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THE SYNTHESIS OF MEVINIC ACIDS

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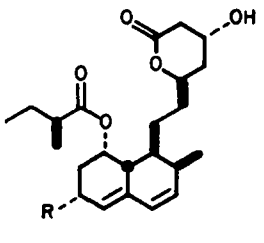
INTRODUCTION

In 1976, Endo *et al.* at the Sankyo Co. and Brown *et al.* at Beecham Pharmaceuticals isolated a potent competitive inhibitor of hydroxymethylglutaryl coenzyme A reductase (HMG CoA reductase) from the metabolites of *Penicillium citrinum* and *P. brevicompactum*, respectively.[1,2] The new compound, shown to have structure **1**, was named ML236B by the Japanese group and compactin by the British workers. In 1980, Alberts *et al.*, at Merck, Sharp & Dohme, reported the isolation of a relative of compactin from *Aspergillus terrus*.[3] The Merck compound was named mevinolin and shown to have the absolute stereostructure **2**. The identical fungal metabolite was isolated from *Monascus ruber* and named monacolin K.[4] The Merck group also discovered that the active forms of compactin and mevinolin are the respective open-chain dihydroxy acids **5** and **6**.

In humans, more than one-half of total body cholesterol is derived from *de novo* synthesis.[5] The rate-limiting step in cholesterol biosynthesis is the reduction of HMG CoA to mevalonic acid.[6]



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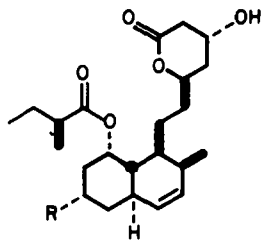

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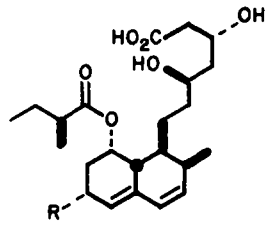

5: R = H
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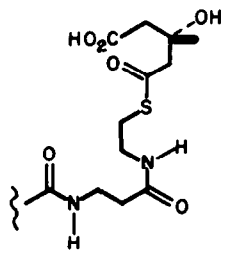
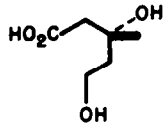


HMG CoA



mevalonic acid

Because of their potent inhibitory activity on this key enzyme, there is the attractive possibility that compactin or some related compound might be useful as a hypocholesterolemic agent. Indeed, compactin has been shown to lower serum cholesterol levels in dogs,[7] cynomolgus monkeys,[8] and humans.[9] Compactin also has been used as a tool by biochemists in elegant studies which have provided insight into the mechanism by which mammalian cells regulate HMG CoA reductase.[10] More recently, the dihydro derivatives of compactin[11] and mevinolin,[12] **3** and **4**, respectively, have been isolated; the class of compounds, distinguished by a highly functionalized hexalin or octalin unit and a β-hydroxy-δ-lactone portion linked by an ethylene bridge, are collectively referred to as mevinic acids. All of the mevinic acids, as well as many synthetic analogs which possess the hydroxy lactone appendage of **1** linked to a unit which is structurally simpler than those found in the natural products, are inhibitors of HMG CoA reductase.[13]

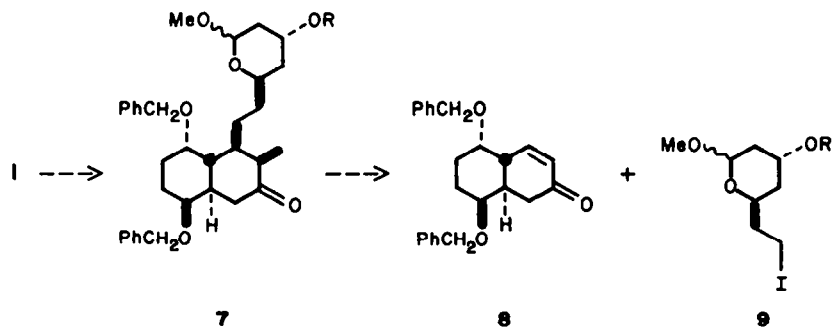
Along with the interest generated by the biological properties of the mevinic acids, their unique structural features have aroused synthetic organic chemists, resulting in an onslaught of activity directed at the synthesis of these challenging targets. Since Sih and co-workers published the first synthesis of (+)-compactin in 1981,[14] numerous publications describing syntheses and synthetic work aimed at the mevinic acids have appeared in the literature. In this report, we have summarized this large body of published material. We have focused on synthetic strategy and emphasized interesting chemical transformations and their mechanistic ramifications when applicable. The discussion is organized into three primary sections: (1) total syntheses, (2) syntheses of the hexalin (and octalin) units, and (3) syntheses of the lactone moiety.

TOTAL SYNTHESES

In 1981, Sih and co-workers communicated the first total synthesis of (+)-compactin.[14] A full paper appeared subsequently.[15] Sih and co-workers' initial strategy envisages assembly of the carbon skeleton of **1** by conjugate addition of the cuprate derived from **9** to enone **8** and trapping of the resulting enolate with an appropriate electrophile which can be elaborated to the β-methyl group in **7** (Scheme 1). Compound **7** possesses suitable latent functionality for elaboration to the conjugated diene present in **1**.

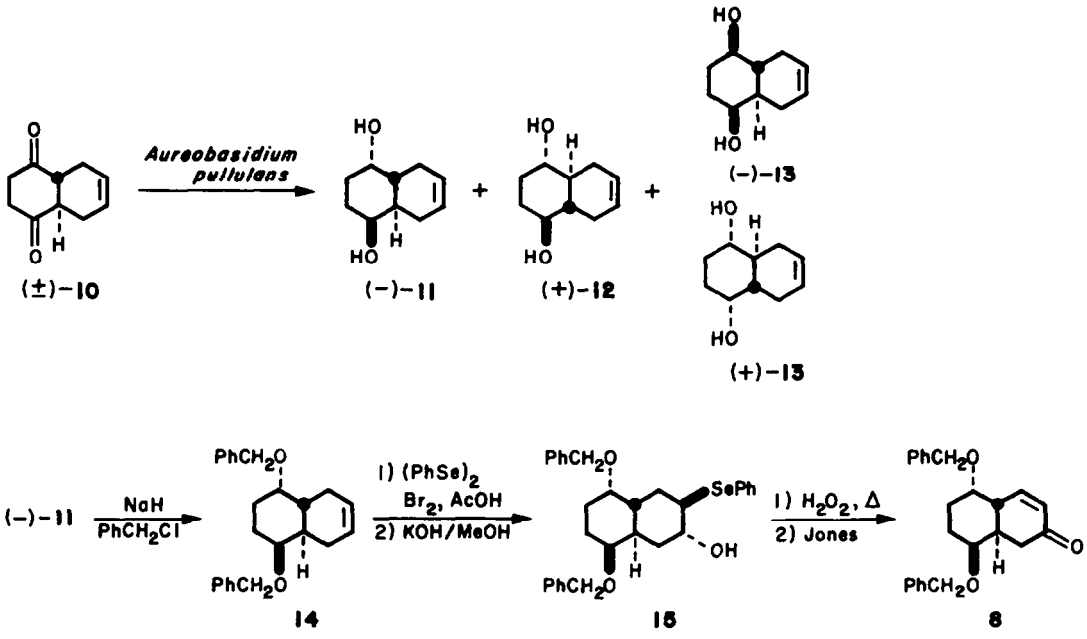
The synthesis of enone **8** is summarized in Scheme 2. Microbiological reduction of racemic *trans*-dione **10**[16] affords (−)-**11** in 33% yield accompanied by (+)-**12** (22% yield) and (±)-**13** (42% yield). Diols **11** and **12** are both obtained in >98% ee. Diol **13** is obtained as a 6:4 mixture of (+)-**13** and (−)-**13**. After chromatographic purification, diol **11** is benzylated to give **14** in 99% yield. Treatment of **14** with phenylselenyl bromide in acetic acid followed by hydrolysis furnishes hydroxy selenide **15** (89%). The C_2 symmetry of **14** eliminates regiochemical problems associated with this olefin functionalization. Oxidation of **15** to the corresponding selenoxide followed by heating (55°, 2 h) and oxidation of the resulting allylic alcohol cleanly affords enone **8** in 71% yield from **15**.

The preparation of racemic iodide **9** is shown in Scheme 3. Conversion of 5-norbornen-2-one (**16**) to iodo lactone **17**[17] and subsequent reduction with tributyltin hydride gives hydroxy lactone **18**. Inversion at the hydroxyl-bearing carbon is accomplished by treatment of **18** with diethyl azodicarboxylate and triphenylphosphine in the presence of benzoic acid. Benzoate ester **19** is



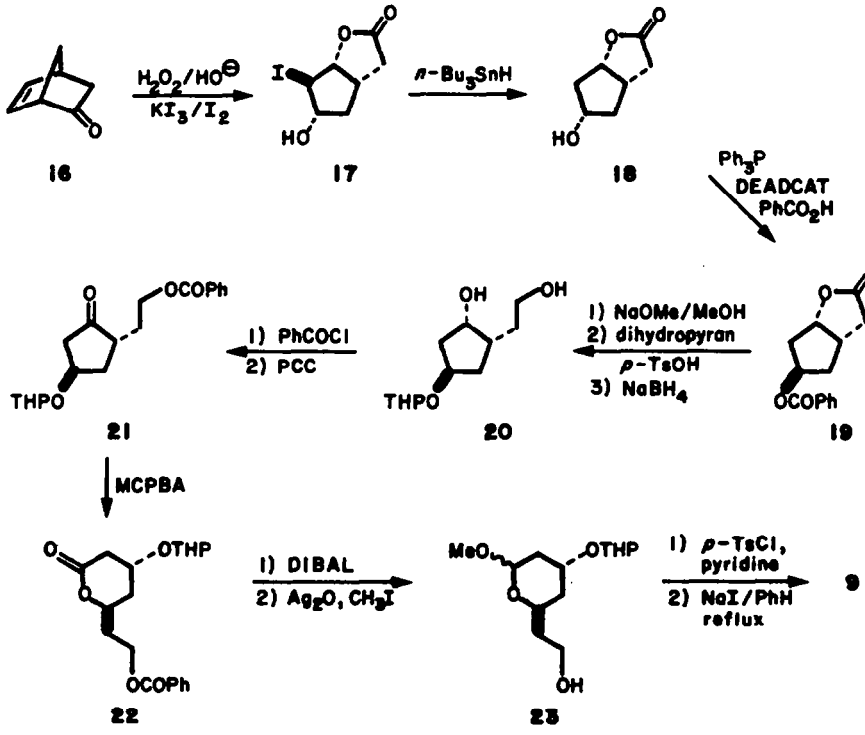
7 8 9

Scheme 1.



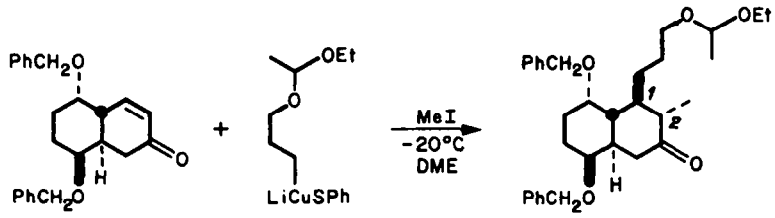
Scheme 2.

saponified and the resulting secondary alcohol is converted to its tetrahydropyranyl ether. Reduction with sodium borohydride gives monoprotected triol **20**. Selective benzoylation of the primary alcohol and oxidation of the secondary hydroxyl group affords ketone **21**, which is transformed into lactone **22** by Baeyer–Villager oxidation. Reduction of **22** with diisobutylaluminum hydride and treatment of the resulting hydroxy acetal with silver oxide and methyl iodide gives methyl glycoside **23** as an anomeric mixture. Tosylation of **23** and displacement with iodide furnishes **9** in 18% overall yield from **16**.



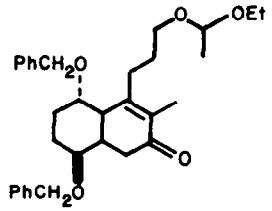
Scheme 3.

Unfortunately, the lithium and Grignard reagents derived from **9** were found to be unstable, and a less convergent method for elaboration of the lactone moiety was ultimately employed. Reaction of enone **8** with the cuprate **24** and alkylation of the resulting enolate gives **25** in 80%



8 **24** **25** (1)

yield (Eq. 1). The cuprate reagent attacks the β face of the enone, presumably so as to avoid an unfavorable 1,3-interaction with the axial benzyloxy substituent; as a result, the stereochemistry at C-1 is established correctly. However, alkylation of the derived enolate occurs exclusively on the α face of the molecule, resulting in the unnatural stereochemistry at C-2.† The C-2 methyl group is introduced with the proper stereochemistry as shown in Scheme 4. Trapping of the enolate resulting from conjugate addition of **24** to **8** with formaldehyde affords **26** as an epimeric mixture (67% yield). Elimination of the derived mesylate gives enone **27** in 95% yield. Hydrogenation of the exocyclic methylene bond in **27** is complicated by isomerization to enone **37**. However, if the



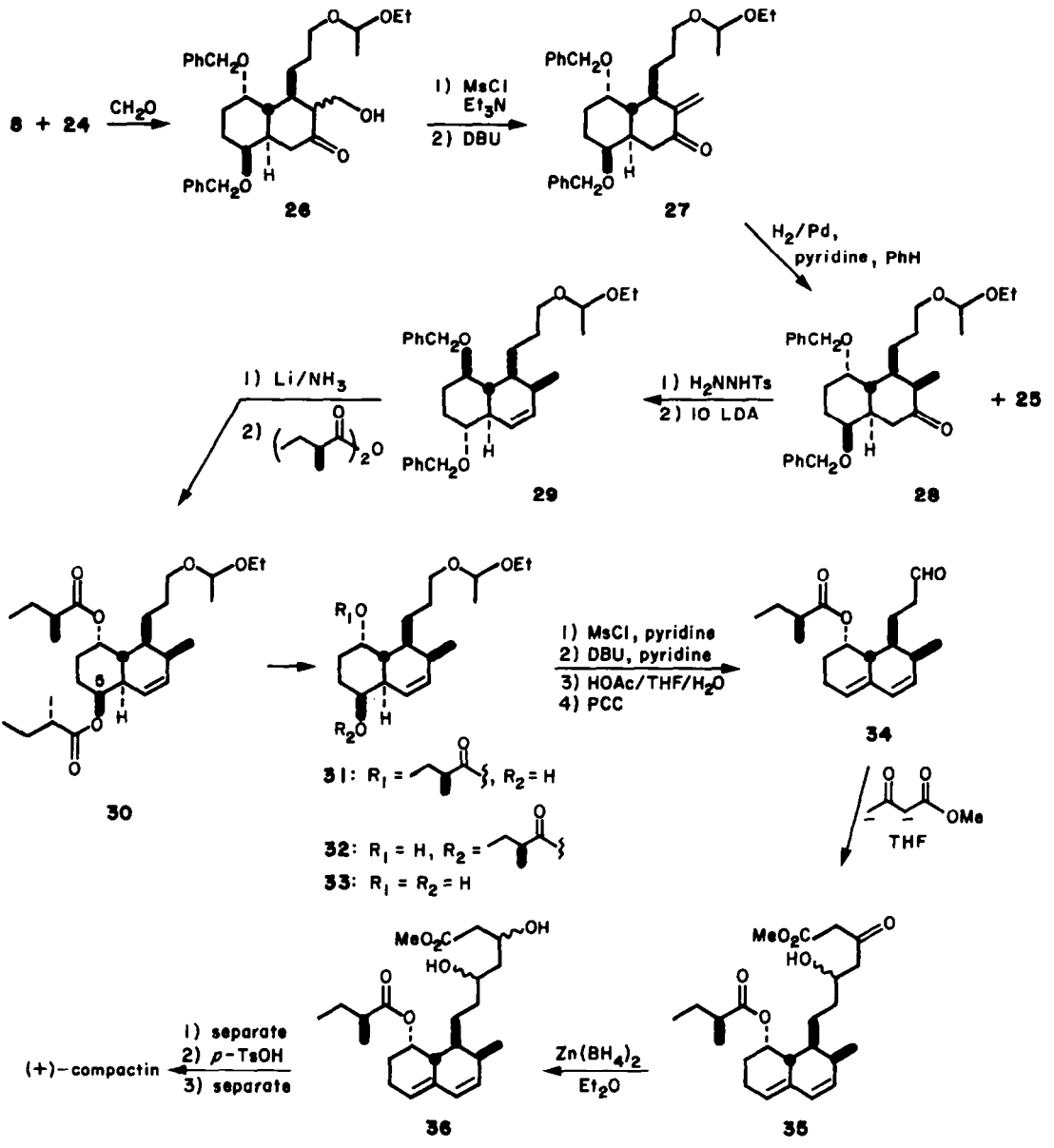
37

hydrogenation of **27** is carried out in the presence of pyridine or triethylamine in benzene this side reaction is suppressed and **28** is obtained in 78% yield while the undesired epimer (**25**) is isolated in only 10% yield. Conversion of **28** to its *p*-toluenesulfonylhydrazone and subsequent treatment with excess lithium diisopropylamide (LDA) furnishes olefin **29** in 62% yield. Debenzylation and exhaustive acylation of the resulting diol with (*S*)-2-methylbutyric anhydride‡ affords diester **30** in 97% yield. Treatment of **30** with a large excess of sodium ethoxide in ethanol results in selective cleavage of the 2-methylbutyryloxy group at C-5; hydroxy ester **31** is obtained in 63% yield along with isomeric hydroxy ester **32** (6.6%), recovered **30** (6.5%), and a trace of diol **33**. A four-step reaction sequence: mesylation, elimination (86%), deprotection, and oxidation (64%) gives aldehyde **34**. Reaction of **34** with the dianion of methyl acetoacetate gives an inseparable 1:1 mixture of hydroxy ketones **35** (68% yield, based on recovered **34**) which are reduced with zinc borohydride to give diols **36** (62%). The mixture is separated into two pairs of diols. Lactonization of the less polar pair of hydroxy esters produces a mixture of lactones (65% yield) the less polar of which is (+)-compactin.

In 1982, Hirama and Uei reported a synthesis of compactin that employs an intramolecular Diels–Alder reaction as the key synthetic maneuver.[18] Since (*E*)-1,7,9-trien-3-one cyclizes exclusively in the *exo* mode to give the *trans*-fused octalone, it was assumed that trienone **38** would cyclize to octalone **39** (Scheme 5). For steric and stereoelectronic reasons, the stereocenter at C-13 in **38** was expected to control the stereochemistry of the four new stereocenters generated in the Diels–Alder

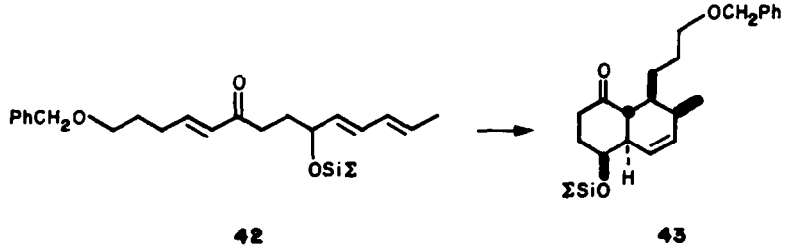
†The equilibrium mixture of **25** and **28** was determined to be 9:1.

‡(*S*)-2-Methylbutyric anhydride is prepared by treatment of the corresponding acid with DCC in dichloromethane.[15]



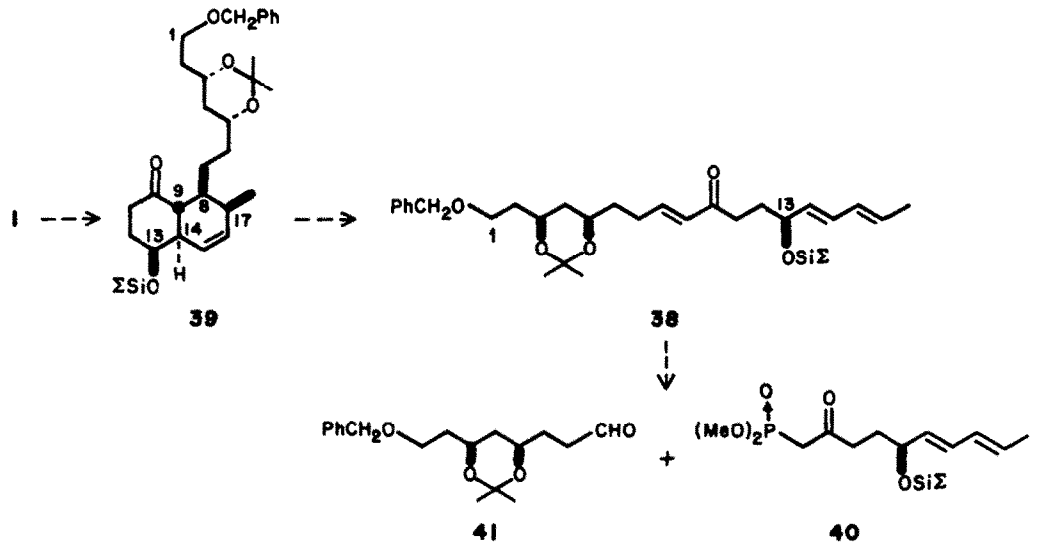
Scheme 4.

cyclization. Furthermore, it was found that cyclization of racemic **42** gives **43**, which has the desired relative stereochemistry (Eq. 2).

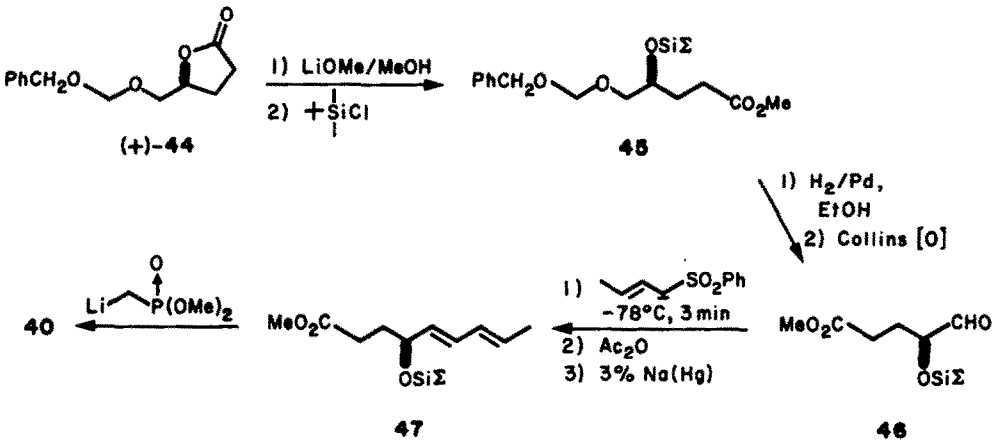


(2)

The synthesis of keto phosphonate **40** is shown in Scheme 6. Methanolysis of optically active lactone **44**[19] and silylation of the resulting secondary alcohol gives a 1 : 1 mixture of recovered **44** and silyloxy ester **45** (94% overall yield). Hydrogenolysis and oxidation affords aldehyde **46** in 79%



Scheme 5.



