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Two-Directional Synthesis and its Use in Natural Product Synthesis

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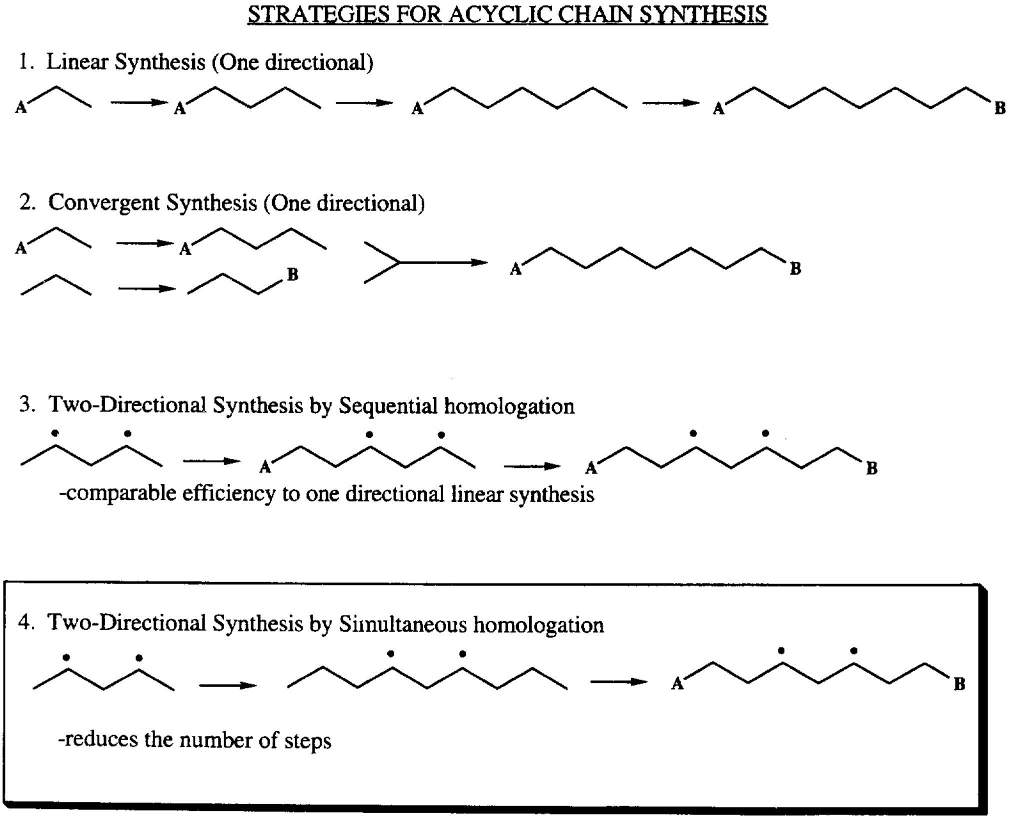
I. INTRODUCTION

The ways in which acyclic chains are synthesized may often be classified into one of four strategies (Scheme 1). The classical one directional *Linear Synthesis* and *Convergent Synthesis* are the approaches most frequently seen in the literature, and their advantages and limitations are well known. The other two strategies involve homologation of the chain in two directions. Such two directional synthesis can be done by *sequential homologation* of one end of the chain, and then the other end; but closer analysis reveals that this approach offers virtually the same challenges as linear one directional synthesis. The fourth strategy, *Two-Directional Synthesis by Simultaneous Homologation*, has received considerable attention over the last few years, largely through the pioneering efforts of Schreiber.[1,2] This strategy involves homologating both ends of the chain at the same time and then desymmetrizing the ends, as required. When applied to appropriate target molecules, namely those with a significant element of symmetry, this strategy offers a highly efficient route to stereochemically pure products in relatively few steps, compared with the other three strategies. This review focuses on *Two-Directional Synthesis by Simultaneous Homologation* and examines its use in natural product synthesis.

Scheme 1



STRATEGIES FOR ACYCLIC CHAIN SYNTHESIS

1. Linear Synthesis (One directional)

2. Convergent Synthesis (One directional)

3. Two-Directional Synthesis by Sequential homologation

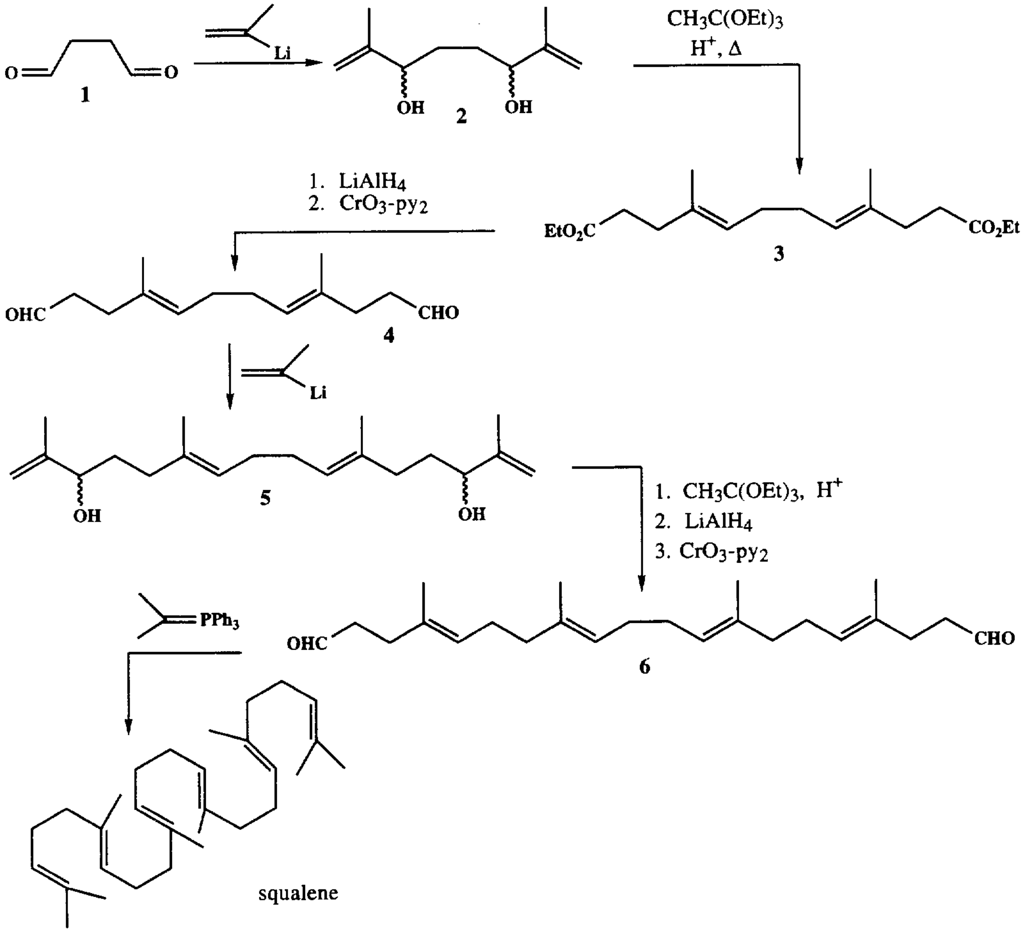
-comparable efficiency to one directional linear synthesis

4. Two-Directional Synthesis by Simultaneous homologation

-reduces the number of steps

Although the great potential of the two-directional technique had not been appreciated until quite recently, the concept of homologating a chain in both directions simultaneously has been known for many years, as illustrated by the Johnson-Faulkner synthesis of squalene (Scheme 2).[3]

Scheme 2

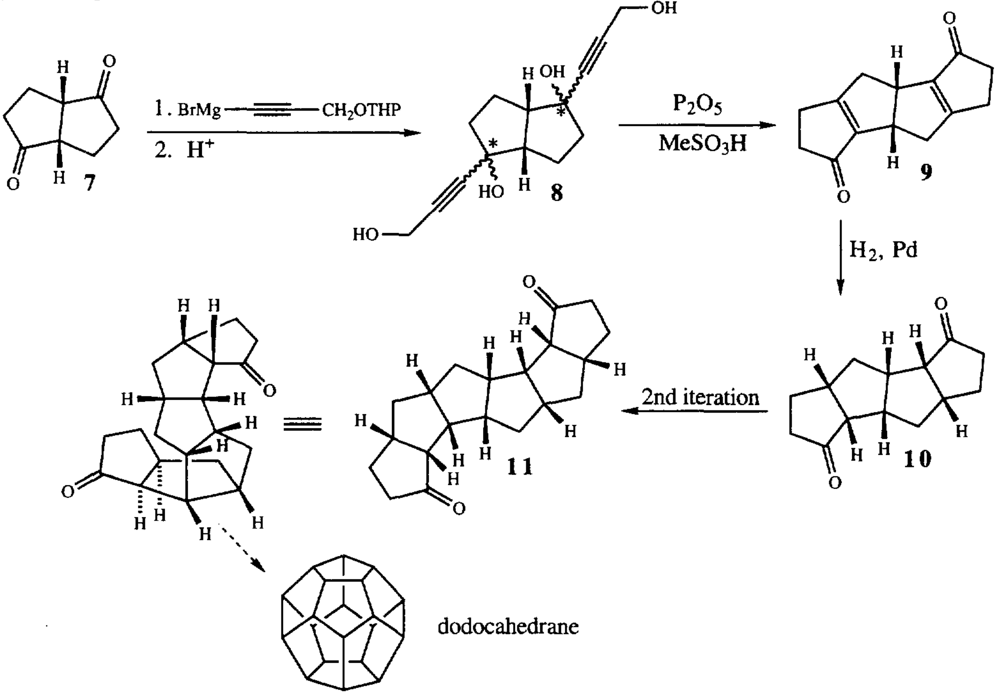


In this work, succinic dialdehyde (**1**) was treated with 2-propenyllithium to form diene diol **2**, as a mixture of stereoisomers. The mixture was heated in the presence of ethyl orthoacetate and acid, and underwent a double orthoester Claisen rearrangement, to give diene diester **3** as the sole product. The diester was then reduced and partially oxidized to diene dialdehyde **4** — a transformation that completed a five-carbon homologation at each end of the starting material **1**, again affording a dialdehyde. A second homologation was then performed in exactly the same manner to produce, first tetraene diol **5**, again as a mixture of stereoisomers, and then the C_{24} tetraene dialdehyde **6**. Finally, the last six carbons were incorporated by a double Wittig reaction, so as to give all *trans*-squalene of over 95% purity.

The beauty of this synthesis is that, even though the diols **2** and **5** are not formed stereoselectively, each stereoisomer gives exactly the same product in the subsequent rearrangement. This outcome is possible because for each stereoisomer the transition state involves a chair with an equatorial substituent. The necessary consequence is that the new double bond has *E*-geometry, regardless of the configuration at the carbinol carbon.

Unfortunately, most two-directional syntheses are not so forgiving, and indeed, for the two-directional synthesis[4] of molecules that contain asymmetric centres, the problem of stereoselectivity becomes an issue of prime concern. Some of these problems are illustrated by consideration of the synthesis of the potential dodecahedrane precursor **11**. This compound was assembled by a route that was an early example of two directional synthesis of compounds with asymmetric centres (Scheme 3).[5]

Scheme 3



The C_{20}-hexaquinane intermediate **11**, which contains an array of six cyclopentane rings with the all *cis-syn* fusion essential for eventual transformation into dodecahedrane, was constructed in a concise manner by the following route: The *cis* starting material **7** was converted by Grignard reaction and Nazarov cyclization into bis(enone) **9**. Although the intermediate tetrol **8** was a mixture of stereoisomers, bis(enone) **9** is a single compound since the starred atoms (see **8**) are converted to sp^2 hybridization in the product. Catalytic hydrogenation then gave the desired *syn-cis* addition product **10**. Creation of the new asymmetric centres in this reaction (**9** → **10**) takes place with partial reagent control (*cis* addition with H_2/Pd) and with partial substrate control (addition of hydrogen to the less hindered face of **9**). In this way, two rings were annelated onto starting material **7**, and a second iteration was then done, leading stereoselectively to dione **11**, to complete the synthesis of the potential dodecahedrane precursor.

The substrate control exhibited during *syn* addition of hydrogen was a result of the "cup shape" of the relatively rigid polycycle. Acyclic systems, on the other hand, lack such rigidity; in these cases, substrate control is based on more subtle effects, and the achievement of good stereoselectivity is more challenging. Although the two-directional sequences of Schemes 2 and 3 represent impressive examples of the technique, they are pioneering cases, and the subject has now been appreciably developed, especially in the area of acyclic compounds.

II. CHAIN SYNTHESIS

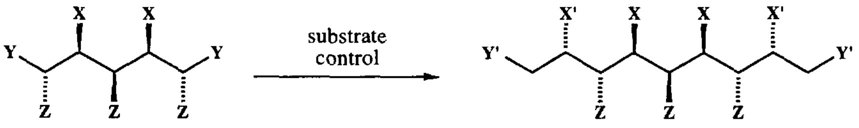
To aid in planning two-directional syntheses of acyclic molecules Schreiber has classified the three types of symmetric chains that are often encountered; and he has identified what kinds of reactions are necessary, in principle, to construct these chains in a stereoselective manner.[1]

II.1. Synthesis by Use of Achiral Chains

The first category is the *Achiral Chain*, which is often a *meso* compound, as shown by the generic structure in Scheme 4. The enantiotopic groups at the chain termini (here denoted by 'Y') may be any functional group that can be used for homologation. *With this class of chain, synthetic manipulations that result in new stereogenic carbons (12 → 13) must proceed by substrate-controlled reactions.*[6] Reactions where the chirality of new stereogenic centres is controlled by a chiral reagent cannot be used for achiral chain homologation. This requirement is understandable by virtue of the fact that both the starting material and the desired product are achiral molecules, and reaction of an achiral substrate with a chiral reagent would give an undesired (chiral) product.

Scheme 4

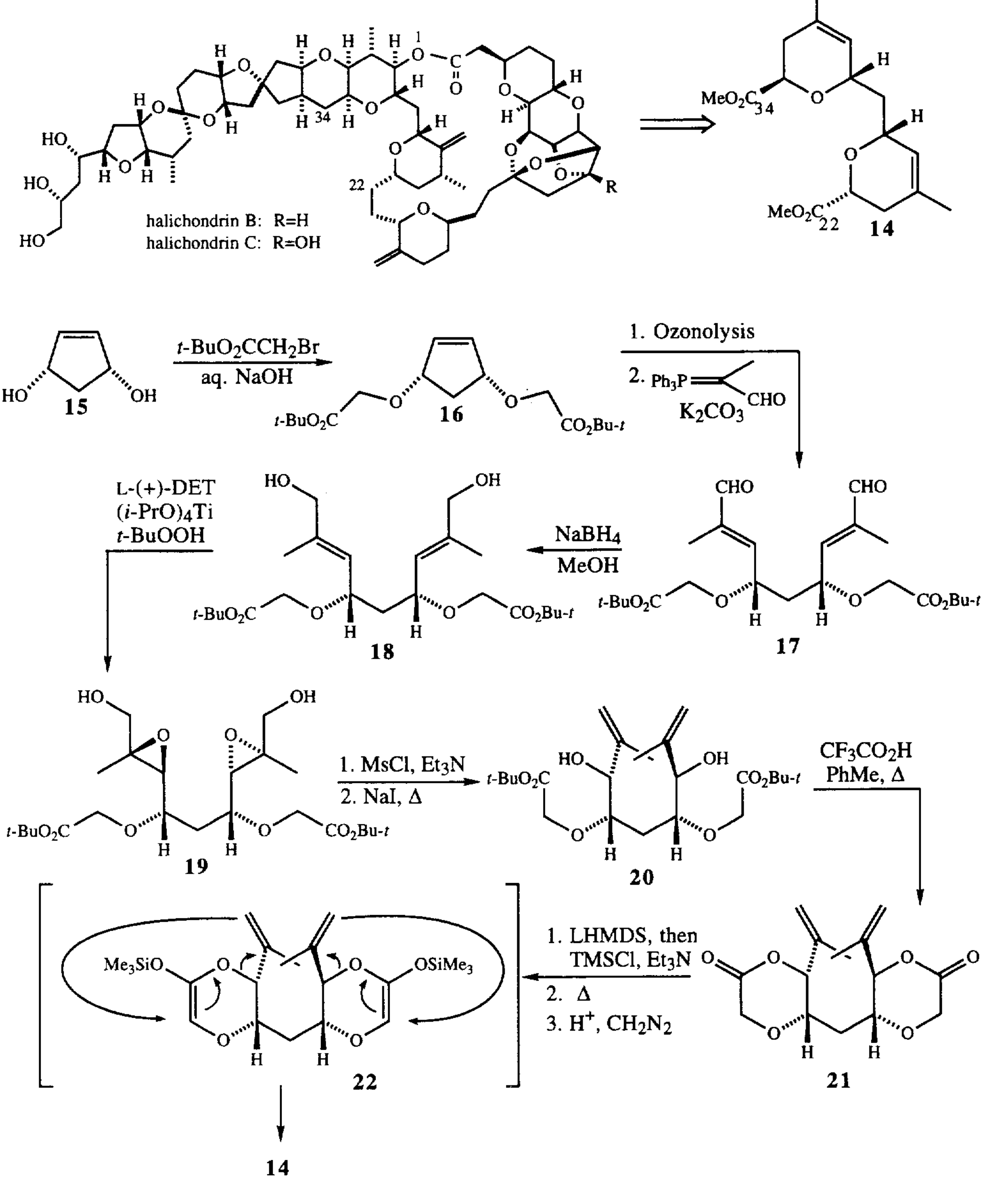
Achiral Chain (including meso compounds).



12 **13**

An example of two-directional synthesis of an achiral chain is found in Burke's approach to bis(dihydropyran) **14**, a precursor of the C(22)-C(34) segment of halichondrins B and C (Scheme 5).[7] Compound **14** represents a stereochemical and functional equivalent of the segment in question. The starting material, *meso* diol **15**, was converted to diester **16** by *O*-alkylation; then ozonolytic ring cleavage, followed by double Wittig homologation, afforded bis(enal) **17**. The aldehyde groups were reduced, and the resulting alcohol **18** was taken stereoselectively to bis(epoxyalcohol) **19** by Sharpless asymmetric epoxidation. This is a clear example of reagent control, in which a chiral product (in this case of high ee) is obtained by treatment of an achiral substrate with a chiral (and optically pure) reagent. Further two-directional elaboration of **19**, which is

Scheme 5

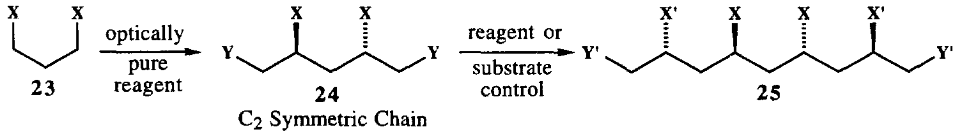


no longer an achiral chain,[8] was carried out as shown in the scheme. Conversion of bis(epoxy alcohol) **19** to the target molecule first required reductive fragmentation of the epoxy alcohol moieties. This step was carried out by heating the corresponding bis(mesylate)[9] with excess iodide (serving as the reductant), to afford the bis(allylic alcohol) **20**. Further heating, in acidic solution, effected closure to bis(dioxanone) **21**. This bis(lactone) was then converted into the corresponding bis(silylketene acetal) **22** which, without isolation, underwent two concurrent [3,3]-sigmatropic rearrangements. Finally, acidification and esterification afforded the desired product **14**.

