Oxo Polyene Macrolide Antibiotics

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Contents

Scott D. Rychnovsky was born in Albuuerque, NM, and was raised in Livermore, CA. He received his B.S. degree in 1981 from the University of California, Berkeley, and his Ph.D. degree in 1986 from Columbia University working under the direction of Gilbert Stork. Following a one year NIH postdoctoral Fellowship at Harvard with David Evans, he moved to the lab of Stuart Schreiber at Yale University for a second postdoctoral appointment. He began his independent research career at the University of Minnesota in 1988 were he curently holds the rank of Associate Professor. In addition to biologically active natural products, his interests include the development of new methods for convergent synthesis and the development of new enantioselective reactions.

I. Introduction

The polyene macrolide antibiotics are a large group of natural products with over 200 members. Several members of this class, such as amphotericin B, nystatin, and pimaricin, are important antifungal agents and have been used extensively in medicine. The resurgence of life-threatening fungal infections has renewed the interest in antifungal agents,[1] and polyene macrolides are still some of the most effective clinical antifungal agents known. All of these natural products are macrolides that incorporate a conjugated polyene ranging from three to seven double bonds in length. They also contain a polyol section made up of a sequence of 1,2-, 1,3-, and 1,4-diols, with 1,3-diols being the most common. Several members of this class have a sugar, usually the amino sugar D-mycosamine, attached by a β-linkage to one of the alcohols in the macrolide ring. The polyene macrolide antibiotics can be further divided into two groups: those that have the polyene across the ring from the lactone carbonyl and those that have the polyene in conjugation with the lactone. This review will be restricted to the latter group, usually described as the oxo polyene macrolides, and covers the period from 1984 through 1994.

Several reviews have been published describing the isolation, synthesis, and biological activity of the polyene macrolide antibiotics. A definitive review on the isolation and structure of the polyene macrolide antibiotics was published by Omura in 1984.[2] Polyene macrolide antibiotics such as amphotericin B are believed to exert their antifungal activity by formation of ion channels in cell membranes. The biological activity of amphotericin B and other polyene macrolides has been extensively reviewed.[3] Small polyene macrolide antibiotics do not form ion channels but rather disrupt membranes through less specific interactions.[4] Most of the oxo polyene macrolides fall into this category with the notable exception of roflamycoin, which has been shown to form sterol-dependent ion channels similar to those observed with amphotericin B.[5] These articles should be consulted for more information on the biological activity and antifungal activity of the oxo polyene macrolide antibiotics.

The structure and especially the stereochemical configuration of the polyene macrolides has been an area of active research since Omura's review. At that time amphotericin B was the only polyene macrolide for which a complete three-dimensional structure was known; its X-ray crystal structure was reported in 1970.[6] By 1984 the constitution of approximately 40 other polyene macrolides had been established through classic degradation studies, NMR spectroscopy, and analyses of mass spectra fragmentation patterns.[2] Since 1984 the stereochemical configuration of 10 polyene macrolide antibiotics have been determined by a variety of methods, and structures for all of these except the oxo polyenes are illustrated in Chart 1. An excellent review article by Beau summarizes this work through 1989.[7] The partial configuration of lienomycin was established by degradation, NMR

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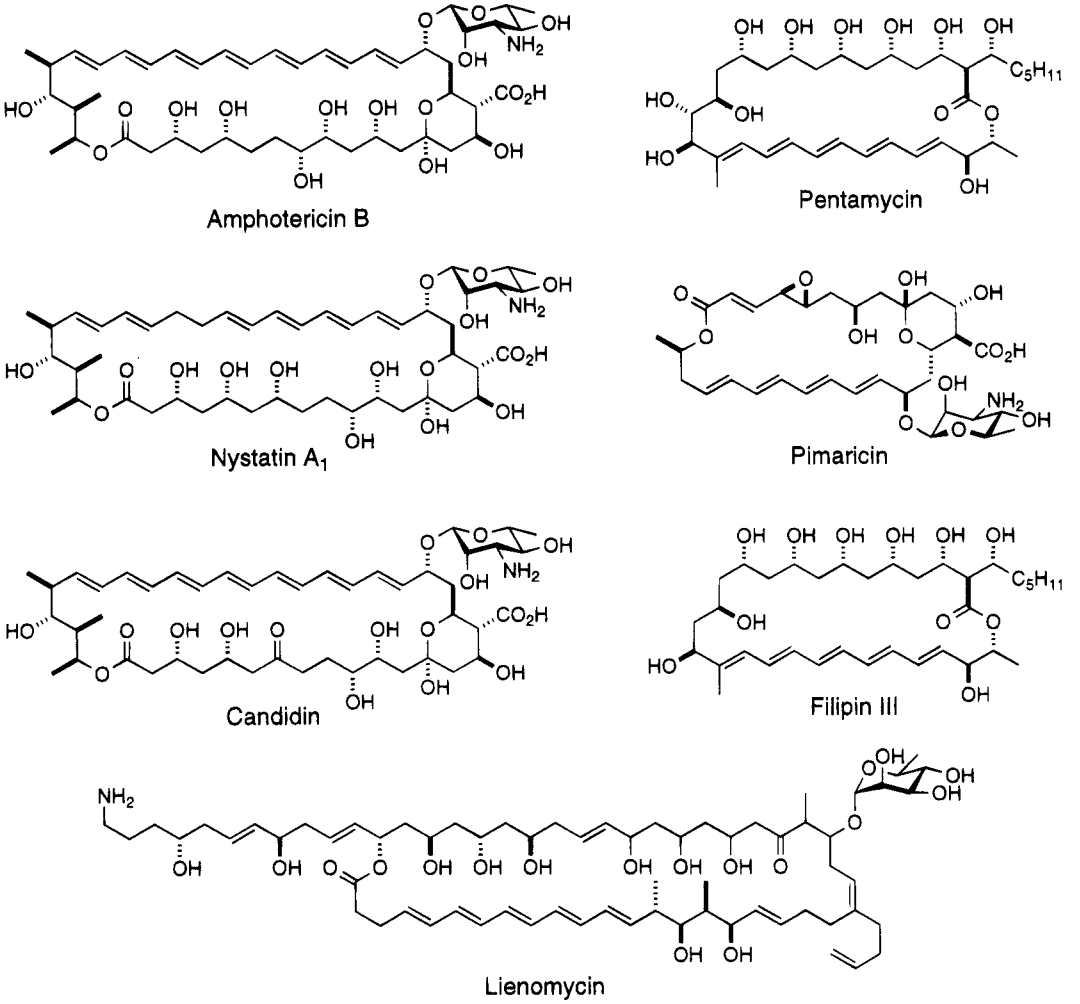
Chart 1. Structures and Configurations of Polyene Macrolide Antibiotics



spectroscopic analysis, synthesis and correlation of fragments, and CD analysis of a derivative.[8] The complete structures of mycoticin A and B were determined by Schreiber's group, and their analysis is described in detail below.[9] The stereochemical structure of roxaticin was determined by Maehr's group in only the second X-ray crystal structure of a polyene macrolide antibiotic derivative.[10] The configuration of both nystatin and pimaricin were determined by Beau's group using chemical degradation and extensive NMR spectroscopic analysis.[11] The configuration of pentamycin was determined by Oishi and Nakata using a systematic degradation of the polyol chain combined with NMR analysis.[12] The configuration of roflamycoin was determined by Rychnovsky's group using degradation and ^{13}C NMR acetonide analysis, and is described in more detail below.[13] In an impressive display of the advances in NMR techniques, the configuration of candidin was determined by Borowski's group using only NMR spectroscopic analysis.[14] Most recently, the configuration of filipin III was identified by Rychnovsky's group using ^{13}C NMR acetonide analysis.[15] Recent structural work on the oxo polyene macrolides will be described below; for other polyene macrolide structure assignments, Beau's review and the original literature should be consulted.

The polyene macrolide antibiotics are challenging targets for synthetic chemists. The early work in this area focused exclusively on amphotericin B because it was the only polyene macrolide with a completely established structure from 1970 until 1987. Many groups worked on the synthesis of amphotericin B, but the only total synthesis was reported by Nicolaou in 1987.[16] Another notable achievement in this area was the total synthesis of amphoteronolide B by Masamune's group in 1988.[17] The synthetic work directed toward the preparation of amphotericin B has been reviewed.[7,18] Recent developments in the synthesis of alternating polyol chains have also been reviewed.[19]

II. Isolation and Constitution of Oxo Polyene Macrolides

The oxo polyene macrolide antibiotics have been isolated from actinomyces soil bacteria, usually of the genera *Streptomyces*. The oxo polyene macrolides are listed in Table 1, and their structures, where known, are presented in Chart 2. Table 1 is organized by molecular formula so that stereoisomers are grouped together. The molecular formulas for AB 315[20] and nigrofungin[21] have not been reported, but each was classified as an oxopentaene macrolide on the basis of its UV spectrum. The smallest member of the class is roxaticin, which is coproduced with the mycoticins.[10] RK-397 was recently isolated by Osada's group and has the constitution of 14-desmethyl

Table 1. Isolation of Oxo Polyene Macrolides

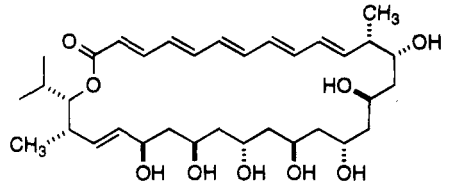
name	alternate name	isolated from	formula	CAS Registry number	ref(s)	notes
AB 315		Gluconobacter sp. W-315		83930-55-6	20	mixture of compounds
nigrofungin		Streptomyces albocyaneus subspecies niger subspecies nova		70852-43-6	21	
roxaticin		Streptomyces sp. X-14994	$C_{34}H_{54}O_9$	121073-99-2	10	coproduced with mycoticins
RK-397		Streptomyces sp. 87−397	$C_{35}H_{56}O_{10}$	154396-73-3	22	
mycoticin A		Streptomyces ruber	$C_{36}H_{58}O_{10}$	29919-25-3	9,23,24	ratio of A/B 1:1
flavofungin A	mycoticin A	Streptomyces flavofungini	$C_{36}H_{58}O_{10}$	38328-44-8	26,27	ratio of A/B 10:1
faeriefungin A	mycoticin A	Streptomyces griseus var. autophicus	$C_{36}H_{58}O_{10}$	123166-67-6	29	ratio of A/B 1:1
fulongmycin A	mycoticin A	Streptomyces sp. B1829	$C_{36}H_{58}O_{10}$	29919-25-3	28	ratio of A/B 2:1
surgumycin		Actinomyces surgutus	$C_{36}H_{60}O_{11}$	51938-50-2	32	
mycoticin B		Streptomyces ruber	$C_{37}H_{60}O_{10}$	29843-28-5	9,23,24	
flavofungin B	mycoticin B	Streptomyces flavofungini	$C_{37}H_{60}O_{10}$	38114-03-3	26,27	
faeriefungin B	mycoticin B	Streptomyces griseus var. autophicus	$C_{37}H_{60}O_{10}$	123166-68-7	29	
fulongmycin B	mycoticin B	Streptomyces sp. B1829	$C_{37}H_{60}O_{10}$	29843-28-5	28	
roseofungin		Actinomyces roseoflavus var. Roseofungini	$C_{39}H_{62}O_{10}$	12687-98-8	33	
dermostatin A		Streptomyces viridogriseus Thirum	$C_{40}H_{64}O_{11}$	51053-36-2	34	
roflamycoin		Streptomyces roseoflavus ARIA 1951 var. jenesis nov. JA 5068	$C_{40}H_{66}O_{12}$	77814-07-4	13,35	Also produced by Streptomyces maghwi
flavomycoin	roflamycoin	Streptomyces roseoflavus ARIA 1951 var. jenesis nov. JA 5068	$C_{40}H_{66}O_{12}$	11076-76-9	13,35	
dermostatin B		Streptomyces viridogriseus Thirum	$C_{41}H_{66}O_{11}$	51141-40-3	34	
brunefungin	antibiotic 2−4	Actinomyces brunneofungus	$C_{41}H_{68}O10$	68248-04-4	38	
flavopentin	antibiotic 703		$C_{41}H_{66}O_{10}$	68248-02-2	38	

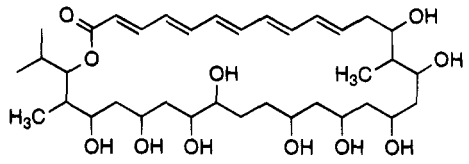
mycoticin A, although its configuration has not been established.[22]

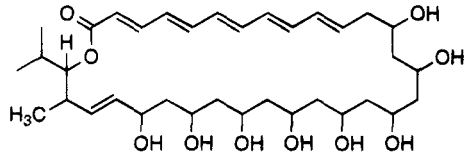
Mycoticin played an important role in the understanding of the oxo polyene macrolides. Mycoticin was the first of the oxo polyene macrolides isolated,[23] and it was the first to have its flat structure determined.[24] The biosynthesis of mycoticin was studied by Wasserman who found, not unexpectedly, that the carbon skeleton was made up of acetate and propionate units.[25] Mycoticin was also the first oxo polyene to have its stereochemical configuration fully elucidated.[9] Mycoticin A and B are apparently widespread secondary metabolites in soil bacteria. Although originally isolated from *Streptomyces ruber*, they have subsequently been isolated from *Streptomyces flavofungini* and called flavofungin A and B.[26] The flavofungins were later found to be identical with the mycoticins.[27] They have also been isolated from *Streptomyces* sp. B1829 and called fulongmycin A and B.[28] The structure diagram in the fulongmycin isolation paper shows a (*Z*)-C10−C11 double bond, but it is clear from the discussion that fulongmycin A and B are identical with mycoticin A and B. The structures of faeriefungin A and B, isolated form *Streptomyces griseus* var. *autophicus*, present a problem.[29] They are described as stereoisomers of the mycoticins on the basis of differences in their biological activity, CD spectrum, and optical rotation. The optical rotations and CD spectra can be very misleading in oxo polyenes because of the presence of olefin isomers. For example, the mycoticins undergo *E/Z* isomerization on exposure to light, and the optical rotation has been reported to range between +63.4° and −41.3° depending upon the duration of light exposure.[30] Thus the optical rotation and CD spectra are very misleading indicators for structural comparison. On the other hand, the reported ^{13}C NMR spectrum for faeriefungin A in DMSO is virtually superimposable with that reported for flavofungin A (mycoticin A) with the largest difference in chemical shift only 0.6 ppm.[31] Without a clear-cut difference in an easily reproducible physical measurement, one must conclude that faeriefungin A and B are identical to mycoticin A and B.

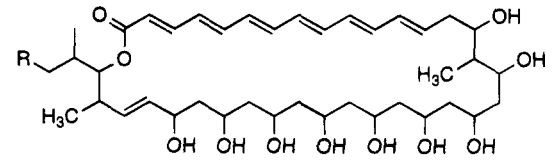
The structure of surgumycin was determined by Shenin and contains a 1,2,4-triol unit reminiscent of amphotericin B.[32] Shenin also determined the structure of roseofungin,[33] which undoubtedly exists as a cyclic hemiacetal rather than as a diketone. The structures of dermostatin A and B were worked out by Reinhart's group and appear to be higher homologs of the mycoticins.[34] Indeed, Maehr's group has proposed that the dermostatins share the same stereochemical structure as roxaticin and the mycoticins, but the configurations of the dermostatins remain unknown.[10] Roflamycoin, originally called flavomycoin, was first isolated by Schlegel's group from *Streptomyces roseoflavus*,[35] and has been reisolated from *Streptomyces maghwi*.[36] The flat structure was determined in collaboration with Borowski's group,[37] and the configuration of roflamycoin was determined by Rychnovsky's group.[13] The molecular formulas for brunefungin and flavopentin have been reported, but their constitutional structures have not been determined.[38]

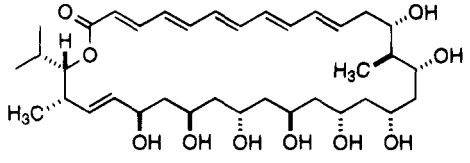
Chart 2. Structures of Oxo Polyene Macrolide Antibiotics

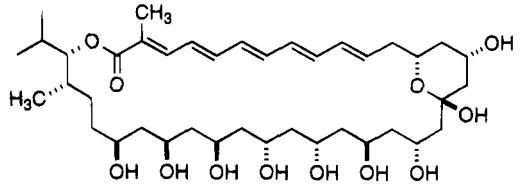

Roxaticin

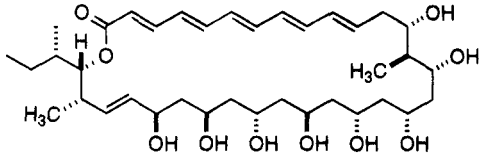

Surgumycin

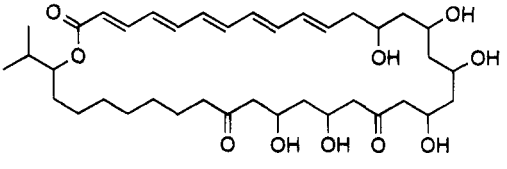

RK-397


Dermostatin A [R = H]
Dermostatin B [R = CH_3]


Mycoticin A


Roflamycoin


Mycoticin B


Roseofungin

In Omura's 1984 review the constitutional structures were known only for mycoticin, dermostatin, and roflamycoin, and the stereochemical configurations were all unknown. In the last 10 years four more constitutional structures have been determined. New methods and strategies have been developed for the stereochemical elucidation of polyol chains, and this has resulted in configurational assignment for four oxo polyene macrolide antibiotics since 1984.

