

was supported by NSF Chemistry Division Grant CHE 7916210.

Registry No. 3, 74087-85-7; 5, 55628-54-1; 6, 79999-47-6; α -8, 74372-90-0; 9, 121654-00-0; 10, 121702-69-0; 11, 121654-01-1; 12, 121702-70-3; 13, 121654-02-2; 17, 82231-32-1; 18, 121654-03-3; 19,

121654-04-4; 20, 121654-05-5; 21, 4064-06-6; 22a, 40246-33-1; 22b, 51532-76-4; 23, 58871-10-6; 24a, 121654-06-6; 24b, 121654-07-7; 24c, 121654-08-8; 25, 121654-09-9; 26a, 121654-10-2; 26b, 121654-11-3; 27, 2216-51-5; 28a, 121654-12-4; 28b, 121654-13-5; 29, 57-88-5; 30a, 121654-14-6; 30b, 121654-15-7.

Synthesis of the ABC Ring System of Brevetoxin B

K. C. Nicolaou,* M. E. Duggan,¹ and C.-K. Hwang

Contribution from the Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104. Received November 30, 1988

Abstract: A synthesis of the ABC ring framework of brevetoxin B is described. The optically active intermediate **2** representing the ABC ring system and equipped with appropriate functionality for further elaboration is constructed from glucal triacetate. The reported stereocontrolled construction proceeds via key intermediates **38** and **45**, which serve as efficient cyclization precursors sequentially leading from a monocyclic to a bicyclic and finally to the desired tricyclic system. The synthesis demonstrates the applicability of the recently developed 6-*endo*-hydroxy epoxide activation method for the construction of tetrahydropyran systems. The stereochemistry of the final product was confirmed by an X-ray crystallographic analysis of the crystalline derivative **50**.

Among the toxins associated with the phenomenon of the "red tide" catastrophes,² brevetoxin B (**1**,³ Scheme I) holds a prominent position as the first member of this new class of marine natural products to be structurally elucidated and as one of the most potent neurotoxins (IC₅₀ = 16 μ g/mL) of its class. This novel compound produced by *Ptychodiscus brevis* Davis (*Gymnodinium breve* Davis) was structurally defined by the groups of Nakanishi and Clardy using spectroscopic and X-ray crystallographic techniques.³ Since then, a number of other brevetoxin structures appeared.⁴

Brevetoxin B (**1**) has a novel polycyclic structure, never encountered in nature before. Its unusual molecular framework contains 11 rings fused together by trans fusions and 23 stereogenic centers. Each ring contains an oxygen in a pattern that points to an intriguing, as yet unknown, biogenesis.⁵ The polycyclic skeleton is rigid except at the region of the oxepane-oxepane junction. The oxocene ring introduces an approximately 30° turn away from the main axis of the remaining backbone. The 11 oxygen-containing rings are in a ladderlike shape, 30 Å long, 6 Å wide, and 6 Å high.

This fascinating molecule exerts its biological effects by activating sodium channels and causing repetitive firings in neurons.⁶ It binds to a receptor different from that of tetrodotoxin and

saxitoxin, two other marine toxins.⁶ The precise nature of its binding site, however, is presently unknown.

Brevetoxin B (**1**) presents an attractive synthetic target⁷ for a number of reasons. This novel and complex structure would almost certainly require new synthetic technology and a carefully designed strategy before yielding to total synthesis. In addition, synthetic fragments and analogues may prove useful in elucidating the puzzling biosynthetic pathways leading to this class of compounds; they may also shine light on their mode of action. Finally, the scarcity of these compounds coupled with the environmental hazards they cause provides further justification for a research program directed toward their synthesis. A number of years ago we decided to embark on such a program, and in this series of papers, we detail stereoselective constructions of the tetrahydropyran systems of brevetoxin B (**1**), beginning with the ABC framework.

Retrosynthetic Analysis

A potentially useful retrosynthetic analysis of brevetoxin B (**1**) is shown in Scheme I. Disconnection of the indicated strategic bonds and a number of standard functional group interchanges disassemble the medium-size rings and lead to the three fragments **2**, **3**, and **4**. These disconnections allow for a highly convergent synthesis involving intermediates containing only tetrahydropyran rings and thus considerably simplify the synthetic problem at hand.

The constructions of fragments ABC (**2**, this article), FG (**3**),⁸ and IJK (**4**)⁹ were based on the synthetic technology described in previous papers.^{7a,10} Scheme II outlines the retrosynthetic analysis of the ABC ring system of brevetoxin B (**1**) as the hydroxycarboxylic acid protected as a *p*-methoxybenzyl ether (**2**). Thus, rupture of the indicated bonds in structure **2** (Scheme II) and simple functional group manipulations lead to hydroxy epoxide **5**, which can be retrosynthetically converted to the α,β -unsaturated

(1) Taken in part from the thesis of M.E.D., Department of Chemistry, University of Pennsylvania, 1987.

(2) (a) Shimizu, Y. *Marine Natural Products*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol 1, Chapter 1. (b) Taylor, D. L.; Seliger, H. H. *Toxic Dinoflagellate Blooms*; Elsevier/North-Holland: New York, 1979. (c) *Toxicon* **1985**, *23*, 4. (d) Baden, D. G.; Bikkazi, G.; Decker, S. J.; Foldes, F. F.; Leung, I. *Toxicon* **1984**, *22*, 75.

(3) Lin, Y.; Risk, M.; Ray, S. M.; Van Engen, D.; Clardy, J.; Golik, J.; James, J. C.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 6773.

(4) Brevetoxin A: Shimizu, Y.; Chou, H.-N.; Bando, H.; VanDuyne, G.; Clardy, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 514; Pawlak, J.; Tempesta, M. S.; Golik, J.; Zagorski, M. G.; Lee, M. S.; Nakanishi, K.; Iwashita, T.; Gross, M. L.; Tomer, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 1144. Brevetoxin C: Golik, J.; James, J. C.; Nakanishi, K.; Lin, Y. Y. *Tetrahedron Lett.* **1982**, *23*, 2535. GB-3 toxin: Chou, H. N.; Shimizu, Y. *Tetrahedron Lett.* **1982**, *23*, 5521. GB-5 and GB-6 toxins: Chou, H. N.; Shimizu, Y.; Van Duyne, G.; Clardy, J. *Tetrahedron Lett.* **1985**, *26*, 2865.

(5) For some biosynthetic studies see: (a) Chou, H.-N.; Shimizu, Y. *J. Am. Chem. Soc.* **1987**, *109*, 2184. (b) Lee, M. S.; Repeta, D. J.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1986**, *108*, 7855.

(6) (a) Catterall, W. A. In *Toxic Dinoflagellates*, Anderson, D. M., White, A. W., Baden, D. G., Eds.; Elsevier: New York, 1985; pp 329-342. (b) Hwang, J. M. C.; Wu, C. H.; Baden, D. G. *J. Pharmacol. Exp. Ther.* **1984**, *229*, 615.

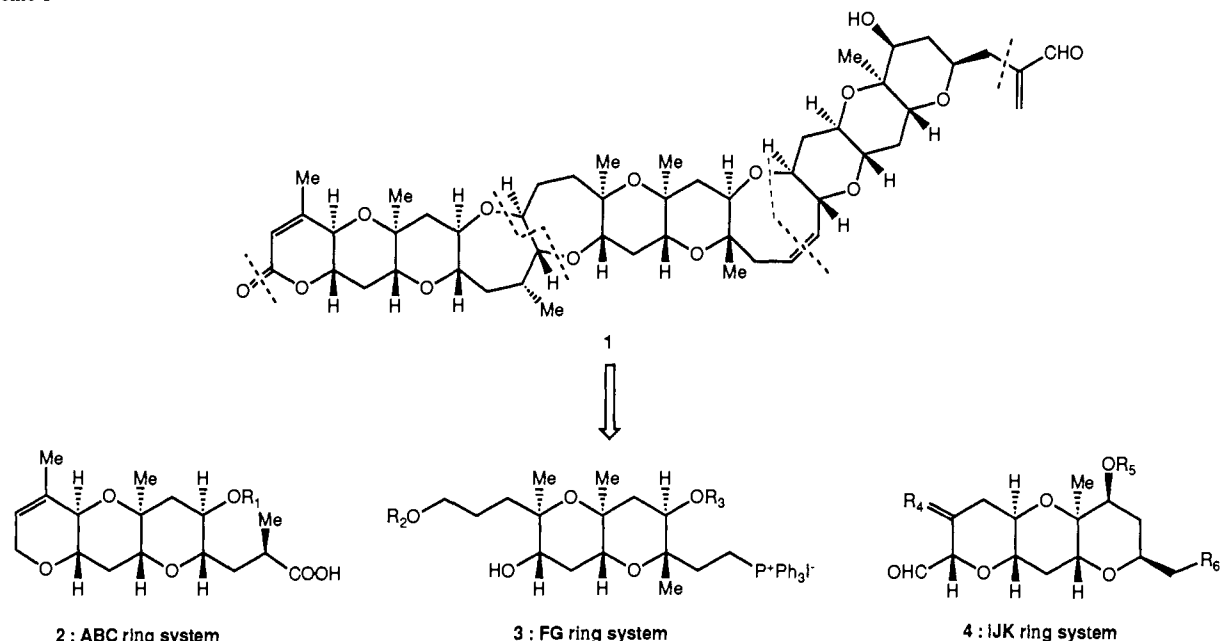
(7) Previous synthetic studies on brevetoxin B and models include: (a) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K.; Somers, K. P. *J. Chem. Soc., Chem. Commun.* **1985**, 1395. (b) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Reddy, K. B.; Marron, B. E.; McGarry, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 6800. (c) Kozikowski, A. P.; Ghosh, A. K. *J. Org. Chem.* **1985**, *50*, 3017.

(8) Nicolaou, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.*, second of three papers in this issue.

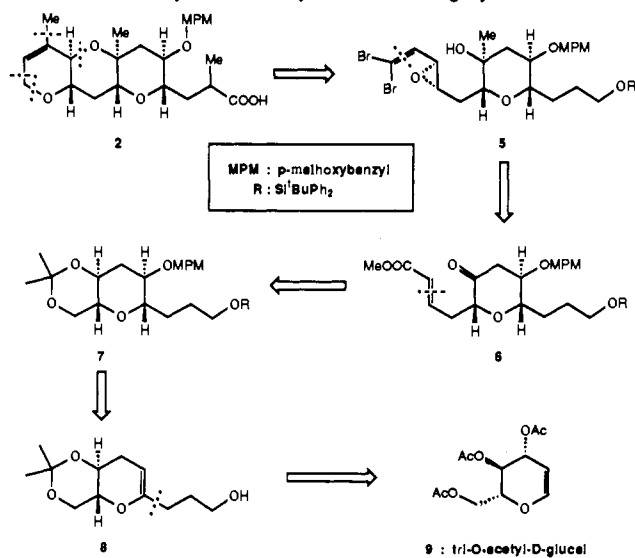
(9) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E. *J. Am. Chem. Soc.*, third of three papers in this issue.

(10) Nicolaou, K. C.; Prasad, C. V. C.; Somers, K. P.; Hwang, C.-K. *J. Am. Chem. Soc.*, in press.

Scheme I



Scheme II. Retrosynthetic Analysis of ABC Ring System 2

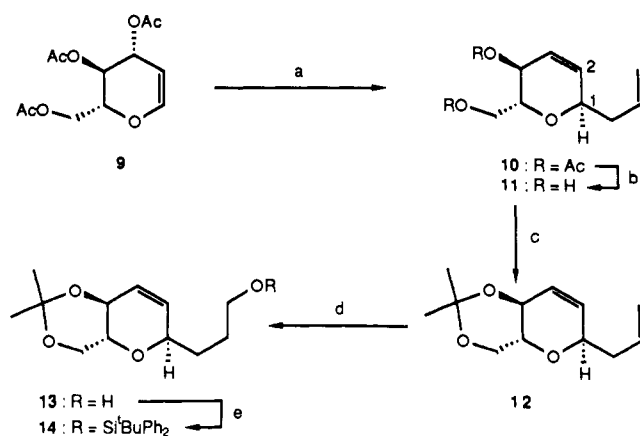


ester **6** by obvious strategies. Stereoselective elaboration of **6** to **5** was anticipated. Continuation of the retrosynthetic process leads sequentially to intermediates **7**, **8**, and **9** as shown in Scheme II. Thus, the readily available and enantiomerically pure tri-*O*-acetyl-*D*-glucal (**9**) became the starting point for this construction.

Synthesis of the ABC Ring System

As described above, tri-*O*-acetyl-*D*-glucal (**9**) was utilized as starting material for the construction of the ABC ring system of brevetoxin B. The synthesis began as outlined in Scheme III. Treatment of **9** with allyltrimethylsilane under the Danishefsky and Kerwin¹¹ conditions followed by methanolysis of the resulting bis(acetate) **10** gave the diol **11** in 95% overall yield and better than 16:1 epimeric ratio. Protection of the diol **11** was accomplished with 2-methoxypropene in the presence of pyridinium *p*-toluenesulfonate (PPTS) in CH₂Cl₂, leading quantitatively to the acetonide **12**. Selective hydroboration of the terminal olefin in **12** with disiamylborane in THF followed by oxidative workup furnished the alcohol **13** in 87% yield. Protection of **13** with *tert*-butylchlorodiphenylsilane and imidazole in DMF gave the silyl ether **14** in 98% yield.

Scheme III

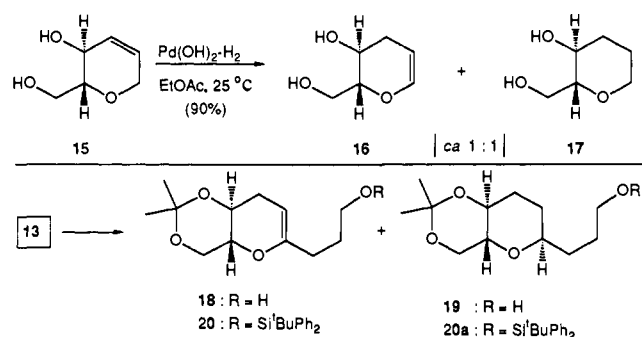


Reagents and conditions: (a) allyltrimethylsilane-TiCl₄, see ref 11; (b) 0.1 equiv of K₂CO₃, MeOH, 25 °C, 4 h, 100%; (c) 1.5 equiv of 2-methoxypropene, 0.5 equiv of PPTS, CH₂Cl₂, 0 °C, 2 h, 100%; (d) 1.3 equiv of BH₃, 3.0 equiv of 2-methyl-2-butene, THF, 0 °C, 1 h, then add **12**, 1 h, then add excess H₂O, 0.12 equiv of 3 N NaOH, 3.5 equiv of 30% H₂O₂, 15 min, 87%; (e) 1.3 equiv of ^tBuPh₂SiCl, 3.0 equiv of imidazole, DMF, 25 °C, 1 h, 98%.

For the next sequence, an efficient method was needed to promote olefin migration in **13** or **14** to the requisite cyclic enol ethers. It was previously observed in these laboratories¹² that attempted reduction of diol **15** (Scheme IV) with H₂ in the presence of Pd(OH)₂ as catalyst produced a mixture of the reduced product **17** and the cyclic enol ether **16** (ca. 1:1 ratio). This observation along with the plethora of other methods for olefin migration encouraged us to explore this transformation in systems **13** and **14**. Scheme IV presents some of the attempted conditions and the results obtained. Treatment of **13** with H₂-Pd(OH)₂ in EtOAc gave the desired migration product **18** (45%) and the reduced product **19** (43%). The isomerization did not occur in the absence of H₂, even at elevated temperatures using Pd(OH)₂, Pd/C, or Rh/C as catalysts. Isomerization of **14** to the enol ether **20** could be achieved with RuH₂(PPh₃)₄¹³ in 85% yield (plus 5% recovered starting material). Unfortunately, however, an excess of the ruthenium complex (2.0 equiv) was needed to realize the

(11) Danishefsky, S.; Kerwin, J. F. *J. Org. Chem.* **1982**, *47*, 3803.

(12) Duggan, M. E.; Hwang, C.-K. Unpublished results, these laboratories.
(13) (a) Levison, J. J.; Robinson, S. D. *J. Chem. Soc. A* **1970**, 2947. (b) Suzuki, H.; Yashima, H.; Hirose, T. *Tetrahedron Lett.* **1980**, *21*, 4927.

Scheme IV^a

Substrate	Conditions	Product (%)	Recovery (%)
13	Pd(OH) ₂ · H ₂ EtOAc, 25 °C	18 (45) 19 (43) 13 (0)	
14	RuH ₂ (PPh ₃) ₄ , benzene, 80 °C	20 (85) — 14 (5)	
13	^t BuOK, DMSO, 100 °C	18 (60) — 13 (25)	

^a Isomerizations of allylic ethers to enol ethers.

above yield, making this procedure unacceptable for large-scale operations. Other transition-metal catalysts such as PdCl₂·MeCN,¹⁴ RhCl₃·3H₂O,¹⁵ RhCl(PPh₃)₃,¹⁶ and RuCl₂(PPh₃)₃¹⁷ were tried but failed to produce the required enol ethers **18** or **20**. However, exposure of **13** to KO^tBu¹⁸ in DMSO at 100 °C led to a mixture of enol ether **18** (60%) and starting allylic ether **13** (25%). Thus, since the recovered starting material could be recycled, this procedure became the method of choice for large-scale preparations of **18**. Interestingly, exposure of the migration products **18** or **20** to any of the isomerization conditions of Scheme IV resulted in no reaction. This observation indicated that the allylic:enol ether ratios obtained in these isomerizations were not representing thermodynamic equilibria.