Scheme 6.

yield. Addition of the anion of *trans*-crotyl phenyl sulfone,† quenching with acetic anhydride, and reductive elimination of the sulfone acetate affords the (*E,E*)-diene **47** in 75% yield. This material is converted to keto phosphonate **40** (85% yield) by treatment with dimethyl lithiomethylphosphonate.‡

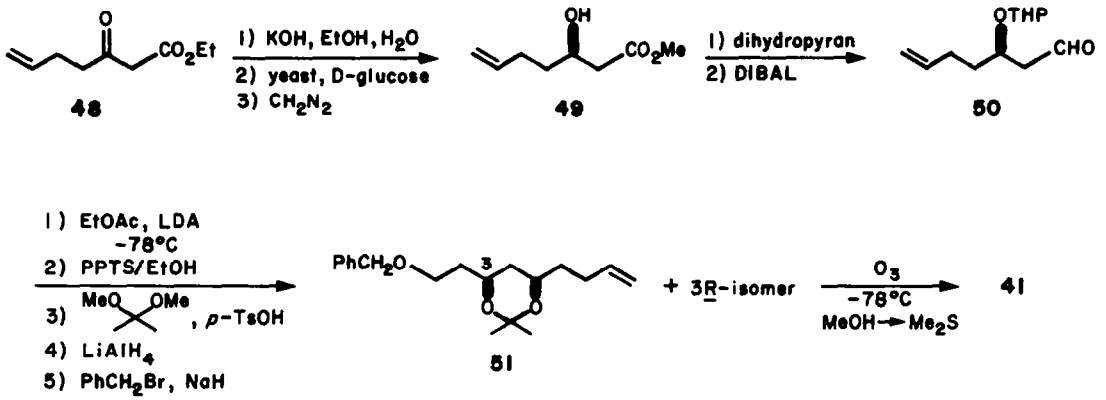
Aldehyde **41** is assembled as shown in Scheme 7. Basic hydrolysis of β-keto ester **48**, yeast reduction of the resulting keto acid, and esterification furnishes **49** in 35% yield (>99% ee).§ Protection of the hydroxyl group and DIBAL reduction gives aldehyde **50** (85% yield). Treatment of **50** with the enolate of ethyl acetate and sequential alcohol deprotection, acetonide formation, ester reduction, and benzylation gives a 1:1 mixture of **51** and its 3*R* isomer in 48% yield. After chromatographic separation, **51** is ozonolyzed to obtain **41** in 88% yield.

Keto phosphonate **40** and aldehyde **41** are coupled to obtain the (*E,E,E*)-trienone **38** in good yield (86%). However, cyclization of **38** furnishes the desired *trans*-octalone in only 28% yield. Surprisingly, the two *cis*-fused isomers predominate in the intramolecular Diels–Alder reaction, being obtained in yields of 45 and 9%. Reduction of the separated *trans* isomer by K-Selectride

†See footnote 12 in Ref. 18.

‡Compounds **40** and **47** are each contaminated by 4% of the *E,Z* and 6% of the *Z,E* isomer.

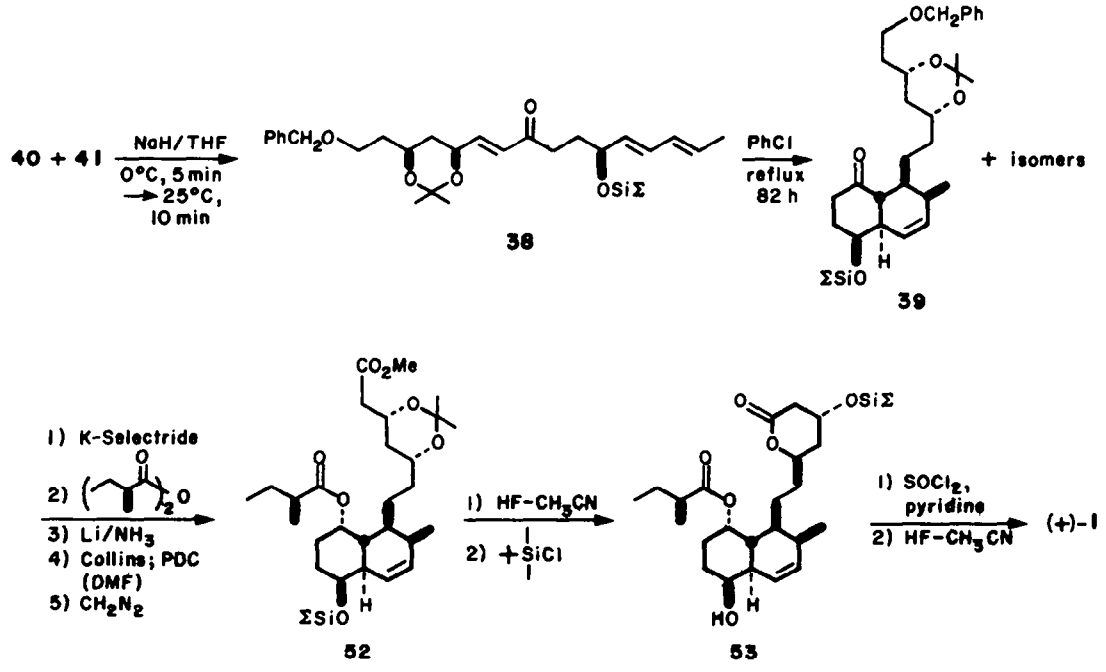
§See Ref. 20 for further information on this reduction.



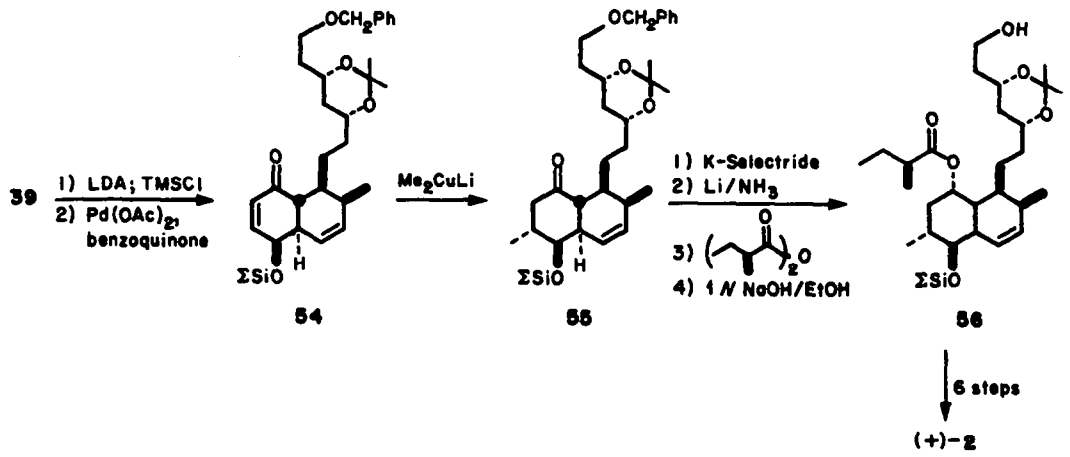
Scheme 7.

(87%) gives the axial secondary alcohol (87%), which is acylated (70%), debenzylated (73%), oxidized and esterified (65%) to obtain methyl ester **52**. Treatment of **52** with aqueous HF in CH_3CN results in desilylation, acetonide cleavage, and lactonization, giving a diol (70%), which is selectively silylated to obtain monoprotected diol **53** (65%). Regioselective dehydration and deprotection (51% yield) completes the synthesis of (+)-compactin (Scheme 8).

Hirama and Iwashita have utilized the key intermediate **39** to achieve the first synthesis of (+)-mevinolin (Scheme 9).[21] Unsaturation is introduced by the Ito method, oxidation of the enolsilane with palladium acetate and benzoquinone; enone **54** is obtained in 57% yield. Conjugate addition of lithium dimethylcuprate to **54** gives exclusively **55**, the product of axial addition (91% yield). Reduction (K-Selectride), debenzylation, acylation and selective hydrolysis of the primary acyl linkage affords alcohol **56** in 55% overall yield from **55**. The benzyl protecting group must be removed prior to the subsequent acylation reaction; attempted debenzylation (Li/NH_3) in the presence of the 2-methylbutyryloxy group also results in deacylation. This problem was not encountered in the similar reaction sequence **39** → **52** (Scheme 8). Compound **56** is converted to (+)-mevinolin (**2**) by a six-step sequence analogous to that employed in the compactin synthesis.

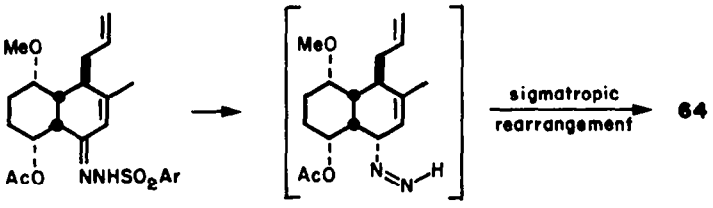


Scheme 8.



Scheme 9.

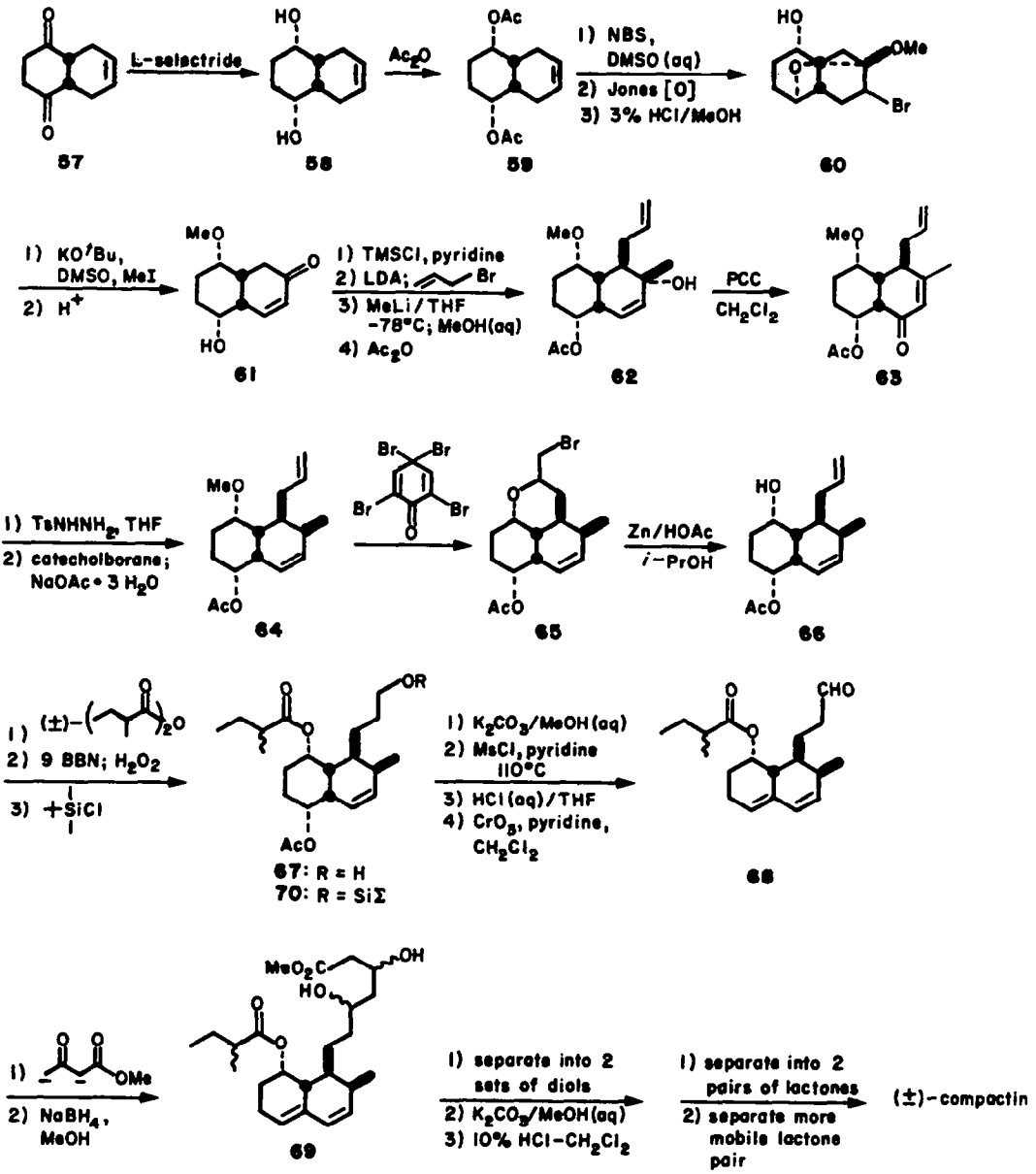
Girotra and Wendler have reported a linear synthesis of compactin beginning with dione **57**, the Diels–Alder adduct of 1,3-butadiene and benzophenone (Scheme 10).†[22] Reduction of **57** with lithium tri-*sec*-butylborohydride gives primarily (85%) the *cis*-diol **58**, which is acetylated to obtain **59**. Compound **59** is converted into a bromohydrin, which is oxidized to the corresponding bromo ketone. Treatment of this material with HCl in methanol furnishes **60**, which is methylated and dehydrobrominated in a single manipulation to give, upon acidification, enone **61** (65% yield from **58**). Protection of the free hydroxyl as its trimethylsilyl ether, allylation (exclusively from the β face), addition of methyllithium, and subsequent desilylation and acetylation affords the tertiary allylic alcohol **62**. Oxidative rearrangement of **62** gives enone **63**. Reduction of the tosylhydrazone of **63** with catecholborane proceeds stereoselectively to give **64** in 65% yield. Presumably, electrophilic attack of the borane reagent occurs on the β face of the molecule resulting in an *endo* diazine which delivers hydrogen selectively from the α face to the methyl-bearing carbon.



Treatment of **64** with 2,4,4,6-tetrabromocyclohexadienone in CH_2Cl_2 results in demethylation and formation of the bromoether **65** (95%), which is reductively cleaved with zinc in acetic acid to obtain hydroxy diene **66**. Acylation with racemic 2-methylbutyric anhydride (quantitative), hydroboration of the terminal olefin (84%) and silylation of the resulting primary alcohol affords **70** as a diastereomeric mixture. This substance is subjected to a four-step reaction sequence involving selective acetate hydrolysis, dehydration, silyl ether cleavage, and oxidation, to obtain aldehyde **68** in 60% yield. Reaction of **68** with the dianion of methyl acetoacetate and sodium borohydride reduction of the derived δ-hydroxy-β-keto esters gives **69** as a mixture of eight diastereomers which are separated into two sets of diols. Saponification of the less polar set of diols and lactonization furnishes a mixture of four diastereomeric lactones (80% yield), which are separated into two lactone pairs. The more mobile lactone pair is separated on a reverse-phase column to obtain (±)-compactin.

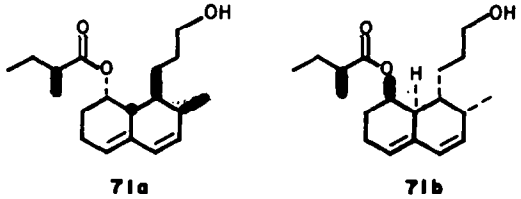
Girotra and Wendler also report that acylation of racemic **66** with optically active (*S*)-2-methylbutyric anhydride affords, after functional group manipulations, separable diastereomers **71a**

†See footnote 3 in Ref. 22.



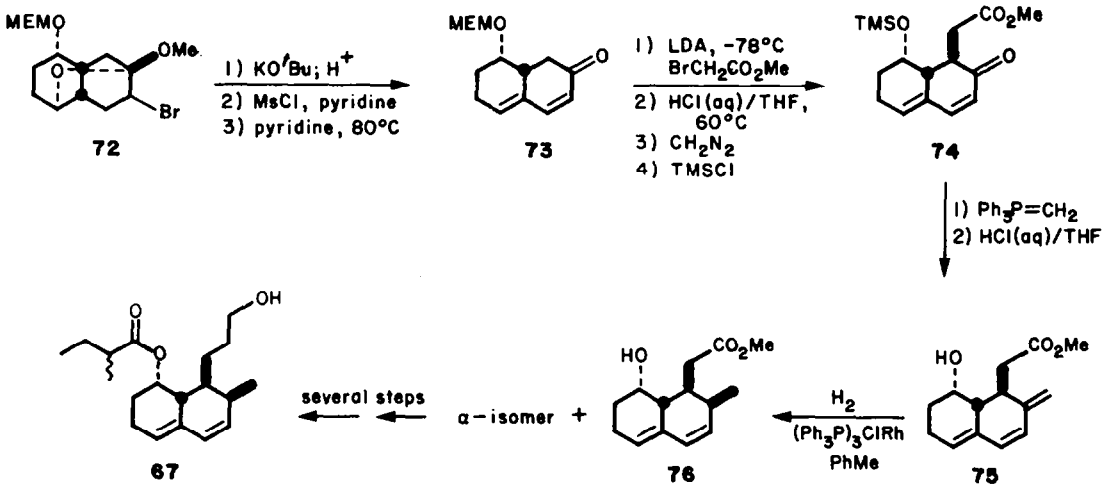
Scheme 10.

and **b**. Since alcohol **71a** is an intermediate in Sih's synthesis of (+)-**1**, its preparation constitutes a formal synthesis of (+)-**1**.



71a **71b**

The Merck group has also published modifications of their synthetic pathway which merit discussion.[23,24] Successive dehydrobromination and dehydration of **72** affords dienone **73** (65%). Alkylation of **73** with methyl bromoacetate proceeds selectively from the β face of the molecule



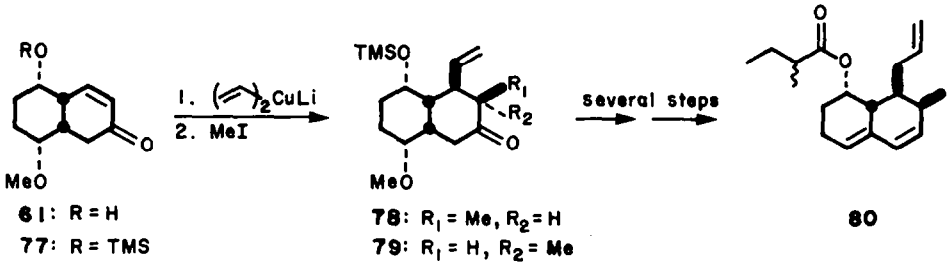
Scheme 11.

(65% yield) to give, after hydrolysis, methylation of the resulting hydroxy acid, and silylation, compound **74**. Wittig olefination and desilylation furnishes triene **75** (65% for the two steps). Hydrogenation of **75** (Wilkinson's catalyst) proceeds regioselectively to give a mixture of **76** and the corresponding α-methyl epimer in 60% yield; a minor amount (*ca* 5%) of tetrahydro product is also isolated. However, the reaction is not stereoselective; the two diastereomers are obtained in a ratio of 1 : 1.† After separation, **76** is converted by a multi-step sequence of reactions to the previously prepared intermediate **67** (Scheme 11).

A second alternative route utilizes enone **77** as a substrate for a conjugate addition–alkylation reaction sequence (Scheme 12).[24] Addition of lithium divinylcuprate to enone **77** and trapping of the resulting enolate with methyl iodide affords a 3 : 2 mixture of **78** and **79** in 85% yield. This result is an interesting contrast to the observation (exclusive α-methylation) reported by Sih with the related *trans*-octalone **8** in a similar sequence (Eq. 1). The diastereomers are separated and **78** is converted after twelve additional steps to the known[23] compactin precursor **80**.

Grieco *et al.* have published a synthesis in which the carbon framework of compactin is constructed in the thermal cycloaddition of olefin **81** and diene **82** (Scheme 13).[25] Reduction of the known Diels–Alder adduct **83** with diimide followed by ester hydrolysis gives the racemic acid **84** in 92% yield. Resolution of **84** followed by esterification (48% from **84**) and elimination (75%) affords optically active unsaturated ester **81** (Scheme 14).

The diene unit is assembled as shown in Scheme 15, beginning with the carbohydrate-derived Corey epoxide **85**.‡§[28] Lithium aluminum hydride epoxide opening (92% selectivity), methylation of the resulting alcohol, and removal of the trityl protecting group gives alcohol **86** (70% yield),

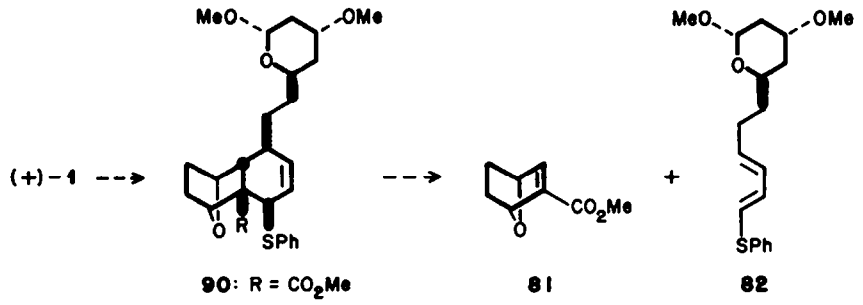


Scheme 12.

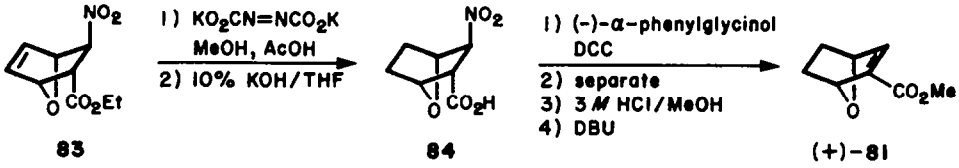
†The triene derived from treatment of **73** with methylenetriphenylphosphorane undergoes hydrogenation to give the corresponding β-methyl compound in good yield.

‡For similar work using epoxide **85**, see Refs 26 and 27.

§For experimental details for the preparation of **85**, see Ref. 26.

