H), 5.48 (d, J = 15.6, 1 H). ^{13}C NMR: δ 28.02, 29.64, 32.73, 34.38, 51.32, 122.49, 142.83, 173.61. IR ($CDCl_3$): 1730, 1465, 1380, 1215 cm^{-1}. Anal. Cald for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.65; H, 10.84.

Calculations. All calculations were conducted on an IBM PC fitted with an 8087 math coprocessor utilizing "PCMODEL", a modified version of Prof. C. Still's (Columbia University) MODEL software program (VAX version 1.1) by Serena Software, Box 3076, Bloomington, IN, 47402-3076, 1987 Edition. MMX calculations for all pentanolides were based on at least 200 iterations to a minimized change of 0.02 kcal/mol. Bond angles were obtained from these minimized structures.[36]

Acknowledgment. We wish to acknowledge the kind financial support of NIEHS (Grant. No. ES04434-01) and Loyola University of Chicago for the purchase of the VXR-300 MHz NMR used in this study. We also wish to thank Prof. D. Crumrine (Loyola University) and Prof. Steven Ley (Imperial College, U.K.) for useful suggestions. We also wish to thank David Baehr for large-scale preparations of 4-PSBA and supporting data.

(36) We wish to thank the referee for recalculation (using PC Model Version 2) of some conformations.

Total Synthesis of (+)-Colletodiol: New Methodology for the Synthesis of Macrolactones[1]

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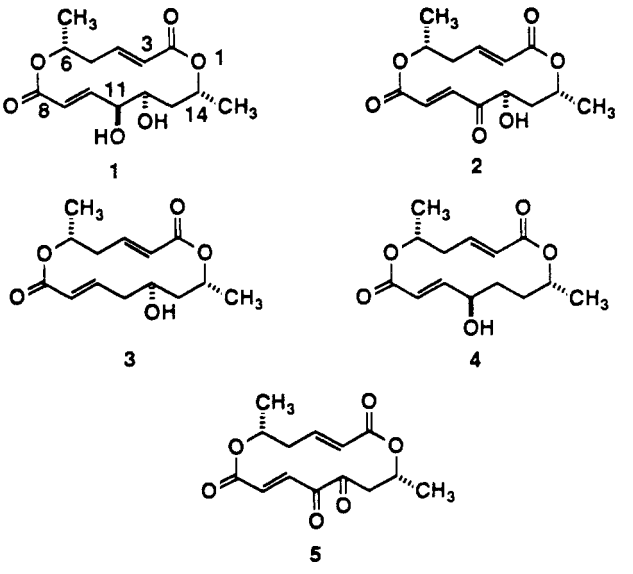
Received May 12, 1988

Synthetic efforts directed toward two different structures suggested for the macrocyclic bis(lactone) colletodiol are detailed. The initial approach to an incorrect structure (C_{11} epi) relies upon the manipulation of methyl α-D-glucopyranoside to set the required stereochemistry for the C_8–C_{14} segment of the C_{11} epi structure. The second approach, initiated after structural revision based upon X-ray crystallographic evidence, employs a Lewis acid mediated addition of allylstannane **33** to β-alkoxy aldehyde **34** to set the stereochemistry of the C_8–C_{14} subunit. This route, which employs a number of new synthetic reactions developed specifically for this problem, gives (+)-colletodiol in nine linear operations and 8.2% overall yield.

Colletodiol is a macrocyclic bis(lactone), which has been isolated as a metabolite of the fungi *Colletorichum capsici* by Grove[2] and from *Chaetomium funicola* by Powell;[3] the gross structure has been elucidated by both Powell[3] and McMillan.[4] McMillan has also reported on the absolute stereochemistry of colletodiol[5] (**1**) and three more cometabolites of *Colletotrichum capsici*: colletoketol (**2**), colletol (**3**), and colletoallol (**4**), although this assignment was later revised.

This class of compounds went largely unnoticed until 1980 when Ronald[6] reported the isolation and structure determination of grahamimycin A_1 (**5**) and also described significant antibacterial activity against a variety of pathogenic microorganisms.

In 1982, Seebach established the absolute configuration of grahamimycin A_1 by total synthesis of the enantiomer from tartaric acid[7] and also reported a revised structure (**7**) for colletodiol based upon X-ray crystallographic analysis.[8] Structures for two other similar macrocyclic antibiotics, grahamimycin A (**8**) and B (**9**) have also been determined;[9] the most potent of these, grahamimycin A



(which is in fact identical with colletoketol[10]), exhibited activity against 36 species of bacteria, eight species of blue-green algae, two species of green algae, and five fungi.

Colletodiol has been synthesized by both Seebach[11] and Mitsunobu.[12] Both groups experienced considerable difficulties, particularly in performing the final macro-

(1) This paper is respectfully dedicated to my postdoctoral mentor, Professor E. J. Corey, on the occasion of his 60th birthday and in appreciation of the opportunity to have worked with him and his exceptional research group.

(2) Grove, J. F.; Speake, R. N.; Ward, G. *J. Chem. Soc. C* **1966**, 230.

(3) Powell, J. W.; Whalley, W. B. *J. Chem. Soc. C* **1969**, 911.

(4) MacMillan, J.; Pryce, R. J. *Tetrahedron Lett.* **1968**, 5497.

(5) MacMillan, J.; Simpson, T. J. *J. Chem. Soc. Perkin Trans. 1* **1973**, 1487.

(6) Ronald, R. C.; Gurusiddaiah, S. *Tetrahedron Lett.* **1980**, *21*, 681.

(7) Seidel, W.; Seebach, D. *Tetrahedron Lett.* **1982**, *23*, 159.

(8) Amstutz, R.; Hungerbuehler, E.; Seebach, D. *Tetrahedron Lett.* **1984**, *25*, 2209.

(9) Gurusiddaih, S.; Ronald, R. C. *Antimicrob. Agents Chemother.* **1981**, *19*, 153.

(10) We thank Professor R. C. Ronald of the Washington State University for supplying samples of grahamimycin A and its sodium borohydride reduction product.

(11) Schnurrenberger, P.; Hungerbühler, E.; Seebach, D. *Tetrahedron Lett.* **1984**, *25*, 2209.

(12) Tsutsui, H.; Mitsunobu, O. *Tetrahedron Lett.* **1984**, *25*, 2159 and 2163.

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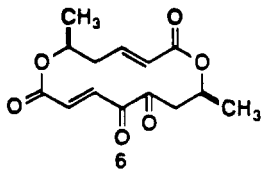
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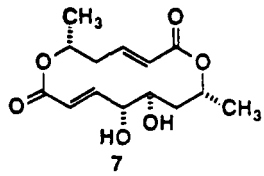
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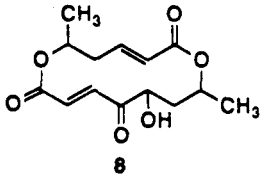
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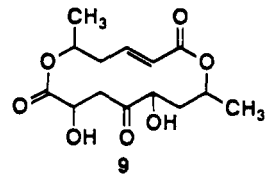
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lactonization, which in the Seebach route proceeded in only 2% yield. In the Mitsunobu route, esterification under standard Mitsunobu conditions[13] required 5 days at low temperature and gave the known acetonide of colletodiol in 45% yield.

Antithetic Analysis. The route that we initially selected for the construction of colletodiol was based upon the preparation and union of two appropriately protected segments corresponding to the two different ω-hydroxy acids present in colletodiol. However, it was necessary to rather carefully consider protecting group strategy and the timing of various a priori independent operations. Thus, for example, the synthesis of colletodiol (assuming that macrolactonization is chosen for preparation of the 14-membered ring) requires one bimolecular esterification event and one macrolactonization event, which could in principle be employed to form either the 1–14 or 7–8 ester linkages.

Although it was difficult to assess in an a priori fashion which macrolactonization event would be more successful, the route involving the 7–8 linkage was judged to be the more promising. The alternate possibility would require an intermediate which appeared vulnerable to intramolecular Michael addition to form a pyran, a process that would be facilitated if an acetonide moiety was chosen for protection of the C_{11} and C_{12} hydroxyls, as was our intention. In addition, **11** would seem to be more vulnerable to acid- or base-catalyzed elimination of the C_6 oxygen substituent than would an intermediate such as **10** (Scheme I). Thus a target such as **10** was selected as the penultimate precursor to colletodiol (McMillan structure).

Numerous protecting group strategies and approaches to the preparation of an intermediate such as **10** have been investigated in the course of this work, and we will not detail those here.[14] The optimal protocols (vide infra) have been incorporated into a "second generation" approach to colletodiol, initiated after the structure was revised by Seebach. Here, we note simply that an approach in which R and R′ are cleaved (to give the hydroxy acid precursor for macrolactonization) in one operation possesses obvious advantages. In addition, the group R′ must be chosen such that cleavage to the acid can be accomplished without β-elimination of the C_6 oxygen substituent, cleavage of the other ester moiety, or Michael addition to either the C_3–C_4 or C_9–C_{10} enoates. These requirements are more formidable than they may appear upon casual inspection. For example, a silyl protecting group cannot be employed as "R" in **10** due to facile elimination upon attempted removal with fluoride ion under a variety of conditions, including "buffered" procedures.[14] Seebach encountered similar difficulties, which, as previously noted, severely compromised his own approach to colletodiol.[11] We describe below our approaches to both "MacMillan colletodiol" (**1**) and colletodiol (**7**) itself.

Synthetic Studies on "MacMillan Colletodiol".[15] Our approach to the C_8–C_{14} segment of "MacMillan colletodiol" (**1**) was based upon the use of a carbohydrate precursor to establish the C_{11}, C_{12}, and C_{14} hydroxyl substituents with correct absolute and relative configuration.

The approach selected, as indicated in Scheme II, relied on Wittig chain extension of an intermediate lactol **13** (via the corresponding hydroxy aldehyde), which could in principle be prepared by deoxygenation of the appropriate sugar (allose) at the C_4 and C_6 positions. In practice, such an approach proved unsatisfactory.[14] However, the glucose-based route described below proved highly efficient and also provided some surprises.

In this approach, the well-known[16] 4,6-benzylidene derivative of α-D-methylglucopyranoside was first converted to the bis(tosylate) **16**. Although this is a known operation,[17] a modified and higher yielding procedure was employed here. The benzylidene moiety was then converted to bromobenzoate **17** according to the general procedure of Hanessian.[18] Deoxygenation at C_6 was most efficiently accomplished (97% yield) via a two-step procedure (routinely performed without purification of intermediates): (1) conversion of bromide to iodide (sodium iodide in refluxing acetone) and (2) hydrogenolysis (Pd/C, H_2, EtOAc/EtOH/H_2O, 8:2:1).[19]

With **15** in hand, we were prepared to effect cleavage of the benzoate with concomitant epoxide formation to yield **14**. Trans diaxial reductive epoxide opening was then expected to result in hydride delivery at C_4 to give the desired relative stereochemistry at C_2 and C_5. However, this well-precedented[20] approach proved unexpectedly difficult. Instead of solely **14**, *three* epoxides (**14**, **18**, and **19**) were formed under almost all basic conditions surveyed to accomplish this transformation.[21] Thus, mixtures of all three epoxides are formed using a variety of alkoxides (NaOMe, KOMe, NaOEt, KOBu^t, and NaO(iPr)) and a variety of solvents (MeOH, EtOH, iPrOH, THF, and ^{t}BuOH). After extensive experimentation, however, conditions that afforded solely the desired epoxide **14** were identified. Exposure of **15** to lithium hydroxide under carefully controlled conditions (dioxane, methanol, water, 3:1:1, 23 °C) gave **14** in 85% isolated yield after purification by recrystallization (Scheme III). Hence crystalline **14** is available from **16** in 70% overall yield and without chromatographic purification at any stage. Moreover, all transformations involved in the route are very simple and amenable to large-scale work.

The expected trans diaxial ring opening proceeded cleanly when **14** was treated with lithium aluminum hy-

(13) (a) Kurihara, T.; Nakajima, Y.; Mitsunobu, O. *Tetrahedron Lett.* **1976**, 2455. (b) Mitsunobu, O. *Synthesis* **1981**, 1. (c) Tsutsui, H.; Mitsunobu, O. *Tetrahedron Lett.* **1984**, *25*, 2163.

(14) For complete details, see: Boden, E. P. Ph.D. Thesis, University of Utah, 1985.

(15) We do not intend to disparage the efforts of MacMillan and co-workers in elucidating the structure of this compound by referring to **1** as "MacMillan colletodiol". This serves merely as a convenient means of placing our own synthetic work in perspective with respect to time.

