$CHCl_3$); IR (film) ν_{max} 3440, 2965, 2935, 2910, 2870, 1726, 1481, 1455, 1400, 1365, 1285, 1162, 1108, 853, 735 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.43-7.23 (m, 5 H, aromatic), 4.55 (s, 2 H, $PhCH_2O$), 4.31 (ddd, J = 11.3, 7.5, 6.1 Hz, 1 H, $CH_2OC(O)$), 4.13 (ddd, J = 11.3, 5.6, 5.0 Hz, 1 H, $CH_2OC(O)$), 4.08 (m, 1 H, CHO), 3.92 (m, 1 H, CHO), 3.69 (s, 1 H, OH), 3.43 (m, 2 H, CH_2O), 3.26 (s, 1 H, OH), 1.76 (m, 2 H, CH_2), 1.61 (m, 2 H, CH_2), 1.19 (s, 9 H, Si-*t-Bu*); HRMS (CI) calcd for $C_{18}H_{28}O_5$ + H 325.2013, found 325.2006 (M + H).

2,4-Dideoxy-3,5-*O*-(1-methylethylidene)-6-*O*-(phenylmethyl)-D-*erythro*-hexitol 1-(2,2-Dimethylpropanoate) (69). Diol **68a** (196 mg, 0.6 mmol) and camphorsulfonic acid (CSA, 3 mg, 0.012 mmol) were dissolved in 2,2-dimethoxypropane (2 mL) at room temperature under argon. The reaction mixture was stirred at that temperature for 30 min and then it was diluted with ether (30 mL) and washed with 10% aqueous $NaHCO_3$ solution (2 mL) and brine (2 mL). Drying ($MgSO_4$) followed by flash column chromatography (silica, 10% ether in petroleum ether) gave acetonide **69** (204 mg, 93%). **69**: colorless oil; R_f 0.25 (silica, 10% ether in petroleum ether); $[\alpha]^{20}_D$ -21.0° (*c* 2.3, $CHCl_3$); IR (film) ν_{max} 2970, 2955, 2935, 2910, 2870, 1728, 1495, 1479, 1455, 1378, 1365, 1281, 1261, 1200, 1158, 1110, 735, 695 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.36 (s, 5 H, aromatic), 4.60, 4.55 (doublets, J = 12.2 Hz, 1 H each, $PhCH_2O$), 4.15 (t, J = 6.3 Hz, 2 H, $CH_2OC(O)$), 4.09 (m, 1 H, CHO), 3.98 (m, 1 H, CHO), 3.51 (dd, J = 9.8, 5.7 Hz, 1 H, CH_2O), 3.37 (dd, J = 9.8, 5.0 Hz, 1 H, CH_2O), 1.78 (dt, J = 6.3, 6.0 Hz, 2 H, CH_2), 1.54 (dt, J = 12.8, 2.5 Hz, 1 H, CH_2), 1.44, 1.40 (singlets, 3 H each, acetonide), 1.33 (dt, J = 12.8, 11.7 Hz, 1 H, CH_2), 1.19 (s, 9 H, *t-Bu*); HRMS (CI) calcd for $C_{21}H_{32}O_5$ + H 365.2326, found 365.2279.

2,4-Dideoxy-6-*O*-[(1,1-dimethylethyl)diphenylsilyl]-3,5-*O*-(1-methylethylidene)-D-*erythro*-hexitol 1-(2,2-Dimethylpropanoate) (71) via Alcohol 70. Benzyl ether **69** (481 mg, 1.34 mmol) was dissolved in CH_2Cl_2 (10 mL), and 10% Pd-C (30 mg) was added. The mixture was vigorously stirred under a H_2 atmosphere at ambient temperature for 4 h (TLC monitoring). Removal of the catalyst by filtration followed by evaporation of the solvent gave essentially pure alcohol **70**, which was dissolved in dry DMF (3 mL) and silylated without further purification as follows. Imidazole (408 mg, 6 mmol) and *t*-$BuPh_2SiCl$ (412 mg ≡ 0.40 mL, 1.5 mmol) were sequentially added under argon at 25 °C, and the reaction mixture was stirred at that temperature for 3 h. The reaction mixture was then diluted with ether (50 mL) and washed with water (2 × 10 mL) and brine (5 mL). The organic phase was dried ($MgSO_4$) and concentrated to give an oily residue, which was flash chromatographed (silica, 10% ether in petroleum ether) to give derivative **71** (500 mg, 73%). **71**: colorless oil; R_f 0.30 (silica, 20% ether in petroleum ether); IR (film) ν_{max} 3070, 3045, 2960, 2930, 2860, 1729, 1480, 1471, 1462, 1427, 1380, 1283, 1200, 11445, 1110, 1055, 1040, 1005, 995, 739, 700 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.73-7.65 (m, 4 H, aromatic), 7.45-7.32 (m, 6 H, aromatic), 4.15 (m, 2 H, $CH_2OC(O)$), 3.97 (m, 2 H, CHO), 3.71 (dd, J = 10.1, 5.2 Hz, 1 H, CH_2O), 3.54 (dd, J = 10.1, 6.1 Hz, 1 H, CH_2O), 1.78 (dt, J = 6.4, 6.4 Hz, 2 H, CH_2), 1.62 (dt, J = 12.5, 2.4 Hz, 1 H, CH_2), 1.39, 1.35 (singlets, 3 H each, acetonide), 1.21 (dt, J = 12.5, 11.8 Hz, 1 H, CH_2), 1.20, 1.06 (singlets, 9 H each, *t-Bu*).

Preparation of Compound 47 from 71. Compound **47** was prepared from pivaloate ester **71** by DIBAL reduction as described above for the preparation of **66a** from **65a**. Used, **71** (285 mg, 0.56 mmol); obtained, **47** (211 mg, 91%). The spectral data of this material were identical with those of a sample obtained from (+)-xylose as described above.

3,5-Dideoxy-6-*O*-[(1,1-dimethylethyl)dimethylsilyl]-1-*O*-(phenylmethyl)-D-*erythro*-hexitol (68b). To a stirred solution of triol **13b** (344 mg, 1.43 mmol) in DMF (2.5 mL) was added imidazole (408 mg, 6.00 mmol) and *t*-$BuMe_2SiCl$ (226 mg, 1.50 mmol). Stirring was continued for 2 h at ambient temperature, and then the reaction mixture was diluted with ether (50 mL). The organic phase was washed with water (3 × 5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated. Purification by flash column chromatography (silica, 70% ether in petroleum ether) gave pure diol **68b** (457 mg, 90%). **68b**: R_f 0.21 (70% ether in petroleum ether); $[\alpha]^{20}_D$ -3.7° (*c* 2.8, $CHCl_3$); IR (film) ν_{max} 3420, 3035, 2955, 2930, 2860, 1470, 1460, 1452, 1390, 1360, 1309, 1255, 1092, 1028, 1005, 938, 835 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.33 (s, 5 H, aromatic), 4.56 (s, 2 H, $PhCH_2O$), 4.08 (m, 3 H, CHO, OH), 3.87 (m, 3 H, H-1, OH), 3.44 (m, 2 H, H-6), 1.64 (m, 4 H, CH_2), 0.89 (s, 9 H, Si-*t-Bu*), 0.08 (s, 6 H, $SiMe_2$); HRMS (CI) calcd for $C_{19}H_{34}O_4Si$ + H 355.2303, found 355.2313 (M + H).

3,5-Dideoxy-6-*O*-[(1,1-dimethylethyl)dimethylsilyl]-2,4-*O*-(1-methylethylidene)-1-*O*-(phenylmethyl)-D-*erythro*-hexitol (56). Compound **56** was prepared (95%) in the same manner as described for **69** from **68a** and was identical by the usual criteria with a sample obtained from (-)-xylose.

Acknowledgment. We wish to express our many thanks to Drs. George Furst and John Dykins of this department for their superb NMR and mass spectroscopic assistance. This work was financially supported by the National Institutes of Health, Merck Sharp & Dohme, and Hoffmann-La Roche.

Total Synthesis of Amphoteronolide B and Amphotericin B. 2. Total Synthesis of Amphoteronolide B†

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Contribution from the Department of Chemistry, University of Pennsylvania, Philadelphia, Pennsylvania 19104. *Received October 19, 1987*

Abstract: The efficient coupling of building blocks **4-8** by four aldehyde-phosphonate type condensation reactions and an esterification reaction leading to advance intermediate keto phosphonate aldehyde **39** are reported. The intramolecular keto phosphonate-aldehyde condensation leading to heptaenone **3** and its elaboration to amphoteronolide B (**1**) are also described.

In the preceding paper[1] we discussed the significance and retrosynthetic analysis of amphotericin B (**1**) and amphoteronolide B (**2**) (Scheme I) and the stereocontrolled construction of key building blocks **5-8** required for the total synthesis of these targets. In this paper we describe (a) the coupling of these building blocks and their elaboration to the cyclic heptaenone **3** (Scheme I), a key intermediate for the synthesis of both amphoteronolide B (**2**) and amphotericin B (**1**), and (b) the total synthesis of amphoteronolide B (**2**).[2,3]

Results and Discussion

Synthesis of Advanced Key Intermediate, Hydroxy Aldehyde 15. The plan for the synthesis of advanced intermediate **15** from aldehyde **5** involved construction of the polyene chain by sequential reaction with two units of phosphonate **4** (Scheme I). The details of the execution of this strategy are presented in Scheme II. Thus, condensation of **5** with the lithio derivative of (E,E)-$(EtO)_2P(O)CH_2CH{=}CHCH{=}CHCOOEt$ (**4**)[4] led predominantly to the

† This paper is dedicated with respect and affection to Professor E. J. Corey on the occasion of his 60th birthday.

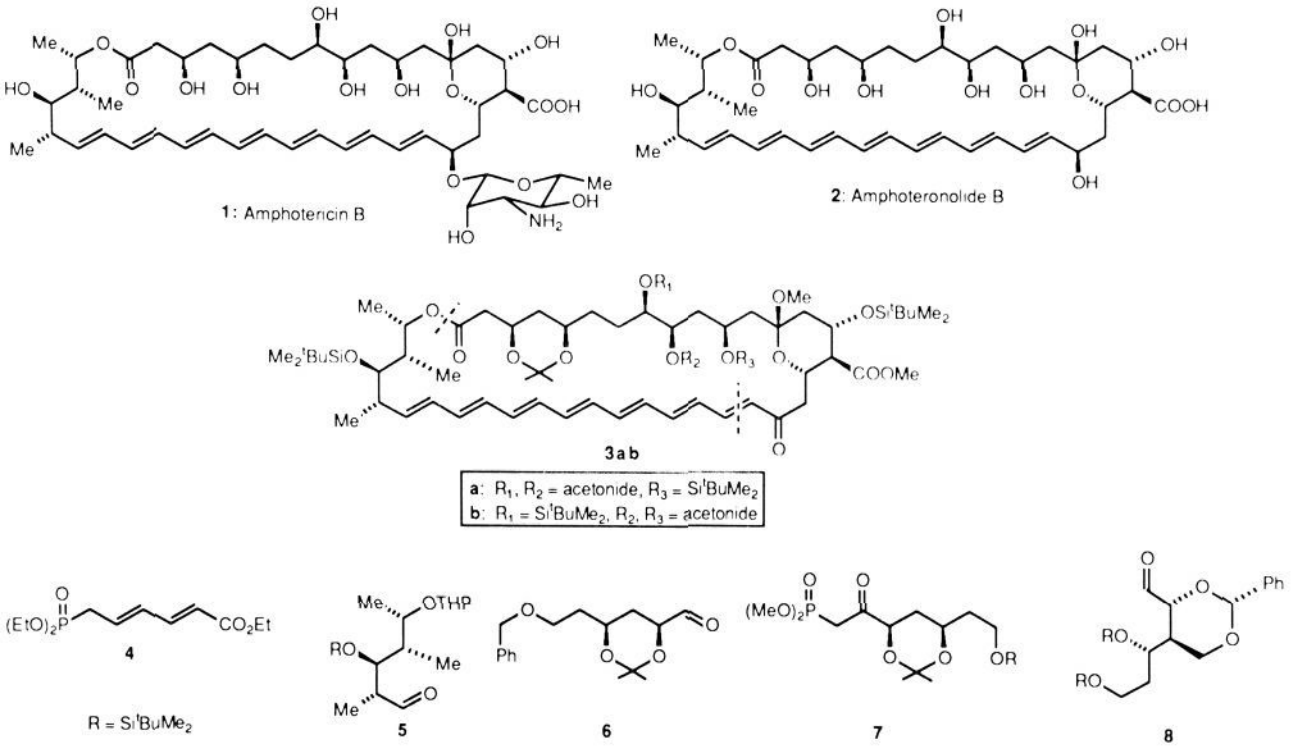
(1) Nicolaou, K. C.; Daines, R. A.; Uenishi, J.; Li, W. S.; Papahatjis, D. P.; Chakraborty, T. K. *J. Am. Chem. Soc.*, preceding paper in this issue.

(2) Preliminary communication: Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1987**, *109*, 2208. Apparently migration of the acetonide group occurred under the reaction conditions (**27** → **28** → **29**). We thank Professor S. Masamune for bringing this possibility to our attention in the form of a manuscript: Kennedy, R. M.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1988**, *29*, 447. See also: Kennedy, R. M.; Abili, A.; Takemasa, T.; Okumoto, H.; Masamune, S. *Tetrahedron Lett.* **1988**, *29*, 451.

(3) Preliminary communication: Nicolaou, K. C.; Chakraborty, T. K.; Daines, R. A.; Simpkins, N. S. *J. Chem. Soc., Chem. Commun.* **1986**, 413.

0002-7863/88/1510-4685$01.50/0

Scheme I



E,E,E-triene ester **9** (90%, small amounts of the *Z* isomer of the newly generated double bond were removed chromatographically). Reduction of ester **9** with DIBAL led quantitatively to alcohol **10**, which was then oxidized to aldehyde **11** with MnO_2 (98%). Reiteration of the condensation process with the litho anion of **4** attached a second triene unit onto trienal **11**, furnishing ester **12** (60%, small quantities of the *Z* isomer of the newly generated double bond formed in this reaction were removed chromatographically), which was subjected to acid-catalyzed depyranylation, leading to hydroxy ester **13** in 82% yield. Finally, DIBAL reduction of **13** followed by MnO_2 oxidation led to the requisite hydroxy aldehyde **15** in 98% overall yield.

Synthesis of Advanced Key Intermediate, Keto Phosphonate Carboxylic Acid 16. The strategy for the construction of keto phosphonate carboxylic acid **16** was based on the retrosynthetic analysis presented in Scheme III. According to this analysis, **16** was to be derived from **29** by appropriate functional group manipulations and introduction of a C_1 unit carrying the dimethyl phosphonate group. With the focus on the phosphonate–aldehyde condensation as the potential coupling reaction, the following retrosynthetic steps were devised. Thus, the tetrahydropyran system in **29** was dismantled by rupture of the indicated strategic bond unravelling to the olefin **27** bearing a methylthio group at C-13. The design of this key intermediate would not only allow regiospecific ring closure to **29** but also points to its further disconnection to phosphonate **25** and aldehyde **8**. Proceeding with the retrosynthesis, it was reasoned that the C-8 hydroxyl group could be derived by stereoselective reduction of a carbonyl group and that introduction of a double bond in conjugation with this carbonyl would allow a further phosphonate–aldehyde condensation to be used in the coupling process. Thus, functional group manipulation of **25** led to enone **17** as a potential precursor to **25**. Finally, enone **17** was dissected as indicated in Scheme III, leading to building blocks **6** and **7** as starting points for the synthesis. Scheme IV outlines the stereocontrolled construction of keto phosphonate carboxylic acid **16** beginning with the coupling of building blocks **6** and **7** (Scheme I). Thus, condensation of **6** and **7** under basic conditions (NaH–DME) smoothly furnished the

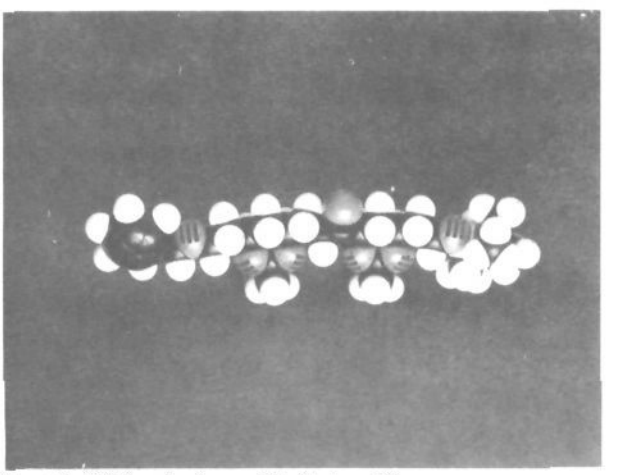


Figure 1. CPK molecular model of ketone **18**.