II.2. Synthesis by Use of C_2 Symmetric Chains

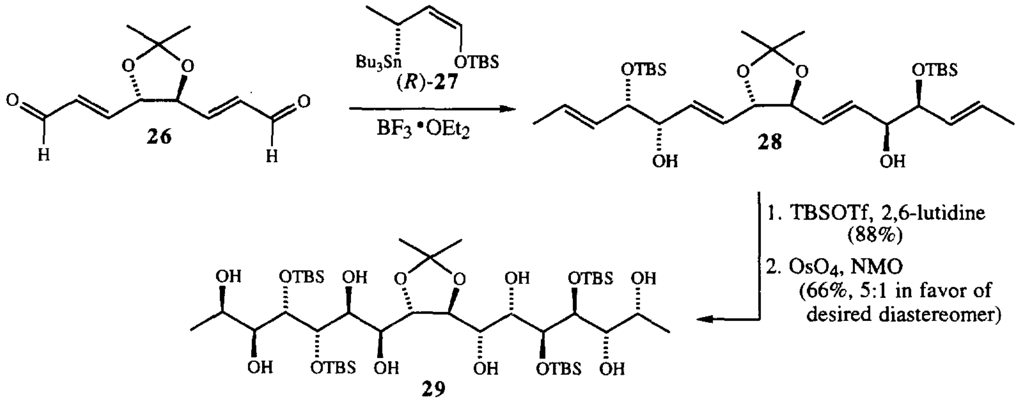
The second class of chain in Schreiber's classification is the *Optically Pure C_2 Symmetric Chain* (Scheme 6). *Such a unit may be constructed by double addition of an optically pure reagent to both ends of an achiral chain (**23** → **24**); then further transformations to generate additional stereogenic carbons (**24** → **25**) may proceed with substrate control, reagent control, or a combination of both.*[1]

Scheme 6



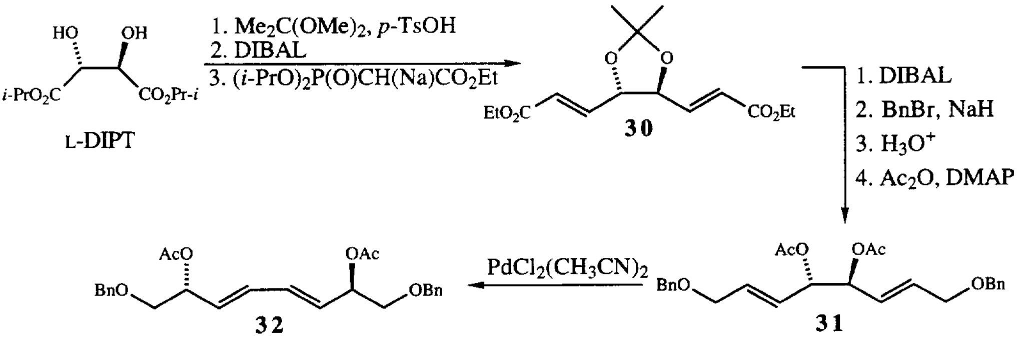
Marshall recently used two-directional synthesis of a C_2 symmetric chain to construct polyol **29** (Scheme 7).[10] Bis homologation of dialdehyde **26** with stannane (*R*)-**27**, a reaction that proceeds with reagent control, gave tetraene **28** in good yield. The hydroxyl groups of **28** were protected, and then substrate-controlled osmylation[11] afforded polyol **29** with good (5:1) selectivity in favor of the isomer shown.

Scheme 7



Saito has also used two-directional synthesis of a C_2 symmetric chain in his route to the functionalized octadiene **32** (Scheme 8).[12] L-DIPT was converted to diester **30** by protection as an acetonide, reduction to the corresponding dialdehyde, and then double Wittig homologation. Compound **30** was then transformed into diene **31**, which underwent a palladium-catalyzed twofold [3,3]-sigmatropic rearrangement to the C_2 symmetric diene **32**.

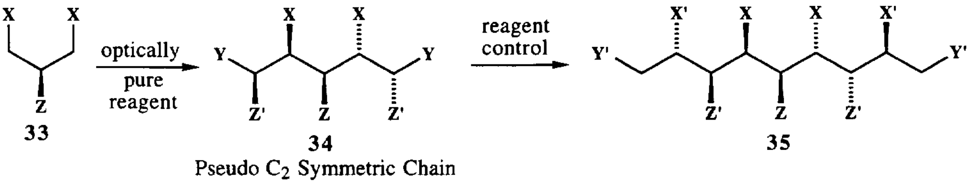
Scheme 8



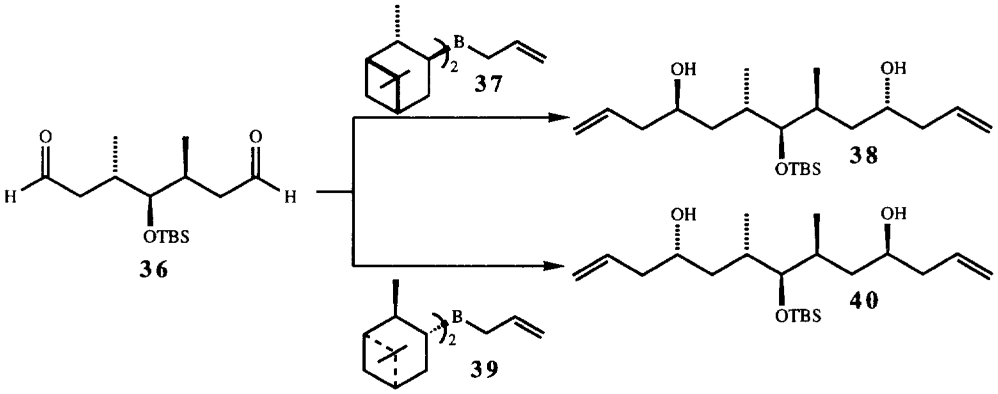
II.3. Synthesis by Use of Pseudo C_2 Symmetric Chains

The third category in Schreiber's classification is the *Pseudo C_2 Symmetric Chain* (Scheme 9).[1] The presence of a central chirotopic but nonstereogenic carbon (i.e. the carbon bearing the Z substituent in **34**) eliminates the C_2 symmetry, hence the different designation from the C_2 symmetric class. *A pseudo C_2 symmetric chain may be constructed by addition of an optically pure reagent to the termini of an appropriate achiral chain (33 → 34), and then synthesis by methods that result in new stereogenic carbons must take place with reagent control (34 → 35).*

Scheme 9

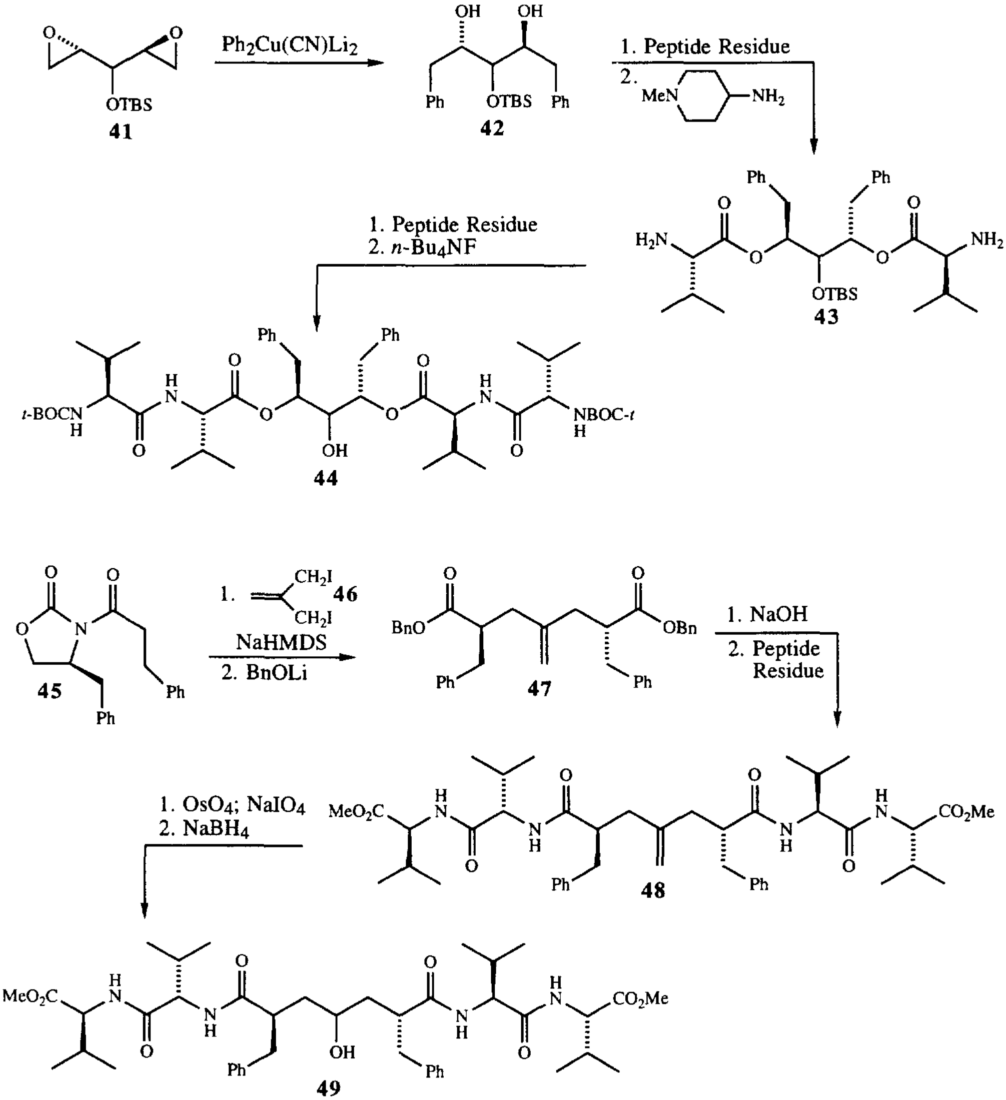


Scheme 10



A hypothetical example of such a process is shown in Scheme 10. The dialdehyde **36** can undergo double addition of the optically pure allyl borane **37**,[13] with allyl addition to the corresponding *si* face of each aldehyde moiety, to give the pseudo C_2 symmetric diol **38**, stereoselectively. Use of the enantiomeric allyl borane **39** proceeds in the opposite stereochemical sense, and leads to stereoselective formation of diol **40**, which is also pseudo C_2 symmetric, but is a diastereomer of **38**.

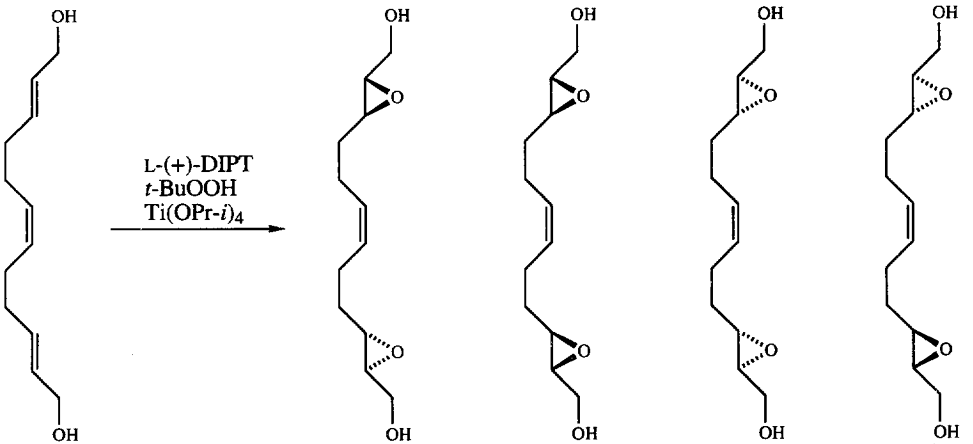
Scheme 11



Babine has used two-directional synthesis of a pseudo C_2 symmetric chain to construct the enzyme inhibitor **44** (Scheme 11).[14] The synthesis of **44** uses a pseudo C_2 symmetric starting material (**41**) and continues with this class of chain throughout the sequence (**41** → **44**), using optically pure peptide residues to introduce asymmetric centres. In related work, pseudo C_2 symmetric **49** was obtained by double addition of optically pure **45** to achiral **46**, to generate C_2 symmetric **47**, followed by homologation of the C_2 symmetric chain with optically pure peptide residues (**47** → **48**), and finally oxidative cleavage and reduction.

One further aspect of Schreiber's homologation strategy for C_2 symmetric and pseudo C_2 symmetric chains involves the benefits of performing concurrent enantioselective reactions simultaneously at two locations.[15] This procedure offers the opportunity to obtain products of extremely high enantiomeric purity, a technique that Hoye and Suhadalnik have studied in some depth for two-directional synthesis.[16]

Scheme 12



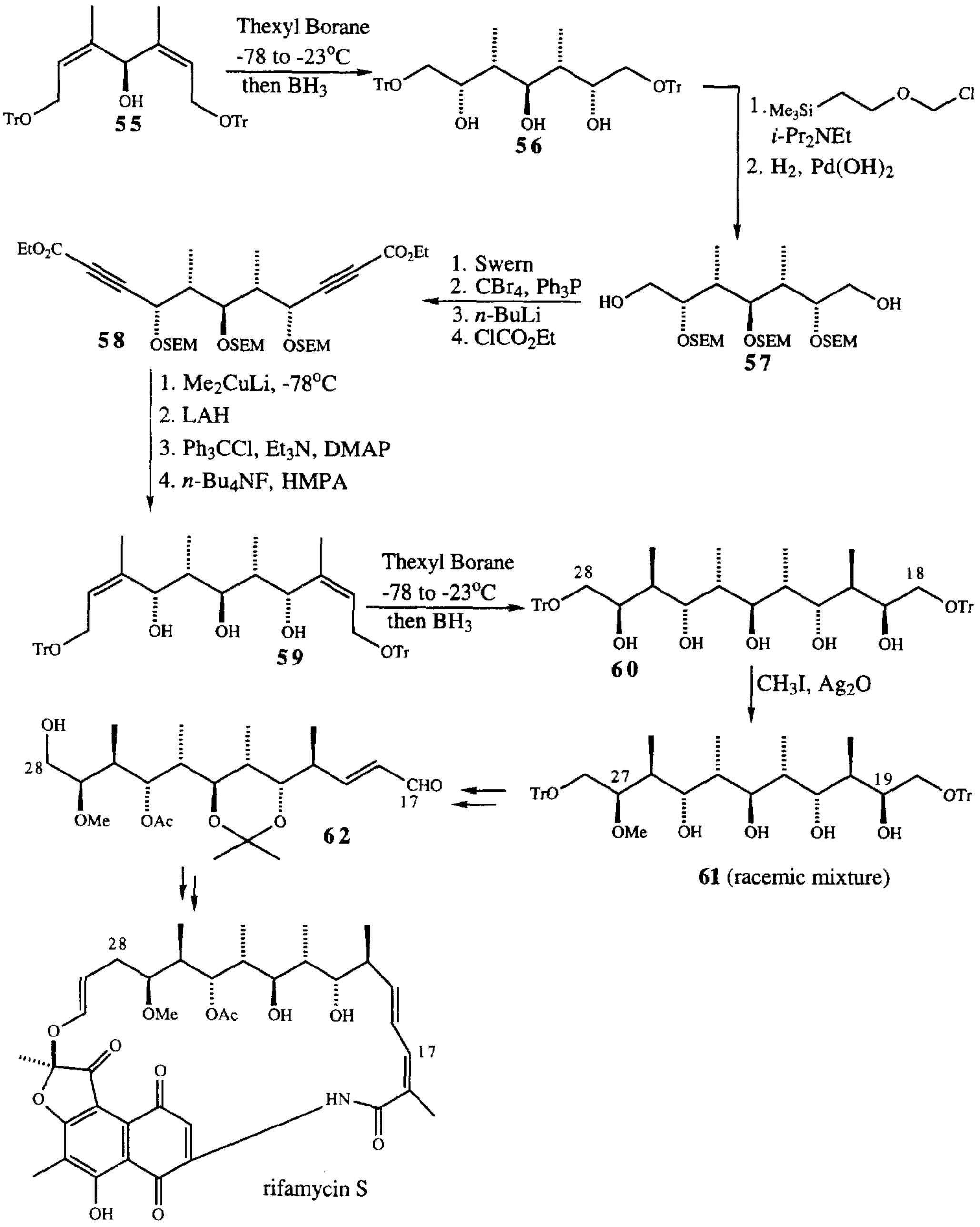
50 **51** (361) **52** (19) **53** (19) **54** (1)

They examined bis(epoxidation) of trienediol **50** by Sharpless reaction, using L-(+)-DIPT. They obtained a mixture of four bis(epoxides), where bis(epoxides) **52** and **53** are identical and bis(epoxide) **51** was the desired product (Scheme 12). If we assume Sharpless epoxidation proceeded with 19:1 enantiofacial selectivity at both allylic alcohols - a selectivity ratio commonly encountered in simple epoxidation of allylic alcohols[17] - then the expected product ratio of **51**:(**52**+**53**):**54** would be $(19{:}1)^2$, or 361:38:1. An experimental product ratio of diastereomers (**51**+**54**):(**52**+**53**) was determined after conversion to appropriate derivatives. This ratio was consistent with the theoretical ratio (362:38) Hoye and co-workers deduced, therefore, that a highly enantioselective formation of **51** (> 99% ee) had been accomplished. A similar effect would also be expected in the double allylborations shown in Scheme 10, leading to highly enantioselective formation of **38** or **40**.

III. CHAIN DESYMMETRIZATION

The work covered in the previous section illustrates efficient syntheses of complex structures that can be carried out in a two-directional manner and also highlights a major problem in application of two-directional

Scheme 13



strategies: namely, that very few natural products are symmetric. Thus, if two-directional synthesis is to be applied widely to natural products, methods are required to desymmetrize the chains stereoselectively, otherwise the potential utility of the approach will be compromised. An early synthesis by Still[18] of an equivalent to the C(17)—C(28) segment of rifamycin S (Scheme 13) nicely illustrates the need for efficient desymmetrization. He used some ten steps of two-directional synthesis to build up efficiently the correct stereochemical array of the ansa chain but, in order to reach the desired rifamycin S intermediate **62**, a desymmetrization was required, and it was only here that the chemical efficiency of the route dropped.

