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.

Acknowledgment. We express our many thanks to Dr. C. Cimarusti, The Squibb Institute for Medical Research, for generous samples of amphotericin B and to Drs. George Furst, Patrick Carroll, and John Dykins for their superb NMR, X-ray crystallographic, 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 Amphotericin B. 3. The Final Stages†

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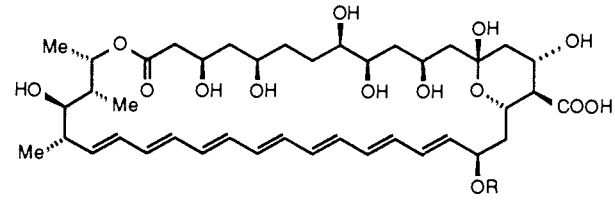
Abstract: The final stages of the total synthesis of amphotericin B (**1**) are described. Mycosamine derivatives **11** and **12** were synthesized and attempts were made to couple them with amphoteronolide B derivative **13**. These glycosidation studies, however, led exclusively to the undesired glycosides **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.

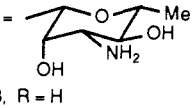
Previous papers in this series described chemistry and degradation of amphotericin B (**1**),[1] construction of key building blocks for the total synthesis of amphoteronolide B (**2**),[2] and the total synthesis of amphoteronolide B (**2**).[3] We describe herein the full account of the final stages 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



1: Amphotericin B, R =



2: Amphoteronolide B, R = H

studies, starting with the readily available precursor **3**.[6] Thus, the carbohydrate derivative **3** was converted to iodide **4** via 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.; 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.; Ganls, 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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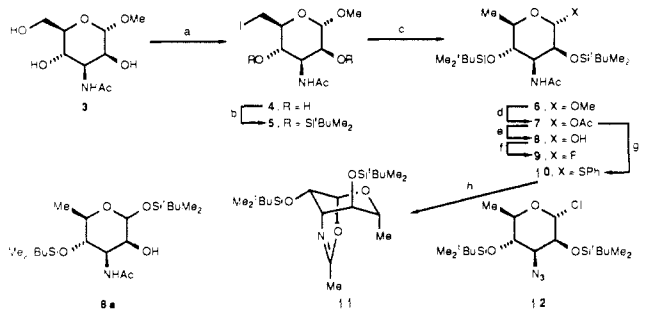
Scheme I[a]



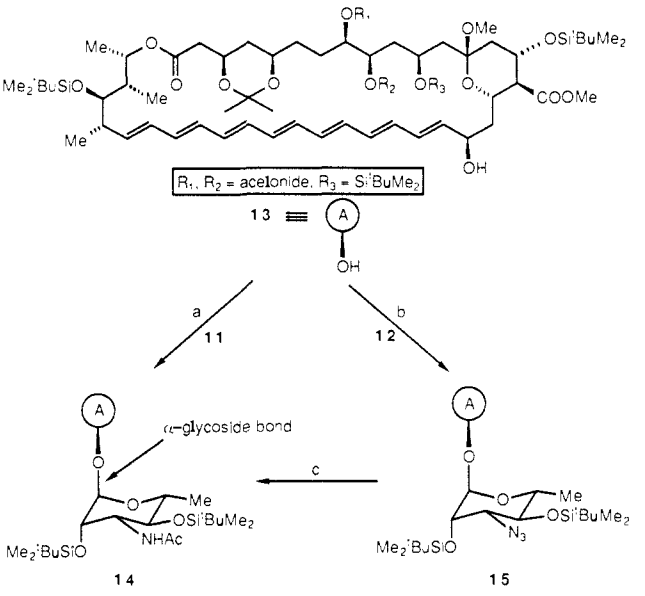
[a] Reagents and conditions: (a) 1.2 equiv of TsCl, pyr, −10 → 25 °C, 3 h, and then 10.0 equiv of NaI, acetone, reflux, 3 h, 68%; (b) 3.0 equiv of *t*-BuMe$_2$SiOTf, 5.0 equiv of 2,6-lutidine, CH_2Cl_2, 0–20 °C, 20 min, 65%; (c) 2.0 equiv of *n*-Bu_3SnH, AIBN catalyst, toluene, reflux, 1 h, 95%; (d) concentrated H_2SO_4 catalyst, Ac_2O, 0–20 °C, 30 min, 75%; (e) 1.1 equiv of K_2CO_3, MeOH, 20 °C, 10 min, 58% of **8**, 38% **8a**; (f) 1.5 equiv of DAST, THF, −30 → 25 °C, 20 min, 95%; (g) 3.0 equiv of ZnI_2, 1.2 equiv of *n*-Bu_4NI, 5.0 equiv of $PhSSiMe_3$, CH_2Cl_2, 25 °C, 83%; (h) 1.3 equiv of NBS, CH_2Cl_2, 25 °C, 10 min, 80%.

corresponding tosylate by standard methods (68% overall yield). Protection of the hydroxyl groups of **4** (*t*-BuMe$_2$SiOTf, 2,6-lutidine, 65%) followed by reductive removal of iodine (*n*-Bu_3SnH–AIBN, 95%) led to compound **6** via intermediate **5**. Exposure of the methyl glycoside **6** to Ac_2O in the presence of H_2SO_4 catalyst gave the acetate **7** (75%). Saponification of **7** (K_2CO_3, MeOH) led to lactol **8** (58%) and to compound **8a** (38%) resulting from migration of the silyl group. The phenyl thioglycoside **10** was conveniently prepared from acetate **7** and $PhSSiMe_3$ in the presence of ZnI_2 and Bu_4NI[7] (80%). The glycosyl fluoride **9** was obtained from lactol **8** by fluorination with DAST[8] (95%). The C-1 stereochemistry of compounds **7–10** was assumed to be as indicated, although it was not rigorously assigned. Attempts to prepare the more reactive glycosyl chloride and bromide corresponding to **9** resulted in a facile ring closure leading to the bicyclic system **11**. This novel compound (**11**) was most conveniently prepared by NBS treatment of phenyl thioglycoside **10**[9] (80%).

Under a variety of activating conditions, derivatives **9** and **10** failed to produce the desired coupling product, decomposition and/or sluggish reaction being observed. With the novel bicycle **11** readily available, we then considered its candidacy as a mycosamine donor. Despite the C-1 stereochemistry of **11** (indicative of an α-glycoside bond forming donor),[10] glycosidation studies with this derivative were still considered worthwhile, in the hope that suitable experimental conditions could be found to form, at least partly, the desired β-glycoside bond via an oxonium species. Furthermore, it was decided that opening entries to α-glycoside analogues of amphotericin B (**1**) would also be a worthwhile goal, in view of the importance of structure–activity relationships in this field. Although numerous experiments directed toward coupling the aglycon derivative **13** with bicycle **11** failed to produce the desired β-glycoside, it was found that smooth coupling of these components (Scheme II) proceeded in benzene under the influence of the mildly acidic catalyst pyridinium *p*-toluenesulfonate (PPTS), leading to the α-glycoside **14** (70%). This derivative was chromatographically and spectroscopically distinguishable from the corresponding β-glycoside derived from natural amphotericin B (**1**).[1]

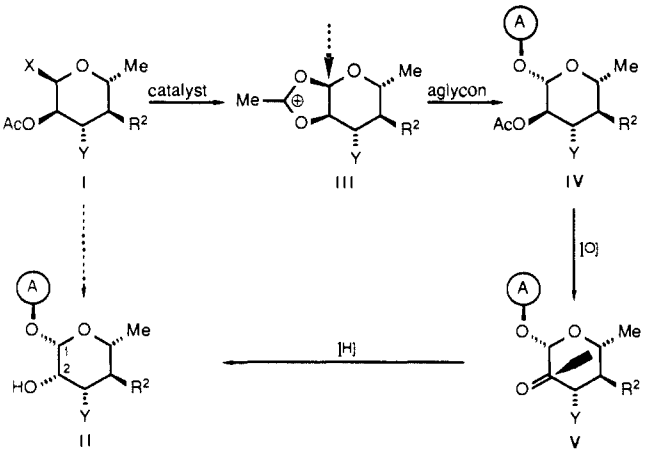
In order to avoid the complications posed by the acetamido group (both in terms of glycosidation and subsequent deprotection), it was, at this point, decided to utilize an azide group as a pregenitor to the amino group of the target molecule. To this end the mycosamine donor **12** (Scheme I) was synthesized by standard chemistry from α-D-methyl glucoside.[11] It was reasoned that conditions favoring an S_N2-type coupling of aglycon **13** with the glycosyl chloride **12** may lead to the desired β-glycosidation. However, these expectations did not meet with success. Instead,

Scheme II[a]



[a] Reagents and conditions: (a) 1.5 equiv of **11**, PPTS catalysts, benzene, 25 °C, 1 h, 77%; (b) 2.8 equiv of **12**, 14 equiv of AgOTf, 31 equiv of collidine, CH_2Cl_2, 25 °C, 12 h, 40%; (c) 10.0 equiv of $HS(CH_2)_3SH$, 10.0 equiv of Et_3N, MeOH, 25 °C, 24 h, and then 2.0 equiv of Ac_2O, 10 equiv of DMAP, CH_2Cl_2, 0–25 °C, 80%.

Scheme III[a]



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(11) The sequence from α-D-methylglucoside to azide **12** involved a series of conventional steps and the intermediacy of the corresponding α-2,3-epoxy-4,6-benzylidine derivative (Richtmyer, N. K. *Methods Carbohydr. Chem.* **1962**, *1*, 107). Thus, S_N2-type opening of the epoxide group at C-2 with $PhCH_2O$ followed by benzoylation at C-3, hydrogenolysis of the benzylidine and benzyl groups, monotosylation at C-6, silylation at C-2 and C-4, and reductive ($LiBEt_3H$) cleavage of the tosylate group with concomitant debenzoylation gave a derivative with a free OH at C-3. Triflate formation and S_N2-type inplantation of the azido group at C-3, followed by acetolysis at C-1 and chloride formation (Kovac, P.; Taylor, R. B.; Glaudemans, C. P. J. *J. Org. Chem.* **1985**, *50*, 5323) completed the sequence. Data for chloride **12**: colorless oil; R_f 0.21 (silica, 2% ether in petroleum ether); $[\alpha]_D^{20}$ +100° (*c* 0.10, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2960, 2940, 2865, 2115 (s, N_3), 1475, 1465, 1360, 1110, 1000, 885, 840 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.81 (d, *J* = 1.3 Hz, 1 H, H-1), 4.09 (m, 1 H, H-2), 3.90 (dq, *J* = 9.3, 6.2 Hz, 1 H, H-5), 3.78 (dd, *J* = 9.5, 2.6 Hz, 1 H, H-3), 3.60 (t, *J* = 9.3 Hz, 1 H, H-4), 1.26 (d, *J* = 6.2 Hz, 3 H, CH_3), 0.90, 0.89 (singlets, 9 H each, Si-*t*-*Bu*), 0.17, 0.14, 0.089, 0.085 (singelts, 3 H each, $SiMe_2$); HRMS (CI) calcd for $C_{18}H_{38}N_3O_3ClSi_2$–*t*-Bu 378.1436, found 378.1391 (M–*t*-Bu).

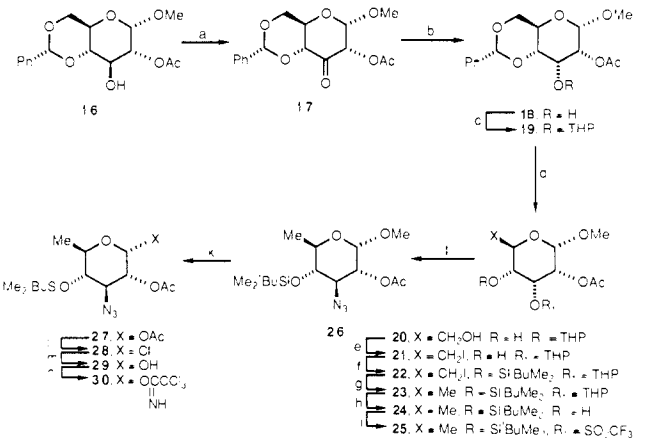
AgOTf-induced coupling of **13** and **12** gave the glycoside **15** (40% yield) as indicated in Scheme II. The α-stereochemistry of this coupling product (**15**) was established by reduction of the azido group ($HS(CH_2)_3SH$–Et_3N)[12] followed by acetylation (Ac_2O–DMAP), a sequence that led to the same α-glycoside obtained from **13** and **11**. At this stage it became apparent that a conceptually different approach had to be considered. The following section describes such an approach, which ultimately provided a successful solution to the problem.

Stereocontrolled Construction of the Amphotericin B Glycoside Bond. Faced with the failure of the above described studies to produce the desired β-glycoside bond of amphotericin B (**1**), an indirect strategy for the stereospecific solution of the problem at hand was designed. According to this rational design, the stereochemistry at C-2 of the carbohydrate framework was to be sacrificed in order to secure, by neighboring group participation, the β-glycosidic stereochemistry. The desired configuration at C-2 was then to be restored at a later stage by inversion. Scheme III outlines the overall strategy according to which an appropriate mycosamine equivalent (I) containing (i) a leaving group (X) at C-1, (ii) a participating group at C-2 with β-glycoside bond directing capability (e.g. Ac), and (iii) a masked amino group (Y) lacking basic and nucleophilic properties at C-3, was to be constructed and coupled to the protected aglycon, to afford the β-glycoside IV via intermediate III. The configuration at C-2 was then to be corrected by inversion involving stereocontrolled reduction of the corresponding ketone (V) to give the desired product II with the requisite 1,2-cis stereorelationship. Subsequent functional group manipulations were then envisioned to lead to amphotericin B (**1**). Of course, this plan had the potential of going astray at the coupling or inversion stages. Specifically, attack by the aglycon at the methyl-bearing electron-deficient site of intermediate III (Scheme III) could lead to an ortho ester linkage, and the reduction of V could proceed with poor stereoselectivity. Molecular modeling and molecular mechanics calculations, however, were reassuring about the potential of a stereoselective reduction of intermediate V from the top face (Scheme III) while counter measures against the formation of an ortho ester could be taken by modification of experimental conditions. In the final scheme, the trichloroacetimidate[13] and the acetate[14] groups were chosen to play the crucial roles of the leaving and participating groups, respectively, whereas the azido group was selected to serve as the nonnucleophilic/nonbasic amino group equivalent.