(16) Richtmyer, N. K. *Methods Carbohydr. Chem.* **1962**, *1*, 107.

(17) (a) Richtmyer, N. K.; Hudson, C. S. *J. Am. Chem. Soc.* **1941**, *63*, 1727. (b) Rosenfeld, D. A.; Richtmyer, N. K.; Hudson, C. S. *J. Am. Chem. Soc.* **1948**, *70*, 2201.

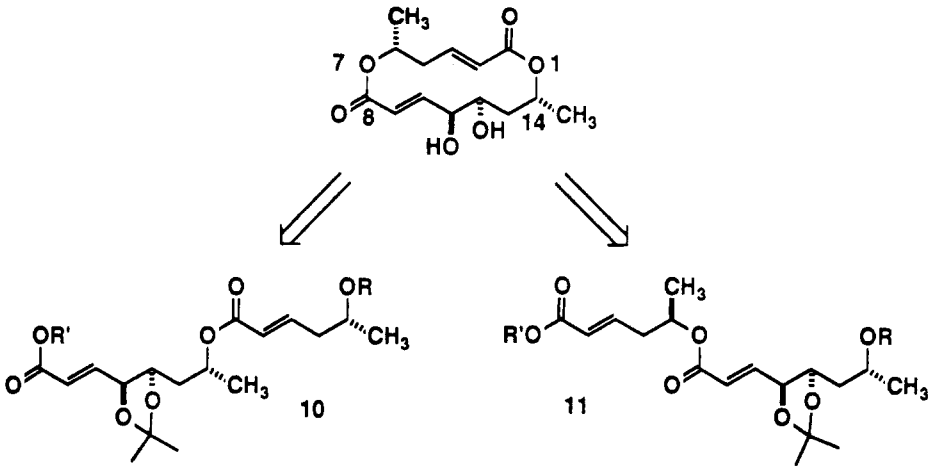
(18) Hanessian, S.; Plessas, N. *J. Org. Chem.* **1969**, *34*, 1035.

(19) Siewert, G.; Westphol, O. *Justus Liebigs Ann. Chem.* **1968**, *720*, 171.

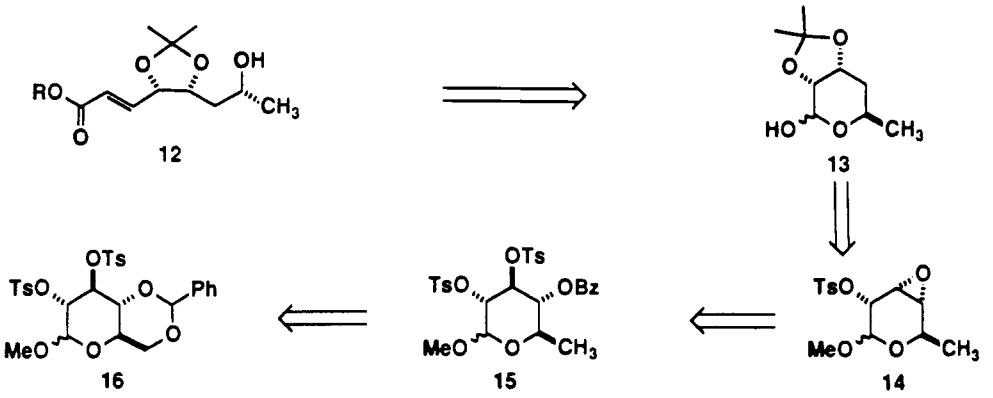
(20) (a) Peat, S.; *Advances in Carbohydrate Chemistry*; Academic: New York, 1946; Vol. II, pp 38–103. (b) Wolfrom, M. L. *Ibid.* 1969; Vol. XXIV, pp 139–198. (c) Schuerch, C.; *Ibid.* 1981; Vol. XXXIX, pp 157–211.

(21) The structures assigned to epoxides **18** and **19** were established by unambiguous independent synthesis.

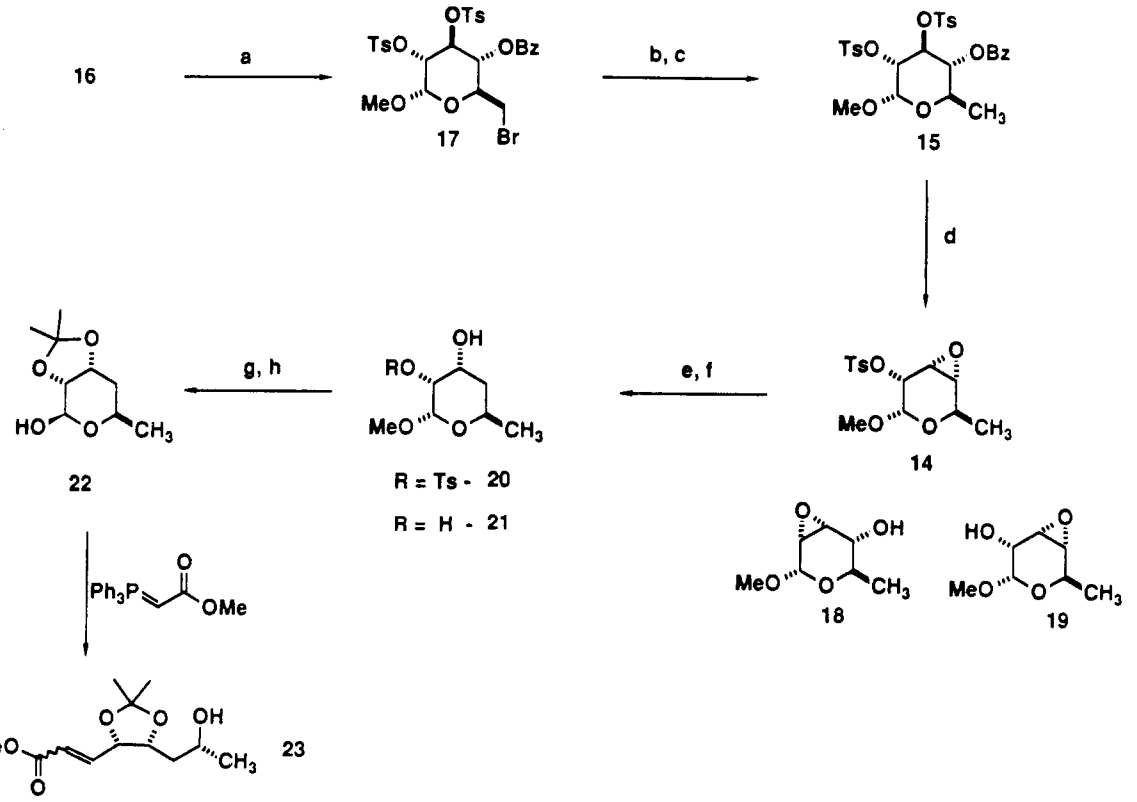
Scheme I



Scheme II

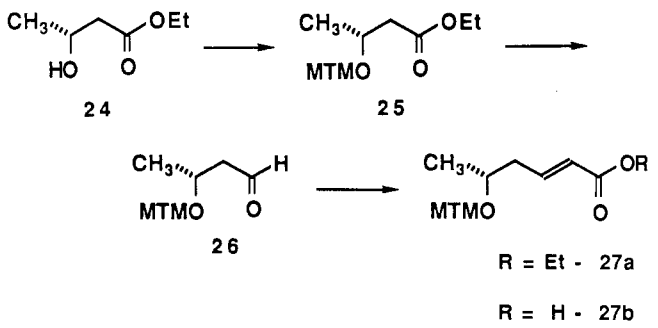


Scheme III[a]



[a] (a) NBS, CCl_4; (b) NaI, acetone; (c) H_2, Pd/C; (d) LiOH, dioxane, methanol, water; (e) $LiAlH_4$; (f) NaOMe, MeOH; (g) Dowex H^+ resin, H_2O; (h) Dowex H^+ resin, acetone.

Scheme IV



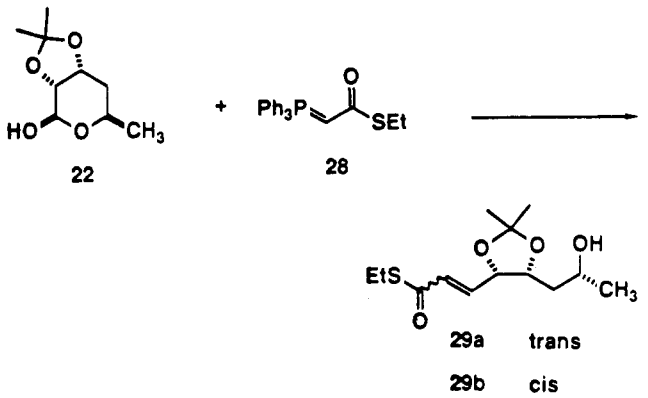
dride in tetrahydrofuran at 0 °C for approximately 30 min to give a nearly quantitative yield of syrupy alcohol **20**. Although this material can be crystallized for analytical purposes, in practice the crude material was treated with a slight excess of sodium methoxide in methanol to effect cleavage of the tosylate.[22] The resulting diol was then isolated by Kugelrohr distillation in 71% overall yield from **14**.

The remaining steps to lactol **22** proved routine and were best accomplished in a two-step procedure without isolation of an intermediate triol. Treatment of **21** with Dowex 50 w H^+ resin in refluxing water for 45 min, filtration of the resin, concentration, and azeotroping with toluene afforded a virtually quantitative yield of triol, which was subsequently exposed to Dowex 50 w H^+ resin and 3-Å molecular sieves in dry acetone to afford acetonide **22** in 85% overall yield from **21**.

Wittig chain extension with (carbomethoxymethylene)triphenylphosphorane in refluxing THF proceeded in accord with expectations based upon literature precedent[23] to give a 44:56 mixture of cis and trans α,β unsaturated esters. At this point, however, we knew that we were directing our efforts toward an incorrect structure, and we attempted to remedy the incorrect C_{11} (colletodiol numbering) stereochemistry. After protection of the C_{14} (colletodiol numbering) hydroxyl substituent as it's *tert*-butyldimethylsilyl ether, numerous attempts to epimerize C_{11} were made.[14] Unfortunately, none of these proved successful. Thus although a reasonably efficient (but somewhat lengthy) route to the C_8–C_{14} subunit of "colletodiol" had been developed, we were unable to remedy the stereochemical deficiency of this route, which had of course arisen from circumstances beyond our control.

In the meantime, however, several other studies relevant to the current investigation were in progress. Particularly germain was the identification of a serviceable C_2–C_6 subunit, namely the (methylthio)methyl (MTM) protected ester **27a**, which could be prepared in good overall yield from commercially available ethyl (*R*)-β-hydroxybutyrate. Reaction of ethyl (*R*)-β-hydroxybutanoate (**24**) with dimethyl sulfoxide and acetic anhydride in the presence of acetic acid,[24] followed by aqueous workup and Kugelrohr distillation, gave the MTM-protected derivative **25** in 72% yield (Scheme IV). Reduction with diisobutylaluminum hydride in methylene chloride at −90 °C, followed by quenching with methanol and stirring with saturated aqueous Rochelle salt, gave aldehyde **26** in 75% yield after purification by distillation. Wittig reaction with (carboethoxymethylene)triphenylphosphorane in chloroform then gave the α,β-unsaturated ester **27a** (9:1 trans/cis) in 76% yield. Hydrolysis of this ester with lithium hydroxide in THF/MeOH (2:1) proceeded smoothly, and with no elimination detectable, to give the corresponding acid **27b** in 93% yield. Moreover, the MTM protecting group in **27a** could be removed under mild conditions without complications from competing elimination. Specifically, the MTM ether was cleaved upon exposure to excess methyl iodide in aqueous acetone buffered with sodium bicarbonate or upon reaction with mercuric trifluoroacetate in methylene chloride buffered with disodium hydrogen phosphate.[25] These observations suggested the use of a thiol ester or other sulfur-based protecting group for the C_8 carboxylate, so that both groups could be cleaved in the same operation.