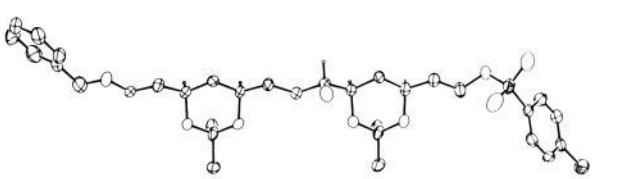
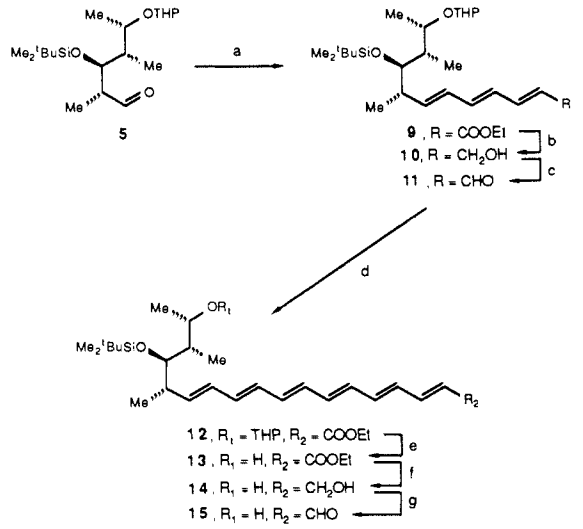


Figure 2. ORTEP drawing of compound **20**.

expected conjugated enone (**17**, Scheme III) in 94% yield, hydrogenation (5% Pd–C, EtOAc, H_2) of which led to the saturated ketone **18** (100%). Molecular modeling studies on this ketone suggested that reduction should occur from the side opposite to that of the adjacent acetonide, particularly by a sterically demanding reagent attacking a frozen conformation of **18** (see Figure 1). The degree of chelation control, solvent, temperature, and precise nature of the reagent were not a priori predictable, and, therefore, a systematic study was launched to define conditions to provide the desired stereoselectivity. Table I details the results of these experiments, clearly showing the success of the sterically demanding reagent-frozen conformation hypothesis (L-Selectride (Aldrich), THF, −110 °C, 98% yield, single stereoisomer detected

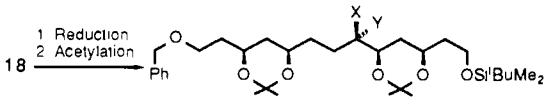
(4) DeKoning, H.; Mallo, G. N.; Springer-Fidder, A.; Subramanian-Erhart, K. E. C.; Huisman, H. O. *Recl. Trav. Chim.* **1973**, 683.

Scheme II[a]



[a] *Synthesis of Hydroxyaldehyde 15. Reagents and conditions*: (a) 1.3 equiv each of (E,E)-$(EtO)_2P(O)CH_2CH{=}CHCH{=}CHCOOEt$–LDA, THF, −78 → 0 °C, 90%; (b) 5.0 equiv of DIBAL, CH_2Cl_2, −78 °C, 100%; (c) 10 equiv of MnO_2, CH_2Cl_2, 25 °C, 96%; (d) 2.0 equiv each of (E,E)-$(EO)_2P(O)CH_2CH{=}CHCH{=}CHCOOEt$–LDA, THF, −78 → 0 °C, 60%; (e) PPTS catalyst, MeOH, 45 °C, 82%; (f) 5.0 equiv of DIBAL, CH_2Cl_2, −78 °C, 100%; (g) 10.0 equiv of MnO_2, CH_2Cl_2, 25 °C, 98%.

Table I. Stereoselectivity in the Reduction of Ketone **18**



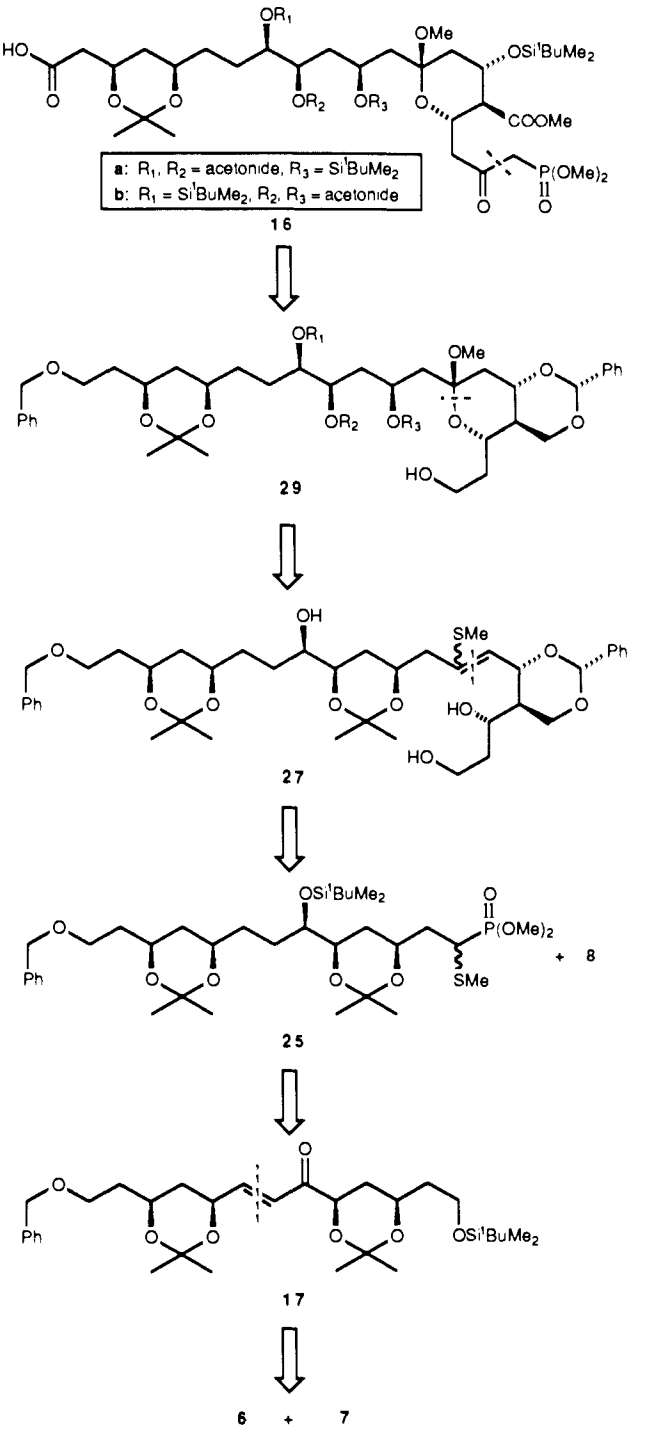
18a : X = OAc, Y = H; **18b** : X = H, Y = OAc

reagent[a,b]	conditions	product ratio (**18a**:**18b**)[c]
L-Selectride	THF/0 °C	3:1
L-Selectride	THF/−78 °C	5:1
L-Selectride	Et_2O/−78 °C	1:1.3
L-Selectride DME/−65 °C	DME/−65 °C	3:1
L-Selectride	THF/−110 °C	1:0
KS-Selectride	THF/0 °C	2:1
KS-Selectride	THF/−78 °C	2:1
$Zn(BH_4)_2$	Et_2O/0 °C	1:1
$Zn(BH_4)_2$	Et_2O/−78 °C	1:1
BH_3-THF	THF/0 °C	2.3:1
Sia_2BH	THF/0 °C	1.5:1
t-$BuNH_2$-BH_3	CH_2Cl_2/0 °C	1:1
t-$BuNH_2$-BH_3	THF/−40 °C	1:1
DIBAL	CH_2Cl_2/−78 °C	2.7:1
DIBAL	THF/−78 °C	1:1
DIBAL	$PhCH_3$/−78 °C	1.2:1

[a] 2.2 equiv of reducing reagent used. [b] 2.0 equiv of Ac_2O, 3.0 equiv of DMAP, CH_2Cl_2, 0 °C. [c] Ratios determined by ^1H NMR spectroscopy (acetate signals) at 250 MHz and are subject to the detection limits of this technique.

by ^1H NMR spectroscopy at 250 MHz). This stereochemical outcome is also in line with the Felkin–Ahn model; the observed increase in selectivity at lower temperature may reflect temperature dependence on $\Delta\Delta G^{\ddagger}$ for the diastereomeric reduction pathways. The stereochemical outcome of this reduction was confirmed by X-ray crystallographic analysis[5] (see Figure 2) of derivative **20** prepared from **19** as indicated in Scheme IV. The striking similarity of the solid state conformation of **20** (Figure 2) with the "frozen" conformation of **18** (Figure 1) is noteworthy. Compound **19** was then functionalized appropriately so as to allow its coupling to fragment **8** as follows. Engagement of the secondary hydroxyl group of **19** with the more stable t-$BuPh_2Si$ group[6] (96%) followed by selective removal of the t-$BuMe_2Si$ group (84%) from the primary hydroxyl furnished compound **22** via **21**. Intermediate **22** was then converted to iodide **23** (98%) via its mesylate, and thence to dimethyl phosphonate **24** by displacement with sodium dimethyl phosphite[7] (97%). It is worth noting that the usual Arbuzov conditions [$(MeO)_3P$, 110 °C, 48 h)] produced **24** from **21** in only 50% yield. Sulfenation of the anion of **24** (LDA, Me_2S_2) then led to a diastereomeric mixture of the α-thiomethyl phosphonate **25** (78%, ca. 1:1 by ^1H NMR analysis). Condensation of the anion of **25** (LDA–THF) with aldehyde **8**

Scheme III[a]

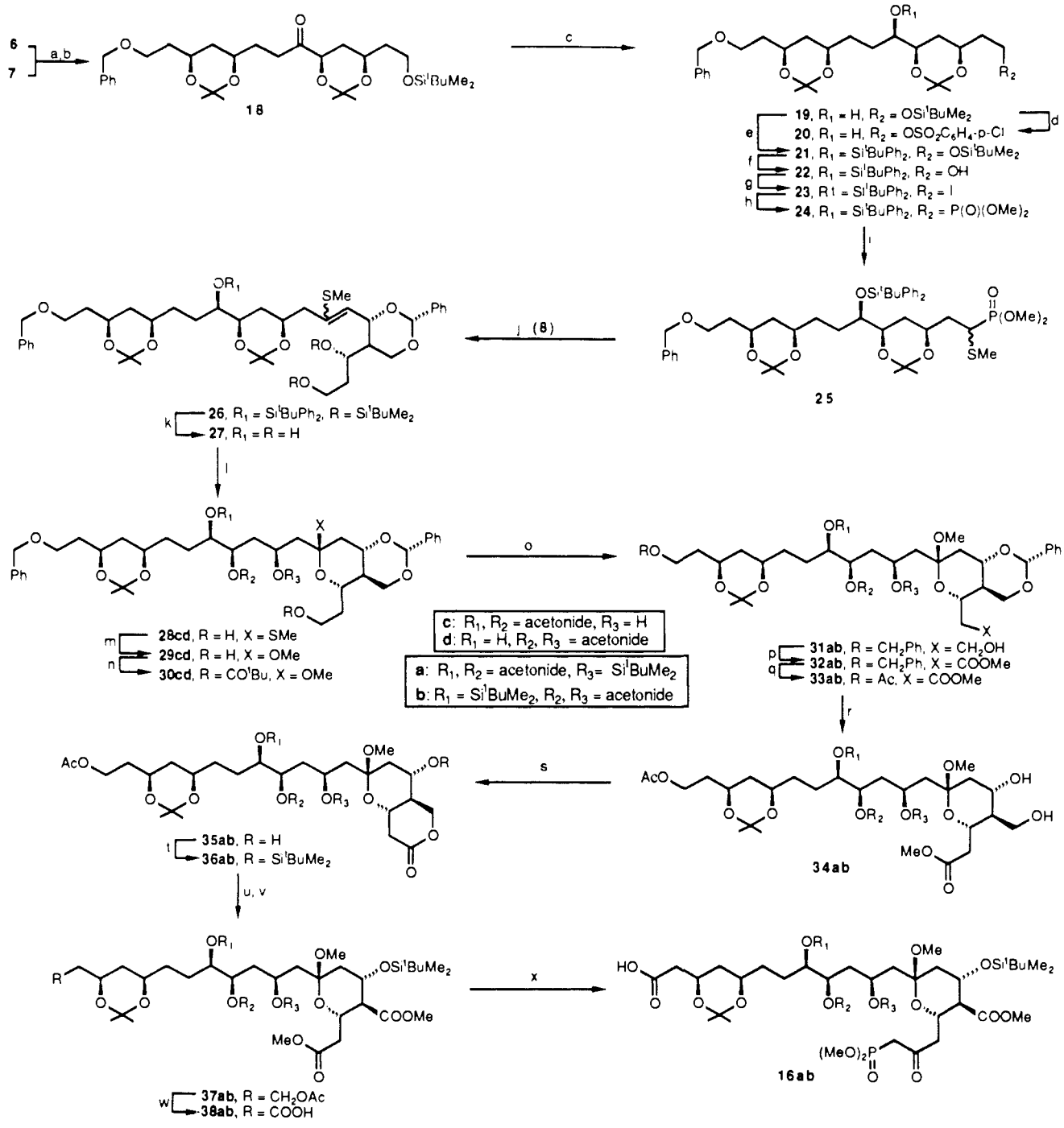


[a] Retrosynthetic analysis of C-1–C-20 fragment, keto phosphonate carboxylic acid **16**.

(5) We thank Dr. Patrick Carroll of this department for his assistance in solving this X-ray structure.

(6) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.
(7) Sturtz, G. *Bull. Soc. Chim. Fr.* **1964**, 2340.

Scheme IV[a]



[a]Synthesis of keto phosphonate carboxylic acid **16ab**. Reagents and conditions: (a) 7, 1.1 equiv of NaH, DME, 0 → 45 °C, then, 1.1 equiv **6**, −65 → −10 °C, 4 h, 94%; (b) 5% Pd–C catalyst, H_2, EtOAc, 25 °C, 3 h, 100%; (c) 2.2 equiv of L-Selectride, THF, −110 °C, 3 h, 98%; (d) 1.5 equiv of *n*-Bu_4NF, THF, 25 °C, 1 h and then 1.1 equiv of *p*-$ClC_6H_4SO_2Cl$, 1.5 equiv of Et_3N, DMAP catalyst, CH_2Cl_2, 0 °C, 4 h, 90%; (e) 2.0 equiv of *t*-$BuPh_2SiCl$, 5.0 equiv of imidazole, DMF, 50 °C, 4 h, 96%; (f) 1.2 equiv of *n*-Bu_4NF, THF, 0 °C, 6 h, 84%; (g) 1.1 equiv of MsCl, 1.3 equiv of Et_3N, CH_2Cl_2, −15 °C, 15 min, and then excess NaI, acetone, 25 °C, 8 h, 98% overall; (h) 2.2 equiv of $(MeO)_2P(O)H$–2.2 equiv of NaH, DME–DMF (3:2), 45 °C, 1 h, 97%; (i) 1.1 equiv of LDA, THF, −78 °C, and then 1.1 equiv of MeSSMe, −78 °C, 5 min, 78%; (j) 1.2 equiv of LDA, THF, −78 °C, and then 1.2 equiv of aldehyde **8**, −78 → 25 °C, 2 h, 90%; (k) 10 equiv of *n*-Bu_4NF, THF, 25 °C, 8 h, 96%; (l) 0.25 equiv of PPTS, CH_2Cl_2, 25 °C, 24 h, 75%; (m) 1.1 equiv of NBS, 3Å molecular sieves, CH_2Cl_2–MeOH (10:1), 0 °C, 10 min, 98%; (n) 1.1 equiv of *t*-BuCOCl, pyr, 0 °C, 4 h, 86%; (o) 2.5 equiv of *t*-$BuMe_2SiCl$, 7.0 equiv of imidazole, DMF, 45 °C, 3 h, 96%, and then 2.5 equiv of DIBAL, CH_2Cl_2, −78 °C, 15 min, 98%; (p) 5.0 equiv of PDC, DMF, 25 °C, 10 h, and then CH_2N_2, Et_2O, 0 °C, 82% overall; (q) 10% Pd–C catalyst, H_2, absolute EtOH, 25 °C, 48 h, and then 2.0 equiv of Ac_2O, 5.0 equiv of DMAP, CH_2Cl_2, 0 °C, 15 min, 67% overall; (r) 10% Pd–C catalyst, H_2, absolute MeOH, 25 °C, 48 h, 76%; (s) 5.0 equiv of imidazole, MeCN, 25 °C, 10 h, 76%; (t) 1.1 equiv of *t*-$BuMe_2SiOTf$, 1.3 equiv of 2,6-lutidine, $CHCl_2$, 10 min, 0 °C, 80%; (u) 1.1 equiv of aqueous LiOH (1.0 M), THF, 0 °C, 20 min, and then CH_2N_2, Et_2O, 0 °C, 98% overall; (v) 5.0 equiv of PDC, DMF, 25 °C, 10 h, and then CH_2N_2, Et_2O, 0 °C, 76% overall; (w) 5.0 equiv of K_2CO_3, MeOH, 0 °C, 30 min, 95%, and then 5.0 equiv of PDC, DMF, 10 h, 79%; (x) 3.0 equiv of $(MeO)_2P(O)Me$; 3.0 equiv of *n*-BuLi, THF, −78 °C, and then **38ab**, −78 °C, 15 min, 62%.

proceeded smoothly to give the coupling product **26** (90%, mixture of geometrical isomers, ca. 1:1 by ^1H NMR analysis) containing the required vinyl sulfide moiety. Complete desilylation of **26** then led to the triol **27** in 96% yield. The next task in the sequence was to engage the secondary hydroxyl group as a ketal with methanol, to produce **29cd**. Direct approaches to this intermediate with mercury salts and other reagents proved fruitless. An indirect two-step approach was, therefore, devised to effect this trans-

formation. Thus, **27** was converted to mixed thioketal **28cd** by acid-catalyzed (TsOH·pyr, CH_2Cl_2) cyclization (75%, mixture of isomers by ^1H NMR analysis) and then to methylketal **29cd** by exposure to NBS–MeOH (98%, ca. 1–3:1 mixture of isomers by ^1H NMR analysis). The cyclization reaction **27** → **28cd** produced at least two isomeric compounds (TLC and ^1H NMR analysis) whereas the exchange reaction **28cd** → **29cd** led cleanly to two isomers initially assumed to be methoxy anomers.[2] Subsequent studies, however, including ^1H NMR decoupling experiments (see the Experimental Section) strongly suggested the indicated 8,9- and 9,11-acetonide isomeric structures. The single methoxy group stereochemistry was tentatively assigned by analogy to the corresponding amphotericin B center. The ratio of these two regioisomers varied somewhat, but the compound was taken through the rest of the sequence to the keto phosphonate acid **16ab**, which proved identical with degradative material.[3,9] Differentiation between the primary and secondary hydroxyls of **29cd** was secured via monopivalate ester **30cd** (86%), which was silylated (96%) and selectively deprotected to afford primary alcohol **31ab** (98%). Conversion of **31ab** to methyl ester **32ab** was achieved by PDC[8] oxidation followed by diazomethane treatment (82% overall yield). The remaining sequence presented a number of protecting group and selectivity challenges. These challenges were met by careful selection of reagents and conditions. Thus, the benzyl ether protecting group in **32ab** was selectively removed by closely monitored hydrogenolysis (H_2, 10% Pd–C, EtOH) and replaced with an acetate group leading to **33ab** (67% overall yield) so as to allow subsequent differentiations. Subsequent removal of the benzylidene group from **33ab** under more persistent hydrogenolysis conditions (H_2, 10% Pd–C, MeOH) furnished diol **34ab** (76% yield). The primary hydroxyl group in **34ab** was temporarily engaged with the carboxyl group as a δ-lactone by treatment with imidazole giving **35ab** (76%). Subsequent silylation of the remaining free hydroxyl group in **35ab** led to the disilyl ether **36ab** in 80% yield. The highly sensitive lactone functionality of **36ab** was then dismantled, without acetate removal, by aqueous base, and the resulting hydroxy acid was converted to the dimethyl ester **37ab** by sequential methylation (CH_2N_2) and PDC[8] oxidation, followed by a second methylation (CH_2N_2, 74% overall yield). The acetate group was then readily removed from **37ab** (K_2CO_3–MeOH, 95%), and the carboxylic acid **38ab** was obtained by PDC[8] oxidation of the resulting primary alcohol (79%). Finally, differentiation of the three carboxyl groups in **38ab** (anion formation at C-1, steric congension at C-16) was observed in the one-step, chemoselective conversion of this intermediate to the requisite keto phosphonate carboxylic acid **16ab** (62%).[9,10]

With the two advanced key intermediates **15** and **16ab** available, we then turn our attention to the serious issue of coupling them and constructing the macrocyclic framework of amphoteronolide B (**2**) and amphotericin B (**1**).