Scheme IV details a highly efficient and stereocontrolled construction of the requisite mycosamine donor **30**, starting from the readily available glucose derivative **16**.[15] Thus, inversion of stereochemistry at C-3 of **16** was achieved by oxidation (PDC, 98%)–reduction ($NaBH_4$, 96%), leading, stereospecifically, to compound **18** via ketone **17**. Literature precedent[16] on similar systems and Dreiding models strongly pointed to an equatorial attack by hydride to give the inverted system **18**. Protection of **18** (dihydropyran, TsOH catalyst) led to **19**, which was then transformed to the diol **20** by hydrogenolysis of the benzylidene group (90%). Intermediate **20** was then transformed to the requisite triflate derivative **25** by the following sequence: (i) selective iodination of the primary hydroxyl group (Ph_3P–I_2–imidazole, **20** → **21**, 89%), (ii) silylation of the secondary hydroxyl groups (*t*-$BuMe_2SiOTf$–2,6-lutidine, **21** → **22**, 94%), (iii) reductive deiodination (*n*-Bu_3SnH–AIBN, **22** → **23**, 99%), (iv) removal of the tetrahydropyranyl group (PPTS catalyst, MeOH, **23** → **24**, 86%), and (v) triflate formation ($(CF_3SO_2)_2O$, pyr, **24** → **25**, 100%). Triflate **25** underwent smooth S_N2-type displacement with NaN_3 in the presence of 15-crown-5 in DMF to give azide **26** in 83% ($J_{2,3}$ = 10.5 Hz, indicating 2,3-diaxial arrangement for H-2 and H-3). With all stereocenters and functionality in place, it remained to activate intermediate **26** at C-1. Resistance of the methoxy group toward conventional aqueous acid hydrolysis dictated us to seek the intermediacy of the corresponding anomeric acetate. This acetate, it was felt, could serve as a precursor to a series of activated mycosamine derivatives. Thus, exchange of the methoxy with an acetoxy group was achieved by exposure of **26** to a catalytic amount of concentrated H_2SO_4 in acetic anhydride leading to **27** in 90% yield. The C-1 acetate group of **27** was then easily replaced with a chloride (Cl_2CHOMe–$ZnCl_2$ catalyst) giving compound **28** in 80% yield. Access to lactol **29** was best gained, via chloride **28**, by $HgBr_2$-assisted hydrolysis ($MeCN$–H_2O, 9:1). The ratio of the α-anomer of lactol **29** to its β-anomer depended on reaction times and could be further increased by exposure to silica gel. Thus, the α/β ca. 1:3 anomeric mixture obtained after 0.5-h hydrolysis time was enriched to ca 9:1 after two flash chromatographic cycles on silica gel [$R_f(\alpha)$ = 0.5, $R_f(\beta)$ = 0.3, ether]. Finally, the trichloroimidate **30** was formed in 90% yield by brief exposure to Cl_3CCN under anhydrous basic conditions (NaH, CH_2Cl_2). It is interesting to note that, in contrast to other systems,[17] the minor β-anomer of **29** did not react under these conditions, leading to a kinetic and convenient separation of the two anomers at this stage. With an efficient route to a number of activated mycosamine derivatives containing a β-director group at C-2 and the appropriate aglycon precursors at hand, we then proceeded with the glycosidation.

The final drive toward amphotericin B (**1**) is presented in Scheme V. The requisite amphoteronolide B derivative **13** was obtained from the synthesized[1,3] heptaenone **31** by $NaBH_4$ reduction as already described.[1,3] The glycosyl chloride **28** was initially employed in the coupling reaction with **13**. Although sluggishly, **28** reacted with **13** under the influence of AgOTf in

Scheme IV[a]



[a] Reagents and conditions: (a) 5.0 equiv of PDC, 4 Å MS, CH_2Cl_2, 25 °C, 16 h, 98%; (b) 1.0 equiv of $NaBH_4$, THF–MeOH (9:1), −15 °C, 1 min, 96%; (c) 1.2 equiv of dihydropyran, TsOH catalyst, CH_2Cl_2, 0 °C, 0.5 h, 91%; (d) H_2, $Pd(OH)_2$ catalyst, EtOAc, 25 °C, 16 h, 90%; (e) 3.0 equiv of PPh_3, 3.0 equiv of imidazole, 2.0 equiv of I_2, benzene, 45 °C, 4 h, 89%; (f) 1.1 equiv of *t*-$BuMe_2SiOTf$, 1.5 equiv of 2,6-lutidine, CH_2Cl_2, 0–25 °C, 1 h, 94%; (g) 2.0 equiv of *n*-Bu_3SnH, AIBN catalyst, toluene, Δ, 2 h, 99%, (h) 0.1 equiv of PPTS, MeOH, 50 °C, 3 h, 86%; (i) 1.1 equiv of $(CF_3SO_2)_2O$, 1.5 equiv of pyr, CH_2Cl_2, −10 to 25 °C, 2 h, 100%; (j) 1.1 equiv of NaN_3, 1.1 equiv of 15-crown-5, DMF, 25 °C, 0.5 h, 83%; (k) Ac_2O, H_2SO_4 catalyst, 0–25 °C, 2 h, 90%; (l) 10 equiv of Cl_2CHOMe, $ZnCl_2$ catalyst, CH_2Cl_2, 25 °C, 2 h, 80%; (m) 1.0 equiv of $HgBr_2$, $MeCN$–H_2O (9:1), 10 equiv of $CaCO_3$, 25 °C, 0.5 h, and then silica gel, 100% (α/β ca. 9:1); (n) 1.1 equiv of NaH, 10 equiv of Cl_3CCN, CH_2Cl_2, 0 °C, 0.5 h, 90%.

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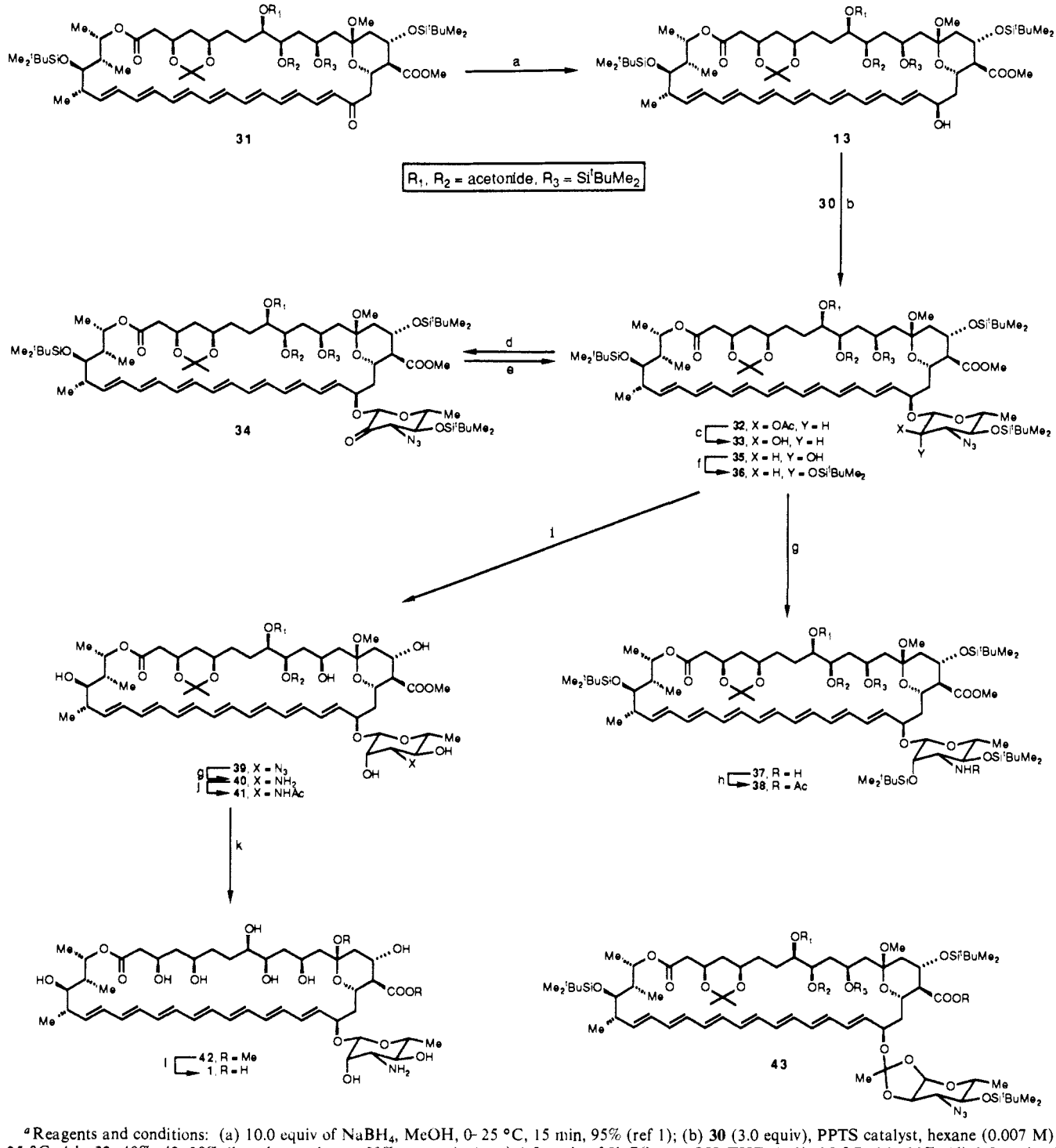
Scheme V[a]



[a] Reagents and conditions: (a) 10.0 equiv of $NaBH_4$, MeOH, 0–25 °C, 15 min, 95% (ref 1); (b) **30** (3.0 equiv), PPTS catalyst, hexane (0.007 M), 25 °C, 4 h, **32**, 40%, **43**, 39% (based on aglycon, 50% conversion); (c) 1.5 equiv of K_2CO_3, MeOH–THF, (3:2), 25 °C, 6 h, 90%; (d) 2.5 equiv of $(CF_3CO)_2O$, 5.0 equiv of DMSO, 5.0 equiv of tetramethylurea, 5.0 equiv of Et_3N, CH_2Cl_2, −78 °C, 2 h; (e) 1.5 equiv of $NaBH_4$, MeOH–THF (3:2), 25 °C, 15 min, 80% overall from **33**; (f) 2.5 equiv of *t*-$BuMe_2SiOTf$, 5.0 equiv of 2,6-lutidine, CH_2Cl_2, 0–25 °C, 2 h, 93%; (g) 10.0 equiv of $HS(CH_2)_3SH$, 10.0 equiv of Et_3N, MeOH, 25 °C, 24 h; (h) 2.0 equiv of Ac_2O, 10 equiv DMAP, CH_2Cl_2, 0–25 °C, 10 min, 85% overall from **36**; (i) excess HF·pyr, MeOH, 50 °C, 48 h, **39**, 40%, monosilyl derivative of **39**, 40%; recycling monosilyl ether of **39** through above conditions gave **39** in 80% yield; (j) 1.2 equiv of Ac_2O, CH_2Cl_2, 0 °C, 10 min, 85% overall from **39**; (k) 1.2 equiv of CSA, MeOH, 25 °C, 2 h, and then H_2O, 25 °C, 4 h, 55% overall from **39**, based on ca. 50% consumption of **40**; (l) 10.0 equiv of LiOH, THF–H_2O (2:1), 0–25 °C, 1 h, 80%.

CH_2Cl_2, but, unfortunately, the only coupling product isolated was the ortho ester **43** (Scheme V) (40% yield based on a 50% aglycon conversion). Variation of experimental conditions (e.g. catalyst, solvent) failed to produce the desired glycoside.[18] We then resorted to the trichloroacetimidate **30** as a glycoside donor. Much to our disappointment, compound **30** (3.0 equiv) reacted with **13** in the presence of pyridinium *p*-toluenesulfonate (PPTS) catalyst in benzene to produce, again, exclusively the ortho ester **43** (80%). Fortunately, it was discovered that by varying the experimental conditions, particularly solvent and concentration, we could influence the outcome of this coupling reaction. As summarized in Table I, optimum conditions for the formation of the desired glycosidation product **32** were realized in dilute hexane solution (PPTS catalyst, 0.007 M in **30**, hexane solution, 25 °C,

(18) The glycosyl bromide corresponding to **28** was also prepared from **27** by the action of Me_3SiBr. Attempts to couple it to the aglycon derivative **13** were, however, unsuccessful.

Table I. Glycosidation Studies

$$13 + 30 \xrightarrow[\text{solvent, 25 °C}]{\text{0.1 equiv of PPTS}} 32 + 43$$

solvent	concn, (M in **30**)[a]	**32** (yield, %)	**43** (yield, %)	recovered **13**
benzene	0.1	0	80	–
CH_2Cl_2	0.1	5.5	49.5	–
hexane	0.1	12	48	–
hexane	0.007	40[b]	39[b]	50

[a] 3 equiv of **30** were used. [b] Based on recovered **13**.

