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SYNTHETIC ROUTES TO FORSKOLIN

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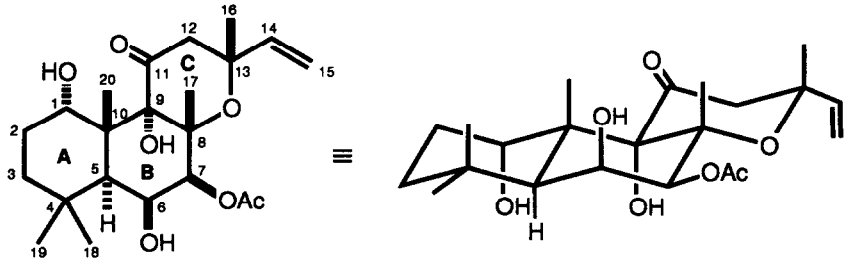
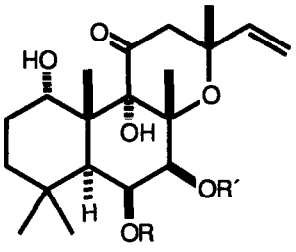
Introduction

As the result of a screening program directed toward the discovery of new leads from Indian medicinal plants at Hoechst Pharmaceutical Research in Bombay (India), in 1977 de Souza *et al.*[1] isolated, from the crude methanolic extract of *Coleus forskohlii* Briq. (Labiatae) that displayed interesting blood pressure lowering and cardioactive properties, a pure compound responsible for these pharmacological effects. The compound comprised 0.1 % of the dry weight of the root and was named **forskolin**.

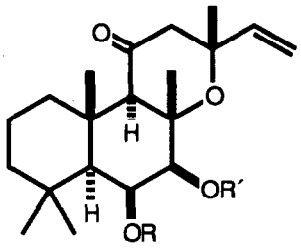


forskolin (1)

The structure and absolute configuration of forskolin (**1**) and related components **2**, **3**, **4**, and **5** of the root extract were determined by extensive spectroscopic, chemical and X-ray crystallographic studies.

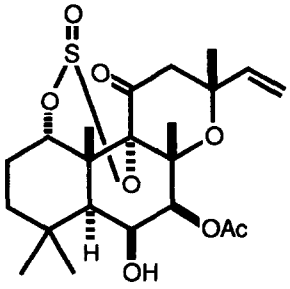


2: R=Ac, R'=H
3: R=R'=H



4: R=H, R'=Ac
5: R=R'=H

That forskolin (**1**) could only be mono-acetylated and failed to undergo typical ketone reactions suggested the hindered nature of two of the hydroxyl and the carbonyl groups.[2] The relative configuration of the C-1 and C-9 hydroxyl groups was further confirmed by the facile formation of the sulfite ester **6**, by treatment of **1** with thionyl chloride and pyridine and the formation of the hemiacetal **7**, through an ozonolysis-acetylation sequence on 1,6-diacetylforskolin, supported the α-configuration of the vinyl group. The circular dichroism data coupled with ^{1}H NMR spectral and chemical information on forskolin and its derivatives, established the *trans*-stereochemistry of the A-B ring junction and the configuration at the following chiral centers: C-1 α-OH, C-5 α-H, C-6 β-OH, C-9 α-OH, C-10 β-CH_3 and C-13 α-vinyl. Application of Mills' rule[3] to the forskolin-derived olefin **8** and to the corresponding deacetyl olefin **9** established the β-configuration of the 7-acetoxy substituent.



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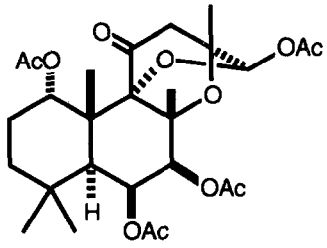

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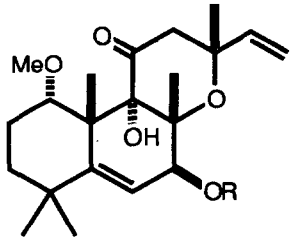
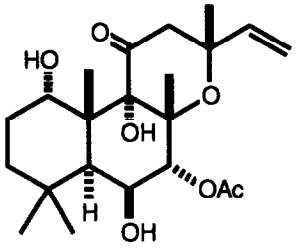


8: R=Ac
9: R=H

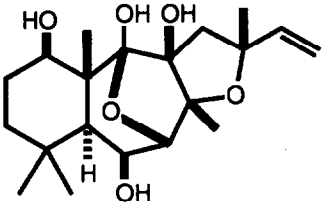
Finally, the stereochemistry and absolute configuration of forskolin (**1**) as 7β-acetoxy-8,13-epoxy-1α,6β,9α-trihydroxylabd-14-en-11-one have been verified by X-ray crystallography of forskolin and 1-benzyl-7-deacetyl-7-bromoisobutyrylforskolin.[4,5]

Independent of the work carried out at Hoescht Pharmaceutical Research, Tandon *et al.* [6] of the Central Drug Research Institute in Lucknow (India) also isolated the active diterpene of *C. forskohlii* but named it coleonol. The structure of coleonol (**10**) was assigned on the basis of chemical and spectral evidence, including X-ray crystallographic analysis.



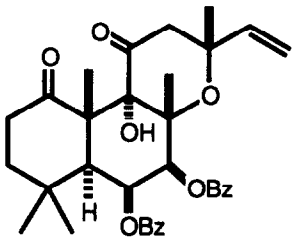
coleonol (10)

The only reported difference between forskolin (**1**) and coleonol (**10**) was the configuration of the C-7 acetoxy moiety. A great deal of confusion existed in the literature regarding the identity of both products,[7] mainly because the proposed structures were based on independent X-ray analyses. However, the issue was unambiguously solved when the rearrangement product from vigorous alkaline hydrolysis from both forskolin and coleonol, was shown to have structure **11**.



11

Furthermore, direct comparison of authentic coleonol and forskolin revealed that both possess identical physical and spectral properties. Consequently, coleonol and forskolin are the same entity represented by the common structure **1**.[8,9] Very recently, an unequivocal confirmation of the absolute stereochemistry of forskolin (**1**) has also been reported[10] by applying the exciton chirality circular dichroism method on the 6,7-dibenzoate derivative **12**.



12

Pharmacologically, forskolin is characterized mainly by potent positive inotropic activity and blood pressure lowering property. These effects, among others, have been attributed to its direct stimulation of the catalytic subunit of the membrane-bound enzyme adenylate cyclase. This unique mode of action of forskolin has attracted considerable attention as a biochemical tool in the understanding of the regulation of the enzyme. In clinical studies, forskolin has shown promising potential as a novel drug useful for the treatment of diseases such as glaucoma, congestive heart failure, and bronchial asthma.[11,12]

A careful analysis of the structure of forskolin (**1**), reveals a rather simple molecular framework that accommodates a particular collection of oxygenated functional groups which, as a consequence of their stereochemistry, generate a number of 1,3 diaxial interactions, making their mode of introduction a very attractive synthetic problem. These unique structural features and biological properties of forskolin have aroused the interest of synthetic organic chemists, and has resulted in enormous activity directed at the synthesis of this challenging target. Consequently, numerous publications have appeared in the literature describing synthetic work aimed at the synthesis of forskolin, as well as the preparation of structural analogues. In this Report we have summarized this large body of published material, focusing our attention on synthetic strategies[13] and interesting chemical transformations.

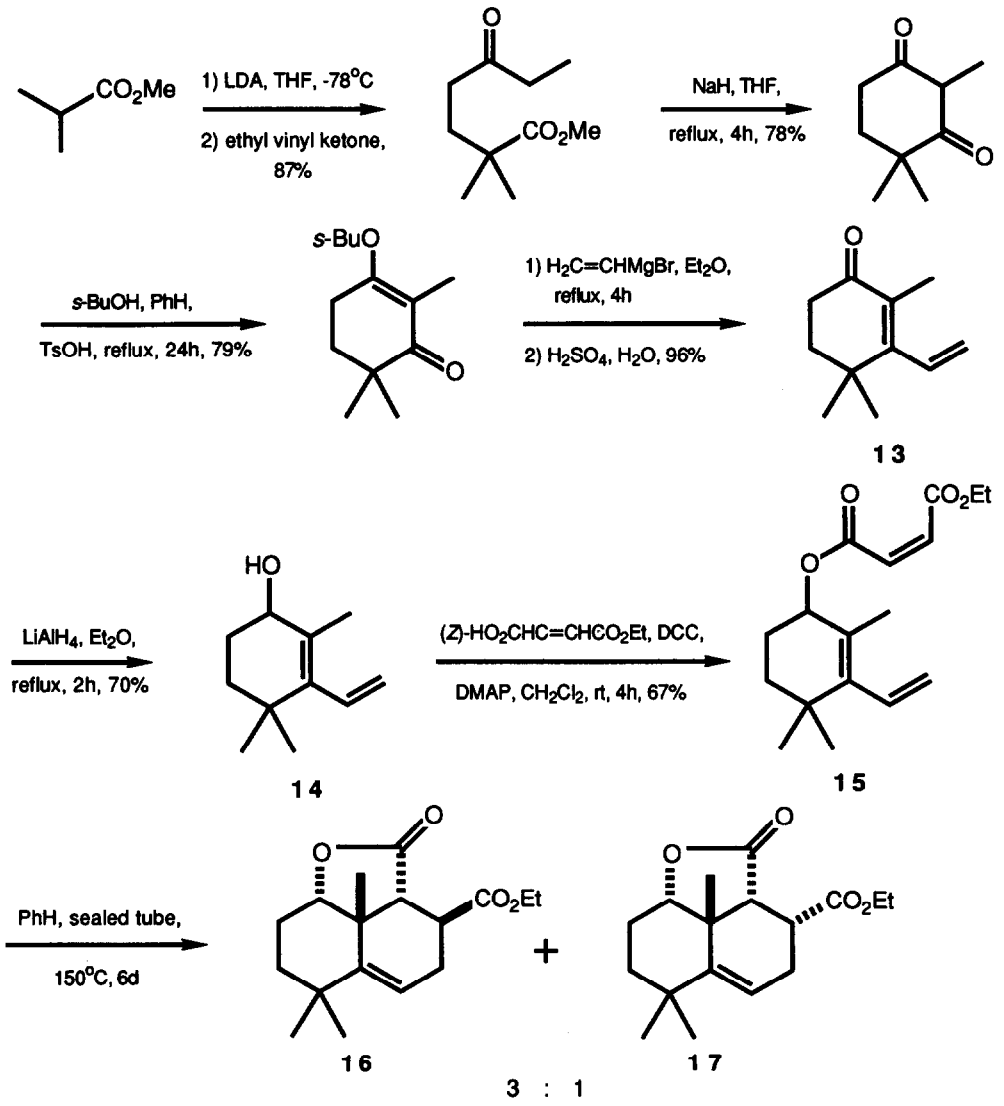
The discussion is organized into eight primary sections: 1) initial approaches toward the A-B ring system, 2) approaches to the construction and elaboration of the C ring, 3) approaches toward the A-B-C ring system, 4) partial syntheses, 5) total syntheses, 6) syntheses of advanced key intermediates, 7) enantioselective routes to key intermediates and 8) chemical studies on forskolin.

Initial Approaches Toward the A-B Ring System of Forskolin
The Intramolecular Diels-Alder Strategy

For the synthesis of the functionalized decalin system present in forskolin (**1**), the intramolecular version of the Diels-Alder reaction was considered as one of the most promising alternatives.[14] Initially, several approaches using this strategy were reported and, interestingly, the three sequences that culminated successfully in the total synthesis of **1**, as will be described later in this Report, are based precisely on this cycloaddition reaction.

In 1984, Jenkins and co-workers[15] reported that the intramolecular Diels-Alder reaction of maleate ester **15** yielded tricyclic lactones **16** and **17** in 56% total yield. The preparation of **15**, through the intermediacy of dienone **13** and dienol **14**, is depicted in Scheme 1, together with the structures of adducts **16** and **17**.

Scheme 1

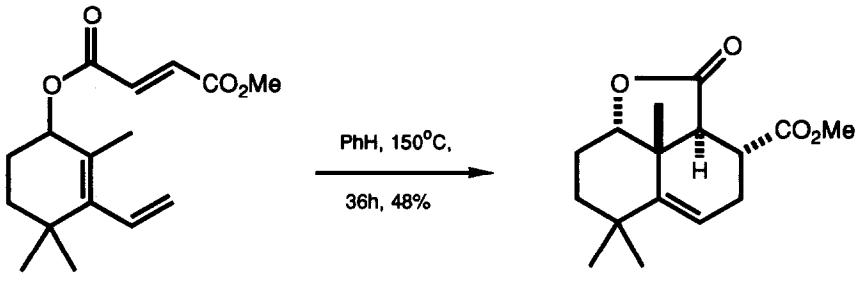


The stereochemistry of the minor product **17**, suggested that at least some of the cyclization had occurred through an *endo*-transition state[14] whereas, that of the major isomer **16**,

in which the stereochemistry of the dienophile is apparently lost, was more difficult to explain. A thermal *cis-trans* isomerization of the dienophile double bond was easily ruled out, since the cycloaddition of the corresponding fumarate ester, led mainly to a different isomeric adduct that was believed to be the result of an *exo*-cyclization. Initially, the authors suggested that a non-synchronous cyclization of a diradical intermediate in the double bond isomerization reaction had occurred to yield the major product **16**.

In subsequent work in collaboration with Magnus *et al.*,[16] the original stereochemical assignment for adducts **16** and **17** (as methyl esters) was confirmed by X-ray crystallography and the cyclization product of the fumarate ester **18** was shown to be the adduct **19**, as depicted in Scheme 2.

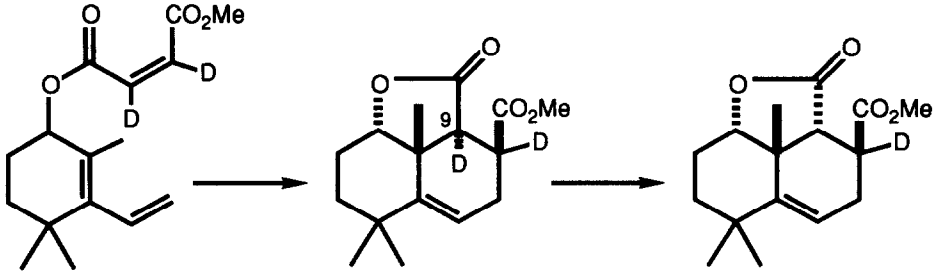
Scheme 2



18 **19**

Furthermore, as shown in Scheme 3, the use of the dideuteromaleate ester **20** under the same conditions determined that the apparent loss of the dienophile stereochemistry in the formation of **16** was due to the epimerization at C-9 of the highly strained lactone **21**. Lactone **21** is the kinetically controlled product generated *via* an *exo*-transition state.

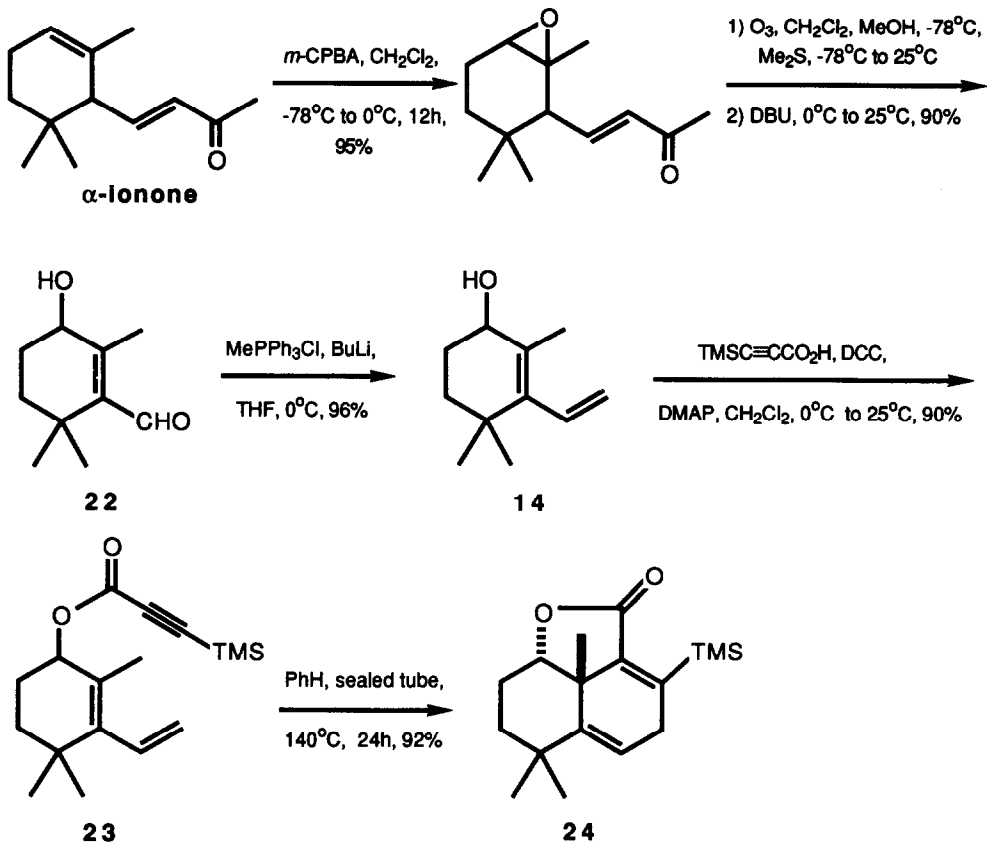
Scheme 3



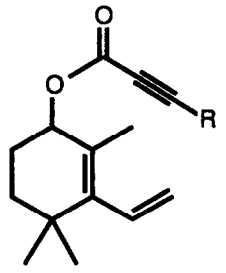
20 **21** d_1-**16**

A similar strategy was used by Nicolaou *et al.*[17] for the construction of a highly functionalized tricyclic lactone **24**. However, a doubly activated acetylene rather than a double bond was used by these authors as the dienophile in the cycloaddition precursor **23**. The synthesis of **23** was also carried out through the intermediacy of dienol **14**, which was prepared by an alternative sequence starting with α-ionone, as shown in Scheme 4.

Scheme 4



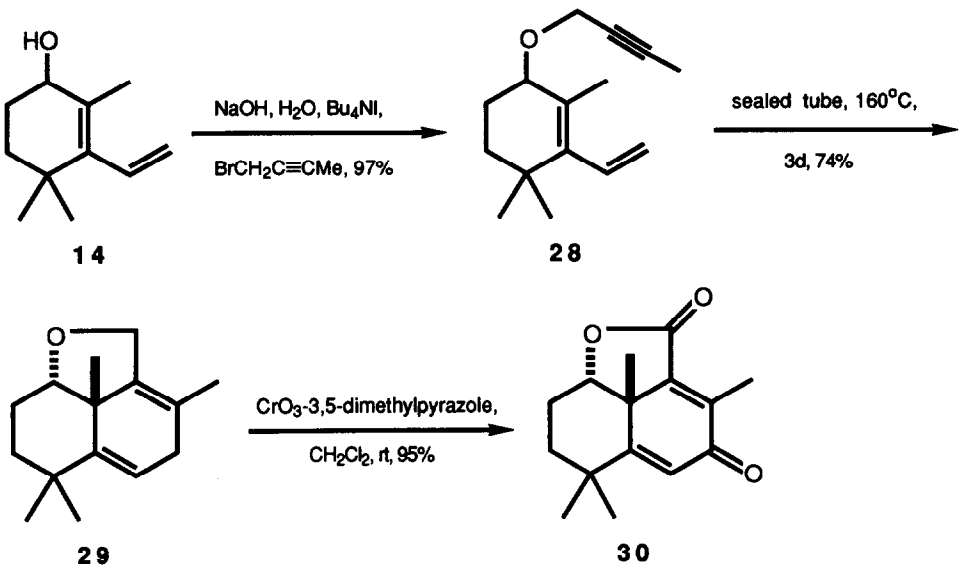
Thermal cyclization of **23** afforded **24** in excellent yield. The activation effect of the silicon group on the cycloaddition reaction was demonstrated by comparison with the cyclization of substrates **25**, **26**, and **27**.



25: R=H
26: R=Me
27: R=CO_2Me

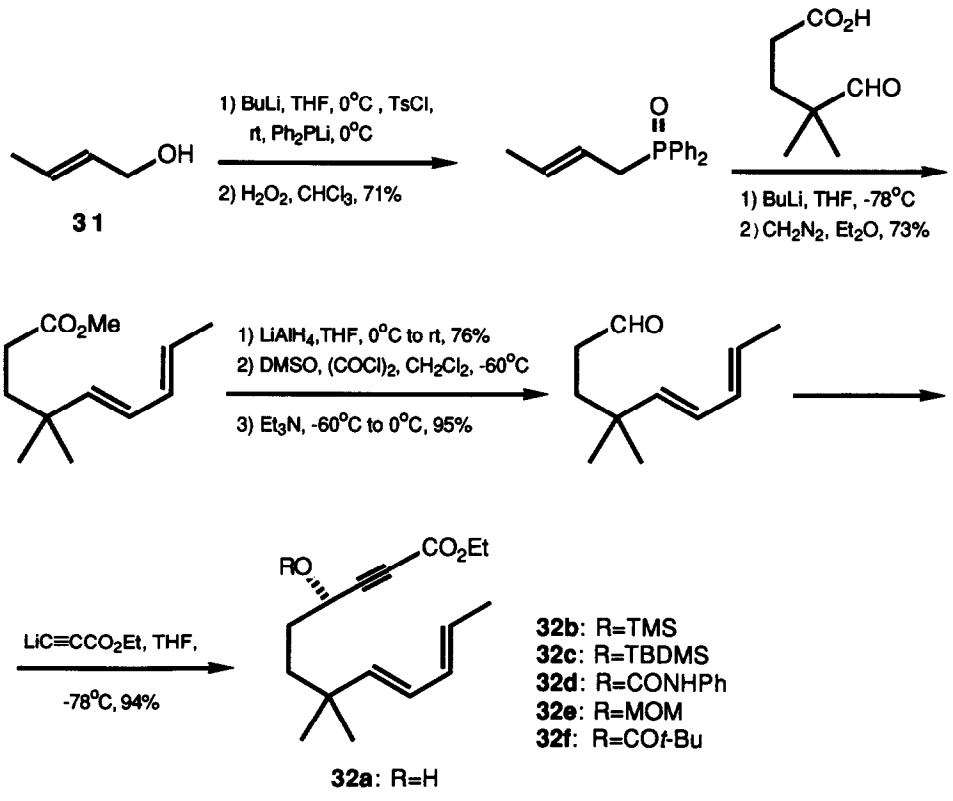
Whereas these substrates under the same reaction conditions afforded the expected Diels-Alder products, the yields were much lower than that obtained with **23**. Since this is probably due to the heterolytic fragmentation of the ester-linked systems, Liu and co-workers[18] decided to study the cyclization of the corresponding ethers. In agreement with previous reports,[19,20] they found that the thermal cyclization of the unactivated dienophile **28** yielded the expected Diels-Alder product **29** as shown in Scheme 5. By further oxidation, **29** afforded the polyfunctionalized tricyclic lactone **30** in excellent yield.

Scheme 5



More recently and by a completely different intramolecular Diels-Alder approach, Trost *et al.*[21] reported the synthesis of a decalin precursor for the A-B ring system of forskolin. The acyclic precursor **32a**, prepared from *E*-crotyl alcohol **31** as depicted in Scheme 6, was first derivatized to substrates **32b-32f**.

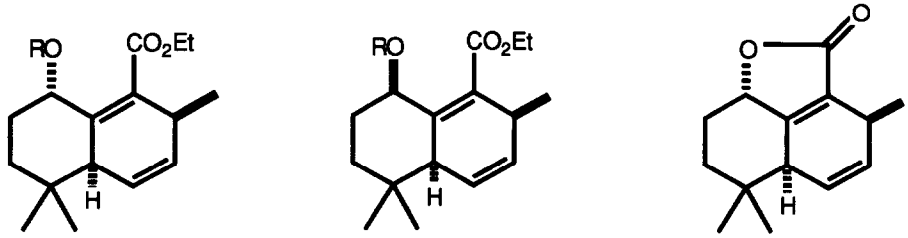
Scheme 6



31

32a: R=H

In a series of exploratory experiments, these substrates were cyclized thermally or under Lewis acid catalyzed conditions to yield the cycloadducts **33**, **34** or **35** depending on the substrate used for the reaction (Table 1).



33 34 35

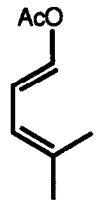
Table 1

		33		34		35	
32b	PhMe, 170°C →	1	:	0	:	0	75%
32b	$EtAlCl_2$, PhMe, 25°C →	0	:	0	:	1	30%
32c	Et_2AlCl, PhMe, 25°C →	0	:	1	:	0	80%
32d	Et_2AlCl, PhMe, 25°C →	1	:	0.83	:	0.17	60%
32d	Et_2AlCl, PhMe, 0°C →	4	:	1	:	0.13	55%
32e	Et_2AlCl, PhMe, 25°C →	4	:	1	:	0	50%
32e	Et_2AlCl, PhMe, 0°C →	6	:	1	:	0	50%
32f	Et_2AlCl, PhMe, rt →	1	:	0	:	0	84%

Analysis of Table 1 reveals some interesting results. The thermolysis of **32b** gives exclusively **33b**; on the other hand, under Lewis acid-catalyzed conditions, the reaction product is the tricyclic lactone **35** although in lower yield. Another striking result is that **32c** and **32f** have shown completely opposite diasterofacial selectivity under essentially the same reaction conditions yielding **34c** and **33f**, respectively, in good yield. A sound explanation based on steric effects has been suggested to explain the remarkable dependence of the stereochemical course of the cyclization on the substituent of the oxygen of the propargylic moiety of the diene-yne precursor; however, unusual stereoelectronic effects have also been considered as alternative possibilities.

The Intermolecular Diels-Alder Strategy

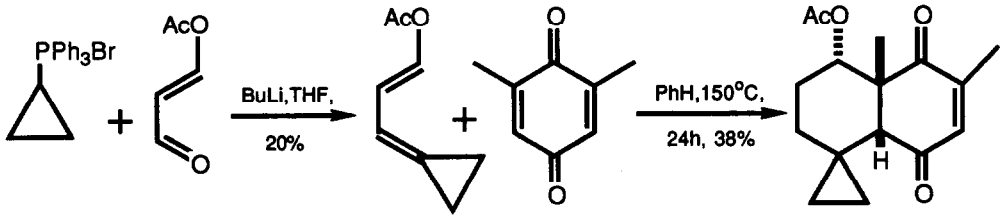
Several synthetic sequences directed toward the A-B ring system of forskolin involving intermolecular Diels-Alder reactions have been reported. In an attempt to avoid the use of an unreactive geminally disubstituted butadiene such as **36**, Snider *et al.*[22] utilized the Diels-Alder reaction of the cyclopropyl derivative **37**.



36

As shown in Scheme 7, reaction of **37** with 2,6-dimethylbenzoquinone (**38**) afforded adduct **39** with the expected regio- and stereochemistry. However, the very low yield in the preparation of **37** and the modest yield in the Diels-Alder reaction prevented further continuation of this route to forskolin.

Scheme 7

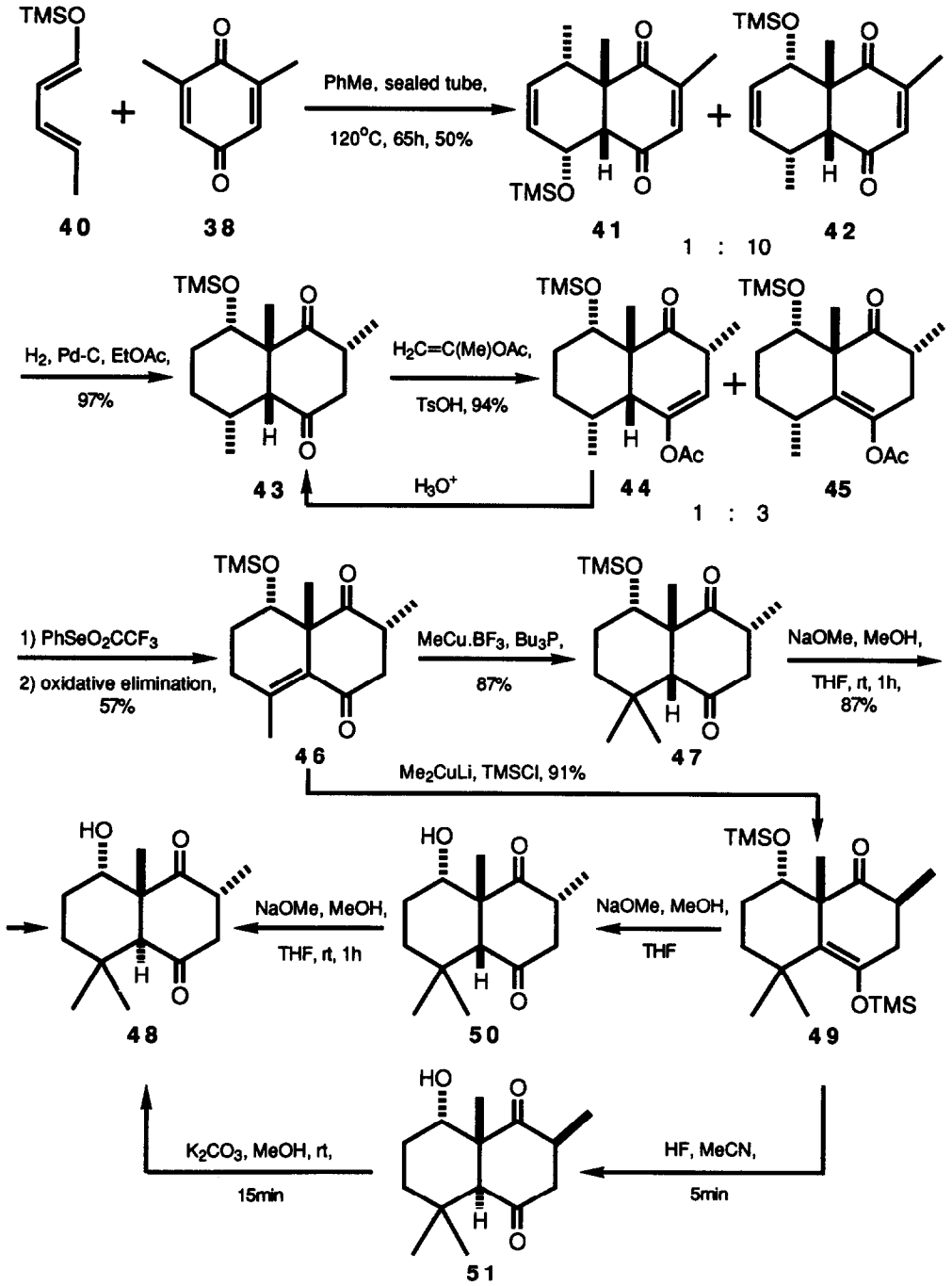


37 **38** **39**

By following a similar approach, Sih *et al.*[23] reported the synthesis of *trans*-diketone **48** by using diene **40**, which is also less hindered than **36**, for the Diels-Alder reaction and introduced the second methyl group at a later stage of the synthesis (Scheme 8).