With the cyclic enol ether **18** at hand, attention was then focused on building the functionality of what was to become ring C of the target molecule. Scheme V summarizes the chemistry employed for the conversion of **18** to **31**. Thus, silylation of **18** under standard conditions afforded the silyl ether **20** in high yield (97%) which was then hydroborated (BH₃·THF) and oxidatively converted to a mixture of the expected alcohols **21** and **22** in 24 and 68% yields, respectively. The structure of the desired compound **22** was determined by decoupling studies on the corresponding acetate **23**. A coupling constant of 9.9 Hz for H_a/H_b established their vicinal/trans diaxial relationship and thus the stereochemistry of **23** and **22**. The facial selectivity observed in this reaction is in accord with previous work by Kozikowski and Ghosh.^{7c} The desired ketone **30** was obtained from **22** by a seven-step sequence (Scheme V). Thus, treatment of the alcohol **22** with KH in THF followed by addition of *p*-methoxybenzyl chloride gave **24** in 84% yield. Removal of the acetonide group from **24** was accomplished in MeOH with amberlyst-15 (H⁺) affording diol **25** in 86% yield. Selective tosylation of **25** led to **26** (85%), which was treated with NaCN in DMSO at 70 °C to furnish nitrile **27** in 91% yield. DIBAL reduction of **27** followed by acidic workup led to the aldehyde **28** (95%), which was reacted immediately with Ph₃P=CHCOOMe to give the α,β-unsaturated ester **29** in 89% yield. Finally, Swern oxidation¹⁹ of **29** produced

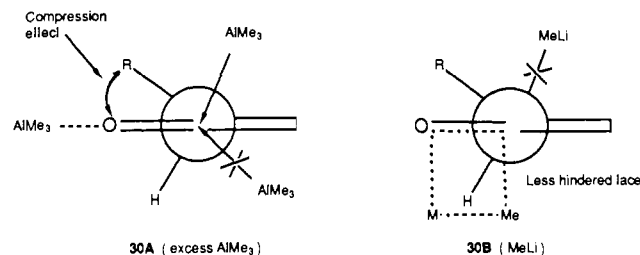
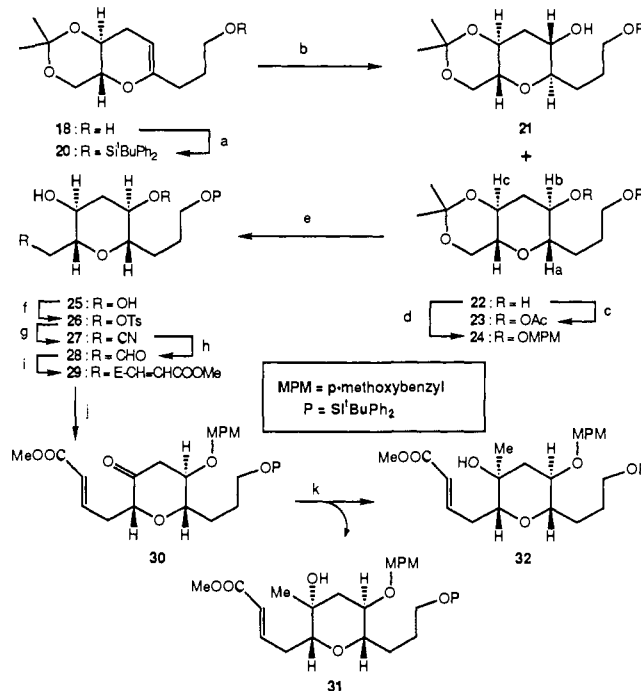


Figure 1. Presumed transition states of the reaction of ketone **30** with AlMe₃ and MeLi.

Scheme V^a

^a Reagents and conditions: (a) 1.2 equiv of ^tBuPh₂SiCl, 3.0 equiv of imidazole, DMF, 0 °C, 1 h, 100%; (b) 0.8 equiv of BH₃, THF, 0 °C, then add excess H₂O, 0.3 equiv of 3 N NaOH, 0.4 equiv of 30% H₂O₂, 15 min, 92%; (c) 3.0 equiv of DMAP, 2.0 equiv of Ac₂O, 25 °C, 30 min, 94%; (d) 1.4 equiv of 4-methoxybenzyl chloride, 1.2 equiv of KH, THF, 25 °C, 3 h, 84%; (e) Amberlyst-15 (H⁺) ion-exchange resin, MeOH, 25 °C, 45 min, 86%; (f) 1.5 equiv of TsCl, pyr, 0 °C, 4 h, 85%; (g) 2.0 equiv of NaCN, DMSO, 70 °C, 2 h, 91%; (h) 2.5 equiv of DIBAL, CH₂Cl₂, -78 °C, 15 min, then 1 N HCl, 95%; (i) 1.5 equiv of Ph₃P=CHCOOMe, benzene, 25 °C, 1 h, 89%; (j) 1.5 equiv of oxalyl chloride, 2.0 equiv of DMSO, CH₂Cl₂, -78 °C, 30 min, then 40 equiv of Et₃N, 25 °C, 15 min, 100%; (k) 2.2 equiv of AlMe₃ (1 M in toluene solution), CH₂Cl₂, -78 °C, 1 h, then 10 °C, 3 h, 94%.

the ketone **30** in quantitative yield.

The transformation of ketone **30** to the tertiary alcohol **32** was accompanied by some interesting observations. Treatment of **30** with MeLi (1.0 equiv, THF, -78 °C) gave a mixture of epimers (**32**:**31** ca. 1:6, 76% yield). The identity of epimers **32** and **31** was assumed at this time on the basis of previous observations and was later confirmed by X-ray crystallographic analysis of a subsequent intermediate (vide infra). As expected from the elegant studies of Ashby,²⁰ addition of ketone **30** to excess of AlMe₃ at -78 → -10 °C resulted in reversal of selectivity, producing the desired alcohol **32** as the major product (**32**:**31** ca. 6:1, 94% yield). However, in contrast to Ashby's results, treatment of **30** with ≤1.0 equiv of AlMe₃ gave a similar ratio of products (**32**:**31** ca. 5:1, 71%). Ashby had observed a reversal of facial selectivity upon using excess of AlMe₃, instead of stoichiometric amounts of the reagent for methylation of ketones. This phenomenon was attributed to an unfavorable interaction within the

(14) Danishefsky, S. J.; Uang, B. J.; Quallich, G. *J. Am. Chem. Soc.* **1985**, *107*, 1285.

(15) Grieco, P. A.; Nishizawa, M.; Marinovic, J.; Ehmann, W. *J. Am. Chem. Soc.* **1976**, *98*, 7102.

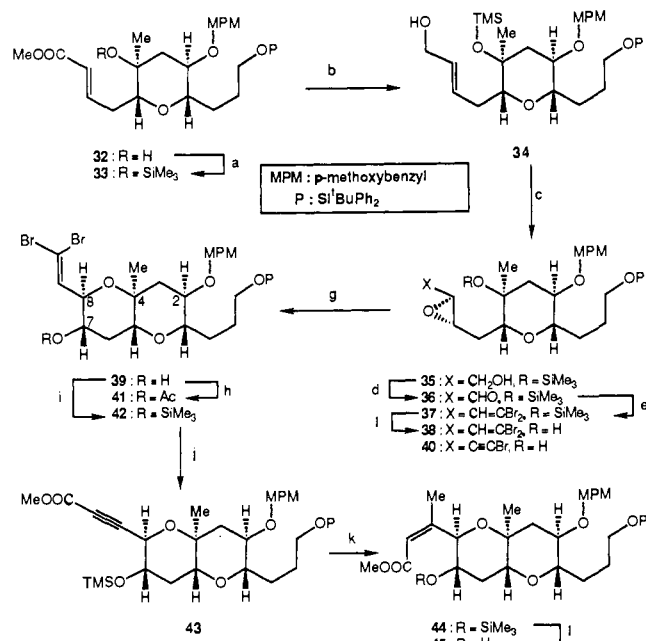
(16) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224.

(17) Golborn, P.; Scheinmann, F. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2870.

(18) Gigg, J.; Gigg, R. *J. Chem. Soc. C* **1966**, 82.

(19) Huang, S. L.; Mancuso, A. J.; Swern, D. *J. Org. Chem.* **1978**, *63*, 2480.

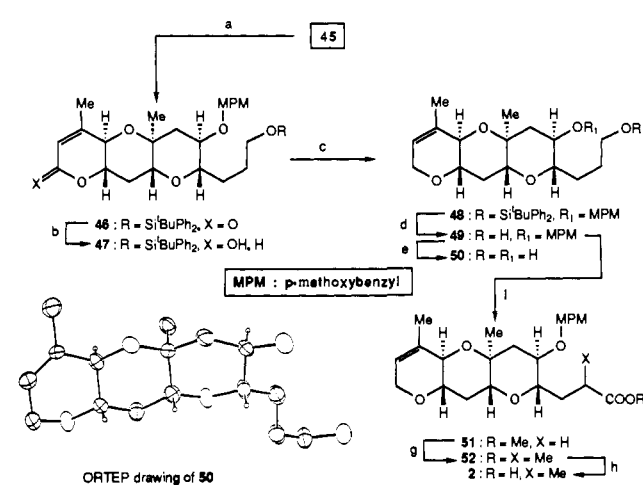
(20) Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521.

Scheme VI^a

^a Reagents and conditions: (a) 1.6 equiv of TMS-imidazole, CH₂Cl₂, 25 °C, 3 h, 100%; (b) 2.5 equiv of DIBAL, CH₂Cl₂, -78 °C, 45 min, 98%; (c) 1.3 equiv of (-)-DET, 1.0 equiv of Ti(O-*i*Pr)₄, 2.5 equiv of ^tBuOOH, CH₂Cl₂, -23 °C, 16 h, 80%; (d) 7.0 equiv of Et₃N, 4.0 equiv of SO₃-pyr, DMSO-CH₂Cl₂ (1:2), 0 °C, 2 h, 95%; (e) 4.0 equiv of Ph₃P, 2.0 equiv of CBr₄, CH₂Cl₂, 0 °C, 30 min, 71%; (f) 2.3 equiv of ⁿBu₄NF, THF, 0 °C, 20 min, 96%; (g) 1.0 equiv of CSA, CH₂Cl₂, 0 °C, 45 min, **39** (83%), **40** (11%); (h) 3.0 equiv of DMAP, 2.0 equiv of Ac₂O, CH₂Cl₂, 25 °C, 90%; (i) same as (a), 100%; (j) 2.4 equiv of MeLi, THF, -78 °C, 45 min, then 1.0 equiv of MeOH, 10 min, 2.0 equiv of MeLi, 30 min, then 1.3 equiv of ClCOOMe, -78 °C, then -25 °C, 20 min, 75%; (k) 3.5 equiv of CuI, 7.0 equiv of MeMgCl, THF, -78 °C, 75%; (l) 0.2 equiv of PPTS, MeOH, 25 °C, 1 h, 100%.

ketone-AlMe₃ complex upon addition of a second molecule of AlMe₃ as illustrated in structure **30A** (transition state, Figure 1). This "compression effect" is not encountered during axial attack which, therefore, becomes the predominant reaction pathway. According to Ashby's predictions addition of ≤1.0 equiv of AlMe₃ should have proceeded through a four-center transition state analogous to that for MeLi addition depicted by structure **30B** (transition state, Figure 1). Apparently, however, even with less than stoichiometric amounts of AlMe₃, this reaction does not proceed via the four-center transition state **30B**; presumably the polyoxygenated nature of the substrate and its topology are responsible for its inability to enter this pathway.

Construction of the B ring was accomplished by the 6-*endo*-hydroxy epoxide activation method^{7a,10} as shown in Scheme VI. Protection of the alcohol in **32** with 1-(trimethylsilyl)imidazole gave the silyl ether **33** (100%), which was treated with DIBAL at -78 °C to furnish the allylic alcohol **34** in 95% yield. Sharpless asymmetric epoxidation²¹ of **34** using (-)-diethyl tartrate as the chiral auxiliary gave the epoxide **35** in 80% yield. Oxidation of epoxy alcohol **35** using SO₃-pyridine complex followed by olefination²² gave the vinyl dibromide **37** in 67% overall yield via aldehyde **36**. Selective desilylation of **37** was easily accomplished by using fluoride ion at -20 → 0 °C to furnish **38** in 96% yield. The 6-*endo* activated epoxide **38** was then treated with camphorsulfonic acid (CSA) at 0 °C to afford the bicycle **39** (83%) accompanied by small amounts of the acetylenic epoxide **40** (11%). The structure of **39** was determined by NMR studies on the corresponding acetate **41**. Thus, decoupling experiments with **41** revealed a coupling constant (*J*) of 9.8 Hz for H-7/H-8, indicating a trans-diaxial relationship for these protons. Irradiation of the

Scheme VII^a

^a Reagents and conditions: (a) 0.3 equiv of DBU, benzene, 70 °C, 1.5 h, 95%; (b) 1.5 equiv of DIBAL, CH₂Cl₂, -78 °C, 45 min, 100%; (c) 4.0 equiv of Et₃SiH, 1.0 equiv of BF₃-Et₂O, CH₂Cl₂, 5 min, 92%; (d) 1.4 equiv of ⁿBu₄NF, THF, 25 °C, 2 h, 97%; (e) 2.0 equiv of DDQ, CH₂Cl₂-H₂O (10:1), 25 °C, 2 h, 94%; (f) Jones' oxidation, then CH₂-N₂, Et₂O, 0 °C, 84%; (g) 1.2 equiv of LDA, -78 °C, 30 min, then 2.5 equiv of MeI, 25 °C, 10 min, 86%; (h) 3.0 equiv of LiOH, THF-H₂O (1:1), 50 °C, 16 h, 100%.

C-4 methyl group (500 MHz, CDCl₃ δ 1.26) produced a significant enhancement of H-8 (δ 4.30) and H-2 (δ 3.22). COSY and NOSY experiments were also in accord with the stereochemical assignment shown. Subsequent X-ray crystallographic analysis on a more advanced intermediate (*vide infra*) confirmed this assignment.

Protection of alcohol **39** to give silyl ether **42** followed by sequential treatment with methyllithium and methyl chloroformate led to the acetylenic ester **43** in 75% yield. The requisite methyl group was stereospecifically delivered by cuprate addition²³ to **43** leading to the *E*-α,β-unsaturated ester **44** (75% yield). Removal of the silyl group from **44** then led to the hydroxy ester **45** in quantitative yield.

Scheme VII outlines the completion of the synthesis of the tricyclic target **2**. Thus, heating of hydroxy ester **45** with DBU in benzene at reflux gave the lactone **46** in 95% yield. Reduction of this lactone (**46**) with DIBAL followed by exposure of the resulting lactol (**47**, mixture of anomers, quantitative yield) to further reduction with Et₃SiH in the presence of BF₃-Et₂O gave the ether **48** in 92% yield. Fluoride-induced deprotection of **48** afforded the alcohol **49** in 97% yield. DDQ deprotection of **49** gave the crystalline diol **50** (mp 91–92 °C from EtOAc-hexane) in 91% yield. An X-ray crystallographic analysis²⁴ of **50** (see ORTEP drawing, Scheme VII) confirmed its structure and the structures of its progenitors. Jones' oxidation of the alcohol **49** followed by diazomethane treatment led to the ester **51** in 84% yield, which was methylated with LDA-MeI to afford product **52** in 86% yield (ca. 1:1 mixture of epimers by ¹H NMR spectroscopy). Finally, basic hydrolysis of **52** with LiOH in aqueous THF afforded the desired ABC ring system **2** in quantitative yield (ca. 1:1 mixture of methyl epimers).

Conclusion

The ABC ring skeleton of brevetoxin B (**1**) has been constructed in optically active form from *tri*-O-acetyl-D-glucal (**9**). The synthesis was based on the recently developed 6-*endo* activation of hydroxy epoxides to form stereoselectivity the second tetrahydropyran system under acidic conditions and on a stereoselective addition of AlMe₃ to a carbonyl function to set the tertiary center. The synthesized intermediate (**2**) and its relative contain appro-

(23) Corey, E. J.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 1851.

(24) This X-ray crystallographic analysis was carried out by Dr. Patrick Carroll of this department.

(21) Katsui, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5976.

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

appropriate end functionalities for further elaboration. These intermediates may, therefore, serve as precursors to brevetoxin B (1) and as model systems in biological investigations regarding the mode of action of this neurotoxin and as possible agonists or antagonists of it. Work currently in progress is addressing these questions. The construction of the FG ring system of brevetoxin B (1) is described in the following paper.⁸

Experimental Section

General Techniques. NMR spectra were recorded on one of the following instruments: IBM WP-200, Bruker WM-250, IBM AF-250, or Bruker AM-500. IR spectra were recorded on a Perkin-Elmer Model 781 infrared spectrophotometer. UV and visible spectra were recorded on a Perkin-Elmer Model 553 ultraviolet-visible spectrophotometer.