III. Configuration of Oxo Polyene Macrolides

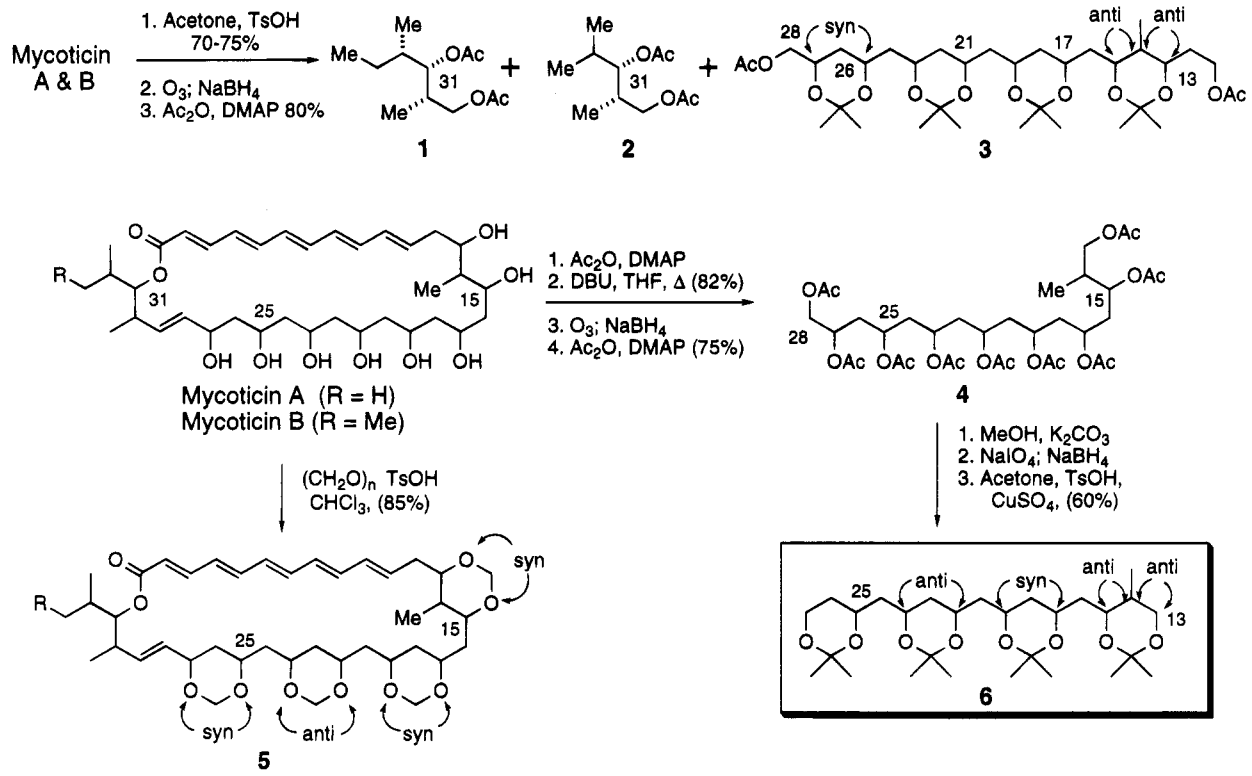
A. Configuration of Mycoticin

The configuration of mycoticin was determined in Schreiber's lab by a combination of chemical derivatization, NMR spectroscopic analysis, and synthesis of degradation fragments. Several derivatives were prepared as illustrated in Scheme 1 and studied by NMR spectroscopy.[9a,b] The most informative of these was the tetraformal **5** (R = H and Me). All of the carbinol methine signals were resolved in the ^1H NMR spectrum and each could be assigned by COSY analysis. It was assumed that each of the four 1,3-dioxane rings adopted a chair conformation, and the relative configuration of the two stereogenic centers in each ring were assigned by NOE experiments. NOE studies also showed that the C14 methyl group was anti to both the C13 and C15 oxygens, which confirmed the assignment on the basis of coupling constants in the tetraacetonide **3**.

Oxidative degradation was used to produce smaller fragments for NMR study and direct correlation (Scheme 1). Mycoticin A and B were protected as tetraacetonides and then oxidized with ozone. Reduction with $NaBH_4$ and acetylation gave a single tetraacetonide **3** and two acetylated diols, **1** and **2**. The isolation of a single tetraacetonide indicates that both mycoticin A and B share a common partial structure in the C11–C28 region. Mycoticin A and B differ by the presence of an extra methylene group in mycoticin B; the degradation fragment **1** arose from mycoticin B while the degradation fragment **2** arose from mycoticin A. The structure and configuration of both **1** and **2** were determined by direct correlation with derivatives prepared by the Evans aldol reaction. Tetraacetonide **3** was too complex to have its structure confirmed by correlation with synthetic material, and so a new degradation sequence was developed.

The octaacetate of mycoticin was prepared and treated with DBU to eliminate the C13 acetate (Scheme 1). Ozonolysis followed by reduction and acetylation gave the saturated peracetate **4**. Compound **4** was further degraded by hydrolysis and periodate cleavage of the C27–C28 bond. Reduction and acetonide formation gave the key tetraacetonide **6**. The relative configuration of C13–C14, C14–C15, C17–C19, and C21–C23 were known from analysis of tetraformal **5**. What remained to be determined were the relationships between C15–C17, C19–C21,

Scheme 1

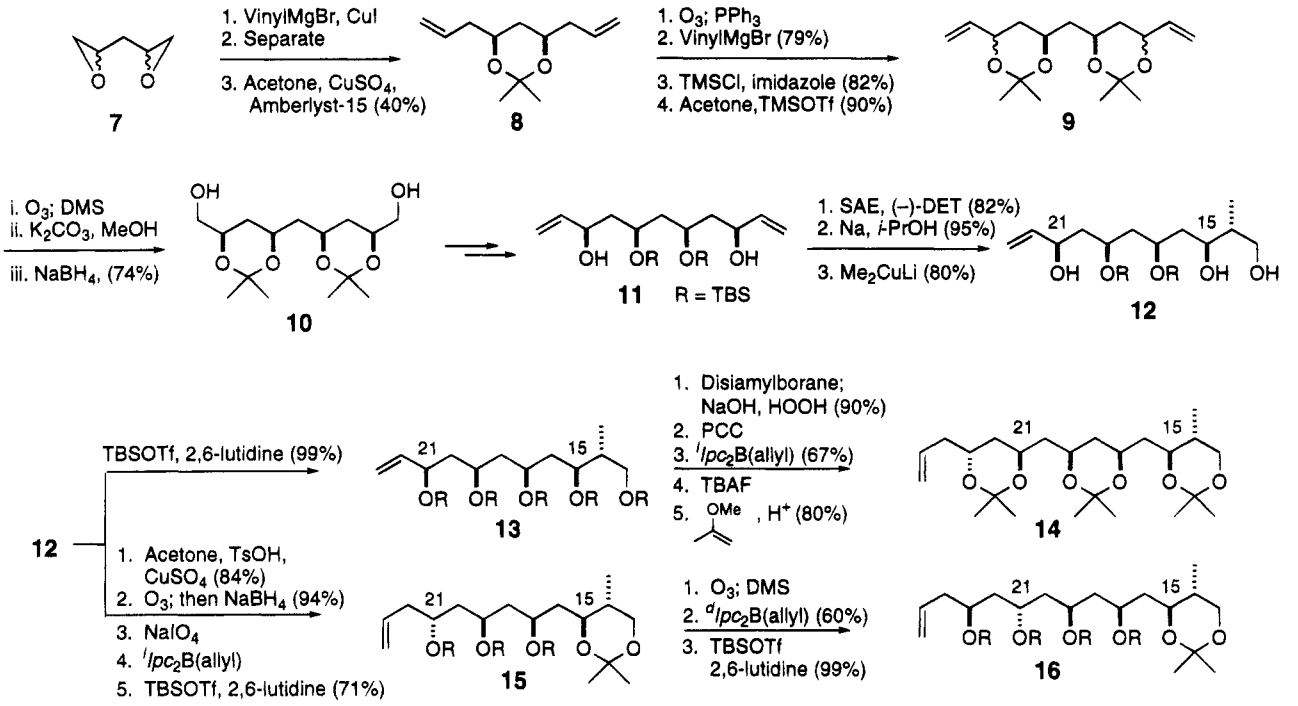


and C23–C25 and the absolute configuration of the material. Thus degradation product **6** was one of 16 possible stereoisomers and one of 8 possible diastereomers. Schreiber and Goulet choose to assign these centers by stereoselective synthesis of the likely isomers and direct correlation with the degradation fragment **6**. The first stereoisomer of **6** that they synthesized had an anti relationship between C15 and C17 and did not match the natural material. The NMR spectra of synthetic and natural **6** showed significant differences in the protons around C15, and Schreiber concluded that the synthetic anti configuration between C15 and C17 was incorrect. Thus four possible stereoisomers of tetraacetonide **6** with a syn relationship at C15–C17 remained: tetraacetonides **17**–**20** in Scheme 3.

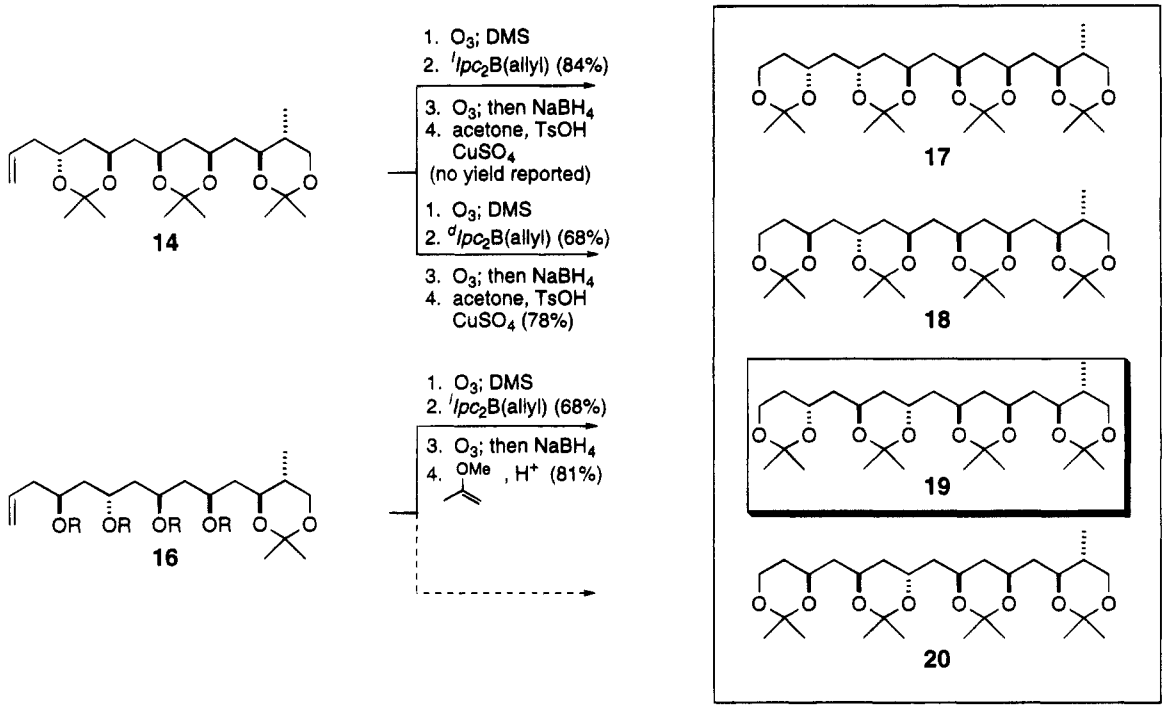
The synthesis of the stereoisomers of tetraacetonide **6** were designed using Schreiber's two-directional chain strategy[39] and Brown's enantioselective allylboron reagents.[40] Syntheses of all four isomers was planned so as to proceed through the common intermediate **11**. The preparation of **11** followed the route outlined in Scheme 2.[41] A random mixture of all possible stereoisomers of diepoxide **7** was treated with vinylmagnesium bromide and CuI. The resulting mixture of stereoisomers was separated, and the syn isomer was protected as an acetonide. Ozonolysis, addition of vinylmagnesium bromide, and reprotection using Noyori's procedure[42] gave tetraacetonide **9**. The all-syn relative configuration was set by equilibration of the corresponding dialdehydes before reduction to give diol **10**. Both Stork[43] and Schreiber[44] had previously used this strategy with aldehydes or ketones adjacent to 1,3-dioxane rings to establish syn 1,3-diol relationships, and Nakata and Oishi's convergent synthesis of alternating polyol chains was based on the same equilibration strategy.[45] Details for the conversion of **10** to **11** have not been reported.[41] Acetonide **10** could also have been prepared by dual 1,2-Wittig rearrangement of the corresponding diallyl ether, but this rearrangement has not been reported for the *tert*-butyldimethylsilyl (TBS)-protected substrate that would give **11**.[46] Meso diol **11** was desymmeterized using the Sharpless asymmetric epoxidation (SAE).[47] Payne rearrangement followed by cuprate addition gave triol **12**, the last common intermediate for tetraacetonides **17**–**20**.

All of the remaining stereogenic centers were introduced using the enantioselective *B*-allyldiisopinocampheylborane reagents developed by Brown, $^{d}Ipc_2$B(allyl) or $^{l}Ipc_2$B(allyl).[40] The synthetic routes are very similar for each of the tetraacetonides and only the synthesis of **19** will be discussed in detail. The configuration at C21 in **12** was incorrect; it was inverted by cleaving the C21–C22 diol with periodate and adding $^{l}Ipc_2$B(allyl) to the resulting aldehyde. Reprotection gave alkene **15**. A standard homologation sequence was used next: ozonolysis, allylation, in this case with $^{d}Ipc_2$B(allyl), and reprotection gave **16** in 60% overall yield as a 11:1 mixture of stereoisomers at the newly formed C23 center. Repeating this sequence once more on **16** introduced the final stereogenic center for tetraacetonide **19** (Scheme 3). Oxidative cleavage of the alkene followed by reduction and reprotection under vigorous conditions gave the tetraacetonide **19**. Tetraacetonide **19** had a ^{1}H NMR spectrum identical with that of the natural degradation fragment **6**. This established the relative configuration of the stereogenic centers in **6**, and the absolute configuration was determined by comparing the CD spectra of the corresponding octaacetate. Compound **6** turned out to be the enantiomer of **19**. The complete stereochemical assignments for mycoticins A and B are illustrated in Chart 2. The

Scheme 2



Scheme 3



stereochemical determination of the mycoticins demonstrated the power of modern synthetic methods in structure assignments.