The cycloaddition of **40** to the dienophile **38** afforded a 1:10 mixture of regioisomers **41** and **42** in 50% total yield. For the transformation of the major regioisomer into substrate **46**, adequately substituted for the introduction of the second methyl group, **42** was first hydrogenated. As expected, the reaction occurred from the convex face of the molecule yielding exclusively diketone **43** in excellent yield. The less hindered carbonyl group of **43** was then converted selectively into the corresponding enol acetates and the thermodynamically favored isomer **45** was transformed into enone **46** by selenenylation followed by oxidative elimination. The kinetic enol acetate **44** was recycled in the synthesis. Presumably due to the presence of a methyl group at the β position, the enone of **46** was unreactive toward conventional methyl cuprates; however, activation of the cuprate with boron trifluoride[24] effected the 1,4 addition of **46** smoothly to yield **47** in excellent yield.

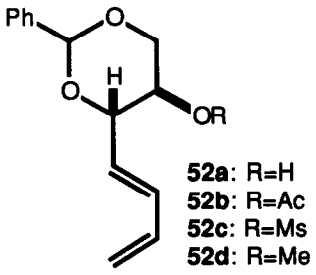
Scheme 8


TMSO
PhMe, sealed tube,
120°C, 65h, 50%
40
38
41
42
1 : 10
H2, Pd-C, EtOAc,
97%
H2C=C(Me)OAc,
TsOH, 94%
H3O+
43
44
45
1 : 3
1) PhSeO2CCF3
2) oxidative elimination,
57%
MeCu.BF3, Bu3P,
87%
NaOMe, MeOH,
THF, rt, 1h,
87%
46
47
Me2CuLi, TMSCl, 91%
HO
NaOMe, MeOH,
THF, rt, 1h
NaOMe, MeOH,
THF
OTMS
48
50
49
K2CO3, MeOH, rt,
15min
HF, MeCN,
5min
51

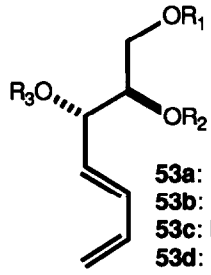
Desilylation and epimerization of **47** with basic methanol furnished the desired *trans*-diketone **48** in very good yield. A similar result was obtained by treatment of **46** with the organo cuprate-trimethyl silyl chloride complex[25] to give the enol silyl ether **49**. Basic hydrolysis of **49** yielded crystalline **50**, whose stereochemistry was established by X-ray crystallography and, by epimerization, yielded also **48**. Alternatively, by liberation of the hydroxyl groups of **49** on treatment with hydrogen fluoride, the epimeric diketone **51** was obtained which, under basic conditions, again afforded **48**. Interestingly, the chloroacetyl ester of (±)-**48** was kinetically resolved by porcine pancreatic lipase to provide (+)-**48**. However, the use of this promising intermediate in the synthesis of forskolin, as well as its absolute configuration, remains unreported.

Suryawanshi, Bhakuni and co-workers[26] also reported an intermolecular Diels-Alder strategy toward the A-B ring system of forskolin. They found that the reaction of the two series of dienes **52a-d** and **53a-d**, derived from D-glucose (Table 2) with the *in situ* generated

Table 2

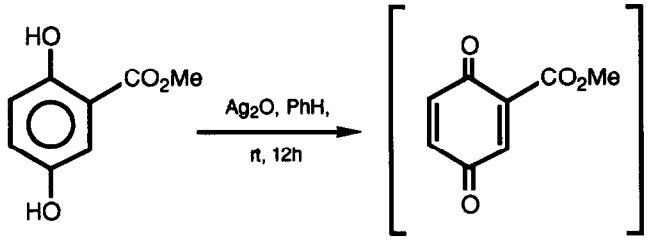


52a: R=H
52b: R=Ac
52c: R=Ms
52d: R=Me



53a: R_1=R_2=R_3=Ac
53b: R_1=R_3=Ac; R_2=THP
53c: R_1=R_2=R_3=Me
53d: R_1=R_3=Me; R_2=THP

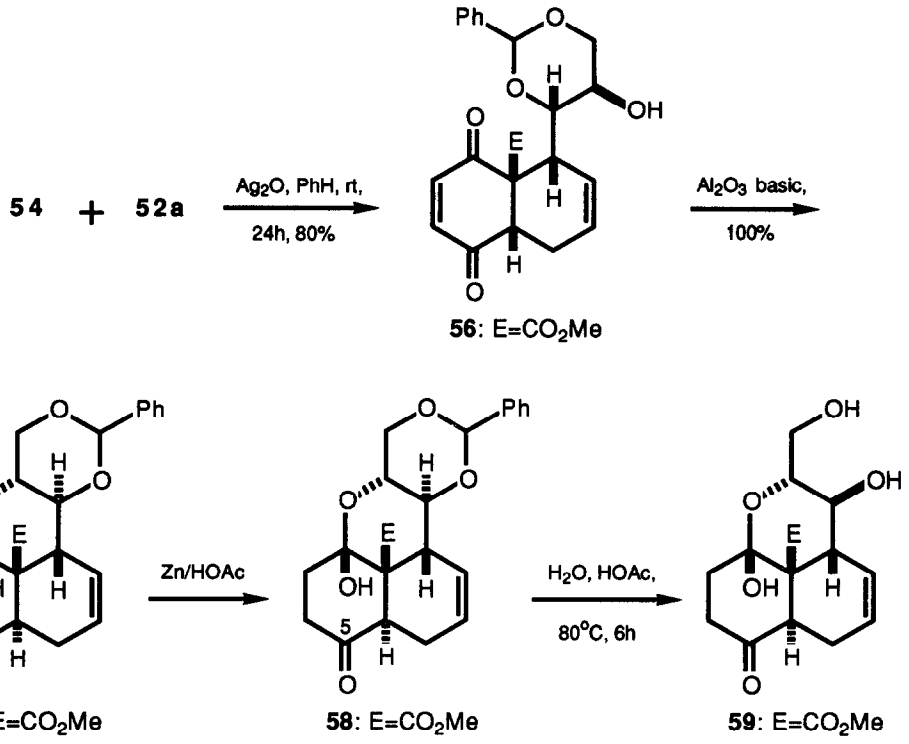
methoxycarbonyl-*p*-quinone **55**[27] afforded cycloadducts with suitable protecting groups for further manipulations in very good yields.



54 **55**

Starting with **52a**, cycloadduct **56** was obtained (Scheme 9). Upon treatment with basic alumina, **56** suffered epimerization to the *trans*-decalin **57** with simultaneous formation of the hemiacetal function. The reduction of the conjugated double bond of **57**, followed by acidic hydrolysis of the protecting group, provided the crystalline compound **59**.

Scheme 9



56: E=CO_2Me

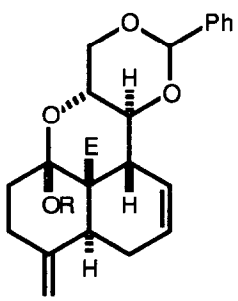
57: E=CO_2Me

58: E=CO_2Me

59: E=CO_2Me

Starting with diene **53a** and following essentially the same sequence as that described for **52a**, compound **59** was obtained, thereby indicating that the Diels-Alder reaction followed the same regio- and stereochemistry with both series of dienes.

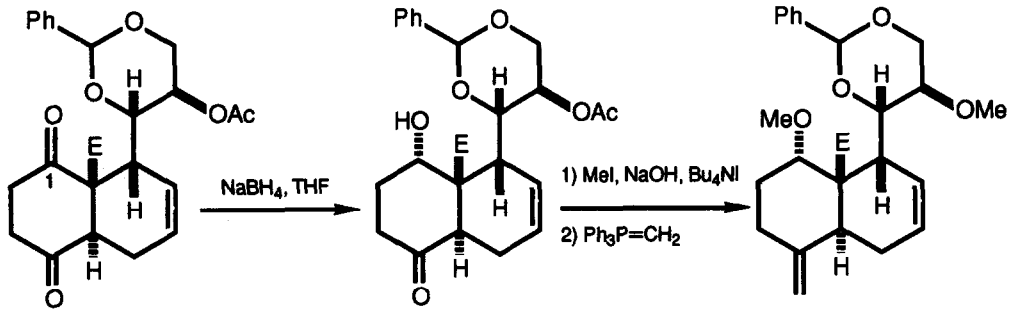
In a subsequent publication, Bhakuni[28] reported that after blocking the hemiacetal function of **58** by methylation, the carbonyl group at C-5 reacted smoothly with base-free methylene-triphenylphosphorane to furnish olefin **60**.



60: E=CO_2Me, R=Me

Furthermore, Bhakuni demonstrated that the carbonyl group at C-1 of the cycloadduct **61**, which was available from diene **52b**, can be reduced chemo- and stereoselectively to yield **62** in quantitative yield as shown in Scheme 10. By protection of the hydroxyl groups as methyl ethers and subsequent Wittig methylenation, the olefin **63** was obtained in greater than 80% yield.

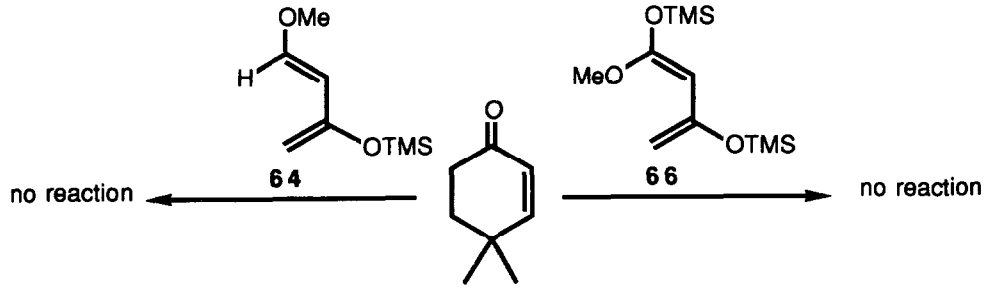
Scheme 10

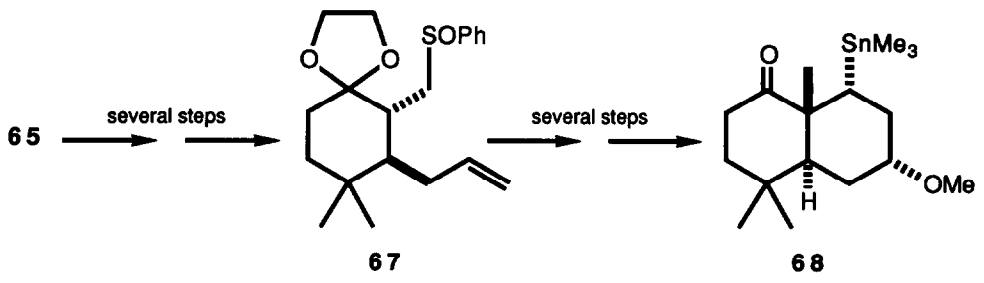


61: E=CO_2Me **62**: E=CO_2Me **63**: E=CO_2Me

As shown in Scheme 11, Welzel *et al.*[29] have reported that all attempts to add the electron-rich dienes **64** and **66** to enone **65** as an approach to the A-B ring system of forskolin were completely unsuccessful. However, they were able to synthesize *trans*-decalin **68** from enone **65** by the cyclization of the unsaturated sulfoxides **67** under the Pummerer reaction conditions followed by further transformations.

Scheme 11

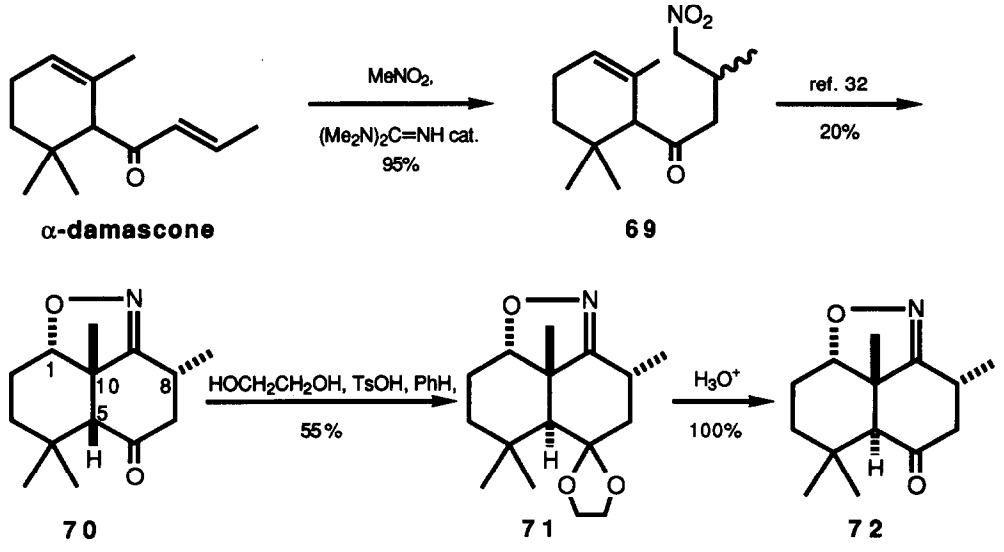




The Intramolecular Nitrile Oxide Cycloaddition Strategy

In 1986, Barco, Pollini and co-workers[30] took advantage of an intramolecular [3+2] nitrile oxide cycloaddition (INOC) reaction[31] to synthesize the tricyclic isoxazoline **72**, a potential precursor of the A-B ring system of forskolin. The Michael adduct **69**, easily prepared by addition of nitromethane to α-damascone (Scheme 12) underwent cyclization upon nitrile oxide generation to yield the *cis*-decalin derivative **70** as a single isomer in low yield. Acetalization of **70** under standard conditions occurred with simultaneous epimerization at C-5 to give the *trans*-decalin **71**, which led to **72** in quantitative yield on treatment with aqueous acid.

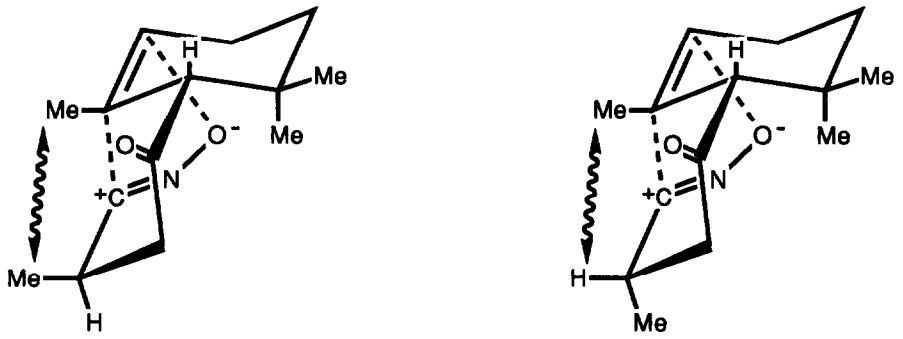
Scheme 12



In a subsequent publication,[33] the same authors suggested, on basis of an analysis of the two possible transition states A and B (Figure 1), an explanation for the stereochemical outcome of the INOC reaction of **69**. They suggested that the nitrile oxide adds to the face of the olefin that bears the side chain, allowing the establishment of the stereochemistry at C-1, C-5, and C-10.

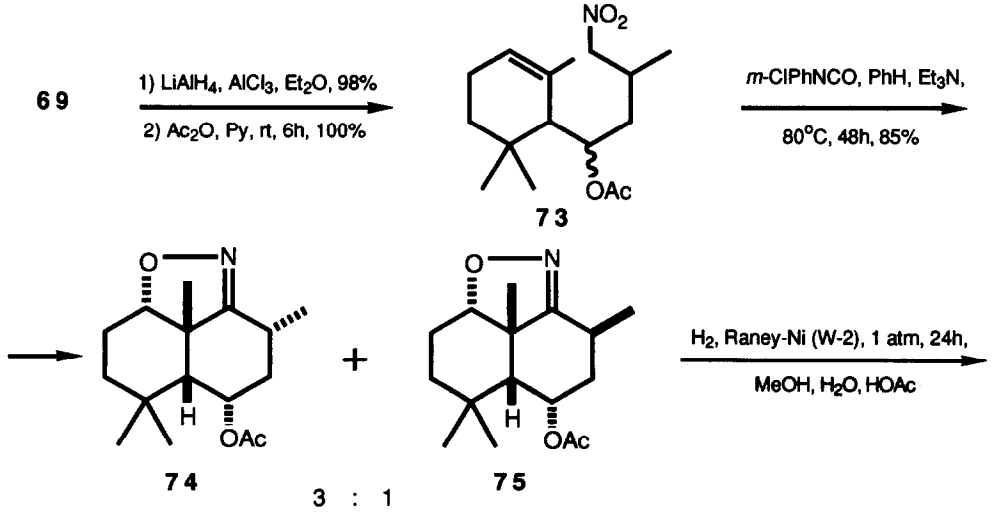
Furthermore, the less congested transition state B, in which the Me-Me interaction is not present would favor the assigned stereochemistry of the methyl group at C-8 of **70**.

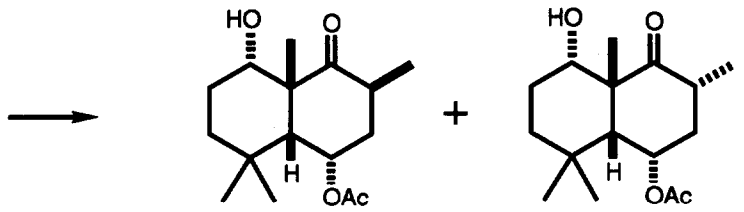
Figure 1



In an attempt to generate a more favorable geometry for the cycloaddition reaction and, as a consequence to improve the yield of this step, ketone **69** was reduced to the corresponding alcohol and acetylated to afford **73**. In fact, the nitrile oxide cycloaddition of **73** led to a 3:1 mixture of isoxazolines **74** and **75** in excellent yield as depicted in Scheme 13. Interestingly, the isoxazoline ring of both **74** and **75** was smoothly cleaved by hydrogenolysis with simultaneous hydrolysis and epimerization at C-8 giving essentially pure β-hydroxy ketone **76**. Under these conditions the formation of **77** was negligible.

Scheme 13





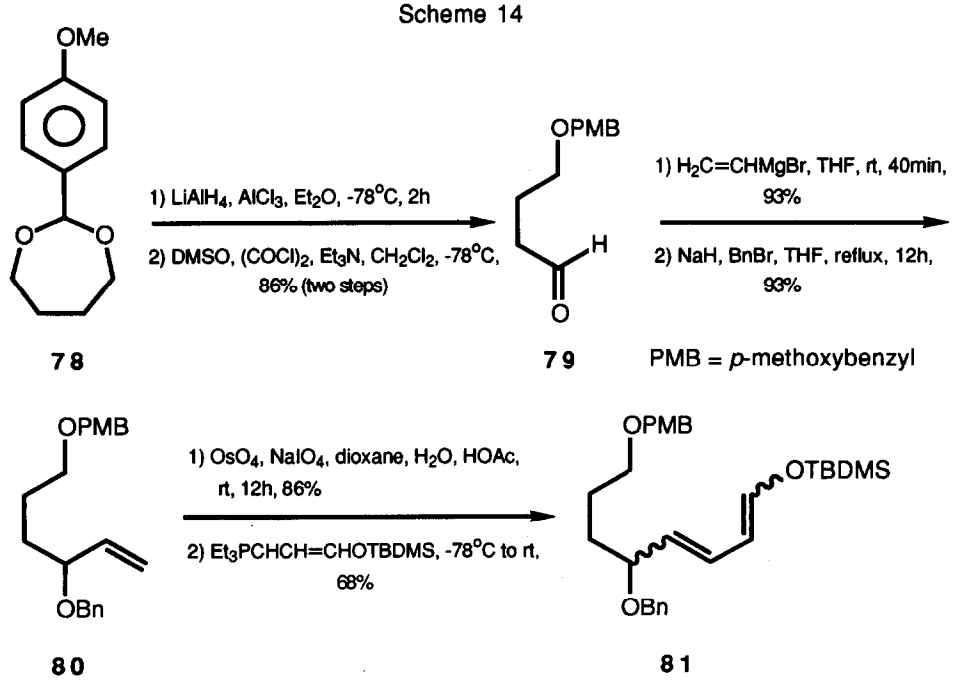
76 **77**

Since the separation of epimers **74** and **75** is not necessary, the sequence described in Scheme 13 makes the polyfunctionalized intermediate **76** a readily available starting material for further transformations into forskolin. As will be discussed later in this Report a model tricyclic compound has been synthesized from **76**.

The Intermolecular Diels-Alder in Tandem with an Intramolecular Nitrile Oxide Cycloaddition Strategy

Kozikowski *et al.*[34] also demonstrated the ability of their [(4+2)+(3+2)] strategy[35] in the construction of highly oxygenated decalin derivatives (**86a**, **86b**) suitable for further elaboration to forskolin. The diene **81**, which was required for the Diels-Alder step of the sequence, was obtained as a mixture of geometric isomers by a six-step sequence from the seven-membered ring acetal **78** (Scheme 14).

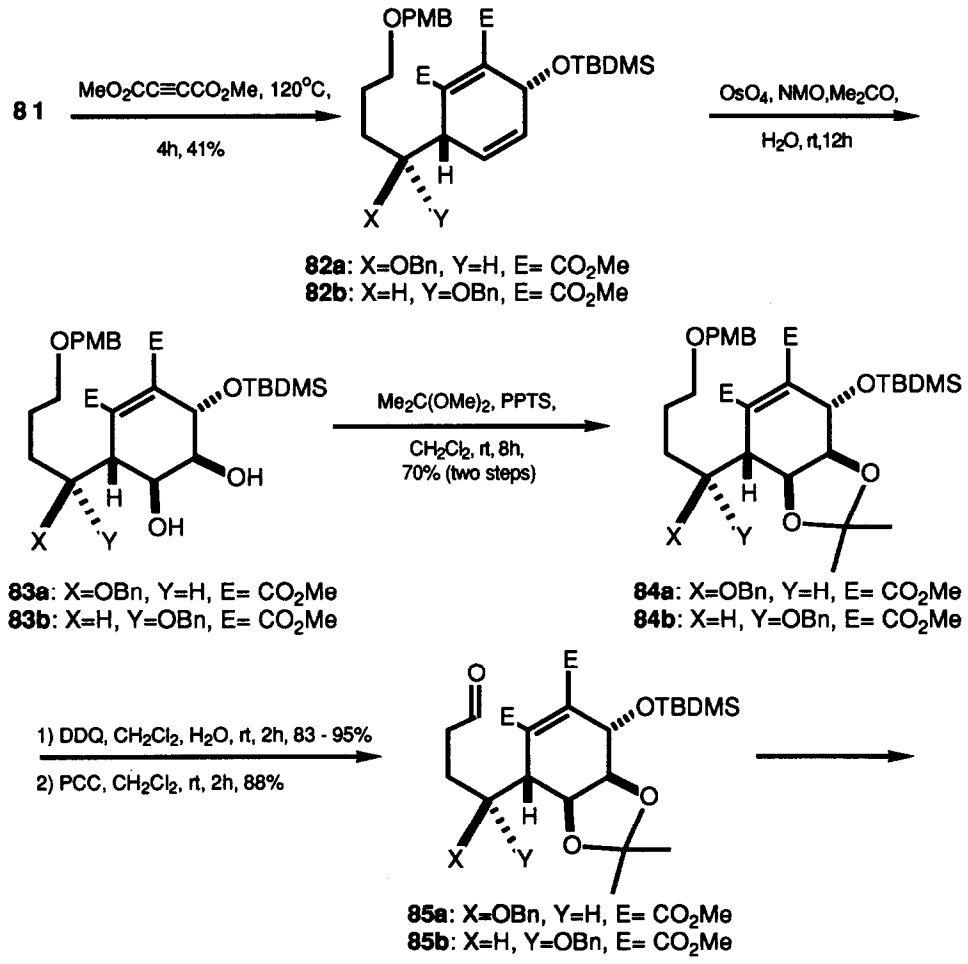
Scheme 14

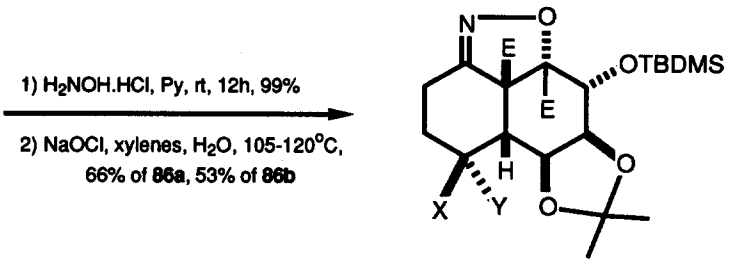


78 **79** **80** **81**

Treatment of the mixture of isomeric dienes **81** (Scheme 15) in which the major component is the *E,E*-isomer, with dimethyl acetylenedicarboxylate afforded an inseparable 2:1 mixture of adducts **82a** and **82b** in 41% yield. The diastereoisomeric diols **83a** and **83b**, obtained upon hydroxylation of the mixture were separable by chromatography and the second step of the proposed strategy, the intramolecular nitrile oxide cycloaddition, was carried out individually with each diol. The diols were first protected as acetonides (**84a** and **84b**), the *p*-methoxybenzyl groups were cleaved and the resulting primary alcohols oxidized to aldehydes **85a** and **85b**. The nitrile oxide intermediates, generated from the corresponding oximes, on treatment with sodium hypochlorite, afforded exclusively the *cis*-fused isoxazolines **86a** and **86b**, respectively.

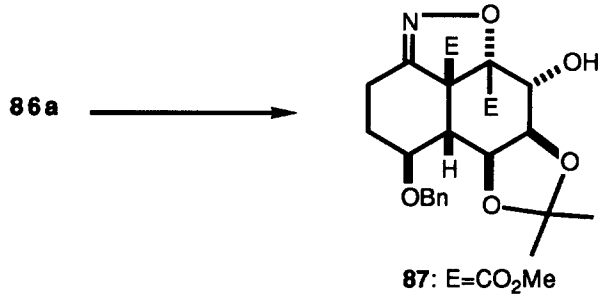
Scheme 15





86a: X=OBn, Y=H, E= CO_2Me
86b: X=H, Y=OBn, E=CO_2Me

That the stereochemistry of the major Diels-Alder adduct is the one depicted in **82a** and that the hydroxylation reaction had occurred from the face *anti* of both allylic substituents was unambiguously established by X-ray crystallography of alcohol **87**, available by cleavage of the silyl ether of **86a**. This stereochemical assignment permitted the π–facial selectivity of Diels-Alder reactions of dienes containing allylic heteroatom substituents and acetylenic dienophiles to be defined.