High-resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VC ZAB E instrument under FAB conditions. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, or Robertson Laboratories, Inc., Madison, NJ.

All reactions were monitored by thin-layer chromatography carried out on 0.25-mm E. Merck silica gel plates (60F-254) by using UV light and 7% ethanolic phosphomolybdic acid-heat as developing agent. Preparative layer chromatography was performed on 0.5 or 0.25 mm \times 20 cm \times 20 cm E. Merck silica gel plates (60F-254). E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography.

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise noted. Yields refer to chromatographically and spectroscopically (¹H NMR) homogeneous materials, unless otherwise stated.

(2R,3S,6R)-6-Allyl-3,6-dihydro-3-hydroxy-2H-pyran-2-methanol (11). A mixture of the bisacetate 10¹¹ (58.5 g, 0.23 mol), potassium carbonate (4.1 g, 0.03 mol), and methanol (230 mL) was stirred at 25 °C for 4 h. Dilution with ether (400 mL) and petroleum ether (400 mL) followed by filtration through a Celite pad and concentration gave the diol 11 (39.1 g, 100%). 11: oil; $R_f = 0.47$ (silica, ether); $[\alpha]_D^{21} -22.7^\circ$ (c 1.10, CHCl₃); IR (neat) ν_{\max} 3370 (s, OH), 3080, 3040, 2980, 2930, 2880, 1645, 1435, 1415, 1385, 1295, 1185, 1080, 1000, 970, 920, 730 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 5.82 (m, 3 H, HC=CH₂, H-2 and H-3), 5.10 (m, 2 H, C=CH₂), 4.25 (m, 1 H, H-1), 4.07 (br d, $J = 7.0$ Hz, 1 H, H-4), 3.80 (m, 2 H, H-6), 3.52 (m, 1 H, H-5), 3.30 (br s, 1 H, OH), 2.95 (br s, 1 H, OH), 2.35 (ddd, $J = 14.0, 7.0, 7.0$ Hz, 1 H, CH₂C=C), 2.25 (ddd, $J = 14.0, 7.0, 7.0$ Hz, 1 H, CH₂C=C); MS m/e (rel intensity) 153 (M - OH, 55), 135 (22), 129 (100), 113 (34), 1110 (53), 107 (25), 95 (28); HRMS calcd for C₉H₁₂O₂ (M - OH) 153.0889, found 153.0889.

(4aR,6R,8aS)-6-Allyl-4,4a,6,8a-tetrahydro-2,2-dimethylpyrano[3,2-d]-m-dioxin (12). 2-Methoxypropene (33.8 mL, 0.35 mol) was added dropwise over a 15-min period to a stirred solution of the diol 11 (40.0 g, 0.24 mol) and pyridinium *p*-toluenesulfonate (3.0 g, 12.0 mmol) in dichloromethane (1.0 L) at 0 °C. After 2 h, additional 2-methoxypropene (22.5 g, 0.24 mol) was added, the cooling bath was removed, and the reaction mixture was stirred for 3 h. Dilution with ether (3 L) followed by washing with H₂O (2 \times 20 mL) and brine (200 mL), drying (MgSO₄), and solvent removal gave the acetone 12 (49.0 g, 100%). 12: oil; $R_f = 0.72$ (silica, 30% ether in petroleum ether); $[\alpha]_D^{21} -19.9^\circ$ (c 2.02, CHCl₃); IR (neat) ν_{\max} 3080, 3050, 3000, 2950, 2890, 1650, 1465, 1440, 1410, 1390, 1380, 1315, 1270, 1225, 1200, 1155, 1100, 1045, 1000, 945, 920, 765, 715 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 5.86 (br d, $J = 10.4$ Hz, 1 H, H-2), 5.82 (m, 1 H, CH=CH₂), 5.72 (ddd, $J = 10.4, 2.5, 2.4$ Hz, 1 H, H-3), 5.12 (m, 2 H, CH=CH₂), 4.27 (m, 1 H, H-4), 4.20 (br dd, $J = 8.5, 1.3$ Hz, 1 H, H-1), 3.88 (dd, $J = 10.6, 5.1$ Hz, 1 H, H-6), 3.75 (dd, $J = 10.6, 10.4$ Hz, 1 H, H-6), 3.54 (m, 1 H, H-5), 2.47 (bbdd, $J = 14.2, 7.6, 6.2$ Hz, 1 H, CH₂CH=C), 2.32 (br ddd, $J = 14.2, 8.0, 6.2$ Hz, 1 H, CH₂CH=C), 1.53, 1.54 (singlets, 3 H, each C(CH₃)₂); MS m/e (rel intensity) 211 (M + 1, 100), 195 (100), 186 (50), 170 (100), 162 (15), 153 (100), 135 (100); HRMS calcd for C₁₂H₁₉O₃ (M + 1) 211.1334, found 211.1314.

(4aR,6R,8aS)-4,4a,6,8a-Tetrahydro-2,2-dimethylpyrano[3,2-d]-m-dioxin-6-propanol (13). A stirred solution of BH₃·THF (305 mL, 0.305 mol), 1 M in THF at 0 °C, was treated dropwise with 2-methyl-2-butene (78.0 mL, 0.73 mol), and stirring was continued for 1 h. Olefin 12 (49.0 g, 0.24 mol) in dry THF (150 mL) was added, and the reaction mixture was stirred for 1 h. Excess disiamylborane was carefully quenched with H₂O (5.0 mL) followed by dropwise addition of a mixture of 3 N NaOH (360 mL, 1.08 mol) and 30% hydrogen peroxide (100 mL, 0.82 mol) over a 30-min period, removal of the cooling bath, and continued stirring for 15 min. The reaction mixture was diluted with ether (1.0 L) and washed with H₂O (2 \times 200 mL) and brine (200 mL). Drying (MgSO₄) and concentration followed by flash chromatography (silica, 90% ether in

petroleum ether) furnished the alcohol 13 (46.7 g, 87%). 13: oil; $R_f = 0.26$ (silica, 80% ether in petroleum ether); $[\alpha]_D^{21} -18.0^\circ$ (c 1.20, CHCl₃); IR (neat) ν_{\max} 3440 (s, OH), 3040, 3000, 2950, 2880, 1375, 1270, 1220, 1200, 1155, 1125, 1100, 1055, 945, 860, 760, 705 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 5.83 (br d, $J = 10.5$ Hz, 1 H, H-2), 5.69 (ddd, $J = 10.5, 2.5, 2.4$ Hz, 1 H, H-3), 4.25 (m, 1 H, H-4), 4.20 (br d, $J = 8.4$ Hz, 1 H, H-1), 3.88 (dd, $J = 10.5, 5.1$ Hz, 1 H, H-6), 3.76 (dd, $J = 10.7, 10.7$ Hz, 1 H, H-6), 3.67 (m, 2 H, CH₂OH), 3.42 (m, 1 H, H-5), 1.91 (br d, 1 H, OH), 1.82–1.59 (m, 4 H, CH₂), 1.55, 1.47 (singlets, 3 H each C(CH₃)₂); MS m/e (rel intensity) 229 (M + 1, 100), 213 (100), 195 (100), 184 (100), 172 (100), 154 (100), 141 (100), 128 (100); HRMS calcd for C₁₂H₂₁O₄ (M + 1) 229.1440, found 229.1474.

(4aR,6R,8aS)-4,4a,6,8a-Tetrahydro-6-[3-(*tert*-butyldiphenylsiloxy)propyl]-2,2-dimethylpyrano[3,2-d]-m-dioxin (14). A stirred mixture of the alcohol 13 (10.0 g, 44.0 mmol), imidazole (9.0 g, 129 mmol) and DMF (100 mL) at 25 °C was treated in one portion with *tert*-butylchlorodiphenylsilane (13.5 mL, 52 mmol). After 1 h the reaction was quenched with ether (500 mL) followed by washings with H₂O (2 \times 100 mL) and brine (100 mL). Drying (MgSO₄), concentration, and flash chromatography (silica, 10% ether in petroleum ether) gave the silyl ether 14 (20.5 g, 98%). 14: oil; $R_f = 0.37$ (silica, 15% ether in petroleum ether); $[\alpha]_D^{21} -8.6^\circ$ (c 2.25, CHCl₃); IR (neat) ν_{\max} 3100, 3080, 3020, 3000, 2940, 2890, 2860, 1965, 1820, 1590, 1485, 1465, 1435, 1385, 1375, 1315, 1270, 1220, 1200, 1145, 1100, 940, 910, 900, 860, 825, 760, 740, 705, 680, 615 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 7.69, 7.39 (multiplets, 10 H, Ar), 5.80 (br d, $J = 10.5$ Hz, 1 H, H-2), 5.68 (ddd, $J = 10.5, 2.3, 2.3$ Hz, 1 H, H-3), 4.17 (m, 2 H, H-4 and H-1), 3.84 (dd, $J = 10.6, 4.8$ Hz, 1 H, H-6), 3.72 (dd, $J = 10.6, 10.5$ Hz, 1 H, H-6), 3.67 (m, 2 H, CH₂OSi), 3.37 (m, 1 H, H-5), 1.87–1.55 (m, 4 H, CH₂), 1.51, 1.43 (singlets, 3 H each, C(CH₃)₂), 1.04 (s, 9 H, *t*-BuSi); MS m/e (rel intensity) 484 (M + NH₄, 14), 467 (85), 451 (11), 409 (100), 391 (34), 351 (64); HRMS calcd for C₂₈H₄₂NO₄Si (M + NH₄) 484.288, found 484.290.

(4aR,8aS)-4,4a,6,8a-Tetrahydro-2,2-dimethylpyrano[3,2-d]-m-dioxin-6-propanol (18) and (4aR,6R,8aS)-Hexahydro-2,2-dimethylpyrano[3,2-d]-m-dioxin-6-propanol (19). Method A. A stirred solution of the olefin 13 (45.0 g, 0.20 mol) in EtOAc (500 mL) was treated with Pd(OH)₂ (4.5 g, 10 wt %). A hydrogen atmosphere was introduced by using a hydrogen-filled balloon (repeated evacuation with aspirator). After 3 h of vigorous stirring, the hydrogen was replaced with argon. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated, followed by flash chromatography (silica, 60% ether in petroleum ether) to afford the enol ether 18 (20.2 g, 45%) along with the reduced product 19 (19.4 g, 43%). 18: oil; $R_f = 0.45$ (silica, 80% ether in petroleum ether); $[\alpha]_D^{21} +68.0^\circ$ (c 2.56, CHCl₃); IR (neat) ν_{\max} 3400 (s, OH), 3000, 2940, 2890, 1675 (s, enol ether), 1450, 1380, 1270, 1240, 1205, 1160, 1105, 1080, 1000, 945, 900, 860, 770, 740 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 4.50 (dd, $J = 5.0, 3.4$ Hz, 1 H, H-2), 3.98 (dd, $J = 10.8, 5.5$ Hz, 1 H, H-6), 3.90 (m, 1 H, H-4), 3.65 (m, 2 H, CH₂OH), 3.59 (m, 1 H, H-5), 2.25–2.00 (4 H, CH₂CH=C), 1.84–1.65 (m, 3 H, OH and CH₂), 1.54, 1.43 (singlets, 2 \times 3 H, C(CH₃)₂); MS m/e (rel intensity) 229 (M + 1, 100), 213 (100), 200 (49), 184 (100), 171 (100), 155 (100), 139 (100), 127 (100); HRMS calcd for C₁₂H₂₁O₄ (M + 1) 229.1440, found 229.1415. Anal. Calcd for C₁₂H₂₁O₄: C, 63.13; H, 8.83. Found: C, 63.16; H, 9.09. 19: oil; $R_f = 0.18$ (silica, 80% ether in petroleum ether); $[\alpha]_D^{21} +29.9^\circ$ (c 1.91, CHCl₃); IR (neat) ν_{\max} 3430 (s, OH), 3000, 2950, 2880, 1460, 1380, 1270, 1230, 1200, 1160, 1100, 940, 880, 850, 755 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 3.91 (ddd, $J = 10.5, 5.4, 5.2$ Hz, 1 H, H-1), 3.76 (dd, $J = 10.5, 5.4$ Hz, 1 H, H-6), 3.71–3.56 (m, 4 H, H-6, H-4 and CH₂OH), 3.44 (ddd, $J = 9.6, 9.6, 5.4$ Hz, 1 H, H-5), 2.16–1.45 (m, 9 H, CH₂ and OH), 1.51, 1.41 (2 \times s, 2 \times 3 H, C(CH₃)₂); MS m/e (rel intensity) 231 (M + 1, 43), 215 (76), 193 (7), 173 (100), 155 (60), 129 (100); HRMS calcd for C₁₂H₂₃O₄ (M + 1) 231.1596, found 231.1578. Anal. Calcd for C₁₂H₂₃O₄: C, 62.58; H, 9.62. Found: C, 62.36; H, 9.62. Method B. A stirred mixture of the olefin 13 (25.0 g, 110 mmol), potassium *tert*-butoxide (16.1 g, 130 mmol), and dry DMSO (275 mL) was heated at 100 °C for 4 h. The cooled reaction mixture was diluted with H₂O (400 mL) and extracted with EtOAc (3 \times 200 mL). The combined organic products were washed with brine (110 mL), dried (MgSO₄), and concentrated, and the resulting crude oil was subjected to flash chromatography (silica, 60% ether in petroleum ether) to furnish the enol ether 18 (15.5 g, 60%) and the starting olefin 13 (6.2 g, 25%), which was recycled.

(4aR,8aS)-4,4a,6,8a-Tetrahydro-6-[3-(*tert*-butyldiphenylsiloxy)propyl]-2,2-dimethylpyrano[3,2-d]-m-dioxin (20). To a stirred mixture of the alcohol 18 (20.0 g, 88.0 mmol), imidazole (18.0 g, 0.26 mol), and dry DMF (200 mL) at 0 °C was added *tert*-butylchlorodiphenylsilane (27.1 mL, 104.0 mmol). After 1 h the reaction was quenched with ether (600 mL) followed by washing with H₂O (2 \times 200 mL) and brine (200 mL). Drying (MgSO₄), concentration, and flash chromatography (silica,

5% ether in petroleum ether) gave the silyl ether **20** (41.0 g, 100%). **20**: oil; $R_f = 0.36$ (silica, 5% ether in petroleum ether); $[\alpha]_D^{25} + 28.6^\circ$ (c 2.15, CHCl_3); IR (neat) ν_{max} 3070, 3050, 3000, 2940, 2860, 1675 (s, enol ether), 1595, 1465, 1430, 1385, 1375, 1365, 1310, 1265, 1240, 1205, 1185, 1160, 1100, 1005, 940, 900, 860, 825, 765, 740, 690, 615 cm^{-1} ; $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 7.69, 7.39 (multiplets, 10 H, Ar), 4.41 (dd, $J = 5.1, 2.1$ Hz, 1 H, $H-2$), 3.96 (dd, $J = 10.8, 5.4$ Hz, 1 H, $H-6$), 3.86 (m, 1 H, $H-4$), 3.75 (dd, $J = 10.8, 10.4$ Hz, 1 H, $H-6$), 3.64 (t, $J = 6.3$ Hz, 3 H, $-\text{CH}_2\text{O}$), 3.52 (ddd, $J = 10.1, 9.9, 5.5$ Hz, 1 H, $H-5$), 2.20–1.99 (m, 4 H, $\text{CH}_2\text{C}=\text{C}$), 1.72 (m, 2 H, CH_2), 1.52, 1.43 (2 \times s, 2 \times 3 H, $\text{C}(\text{CH}_3)_2$), 1.04 (s, 9 H, $^t\text{BuSi}$); MS m/e (rel intensity) 467 (M + 1, 19), 451 (19), 410 (100), 389 (22), 351 (100), 331 (33), 295 (100), 273 (100), 211 (100), 183 (43); HRMS calcd for $\text{C}_{28}\text{H}_{39}\text{O}_4\text{Si}$ (M + 1) 467.2618, found 467.2620.