Of a number of such groups surveyed,[14] by far the best results were realized by using an ethylthiol ester. The crystalline Wittig reagent **28** was easily prepared from bromoacetic acid and reacted smoothly with lactol **22** in refluxing chloroform to yield the cis and trans thiol esters **29** in a ratio of 1:4, respectively. A serendipitous obser-



vation made during the next step of the route to "MacMillan colletodiol" proved extremely valuable. When the 4:1 trans/cis mixture of α,β-unsaturated thiol esters was subjected to Steglich[26] esterification (DCC, catalytic DMAP, CH_2Cl_2) with carboxylic acids, only trans α,β-unsaturated thiol ester products were isolated. Clearly, isomerization of the cis material must have occurred under the reaction conditions. Indeed, it was found that exposure of the pure cis α,β-unsaturated thiol ester (isolated by column chromatography of the mixture) to a catalytic amount of DMAP in CH_2Cl_2 at room temperature resulted in quantitative conversion to the trans material. In contrast, simple alkyl esters (carbomethoxy, etc.) were unaffected by such treatment. Hence the use of the thiol ester ylide **28** very nicely solves the problem associated with the ca. 1:1 cis/trans mixtures commonly obtained upon reaction of lactols such as **22** with more conventional stabilized Wittig reagents.[40]

(22) The tosylate could also be cleaved by conducting the LAH reduction under more forcing conditions, but yields were inferior to those obtained by the two-step protocol described.

(23) Zhdanov, Y. A.; Alexeev, Y. E.; Alexeeva, V. G. *Adv. Carbohydr. Chem. Biochem.* **1972**, *27*, 227.

(24) (a) Ho, T. L.; Wong, C. M. *J. Chem. Soc., Chem. Commun.* **1973**, 224. (b) Pojer, P. M.; Angyal, S. J. *Aust. J. Chem.* **1978**, *31*, 1031.

(25) (a) Ho, T. L.; Wong, C. M. *J. Chem. Soc., Chem. Commun.* **1973**, 224. (b) Pojer, P. M.; Angyal, S. J. *Aust. J. Chem.* **1978**, *31*, 1031. (d) Wade, L. G.; Gerdes, J. M.; Wirth, R. P. *Tetrahedron Lett.* **1978**, 731.

(26) Nieses, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.

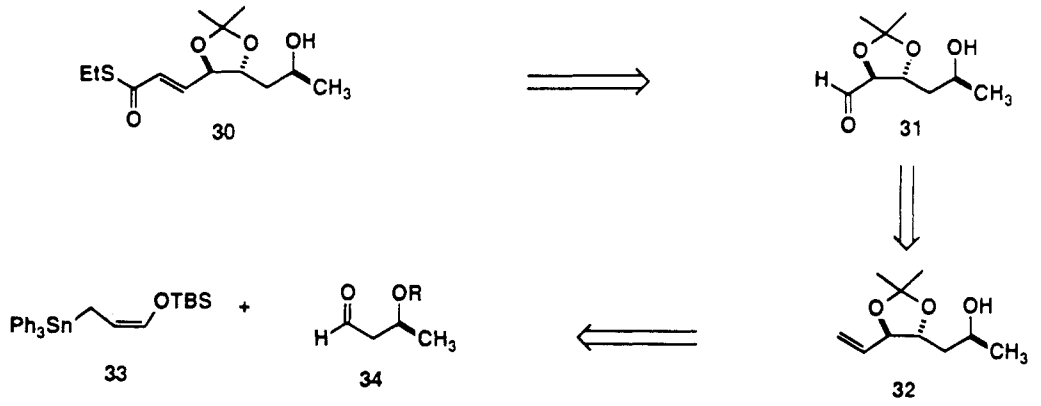
(27) (a) Keck, G. E.; Boden, E. P. *Tetrahedron Lett.* **1984**, *25*, 265 and 1879. (b) Keck, G. E.; Abbott, D. E. *Ibid.* **1984**, *25*, 1883. (c) Keck, G. E.; Abbott, D. E.; Boden, E. P.; Enholm, E. E. *Ibid.* **1984**, *25*, 3927.

(28) Reetz, M. T.; Kesseler, K.; Jung, A. *Tetrahedron Lett.* **1984**, *25*, 729. Reetz, M. T.; Jung, A. *J. Am. Chem. Soc.* **1983**, *105*, 4833.

(29) Keck, G. E.; Castellino, S.; Wiley, M. R. *J. Org. Chem.* **1986**, *51*, 5478.

(30) (a) Evans, D. A.; Andrews, G. C.; Buckwalter, B. *J. Am. Chem. Soc.* **1974**, *96*, 5560. (b) Still, W. C.; MacDonald, T. L. *J. Am. Chem. Soc.* **1974**, *96*, 5561.

Scheme V



Total Synthesis of Colletodiol. At this point, a route to C_8–C_{14} of C_{11}-*epi*-colletodiol was in hand, and considerable progress had been made in the synthesis of the C_6–C_{12} segment and in identifying viable protecting group strategies. However, a new route to the C_8–C_{14} "bottom" half was clearly desirable in view of the structure revision by Seebach. Although a simple modification of our carbohydrate-based approach was possible, simply by starting from the proper sugar (in this case mannose) we also desired a shorter, more direct approach to this segment. A solution emerged from parallel studies in our laboratories on stereocontrolled additions of allylstannanes to aldehydes.

For some time, we had been investigating potential control elements for the addition of various allylstannanes, such as crotyltri-*n*-butylstannane,[27] to α- and β-alkoxy aldehydes and had enjoyed some success in defining variables that contribute to the stereoselectivity realized in such reactions. It was thus natural for us to consider an intermediate such as aldehyde **31** as arising from oxidative cleavage of a vinyl unit in an intermediate such as **32**. This material, with a syn disposition of the vicinal hydroxyl substituents, could arise from a Lewis acid mediated addition of a stannane such as **33** to a simple β-alkoxy aldehyde derivative (**34**). The issue of diastereofacial selectivity was of concern here (vis a vis the relative disposition of the C_{12} and C_{14} stereocenters (colletodiol numbering), but all that would really be required is a reasonable level of diastereofacial selectivity in such an addition, irrespective of its sense. That is, since **30** was to be coupled at C_{14} with a carboxylic acid, we could choose an esterification procedure, which proceeded either with retention (e.g. the Steglich[26] procedure) or inversion (e.g. the Mitsunobu[13] procedure) of configuration at C_{14}. Considerable precedent suggested that synthetically useful levels of diastereoselectivity should be realized in such a bond construction event. Reetz had shown that allyltrimethylsilane adds to **34** (R = CH_2Ph) in the presence of $TiCl_4$ as Lewis acid with very good (95:5) diastereoselectivity for production of the anti 1,3-diol derivative.[28] Our own work had shown that the same was true of allylstannanes,[29] hence the prospects for success here seemed relatively high (Scheme V).

The requisite stannane **33** was very easily prepared. Metalation of the TBDMS derivative of allyl alcohol (sec-BuLi, HMPA-THF, −80 °C) and quenching of the resulting anion with triphenyltin chloride afforded **33** in 82% yield after purification by column chromatography. It should be noted that the material so produced is exclusively cis, as might be expected[30] based upon its mode of preparation.

With respect to the β-hydroxybutyrate **34**, the only decisions involved the choice of protecting group. Previous work in our laboratories[29] had shown that to realize high levels of diastereofacial selectivity in Lewis acid mediated additions of stannanes to such materials, two requirements must be met: (a) the protecting group must be chosen so as to permit effective bidentate chelation between the aldehyde carbonyl and ether oxygen, and (b) the protecting group must be sufficiently bulky to force the methyl substituent into an axial position in the six-ring chelate formed upon bidentate complexation of the Lewis acid.

Of three protecting groups surveyed (CH_2Ph, CH_2OCH_2Ph, and CH_3SCH_3), similar levels of diastereoselectivity and chemical yield were obtained, ca. 4–6:1 facial selectivity for production of the anti diol derivative (complete simple diastereoselectivity) and 46–65% chemical yields on large scale.[41] Thus, the levels of diastereoselectivity are modest compared to those in which $TiCl_4$ can be utilized as Lewis acid and the reaction conducted at low (ca. −80 °C) temperatures. Unfortunately, reagents such as **33** are unstable in the presence of such strong Lewis acids, and their relatively low nucleophilicity requires ca. room temperature for $MgBr_2$-mediated reactions to proceed at a convenient rate. Hence the choice of protecting group here was based solely upon practical considerations (i.e. ease of installation and removal) and thus the (methylthio)methyl (MTM) protecting group was employed for preparative work.

Although the diastereomers produced upon reaction of **33** with **35** were inseparable at this point, MTM cleavage (MeI, aqueous acetone, $NaHCO_3$) afforded an easily separable mixture of diols from which the major (anti) diol

(31) (a) Stork, G.; Paterson, I.; Lee, F. K. L. *J. Am. Chem. Soc.* **1982**, *104*, 4686. (b) Schreiber, S.; Sommer, T. *Tetrahedron Lett.* **1983**, *24*, 4781.

(32) Significant side products were also observed in the esterification of **27b** with simple alcohols such as isopropyl alcohol.

(33) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Rousch, W. P.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(34) Lombordo, L.; Taylor, R. J. K. *Synth. Commun.* **1978**, *8*, 463.

(35) Benzene proved to be a superior solvent for this reaction rather than THF, the standard solvent for Mistunobu esterifications.[13]

(36) (a) Masamume, S.; Hayase, Y.; Schilling, W.; Oran, W. K.; Bates, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 6756. (b) Masmune, S. *Aldrichimica Acta* **1978**, *111*, 23.

(37) Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1975**, 3269.

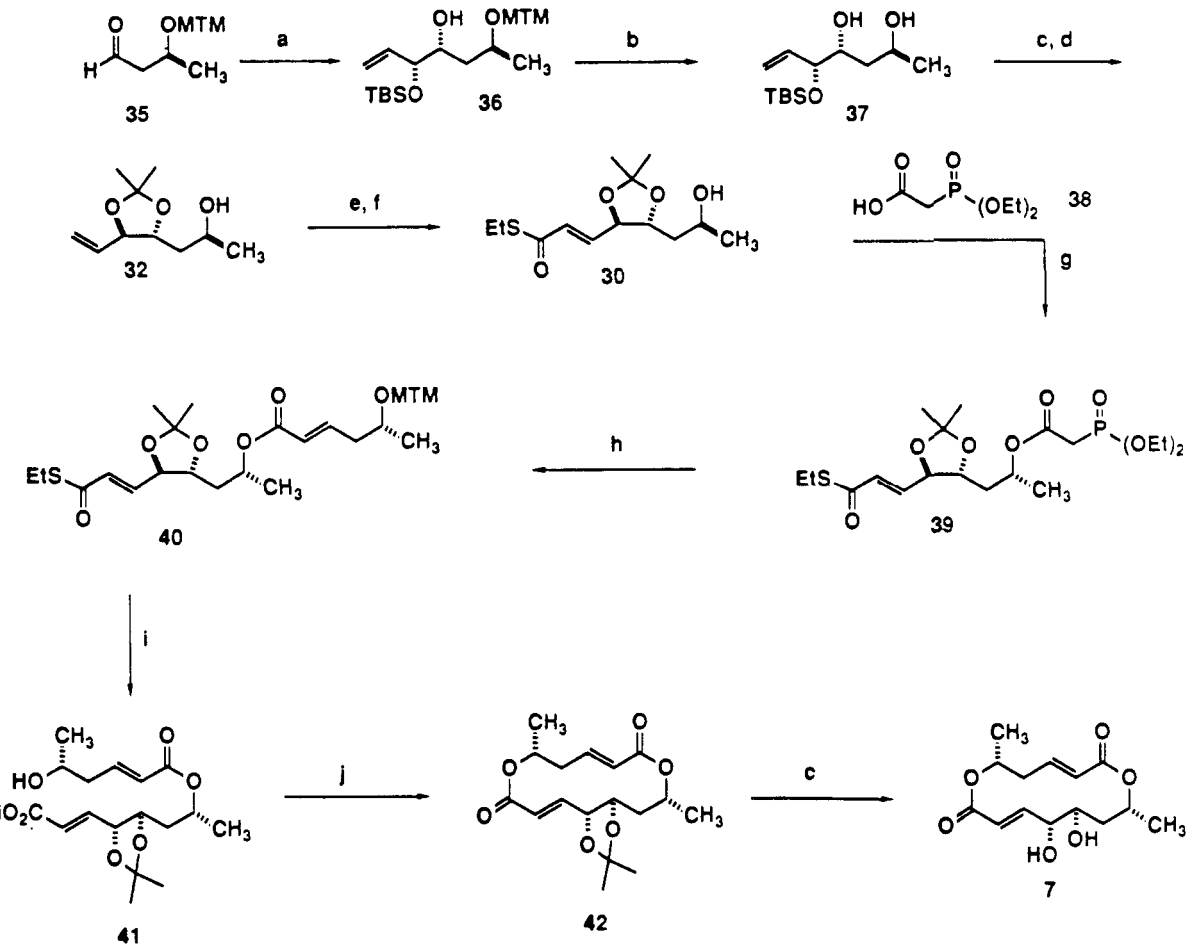
(38) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.