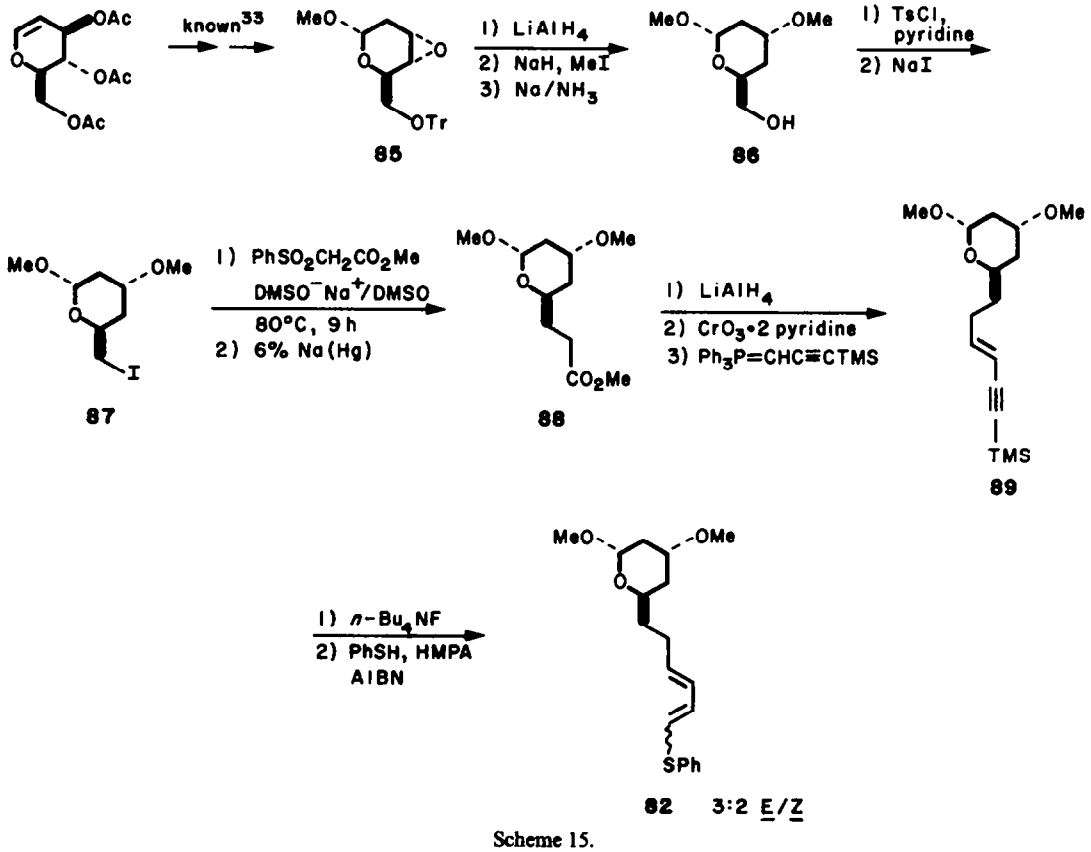


Scheme 13.

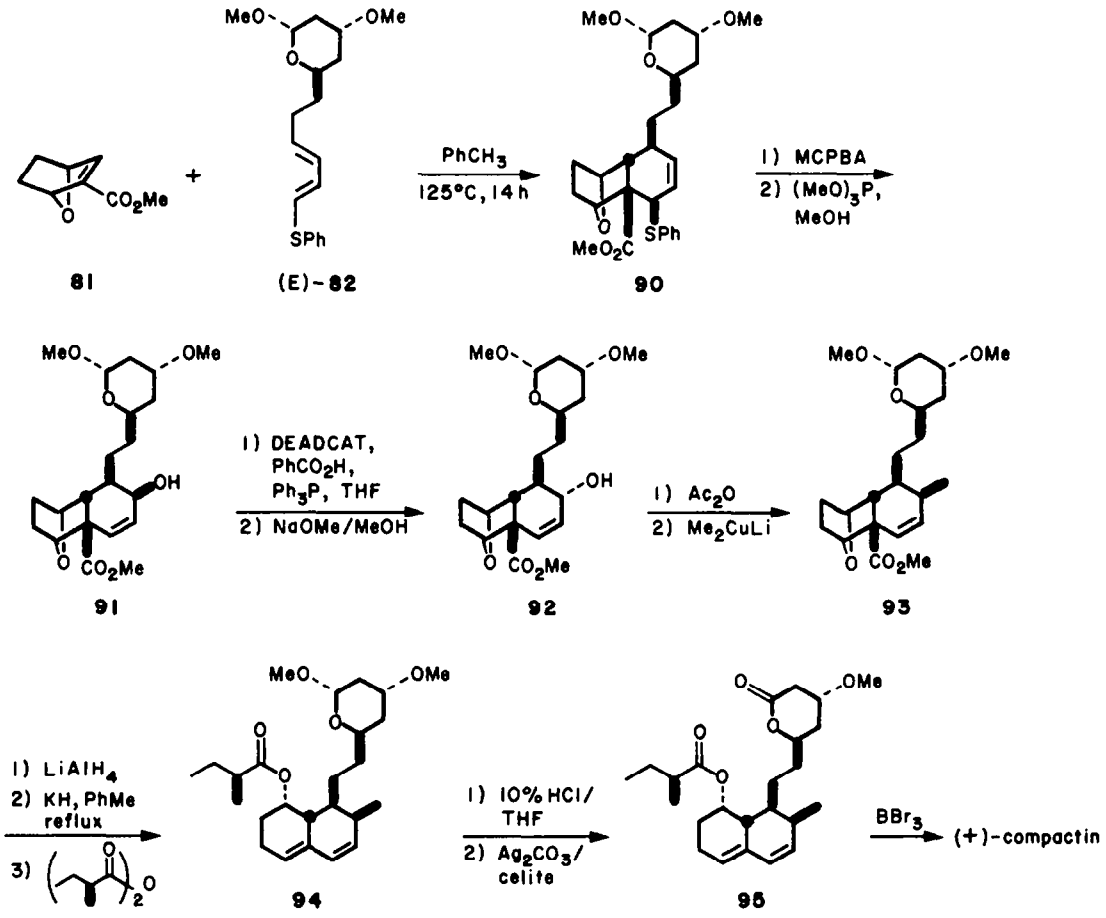


Scheme 14.

which is converted to the primary iodide **87** in the standard manner. Alkylation of the anion of methyl phenylsulfonylacetate with **87** and desulfonylation furnishes ester **88** in 78% yield from **86**. Reduction of **88** followed by oxidation and condensation of the resulting aldehyde with trimethylsilyl propargylidenetriphenylphosphorane provides acetylene **89** in 77% yield. Desilylation of **89** and addition of thiophenol to the triple bond affords **82** as a 3:2 mixture of *E* and *Z* isomers in 94% yield; the *Z* isomer does not react with **81** in the subsequent Diels–Alder reaction.

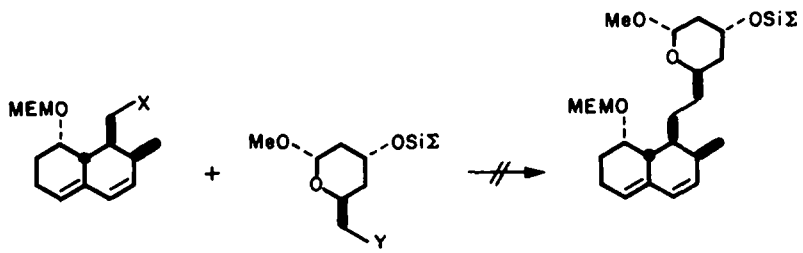


Scheme 15.

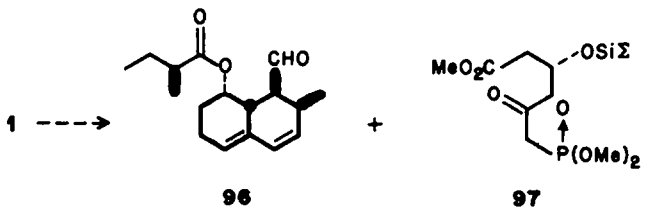


Scheme 16.

The Diels–Alder reaction of diene **82** (300 mol %) and dienophile **81** follows the Alder–Stein rule and occurs on the *exo* face of **81** to afford adduct **90** in 70% yield (Scheme 16). Oxidation of sulfide **90** with *m*-chloroperoxybenzoic acid does not afford the corresponding sulfoxide. Instead, the rearranged allylic sulfenate is isolated as the sole product; subsequent treatment with trimethylphosphite affords alcohol **91** in 70% yield. Inversion of configuration of the hydroxyl-bearing carbon (**91** → **92**, 79% yield) followed by acetylation and displacement with lithium dimethylcuprate stereospecifically introduces the allylic methyl group, affording **93** in 86% yield. The ester is reduced and the resulting alcohol is subjected to Grob fragmentation to create the conjugated diene unit. Subsequent acylation of the resulting secondary alcohol gives **94** in about 40% yield. Acidic hydrolysis and oxidation of the resulting hemiacetal with Fetizon's reagent provides masked hydroxy lactone **95** (71%) which is demethylated with boron tribromide to obtain (+)-compactin (31%).



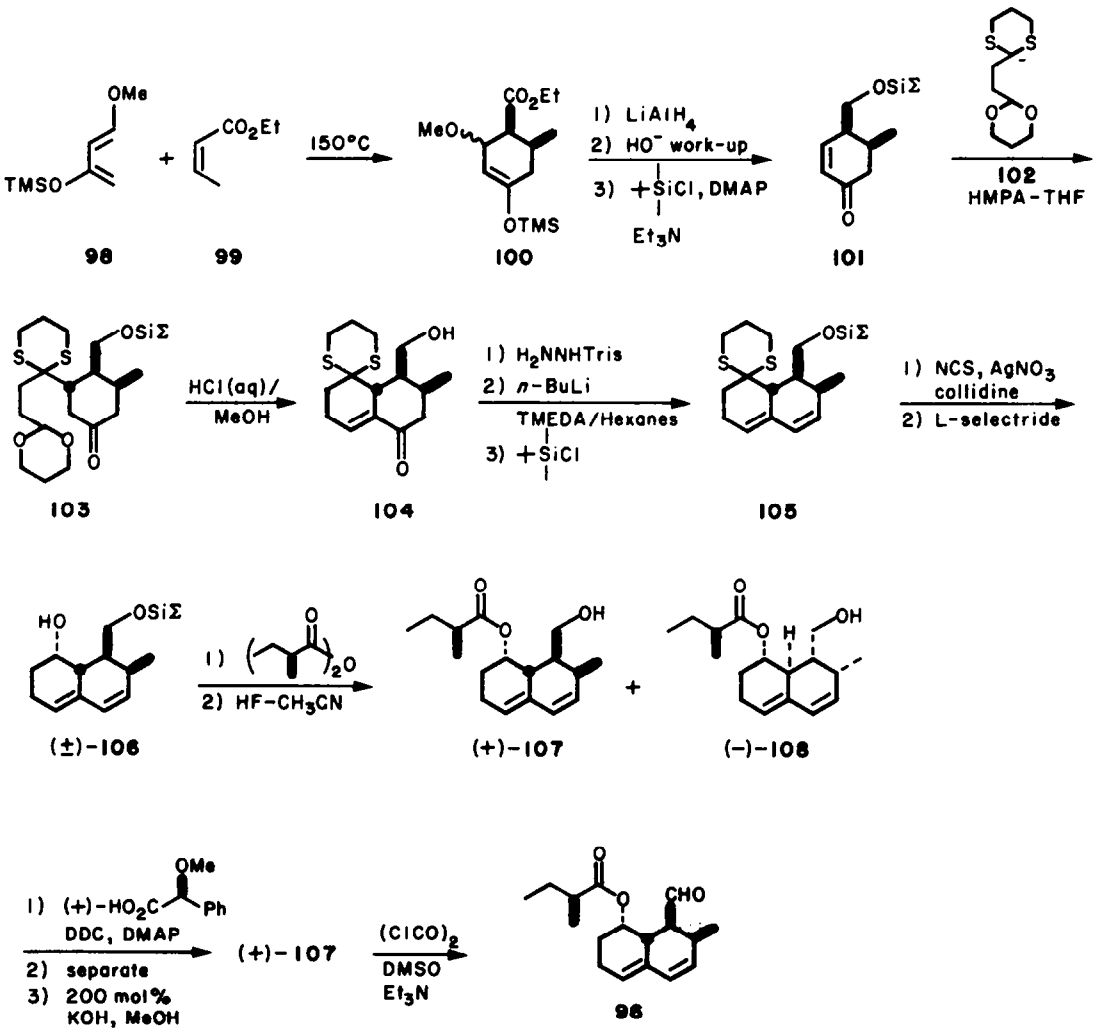
Our first approach to the carbon framework of **1** was based on coupling a hexalin unit[29,30] with an appropriate synthon for the lactone portion[26] of **1**. However, various attempts to form the critical carbon–carbon bond with a preformed lactone or equivalent acetal unit were unsuccessful. We thus took an alternative approach, employing a Horner–Emmons bond-forming reaction (Scheme 17).[31]



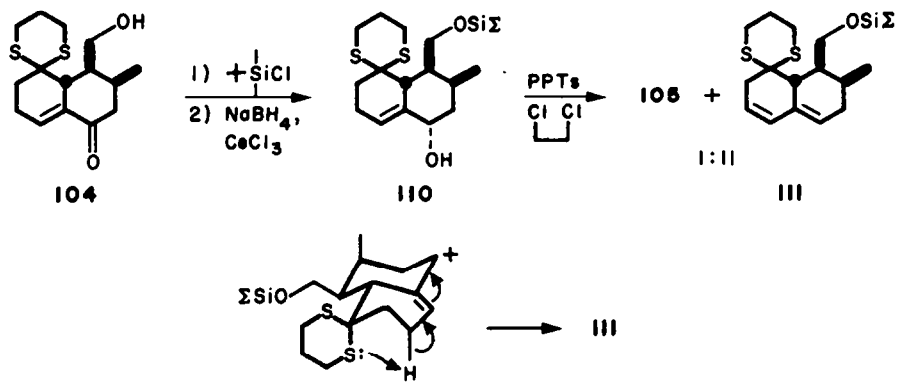
Scheme 17.

The synthesis of aldehyde **96** is summarized in Scheme 18. Diels–Alder reaction of Danishefsky's diene and ethyl (*Z*)-crotonate affords cycloadduct **100** in 78% yield. Lithium aluminum hydride reduction, basic work-up, and silylation provides enone **101** in 72% yield. Dithiane anion **102** adds to the less hindered α face of **101** (57–74% yield) to give **103**. Acidic hydrolysis with concomitant intramolecular aldol condensation affords hydroxy enone **104** (74%).

The 3,4-double bond of the hexalin unit is cleanly introduced using a modification of the Shapiro olefin synthesis. Enone **104** is converted to its triisopropylbenzenesulfonyl hydrazone (81% yield) which gives diene **105** in 74% yield upon treatment with n-butyllithium and silylation. Dithiane hydrolysis and reduction of the resulting ketone with L-Selectride affords axial alcohol **106** (74% yield). Acylation of racemic **106** with (*S*)-2-methylbutyric anhydride and subsequent cleavage of the



Scheme 18



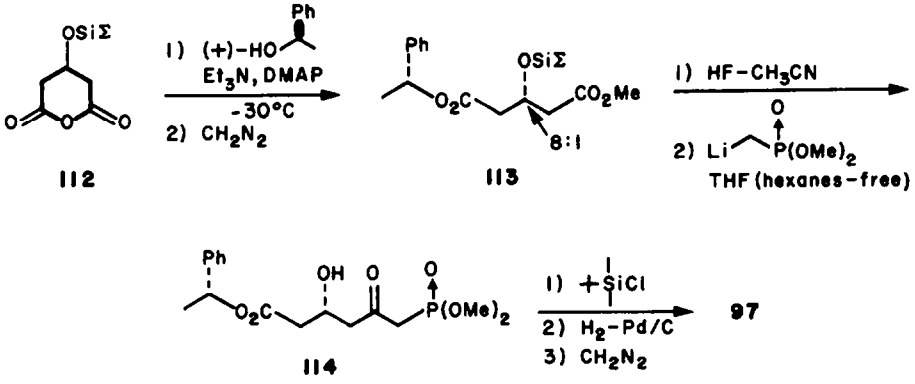
Scheme 19.

silyl protecting group gives an inseparable mixture of optically active diastereomers **107** and **108** (quantitative yield). However, acylation of the mixture with (+)-O-methylmandelic acid (**109**) provides diastereomers (94% yield) which are separated by HPLC. After separation, the primary acyl linkage is selectively hydrolyzed to obtain enantiomerically homogeneous alcohol **107** which is oxidized to obtain aldehyde **96** in 90% yield for the two steps.

An initial attempt at elaboration of the conjugated diene is shown in Scheme 19. Silylation of **104** and subsequent reduction with sodium borohydride gives equatorial alcohol **110**, which is dehydrated under mildly acidic conditions to obtain a mixture of dienes. The diene chromophore in the major product (11 : 1) is isomeric to that in the natural product. This observed selectivity may result from intramolecular proton abstraction in the intermediate allylic cation by the axial sulfur atom of the dithiane moiety.

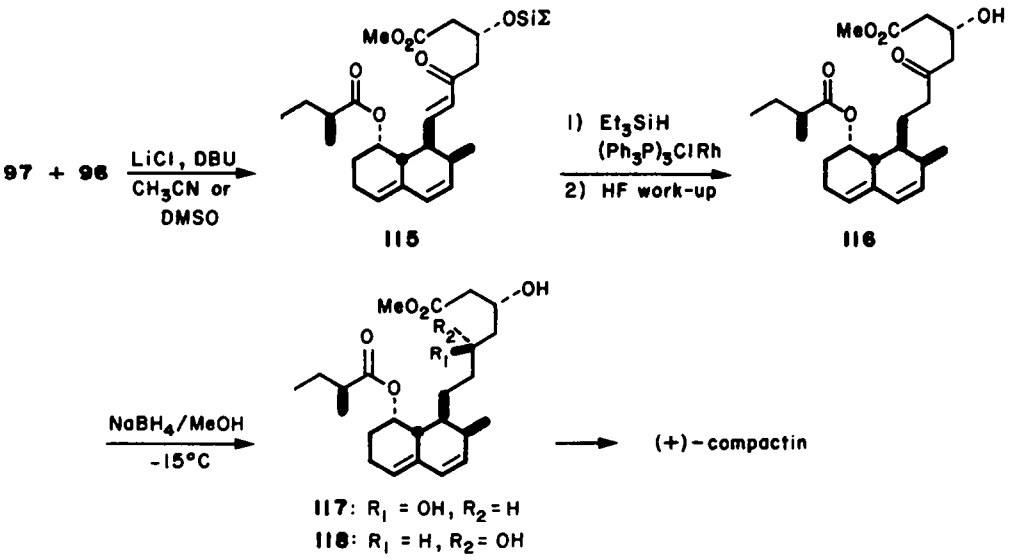
The synthesis of keto phosphonate **97** is summarized in Scheme 20. Opening of anhydride **112**[32] with (+)-phenethyl alcohol and subsequent esterification with diazomethane gives optically active diester **113** and the corresponding epimer at the silyloxy-bearing carbon in 65–75% yield. The anhydride opening proceeds with a surprisingly high degree of asymmetric induction; the diastereomers are obtained in a ratio of 8 : 1.† After desilylation, the resulting hydroxy diester is treated with dimethyl lithiomethylphosphonate to obtain **114** in 43% yield. The product isolated is derived exclusively from attack on the methyl ester. Sequential silylation, hydrogenolysis, and esterification affords optically active keto phosphonate **97** in 79% yield.

Condensation of **97** and aldehyde **96**, employing the method of Blanchette *et al.*,[33] affords enone **115** in 35–60% yield along with recovered **96** (35–50%) (Scheme 21). Selective 1,4-reduction of the enone is accomplished with triethylsilane in the presence of Wilkinson's catalyst; concentration



Scheme 20.

†Subsequent development of this reaction has resulted in an improvement of the prochiral recognition to 12 : 1 using 1-phenylethanol and to > 35 : 1 using 1-(1′-naphthyl)ethanol; P. Thiesen and C. H. Heathcock, unpublished results.

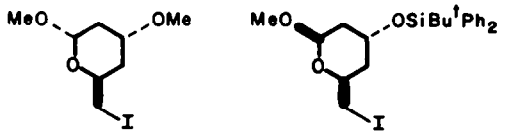


Scheme 21.

of the reaction mixture and treatment of the residue with aqueous HF in acetonitrile furnishes hydroxy ketone **116** in 87% yield. Sodium borohydride reduction of **116** gives diols **117** and **118** in a ratio of about 2 : 1. After separation, the major product is lactonized to give (+)-compactin (70% yield).

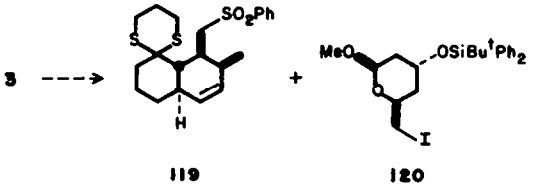
The first total synthesis of dihydrocompactin (**3**) was reported by Falck and co-workers in 1984.[34] The key step in this synthesis is the alkylation of the dianion derived from sulfone **119** with iodide **120** (Scheme 22).

Assembly of the octalin unit begins with (*E*,*E*)-octa-4,6-diene-1-ol (**121**) (Scheme 23).[35] The derived tosylate is treated with thiophenoxide and the resulting sulfide oxidized to obtain sulfone **122** in 68% yield. Diels–Alder reaction of **122** and maleic anhydride proceeds in an *endo* manner to produce the cycloadduct **123** in 70% yield. Intramolecular sulfone acylation is effected under carefully controlled conditions; subsequent esterification, desulfonylation, and equilibration of the resulting mixture of *cis*- and *trans*-fused octalones furnishes *trans*-octalone **124** in 28–37% overall yield from **123**. Ketalization and reduction of the methyl ester gives primary alcohol **125** (91%). Simultaneous ketal cleavage and alcohol–iodide interchange is accomplished with trimethylsilyl iodide; subsequent sulfonylation and thioketalization provides **119** in 73% yield.



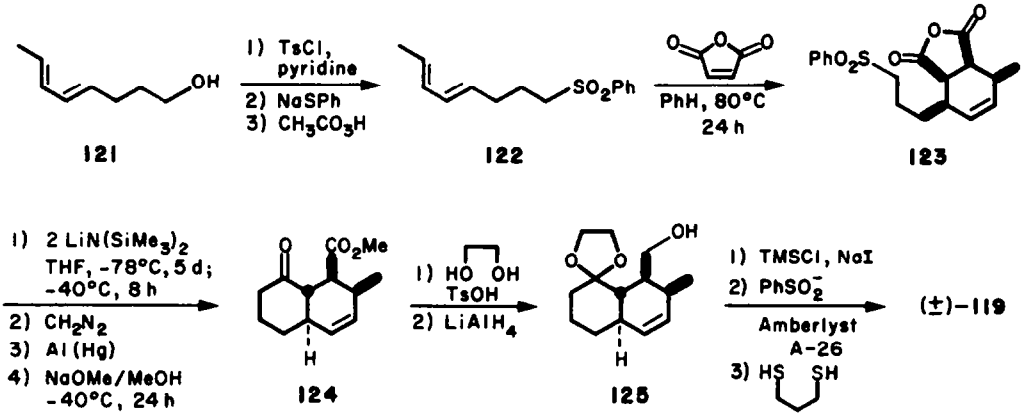
87 **120**

The iodide **120** is prepared [27] from the Corey epoxide **85** in a manner analogous to the synthesis of **87** (see Scheme 15). The difference in absolute configuration at the anomeric carbon in these two compounds is a result of the different procedures employed for detritylation. Falck and co-workers employ catalytic *p*-toluenesulfonic acid in methanol and obtain an equilibrium mixture of anomers



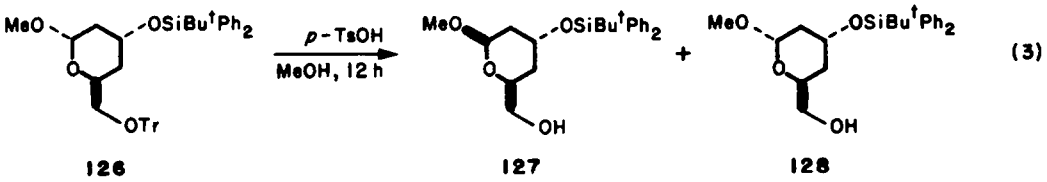
119 **120**

Scheme 22.