2,6-Anhydro-9-O-(tert-butylidiphenylsilyl)-4,7,8-trideoxy-1,3-O-isopropylidene-D-manno-nonitol (21) and **4,8-Anhydro-1-O-(tert-butylidiphenylsilyl)-2,3,6-trideoxy-7,9-O-isopropylidene-D-allo-nonitol (22)**. To a stirred solution of the cyclic enol ether **20** (41.0 g, 88.0 mmol) in dry THF (200 mL) at 0 °C was added $\text{BH}_3\cdot\text{THF}$ (60.0 mL, 60.0 mmol, 1 M in THF) dropwise over a 20-min period. After stirring for an additional 1 h, the excess borane was quenched carefully with H_2O (5.0 mL). Dropwise addition of a mixture of 3 N NaOH (70.0 mL, 0.21 mol) and 30% hydrogen peroxide (21.0 mL, 0.31 mol) over 15 min, removal of the cooling bath, and continued stirring for 15 min resulted in a white heterogeneous mixture. Dilution with ether (500 mL), followed by washing with H_2O (2 \times 100 mL) and brine (100 mL), drying (MgSO_4), concentration, and flash chromatography (silica, 40 \rightarrow 60% ether in petroleum ether) produced, in order of elution, the desired alcohol **22** (28.8 g, 68%) and its diastereomer **21** (10.2 g, 24%). **22**: oil; $R_f = 0.26$ (silica, 50% ether in petroleum ether); IR (neat) ν_{max} 3450 (s, OH), 3075, 3050, 3000, 2940, 2860, 1595, 1475, 1465, 1430, 1380, 1275, 1205, 1185, 1165, 1100, 1030, 990, 940, 865, 740, 705, 690, 615 cm^{-1} ; $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 7.68, 7.39 (multiplets, 10 H, Ar), 3.85 (dd, $J = 10.8, 5.3$ Hz, 1 H, $H-6$), 3.68 (t, $J = 6.4$ Hz, 2 H, $-\text{CH}_2\text{O}$), 3.64 (dd, $J = 10.8, 10.6$ Hz, 1 H, $H-6$), 3.57 (m, 1 H, $H-4$), 3.43 (m, 1 H, $H-2$), 3.10 (m, 2 H, $H-1$ and $H-5$), 2.29 (ddd, $J = 11.3, 4.4, 4.3$ Hz, 1 H, $H-3\beta$), 2.03–1.73 (m, 3 H, CH_2), 1.68 (d, $J = 5.0$ Hz, 1 H, OH), 1.65–1.45 (m, 2 H, CH_2), 1.48, 1.43 (singlets, 2 \times 3 H, $\text{C}(\text{CH}_3)_2$), 1.06 (s, 9 H, $^t\text{BuSi}$); MS m/e (rel intensity) 485 (M + 1, 16), 469 (20), 427 (100), 351 (36), 291 (82), 269 (41), 221 (50), 199 (91); HRMS calcd for $\text{C}_{28}\text{H}_{41}\text{O}_5\text{Si}$ (M + 1) 485.2723, found 485.2678. **21**: oil; $R_f = 0.10$ (silica, 50% ether in petroleum ether); $[\alpha]_D^{25} + 15.5^\circ$ (c 2.10, CHCl_3); IR (neat) ν_{max} 3450 (s, OH), 3080, 3050, 3000, 2950, 2900, 2860, 1595, 1475, 1430, 1380, 1365, 1275, 1240, 1200, 1100, 1010, 940, 875, 825, 740, 705, 690, 615 cm^{-1} ; $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 7.68, 7.39 (multiplets, 10 H, Ar), 4.02 (ddd, $J = 9.7, 9.4, 2.5$ Hz, 1 H, $H-1$), 3.86 (m, 1 H, $H-2$), 3.77–3.67 (m, 5 H, $-\text{CH}_2\text{O}$, $H-6$ and $H-4$), 3.40 (m, 1 H, $H-5$), 2.05–1.50 (m, 6 H, CH_2), 1.51, 1.41 (singlets, 2 \times 3 H, $\text{C}(\text{CH}_3)_2$), 1.06 (s, 9 H, $^t\text{BuSi}$); MS m/e (rel intensity) 485 (M + 1, 19), 469 (28), 427 (100), 351 (47), 291 (98), 269 (42), 229 (94), 199 (100), 153 (100); HRMS calcd for $\text{C}_{28}\text{H}_{41}\text{O}_5\text{Si}$ (M + 1) 485.2723, found 485.2668.

4,8-Anhydro-1-O-(tert-butylidiphenylsilyl)-2,3,6-trideoxy-7,9-O-isopropylidene-5-O-(acetyl)-D-allo-nonitol (23). To a stirred solution of the alcohol **22** (30.0 mg, 0.06 mmol) and DMAP (22.6 mg, 0.18 mmol) in dichloromethane (500 μL) at 25 °C was added acetic anhydride (11.3 μL , 0.12 mmol). After 30 min the solvent was removed in vacuo, and the residue was chromatographed (silica, 15% ether in petroleum ether) to afford the acetate **23** (30.6 mg, 94%). **23**: oil; $R_f = 0.81$ (silica, 50% ether in petroleum ether); $[\alpha]_D^{25} - 25.8^\circ$ (c 2.08, CHCl_3); IR (neat) ν_{max} 3080, 3050, 3000, 2960, 2940, 2860, 1745 (s, OAc), 1465, 1430, 1380, 1275, 1240, 1200, 1185, 1100, 1030, 980, 910, 860, 825, 735, 705, 685, 615 cm^{-1} ; $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 7.68, 7.36 (multiplets, 10 H, Ar), 4.62 (ddd, $J = 10.9, 9.9, 4.7$ Hz, 1 H, $H-2$), 3.85 (dd, $J = 10.7, 5.3$ Hz, 1 H, $H-6$), 3.69–3.55 (m, 4 H, $-\text{CH}_2\text{O}$, $H-4$ and $H-6$), 3.32 (ddd, $J = 9.9, 9.4, 1.8$ Hz, 1 H, $H-1$), 3.13 (ddd, $J = 9.9, 9.9, 5.2$ Hz, 1 H, $H-5$), 2.34 (m, 1 H, $H-3\beta$), 2.03 (s, 3 H, Ac), 1.83–1.30 (m, 5 H, CH_2), 1.48, 1.40 (singlets, 2 \times 3 H, $\text{C}(\text{CH}_3)_2$), 1.04 (s, 9 H, $^t\text{BuSi}$); MS m/e (rel intensity) 527 (M + 1, 33), 511 (36), 369 (100), 411 (38), 351 (68), 271 (24), 241 (100), 199 (85); HRMS calcd for $\text{C}_{30}\text{H}_{43}\text{O}_6\text{Si}$ (M + 1) 527.2829, found 527.2785.

4,8-Anhydro-1-O-(tert-butylidiphenylsilyl)-2,3,6-trideoxy-7,9-O-isopropylidene-5-O-(p-methoxybenzyl)-D-allo-nonitol (24). To a stirred, cold (0 °C) solution of the alcohol **22** (24.8 g, 50.0 mmol) in dry THF (200 mL) was added potassium hydride (6.4 g, 56.2 mmol, 36% dispersion in mineral oil). After 15 min, 4-methoxybenzyl chloride (9.5 mL, 70.0 mmol) was added followed by removal of the cooling bath and continued stirring for 3 h. Dilution with ether (400 mL) followed by washing with H_2O (2 \times 100 mL) and brine (100 mL), drying (MgSO_4), concentration, and flash chromatography (silica, 15% ether in petroleum ether) gave the benzyl ether **24** (25.4 g, 84%). **24**: oil; $R_f = 0.33$ (silica,

20% ether in petroleum ether); $[\alpha]_D^{25} - 33.3^\circ$ (c 1.93, CHCl_3); IR (neat) ν_{max} 3070, 3050, 3000, 2940, 2860, 1615, 1590, 1520, 1465, 1430, 1385, 1305, 1275, 1250, 1200, 1185, 1175, 1110, 1085, 1040, 1000, 910, 860, 825, 735, 705, 690, 615 cm^{-1} ; $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 7.67, 7.37 (multiplets, 10 H, Ar), 7.22 (6.84 (doublets, $J = 8.7$ Hz, 2 \times 2 H, $\text{C}_6\text{H}_4\text{OCH}_3$), 4.55, 4.37 (doublets, $J = 11.1$ Hz, 2 \times 1 H, CH_2Ar), 3.86 (dd, $J = 10.6, 5.2$ Hz, 1 H, $H-6$), 3.77 (s, 3 H, OCH_3), 3.70–3.58 (m, 3 H, $-\text{CH}_2\text{O}$ and $H-6$), 3.48 (m, 1 H, $H-4$), 3.30–3.07 (m, 3 H, $H-1, H-2$ and $H-5$), 2.44 (m, 1 H, $H-3\beta$), 2.05 (m, 1 H, CH_2), 1.85–1.45 (m, 4 H, CH_2), 1.47, 1.41 (singlets, 2 \times 3 H, $\text{C}(\text{CH}_3)_2$), 1.05 (s, 9 H, $^t\text{BuSi}$); MS m/e (rel intensity) 605 (M + 1, 10), 547 (38), 517 (11), 409 (28), 325 (32), 269 (66), 199 (100), 122 (100); HRMS calcd for $\text{C}_{36}\text{H}_{49}\text{O}_6\text{Si}$ (M + 1) 605.3298, found 605.3260.

4,8-Anhydro-1-O-(tert-butylidiphenylsilyl)-2,3,6-trideoxy-5-O-(p-methoxybenzyl)-D-allo-nonitol (25). A mixture of the acetonide **24** (22.1 g, 36.5 mmol), amberlyst-15 (H^+) ion-exchange resin (5.0 g), and methanol (300 mL) was stirred at 25 °C for 45 min. The amberlyst resin was removed by filtration, the filtrate was concentrated, and the residue was subjected to flash chromatography (silica, 90% ether in petroleum ether) to furnish the diol **25** (17.7 g, 86%). **25**: oil; $R_f = 0.35$ (silica, ether); $[\alpha]_D^{25} - 29.7^\circ$ (c 1.79, CHCl_3); IR (neat) ν_{max} 3410 (s, OH), 3080, 3050, 3000, 2940, 2860, 1620, 1595, 1465, 1430, 1310, 1250, 1175, 1100, 1040, 825, 740, 705, 690, 615 cm^{-1} ; $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 7.67, 7.38 (multiplets, 10 H, Ar), 7.22, 6.83 (doublets, $J = 8.6$ Hz, 2 \times 2 H, $\text{C}_6\text{H}_4\text{OCH}_3$), 4.59, 4.39 (doublets, $J = 11.1$ Hz, 2 \times 1 H, CH_2Ar), 3.85–3.52 (m, 3 H, $H-6$ and $H-4$), 3.78 (s, 3 H, OCH_3), 3.67 (t, $J = 5.2$ Hz, 2 H, $-\text{CH}_2\text{O}$), 3.26–3.07 (m, 3 H, $H-1, H-2$ and $H-5$), 2.55 (ddd, $J = 12.1, 5.2, 5.0$ Hz, 1 H, $H-3\beta$), 2.38 (br s, 1 H, OH), 2.14 (br s, 1 H, OH), 2.03 (m, 1 H, CH_2), 1.79–1.34 (m, 4 H, CH_2), 1.05 (s, 9 H, $^t\text{BuSi}$); MS m/e (rel intensity) 563 (M – 1, 10), 507 (12), 457 (8), 429 (7), 387 (24), 309 (88), 269 (20), 241 (43), 199 (100), 122 (100); HRMS calcd for $\text{C}_{33}\text{H}_{43}\text{O}_6\text{Si}$ (M – 1) 563.2829, found 563.2827.

4,8-Anhydro-1-O-(tert-butylidiphenylsilyl)-2,3,6-trideoxy-5-O-(p-methoxybenzyl)-D-allo-nonitol 9-p-Toluenesulfonate (26). To a stirred solution of the diol **25** (8.4 g, 14.9 mmol) in pyridine (30 mL) at 0 °C was added *p*-toluenesulfonyl chloride (4.2 g, 22.0 mmol). After 4 h at 0 °C the excess *p*-toluenesulfonyl chloride was quenched with methanol (5.0 mL), and the heterogeneous mixture stirred for 20 min. The reaction mixture was diluted with ether (200 mL) and then sequentially washed with H_2O (2 \times 50 mL) and brine (50 mL). Drying (MgSO_4), concentration, and flash chromatography (silica, 70% ether in petroleum ether) yielded the tosylate **26** (9.1 g, 85%). **26**: oil; $R_f = 0.62$ (silica, ether); $[\alpha]_D^{25} - 21.3^\circ$ (c 2.12, CHCl_3); IR (neat) ν_{max} 3420 (s, OH), 3080, 3050, 2960, 2940, 2860, 1615, 1600, 1590, 1520, 1430, 1360, 1250, 1180, 1100, 1040, 980, 820, 740, 705, 690, 675, 615 cm^{-1} ; $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 7.79, 7.32 (doublets, $J = 9.0$ Hz, 4 H, $\text{O}_2\text{SC}_6\text{H}_4$), 7.68, 7.38 (multiplets, 10 H, Ar), 7.22, 6.85 (doublets, $J = 8.6$ Hz, 2 \times 2 H, $\text{C}_6\text{H}_4\text{OCH}_3$), 4.52, 4.37 (doublets, $J = 11.1$ Hz, 2 \times 1 H, CH_2Ar), 4.30 (dd, $J = 11.2, 4.1$ Hz, 1 H, $H-6$), 4.12 (dd, $J = 11.2, 2.0$ Hz, 1 H, $H-6$), 3.77 (s, 3 H, OCH_3), 3.62 (m, 3 H, CH_2OS and $H-4$), 3.22–3.16 (m, 3 H, $H-1, H-2$ and H_3), 2.55 (m, 1 H, $H-3\beta$), 2.40 (s, 3 H, CH_3Ar), 2.38 (d, $J = 9.0$ Hz, 1 H, OH), 1.99 (m, 1 H, CH_2), 1.78–1.25 (m, 4 H, CH_2), 1.04 (s, 9 H, $^t\text{BuSi}$); MS m/e (rel intensity) 736 (M + NH_4), 661 (9), 599 (36), 542 (23), 228 (43); HRMS calcd for $\text{C}_{40}\text{H}_{54}\text{NO}_6\text{Si}$ (M + NH_4) 736.333, found 736.334.

3,7-Anhydro-10-O-(tert-butylidiphenylsilyl)-2,5,8,9-tetradecoxy-6-O-(p-methoxybenzyl)-1-*allo*-decononitrile (27). A mixture of the tosylate **26** (8.6 g, 12.0 mmol), sodium cyanide (1.2 g, 24.0 mmol), and dry DMSO (24.0 mL) was stirred at 70 °C for 2 h. The cooled reaction mixture was diluted with ether (200 mL) and sequentially washed with H_2O (3 \times 30 mL) and brine (20 mL). Drying (MgSO_4), concentration, and flash chromatography (silica, 80% ether in petroleum ether) afforded the nitrile **27** (6.2 g, 91%). **27**: oil; $R_f = 0.26$ (silica, 80% ether in petroleum ether); $[\alpha]_D^{25} - 25.4^\circ$ (c 2.42, CHCl_3); IR (neat) ν_{max} 3480 (s, OH), 3100, 3080, 3050, 2960, 2940, 2860, 2260 (w, $\text{C}\equiv\text{N}$), 1620, 1590, 1520, 1485, 1430, 1395, 1365, 1310, 1255, 1180, 1100, 1040, 1000, 830, 745, 710, 680, 615 cm^{-1} ; $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 7.68, 7.40 (multiplets, 10 H, Ar), 7.20, 6.85 (doublets, $J = 10.5$ Hz, 2 \times 2 H, $\text{C}_6\text{H}_4\text{OCH}_3$), 4.53, 4.40 (doublets, $J = 11.1$ Hz, 2 \times 1 H, CH_2Ar), 3.78 (s, 3 H, OCH_3), 3.69 (m, 2 H, CH_2O), 3.45 (m, 1 H, $H-4$), 3.30–3.12 (m, 3 H, $H-1, H-2$ and $H-5$), 2.73 (dd, $J = 16.8, 3.7$ Hz, 1 H, $H-6$), 2.59 (dd, $J = 16.8, 6.2, 1$ H, $H-6$), 2.52 (m, 1 H, $H-3$), 2.06 (m, 1 H, CH_2), 1.89–1.35 (m, 4 H, CH_2), 1.05 (s, 9 H, $^t\text{BuSi}$); MS m/e (rel intensity) 591 (M + NH_4), 567 (5), 516 (100), 396 (8), 318 (10), 269 (15), 199 (94), 131 (100); HRMS calcd for $\text{C}_{34}\text{H}_{47}\text{N}_2\text{O}_5\text{Si}$ (M + NH_4) 591.3254, found 591.3249.

3,7-Anhydro-10-O-(tert-butylidiphenylsilyl)-2,5,8,9-tetradecoxy-6-O-(p-methoxybenzyl)-1-*allo*-deconal (28). DIBAL (28.0 mL, 28.0 mmol, 1 M in hexanes) was added dropwise to a stirred solution of the nitrile **27** (6.2 g, 10.8 mmol) in dichloromethane (70 mL) at -78 °C over a

15-min period. After 45 min, the reaction was quenched with 1 N HCl (40.0 mL, 40.0 mmol), the cooling bath was removed, and the mixture was stirred vigorously for 15 min. Dilution with ether (300 mL), separation of the aqueous phase, and sequential washing of the organic phase with 1 N HCl (15 mL) and brine (25 mL) removed the aluminum salts. Drying (MgSO₄) and concentration gave the aldehyde **28** (6.0 g, ca 95% pure by ¹H NMR spectroscopy), which was used directly. **28**: oil; *R*_f = 0.32 (silica, 80% ether in petroleum ether); [α]_D²¹ -24.9° (c 1.75, CHCl₃); IR (neat) ν_{max} 3440 (s, OH), 3070, 3050, 2960, 2940, 2860, 2740 (w, H—C=O), 1730 (s, HC=O), 1615, 1590, 1520, 1475, 1465, 1430, 1305, 1250, 1175, 1100, 825, 740, 705, 690, 615 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 9.74 (dd, *J* = 2.0, 1.9 Hz, 1 H, HC=O), 7.69, 7.40 (multiplets, 10 H, Ar), 7.22, 6.84 (doublets, *J* = 8.7 Hz, 2 × 2 H, C₆H₄OCH₃), 4.54, 4.40 (doublets, *J* = 11.1 Hz, 2 × 1 H, CH₂Ar), 3.78 (s, 3 H, OCH₃), 3.67 (m, 2 H, CH₂O), 3.58 (ddd, *J* = 8.6, 8.5, 5.1 Hz, 1 H, H-6), 3.35 (m, 1 H, H-4), 3.26–3.10 (m, 2 H, HCO), 2.80 (dd, *J* = 16.2, 1.9 Hz, 1 H, H-6), 2.58 (m, 1 H, H-3β), 2.51 (dd, *J* = 16.2, 2.0 Hz, 1 H, H-6), 2.05 (m, 1 H, CH₂), 1.80 (d, *J* = 6.0 Hz, 1 H, OH), 1.79–1.30 (m, 4 H, CH₂), 1.05 (s, 9 H, ^tBuSi); MS *m/e* (rel intensity) 594 (M + NH₄, 24), 575 (28), 560 (10), 536 (100), 519 (82), 505 (23), 491 (15), 479 (32), 467 (38), 455 (32), 441 (28), 560 (10), 536 (100), 505 (23), 491 (15), 479 (32), 467 (38), 455 (32), 441 (28), 429 (44), 417 (53); HRMS calcd for C₃₄H₄₈NO₆Si (M + NH₄) 594.3251, found 594.3291.