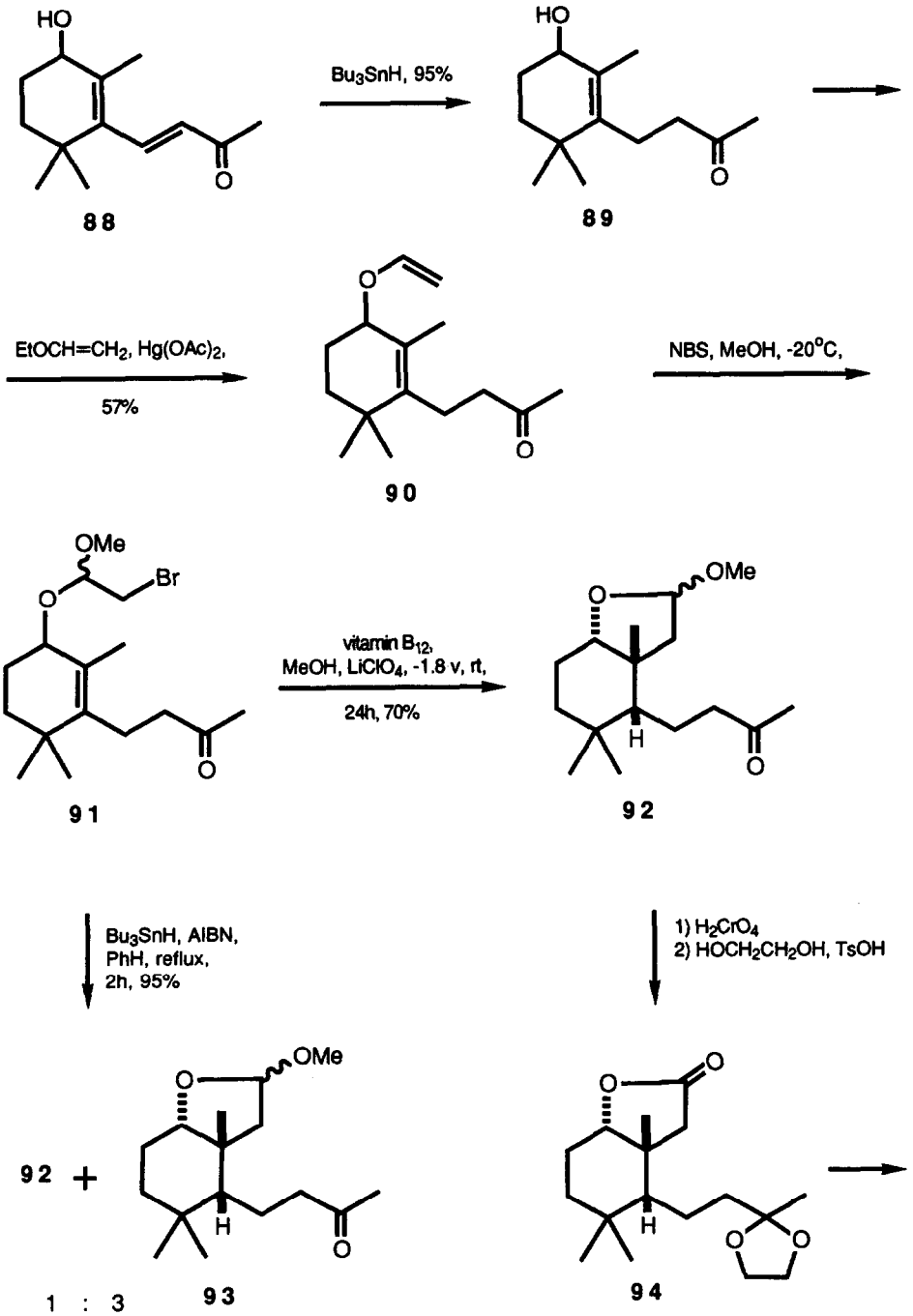


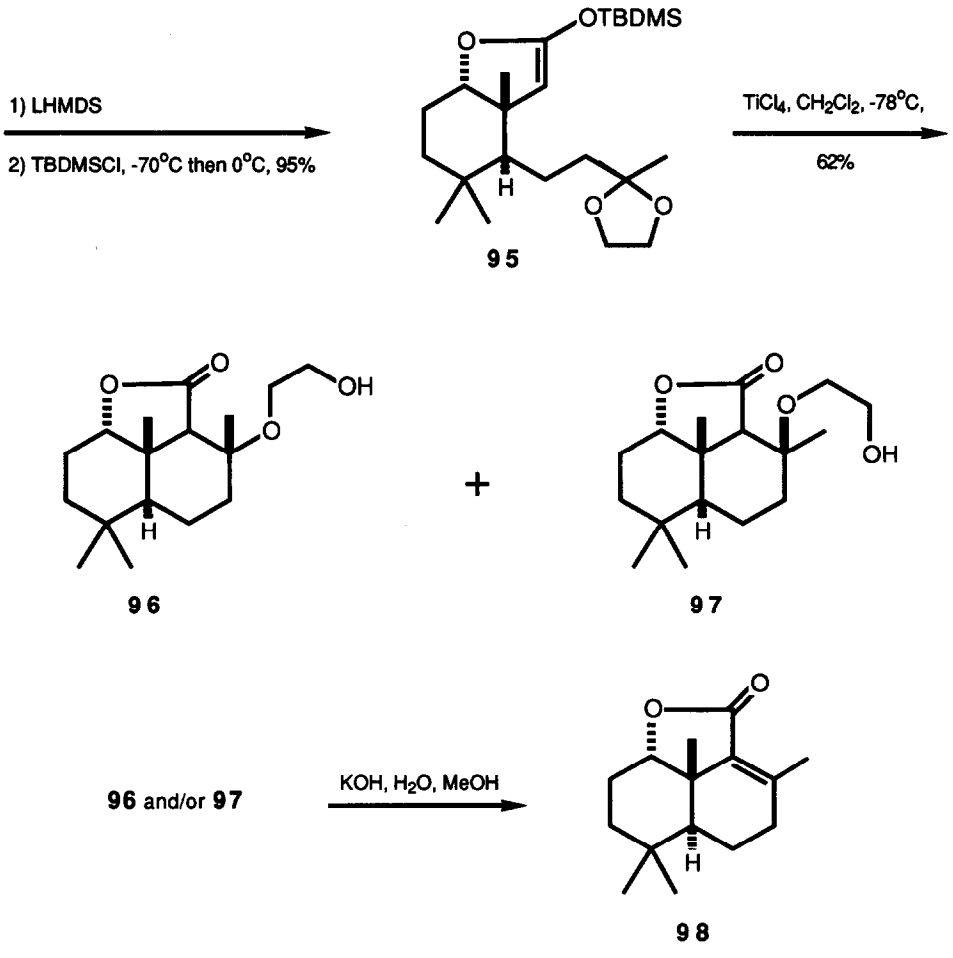
87: E=CO_2Me

The Intramolecular Radical Mediated Cyclization in Tandem with a Mukaiyama Aldolization Strategy

By using a stereoselective radical cyclization followed by an intramolecular Mukaiyama aldolization, Pattenden *et al.*[36] achieved the synthesis of tricyclic lactone **98** *en route* to the A-B ring system of forskolin (Scheme 16). These authors found that the diastereoisomeric mixture of bromo acetals **91**, prepared in three steps from the readily available hydroxy β-ionone **88** in the presence of catalytic cobalt(I) (electrochemically generated from vitamin B_{12}) underwent a 5-*Exo-Trig* ring closure to afford the *trans*-bicyclic acetal **92** along with less than 5% of the corresponding *cis*-isomer **93**. However, when the cyclization of **91** was carried out in the presence of tri-*n*-butyltin hydride, a 3:1 mixture of cycloadducts **93** and **92** was obtained in excellent yield.

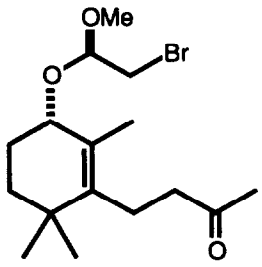
Scheme 16


HO
O
88
Bu3SnH, 95%
HO
O
89
EtOCH=CH2, Hg(OAc)2,
57%
O
O
90
NBS, MeOH, -20°C,
OMe
Br
O
O
91
vitamin B12,
MeOH, LiClO4, -1.8 v, rt,
24h, 70%
OMe
O
H
O
92
Bu3SnH, AIBN,
PhH, reflux,
2h, 95%
1) H2CrO4
2) HOCH2CH2OH, TsOH
92 +
OMe
O
H
O
1 : 3
93
O
O
H
O
O
94

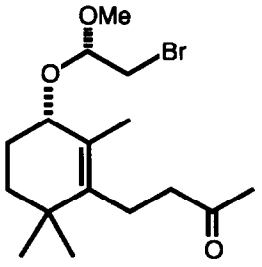


Jones oxidation and acetalization of **92** followed by treatment of the corresponding silyl enol ether **95** under the Mukaiyama aldolization conditions afforded a mixture of *trans*- decalins **96** and **97**. Finally, elimination of ethylene glycol with potassium hydroxide in aqueous methanol gave the α,β-unsaturated *trans*-decalin lactone **98**.

In a subsequent short communication[37] and later in a full report,[38] Pattenden *et al.* suggested an explanation for the interesting dichotomy in the cobalt- and stannane- mediated stereoselective cyclization of **91** which leads predominantly to the *trans*- and *cis*-bicyclic acetals **92** and **93**, respectively. By analyzing the stereochemistry of the cycloadducts obtained by cyclization of diastereoisomeric bromo acetals **99** and **100** under several initiation conditions, they concluded that the stereochemical outcome depends on the preferred conformations adopted by the transition state-radical intermediate in both reactions. Furthermore, a cobalt-bonded intermediate was also suggested to explain the stereochemistry of the cobalt(I)-mediated cyclization.

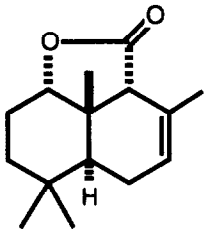


99



100

They also reported in the same publication[38] that the product obtained by elimination of ethylene glycol from **96** and **97** (Scheme 16) depends on the reaction conditions. By using solid potassium hydroxide in refluxing methanol, the deconjugated tricyclic lactone **101** was obtained exclusively, instead of the expected product **98**. Apparently, **101** is the thermodynamically controlled product of the reaction. As will be discussed later in this Report, lactone **101** proved to be a key intermediate *en route* to forskolin.

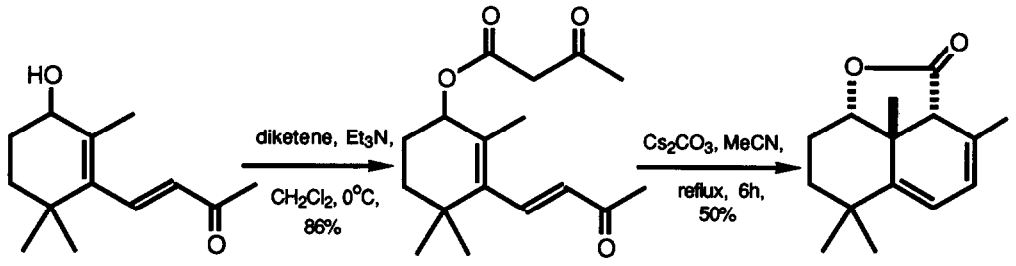


101

The Intramolecular Michael-Aldol Condensation Strategy

An alternative and rapid entry into a precursor for the A-B ring system of forskolin was developed by Koft and co-workers.[39] They found that the treatment of the acetoacetate ester **102**, prepared from hydroxy β-ionone (**88**) and diketene, with cesium carbonate in acetonitrile afforded tricyclic lactone **103** (Scheme 17). The structure of **103** suggested that an intramolecular Michael addition followed by an aldol condensation, a deacetylation, and a double bond migration had occurred in a single operation. That **103** had not been formed by an intramolecular Diels-Alder reaction *via* the enolate of **102** followed by deacetylation, was demonstrated when the propionylacetate analog of **102**, submitted to the same reaction conditions, also yielded **103**.

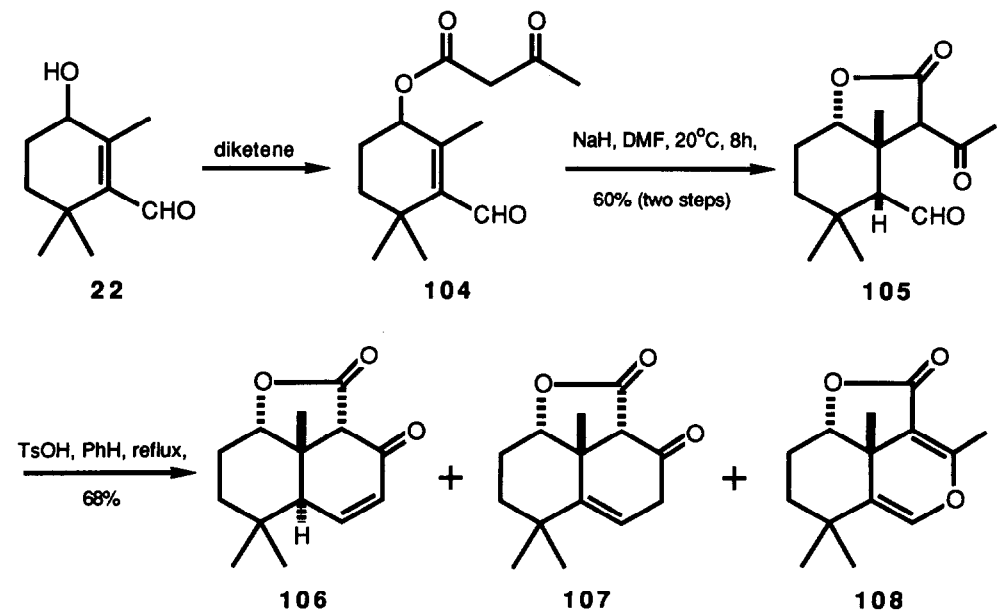
Scheme 17



88 **102** **103**

By following a conceptually similar approach, Li and Wu[40] reported the synthesis of tricyclic lactone **106** which was adequately functionalized for further elaboration toward forskolin. As shown in Scheme 18, treatment of acetoacetate ester **104** with sodium hydride afforded adduct **105** in good overall yield, from 3-hydroxycyclocitral **22**. All attempts to transform **105** into the aldol product **106** under basic conditions failed. However, under acidic conditions **106** was obtained in good yield by direct crystallization of the crude reaction product. By chromatography of the mother liquors, compounds **107** and **108** were also obtained in 12% and 13.5% yield, respectively.

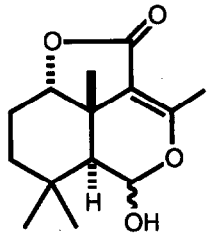
Scheme 18



22 **104** **105**

106 **107** **108**

Independently, we have synthesized the same tricyclic lactone (**106**)[41] and we have further demonstrated its utility as a valuable precursor of advanced intermediates toward forskolin.[42] These issues will be discussed later in this Report. For the synthesis of **106** we have initially used potassium carbonate in ethanol in the first step and *p*-toluenesulfonic acid in benzene at room temperature in the second one. However, under these conditions an appreciable amount of the hemiacetal **109**, the precursor of **108**, was formed and furthermore, the reaction time had to be carefully controlled to avoid the formation of the more stable β,γ-unsaturated ketone **107**. Recently,[43] we have overcome these drawbacks by using potassium *tert*-butoxide in refluxing benzene for the Michael addition. A dilute, refluxing solution of **105** in 1,2-dichloroethane in the presence of an equimolecular amount of *p*-toluenesulfonic acid monohydrate effected smoothly the aldol condensation. Under these conditions the formation of **107** was negligible.

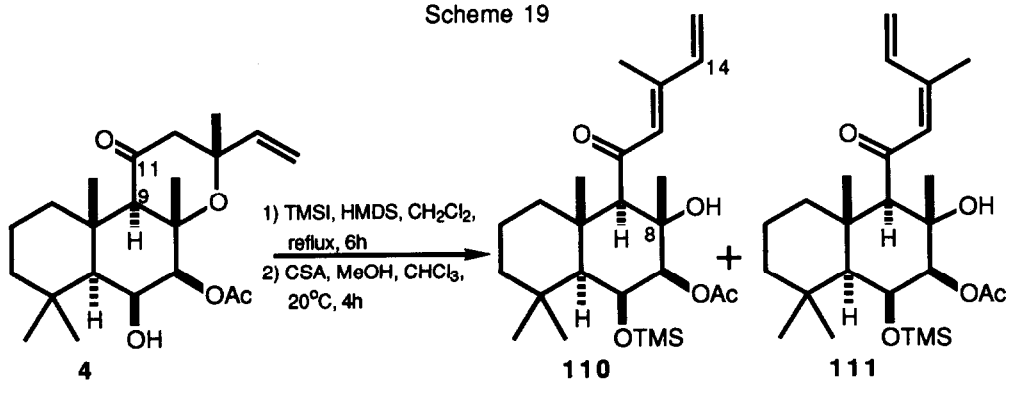


109

Approaches to the Construction and Elaboration of the C-Ring of Forskolin

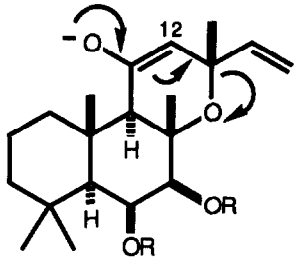
Attention was also focused on the construction and elaboration of the C-ring portion of forskolin and several approaches toward this end have been reported. In 1986, Welzel *et al.*,[44] in an attempt to prepare the 9(11) silyl enol ether of natural 1,9-dideoxyforskolin (**4**) as a model for testing the feasibility of a synthetic scheme directed to **1**, found that the treatment of **4** with trimethylsilyl iodide and hexamethyldisilazane (HMDS) afforded, after selective cleavage of the silyl ether at C-8, bicyclic products **110** and **111** in 45% and 18% yield, respectively (Scheme 19).

Scheme 19



4 **110** **111**

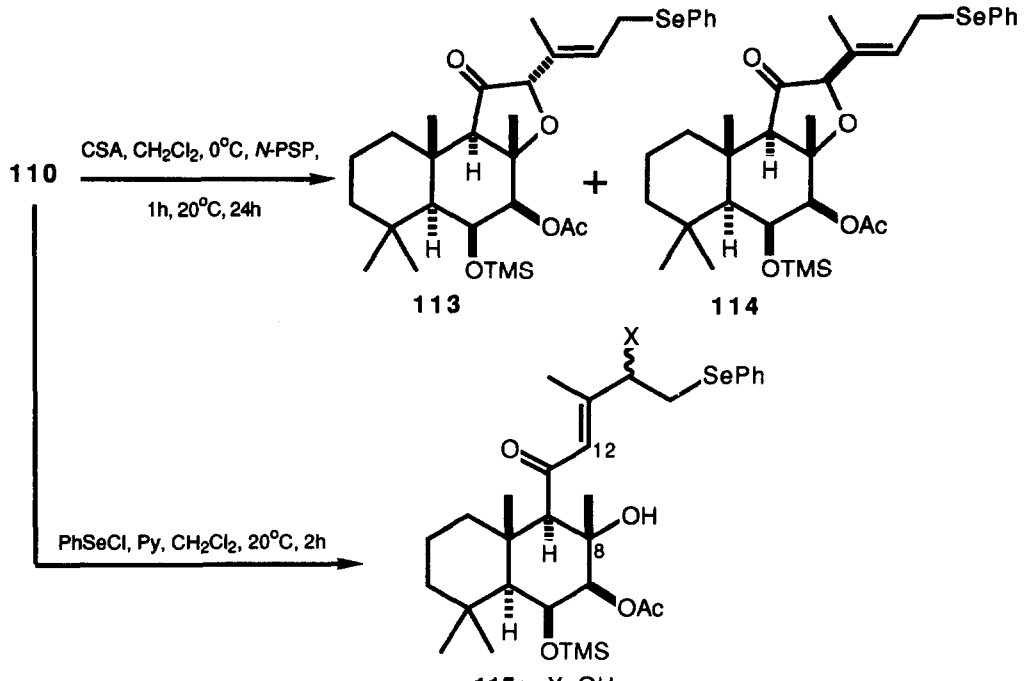
However, attempts to reconstitute the tetrahydropyran ring of **4**, starting with **110** and **111** were unsuccessful. The conjugate addition of the C-8 hydroxyl group to the enone unit under acidic or basic conditions failed. Apparently, the intermediate enols or enolates of type **112** reverse easily to the bicyclic starting materials.



112

In view of these results, some organoselenium-mediated cyclization reactions were studied, assuming that, under these conditions, the electrophilic reagent would attack C-12 to trap intermediate **112**. However, as shown in Scheme 20, treatment of **110** with *N*-phenylselenophthalimide (*N*-PSP) in the presence of camphorsulfonic acid led exclusively to the

Scheme 20

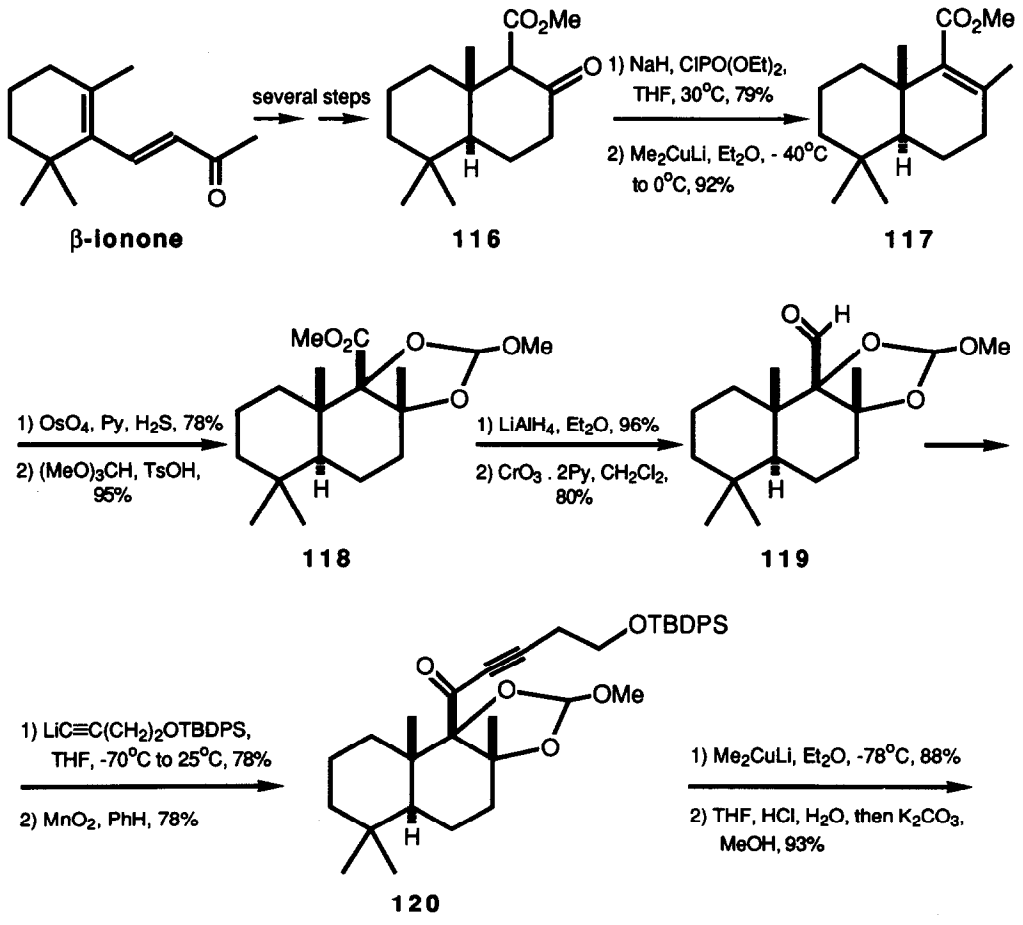


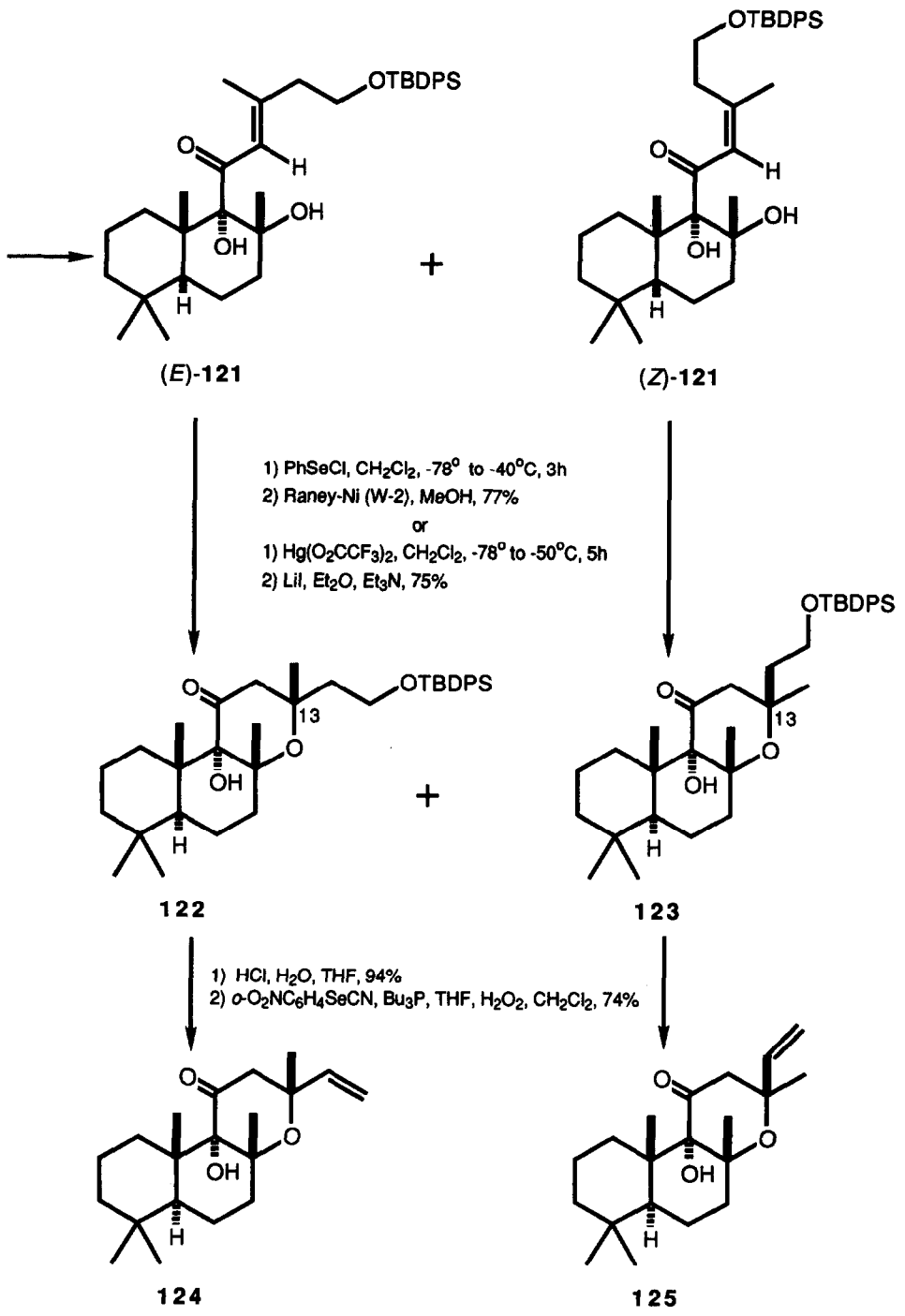
115a: X=OH
115b: X=Cl

unstable tetrahydrofurans **113** and **114** in 21% and 7% yield, respectively. The isolation of **115a** in 14% yield, presumably formed from **115b** during the chromatographic separation of the reaction mixture obtained when **110** was treated with phenylselenenyl chloride, led the authors to suggest that the reaction with *N*-phenylselenophthalimide proceeds through an intermediate of type **115**, from which **113** and **114** are formed by an S_N2' substitution process involving the nucleophilic attack of the C-8 hydroxyl at C-12.

Soon thereafter, Ikegami *et al.*[45] provided several solutions to the problem of the C-ring elaboration of forskolin. They found that separate cyclization of *E*-**121** and *Z*-**121**, prepared from β-ionone as shown in Scheme 21, with phenylselenenyl chloride or mercuric trifluoroacetate afforded, after reductive work-up, tetrahydropyran-4-ones **122** and **123** in good yield.

Scheme 21

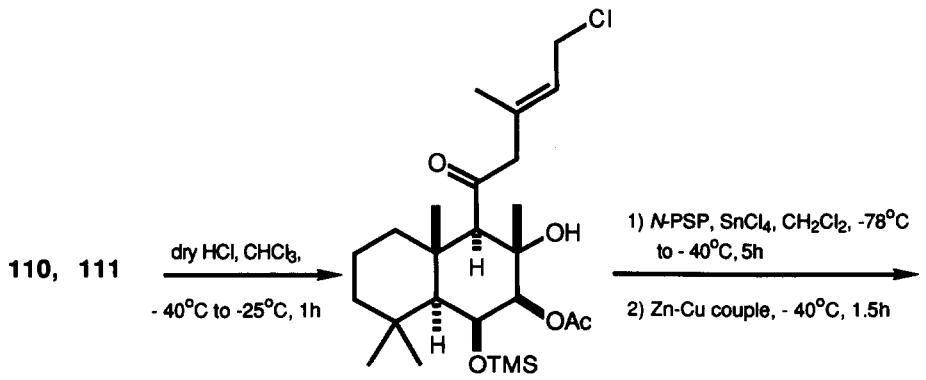



OTBDPS
O
H
OH
OH
H
(E)-121
(Z)-121
1) PhSeCl, CH2Cl2, -78° to -40°C, 3h
2) Raney-Ni (W-2), MeOH, 77%
or
1) Hg(O2CCF3)2, CH2Cl2, -78° to -50°C, 5h
2) LiI, Et2O, Et3N, 75%
13
122
123
1) HCl, H2O, THF, 94%
2) o-O2NC6H4SeCN, Bu3P, THF, H2O2, CH2Cl2, 74%
124
125

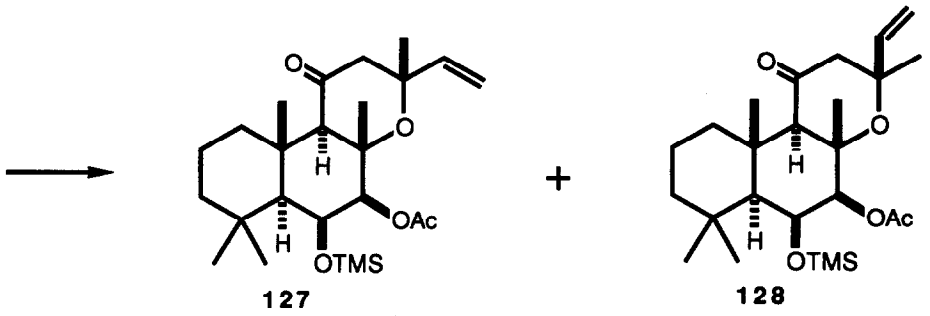
The organoselenium-mediated cyclization was shown to be a stereospecific reaction, the stereochemistry at C-13 of the tricyclic products depends on the geometry of the double bond of the starting alkene. The olefin with the *E*-configuration (*E*-**121**) afforded **122** as the major product [**122:123** (82:12)], whereas the geometric isomer with the *Z*-configuration (*Z*-**121**), under the same reaction conditions, yielded predominantly **123** [**122:123** (27:73)]. In clear contrast, when the ring closure was carried out with mercuric trifluoroacetate, the major product was that with the desired stereochemistry at C-13 (**122**), independent of the geometry of the starting alkene [**122** : **123** (80:20) from *E*-**121**; **122:123** (88:12) from *Z*-**121**]. The stereochemical outcome of this reaction was rationalized by invoking a mercury-stabilized carbonium ion, thus allowing rotation about the C-12, C-13 bond and cyclization through a chair-like transition state with the bulky alkyl chain equatorially disposed. The stereospecific oxyselenation cyclization reaction occurred by attack of the C-8 hydroxyl group on an episelenonium ion, again through a chair-like transition state. Finally, cleavage of the silyl ether protecting group of **122** followed by dehydration of the resulting primary alcohol by application of Grieco's methodology[46] afforded (±)-1,6,7-trideoxyforskolin **124**. The transformation of **123** into **125** was also carried out. By comparison of the NOE between the C-8 and C-13 methyl groups of **124** and **125**, the stereochemistry at C-13 in both compounds and also in **122** and **123** was firmly established.