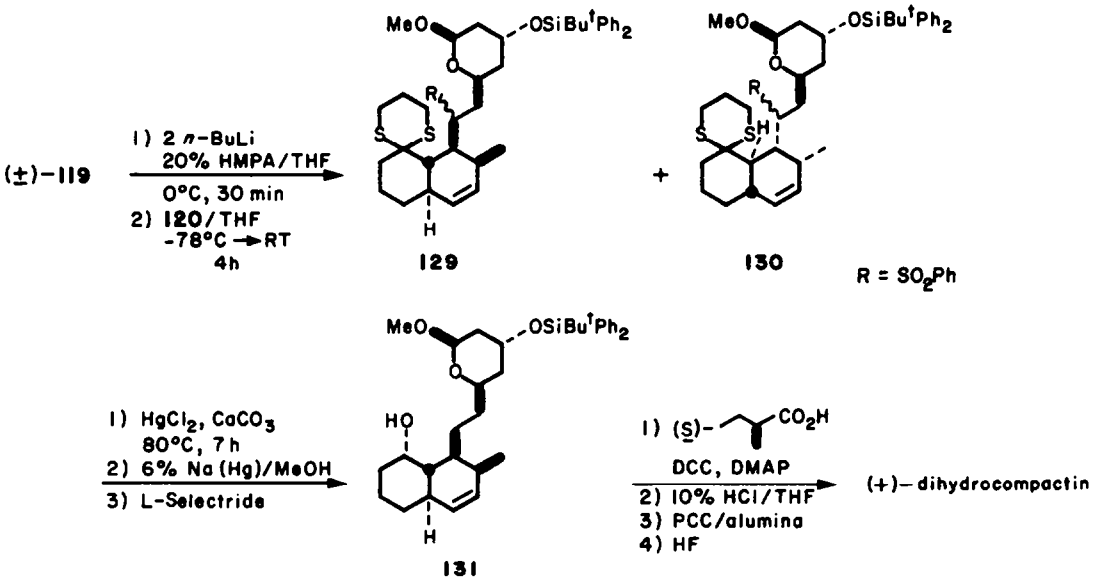
Scheme 23.

127 and **128** (9 : 1, 89% yield) (Eq. 3). After separation, **127** is used in subsequent manipulations to obtain **120**.

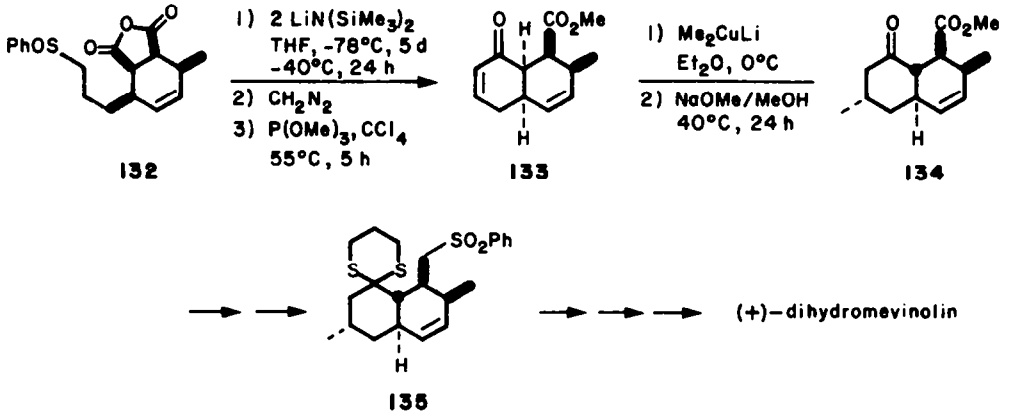


Coupling of the dianion of racemic **119** and enantiomerically homogeneous **120** gives a mixture of diastereomers **129** and **130** in 93% yield based on recovered **119**. Hydrolysis of the dithiane moiety, desulfonylation, and stereospecific reduction of the ketone furnishes axial alcohol **131** and the corresponding diastereomer derived from **130** in 40–60% yield; the alcohols are separable. Acylation, hydrolysis of the methyl glycoside, oxidation of the resulting acetal and desilylation gives the natural product in 48% yield for the four-step sequence (Scheme 24).

Falck and Yang have adapted the foregoing approach to achieve the first total synthesis of (+)-dihydromevinolin (**4**) (Scheme 25).[36] Intramolecular acylation of sulfoxide **132** followed by esterification of the resulting acid and thermal dehydrosulfenylation gives primarily the *cis*-fused



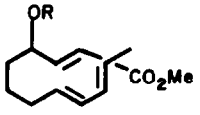
Scheme 24.



Scheme 25.

dienone **133**. Conjugate addition of lithium dimethyl cuprate and subsequent methoxide-catalyzed equilibration provides *trans*-octalone **134** in 35% yield from **132**. Compound **134** is converted via sulfone **135** to dihydromevinolin using chemistry analogous to that developed for the synthesis of **3**.

Funk and Zeller have completed syntheses of (+)-compactin and (+)-dihydrocompactin employing variants of the intramolecular Diels–Alder reaction. Their approaches also involve dissection of the natural products into a hexalin (or octalin) unit and a lactone synthon. The hexalin portion of compactin is constructed by intramolecular cyclization of dodecatrienoate **136**.[37] The

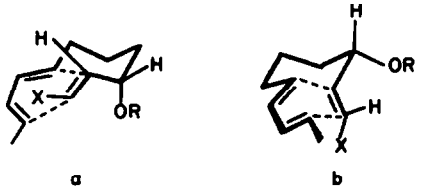


136

cyclization is expected to proceed through a chair-like *endo* (a or b) transition state as opposed to the alternative *exo* modes, particularly in the presence of a Lewis acid catalyst (Scheme 26). Thus, three of the contiguous asymmetric centers present in the hexalin portion of **1** should be established with the proper relative configuration; the stereorelationship of the alkoxy-bearing carbon is less predictable.

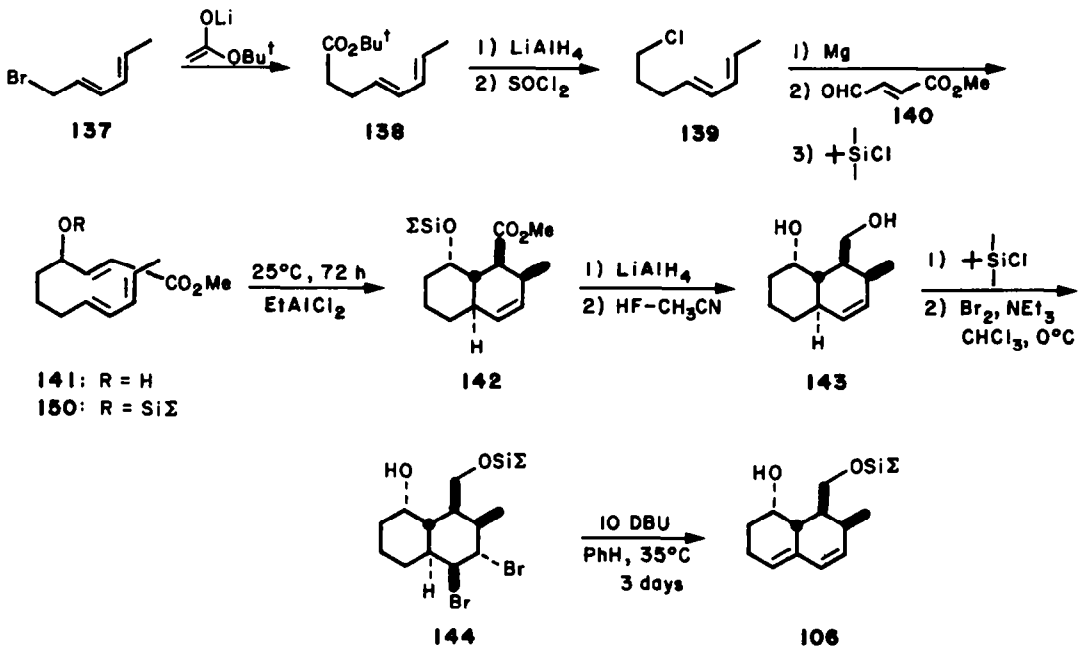
Application of the approach is outlined in Scheme 27. Alkylation of t-butyl lithioacetate with sorbyl bromide (**137**) provides **138** in 81% yield. The ester is reduced with lithium aluminum hydride and the resulting alcohol treated with thionyl chloride to obtain chloride **139** in 61% yield for the two-step sequence. Generation of the Grignard reagent derived from **139** and condensation with aldehyde **140** gives the hydroxy trienoate **141**. Intramolecular cycloaddition of **141** (155°, 60 h) affords a mixture of **145–147**, with **145** as the minor component (Scheme 28).

However, when the Diels–Alder reaction is carried out under Lewis acid catalysis ($EtAlCl_2$) **145** and **146** are obtained in a ratio of 55:45; only a trace of *exo* product **147** is produced under these conditions. The silyl derivative **150** (140°, 120 h) gives a 65:13:22 mixture of **142, 148** and **149**. However, in the presence of $EtAlCl_2$, **142** and **148** are obtained in a 98:2 ratio in 65–73% yield; none of isomer **149** is produced under these conditions. It is postulated that an A^{1-3}-type interaction between the pseudoequatorial hydroxyl and the C-2 hydrogen may destabilize transition state b

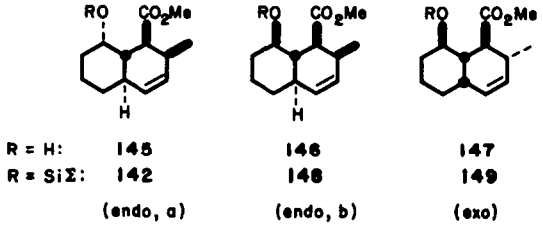


a b

Scheme 26.



Scheme 27.

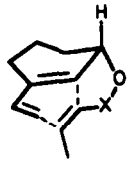


Scheme 28.

(Scheme 26). Funk also suggests molecular orbital overlap considerations which may account for the observed selectivity.

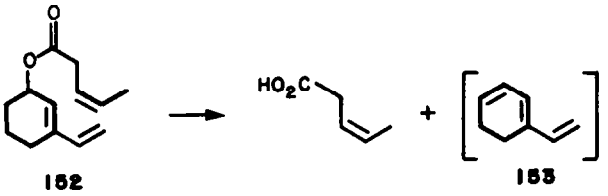
Reduction of ester **142** and hydrolysis of the silyl ether gives diol **143** in 94% yield. Selective protection of the primary alcohol (80% yield) and bromination affords the highly functionalized decalin **144** (90% yield). Dehydrohalogenation of the dibromide provides the desired hexalin **106** in 51% yield.

Funk *et al.* have reported an alternative Diels–Alder route to the system.[38] The strategy employed envisages intramolecular cycloaddition of a substrate such as **151** which is expected to proceed through a sterically uncongested *exo* transition state with delivery of the unactivated dienophilic side-chain from the same face of the molecule as the oxygen atom. The resulting adduct would possess the proper relative stereochemistry at the four contiguous asymmetric centers found in the natural product.



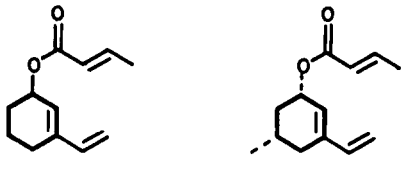
151

Thermolysis of **152** (170°, 12 h) affords no cycloadduct. Isolated instead are (*Z*)-3-pentenoic



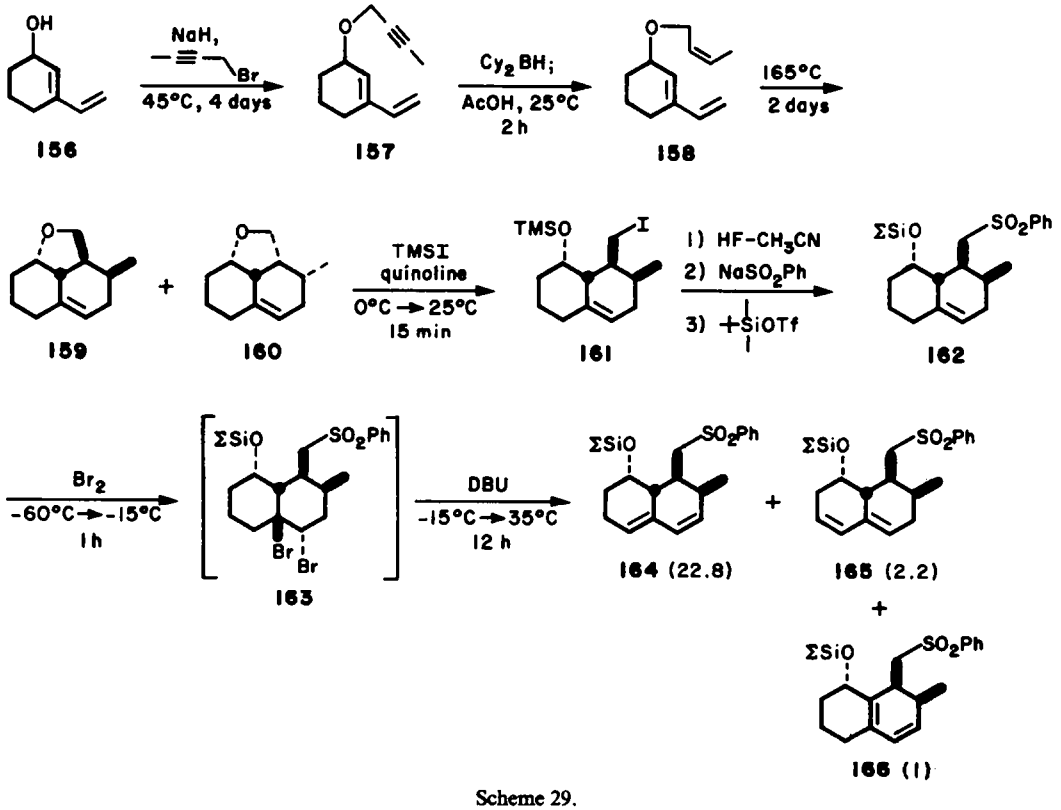
152 153 (4)

acid and uncharacterized materials presumably derived from triene **153** (Eq. 4). We have made similar observations with the related crotonates **154** and **155**.[39]

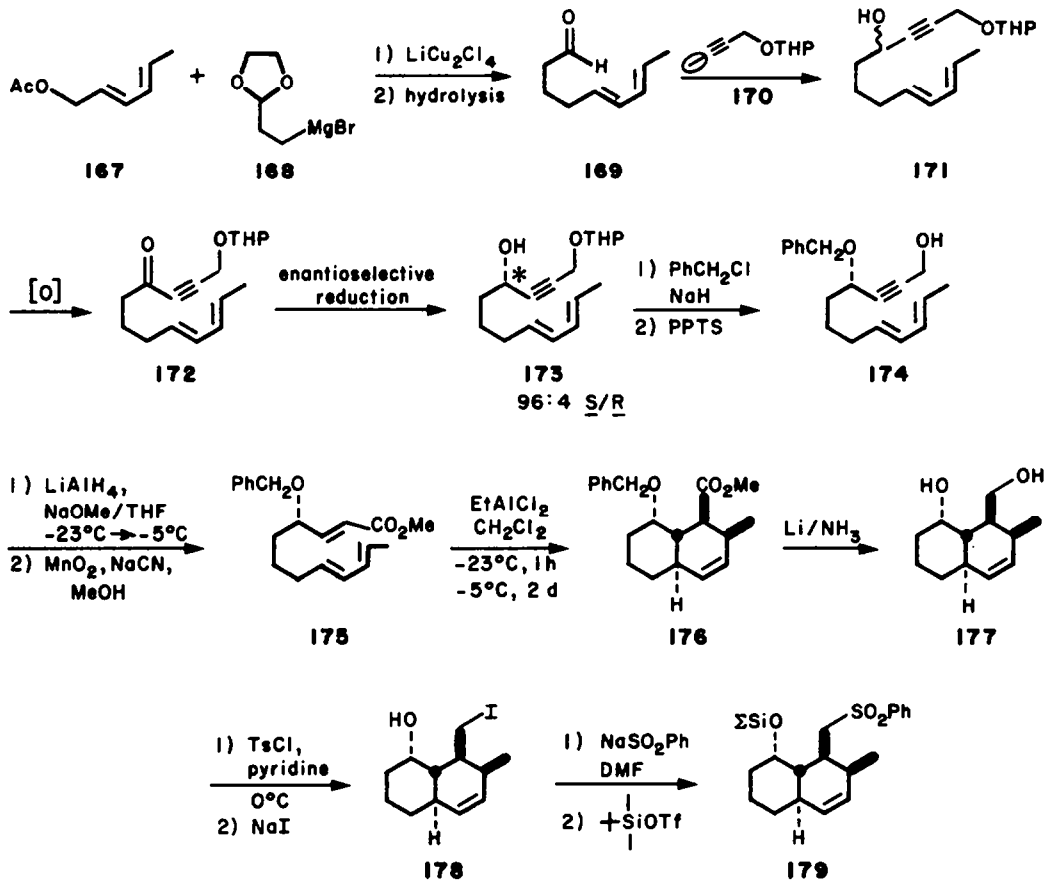


154 155

Funk's successful sequence is shown in Scheme 29. In order to circumvent the problem of elimination, the ester linkage is replaced with the more stable ether function. Alkylation of the sodium alkoxide of **156** with 1-bromo-2-butyne gives dienyne **157** in 79% yield. Selective hydroboration with dicyclohexylborane and subsequent protonolysis of the resulting alkenylborane affords Diels–Alder precursor **158** in 78% yield. Upon heating, this substance gives a mixture of isomers **159** and **160** in a ratio of 4:1 (69% yield). After chromatographic separation, the cyclic ether is cleaved regiospecifically with trimethylsilyl iodide in the presence of quinoline to obtain iodide **161** in 70% yield. Sequential cleavage of the trimethylsilyl ether, displacement of iodide with sodium benzenesulfinate, and protection of the secondary alcohol provides sulfone **162** in 60% yield. A one-pot procedure was developed for elaboration of the conjugated diene moiety. Bromination of olefin **162** and treatment of the resulting dibromide (**163**) with DBU affords a mixture of dienes **164–166** (22.8:2.2:1, 62% yield). The isomers are separated by HPLC.

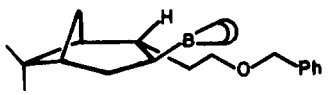


Scheme 29.



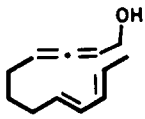
Scheme 30.

The preparation of the dihydrocompactin precursor (**179**), in optically enriched form, is summarized in Scheme 30.[40] Alkylation of the Grignard reagent **168** with sorbyl acetate (**167**) gives, after hydrolysis, aldehyde **169** in 70% yield along with the regioisomeric product derived from S_N2' alkylation (8%). Condensation of **169** with acetylide **170** provides the racemic alcohol **171** which is oxidized to obtain ynone **172**. Reduction of **172** with nopol benzyl ether 9-BBN (**180**), employing



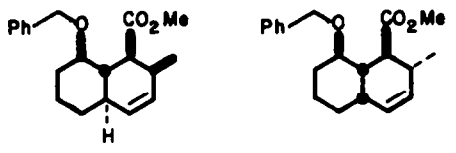
180

the conditions developed by Midland, gives the *S*-propargyl alcohol **173** (96 : 4) which is benzylated and selectively deprotected to afford mono protected diol **174**. Reduction of **174** with $LiAlH_4$ and NaOMe in THF furnishes the corresponding *trans* allylic alcohol (90%) which is contaminated with less than 3% of allene **181**. Oxidation with MnO_2 in the presence of NaCN and MeOH furnishes



181

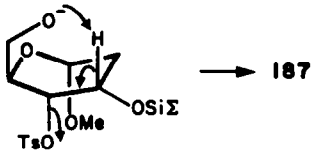
the Diels–Alder precursor (**175**) in 89% yield. Treatment of trienoate **175** with ethylaluminum dichloride in CH_2Cl_2 affords the desired cycloadduct **176** in 79% yield. Also isolated are the equatorial benzyl ether **182** (5%) and the *exo* adduct **183** (3%). Simultaneous debenzylation and ester reduction is accomplished with lithium in ammonia to provide diol **177** (quantitative yield).



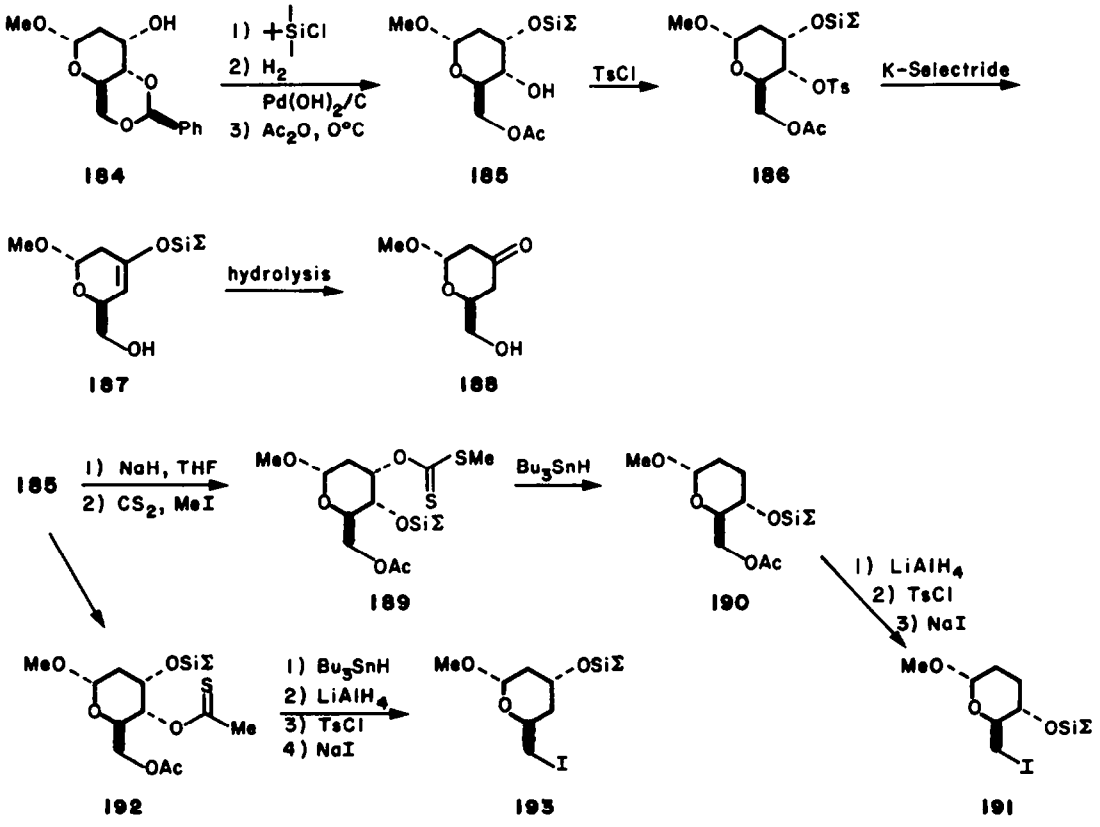
182 183

Selective tosylation of the primary hydroxyl followed by Finkelstein iodide displacement gives hydroxy iodide **178** (90% yield) which is transformed to the corresponding sulfone using sodium benzenesulfinate (70% yield). A small amount (10%) of the corresponding O-alkylated sulfinate ester is also isolated. Silylation furnishes the desired octalin synthon **179**.