B. Configuration of Roxaticin

The structure determination of roxaticin was unambiguous. Maehr's group at Hoffmann-La Roche solved the X-ray crystal structure of the roxaticin heptaacetate, Figure 1.[10] This was only the second X-ray structure reported for any polyene macrolide antibiotic, the first being that of an amphotericin B derivative in 1970.[6] The absolute configuration was assigned by chemical degradation rather than crystallography as outlined in Scheme 4. Ozonolysis of natural roxaticin followed by hydrogenation of the ozonide and borohydride reduction gave a mixture of polyols from which the diol **21** was isolated in 13% overall yield. Comparison of the optical rotation with that reported in the literature allowed **21** to be assigned the (*S,S*) configuration, and roxaticin the configuration shown in Scheme 4.

Maehr recognized that mycoticin and roxaticin had the same relative and absolute configurations in the

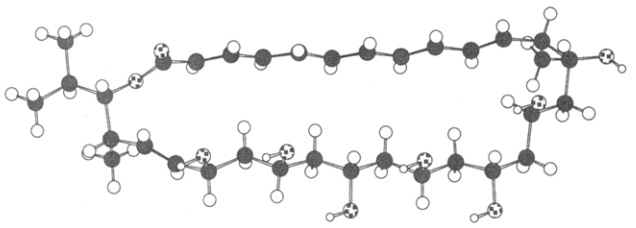
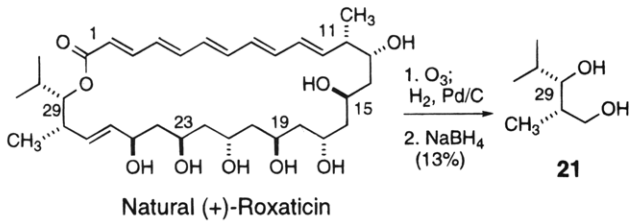


Figure 1. Roxaticin heptaacetate X-ray crystal structure. The acetates have been omitted for clarity.

Scheme 4



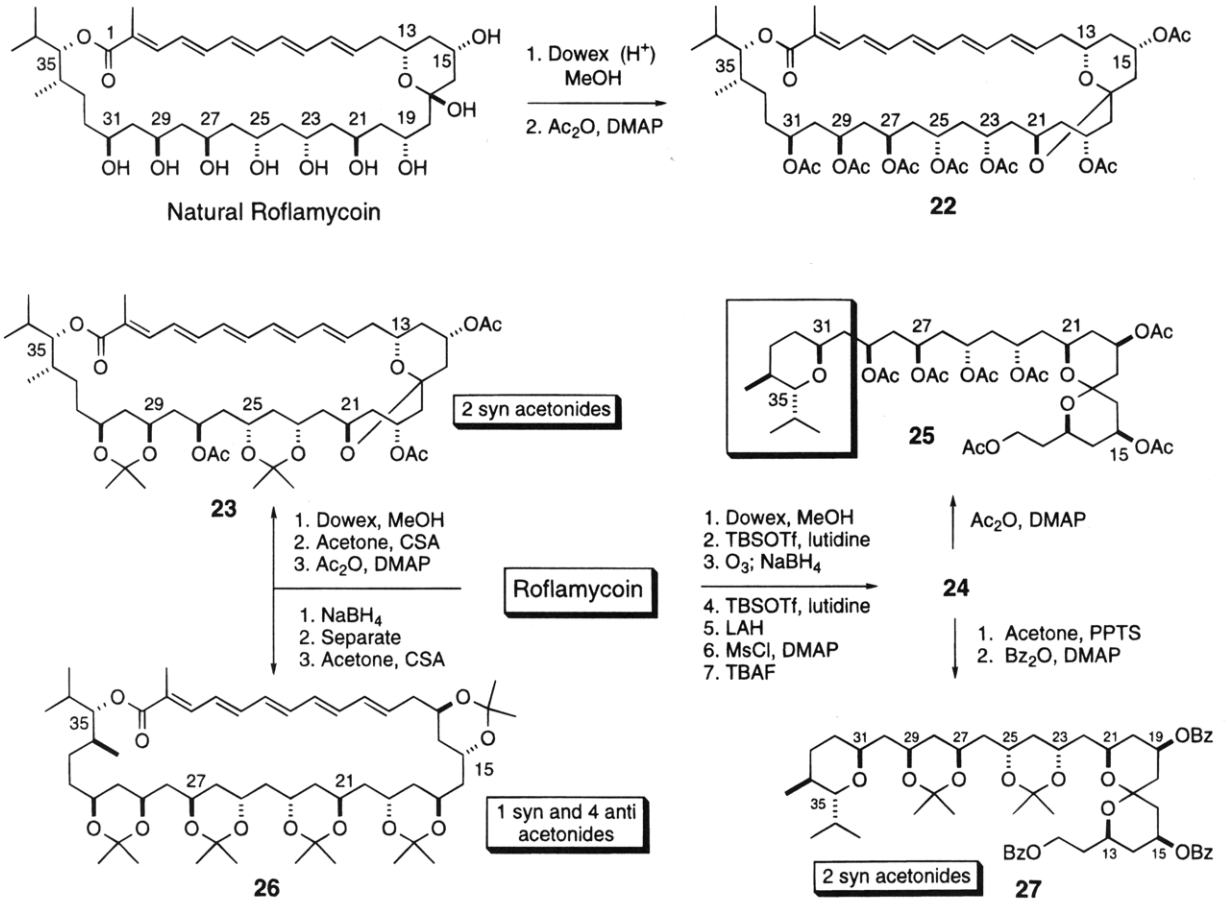
polyol chain and suggested that other polyene macrolides might share the same stereochemical pattern. Presumably the oxo polyene macrolides were assembled by similar enzymatic pathways that would lead to identical polyol configurations. Maehr suggested that roflamycoin and dermostatin may share the same configuration as mycoticin and roxaticin in the overlapping polyol sequence. The stereochemical assignment of roflamycoin, described below, showed that Maehr's proposal was incorrect, and the question remains unresolved with respect to the configurations of dermostatin A and B.

C. Configuration of Roflamycoin

The stereochemical assignment of roflamycoin was carried out in Rychnovsky's group using chemical degradation and the ^{13}C NMR acetonide method to assigning relative configurations.[13] Rychnovsky's group has shown that the ^{13}C NMR signals of the methyl groups in syn 1,3-diol acetonides occur at 19 and 30 ppm, whereas the ^{13}C NMR signals of the methyl groups in anti 1,3-diol acetonides occur at 25 ppm.[48] The syn 1,3-diol acetonides adopt a chair conformation with one methyl axial (19 ppm) and one methyl equatorial (30 ppm).[49] The anti 1,3-diol acetonides adopt a twist-boat conformation with "local" C_2 symmetry, and both methyl groups have the same chemical shift at about 25 ppm. This analysis was later extended to polypropionate chains by Evans.[50]

Natural roflamycoin was treated with Dowex and methanol to form the C17−C21 spiroacetal and then acetylated to give **22**. Coupling constants were analyzed to determine that the relative configurations at C13−15 and C19−C21 are anti, and NOESY analysis on spiroacetal **23**, *vide infra*, allowed the relative configuration at C15−C19 to be assigned as syn. Diacetonide **23** was prepared from the spiroacetal by treatment with acetone, 2,2-dimethoxypropane (2,2-DMP) and camphorsulfonic acid (CSA) followed by acetylation. A mixture of three isomeric diacetonides was produced, and isomer **23** was separated from the other two by reversed-phase HPLC. The position of the acetate in the C23−C31 section

Scheme 5



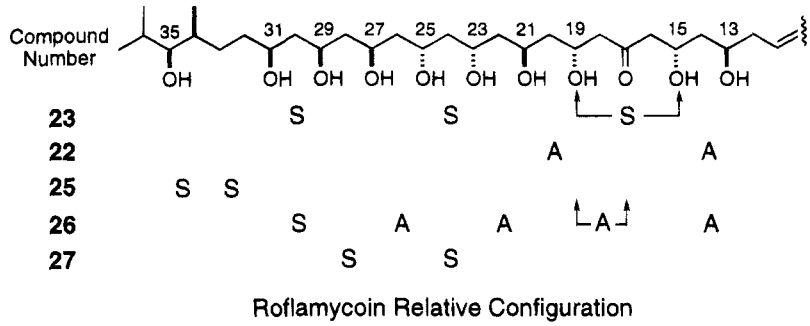
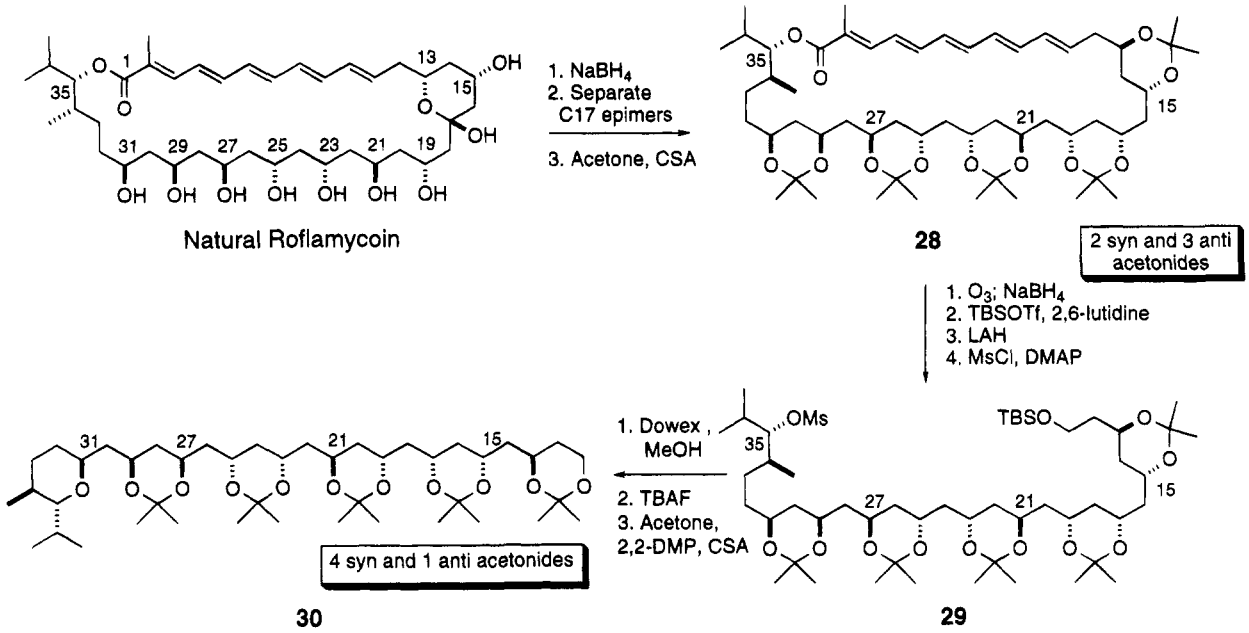


Figure 2. Summary of the relative stereochemical assignments for natural roflamycoin. An "S" indicates a syn relative configuration and an "A" indicates an anti relative configuration.

Scheme 6



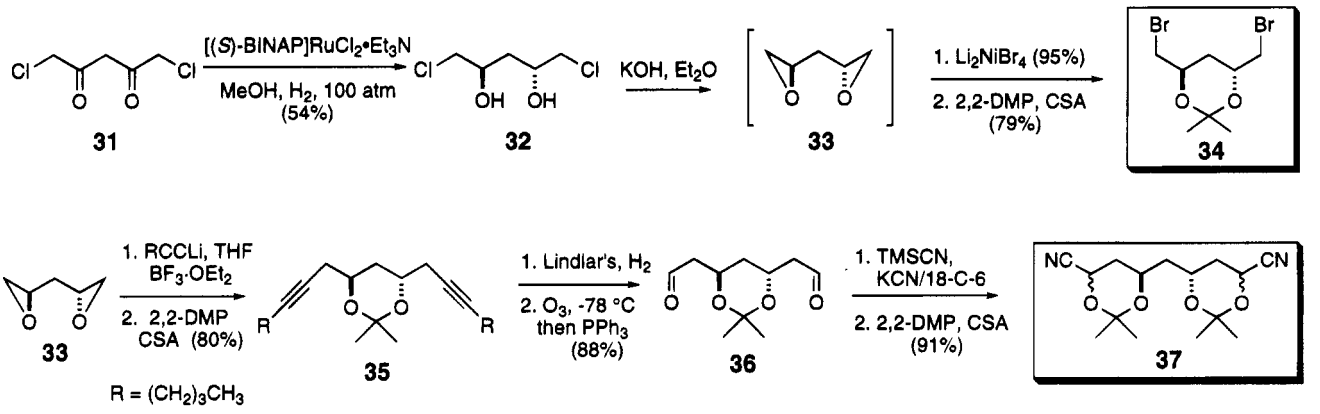
was identified as C27 by COSY analysis. The ^{13}C NMR analysis showed peaks at 30.65, 30.48, 19.54, and 19.47 ppm that are only consistent with a syn stereochemical relationship at C23–C25 and C29–C31. Reduction of the ketone at C17 in roflamycoin followed by separation of the C17 epimers and acetonide formation gave pentaacetonide **26**. Pentaacetonide **26** showed four anti and one syn 1,3-diol acetonide rings by ^{13}C NMR analysis. The C29–C31 relationship had already been shown to be syn, so the remaining four relationships (C13–C15, C17–C19, C21–C23, and C25–C27) must be anti.

A more elaborate oxidative degradation sequence was developed to identify the relative configuration at C34 and C35. Spiroacetal formation, silylation, and ozonolysis followed by sodium borohydride reduction cleaved the polyene chain and left the C35 alcohol protected as a lactate ester. Reduction with LAH removed the C35 ester and mesylation followed by treatment with tetrabutylammonium fluoride solution (TBAF) led to the formation of a C31–C35 tetrahydropyran **24**. Acetylation gave compound **25**, and analysis of the coupling constants in the tetrahydropyran fragment led to the assignments shown for the relative configuration between C31, C34, and C35. The final assignment between C27 and C29 was made by preparing diacetonide **27** from tetrahydropyran **24**. Diacetonide **27** showed ^{13}C NMR signals characteristic of two syn 1,3-diol acetonide rings, and this final determination completed the relative stereochemical assignment of roflamycoin. The analysis is illustrated in Figure 2, where five derivatives led to the assignment of the indicated stereochemical relationships. Overlapping acetonide rings in different derivatives are the key to assigning the relative configuration of a polyol chain using the ^{13}C NMR acetonide method. The absolute configuration at C35 was determined to be *S* by the advanced Mosher method,[51] and the complete configuration of natural roflamycoin is illustrated in Chart 2.

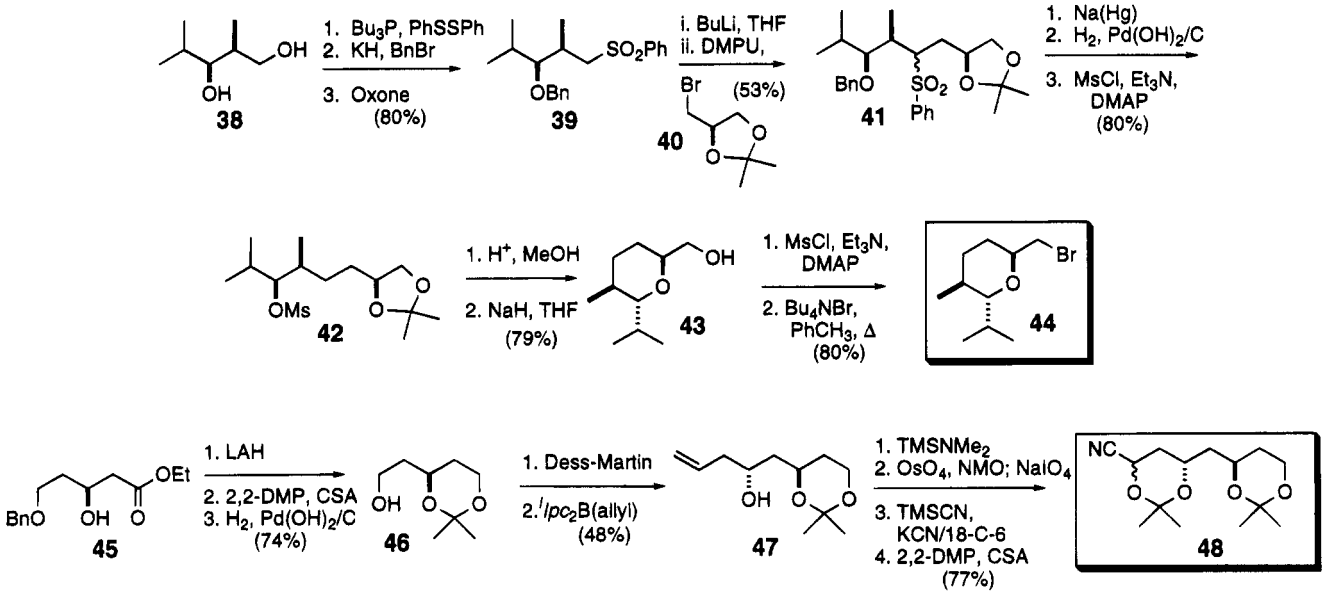
The configuration of roflamycoin was confirmed by the total synthesis of the degradation fragment **30**.[13b] The degradation sequence leading to **26** also gave pentaacetonide **28** (Scheme 6). Oxidative degradation of **28** followed by reduction and mesylation gave mesylate **29**. Deprotection and treatment with base led to cyclization of the C31 alcohol onto the C35 mesylate to give pentaacetonide **30** after protection. As expected, ^{13}C NMR analysis showed 1 anti and 4 syn acetonides (including the terminal acetonide) and was consistent with the assigned configuration. The synthesis of **30** is outlined in Schemes 7–9.

