the National Institutes of Health, the donors of the Petroleum Research Fund, administered by the American Chemical Society, the State University of New York at Stony Brook, and the University of Notre Dame. The 300-MHz NMR spectrometers used in this work were purchased in part by funds provided by the National Science Foundation. P.H. also thanks Professor Björn Åkermark and the Royal Institute of Technology (Stockholm, Sweden) for providing a Visiting Scientist position (1986).

Supplementary Material Available: Further experimental data, including general remarks, procedures for preparation of *rac*-**8a** and *rac*-**11**, detailed description of X-ray structure determinations, supplementary literature references for these procedures, and Tables I-VII of X-ray diffraction bond lengths, bond angles, refinement data, thermal parameters, and hydrogen atom coordinates for *rac*-**5a**, *rac*-**6a**, and (*S*)-**5b** (41 pages). Ordering information is given on any current masthead page.

Chemistry of Amphotericin B. Degradation Studies and Preparation of Amphoteronolide B†

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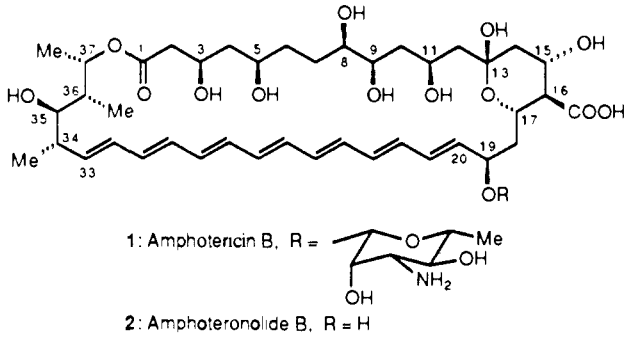
Abstract: Amphotericin B (**1**) was converted to a series of protected derivatives (**3-5**, **27**). Compound **5** was degraded by ozonolysis and further elaborated to fragments **8**, **14**, and **15**, three potential intermediates in a projected total synthesis of amphotericin B (**1**). A novel oxidative deglycosidation procedure based on radical bromination was devised and applied to the degradation of **5** and **27** to heptaenones **21** and **28**, respectively. These heptaenones were stereospecifically reduced with sodium borohydride to amphoteronolide B derivatives **23** and **29**, respectively. The *R* stereochemistry of the C-19 hydroxyl group arising from the reduction of these polyenones was confirmed by using Nakanishi's CD method on derivative **26** obtained by appropriate chemical manipulations of the reduction products. The aglycon of amphotericin B, amphoteronolide B (**2**), was obtained from **29** by desilylation followed by methyl ester hydrolysis.

The polyene macrolide class of antibiotics, encompassing hundreds of compounds, is one of the most challenging areas of natural products chemistry due to the complexity and biomedical importance of its members.[1] Amphotericin B (**1**),[2] the most prominent member of this class and a widely used antifungal agent, is produced by *Streptomyses nodosus* and is the only member of this family of compounds whose structure has been fully established by X-ray crystallographic analysis.[3] Serious difficulties in the chemistry of these natural products have long been recognized and are responsible for the notable scarcity of full structural elucidations and the lack of semisynthetic materials for biological and chemical investigations. The origin of these problems rests in the high molecular weight of these compounds and their lack of crystallinity and solubility in common organic solvents, as well as high chemical and photosensitivities. It is, therefore, not surprising that despite many attempts, this field remains largely unexplored. With the long term intention of opening the field to chemical and biological investigations, we recently embarked on a program directed toward the exploration of the chemistry of amphotericin B (**1**). Our immediate goals were the derivatization and degradation of amphotericin B (**1**) and the preparation of its aglycon, amphoteronolide B (**2**), as a prelude to eventual total syntheses of these and other potentially bioactive materials.



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

Amphoteronolide B (**2**) and its derivatives are important chemical entities from a number of perspectives, including (a) possible biological activity and natural occurrence, (b) potential starting points for enzymatic and chemical preparation of amphotericin B analogues, and (c) advanced intermediates and comparison/relay stages for an eventual total synthesis of amphotericin B (**1**) itself. In this paper we describe our studies on the chemistry of amphotericin B (**1**), including protection and degradation,[4] oxidative deglycosidation, and conversion to amphoteronolide B (**2**).[5]

Results and Discussion

Protection and Degradation of Amphotericin B (1). After a brief encounter with amphotericin B (**1**) it was soon recognized that a prerequisite to the development of its chemistry was to produce derivatives that were soluble in common organic solvents, facilitating both chromatographic and spectroscopic work. Previous work[6] has shown that selective acetylation of the amino group (Ac_2O) followed by methylation of the carboxyl group (CH_2N_2) leads to the *N*-acetylamphotericin B methyl ester (**3**) with improved physical properties over **1** but still presenting solubility and chromatographic problems. Further protection, preferably differentiating the various hydroxyl groups, was, therefore, sought.

(1) For reviews on this subject, see: (a) *Macrolide Antibiotics, Chemistry, Biology and Practice*; Omura, S., Ed.; Academic: New York, 1984. (b) Ryley, J. F.; Wilson, R. G.; Gravestock, M. B.; Poyser, J. P. *Adv. Pharmacol. Chemother.* **1981**, *18*, 49. (c) Hammond, S. M. *Prog. Med. Chem.* **1977**, *14*, 105. (d) Tereshin, I. M. *Polyene Antibiotics—Present and Future*; University of Tokyo; Tokyo, Japan, 1976. (e) Hamilton-Miller, J. M. T. *Bactiriol. Rev.* **1973**, *37*, 166.

(2) Vandeputte, J.; Watchtel, J. L.; Stiller, E. T. *Antibiot. Annu.* **1956**, 587.

(3) 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.

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

(5) Preliminary communication: Nicolaou, K. C.; Chakraborty, T. K.; Daines, R. A.; Ogawa, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 686.

(6) Schaffner, C. P. *J. Antibiot.* **1972**, *25*, 256. Pandey, R. C.; Rinehart, K. L., Jr. *J. Antibiot.* **1977**, *30*, 158.

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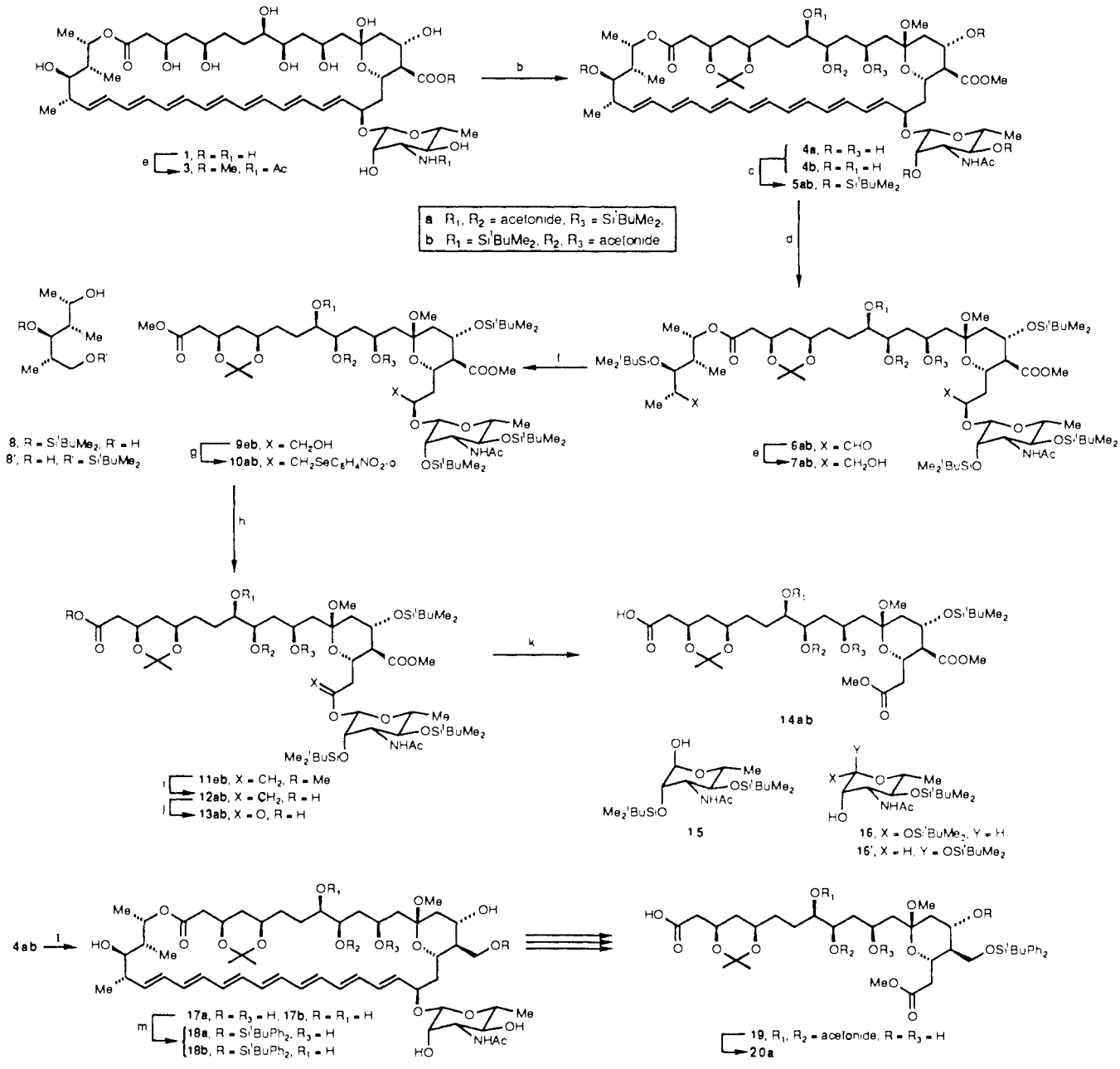
Scheme I[a]



[a] (a) 1.1 equiv of Ac_2O, DMSO–MeOH (1:1), 0 °C, 0.5 h and then excess CH_2N_2–Et_2O, 0 °C, 0.5 h; (b) CSA catalyst, MeOH–$Me_2C(OMe)_2$ (3:1), 25 °C, 1 h, 66% overall from amphotericin B (**1**); (c) 6.5 equiv of *t*-$BuMe_2SiOTf$, 9.0 equiv of 2,6-lutidine, 0 °C, 15 min, 75%; (d) O_3, MeOH–CH_2Cl_2 (1:15), −78 °C and then 10.0 equiv of Ph_3P, −78 to 25 °C, 16 h, 60%; (e) 15.0 equiv of $NaBH_4$, MeOH, 0–25 °C, 0.5 h, 95%; (f) 1.2 equiv of K_2CO_3, MeOH, 25 °C, 8 h, **9ab**: 93%, **8** and **8'**: 90%; (g) 10.0 equiv of *o*-$O_2NC_6H_4SeCN$, 10.0 equiv of *n*-Bu_3P, THF–pyr (2:1), 0 °C, 3 h, 85%; (h) O_3, CH_2Cl_2, −78 °C and then 10.0 equiv of *i*-Pr_2NH, benzene, reflux, 3 h, 74%; (i) 1.5 equiv of LiOH, THF–H_2O (2:1), 0–25 °C, 3 h; (j) O_3, CH_2Cl_2, −78 °C and then 2.0 equiv of Ph_3P, −78 to 25 °C, 4 h, 75% overall from **11ab**; (k) 2.5 equiv of K_2CO_3, MeOH, 25 °C, 2 h, 90%; (l) 15.0 equiv of $NaBH_4$, MeOH, 40 °C, 15 min, 85%; (m) 3.0 equiv of *t*-$BuPh_2SiCl$, 5.0 equiv of imidazole, DMF, 0–25 °C, 6 h, 80%.

The breakthrough came when the acetamide methyl ester derivative **3** was treated with MeOH–$Me_2C(OMe)_2$ (3:1) under acid catalysis (CSA) at 25 °C, and the reaction was carefully monitored by TLC, furnishing the diacetonide methyl ester derivative **4ab** as a mixture of two isomers (Scheme I) in 66% overall yield (ca 1–5:1 ratio, depending on reaction time) from amphotericin B (**1**). The initially assigned nature of these isomers as methoxy anomers of the 3,5-, 9,11-diacetonide **4b** was revised to the regioisomers **4a** and **4b** with a single methoxy orientation[11] as shown in Scheme I. These assignments were based on ^1H NMR studies on derivatives related to **4a** and **4b** as will be discussed below. This derivative (**4ab**) and compounds derived from it exhibited good solubility properties in common organic solvents and behaved chromatographically and spectroscopically quite reasonably. With this initial prequisite satisfied, the remaining chemistry outlined in Scheme I then became possible, producing a number of amphotericin B derivatives and degradation products. Our next objective was to explore the possibility of extracting useful

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(8) Gilman, S.; Grieco, P. A.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.
(9) Nicolaou, K. C.; Daines, R. A.; Uenishi, J.; Li, W. S.; Papahatjis, D. P.; Chakraborty, T. K. *J. Am. Chem. Soc.*, accompanying paper in this issue.
(10) Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.*, accompanying paper in this issue.
(11) We thank Professor S. Masamune for bringing to our attention this possibility in the form of a manuscript: Kennedy, R. M.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1988**, *29*, 447. Appropriate revisions should be noted for communications 4 and 5.

fragments from the amphotericin B framework for possible semisynthetic studies and comparison purposes. To this end, exposure of **4ab** to excess *t*-BuMe$_2$SiOTf in the presence of 2,6-lutidine[7] led to the pentasilyl ether derivative **5ab** in 75% yield (mixture of two isomers, ca. 3:1 by ^{1}H NMR). Compound **5ab** was then exhaustively ozonized in CH_2Cl_2–MeOH (15:1) followed by exposure of the resulting ozonide to Ph_3P, producing dialdehyde **6ab** in 60% yield. This dialdehyde (**6ab**) was then reduced further by the action of $NaBH_4$ in MeOH, leading to the dihydroxy compound **7ab** (95% yield). Transesterification of **7ab** with K_2CO_3 in absolute MeOH gave methyl ester **9ab** (93% yield) and diols **8** (60%) and **8′** (30%, by silyl group migration). The next stage involved removal of the mycosamine unit from fragment **9ab**, a task made difficult by the rather acid-sensitive nature of **9ab** and the reluctance of the nitrogenous carbohydrate moiety to depart. An indirect sequence was, therefore, devised in order to achieve this objective. The designed scheme called for the generation of an ester such as **13ab** (Scheme I), which could be cleaved by saponification, causing the desired separation of fragments. Thus, the primary alcohol **9ab** was converted to the corresponding *o*-nitrophenyl selenide **10ab** by the standard procedure (*o*-$NO_2C_6H_4SeCN$–*n*-Bu_3P, 85% yield)[8] followed by oxidation–syn-elimination to furnish the enol ether **11ab** (74% yield). Selective hydrolysis of the methyl ester in **11ab** (LiOH) (thus, differentiating C-1 from C-19) followed by ozonolysis (CH_2Cl_2, −78 °C) of the terminal olefin and reaction with Ph_3P led to the targeted carbohydrate ester **13ab** (75% overall yield from **11ab**) via compound **12ab**. Dismantling of compound **13ab** was then easily achieved under basic conditions (K_2CO_3–absolute MeOH), leading to dimethyl ester **14ab** (90%, mixture of isomers, ca. 3:1 by ^{1}H NMR) and mycosamine derivatives **15** (35%), **16** (18%), and **16′** (35%). Fragments **8**,[9] **14ab**,[10] and **15**[12] served as authentic samples for comparison of synthetic materials.

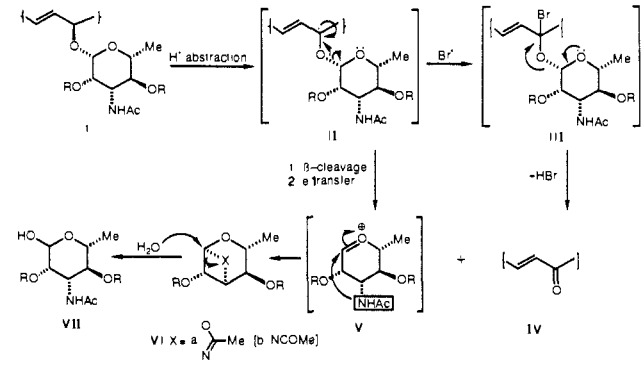
The degradation products **19** (R = H) and **20a** (R = Si-*t*-BuMe$_2$) (with the C-16 carboxyl group reduced) were also obtained at the initial stages of this program from the amphotericin B derivative **4ab** via compounds **17ab** and **18ab** by similar or slightly modified chemistry. Whereas the majority of the steps are too closely related to the above described sequence to warrant separate discussion, the initial chemoselective reactions are worth pointing out. Thus, the successful $NaBH_4$-induced reduction of the methyl ester in **4ab** (MeOH, 40 °C, 85% yield) is most likely due to a neighboring group participation (C-15 hydroxyl and/or carbohydrate unit). In support of this hypothesis is the observation that the fully protected derivative **5ab** is not reduced under the same conditions. Selective monosilylation of **17ab** to **18ab** was also highly efficient under standard conditions (*t*-BuPh$_2$SiCl–imidazole), allowing differentiation of the primary and secondary hydroxyl groups in this series of compounds.

With the major objectives of this part of our program accomplished, we then turned our attention to another goal, the deglycosidation of amphotericin B (**1**).

Novel Oxidative Deglycosidation of Amphotericin B. For purposes already mentioned above, it was desirable to remove the carbohydrate unit from amphotericin B (**1**), cleanly leaving behind the intact aglycon or protected derivatives of it. Numerous and persistent attempts in these and other laboratories failed to reach this objective. The two primary reasons for this failure must be (a) the stubborn resistance of the nitrogenous sugar toward acid hydrolysis and (b) the rather sensitive nature of amphotericin B (**1**) and its targeted aglycon, amphoteronolide B (**2**), and their derivatives toward a variety of potential cleaving reagents, particularly acidic ones. To circumvent these problems, a new method for deglycosidation of amphotericin B (**1**) (and hopefully other similar polyene macrolide antibiotics) involving oxidative removal of the carbohydrate unit under mild and neutral conditions was devised. Scheme II presents the mechanistic rationale on which this novel reaction was based. It was anticipated that the polyenic system of a suitable amphotericin B system (I) would facilitate

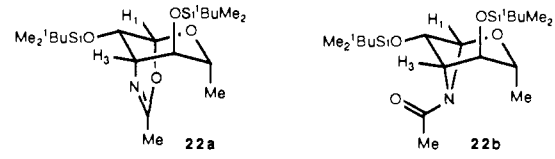
(12) Nicolaou, K. C.; Chakraborty, T. K.; Daines, R. A.; Ogawa, Y. *J. Am. Chem. Soc.*, accompanying paper in this issue.