Methyl (E)-(2R,3S,5R,6S)-6-[3-(tert-Butyldiphenylsilyloxy)propyl]tetrahydro-3-hydroxy-5-(p-methoxybenzyl)oxy]-2H-pyran-2-crotonate (29). A mixture of the aldehyde **28** (6.0 g, 10.0 mmol), dry benzene (50 mL), and methyl (triphenylphosphoranylidene)acetate (5.0 g, 15.0 mmol) was stirred at 25 °C for 1 h. The benzene was evaporated and the residue chromatography (silica, 60% ether in petroleum ether) to furnish the *E*-olefin **29** (5.6 g, 89%). **29**: oil; *R*_f = 0.32 (silica, 80% ether in petroleum ether); [α]_D²¹ -177.5° (c 2.31, CHCl₃); IR (neat) ν_{max} 3450 (s, OH), 3070, 3050, 3000, 2960, 2940, 2860, 1730 (s, CO₂CH₃), 1665 (m, CH=CHCO₂CH₃), 1620, 1590, 1520, 1465, 1430, 1305, 1250, 1180, 1100, 1040, 985, 825, 740, 705, 690, 615 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 7.69, 7.38 (multiplets, 10 H, Ar), 7.23, 6.83 (doublets, *J* = 8.7 Hz, 2 × 2 H, C₆H₄OCH₃), 7.01 (dt, *J* = 15.7, 6.0 Hz, 1 H, HC=CHCO₂), 5.90 (d, *J* = 15.7 Hz, 1 H, C=CHCO₂), 4.53, 4.39 (singlets, 3 H, OCH₃, COOCH₃), 3.67 (m, 2 H, CH₂O), 3.32 (m, 1 H, H-4), 3.15 (m, 3 H, H-1, H-2 and H-5), 2.68 (m, 1 H, H-6), 2.51 (m, 1 H, H-3β), 2.35 (ddd, *J* = 15.0, 14.0, 7.2 Hz, 1 H, H-6), 2.04 (m, 1 H, CH₂), 1.83–1.30 (m, 5 H, OH and CH₂), 1.05 (s, 9 H, ^tBuSi); MS *m/e* (rel intensity) 650 (M + NH₄, 14), 575 (100), 455 (10), 297 (12), 269 (21), 241 (21), 199 (100); HRMS calcd for C₃₇H₅₂NO₇Si (M + NH₄) 650.3515, found 650.3579.

Methyl (E)-(2R,3S,5R,6S)-6-[3-(tert-Butyldiphenylsilyloxy)propyl]tetrahydro-3-keto-5-(p-methoxybenzyl)oxy]-2H-pyran-2-crotonate (30). Dry DMSO (1.1 mL, 15.6 mmol) was added dropwise to a stirring solution of oxalyl chloride (1.0 mL, 11.7 mmol) in dry dichloromethane (36 mL) at -78 °C, followed by addition of the alcohol **29** (4.9 g, 7.8 mmol) in dichloromethane (15 mL). After 45 min, triethylamine (4.3 mL, 31.2 mmol) was added dropwise, the cooling bath was removed, and the reaction was stirred for an additional 15 min. Dilution with ether (200 mL) and sequential washing with H₂O (2 × 25 mL) and brine (25 mL), drying (MgSO₄), and concentration yielded the ketone **30** (4.9 g, 100%). **30**: oil; *R*_f = 0.80 (silica, 80% ether in petroleum ether); [α]_D²¹ +18.2° (c 2.28, CHCl₃); IR (neat) ν_{max} 3070, 3050, 3000, 2960, 2940, 2860, 1730 (s, C=O), 1665 (m, HC=CHCO₂), 1615, 1590, 1520, 1465, 1475, 1430, 1305, 1270, 1175, 1100, 1035, 825, 740, 705, 690, 615 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 7.69, 7.40 (multiplets, 10 H, Ar), 7.19, 6.84 (doublets, *J* = 8.6 Hz, 2 × 2 H, C₆H₄OMe), 6.92 (ddd, *J* = 15.7, 7.0, 5.3 Hz, 1 H, HC=CHCO₂), 5.90 (d, *J* = 15.7 Hz, 1 H, C=CHCO₂), 4.48, 4.35 (2 × d, *J* = 11.3 Hz, 2 × 1 H, CH₂Ar), 3.86 (dd, *J* = 8.0, 3.9 Hz, 1 H, H-5), 3.78 (s, 3 H, OCH₃), 3.70 (s, 3 H, OCH₃), 3.73–3.58 (m, 4 H, -CH₂O, H-1 and H-2), 2.81 (dd, *J* = 15.3, 4.3 Hz, 1 H, H-3β), 2.72 (m, 1 H, H-6), 2.55 (dd, *J* = 15.3, 6.0 Hz, 1 H, H-3), 2.45 (ddd, *J* = 16.0, 8.0, 7.0 Hz, 1 H, H-6), 1.94–1.55 (m, 4 H, CH₂), 1.05 (s, 9 H, ^tBuSi); MS *m/e* (rel intensity) 648 (M + NH₄, 13), 573 (100), 435 (6), 269 (13), 199 (75), 122 (100); HRMS calcd for C₃₇H₅₀NO₇Si (M + NH₄) 648.3356, found 648.3341.

Methyl (E)-(2R,3S,5R,6S)-6-[3-(tert-Butyldiphenylsilyloxy)propyl]tetrahydro-3-hydroxy-5-(p-methoxybenzyl)oxy]-3-methyl-2H-pyran-2-crotonate (32) and Methyl (E)-(2R,3S,5R,6S)-6-[3-(tert-Butyldiphenylsilyloxy)propyl]tetrahydro-3-hydroxy-5-(p-methoxybenzyl)oxy]-3-methyl-2H-pyran-2-crotonate (31). To a stirred solution of the ketone **30** (4.5 g, 7.0 mmol) in dry dichloromethane (50 mL) at -78 °C was added trimethylaluminum (10.0 mL, 2 M in toluene, 15.0 mmol). The reaction mixture was warmed to -10 °C and stirred at that temperature for 4 h. Upon recooling to -78 °C, methanol (10.0 mL) was added carefully to quench the excess trimethylaluminum, followed by removal

of the cooling bath and continued stirring for 20 min. The mixture was diluted with EtOAc (200 mL) and washed with saturated aqueous sodium potassium tartrate (70 mL). Drying (MgSO₄) and concentration followed by flash chromatography (silica, 60% ether in petroleum ether) afforded, in reverse order of elution, the desired tertiary alcohol **32** (3.6 g, 81%) and its epimer **31** (0.6 g, 13%). **32**: oil; *R*_f = 0.23 (silica, 70% ether in petroleum ether); [α]_D²¹ -5.6° (c 1.53, CHCl₃); IR (neat) ν_{max} 3460 (s, OH), 3080, 3050, 2950, 2860, 1730 (s, C=O), 1665 (m, HC=CHCO₂), 1615, 1590, 1520, 1465, 1430, 1250, 1100, 830, 745, 705, 690, 615 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 7.69, 7.39 (multiplets, 10 H, Ar), 7.22, 6.83 (doublets, *J* = 8.7 Hz, 2 × 2 H, C₆H₄OMe), 7.00 (ddd, *J* = 15.7, 6.8, 5.2 Hz, 1 H, HC=CHCO₂), 5.87 (d, *J* = 15.7 Hz, 1 H, C=CHCO₂), 4.51, 4.38 (2 × d, *J* = 11.0 Hz, 2 × 1 H, CH₂Ar), 3.78 (s, 3 H, OCH₃), 3.68 (s, 3 H, OCH₃), 3.68 (m, 2 H, -CH₂O), 3.21–3.10 (m, 3 H, H-1, H-2 and H-5), 2.55 (bdd, *J* = 14.0, 6.8 Hz, 1 H, H-6), 2.33–1.97 (m, 3 H, H-6 and H-3), 1.85–1.30 (m, 5 H, OH and CH₂), 1.05 (s, 9 H, ^tBuSi); MS *m/e* (rel intensity) 589 (M - ^tBu, 100), 516 (16), 469 (28), 339 (13); HRMS calcd for C₃₄H₄₁O₇Si (M - ^tBu) 589.2621, found 589.2691. Anal. Calcd for C₄₀H₅₆O₆Si₂: C, 70.55; H, 7.79. Found: C, 70.21; H, 8.01. **31**: oil; *R*_f = 0.33 (silica, 70% ether in petroleum ether); [α]_D²¹ -6.1° (c 1.78, CHCl₃); IR (neat) ν_{max} 3550 (w, OH), 3100, 3080, 2960, 2940, 2860, 1735 (s, C=O), 1665 (m, HC=CHCO₂), 1620, 1595, 1520, 1490, 1435, 1255, 1180, 1115, 1095, 1040, 830, 750, 710, 680, 615 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 7.70, 7.38 (m, 10 H, Ar), 7.21, 6.82 (doublets, *J* = 8.7 Hz, 2 × 2 H, C₆H₄OMe), 7.02 (dt, *J* = 15.7, 7.0 Hz, 1 H, HC=CHCO₂), 5.86 (d, *J* = 15.7 Hz, 2 × 1 H, CH₂Ar), 3.75 (s, 3 H, OCH₃), 3.66 (s, 3 H, OCH₃), 3.64 (m, 2 H, -CH₂O), 3.31 (ddd, *J* = 9.1, 8.3, 4.1 Hz, 1 H, H-2), 3.24–3.10 (dd, *J* = 14.0, 5.0 Hz, 1 H, H-3β), 2.11 (m, 1 H, CH₂), 2.10 (s, 1 H, OH), 1.87–1.36 (m, 4 H, CH₂), 1.17 (s, 3 H, CH₃), 1.05 (s, 9 H, ^tBuSi); MS *m/e* (rel intensity) 664 (M + NH₄, 9), 589 (100), 467 (7), 199 (45), 122 (100); HRMS calcd for C₃₈H₅₄NO₇Si (M + NH₄) 664.366, found 664.367.

Methyl (E)-(2R,3S,5R,6S)-6-[3-(tert-Butyldiphenylsilyloxy)propyl]tetrahydro-5-(p-methoxybenzyl)oxy]-3-(trimethylsilyloxy)-3-methyl-2H-pyran-2-crotonate (33). A mixture of the tertiary alcohol **32** (2.9 g, 4.5 mmol), 1-(trimethylsilyl)imidazole (1.3 mL, 8.8 mmol), and dry 1,2-dichloroethane (15 mL) was stirred at 25 °C for 3 h. The excess 1-(trimethylsilyl)imidazole was quenched with methanol (2.0 mL), and after 5 min, the mixture was diluted with ether (50 mL), dried (MgSO₄), and concentrated to furnish the silyl ether **33** (3.5 g, 100%). **33**: oil; *R*_f = 0.23 (silica, 10% ether in petroleum ether); [α]_D²¹ -8.7° (c 2.77, CHCl₃); IR (neat) ν_{max} 3080, 3050, 3000, 2960, 2940, 2860, 1730 (s, C=O), 1665 (m, HC=CHCO₂), 1615, 1590, 1520, 1470, 1430, 1380, 1330, 1305, 1250, 1175, 1140, 1100, 1040, 845, 825, 745, 705, 690, 615 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) 7.70, 7.38 (multiplets, 10 H, Ar), 7.21, 6.82 (doublets, *J* = 8.7 Hz, 2 × 2 H, C₆H₄OMe), 7.02 (dt, *J* = 15.7, 7.0 Hz, 1 H, HC=CHCO₂), 5.83 (d, *J* = 15.6 Hz, 1 H, C=CHCO₂), 4.49, 4.39 (doublets, *J* = 11.1 Hz, 2 × 1 H, CH₂Ar), 3.78 (s, 3 H, OCH₃), 3.66 (s, 3 H, OCH₃), 3.64 (m, 2 H, -CH₂O), 3.20–3.02 (m, 3 H, H-1, H-1 and H-5), 2.52 (bdd, *J* = 14.2, 8.0 Hz, 1 H, H-6), 2.22 (m, 1 H, H-6), 2.08 (m, 1 H, CH₂), 1.85–1.30 (m, 4 H, CH₂), 1.17 (s, 3 H, CH₃), 1.05 (s, 9 H, ^tBuSi), 0.12 (s, 9 H, Me₃Si); MS *m/e* (rel intensity) 736 (M + NH₄, 40), 662 (100), 521 (34), 429 (18), 181 (18); HRMS calcd for C₄₁H₆₂NO₇Si₂ (M + NH₄) 736.406, found 736.394.

(E)-4-[(2R,3S,5R,6S)-6-[3-(tert-Butyldiphenylsilyloxy)propyl]tetrahydro-5-(p-methoxybenzyl)oxy]-3-(trimethylsilyloxy)-3-methyl-2H-pyran-2-yl]-2-buten-1-ol (34). DIBAL (12.5 mL, 1 M in hexanes, 12.5 mmol) was added dropwise to a stirred solution of the ester **33** (3.5 g, 4.9 mmol) in dry dichloromethane (30.0 mL) at -78 °C over a 5-min period. After 45 min, the mixture was diluted with EtOAc (100 mL) and washed with saturated aqueous sodium potassium tartrate (50 mL). Drying (MgSO₄) and concentration followed by flash chromatography (silica, 30% ether in petroleum ether) afforded the allylic alcohol **34** (3.2 g, 95%). **34**: oil; *R*_f = 0.42 (silica, 40% ether in petroleum ether); [α]_D²¹ -9.8° (c 1.72, CHCl₃); IR (neat) ν_{max} 3440 (s, OH), 3080, 3050, 2960, 2940, 2860, 1615, 1590, 1520, 1465, 1435, 1380, 1305, 1250, 1175, 1100, 1040, 870, 840, 825, 740, 705, 690, 615 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 7.70, 7.39 (multiplets, 10 H, Ar), 7.21, 6.83 (doublets, *J* = 8.7 Hz, 2 × 2 H, C₆H₄OMe), 5.72 (m, 2 H, HC=CH), 4.49, 4.38 (doublets, *J* = 11.1 Hz, 2 × 1 H, CH₂Ar), 4.04 (d, *J* = 4.7 Hz, 2 H, CH₂OH), 3.77 (s, 3 H, OCH₃), 3.67 (m, 2 H, CH₂OSi), 3.08 (m, 3 H, H-1, H-3 and H-5), 2.37 (br dd, *J* = 15.0, 5.0 Hz, 1 H, CH₂), 2.23 (m, 1 H, CH₂), 2.10–1.90 (m, 3 H, CH₂), 1.85–1.26 (m, 5 H, OH and CH₂), 1.13 (s, 3 H, CH₃), 1.05 (s, 9 H, ^tBuSi), 0.10 (s, 9 H, Me₃Si). Anal. Calcd for C₄₀C₅₆O₆Si₂: C, 69.72; H, 8.19. Found: C, 69.43; H, 8.40. MS *m/e* (rel intensity) 709 (M + NH₄, 9), 601 (36), 543 (27), 463 (11), 181 (38); HRMS calcd for C₄₀C₅₆O₆Si₂ (M + NH₄) 708.411, found 708.412.