Syntheses of the optically pure fragments leading to **30** are shown in Schemes 7 and 8. Noyori enantioselective hydrogenation of diketone **31** gave

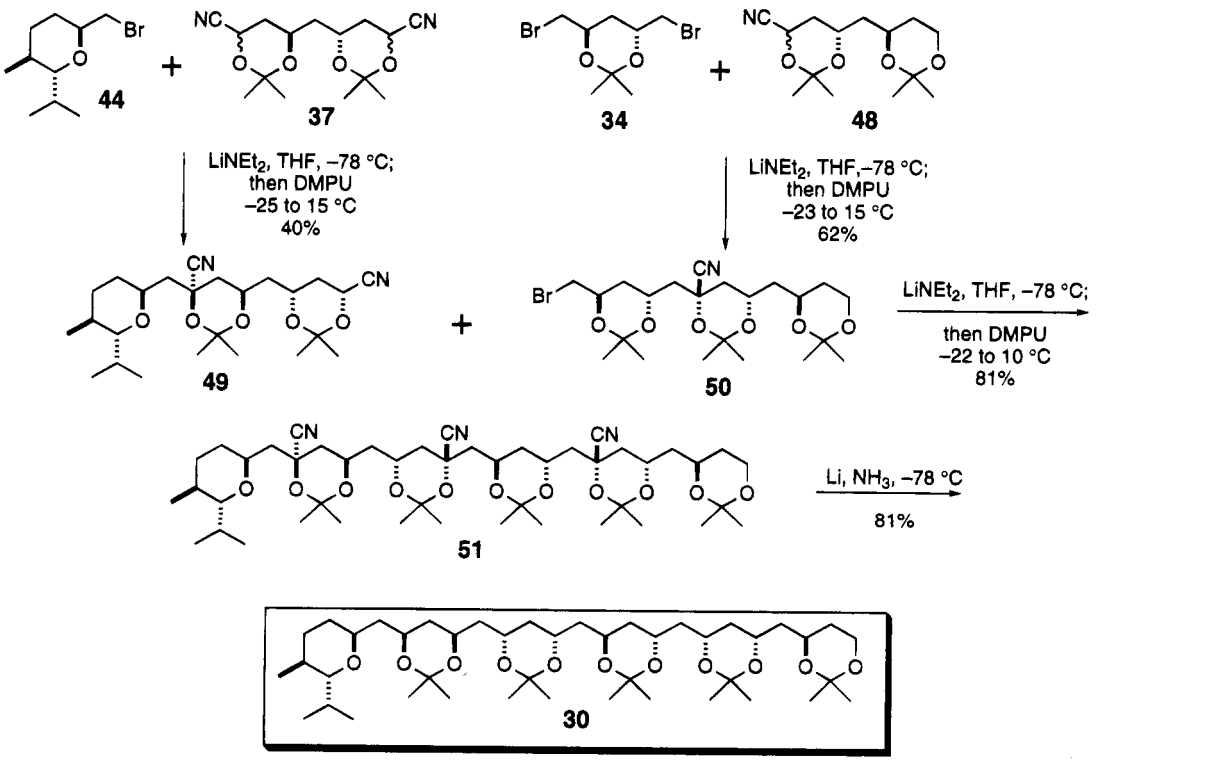
Scheme 7



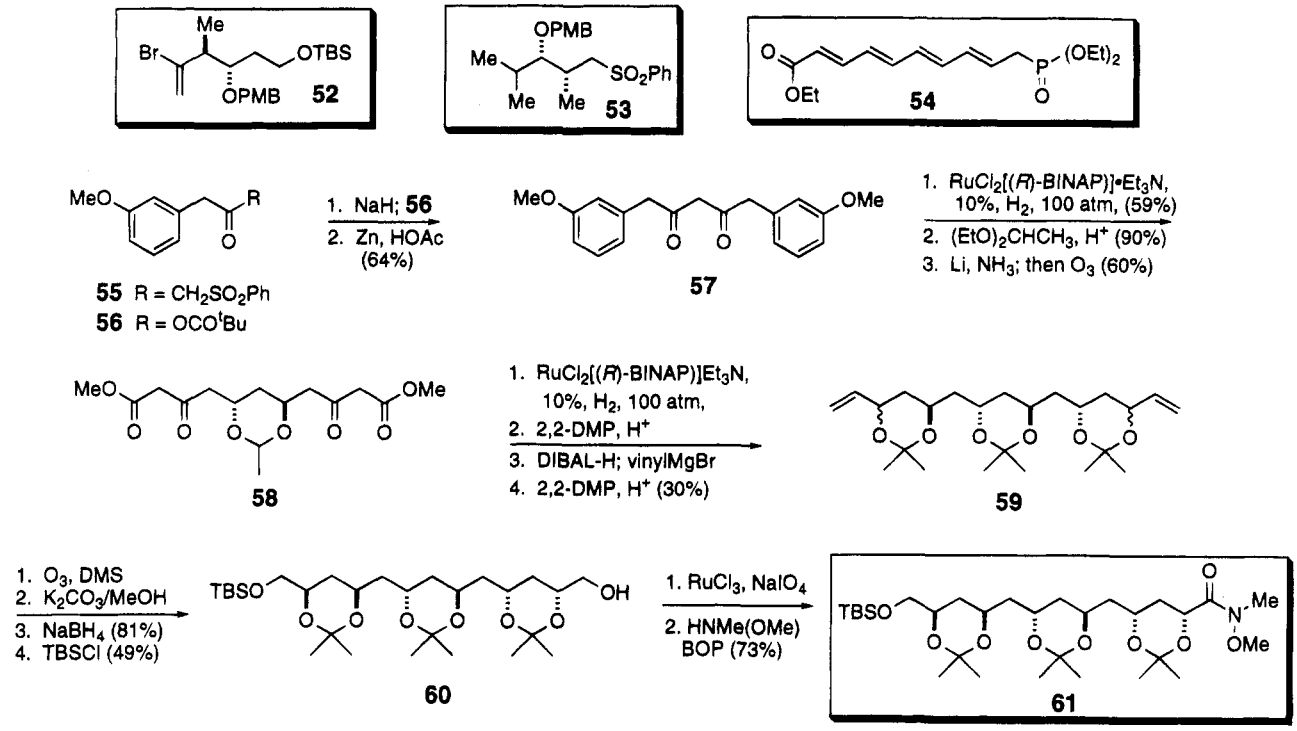
Scheme 8



Scheme 9



Scheme 10



the optically pure, crystalline anti diol **32**. KOH treatment gave diepoxide **33** that could be further converted into dibromide acetonide **34**. Diepoxide **33** is a very useful precursor to anti 1,3-diols, and dibromide **34** is an important precursor to protected anti 1,3-diols.[52] The preparation of dinitrile **37** began with the addition of hexynyllithium to diepoxide **33**. Protection, Lindlar's hydrogenation, and ozonolysis gave the dialdehyde **36**. Cyanohydrin formation and acetonide protection gave a mixture of dinitrile stereochemical isomers **37**. Tetrahydropyran **44** was prepared from diol **38** as illustrated in Scheme 8. Diol **38**, which can be prepared by Evans's aldol chemistry, was converted to sulfone **39** using standard methods. The anion of **39** was alkylated with bromide **40**, itself prepared from D-mannitol. Reductive desulfonation followed by standard transformations gave bromo tetrahydropyran **44**. The final fragment, cyanohydrin **48**, was synthesized from hydroxy ester **45**. Ester **45** was prepared using a Noyori asymmetric hydrogenation.[53] Reduction, acetonide formation, and hydrogenolysis of the benzyl ether gave the chiral alcohol **46**. Oxidation and enantioselective allyl addition using $^{t}Ipc_2$B(allyl) introduced the second stereogenic center. Oxidation of alkene **47** to an aldehyde, cyanohydrin formation, and reprotection with 2,2-dimethoxypropane (2,2-DMP) and camphorsulfonic acid (CSA) gave diacetonide **48**. These four compounds were the precursors to **30**.

The preparation of **30** used the cyanohydrin acetonide chemistry previously developed by Rychnovsky's group.[54] Deprotonation of **37** and alkylation with **44** gave the coupled fragment **49** in modest yield as illustrated in Scheme 9. Effective monoalkylation of dinitrile **37** remains an unsolved problem. The other half of **30**, bromide **50**, was prepared by deprotonation of **48** and alkylation with dibromide **34**. The two halves were coupled by deprotonation of **49** and alkylation with **50** to give **51**. Reductive decyanation of **51** gave **30** in very good yield. Synthetic pentaacetonide **30** was identical to degradation product **30** by ^{1}H NMR spectroscopy, confirming the stereochemical assignment of roflamycoin. The synthesis of **30** appeared in 1995, making it the most recent approach to a complex polyol chain to be discussed in this review.

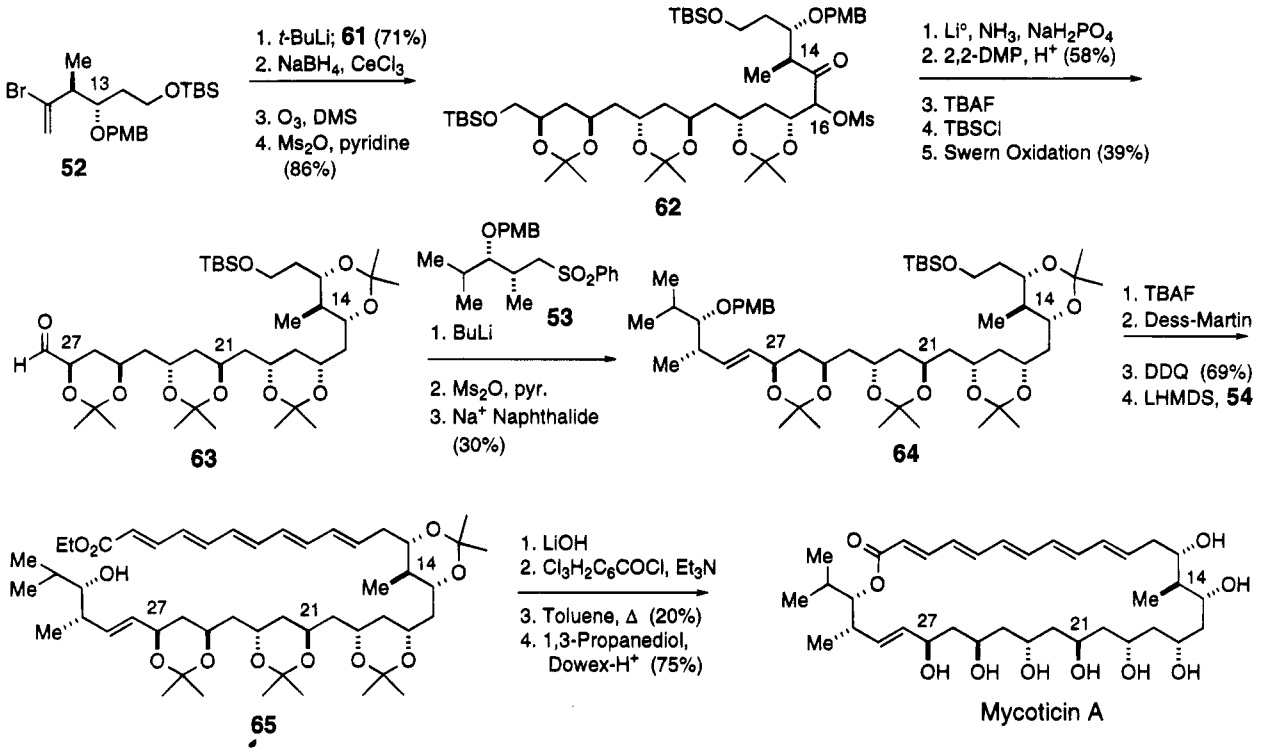
IV. Syntheses of Oxo Polyene Macrolides

A. Synthesis of Mycoticin

The first total synthesis of an oxo polyene macrolide antibiotic was the synthesis of mycoticin reported by Schreiber's group in 1993.[55] As with Schreiber's earlier preparation of mycoticin degradation fragments, his total synthesis was designed around a two-directional chain synthesis strategy.[39] The mycoticin synthesis has appeared only as a communication, and routes for the preparation of compounds **52**, **53**, and **54** have not been reported. However Mori subsequently reported a synthesis of roxaticin that made use of both **53** and **54**, and he has published a route to **53** that is summarized in the roxaticin discussion.

The central fragment of mycoticin was prepared using a class B (C_2 symmetric) two-directional chain synthesis as illustrated in Scheme 10.[39] The sodium anion of α-keto sulfone **55** was acylated with mixed anhydride **56** followed by reductive desulfonation with zinc metal to give the symmetric β-diketone **57** in 64% overall yield. Noyori asymmetric hydrogenation gave a C_2 symmetric 1,3-diol that was protected as a cyclic acetaldehyde acetal. Birch reduction followed by ozonolysis gave the bis β-keto ester **58**. A second Noyori asymmetric hydrogenation followed by protection of the polyol as a diacetonide, in situ DIBAL-H reduction and trapping with excess vinyl Grignard reagent, and reprotection gave the triacet-

Scheme 11



onide **59** as a mixture of stereoisomers in 30% overall yield. The stereochemical mixture was equilibrated to a single dialdehyde stereoisomer by ozonolysis and treatment with base. This strategy was used previously in the synthesis of syn diol **11**. Reduction gave a C_2 symmetric diol that was desymmetrized by treatment with 1 equiv of TBSCl in 49% yield. This statistical monoprotection gave unprotected and bisprotected diol that could be recycled. Sharpless RuO_4 oxidation followed by coupling with *N,O*-dimethylhydroxylamine gave the Weinreb amide **61** in 15 steps from the sulfone **55**.

