Total Synthesis of the Antiparasitic Agent Avermectin B_{1a}

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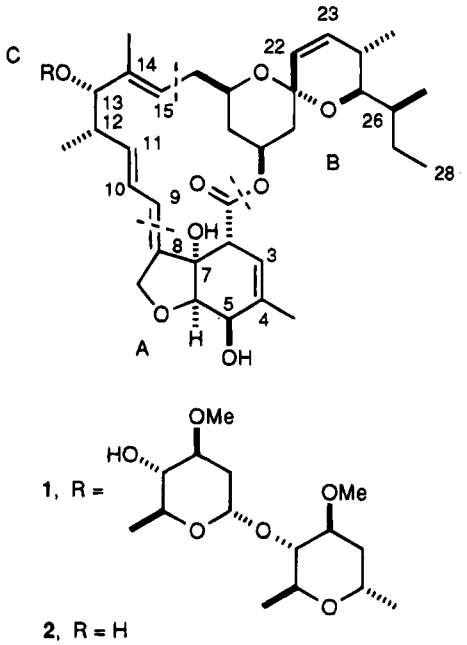
Abstract: The synthesis of avermectin B_{1a} has been completed by a route that assembles the aglycon from three subunits consisting of the hexahydrobenzofuran moiety (**A**), the spiroketal segment (**B**), and the acyclic portion (**C**) comprising C9−C15. Connection is made in a **B** + **C** → (**B** − **C**) + **A** sequence, and the synthesis is concluded by attachment to the aglycon of the L-oleandrosyl-L-oleandrose disaccharide via the pyridylthio glycoside.

The discovery of the milbemycins in the mid 1970s, and soon thereafter the avermectin family of macrolides, represents one of the most significant developments in the treatment of parasitic diseases.[1] Members of these two classes of natural products have been shown to possess broad-spectrum anthelmintic activity with relatively low toxicity in both humans and animals.[2] The avermectins are particularly effective against two major classes of parasites, the nematodes and arthropods,[3] and ivermectin, a semisynthetic mixture containing principally the 22,23-dihydro derivative of avermectin B_{1a} (**1**), has assumed commercial significance as a method for controlling parasitic infections in domestic animals.[4] The recent emergence of nemadectins,[5] many of which surpass the avermectins in antiparasitic activity, has added a new chapter to the large body of work devoted to this area of infectious diseases.

The central importance of avermectin B_{1a} (**1**) among this group of antiparasitic agents has made it the focal point of numerous synthetic efforts. Total syntheses of **1** have been achieved by Hanessian[6] and Ley,[7] and a synthesis of the closely related avermectin A_{1a} has been reported by Danishefsky.[8] In addition, synthetic routes to the structurally less complex milbemycins, including β_3,[9] β_1,[10] and E,[11] have been described. These efforts have laid the groundwork for broad-ranging synthetic studies that now encompass the nemadectins,[12] certain avermectin−nemadectin hybrids,[13] and a new member of the class, lacrimin A.[14]

The complex architecture of **1**, particularly the sensitive hexahydrobenzofuran subunit present in the aglycon portion **2**, offers a formidable synthetic challenge. The 12 stereogenic



2, R = H

centers in **2**, the interplay of functional groups, and the subtle conformational effects, which, for example, fold the C13

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(1) For recent reviews, see: (a) Davies, H. G.; Green, R. H. *Chem. Soc. Rev.* **1991**, *20*, 211, 271. (b) Blizzard, T.; Fisher, M. H.; Mrozik, H.; Shih, T. L. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer-Verlag: New York, 1990; p 65. (c) Crimmins, M. T.; Hollis, W. G., Jr.; O'Mahony, R. In *Studies in Natural Product Chemistry;* Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1988; Vol. 1, p 435.

(2) Fisher, M. H. *Pure Appl. Chem.* **1990**, *62*, 1231.

(3) Fisher, M. H. In *Recent Advances in the Chemistry of Insect Control*; Janes, N. F., Ed.; The Royal Society of Chemistry: London, 1985; p 53.

(4) Campbell, W. C. *Ivermectin and Abamectin*; Springer-Verlag: New York, 1989.

(5) (a) Tsou, H. R.; Ahmed, Z. H.; Fiala, R. R.; Bullock, M. W.; Carter, G. T.; Goodman, J. J.; Borders, D. B. *J. Antibiot.* **1989**, *42*, 398. (b) Ramsay, M. V. J.; Roberts, S. M.; Russell, J. C.; Shingler, A. H.; Slawin, A. M. Z.; Sutherland, D. R.; Tiley, E. P.; Williams, D. J. *Tetrahedron Lett.* **1988**, *29*, 2595.

(6) (a) Hanessian, S.; Ugolini, A.; Dubé, D.; André, C. *J. Am. Chem. Soc.* **1986**, *108*, 2776. (b) Hanessian, S.; Ugolini, A.; Hodges, P. J.; Beaulieu, P.; Dubé, D.; André, C. *Pure Appl. Chem.* **1987**, *59*, 299. These reports describe a partial synthesis of **1** from a spiroketal segment obtained synthetically and an oxahydrindene subunit derived from degradation of natural avermectin B_{1a}. Subsequently, the oxahydrindene was synthesized from (−)-quinic acid (Dubé, D. Ph.D. Thesis, University of Montreal, 1988).

(7) Ley, S. V.; Armstrong, A.; Diez-Martin, D.; Ford, M. J.; Grice, P.; Knight, J. G.; Kolb, H. C.; Madin, A.; Marby, C. A.; Mukherjee, S.; Shaw, A. N.; Slawin, A. M. Z.; Vile, S.; White, A. D.; Williams, D. J.; Woods, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 667.

(8) Danishefsky, S. J.; Armistead, D. M.; Wincott, F. E.; Selnick, H. G.; Hungate, R. *J. Am. Chem. Soc.* **1989**, *111*, 2967.

(9) (a) Williams, D. R.; Barner, B. A.; Nishitani, K.; Phillips, J. G. *J. Am. Chem. Soc.* **1982**, *104*, 4708. (b) Schow, S. R.; Bloom, J. D.; Thompson, A. S.; Winzenberg, K. N.; Smith, A. B., III *J. Am. Chem. Soc.* **1986**, *108*, 2662. (c) Barrett, A. G. M.; Carr, R. A. E.; Atwood, S. V.; Richardson, G.; Walshe, N. D. A. *J. Org. Chem.* **1986**, *51*, 4840. (d) Baker, R.; O'Mahony, M. J.; Swain, C. J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1623. (e) Kocienski, P. J.; Street, S. D. A.; Yeates, C.; Campbell, S. F. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2171, 2183, 2189. (f) Crimmins, M. T.; Bankaitis-Davis, D. M.; Hollis, W. G., Jr. *J. Org. Chem.* **1988**, *53*, 652.

(10) Ley, S. V.; Anthony, N. J.; Armstrong, A.; Brasca, M. G.; Clarke, T.; Culshaw, D.; Greck, C.; Grice, P.; Jones, A. B.; Lygo, B.; Madin, A.; Sheppard, R. N.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron* **1989**, *45*, 7161.

(11) Parmee, E. F.; Steel, P. J.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1989**, 1250.

(12) Mowbray, C. E.; Ramsay, M. V. J.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1813.

(13) Shih, T. L.; Holmes, M. A.; Mrozik, H.; Fisher, M. H. *Tetrahedron Lett.* **1991**, *32*, 3663.

(14) Takie, A.; Kocienski, P. *Tetrahedron* **1990**, *46*, 4503.

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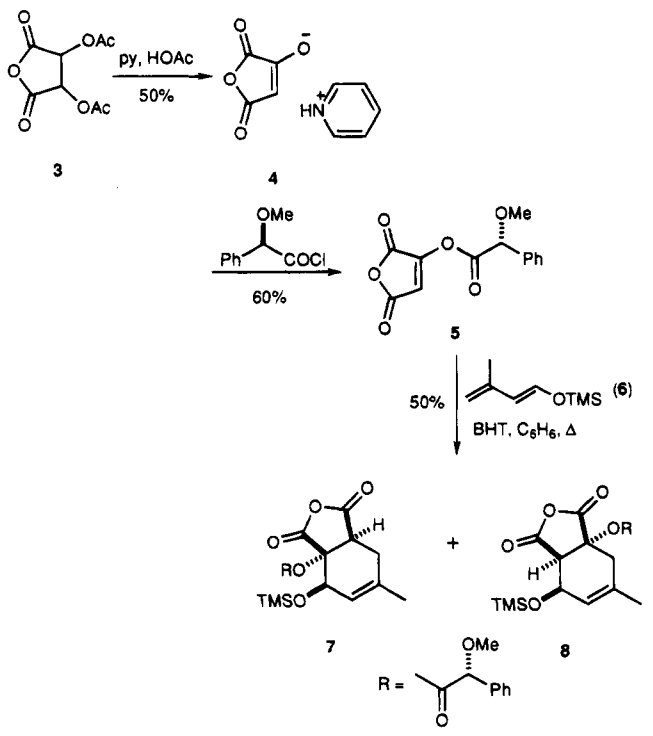
hydroxyl group under the macrolide to make it much less accessible than a planar projection would suggest, all combine to render its synthesis a demanding exercise. Our response to this challenge was to subdivide **2** into three segments **A**, **B**, and **C** that would be synthesized separately and then annealed in a **B** + **C** → **A** + (**B** − **C**) sequence before final closure of the macrolactone. The disaccharide L-oleandrosyl-L-oleandrose would be attached to **2** as the finale to the synthesis. We now describe the realization of this plan, which follows a significantly different course from other approaches to **1**[6,7] and which is sufficiently versatile to accommodate structural variants such as those found in the nemadectins.[5]

Results and Discussion

Of the three subunits, **A**, **B**, and **C**, identified in the trisection of **2**, the hexahydrobenzofuran moiety **A** appeared likely to present the most difficulty. Synthesis of this segment was therefore addressed first.

The Hexahydrobenzofuran Unit (A).[15] It was recognized that this segment would need to be prepared in enantiomerically pure form if efficient convergence with fragments **B** and **C** was to be achieved, and we initially attempted to construct **A** by an asymmetric route employing a Diels−Alder reaction. Specifically, the dienophile **5** was prepared bearing a (*R*)-(−)-mandelate as a chiral auxiliary in the hope that its cycloaddition with an appropriate diene would lead to an adduct with all of the functionality, including the angular hydroxyl substituent, needed for **A**.[16] To this end, the anhydride **3** was converted to the pyridinium enolate **4** of hydroxymaleic anhydride,[17] and the latter was esterified with (*R*)-(−)-mandelyl chloride. The resulting anhydride **5** was reacted with 3-methyl-1-[(trimethylsilyl)oxy]-1,3-butadiene (**6**)[18] in refluxing benzene to give two endo Diels−Alder adducts, **7** and **8**, in a 1:1 ratio. When these two anhydrides were separated, both were found to be racemic. This disappointing result forced us to revise and simplify our Diels−Alder strategy by replacing **5** with maleic anhydride itself, anticipating that subsequent optical resolution could be effected.[19] Cycloaddition of maleic anhydride with **6** afforded as the sole product the endo anhydride **9** in good yield. Although **9** is racemic and also lacks the angular hydroxyl substituent needed for segment **A**, both of these defects proved to be easily rectified at later stages of the synthesis.



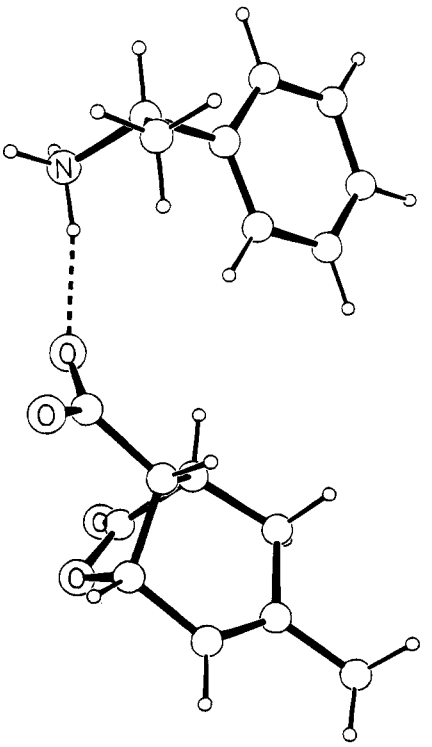


Figure 1. X-ray crystal structure of one of the two (*S*)-(−)-α-methylbenzylamine salts of (±)-**10**. The absolute configuration of the carboxylate in this diastereomer is opposite to that required for the synthesis of subunit **A**.

Cleavage of the silyl ether **9** with tetra-*n*-butylammonium fluoride was followed by spontaneous intramolecular acylation to yield the bridged γ-lactone **10**. The racemic acid readily formed diastereomeric salts with (*S*)-(−)-α-methylbenzylamine that were separated by crystallization.[20] The enantiomerically pure acids were recovered upon acidification. One of the two diastereomeric amine salts afforded crystals suitable for X-ray analysis, thus allowing the absolute configuration of the carboxylic acid component to be established (Figure 1). The desired enantiomer of **10** was then obtained by crystallization of the salt **11** prepared with (*R*)-(+)-α-methylbenzylamine and was characterized as its methyl ester **12**.

Elaboration of the resolved carboxylic acid **10** toward the bicyclic nucleus of **A** was envisioned via homologation of **10**

(15) A wide variety of approaches to this portion of the avermectin framework have been reported: (a) Fraser-Reid, B.; Prashad, M. *J. Org. Chem.* **1985**, *50*, 1566. (b) Kozikowski, A. P.; Maloney-Huss, K. E. *Tetrahedron Lett.* **1985**, *26*, 5759. (c) Crimmins, M. T.; Lever, J. G. *Tetrahedron Lett.* **1986**, *27*, 291. (d) Ireland, R. E.; Obrecht, D. M. *Helv. Chim. Acta* **1986**, *69*, 1273. (e) Hanessian, S.; Beaulieu, P.; Dubé, D. *Tetrahedron Lett.* **1986**, *27*, 5071. (f) Ardisson, J.; Ferezou, J. P.; Julia, M.; Panerazi, A. *Tetrahedron Lett.* **1987**, *28*, 2001. (g) Parsons, P. J.; Willis, P. A.; Eyley, S. C. *J. Chem. Soc., Chem. Commun.* **1988**, 283. (h) Hirama, M.; Noda, T.; Itô, S.; Kabuto, C. *J. Org. Chem.* **1988**, *53*, 706. (i) Williams, D. R.; Klingler, F. D.; Dabral, V. *Tetrahedron Lett.* **1988**, *29*, 3415. (j) Barrett, A. G. M.; Arta, T. E.; Flygore, J. A.; Sabat, M.; Spilling, C. D. *J. Org. Chem.* **1990**, *55*, 2409. (k) Lee, K.-C.; Wu, J. C. C.; Yen, K.-F.; J-Uang, B. *Tetrahedron Lett.* **1990**, *31*, 3563. (l) Smith, A. B., III; Fujiwara, S. *Tetrahedron Lett.* **1992**, *33*, 1185.

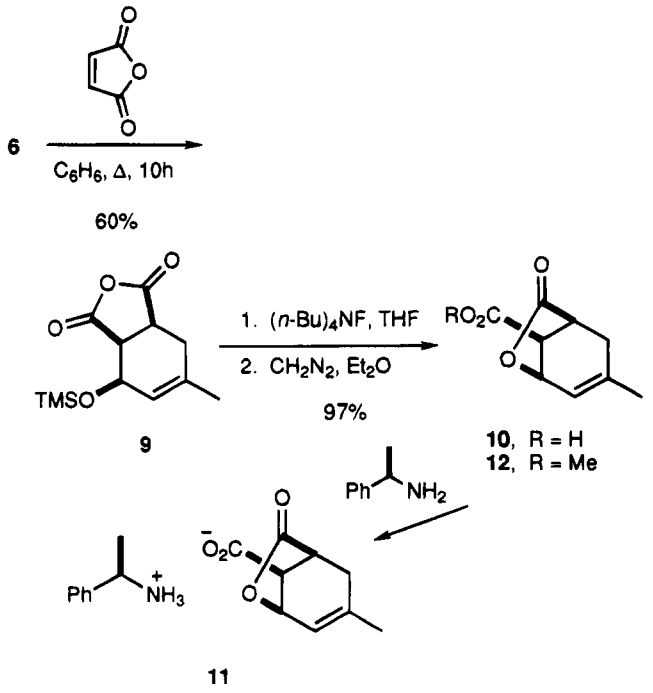
(16) Ireland, R. E.; Thompson, W. J. *J. Org. Chem.* **1979**, *44*, 3041.

(17) Kayser, M. M.; Breau, L.; Eliev, S.; Morand, P.; Ip, H. S. *Can. J. Chem.* **1986**, *64*, 104.

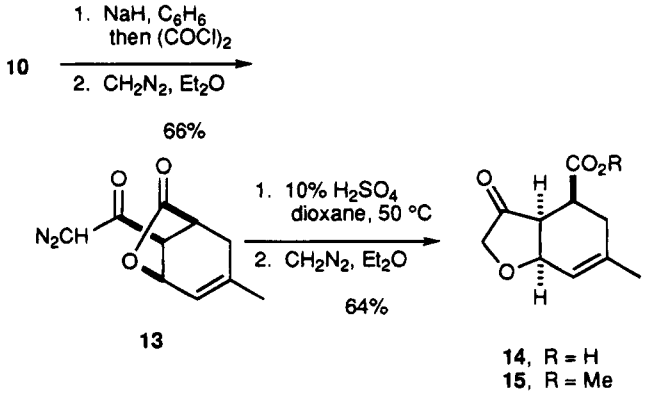
(18) Trost, B. M.; McDougal, P. G.; Haller, K. J. *J. Am. Chem. Soc.* **1984**, *106*, 383.

(19) White, J. D.; Dantanarayana, A. P. *Tetrahedron Lett.* **1987**, *28*, 6417.

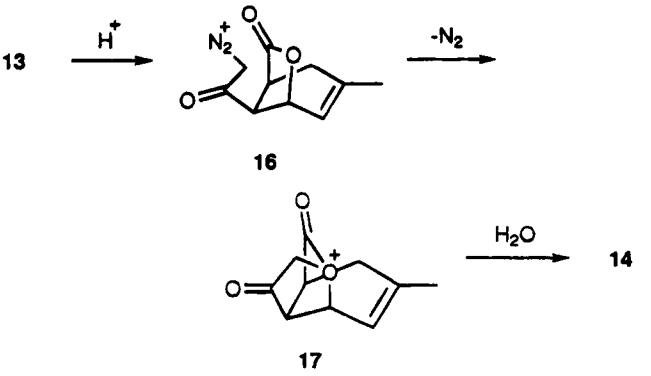
(20) Corey, E. J.; Mann, J. *J. Am. Chem. Soc.* **1973**, *95*, 6832.



to a diazo ketone. This would be followed by acidic conversion to the diazonium species that was expected to undergo displacement by the lactone oxygen to yield a benzofuranone system.

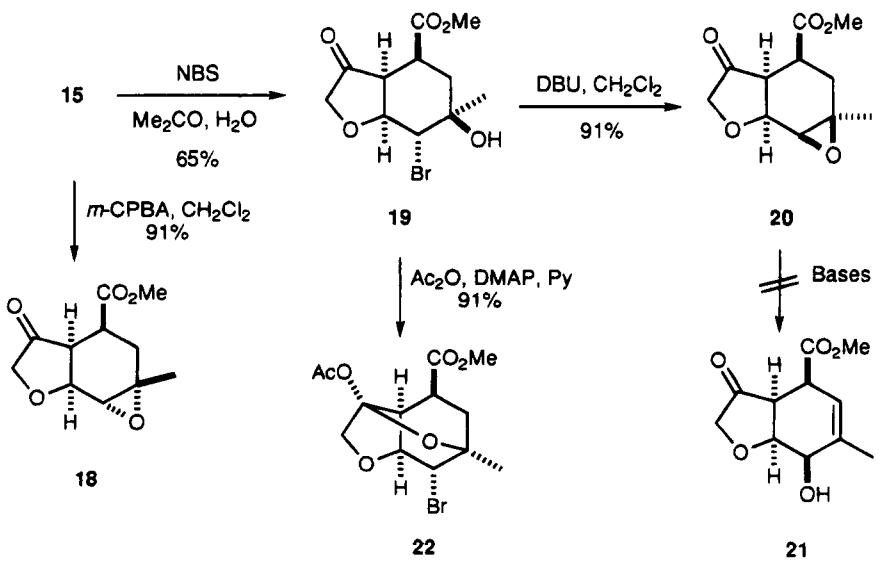


A simpler version of this annulation has been employed to prepare 3-furanones.[21] Conversion of **10** to its acyl chloride and treatment with ethereal diazomethane furnished **13**, which, upon warming in a solution of sulfuric acid in dioxane, gave the cis-fused furan-3-one **14**. The carboxyl group of **14** was esterified with diazomethane to provide **15**. The path by which **14** is formed from **13** takes advantage of the cis relationship of the exo carboxyl substituent and the γ-lactone bridge and presumably involves the tricyclic oxonium ion **17** produced by internal displacement of the protonated diazonium ion **16**. Hydrolysis of **17** would then lead directly to **14**.



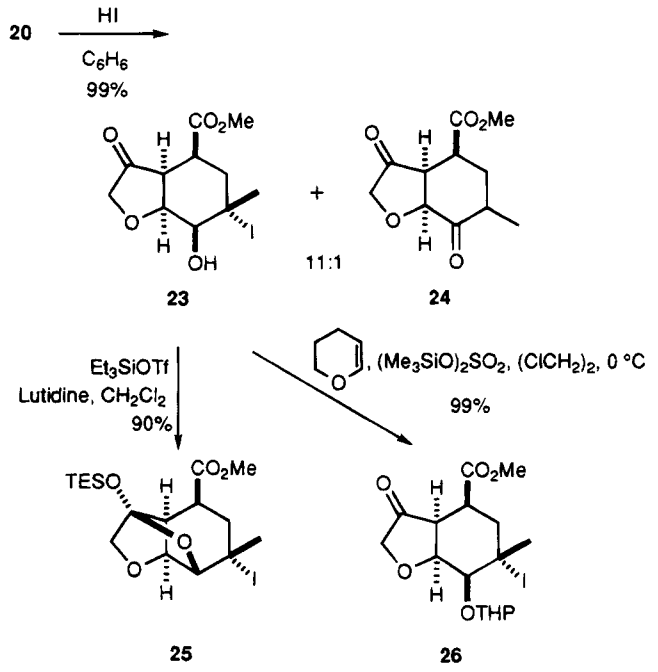
The sterically crowded environment of the endo C5 hydroxyl group of **2** suggested that its insertion by means of direct epoxidation of **15** would not be successful, and, as expected, the reaction of **15** with *m*-chloroperbenzoic acid gave only the exo epoxide **18** (Scheme 1). An option for acquiring the more sterically encumbered oxirane from an alkene is usually available via the halohydrin, and for this purpose, **15** was treated with *N*-bromosuccinimide in aqueous acetone.[22] The trans bromohydrin **19** resulting from Markovnikov opening of the exo bromonium ion was produced with complete regioselectivity, and upon exposure to 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU), this substance afforded endo epoxide **20**. However, attempts to effect elimination of this epoxide to **21** under basic conditions met with failure, the outcome in every case being recovered starting material. The explanation for the lack of reactivity of **20**, confirmed by deuteriation, is to be found in its facile deprotonation at the ring fusion to form a ketone enolate that is inert to the further action of base. In seeking to circumvent this problem, we attempted to acetylate the bromohydrin **19**, but instead of the expected tertiary acetate, the esterified ketal **22** was obtained. The endo orientation of the

Scheme 1



C4 hydroxyl group allows it to bridge the concave face of **19**, and although there is no direct evidence for an internal hemiketal in equilibrium with **19**, the exo hydroxyl substituent at C8 resulting from hemiketalization is clearly more accessible for acetylation than the alcohol function of **19**.

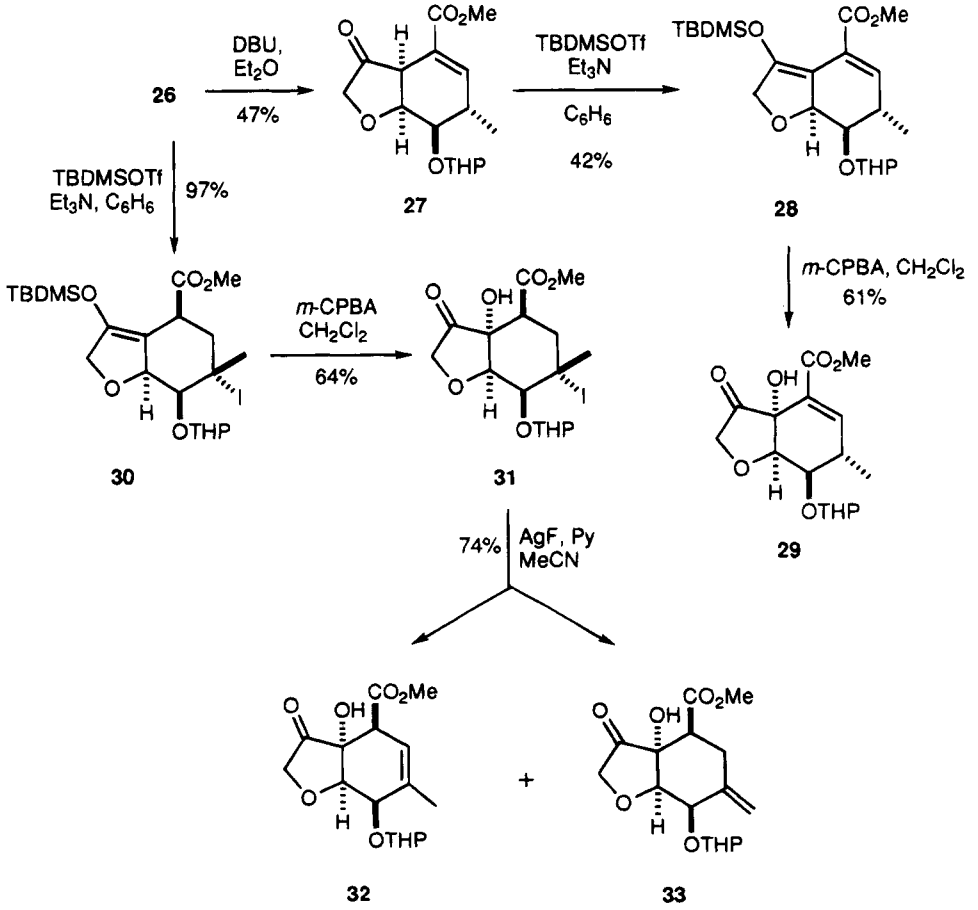
In view of the unsuccessful base-mediated elimination of **20**,



opening of the epoxide under acidic conditions was examined as an approach to the desired cyclohexenol moiety of **A**. Thus, **20** was reacted with hydriodic acid in benzene to give **23** as the major product, accompanied by a small quantity of ketone **24** resulting from a 1,2-hydride shift to the intermediate tertiary carbocation. Iodohydrin **23** was found to be unstable, slowly reconverting to **20** at room temperature, and it was therefore decided to protect this alcohol before attempting elimination of the iodide to an alkene. Again, internal hemiketalization interfered with this process, the reaction of **23** with triethylsilyl triflate leading to the bridged structure **25** rather than the secondary silyl ether. Initial attempts to protect **23** as its tetrahydropyranyl ether under acidic conditions were also unsuccessful, but when bis(trimethylsilyl) sulfate[23] was used as a catalyst in dichloroethane with **23** and 3,4-dihydro-2H-pyran, the desired ether **26** was produced in quantitative yield. The anhydrous, essentially neutral conditions under which this alcohol protection is carried out is noteworthy for its mildness and efficiency.

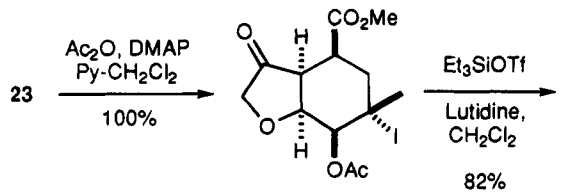
With **26**, a prospective route to the cyclohexene double bond of segment **A** was at hand through elimination of the tertiary iodide (Scheme 2). Treatment of **26** with amine bases did, indeed, lead to elimination of HI, but in every instance, the product was the conjugated ester **27**. Facile isomerization of the $\Delta^{3,4}$ bond into conjugation with the ester at C2 has been encountered in previous chemical transformations in the avermectin series,[8] and although the process can be reversed by kinetic reprotonation,[6a] attempts to deconjugate **27** led to no useful result.[24] Again, this was found to be a consequence of enolization of the ketone toward the ring fusion. This property, although frustrating attempts to deprotonate at C4, enabled us to introduce the angular hydroxyl group into the hexahydrobenzofuran nucleus. Thus, when enol ether **28** was prepared by silylation of **27** with *tert*-butyldimethylsilyl triflate and then was epoxidized with *m*-chloroperbenzoic acid, the α-hydroxy ketone

Scheme 2



29 was produced after an acidic workup.[25] However, the α,β-unsaturated ester again refused to undergo deconjugation. In an attempt to negotiate this obstacle, the sequence of steps from 26 was reversed. Epoxidation of silyl enol ether 30, prepared from 26, led to α-hydroxy ketone 31, which, however, gave mainly aromatic products when elimination was carried out with DBU. Treatment of 31 with silver fluoride, a mild protocol known to be effective where elimination of iodides with basic reagents is unsuccessful,[26] initially appeared more promising and afforded a mixture of endo and exo olefins, 32 and 33. Unfortunately, these isomers were only separable by means of tedious chromatography that invariably caused 32 to undergo the familiar double-bond shift into conjugation with the ester.

The discovery that it was possible to acetylate iodohydrin 23 without complications arising from transannular hemiketalization opened another line of attack on segment A, which, we hoped, would install the $\Delta^{3,4}$ bond through an elimination in which the acetate could participate. Accordingly, 34 was converted to its silyl enol ether 35, and the latter was epoxidized to afford 36. As with 31, attempts to remove the elements of



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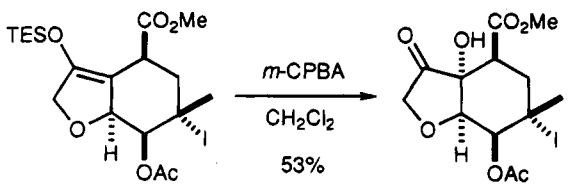
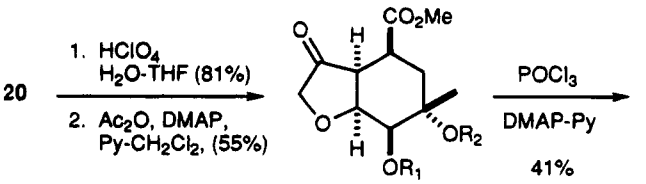


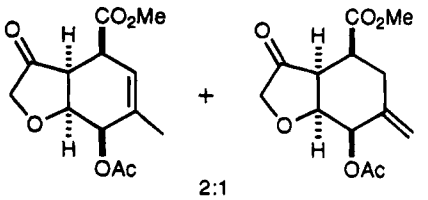
35 36

HI from 36 led to benzenoid products that clearly arose from exhaustive elimination processes.

Experiments designed to probe the reactivity of endo epoxide 20 led to the finding that the oxirane was easily opened in aqueous acid to yield diol 37, which could be acetylated to afford principally the monoacetate 38, accompanied by a small quantity of diacetate 39. The availability of 38 appeared to offer an excellent opportunity to reach our target since Hanessian had reported that a closely related alcohol 40 underwent elimination to 41, in which not only has the correct alkene been installed but also epimerization of the ester substituent to the natural 2α configuration has taken place. However, dehydration of 38 did not follow the same course as 40, producing an inseparable 1:1 mixture of endo and exo olefins, 42 and 43, respectively, in which no epimerization of the ester substituent had occurred. A rationale for the conspicuously different behavior of 38 and

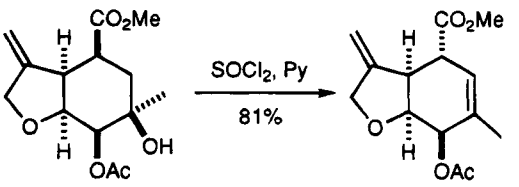


37, $R_1 = R_2 = H$
38, $R_1 = Ac$, $R_2 = H$
39, $R_1 = R_2 = Ac$



42 43

40 can be found in the reversed configuration of the tertiary hydroxyl group. Trans diaxial elimination from 40 imposes



40 41

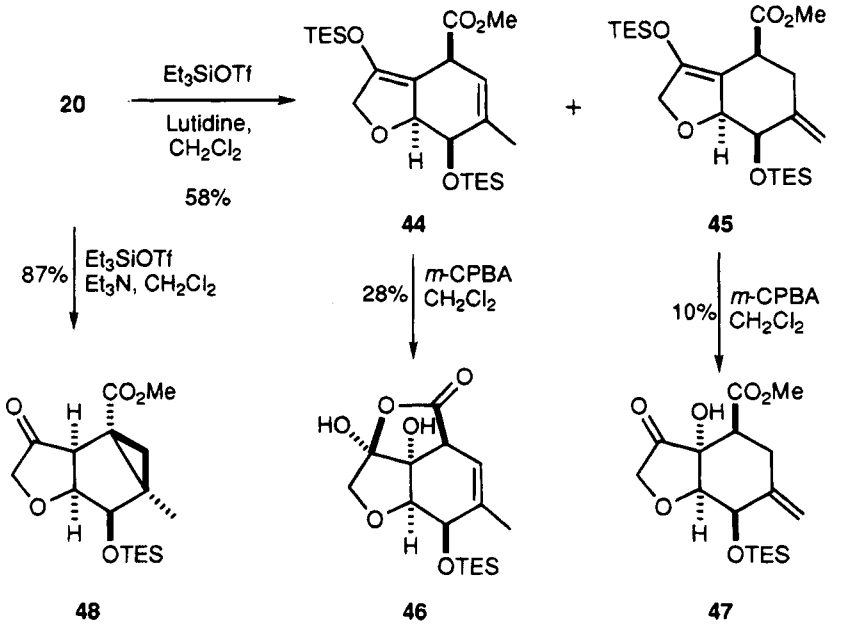
greater $A_{1,3}$ strain within a cyclohexane chair conformation of 40 compared to 38 and would be expected to accelerate ester epimerization as well as endo olefin formation.

The oxirane of 20 was opened readily with silyl triflates, the result being dependent on the nature of the silylating agent and on the conditions. For example, when triethylsilyl triflate was used in the presence of 2,6-lutidine (Scheme 3), a mixture of the endo and exo elimination products 44 and 45 was obtained in which an enol ether had been formed from the keto group in each case. Epoxidation of the mixture afforded the expected α-hydroxy ketone 47 from 45, but, to our surprise, 44 gave the bridged lactone 46. The latter, which presumably originates from intramolecular participation by the ester carbonyl in opening of the oxirane derived from enol ether 44, reflects the preference of the cyclohexene ring of 44 or the derived epoxide for a boat conformation. When silylation of 20 was carried out in the presence of triethylamine rather than lutidine, a quite different outcome was observed and cyclopropane 48 was produced in high yield. The striking mechanistic divergence underlying the silylation of 20 in the presence of lutidine, as contrasted with triethylamine, is not presently understood but presumably entails formation of a tertiary carbocation in the first case, whereas a concerted 1,3-elimination is favored in the second.

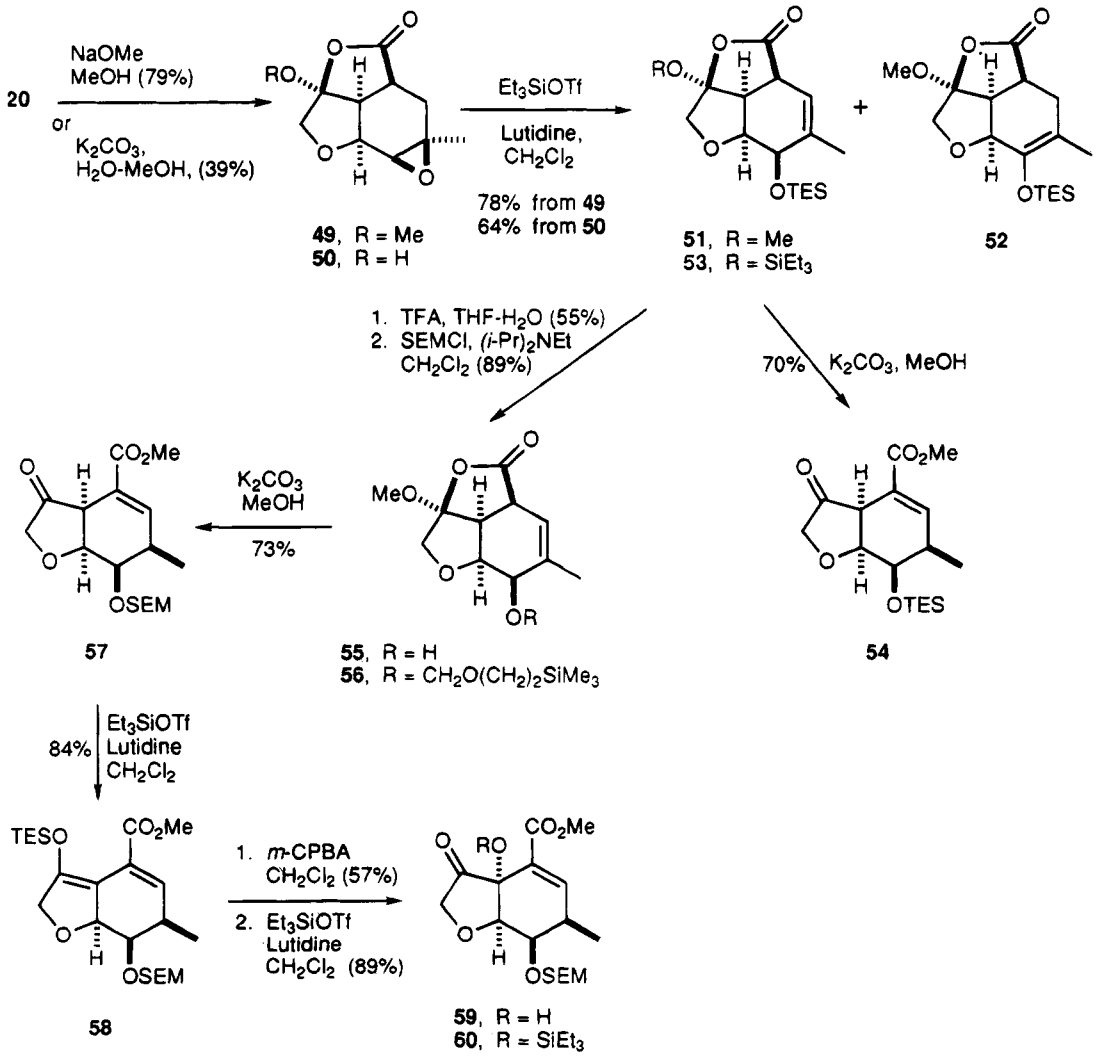
In view of the difficulties experienced with attempts to modify the epoxide function of 20, attention was turned to epimerization of the ester group in the hope that inversion at C2 to the natural configuration would afford a more compliant intermediate. Again, a surprise awaited us; for when 20 was reacted with sodium methoxide (Scheme 4), the crystalline methoxy γ-lactone 49 was produced in excellent yield. An X-ray crystallographic analysis of 49 fully confirmed the structural assignment. Analogous treatment of 20 with potassium carbonate in aqueous methanol gave 50, although in lower yield. The serendipitous preparation of 49 and 50 placed in our hands an ideal system

(21) (a) Marshall, E. R.; Kuck, J. A.; Elderfield, R. C. *J. Org. Chem.* **1942**, *7*, 444. (b) Bose, A. K.; Yates, P. *J. Am. Chem. Soc.* **1952**, *74*, 4703.
(22) Roberts, M. R.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1981**, *103*, 724.
(23) Morizawa, Y.; Mori, I.; Hiyama, T.; Nozaki, H. *Synthesis* **1981**, 899.
(24) Cf.: Fraser-Reid, B.; Wolleb, H.; Faghih, R.; Barchi, J., Jr. *J. Am. Chem. Soc.* **1987**, *109*, 933.
(25) Rubottom, G. M.; Gruber, J. M. *Tetrahedron Lett.* **1978**, 4603.
(26) Ireland, R. E.; Wuts, P. G. M.; Ernst, B. *J. Am. Chem. Soc.* **1981**, *103*, 3205.