Scheme II[a]



[a] Presumed mechanism for the oxidative deglycosidation of amphotericin B.

Table I. Spectroscopic Data of Compounds a, b and **22**

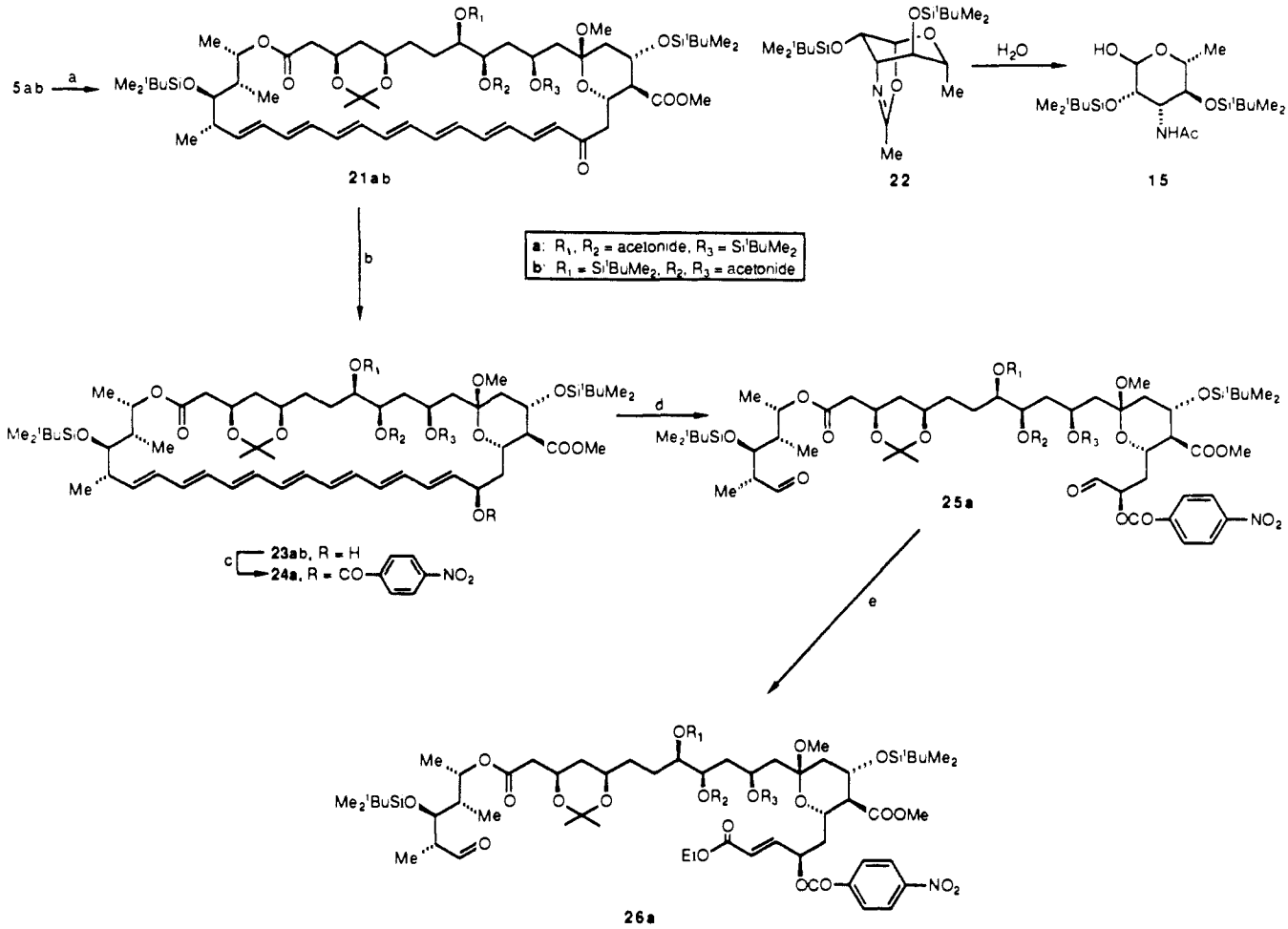


IR ($CHCl_3$) ν_{max}	1675 cm^{-1} (C=N)	1680 cm^{-1} (C=N)	1630 cm^{-1} (C=O)
^{13}C NMR ($CDCl_3$)	δ 157.35 (C=N)	δ 157.69 (C=N)	δ 170.42 (C=O)
^{1}H NMR (250 MHz, $CDCl_3$)	δ 1.85 (s, CH_3)	δ 1.93 (s, CH_3)	δ 1.85 (s, CH_3)

radical formation at C-19 by H· abstraction under appropriate conditions (e.g. *N*-bromosuccinimide homolysis). The generated radical (II) would then proceed to the labile bromo derivative III or collapse directly by β-cleavage to form the enone IV and a mycosaminyl radical, which upon electron transfer–oxidation would lead to the oxonium species V. The same species IV and V would also be expected to result from rapid collapse of bromide III with assistance from the ring oxygen as indicated in Scheme II. The reactive oxonium intermediate V could then undergo intramolecular capture by the acetamide group leading to bicycle VIa (or VIb), a potential pregenitor of mycosamine derivative VII. In practice, this scenario proved to be viable: *N*-bromosuccinimide in carbon tetrachloride was found to be an effective cleaving agent, producing enone IV and bicyclic system VIa from amphotericin B derivative I. The novel heterocycle VI, being easily hydrolyzed to the monocyclic mycosamine derivative VII, was isolated by careful chromatographic procedures and spectroscopically characterized (vide infra).

Scheme III demonstrates the initial degradation chemistry made possible by this neutral and mild deglycosidation reaction and the preparation of a number of amphoteronolide B derivatives. Thus, treatment of *N*-acetylamphotericin B methyl ester **5ab** (Scheme I) with a slight deficiency of NBS in CCl_4 and in the presence of $CaCO_3$ as buffer, led to heptaenone **21ab** (18–30% yield, 26–43% based on 30% recovered starting material) together with the bicyclic system **22** (10% yield), mycosamine derivative **15** (9% yield), and several other unidentified products (30% recovery of starting material **5ab**). Compounds **21ab**, **22**, and **15** were isolated by careful chromatographic procedures on silica gel and fully characterized by spectroscopic means. Thus, the brilliantly orange heptaenone **21ab** exhibitied a UV–vis ($CHCl_3$) maximum at λ_{max} 422 nm and ^{13}C NMR ($CDCl_3$) signals at δ 199.55 and 199.61 (two isomers). The novel bicyclo **22** exhibited an IR ($CHCl_3$) band at ν_{max} 1680 cm^{-1}, a ^{13}C NMR ($CDCl_3$) signal at δ 157.69, and in the ^{1}H NMR (250 MHz, $CDCl_3$) a signal at δ 1.93 (s, CH_3) and a coupling constant ($J_{1,3}$) of 2.3 Hz (Table I). This relatively strong *W*-type coupling, reminiscent of the thromboxane

Scheme III[a]



[a] (a) 0.95 equiv of NBS, 10.0 equiv of $CaCO_3$, CCl_4, 25 °C, 3–12 h, 18–30%; (b) 10.0 equiv of $NaBH_4$, MeOH, 0 °C, 15 min, 98%; (c) 1.2 equiv of *p*-NO_2–C_6H_4COCl, 1.5 equiv of DMAP, CH_2Cl_2, 0–25 °C, 15 min, 95%; (d) O_3, MeOH–CH_2Cl_2 (1:10), −78 °C and then 10.0 equiv of Ph_3P, −78 to 25 °C, 16 h; (e) 2.5 equiv of Ph_3P=CHCOOEt, benzene, 25 °C, 2 h, 78% overall from **24a**.

A_2 skeleton models[13] suggested the possibility of the bicyclo[3.1.1] structure **22b** (Table I) as an alternative structure for compound **22**. To resolve this issue the two model compounds, oxazine a[14] and azetidine b (Table I) were synthesized by standard procedures for spectroscopic comparisons. As Table I shows, the IR and ^{13}C NMR data strongly suggest the oxazine structure **22a** for **22** rather than the azetidine skeleton **22b**. Furthermore, Dreiding molecular models indicate a rigid framework for **22a** in which H_1 and H_3 occupy positions on a well-defined *W*, accommodating the 2.3-Hz coupling constant between H_1 and H_3. Thus, structure **22a** was assigned for the initial degradation product.

Having achieved the disconnection of the aglycon and carbohydrate fragments, we then considered the reduction of the resulting heptaenone **21**. CPK molecular models of this compound indicated two preferred conformations (carbonyl pointing β or α to the plane, see structure **21**, Scheme III), but in the absence of molecular mechanics calculations[15] it was not possible to ascertain the thermodynamically most stable one. It was clear, however, that peripheral attack on the carbonyl of **21** would result in a highly stereoselective, if not stereospecific, reduction. In the event, this expectation was fully realized. Thus, $NaBH_4$ reduction of heptaenone **21ab** in MeOH at 0 °C resulted in a single hydroxy stereoisomer **23ab** in 98% yield. The issue of stereochemistry of the newly generated hydroxyl group at C-19 was resolved by employing Nakanishi's CD method.[16] To this end, the *p*-nitrobenzoate **24a** was prepared in 95% yield from derivative **23a** by reaction with *p*-$NO_2C_6H_4COCl$ in the presence of 4-(dimethylamino)pyridine (DMAP). The UV–vis spectrum of compound **24a** ($CHCl_3$, λ_{max} 413, 390, 370, 350, and 272 nm) pointed to its unsuitability for the CD studies in mind, and, therefore, a second generation derivative was sought. Ozonolysis of **24a** in CH_2Cl_2–MeOH (−78 °C) followed by Ph_3P workup led to the dialdehyde **25a** in 85% yield, which was then reacted with 1.2 equiv

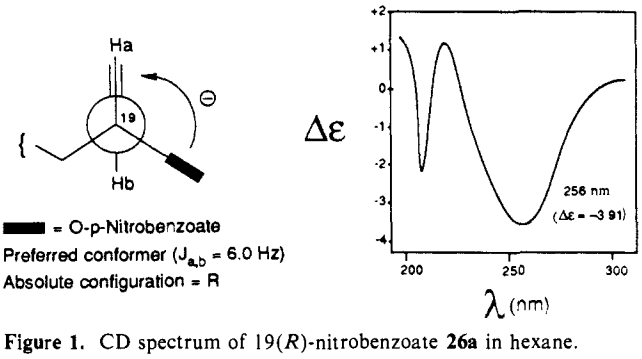


Figure 1. CD spectrum of 19(*R*)-nitrobenzoate **26a** in hexane.

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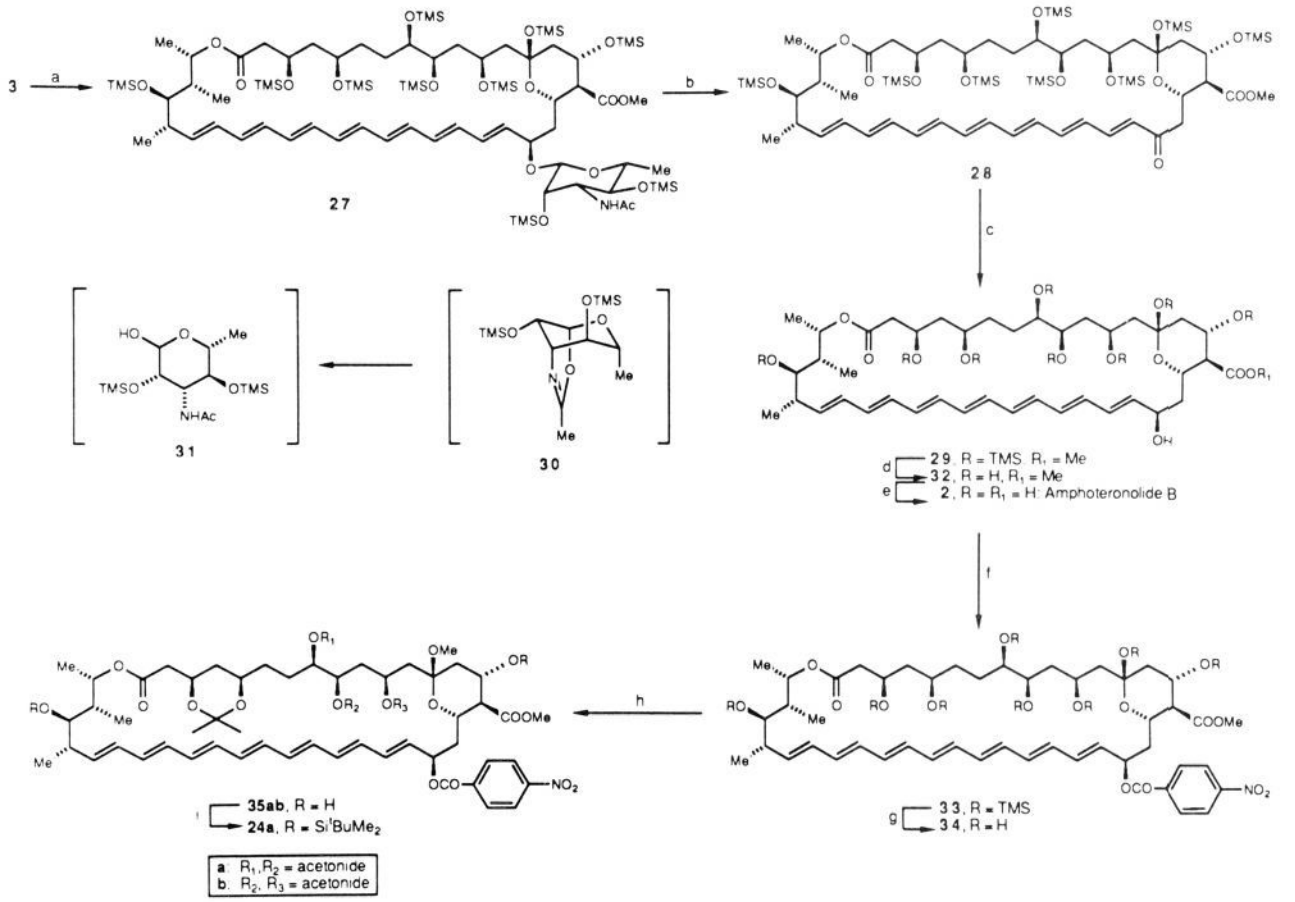
(14) Witte, H.; Seelinger, W. *Justus Liebigs Ann. Chem.* **1974**, *19*, 996. For studies on a number of other oxazines see: Meyers, A. I. *J. Org. Chem.* **1961**, *26*, 218. Myers, A. I.; Nabeya, A.; Adickes, H. W.; Politzer, I. R.; Malone, G. R.; Kovelesky, A. C.; Nolen, R. L.; Portnoy, R. C. *J. Org. Chem.* **1973**, *38*, 36.

(15) The complexity of this molecular framework prevented routine MM2 calculations to be carried out. Special techniques, however, may be envisioned for performing such calculations in the future.

(16) Gonella, N. C.; Nakanishi, K.; Martin, V. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1982**, *104*, 3775.

Scheme IV[a]



[a] (a) 12.0 equiv of Me_3SiOTf (TMSOTf), 15.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 15 min, 90%; (b) 0.95 equiv of NBS, 10.0 equiv of $CaCO_3$, CCl_4, 25 °C, 12 h, 20–25%; (c) 10.0 equiv of $NaBH_4$, MeOH, 0 °C, 15 min, 96%; (d) excess HF·pyr, THF, 0 °C, 15 min, 85%; (e) 10.0 equiv of LiOH, THF–H_2O (1:1), 0–25 °C, 1 h, 80% (75% conversion); (f) 1.2 equiv of *p*-$NO_2C_6H_4COCl$, 1.5 equiv of DMAP, CH_2Cl_2, 0–25 °C, 15 min, 95%; (g) same as (d), 90%; (h) CSA catalyst, MeOH–$Me_2C(OMe)_2$ (3:1), 25 °C, 0.5 h, 68%; (i) 4.5 equiv of *t*-$BuMe_2SiOTf$, 6.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 15 min, 85%.

of $Ph_3P{=}CHCOOEt$ in benzene to produce, chemoselectively, the α,β-unsaturated system **26a** (92%). The regiochemical outcome of this Wittig condensation was evident from the absence of one of the aldehydic proton signals and the appearance of an olefinic signal at δ 6.94 (dd, J = 15.5, 6.0 Hz for H-20) assigned by decoupling experiments. Steric hindrance at C-33 maybe responsible for the observed lower reactivity at this site. Compound **26a** [UV (MeOH) λ_{max} 258 and 204 nm] exhibited a negative Cotton effect in its CD spectrum (MeOH) indicating the 19*R* configuration for **26a** and its pregenitors **23a–25a** (see computer-simulated spectrum and Nakanishi's rule,[16] Figure 1). Subsequent synthesis of the amphotericin B derivative **5a**[12] from the aglycon derivative **23a** confirmed this configurational assignment at C-19. From this result it can be reasonably inferred that the average conformation of heptaenone **21** may closely resemble that shown in Figure 2. Although it was possible to remove the protecting groups from **23ab** and generate amphoteronolide B (**2**) and its methyl ester **32** it was decided to seek a more direct and convenient route to these targets by avoiding the relatively slow departing acetonide and *tert*-butyldimethylsilyl protecting groups.