A double hydroboration of the allylic alcohol subunits of *meso* alcohol **55** generated *meso* triol **56** and the corresponding *d,l* pair in a 5:1 ratio. Triol **56** was separated, protected (SEM-chloride), and detritylated to diol **57**. Swern oxidation, conversion to the acetylide, followed by trapping with ethyl chloroformate, furnished diester **58**. Conjugate addition of dimethyl cuprate, hydride reduction of the ester groups, tritylation, and desilylation afforded triol **59**. The remaining four stereogenic carbons required in the final product **62** were introduced, again by hydroboration of the allylic alcohol subunits, giving the desired *meso* pentol **60**, this time in a 4:1 ratio with the corresponding *d,l* pair. The stereochemical array of pentol **60** corresponds well with the ansa chain of the natural product. At this point a desymmetrization was attempted by monomethylation of one of the less hindered hydroxyl groups [i.e. at C(19) or C(27)]. However, two obstacles were encountered. First was the problem of bis(methylation), since methylation of one hydroxyl group had little effect on the rate of reaction of the other. Of greater significance though, was the fact that the corresponding hydroxyl groups — at C(19) and C(27) — in the substrate are enantiotopic. Consequently, methylation at one end of the molecule produced the enantiomer of the product formed by methylation at the opposite end. Thus, the desymmetrization gave racemic material (**61**), and in the event this was taken on to the rifamycin S intermediate **62**.[19]

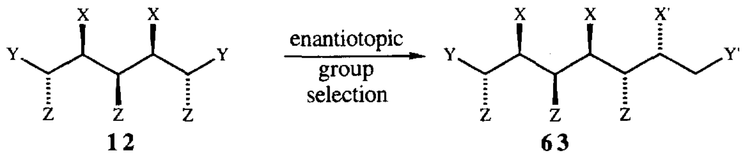
Besides laying out the theoretical basis for successful homologation of the three classes of chains, Schreiber has also recognized the requirements for selective desymmetrization of each of these classes.[1] In the last few years significant effort has gone into developing nonenzymatic[20] desymmetrization techniques,[21] and a survey of these is presented in the following sections (III.1. to III.3.).

III.1. Desymmetrization of Achiral Chains

Desymmetrization of an achiral chain[1] (Scheme 14) usually requires an enantiotopic group selection[†] — that is, a choice of one terminus over the other. This operation is also often combined with diastereofacial selection at the chosen terminus. ***These desymmetrizations (12 → 63) always involve an optically pure catalyst or reagent, but their effectiveness is also dependant on an interplay between substrate and reagent control.*** The use of optically pure reagents *can* provide access to either enantiomer, normally with very high ee.

Scheme 14

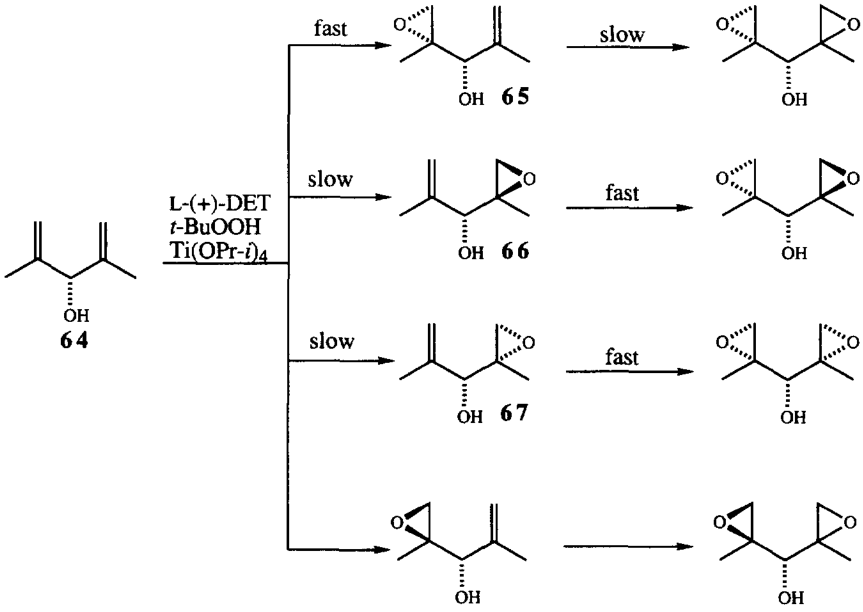
Achiral Chain (including meso compounds)



[†] But see section III.1.ii (Scheme 30), especially ref. 37 for an alternative.

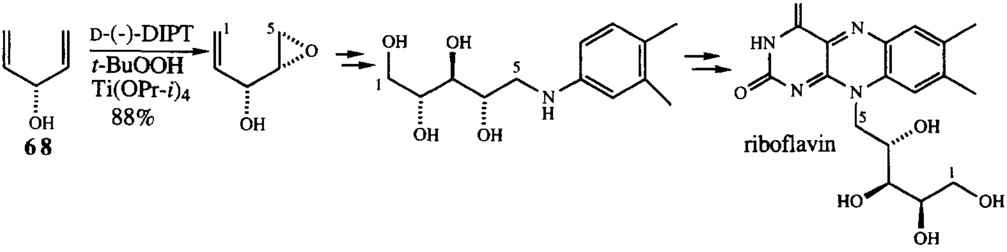
III.1.i. Desymmetrization of Achiral Divinyl Carbinols. Several desymmetrization techniques for achiral chains are based on the properties of divinyl carbinols. One such case, which illustrates the remarkable selectivity that can be achieved, involves Sharpless asymmetric epoxidation of divinyl carbinol **64** (Scheme 15).[22] When **64** undergoes an epoxidation, of the four possible products, only epoxy alcohol **65** is formed to any appreciable extent. The yield is good and the stereochemical purity is extremely high. This desymmetrization involves both reagent control, through the facial discriminating characteristics of the optically pure reagent system,[17] and substrate control, which favours the erythro (*syn*) epoxy alcohol.[23] These selectivities are also coupled with a kinetic resolution, since the minor stereoisomers **66** and **67** are "destroyed" by rapid conversion to their bis epoxides. As **66** is destroyed, the de of **65** will increase; and as **67** is destroyed, the ee of **65** will increase.

Scheme 15



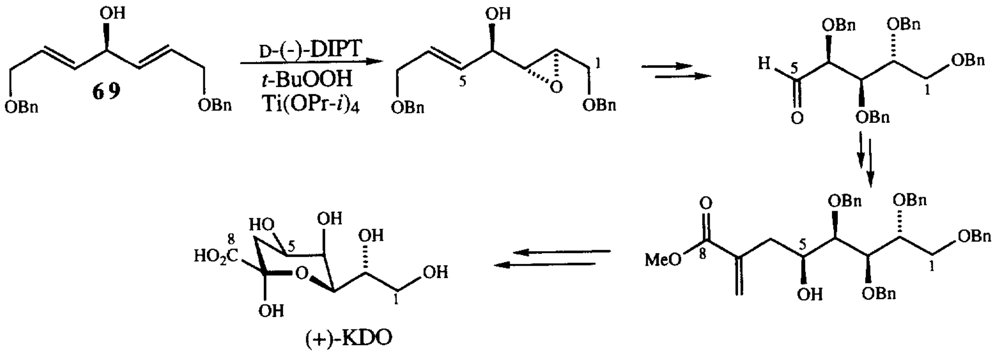
65 isolated in 85% yield with >99% ee and >99% de

Scheme 16



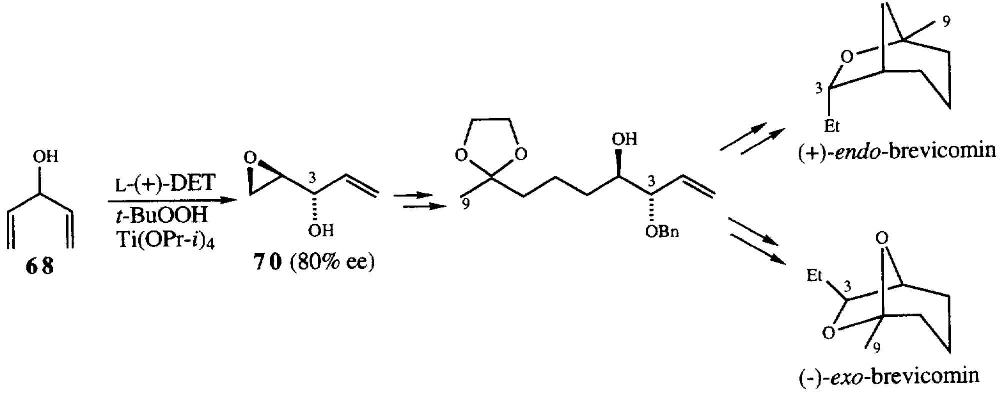
Schreiber has studied this desymmetrization extensively, providing a mathematical model that describes the increase in enantiomeric excess of the desired stereoisomer as the reaction proceeds.[22,24] He has also applied the technique to a formal synthesis of (-)-riboflavin from divinyl carbinol **68** (Scheme 16) and to a total synthesis of (+)-KDO from divinyl carbinol **69** (Scheme 17).[25]

Scheme 17



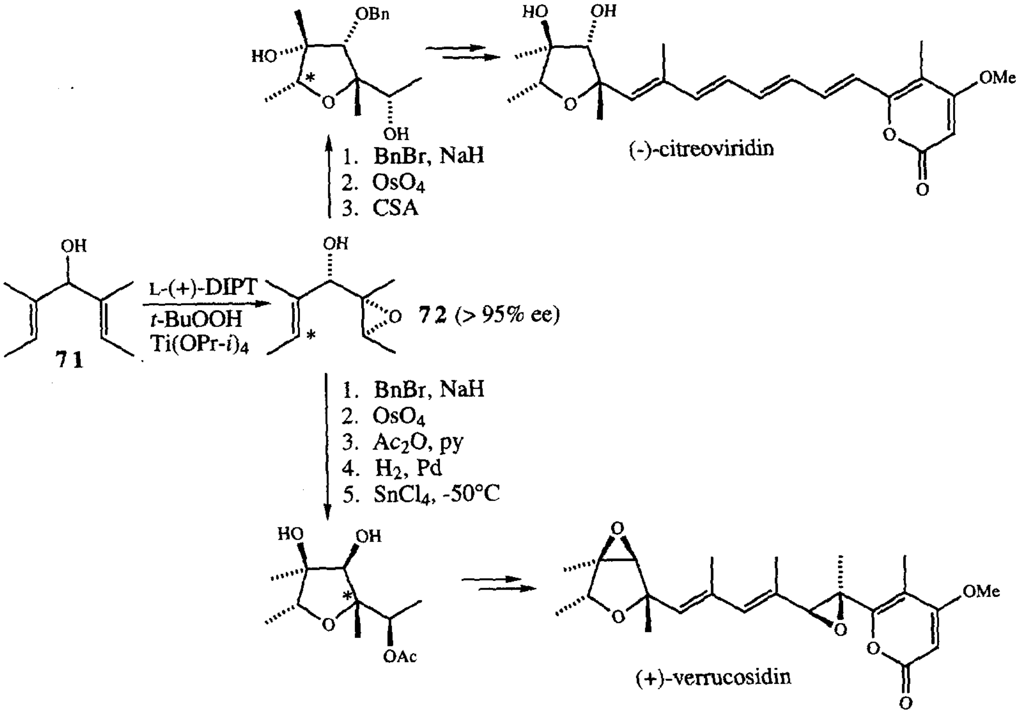
Takano was actually the first to publish this type of desymmetrization, using divinyl carbinol **68** in a synthesis of (+)-*endo*- and (-)-*exo*-brevicomin (Scheme 18).[26] The stereoselectivity actually possible with this reaction was not fully exploited here, as epoxide **70** was formed with only 80% ee. More recently, Takano

Scheme 18

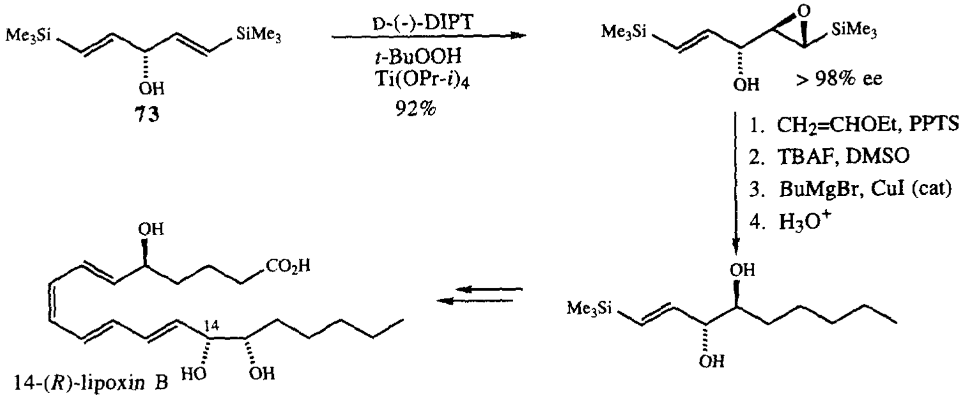


used divinyl carbinol **71** to complete the first total synthesis of (+)-verrucosidin and as well as a formal synthesis of (-)-citreoviridin,[27] and in these works an ee of over 95% was achieved for the desymmetrized product **72** (Scheme 19).

Scheme 19

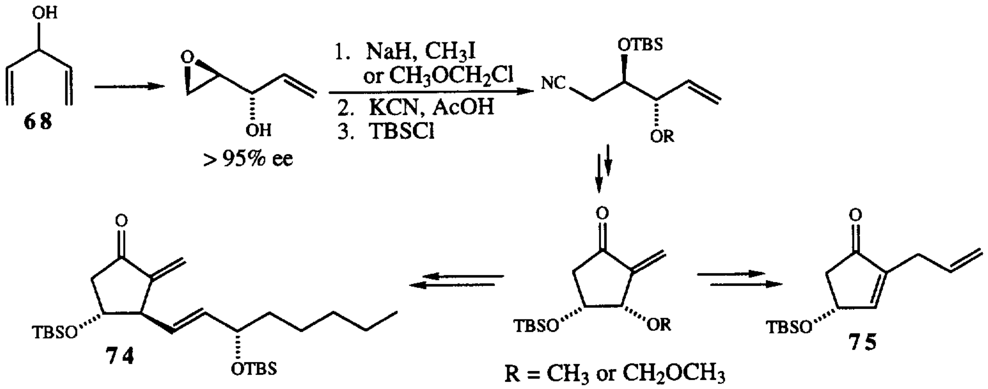


Scheme 20



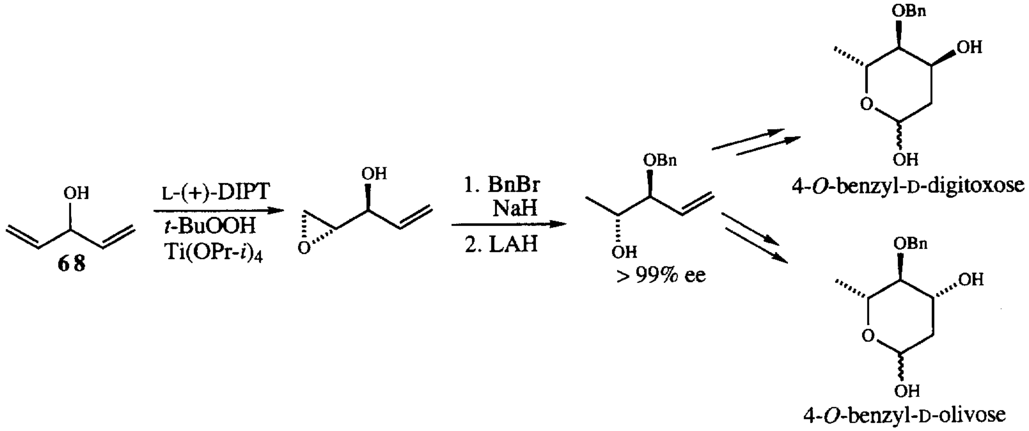
Sato has also used this technique to desymmetrize divinyl carbinol **73**,[28] in a process constituting a formal synthesis of lipoxin B (Scheme 20). He also desymmetrized divinyl carbinol **68**,[29] in a synthetic route to the prostaglandin intermediates **74** and **75** (Scheme 21).

Scheme 21



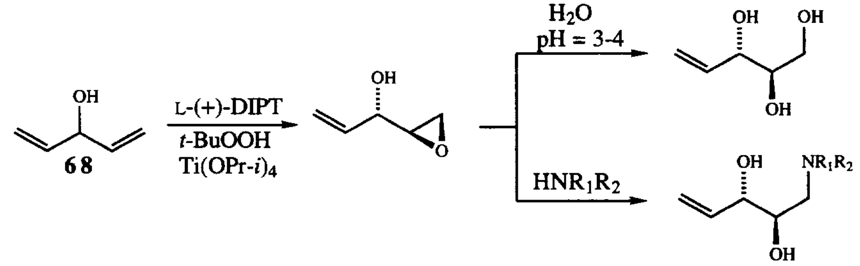
Also noteworthy for its desymmetrization are Babine's syntheses of protected D-digitoxose and protected D-olivose from divinyl carbinol **68** (Scheme 22),[30] as well as Jäger's extensive work on the stereocontrolled syntheses of *erythro*-4-pentenetriols[31] and amino-4-pentenediols (Scheme 23).[32]

Scheme 22



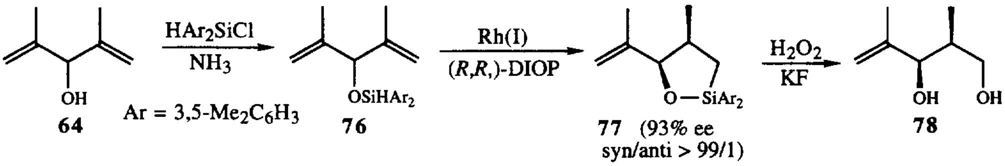
A second method for desymmetrizing divinyl carbinols, that was developed by Ito and co-workers,[33] involves catalytic asymmetric intramolecular hydrosilation (Scheme 24). Divinyl carbinol **64** was converted to silyloxy derivative **76**, and this underwent intramolecular hydrosilation in the presence of a rhodium(I) complex incorporating an optically active phosphine ligand [(*R*,*R*)-DIOP or (*R*)-BINAP]. The hydrosilation was

Scheme 23



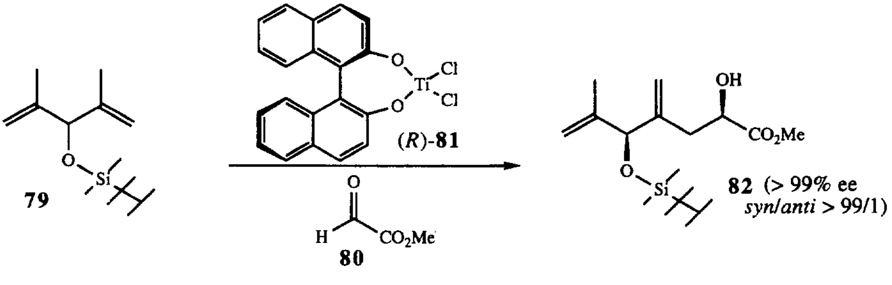
enantiogroup selective (the pro S vinyl group being favoured) and diastereofacially selective (*syn* being favoured over *anti*), giving desymmetrized **77**, which could be oxidized to diol **78** with good overall de and ee.

