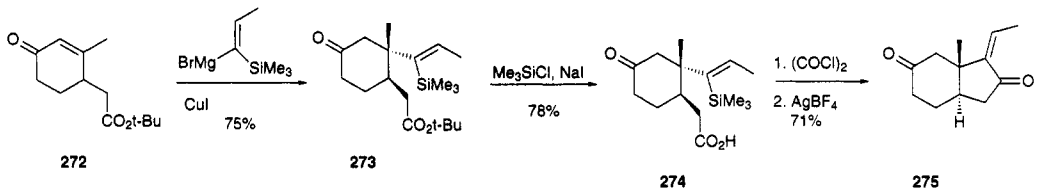
265 266 267 268

Scheme 69

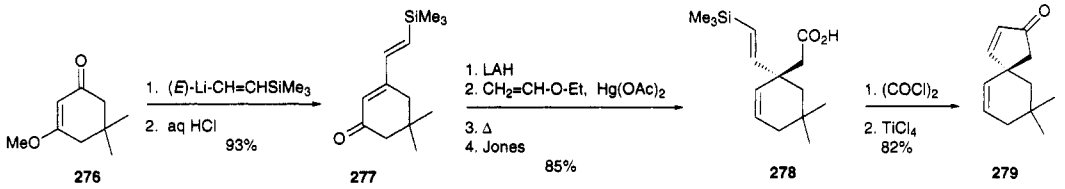


269 270 271

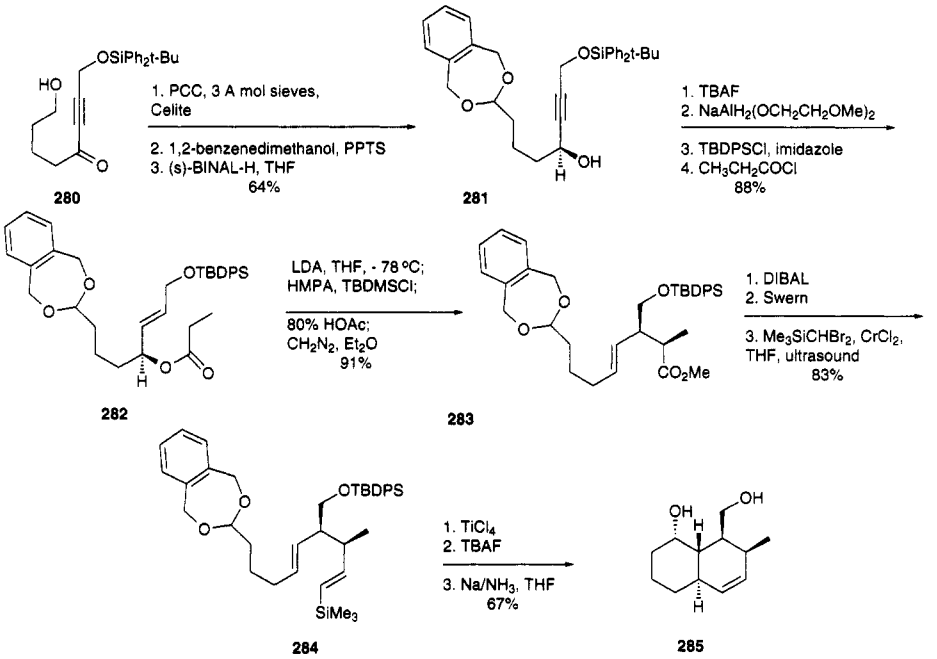
Scheme 70



Scheme 71



Scheme 72



3. Vinylsilane-Terminated Bicyclizations

3.1. Total Syntheses of (+)-Dihydrocompactin and (+)-Compactin

Syntheses of (+)-dihydrocompactin (**287**) and (+)-compactin (**288**) featuring cationic polyene cyclizations mediated by a vinylsilane have been reported by Burke.[115]

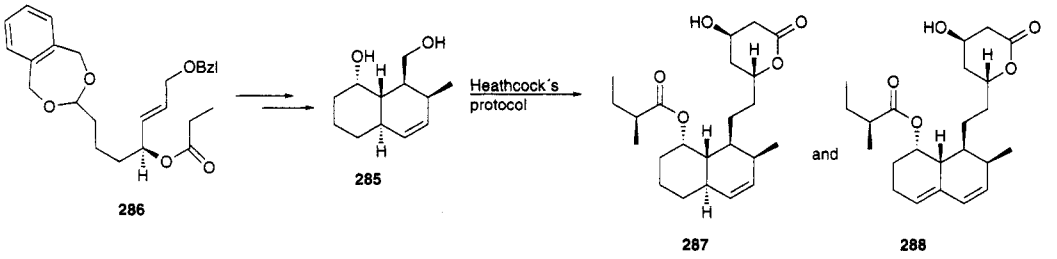
Achiral ynone **280** was constructed by addition of an appropriate acetylide to δ-valerolactone (Scheme 72). Oxidation to the aldehyde followed by formation of the acetal with 1,2-benzenedimethanol yielded the protected propargyl ketone. Asymmetric reduction with S-BINAL-H provided propargyl alcohol **281** in 90% enantiomeric excess. Protecting group manipulation (temporary desilylation and resilylation), stereoselective alkyne reduction with sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al), and acetylation with propionyl chloride resulted in the formation of the *trans*-allylic propionate **282**. Two contiguous chiral centers in **283** were established via an Ireland–Claisen rearrangement which proceeds via the (*E*)-silylketene acetal. Formation of the required vinylsilane residue was accomplished by synthesis of the aldehyde and employing Takai's[116] procedure to give *trans*-vinylsilane **284**. Acetal **284** was treated with titanium tetrachloride to give bicyclic octalins in 73% yield which were separated by flash chromatography. Fluoride-induced cleavage of the silyl ether and reductive removal of the acetal remnant gave **285**. By the use of a different protecting group in **286** (benzyl ether) the stereoselectivity of the Ireland–Claisen rearrangement could be increased to 13:1.

After deprotection of the benzylic ether linkages with sodium in ammonia scalemic diol **285** could be obtained in 12 steps from δ-valerolactone. Dihydrocompactin **287** and compactin **288** were obtained using Heathcock's protocol[117] (Scheme 73).

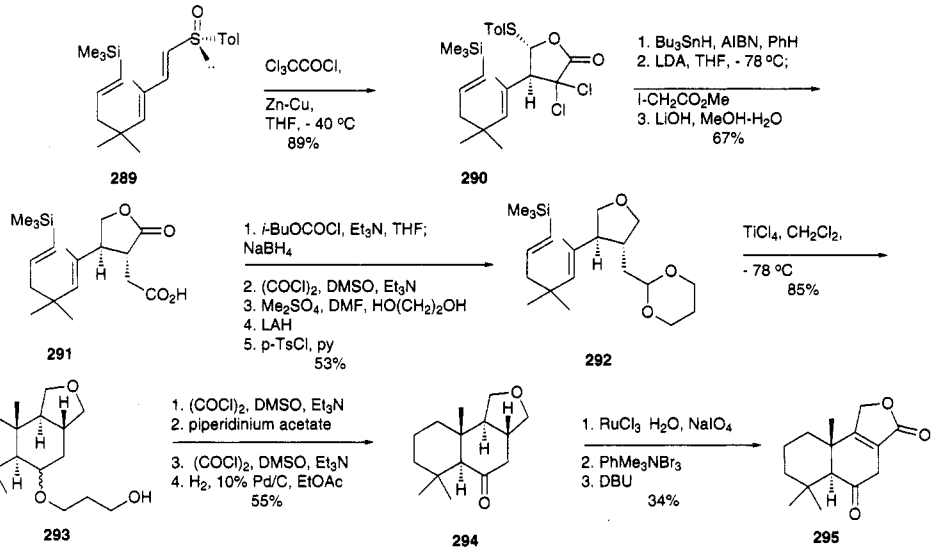
3.2. Total Syntheses of (+)-Fragolide and (–)-Pereniporin B