Funk and Zeller have approached the construction of a lactone synthon (Scheme 31) in a fashion similar to that described by workers at Merck which is discussed at a later point in this report.[40] Silylation of the D-glucose derived benzylidene **184** (96%) followed by hydrogenolysis using Pearlman's catalyst (quantitative) and selective acetylation of the resulting diol (76%) provides **185**. Tosylation of the secondary hydroxyl gives **186** in 92% yield; however, attempted reductive deoxygenation with K-Selectride (400 mol %) affords enol ether **187** (75%). It is hypothesized that

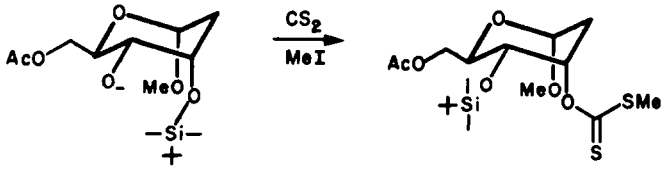


the observed product may result from an *anti* elimination proceeding through a boat-like transition state with intramolecular proton abstraction. Hydrolysis of **187** gives **188** which, based upon Danishefsky's work (*vide infra*), could be reduced selectively to provide the desired axial alcohol. However, an alternative deoxygenation procedure was investigated. Generation of the alkoxide of

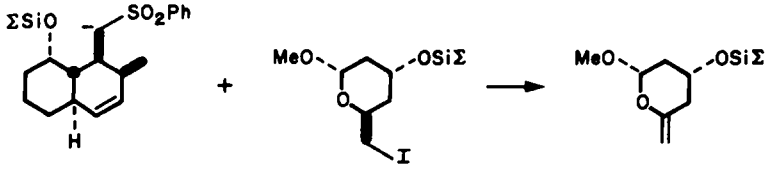


Scheme 31.

185 (NaH, THF) and subsequent treatment with CS_2 and methyl iodide gives xanthate **189** (62%) which is reduced with tributyltin hydride to obtain acetate **190** (71%). It is proposed that the product is derived from an intramolecular silyl rearrangement in the alkoxide of **185** followed by subsequent trapping with CS_2 and that the rearrangement proceeds to completion in order to partially relieve the 1,3-diaxial interaction with the anomeric methoxy group. The problem is solved by generating the alkoxide of **185** in CS_2 instead of THF. After methylation, the desired xanthate (**192**) is obtained in 74% yield. Reduction of **192** with Bu_3SnH (70%) and subsequent treatment with $LiAlH_4$, TsCl, and NaI affords iodide **193** in 82% yield; iodide **191** is obtained in an analogous manner.

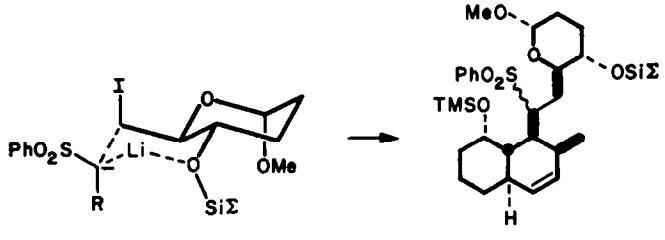


A second lactone synthon was constructed as shown in Scheme 32.[40] Treatment of the optically active aldehyde **194**, derived from L-malic acid, with β-allyldiisopinocamphenyl borane gives epimers **195** and **196** in a ratio of 85:15. Silylation of **195** (91%) and acetonide hydrolysis gives diol **197**. Selective tosylation of the primary alcohol and exposure of the resulting hydroxy tosylate to base gives epoxide **198** (74%). Oxidative cleavage of olefin **198** gives the unstable acid **199**.



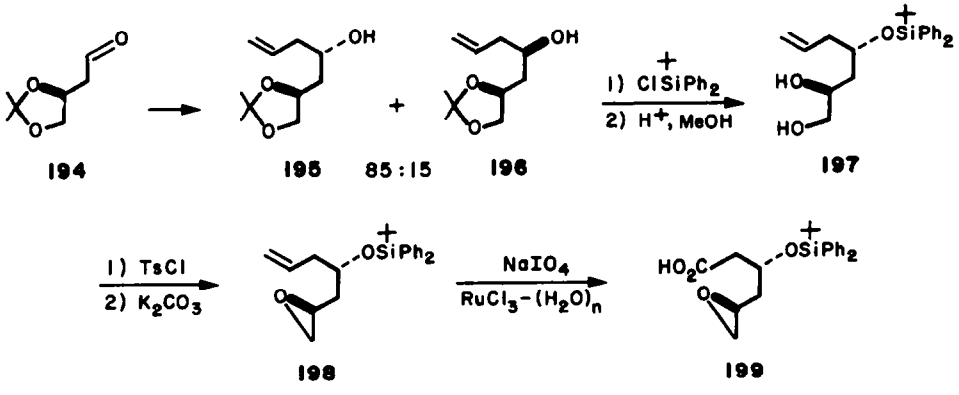
200 **193** **201**

Numerous attempts to alkylate sulfone anion **200** with iodide **193** were unsuccessful. Enol ether **201**, the product of dehydroiodination is the primary product. These results are consistent with observations we have made in attempting similar alkylation reactions. Interestingly, **200** is alkylated with the regioisomeric iodide **191** to obtain **202**. Presumably, the proximate silyloxy substituent in



202

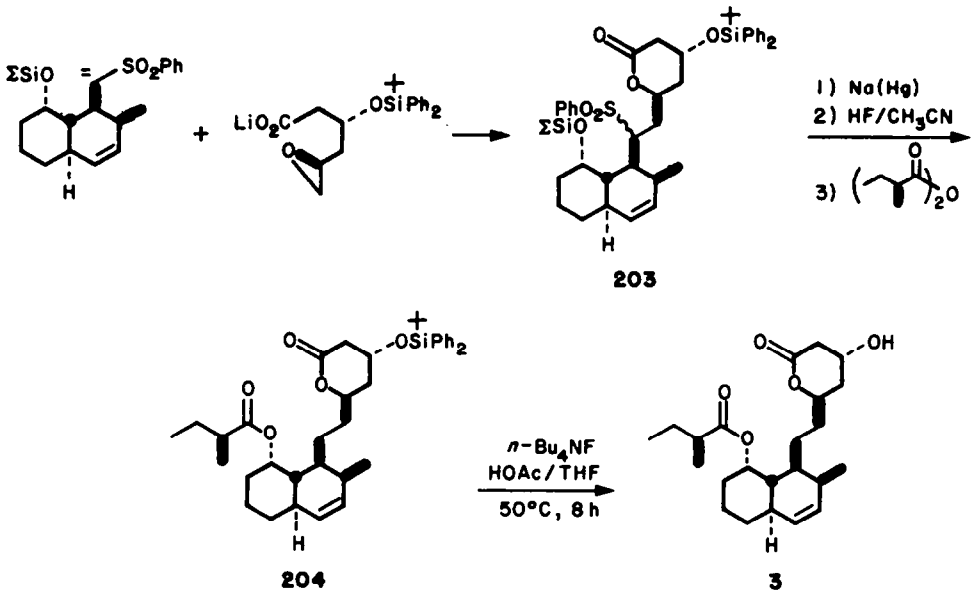
191 acts to coordinatively assist the alkylation. However, alkylation of the dianion of **179** with the lithium carboxylate of **199** is successful (Scheme 33); adduct **203** is obtained in 51% yield along



194 **195** **196** **197**

198 **199**

Scheme 32.

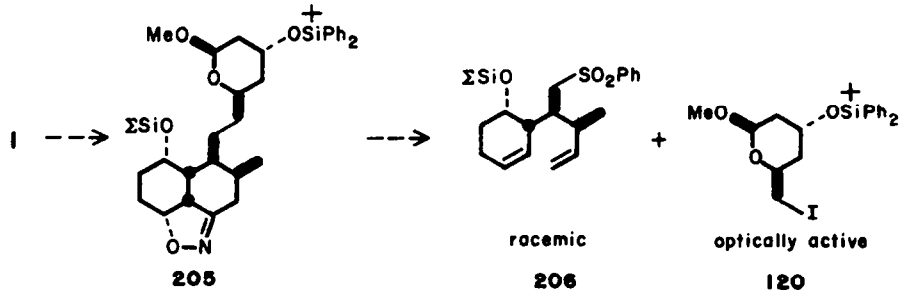


Scheme 33.

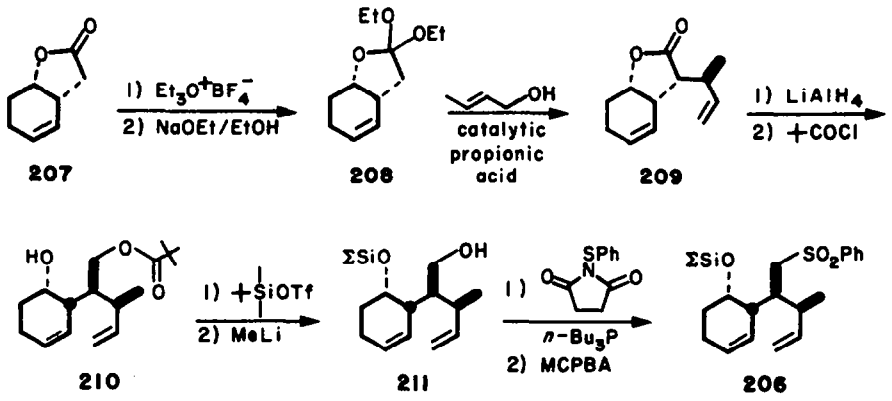
with recovered **179** (10%). Epoxide **199** is less sterically hindered than iodide **193** and is not prone (being an epoxide) to the β-elimination reaction that gives **201**. Desulfonylation is accomplished with sodium amalgam (60% yield). Subsequent selective desilylation (quantitative) and acylation (78%) provides **204** which is desilylated to give dihydrocompactin (94%). Similarly, the dianion of **164** undergoes alkylation with the lithium carboxylate of **199** (43% yield, 15% recovered **164**), and the resulting adduct is elaborated, without incident, to give compactin.

Kozikowski and Li have completed a synthesis of compactin in which an isoxazoline ring, generated by an intramolecular nitrile oxide cyclization (INOC), functions as a synthon for the 1,3-diene function of the hexalin portion of the molecule.[41] Their retrosynthetic analysis is shown in Scheme 34. The preparation of sulfone **206** is depicted in Scheme 35. Conversion of γ-lactone **207**[42] to its *ortho* ester (**208**) followed by treatment with crotyl alcohol in the presence of catalytic propionic acid gives the Claisen product **209** (75% yield, 5 : 1 diastereomer ratio). Reduction of lactone **209** followed by blocking of the primary alcohol affords hydroxy pivaloyl ester **210** which is silylated and treated with excess methyllithium to produce monoprotected diol **211**. Conversion of the hydroxyl function to the corresponding phenyl sulfone gives **206** in an efficient 49% overall yield from **209**.

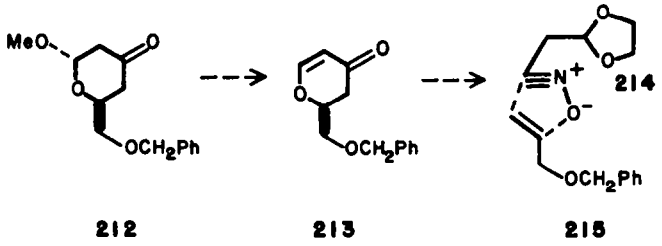
Kozikowski and Li's retrosynthetic analysis of a lactone synthon is shown in Scheme 36.[43] The strategy employed involves dipolar cycloaddition of the nitrile oxide **214** to dipolarophile **215** which provides a masked β-keto aldehyde unit. Subsequent unmasking of this unit followed by cyclization is expected to provide **213**, a viable synthon for **212**. Application of this strategy is shown in Scheme 37. Treatment of the known bromoacetal derived from acrolein and ethylene glycol with $NaNO_2$ provides **216**. Reaction of this nitro compound with allyl benzyl ether (PhNCO, Et_3N) gives



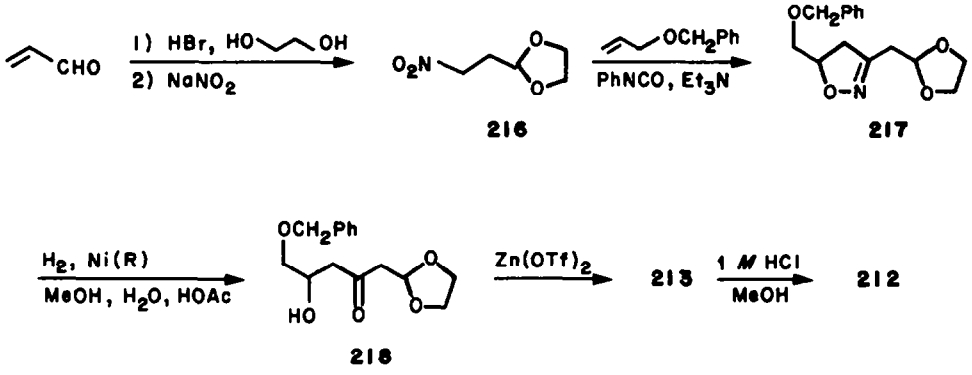
Scheme 34.



Scheme 35.



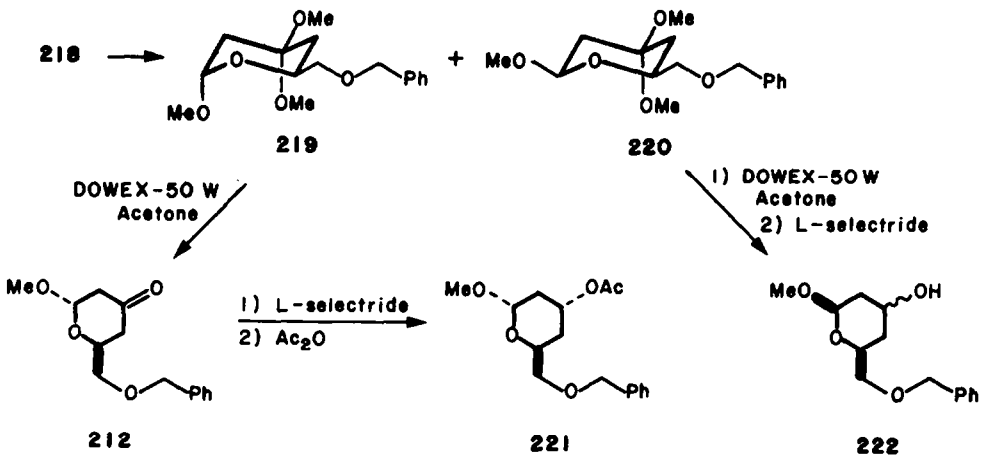
Scheme 36.



Scheme 37.

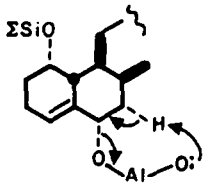
cycloadduct **217** in 85% yield. Hydrogenation of isoxazoline **217** furnishes β-keto dioxolane **218** which is cyclized with methanolic HCl to obtain pyranone **213** in low yield.† In an effort to optimize this cyclization, **218** was stirred with Dowex-50W acidic ion exchange resin (Scheme 38) to furnish a mixture of **219** (major isomer) and **220** which were separated. Deketalization of **219** affords **212** (quantitative) which gives **221** upon L-Selectride reduction and acetylation. However, deketalization of **220** followed by reduction gives a diastereomeric mixture of alcohols **222**. Thus, it was necessary to prepare **212** or **219** stereospecifically. Treatment of **218** with $Zn(OTf)_2$ produces **213** in high yield. It was found that addition of a solution of **213** to 1 M methanolic HCl (15 min) produces, after quenching with $NaHCO_3$, **212** in 79% yield along with minor amounts of **219** and **220**. Extension of this route to the preparation of an optically active synthon is shown in Scheme 39. Reaction of

†It should be noted that Danishefsky and co-workers had previously reported a one-step preparation of **213**, and also converted it via acetal **212** into **221** (Scheme 38).[44a]

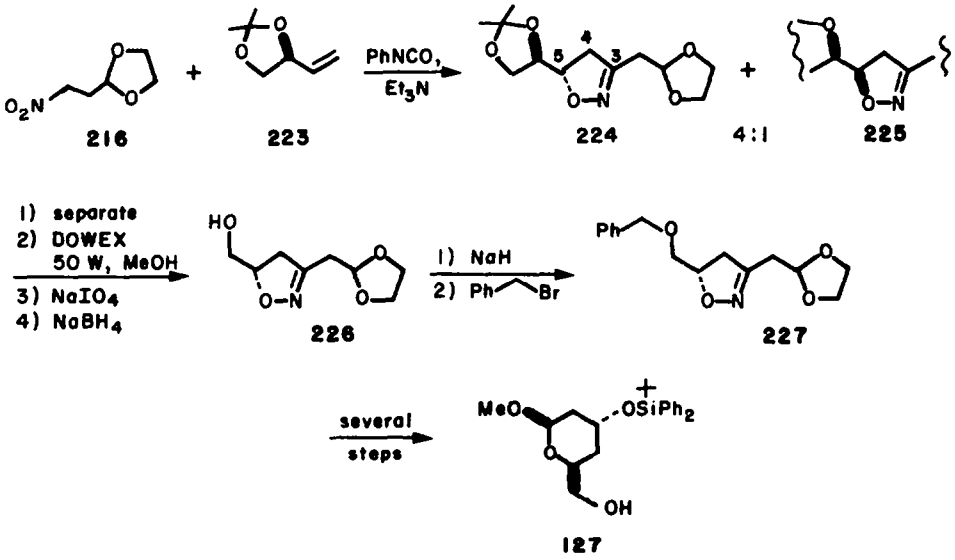


Scheme 38.

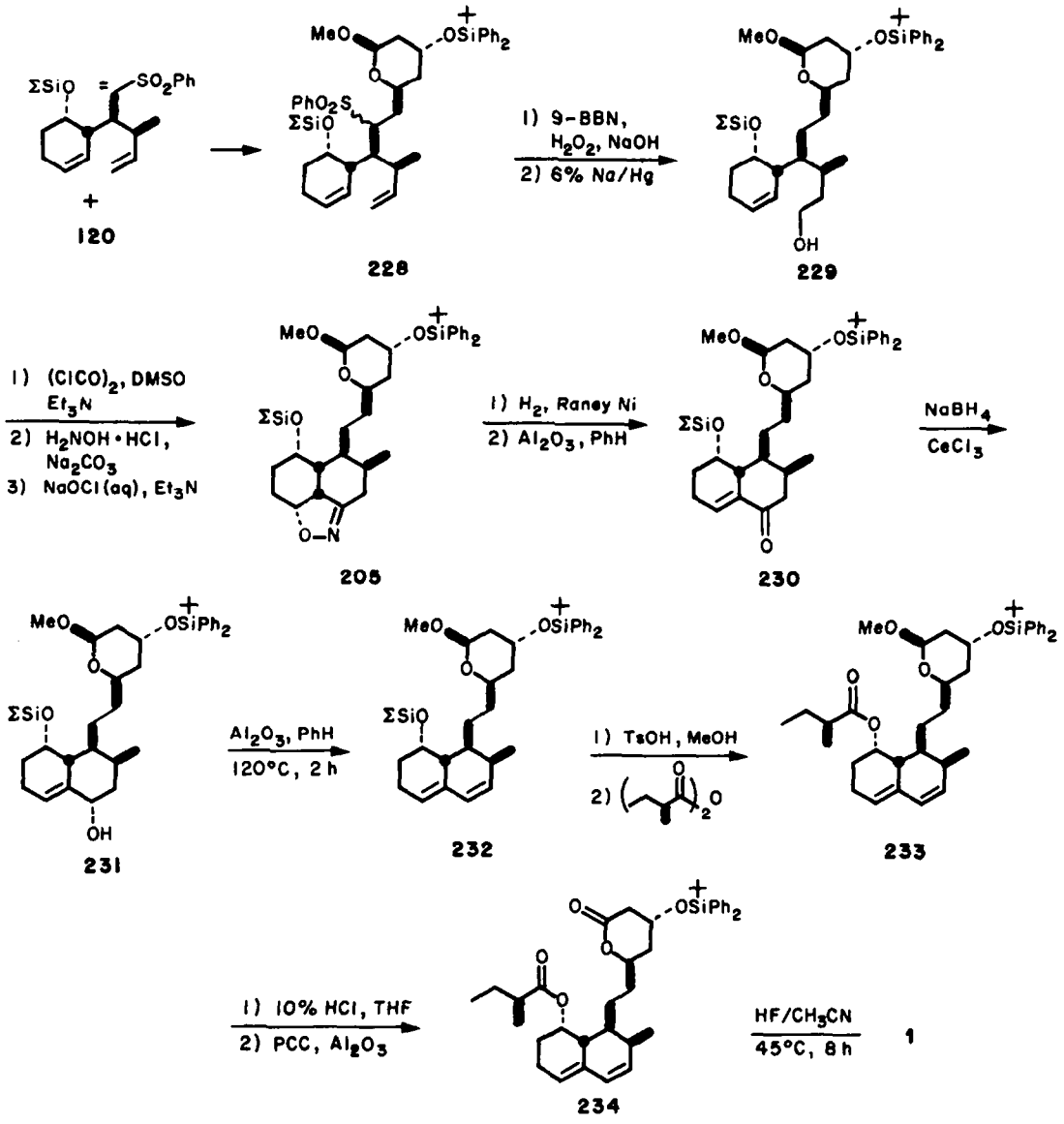
nitroacetal **216** and D-glyceraldehyde derived olefin **223** (PhNCO, Et_3N) produces a 4 : 1 mixture of diastereomers, the major isomer possessing the proper absolute stereochemistry at C-5 of the isoxazoline ring for ultimate elaboration to **127**; this result is precedented based on earlier studies on additions of nitrile oxides to **223**.[45] Deprotection of **224** followed by a two-step oxidative cleavage/reduction sequence furnishes **226** which is benzylated to obtain **227**. After several steps, **227** is converted to the optically active alcohol **127** prepared earlier by Falck.



Coupling of the dianion of the racemic sulfone **206** with optically active iodide **120** gives **228** and the corresponding diastereomer which are chromatographically separable (Scheme 40). Hydroboration of the terminal olefin followed by reductive desulfonylation gives alcohol **229**. Oxidation, conversion to the corresponding oxime and INOC reaction furnishes the isoxazoline **205** in 47% yield from **229**. The isoxazoline ring is hydrogenated and the resulting β-hydroxy ketone



Scheme 39.