On the basis of the mode of reaction of **110** with phenylselenenylchloride[44] (Scheme 20) and in light of the results reported by Ikegami *et al.*,[45] Welzel and co-workers[47] decided to study the cyclization reaction with a protected form of the diene in anticipation of obtaining the tetrahydropyran-4-one moiety present in forskolin. They found, as shown in Scheme 22, that by reaction of both bicyclic products **110** and **111** with hydrogen chloride at low temperature a mixture of addition products was obtained from which the 1,4-adduct **126** was isolated in low yield. As expected, when **126** was subjected to cyclization with *N*-phenylselenophthalimide-tin tetrachloride followed by reductive elimination, the trimethylsilyl ether of 1,9-dideoxyforskolin (**127**) was obtained in 41% yield along with the C-13 epimer **128** in 12% yield.

Scheme 22



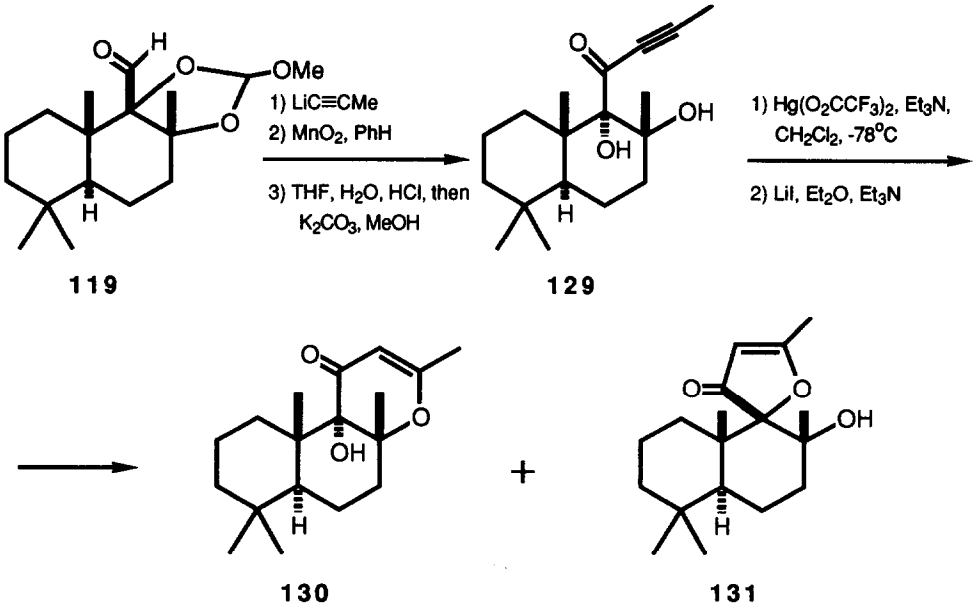
126



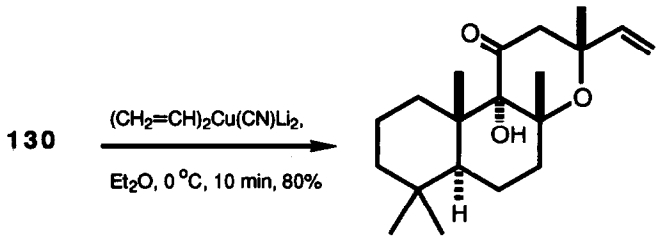
127 **128**

At this time, Ikegami *et al.*[45] also reported an alternative and convenient route to **124** by using a mercuric trifluoroacetate-mediated cyclization followed by a conjugate addition of a vinyl cuprate (Scheme 23). They demonstrated that the acetylenic ketone **129** underwent regioselective ring closure affording the dihydropyran-4-one **130** in 71% yield along with 7% of the dihydrofuran-3-one **131**. The key introduction of the vinyl group to **130** proceeded smoothly by using the higher-order cuprate $[(H_2C{=}CH)_2Cu(CN)Li_2]$[48] that afforded exclusively the desired isomer **124** in good yield.

Scheme 23



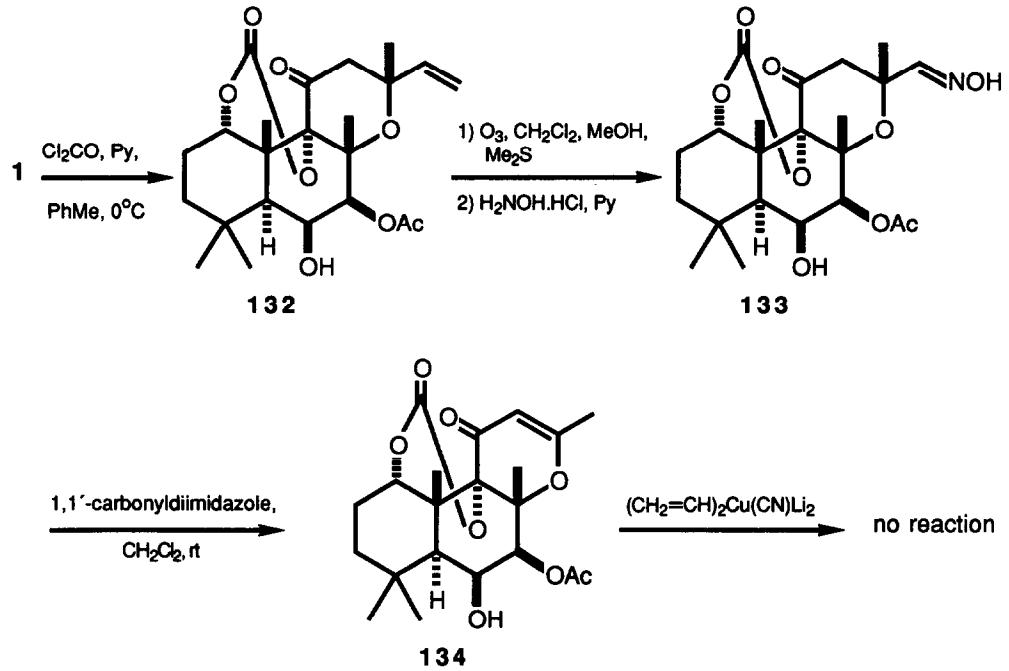
119 **129** **130** **131**



124

The success of the vinyl cuprate addition is especially significant in view of the problems reported by Saksena *et al.*[49] in their attempts to obtain **132** by addition of the same higher-order cuprate to the dihydropyran-4-one **134**, which is available by degradation of natural forskolin (Scheme 24).

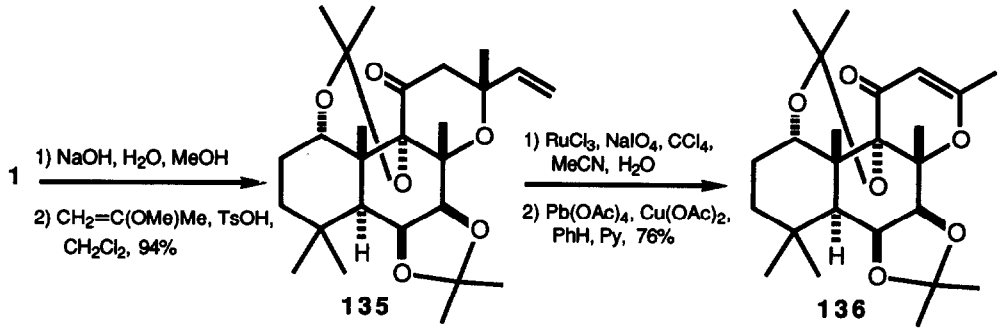
Scheme 24



132 133 134

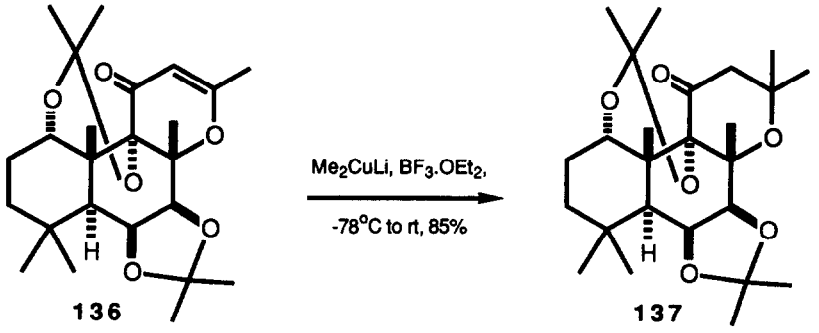
Subsequently, Delpech and Lett[50] described several attempts to effect cuprate addition to dihydropyran-4-ones derived from natural forskolin, in particular, to di-acetonide **136**, which is efficiently prepared as shown in Scheme 25.

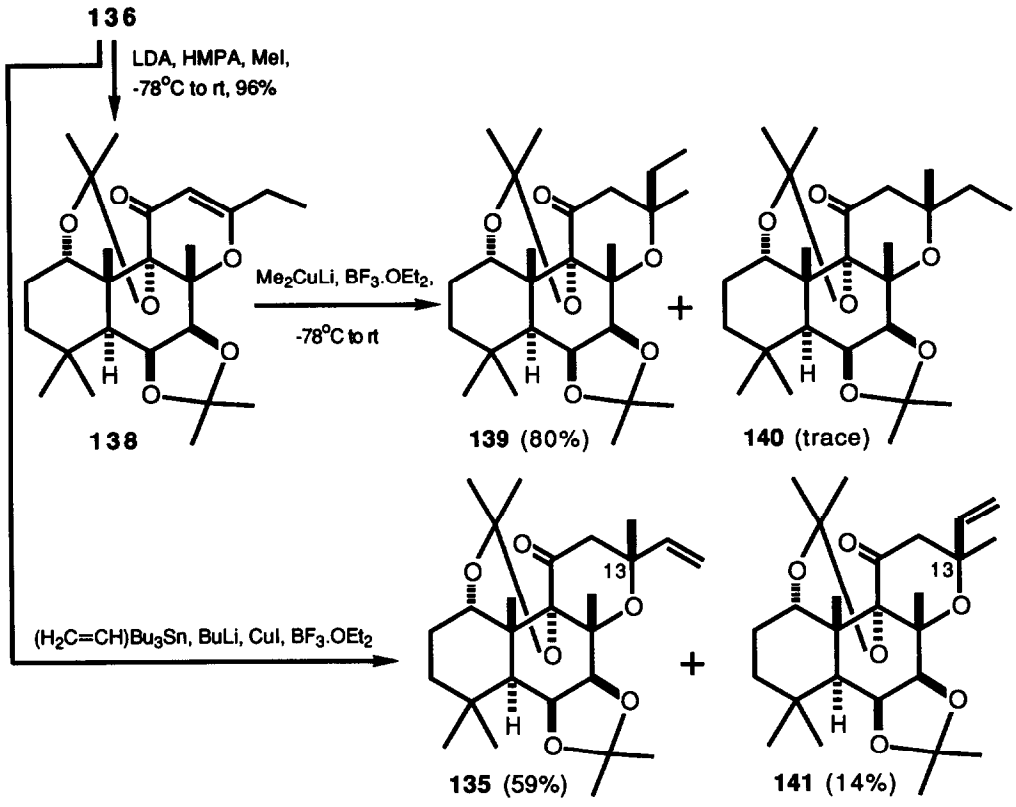
Scheme 25



As shown in Scheme 26, these authors found that lithium dimethylcuprate in the presence of boron trifluoride etherate[24] reacts with **136** affording the 1,4-addition product **137** in very good yield. To establish the stereochemistry of the conjugate addition reaction, **136** was first homologated to **138** and then treated as described above. Two addition products were isolated from the reaction mixture. The minor isomer **140** correlated with the dihydro derivative of the diacetonide of 7-deacetylforskolin (**135**), indicating that the major product must be **139**. Consequently, the addition reaction occurred almost exclusively from the α-face of **138**. Interestingly, they were also able to achieve the conjugate addition of vinyl cuprate to **136** obtaining **135** as the major product along with a small amount of the epimer at C-13 (**141**). No mention of the transformation of **135** into forskolin was made.

Scheme 26



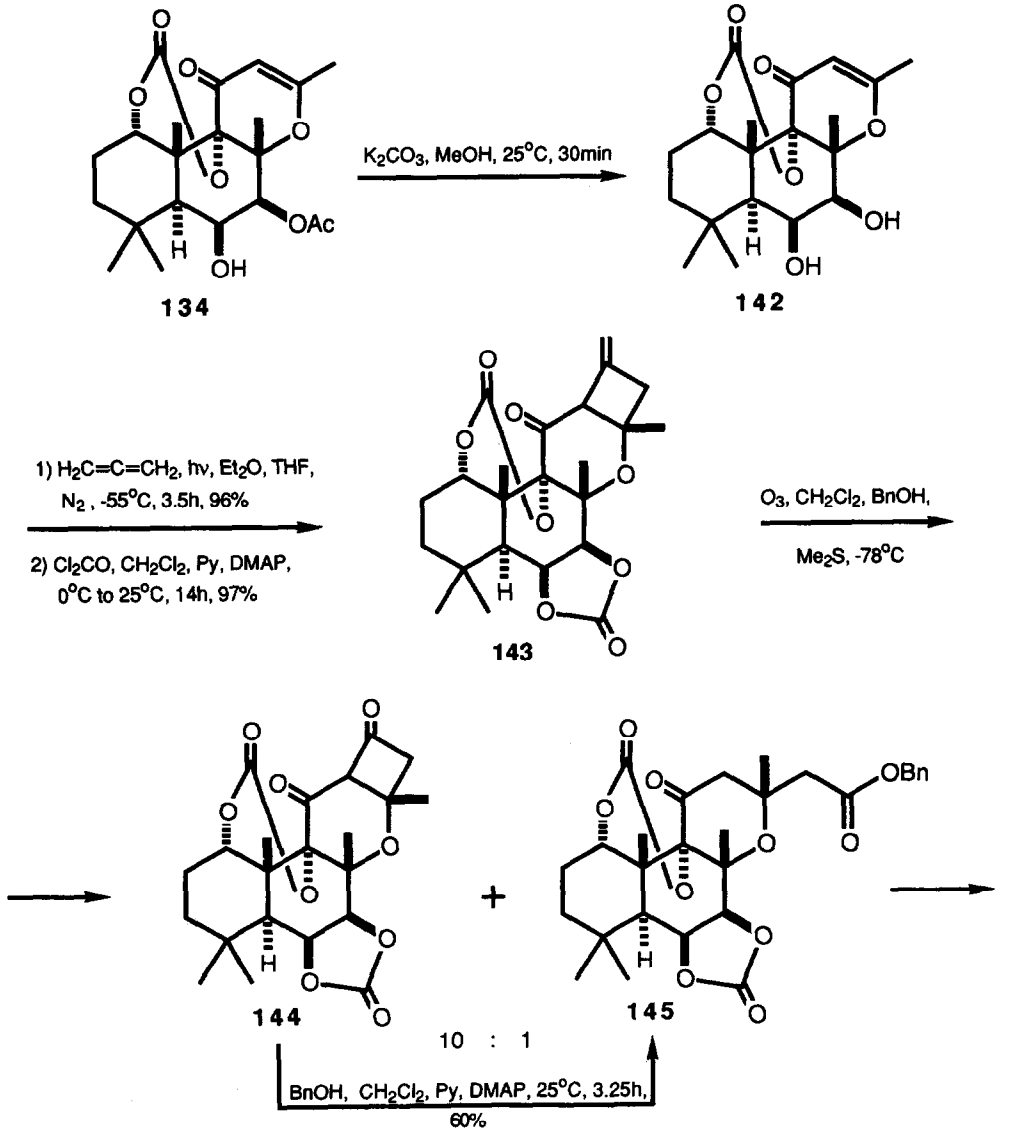


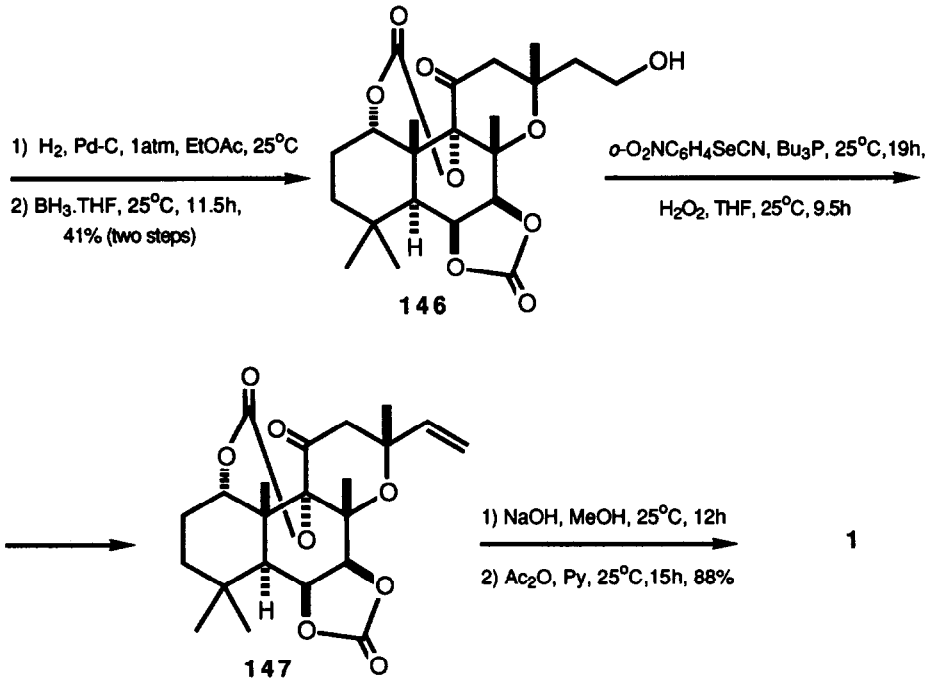
In spite of the stereoselectivity of the additions described by Delpech and Lett[50] and that reported by Ikegami *et al.*[45] (Scheme 23) that occurred preferentially from the α-face of the dihydropyran-4-one moiety, the French authors concluded that care should be taken in predicting the stereochemistry of this type of reaction since, as they have observed, **136** reacts with lithium di-*n*-butyl cuprate under the same reaction conditions to afford the major β–1,4-addition product in 61% yield together with the corresponding α-adduct in 23% yield. A similar stereochemical result in a related transformation was reported by Corey *et al.*[51] in a total synthesis of forskolin, as will be discussed later in this Report.

By using a photochemical reaction as the key step, Ziegler *et al.*[52] developed a completely different approach to add the C-ring vinyl group of forskolin (Scheme 27). Irradiation of **142**, prepared from the known degradation product of forskolin **134** (Scheme 24), in the presence of allene afforded in excellent yield a single photoadduct, which was transformed into its cyclic carbonate **143**. Although the regio- and stereochemistry of the photoadduct could not be established at this point, further chemical transformations demonstrated that the addition had occurred in the desired manner. Ozonolysis of the exocyclic double bond of **143** followed by a Haller-Bauer cleavage of the resulting diketone **144** afforded benzyl ester **145**, thereby establishing the regiochemistry of the photoaddition reaction. Hydrogenolysis of **145** yielded a carboxylic acid which was selectively reduced to alcohol **146**. Finally, by application of Grieco's

procedure[46] to **146**, di-carbonate **147** was obtained. Since compound **147** was identical to the product prepared by treatment of 7-deacetylforskolin (**3**) with phosgene in pyridine, the stereochemistry of the original photoadduct **143** was established. Further evidence of the success of this route was obtained when the di-carbonate **147** gave forskolin (**1**) upon hydrolysis and selective acetylation.[2]

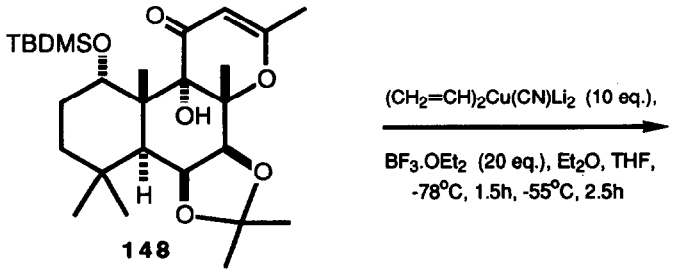
Scheme 27

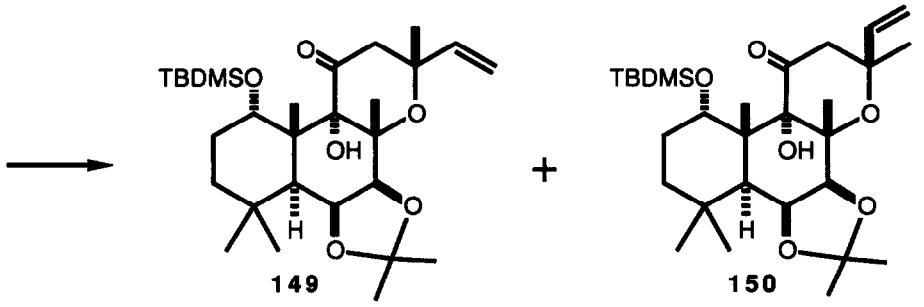




In addition, Ziegler *et al.* [53] subsequently reported conditions for adding a vinyl group directly to the synthetic dihydropyran-4-one **148**. By using the higher-order cuprate, previously used by Ikegami *et al.*[45] (Scheme 23), in the presence of a large excess of boron trifluoride etherate, **148** afforded the α-vinyl isomer **149** in 54% yield along with 6% of the β-vinyl isomer **150**, as shown in Scheme 28. The synthesis of **148** will be discussed later in this Report.

Scheme 28

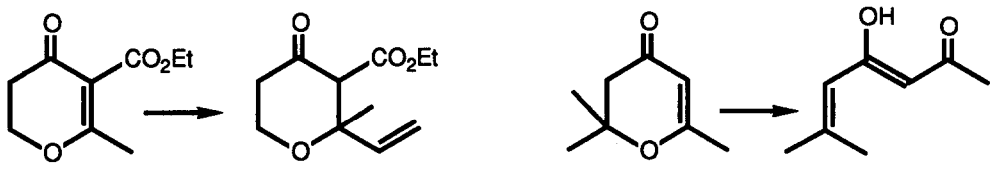




149 150

After discussing several studies directed to the final elaboration of ring C of forskolin by addition of a vinyl anion equivalent to a more or less functionalized dihydropyran-4-one moiety, we consider it worthwhile to discuss also the report of Boring and Sindelar.[54] In an attempt to synthesize promising partial derivatives of forskolin to elucidate the essential pharmacophore of this biologically active natural product, these authors carried out a careful study of conjugate addition methods for the precise introduction of a vinyl group to simple dihydropyran-4-ones. In all cases studied they found that ester **151** afforded high yields of the expected 1,4-addition product **152**. On the other hand, pyran-4-one **153** suffered exclusive ring opening under a variety of reaction conditions leading to product **154** (Scheme 29).

Scheme 29



151 152 153 154

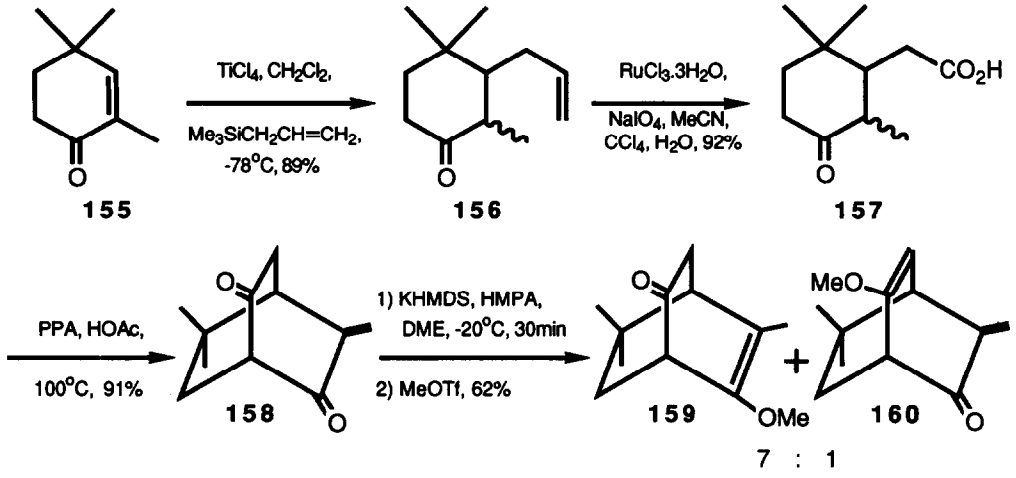
On the basis of these results and those previously discussed, additional work is necessary to improve the organocuprate addition to dihydropyran-4-ones into a predictable synthetic operation.

Approaches toward the A-B-C Ring System of Forskolin
The Anionic Oxy-Cope Rearrangement

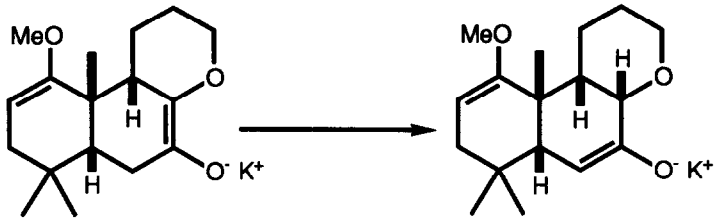
In 1987, Paquette *et al.*[55] communicated a synthetic sequence toward the model tricyclic compound **167** (Scheme 31), by using an anionic oxy-Cope rearrangement as the key step. The bicyclic ketone **159**, which is required for the preparation of the substrate necessary for the rearrangement process, was prepared in four steps starting from enone **155** (Scheme 30). Although the last step of the sequence required considerable experimentation, the major ketone

159 could be readily separated by chromatography from its regioisomer **160**.

Scheme 30

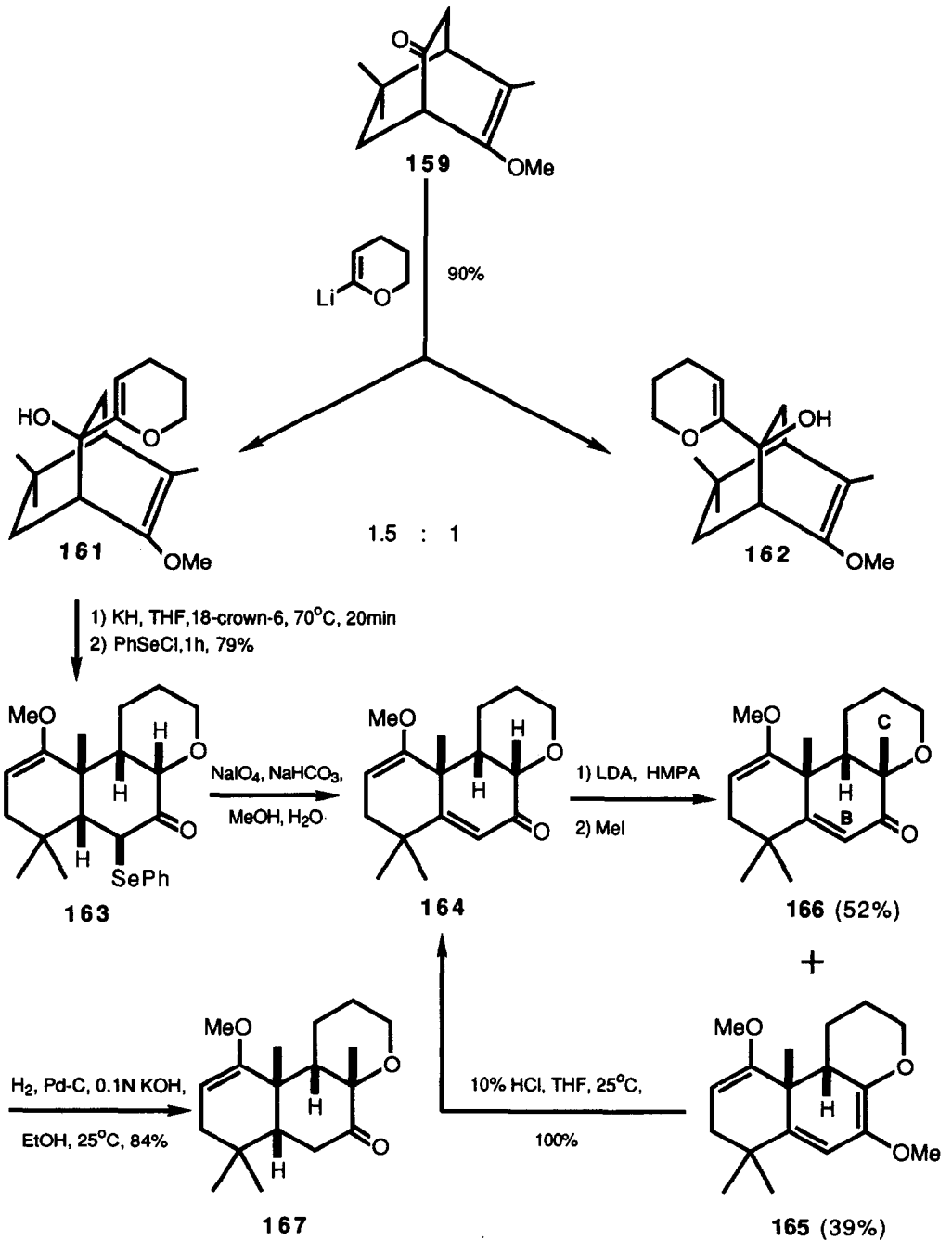


As shown in Scheme 31, addition of 2-lithiodihydropyran to ketone **159** resulted in the formation of a 1.5:1 mixture of the desired alcohol **161** and the epimer **162** in 90% yield. When the potassium salt of alcohol **161** was heated at 70°C for 20 minutes followed by trapping of the enolate with phenylselenenyl chloride, the rearrangement product **163** was obtained. Apparently, the initially formed enolate **168** equilibrated completely to **169** at this temperature to afford the tricyclic compound **163** after reaction with the electrophile.