In a second set of syntheses, using a vinylsilane-mediated cationic bicyclization with acetal cleavage as the initiator, Burke demonstrated again the usefulness of such a strategy. Enantioselective syntheses of (+)-fragolide (**295**) and (−)-pereniporin B

Scheme 73



Scheme 74



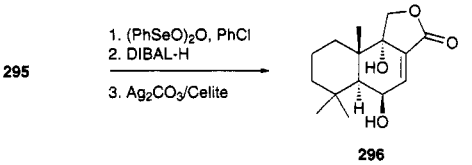
(**296**) were reported with a transfer of chirality from sulfur to carbon.[118]

Treatment of vinylsulfoxide **289** with dichloroketene, generated *in situ*, gave the desired lactone **290** in 89% yield (Scheme 74). By a [3,3] sigmatropic rearrangement via a chair-like transition state the asymmetric β- and γ-carbon stereocenters were established from asymmetry in sulfur. Dehalogenation and desulfurization were achieved by a radical reaction with tributyltin hydride/AIBN. The acetate side chain was hooked on by a stereoselective alkylation of lactone enolate with iodoacetate, to give, after ester hydrolysis, the *trans*-disubstituted lactonic acid **291**. After adjusting the oxidation states acetal **292** was formed by a procedure developed by Kantlehner using DMF/dimethylsulfate.[119] Lactone failed to give the desired bicyclization with a variety of Lewis acids, probably due to bidendate coordination of the Lewis acid with the acetal. This hypothesis could be supported by the easy bicyclization of tetrahydrofuran **292**, providing a 6:1 mixture of axial and equatorial epimers **293**. The acetal remnant was removed by Johnson's procedure;[120] Swern oxidation of the alcohols and catalytic hydrogenation provided the tricyclic ketone **294**.

Oxidation, bromination, and elimination of **294** gave (+)-fragolide (**295**) which was further transformed in three steps to (−)-pereniporin (**296**).

Compound **295** was transformed into the allylic selenoxide by treatment with benzeneselenic anhydride, which underwent a [2,3] shift to afford the allylic alcohol. DIBAL-H reduction provided ketone and lactone reduction. Reoxidation of the lactols with

Scheme 75



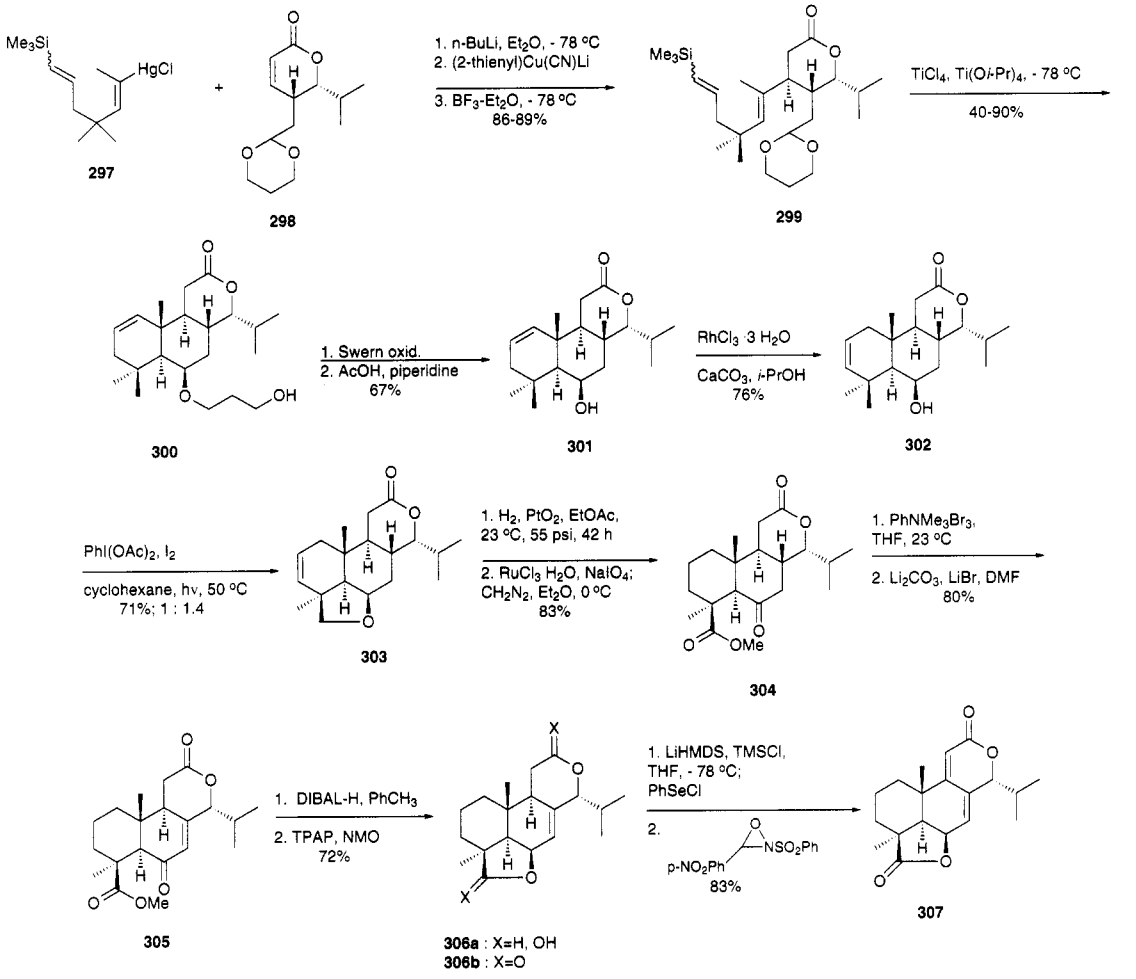
Fetizon's reagent gave (−)-pereniporin (**296**) (Scheme 75).

3.3. Total Synthesis of (−)-Nagilactone F

Very recently, Burke has synthesized (−)-nagilactone F (**307**) using a high yielding acetal-initiated/vinylsilane-terminated polyene cyclization.[121] The vinylsilane moiety was introduced by a conjugate addition of a cuprate prepared from **297** to optically pure pentenolide **298** in order to give δ-lactone **299** (Scheme 76).

Cationic bicyclization was achieved by treatment of **299** and a mixture of titanium tetrachloride and titanium tetraisopropoxide at low temperature. Both, the *Z*- and *E*-isomers of **299** cyclized to provide the *trans,anti,trans* tricyclic product **300**. Cleavage of the acetal remnant was accomplished by Swern oxidation of the hydroxypropyl ether side chain and subsequent elimination using Johnson's protocol to obtain **301**. A rhodium-catalyzed isomerization gave the thermodynamically more stable olefin **302** in 76% yield. Execution of the hypoiodite reaction using photochemical conditions established by Suárez[122] resulted in remote C−H activation to give the desired AB-ring bridging tetrahydrofuran **303** and its C10 angular methyl-derivatized isomer in a 1:1.4 ratio.

Scheme 76



Catalytic hydrogenation and subsequent oxidation of the resulting tetracyclic compound gave, after work-up with diazomethane, the desired tricyclic keto ester **304**. Bromination, dehydrobromination gave compound **305** in 80% yield which was reduced with excess of DIBAL-H in toluene at low temperature to obtain the reduced C-ring lactone carbonyl, stereoselective 1,2-enone reduction at C6, and reduction of the methyl ester to the corresponding aldehyde. Concomitant ring closure to the bis(hemiacetal) **306** and subsequent oxidation with the Davis oxaziridine[123] to trigger selenoxide elimination, followed by introduction of the final double bond provided (−)-nagilactone F (**307**).

4. Stereospecific Iminium Ion–Vinylsilane Cyclizations

4.1. Total Synthesis of (+)-Pumiliotoxin 251 D

A whole series of total syntheses of complex natural products focusing on alkaloids of the pumiliotoxin A class were reported by Overman. These alkaloids, isolated from the Ecuadoran poison-dart frog, have in common the unusual (*Z*)-6-alkylideneindolizidin (1-azabicyclo[4.3.0]nonane) ring skeleton and differ only in the side chain.