Preparation of Amphoteronolide B (2) from Amphotericin B (1). Having designed and tested the oxidative deglycosidation reaction as described above we then focused our attention on a preparative procedure to produce amphoteronolide B (**2**) and its methyl ester **32** from amphotericin B (**1**). It was soon determined that the success of this reaction depended heavily on appropriate protection of the molecule and, therefore, a suitable strategy was designed as outlined in Scheme IV. The TMS group was chosen to protect the hydroxyl groups for its ease of attachment and removal. Thus, *N*-acetylamphotericin B methyl ester (**3**) was

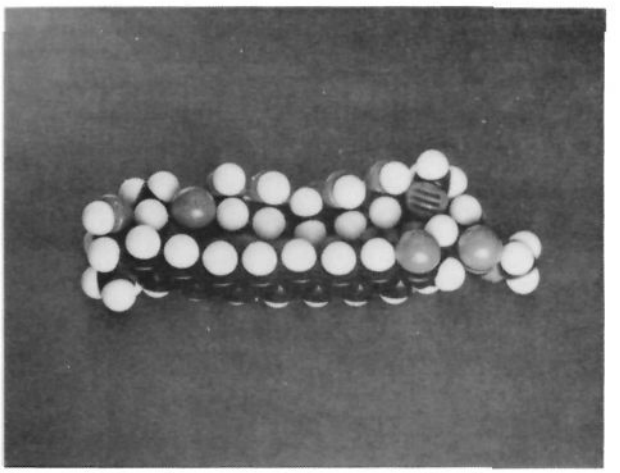


Figure 2. CPK model representing heptaenones **21** and **28**.

persilylated (excess TMSOTf, 2,6-lutidine, 90%) and then subjected to NBS-induced degradation in CCl_4 as described above to produce the persilylated heptaenone **28** (20–25% yield) and presumably the expected **30** and **31** (not isolated) as well as several other unidentified products. Again, CPK models of **28** indicated clear orientationl preferences in which the carbonyl group was exposed to peripheral attack pointing to a stereoselective reduction. Indeed, $NaBH_4$ reduction of **28** in MeOH at 0 °C produced **29** as a single stereoisomer at C-19, as in the case of **21ab** → **23ab**,

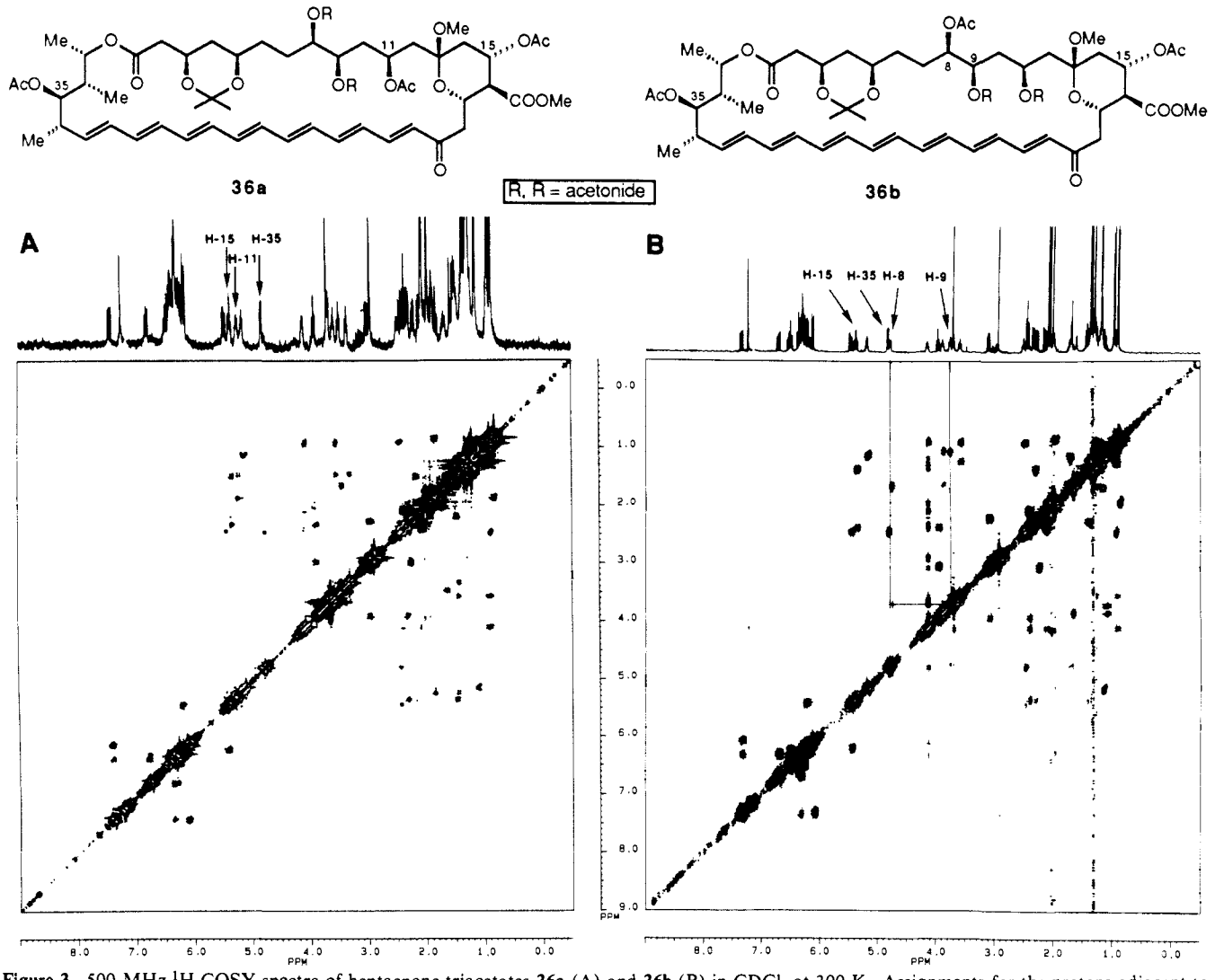


Figure 3. 500-MHz ^1H COSY spectra of heptaenone triacetates **36a** (A) and **36b** (B) in $CDCl_3$ at 300 K. Assignments for the protons adjacent to the acetate groups and the 1D spectra are given above (for more details see the Experimental Section).

in 96% yield. In order to establish the configuration of the newly generated hydroxyl group at C-19 it was necessary to correlate compound **29** with **24a** whose configuration was fully established as described above. This was done by the following sequence (Scheme IV): (i) *p*-nitrobenzoylation (*p*-$NO_2C_6H_4COCl$-DMAP, **29** → **33**, 95%), (ii) desilylation (excess HF·pyr, **33** → **34**, 90%), (iii) acetonization–methylketalization ($MeOH–Me_2C(OMe)_2$ (3:1), **34** → **35ab**, 68%), and (iv) persilylation (excess *t*-$BuMe_2SiOTf$–2,6-lutidine, **35a** → **24a**, 85%). The resulting derivative **24a** was chromatographically and spectroscopically (IR, UV–vis, ^1H NMR, ^{13}C NMR) identical with a sample obtained previously from **21a** according to Scheme III. This sequence, therefore, established the 19*R* configuration for **29** as intended for amphoteronolide B (**2**) and suggested similar conformational preferences for **28** and **21ab**, despite the different protecting groups around the periphery of the macroring.

The liberation of amphoteronolide B methyl ester (**32**) from **29** was easily achieved by brief exposure to excess HF·pyr in THF (85% yield). Finally, amphoteronolide B itself (**2**) was obtained by saponification of **32** by treatment with LiOH in $THF–H_2O$ (1:1) (80% yield based on ca. 75% conversion). Remethylation of **2** with excess CH_2N_2 in ether regenerated **32**, establishing that no stereochemical changes occurred during the saponification reaction.

The issue of the isomeric nature of compounds **4a** and **4b** and their derivatives (methoxy anomers vs 8,9- and 9,11-acetonide regioisomers) was settled by chemical and ^1H NMR spectroscopic means. Thus, the triacetate heptaenones **36a** and **36b** (Figure 3) were prepared from **4ab** via heptaenones **21a**[10] and **21b**, respectively, or more conveniently their TMS analogues, by desilylation followed by acetylation. ^1H NMR decoupling and ^1H COSY experiments defined the signals corresponding to the protons adjacent to the acetate groups in **36a** and **36b**. Furthermore, the 2D spectrum of **36b** exhibited a cross peak between resonances at 4.8 and 3.7 ppm corresponding to coupling between H-8 and H-9, whereas such a cross peak was absent in the spectrum of **36a** (Figure 3). In addition, decoupling experiments on **36a** pinpointed H-8 and H-9 at δ 3.37 and 3.50, respectively, indicating occupancy of these positions by an acetonide group and thus providing further support for these structural assignments.

Conclusion

A body of new chemistry of amphotericin B (**1**) is described in this paper, including useful protections, degradations, and a deglycosidation. The developed chemistry allowed, for the first time, the preparation of a series of well-characterized derivatives of this polyene macrolide antibiotic. Controlled degradation of these derivatives led to fragments of amphotericin B (**1**), useful in partial or total synthetic studies in the amphotericin B area as comparison stages and/or relay points.

A method for the oxidative deglycosidation of amphotericin B (**1**) has been developed. This novel, NBS-induced degradation procedure operates successfully on protected derivatives of this polyene macrolide antibiotic, producing the corresponding heptaenone systems. Subsequent $NaBH_4$-based reduction of the carbonyl functionality produces stereospecifically the 19(*R*)-hydroxy compounds, which could then be deprotected to amphoteronolide B (**2**) and its methyl ester (**32**). These derivatives

may now serve as starting points for further chemical manipulations and for the synthesis of a series of amphotericin B (**1**) analogues for biological investigations.

Furthermore, the described chemistry may find applications in the exploration of the chemistry of other members of the polyene macrolide class of antibiotics.[1] Such studies may open the way for structural elucidations, structural modifications, and partial and total syntheses in this biomedically important field of natural products. Plans in these directions are currently under consideration in these laboratories.[17]

Experimental Section

General Methods. NMR spectra were recorded on one of the following instruments: IBM WP-200, Bruker WM-250, IBM AF-250, or Bruker AM-500. IR spectra were recorded on a Perkin-Elmer Model 781 infrared spectrophotometer. UV and visible spectra were recorded on a Perkin-Elmer Model 553 ultraviolet and visible spectrophotometer. High-resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VC ZAB E instrument under FAB conditions. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, or Robertson Laboratories, Inc., Madison, NJ.

All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) with UV light and 7% ethanolic phosphomolybdic acid–heat as developing agent or by HPLC on Waters Delta Model 3000 (UV–vis detector). Preparative thin-layer chromatography was performed on 0.5 or 0.25 mm × 20 cm × 20 cm E. Merck silica gel plates (60F-254). E Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography.

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

***N*-Acetylamphotericin B Methyl Ester (3).**[6] Amphotericin B (**1**) (20.0 g, 0.02 mol, based on 90% purity) was dissolved in dry DMSO (200 mL) by vigorous magnetic stirring to give a deep yellow-orange solution (argon atmosphere). Dry MeOH (200 mL) was then added, causing partial precipitation. The stirred suspension was cooled to 0 °C and dropwise treated with freshly distilled Ac_2O (2.4 g ≡ 2.22 mL, 0.024 mol). After 10 min of stirring, the reaction was complete as indicated by total dissolution of the precipitated amphotericin B. To the resulting solution, excess diazomethane in ether (200 mL, ca. 0.07 mol) was added at 0 °C, and the mixture was stirred for 30 min, after which time excess diazomethane was removed from the solution by a stream of argon. The solution was transferred to a 3-L round-bottom flask and diluted with 2.5 L of ether. The immediately formed yellow precipitate was allowed to settle, and the supernatant liquid was decanted. Filtration of the solid, followed by washing with ether (3 × 500 mL) and drying in vacuo gave crude *N*-acetylamphotericin B methyl ester **3** (20 g) pure enough for the next step. Further purification could be achieved by flash column chromatography (silica, 5–20% MeOH in CH_2Cl_2). **3**: R_f 0.34 (silica, 20% MeOH in CH_2Cl_2); $[\alpha]^{20}_D$ +387° (*c* 0.21, DMF); UV–vis (MeOH–CH_2Cl_2, 10:1) λ_{max} 405 (E_{1cm}1% 1155), 382 (1018), 362 (628), 344 nm (266); IR (KBr) ν_{max} 3350 (s, OH), 1725 (C=O, ester, lactone), 1655 cm^{-1} (s, C=O, *N*-acetate); ^{1}H NMR (500 MHz, DMSO-d_6–D_2O, ca. 10:1, TMS) δ 6.47–6.05 (m, 12 H, olefinic), 5.92 (dd, *J* = 15.2, 8.8 Hz, 1 H, H-20), 5.45 (dd, *J* = 15.0, 9.9 Hz, 1 H, H-33), 5.20 (dq, *J* = 6.4, 2.6 Hz, 1 H, H-37), 4.36 (m, 1 H, H-19), 4.32 (s, 1 H, H-1′), 4.23 (m, 2 H, H-15, H-3), 3.68–3.42 (m, 4 H, H-5, H-8, H-2′, H-3′), 3.66 (s, 3 H, $COOCH_3$), 3.20–3.10 (m, 4 H, H-4′, H-5′, H-9, H-35), 2.29 (m, 1 H, H-34), 2.18 (m, 2 H, H-2), 2.09 (t, *J* = 10.5 Hz, 1 H, H-16), 1.95–1.10 (m, 15 H, CH_2, CH), 1.86 (s, 3 H, $NCOCH_3$), 1.17 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.11 (d, *J* = 6.4 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); the NH and OH signals were suppressed in this solvent system due to exchange with D_2O; HRMS (FAB) calcd for $C_{50}H_{77}NO_{18}$ + Na 1002.5037, found 1002.5012 (M + Na).

***N*-Acetyl-3,5:9,11-di-*O*-isopropylidene-13-*O*-methylamphotericin B Methyl Ester and Isomer (4ab).** To a suspension of *N*-acetylamphotericin B methyl ester (**3**) (10 g, crude from previous experiment, ca. 90% pure, 9.18 mmol) in anhydrous MeOH (150 mL) and 2,2-dimethoxypropane ($Me_2C(OMe)_2$, 50 mL) (argon atmosphere) was added at room temperature camphorsulfonic acid (CSA, 500 mg, 2.15 mmol). The reaction mixture was stirred at that temperature until all the solid dissolved (ca. 1 h, careful TLC monitoring). Dilution with ethyl acetate (400 mL) followed by washing with saturated aqueous $NaHCO_3$ solution (200 mL), water (100 mL), and brine (200 mL) gave a solution of the product, which was dried ($MgSO_4$) and concentrated. Flash column chromatograpny (silica, 10% MeOH in CH_2Cl_2) gave pure **4ab** as a yellow amorphous solid (6.51 g, 66% yield based on 90% purity of starting material). **4ab** (mixture of two isomers, ca. 3.1:1 depending on the run): R_f 0.29 (silica, 10% MeOH in CH_2Cl_2); $[\alpha]^{20}_D$ +126° (ca. 1.18:1 mixture of isomers, *c* 0.09, $CHCl_3$); UV–vis ($CHCl_3$, ca. 3:1 isomeric mixture) λ_{max} 412 (E_{1cm}1% 743), 388 (721), 368 (446), 350 nm (216); IR ($CHCl_3$, ca. 3:1 isomeric mixture) ν_{max} 3480 (s, OH), 3440 (s, NH, amide), 1730 (s, C=O, ester, lactone), 1660 cm^{-1} (s, C=O, amide); ^{1}H NMR (250 MHz, $CDCl_3$, TMS, ca. 3:1 isomeric mixture) δ 6.60 (d, *J* = 7.6 Hz, 1 H, NH), 6.29 (m, 12 H, olefinic), 5.84 (dd, $J_{20,21}$ = 14.0 Hz, $J_{20,19}$ = 6.3 Hz, 1 H, H-20), 5.42 (dd, $J_{33,32}$ = 14.9 Hz, $J_{33,34}$ = 9.3 Hz, 1 H, H-33), 5.21 (m, 1 H, H-37), 4.50 (s, 1 H, H-1′), 4.61–3.25 (m, 12 H, CHO), 3.72 (s, 3 H, $COOCH_3$), 3.05 and 2.97 (singlets, ca. 3:1 ratio, 3 H total, OCH_3), 2.94 (m, 1 H, H-3′), 2.50–2.11 (m, 4 H, allylic CH, CH_2C(O), CHC(O)), 2.06 (s, 3 H, $NCOCH_3$), 2.00–1.45 (m, 15 H, CH, CH_2), 1.39, 1.34, 1.31, 1.30 (singlets, 15 H total, acetonides, CH_3), 1.17 (d, *J* = 6.3 Hz, 3 H, CH_3), 1.09 (d, *J* = 6.4 Hz, 3 H, CH_3), 0.98 (d, *J* = 7.0 Hz, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.25, 173.21, 172.81, 172.78, 169.61, 169.51, 135.83, 134.07, 133.98, 133.34, 133.22, 133.13, 133.05, 132.92, 132.82, 132.76, 132.54, 132.36, 132.29, 132.21, 131.96, 131.86, 130.33, 130.15, 108.43, 100.98, 100.16, 98.56, 98.44, 97.27, 97.23, 81.06, 79.96, 78.39, 78.23, 75.03, 74.85, 73.77, 73.53, 72.52, 69.88, 69.71, 69.67, 68.53, 67.85, 66.94, 66.86, 66.58, 66.15, 66.12, 65.29, 65.15, 64.51, 55.77, 55.34, 52,13, 48.25, 48.10, 42.60, 42.45, 42.9, 41.61, 41.40, 40.68, 39.99, 36.88, 36.77, 36.61, 33.25, 32.49, 30.15, 30.08, 29.95, 29.64, 27.96, 27.50, 27.28, 27.24, 23.06, 19.90, 19.71, 18.32, 18.27, 17.50, 17.13, 17.09, 11.41, 11.36; HRMS (FAB). Calcd for $C_{57}H_{87}NO_{18}$ + Na: 1096.5819, found 1096.5898 (M + Na). 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.