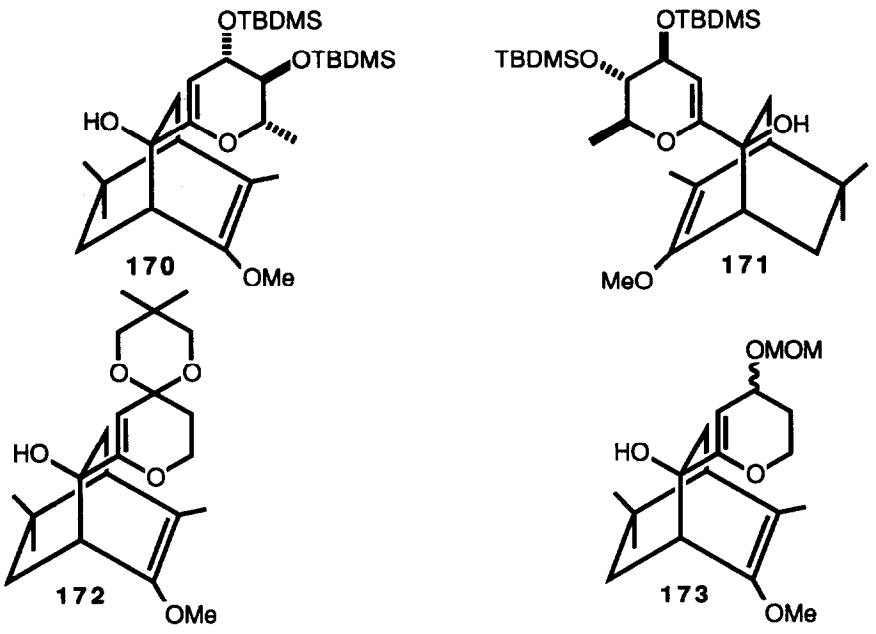


Oxidative elimination of **163** to **164**, and deprotonation followed by methylation afforded **165** and **166**. Presumably, the formation of a considerable amount of **165**, which can be easily reconverted into **164**, is a consequence of the 1,3-diaxial Me-Me interaction that is encountered during the introduction of the angular methyl group. The *cis* nature of the B-C ring fusion of **166** prevented the use of dissolving metals for the selective reduction of the conjugated double bond to generate a *trans*-A-B decalin system since the axially disposed C-8 oxygen bond is rapidly cleaved under these reaction conditions. In contrast, catalytic hydrogenation of **166** afforded exclusively the non-epimerizable *cis*-A-B fused ketone **167**.

Scheme 31


159
OMe
Li
90%
HO
161
OMe
1.5 : 1
OH
162
OMe
1) KH, THF,18-crown-6, 70°C, 20min
2) PhSeCl,1h, 79%
MeO
H
O
H
H
O
SePh
163
NaIO4, NaHCO3,
MeOH, H2O
MeO
H
O
H
O
164
1) LDA, HMPA
2) MeI
MeO
C
O
H
B
O
166 (52%)
+
H2, Pd-C, 0.1N KOH,
EtOH, 25°C, 84%
MeO
O
H
H
O
167
10% HCl, THF, 25°C,
100%
MeO
O
H
OMe
165 (39%)

In an attempt to expand this approach to the synthesis of more advanced tricyclic intermediates *en route* to forskolin, Paquette *et al.*[56] reported the preparation of several highly functionalized 3,4-dihydro-2H-pyrones including some in enantiomerically pure form. However, the metalation of these heterocycles was complicated and some adducts with ketone **159** could not be obtained. Furthermore, no indication of the oxy-Cope rearrangement was observed, even under a variety of reaction conditions for the adducts **170**, **171**, **172**, and **173**. Apparently, the steric and/or electronic effects of the substituents at the dihydropyran ring prevent the [3,3] sigmatropic rearrangement.

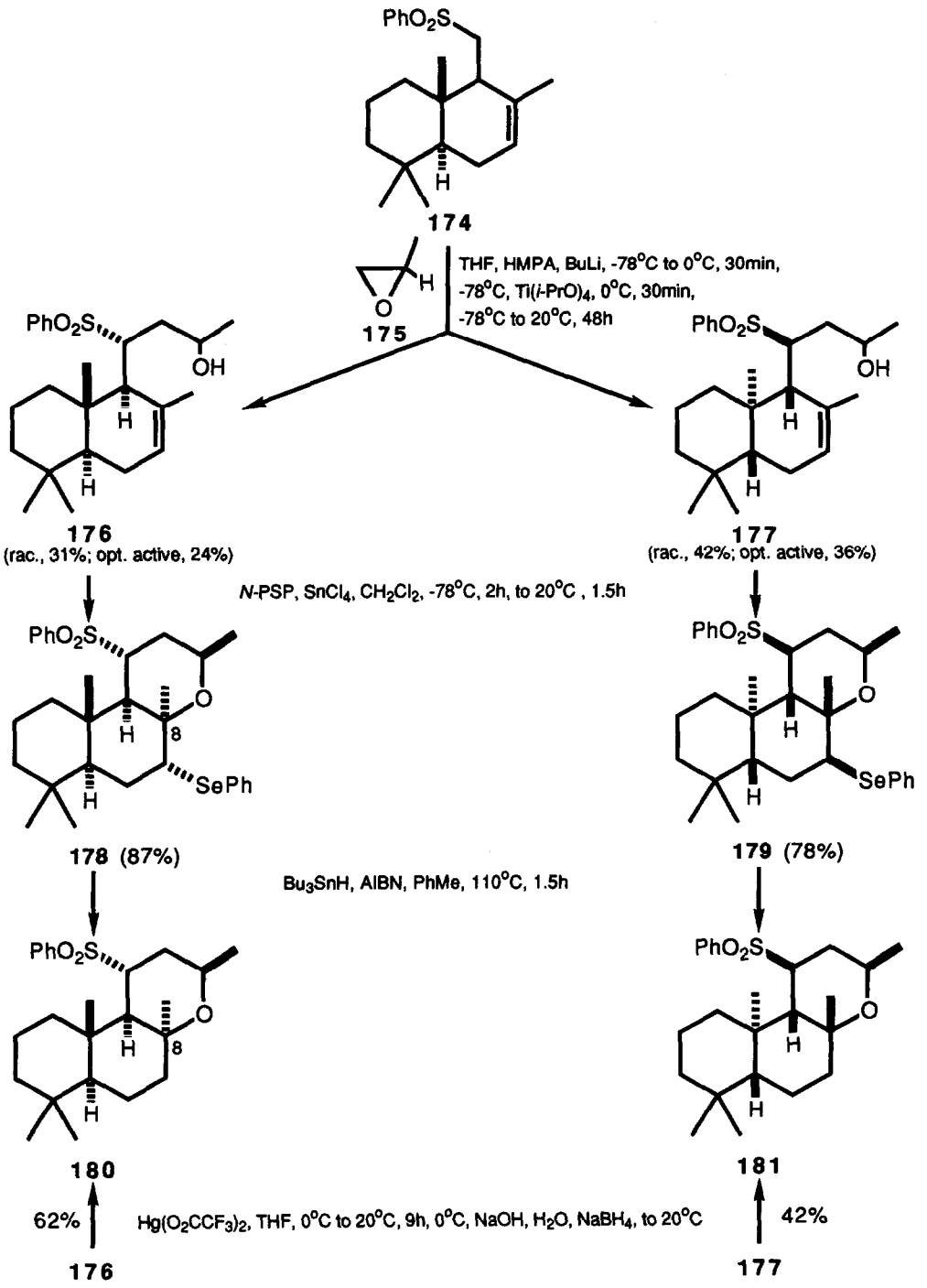


The Selenium- and Mercuric Trifluoroacetate-Mediated Cyclizations of a Drimane-Type Sulfone Approach

A second approach to the skeleton of forskolin was reported by Welzel and co-workers.[57] As shown in Scheme 32, they found that the titanium(IV) isopropoxide assisted reaction of the lithio derivative of the racemic form of the drimane-type sulfone **174**,[58] with both racemic and the (R)-methyloxirane **175**, afforded the diastereoisomeric alcohols **176** and **177** in racemic and optically active form, respectively. Selenium-induced cyclization of **176** and **177** afforded the corresponding tricyclic products **178** and **179** (87% and 78% yield), which were reductively converted into **180** and **181** upon treatment with tri-*n*-butyltin hydride. Alternatively, **176** and **177** were also cyclized by reaction with mercuric trifluoroacetate followed by reduction with sodium borohydride to give **180** and **181** in 62% and 42% yield, respectively.

Because of the incorrect stereochemistry at C-8, the tricyclic compounds **178** and **180** were not suitable for further transformations into more advanced intermediates toward forskolin.

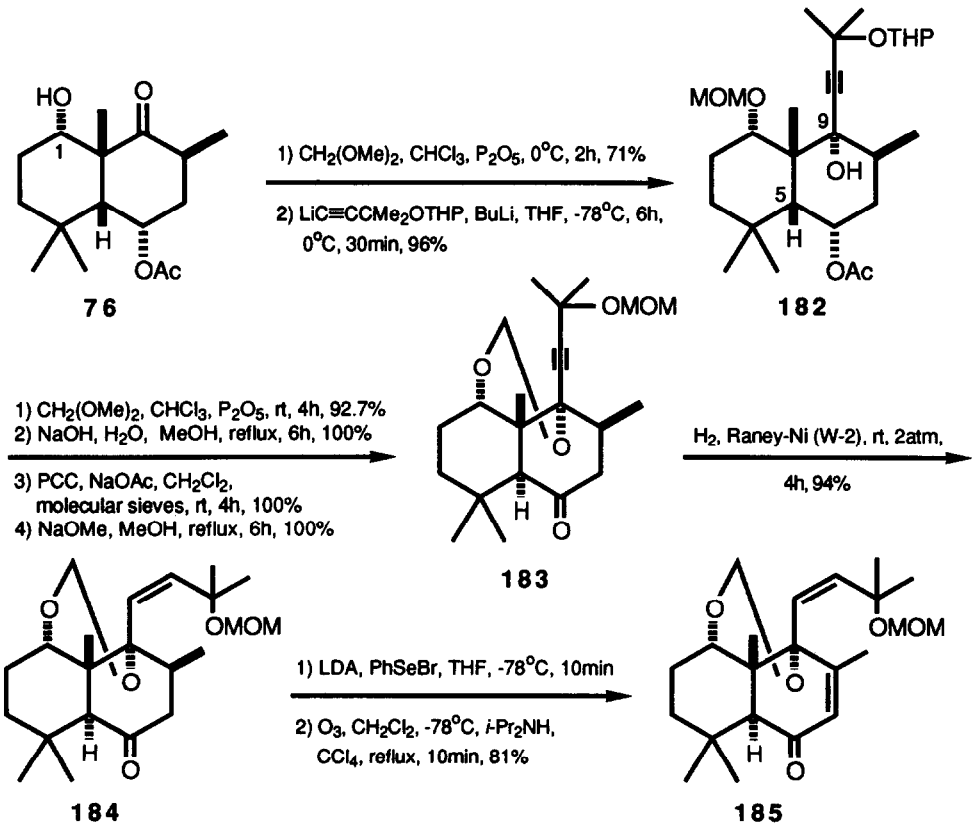
Scheme 32

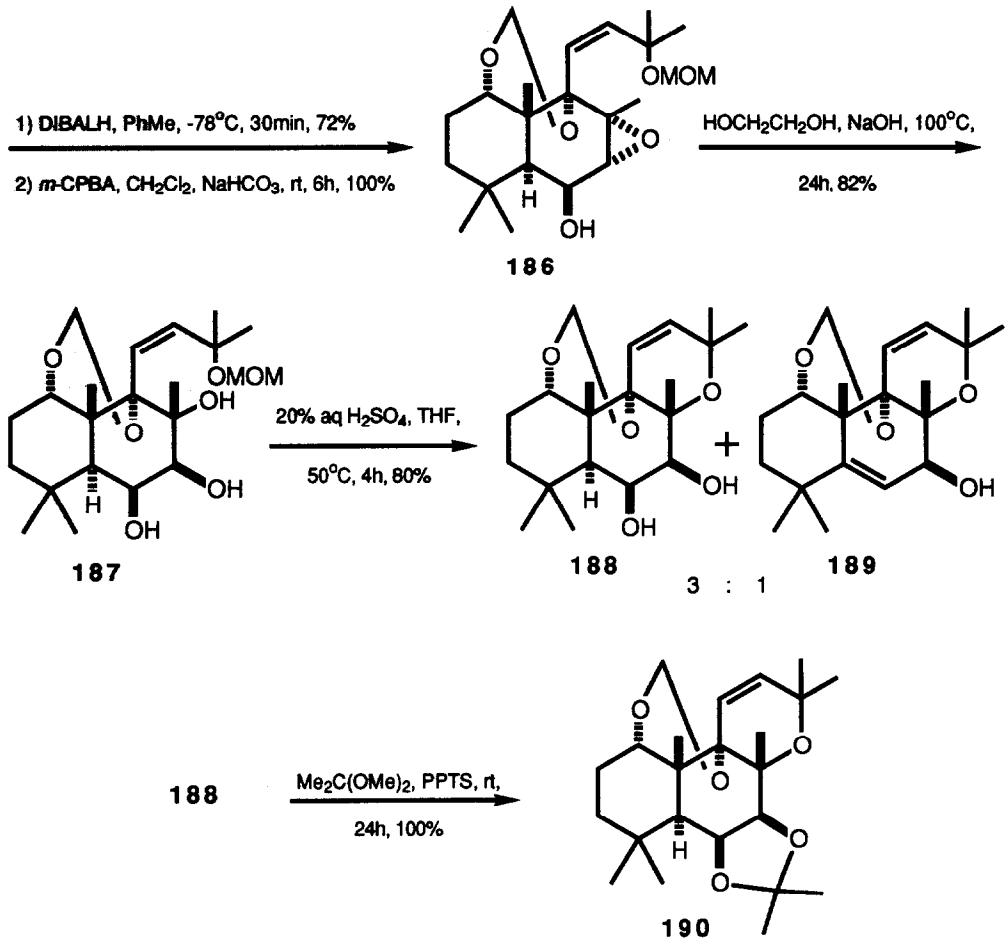

PhO2S
174
175
THF, HMPA, BuLi, -78°C to 0°C, 30min,
-78°C, Ti(i-PrO)4, 0°C, 30min,
-78°C to 20°C, 48h
176
(rac., 31%; opt. active, 24%)
177
(rac., 42%; opt. active, 36%)
N-PSP, SnCl4, CH2Cl2, -78°C, 2h, to 20°C , 1.5h
178 (87%)
179 (78%)
Bu3SnH, AIBN, PhMe, 110°C, 1.5h
180
181
62%
Hg(O2CCF3)2, THF, 0°C to 20°C, 9h, 0°C, NaOH, H2O, NaBH4, to 20°C
42%
176
177

Cationic Cyclization of a Highly Functionalized Decalin Derived from the INOC Cycloaddition Strategy

As was noted earlier, an INOC reaction was employed in the synthesis of the functionalized intermediate **76** (Scheme 13). Starting with **76**, Barco, Pollini and co-workers,[33] continuing with their study on the synthesis of forskolin, synthesized the tricyclic model compound **190** (Scheme 33). Protection of the hydroxyl group at C-1 of **76** followed by ethynylation with the tetrahydropyranyl ether of 4-lithio-2-methyl-3-butyn-2-ol provided **182** as the sole product in good yield. Although the stereochemistry of this tertiary alcohol was not unambiguously determined at this juncture, the concave nature of the *cis*-decalin dictated that the addition of the acetylide ion would occur with the correct stereochemistry at C-9. The acetylenic tertiary alcohol **182** was then protected and, by a sequence involving saponification of the acetate group, oxidation of the resulting alcohol, and epimerization at C-5 gave the *trans*-decalin **183**.

Scheme 33



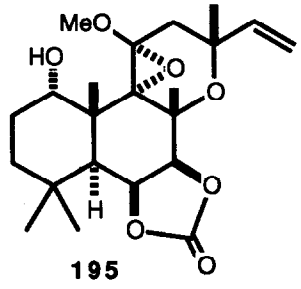


The triple bond of **183** was cleanly reduced to olefin **184** and its stereochemistry was confirmed by X-ray analysis. Ketone **184** was transformed into enone **185** in good yield by selenenylation followed by oxidative elimination. The epoxidation of the axial allylic alcohol, obtained by stereoselective reduction of **185** with *m*-chloroperoxybenzoic acid, afforded regio- and stereoselectively the α-epoxide **186** which, upon basic ring opening, led to the triol **187**. Exposure of **187** to acidic conditions gave a 3:1 mixture of the desired tricyclic compound **188** and the dehydration product **189** in good yield. To study the functionalization of the double bond of **188**, the *cis*-diol unit was protected as the acetonide **190**; however, all attempts to functionalize its double bond failed. Although no further transformation could be carried out on **190**, it is worthwhile mentioning that this tricyclic model compound possesses the complete array of oxygenated functional groups found in the A-B rings of forskolin.

Partial Syntheses of Forskolin

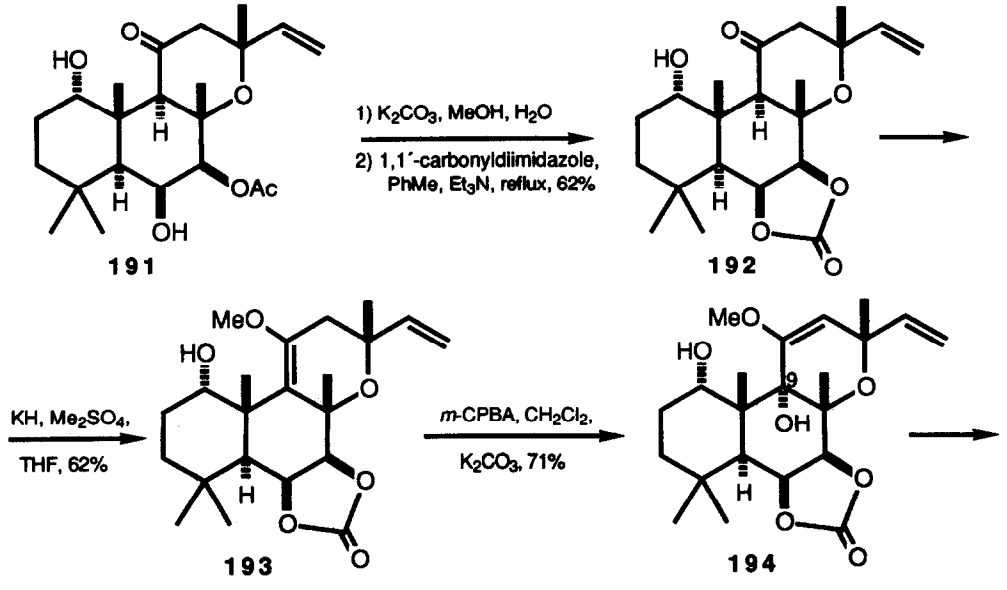
As mentioned in the Introduction, several diterpenes related to forskolin (**1**), such as **2**, **3**, **4**, and **5**, were also isolated from *C. forskohlii.* More recently, 9-deoxyforskolin (**191**) was also isolated from the same source.[59] Consequently, several groups were interested in using these biologically less-active natural products as starting materials for the partial synthesis of forskolin through the development of efficient oxygenation procedures.

In 1987, Hrib[60] reported the chemical transformation of **191** into forskolin (Scheme 34) *via* regio- and stereoselective hydroxylation of methyl enol ether **193**. Treatment of **193**, prepared regiospecifically from carbonate **192**, with *m*-chloroperoxybenzoic acid afforded the 9-hydroxylated enol ether **194** in good yield. Presumably, **193** led to the α-epoxide **195** which, under the reaction conditions, suffered ring opening to yield **194**. Hydrolysis of the methyl enol ether, saponification of the cyclic carbonate, and selective acetylation[2] afforded forskolin (**1**) in 12 % overall yield.

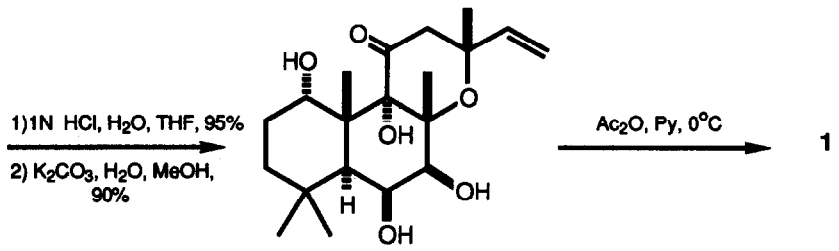


195

Scheme 34

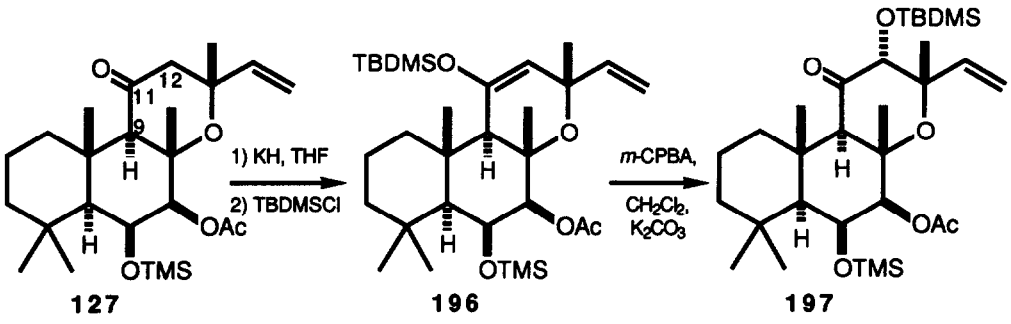


191 **192** **193** **194**



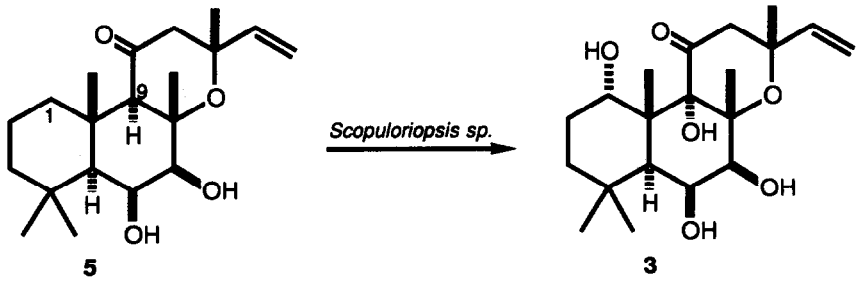
A related study by Welzel and co-workers[61] is noteworthy because the 1,9-dideoxyforskolin derivative **127** (Scheme 22) reacted under Hrib's reaction conditions to give exclusively the 11(12) enolate which, upon trapping with *tert*-butyldimethylsilyl chloride (TBDMSCl), yielded **196** instead of the expected enolate with the double bond at 9(11)-position (Scheme 35). The same results were obtained when the corresponding methyl enol ethers were prepared. Epoxidation of **196** with *m*-chloroperoxybenzoic acid yielded the 12-α-silyloxyketone **197**.

Scheme 35



A microbial oxidation strategy for the transformation of 1,9-dideoxyforskolin (**4**) into forskolin was also reported. During a screening of hydroxylating fungi Khandelwal *et al.*[62] found that a *Scopuloriopsis* species transformed 7-deacetyl-1,9-dideoxyforskolin (**5**) into 7-deacetylforskolin (**3**) although in very low yield (0.76%) (Scheme 36).

Scheme 36



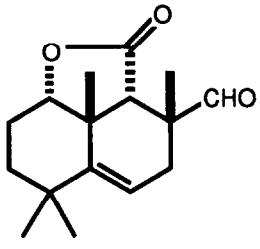
Tetraol **3** is readily convertible into forskolin (**1**) by the selective acetylation procedure described earlier.[2]

Total Syntheses of Forskolin

Three synthetic sequences that culminated successfully in the total synthesis of forskolin have appeared in the literature. As had been mentioned earlier in this Report, the intramolecular Diels-Alder reaction was selected as the key step in these sequences for the construction of an adequately functionalized A-B ring system and all pass through **206**. In all cases the elaboration of ring C was carried out at the final stages of the synthesis.

The Ziegler Approach

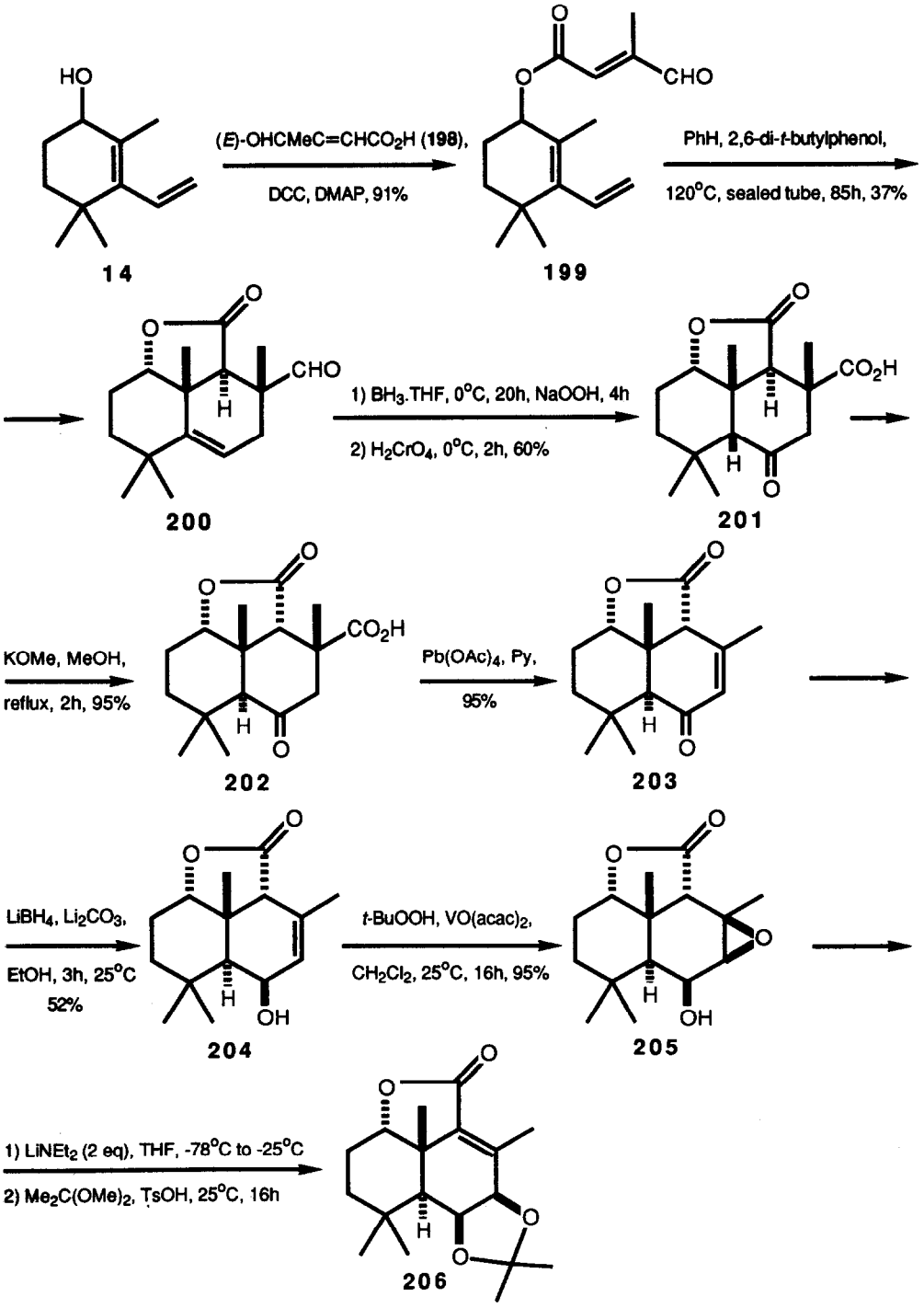
In 1985, Ziegler and co-workers[63] reported the synthesis of tricyclic lactone **206**, as shown in Scheme 37. The triene **199**, carrying a double activated dienophile, was obtained by esterification of the known alcohol **14** with acid **198**. Thermolysis of **199** led to tricyclic lactone **200** with the stereochemistry expected for an *exo*-cyclization together with recovered starting material (55%). By working at higher temperature (160°C) a better yield of **200** was obtained; however, the isomeric lactone **207** was also produced. Apparently, the *trans*-lactone **200**



207

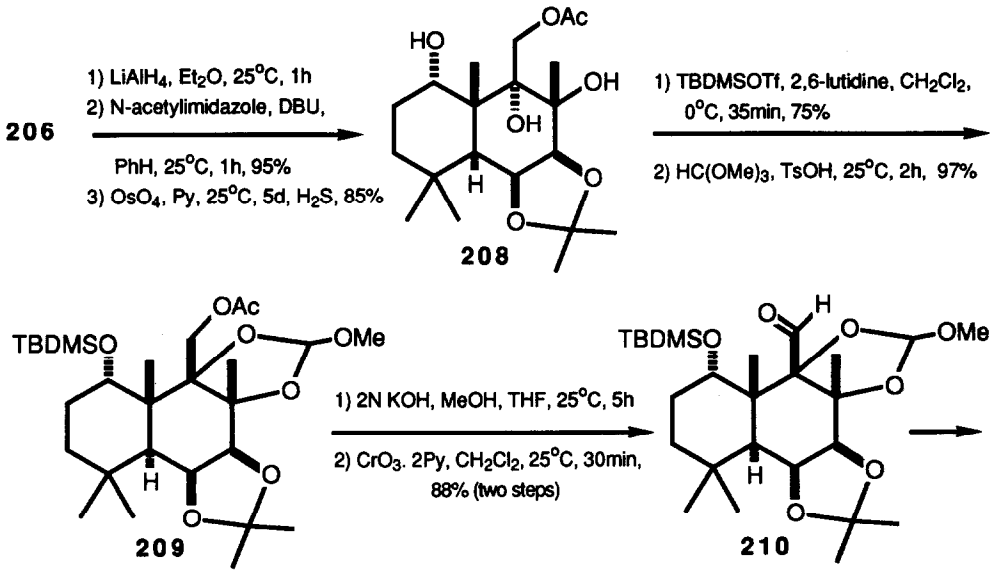
epimerized, under these conditions, to the thermodynamically favored *cis*-lactone **207**. Hydroboration of **200** followed by Jones oxidation of the resultant diol afforded the crystalline keto acid **201** in 60% overall yield. The stereochemistry of compound **201** and, at the same time, of the Diels-Alder adduct **200**, was unambiguously determined by a single X-ray analysis. Equilibration of keto acid **201** under basic conditions afforded the isomeric keto acid **202** that upon oxidative decarboxylation, yielded exclusively the conjugated ketone **203**. For the introduction of the C-6, C-7 oxygen functionality found in forskolin, a stereochemically efficient sequence was developed starting with **203**. This sequence involved the stereoselective reduction of the keto group of **203** to the corresponding axial alcohol **204** followed by a Sharpless-type hydroxyl-directed epoxidation to **205**. Finally, base-catalyzed rearrangement of epoxide **205** afforded a diol that was transformed into the acetonide **206**.