40% based on 50% aglycon consumption, ca. 1:1 glycoside:ortho ester ratio). The precise reasons behind this interesting solvent and concentration effects are not presently well understood, and further studies are under way in order to clarify these phenomena and to increase glycoside–ortho ester ratio. The β-stereochemistry of glycoside **32** was inferred at this stage by the observed $J_{1',2'}$ = 7.9 Hz (axial–axial arrangement for H-1′ and H-2′), whereas the structure of the ortho ester **43** (stereochemistry of Me group unassigned) was evident from the presence of two characteristic ^{1}H NMR signals: δ 5.64 (d, $J_{1',2'}$ = 5.3 Hz, 1 H, H-1′) and 2.08 (s, 3 H, CH_3 ortho ester) and ortho ester carbon signal at 120.6 ppm in the ^{13}C NMR spectrum. Deacetylation of **32** at C-2 (K_2CO_3, 90%) followed by Swern oxidation [$(CF_3CO)_2O$–DMSO, Et_3N] led to ketone **34** via hydroxy compound **33**. The anticipated stereocontrolled (equatorial attack) reduction of **34** proceeded smoothly with $NaBH_4$ (MeOH–THF, 25 °C) to afford, as the sole isolated product, hydroxy compound **35** (80% overall yield from **33**).[19] The fact that this compound (**35**) was chromatographically and spectroscopically distinct from **33** and the value of <1.0 Hz for $J_{1',2'}$ (axial–equatorial) confirmed the inversion of stereochemistry at C-2. Further confirmation of the stereochemistry of compound **35**, including the 19(*R*) configuration of the β-glycoside bond, came upon protection of **35** as the *tert*-butyldimethylsilyl ether **36** (*t*-BuMe$_2$SiOTf, 2,6-lutidine, 95%), reduction of the azido group (**36** → **37**, $HS(CH_2)_3SH$, Et_3N, 90%)[12] and acetylation of the resulting amine (Ac_2O, DMAP, 98%) to give the amphotericin B derivative **38**. Synthetic **38** was chromatographically and spectroscopically [IR, ^{1}H NMR, ^{13}C NMR, UV–vis, $[\alpha]_D$] identical with an authentic sample derived from amphotericin B (**1**) as described elsewhere.[1]

With all the necessary functionality and proper stereochemistry installed in the amphotericin B derivative **35**, it remained to deprotect the molecule and to generate the requisite amino group from the azido group. The following sequence proved to be successful in achieving the desired goal. Thus **35** was desilylated (HF·pyr, MeOH) to afford **39**. Optimum results were obtained when this reaction was allowed to proceed to a mixture of the fully desilylated product **39** and a monosilylated derivative of unassigned regioisomeric nature (ca. 40% yield each) and the isolated monosilylated product recycled under similar conditions to afford **39** (80% yield). Reduction of **39** as described above ($HS(CH_2)_3SH$–Et_3N, 90%)[12] followed by deacetonization (CSA catalyst, MeOH then H_2O, 55% yield based on ca. 50% conversion) led to amphotericin B methyl ester **42** via compound **40**. Due to its sensitivity, compound **40** was characterized as its *N*-acetate **41**. Finally, alkaline hydrolysis of methyl ester **2** (LiOH, THF–H_2O) led to amphotericin B (**1**) in 80% yield and essentially in pure form. Further purification of **1** could be achieved by the procedure of Taylor[20] (see the Experimental Section). Upon methylation with etherial diazomethane, this material led back to methyl ester **42**, identical with the starting methyl ester, thus establishing maintenance of stereochemical integrity during the saponification reaction. Synthetic amphotericin B (**1**) and amphotericin B methyl ester **42** were identical with authentic samples chromatographically and spectroscopically [IR, ^{1}H NMR, ^{13}C NMR, UV–vis, $[\alpha]_D$]. Thus, the total synthesis of amphotericin B (**1**) was accomplished.

(19) Miljkovic, M.; Gligorijevic, M.; Miljkovic, D. *J. Org. Chem.* **1974**, *39*, 2118.

(20) We thank Dr. S. Taylor, E. R. Squibb & Sons, New Brunswick, NJ, for communicating to us this purification procedure for amphotericin B (**1**).

Conclusion

The described total synthesis of amphotericin B (**1**) demonstrates the power of modern organic synthesis. The general concepts of the original strategy were, for the most part, followed through in the execution of the synthesis. Demonstrated[2,3] in this endeavor, are (i) the value of the recognition of subtle symmetry elements in the target molecule by careful retrosynthetic analysis, (ii) the power of the Sharpless asymmetric epoxidation reaction, and (iii) the usefulness of the chiral pool in providing optically active starting materials for total synthesis. The Wittig–phosphonate type reaction emerged as perhaps the "most valuable coupling reaction" in this total synthesis being utilized efficiently five times to provide the basic amphoteronolide B skeleton. Most remarkable was the application of this type of reaction in its intramolecular keto phosphonate–aldehyde version to construct the polyene macrolide ring of amphotericin B quite efficiently. Fortunately, the restriction of rotational freedom, attained by the presence of a plethora of substituents, double bonds, and rings on the backbone of the open-chain precursor of the macroring precursor was instrumental in the success of this macroring forming reaction. It now appears, from this and other studies, that the intramolecular keto phosphonate–aldehyde condensation reaction is a most powerful method for constructing macrorings, and, therefore, it should be placed high on the list of choices for such operations when applicable.

A number of other concepts were successfully utilized in this total synthesis, including the stereocontrolled installation of hydroxy-bearing stereocenters by reduction of carbonyl groups on appropriately designed open-chain precursors and rings of common or large size. Molecular modeling was found to be useful in designing and guiding these studies. A number of chemoselective reactions were also observed in this sequence, demonstrating subtle and as yet unexplained conformational and/or functional interactions in the rather complex intermediates involved.

Finally, the glycosidation studies on amphotericin B, although successful, reemphasized the difficulties encountered in this important area of synthesis. The β-glycoside bond linking the aglycon with the N-containing mycosamine in combination with the requisite 1′,2′-cis stereorelationship, of course, presented a most severe test to the currently available glycosidation technology. The technology failed to provide a direct solution, and it was after the design of an indirect strategy that the problem was finally solved. Even with this successful result, however, one cannot feel comfortable with the present state-of-the-art, and further methodological studies are clearly in order in this area. General efficient and stereoselective glycosidation methods will, of course, have implications far beyond the improvement of the present synthesis of amphotericin B. Studies in this direction are now in progress in this laboratory. Studies directed toward applying the gathered knowledge from this investigation to the synthesis and structural elucidation of other polyene macrolide antibiotics are also being pursued.

Experimental Section

General Methods. See ref 1.

Methyl 3-(Acetylamino)-6-iodo-3,6-dideoxy-α-D-mannopyranoside (4). Methyl 3-(acetylamino)-3-deoxy-α-D-mannopyranoside (**3**) (2.35 g, 10 mmol) was suspended in dry pyridine (40 mL), cooled to −10 °C, and stirred under argon. Tosyl chloride (2.29 g, 12 mmol) dissolved in dry pyridine (16 mL) was slowly added over a period of 20 min. The cooling bath was removed, and the reaction mixture was stirred at ambient temperature for 2 h before being quenched with MeOH (5 mL). The solvents were removed in vacuo, and the residue was azeotropically dried with toluene (50 mL). Dissolution in dry acetone (50 mL), addition of NaI (15 g, 100 mmol), and refluxing for 4 h gave a solution of iodide **4**, which was isolated by removal of the solvent and purification by flash column chromatography (silica, 50–60% acetone in benzene) to furnish **4** (2.35 g, 68% yield) as a colorless amorphous solid: R_f 0.30 (silica, 60% acetone in benzene); $[\alpha]_D^{20}$ +39.2° (*c* 1.60, EtOH); IR (Nujol) ν_{max} 3475 (m, NH), 3310 (m, OH), 1648 (s, C=O, *N*-acetate), 1555, 1465, 1380, 1040 cm^{-1}; ^{1}H NMR (250 MHz, CD_3OD–$CDCl_3$ ca. 1:10) δ 6.37 (d, *J*

= 6.9 Hz, 1 H, N*H*), 4.69 (br s, 1 H, H-1), 4.23 (d, *J* = 2.9 Hz, 1 H, H-2), 4.16 (m, 1 H, H-3), 3.76 (br d, *J* = 9.2 Hz, 1 H, H-6), 3.62 (d, *J* = 9.2 Hz, 1 H, H-6), 3.45 (s, 3 H, OCH_3), 3.45–3.30 (m, 2 H, H-4, H-5), 2.06 (s, 3 H, NHCOCH_3); HRMS (CI) calcd for $C_9H_{16}INO_5$ + H 346.0151, found 346.0147 (M + H).

Methyl 3-(Acetylamino)-3,6-dideoxy-2,4-bis-*O*-[(1,1-dimethylethyl)-dimethylsilyl]-6-iodo-α-D-mannopyranoside (5). To a stirred solution of diol **4** (345 mg, 1.0 mmol) and 2,6-lutidine (536 mg ≡ 0.583 mL, 5.0 mmol) in dry CH_2Cl_2 (7.5 mL) under argon was added dropwise *t*-BuMe$_2$SiOTf (793 mg ≡ 0.689 mL, 3.0 mmol) at 0 °C. The cooling bath was removed and stirring was continued at ambient temperature for 20 min. The reaction mixture was diluted with ether (50 mL) and poured onto saturated aqueous $NaHCO_3$ solution (50 mL). The organic phase was washed successively with saturated aqueous $CuSO_4$ solution (3 × 20 mL), H_2O (20 mL), and brine (20 mL). Drying ($MgSO_4$), concentration, and flash column chromatography (silica, 10 → 50% ether in petroleum ether) gave pure disilyl ether **5** (373 mg, 65%). **5**: colorless amorphous solid; R_f 0.40 (silica, 50% ether in petroleum ether); $[\alpha]_D^{20}$ +25.7° (*c* 0.75, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3450 (m, NH), 2930, 1675 (s, C=O, *N*-acetate), 1510, 1260, 1135 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.38 (d, *J* = 9.1 Hz, 1 H, N*H*), 4.48 (br s, 1 H, H-1), 4.30 (dt, *J* = 9.1, 2.3 Hz, 1 H, H-3), 3.79 (br s, 1 H, H-2), 3.70–3.20 (m, 4 H, H-4, H-5, H-6), 3.39 (s, 3 H, OCH_3), 1.96 (s, 3 H, NHCOCH_3), 0.93, 0.84 (singlets, 9 H each, Si-*t*-*Bu*), 0.13, 0.06, 0.04 (singlets, 12 H total, SiMe_2); HRMS (CI) calcd for $C_{21}H_{44}INO_5Si_2$ + H 574.1881, found 574.1942 (M + H). Anal. Calcd for $C_{21}H_{44}O_5INO_5Si_2$: C, 43.97; H, 7.73; N, 2.44. Found: C, 43.88; H, 8.00; N, 2.39.

Methyl 3-(Acetylamino)-3,6-dideoxy-2,4-bis-*O*-[(1,1-dimethylethyl)-dimethylsilyl]-α-D-mannopyranoside (6). A solution of iodide **5** (574 mg, 1.0 mmol), *n*-Bu_3SnH (583 mg, 2.0 mmol), and AIBN (10 mg) in toluene (15 mL) was refluxed under argon for 1 h. The solvent was removed, and the residue was taken up in ether (100 mL) and stirred for 1 h with 10% aqueous KF solution (50 mL). Removal of the insoluble material was followed by separation of the organic phase, drying ($MgSO_4$), and concentration. Flash column chromatography (silica, 10 → 50% ether in petroleum ether) gave pure **6** (425 mg, 95%). **6**: colorless crystalline solid, mp 147–148 °C (hexane); R_f 0.40 (silica, 50% ether in petroleum ether); $[\alpha]_D^{20}$ +11.7° (*c* 0.52, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3480 (m, NH), 2945, 1680 (s, C=O, *N*-acetate), 1540, 1265, 1140, 1120, 845 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.38 (d, *J* = 10.0 Hz, 1 H, N*H*Ac), 4.41 (d, *J* = 1.0 Hz, 1 H, H-1), 4.24 (dt, *J* = 10.0, 2.0 Hz, 1 H, H-3), 3.80 (dd, *J* = 2.0, 1.0 Hz, 1 H, H-2), 3.67 (dq, *J* = 10.0, 6.2 Hz, 1 H, H-5), 3.40 (t, *J* = 10.0 Hz, 1 H, H-4), 3.32 (s, 3 H, OCH_3), 1.96 (s, 3 H, NHCOCH_3), 1.23 (d, *J* = 3.5 Hz, 3 H, CH_3), 0.92, 0.86 (singlets, 9 H each, Si-*t*-*Bu*), 0.06, 0.05, 0.03 (singlets, 12 H total, SiMe_2); HRMS (CI) calcd for $C_{21}H_{45}NO_5Si_2$ + H 448.2915, found 448.2896 (M + H). Anal. Calcd for $C_{21}H_{45}NO_5Si_2$: C, 56.33; H, 10.13; N, 3.13. Found: 56.09; H, 10.26; N, 2.99.

3-(Acetylamino)-3,6-dideoxy-2,4-bis-*O*-[(1,1-dimethylethyl)dimethylsilyl]-α-D-mannopyranose Acetate (7). The methyl glycoside **6** (448 mg, 1.0 mmol) was suspended in Ac_2O (4.5 mL) and stirred under argon at 0 °C; 0.4 mL of an Ac_2O solution of concentrated H_2SO_4 (5 drops in 0.7 mL of Ac_2O) was added, and the cooling bath was removed. Stirring was continued until completion of the reaction (TLC monitoring, 0.5–1 h), after which the reaction was quenched with solid anhydrous $NaHCO_3$ (0.2 g). After being stirred for 10 min at 25 °C, the mixture was diluted with ether (75 mL) and saturated aqueous $NaHCO_3$ solution (150 mL). When the bubbling ceased, the organic phase was separated and the aqueous layer was reextracted with ether (50 mL). The combined ethereal solution was washed with H_2O (25 mL) and brine (25 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography (silica, 20 → 50% ether in petroleum ether) gave acetoxy derivative **7** (357 mg, 75%). **7**: colorless crystalline solid; mp 123 °C (hexane); R_f 0.24 (silica, 50% ether in petroleum ether); $[\alpha]_D^{20}$ +13.6° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3455 (m, NH), 2960, 2940, 2860, 1755, (s, C=O, *O*-acetate), 1678 (s, C=O, *N*-acetate), 1515, 1260, 1120, 840 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.82 (d, *J* = 1.5 Hz, 1 H, H-1), 5.45 (d, *J* = 11.0 Hz, 1 H, N*H*), 4.28 (t, *J* = 11.0, 4.0 Hz, 1 H, H-3), 3.80 (m, 2 H, H-2, H-5), 3.46 (dd, *J* = 11.0, 10.0 Hz, 1 H, H-4), 2.11 (s, 3 H, OCOCH_3), 1.98 (s, 3 H, NHCOCH_3), 1.25 (d, *J* = 5.2 Hz, 3 H, CH_3), 0.94, 0.88 (singlets, 9 H each, Si-*t*-*Bu*), 0.13, 0.08, 0.07, 0.05 (singlets, 12 H total, SiMe_2); $C_{22}H_{45}NO_6Si_2$: C, 55.54; H, 9.53; N, 2.94. Found: C, 55.77; H, 9.28; N, 2.74.