Scheme 3

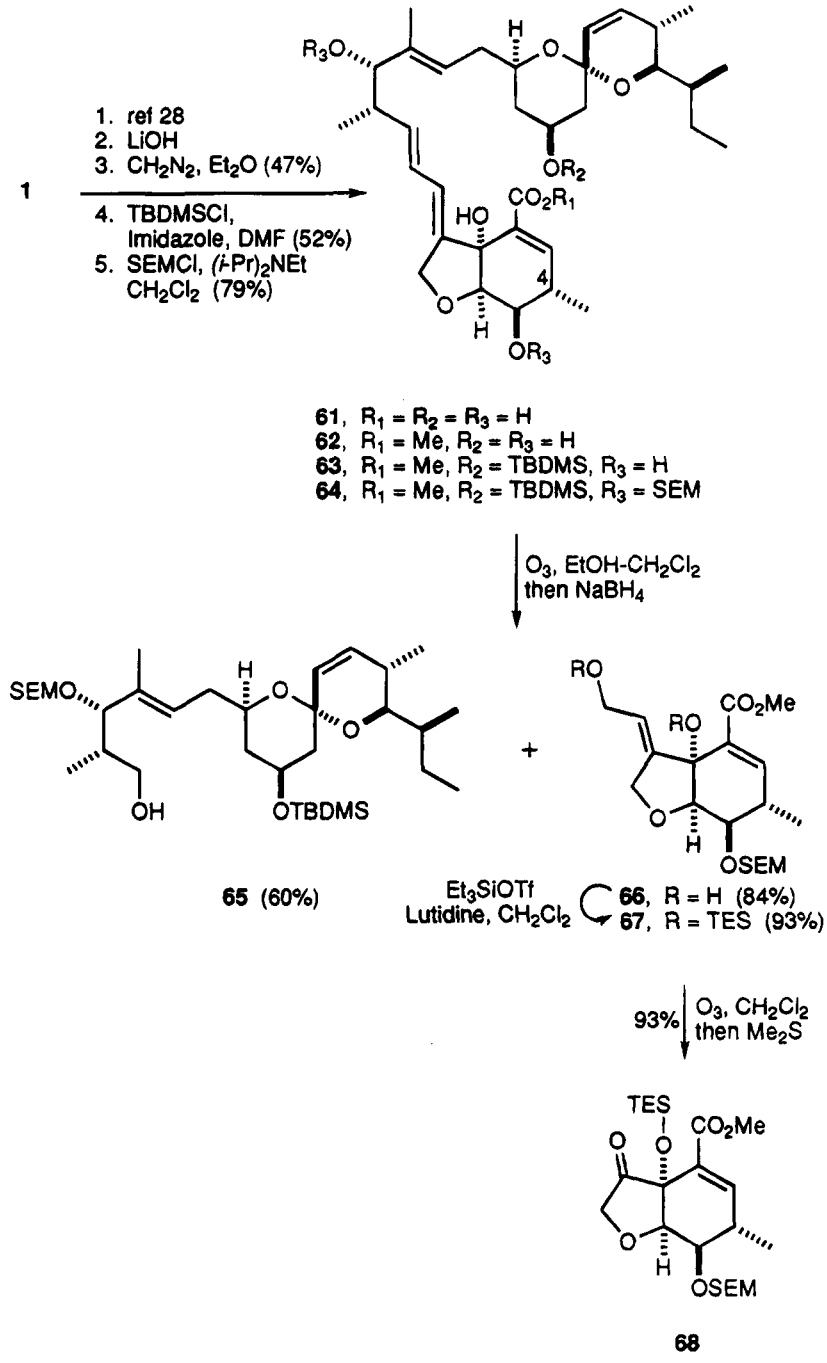


Scheme 4



for elaborating the cyclohexenol moiety of **A**, since the bowl-shaped conformation of these structures prevents isomerization of a $\Delta^{3,4}$ bond into conjugation with the lactone. Indeed, exposure of **49** to triethylsilyl triflate furnished **51** in good yield, accompanied by a small quantity of a product believed to be enol ether **52**. Similar treatment of **50** gave **53**. Lactone **51** proved to be more amenable to elaboration than **53**, and although basic methanolysis of **51** was found to yield the α,β-unsaturated ester **54** resulting from double-bond migration, acidic treatment effected clean scission of the silyl ether to give **55**. At this

Scheme 5



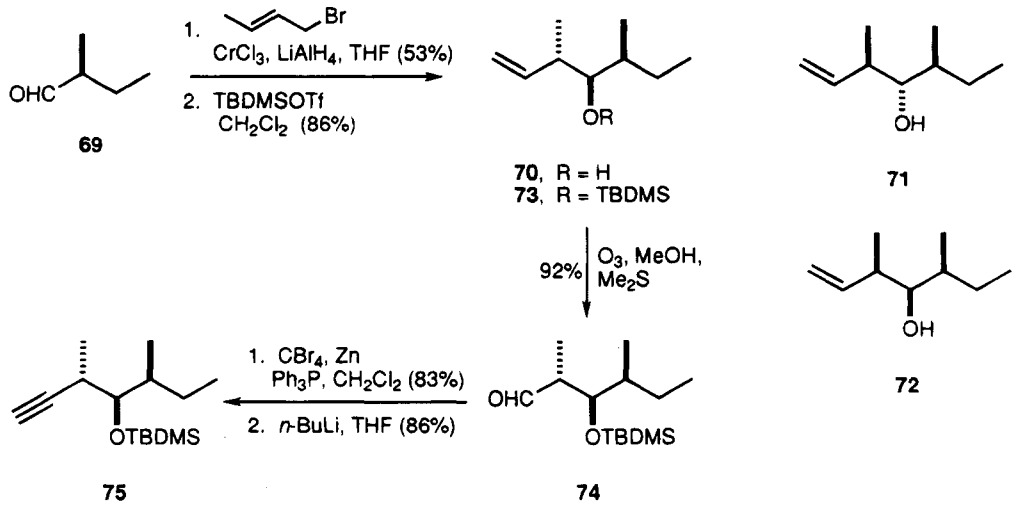
stage, it appeared that our synthetic route to subunit **A** could be brought into convergence with a known degradative pathway from avermectin B_{1a}[27] that excised the intact hexahydrobenzofuran subunit from **1**. Since the degradative sequence had been carried out with the C5 alcohol protected as its [2-(trimethylsilyl)ethoxy]methyl (SEM) ether, **55** was first converted to **56** and then subjected to basic methanolysis to give **57**. Following the previous protocol with **27**, **57** was reacted with triethylsilyl triflate in 2,6-lutidine to give the unstable diene **58**, which was immediately epoxidized to α-hydroxy ketone **59**.[25] The angular hydroxyl group was resistant to most protection devices but, fortunately, could be converted efficiently to its triethylsilyl ether **60**.

The availability of avermectin B_{1a} (**1**) from fermentation together with well-established degradation pathways from its aglycon **2** suggested that access to subunit **A** from the natural source would be an attractive alternative to total synthesis. Indeed, Hanessian's synthesis of **1** makes effective use of this strategy. Basic hydrolysis of **2**[28] followed by acidification afforded the $\Delta^{2,3}$-seco acid **61** (Scheme 5) accompanied by ca. 5% of its C4 epimer. The derived methyl ester **62** was selectively protected at the C19 hydroxyl with *tert*-butyldimethylsilyl chloride, and the resulting diol **63** was converted to its bis(SEM) ether **64**. Ozonolysis of **64** followed by reduction with sodium borohydride furnished saturated alcohol **65** and allylic alcohol **66**. The latter was treated with triethylsilyl triflate to give the bis silylated derivative **67**. Ozonolysis of this material afforded **68**, which was found to be epimeric with **60** at C4. The origin of reversed configuration of the methyl substituent in **68** as compared with **60** appears to lie in

(27) Hanessian, S.; Ugolini, A.; Hodges, P. J.; Dubé, D. *Tetrahedron Lett.* **1986**, *27*, 2699.

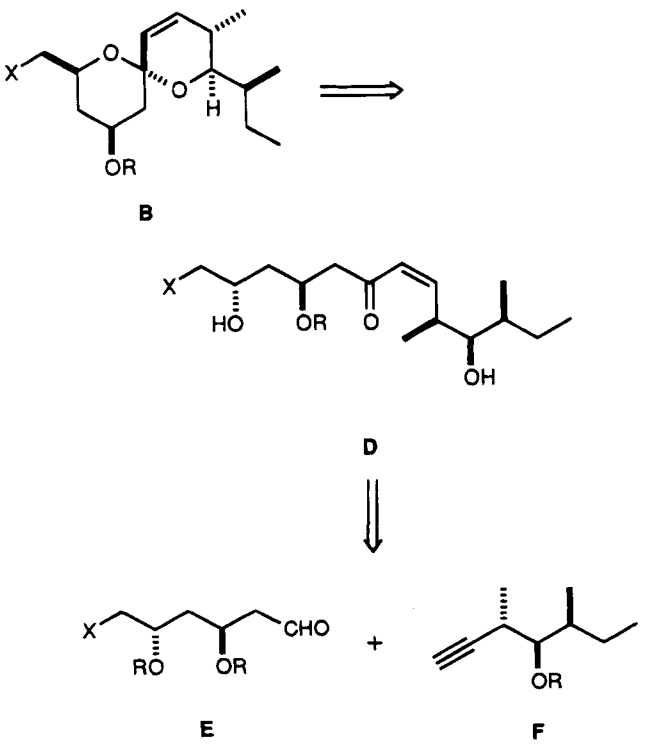
(28) Mrozik, H.; Eskola, P.; Arison, B. H.; Albers-Schönberg, G.; Fisher, M. H. *J. Org. Chem.* **1982**, *47*, 489.

Scheme 6



different conformations of the cyclohexene ring at the stage of double-bond isomerization. In the absence of a constraining macrolactone, the oxahydrindene **60** can assume a stable boat conformation in which the methyl substituent prefers an equational (β) orientation. In contrast, the rigid structure of macrolide **2** enforces a pseudochair conformation on the cyclohexene so that, after double-bond isomerization (but before opening to the seco acid), the 4-methyl substituent is more stable in an exo (α) configuration. This stereochemistry is then retained throughout the degradative sequence to **68**. A parallel degradation departing from the minor C4 epimer obtained with **61** produced **60**, identical with synthesized material. However, this route was impractical as a means for acquiring a sufficient quantity of **60** for use as a relay substance. Furthermore, although it was possible to equilibrate **60** and **68** under basic conditions, the inefficient separation of these epimers, combined with material loss due to aromatization, rendered this tactic ineffective. Ultimately, therefore, we were forced to resort to the synthesized substance **60** as the surrogate for subunit **A**.

The Spiroketal Subunit (B). The structural component of **1** containing the spiroketal moiety distinguishes this particular member of the avermectin family from the milbemycins as well as avermectins of the 1b and 2b series by virtue of the extra carbon atom (C28) and consequently the additional stereogenic center at C26. Hence, although numerous routes to the spiroketal subunit of milbemycins have been described,[29] few of these can be extended in straightforward fashion to the homologous system found in avermectin B_{1a}. Our own strategy for assembling subunit **B**, like that of Hanessian's,[6a] foresaw spiroketalization from an acyclic precursor **D** which could be prepared by the coupling of two smaller segments, **E** and **F**.[30] An assumption underlying this approach was that cyclization of **D** would lead to stereogenicity at the spiroketal carbon corresponding to the natural configuration of **1**. This supposition was based on a conformational model for **B** that presumed that thermodynamically controlled spiroketalization would take advantage of not only the anomeric effect but also the placement of all four substituents on the perimeter of the spiroketal in an equatorial orientation.



Construction of the acyclic precursor required for **B** began with the synthesis of alkyne **F**. (2*S*)-2-Methylbutanal (**69**), obtained by Swern oxidation of the corresponding alcohol, was treated with trans crotyl bromide in the presence of chromous chloride[31] to give **70** (Scheme 6). The configuration of the two new stereogenic centers of **70** follows from the chairlike Zimmerman–Traxler transition state believed to operate in this Barbier–Grignard addition. The observed preference for *re* face attack on **69** is predicted by the Felkin model.[32] Two minor

(29) (a) Smith, A. B., III; Schow, S. R.; Bloom, J. D.; Thompson, S.; Winzenberg, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 4708. (b) Baker, R.; Boyes, R. H. O.; Broom, D. M. P.; Devlin, J. A.; Swain, C. J. *J. Chem. Soc., Chem. Commun.* **1983**, 829. (c) Kocienski, P.; Street, S. D. A. *J. Chem. Soc., Chem. Commun.* **1984**, 571. (d) Godey, J.; Ley, S. V.; Lygo, B. *J. Chem. Soc., Chem. Commun.* **1984**, 1381. (e) Baker, R.; Swain, C. J.; Head, J. C. *J. Chem. Soc., Chem. Commun.* **1985**, 309. (f) Hirama, M.; Nakamine, T.; Ito, S. *Tetrahedron Lett.* **1986**, *27*, 5281.

(30) Fox, C. M. J.; Hiner, R. N.; Warrier, U. S.; White, J. D. *Tetrahedron Lett.* **1988**, *29*, 2923.

(31) (a) Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 1037. (b) Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561.

(32) Lewis, M. D.; Kishi, Y. *Tetrahedron Lett.* **1982**, *23*, 2343.

(33) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

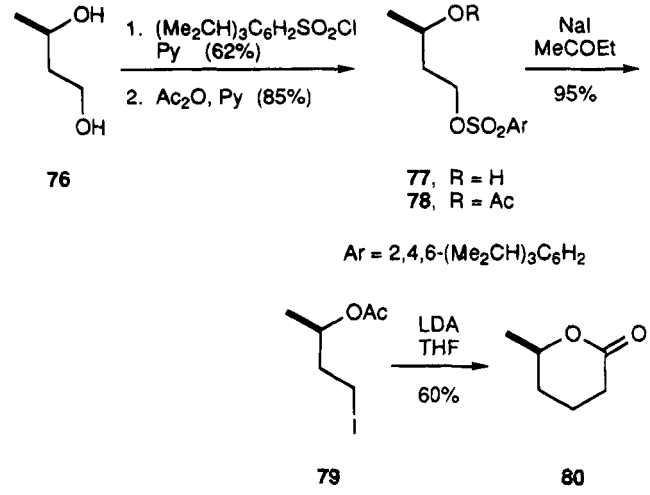
(34) (a) Ogura, H.; Takahashi, H.; Otoh, T. *J. Org. Chem.* **1972**, *37*, 72. (b) Chabala, J. C.; Vincent, J. E. *Tetrahedron Lett.* **1978**, 937.

(35) Hanessian, S.; Ugolini, A.; Therien, M. *J. Org. Chem.* **1983**, *48*, 4427.

(36) (a) Ogura, H.; Takahashi, H. *Synth. Commun.* **1973**, *3*, 135. (b) Lin, C. H.; Stein, S. J. *Synth. Commun.* **1976**, *6*, 503. (c) Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauve, T.; Saunders, J. K. *Can. J. Chem.* **1981**, *59*, 1105. (d) Lin, C. H.; Alexander, D. L. *J. Org. Chem.* **1982**, *47*, 615. (e) Jacobson, R.; Taylor, F. J.; Williams, H. J.; Smith, L. R. *J. Org. Chem.* **1982**, *47*, 3140.

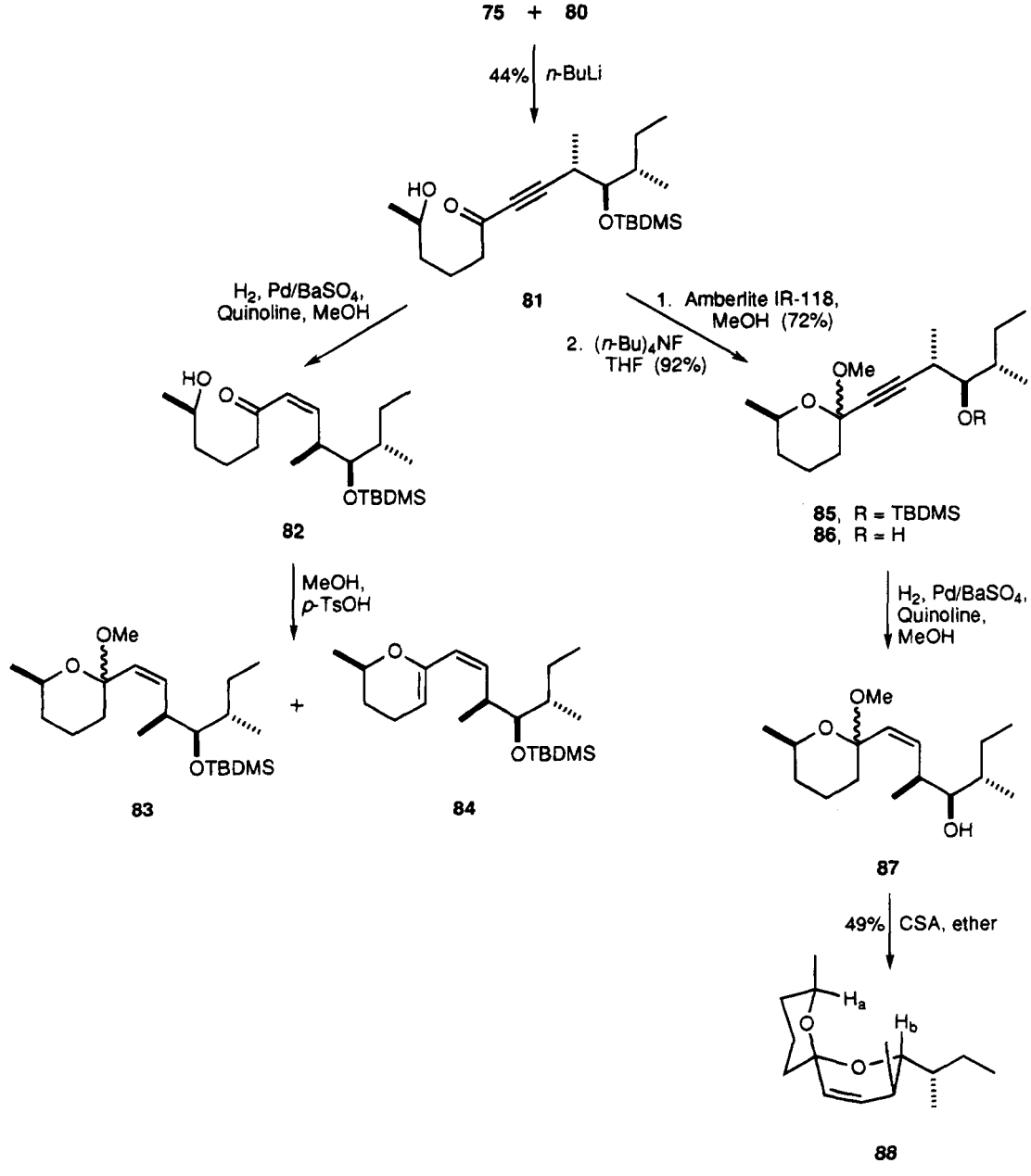
alcohols, **71** and **72**, were also isolated from the crotylation of **69**. Homologation of **70** to alkyne **75** was accomplished via aldehyde **74** obtained upon ozonolysis of the protected alcohol **73**. Treatment of **74** with carbon tetrabromide, triphenylphosphine, and activated zinc yielded the 1,1-dibromoalkene, which, upon reaction with *n*-butyllithium, gave **75**.[33]

Before attempting to link **75** to its counterpart **E**, we investigated coupling with a model system in the form of δ-lactone **80** to ensure that the acetylide anion from **75** would behave satisfactorily as a nucleophile. Although precedent exists for addition of metal acetylides to lactones[34] and approaches to the milbemycin,[29e] avermectin,[35] and other spiroketals[36] have used this strategy successfully, the addition is easily reversed, and competing deprotonation can occur α to the lactone carbonyl. For present purposes, (*R*)-caprolactone (**80**) was chosen as the partner for **75** and was prepared by a novel sequence departing from (*R*)-1,3-dihydroxybutane (**76**). Selective sulfonation of the primary hydroxyl group of **76** with 2,4,6-triisopropylbenzenesulfonyl chloride gave **77** which was acetylated to yield **78**. Displacement of the sulfonate by iodide,

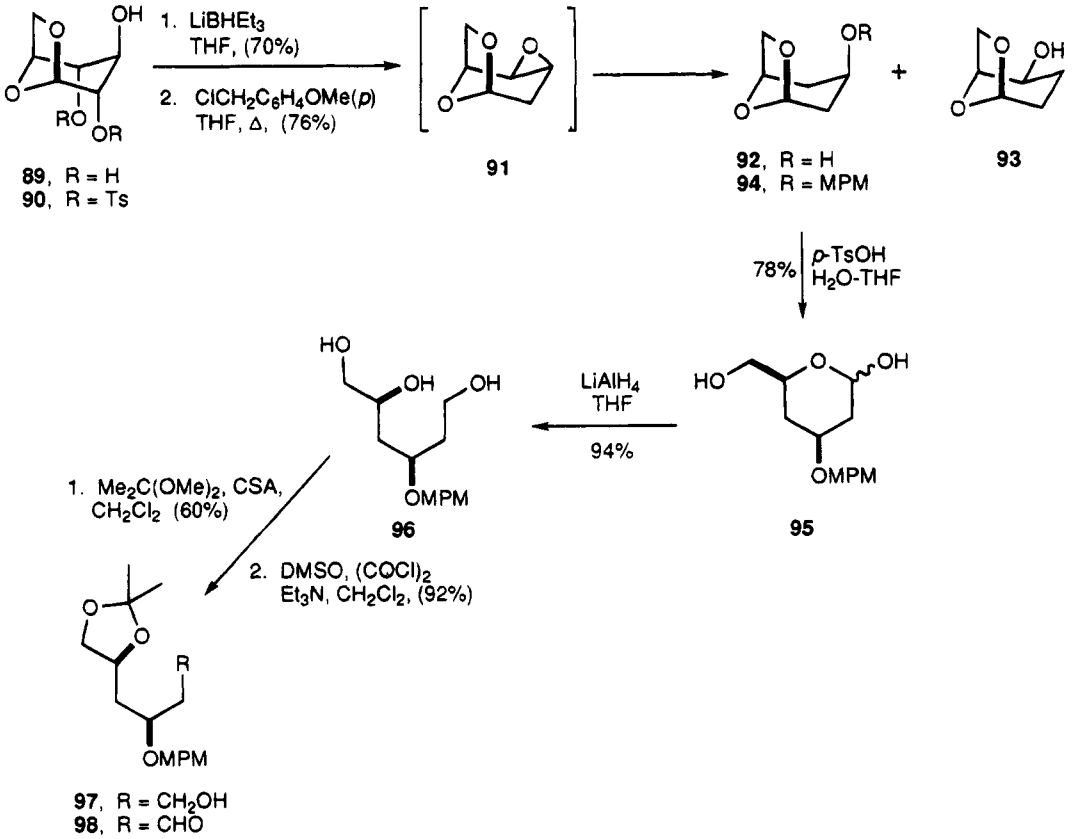


followed by deprotonation of iodo acetate **79** with base, resulted in cyclization to δ-lactone **80**. This route to **80** (or its enantiomer from (*S*)-**76**) is a significant improvement over

Scheme 7



Scheme 8



existing syntheses,[37] including one previously described by us,[38] and affords material of high optical purity.

Condensation of the lithium acetylide derived from **75** with **80** led to a low yield of **81** (Scheme 7) and much recovered starting material. In spite of numerous experimental variations, including the use of a cerium acetylide,[39] this unsatisfactory result could not be improved. Hence, it must be concluded that the β-alkoxy substituent present in the δ-lactone substrates examined by Baker[29e] and Hanessian[35] contributes to a more successful outcome, perhaps by suppressing α deprotonation. It was, nevertheless, possible to advance the acetylenic ketone **81** to the cis alkene **82** by hydrogenation over Lindlar catalyst. The latter was found to undergo rapid hemiketalization accompanied by dehydration to form a mixture of **83** and **84**, but removal of the silyl protecting group from this mixture under acidic conditions resulted only in a very low yield of spiroketal. Modification of the sequence following Baker's protocol[29e] was more productive, and treatment of **81** with methanol in the presence of Amberlite resin (acid form) gave a stereoisomeric mixture of acetals **85** from which the silyl blocking group could be removed in high yield. Semihydrogenation of the resulting alkyne **86** afforded **87**, which, upon exposure to camphorsulfonic acid, gave spiroketal **88** as a single isomer. The assignment of configuration at the spiro carbon of **88** is supported by its ^{1}H NMR spectrum, which exhibits characteristic deshielding of H_a and H_b (δ 3.48 and 3.90, respectively) due to their 1,3 diaxial relationship to the oxygen atoms of the adjacent ring. A more rigorous proof of configuration of the spiroketal center was obtained in the product containing the full complement of substituents of subunit **B**.

Segment **E**, required for coupling with **75**, was synthesized from laevoglucosan (**89**), which was prepared by a known route from glucose pentaacetate.[40] The central hydroxyl function of **89** resists tosylation, thereby allowing conversion of the triol to ditosylate **90**[41] (Scheme 8). Reduction of **90** with Super-Hydride (Aldrich) afforded a mixture of alcohols **92** and **93** in the ratio 5:1.[42] Careful examination of the reduction medium revealed that both **92** and **93** originate from epoxide **91**. The major alcohol **92** was protected as its *p*-methoxybenzyl (MPM) ether **94**, which was hydrolyzed under acidic conditions to give lactol **95**. Reduction of **95** afforded triol **96** which was selectively protected as the 1,2-acetonide **97**. Swern oxidation of the remaining primary alcohol gave **98**.

Several acetylide derivatives of **75**, including the cerium species, were examined for coupling with **98**, but the most effective proved to be the Grignard reagent prepared with ethylmagnesium bromide (Scheme 9). The resultant alcohol **99** was oxidized under Swern conditions to ketone **100**, and a sequence analogous to that developed with **81** was used to transform **100** to spiroketal **104**. Thus, treatment of **100** with acidic methanol led, as expected, to **101**, resulting from initial methanolysis of the acetonide followed by internal ketalization. Subsequent cleavage of the silyl ether and semihydrogenation of alkyne **102** yielded cis alkene **103** which underwent rapid spiroketalization to **104** in the presence of camphorsulfonic acid. Removal of the *p*-methoxybenzyl group from **104** with ceric ammonium nitrate gave the crystalline diol **105** whose configuration was confirmed by an X-ray crystal structure determination (Figure 2). Finally, in preparation for its connection to subunit **C**, **104** was oxidized to aldehyde **106**.

The Acyclic (C9−C15) Subunit (C) and Its Coupling to B. The acyclic segment linking the hexahydrobenzofuran

(37) (a) Kuhn, R.; Kum, K. *Chem. Ber.* **1962**, *95*, 2009. (b) MacMillan, J.; Simpson, T. J. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1487. (c) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1979**, *44*, 2169.

(38) White, J. D.; Somers, T. C.; Reddy, G. N. *J. Org. Chem.* **1992**, *57*, 4991.

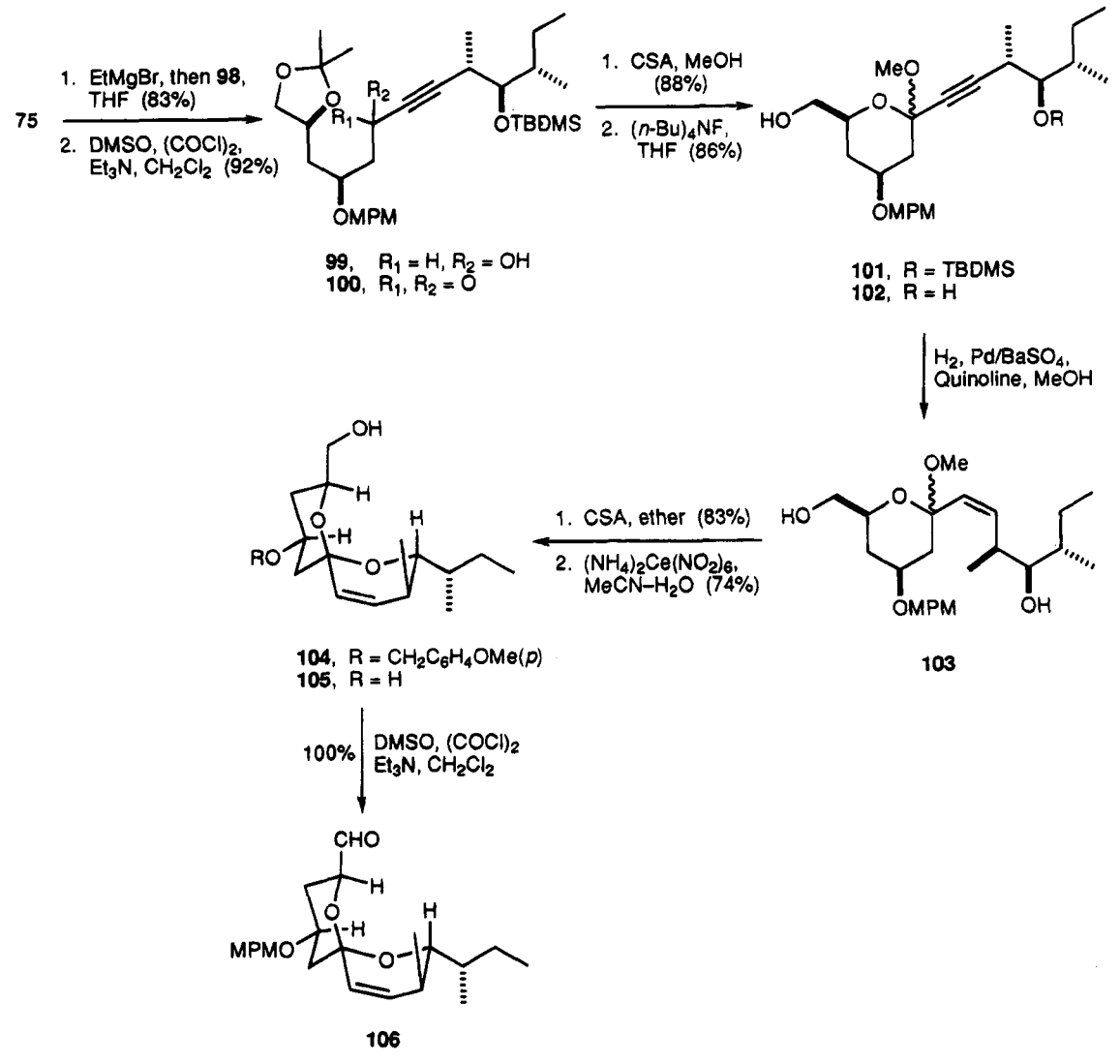
(39) Imamoto, T.; Sugiura, Y.; Nobuyuki, T. *Tetrahedron Lett.* **1984**, *25*, 4233.

(40) Coleman, G. H. *Methods Carbohydr. Chem.* **1963**, *2*, 374.

(41) Cêrny, M.; Kolvada, L.; Pacak, J. *Collect. Czech. Chem. Commun.* **1968**, *33*, 1143.

(42) Kelly, A. G.; Roberts, J. S. *Carbohydr. Res.* **1979**, *77*, 231.

Scheme 9



subunit **A** with the spiroketal moiety **B** was synthesized from ethyl levulinate. The latter was brominated and then dehydrohalogenated in situ to furnish **107**[43] (Scheme 10), which was ketalized with 2,2-dimethyl-1,3-propanediol. Reduction of **108** afforded allylic alcohol **109** accompanied by ca. 10% of the corresponding saturated alcohol. Asymmetric epoxidation[44] of **109** in the presence of (−)-tartrate furnished **110** which was shown by preparation of its Mosher ester[45] to be >98% enantiomerically pure. Treatment of **110** with lithium dimethyl cuprate at low temperature resulted in regioselective opening of the epoxide to yield **111**,[46] possessing the absolute configuration corresponding to C12 and C13 of **2**. The primary alcohol **111** was selectively protected as its pivalate, but attempts to protect the sterically hindered secondary alcohol of **111** were to no avail. This problem was circumvented by hydrolysis of the ketal, which proceeded uneventfully to give **113**. With the secondary hydroxyl group now more accessible, it was protected as its SEM ether **114**.

The plan for connecting ketone **114** to the spiroketal subunit was based on a crossed aldol coupling of the ketone enolate with aldehyde **106**. Before attempting this crucial coupling,

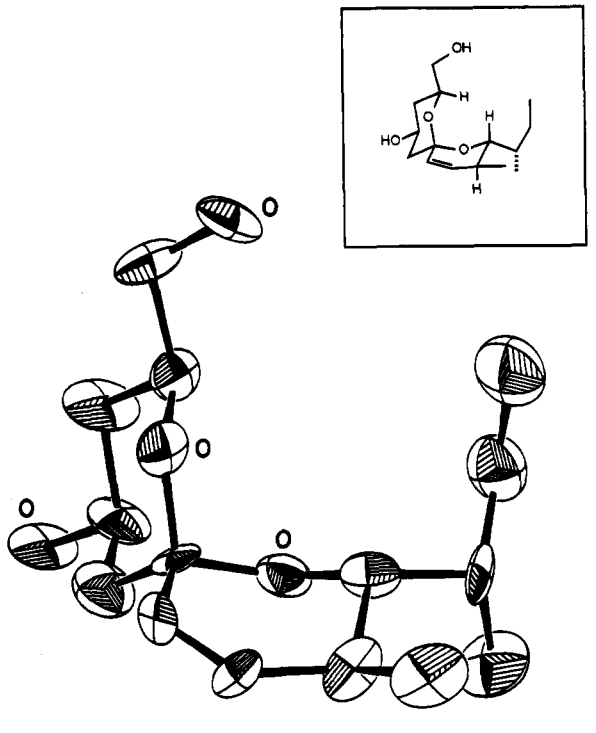
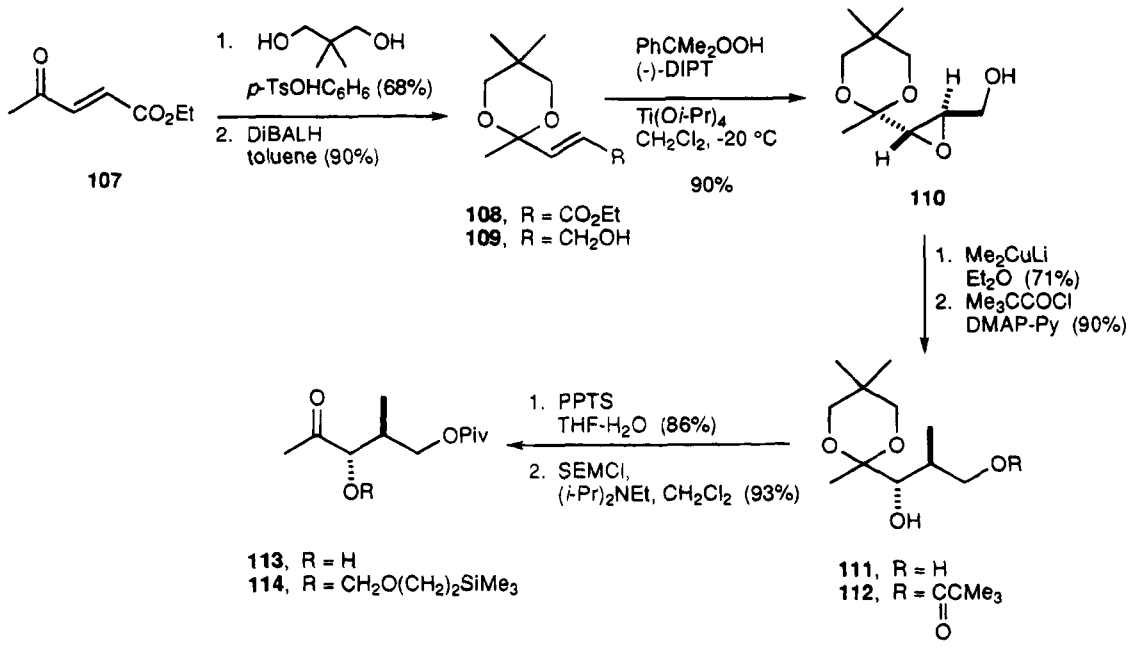


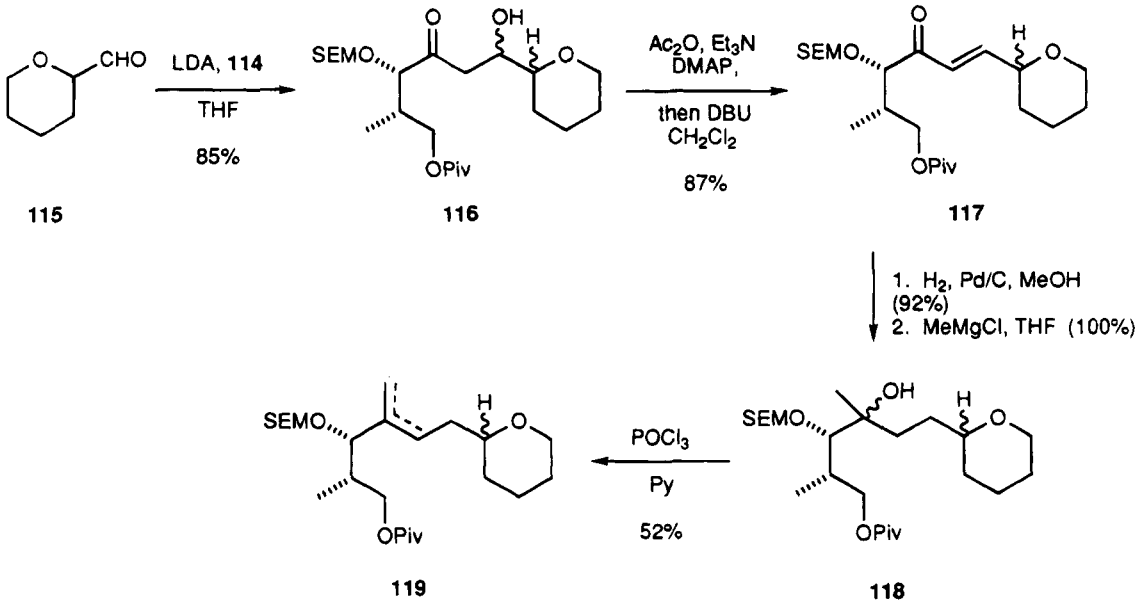
Figure 2. ORTEP representation of the X-ray crystal structure of **105**.