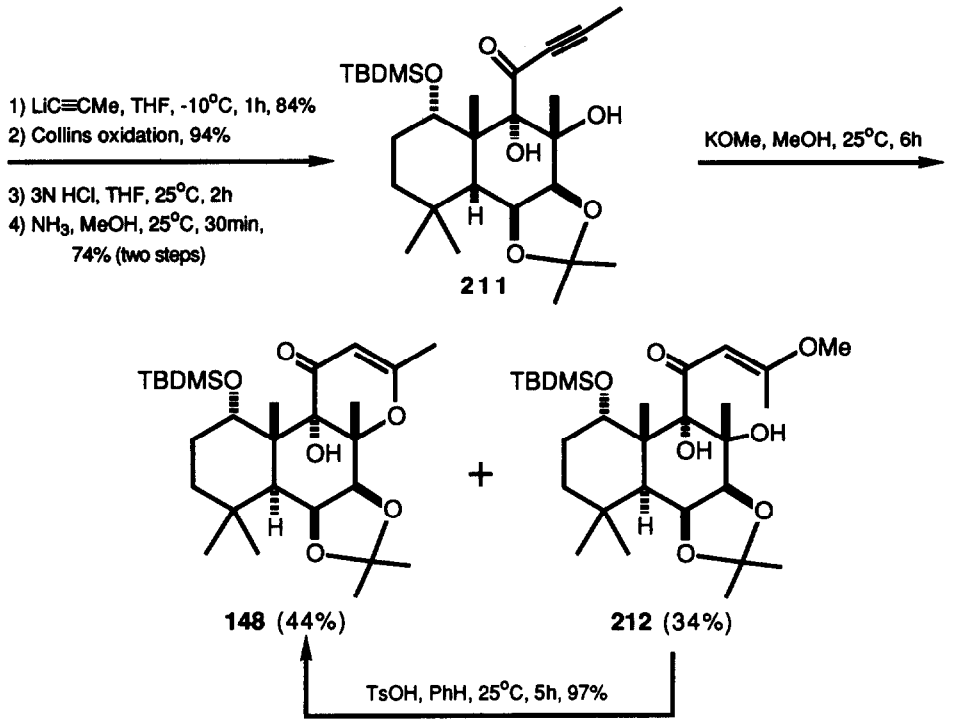
Scheme 37


HO
(E)-OHCMeC=CHCO2H (198),
DCC, DMAP, 91%
CHO
PhH, 2,6-di-t-butylphenol,
120°C, sealed tube, 85h, 37%
14
199
CHO
200
1) BH3.THF, 0°C, 20h, NaOOH, 4h
2) H2CrO4, 0°C, 2h, 60%
CO2H
201
KOMe, MeOH,
reflux, 2h, 95%
CO2H
202
Pb(OAc)4, Py,
95%
203
LiBH4, Li2CO3,
EtOH, 3h, 25°C
52%
OH
204
t-BuOOH, VO(acac)2,
CH2Cl2, 25°C, 16h, 95%
OH
205
1) LiNEt2 (2 eq), THF, -78°C to -25°C
2) Me2C(OMe)2, TsOH, 25°C, 16h
206

In a subsequent publication, Ziegler *et al.* [64] reported an efficient sequence for the synthesis of dihydropyran-4-one **148** (Scheme 38) and starting from it prepared compound **142** (Scheme 39), a link between the photochemical route described in Scheme 27 and the chemical synthesis of forskolin. As shown in Scheme 38, lactone **206** was first reduced with lithium aluminum hydride and the resulting primary alcohol regioselectively protected as its acetate. A sluggish but stereoselective stoichiometric osmylation afforded triol **208**. The stereochemistry of the *cis*-diol unit of **208** was not determined at this juncture, but it was confirmed by further chemical transformations. For the elaboration of the ring C carbon framework, the hydroxyl groups on the skeleton of **208** were first protected. Regioselective silylation of the secondary alcohol followed by acid-catalyzed treatment with methyl orthoformate afforded **209** as a mixture of diastereomers. The primary alcohol of **209** was then liberated by saponification and immediately oxidized to **210** in good overall yield. Addition of 1-lithiopropyne to **210** followed by a second oxidation, afforded an acetylenic ketone from which, the orthoformate group was removed in two operations, to yield **211**. Finally, treatment of diol **211** with potassium methoxide in methanol led to a mixture of the cyclized dihydropyran-4-one **148** and the *E*-olefin **212**. Presumably, the precursor of **148** is the *Z*-isomer of **212** which, if the transition state for the 6-*Endo-Trig* closure is chair-like, experiences a relatively minor 1,3-diaxial Me-OMe interaction, whereas for the *E*-olefin to cyclize, a more sterically demanding Me-Me diaxial interaction would be required. However, under acid-catalyzed conditions the *E*-isomer **212** was smoothly converted into **148** raising significantly its overall yield.

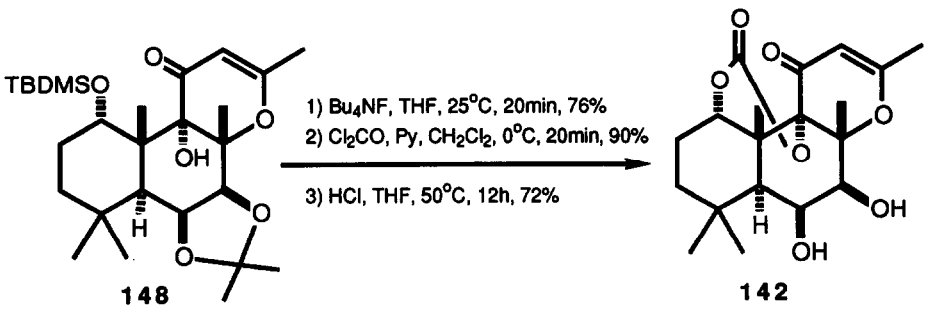
Scheme 38





As shown in Scheme 39, a series of protecting group manipulations transformed **148** into **142**, which was readily available from a known degradation product of natural forskolin (Scheme 27).

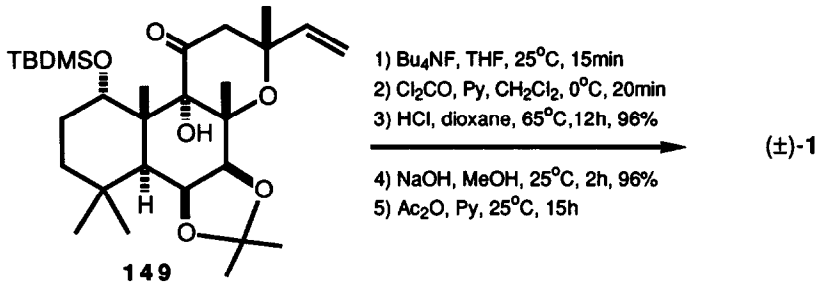
Scheme 39



It is important to emphasize that the chemical synthesis of (±)-**142**, together with the photochemical route already discussed (Scheme 27), constitutes a formal synthesis of forskolin (**1**). As previously discussed (Scheme 28), **148** was transformed into **149** by a Lewis acid-mediated higher-order cuprate addition reaction and, as shown in Scheme 40, **149** was also converted into

(±)-**1**. In addition to shortening the previous formal synthetic route to **1**, this work represents the first total synthesis of (±)-forskolin.

Scheme 40

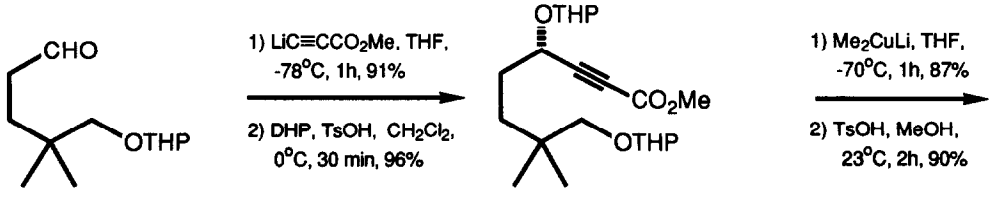


149

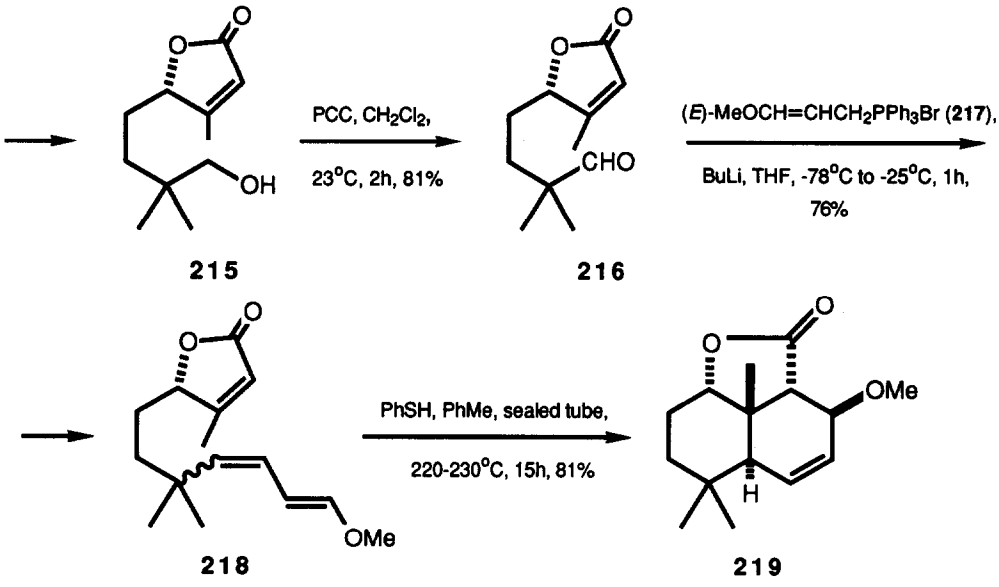
The Ikegami Approach

The second total synthesis of forskolin was achieved by Ikegami *et al.*.[65] Their approach was also based on the construction of tricyclic lactone **206** that had been synthesized previously by Ziegler *et al.*[63] (Scheme 37). However, both sequences are clearly different, particularly, in the selection of the triene required for the intramolecular Diels-Alder reaction. The synthesis described by Ziegler *et al.*[63] started with the A ring already present in the substrate and the B ring was then formed with the fused lactone moiety (**199** –> **200**, Scheme 37). In the synthesis by Ikegami and co-workers, the lactone group is already present and then both the A and B rings are simultaneously formed. By this strategy butenolide **216** is the dienophile that was synthesized as shown in Scheme 41. The Wittig reaction of **216** with phosphorane **217** yielded triene **218** as a mixture of geometric isomers which, upon thermolysis in the presence of a catalytic amount of thiophenol, afforded adduct **219** in good yield. Under these reaction conditions, the *Z,E*-diene of **218** suffered double bond isomerization to the corresponding *E,E*-isomer which, through an *exo*-transition state, led exclusively to **219**.

Scheme 41

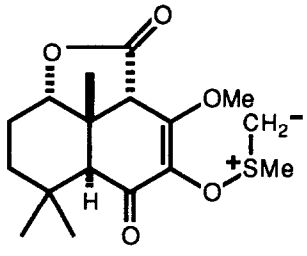


213 **214**



215 **216** **218** **219**

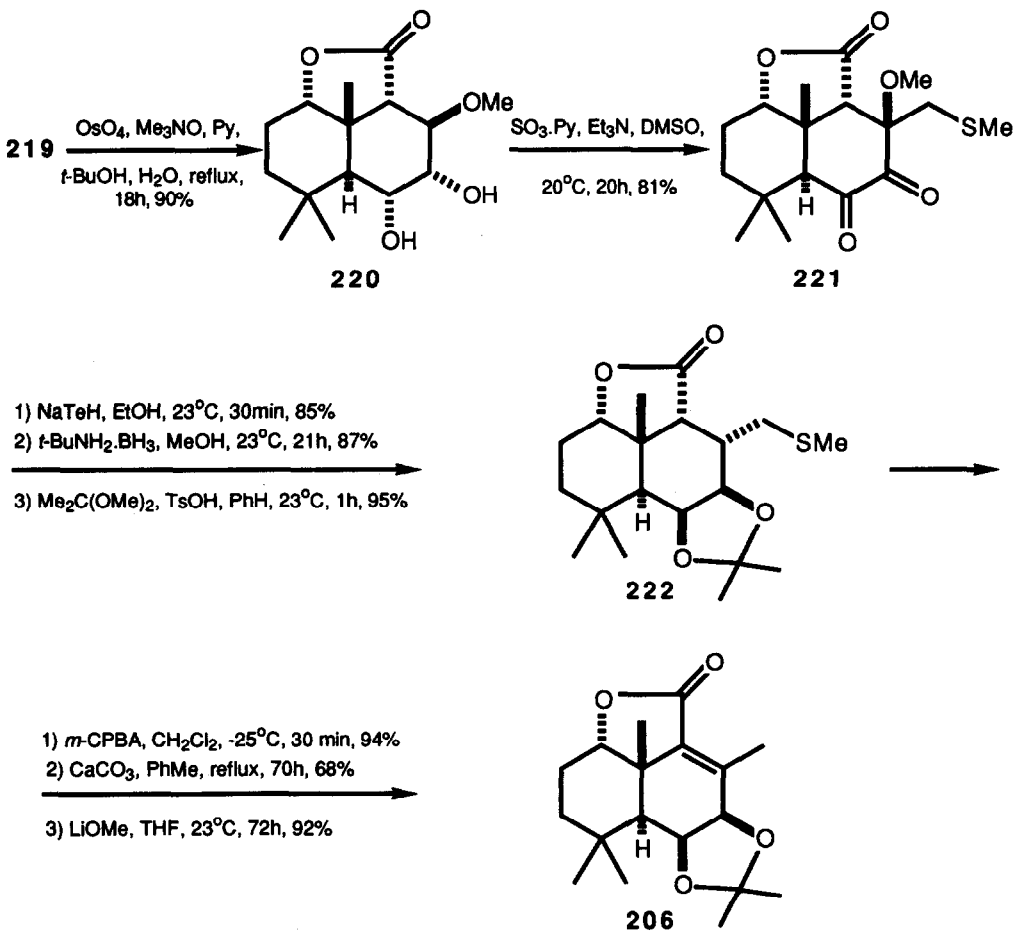
For the introduction of the *cis*-diol unit present in forskolin, Ikegami *et al.* decided to take advantage of the double bond of **219**. However, osmium tetraoxide catalyzed hydroxylation of **219** occurred exclusively from the less hindered concave face of the molecule, affording the 6α,7α-diol **220** in 90% yield (Scheme 42). The required inversion of the configurations at C-6 and C-7 was carried out by oxidation and stereoselective reduction of the corresponding carbonyl groups. By reaction of **220** with the Parikh-modified Moffat reagent, the 6,7-diketone **221**, with a methylthiomethyl group at C-8, suggested that a [2,3] sigmatropic rearrangement of the sulfur ylide **223** had occurred during the oxidation



223

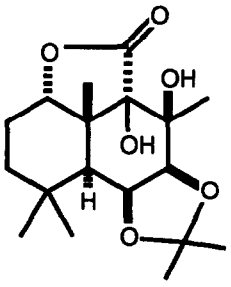
By reductive removal of the methoxyl group at C-8 followed by stereoselective reduction of the carbonyl groups of **221** with the bulky *tert*-butylamine borane, the desired 6β,7β–diol was obtained which, after protection, yielded acetonide **222**. Thermolysis of the sulfoxide obtained by oxidation of **222** followed by base-catalyzed isomerization of the resultant exocyclic double bond gave the conjugated lactone **206**.

Scheme 42



Starting with **206** and following a sequence similar to that previously reported by the same authors[45] for the synthesis of (±)-1,6,7-trideoxyforskolin **124** (Schemes 21 and 23), the total synthesis of (±)-forskolin (**1**) was completed, as shown in Scheme 43. There are, however, some interesting aspects of the synthesis that deserve some comment.

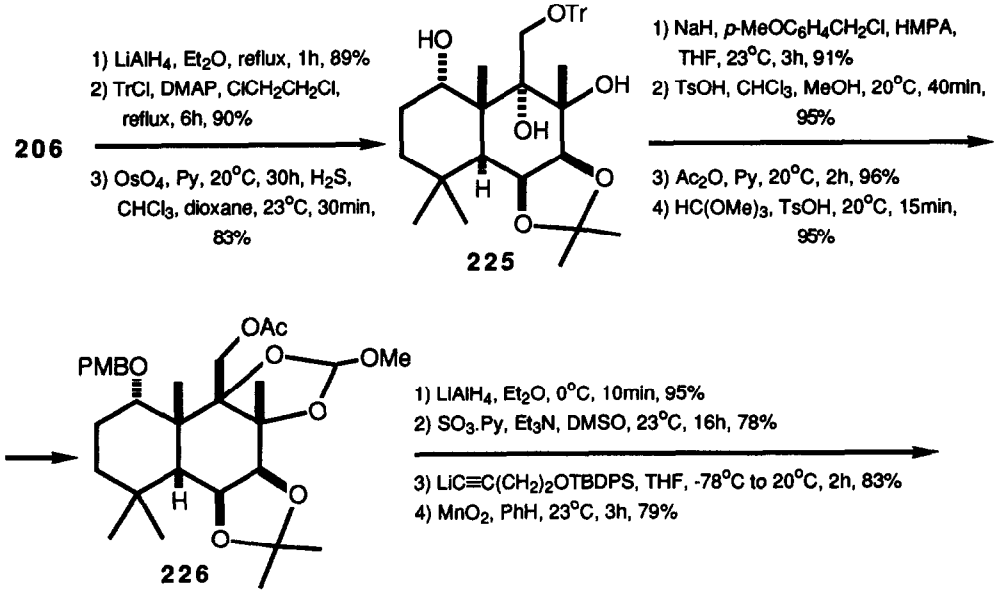
In an attempt to introduce the C-8, C-9 oxygen functional groups found in forskolin, lactone **206** was hydroxylated with osmium tetraoxide under stoichiometric conditions. However, the reaction occurred preferentially from the β-face, affording the diol **224** as the sole product in 83% yield. Similar to the results described by Ziegler *et al.*,[64] (**206** –> **208**, Scheme 38), the bicyclic compound obtained by reduction of the lactone moiety of **206** afforded exclusively the desired 8α,9α-diol **225**. Another interesting result is the organoselenium-mediated cyclization of **228** to give **229** in 78% yield along with only 6% of the corresponding C-13 epimer. In clear contrast to

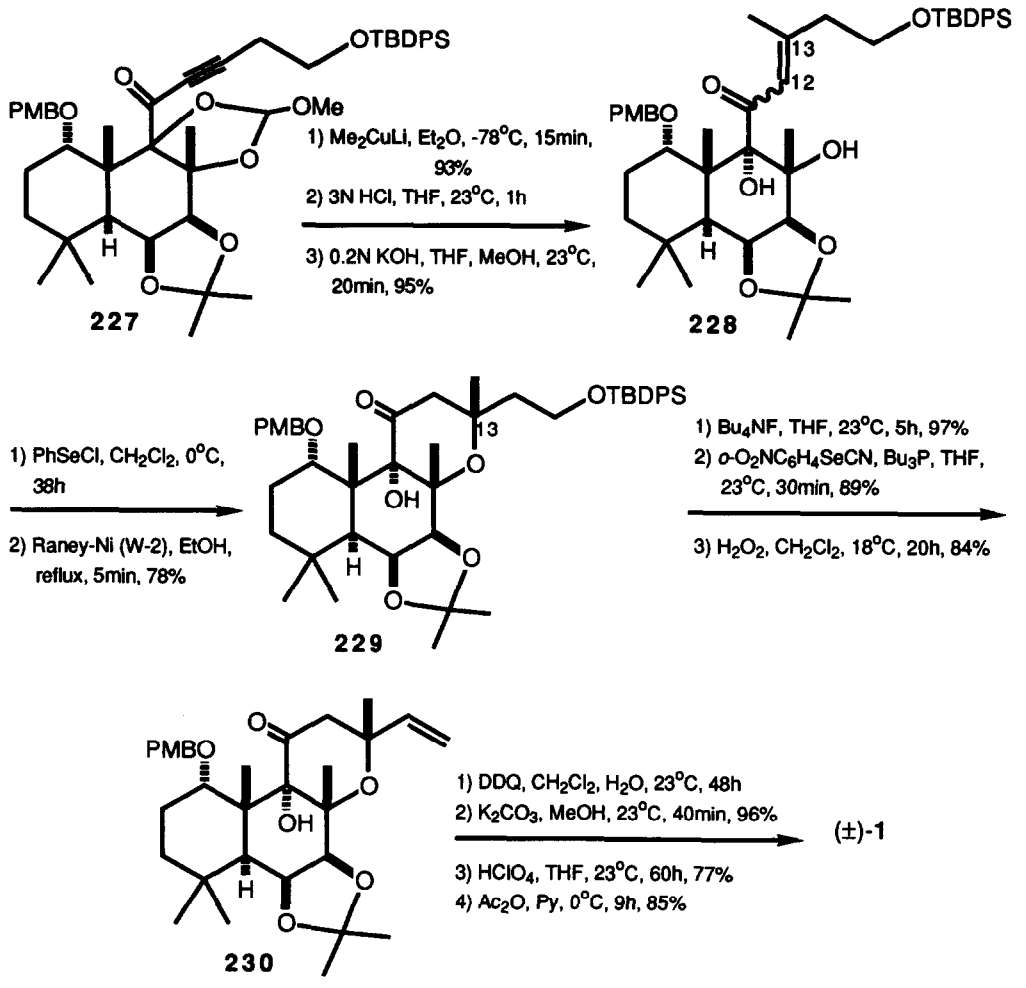


224

earlier model studies (Scheme 21), the starting double bond geometry in **228** did not influence the stereochemical outcome at C-13 in the reaction product (*E*-**228** afforded **229** and its epimer in 79% and 5% yield, respectively; *Z*-**228** afforded **229** and its epimer in 80% and 6% yield). The authors rationalized these results by assuming that the intermediate episelenonium ion can open to a stable cation allowing, in this way, the rotation of the C-12, C-13 bond to direct the methyl group at an axial position of the chair-like transition state. Finally, the advanced intermediate **229** was transformed into (±)-forskolin (**1**) by selective liberation of the primary alcohol followed by its dehydration (**230**), cleavage of the remaining protecting groups, and regioselective acetylation.[2]

Scheme 43





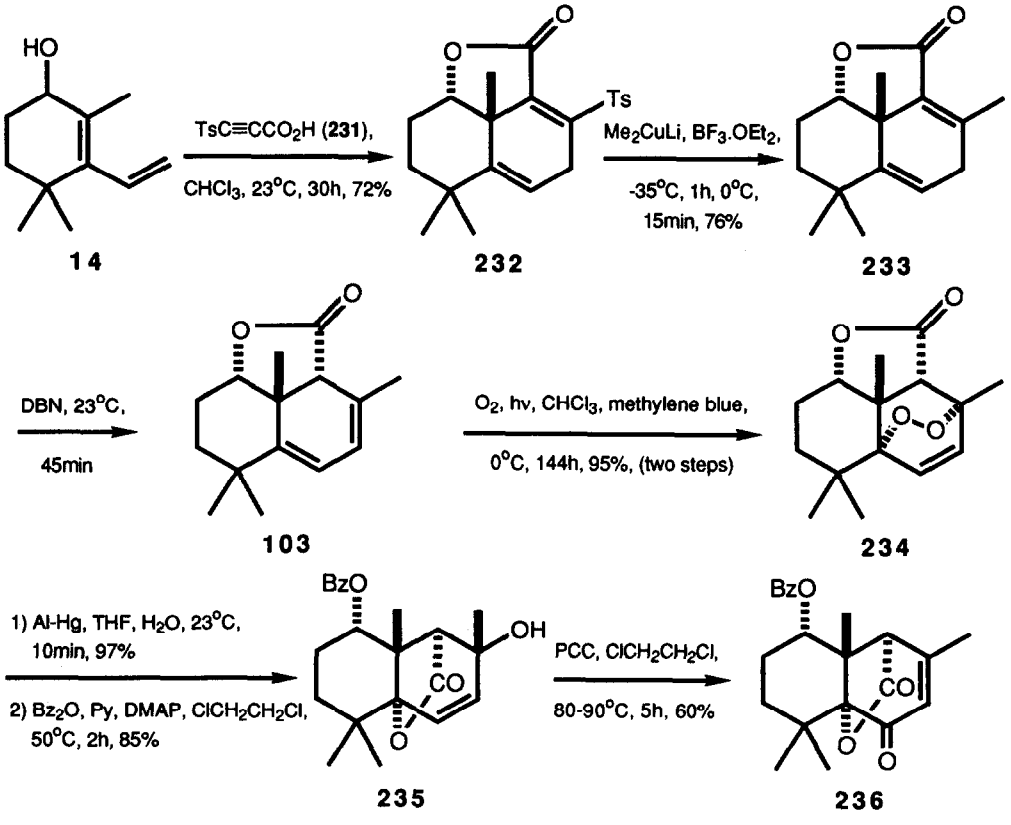
The Corey Approach

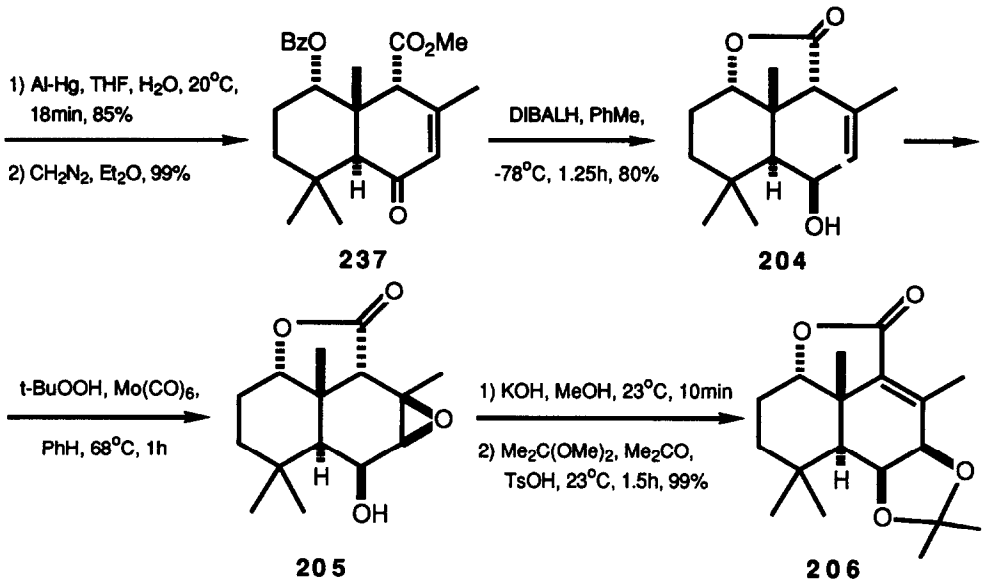
The third total synthesis of forskolin was reported by Corey and co-workers.[51] The key step in this synthesis is also an intramolecular Diels-Alder reaction similar to that used by Ziegler *et al.*[63] (Scheme 37) in the sense that A ring is already present and the B ring and the lactone are formed in the cycloaddition reaction. Another point in common with the previously discussed synthetic sequences, is that tricyclic lactone **206** was also selected as a precursor for the A-B rings of forskolin.