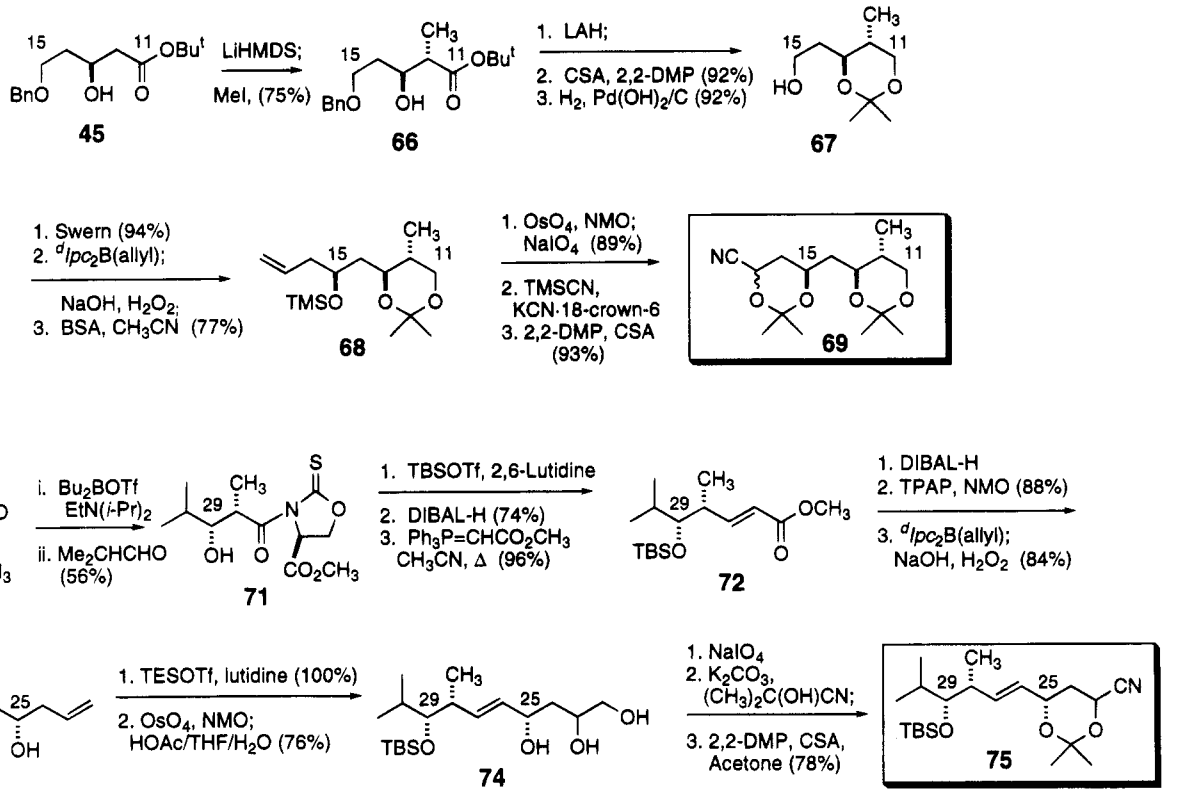
The components of mycoticin were brought together in the series of reactions illustrated in Scheme 11. Vinyl bromide **52** was metalated with *t*-BuLi and added to Weinreb amide **61** in 71% yield. Luche reduction gave a 1:1 mixture of stereoisomers at the C16 alcohol center. Ozonolysis and mesylation of the C16 alcohol set up a lithium in ammonia reduction that removed the C16 mesylate and the *p*-methoxybenzyl (PMB) ether at C13. The C15 ketone was also reduced in this unusual dissolving metal reduction to give the *R* alcohol with >15:1 selectivity. A multistep reprotection followed by Swern oxidation gave the aldehyde **63**. Aldehyde **63** was identical to material prepared from natural mycoticin (see Scheme 1) and the remainder of the synthesis was completed with material derived from degradation. Julia coupling with the sulfone **53** proceeded in 30% overall yield to give the *E* alkene **64**. The C11 aldehyde was prepared in several steps and coupled with the polyene phosphonate **54** to give the pentaene ester **65**. The macrolactonization was carried out on the corresponding hydroxy acid using Yamaguchi's procedure in 20% overall yield. Final deprotection with 1,3-propanediol and acidic Dowex resin completed the synthesis of (+)-mycoticin. The synthesis was completed in 35 steps from sulfone **55**. Most of the stereochemistry was set using Noyori asymmetric hydrogenations and substrate-based stereoselective reactions. Protecting group manipulations added a number of steps to the synthesis, and the macrolactonization proceeded in modest yield. The synthesis of mycoticin demonstrates the advantages of a two-directional chain synthesis strategy but leaves room for improvement in the handling of protecting groups and in the cyclization strategy.

B. Synthesis of (−)-Roxaticin

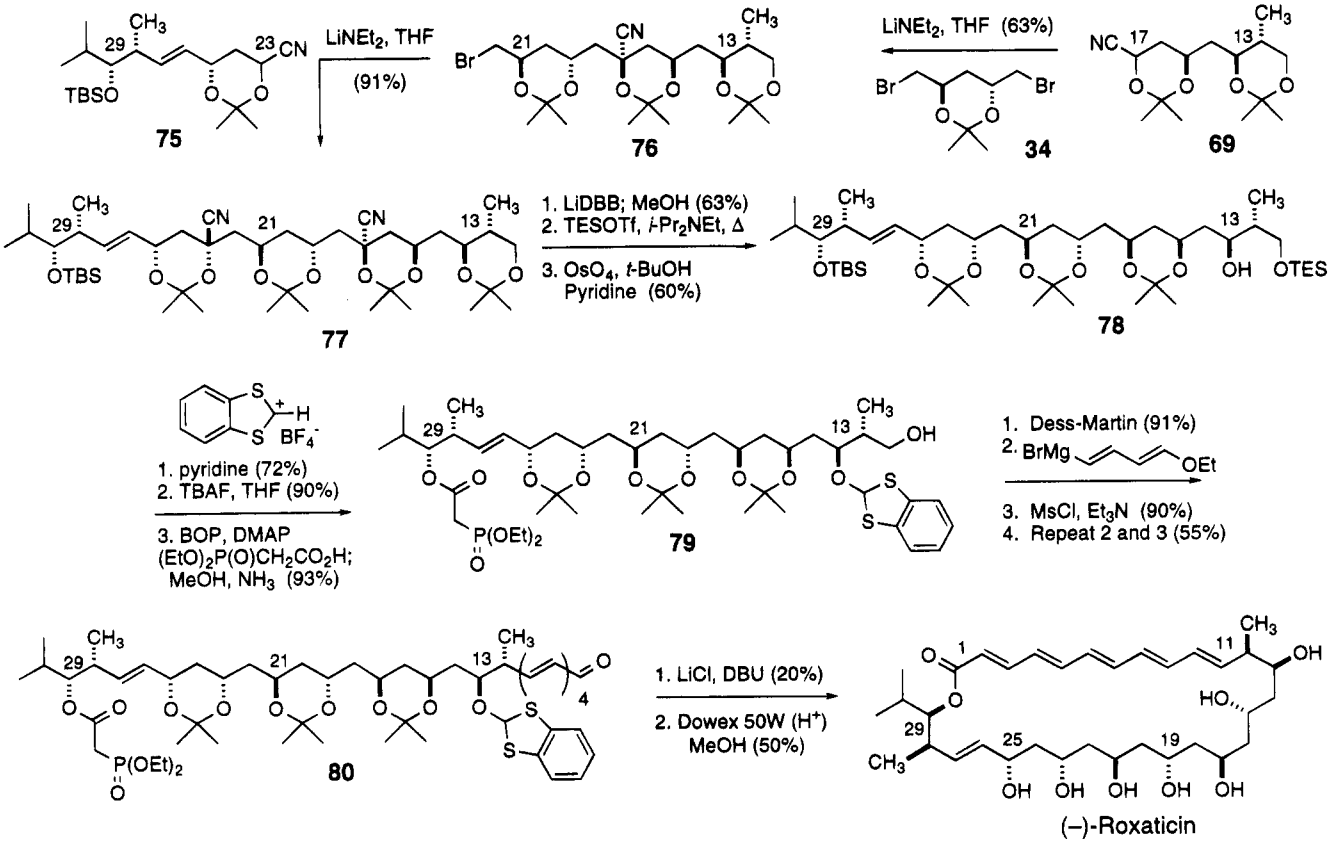
The first total synthesis of roxaticin was reported in 1994 by Rychnovsky's group.[56] The synthesis used a highly convergent strategy based on the alkylation and reductive decyanation of cyanohydrin acetonides.[54] Three components were coupled to prepare the optically pure polyol chain: dibromide **34** and cyanohydrin acetonides **69** and **75**. The preparation of **34** was described in Scheme 7, and the preparations of **69** and **75** are outlined in Scheme 12. The preparation of roxaticin was carried out prior to the synthesis of **30**, the degradation fragment of roflamycoin, but used a similar strategy.

The C11−C17 fragment of roxaticin was prepared beginning with the optically pure β-hydroxy ester **45**. Frater−Seebach alkylation introduced the α-methyl group with 10:1 anti to syn selectivity.[57] LAH reduction, acetonide formation, and hydrogenolysis of the benzyl ether gave the alcohol **67** in excellent yield. The third stereogenic center was introduced by adding $^{d}Ipc_2B$(allyl) to the corresponding aldehyde.[40] Oxidative cleavage of the alkene with OsO_4 and periodate followed by cyanohydrin formation and diol protection gave cyanohydrin acetonide **69** in 10 steps from hydroxy ester **45**. The synthesis of the C23−C29 fragment began with a modification of Helquist's preparation of unsaturated ester **72**.[58] Enantiose-

Scheme 12

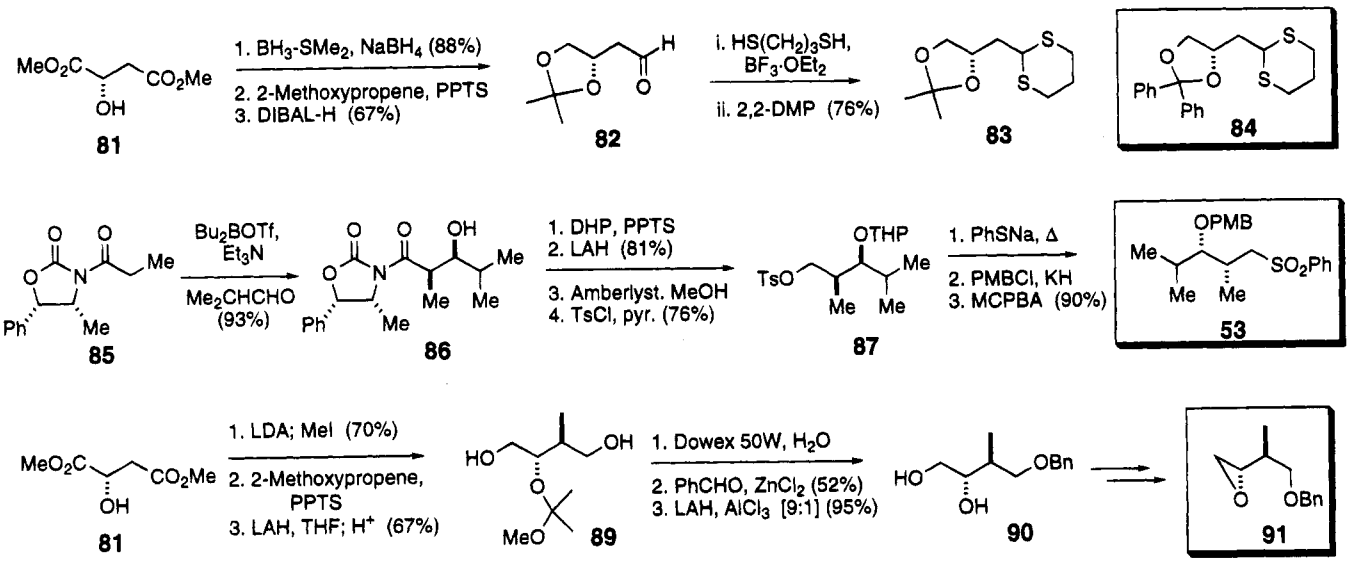


Scheme 13



lective aldol reaction with isobutyraldehyde, silylation, DIBAL-H reduction, and a modified Wittig reaction gave optically pure **72**. The third stereogenic center was introduced by adding $^{d}Ipc_2B$(allyl) to the corresponding aldehyde. The terminal alkene was selectively cleaved by OsO_4 oxidation of the TES-protected allylic alcohol followed by oxidation with periodate. Cyanohydrin acetonide formation gave the C23–C29 fragment **75** in a total of 12 steps from isobutyraldehyde.

Scheme 14



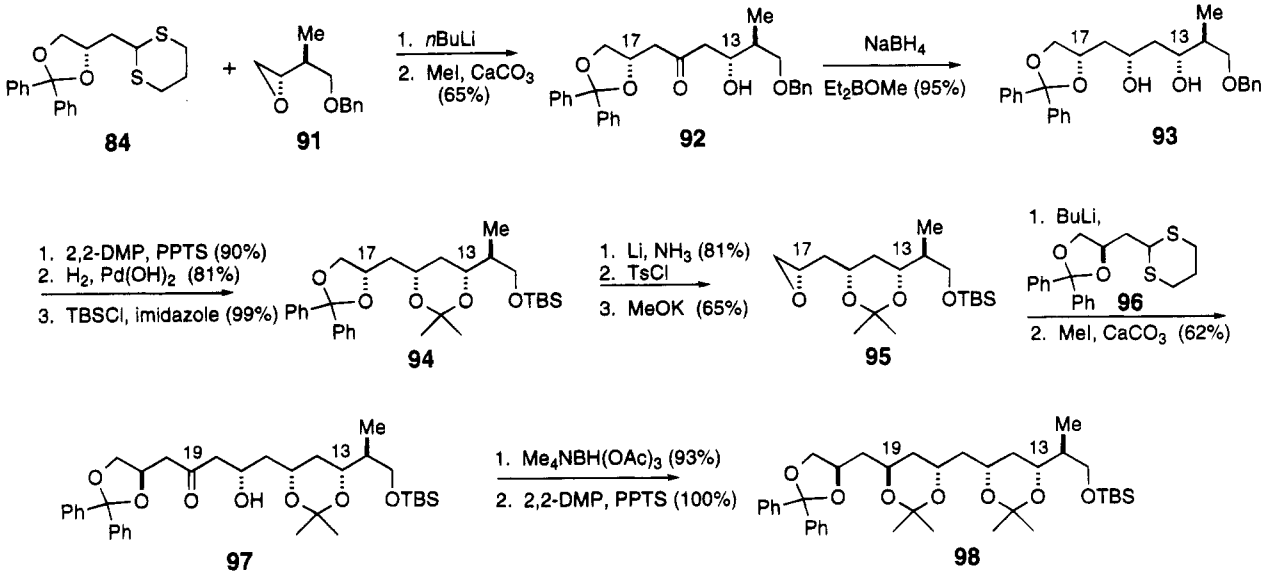
The three optically pure fragments, **34**, **69**, and **75**, were coupled to form roxaticin as outlined in Scheme 13. The anion of **69** was alkylated with an excess of C_2 symmetric dibromide **34** to give bromide **76** in 63% yield. A modest excess of the anion of **75** was used to alkylate **76** to give the dinitrile **77** in 91% yield. Reductive decyanation was carried out using lithium di-*tert*-butylbiphenylide in THF to make the bis-anion before protonation with methanol. This reductive decyanation gave the same stereochemical outcome as a lithium in ammonia reduction, axial protonation of the acetonide anion, but avoided reduction of the allylic ether at C25. An unusual deprotection sequence gave compound **78** with a free alcohol at C13 that was reprotected as a 1,3-benzodithiolan-2-yl (BDT) ether. The BDT protecting group was chosen because it could be introduced under neutral conditions, was stable to base, and could be removed with mild acid. Removal of the silyl groups gave the expected 11,29-diol. Selective esterification of the more hindered C29 alcohol was accomplished in a one-pot transformation: complete esterification with diethyl phosphonoacetic acid and removal of the primary ester with ammonia-saturated methanol gave alcohol **79** in excellent yield. The polyene chain was introduced using a modification of Wollenberg's procedure[59] on the corresponding aldehyde to prepare the dienal and then the tetraenal **80**. Cyclization using the Roush–Masamune conditions, LiCl and DBU, gave the pentaene ester in 20% yield. Deprotection with Dowex 50W resin in methanol gave (−)-roxaticin in about 50% yield. The synthesis was completed in 26 steps from isobutyraldehyde. Most of the stereogenic centers were introduced using the Noyori asymmetric hydrogenation, Brown's enantioselective allylation, or Rychnovsky's reductive decyanation methodology. The macrocycle formation proceeded in about the same low yield as the Yamaguchi macrolactonization used by Schreiber in the synthesis of mycoticin. Synthetic (−)-roxaticin is the enantiomer of the naturally occurring (+)-roxaticin, and it was selected as a synthetic target to act as a probe of sterol interactions associated with its antifungal activity. Sterol interactions in amphotericin B ion channels were evaluated by the Rychnovsky group using a complementary strategy with synthetic *ent*-cholesterol.[60]