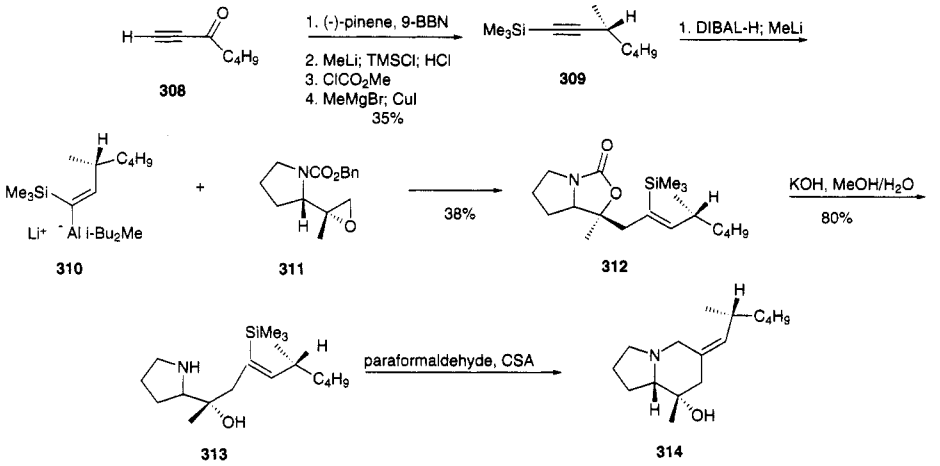
The first total synthesis was finished for dendrobatid toxin 251 D (**314**) in which, as the key step, a vinylsilane-terminated cyclization via exo-mode was realized.[124]

The functionalized side chain was synthesized by an asymmetric reduction of 1-heptyn-3-one **308** using Midland's[125] procedure with B-3-pinyl-9-borabicyclo-[3.3.1]nonane, prepared *in situ* from (−)-α-pinene and 9-BBN. The resulting (*S*)-1-heptyn-3-ol was obtained 92% ee and was further transformed into silyl carbonate. Subsequent cuprate addition afforded the desired propargylic coupling product **309** (Scheme 77).

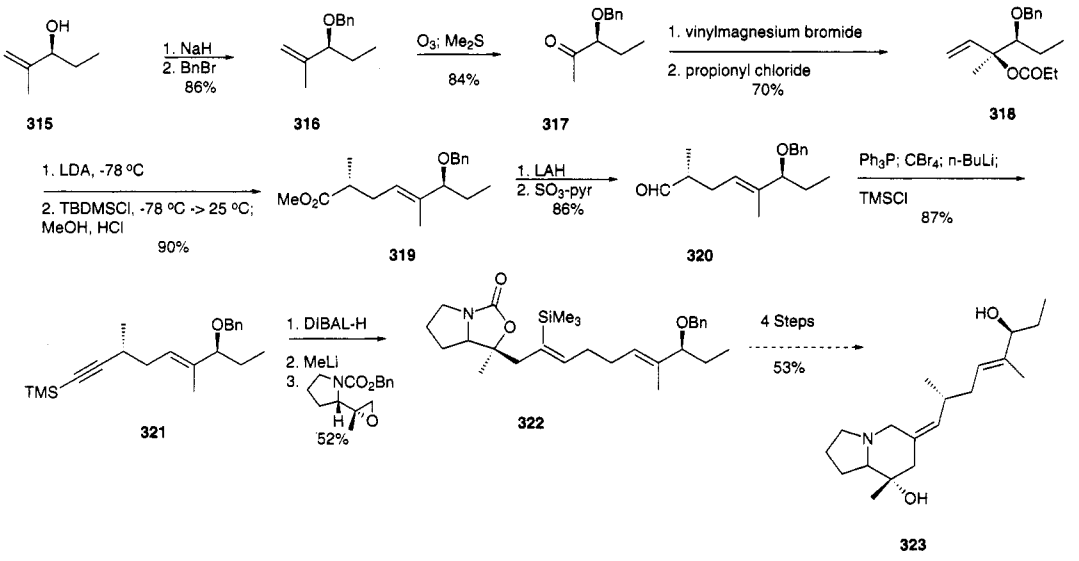
The cyclic portion was prepared starting from *N*-(carbobenzyloxy)-(*S*)-proline methyl ester. Addition of methylmagnesium iodide, followed by dehydration of the resulting alcohol with thionyl chloride yielded the desired olefin; epoxidation proceeded without any asymmetric induction to give a 1:1 mixture of epoxides which could be separated by chromatography to give **311**. In order to couple the two pieces compound **309** was *in situ* transformed into silylvinyl alanate **310** by addition of DIBAL-H and methyllithium. Alanate **310** reacted with epoxide **311** to generate the bicyclic carbamate **312**. The final step was accomplished when **312** was treated in refluxing ethanol with paraformaldehyde and *d*-10-camphorsulfonic acid (CSA) to yield pumiliotoxin 251 D (**314**).

The same general approach has been used to synthesize pumiliotoxin A[126] and B[127] containing more complex side chains.

Scheme 77



Scheme 78



4.2. Total Synthesis of (+)-Pumiliotoxin A

The complex side chain in pumiliotoxin A was synthesized starting with (*S*)-(−)-2-methyl-1-penten-3-ol (**313**) obtained by a Sharpless resolution. Benzylation and subsequent ozonolysis yielded ketone **317**. Addition of vinyl magnesium bromide following the cyclic Cram model gave in >99% stereoselectivity the desired allyl alcohol which was trapped *in situ* with propionyl chloride to provide ester **318**. Ireland–Claisen conditions (deprotonation with lithium diisopropylamide, addition of *tert*-butyldimethyl silyl chloride) afforded the rearranged ester **319** with complete stereocontrol. Reduction, oxidation, and transformation with the Corey–Fuchs protocol to the silylated acetylene side chain **321** demonstrated a powerful strategy to approach the problem of synthesizing the functionalized side chain. *In situ* preparation of the aluminum ate complex and epoxide opening gave the cyclic carbamate **322**. This was taken on by the way described before to obtain (+)-pumiliotoxin A (**323**) (Scheme 78).

4.3. Total Synthesis of (+)-Pumiliotoxin B

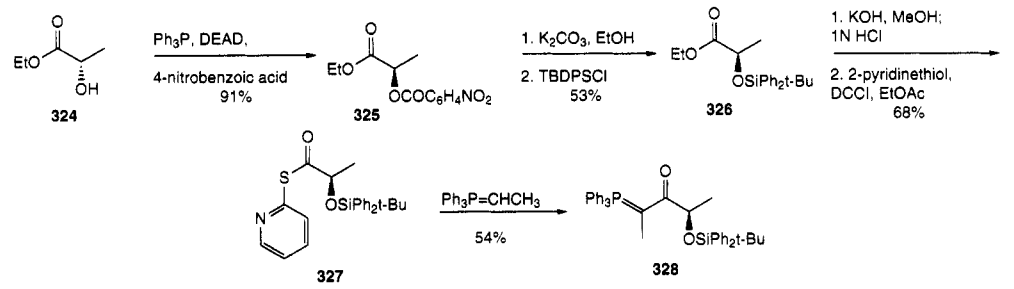
Finally, pumiliotoxin B (**336**) was synthesized using the same strategy for a different side chain. Mitsunobu reaction of ethyl L-lactate (**324**) gave the (*R*)-*p*-nitrobenzoyl ester **325** which was transformed in a straightforward way into the desired ylide **328** (Scheme 79).

The readily available nitrile **329** was reduced with DIBAL-H to a propanal derivative, which was directly condensed with ethynyllithium to give the racemic propargyl alcohol **330**. Chromatographic resolution of the diastereomeric carbamates, followed by carbamate cleavage gave the *R*-alcohol **332**. A Mitsunobu inversion yielded compound **333**. Hydroalumination with DIBAL-H, subsequent addition of methyllithium, and reaction with cyclic carbamate **311** gave compound **335**. Debenzylation, Swern oxidation, and final reaction with ylide **328** prepared previously, gave pumiliotoxin B (**336**) after cleavage of the silyl protecting group (Scheme 80).