Scheme 24



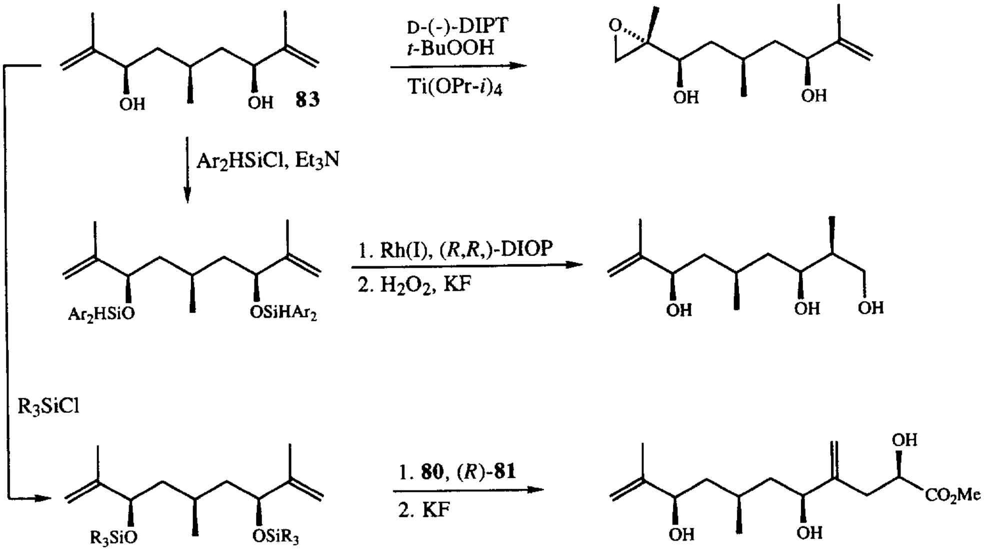
Mikami has also reported a desymmetrization of divinyl carbinols,[34] by using an enantioselective carbonyl-ene reaction (Scheme 25). Protected divinyl carbinol **79** was allowed to react with methyl glyoxylate (**80**) in the presence of the chiral titanium-BINOL derivative **81**. Again, an enantiogroup selective and diastereofacially selective reaction occurred, to give desymmetrized **82** of high stereopurity. This desymmetrization is one of only two examples reported so far that involves C-C bond formation.

Scheme 25



While each of these desymmetrization techniques — epoxidation, hydrosilation, and ene reaction — has been studied for simple divinyl carbinols, it is not difficult to envisage how they could each be applied to longer chain substrates[2] such as the hypothetical diene diol **83** (Scheme 26). Schreiber has used the Sharpless epoxidation desymmetrization for similar substrates in the structure determination of (+)-mycotin A and B, as described later (see Sec.IV.1.).

Scheme 26

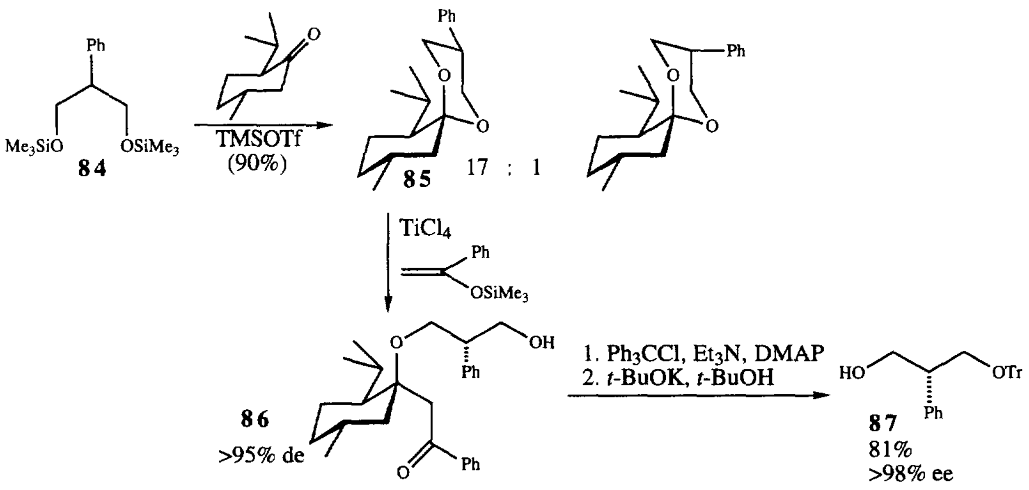


III.1.ii. Desymmetrization of Achiral Polyols. Significant effort has also gone into developing desymmetrization techniques for achiral polyols. Harada and Oku have made a detailed study of a spiroketalization method[35] for desymmetrizing 1,3-diols (Scheme 27). Treatment of bis(silyl ether) **84**[35a] with *l*-menthone and a catalytic amount of trimethylsilyl triflate gave a mixture of two diastereomeric ketals, with a large preponderance of the isomer (**85**) having an equatorial phenyl group. The spiroketals were separated by flash chromatography and the major diastereomer was then treated with the trimethylsilyl enol ether of acetophenone, in the presence of $TiCl_4$. This operation gave almost exclusively the monoprotected propane diol derivative **86**. The stereochemical bias of ring cleavage is explained by considering that the $TiCl_4$ will preferentially coordinate to the less hindered equatorial oxygen of **85**, resulting in breakage of the bond between that oxygen and the ring carbon. It is the breakage of this bond that establishes the absolute stereochemistry at C(2) of **87**. With **86** in hand, protection of the hydroxyl, followed by ring cleavage gave the desymmetrized monoprotected compound **87** of high enantiomeric purity.

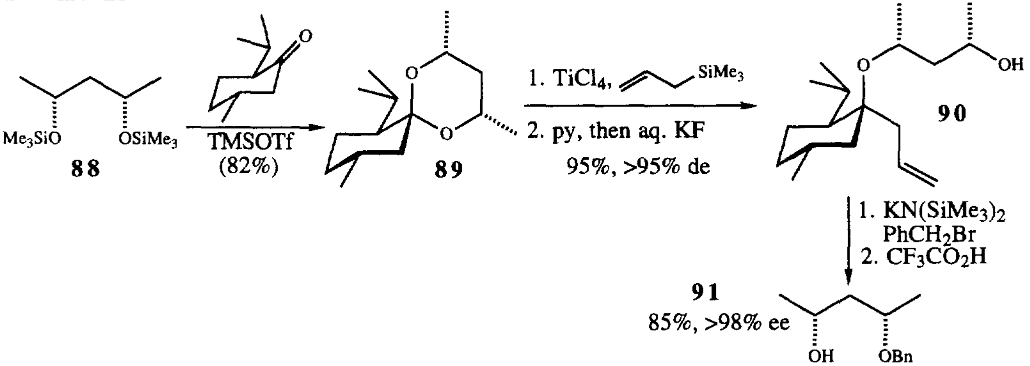
The method is also applicable to *meso* substrates, such as **88**[35e] (Scheme 28). Treatment with *l*-menthone gives spiroketal **89** preferentially (as opposed to the corresponding diastereomer with axial methyl groups on the acetal ring), and this undergoes an analogous $TiCl_4$-mediated reaction with allyltrimethylsilane to afford almost exclusively the monoprotected compound **90**. This alcohol was then *O*-benzylated, and the required desymmetrized product **91** was detached, and obtained in high yield and optical purity.

Harada and Oku have extended their method to substrates such as pentane triol **92** (Scheme 29).[35f,h]

Scheme 27

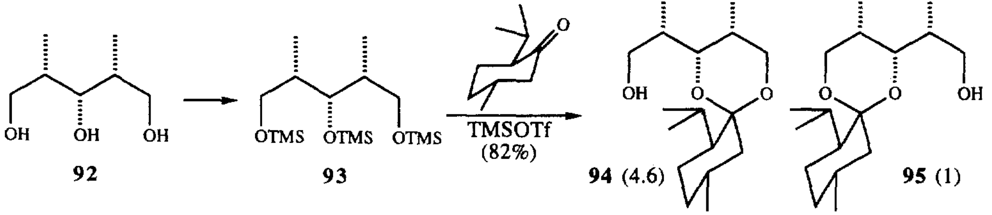


Scheme 28



Here, the desymmetrization involves an enantiodifferentiating protection. The triol was converted into tris(silyl ether) **93** and then derivatized with *l*-menthone to give spiroketal **94** together with the minor diastereomer **95** in a 4:1 ratio. The small energy difference associated with this product ratio is not easily explained, although the authors offer an interesting suggestion based on van der Waals attractive interactions.

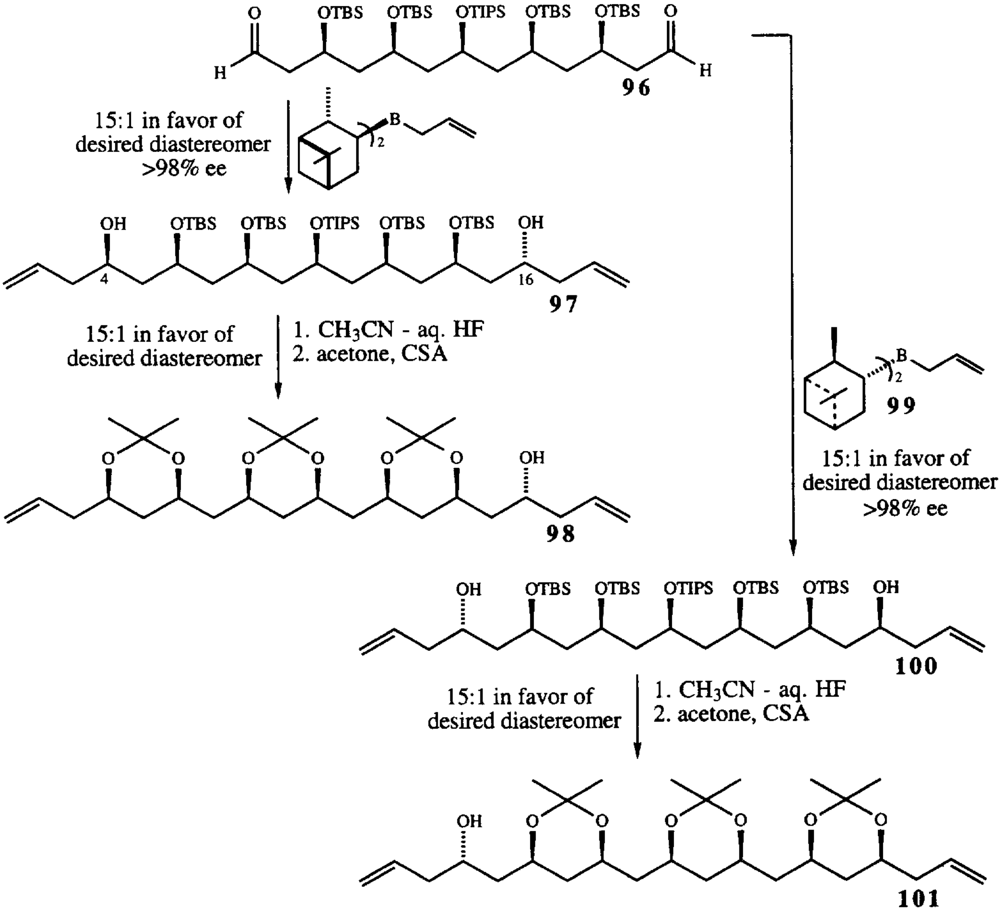
Scheme 29



The method described above for desymmetrizing pentane triols was extended still further so that it could be applied in a desymmetrization step during the synthesis of the rifamycin S ansa chain (see Sec IV.1.).

A second desymmetrization technique for skipped polyols has been reported by Wang (Scheme 30).[36] *Meso*-dialdehyde **96** was treated with (+)-diisopinylcampheyl allylborane[13] to give diene **97** in high purity. The reaction is exclusively reagent-controlled, as allyl addition proceeds to the *si* face of both aldehyde groups. Although the σ symmetry in the starting material had been destroyed (i.e. the starting material has been desymmetrized), there still remained the problem of differentiating between the hydroxyl groups at C(4) and C(16). The existing stereochemistry of the molecule was used to accomplish this diastereotopic group differentiation. The silyl groups were removed, and then ketalization with acetone served to effect the required differentiation, since the desymmetrized tris(acetonide) **98** was formed almost exclusively.[37] The rationale for the selectivity observed in this reaction is the thermodynamic preference for *syn*-1,3-acetonides over *anti*-1,3-acetonides. This preference, in turn, is based on the fact that only the *syn* configuration has both pendants on

Scheme 30

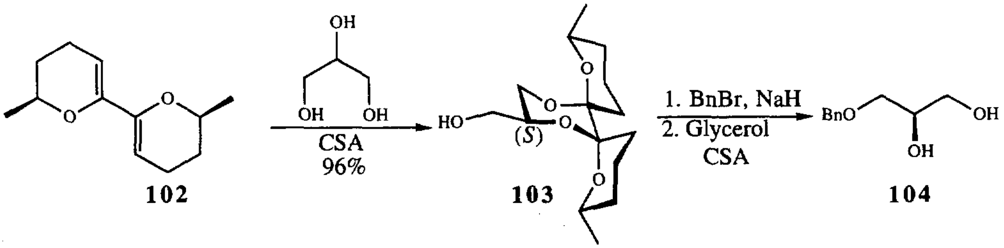


the dioxane ring equatorial.

When the enantiomeric allyl boron reagent **99** was used, allyl addition proceeded to the *re* face of both aldehyde moieties to give diene **100**, which was taken through the same series of protecting group manipulations, to afford tris(acetonide) **101**, the enantiomer of **98**.

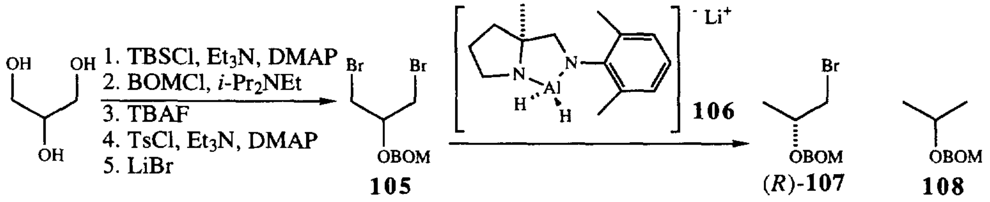
Two other desymmetrization techniques for achiral polyols deal with glycerol and its derivatives. Ley has developed a method that desymmetrizes by enantiogroup selection during formation of dispiroketals (Scheme 31).[38] Reaction of glycerol with optically pure bipyran **102**, in the presence of a catalytic amount of acid, leads exclusively to dispiroketal **103**. The selectivity is understandable by recognizing that the absolute stereochemistry of the spirocentres will be controlled by a combination of multiple anomeric effects and by the preference of the methyl groups to adopt equatorial conformations. Similarly, the dispiroketal will form preferentially with the hydroxymethylene substituent on the dioxane also equatorial. These factors result in exclusive formation of **103** with (*S*)-stereochemistry at C(2) of the glycerol unit. The hydroxyl group of **103** was then benzylated, and ketal exchange gave **104** in enantiomerically pure form.

Scheme 31



Desymmetrization that involves an enantiogroup selection coupled with kinetic resolution of glycerol derivative **105** has been reported by Chong (Scheme 32).[39] Glycerol was converted to dibromide **105**, which

Scheme 32

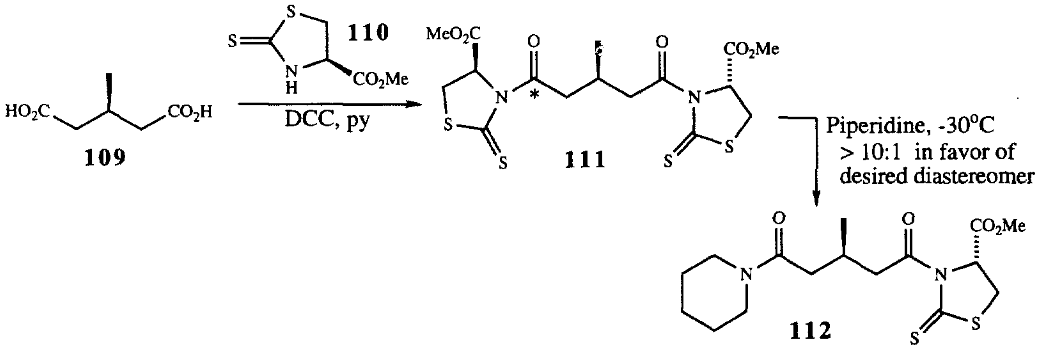


Entry	Time (min)	Product Distribution **105**:**107**:**108**	Yield of **107** (%)	% ee of **107**
1	30	26 : 69 : 2	55	25
2	60	3 : 91 : 6	74	53
3	240	0 : 18 : 82	17	87

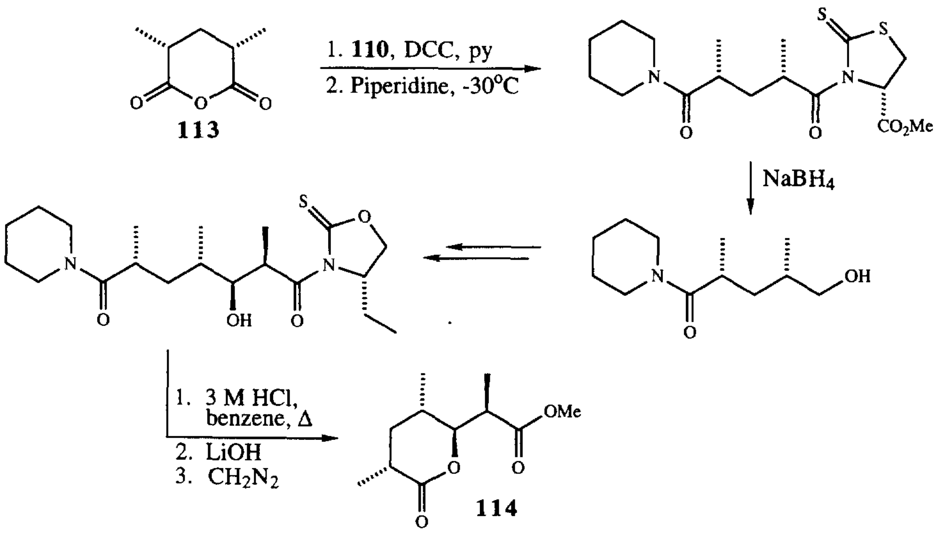
was treated with the optically pure reducing agent **106**. This chiral reagent provided only modest enantioselectivity, and gave the desired monoreduced **107** with a low ee initially (entry 1). A kinetic resolution was also involved, however, since the ee of **107** increased steadily while the reaction proceeded, but of course, at the expense of the yield as **107** was reduced to compound **108**.