Construction of the Macrocycle and Completion of the Synthesis of Amphoteronolide B. As already discussed[1] heptaenone **3** was targeted as the common precursor to both amphotericin B (**1**) and amphoteronolide B (**2**). This macrocyclic subtarget could be reached from advanced key intermediates **15** and **16** by one of two alternative ways. The first approach would involve the formation of the ester linkage followed by macrocyclization by an intramolecular keto phosphonate–aldehyde condensation. A second approach would entail the construction of the polyenone system first, followed by formation of the macrocyclic ring by lactonization. Past experience in these laboratories[11] pointed to the former approach as the most promising sequence to reach **3**. Thus, esterification of **16ab** with **15** (DCC, DMAP, CH_2Cl_2, 70%) produced the open chain precursor **39ab** (Scheme V). The crucial macrocyclization step was then successfully carried out under mild basic conditions (K_2CO_3–18-crown-6, toluene, 65 °C[11] or DBU–LiCl, CH_3CN, 25 °C[12]), leading to heptaenone **3ab** (70% yield).[9,10] From this point on, the total synthesis of amphotericin B (**1**) and amphoteronolide B (**2**) diverge. The former sequence will be discussed in the following paper[13] whereas the remaining steps to amphoteronolide B (**2**) are described below.

For the conversion of heptaenone **3** to amphoteronolide B (**2**), stereoselective carbonyl reduction and deprotection were required. After some experimentation, it became apparent that the most successful route would involve deprotection of all secondary hydroxyls prior to the generation of the rather labile allylic hydroxyl group followed by final demethylations. More specifically the completion of the synthesis followed the sequence outlined in Scheme V. Thus desilylation of the major compound **3a** (HF·pyr–MeOH) afforded triol **40** (55%), which was then subjected to deacetonization (CSA–MeOH), leading to heptahydroxyheptaenone **41** (50% yield based on ca. 50% conversion). Sodium borohydride mediated reduction of **41** then led, stereospecifically, to amphoteronolide B derivative **42** (95%). The 19(*R*) configuration of the reduction product was confirmed by comparisons to materials derived from amphotericin B (**1**) by degradation and CD studies as already discussed in a preceding paper in this series.[9] Finally, sequential demethylation of **42** (CSA, MeOH–H_2O, 97%) followed by LiOH hydrolysis (80% yield based on ca. 75% conversion) led to amphoteronolide B (**2**) via its methyl ester **43**, identical with a sample derived from amphotenicin B (**1**).[9]

Conclusion

The efficient coupling of building blocks **4–8** was achieved by employing four aldehyde–phosphonate type condensation reactions and an esterification reaction producing the acyclic keto phosphonate aldehyde precursor **39ab**. The crucial macrocycle formation was demonstrated to proceed efficiently via intramolecular keto phosphonate–aldehyde condensation producing the 38-membered ring **3**. The remarkable success of this reaction, considering the complexity and rather large size of the ring produced, is, at least partially, due to the minimization of the degrees of freedom in **39ab** imposed by (a) the double bonds, (b) the substituents on the backbone, and (c) the three ring systems present in the acyclic precursor. Finally a stereoselective reduction and final elaboration completed the first total synthesis of amphoteronolide B (**2**). Although this target was reached from the major isomer **3a**, similar chemistry should be applicable to the conversion of **3b** to **2**. The elaboration of heptaenone **3** to amphotericin B (**1**) is described in the following paper.[13]

Experimental Section

General Methods. See ref 9.

Ethyl (2*E*,4*E*,6*E*,8*S*,9*R*,10*S*,11*S*)-9-[(*tert*-Butyldimethylsilyl)oxy]-8,10-dimethyl-11-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2,4,6-dodecatrienoate (9). To a stirred solution of freshly distilled diisopropylamine (DIPA, 0.816 g ≡ 1.13 mL, 8.06 mmol) in dry THF (3.2 mL) at −78 °C under argon was dropwise added *n*-BuLi (3.22 mL, 2.5 M solution in hexane, 8.05 mmol). After 5 min, the mixture was warmed to 0 °C and stirred at that temperature for 15 min before it was cooled back again to −78 °C. A solution of phosphonate **4** (2.23 g, 8.06 mmol) in dry THF (5 mL) was added dropwise. After 15 min of being stirred at −78 °C, the aldehyde **5** (2.22 g, 6.2 mmol) in dry THF (5 mL) was dropwise added to the stirred phosphonate anion solution. The reaction mixture was stirred at −78 °C for 15 min and then at 0 °C for 15 min before it was quenched with saturated aqueous NH_4Cl (30 mL). The product was extracted with ether (40 mL), the organic extract was washed with brine (30 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography (silica, 10% ether in petroleum ether) gave the product as a mixture of two THP anomers (2.68 g, 90%). **9** (mixture of THP isomers, ca. 1:1 ratio): colorless oil; R_f 0.16 and 0.21 (silica, 10% ether in petroleum ether); $[\alpha]^{20}_D$ −6.5° (*c* 3.49, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2960, 2940, 2860, 1705 (s, C=O), 1620 (s, C=C), 1460, 1370 cm^{-1}; UV

(8) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(9) Nicolaou, K. C.; Chakraborty, T. K.; Ogawa, Y.; Daines, R. A.; Simpkins, N. S.; Furst, G. T. *J. Am. Chem. Soc.*, preceding paper in this issue.

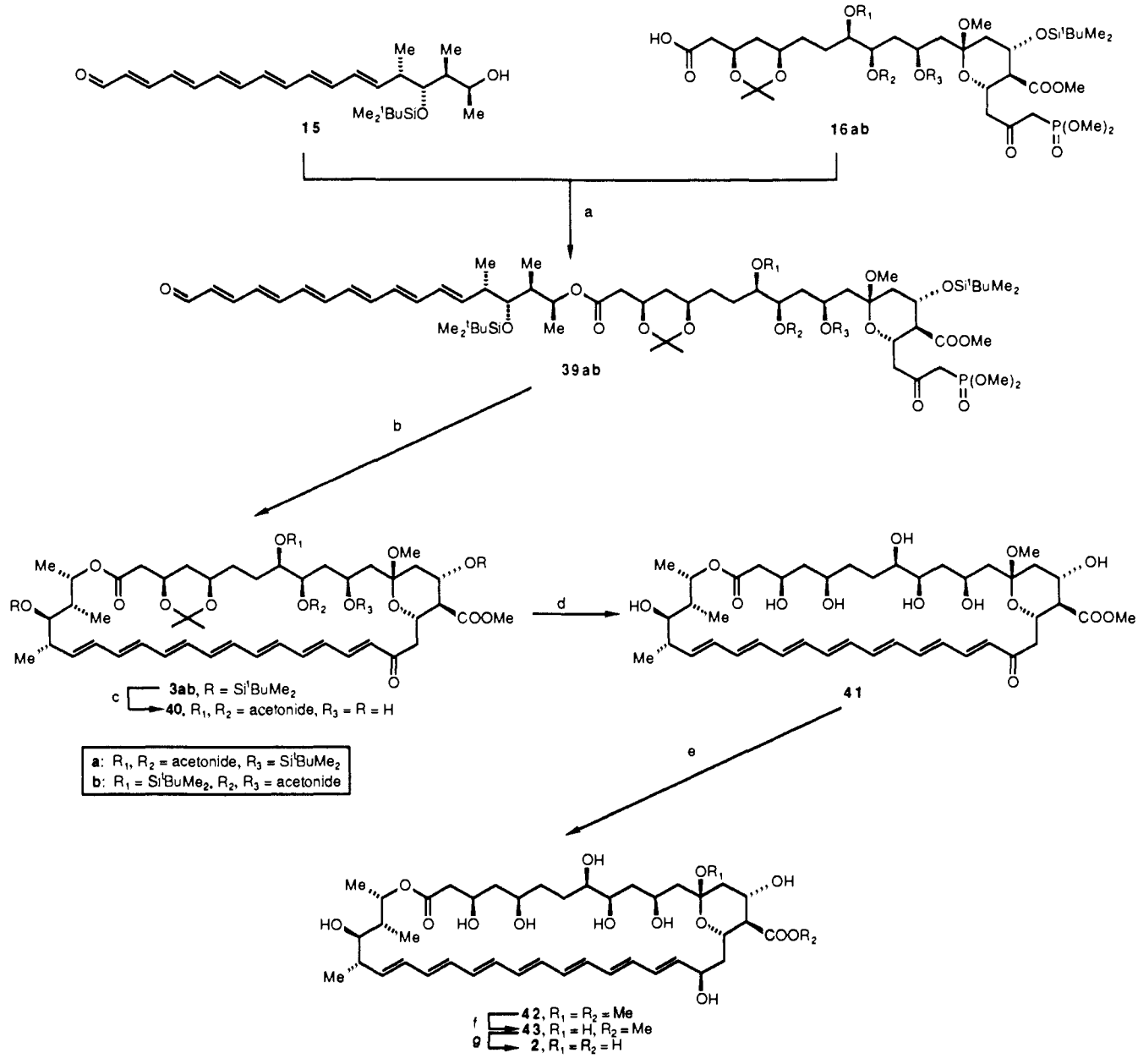
(10) Synthetic and degradative samples of this compound were spectroscopically and chromatographically identical although the ratio of the two isomers varied. Compounds **28–38** and **16** were carried through the sequence as mixtures of isomers.

(11) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. P. *J. Am. Chem. Soc.* **1982**, *104*, 2030.

(12) Blanehette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. P.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(13) Nicolaou, K. C.; Daines, R. A.; Ogawa, Y.; Chakraborty, T. K. *J. Am. Chem. Soc.*, accompanying paper in this issue.

Scheme V[a]



[a] Total synthesis of amphoteronolide B (**2**). Reagents and conditions: (a) 1.0 equiv of **16ab**, 1.2 equiv of **15**, 1.2 equiv of DCC, 0.3 equiv of DMAP, CH_2Cl_2, (1.0 M), 25 °C, 4 h, 70%; (b) 6.0 equiv of K_2CO_3, 13.0 equiv of 18-crown-6, toluene (0.001 M), 65 °C, 14 h, or 5.0 equiv of LiCl, 5.5 equiv of DBU, MeCN (0.01 M), 25 °C, 4 h, 70%; (c) excess HF–pyr, MeOH, 45 °C, 48 h, 55%; (d) 0.1 equiv of CSA, MeOH, 0 → 25 °C, 1 h, 50% based on 50% conversion; (e) 10 equiv of $NaBH_4$, MeOH, 0 °C, 15 min, 95%; (f) 0.1 equiv of CSA, MeOH–H_2O (9:1), 0 → 25 °C, 1 h, 97%; (g) 10 equiv of 1 N LiOH, H_2O, 0 → 25 °C, 1 h, 80% based on 75% conversion.

(hexane) λ_{max} 297 (E_{1cm} 1% 829), 308 nm (718); ^{1}H NMR (250 MHz, $CDCl_3$, TMS) δ 7.28 (dd, J = 15.3, 11.2 Hz, 1 H, H-3), 6.50 (dd, J = 14.9, 10.0 Hz, 1 H, olefinic), 6.27–5.77 (m, 4 H, olefinic), 4.60, 4.51 (m, ca. 1:1 ratio, 1 H, OC*H*O), 4.17 (q, J = 7.1 Hz, 2 H, $COOCH_2CH_3$), 3.94–3.35 (m, 4 H, CH_2O, C*H*O), 2.48 (m, 1 H, C*H*), 1.95–1.40 (m, 7 H, CH_2,C*H*), 1.27 (t, J = 7.1 Hz, 3 H, $COOCH_3CH_3$), 1.15–0.75 (m, 18 H, Si-*t*-*Bu*, CH_3), 0.030–0.010 (singlets,, 6 H total, $SiMe_2$); HRMS (CI) calcd for $C_{27}H_{48}O_5Si$ + H 481.3349, found 481.3431 (M + H).

(2*E*,4*E*,6*E*,8*S*,9*R*,10*S*,11*S*)-9-[(*tert*-Butyldimethylsilyl)oxy]-8,10-dimethyl-11-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2,4,6-dodecatrien-1-ol (10). To a stirred solution of ester **9** (2.64 g, 5.5 mmol) in dry CH_2Cl_2 (22 mL) at −78 °C under argon was dropwise added DIBAL (27.5 mL, 1 M solution in hexane, 27.5 mmol). The reaction mixture was stirred at that temperature for 0.5 h before it was quenched with MeOH (0.6 mL). It was then diluted with ether (100 mL) and shaken with saturated aqueous potassium–sodium tartrate (60 mL). The organic layer was washed with brine (60 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography (silica, 40% ether in petroleum ether) gave allylic alcohol **10** as a mixture of two THP anomers (2.41 g, 100%). **10** (mixture of THP isomers, ca. 1:1 ratio): colorless oil; R_f 0.21 (silica, 40% ether in petroleum ether); $[\alpha]^{20}_D$ −9.2° (*c* 1.53, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3610 (m, OH), 3000, 2950, 2930, 2880, 2860, 1635 (s, C=C), 1460, 1380 cm^{-1}; UV (hexane) λ_{max} 261 (E_{1cm} 1% 1070), 270 (1370), 281 nm (1052); ^{1}H NMR (250 MHz, $CDCl_3$, TMS) δ 6.55–5.30 (m, 6 H, olefinic), 4.61 and 4.51 (multiplets, ca. 1:1 ratio, 1 H total, OC*H*O), 4.20–3.38 (m, 6 H, C*H*O, CH_2O), 2.85 (m, 1 H, O*H*), 2.41 (m, 1 H, C*H*), 1.95–1.40 (m, 7 H, CH_2, C*H*), 1.15–0.80 (m, 18 H, Si-*t*-*Bu*, CH_3), 0.030, 0.010, and −0.020 (singlets, 6 H total, $SiMe_2$); HRMS (CI) calcd for $C_{25}H_{46}O_4Si$ + H 439.3244, found 439.3285 (M + H).

(2*E*,4*E*,6*E*,8*S*,9*R*,10*S*,11*S*)-9-[(*tert*-Butyldimethylsilyl)oxy]-8,10-dimethyl-11-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2,4,6-dodecatrienal (11). To a stirred solution of allylic alcohol **10** (2.19 g, 5.0 mmol) in dry CH_2Cl_2 (20 mL) was added MnO_2 (4.35 g, 50 mmol) at 25 °C under argon. The reaction mixture was stirred for 12 h. It was then filtered through a pad of Celite and concentrated. Flash column chromatography (silica, 20% ether in petroleum ether) gave aldehyde **11** as a mixture of THP anomers (2.14 g, 98%). **11** (mixture of THP isomers, ca. 1:1 ratio): colorless oil; R_f = 0.20 and 0.24 (silica, 20% ether in petroleum ether); $[\alpha]^{20}_D$ +29.7° (*c* 2.13, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2960, 2940, 2900, 2860, 1675 (s, C=O), 1615 (s, C=C), 1475, 1470, 1380 cm^{-1}; UV ($CHCl_3$)

λ_{max} 327 nm (E_{1cm} 1% 785); ^{1}H NMR (250 MHz, $CDCl_3$, TMS) δ 9.53 and 9.52 (doublets, ca. 1:1 ratio, J = 8.0 Hz, 1 H total, aldehyde), 7.10 (dd, J = 15.0, 11.1 Hz, 1 H, olefinic), 6.62 (dd, J = 15.0, 9.6 Hz, 1 H, olefinic), 6.40–5.95 (m, 4 H, olefinic), 4.60 and 4.52 (multiplets, ca. 1:1 ratio, 1 H total, OC*H*O), 3.95–3.35 (m, 4 H, CH_2O, C*H*O), 2.50 (m, 1 H, H-34), 1.91–1.47 (m, 7 H, CH_2, C*H*), 1.15–0.80 (m, 18 H, Si-*t-Bu*, CH_3), 0.020, and −0.010 (singlets, 6 H total, SiMe_2); HRMS (CI) calcd for $C_{25}H_{44}O_4Si$ + H 437.3087, found 437.3047 (M + H).