3-(Acetylamino)-3,6-dideoxy-2,4-bis-*O*-[(1,1-dimethylethyl)dimethylsilyl]-D-mannopyranose (8). The acetate **7** (476 mg, 1.0 mmol) was dissolved in absolute MeOH (15 mL) and stirred under argon with powdered anhydrous K_2CO_3 (152 mg, 1.1 mmol) at room temperature. Upon completion of the reaction (TLC monitoring, ca. 10 min), the reaction mixture was diluted with ether (50 mL) and saturated aqueous NH_4Cl solution (30 mL). The organic phase was separated, the aqueous phase was reextracted with ether (50 mL), and the combined organic solution was dried ($MgSO_4$) and concentrated. The crude mixture, so obtained, (423 mg) consisted of lactol **8** and migration product **8a** (ca. 3:2). Flash column chromatography (silica, 20 → 80% ether in petroleum ether) gave pure **8** (252 mg, 58%) and **8a** (165 mg, 38%) identical with samples obtained from amphotericin B (**1**) by protection and degradation (for spectral and other data see ref 1).

3-(Acetylamino)-3,6-dideoxy-2,4-bis-*O*-[(1,1-dimethylethyl)dimethylsilyl]-D-mannopyranosyl Fluoride (9). To a cold (−30 °C), magnetically stirred solution of lactol **8** (436 mg, 1.0 mmol) in dry THF (7 mL) under argon was added DAST (242 mg ≡ 0.183 mL, 1.5 mmol). The reaction mixture was allowed to reach room temperature, and stirring was continued for 20 min before it was cooled to −30 °C and quenched with ice-cooled saturated aqueous NH_4Cl solution (10 mL). The product was extracted with ether (2 × 100 mL), and the combined extract was washed with H_2O (50 mL) and brine (50 mL), dried, and concentrated. Flash column chromatography gave fluoride **9** (415 mg, 95%). **9**: colorless amorphous solid; R_f 0.33 (silica, 40% ether in petroleum ether); $[\alpha]_D^{20}$ −14.7° (*c* 0.76, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3460 (m, NH), 2970, 2940, 2870, 1685, 1515, 1260, 1130, 845 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.38 (d, *J* = 10 Hz, 1 H, N*H*), 5.30 (dd, *J* = 49.6, 1.3 Hz, 1 H, H-1), 4.29 (dt, *J* = 9.5, 1.4 Hz, 1 H, H-3), 3.93 (t, *J* = 1.3 Hz, 1 H, H-2), 3.86 (dq, *J* = 9.3, 6.3 Hz, 1 H, H-5), 3.44 (t, *J* = 9.4 Hz, 1 H, H-4), 1.97 (s, 3 H, NHCOCH_3), 1.25 (d, *J* = 6.2 Hz, 3 H, CH_3), 0.91, 0.85 (singlets, 9 H each, Si-*t*-*Bu*), 0.06, 0.03 (singlets, 12 H total, SiMe_2); HRMS (CI) calcd for $C_{20}H_{42}FNO_4Si_2$ + H 436.2714, found 436.2764 (M + H). Anal. Calcd for $C_{20}H_{42}FNO_4Si_2$: C, 54.88; H, 10.13; N, 3.20. Found: C, 55.17; H, 10.16; N, 2.98.

Phenyl 3-(Acetylamino)-3,6-dideoxy-2,4-bis-*O*-[(1,1-dimethylethyl)-dimethylsilyl]-1-thio-D-mannopyranoside (10). A mixture of acetate **7** (476 mg, 1.0 mmol), *n*-Bu_4NI (443 mg 1.2 mmol), ZnI_2 (958 mg, 3.0 mmol), and $PhSSiMe_3$ (912 mg ≡ 0.947 mL, 5.0 mmol) in CH_2Cl_2 (10 mL) was stirred at 25 °C under argon for 15 min. The reaction mixture was diluted with ether (100 mL) and washed with saturated aqueous $NaHCO_3$ solution (2 × 150 mL), water (20 mL), and brine (20 mL). Drying ($MgSO_4$) followed by concentration and flash column chromatography (silica, 5 → 30% ether in petroleum ether) gave thioglycoside **10** (436 mg, 83%). **10**: colorless needles; mp 181–182 °C (hexane); R_f 0.22 (silica, 30% ether in petroleum ether); $[\alpha]_D^{20}$ +85.3° (*c* 1.5, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3460 (m, NH), 2960, 2940, 2860, 1677 (s, *N*-acetate), 1510, 1475, 1260, 1110, 1000, 878, 840 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.47–7.44 (m, 2 H, aromatic), 7.32–7.24 (m, 3 H, aromatic), 5.41 (d, *J* = 9.1 Hz, 1 H, N*H*), 5.20 (d, *J* = 1.5 Hz, 1 H, H-1), 4.29 (t, *J* = 9.1, 3.0 Hz, 1 H, H-3), 4.15–3.40 (m, 2 H, H-2, H-5), 3.49 (t, *J* = 9.1 Hz, 1 H, H-4), 1.97 (s, 3 H, NHCOCH_3), 1.22 (d, *J* = 6.2 Hz, 3 H, CH_3), 0.90, 0.87 (singlets, 9 H each, Si-*t*-*Bu*), 0.07, 0.05, 0.02 (singlets, 12 H total, SiMe_2); HRMS (CI) calcd for $C_{26}H_{47}NO_4SSi_2$ + H 526.2842, found 526.2904. Anal. Calcd for $C_{26}H_{47}NO_4SSi_2$: C, 59.38; H, 9.01; N, 2.66. Found: C, 59.26; H, 9.00; N, 2.70.

[1*S*-(3-*endo*,4-*exo*-*syn*)]-3,7-Dimethyl-4,9-bis[[(1,1-dimethylethyl)-dimethylsilyl]oxy]-2,8-dioxa-6-azabicyclo[3.3.1]non-6-ene (Bicyclic System 11) from 10. The thioglycoside **10** (52.6 mg, 0.1 mmol) was dissolved in dry CH_2Cl_2 (1.0 mL), stirred at room temperature under an argon atmosphere, and treated with freshly recrystallized *N*-bromosuccinimide (17.8 mg, 0.1 mmol). Stirring was continued at that temperature for 15 min, and then the reaction mixture was diluted with ether (20 mL). Washing with saturated aqueous $NaHCO_3$ (2 × 5 mL), H_2O (5 mL), and brine (5 mL) followed by drying ($MgSO_4$), concentration, and flash column chromatography (silica, 40% ether in petroleum ether) gave bicyclic compound **11** (23.3 mg, 56%) as a colorless oil and lactol **8** (14.3 mg, 33%). Use of 2% Et_3N in the above solvent system improved the yield of bicyclic compound **11** to 80% at the expense of lactol **8** (10%). **11**: colorless oil; R_f 0.5 (silica, 50% ether in petroleum ether); $[\alpha]_D^{20}$ −2.0° (*c* 0.10, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2960, 2940, 2900, 2860, 1680 (s, N=C), 1475, 1465, 1380, 1250 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.2 (t, *J* = 2.3 Hz, 1 H, H-1), 4.1 (t, *J* = 2.3 Hz, 1 H, H-9), 3.82 (t, *J* = 2.7 Hz, 1 H, H-4), 3.73 (dq, *J* = 7.2, 2.7 Hz, 1 H, H-3), 3.46 (m, 1 H, H-5), 1.93 (s, 3 H, NHCOCH_3), 1.17 (d, *J* = 7.2 Hz, 3 H, CH_3), 0.88, 0.86 (singlets, 18 H total, Si-*t*-*Bu*), 0.09, 0.06 singlets, 12 H total, SiMe_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.74, 94.14, 94.09, 74.38, 72.96, 59.74, 59.67, 56.61, 56.55, 25.68, 21.27, 17.99, 17.89, −4.74, −5.08; HRMS (CI) calcd for $C_{20}H_{41}NO_4Si_2$ + H 416.2652, found 416.2648 (M + H).

Coupling of Amphoteronolide Derivative 13 and Bicyclic Sugar 11. α-Glycoside 14. To a solution of aglycon **13** (61.5 mg, 0.05 mmol) and bicyclic sugar **11** (31.2 mg, 0.075 mmol) in dry benzene (0.5 mL) was added PPTS (3.8 mg, 0.015 mmol) under an argon atmosphere. The reaction mixture was stirred at room temperature for 2 h before being quenched with saturated aqueous $NaHCO_3$ (10 mL). The product was extracted with ether (20 mL) and the organic phase was washed with

brine (10 mL), dried ($MgSO_4$) and concentrated. Flash column chromatography (silica, 40% ether in petroleum ether) gave pure α-glycoside **14** (63.3 mg, 77%). **14**: yellow amorphous solid; R_f 0.41 (silica, 50% ether in petroleum ether); $[\alpha]_D^{20}$ +94.7° (*c* 0.30, $CHCl_3$); UV-vis ($CHCl_3$) λ_{max} 413 ($E_{1cm}^{1\%}$ 738), 389 (705), 369 (428), 350 nm (202); IR ($CHCl_3$) ν_{max} 3000, 2960, 2940, 2900, 2860, 1730 (s, C=O, ester, lactone), 1680 (s, C=O, *N*-acetate), 1510, 1475, 1380, 1260, 1110, 1010, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.22–5.95 (m, 12 H, olefinic), 5.52 (m, 2 H, H-33, H-20), 5.39 (d, *J* = 9.7 Hz, 1 H, N*H*), 4.84 (m, 1 H, H-37), 4.55 (d, *J* = 1.4 Hz, 1 H, H-1′), 4.37–3.28 (m, 11 H, C*H*O, C*H*N), 3.72 (m, 1 H, H-2′), 3.68 (s, 3 H, $COOCH_3$), 3.36 (t, *J* = 9.3 Hz, 1 H, H-4′), 3.09 (s, 3 H, CH_3), 2.35–1.10 (m, 18 H, allylic C*H*, $CH_2C(O)$, CH_2, C*H*), 2.77 (t, *J* = 10.2 Hz, 1 H, H-16), 1.94 (s, 3 H, $NHCOCH_3$), 1.39, 1.31, 1.30, 1.28 (singlets, 3 H each, acetonides), 1.21 (d, *J* = 6.3 Hz, 3 H, CH_3), 1.17 (d, *J* = 6.2 Hz, 3 H, CH_3), 0.97 (d, *J* = 6.6 Hz, 3 H, CH_3), 0.89 (d, *J* = 7.3 Hz, 3 H, CH_3), 0.871, 0.869, 0.860, 0.830, 0.792 (singlets, 9 H each, Si-*t*-*Bu*), 0.071, 0.066, 0.041, 0.031, 0.021, 0.008, 0.001, −0.006, −0.037, −0.051 (singlets, 3 H each, $SiMe_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.82, 170.05, 169.03, 134.42, 133.54, 133.33, 133.01, 132.93, 132.86, 132.77, 132.71, 132.38, 131.97, 131.85, 130.09, 107.95, 100.44, 98.44, 95.30, 80.50, 76.49, 72.58, 72.49, 72.13, 71.40, 69.32, 67.93, 67.72, 67.20, 65.92, 65.01, 55.72, 52.22, 51.63, 47.83, 42.92, 41.88, 40.95, 40.45, 38.57, 36.95, 32.98, 30.04, 27.38, 27.32, 26.91, 25.73, 25.65, 24.36, 23.89, 19.56, 18.71, 18.23, 17.96, 17.71, 11.30, −3.72, −3.86, −4.19, −4.36, −4.66, −5.12; HRMS (FAB) calcd for $C_{87}H_{157}NO_{18}Si_5$ + H 1645.024, found 1645.0340 (M + H).

Coupling of 13 and Glycosyl Chloride 12. α-Glycoside 15. To a magnetically stirred solution of aglycon **13** (45 mg, 0.0366 mmol), glycosyl chloride **12** (45 mg, 0.103 mmol), and collidine (138 mg ≡ 0.15 mL, 1.13 mmol) in dry CH_2Cl_2 (0.5 mL) was added AgOTf (130 mg, 0.515 mmol) at ambient temperature under argon. The mixture was stirred for 12 h before the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and diluted with ether (40 mL). The ethereal layer was separated, washed with saturated aqueous $CuSO_4$ (2 × 10 mL), H_2O (5 mL), saturated aqueous $NaHCO_3$ (5 mL), and brine (5 mL), and dried ($MgSO_4$). Concentration and purification by preparative TLC (0.5 mm silica plate; 15% ether in petroleum ether) gave pure α-glycoside **15** (23.8 mg, 40%). **15**: yellow amorphous solid; R_f 0.42 (silica, 20% ether in petroleum ether); $[\alpha]_D^{20}$ +18.0° (*c* 0.29, $CHCl_3$); UV-vis ($CHCl_3$) λ_{max} 412 ($E_{1cm}^{1\%}$ 648), 388 (641), 370 (398), 350 nm (200); IR ($CHCl_3$) ν_{max} 2950, 2920, 2850, 2100 (s, N_3), 1730 (s, C=O, ester, lactone), 1470, 1460, 1380, 1255, 1110, 1000, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.35–5.90 (m, 12 H, olefinic), 5.58 (dd, *J* = 14.3, 8.0 Hz, 1 H, H-20), 5.53 (dd, *J* = 15.0, 9.3 Hz, 1 H, H-33), 4.85 (m, 1 H, H-37), 4.58 (d, *J* = 1.5 Hz, 1 H, H-1′), 4.40–3.30 (m, 12 H, C*H*O, C*H*N), 3.87 (t, *J* = 2.2 Hz, 1 H, H-2′), 3.66 (s, 3 H, $COOCH_3$), 3.11 (s, 3 H, OCH_3), 2.40–1.10 (m, 19 H, $H_2C(O)$, C*H*C(O), allylic C*H*, CH_2, C*H*). 1.40, 1.323, 1.317, 1.29 (singlets, 3 H, acetonides), 1.23 (d, *J* = 6.0 Hz, 3 H, CH_3), 1.18 (d, *J* = 6.2 Hz, 3 H, CH_3), 0.98 (d, *J* = 6.7 Hz, 3 H, CH_3), 0.90 (d, *J* = 6.7 Hz, 3 H, CH_3), 0.886, 0.876, 0.861, 0.809 (singlets, 45 H total, Si-*t*-*Bu*), 0.166, 0.094, 0.087, 0.082, 0.046, 0.036, 0.018, 0.002, −0.038 (singlets, 30 H total, $SiMe_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.96, 170.07, 134.02, 133.44, 133.34, 133.00, 132.93, 132.82, 132.61, 132.50, 131.95, 131.84, 130.09, 108.00, 98.48, 96.22, 80.46, 72.49, 72.08, 71.95, 69.67, 68.64, 67.59, 67.13, 66.06, 65.39, 55.83, 51.53, 47.87, 42.92, 42.05, 41.00, 40.64, 38.89, 37.111, 32.99, 30.09, 27.37, 26.39, 26.02, 25.91, 25.68, 25.62, 19.60, 18.48, 18.17, 18.05, 18.00, 17.76, −3.67, −3.83, −4.24, −4.35, −4.93, −5.13; HRMS (FAB) calcd for $C_{85}H_{35}N_3O_{17}Si_5$ + H 1629.0124, found 1629.0100 (M + H).