***N*-Acetylpentakis-*O*-(*tert*-butyldimethylsilyl)-3,5:9,11-di-*O*-isopropylidene-13-*O*-methylamphotericin B Methyl Ester and Isomer (5ab).** To a cold (0 °C), stirred solution of diacetonide **4ab** (1.074 g, 1.0 mmol) and 2,6-lutidine (0.96 g ≡ 1.05 mL, 9.0 mmol) in dry CH_2Cl_2 (10 mL) was added *t*-BuMe_2SiOTf (1.72 g ≡ 1.49 mL, 6.5 mmol) dropwise. The reaction mixture was stirred at 0 °C for 15 min (TLC monitoring) and then diluted with ether (100 mL). The solution was washed with saturated aqueous $NaHCO_3$ solution (50 mL), saturated aqueous $CuSO_4$ solution (50 mL), H_2O (30 mL), and brine (30 mL) and then dried ($MgSO_4$). Concentration followed by flash column chromatography (silica, 40% ether in petroleum ether) gave the pentasilyl diacetonide **5** (1.233 g, 75%) as a mixture of two isomers. The two isomers could be separated by preparative thin-layer chromatography (silica, 40% ether in petroleum ether). **5a** (faster moving isomer): yellow amorphous solid; R_f 0.31 (silica, 40% ether in petroleum ether); $[\alpha]^{20}_D$ +94.4° (*c* 0.17, $CHCl_3$); UV–vis ($CHCl_3$) λ_{max} 412 (E_{1cm}1% 973), 390 (920), 370 (547), 350 nm (240); IR ($CHCl_3$) ν_{max} 3000, 2960, 2940, 2890, 2860, 1730 (s, C=O, lactone, ester), 1680 (s, C=O, amide), 1520 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.3–5.9 (m, 12 H, olefinic), 5.79 (dd, *J* = 14.2, 7.5 Hz, 1 H, H-20), 5.61 (d, *J* = 9.4 Hz, 1 H, NH), 5.5 (dd, *J* = 15.0, 9.1 Hz, 1 H, H-33), 4.85 (m, 1 H, H-37), 4.48 (m, 1 H, H-19), 4.39 (s, 1 H, H-1′), 4.3–3.2 (m, 11 H, CH-O, H-3′, H-4′, H-5′), 3.83 (d, *J* = 3 Hz, 1 H, H-2′), 3.7 (s, 3 H, $COOCH_3$), 3.1 (s, 3 H, OCH_3), 2.45–0.70 (m, 19 H, CH_2C(O), CHC(O), allylic CH, CH_2, CH), 1.96 (s, 3 H, $NHCOCH_3$), 1.40, 1.33, 1.31, and 1.29 (singlets, 12 H total, acetonides), 1.21 (d, *J* = 6.2 Hz, 3 H, CH_3), 1.18 (d, *J* = 6.1 Hz, 3 H, CH_3), 0.98 (d, *J* = 6.7 Hz, 3 H, CH_3), 0.91–0.80 (singlets, 48 H total, CH_3, Si-*t*-*Bu*), 0.15–0.05 (singlets, 30 H total, SiMe_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.97, 170.05, 169.20, 135.92, 133.66, 133.47, 133.29, 133.11, 132.81, 132.75, 132.55, 132.47, 132.02, 130.06, 107.99, 100.60, 98.49, 98.22, 80.55, 76.24, 74.12, 72.24, 72.17, 72.04, 68.02, 67.62, 66.87, 66.06, 65.15, 55.96, 55.35, 51.74, 47.97, 42.94, 42.18, 41.01, 40.69, 37.22, 37.13, 33.02, 30.09, 27.37, 27.33, 26.09, 26.02, 25.86, 25.74, 25.64, 23.72, 19.60, 18.99, 18.41, 18.27, 18.17, 18.00, 17.97, 17.76, -3.59, -3.69, -3.84, -3.91, -4.03, -4.15, -4.35, -5.09. **5ab** (mixture, ca. 1.2:1 faster–slower moving isomers): yellow amorphous solid; R_f 0.31 and 0.25 (silica, 40% ether in petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.22–5.98 (m, 12 H, olefinic), 5.72 (m, 1 H, H-20), 5.61–5.48 (m, 2 H, NH, H-33), 4.84 (m, 1 H, H-37), 4.6–3.05 (m, 12 H, CH-O, CH-N), 4.37 (s, 1 H, H-1′), 3.83 (d, *J* = 2.8 Hz, 1 H, H-2′), 3.679 and 3.676 (singlets, 3 H, total $COOCH_3$, 1:1.2 ratio), 3.08 and 2.96 (singlets, 3 H total, OCH_3, 1:1.2 ratio), 2.4–1.1 (m, 37 H, allylic CH, CHC(O), CH_2C(O), CH_2, CH, acetonides, two CH_3), 1.96 (s, 3 H, $NHCOCH_3$), 1.0–0.7 (m, 51 H, Si-*t*-*Bu*, two CH_3), 0.15 to -0.06 (m, 30 H, SiMe_2); ^{13}C NMR (125 MHz, $CDCl_3$)

(17) For example nystatin,[18] another polyene macrolide antibiotic. Although the gross structure of this clinically used antifungal agent is known, the stereochemistry of a number of its stereogenic centers remains unsettled.

(18) Borowski, E.; Zielinski, J.; Falkowski, L.; Ziminski, T.; Goli, J.; Kolodziewjczyk, P.; Jereczek, E.; Colulewicz, M. *Tetrahedron Lett.* **1971**, *8*, 685 and references cited therein.

δ 173.01, 172.96, 170.04, 169.80, 169.19, 169.15, 135.89, 135.73, 133.65, 133.47, 133.37, 133.27, 133.11, 132.86, 132.79, 132.55, 132.47, 132.10, 132.01, 131.91, 131.70, 130.52, 130.05, 107.97, 100.58, 100.05, 98.47, 98.42, 98.21, 98.05, 80.52, 76.23, 75.78, 74.79, 74.10, 72.57, 72.24, 72.03, 71.50, 68.20, 68.01, 67.60, 66.79, 66.03, 65.12, 64.65, 64.32, 56.15, 55.92, 55.35, 51.75, 47.94, 43.15, 42.92, 42.56, 42.13, 41.16, 40.98, 40.65, 37.20, 37.10, 36.59, 36.31, 33.00, 32.82, 31.79, 30.10, 30.02, 27.36, 27.32, 27.25, 26.09, 26.01, 25.89, 25.85, 25.73, 25.62, 23.73, 19.71, 19.61, 19.58, 19.52, 18.97, 18.40, 18.25, 17.96, 17.83, 17.74, -3.57, -3.70, -3.85, -4.16, -4.37, -4.73, -5.10; HRMS (FAB) calcd for $C_{87}H_{157}NO_{18}Si_5$ 1644.0246, found 1644.0221 (M^+). Anal. Calcd for $C_{87}H_{157}NO_{18}Si_5$: C, 63.50; H, 9.62; N, 0.85. Found: C, 63.19; H, 10.01; N, 0.74.

Ozonolysis of Amphotericin B Derivative 5ab. Preparation of Dialdehyde 6ab. Ozone was passed through the yellow solution of amphotericin B derivative **5** (5.2 6g, 3.2 mmol) in CH_2Cl_2 (60 mL) and MeOH (4 mL) at −78 °C until the solution became first colorless and then slightly blue. Excess ozone was displaced by a stream of argon (solution became colorless), and Ph_3P (8.39 g, 32 mmol) was added at −78 °C with stirring. The reaction mixture was allowed to reach ambient temperature, and stirring was continued for 16 h. Concentration followed by flash column chromatography (silica, 50% ether in petroleum ether) gave dialdehyde **6** (2.92 g, 60%) as a rather labile colorless amorphous solid. The material was immediately used for the next step. The following data for **6ab** were recorded. **6ab** (ca. 1:1 ratio of isomers): R_f 0.42 and 0.48 (silica, 60% ether in petroleum ether); $[\alpha]^{20}_D$ −14.2° (*c* 0.12, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3450, 3000, 2960, 2930, 2890, 2860, 1730 (s, C=O, ester, aldehydes), 1675 (s, C=O, *N*-acetate), 1470, 1460, 1380, 1255, 1110, 840 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.64 (s, 1 H, C*H*O), 9.46 and 9.47 (2 overlapping doublets, *J* = 2.2 Hz, 1 H, C*H*O), 6.0 (m, 1 H, N*H*), 5.02 (quintet, *J* = 6.5 Hz, 1 H, H-37), 4.54 (s, 1 H, H-1′), 4.30–3.0 (m, 13 H, C*H*O, C*H*N), 3.65 (s, 3 H, $COOCH_3$), 3.12 and 3.08 (singlets, ca. 1:1 ratio, 3 H total, OCH_3), 2.55–1.10 (m, 34 H, C*H*C(O), $CH_2C(O)$, CH_2, C*H*, acetonides, CH_3), 1.97 (s, 3 H, $NHCOCH_3$), 1.17 (d, *J* = 6.2 Hz, 3 H, CH_3), 1.13 (d, *J* = 7.2 Hz, 3 H, CH_3), 0.93–0.80 (singlets, 48 H, Si-*t*-*Bu*, CH_3), 0.10 to −0.05 (singlets, 30 H, $SiMe_2$).

Reduction of Dialdehyde 6ab. Preparation of Diol 7ab. To a stirred solution of dialdehyde **6** (2.432 g, 1.6 mmol) in MeOH (32 mL) was added portionwise over a period of 15 min $NaBH_4$ (912 mg, 24.0 mmol) at 0 °C under argon. The reaction mixture was allowed to reach room temperature and stirred for an additional 15-min period. Aqueous saturated NH_4Cl solution (50 mL) was added, and the product was extracted with ether (2 × 50 mL). The combined organic phase was washed with brine (50 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography (silica, 60% ether in petroleum ether) gave diol **7ab** (2.32 g, 95%) as a colorless amorphous solid. **7ab** (ca. 2.5:1 ratio of isomers): R_f 0.20 and 0.26 (silica, 75% ether in petroleum eter); $[\alpha]^{20}_D$ −15.8° (*c* 0.12, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3640, 3460, 3000, 2980, 2965, 2940, 2930, 1730 (s, C=D, ester), 1680 (s, C=O, *N*-acetate), 1510, 1475, 1465 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.51 (d, *J* = 9.2 Hz, 1 H, N*H*), 4.99 (dq, *J* = 6.7 Hz, 1 H, H-37), 4.45 and 4.44 (singlets, ca. 2.5:1 ratio, 1 H total, H-1′), 4.3–3.3 (m, 19 H, C*H*O, CH_2O, C*H*N, O*H*), 3.66 (s, 3 H, $COOCH_3$), 3.1 and 3.06 (singlets, ca. 2.5:1 ratio, 3 H total, OCH_3), 2.55–1.23 (m, 19 H, C*H*, CH_2, C*H*C(O), $CH_2C(O)$), 1.96 (s, 3 H, $NHCOCH_3$), 1.41, 1.33, 1.32 (singlets, 12 H total, acetonides), 1.26 (d, *J* = 5.0 Hz, 3 H, CH_3), 1.16 (d, *J* = 6.3 Hz, 3 H, CH_3), 0.9–0.81 (singlets, 51 H, Si-*t*-Bu, CH_3), 0.07 to −0.04 (singlets, 30 H, $SiMe_2$); HRMS (FAB) calcd for $C_{75}H_{149}NO_{20}Si_5$ + H 1524.9596, found 1524.9618 (M + H). Anal. Calcd for $C_{75}H_{149}NO_{20}Si_5$: C, 59.05; H, 9.85; N, 0.92. Found: C, 59.24; H, 9.99; N, 0.88.

Methanolysis of Compound 7ab. Preparation of Fragments 8, 8′, and 9ab. To a stirred solution of compound **7ab** (mixture of isomers, 2.01 g, 1.32 mmol) in absolute MeOH (13 mL) was added powdered anhydrous K_2CO_3 (219 mg, 1.58 mmol) at room temperature and under argon. Stirring was continued for 8 h, and then the reaction mixture was poured onto saturated aqueous NH_4Cl solution (30 mL). Extraction with ether (2 × 50 mL) followed by washing of the combined organic phase with brine (25 mL), drying ($MgSO_4$), and concentration gave an oily residue. Flash column chromatography (silica, 10–30% EtOAc in CH_2Cl_2) gave, in order of elution, compounds **9ab** (two isomers, R_f 0.67 and 0.64 (silica, 30% EtOAc in CH_2Cl_2)), **8′** (109 mg, 30%), and **8** (219 mg, 60%). The dimethyl ester **9ab** was repurified by further flash column chromatography (silica, 75% ether in petroleum ether) to give pure **9ab** (1.57 g, 93%). **9ab** (ca. 1:1.1 ratio of isomers): R_f 0.37 and 0.33 (silica, 75% ether in petroleum ether); $[\alpha]^{20}_D$ −23.3° (*c* 0.24, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3460, 3000, 2960, 2930, 2890, 2860, 1730 (s, C=O, esters), 1675 (s, C=O, *N*-acetate), 1510, 1475, 1465, 1440, 1380, 1260, 1110, 1070 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.50 (d, *J* = 9.3 Hz, 1 H, N*H*), 4.46 and 4.44 (singlets, ca. 1:1.1 ratio, 1 H total H-1′), 4.26 (m, 1 H, C*H*O), 4.24 and 4.20 (double triplets, *J* = 10.3, 5.0 Hz, 1 H total, H-15), 4.04 (m, 1 H, C*H*O), 3.99 (m, 1 H, C*H*O), 3.88 (d, *J* = 2.2 Hz, 1 H, H-2′), 3.88–3.37 (m, 10 H, C*H*O, CH_2O, O*H*), 3.663 and 3.660 (singlets, 3 H each, $COOCH_3$), 3.10 and 3 07 (singlets, ca. 1:1.1 ratio, 3 H total, OCH_3), 2.53 (dd, *J* = 15.5, 6.8 Hz, 1 H, H-2), 2.36 (dd, *J* = 15.5, 6.1 Hz, 1 H, H-2), 2.25 (t, *J* = 10.3 Hz, 1 H, H-16), 2.22 and 2.10 (multiplets, 2 H, H-14), 2.02–1.10 (m, 27 H, acetonides, CH_2, CH_3), 1.96 (s, 3 H, $NHCOCH_3$), 0.90–0.81 (singlets, 36 H total, Si-*t*-*Bu*), 0.07 to −0.04) (singlets, 24 H total, $SiMe_2$); HRMS (FAB) calcd for $C_{62}H_{121}NO_{18}Si_4$ + H 1280.7737, found 1280.7747 (M + H). Anal. Calcd for $C_{62}H_{121}NO_{18}Si_4$: C, 58.13; H, 9 52; N, 1.09. Found: C, 58.30; H, 9.74; N, 0.99. Compound **8**: white solid; R_f 0.12 (silica, 60% ether in petroleum ether); $[\alpha]^{20}_D$ +18.7° (*c* 2.81, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3630, 3470 (s, OH), 3000, 2960, 2930, 2880, 2860, 1475, 1465, 1390, 1255, 1120, 1030, 1020, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$ amphotericin B numbering) δ 3.88 (dd, *J* = 5.0. 3.0 Hz, 1 H, H-35), 3.65 (dq, *J* = 9.0, 6.1 Hz, 1 H, H-37), 3.56 (dd, *J* = 10.5, 4.6 Hz, 1 H, H-33), 3.44 (dd, *J* = 10.5, 7.8 Hz, 1 H, H-33), 3.10 (br s, 2 H, O*H*), 1.80 (m, 1 H, H-34), 1.65 (m, 1 H, H-36), 1.15 (d, *J* = 6.1 Hz, 3 H, CH_3), 0.89 and 0.87 (singlets, 12 H total, Si-*t*-*Bu*, CH_3), 0.82 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.08 and 0.06 (singlets, 3 H each $SiMe_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 75.46, 70.13, 65.37, 45.01, 38.99, 25.93, 20.97, 18.15, 14.19, 12.18, −4.29, −4.62; HRMS (CI) calcd for $C_{14}H_{32}O_3Si$ + H 277.2199, found 277.2196 (M + H). Anal. Calcd for $C_{14}H_{32}O_3Si$: C, 60.82; H, 11.67. Found: C, 60.94; H, 11.94. Compound **8** colorless oil; R_f 0.25 (silica, 60% ether in petroleum ether); $[\alpha]^{20}_D$ +4.6° (*c* 0.8, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3620, 3440 (s, OH), 2990, 2960, 2930, 2900, 2880, 2860, 1470, 1460, 1255, 1090, 1020, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.50 (s, 1 H, O*H*), 4.15 (s, 1 H, O*H*), 3.81–3.74 (m, 3 H, C*H*O, CH_2O), 3.68 (dd, *J* = 9.9, 3.9 Hz, 1 H, C*H*O), 1.74 (m, 1 H, H-34), 1.52 (m, 1 H, H-36), 1.13 (d, *J* = 6.2 Hz, 3 H, CH_3), 0.93 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.85 (s, 9 H, Si-*t*-*Bu*), 0.68 (d, *J* = 6.9 Hz, 3 H, CH_3), 0.04 and 0.03 (singlets, 3 H each, $SiMe_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 86.74, 72.34, 69.52, 42.31, 35.58, 25.75, 20.93, 18.09, 12.71, 8.88, −5.67, −5.75; HRMS (CI) calcd for $C_{14}H_{32}O_3Si$ + H 277.2199, found 277.2199 (M + H).

Preparation of Selenide 10ab. To a cold (0 °C) stirred solution of alcohol **9ab** (1.22 g, 0.95 mmol) in dry THF (12 mL) and pyridine (6 mL) was sequentially added under argon *o*-$NO_2C_6H_4SeCN$ (2.16 g, 9.5 mmol) and *n*-Bu_3P (1.92 g ≡ 2.37 mL, 9.5 mmol). The cooling bath was removed, and the reaction mixture was allowed to stir at room temperature for 3 h before it was poured into NaOH solution (1 M, 50 mL). The mixture was extracted with ether (100 mL), and the ether extract was washed successively with H_2O (50 mL), saturated aqueous $CuSO_4$ solution (50 mL), and brine (50 mL). Drying ($MgSO_4$) followed by concentration and flash column chromatography (silica, 40% ether in petroleum ether) gave pure selenide **10ab** (1.18 g, 85%). **10ab** (ca. 1:1 ratio of isomers): light yellow solid; R_f 0.31 and 0.27 (silica, 50% ether in petroleum ether); $[\alpha]^{20}_D$ −28.2° (*c* 0.11, $CHCl_3$); UV-vis (hexane) λ_{max} 252 (E_{1cm}1% 77.5), 273 (37.7), 384 nm (21.5); IR ($CHCl_3$) ν_{max} 3460, 3000, 2950, 2930, 2890, 2860, 1730 (s, C=O, esters), 1675 (s, C=O, *N*-acetate), 1520, 1470, 1380, 1250, 1110 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.25, 7.63, 7.47, 7.27 (multiplets, 4 H, aromatic), 5.59 (d, *J* = 9.3 Hz, 1 H, N*H*), 4.53, 4.52 (singlets, ca. 1:1 ratio, 1 H total, H-1′), 4.27 (m, 1 H, C*H*O), 4.22, 4.19 (double triplets, *J* = 10.4, 4.3 Hz, 1 H, H-15), 4.02 (m, 1 H, C*H*O), 4.01, 3.99 (double triplets, *J* = 9.0, 2.9 Hz, 1 H, H-3′), 3.861, 3.857 (doublets, *J* = 2.9 Hz, 1 H, H-2′), 3.85–3.49 (m, 5 H, C*H*O), 3.663, 3.660 (singlets, ca. 1:1 ratio, 3 H total, $COOCH_3$), 3.55, 3.50 (singlets, ca. 1:1 ratio, 3 H total, $COOCH_3$), 3.45 (t, *J* = 9.0 Hz, 1 H, H-4′), 3.38 (m, 1 H, H-5′), 3.25 (m, 1 H, C*H*Se), 3.05 (m, 1 H, C*H*Se), 3.06, 2.99 (singlets, ca. 1:1 ratio, 3 H total, OCH_3), 2.52, 2.50 (double doublets, *J* = 15.6, 7.0 Hz, 1 H, H-2), 2.36, 2.34 (double doublets, *J* = 15.6, 6.1 Hz, 1 H, H-2), 2.24, 2.21 (triplets, *J* = 10.4 Hz, 1 H, H-16), 2.20–1.10 (m, 14 H, CH_2), 1.96 (s, 3 H, $NHCOCH_3$), 1.42, 1.40, 1.37, 1.33, 1.31, 1.30, 1.30, 1.29 (singlets, 15 H total, acetonides, CH_3), 0.91–0.79 (singlets, 36 H total, Si-*t*-*Bu*), 0.11 to −0.06 (singlets, 24 H total, $SiMe_2$); HRMS (FAB) calcd for $C_{68}H_{124}N_2O_{19}SeSi_4$ + H 1465.7117 found 1465.7118 (M + H). Anal. Calcd for $C_{68}H_{124}N_2O_{19}SiSi_4$: C, 55.75; H, 8.53; N, 1.91. Found: C, 55.88; H, 8.61; N, 1.87.