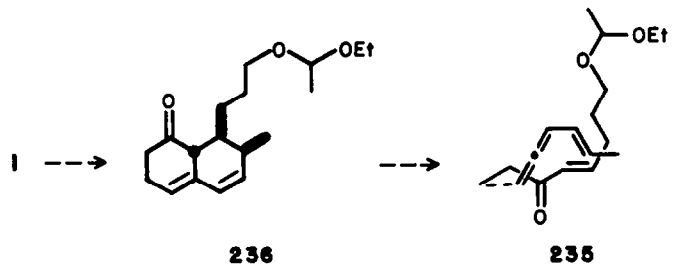


Scheme 40.

dehydrated to obtain **230** in 55% yield. Reduction of this enone (100%) and dehydration of the resulting allylic alcohol (**231**) with aluminum oxide regioselectively provides diene **232** (45%). It is suggested that the observed selectivity in the dehydration reaction results from complexation of the aluminum center to the oxygen atom of the alcohol and subsequent elimination via a cyclic six-membered transition state. Cleavage of the t-butyldimethyl silyl ether and acylation provides **233** in 57% yield. Hydrolysis of the methyl glycoside and oxidation of the resulting hemiacetal gives **234** (51%) which is deprotected to obtain the natural product (**1**).

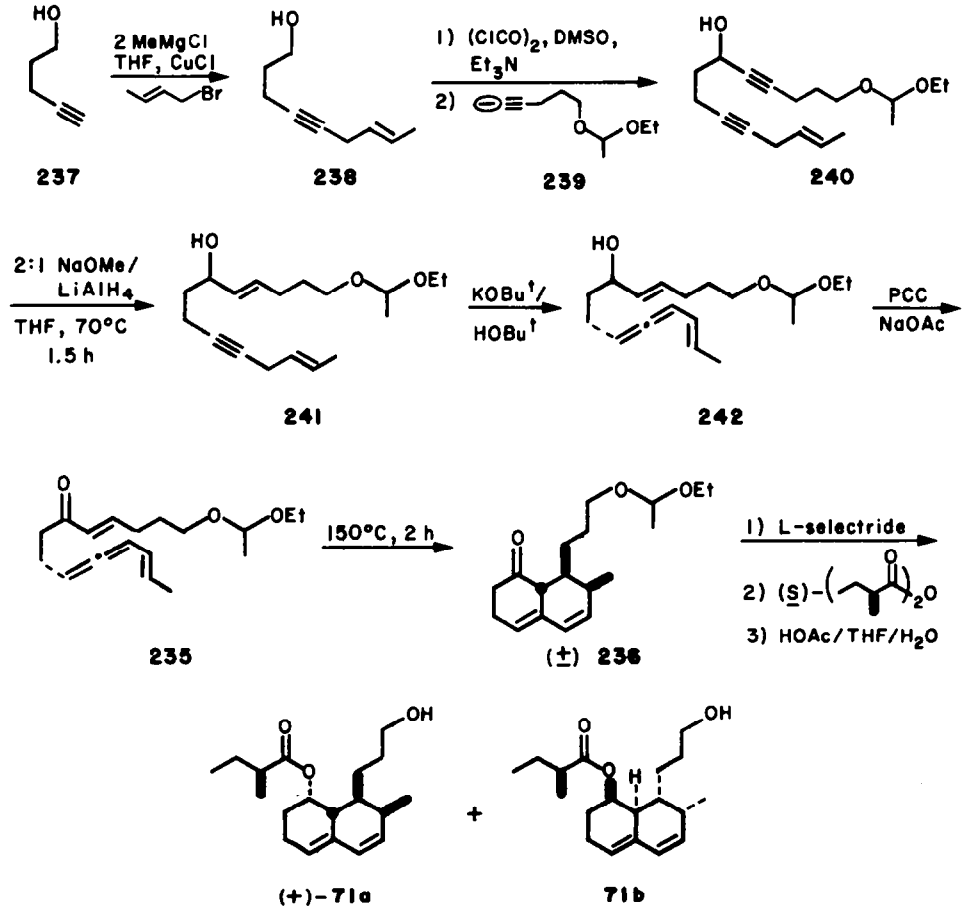
SYNTHESIS OF THE HEXALIN AND OCTALIN UNITS OF 1–4

Deutsch and Snider have chosen an approach to the hexalin portion of **1** in which the key transformation is the intramolecular Diels–Alder reaction of vinylallene **235** (Scheme 41).[46a] Although the use of vinylallenes as dienes in Diels–Alder reactions is well known, the intramolecular variant is rare, and stereochemical information is not available. Examination of models suggested that cyclization of **235** would lead to the *exo* adduct **236** due to steric constraints imparted by the rigidity of the allene function, thus establishing the diene and three of the four chiral centers present in the hexalin unit in a single synthetic manipulation.



Scheme 41.

The construction of **235** is outlined in Scheme 42. Alkylation of the dianion of 4-pentyn-1-ol (**237**) with crotyl bromide gives a 10 : 1 mixture of enyne **238** and the product derived from S_N2' alkylation. Swern oxidation of the mixture affords the corresponding mixture of aldehydes, which is treated directly with the magnesium acetylide of the ethoxyethyl ether of 4-pentyn-1-ol (**239**) to obtain, after chromatographic purification, diyne **240** (60% yield from **237**). Selective reduction of **240** furnishes allylic alcohol **241** in 90% yield. Base-catalyzed isomerization of **241** gives a mixture of products which contains about 50% of allene **242** along with conjugated enynes and unreacted **241**. Oxidation affords Diels–Alder precursor **235** which cyclizes upon heating to give **236**; no isomeric Diels–Alder adducts are detected. Immediate reduction with L-Selectride provides the corresponding axial alcohol in 30% yield from **241**. Subsequent acylation with (*S*)-2-methylbutyric anhydride and hydrolysis of the ethoxyethyl ether gives a mixture of optically-active esters **71a** and **b**, which have been separated.[22] Alcohol **71a** is an intermediate in Sih's compactin synthesis.

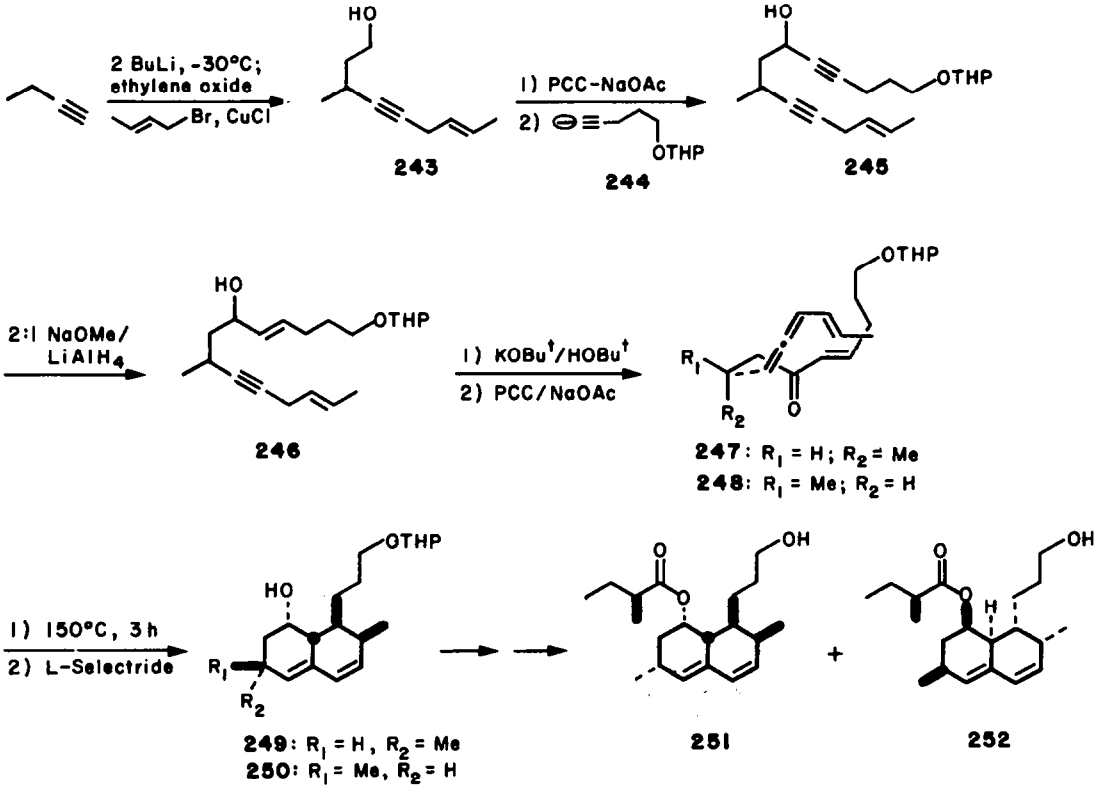


Scheme 42.

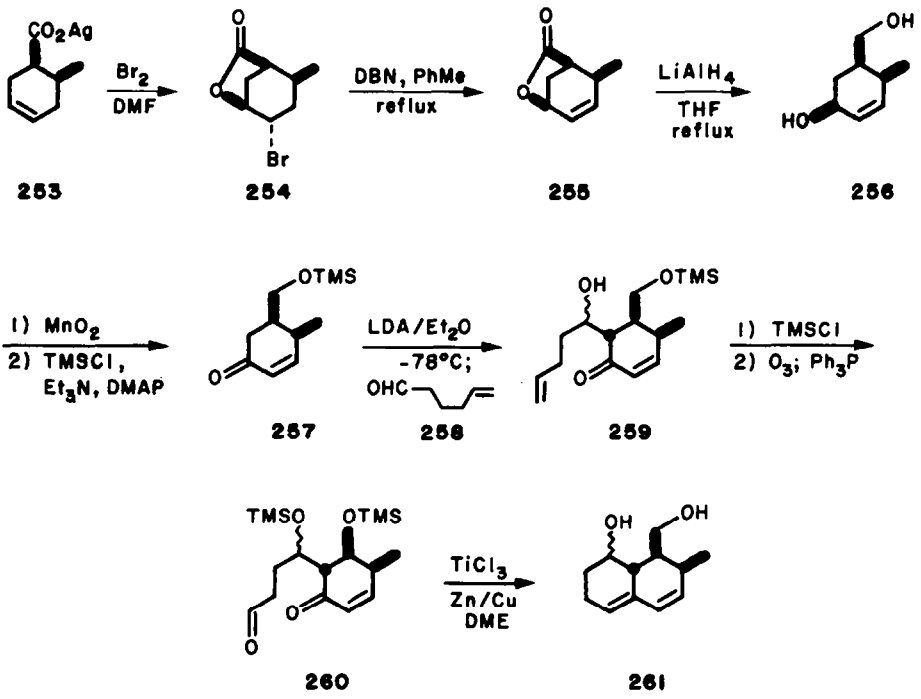
Deutsch and Snider have extended this approach to a synthesis of the hexalin portion of mevinolin (Scheme 43).[46b] Treatment of the dianion of 1-butyne with ethylene oxide followed by coupling with crotyl bromide gives enyne **243** in 55% yield. Oxidation to the corresponding aldehyde and addition of acetylide **244** furnishes alcohol **245** in 50% yield. Reduction of **245** gives a mixture of **246** and material which has already isomerized to the allene in 90% yield. Base-catalyzed isomerization of this mixture gives a mixture which contains about 50% of allene along with conjugated enynes and unreacted **246**. Oxidation of this crude material provides a 1 : 1 mixture of diastereomeric allenes **247** and **248** (80% yield). Thermolysis of **247** and **248** and subsequent reduction with L-Selectride gives, after chromatographic purification, **249** and **250** (each in 5% yield from **245**). Esterification of **249** with (*S*)-2-methylbutyric anhydride and deprotection produces optically active esters **251** and **252**, which are separated by reverse phase HPLC, in 46% yield.

Clive and co-workers have assembled a racemic hexalin unit as summarized in Scheme 44.[47] Bromolactonization of the silver carboxylate **253** gives bromide **254** (76% yield). This material is treated with DBN in toluene to obtain the unsaturated lactone **255** in 89% yield. Lithium aluminum hydride reduction gives diol **256** (91% yield). Selective oxidation of the allylic hydroxyl and protection of the primary alcohol gives silyloxy enone **257** (83%). Kinetic deprotonation of **257** and subsequent condensation with 4-pentenal provides **259** as a diastereomeric mixture of aldols in about 80% yield. Protection of the secondary alcohol (89% yield) and ozonolysis of the terminal olefin produces keto aldehyde **260** (76%) which undergoes an intramolecular McMurry reaction upon treatment with low valent titanium to afford the target diene **261** (72% yield, 1.3 : 1 mixture of isomers). Clive and co-workers note that it is likely that both the **8α** and **8β** isomers can serve as precursors to compactin, since precedent strongly suggests that the corresponding ketone will be reduced selectively from the β face of the molecule.

Burke *et al.* have published a conceptually unique synthesis of the octalin portion of dihydrocompactin utilizing a vinylsilane-mediated polyene cyclization and variants of the Claisen rearrangement for regio- and stereochemical control.[48] Their retrosynthetic analysis is shown in Scheme 45. Two routes to the precursor of **263** are summarized in Scheme 46. Condensation of



Scheme 43.

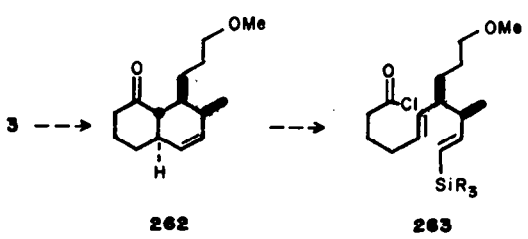


Scheme 44.

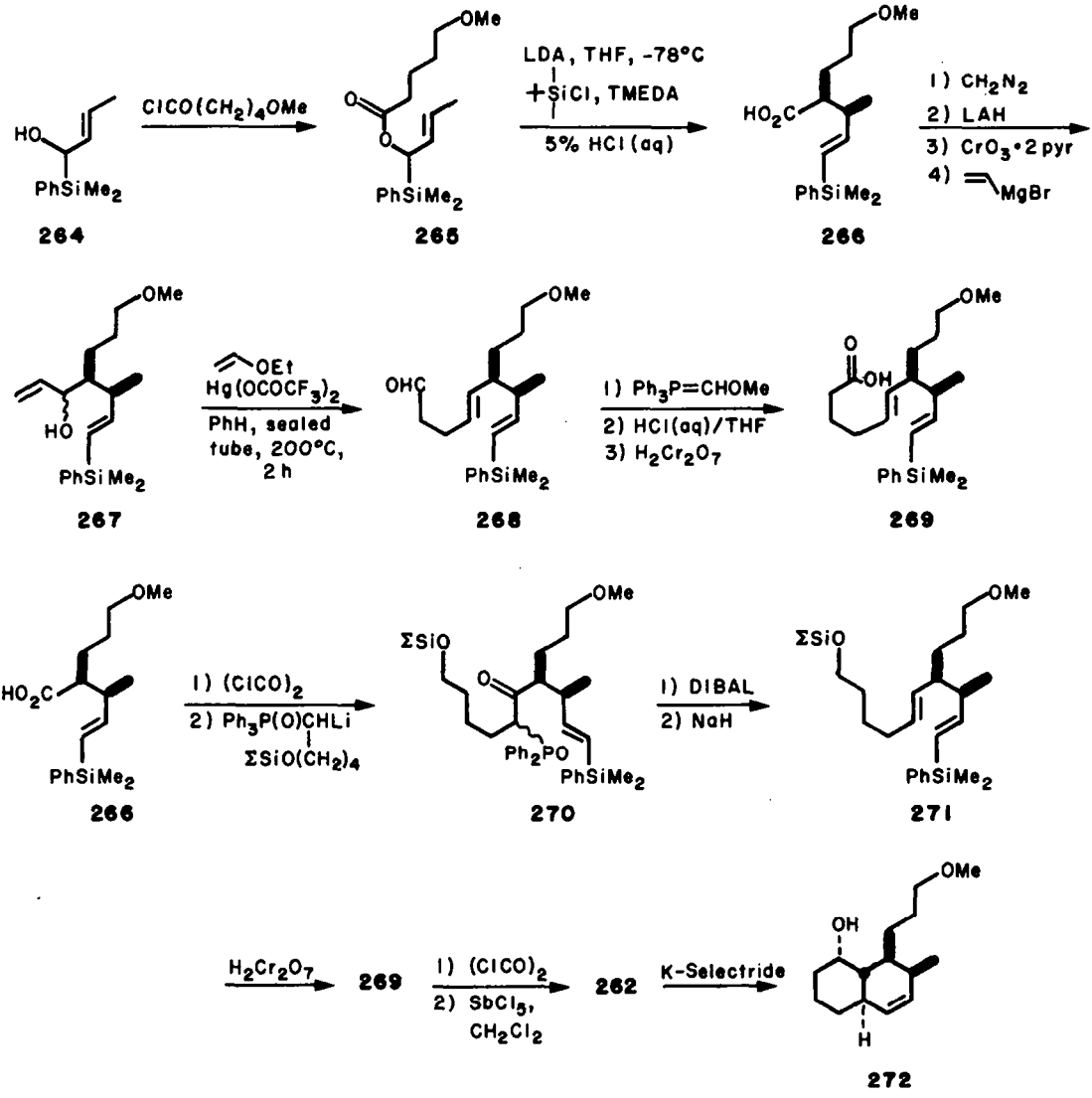
phenyldimethylsilyllithium and *trans*-crotonaldehyde gives allylic alcohol **264** in 55% yield. Acylation (87% yield) followed by ester enolate Claisen rearrangement, using the Ireland protocol, gives diastereomer **266** in a ratio of 42:1. This ratio reflects the *trans/cis* isomeric purity of the crotonaldehyde. Esterification with diazomethane (64% from **265**), two-step conversion to the corresponding aldehyde (89%), and addition of vinylmagnesium bromide gives diastereomeric alcohols **267** (75%) which converge to a single aldehyde (**268**) (81% yield). Wittig homologation and hydrolysis (98%) followed by oxidation of the resulting aldehyde produces the carboxylic acid **269**.

The second route to **269** begins with the coupling of the acid chloride derived from **266** and [1-litho-5-(t-butyldimethylsilyloxy)pentyl]diphenylphosphine oxide to give **270** (83%). Ketone reduction and subsequent reaction with NaH furnishes diene **271**; exposure of **271** to Jones' reagent results in silyl ether cleavage and oxidation to the corresponding carboxylic acid **269** (85%). Compound **269** is converted to its acid chloride and treated with $SbCl_5$ to induce cyclization. The desired octalone (**262**) is isolated in 51% yield; subsequent reduction with K-Selectride affords axial alcohol **272** (74%).

Funk and Zeller have completed a synthesis of the hexalin portion of (+)-mevinolin, employing a strategy closely related to that developed for their synthesis of **1** (Scheme 47).[40] The known enone **273** is available in optically pure form from (+)-pulegone.[49] Addition of vinylmagnesium bromide (95%) and acid-catalyzed rearrangement of the resulting adduct (**274**) affords **275** (70% yield) as a mixture of epimers. Oxidation of the mixture followed by reduction with $LiAlH_4$ produces alcohol

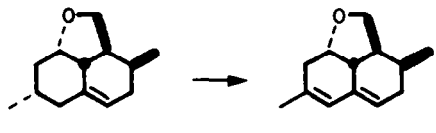


Scheme 45.



Scheme 46.

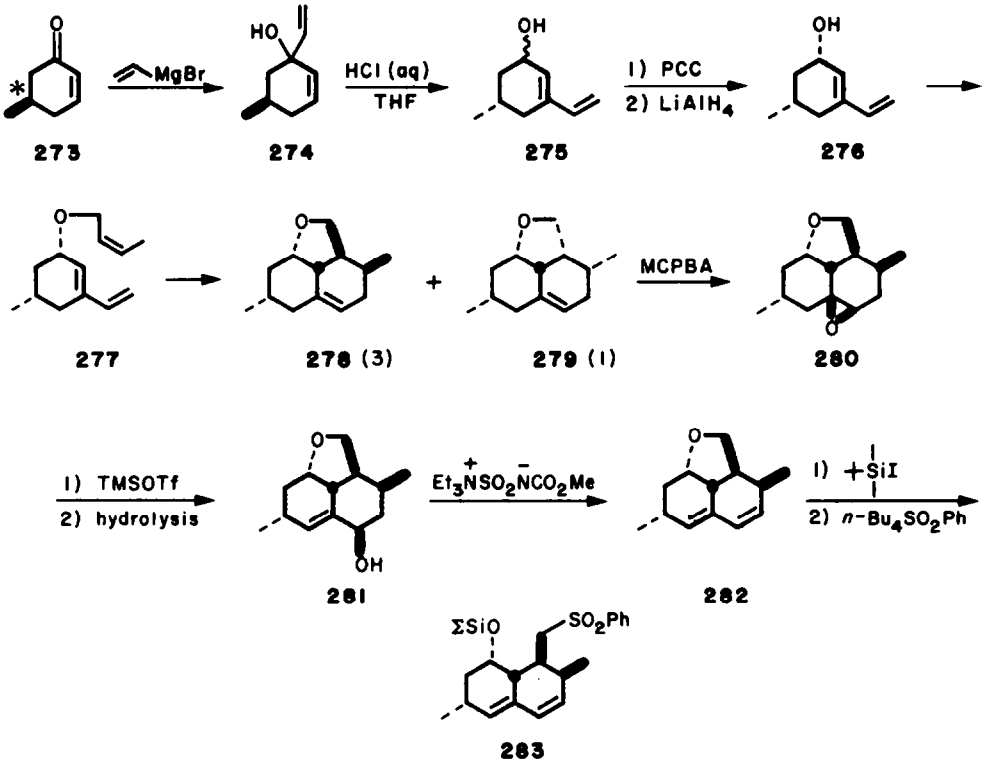
276 and the epimeric *trans*-alcohol in a ratio of 19 : 1. Conversion of **276** to triene **277** is accomplished using the protocol developed earlier; cyclization of **277** produces a 3 : 1 mixture of cycloadducts **278** and **279**. The bromination–dehydrobromination sequence which was successful for the synthesis of the hexalin portion of compactin provides, in this case, predominantly the more substituted diene isomer **284** (Eq. 5). Thus, an alternative procedure was developed. Epoxidation of **278** furnishes



278 284 (5)

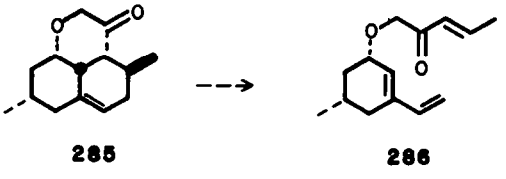
280 which reacts with trimethylsilyl triflate to provide, after hydrolysis, the allylic alcohol **281** (70% yield from **280**). Treatment of **281** with Burgess' salt affords the desired diene in 78% yield. Regiospecific cleavage of the tetrahydrofuran ring with t-butyldimethylsilyl iodide and conversion to the derived sulfone gives the desired hexalin **283**.