Reduction–Acetylation of Azide 15. Glycoside 14 from 15. The reduction of azide **15** (16.3 mg, 0.01 mmol) was carried out by the procedure described for conversion of **36** to **38**. The resulting product was purified by flash column chromatography (silica, 20% ether in petroleum ether) affording *N*-acetate **14** (12.9 mg, 80%). This compound was chromatographically and spectroscopically identical with the compound that was obtained from the coupling reaction with bicyclic compound **11**.

Methyl (*R*)-4,6-*O*-Benzylidene-α-D-*ribo*-hexopyranosid-3-ulose Acetate (17). To a magnetically stirred solution of alcohol **16** (3.25 g, 10.0 mmol) and ground 3A molecular sieves (19.5 g) in CH_2Cl_2 (80 mL) was added PDC (18.8 g, 50 mmol). The mixture was stirred for 14–16 h (TLC monitoring), diluted with CH_2Cl_2–EtOAc mixture (1:1, 150 mL), and poured onto a Florisil column. Elution with the same solvent system gave essentially pure ketone **17** (3.16 g, 98%). An analytical sample could be obtained by silica gel column chromatography (1% MeOH in CH_2Cl_2). **17**: colorless amorphous solid; R_f 0.23 (1% MeOH in CH_2Cl_2); $[\alpha]_D^{20}$ +60.4° (*c* 0.83, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3040, 2940, 2890, 1770, 1755, 1380 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51–7.35 (m, 5 H, aromatic), 5.56 (s, 1 H, PhC*H*O), 5.38 (d, *J* = 4.0 Hz, 1 H, H-1), 5.20 (d, *J* = 4.0 Hz, 1 H, H-2), 4.41 (dd, *J* = 10.3, 4.6 Hz, 1 H, H-6), 4.37 (d, *J* = 9.8 Hz, 1 H, H-4), 4.10 (dt, *J* = 9.9, 4.6 Hz, 1 H, H-5), 3.95 (t, *J* = 10.2 Hz, 1 H, H-6), 3.45 (s, 3 H, OCH_3), 2.22 (s, 3 H, $CH_3C(O)$); HRMS (CI) calcd for $C_{16}H_{18}O_7$ + H 323.1131, found 323.1150 (M + H). Anal. Calcd for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63. Found: C, 59.41; H, 5.69.

Methyl (*R*)-4,6-*O*-Benzylidene-α-D-allopyranoside 2-Acetate (18). A magnetically stirred solution of ketone **17** (3.23 g, 10.0 mmol) in THF (85 mL) and MeOH (10 mL) was cooled to −15 °C. To this mixture was added $NaBH_4$ (377 mg, 10 mmol), and stirring was continued until all of the $NaBH_4$ had dissolved (~1 min). The reaction mixture was poured into a saturated aqueous NH_4Cl–ice mixture and diluted with EtOAc (350 mL). The organic phase was separated, washed with H_2O (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated. Purification by flash column chromatography (silica, 80% ether in petroleum ether) afforded pure alcohol **18** (3.11 g, 96%). **18**: white foam; R_f 0.26 (silica, ether); $[\alpha]_D^{20}$ +66.5° (*c* 0.26, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3540, 3020, 2950, 2880, 1750 (s, C=O), 1380 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.51–7.34 (m, 5 H, aromatic), 5.58 (s, 1 H, PhC*H*O), 4.90 (d, *J* = 3.6 Hz, 1 H, H-1), 4.85 (dd, *J* = 6.9, 3.6 Hz, 1 H, H-2), 4.38 (m, 2 H, H-3, H-6), 4.20 (dt, *J* = 10.0, 5.1 Hz, 1 H, H-5), 3.77 (t, *J* = 10.3 Hz, 1 H, H-6), 3.60 (dd, *J* = 10.0, 2.6 Hz, 1 H, H-4), 3.45 (s, 3 H, OCH_3), 3.03 (d, *J* = 6.9 Hz, 1 H, O*H*), 2.17 (s, 3 H, $CH_3C(O)$); HRMS (CI) calcd for $C_{16}H_{20}O_7$ + H 325.1287, found 325.1292 (M + H). Anal. Calcd for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 59.12; H, 6.04.

Methyl (*R*)-4,6-*O*-Benzylidene-3-*O*-(tetrahydro-2*H*-pyran-2-yl)-α-D-allopyranoside 2-Acetate (19). To a magnetically stirred solution of alcohol **18** (3.24 g, 10.0 mmol) and dihydropyran (0.99 g ≡ 1.08 mL, 12.0 mmol) in CH_2Cl_2 (45 mL) at 0 °C was added *p*-toluenesulfonic acid (94 mg, 0.50 mmol). The resulting solution was stirred for 30 min, diluted with Et_2O (120 mL), washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL), dried ($MgSO_4$), and concentrated. Purification by flash column chromatography (silica, 60% ether in petroleum ether) gave pure THP ether **19** (3.72 g, 91%). **19**: white foam; R_f 0.26 and 0.29 (silica, 60% ether in petroleum ether, two THP anomers); $[\alpha]_D^{20}$ +22.6° (*c* 0.73, $CHCl_3$, ca. 2.9:1 mixture of THP anomers); IR ($CHCl_3$) ν_{max} 3020, 2960, 2880, 1740 (s, C=O), 1440, 1380 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of THP anomers) δ 7.50–7.33 (m, 5 H, aromatic), 5.56, 5.52 (singlets, ca. 1:2.9 ratio, 1 H total, PhC*H*O), 5.12–4.73 (m, 3 H, H-1, H-2, OC*H*O), 4.50–4.07 (m, 5 H, H-3, H-6, H-5, CH_2O), 3.74–3.62 (m, 2 H, H-6, H-4), 3.43, 3.40 (singlets, ca. 2.9:1 ratio, 3 H total, OCH_3), 2.16, 2.13 (singlets, ca. 2.9:1 ratio, 3 H total, $CH_3C(O)$), 2.00–1.45 (m, 6 H, CH_2); HRMS (CI) calcd for $C_{21}H_{28}O_8$ + NH_4 426.2127, found 426.2117 (M + NH_4).

Methyl 3-*O*-(Tetrahydro-2*H*-pyran-2-yl)-α-D-allopyranoside 2-Acetate (20). To a stirred solution of the THP ether **19** (4.08 g, 10.0 mmol) in EtOAc (75 mL) was added 20% $Pd(OH)_2/C$ (0.32 g). The reaction flask was then flushed with H_2 (1 atm) and stirred for 16 h. H_2 was replaced with Ar and the reaction was diluted with EtOAc (120 mL). Removal of the catalyst by filtration followed by concentration and purification by flash column chromatography (silica, 5% MeOH in CH_2Cl_2) afforded pure diol **20** (2.88 g, 90%). **20**: white foam; R_f 0.19 and 0.12 (silica, 5% MeOH in CH_2Cl_2, two THP anomers); $[\alpha]_D^{20}$ +51.2° (*c* 0.26, $CHCl_3$, ca. 2.9:1 mixture of THP anomers); IR ($CHCl_3$) ν_{max} 3420 (OH), 3020, 2950, 1745 (s, C=O), 1450, 1380 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of THP anomers) δ 4.82 (m, 1 H, OC*H*O), 4.77, 4.76 (singlets, ca. 1:2.9 ratio, 1 H total, H-1), 4.67 (dd, *J* = 7.1, 2.3 Hz, 1 H, H-2), 4.42–3.51 (m, 8 H, H-3, H-4, H-5, CH_2O, O*H*), 3.41, 3.38 (singlets, ca. 1:2.9 ratio, 3 H total, OCH_3), 3.20 (d, *J* = 9.1 Hz, 1 H, O*H*), 2.26–1.47 (m, 6 H, CH_2), 2.15, 2.13 (singlets, ca. 1:2.9 ratio, 3 H total, $CH_3C(O)$); HRMS (CI) calcd for $C_{14}H_{24}O_8$ + NH_4 338.1815, found 338.1820 (M + NH_4).

Methyl 6-Deoxy-6-iodo-3-*O*-(tetrahydro-2*H*-pyran-2-yl)-α-D-allopyranoside 2-Acetate (21). To a mixture of diol **20** (3.20 g, 10.0 mmol), Ph_3P (7.87 g, 30.0 mmol), and imidazole (2.04 g, 30.0 mmol) in benzene (100 mL) was added I_2 (5.07 g, 20.0 mmol). The mixture was heated to 45 °C and stirred for 4 h. After being cooled to room temperature, the reaction mixture was diluted with ether (200 mL) and washed with H_2O (2 × 30 mL), 10% aqueous $Na_2S_2O_3$ (30 mL), and brine (30 mL). Drying ($MgSO_4$) and concentration followed by purification by flash column chromatography (silica, 60% ether in petroleum ether) afforded pure iodide **21** (3.82 g, 89%). **21**: colorless oil; R_f 0.20 and 0.11 (silica, 60% ether in petroleum ether, two THP anomers); $[\alpha]_D^{20}$ +34.7° (*c* 3.0, $CHCl_3$, ca. 2.4:1 mixture of THP anomers); IR ($CHCl_3$) ν_{max} 3400 (OH), 3020, 2940, 1745 (s, C=O), 1450, 1380 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, mixture of THP anomers) δ 4.83 (m, 1 H, OC*H*O), 4.80, 4.79 (singlets, ca. 1:2.4 ratio, 1 H total, H-1), 4.66 (dd, *J* = 7.5, 2.3 Hz, 1 H, H-2), 4.40–3.90 (m, 3 H, C*H*O), 3.72–3.21 (m, 6 H, C*H*O, CH_2I, O*H*), 3.48–3.46 (singlets, ca. 2.4:1 ratio, 3 H total, OCH_3), 2.15, 2.13 (singlets, ca. 1:2.4 ratio, 3 H total, $CH_3C(O)$), 1.97–1.49 (m, 6 H, CH_2); HRMS (CI) calcd for $C_{14}H_{23}IO_7$ + NH_4 448.0832, found 448.0772 (M + NH_4).

Methyl 4-*O*-(*tert*-Butyldimethylsilyl)-6-deoxy-6-iodo-3-*O*-(tetrahydro-2*H*-pyran-2-yl)-α-D-allopyranoside 2-Acetate (22). To a solution of iodide **21** (4.32 g, 10.0 mmol) and 2,6-lutidine (1.61 g ≡ 1.76 mL, 15.1 mmol) in CH_2Cl_2 (40 mL) at 0 °C was slowly added *t*-$BuMe_2SiOTf$ (2.92 g ≡ 2.54 mL, 11.1 mmol). The solution was allowed to reach room temperature and stirred for 1 h. The reaction mixture was diluted with ether (100 mL) and washed sequentially with H_2O (2 × 20 mL), 5% aqueous HCl (10 mL), saturated aqueous $NaHCO_3$ (20 mL), and brine and dried over $MgSO_4$. Concentration followed by purification by flash column chromatography (silica, 30% ether in petroleum ether) yielded silyl ether **22** (5.12 g, 94%). **22**: colorless oil; R_f 0.27 and 0.14 (silica, 30% ether in petroleum ether, two THP anomers); $[\alpha]_D^{20}$ +19.9° (*c* 0.98, $CHCl_3$, slower THP anomer); IR ($CHCl_3$) ν_{max} 3010, 2960, 2860, 1740 (s, C=O), 1470, 1375 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, slower THP anomer) δ 4.76 (m, 2 H, H-1, OC*H*O), 4.60 (t, *J* = 3.8 Hz, 1 H, H-2), 4.22 (m, 2 H, C*H*O, H-3), 3.97 (dt, *J* = 8.8, 2.5 Hz, 1 H, H-5), 3.54 (dd, *J* = 10.4, 2.6 Hz, 1 H, H-6), 3.48 (s, 3 H, OCH_3), 3.45 (dd, *J* = 9.1, 2.6 Hz, 1 H, H-6), 3.40 (m, 1 H, C*H*O), 3.12 (dd, *J* = 10.3, 8.7 Hz, 1 H, H-4), 2.13 (s, 3 H, $CH_3C(O)$), 1.90–1.45 (m, 6 H, CH_2), 0.90 (s, 9 H, Si-*t*-*Bu*), 0.15, 0.11 (singlets, 3 H each, $SiMe_2$); HRMS (CI) calcd for $C_{20}H_{37}IO_7Si + NH_4$ 562.1659, found 562.1710 (M + NH_4).