(43) McMurry, J. E.; Blaszczak, L. C. *J. Org. Chem.* **1974**, *39*, 2217.
(44) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
(45) Dale, J. A.; Sull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.
(46) Kishi, Y.; Nagaoka, H. *Tetrahedron* **1981**, *37*, 3873.

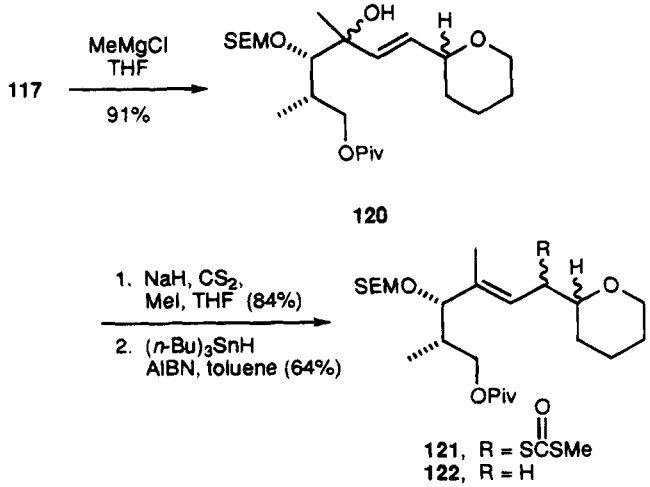
Scheme 10



Scheme 11



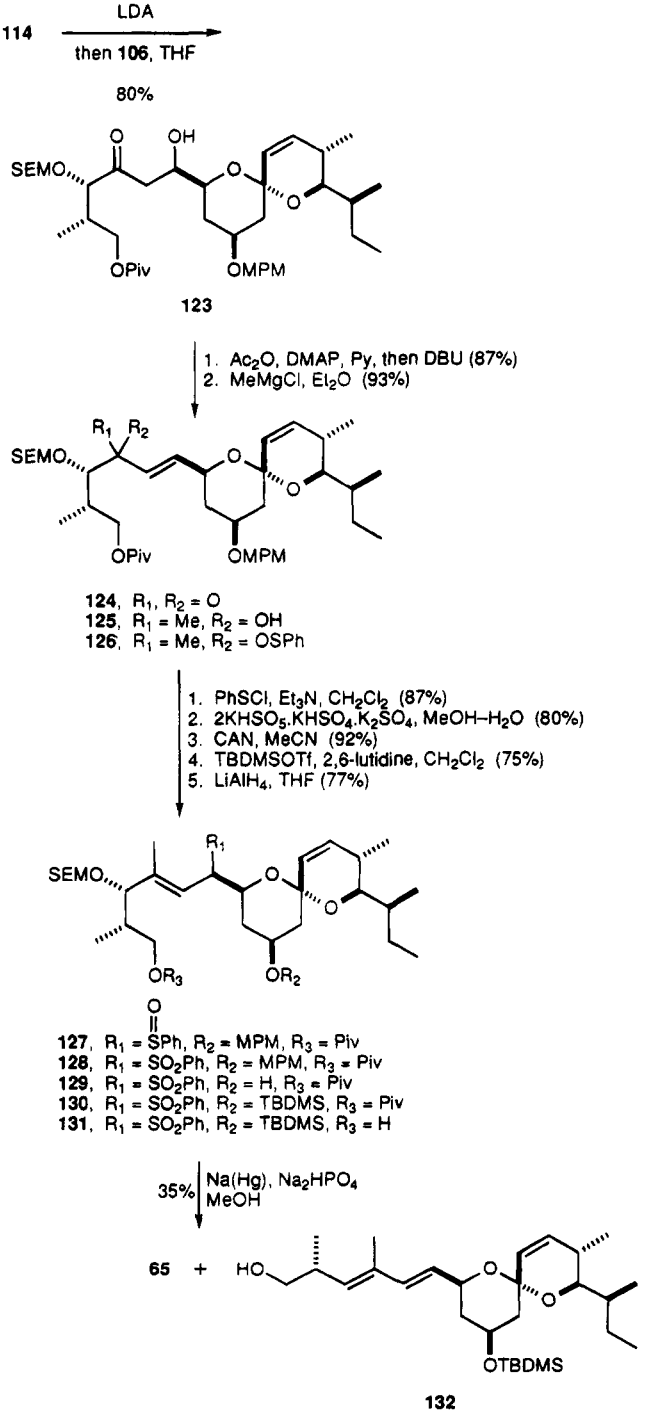
we examined a model sequence employing aldehyde **115**, obtained by Swern oxidation of tetrahydropyran-2-methanol.



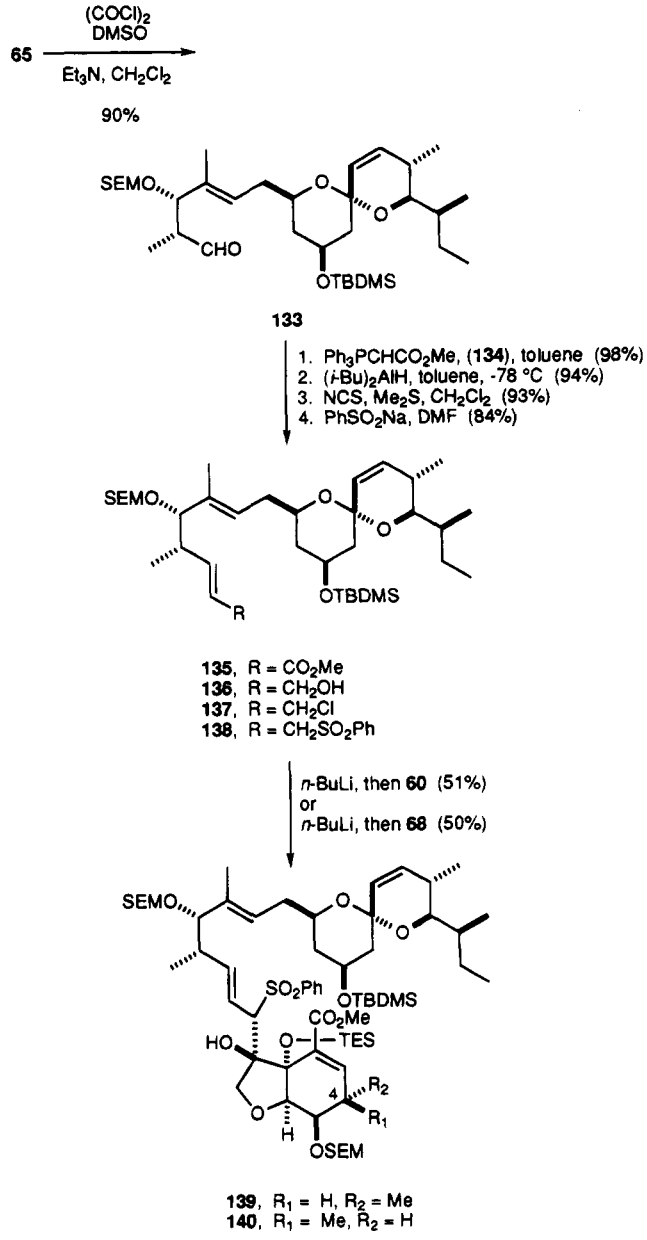
After determining that the enolate of **114** could be produced regioselectively and without epimerization α to the carbonyl, we explored its addition to **115** (Scheme 11). The reaction was found to give **116** as a mixture of diastereomers in high yield. Acetylation of the mixture followed by β elimination cleanly furnished enone **117**. Saturation of this olefin and exposure of the product to methylmagnesium chloride afforded **118**, but dehydration of this tertiary alcohol invariably yielded a 1:1 mixture of exo and in-chain alkenes **119** that could not be separated. This obstacle was avoided by employing allylic alcohol **120**, prepared by Grignard addition to **117**, and exploiting rearrangement of the derived xanthate to the dithiocarbonate **121**. Stannane-mediated reduction of **121** gave exclusively the trisubstituted alkene **122** of *E* configuration.

Following this precedent, aldol condensation of the enolate of **114** with **106** was accomplished in excellent yield. The presence of oxygen substituents α to each of the carbonyl partners in this aldol coupling appears to facilitate condensation, and hydroxy ketone **123** was formed as the sole product of the

reaction. The derived enone **124**, upon treatment with methylmagnesium chloride, afforded tertiary alcohol **125** as a single diastereomer, presumably as a result of chelation-controlled addition of the Grignard reagent,[47] but the sequence that had led from **120** to **122** was much less successful with **125**. An approach employing 1,3-transposition of the sulfenate **126** was more fruitful, exposure of **125** to phenylsulfenyl chloride leading directly to sulfoxide **127**.[48] The latter was converted with



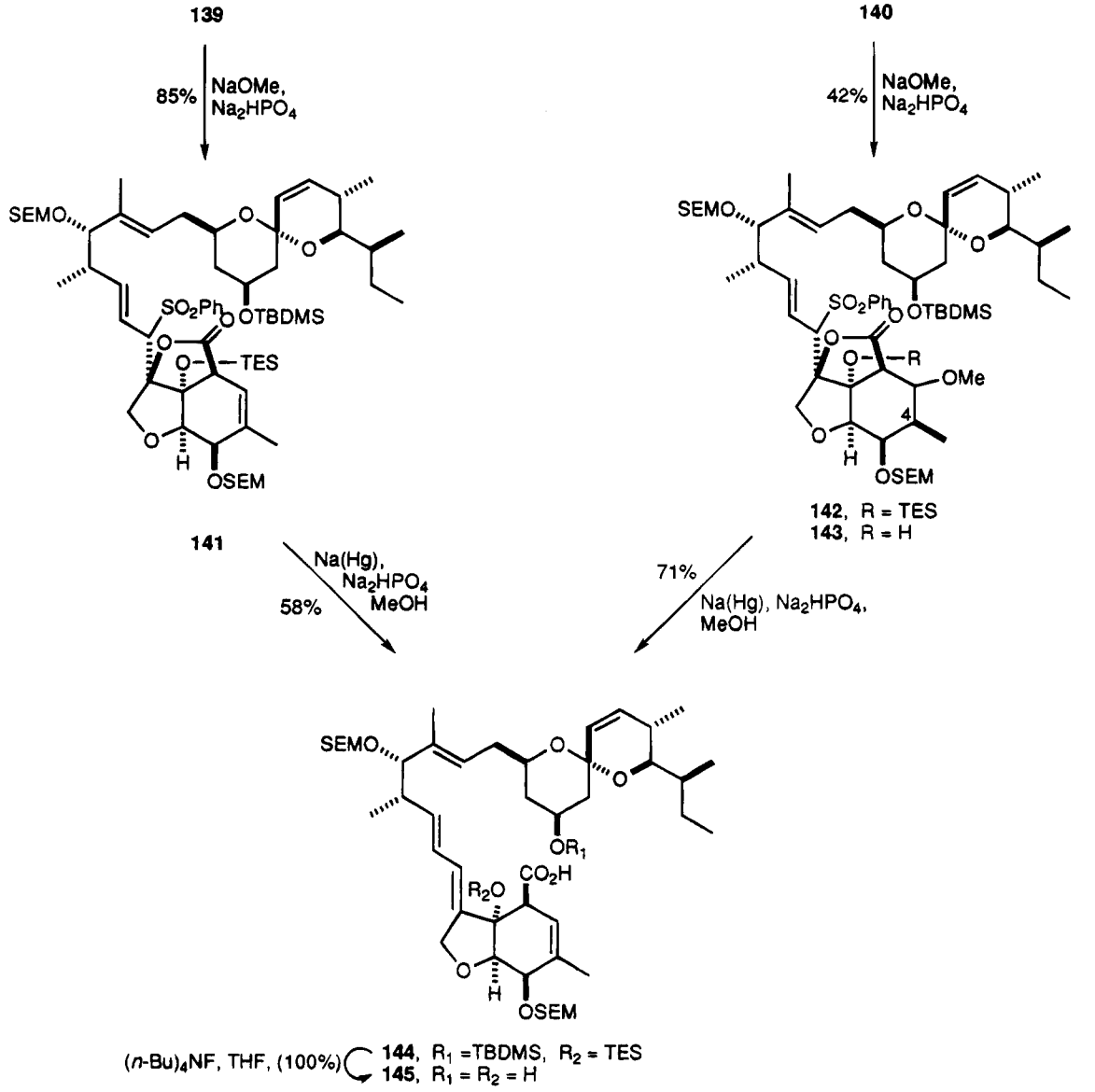
Oxone[49] to sulfone **128** in anticipation of its eventual reductive removal. However, it was first necessary to replace the *p*-methoxybenzyl substituent of **128** by a more robust protecting group, and for this purpose, the ether was unmasked with ceric ammonium nitrate and the liberated alcohol **129** was reprotected as its *tert*-butyldimethylsilyl ether **130**. This interchange had the further advantage of bringing the synthetic route into convergence with **65** obtained from degradation of **1**. Thus, reduction of **130**, first with lithium aluminum hydride to cleave the pivalate and then with sodium amalgam to remove the phenylsulfonyl group from **131**, led to **65**, corresponding in all details, including optical rotation, with the substance acquired from natural avermectin B_{1a}. The modest yield of **65** obtained in the reduction of **131** was due to competing 1,4-elimination that led to a substance identified as the conjugated diene **132**.



Before its coupling to the hexahydrobenzofuran subunit (**A**), alcohol **65** required two-carbon homologation to a system that would afford a nucleophilic site at C9 for its attachment to the keto function of **60**. An allylic sulfone was planned for the latter purpose, and consequently, **65** was first oxidized to aldehyde **133**, which was then subjected to a Wittig reaction with phosphorane **134**. The resultant *E* α,β-unsaturated ester **135** was reduced to alcohol **136**, and the latter was converted to chloride **137**. Displacement of the halogen with phenyl sulfinate proceeded smoothly to yield sulfone **138**.

(47) Still, W. C.; McDonald, J. H., III *Tetrahedron Lett.* **1980**, *21*, 1031.
(48) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147.
(49) Trost, B. M.; Curran, D. P. *Tetrahedron Lett.* **1981**, *21*, 1287.

Scheme 12



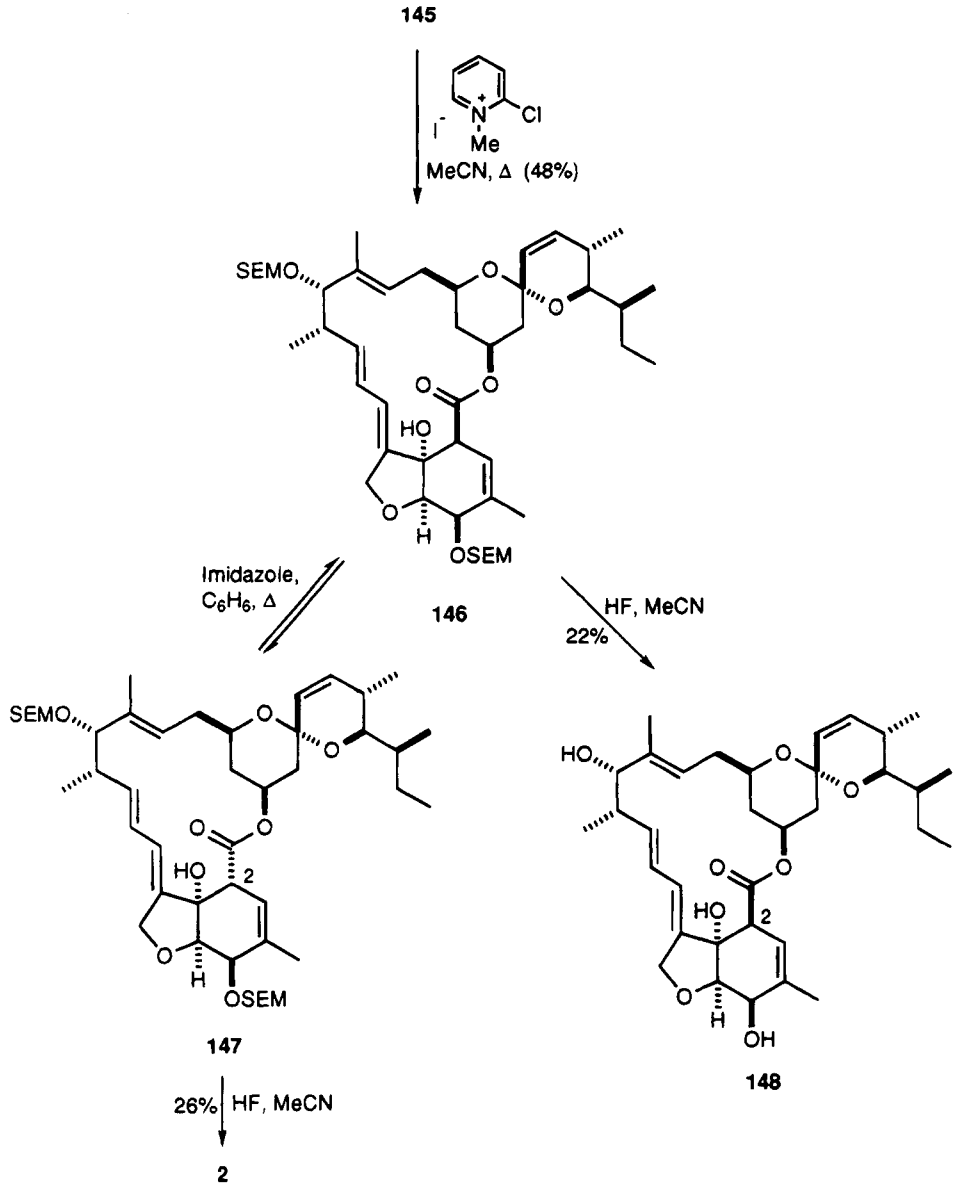
Coupling of the BC Subunit to A and Glycosylation. Avermectin B_{1a}. With ketone **60** and sulfone **138** in hand, the pivotal step linking these two components could be undertaken with the expectation that a Julia coupling[50] would lead to the $\Delta^{8,9}$ olefin. Before investing synthetic ketone **60** in this sequence, however, we decided to test the naturally derived epimeric substance **68** in this process. When **68** was reacted with the anion of **138**, a single product was obtained which, on the basis of its subsequent transformation, could be assigned the endo tertiary alcohol configuration of **139**. To our surprise, treatment of **139** with sodium amalgam did not lead to reductive elimination but instead gave lactone **141** (Scheme 12) in which the cyclohexene double bond had undergone deconjugation. It was subsequently found that the same transformation could be effected in higher yield simply by exposing **139** to sodium methoxide. The facility with which this lactonization occurs is apparently a consequence of the close proximity of the endo hydroxyl and ester substituents in **139**. The olefin presumably reverts to the more stable $\Delta^{3,4}$ position since conjugation with the bridged lactone carbonyl is no longer possible.

The unanticipated, but nevertheless welcome, transformation leading to bridged γ-lactone **141** afforded a new, more compliant substrate on which to attempt reductive elimination of the sulfonyl group, and treatment of this compound with buffered sodium amalgam gave carboxylic acid **144** in which the new $\Delta^{8,9}$ olefin was generated exclusively with *E* configuration while the existing cyclohexene double bond was retained in place. This led to a protected seco acid with the unnatural C2 epi configuration.

With the expectation that coupling of the anion of **138** with **60** would follow the same course, the 4β epimer **140** was prepared, again as a single diastereomer. However, treatment of **140** with sodium methoxide afforded γ-lactone **142** in which methanol addition rather than deconjugation of the $\Delta^{2,3}$ double bond had occurred. Although the configuration of the methoxy group in **142** was not determined, the different behavior of **139** and **140** toward methoxide probably reflects the more facile elimination of methanol from the 4α epimer corresponding to **142**, suggesting that the methoxy substituent in these structures may be α. In any event, reduction of **143** with buffered sodium amalgam led to the same carboxylic acid, **144**, as was obtained from **141**, thereby bringing the fully synthetic route into convergence with the semisynthetic pathway via **139**. The fact that no C2 epimer of **144**, nor any α,β-unsaturated carboxylic acid, was observed in this reaction implies that elimination of

(50) Julia, M. *Pure Appl. Chem.* **1985**, *57*, 763.

Scheme 13



methanol from **142** occurs before reduction of the sulfone–lactone moiety.

In order to complete the conversion of **144** to avermectin B_{1a} aglycon (**2**), the two silyl ethers were first cleaved to afford protected seco acid **145**, which was lactonized under Mukaiyama conditions to yield **146** (Scheme 13). Treatment of **146** with imidazole in refluxing benzene[6] resulted in a 3:2 mixture of the 2α and 2β macrolactones, respectively, along with ca. 15% of the conjugated $\Delta^{2,3}$ isomer. The latter was readily separated from the mixture of lactones **146** and **147** by chromatography. Cleavage of the pair of SEM ethers from the mixture of **146** and **147** with hydrogen fluoride, followed by chromatographic purification, furnished the aglycon **2** of avermectin B_{1a}, identical by comparison of IR, ^1H NMR, and ^{13}C NMR spectra with material obtained by acidic hydrolysis of natural avermectin B_{1a}.[51] The aglycon **148** of 2-epiavermectin B_{1a} was also obtained from this reaction.[52]

The sterically hindered environment of the C13 hydroxyl group of **2** makes glycosylation at this position unusually difficult, and protocols for attachment of the disaccharide unit of **1** have met with only limited success.[6,7,53] Initially, we chose to explore a glycosylation strategy, first advanced by Inanaga,[54] which employed the 3,4-dimethoxybenzyl (DMB) acetal of L-oleandrosyl-L-oleandrose as a means for activating the sugar moiety. We also wished to take advantage of the markedly different reactivity of the three hydroxyl groups of **2**, first protecting at C5, then glycosylating at C13, while leaving the tertiary alcohol at C7 unblocked.

Avermectin B_{1a} aglycon (**2**) was silylated to give the C5-protected species **149**[53] in high yield (Scheme 14). The C4″-silylated derivative **150**[55] of L-oleandrosyl-L-oleandrose was converted to the DMB derivative **151** by treatment with 3,4-dimethoxybenzyl chloride in the presence of cesium carbonate. Although exposure of a mixture of **149** and **151** to dichlorodicyanobenzoquinone in acetonitrile resulted in formation of a significant quantity of 3,4-dimethoxybenzaldehyde, no coupled

(51) The aglycon **2** obtained by acidic hydrolysis of natural avermectin B_{1a} was found to have $[\alpha]^{24}_D$ +142.7°. This material contains a small quantity of the aglycon of avermectin B_{1b} which accompanies natural **1** through the isolation procedure.

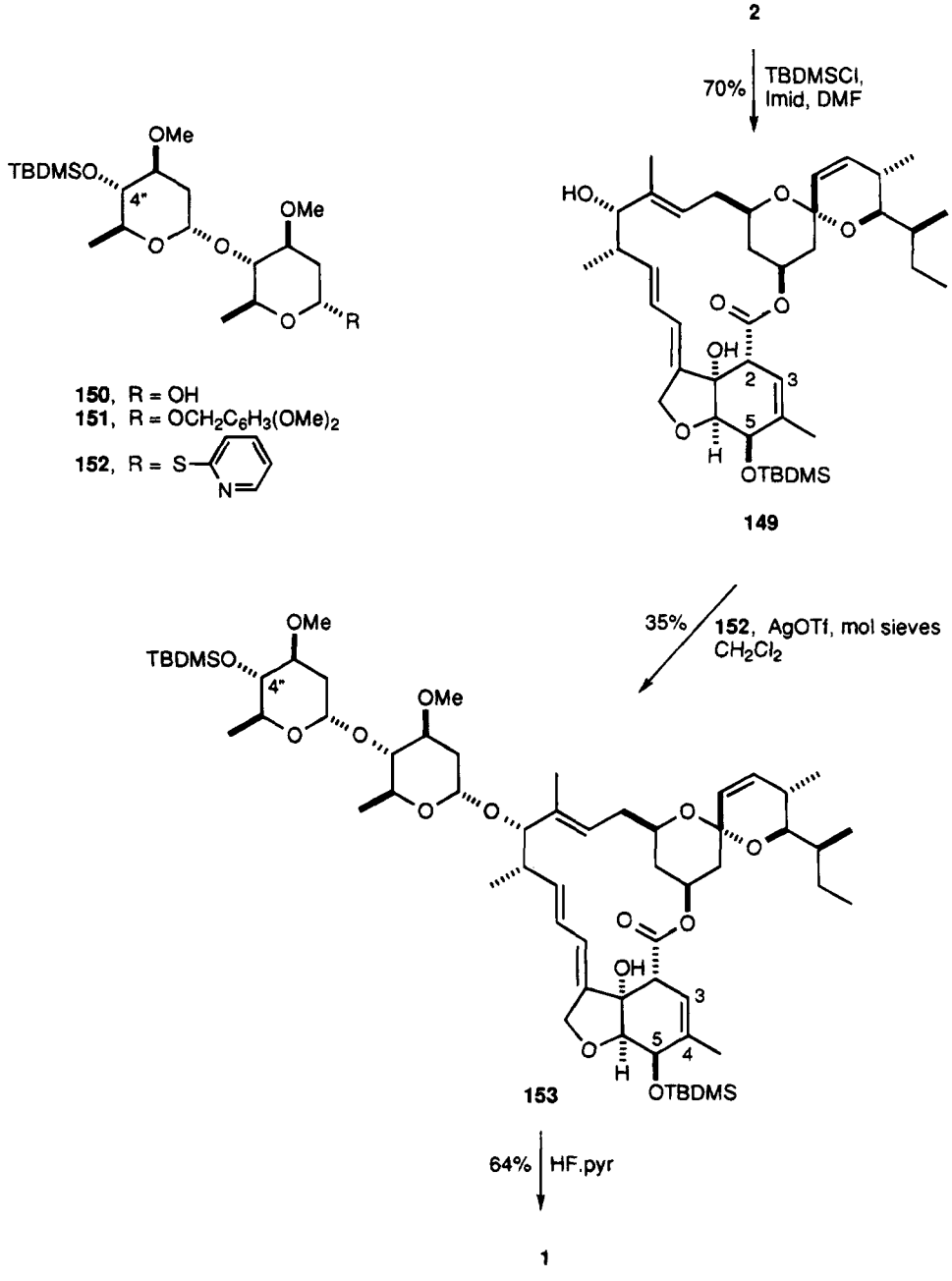
(52) For a preliminary account of the synthesis of avermectin B_{1a} aglycon and its C2 epimer, see: White, J. D.; Bolton, G. L. *J. Am. Chem. Soc.* **1990**, *112*, 1626.

(53) Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 4189.

(54) Inanaga, J.; Yokoyama, Y.; Hanamoto, T. *Chem. Lett.* **1993**, 85.

(55) Blizzard, T. A.; Marino, G.; Mrozik, H.; Fisher, M. J. *J. Org. Chem.* **1989**, *54*, 1756.

Scheme 14



product could be detected. This result contrasts with those obtained by Inanaga[54] who reported that hindered secondary alcohols, and even a tertiary alcohol, could be glycosylated by this method.

The failure of **149** to couple with **151** forced us to examine other derivatives of **150** for this purpose. The thiopyridyl glycoside **152**, previously employed by Hanessian in a synthesis of **1** from the $\Delta^{2,3}$ (conjugated) isomer of **149**,[6] reacted with **149** in the presence of anhydrous silver triflate to give **153** as a single anomer and with no detectable isomerization of the $\Delta^{3,4}$ bond into conjugation. Both silyl protecting groups could be cleanly removed from **153** by treatment with pyridine–hydrogen fluoride complex in pyridine and gave avermectin B_{1a} (**1**), identical by spectral comparison with natural material. In the absence of pyridine as solvent, cleavage of the glycosidic linkage in the disaccharide of **1** occurred. No useful result could be obtained from attempts to deprotect **153** with tetra-*n*-butylammonium fluoride, an observation that is consistent with the known sensitivity of **1** toward base but which appears to conflict with published reports.[6,53]

In summary, a highly convergent synthesis of avermectin B_{1a} (**1**) has been completed from three principal subunits, followed by glycosylation. The linear sequences used to reach the correct enantiomer of each subunit consist of 7, 14, and 15 steps. Assembly of the subunits into avermectin B_{1a} aglycon required 21 steps in which the average yield per step was 73%.

Experimental Section

Analytical thin-layer chromatography (TLC) was carried out on silica-coated aluminum plates (silica gel 60 F-254, 0.2 mm layer thickness, manufactured by E. Merck). Column chromatography was carried out with E. Merck silica gel 60 (230–400 mesh ASTM). Melting points were measured on a hot-stage microscope and are uncorrected. Infrared spectra (IR) were measured on a Perkin-Elmer Model 727B spectrometer or a Nicolet 5DXB FT-IR spectrometer. Mass spectra (MS) were recorded on a Varian MAT CH-7 or a Finnigan 4500 spectrometer at an ionization potential of 70 eV. High-resolution mass spectra (HRMS) were determined on a CEC-110C spectrometer at an ionization potential of 70 eV or on a Kratos MS 50 mass spectrometer. Nuclear magnetic resonance (NMR) spectra were determined on a Varian FT-80 A, an IBM NR-80F, or a Bruker AM-

400 spectrometer. Carbon NMR spectra were measured on a Bruker AM-400 spectrometer. Chemical shifts are reported downfield from tetramethylsilane on the δ scale; the abbreviations s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and bs = broad singlet are used throughout. Optical rotations were measured in 1 dm cells of 1 mL capacity using a Perkin-Elmer Model 243 polarimeter. Elemental analyses were performed by Desert Analytics, Tucson, AZ.

3-Methyl-1-[(trimethylsilyl)oxy]-1,3-butadiene (6). To *n*-butyllithium (46.7 mL of a 1.5 M solution, 0.070 mol) in hexane was added 1-acetoxy-3-methyl-1,3-butadiene (4.33 g, 0.034 mol) in tetrahydrofuran (10 mL) dropwise at −78 °C. After the addition was complete (0.5 h), the solution was warmed to 0 °C and neat trimethylsilyl chloride (7.93 g, 0.033 mol) was added. The mixture was stirred at 0 °C for 0.5 h, diluted with pentane (100 mL), and quenched slowly with saturated, aqueous sodium bicarbonate at 0 °C. The mixture was further diluted with pentane (75 mL), washed with 10% aqueous sodium bisulfite (20 mL), saturated, aqueous sodium bicarbonate (20 mL), and brine (20 mL), and dried (sodium sulfate). The solvent was removed in vacuo, and the residue was distilled through a Vigreux column to yield 2.1 g (40%) of **6** in a fraction boiling at 30 °C (10 mm): ^{1}H NMR ($CDCl_3$) δ 0.30 (9H, s), 1.84 (3H, s), 4.68 (2H, m), 5.60 (1H, d, J = 12 Hz), 6.40 (1H, d, J = 12 Hz).

(3aα,4β,7aα)-3a,4,7,7a-Tetrahydro-6-methyl-4-[(trimethylsilyl)oxy]-1,3-isobenzofurandione (9). A stirred solution of **6** (8.36 g, 0.053 mol), maleic anhydride (5.35 g, 0.055 mol), and 2,6-di-*tert*-butyl-4-methylphenol (0.01 g) in dry benzene (8.0 mL) was refluxed for 10 h. Upon cooling, the solvent was removed in vacuo and the residue was chromatographed on silica using 20% ethyl acetate in hexane as eluant. This afforded 8.1 g (60%) of **9** as an oil: IR (neat) 2950, 1860, 1790, 1440, 1240 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (9H, s), 1.70 (3H, s), 2.40 (2H, m), 2.85−3.45 (2H, m), 4.50 (1H, d, J = 4 Hz), 5.70 (1H, m); MS m/z 254 (M^+), 239, 195, 167, 156, 103; HRMS m/z 254.0986 (calcd for $C_{12}H_{18}O_4Si$: 254.0974). Anal. Calcd for $C_{12}H_{18}O_4Si$: C, 56.67; H, 7.13. Found: C, 56.97; H, 6.83.

Resolution of *anti*-3-Methyl-7-oxo-6-oxabicyclo[3.2.1]oct-3-ene-8-carboxylic Acid (10). (*S*)-(−)-α-Methylbenzylamine (480 mg, 3.96 mmol) was added to (±)-**10** (544 mg, 2.98 mmol) at 0 °C. The mixture solidified spontaneously. Acetone (10 mL) was added, and the solution was heated until the solid was completely dissolved. The cloudy solution was left at room temperature overnight. The deposited crystals (352 mg) were recrystallized four times from acetone and once from methanol−ether (3:1) to give 46.0 mg of the α-methylbenzylammonium salt of **10**: mp 163−164 °C; $[\alpha]^{22}_D$ +122.5° (c 0.9, MeOH); ^{1}H NMR (CD_3OD) δ 1.60 (3H, d, J = 7 Hz), 1.70 (3H, s), 2.59 (2H, m), 2.83 (1H, s), 4.41 (1H, q, J = 7 Hz), 4.90 (1H, m), 5.98 (1H, m), 7.42 (5H, m); ^{13}C NMR ($CDCl_3$) δ 20.9, 21.9, 35.2, 43.2, 52.3, 54.6, 79.2, 125.1, 127.7, 130.3, 140.0, 141.0, 178.1, 182.1.

The salt $C_9H_{10}O_4 \cdot C_8H_{11}N$ crystallized in space group $P2_12_12_1$ with a = 6.715(5) Å, b = 12.602(1) Å, c = 19.451(2) Å, Z = 4, d_{calc} = 1.224 g/cm^3, and d_{obsd} = 1.223 g/cm^3. The intensity data were measured on an Enraf-Nonius CAD4 diffractometer (Ni-filtered Cu Kα radiation, $\omega-2\theta$ scans). The size of the crystal used for data collection was approximately 0.48 × 0.44 × 1.27 mm, and the data were corrected for absorption. Of the 1437 independent reflections for θ < 60°, 1362 were considered to be observed $\{I > 3.0\sigma(I)\}$. The structure was solved by a multiple-solution procedure and was refined by full matrix least-squares. Fourteen reflections that were strongly affected by extinction were excluded from the final refinement and difference map. In the final refinement, anisotropic thermal atoms and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices were R = 0.039 and R_w = 0.054 for the remaining 1348 observed reflections.

By the same procedure as described above, a solution of **10** (578 mg, 3.16 mmol) and (*R*)-(+)-α-methylbenzylamine (510 mg, 4.20 mmol) was recrystallized four times from acetone to give 131.4 mg (12%) of **11**: mp 161−162 °C; $[\alpha]^{22}_D$ −122.0° (c 0.9, MeOH). An aqueous solution of this amine salt (131.0 mg) was acidified with 1 N hydrochloric acid, and the liberated carboxylic acid was thoroughly extracted with ether (4×). The combined ether layers were washed with brine and dried (magnesium sulfate). The solution was concentrated to 10 mL and treated with diazomethane to afford, after chromatography on silica using 25% ethyl acetate in hexane as eluant, 77 mg of (−)-**12**: mp 106−109 °C; $[\alpha]^{22}_D$ −197.8° (c 0.97, MeOH).

Methyl *anti*-3-Methyl-7-oxo-6-oxabicyclo[3.2.1]oct-3-ene-8-carboxylate (12). To a solution of **9** (105 mg, 0.41 mmol) in tetrahydrofuran (6 mL) was added a 1.00 M solution of tetra-*n*-butylammonium fluoride in tetrahydrofuran (0.4 mL, 0.4 mmol). After stirring for 30 min at 0 °C, the mixture was acidified to pH 6 and extracted with ethyl acetate (3×). The organic extract was washed with brine and dried (magnesium sulfate). Removal of the solvent in vacuo afforded **10** as a light yellow oil, which was taken up in ether (10 mL) and treated with diazomethane. After 2 h, the solvent was removed in vacuo to leave a residue that was chromatographed on silica, using 25% ethyl acetate in hexane as eluant, to furnish 77 mg (97%) of **12**: mp 126 °C; IR (KBr) 2950, 1770, 1720, 1440, 1380 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.67 (3H, s), 2.42 (2H, br s), 3.02 (1H, s), 3.20 (1H, br s), 3.71 (3H, s), 4.90 (1H, m), 5.90 (1H, m); ^{13}C NMR ($CDCl_3$) δ 21.8, 33.9, 40.4, 50.8, 52.6, 75.2, 123.1, 139.9, 170.8, 177.2; MS m/z 196 (M^+), 152, 137, 109, 93; HRMS m/z 196.0732 (calcd for $C_{10}H_{12}O_4$: 196.0735). Anal. Calcd for $C_{10}H_{12}O_4$: C, 61.23; H, 6.16. Found: C, 60.95; H, 6.18.

***anti*-8-(Diazoacetyl)-3-methyl-6-oxabicyclo[3.2.1]oct-3-en-7-one (13).** To a stirred suspension of 60% sodium hydride in oil (23.6 mg, 0.55 mmol) in dry benzene (5 mL) was added a solution of **10** (100 mg, 0.55 mmol) in benzene (5 mL). The suspension was stirred for 1 h and cooled to 0 °C. Oxalyl chloride (0.675 mL) was added, and the mixture was stirred for 10 min at 0 °C and for 1 h at room temperature. Filtration under nitrogen and evaporation of the filtrate at reduced pressure gave a pale yellow oil that was taken up in benzene (3 mL). The solution was added slowly to an ethereal solution of diazomethane at 0 °C, and after 15 min, the excess diazomethane was removed with a stream of nitrogen. The mixture was concentrated in vacuo to give a yellow residue that was subjected to chromatography on silica, using 60% ethyl acetate in hexane as eluant, to yield 77.1 mg (66%) of **13** as a pale yellow solid: mp 95−99 °C dec; $[\alpha]^{23}_D$ −165.1° (c 0.47, MeOH); IR (neat) 2100, 1780, 1770, 1635, 1380 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.70 (3H, d, J = 2 Hz), 2.48 (2H, m), 2.95 (1H, s), 3.10 (1H, m), 4.80 (1H, dd, J = 2 and 6 Hz), 5.38 (1H, s), 5.95 (1H, m); MS m/z 178 (M^+ − 28), 133, 132, 123, 93; HRMS 178.0630 (calcd for $C_{10}H_{10}O_3$: 178.0630).