Ethyl (2*E*,4*E*,6*E*,8*E*,10*E*,12*E*,14*S*,15*R*,16*S*,17*S*)-15-[(*tert*-Butyldimethylsilyl)oxy]-14,16-dimethyl-17-[(tetrahydro-2*H*-pyran-2-yl)oxy]-2,4,6,8,10,12-octadecahexaenoate (12). Aldehyde **11** (2.10 g, 4.80 mmol) was converted to the hexaene ester **12** via the same procedure as described above for the preparation of ester **9**. The product was purified by flash column chromatography (silica, 20% ether in petroleum ether) to give **12** as a mixture of THP anomers (1.61 g, 60%). **12** (mixture of THP isomers, ca. 1:1 ratio): yellow oil; R_f 0.34 and 0.39 (silica, 20% ether in petroleum ether); $[\alpha]^{20}_D$ +11.6° (*c* 1.80, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2960, 2940, 2900, 2860, 1700 (s, C=O), 1625 (s, C=C), 1570, 1470, 1380 cm^{-1}; UV-vis (hexane) λ_{max} 402 (E_{1cm} 1% 1160), 380 (1320), 361 (948), 342 nm (510); ^{1}H NMR (250 MHz, $CDCl_3$, TMS) δ 7.30 (dd, J = 15.2, 11.4 Hz, 1 H, olefinic), 6.58 (dd, J = 14.5, 11.0 Hz, 1 H, olefinic), 6.50–5.68 (m, 9 H, olefinic), 5.83 (d, J = 15.2 Hz, 1 H, olefinic), 4.61 and 4.51 (multiplets, ca. 1:1 ratio, 1 H total, OC*H*O), 4.18 (q, J = 7.1 Hz, 2 H, COOCH_2CH$_3$), 4.00–3.35 (m, 4 H, CH_2O, C*H*O), 2.44 (m, 1 H, C*H*), 1.95–1.40 (m, 7 H, CH_2, C*H*), 1.27 (t, J = 7.1 Hz, 3 H, COOCH$_2$CH_3), 1.15–0.80 (m, 18 H, Si-*tert-Bu*, CH_3), 0.030, 0.020, and −0.010 (singlets, 6 H total, SiMe_2); HRMS (FAB) calcd for $C_{33}H_{54}O_5Si$ 558.3740, found 558.3800 (M$^+$).

Ethyl (2*E*,4*E*,6*E*,8*E*,10*E*,12*E*,14*S*,15*R*,16*S*,17*S*)-15-[(*tert*-Butyldimethylsilyl)oxy]-17-hydroxy-14,16-dimethyl-2,4,6,8,10,12-octadecahexaenoate (13). To a stirred solution of THP ether **12** (1.56 g, 2.80 mmol) in dry MeOH (11 mL) was added pyridinium *p*-toluenesulfonate (PPTS, 70 mg, 0.28 mmol) at 25 °C under argon. The reaction mixture was heated at 45 °C for 3 h. After being cooled to room temperature, the mixture was poured onto saturated aqueous $NaHCO_3$ (40 mL) and extracted with ether (100 mL). The ether extract was washed with brine (40 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography (silica, 30% ether in petroleum ether) gave pure hexaene ester **13** (1.09 g, 82%). **13**: yellow amorphous solid; R_f = 0.19 (silica, 30% ether in petroleum ether); $[\alpha]^{20}_D$ −13.9° (*c* 0.86, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3500 (m, OH), 3000, 2970, 2940, 2860, 1700 (s, C=O), 1620 (s, C=C), 1575, 1470, 1370 cm^{-1}; UV-vis (hexane) λ_{max} 401 (E_{1cm} 1% 1570), 379 (1790), 360 (1317), 340 nm (733); ^{1}H NMR (250 MHz, $CDCl_3$), TMS) δ 7.30 (dd, J = 15.2, 11.4 Hz, 1 H, olefinic), 6.58 (dd, J = 14.4, 10.8 Hz, 1 H, olefinic), 4.58–6.04 (m, 8 H, olefinic), 5.83 (d, J = 15.2 Hz, 1 H, olefinic), 5.73 (dd, J = 14.9, 7.9 Hz, 1 H, olefinic), 4.18 (q, J = 7.1 Hz, 2 H, COOCH_2CH$_3$), 3.68 (m, 1 H, C*H*O), 3.50 (t, J = 5.1 Hz, 1 H, C*H*O), 3.08 (m, 1 H, O*H*), 2.45 (m, 1 H, C*H*), 1.64 (m, 1 H, C*H*), 1.27 (t, J = 7.1 Hz, 3 H, COOCH$_2$CH_3), 1.11 (d, J = 6.2 Hz, 3 H, CH_3), 1.02 (d, J = 6.9 Hz, 3 H, CH_3), 0.90 (s, 9 H, Si-*t-Bu*), 0.81 (d, J = 7.0 Hz, 3 H, CH_3), 0.080 and 0.050 (singlets, 6 H total, SiMe_2); HRMS (CI) calcd for $C_{28}H_{46}O_4Si$ 474.3165, found 474.3225 (M$^+$).

(2*E*,4*E*,6*E*,8*E*,10*E*,12*E*,14*S*,15*R*,16*S*,17*S*)-15-[(*tert*-Butyldimethylsilyl)oxy]-14,16-dimethyl-2,4,6,8,10,12-octadecahexaene-1,17-diol (14). Hexaene ester **13** (1.04 g, 2.20 mmol) was reduced with DIBAL (11.0 mL, 1 M solution in hexane, 11.0 mmol) in the same manner as described above for the preparation of alcohol **10**. The resulting unstable alcohol **14** was used directly for the next step without further purification. **14**: yellow amorphous solid; R_f 0.13 (silica, 50% ether in petroleum ether).

(2*E*,4*E*,6*E*,8*E*,10*E*,12*E*,14*S*,15*R*,16*S*,17*S*)-15-[(*tert*-Butyldimethylsilyl)oxy]-17-hydroxy-14,16-dimethyl-2,4,6,8,10,12-octadecahexaenal (15). The crude alcohol **14** (ca. 2.20 mmol) prepared above was dissolved in dry CH_2Cl_2 (9 mL) and oxidized with MnO_2 (1.91 g, 22.0 mmol) as described above for aldehyde **11**. Flash column chromatography (silica, 40% ether in petroleum ether) gave pure hexaene aldehyde **15** (0.91 g, 96% overall from **13**). **13**: yellow amorphous solid; R_f 0.10 (silica, 40% ether in petroleum ether); $[\alpha]^{20}_D$ +4.9° (*c* 0.78, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3500 (m, OH), 3000, 2960, 2940, 2860, 1670 (s, C=O), 1610 (s, C=C), 1570, 1470, 1380 cm^{-1}; UV-vis ($CHCl_3$) λ_{max} 407 nm (E_{1cm} 1% 1295); ^{1}H NMR (500 MHz, $CDCl_3$, TMS, amphotericin B numbering) δ 9.54 (d, J = 8.0 Hz, 1 H, aldehyde), 7.11 (dd, J = 15.0, 11.4 Hz, 1 H, H-23), 6.69 (dd, J = 14.6, 11.3 Hz, 1 H, olefinic), 6.51–6.08 (m, 9 H, olefinic), 5.77 (dd, J = 15.2, 8.0 Hz, 1 H, H-33), 3.68 (m, 1 H, H-37), 3.52 (t, J = 5.1 Hz, 1 H, H-35), 2.98 (m, 1 H, O*H*), 2.46 (m, 1H, H-34), 1.64 (m, 1 H, H-36), 1.11 (d, J = 6.2 Hz, 3 H, CH_3), 1.02 (d, J = 6.8 Hz, 3 H, CH_3), 0.90 (s, 9 H, Si-*t-Bu*), 0.82 (d, J = 7.0 Hz, 3 H, CH_3), 0.080 and 0.050 (singlets, 6 H total, SiMe_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.35, 151.77, 142.77, 139.90, 139.02, 136.86, 135.61, 131.79, 131.24, 131.06, 130.77, 130.55, 129.63, 80.95, 69.75, 44.10, 43.04, 26.03, 20.73, 18.21, 15.66, −4.05; HRMS (CI) calcd for $C_{26}H_{42}O_3Si$ 430.2903, found 430.2831 (M$^+$).

Enone 17. To a magnetically stirred cooled (0 °C) solution of keto phosphonate **7** (8.11 g, 19.1 mmoL) in dry DME (85 mL) was added NaH (0.772 g, 60% in mineral oil, 19.3 mmol) under argon. The reaction mixture was warmed to 45 °C and stirred for 20 min followed by cooling to −60 °C. A solution of aldehyde **6** (5.37 g, 19.3 mmol) in dry DME (20 mL) was then added dropwise. The reaction mixture was allowed to warm slowly to −10 °C over 4 h and maintained at that temperature for an addition 0.5 h. The reaction mixture was then diluted with ether (250 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 30 mL) and brine (30 mL) and dried ($MgSO_4$). Evaporation and purification by flash column chromatography (silica, 30% ether in petroleum ether) afforded pure enone **17** (10.3 g, 94%). **17**: colorless oil; R_f 0.32 (silica, 40% ether in petroleum ether); $[\alpha]^{20}_D$ +12.5° (*c* 0.24, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3015, 2970, 2870, 1700 and 1650 (m, C=O), 1390 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$, TMS) δ 7.36–7.28 (m, 5 H, aromatic), 6.91 (dd, J = 15.7, 4.2 Hz, 1 H, β-vinyl), 6.69 (dd, J = 15.7, 1.6 Hz, 1 H, α-vinyl), 4.51 (m, 2 H, C*H*O), 4.53, 4.47 (doublets, J = 12.0 Hz, 2 H, benzyl), 4.10 (m, 2 H, C*H*O), 3.76–3.48 (m, 4 H, CH_2O), 1.81–1.18 (m, 8 H, CH_2), 1.37 and 1.43 (singlets, 12 H total, acetonides), 0.89 (s, 9 H, Si-*t-Bu*), 0.047 (s, 6 H, SiMe_2); HRMS (CI) calcd for $C_{32}H_{52}O_7Si$ 576.3482, found 576.3451 (M$^+$). Anal. Calcd for $C_{32}H_{52}O_7Si$: C, 66.63; H, 9.08. Found: C, 66.43; H, 9.25.

Ketone 18. To a magnetically stirred solution of enone **17** (9.90 g, 17.1 mmol) in EtOAc (100 mL) was added 5% Pd–C (500 mg). The reaction mixture was stirred under a H_2 atmosphere for 3 h. The H_2 was purged with argon, and the solution was filtered through a pad of Celite. Evaporation and purification by flash column chromatography (silica, 30% ether in petroleum ether) gave pure ketone **18** (9.92g, 100%). **18**: colorless oil; R_f 0.32 (silica, 40% ether in petroleum ether); $[\alpha]^{20}_D$ +23.3° (*c* 0.24, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3010, 2960, 2870, 1720 (s, C=O), 1390 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$, TMS) δ 7.39–7.17 (m, 5 H, aromatic), 4.52, 4.46 (doublets, J = 12.0 Hz, 2 H, benzyl), 4.32 (dd, J = 12.1, 2.9 Hz, 1 H, α-C*H*O), 4.05 (m, 2 H, C*H*O), 3.85–3.47 (m, 5 H, C*H*O, CH_2), 2.63 (m, 2 H, α-CH_2), 1.80–1.10 (m, 10 H, CH_2), 1.45, 1.39, and 1.35 (singlets, 12 H total, acetonides), 0.89 (s, 9 H, Si-*t-Bu*), 0.044 (s, 6 H, SiMe_2); HRMS (CI) calcd for $C_{32}H_{54}O_7Si$ − Me 563.3404, found 563.3306 (M − Me). Anal. Calcd for $C_{32}H_{54}O_7Si$: C, 66.40; H, 9.40. Found: C, 66.56; H, 9.61.

Alcohol 19. A magnetically stirred solution of ketone **18** (9.92 g, 17.1 mmol) in dry THF (350 mL) under argon was cooled to −110 °C. To this was slowly added L-Selectride (Aldrich; 37.6 mL, 1 M solution in THF, 37.6 mmol) by dropwise addition. The mixture was stirred and allowed to warm slowly to −78 °C over a period of 3 h, at which time it was then warmed to 0 °C. It was then treated with aqueous NaOH (30 mL, 6 N solution, 180 mmol) and 30% H_2O_2 (25 mL) and vigorously stirred for 0.5 h. The reaction mixture was diluted with ether (500 mL), and the organic layer was separated. The organic phase was washed with 10% aqueous $NaHSO_3$ (50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), and brine (50 mL) and dried ($MgSO_4$). Concentration and removal of *sec*-butyl alcohol in vacuo provided essentially pure alcohol **19** (9.37 g, 98%), which could be used without further purification. An analytical sample was purified by flash column chromatography (silica, 50% ether in petroleum ether) to afford pure alcohol **19**. **19**: colorless oil: R_f 0.28 (silica, 50% ether in petroleum ether); $[\alpha]^{20}_D$ +6.7° (*c* 0.21, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3600 (w, OH), 3010, 2960, 2870, 1390 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$, TMS) δ 7.35–7.27 (m, 5 H, aromatic), 4.53, 4.47 (doublets, J = 12.0 Hz, 2 H, benzyl) 4.09–3.38 (m, 9 H, C*H*O, CH_2O), 2.74 (d, J = 3.6 Hz, 1 H, O*H*), 1.79–1.15 (m, 12 H, C*H*, CH_2), 1.43, 1.42, 1.39, and 1.37 (singlets, 12 H total, acetonides), 0.89 (s, 9 H, Si-*t-Bu*), 0.046 (s, 6 H, SiMe_2); HRMS (CI) calcd for $C_{32}H_{56}O_7Si$ + H 581.3874, found 581.3892 (M + H).

***p*-Chlorobenzenesulfonate 20.** To a magnetically stirred solution of alcohol **19** (150 mg, 0.258 mmol) in THF (2 mL) was added *n*-Bu_4NF (0.40 mL, 1 M solution in THF, 0.40 mmol) at ambient temperature. After the reaction was complete (1 h), the solution was diluted with EtOAc (60 mL), washed with H_2O (2 × 5 mL) and brine (5 mL), and dried ($MgSO_4$). Evaporation and flash column chromatography (silica, 5% MeOH in CH_2Cl_2) gave pure diol (120 mg, 100%). Diol: white semisolid; R_f 0.26 (silica, 5% MeOH in CH_2Cl_2); $[\alpha]^{20}_D$ +4.6° (*c* 0.71, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3540 (m, OH), 3000, 2960, 2880, 1390 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$, TMS) δ 7.33 (m, 5 H, aromatic), 4.53, 4.47 (doublets, J = 12.0 Hz, 2 H, benzyl), 4.14–3.39 (m, 9 H, C*H*O, CH_2O), 2.80 (d, J = 3.8 Hz, 1 H, O*H*), 2.52 (t, J = 4.7 Hz, 1 H, O*H*), 1.87–1.05 (m, 12 H, CH_2), 1.46, 1.42, 1.40, and 1.37 (singlets, 12 H total, acetonides); HRMS (CI) calcd for $C_{26}H_{42}O_7$ + H 467.3009, found 467.3069 (M + H).

To a magnetically stirred solution of the above prepared diol (120 mg, 0.258 mmol) in dry CH_2Cl_2 (2.5 mL) were added triethylamine (39.2 mg

≡ 0.54 mL, 0.387 mmol) and DMAP (1.6 mg, 0.0129 mmol) under argon. The solution was cooled to 0 °C, and 4-chlorobenzenesulfonyl chloride (60.0 mg, 0.284 mmol) was added. The reaction mixture was stirred for 4 h at 0 °C and then diluted with EtOAc (60 mL), washed with H_2O (2 × 5 mL), 5% aqueous HCl (5 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), and dried ($MgSO_4$). Evaporation and purification by flash column chromatography (silica, 2% MeOH in CH_2Cl_2) afforded pure benzenesulfonate **20** (149 mg, 90%). Recrystallization from EtOAc produced a suitable crystal for X-ray analysis. **20**: colorless needles; mp 149–150 °C (EtOAc); R_f 0.35 (silica, 5% MeOH in CH_2Cl_2), $[\alpha]^{20}_D$ +10.5° (*c* 0.55, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3600 (w, OH), 3000, 2960, 2880, 1450, 1390 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, TMS) δ 7.9 (m, 2 H, aromatic), 7.6 (m, 2 H, aromatic), 7.32 (m, 5 H, aromatic), 4.50 (s, 2 H, benzyl), 4.05–3.35 (m, 7 H, C*H*O, CH_2O), 3.20 (m, 2 H, C*H*OSO_2Ar), 2.70 (br s, 1 H, O*H*), 2.05–1.11 (m, 12 H, CH_2), 1.41, 1.36, and 1.33 (singlets, 12 H total, acetonides); HRMS (FAB) calcd for $C_{32}H_{45}O_9SCl$ + H 641.2551, found 641.2527 (M + H).