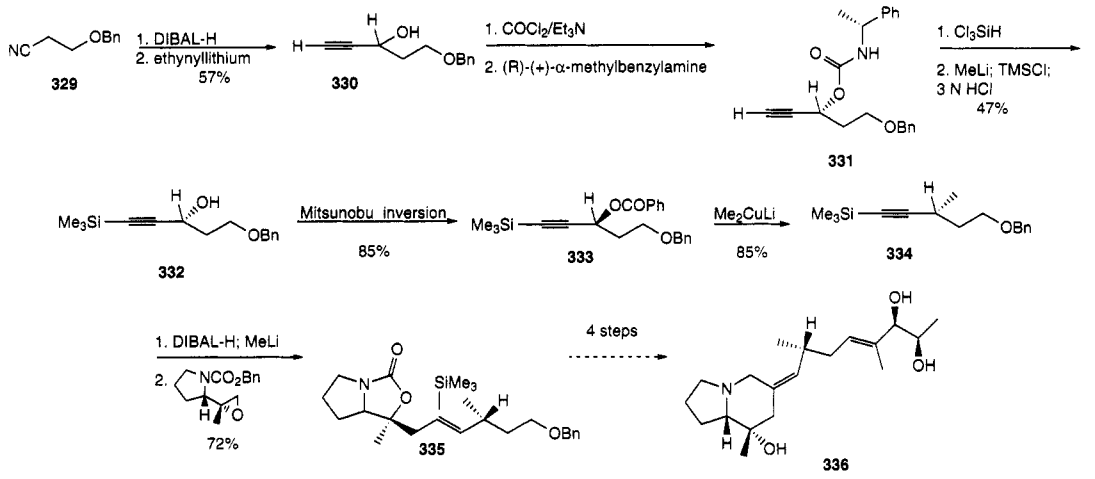
4.4. Total Synthesis of (±)-Epielwesine

A short synthesis of the *Amaryllidaceae* alkaloid epielwesine (**342**) was reported by Overman.[128] Sequential alkylation with [3,4-(methylenedioxy)phenyl]acetonitrile (**337**) with (*Z*)-(4-bromo-1-butenyl)-trimethylsilane and 1-bromo-2-chloroethane gave **338** in 62% yield. Reduction at low temperature of nitrile **338** with DIBAL-H provided Δ^1-pyrroline **339**, which was cyclized in the presence of trifluoroacetic acid in

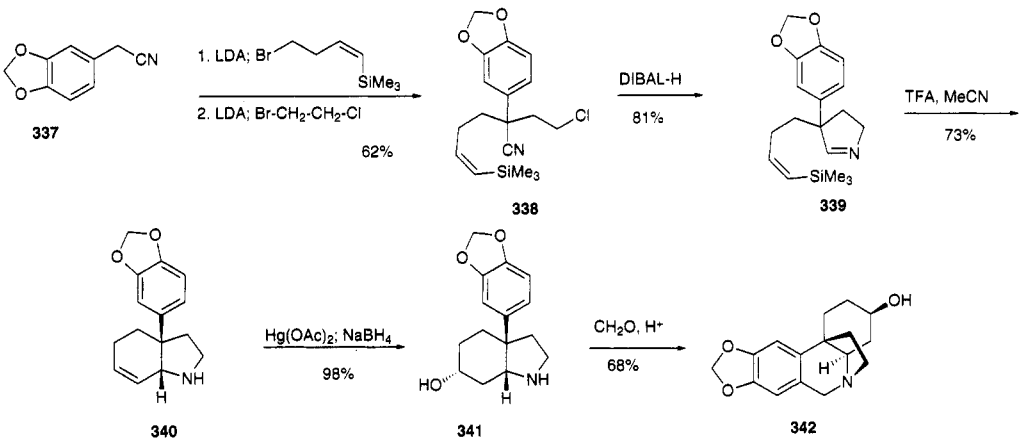
Scheme 79



Scheme 80



Scheme 81



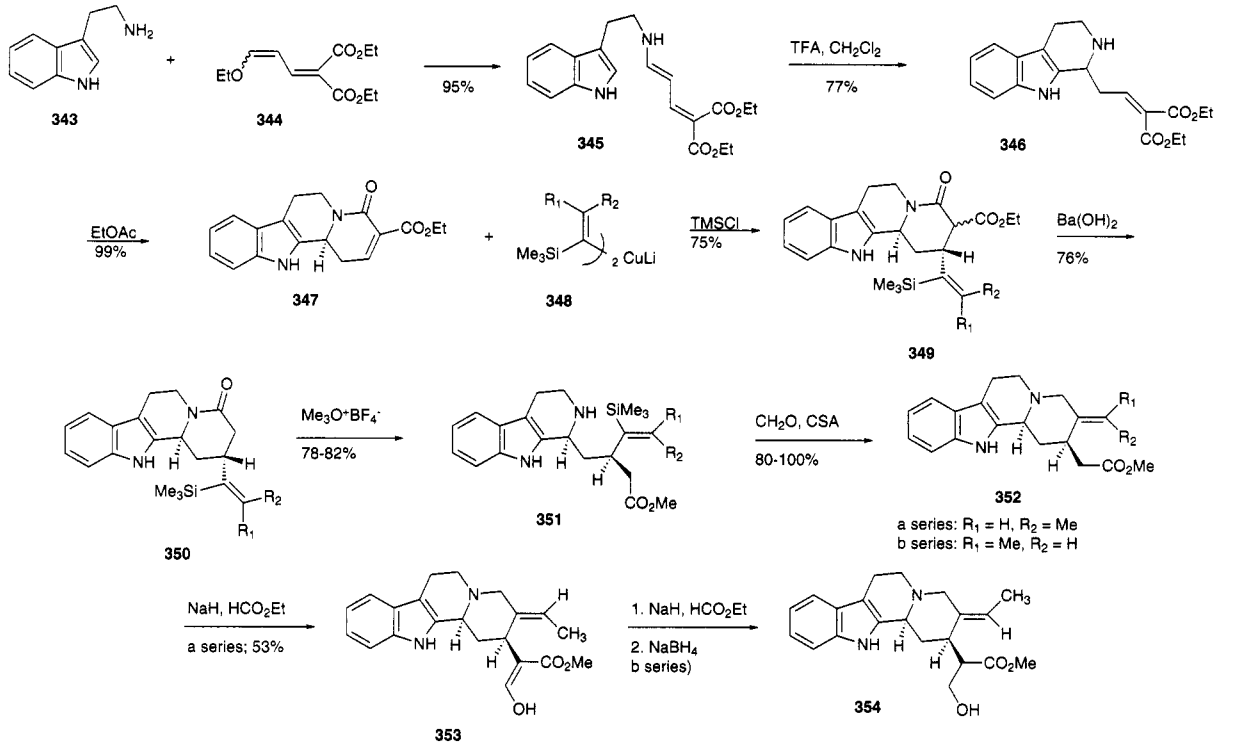
refluxing acetonitrile. Treatment of **340** with mercuric acetate followed by addition of sodium borohydride gave amino alcohol **341**. Pictet–Spengler cyclization gave *racemic* epielwesine (**342**) in 68% yield (Scheme 81).

