Pergamon

Tetrahedron 55 (1999) 5641–5679

TETRAHEDRON

Tetrahedron report number 491

Total Synthesis of Aphidicolane and Stemodane Diterpenes

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Received 2 March 1999

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1. Introduction

More than two decades ago, the structure of a tetracyclic diterpenoid antibiotic, aphidicolin (**1**), isolated from *Cephalosporium aphidicola*[1] and later found to occur in *Nigrospora sphaerica*,[2] was reported by Hesp and his co-workers[1,3] and shortly thereafter, several related stemodane diterpenes (**4** - **7**) isolated from *Stemodia maritima* L. were described.[4,5,6] The relationship between aphidicolane and stemodane diterpenoid is topographical in nature[7] (identical ring system but epimeric at C-9). Namely, the fusion of the five-membered C ring to B in stemodane is *cis* in contrast to the *trans* fusion in aphidicolane.

The aphidicolin (**1**) and stemodane (**4** - **7**) families have spiro fused bicyclo[3.2.1]octane moiety which comprises the C and D rings. In addition, these diterpenes possess more than six stereogenic centers of which five are associated with ring junctions. Especially, the presence of two adjacent chiral quaternary centers (C-9 and C-10) makes these diterpenes quite crowded. Little is known about the substantial biological activity of stemodane diterpenes, however, aphidicolin (**1**) shows marked activity against Herpes simplex.[8] Apart from its antifeedant property,[9] aphidicolin (**1**) inhibits DNA replication and growth of several human and murine neoplastic cells.[10]

Due to its poor water solubility, **1** has been considered to be not suitable for its parenteral administration.

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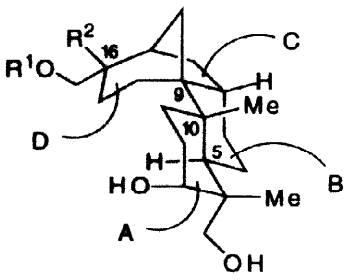
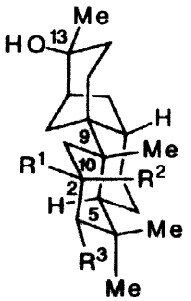
PII: S0040-4020(99)00216-1



R^1 = H, R^2 = OH; Aphidicolin (**1**)
R^1 = $COCH_2NH_2$ • HCl, R^2 = OH; Aphidicolin-17-glycinate HCl salt (**2**)
R^1 = H, R^2 = F; 16-Fluoroaphidicolin (**3**)



R^1 = OH, R^2 = R^3 = H; Stemodin (**4**)
R^1 = R^2 = O, R^3 = H; Stemodinone (**5**)
R^1 = R^2 = R^3 = H; 2-Desoxystemodinone
R^1 = R^2 = H, R^3 = OH; Maritimol (**7**)

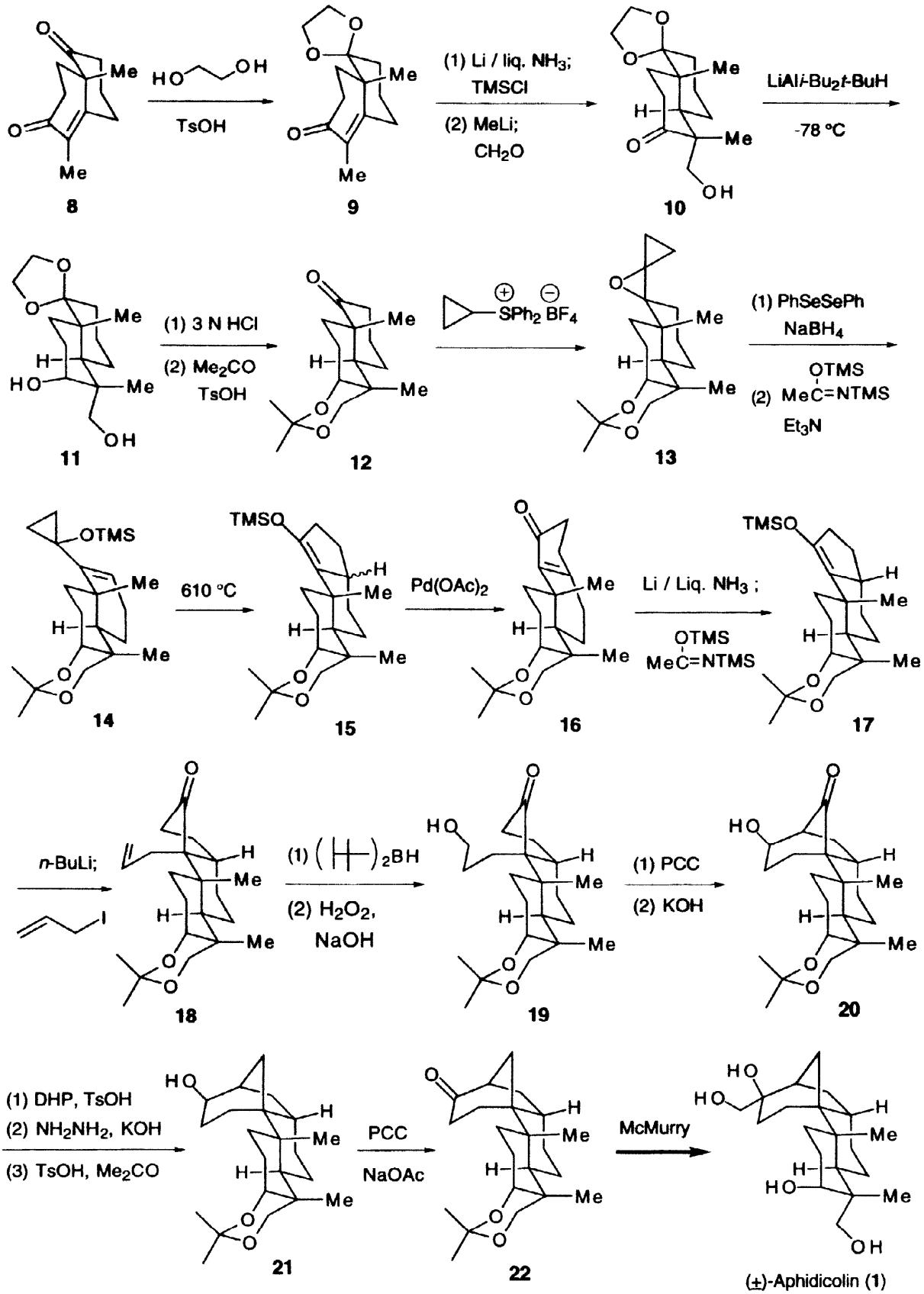
However, recent reports of enhanced antitumor activity associated with the more water-soluble compounds such as aphidicolin-17-glycinate HCl salt (**2**)[11] and 16-fluoroaphidicolin (**3**),[12] synthesized as prodrug, might revive interest in aphidicolin (**1**) and its analogues as a potential anticancer agent.

Since the early 1970s, when the structures of aphidicolin (**1**) and stemodane diterpenes (**4** - **7**) were established, numerous total and formal syntheses of aphidicolin (**1**) and stemodane diterpenes (**4** - **7**) have been reported. This review covers total and formal syntheses of aphidicolane and stemodane diterpenes from the late 1970s until approximate 1998. This review is divided into three sections, namely, (1) introduction, (2) aphidicolin synthesis, and (3) stemodane synthesis. Each synthetic section is organized broadly around the sequence of ring construction.

2. Synthesis of Aphidicolin

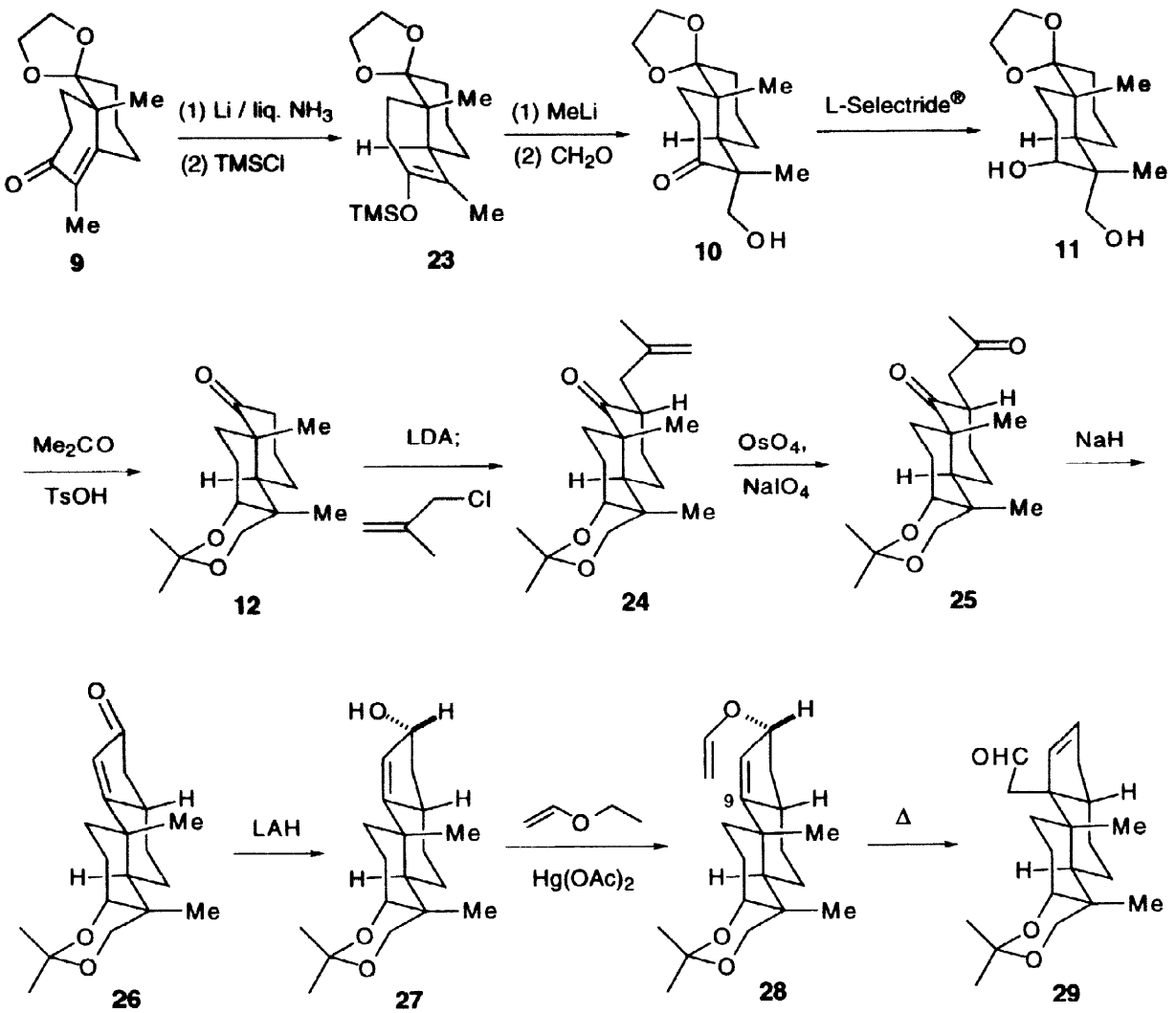
2.1. From AB Ring System

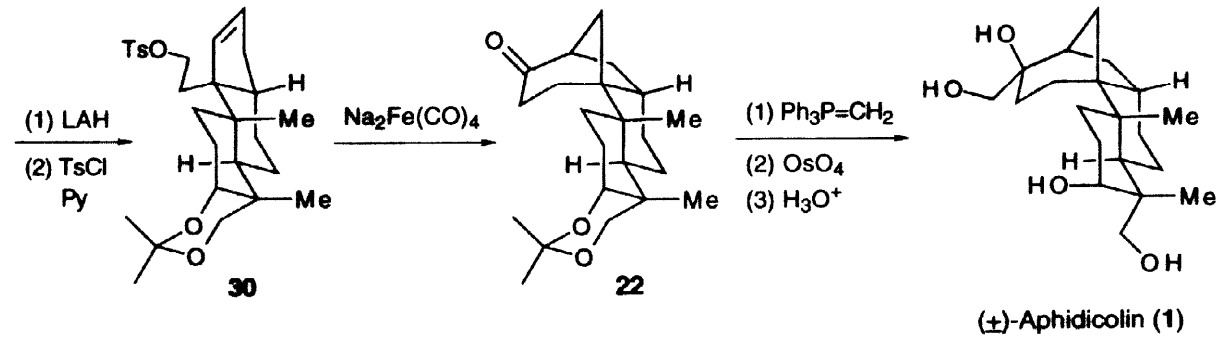
The first total syntheses of aphidicolin (**1**) were accomplished independently by Trost[13] and by McMurry[14] and their co-workers in 1979. In the Trost synthesis (**Scheme 1**), the novel cyclopentanone annulation reaction (**12**→**15**) *via* the oxaspiropentane **13**, originally developed by themselves, is used as key step to construct the C ring part of **1** on the preexisting AB bicyclic system. The ketone **12** is prepared from the well-known enone **8** as shown in **Scheme 1**. After ketalization of **8**, the enone part of **9** is stereoselectively reduced by means of Birch reduction, whereupon the resulting lithium enolate is trapped with TMSCl. The aldol functionality is installed by Stork's method. Stereoselective reduction of the ketone **10** provides the diol **11**, which is successively subjected to acidic treatment and protection of the corresponding diol moiety, affording the compound **12**. Condensation of the ketone **12** with diphenylsulfonium cyclopropylide under the established conditions proceeds smothly to give the oxaspiropentane **13**. Treatment of **13** with sodium phenylselenide furnishes alkylidene-cyclopropanol, which is silylated to **14**. Thermal rearrangement *via* flash vaccum pyrolysis (FVP) of **14** gives **15** as a 2 : 1 mixture of epimers **15**. The mixture **15** is transformed into the enone **16** by using Saegusa reaction. Birch reduction forms the desired enol silane **17**, which is successively treated with *n*-BuLi and allyl iodide. After conversion of the resulting olefin **18** to the aldehyde *via* the alcohol **19**, intramolecular aldol reaction is conducted with KOH in order to construct the D ring part of **1**. Finally, the alcohol **21** is transformed into (±)-aphidicolin (**1**).


TsOH
(1) Li / liq. NH3; TMSCl
(2) MeLi; CH2O
LiAlH(Oi-Bu)2t-BuH
-78 °C
(1) 3 N HCl
(2) Me2CO TsOH
(1) PhSeSePh NaBH4
(2) MeC=NTMS Et3N
610 °C
Pd(OAc)2
Li / Liq. NH3 ;
n-BuLi;
(1) (2) H2O2, NaOH
(1) PCC
(2) KOH
(1) DHP, TsOH
(2) NH2NH2, KOH
(3) TsOH, Me2CO
PCC
NaOAc
McMurry
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
(±)-Aphidicolin (1)

Scheme 1

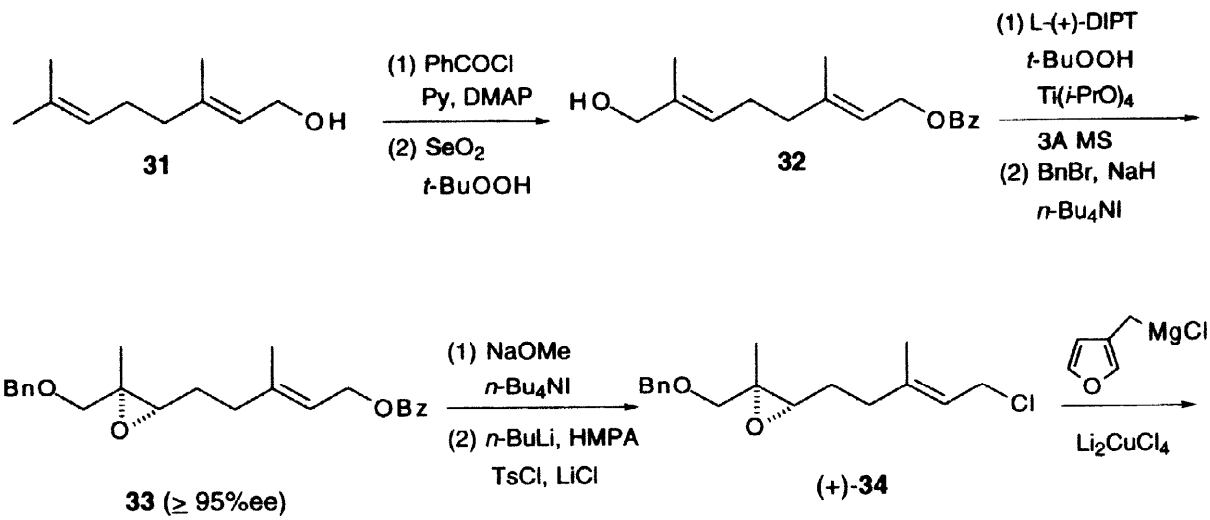
The synthesis of (±)-aphidicolin (**1**) by McMurry[14] and his co-workers, like that of Trost, makes use of the bicyclic enone **9** as the starting material. This synthesis features stereoselective introduction of the carbon side chain at C-9 position employing Claisen rearrangement and the D ring construction using "Collman's Reagent" (**Scheme 2**). The preparation of the ketone **12** is carried out in the same order as that of Trost. Alkylation of **12** with methallyl iodide affords **24**, whose olefinic bond is oxidatively cleaved to provide the methyl ketone **25**. After the intramolecular aldol condensation of **25** in the presence of NaH, the resulting enone **26** is next stereoselectively reduced with LAH to furnish the allylic alcohol **27**. The compound **27** is converted to its vinyl ether **28** in the usual way, whereupon vapor phase pyrolysis of **28** at 360 °C gives rise to the aldehyde **29**. LAH reduction of **29**, followed by tosylation, provides the unsaturated tosylate **30**. Treatment of **30** with disodium tetracarbonylferrate gives the ketone **22**, which is successively subjected to Wittig reaction, dihydroxylation, and deprotection to afford (±)-aphidicolin (**1**).