As shown in Scheme 44, Corey and co-workers found that the reaction of the already used dienol **14** with the base-sensitive acetylenic acid **231** under very mild reaction conditions afforded adduct **232** upon sequential esterification and cycloaddition. Treatment of adduct **232** with lithium dimethylcuprate in the presence of boron trifluoride etherate resulted in the replacement of the tosyl

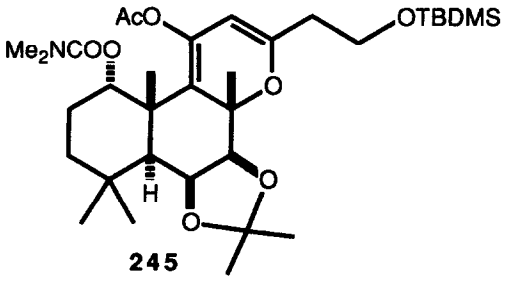
group by a methyl group (**233**). Base-catalyzed double bond isomerization gave the more stable tricyclic lactone **103**. Lactone **103** had been prepared previously by Koft *et al.*[39] by an intramolecular Michael addition in tandem with an aldol condensation (Scheme 17). For the introduction of the C-6, C-7 oxygen functional groups present in **206**, Corey *et al.*[51] used a dye-sensitized cycloaddition of singlet oxygen to transform **103** into endoperoxide **234**, and then, by reduction and selective benzoylation, into the monobenzoate **235**. The presence of an allylic tertiary alcohol moiety allowed **235** to undergo a 1,3-oxidative rearrangement to afford enone **236**. By reductive cleavage of the lactone group of **236** followed by esterification with diazomethane, enone **237**, with the thermodynamically favored *trans*-ring junction, was obtained. The stereoselective reduction of the ketone carbonyl group from the less hindered α-face of **237**, with simultaneous reduction of the ester function and subsequent lactonization, afforded the axial alcohol **204**. The final stages of the synthesis of **206** are similar to those previously reported by Ziegler *et al.*[63] and already discussed in this Report (Scheme 37).

Scheme 44



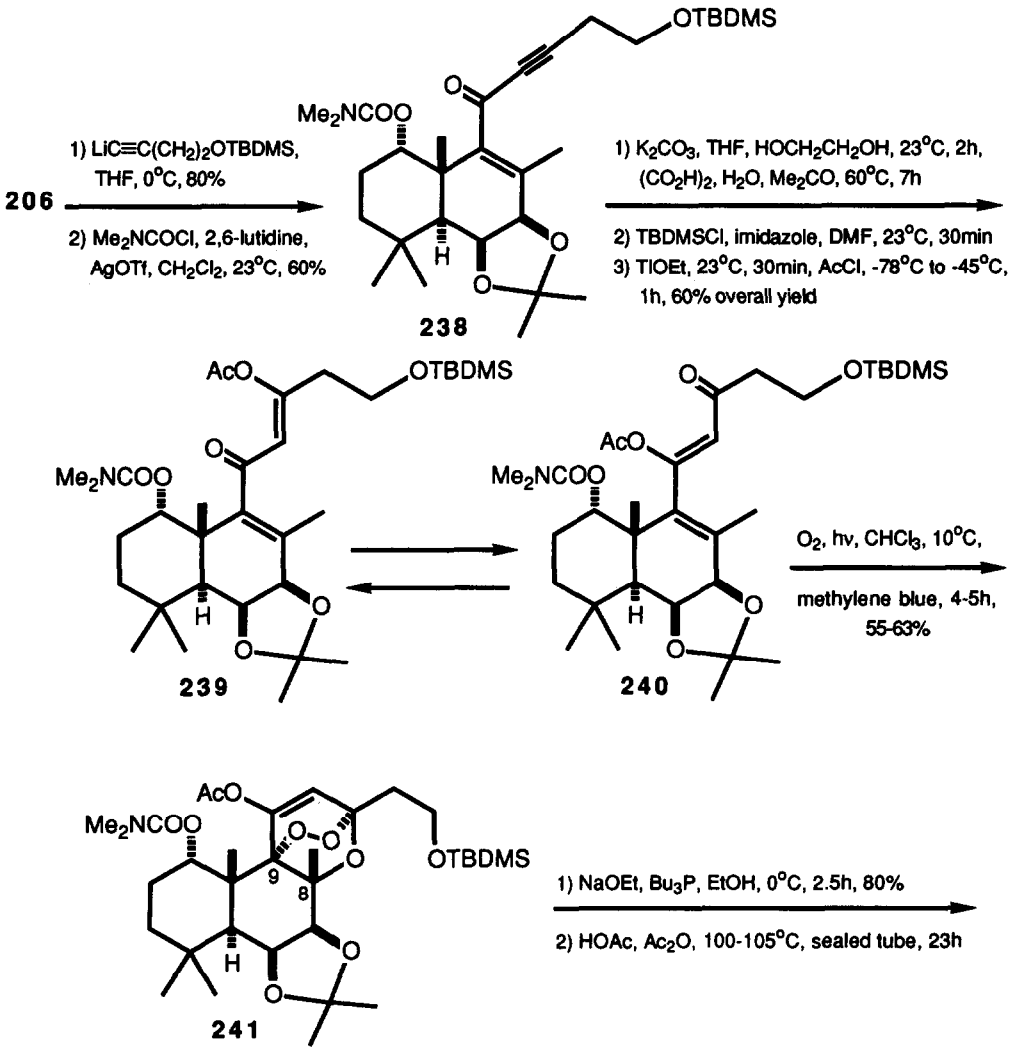


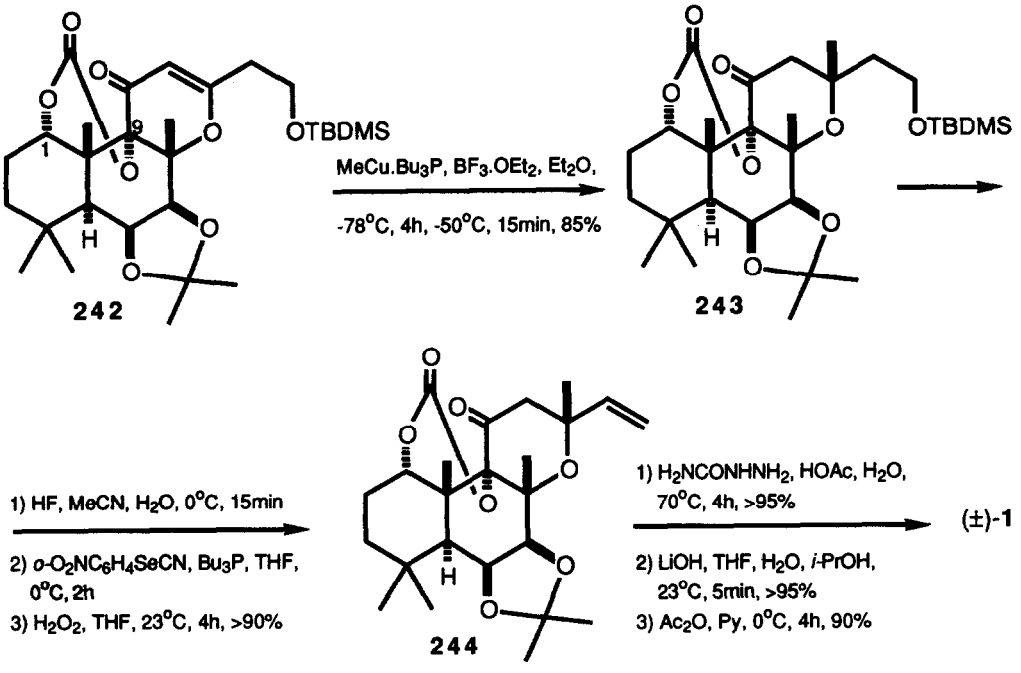
The strategy followed by Corey *et al.*[51] for the elaboration of the ring C of forskolin was, however, clearly different from those already described in Schemes 38 and 43, in which a cyclization of the C-8 hydroxyl group onto an ynone or enone appendage was used as the key step to form the pyranone ring. As shown in Scheme 45, the direct ethynylation of lactone **206** followed by protection of the C-1 hydroxyl group with dimethylcarbamoyl chloride afforded **238**. The conjugate addition of a hydroxyl group to ynone **238**, followed by resilylation of the primary alcohol and acetylation yielded the β-acetoxy enone **239** which, by analysis of its ^{1}H NMR spectrum, was shown to be rapidly interconverting with the isomeric β-acetoxy enone **240** at room temperature. By taking advantage of this interconversion, the β-acetoxy enones were irradiated in chloroform solution containing methylene blue and saturated with oxygen to afford the endoperoxide **241** in 55-63% yield. Presumably, this remarkable transformation through which the C-8 and C-9 oxygen functional groups are stereoselectively introduced occurs by a double bond isomerization of the *Z*-olefin of **240** to the corresponding *E*-isomer followed by an electrocyclization reaction to give the intermediate **245**, which then undergoes a [4+2] cycloaddition reaction with singlet oxygen from the α-face of the molecule to afford **241**.



By treatment of **241** with sodium ethoxide in the presence of tributylphosphine followed by acetic acid - acetic anhydride, pyran-4-one **242** having the hydroxyl groups at C-1 and C-9 appropriately protected, was obtained. Finally, when **242** was treated with methyl copper-tributylphosphine complex in the presence of boron trifluoride etherate, β-conjugate addition product **243** was obtained in 85% yield. Although the α-selectivity would be expected for this reaction on the basis of previous reports, it is, however, important to point out the observation of Delpech and Lett[50] that the stereochemistry of this type of reactions is, at the moment, difficult to predict. Starting with **243** and by a series of functional group manipulations, (±)-forskolin was obtained.

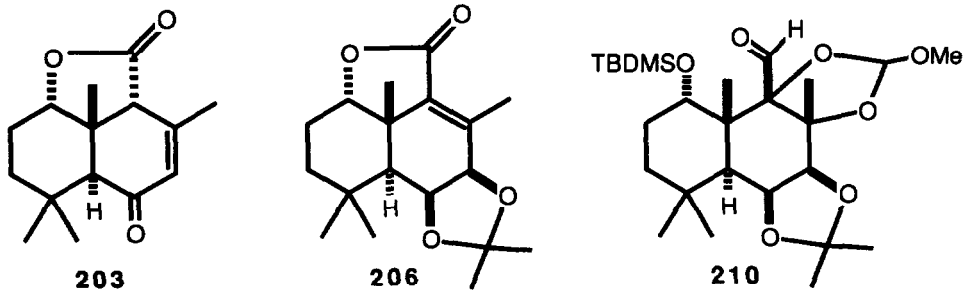
Scheme 45





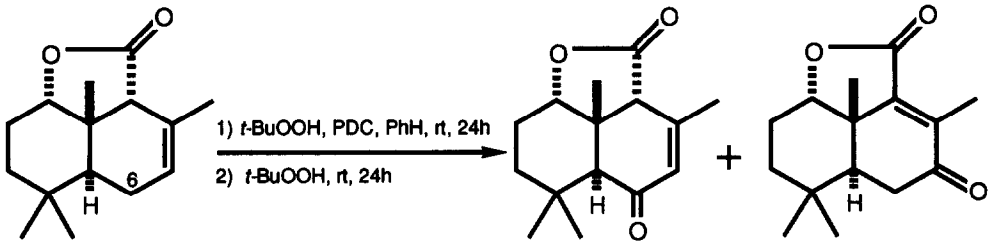
Syntheses of Advanced Intermediates in the Total Synthesis of Forskolin

Aside from the three total syntheses of forskolin just described, a number of reports describing synthetic approaches toward advanced intermediates, used in the total synthesis sequences, have appeared in the literature. In particular, much effort has been devoted to the synthesis of the key tricyclic lactones **203** and **206** and also of the aldehyde **210**, first synthesized by Ziegler *et al.*,[63,64] as was shown in Schemes 37 and 38.



In an attempt to establish a linkage between tricyclic lactone **101**, prepared by a radical cyclization in tandem with an intramolecular Mukaiyama aldolization, and key intermediate **203** *en route* to forskolin, Pattenden *et al.*[38] studied the oxidation of **101**. After considerable experimentation, they found that a combination of pyridinium dichromate and *tert*-butylhydroperoxide transformed **101** into **203** in 34% yield. The isomeric enone **246** (37%) and recovered starting material (**101**, 19%) were also isolated from the reaction mixture (Scheme 46). The difficulty found in this oxidation reaction is a consequence of the severe steric crowding at C-6 of the tricyclic lactone **101**.

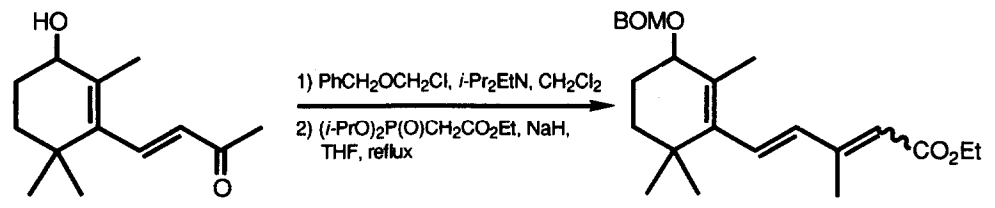
Scheme 46



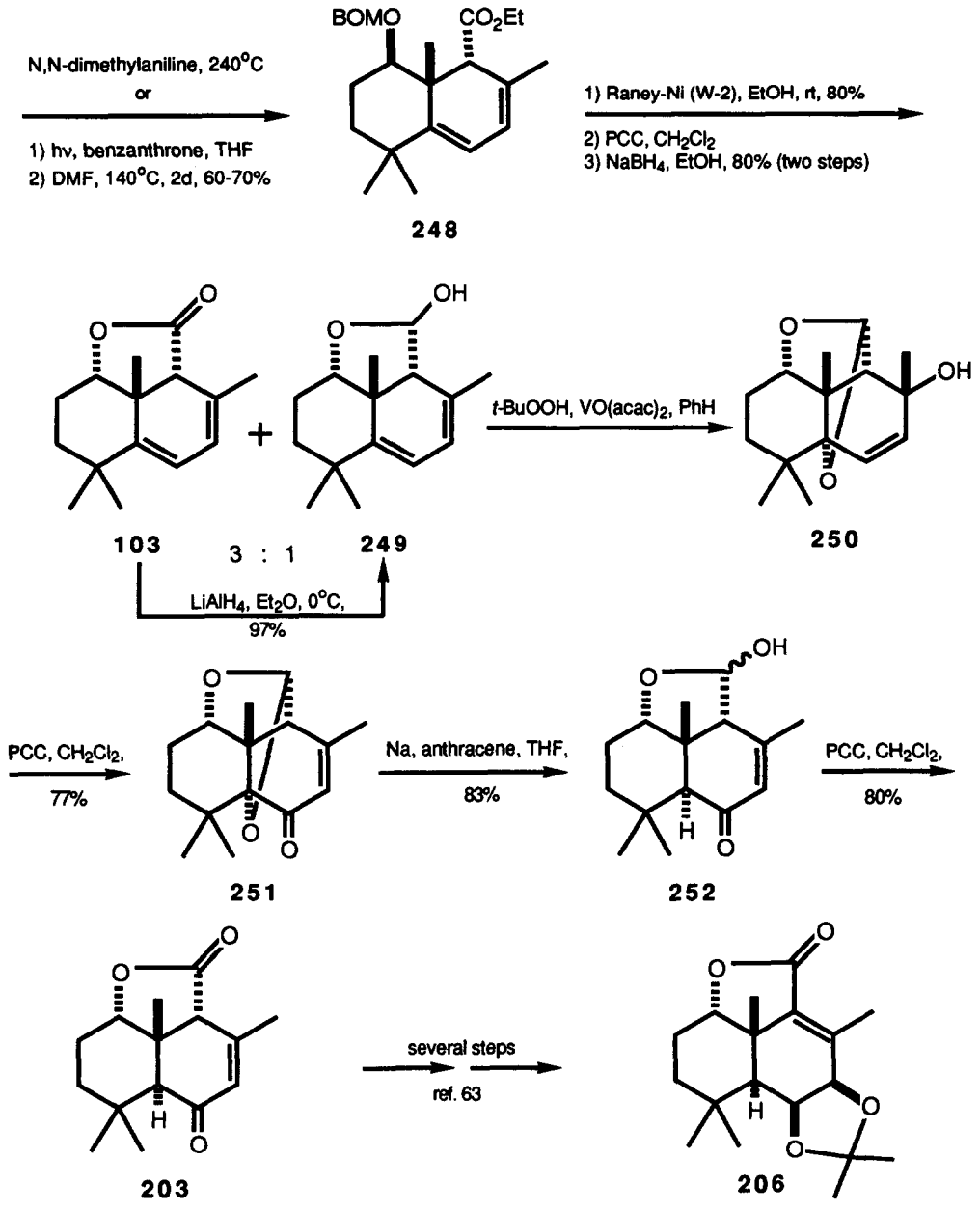
101 **203** **246**

By using an electrocyclization approach, Cha *et al.*[66] reported the synthesis of **203** and converted it into advanced intermediate **206** using Ziegler's procedure. By application of a known thermolysis procedure[67] to the readily available trienecarboxylic ester **247**, or more conveniently, by a two-step sequence, involving first, the photolysis of **247** and then the thermolysis, bicyclic ester **248** was obtained in 60-70% yield (Scheme 47). To establish the correct stereochemistry at the C-1 hydroxyl group, the protecting group of **248** was cleaved and, by an oxidation-reduction sequence, a mixture of the known lactone **103** (Schemes 17 and 44) and its corresponding lactol **249** was obtained. For the introduction of the ketone carbonyl group at C-6, lactol **249**, also

Scheme 47



88 **247**

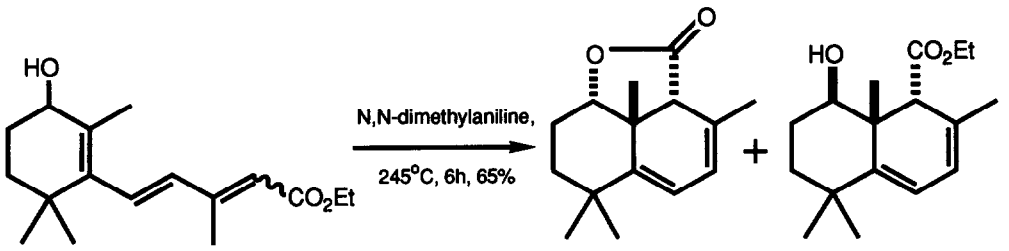


obtained by reduction of **103**, was first submitted to a transition metal-catalyzed epoxidation yielding directly tertiary alcohol **250** which, upon 1,3-oxidative rearrangement, afforded enone **251**. Reductive cleavage of the oxygen bridge of **251** by reaction with sodium anthracenide

yielded lactol **252** with the correct *trans*-ring junction. Finally, oxidation of **252** afforded the intermediate **203**.

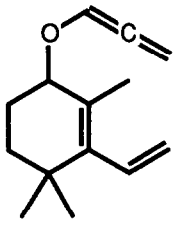
Soon thereafter, Leclaire and Lallemand[68] reported that, in sharp contrast to the results described by Cha *et al.*[66] by thermolysis or photolysis of **247**, a complex mixture of products is obtained, from which, the tricyclic lactone **103** was isolated in low yield. The isolation of **103** prompted the authors to submit the unprotected trienecarboxylic ester **253** to the thermolysis reaction. Under these conditions **253** afforded a 1.5:1 mixture of lactone **103** and the hydroxy ester **254**, in a combined 65% yield (Scheme 48). This is another synthetic route to **103** beside those already described (Schemes 17, 44 and 47).

Scheme 48



253 **103** 1.5 : 1 **254**

Kanematsu *et al.*[69] also reported a synthesis of the Ziegler intermediate **203** by using an allenyl ether intramolecular cycloaddition reaction. As depicted in Scheme 49, when the propynyl ether **255** was treated with potassium *tert*-butoxide in refluxing *tert*-butanol, adduct **256** was obtained *via* the allenyl ether **261** in excellent yield.

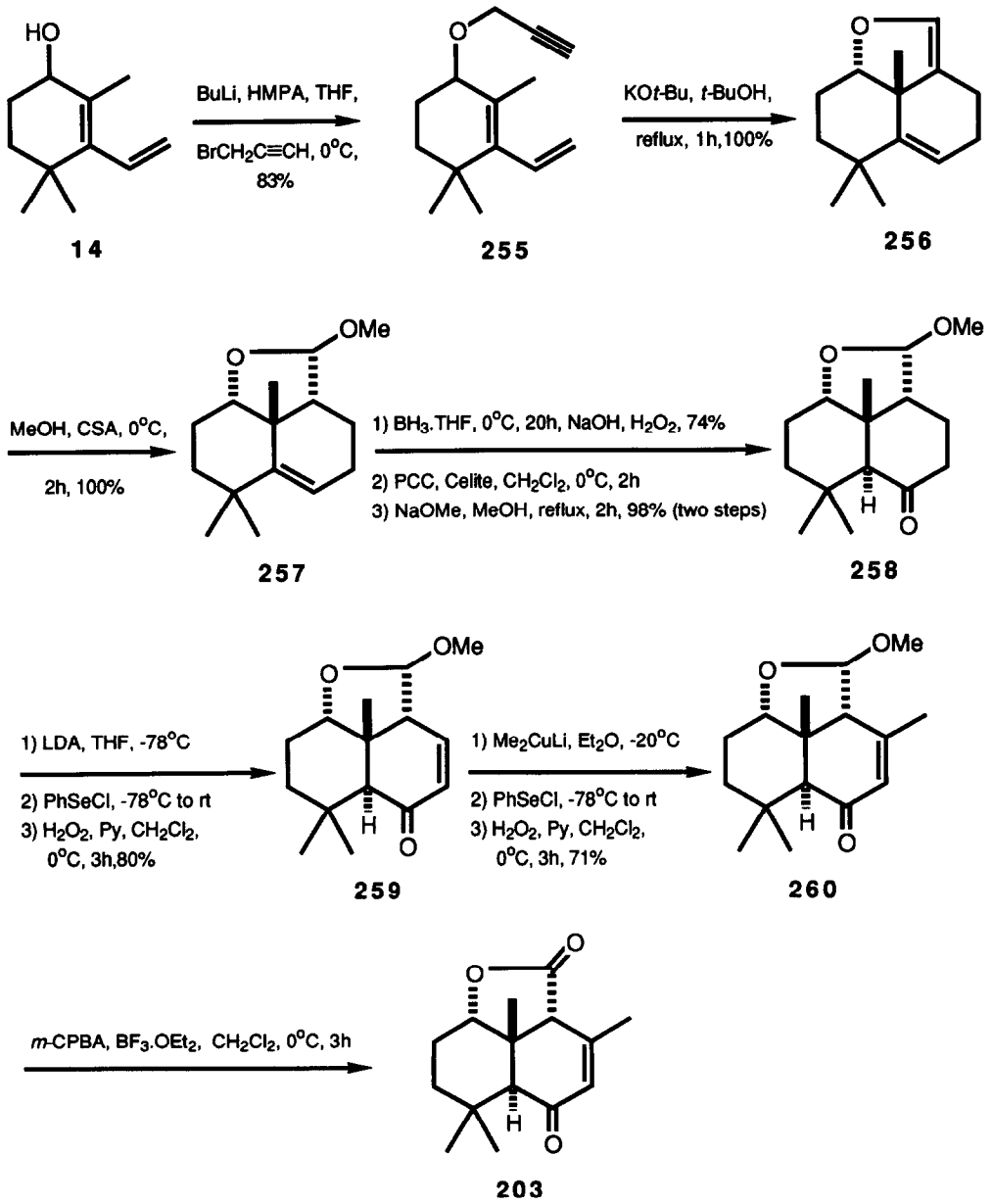


261

The acid-catalyzed addition of methanol to **256** afforded the methyl acetal **257** which, for the introduction of the keto carbonyl group at C-6, was submitted to a three-step sequence involving hydroboration, oxidation of the resultant alcohol, and equilibration to give ketone **258**, with the required *trans*-decalin ring junction. Ketone **258** was then converted into the corresponding enone **259**. The conjugate addition of lithium dimethyl cuprate to **259** followed by regeneration of the double bond led to methyl acetal **260**. Finally, the oxidation of the acetal moiety

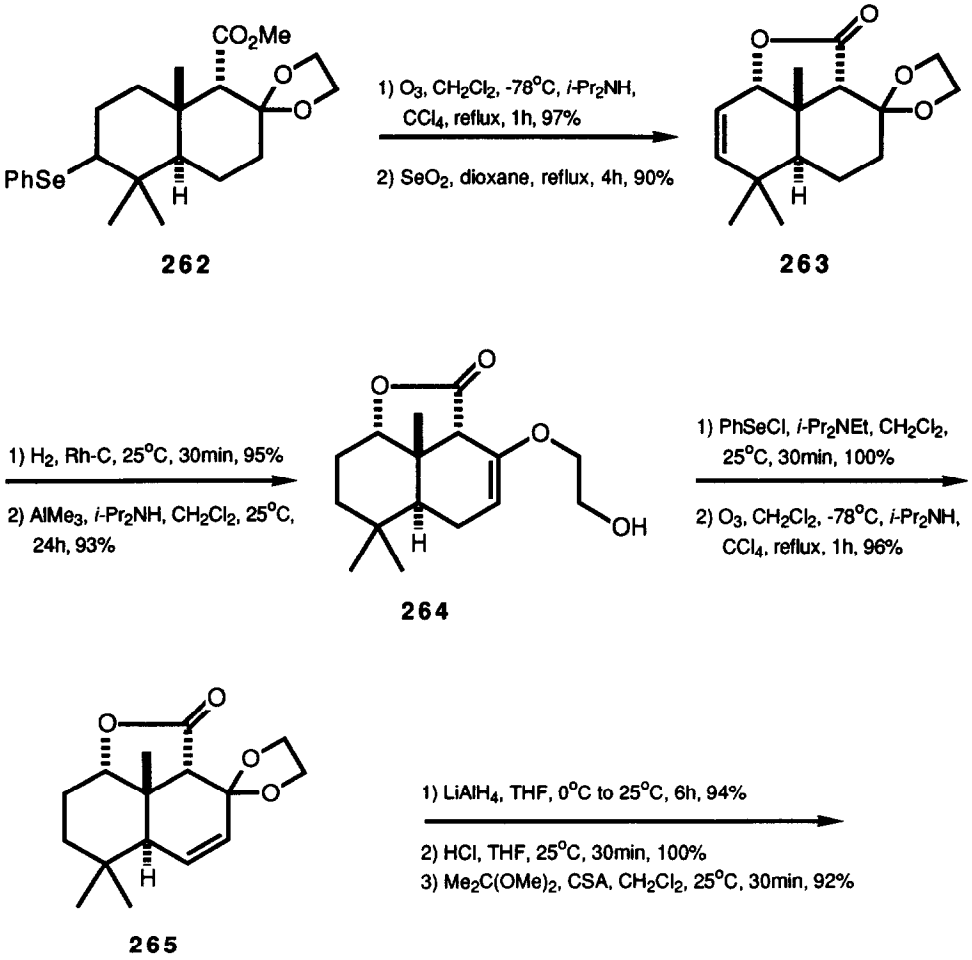
of **260** by reaction with *m*-chloroperoxybenzoic acid in the presence of boron trifluoride etherate afforded the Ziegler intermediate **203**.

Scheme 49

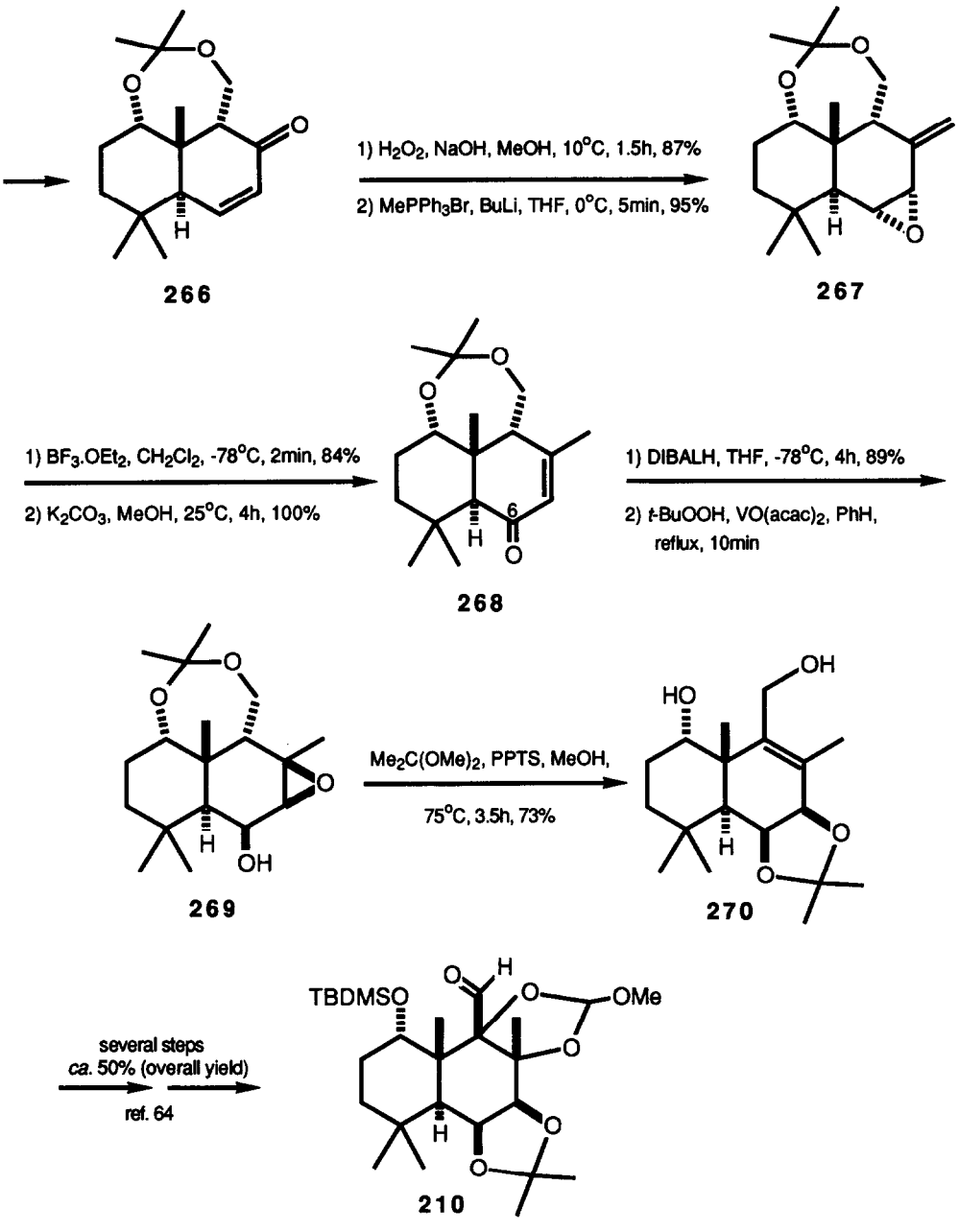


By using an approach completely different from that previously discussed (Scheme 4),[17] Nicolaou *et al.*[70] reported, in 1989, a synthetic route to the aldehyde **210**. As shown in Scheme 50, bicyclic selenide **262**, prepared by a cation-mediated polyene cyclization based on known procedures,[71,72] was oxidized to the corresponding selenoxide which, on oxidative elimination and selenium dioxide oxidation, afforded directly lactone **263**. Catalytic hydrogenation of **263** and regioselective opening of its ketal by reaction with the aluminum amide base $Me_2AlN(i\text{-}Pr)_2$ yielded **264** which, upon selenium-mediated reclosure of the ketal group followed by oxidation-elimination of the corresponding selenide, led to **265**.