4.5. Total Syntheses of (±)-Geissoschizine and (±)-(Z)-Isositsirikine

Total syntheses of (±)-geissoschizine (**353**) and (±)-(*Z*)-isositsirikine (**354**), intermediates in the biosynthesis of polycyclic indole alkaloids of the *Corynantheine-Yohimbine, Strychnos, Aspidosperma,* and *Iboga* groups, have been reported by Overman.[129]

Tryptamine **343** and alkoxy diene ester **344** condensed in ethanol give **345** as a single stereoisomer. Pictet–Spengler cyclization in the presence trifluoroacetic acid provided the labile tetrahydro-β-carbolin (**346**). The tetracyclic lactam **347** was best obtained by heating in ethyl acetate. The desired 1,4-addition was accomplished with cuprate reagent **348** in the presence of trimethylsilyl chloride to give compound **349**. After removal of the carbethoxy substituent by treatment with aqueous $Ba(OH)_2$ the facial selectivity (93%) of the 1,4-addition could be determined. Lactams **350** could be cleaved by addition of freshly prepared trimethyloxonium tetrafluoroborate in the presence of 2 equiv of 2,6-di-*tert*-butylpyridine at room temperature and subsequent hydrolysis of the resulting imidate salt to provide vinylsilane esters **351**. Cyclization was achieved under standard conditions (paraformaldehyde, camphorsulfonic acid) to give (a series) (19*Z*)-methyl geissoschizoate, which was taken on to geissoschizine (**353**) by formylation using Winterfeldt's[130] procedure. (*Z*)-Isositsirikine (**354**, b series) was obtained via a final reduction with

Scheme 82



sodium borohydride using Winterfeldt's protocol (Scheme 82).

5. Stereospecific Acyliminium Ion–Vinylsilane Cyclizations

5.1. Total Synthesis of (+)-Streptazolin

Overman's approach on (+)-streptazolin (**364**) was based on two considerations: (1) The absolute stereochemistry of L-tartaric acid transcripts directly into carbons 2a and 3 of the target molecule, and (2) tetrahydropyridines should be readily available via acyliminium ion–vinylsilane cyclizations.[131]

The amine **355** is available from 3-butyn-1-ol in six steps and was heated under dehydration conditions with the known anhydride **356** to give the desired cyclic imide **357**. Reduction of **357** with sodium borohydride, followed by cyclization initiated via addition of trifluoroacetic acid afforded a single bicyclic product **359**. A crystalline carbamate ester **360** was obtained by *O*-alkylation of the amide and subsequent trapping with ethyl chloroformate. Simple treatment of **360** with *sec*-butyllithium gave bicyclic enone **361** which was further manipulated by additon of boron tribromide to provide epoxy ketone **362**. The synthesis of (+)-streptazolin (**364**) was completed by a three-step sequence earlier developed by Kozikowski and Park.[132] Compound **362** was treated with ethylidenetriphenylphosphorane, sodium acetate, and sodium methoxide to provide a 1:2 mixture of (+)-streptazolin (**364**) and its *E*-ethylidene stereoisomer (Scheme 83).

6. Radical-Initiated Cyclization Terminated by a Vinylsilane

6.1. Total Synthesis of (–)-Dihydroxyheliotridine

(–)-Dihydroxyheliotridine (**371**) was recently synthesized by Hart et al. via a radical-initiated cyclization terminated by a vinylsilane.[133] A simple acetylene precursor **365** was transformed in two steps into the desired vinylsilane **366**. Mitsunobu reaction with chiral imine **367** provided N-alkylated imine **368** in 96% yield. Subsequent reduction with sodium borohydride and transformation with thiophenol gave the cyclization precursor **369**. Radical-initated cyclization with tributyltin hydride in the presence of AIBN gave pyrrolizidine **370** in 63% yield. The synthesis was completed by sila Baeyer–Villiger rearrangement, followed by acetate cleavage with lithium aluminum hydride to give (–)-dihydroxyheliotridine (**371**) in 78% yield (Scheme 84).

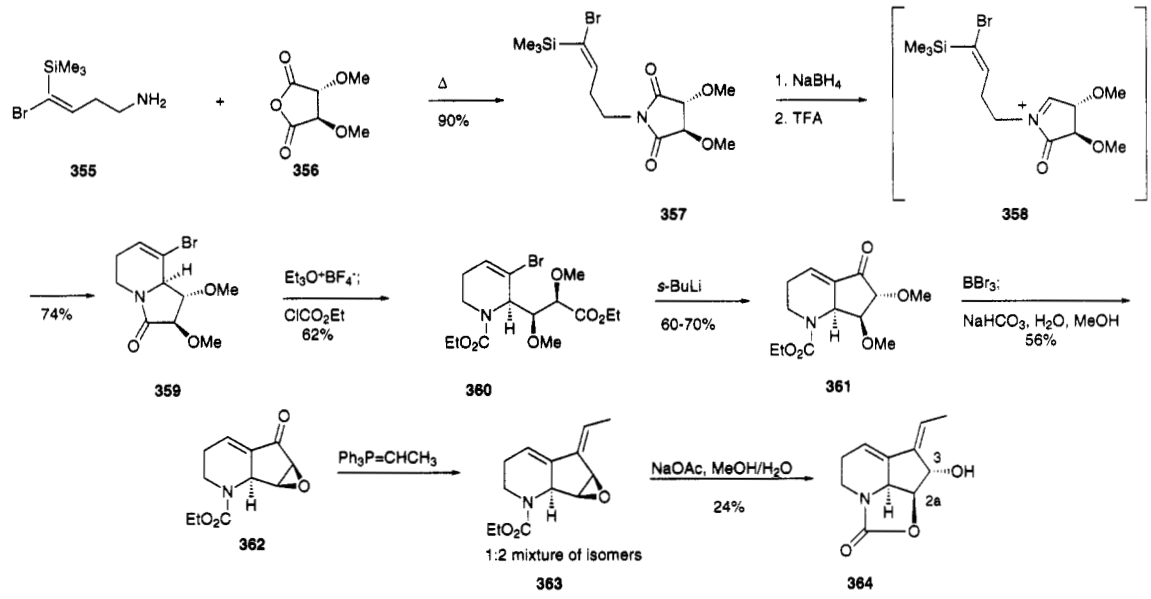
7. Stereospecific Oxonium Ion–Vinylsilane Cyclizations

7.1. Total Synthesis of (–)-Laurenyne

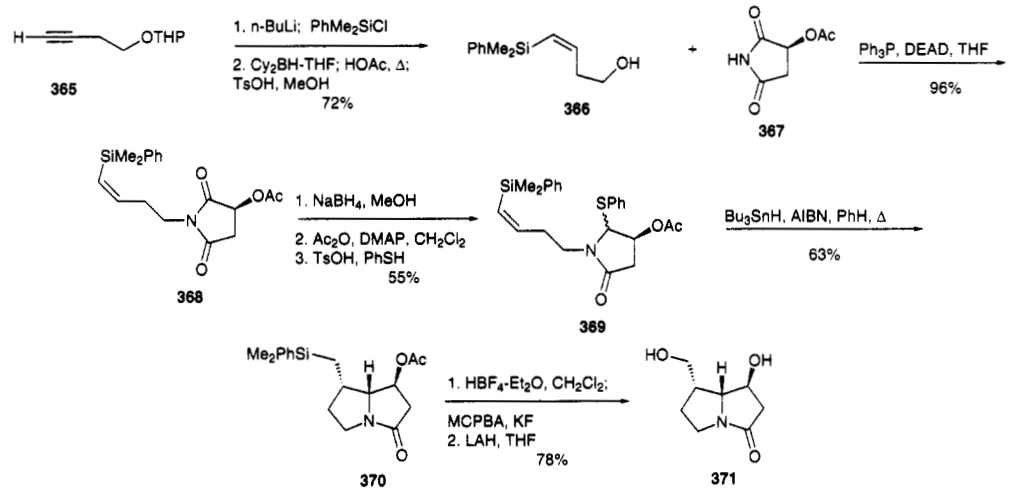
A highly stereocontrolled and enantioselective synthesis of (–)-laurenyne (**386**) was reported by Overman.[134] Key step in this synthesis is an oxonium ion–alkene cyclization by way of an intramolecular ene reaction of a mixed acetal. The synthesis also demonstrated that the absolute configuration for natural laurenyne had to be revised to 2*R*,7*R*,8*R*.