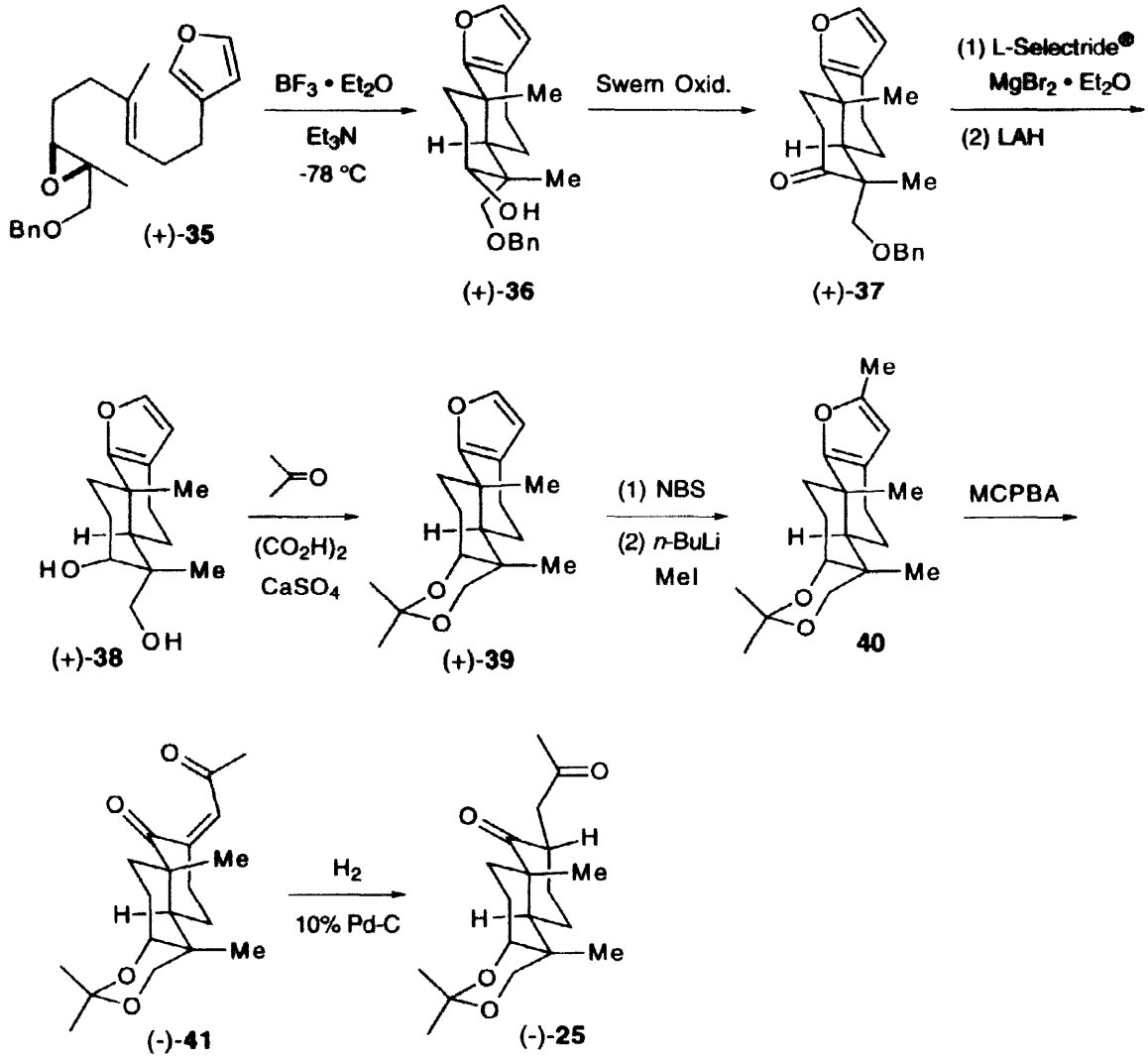




Scheme 2

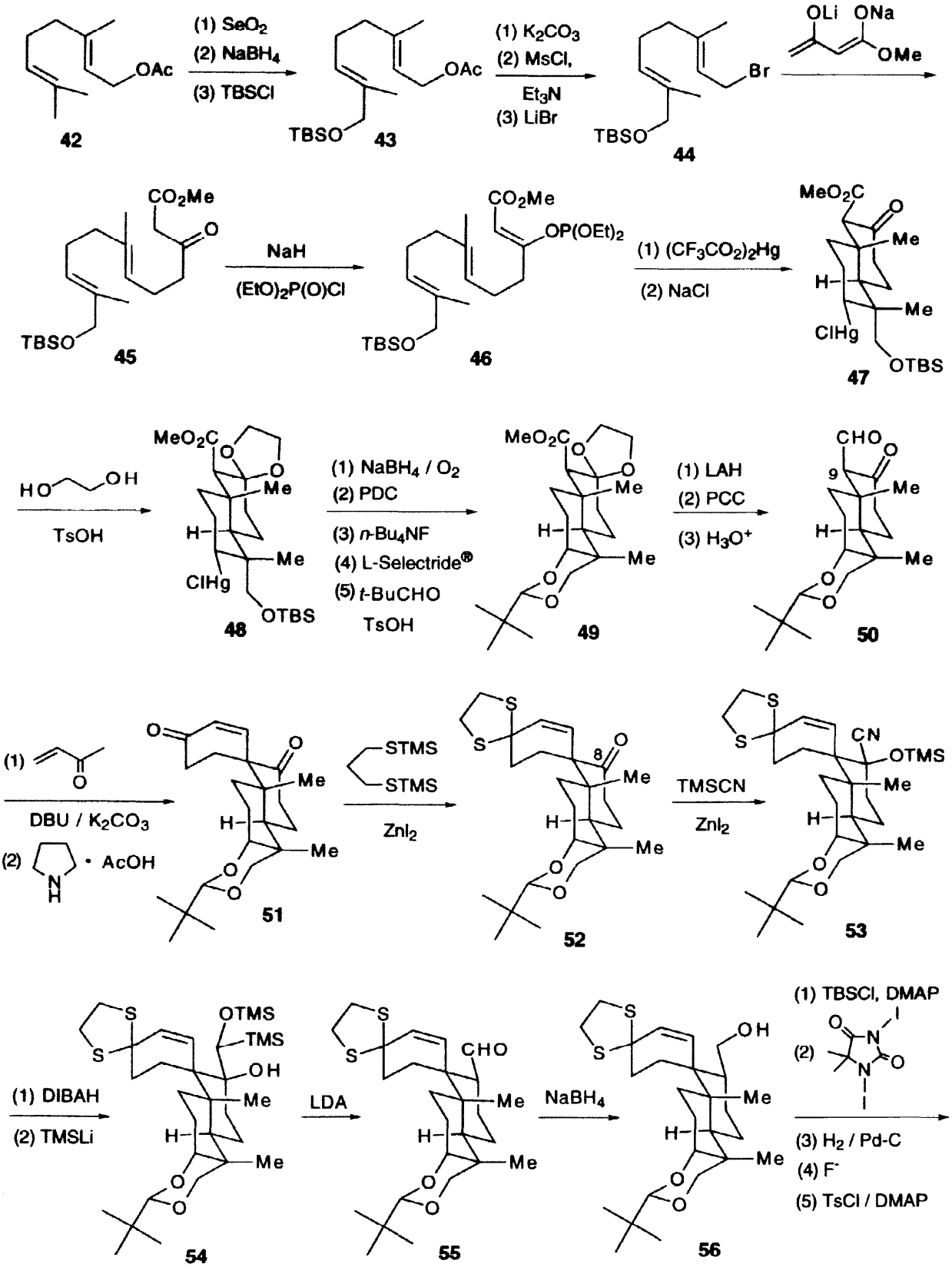
An alternative approach to the formation of AB *trans* ring system of (+)-**1** is illustrated in the work of Tanis[15] and his co-workers. The key transformation in the synthesis is a furan-terminated-epoxide-initiated cationic cyclization of **35** to form the tricyclic aphidicolin precursor **36**. Benzoylation of geraniol, followed by catalytic allylic hydroxylation, gives rise to 8-hydroxygeranyl benzoate (**32**). Stoichiometric Sharpless asymmetric epoxidation provides the corresponding epoxy alcohol, whose optical purity is judged to be ≥95% ee by HPLC analyses of its Mosher ester. After benzylation, benzoate saponification of **33**, followed by chlorination, furnishes the chloride **34**, which is coupled with furan-3-methylmagnesium chloride in the presence of Li_2CuCl_4 to give the key substrate **35**. The pivotal cyclization reaction of (+)-**35** is conducted with $BF_3{\cdot}Et_2O$ to yield the tricyclic product **36**. Swern oxidation of (+)-**36** gives the ketone **37**, which is transformed into the diol **38** after stereoselective reduction and debenzylation. Bromination of the acetonide **39**, followed by metal-halogen exchange and alkylation, provides the compound **40**, which is oxidized with MCPBA to furnish the ene dione **41**. Finally, catalytic hydrogenation of (-)-**41** gives rise to the desired dione **25**. Since (±)-**25** had been converted to (±)-aphidicolin (**1**) by McMurry and his co-workers, the preparation of (-)-**25** provides a formal synthetic route to (+)-aphidicolin (**1**) (**Scheme 3**).

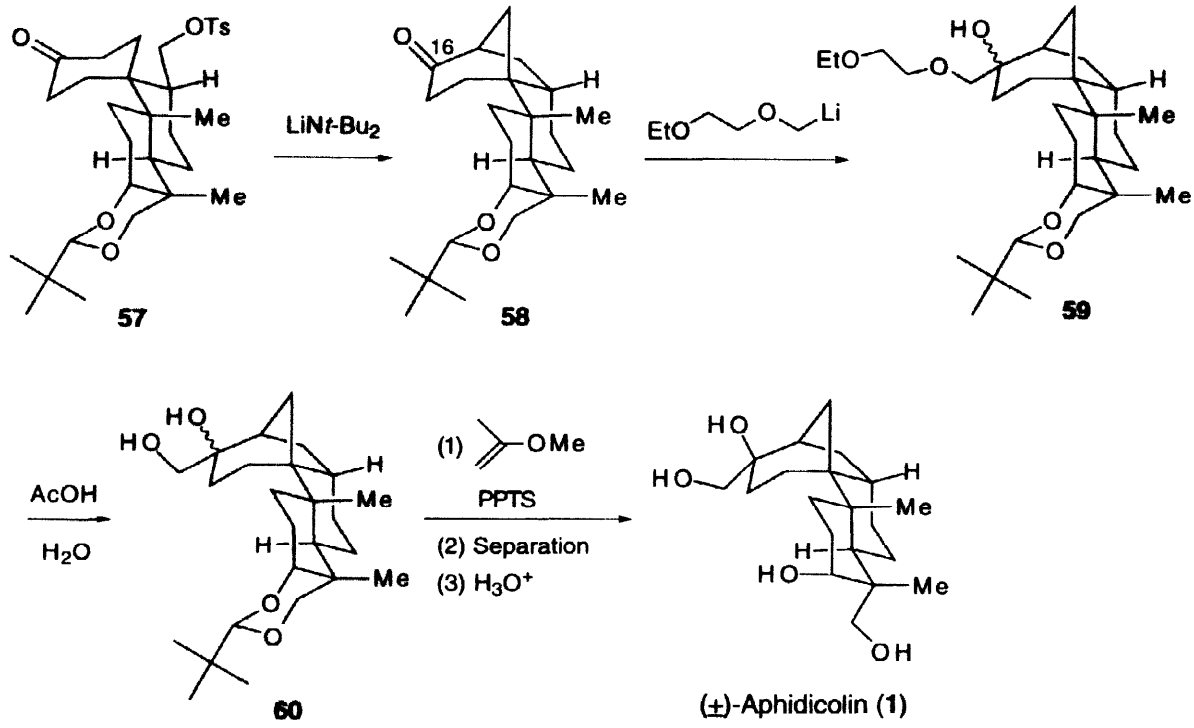




Scheme 3

The synthesis of (±)-aphidicolin (**1**) by Corey[16] and his co-workers is depicted in **Scheme 4**. Two critical reactions in this route are mercuric trifluoroacetate-promoted polyene cyclization reaction of the enol phosphonate **46** to form the bicyclic keto ester **47** in stereoselective manner and the introduction of formyl group at C-8 position of the ketone **52** utilizing a novel reaction developed in Corey's lab. To investigate the first key step, the acetate **42** is converted to **46** by the following sequence. Allylic oxidation of **42**, followed by $NaBH_4$ reduction of the resulting aldehyde and protection, provides the compound **43**, which in turn is subjected to hydrolysis of the acetate moiety, mesylation of the resulting primary alcohol, and bromination with LiBr to give rise to **44**. The unstable bromide **44** is treated with lithiosodio derivative of methyl acetoacetate to furnish the β-keto ester **45**, which is transformed into the enol phosphonate ester **46**. Polyene cyclization reaction of **46** is conducted with mercuric trifluoroacetate to give the corresponding bicyclic product, which upon treatment with NaCl yields the mercurated keto ester **47**. After ketalization of **47**, the compound **48** is converted to the acetonide **49** in 5 steps.


(1) SeO2
(2) NaBH4
(3) TBSCl
(1) K2CO3
(2) MsCl,
Et3N
(3) LiBr
OLi ONa
OMe
42
43
44
NaH
(EtO)2P(O)Cl
(1) (CF3CO2)2Hg
(2) NaCl
45
46
47
TsOH
(1) NaBH4 / O2
(2) PDC
(3) n-Bu4NF
(4) L-Selectride®
(5) t-BuCHO
TsOH
(1) LAH
(2) PCC
(3) H3O+
48
49
50
DBU / K2CO3
(2) · AcOH
STMS
STMS
ZnI2
TMSCN
ZnI2
51
52
53
(1) DIBAH
(2) TMSLi
LDA
NaBH4
(1) TBSCl, DMAP
(2)
(3) H2 / Pd-C
(4) F-
(5) TsCl / DMAP
54
55
56



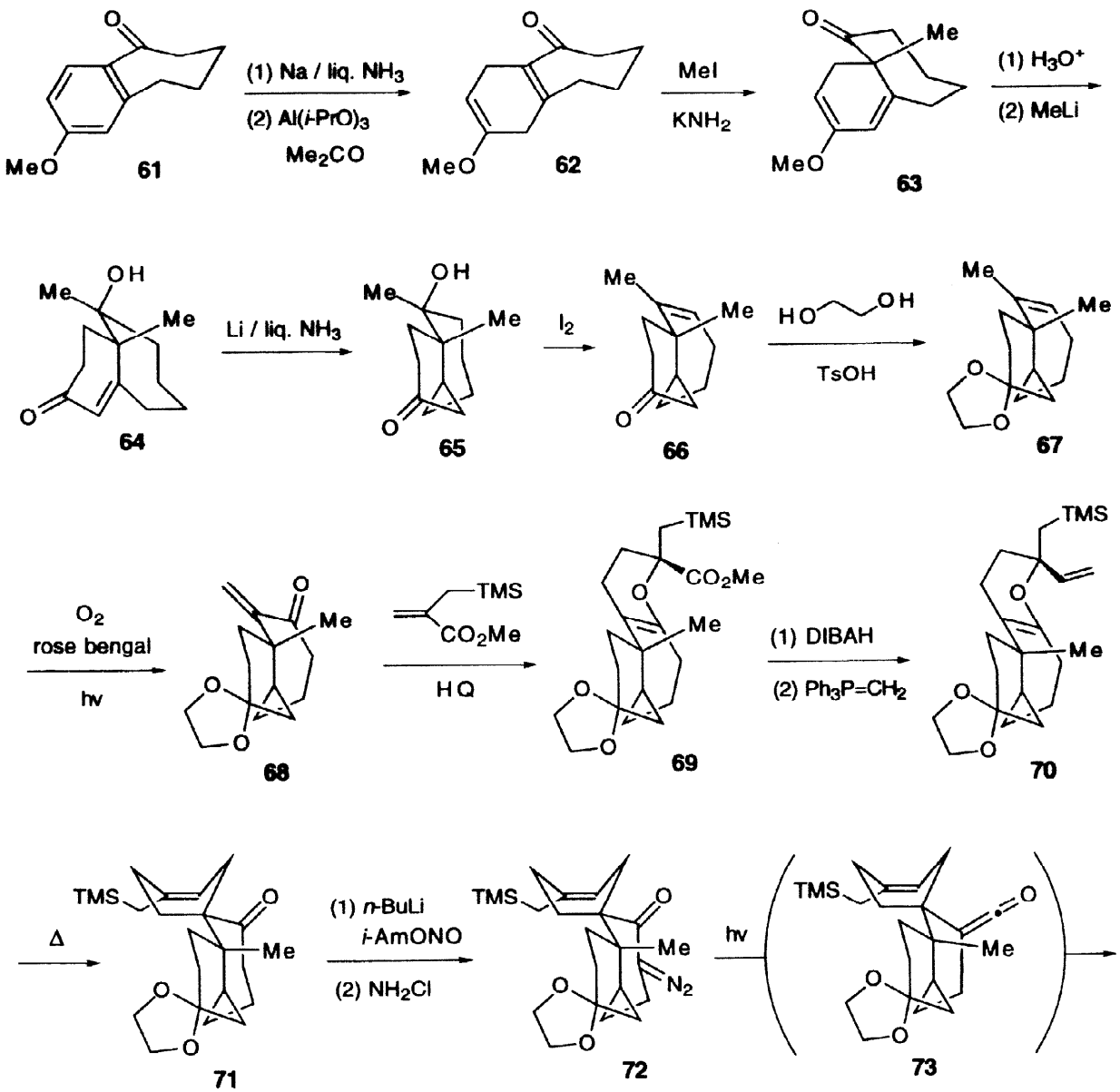
Scheme 4

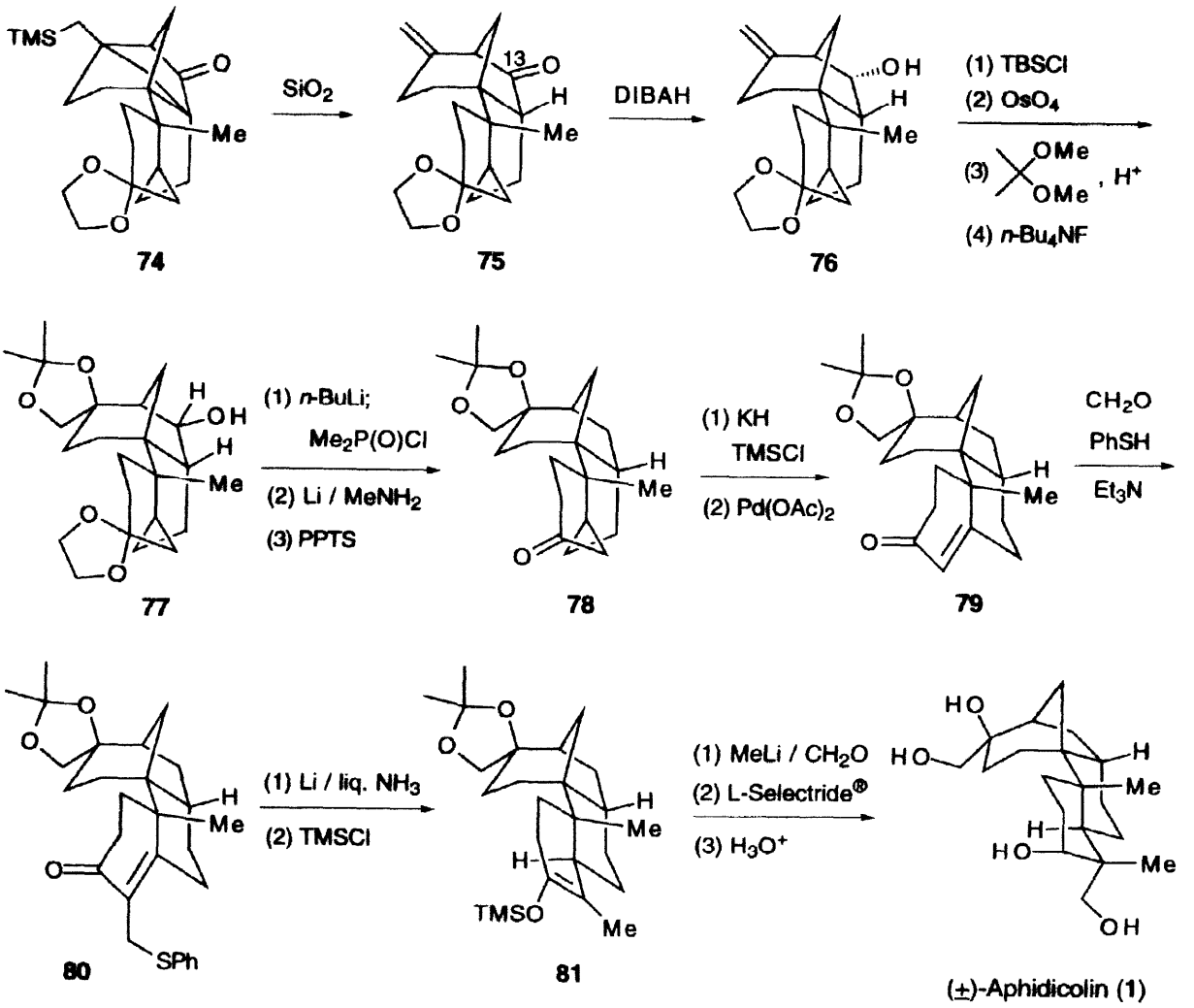
After transformation of the ester group of **49** into formyl group in 3 steps, the introduction of the spiro ring at C-9 position of **50** is performed by the following sequence: (i) Michael reaction with methyl vinyl ketone in the presence of K_2CO_3 and DBU, and (ii) Robinson spiroannulation reaction of the resulting Michael product with pyrrolidinium acetate.

Chemoselective thioketalization of the enone **51** gives the compound **52**. In order to introduce a formyl group at C-8 position of **52**, a new method, which offers a solution to the problem of attaching carbon to very hindered ketone, was developed by Corey and his co-workers. Accordingly, the ketone **52** is treated with TMSCN in the presence of ZnI_2 to afford TMS ether **53**, whose cyano group is reduced with DIBAH giving the corresponding aldehyde. After reaction with trimethylsilyllithium, the resulting bistrimethylsilyl compound **54** is treated with LDA to yield the aldehyde **55**. Transformation of **55** into the tosylate **57** is accomplished as presented in the Scheme. To prepare the C ring system of (±)-**1**, intramolecular displacement reaction of **57** is conducted to provide the ketone **58**. Finally, hydroxymethyl group at C-16 position of **58** is introduced with 1-ethoxyethoxymethyllithium to give rise to (±)-aphidicolin (**1**) after acidic treatment. In order to separate a 1 : 1 mixture of (±)-**1** and the epimer at C-16, the mixture is converted to the corresponding mixture of diacetonides.