III.1.iii. Desymmetrization of Achiral Diacids. A group of desymmetrization techniques reported some years ago dealt with desymmetrizing some achiral diacids. The first of these, described by Fujita,[40] involved treatment of diacid **109** with optically pure thiazolidine **110** to produce diamide **111**, which no longer has the σ symmetry of the starting material **109** (Scheme 33). To complete the desymmetrization,[41] a diastereotopic group selection was performed with piperidine, which preferentially attacked the pro-*S* carbonyl (See **111**, starred atom) to give desymmetrized product **112**. This compound was separated from the minor diastereomer

Scheme 33



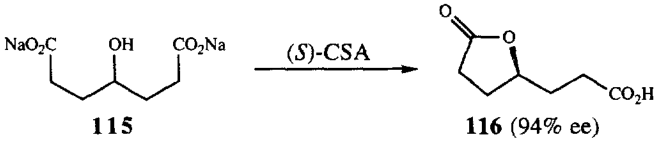
Scheme 34



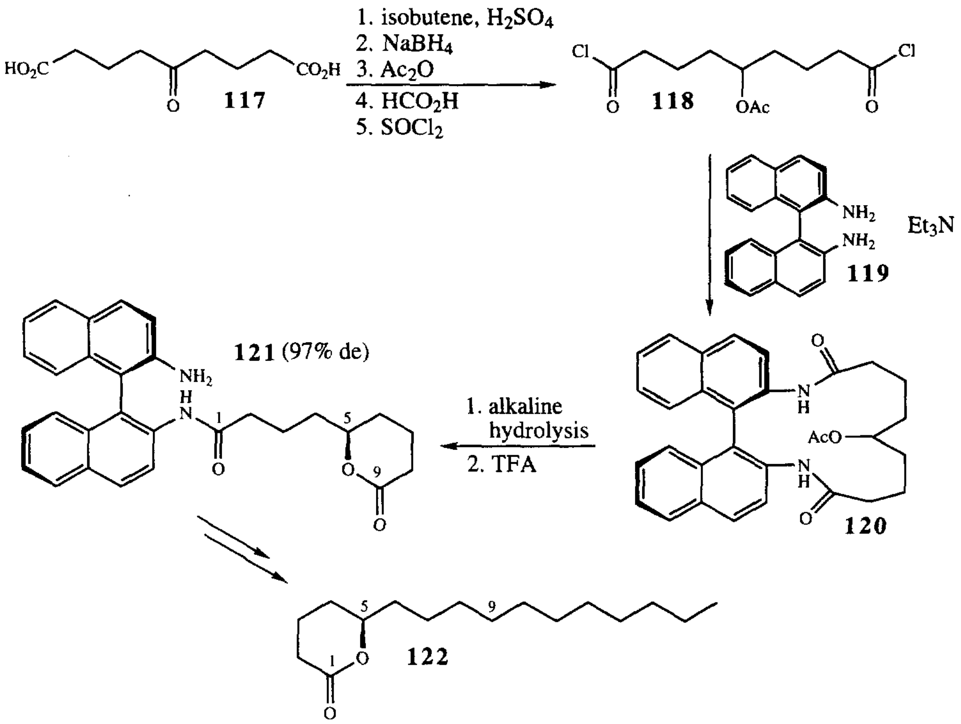
(formed by reaction at the pro-*R* carbonyl) by flash chromatography. The authors rationalized the selectivity on the basis of intricate steric arguments after examining molecular models and the X-ray crystallographic structure of intermediate **111**. Fujita has used his methodology to construct (+)-Prelog-Djerassi lactonic acid methyl ester **114** from *meso* anhydride **113** (Scheme 34).[41,42]

A second desymmetrization technique for an achiral diacid is illustrated by the enantioselective lactonization (Scheme 35) of sodium 4-hydroxypimelate (**115**),[43] which, when carefully neutralized with (*S*)-camphorsulfonic acid, preferentially gave lactone **116**. The enantioselectivity is extremely sensitive to reaction conditions, as the optimum recorded ee of 94% falls off significantly when substrate and water concentrations are varied slightly. Evidently, a high degree of association between the CSA and the substrate is required for the enantiogroup discrimination, but this association is sensitive to reaction conditions.

Scheme 35



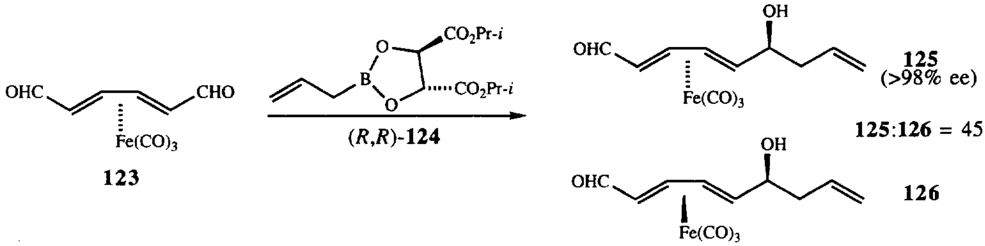
Scheme 36



The remaining desymmetrization technique suitable for achiral diacids was reported by Oda (Scheme 36).[44] Ketodiacid **117** was converted into acid chloride **118**, and then condensed with (*R*)-(+)-BINAL (**119**), to produce the key intermediate **120**.[41] The acetate group was removed, and the resulting alcohol then underwent a diastereoselective acid-catalyzed lactonization to **121** with high de. This desymmetrized intermediate (**121**) was carried on to complete a highly enantioselective synthesis of the naturally occurring pheromone (*R*)-(+)-5-hexadecanolide (**122**).

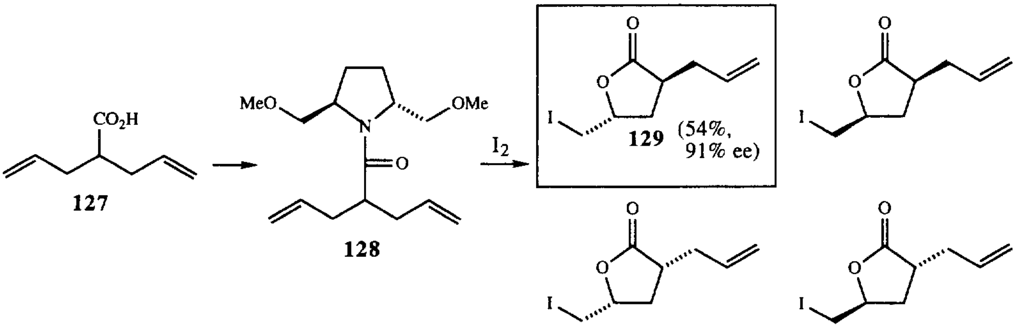
III.1.iv. Desymmetrization of Miscellaneous Achiral Compounds. In his work with asymmetric allylboration of diene aldehyde Fe(CO)3 derivatives, Roush has described a highly enantiotopic group- and diastereotopic face-selective allylboration of *meso* diene dialdehyde **123** (Scheme 37).[45] Reaction of **123** with the tartrate-derived allyl boronate (*R*,*R*)-**124**, resulted in a 45:1 mixture of **125** and **126**, in which the enantiomeric purity of **125** was found to be >98%. Use of the Fe(CO)3 complex led to significantly improved enantioselectivity compared with the parent diene dialdehyde, and this improvement was attributed to an electronic (dipole) effect of the metal carbonyl ligand[46] rather than to steric or inductive factors.

Scheme 37



Fuji has reported a desymmetrization of achiral diene acid **127** that involved an iodolactonization employing a chiral auxiliary. The process affords chiral lactones in an enantioselective manner (Scheme 38).[47] Acid **127** was converted into amide **128**, which underwent iodolactonization under kinetic conditions to form iodolactone **129** in acceptable yield and with good ee. The selectivity has been explained by steric arguments applied to proposed transition states to each of the four possible iodolactones. A detailed consideration of these

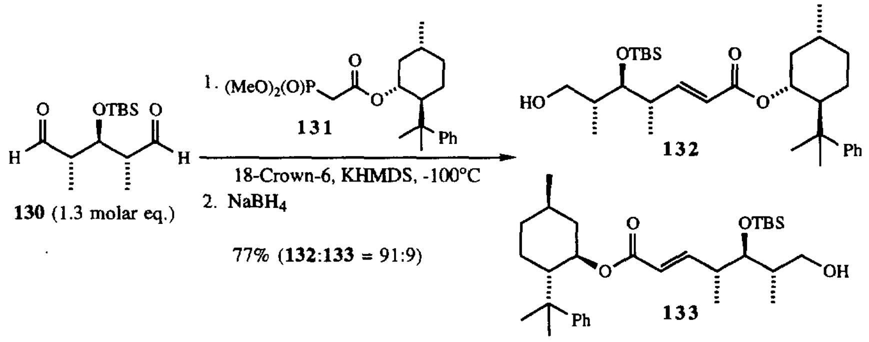
Scheme 38



transition states showed that only the one leading to the observed product is free of serious non-bonded interactions.

Rein has recently reported initial results of an asymmetric Horner-Wadsworth-Emmons reaction (Scheme 39).[48] Like the desymmetrization of Scheme 25, this technique involves C-C bond formation. *Meso*-dialdehyde **130** was treated with optically pure **131**, and the resulting aldehyde mixture was reduced to give the desired olefin **132** along with a small amount of olefin **133**. Compounds **132** and **133** were separated by chromatography.

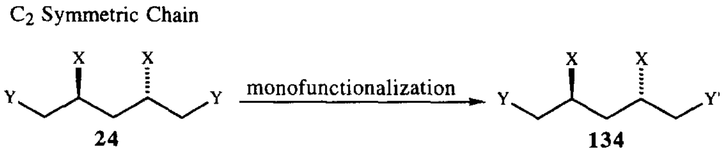
Scheme 39



III.2. Desymmetrization of C_2 Symmetric Chains

Desymmetrization of a C_2 symmetric chain (Scheme 40) is probably the least complicated of the three classes of chains used in two-directional synthesis. This feature is due to the fact that the two termini are homotopic, and so selective functionalization — a choice of one terminus over the other — is not required. *All that is necessary is monofunctionalization (24 → 134), since altering either of the termini will give exactly the same product.*[1]

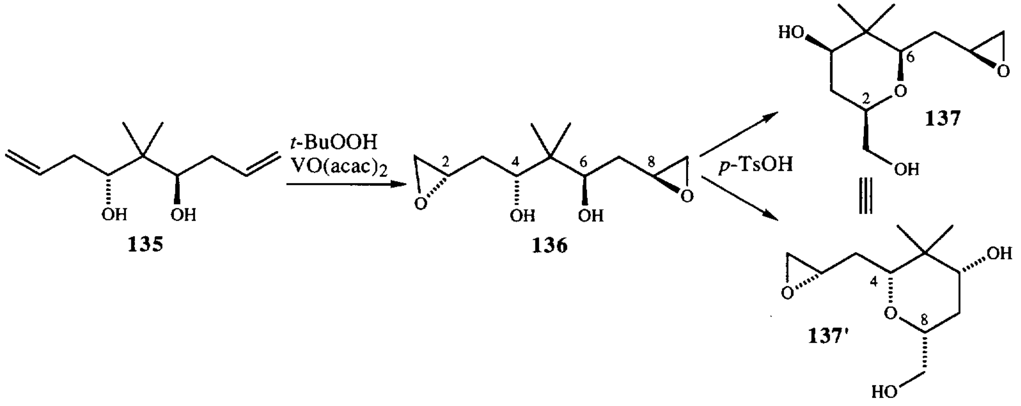
Scheme 40



In the case of the C_2 symmetric chain the symmetry is beneficial, as it eliminates the need for group selectivity.[49] A problem that does arise though is one of bis(functionalization). Because the termini of a C_2 symmetric chain are homotopic, they will react at identical rates, and if altering one terminus has little effect on the reactivity of the other terminus, then statistically the maximum yield available (with one equivalent of reagent) would be 50%. In most cases, desymmetrizations of C_2 symmetric chains proceed in this manner (see Sec. IV.2.), but there are some noteworthy examples where an element of control over the problem of bis(functionalization) has been achieved.

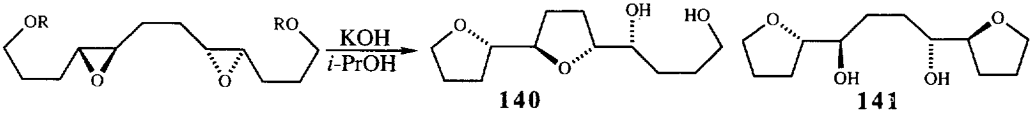
III.2.i. Avoidance of Bis(functionalization) by Use of Intramolecular Functionalization. One method for suppressing bis(functionalization) is by use of intramolecular functionalization. In the example of Scheme 41, racemic diol **135**[50] was taken stereoselectively to bis(epoxide) **136**, from which acid catalyzed cyclization proceeded via one of two paths. If the hydroxyl group on C(4) closed onto C(8) then pyran **137** would be formed, and if the hydroxyl group on C(6) closed onto C(2) then pyran **137'** would be formed. These two products though, are identical. This type of desymmetrization completely eliminates the problem of bis(functionalization), because once one ring is formed the unreacted epoxide cannot be functionalized in the same manner.

Scheme 41



A second example that used an internal functionalization to desymmetrize a C_2 symmetric molecule involves a special use of protecting groups (Scheme 42).[51] During his work on epoxide cascade reactions, Hoye needed to desymmetrize racemic bis(epoxy alcohol) **138**[52] and convert it into unsymmetrical diol **140**. As with the previous example (Scheme 41), it did not matter which hydroxyl group closed first onto its target epoxide, since either possibility would lead to the same product. A problem that did arise, however, was formation of significant amounts of C_2 symmetric byproduct **141**. This problem was solved efficiently by conversion of bis(epoxy alcohol) **138** first into bis(pivalate) **139**. Cyclization of this compound, now proceeded almost exclusively to the desired diol **140**. Here, protecting group removal was considerably slower

Scheme 42



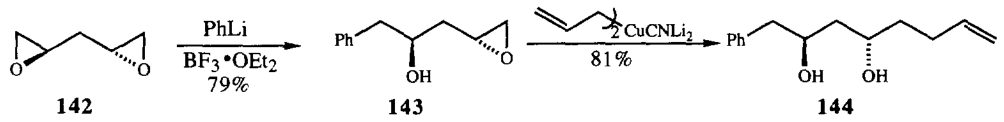
138 : R = H
139 : R = Me_3CCO

Starting	Product Distribution	
Material	140	141
138	60	40
139	98	2

than the cyclization steps, so that once one protecting group was removed, the second step of the cascade proceeded quickly before loss of the second protecting group.

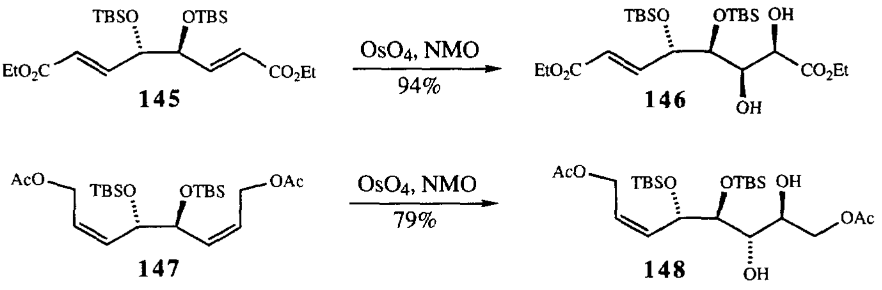
III.2.ii. Avoidance of Bis(functionalization) by Use of Steric Proximity Effects. The other method for suppressing bis(functionalization) takes advantage of the steric proximity of the termini as a control strategy. Rychnovsky recently reported the desymmetrization of bis(epoxide) **142** and of its enantiomer (Scheme 43).[53] Reaction of **142** with 1.1 equivalents of an alkyllithium (e.g. PhLi), promoted by boron trifluoride etherate, proceeded in a stepwise fashion (with the first addition faster than the second) and led to a significant preponderance of monofunctionalized material **143**. The lower rate observed for the second addition is not easily explained, but the steric proximity of the two epoxide units is probably one factor that contributes to the effect.[54,55] It has been proposed that increased steric hindrance around the epoxide may inhibit activation by boron trifluoride during the second addition. Desymmetrized **143** was then treated with a second nucleophile (e.g. an allyl cuprate), to give diol **144**.

Scheme 43



A second desymmetrization of a C_2 symmetric chain that again involves a preponderance of monofunctionalization over bis(functionalization) and is also based upon proximity effects between the reacting sites has been reported by Saito *et al.* (Scheme 44).[11] In this case though, the desymmetrization also required a diastereofacial selection. Dienes **145** and **147** were treated with osmium tetroxide, to give diols **146** and **148**, respectively with >99% de. A conformational analysis has been provided[11,56] to explain both the exceptional diastereoselectivity and how incorporation of hydroxyls at one double bond prevents reaction at the other.

Scheme 44

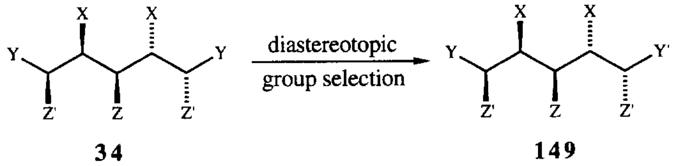


III.3. Desymmetrization of Pseudo C_2 Symmetric Chains

Desymmetrization of pseudo C_2 symmetric chains (Scheme 45) requires a diastereotopic group selection of one terminus over the other (34 → 149).[1,57] There are relatively few examples of desymmetrizations of

Scheme 45

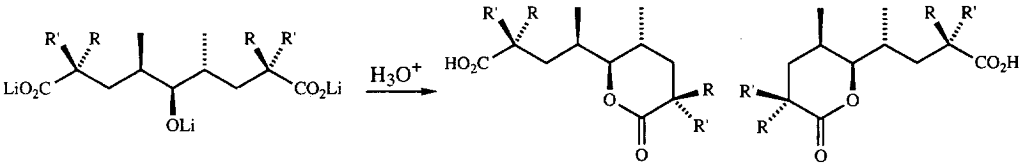
Pseudo C_2 Symmetric Chain



pseudo C_2 symmetric chains, but this is probably due more to the fact that this chain type is used relatively infrequently, rather than to an inherent difficulty in performing the desymmetrizations.

One example involves Hoye's work on the lactonization of diacid salts **150** and **153** (Scheme 46).[58,59] Salt **150** may cyclize to either lactone **151** or diastereomeric lactone **152**, while salt **153** may close to either lactone **154** or its diastereomer **155**. Lactonizations were done under both thermodynamic and kinetic conditions,[60] and for salt **150** there was virtually no kinetic preference for **151** or **152**, but a significant thermodynamic preference was seen for the formation of **151** over **152**. Conversely for salt **153**, there was only a small thermodynamic preference for the formation of **154** over **155**, but a large preponderance of **154** was formed under kinetic conditions. Of the four possible transition states leading to either **154** or **155**, only one has all ring substituents equatorial, and this transition state leads to **154** — the strongly favored kinetic

Scheme 46

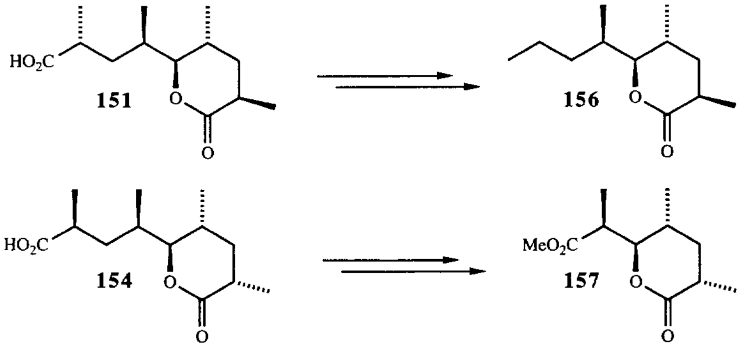


150: R = Me, R' = H
153: R = H, R' = Me

151: R = Me, R' = H
154: R = H, R' = Me

152: R = Me, R' = H
155: R = H, R' = Me

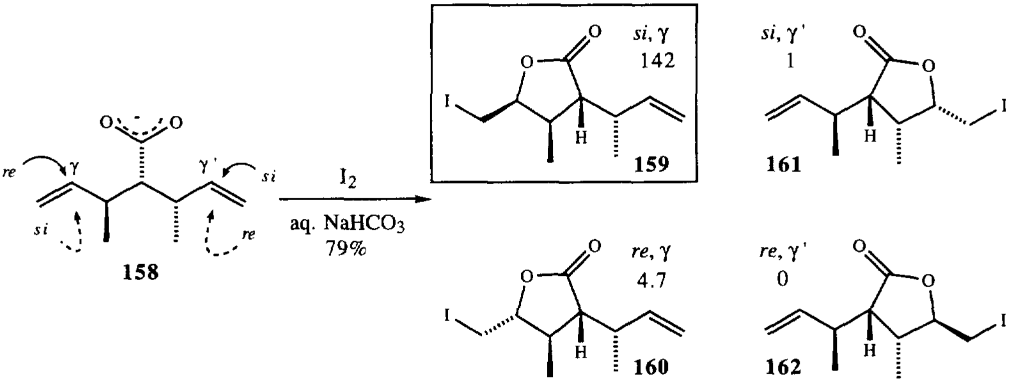
Starting Material	Product Ratio	Kinetic Conditions	Thermodynamic Conditions
150	**151** : **152**	1.2 : 1	14.6 : 1
153	**154** : **155**	350 : 1	4.2 : 1



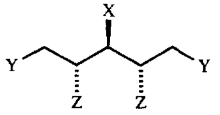
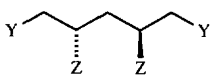
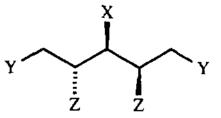
product. Hoye used lactone **151** in a synthesis of *d,l*-invictolide (**156**), and lactone **154** to complete a synthesis of the methyl ester of the Prelog-Djerassi lactone (**157**).