2,3,5,9-Dianhydro-12-O-(tert-butylidiphenylsilyl)-4,7,10,11-tetra-deoxy-8-O-(p-methoxybenzyl)-6-C-methyl-6-O-(trimethylsilyl)-L-

erythro-L-*altro*-dodecitol (35). To a stirred mixture of the allylic alcohol **34** (3.5 g, 5.0 mmol), diethyl L-tartrate (1.1 mL, 6.5 mmol), and dry dichloromethane (30 mL) at -23°C was added titanium(IV) isopropoxide (1.5 mL, 5.0 mmol). After 10 min, *tert*-butyl hydroperoxide (3.1 mL, 12.5 mmol, 4.0 M in 1,2-dichloroethane) was added, and the reaction mixture was stored at -20°C for 16 h. Cooling was stopped, ether (30 mL) was added, and saturated aqueous sodium sulfate (1.5 mL) was added to the vigorously stirred mixture. The solution was filtered through a Celite pad, the filtrate was concentrated, and the residue was subjected to flash chromatography (silica, 35% ether in petroleum ether) to give the epoxy alcohol **35** (2.8 g, 80%); $R_f = 0.24$ (silica, 40% ether in petroleum ether); $[\alpha]_D^{25} -14.3^{\circ}$ (*c*, 2.07, CHCl_3); IR (neat) ν_{max} 3460 (m, OH) 3080, 3050, 2960, 2940, 2860, 1620, 1590, 1520, 1465, 1430, 1380, 1305, 1255, 1175, 1140, 115, 1090, 1040, 910, 875, 845, 825, 735, 710, 690, 615 cm^{-1} ; $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 7.69, 7.39 (multiplets, 10 H, Ar), 7.32, 6.84 (doublets, $J = 8.6$ Hz, 2×2 H, $\text{C}_6\text{H}_4\text{OMe}$), 4.52, 4.40 (doublets, $J = 11.0$ Hz, 2×1 H, CH_2Ar), 3.87 (br d, $J = 13.0$ Hz, 1 H, CH_2OH), 3.77 (s, 3 H, OCH_3), 3.69 (m, 2 H, CH_2OSi), 3.58 (br ddd, $J = 13.0, 6.0, 6.0$ Hz, 1 H, CH_2OH), 3.20–3.02 (m, 4 H, *H*-1, *H*-2 and *H*-5), 2.93 (m, 1 H, *H*-epox), 2.23 (dd, $J = 11.0, 4.0$ Hz, 1 H, *H*-3 β), 2.05 (m, 1 H, CH_2), 1.90–1.29 (m, 5 H, *OH* and CH_2), 1.12 (s, 3 H, CH_3), 1.05 (s, 9 H, *BuSi*), 0.01 (s, 9 H, *Me}_3\text{Si}*); MS *m/e* (rel intensity) 724 ($\text{M} + \text{NH}_4$, 50), 661 (18), 617 (9), 559 (11), 269 (13); HRMS calcd for $\text{C}_{40}\text{H}_{62}\text{NO}_7\text{Si}_2$ ($\text{M} + \text{NH}_4$) 724.406, found 724.412.

2,3,5,9-Dianhydro-12-O-(*tert*-butyldiphenylsilyl)-4,7,10,11-tetra-deoxy-8-O-(*p*-methoxybenzyl)-6-C-methyl-6-O-(trimethylsilyl)-L-erythro-L-*altro*-docose (36). To a stirred mixture of the epoxy alcohol **35** (2.0 g, 2.9 mmol), triethylamine (2.8 mL, 20.3 mmol), dry DMSO (5.0 mL), and dichloromethane (10.0 mL) at 0°C was added sulfur trioxide-pyridine complex (2.0 g, 11.6 mmol). After 2 h, the reaction mixture was diluted with ether (50 mL) and washed with H_2O (2×15 mL) and brine (15 mL), dried (MgSO_4), and concentrated to furnish the aldehyde **36** (2.0 g, ca 95% pure), which was used directly for the next step. **36:** oil; $R_f = 0.31$ (streak, silica, 20% ether in petroleum ether); $[\alpha]_D^{25} +8.0^{\circ}$ (*c* 1.67, CHCl_3); ν_{max} 3080, 3050, 2960, 2940, 2860, 1735 (s, $\text{C}=\text{O}$), 1620, 1590, 1525, 1465, 1430, 1380, 1305, 1255, 1175, 1140, 1115, 1090, 1040, 875, 840, 825, 745, 705, 690, 615 cm^{-1} ; $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 8.94 (d, $J = 6.4$ Hz, 1 H, $\text{HC}=\text{O}$), 7.69, 7.39 (multiplets, 10 H, Ar), 7.22, 6.85 (multiplets, $J = 8.6$ Hz, 2×2 H, $\text{C}_6\text{H}_4\text{OMe}$), 4.52, 4.40 (doublets, $J = 11.0$ Hz, 2 H, CH_2Ar), 3.78 (s, 3 H, OCH_3), 3.60 (m, 2 H, CH_2OSi), 3.33 (ddd, $J = 5.1, 4.8, 1.7$ Hz, 1 H, *H*-epox), 3.21–3.02 (m, 4 H, *H*-1, *H*-2, *H*-5 and *H*-epox), 2.24 (dd, $J = 13.0, 4.0$ Hz, 1 H, *H*-3 β), 2.06 (m, 1 H, CH_2), 1.92–1.33 (m, 6 H, CH_2), 1.12 (s, 3 H, CH_3), 1.05 (s, 9 H, *BuSi*), 0.10 (s, 9 H, *Me}_3\text{Si}*); MS *m/e* (rel intensity) 722 ($\text{M} + \text{NH}_4$, 100), 647 (17), 557 (53), 507 (33), 361 (100), 295 (40); HRMS calcd for $\text{C}_{40}\text{H}_{60}\text{NO}_7\text{Si}_2$ ($\text{M} + \text{NH}_4$) 722.390, found 722.384.

3,4,6,10-Dianhydro-1,1-dibromo-13-O-(*tert*-butyldiphenylsilyl)-1,2,5,8,11,12-hexa-deoxy-9-O-(*p*-methoxybenzyl)-7-C-methyl-7-O-(trimethylsilyl)-L-*altro*-tridec-1-enitol (37). Triphenylphosphine (3.1 g, 11.6 mmol) was added to a stirred solution of carbon tetrabromide (1.9 g, 5.8 mmol) in dry dichloromethane (20 mL) at 0°C . After 1 h the bright orange solution was cooled to -78°C and treated dropwise with the aldehyde **36** (2.0 g, ~ 2.8 mmol) in dichloromethane (10 mL) over a 2-min period. After 20 min, the reaction was treated with triethylamine (2.0 mL, 14.5 mmol) and then poured into stirring hexanes (400 mL). The solids were removed by filtration, the filtrate was concentrated, and the residue chromatographed (silica, 8% ether in petroleum ether) to afford the allylic epoxide **37** (1.7 g, 71%); **37:** oil; $R_f = 0.41$ (silica, 20% ether in petroleum ether); $[\alpha]_D^{25} -10.5^{\circ}$ (*c* 1.39, CHCl_3); IR (neat) ν_{max} 3080, 3050, 2960, 2940, 2850, 1620, 1590, 1520, 1480, 1435, 1380, 1305, 1255, 1175, 1140, 1115, 1090, 1040, 840, 815, 740, 705, 690, 615 cm^{-1} ; $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 7.69, 7.39 (multiplets, 10 H, Ar), 7.22, 6.83 (doublets, $J = 8.6$ Hz, 2×2 H, $\text{C}_6\text{H}_4\text{OMe}$), 6.09 (d, $J = 7.7$ Hz, 1 H, $\text{HC}=\text{CBr}_2$), 4.50, 4.45 (doublets, $J = 11.0$ Hz, 2×1 H, CH_2Ar), 3.78 (s, 3 H, OCH_3), 3.68 (m, 2 H, CH_2OSi), 3.33 (dd, $J = 7.7, 2.1$ Hz, 1 H, *H*-epox), 1.88–1.30 (m, 6 H, CH_2), 1.13 (s, 3 H, CH_3), 1.06 (s, 9 H, *BuSi*), 0.11 (s, 9 H, *Me}_3\text{Si}*); HRMS calcd for $\text{C}_{41}\text{H}_{57}\text{Br}_2\text{O}_6\text{Si}_2$ ($\text{M} + 1$) 859.206, found 859.212.

3,4,6,10-Dianhydro-1,1-dibromo-13-O-(*tert*-butyldiphenylsilyl)-1,2,5,8,11,12-hexa-deoxy-9-O-(*p*-methoxybenzyl)-7-C-methyl-L-erythro-L-*altro*-tridec-1-enitol (38). To a stirred solution of the bisallyl ether **37** (1.5 g, 1.7 mmol) in dry THF (10.0 mL) at -20°C was added tetrabutylammonium fluoride (4.0 mL, 1 M in THF, 4.0 mmol). The mixture was then warmed to 0°C , and stirring was continued for 20 min. Dilution with ether (40 mL) followed by washing with H_2O (2×1 mL) and brine (10 mL), drying (MgSO_4), concentration, and flash chromatography (silica, 40 \rightarrow 80% ether in petroleum ether) gave the tertiary alcohol **38** (1.3 g, 96%); **38:** oil; $R_f = 0.46$ (silica, 70% ether in petroleum ether); $[\alpha]_D^{25} -8.7^{\circ}$ (*c* 1.46, CHCl_3); IR (neat) ν_{max} 3450 (m, OH),

3080, 3050, 2940, 2860, 1620, 1590, 1470, 1435, 1255, 1170, 1100, 1035, 1010, 825, 740, 710, 690, 615 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3) δ 7.69, 7.39 (multiplets, 10 H, Ar), 7.23, 6.85 (doublets, $J = 8.6$ Hz, 2×2 H, $\text{C}_6\text{H}_4\text{OMe}$), 6.12 (d, $J = 7.7$ Hz, 1 H, $\text{HC}=\text{CBr}_2$), 4.53, 4.39 (doublets, $J = 11.1$ Hz, 2×1 H, CH_2Ar), 3.77 (s, 3 H, OCH_3), 3.69 (m, 2 H, $-\text{CH}_2\text{O}$), 3.38 (dd, $J = 7.7, 1.9$ Hz, 1 H, *H*-epox), 3.29–3.05 (m, 4 H, *H*-1, *H*-2, *H*-3 and *H*-epox), 2.30 (dd, $J = 13.0, 4.0$ Hz, 1 H, *H*-3 β), 2.06 (m, 1 H, CH_2), 1.90–1.37 (m, 6 H, CH_2), 1.41 (s, 1 H, *OH*), 1.14 (s, 3 H, CH_3), 1.05 (s, 9 H, *BuSi*); HRMS calcd for $\text{C}_{38}\text{H}_{49}\text{Br}_2\text{O}_6\text{Si}$ ($\text{M} + 1$) 787.167, found 787.173.

4,8,7,11-Dianhydro-13,13-dibromo-1-O-(*tert*-butyldiphenylsilyl)-2,3,6,9,12,13-hexa-deoxy-5-O-(*p*-methoxybenzyl)-7-C-methyl-D-erythro-D-*allo*-tridec-12-enitol (39) and 3,4,6,10-Dianhydro-1-bromo-13-O-(*tert*-butyldiphenylsilyl)-1,1,2,2-tetra-dehydro-1,2,5,8,11,12-hexa-deoxy-9-O-(*p*-methoxybenzyl)-7-C-methyl-7-O-(trimethylsilyl)-L-erythro-L-*altro*-tridec-1-ynitol (40). A stirred solution of the epoxide **38** (1.2 g, 1.5 mmol) in dry dichloromethane (15.0 mL) at 0°C was treated with camphorsulfonic acid (0.34 g, 0.15 mmol). After 45 min, triethylamine (0.42 mL, 0.30 mmol) was added, followed by concentration and flash chromatography (silica, 30% ether in petroleum ether) to give the bicycle **39** (1.0 g, 83%) and the bromoacetylene **40** (0.12 g, 11%). **39:** oil; $R_f = 0.77$ (silica, 70% ether in petroleum ether); $[\alpha]_D^{25} -3.8^{\circ}$ (*c* 2.32, CHCl_3); IR (neat) ν_{max} 3450 (m, OH), 3080, 3050, 2960, 2940, 2860, 1615, 1590, 1515, 1465, 1430, 1385, 1305, 1250, 1175, 1100, 1035, 900, 825, 790, 745, 705, 690, 615 cm^{-1} ; $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 7.69, 7.39 (multiplets, 10 H, Ar), 7.22, 6.82 (doublets, $J = 8.6$ Hz, 2×2 H, $\text{C}_6\text{H}_4\text{OMe}$), 6.41 (d, $J = 8.4$ Hz, 1 H, $\text{HC}=\text{CBr}_2$), 4.51, 4.63 (doublets, $J = 11.0$ Hz, 2×1 H, CH_2Ar), 4.15 (dd, $J = 8.6, 8.4$ Hz, 1 H, $-\text{OCHC}=\text{C}$), 3.77 (s, 3 H, OCH_3), 3.69 (m, 2 H, $-\text{CH}_2\text{O}$), 3.55 (m, 1 H, $-\text{HCOH}$), 3.26 (m, 2 H, *H*-1 and *H*-2), 3.08 (dd, $J = 12.3, 3.7$ Hz, 1 H, *H*-5), 2.33 (m, 1 H, *H*-3 β), 2.27 (dd, $J = 13.0, 4.0, 4.0$ Hz, 1 H, *H*-6 α), 2.06 (m, 1 H, CH_2), 1.86–1.37 (m, 6 H, CH_2), 1.67 (d, $J = 4.7$ Hz, 1 H, *OH*), 1.22 (s, 3 H, CH_3), 1.06 (s, 9 H, *BuSi*); HRMS calcd for $\text{C}_{38}\text{H}_{49}\text{Br}_2\text{O}_6\text{Si}$ ($\text{M} + 1$) 787.167, found 787.169. **40:** $R_f = 0.41$ (silica, 70% ether in petroleum ether); $[\alpha]_D^{25} -9.2^{\circ}$ (*c* 2.11, CHCl_3); IR (neat) ν_{max} 3450 (m, OH), 3080, 3050, 2970, 2860, 2230 (w, $\text{C}\equiv\text{C}$), 1620, 1590, 1520, 1470, 1435, 1385, 1305, 1255, 1165, 1100, 1040, 1010, 940, 905, 850, 825, 745, 710, 690, 615 cm^{-1} ; $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 7.69, 7.39 (multiplets, 10 H, Ar), 7.22, 6.83 (doublets, $J = 8.6$ Hz, 2×2 H, $\text{C}_6\text{H}_4\text{OMe}$), 4.51, 4.37 (doublets, $J = 11.0$ Hz, 2×1 H, CH_2Ar), 3.77 (s, 3 H, OCH_3), 3.69 (m, 2 H, $-\text{CH}_2\text{O}$), 3.26 (br dd, $J = 5.1, 4.7$ Hz, 1 H, *H*-epox), 3.17 (d, $J = 2.2$ Hz, 1 H, *H*-epox), 3.17–3.06 (m, 3 H, *H*-1, *H*-2 and *H*-5), 2.28 (dd, $J = 13.0, 4.0$ Hz, 1 H, *H*-3 β), 2.06 (m, 1 H, CH_2), 1.90–1.30 (m, 6 H, CH_2), 1.57 (br s, 1 H, *OH*), 1.11 (s, 3 H, CH_3), 1.06 (s, 9 H, *BuSi*); MS *m/e* (rel intensity) 724 ($\text{M} + \text{NH}_4$, 7), 633 (10), 579 (8), 529 (10), 199 (100); HRMS calcd for $\text{C}_{38}\text{H}_{51}\text{NO}_6\text{Si}$ ($\text{M} + \text{NH}_4$) 724.266, found 724.259. Anal. Calcd for $\text{C}_{38}\text{H}_{47}\text{BrO}_6\text{Si}$: C, 64.48; H, 6.69. Found: C, 64.43; H, 6.87.

4,8,7,11-Dianhydro-13,13-dibromo-1-O-(*tert*-butyldiphenylsilyl)-2,3,6,9,12,13-hexa-deoxy-10-O-(acetyl)-5-O-(*p*-methoxybenzyl)-7-C-methyl-D-erythro-D-*allo*-tridec-12-enitol (41). To a stirred mixture of the alcohol **39** (40.0 mg, 0.05 mmol), DMAP (18.3 mg, 0.15 mmol), and dichloromethane (0.5 mL) at 25°C was added acetic anhydride (94 μL , 0.10 mmol). After 30 min, the solvents were removed in vacuo, and the residue was subjected to flash chromatography (silica, 20% ether in petroleum ether) to furnish the acetate **41** (38.0 mg, 90%). **41:** oil; $R_f = 0.85$ (silica, 50% ether in petroleum ether); $[\alpha]_D^{25} -14.5^{\circ}$ (*c* 2.10, CHCl_3); IR (neat) ν_{max} 6080, 3050, 2960, 2860, 1750 (s, OAc), 1620, 1590, 1520, 1470, 1435, 1385, 1305, 1250, 1180, 1100, 1040, 900, 830, 800, 745, 710, 690, 615 cm^{-1} ; $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 7.66, 7.28 (multiplets, 10 H, Ar), 7.20, 6.83 (doublets, $J = 8.6$ Hz, 2×1 H, $\text{C}_6\text{H}_4\text{OMe}$), 6.36 (d, $J = 8.3$ Hz, 1 H, $\text{HC}=\text{CBr}_2$), 4.71 (ddd, $J = 11.0, 9.8, 5.3$ Hz, 1 H, $-\text{CHOAc}$), 4.51, 4.36 (doublets, $J = 11.0$ Hz, 2×1 H, CH_2Ar), 4.30 (dd, $J = 9.8, 8.6$ Hz, 1 H, $\text{C}=\text{CCHO}$), 3.77 (s, 3 H, OCH_3), 3.66 (m, 2 H, CH_2OSi), 3.22 (m, 2 H, *H*-1 and *H*-2), 3.12 (dd, $J = 12.4, 3.8$ Hz, 1 H, *H*-5), 2.28 (m, 1 H, *H*-6 β), 2.18 (m, 1 H, *H*-6 α), 2.04 (s, 3 H, *Ac*), 2.10–1.37 (m, 6 H, CH_2), 1.26 (s, 3 H, CH_3), 1.05 (s, 9 H, *BuSi*); HRMS calcd for $\text{C}_{40}\text{H}_{51}\text{Br}_2\text{O}_7\text{Si}$ ($\text{M} + 1$) 829.176, found 829.175.