The alkenyllithium reagent derived from 1-bromo-1-(trimethylsilyl)ethene (**372**) was alkylated by oxetane in the presence of borontrifluoride etherate. Oxidation of the resulting alcohol was followed by a *Z*-stereoselective Horner–Wittig reaction to generate the *Z*-dienoate **374** and its *E*-isomer in a ratio of 25:1. Compound **374** was reduced with DIBAL-H to provide the *cis*-disubstituted allylic alcohol **375**. Sharpless catalytic asymmetric epoxidation of **375** afforded epoxide **376** in chemical yields of 78–85% with an enantiomeric excess of 78–81%. Epoxide **376** was regioselectively opened with chloride ion at the 3-position in the presence of Ti(O*i*-Pr)$_4$. The

Scheme 83



Scheme 84



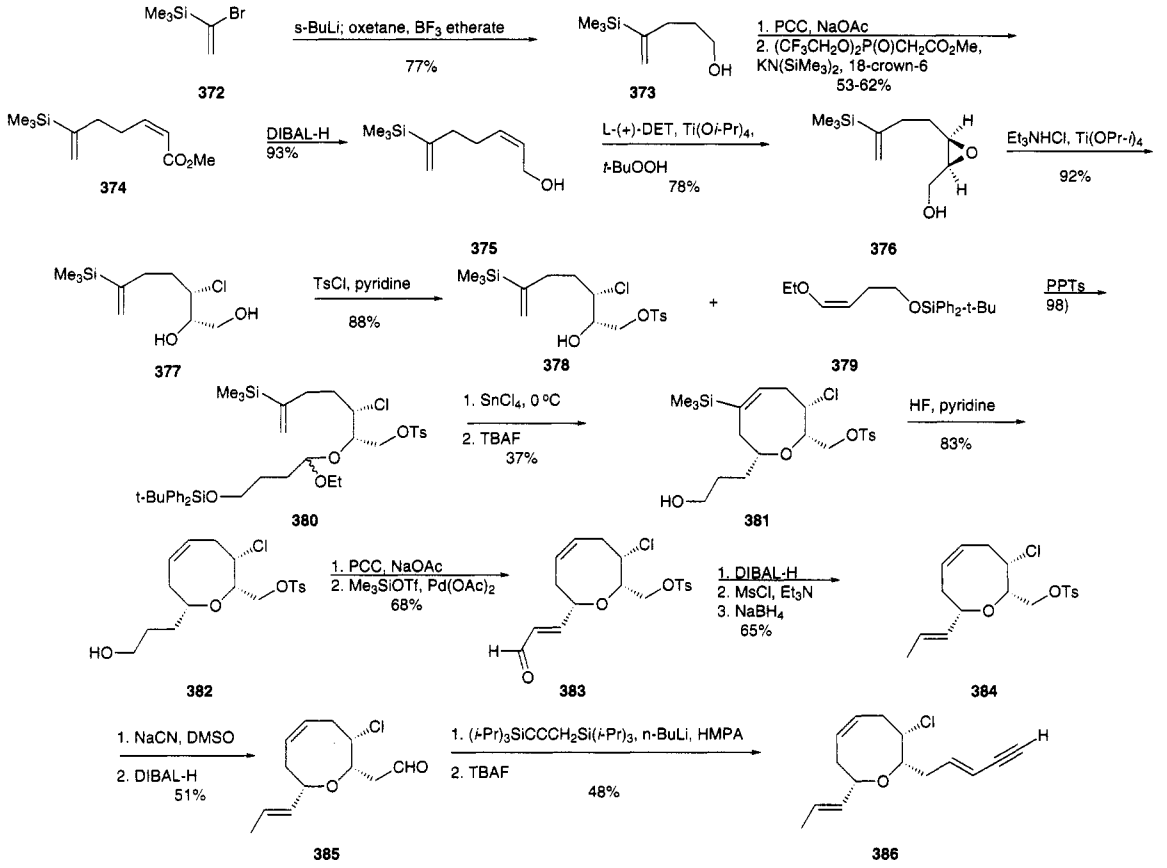
chloro diol **377** and its regioisomer were produced in a 3:1 ratio. The primary alcohol in **377** was converted into the tosylate. Key acetal **380** was prepared in the presence of pyridinium *p*-toluenesulfonate in 98% yield by reaction with a slight excess of enol ether **379**. Cyclization was brought about with stannic chloride followed by *O*-desilylation to produce cyclic ether product **381**. Protodesilylation followed by PCC oxidation to the aldehyde, and subsequent Saegusa–Ito oxidation gave compound **383**. Introduction of the propenyl side chain was achieved by reduction, mesylation, and displacement with sodium borohydride to give **384**. The remainder of the synthesis was completed by displacement of the tosylate with sodium cyanide, DIBAL-H reduction, followed by Peterson olefination, and a final desilylation to provide (−)-laurenyne (**386**) (Scheme 85).

7.2. Total Synthesis of (+)-Isolaurepinnacin

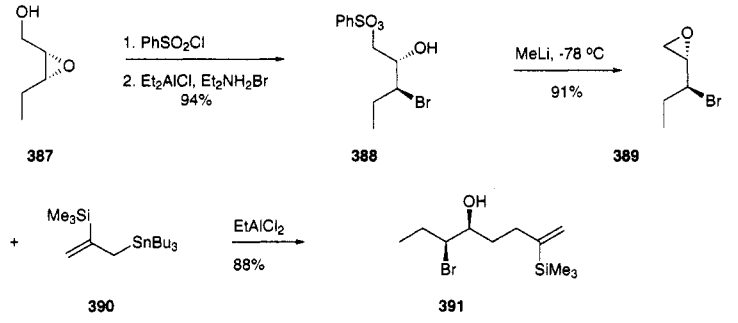
The first total synthesis of (+)-isolaurepinnacin (**400**) has been achieved by Overman[135] with high stereoselectivity in 12 steps and 15% overall yield. The natural product **400** was approached starting from *cis*-2-penten-1-ol which was epoxidized using Sharpless' protocol to give epoxy alcohol **387** in 78% yield and 80% ee. Phenylsulfonylation of **387** followed by regioselective opening of the epoxy sulfonate afforded bromohydrin **388** in 94% yield. Transformation of **388** to the volatile bromo epoxide **389** was achieved with methyllithium at low temperature. Reaction of **389** in the presence of ethylaluminum dichloride with the allyltin reagent **390** gave vinylsilane alcohol **391** (Scheme 86).

The (*R*)-α-chloroacetal **397** was synthesized from commercially available 2,2-dimethoxyethanol (**392**). Swern oxidation followed by *in situ* reaction of glyoxal dimethyl acetal with [3-(triisopropylsiloxy)propynyl]-lithium gave **393**. Alcohol **393** was oxidized using Jones' protocol and finally enantioselectively reduced by Noyori's[136] procedure to obtain enantiopure (*S*)-alcohol after chromatography. Catalytic hydrogenation provided **394**, and subsequent triflate formation followed by reaction with tetrabutylammonium chloride gave enantiopure (*R*)-α-chloroacetal **395** in 71% yield. Exchange of the methoxy group by bromine provided the corresponding α-bromo ether **396** (Scheme 87).

Scheme 85



Scheme 86



The synthesis of (+)-isolaurepinnacin (**400**) was efficiently finished by coupling of the optically active fragments **391** and **396** to provide cyclization precursor **397** in 95% yield. Cyclization was achieved best with boron trichloride in methylene chloride to give polyfunctionalized 7-membered ring ether **398** in 90% yield including removal of the silyl protecting group. Finally, the enyne side chain was elaborated, by first oxidation using the Dess–Martin[137] protocol, followed by reaction with ethynylmagnesium bromide to afford **399**. Dehydration was achieved via the corresponding hexacarbonyldicobalt complex, subsequent triflate formation, and final oxidative decomplexation with ceric ammonium nitrate to obtain (+)-isolaurepinnacin (**400**) in 65% yield.