Preparation of Enol Ether Derivative 11ab. Ozone was passed through a solution of selenide **10ab** (733 mg, 0.5 mmol) in CH_2Cl_2 (10 mL) at −78 °C until a slightly blue coloration appeared, indicating completion of the reaction (confirmed by TLC). The solvent was removed in vacuo at ambient temperature and the residue was dissolved in dry benzene (10 mL). Diisopropylamine (0.51 g = 0.71 mL, 5.0 mmol) was added, and the mixture was refluxed for 3 h (TLC monitoring). The mixture was cooled to room temperature, poured onto saturated aqueous NH_4Cl solution (30 mL), and extracted with ether (2 × 50 mL). The combined organic phase was washed with brine (30 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography (silica, 50% ether in petroleum ether) gave enol ether derivative **11ab** (467 mg, 74%). **11ab** (ca.

3.5:1 ratio of isomers): white amorphous solid; R_f 0.32 and 0.24 (silica, 50% ether in petroleum ether); $[\alpha]^{20}_D$ −15.2° (*c* 0.27, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3450, 3000, 2960, 2930, 2890, 2860, 1735 (s, C=O, esters), 1675 (s, C=O, *N*-acetate), 1510, 1475, 1465, 1380, 1370, 1260 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.62 (d, *J* = 9.1 Hz, 1 H, N*H*), 4.79 (s, 1 H, H-1′), 4.35–3.35 (m, 13 H, C*H*O, C*H*N, olefinic), 3.67, 3.60, 3.58 (singlets, 6 H total, $COOCH_3$), 3.10, 3.05 (singlets, ca. 3.5:1 ratio, 3 H total, OCH_3), 2.6–1.2 (m, 17 H, $CH_2C(O)$, CHC(O), CH_2), 1.98 (s, 3 H, $NHCOCH_3$), 1.410, 1.334, 1.327, 1.310 (singlets, 12 H total, acetonides), 1.22 (d, *J* = 5.9 Hz, 3 H, CH_3), 0.93–0.80 (singlets, 36 H total, Si-*t*-*Bu*), 0.12 to −0.04 (singlets, 24 H total, $SiMe_2$); HRMS (FAB) calcd for $C_{62}H_{119}NO_{17}Si_4$ + Na 1284.7452, found 1284.7543 (M + Na).

Selective Hydrolysis and Ozonolysis of Methyl Ester Enol Ether 11ab. Preparation of Compound 13ab via 12ab. To a stirred solution of diester **11ab** (379 mg, 0.3 mmol) in THF (2 mL) and H_2O (0.5 mL) was added at 0 °C and under argon LiOH solution (1.0 M, 0.45 mL, 0.45 mmol). The reaction mixture was allowed to reach room temperature and stirred for 3 h (TLC monitoring) before it was poured onto saturated aqueous NH_4Cl solution (20 mL). The product was extracted with ether (2 × 50 mL), the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The resulting residue (crude **12ab**) was dissolved in CH_2Cl_2 (10 mL) and MeOH (0.1 mL) and cooled to −78 °C. Ozone was passed through the solution until a faint blue color appeared. Excess ozone was removed by a stream of argon, and Ph_3P (157 mg, 0.6 mmol) was added (−78 °C) with stirring. The cooling bath was removed and stirring was continued for 4 h. Removal of the solvents followed by flash column chromatography (silica, 5% MeOH in ether) gave pure **13ab** (281 mg, 75%). **13ab** (ca. 2.5:1 ratio of isomers): white amorphous solid; R_f 0.54 and 0.45 (silica, 5% MeOH in ether); $[\alpha]^{20}_D$ −21° (*c* 0.21, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3460 (w, COOH), 3000, 2960, 2930, 2880, 2860, 1760 and 1730 (s, C=O, esters), 1680, 1670, 1650, 1510, 1470, 1460, 1380, 1260 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.67, 5.64 (singlets, ca. 2.5:1 ratio, 1 H, H-1′), 5.58 (d, *J* = 8.9 Hz, 1 H, N*H*), 4.4–3.4 (m, 11 H, C*H*O, C*H*N), 3.65 (s, 3 H, $COOCH_3$), 3.20, 3.12 (singlets, ca. 2.5:1 ratio, 3 H total, OCH_3), 2.7–1.2 (m, 17 H, $CH_2C(O)$, CHC(O), CH_2), 2.03, 2.02 (singlets, ca. 2.5:1 ratio, 3 H, $NHCOCH_3$), 1.43–1.31 (singlets, 12 H total, acetonides), 1.23 (d, *J* = 5.2 Hz, 3 H, CH_3), 0.94–0.80 (singlets, 36 H total, Si-*t*-*Bu*), 0.13 to −0.05 (singlets, 24 H total, $SiMe_2$), COO*H* signal not identified; HRMS (FAB) calcd for $C_{60}H_{115}NO_{18}Si_4$ + Na 1272.7088, found 1272.6980 (M + Na).

Methanolysis of Mycosamyl Ester 13ab. Preparation of Dimethyl Ester Carboxylic Acid 14ab and Mycosamine Derivatives 15, 16, and 16′. To a stirred solution of mycosamyl ester **13ab** (125 mg, 0.1 mmol) in absolute MeOH (2 mL) was added powdered anhydrous K_2CO_3 (35 mg, 0.25 mmol) at room temperature. After being stirred for 2 h at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with ether (2 × 40 mL). The combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash column chromatography (silica, 5% MeOH in ether), gave, in order of elution, compounds **15** (15 mg, 35%), **16** (8 mg, 18%), **16′** (15 mg, 35%), and **14ab** (76 mg, 90%). **14ab** (ca. 1.5:1 ratio of isomers): white amorphous solid; R_f 0.34 (silica, 2.5% MeOH in ether); $[\alpha]^{20}_D$ −8.6° (*c* 0.7, MeOH); IR ($CHCl_3$) ν_{max} 3000, 2960, 2930, 2860, 1735 (s, C=O, esters, acid), 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, 3.64 (singlets, 6 H total, $COOCH_3$), 3.17, 3.12 (singlets, ca. 1.5:1 ratio, 3 H total, OCH_3), 2.50–1.80 (m, 5 H, $CH_2C(O)$, CHC(O)), 1.77–1.10 (m, 12 H, CH_2, C*H*), 1.42–1.23 (singlets, 12 H total, acetonides), 0.86, 0.80 (singlets, 18 H, Si-*t*-*Bu*), 0.054 to −0.034 (singlets, 12 H, $SiMe_2$), COO*H* signal was not assigned; HRMS (FAB) calcd for $C_{41}H_{76}O_{14}Si_2$ + K 887.4410, found 887.4460 (M + K). Mycosamine derivative **15**: white amorphous solid; R_f 0.48 (silica, ether) $[\alpha]^{20}_D$ −15.7° (*c* 0.89, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3610, 3460, 2960, 2940, 2865, 1675 (s, C=O, *N*-acetate), 1520, 1260, 1120, 840 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.43 (d, *J* = 10.0 Hz, 1 H, N*H*), 4.96 (s, 1 H, H-1), 4.36 (dt, *J* = 10.0, 3.8 Hz, 1 H, H-3), 3.95 (dq, *J* = 10.0, 6.0 Hz, 1 H, H-5), 3.86 (m, 1 H, H-2), 3.42 (t, *J* = 10.0 Hz, 1 H, H-4), 3.28 (d, *J* = 3.5 Hz, 1 H, O*H*), 1.99 (s, 3 H, $NHCOCH_3$), 1.22 (d, *J* = 6.0 Hz, 3 H, CH_3), 0.95, 0.88 (singlets, 9 H each, Si-*t*-*Bu*), 0.07–0.03 (singlets, 12 H total, $SiMe_2$); HRMS (CI) calcd for $C_{20}H_{43}NO_5Si_2$ + H 434.2758, found 434.2796 (M + H). Mycosamine derivative **16**: white amorphous solid; R_f 0.29 (silica, ether); $[\alpha]^{20}_D$ −37.6° (*c* 1.44, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3580, 3450, 2970, 2940, 2865, 1675 (s, C=O, *N*-acetate), 1515, 1260, 1140, 1065, 880, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.83 (d, *J* = 10.0 Hz, 1 H, N*H*), 4.81 (d, *J* = 1.2 Hz, 1 H, H-1), 4.10 (dt, *J* = 9.7, 3.0 Hz, 1 H, H-3), 3.70 (m, 1 H, H-2), 3.43 (dd, *J* = 9.7, 8.9 Hz, 1 H, H-4), 3.33 (dq, *J* = 8.9, 6.2 Hz, 1 H, H-5), 2.39 (d, *J* = 1.4 Hz, 1 H, O*H*), 2.00 (s, 3 H, $NHCOCH_3$), 1.25 (d, *J* = 6.2 Hz, 3 H, CH_3), 0.88, 0.84 (singlets, 9 H each, Si-*t*-*Bu*), 0.12–0.02 (singlets, 12 H total, $SiMe_2$); HRMS (CI) calcd for $C_{20}H_{43}NO_5Si_2$ + H 434.2758, found 434.2796 (M + H). Mycosamine derivative **16′**: white amorphous solid; R_f 0.10 (silica, ether) $[\alpha]^{20}_D$ +24.4° (*c* 0.16, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3440, 3000, 2960, 2930, 2900, 2860, 1670 (s, C=O, *N*-acetate), 1510, 1470, 1465, 1260, 1080, 1060, 870, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.72 (d, *J* = 8.9 Hz, 1 H, N*H*), 4.97 (d, *J* = 1.7 Hz, 1 H, H-1), 4.21 (dt, *J* = 9.3, 2.8 Hz, 1 H, H-3), 3.83 (dq, *J* = 9.3, 6.3 Hz, 1 H, H-5), 3.72 (m, 1 H, H-2), 3.42 (t, *J* = 9.3 Hz, 1 H, H-4), 2.38 (d, *J* = 7.1 Hz, 1 H, O*H*), 1.99 (s, 3 H, $NHCOCH_3$), 1.20 (d, *J* = 6.3 Hz, 3 H, CH_3), 0.89, 0.86 (singlets, 9 H each, Si-*t*-*Bu*), 0.102–0.038 (singlets, 12 H, $SiMe_2$); HRMS (CI) calcd for $C_{20}H_{43}NO_5Si_2$ + H 434.2758, found 434.2807 (M + H).

Reduction of Amphotericin B Methyl Ester Derivative 4ab. Preparation of Compound 17ab. The amphotericin B methyl ester derivative **4ab** (1.075 g, 1.0 mmol) was dissolved in absolute MeOH (40 mL), and the solution was heated at 40–45 °C under argon. Sodium borohydride (560 mg, 15.0 mmol) was added in portions over a period of 5 min with stirring. On completion of the reaction (15 min total), the reaction mixture was allowed to cool to room temperature and quenched with saturated aqueous NH_4Cl solution (25 mL). The resulting solution was extracted with EtOAc (3 × 50 mL), and the combined organic phase was washed with brine (50 mL). Drying of the solution ($MgSO_4$) followed by concentration and flash column chromatography (silica, 4–15% MeOH in CH_2Cl_2) gave the hexaol **17ab** (889 mg, 85%). **17ab** (ca. 1:1 ratio of isomers): yellow amorphous solid; R_f 0.42 (silica, 20% MeOH in CH_2Cl_2); $[\alpha]^{20}_D$ +208.6° (*c* 0.36, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3420 (s, OH), 2990, 2930, 1725 (s, C=O, lactone), 1650 (C=O, *N*-acetate), 1375, 1160, 1060, 1000 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, TMS, ca. 5:1 ratio of isomers) δ 6.85 (d, *J* = 7.5 Hz, 1 H, N*H*), 6.23 (m, 12 H, olefinic), 5.94 (dd, *J* = 14.0, 6.0 Hz, 1 H, H-20), 5.43 (dd, *J* = 15.0, 10.0 Hz, 1 H, H-33), 5.25 (m, 1 H, H-37), 4.80–3.20 (m, 16 H, C*H*O, CH_2O, C*H*N), 3.06 and 2.97 (singlets, ca. 5:1 ratio, 3 H total, OCH_3), 2.60–2.00 (m, 3 H, allylic C*H*, $CH_2C(O)$), 2.04 (s, 3 H, $NHCOCH_3$), 2.00–1.10 (m, 16 H, CH_2, C*H*), 1.40, 1.34, 1.32, 1.30 (singlets, 12 H total, acetonides), 1.24 (d, *J* = 6.1 Hz, 3 H, CH_3), 1.17 (d, *J* = 6.1 Hz, 3 H, CH_3), 1.09 (d, *J* = 5.9 Hz, 3 H, CH_3), 0.98 (d, *J* = 7.1 Hz, 3 H, CH_3), O*H* signals were not assigned; HRMS (FAB) calcd for HRMS $C_{56}H_{87}NO_{17}$ + H 1406.6051, found 1046.6070 (M + H).

Monosilylation of Hexaol 17ab. Preparation of *tert*-Butyldiphenylsilyl Ether Derivative 18ab. Hexaol **17ab** (1.045 g, 1.0 mmol) and imidazole (340 mg, 5.0 mmol) were dissolved in dry DMF (12 mL) and magnetically stirred at 0 °C. *tert*-Butylchlorodiphenylsilane (823 mg, 3.0 mmol) was added and the reaction mixture was allowed to reach ambient temperature and stirred for 6 h. The mixture was then poured onto brine (30 mL) and extracted with EtOAc (3 × 30 mL). The combined organic phase was washed with water (20 mL) and brine (20 mL) and dried ($MgSO_4$). Concentration followed by flash column chromatography (silica, 2–10% MeOH in CH_2Cl_2) gave *tert*-butyldiphenylsilyl ether derivative **18ab** (1.027 g, 80%). **18ab**: yellow amorphous solid; R_f 0.43 (silica, 10% MeOH in $CHCl_2$); $[\alpha]^{20}_D$ +176.7° (ca. 1:1 mixture of isomers, *c* 0.15, $CHCl_3$); UV-vis ($CHCl_3$) λ_{max} 352 (E_{1cm}1% 260), 370 (560), 388 (920), 414 nm (960); IR ($CHCl_3$) ν_{max} 3510 (s, OH), 3450 (s, OH), 3010, 2945, 1735 (s, C=O, lactone), 1660 (C=O, *N*-acetate), 1385, 1170, 1115, 1075, 1010 cm^{-1}; ^1H NMR (ca. 4:1 mixture of isomers, 250 MHz, $CDCl_3$) δ 7.66 (m, 4 H, aromatic), 7.55 (m, 6 H, aromatic), 5.23 (m, 12 H, olefinic), 5.77 (dd, *J* = 14.0, 6.3 Hz, 1 H, H-20), 5.43 (dd, *J* = 15.0, 9.6 Hz, 1 H, H-33), 5.21 (m, 1 H, H-37), 4.40–3.20 (m, 15 H, C*H*O, CH_2O), 3.09 and 2.96 (singlets, ca. 4:1 ratio, 3 H total, OCH_3), 2.72 (m, 1 H, C*H*O), 2.46–2.12 (m, 3 H, allylic C*H*, $CH_2C(O)$), 2.04 and 2.03 (singlets, ca. 4:1 ratio, 3 H total, $NHCOCH_3$), 2.00–1.44 (m, 16 H, CH_2, C*H*), 1.40, 1.34, 1.33, 1.31 (singlets, 12 H total, acetonides), 1.27 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.17 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.09 (d, *J* = 6.4 Hz, 3 H, CH_3), 1.04 (s, 9 H, Si-*t*-*Bu*), 0.99 (d, *J* = 7.1 Hz, 3 H, CH_3), OH signals were not assigned; HRMS (FAB) calcd for $C_{72}H_{105}NO_{17}Si$ + Na 1306.7049, found 1306.7100 (M + Na).

Data for compound 19 (faster moving isomer, R = H): colorless amorphous solid; R_f = 0.58 (silica, 15% MeOH in CH_2Cl_2); $[\alpha]^{20}_D$ −13.1° (*c* 0.42, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3510, 3010, 2940, 1740 (s, C=O, ester, acid), 1595, 1440, 1430, 1380, 1260, 1110, 710 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.64 (m, 4 H, aromatic), 7.41 (m, 6 H, aromatic), 4.35–3.65 (m, 11 H, CH_2O, C*H*O, O*H*), 3.62 (s, 3 H, $COOCH_3$), 3.17 (s, 3 H, OCH_3), 2.60–1.80 (m, 4 H, $CH_2C(O)$), 1.87–1.10 (m, 13 H, CH_2, C*H*), 1.42, 1.35, 1.34, 1.33 (singlets, 12 H total, acetonides), 1.04 (s, 9 H, Si-*t*-*Bu*); COO*H* signal not assigned; HRMS (FAB) calcd for $C_{44}H_{66}O_{13}Si$ + Na 853.4272, found 853.4215 (M + Na).