A second desymmetrization of a pseudo C_2 symmetric chain has been accomplished through iodolactonization of the diene carboxylic acid **158** (Scheme 47).[61] Iodolactonization could theoretically proceed to four different diastereomeric products: Closure to the γ carbon from the *si* face (**159**) or *re* face (**160**), and closure to the γ' carbon from the *si* face (**161**) or *re* face (**162**). When the iodolactonization was done under kinetic conditions,[62] a remarkable selectivity was found for the *si*-γ mode of closure, giving iodolactone **159** as the major product. The product ratio of **159** to **161** indicates a group selectivity for the γ side of the molecule

Scheme 47



Scheme 48

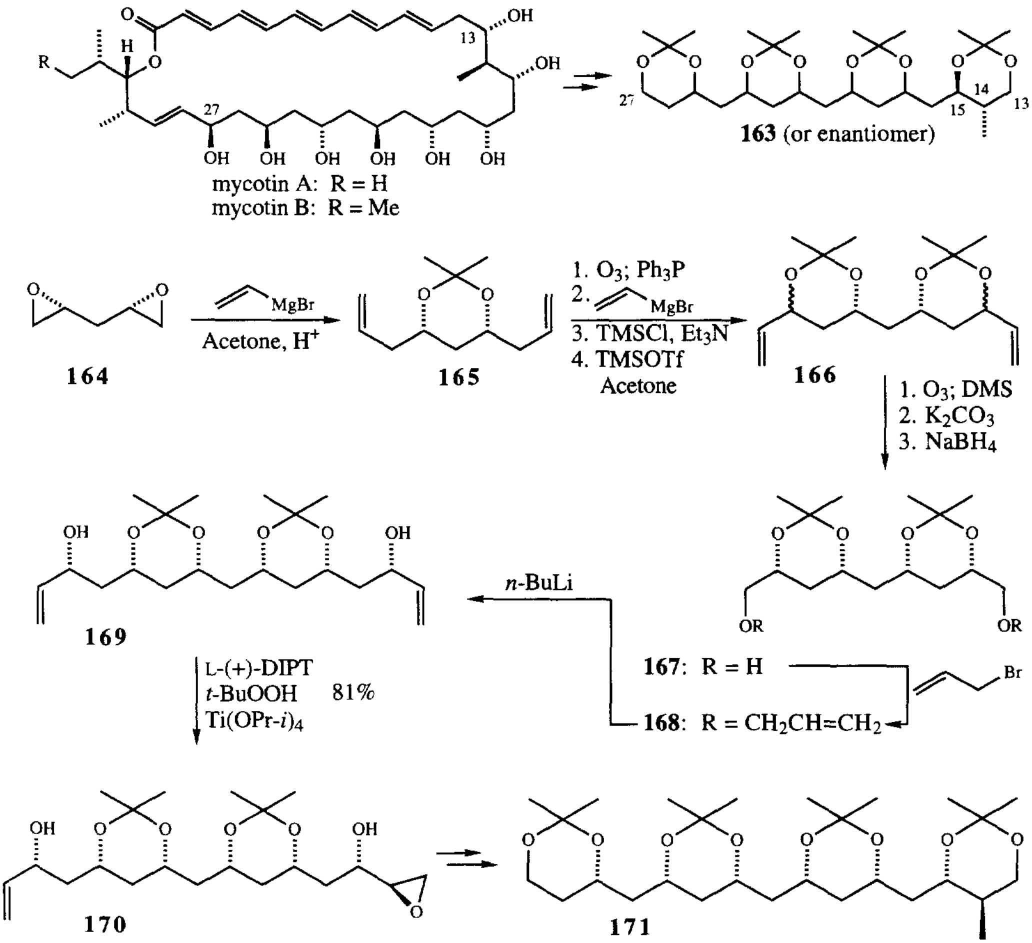
Chain Type	Synthesis	Desymmetrization
 Achiral (including meso)	Generation of new stereogenic centres requires substrate control	Requires enantiotopic group selection & often diastereofacial selection Requires substrate & reagent control
 C_2 Symmetric	Generation of new stereogenic centres requires substrate or reagent control	Corresponding groups are homotopic Requires monofunctionalization
 Pseudo C_2 Symmetric	Generation of new stereogenic centres requires reagent control	Requires diastereotopic group selection

of 140:1, and this result is easily understood by consideration of Newman projections of the preclosure conformations.[61] Similarly, the product ratio of **159** to **160**, reveals a facial selectivity for *si* attack of 30:1, although this selectivity is not so easily explained.[63]

IV. NATURAL PRODUCT SYNTHESIS

The wide array of desymmetrization techniques, and an understanding of the strategies for two-directional chain synthesis and desymmetrization[1] (a summary of which is presented in Scheme 48) have developed largely in response to problems associated with natural product synthesis, and this work is reviewed in the following sections (IV.1. to IV.3.).

Scheme 49



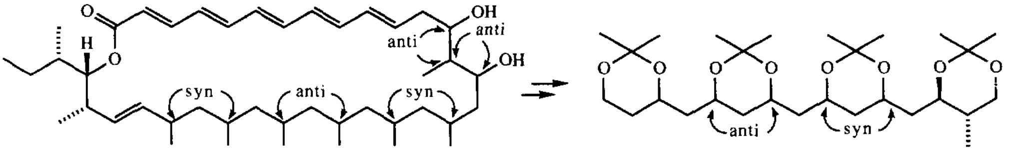
IV.1. Syntheses by Use of Achiral Chains

Schreiber used two-directional synthesis of an achiral chain to prepare a reference compound needed to establish the stereochemistry of the skipped polyol segment, C(13) — C(27), of mycotin A and B (Scheme 49).[64,65] At the outset of that work, little was known about the configuration of the natural product. Mycotin A could be converted to degradation product **163**, where only the relative configuration at C(14) and C(15) was known. Based upon analogies to the distant relative, amphotericin B,[66] Schreiber first considered the synthesis of the all *syn* protected polyol **171** as a possible equivalent to degradation product **163**.[64]

Bis(epoxide) **164** was opened with vinyl magnesium bromide, and the product was then protected as its acetonide **165**. This derivative was ozonized and again treated with vinyl magnesium bromide. Protection of the resulting alcohol gave bis(acetonide) **166** as a mixture of stereoisomers. Ozonolysis, followed by epimerization to the more stable all *syn* bis(acetonide), and reduction gave diol **167**. This diol, in turn, was converted to the bis(vinyl ether) **168**, which underwent a stereoselective 1,2 Wittig rearrangement,[67] on treatment with BuLi, to furnish diol **169**. Comparison of diol **169** with protected polyol **171** shows that the desired stereochemistry of the central six hydroxylated carbons had been achieved, and Schreiber now had to attempt a desymmetrization. He accomplished this goal using asymmetric Sharpless epoxidation — a technique described earlier (Sec. III.1.i.). Epoxidation in the presence of L-(+)-DIPT gave in good yield epoxide **170**, which was then converted to protected polyol **171**. Spectral comparison of **171** with degradation product **163** showed them to have an isomeric relationship, and thus ruled out the all *syn* stereochemical array for the natural product.

While this work was being carried out, further information on the stereochemistry of the polyol backbone of mycotin A had been obtained,[68] and a summary of the data is shown in Scheme 50.

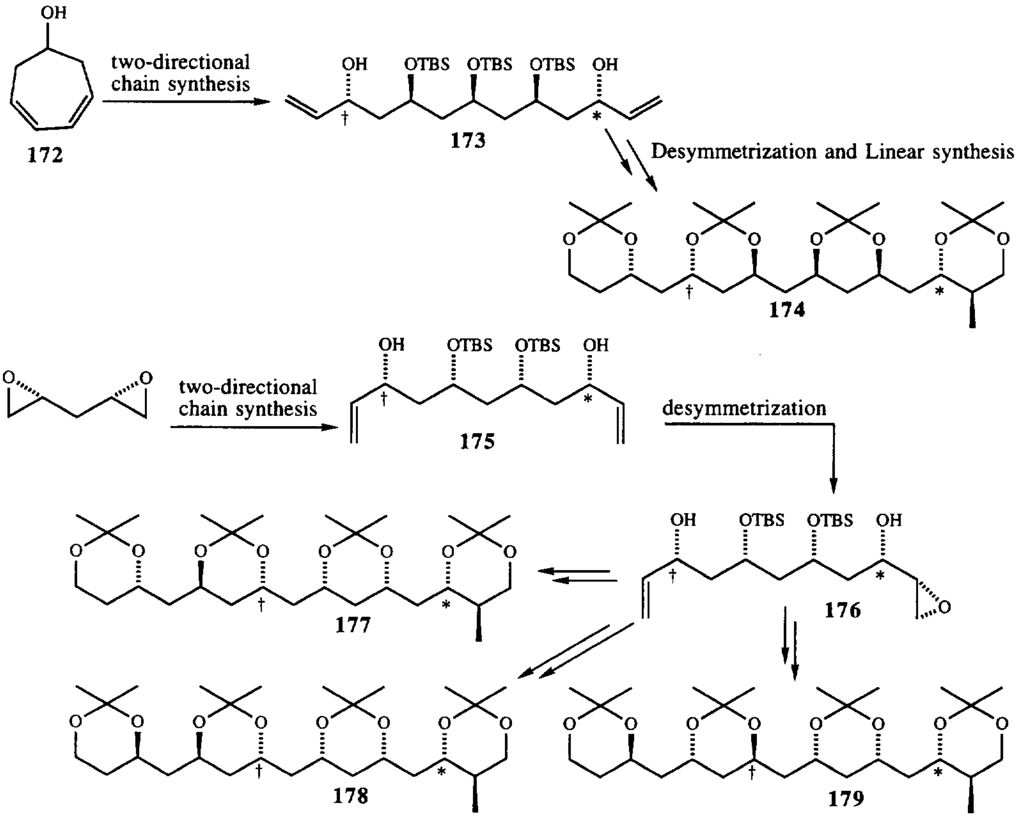
Scheme 50



163' (or enantiomer)

Having established that two-directional synthesis could be used effectively to construct a polyol chain,[64] Schreiber and co-workers set about synthesizing the possible diastereomers of the degradation product **163'**,[65] in light of the updated stereochemical information.[68] Their syntheses are summarized in Scheme 51. Of the eight possible diastereomers, they prepared four (**174**, **177-179**). In the case of diastereomer **174**, two-directional synthesis was used to construct the chain of five stereogenic carbons of intermediate **173**, whereas diastereomers **177**, **178**, and **179** were all made from common intermediate **175**, which contains four fixed stereogenic carbons. Desymmetrization of both intermediates (**173** and **175**) was carried out efficiently by Sharpless asymmetric epoxidation, and then linear synthesis was used to complete the routes to the different diastereomers. Diastereomer **179** had the same relative stereochemistry as the mycotin A degradation product **163'**; and **179** and **163'** showed an enantiomeric relationship. Thus the question of stereochemistry in the polyol backbone of mycotin A and B was solved.

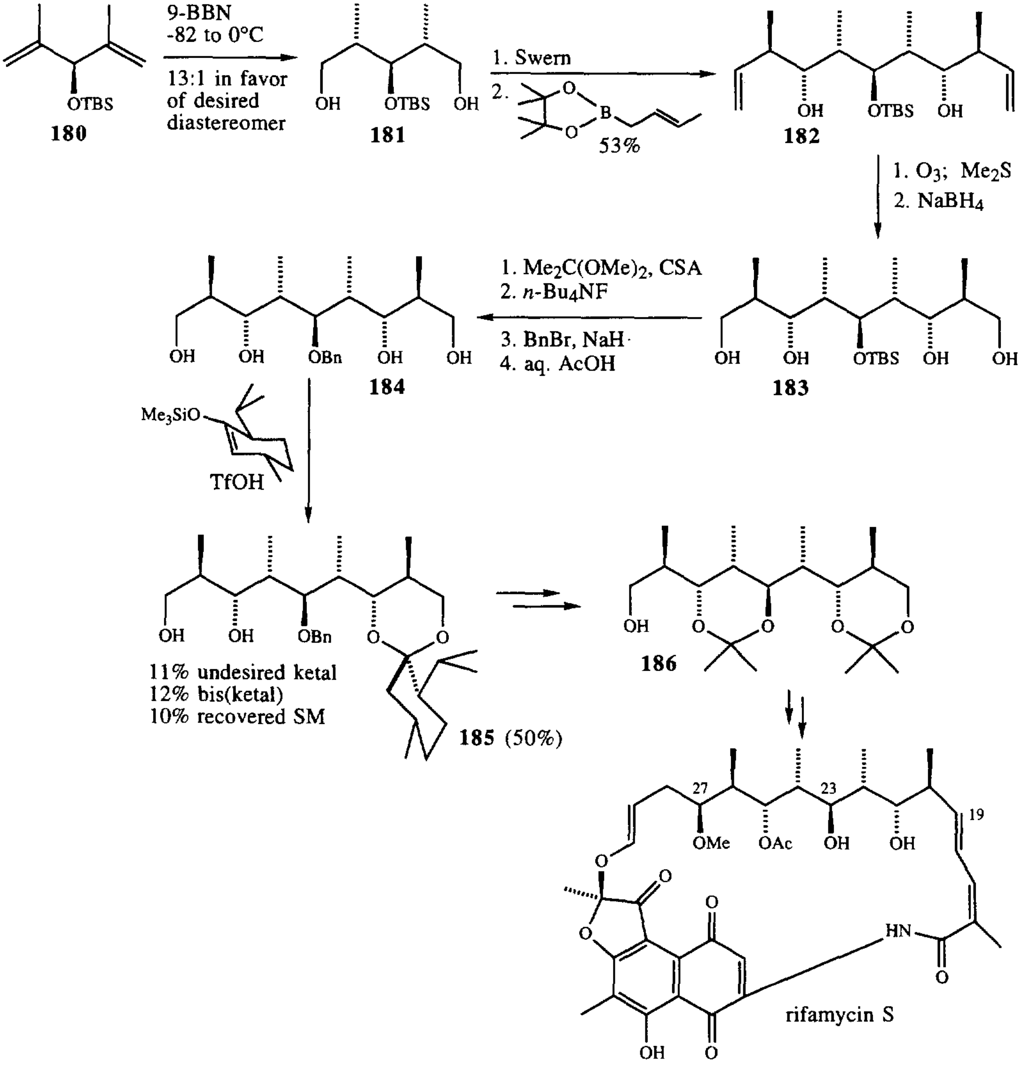
Scheme 51



A second example, again from the natural product field, of two-directional synthesis of an achiral chain is the construction of the C(19) — (27) segment of rifamycin S (Scheme 52).[69] If the C(20) — C(26) segment is considered, then a high degree of σ symmetry is apparent if C(23) is regarded as the central carbon. Harada and Oku used this symmetry to their advantage, starting with protected divinyl carbinol **180**. Double hydroboration[70] furnished diol **181** with high stereoselectivity, and the diol was oxidized to the corresponding dialdehyde. Then the remaining four stereogenic carbons were introduced convergently by double crotylboration,[71] to give *meso* **182** as a pure compound. Ozonolysis, followed by reduction, gave tetrol **183**, which was taken through a four-step procedure to replace the silyl protecting group with a benzyl group (**183** → **184**). This replacement was done because the silyl group was found to lower the selectivity of the upcoming desymmetrization, whereas use of the benzyl analogue of the starting material **180** made the separation of diastereomers at the hydroboration and crotylboration steps more difficult.