Disilyl Ether (21). Alcohol **19** (9.73 g, 16.7 mmol) was dissolved in DMF (20 mL) and treated with imidazole (5.80 g, 85 mmol) and *t*-$BuPh_2SiCl$ (9.4 g ≡ 8.9 mL, 34.2 mmol) under argon. The reaction mixture was stirred at 50 °C for 4 h. After the mixture was cooled to room temperature, the reaction was quenched with MeOH (2 mL) and stirred for an additional 10 min. It was then diluted with ether (100 mL), washed with H_2O (3 × 20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL), and dried ($MgSO_4$). Evaporation and purification by flash column chromatography (silica, 10% ether in petroleum ether) afforded pure disilyl ether **21** (13.1 g, 96%). **21**: colorless oil; R_f 0.31 (silica, 20% ether in petroleum ether); $[\alpha]^{20}_D$ −3.1° (*c* 0.35, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3010, 2970, 2870, 1390 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, TMS) δ 7.75–7.25 (m, 15 H, aromatic), 4.52, 4.46 (doublets, *J* = 12.0 Hz, 2 H, benzyl), 3.80 (m, 3 H, C*H*O), 3.50 (m, 6 H, C*H*O, CH_2O), 1.70 (dq, *J* = 6.3 Hz, 2 H, CH_2), 1.57 (dq, *J* = 6.4 Hz, 2 H, CH_2), 1.45 (m, 4 H, CH_2), 1.38–0.95 (m, 4 H, CH_2), 1.31, 1.30, 1.23, and 1.17 (singlets, 12 H total, acetonides), 1.03 (s, 9 H, Si-*t-Bu*), 0.87 (s, 9 H, Si-*t-Bu*), 0.022 (s, 6 H, $SiMe_2$); HRMS (FAB) calcd for $C_{48}H_{74}O_7Si_2$ + H 819.5051, found 819.5080 (M + H).

Primary Alcohol 22. A magnetically stirred solution of disilyl ether **21** (13.5 g, 16.5 mmol) in THF (165 mL) was cooled to 0 °C, to this was slowly added a tetrabutylammonium fluoride solution (20 mL, 1 M solution in THF, 20 mmol), and the mixture was maintained under argon at 0 °C for 6 h. The reaction mixture was diluted with ether (300 mL), washed with H_2O (3 × 20 mL) and brine (20 mL), and dried ($MgSO_4$). Evaporation and flash column chromatography (silica, 60% ether in petroleum ether) provided pure alcohol **22** (9.77 g, 84%). **22**: colorless oil; R_f 0.23 (silica, 60% ether in petroleum ether); $[\alpha]^{20}_D$ −4.3° (*c* 0.61, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3510 (m, OH), 3000, 2950, 2860, 1390 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, TMS) δ 7.73–7.27 (m, 15 H, aromatic), 4.53, 4.47 (doublets, *J* = 12.0 Hz, 2 H, benzyl), 4.05–3.45 (m, 9 H, C*H*O, CH_2O), 2.54 (dd, *J* = 6.1, 4.8 Hz, 1 H, O*H*), 1.80–1.10 (m, 12 H, CH_2), 1.32, 1.31, 1.28, and 1.20 (singlets, 12 H total acetonides), 1.04 (s, 9H, Si-*t-Bu*); HRMS (FAB) calcd for $C_{42}H_{60}O_7Si$ + H 705.4187, found 705.4191 (M + H).

Iodide 23. To a magnetically stirred solution of alcohol **22** (8.00 g, 11.3 mmol) in dry CH_2Cl_2 (100 mL) was added triethylamine (1.79 g ≡ 2.4 mL, 17.0 mmol) under argon. The reaction mixture was cooled to −15 °C and treated with methanesulfonyl chloride (1.68 g, ≡ 1.2 mL, 14.7 mmol). After being stirred for 15 min, the mixture was diluted with ether (200 mL), washed with H_2O (2 × 20 mL), 5% aqueous HCl (20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL), and dried ($MgSO_4$). Evaporation gave essentially pure mesylate, which was used without further purification.

Mesylate (ca. 11.3 mmol) prepared above was dissolved in dry acetone (75 mL) and treated with an excess of NaI (16.0 g, 106 mmol) under an argon atmosphere. After being stirred for 8 h, the reaction mixture was diluted with ether (300 mL), washed with H_2O (2 × 30 mL), saturated aqueous $Na_2S_2O_3$ (30 mL), saturated aqueous $NaHCO_3$ (30 mL), and brine (30 mL), and dried ($MgSO_4$). Evaporation and purification by flash column chromatography (silica, 10% ether in petroleum ether) produced pure iodide **23** (9.02 g, 98%). **23**: colorless oil; R_f 0.30 (silica, 20% ether in petroleum ether); $[\alpha]^{20}_D$ +9.8° (*c* 1.23, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3000, 2950, 2860, 1370 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, TMS) δ 7.73–7.27 (m, 15 H, aromatic), 4.53, 4.47 (doublets, *J* = 12.0 Hz, 2 H, benzyl), 3.94–3.47 (m, 7 H, C*H*O, CH_2O), 3.20 (m, 2 H, CH_2I), 1.88 (m, 2 H, CH_2), 1.72 (m, 2 H, CH_2), 1.5–1.0 (m, 8 H, CH_2), 1.32, 1.31, 1.26, and 1.18 (singlets, 12 H total, acetonides), 1.05 (s, 9 H, Si-*t-Bu*); HRMS (FAB) calcd for $C_{42}H_{59}O_6SiI$ − *t*-Bu 757.2421, found, 757.2404 (M − *t*-Bu).

Phosphonate 24. To a magnetically stirred solution of dimethyl phosphite (2.67 g ≡ 2.2 mL, 24.2 mmol) in dry DME (25 mL) and dry DMF (15 mL) was added NaH (0.968 g, 60% in mineral oil, 24.2 mmol) under argon at 25 °C. The mixture was heated to 45 °C, stirred for 0.5 h, and then cooled to room temperature. To this was added iodide **23** (9.02 g, 11.0 mmol) in DME (20 mL), and the mixture was once again heated to 45 °C. After 1 h, the reaction was complete and the solution was cooled and diluted with ether (300 mL), washed with H_2O (3 × 20 mL) and brine (20 mL), and dried ($MgSO_4$). Removal of the solvent and purification by flash column chromatography (silica, 2.5% MeOH in ether) gave pure phosphonate **24** (8.50 g, 97%). **24**: colorless oil; R_f 0.25 (silica, 2.5% MeOH in ether); $[\alpha]^{20}_D$ +4.3° (*c* 0.28, MeOH); IR ($CHCl_3$) ν_{max} 3000, 2960, 2870, 1390 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, TMS) δ 7.72–7.27 (m, 15 H, aromatic), 4.54, 4.48 (doublets, *J* = 12.0 Hz, 2 H, benzyl), 4.09–3.49 (m, 7 H, C*H*O, CH_2O), 3.72 (d, *J* = 10.8 Hz, 3 H, $P(O)OCH_3$), 3.71 (d, *J* = 11.2 Hz, 3 H, $P(O)OCH_3$), 1.94–0.98 (m, 12 H, CH_2), 1.75 (m, 2 H, $CH_2P(O)$), 1.32, 1.31, 1.22, and 1.18 (singlets, 12 H total, acetonides), 1.04 (s, 9 H, Si-*t-Bu*); HRMS (FAB) calcd for $C_{44}H_{65}O_9PSi$ + H 797.4214, found 797.4182 (M + H). Anal. Calcd for $C_{44}H_{65}O_9PSi$: C, 66.30; H, 8.22; P, 3.89. Found: C, 66.06; H, 7.99; P, 3.67.

Methylthio Phosphonate 25. A solution of phosphonate **24** (8.13 g, 10.2 mmol) in dry THF (100 mL) was degassed by bubbling a stream of argon through the solution for 20–30 min. This solution of phosphonate **22** was then added to a stirred solution of LDA (11.4 mmol), prepared from diisopropylamine (DIPA, 1.15 g ≡ 1.6 mL, 11.4 mmol) and *n*-BuLi (7.1 mL, 1.6 M solution in hexane, 11.4 mmol), in THF (10 mL) at −78 °C under argon. The solution was stirred for 0.5 h and then transferred via canula into a cooled (−78 °C) solution of Me_2S_2 (1.05 g ≡ 51.0 mL, 11.2 mmol) in THF (5 mL). The reaction mixture was stirred at −78 °C for 5 min and then quenched with saturated aqueous NH_4Cl (20 mL) and diluted with ether (250 mL). The organic layer was separated and washed with 5% aqueous HCl (10 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL) and dried ($MgSO_4$). Evaporation and flash column chromatography (silica, 1% MeOH in ether) afforded pure α-methylthio phosphonate **25** (6.71 g, 78%) as a diastereomeric mixture (ca. 1:1 ratio). **25**: colorless oil; R_f 0.23 (silica, ether); $[\alpha]^{20}_D$ +4.6° (*c* 0.24, $CHCl_3$, ca. 2:1 ratio); IR ($CHCl_3$) ν_{max} 3000, 1960, 2860, 1430, 1380 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, TMS) δ 7.72–7.28 (m, 15 H, aromatic), 4.54, 4.48 (doublets, *J* = 12.0 Hz, 2 H, benzyl), 4.15–3.49 (m, 7 H, C*H*O, CH_2O), 3.80 (d, *J* = 10.4 Hz, 3 H, $P(O)OCH_3$), 3.70 (d, *J* = 10.4 Hz, 3 H, $P(O)OCH_3$), 2.95 and 2.80 (multiplets, ca. 2:1 ratio, 1 H total, C*H*P(O)), 2.24 and 2.22 (singlets, ca. 2:1 ratio, 3 H total, epimeric S*Me*), 1.97–0.98 (m, 12 H, CH_2), 1.30, 1.23, and 1.15 (singlets, 12 H total, acetonides), 1.02 (s, 9 H, Si-*t-Bu*); HRMS (FAB) calcd for $C_{45}H_{67}O_9PSSi$ + H 843.4091, found 843.4019 (M + H). Anal. Calcd for $C_{45}H_{67}O_9PSSi$: C, 64.10; H, 8.01; P, 3.67; S, 3.80. Found: C, 64.40; H, 7.82; P, 3.45; S, 3.91.

Vinyl Sulfide 26. A solution of phosphonate **25** (7.26 g, 8.61 mmol) in dry THF (40 mL) was degassed by bubbling a stream of argon through the solution for 20–30 min. The solution of phosphonate **23** was then added to a stirred solution of LDA (10.7 mmol), prepared from diisopropylamine (DIPA, 1.08 g ≡ 1.5 mL, 10.7 mmol) and *n*-BuLi (6.7 mL, 1.6 M solution in hexane, 10.7 mmol), in dry THF (5 mL), at −78 °C under argon. After the mixture was stirred for 0.5 h, a solution of aldehyde **8** (5.08 g, 10.3 mmol), which had also been degassed in a similar fashion, in dry THF (15 mL), was dropwise added to the solution containing the phosphonate anion. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. After a total reaction time of 2 h, the mixture was diluted with ether (200 mL), washed with saturated aqueous $NaHCO_3$ (3 × 20 mL) and brine (20 mL), and dried (Na_2SO_4). Removal of the solvent and flash column chromatography (silica, 30% ether in petroleum ether) produced pure vinyl sulfide **26** (9.37 g, 90%) as a mixture of geometrical isomers (ca. 1:1 ratio). **26**: white amorphous solid; R_f 0.16 and 0.19 (silica, 20% ether in petroleum ether); $[\alpha]^{20}_D$ −48.5° (*c* 1.06, $CHCl_3$, more polar isomer); IR ($CHCl_3$) ν_{max} 3000, 2960, 2940, 2860, 1475, 1385 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, TMS, more polar isomer) δ 7.75–7.25 (m, 10 H, aromatic), 5.62 (d, *J* = 8.7 Hz, 1 H, vinyl), 5.52 (s, 1 H benzylidene), 4.81 (dd, *J* = 10.4, 8.7 Hz, 1 H, C*H*O), 4.52, 4.46 (doublets, *J* = 12.0 Hz, 2 H, benzyl), 4.35 (dd, *J* = 11.2, 4.4 Hz, 1 H, C*H*O), 4.0–3.4 (m, 11 H, C*H*O, CH_2O), 2.45 (dd, *J* = 15.0, 7.0 Hz, 1 H, allylic), 2.35 (dd, *J* = 15.0, 4.2 Hz, 1 H, allylic), 2.20 (s, 3 H, S*Me*), 1.80–0.85 (m, 13 H, C*H*, CH_2), 1.30, 1.28, 1.23, and 1.20 (singlets, 12 H total, acetonides), 1.02, 0.88, and 0.87 (singlets, 27 H total, Si-*t-Bu*), 0.73, 0.030, and 0.011 (singlets, 12 H total, $SiMe_2$); HRMS (FAB) calcd for $C_{69}H_{106}O_{10}Si_3S$ + NH_4 1228.7158, found 1228.7130 (M + NH_4). Anal. Calcd for $C_{69}H_{106}O_{10}Si_3S$: C, 68.38; H, 8.82; S, 2.64. Found: C, 68.19; H, 8.92; S, 2.65.

Diol 27. To a magnetically stirred solution of vinyl sulfide **26** (9.37 g, 7.73 mmol) in THF (10 mL) under argon was added a solution of tetrabutylammonium fluoride (80 mL, 1 M solution in THF, 80 mmol), and stirring was continued for 10 h. The reaction mixture was diluted

with EtOAc (250 mL), washed with H_2O (3 × 20 mL) and brine (20 mL), and dried (Na_2SO_4). Evaporation and purification of flash column chromatography (silica, 75% EtOAc in petroleum ether) afforded pure triol **27** (5.53 g, 96%) as a mixture of geometrical isomers (ca. 1:1 ratio). **27**: white amorphous solid; R_f 0.38 (silica, EtOAc); $[\alpha]^{20}_D$ −28.5° (*c* 0.73, $CHCl_3$, ca. 2.3:1 ratio); IR ($CHCl_3$) ν_{max} 3500 (m, OH), 3010, 2960, 1390 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, TMS) δ 7.51–7.27 (m, 10 H, aromatic), 5.72 and 5.35 (doublets, ca. 2.3:1 ratio, *J* = 9.0 Hz, 1 H total, vinyl), 5.55 and 5.51 (singlets, ca. 2.3:1 ratio, 1 H total, benzylidene), 4.89 and 4.63 (double doublets, ca. 2.3:1 ratio, *J* = 9.5 Hz, 1 H total, C*H*O), 4.52, 4.46 (doublets, *J* = 12.0 Hz, 2 H, benzyl), 4.35 (dd, *J* = 11.2, 4.5 Hz, 1 H, C*H*O), 4.25–3.40 (m, 11 H, C*H*O, CH_2O), 3.23 and 3.10 (doublets, ca. 2.3:1 ratio, *J* = 2.7 Hz, 1 H total, O*H*), 3.05 (m, 2 H, O*H*), 2.82 (dd, *J* = 14.5, 4.2 Hz, 1 H, allylic) 2.68 (dd, *J* = 14.6, 6.0 Hz, 1 H, allylic), 2.40–2.10 (m, 3 H, C*H*, CH_2), 2.27 (s, 3 H, S*Me*), 1.80–1.10 (m, 10 H, C*H*, CH_2), 1.47, 1.43, 1.40, and 1.38 (singlets, 12 H total, acetonides); HRMS (FAB) calcd for $C_{41}H_{60}O_{10}S$ 744.3907, found: 744.3901 (M^+).

Methyl 19-*O*-Benzyl-4^1,5-*O*-benzylidene-2,4,6,8,10,13,14,16,18-nonadeoxy-4-(hydroxymethyl)-9,11:15,17-di-*O*-isopropylidene-7-thio-L-*glycero*-L-*gulo*-L-*lyxo*-7-nonadeculo-7,3-pyranoside and Isomer (28cd). To a magnetically stirred solution of vinyl sulfide **27** (2.60 g, 3.48 mmol) in dry CH_2Cl_2 (340 mL) under argon was added pyridinium *p*-toluenesulfonate (PPTS, 220 mg, 0.87 mmol). Stirring was continued for 24 h at which time the reaction was quenched with saturated aqueous $NaHCO_3$ (30 mL) and the organic layer was washed with brine (30 mL) and dried ($MgSO_4$). Evaporation and purification by flash column chromatography (silica, 1% MeOH in ether) gave pure mixed thioketal **28cd** (1.94 g, 75%) as a mixture of at least two isomers. **28cd**: white amorphous solid; R_f 0.26 and 0.30 (silica, 1% MeOH in ether); $[\alpha]^{20}_D$ −51.5° (*c* 0.56, $CHCl_3$, ca. 2:1 ratio); IR ($CHCl_3$) ν_{max} 3500 (m, OH), 3000, 2940, 2920, 1380 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, TMS) δ 7.50–7.28 (m, 10 H, aromatic), 5.61 and 5.59 (singlets, ca. 2:1 ratio, 1 H total, benzylidene), 4.52, 4.46 (doublets, *J* = 12.0 Hz, 2 H, benzyl), 4.30–3.40 (m, 13 H, C*H*O, CH_2O), 2.77 (d, *J* = 3.8 Hz, 1 H, O*H*), 2.73 (m, 1 H, O*H*), 2.30–1.15 (m, 17 H, C*H*, CH_2), 2.01 and 1.95 (singlets, ca. 2:1 ratio, 3 H total, S*Me*), 1.45, 1.42, and 1.36 (singlets, 12 H total, acetonides); HRMS (FAB) calcd for $C_{41}H_{60}O_{10}S$ + H 745.3985, found 745.3947 (M + H).