C. Synthesis of (+)-Roxaticin

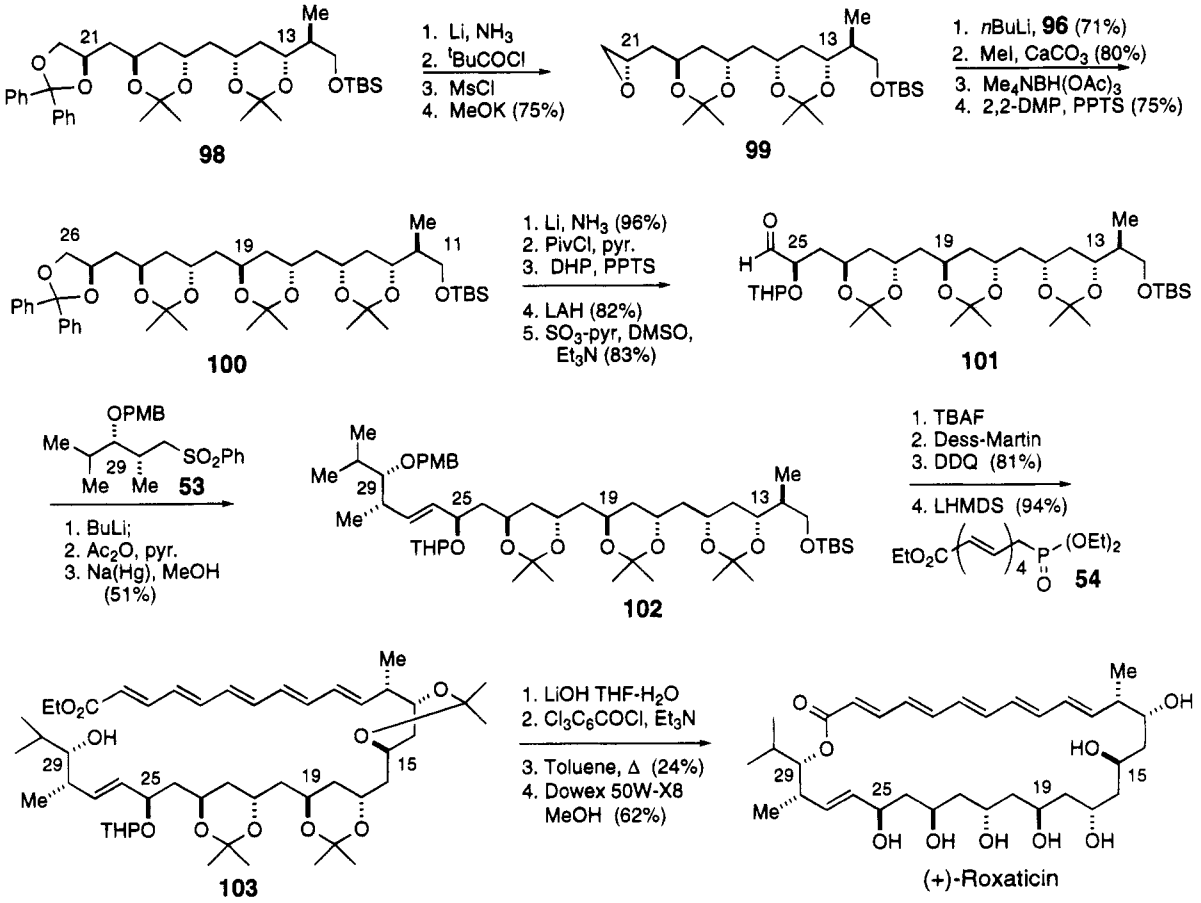
Mori's report on the synthesis of (+)-roxaticin[61] was the culmination of a series of papers describing the development of his convergent approach to polyol chains.[62] Mori's convergent method began with (*S*)-malic acid that was converted to the optically pure 1,3-diol synthon **83** as shown in Scheme 14. Esterification and selective reduction of (*S*)-malic acid, gave methyl (*S*)-3,4-dihydroxybutanoate. Protection, DIBAL-H reduction, dithiane formation, and reprotection completed the synthesis of dithiane acetonide **83**. To prepare polyol chains, **83** was deprotonated and added to an epoxide. The dithiane was hydrolyzed and the resulting β-hydroxy ketone was reduced to a syn or anti 1,3-diol using a hydroxyl-directed reduction. The 1,3-diol was protected and the 1,2-acetonide was converted into an epoxide in several steps, setting up the next dithiane anion addition. This iterative sequence has been used to prepare polyol chains of differing configurations.[62d]

The synthesis of (+)-roxaticin began with the preparation of an improved 1,3-diol synthon, dithiane **84**. It was presumably synthesized in a sequence analogous to the preparation of **83**. Synthesis of the two other fragments, **53** and **91**, are illustrated in Scheme 14. Sulfone **53** was prepared from Evans's aldol product **86** by standard protecting group manipulations and introduction of the sulfone. Schreiber's synthesis of mycoticin made use of sulfone **53** without describing its preparation. The synthesis of epoxide **91** also began with (*S*)-malic acid.[63] Frater–Seebach alkylation of dimethyl (*S*)-malate followed by protection and LAH reduction gave the diol **89**. Deprotection and reprotection with benzaldehyde and zinc chloride gave the 1,3-dioxane in preference to the 1,3-dioxolane. LAH–$AlCl_3$ reduction cleaved the dioxane ring and gave the primary benzyl ether **90** as the major product in excellent yield.[63] Details for conversion of the diol **90** into the epoxide **91** have not been reported. The fragments were coupled as illustrated in Scheme 15. The anion

Scheme 15



Scheme 16



of dithiane **84** was added to epoxide **91**, and the resulting dithiane was deprotected to give β-hydroxy ketone **92**. Syn selective reduction using the method of Prasad, $NaBH_4$ with Et_2BOMe, gave the diol **93** in excellent yield and >99:1 selectivity.[64] Reprotection gave compound **94** that was selectively deprotected by reduction with lithium in ammonia. Selective deprotection was possible because the acetonide in synthon **83** had been replaced by a benzophenone acetal in the improved synthon **84**. Epoxide formation set up the next dithiane anion addition with **96**, the enantiomer of synthon **84**. Hydrolysis of the dithiane and selective reduction using tetramethylammonium triacetoxyborohydride as described by Evans gave the expected anti diol.[65] Protection gave the diacetonide **98** in excellent yield.

The synthesis was completed as illustrated in Scheme 16. Selective deprotection of the benzophenone acetal in **98** with lithium in ammonia gave a 1,2-diol that was monoprotected by treatment with pivaloyl chloride. Mesylation of the secondary alcohol followed by treatment with potassium methoxide

gave the epoxide **99** with inversion at the C21 stereogenic center. This epoxide synthesis is complementary to the preparation of epoxide **95**, where activation of the primary alcohol led to retention of configuration at the C17 stereogenic center. The four-step sequence leading from **95** to **98** was repeated with **99** to give the triacetonide **100**. Selective deprotection of the benzophenone acetal followed by a standard reprotection and oxidation sequence gave the aldehyde **101**. Following the precedent in Schreiber's mycoticin synthesis, Julia coupling with sulfone **53** gave *E* alkene **102** in the improved yield of 51%. The C11 TBS group was removed with TBAF, and the alcohol was oxidized to an aldehyde using the Dess–Martin reagent. Deprotection of the C29 PMB ether followed by Wittig coupling with unsaturated phosphonate ester **54** gave the pentaene **103** in good yield. Yamaguchi esterification gave the macrocyclic ring in 24% yield, and deprotection with Dowex 50W-X8 in methanol gave synthetic (+)-roxaticin in 62% yield. The conversion of aldehyde **101** to roxaticin was essentially identical to the sequence developed by Schreiber to prepare mycoticin. The macrocycle was prepared in about the same low yield as Rychnovsky's phosphonate Wittig cyclization in the (−)-roxaticin synthesis and Schreiber's Yamaguchi cyclization to make mycoticin. Synthetic (+)-roxaticin was prepared in 24 steps from dithiane **84** and approximately 29 steps from (*S*)-malic acid.

D. An Approach to *all-syn*-Roflamycoin

Synthetic approaches to roflamycoin were developed prior to its stereochemical elucidation with the result that each research group selected a different stereoisomer of roflamycoin as its target. The first published approach to the polyol portion of a roflamycoin was reported by Lipshutz's group, and their *all-syn*-roflamycoin target, **104**, is shown in Figure 3. The second and final synthesis reported to date was carried out in Rychnovsky's lab, and their target, **105**, was based on Maehr's proposal for the configuration of roflamycoin. No one has yet described an approach to the natural stereoisomer of roflamycoin beyond the previously described synthesis of degradation fragment **30** reported as part of the structure elucidation.[13b]

The Lipshutz approach to *all-syn*-roflamycoin was published in 1989,[66] between Schreiber's structure elucidation of mycoticin and his synthesis of mycoticin. Lipshutz's most advanced intermediate was the all-syn polyol **121**; his group did not synthesize the polyene or close the macrocyclic ring. Dithiane anion alkylations were used to couple fragments in this highly convergent strategy. Mori's group used a similar approach to assemble the pieces of roxaticin. The optically pure building blocks of roflamycoin were prepared as shown in Scheme 17.

The dithiane **107** was prepared from isobutyraldehyde in seven steps. The stereogenic centers were introduced with a Sharpless asymmetric epoxidation (SAE). Opening epoxide **106** at the C34 center with dithiane anion followed by deoxygenation of the primary alcohol and protection gave **107**. Epoxide **110** was a key building block in Lipshutz's approach to *all-syn*-roflamycoin. Benzyl glycidyl ether **108** was

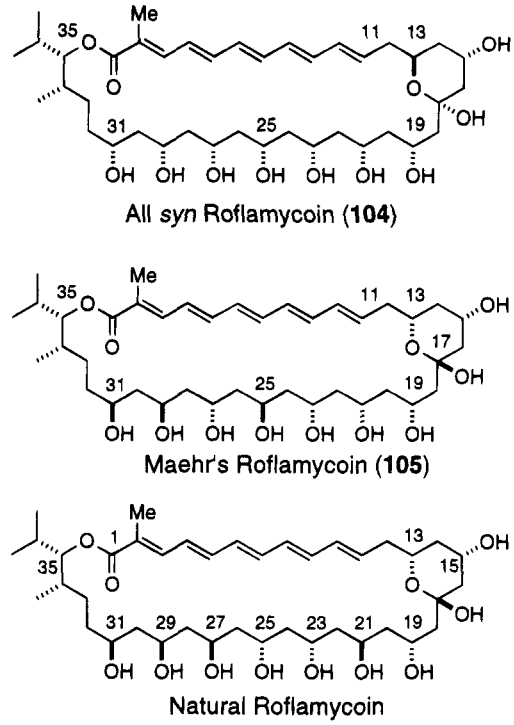
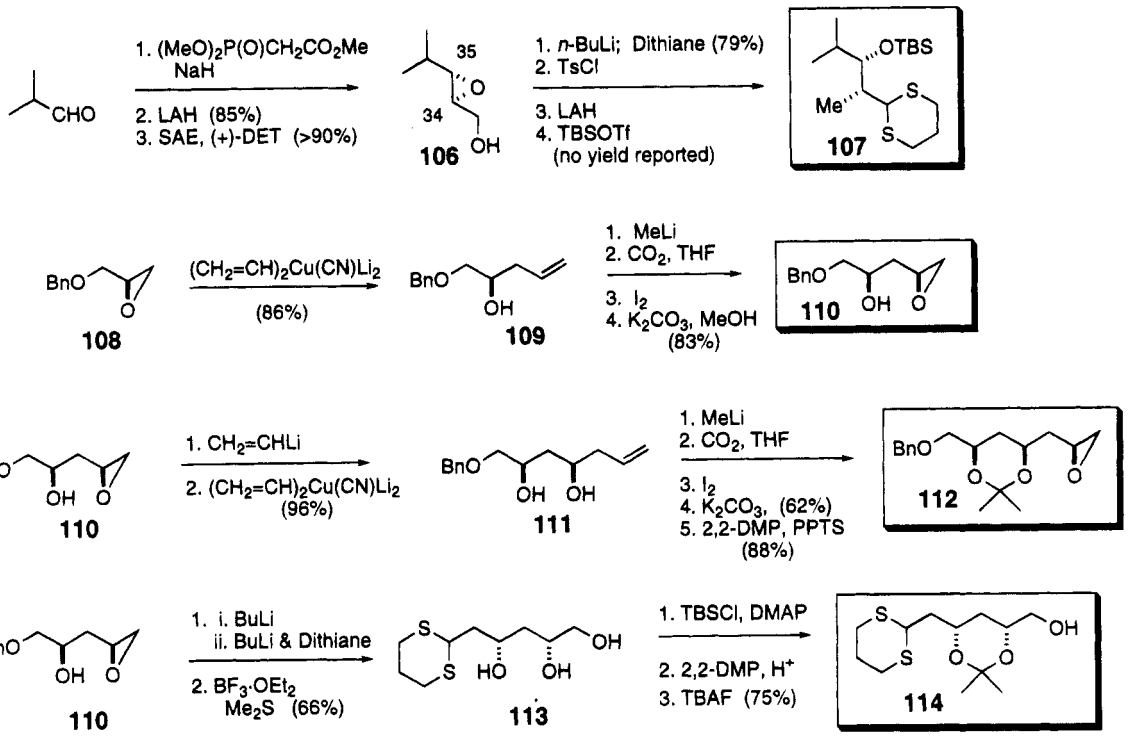


Figure 3. Proposed configurations of roflamycoin.

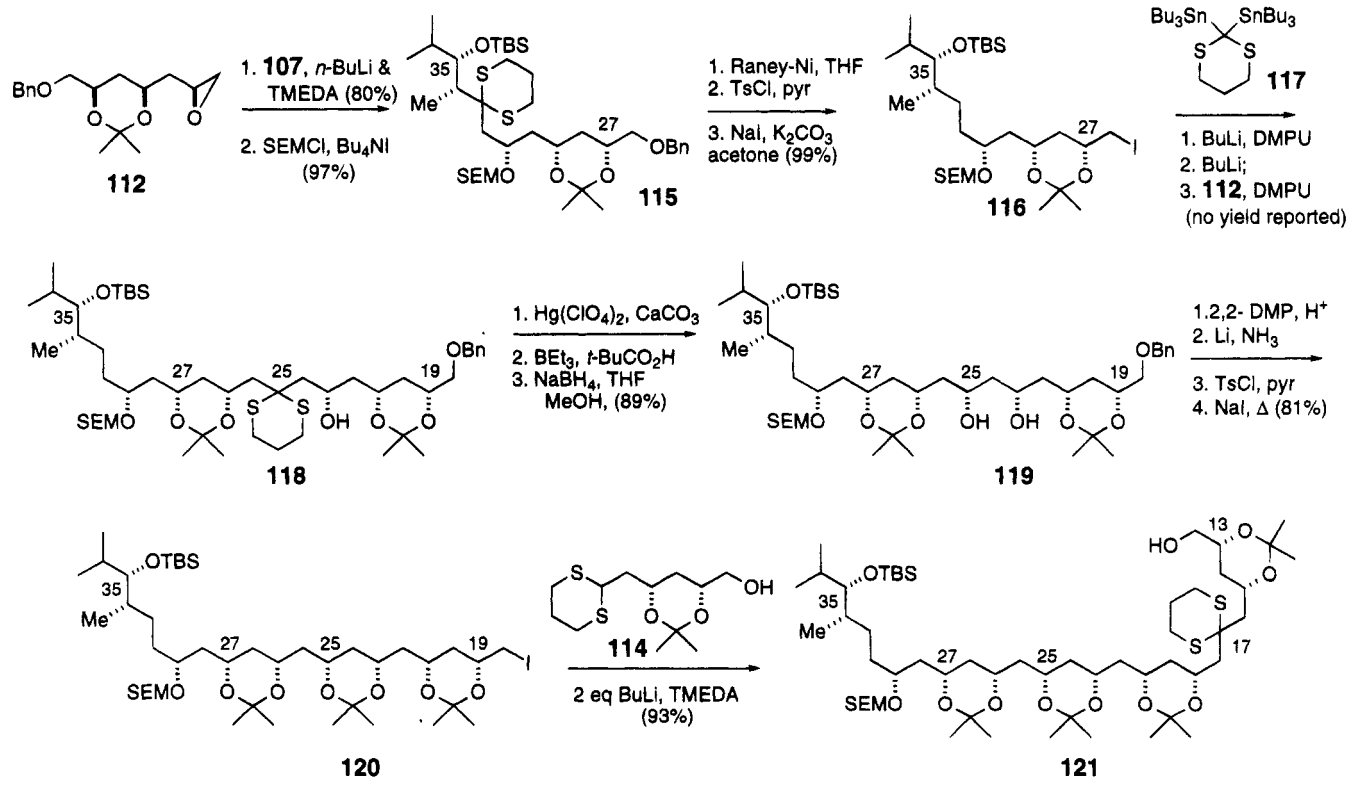
treated with a higher order vinyl cuprate to give **109**. Stereoselective epoxidation was effected using Cardillo's carbonate iodocyclization followed by base treatment to give **110**.[67] This indirect epoxidation proceeded with 10 to 15:1 selectivity for the syn isomer.[68] Epoxide **112** was prepared from **110**. Addition of a higher order vinyl cuprate to **110** gave syn diol **111**. Cardillo's epoxidation sequence followed by protection gave epoxy acetonide **112**. The final fragment, dithiane **114**, was also prepared from epoxide **110**. Dithiane anion addition and deprotection gave triol **113** that was reprotected in three steps to give dithiane **114**. Dithiane **114** was prepared in about 10 steps from epoxide **108**.