With *meso* tetrol **184** in hand, the desymmetrization was attempted, the problem here being one of differentiating the two enantiotopic 1,3-diol moieties. Based upon earlier work on kinetic resolution of racemic

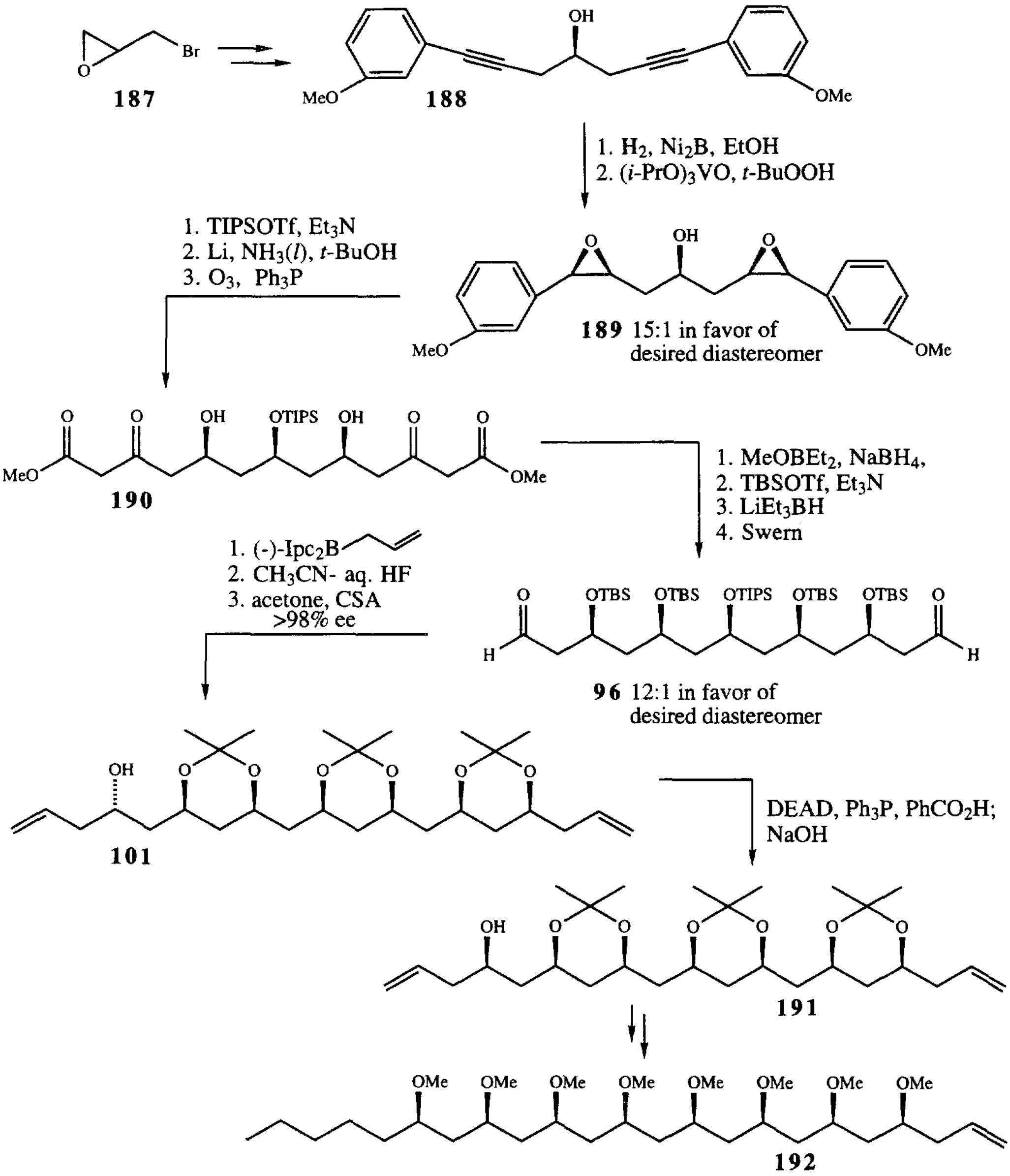
Scheme 52



mixtures of 1,3-diols,[72] **184** was treated with *d*-menthone trimethylsilyl enol ether, an operation that gave a 4.5:1 ratio of the desired monoketal **185** to the undesired monoketal, along with some bis(ketal) and recovered starting material. The desymmetrization had thereby been accomplished in a way that provided stereochemically pure **185** in acceptable yield. The desymmetrized diol **185** was carried forward to bis(acetonide) **186**, which corresponds well to the C(19) — C(27) segment of rifamycin S, and was, in fact, an intermediate in Kishi's synthesis of the natural product.[73]

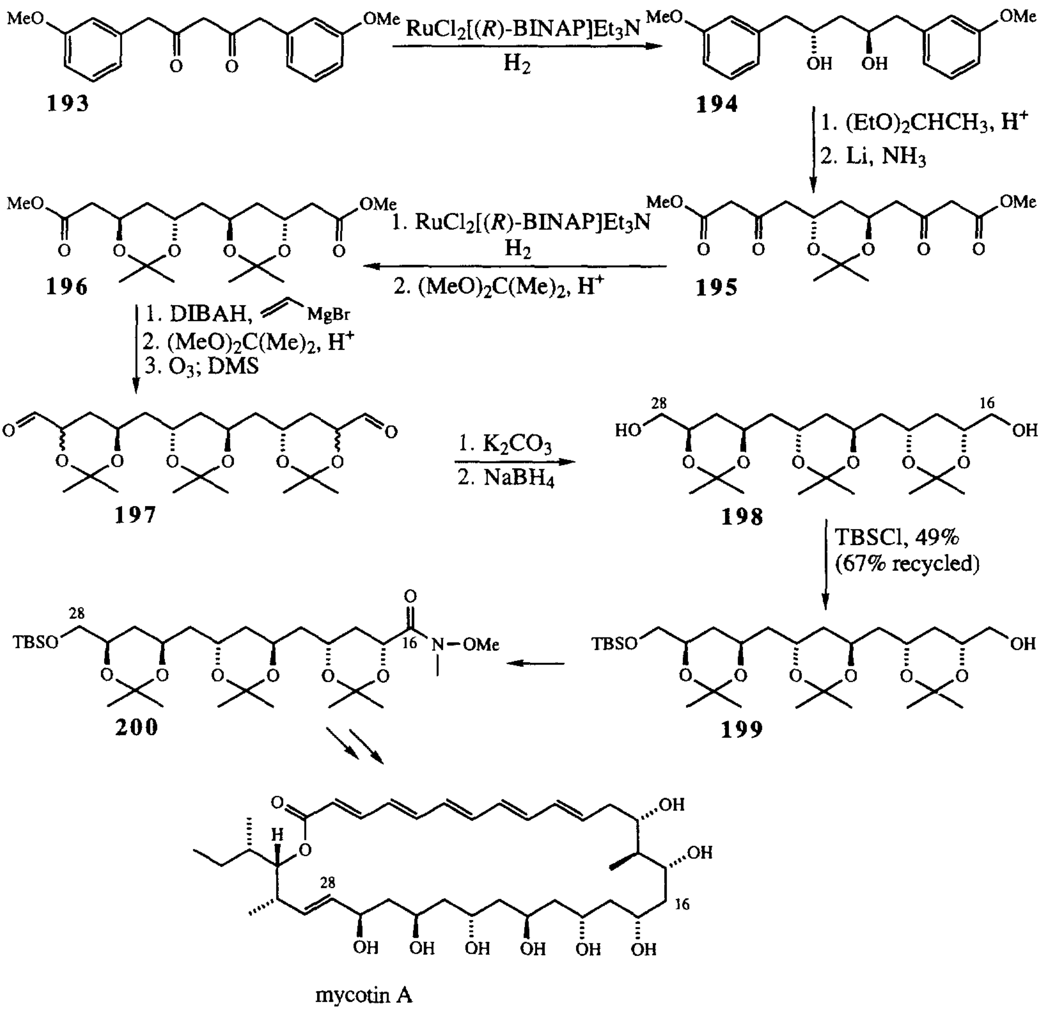
A third natural product example where two-directional synthesis of an achiral chain was used (Scheme 53) is the work on the polymethoxy compound **192**, by Wang.[36] The route followed is an application of Wang's innovative *meso* polyol desymmetrization that was examined earlier (see Scheme 30).

Scheme 53



Epoxide **187** was converted into *meso* carbinol **188**, from which semihydrogenation, followed by stereoselective epoxidation, gave bis(epoxide) **189** with good diastereoselectivity. Hydroxyl protection, followed by Birch reduction and ozonolysis, afforded diol **190**, which was converted stereoselectively into dialdehyde **96** by chelation controlled reduction, then silylation, reduction, and Swern oxidation. At this point, Wang desymmetrized **96** by converting it into tris(acetonide) **101**, using transformations considered earlier (see Sec. III.1.ii.). Mitsunobu inversion of the remaining hydroxyl group gave tris(acetonide) **191**, which was converted to the polymethoxy compound **192**, a substance isolated from a tolytoxin-producing blue green algae.[74]

Scheme 54

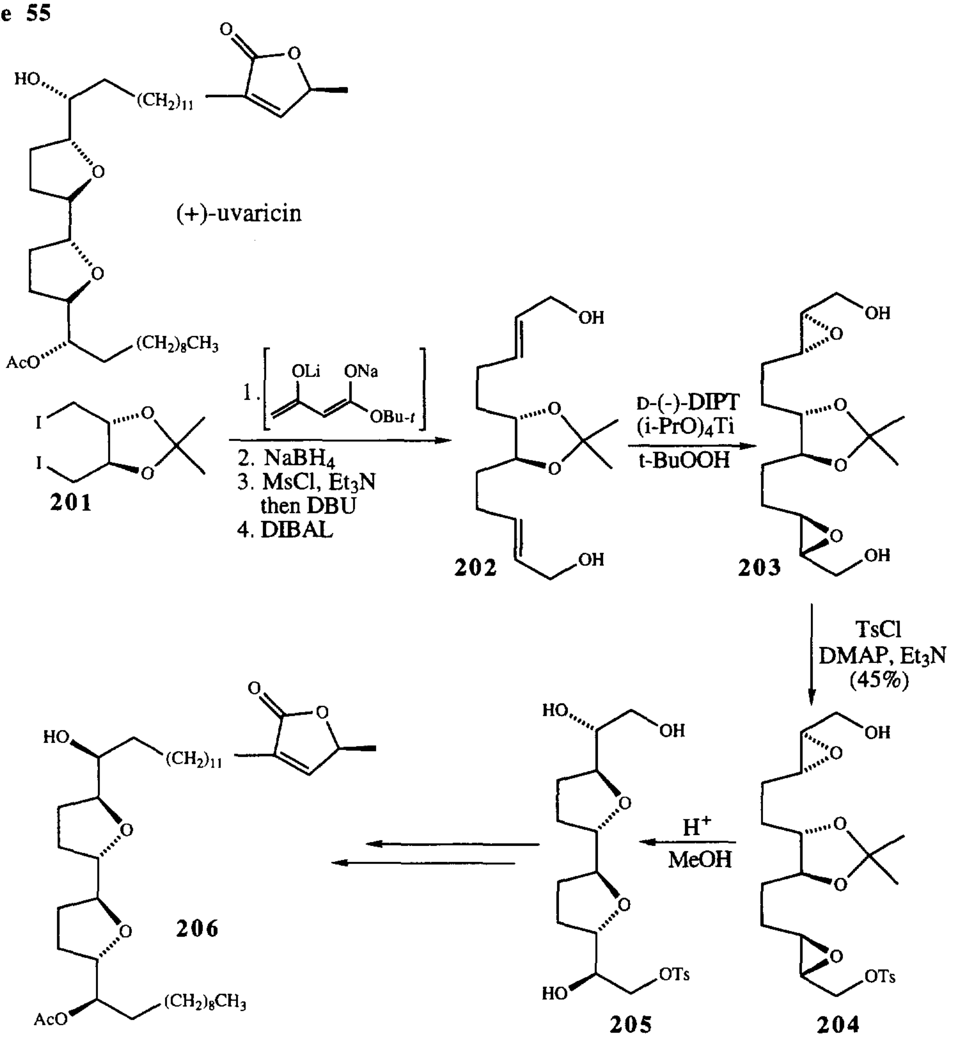


IV.2. Syntheses by Use of C_2 Symmetric Chains

Besides his work on the stereochemical assignment of mycotin A (Sec. IV.1.), Schreiber has also used two-directional synthesis to make the natural product itself (Scheme 54).[75] Instead of two-directional synthesis of an achiral chain, as in his structural studies (Schemes 49 - 51), he used a C_2 symmetric chain to construct the C(16) — C(28) fragment of the natural product.

Achiral dione **193** was subjected to a double catalytic asymmetric reduction[76] to afford C_2 symmetric diol **194**, which was then converted to dione **195**. A second asymmetric reduction (under the same conditions), followed by ketalization under equilibrating conditions, gave fully protected tetrol diester **196**. Partial reduction, Grignard addition, ketalization, and ozonolysis then afforded **197**. Finally, base catalyzed epimerization and reduction, gave diol **198**. This compound corresponds closely to the C(16) — C(28)

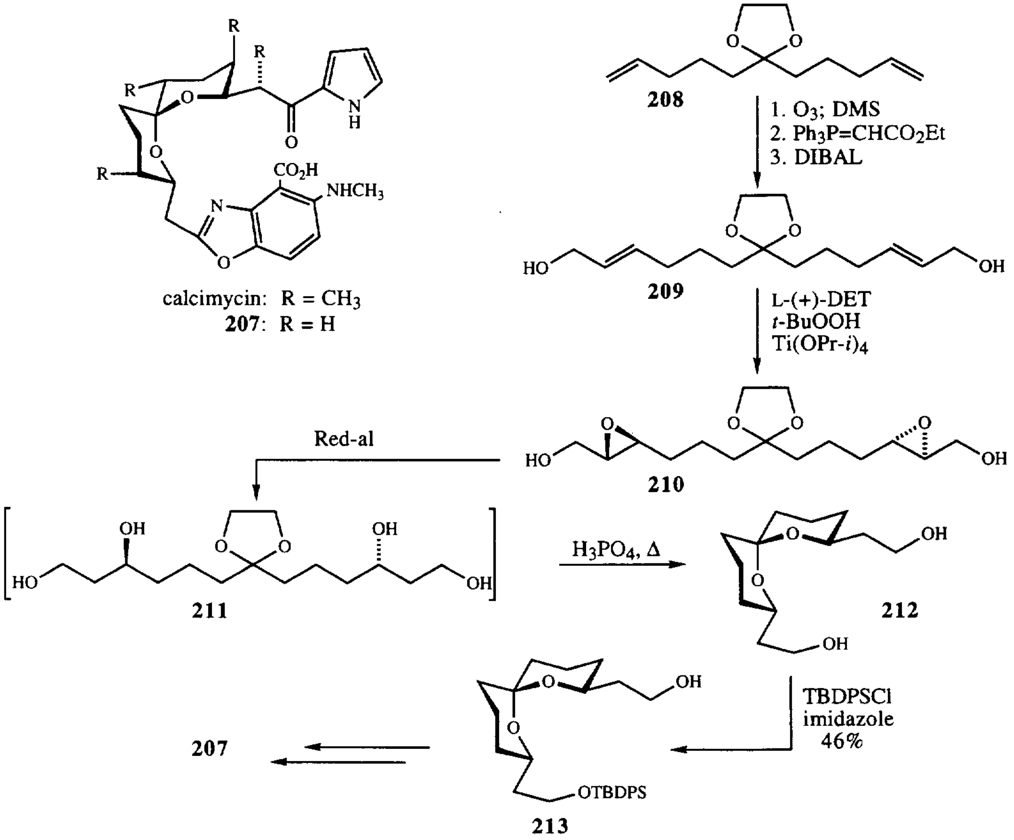
Scheme 55



segment of the natural product. Desymmetrization of **198** was effected by monoprotection of the homotopic hydroxyl groups. As is common with C_2 symmetric chain desymmetrizations (see Sec. III.2.), the product distribution was a near-statistical mixture of monoprotected **199** and the corresponding fully protected compound, although additional **199** was obtained when the bis(protected) material was recycled. The desymmetrized alcohol **199** was converted to amide **200**, and this was used in a convergent sequence to complete the synthesis of mycotin A.

Two other examples that feature a statistical distribution of products in the desymmetrization step involve the synthesis of a natural product analog. In his synthesis of the unnatural analog (**206**) of (+)-uvaricin (Scheme 55),[77] Hoye chose L-(+)-diethyl tartrate as a C_2 symmetric starting material and converted it into diiodide **201**. This product was subjected to Weiler dianion alkylation,[78] followed by ketone reduction, dehydration via the bis(mesylate), and ester reduction. These operations gave bis(allylic alcohol) **202**. Reagent-controlled epoxidation then gave bis(epoxy alcohol) **203**, which Hoye wished to desymmetrize. This goal was accomplished through monotosylation of the homotopic hydroxyl groups to give a near-statistical mixture of monotosylate **204** and the corresponding bis(tosylate). Acid catalyzed acetonide removal and

Scheme 56



epoxide opening gave monotosylate **205**, which was used to complete the synthesis of the diastereomeric analog **206** of uvaricin.

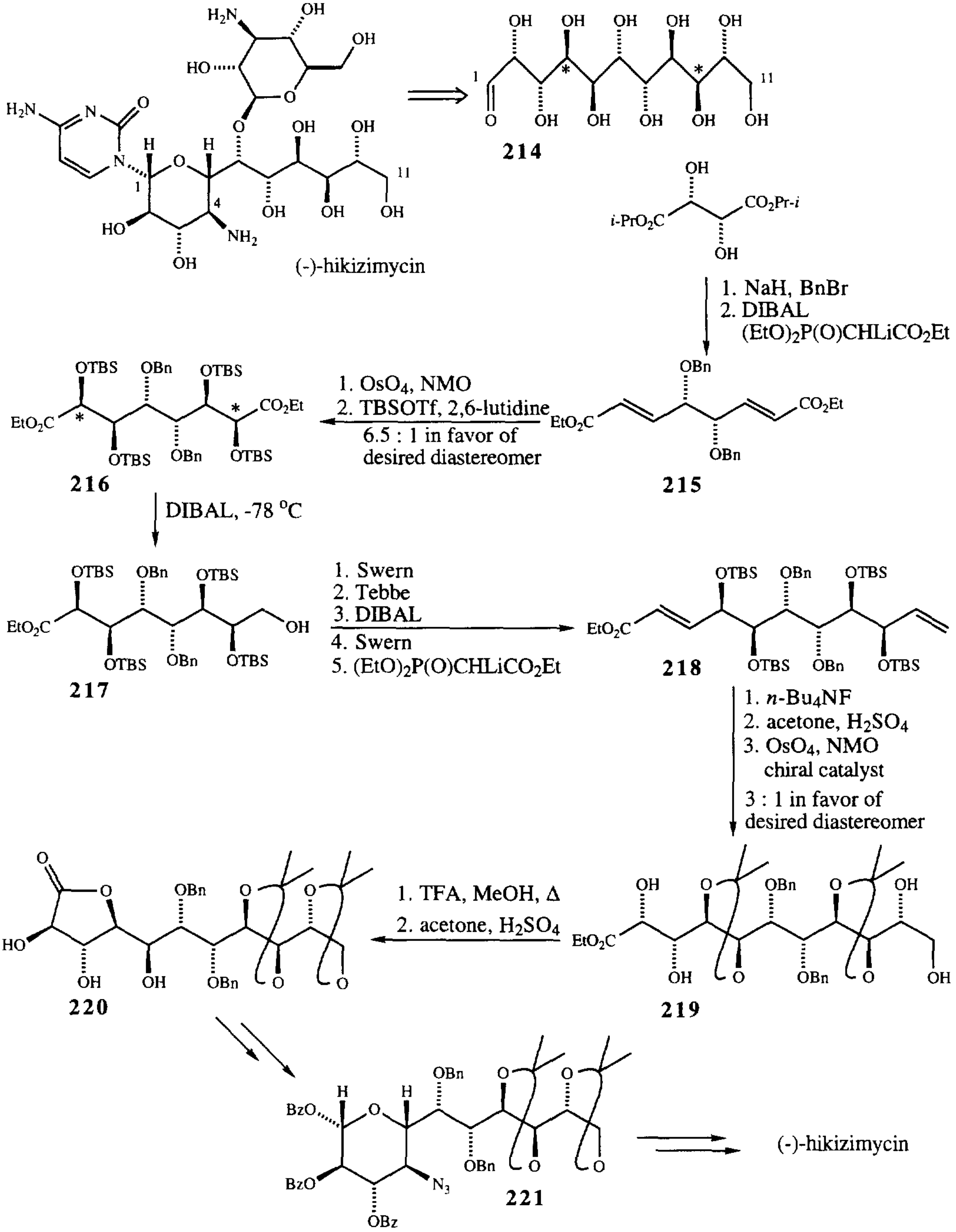
Nakahara and coworkers have used two-directional synthesis of a C_2 symmetric chain in the construction of the tetranormethyl analog (**207**) of calcimycin (Scheme 56).[79] Achiral diene **208** was ozonized to the corresponding dialdehyde, then homologated by double Wittig reaction, and reduced to give achiral bis(allylic alcohol) **209**. C_2 symmetric bis(epoxy alcohol) **210** was then made by a Sharpless asymmetric epoxidation. Regioselective epoxide opening with Red-al afforded tetrol **211** which, without isolation, underwent acid catalyzed acetonide removal and spiroketalization to C_2 symmetric diol **212**. This diol, in turn, was desymmetrized through monofunctionalization with a bulky protecting group (**212** → **213**). However, only a near-statistical product distribution was obtained. Product **213** was carried forward to complete the synthesis of tetranormethylcalcimycin (**207**).