Methyl 4-*O*-(*tert*-Butyldimethylsilyl)-6-deoxy-3-*O*-(tetrahydro-2*H*-pyran-2-yl)-α-D-allopyranoside 2-Acetate (23). To a mixture of iodide (5.44 g, 10.0 mmol) and *n*-Bu_3SnH (5.82 g ≡ 5.38 mL, 20.0 mmol) in toluene (80 mL) at ambient temperature was added AIBN (30 mg), and the reaction mixture was refluxed with stirring for 2 h. After the mixture was cooled to ambient temperature, the toluene was removed at reduced pressure and the residue was dissolved in ether (80 mL). The ethereal solution was treated with aqueous KF (4.2 g $KF{\cdot}2H_2O$ in 40 mL of H_2O, vigorous stirring for 0.5–1 h), the insoluble *n*-Bu_3SnF was removed by filtration, and the organic phase was separated. The aqueous phase was extracted with ether (80 mL), and the combined organic extract was washed with brine (30 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography (silica, 30% ether in petroleum ether) gave pure deoxy sugar **23** (4.14 g, 99%). **23**: colorless oil; R_f 0.30 and 0.18 (silica, 30% ether in petroleum ether, two THP anomers); $[\alpha]_D^{20}$ +24.2° (*c* 0.36, $CHCl_3$, slower THP anomer); IR ($CHCl_3$) ν_{max} 3010, 2940, 2840, 1740 (s, C=O), 1470, 1375 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, slower THP anomer) δ 4.78 (dd, *J* = 4.2, 3.6 Hz, 1 H, H-2), 4.70 (d, *J* = 4.2 Hz, 1 H, H-1), 4.60 (dd, *J* = 4.1, 3.9 Hz, 1 H, OC*H*O), 4.10 (m, 3 H, H-3, H-5, CH_2O), 3.38 (s, 3 H, OCH_3), 3.42 (m, 1 H, CH_2O), 3.35 (dd, *J* = 9.4, 2.7 Hz, 1 H, H-4), 2.14 (s, 3 H, $CH_3C(O)$), 2.11–1.42 (m, 6 H, CH_2), 1.2 (d, *J* = 6.4 Hz, 3 H, CH_3), 0.90 (s, 9 H, Si-*t*-*Bu*), 0.10 (s, 6 H, $SiMe_2$); HRMS (CI) calcd for $C_{20}H_{38}O_7Si + NH_4$ 436.2731, found 436.2720 (M + NH_4). Anal. Calcd for $C_{20}H_{38}O_7Si$: C, 57.38; H, 9.15. Found: C, 57.38; H, 9.39.

Methyl 4-*O*-(*tert*-Butyldimethylsilyl)-6-deoxy-α-D-allopyranoside 2-Acetate (24). A mixture of THP ether **23** (4.19 g, 10.0 mmol) and PPTS (0.25 g, 1.00 mmol) in dry MeOH (40 mL) was stirred at 50 °C for 3 h. After being cooled to ambient temperature and diluted with ether (200 mL), the solution was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography (silica, 40% ether in petroleum ether) afforded pure alcohol **24** (2.88 g, 86%). **24**: colorless oil; R_f 0.18 (silica, 40% ether in petroleum ether); $[\alpha]_D^{20}$ +91.8° (*c* 0.65, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3500 (OH), 2920, 2850, 1735 (s, C=O), 1470, 1370 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.80 (m, 2 H, H-1, H-2), 4.10 (m, 1 H, H-3), 3.92 (m, 1 H, H-5), 3.41 (s, 3 H, OCH_3), 3.35 (dd, *J* = 9.5, 2.9 Hz, 1 H, H-4), 2.17 (s, 3 H, $CH_3C(O)$), 1.26 (d, *J* = 6.3 Hz, 3 H, CH_3), 0.92 (s, 9 H, Si-*t*-*Bu*), 0.12 (s, 6 H, $SiMe_2$); HRMS (CI) calcd for $C_{15}H_{30}O_6Si + NH_4$ 352.2155, found 352.2193 (M + NH_4).

Methyl 4-*O*-(*tert*-Butyldimethylsilyl)-6-deoxy-α-D-allopyranoside 2-Acetate 3-(Trifluoromethanesulfonate) (25). To a magnetically stirred solution of alcohol **24** (335 mg, 1.00 mmol) and pyridine (128 mg ≡ 0.131 mL, 1.50 mmol) in CH_2Cl_2 (5.0 mL) at −10 °C was slowly added triflic anhydride (311 mg ≡ 0.186 mL, 1.10 mmol). Stirring was continued for 10 min at −10 °C and then for 2 h at room temperature. The mixture was diluted with ether (50 mL) and washed sequentially with H_2O (10 mL), 5 % aqueous HCl (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), dried ($MgSO_4$), and concentrated to give triflate **25** (467 mg, crude), which was used without further purification.

Methyl 3-Azido-4-*O*-(*tert*-butyldimethylsilyl)-3,6-dideoxy-α-D-glucopyranoside 2-Acetate (26). To a stirred solution of triflate (467 mg, 1.00 mmol) and 15-crown-5 (242 mg ≡ 0.219 mL, 1.10 mmol) in dry DMF (4.0 mL) was added NaN_3 (72 mg, 1.10 mmol), and stirring was continued for 30 min. The mixture was diluted with ether (50 mL), washed with H_2O (3 × 10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), dried ($MgSO_4$), and concentrated. Purification by flash column chromatography (silica, 30% ether in petroleum ether) gave pure azide **26** (298 mg, 83% from **24**). **26**: white amorphous solid: R_f 0.21 (silica, 10% ether in petroleum ether); $[\alpha]_D^{20}$ +83.5° (*c* 0.96, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2940, 2860, 2120 (s, N_3), 1740 (s, C=O), 1475, 1370 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 4.81 (d, *J* = 3.6 Hz, 1 H, H-1), 4.71 (dd, *J* = 10.5, 3.6 Hz, 1 H, H-2), 3.72 (dd, *J* = 10.5, 9.2 Hz, 1 H, H-3), 3.65 (m, 1 H, H-5), 3.38 (s, 3 H, OCH_3), 3.09 (t, *J* = 9.2 Hz, 1 H, H-4), 2.16 (s, 3 H, $CH_3C(O)$), 1.23 (d, *J* = 6.3 Hz, 3 H, CH_3), 0.91 (s, 9 H, Si-*t*-*Bu*), 0.18, 0.10 (singlets, 3 H each, $SiMe_2$); HRMS (CI) calcd for $C_{15}H_{29}N_3O_5Si + NH_4$ 377.2220, found 377.2210 (M + NH_4). Anal. Calcd for $C_{15}H_{29}N_3O_5Si$: C, 50.11; H, 8.71; N, 11.69. Found: C, 50.03; H, 8.45; N, 11.49.

3-Azido-4-*O*-(*tert*-butyldimethylsilyl)-3,6-dideoxy-α-D-glucopyranose 1,2-Diacetate (27). To a stirred solution of azide **26** (360 mg, 1.00 mmol) in Ac_2O (2.0 mL) at 0 °C was added a solution of concentrated H_2SO_4 in Ac_2O (0.2 mL; 3 drops of concentrated H_2SO_4 in 0.3 mL of Ac_2O). The reaction was allowed to reach room temperature and stirred for 2 h. The reaction mixture was poured into saturated aqueous $NaHCO_3$ (5 mL) and vigorously stirred for 1 h. The mixture was then diluted with ether (50 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ (3 × 10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography of the crude product (silica, 10% ether in petroleum ether) gave pure diacetate **27** (349 mg, 90%). **27**: colorless oil; R_f 0.13 (silica, 10% ether in petroleum ether); $[\alpha]_D^{20}$ +54.1° (*c* 0.27 $CHCl_3$); IR ($CHCl_3$) ν_{max} 2940, 2860, 2120 (s, N_3), 1760 (s, C=O), 1475, 1375 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.20 (d, *J* = 3.7 Hz, 1 H, H-1), 4.88 (dd, *J* = 10.6, 3.7 Hz, 1 H, H-2), 3.80 (m, 1 H, H-5), 3.70 (dd, *J* = 10.6, 9.4 Hz, 1 H, H-3), 3.15 (t, *J* = 9.3 Hz, 1 H, H-4), 2.18, 2.09 (singlets, 3 H each, $CH_3(O)$), 1.24 (d, *J* = 6.3 Hz, 3 H, CH_3), 0.92 (s, 9 H, Si-*t*-*Bu*), 0.20, 0.12 (singlets, 3 H each, $SiMe_2$); HRMS (CI) calcd for $C_{16}H_{29}N_3O_6Si + NH_4$ 405.2169, found 405.2143 (M + NH_4).

3-Azido-4-*O*-(*tert*-butyldimethylsilyl)-3,6-dideoxy-α-D-glucopyranosyl Chloride 2-Acetate (28). To a stirred solution of diacetate **27** (388 mg, 1.00 mmol) and Cl_2CHOMe (1.15 g ≡ 0.905 mL, 10.0 mmol) in dry CH_2Cl_2 (2.0 mL) was added $ZnCl_2$ (1.4 mg, 0.01 mmol; freshly dried in vacuo at 290 °C). The reaction mixture was stirred for 2 h at room temperature and then diluted with ether (30 mL). The solution was washed with saturated aqueous $NaHCO_3$ (3 × 5 mL) and brine (5 mL), dried ($MgSO_4$), and concentrated to give glycosyl chloride **28**, which was used without purification. An analytical sample was obtained by purification by flash column chromatography (silica, 5% ether in petroleum ether). **28**: colorless oil; R_f 0.24 (silica, 5% ether in petroleum ether); $[\alpha]_D^{20}$ +138.3° (*c* 0.42, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2940, 2860, 2120 (s, N_3), 1755 (s, C=O), 1475, 1370 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.20 (d, *J* = 3.9 Hz, 1 H, H-1), 4.78 (dd, *J* = 10.4, 3.9 Hz, 1 H, H-2), 4.00 (m, 1 H, H-5), 3.81 (dd, *J* = 10.2, 9.3 Hz, 1 H, H-3), 3.15 (t, *J* = 9.3 Hz, 1 H, H-4), 2.17 (s, 3 H, $CH_3C(O)$), 1.28 (d, *J* = 6.3 Hz, 3 H, CH_3), 0.92 (s, 9 H, Si-*t*-*Bu*), 0.19, 0.11 (singlets, 3 H each, $SiMe_2$); HRMS (CI) calcd for $C_{14}H_{26}ClN_3O_4Si + NH_4$ 381.1724, found 381.1685 (M + NH_4).

3-Azido-4-*O*-(*tert*-butyldimethylsilyl)-3,6-dideoxy-α-D-glucopyranose 2-Acetate (29). To a stirred solution of chloride **28** (364 mg, 1.00 mmol) and $CaCO_3$ (1.00 g, 10.0 mmol) in MeCN–H_2O mixture (2.5 mL, MeCN:H_2O = 9:1) was added $HgBr_2$ (360 mg, 1.00 mmol); stirring was continued for 30 min. The reaction mixture was diluted with ether (30 mL) and filtered. The filtrate solution was washed with H_2O (2 × 5 mL), 5% aqueous HCl (5 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (5 mL). Drying ($MgSO_4$) and concentration afforded predominantly the β-anomer. Repeated flash column chromatography (two to three times) (silica, 5 → 40% ether in petroleum ether) increased the amount of the α-anomer **29** (345 mg, α:β = ca. 9:1, 100%). **29**: white amorphous solid; R_f 0.34 (silica, 40% ether in petroleum ether); $[\alpha]_D^{20}$ +45.8° (*c* 0.60, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3600 (OH), 2960, 2940, 2860, 2120 (s, N_3), 1750 (s, C=O), 1475, 1380 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.34 (t, *J* = 3.5 Hz, 1 H, H-1), 4.70 (ddd, *J* = 10.6, 3.6, 1.3 Hz, 1 H, H-2), 3.95 (m, 1 H, H-5), 3.80 (dd, *J* = 10.6, 9.3 Hz, H-3), 3.10 (t, *J* = 9.3 Hz, 1 H, H-4), 2.71 (dd, *J* = 3.6, 1.3 Hz, 1 H, O*H*), 2.17 (s, 3 H, $CH_3C(O)$), 1.23 (d, *J* = 6.3 Hz, 3 H, CH_3), 0.91 (s, 9 H, Si-*t*-*Bu*), 0.18, 0.10 (singlets, 3 H each, $SiMe_2$); HRMS (CI) calcd for $C_{14}H_{27}N_3O_5Si + NH_4$ 363.2064, found 363.2067 (M + NH_4).

3-Azido-4-*O*-(*tert*-butyldimethylsilyl)-3,6-dideoxy-α-D-glucopyranosyl 2-Acetate 1-(2,2,2-Trichloroacetimidate) (30). To a cooled solution (0 °C) of lactol **29** (345 mg, 1.00 mmol) and CCl_3CN (1.44 g ≡ 1.00 mL, 10.0 mmol) in CH_2Cl_2 (2.0 mL) was added NaH (44 mg, 60% in mineral oil, 1.10 mmol) with stirring. After being stirred for 30 min at 0 °C, the reaction mixture was diluted with ether (30 mL) and poured into H_2O (20 mL). The organic phase was washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Purification by flash column chromatography gave pure imidate **30** (440 mg, 90%). **30**: colorless oil; R_f 0.30 (silica, 20% ether in petroleum ether); $[\alpha]_D^{20}$ +62.8° (*c* 1.55, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3360 (NH), 2940, 2860, 2110 (s, N_3), 1740 (s, C=O),

1680 (s, C=N), 1470, 1370 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.60 (s, 1 H, =N*H*), 6.40 (d, J = 3.6 Hz, 1 H, H-1), 4.90 (dd, J = 10.6, 3.6 Hz, 1 H, H-2), 3.91–3.78 (m, 2 H, H-3, H-5), 3.20 (t, J = 9.3 Hz, 1 H, H-4), 2.10 (s, 3 H, CH_3C(O)), 1.26 (d, J = 6.3 Hz, 3 H, CH_3), 0.92 (s, 9 H, Si-*t*-*Bu*), 0.20, 0.12 (singlets, 3 H each, SiMe_2); HRMS (CI) calcd for $C_{14}H_{27}Cl_3N_4O_5Si$ – OH 471.0789, found 471.0801 (M – OH). Anal. Calcd for $C_{14}H_{27}Cl_3N_4O_5Si$: C, 39.23; H, 5.54; Cl, 21.71; N, 11.44. Found: C, 39.53; H, 5.33; Cl, 21.91; N, 11.53.