Methyl (3aα,4β,7aα)-3a,4,5,7a-Hexahydro-6-methyl-3-oxo-4-benzofurancarboxylate (15). To a solution of diazo ketone **13** (100.0 mg, 0.48 mmol) in dioxane (6 mL) was added 10% aqueous sulfuric acid (2 mL). The mixture was stirred at 50−55 °C for 1 h, cooled to room temperature, and diluted with water. The mixture was extracted with ethyl acetate (4×) and the organic extract was washed with brine. After drying (magnesium sulfate), the solvent was evaporated to yield a yellow residue, which was taken up in 5 mL of ether and treated with diazomethane. After 2 h, the solvent was removed in vacuo to give a residue that was chromatographed on silica, using 40% ethyl acetate in hexane as eluant, to give 65.0 mg (64%) of **15** as a solid: mp 39−44 °C; $[\alpha]^{22}_D$ +97.2° (c 1.03, MeOH); IR (neat) 2975, 1760, 1735, 1440 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.68 (3H, s), 2.07−2.23 (2H, m), 2.80 (1H, m), 3.28 (1H, d, J = 4 Hz), 3.72 (3H, s), 3.75 and 3.90 (2H, 2d, J = 17 and 17 Hz), 4.96 (1H, d, J = 6 Hz), 5.41 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 23.5, 27.9, 37.2, 46.0, 52.1, 68.1, 75.7, 120.9, 139.8, 172.7, 214.1; MS m/z 210 (M^+), 168, 151, 149, 93; HRMS m/z 210.0900 (calcd for $C_{11}H_{14}O_4$: 210.0890). Anal. Calcd for $C_{11}H_{14}O_4$: C, 62.85; H, 6.71. Found: C, 62.74; H, 6.88.

Methyl (1aα,3α,3aβ,6aβ,6bα)-Octahydro-1a-methyl-4-oxooxireno[g]benzofuran-3-carboxylate (18). To a stirred solution of **15** (11.0 mg, 0.052 mmol) in methylene chloride (3 mL) was added *m*-chloroperoxybenzoic acid (9.1 mg, 0.052 mmol, based on 85% purity) in methylene chloride (5 mL) over 5 min. The mixture was stirred for 10 h, washed successively with 10% aqueous sodium thiosulfate, saturated, aqueous sodium bicarbonate, and brine, and dried (magnesium sulfate). After evaporation of the solvent, chromatography of the residual oil on silica, using 40% ethyl acetate in hexane as eluant, provided 10.7 mg (91%) of **18**: IR (neat) 2950, 1755, 1735, 1435 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (3H, s), 1.78−2.25 (2H, m), 2.75 (1H, m), 2.95 (1H, s), 3.25 (1H, dd, J = 4 and 10 Hz), 3.70 (3H, s), 3.90 and 3.95 (2H, AB q, J = 2 and 14 Hz), 4.85 (1H, d, J = 10 Hz); MS m/z 226 (M^+), 195, 194, 167, 153, 109; HRMS m/z 226.0840 (calcd for

$C_{11}H_{14}O_5$: 226.0840). Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.62; H, 6.09.

Methyl (3aα,4β,6β,7α,7aα)-7-Bromooctahydro-6-hydroxy-6-methyl-3-oxo-4-benzofurancarboxylate (19). To a solution of **15** (210.0 mg, 0.95 mmol) in acetone and water (5 mL, 1:1) was added *N*-bromosuccinimide (210.0 mg, 1.14 mmol). The reaction was stirred at 0 °C for 1 h, diluted with water, and extracted with ethyl acetate (3×). The combined ethyl acetate extracts were washed with brine, dried (sodium sulfate), and concentrated in vacuo. The resulting oil was purified by chromatography on silica, using 50% ethyl acetate in hexane as eluant, to yield 200.0 mg (65%) of **19** as a crystalline solid: mp 119 °C; $[\alpha]^{23}_D$ +58.7° (*c* 1.03, MeOH); IR (neat) 3500, 2890, 1720−1750 (br), 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (3H, s), 1.85 (2H, m), 2.50 (2H, m), 3.25 (1H, d, *J* = 8 Hz), 3.70 (2H, d, *J* = 6 Hz), 3.75 (3H, s), 4.50 (1H, d, *J* = 6 Hz), 5.90 (1H, s); MS *m/z* 308 (M^+), 306 (M^+), 293, 227, 213, 197; HRMS *m/z* 306.0110 (calcd for $C_{11}H_{15}O_5Br$: 306.0100). Anal. Calcd for $C_{11}H_{15}O_5Br$: C, 43.02; H, 4.92. Found: C, 43.04; H, 4.81.

Methyl (1aα,3β,3aα,6aα,6bα)-Octahydro-1a-methyl-4-oxooxireno[g]benzofuran-3-carboxylate (20). To a solution of **19** (552.0 mg, 1.78 mmol) in dry methylene chloride (6 mL) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.31 mL, 2.16 mmol). After 10 min, the reaction mixture was chromatographed on silica, using 50% ethyl acetate in hexane as eluant, to yield 367.0 mg (91%) of **20** as a crystalline solid: mp 100 °C; $[\alpha]^{22}_D$ +16.3° (*c* 0.88, MeOH); IR (neat) 2900, 1760, 1730, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (3H, s), 1.95 (1H, m), 2.38 (1H, d, *J* = 8 Hz), 2.85 (2H, m), 3.27 (1H, d, *J* = 3 Hz), 3.73 (3H, s), 3.94 and 4.23 (2H, 2d, *J* = 17 and 16 Hz), 4.75 (1H, dd, *J* = 3 and 8 Hz); ^{13}C NMR ($CDCl_3$) δ 23.0, 27.5, 36.8, 43.3, 52.3, 59.2, 59.7, 71.0, 75.0, 173.2, 211.2; MS *m/z* 226 (M^+) 194, 167, 140, 139. Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.64; H, 6.23.

Methyl (2α,4β,4aβ,5α,7aβ,8R*)-7a-(Acetyloxy)-8-bromohexahydro-2-methyl-2,5-methano-2*H*-furo[3,4-*b*]pyran-4-carboxylate (22). To a solution of **19** (18.0 mg, 0.05 mmol) in methylene chloride (3 mL) were added dry pyridine (0.15 mL), acetic anhydride (0.10 mL), and 4-(dimethylamino)pyridine (1.5 mg). The mixture was stirred for 2 h, diluted with water (10 mL), and extracted with ethyl acetate (3 × 15 mL). The combined ethyl acetate extracts were washed with 1 N hydrochloric acid and brine and dried (magnesium sulfate). The solvent was evaporated to give a residue that was chromatographed on silica, using 40% ethyl acetate in hexane as eluant, to yield 16.0 mg (91%) of **22**: IR (neat) 2900, 1743, 1735, 1435, 1371 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (3H, s), 2.02 (3H, s), 2.28 (2H, d, *J* = 10 Hz), 2.97 (1H, d, *J* = 6 Hz), 3.10 (1H, t, *J* = 10 Hz), 3.71 (1H, s), 3.76 (3H, s), 3.76 (1H, d, *J* = 8 Hz), 4.23 (1H, d, *J* = 8 Hz), 4.52 (1H, d, *J* = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 21.1, 24.0, 28.6, 31.0, 39.6, 52.3, 54.9, 72.9, 73.5, 80.5, 102.5, 168.5, 172.9; MS *m/z* 350 (M^+), 348 (M^+), 306, 197, 151; HRMS *m/z* 348.0210 (calcd for $C_{13}H_{17}O_6Br$: 348.0208).

Methyl (3aα,4β,6α,7β,7aα)-Octahydro-7-hydroxy-6-iodo-6-methyl-3-oxo-4-benzofurancarboxylate (23) and Methyl (3aα,4β,7aα)-Octahydro-3,7-dioxo-6-methyl-4-benzofurancarboxylate (24). To a solution of **20** (130.4 mg, 0.55 mmol) in benzene (3 mL) was added hydriodic acid (0.5 mL), and the resulting two-phase solution was stirred for 1 h at room temperature. The reaction mixture was diluted with ether and washed with 50% aqueous sodium bicarbonate and water. The combined aqueous phases were extracted with ether (2×), and the ethereal layers were washed with brine and dried (sodium sulfate). Removal of the solvent, followed by chromatography on silica gel, using 50% ethyl acetate in hexane as eluant, furnished 187.1 mg (91%) of **23** and 11.8 mg (8%) of **24**.

23: IR (neat) 3450, 1760, 1730, 1440, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.98 (2H, m), 2.18 (3H, s), 3.15 (1H, dd, *J* = 7 and 8 Hz), 3.27 (1H, dd, *J* = 7 and 8 Hz), 3.76 (3H, s), 4.10 (2H, d, *J* = 16 Hz), 4.20 (1H, t, *J* = 4 Hz), 5.24 (1H, dd, *J* = 4 and 8 Hz); MS *m/z* 354 (M^+), 323, 278, 265, 254, 227, 209, 195; HRMS *m/z* 353.9960 (calcd for $C_{11}H_{15}O_5I$: 353.9970).

24: IR ($CHCl_3$) 2900, 1770, 1730, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (3H, d, *J* = 7 Hz), 1.54 (3H, m), 2.30 (1H, m), 2.45 (1H, m), 3.15 (1H, m), 3.76 and 3.90 (2H, AB q, *J* = 2 and 18 Hz), 4.95 (1H, d, *J* = 10 Hz); MS *m/z* 195 (M^+ − 31), 167, 156, 142; HRMS *m/z* 195.0660 (calcd for $C_{10}H_{11}O_4$: 195.0660).

Methyl (3α,3aα,4β,6α,7β,7aβ)-Octahydro-6-iodo-6-methyl-3-[(triethylsilyl)oxy]-3,7-epoxybenzofuran-4-carboxylate (25). To a solution of **23** (24 mg, 0.07 mmol) in methylene chloride (3 mL) were added 2,6-lutidine (0.033 mL, 0.28 mmol) and triethylsilyl trifluoromethanesulfonate (0.051 mL, 0.14 mmol). The mixture was stirred for 1 h, diluted with ether, washed with saturated, aqueous sodium bicarbonate and brine, and dried (magnesium sulfate). Evaporation of the solvent gave a residue that was chromatographed on silica, using 10% ethyl acetate in hexane as eluant, to yield 31 mg (90%) of **25** as a colorless oil: IR (neat) 1743, 1288, 1274 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.55 (6H, q, *J* = 8 Hz), 0.90 (9H, t, *J* = 8 Hz), 1.99 (3H, s), 2.09 (1H, d, *J* = 15 Hz), 2.31 (1H, d, *J* = 16 Hz), 2.69 (1H, t, *J* = 3 Hz), 3.02 (2H, m), 3.57 (2H, d, *J* = 6 Hz), 3.67 (2H, s), 4.12 (1H, s), 4.75 (1H, d, *J* = 2 Hz); MS *m/z* 468 (M^+), 440, 341, 311; HRMS *m/z* 468.0831 (calcd for $C_{17}H_{29}O_5SiI$: 468.0829).

Methyl (3aα,4β,6α,7β,7aα)-Octahydro-6-iodo-6-methyl-3-oxo-7-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-benzofurancarboxylate (26). To a solution of **23** (79.0 mg, 0.23 mmol) in methylene chloride (3.0 mL) were added 3,4-dihydro-2*H*-pyran (0.018 mL, 0.26 mmol) and bis(trimethylsilyl) sulfate (0.01 mL) in 1,2-dichloroethane. After 3.5 h at 0 °C, the reaction was complete and was quenched with pyridine (0.2 mL) and diluted with methylene chloride (10 mL). The organic layer was washed with saturated, aqueous sodium bicarbonate and brine and dried (magnesium sulfate). Evaporation of the solvent gave a residue that was chromatographed on silica, eluting with 50% ethyl acetate in hexane, to give 99.0 mg (99%) of **26** as a mixture of epimers at the tetrahydropyranyl group.

26a: IR (neat) 2900, 1760, 1725, 1430 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35−1.63 (6H, bm), 1.76 (1H, br s), 1.92 (1H, d, *J* = 4 Hz), 2.17 (3H, s), 3.18 (1H, m), 3.25 (1H, t, *J* = 8 Hz), 3.42 (1H, m), 3.70 (3H, s), 3.90 (3H, m), 4.33 (1H, d, *J* = 4 Hz), 4.57 (1H, d, *J* = 2 Hz), 5.38 (1H, d, *J* = 4 Hz); MS *m/z* 354 (M^+ − 84), 333, 311, 287.

26b: IR ($CHCl_3$) 2900, 1760, 1730, 1435 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (3H, m), 1.50−1.79 (4H, m), 1.90 (1H, dd, *J* = 4 and 5 Hz), 2.12 (3H, s), 3.13 (1H, m), 3.24 (1H, t, *J* = 8 Hz), 3.42 (1H, m), 3.75 (3H, s), 3.93 and 4.38 (2H, 2d, *J* = 16 Hz), 4.02 (1H, m), 4.23 (1H, d, *J* = 4 Hz), 4.44 (1H, dd, *J* = 2 and 2 Hz), 5.34 (1H, d, *J* = 4 Hz); MS *m/z* 438 (M^+), 354 (M^+ − 84), 227, 167, 151, 111, 109, 93.

Methyl (3aα,7β,7aα)-2,3,3a,6,7,7a-Hexahydro-6-methyl-3-oxo-7-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-benzofurancarboxylate (27). To a solution of **26** (46.0 mg, 0.105 mmol) in ether was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.13 mL, 0.99 mmol). The mixture was refluxed for 6 h, and the ether was evaporated. The pale yellow residue was chromatographed on silica, using 30% ethyl acetate in hexane as eluant, to afford 15.2 mg (47%) of **27**: IR (neat) 2900, 1760, 1700, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.08 (3H, d, *J* = 3 Hz), 1.45−1.75 (6H, m), 2.78−2.87 (1H, m), 3.50 (1H, m), 3.72 (1H, m), 3.81 (3H, s), 3.89 (2H, d, *J* = 3 Hz), 4.16 (2H, d, *J* = 16 Hz), 4.70−4.85 (2H, m), 6.83 (1H, d, *J* = 8 Hz); MS *m/z* 310 (M^+), 226, 167, 121; HRMS *m/z* 310.1435 (calcd for $C_{16}H_{22}O_6$: 310.1417). Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 62.01; H, 7.09.

Methyl (7β,7aα)-2,6,7,7a-Tetrahydro-3-[(*tert*-butyldimethylsilyl)oxy]-6-methyl-7-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-benzofurancarboxylate (28). To a solution of **27** (27.0 mg, 0.09 mmol) in dry benzene (3.0 mL) were added triethylamine (0.059 mL, 0.44 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.059 mL, 0.26 mmol). After the mixture had stirred for 20 h, it was added to a saturated, aqueous sodium carbonate solution and was extracted with ethyl acetate (3×). The organic layer was washed with brine and dried (magnesium sulfate). Evaporation of the solvent gave a residue that was chromatographed on silica, using 20% ethyl acetate in hexane as eluant, to yield 15.7 mg (42%) of **28**: IR (neat) 2900, 1720, 1680, 1600, 1520, 1420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.11 (3H, s), 0.15 (3H, s), 0.92 (9H, s), 1.07 (3H, d, *J* = 8 Hz), 1.55 (6H, m), 2.65 (1H, m), 3.56 (1H, m), 3.80 (3H, s), 3.80−4.10 (2H, m), 4.50−4.65 (2H, m), 4.80−4.90 (2H, m), 6.40 (1H, d, *J* = 5 Hz); MS *m/z* 310 (M^+ − 114), 226, 177, 85; HRMS *m/z* 226.0842 (calcd for $C_{11}H_{14}O_5$: 226.0841).

Methyl (3aα,7β,7aα)-2,3,3a,6,7,7a-Hexahydro-3a-hydroxy-6-methyl-3-oxo-7-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-benzofurancarboxylate (29). To a stirred suspension of sodium bicarbonate (3.6 mg, 0.043 mmol) and **28** (18.0 mg, 0.043 mmol) in methylene chloride (3.0 mL) was added a solution of *m*-chloroperoxybenzoic acid (8.7

mg, 0.05 mmol) in dry methylene chloride (2.0 mL). After the solution was storred for 30 min at 0 °C, the mixture was diluted with methylene chloride (10.0 mL) and washed with 10% aqueous sodium thiosulfate, saturated, aqueous sodium bicarbonate, and brine. The organic layer was dried (magnesium sulfate), and the solvent was evaporated to leave a residue that was purified by chromatography on silica. Elution with 40% ethyl acetate in hexane provided 8.5 mg (61%) of **29**: IR (neat) 3400−3500 (br), 2950, 1775, 1705, 1450, 1350, 1300 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (3H, d, J = 7 Hz), 1.54−1.85 (6H, bm), 2.87 (1H, m), 3.52 (1H, m), 3.66 (1H, d, J = 2 Hz), 3.79 (3H, s), 3.96 (1H, m), 4.09−4.37 (2H, m), 4.51 (1H, d, J = 2 Hz), 4.67 (1H, d, J = 3 Hz), 4.90 (1H, s), 6.96 (1H, d, J = 2 Hz); MS m/z 242 (M^+ − 84), 184, 167, 136, 85; HRMS m/z 242.0778 (calcd for $C_{11}H_{14}O_6$: 242.079). Anal. Calcd for $C_{16}H_{22}O_7$: C, 58.89; H, 6.79. Found: C, 59.07; H, 6.73.

Methyl (4β,6α,7β,7aα)-2,4,5,6,7,7a-Hexahydro-6-iodo-6-methyl-7-[(tetrahydro-2*H*-pyran-2-yl)oxy]-3-[(*tert*-butyldimethylsilyl)oxy]-4-benzofurancarboxylate (30). To a stirred solution of **26** (27.0 mg, 0.06 mmol) in dry benzene (3.0 mL) were added triethylamine (0.019 mL, 0.12 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.028 mL, 0.12 mmol). The reaction mixture was stirred for 40 h at room temperature and diluted with ethyl acetate, and the separated organic layer was washed with saturated, aqueous sodium bicarbonate and brine and dried (magnesium sulfate). The solvent was evaporated to give a residue that was chromatographed on silica gel. Elution with 20% ethyl acetate in hexane gave 32.5 mg (97%) of **30** as a colorless oil: IR ($CHCl_3$) 2950, 1735, 1710, 1450, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.14 (3H, s), 0.15 (3H, s), 0.92 (9H, s), 1.50−1.90 (8H, m), 2.15 (3H, s), 3.45 (1H, m), 3.48 (1H, m), 3.76 (3H, s), 4.07−4.12 (2H, m), 4.13 (1H, d, J = 3 Hz), 4.40−4.54 (1H, m), 4.75 (1H, t, J = 3 Hz), 5.57 (1H, m); MS m/z 425 (M^+ − 127), 341, 324, 309, 283, 213, 85.

Methyl (3aα,4β,6α,7β,7aα)-Octahydro-3a-hydroxy-6-iodo-6-methyl-3-oxo-7-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-benzofurancarboxylate (31). To a stirred suspension of sodium bicarbonate (4.5 mg, 0.06 mmol) and **30** (34.0 mg, 0.06 mmol) in dry methylene chloride (2 mL) was added a solution of *m*-chloroperoxybenzoic acid (12.7 mg, 0.07 mmol) in dry methylene chloride (3 mL) at 0 °C. After 30 min, the mixture was diluted with methylene chloride (10 mL) and washed with 10% aqueous sodium thiosulfate and brine. The organic layer was dried (magnesium sulfate), and the solvent was evaporated in vacuo. The crude product was purified by chromatography on silica, using 40% ethyl acetate in hexane as eluant, to yield 17.2 mg (64%) of **31** as a colorless oil: IR ($CHCl_3$) 3500, 2950, 1760, 1705, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 and 1.68 (8H, m), 2.13 (3H, s), 3.34 (1H, d, J = 5 Hz), 3.43 (1H, m), 3.89 (3H, s), 4.02 (1H, m), 4.20−4.36 (4H, m), 4.49 (1H, bs), 4.95 (1H, bs); MS m/z 454 (M^+), 370, 243, 168, 167, 85.

Methyl (3aα,4β,7β,7aα)-2,3,3a,4,7,7a-Hexahydro-3a-hydroxy-6-methyl-3-oxo-7-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-benzofurancarboxylate (32) and Methyl (3aα,4β,7β,7aα)-Octahydro-3a-hydroxy-6-methylene-3-oxo-7-[(tetrahydro-2*H*-pyran-2-yl)oxy]-4-benzofurancarboxylate (33). A solution of **31** (16.0 mg, 0.037 mmol), silver fluoride (9.4 mg, 0.074 mmol), and pyridine (23.6 μL, 0.29 mmol) in acetonitrile (3 mL) was stirred for 4 h at room temperature. The dark purple solution was diluted with ethyl acetate (10 mL), and water was added (5 mL). The separated organic layer was washed with brine, dried (sodium sulfate), and evaporated. The residue was chromatographed on silica, eluting with 50% ethyl acetate in hexane, to give 8.5 mg (74%) of an inseparable (ca. 1:1) mixture of **32** and **33**: IR ($CHCl_3$) 2950, 1765, 1735, 1450, 1350 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50−1.70 (6H, m, both isomers), 1.85 (3H, s, endo isomer), 2.10−2.35 (3H, m, exo isomer, 1H, m, endo isomer), 3.32 (1H, dd, J = 3 and 4 Hz, both isomers), 3.44−3.72 (2H, m, both isomers), 3.74 (3H, s), 3.78 (3H, s), 4.03−4.18 (2H, m, both isomers), 4.26−4.64 (2H, m, exo isomer), 4.79 (1H, dd, J = 3 and 4 Hz, exo isomer), 5.66 (1H, d, J = 3 Hz, endo isomer); MS m/z 310 (M^+).

Methyl (3aα,4β,6α,7β,7aα)-7-(Acetyloxy)octahydro-6-iodo-6-methyl-3-oxo-4-benzofurancarboxylate (34). To a solution of **23** (53.0 mg, 0.14 mmol) in dry methylene chloride (4 mL) were added pyridine (0.20 mL), 4-(dimethylamino)pyridine (2 mg), and acetic anhydride (0.20 mL). After 2 h, the mixture was diluted with ether, washed with saturated, aqueous sodium bicarbonate and brine, and dried (magnesium sulfate). Evaporation of the solvent gave a residue that was chromatographed on silica, using 40% ethyl acetate in hexane as eluant, to yield 59.0 mg (100%) of **34**: IR ($CHCl_3$) 2900, 1751, 1748, 1440, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (1H, dd, J = 13 and 16 Hz), 2.00 (3H, s), 2.05 (3H, s), 2.10 (1H, m), 3.20 (1H, m), 3.38 (1H, t, J = 8 Hz), 3.78 (3H, s), 3.97 (2H, d, J = 16 Hz), 5.40 (1H, dd, J = 4 and 9 Hz), 5.60 (1H, d, J = 4 Hz); ^{13}C NMR ($CDCl_3$) δ 20.8, 34.0, 35.1, 39.7, 44.4, 44.6, 52.1, 70.1, 75.0, 75.9, 168.5, 172.2, 209.0; MS m/z 396 (M^+), 354, 323, 269, 227, 209, 197; HRMS m/z 396.0090 (calcd for $C_{13}H_{17}O_6I$: 396.0070). Anal. Calcd for $C_{13}H_{17}O_6I$: C, 39.41; H, 4.33. Found: C, 39.19; H, 4.38.

Methyl (4β,6α,7β,7aα)-2,4,5,6,7,7a-Hexahydro-7-(acetyloxy)-6-iodo-6-methyl-3-[(triethylsilyl)oxy]-4-benzofurancarboxylate (35). To a solution of **34** (50.0 mg, 0.12 mmol) in methylene chloride (3 mL) were added 2,6-lutidine (0.06 mL, 0.48 mmol) and triethylsilyl trifluoromethanesulfonate (0.12 mL, 0.48 mmol). After 20 h, the mixture was diluted with ether, washed with saturated, aqueous sodium bicarbonate and brine, and dried (magnesium sulfate). After evaporation of the solvent, the pale yellow residue was chromatographed on silica, using successively 10% and 20% ethyl acetate in hexane as eluants, to supply 53.0 mg (82%) of **35**: IR (neat) 2915, 1748, 1705, 1304, 1166 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.64 (6H, q, J = 8 Hz), 0.99 (9H, t, J = 8 Hz), 1.78 (1H, d, J = 12 Hz), 2.01 (1H, m), 2.04 (3H, s), 2.07 (3H, s), 3.42 (1H, m), 3.77 (3H, s), 4.33−4.45 (2H, m), 5.44 (1H, d, J = 3 Hz), 5.56 (1H, m); ^{13}C NMR ($CDCl_3$) δ 5.3, 6.4, 20.6, 34.2, 41.5, 41.8, 45.2, 51.8, 73.5, 75.7, 82.7, 102.8, 142.4, 169.6, 172.1; MS m/z 481 (M^+ − 29), 383; HRMS m/z 383.1889 (calcd for $C_{19}H_{31}O_6SiI$: 383.1889).

Methyl (3aα,4β,6α,7β,7aα)-7-(Acetyloxy)octahydro-3a-hydroxy-6-iodo-6-methyl-3-oxo-4-benzofurancarboxylate (36). To a stirred solution of **35** (26.0 mg, 0.05 mmol) in dry methylene chloride (3 mL) was added *m*-chloroperoxybenzoic acid (10.4 mg, 0.06 mmol) in methylene chloride (2 mL) dropwise at 0 °C during 5 min. The mixture was stirred at 0 °C for 30 min and diluted with ether. The solution was washed with saturated, aqueous sodium bisulfite, saturated, aqueous sodium bicarbonate, and brine and dried (magnesium sulfate). The solution was filtered, the solvent was evaporated, and the colorless residue was chromatographed on silica, using 30% ethyl acetate in hexane as eluant, to yield 11.0 mg (53%) of **36** as an oil: IR (neat) 3600, 2915, 1771, 1755, 1243, 1022 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.53 (1H, dd, J = 13 and 13 Hz), 2.00 (3H, s), 2.05 (3H, s), 2.16 (1H, m), 3.42 (1H, dd, J = 5 and 13 Hz), 3.82 (1H, d, J = 16 Hz), 3.85 (3H, s), 4.37 (1H, d, J = 16 Hz), 5.02 (1H, d, J = 5 Hz), 5.08 (1H, s), 5.61 (1H, J = 4 Hz); ^{13}C NMR ($CDCl_3$) δ 20.7, 33.5, 36.5, 42.6, 45.3, 52.8, 68.4, 74.0, 76.4, 80.8, 168.4, 173.0, 207.7; MS m/z 353 (M^+ − 59), 285; HRMS m/z 285.0976 (calcd for $C_{13}H_{14}O_7$: 285.0974). Anal. Calcd for $C_{13}H_{17}O_7I$: C, 37.88; H, 4.16. Found: C, 37.61; H, 4.00.

Methyl (3aα,4β,6α,7β,7aα)-Octahydro-6,7-dihydroxy-6-methyl-3-oxo-4-benzofurancarboxylate (37). To a solution of **20** (81.0 mg, 0.36 mmol) in 1:1 aqueous tetrahydrofuran (6.0 mL) was added 3 N perchloric acid (1.5 mL). The solution was stirred for 12 h, diluted with water (5 mL), and extracted with ethyl acetate (3×). The combined extracts were washed with saturated, aqueous sodium bicarbonate and brine and dried (magnesium sulfate). Removal of the solvent under reduced pressure gave a residue that was chromatographed on silica, using 60% ethyl acetate in hexane as eluant, to supply 71.5 mg (81%) of **37**: IR (neat) 3600, 2900, 1760, 1730, 1440 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (3H, s), 1.58 (2H, bm), 1.95 (2H, m), 3.08 (1H, m), 3.30 (1H, dd, J = 7 and 9 Hz), 3.76 (3H, s), 3.77 (1H, bs), 4.09 (2H, d, J = 2 Hz), 4.85 (1H, d, J = 4 Hz); MS m/z 244 (M^+), 212, 153, 128; HRMS m/z 244.0950 (calcd for $C_{11}H_{16}O_6$: 244.0950). Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 53.98; H, 6.61. Further elution gave 12 mg (15%) of **24**.

Methyl (3aα,4β,6α,7β,7aα)-7-(Acetyloxy)octahydro-6-hydroxy-6-methyl-3-oxo-4-benzofurancarboxylate (38) and Methyl (3aα,-4β,6α,7β,7aα)-6,7-Bis(acetyloxy)octahydro-4-methyl-3-oxo-4-benzofurancarboxylate (39). To a solution of **37** (71.0 mg, 0.29 mmol) in dry methylene chloride (4 mL) were added pyridine (0.117 mL, 1.45 mmol), acetic anhydride (0.136 mL, 1.45 mmol), and 4-(dimethylamino)pyridine (2.0 mg). After stirring for 15 h, the mixture was diluted with ether, washed with saturated, aqueous sodium bicarbonate and brine, and dried (magnesium sulfate). The ethereal solution was concentrated to give 56.0 mg of crude product that was chromato-

graphed on silica, using 30% ethyl acetate in hexane as eluant, to afford 30.0 mg (37%) of monoacetate **38** and 17.0 mg (18%) of diacetate **39**.

38: IR (neat) ($CHCl_3$) 3500, 2850, 1760−1740 (br), 1440, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21 (3H, s), 1.82 (2H, m), 2.05 (3H, s), 3.12 (1H, sextet, J = 6 and 7 Hz), 3.36 (1H, t, J = 8 Hz), 3.76 (3H, s), 3.83 and 4.07 (2H, 2d, J = 16 and 16 Hz), 4.98 (1H, dd, J = 5 and 9 Hz), 5.21 (1H, d, J = 4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.3, 27.5, 31.0, 33.9, 44.8, 52.0, 70.4, 71.8, 74.0, 75.6, 169.3, 173.4, 210.0; MS *m/z* 286 (M^+), 244, 213, 212, 155, 128, 124; HRMS *m/z* 286.1060 (calcd for $C_{13}H_{18}O_7$: 286.1050). Anal. Calcd for $C_{13}H_{18}O_7$: C, 54.54; H, 6.34. Found: C, 54.58; H, 6.28.

39: IR (neat) 1735−1750 (br), 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (3H, s), 1.85 (1H, t, J = 14 Hz), 2.03 (3H, s), 2.06 (3H, s), 2.49 (1H, dd, J = 15 and 5 Hz), 2.85 (1H, m), 3.37 (1H, t, J = 8 Hz), 3.77 (3H, s), 3.82 and 4.01 (2H, 2d, J = 2 and 16 Hz), 4.81 (1H, dd, J = 4 and 8 Hz), 5.68 (1H, d, J = 4 Hz); MS *m/z* 328 (M^+), 286, 268, 255, 226, 213, 209, 195.

Methyl (3aα,4β,7β,7aα)-7-(Acetyloxy)-2,3,3a,4,7,7a-hexahydro-6-methyl-3-oxo-4-benzofurancarboxylate (42) and Methyl (3aα,4β,7β,-7aα)-7-(Acetyloxy)octahydro-6-methylene-3-oxo-4-benzofurancarboxylate (43). To a stirred solution of **38** (28.0 mg, 0.10 mmol) in pyridine (3 mL) were added phosphorus oxychloride (0.037 mL, 0.40 mmol) and 4-(dimethylamino)pyridine (0.015 mg). After stirring for 7 h at room temperature, the mixture was diluted with ethyl acetate, and the organic layer was washed with 1 N hydrochloric acid, saturated, aqueous sodium bicarbonate, and brine and dried (magnesium sulfate). Evaporation of the solvent gave a light yellow oil that was chromatographed on silica. Elution with 40% ethyl acetate in hexane furnished, in addition to 12 mg (42%) of unreacted **38**, 11.0 mg (41%) of a 2:1 mixture of **42** and **43** as a colorless oil: IR (neat) 2915, 1743, 1720, 1205, 1094, 906 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.80 (3H, s), 2.04 (3H, s), 2.20 (3H, s), 2.43 (2H, m), 2.73 (1H, m), 3.15 (1H, m), 3.32 (2H, m), 3.77 (3H, s), 3.81 (3H, s), 3.82−41.2 (4H, m), 4.62 (1H, d, J = 5 Hz), 5.06 (1H, d, J = 5 Hz), 5.09 (1H, s), 5.19 (1H, s), 5.27 (1H, m), 5.56 (1H, d, J = 5 Hz), 6.02 (1H, m); MS *m/z* 268 (M^+), 209, 193, 176; HRMS *m/z* 268.0947 (calcd for $C_{13}H_{16}O_6$: 268.0949).

Methyl (4β,7β,7aα)-2,4,7,7a-Tetrahydro-6-methyl-3,7-bis[(triethylsilyl)oxy]-4-benzofurancarboxylate (44) and Methyl (4β,7β,7aα)-2,4,5,6,7,7a-Hexahydro-6-methylene-3,7-bis[(triethylsilyl)oxy]-4-benzofurancarboxylate (45). To a solution of **20** (34.0 mg, 0.15 mmol) in dry methylene chloride (4 mL) were added 2,6-lutidine (0.069 mL, 0.601 mmol) and triethylsilyl trifluoromethanesulfonate (0.067 mL, 0.30 mmol). The mixture was stirred for 38 h, diluted with ether, washed with saturated, aqueous sodium bicarbonate and brine, and dried (magnesium sulfate). The ethereal solution was concentrated under reduced pressure, and the residue was chromatographed on silica, using 10% ethyl acetate in hexane as eluant, to give 41 mg (58%) of a mixture of **44** and **45**: IR (neat) 1747, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.47 (12H, m), 0.89 (18H, m), 1.85 (3H, s), 2.15 (1H, d, J = 4 Hz), 2.70 (1H, m), 2.90 (1H, m), 3.68 (3H, s), 3.74 (3H, s), 4.03 (1H, d, J = 4 Hz), 4.26 (1H, d, J = 3 Hz), 4.40−4.67 (5H, m), 4.86 (1H, s), 5.38 (1H, m).

(2aα,4aα,7β,7aα,7bα)-2,2a,4a,7,7a,7b-Hexahydro-2a,7b-dihydroxy-6-methyl-7-[(triethylsilyl)oxy]-4*H*-furo[2,3,4-*cd*]benzofuran-4-one (46) and Methyl (3aα,4β,7β,7a)-Octahydro-6-methylene-7-[(triethylsilyl)-oxy]-3-oxo-4-benzofurancarboxylate (47). To a stirred suspension of the mixture of **44** and **45** (52 mg, 0.12 mmol) and sodium bicarbonate (15 mg) in methylene chloride (5 mL) was added a solution of *m*-chloroperoxybenzoic acid (29.2 mg, 0.14 mmol) in methylene chloride (2 mL) dropwise at 0 °C during 5 min. The mixture was stirred at 0 °C for 30 min, diluted with ether (15 mL), and washed with saturated, aqueous sodium bisulfite, saturated, aqueous sodium bicarbonate, and brine, and dried (magnesium sulfate). The solution was filtered, and the filtrate was evaporated under reduced pressure. The residual colorless oil was chromatographed on silica, using 10% ethyl acetate in hexane as eluant, to yield 12 mg (28%) of **46** and 4.10 mg (10%) of **47**.

46: IR (neat) 3420, 3916, 1762, 1237, 1076 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.68 (6H, q, J = 8 Hz), 0.95 (9H, t, J = 8 Hz), 1.85 (3H, s), 3.19 (1H, m), 3.31 (1H, s), 3.56 (1H, d, J = 10 Hz), 3.87 (1H, d, J = 4 Hz), 4.17 (1H, d, J = 10 Hz), 4.41 (1H, m), 5.50 (1H, m); MS *m/z* 313 (M^+ − 29), 279, 167; HRMS *m/z* 313.1107 (calcd for $C_{14}H_{21}O_6Si$: 313.1107).

47: IR (neat) 1771, 1752, 1709, 1437, 1264 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.55 (6H, q, J = 8 Hz), 0.90 (9H, t, J = 8 Hz), 2.36 (1H, dd, J = 14 and 14 Hz), 2.54 (1H, dd, J = 13 and 14 Hz), 2.74 (1H, dd, J = 13 and 13 Hz), 3.80 (3H, s), 4.00 (1H, d, J = 4 Hz), 4.10 and 4.25 (2H, 2d, J = 16 Hz), 4.40 (1H, d, J = 4 Hz), 4.85 (1H, s), 4.95 (1H, s), 4.97 (1H, s); ^{13}C NMR ($CDCl_3$) δ 4.6, 6.6, 27.0, 44.6, 52.5, 69.3, 74.8, 75.5, 84.3, 113.1, 144.0, 173.3, 207.9; MS *m/z* 356 (M^+), 328, 327, 309, 298, 297, 281, 269; HRMS *m/z* 356.1656 (calcd for $C_{17}H_{28}O_6Si$: 356.1656). Anal. Calcd for $C_{17}H_{28}O_6Si$: C, 57.28; H, 7.92. Found: C, 56.98; H, 7.84.

Methyl (3aα,3bα,4aα,5β,5aα)-Hexahydro-4a-methyl-3-oxo-5-[(triethylsilyl)oxy]cyclopropa[3,4]cyclopenta[1,2-*b*]furan-3b(2*H*)-carboxylate (48). To a stirred solution of **20** (6.2 mg, 0.027 mmol) in methylene chloride (4 mL) were added triethylamine (0.016 mL, 0.112 mmol) and triethylsilyl trifluoromethanesulfonate (0.025 mL, 0.112 mmol). After 6 h, the mixture was diluted with ether, washed with saturated, aqueous sodium bicarbonate and brine, and dried (magnesium sulfate). The solution was filtered and concentrated to give a light yellow oil that was chromatographed on silica, using successively 10% and 20% ethyl acetate in hexane as eluants, to afford 8.0 mg (87%) of **48**: IR (neat) 2916, 1765, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.67 (6H, q, J = 8 Hz), 0.76 (1H, d, J = 5 Hz), 0.97 (9H, t, J = 8 Hz), 1.08 (1H, d, J = 5 Hz), 1.42 (3H, s), 3.18 (1H, d, J = 8 Hz), 3.75 (3H, s), 4.04 and 4.13 (2H, d, J = 16 Hz), 4.12 (1H, d, J = 5 Hz), 4.44 (1H, dd, J = 5 and 8 Hz); ^{13}C NMR ($CDCl_3$) δ 0.0, 4.9, 6.8, 14.4, 25.7, 33.6, 36.6, 51.2, 51.7, 73.3, 81.6, 171.7, 211.6; MS *m/z* 340 (M^+), 311, 283, 253; HRMS *m/z* 340.1706 (calcd for $C_{17}H_{28}O_5Si$: 340.1706). Anal. Calcd for $C_{17}H_{28}O_5Si$: C, 60.00; H, 7.92. Found: C, 59.84; H, 7.81.