Data for compound 20a (single isomer, R = Si-*t*-$BuMe_2$): colorless amorphous solid; R_f 0.13 (silica, 5% MeOH in CH_2Cl_2); $[\alpha]^{20}_D$ +18.3° (*c* 0.30, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2940, 2865, 1740 (s, C=O, ester, acid), 1385, 1115, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.62 (m, 4 H, aromatic), 7.24 (m, 6 H, aromatic), 4.35–3.50 (m, 9 H, C*H*O, CH_2O), 3.63 (s, 3 H, $COOCH_3$), 3.16 (s, 3 H, OCH_3), 2.65–1.95 (m,

4 H, $CH_2C(O)$), 1.80–1.20 (m, 13 H, CH_2, CH), 1.43, 1.37, 1.32, 1.31 (singlets, 12 H, acetonides), 1.06, 0.86, 0.75 (singlets, 9 H each, Si-*t*-*Bu*), 0.047, 0.041, −0.007, −0.132 (singlets, 3 H each, $SiMe_2$), COO*H* signal not assigned; HRMS (FAB) calcd for $C_{56}H_{94}O_{13}Si_3$ − OH 1041.1574, found 1041.6014 (M − OH). Anal. Calcd for $C_{56}H_{94}O_{13}Si_3$: C, 63.48; H, 8.94. Found: C, 63.19; H, 9.23.

Oxidative Deglycosidation of Amphotericin B Derivative 5ab. Preparation of Heptaenone 21ab and Bicyclic Compound 22. Pentakis(*tert*-butyldimethylsilyl ether) diacetonide derivative of amphotericin B (**5ab**) (1.644 g, ca. 3:2 mixture of isomers, 1.0 mmol) was dissolved in dry CCl_4 (6.5 mL). With magnetic stirring and under an argon atmosphere, $CaCO_3$ (1.0 g, 10 mmol) was added, followed by freshly recrystallized *N*-bromosuccinimide (170 mg, 0.95 mmol) at room temperature. The reaction mixture was allowed to stir at that temperature for 3–12 h (careful TLC monitoring), turning gradually from yellow to deep orange. The reaction mixture was then applied directly, without workup, on a silica gel column and flash chromatographed (10% ether in petroleum ether → 100% ether, containing 1% Et_3N) giving the following compounds in order of elution: bicyclic compound **22** (41.5 mg, 10%, 14% based on 30% recovered starting material), starting material **5ab** (490 mg, 30%), heptaenone **21ab** (faster moving isomer, 134 mg, 11%, 16% based on 30% recovery of starting material; slower moving isomer, 82 mg, 7%, 10% based on 30% recovered starting material), and lactol **15** (36 mg, 9%, 13% based on 30% recovered starting material). Numerous other unidentified products were observed in this reaction, which made the purification of the above compounds rather tedious. Runs on smaller scales gave higher yields of heptaenone **21ab** (up to 30% total for the two isomers). The Et_3N could be omitted from the eluting solvent when there was no need to isolate the rather acid-labile bicyclic system **22**, although use of triethylamine improved the yield of heptaenone **21ab** to some extent as well. Bicyclic compound **22**: colorless oil; R_f 0.36 (silica, 40% ether in petroleum ether); $[\alpha]^{20}_D$ −2.0° (*c* 0.10, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2970, 2940, 2910, 2870, 1680 (C=N), 1470, 1460, 1380, 1250, 1140, 1080, 1010, 880, 840, 770 cm^{-1}; ^1H 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-2), 3.82 (t, J = 2.7 Hz, H-4), 3.73 (dq, J = 2.7, 7.2 Hz, 1 H, H-5), 3.46 (m, 1 H, H-3), 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 157.69 (C=N), 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). Heptaenone **21a** (faster moving isomer): orange amorphous solid; R_f 0.25 (silica, 50% ether in petroleum ether); $[\alpha]^{20}_D$ +55.0° (*c* 0.10, $CHCl_3$); UV-vis ($CHCl_3$) λ_{max} 422 nm (E_{1cm}1% 663); IR ($CHCl_3$) ν_{max} 3000, 2960, 2940, 2860, 1730 (s, C=O, ester, lactone), 1640, 1550, 1380, 1260, 1160, 1010, 840 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (dd, J = 15.4, 11.1 Hz, 1 H, H-21), 6.67 (dd, J = 14.5, 11.5 Hz, 1 H, H-23), 6.46–5.98 (m, 10 H, olefinic), 6.14 (d, J = 15.4 Hz, 1 H, H-20), 5.58 (dd, J = 14.9, 9.0 Hz, 1 H, H-33), 4.74 (m, 1 H, H-37), 4.29–3.35 (m, 8 H, *CH*O), 3.68 (s, 3 H, $COOCH_3$), 2.99 (dd, J = 12.1, 10.5 Hz, 1 H, $CH_2C(O)$), 2.92 (s, 3 H, OCH_3), 2.40–1.10 (m, 17 H, allylic *CH*, $CH_2C(O)$, CH_2, *CH*), 2.32 (t, J = 10.2 Hz, 1 H, H-16), 1.35, 1.34, 1.28, 1.26 (singlets, 3 H each, acetonides), 1.17 (d, J = 6.1 Hz, 3 H, CH_3), 0.97 (d, J = 6.8 Hz, 3 H, CH_3), 0.90 (d, J = 7.2 Hz, 3 H, CH_3), 0.88, 0.87, 0.81 (singlets, 9 H each, Si-*t*-*Bu*), 0.05 to −0.04) (singlets, 18 H total, $SiMe_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.55, 172.38, 169.87, 145.34, 141.53, 137.78, 136.14, 135.20, 134.29, 132.13, 132.07, 131.67, 131.42, 131.06, 130.63, 129.88, 107.97, 100.53, 98.52, 80.80, 71.80, 69.10, 67.64, 67.41, 66.01, 65.20, 57.32, 51.76, 47.72, 43.51, 42.88, 42.53, 41.05, 40.76, 37.43, 33.20, 30.08, 29.69, 27.55, 27.31, 27.11, 26.09, 25.97, 25.57, 19.60, 18.33, 18.21, 18.07, 18.01, 17.70, −3.82, −3.89, −4.21, −4.43, −5.12; HRMS (FAB) calcd for $C_{67}H_{114}O_{14}OSi_3$ 1226.7516, found 1226.7604 (M^+). Heptaenone **21b** (slower moving isomer): orange amorphous solid; R_f 0.16 (silica, 50% ether in petroleum ether); $[\alpha]^{20}_D$ +200.0° (*c* 0.12, $CHCl_3$); UV-vis ($CHCl_3$) λ_{max} 422 nm (E_{1cm}1% 555); IR ($CHCl_3$) ν_{max} 2960, 2930, 2860, 1730 (s, C=O, ester, lactone); 1640, 1550, 1380, 1260 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (dd, J = 15.6, 11.3 Hz, 1 H, H-21), 6.64 (dd, J = 14.7, 11.0 Hz, 1 H, H-23), 6.45–5.99 (m, 10 H, olefinic), 6.09 (d, J = 15.6 Hz, 1 H, H-20), 5.52 (dd, J = 14.9, 9.5 Hz, 1 H, H-33), 4.80 (m, 1 H, H-37), 4.30–3.46 (multiplets, 8 H, *CH*O), 3.69 (s, 3 H, $COOCH_3$), 3.04 (dd, J = 12.4, 10.3 Hz, 1 H, $CH_2C(O)$), 2.84 (s, 3 H, OCH_3), 2.41–1.10 (multiplets, 17 H, allylic *CH*, $CH_2C(O)$, CH_2, *CH*), 2.27 (t, J = 10.3 Hz, 1 H, H-16), 1.36, 1.34, 1.28 (singlets, 12 H total, acetonides), 1.18 (d, J = 6.2 Hz, 3 H, CH_3), 0.97 (d, J = 6.8 Hz, 3 H, CH_3), 0.89 (d, J = 7.1, 1 Hz, 3 H, CH_3), 0.89, 0.86, 0.81 (singlets, 9 H each, Si-*t*-*Bu*), 0.05 to −0.02 (singlets, 18 H total, $SiMe_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.61, 172.23, 169.72, 147.24, 141.24, 137.17, 135.64, 134.79, 133.88, 132.35, 132.12, 131.80, 130.88, 130.79, 130.07, 100.23, 98.47, 98.23, 75.10, 72.88, 71.57, 68.92, 68.14, 67.77, 64.66, 64.29, 57.38, 51.79, 47.62, 44.03, 42.88, 42.58, 41.21, 36.86, 32.73, 32.36, 30.06, 30.00, 27.40, 26.03, 26.00, 25.72, 25.59, 19.61, 19.58, 18.41, 18.26, 18.19, 18.02, 17.82, 10.65, −3.74, −4.15, −4.36, −4.62, −5.07; HRMS (FAB) calcd for $C_{67}H_{114}O_{14}Si_3$ 1226.7516, found 1226.7577 (M^+). Anal. Calcd for $C_{67}H_{114}O_{14}Si_3$: C, 65.54; H, 9.36. Found: C, 65.30; H, 9.38.

5,6-Dihydro-2-methyl-4*H*-1,3-oxazine (a). This compound was prepared from 3-amino-1-propanol according to a literature procedure[13] and exhibited the following properties: bp 132–133 °C (760 mmHg) [lit.[13] bp 134 °C (760 mmHg)]; IR ($CHCl_3$) ν_{max} 1675 cm^{-1} (O-C=N); ^1H NMR (250 MHz, $CDCl_3$) δ 4.14 (t, J = 5.6 Hz, CH_2, 2 H), 3.33 (t, J = 5.6 Hz, CH_2, 2 H), 1.854 (s, 3 H, CH_3), 1.849 (quintet, J = 5.6 Hz, 2 H, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.35 (OC=N), 64.41, 41.79, 21.35.

Azetidine *N*-Acetate (b). Azetidine (250 mg, 0.438 mmol) was dissolved in dry $CDCl_3$ (5 mL) and cooled to 0 °C under argon. With stirring, 4-(dimethylamino)pyridine (DMAP, 535 mg, 0.438 mmol) was added followed by Ac_2O (410 μL, 0.438 mmol). After being stirred for 5 min, the reaction mixture was washed with D_2O (2 × 5 mL), and the organic phase was dried ($MgSO_4$) and filtered. The following spectroscopic data were collected by using directly this resulting $CDCl_3$ solution: IR ($CDCl_3$) ν_{max} 1630 cm^{-1} (C=O); ^1H NMR (250 MHz, $CDCl_3$) δ 4.15 (t, J = 7.5 Hz, 2 H), 4.03 (t, J = 7.5 Hz, 2 H), 2.26 (quintet, J = 7.5 Hz, 2 H), 1.85 (s, 3 H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.42 (C=O), 50.33, 47.74, 18.36, 14.77.

Reduction of Heptaenone 21a. Preparation of 11,15,35-Tris-*O*-(*tert*-butyldimethylsilyl)-19-*O*-de(3-amino-3,6-dideoxy-β-D-manno-pyranosyl)-3,5:8,9-di-*O*-isopropylidene-13-*O*-methylamphotericin B Methyl Ester 23a. Heptaenone **21a** (123 mg, 0.1 mmol) was dissolved in absolute MeOH (1 mL), cooled to 0 °C, and magnetically stirred under an argon atmosphere. Sodium borohydride (38 mg, 1.0 mmol) was added, and the reaction mixture was stirred at 0 °C for 15 min (color change from deep orange to light yellow) before quenching with saturated aqueous NH_4Cl solution (20 mL). The product was extracted with ether (20 mL), and the yellow ether extract was washed with H_2O (5 mL) and brine (5 mL). Drying ($MgSO_4$) followed by evaporation and flash column chromatography (silica, 50% ether in petroleum ether) gave the amphoteronolide B derivative **23a** (120 mg, 98%) as a yellow amorphous solid. **23a**: R_f 0.58 (silica, 75% ether in petroleum ether); $[\alpha]^{20}_D$ +47.0° (*c* 0.21, $CHCl_3$); IR ($CHCl_3$) ν_{max} 2960, 2940, 2860, 1740 and 1730 (s, C=O, ester, lactone), 1600 (s, C=C), 1560, 1380 cm^{-1}; UV-vis ($CHCl_3$) λ_{max} 412 (E_{1cm}1% 464), 389 (454), 369 (300), 350 nm (136); ^1H NMR (500 MHz, $CDCl_3$) δ 6.30–5.95 (m, 12 H, olefinic), 5.85 (dd, J = 14.7, 5.8 Hz, 1 H, H-20), 5.63 (dd, J = 15.1, 8.6 Hz, 1 H, H-33), 4.79 (m, 1 H, H-37), 4.51 (m, 1 H, H-19), 4.25 (dt, J = 10.5, 4.3 Hz, 1 H, *CH*O), 4.13 (m, 1 H, *CH*O), 4.01 (m, 1 H, *CH*O), 3.94 (m, 1 H, *CH*O), 3.70–3.65 (m, 2 H, *CH*O), 3.67 (s, 3 H, $COOCH_3$), 3.56 (m, 2 H, *CH*O, *OH*), 3.34 (t, J = 8.4 Hz, 1 H, *CH*O), 3.09 (s, 3 H, OCH_3), 2.45–1.20 (m, 18 H, allylic *CH*, $CH_2C(O)$, CH_2, *CH*), 2.26 (t, J = 10.5 Hz, 1 H, H-16), 1.38, 1.34, 1.30 and 1.29 (singlets, 12 H total, acetonides), 1.17 (d, J = 6.1 Hz, 3 H, CH_3), 0.99 (d, J = 6.8 Hz, 3 H, CH_3), 0.91 (d, J = 7.1 Hz, 3 H, CH_3), 0.88, 0.87 and 0.81 (singlets, 9 H each, Si-*t*-*Bu*), 0.07 to −0.05 (six singlets, 3 H each, $SiMe_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.28, 169.95, 138.11, 133.55, 133.35, 133.20, 133.15, 132.96, 132.94, 132.65, 132.47, 131.68, 131.64, 129.96, 127.88, 108.00, 100.70, 98.51, 80.34, 69.06, 68.03, 67.30, 66.15, 66.07, 65.22, 56.49, 51.61, 48.09, 43.00, 42.35, 40.97, 40.65, 40.15, 37.34, 33.06, 30.10, 27.42, 27.26, 26.06, 25.99, 25.62, 19.59, 18.21, 18.00, 17.84, 17.74, −3.69, −4.15, −4.37, −5.09; HRMS (FAB) calcd for $C_{67}H_{116}O_{14}Si_3$ + H 1229.7750, found 1229.7820 (M + H). Reduction of the slower moving isomer of heptaenone **21b** in the same way gave the corresponding alcohol **23b**. **23b**: R_f 0.45 (silica, 75% ether in petroleum ether); $[\alpha]^{20}_D$ +66.0° (*c* 0.24, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 6.22–6.00 (m, 12 H, olefinic), 5.82 (dd, J = 14.6, 5.0 Hz, 1 H, H-20), 5.69 (dd, J = 15.1, 8.1 Hz, 1 H, H-33), 4.85 (m, 1 H, H-37), 4.52 (m, 1 H, H-19), 4.21 (dt, J = 10.3, 4.3 Hz, 1 H, *CH*O), 4.11 (m, 1 H, *CH*O), 3.87 (m, 1 H, *CH*O), 3.76 (m, 1 H, *CH*O), 3.66 (s, 3 H, $COOCH_3$), 3.62 (m, 2 H, *CH*O), 3.55 (m, 2 H, *CH*O, *OH*), 3.43 (m, 1 H, *CH*O), 2.99 (s, 3 H, OCH_3), 2.37–1.05 (m, 18 H, allylic *CH*, H-2, CH_2, *CH*), 2.29 (t, J = 10.3 Hz, 1 H, H-16), 1.40, 1.32, 1.30, 1.29 (singlets, 12 H, acetonides), 1.16 (d, J = 6.2 Hz, 3 H, CH_3), 0.98 (d, J = 6.8 Hz, 3 H, CH_3), 0.90 (d, J = 7.3 Hz, 3 H, CH_3), 0.89, 0.85, 0.81 (singlets, 9 H each, Si-*t*-*Bu*), 0.4 to −0.03 (six singlets, 3 H each, $SiMe_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.26, 169.65, 138.26, 133.66, 133.42, 133.23, 133.21, 133.18, 132.65, 132.52, 132.25, 131.28, 131.24, 129.74, 127.49, 100.12, 98.42, 98.05, 74.71, 72.47, 71.56, 68.82, 68.08, 68.02, 66.07, 64.59, 64.32, 56.61, 51.59, 47.94, 43.00, 42.33, 41.07, 39.98, 36.55, 32.80, 31.89, 30.09, 30.03, 27.16, 26.03, 25.97, 25.61, 19.71, 19.61, 18.40, 18.19, 17.84, 17.38, −3.81, −4.31, −4.41, −4.68; HRMS (FAB) calcd for $C_{67}H_{116}O_{14}Si_3$ + H 1229.7750, found 1229.7900 (M + H).

Preparation of *p*-Nitrobenzoate Derivative 24a. Amphoteronolide B derivative **23a** (123 mg, 0.1 mmol) was dissolved in dry CH_2Cl_2 (1 mL)

and cooled to 0 °C under argon. The magnetically stirred solution was treated sequentially with 4-(dimethylamino)pyridine (DMAP, 18 mg, 0.15 mmol) and *p*-nitrobenzoyl chloride (22 mg, 0.12 mmol), in that order. The reaction mixture was stirred at 0 °C for 15 min (TLC monitoring), diluted with ether (10 mL), and washed with 10% aqueous $NaHCO_3$ (5 mL), water (5 mL), and brine (5 mL). The yellow solution was dried ($MgSO_4$) and concentrated, and the residue was flash chromatographed (silica, 30% ether in petroleum ether) to afford pure *p*-nitrobenzoate derivative **24a** (131 mg, 95%) as an amorphous yellow solid. **24a**: R_f 0.30 (silica, 30% ether in petroleum ether); $[\alpha]^{20}_D$ +67.7° (*c* 0.20, $CHCl_3$); UV-vis ($CHCl_3$) λ_{max} 413 (E_{1cm}1% 669), 390 (675), 370 (425), 350 (212), 262 nm (122); IR ($CHCl_3$) ν_{max} 2950, 2930, 2850, 1730 (s, C=O, ester, lactone), 1610, 1530, 1270 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.25 (m, 4 H, aromatic), 6.40–5.98 (m, 12 H, olefinic), 5.86 (m, 2 H, H-20, H-19), 5.59 (dd, $J_{33,32}$ = 14.5 Hz, $J_{33,34}$ = 8.9 Hz, 1 H, H-33), 4.81 (m, 1 H, H-37), 4.3–3.1 (m, 8 H, C*H*O), 3.59 (s, 3 H, $COOCH_3$), 3.14 (s, 3 H, OCH_3), 2.5–0.6 (m, 19 H, allylic C*H*, CH_2C(O), C*H*C(O), CH_2, C*H*), 1.38, 1.33, 1.30 (singlets, 12 H total, acetonides), 1.17 (d, *J* = 6.1 Hz, 3 H, CH_3), 0.98 (d, *J* = 6.6 Hz, 3 H, CH_3), 0.920, 0.881, 0.800 (singlets, 30 H total, CH_3, Si-*t*-*Bu*), 0.083, 0.043, 0.033, 0.017, −0.062 (singlets, 18 H total, $SiMe_2$). Anal. Calcd for $C_{74}H_{119}NO_{17}Si_3$: C, 64.45; H, 8.70; N, 1.02. Found: C, 64.09; H, 9.05; N, 1.03.