Coupling of Amphoteronolide Derivative 13 and Trichloroacetimidate 30. Glycoside 32 and Ortho Ester 43. The amphoteronolide derivative **13** (340 mg, 0.277 mmol) and trichloroacetimidate **30** (407 mg, 0.831 mmol) were dissolved in dry hexane (118 mL, 0.002 M in **13**, 0.007 M in **30**) under an argon atmosphere. To the magnetically stirred solution was added pyridinium *p*-toluenesulfonate (PPTS, 20 mg, 0.083 mmol) at room temperature, and stirring was continued for 4 h. The mixture was then treated with saturated aqueous $NaHCO_3$ (20 mL) and diluted with ether (100 mL), and the organic phase was separated. The organic solution was washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography (silica, 5 → 50% ether in petroleum ether) gave, in order of elution, recovered trichloroacetimidate **30** (232 mg, 43%), ortho ester **43** (84 mg, 39%), glycoside **32** (86 mg, 40%), and recovered aglycon derivative **13** (169 mg, 50%). Glycoside **32**: yellow amorphous solid; R_f 0.22 (silica, 20% ether in petroleum ether); $[\alpha]_D^{20}$ +152.9° (c 0.35, $CHCl_3$); UV–vis ($CHCl_3$) λ_{max} 412 (E_{1cm}1% 512), 388 (504), 369 (304), 350 nm (144); IR ($CHCl_3$) ν_{max} 2960, 2940, 2860, 2110 (s, N_3), 1740 (s, C=O, ester, lactone), 1470, 1385, 1260 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.35–5.95 (m, 12 H, olefinic), 5.85–5.65 (m, 2 H, H-20, H-33), 4.92 (dd, J = 10.0, 7.9 Hz, 1 H, H-2′), 4.77 (m, 1 H, H-37), 4.50 (m, 1 H, H-19), 4.35 (d, J = 7.9 Hz, 1 H, H-1′), 4.25–3.10 (m, 11 H, C*H*O, C*H*N, H-5′), 3.69 (s, 3 H, COOCH_3), 2.97 (s, 3 H, OCH_3), 2.45–0.70 (m, 19 H, CH_2C(O), C*H*C(O), allylic C*H*, CH_2, C*H*), 2.24 (s, 3 H, OCOCH_3), 1.36 and 1.29 (singlets, 12 H total, acetonides), 1.21 (d, J = 6.0 Hz, 3 H, CH_3), 1.16 (d, J = 6.0 Hz, 3 H, CH_3), 1.00 (d, J = 6.7 Hz, 3 H, CH_3), 0.88–0.80 (singlets, 39 H total, CH_3, Si-*t*-*Bu*), 0.15 to –0.07) (singlets, 24 H total, SiMe_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.09, 169.84, 169.68, 137.41, 136.01, 133.90, 133.62, 133.49, 133.17, 132.97, 132.79, 132.35, 132.06, 131.48, 131.19, 129.87, 127.70, 108.00, 100.68, 98.52, 98.04, 80.20, 74.74, 74.18, 73.39, 71.94, 68.57, 68.03, 66.98, 66.04, 65.57, 65.22, 56.91, 51.53, 48.18, 43.14, 42.49, 40.90, 40.64, 37.52, 36.21, 33.07, 30.08, 27.46, 27.16, 26.89, 26.08, 25.95, 24.83, 25.72, 25.59, 20.58, 19.58, 18.53, 18.13, 18.08, 17.98, 17.82, 17.71, 11.66, –3.59, –3.69, –4.11, –4.30, –5.16; HRMS (FAB) calcd for $C_{81}H_{141}N_3O_{18}Si_4$ + H 1556.9365, found 1556.9309 (M + H).

Ortho ester 43: yellow amorphous solid; R_f 0.25 (silica, 20% ether in petroleum ether); $[\alpha]_D^{20}$ +51.2° (c 0.26, $CHCl_3$); UV–vis ($CHCl_3$) λ_{max} 412 ($E_{1cm}^{1\%}$ 438), 388 (425), 368 (256), 350 nm (119); IR ($CHCl_3$) ν_{max} 2960, 2940, 2860, 2110 (s, N_3), 1730 (s, C=O, ester, lactone), 1470, 1360 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.3–5.95 (m, 12 H, olefinic), 5.80–5.65 (m, 2 H, H-20, H-33), 5.64 (d, J = 5.3 Hz, 1 H, H-1′), 4.76 (m, 1 H, H-37), 4.43 (m, 1 H, H-19), 4.08 (t, J = 5.3 Hz, 1 H, H-2′), 3.67 (s, 3 H, COOCH_3), 3.43 (dd, J = 6.8, 5.4 Hz, 1 H, H-3′), 3.24 (dd, J = 8.8, 6.9 Hz, 1 H, H-4′), 3.06 (s, 3 H, OCH_3), 4.30–3.30 (m, 9 H, C*H*O, H-5′), 2.45–0.80 (m, 19 H, CH_2C(O), C*H*C(O), allylic C*H*, CH_2, C*H*), 1.63 (s, 3 H, CH_3), 1.37, 1.35, 1.30, 1.29 (singlets, 3 H each, acetonides), 1.24 (d, J = 6.3 Hz, 3 H, CH_3), 1.18 (d, J = 6.5 Hz, 3 H, CH_3), 1.00 (d, J = 6.8 Hz, 3 H, CH_3), 0.91 (d, J = 7.2 Hz, 3 H, CH_3), 0.89–0.78 (singlets, 36 H total, Si-*t*-*Bu*), 0.15 to –0.054) (singlets, 24 H total, SiMe_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 120.59 (ortho ester); HRMS (FAB) calcd for $C_{81}H_{141}N_3O_{18}Si_4$ + H 1556.9365, found 1556.9299.

Deacetylation of Compound 32. Preparation of Alcohol 33. To a magnetically stirred solution of acetate **32** (190 mg, 0.122 mmol) in absolute MeOH (1.8 mL) and THF (1.2 mL) under argon was added powdered anhydrous K_2CO_3 (25 mg, 0.183 mmol) at room temperature. The mixture was stirred under those conditions for 6 h and then diluted with ether (40 mL). Washing with H_2O (10 mL) and brine (10 mL) followed by drying ($MgSO_4$) and concentration gave the crude product, which was purified by flash column chromatography (silica, 20% ether in petroleum ether), yielding alcohol **33** (166 mg, 90%). **33**: R_f 0.30 (silica, 30% ether in petroleum ether); $[\alpha]_D^{20}$ +101.6° (c 0.23, $CHCl_3$); UV–vis ($CHCl_3$) λ_{max} 412 ($E_{1cm}^{1\%}$ 833), 388 (802), 370 (489), 350 nm (229); IR ($CHCl_3$) ν_{max} 3520 (m, OH), 2950, 2920, 2105 (s, N_3), 1730 (s, C=O, ester, lactone), 1460, 1380 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.35–5.90 (m, 12 H, olefinic), 5.85 (dd, J = 14.8, 5.3 Hz, 1 H, H-20), 5.57 (dd, J = 14.2, 8.9 Hz, 1 H, H-33), 4.80 (m, 1 H, H-37), 4.40 (m, 1 H, H-19), 4.20 (d, J = 7.5 Hz, 1 H, H-1′), 4.25–3.00 (m, 12 H, C*H*O, C*H*N), 3.70 (s, 3 H, COOCH_3), 3.06 (s, 3 H, OCH_3), 2.50–0.50 (m, 19 H, CH_2C(O), C*H*C(O), allylic C*H*, CH_2, C*H*, O*H*), 1.37, 1.31 and 1.29 (singlets, 12 H total, acetonides), 1.21 (d, J = 6.2 Hz, 3 H, CH_3), 1.17 (d, J = 7.0 Hz, 3 H, CH_3), 0.98 (d, J = 6.7 Hz, 3 H, CH_3), 0.90–0.75 (singlets, 39 H total, CH_3, Si-*t*-*Bu*), 0.18 to –0.06) (singlets, 24 H total, SiMe_2); HRMS (FAB) calcd for $C_{79}H_{139}N_3O_{17}Si_4$ + H 1514.9260, found 1514.9318 (M + H).

Oxidation–Reduction of Alcohol 33. Preparation of Alcohol 35 via Ketone 34. DMSO (16 μL, 0.231 mmol) was added to cold (–78 °C), magnetically stirred dry CH_2Cl_2 (3 mL) under argon. Tetramethylurea (28 μL, 0.231 mmol) was added to the solution followed by dropwise addition of trifluoroacetic anhydride (16 μL, 0.116 mmol). The reaction mixture was stirred at –78 °C for 20 min before the dropwise addition of alcohol **33** (70 mg, 0.046 mmol) in dry CH_2Cl_2 (4 mL) (vigorous stirring). After the mixture was stirred at that temperature for 2 h, triethylamine (32 μL, 0.231 mmol) was slowly added, and stirring was continued for 15 min. Dry ether (10 mL) was slowly added with stirring to the mixture at –78 °C, and then the solution was diluted further with ether (10 mL) at ambient temperature. Rapid and successive washings with H_2O (2 × 5 mL), saturated aqueous $NaHCO_3$ (5 mL), and brine (5 mL) followed by drying ($MgSO_4$) and concentration gave crude ketone **22** (65 mg, 93% crude yield) (R_f 0.21, silica, 40% ether in petroleum ether). Due to its rather unstable nature this compound was not purified or characterized further but was directly used for the next step.

The crude ketone obtained above (65 mg) was dissolved in MeOH (0.6 mL) and THF (0.4 mL) and treated (magnetic stirring) with $NaBH_4$ (2.6 mg, 0.069 mmol) at room temperature under argon. After 15 min, the mixture was diluted with ether (20 mL), and the resulting solution was washed with H_2O (2 × 5 mL) and brine (5 mL) and dried ($MgSO_4$). Concentration followed by flash column chromatography (silica, 30% ether in petroleum ether) gave hydroxy compound **35** (56 mg, 80% based on alcohol **33**). **35**: yellow amorphous solid; R_f 0.26 (silica, 30% ether in petroleum ether); $[\alpha]_D^{20}$ +70.3° (c 0.35, $CHCl_3$); UV–vis ($CHCl_3$) λ_{max} 412 ($E_{1cm}^{1\%}$ 802), 390 (772), 369 (473), 350 nm (216); IR ($CHCl_3$) ν_{max} 3580 (m, OH), 2950, 2920, 2105 (s, N_3), 1730 (s, C=O, ester, lactone), 1420, 1360 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.40–5.80 (m, 13 H, olefinic), 5.60 (dd, J = 14.4, 8.7 Hz, 1 H, H-33), 4.80 (m, 1 H, H-37), 4.56 (m, 1 H, H-19), 4.45 (s, 1 H, H-1′), 4.30–3.10 (m, 1 H, C*H*O, C*H*N, H-5′), 4.10 (br s, 1 H, H-2′), 3.67 (s, 3 H, COOCH_3), 3.07 (s, 3 H, OCH_3), 2.45–0.60 (m, 19 H, CH_2C(O), C*H*C(O), allylic C*H*, CH_2, C*H*), 1.37, 1.35, 1.30 and 1.29 (singlets, 12 H total, acetonides), 1.26 (d, J = 6.2 Hz, 3 H, CH_3), 1.17 (d, J = 6.0 Hz, 3 H, CH_3), 0.98 (d, J = 6.8 Hz, 3 H, CH_3), 0.94 (d, J = 7.0 Hz, 3 H, CH_3), 0.88–0.80 (singlets, 36 H total, Si-*t*-*Bu*), 0.085 to –0.085) (singlets, 24 H total, SiMe_2); HRMS (FAB) calcd for $C_{79}H_{139}N_3O_{17}Si_4$ + H 1514.9260, found 1514.9347 (M + H).

Silylation of Alcohol 35. Preparation of Pentakis(*tert*-butyldimethylsilyl) Azide 36. To a magnetically stirred solution of **35** (60 mg, 0.040 mmol) and 2,6-lutidine (21 mg ≡ 23 μL, 0.20 mmol) in dry $CHCl_3$ (0.3 mL) under argon was added *t*-BuMe_2SiOTf (26 mg ≡ 23 μL, 0.10 mmol) at 0 °C. Cooling was removed and stirring was continued for 2 h at room temperature. Saturated aqueous $NaHCO_3$ (1 mL) was added followed by dilution with ether (50 mL). The organic phase was washed with saturated aqueous $CuSO_4$ (3 × 5 mL), H_2O (5 mL), saturated aqueous $NaHCO_3$ (5 mL), brine (5 mL) and dried ($MgSO_4$). Concentration followed by preparative TLC (0.5 mm silica plate, 15% ether in petroleum ether) gave pure **36** as a yellow amorphous solid (60 mg, 93%). **36**: R_f 0.23 (silica, 15% ether in petroleum ether); $[\alpha]_D^{20}$ +105.9° (c 0.22, $CHCl_3$); UV–vis ($CHCl_3$) λ_{max} 412 ($E_{1cm}^{1\%}$ 800), 388 (773), 370 (472), 350 nm (218); IR ($CHCl_3$) ν_{max} 2960, 2940, 2860, 2110 (s, N_3), 1735 (s, C=O, ester, lactone), 1480, 1390 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30–5.90 (m, 12 H, olefinic), 5.80 (dd, J = 14.4, 6.7 Hz, 1 H, H-20), 5.54 (dd, J = 15.0, 9.2 Hz, 1 H, H-33), 4.83 (m, 1 H, H-37), 4.50 (m, 1 H, H-19), 4.27 (s, 1 H, H-1′), 4.27–3.10 (m, 11 H, C*H*O, C*H*N), 3.98 (d, J = 2.5 Hz, 1 H, H-2′), 3.67 (s, 3 H, COOCH_3), 3.08 (s, 3 H, OCH_3), 2.45–0.70 (m, 19 H, CH_2C(O), C*H*C(O), allylic C*H*, CH_2, C*H*), 1.39, 1.34, 1.31, 1.29 (singlets, 3 H each, acetonides), 1.21 (d, J = 6.2 Hz, 3 H, CH_3), 1.17 (d, J = 6.1 Hz, 3 H, CH_3), 0.98 (d, J = 6.8 Hz, 3 H, CH_3), 0.90, 0.89, 0.884, 0.878, 0.870 (singlets, 39 H total, CH_3, Si-*t*-*Bu*), 0.15 to –0.04 (singlets, 30 H, total, SiMe_2); HRMS (FAB) calcd for $C_{85}H_{153}N_3O_{17}Si_5$ + H 1629.0124, found 1629.0050 (M + H).