(2aα,4aα,5aα,6aα,6bα,6cα)-Octahydro-2a-methoxy-5a-methyl-4*H*-furo[2,3,4-*cd*]oxireno[*g*]benzofuran-4-one (49). To a solution of **20** (81.0 mg, 0.36 mmol) in dry methanol (4 mL) was added a solution of sodium (16.5 mg, 0.72 mmol) in dry methanol (3 mL) via cannula. The resulting mixture was stirred at 0 °C for 15 min and for 1.5 h at room temperature and was partitioned between ethyl acetate and saturated, aqueous sodium chloride. The aqueous layer was thoroughly extracted with ethyl acetate, and the combined organic layers were dried (magnesium sulfate), filtered, and concentrated under reduced pressure. The residue was chromatographed on silica, eluting with 60% ethyl acetate in hexane, to give 63.8 mg (79%) of **49** as a crystalline solid: mp 123−124 °C; IR (neat) 1780, 1440, 1380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (3H, s), 2.03 (1H, dd, J = 6 and 15 Hz), 2.50 (1H, dd, J = 1 and 15 Hz), 2.85 (2H, m), 3.17 (1H, d, J = 2 Hz), 3.39 (3H, s), 4.07 and 4.12 (2H, 2d, J = 10 Hz), 4.63 (1H, dd, J = 2 and 9 Hz); MS *m/z* 226 (M^+), 195, 194, 169, 167, 93; HRMS *m/z* 226.0839 (calcd for $C_{11}H_{14}O_5$: 226.0841). Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.50; H, 6.38.

Compound **49** crystallized in space group $P2_12_12_1$ with a = 12.705-(2) Å, b = 5.725(1) Å, c = 14.617(2) Å, α = 90°, β = 90°, γ = 90°, V = 1063 Å^3, Z = 2, d_{calc} = 1.41 g/cm^3, and d_{obsd} = 1.43 g/cm^3. All nonequivalent reflections in the range $2° < 2\theta < 65°$ were measured by the $\theta-2\theta$ technique on a Syntex P1 diffractometer with graphite-monochromatized Mo Kα radiation. After refinement, a total of 1690 independent reflections having $F^2 > 3\alpha(F^2)$ afforded R = 0.043 and R_w = 0.053.

(2aα,4aα,5aα,6aα,6bα,6cα)-Octahydro-2a-hydroxy-5a-methyl-4*H*-furo[2,3,4-*cd*]oxireno[*g*]benzofuran-4-one (50). To a stirred solution of **20** (22 mg, 0.097 mmol) in methanol and water (1:1) (5 mL) was added potassium carbonate (5.5 mg, 0.097 mmol) in water at 0 °C. After being stirred for 1 h at room temperature, the mixture was acidified with 1 N hydrochloric acid and extracted with ethyl acetate (3×). The combined extracts were washed with aqueous sodium bicarbonate and brine and dried (magnesium sulfate). Evaporation of the solvent under reduced pressure gave a light yellow oil that was chromatographed on silica, using 70% ethyl acetate in hexane as eluant, to give 6.0 mg (39%) of **50**: IR (neat) 3414, 1761 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (3H, s), 2.02 (1H, dd, J = 6 and 15 Hz), 2.48 (1H, dd, J = 1 and 15 Hz), 2.82 (1H, dd, J = 4 and 10 Hz), 3.00 (1H, m), 3.17 (1H, d, J = 2 Hz), 3.76 (1H, s), 3.94 (1H, d, J = 10 Hz), 4.15

(1H, d, J = 10 Hz), 4.66 (1H, dd, J = 9 and 2 Hz); MS m/z 212 (M^+), 194, 186, 167; HRMS m/z 212.0685 (calcd for $C_{10}H_{12}O_5$: 212.0685).

(2aα,4aα,7β,7aα,7bα)-2,2a,4a,7,7a,7b-Hexahydro-2a-methoxy-6-methyl-7-[(triethylsilyl)oxy]-4*H*-furo[2,3,4-*cd*]benzofuran-3-one (51). To a solution of **49** (88.0 mg, 0.39 mmol) in dry methylene chloride (3 mL) were added 2,6-lutidine (0.18 mL, 1.56 mmol) and triethylsilyl trifluoromethanesulfonate (0.26 mL, 1.17 mmol). The mixture was stirred for 2.5 h at room temperature, diluted with ether, washed with saturated, aqueous sodium bicarbonate and brine, and dried (magnesium sulfate). The solvent was evaporated to give an oily residue that was chromatographed on silica, using 30% ethyl acetate in hexane as eluant, to furnish 103 mg (78%) of **51**: IR (neat) 1780, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.65 (6H, q, J = 8 Hz), 0.94 (9H, t, J = 8 Hz), 1.82 (3H, d, J = 2 Hz), 3.02 (1H, m), 3.30 (1H, m), 3.42 (3H, s), 3.91 and 4.22 (2H, 2d, J = 11 Hz), 4.16 (1H, dd, J = 4 and 6 Hz), 5.55 (1H, bs); ^{13}C NMR ($CDCl_3$) δ 4.9, 5.5, 6.7, 19.4, 39.1, 44.6, 52.8, 68.5, 75.2, 78.9, 116.2, 136.6, 174.6; MS m/z 340 (M^+), 311, 223, 175, 119; HRMS m/z 340.1752 (calcd for $C_{17}H_{28}O_5Si$: 340.1706).

(2aα,4aα,7β,7aα,7bα)-2,2a,4a,7,7a,7b-Hexahydro-2a,7-bis[(triethylsilyl)oxy]-4*H*-furo[2,3,4-*cd*]benzofuran-4-one (53). To a stirred solution of **50** (6.0 mg, 0.028 mmol) in methylene chloride (3 mL) were added 2,6-lutidine (0.013 mL, 0.112 mmol) and triethylsilyl trifluoromethanesulfonate (0.026 mL, 0.112 mmol). After 5 h, the mixture was diluted with ether, washed with saturated, aqueous sodium bicarbonate and brine, and dried (magnesium sulfate). The solution was concentrated to give material that was chromatographed on silica, using 10% ethyl acetate in hexane as eluant, to afford 8.0 mg (64%) of **53**: IR (neat) 2915, 1786, 1736, 1269, 1237, 1103 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.63 (12H, m), 0.92 (18H, m), 1.81 (3H, m), 2.87 (1H, dd, J = 5 and 6 Hz), 3.30 (1H, m), 3.54−4.21 (3H, m), 4.42 (1H, m), 5.55 (1H, m); MS m/z 440 (M^+), 411, 279, 275; HRMS m/z 440.2430 (calcd for $C_{22}H_{40}O_5Si_2$: 440.2414).

Methyl (3aα,7β,7aα)-2,3,3a,6,7,7a-Hexahydro-6-methyl-3-oxo-7-[(triethylsilyl)oxy]-4-benzofurancarboxylate (54). To a solution of **53** (20.0 mg, 0.06 mmol) in methanol was added potassium carbonate (16.5 mg, 0.12 mmol). After stirring for 2 h, the mixture was partitioned between ether and water. The aqueous layer was thoroughly extracted with ether, and the combined ether layers were washed with saturated, aqueous sodium chloride and dried (magnesium sulfate). After removal of the solvent, the residue was chromatographed on silica, using 30% ethyl acetate in hexane as eluant, to give 14 mg (70%) of **54**: IR (neat) 1770, 1720, 1440, 1420 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.63 (6H, q, J = 8 Hz), 0.93 (9H, t, J = 8 Hz), 1.16 (3H, d, J = 8 Hz), 2.43 (1H, m), 3.65 (1H, d, J = 9 Hz), 3.80 (3H, s), 4.09 (1H, m), 4.13 (2H, d, J = 26 Hz), 4.59 (1H, dd, J = 3 and 9 Hz), 6.56 (1H, br s); MS m/z 340 (M^+), 311, 283; HRMS m/z 340.1741 (calcd for $C_{17}H_{28}O_5Si$: 340.1706). Anal. Calcd for $C_{17}H_{28}O_5Si$: C, 60.00; H, 7.92. Found: C, 60.40; H, 8.02.

(2aα,4aα,7β,7aα,7bα)-2,2a,4a,7,7a,7b-Hexahydro-2a-methoxy-7-hydroxy-4*H*-furo[2,3,4-*cd*]benzofuran-4-one (55). To a solution of **53** (66 mg, 0.19 mmol) in tetrahydrofuran (3 mL) and water (0.5 mL) was added trifluoroacetic acid (2 drops). The solution was stirred for 1 h at room temperature and partitioned between ethyl acetate and saturated, aqueous sodium bicarbonate. The aqueous phase was extracted with ethyl acetate (3×) and the combined organic extracts were washed with brine and dried (magnesium sulfate). The solvent was removed, and the residue was chromatographed on silica, eluting with 70% ethyl acetate in hexane, to give 24 mg (55%) of **55** as a colorless oil: $[\alpha]^{23}_D$ +25.4° (c 1.25, $CHCl_3$); IR (neat) 3489, 2877, 1774, 1235, 1205, 1101, 1062, 1043, 944 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85 (3H, br s), 2.25 (1H, m), 3.03 (1H, dd, J = 11 and 6 Hz), 3.32 (1H, m), 3.43 (3H, s), 3.73 (1H, d, J = 10 Hz), 4.19 (1H, d, J = 10 Hz), 4.26 (2H, m), 5.57 (1H, br s); ^{13}C NMR ($CDCl_3$) δ 19.0, 38.8, 43.8, 52.8, 67.5, 74.8, 77.6, 116.4, 118.2, 136.0, 174.4; MS m/z 226 (M^+), 169, 137, 122, 110, 109, 100, 94, 93, 83. Anal. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.46; H, 6.09.

(2aα,4aα,7β,7aα,7bα)-2,2a,4a,7,7a,7b-Hexahydro-2a-methoxy-7-[[2-(trimethylsilyl)ethoxy]methoxy]-4*H*-furo[2,3,4-*cd*]benzofuran-4-one (56). To a solution of **55** (24 mg, 0.11 mmol) in methylene chloride (2 mL) were added diisopropylethylamine (92 μL, 0.53 mmol) and [2-(trimethylsilyl)ethoxy]methyl chloride (75 μL, 0.42 mmol). The solution was heated at reflux for 3 h. After cooling, the mixture was partitioned between methylene chloride and water and the aqueous phase was extracted with methylene chloride (3×). The combined organic extracts were washed with brine and dried (magnesium sulfate). After removal of the solvent, the residue was chromatographed on silica, eluting with 40% ethyl acetate in hexane, to give 34 mg (89%) of **56** as a colorless oil: $[\alpha]^{24}_D$ +33.4° (c 1.82, $CHCl_3$); IR (neat) 2953, 1780, 1248, 1235, 1205, 1058, 1035, 940, 861, 834 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (9H, s), 0.95 (2H, m), 1.83 (3H, br s), 3.02 (1H, dd, J = 11 and 6 Hz), 3.32 (1H, m), 3.43 (3H, s), 3.70 (3H, m), 4.22 (1H, d, J = 10 Hz), 4.30 (1H, m), 4.34 (1H, d, J = 10 Hz), 4.77 (1H, d, J = 7 Hz), 4.87 (1H, d, J = 7 Hz), 5.6 (1H, br s); ^{13}C NMR ($CDCl_3$) δ −1.5, 18.2, 19.3, 39.0, 44.1, 65.5, 72.8, 75.3, 94.6, 117.0, 118.1, 134.8, 174.5.

Methyl (3aα,7β,7aα)-2,3,3a,6,7,7a-Hexahydro-6-methyl-3-oxo-7-[[2-(trimethylsilyl)ethoxy]methoxy]-4-benzofurancarboxylate (57). To a solution of **56** (33.0 mg, 0.093 mmol) in dry methanol (3 mL) was added potassium carbonate (38 mg, 0.28 mmol). The mixture was stirred for 1 h at room temperature, diluted with ether, and washed with saturated, aqueous ammonium chloride. The aqueous phase was extracted with ether (2×), and the combined organic extracts were washed with brine and dried (magnesium sulfate). The solvent was removed, and the residue was chromatographed on silica, eluting with 40% ethyl acetate in hexane, to afford 24 mg (73%) of **57** as a colorless oil: $[\alpha]^{24}_D$ +51.9° (c 0.97, $CHCl_3$); IR (neat) 2953, 1766, 1721, 1263, 1248, 1025, 861, 837 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.02 (9H, s), 0.88 (2H, m), 1.22 (3H, d, J = 7 Hz), 2.51 (1H, m), 3.42 (1H, m), 3.72 (2H, m), 3.81 (3H, s), 3.97 (1H, dd, J = 3 and 2 Hz), 4.03 (1H, d, J = 16 Hz), 4.16 (1H, d, J = 16 Hz), 4.63 (1H, d, J = 7 Hz), 4.67 (1H, dd, J = 9 and 3 Hz), 4.81 (1H, d, J = 7 Hz), 6.64 (1H, br s); ^{13}C NMR ($CDCl_3$) δ −1.5, 15.9, 18.0, 34.6, 44.4, 52.0, 66.3, 70.0, 77.2, 78.3, 96.0, 124.3, 142.7, 166.0, 208.2. Anal. Calcd for $C_{17}H_{28}O_6Si$: C, 57.26; H, 7.92. Found: C, 56.93; H, 7.77.

Methyl (7α,7aβ)-2,6,7,7a-Tetrahydro-3-[(trimethylsilyl)oxy]-6-methyl-7-[[2-(trimethylsilyl)ethoxy]methoxy]-4-benzofurancarboxylate (58). To a solution of **57** (12 mg, 0.034 mmol) in methylene chloride (1 mL) at 0 °C were added 2,6-lutidine (16 μL, 0.13 mmol) and triethylsilyl trifluoromethanesulfonate (23 μL, 0.10 mmol). The solution was allowed to warm to room temperature and was stirred for 2 h. The solution was diluted with methylene chloride and poured into saturated, aqueous sodium bicarbonate. The aqueous phase was extracted with methylene chloride (3×) and the combined extracts were washed with brine and dried (sodium sulfate). After removal of the solvent, chromatography on Florisil, using 20% ethyl acetate in hexane as eluant, afforded 13.3 mg (84%) of **58** as an unstable, colorless oil: ^1H NMR ($CDCl_3$) δ 0.01 (9H, s), 0.67 (6H, m), 0.97 (11H, m), 1.20 (3H, d, J = 7 Hz), 2.69 (1H, m), 3.53 (1H, m), 3.76 (3H, s), 3.77 (1H, m), 3.94 (1H, m), 4.43 (1H, dd, J = 12 and 5 Hz), 4.62 (1H, dd, J = 12 and 3 Hz), 4.70 (1H, d, J = 7 Hz), 4.93 (1H, m), 4.94 (1H, d, J = 7 Hz), 6.13 (1H, d, J = 2 Hz). This material was used promptly in the next reaction.

Methyl (3aα,7β,7aα)-2,3,3a,6,7,7a-Hexahydro-3a-hydroxy-6-methyl-3-oxo-7-[[2-(trimethylsilyl)ethoxy]methoxy]-4-benzofurancarboxylate (59). To a solution of **58** (11.5 mg, 0.024 mmol) in methylene chloride (0.5 mL) at 0 °C was added dropwise a solution of *m*-chloroperoxybenzoic acid (5.5 mg, 0.027 mmol) in methylene chloride (0.5 mL). After stirring for 30 min at 0 °C, the solution was diluted with methylene chloride, washed with aqueous sodium sulfite, aqueous sodium bicarbonate, and brine, and dried (magnesium sulfate). After removal of the solvent, chromatography on silica, using 35% ethyl acetate in hexane as eluant, afforded 5.2 mg (57%) of **59**: $[\alpha]^{24}_D$ +66.0° (c 0.52, $CHCl_3$); IR (neat) 3500, 2954, 1773, 1701, 1264, 1249, 1021, 861, 837 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (9H, s), 0.93 (2H, m), 1.27 (3H, d, J = 7 Hz), 2.75 (1H, m), 3.55 (1H, m), 3.74 (1H, m), 3.83 (3H, s), 4.05 (1H, dd, J = 4 and 3 Hz), 4.13 (1H, d, J = 17 Hz), 4.31 (1H, d, J = 17 Hz), 4.35 (1H, d, J = 3 Hz), 4.70 (1H, d, J = 7 Hz), 4.83 (1H, d, J = 7 Hz), 5.27 (1H, s), 6.95 (1H, d, J = 3 Hz); ^{13}C NMR ($CDCl_3$) δ −1.5, 15.3, 18.0, 34.2, 52.3, 66.1, 68.9, 74.4, 76.0, 83.9, 95.4, 124.4, 148.0, 166.9, 208.7; MS m/z 300, 282, 268, 242, 224, 199, 168, 152, 136, 109, 73.

Methyl (3aα,6β,7β,7aα)-2,3,3a,6,7,7a-Hexahydro-6-methyl-3-oxo-3a-[(triethylsilyl)oxy]-7-[[2-(trimethylsilyl)ethoxy]methoxy]-4-benzofurancarboxylate (60). To a solution of **59** (4.2 mg, 0.011 mmol) in methylene chloride (1 mL) was added dropwise 2,6-lutidine (4 μL,

0.034 mmol), followed by triethylsilyl trifluoromethanesulfonate (3.8 μL, 0.017 mmol). After 4 h, the mixture was diluted with ether, washed with saturated, aqueous sodium bicarbonate and brine, and dried (magnesium sulfate). The solvent was removed, and the residue was chromatographed, using 15% ethyl acetate in hexane as eluant, to give 4.9 mg (89%) of **60** as a colorless oil: $[\alpha]^{24}_D$ +46.0° (*c* 0.67, $CHCl_3$); IR (neat) 2954, 2878, 1780, 1723, 1250, 1249, 1114, 1049, 1034, 1003, 860, 836, 744, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (9H, s), 0.63 (6H, m), 0.93 (11H, m), 1.29 (3H, d, *J* = 7 Hz), 2.84 (1H, m), 3.66 (2H, q, *J* = 9 Hz), 3.73 (3H, s), 4.01 (1H, d, *J* = 17 Hz), 4.13 (1H, dd, *J* = 6 and 2 Hz), 4.21 (1H, d, *J* = 2 Hz), 4.22 (1H, d, *J* = 17 Hz), 4.77 (2H, dd, *J* = 10 and 7 Hz), 7.11 (1H, d, *J* = 5 Hz); ^{13}C NMR ($CDCl_3$) δ −1.5, 4.3, 6.2, 6.6, 6.9, 14.6, 18.1, 33.1, 51.7, 65.8, 69.4, 71.9, 77.2, 78.8, 84.3, 94.0, 126.0, 148.8, 166.0, 208.6.

Seco Ester 64. To a solution of **2**[28] (1.00 g, 1.71 mmol) in tetrahydrofuran (50 mL), water (13 mL), and methanol (13 mL) was added lithium hydroxide (718 mg, 17.1 mmol), and the solution was stirred for 40 h at room temperature. The mixture was cooled to 0 °C, acidified to pH 2 with 10% hydrochloric acid, and partitioned between methylene chloride and water. The separated aqueous phase was extracted with methylene chloride (3×), and the combined organic extracts were washed with brine, dried (magnesium sulfate), and concentrated to give a yellow foam that was taken up in ether and treated with an excess of ethereal diazomethane. After removal of the solvent, chromatography on silica, using 80% ethyl acetate in hexane as eluant, afforded 493 mg (47%) of **62** as a pale yellow foam: ^1H NMR ($CDCl_3$) δ 0.84−1.00 (11H, m), 1.12−1.28 (5H, m), 1.34−1.42 (2H, m), 1.53−1.61 (7H, m), 1.90 (1H, d, *J* = 9 Hz), 1.91−2.02 (2H, m), 2.19−2.26 (2H, m), 2.32−2.39 (2H, m), 2.59 (1H, m), 3.40 (1H, dd, *J* = 10 and 1 Hz), 3.55 (1H, dt, *J* = 9 and 2 Hz), 3.69−3.81 (2H, m), 3.78 (3H, s), 4.04 (1H, d, *J* = 2 Hz), 4.12 (1H, m), 4.50 (1H, dd, *J* = 14 and 2 Hz), 4.61 (1H, dd, *J* = 14 and 2 Hz), 4.82 (1H, s), 5.41 (1H, t, *J* = 7 Hz), 5.56 (1H, dd, *J* = 10 and 2 Hz), 5.64−5.74 (2H, m), 5.69 (1H, dd, *J* = 15 and 11 Hz), 6.32 (1H, d, *J* = 11 Hz), 6.64 (1H, d, *J* = 2 Hz). There was also isolated 140 mg (13%) of a mixture of the 4α-methyl and 4β-methyl seco esters from which pure 4β-methyl seco ester could be obtained after a second passage of the mixture through a silica column.

To a solution of **62** (126 mg, 0.20 mmol) in dimethylformamide (1 mL) were added imidazole (35 mg, 0.51 mmol) and *tert*-butyldimethylsilyl chloride (37 mg, 0.25 mmol). The mixture was stirred for 24 h at room temperature and was partitioned between ether and water. The aqueous phase was extracted with ether (3×) and the combined ethereal extracts were washed with water and brine and dried (magnesium sulfate). Removal of the solvent and chromatography of the residue on silica, eluting with a gradient from 50% ethyl acetate in hexane to pure ethyl acetate, provided 78 mg (52%) of **63**: ^1H NMR ($CDCl_3$) δ 0.05 (3H, s), 0.06 (3H, s), 0.81−0.94 (11H, m), 0.88 (9H, s), 1.16−1.32 (5H, m), 1.34−1.44 (2H, m), 1.54−1.60 (7H, m), 1.81−1.89 (2H, m), 2.15−2.24 (2H, m), 2.31−2.37 (2H, m), 2.59 (1H, m), 3.37 (1H, dd, *J* = 10 and 2 Hz), 3.37 (1H, dd, *J* = 10 and 2 Hz), 3.54 (1H, dd, *J* = 10 and 2 Hz), 3.66 (1H, d, *J* = 9 Hz), 3.75 (1H, m), 3.78 (3H, s), 4.05 (1H, d, *J* = 2 Hz), 4.10 (1H, m), 4.50 (1H, dd, *J* = 14 and 2 Hz), 4.66 (1H, dd, *J* = 14 and 2 Hz), 4.80 (1H, s), 5.44 (1H, t, *J* = 7 Hz), 5.54 (1H, dd, *J* = 10 and 2 Hz), 5.56−5.72 (2H, m), 5.97 (1H, dd, *J* = 15 and 11 Hz), 6.31 (1H, dt, *J* = 9 and 2 Hz), 6.63 (1H, d, *J* = 2 Hz). In addition, 25 mg of recovered **62** was isolated.

To a solution of **63** (298 mg, 0.41 mmol) in methylene chloride (5 mL) were added diisopropylethylamine (0.284 mL, 1.63 mmol) and [2-(trimethylsilyl)ethoxy]methyl chloride (0.217 mL, 1.22 mmol), and the solution was heated at reflux for 6 h. After cooling, the mixture was partitioned between methylene chloride and water and the aqueous phase was extracted with methylene chloride (3×). The combined organic extracts were washed with brine, dried (magnesium sulfate), and concentrated. Chromatography of the residue on silica, eluting with 20% ethyl acetate in hexane, gave 319 mg (79%) of **64** as a white foam: ^1H NMR ($CDCl_3$) δ 0.01−0.03 (24H, m), 0.79−1.02 (24H, m), 1.16−1.29 (2H, m), 1.21 (3H, d, *J* = 7 Hz), 1.34−1.44 (3H, m), 1.50−1.58 (7H, m), 1.81−1.88 (2H, m), 2.15−2.22 (2H, m), 2.31−2.43 (2H, m), 2.76 (1H, m), 3.37−3.48 (2H, m), 3.58 (1H, dd, *J* = 10 and 2 Hz), 3.62−3.78 (5H, m), 3.73 (3H, s), 4.10 (2H, m), 4.47 (2H, m), 4.63 (1H, m), 4.74 (1H, d, *J* = 7 Hz), 4.87 (1H, d, *J* = 7 Hz), 5.39 (1H, m), 5.54 (1H, dd, *J* = 10 and 3 Hz), 5.69 (1H, dd, *J* = 10 and 2 Hz), 5.87 (1H, m), 6.28 (1H, d, *J* = 10 Hz), 6.60 (1H, d, *J* = 2 Hz).

Ozonolysis of 64. To a solution of **64** (319 mg, 0.32 mmol) in methylene chloride (9 mL) and ethanol (3 mL) was added one drop of a solution of Sudan 7B in ethanol. The solution was cooled to −78 °C and purged with argon for 10 min. Ozone was introduced (flow rate of 2.0 L/min, 0.40 A) in 10−20 s intervals until complete consumption of the starting material was observed. The solution was purged with argon for 10 min, and sodium borohydride (250 mg) was added in one portion. The mixture was allowed to warm to room temperature and was stirred for 1 h. An aqueous solution of potassium dihydrogen phosphate was added dropwise until evolution of hydrogen ceased. The mixture was partitioned between methylene chloride and aqueous potassium dihydrogen phosphate, and the aqueous phase was extracted with methylene chloride (3×). The combined organic extracts were washed with brine, dried (magnesium sulfate), and concentrated. Chromatography of the residue on silica, eluting with a gradient from 30% ethyl acetate in hexane to pure ethyl acetate, afforded 121 mg (60%) of **65** and 108 mg (84%) of **66** as colorless oils.

65: $[\alpha]^{23}_D$ −15.0° (*c* 2.95, $CHCl_3$); IR (neat) 3500, 2959, 2931, 2885, 1112, 1072, 1037, 995, 863, 837 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (9H, s), 0.05 (6H, s), 0.74 (3H, d, *J* = 7 Hz), 0.88 (9H, s), 0.91 (11H, m), 1.20 (2H, m), 1.40 (3H, m), 1.55 (3H, s), 1.57 (2H, m), 1.85 (2H, m), 1.95 (1H, m), 2.20 (2H, m), 2.33 (1H, m), 3.37 (1H, dd, *J* = 10 and 1 Hz), 3.49 (1H, m), 3.64 (2H, m), 3.78 (2H, m), 4.10 (1H, m), 4.53 (1H, d, *J* = 7 Hz), 4.59 (1H, d, *J* = 7 Hz), 5.41 (1H, t, *J* = 7 Hz), 5.54 (1H, dd, *J* = 10 and 3 Hz), 5.69 (1H, dd, *J* = 10 and 2 Hz); ^{13}C NMR ($CDCl_3$) δ −4.7, −1.4, 10.9, 12.3, 12.5, 14.1, 16.5, 18.1, 18.2, 25.9, 27.9, 30.5, 34.3, 35.3, 37.0, 40.8, 44.7, 65.5, 65.6, 67.5, 68.8, 75.2, 77.6, 91.4, 95.6, 127.1, 128.5, 134.0, 135.0; MS *m/z* 626 (M^+), 608, 567, 551, 509, 449, 401, 353, 309, 255, 221, 187, 131, 73. Anal. Calcd for $C_{34}H_{66}O_6Si_2$: C, 65.12; H, 10.61. Found: C, 64.99; H, 10.86.

66: ^1H NMR ($CDCl_3$) δ 0.00 (9H, s), 0.92 (2H, t, *J* = 7 Hz), 1.27 (3H, d, *J* = 7 Hz), 2.74 (1H, m), 3.63 (1H, d, *J* = 6 Hz), 3.67 (2H, t, *J* = 6 Hz), 3.79 (3H, s), 4.13 (3H, m), 4.41 and 4.58 (2H, 2d, *J* = 12 Hz), 4.77 and 4.87 (2H, AB q, *J* = 7 Hz), 5.91 (1H, m), 6.86 (1H, d, *J* = 5 Hz).

Methyl (3aα,6α,7β,7aα)-2,3,3a,6,7,7a-Hexahydro-6-methyl-3(*E*)-[2-[(triethylsilyl)oxy]ethylidene]-3a-[(triethylsilyl)oxy]-7-[[2-(trimethylsilyl)ethoxy]methoxy]-4-benzofurancarboxylate (67). To a solution of **66** (15.0 mg, 0.038 mmol) in methylene chloride (10 mL) at 0 °C was added pyridine (26 μL, 0.23 mmol), followed by triethylsilyl trifluoromethanesulfonate (34 μL, 0.15 mmol). The solution was stirred for 15 min and poured into saturated, aqueous sodium bicarbonate, and the separated aqueous layer was extracted with methylene chloride (2×). The combined organic extract was dried (magnesium sulfate) and concentrated, and the residue was chromatographed on silica, eluting with 15% ethyl acetate in hexane, to give 22 mg (93%) of **67**: ^1H NMR ($CDCl_3$) δ 0.01 (9H, s), 0.59 (6H, q, *J* = 8 Hz), 0.66 (6H, q, *J* = 8 Hz), 0.95 (9H, t, *J* = 6 Hz), 0.97 (9H, t, *J* = 6 Hz), 1.21 (3H, d, *J* = 7 Hz), 2.69 (1H, m), 3.57−3.74 (5H, m), 3.70 (3H, s), 4.03 (1H, d, *J* = 2 Hz), 4.15 (2H, d, *J* = 5 Hz), 4.36 (1H, d, *J* = 14 Hz), 4.55 (1H, d, *J* = 14 Hz), 4.75 (1H, d, *J* = 7 Hz), 4.87 (1H, d, *J* = 7 Hz), 6.01 (1H, m), 6.69 (1H, d, *J* = 2 Hz).

Methyl (3aα,6α,7β,7aα)-2,3,3a,6,7,7a-Hexahydro-6-methyl-3-oxo-3a-[(triethylsilyl)oxy]-7-[[2-(trimethylsilyl)ethoxy]methoxy]-4-benzofurancarboxylate (68). A solution of **67** (72 mg, 0.11 mmol) in methylene chloride (4 mL) and ethanol (1 mL) was cooled to −78 °C, and argon was bubbled through the solution for 10 min. Ozone was introduced (flow rate of 2.0 L/min, 0.40 A) in 10 s intervals until complete consumption of the starting material had occurred (~40 s). Argon was bubbled through the mixture for 10 min, dimethyl sulfide (10 mL) was added, and the mixture was allowed to warm to room temperature and was stirred for 1 h. Removal of the solvent and chromatography of the residue, eluting with 20% ethyl acetate in hexane, provided 52 mg (93%) of **68** as a colorless oil: $[\alpha]^{23}_D$ +180.0° (*c* 0.51, $CHCl_3$); IR (neat) 1779, 1724, 1250, 1121, 1046, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (9H, s), 0.63 (2H, t, *J* = 8 Hz), 0.65 (2H, t, *J* = 8 Hz), 0.67 (2H, t, *J* = 8 Hz), 0.88 (2H, t, *J* = 7 Hz), 0.96 (9H, t, *J* = 7 Hz), 1.27 (3H, d, *J* = 7 Hz), 2.81 (1H, m), 3.61−3.77 (3H, m), 3.72 (3H, s), 3.98 (1H, d, *J* = 17 Hz), 4.25 (1H, d, *J* = 17 Hz), 4.26 (1H, d, *J* = 2 Hz), 4.77 (1H, d, *J* = 7 Hz), 4.87 (1H, d, *J* = 7

Hz), 6.96 (1H, d, $J = 2$ Hz); ^{13}C NMR ($CDCl_3$) δ −1.5, 6.2, 6.9, 16.7, 18.1, 32.6, 51.7, 65.4, 69.7, 77.0, 79.4, 81.4, 94.7, 125.9, 149.2, 165.8, 209.1. Anal. Calcd for $C_{23}H_{42}O_7Si_2$: C, 56.75; H, 8.70. Found: C, 56.49; H, 8.81.

(*S*)-(−)-2-Methylbutanal (69). A solution of oxalyl chloride (5.40 mL, 62.4 mmol) in methylene chloride (142 mL) was placed in a 500 mL three-necked flask equipped with a mechanical stirrer and two pressure-equalizing dropping funnels containing dimethyl sulfoxide (8.90 mL, 125 mmol) in methylene chloride (30.0 mL) and (*S*)-(−)-2-methyl-1-butanol (5.00 g, 57.0 mmol) in methylene chloride (60.0 mL). The two solutions were added simultaneously and dropwise to the oxalyl chloride solution at −65 °C, and the mixture was stirred for 15 min. Triethylamine (39.7 mL, 284 mmol) was added, and the mixture was stirred for a further 10 min before it was warmed to room temperature. Water (300 mL) was added to the reaction mixture, and the aqueous layer was separated and extracted twice with methylene chloride (150 mL). The combined organic layers were washed with 2% aqueous hydrochloric acid until the aqueous layer was slightly acidic (pH ~ 3). The organic phase was then washed with a 20 mL portion of 5% aqueous sodium carbonate solution and dried (sodium sulfate). Distillation using a Vigreux column removed methylene chloride and dimethyl sulfide, and the residue was distilled through a short-path column to give 3.98 g (82%) of **69**: bp 82−85 °C; $[\alpha]^{25}_D$ +32.6° (*c* 2.73, acetone); IR (neat) 2725, 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (3H, t, $J = 7$ Hz), 1.09 (3H, d, $J = 7$ Hz), 1.44 (1H, m), 1.75 (1H, m), 2.28 (1H, m), 9.63 (1H, d, $J = 2$ Hz); ^{13}C NMR ($CDCl_3$) δ 10.5, 12.2, 23.1, 47.2, 203.9; MS *m/z* 86 (M^+), 57, 29. The aldehyde was found to undergo trimerization and was used promptly.

(3*S*,4*R*,5*S*)-4-Hydroxy-3,5-dimethyl-1-heptene (70). To a solution of chromium trichloride (13.1 g, 83.1 mmol) in tetrahydrofuran (80 mL) at 0 °C was added lithium aluminum hydride (1.50 g, 41.8 mmol) in small portions over a period of 0.5 h, during which the mixture changed from purple to dark green. The mixture was stirred for 10 min, and a solution containing **69** (1.50 g, 16.6 mmol) and crotyl bromide (5.60 g, 41.1 mmol) in tetrahydrofuran (55.0 mL) was added. The resulting mixture was stirred for 3 h at room temperature, during which its color changed to dark brown. Water (150 mL) was added, followed by ether (75 mL). The aqueous layer was separated and extracted with ether (2 × 20 mL), and the organic layers were combined, washed with brine (2 × 25 mL), and dried (sodium sulfate). The solvent was removed by distillation, and the residue was purified by chromatography on silica, using 10% ether in pentane as eluant, to yield 1.30 g (53%) of **70**: $[\alpha]^{25}_D$ +1.43° (*c* 0.82, $CHCl_3$); IR (neat) 3410, 1640, 1420 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, d, $J = 6$ Hz), 0.92 (3H, t, $J = 5$ Hz), 0.98 (3H, d, $J = 7$ Hz), 1.43 (1H, m), 1.5 (3H, m), 2.29 (1H, m), 3.23 (1H, dd, $J = 4$ and 2 Hz), 5.13 (2H, m), 5.75 (1H, m); MS *m/z* 125 ($M^+ - 17$), 87, 85, 69, 57, 55. Alcohol **70** was further characterized as its 3,5-dinitrobenzoate: $[\alpha]^{25}_D$ −3.98° (*c* 0.44, $CHCl_3$). Anal. Calcd for $C_{16}H_{20}N_2O_6$: C, 57.17; H, 5.99; N, 8.33. Found: C, 57.19; H, 5.92; N, 8.11.

(3*S*,4*R*,5*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3,5-dimethyl-1-heptene (73). To a solution of **70** (1.00 g, 7.00 mmol) in methylene chloride (60 mL) was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (2.10 mL, 9.10 mmol). The mixture was stirred for 3 h and poured into a saturated, aqueous solution of sodium bicarbonate (70 mL). The aqueous layer was separated and washed with methylene chloride (3 × 50 mL). The organic layers were combined, dried (sodium sulfate), and concentrated, and the residue was purified by chromatography on silica, using 8% ethyl acetate in hexane as eluant, to give 1.51 g (86%) of **73**: $[\alpha]^{25}_D$ −2.06° (*c* 2.77, $CHCl_3$); IR (neat) 1640, 1420 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.03 (3H, s), 0.04 (3H, s), 0.84 (3H, t, $J = 5$ Hz), 0.85 (3H, d, $J = 6$ Hz), 0.89 (9H, s), 0.99 (3H, d, $J = 7$ Hz), 0.98−1.15 (1H, m), 1.38−1.47 (2H, m), 2.33 (1H, m), 3.38 (1H, t, $J = 4$ Hz), 4.90−4.96 (2H, m), 5.80−5.89 (1H, m); ^{13}C NMR ($CDCl_3$) δ −3.8, −2.9, 12.2, 14.7, 17.9, 25.7, 26.2, 38.9, 42.4, 79.3, 113.6, 142.4; MS *m/z* 256 (M^+), 241, 201, 199, 57.

(2*S*,3*R*,4*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]-2,4-dimethylhexanal (74). A solution of **73** (1.20 g, 4.70 mmol) in absolute methanol (50 mL) was cooled to −78 °C, and ozone gas was bubbled through the solution for 10 min. The blue solution was flushed with argon, and dimethyl sulfide (20 mL) was added slowly. The mixture was allowed to warm to room temperature and was stirred for 12 h. After the absence of ozonide was confirmed with starch paper, water (30 mL) was added followed by pentane (30 mL). The aqueous layer was separated and extracted with pentane (2 × 30 mL), and the organic layers were combined and dried (sodium sulfate). The solution was concentrated to give 1.19 g (92%) of **74**: $[\alpha]^{25}_D$ −38.8° (*c* 1.03, $CHCl_3$); IR (neat) 1730, 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.05 (3H, s), 0.06 (3H, s), 0.89 (15H, m), 1.08 (4H, m), 1.52 (2H, m), 2.54 (1H, m), 3.77 (1H, t, $J = 4$ Hz), 9.73 (1H, d, $J = 3$ Hz); ^{13}C NMR ($CDCl_3$) δ −4.3, −4.0, 12.2, 12.4, 14.4, 18.3, 25.7, 26.0, 40.0, 49.9, 78.1, 205.7; MS *m/z* 258 ($M^+ + 1$), 201, 131, 115, 57.

Aldehyde **74** was further characterized as its 2,4-dinitrophenylhydrazone: $[\alpha]^{25}_D$ +7.04° (*c* 0.49, $CHCl_3$). Anal. Calcd for $C_{20}H_{34}N_4O_5Si$: C, 54.80; H, 7.76; N, 12.79. Found C, 55.40; H, 7.99; N, 12.93.

(3*S*,4*R*,5*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3,5-dimethyl-1-heptyne (75). To a solution of **74** (0.90 g, 3.30 mmol) in methylene chloride (60 mL) was added freshly sublimed carbon tetrabromide (2.20 g, 7.00 mmol), and the mixture was stirred for 15 min. Activated zinc dust (0.40 g, 7.00 mmol) was added, and the solution was stirred for a further 15 min. A solution of triphenylphosphine (1.60 g, 7.00 mmol) in methylene chloride (30 mL) was added dropwise over 20 min, and the resulting brown mixture was stirred for 4 h. Removal of the solvent left a brown oil that was dissolved in acetonitrile (50 mL). The solution was extracted with pentane (3 × 30 mL), and the pentane extracts were combined and concentrated. Hexane (10 mL) was added to the residue, and the solution was allowed to stand for 4 h. The resultant precipitate was filtered off, and the filtrate was concentrated and subjected to chromatography on silica, using 5% ethyl acetate in hexane as eluant, to give 1.10 g (83%) of (3*S*,4*R*,5*S*)-1,1-dibromo-4-[(*tert*-butyldimethylsilyl)oxy]-3,5-dimethyl-1-heptene: $[\alpha]^{25}_D$ −2.27° (*c* 1.15, $CHCl_3$); IR (neat) 1650, 1125 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.05 (3H, s), 0.07 (3H, s), 0.87 (3H, t, $J = 7$ Hz), 0.87 (3H, d, $J = 7$ Hz), 0.92 (9H, s), 1.00 (3H, d, $J = 7$ Hz), 1.06 (1H, m), 1.48 (2H, m), 2.64 (1H, m), 3.46 (1H, t, $J = 4$ Hz), 6.45 (1H, d, $J = 10$ Hz); ^{13}C NMR ($CDCl_3$) δ −4.1, −3.9, 12.4, 14.9, 17.7, 18.3, 25.3, 26.1, 40.3, 41.6, 79.0, 87.1, 141.9; MS *m/z* 357 ($M^+ - 57$), 271, 201, 115, 57.