The components of *all-syn*-roflamycoin were assembled as outlined in Scheme 18. Deprotonation of **107** and alkylation with **112** gave an alcohol that was protected as a SEM ether. The resulting C26–C35 fragment **115** was treated with Raney-Ni to remove the dithiane and the benzyl ether. The C26 alcohol was converted into an iodide by tosylation and iodide displacement in preparation for coupling. Iodide **116** was alkylated with the anion of dithiane **117**. Transmetalation of the resulting tin dithiane followed by alkylation with epoxide **112** gave the dithiane alcohol **118**. The yield for this key coupling reaction was not reported. Deprotection of the dithiane and stereoselective reduction gave the syn β-diol **119** in excellent yield and >25:1 selectivity. This sequence is very similar to the one Mori later used to prepare **93** (Scheme 15). Acetonide formation, benzyl deprotection, and introduction of the iodide at C18 set up the final coupling. The dianion of **114** was added to iodide **120** to give primary alcohol **121** in excellent yield. The alcohol of **121** was converted into an iodide, but no further progress has been reported. A number of steps would be required to complete the synthesis assuming the protecting group strategy was successful. Protected polyol **121**

Scheme 17



Scheme 18

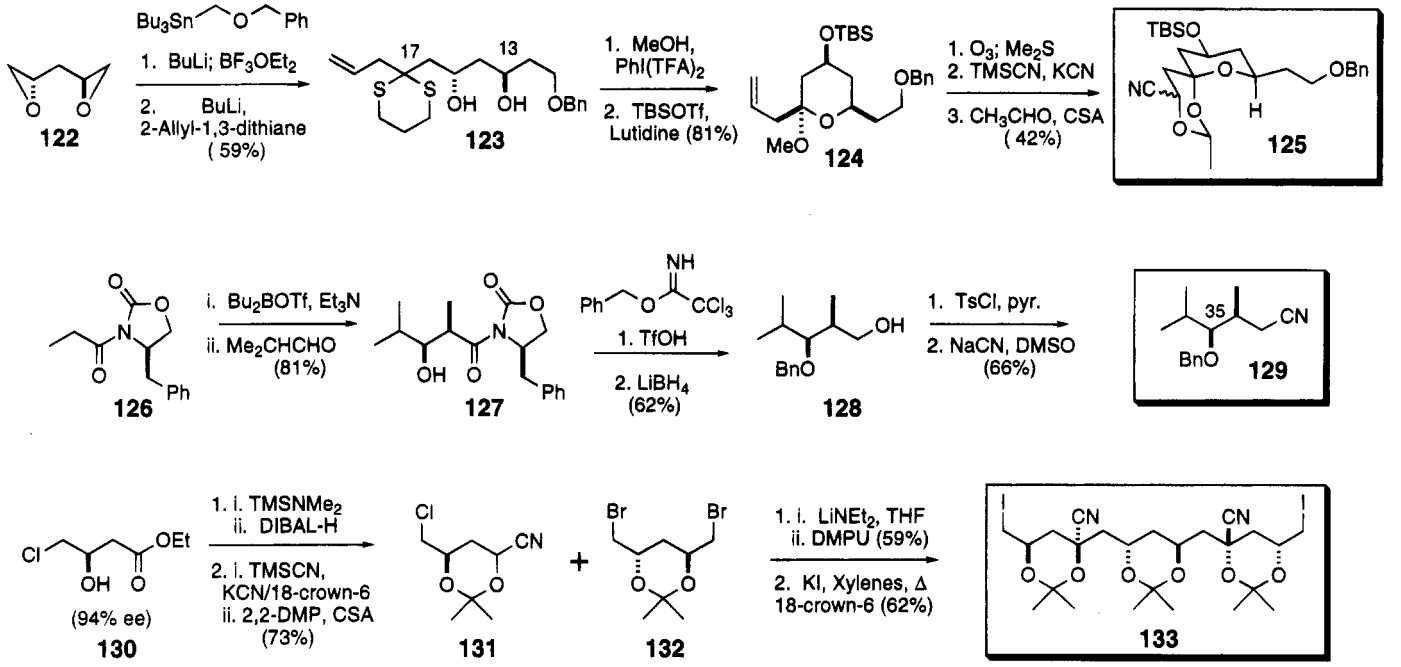


was prepared in 22 steps from benzyl glycidyl ether **108**. The stereogenic centers were introduced from epoxide **108**, by the Sharpless asymmetric epoxidation, or by diastereoselective reduction.

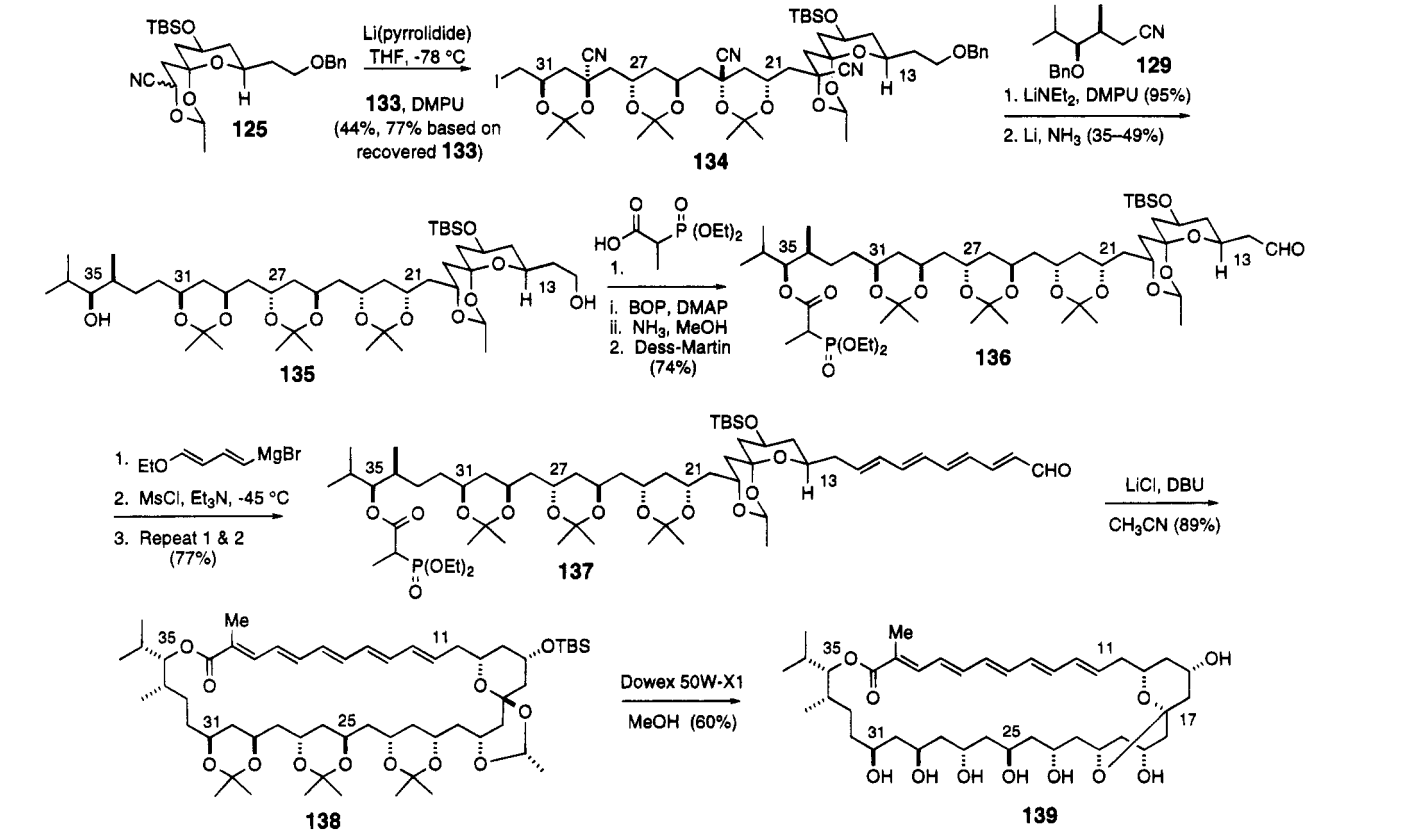
E. An Approach to Maehr's Roflamycoin

Maehr's proposal for the configuration of roflamycoin defined the C19–C35 polyol chain as having the same stereochemical configuration as roxaticin and mycoticin.[10] The two remaining independent stereogenic centers, C13 and C15, were selected on the basis of the convenience to produce the synthetic target for the Rychnovsky group's approach to roflamycoin, compound **105**.[69] Not surprisingly, the proposed common stereochemical pattern between mycoticin, roxaticin, and roflamycoin led to some similarity in the synthetic strategies for these three targets. Cyanohydrin acetonide chemistry was used

Scheme 19



Scheme 20



to couple fragments of the polyol chain in both roxaticin and roflamycoin. The two-directional synthetic analysis applied to mycoticin by Schreiber led to compound **60** (Scheme 10), and in Rychnovsky's analysis of roflamycoin a two-directional, convergent approach led to compound **133** (Scheme 19).

The building blocks for the synthesis of roflamycoin were prepared as outlined in Scheme 19. Diepoxide **122**, the enantiomer of **33** (Scheme 7) was reacted with benzyloxomethyllithium and BF_3·OEt_2 at −78 °C to give the monoepoxide in a better than statistical ratio.[52] Addition of the anion of 2-allyl-1,3-dithiane gave the unsymmetric anti β-diol **123** in 59% overall yield. Deprotection of the dithiane using Stork's procedure[70] followed by protection with TBSOTf gave tetrahydropyran **124**. The double bond in **124** was cleaved with ozone and the resulting aldehyde was converted into a cyanohydrin. Treatment with acetaldehyde and acid gave spiroacetal **125**. The nitrile **129** was prepared from Evans aldol product **126** in a

simple four-step sequence. The C_2 symmetric diiodide **133** was prepared from the optically active ester **130** previously reported by Noyori.[71] Silylation, reduction, and cyanohydrin acetonide formation gave chloro cyanohydrin **131** in 73% overall yield. Cyanohydrin **131** had been developed as a syn β-diol synthon by Rychnovsky and Griesgraber.[72] Coupling dibromide **132**, the enantiomer of **34** (Scheme 7) with a modest excess of the anion of **131** gave a C_2 symmetric dichloride that was converted into the diiodide **133** by treatment with potassium iodide in xylenes at reflux. An X-ray crystal structure of the dichloride corresponding to **133** confirmed its relative and absolute configuration.

The three building blocks of roflamycoin were coupled as illustrated in Scheme 20. Alkylation of the anion of **125** with excess diiodide **133** gave iodide **134** in 77% yield based on recovered nitrile. Alkylation of **134** using an excess of the anion from nitrile **129** gave a tetranitrile that was reduced with lithium in ammonia. Stereoselective cleavage of the nitriles was accompanied by debenzylation to give diol **135** in modest yield. The remaining steps were very similar to the sequence in Rychnovsky's roxaticin synthesis. Esterification of the more hindered alcohol followed by oxidation of the primary alcohol with Dess–Martin reagent gave aldehyde **136**. A modified Wollenberg sequence applied twice converted the aldehyde **136** to tetraenal **137**. A Wittig phosphonate ester cyclization under the Roush–Masamune conditions proceeded in a remarkable 89% yield to give pentaene **138**. Deprotection with Dowex 50X-X1 in methanol did not give the desired hemiacetal but rather the spiroacetal **139** in 60% yield. The synthesis of roflamycoin spiroacetal **139** required 18 steps from diepoxide **122**. The yield in the macrocyclization was exceptional when compared to the corresponding yields reported for roxaticin and mycoticin. Presumably the macrocycle **138** was relatively unstrained and the conformation of **137** favored cyclization. The stereogenic centers were introduced using Noyori's asymmetric hydrogenation, stereoselective reductive decyanations, and Evans aldol chemistry. The spiroacetal **139** was compared with the spiroacetal of natural roflamycoin, and the two were found to differ in the ^{1}H NMR spectra. This comparison cast doubt on Maehr's proposal for the configuration of roflamycoin and led to the structure elucidation of natural roflamycoin described above. No synthetic approach to natural roflamycoin has yet been reported.

V. Related Synthetic Work

Many groups have developed methods for the synthesis of polyol chains, and this work has been recently reviewed.[19] A number of groups have synthesized members of the family of permethylated isotactic alternating polyol first isolated from the blue-green alga *Tolypothrix conglutinata* var. *chlorata*.[73] Both Mori's[74] and Rychnovsky's[72] syntheses of these natural products led to new methods that were later applied to the syntheses of oxo polyene macrolides. Oishi and Nakata developed one of the first convergent approaches to a permethylated all-syn polyol,[75] and Wang reported a meso two-directional chain synthesis strategy to another member of the family.[76] The family of permethylated isotactic alternating polyols has been a testing ground for developing convergent methods for the synthesis of alternating polyol chains.

VI. Conclusions

Significant advances in the structure elucidation and synthesis of oxo polyene macrolide antibiotics have been made since Omura's review in 1984. Three syntheses of relatively simple oxo polyene macrolides and a number of partial syntheses have now been reported, while in 1984 there was no successful synthesis of any polyene macrolide antibiotic. Increasing occurrences of life-threatening fungal infections have renewed the interest in antifungal agents,[1] and polyene macrolides are still some of the most effective clinical antifungal agents known. The structural and synthetic methods are now in place to reexamine the role of polyene macrolides and their analogs in the treatment of fungal infections.

VII. Acknowledgments

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Supporting Information Available. Tabular comparison of the ^{13}C NMR spectra of flavofungin[31] and faeriefungin[29] (1 page). Ordering information is given on any current masthead page.