4,8,7,11-Dianhydro-13,13-dibromo-1-O-(*tert*-butyldiphenylsilyl)-2,3,6,9,12,13-hexa-deoxy-10-O-(trimethylsilyl)-5-O-(*p*-methoxybenzyl)-7-C-methyl-D-erythro-D-*allo*-tridec-12-enitol (42). A solution of the alcohol **39** (1.0 g, 1.2 mmol), 1-(trimethylsilyl)imidazole (0.1 mL, 1.3 mmol), and dry dichloromethane (5.0 mL) was stirred at 25°C for 1 h. The excess 1-(trimethylsilyl)imidazole was quenched with methanol (1.0 mL). After 5 min the mixture was diluted with petroleum ether (20 mL) and washed with H_2O (2×5 mL) and brine (5 mL), dried (MgSO_4), and concentrated to furnish the silyl ether **42** (1.1 g, 100%). **42:** oil; $R_f = 0.63$ (silica, 10% ether in petroleum ether); $[\alpha]_D^{25} -6.2^{\circ}$ (*c* 1.55, CHCl_3); IR (neat) ν_{max} 3080, 3050, 2960, 2850, 1620, 1590, 1520, 1485,

1435, 1390, 1310, 1255, 1160, 1100, 1040, 885, 850, 825, 790, 745, 705, 690, 615 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 7.69, 7.39 (multiplets, 10 H, Ar), 7.22, 6.83 (doublets, $J = 8.6$ Hz, 2×2 H, $\text{C}_6\text{H}_4\text{OMe}$), 6.29 (d, $J = 8.4$ Hz, 1 H, $\text{HC}=\text{CBr}_2$), 4.51, 4.36 (doublets, $J = 11.0$ Hz, 2×1 H, CH_2Ar), 4.14 (dd, $J = 8.6, 8.4$ Hz, 1 H, $\text{HC}-\text{CH}=\text{CBr}_2$), 3.77 (s, 3 H, OCH_3), 3.68 (m, 2 H, $-\text{CH}_2\text{O}$), 3.49 (ddd, $J = 8.6, 8.4, 4.7$ Hz, 1 H, HCOSi), 3.26 (m, 2 H, $H-1$ and $H-2$), 3.06 (dd, $J = 12.0, 4.0$ Hz, 1 H, $H-5$), 2.33 (m, 1 H, $H-3\beta$), 2.02 (m, 2 H, $H-6\alpha$ and CH_2), 1.85–1.35 (m, 5 H, CH_2), 1.21 (s, 3 H, CH_3), 1.05 (s, 9 H, $^t\text{BuSi}$), 0.13 (s, 9 H, Me_3Si); HRMS calcd for $\text{C}_{41}\text{H}_{57}\text{Br}_2\text{O}_6\text{Si}_2$ ($M + 1$) 859.206, found 859.208. Anal. Calcd for $\text{C}_{41}\text{H}_{56}\text{Br}_2\text{O}_6$: C, 57.20; H, 6.56. Found: C, 57.19; H, 6.41.

Methyl 4,8:7,11-Dianhydro-14-O-(tert-butylidiphenylsilyl)-2,3,3-tetradecyloxy-10-O-(p-methoxybenzyl)-8-C-methyl-5-O-(trimethylsilyl)-L-erythro-L-allo-tetradec-2-enone (43). The vinyl dibromide **42** (1.1 g, 1.3 mmol) in a stirred solution of dry THF (10.0 mL) at -78°C was treated dropwise with methylolithium (2.3 mL, 3.2 mmol, 1.4 M in ether). After 45 min the mixture of the monovinyl bromide and acetylene anions was quenched with methanol (53 μL , 1.3 mmol), and after 10 min the mixture was again treated with methylolithium (1.8 mL, 1.4 M in ether, 2.6 mmol). After 30 min, methyl chloroformate (0.50 mL, 6.5 mmol) was added, the cooling bath was removed, and stirring was continued for 20 min. Dilution with ether (30 mL) followed by washing with saturated NaHCO_3 (5 mL) and brine (5 mL), drying (MgSO_4), concentration, and flash chromatography (silica, 10% ether in petroleum ether) afforded the acetylenic ester **43** (0.74 g, 75%). **43**: oil; $R_f = 0.32$ (silica, 20% ether in petroleum ether); $[\alpha]_D^{25} -11.5^\circ$ (c 1.15, CDCl_3); IR (neat) ν_{max} 3080, 3050, 2960, 2940, 2860, 2255 (s, $\text{C}\equiv\text{C}$), 1620, 1590, 1520, 1480, 1435, 1390, 1365, 1330, 1310, 1260, 1180, 1100, 1040, 880, 850, 830, 745, 710, 690, 620 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 7.69, 7.39 (multiplets, 10 H, Ar), 7.21, 6.83 (doublets, $J = 8.6$ Hz, 2×2 H, $\text{C}_6\text{H}_4\text{OMe}$), 4.51, 4.36 (doublets, $J = 11.0$ Hz, 2×1 H, CH_2Ar), 4.22 (d, $J = 9.4$ Hz, 1 H, $\text{HCC}\equiv\text{C}$), 3.77 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 3.73 (m, 1 H, HCOSi), 3.66 (m, 2 H, $-\text{CH}_2\text{O}$), 3.25 (m, 2 H, $H-1$ and $H-5$), 3.09 (dd, $J = 12.3, 3.9$ Hz, 1 H, $H-5$), 2.33 (br d, $J = 12.0$ Hz, 1 H, $H-3\beta$), 2.10–1.95 (m, 2 H, CH_2), 1.84–1.35 (m, 5 H, CH_2), 1.15 (s, 3 H, CH_3), 1.04 (s, 9 H, $^t\text{BuSi}$), 0.17 (s, 9 H, Me_3Si); MS m/e (rel intensity) 776 ($M + \text{NH}_4$, 19), 317 (6), 267 (6); HRMS calcd for $\text{C}_{43}\text{H}_{62}\text{NO}_8\text{Si}_2$ ($M + \text{NH}_4$) 776.401, found 776.390.

Methyl (Z)-4,8:7,11-Dianhydro-14-O-(tert-butylidiphenylsilyl)-2,3,6,9,12,13-hexadeoxy-10-O-(p-methoxybenzyl)-3-methyl-8-C-methyl-5-O-(trimethylsilyl)-L-erythro-L-allo-tetradec-2-enone (44). To a stirred suspension of cuprous iodide (10.7 g, 56.0 mmol) in dry THF (80.0 mL) at -40°C was added methylmagnesium chloride (38.6 mL, 2.9 M in THF, 112.0 mmol) dropwise. Stirring was continued for 45 min. The beige solution was cooled to -78°C , and the acetylene **43** (12.1 g, 16.0 mmol) in dry THF (40.0 mL) was added dropwise over a 5-min period. After 1.5 h, the reaction was carefully quenched with saturated NH_4Cl (10 mL) and diluted with ether (200 mL). The ethereal portion was dried (MgSO_4) and concentrated, and the residue subjected to flash chromatography (silica, 10% ether in petroleum ether) to afford the Z -olefin **44** (9.3 g, 75%). **44**: oil; $R_f = 0.34$ (silica, 20% ether in petroleum ether); $[\alpha]_D^{25} -3.7^\circ$ (c 18.6, CHCl_3); IR (neat) ν_{max} 3080, 3050, 2960, 1730 (s, CO_2Me), 1665 (m, $\text{C}=\text{CCO}_2\text{Me}$), 1620, 1590, 1520, 1470, 1430, 1380, 1310, 1250, 1160, 1100, 915, 890, 850, 825, 735, 710, 690, 650, 615 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 7.69, 7.39 (multiplets, 10 H, Ar), 7.22, 6.82 (doublets, $J = 8.6$ Hz, 2×2 H, $\text{C}_6\text{H}_4\text{OMe}$), 5.80 (d, $J = 1.4$ Hz, 1 H, $\text{C}=\text{CHCO}_2\text{Me}$), 5.54 (d, $J = 9.4$ Hz, 1 H, $-\text{HC}-\text{C}=\text{C}$), 4.52, 4.36 (doublets, $J = 11.0$ Hz, 2×1 H, CH_2Ar), 3.77 (s, 3 H, OCH_3), 3.67 (s, 3 H, OCH_3), 3.67 (m, 2 H, $-\text{CH}_2\text{O}$), 2.56 (ddd, $J = 9.4, 9.0, 5.4$ Hz, 1 H, $-\text{HCOSiMe}_3$), 3.27 (m, 2 H, $H-1$ and $H-2$), 3.07 (dd, $J = 12.3, 3.5$ Hz, 1 H, $H-5$), 2.33 (m, 1 H, $H-3\beta$), 2.10–1.96 (m, 2 H, CH_2), 1.86 (d, $J = 1.4$ Hz, 1 H, $\text{C}=\text{CCH}_3$), 1.84–1.35 (m, 5 H, CH_2), 1.25 (s, 3 H, CH_3), 1.05 (s, 9 H, $^t\text{BuSi}$), 0.04 (s, 9 H, Me_3Si); MS m/e (rel intensity) 775 ($M + 1$, 13), 671 (6), 627 (19), 579 (10), 199 (20); HRMS calcd for $\text{C}_{44}\text{H}_{63}\text{O}_8\text{Si}_2$ ($M + 1$) 775.406, found 775.408.

Methyl (Z)-4,8:7,11-Dianhydro-14-O-(tert-butylidiphenylsilyl)-2,3,5,6,9,12,13-hexadeoxy-10-O-(p-methoxybenzyl)-3-methyl-8-C-methyl-L-erythro-L-allo-tetradec-2-enone (45). A mixture of the bis-silyl ether **44** (11.0 g, 14.1 mmol), pyridinium p -toluenesulfonate (0.5 g, 2.0 mmol), and methanol (70.0 mL) was stirred at 25°C for 1 h. The reaction mixture was diluted with ether (300 mL), washed with H_2O (2×50 mL) and brine (50 mL), dried (MgSO_4), and concentrated to furnish the alcohol **45** (9.9 g, 100%). **45**: oil; $R_f = 0.20$ (silica, 40% ether in petroleum ether); $[\alpha]_D^{25} -14.8^\circ$ (c 2.06, CHCl_3); IR (neat) ν_{max} 3460 (s, OH), 3080, 3050, 2950, 2870, 1725 (s, CO), 1665 (m, $\text{C}=\text{CCO}_2$), 1620, 1590, 1520, 1435, 1380, 1305, 1250, 1170, 1100, 1050, 830, 745, 710, 690, 615 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 7.69, 7.39 (multi-

plets, 10 H, Ar), 7.22, 6.83 (doublets, $J = 8.6$ Hz, 2×2 H, $\text{C}_6\text{H}_4\text{OMe}$), 5.94 (d, $J = 0.8$ Hz, 1 H, $\text{C}=\text{CHCO}_2\text{Me}$), 5.24 (d, $J = 9.5$ Hz, 1 H, $-\text{HC}-\text{C}=\text{C}$), 4.52, 4.27 (doublets, $J = 11.0$ Hz, 2×1 H, CH_2Ar), 3.77 (s, 3 H, OCH_3), 3.71 (s, 3 H, OCH_3), 3.68 (m, 2 H, CH_2OSi), 3.50 (m, 1 H, $-\text{HCOH}$), 3.40 (d, $J = 6.0$ Hz, 1 H, OH), 3.26 (m, 2 H, $H-1$ and $H-2$), 3.06 (dd, $J = 12.3, 3.7$ Hz, 1 H, $H-5$), 2.25 (m, 2 H, CH_2), 2.03 (m, 1 H, CH_2), 1.93 (d, $J = 0.8$ Hz, 1 H, $\text{C}=\text{CCH}_3$), 1.85–1.37 (m, 5 H, CH_2), 1.20 (s, 3 H, CH_3), 1.05 (s, 9 H, $^t\text{BuSi}$); HRMS calcd for $\text{C}_{41}\text{H}_{55}\text{O}_8\text{Si}$ ($M + 1$) 703.365, found 703.366.

4,8:7,11-Dianhydro-14-O-(tert-butylidiphenylsilyl)-2,3,6,9,12,13-hexadeoxy-10-O-(p-methoxybenzyl)-3-methyl-8-C-methyl-L-erythro-L-allo-tetradec-2-enonic Acid, δ -Lactone (46). A stirred solution of the alcohol **45** (8.8 g, 12.5 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 0.5 mL, 3.3 mmol) and dry benzene was heated at 70°C for 1.5 h. The benzene was evaporated from the cooled reaction mixture, and the residue chromatographed (silica, 50% ether in petroleum ether) to give the lactone **46** (8.0 g, 95%). **46**: oil; $R_f = 0.24$ (silica, 40% ether in petroleum ether); $[\alpha]_D^{25} -21.4^\circ$ (c 1.79, CHCl_3); IR (neat) ν_{max} 3080, 3050, 2960, 2940, 2860, 1740 (s, δ -lactone), 1645 (m, $\text{C}=\text{CCO}_2$), 1625, 1590, 1520, 1470, 1425, 1425, 1385, 1310, 1270, 1250, 1185, 1100, 885, 850, 825, 745, 710, 690, 620 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 7.69, 7.39 (multiplets, 10 H, Ar), 7.22, 6.85 (doublets, $J = 8.6$ Hz, 2×2 H, $\text{C}_6\text{H}_4\text{OMe}$), 5.74 (d, $J = 1.6, 0.8$ Hz, 1 H, $\text{HC}=\text{C}$), 4.55, 4.38 (doublets, $J = 11.0$ Hz, 2×1 H, CH_2Ar), 4.26 (br d, $J = 10.5$ Hz, 1 H, $-\text{HCC}=\text{C}$), 3.99 (ddd, $J = 11.6, 10.5, 4.6$ Hz, 1 H, CO_2CH), 3.78 (s, 3 H, OCH_3), 3.69 (m, 2 H, CH_2OSi), 3.38–3.20 (m, 2 H, $H-1$ and $H-2$), 3.13 (dd, $J = 12.2, 3.9$ Hz, 1 H, $H-5$), 2.37 (dd, $J = 11.3, 3.9$ Hz, 1 H, $H-3\beta$), 2.25 (ddd, $J = 11.5, 4.7, 4.6$ Hz, 1 H, $H-6\alpha$), 2.03 (m, 1 H, CH_2), 1.97 (d, $J = 1.6$ Hz, 3 H, $\text{C}=\text{CCH}_3$), 1.95–1.39 (m, 5 H, CH_2), 1.23 (s, 3 H, CH_3), 1.05 (s, 9 H, $^t\text{BuSi}$); MS m/e (rel intensity) 671 ($M + 1$), 613 (54), 199 (15); HRMS calcd for $\text{C}_{40}\text{H}_{51}\text{O}_7\text{Si}$ ($M + 1$) 671.340, found 671.332. Anal. Calcd for $\text{C}_{40}\text{H}_{50}\text{O}_7\text{Si}$: C, 71.61; H, 7.51. Found: C, 71.45; H, 7.22.

4,8:7,11-Dianhydro-14-O-(tert-butylidiphenylsilyl)-2,3,6,9,12,13-hexadeoxy-10-O-(p-methoxybenzyl)-3-methyl-8-C-methyl-L-erythro- α -L-allo-tetradec-2-enopyranol (47). DIBAL (12.0 mL, 1 M in hexanes, 12.0 mmol) was added dropwise to a stirred solution of the lactone **46** (5.7 g, 8.5 mmol) in dry dichloromethane (50 mL) at -78°C over a 5-min period. After 45 min, the reaction mixture was poured into a stirring mixture of saturated aqueous sodium potassium tartrate (45 mL) and EtOAc (200 mL). After 20 min the organic portion was separated and dried (MgSO_4), and the solvents were removed to give the lactol **47** (5.7 g, 100%). **47**: oil; $R_f = 0.41$ (silica, 50% ether in petroleum ether); IR (neat) ν_{max} 3420 (s, OH), 3070, 3050, 2950, 2860, 1665, 1620, 1590, 1520, 1470, 1430, 1385, 1305, 1250, 1175, 1100, 1040, 1000, 825, 740, 705, 690, 615 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 7.69, 7.39 (multiplets, 10 H, Ar), 7.21, 6.85 (doublets, $J = 8.6$ Hz, 2×2 H, $\text{C}_6\text{H}_4\text{OMe}$), 5.42 (d, $J = 1.7$ Hz, 1 H, $\text{HC}=\text{C}$), 5.34 (m, 1 H, HOCHO), 4.55, 4.36 (doublets, $J = 11.0$ Hz, 2×1 H, CH_2Ar), 3.88 (br d, $J = 9.5$ Hz, 1 H, $\text{C}=\text{CCHO}$), 3.78 (s, 3 H, OCH_3), 3.67 (m, 3 H, $-\text{HCO}$ and CH_2OSi), 3.36–3.22 (m, 2 H, $H-1$ and $H-2$), 3.19 (dd, $J = 12.2, 3.8$ Hz, 1 H, $H-5$), 2.77 (br d, $J = 5.2$ Hz, 1 H, OH), 2.36 (dd, $J = 11.3, 4.2$ Hz, 1 H, $H-3\beta$), 2.13–1.95 (m, 2 H, CH_2), 1.83–1.35 (m, 5 H, CH_2), 1.75 (d, $J = 1.7$ Hz, 3 H, $\text{C}=\text{CCH}_3$), 1.23 (s, 3 H, CH_3), 1.05 (s, 9 H, $^t\text{BuSi}$); HRMS calcd for $\text{C}_{40}\text{H}_{52}\text{O}_7\text{Si}$ ($M + 1$) 673.355, found 673.351.