To a solution of the dibromo compound (0.20 g, 0.50 mmol) in tetrahydrofuran (10 mL) at −78 °C was added slowly a 1.5 M solution of *n*-butyllithium (0.8 mL, 1.25 mmol) in hexane. The mixture was stirred as it warmed slowly to room temperature during 0.5 h. A saturated, aqueous solution of ammonium chloride (7 mL) was added, and the mixture was extracted with ether (3 × 15 mL). The organic extract was dried (sodium sulfate) and concentrated, and the residual oil was purified by chromatography on silica, using 8% ethyl acetate in hexane as eluant, to give 0.12 g (86%) of **75**: $[\alpha]^{25}_D$ +3.36° (*c* 0.57, $CHCl_3$); IR (neat) 2114, 1125 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.06 (3H, s), 0.09 (3H, s), 0.88 (3H, t, $J = 7$ Hz), 0.88 (3H, d, $J = 7$ Hz), 0.91 (9H, s), 1.18 (3H, d, $J = 7$ Hz), 1.25 (1H, m), 1.52 (2H, m), 2.03 (1H, d, $J = 3$ Hz), 2.63 (1H, m), 3.53 (1H, d, $J = 4$ Hz); ^{13}C NMR ($CDCl_3$) δ −4.0, −3.9, 12.0, 14.4, 17.5, 18.4, 26.1, 27.1, 31.5, 38.4, 69.8, 77.6, 87.7; MS *m/z* 255 ($M^+ + 1$) 201, 197, 57. Anal. Calcd for $C_{15}H_{30}OSi$: C, 70.87; H, 11.81. Found C, 71.03; H, 11.74.

(3*R*)-1-[[(2,4,6-Triisopropylphenyl)sulfonyl]oxy]butan-3-ol (77). A solution of (*R*)-(−)-1,3-butanediol (2.50 g, 30 mmol) in pyridine (100 mL) was cooled to 0 °C, and 2,4,6-triisopropylbenzenesulfonyl chloride (11.70 g, 40 mmol) was added in several portions. The mixture was warmed to room temperature, stirred for 5 h, and poured into ice-cold 3 N hydrochloric acid (320 mL). The aqueous solution was extracted with ether (3 × 100 mL), and the organic extract was dried (sodium sulfate). The solvent was removed, and the residue was chromatographed on silica. Elution with 5% ethyl acetate in hexane, followed by crystallization from hexane, gave 6.01 g (62%) of **77**: mp 73−75 °C; $[\alpha]^{25}_D$ −6.25° (*c* 1.37, $CHCl_3$); IR (KBr) 3300, 1351, 1176 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (3H, d, $J = 6$ Hz), 1.26 (18H, d, $J = 7$ Hz), 1.76 (2H, m), 1.88 (1H, m), 2.91 (1H, septet, $J = 7$ Hz), 4.00 (1H, m), 4.14 (3H, m), 4.27 (1H, m), 7.19 (2H, s); ^{13}C NMR ($CDCl_3$) δ 23.6, 23.7, 24.7, 29.6, 34.3, 38.1, 64.2, 66.6, 123.8, 129.3, 150.8, 153.7; MS *m/z* 356 (M^+), 283, 267, 202, 187. Anal. Calcd for $C_{19}H_{32}O_4S$: C, 64.01; H, 9.04. Found: C, 63.74; H, 9.31.

(3*R*)-3-Acetoxy-1-[[(2,4,6-triisopropylphenyl)sulfonyl]oxy]-butane (78). A solution of **77** (1.90 g, 5.33 mmol) in pyridine (55 mL) was cooled to 0 °C, and acetic anhydride (3.01 mL, 31.97 mmol)

was added dropwise. The mixture was warmed to room temperature, stirred for 10 h, and poured into ice-cold 3 N hydrochloric acid (180 mL). The aqueous solution was extracted with ether (3 × 60 mL), and the combined organic extracts were washed with saturated, aqueous sodium bicarbonate (2 × 50 mL) and brine (50 mL). The organic solution was dried (sodium sulfate), the solvent was removed, and the residue was chromatographed on silica. Elution with 20% ethyl acetate in hexane gave 1.79 g (85%) of **78** as a colorless oil: $[\alpha]^{25}_D$ −8.23° (*c* 1.92, $CHCl_3$); IR (neat) 1735, 1240, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (3H, d, J = 6 Hz), 1.26 (18H, d, J = 7 Hz), 1.97 (2H, m), 2.00 (3H, s), 2.93 (1H, septet, J = 7 Hz), 4.12 (2H, t, J = 7 Hz), 4.14 (2H, septet, J = 7 Hz), 4.98 (1H, m), 7.18 (2H, s); ^{13}C NMR ($CDCl_3$) δ 20.0, 21.1, 23.6, 24.7, 29.6, 34.3, 35.2, 65.6, 67.5, 123.8, 129.4, 150.8, 153.7, 170.4; MS *m/z* 398 (M^+), 283, 202, 187, 159, 115, 55. Anal. Calcd for $C_{21}H_{34}O_5S$: C, 63.29; H, 8.59. Found: C, 63.09; H, 8.40.

(3*R*)-3-Acetoxy-1-iodobutane (79). To a solution of **78** (5.02 g, 12.50 mmol) in 2-butanone (200 mL) was added sodium iodide (5.63 g, 37.5 mmol). The resulting yellow solution was gently refluxed for 1 h, the solvent was removed, and the residue was diluted with water (150 mL). A small amount of sodium thiosulfate was added, resulting in decolorization, and the solution was extracted with methylene chloride (3 × 100 mL). The organic extract was dried (sodium sulfate), the solvent was removed, and the residue was chromatographed on silica, eluting with 12% ethyl acetate in hexane, to give 2.86 g (95%) of **79** as a pale yellow oil: $[\alpha]^{25}_D$ −7.09° (*c* 1.65, $CHCl_3$); IR (neat) 1737, 1241 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.25 (3H, d, J = 7 Hz), 2.05 (3H, s), 2.14 (2H, m), 3.14 (2H, m), 4.94 (1H, m); ^{13}C NMR ($CDCl_3$) δ −0.2, 19.4, 21.1, 39.5, 70.8, 170.4; MS *m/z* 243 (M^+ + 1), 199, 183, 127, 115.

(*R*)-δ-Caprolactone (80). A solution of diisopropylamine (8.10 mL, 58.1 mmol) in tetrahydrofuran (70 mL) was cooled to −78 °C, and *n*-butyllithium (23.2 mL of a 1.5 M solution in hexane, 34.90 mmol) was added slowly. The mixture was stirred at −78 °C for 1 h, after which a solution of **79** (2.80 g, 11.6 mmol) in tetrahydrofuran (50 mL) was added. The mixture was stirred at −78 °C for 1 h, and saturated, aqueous ammonium chloride (40 mL) was introduced. The resulting mixture was extracted with ether (3 × 50 mL), and the separated aqueous layer was continuously extracted with ether. The organic extract was dried (sodium sulfate), the solvent was removed, and the residue was purified by chromatography on silica. Elution with 25% ethyl acetate in hexane gave 0.78 g (60%) of **80** as a colorless oil: $[\alpha]^{25}_D$ +31.6° (*c* 1.22, EtOH); IR (neat) 1730, 1240, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (3H, d), 1.48−1.58 (1H, m), 1.82−1.90 (3H, m), 2.40−2.62 (2H, m), 4.42−4.50 (1H, m); ^{13}C NMR ($CDCl_3$) δ 18.5, 21.7, 29.2, 29.6, 76.9, 171.9.

(2*R*,9*S*,10*R*,11*S*)-10-[(*tert*-Butyldimethylsilyl)oxy]-2-hydroxy-9,11-dimethyl-6-oxotridec-7-yne (81). To a solution of **75** (400 mg, 1.00 mmol) in tetrahydrofuran (30 mL) at −78 °C was added *n*-butyllithium (1.5 mL of a 1.5 M solution in hexane, 2.2 mmol), and the mixture was stirred for 30 min. This solution was added via cannula to a stirred solution of **80** (111 mg, 1.00 mmol) in tetrahydrofuran (20 mL) at −78 °C. The mixture was allowed to warm to room temperature and was stirred for 8 h. Saturated, aqueous ammonium chloride (20 mL) was added to the mixture which was extracted with ether (3 × 20 mL). The organic extract was dried (sodium sulfate), the solvent was evaporated, and the residue was subjected to chromatography on silica. Elution with 10% ethyl acetate in hexane gave 156 mg (44%) of **81** as a colorless oil: $[\alpha]^{25}_D$ +1.20° (*c* 1.25, $CHCl_3$); IR (neat) 3601, 2213, 1669, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (3H, s), 0.09 (3H, s), 0.89 (3H, d, J = 7 Hz), 0.91 (3H, t, J = 4 Hz), 0.92 (9H, s), 1.20 (3H, d, J = 7 Hz), 1.23 (3H, d, J = 7 Hz), 1.34−1.73 (7H, m), 2.56 (2H, t, J = 7 Hz), 2.78 (1H, m), 3.54 (1H, t, J = 4 Hz), 3.79 (1H, m); ^{13}C NMR ($CDCl_3$) δ −4.2, −4.0, 12.1, 14.6, 17.5, 18.3, 20.1, 23.5, 26.0, 26.3, 31.5, 38.4, 39.4, 45.2, 67.5, 77.7, 82.4, 97.2, 188.0; MS *m/z* 368 (M^+), 351, 311, 201, 115, 57.

(2*RS*,6*R*)-2-[(3*S*,4*R*,5*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-3,5-dimethyl-1-heptynyl]-2-methoxy-6-methyltetrahydropyran (85). To a solution of **81** (32.6 mg, 0.09 mmol) in methanol (3 mL) was added Amberlite IR-118 ion-exchange resin, and the suspension was stirred at room temperature for 2 h. The mixture was filtered and the resin was washed thoroughly with methanol. Removal of the solvent, followed by chromatography of the residual oil on silica and elution with 20% ether in hexane, gave 24.5 mg (72%) of a 2:1 mixture of diastereomers of **85** as a colorless oil: IR (neat) 2231, 1110 cm^{-1}; ^1H NMR ($CDCl_3$) of major isomer δ 0.04 (3H, s), 0.06 (3H, s), 0.87 (3H, d, J = 7 Hz), 0.88 (3H, t, J = 7 Hz), 0.90 (9H, s), 1.16 (3H, d, J = 6 Hz), 1.18 (3H, d, J = 7 Hz), 1.22 (2H, m), 1.56 (4H, m), 1.85 (3H, m), 2.67 (1H, m), 3.35 (3H, s), 3.53 (1H, t, J = 4 Hz), 3.70 (1H, m); MS *m/z* 351 (M^+ − OMe), 325, 201, 115, 57; HRMS *m/z* 351.2719 (calcd for $C_{21}H_{39}O_2Si$: 351.2721).

(2*RS*,6*R*)-2-[(3*S*,4*R*,5*S*)-3,5-Dimethyl-4-hydroxy-1-heptynyl]-2-methoxy-6-methyltetrahydropyran (86). To a solution of **85** (24.5 mg, 0.06 mmol) in tetrahydrofuran (3 mL) was added tetra-*n*-butylammonium fluoride (128 μL of a 1 M solution in tetrahydrofuran, 0.13 mmol). The resulting pale yellow solution was stirred at 50 °C for 3 h, cooled to room temperature, and partitioned between ether and saturated, aqueous sodium bicarbonate. The aqueous layer was separated and extracted with ether, and the organic extract was washed with brine and dried (magnesium sulfate). After removal of the solvent, the residue was chromatographed on silica. Elution with 50% ether in hexane gave 15.8 mg (92%) of **86** as a colorless oil: IR (neat) 3410, 2240 cm^{-1}; ^1H NMR ($CDCl_3$) of major isomer δ 0.91 (3H, d, J = 7 Hz), 0.93 (3H, t, J = 7 Hz), 1.19 (3H, d, J = 6 Hz), 1.22 (3H, d, J = 7 Hz), 1.23 (2H, m), 1.54 (4H, m), 1.88 (3H, m), 2.75 (1H, m), 3.26 (1H, t), 3.35 (3H, s), 3.71 (1H, m); MS *m/z* 237 (M^+ − OMe), 211, 182, 150, 135, 121, 87, 57; HRMS *m/z* 237.1854 (calcd for $C_{15}H_{26}O_2$: 237.186).

(2*R*,3*S*,6*R*,8*R*)-3,8-Dimethyl-2-[(1*S*)-1-methylpropyl]-1,7-dioxaspiro-[5.5]undec-4-ene (88). To a solution of **86** (12.9 mg, 0.048 mmol) in methanol (2 mL) was added quinoline (3.20 mg), followed by palladium on barium sulfate (4.20 mg). The suspension was stirred under an atmosphere of hydrogen for 20 min and filtered through Celite. The filtrate was evaporated, and the residue was taken up into ether (3 mL). The solution was acidified with camphorsulfonic acid, and the mixture was stirred at room temperature for 1.5 h. The quinolinium camphorsulfonate was removed by filtration and was washed with ether. The filtrate was washed with saturated, aqueous sodium bicarbonate, water, and brine and was dried (magnesium sulfate). Removal of the solvent, followed by chromatography of the residue on silica and elution with 10% ether in hexane, gave 5.60 mg (49%) of **88** as a colorless oil: $[\alpha]^{25}_D$ +63.3° (*c* 0.26, $CHCl_3$); IR (neat) 1640, 1450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (3H, d, J = 6 Hz), 0.90 (3H, d, J = 7 Hz), 0.93 (3H, t, J = 7 Hz), 1.13 (3H, d, J = 6 Hz), 1.25 (2H, m), 1.38−1.62 (7H, m), 2.23 (1H, m), 3.48 (1H, dd, J = 10 and 1 Hz), 3.90 (1H, m), 5.55 (1H, dd, J = 10 and 3 Hz), 5.69 (1H, dd, J = 10 and 1 Hz); ^{13}C NMR ($CDCl_3$) δ 12.1, 12.8, 16.5, 19.0, 22.1, 27.6, 30.8, 32.6, 34.7, 35.4, 66.1, 74.6, 94.0, 129.7, 135.1; MS *m/z* 238 (M^+), 181, 152; HRMS *m/z* 238.1933 (calcd for $C_{15}H_{26}O_2$: 238.1934). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.81; H, 11.07.

2,4-Dideoxylaevoglucosan (92) and 3,4-Dideoxylaevoglucosan (93). To a stirred solution of laevoglucosan[40] (6.87 g, 42.4 mmol) in dry pyridine (34 mL) was added a solution of *p*-toluenesulfonyl chloride (16.80 g, 88.1 mmol) in a mixture of dry pyridine (48 mL) and chloroform (69 mL) at 0 °C. After stirring for 50 h at room temperature, the mixture was diluted with 10 mL of water and 50 mL of methylene chloride and was stirred vigorously for 1 h. The organic layer was separated and washed with 5% aqueous sulfuric acid and water. After drying (sodium sulfate), the solvent was removed to give 17.99 g (90%) of **90** as a yellow foam.

A solution of **90** (10.54 g, 22.41 mmol) in tetrahydrofuran (100 mL) was treated with lithium triethylborohydride (135 mL of a 1.0 M solution in tetrahydrofuran, 135 mmol) at 0 °C. After the mixture was stirred at 5 °C for 12 h and at room temperature for 18 h, it was cooled to 0 °C and treated cautiously with water, followed by a mixture of hydrogen peroxide (60.0 mL of a 30% aqueous solution, 529 mmol) and sodium hydroxide (76.5 mL of a 3.0 M aqueous solution, 229 mmol). After 1.5 h at room temperature, the mixture was saturated with sodium chloride and the pH was adjusted to 10 with solid potassium carbonate. The mixture was extracted with methylene chloride (100 mL), and the extract was dried (magnesium sulfate). Removal of the solvent left an oil that was purified by chromatography on silica, using 6% methanol in ethyl acetate as eluant, to yield 2.05 g (70%) of a mixture of **92** and **93** as a colorless semisolid: IR (neat) 3450 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30−2.50 (4H, m), 2.85 (1H, d, J =

7 Hz), 3.80 (1H, m), 4.05 (1H, m), 4.34 (1H, d, J = 6 Hz), 4.58 (1H, m), 5.33 (0.21H, s), 5.66 (0.79H, s). **92:** ^{13}C NMR ($CDCl_3$) δ 36.8, 39.0, 64.2, 68.5, 72.6, 101.5. **93**: ^{13}C NMR ($CDCl_3$) δ 26.4, 28.0, 68.3, 69.2, 73.0, 103.2. This mixture was used in the next reaction without further purification.

(1*S*,3*R*,5*R*)-4-[(*p*-Methoxybenzyl)oxy]-6,8-dioxobicyclo[3.2.1]-octane (94). A solution containing a mixture of **92** and **93** (1.10 g, 8.43 mmol) in tetrahydrofuran (10 mL) was added slowly to a stirred suspension of potassium hydride (1.56 g of a 30% oil dispersion, 13.6 mmol) in tetrahydrofuran (10 mL) at 0 °C. After warming to room temperature, the mixture was cooled to 0 °C and *p*-methoxybenzyl chloride (1.46 mL, 10.6 mmol) was added. After 20 h at room temperature, the solution was heated at reflux for 3 h, cooled, and cautiously diluted with water (25 mL). The aqueous layer was extracted with ether (4 × 25 mL), and the combined extract was washed with water and dried (magnesium sulfate). Removal of the solvent left a yellow oil that was purified by radial chromatography on silica, using 45% ether in pentane as eluant, to afford 1.61 g (76%) of **94** as a pale yellow oil: IR (neat) 1615, 1590, 1510, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.60–2.30 (4H, m), 3.58–3.90 (2H, m), 3.78 (3H, s), 4.20–4.65 (4H, m), 5.55 (1H, s), 7.06 (4H, m); ^{13}C NMR ($CDCl_3$) δ 34.2, 35.4, 55.3, 67.9, 69.7, 70.3, 71.3, 100.4, 114.1, 129.0, 131.1, 159.5; MS *m/z* 250 (M^+), 150, 137, 121, 83. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.23; H, 7.24.

2,4-Dideoxy-3-*O*-(*p*-methoxybenzyl)glucopyranose (95). A solution of **94** (43.9 mg, 0.18 mmol) in tetrahydrofuran–water (1:1, 3 mL) containing *p*-toluenesulfonic acid (5 mg) was heated at reflux for 5 h. The mixture was cooled to room temperature and partitioned between ethyl acetate and saturated, aqueous sodium bicarbonate. The layers were separated, and the aqueous phase was extracted with ethyl acetate (3×). The combined extract was dried (magnesium sulfate), and the solvent was removed. Chromatography of the residue on silica, eluting with ethyl acetate, gave 36.5 mg (78%) of **95** as a viscous, colorless oil as a 3:2 mixture of anomers: IR (neat) 3413, 2933, 1613, 1514, 1361, 1248, 1082, 1034, 738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.24–1.40 (1.4H, m), 1.54 (0.6H, m), 1.89 (0.4H, m), 1.98 (0.6H, m), 2.21 (0.6H, m), 2.31 (0.4H, m), 3.50 (0.4H, m), 3.55–3.66 (2.4H, m), 3.80 and 3.81 (3H, 2s), 3.97 (0.6H, m), 4.09 (0.6H, m), 4.49 (2H, m), 4.73 (0.4H, dd, J = 10 and 2 Hz), 5.47 (0.6H, d, J = 3 Hz), 6.87 (2H, d, J = 8 Hz), 6.88 (2H, d, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ 32.9, 33.8, 36.6, 39.5, 55.3, 65.5, 65.9, 68.9, 69.6, 69.8, 72.6, 73.1, 92.8, 94.7, 113.9, 129.2; MS *m/z* 250 ($M^+ - H_2O$), 150, 138, 137, 122, 121.

(2*S*,4*R*)-1,2,6-Trihydroxy-4-[(*p*-methoxybenzyl)oxy]hexane (96). To a solution of **95** (46.6 mg, 0.17 mmol) in tetrahydrofuran (4 mL) at 0 °C was added lithium aluminum hydride (26 mg, 0.69 mmol) in one portion. The solution was allowed to warm to room temperature and was stirred for 5 h. The reaction was quenched by dropwise addition of a saturated Rochelle's salt solution until a granular precipitate had formed. The precipitate was filtered off and was washed with ethyl acetate. The solvent was removed to give 44.3 mg (94%) of **96**: ^{1}H NMR ($CDCl_3$) δ 1.60–1.88 (4H, m), 3.44 (1H, dd, J = 11 and 7 Hz), 3.60 (1H, dd, J = 11 and 3 Hz), 3.67–3.80 (2H, m), 3.79 (3H, s), 3.95 (2H, m), 4.50 (2H, a), 6.88 (2H, d, J = 8 Hz), 7.26 (2H, d, J = 8 Hz). This material was used without further purification.

Acetonide 97. Dimethoxypropane (200 μL, 1.64 mmol) was added dropwise to a solution of **96** (44.3 mg, 0.164 mmol) in methylene chloride (4 mL) containing a trace of camphorsulfonic acid, and the solution was stirred at room temperature for 1.5 h. The mixture was partitioned between methylene chloride and saturated, aqueous sodium bicarbonate, and the layers were separated. The aqueous phase was extracted with methylene chloride, and the combined extract was washed with water and brine and dried (magnesium sulfate). Removal of the solvent, followed by chromatography of the residue on silica eluting with 70% ethyl acetate in hexane, gave 30.3 mg (60%) of **97** as a colorless oil: $[\alpha]^{23}_D$ −1.62° (*c* 1.05, $CHCl_3$); IR (neat) 3451 (br), 2919, 1614, 1515, 1380, 1250, 1051, 822 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.36 (3H, s), 1.41 (3H, s), 1.73–1.92 (4H, m), 3.51 (1H, t, J = 8 Hz), 3.73 (1H, m), 3.80 (3H, s), 3.83 (2H, m), 4.06 (1H, dd, J = 8 and 6 Hz), 4.23 (1H, m), 4.50 (1H, d, J = 11 Hz), 4.54 (1H, d, J = 11 Hz), 6.88 (2H, d, J = 8 Hz), 7.27 (2H, d, J = 9 Hz); ^{13}C NMR ($CDCl_3$) δ 25.8, 27.0, 36.5, 38.7, 55.3, 60.0, 70.0, 71.5, 73.4, 75.2, 108.6, 113.9, 129.2, 129.6; MS *m/z* 310 (M^+), 179, 137, 135, 121. Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.87; H, 8.55.

Aldehyde 98. Dimethyl sulfoxide (156 μL, 2.19 mmol) in methylene chloride (1 mL) was added to a solution of oxalyl chloride (96 μL, 1.10 mmol) in methylene chloride (3 mL) at −78 °C, and the mixture was stirred for 5 min. A solution of **97** (170 mg, 0.55 mmol) in methylene chloride (1 mL) was added dropwise, and the mixture was stirred for a further 30 min. Triethylamine (764 μL, 5.48 mmol) was added, and the solution was allowed to warm to room temperature and was partitioned between methylene chloride and water. The aqueous phase was extracted with methylene chloride, and the combined extract was washed with water and brine and dried (magnesium sulfate). Removal of the solvent, followed by chromatography of the residue on silica eluting with 50% ethyl acetate in hexane, gave 155 mg (92%) of **98** as a colorless oil: $[\alpha]^{27}_D$ −17.0° (*c* 1.5, $CHCl_3$); IR (neat) 2986, 2937, 1723, 1613, 1515, 1371, 1249, 1053, 822 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (3H, s), 1.40 (3H, s), 1.77 (1H, ddd, J = 14, 8, and 4 Hz), 1.82 (1H, ddd, J = 14, 9, and 4 Hz), 2.69 (2H, dt, J = 6 and 2 Hz), 3.51 (1H, dd, J = 8 and 8 Hz), 3.80 (3H, s), 4.05 (1H, dd, J = 8 and 6 Hz), 4.16 (1H, m), 4.23 (1H, m), 4.49 (1H, d, J = 11 Hz), 4.54 (1H, d, J = 11 Hz), 6.87 (2H, d, J = 9 Hz), 7.24 (2H, d, J = 9 Hz), 9.80 (1H, t, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ 25.8, 27.0, 39.5, 49.0, 55.3, 70.0, 71.7, 71.9, 73.1, 108.8, 113.9, 129.5, 130.1, 159.4, 201.0; MS *m/z* 308 (M^+), 281, 232, 137, 136, 135, 121; HRMS *m/z* 308.1617 (calcd for $C_{17}H_{24}O_5$: 308.1617).

Alcohol 99. To a solution of **75** (49 mg, 0.19 mmol) in tetrahydrofuran (0.5 mL) at 0 °C was added ethylmagnesium bromide (3.0 M in ether, 61 μL, 0.18 mmol). The mixture was warmed to room temperature with stirring and cooled to −78 °C, and a solution of **98** (35 mg, 0.11 mmol) in tetrahydrofuran (0.5 mL) was added dropwise. The mixture was stirred for 15 min at −78 °C, warmed to room temperature, poured into saturated, aqueous ammonium chloride, and extracted with ether (3×). The ether extract was washed with brine and dried (magnesium sulfate), and the solvent was evaporated to leave a viscous oil that was chromatographed on silica. Elution with 30% ethyl acetate in hexane gave 26 mg of recovered **75** and 53 mg (83%) of **99** as a 1:1 mixture of stereoisomers: IR (neat) 3420, 2958, 2857, 2240, 1613, 1515, 1465, 1375, 1250, 1065, 836, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.06 (3H, s), 0.08 (3H, s), 0.87 (3H, d, J = 7 Hz), 0.88 (3H, t, J = 7 Hz), 0.91 (9H, s), 1.16 (3H, d, J = 7 Hz), 1.20 (1H, m), 1.36 (3H, s), 1.46 (3H, s), 1.50 (1H, m), 1.60 (1H, m), 1.85–1.92 (3H, m), 2.05 (1H, m), 2.65 (1H, m), 3.50 (2H, m), 3.79 and 3.80 (3H, 2s), 3.83 (0.5H, m), 4.05 (0.5H, m), 4.10 (1H, dd, J = 8 and 6 Hz), 4.23 (1H, m), 4.55 (2H, s), 4.60 (1H, m), 6.87 (2H, d, J = 9 Hz), 7.25 (2H, d, J = 9 Hz); ^{13}C NMR ($CDCl_3$) δ −4.0, −3.9, 12.1, 14.8, 17.6, 18.4, 25.9, 26.1, 27.0, 27.1, 31.6, 38.7, 38.8, 42.3, 43.4, 55.3, 60.3, 60.8, 71.9, 73.3, 74.5, 75.0, 77.7, 82.5, 88.7, 108.6, 113.9, 129.5, 129.7, 130.3, 159.3; MS *m/z* 563 ($M^+ + 1$), 458, 314, 201, 171, 162, 254, 138, 132, 121.

Ketone 100. To a solution of oxalyl chloride (163 μL, 1.86 mmol) in methylene chloride (5 mL) at −78 °C was added a solution of dimethyl sulfoxide (265 μL, 3.73 mmol) in methylene chloride (5 mL). After 5 min, a solution of **99** (524 mg, 0.93 mmol) in methylene chloride (5 mL) was added and the mixture was stirred at −78 °C for 0.5 h. Triethylamine (1.30 mL, 9.32 mmol) was added, and the mixture was allowed to warm to room temperature. Brine (10 mL) was added, and the organic layer was separated and dried (magnesium sulfate). Removal of the solvent and chromatography of the residue on silica using 20% ethyl acetate in hexane as eluant gave 478 mg (92%) of **100** as a colorless oil: $[\alpha]^{25}_D$ −16.2° (*c* 1.35, $CHCl_3$); IR (neat) 2934, 2858, 2211, 1674, 1471, 1464, 1250, 1119, 1070, 836, 775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.06 (3H, s), 0.09 (3H, s), 0.88 (3H, d, J = 7 Hz), 0.91 (3H, t, J = 7 Hz), 0.91 (9H, s), 1.20 (1H, m), 1.23 (3H, d, J = 7 Hz), 1.34 (3H, s), 1.39 (3H, s), 1.50–1.58 (2H, m), 1.77 (2H, m), 2.73 (1H, dd, J = 16 and 6 Hz), 2.79 (1H, d, J = 7 Hz), 2.91 (1H, dd, J = 16 and 6 Hz), 3.50 (1H, dd, J = 8 and 8 Hz), 3.54 (1H, dd, J = 4 and 4 Hz), 3.79 (3H, s), 4.03 (1H, dd, J = 8 and 6 Hz), 4.17–4.23 (2H, m), 4.44 (1H, d, J = 11 Hz), 4.45 (1H, d, J = 11 Hz), 6.86 (2H, d, J = 8 Hz), 7.24 (2H, d, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ −4.1, −3.9, 12.1, 14.6, 17.4, 18.3, 25.8, 26.0, 26.4, 27.0, 31.6, 39.4, 39.4, 51.2, 55.3, 69.9, 71.9, 72.8, 73.1, 77.7, 82.8, 97.8, 108.6, 113.8, 129.5, 130.3,

159.2, 185.5. Anal. Calcd for $C_{32}H_{52}O_6Si$: C, 68.53; H, 9.34. Found: C, 68.72; H, 9.41.

Tetrahydropyran 101. A solution of **100** (68.7 mg, 0.12 mmol) in methanol (5 mL) containing camphorsulfonic acid (5 mg) was stirred at room temperature for 3 h. Solid sodium bicarbonate was added, and the suspension was stirred vigorously for 10 min and filtered. The filtrate was evaporated, and the residue was chromatographed on silica. Elution with 40% ethyl acetate in hexane gave 57.4 mg (88%) of **101** as a 3:1 anomeric mixture: IR (neat) 3069, 2974, 2859, 2240, 1614, 1514, 1493, 1382, 1353, 1250, 1119, 837, 775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (3H, s), 0.08 (3H, s), 0.88 (3H, d, J = 7 Hz), 0.89 (3H, t, J = 7 Hz), 0.92 (9H, s), 1.20 (3H, d, J = 7 Hz), 1.19−1.25 (2H, m), 1.45 (1H, m), 1.50−1.62 (2H, m), 1.73 (1H, dd, J = 12 and 11 Hz), 1.95 (1H, m), 2.45 (1H, m), 2.69 (1H, m), 3.31 and 3.51 (3H, 2s), 3.45 (1H, m), 3.60−3.68 (2H, m), 3.80 (3H, s), 3.88 (1H, m), 4.47 (2H, s), 6.87 (2H, d, J = 9 Hz), 7.25 (2H, d, J = 9 Hz); ^{13}C NMR ($CDCl_3$) δ −4.2, −4.1, 12.1, 15.0, 15.4, 17.1, 18.3, 18.5, 20.0, 26.3, 26.8, 30.8, 31.2, 33.0, 33.3, 39.1, 39.9, 42.6, 43.1, 50.2, 51.5, 55.2, 65.6, 65.6, 69.7, 69.8, 70.0, 70.5, 72.0, 72.7, 77.6, 78.0, 79.2, 87.9, 91.5, 96.1, 96.8, 113.8, 129.1, 130.5, 130.6, 159.2; MS m/z 533 (M^+ − 1), 412, 396, 380, 364, 355, 340, 323, 309, 296, 166, 250, 131.

Alcohol 102. Tetra-*n*-butylammonium fluoride (322 μL of a 1 M solution in tetrahydrofuran, 0.32 mmol) was added dropwise to a solution of **101** (57.4 mg, 0.11 mmol) in tetrahydrofuran (5 mL), and the pale yellow solution was heated at 50 °C for 1 h. The mixture was cooled to room temperature and partitioned between ether and water (1:1, 25 mL), and the layers were separated. The aqueous phase was extracted with ether, and the combined extract was washed with water and brine and dried (magnesium sulfate). Removal of the solvent, followed by chromatography of the residue on silica and elution with 70% ethyl acetate in hexane, gave 38.6 mg (86%) of **102** as a viscous oil: IR (neat) 3445, 2974, 2873, 2240, 1614, 1514, 1461, 1379, 1249, 1117, 1042, 986, 823 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3H, d, J = 7 Hz), 0.91 (3H, d, J = 7 Hz), 0.92 (3H, d, J = 7 Hz), 1.19 (3H, d, J = 7 Hz), 1.21 (3H, d, J = 7 Hz), 1.24−1.36 (2H, m), 1.49−1.56 (2H, m), 1.75 (1H, dd, J = 12 and 11 Hz), 1.94 (1H, m), 2.35 (1H, m), 2.44 (1H, m), 2.74 (1H, m), 3.25 (1H, m), 3.32 (3H, s), 3.51 (3H, s), 3.52−3.58 (3H, m), 3.80 (3H, s), 3.85 (1H, m), 4.47 (2H, s), 4.49 (2H, s), 6.87 (2H, d, J = 9 Hz), 7.24 (2H, d, J = 9 Hz); ^{13}C NMR ($CDCl_3$) δ 11.5, 13.4, 17.7, 17.8, 26.4, 30.9, 33.0, 33.3, 37.9, 38.0, 42.8, 43.2, 50.3, 51.8, 55.3, 65.5, 69.7, 70.4, 72.3, 72.4, 77.4, 78.1, 80.2, 86.5, 90.9, 96.2, 96.8, 113.9, 129.2, 130.4, 130.6, 159.3; MS m/z 419 (M^+ − 1), 388, 333, 282, 252, 177, 163, 85.

Spiroketal 104. To a solution of **102** (34.1 mg, 0.081 mmol) and quinoline (9.5 mg, 0.074 mmol) in methanol (2 mL) under a hydrogen atmosphere was added palladium-on-barium sulfate (11.9 mg). The suspension was stirred vigorously for 0.5 h and filtered through a pad of Celite. The filtrate was concentrated to give a residue containing crude **103** and quinoline which was taken up into ether (20 mL) and acidified to pH 3 with camphorsulfonic acid. The resulting solution was stirred at room temperature for 15 min, after which solid sodium bicarbonate was added and the mixture was stirred vigorously for 5 min and filtered. The solvent was removed, and the residue was chromatographed on silica, eluting with 50% ethyl acetate in hexane, to give 26.4 mg (83%) of **104** as a colorless oil: $[\alpha]^{24}_D$ +100.6° (c 2.02, $CHCl_3$); IR (neat) 3458, 2970, 2875, 1613, 1514, 1458, 1381, 1249, 1118, 1076, 822, 734 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3H, d, J = 7 Hz), 0.92 (3H, d, J = 7 Hz), 0.93 (3H, t, J = 7 Hz), 1.33 (1H, ddd, J = 12, 11, and 11 Hz), 1.36 (1H, m), 1.39 (1H, m), 1.43 (1H, dd, J = 12 and 11 Hz), 1.57 (1H, m), 1.93 (1H, dddd, J = 12, 5, 5, and 3 Hz), 2.12 (1H, ddd, J = 12, 5, and 2 Hz), 2.26 (1H, dddd, J = 10, 8, 3, and 2 Hz), 3.39 (1H, dd, J = 10 and 2 Hz), 3.59 (1H, dd, J = 15 and 9 Hz), 3.63 (1H, brd, J = 15 Hz), 3.80 (3H, s), 3.89 (1H, dddd, J = 10, 7, 4, and 3 Hz), 3.94 (1H, dddd, J = 11, 11, 4, and 4 Hz), 4.48 (2H, s), 5.56 (1H, dd, J = 10 and 3 Hz), 5.74 (1H, ddd, J = 10, 2, and 1 Hz), 6.87 (2H, d, J = 9 Hz), 7.25 (2H, d, J = 9 Hz); ^{13}C NMR ($CDCl_3$) δ 12.2, 12.6, 16.5, 27.8, 30.1, 33.5, 35.4, 41.4, 55.3, 66.0, 69.6, 69.9, 71.2, 75.6, 95.8, 113.8, 128.2, 129.3, 130.8, 135.7, 159.2; MS m/z CI (NH_3) 391 (M^+ + 1), 287, 271, 253, 155, 138, 121. Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.60; H, 8.63.

Diol 105. To a solution of **104** (15.0 mg, 0.038 mmol) in acetonitrile−water (0.6 mL, 3:1, respectively) was added ceric ammonium nitrate (84 mg, 0.15 mmol), and the solution was stirred at room temperature for 15 min. The mixture was partitioned between ether and water (1:1, 5 mL), the ethereal layer was separated, and the aqueous layer was extracted with ether. The combined organic extract was washed with saturated, aqueous sodium bicarbonate and brine and dried (magnesium sulfate). The solvent was removed, and the residue was chromatographed on silica. Elution with 70% ethyl acetate in hexane gave 7.7 mg (74%) of **105**: ^1H NMR ($CDCl_3$) δ 0.87 (3H, d, J = 7 Hz), 0.94 (3H, t, J = 7 Hz), 1.25−1.47 (4H, m), 1.57 (1H, m), 1.61−1.86 (2H, s), 1.87 (1H, m), 2.03 (1H, ddd, J = 12, 5, and 2 Hz), 2.26 (1H, m), 3.40 (1H, dd, J = 10 and 2 Hz), 3.57 (1H, dd, J = 12 and 6 Hz), 3.67 (1H, dd, J = 12 and 3 Hz), 3.91 (1H, m), 4.20 (1H, m), 5.57 (1H, dd, J = 10 and 3 Hz), 5.76 (1H, dd, J = 10 and 2 Hz).

Compound **105** was crystallized from methylene chloride−hexane. Crystals of **105** were monoclinic and belonged to the space group $P2_1$ with a = 11.77(2) Å, b = 7.70(4) Å, c = 177.07(9) Å, β = 103.0(4)°, Z = 4, and d_{calc} = 1.13 g/cm^3. The intensity data were measured on a Rigaku diffractometer using graphite monochromated Mo Kα radiation (λ = 0.710 69). The unique reflections [$I > 2.00\sigma(I)$] for $2\theta_{max}$ = 50.1° were 968. The structure was solved with SHELXTL PLUS, and full-matrix least-squares refinement with anisotropic temperature factors and calculated hydrogen atom positions led to final discrepancy indices of R = 0.068 and R_w = 0.067.