(39) This procedure is thus superior to the aqueous CF_3CO_2H procedure utilized by Mitsunobu (57% yield). See ref 12.

(40) Keck, G. E.; Boden, E. P.; Maybury, S. *J. Org. Chem.* **1985**, *50*, 709.

(41) Keck, G. E.; Abbott, D. A.; Wiley, M. R. *Tetrahedron Lett.* **1987**, *28*, 139. The higher yields and ratios reported in this communication were for small scale reactions (0.2–1.0 mmol). Unfortunately, both stereoselectivity and isolated yields were somewhat compromised upon scale up.

Scheme VI[a]



[a] Reagents: (a) stannane **33**, $MgBr_2 \cdot OEt_2$; (b) MeI, aqueous acetone, $NaHCO_3$; (c) Dowex H^+ resin, MeOH; (d) Dowex H^+ resin, acetone; (e) OsO_4, $NaIO_4$; (f) ylid **28**, $CHCl_3$, Δ; DMAP; (g) $P(Ph)_3$, DEAD, benzene; (h) aldehyde **26**, LiCl, $(iPr)_2NEt$, CH_3CN; (i) $AgNO_3$, 2,6-lutidine, aqueous THF; (j) DCC, DMAP, DMAP·HCl, $CHCl_3$.

37 was obtained in analytically pure form. This material was then converted to acetonide **32** in a two-step procedure deliberately designed to avoid aqueous workup or isolation of the intermediate triol. The TBDMS protecting group was hydrolyzed by exposure to methanol and Dowex 50 w H^+ resin at room temperature. After consumption of starting material was complete, the mixture was filtered and concentrated, and the residue was taken up in acetone and reexposed to Dowex 50 w H^+ resin to give acetonide **32** in 92% overall yield. The isomeric 1,3-dioxane, a potential side product of this sequence, was not detected, presumably since this dioxane would possess an axial substituent at either C_4 or C_6,[31] while the 1,3-dioxolane **32** enjoys a trans disposition of the C_4 and C_5 substituents.

Conversion to the key unsaturated thiol ester **30** proceeded without incident along the lines previously recorded: oxidative cleavage of the olefin (OsO_4; $NaIO_4$), immediate Wittig reaction of the crude aldehyde so produced with phosphorane **28**, and DMAP-catalyzed olefin isomerization afforded **30** in 72% isolated yield (Scheme VI).

At this point the stage was set for union of **30** with the "top-half" carboxylic acid **27b**. Since this transformation required inversion of configuration at C_{14} (colletodiol numbering) the Mitsunobu[13] procedure was employed. However, esterification reactions with **27b** proved unexpectedly difficult and resulted in the formation of significant quantities of side products. This problem was definitely unique to "top-half" materials containing the MTM protecting group as other protected derivatives of this unit could be coupled with the "lower half" material under both Steglich and Mitsunobu conditions without incident.[32]

It was thus clear that an alternative strategy for the union of "top" and "bottom" halves of the structure was necessary. At this point our attention was drawn to the Rousch–Masamune conditions[33] for Emmons reactions, which appeared to be sufficiently mild to be compatible with the rather sensitive substrates necessary for our purposes. Thus, in a somewhat unusual step, alcohol **30** was coupled with the known, readily available β-phosphono acid **38**[34] under Mitsunobu[35] conditions to give the phosphonate **39** in 80% isolated yield after purification by column chromatography. Although the use of DBU in the Rousch–Masamune coupling with aldehyde **26** led to extensive elimination of the C_6 alkoxy substituent, the protocol employing diisopropylethylamine as base afforded the key intermediate **40** in 80% isolated yield. All that remained in the route to colletodiol was cleavage of the MTM and thiol ester protecting groups, macrolactonization, and hydrolytic removal of the acetonide protecting group from the C_{11} and C_{12} hydroxyl substituents.

Cleavage of the MTM and thiol ester using mercuric ion[36] under a wide variety of conditions proved exceptionally difficult and capricious and gave at best only 50% yields of hydroxy acid. This reaction was also difficult to reproduce. Finally it was found that the desired hydrolysis could be accomplished very cleanly by reaction of **40** with

silver nitrate and 2,6-lutidine in THF–water (4:1).[37] Macrolactonization of the resulting hydroxy acid was then accomplished according to our previously reported[38] method (which was developed specifically for this case) to give the known[3] acetonide derivative of colletodiol (**42**) in 82% isolated yield after purification by column chromatography. The richly detailed 300-MHz ^{1}H NMR spectrum of this material was indistinguishable from that of a spectrum obtained on naturally derived material. Finally, acetonide hydrolysis by exposure to Dowex H^+ resin in methanol gave (+)-colletodiol in 76% yield.[39] This material was indistinguishable from a sample of natural material by optical rotation, TLC R_f, melting point, and IR, ^{1}H NMR, and ^{13}C NMR analyses.

The route described finishes synthetic (+)-colletodiol in nine linear operations (some of which are quite trivial) and 8.2% overall yield. The only yield below 80% (46%) fortunately occurs in the first linear step of the route, namely the coupling between stannane **33** and aldehyde **35**.

Summary and Conclusions

The work described in this paper summarizes the highlights of our synthetic work on colletodiol and related members of this family of structures. It has become clear to us in the course of this work that synthetic challenges are not always measured merely by conventional criteria such as size, number of asymmetric centers, or estimates of molecular complexity. By these standards, colletodiol is a very simple structure whose laboratory reconstruction should prove to be a straightforward exercise. In our hands, at least, this has not proven to be the case, particularly if one demands a reasonably streamlined synthesis. Several new methods were developed during the evolution of this work in response to problems posed by this rather simple structure, among them the use of thiol ester ylide **28** to afford trans α,β-unsaturated thiol esters,[40] the use of stannane **33** for reaction with alkoxy aldehydes,[41] and a simple and highly efficient procedure for macrolactonization.[38] The coupling of β-phosphono acid **38** with alcohols to generate complex phosphonates may also find further application in synthesis, particularly in view of the success of Nicolaou and others in applying intramolecular Emmons reactions for the construction of macrocycles.[42]

Given the difficulties encountered by others who have successfully synthesized colletodiol or 11-*epi*-colletodiol in accomplishing the macrolactonization event,[11,12] it seems likely that the procedure developed in the course of our work will prove applicable in other demanding situations. It should be mentioned that Stork and Rychnovsky have applied this procedure in their synthesis of erythronolide B with quite satisfactory results.[43]

The successful approach described herein should, in principle, and with minor modifications, be applicable to the synthesis of a number of natural and unnatural macrolides related to colletodiol in quantities adequate to allow for biological evaluation of the antibiotic and antifungal efficacy of these compounds. The results of such studies will be reported in due course.

Experimental Section

General Procedures. All reactions were carried out under an atmosphere of argon. Solvents were purified according to the guidelines in *Purification of Common Laboratory Chemicals* (Perrin, Armarego, and Perrin, Pergamon: Oxford, 1966). Reagent-grade DMSO, Ac_2O, AcOH, MeOH, and acetone were purchased and used without further purification. Ethanol-free $CHCl_3$ was prepared by passing reagent-grade $CHCl_3$ over a column of activated alumina. Yields were calculated for material judged homogeneous by TLC and NMR. TLC was performed on Merck Kieselgel 60 F_{254} plates, visualizing with a 254-nm UV lamp and staining with an ethanol solution of 12-molybdophosphoric acid. Column chromatography was performed with use of W. G. Grace Davisil 62 silica gel, slurry packed in glass columns. MPLC was performed with Altex columns packed with W. G. Grace Davisil 633 silica gel. Solvents were pumped with an FMI lab pump operating between 60 and 100 psi, and fractions were collected with Gilson fractionators. Capillary GC analyses were carried out on J and W DB-5 or DX-4 columns 30 m in length with a film thickness of 1 μm (DB-5) and 0.25 μm (DX-4), with He as the carrier gas (80 psi) and a flame ionization detection.

Melting points are uncorrected. Optical rotations listed in italics are corrected for the 79.9% ee in the ethyl β-hydroxybutyrate starting material.[44] ^{13}C NMR spectra were acquired at 75 MHz. Exact mass values were calculated by peak matching with an internal standard whose mass was within ±10% of the unknown compound.

Preparation of (*R*)-Ethyl 3-[(Methylthio)methoxy]-butyrate (25). To a solution of dimethyl sulfoxide, acetic anhydride, and acetic acid (560 mL, 15:10:3 volume ratio) was added (*R*)-ethyl β-hydroxybutyrate[44] (19.8 g, 0.15 mol), and the solution was allowed to stand for 48 h. The mixture was then poured slowly into 1 L of saturated aqueous $NaHCO_3$ with stirring, and then solid $NaHCO_3$ was added until the acid was neutralized. The layers were separated, and the aqueous phase was extracted four times with dichloromethane. The combined organics were dried with $MgSO_4$, filtered, and concentrated. The low-boiling impurities were distilled at 40 °C (0.9 mmHg) and then the products at 78 °C. The product mixture was then chromatographed over silica gel, eluting with a solvent gradient from hexanes through 15% EtOAc/hexanes. The product-containing fractions were concentrated to yield 14.5 g (50%) of colorless oil. The same procedure was employed with (*S*)-ethyl β-hydroxybutyrate[44] (79.8% ee) to give the epimer of **25**: (**25**) $[\alpha]_D$ +39.5° (*c* 17.2, $CHCl_3$), (*epi*-**25**) $[\alpha]_D$ −49.5° (*c* 20.0, $CHCl_3$); R_f 0.61 (35% EtOAc/hexanes); 300-MHz ^{1}H NMR ($CDCl_3$) δ 4.65 (AB q, 2 H), 4.23 (m, 1 H), 4.14 (q, J = 7.1 Hz, 2 H), 2.59 (dd, J = 7.5, 15.1 Hz, 1 H), 2.42 (dd, J = 5.6, 15.1 Hz, 1 H), 2.14 (s, 3 H), 1.27 (t, J = 7.1 Hz, 3 H), 1.23 (d, J = 6.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 171.2, 72.8, 69.5, 60.5, 41.9, 19.6, 14.2, 13.8; IR (neat) 2980, 2920, 1730, 1430, 1370, 1300, 1250, 1180, 1060, 1040; mass spectrum (CI, methane), m/z (relative intensity) (M + 1) 193 (0.26), 145 (100), 115 (13.6), 73 (9.3), 61 (55.7). Anal. Calcd for $C_8H_{16}O_3S$: C, 49.97; H, 8.39. Found: C, 50.06; H, 8.43.

Preparation of (*R*)- or (*S*)-3-[(Methylthio)methoxy]butanal (35 or 26). To a stirring solution of **25** or *epi*-**25** (5 g, 26.0 mmol) in methylene chloride (150 mL) at −90 °C, was added a 1.5 M solution of diisobutylaluminum hydride in toluene (22.5 mL, 34 mmol) via syringe pump over 2 h. After complete addition and 15 min, methanol (5 mL) was added and the flask was allowed to warm to room temperature. The mixture was poured into saturated aqueous Rochelle salts (500 mL) and stirred for 8 h. The layers were separated, and the aqueous phase was extracted three times with ethyl acetate. The combined organic phase was dried with $MgSO_4$, filtered, and concentrated. The aldehyde was isolated by MPLC with a solvent gradient from hexanes through 20% EtOAc/hexanes. The product-containing fractions were concentrated, and the product was Kugelrohr distilled at 50 °C (0.3 mmHg) to yield 2.9 g (75%) of colorless oil: (**35**) $[\alpha]_D$ +100.7° (*c* 28.5 $CHCl_3$), (**26**) $[\alpha]_D$ −127° (*c* 38.9, $CHCl_3$); R_f 0.25 (35% EtOAc/hexanes); 300-MHz ^{1}H NMR ($CDCl_3$) δ 9.80 (dd, J = 1.7, 2.7 Hz, 1 H), 4.65 (AB q, 2 H), 4.37 (ddq, J = 4.9, 7.7, 6.2 Hz, 1 H), 2.66 (ddd, J = 2.7, 7.7, 16.4 Hz, 1 H), 2.53 (ddd, J = 1.7, 4.9, 16.4 Hz, 1 H); 2.14 (s, 3 H), 1.26 (d, J = 6.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 201.1, 72.7, 67.7, 50.3, 19.5, 13.9; IR (neat) 2970, 2920, 2840, 2720, 1720, 1430, 1370, 1300, 1260, 1080, 1040, 725, 680, mass spectrum (EI, 70 eV), m/z (relative intensity) (M) 148 (0.6), 101 (100), 71 (64.9), 61 (60.0), 48 (30.9), 43 (79.1); exact mass calcd

(42) Nicolaou, K. C.; Seitz, S.; Puria, M.; Petasis, N. *J. Org. Chem.* **1979**, *44*, 4011.
(43) Stork, G.; Rychnovsky, S. *J. Am. Chem. Soc.* **1987**, *109*, 1565.
(44) Seebach, D.; Züger, M. *Helv. Chim. Acta* **1982**, *65*, 495.

for $C_6H_{12}O_2S$ 148.05580, found 148.05563.