4,8:7,11:10,14-Trihydro-1-O-(tert-butylidiphenylsilyl)-2,3,6,9,12,13-hexadeoxy-5-O-(p-methoxybenzyl)-12-methyl-7-C-methyl-D-erythro-D-allo-tetradec-12-enitol (48). To a stirred solution of the lactol **47** (5.1 g, 7.6 mmol), triethylsilane (4.8 mL, 30.0 mmol), and dry dichloromethane (38 mL) at -10°C was added boron trifluoride etherate (0.9 mL, 7.6 mmol). After 5 min, the reaction mixture was diluted with ether (150 mL), washed with saturated NaHCO_3 (2×30 mL) and brine (30 mL), dried (MgSO_4), and concentrated. Flash chromatography (silica, 25% ether in petroleum ether) afforded the tricycle **48** (4.6 g, 92%). **48**: oil; $R_f = 0.81$ (silica, 50% ether in petroleum ether); $[\alpha]_D^{25} -8.5^\circ$ (c 0.73, CHCl_3); IR (neat) ν_{max} 3080, 3050, 2940, 2860, 1620, 1590, 1520, 1470, 1430, 1385, 1305, 1250, 1175, 1100, 1040, 1010, 1000, 825, 740, 705, 685, 615 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 7.69, 7.39 (multiplets, 10 H, Ar), 7.21, 6.85 (doublets, $J = 8.6$ Hz, 2×2 H, $\text{C}_6\text{H}_4\text{OMe}$), 5.36 (br d, 1 H, $\text{HC}=\text{C}$), 4.55, 4.36 (doublets, $J = 11.0$ Hz, 2×1 H, CH_2Ar), 4.26, 4.15 (br doublets, $J = 16.0$ Hz, 2×1 H, $\text{C}=\text{CCH}_2\text{O}$), 3.97 (br d, $J = 8.0$ Hz, 1 H, $\text{C}=\text{CCHO}$), 3.77 (s, 3 H, OCH_3), 3.69 (m, 2 H, CH_2OSi), 3.40–3.19 (m, 3 H, $H-1$, $H-2$ and $-\text{HCO}$), 3.17 (dd, $J = 11.9, 5.7$ Hz, 1 H, $H-5$), 2.36 (dd, $J = 11.4, 4.4$ Hz, 1 H, $H-3\beta$), 2.13–1.95 (m, 2 H, CH_2), 1.85–1.30 (m, 5 H, CH_2), 1.71 (br s, 3 H, $\text{C}=\text{CCH}_3$), 1.21 (s, 3 H, CH_3), 1.05 (s, 9 H, $^t\text{BuSi}$); MS m/e (rel intensity) 674 ($M + \text{NH}_4$, 9), 599 (14), 162 (12); HRMS calcd for $\text{C}_{40}\text{H}_{56}\text{O}_6\text{NSi}$ ($M + \text{NH}_4$) 674.387, found 674.387.

4,8:7,11:10,14-Trihydro-2,3,6,9,12,13-hexadeoxy-5-O-(p-methoxybenzyl)-12-methyl-7-C-methyl-D-erythro-D-allo-tetradec-12-enitol (49).

A mixture of the silyl ether **48** (4.5 g, 6.8 mmol), tetrabutylammonium fluoride (10.0 mL, 1 M in THF, 10.0 mmol), and THF (20 mL) was stirred at 25 °C for 2 h. Concentration and flash chromatography (silica, 40 → 80% ether in petroleum ether) gave the alcohol **49** (2.8 g, 97%). **49**: oil; $R_f = 0.16$ (silica, 60% ether in petroleum ether); $[\alpha]_D^{21} -11.2^\circ$ (c 2.1, CHCl_3); IR (neat) ν_{max} 3450 (s, OH), 3050, 2950, 2870, 1615, 1590, 1520, 1465, 1455, 1430, 1385, 1360, 1305, 1280, 1255, 1175, 1100, 1035, 1010, 970, 875, 825, 735, 705 cm^{-1} ; $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 7.24, 6.88 (doublets, $J = 8.8$ Hz, 2×2 H, $\text{C}_6\text{H}_4\text{OMe}$), 5.36 (d, $J = 1.1$ Hz, 1 H, $\text{HC}=\text{C}$), 4.56, 4.36 (doublets, $J = 11.0$ Hz, 2×1 H, CH_2Ar), 4.26, 4.13 (br doublets, $J = 16.0$ Hz, 2×1 H, $\text{C}=\text{CCH}_2\text{O}$), 3.98 (br d, $J = 8.0$ Hz, 1 H, $\text{C}=\text{CCHO}$), 3.81 (s, 3 H, OCH_3), 3.65 (m, 2 H, CH_2OH), 3.43–3.29 (m, 3 H, $H-1$, $H-2$ and $-\text{HCO}$), 3.25 (dd, $J = 12.2$, 4.1 Hz, 1 H, $H-5$), 2.40 (dd, $J = 11.3$, 4.2 Hz, 1 H, $H-3\beta$), 2.24–1.95 (m, 3 H, OH and CH_2), 1.71 (s, 3 H, $\text{C}=\text{CCH}_3$), 1.70–1.42 (m, 5 H, CH_2), 1.22 (s, 3 H, CH_3); MS m/e (rel intensity) 419 ($M + 1$, 19), 381 (8), 307 (13), 282 (10), 262 (7), 205 (11), 183 (15), 162 (27), 121 (100); HRMS calcd for $\text{C}_{24}\text{H}_{35}\text{O}_6$ ($M + 1$) 419.2433, found 419.2428.

4,8,7,11:10,14-Trihydro-2,3,6,9,12,13-hexa-deoxy-12-methyl-7-C-methyl-D-erythro-D-allo-tetradec-12-enitol (50). To a vigorously stirred mixture of the alcohol **49** (215.0 mg, 0.51 mmol), dichloromethane (1.0 mL), and H_2O (0.1 mL) at 25 °C was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 227.0 mg, 1.0 mmol). After 2 h the reaction mixture was diluted with ether (10 mL), and the excess H_2O was removed by addition of MgSO_4 . Filtration followed by concentration gave a crude orange oil which was subjected to flash column chromatography (silica, 90% ether in petroleum ether) to furnish the diol **50** (145.0 mg, 94%). **50**: colorless plates, mp 91–92 °C (from EtOAc/hexane); $R_f = 0.25$ (silica, ether); $[\alpha]_D^{21} +25.9^\circ$ (c 0.70, CHCl_3); IR (neat) ν_{max} 3380 (s, OH) 2950, 2870, 1455, 1380, 1270, 1100, 1075, 1045, 1000, 740 cm^{-1} ; $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 5.36 (br s, 1 H, $\text{HC}=\text{C}$), 4.25, 4.13 (br doublets, $J = 16.0$ Hz, 2×1 H, $\text{C}=\text{C}-\text{CH}_2\text{O}$), 3.96 (br d, $J = 8.0$ Hz, 1 H, $\text{C}=\text{CHO}$), 3.70–3.50 (m, 3 H, CH_2OH and CHO), 3.27–3.08 (m, 3 H, CHO), 2.31–1.90 (m, 5 H, OH , CH_2 and OH), 1.40 (s, 3 H, $\text{C}=\text{CCH}_3$), 1.68–1.42 (m, 5 H, CH_2), 1.26 (s, 3 H, CH_3); HRMS calcd for $\text{C}_{16}\text{H}_{26}\text{O}_5$ 299.1858, found: 299.1851.

Methyl 4,8,7,11:10,14-Trihydro-2,3,6,9,12,13-hexa-deoxy-5-O-(p-methoxybenzyl)-12-methyl-7-C-methyl-D-erythro-D-allo-tetradec-12-enonate (51). Jones' reagent (ca. 20 drops, prepared from 3.7 g of CrO_3 , 3.2 mL of concentrated H_2SO_4 , and 8.3 mL of H_2O) was added dropwise to a stirred solution of the alcohol **49** (50.2 mg, 0.12 mmol) in acetone (5.0 mL) at 0 °C. After 45 min, isopropyl alcohol (0.5 mL) was added to quench the excess reagent, followed by dilution with ether (100 mL). The ethereal solution was washed with H_2O (2×10 mL) and brine (10 mL), dried (MgSO_4), and evaporated. The resulting crude carboxylic acid was dissolved in ether (5 mL) and treated with excess diazomethane (ether solution) at 0 °C to afford, after flash chromatography (silica, 40% ether in petroleum ether) the methyl ester **51** (45.0 mg, 84%). **51**: oil; $R_f = 0.39$ (silica, 50% ether in petroleum ether); $[\alpha]_D^{21} -20.5^\circ$ (c 0.73, CHCl_3); IR (neat) ν_{max} 2950, 2870, 1740 (s, CO_2CH_3), 1615, 1590, 1520, 1450, 1385, 1355, 1305, 1270, 1250, 1175, 1100, 1035, 1010, 865, 825, 740, 705 cm^{-1} ; $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 7.24, 6.87 (doublets, $J = 8.6$ Hz, 2×2 H, $\text{C}_6\text{H}_4\text{OMe}$), 5.36 (d, $J = 1.5$ Hz, 1 H, $\text{C}=\text{CH}$), 4.56, 4.36 (doublets, $J = 11.0$ Hz, 2×1 H, CH_2Ar), 4.25, 4.13 (br doublets, $J = 16.0$ Hz, 2×1 H, $\text{C}=\text{CCH}_2\text{O}$), 3.97 (br d, $J = 8.0$ Hz, 1 H, $-\text{OHCC}=\text{C}$), 3.80 (s, 3 H, OCH_3), 3.65 (s, 3 H, OCH_3), 3.40–3.15 (m, 3 H, $H-1$, $H-2$ and $-\text{HCO}$), 3.17 (dd, $J = 12.1$, 4.2 Hz, 1 H, $H-5$), 2.58–2.19 (m, 4 H, CH_2CO_2 , $H-3\beta$ and CH_2), 2.11 (ddd, $J = 11.5$, 3.2, 3.1 Hz, 1 H, $H-6\alpha$), 1.80–1.42 (m, 5 H, CH_2), 1.71 (s, 3 H, $\text{C}=\text{CCH}_3$), 1.20 (s, 3 H, CH_3); MS m/e (rel intensity) 447 ($M + 1$, 23), 363 (11), 310 (76), 241 (92), 209 (52), 184 (73), 165 (18), 121 (100); HRMS calcd for $\text{C}_{25}\text{H}_{35}\text{O}_7$ ($M + 1$) 447.2382, found 447.2371. Anal. Calcd

for $\text{C}_{25}\text{H}_{34}\text{O}_7$: C, 67.24; H, 7.68. Found: C, 67.53; H, 7.39.

Methyl 4,8,7,11:10,14-Trihydro-2,3,6,9,12,13-hexa-deoxy-5-O-(p-methoxybenzyl)-2,12-dimethyl-7-C-methyl-D-erythro-D-allo-tetradec-12-enoate (52). The ester **51** (610 mg, 1.36 mmol) in dry THF (13.5 mL) was added dropwise to lithium diisopropylamine (1.63 mL, 1 M in THF/hexanes, 1.63 mmol) at -78 °C over 5 min. After 30 min, methyl iodide (0.2 mL, 3.2 mmol) was added in one portion, and stirring was continued for 30 min. The cooling bath was removed, and the reaction mixture was stirred for an additional 10 min. Dilution with ether (30 mL) followed by washing with saturated NH_4Cl (10 mL), drying (MgSO_4), concentration, and flash chromatography (silica, 20% ether in petroleum ether) afforded the methyl epimers **52** (540 mg, 86%). **52**: oil; $R_f = 0.59$ (silica, 50% ether in petroleum ether); IR (neat) ν_{max} 2950, 2870, 1735 (s, CO_2CH_3), 1615, 1590, 1515, 1465, 1385, 1305, 1250, 1170, 1100, 1035, 1010, 870, 825, 740, 705, 685 cm^{-1} ; $^1\text{H NMR}$ (250 MHz, CDCl_3) δ 7.23, 6.86 (doublets, $J = 8.6$ Hz, 2×2 H, $\text{C}_6\text{H}_4\text{OMe}$), 5.35 (br s, 1 H, $\text{C}=\text{CH}$), 4.58, 4.57, 4.37, 4.36 (doublets, $J = 11.0$ Hz, 2×1 H, CH_2Ar), 4.26, 4.12 (br doublets, $J = 16.0$ Hz, 2×1 H, $\text{C}=\text{CH}_2\text{O}$), 3.96 (m, 1 H, $\text{C}=\text{CCHO}$), 3.81 (s, 3 H, OCH_3), 3.63, 3.56 (singlets, 3 H, OCH_3), 3.35–3.08 (m, 4 H, $H-1$, $H-2$, $H-5$ and $-\text{CHO}$), 2.77 (m, 0.5 H, CHCO_2), 2.42–1.35 (m, 7.5 H, CH_2 and CHCO_2), 1.71 (br s, 3 H, $\text{C}=\text{CCH}_3$), 1.20, 1.18 (singlets, 3 H total, CH_3), 1.16, 1.15 (doublets, $J = 7.1$ Hz, 3 H total, CH_3CHCO_2); MS m/e (rel intensity) 461 ($M + 1$, 100), 377 (28), 353 (100), 325 (100), 306 (100), 242 (100), 215 (100); HRMS calcd for $\text{C}_{26}\text{H}_{37}\text{O}_7$ ($M + 1$) 461.2229, found 461.2227.

4,8,7,11:10,14-Trihydro-2,3,6,9,12,13-hexa-deoxy-5-O-(p-methoxybenzyl)-2,12-dimethyl-7-C-methyl-D-erythro-D-allo-tetradec-12-enoic Acid (2). A mixture of the esters **52** (480 mg, 1.04 mmol), 1 N LiOH (3.0 mL, 3.0 mmol), H_2O (3.0 mL), and THF (3.0 mL) was vigorously stirred at 50 °C for 16 h. The cooled reaction mixture was diluted with EtOAc (20 mL) and carefully acidified with 1 N HCl (4.0 mL). The organic portion was separated, dried (MgSO_4), and concentrated to furnish the free acid **2** (465 mg, 100%). **2**: oil; $R_f = 0.72$ (silica, ether); IR (neat) ν_{max} 3400–2500 (br, CO_2H), 3100, 3080, 3020, 2950, 2880, 1710 (s, CO_2H), 1615, 1590, 1520, 1485, 1465, 1385, 1305, 1250, 1175, 1130, 1100, 1080, 1040, 825, 680 cm^{-1} ; $^1\text{H NMR}$ (250 MHz, CDCl_3) (ca. 3:2 mixture of diastereomers) δ 7.25, 7.22 (doublets, $J = 8.5$ Hz, 2×1 H, $\text{C}_6\text{H}_4\text{OMe}$), 6.87 (d, $J = 8.5$ Hz, 2 H, $\text{C}_6\text{H}_4\text{OMe}$), 5.34 (br s, 1 H, $\text{C}=\text{CH}$), 4.57, 4.54 (doublets, $J = 11.0$ Hz, 1 H, CH_2Ar), 4.40, 4.35 (doublets, $J = 11.0$ Hz, 1 H, CH_2Ar), 4.25, 4.13 (br doublets, $J = 16.0$ Hz, 2×1 H, $\text{C}=\text{CCH}_2\text{O}$), 3.95 (m, 1 H, $\text{C}=\text{CCHO}$), 3.80 (s, 3 H, OCH_3), 3.38–3.10 (m, 4 H, $H-1$, $H-2$, $H-5$ and $-\text{CHO}$), 2.70 (m, 1 H, CH_2CO_2), 2.41–2.20 (m, 2 H, CH_2CO_2 and CH_2), 2.16–1.37 (m, 6 H, CH_2 and CO_2H), 1.70 (br s, 3 H, $\text{C}=\text{CCH}_3$), 1.19 (m, 6 H, CH_3); MS m/e (rel intensity) 447 ($M + 1$, 12), 310 (30), 241 (14), 209 (64), 183 (35), 122 (100); HRMS calcd for $\text{C}_{25}\text{H}_{35}\text{O}_7$ ($M + 1$) 447.2383, found 447.2315. Anal. Calcd for $\text{C}_{25}\text{H}_{34}\text{O}_7$: C, 67.24; H, 7.68. Found: C, 66.93; H, 7.68.

Acknowledgment. We thank Drs. George Furst, Patrick Carrol, and John Dykins for their superb assistance as Directors of NMR, X-ray, and mass spectroscopic facilities of this department. Financial support for this work was provided by the National Institutes of Health, Merck Sharp and Dohme, Hoffmann La Roche, and Smith Kline Beckman, USA.

Supplementary Material Available: X-ray crystallographic data for **50** and ^{13}C NMR data for **2** (mixture of epimers) (8 pages). Ordering information is given on any current masthead page.