An approach to the synthesis of the hexalin skeleton of mevinolin that is conceptually similar to that of Funk's has been investigated in our group.[50] In order to circumvent the problems associated with the thermal cyclization of **155**, the plausibility of inserting a methylene unit between the "acyl"

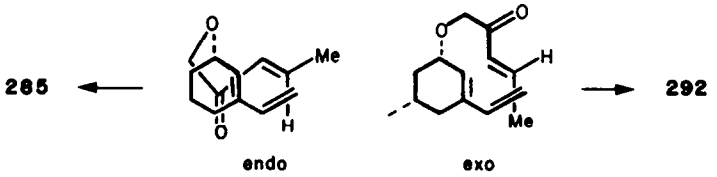


Scheme 47.

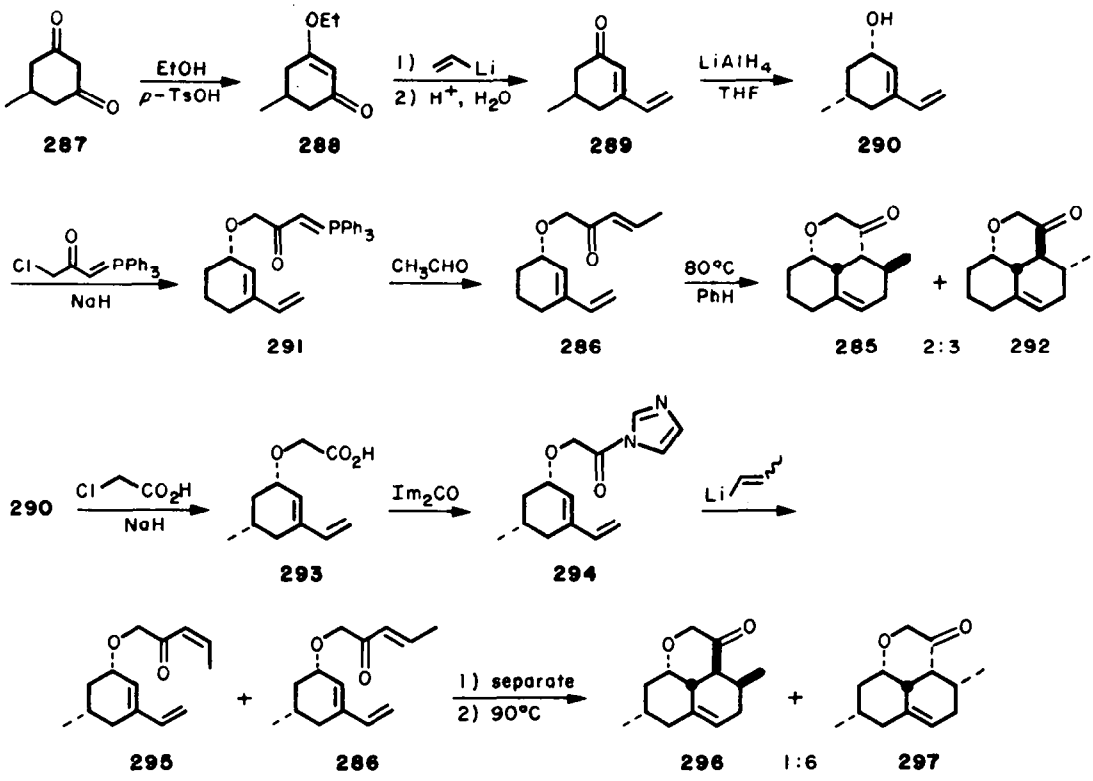
and "alkoxy" units of ester **155** was examined. This strategy would disfavor fragmentation since the leaving group would be alkoxide as opposed to carboxylate. Cyclization of **286** through an *endo* transition state would provide pyranone **285**, and the additional carbon atom could be retained or



excised during appropriate modification to a suitable synthon for coupling with a lactone fragment. The synthesis of **286** is shown in Scheme 48. Addition of vinyllithium to the ethyl enol ether of dihydroorcinol followed by acidic hydrolysis affords dienone **289** in 91% yield. Lithium aluminum hydride reduction of **289** gives alcohol **290** (74%) which is alkylated to obtain stabilized phosphorane **291** (65%). Treatment of **291** with acetaldehyde gives *trans*-enone **286** in 65% yield. However, Diels–Alder cyclization of **286** gives a 2:3 ratio of *endo* (desired) and *exo* (undesired) adducts **285** and **292**. Inspection of the *exo* and *endo* transition states leading to **285** and **292** suggests that there is

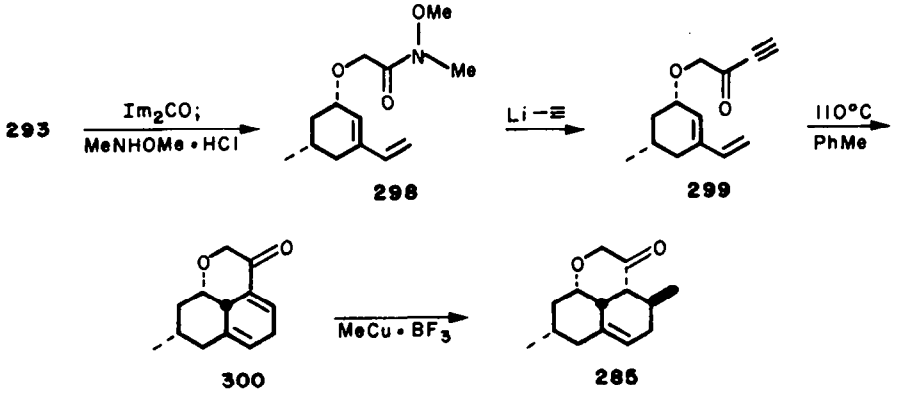


an unfavorable eclipsing interaction between the β-methyl of the enone and vinyl terminus of the diene in the *exo* mode of cyclization. Thus, it was hypothesized that removal of this interaction might lead to a greater preference for the *exo* product. Furthermore, the *cis*-enone **295** would not only eliminate this interaction in the *exo* transition state, but it would incorporate a similar interaction in the *endo* transition state. Thus, **295** was prepared as shown in Scheme 48. Alkylation of **290**



Scheme 48.

with chloroacetic acid affords carboxylic acid **293** in 81% yield. Conversion to the corresponding imidazolide and subsequent treatment with a mixture of (*E*)- and (*Z*)-propenyllithium provides a mixture of **295** and **286** which are separated by column chromatography. Thermal cyclization of **295**, however, produces a 6:1 mixture of adducts **297** and **296**; the major product results from the *endo* mode of cyclization. These results required that an alternative strategy be employed in order to circumvent the problem of stereochemical control (Scheme 49). Carboxylic acid **293** is converted to N-methoxy, N-methyl amide **298**. Reaction of **298** with lithium acetylide/ethylene diamine complex provides acetylenic ketone **299** which is immediately heated in toluene to obtain dienone **300** (60% from **293**). Treatment of this dienone with methylcopper–boron trifluoride complex gives exclusively the product of axial addition, pyranone **285**. Application of intermediate **285** in a synthesis of dihydromevinolin is reported in the Addendum.



Scheme 49.

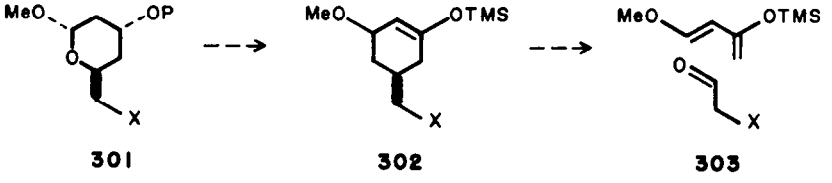
SYNTHESIS OF THE LACTONE MOIETY

In the early studies on the Lewis acid catalyzed cyclocondensation of silyloxy dienes with aldehydes, Danishefsky *et al.* described an application of the process to the synthesis of the masked pyranone segment of compactin.[44a] The synthetic strategy is shown in Scheme 50. Silyl enol ether **302**, the product of formal cycloaddition of heterodienophile **303** and Danishefsky's diene, is envisioned as a precursor to **301**.

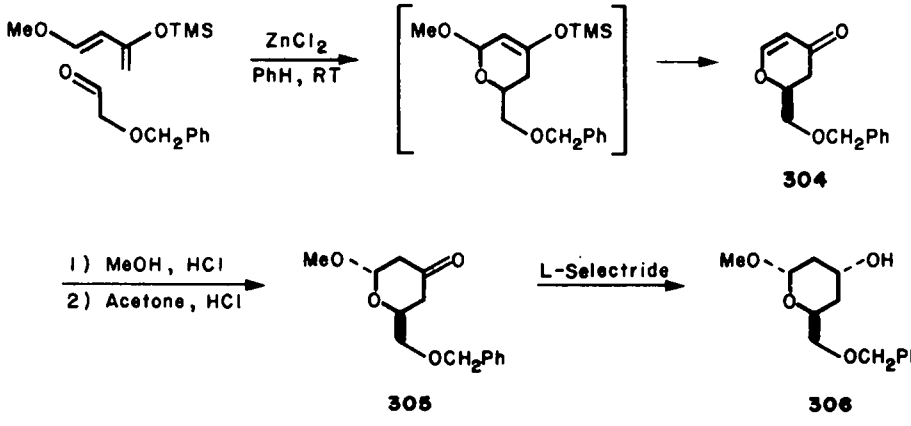
To this end, reaction of benzyloxyacetaldehyde and 1-methoxy-3-trimethylsilyloxybutadiene in the presence of anhydrous zinc chloride proceeds to give adduct **304** in 87% yield (Scheme 51). Treatment of **304** with methanolic hydrochloric acid produces a methyl glycoside with concomitant ketalization (69% yield); deketalization with acetone containing a trace of HCl affords **305**. Reduction of **305** with L-Selectride proceeds with selective equatorial delivery of hydride to give the desired racemic synthon (**306**) in 88% yield. By starting with the acetonide of glyceraldehyde, rather than with benzyloxyacetaldehyde, the synthesis may be manipulated so as to provide an optically-active, protected version of **306**.[44b]

Prugh and Deana of Merck have described the preparation of an optically active lactone synthon utilizing D-glucose as the educt (Scheme 52).[51] The known benzylidene **184** is obtained readily in four steps from α-D-glucopyranoside (**307**). Benzylation of the secondary alcohol provides **308**. Hydrolysis of the benzylidene group gives a diol which is selectively protected to give hydroxy trityl ether **309**. Tosylation and hydrolysis of the trityl ether gives **310**, which is reduced with sodium borohydride in DMSO (4 days, 80°, 81% yield) to obtain the 2,4-dideoxy derivative **311** (this result is in contrast to attempted deoxygenation of a similar substrate by Funk (Scheme 31)). Sequential tosylation and iodide displacement afford the desired synthon. The authors reported that all new transformations in the synthetic sequence proceed in ⩾80% yield.

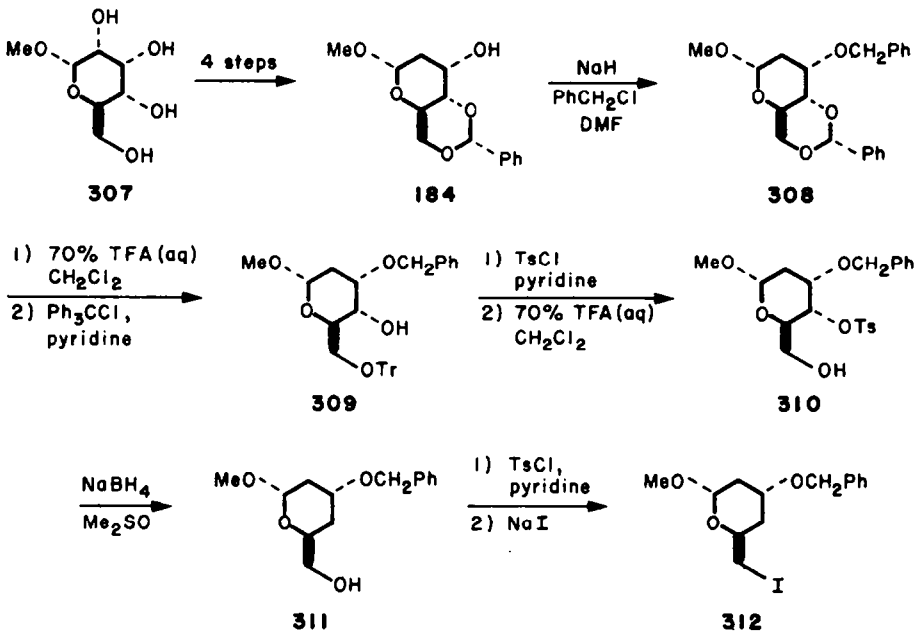
Prior to our successful synthesis of a series of lactone synthons derived from Corey epoxide (**85**), we investigated two alternative routes to optically active lactone synthons.[26] We first examined the possibility of employing D-gulono-γ-lactone as a precursor to **313** (Scheme 53). Carbohydrate **314** possesses the necessary absolute configuration at C-3 and C-5 and requires deoxygenation at the 2- and 4-positions. Thus, the known bis(acetonide) lactone **315** is saponified and the resulting hydroxy carboxylate converted directly to xanthate ester **316**. Application of the Barton deoxygenation



Scheme 50.



Scheme 51.



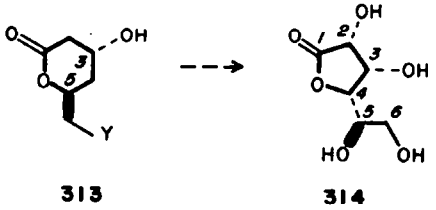
Scheme 52.

procedure to **316** provides the 4-deoxy product **317** in 70% yield from **315**. However, numerous attempts to remove the oxygen functionality at C-2 were unsuccessful. Treatment of **317** with lithium-bronze affords the desired alcohol (**318**), but the yield (10%) is unsatisfactory (Scheme 54).

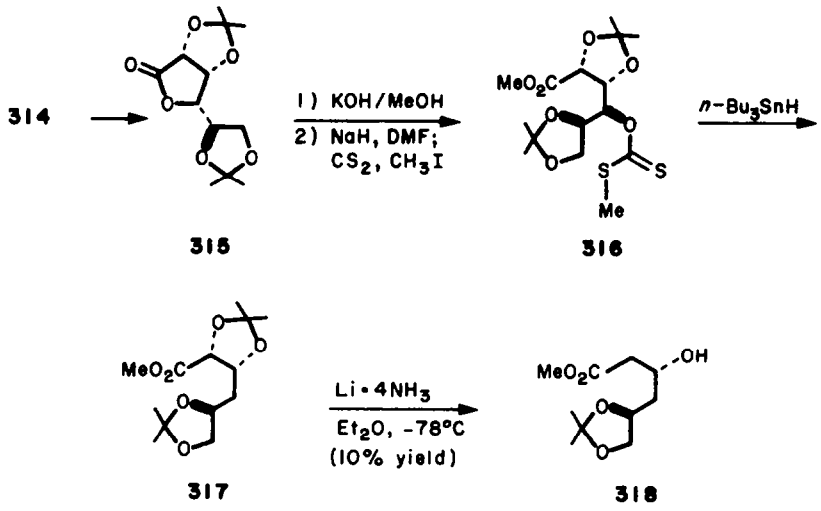
In an effort to circumvent this problem, we examined the feasibility of first deoxygenating C-2 of **315** and then applying the Barton procedure for the deoxygenation of the 4-position (Scheme 55). Reduction of γ-lactone **315** with diisobutylaluminum hydride provides hemiacetal **319** in a yield of 90%. Reaction of **319** with hexamethylphosphorus triamide and carbon tetrachloride and reduction of the resulting phosphonium chloride adduct (80% yield) and subsequent hydroxyl protection gives SEM ether **320**. Hydroxylation (74%) and oxidation (53%) produces lactone **321**. However, treatment of **321** with potassium hydroxide in methanol followed by attempted xanthate formation results in structural decomposition.

Because of these difficulties, we investigated the use of optically active aldehyde **194**, as a chiral educt for elaboration to the lactone synthon (Scheme 56). Addition of the lithium enolate of ethyl acetate to **194** and silylation of the resulting mixture of epimeric alcohols furnishes **323** in 88% yield. Lactonization (60% yield) and subsequent tosylation provides **324** and **325** which are separated easily by chromatography (91% combined yield). The inefficiency of having to perform this isomer separation led ultimately to our use of **85** as a starting point.

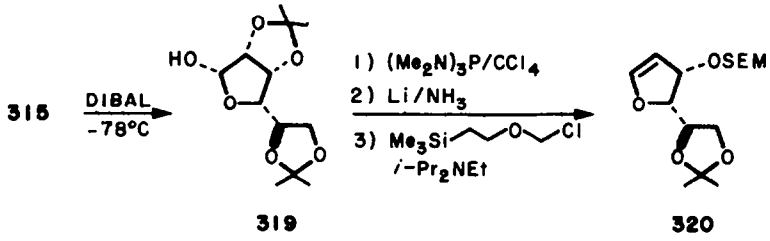
Clive and co-workers utilized L-malic acid derivative **326** as a precursor to lactone synthon **331** (Scheme 57).[52] Benzylation of **326** and hydrolysis of the acetonide affords monoprotected triol **327** in 86% yield. Mesylation and subsequent treatment with Triton B provides optically active epoxide **328** (65% yield), which is opened with vinylmagnesium bromide to obtain hydroxy olefin **329** in 92% yield. The lithium alkoxide of **329** is treated sequentially with carbon dioxide and iodine to

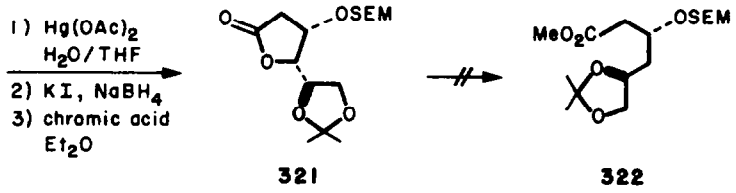


Scheme 53.

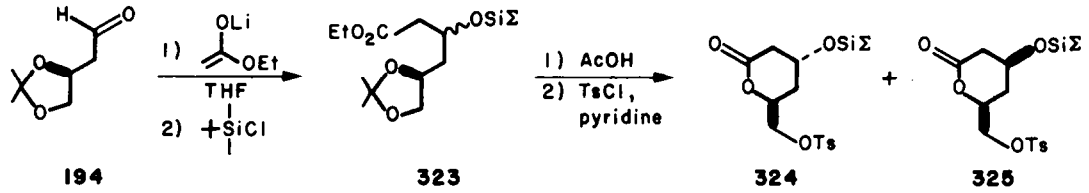


Scheme 54.



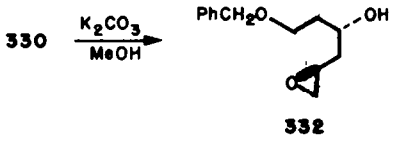


Scheme 55.

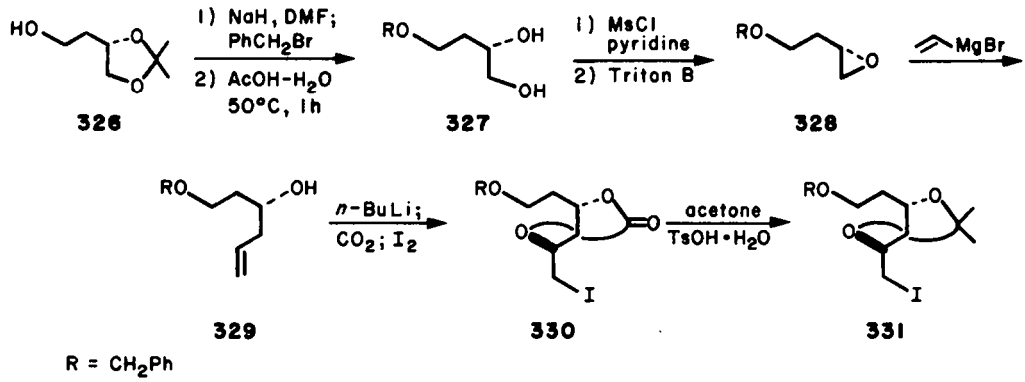


Scheme 56.

produce the 3*S*,5*S* iodo carbonate **330** in 69% yield. This material is contaminated with less than 10% of the 3*S*,5*R* isomer. Reaction of **330** with potassium carbonate in methanol gives epoxide **332**, also as a mixture of isomers (74% yield) (Eq. 6). However, hydrolysis of **330** with simultaneous acetonide formation followed by chromatographic purification gives isomerically pure ketal **331**.



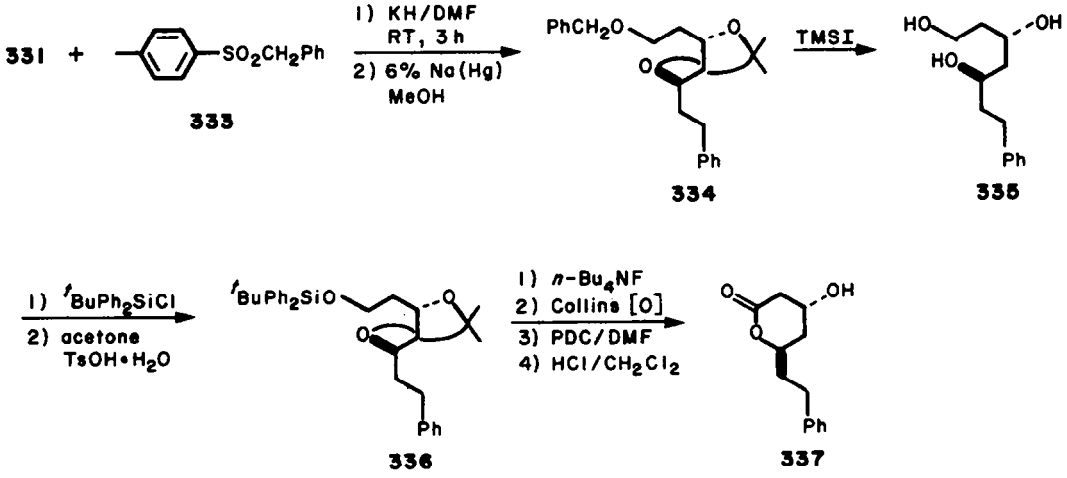
(6)



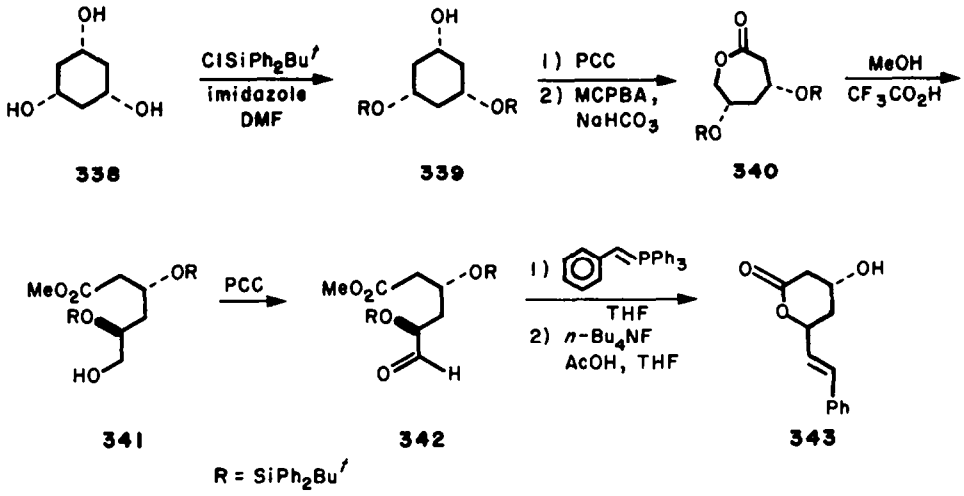
Scheme 57.