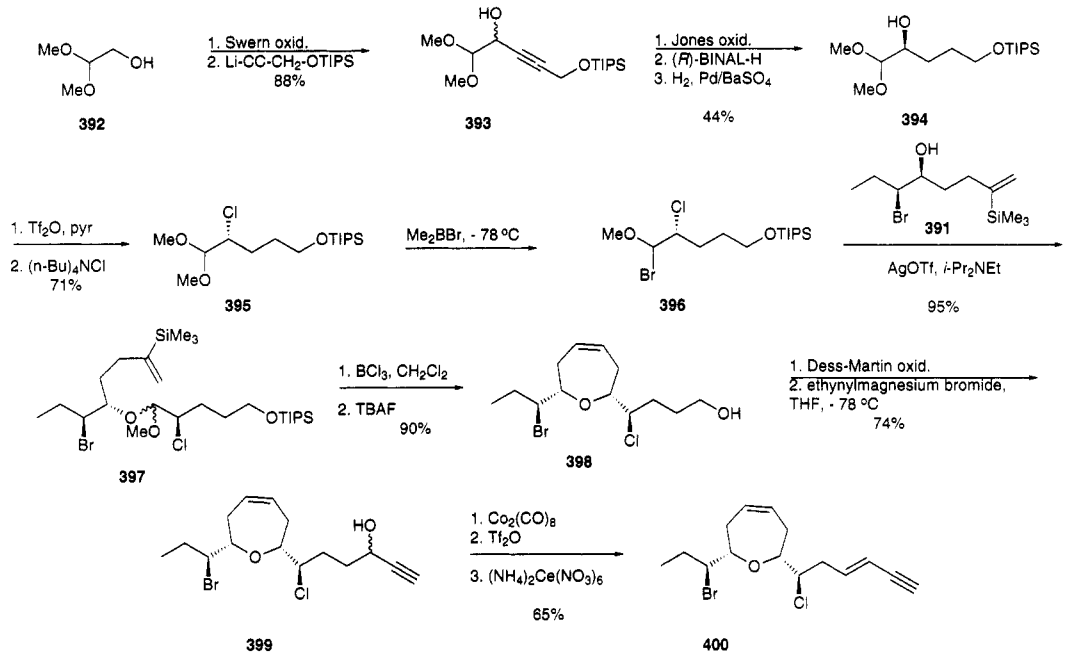
8. Miscellaneous Vinylsilane-Mediated Syntheses

8.1. An Approach to Total Synthesis of (+)-Lycoricidine

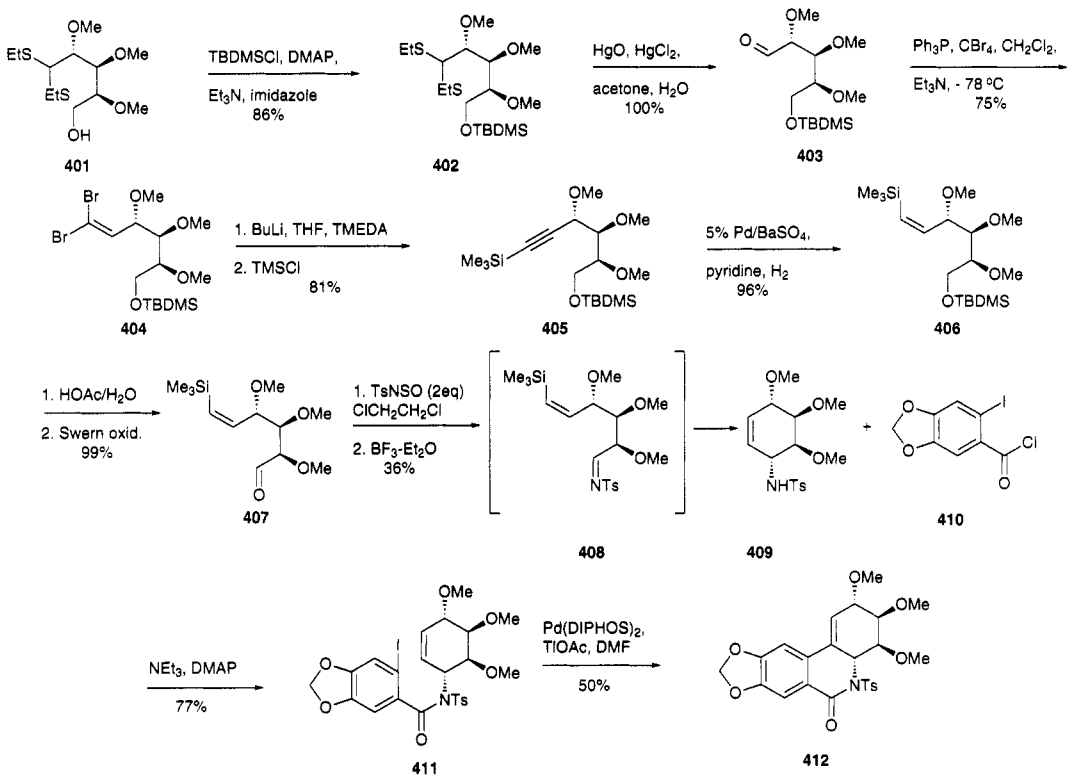
A convergent synthesis of a protected version of (+)-lycoricidine (**412**) has been achieved in 13 steps starting from L-arabinose by Weinreb.[138] Key steps are a novel vinylsilane-terminated *N*-sulfonium ion cyclization and an intramolecular Heck reaction to close B-ring of (+)-lycoricidine (**412**) (Scheme 88).

Compound **401**, a known compound available in three steps from L-arabinose, was protected as silyl ether **402** using standard conditions. Deprotection of the dithioacetal moiety gave aldehyde **403** which was further elaborated by the Corey–Fuchs[139] protocol to give **404** which was finally converted to the desired acetylene derivative **405**. Catalytic hydrogenation was used to introduce the vinylsilane functionality in **406**. The maximum *Z*/*E* selectivity was accomplished with an OTBDMS protecting group and a concentration of ca. 0.22 M of substrate in pyridine. Deblocking of the silyl ether under acidic conditions and subsequent Swern oxidation provided aldehyde **407**. Compound **407** was first converted to *N*-sulfonimine **408** under neutral (thermal) conditions and then treated *in situ* with boron trifluoride etherate to yield aminocyclitol **409** as a single diastere-

Scheme 87



Scheme 88



omer. Coupling of 6-iodopiperonyl chloride (**410**) and aminocyclitol afforded *N*-acylsulfonamide **411** which was finally closed to give **412** via an intramolecular Heck reaction.

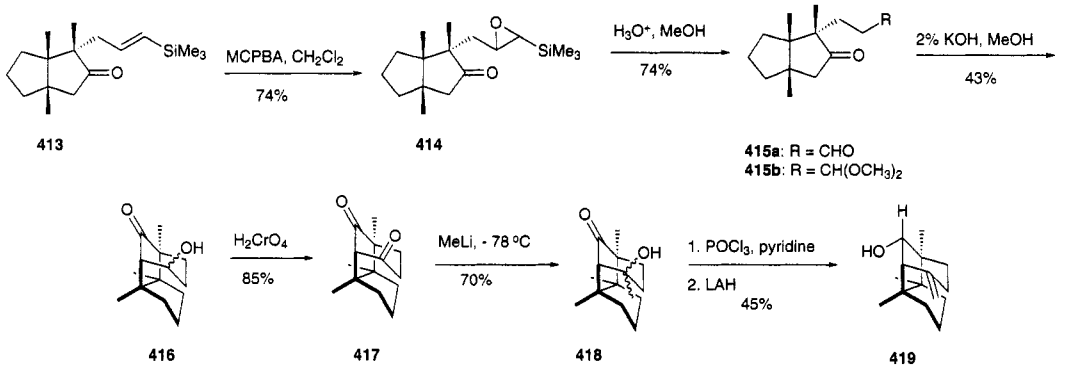
In addition, a related cyclization using aldehyde **407** was used to approach the conduritol and cyclitol frameworks.[140]