The Ireland approach[17] to the synthesis of (±)-aphidicolin (**1**) is based on the spiroannulation of the methylene ketone **68** through hetero-Diels-Alder reaction followed by Claisen rearrangement of the allyl vinyl ether **70**. A central feature of the synthesis is the rearrangement of the intermediate ((trimethylsilyl)methyl)cyclobutanone to the aphidicolane bicyclo[3.2.1]octane ring system. The requisite methylene ketone **68** for the first key step is practically prepared from 2-methoxybenzosuberone (**61**) as depicted in **Scheme 5**. The reaction sequence involves Birch reduction, followed by oxidation of the resulting allylic

alcohol to give the enone **62**, which is subjected to methylation to provide the ketone **63**. After hydrolysis of the enol ether moiety of **63**, methyl lithium is added to the saturated ketone from less hindered side, whereupon the enone part of **64** is reduced by a standard sequence. The keto alcohol **65** is converted by functional group manipulation sequence to the olefin **67**. Introduction of the enone system is next performed through photo-ene process, furnishing the key substrate **68**. Intermolecular hetero-Diels-Alder reaction of **68** and methyl ((trimethylsilyl)methyl)acrylate is conducted at 125 °C in a sealed tube in the presence of hydroquinone to give rise to the desired β-carbomethoxy adduct **69** as the major isomer (7 : 3).



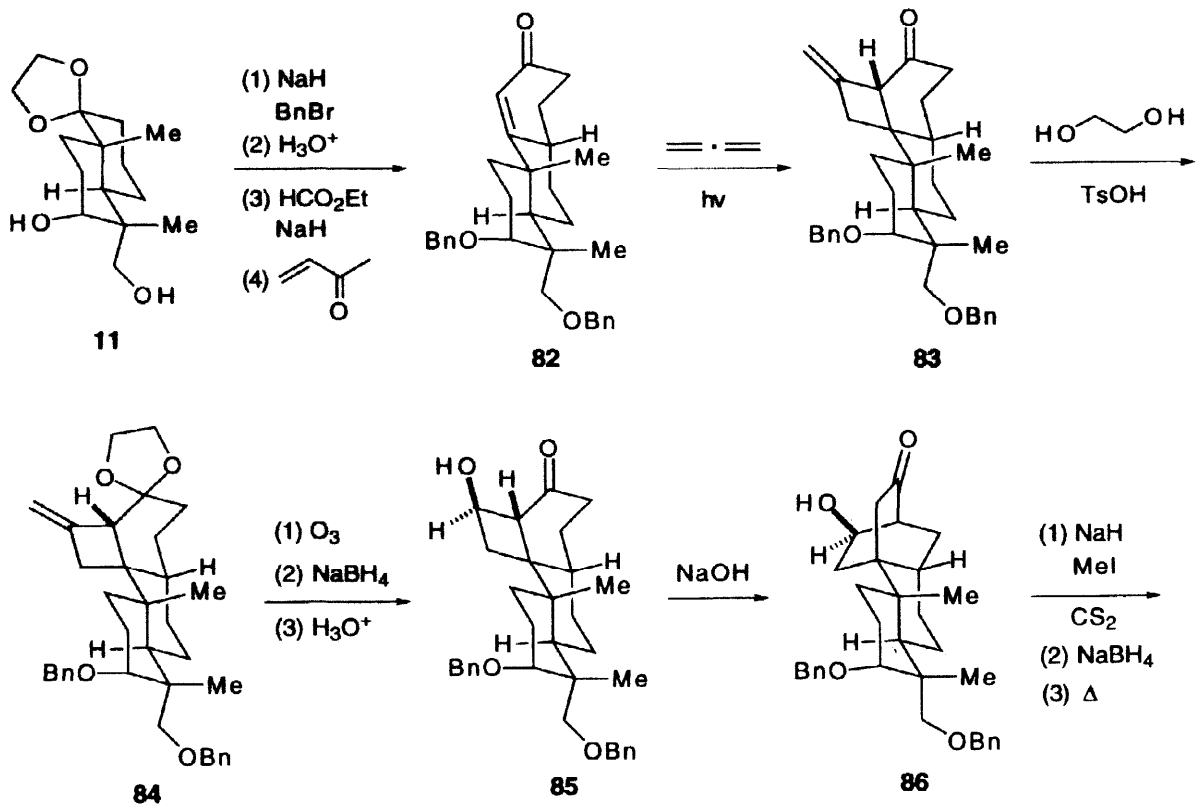


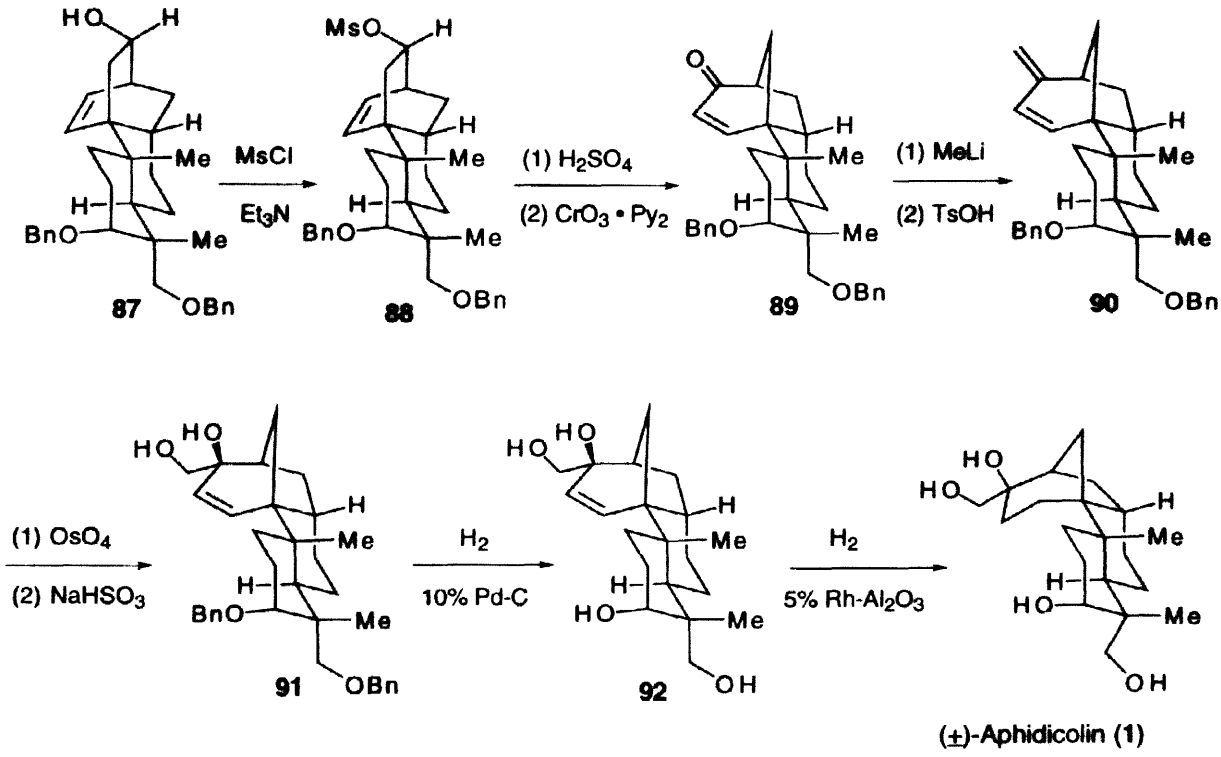
Scheme 5

Transformation of **69** into the β-vinyldihydropyran **70** is carried out in two steps. Heat-promoted Claisen rearrangement of **70** provides the spiroketone **71**, which in turn is subjected to oximination and chloramine oxidation to afford the diazo ketone **72**. Photolysis of **72** is performed to generate the unstable cyclobutanone derivative **74** *via* the intermediate ketene **73**. Although it is too unstable to isolate **74**, the rearrangement of the (trimethylsilyl)cyclobutanone component **74** is effected by silica gel column chromatography. The C-13 carbonyl group serves an important funcion for the purpose of the stereospecific introduction of the C-16, C-17 diol. To this end, the ketone **75** is stereoselectively reduced with DIBAH to the C-13 α-oriented alcohol **76**, which is protected as the TBS ether. Dihydroxylation with OsO_4, followed by acetonide formation and removal of the silyl group, yields the compound **77**. Deoxygenation of **77** is achieved by applying Ireland's technique. AB-*trans* ring juncture is established *via* the enone **79**. Namely, the silyl enol ether of **78** is treated with palladium acetate to give **79**, which is subjected to Petrow reaction to furnish the phenyl thiomethyl enone **80**. Birch reduction of **80**, followed by trapping of the corresponding lithium enolate with TMSCl, gives rise to the silyl enol ether **81**. The aldol functionality is installed by the general method of Stork. The compound **81** is treated with MeLi,

whereupon the resulting lithium enolate is subjected to react with gaseous formaldehyde to provide the aldol, which is reduced with L-Selectride®. After acidic treatment of the corresponding diol, total synthesis of (±)-aphidicolin (**1**) is accomplished (**Scheme 5**).

To achieve the synthesis of (±)-aphidicolin (**1**), Bettolo[18] and his co-workers employs Wiesner allen photocycloaddition and the biomimetic rearrangement of a bicyclo[2.2.2]octane to a bicyclo[3.2.1]octane ring system for preparing the CD ring part of **1**. The starting material is the known diol **11**. The diol is dibenzylated by standard procedure to give the corresponding dibenzyl ether, which is subjected to acidic treatment to afford the ketone. This ketone is converted to the enone **82** by Robinson annulation with 3-buten-2-one. Photoaddition of allene to **82** proceeds regio- and stereospecifically to provide the adduct **83**, which is transformed into the β-oriented alcohol **85** through the ketal **84** in 4 steps. Basic teratment of **85** yields the keto alcohol **86** *via* a consecutive retro-aldol and aldol reaction. Dehydration of **86** is carried out using Chugaev reaction. Namely, **86** is converted to the corresonding xanthate, whereupon it is subjected to thermal condition to give rise to the olefin **87**. After mesylation of the unsaturated alcohol **87**, rearrangement of the resulting mesylate **88** provides stereospecifically the unsaturated alcohol, which is oxidized with PDC to afford the enone **89**. The enone **89** is next converted to the diene **90** by reaction with MeLi, followed by dehydration with TsOH. The less hindered exo olefin part of **90** is selectively dihydroxylated with OsO_4 to furnish the diol **91**. After debenzylation of **91** by means of catalytic hydrogenation in the presence of 10% Pd-C, the double bond of **92** is finally reduced under pressure in the presence of 5% Rh/Al_2O_3 to provide (±)-aphidicolin (**1**) (**Scheme 6**).



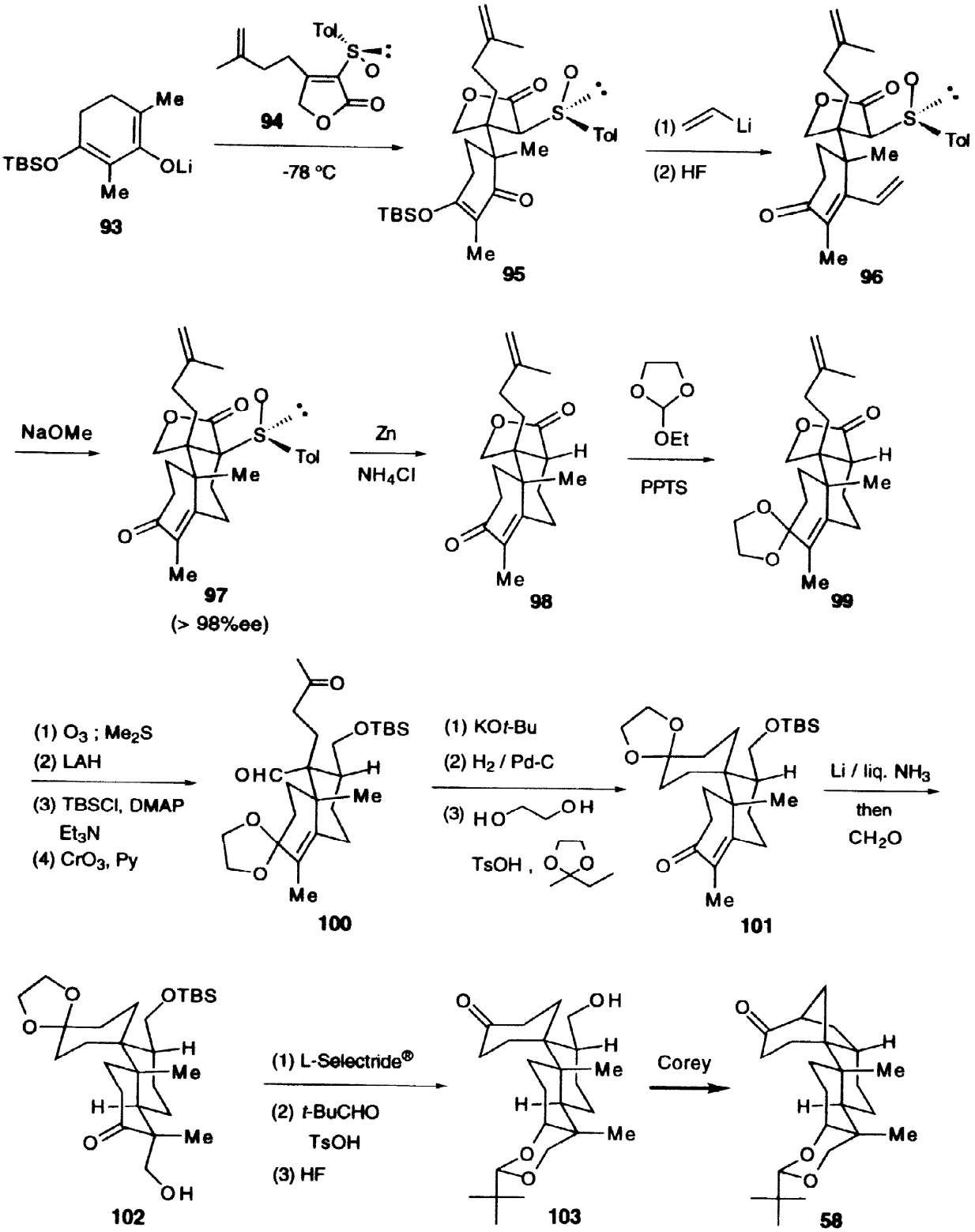


Scheme 6

2.2. From A Ring System

The first enantioselective total synthesis of (+)-aphidicolin (**1**) is achieved by Holton[19] and his co-workers. The synthesis features diastereoselective Michael reaction to form the contiguous quaternary centers (C-9 and C-10). Namely, Michael addition of the cross-conjugated lithium enolate **93** to the (*S*)-(+)-sulfinyl butenolide **94** gives rise to a 7.4 : 1 mixture of diastereomeric sulfinyl lactones. After recrystallization of this mixture, pure **95** is obtained. 1,2-Addition of vinyllithium to **95** is followed by treatment with HF to furnish the dienone **96**. Stereoselective intramolecular Michael addition of **96** is next carried out in the presence of NaOMe in wet MeOHto afford the tricyclic compound **97** (> 98% ee). The above-mentioned transformation (**93**→**97**) is also accomplished in a single synthetic operation. The conversion of **97** to the keto aldehyde **100** is outlined in **Scheme 7**. After reductive desulfurization of **97**, the enone **98** is subjected to protection to give the compound **99**. Selective ozonolysis of the *exo*-olefin moiety of **99** is followed by LAH reduction, selective silylation of primary alcohol, and oxidation to provide the keto aldehyde **100.**

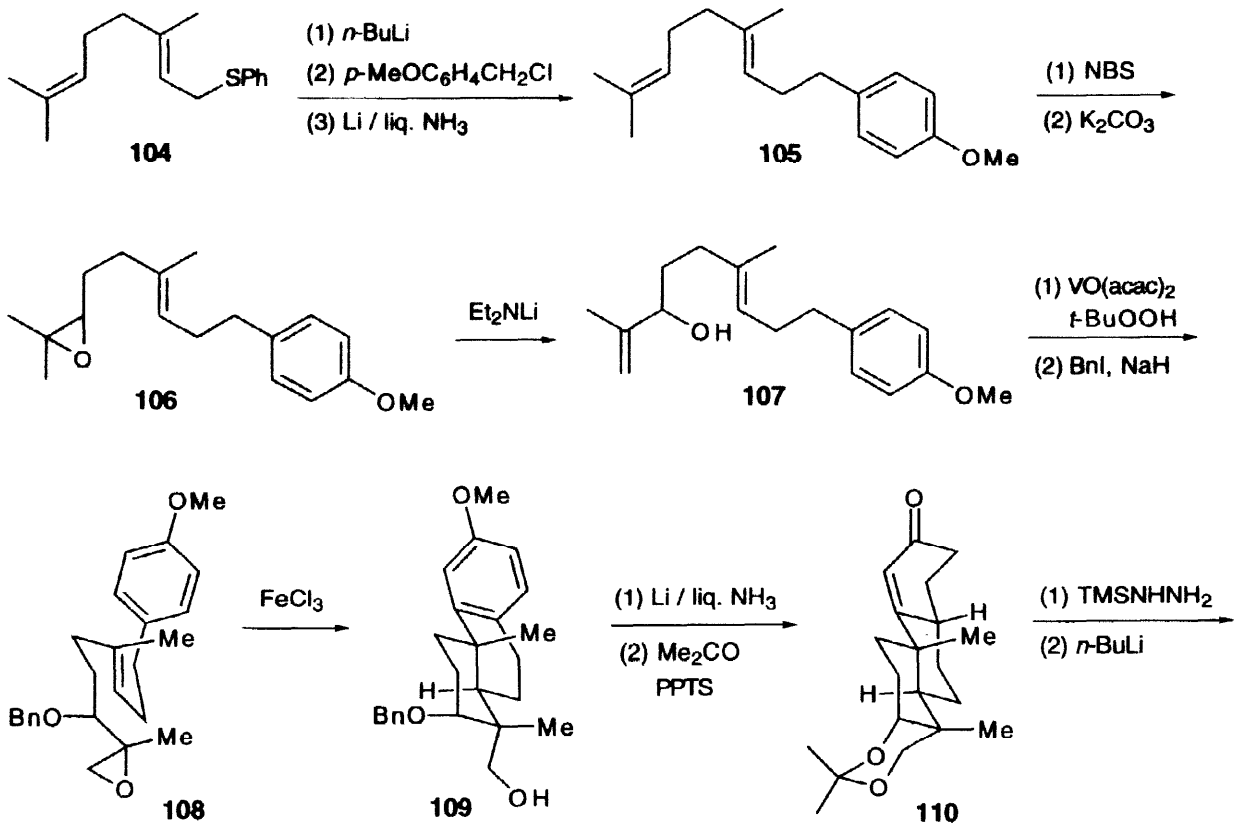
In order to construct the D ring part of (+)-**1**, intramolecular aldol condensation of **100** is carried out in the presence of KO*t*-Bu to yield the enone, which is subjected to selective hydrogenation. After transketalization, the enone **101** is obtained. AB-*trans* ring juncture is established by use of Birch reduction. The aldol **102** is transformed into the Corey intermediate **103**, and then **103** is converted to **58** in the same way as Corey[16] and his co-workers.