Ozonolysis of *p*-Nitrobenzoate Derivative 24a. Preparation of Dialdehyde 25a. Ozone was passed through the yellow solution of *p*-nitrobenzoate **24a** (138 mg, 0.1 mmol) in CH_2Cl_2 (2 mL) and MeOH (0.2 mL) at −78 °C until the solution became first colorless and then slightly blue. Excess ozone was displaced by an argon stream (5 min, colorless solution), and then Ph_3P (262 mg, 1.0 mmol) was added with stirring at −78 °C. The cooling bath was removed, and the reaction mixture was allowed to stir at ambient temperature for 16 h. Concentration in vacuo followed by flash column chromatography (silica, 50% ether in petroleum ether) gave the rather sensitive dialdehyde **25a** (107 mg, 85%). **25a**: white amorphous solid; R_f 0.17 (silica, 60% ether in petroleum ether); $[\alpha]^{20}_D$ +8.0° (*c* 0.15, MeOH); UV-vis ($CHCl_3$) λ_{max} 262 nm (E_{1cm}1% 90); IR ($CHCl_3$) ν_{max} 3000, 2960, 2930, 2850, 1730 (s, C=O, ester), 1530, 1380, 1260, 1100, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.64 (s, 1 H, aldehyde-33), 9.55 (s, 1 H, aldehyde-20), 8.28 (m, 4 H, aromatic), 5.44 (m, 1 H, H-19) 5.00 (dq, *J* = 6.3, 3.6 Hz, 1 H, H-37), 4.32–3.50 (m, 8 H, C*H*O), 3.66 (s, 3 H, $COOCH_3$), 3.06 (s, 3 H, OCH_3), 2.47–1.18 (multiplets, 19 H total, CH_2C(O), C*H*C(O), CH_2, C*H*), 1.40, 1.32, 1.31, 1.29 (singlets, 12 H total, acetonides), 1.17 (d, *J* = 6.3 Hz, 3 H, CH_3), 1.13 (d, *J* = 7.1 Hz, 3 H, CH_3), 0.90 (d, *J* = 7.1 Hz, 3 H, CH_3), 0.86, 0.85, 0.81 (singlets, 9 H each, Si-*t*-*Bu*), 0.07 to −0.03 (singlets, 18 H total, $SiMe_2$).

Preparation of α,β-Unsaturated Ester 26a. To a stirred solution of aldehyde **25a** (125 mg, 0.1 mmol) in dry benzene (2 mL) was added (carbethoxymethylene)triphenylphosphorane (87 mg, 0.25 mmol) at 25 °C. After being stirred at that temperature for 2 h, the reaction mixture was directly applied to a silica column and flash chromatographed (40% ether in petroleum ether) to give pure α,β-unsaturated ester **26a** (122 mg, 92%). **26a**: colorless amorphous solid; R_f 0.26 (silica, 40% ether in petroleum ether); $[\alpha]^{20}_D$ −7.9° (*c* 0.44, $CHCl_3$); UV (MeOH) λ_{max} 258 (E_{1cm}1% 97), 204 nm (253); IR ($CHCl_3$) ν_{max} 3005, 2995, 2970, 2940, 2935, 1730 (s, C=O, esters), 1535, 1450, 1390 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$, amphotericin B numbering) δ 9.64 (s, 1 H, C*H*O), 8.26 (m, 4 H, aromatic), 6.94 (dd, $J_{20,19}$ = 6.0 Hz, $J_{20,21}$ = 15.5 Hz, 1 H, H-20), 6.0 (dd, $J_{21,19}$ = 1.1 Hz, $J_{21,20}$ = 15.5 Hz, 1 H, H-21), 5.83 (m, 1 H, H-19), 5.0 (dq, *J* = 7.2, 7.2 Hz, 1 H, H-37), 4.3–3.53 (m, 8 H, C*H*O), 4.17 (q, *J* = 7.1 Hz, 2 H, CH_3CH_2C(O)), 3.66 (s, 3 H, $COOCH_3$), 3.12 (s, 3 H, OCH_3), 2.55–0.64 (m, 43 H, C*H*C(O), CH_2-C(O), CH_2, C*H*, CH_3), 0.82, 0.76 (singlets, 27 H total, Si-*t*-*Bu*), 0.07, 0.05, 0.01, −0.04, −0.06 (singlets, 18 H total, $SiMe_2$). Anal. Calcd for $C_{66}H_{113}NO_{20}Si_3$: C, 59.83; H, 8.60; N, 1.06. Found: C, 59.65; H, 8.90; N, 1.02.

Amphotericin B Persilylated Derivative 27. *N*-Acetylamphotericin B methyl ester **3** (6.367 g, 6.5 mmol) was suspended in dry CH_2Cl_2 (65 mL), and 2,6-lutidine (10.448 g ≡ 11.37 mL, 97.5 mmol) was added. To the cold (0 °C), magnetically stirred mixture was added dropwise, trimethylsilyl trifluoromethanesulfonate ($Me_3SiOSO_2CF_3$, 17.336 g ≡ 15.07 mL, 78.0 mmol). Stirring was continued for 15 min at 0 °C, after which time complete dissolution was observed and TLC indicated completion of the reaction. Ether (200 mL) was then added, and the solution was washed sequentially with saturated aqueous $NaHCO_3$ solution (100 mL), saturated aqueous $CuSO_4$ solution (2 × 100 mL), H_2O (100 mL), and brine (100 mL). Drying ($MgSO_4$) of the solution followed by concentration in vacuo and flash column chromatography (silica, 50% ether in petroleum ether) gave the persilylated derivative **27** as a yellow amorphous solid (9.94 g, 90%). **27**: R_f 0.22 (silica, 50% ether in petroleum ether); $[\alpha]^{20}_D$ +175° (*c* 0.29, $CHCl_3$); UV-vis ($CHCl_3$) λ_{max} 412 (E_{1cm}1% 701), 388 (686), 368 (419), 350 nm (197); IR ($CHCl_3$) ν_{max} 2970, 1730 (s, C=O, ester, lactone), 1680 (s, C=O, *N*-acetate), 1510, 1380, 1250 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.32–6.06 (m, 12 H, olefinic), 5.73 (dd, *J* = 15.1, 7.4 Hz, 1 H, H-20), 5.49 (dd, *J* = 14.6, 9.2 Hz, 1 H, H-33), 5.46 (d, *J* = 9.4 Hz, 1 H, N*H*), 4.99 (quintet, *J* = 6.3 Hz, 1 H, H-37), 4.60 (d, *J* = 8.7 Hz, 1 H, C*H*O), 4.43 (m, 2 H, C*H*O), 4.37 (s, 1 H, H-1′), 4.15–4.05 (m, 2 H, C*H*O), 3.96 (dt, *J* = 9.4, 3.2 Hz, 1 H, H-3′), 3.87 (m, 1 H, C*H*O), 3.83 (d, *J* = 3.2 Hz, 1 H, H-2′), 3.70 (s, 3 H, $COOCH_3$), 3.62 (m, 1 H, C*H*O), 3.48–3.40 (m, 2 H, C*H*O), 3.36 (t, *J* = 9.4 Hz, 1 H, H-4′), 3.25 (m, 1 H, H-5′), 2.60 (dd, *J* = 10.9, 8.7 Hz, 1 H, H-16), 2.50–2.28 (m, 3 H, allylic C*H*, CH_2C(O)), 2.04–1.12 (m, 15 H, CH_2, C*H*), 1.99 (s, 3 H, $NHCOCH_3$), 1.21 (d, *J* = 6.2 Hz, 3 H, CH_3), 1.15 (d, *J* = 6.3 Hz, 3 H, CH_3), 0.99 (d, *J* = 6.7 Hz, 3 H, CH_3), 0.90 (d, *J* = 7.1 Hz, 3 H, CH_3), 0.18 to 0.005 (singlets, 90 H total, $SiMe_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.02, 170.53, 169.16, 152.71, 136.79, 134.05, 133.09, 132.99, 132.86, 132.79, 132.60, 132.47, 131.40, 130.84, 130.57, 102.24, 98.43, 79.01, 76.12, 75.47, 73.81, 72.80, 72.33, 72.20, 71.64, 71.23, 70.06, 67.67, 67.59, 66.69, 54.80, 52.28, 52.03, 46.86, 43.19, 41.49, 41.37, 41.27, 38.53, 37.03, 34.58, 27.01, 23.71, 19.10, 18.33, 17.59, 11.86, 0.76, 0.70, 0.65, 0.44, −0.0024. Anal. Calcd for $C_{80}H_{157}NO_{18}Si_{10}$: C, 56.47; H, 9.30; N, 0.82. Found: C, 56.71; H, 9.58; N, 0.87.

Oxidative Deglycosidation of Persilylated Amphotericin B Derivative 27. Preparation of Heptaenone 28. The fully trimethylsilylated *N*-acetylamphotericin B methyl ester derivative **27** (1.70 g, 1.0 mmol) was dissolved in dry CCl_4 (50 mL). With magnetic stirring, $CaCO_3$ (1.0 g, 10 mmol) was added at ambient temperature followed by freshly recrystallized *N*-bromosuccinimide (170 mg, 0.95 mmol). The yellow reaction mixture was stirred at room temperature for 12 h, gradually acquiring a bright orange coloration. Direct application of the reaction mixture on a silica column followed by flash chromatography (30% ether in petroleum ether) gave heptaenone **28** (270 mg, 20%). **28**: bright orange amorphous solid; R_f 0.18 (silica, 30% ether in petroleum ether) $[\alpha]^{20}_D$ +410° (*c* 0.25, $CHCl_3$); UV-vis ($CHCl_3$) λ_{max} 432 nm (E_{1cm}1% 328); IR ($CHCl_3$) ν_{max} 2950, 1725 (s, C=O, ester, lactone), 1670, 1630, 1590, 1540, 1250, 1070 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 15.4, 11.1 Hz, 1 H, H-21), 6.92 (dd, *J* = 14.6, 11.4 Hz, 1 H, H-23), 6.6–6.07 (m, 11 H, olefinic), 5.43 (dd, *J* = 14.6, 9.4 Hz, 1 H, H-33), 4.76 (quintet, *J* = 6.1 Hz, 1 H, H-37), 4.76–3.10 (m, 8 H, C*H*O), 3.72 (s, 3 H, $COOCH_3$), 2.61–2.14 (m, 6 H, allylic C*H*, CH_2C(O), C*H*C(O)), 1.87–1.10 (m, 13 H, CH_2, C*H*), 1.15 (d, *J* = 6.1 Hz, 3 H, CH_3), 0.97 (d, *J* = 6.7 Hz, 3 H, CH_3), 0.90 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.14 to −0.145) (singlets, 72 H total, $SiMe_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.74, 172.39, 170.22, 152.61, 146.80, 143.08, 139.03, 138.55, 137.53, 136.49, 135.19, 131.68, 131.21, 130.74, 130.66, 129.88, 129.81, 129.44, 101.74, 75.33, 73.60, 72.19, 71.87, 70.16, 69.26, 66.69, 66.36, 53.34, 52.07, 46.88, 44.04, 43.15, 42.85, 40.46, 38.58, 34.38, 26.74, 19.47, 18.30, 11.42, 0.67, 0.61, 0.47, 0.40, 0.00; HRMS (FAB) calcd for $C_{66}H_{126}O_{14}Si_8$ + H 1367.7380, found 1367.7302 (M + H).

Reduction of Heptaenone 28. Preparation of Amphoteronolide B Derivative 29. Per(trimethylsilyl) heptaenone **28** (137 mg, 0.1 mmol) in absolute MeOH (1 mL) was reduced to the corresponding hydroxy compound according to the procedure described above for the reduction of **21**. Purification was carried out by flash column chromatography (silica, 50% ether in petroleum ether) to afford amphoteronolide B derivative **29** (131 mg, 96%) as a yellow amorphous solid. **29**: R_f 0.26 (silica, 50% ether in petroleum ether); $[\alpha]^{20}_D$ +252° (*c* 0.21, $CHCl_3$); UV-vis ($CHCl_3$) λ_{max} 412 (E_{1cm}1% 435), 388 (448), 269 (285), 350 nm (143); IR ($CHCl_3$) ν_{max} 3600, 3450, 3000, 2960, 1735 (s, C=O, ester, lactone), 1680, 1440, 1370, 1255, 1170 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.41–6.06 (m, 12 H, olefinic), 5.8 (dd, *J* = 14.5, 6.5 Hz, 1 H, H-20), 5.52 (dd, *J* = 15.0, 9.1 Hz, 1 H, H-33), 4.98 (quintet, *J* = 6.2 Hz, 1 H, H-37), 4.65–3.4 (m, 8 H, C*H*O), 4.49 (m, 1 H, H-19), 3.73 (s, 3 H, $COOCH_3$), 2.67–2.3 (m, 4 H, allylic C*H*, CH_2C(O), C*H*C(O)), 2.03–0.72 (m, 15 H, CH_2, C*H*), 1.15 (d, *J* = 6.2 Hz, 3 H, CH_3), 1.0 (d, *J* = 6.6 Hz, 3 H, CH_3), 0.9 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.13–0.03 (singlets, 72 H total, $SiMe_3$), O*H* was not assigned. Anal. Calcd for $C_{66}H_{128}O_{14}Si_8$: C, 57.86; H, 9.42. Found: C, 58.01; H, 9.44.

Amphoteronolide B Methyl Ester (32). The octakis(trimethylsilyl) derivative of amphoteronolide B methyl ester **29** (68 mg, 0.05 mmol) was dissolved in dry THF (2 mL) in a plastic bottle and cooled to 0 °C. A 170-μL portion of dilute HF·pyr solution (prepared as follows: 1 mL of commercial HF·pyr, Aldrich, ca. 70%, in a plastic bottle under argon at −20 °C was dropwise diluted with 4 mL of dry pyridine) was added dropwise, and the reaction mixture was stirred for 15 min (TLC monitoring). The reaction mixture was poured onto saturated aqueous $NaHCO_3$ solution (20 mL), and the product was extracted with 20% MeOH in CH_2Cl_2 until the aqueous layer became colorless (4 × 25 mL). The combined extract was diluted with benzene (50 mL), concentrated in vacuo, and flash chromatographed (silica, 15% MeOH in CH_2Cl_2) to give

amphoteronolide B methyl ester **32** (33.0 mg, 85%) as a yellow amorphous solid. **32**: R_f 0.20 (silica, 15% MeOH in CH_2Cl_2); $[\alpha]^{20}_D$ +228° (*c* 0.25, 20% MeOH in CH_2Cl_2); UV-vis (DMF) λ_{max} 412 ($E_{1cm}1\%$ 1250), 390 (1202), 368 (731), 350 nm (347); IR (Nujol) ν_{max} 3350 (s, OH), 1730 cm^{-1} (s, C=O, ester, lactone); ^1H NMR (500 MHz, DMSO-d_6–D_2O, ca. 10:1, TMS) δ 6.40–6.05 (m, 12 H, olefinic), 5.81 (dd, *J* = 7.8, 15.1 Hz, 1 H, H-20), 5.53 (dd, *J* = 9.6, 14.9 Hz, 1 H, H-33), 5.06 (m, 1 H, H-37), 4.52–3.07 (multiplets, 9 H, C*H*O), 3.67 (s, 3 H, COOCH_3), 2.37–1.05 (multiplets, 19 H, CH_2C(O), C*H*C(O), allylic C*H*, CH_2, C*H*), 1.11 (d, *J* = 6.2 Hz, 3 H, CH_3), 1.03 (d, *J* = 6.4 Hz, 3 H, CH_3), 0.91 (d, *J* = 7.0 Hz, 3 H, CH_3), the spectrum is similar in pure DMSO-d_6 with the appearance of several additional signals corresponding to the hydroxyl protons; ^{13}C NMR (125 MHz, DMSO-d_6–D_2O, ca. 10:1, TMS) δ 173.04, 170.66, 151.36, 138.31, 137.15, 133.88, 133.73, 133.64, 133.50, 133.24, 132.84, 132.80, 132.63, 132.03, 131.89, 130.99, 128.98, 128.51, 103.20, 76.97, 73.63, 73.34, 71.93, 69.84, 69.71, 68.24, 67.18, 66.55, 65.78, 53.17, 51.94, 44.07, 42.30, 42.15, 41.87, 40.23, 34.99, 29.35, 18.59, 17.50, 12.15, the remaining ^{13}C signal is presumed to be obscured by the solvent; HRMS (FAB) calcd for $C_{42}H_{64}O_{14} - H_2O + Na$ 797.4087, found 797.4118 (M – H_2O + Na). Anal. Calcd for $C_{42}H_{64}O_{14}$: C, 63.60; H, 8.14. Found: C, 63.17; H, 8.55.

Amphoteronolide B (2). Methyl ester **32** (12 mg, 0.015 mmol) was dissolved in THF (0.8 mL) and H_2O (0.4 mL) and cooled to 0 °C. Then, 1 N aqueous LiOH (0.10 mL, 0.10 mmol) was added, and the reaction mixture was stirred for 30 min. The solution was diluted with H_2O (2 mL), washed with EtOAc (2 mL), and acidified with 0.1 N aqueous HCl to pH 5.5. The aqueous phase was then freeze-dried. The resulting solid was dissolved in MeOH/CH_2Cl_2 (1:1) and passed through a short silica gel column to give pure aglycon **2** as a yellow amorphous solid. **2**: R_f 0.15 (silica, 40% MeOH in CH_2Cl_2); IR (Nujol) ν_{max} 3350 (s, OH), 1730 cm^{-1} (s, C=O, acid, lactone); ^1H NMR (250 MHz, DMSO-d_6, TMS) δ 6.60–6.00 (m, 12 H, olefinic), 5.92 (dd, *J* = 7.8, 15.1 Hz, 1 H, H-20), 5.50 (dd, *J* = 9.6, 14.9 Hz, 1 H, H-33), 5.12 (m, 1 H, H-37), 5.00–3.00 (multiplets 19 H, C*H*O, O*H*, COO*H*), 2.50–1.00 (multiplets, 19 H, CH_2C(O), C*H*C(O), allylic C*H*, CH_2, C*H*), 1.11 (d, *J* = 6.2 Hz, 3 H, CH_3), 1.03 (d, *J* = 6.4 Hz, 3 H, CH_3), 0.91 (d, *J* = 7.0 Hz, 3 H, CH_3).