Scheme 50



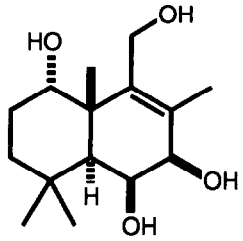
262 **263** **264** **265**



266 **267** **268** **269** **270** **210**

Reduction of the lactone group of **265**, liberation of the keto carbonyl group, and protection of the resultant 1,4-diol moiety gave acetonide **266**. The C-6 carbonyl group required for the introduction of the C-6, C-7 oxygen functional groups present in **210** was generated by taking

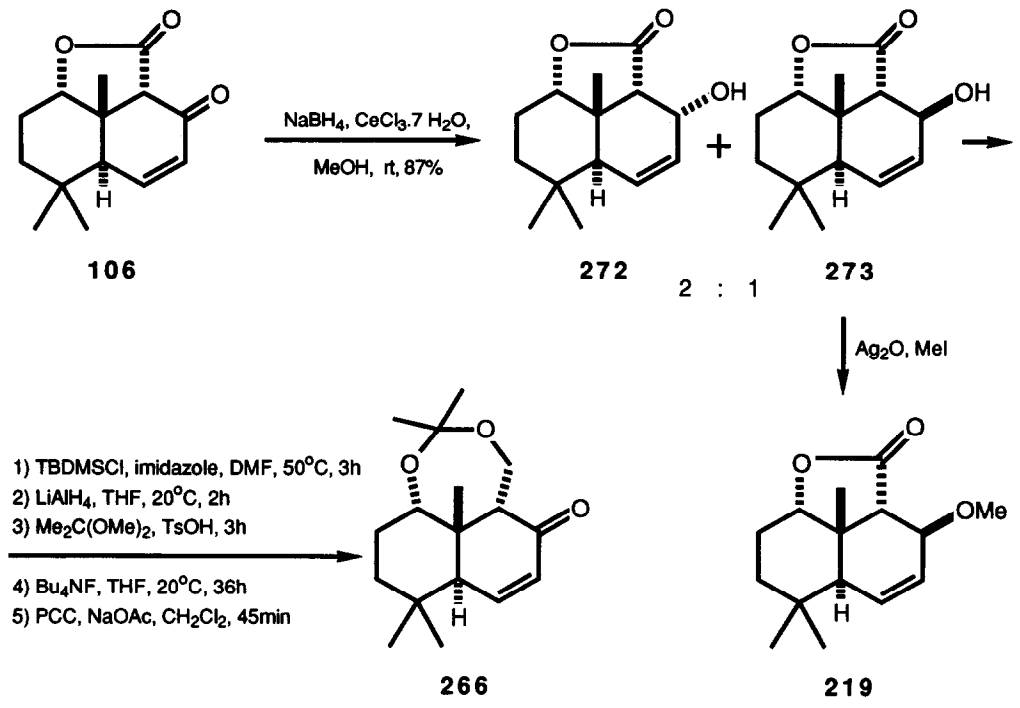
advantage of the presence of the α,β-unsaturated ketone in **266**. Basic hydrogen peroxide epoxidation afforded a single epoxide, presumably with the α-configuration which, by a Wittig olefination reaction, led to **267**. When **267** was submitted to a Lewis acid-catalyzed epoxide rearrangement followed by conjugation of the β,γ–double bond under basic conditions, enone **268** was obtained cleanly. Stereoselective reduction of **268** and subsequent epoxidation by the Sharpless procedure furnished the desired β–epoxide **269** in 40% yield together with 53% of the starting ketone **268** which could be recycled. Finally, treatment of **269** with 2,2-dimethoxypropane in methanol solution in the presence of pyridinium *p*-toluenesulfonate (PPTS), afforded **270** in good yield. Under these conditions, the 1,4-diol is liberated from the 7-membered ring acetonide, the epoxide is opened regiospecifically, and the 5-membered ring acetonide of the resultant diol is formed. It is worthwhile mentioning that treatment of **270** with pyridinium *p*-toluenesulfonate in refluxing methanol led to the crystalline diol **271**, whose stereochemistry was unambiguously confirmed by X-ray crystallographic analysis. Starting with **270** and following essentially the same sequence previously described (Scheme 38), the Ziegler advanced intermediate **210** was obtained.



271

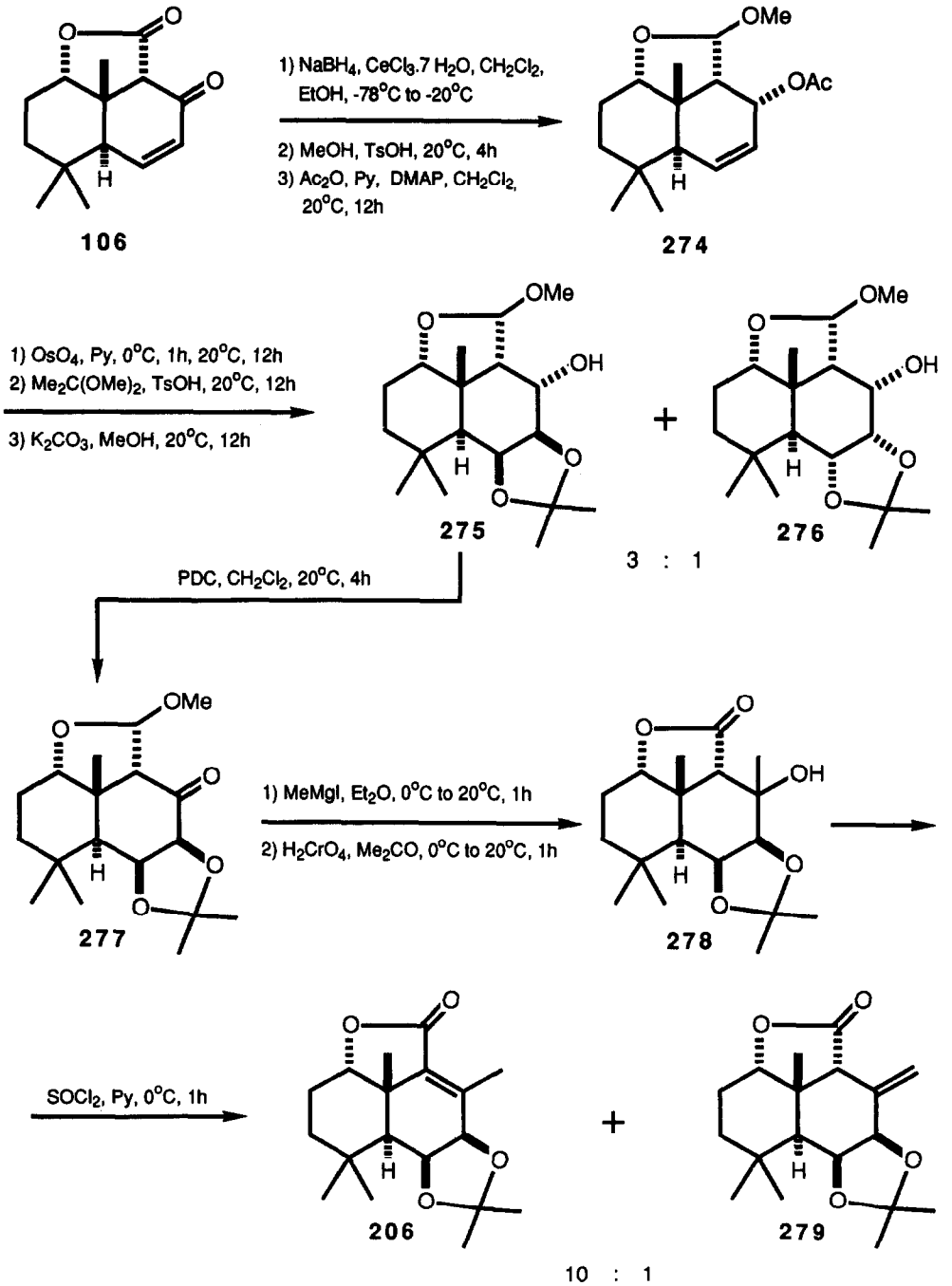
As mentioned earlier in this Report, by using an intramolecular Michael-aldol condensation approach essentially identical to that developed by Li and Wu,[40] we have independently synthesized tricyclic lactone **106**, as shown in Scheme 18. Furthermore, we have demonstrated the utility of **106** as a starting material in the construction of advanced intermediates in the synthesis of forskolin.[41] Sodium borohydride reduction of **106** in the presence of cerium(III) chloride afforded a mixture of epimeric allylic alcohols **272** and **273** (Scheme 51). Methylation of **273** led to the methyl ether **219**. Interestingly, **219** had been synthesized by Ikegami *et al.*[65] by an intramolecular Diels-Alder reaction (Scheme 41) and was used as a key intermediate in the total synthesis of forskolin. Also starting with **273** (Scheme 51), a simple and high-yield sequence was developed for the preparation of acetonide **266**, an intermediate used by Nicolaou *et al.*[70] (Scheme 50) in the synthesis of the Ziegler intermediate **210** (Scheme 38).[64] Although we have chosen the minor alcohol **273** as a starting material, the same result should be obtained with **272** or with the mixture of both epimeric allylic alcohols.

Scheme 51



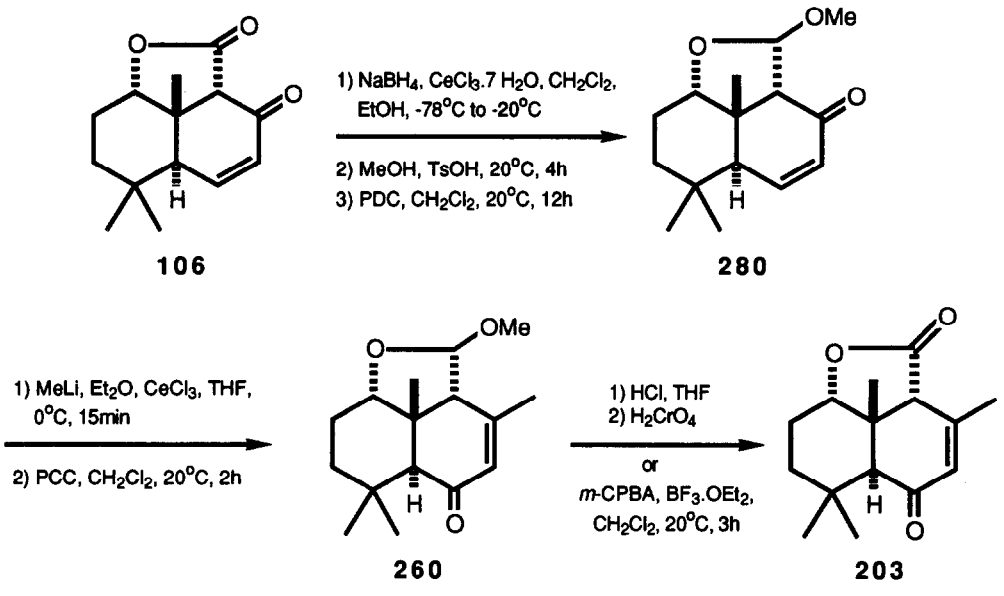
We have also developed a simple and efficient sequence directed toward the Ziegler intermediate **206**.[42] As shown in Scheme 52, reduction of **106** with excess of sodium borohydride in the presence of cerium(III) chloride gave a mixture of hemiacetals which, upon exposure to methanol under acidic conditions followed by acetylation, afforded acetate **274**. By treatment of **274** with osmium tetraoxide under stoichiometric conditions and through the influence of the pseudoequatorial acyloxy group, the double bond was preferentially hydroxylated from the β-face affording the desired diol as the major component in a 3:1 mixture of diastereomers. Noteworthy is the observation that when **219**, which bears an allylic methoxyl group in the pseudoaxial position, was submitted to similar reaction conditions, completely opposite selectivity was observed (Scheme 42).[65] The diols obtained from **274** were then transformed into their corresponding acetonides **275** and **276**. The major isomer **275** was oxidized to the ketone **277** and treated with an excess of methyl magnesium iodide to give a single tertiary alcohol, which was transformed into lactone **278** by oxidation with Jones reagent. Finally, dehydration of **278** furnished a 10:1 mixture of **206** and **279** in quantitative yield. As **279** has efficiently been converted into **206**,[65] its formation does not represent a serious disadvantage.

Scheme 52


1) NaBH4, CeCl3.7 H2O, CH2Cl2, EtOH, -78°C to -20°C
2) MeOH, TsOH, 20°C, 4h
3) Ac2O, Py, DMAP, CH2Cl2, 20°C, 12h
106
274
1) OsO4, Py, 0°C, 1h, 20°C, 12h
2) Me2C(OMe)2, TsOH, 20°C, 12h
3) K2CO3, MeOH, 20°C, 12h
275
276
3 : 1
PDC, CH2Cl2, 20°C, 4h
277
1) MeMgI, Et2O, 0°C to 20°C, 1h
2) H2CrO4, Me2CO, 0°C to 20°C, 1h
278
SOCl2, Py, 0°C, 1h
206
279
10 : 1

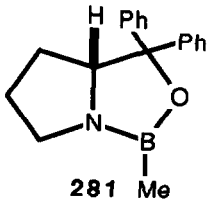
More recently, we have also synthesized the Ziegler intermediate **203** from **106** (Scheme 53).[73] Treatment of enone **280**, easily obtained from **106**, with methyllithium in the presence of cerium(III) chloride,[74] furnished a mixture of tertiary alcohols which were submitted to a 1,3-oxidative rearrangement without separation to afford enone **260** in good yield. The enone **260**, which had been previously described by Kanematsu *et al.*[69] (Scheme 49), was readily transformed into **203**.

Scheme 53



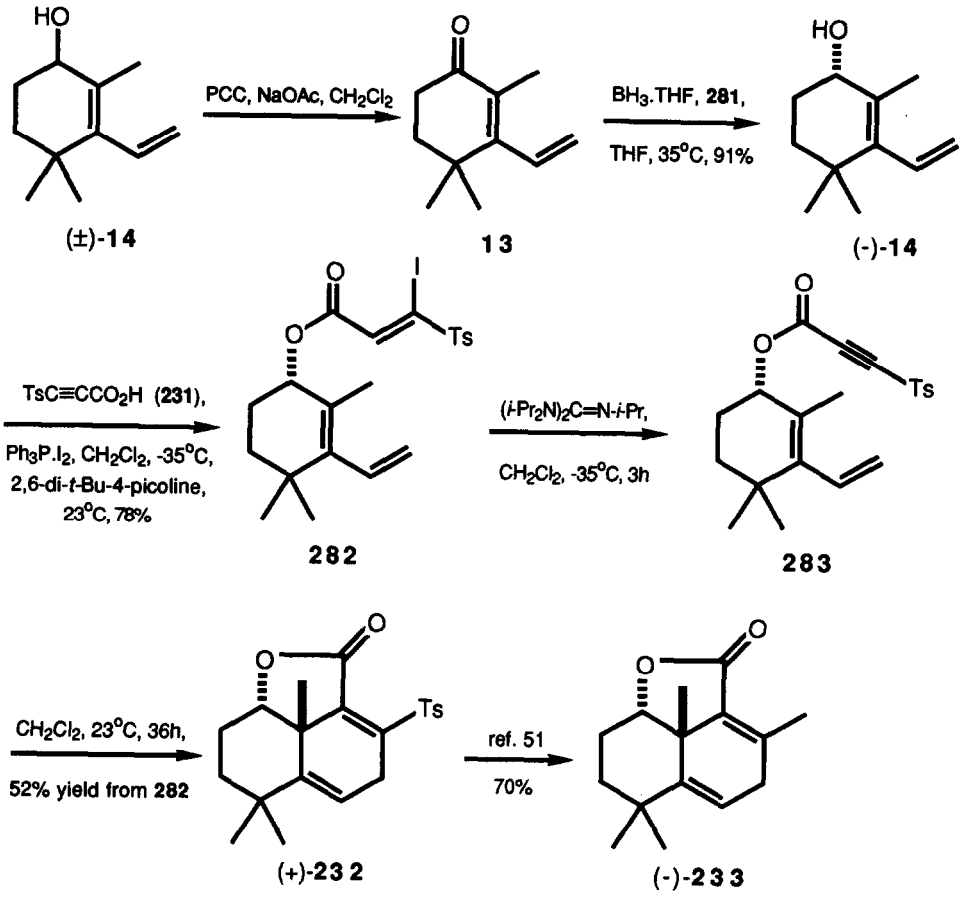
Enantioselective Routes to Key Intermediates in the Total Synthesis of Forskolin

Three sequences toward optically pure intermediates used in the total synthesis of forskolin (**1**) have been reported in the literature. These sequences are based on the use of the chiral-oxazaborolidine-catalyzed borane reduction of achiral ketones, recently developed by Corey, Bakshi and Shibata (CBS reduction).[75] In 1988, Corey *et al.*[76] reported that the reduction of dienone **13**, readily obtained by oxidation of the extensively used dienol **14**, with (R)-oxazaborolidine **281** as chiral catalyst and borane as the reducing agent afforded the (S)-alcohol **14** in excellent yield. As shown in Scheme 54 and following an essentially identical sequence to that previously described by the same authors (Scheme 44),[51] the tricyclic lactone **233** was obtained in optically active form.



281

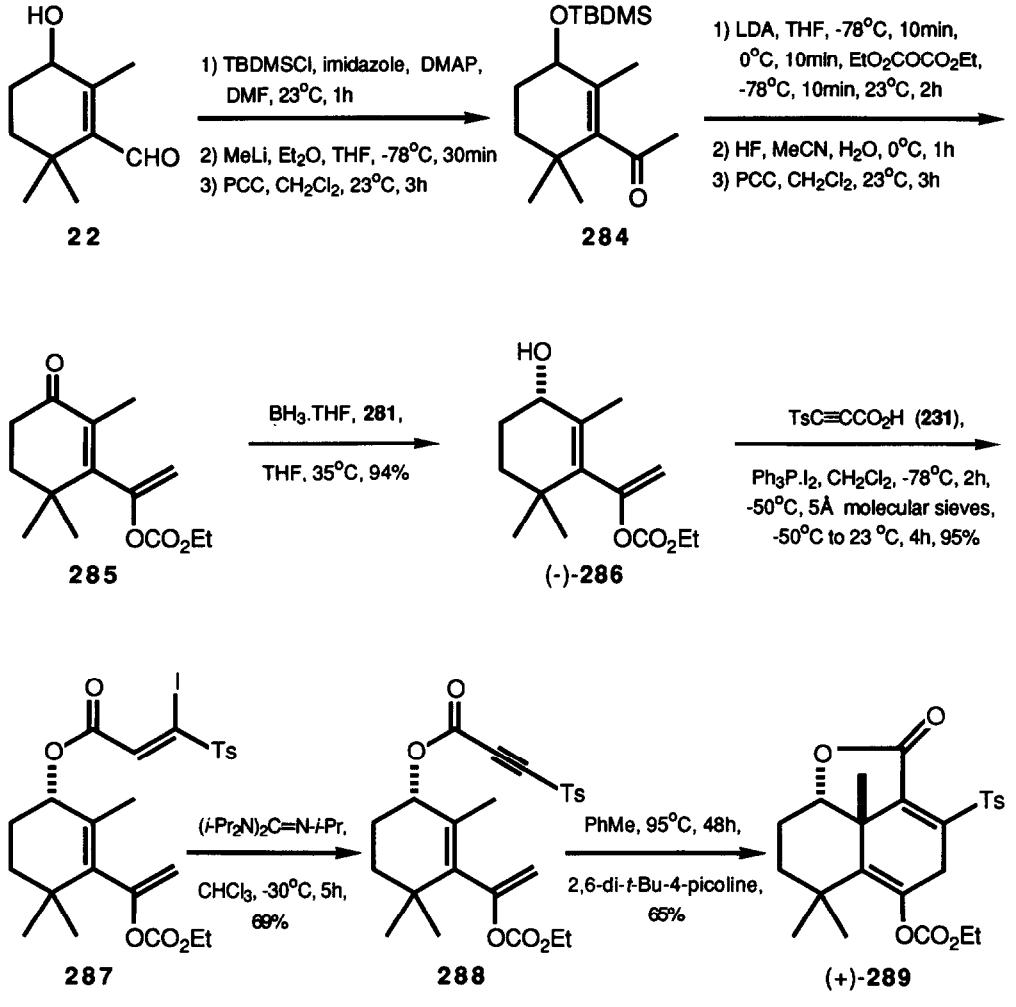
Scheme 54

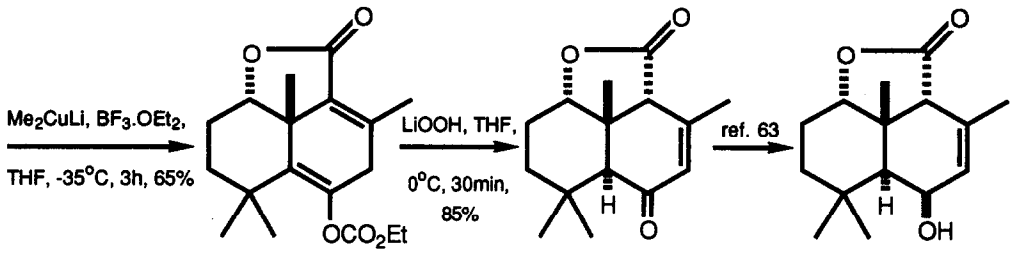


In a subsequent publication, Corey *et al.*[77] reported a new route to the Ziegler intermediate **203** in optically active form. As shown in Scheme 55, the authors avoided the difficulty found in their previous synthesis for the introduction of the C-6 oxygen functional group (Scheme 44) by employing enone **285** as starting material. The CBS reduction of **285** afforded the (S)-alcohol

286, which was transformed into the tricyclic lactone **290** in good overall yield using the functionalized diene **288** in the crucial intramolecular Diels-Alder step. Finally, treatment of **290** with lithium hydroperoxide in tetrahydrofuran furnished crystalline (–)-**203**. Interestingly, it was demonstrated that under these conditions the isomerization of the $\Delta^{5,8}$-diene to the $\Delta^{5,7}$-diene occurred before the hydrolysis of the enol ester. The structure of **203** was further confirmed by reduction to the axial allylic alcohol **204** which had been previously synthesized (Scheme 37)[63] and converted to forskolin.

Scheme 55



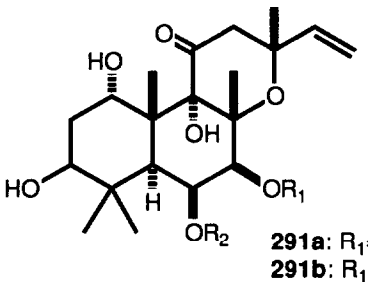


(-)-**290** (-)-**203** **204**

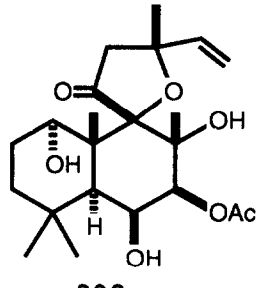
More recently, Kanematsu *et al.*[78] reported that starting with (–)-**14**, prepared by enantioselective reduction of **13** by the CBS procedure,[75] and following the sequence previously described (Scheme 49), the Ziegler intermediate **203** was also obtained in optically active form.[79]

Chemical Studies on Forskolin

Although not the main topic of this Report, it is worthwhile mentioning that, since its isolation in 1977,[1] forskolin (**1**) has been subjected to numerous chemical studies. As briefly outlined in the Introduction at the time of the structure elucidation, the reactivity of the functional groups has been studied by acylation, alkylation, dehydration, oxidation, reduction and rearrangement reactions.[2,8,80] Later, for the derivation of structure-activity relationships and to improve the metabolic stability and aqueous solubility of forskolin, a large number of derivatives have been prepared.[12,59,81-83] The synthesis of 12-oxo-, 12-bromo-, 12-chloro-, and 12-fluoro-forskolin, as well as 14,15-dehydroforskolin, have also been reported.[84-86] By a combination of microbial and chemical transformations of 7-deacetylforskolin (**3**), the main metabolites of forskolin in rats and dogs, namely 3β-hydroxyforskolin (**291a**) its deacetyl derivative (**291b**) and the corresponding 7-deacetyl-6-acetyl isomer (**291c**) have been synthesized.[87] It was also reported[88] that forskolin suffers a Lewis acid-induced rearrangement affording spiroforskolin (**292**) that, when kept in methanol at room temperature for several days, reverts to natural forskolin. Interestingly, the structure of spiroforskolin is reminiscent to the dihydrofuran-3-one (**131**), previously obtained as a by-product by Ikegami *et al.*,[45] during their study on the C-ring elaboration of forskolin (Scheme 23).



291a: R_1=H, R_2=Ac
291b: R_1=R_2=H
291c: R_1=Ac, R_2=H



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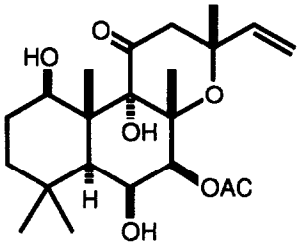
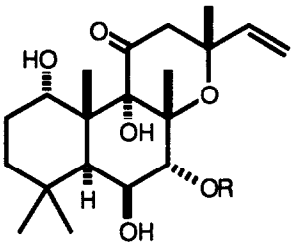
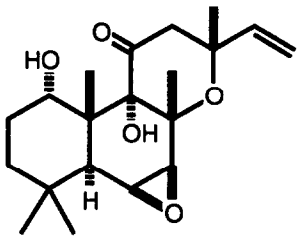
More recently, Vishwakarma and Tandon[89] have reported the preparation of some unnatural epimers of forskolin, by application of Mitsunobu's procedure. The treatment of forskolin (**1**) under the classical conditions afforded 1β-benzyloxy-1-deoxyforskolin which, upon alkaline hydrolysis followed by selective acetylation afforded 1-*epi*-forskolin (**293**). On the other hand, when 7-deacetylforskolin (**3**) was treated under the recently modified Mitsunobu's procedure,[90] 7-deacetyl-7-*epi*-trifluoroacetylforskolin (**294a**) was obtained. Hydrolysis of **294a** in refluxing methanol led to 7-deacetyl-7-*epi*-forskolin (**294b**). The 6,7-epoxy derivative (**295**) was formed when 7-deacetylforskolin (**3**) reacted with the triphenylphosphine-diethylazodicarboxylate complex in the absence of the acidic component.



293



294a: R=$COCF_3$
294b: R=H



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Concluding Remarks

Since its isolation in 1977, a great deal of effort has been dedicated to the chemistry of forskolin (**1**). A large body of publications has appeared in the literature, including numerous patents and several dissertations. We have restricted this Report to the synthetic routes toward this attractive natural product since 1984, although some comments on relevant structural modifications have also been made. The application of a great variety of synthetic methodology can be observed in the description of the sequences. However, it is remarkable that the construction of an adequately functionalized A-B ring system was usually followed by the elaboration of the C-ring. Although the predominant methodology used for the synthesis of the required highly functionalized decalin system was the intramolecular Diels-Alder reaction, other approaches have shown promising possibilities that could, in principle, be utilized for the synthesis of other polyhydroxylated natural products. The enantioselective synthesis of key intermediates, representing formal syntheses of forskolin in optically active form, have also been carried out and reviewed in this Report.

The promising biological activity and unique structural features of forskolin are likely to stimulate a second generation of synthetic strategies that will soon appear in the literature. The construction of the C-ring with the *cis*-diol functionality from a carbohydrate precursor, followed by the elaboration of the B- and A-ring or the improvement of the microbial hydroxylation processes of related products, are just two examples of the many possibilities still open in the chemistry of this fascinating natural product.

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