References

(1) Sternberg, S. *Science* **1994**, *266*, 1632–1634.
(2) Omura, S.; Tanaka, H. In *Macrolide Antibiotics: Chemistry, Biology and Practice*; Omura, S., Ed.; Academic Press: New York, 1984; pp 351–404.
(3) (a) Bolard, J. *Biochim. Biophys. Acta* **1986**, *864*, 257–304. (b) Hartsel, S. C.; Hatch, C.; Ayenew, W. *J. Liposome Res.* **1993**, *3*, 377–408.
(4) (a) Gale, E. F. In *Macrolide Antibiotics: Chemistry, Biology and Practice*; Omura, S., Ed.; Academic Press: New York, 1984; Chapter 11, pp 425–455. (b) Kotler-Brajtburg, J.; Medoff, G.; Kobayashi, G. S.; Boggs, S.; Schlessinger, D.; Pandey, R. C.; Rinehart, K. L., Jr. *Antimicrob. Agents Chemother.* **1979**, *15*, 716–722.
(5) (a) Schlegel, R.; Grigorjev, P. A.; Thrum, H. *Stud. Biophys.* **1982**, *92*, 135–140. (b) Grigorjev, P.; Schlegel, R.; Thrum, H.; Ermishkin, L. *Biochim. Biophys. Acta* **1985**, *821*, 297–304.
(6) (a) Mechlinski, W.; Schaffner, C. P.; Ganis, P.; Avitabile, G. *Tetrahedron Lett.* **1970**, 3873–3876. (b) Ganis, P.; Avitabile, G.; Mechinski, W.; Schaffner, C. P. *J. Am. Chem. Soc.* **1971**, *93*, 4560–4564
(7) Beau, J.-M. In *Recent Prog. Chem. Synth. Antibiot.*; Lukacs, G., Ohno, M. Ed.; Springer: Berlin, 1990; pp 135–182.
(8) Pawlak, J.; Nakanishi, K.; Iwashita, T.; Borowski, E. *J. Org. Chem.* **1987**, *52*, 2896–2901.
(9) (a) Schreiber, S. L.; Goulet, M. T.; Sammakia, T. *Tetrahedron Lett.* **1987**, *28*, 6005–6008. (b) Schreiber, S. L.; Goulet, M. T. *Tetrahedron Lett.* **1987**, *28*, 6001–6004. (c) Schreiber, S. L.; Goulet, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8120–8122. (d)

Schreiber, S. L.; Goulet, M. T.; Schulte, G. *J. Am. Chem. Soc.* **1987**, *109*, 4718–4720.
(10) Maehr, H.; Yang, R.; Hong, L. N.; Liu, C. M.; Hatada, M. H.; Todaro, L. J. *J. Org. Chem.* **1989**, *54*, 3816–3819.
(11) Nystatin: (a) Lancelin, J.-M.; Beau J.-M. *Tetrahedron Lett.* **1989**, *30*, 4521–4524. (b) Prandi, J.; Beau J.-M. *Tetrahedron Lett.* **1989**, *30*, 4517–4520. Pimaricin: (c) Lancelin, J.-M.; Beau J.-M. *J. Am. Chem. Soc.* **1990**, *112*, 4060–4061.
(12) (a) Oishi T. *Pure Appl. Chem.* **1989**, *61*, 427–430. (b) Nakata, T.; Hata, N.; Suenaga, T.; Oishi, T. Abstract of Papers, 30th Symposium on the Chemistry of Natural Products, Fukuoka, Oct 1988; p 540.
(13) (a) Rychnovsky, S. D.; Griesgraber, G.; Schlegel, R. *J. Am. Chem. Soc.* **1994**, *116*, 2623–2624. (b) Rychnovsky, S. D.; Griesgraber, G.; Schlegel, R. *J. Am. Chem. Soc.* **1995**, *117*, 197–210.
(14) Pawlak, J.; Sowinski, P.; Borowski, E.; Gariboldi, P. *J. Antibiot.* **1993**, *46*, 1598–1603.
(15) Rychnovsky, S. D.; Richardson, T. I. *Angew. Chem.* **1995**, in press.
(16) (a) Nicolaou, K. C.; Daines, R. A.; Uenishi, J.; Li, W. S.; Papahatjis, D. P.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1987**, *109*, 2205–2208. (b) Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1987**, *109*, 2208–2210. (c) Nicolaou, K. C.; Chakraborty, T. K.; Ogawa, Y.; Daines, R. A.; Simpkins, N. S.; Furst, G. T. *J. Am. Chem. Soc.* **1988**, *110*, 4660–4672. (d) Nicolaou, K. C.; Daines, R. A.; Uenishi, J.; Li, W. S.; Papahatjis, D. P.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4672–4685. (e) Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.* **1988**, *110*, 4685–4696. (f) Nicolaou, K. C.; Daines, R. A.; Ogawa, Y.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4696–4705.
(17) Kennedy, R. M.; Abiko, A.; Takenasa, T.; Okumoto, H.; Masamune, S. *Tetrahedron Lett.* **1988**, *29*, 451–454.
(18) (a) Nicolaou, K. C.; Ogilivie, W. W. *Chemtracts-Org. Chem.* **1990**, *3*, 327–349. (b) Masamune, S. *Ann. N.Y. Acad. Sci.* **1989**, 168–179.
(19) Oishi, T.; Nakata, T. *Synthesis* **1990**, 635–645.
(20) (a) Watanabe, T.; Izaki, K.; Takahashi, H. *J. Antibiot.* **1982**, *35*, 1148–1155. (b) Watanabe, T.; Izaki, K.; Takahashi, H. *J. Antibiot.* **1982**, *35*, 1141–1147.
(21) Konev, Y. E.; Poltorak, V. A.; Rozynov, B. V. *Biol. Nauki* **1979**, 71–75; *Chem. Abstr.* **1979**, *91*, 52551.
(22) (a) Kobinata, K.; Koshino, H.; Kudo, T.; Isono, K.; Osada, H. *J. Antibiot.* **1993**, *46*, 1616–1618. (b) Koshino, H.; Kobinata, K.; Isono, K.; Osada, H. *J. Antibiot.* **1993**, *46*, 1619–1621.
(23) Burke, R. C.; Swartz, J. H.; Chapman, S. S.; Huang, W.-Y. *J. Invest. Dermatol.* **1954**, *23*, 163–168.
(24) Wasserman, H. H.; Van Verth, J. E.; McCaustland, D. J.; Borowitz, I. J.; Kamber, B. *J. Am. Chem. Soc.* **1967**, *89*, 1535–1536.
(25) Wasserman, H. H.; Zoretic, P. A.; Mariano, P. S. *J. Chem. Soc. D* **1970**, 1634–1635.
(26) Uri, J.; Bekesi, I. *Nature*, **1958**, *181*, 908.
(27) (a) Bognar, R.; Brown, B. O.; Lockley, W. J. S.; Makleit, S.; Toube, T. P.; Weedon, B. C. L.; Zsupan, K. *Tetrahedron Lett.* **1970**, 471–474. (b) Bognar, R.; Makleit, S.; Zsupan, K.; Brown, B. O.; Lockley, W. J. S.; Toube, T. P.; Weedon, B. C. L. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1848–1856.
(28) Wang, N.; Zhang, X.; Fu, Y.; Zhang, W.; Sun, J.; Huang, M. *Zhongguo Kangshengsu Zazhi* **1988**, *13*, 402–407; *Chem. Abstr.* **1989**, *111*, 20568; *Chem. Abstr.* **1991**, *115*, 251753.
(29) Nair, M. G.; Putnam, A. R.; Mishra, S. K.; Mulks, M. H.; Taft, W. H.; Keller, J. E.; Miller, J. R.; Zhu, P. P.; Meinhart, J. D.; Lynn, D. G. *J. Nat. Prod.* **1989**, *52*, 797–809.
(30) McCaustland, D. J. Ph.D. dissertation, Yale University, 1960.
(31) NMR spectrum of flavofungin: Szilagyi, L.; Sandor, P. *Magn. Reson. Chem.* **1990**, *28*, 963–972. See the Supporting Information for a table comparing the spectra of flavofungin and fairefungin.
(32) (a) Severinets, L. Y.; Konev, Y. E. *Antibiotiki* **1974**, *19*, 291–294; *Chem. Abstr.* **1974**, *81*, 96368. (b) Shenin, Y. D. *Antibiot. Khimioter.* **1990**, *35*, 5–8; *Chem. Abstr.* **1990**, *112*, 194987.
(33) (a) Vetlugina, L. A. *Antibiotiki* **1968**, *13*, 992–997; *Chem. Abstr.* **1969**, *70*, 44189. (b) Shenin, Y. D.; Daurenbekova, A. S.; Morgunova, A. F.; Vetlugina, L. A.; Yakovlev, A. A.; Lifshits, M. I. *Antibiot. Med. Biotekhnol.* **1986**, *31*, 341–349; *Chem. Abstr.* **1987**, *106*, 156110.
(34) (a) Bhate, D. S.; Ambekar, G. R.; Bhatnagar, K. K. *Hind. Antibiot. Bull.* **1962**, *4*, 159–162; *Chem. Abstr.* **1962**, *57*, 13013. (b) Pandey, R. C.; Rinehart, K. L., Jr.; Millington, D. S.; Swami, M. B. *J. Antibiot.* **1973**, *26*, 475–477. (c) Pandey, R. C.; Rinehart, K. L., Jr.; Millington, D. S. *Hind. Antibiot. Bull.* **1980**, *22*, 47–61; *Chem. Abstr.* **1981**, *95*, 42296.
(35) (a) Schlegel, R.; Thrum, H. *Experientia* **1968**, *24*, 11–12. (b) Schlegel, R.; Fugner, R.; Bradler, G.; Thrum, H. *Z. Allg. Mikrobiol.* **1971**, *11*, 661–670. (c) Schlegel, R.; Thrum, H. *J. Antibiot.* **1971**, *24*, 360–367. (d) Schlegel, R.; Thrum, H. *J. Antibiot.* **1971**, *24*, 368–74.
(36) Afzal, M.; Nimer, N. D.; Nazar, M. *Z. Allg. Mikrobiol.* **1983**, *23*, 411–418.
(37) Schlegel, R.; Thrum, H.; Zielinski, J.; Borowski, E. *J. Antibiot.* **1981**, *34*, 122–123.
(38) Kulalaeva, Z. I.; Gibalov, V. I.; Poltorak, V. A.; Silaev, A. B. *Bioorg. Khim.* **1978**, *4*, 1244–1249; *Chem. Abstr.* **1979**, *90*, 54795.
(39) (a) Schreiber, S. L. *Chem. Scr.* **1987**, *27*, 563–566. (b) Poss, C.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9–17. (c) Magnuson, S. *Tetrahedron*, **1995**, *51*, 2167–2213.
(40) (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092–2093. (b) Jadhav, P. K.; Bhat, K. S.; Perumal, P. T.; Brown, H. C. *J. Org. Chem.* **1986**, *51*, 432–439. (c) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401–404. $^{d}Ipc_2$B(allyl) was prepared from (+)-α-pinene, and $^{l}Ipc_2$B(allyl) was prepared from (−)-α-pinene. It should be noted that (+)-Ipc2B(allyl) is identical to $^{l}Ipc_2$B(allyl).
(41) Goulet M. T. Ph.D. dissertation, Yale University, 1988.
(42) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357–1358.
(43) Stork, G.; Paterson, I.; Lee, F. K. C. *J. Am. Chem. Soc.* **1982**, *104*, 4686–4688.
(44) Schreiber, S. L.; Hoyveda, A. H. *J. Am. Chem. Soc.* **1984**, *106*, 7200–7202.
(45) Nakata, T.; Suenaga, T.; Oishi, T. *Tetrahedron Lett.* **1989**, *30*, 6525–6528.
(46) Schreiber, S. L.; Goulet, M. T. *Tetrahedron Lett.* **1987**, *28*, 1043–1046.
(47) Schreiber, S. L.; Schreiber, T. S.; Smith, D. B. *J. Am. Chem. Soc.* **1987**, *109*, 1525–1529.
(48) (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945–948. (b) Rychnovsky, S. D.; Rogers, B.; Yang, G. *J. Org. Chem.* **1993**, *58*, 3511–3515.
(49) Rychnovsky, S. D.; Yang, G.; Powers, J. P. *J. Org. Chem.* **1993**, *58*, 5251–5255.
(50) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099–7100.
(51) (a) Kusumi, T.; Ohtani, I.; Inouye, Y.; Kakisawa, H. *Tetrahedron Lett.* **1988**, *29*, 4731–4734. (b) Ohtani, I.; Kusumi, T.; Ishitsuka, O. M.; Kakisawa, H. *Tetrahedron Lett.* **1989**, *30*, 3147–3150. (c) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096.
(52) Rychnovsky, S. D.; Griesgraber, G.; Zeller, S.; Skalitzky, D. J. *J. Org. Chem.* **1991**, *56*, 5161–5169.
(53) (a) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629–631. (b) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856–5858. (c) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345–350. (d) Ikariya, T.; Ishii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S. *J. Chem. Soc., Chem. Commun.* **1985**, 922–924. (e) Kawano, H.; Ishii, Y.; Saburi, M.; Uchida, Y. *J. Chem. Soc., Chem. Commun.* **1988**, 87–88.
(54) Rychnovsky, S. D.; Zeller, S.; Skalitzky, D. J.; Griesgraber, G. *J. Org. Chem.* **1990**, *55*, 5550–5551.
(55) Poss, C. S.; Rychnovsky, S. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 3360–3361.
(56) (a) Rychnovsky, S. D.; Rodriguez, C. *J. Org. Chem.* **1992**, *57*, 4793–4795. (b) Rychnovsky, S. D.; Hoye, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 1753–1765.
(57) (a) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825–2828. (b) Seebach, D.; Wasmuth, D. *Helv. Chim. Acta* **1980**, *63*, 197–200.
(58) Kazmierczak, F.; Helquist, P. *J. Org. Chem.* **1989**, *54*, 3988–3992.
(59) Wollenberg, R. H. *Tetrahedron Lett.* **1978**, 717–720.
(60) Mickus, D. E.; Levitt, D. G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1992**, *114*, 359–360.
(61) (a) Mori, Y.; Asai, M.; Furukawa, H. *Heterocycles* **1992**, *34*, 1281–1284. (b) Mori, Y.; Asai, M.; Kawade, J.-I.; Okumura, A.; Furukawa, H. *Tetrahedron Lett.* **1994**, *35*, 6503–6506.
(62) (a) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419–5422. (b) Mori, Y.; Takeuchi, A.; Kageyama, H.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5423–5426. (c) Mori, Y.; Suzuki, M. *Tetrahedron Lett.* **1989**, *30*, 4383–4386. (d) Mori, Y.; Suzuki, M. *Tetrahedron Lett.* **1989**, *30*, 4387–4388.
(63) Aebi, J. D.; Sutter, M. S.; Wasmuth, D.; Seebach, D. *Liebigs Ann. Chem.* **1983**, 2114–2126.
(64) Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155–158.
(65) Evans D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Soc. Chem.* **1988**, *110*, 3560–3578.
(66) (a) Lipshutz, B. H.; Kotsuki, H.; Lew, W. *Tetrahedron Lett.* **1986**, *27*, 4825–4828. (b) Lipshutz, B. H.; Moretti, R.; Crow, R. *Tetrahedron Lett.* **1989**, *30*, 15–18.
(67) Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Org. Chem.* **1982**, *47*, 4626–4633.
(68) Lipshutz, B. H.; Kozlowski, J. A. *J. Org. Chem.* **1984**, *49*, 1147–1149.
(69) Rychnovsky, S. D.; Griesgraber, G.; Kim, J. *J. Am. Chem. Soc.* **1994**, *116*, 2621–2622.
(70) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287–290.

(71) Kitamura, M.; Ohkuma, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 1555–1556.
(72) Rychnovsky, S. D.; Griesgraber, G. *J. Org. Chem.* **1992**, *57*, 1559–1563
(73) Mynderse, J. S.; Moore, R. E. *Phytochemistry* **1979**, *18*, 1181–1183.
(74) (a) Mori, Y.; Kohchi, Y.; Suzuki, M.; Carmeli, S.; Moore, R. E.; Patterson, G. M. L. *J. Org. Chem.* **1991**, *56*, 631–637. (b) Mori, Y.; Kohchi, Y.; Noguchi, H.; Suzuki, M.; Carmeli, S.; Moore, R. E.; Patterson, G. M. L. *Tetrahedron* **1991**, *47*, 4889–4904. (c) Mori, Y.; Kawajiri, N.; Furukawa, H.; Moore, R. E. *Tetrahedron* **1994**, *50*, 11133–11142.
(75) Nakata, T.; Suenaga, T.; Nakashima, K.; Oishi, T. *Tetrahedron Lett.* **1989**, *30*, 6529–6532.
(76) Wang, Z.; Deschenes, D. *J. Am. Chem. Soc.* **1992**, *114*, 1090–1091.

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