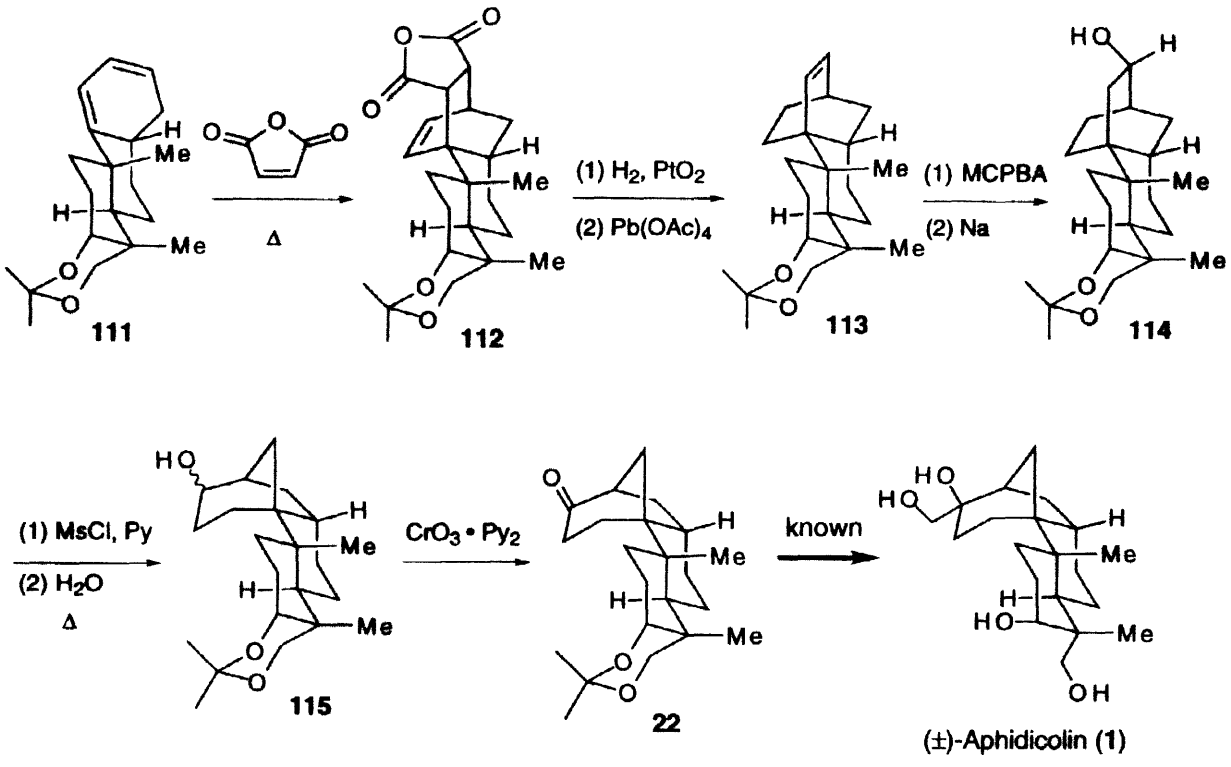

Me
TBSO
OLi
Me
93
Tol
S
O
94
O
-78 °C
TBSO
Me
95
(1)
Li
(2) HF
Me
96
NaOMe
Tol
Me
97
(> 98%ee)
Zn
NH4Cl
H
Me
98
OEt
PPTS
H
Me
99
(1) O3 ; Me2S
(2) LAH
(3) TBSCl, DMAP
Et3N
(4) CrO3, Py
OHC
OTBS
H
Me
100
(1) KOt-Bu
(2) H2 / Pd-C
(3) HO
OH
TsOH ,
OTBS
H
Me
101
Li / liq. NH3
then
CH2O
OTBS
H
Me
H
Me
OH
102
(1) L-Selectride®
(2) t-BuCHO
TsOH
(3) HF
OH
H
Me
H
Me
103
Corey
H
Me
H
Me
58

Scheme 7

2.3 From D Ring System

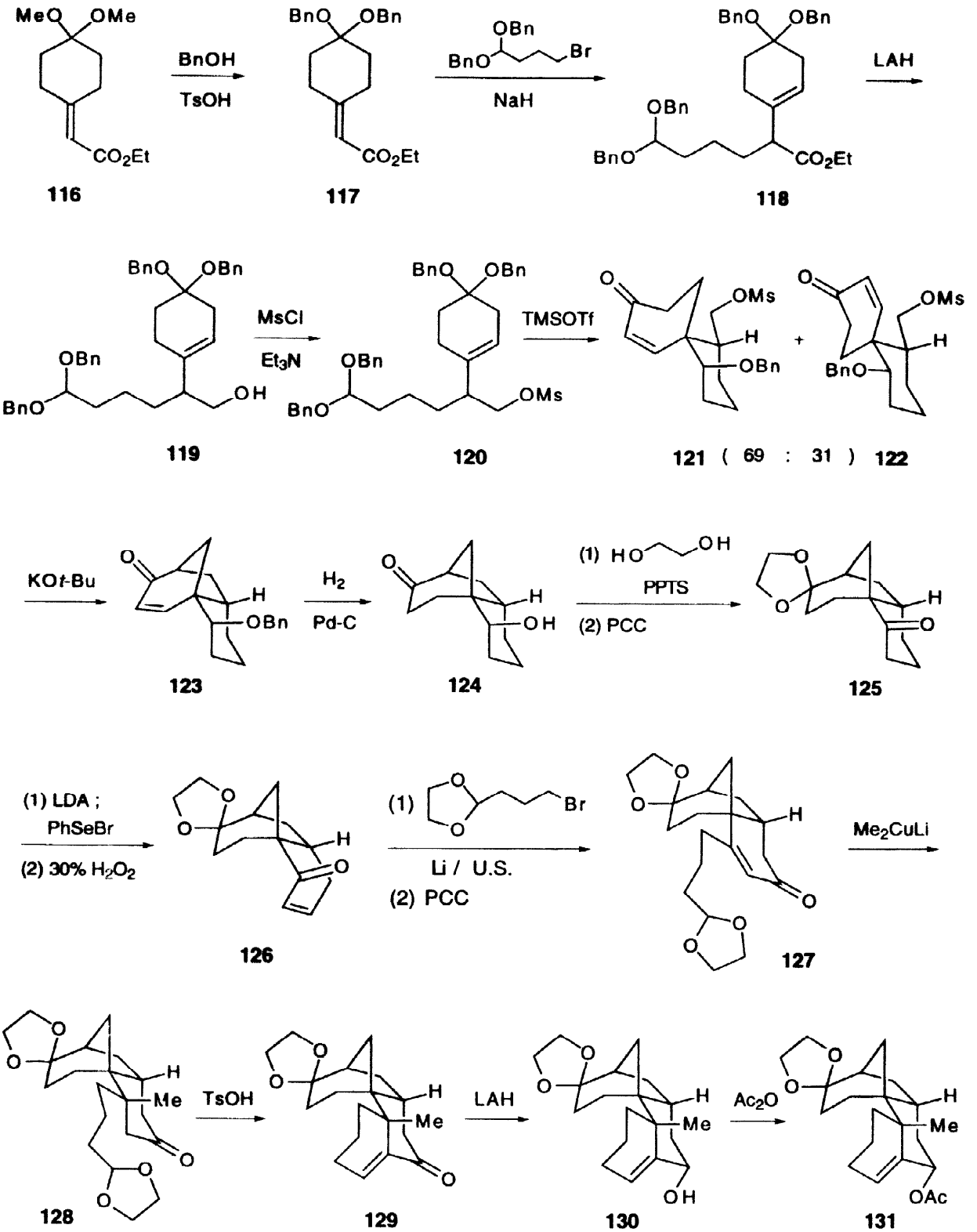
van Tamelen[20] and his co-workers also make use of polyene cyclization reaction as a key step. The requisite substrate **108** for biomimetic cyclization is prepared as shown in **Scheme 8**. Namely, treatment of phenylgeranyl thioether anion with *p*-methoxybenzyl chloride, followed by reductive desulfuryzation, affords the diene **105**. Regioselective epoxidation of the terminal olefin is achieved in 2 steps through bromohydrin formation. Basic treatment of the resulting epoxide **106** yields the allylic alcohol **107**, which is subjected to Sharpless epoxidation and *O*-benzylation to give rise to the compound **108**. Although the yield is low, polyene cyclization of **108** is conducted in the presence of $FeCl_3$ to provide the hydrophenanthrene **109**. Simultaneous de-*O*-benzylation and Birch reduction of the aromatic ring affords the corresponding methyl enol ether, which is treated with acetone in the presence of TsOH to give the acetonide **110**. Shapiro reaction of **110** provides the compound **111**, which is used as diene in the following intramolecular Diels-Alder reaction for construction of the CD ring system of **1**. Cycloaddition of **111** with maleic anhydride furnishes the adduct **112** as a sole product. After catalytic hydrogenation of **112**, $Pb(OAc)_4$-promoted decarboxylation is carried out to generate the olefin **113**, which is transformed into the desired alcohol **114** in 2 steps *via* stereoselective epoxidation of **113**. To prepare bicyclo[3.2.1]octane ring system from the bicyclo[2.2.2]octane derivative **114**, solvolytic rearrangement of the mesylate of **114** is performed affording the alcohol **115**. After PDC oxidation of **115**, the known ketone **22** is obtained.

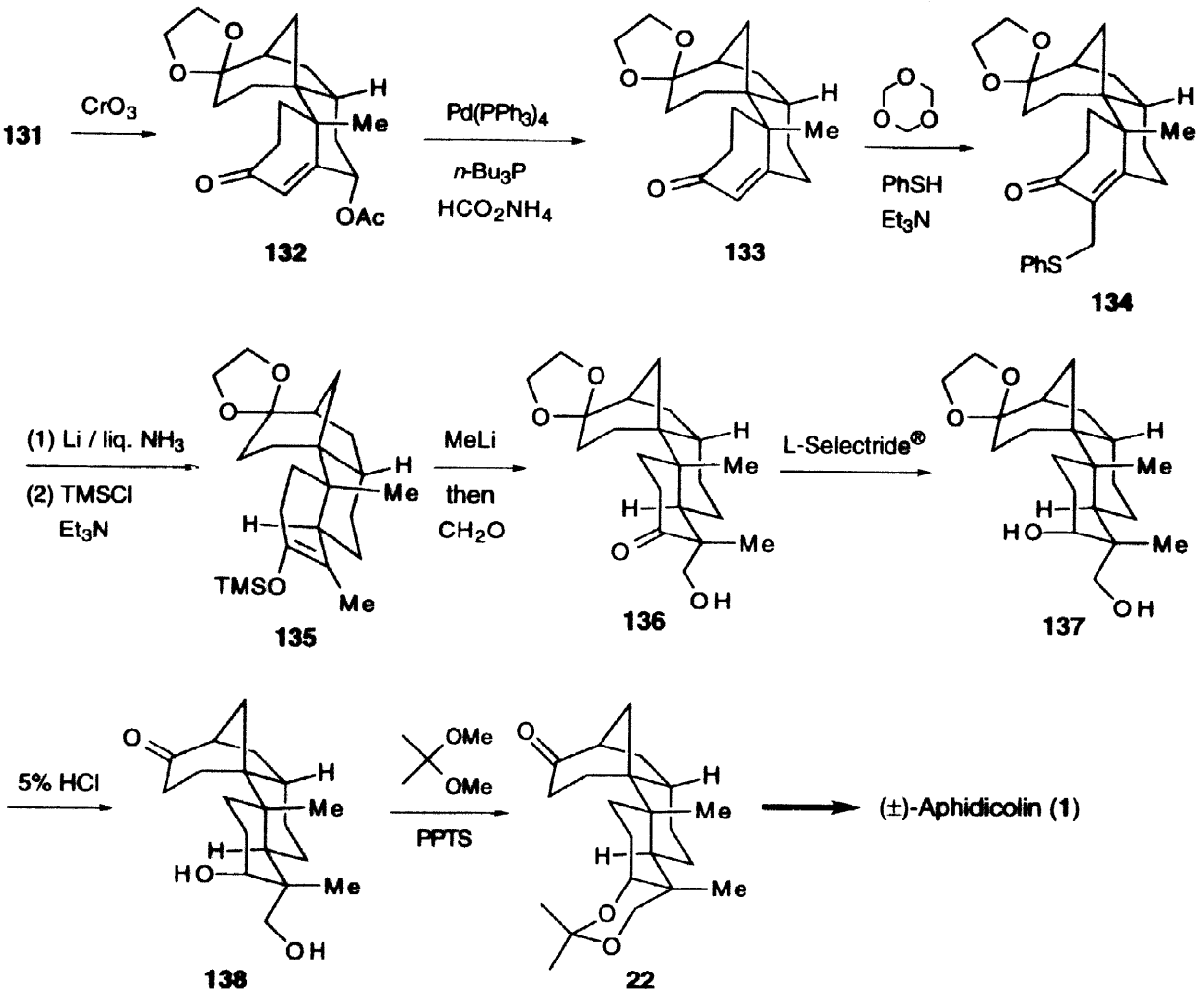




Scheme 8

An alternative stereoselective formal synthesis of (±)-aphidicolin (**1**) from the D ring precursor is accomplished by Iwata[21] and his co-workers. A Lewis acid-promoted spiroannulation reaction of the mesylate **120** is characteristic of the synthesis. The compound **120** is prepared from the dimethyl acetal **116** as depicted in **Scheme 9**. After transacetalization, deconjugative alkylation of the α,β-unsaturated ester **117**, followed by LAH reduction, gives rise to the alcohol **119**, which is mesylated to provide **120**. When TMSOTf is used as Lewis acid, spiroannulation reaction proceeds smoothly, giving a 2 : 1 mixture of the bicyclic enone **121** and the stereoisomer **122** which is not separable. The mixture is subjected to intramolecular displacement reaction in the presence of *t*-BuOH to provide the desired tricyclic compound **123** and undesired stereoisomers in a ratio of 2 : 1. Catalytic hydrogenation of **123**, followed by ketalization of **124**, yields the alcohol, which is oxidized with PCC to furnish the ketone **125**. After conversion of **125** to the enone **126** by means of α-selenenylation-oxidation procedure, the resulting enone **126** is subjected to Barbier reaction under ultrasonic irradiation to generate the corresponding allylic alcohol, which is treated with PCC. 1,4-Conjugate addition of methyl group to the resulting enone **127** proceeds diastereoselectively affording the ketone **128**. Intramolecular aldol condensation reaction of **128** is conducted with TsOH to give rise to the enone **129**. The compound **129** undergoes stereoselective reduction with LAH to give the alcohol **130**. After acetylation of **130**, allylic oxidation is carried out using chromium trioxide-3,5-dimethylpyrazole system to afford the enone **132**. Hydrogenation of **132** is achieved by means of palladium chemistry, furnishing the desired product **133**. Finally, the transformation of **133** into the ketone **22** is accomplished according to Ireland's technique (**Scheme 9**).

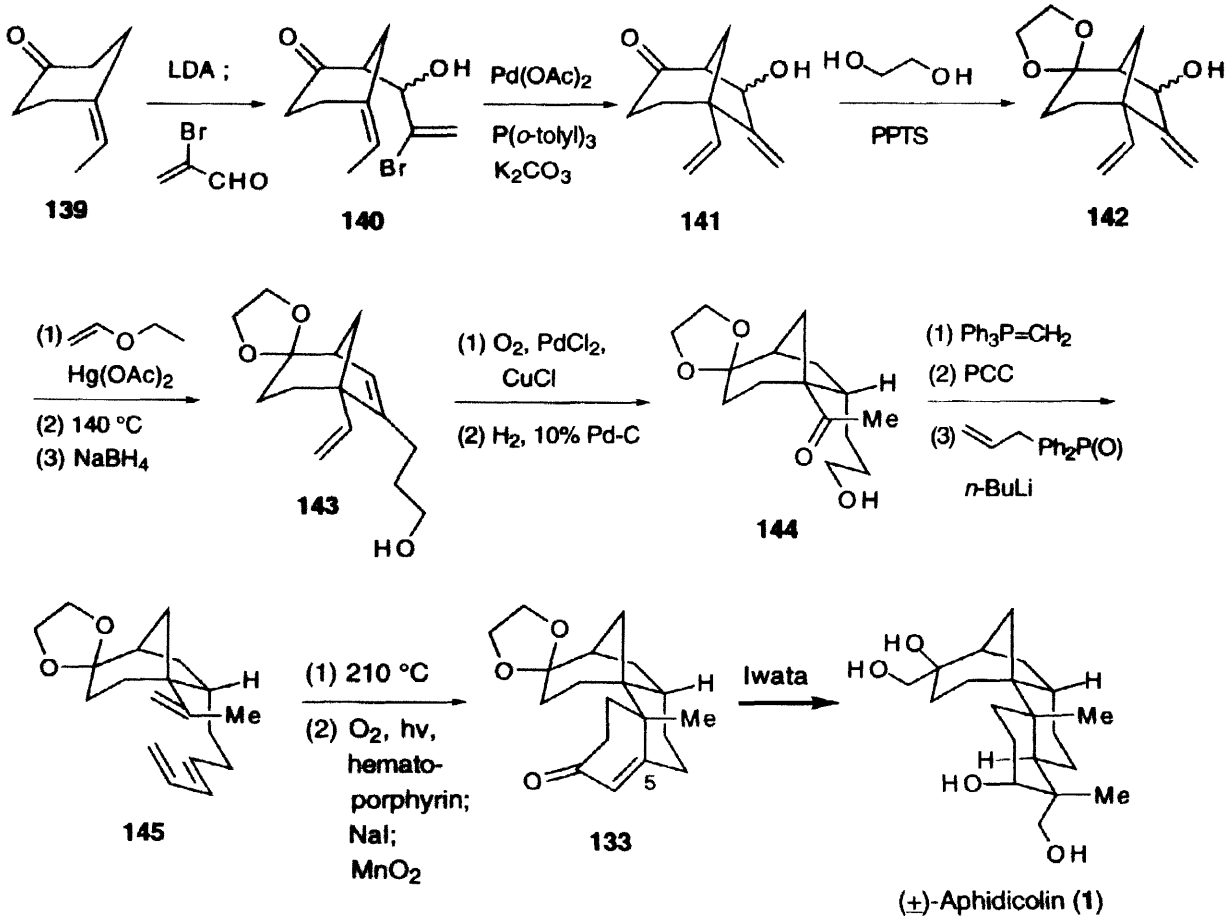

MeO OMe
CO2Et
116
BnOH
TsOH
BnO OBn
CO2Et
117
OBn
BnO
Br
NaH
OBn
BnO
OBn
CO2Et
118
LAH
OBn
BnO
OH
119
MsCl
Et3N
OBn
BnO
OMs
120
TMSOTf
O
OMs
H
OBn
+
BnO
121 (69 : 31) 122
KOt-Bu
O
H
OBn
123
H2
Pd-C
O
H
OH
124
(1) HO OH
PPTS
(2) PCC
O
O
H
O
125
(1) LDA ;
PhSeBr
(2) 30% H2O2
O
O
H
O
126
(1)
O
O
Br
Li / U.S.
(2) PCC
O
O
H
O
O
127
Me2CuLi
H
Me
O
128
TsOH
H
Me
O
129
LAH
H
Me
OH
130
Ac2O
H
Me
OAc
131



Scheme 9

In order to achieve an expeditious and efficient synthesis of aphidicolin (**1**), Toyota and Fukumoto planned the following synthetic route which features an intramolecular Heck reaction to generate the CD ring system of **1** and an intramolecular Diels-Alder reaction to form the AB ring part. The synthesis[22] is presented in **Scheme 10**. The requisite substrate **140** for the first key step was prepared by means of intermolecular aldol reaction of 4-ethylidenecyclohexan-1-one **139** and α-bromoacrolein. The critical Heck cyclization of **140** proceeded cleanly in the presence of 10 mol % $Pd(OAc)_2$, 20 mol % P(*o*-tolyl)$_3$, and 2 equiv of K_2CO_3 to provide the bicyclo[3.2.1]octane compound **141**. After ketalization of **141**, conversion of **142** to the alcohol **143** was performed by means of Claisen rearrangement of the vinyl ether of **142**. At this stage, there is no need to separate a 3 : 1 mixture of the alcohol **141**. Both isomers give the same product. Regioselective Wacker reaction was next conducted to give rise to the corresponding methyl ketone, which is subjected to catalytic hydrogenation to yield the saturated alcohol **144**. As a consequence of steric congestion on the *endo* surface of the bicyclo[3.2.1]octane subunit, the hydrogenation gave solely **144**. The triene **145** for the next key step of this synthesis was prepared in 3 steps. An intramolecular Diels-Alder reaction of the triene **145** was conducted in the presence of methylene blue to furnish the desired tetracyclic adduct, which is transformed into the enone **133** by applying Nickon's

method. Probably due to the $A^{1,3}$ strain with the bicyclo[3.2.1]octane system, the conformation of the dienophile part is fixed, and the stereochemistry of C-10 methyl group is cotrolled. On top of that, both C-5 epimers, produced on the occasion of the cycloaddition, undergo singlet oxygen-promoted allylic oxidation to provide the same enone **133**. The conversion of the enone **133** to (±)-aphidicolin (**1**) has been carried out previously.