Preparation of Ethyl (2*E*,5*R*)-5-[(Methylthio)methoxy]-2-hexenoate (27a). A solution of 0.239 g (weight based on a theoretical yield from the Dibal reduction, vide supra) of crude aldehyde **26** and 0.870 g (1.5 equiv) of (carbethoxymethylene)-triphenylphosphorane in 8 mL of chloroform was stirred for 16 h. The solution was then concentrated in vacuo and distilled (Kugelrohr) at 150 °C (0.7 mmHg) to yield 0.268 g (76.0% overall yield from ester **25**) of a clear colorless liquid: $[\alpha]_D$ −35.2° (*c* 1.39, chloroform); 90-MHz ^1H NMR ($CDCl_3$) δ 6.93 (dt, *J* = 15, 7 Hz, 1 H), 6.18 (dt, *J* = 15, 1.5 Hz, 1 H), 4.62 (s, 2 H), 4.15 (q, *J* = 7 Hz, 2 H), 3.93 (q, *J* = 6 Hz, 1 H), 2.38 (t, *J* = 7 Hz, 2 H), 2.14 (s, 3 H), 1.28 (t, *J* = 7 Hz, 3 H), 1.18 (d, *J* = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.0, 145.1, 123.6, 72.6, 70.8, 60.0, 39.2, 19.3, 14.3, 13.7; IR (neat) 2980, 2920, 1715, 1650; mass spectrum, EI exact mass measurement, observed (calculated) 170.0923 (170.0943, loss of CH_3S), 141.0915, loss of CH_3SCH_2O).

Preparation of (2*E*,5*R*)-5-[(Methylthio)methoxy]-2-hexenoic Acid (27b). To a solution of 0.206 g of ester **27a** in 9 mL of THF/methanol (2:1) was added 3.0 mL (5 equiv) of an aqueous solution of LiOH (1.57 M). After being stirred for 16 h, the solution was poured into 30 mL of water, extracted once with methylene chloride, acidified with 10% HCl, and then extracted three times with methylene chloride. The latter organic phases were dried over Na_2SO_4 and concentrated in vacuo to yield 0.178 g (99%) of a clear colorless oil: 90-MHz ^1H NMR ($CDCl_3$) δ 11.02 (1 H), 7.06 (dt, *J* = 16, 7 Hz, 1 He, 5.83 (dt, *J* = 16, 1.5 Hz, 1 H), 4.60 (s, 2 H), 3.93 (q, *J* = 6 Hz, 1 He, 2.40 (t, *J* = 6 Hz, 2 H), 2.11 (s, 3 H), 1.19 (d, *J* = 6 Hz, 3 H); IR (neat) 3700–2400 (br), 2960, 2920, 1690, 1640, 1420.

Preparation of Methyl 4,6-Benzylidene-2,3-bis(tolylsulfonyl)-α-D-glucopyranoside (16). A solution of 24.75 g of (+)-4,6-benzylidene-α-D-methylglucopyranoside and 42.0 g (2.5 eq) of *p*-toluenesulfonyl chloride in 95 mL of pyridine was heated at 80 °C for 48 h. The solution was then poured slowly into 500 mL of water, which was being stirred vigorously with a mechanical stirrer. The tan granular crystals that formed were isolated by filtration, dissolved in a minimal amount of chloroform, and diluted with two volumes of methanol. This produced 4.5 g of fluffy colorless crystals (mp 155–156 °C). A second crop was similarly isolated (5.25 g, mp 155–156 °C) to give a combined yield of 92.2% (lit.[17] mp 154–155 °C). Anal. Calcd for $C_{28}H_{30}O_{10}S_2$: C, 56.94; H, 4.97. Found: C, 56.93; H, 5.12.

Preparation of Methyl 4-Benzoyl-6-bromo-6-deoxy-2,3-bis(tolylsulfonyl)-α-D-glucopyranoside (17). A 1000-mL three-necked flask equipped with a reflux condensor and mechanical stirrer was charged with 23.10 g of **16**, 9.06 g (1.3 equiv) of NBS, and 4.40 g (0.57 equiv) of $BaCO_3$ in 500 mL of carbon tetrachloride and heated at reflux for 2 h. The solution was then filtered, and the cake was washed several times with hot carbon tetrachloride. The filtrate was concentrated in vacuo, redissolved in ether, washed with water and brine, then dried over Na_2SO_4, and concentrated in vacuo to a solid foam. This foam was dissolved in 250 mL of methanol and 60 mL of ether and allowed to stand at −10 °C for 16 h to yield 9.68 g of colorless crystals (mp 88–99 °C). A second crop was similarly isolated (13.76 g, mp 104–5 °C)[45] to give a combined yield of 89.5%: $[\alpha]_D$ +9.2° (*c* 1.0, chloroform); 90-MHz ^1H NMR ($CDCl_3$) δ 8.0–6.9 (m, 13 H), 5.31 (t, *J* = 9 Hz, 1 H), 5.13 (t, *J* = 9 Hz, 1 H), 4.96 (d, *J* = 3 Hz, 1 He, 4.34 (m, 2 H), 4.03 (m, 1 H), 3.06 (s, 3 H), 3.02 (m, 1 H), 2.39 (s, 3 H). 2.21 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.7, 145.4, 144.6, 133.6, 132.3, 130.1, 129.8, 129.5, 128.6, 128.2, 127.5, 97.0, 76.5, 75.6, 70.6, 68.9, 60.5, 55.9, 30.9, 21.65, 21.5; IR ($HCCl_3$) 2920, 2860, 1720, 1600, 1450, 1370, 1260, 1190, 1175.

Preparation of Methyl 4-Benzyl-6-deoxy-2,3-bis(tolylsulfonyl)-α-D-glucopyranoside (15). A solution of 10.22 g of **17** and 6.87 g (3.0 eq) of NaI in 110 mL of acetone was heated at reflux for 16 h. The reaction was then partially concentrated in vacuo and partitioned between chloroform and water. After separation of the layers, the aqueous layer was washed twice with chloroform, and then the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to 11.5 g of a light yellow oil. This iodide was immediately subjected to hydrogenolysis as described below: 90-MHz ^1H NMR ($CDCl_3$) δ 8.24–74.11 (m, 13 H), 5.44 (t, *J* = 9 Hz, 1 H), 5.19 (t, *J* = 9 Hz, 1 H), 5.10 (d, *J* = 2 Hz, 1 H, 4.44 (m, 2 H), 3.94 (dt, *J* = 9, 3 Hz, 1 H), 3.5 (s, 3 H), 3.18 (m, 1 H), 2.46 (s, 3 H), 2.28 (s, 3 H).

A solution of this iodide, 0.5 g of 10% palladium on carbon, and 2.50 g of NaOAc in 275 mL of EtOAc/EtOH/H_2O (8:2:1) was vigorously stirred under an atmosphere of hydrogen for 16 h. The solution was then filtered through Celite, and the cake was washed several times with ethyl acetate. The fitrate was then washed with saturated aqueous sodium thiosulfate solution, water, and brine, dried over Na_2SO_4, and concentrated in vacuo to give 9.15 g (100%) of a colorless solid foam (mp 75–78 °C): $[\alpha]_D$ −9.9° (*c* 1.20, chloroform); R_f 0.33 (35% ethyl acetate/hexanes); 90-MHz ^1H NMR ($CDCl_3$) δ 8.26–7.08 (m, 13 H), 5.44 (t, *J* = 9 Hz, 1 H), 5.16 (t, *J* = 9 Hz, 1 H), 5.08 (d, *J* = 4 Hz, 1 H), 4.46 (dd, *J* = 9, 4 Hz, 1 H), 4.07 (m, 1 H). 3.16 (s, 3 H), 2.49 (s, 3 H), 2.29 (s, 3 H), 1.21 (d, *J* = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 164.9, 145.3, 144.5, 134.0, 133.4, 132.6, 129.9, 129.8, 129.5, 129.0, 128.2, 127.5, 97.2, 77.0, 76.2, 73.3, 65.5, 55.7, 21.5, 21.4, 17.1; IR ($HCCl_3$) 2950, 1720, 1595, 1445, 1365, 1260, 1190, 1171; mass spectrum (CI, isobutane), *m/z* (relative intensity) 559 (100), 405 (7), 387 (11), 233 (7). Anal. Calcd for $C_{28}H_{30}O_{10}S_2$: C, 56.94; H, 5.12. Found: C, 56.74; H, 5.05.

Preparation of Methyl 3,4-Anhydro-6-deoxy-2-(tolylsulfonyl)allopyranoside (14). A solution of 9.15 g of **15** and 3.26 g (3.0 equiv) of LiOH in 100 mL of dioxane/MeOH/H_2O (60:20:20) was stirred for 16 h. The mixture was then partitioned between chloroform and water. After separation of the layers, the aqueous layer was washed twice with chloroform, the organic layer was dried over Na_2SO_4 and partially concentrated in vacuo to approximately 9 g of a colorless liquid. After being diluted with 110 mL of methanol and allowed to stand at −10 °C for 20 h, 3.78 g of colorless saltlike crystals were isolated (mp 124 °C). A second crop was similarly isolated (0.28 g, mp 123–4 °C) to give a combined yield of 84.6% based on bromide **17**: $[\alpha]_D$ +19.3° (*c* 1.84, chloroform); R_f 0.23 (35% ethyl acetate/hexanes); 90-MHz ^1H NMR ($CDCl_3$) δ 8.06 (d, *J* = 9 Hz, 2 H), 7.54 (d, *J* = 9 Hz, 2 H), 4.98 (dd, *J* = 5, 3 Hz, 1 H), 4.65 (d, *J* = 5 Hz, 1 H), 4.22 (q, *J* = 7 Hz, 1 H), 3.46 (m, 1 H), 3.33 (s, 3 H), 2.5 (s, 3 H), 1.36 (d, *J* = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 144.7, 133.8, 129.5, 127.5, 96.0, 73.8, 63.1, 58.0, 56.2, 49.2, 21.1, 18.2; IR ($HCCl_3$) 3010, 2915, 2820, 1590, 1445, 1365, 1210, 1190, 1175; mass spectrum (CI, isobutane), *m/z* (relative intensity) 283 (100). Anal. Calcd for $C_{14}H_{18}O_6S$: C, 56.66; H, 5.47. Found: C, 53.44; H, 5.78.

Preparation of Methyl 4,6-Dideoxy-2-(tolylsulfonyl)-*ribo*-hexopyranoside (20). To a solution of 0.472 g (1.3 equiv) of lithium aluminum hydride in 30 mL of THF at 0 °C was added 3.0 g of crystalline **14**. The solution was stirred at 0 °C for 30 min, the ice bath was removed, and the reaction was quenched 30 min later with $Na_2SO_4 \cdot 10H_2O$/Celite. After being stirred for 2–3 h, the slurry was filtered through Celite, and the cake was washed several times with THF. The filtrate was concentrated in vacuo to give a quantitative yield of alcohol, which was used crude for the next step. However, this compound may be crystallized from ether/pentane to afford an 84% yield of colorless saltlike crystals (mp 88–88.5 °C): $[\alpha]_D$ +43.5° (*c* 1.58, chloroform); R_f 0.75 (5% MeOH/$HCCl_3$); 90-MHz ^1H NMR ($CDCl_3$) δ 8.07 (d, *J* = 9 Hz, 2 H), 7.56 (d, *J* = 9 Hz, 2 H), 4.83 (d, *J* = 4 Hz, 1 H), 4.56 (t, *J* = 4 Hz, 1 H), 4.42–3.92 (m, 2 H), 3.46 (s, 3 H), 3.42 (m, 1 H), 2.51 (s, 3 H), 1.97 (ddd, *J* = 15, 3, 3 Hz, 1 H), 1.56 (ddd, *J* = 15, 12, 3 Hz, 1 H), 1.19 (d, *J* = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 144.9, 133.6, 129.7, 127.5, 98.6, 75.9, 66.5, 59.0, 55.6, 40.0, 21.4, 20.0; IR ($HCCl_3$) 3500 (br), 2920, 1590, 1350, 1190, 1170. Anal. Calcd for $C_{14}H_{16}O_6S$: C, 53.32; H, 6.07. Found: C, 53.06; H, 6.16.