As discussed earlier (Sec. III.2.), in certain cases it is possible to achieve a significant preponderance of monofunctionalized over bis(functionalized) material during desymmetrization of a C_2 symmetric chain. One such example is found in Schreiber's elegant synthesis of (-)-hikizimycin (Scheme 57).[80] Inspection of the polyhydroxy segment of the molecule [C(1) — C(11)] reveals that replacement of the amino group [C(4)] by a hydroxyl group, with inversion of configuration, can lead to polyol aldehyde **214**, which exhibits a high degree of C_2 symmetry. This retrosynthetic analysis generated confidence that two-directional synthesis of a C_2 symmetric chain could be used to build up the proper stereochemistry of the C(1) — C(11) segment.

The researchers chose L-(+)-DIPT as the starting material and converted it into bis(α,β-unsaturated ester) **215** by first protecting the hydroxyl groups and then performing a reduction/homologation procedure. Vicinal dihydroxylation,[11] followed by silylation, provided diester **216** with good stereoselectivity. The six stereogenic carbons in **216** correspond closely to those in polyhydroxy aldehyde **214**. At this stage desymmetrization was effected by addition of DIBAL slowly at -78°C, which reduced only one of the ester groups to the alcohol. An 80% yield of the desired monoreduced product (**217**) was isolated along with only 10% of the doubly reduced material and an even smaller amount of partially reduced (aldehyde) byproducts. The remarkably high level of monoreduction is dependent on the nature of the hydroxyl protecting groups, and it was found that when the hydroxyl oxygens were protected as acetonides the selectivity in the reduction was poor. Presumably, high selectivity requires a sufficiently flexible chain to permit folding in such a way that access to one of the ester groups is hindered.

Schreiber's team then continued with a sequential homologation of **217** in two directions by first oxidizing the hydroxyl to the aldehyde and then homologating it with Tebbe's reagent. At this stage, the other end of the molecule was manipulated by reduction of the ester group, partial oxidation of the resulting hydroxyl, and then homologation of the aldehyde to the non-symmetric diene **218**. Further two-directional synthesis by simultaneous homologation of the non-symmetric intermediate **218**[8,81] was performed. Protecting group manipulations, followed by osmylation in the presence of a chiral amine catalyst[82] gave tetrol **219** stereoselectively. Exposure to acid effected hydrolysis of the acetonides and induced stereoselective lactonization. Selective ketalization gave lactone **220**. Finally, this lactone was elaborated to the intermediate **221** and then to (-)-hikizimycin.

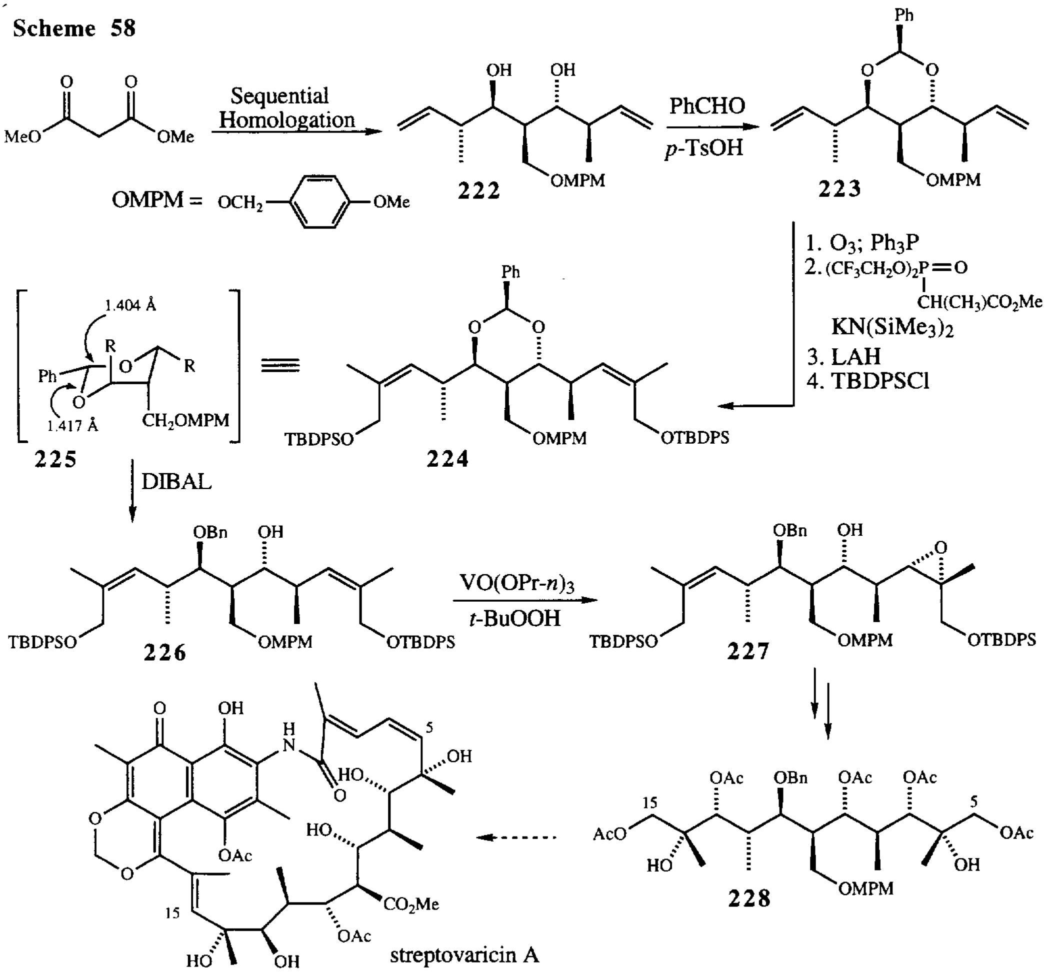
Scheme 57


(-)-hikizimycin
214
1. NaH, BnBr
2. DIBAL
(EtO)2P(O)CHLiCO2Et
215
1. OsO4, NMO
2. TBSOTf, 2,6-lutidine
6.5 : 1 in favor of desired diastereomer
216
DIBAL, -78 °C
217
1. Swern
2. Tebbe
3. DIBAL
4. Swern
5. (EtO)2P(O)CHLiCO2Et
218
1. n-Bu4NF
2. acetone, H2SO4
3. OsO4, NMO
chiral catalyst
3 : 1 in favor of desired diastereomer
219
1. TFA, MeOH, Δ
2. acetone, H2SO4
220
221
(-)-hikizimycin

IV.3. Syntheses by Use of Pseudo C_2 Symmetric Chains

Two-directional synthesis of a pseudo C_2 symmetric chain was utilized in Schreiber's stereoselective approach to the C(5) — C(15) segment of streptovaricin A (Scheme 58).[83] Diol **222** was prepared by sequential homologation of dimethyl malonate in two directions,[84] and acetalization then gave acetal **223** stereoselectively. At this point the chain was homologated in two directions to diene **224**, which Schreiber wished to desymmetrize. X-Ray analysis suggested that **224** preferentially adopts the conformation shown in **225**, with the phenyl group equatorial and the benzyloxy substituent axial. Closer analysis revealed that one of the C-O bonds of the acetal is 0.014 Å longer than the other C-O bond, as indicated in the diagram. Based upon this fact, the desymmetrization was performed by reaction of **224** with DIBAL, an operation that resulted in diastereotopic group selection by cleavage of the weaker (longer) C-O bond of the acetal, to give almost exclusively monobenzyl ether **226**. Sharpless epoxidation of **226** afforded epoxide **227** stereoselectively, and this compound was elaborated into diol **228**, which corresponds closely to the C(5) — C(15) segment of

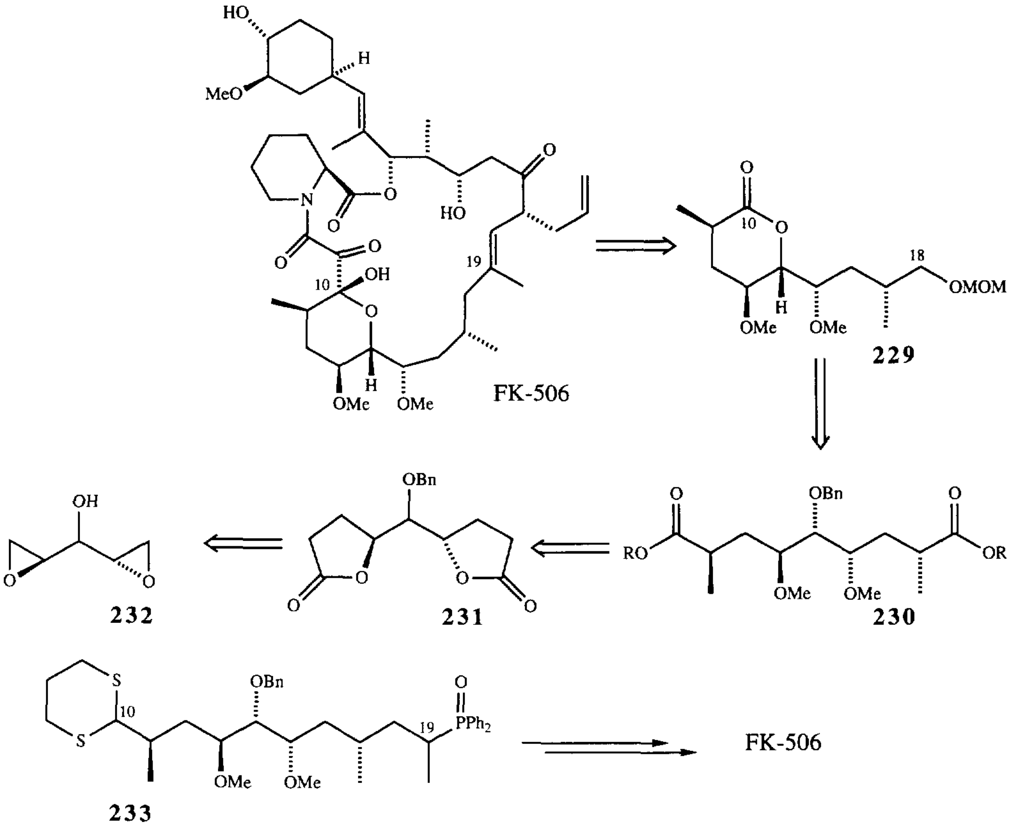
Scheme 58



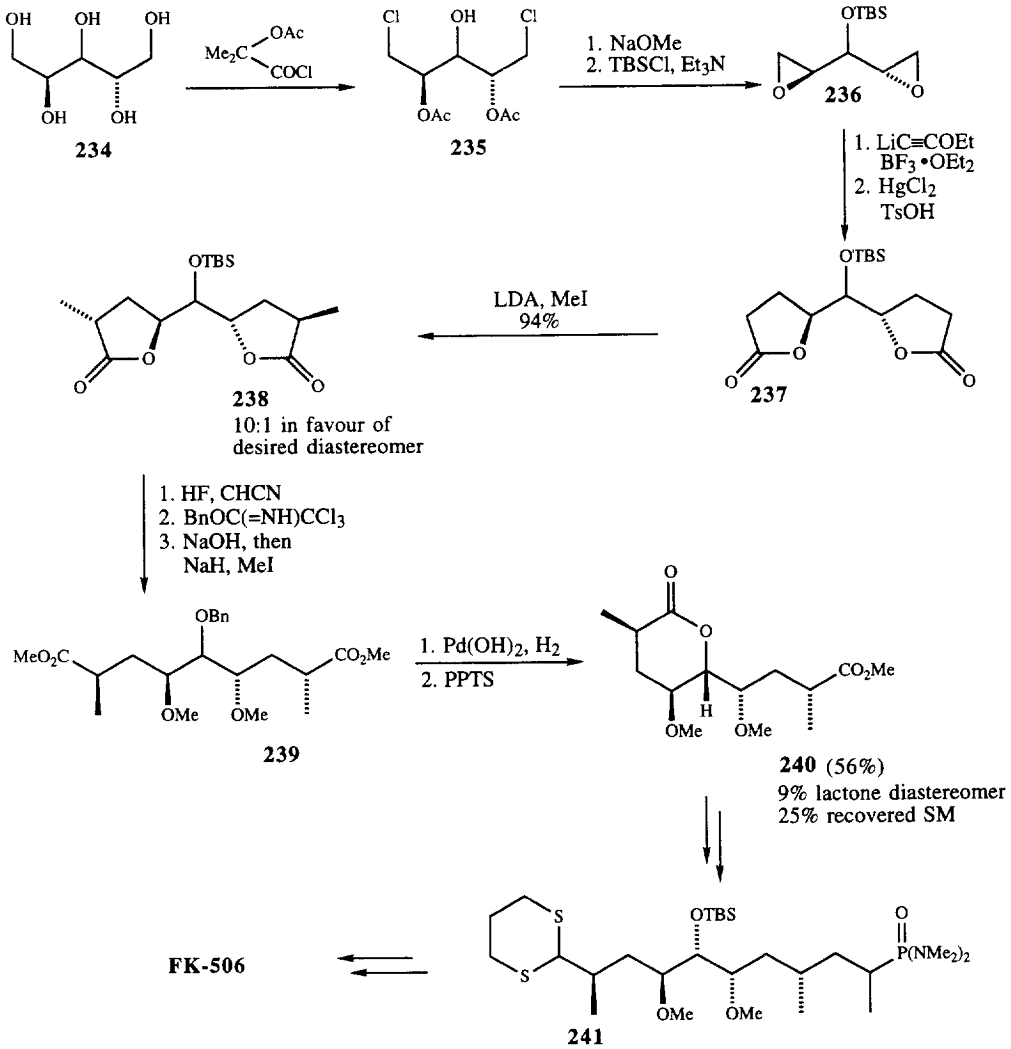
streptovaricin A.

The final example to be considered is the two-directional synthesis of the C(10) — C(19) segment of FK-506. Merck chemists carried out a retrosynthetic analysis (Scheme 59)[85] by first envisioning the C(10) — C(18) segment as the six-membered lactone **229**. The lactone would be available from diester **230** if a diastereoselective lactonization were possible. Diester **230** is highly analogous to the diacid Hoye used[58] in his kinetic lactonization work (see Sec. III.3.), so there was good reason to believe that **230** could be transformed into **229** selectively. Diester **230** would be available from optically pure bis(lactone) **231** after diastereoselective methylation α to the carbonyls. Bis(lactone) **231** would, in turn, be accessible from bis(epoxide) **232**. Intermediates **232**, **231**, and **230** are all pseudo C_2 symmetric molecules, and so execution of this plan would involve two-directional synthesis of this class of chain. Having completed their careful analysis, the Merck group expressed some concern about the desymmetrization, and then proceeded to carry out a one-directional synthesis of **233** (a synthetic equivalent of **229**),[86] which they carried on to complete their synthesis of FK-506.

Scheme 59



Scheme 60



Less than a year after the Merck communication, Schreiber published a synthesis[87] of the C(10) - C(19) segment of FK-506 (Scheme 60). The route started with commercially available optically pure pentol **234**. Treatment with Moffat's acid chloride reagent[88] gave diacetoxy dichloride intermediate **235** which, on acetate saponification, epoxide formation, and hydroxyl group protection, gave bis(epoxide) **236**. Treatment of **236** with the lithium anion of ethoxyacetylene in the presence of boron trifluoride etherate, followed by exposure to acid, furnished bis(lactone) **237**. Methylation proceeded with high diastereofacial selectivity[59] to dimethyl bis(lactone) **238**. The silyl protecting group was replaced with a benzyl group, and then the lactones were opened, followed by exhaustive methylation to dimethoxy dimethyl ester **239**. Debenzylation prepared the diester for the key desymmetrization, which was carried out by acid catalyzed lactonization.[89] As expected, the lactonization exhibited a diastereotopic group selection, and the desired lactone **240** was formed in a 6:1 ratio with the undesired lactone, together with an appreciable amount of starting material. Any attempt to push the reaction to completion resulted in reduced selectivity. The desymmetrized product was transformed into FK-506 precursor **241**, which Schreiber used to complete his synthesis of the natural product.[90] Schreiber's FK-506 precursor (**241**) corresponds closely to the Merck FK-506 precursor (**233**, Scheme 59), and so a comparison of the syntheses of these molecules illustrates nicely the efficiency that can be obtained with two-directional synthesis. The one directional route to **233** required 25 steps and gave an overall yield of 3.1%, while the Schreiber synthesis of **241**, which utilized two-directional methodology, needed only 17 steps and gave nearly twice the overall yield (6.0%).

V. CONCLUSIONS

The syntheses covered in this review illustrate the wide array of structures to which the two-directional strategies may be applied. This fact is particularly true of the expanding field of techniques that can differentiate the termini of a chain. Although most examples of two-directional synthesis have appeared quite recently, the strategy is clearly a powerful tool for efficient construction of a large number of natural products.

VI. ACRONYMS

9-BBN	9-borabicyclo[3.3.1]nonane
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BOM	benzyloxymethyl
CSA	10-camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate
DIBAL	diisobutylaluminum hydride
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPT	diisopropyl tartrate
DMAP	4-dimethylaminopyridine
DMS	dimethyl sulfide
HMPA	hexamethylphosphoramide
Ipc	Isopinylcampheyl
KHMDS	potassium 1,1,1,3,3,3-hexamethyldisilazide
LDA	lithium diisopropylamide
LHMDS	lithium 1,1,1,3,3,3-hexamethyldisilazide
NMO	4-methylmorpholine *N*-oxide
PPTS	pyridinium *p*-toluenesulfonate
TBAF	tetrabutylammonium fluoride
TBDPS	*t*-butyldiphenylsilyl
TBS	*t*-butyldimethylsilyl
TFA	trifluoroacetic acid
TIPS	triisopropylsilyl
TMS	trimethylsilyl

ACKNOWLEDGEMENT

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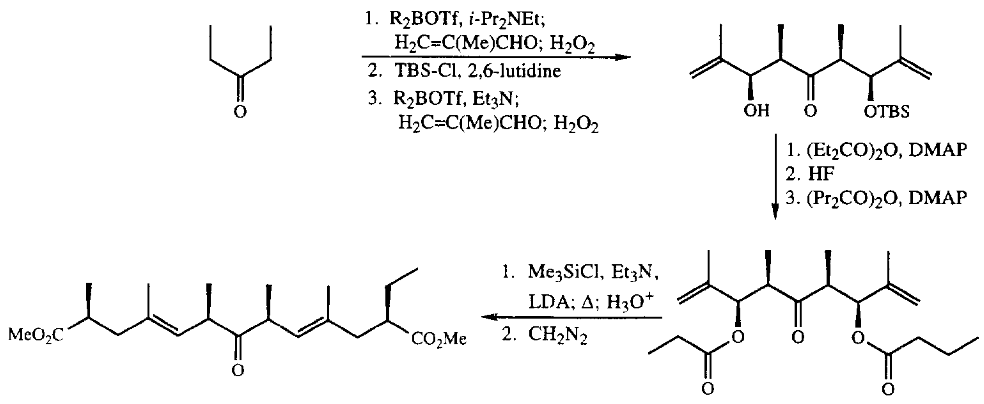
Scheme 61



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