Reduction–Acetylation of Azide 36. Preparation of *N*-Acetylamphotericin B Methyl Ester Derivative 38 via Amine 37. To a magnetically stirred solution of azide **36** (16.3 mg, 0.01 mmol) in absolute MeOH (0.5 mL) under argon were added propanedithiol (10 μL, 0.1 mmol) and triethylamine (14 μL, 0.1 mmol) at room temperature. The reaction mixture was stirred at ambient temperature for 24 h. The solvent and excess reagents were removed under vacuum, and the residue was subjected to PTLC (silica, 5% ether in CH_2Cl_2) to afford reasonably pure amine **37** (coeluting reagent-derived byproducts were difficult to remove completely), which was acetylated as follows.

The amine obtained above (16 mg) was dissolved in dry CH_2Cl_2 (1.0 mL), cooled to 0 °C, and stirred under argon. 4-(Dimethylamino)-

pyridine (DMAP, 12 mg, 0.1 mmol) and acetic anhydride (2 μL, 0.02 mmol) were sequentially added, and stirring was continued for 10 min (0 → 25 °C). The reaction mixture was then diluted with ether (50 mL), washed with H_2O (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL), and dried ($MgSO_4$). Concentration followed by flash column chromatography (silica, 20% ether in petroleum ether) gave *N*-acetylamphotericin B methyl ester derivative **38** (14 mg, 85%), identical with an authentic sample obtained from natural amphotericin B [TLC, $[\alpha]_D$, UV-vis, IR ^1H and ^{13}C NMR].[1]

Desilylation of Compound 35. Preparation of Amphotericin B Derivative 39. The tetrakis(*tert*-butyldimethylsilyl) derivative **35** (76 mg, 0.05 mmol) was dissolved in absolute MeOH (1.0 mL) in a plastic bottle. Diluted HF·pyr (190 μL of a solution prepared as follows: 10 mL of commercial HF·pyr, Aldrich, ca. 70%, in a plastic bottle under argon at −20 °C was dropwise diluted with 4 mL dry pyridine) was dropwise added at ambient temperature under argon. The mixture was stirred at 50 °C for 48 h before being cooled to room temperature and poured onto saturated aqueous $NaHCO_3$ solution (20 mL). The organic compounds were extracted with EtOAc (2 × 10 mL), and the extract was washed with saturated aqueous $CuSO_4$ (20 mL) and brine (20 mL). Drying ($MgSO_4$) followed by concentration and flash column chromatography (silica, 5% MeOH in CH_2Cl_2) gave, in order of elution, a monosilylated derivative of **39** (23 mg, 40%, R_f 0.20) and the desired derivative **39** (21 mg, 40%). **39**: yellow amorphous solid; R_f 0.10 (5% MeOH in CH_2Cl_2); $[\alpha]_D^{20}$ +150.6° (*c* 0.34, $CHCl_3$); UV-vis ($CHCl_3$) λ_{max} 412 ($E_{1cm}^{1\%}$ 798), 388 (854), 368 (558), 349 nm (296); IR ($CHCl_3$) ν_{max} 3600, 3500, 3000, 2940, 2880, 2100 (s, N_3), 1730 (s, C=O, ester, lactone), 1460, 1440, 1380, 1160, 1070, 1010 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.31–6.02 (m, 12 H, olefinic), 5.83 (dd, *J* = 14.6, 5.6 Hz, 1 H, H-20), 5.43 (dd, *J* = 14.7, 9.2 Hz, 1 H, H-33), 5.20 (m, 1 H, H-37), 4.60 (m, 1 H, H-19), 4.49 (s, 1 H, H-1′), 4.28–3.03 (m, 17 H, C*H*O, H-3′, O*H*), 3.73 (s, 3 H, $COOCH_3$), 3.07 (s, 3 H, OCH_3), 2.46–0.90 (m, 18 H, allylic C*H*, $CH_2C(O)$, C*H*C(O), CH_2, C*H*), 2.28 (t, *J* = 10.4 Hz, 1 H, H-16), 1.40–1.31 (singlets, 15 H total, acetonides, CH_3), 1.18 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.10 (d, *J* = 6.6 Hz, 3 H, CH_3), 0.99 (d, *J* = 7.2 Hz, 3 H, CH_3).

Reduction of Azide 39. Preparation of Amphotericin B Derivative 40. The reduction of azide **39** (10.5 mg, 0.01 mmol) was carried out by the procedure described for the reduction of **36** to **37**. The resulting product was purified by flash column chromatography (silica, 60% MeOH in CH_2Cl_2), affording pure amphotericin B derivative **40** (9.2 mg, 89%) as a yellow amorphous solid. Since this compound was rather unstable, it was immediately used for the next step. A sample of this compound was acetylated by standard method (Ac_2O in CH_2Cl_2, 0 °C, 10 min) for characterization. **41** (in Scheme V): R_f 0.29 (silica, 10% MeOH in CH_2Cl_2); $[\alpha]_D^{20}$ +171° (*c* 0.07 $CHCl_3$); UV-vis ($CHCl_3$) λ_{max} 412 ($E_{1cm}^{1\%}$ 743), 388 (721), 368 (446), 350 nm (216); IR (film) ν_{max} 3480 (OH), 3440 (NH), 1730 (s, C=O, ester, lactone), 1660 (s, C=O, *N*-acetate) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.46 (d, *J* = 7.4 Hz, 1 H, N*H*), 6.40–6.10 (m, 12 H, olefinic), 5.86 (dd, *J* = 14.6, 5.4 Hz, 1 H, H-20), 5.42 (dd, *J* = 15.1, 9.6 Hz, 1 H, H-33), 5.23 (m, 1 H, H-37), 4.54 (d, *J* = 0.9 Hz, 1 H, H-1′), 4.65–3.10 (m, 13 H, C*H*N, C*H*O), 3.75 (s, 3 H, $COOCH_3$), 3.09 (s, 3 H, OCH_3), 2.60–2.10 (m, 4 H, allylic C*H*, C*H*C(O), $CH_2C(O)$), 2.09 (s, 3 H, $NHCOCH_3$), 2.02–1.45 (m, 15 H, CH_2, C*H*), 1.42, 1.37, 1.35, 1.33 (singlets, 12 H total, acetonides), 1.33 (d, *J* = 6.0 Hz, 3 H, CH_3), 1.20 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.12 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.01 (d, *J* = 7.2 Hz, 3 H, CH_3); HRMS (FAB) calcd for $C_{57}H_{87}NO_{18}$ + Na 1096.5819, found 1096.5898. Anal. Calcd for $C_{57}H_{87}NO_{18}$: C, 63.71; H, 8.17; N, 1.30. Found: C, 63.32; H, 8.19; N, 1.29.

Synthesis of Amphotericin B Methyl Ester (42). To a stirred solution of diacetonide **40** (10.4 mg, 0.01 mmol) in absolute MeOH at 25 °C (0.4 mL) was added camphorsulfonic acid (2.8 mg, 0.012 mmol) under argon. The reaction mixture was stirred at ambient temperature for 2 h, H_2O (0.1 mL) was added, and stirring was continued for an additional 4 h. The mixture was then diluted with CH_2Cl_2 (1 mL), and solid $NaHCO_3$ (10 mg) was added. After the mixture was stirred for 15 min, the solid was filtered off, and the solution was concentrated in vacuo. Flash column chromatography (silica, 50% MeOH in CH_2Cl_2) gave essentially pure amphotericin B methyl ester (**42**) (2.6 mg, 55% overall from **39**, based on ca. 50% conversion of **40**). Further purification for analytical purposes was achieved either by PTLC (silica, 60% MeOH in CH_3CN) or HPLC (reverse phase, Whatman Partisil 10 ODS, 4.6 × 250 mm; gradient solvent system: 60% B in MeOH to 10% B in MeOH in 5 min; B=2% $EtNH_2$ in H_2O; product injected in DMSO solution; t_R 9.8 min; flow rate 1.5 mL/min). **42**: yellow amorphous solid; R_f 0.13 (silica, 60% MeOH in CH_2Cl_2); $[\alpha]_D^{20}$ +392° (*c* 0.33, DMF); UV-vis (MeOH–$CHCl_3$, 2:1) λ_{max} 407 ($E_{1cm}^{1\%}$ 1342), 384 (1242), 364 (742), 346 nm (342); IR (Nujol) ν_{max} 3400 (s, OH, NH_2), 1725 cm^{-1} (s, C=O, ester, lactone); ^1H NMR (500 MHz, DMSO-d_6–D_2O, 10:1, TMS) δ 6.47–6.08 (m, 12 H, olefinic), 5.93 (dd, *J* = 15.3, 8.9 Hz, 1 H, H-20), 5.45 (dd, *J* = 14.9, 9.9 Hz, 1 H, H-33), 5.21 (m, 1 H, H-37), 4.36 (m, 1 H, H-19), 4.25 (s, 1 H, H-1′), 4.23 (m, 2 H, H-11, H-17), 4.05 (m, 2 H, H-3, H-15), 3.65–3.30 (m, 4 H, C*H*O), 3.63 (s, 3 H, $COOCH_3$), 3.10 (br t, *J* = 7.7 Hz, 1 H, H-35), 3.05 (dq, *J* = 9.3, 6.1 Hz, 1 H, H-5′), 2.87 (dd, *J* = 9.3 Hz, 1 H, H-4′), 2.29 (m, 2 H, H-3′, H-34), 2.18 (m, 2 H, H-2), 2.08 (t, *J* = 10.5 Hz, 1 H, H-16), 1.95–1.00 (m, 15 H, CH_2), 1.15 (d, *J* = 6.1 Hz, 3 H, CH_3), 1.11 (d, *J* = 6.3 Hz, 3 H, CH_3), 1.04 (d, *J* = 6.4 Hz, 3 H, CH_3), .092 (d, *J* = 7.1 Hz, 3 H, CH_3), a broad HOD peak appears around 3.5 ppm; HRMS (FAB) calcd for $C_{48}H_{75}NO_{17}$ + H 938.5112, found 938.5040 (M + H).

Amphotericin B (1). To a stirred solution of amphotericin B methyl ester (**42**) (9.4 mg, 0.01 mmol) in THF (0.2 mL) and H_2O (0.1 mL) under argon was added aqueous LiOH solution (0.1 mL, 1 M) at 0 °C. The cooling bath was removed and the mixture was stirred at ambient temperature with TLC monitoring (silica, *n*-BuOH–EtOH–Me_2CO–concentrated NH_4OH, 2:5:1:3). On complete reaction (ca. 1 h), the reaction mixture was acidified to pH 5 with dilute aqueous hydrochloric acid solution, resulting in partial precipitation of the product. The solvents were removed in vacuo (ambient temperature), and the residue was dissolved in DMSO (0.2 mL) and injected into an HPLC column (reverse phase, Whatman Partisil 10 ODS, 4.6 × 250 mm). Elution with a gradient solvent system (60% B in MeOH to 10% B in MeOH in 5 min; B = 1.4% aqueous NH_4OH) gave a solution of amphotericin B (**1**) (t_R 7.2 min, flow rate 1.5 mL/min). Evaporation of the solvents in vacuo gave essentially pure amphotericin B (**1**), which was purified further by the following procedure provided by Dr. S. Taylor, Squibb Laboratories. Amphotericin B (**1**) obtained above was suspended in a mixture (1 mL) of H_2O–MeOH–DMF–CH_2Cl_2 (1:2:1:0.5). The pH was adjusted to ca. 6.5 with 10% aqueous citric acid solution, and the suspension was heated to 45–50 °C for 20 min with stirring. Cooling to room temperature followed by filtration, washing with H_2O and acetone, and drying under vacuum gave pure amphotericin B (**1**) (7 mg, 80%) as a microcrystalline yellow solid: mp 168 °C dec; R_f 0.41 (silica, *n*-BuOH–EtOH–Me_2CO–concentrated NH_4OH, 2:5:1:3), $[\alpha]_D^{20}$ +381.9° (*c* 0.16, DMF); UV-vis (CH_3OH) λ_{max} 405 ($E_{1cm}^{1\%}$ 1725), 381 (1542), 361 (912), 344 nm (412); IR (Nujol) ν_{max} 3380 (s, OH, NH_2), 1700 (s, C=O, acid, ester), 1560 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6–D_2O, 10:1, TMS) δ 6.47–6.08 (m, 12 H, olefinic), 5.98 (dd, *J* = 14.1, 8.7 Hz, 1 H, H-20), 5.44 (dd, *J* = 14.9, 9.9 Hz, 1 H, H-33), 5.21 (m, 1 H, H-37), 4.53 (s, 1 H, H-1′), 4.37 (m, 1 H, H-19), 4.24 (m, 1 H, H-11), 4.19 (t, *J* = 9.8 Hz, 1 H, H-17), 4.05 (m, 1 H, H-3), 3.96 (dt, *J* = 9.8, 4.5 Hz, 1 H, H-15), 3.77 (d, *J* = 3.2 Hz, 1 H, H-2′), 3.58–3.45 (br HOD peak plus 3 H, C*H*O), 3.21 (m, 1 H, H-5′), 3.10 (m, 2 H, H-4′, H-35), 2.78 (m, 1 H, H-3′), 2.28 (m, 1 H, H-34), 2.20–2.12 (m, 3 H, H-2, H-18), 1.88–1.05 (m, 14 H, CH_2, C*H*), 1.86 (t, *J* = 9.8 Hz, 1 H, H-16), 1.17 (d, *J* = 6.0 Hz, 3 H, CH_3), 1.11 (d, *J* = 6.3 Hz, 3 H, CH_3), 1.04 (d, *J* = 6.4 Hz, 3 H, CH_3), 0.92 (d, *J* = 7.1 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, DMSO, TMS) δ 177.43, 170.50, 136.67, 133.85, 133.38, 133.13, 132.41, 132.12, 131.83, 131.19, 128.53, 96.95, 95.52, 77.13, 74.30, 73.98, 73.48, 72.49, 69.22, 68.73, 67.67, 66.19, 65.53, 58.73, 56.06, 46.37, 44.64, 44.28, 42.44, 41.90, 35.06, 29.09, 18.45, 17.84, 16,86, 11.99. Anal. Calcd for $C_{47}H_{73}NO_{17}$: C, 61.09; H, 7.96; N, 1.51. Found: C, 61.18, H, 8.01; N, 1.55.

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