Aldehyde 106. To a solution of oxalyl chloride (12.5 μL, 0.14 mmol) in methylene chloride (0.5 mL) at −78 °C was added dropwise a solution of dimethyl sulfoxide (20 μL, 0.29 mmol) in methylene chloride (0.5 mL). The mixture was stirred for 5 min, and a solution of **104** (14.0 mg, 0.03 mmol) in methylene chloride (0.5 mL) was added. After 30 min at −78 °C, triethylamine (100 μL, 0.71 mmol) was added and the mixture was allowed to warm to room temperature and was partitioned between methylene chloride and water (1:1, 5 mL). The aqueous phase was extracted with methylene chloride (3×), and the combined extract was washed with brine and dried (magnesium sulfate). The solvent was removed, and the residue was chromatographed on silica, eluting with 35% ethyl acetate in hexane, to give 14.0 mg (100%) of **106** as a colorless oil: $[\alpha]^{24}_D$ +94.7° (c 1.33, $CHCl_3$); IR (neat) 2964, 2933, 1738, 1513, 1248, 1170, 1110, 1073, 1038, 997 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (3H, d, J = 7 Hz), 0.89 (3H, t, J = 7 Hz), 0.93 (3H, d, J = 7 Hz), 1.22−1.39 (3H, m), 1.47−1.68 (2H, m), 2.12 (1H, ddd, J = 13, 4, and 2 Hz), 2.21−2.34 (2H, m), 3.43 (1H, dd, J = 10 and 2 Hz), 3.80 (3H, s), 3.87−3.99 (1H, m), 4.18 (1H, dd, J = 13 and 3 Hz), 4.47 (1H, d, J = 11 Hz), 4.52 (1H, d, J = 11 Hz), 5.62 (1H, dd, J = 10 and 3 Hz), 5.80 (1H, dd, J = 10 and 2 Hz), 6.87 (2H, d, J = 9 Hz), 7.26 (2H, d, J = 9 Hz), 9.68 (1H, s); ^{13}C NMR ($CDCl_3$) δ 12.1, 12.5, 16.3, 27.7, 30.5, 32.1, 35.2, 41.4, 55.3, 69.7, 70.6, 74.3, 75.8, 96.3, 113.8, 127.4, 129.3, 130.4, 136.2, 159.2, 201.4; MS m/z 389 (M^+ + 1), 360, 287, 253, 193, 153, 123, 122, 121, 109, 95, 77. Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.11; H, 8.30. Found: C, 70.86; H, 8.17.

Ethyl 4-[2-(5,5-Dimethyl-1,3-dioxanyl)]pent-2-enoate (108). A solution of **107**[43] (1.90 g, 0.18 mmol), *p*-toluenesulfonic acid (5 mg), and 2,2-dimethyl-1,3-propanediol (1.60 g, 0.015 mmol) in dry benzene (25 mL) was heated at reflux in a water separator. After 4 h, the benzene was evaporated and the residue was chromatographed on silica, using 30% ethyl acetate in hexane as eluant, to give 2.02 g (68%) of **108**: IR (neat) 1724, 1303, 1271, 1180, 1081 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.70 (3H, s), 1.16 (3H, s), 1.31 (3H, t, J = 7 Hz), 1.43 (3H, s), 3.37 (2H, d, J = 11 Hz), 3.51 (2H, d, J = 11 Hz), 4.21 (2H, q, J = 7 Hz), 6.10 (1H, d, J = 16 Hz), 6.84 (2H, d, J = 16 Hz); MS m/z 229 (M^+ + 1), 213, 183, 143, 129, 115, 69.

2-(3-Hydroxy-1-propenyl)-2,5,5-trimethyl-1,3-dioxane (109). To a solution of **108** (2.02 g, 8.10 mmol) in toluene (14 mL) at −78 °C was added diisobutylaluminum hydride (32.0 mL of a 1.0 M solution in hexane, 32.0 mmol), and the mixture was stirred for 45 min. Methanol (2 mL) was added dropwise, and the mixture was allowed to warm to room temperature. Saturated, aqueous sodium chloride was added, followed by ether (700 mL) and anhydrous magnesium sulfate (5 g). The resulting mixture was stirred for 1 h at room temperature, filtered, and concentrated. The residue was chromatographed on silica, using 40% ethyl acetate in hexane as eluant, to give 1.35 g (90%) of **109**: IR (neat) 3424, 2944, 2880, 1484, 1372, 1116, 1090, 1070, 1050

cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.66 (3H, s), 1.10 (3H, s), 1.36 (3H, s), 1.47 (1H, t, J = 5 Hz), 3.28 (2H, d, J = 11 Hz), 3.52 (2H, d, J = 11 Hz), 4.18 (2H, t, J = 5 Hz), 5.62 (1H, dt, J = 16 and 1 Hz), 5.91 (1H, dt, J = 16 and 5 Hz); ^{13}C NMR ($CDCl_3$) δ 22.0, 22.7, 28.5, 30.1, 62.7, 71.5 (×2), 98.4, 131.1, 132.6; MS m/z 187 (M^+ + 1), 171, 129, 69. Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.56; H, 9.77.

(1*S*,2*R*)-2-(3-Hydroxy-1,2-oxiranylpropyl)-2,5,5-trimethyl-1,3-dioxane (110). To a suspension of powdered 4 Å molecular sieves in methylene chloride (25 mL) was added (−)-diisopropyl tartrate (0.193 mL, 1.38 mmol), followed by **109** (2.79 g, 15.0 mmol). The suspension was cooled to 0 °C, titanium tetraisopropoxide (0.295 mL, 0.99 mmol) was added, and the mixture was stirred for 30 min. The mixture was cooled to −20 °C, and cumene hydroperoxide (8.9 mL, 48.0 mmol) was added dropwise. The mixture was stirred for 8 h at −20 °C and stored for 12 h at 0 °C. The excess peroxide was quenched at 0 °C by addition of trimethyl phosphite (5 mL), the mixture was stirred for 30 min at room temperature and partitioned between methylene chloride and brine, and the aqueous phase was extracted with methylene chloride (3×). The combined organic extracts were dried (magnesium sulfate), filtered, and concentrated, and the residue was chromatographed on silica. Elution with 50% ethyl acetate in hexane gave 2.72 g (90%) of **110** as a colorless oil: $[\alpha]^{24}_D$ +21.1° (*c* 2.37, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.93 (3H, s), 1.00 (3H, s), 1.39 (3H, s), 1.73 (1H, s), 3.18 (1H, d, J = 2 Hz), 3.24−3.26 (1H, m), 3.53−3.70 (5H, m), 3.96 (1H, dd, J = 3 and 13 Hz). This compound was unstable and was used promptly in the next reaction.

(1*S*,2*R*)-2-(1,3-Dihydroxy-2-methylpropyl)-2,5,5-trimethyl-1,3-dioxane (111). A solution of cuprous bromide−dimethyl sulfide complex (545 mg, 2.65 mmol) in dimethyl sulfide (2 mL) and ether (2 mL) was cooled to 0 °C, and methyllithium (3.55 mL of a 1.4 M solution in ether, 4.97 mmol) was added dropwise. The resulting cloudy mixture was warmed to room temperature, stirred for 20 min, and then cooled to −50 °C, and a solution of **110** (223 mg, 1.10 mmol) in ether (1 mL) was added dropwise. The mixture was allowed to warm slowly to room temperature and was partitioned between ethyl acetate and saturated, aqueous ammonium chloride (pH ~ 8, adjusted with ammonium hydroxide). The aqueous layer was extracted with ethyl acetate (3×), and the combined organic extracts were washed with brine, dried (magnesium sulfate), filtered, and concentrated. Chromatography of the residue on silica, eluting with 60% ethyl acetate in hexane, gave 170 mg (71%) of **111** as a colorless oil: $[\alpha]^{24}_D$ +6.23° (*c* 1.54, $CHCl_3$); IR (neat) 3419, 2955, 2871, 1469, 1373, 1144, 1090, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (3H, s), 1.00 (3H, d, J = 7 Hz), 1.11 (3H, s), 1.41 (3H, s), 2.05 (1H, m), 2.87 (1H, d, J = 3 Hz), 3.47 (3H, m), 3.67 (3H, m); MS m/z 203, 160, 155, 129, 115, 89, 69, 45, 43, 41.

(2*S*,3*S*)-3-Hydroxy-2-methyl-4-(2,2-dimethyl-1,3-propylenedioxy)-pentyl Pivalate (112). To a solution of **111** (90 mg, 0.41 mmol) in methylene chloride (2 mL) were added pyridine (0.100 mL, 1.24 mmol), pivaloyl chloride (0.102 mL, 0.83 mmol), and 4-(dimethylamino)-pyridine (10 mg, 0.093 mmol), and the solution was stirred for 2 h at room temperature. The mixture was partitioned between ether and water, the separated aqueous phase was extracted with ether (3×), and the combined organic extracts were washed with brine and dried (magnesium sulfate). Removal of the solvent and chromatography of the residue on silica, eluting with 30% ethyl acetate in hexane, provided 112 mg (90%) of **112** as colorless crystals: mp 80−81 °C; $[\alpha]^{24}_D$ −23.5° (*c* 1.71, $CHCl_3$); IR (neat) 3500, 2959, 2871, 1727, 1480, 1286, 1168, 1114, 1088, 1059 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.83 (3H, s), 1.08 (3H, s), 1.08 (3H, d, J = 7 Hz), 1.20 (9H, s), 1.41 (3H, s), 2.08−2.19 (1H, m), 2.40−2.62 (1H, m), 3.42 (2H, dd, J = 9 and 3 Hz), 3.52 (1H, d, J = 5 Hz), 3.63 (2H, dd, J = 11 and 7 Hz), 4.08 (1H, dd, J = 11 and 7 Hz), 4.35 (1H, dd, J = 11 and 4 Hz); MS m/z 303 (M^+ + 1), 287, 201, 183, 157, 129, 115, 87, 69, 57, 43, 41. Anal. Calcd for $C_{16}H_{30}O_5$: C, 63.55; H, 10.00. Found: C, 63.76; H, 10.10.

(2*S*,3*S*)-3-Hydroxy-2-methyl-4-oxopentyl Pivalate (113). A solution of **112** (65 mg, 0.22 mmol) and pyridinium *p*-toluenesulfonate (2 mg) in tetrahydrofuran (2 mL) and water (1 mL) was heated at 50 °C for 36 h. The solution was partitioned between ether and saturated, aqueous sodium bicarbonate, and the separated aqueous phase was extracted with ether (3×). The combined organic extracts were washed with brine, dried (magnesium sulfate), and concentrated. Chromatography of the residue on silica, eluting with 30% ethyl acetate in hexane, afforded 40 mg (86%) of **113** as a colorless oil: $[\alpha]^{24}_D$ +83.5° (*c* 2.17, $CHCl_3$); IR (neat) 3476, 2974, 2937, 1728, 1724, 1482, 1462, 1400, 1363, 1284, 1159, 1154, 1128, 1032 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (9H, s), 1.17 (3H, d, J = 7 Hz), 2.30 (3H, s), 2.48−2.58 (1H, m), 3.59 (1H, d, J = 4 Hz), 3.85 (1H, dd, J = 11 and 5 Hz), 3.98 (1H, dd, J = 11 and 9 Hz), 4.05 (1H, dd, J = 4 and 2 Hz); ^{13}C NMR ($CDCl_3$) δ 15.4, 25.6, 27.0, 35.8, 38.6, 64.2, 79.0, 178.3, 208.5; MS m/z 217 (M^+ + 1), 199, 173, 115, 103, 85, 71, 57, 43, 41.

(2*S*,3*S*)-3-[[2-(Trimethylsilyl)ethoxy]methoxy]-2-methyl-4-oxopentyl Pivalate (114). To a solution of **113** (663 mg, 3.07 mmol) in methylene chloride (6 mL) was added diisopropylethylamine (1.60 mL, 9.21 mmol), followed by [2-(trimethylsilyl)ethoxy]methyl chloride (1.09 mL, 6.14 mmol). The solution was heated at reflux for 4 h and, after cooling, was partitioned between methylene chloride and water. The aqueous phase was extracted with methylene chloride (3×), and the combined organic extracts were washed with brine, dried (magnesium sulfate), and concentrated. Chromatography of the residue on silica, eluting with 20% ethyl acetate in hexane, afforded 987 mg (93%) of **114** as a colorless oil: $[\alpha]^{24}_D$ −29.4° (*c* 1.04, $CHCl_3$); IR (neat) 2957, 1730, 1284, 1250, 1157, 1109, 1056, 1034, 920, 861, 836 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.01 (9H, s), 0.87 (2H, dd, J = 10 and 7 Hz), 0.96 (3H, d, J = 7 Hz), 1.17 (9H, s), 2.19 (3H, s), 2.25 (1H, m), 3.59 (2H, m), 3.81 (1H, d, J = 7 Hz), 4.02 (1H, dd, J = 11 and 6 Hz), 4.08 (1H, dd, J = 11 and 6 Hz), 4.64 (1H, d, J = 7 Hz), 4.67 (1H, d, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ −1.5, 13.6, 17.9, 26.6, 27.1, 35.5, 38.8, 64.9, 66.0, 84.3, 95.2, 178.2, 209.1; MS m/z 303, 271, 259, 247, 245, 217, 199, 187, 171, 159, 143, 127, 115, 103, 73, 57, 43. Anal. Calcd for $C_{17}H_{34}O_5Si$: C, 58.92; H, 9.89. Found: C, 58.95; H, 10.18.

Aldol Condensation of 106 with 114. Hydroxy Ketone 123. To a solution of diisopropylamine (24 μL, 0.17 mmol) in tetrahydrofuran (0.5 mL) at 0 °C was added dropwise *n*-butyllithium (115 μL of a 1.46 M solution in hexane, 0.17 mmol). After the solution was stirred for 15 min at 0 °C, it was cooled to −78 °C and a solution of **114** (49 mg, 0.14 mmol) in tetrahydrofuran (0.5 mL) was added slowly. The mixture was stirred for 30 min at −78 °C, and a solution of **106** (50 mg, 0.13 mmol) in tetrahydrofuran (0.5 mL) was added rapidly. After the mixture was stirred for 30 min at −78 °C, it was allowed to warm to 0 °C and was partitioned between ether and saturated, aqueous sodium bicarbonate solution. The separated aqueous phase was extracted with ether (3×), and the combined organic extracts were washed with brine and dried (magnesium sulfate). The solvent was removed, and the residual oil was chromatographed on silica, eluting with 25% ethyl acetate in hexane, to give 76 mg (80%) of **123** as a 3:2 mixture of diastereomers: IR (neat) 3500 (br), 2962, 2934, 1729, 1514, 1248, 1161, 1059, 1036, 994, 860, 836 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.37 (9H, s), 0.93 (14H, m), 1.19 (9H, s), 1.38 (4H, m), 1.56 (1H, m), 2.22 (4H, m), 2.75 (3H, m), 3.33 (1H, d, J = 10 Hz), 3.59 (2H, m), 3.75 (1H, m), 3.79 (3H, s), 3.90 (2H, m), 4.07 (3H, m), 4.48 (2H, m), 4.66 (2H, m), 5.54 (1H, m), 5.70 (1H, dd, J = 8 and 3 Hz), 6.86 (2H, d, J = 8 Hz), 7.25 (2H, d, J = 8 Hz); ^{13}C NMR ($CDCl_3$) δ −1.5, 12.3 (2×), 12.5, 13.5, 13.7, 16.3, 16.5, 16.6, 17.9, 27.2, 27.7, 27.8, 30.5, 32.1, 32.8, 32.9, 35.2, 35.4, 38.8, 41.4, 41.5, 42.2, 55.2, 65.0, 66.1 (2×), 69.5, 69.7, 69.9, 70.6, 71.2, 71.4, 74.3, 75.7 (2×), 83.9, 84.5, 95.1, 95.2, 95.8, 113.8, 128.2, 128.3, 129.2, 130.7, 135.2 (2×), 159.1, 178.2, 210.7, 211.0; MS m/z 597, 523, 510, 467, 449, 396, 359, 325, 293, 287, 267, 245, 239, 221, 193, 179, 167, 143, 121, 109, 73, 57.

α,β-Unsaturated Ketone 124. To a solution of **123** (128 mg, 0.17 mmol) in methylene chloride (2 mL) was added triethylamine (73 μL, 0.52 mmol), followed by acetic anhydride (33 μL, 0.35 mmol) and 4-(dimethylamino)pyridine (1 mg). The mixture was stirred for 1.5 h and cooled to 0 °C, and 1,8-diazabicyclo[5.4.0]undec-7-ene (104 μL, 0.70 mmol) was added. After 1 h at 0 °C, the mixture was partitioned between ether and water and the separated aqueous phase was extracted with ether (3×). The combined organic extracts were washed with brine, dried (magnesium sulfate), and concentrated. Chromatography of the residue on silica, eluting with 20% ethyl acetate in hexane, gave 109 mg (87%) of **124** as a colorless oil: $[\alpha]^{22}_D$ −3.19° (*c* 0.94, $CHCl_3$); IR (neat) 2962, 2943, 2934, 2878, 1730, 1699, 1633, 1514, 1461, 1379, 1364, 1301, 1284, 1249, 1215, 1160, 1111, 1098, 1073, 1058, 1036, 993, 973, 943, 860, 836 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (9H, s), 0.87 (3H, d, J = 7 Hz), 0.88 (3H, t, J = 7 Hz), 0.91 (3H, d, J = 7 Hz), 0.95

(3H, d, J = 7 Hz), 1.18 (9H, s), 1.20−1.76 (5H, m), 2.09−2.18 (2H, m), 2.20−2.31 (2H, m), 3.39 (1H, dd, J = 10 and 3 Hz), 3.50−3.66 (2H, m), 3.80 (3H, s), 3.90−3.99 (1H, m), 4.02 (1H, d, J = 7 Hz), 4.07−4.15 (2H, m), 4.39−4.49 (1H, m), 4.49 (2H, s), 4.62 (1H, d, J = 7 Hz), 4.67 (1H, d, J = 7 Hz), 5.58 (1H, dd, J = 10 and 3 Hz), 5.75 (1H, dd, J = 10 and 2 Hz), 6.60 (1H, dd, J = 17 and 3 Hz), 6.87 (2H, d, J = 9 Hz), 6.94 (1H, dd, J = 16 and 5 Hz), 7.26 (2H, d, J = 9 Hz); ^{13}C NMR ($CDCl_3$) δ −1.5, 12.1, 12.7, 13.6, 16.4, 17.9, 27.2, 27.6, 30.6, 35.1, 35.6, 36.9, 38.8, 41.1, 55.2, 64.9, 65.9, 68.3, 69.7, 71.2, 75.2, 82.8, 94.6, 96.0, 113.8, 123.8, 128.1, 129.3, 130.5, 135.5, 146.9, 159.2, 178.2, 199.2; MS *m/z* 287, 245, 209, 193, 157, 143, 121, 73. Anal. Calcd for $C_{40}H_{64}O_9Si$: C, 67.00; H, 9.00. Found: C, 66.71; H, 8.99.

Alcohol 125. To a solution of **124** (54 mg, 0.075 mmol) in tetrahydrofuran (2 mL) at 0 °C was added dropwise methylmagnesium chloride (50 μL, 0.15 mmol). After 30 min at 0 °C, the mixture was partitioned between ether and saturated, aqueous ammonium chloride. The separated aqueous phase was extracted with ether (3×), and the combined organic extracts were washed with brine, dried (magnesium sulfate), and concentrated. Chromatography of the residue on silica, eluting with 25% ethyl acetate in hexane, gave 51 mg (93%) of **125** as a colorless oil: $[\alpha]^{22}_D$ +26.6° (*c* 0.94, $CHCl_3$); IR (neat) 3450 (br), 2962, 2934, 2878, 1727, 1514, 1249, 1188, 1160, 1097, 1072, 1058, 1028, 979, 859, 836 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.02 (9H, s), 0.81−0.98 (11H, m), 1.05 (3H, d, J = 7 Hz), 1.19 (9H, s), 1.31 (3H, s), 1.25−1.75 (6H, m), 2.00−2.12 (3H, m), 2.18−2.28 (1H, m), 3.29 (1H, d, J = 3 Hz), 3.40 (1H, d, J = 10 Hz), 3.80 (3H, s), 3.58−3.95 (4H, m), 4.30 (1H, dd, J = 11 and 4 Hz), 4.44−4.51 (2H, m), 4.69 (1H, d, J = 7 Hz), 4.78 (1H, d, J = 7 Hz), 5.57 (1H, dd, J = 10 and 2 Hz), 5.69 (1H, dd, J = 10 and 2 Hz), 5.74−5.84 (2H, m), 6.86 (2H, d, J = 9 Hz), 7.26 (2H, d, J = 9 Hz); ^{13}C NMR ($CDCl_3$) δ −1.4, 12.2, 12.7, 16.4, 17.4, 18.0, 24.8, 27.2, 27.6, 30.6, 34.3, 35.2, 37.7, 38.7, 41.2, 55.2, 66.2, 66.3, 69.4, 69.5, 71.3, 74.5, 74.9, 91.1, 95.7, 97.8, 113.7, 128.6, 129.2, 130.0, 130.8, 133.8, 135.2, 159.1, 178.4; MS *m/z* 477, 447, 429, 412, 363, 359, 321, 291, 287, 245, 193, 143, 122, 121, 109, 73, 57.

Sulfoxide 127. To a solution of **125** (12 mg, 0.016 mmol) in methylene chloride (1 mL) was added triethylamine (23 μL, 0.16 mmol), and, after the mixture was cooled to −78 °C, a solution of phenylsulfenyl chloride (5 mg, 0.033 mmol) in methylene chloride (0.5 mL) was added dropwise. The mixture was allowed to warm to room temperature and was recooled to −78 °C, and two additional portions of triethylamine (23 μL) and benzenesulfenyl chloride (5 mg in 0.5 mL of methylene chloride) were added. After warming to room temperature, the mixture was diluted with methylene chloride, washed with water and brine, and dried (magnesium sulfate). Removal of the solvent and chromatography of the residue on silica, eluting with a gradient of 20% to 30% ethyl acetate in hexane, gave 12 mg (87%) of **127**: $[\alpha]^{23}_D$ +2.2° (*c* 2.04, $CHCl_3$); IR (neat) 2961, 2932, 2879, 1728, 1514, 1461, 1284, 1249, 1156, 1129, 1107, 1092, 1075, 1047, 1036, 997, 980, 860, 836 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ −0.01 (9H, s), 0.29 (3H, d, J = 7 Hz), 0.89 (3H, d, J = 7 Hz), 0.85−0.95 (2H, m), 0.96 (3H, d, J = 7 Hz), 1.02 (3H, t, J = 7 Hz), 1.15 (3H, s), 1.20 (9H, s), 1.15−1.28 (2H, m), 1.36−1.52 (2H, m), 1.65−1.80 (2H, m), 2.08−2.19 (2H, m), 2.22−2.36 (1H, m), 3.38−3.55 (2H, m), 3.58−3.73 (3H, m), 3.79 (3H, s), 3.85 (1H, dd, J = 11 and 7 Hz), 3.89−3.98 (1H, m), 4.14 (1H, dd, J = 11 and 3 Hz), 4.30 (1H, t, J = 10 Hz), 4.39−4.53 (4H, m), 5.44 (1H, d, J = 10 Hz), 5.63 (1H, dd, J = 10 and 3 Hz), 5.78 (1H, dd, J = 10 and 2 Hz), 6.85 (2H, d, J = 9 Hz), 7.22 (2H, d, J = 9 Hz), 7.35−7.46 (3H, m), 7.51 (2H, d, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ −1.4, 11.8, 12.0, 12.7, 13.6, 16.9, 18.0, 27.3, 27.6, 30.6, 35.0, 35.8, 36.0, 38.9, 41.5, 55.3, 65.5, 66.0, 67.4, 69.4, 69.7, 71.2, 77.2, 82.4, 91.4, 95.9, 113.8, 118.8, 124.3, 127.8, 128.8, 129.3, 130.0, 130.6, 135.7, 141.1, 143.2, 159.1, 178.4; MS *m/z* 595, 576, 445, 429, 359, 315, 287, 219, 193, 192, 179, 166, 159, 149, 135, 121, 109, 73, 57.

Sulfone 128. To a solution of **127** (7 mg, 0.008 mmol) in methanol (0.5 mL) at 0 °C was added a solution of Oxone (15 mg, 0.025 mmol) in water (0.25 mL). The white suspension was warmed to room temperature and stirred for 24 h. The mixture was partitioned between methylene chloride and water, and the separated aqueous phase was extracted with methylene chloride (3×). The combined organic extracts were washed with brine, dried (magnesium sulfate), and concentrated. Chromatography of the residue on silica, eluting with 25% ethyl acetate in hexane, gave 63 mg (88%) of **128** as a colorless foam: IR (neat) 2960, 2930, 2877, 1729, 1514, 1307, 1285, 1249, 1150, 1096, 1085, 1035, 993, 859, 836 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.01 (9H, s), 0.68 (3H, d, J = 7 Hz), 0.87 (3H, d, J = 7 Hz), 0.85−0.94 (2H, m), 0.96 (3H, d, J = 7 Hz), 1.02 (3H, t, J = 7 Hz), 1.22 (9H, s), 1.18−1.33 (2H, m), 1.38−1.48 (1H, m), 1.49 (3H, s), 1.56−1.73 (2H, m), 1.88−2.05 (2H, m), 2.20−2.31 (2H, m), 3.44−3.54 (2H, m), 3.68−3.77 (1H, m), 3.79 (3H, s), 3.82 (1H, d, J = 10 Hz), 3.88−3.97 (1H, m), 3.98 (1H, dd, J = 11 and 6 Hz), 4.16 (1H, dd, J = 11 and 7 Hz), 4.24 (1H, dd, J = 11 and 3 Hz), 4.44 (1H, d, J = 11 Hz), 4.47 (1H, d, J = 11 Hz), 4.47−4.55 (3H, m), 5.21 (1H, dd, J = 10 and 3 Hz), 5.44 (1H, d, J = 11 Hz), 5.60 (1H, dd, J = 10 and 2 Hz), 6.85 (2H, d, J = 9 Hz), 7.23 (2H, d, J = 9 Hz), 7.45 (2H, t, J = 8 Hz), 7.56 (1H, t, J = 7 Hz), 7.85 (2H, d, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ −1.4, 11.9, 12.1, 12.6, 13.6, 16.6, 18.0, 27.3, 27.5, 30.4, 34.8, 35.4, 35.6, 38.9, 41.3, 55.3, 65.5, 65.9, 67.9, 68.4, 69.6, 70.8, 76.4, 82.2, 91.5, 95.8, 113.8, 119.0, 127.7, 128.3, 128.7, 129.3, 130.6, 133.0, 134.9, 141.1, 143.8, 159.1, 178.4.

In a few runs, it was found that oxidation of **127** was incomplete under these conditions, affording a ca. 3:1 mixture of **128** and **127**, respectively. These two compounds are indistinghishable by thin-layer chromatography. In these cases, the mixture was resubjected to the oxidation conditions described above.

Alcohol 129. To a solution of **128** (16 mg, 0.019 mmol) in acetonitrile (1.5 mL) and water (0.5 mL) at 0 °C was added ceric ammonium nitrate (41 mg, 0.075 mmol). The solution was allowed to warm to room temperature and was stirred for 1 h. The mixture was partitioned between ether and water, and the separated aqueous phase was extracted with ether (3×). The combined organic extracts were washed with brine, dried (magnesium sulfate), and concentrated. Chromatography of the residue on silica, eluting with 30% ethyl acetate in hexane, gave 12.6 mg (92%) of **129** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.00 (9H, s), 0.73 (3H, d, J = 7 Hz), 0.85 (3H, d, J = 7 Hz), 0.88 (2H, m), 0.93 (3H, d, J = 7 Hz), 0.99 (3H, t, J = 7 Hz), 1.19 (9H, s), 1.20 (2H, m), 1.40 (1H, m), 1.47 (3H, d, J = 7 Hz), 1.64 (3H, m), 1.92 (2H, m), 2.17 (2H, m), 3.47 (2H, m), 3.71 (1H, m), 3.81 (1H, d, J = 8 Hz), 3.89 (1H, dd, J = 11 and 7 Hz), 4.13 (1H, dd, J = 11 and 7 Hz), 4.16 (1H, m), 4.23 (1H, dd, J = 11 and 3 Hz), 4.45 (1H, d, J = 7 Hz), 4.50 (1H, m), 4.51 (1H, d, J = 7 Hz), 5.20 (1H, dd, J = 10 and 3 Hz), 5.41 (1H, d, J = 10 Hz), 5.59 (1H, dd, J = 10 and 2 Hz), 7.43 (2H, t, J = 7 Hz), 7.54 (1H, t, J = 7 Hz), 7.82 (2H, d, J = 7 Hz).

***tert*-Butyldimethylsilyl Ether 130.** To a solution of **129** (5.3 mg, 0.0072 mmol) in methylene chloride (1 mL) at 0 °C was added dropwise 2,6-lutidine (4.2 μL, 0.036 mmol), followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (4.2 μL, 0.018 mmol). After the solution was stirred for 10 min at 0 °C, it was partitioned between ether and saturated, aqueous sodium bicarbonate and the aqueous phase was extracted with ether (3×). The combined organic extracts were washed with brine, dried (magnesium sulfate), and concentrated, and the residue was chromatographed on silica, eluting with 20% ethyl acetate in hexane, to give 4.6 mg (75%) of **130** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.00 (9H, s), 0.01 (3H, s), 0.02 (3H, s), 0.65 (3H, d, J = 7 Hz), 0.82 (2H, m), 0.83 (9H, s), 0.84 (3H, d, J = 7 Hz), 0.93 (3H, d, J = 7 Hz), 1.00 (3H, t, J = 7 Hz), 1.20 (9H, s), 1.25 (3H, m), 1.48 (3H, d, J = 1 Hz), 1.60 (2H, m), 1.86 (1H, m), 1.93 (2H, m), 2.18 (1H, m), 3.45 (2H, m), 3.68 (1H, m), 3.79 (1H, d, J = 10 Hz), 3.94 (1H, dd, J = 11 and 6 Hz), 4.11 (1H, m), 4.13 (1H, dd, J = 11 and 7 Hz), 4.23 (1H, dd, J = 11 and 3 Hz), 4.42 (1H, m), 4.47 (2H, s), 5.18 (1H, dd, J = 10 and 2 Hz), 5.42 (1H, d, J = 11 Hz), 5.57 (1H, dd, J = 10 and 2 Hz), 7.43 (2H, t, J = 7 Hz), 7.52 (1H, t, J = 7 Hz), 7.82 (2H, d, J = 7 Hz).

Alcohol 131. Lithium aluminum hydride (2 mg) was added to a solution of **130** (11 mg, 0.013 mmol) in tetrahydrofuran (1 mL) at 0 °C, and the mixture was stirred for 15 min at 0 °C. An aqueous solution of Rochelle's salt was added dropwise to quench the reaction, and the mixture was diluted with ether, dried (magnesium sulfate), filtered, and concentrated. Chromatography of the residue on silica, eluting with 35% ethyl acetate in hexane, afforded 7.6 mg (77%) of **131** as a colorless foam: ^{1}H NMR ($CDCl_3$) δ 0.04 (9H, s), 0.04 (3H, s), 0.05 (3H, s), 0.67 (3H, d, J = 7 Hz), 0.86 (9H, s), 0.87 (3H, d, J = 7 Hz),

0.94 (2H, m), 0.95 (3H, d, J = 7 Hz), 1.02 (3H, t, J = 7 Hz), 1.24 (2H, m), 1.42 (1H, m), 1.50 (3H, s), 1.63 (3H, m), 1.80 (1H, m), 1.89 (1H, m), 2.01 (1H, m), 2.22 (1H, m), 3.46 (2H, m), 3.60 (2H, m), 3.77 (1H, m), 3.88 (1H, d, J = 9 Hz), 4.13 (1H, dd, J = 11 and 7 Hz), 4.14 (1H, m), 4.47 (1H, m), 4.51 (1H, d, J = 7 Hz), 4.54 (1H, d, J = 7 Hz), 5.21 (1H, dd, J = 10 and 3 Hz), 5.45 (1H, d, J = 11 Hz), 5.60 (1H, dd, J = 10 and 1 Hz), 7.45 (2H, t, J = 8 Hz), 7.56 (1H, t, J = 7 Hz), 7.84 (2H, d, J = 7 Hz).

Reductive Cleavage of 131. Alcohol 65. To a solution of **131** (4.2 mg, 0.0055 mmol) in methanol (1 mL) was added disodium hydrogen phosphate (3.1 mg, 0.002 mmol), followed by sodium amalgam (19.7 mg, 2.5%, 0.021 mmol), and the mixture was stirred vigorously at room temperature for 1 h. Additional portions of disodium hydrogen phosphate (5 mg) and sodium amalgam (20 mg) were added, and the mixture was stirred for a further 1 h. The mixture was diluted with ether and filtered, and the filtrate was washed with saturated, aqueous ammonium chloride and brine and dried (magnesium sulfate). Removal of the solvent and chromatography of the residual oil on silica, eluting with 20% ethyl acetate in hexane, afforded 1.2 mg (35%) of **65**, identical with the substance obtained from **64**. In addition, 1.0 mg (38%) of **132** was isolated: ^{1}H NMR ($CDCl_3$) δ 0.07 (6H, s), 0.89 (9H, s), 0.92 (12H, m), 1.50 (6H, m), 1.79 (3H, s), 1.87 (2H, m), 2.24 (1H, m), 2.75 (1H, m), 3.39 (1H, dd, J = 10 and 8 Hz), 3.44 (1H, d, J = 10 Hz), 3.52 (1H, dd, J = 10 and 6 Hz), 4.18 (1H, m), 4.30 (1H, m), 5.24 (1H, d, J = 10 Hz), 5.57 (1H, dd, J = 10 and 2 Hz), 5.62 (1H, dd, J = 16 and 7 Hz), 5.69 (1H, dd, J = 10 and 1 Hz), 6.21 (1H, d, J = 16 Hz).

Aldehyde 133. To a solution of oxalyl chloride (54 μL, 0.62 mmol) in methylene chloride (5 mL) at −78 °C was added dropwise a solution of dimethyl sulfoxide (88 μL, 1.25 mmol) in methylene chloride (2 mL). After 5 min, a solution of **65** (130 mg, 0.21 mmol) in methylene chloride (2 mL) was added dropwise. The mixture was stirred for 30 min at −78 °C, triethylamine (0.43 mL, 3.12 mmol) was added, and the mixture was allowed to warm to room temperature and was partitioned between methylene chloride and water. The aqueous phase was extracted with methylene chloride (3×), and the combined organic extracts were washed with brine, dried (magnesium sulfate), and concentrated. Chromatography of the residue on silica, eluting with 10% ethyl acetate in hexane, gave 117 mg (90%) of **133** as a colorless oil: $[\alpha]^{23}_D$ −13.1° (c 1.91, $CHCl_3$); IR (neat) 2959, 2932, 2885, 2859, 1732, 1251, 1155, 1117, 1099, 1074, 1059, 1023, 1001, 987, 871, 860, 836, 776 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.02 (9H, s), 0.05 (6H, s), 0.88 (9H, s), 0.90 (14H, m), 1.20 (2H, m), 1.39 (3H, m), 1.55 (3H, s), 1.85 (2H, m), 2.23 (2H, m), 2.34 (1H, m), 2.60 (1H, m), 3.41 (2H, m), 3.69 (1H, m), 3.76 (1H, m), 4.10 (1H, m), 4.11 (1H, d, J = 10 Hz), 4.50 (1H, d, J = 7 Hz), 4.58 (1H, d, J = 7 Hz), 5.50 (1H, t, J = 7 Hz), 5.54 (1H, dd, J = 10 and 3 Hz), 5.69 (1H, dd, J = 10 and 2 Hz), 9.72 (1H, d, J = 3 Hz); ^{13}C NMR ($CDCl_3$) δ −4.7, −1.4, 10.8, 11.1, 12.3, 12.5, 16.5, 18.0, 18.2, 25.9, 27.9, 30.5, 34.4, 35.3, 40.8, 44.7, 48.2, 65.4, 68.6, 75.2, 77.2, 82.5, 91.2, 95.6, 128.4 (×2), 132.5, 135.1, 204.3; MS m/z 625 (M^+ + 1), 624 (M^+), 623, 609, 581, 567, 551, 538, 509, 493, 477, 451, 419, 377, 353, 345, 311, 295, 221, 187. Anal. Calcd for $C_{34}H_{64}O_6Si_2$: C, 65.33; H, 10.32. Found: C, 65.54; H, 10.22.

Ester 135. A solution of **133** (115 mg, 0.18 mmol) and (carbomethoxymethylene)triphenylphosphorane (**134**, 123 mg, 0.37 mmol) in toluene (5 mL) was heated at reflux for 3 h. The solvent was evaporated, and the residue was chromatographed on silica, eluting with 10% ethyl acetate in hexane, to give 122 mg (98%) of **135** as a colorless oil: $[\alpha]^{22}_D$ +1.6° (c 1.75, $CHCl_3$); IR (neat) 2958, 2932, 1729, 1251, 1116, 1073, 1037, 1023, 998, 988, 860, 837 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.00 (9H, s), 0.05 (6H, s), 0.88 (9H, s), 0.90 (14H, m), 1.18 (2H, m), 1.38 (3H, m), 1.53 (3H, s), 1.85 (2H, m), 2.20 (2H, m), 2.35 (1H, m), 2.53 (1H, m), 3.39 (2H, m), 3.71 (3H, s), 3.72 (3H, m), 4.10 (1H, m), 4.48 (1H, d, J = 7 Hz), 4.55 (1H, d, J = 7 Hz), 5.43 (1H, t, J = 7 Hz), 5.55 (1H, dd, J = 10 and 2 Hz), 5.69 (1H, dd, J = 10 and 2 Hz), 5.87 (1H, dd, J = 10 and 1 Hz), 7.02 (1H, dd, J = 16 and 8 Hz); ^{13}C NMR ($CDCl_3$) δ −4.7, −1.5, 10.8, 12.3, 12.5, 16.5 (×2), 17.9, 18.2, 25.9, 27.9, 30.5, 34.3, 35.3, 38.9, 40.8, 44.7, 51.4, 65.3, 65.4, 68.7, 75.1, 77.2, 85.2, 91.1, 95.6, 120.6, 127.7, 128.5, 133.7, 135.1, 152.7, 167.0; MS m/z 680 (M^+), 667, 666, 638, 625, 624, 608, 551, 550, 534, 353.

Alcohol 136. To a solution of **135** (18 mg, 0.026 mmol) in toluene (2 mL) at −78 °C was added diisobutylaluminum hydride (79 μL of a 1.0 M solution in hexane, 0.079 mmol). The solution was stirred for 30 min at −78 °C, and the reaction was quenched by pouring the solution into ether and saturated, aqueous Rochelle's salt solution. The separated aqueous phase was extracted with ether (3×), and the combined organic extracts were washed with brine, dried (magnesium sulfate), and concentrated. Chromatography of the reside on silica, eluting with 25% ethyl acetate in hexane, afforded 16.2 mg (94%) of **136** as a colorless oil: $[\alpha]^{22}_D$ −3.0° (c 1.65, $CHCl_3$); IR (neat) 3500 (br), 2959, 2931, 2884, 1251, 1117, 1098, 1064, 1041, 1023, 1000, 988, 860, 837 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.02 (9H, s), 0.05 (6H, s), 0.88 (9H, s), 0.90 (14H, m), 1.20 (2H, m), 1.41 (4H, m), 1.53 (3H, s), 1.84 (2H, m), 2.21 (2H, m), 2.37 (2H, m), 3.42 (2H, m), 3.67 (1H, d, J = 9 Hz), 3.74 (2H, m), 4.10 (3H, m), 4.51 (1H, d, J = 7 Hz), 4.57 (1H, d, J = 7 Hz), 5.39 (1H, t, J = 7 Hz), 5.54 (1H, dd, J = 10 and 2 Hz), 5.71 (3H, m); ^{13}C NMR ($CDCl_3$) δ −4.7, −1.4, 11.0, 12.3, 12.5, 16.5, 17.4, 18.0, 18.2, 25.9, 27.9, 30.5, 34.2, 35.3, 38.6, 40.7, 44.7, 63.9, 65.2, 65.5, 68.8, 75.1, 85.9, 91.3, 95.6, 126.7, 128.5, 128.7, 134.3, 135.1, 136.4; MS m/z 653 (M^+ + 1), 652 (M^+), 651, 637, 635, 579, 567, 521, 509, 505, 407, 373, 353, 293, 275, 118, 103, 101, 75, 73. Anal. Calcd for $C_{36}H_{68}O_6Si_2$: C, 66.25; H, 10.50. Found: C, 66.22; H, 10.47.