Clive and co-workers conducted model studies to find a method for elaboration of the masked lactone that will be compatible with the double bonds present in the natural product. The most efficient sequence is summarized in Scheme 58. Coupling of **331** and sulfone **333** followed by desulfonylation affords adduct **334** (78% yield), which is deprotected to give triol **335** (73% yield, 94% yield with one recycling of **334**). Oxidation of **335** with Fetizon's reagent (Ag_2CO_3/Celite) affords **337**, but the yield is only 20%. Therefore, a multi-step procedure is employed. Selective protection of the primary alcohol and acetonide formation produces **336**. Desilylation and subsequent oxidation and lactonization provides the desired lactone **337** in 33% overall yield from **335**.

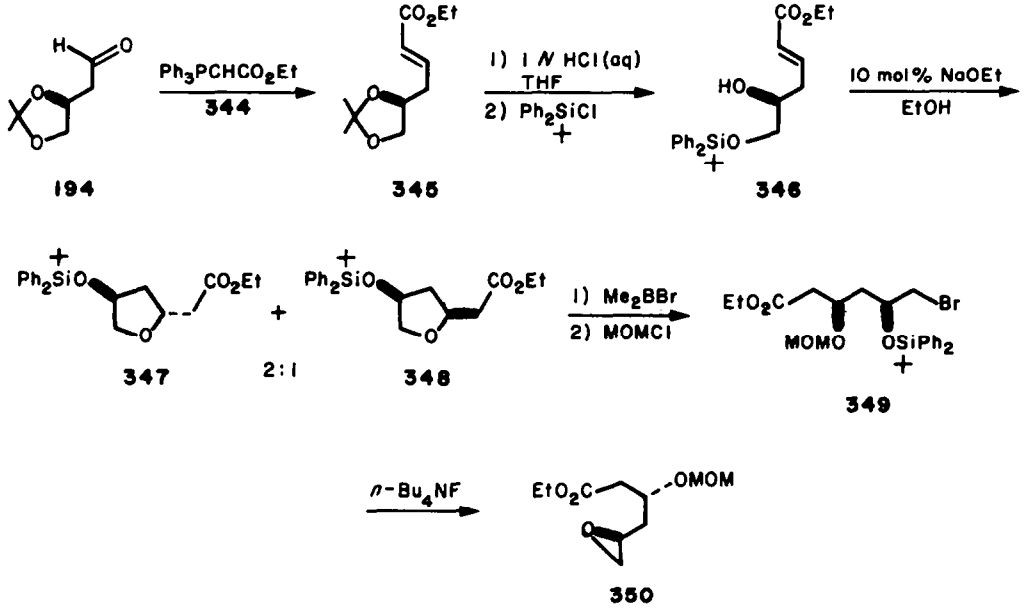
Prasad and Repic have published an approach to the lactone system that begins with *cis*-cyclohexane-1,3,5-triol (Scheme 59).[53] Conversion of the triol **338** to *bis* silyl ether **339** (40% yield) followed by PCC oxidation (93% yield) and Baeyer–Villager oxidation affords lactone **340** in 77% yield. Methanolysis and oxidation of the resulting hydroxy ester provides aldehyde **342** (95% yield). Wittig coupling (77% yield) and desilylation provides the unmasked lactone **343** in 45% yield. Guindon *et al.* at Merck Frosst, Canada, have synthesized an optically active synthon for the lactone portion of the mevinic acids, once again utilizing the (L)-malic acid derived aldehyde **194** (Scheme 60).[54] Condensation of **194** with stabilized phosphorane **344** provides unsaturated ester **345** in 84% yield. Hydrolysis of the acetonide moiety and selective silylation of the primary hydroxyl affords monoprotected diol **346**. Treatment of **346** with catalytic ethoxide establishes an equilibrium between **346** and its isomer **351**. Ensuing intramolecular Michael reaction displaces the equilibrium, and tetrahydrofurans **347** and **348** are obtained in 87% yield (2:1 ratio). Cleavage of **347** with dimethylboron bromide proceeds regiospecifically (82% yield) to produce, after protection, bromide **349** (94%). Cleavage of the silyl ether affords directly the desired epoxide **350** in 80% yield.



Scheme 58.



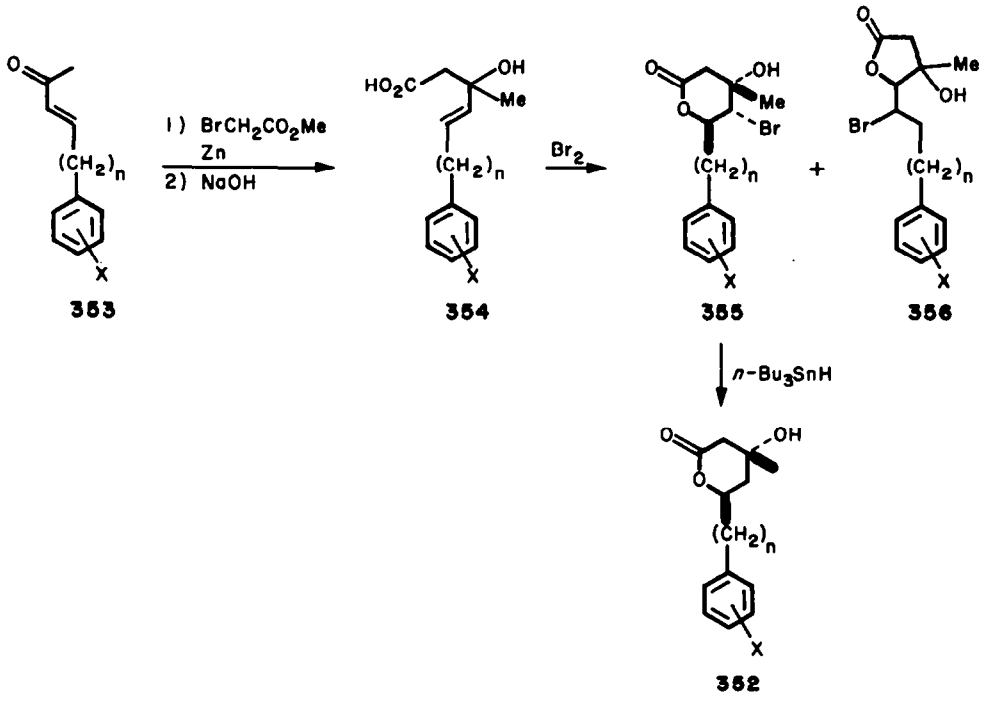
Scheme 59.



Scheme 60.

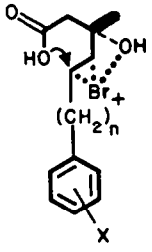
In related work, researchers at Sankyo Co. have prepared a number of racemic mevalonolactone derivatives of the general form **352**.[55] The strategy employed in the synthesis of these derivatives

involves the stereo- and regioselective halolactonization of acyclic γ,δ-unsaturated acids, anticipating neighboring group participation by the C-3 hydroxyl group (Scheme 61). Ketones **353** are prepared in good yield by Wittig condensation with the corresponding aldehydes. Reformatsky reaction



Scheme 61.

followed by basic hydrolysis affords the carboxylic acids (**354**). Treatment of **354** (X = H, $n = 2$) with Br_2 in a nonpolar solvent such as CCl_4 gives bromolactone **355** in low yield. However, in a polar solvent such as MeOH or DMF (0°, $NaHCO_3$), the same compound gives a mixture of **355**, a stereoisomer and a regioisomer **356**. At lower temperature (−70°), the bromolactonization occurs stereo- and regioselectively to give **355** in 70% yield along with a small amount of **356**. In some of

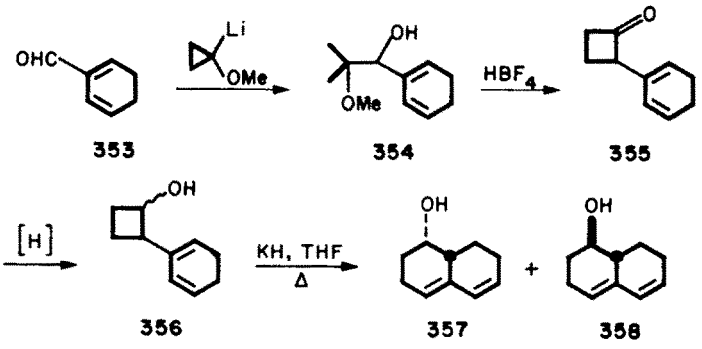


the numerous bromolactonizations examined, less stereoselectivity is achieved. The authors note that generally the halolactonization of γ,δ-unsaturated acids affords γ-lactones in preference to δ-lactones. The reversal of selectivity in their system, along with the stereoselectivity observed leads them to postulate a mechanism involving participation of the hydroxyl substituent. Thus, it is proposed that a cyclic bromonium ion associated with the hydroxyl group is generated and intramolecular attack of the carboxyl group occurs in this intermediate to selectively provide the observed product. Reduction of **355** with n-Bu_3SnH furnishes the desired mevalonolactone analog (**352**) in 83% yield.

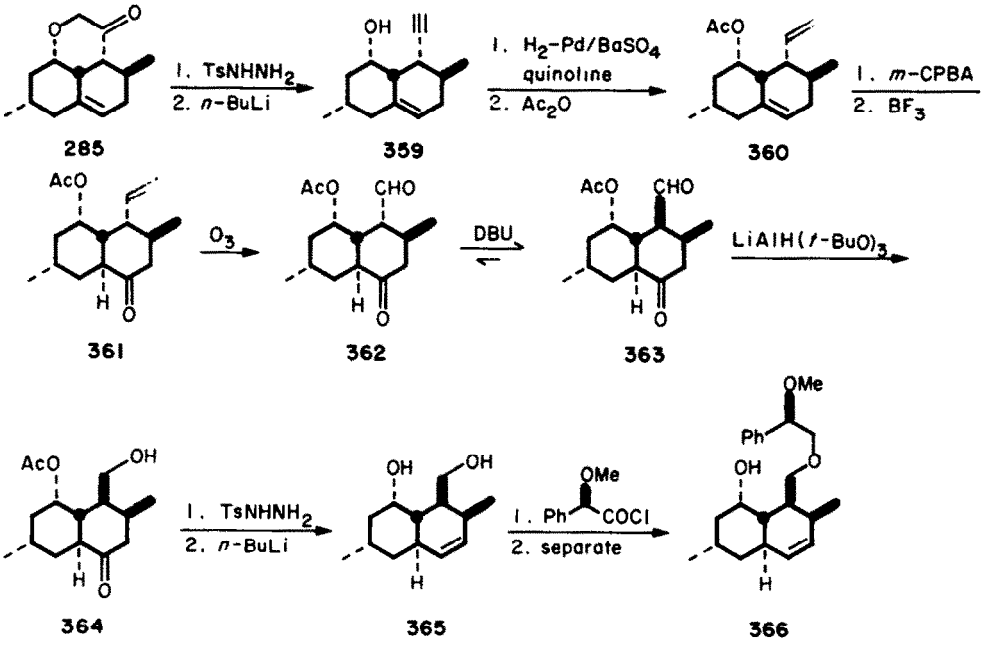
ADDENDUM

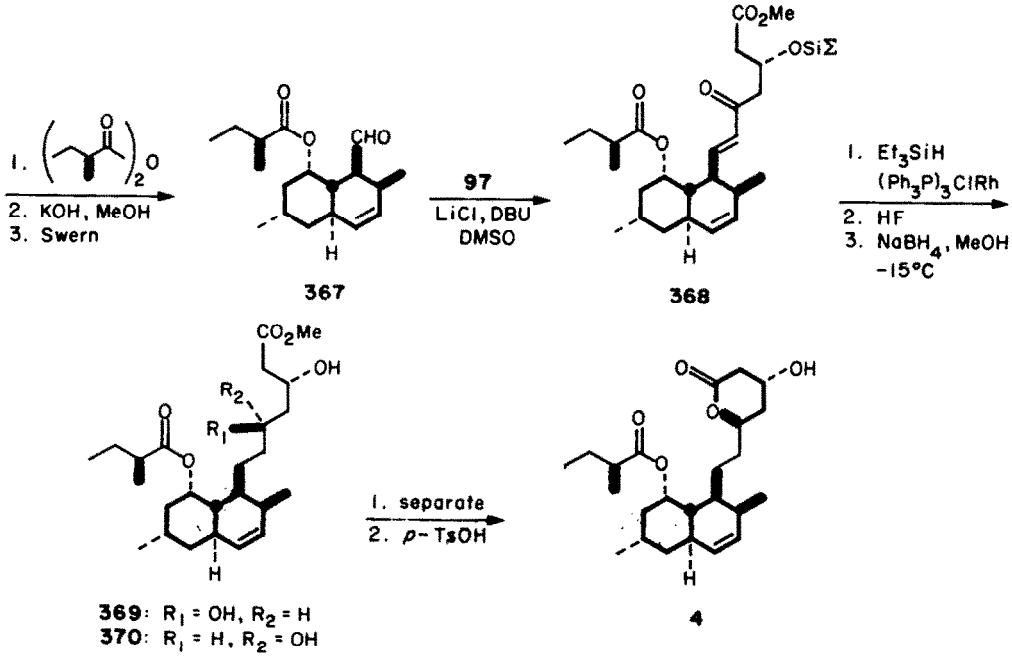
Since the initial submission of this report (July 1985), we have become aware of one additional pertinent paper, and several other relevant publications have appeared. In this section, we will briefly update the record as of March 1986.

Cohen *et al.* have reported the interesting study summarized in Scheme 62.[56] Addition of 1-lithio-1-methoxycyclopropane to aldehyde **353** provides **354**, which is rearranged by treatment with



Scheme 62.





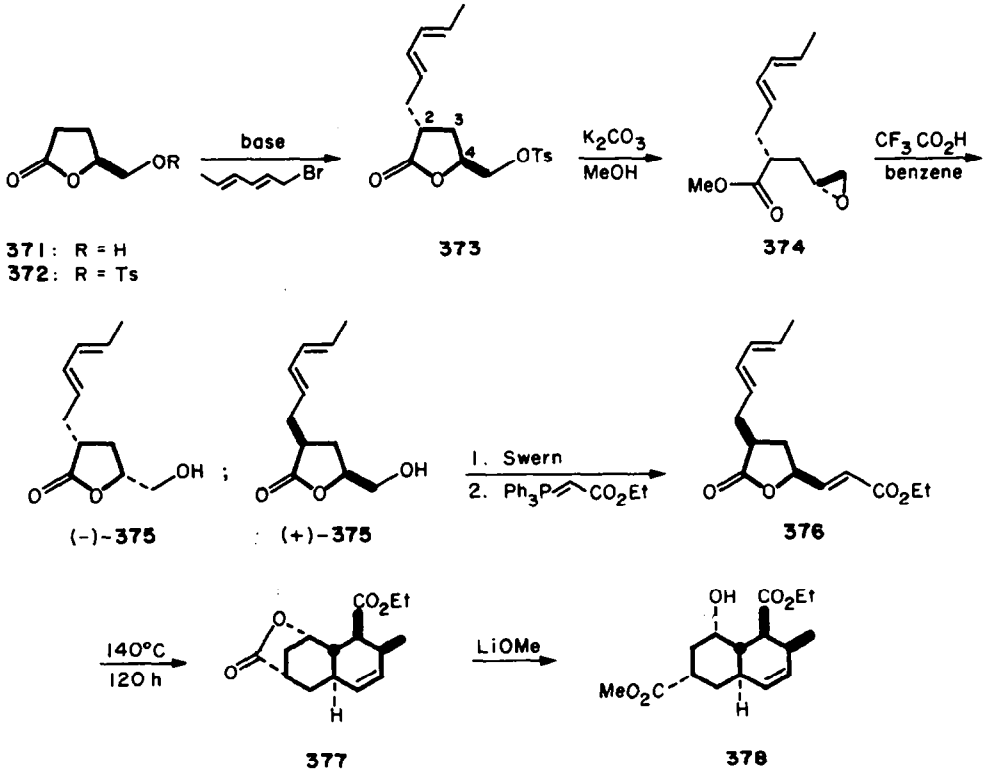
Scheme 63.

fluoboric acid to obtain cyclobutanone **355**. Reduction of **355** with lithium aluminum hydride gives the *trans* and *cis* isomers of **356** in a ratio of 7:3; if K-Selectride is employed, the *cis* isomer is the only product obtained. Application of the alkoxide-promoted vinylcyclobutane rearrangement to **356** gives dienes **357** and **358** in a ratio of 92:8 for *trans*-**356** or 72:28 for *cis*-**356**.

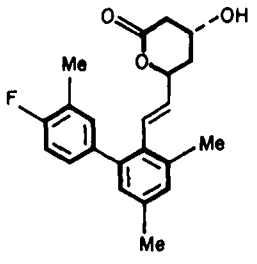
Pyranone **285** (Scheme 49) has now been transformed into (+)-dihydromevinolin.[57] As shown in Scheme 63, **285** is subjected to Bamford–Stevens conditions to obtain the acetylenic alcohol **359**. Partial hydrogenation of the triple bond and acetylation afford **360**. This material undergoes selective epoxidation from the β face, giving an epoxide which rearranges cleanly to the *trans*-fused decalone **361** upon treatment with boron trifluoride. Ozonolytic cleavage of the remaining double bond gives aldehyde **362**. Treatment of this substance with DBU in methylene chloride establishes an equilibrium (**362**:**363**) in which the latter predominates by a factor of 20. Selective reduction of the aldehyde carbonyl yields **364**, which is subjected to a second Bamford–Stevens sequence to obtain unsaturated diol **365**. Resolution is accomplished by formation of the O-methylmandelate esters, which are separable by simple crystallization. The desired diastereomer (**366**) is esterified with the anhydride of (*S*)-2-methylbutanoic acid and the resulting diester is selectively saponified to obtain a primary alcohol. The latter compound is then oxidized by the Swern method to obtain aldehyde **367**. The remainder of the synthesis closely parallels the earlier Rosen–Heathcock compactin synthesis (Scheme 21).

Davidson *et al.* have reported the imaginative approach to dihydromevinolin that is summarized in Scheme 64.[58] Lactone **371**, available from L-glutamic acid, is converted into the tosylate ester, which is alkylated with 1-bromohexa-2,4-diene to obtain **373** (along with about 7% of the *cis* isomer). Methanolysis gives **374**, which is subjected to acidic closure to obtain the *cis* compound (−)-**375**. In this manner, epimerization of the initial *trans* product **373** at C-4 is achieved. The synthesis is continued with (+)-**375**, obtained from **371** by a somewhat more laborious route involving epimerization at C-2. Swern oxidation gives an unstable aldehyde, which is trapped with the stabilized phosphorane to obtain **376**. Intramolecular Diels–Alder reaction of **376** requires rather strenuous conditions, and affords lactone **377**. Methanolysis of the lactone ring gives **378**. The synthesis of **377** is notably brief (6 steps, 30% yield).

Prugh *et al.* have utilized **312** (Scheme 52) in a synthesis of **379**, a potent synthetic analog of

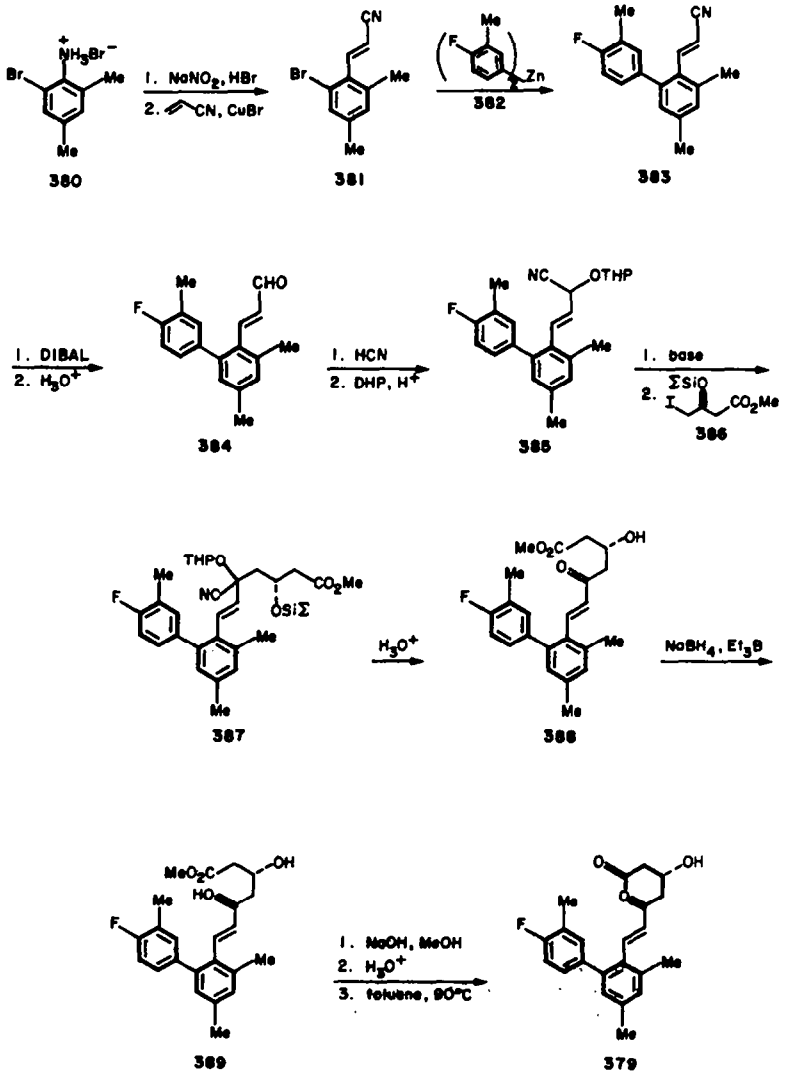


Scheme 64.



379

compactin.[59] A related publication from another Merck group reports the synthesis of **379** that is outlined in Scheme 65.[60] The biphenyl-substituted acrolein derivative **384**, prepared as shown, is converted into the protected cyanohydrin **385**. This material is lithiated and alkylated with iodide **386**, prepared in five steps from isoascorbic acid. The resulting adduct, **387**, is deprotected with acid to obtain enone **388**. Reduction of this material with sodium borohydride and triethylborane is highly stereoselective, affording dihydroxy ester **389** as the only diastereomer. The ester is saponified and the resulting dihydroxy acid converted into analog **379** as shown.



Scheme 65.

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