Preparation of Methyl 4,6-Dideoxy-*ribo*-hexopyranoside (21). A solution of 3.02 g of crude **20** and 2.6 g (5.0 equiv) of commercial NaOMe in 75 mL of methanol was heated at reflux for 24 h. TLC analysis in 10% MeOH/$HCCl_3$ indicated the presence of starting material, so another 1.0 g of NaOMe (2.0 equiv) was added, and the reaction was heated at reflux for another 24 h. The solution was then diluted with 100 mL of water and continuously extracted with chloroform for 16 h. Concentration in vacuo yielded 2.62 g of a yellow oil. Distillation (Kugelrohr) of this material at 125 °C (0.35 mmHg) afforded 1.10 g (71.1%)

(45) Although each of these crops of crystals are analytically pure, their melting points are different due to difference in crystal structure (i.e., the former crystals are needles and the latter are more granular). For a similar case see ref 17.

of a viscous, colorless oil: $[\alpha]_D$ +111° (c 1.97, MeOH); R_f 0.26 (5% MeOH/$HCCl_3$); 90-MHz ^1H NMR ($CDCl_3$) δ 4.77 (d, J = 4 Hz, 1 H), 4.03 (m, 2 H), 3.60 (t, J = 4 Hz, 1 H), 3.47 (s, 3 H), 3.10 (br, 2 H), 1.97 (ddd, J = 15, 3, 3 Hz, 1 H), 1.58 (ddd, J = 15, 12, 3 Hz, 1 H), 1.20 (d, J = 6 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 101, 68.4, 67.9, 58.5, 55.5, 39.3, 20.3; IR (neat) 3700–3000 (br), 2960, 2920, 2840. Anal. Calcd for $C_7H_{14}O_4$: C, 51.84; H, 8.70. Found: C, 51.86; H, 8.64.

Preparation of 4,6-Dideoxy-2,3-isopropylidene-*ribo*-hexose (22). A solution of 0.1705 g of **52** and 0.050 g of Dowex 50W-8 H^+ resin in 3.0 mL of water was heated at reflux for 45 min, cooled, and filtered through a plug of glass wool. The reaction flask and resins were washed with acetone, andd the aqueous acetone solution was diluted with toluene and concentrated in vacuo to yield 0.152 g (97.6%) of solid triol. An analytical sample may be obtained by recrystallization from a combination of ethanol, ether, and hexanes (mp 103 °C). Due to the mixture of anomers and to the presence of three hydroxyls, the proton NMR is very uniformative: $[\alpha]_D$ −46.1° (c 0.86, MeOH); R_f 0.22 (15% MeOH/$HCCl_3$); 90-MHz ^1H NMR (DMSO-d_6) δ 6.29–5.93 (1 H), 5.03–4.40 (3 H), 3.97–3.70 (2 H), 2.99–2.87 (1 H), 1.80–1.27 (2 H), 1.08 (d, J = 6 Hz, 3 H); IR (neat) 3600–3000 (br), 2960, 2910, 2890. Anal. Calcd for $C_6H_{12}O_4$: C, 48.64; H, 8.16. Found: C, 48.73; H, 8.00.

A solution of 0.152 g of crude triol, 0.050 g of Dowex 50W-8 H^+ resin, and 8–10 3-Å (8–12-mesh beads) MCB molecular sieves, which had been dried prior to use, in 8 mL of acetone was stirred for 16 h. Thin-layer chromatographic analysis in 15% MeOH/$HCCl_3$ revealed a trace of starting material; however, the reaction was worked up at this point. This workup consisted of filtering the mixture through Celite, washing the cake with acetone, and concentrating in vacuo to afford 0.189 g (95.5% overall yield from **21**) of a light yellow oil: R_f 0.57 (15% MeOH/$HCCl_3$); 90-MHz ^1H NMR ($CDCl_3$) δ 4.92 (d, J = 6 Hz, 1 H), 4.52 (m, 1 He, 4.07 (m, 1 H), 3.88 (t, J = 6 Hz, 1 H), 2.02 (ddd, J = 15, 3, 3 Hz, 1 H), 1.70 (ddd, J = 15, 10, 4 Hz, 1 H), 1.56 (s, 3 H), 1.08 (s, 3 H), 1.27 (d, J = 6 Hz, 3 H), ^{13}C NMR ($CDCl_3$) δ 109.1, 96.2, 76.3, 72.9, 66.6, 34.4, 27.9, 25.9, 21.1; IR (neat) 3700–3100 (br), 2980, 2930, 1450, 1375; mass spectrum (EI, 70 eV), exact mass calcd for $C_8H_{13}O_4$ (loss of CH_3) 173.0814, found 173.0834.

Preparation of Ethyl (2*E*,4*S*,5*R*,7*R*)- or (2*Z*,4*S*,5*R*,7*R*)-7-Hydroxy-4,5-(isopropylidenedioxy)-2-octenethioate (29a or 29b). An 8-mL vial sealed with an NMR cap was charged with 0.189 g of crude **22** and 0.732 g (2.0 equiv) of **28** in 4 mL of chloroform and heated at 80 °C for 2 days. Thin-layer chromatographic analysis in toluene/dioxane/acetic acid (40:10:1) revealed a small amount of cis material (**29b**) (R_f 0.54), and the trans product (**29a**) (R_f 0.40). Thin-layer analysis in 35% THF/hexane differentiated the cis (R_f 0.44) from the trans (R_f 0.36) product but not the trans from the starting material (R_f 0.36). The solution was concentrated in vacuo and chromatographed on a 30 cm × 1.5 cm silica gel column (slurry packed in hexane and collecting 7-mL fractions), eluting with hexane (50 mL), 5% THF in hexane (100 mL), 10% THF in hexane (100 mL), and finally 15% THF in hexane (200 mL). Fractions 24–29 contained pure cis product (0.032 g), 30–33 contained cis/trans overlap (0.0355 g), and 34–36 contained pure trans product (0.1485 g) for a combined yield of 78.4%. Spectral data for trans isomer: 300-MHz ^1H NMR ($CDCl_3$) δ 6.72 (dd, J = 5.7, 15.5 Hz, 1 H), 6.35 (dd, J = 1.4, 15.5 Hz, 1 H), 4.72 (dt, J = 1.4, 6.7 Hz, 1 H), 4.46 (ddd, J = 10.2, 6.6, 3.6 Hz, 1 H), 4.00 (m, 1 H), 3.49 (br, 1 H), 2.97 (q, J = 7.4 Hz, 2 H), 1.55 (s, 3 H), 1.43 (s, 3 H), 1.30 (t, J = 7.4 Hz, 3 H), 1.20 (d, J = 6.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 180.2, 138.6, 129.8, 109.5, 104.9, 77.6, 77.3, 66.8, 39.3, 28.0, 25.5, 23.3, 14.7; IR (neat) 3700–3100 (br), 2980, 2930, 2870, 1665, 1630, 1370, 12.15; mass spectrum (EI, 70 eV), exact mass calcd for $C_{12}H_{19}O_5$ (loss of CH_3), 259.1004, found 259.1005.

Preparation of (*Z*)-1-[(*tert*-Butyldimethylsilyl)oxy]-3-(triphenylstannyl)-1-propene (33). To a stirring solution of *tert*-butyldimethylsilyl allyl ether (15 g, 94 mmol) in dry THF (250 mL) at −78 °C was added *sec*-butyllithium (72 mL of 1.3 M in cyclohexane, 94 mmol) followed by hexamethylphosphoramide (15 mL). After 30 min a solution of triphenylchlorostannane (33 g, 86 mmol) in THF (75 mL) was added via an addition funnel. After 12 h the reaction was diluted with ether (200 mL) and water (200 mL). The layers were separated, and the organic phase was washed three times with water (150 mL). The organic phase was dried with $MgSO_4$, filtered, and concentrated. The product was chromatographed over a silica gel column (30 cm × 7 cm), eluting with hexanes through 5% EtOAc/hexanes. The product-containing fractions were combined and concentrated to give 36 g (82%) of a thick colorless oil, which formed an amorphous solid upon standing. The reagent was used directly, but an analytical sample was prepared by recrystallization from ethanol to give colorless needles: mp 39–40 °C; R_f 0.69 (20% EtOAc/hexane); 90-MHz ^1H NMR ($CDCl_3$) δ 7.17–7.57 (m, 15 H), 6.05 (d, J = 6 Hz, 1 H), 4.70 (dt, J = 6, 9 Hz, 1 H), 2.38 (d, J = 9 Hz, 2 H), 0.90 (s, 9 H), 0.00 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 138.9, 136.8, 136.5, 128.5, 128.0, 106.3, 25.6, 18.2, 7.6, −5.4; IR (neat) 3040, 2950, 2925, 1640, 1425, 1250, 1145, 1085, 855, 830, 765, 720, 695; mass spectrum (CI, methane), m/z (relative intensity) (M + 1) 522 (6.3), 443 (10.1), 351 (100), 272 (2.8), 197 (9.7), 73 (54.1). Anal. Calcd for $C_{27}H_{34}OSiSn$: C, 62.20; H, 6.57. Found: C, 62.06; H, 6.50.

Preparation of (3*R*,4*R*,6*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4-hydroxy-6-[(methylthio)methoxy]-1-heptene (36). To a stirring suspension of $MgBr_2{\cdot}OEt_2$ (5.1 g, 19.6 mmol) in methylene chloride (100 mL) at −23 °C was added **35** (2.9 g, 19.6 mmol), and the solution was allowed to stir for 30 min. To this mixture was added via cannula a solution of stannane **33** (12.5 g, 24.5 mmol) in methylene chloride (20 mL) at −23 °C. The cold bath was then left unattended to slowly warm to room temperature. After 12 h, the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (5 mL). The aqueous layer was separated and extracted two times with ethyl acetate, and the combined organic phase was concentrated and redissolved in ether (150 mL). To this solution was added saturated aqueous KF (25 mL), and after stirring for 30 min the mixture was flushed through a column of alumina with ether. The solvent was removed under reduced pressure, and the product was isolated by MPLC with a solvent gradient of hexanes through 20% EtOAc/hexanes. The product-containing fractions were concentrated to yield 2.8 g (46%) of a colorless oil (4.1:1 mixture of inseparable diastereomers): R_f 0.45 (35% EtOAc/hexanes); capillary GC (DB-5, 200–225 °C, 1 °C/min) (major) 13.36 min, (minor) 13.56 min, (DX-4, 175–200 °C, 1 °C/min) (major) 7.83 min, (minor) 8.00 min; 300-MHz ^1H NMR ($CDCl_3$) δ 5.78–5.89 (m, 1 H), 5.16–5.27 (m, 2 H), 4.66 (AB q, 2 H), 3.91–4.06 (m, 2 H), 3.65–3.72 (m, 1 H), 2.66 (d, J = 4.2 Hz, 1 H), 2.17 (s, 3 H), 1.58–1.66 (m, 1 H), 1.46 (ddd, J = 3.2, 10.3, 14.3 Hz, 1 H), 1.19 (d, J = 6.2 Hz, 3 H), 0.91 (s, 9 H), 0.09 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 137.9, 116.7, 77.7, 73.1, 70.9, 70.0, 39.9, 25.9, 20.0, 18.2, 14.1, −4.1, −4.8; IR (neat) 3320–3640 (br), 2970, 2940, 2870, 1470, 1380, 1300, 1260, 1010–1170 (br), 930, 840, 780; mass spectrum (CI, methane), m/z (relative intensity) (M + 1) 321 (8.4), 273 (14.1), 215 (10.6), 171 (16.2), 141 (62.6), 61 (100). Anal. Calcd for $C_{15}H_{32}O_3SiS$: C, 56.20; H, 10.06. Found: C, 56.22; H, 10.35.