Methyl 19-*O*-Benzyl-4^1,5-*O*-benzylidene-2,4,6,8,10,13,14,16,18-nonadeoxy-4-(hydroxymethyl)-9,11:15,17-di-*O*-isopropylidene-L-*glycero*-L-*gulo*-L-*lyxo*-7-nonadeculo-7,3-pyranoside and Isomer (29cd). A solution of thioketal **28cd** (1.68 g, 2.26 mmol) and ground 3A molecular sieves (5 g) in dry CH_2Cl_2 (100 mL) was stirred under argon for 0.5 h. To this was added anhydrous MeOH (10 mL), and the mixture was cooled to 0 °C. After an additional 10 min, freshly recrystallized *N*-bromosuccinimide (40.2 mg, 2.26 mmol) was added, and the reaction mixture was allowed to stir for 10 min. The mixture was diluted with ether (250 mL), filtered through a pad of Celite, washed with saturated aqueous $Na_2S_2O_3$ (20 mL), 10% aqueous KOH (3 × 20 mL), H_2O (20 mL), and brine (20 mL), and dried ($MgSO_4$). Evaporation and flash column chromatography (silica, 2.5% MeOH in ether) provided pure methyl ketal **29cd** (1.61 g, 98%) as a mixture of two isomers. **29cd**: white amorphous solid; R_f 0.20 and 0.38 (silica, 2.5% MeOH in ether); $[\alpha]^{20}_D$ −34.4° (*c* 0.75, $CHCl_3$, ca. 1.5:1 ratio); IR ($CHCl_3$) ν_{max} 3500 (m, OH), 3000, 2950, 2880, 1385 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, TMS) δ 7.50–7.27 (m, 10 H, aromatic), 5.60 and 5.58 (singlets, ca. 1.5:1 ratio, 1 H total, benzylidene), 4.52, 4.46 (doublets, *J* = 12.0 Hz, 2 H, benzyl), 4.20–3.41 (m, 13 H, C*H*O, CH_2O), 3.24 and 3.20 (singlets, ca. 1.5:1 ratio, 3 H total, O*Me*), 2.77 (d, *J* = 3.8 Hz, 1 H, O*H*), 2.72 (m, 1 H, O*H*), 2.22–1.14 (m, 17 H, C*H*, CH_2), 1.41 and 1.36 (singlets, 12 H total, acetonides); HRMS (FAB) calcd for $C_{41}H_{60}O_{11}$ + H 729.4214, found 729.4202 (M + H). Anal. Calcd for $C_{41}H_{60}O_{11}$: C, 67.56; H, 8.30. Found: C, 67.50; H, 8.39. The two isomers **29c** and **29d** were chromatographically separated, and their diacetates were prepared under standard conditions for ^1H NMR studies. Thus, the ^1H NMR spectrum (500 MHz) of the acetate derived from **29d** exhibited signals at δ 4.85 and 3.95 for (amphotericin B numbering) H-8 and H-9, respectively, which were coupled to each other (decoupling, $J_{8,9}$ = 5 Hz). Such coupling was absent in the ^1H NMR spectrum of the acetate of **29c** thus confirming the structural assignments of these isomers.

Methyl 19-*O*-Benzyl-4^1,5-*O*-benzylidene-2,4,6,8,10,13,14,16,18-nonadeoxy-4-(hydroxymethyl)-9,11:15,17-di-*O*-isopropylidene-L-*glycero*-L-*gulo*-L-*lyxo*-7-nonadeculo-7,3-pyranoside 1-Pivalate and Isomer (30cd). Trimethylacetyl chloride (0.293 g ≡ 0.30 mL, 2.43 mmol) was slowly added to a stirred solution of alcohol **29cd** (1.61 g, 2.21 mmol) in dry pyridine (20 mL) at 0 °C under argon. The reaction mixture was maintained at 0 °C for 4 h and then diluted with ether (200 mL), washed with H_2O (3 × 20 mL), saturated aqueous $CuSO_4$ (2 × 20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL), and dried ($MgSO_4$). Evaporation and purification by flash column chromatography (silica, 70% ether in petroleum ether) afforded pure pivalate **30cd** (1.56 g, 86%) as a mixture of isomers. **30cd**: white foam; R_f 0.12 and 0.22 (silica, 60% ether in petroleum ether); $[\alpha]^{20}_D$ −39.5° (*c* 0.59, $CHCl_3$, ca. 1.6:1 ratio); IR ($CHCl_3$) ν_{max} 3520 (m, OH), 3000, 1730 (s, C=O), 1390 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, TMS) δ 7.50–7.27 (m, 10 H, aromatic), 5.60 and 5.58 (singlets, ca. 1.6:1 ratio, 1 H total, benzylidene), 4.52, 4.47 (doublets, *J* = 12.0 Hz, 2 H, benzyl), 4.30–3.35 (m, 13 H, C*H*O, CH_2O), 3.20 and 3.12 (singlets, ca. 1.6:1 ratio, 3 H total, OCH_3), 2.22 and 2.20 (double doublets, ca. 1.6:1 ratio, *J* = 13.0, 4.4 Hz, 1 H total, H-6), 2.05–1.95 (m, 1 H, H-6′), 2.05–1.10 (m, 15 H, C*H*, CH_2), 1.41, 1.37, and 1.35 (singlets, 12 H total, acetonides), 1.20 (s, 9 H, *t-Bu*); HRMS (FAB) calcd for $C_{46}H_{68}O_{12}H$ H 811.4631, found 811.4626 (M − H).

Methyl 19-*O*-Benzyl-4^1,5-*O*-benzylidene-12-*O*-(*tert*-butyldimethylsilyl)-2,4,6,8,10,13,14,16,18-nonadeoxy-4-(hydroxymethyl)-9,11:15,17-di-*O*-isopropylidene-L-*glycero*-L-*gulo*-L-*lyxo*-7-nonadeculo-7,3-pyranoside and Isomer (31ab). Hydroxy pivalate ester **30cd** (1.56 g, 1.92 mmol) was dissolved in dry DMF (4 mL) and treated with imidazole (920 mg, 13.4 mmol) and *t*-BuMe_2SiCl (720 mg, 4.80 mmol) under argon. The reaction mixture was heated to 45 °C and stirred for 3 h. The mixture was cooled to room temperature, diluted with ether (100 mL), washed with H_2O (3 × 20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL), and dried ($MgSO_4$). Removal of the solvent and purification of flash column chromatography (silica, 30% ether in petroleum ether) provided pure silyloxy pivalate (1.71 g, 96%) as a mixture of isomers. Silyloxy pivalate: white foam; R_f 0.17 (silica, 30% ether in petroleum ether); $[\alpha]^{20}_D$ −32.2° (*c* 1.05, $CHCl_3$, ca. 1.2:1 ratio); IR ($CHCl_3$) ν_{max} 3000, 2960, 1730 (s, C=O), 1390 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, TMS) δ 7.50–7.27 (m, 10 H, aromatic), 5.59 and 5.58 (singlets, ca. 1.2:1 ratio), 1 H total, benzylidene), 4.52, 4.46 (doublets, *J* = 12.0 Hz, 2 H, benzyl), 4.32–3.40 (m, 13 H, C*H*O, CH_2O), 3.25 and 3.11 (singlets, ca. 1.2:1 ratio, 3 H total, OCH_3), 3.23 and 2.25 (double doublets, ca. 1.2:1 ratio, *J* = 13.4, 4.4 Hz, 1 H total, H-6), 2.10 (dd, *J* = 13.4, 4.2 Hz, 1 H, H-6′), 1.93–1.11 (m, 15 H, C*H*, CH_2), 1.39 and 1.36 (singlets, 12 H total, acetonides), 1.20 (s, 9 H, *t-Bu*), 0.89 and 0.87 (singlets, ca. 1.2:1 ratio, 9 H total, Si-*t-Bu*), 0.10, 0.083 and 0.045 (singlets, 6 H total, SiMe_2); HRMS (FAB) calcd for $C_{52}H_{82}O_{12}Si$ − H 925.5497, found 925.5459 (M − H).

To a magnetically stirred solution of the above prepared silyloxy pivalate (1.71 g, 1.83 mmol) in dry CH_2Cl_2 (10 mL) at −78 °C under argon was added DIBAL (5.5 mL, 1 M solution in hexane, 5.5 mmol). After 15 min, the reaction was quenched with EtOAc (5 mL) and warmed to room temperature. The mixture was diluted with ether (100 mL), washed with saturated aqueous potassium sodium tartrate (20 mL) and brine (20 mL), and dried ($MgSO_4$). Evaporation and flash column chromatography (silica, 80% ether in petroleum) afforded pure primary alcohol **31ab** (1.51 g, 98%) as a mixture of isomers. **31ab**: white amorphous solid; R_f 0.22 (silica, 80% ether in petroleum ether); $[\alpha]^{20}_D$ −24.8° (*c* 0.21, $CHCl_3$, ca. 1.2:1 ratio); IR ($CHCl_3$) ν_{max} 3520 (m, OH), 3000, 2960, 1390 cm^{-1}; ^1H NMR (250 Hz, $CDCl_3$, TMS) δ 7.50–7.25 (m, 10 H, aromatic), 5.57 (s, 1 H, benzylidene), 4.52, 4.46 (doublets, *J* = 12.0 Hz, 2 H, benzyl), 4.16–3.44 (m, 13 H, C*H*O, CH_2O), 3.16 (s, 3 H, OCH_3), 2.40 (m, 1 H, O*H*), 2.25 (dd, *J* = 14.0, 4.4 Hz, 1 H, H-6), 2.05 (dd, *J* = 14.0, 4.2 Hz, 1 H, H-6′), 1.90–1.10 (m, 15 H, C*H*, CH_2), 1.39, 1.34, and 1.32 (singlets, 12 H total, acetonides), 0.87 (s, 9 H, Si-*t-Bu*), 0.088 and 0.068 (singlets, 6 H total, SiMe_2); HRMS (FAB) calcd for $C_{47}H_{74}O_{11}Si$ + H 843.5079, found 843.5066 (M + H). Anal. Calcd for $C_{47}H_{74}O_{11}Si$: C, 66.95; H, 8.85. Found: C, 67.26; H, 8.86.

Methyl [Methyl 19-*O*-benzyl-4^1,5-*O*-benzylidene-12-*O*-(*tert*-butyldimethylsilyl)-2,4,6,8,10,13,14,16,18-nonadeoxy-4-(hydroxymethyl)-9,11:15,17-di-*O*-isopropylidene-L-*glycero*-L-*gulo*-L-*lyxo*-7-nonadeculo-7,3-pyranosid]onate and Isomer (32ab). To a magnetically stirred solution of alcohol **31ab** (1.45 g, 1.72 mmol) in dry DMF (7 mL) under argon was added PDC (3.20 g, 8.60 mmol). The reaction mixture was stirred for 10 h and then diluted with DMF (7 mL) and poured into ether (150 mL). The ethereal solution was washed with H_2O (4 × 20 mL) and brine (20 mL). The solvent volume was reduced to about 10 mL and then cooled to 0 °C. This solution was then treated with an ethereal solution of diazomethane followed by removal of the excess diazomethane (stream of argon) and drying ($MgSO_4$). Evaporation and flash column chromatography (silica, 50% ether in petroleum ether) produced pure methyl ester **32ab** (1.23 g, 82%) as a mixture of isomers. **32ab**: white amorphous solid; R_f 0.12 (silica, 40% ether in petroleum ether); $[\alpha]^{20}_D$ −33.4° (*c* 1.05, $CHCl_3$, ca. 1.2:1 ratio); IR ($CHCl_3$) ν_{max} 3000, 2960, 2860, 1740 (s, C=O), 1385 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, TMS) δ 7.50–7.27 (m, 10 H, aromatic), 5.59 and 5.58 (singlets, ca. 1.2:1 ratio, 1 H total, benzylidene), 4.50 (s, 2 H, benzyl), 4.15–3.48 (m, 11 H, C*H*O, CH_2O), 3.70 (s, 3 H, methyl ester), 3.22 and 3.17 (singlets, ca. 1.2:1 ratio, 3 H total, OCH_3), 2.45 (m, 2 H, CH_2COOMe), 2.30 (m, 1 H,

H-6), 2.10 (dd, J = 15.0, 4.4 Hz, 1 H, H-6'), 1.92–1.05 (m, 13 H, C*H*, CH_2), 1.41, 1.39, 1.35, 1.33, and 1.32 (singlets, 12 H total, acetonides), 0.88 and 0.87 (singlets, ca. 1.2:1 ratio, 9 H total, Si-*t*-Bu), 0.094, 0.078 and 0.043 (singlets, 6 H total, Si-*t*-Me_2); HRMS (FAB) calcd for $C_{48}H_{74}O_{12}Si$ – H 869.4871, found 869.4903 (M – H).

Methyl [Methyl 19-*O*-benzyl-4^1,5-*O*-benzylidene-12-*O*-(*tert*-butyldimethylsilyl)-2,4,6,8,10,13,14,16,18-nonadeoxy-4-(hydroxymethyl)-9,11:15,17-di-*O*-isopropylidene-L-*glycero*-L-*gulo*-L-*lyxo*-7-nonadeculo-7,3-pyranosid]onate 19-Acetate and Isomer (33ab). A solution of benzyl ether **32ab** (2.02 g, 2.32 mmol) in absolute EtOH (100 mL) and 10% Pd–C (200 mg) was vigorously stirred under a H_2 atmosphere for 48 h. The H_2 was purged with argon, and the solution was filtered through a pad of Celite. Evaporation and flash column chromatography (silica, 80% ether in petroleum ether) provided pure primary alcohol (1.21 g, 67%) as a mixture of isomers. Primary alcohol: white amorphous solid; R_f 0.23 (silica, ether); $[\alpha]^{20}_D$ –35.2° (c 0.60, $CHCl_3$, ca. 1.2:1 ratio); IR ($CHCl_3$) ν_{max} 3500 (m, OH), 3000, 2860, 3860, 1740 (s, C=O), 1385 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$, TMS) δ 7.50–7.32 (m, 5 H, aromatic), 5.60 and 5.59 (singlets, ca. 1.2:1 ratio), 1 H total, benzylidene), 4.20–3.50 (m, 11 H, C*H*O, CH_2O), 3.71 and 3.70 (singlets, ca. 1.2:1 ratio, 3 H total, methyl ester), 3.22 and 3.18 (singlets, ca. 1.2:1 ratio, 3 H total, OCH_3), 3.55 (m, 1 H, O*H*), 2.45 (m, 2H, CH_2COOMe), 2.27 (m, 1 H, H-6), 2.10 (dd, J = 14.9, 4.6 Hz, 1 H, H-6'), 1.95–0.80 (m, 13 H, C*H*, CH_2), 1.45, 1.44, 1.39, 1.37, 1.36, and 1.33 (singlets, 12 H total, acetonides), 0.89 and 0.87 (singlets, ca. 1.2:1 ratio, 9 H total, Si-*t*-*Bu*), 0.096, 0.080 and 0.047 (singlets, 6 H total, SiMe_2); HRMS (FAB) calcd for $C_{41}H_{68}O_{12}Si$ – H 779.4402, found 779.4420 (M – H).

The primary alcohol prepared above (1.21 g, 1.55 mmol) and DMAP (944 mg, 7.74 mmol) were dissolved in dry CH_2Cl_2 (20 mL) under argon and cooled to 0 °C. This solution was treated with Ac_2O (0.316 g ≡ 0.29 mL, 3.10 mmol) and stirred for 10 min. The reaction mixture was diluted with ether (200 mL), washed with H_2O (2 × 20 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine (20 mL), and dried ($MgSO_4$). Evaporation and purification by flash column chromatography (silica, 50% ether in petroleum ether) gave pure acetate **33ab** (1.27 g, 100%) as a mixture of methoxy anomers (ca. 1:1 ratio). **33ab**: white amorphous solid; R_f 0.30 (silica, 60% ether in petroleum ether); $[\alpha]^{20}_D$ –31.1° (c 0.64, $CHCl_3$, ca. 1.1:1 ratio); IR ($CHCl_3$) ν_{max} 3000, 2960, 2860, 1740 (s, C=O), 1390 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$, TMS) δ 7.50–7.32 (m, 5 H, aromatic), 5.60 and 5.58 (singlets, ca. 1.1:1 ratio, 1 H total, benzylidene), 4.16 (t, J = 6.5 Hz, 2 H, CH_2OAc), 4.10–3.50 (m, 9H, C*H*O, CH_2O), 3.71 and 3.70 (singlets, ca. 1.1:1 ratio, 3 H total, methyl ester), 3.22 and 3.18 (singlets, ca. 1.1:1 ratio, 3 H total, OCH_3), 2.45 (m, 2 H, CH_2COOMe), 2.33–2.15 (m, 2 H, H-6, H-6'), 2.04 (s, 3 H, acetate), 2.0–1.10 (m, 13 H, C*H*, CH_2), 1.40, 1.39, 1.36, 1.33, and 1.32 (singlets, 12 H total, acetonides), 0.88 and 0.87 (singlets, ca. 1.1:1 ratio, 9 H total, Si-*t*-*Bu*), 0.095, 0.079 and 0.045 (singlets, 6 H total, SiMe_2); HRMS (FAB) calcd for $C_{43}H_{70}O_{13}Si$ – H 821.4508, found 821.4505. Anal. Calcd for $C_{43}H_{70}O_{13}Si$: C, 62.74; H, 8.57. Found: C, 62.84; H, 8.73.