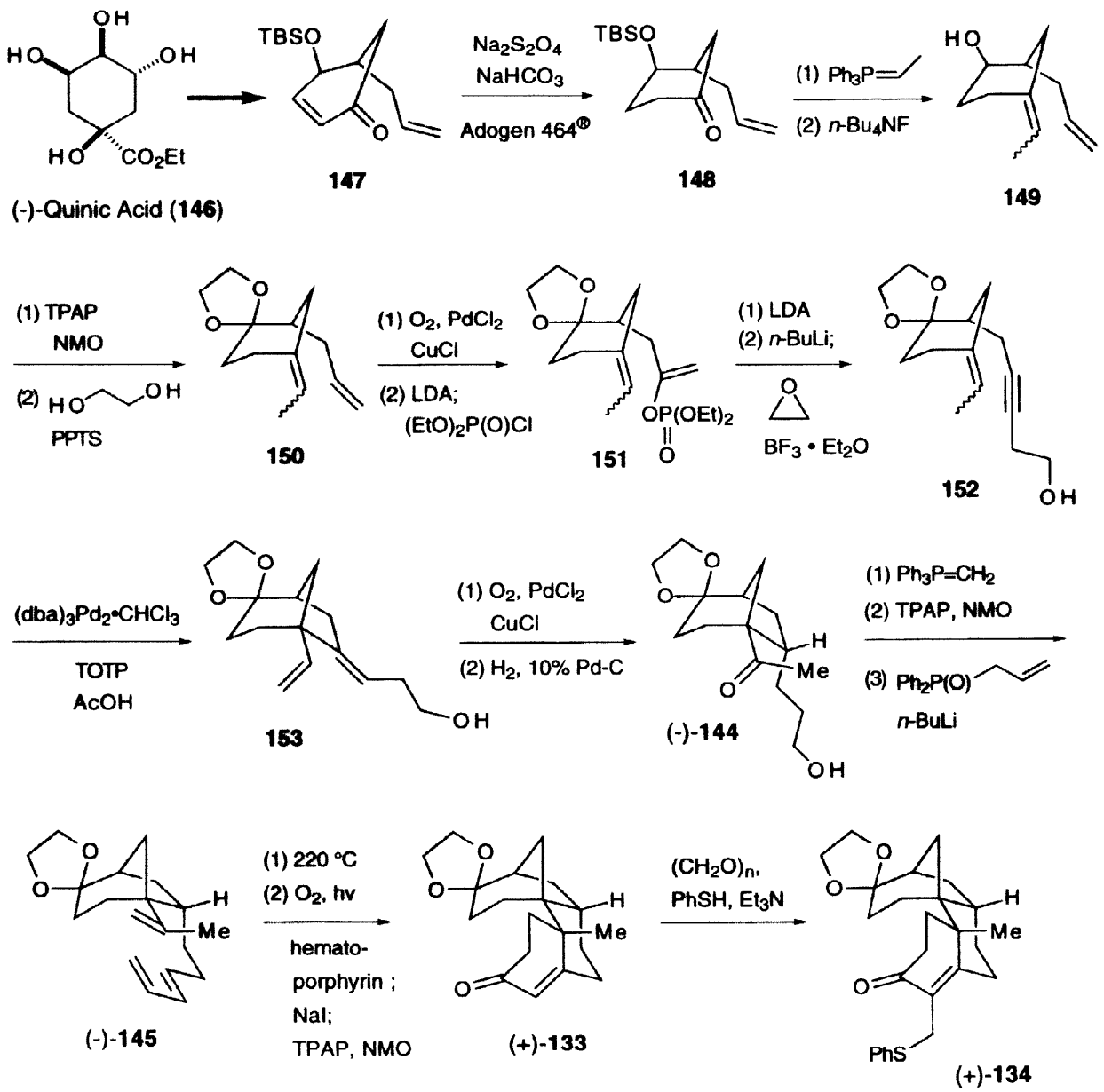


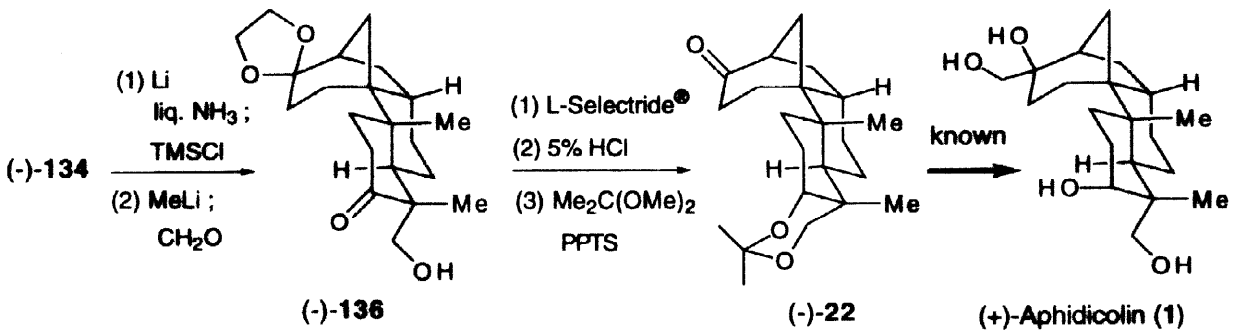
Scheme 10

The above synthetic route is adaptable for (+)-aphidicolin (**1**) synthesis. Toyota and Fukumoto elected (-)-quinic acid (**146**) as the starting material. The transformation of **146** into the enone **147** has already been demonstrated by Overman[23] and his co-workers. To prepare the palladium-catalyzed cycloisomerization precursor **152**, the enantiopure enone **147** was reduced with sodium hydrosulphite in the presence of Adogen 464® and sodium hydrogencarbonate to provide the ketone **148**, which was subjected to Wittig reaction and deprotection, affording the ethylidene derivative **149** as a 1 : 1 mixture of *E* and *Z* stereoisomers. Stereoselectivity in the Wittig reaction was of no consequence, since both double bond isomers were converted to the bicyclo[3.2.1]octane derivative **153**. After TPAP oxidation, the carbonyl group was ketalized. Regioselective Wacker oxidation of **150** was achieved by Tsuji's technique.[24] After examination of various reaction conditions for introducing the enyne functionality of the side chain, they adopted the following process as shown in **Scheme 11**. Treatment of the Wacker oxidation product with LDA under kinetic conditions, followed by

trapping of the resulting enolate with diethyl chlorophosphate, gave the enol phosphate **151**. Basic treatment of **151** with LDA furnished the acetylene, which was subjected to alkylation reaction by applying Kotsuki's procedure.[25] Before testing of cycloisomerization reaction, it was confirmed that epimerization does not take place during the ketalization process (**149** → **150**). After careful investigation of the key reaction, the following conditions were found to be optimal: a mixture of 5 mol % AcOH, 2.5 mol % $(dba)_3Pd_2{\cdot}CHCl_3$, 5 mol % tri-*o*-tolylphosphine and **152** in benzene was heated in a sealed tube for 15 h. Selective Wacker oxidation of **153** followed by catalytic hydrogenation afforded the keto alcohol (-)-**144**. Transformation of (-)-**144** into (+)-**133** was performed by following the reported procedure.

Following Iwata's protocol, a stereoselective formal synthesis of (+)-aphidicolin (**1**) was achieved.

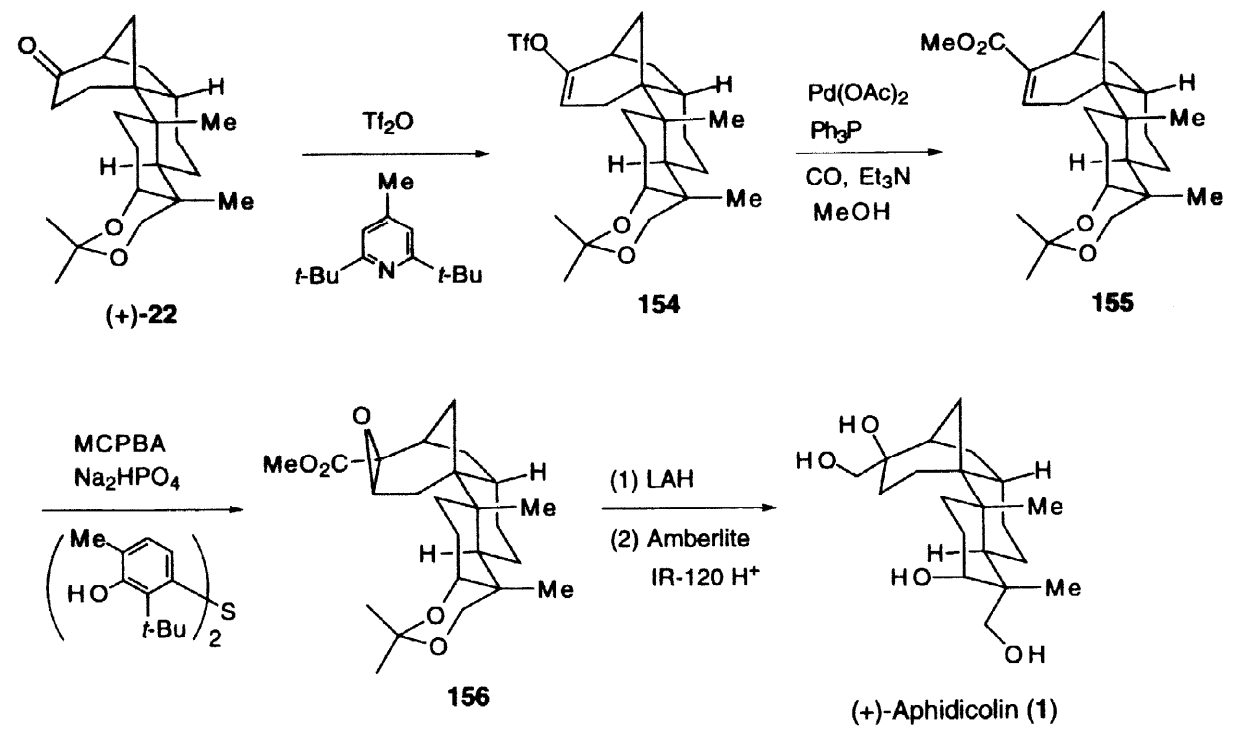




Scheme 11

2.4. Functionalization at C-16

In aphidicolin synthesis, the problem of stereoselective construction of the C-16 functionality is open. Smith III and his co-workers[26] have recently reported an efficient method for preparing the glycol moiety of aphidicolin (**1**) by means of palladium(0)-catalyzed carbonylation reaction and stereoselective epoxidation. After conversion of the ketone **22** to the enol triflate **154**, palladium-catalyzed carbonylation of **154** provides the α,β-unsaturated ester **155**. Stereoselective epoxidation of **155**, followed by LAH reduction, affords the diol, which is subjected to hydrolysis to give (+)-aphidicolin (**1**) (**Scheme 12**).



Scheme 12

3. Synthesis of Stemodin

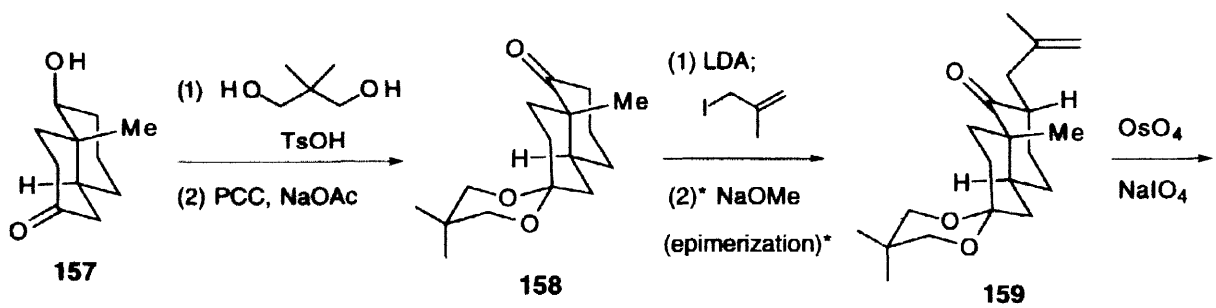
3.1. From AB Ring System

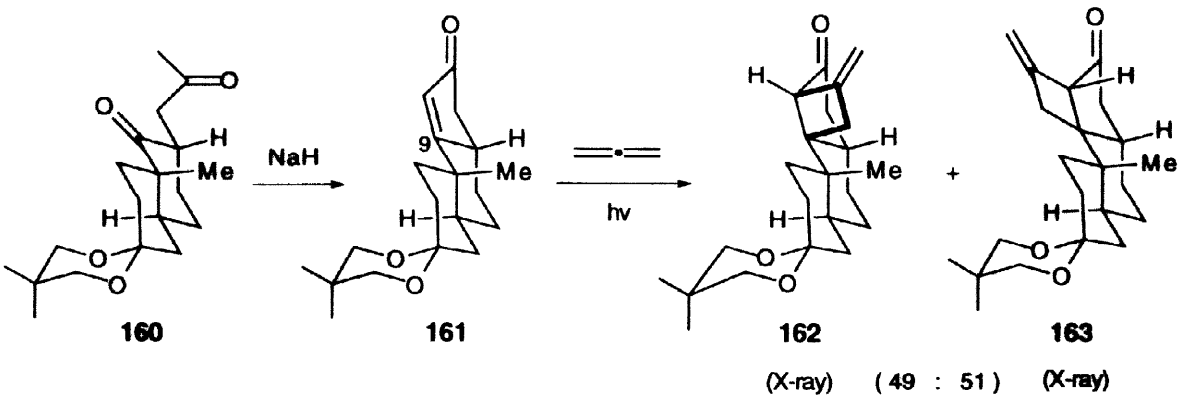
From a common precursor, stereoselective syntheses of stemodin (**4**), stemodinone (**5**), 2-desoxystemodinone (**6**) and maritimol (**7**) are achieved by Piers[27] and his co-workers. Key reactions of the syntheses are photoaddition of allene to introduce alkyl side chain at C-9 position and Thorpe-Ziegler reaction to generate the D ring part of the above natural products. Transformation of the keto alcohol **157** into pentacyclic compounds **162** and **163** is depicted in **Scheme 13**. Namely, ketalization of the compound **157**, prepared from Wieland-Miescher ketone, followed by PCC oxidation, gives rise to the ketone **158**. After alkylation of **158** with methallyl iodide in the presence of LDA, epimerization reaction of the resulting stereoisomeric mixture is carried out with NaOMe to produce the equatorial isomer **159** as the major product (~95 : 5). The *exo*-olefin **159**, upon reaction with a catalytic amount of osmium tetroxide and excess of sodium metaperiodate, is converted to the methyl ketone **160**. Base-promoted intramolecular aldol condensation of the diketone **160** provides the enone **161** as the major product. In order to introduce a functionalized two-carbon side chain at C-9 position, photoaddition of allene to **161** is conducted to afford the two major adducts **162** and **163** (~1 : 1).

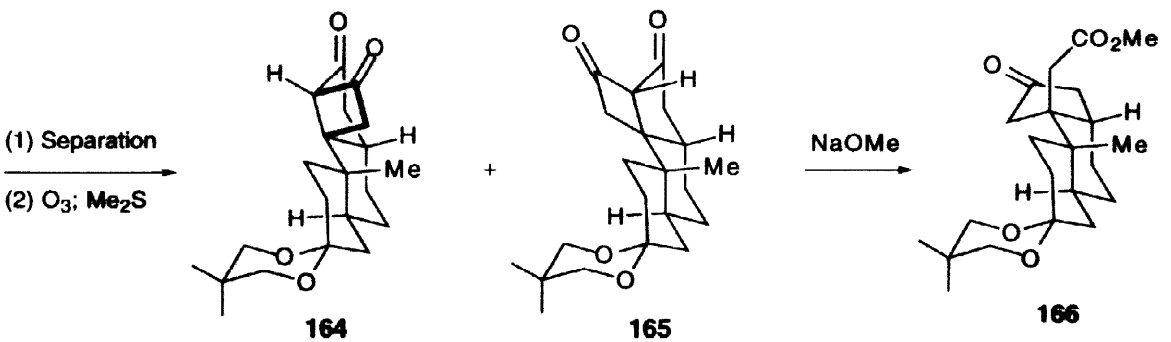
After ozonolysis, each diketone **164** and **165** is subjected to the same transformational conditions (basic treatment), which yield the same product **166** in both instances. Since both of the major photoadducts **162** and **163** are converted efficiently to the keto ester **167**, the non-stereoselectivity of the photoaddition is not crucial. As a plausible mechanism that accounts for the observation, they propose the following explanation as shown in **Scheme 13**. The diketone **165** undergoes ring opening reaction to yield **167** and **169**. **167** forms the diketone **168**, cleavable to **166**. The cyclobutanone **169** recondenses to **164**.

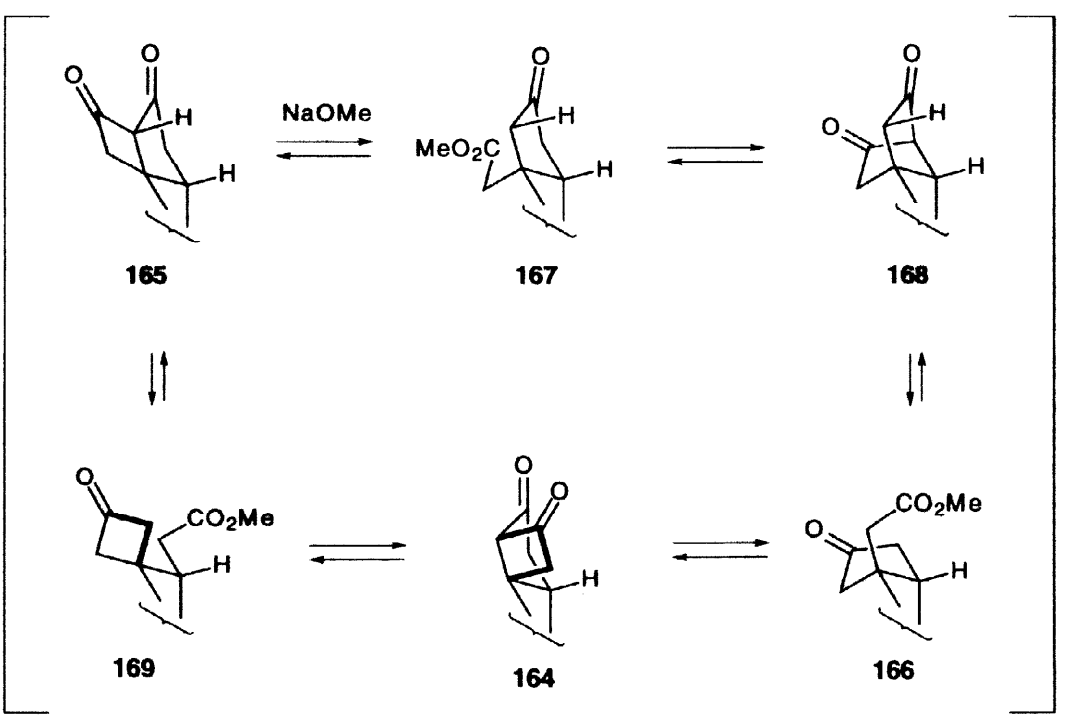
166 is transformed conveniently into the diketone **172** through Thorpe-Ziegler reaction without purification of the intermediates. Saegusa reaction of the bis silyl enol ether of **172**, followed by dimethylation, affords the bis enone **175** as a major product. Catalytic hydrogenation of **175** provides the diketone **176**.