Chloride 137. To a solution of N-chlorosuccinimide (99 mg, 0.74 mmol) in methylene chloride (10 mL) at 0 °C was added dimethyl sulfide (65 μL, 0.89 mmol). The resulting suspension was stirred for 5 min, and a solution of **136** (97 mg, 0.15 mmol) in methylene chloride (2 mL) was added. The mixture was stirred at 0 °C for 15 min and at room temperature for 15 min and partitioned between methylene chloride and water, and the aqueous phase was extracted with methylene chloride (3×). The combined organic extracts were washed with brine, dried (magnesium sulfate), and concentrated. Chromatography of the residue on silica, eluting with 5% ethyl acetate in hexane, afforded 93 mg (93%) of **137** as a colorless oil: $[\alpha]^{22}_D$ −4.1° (c 2.70, $CHCl_3$); IR (neat) 2958, 2932, 2884, 1251, 1116, 1099, 1073, 1059, 1040, 1025, 998, 989, 859, 836, 776 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.02 (9H, s), 0.05 (6H, s), 0.87 (14H, m), 0.88 (9H, s), 1.17 (2H, m), 1.39 (3H, m), 1.53 (3H, s), 1.84 (2H, m), 2.20 (2H, m), 2.37 (2H, m), 3.40 (2H, m), 3.66 (1H, d, J = 9 Hz), 3.73 (2H, m), 4.07 (3H, m), 4.50 (1H, d, J = 7 Hz), 4.56 (1H, d, J = 7 Hz), 5.38 (1H, t, J = 7 Hz), 5.54 (1H, dd, J = 10 and 2 Hz), 5.68 (2H, m), 5.83 (1H, dd, J = 15 and 7 Hz); ^{13}C NMR ($CDCl_3$) δ −4.7, −1.4, 11.0, 12.3, 12.5, 16.5, 17.0, 18.0, 18.2, 25.9, 27.9, 30.5, 34.3, 35.3, 38.5, 40.7, 44.7, 45.4, 63.9, 65.3, 65.5, 68.8, 75.1, 77.2, 85.6, 91.2, 95.6, 125.5, 127.0, 128.5, 134.1, 135.1, 139.0; MS m/z 679 and 670 (M^+), 671 and 669, 650, 635, 613, 584, 577, 567, 553, 523, 509, 465, 447, 419, 391, 381, 377, 353, 331, 309, 287, 253, 221, 187, 73.

Sulfone 138. A solution of **137** (92 mg, 0.14 mmol) and sodium benzenesulfinate (113 mg, 0.69 mmol) in dimethylformamide (2 mL) was stirred for 42 h at room temperature. The mixture was partitioned between ether and water, and the separated aqueous phase was extracted with ether (3×). The combined organic extracts were washed with water and brine and dried (magnesium sulfate). Removal of the solvent and chromatography of the residue on silica, eluting with 15% ethyl acetate in hexane, provided 90 mg (84%) of **138** as a colorless oil: $[\alpha]^{22}_D$ −15.7° (c 1.34, $CHCl_3$); IR (neat) 2958, 2931, 1318, 1251, 1148, 1079, 1025, 993, 863, 836, 774, 737 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ −0.01 (9H, s), 0.05 (6H, s), 0.71 (3H, d, J = 7 Hz), 0.87 (11H, m), 0.88 (9H, s), 1.21 (2H, m), 1.39 (2H, m), 1.47 (3H, s), 1.55 (1H, m), 1.84 (2H, m), 2.18 (2H, m), 2.32 (2H, m), 3.36 (2H, m), 3.65 (3H, m), 3.69 (1H, dd, J = 14 and 7 Hz), 3.80 (1H, dd, J = 14 and 6 Hz), 4.08 (1H, m), 4.42 (1H, d, J = 7 Hz), 4.49 (1H, d, J = 7 Hz), 5.33 (1H, t, J = 7 Hz), 5.50 (2H, m), 5.52 (1H, dd, J = 10 and 3 Hz), 5.69 (1H, dd, J = 10 and 2 Hz), 7.54 (2H, m), 7.64 (1H, m), 7.85 (2H, m); ^{13}C NMR ($CDCl_3$) δ −4.7, −1.4, 11.0, 12.3, 12.5, 16.5, 17.0, 17.9, 18.2, 25.9, 27.9, 30.5, 34.2, 35.3, 39.1, 40.7, 44.7, 60.2, 65.1, 65.4, 68.7, 75.1, 85.5, 91.3, 95.6, 115.8, 127.0, 128.5, 128.6, 128.9, 133.5, 133.9, 135.1, 138.3, 144.7; MS m/z 775 (M^+ − 1), 761, 645, 629, 577, 417, 353, 225, 171, 161, 143, 133, 125, 117, 115. Anal. Calcd for $C_{42}H_{72}O_7SSi_2$: C, 64.90; H, 9.34. Found: C, 64.81; H, 9.32.

Coupling of 68 with 138. Hydroxy Sulfone 139. To a solution of **138** (123 mg, 0.16 mmol) in tetrahydrofuran (2 mL) at −78 °C was added n-butyllithium (103 μL of a 1.53 M solution in hexane, 0.16 mmol), and the resultant yellow solution was stirred for 30 min at −78

°C. A solution of **68** (52 mg, 0.11 mmol) in tetrahydrofuran (0.5 mL) was added rapidly, and the mixture was stirred for 1 h at −78 °C. Aqueous ammonium chloride (1 mL) was added, and the mixture was warmed to room temperature and was partitioned between ether and water. The separated aqueous phase was extracted with ether (3×), and the combined extracts were washed with brine, dried (magnesium sulfate), and concentrated. Chromatography of the residue on silica, eluting with 20% ethyl acetate in hexane, gave 68 mg (50%) of **139**: $[\alpha]^{24}_D$ +72.9° (*c* 0.75, $CHCl_3$); IR (neat) 3434, 2957, 2932, 2880, 1722, 1305, 1249, 1147, 1113, 1082, 1058, 1039, 998, 860, 836, 757, 730, 630 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.02 (9H, s), 0.01 (9H, s), 0.04 (6H, s), 0.59 (6H, q, *J* = 8 Hz), 0.77 (3H, d, *J* = 7 Hz), 0.87 (9H, s), 0.90 (10H, m), 0.93 (9H, t, *J* = 8 Hz), 1.20 (3H, d, *J* = 8 Hz), 1.10−1.25 (2H, m), 1.35−1.46 (3H, m), 1.46 (3H, s), 1.56 (1H, m), 1.69 (1H, d, *J* = 3 Hz), 1.84 (2H, td, *J* = 12 and 4 Hz), 2.16−2.35 (4H, m), 2.66 (1H, m), 3.38 (1H, dd, *J* = 10 and 1 Hz), 3.44−3.74 (8H, m), 3.75 (3H, s), 3.96−4.00 (3H, m), 4.09 (1H, m), 4.49 (1H, d, *J* = 7 Hz), 4.56 (1H, d, *J* = 7 Hz), 4.58 (1H, s), 4.63 (1H, d, *J* = 7 Hz), 4.74 (1H, d, *J* = 7 Hz), 4.86 (1H, d, *J* = 10 Hz), 5.35−5.46 (2H, m), 5.54 (1H, dd, *J* = 10 and 3 Hz), 5.67 (1H, dd, *J* = 10 and 10 Hz), 5.79 (1H, dd, *J* = 15 and 8 Hz), 6.87 (1H, d, *J* = 2 Hz), 7.47 (2H, t, *J* = 7 Hz), 7.56 (1H, t, *J* = 9 Hz), 7.89 (2H, d, *J* = 9 Hz); ^{13}C NMR ($CDCl_3$) δ −4.7, −1.5, −1.3, 6.3, 7.3, 11.2, 12.3, 12.5, 16.5, 17.0, 17.5, 17.9, 18.1, 18.2, 25.9, 27.9, 30.5, 31.1, 34.3, 35.3, 39.8, 40.7, 44.7, 51.9, 65.3, 65.4, 65.5, 68.8, 70.3, 73.6, 75.1, 75.9, 77.2, 82.6, 84.1, 85.3, 85.8, 92.1, 92.5, 95.6, 120.0, 126.3, 128.5, 129.2, 130.0, 133.1, 134.4, 135.0, 140.0, 144.6, 147.5, 167.4.

Coupling of 60 with 138. Hydroxy Sulfone 140. To a solution of **138** (25.0 mg, 0.32 mmol) in tetrahydrofuran (0.7 mL) at −78 °C was added *n*-butyllithium (22 μL of a 1.45 M solution in hexane, 0.32 mmol), and the mixture was stirred for 30 min at −78 °C. To the resulting yellow solution was added a solution of **60** (6.0 mg, 0.012 mmol) in tetrahydrofuran (0.5 mL), and the mixture was stirred for 1 h at −78 °C. Saturated, aqueous ammonium chloride (0.2 mL) was added to quench the reaction that was partitioned between ether and water. The separated aqueous layer was extracted with ether (2×), and the combined extracts were washed with brine, dried (magnesium sulfate), and concentrated. The residue was purified by chromatography on silica, using 15% ethyl acetate in hexane as eluant, to give 8.0 mg (51%) of **140**: $[\alpha]^{22}_D$ +27.7° (*c* 0.74, $CHCl_3$); IR (neat) 3316, 2958, 2932, 2880, 2860, 1722, 1460, 1380, 1307, 1250, 1152, 1114, 1036, 980, 859, 836, 665 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (9H, s), 0.01 (9H, s), 0.05 (6H, s), 0.52−0.68 (6H, m), 0.75 (3H, d, *J* = 7 Hz), 0.87 (9H, s), 0.79−1.02 (24H, m), 1.25 (3H, d, *J* = 7 Hz), 1.39 (3H, s), 1.09−1.55 (4H, m), 1.79−1.88 (2H, m), 2.10−2.33 (4H, m), 2.62−2.66 (1H, m), 3.36−3.63 (5H, m), 3.83 (3H, s), 3.67−3.87 (3H, m), 3.98−4.14 (4H, m), 4.40 (1H, d, *J* = 7 Hz), 4.47 (1H, d, *J* = 7 Hz), 4.79 (1H, d, *J* = 7 Hz), 4.83 (1H, d, *J* = 7 Hz), 5.17 (1H, d, *J* = 9 Hz), 5.28 (1H, t, *J* = 7 Hz), 5.38−5.56 (3H, m), 5.69 (1H, dd, *J* = 10 and 2 Hz), 6.92 (1H, d, *J* = 3 Hz), 7.44 (2H, t, *J* = 7 Hz), 7.52 (1H, t, *J* = 7 Hz), 7.96 (2H, d, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$) δ −4.7, −1.4, −1.3, 6.2, 7.1, 11.5, 12.3, 12.5, 15.4, 16.5, 17.2, 18.0, 18.1, 18.2, 25.9, 27.9, 30.5, 33.2, 33.5, 34.3, 35.4, 39.3, 40.8, 44.8, 51.9, 65.3, 65.5, 66.2, 68.9, 69.1, 75.1, 75.3, 83.4, 83.9, 85.7, 87.4, 92.4, 95.4, 95.6, 120.8, 125.7, 128.2, 128.6, 129.4, 130.1, 132.5, 134.7, 135.0, 140.8, 143.4, 147.2, 166.6; MS *m/z* 1100, 944, 892, 793, 720, 691, 646, 630, 594, 510, 496, 377, 353, 215, 187, 103, 75.

β,γ-Unsaturated Lactone 141. A solution of sodium (1 mg) in dry methanol (3 mL) was cooled to 0 °C, and tetrahydrofuran (3 mL) and disodium hydrogen phosphate (101 mg, 0.71 mmol) were added. A solution of **139** (60.0 mg, 0.047 mmol) in tetrahydrofuran (6 mL) was added, and after 30 min at 0 °C, the mixture was partitioned between ether and aqueous ammonium chloride. The separated aqueous phase was extracted with ether (3×), and the combined organic extracts were washed with brine, dried (magnesium sulfate), and concentrated. Chromatography of the residue on silica, eluting with 20% ethyl acetate in hexane, afforded 50 mg (85%) of **141** as a colorless solid: $[\alpha]^{24}_D$ +49.8° (*c* 1.23, $CHCl_3$); IR (neat) 2957, 2928, 2881, 2854, 1786, 1321, 1314, 1249, 1203, 1151, 1127, 1099, 1079, 1056, 1031, 1002, 989, 860, 836, 777, 740, 690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (9H, s), 0.04 (15H, s), 0.69 (3H, d, *J* = 7 Hz), 0.72−0.81 (6H, m), 0.87 (9H, s), 0.84−0.99 (11H, m), 1.02 (1H, m), 1.04 (9H, t, *J* = 8 Hz), 1.18 (1H, q, *J* = 12 Hz), 1.39 (3H, m), 1.49 (2H, s), 1.54 (1H, m), 1.64 (1H, d, *J* = 3 Hz), 1.83 (2H, m), 1.87 (3H, s), 2.22 (2H, m), 2.32 (2H, m), 3.34 (1H, d, *J* = 11 Hz), 3.36 (1H, dd, *J* = 10 and 1 Hz), 3.53 (1H, q, *J* = 8 Hz), 3.63−3.89 (8H, m), 4.09 (1H, m), 4.42 (1H, d, *J* = 11 Hz), 4.48 (1H, m), 4.55 (1H, d, *J* = 7 Hz), 4.60 (1H, d, *J* = 7 Hz), 4.76 (1H, dd, *J* = 15 and 11 Hz), 4.78 (1H, d, *J* = 7 Hz), 4.86 (1H, d, *J* = 7 Hz), 5.41 (1H, t, *J* = 8 Hz), 5.53 (1H, dd, *J* = 10 and 2 Hz), 5.68 (1H, dd, *J* = 10 and 2 Hz), 5.70 (1H, m), 5.96 (1H, dd, *J* = 15 and 8 Hz), 7.47 (2H, t, *J* = 8 Hz), 7.57 (1H, t, *J* = 7 Hz), 7.91 (2H, d, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$) δ −4.7, −1.5, −1.3, 5.9, 7.0, 10.9, 12.4, 12.5, 16.5, 17.3, 18.1, 18.2, 19.1, 25.9, 27.9, 30.5, 34.3, 35.3, 39.5, 40.8, 44.7, 47.1, 65.4, 65.6, 68.7, 70.3, 72.0, 75.1, 77.2, 82.9, 84.8, 85.2, 91.4, 94.1, 94.5, 95.6, 117.5, 118.5, 127.3, 128.2, 128.5, 131.0, 133.3, 133.7 (×2), 135.1, 138.6, 145.2, 173.6; MS *m/z* 849, 592, 565, 507, 469, 410, 351, 247, 219, 196, 130, 102, 75. Anal. Calcd for $C_{64}H_{110}O_{13}SSi_4$: C, 62.40; H, 9.00. Found: C, 62.51; H, 9.11.

β-Methoxy Lactone 142. To a solution of sodium methoxide (24 μL of a 0.1 M solution in methanol, 0.0024 mmol) and disodium hydrogen phosphate (48 mg, 0.33 mmol) in methanol−tetrahydrofuran (1:1, 0.8 mL) at 0 °C was added a solution of **140** (88.0 mg, 0.022 mmol) in tetrahydrofuran (5 mL). Stirring was continued for 2 h at 0 °C and for 2 h at room temperature, and the mixture was diluted with ether and washed with water. The separated aqueous layer was extracted with ether (2×), and the combined ethereal extracts were washed with brine, dried (magnesium sulfate), and concentrated. Chromatography of the residue on silica, eluting with 20% ethyl acetate in hexane, gave 11.6 mg (42%) of **142**: IR (neat) 2956, 2931, 2880, 2859, 1786, 1461, 1449, 1381, 1322, 1314, 1249, 1202, 1172, 1153, 1131, 1115, 1090, 1081, 1057, 1032, 1029, 1000, 967, 919, 860, 836, 775, 746, 731, 689 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.01 (9H, s), 0.03 (9H, s), 0.05 (6H, s), 0.87 (9H, s), 1.04 (9H, t, *J* = 8 Hz), 0.69−1.06 (25H, m), 1.16−1.47 (6H, m), 1.50 (3H, s), 1.80−1.88 (2H, m), 2.22−2.50 (2H, m), 3.28 (1H, d, *J* = 11 Hz), 3.36 (1H, d, *J* = 11 Hz), 3.43 (3H, s), 3.50−3.91 (8H, m), 4.01 (1H, m), 4.09 (1H, m), 4.26−4.30 (1H, m), 4.41 (1H, d, *J* = 11 Hz), 4.48−4.60 (4H, m), 4.75−4.87 (4H, m), 5.40 (1H, t, *J* = 7 Hz), 5.53 (1H, dd, *J* = 11 and 2 Hz), 5.69 (1H, d, *J* = 11 Hz), 5.90 (1H, dd, *J* = 16 and 8 Hz), 7.48 (2H, t, *J* = 8 Hz), 7.56 (1H, t, *J* = 8 Hz), 7.90 (2H, d, *J* = 7 Hz).

In addition, 4.4 mg (17%) of **143** was isolated: IR (neat) 3416, 2957, 2929, 2893, 2886, 2858, 1788, 1250, 1151, 1099, 1083, 1057, 1028, 998, 860, 836, 775, 689, 666 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (9H, s), 0.02 (9H, s), 0.05 (6H, s), 0.57 (3H, d, *J* = 7 Hz), 0.88 (9H, s), 1.07 (3H, d, *J* = 7 Hz), 1.43 (3H, t, *J* = 3 Hz), 0.77−1.57 (15H, m), 1.79−1.95 (2H, m), 2.21−2.32 (4H, m), 2.89 (1H, s), 3.28 (3H, s), 3.30−3.48 (3H, m), 3.55−3.82 (8H, m), 3.95−4.34 (4H, m), 4.48 (1H, d, *J* = 5 Hz), 4.53 (1H, d, *J* = 5 Hz), 4.71−4.79 (3H, m), 5.26−5.32 (1H, m), 5.38 (1H, t, *J* = 7 Hz), 5.52 (1H, dd, *J* = 10 and 3 Hz), 5.70 (1H, d, *J* = 10 Hz), 7.53 (2H, t, *J* = 8 Hz), 7.61−7.67 (1H, m), 7.84 (2H, d, *J* = 8 Hz).

Carboxylic Acid 144. A. From 141. To a solution of **141** (11.5 mg, 0.009 mmol) in methanol at 0 °C (2.5 mL) was added disodium hydrogen phosphate (55 mg, 0.12 mmol), followed by 5% sodium amalgam (25 mg, 0.17 mmol), and the mixture was stirred for 8 h. The mixture was diluted with ether, and the separated aqueous layer was acidified with 1 N hydrochloric acid to pH 2−3 and was extracted with ether (2×). The combined ethereal extracts were washed with brine, dried (magnesium sulfate), and concentrated. Chromatography of the residue on silica, eluting with a gradient of 15−25% ethyl acetate in hexane, gave 5.8 mg (58%) of **144**: $[\alpha]^{23}_D$ +53.6° (*c* 1.00, $CHCl_3$); IR (neat) 2957, 2931, 2880, 2859, 1710, 1380, 1249, 1155, 1113, 1059, 1039, 1021, 1003, 989, 938, 919, 859, 836, 776, 744, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.02 (9H, s), 0.03 (9H, s), 0.05 (6H, s), 0.71 (6H, s), 0.74 (3H, d, *J* = 7 Hz), 0.87 (9H, s), 0.83−0.98 (12H, m), 0.97 (9H, t, *J* = 8 Hz), 1.10−1.28 (2H, m), 1.25−1.45 (3H, m), 1.50 (3H, s), 1.55 (1H, m), 1.83 (3H, s), 1.79−1.88 (2H, m), 2.16−2.23 (2H, m), 2.23−2.38 (2H, m), 3.16 (1H, m), 3.38 (1H, dd, *J* = 10 and 1 Hz), 3.47 (1H, q, *J* = 8 Hz), 3.57−3.87 (5H, m), 4.09 (1H, m), 4.20−4.25 (2H, m), 4.48 (1H, d, *J* = 7 Hz), 4.53 (1H, d, *J* = 4 Hz), 4.53 (1H, d, *J* = 7 Hz), 4.64 (1H, dd, *J* = 14 and 2 Hz), 4.80 (1H, d, *J* = 7 Hz), 4.89 (1H, d, *J* = 7 Hz), 5.38 (1H, t, *J* = 7 Hz), 5.54 (1H, dd, *J* = 10 and 2 Hz), 5.69 (1H, dd, *J* = 10 and 2 Hz), 5.79−5.82 (3H, m), 6.17 (1H, m); ^{13}C NMR ($CDCl_3$) δ −4.7, −1.5, −1.2, 5.8, 6.8, 11.2, 12.3,

12.5, 16.5, 17.3, 17.7, 18.0, 18.2, 25.9, 27.9, 30.5, 34.2, 35.3, 39.6, 40.7, 44.7, 50.1, 65.2, 65.5, 65.7, 68.8, 71.5, 75.2, 76.2, 77.2, 83.6, 85.7, 87.2, 91.6, 94.9, 95.6, 116.2, 123.6, 125.4, 126.6, 128.5, 134.4, 135.1, 139.4, 144.0, 141.9, 169.6; MS *m/z* 766, 751, 709, 649, 634, 619, 533, 487, 453, 401, 353, 295, 221, 171, 153, 115, 101, 75, 73. Anal. Calcd for $C_{58}H_{106}O_{11}Si_4$: C, 63.81; H, 9.79. Found: C, 63.44; H, 10.08.

B. From 142. To a solution of **142** (23.8 mg, 0.019 mmol) in methanol (2 mL) at 0 °C was added disodium hydrogen phosphate (41 mg, 0.29 mmol), followed by 5% sodium amalgam (89 mg, 0.19 mmol). The mixture was stirred for 1.5 h, and another portion of 5% sodium amalgam (50 mg) was added. The mixture was stirred for an additional 1.5 h at 0 °C and was triturated with ether. The decanted organic phase was washed with water, and the aqueous phase was adjusted to pH 3 with 5% hydrochloric acid and extracted with ether (2×). The combined organic extracts were washed with brine, dried (magnesium sulfate), and concentrated. Chromatography of the residue on silica, eluting with 30% ethyl acetate in hexane, gave 13.9 mg (71%) of **144**.

Dihydroxy Acid 145. To a solution of **144** (10.0 mg, 0.0092 mmol) in tetrahydrofuran (2 mL) was added tetra-*n*-butylammonium fluoride (27 μL of a 1.0 M solution in tetrahydrofuran, 0.027 mmol), and the mixture was stirred for 15 h at room temperature. Two additional portions of tetra-*n*-butylammonium fluoride (20 μL each) were added after 3 and 5 h. The mixture was partitioned between ethyl acetate and 5% hydrochloric acid, and the separated aqueous phase was extracted with ethyl acetate (3×). The combined organic extracts were washed with brine, dried (magnesium sulfate), and concentrated to afford 8.1 mg (100%) of **145** that was used without further purification.

2-Epiavermectin B_{1a} Aglycon 5,13-Bis[[2-(trimethylsilyl)ethoxy]-methyl] Ether (146). To a solution of triethylamine (27 μL, 0.19 mmol) and 2-chloro-*N*-methylpyridinium iodide (21 mg, 0.081 mmol) in refluxing acetonitrile (6 mL) was added a solution of **145** (14.0 mg, 0.016 mmol) in acetonitrile (1 mL) and methylene chloride (1 mL) during 2 h via syringe pump. After addition was complete, the solution was refluxed for an additional 30 min, cooled, and concentrated. Chromatography of the residue on silica, eluting with 20% ethyl acetate in hexane, gave 5.7 mg (42%) of **146** as a colorless oil: $[\alpha]^{23}_D$ +185.0° (*c* 0.56, $CHCl_3$); IR (neat) 2957, 2928, 2896, 2877, 1730, 1261, 1160, 1114, 1054, 1031, 996, 965, 860, 836 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.00 (9H, s), 0.01 (9H, s), 0.75 (1H, q, *J* = 12 Hz), 0.83−0.98 (13H, m), 1.12 (2H, d, *J* = 7 Hz), 1.46 (3H, s), 1.43−1.69 (4H, m), 1.86 (3H, s), 1.80−1.93 (2H, m), 2.22−2.30 (3H, m), 2.46 (1H, m), 3.15 (1H, m), 3.45−3.89 (8H, m), 4.13 (1H, s), 4.18 (1H, dd, *J* = 13 and 2 Hz), 4.28 (1H, s), 4.31 (1H, d, *J* = 2 Hz), 4.66 (1H, d, *J* = 7 Hz), 4.78 (1H, d, *J* = 7 Hz), 4.88 (1H, d, *J* = 7 Hz), 5.12 (1H, d, *J* = 8 Hz), 5.43 (1H, m), 5.56 (1H, dd, *J* = 10 and 2 Hz), 5.58 (1H, d, *J* = 7 Hz), 5.59 (1H, d, *J* = 15 Hz), 5.67 (2H, m), 5.76 (1H, dd, *J* = 10 and 2 Hz), 5.90 (1H, d, *J* = 7 Hz); ^{13}C NMR ($CDCl_3$) δ −1.5, 12.1, 12.8, 15.0, 16.4, 18.0 (×2), 18.6, 19.1, 27.5, 30.6, 34.4, 35.2, 36.7, 40.2, 40.3, 51.4, 65.4, 65.6, 68.2, 68.4, 70.5, 75.1, 76.1, 77.2, 80.5, 82.7, 86.1, 93.7, 94.2, 95.6, 114.6, 118.1, 123.0, 125.6, 128.9, 135.0, 136.3, 138.4, 140.3, 140.5, 170.8.

Epimerization of 146. Avermectin B_{1a} Aglycon 5,13-Bis[[2-(trimethylsilyl)ethoxy]methyl] Ether (147). A solution of **146** (25 mg, 0.026 mmol) and imidazole (532 mg, 7.81 mmol) in benzene (3.0 mL) was refluxed for 1.5 h. After cooling to room temperature, the resulting yellow solution was partitioned between ether and 0.1 N hydrochloric acid, and the separated aqueous layer was extracted with ether (2×). The combined extracts were washed with brine, dried (magnesium sulfate), and concentrated. The residue was purified by chromatography on silica, using 15% ethyl acetate in hexane as eluant, to give 9.8 mg (79%) of an inseparable mixture of **146** and **147** in the ratio 7:10, respectively. In addition, 3.8 mg (15%) of the conjugated ($\Delta^{2,3}$) isomer was isolated.

Avermectin B_{1a} Aglycon (2) and 2-Epiavermectin B_{1a} Aglycon (148). To a solution of **146** and **147** (19.8 mg, 0.023 mmol) in acetonitrile (2.5 mL) was added 48% hydrofluoric acid (7 drops), and stirring was continued for 108 h at room temperature. The mixture was diluted with ether and washed with water, and the separated aqueous layer was extracted with ether (2×). The combined extracts were washed with saturated sodium bicarbonate and brine and dried (magnesium sulfate). Removal of the solvent left a residue that was purified by preparative thin-layer chromatography. Two elutions with 40% ethyl acetate in hexane gave 3.6 mg (26%) of **2**: $[\alpha]^{23}_D$ +126.1° (*c* 0.36, $CHCl_3$) (lit.[28] $[\alpha]_D$ +65.6°); IR (neat) 3468, 2965, 2931, 2895, 2877, 1714, 1456, 1378, 1339, 1216, 1183, 1161, 1120, 1071, 1038, 995, 967, 949, 909, 866, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.57 (1H, q, *J* = 12 Hz), 0.91 (6H, d, *J* = 7 Hz), 0.96 (2H, t, *J* = 7 Hz), 1.17 (3H, d, *J* = 7 Hz), 1.30 (1H, m), 1.58 (3H, s), 1.42−1.61 (3H, m), 1.76 (1H, m), 1.87 (3H, s), 2.01 (1H, dd, *J* = 8 and 3 Hz), 2.23−2.34 (3H, m), 2.46 (1H, dd, *J* = 10 and 1 Hz), 2.52 (1H, m), 3.27 (1H, m), 3.38 (1H, d, *J* = 3 Hz), 3.87 (1H, m), 3.96 (1H, d, *J* = 6 Hz), 4.00 (1H, s), 4.29 (1H, t, *J* = 8 Hz), 4.68 (3H, m), 5.33−5.40 (2H, m), 5.41 (1H, s), 5.54 (1H, dd, *J* = 10 and 3 Hz), 5.71−5.82 (4H, m); ^{13}C NMR ($CDCl_3$) δ 12.1, 12.8, 14.5, 16.3, 19.1, 19.9, 27.5, 30.5, 34.3, 35.2, 36.4, 40.0, 40.6, 45.6, 67.6, 68.2, 68.3, 68.4, 75.1, 77.2, 79.1, 80.2, 95.7, 117.0, 118.1, 120.3, 124.7, 127.7, 136.2, 137.0, 137.7, 138.6, 139.6, 173.4.

In addition, there was obtained 3.0 mg (22%) of **148**: $[\alpha]^{23}_D$ +229.3° (*c* 0.30, $CHCl_3$); IR (neat) 3456, 2964, 2927, 2858, 1706, 1265, 1161, 1077, 1045, 995, 757 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.77 (1H, q, *J* = 12 Hz), 0.87 (3H, d, *J* = 7 Hz), 0.90 (3H, d, *J* = 7 Hz), 0.94 (3H, t, *J* = 7 Hz), 1.14 (3H, d, *J* = 7 Hz), 1.48 (3H, s), 1.44−1.61 (2H, m), 1.66 (1H, d, *J* = 12 Hz), 1.86 (3H, s), 1.77−1.92 (3H, m), 2.20−2.31 (3H, m), 2.46 (1H, m), 2.64 (1H, br s), 3.19 (1H, q, *J* = 3 Hz), 3.47 (1H, dd, *J* = 10 and 1 Hz), 3.91 (1H, m), 3.99 (1H, s), 4.13 (1H, dd, *J* = 18 and 2 Hz), 4.24 (1H, s), 4.32 (1H, t, *J* = 3 Hz), 4.42 (1H, s), 4.61 (1H, d, *J* = 13 Hz), 5.28 (1H, d, *J* = 8 Hz), 5.47 (1H, m), 5.57 (1H, dd, *J* = 10 and 2 Hz), 5.69−5.73 (3H, m), 5.77 (1H, dd, *J* = 10 and 2 Hz), 5.91−5.94 (1H, m); ^{13}C NMR ($CDCl_3$) δ 12.1, 12.8, 14.7, 16.4, 18.3, 18.9, 27.5, 30.5, 34.3, 35.1, 36.6, 40.2, 40.3, 50.8, 68.3, 70.6, 71.1, 75.1, 77.2, 77.8, 80.2, 87.7, 95.6, 114.8, 117.1, 123.2, 125.6, 127.8, 136.3, 137.7, 138.3, 140.5, 141.2, 170.9.

Avermectin B_{1a} Aglycon 5-*tert*-Butyldimethylsilyl Ether (149). To a solution of **2** (0.501 g, 0.86 mmol) and imidazole (0.35 g, 5.16 mmol) in dimethylformamide (13 mL) at 0 °C was added *tert*-butyldimethylchlorosilane (0.388 g, 2.57 mmol), and the mixture was stirred for 3 h while gradually warming to room temperature. Saturated, aqueous ammonium chloride (15 mL) and ether (15 mL) were added, the layers were separated, and the aqueous layer was extracted with ether (2 × 25 mL). The combined organic layers were washed with water and brine, dried (magnesium sulfate), and concentrated. The residue was chromatographed on silica, eluting with 15% ethyl acetate in hexane, to give 0.421 g (70%) of **149** as a colorless foam: $[\alpha]^{23}_D$ +120.5° (*c* 0.91, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.12 (6H, s), 0.86−0.97 (11H, m), 0.92 (9H, s), 1.16 (3H, d, *J* = 7 Hz), 1.41−1.71 (8H, m), 1.78 (3H, s), 2.02 (1H, dd, *J* = 12 and 4 Hz), 2.23−2.32 (3H, m), 2.51 (1H, m), 3.25 (1H, d, *J* = 2 Hz), 3.45 (1H, d, *J* = 10 Hz), 3.80−3.90 (2H, m), 4.00 (2H, d, *J* = 5 Hz), 4.42 (1H, d, *J* = 3 Hz), 4.57 (1H, d, *J* = 15 Hz), 4.67 (1H, d, *J* = 15 Hz), 5.27−5.36 (3H, m), 5.53 (1H, dd, *J* = 10 and 2 Hz), 5.65−5.80 (4H, m); ^{13}C NMR ($CDCl_3$) δ −4.9, −4.6, 12.1, 12.8, 14.6, 16.4, 18.4, 19.2, 20.0, 25.9, 27.6, 30.5, 34.4, 35.3, 36.4, 40.0, 40.6, 45.8, 67.9, 68.4 (×2), 69.4, 75.2, 77.6, 80.1 (×2), 95.7, 117.1, 117.4, 119.4, 124.9, 127.0, 136.1, 136.5, 137.4, 138.7, 140.3, 173.7; MS *m/z* 699 ($M + H^+$), 688, 641, 623, 567, 549, 456, 438, 399, 375; HRMS *m/z* 698.4212 (M^+) (calcd for $C_{40}H_{63}O_8Si$: 698.4213).

Avermectin B_{1a} 4″,5-Bis(*tert*-butyldimethylsilyl) Ether (153). To a solution of thoroughly dried (by azeotropic distillation with benzene) **149** (4.6 mg, 0.007 mmol) and **152** (10.0 mg, 0.019 mmol) in methylene chloride (200 μL) was added powdered 4 Å molecular sieves, and the mixture was stirred at room temperature for 20 min. A solution of dried (by azeotropic distillation with toluene) silver trifluoromethanesulfonate (22.0 mg, 0.084 mmol) in toluene (200 μL) was prepared, and a portion (50 μL, 0.021 mmol) was added to the mixture that was stirred for a further 20 min. Methylene chloride (2 mL) was added, followed by saturated, aqueous sodium bicarbonate (2 mL), and the layers were separated. The aqueous layer was extracted with methylene chloride (3 × 5 mL), and the combined organic layers were washed with water and brine and dried (magnesium sulfate). Removal of the solvent and chromatography of the residue on silica, eluting with 3% ethyl acetate in methylene chloride, gave 1.7 mg (36%) of recovered **149** and 2.5 mg (35%, 56% based on recovered starting material) of **153**: $[\alpha]^{23}_D$ +43.0° (*c* 0.63, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.08 (3H, s), 0.10 (3H, s), 0.13 (6H, s), 0.77−0.97 (11H, m), 0.89 (9H, s), 0.93

(9H, s), 1.16 (3H, d, J = 7 Hz), 1.21 (3H, d, J = 7 Hz), 1.25 (3H, d, J = 6 Hz), 1.43−1.59 (5H, m), 1.50 (3H, s), 1.76 (1H, m), 1.79 (3H, s), 2.01 (1H, dd, J = 13 and 4 Hz), 2.19−2.35 (5H, m), 2.51 (1H, m), 3.14 (1H, t, J = 9 Hz), 3.21 (1H, t, J = 9 Hz), 3.29−3.40 (2H, m), 3.34 (3H, s), 3.44 (3H, s), 3.46 (1H, d, J = 10 Hz), 3.58−3.71 (2H, m), 3.82−3.87 (3H, m), 3.94 (1H, s), 4.10 (1H, s), 4.43 (1H, s), 4.58 (1H, d, J = 15 Hz), 4.68 (1H, d, J = 15 Hz), 4.77 (1H, d, J = 3 Hz), 5.00 (1H, m), 5.31−5.40 (3H, m), 5.56 (1H, dd, J = 10 and 2 Hz), 5.71−5.78 (3H, m), 5.83 (1H, m); ^{13}C NMR ($CDCl_3$) δ −4.9, −4.7, −4.6, −4.0, 12.0, 13.0, 15.1, 16.4, 18.3, 18.4, 20.0, 20.3, 25.9, 26.0, 27.5, 29.7, 30.6, 34.3, 34.6, 35.2, 36.6, 39.7, 40.5, 45.8, 50.5, 56.3, 56.6, 67.3, 68.0, 68.4, 68.5, 69.1, 69.5, 74.9, 77.2, 78.6, 79.3, 80.1, 80.3, 80.4, 82.0, 95.0, 95.8, 98.6, 117.3, 118.3, 119.4, 124.8, 127.8, 134.7, 135.2, 136.2, 137.6, 140.3, 174.1.

Avermectin B_{1a} (1). A solution of **153** (25.2 mg, 0.02 mmol) and pyridinium hydrofluoride (200 μL) in acetonitrile (500 μL) and pyridine (200 μL) was stirred for 22 h at room temperature, after which additional quantities of pyridinium hydrofluoride (100 μL) and pyridine (100 μL) were added. The mixture was stirred for a further 8 h, and ether (2 mL) was added. Saturated, aqueous sodium bicarbonate was added slowly, the layers were separated, and the aqueous layer was extracted with ether (3 × 10 mL). The combined ethereal extracts were washed with 5% hydrochloric acid, saturated, aqueous sodium bicarbonate, water, and brine and dried (sodium sulfate). The solvent was removed under vacuum, and the residue was chromatographed on silica, eluting with 65% ethyl acetate in hexane, to furnish 12.7 mg (64%) of **1** as a colorless foam: $[\alpha]^{23}_D$ +62.2° (c 0.78, $CHCl_3$) (lit.[7] $[\alpha]^{20}_D$ +63.7° (c 0.98, $CHCl_3$), lit.[56] $[\alpha]^{27}_D$ +55.7° (c 1.06, $CHCl_3$)). Chromatographic properties as well as ^{1}H and ^{13}C NMR spectra matched those recorded on a sample of natural avermectin B_{1a}.

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Supplementary Material Available: Procedures for the preparation of **115**−**122** and X-ray crystallographic data for the (*S*)-(−)-α-methylbenzylamine salt of (±)-**10** and for **105** (35 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(56) Albers-Schönberg, G.; Arison, B. H.; Chabala, J. C.; Douglas, A. W.; Eskola, P.; Fisher, M. H.; Lusi, A.; Mrozik, H.; Smith, J. L.; Tolman, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 4216.