Methyl [Methyl 12-*O*-(*tert*-butyldimethylsilyl)-2,4,6,8,10,13,14,16,18-nonadeoxy-4-(hydroxymethyl)-9,11:15,17-di-*O*-isopropylidene-L-*glycero*-L-*gulo*-L-*lyxo*-7-nonadeculo-7,3-pyranosid]onate 19-Acetate (34ab). A solution of acetate **33ab** (2.68 g, 3.25 mmol) in absolute MeOH (60 mL; distilled from $Mg(OMe)_2$ and 10% Pd–C (480 mg) was vigorously stirred under a H_2 atmosphere for 48 h. The H_2 was purged with argon, and the solution was filtered through a pad of Celite. Evaporation and flash column chromatography (silica, 5% MeOH in CH_2Cl_2) provided pure diol **34ab** (1.82 g, 76%) as a mixture of isomers. **34ab**: white amorphous solid; R_f 0.14 and 0.16 (silica, 5% MeOH in CH_2Cl_2); $[\alpha]^{20}_D$ –22.9° (c 0.84, $CHCl_3$, ca. 2.4:1 ratio); IR ($CHCl_3$) ν_{max} 3450 (m, OH), 3000, 2960, 2860, 1740 (s, C=O), 1385, 1250 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$, TMS) δ 4.16 (t, J = 6.5 Hz, 2 H, CH_2OAc), 4.10–3.45 (m, 9 H, C*H*O, CH_2O), 3.70 and 3.69 (singlets, ca. 1.2:4 ratio, 3 H total, methyl ester), 3.15 and 3.12 (singlets, ca. 1:2.4 ratio, 3 H total, OCH_3), 2.85–2.15 (m, 6 H, CH_2C(O), CH_2, O*H*), 2.02 (s, 3 H, acetate), 1.90–1.10 (m, 13 H, C*H*, CH_2), 1.41 and 1.36 (singlets, 12 H total, acetonides), 0.89 and 0.87 (singlets, ca. 1:2.4 ratio, 9 H total, Si-*t*-*Bu*), 0.10, 0.084 and 0.049 (singlets, 6 H total, SiMe_2); HRMS (FAB) calcd for $C_{36}H_{66}O_{13}Si$ – Me 719.4038, found 719.4006 (M – Me).

[Methyl 12-*O*-(*tert*-butyldimethylsilyl)-2,4,6,8,10,13,14,16,18-nonadeoxy-4-(hydroxymethyl)-9,11:15,17-di-*O*-isopropylidene-L-*glycero*-L-*gulo*-L-*lyxo*-7-nonadeculo-7,3-pyranosid]onic Acid 1,4^1-Lactone 19-Acetate and Isomer (35ab). To a magnetically stirred solution of diol **34ab** (1.82 g, 2.47 mmol) and ground 3A molecular sieves in dry acetonitrile (25 mL) under argon was added imidazole (844 mg, 12.4 mmol). The reaction mixture was stirred for 10 h at 25 °C and then diluted with ether (200 mL) and filtered through a pad of Celite. The solution was then washed with H_2O (2 × 20 mL) and brine (20 mL) and dried ($MgSO_4$). Evaporation and flash column chromatography (silica, 5% MeOH in CH_2Cl_2) produced pure lactone **35ab** (1.32 g, 76%) as a mixture of isomers. **35ab**: white amorphous solid; R_f 0.28 and 0.33 (silica, 5% MeOH in CH_2Cl_2); $[\alpha]^{20}_D$ +6.9° (c 0.85, $CHCl_3$, ca. 1.9:1 ratio); IR ($CHCl_3$) ν_{max} 3450 (m, OH), 3000, 2960, 2940, 2860, 1740 (s, C=O), 1390 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$, TMS) δ 4.73 (dd, J = 11.5, 4.9 Hz, 1 H, C*H*O (lactone)), 4.16 (t, J = 6.5 Hz, 2 H, CH_2OAc), 4.10–3.50 (m, 8 H, C*H*O, C*H*O (lactone), 3.15 and 3.09 (singlets, ca. 1.9:1 ratio, 3 H total, OCH_3), 2.95 (dd, J = 17.6, 6.1 Hz, 1 H, C*H*C(O)), 2.60–2.30 (m, 3 H, C*H*C(O), CH_2), 2.13 (d, J = 3.1 Hz, 1 H, O*H*), 2.05 (s, 3 H, acetate), 1.82–1.10 (m, 13 H, C*H*, CH_2), 1.41, 1.36, and 1.34 (singlets, 12 H total, acetonides), 0.90 and 0.88 (singlets, ca. 1.9:1 ratio, 9 H total, Si-*t*-*Bu*), 0.10, 0.099 and 0.053 (singlets, 6 H total, SiMe_2); HRMS (FAB) calcd for $C_{35}H_{62}O_{12}Si$ + H 703.4089, found 703.4063 (M + H).

[Methyl 5,12-bis-*O*-(*tert*-butyldimethylsilyl)-2,4,6,8,10,13,14,16,18-nonadeoxy-4-(hydroxymethyl)-9,11:15,17-di-*O*-isopropylidene-L-*glycero*-L-*gulo*-L-*lyxo*-7-nonadeculo-7,3-pyranosid]onic Acid 1,4^1-Lactone 19-Acetate and Isomer (36ab). To a magnetically stirred solution of alcohol and isomer **35ab** (1.32 g, 1.88 mmol) in dry CH_2Cl_2 (15 mL) was added 2,6-lutidine (0.261 g ≡ 0.28 mL, 2.44 mmol) under argon; the solution was then cooled to 0 °C. To this was slowly added *t*-$BuMe_2SiOTf$ (0.547 g ≡ 0.48 mL, 2.07 mmol), and stirring was continued for 10 min at 0 °C. The reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL), and the mixture was diluted with ether (100 mL). The organic layer was washed with saturated aqueous $CuSO_4$ (2 × 15 mL), saturated aqueous $NaHCO_3$ (15 mL), and brine (15 mL), and dried ($MgSO_4$). Evaporation and purification by flash column chromatography (silica, 70% ether in petroleum ether) afforded pure disilyl ether **36ab** (1.23 g, 80%) as a mixture of isomers. **36ab**: white amorphous solid; R_f 0.16 and 0.22 (silica, 60% ether in petroleum ether); $[\alpha]^{20}_D$ +8.8° (c 1.03, $CHCl_3$, ca. 1:1 ratio); IR ($CHCl_3$) ν_{max} 3000, 2960, 2940, 2860, 1740, (s, C=O), 1385 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$, TMS) δ 4.55 (dd, J = 11.5, 6.1 Hz, 1 H, C*H*O (lactone)), 4.14 (t, J = 6.5 Hz, 2 H, CH_2OAc), 4.10–3.50 (m, 8 H, C*H*O, C*H*O (lactone)), 3.12 and 3.07 (singlets, ca. 1:1 ratio, 3 H total, OCH_3), 2.90 (dd, J = 17.6, 6.1 Hz, 1 H, C*H*C(O)), 2.48 (dd, J = 17.6, 11.4 Hz, 1 H, C*H*C(O)), 2.20 (m, 2 H, CH_2), 2.02 (s, 3 H, acetate), 1.95–1.00 (m, 13 H, C*H*, CH_2), 1.38, 1.33, and 1.32 (singlets, 12 H total, acetonides), 0.87 and 0.85 (singlets, 18 H total, Si-*t*-*Bu*), 0.067, 0.042, 0.028, and 0.016 (singlets, 12 H total, SiMe_2); HRMS (FAB) calcd for $C_{41}H_{76}O_{12}Si_2$ 817.4954, found 817.4938 (M + H); Anal. Calcd for $C_{41}H_{76}O_{12}Si_2$: C, 60.26; H, 9.37. Found: C, 60.33; H, 9.18.

[Methyl 5,12-bis-*O*-(*tert*-butyldimethylsilyl)-4-carboxy-2,4,6,8,10,13,14,16,18-nonadeoxy-9,11:15,17-di-*O*-isopropylidene-L-*glycero*-L-*gulo*-L-*lyxo*-7-nonadeculo-7,3-pyranosid]onic Acid Dimethyl Ester 19-Acetate and Isomer (37ab). To a magnetically stirred solution of lactone **36ab** (1.23 g, 1.51 mmol) in THF (15 mL) at 0 °C was added aqueous LiOH (2.66 mL, 1 M solution, 1.66 mmol), and the mixture was stirred for 20 min. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and diluted with ether (75 mL). The organic layer was washed with H_2O (5 mL) and brine (5 mL) and concentrated. The residue was diluted with ether (10 mL), cooled to 0 °C, and treated with diazomethane as previously described for methyl ester **32ab**. Evaporation and flash column chromatography (silica, 60% ether in petroleum ether) afforded pure hydroxy ester (1.26 g, 98%) as a mixture of isomers. Hydroxy ester: white amorphous solid; R_f 0.28 (silica, 60% ether in petroleum ether); $[\alpha]^{20}_D$ –0.83° (c 0.72, $CHCl_3$, ca. 1.9:1 ratio); IR ($CHCl_3$) ν_{max} 3500 (w, OH), 3000, 2960, 2940, 2870, 1740 (s, C=O), 1390 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.14 (t, J = 6.5 Hz, 2 H, CH_2OAc), 4.10–3.50 (m, 9 H, C*H*O, CH_2O), 3.66 (s, 3 H, methyl ester), 3.12 and 3.07 (singlets, ca. 1:1.9 ratio, 3 H total, OCH_3), 2.80 (m, 1 H, CH_2C(O)), 2.50 (m, 1 H, CH_2C(O)), 2.20 (m, 1 H, C*H*), 2.05–1.00 (m, 15 H, C*H*, CH_2), 2.02 (s, 3 H, acetate), 1.38, 1.33, and 1.31 (singlets, 12 H total, acetonides), 0.86 and 0.85 (singlets, 18 H total, Si-*t*-*Bu*), 0.086–0.023 (singlets, 12 H total, SiMe_2); HRMS (FAB) calcd for $C_{42}H_{80}O_{13}Si_2$ + H 849.5216, found 849.5200 (M + H).

The above prepared hydroxy ester (1.26 g, 1.48 mmol) was dissolved in dry DMF (10 mL) and treated with PDC (2.78 g, 7.40 mmol) followed by diazomethane treatment as previously described for methyl ester **32ab** and flash column chromatography (silica, 50% ether in petroleum ether) produced pure dimethyl ester **37ab** (987 mg, 76%) as a mixture of isomers. **37ab**: colorless oil; R_f 0.32 and 0.34 (silica, 50% ether in petroleum ether); $[\alpha]^{20}_D$ –2.8° (c 0.71, $CHCl_3$, ca. 1.4:1 ratio); IR ($CHCl_3$) ν_{max} 3000, 2960, 2840, 1740 (s, C=O), 1440, 1385, 1375 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.31–3.50 (m, 7 H, C*H*O, CH_2O), 4.13 (t, J = 6.5 Hz, 2 H, CH_2OAc), 3.65–3.63 (singlets, 6 H total, methyl esters), 3.17 and 3.12 (singlets, ca. 1:1.4 ratio, 3 H total, OCH_3), 2.50–1.00 (m, 17 H, C*H*C(O), CH_2C(O), CH_2), 2.02 (s, 3 H, acetate), 1.38, 1.32, and 1.30 (singlets, 12 H total, acetonides), 0.84 and 0.80 (singlets, 18 H total, Si-*t*-*Bu*), 0.047 to –0.042) (singlets, 12 H total, SiMe_2); HRMS (FAB) calcd for $C_{43}H_{80}O_{14}Si_2$ + H 877.5165, found 877.5148 (M + H).

[Methyl 5,12-bis-*O*-(*tert*-butyldimethylsilyl)-4-carboxy-2,4,6,8,10,13,14,16,18-nonadeoxy-9,11:15,17-di-*O*-isopropylidene-L-*glycero*-L-*gulo*-L-*lyxo*-7-nonadeculo-7,3-pyranosid]aric Acid 1,4-Dimethyl Ester and Isomer (38ab). To a magnetically stirred solution of acetate **37ab** (2.19 g, 2.50 mmol) in anhydrous MeOH (10 mL) at 0 °C under argon was added finely ground K_2CO_3 (1.73 g, 12.5 mmol). After 30 min, the reaction was diluted with ether (200 mL), washed with saturated aqueous NH_4Cl (10 mL), H_2O (10 mL) and brine (20 mL), and dried ($MgSO_4$). Evaporation and purification by flash column chromatography (silica, 80% ether in petroleum ether) afforded pure primary alcohol (1.99 g, 95%) as a mixture of isomers. Primary alcohol: white amorphous solid; R_f 0.30 and 0.34 (silica, 80% ether in petroleum ether); $[\alpha]^{20}_D$ −1.2° (*c* 0.81, $CHCl_3$, ca. 1.4:1 ratio); IR ($CHCl_3$) ν_{max} 3510 (m, OH), 3000, 2940, 2840, 1740 (s, C=O), 1440, 1390 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.35–3.51 (m, 9 H, C*H*O, CH_2O), 3.76, 3.74, 3.65, and 3.64 (singlets, 6 H total, methyl esters), 3.17 and 3.12 (singlets, ca. 1:1.4 ratio, 3 H total, OCH_3), 2.54–0.95 (m, 18 H, C*H*C(O), $CH_2C(O)$, CH_2, O*H*), 1.42, 1.38, and 1.35 (singlets, 12 H total, acetonides), 0.81 and 0.80 (singlets, 18 H total, Si-*t-Bu*), 0.049 to −0.038) (singlets, 12 H total, SiMe_2); HRMS (FAB) calcd for $C_{41}H_{78}O_{13}Si_2$ + H 835.5059, found 835.5055 (M + H).

The above prepared alcohol (1.99 g, 2.38 mmol) was dissolved in dry DMF (12 mL) and treated with PDC (4.48 g, 11.9 mmol) under argon and stirred for 10 h at 25 °C. The reaction mixture was diluted with DMF (12 mL) and poured into ether (200 mL). The ethereal solution was washed with H_2O (4 × 20 mL) and brine (20 mL) and dried ($MgSO_4$). Evaporation and flash column chromatography (silica, 2.5% MeOH in ether) provided pure carboxylic acid **38ab** (1.59 g, 79%) as a mixture of isomers. **38ab**: white amorphous solid; R_f 0.34 (silica, 2.5% MeOH in ether); $[\alpha]^{20}_D$ −8.6° (*c* 0.7, MeOH, ca. 1.5:1 ratio); IR ($CHCl_3$) ν_{max} 3000, 2960, 1735 (s, C=O), 1385, 1260, 1110 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.40–3.10 (m, 7 H, C*H*O), 3.66, 3.65, and 3.64 (singlets, 6 H total, methyl esters), 3.17 and 3.12 (singlets, ca. 1.5:1 ratio, 3 H total, OCH_3), 2.50–1.80 (m, 5 H, C(O)C*H*, $C(O)CH_2$), 1.77–1.10 (m, 12 H, C*H*, CH_2), 1.42, 1.39, 1.46, 1.32, 1.31, 1.27, 1.26, 1.23 (singlets, 12 H total, acetonides), 0.86 and 0.80 (singlets, 18 H total, Si-*t-Bu*), 0.054, 0.026, −0.015, and −0.034 (singlets, 12 H total, SiMe_2); HRMS (FAB) calcd for $C_{41}H_{76}O_{14}Si_2$ + K 887.4410, found 887.4460 (M + K).

[Methyl 8,15-bis-*O*-(*tert*-butyldimethylsilyl)-16-carboxy-2,4,6,7,10,12,14,16,18,20-decadeoxy-3,5:9,11-di-*O*-isopropylidene-20-phosphono-L-*arabino*-D-*glycero*-D-*gulo*-13,19-eicosadiulo-13,17-pyranosid]onic Acid 16,20,20-Trimethyl Ester and Isomer (16ab). To a solution of dimethyl methylphosphonate (0.744 g ≡ 0.65 mL, 6.0 mmol) in dry THF (5 mL) at −78 °C under argon was added droswise *n*-BuLi (2.4 mL, 2.5 M solution in hexane, 6.0 mmol). After stirring for 10 min, the diester **38ab** (1.70 g, 2.0 mmol) in dry THF (14 mL) was added dropwise to the solution of phosphonate anion. After being stirred for 15 min at −78 °C, the reaction mixture was warmed to 0 °C and stirred for an additional 15 min before it was quenched with saturated aqueous NH_4Cl (60 mL). It was extracted with EtOAc (100 mL), and the organic layer was washed with brine (60 mL) and dried ($MgSO_4$). Evaporation and flash column chromatography (silica, 10% MeOH in ether) gave pure keto phosphonate **16ab** (1.17 g, 62%) as a mixture of isomers. **16ab**: white amorphous solid; R_f 0.20 (silica, 10% MeOH in ether); $[\alpha]^{20}_D$ +3.1° (*c* 0.16, MeOH, ca. 3:1 ratio); IR ($CHCl_3$) ν_{max} 3000, 2960, 2930, 2860, 1730 (s, C=O), 1580, 1435, 1380 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.35–3.05 (m, 9 H, C*H*O, P(O)CH_2), 3.77 and 3.75 (doublets, *J* = 11.3 Hz, 6 H total, P(OMe)$_2$), 3.66 and 3.65 (singlets, ca. 3:1 ratio, 3 H total, methyl ester), 3.16 and 3.10 (singlets, ca. 3:1 ratio, 3 H total, OCH_3), 2.81–1.10 (m, 17 H, $CH_2C(O)$, C*H*C(O), C*H*, CH_2), 1.43, 1.36, 1.31, and 1.30 (singlets, 12 H total, acetonides), 0.85 and 0.80 (singlets, 18 H total, Si-*t-Bu*), 0.051 to −0.046 (singlets, 12 H total, SiMe_2); HRMS (FAB) calcd for $C_{43}H_{81}O_{16}Si_2P$ + H 941.4678, found 941.4907 (M + H). Anal. Calcd for $C_{43}H_{81}O_{16}Si_2P$: C, 54.87; H, 8.67. Found: C, 54.85; H, 8.71.