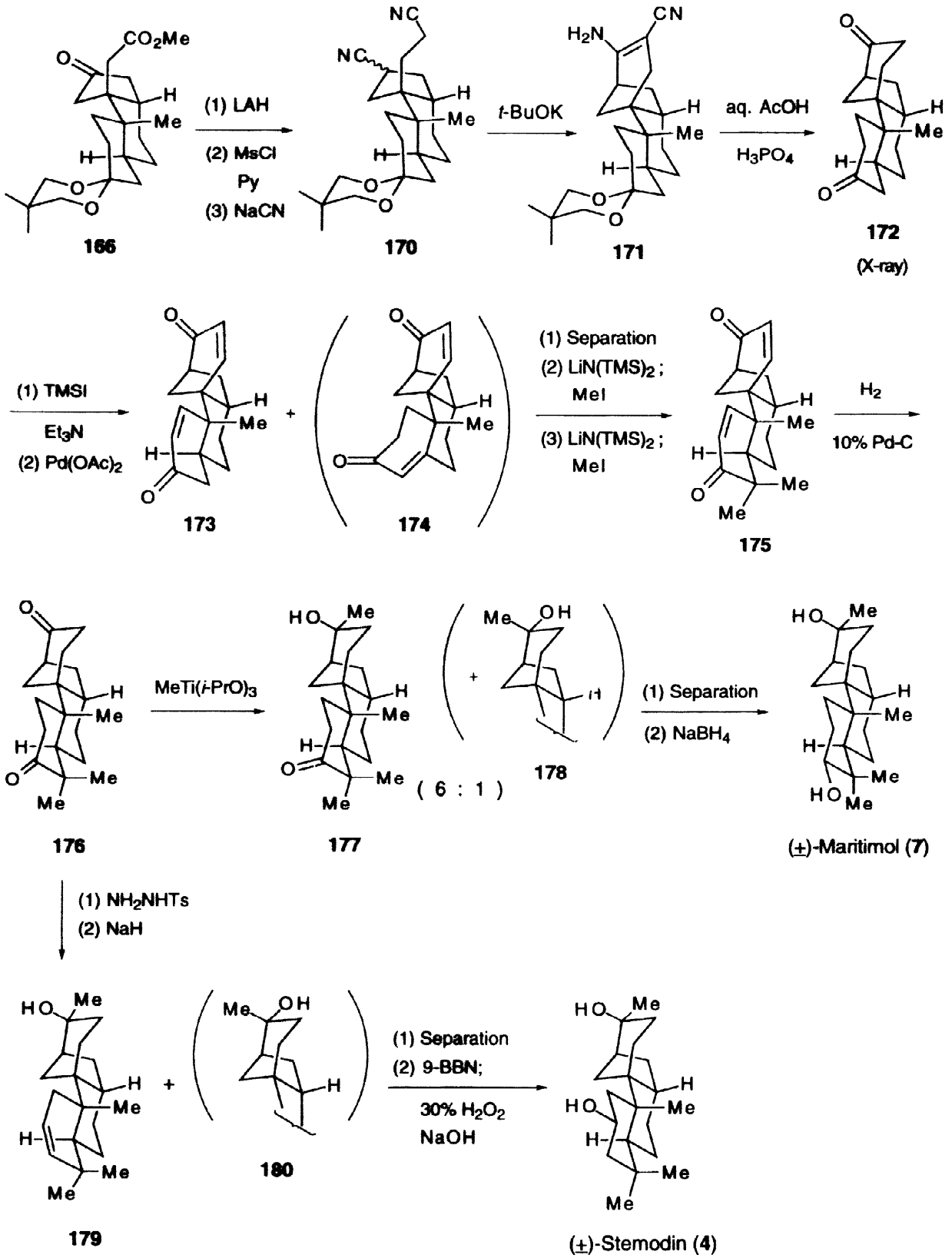
Regioselective 1,2-addition reaction to the diketone **176** is achieved with methyltriisopropoxy-titanium. While the resulting keto alcohol **177** is converted to maritimol (**7**) after $NaBH_4$ reduction, **177** is transformed into (±)-stemodin (**4**) by means of Shapiro reaction and hydroboration-oxidation process. Since the conversions (**177** → (±)-2-desoxystemodinone (**6**) and **162** → (±)-stemodinone (**5**)) are accomplished previously, the work provides formal syntheses of **5** and **6**.




NaH
hv
160
161
162
163
(X-ray)
(49 : 51)
(X-ray)

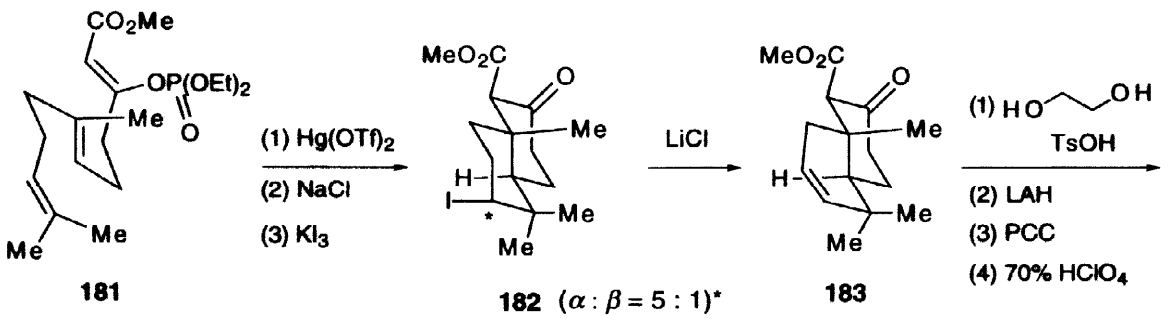

(1) Separation
(2) O3; Me2S
NaOMe
164
165
166


NaOMe
MeO2C
CO2Me
165
167
168
169
164
166

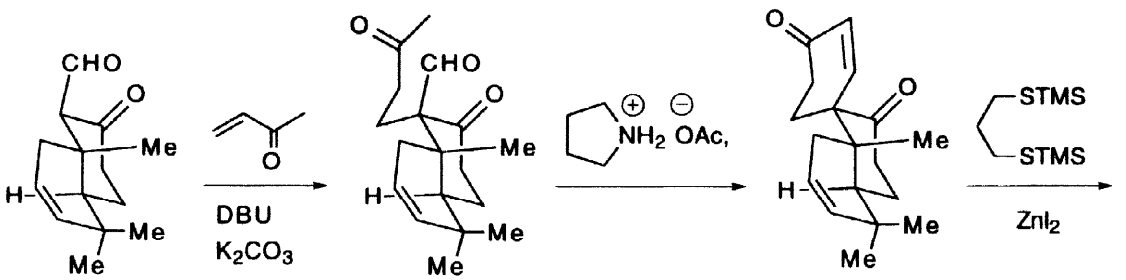

CO2Me
(1) LAH
(2) MsCl
Py
(3) NaCN
NC
CN
t-BuOK
H2N
aq. AcOH
H3PO4
166
170
171
172
(X-ray)
(1) TMSI
Et3N
(2) Pd(OAc)2
173
174
(1) Separation
(2) LiN(TMS)2;
MeI
(3) LiN(TMS)2;
MeI
175
H2
10% Pd-C
MeTi(i-PrO)3
176
177
(6 : 1)
178
(1) Separation
(2) NaBH4
(±)-Maritimol (7)
(1) NH2NHTs
(2) NaH
179
180
(1) Separation
(2) 9-BBN;
30% H2O2
NaOH
(±)-Stemodin (4)

Scheme 13

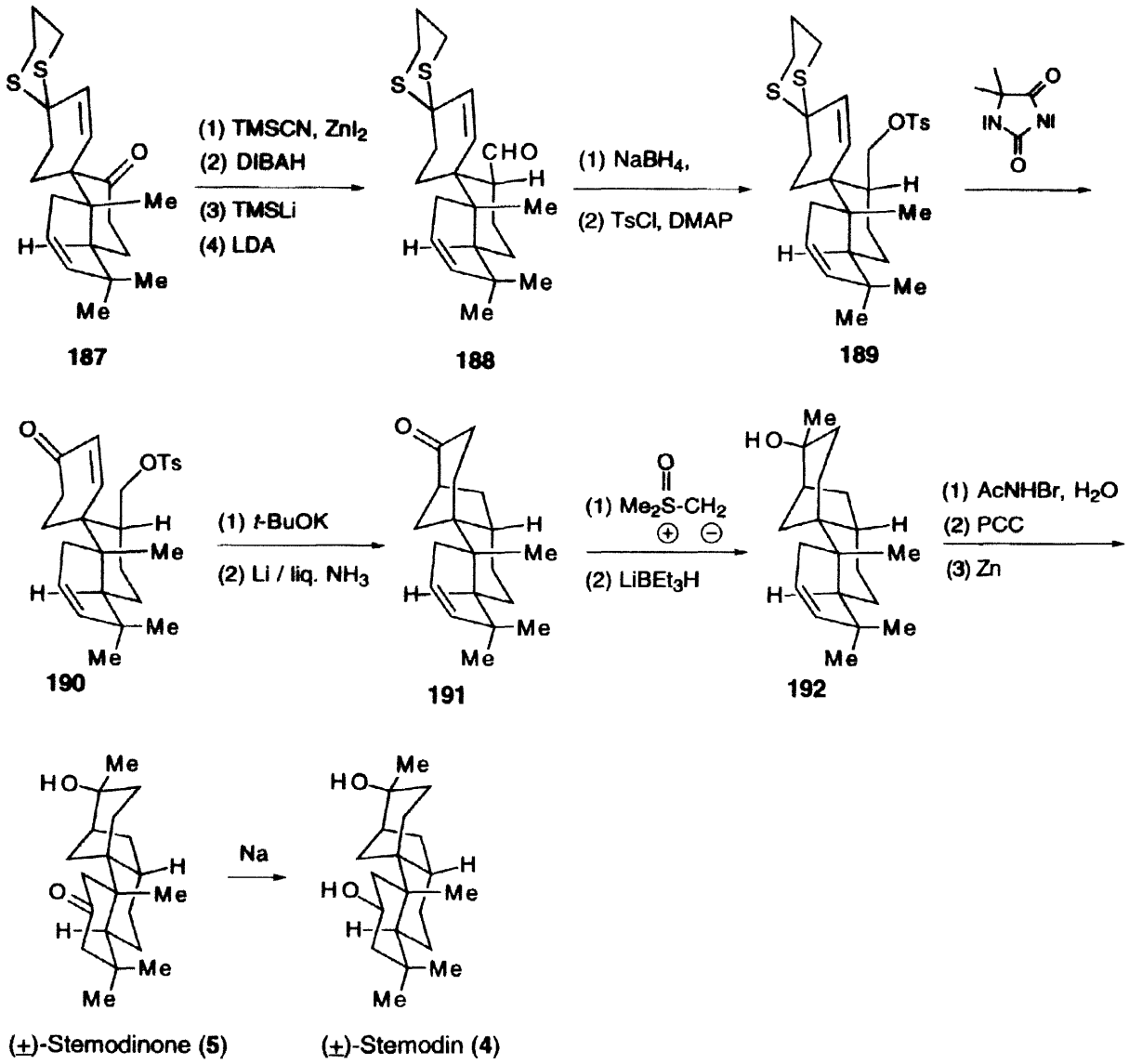
Corey[28] and his co-workers' approach to the syntheses of (±)-stemodin (**4**) and (±)-stemodinone (**5**) is based on a mercuric ion-catalyzed biomimetic polyene cyclization reaction in the same way to that used for aphidicolin synthesis. The enol phosphate **181**, upon reaction with mercuric trifluoroacetate, followed by NaCl, is converted to the bicyclic compound, which is subjected to displacement reaction of the chloromercury with potassium triiodide to give the iodide **182** as a 5 : 1 mixtute. Treatment of **182** with LiCl affords the unsaturated β-keto ester **183**. After transformation of **183** into the keto aldehyde **184** in 4 steps, Michael reaction of **184** with methyl vinyl ketone in the presence of DBU and K_2CO_3 furnishs the compound **185** which, upon treatment with pyrrolidinium acetate, provides the enone **186**. Selective thioketalization of the less hindered carbonyl group of **186** yields **187**, which is converted to the aldehyde **188** by means of the same technique described in their aphidicolin synthesis (**Scheme 14**). After reduction of the aldehyde **188**, followed by tosylation of the resulting alcohol, thioketal cleavage of **189** is achieved by using 1,3-diiodo-5,5-dimethylhydantoin to produce the enone **190**. Ring formation reaction of **190** in the presence of *t*-BuOK, followed by Birch reduction of the corresponding enone, gives rise to the unsaturated ketone **191**. C-18 Methyl group is introduced to **191** *via* spiro epoxide formation reaction with dimethylsulfonium methylide, followed by Super Hydride® reduction. Transformation of the resulting **192** into (±)-stemodinone (**5**) is achieved through a sequence of bromohydrin formation, oxidation, and debromination. Finally, stemodinone (**5**) is reduced with Na to generate stemodin (**4**).



181 **182** ($\alpha : \beta = 5 : 1$)* **183**



184 **185** **186**

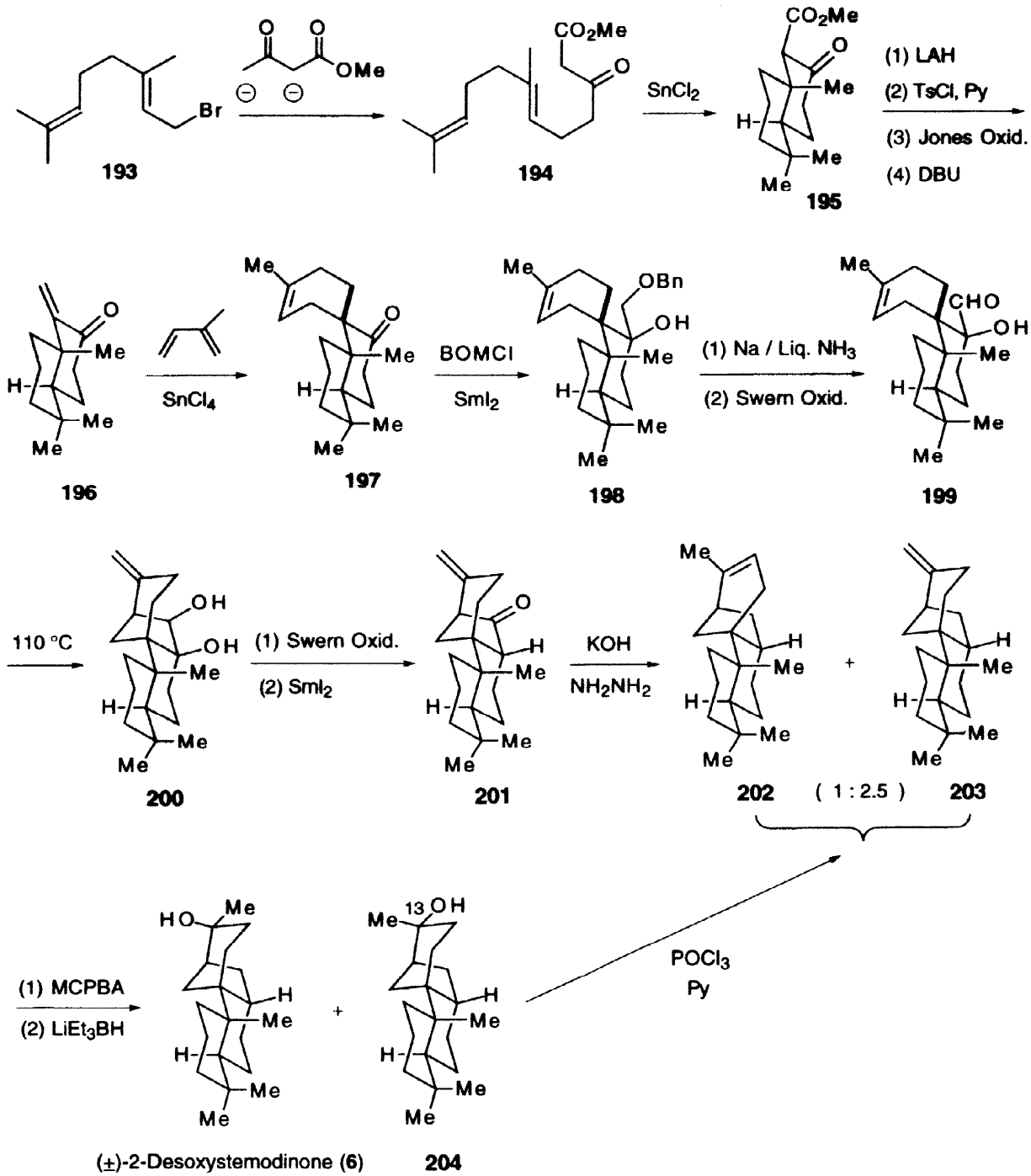


Scheme 14

After reduction of the aldehyde **188**, followed by tosylation of the resulting alcohol, thioketal cleavage of **189** is achieved by using 1,3-diiodo-5,5-dimethylhydantoin to produce the enone **190**. Ring formation reaction of **190** in the presence of *t*-BuOK, followed by Birch reduction of the corresponding enone, gives rise to the unsaturated ketone **191**. C-18 Methyl group is introduced to **191** *via* spiro epoxide formation reaction with dimethylsulfonium methylide, followed by Super Hydride® reduction. Transformation of the resulting **192** into (±)-stemodinone (**5**) is achieved through a sequence of bromohydrin formation, oxidation, and debromination. Finally, stemodinone (**5**) is reduced with Na to generate stemodin (**4**).

The key steps in the synthesis of 2-desoxystemodinone by White[29] and his co-workers are an intermolecular Diels-Alder reaction to generate the D ring system and a hydroxy-assisted intramolecular ene reaction to form the C ring system. The AB ring part is prepared by means of biomimetic polyene cyclization process. Dianion of methyl acetoacetate is alkylated with **193** to form the keto ester **194**. The formation of the *trans*-fused decalin

derivative **195** is achieved by stannic chloride-promoted cyclization reaction of **194**. Transformation of the β-keto ester **195** into the enone **196** is carried out by a sequence of LAH reduction, tosylation of the resulting primary alcohol, oxidation of the secondary alcohol, and elimination with DBU. Regioselective access to **197** is provided through stannic chloride-catalyzed intermolecular Diels-Alder reaction of **196** with isoprene.