Preparation of (3*R*,4*R*,6*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-4,6-dihydroxy-1-heptene (37). To a stirring suspension of $NaHCO_3$ (1.0 g, 12.3 mmol) in acetone/methyl iodide/water (50 mL, 15:1:1 volume ratio) was added **36** (1.3 g, 4.1 mmol). The solution was heated at reflux for a period of 20 h. The mixture was flushed through a column of alumina with ether, and the solvent was removed under reduced pressure. The stereoisomers were separated by MPLC by using a solvent gradient from 10% EtOAc/hexanes through 50% EtOAc/hexanes. The product-containing fractions were combined and concentrated to yield 0.71 g (84%) of a colorless oil: $[\alpha]_D$ +14.6° (c 19.4, $CHCl_3$); R_f 0.22, R_f of minor isomer 0.29 (35% EtOAc/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 5.74 (ddd, J = 7.1, 10.4, 17.4 Hz, 1 H), 5.21 (ddd, J = 0.9, 1.7, 17.4 Hz, 1 H), 5.16 (ddd, J = 0.9, 1.7, 10.4 Hz, 1 H), 4.07 (m, 1 H), 3.92 (ddt, J = 6.8, 7.1, 0.9 Hz, 1 H), 3.68 (m, 1 H), 2.73 (br s, 2 H), 1.53 (dd, J = 5.4, 6.1 Hz, 2 H), 1.18 (d, J = 6.3 Hz, 3 H), 0.87 (s, 9 H), 0.10 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 137.7, 117.5, 77.9, 72.1, 65.1, 40.2, 25.9, 23.5, 18.2, −3.9, −4.8; IR (neat) 3140–3640 (br), 2950, 2930, 2850, 1460, 1400, 1300, 1030–1160 (br), 925, 870, 830, 770; mass spectrum (CI, methane), m/z (relative intensity) (M + 1) 261 (19.8), 243 (6.4), 227 (6.6), 185 (100), 172 (49.2), 111 (98.5). Anal. Calcd for $C_{13}H_{28}O_3Si$: C, 59.95; H, 10.84. Found: C, 59.74; H, 10.84.

Preparation of (3*R*,4*R*,6*S*)-6-Hydroxy-3,4-(isopropylidenedioxy)-1-heptene (32). To a stirring solution of **36** (1.23 g, 4.7 mmol) in methanol (100 mL) was added Dowex 50W-8

H^+ resin (50 mg). After 60 h the mixture was filtered and concentrated, and the product was dissolved in acetone (100 mL). To the stirring solution was added Dowex 50W-8 H^+ resin (50 mg). After 12 h the reaction was filtered and concentrated. The product was purified by MPLC with use of a solvent gradient from hexanes through 35% EtOAc/hexanes. The product containing fractions were combined and concentrated to yield 0.81 g (92%) of a colorless oil: $[\alpha]_D$ +16.3° (*c* 34.4, $CHCl_3$); R_f 0.54 (50% THF/hexanes); 300-MHZ ^1H NMR ($CDCl_3$) δ 5.80 (ddd, *J* = 7.3, 10.3, 17.2 Hz, 1 H), 5.37 (ddd, *j* = 1.0, 1.3, 17.2 Hz, 1 H), 5.27 (ddd, *J* = 1.0, 1.3, 10.3 Hz, 1 H), 4.03–4.11 (m, 1 H), 3.93 (ddd, *J* = 3.7, 7.5, 8.6 Hz, 1 H), 2.43 (br s, 1 H), 1.73 (ddd, *J* = 3.7, 7.5, 14.4 Hz, 1 H), 1.65 (ddd, *J* = 3.5, 8.0, 14.4 Hz, 1 H), 1.44 (s, 3 H), 1.43 (s, 3 H), 1.24 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 134.6, 119.2, 108.8, 82.3, 77.8, 65.0, 39.3, 27.3, 27.0, 23.7; IR (neat) 3180–3620 (br), 2980, 2929, 1370, 1240, 1170, 1080, 1040; mass spectrum (CI, methane), *m/z* (relative intensity) (M + 1) 187 (13.7), 171 (17.2), 129 (26.5), 111 (100), 98 (29.7), 69 (28.8); exact mass calcd for $C_{10}H_{19}O_3$ 187.13341, found 187.13318.

Preparation of Ethyl (2*E*,4*R*,5*R*,7*S*)-7-Hydroxy-4,5-(isopropylidenedioxy)-2-octenethioate (30). To a stirring solution of **32** (1.0 g, 5.37 mmol) in THF/water (100 mL, 2:1 volume ratio) was added a solution of OsO_4 in THF (50 drops, 0.01 g/L) followed by $NaIO_4$ (2.4 g, 11.1 mmol). After being stirred for 16 h (this reaction was monitored by TLC eluting with 10% MeOH/$CHCl_3$), the mixture was diluted with ethyl acetate (50 mL) and the layers were separated. The aqueous layer was saturated with NaCl and extracted three times with ethyl acetate. The combined organic phases were dried with $MgSO_4$, filtered, and concentrated. The crude was redissolved in chloroform (50 mL), and to this stirring solution was added ylide **28** (1.93 g, 5.3 mmol). The reaction was heated at reflux for 12 h and then returned to room temperature. To this stirring solution was added 4-(dimethylamino)pyridine (0.050 g, mmol), and after 20 h, the solution was partially concentrated and then diluted with hexanes until cloudiness persisted. After having stood for 24 h, the solution was decanted off, and the precipitate was then washed with hexanes. The solution was concentrated and chromatographed over a silica gel column (32 cm × i cm), eluting with a solvent gradient from hexanes through 20% EtOAc/hexanes. The product containing fractions were combined and concentrated to yield 1.06 g (72%) of a thick colorless oil: $[\alpha]_D$ +32.8° (*c* 15.5, $CHCl_3$); R_f 0.53 (50% THF/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 6.79 (dd, *J* = 5.5, 15.5 Hz, 1 H), 6.39 (dd, *J* = 1.4, 15.5 Hz, 1 H), 4.23 (ddd, *J* = 1.4, 5.5, 8.6 Hz, 1 H), 3.97–4.11 (m, 1 H), 2.97 (q, *J* = 7.4 Hz, 2 H), 2.36 (br s, 1 H), 1.76 (t, *J* = 4.2 Hz, 1 H), 1.46 (s, 3 H), 1.43 (s, 3 H), 1.29 (t, *J* = 7.4 Hz, 3 H), 1.25 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 189.7, 138.9, 129.3, 109.7, 79.8, 77.9, 65.0, 39.8, 27.2, 26.6, 23.8, 23.5, 14.7; IR (neat) 3180–3620 (br), 2980, 2970, 2930, 1665, 1630, 1450, 1370, 1180–1290 (br); mass spectrum (CI, methane), *m/z* (relative intensity) (M + 1) 275 (6.9), 259 (9.5), 217 (9.5), 199 (14.8), 186 (17.3), 155 (77.5), 128 (100). Anal. Calcd for $C_{13}H_{22}O_4S$: C, 56.91; H, 8.08. Found: C, 56.54; H, 8.19.

Preparation of Ethyl (2*E*,4*R*,5*R*,7*R*)-10-(Diethylphosphono)-4,5-(isopropylidenedioxy)-7-methyl-9-oxo-8-oxadecanethioate (39). To a stirring solution of **30** (260 mg, 0.95 mmol), phosphonate **38** (315 mg, 1.6 mmol), and triphenylphosphine (419 mg, 1.6 mmol) in dry benzene (20 mL) was added a solution of diethyl azodicarboxylate (279 mg, 1.6 mmol) in benzene (5 mL) dropwise via an addition funnel. After 1 h the reaction was concentrated under reduced pressure and diluted with ethyl acetate (3 mL), and then hexanes was added until cloudiness persisted. After standing for 48 h the solution was decanted off and concentrated. The product was isolated by MPLC, eluting with a solvent gradient using 200-mL portions of 10% EtOAc/hexanes, 20%, 35%, 50%, 63%, and finally 75% EtOAc/hexanes. Fractions of 20 mL were collected, and pure product was found in fractions 44–57. The product was concentrated to yield 344 mg (80%) of a clear colorless oil: $[\alpha]_D$ +23.1° (*c* 57.5, $CHCl_3$); R_f 0.29 (50% THF/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 6.75 (dd, *J* = 5.6, 15.4 Hz, 1 H), 6.39 (dd, *J* = 1.4, 15.4 Hz, 1 H), 5.16 (m, 1 H), 4.17 (quintet, *J* = 7.1 Hz, 4 H), 4.17 (m, 1 H), 3.81 (dt, *J* = 3.7, 8.3 Hz, 1 H), 2.97 (q, *J* = 7.4 Hz, 2 H), 2.95 (d, *J* = 21.5 Hz, 1 H), 2.94 (d, *J* = 21.5 Hz, 1 H), 1.98 (ddd, *J* = 6.2, 8.3, 14.3 Hz, 1 H), 1.81 (ddd, *J* = 3.7, 6.7, 14.3 Hz, 1 H), 1.43 (s, 3 H), 1.40 (s, 3 H), 1.35 (t, *J* = 7.1 Hz, 6 H), 1.31 (d, *J* = 6.3 Hz, 3 H), 1.29 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 189.5, 165.1 (d, *J* = 6.4 Hz), 138.6, 129.6, 109.8, 79.9, 77.4, 69.6, 62.6 (d, *J* = 6.2 Hz), 37.5, 35.4, 33.7, 26.9 (d, *J* = 43.9 Hz), 23.3, 19.6, 16.3 (d, *J* = 6.2 Hz), 14.6; IR (neat) 2980, 2940, 2910, 1735, 1670, 1640, 1450, 1380, 1370, 1200–1320 (br), 1170, 1000–1070 (br), 970; mass spectrum (FAB, glycerol), *m/e* (relative intensity) (M + 1) 453 (5.6), 395 (2.4), 333 (15.7), 197 (97.5), 178 (100), 169 (10.6), 151 (40.9), 137 (40.5); exact mass calcd for $C_{19}H_{34}O_8PS$ 453.17119, found 453.17224.

Preparation of Ethyl (2*E*,4*R*,5*R*,7*R*,10*E*,13*R*)-4,5-(Isopropylidenedioxy)-7-methyl-13-[(methylthio)methoxy]-9-oxo-8-oxatetradeca-2,10-dienethioate (40). To a stirring solution of **39** (222 mg, 0.49 mmol) in acetonitrile (10 mL) was added LiCl (43 mg, 1.1 mmol), followed by diisopropylethylamine (81.8 mg, 0.63 mmol) and finally aldehyde **26** (117 mg, 0.79 mmol). After being stirred for 20 h, the reaction mixture was concentrated under reduced pressure, and the product was isolated by MPLC, collecting 20-mL fractions and using a solvent gradient from hexanes through 20% EtOAc/hexanes (1 L total solvent volume). The product was found in fractions 18–26 and concentrated to give 176 mg (80%) of a clear colorless oil: $[\alpha]_D$ +2.8° (*c* 18.0, $CHCl_3$); R_f 0.77 (50% THF/hexanes); 300-MHz ^1H NMR ($CDCl_3$) δ 6.95 (dt, *J* = 15.6, 7.4 H), 1 H), 6.76 (dd, *J* = 5.6, 15.5 Hz, 1 H), 6.38 (dd, *J* = 1.4, 15.5 Hz, 1 H), 5.87 (dt, *J* = 15.6, 1.4 Hz, 1 H), 5.17 (m, 1 H), 4.64 (AB q, 2 H), 4.18 (ddd, *J* = 1.4, 5.6, 8.4 Hz, 1 H), 3.96 (m, 1 H), 3.82 (m, 1 H), 2.97 (q, *J* = 7.4 Hz, 2 H), 2.40 (m, 2 H), 2.15 (s, 3 H), 1.99 (ddd, *J* = 6.4, 8.0, 14.2 Hz, 1 H), 1.82 (ddd, *J* = 3.8, 6.2, 14.2 Hz, 1 H), 1.42 (s, 3 H), 1.39 (s, 3 H), 1.30 (d, *J* = 6.2 Hz, 3 H), 1.29 (t, *J* = 7.4 Hz, 3 H), 1.18 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 189.6, 165.5, 145.3, 138.7, 129.5, 123.7, 109.7, 79.9, 77.4, 72.6, 70.8, 67.9, 39.1, 37.6, 27.2, 26.6, 23.4, 19.9, 19.3, 14.7, 13.8; IR (neat) 2990, 2940, 1720, 1680, 1460, 1380, 1330, 1270, 1225, 1050, 980; mass spectrum (FAB, *p*-nitrobenzyl alcohol + NaCl), *m/z* (M + Na) 469; exact mass calcd for $C_{21}H_{34}NaO_6S_2$ 469.16944, found 469.16953.