Preparation of *p*-Nitrobenzoate Derivative 33. The preparation of *p*-nitrobenzoate derivative **33** was carried out from the polyenic alcohol **29** (137 mg, 0.1 mmol) according to the procedure described above for the conversion of **23** to **24**. The crude product obtained after concentration was directly used in the next step without further purification due to its rather labile nature on silica gel (144 mg, 95%, essentially homogeneous by TLC and ^1H NMR). **33**: amorphous yellow solid; R_f 0.33 (silica, 25% ether in petroleum ether); UV-vis ($CHCl_3$) λ_{max} 413, 390, 370, 350, 266 nm; IR ($CHCl_3$) ν_{max} 3000, 2960, 2900, 1730 (s, C=O, esters, lactone), 1680, 1610, 1530, 1440, 1350, 1250, 1160 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.25 (m, 4 H, aromatic), 6.47–6.02 (m, 12 H, olefinic), 5.84 (m, 2 H, H-20, H-19), 5.51 (dd, *J* = 9.1, 14.7 Hz, 1 H, H-33), 4.96 (quintet, *J* = 6.1 Hz, 1 H, H-37), 4.64–3.25 (m, 8 H, C*H*O), 3.59 (s, 3 H, COOCH_3), 2.7–0.7 (m, 19 H, allylic C*H*, CH_2C(O), C*H*C(O), CH_2, C*H*), 1.15 (d, *J* = 6.1 Hz, 3 H, CH_3), 0.99 (d, *J* = 6.6 Hz, 3 H, CH_3), 0.9 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.2 to –0.02 (singlets, 72 H total, SiMe_3).

Desilylation of Amphoteronolide B Derivative 33. Preparation of Amphoteronolide B Methyl Ester *p*-Nitrobenzoate (34). The octakis(trimethylsilyl) derivative **33** (121 mg, 0.08 mmol) in dry THF (3.5 mL) was desilylated by the same procedure as described above for the desilylation of **29** to **30** giving, after flash column chromatography (silica, 10% MeOH in CH_2Cl_2), the *p*-nitrobenzoate derivative of amphoteronolide B methyl ester **34** (67.0 mg, 90%) as a yellow amorphous solid. **34**: R_f 0.29 (silica, 10% MeOH in CH_2Cl_2); $[\alpha]^{20}_D$ +274° (*c* 0.15, DMF); UV-vis ($CHCl_3$/MeOH, 1:1) λ_{max} 3400, 3000, 2980, 2800, 1730 (s, C=O, ester, lactone), 1530, 1440, 1350, 1270, 1110, 1010 cm^{-1}; ^1H NMR (250 MHz, DMSO-d_6) δ 8.27 (m, 4 H, aromatic), 6.5–5.95 (m, 13 H, olefinic), 5.67 (m, 1 H, H-19), 5.46 (dd, $J_{33,32}$ = 14.0, $J_{33,34}$ = 8.9 Hz, 1 H, H-33), 5.12 (m, 1 H, H-37), 5.1–3.0 (m, 8 H, C*H*O), 3.50 (s, 3 H, COOCH_3), 2.45–0.80 (m, 19 H, allylic C*H*, CH_2C(O), C*H*C(O), CH_2, C*H*), 1.1 (d, *J* = 6.1 Hz, 3 H, CH_3), 1.03 (d, *J* = 6.2 Hz, 3 H, CH_3), 0.91 (d, *J* = 6.6 Hz, 3 H, CH_3), the O*H* protons appear in the range of 5.1–3.5 (8 H); HRMS (FAB) calcd for $C_{49}H_{67}NO_{17}$ + H 942.4487, found 942.4442 (M + H). Anal. Calcd for $C_{49}H_{67}NO_{17}$: C, 62.46; H, 7.17; N, 1.49. Found: C, 62.62; H, 6.95; N, 1.53.

Acetonization/Methoxylation of *p*-Nitrobenzoate 34. Preparation of Trihydroxy *p*-Nitrobenzoate Derivative 35ab. *p*-Nitrobenzoate derivative **34** (94 mg, 0.1 mmol) was suspended in MeOH (1.5 mL) and dimethoxypropane ($Me_2C(OMe)_2$, 0.5 mL) under argon. To the resulting stirred suspension was added camphorsulfonic acid (CSA, 5 mg, 0.02 mmol) at room temperature, and the reaction was allowed to proceed for 30 min (TLC monitoring) before dilution with EtOAc (20 mL) and washing with saturated aqueous $NaHCO_3$ solution (10 mL), H_2O (10 mL), and brine (10 mL). The organic layer was dried ($MgSO_4$) and concentrated, and the residue flash chromatographed (silica, 5% MeOH in CH_2Cl_2) to afford the diacetonide methyl ether **35ab** (70 mg, 68%) as a mixture of two isomers. The two isomers could be separated by preparative thin-layer chromatography (silica, 5% MeOH in CH_2Cl_2). **35a**: yellow amorphous solid; R_f 0.27 (silica, 5% MeOH in CH_2Cl_2); $[\alpha]^{20}_D$ +49.9° (*c* 0.23, MeOH); UV-vis ($CHCl_3$) λ_{max} 413 ($E_{1cm}1\%$ 1072), 389 (1082), 369 (692), 350 (347), 262 nm (185); IR ($CHCl_3$) ν_{max} 3600, 3500, 3000, 2940, 2870, 1730 (s, C=O, esters, lactone), 1610, 1530, 1380, 1270, 1170, 1100, 1010 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 8.25 (m, 4 H, aromatic), 6.39–6.12 (m, 12 H, olefinic), 5.86 (m, 2 H, H-20, H-19), 5.43 (dd, $J_{33,32}$ = 15.0, $J_{33,34}$ = 9.7 Hz, 1 H, H-33), 5.2 (dq, *J* = 6.3, 6.3 Hz, 1 H, H-37), 4.3–3.08 (m, 8 H, C*H*O), 3.64 (s, 3 H, COOCH_3), 3.13 (s, 3 H, OCH_3), 2.5–0.9 (m, 19 H, allylic C*H*, CH_2C(O), C*H*C(O), CH_2, C*H*), 1.41, 1.36, 1.34, 1.31 (singlets, 12 H total, acetonides), 1.18 (d, *J* = 6.3 Hz, 3 H, CH_3), 1.10 (d, *J* = 6.5 Hz, 3 H, CH_3), 0.99 (d, *J* = 7 Hz, 3 H, CH_3). Anal. Calcd for $C_{56}H_{77}NO_{17}$: C, 64.89; H, 7.49; N, 1.35. Found: C, 65.02; H, 7.54; N, 1.23.

Silylation of Trihydroxy *p*-Nitrobenzoate 35a. Preparation of *p*-Nitrobenzoate Derivative 24a. To a stirred solution of diacetonide methyl ester **35a** (52m g, 0.05 mmol) and 2,6-lutidine (32 mg ≡ 35 μL, 0.3 mmol) in dry CH_2Cl_2 (0.5 mL) was added *t*-BuMe_2SiOTf (59 mg ≡ 52 μL, 0.225 mmol) dropwise at 0 °C and under argon. After 15 min of stirring at 0 °C, the reaction mixture was diluted with ether (20 mL) and washed with saturated aqueous $NaHCO_3$ solution (10 mL), saturated $CuSO_4$ solution (10 mL), and brine (10 mL). Drying ($MgSO_4$) followed by concentration and flash column chromatography (silica, 40% ether in petroleum ether) gave *p*-nitrobenzoate derivative **24a** (59 mg, 85%). The chromatographic (TLC) and spectroscopic ($[\alpha]_D$, ^1H NMR, IR, UV) properties of this sample were identical with those of a sample obtained from **23a** as described above.

Preparation of Heptaenone Triacetates 36a and 36b. The per(*tert*-butyldimethylsilyl) derivatives **5ab** or more conveniently the corresponding per(trimethylsilyl) derivative were oxidatively deglycosylated with NBS as described above, and the two heptaenones obtained were chromatographically separated. Desilylation of **21a** and **21b** or their TMS counterparts using fluoride ion as described above gave the corresponding triols (fast moving → fast moving, slow moving → slow moving), R_f 0.34 and 0.32 in 8% MeOH in CH_2Cl_2), which were acetylated as follows. The triol from **5a** (20 mg, 0.023 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and treated sequentially with pyridine (18 μL, 0.23 mmol), DMAP (2 mg, 0.016 mmol), and Ac_2O (23 μL, 0.23 mmol) at 0 °C and under argon. After 2 h at ambient temperature, the reaction was quenched with saturated NaHCO3 solution (0.5 mL) and diluted with ethyl acetate (10 mL). Standard workup followed by PTLC gave pure heptaenone triacetates **36a** (20 mg, 88%). Compound **36b** was similarly obtained (20 mg, 88%). **36a** (from faster moving triol): orange amorphous solid; R_f 0.39 (silica, 50% EtOAc in petroleum ether); $[\alpha]^{20}_D$ +210° (*c* 0.083, CH_2Cl_2); UV-vis (CH_2Cl_2) λ_{max} 400 (shoulder), 422, 440 (shoulder) nm; IR ($CHCl_3$) ν_{max} 2990, 2940, 1733 (s, C=O, ester, lactone), 1640, 1550, 1382, 1372, 1245, 1165, 1010 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 15.8, 11.1 Hz, 1 H, H-21), 6.79 (dd, *J* = 14.4, 11.3 Hz, 1 H, H-23), 6.47 (dd, *J* = 14.4, 11.1 Hz, 1 H, H-22), 6.40–6.15 (m, 9 H, olefinic), 6.15 (d, *J* = 15.8 Hz, 1 H, H-20), 5.47 (dd, *J* = 14.7, 9.8 Hz, 1 H, H-33), 5.37 (dt, *J* = 10.7, 5.0 Hz, 1 H, H-15), 5.25 (m, 1 H, H-11), 5.16 (m, 1 H, H-37), 4.82 (dd, *J* = 9.3, 3.1 Hz, 1 H, H-35), 4.13 (m, 1 H, H-3), 3.93 (dt, *J* = 10.4, 1.4 Hz, 1 H, H-17), 3.70 (s, 3 H, COOCH_3), 3.60 (br t, *J* = 12 Hz, 1 H, H-5), 3.50 (br t, *J* = 8 Hz, 1 H, H-9), 3.37 (br t, *J* = 8 Hz, 1 H, H-8), 3.01 (dd, *J* = 12.3, 10.2 Hz, 1 H, H-18), 2.96 (s, 3 H, OCH_3), 2.50 (m, 1 H, H-34), 2.44 (dd, *J* = 16.8, 6.0 Hz, 1 H, H-2), 2.37 (t, *J* = 10.6 Hz, 1 H, H-16), 2.31 (dd, *J* = 12.3, 4 Hz, 1 H, H-18), 2.22 (dd, *J* = 12.8, 5.0 Hz, 1 H, H-14), 2.12 (dd, *J* = 16.8, 6.5 Hz, 1 H, H-2), 2.07, 2.06, 1.97 (singlets, 3 H each, CH_3C(O)O), 1.90 (m, 1 H, H-36), 1.90 (t, *J* = 15.0 Hz, 1 H, H-12), 1.84 (dd, *J* = 15.0, 2.4 Hz, 1 H, H-12), 1.70 (m, 1 H, H-10), 1.54 (m, 1 H, H-14), 1.37, 1.35, 1.28, 1.27 (singlets, 3 H each, acetonides), 1.16 (d, *J* = 6.4 Hz, 3 H, *Me*-37), 1.0 (m, 1 H, H-4), 0.94 (d, *J* = 6.6 Hz, 3 H, *Me*-34), 0.89 (d, *J* = 7.0 Hz, 3 H, *Me*-36), 1.50–1.10 (complex, 6 H, H-4, H-6, H-7, H-10); HRMS (FAB) calcd for $C_{55}H_{87}O_{17}$ 1010.5239, found 1010.5255. **36b** (from slow moving triol): orange amorphous solid; R_f same as **36a**; $[\alpha]^{20}_D$ +196° (*c* 1.0, $CHCl_3$); UV-vis ($CHCl_3$) λ_{max} 399 (shoulder), 420, 438 (shoulder) nm; IR ($CHCl_3$) ν_{max} 2990, 2935, 1730 (s, C=O, ester, lactone), 1635, 1545, 1380, 1372, 1245, 1160, 1010 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 15.5, 11.1 Hz, 1 H, H-21), 6.71 (dd, 14.6, 11.3 Hz, 1 H, H-23), 6.51 (dd, *J* = 14.6, 11.1 Hz, 1 H, H-22), 6.40–6.15 (m, 9 H, olefinic), 5.46 (dd, *J* = 14.5, 10.0 Hz, 1 H, H-33), 5.37 (dt, *J* = 11.0, 4.7 Hz, 1 H, H-15), 5.18 (m, 1 H, H-37), 4.82 (dd, *J* = 9.5, 3.1 Hz, 1 H, H-35), 4.77 (m, 1 H, H-8), 4.13 (m, 1 H, H-3), 3.95 (dt, *J* = 9.7, 1.2 Hz, 1 H, H-17), 3.87 (m, 1 H, H-11), 3.74 (m, 1 H, H-9), 3.70 (s, 3 H, COOCH_3), 3.57 (br t, *J* =

10 Hz, 1 H, H-5), 3.09 (br t, J = 11.5 Hz, 1 H, H-18), 2.92 (s, 3 H, OCH_3), 2.47 (m, 1 H, H-34), 2.41 (t, J = 10.5 Hz, 1 H, H-16), 2.41 (dd, J = 16.9, 6.8 Hz, 1 H, H-2), 2.30 (dd, J = 13.0, 4.9 Hz, 1 H, H-14), 2.24 (br d, J = 12 Hz, 1 H, H-18), 2.12 (dd, J = 17.1, 5.7 Hz, 1 H, H-2), 2.06, 2.03, 1.98 (singlets, 3 H each, $CH_3C(O)O$), 1.96 (m, 1 H, H-36), 1.40 (br t, J = 12 Hz, 1 H, H-14), 1.10 (m, 1 H, H-10), 0.95 (m, 1 H, H-4), 1.15 (d, J = 6.4 Hz, 3 H, *Me*-37), 0.94 (d, J = 6.5 Hz, 3 H, *Me*-34), 0.87 (d, J = 7.0 Hz, 3 H, *Me*-36), 1.80–1.15 (m, 8 H total, H-4, H-6, H-7, H-10, H-12); HRMS calcd for $C_{55}H_{78}O_{17}$ 1010.5239, found 1010.5274. Phase-sensitive ^{1}H COSY spectra of **36a** and **36b** were collected by the TPPI method: 512 experiments of 16 scans each; relaxation delay of 1.5 s; size 1 K data points; spectral width in F1 and F2 6000 Hz; no zero filling in F2, and to 1 K in F1, apodization in both dimensions squared sinebell.

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Total Synthesis of Amphoteronolide B and Amphotericin B. 1. Strategy and Stereocontrolled Construction of Key Building Blocks†

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Abstract: The retrosynthetic analysis and strategy for the total synthesis of amphotericin B (**1**) and amphoteronolide B (**2**) is discussed. Focusing on subtle and repeated structural units, a retrosynthetic scheme was constructed that led to the recognition of readily available and enantiomerically related compounds as starting materials for the total synthesis of **1** and **2**. Thus, the four key building blocks **8**–**11** were defined as subtargets and synthesized in optically active forms. Segments **8** and **11** were derived from epoxide **15**, which is readily available from (+)-DET. Segments **9** and **10** were obtained from (+)- and (−)-xylose, respectively, or from the prostereogenic allylic alcohol **14** and (−)- and (+)-DET, respectively, via a stereocontrolled sequence based on the Sharpless asymmetric epoxidation reaction. This latter sequence provides a general and flexible entry into the 1,3,5,···($2n$ + 1) polyol series of compounds, reminiscent of substructures occurring in polyene macrolide antibiotics.

Amphotericin **B** (**1**) and its aglycon amphoteronolide B (**2**) represent important synthetic targets,[1] providing unique opportunities for the development of both new and existing synthetic technologies. Accomplishments in this area may have broad applications to the problem of structure elucidation and eventual total synthesis of the biomedically important polyene macrolide antibiotics. In the preceding paper[2] we described some chemistry of amphotericin B (**1**) culminating in its conversion[3,4] to its aglycon amphoteronolide B (**2**). In this series of papers we describe the total synthesis of both amphoteronolide B (**2**) and amphotericin B (**1**). In the present paper we describe the general synthetic strategy and the stereocontrolled construction of the requisite key building blocks[5] for this undertaking.

Results and Discussion

Strategy and Retrosynthetic Analysis. Our general strategy for the construction of amphotericin B (**1**) and its aglycon (**2**) is presented in Scheme I. The heptaenone **3** was recognized as the key intermediate from which both **1** and **2** could be derived. Thus, stereocontrolled reduction of the carbonyl group of **3**, or of a compound derived from **3**, was expected to lead to an amphoteronolide B derivative from which target **2** could be liberated. Glycosidation of amphoteronolide B derivatives derived from **3** with a mycosamine equivalent followed by functional group manipulations was projected as the final sequence toward amphotericin B (**1**). CPK models of **3** and analogous structures pointed to a stereoselective reduction by peripheral attack, although it was not a priori possible to predict with confidence which of the two possible C-19 epimers would result.[2] However, if necessary, inversion of configuration at C-19 would correct the situation at that stage. Despite the plethora of macrolide-forming reactions[6] currently at our disposal, the construction of the heptaenone **3**, due to its size and complexity, presented a rather formidable problem. Inspection of **3** revealed two rather obvious strategic bonds for disconnection in the retrosynthetic sense, on the basis of a macrocyclization reaction, namely the lactone linkage and the C-20 double bond.

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

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