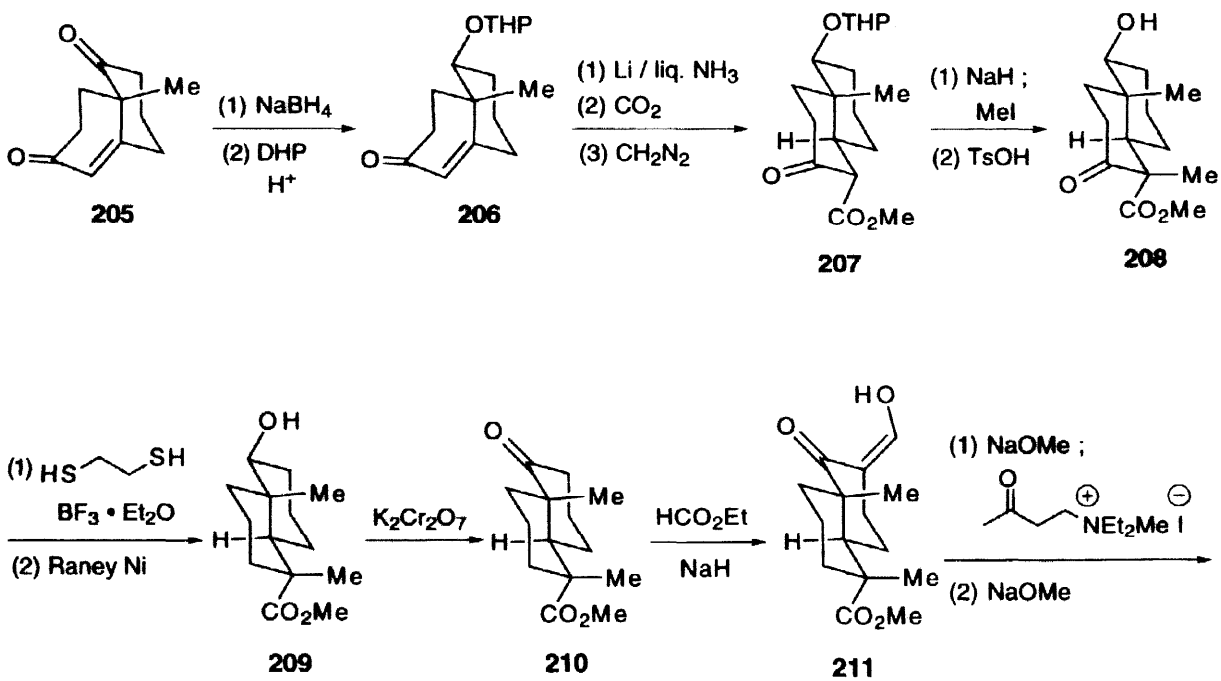


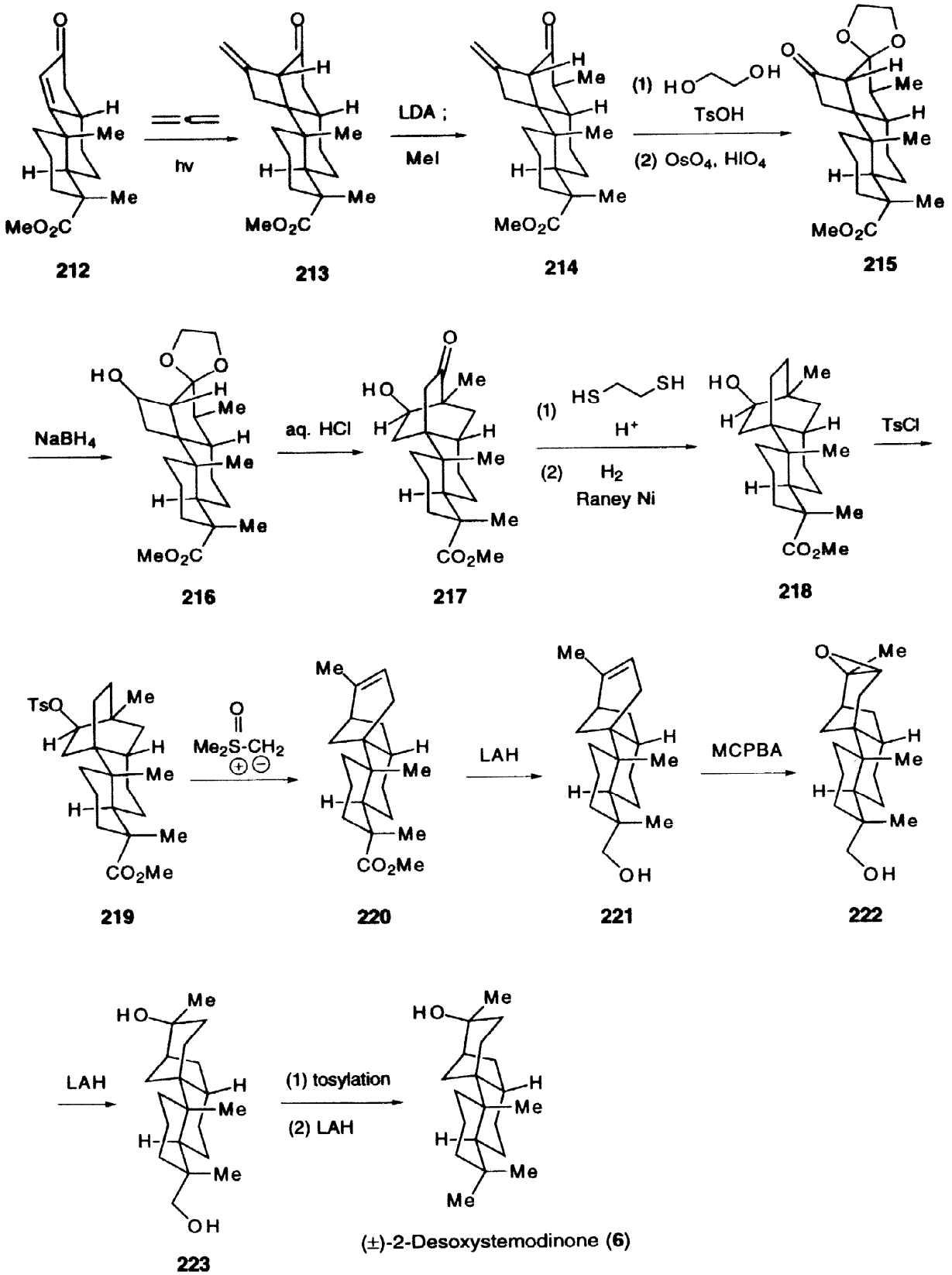
Scheme 15

Nucleophilic addition to the carbonyl group of **197** is hampered by the surrounding steric hindrance. However, coupling reaction of **197** with benzyl chloromethyl ether in the presence of samarium diiodide gives the alcohol **198**, which is subjected to reductive debenzylation under Birch conditions followed by oxidation of the resulting primary alcohol to afford the α-hydroxy aldehyde **199**. The key ene reaction of this synthesis (**199** → **200**) is conducted under thermal conditions. After Swern oxidation of **200**, reductive removal of the hydroxyl group of the resulting compound by Molander's procedure,[30] followed by Huang-Minlon reduction produces a 2.5 : 1 mixture of the *exo* and *endo* olefins **203**, and **202**, respectively (**Scheme 15**).

Upon treatment of the mixture of the olefins **202** and **203** with MCPBA, a mixture of epoxides is produced. This mixture is subjected to Super Hydride® reduction to generate a 1.4 : 1 mixture of (±)-2-desoxystemodinone (**6**) and its C-13 isomer **204**, which is recycled to a mixture of **202** and **203** by dehydration with $POCl_3$.

In the synthesis of 2-desoxystemodinone by Kelly and his co-workers,[31] photoaddition reaction of allene to an enone and two subsequent skeletal rearrangement reactions are the key processes. After usual conversion of Wieland-Miescher ketone (**205**) to the THP ether **206**, reductive carboxylation of **206** followed by esterification of the resulting carboxylic acid generates the β-keto ester **207**. Subsequent methylation and deprotection are next performed to furnish the keto alcohol **208**, whose carbonyl group is removed by standard method. Oxidation of **209** leads to the keto ester **210**, which is transformed into the enone **212** by a sequence of formylation, Michael reaction and a simultaneous intramolecular aldol condensation and deformylation (**Scheme 16**).




212
213
214
215
216
217
218
219
220
221
222
223
hν
LDA ;
MeI
(1) HO OH
TsOH
(2) OsO4, HIO4
NaBH4
aq. HCl
(1) HS SH
H+
(2) H2
Raney Ni
TsCl
LAH
MCPBA
LAH
(1) tosylation
(2) LAH
(±)-2-Desoxystemodinone (6)

Scheme 16

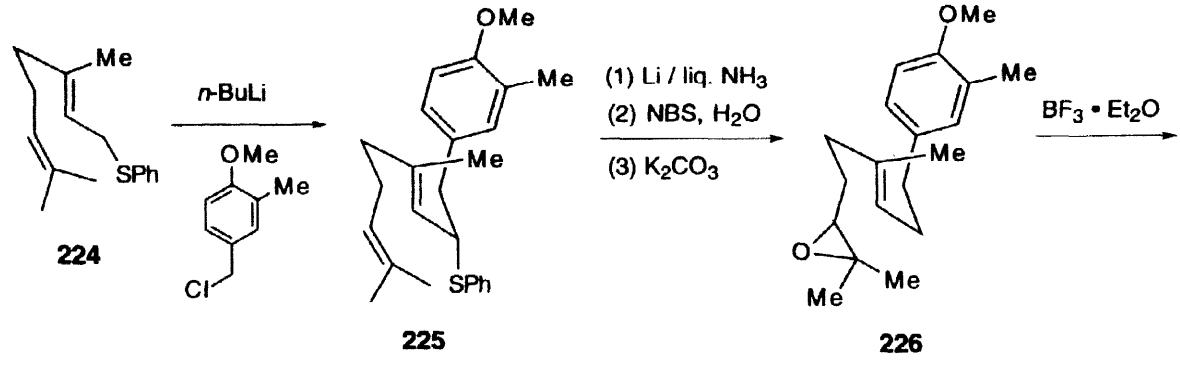
Stereoselective photoaddition of allene to the enone **212** provides the adduct **213**, which is subjected to methylation under kinetic conditions to give the compound **214**. After ketalization of **214**, followed by Lemieux-Johnson oxidation, the resulting cyclobutanone **215** is reduced with $NaBH_4$ to produce the alcohol **216** which, upon treatment with diluted HCl solution, gives the corresponding bicyclo[2.2.2]octane derivative **217** as a major product through tandem retro-aldol-aldol reaction. Thioketalization of **217**, followed by desulfurization reaction, furnishes the alcohol **218**, which is tosylated to provide **219**.

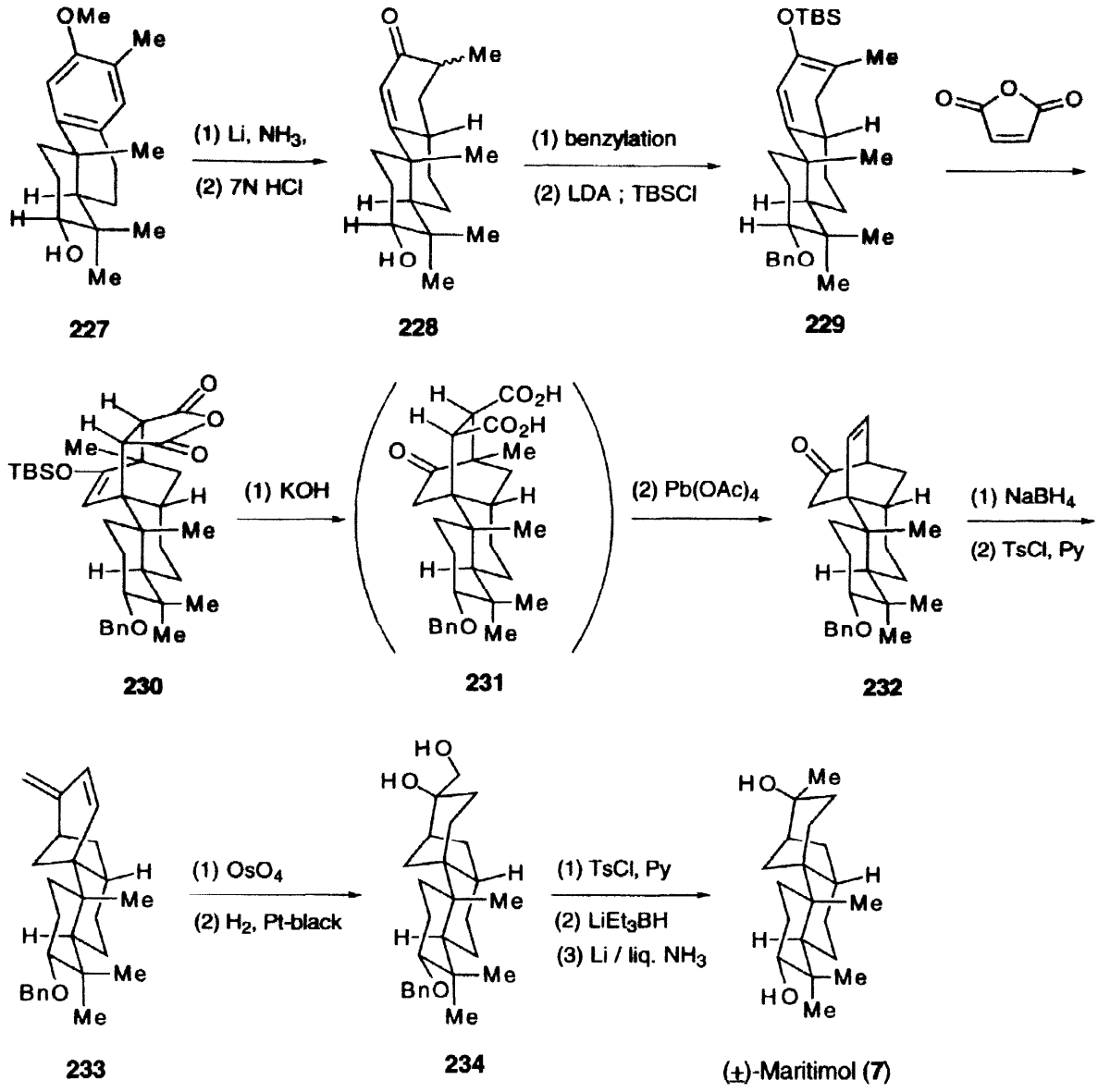
Rearrangement reaction of the tosylate **219** is conducted with methyl sulfinyl carbanion to afford the bicyclo[3.2.1]octane derivative **220**, which is subjected to reduction with LAH to give the alcohol **221**. After stereoselective epoxidation of **221** with MCPBA, the resulting epoxide **222** is reduced with LAH to provide the diol **223**. Finally, **223** is converted to (±)-2-desoxystemodinone (**6**) by succesive tosylation and LAH reduction (**Scheme 16**).

3.2. From C Ring System

The first total synthesis of (±)-maritimol (**7**) is accomplished by van Tamelen[32] and his co-workers by means of a biomimetic polyene cyclization reaction and intermolecular Diels-Alder reaction as the key steps. The requisite substrate **226** for the first key step is prepared as presented in **Scheme 17**. The treatment of the phenylgeranyl thioether anion with 2-methyl-4-(chloromethyl)anisole gives the diene **225**, which is subjected to desulfurization reaction under Birch condition and bromohydrin formation followed by basic treatment to provide the epoxide **226**. BF_3•Et_2O-promoted biomimetic polyene cyclization reaction of **226** is achieved to generate the alcohol **227**, which is transformed into the enone **228** by a sequence of Birch reduction and acidic treatment. After benzylation of **228**, the resulting compund is successively treated with LDA and TBSCl to yield the cross-conjugated silyl enol ether **229** (**Scheme 17**).

In order to construct the bicyclo[2.2.2]octane ring system, intramolecular Diels-Alder reaction of **229** with maleic anhydride is performed to furnish the pentacyclic compound **230**. Hyrolysis of **230** followed by oxidative decarboxylation of the resulting diacid **231** gives rise to the unsaturated ketone **232**, which in turn is subjected to $NaBH_4$ reduction. Skeletal rearrangement of the resulting β-oriented alcohol is achieved with TsCl in the presence of pyridine to lead to the bicyclo[3.2.1]octane derivative **233**. Regioselective dihyroxylation with OsO_4 of **233** affords the unsaturated glycol, which is hydrogenated to produce **234**. After tosylation of the primary hydroxyl group of **234**, Super Hydride® reduction followed by debenzylation produces (±)-maritimol (**7**).

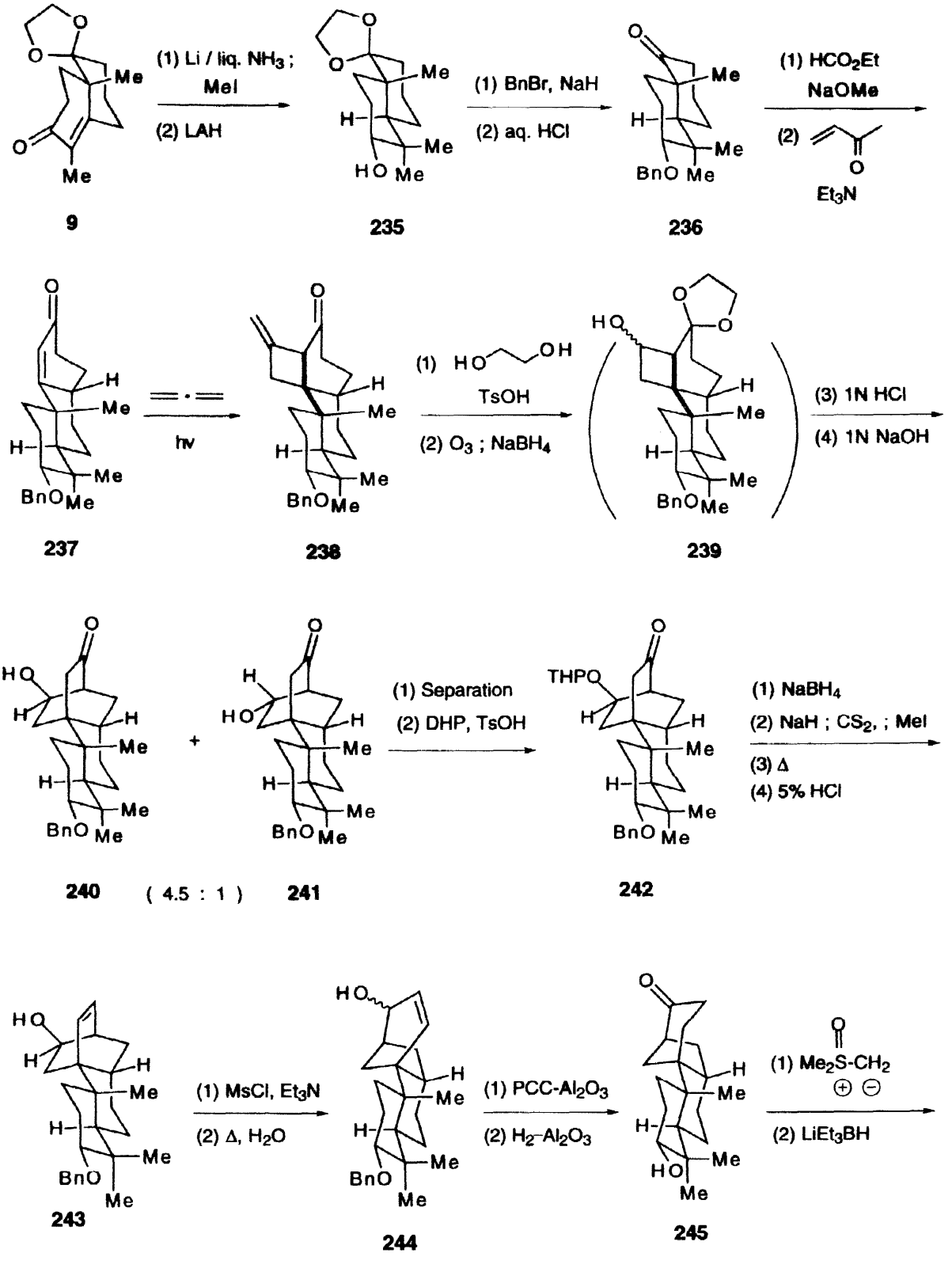


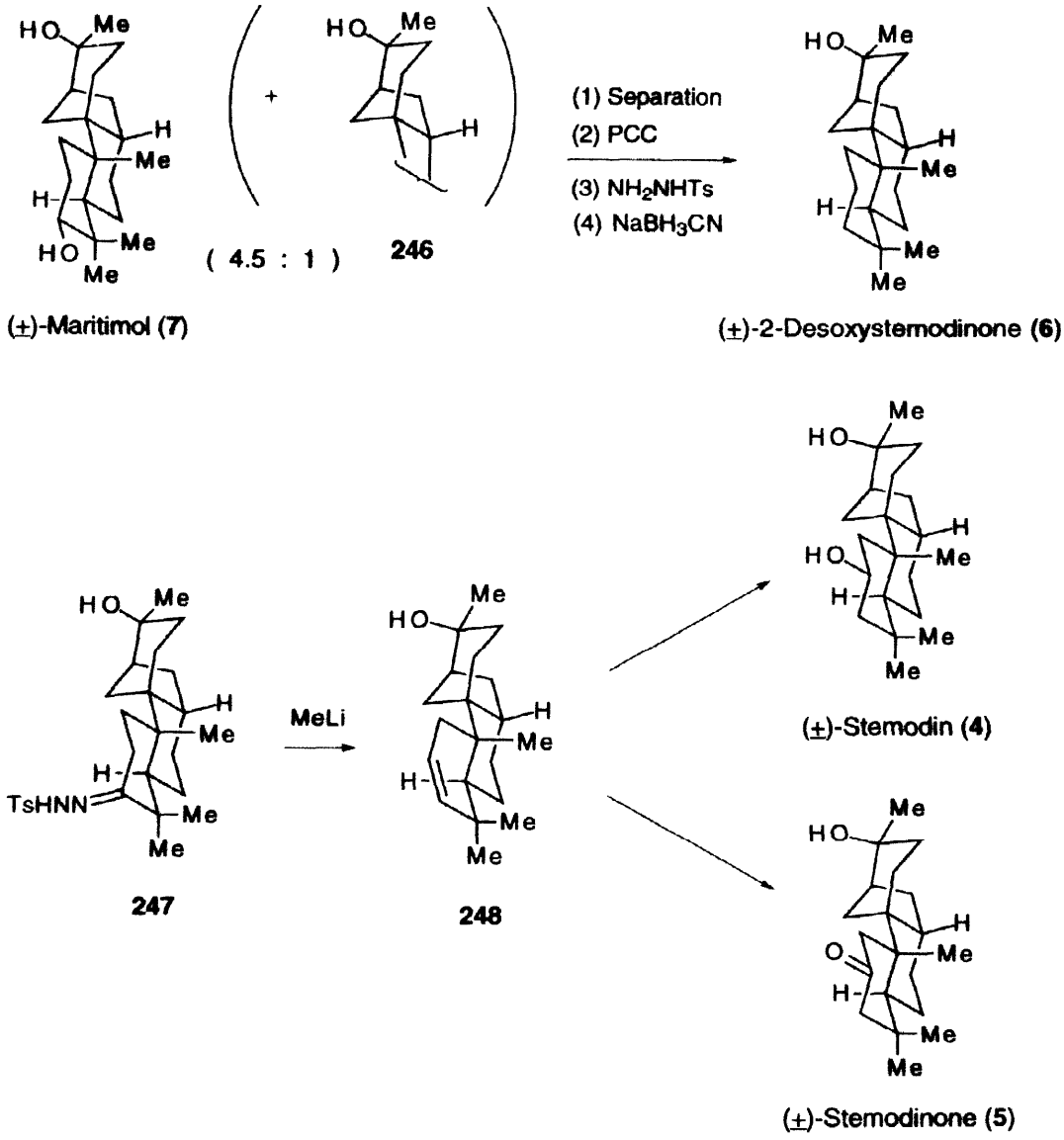


Scheme 17

3.3. From ABC Ring System

Four stemodane diterpenoids (**4** - **7**) are stereoselectively synthesized by Bettolo and his co-workers.[33] The synthesis is characteristic of photocycloaddition of allene and skeletal rearrangement process (from bicyclo[2.2.2]octane to bicyclo[3.2.1]octane) as shown previously. Reductive methylation of the easily available ketone **9**, followed by LAH reduction of the resulting ketone, gives stereoselectively the alcohol **235**, which is transformed into the benzyl ether **236** in 2 steps. The tricyclic enone **237** is prepared by a sequence of formylation and Michael reacion, followed by aldol condensation-deformylation. After photocycloaddition of allene to **237**, conversion of the resulting ketone **238** to the bicyclo[2.2.2]octane derivative **242**, is performed as depicted in **Scheme 18.**