Preparation of (2*E*,4*R*,5*R*,7*R*,10*E*,13*R*)-13-Hydroxy-4,5-(isopropylidenedioxy)-7-methyl-9-oxo-8-oxatetradeca-2,10-dienoic Acid (41). To a stirring solution of **40** (164 mg, 0.37 mmol) in THF/water (5 mL, 4:1 volume ratio) was added 2,6-lutidine (296 mg, 2.76 mmol) followed by $AgNO_3$ (937 mg, 5.52 mmol). The mixture was heated to reflux for 20 h and then cooled to room temperature. The mixture was acidified with acetic acid, diluted with ether (20 mL), and filtered through Celite. After washing the Celite with ether (75 mL), the combined organic phase was washed two times with saturated aqueous $CuSO_4$ (15 mL) and once with brine. The solvent was evaporated, and the product was isolated by chromatography over a silica gel column (1.5 cm × 15 cm) eluting with 100-mL portions of 1% AcOH/$CHCl_3$ and AcOH/MeOH/$CHCl_3$ (1:1:98 volume ratio). Fractions of 7 mL were collected, and the product was found in fractions 12–23. The solvent was removed under reduced pressure, and the residual acetic acid was removed as an azeotrope with toluene to yield 99 mg (79%) of a colorless oil: $[\alpha]_D$ +0.6° (*c* 50.0, $CHCl_3$); R_f 0.33 (toluene/dioxane/AcOH, 20:10:1 volume ratio); 300-MHz ^1H NMR ($CDCl_3$) δ 6.96 (m, 1 H), 6.91 (dd, *J* = 5.8, 15.6 Hz, 1 H), 6.9 (br s, 1 H), 6.13 (dd, *J* = 1.2, 15.6 Hz, 1 H), 5.88 (dt, *J* = 15.7, 1.2 Hz, 1 H), 5.13 (m, 1 H), 4.21 (ddd, *J* = 1.2, 5.8, 8.4 Hz, 1 H), 3.99 (m, 1 H), 3.88 (m, 1 H), 2.37 (t, *J* = 7.1 Hz, 1 H), 2.37 (t, *J* = 5.6 Hz, 1 H), 2.06 (dt, *J* = 14.2, 7.0 Hz, 1 H), 1.87 (dt, *J* = 14.2, 5.2 Hz, 1 H), 1.43 (s, 3 H), 1.40 (s, 3 H), 1.31 (d, *J* = 6.3 Hz, 3 H), 1.24 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.8, 165.7, 145.6, 145.5, 123.8, 122.5, 109.7, 79.7, 77.3, 68.0, 66.8, 41.7, 37.5, 27.1, 26.5, 23.0, 19.9; IR (neat) 2400–3600 (br), 2970, 2940, 1690, 1650; mass spectrum (FAB, glycerol), *m/z* (relative intensity) (M + 1) 343 (48.2), 285 (43.4), 185 (100), 155 (86.7); exact mass calcd for $C_{17}H_{27}O_7$ 343.17494, found 343.17564.

Preparation of (3*E*,6*R*,9*E*,11*R*,12*R*,14*R*)-11,12-(Isopropylidenedioxy)-6,14-dimethyl-1,7-dioxacyclotetradeca-3,9-diene-2,8-dione (42). To a stirring solution of dicyclohexylcarbodiimide (288.9 mg, 1.4 mmol), 4-(dimethylamino)-pyridine (171 mg, 1.4 mmol), and 4-(dimethylamino)pyridine hydrochloride (222 mg, 1.4 mmol) in ethanol-free chloroform (20 mL) at reflux was added via syringe pump a solution of **41** (99 mg, 0.29 mmol) in ethanol-free chloroform (1 mL) over a period of 16 h. The residual contents of the syringe and needle were rinsed into a tared flask and concentrated to give 16 mg of re-

covered starting material. The solution was cooled to room temperature and quenched by the addition of methanol (3 mL) and 10 drops of acetic acid. The solution was transferred to a 100-mL round-bottom flask and concentrated to a volume of 5 mL, diluted with ether, and filtered through a pad of Celite. The solvent was removed under reduced pressure, and the product was isolated by MPLC, collecting 8-mL fractions and eluting with hexanes (80 mL), 5% EtOAc/hexanes (80 mL), 10% EtOAc/hexanes (120 mL), and 20% EtOAc/hexanes (200 mL). The product was found in fractions 40–49 and concentrated to give 65 mg (82%) of a colorless oil: $[\alpha]_D$ −68.3° (*c* 32.5, $CHCl_3$); R_f 0.70 (toluene/dioxane/AcOH, 20:10:1 volume ratio); 300-MHz ^1H NMR ($CDCl_3$) δ 6.73 (ddd, *J* = 4.8 11.1, 15.7 Hz, 1 H), 6.57 (dd, *J* = 6.6, 15.6 Hz, 1 H), 6.14 (dd, *J* = 0.9, 15.6 Hz, 1 H), 5.74 (br d, *J* = 15.7 Hz, 1 H), 5.29 (ddq, *J* = 3.6, 11.1, 6.3 Hz, 1 H), 4.89 (ddq, *J* = 4.8, 6.6, 6.3 Hz, 1 H), 4.04 (ddd, *J* = 0.9, 6.6, 8.6 Hz, 1 H), 3.90 (ddd, *J* = 5.1, 5.8, 8.6 Hz, 1 H), 2.55 (dddd, *J* = 1.4, 3.6, 4.8, 12.8 Hz, 1 H), 2.29 (br dt, *J* = 12.8, 11.1 Hz, 1 H), 1.99 (ddd, *J* = 5.1, 6.6, 15.0 Hz, 1 H), 1.89 (ddd, *J* = 4.8, 5.8, 15.0 Hz, 1 H), 1.49 (s, 3 H), 1.43 (s, 3 H), 1.39 (d, *J* = 6.3 Hz, 3 H), 1.35 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.1, 165.4, 144.4, 142.1, 125.5, 125.4, 109.2, 79.0, 78.6, 69.1, 68.3, 40.9, 35.3, 27.2, 26.8, 20.5, 19.8; IR (neat) 2980, 2930, 1715, 1650, 1440, 1370, 1310, 1220, 1165, 970, 750; mass spectrum (FAB, *p*-nitrobenzyl alcohol), *m/e* (relative intensity) (M + 1) 325 (55.8), 309 (20.5), 289 (8.3), 279 (14.6), 267 (100e, 183 (55.5); exact mass calcd for $C_{17}H_{25}O_6$ 325.16511, found 325.16486.

Preparation of Colletodiol, (3*E*,6*R*,9*E*,11*R*,12*R*,14*R*)-11,12-Dihydroxy-6,14-dimethyl-1,7-dioxacyclotetradeca-3,9-diene-2,8-dione (7). To a stirring solution of **42** (63 mg, 0.19 mmol) in methanol (10 mL) was added Dowex 50W-8 H^+ resin (50 mg), and the reaction mixture was heated at reflux for a period of 36 h. The solution was cooled to room temperature, filtered, and concentrated. The product was purified by MPLC, collecting 7-mL fractions and eluting with 125-mL portions of 20% EtOAc/hexanes, 35% EtOAc/hexanes, 50% EtOAc/hexanes, and finally 75% EtOAc/hexanes. The product was found in fractions 50–59 and concentrated to give 41 mg (76%) of colletodiol, which was identical in every way with a natural sample: mp 165 °C (lit.[3] mp 164–167 °C); $[\alpha]_D$ +36.9° (*c* H), $CHCl_3$) (lit.[3] $[\alpha]_D$ +36° (*c* 1.0, $CHCl_3$)); R_f 0.37 (toluene/dioxane/AcOH, 20:10:1 volume ratio); 300-MHz ^1H NMR ($CDCl_3$) δ 6.74 (dd, *J* = 5.6, 15.7 Hz, 1 H), 6.72 (ddd, *J* = 4.9, 11.1, 15.6 Hz, 1 H), 6.14 (dd, *J* = 1.2, 15.7 Hz, 1 H), 5.73 (br d, *J* = 15.6 Hz, 1 H, 5.32 (ddq, *J* = 3.1, 11.1, 6.4 Hz, 1 H), 5.18 (ddq, *J* = 2.0, 4.5, 6.7 Hz, 1 H), 4.08 (ddd, *J* = 1.2, 5.6, 9.0 Hz, 1 H), 3.67 (ddd, *J* = 1.6, 5.9, 9.0 Hz, 1 H), 2.6 (br s, 2 H), 2.52 (dddd, *J* = 1.3, 3.1, 4.6, 12.6 Hz, 1 H), 2.24 (br dt, *J* = 12.6, 11.1 Hz, 1 H), 2.02 (ddd, *J* = 1.6, 4.5, 15.8, Hz, 1 H), 1.50 (ddd, *J* = 2.0, 5.0, 15.8 Hz, 1 H), 1.37 (d, *J* = 6.3 Hz, 3 H), 1.36 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.5, 165.1, 146.2, 144.1, 125.7, 123.9, 73.9, 71.8, 68.7, 67.9, 41.1, 36.2, 20.4, 18.1; IR ($CHCl_3$) 3240–3620 (br), 2980, 2950, 2860, 1715, 1655, 1445, 1350, 1315, 1260, 1170, 1105, 1055, 980; mass spectrum (CI, methane), *m/z* (relative intensity) (M + 1) 285 (3.4), 267 (6.3), 249 (5.9), 201 (4.0), 183 (13.7), 155 (11.0)e, 137 (16.0), 113 (100), 95 (14.8).

Acknowledgment. Financial support of this research by the National Institutes of Health (through Grant GM 28961) is gratefully acknowledged. We are also indebted to Professors Rob Ronald and Jake MacMillan for supplying us with natural samples of colletodiol and related materials.

Registry No. **7**, 21142-67-6; **14**, 116809-48-4; **15**, 116809-49-5; **16**, 6884-01-1; **16** (2,3-diol), 3162-96-7; **17**, 101155-76-4; **17** (iodide), 116809-47-3; **20**, 101155-81-1; **21**, 72212-13-6; **22**, 94498-98-3; **22** (triol), 116907-46-1; α-**22** (triol), 116907-47-2; **24**, 24915-95-5; (*S*)-**24**, 56816-01-4; **25**, 116809-41-7; *epi*-**25**, 116809-42-8; **26**, 116809-44-0; **27a**, 116809-45-1; **27b**, 116809-46-2; **28**, 32443-51-9; **29a**, 94499-07-7; **29b**, 94595-41-2; **30**, 116907-49-4; **32**, 116809-52-0; **33**, 110410-39-4; **35**, 116809-43-9; **36**, 116809-50-8; **36** (diastereomer), 116907-48-3; **37**, 116809-51-9; **38**, 3095-95-2; **39**, 116840-66-5; **40**, 116809-53-1; **41**, 116908-88-4; **42**, 91273-95-9; $Ph_3P{=}CHCOOEt$, 1099-45-2; $CH_2{=}CHCH_2OTBS$, 85807-85-8.

Synthesis of Sulfur-Substituted Phospholipid Analogues as Mechanistic Probes of Phospholipase A_2 Catalysis

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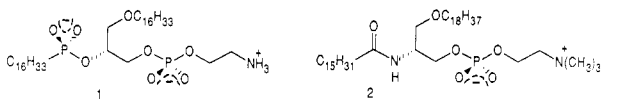
Received August 30, 1988

Phospholipid analogues with sulfur-containing functional groups that replace the ester at the 2-position of the glycerol backbone have been prepared. Thiophosphonate analogues in which one of the nonbridging phosphonate oxygens is replaced by sulfur were synthesized by a newly developed route. Both phosphorus stereoisomers were prepared. The synthesis involves the reaction of phosphoroamidites with hydrogen sulfide in the presence of tetrazole to give thiophosphites, which react with terminal olefins in the presence of a radical initiator to give thiophosphonates. A phospholipid analogue in which the ester at the 2-position was replaced with a thioamide was found to readily cyclize to the thiazoline. To circumvent this problem, amide and thioamide analogues were prepared that contain a phosphonate group linked to carbon 3 of the glycerol backbone in place of the phosphate group.

Introduction

Recently we reported that a phospholipid analogue **1** containing a phosphonate in place of the ester at the 2-position of the glycerol backbone was a tight-binding inhibitor of phospholipase A_2.[1] Compound **1** binds some 2000-fold tighter to the enzyme than the analogous ester substrate. Others have reported that amide analogous such as **2** are also good inhibitors, binding some 40-fold tighter than the substrate.[2]



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