(4*R*,6*R*)-6-[(3*R*)-3-(*tert*-Butyldimethylsiloxy)-3-[(4*R*,6*S*)-6-[[(4*S*,5*S*,6*S*)-4-(*tert*-butyldimethylsiloxy)-5-carboxy-2-methoxy-6-(3-phosphonoacetonyl)-tetrahydro-2*H*-pyran-2-yl]methyl]-2,2-dimethyl-*m*-dioxan-4-yl]propyl]-2,2-dimethyl-*m*-dioxane-4-acetic Acid, 6-Trimethyl Ester, 4-Ester with (*all-E*)-(14*S*,15*R*,16*S*,17*S*)-15-(*tert*-Butyldimethylsiloxy)-17-hydroxy-14,16-dimethyl-2,4,6,8,10,12-octadecahexaenal and Isomer (39ab). To a solution of acid **16ab** (471 mg, 0.500 mmol) and alcohol **15** (646 mg, 1.50 mmol) in dry CH_2Cl_2 (0.5 mL) was added DCC (124 mg, 0.60 mmol) and DMAP (6.1 mg, 0.05 mmol), and the mixture was stirred for 4 h under argon. The reaction mixture was then directly subjected to flash column chromatography (silica, ether → 2.5% MeOH in ether) to give pure keto phosphonate **39ab** (474 mg, 70%) as a mixture of isomers and unreacted aldehyde **15** (409 mg). **39ab**: orange amorphous solid; R_f 0.41 (silica, 2.5% MeOH in ether); $[\alpha]^{20}_D$ +16.5° (*c* 0.20, $CHCl_3$, ca. 2.5:1 ratio); IR ($CHCl_3$) ν_{max} 3000, 2960, 2930, 2860, 1720 (s, C=O, ester), 1670 (s, C=O, aldehyde), 1600 (s, C=C), 1560, 1380 cm^{-1}; UV-vis ($CHCl_3$) λ_{max} 410 nm (E_{1cm} 1% 1210); ^1H NMR (250 MHz, $CDCl_3$, amphotericin numbering) δ 9.53 (d, *J* = 8.0 Hz, 1 H, aldehyde), 7.12 (dd, *J* = 14.6, 11.3 Hz, 1 H, H-23), 6.70 (dd, *J* = 14.7, 11.5 Hz, 1 H, olefinic), 6.55–6.02 (m, 9 H, olefinic), 5.72 (dd, *J* = 15.0, 8.0 Hz, 1 H, H-33), 5.06 (dq, *J* = 6.3 Hz, 1 H, H-37), 4.35–3.00 (m, 10 H, C*H*O, PCH_2C(O)), 3.75 (d, *J* = 11.3 Hz, 6 H, P(OMe)$_2$), 3.65 (s, 3 H, methyl ester), 3.16 and 3.10 (singlets, ca. 2.5:1 ratio, 3 H total, OCH_3), 2.90–1.0 (m, 19 H, allylic C*H*C(O), C*H*, CH_2), 1.41, 1.32, and 1.30 (singlets, 12 H total, acetonides) 1.10 (d, *J* = 6.3 Hz, 3 H, CH_3), 1.0 (d, *J* = 6.7 Hz, 3 H, CH_3), 0.88–0.80 (singlets, 30 H total, CH_3, Si-*t-Bu*), 0.05 to −0.05) (singlets, 18 H total, SiMe_2); HRMS (FAB) calcd for $C_{69}H_{121}O_{18}Si_3P$ − ($C_{15}H_{18}O$) 1139.6319, found 1139.6281 [M − ($C_{15}H_{18}O$), cleavage of polyene unit at C-34/C-35 bond].

8,15,35-Tris-*O*-(*tert*-butyldimethylsilyl)-19-de[(3-amino-3,6-dideoxy-β-D-mannopyranosyl)oxy]-3,5:9,11-di-*O*-isopropylidene-13-*O*-methyl-19-oxoamphotericin B Methyl Ester and Isomer (3ab). To a solution of keto phosphonate–aldehyde **39ab** (406 mg, 0.30 mmol) in dry MeCN (3.0 mL) was added anhydrous LiCl (63.6 mg, 1.5 mmol) followed by the addition of DBU (0.228 g ≡ 224 μL, 1.5 mmol). The reaction was stirred at 25 °C under argon for 4 h. The reaction mixture was directly subjected to flash column chromatography (silica, 40% ether in petroleum ether) to give pure macrocyclic enone **3ab** as a mixture of separable isomers (258 mg, 70%) identical with samples obtained from amphotericin B (**1**) by protection and degradation (for spectral and other data see ref 9).

19-De[(3-amino-3,6-dideoxy-β-D-mannopyranosyl)oxy]-3,5:9,11-di-*O*-isopropylidene-13-*O*-methyl-19-oxoamphotericin B Methyl Ester (40). The heptaenone **3a** (246 mg, 0.20 mmol, faster isomer) was dissolved in dry MeOH (2 mL) in a plastic reaction vessel under argon. Dilute HF·py (0.60 mL) solution (prepared as follows: 1 mL of commercial HF·py, Aldrich, ca. 70%, in a plastic bottle under argon at −20 °C was slowly diluted with 4 mL of dry pyridine) was added dropwise and the reaction mixture was heated with stirring at 45 °C for 48 h. After cooling, it was poured onto saturated aqueous $NaHCO_3$ (20 mL) and extracted with EtOAc (40 mL). The organic extract was washed with saturated aqueous $CuSO_4$ (10 mL) and brine (20 mL) and dried ($MgSO_4$). Evaporation and flash column chromatography (silica, 5% MeOH in CH_2Cl_2) afforded pentahydroxy enone **40** (97.3 mg, 55%) as a single isomer. **40**: deep orange amorphous solid; R_f 0.34 (silica, 8% MeOH in CH_2Cl_2); $[\alpha]^{20}_D$ +349.7° (*c* 0.37, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3510 (m, OH), 3000, 2940, 2880, 1730 (s, C=O), 1640, 1620, 1600, 1550, 1380 cm^{-1}; UV-vis ($CHCl_3$) λ_{max} 422 nm (E_{1cm} 1% 735); ^1H NMR (250 MHz, $CDCl_3$, TMS) δ 7.39 (*J* = 15.7, 11.2 Hz, 1 H, H-21), 6.76 (dd, *J* = 14.4, 10.9 Hz, 1 H, H-23), 6.5–6.05 (m, 10 H, olefinic), 6.11 (d, *J* = 15.7 Hz, 1 H, H-20), 5.38 (dd, *J* = 14.8, 10.1 Hz, 1 H, H-33), 5.27 (m, 1 H, H-37), 4.4–3.0 (m, 12 H, C*H*O, $CH_2(O)O$*H*), 3.76 (s, 3 H, methyl ester), 2.90 (s, 3 H, OCH_3), 2.55–0.90 (m, 8 H, allylic C*H*, C*H*C(O), $CH_2C(O)$, C*H*, CH_2), 1.40, 1.36, 1.33, and 1.29 (singlets, 12 H total, acetonides), 1.17 (d, *J* = 6.3 Hz, 3 H, CH_3), 1.10 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.00 (d, *J* = 6.9 Hz, 3 H, CH_3); HRMS (FAB) calcd for $C_{49}H_{72}O_{14}$ + Na 907.4820, found 907.4766 (M + Na). Anal. Calcd for $C_{49}H_{72}O_{14}$: C, 66.48; H, 8.20. Found: C, 66.37; H, 8.12.

19-De[(3-amino-3,6-dideoxy-β-D-mannopyranosyl)oxy]-13-*O*-methyl-19-oxoamphotericin B Methyl Ester (41). To a solution of the diacetonide **40** (88.4 mg, 0.10 mmol) in dry MeOH (1 mL) was added camphorsulfonic acid (CSA, 4.6 mg, 0.02 mmol). The reaction mixture was stirred at room temperature under argon for 1 h before it was quenched with saturated aqueous $NaHCO_3$ (10 mL) followed by extraction with EtOAc (20 mL). The organic extract was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography (silica, 10% MeOH in CH_2Cl_2) gave heptaenone ester **41** (28.2 mg, 50% based on 50% conversion) as a single methoxy anomer. **41**: deep orange amorphous solid; R_f 0.18 (silica, 10% MeOH in CH_2Cl_2); $[\alpha]^{20}_D$ +172.9° (*c* 0.70, $CHCl_3$); UV-vis ($CHCl_3$) λ_{max} 424 nm (E_{1cm} 1% 767); IR ($CHCl_3$) ν_{max} 3450, 3000, 2930, 2860, 1730 (s, C=O, ester, lactone), 1640, 1590, 1550 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, TMS) δ 7.20 (dd, *J* = 16.1, 11.7 Hz, I H, H-21), 6.71 (dd, *J* = 13.5, 11.7 Hz, 1 H, H-23), 6.5–6.1 (m, 10 H, olefinic), 6.21 (d, *J* = 16.1 Hz, 1 H, H-20), 5.35 (m, 2 H, H-33, H-37), 4.4–3.0 (m, 9 H, C*H*O, $CH_2C(O)$), 3.77 (s, 3 H, methyl ester), 3.05 (s, 3 H, OCH_3), 2.5–0.8 (m, 18 H, allylic C*H*, $CH_2C(O)$, C*H*C(O), CH_2, C*H*), 1.19 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.11 (d, *J* = 6.3 Hz, 3 H, CH_3), 1.02 (d, *J* = 6.7 Hz, 3 H, CH_3), hydroxyl protons are not included; HRMS (FAB) calcd for $C_{43}H_{64}O_{14}$ + Na 827.4194, found 827.4107 (M + Na).

13-*O*-Methylamphoteronolide B Methyl Ester (42). To a solution of the heptaenone **41** (16.1 mg, 0.02 mmol) in MeOH (1 mL) at −10 °C was added $NaBH_4$ (7.6 mg, 0.2 mmol). The reaction was over immediately as indicated by the change of color from deep orange to light

yellow. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (10 mL). The EtOAc extract was washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography (silica, 15% MeOH in CH_2Cl_2) gave pure heptaene alcohol **42** (15.3 mg, 95%) as a single methoxy anomer. **42**: yellow amorphous solid; R_f 0.37 (silica, 15% MeOH in CH_2Cl_2); $[\alpha]^{20}_D$ +73.3° (*c* 0.60, CH_3OH); UV-vis (MeOH) λ_{max} 405 (E_{1cm} 1% 909), 380 (864), 362 (530), 344 nm (264); IR (Nujol) ν_{max} 3400, 1430 (s, C=O, ester, lactone), 1600 cm^{-1}; ^1H NMR (250 MHz, CD_3OD, TMS) δ 6.48-6.10 (m, 12 H, olefinic), 5.80 (dd, J = 15.1, 7.4 Hz, 1 H, H-20), 5.47 (dd, J = 14.6, 9.2 Hz, 1 H, H-33), 5.25 (m, 1 H, H-37), 4.49-3.12 (m, 9 H, C*H*O), 3.74 (s, 3 H, methyl ester), 3.18 (s, 3 H, OCH_3), 2.4-1.2 (m, 19 H, allylic C*H*, CH_2C(O), C*H*C(O), CH_2, C*H*), 1.22 (d, J = 6.7 Hz, 3 H, CH_3), 1.12 (d, J = 6.2 Hz, 3 H, CH_3), 1.02 (d, J = 6.9 Hz, 3 H, CH_3), hydroxyl protons are not included; HRMS (FAB) calcd for $C_{43}H_{66}O_{14}$ + Na 829.4350, found 829.4340 (M + Na).

Amphoteronolide B Methyl Ester (43). To a solution of polyenic alcohol **42** (12.1 mg, 0.015 mmol) in MeOH-H_2O (1 mL, 5:1 ratio) was added camphorsulfonic acid (CSA, 0.7 mg, 0.003 mmol). After being stirred for 1 h at room temperature, the reaction was diluted with CH_2Cl_2 (2 mL) and solid $NaHCO_3$ (20 mg) was added. The mixture was stirred for 10 min and then added directly to a column (silica). Flash chromatography (15% MeOH in CH_2Cl_2) gave pure methyl ester of amphoteronolide **43** (11.5 mg, 97%) identical with samples obtained from amphotericin B (**1**) by protection and degradation (for spectral and other data see ref 9).

Amphoteronolide B (2). Amphoteronolide B (**2**) was prepared from its methyl ester **43** as previously described.[9] For spectral and other data see ref 9.

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Total Synthesis of Amphotericin B. 3. The Final Stages†

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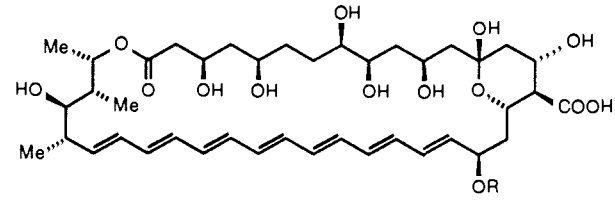
Abstract: The final stages of the total synthesis of amphotericin B (**1**) are described. Mycosamine derivatives **11** and **12** were synthesized and attempts were made to couple them with amphoteronolide B derivative **13**. These glycosidation studies, however, led exclusively to the undesired glycosides **14** and **15**, respectively. The successful strategy for the completion of the synthesis involved an indirect route involving the mycosamine equivalent **30** containing (i) a trichloroacetimidate group at C-1 as a leaving group, (ii) an acetoxy group at C-2 with a β-glycoside bond directing capability, and (iii) an azido group at C-3 as a pregenitor to the desired amino group. After the stereospecific attachment of the carbohydrate fragment (**30**) onto the aglycon (**13**), the configuration at C-2 was corrected by stereocontrolled reduction of the corresponding ketone. Further chemical manipulations and functional group deprotections led to amphotericin B (**1**), thus completing the first total synthesis of this complex polyene macrolide antibiotic.

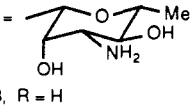
Previous papers in this series described chemistry and degradation of amphotericin B (**1**),[1] construction of key building blocks for the total synthesis of amphoteronolide B (**2**),[2] and the total synthesis of amphoteronolide B (**2**).[3] We describe herein the full account of the final stages of the amphotericin B (**1**)[4] project culminating in the total synthesis[5] of this clinically useful antibiotic. Our strategy for the total synthesis of this target required attachment of a suitable mycosamine unit to an appropriately protected derivative of the aglycon **2**. This glycosidation procedure was recognized from the outset as a thorny problem, principally in view of the following concerns: (a) the rather labile nature of amphoteronolide B (**2**) and amphotericin B (**1**) and their derivatives, (b) the presence of a basic nitrogen in the carbohydrate moiety, and (c) the requirement for a β-glycoside bond in a 1,2-cis relationship with the C-2 hydroxyl group of the carbohydrate unit. The latter requirement is one of the most difficult to fulfill in the area of oligosaccharide synthesis. These circumstances and requirements amounted to a rather formidable challenge. Having synthesized the requisite aglycon derivatives both by partial[1] and total synthesis,[3] we then focused our efforts on the final drive toward amphotericin B (**1**). To this end, systematic studies were undertaken to construct appropriate mycosamine donors and to develop a viable glycosidation process for the required coupling.

Results and Discussion

Initial Glycosidation Studies. Our initial attempts focused on the construction of appropriate mycosamine donors and their attachment to the aglycon derivative **13**. Scheme I summarizes a short route to a number of mycosamine derivatives used in these studies, starting with the readily available precursor **3**.[6] Thus, the carbohydrate derivative **3** was converted to iodide **4** via the



1: Amphotericin B, R =



2: Amphoteronolide B, R = H

† This paper is dedicated with respect and affection to Professor E. J. Corey on the occasion of his 60th birthday.

(1) Nicolaou, K. C.; Chakraborty, T. K.; Daines, R. A.; Ogawa, Y.; Simpkins, N. S.; Furst, G. T. *J. Am. Chem. Soc.*, previous paper in this issue.

(2) Nicolaou, K. C.; Daines, R. A.; Uenishi, J.; Li, W. S.; Papahatjis, D. P.; Chakraborty, T. K. *J. Am. Chem. Soc.*, previous paper in this issue.

(3) Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.*, previous paper in this issue.

(4) Isolation: Vandeputte, J.; Watchtel, J. L.; Stiller, E. T. *Antibiot. Annu.* **1956**, 587. X-ray structure: Mechinski, W.; Shaffner, C. P.; Ganis, P.; Avitabile, G. *Tetrahedron Lett.* **1970**, 3873. Ganis, P.; Avitabile, G.; Mechinski, W.; Shaffner, C. P. *J. Am. Chem. Soc.* **1971**, *93*, 4560.

(5) Preliminary communication: Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.* **1987**, *109*, 2821. Note that in this communication the structure of **31** was incorrectly assumed to be the regioisomer with groups R_1 and R_3 interchanged. This misassignment, however, was of no consequence in the overall total synthesis.

(6) The precursor **3** was prepared according to the reported procedure (Richardson, A. C. *J. Chem. Soc., Chem. Commun.* **1962**, 373) with some modifications. Namely, the corresponding nitro sugar was reduced by Pd-$(OH)_2CH_2$, (H_2, MeOH-H_2O, 2:1, 25 °C, 2 days), and the product was purified by flash column chromatography (silica, 20% MeOH in CH_2Cl_2) and recrystallization (EtOH).

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