(1) Li / liq. NH3 ; MeI
(2) LAH
(1) BnBr, NaH
(2) aq. HCl
(1) HCO2Et NaOMe
(2)
Et3N
(1) HO OH TsOH
(2) O3 ; NaBH4
hν
(3) 1N HCl
(4) 1N NaOH
(1) Separation
(2) DHP, TsOH
(1) NaBH4
(2) NaH ; CS2, ; MeI
(3) Δ
(4) 5% HCl
(1) MsCl, Et3N
(2) Δ, H2O
(1) PCC-Al2O3
(2) H2-Al2O3
(1) Me2S-CH2
(2) LiEt3BH
9
235
236
237
238
239
240
(4.5 : 1)
241
242
243
244
245



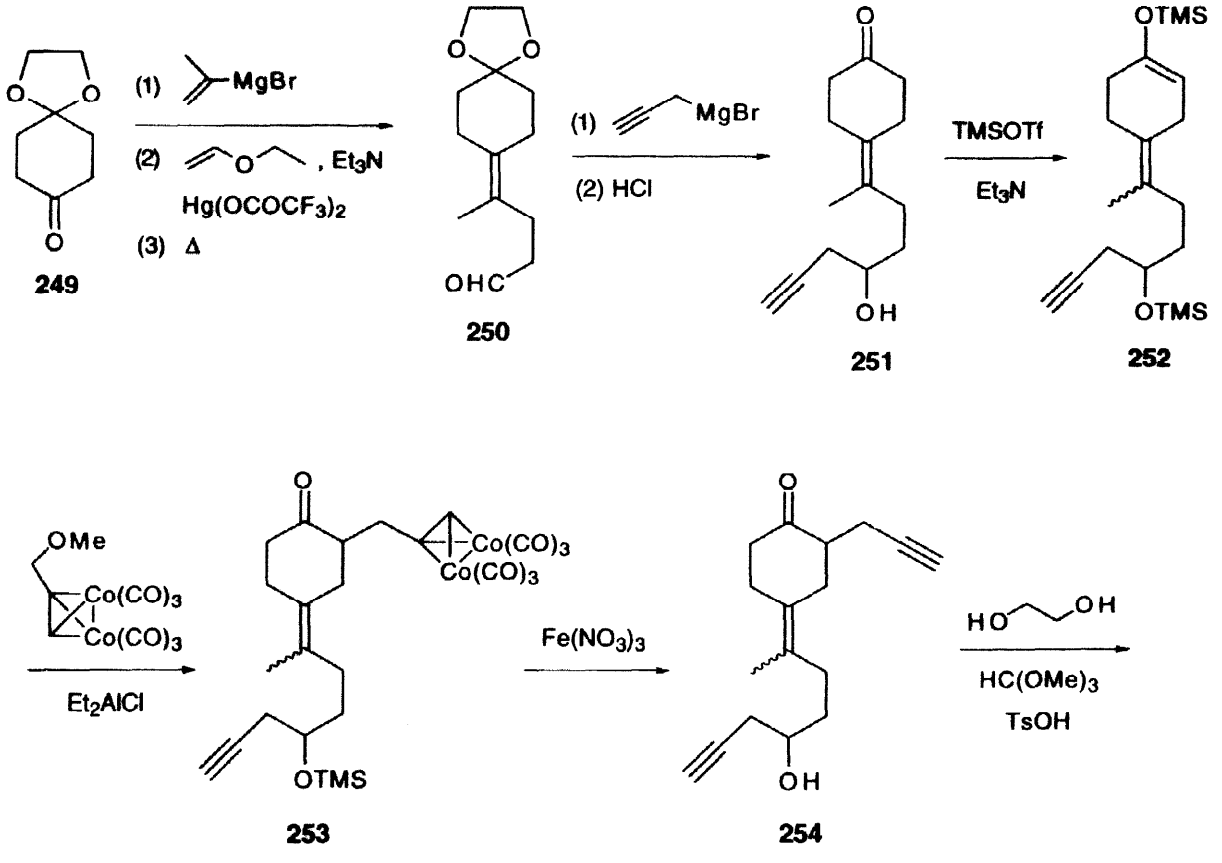
Scheme 18

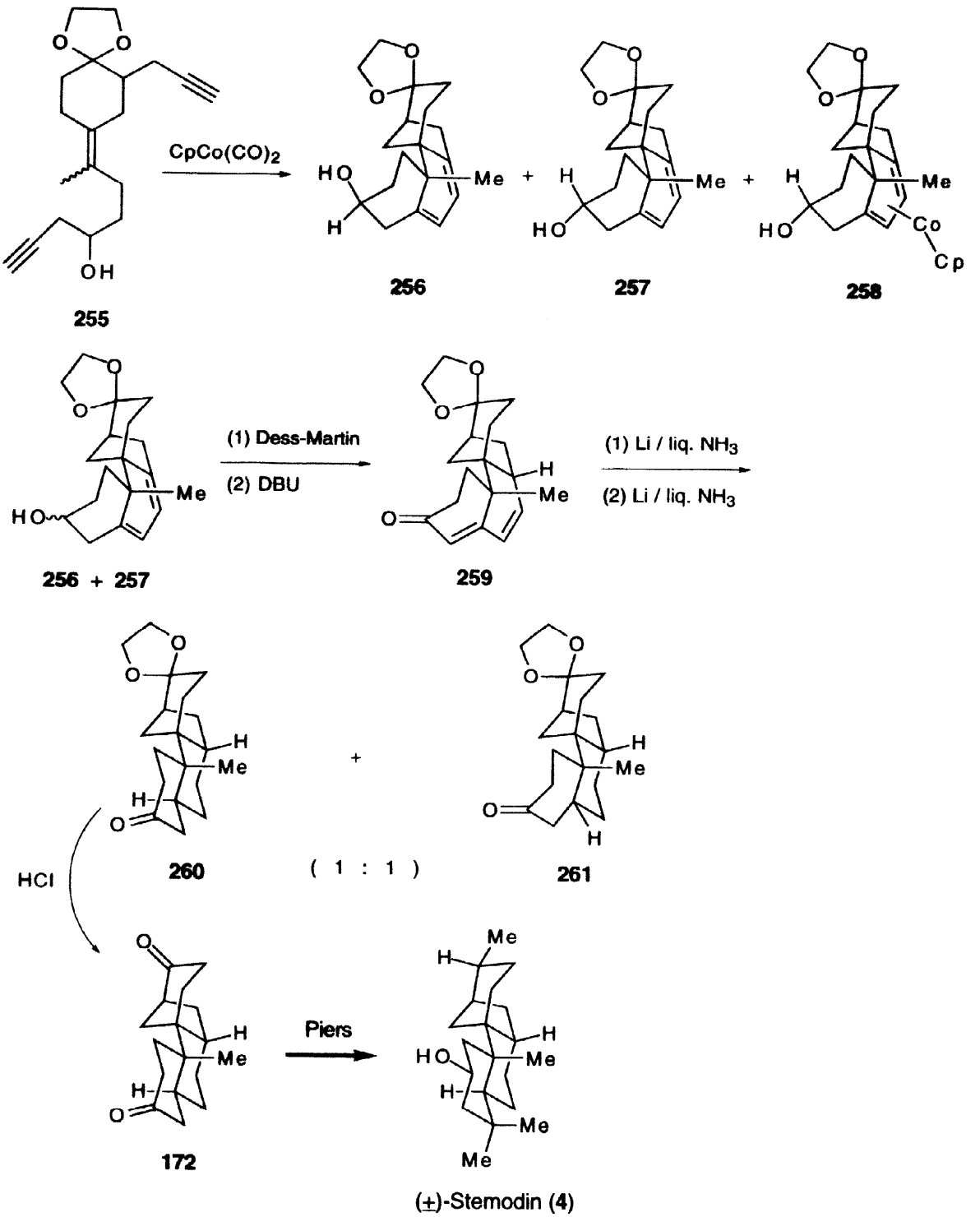
$NaBH_4$ reduction of **242** affords the corresponding alcohol, which is subjected to Chugaev reaction to generate the unsaturated alcohol **243**. After mesylation of **243**, skeletal rearrangement reaction of the resulting mesylate is conducted under thermal conditions to provide the desired bicyclo[3.2.1]octane derivative **244**. PCC oxidation of **244**, followed by hydrogenation, furnishes the ketone **245**, which is converted to (±)-maritimol (**7**) by means of Corey-Chaykovsky reaction.[34] (±)-2-Desoxystemodinone (**6**) is prepared from **7** in 3 steps through the hydrazone **247**. The compound **247** is finally transformed into the unsaturated alcohol **248**. Since **248** has already been converted to both stemodin (**4**) and stemodinone (**5**), the synthesis constitutes formal total syntheses of these natural products (**Scheme 18**).

3.4. From D Ring System

Vollhardt and his co-workers[35] employ a cobalt-catalyzed cyclization reaction for the one-step construction of stemodin framework. Starting from the ketone **249**, the unsaturated **250** is prepared by a sequence of 1,2-addition of propenyl-2-magnesium bromide, vinyl etherification of the resulting alcohol, followed by [3,3]sigmatropic rearrangement reaction. After chain extension of the aldehyde **250** by using Grignard reagent followed by protection of the resulting alcohol, Et_2AlCl-promoted intermolecular Nicholas reaction of the silyl enol ether **252** is performed to generate the Co-complex **253**, which is subjected to oxidative demetalation followed by ketalization to give **255**. The key step of this synthesis is conducted with $CpCo(CO)_2$ to yield two major prducts **256** and **257**.

The transfomation of the mixture of the above products into the dienone **259** is achieved by successive oxidation with Dess-Martin reagent and isomerization reaction with DBU. In order to construct AB-*trans* ring juncture, two sequentical Birch reduction of **259** is used. Finally, the acetal **260** is treated with acid to give rise to the diketone **172**, convertible to (±)-stemodin (**4**) (**Scheme 19**).



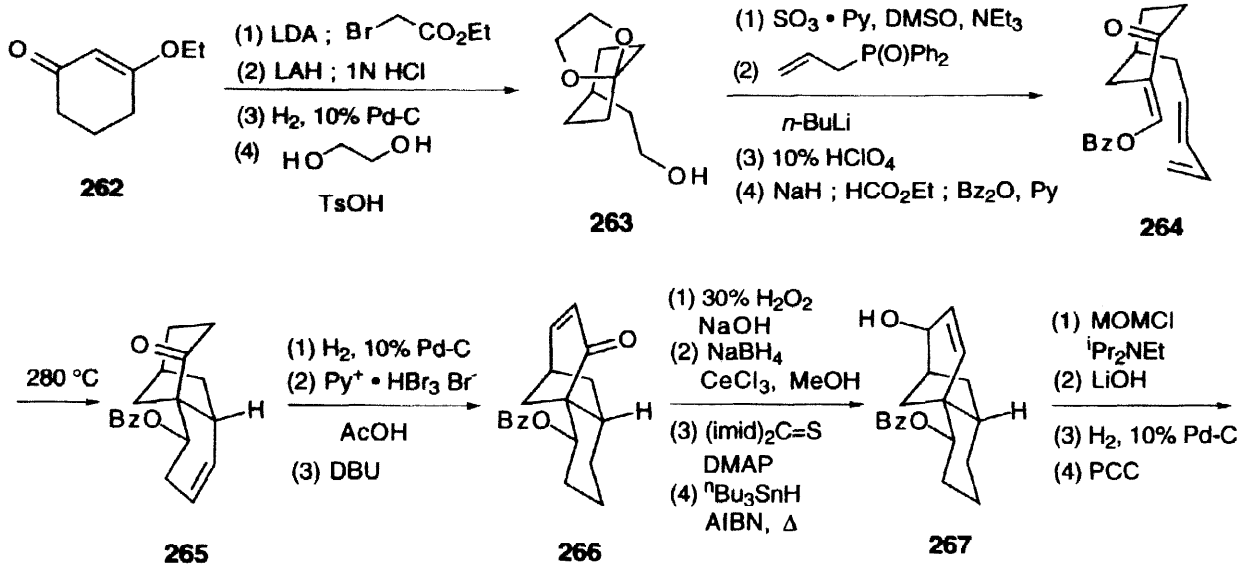


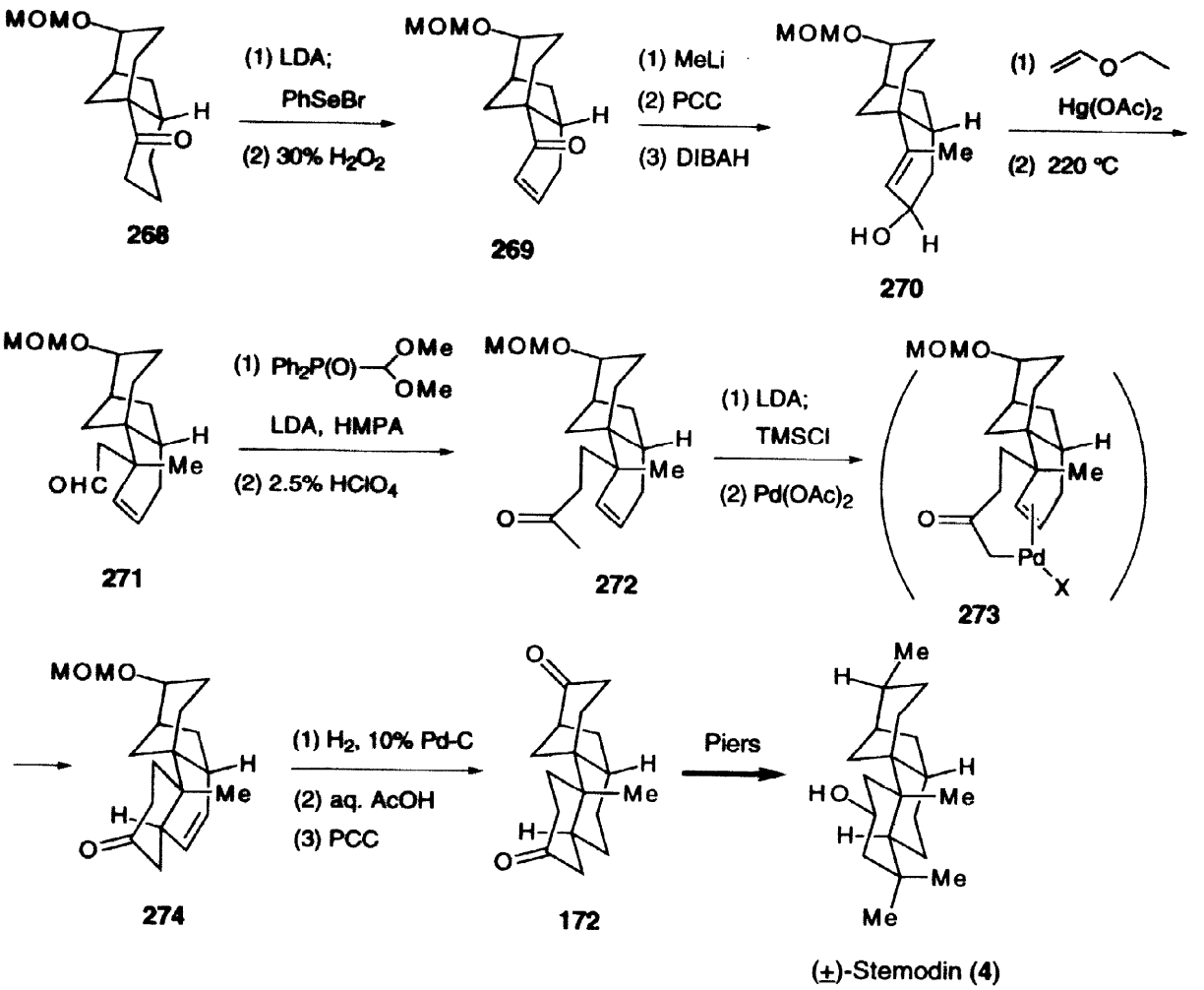
Scheme 19

The key reactions in stemodin (**4**) synthesis[36] by Toyota and Fukumoto are *nonsynchronous* Diels-Alder reaction to prepare the BC ring system and palladium-catalyzed cyclization reaction to form the AB-*trans* ring juncture. The transfomation of 3-ethoxy-2-cyclohexen-1-one (**262**) into the alcohol **263** was accomplished by

means of Stork-Danheiser's procedure.[37] Oxidation of **263**, selective preparation of the *E*-diene of the resulting aldehyde, followed by hydrolysis, provided the ketone, which was converted to the triene **264** in the usual way. Heating **264** in the presence of methylene blue at 280 °C produced the tricyclic adduct **265** as a major product. The preferred formation of **265** could be due to a "*concerted but nonsynchronous*" mechanism[38] for the cyclization. After hydrogenation of **265**, the enone system of **266** is constructed by bromination, followed by elimination. Interestingly, **266** exhibited quite strong cytotoxicity against L1210 murine leukemia cell with IC_{50} value of 0.019 μg/mL, and KB human epidermoid carcinoma cell with that of 0.027 μg/mL. 1,3-Transposition reaction of the carbonyl group in **266** was performed in 4 steps *via* the epoxy thioimidazolide formation to afford the allylic alcohol **267**. Protection of **267**, hydrolysis of the benzoyl group, hydrogenation, followed by PCC oxidation, led to the ketone **268**, which was transformed into the enone **269** by α-selelenylation-oxidation process. 1,2-Addition of MeLi to **269** produced the allylic alcohol, which was allowed to react with PCC, furnishing the enone. In the next DIBAH reduction, the high preference for a hydride ion attack from the *re*-face can be explained by "Cieplak effect".[39] Stereoselective chain extension was achieved by employing Claisen rearrangement reaction.

The methyl ketone moiety of **272** was constructed by means of Wittig-like reaction followed by acidic treatment. Careful consideration of molecular model of **272** suggested that **272** was an attractive progenitor of the AB-*trans* tetracyclic compound **274** since diastereoface-selective palladium-promoted cyclization reaction of the TMS enol ether of the methyl ketone **272** from less-hindered face would set the stereochemistry required for stemodin synthesis. As expected, palladium-promoted cyclization of the silyl enol ether of **272** provided the desired unsaturated ketone **274**, presumably, through the intermediacy of the alkylpalladium complex **273**. Finally, successive catalytic hydrogenation, deprotection, and PCC oxidation gave the diketone **172**, thus completing a formal synthesis of (±)-stemodin (**4**) (**Scheme 20**).





Scheme 20

Ackowledgement

We would like to thank Dr. Akemi Toyota who produced all the chemical structures in this review.

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