8.2. Vinylsilane-Mediated Total Synthesis of (±)-Gymnomitrol

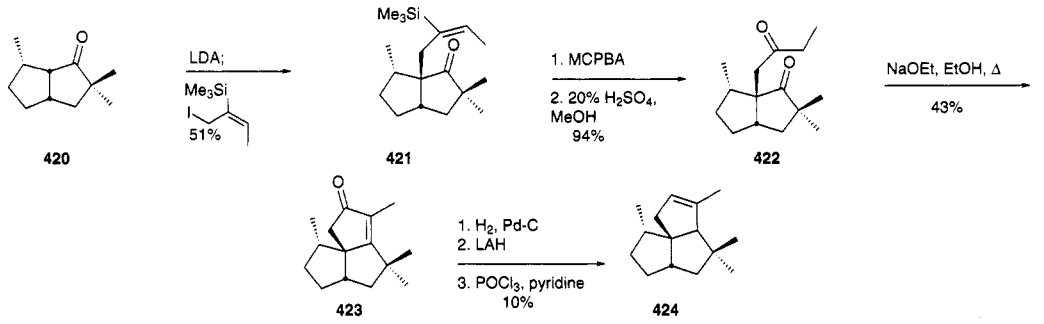
A stereoselective synthesis of (±)-gymnomitrol (**419**) was accomplished by Paquette via a vinylsilane reagent[141] (Scheme 89).

Vinylsilane **413** has been synthesized by standard operations starting with a simple bicyclooctane. Epoxidation of **413** led to silyl epoxide, which was directly transformed into compound **414** by hydrolysis with 20% sulfuric acid–methanol. Chromatography of the crude product yielded two fractions (**415a/415b** = 45:55, 74%) which were hydrolyzed with acetic acid–water to give pure **415a**. *In situ* subjection to potassium hydroxide led to cyclization and generated compound **416** which was further elaborated by addition of methyllithium into tertiary alcohol **418**. Dehydration with phosphorus oxy chloride in pyridine followed (1:1 mixture of gymnomi-

Scheme 89



Scheme 90



trone and its double bond isomer), and final reduction with lithium aluminum hydride provided (±)-gymnomitrol (**419**) in 45% yield.

8.3. An Approach to Total Synthesis of (±)-Senoxydene

A totally stereocontrolled route to angular triquinanes has been described by Paquette which involves a vinylsilane-mediated annulation to elaborate the third, unsaturated 5-membered ring[142] (Scheme 90).

Alkylation of **420** provided bicyclooctane **421** in 51% yield. Diketone **422** was synthesized by sequential treatment of **421** with *m*-chloroperbenzoic acid and dilute sulfuric acid in hot methanol. The best conditions to run the desired intramolecular aldol reaction were a 20% solution of sodium ethoxide in ethanol; aldol product **423** was isolated in 43% yield. Catalytic hydrogenation over palladium on charcoal gave rise to a stereoisomerically homogeneous saturated ketone, which was treated first with lithium aluminum hydride to give the secondary alcohol, and finally eliminated to generate angular triquinane (**424**).

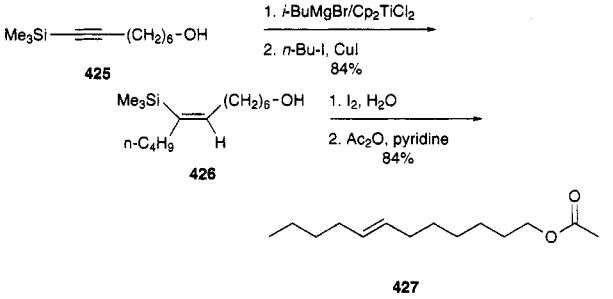
8.4. Synthesis of 7-(E)-Dodecenyl Acetate and Dihydrojasmone

Dialkyl vinylsilanes have been prepared by Sato via hydromagnesiation of 1-(trimethylsilyl)-1-alkynes with Grignard reagents in the presence of cp_2TiCl_2[143] (Scheme 91).

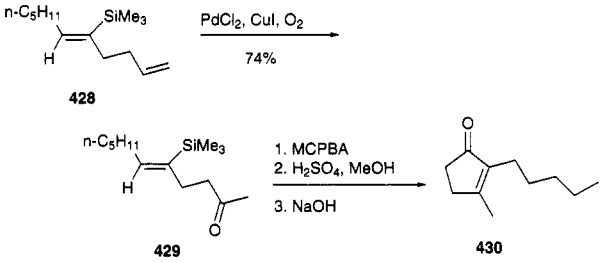
Vinylsilane **426** was prepared by hydromagnesiation and subsequent alkylation with butyl iodide. Desilylation with iodine followed by acetylation gave pheromone **427** (E/Z = 96:4) in 84% yield.

The same technique has been used to synthesize dihydrojasmone (**430**). Trisubstituted vinylsilane **428** was oxidized in the presence of palladium dichloride (Wacker oxidation) to provide ketone **429**. Epoxidation of vinylsilane, followed by hydrolysis, and intramolecular aldol condensation gave **430** (Scheme 92).

Scheme 91



Scheme 92

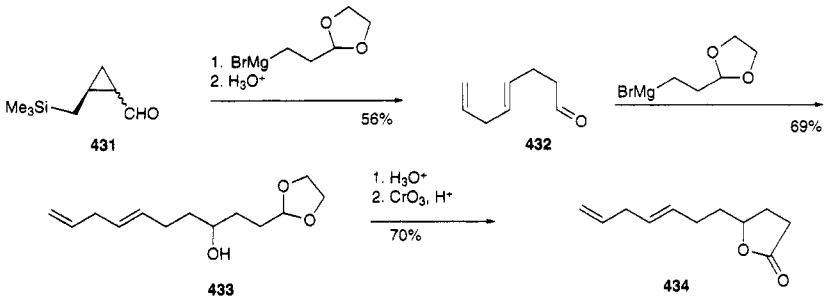


V. Miscellaneous Reactions

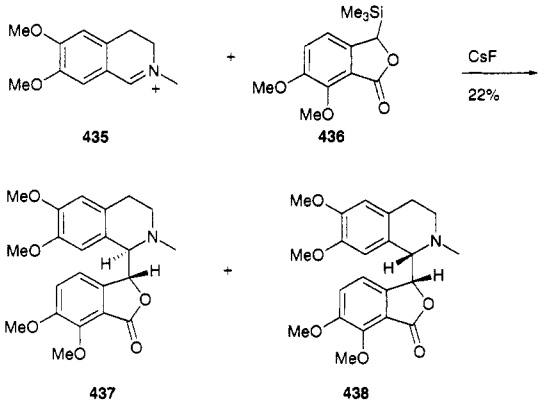
1. Synthesis of the Melon Fly Pheromone

Wilson has reported a silicon-directed solvolysis of cyclopropane **431** which generated a diene **432**.[144] A second addition of (1,3-dioxolan-2-ylethyl)magnesium bromide, followed by acid hydrolysis, subsequent oxidation, and lactonization gave pheromone **434** (Scheme 93).

Scheme 93



Scheme 94



2. Synthesis of the Isoquinoline Alkaloid (±)-Cordrastine

Carbanions generated by fluorodesilylation have been used in coupling reactions with iminium ions to construct isoquinoline alkaloids.[145] Kessar took isoquinolinium ion **435** and coupled it in the presence of cesium fluoride with **436** to get cordrastine as a mixture of diastereomers (**437**/**438** = 46:30%) (Scheme 94).

By the same technique the alkaloid hydrastine was synthesized.

VI. Concluding Remarks

During the last decade silicon-containing compounds, in particular allyl-, propargyl- , and vinylsilanes, have reached a high and important level for cyclization-based reactions in organic synthesis. Many different types of structures including carbocycles as well as nitrogen- and oxygen-containing molecules could be either approached or successfully synthesized. Most of these syntheses could be carried out asymmetrically. We are very confident that in future years from the continued development of cyclization chemistry using terminators with highly nucleophilic π-systems trapped by various initiators will emerge a high standard in organic synthesis. A future effort will be a detailed mechanistic study to bring more light into reactions surrounding Lewis acid-promoted reactions.

VII. Acknowledgments

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