Total Synthesis of Amphotericin B

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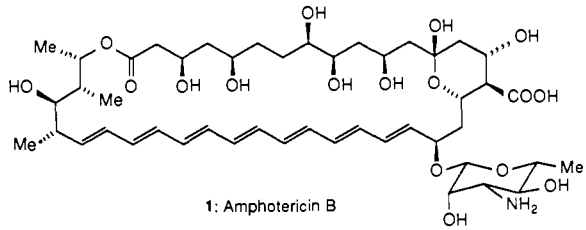
In previous communications, we reported the stereocontrolled construction of key building blocks[1] for the synthesis of amphotericin B (**1**) and the first total synthesis[2] of amphoteronolide B, the aglycon of **1**. We now record the first total synthesis of

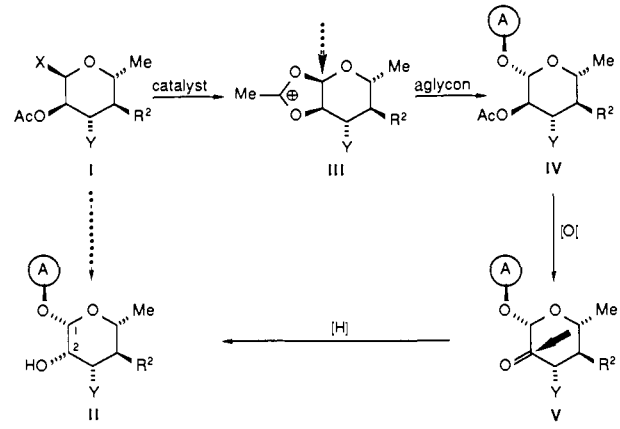


1: Amphotericin B

amphotericin B (**1**)[3-5] in its naturally occurring enantiomeric form. The thorny nature of an eventual total synthesis of this complex and widely used antibiotic has long been recognized, particularly in view of the glycosidation step. Justified concerns stemmed from (a) the rather labile nature of amphoteronolide B[6] and amphotericin B (**1**) and their derivatives, (b) the presence of a basic nitrogen in the carbohydrate moiety, and (c) the requirement for a β-glycoside bond in a 1,2-cis relationship with the C-2 hydroxyl group of the carbohydrate unit. These circumstances and requirements presented a rather formidable challenge which was finally met by the construction of a suitable mycosamine equivalent and its stereospecific attachment to a properly protected aglycon derivative.

The designed strategy for a stereospecific solution to the problem at hand is presented in Scheme I. According to this plan, an appropriate mycosamine equivalent (I) containing (i) a leaving group (X) at C-1, (ii) a participating group at C-2 with β-glycoside bond directing capability (e.g., Ac), and (iii) a masked amino group (Y) lacking basic and nucleophilic properties at C-3 was to be constructed and coupled to advanced aglycon intermediate **8** (Scheme III) to afford the β-glycoside IV via intermediate III. The configuration at C-2 was then to be corrected by inversion involving stereocontrolled reduction of the corresponding ketone (V) to give the desired product II with the requisite 1,2-cis stereorelationship. Subsequent functional group manipulations were then envisioned to lead to amphotericin B (**1**). In the final scheme, the trichloroacetimidate[7] and the acetate[8] groups were chosen to play the crucial roles of the leaving and participating groups, respectively, whereas the azido group was selected to serve as the nonnucleophilic/nonbasic amino group equivalent.[9]

Scheme I. General Strategy for Stereospecific Construction of the 1,2-Cis Bonds in Amphotericin B (**1**)



Scheme II details a highly efficient and stereocontrolled construction of the requisite carbohydrate donor **7**, starting from the readily available glucose derivative **2**.[10] Thus, inversion of stereochemistry at C-3 was achieved by oxidation (PDC, 98%)–reduction ($NaBH_4$, 96%), leading, after protection (THP, 91%)–deprotection (H_2–$Pd(OH)_2$ catalyst, 90%), to intermediate **4** via ketone **3**.[11] The triflate **5** was then formed by sequential iodonation at C-6 (PPh_3–I_2, 89%), silylation of the C-4 hydroxyl (t-$BuMe_2SiOSO_2CF_3$, 94%), reduction (n-Bu_3SnH–AIBN, 99%), deprotection of the C-3 hydroxyl (PPTS, 86%), and exposure to triflic anhydride ($(CF_3SO_2)_2O$, 100%). S_{N2} displacement of the triflate in **5** with sodium azide in the presence of 15-crown-5 led to the azide **6** in 83% yield. The methyl glycoside **6** was then converted to the desired trichloroacetimidate derivative **7**, in 65% overall yield, by the following sequence: (i) acetoxylation at C-1 (Ac_2O–H_2SO_4 catalyst), (ii) selective replacement of the C-1 acetate by chloride (Cl_2CHOMe–$ZnCl_2$ catalyst), (iii) lactol generation ($HgBr_2$–MeCN–H_2O),[12] and (iv) trichloroacetimidate formation (NaH–Cl_3CCN).[12] With the requisite partners **7** and **8**[2,6] now at hand, the quest for amphotericin B (**1**) was closer.

The final drive toward amphotericin B (**1**) is presented in Scheme III. Thus, the aglycon derivative **8**,[13] the total synthesis of which is recorded in previous communications,[2,6] was reacted with the trichloroacetimidate **7** in the presence of PPTS (hexane, 0.007 M, 25 °C)[14] to afford, stereospecifically, the β-glycoside **9**[15] (40%, based on ca. 50% aglycon conversion).[16] Having served its function as a β-glycoside bond director, the acetate group was then removed (K_2CO_3–MeOH, 90%) and the stereochemistry of the resulting hydroxyl group was inverted stereospecifically by oxidation (Swern)–reduction ($NaBH_4$, 80% overall), leading to compound **11** via ketone **10**.[11] The stereochemical requirements for amphotericin B (**1**) were thus met and confirmed at this stage by silylation (t-$BuMe_2SiOSO_2CF_3$, 95%), reduction of the azido group ($HS(CH_2)_3SH$-Et_3N, 85%),[17] and N-acetylation (Ac_2O,

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

(2) Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K. *J. Am. Chem. Soc.*, in press.

(3) Isolation: Vandeputte, J.; Watchtel, J. L.; Stiller, E. T. *Antibiotic Annu.* **1956**, 587.

(4) X-ray structure: Mechinski, W.; Shaffner, C. P.; Ganis, P.; Avitabile, G. *Tetrahedron Lett.* **1970**, 3873. Ganis, P.; Avitabile, G.; Mechinski, W.; Shaffner, C. P. *J. Am. Chem. Soc.* **1971**, *93*, 4560.

(5) Synthetic studies: see footnote 3, ref 2.

(6) For the preparation of amphoteronolide B and derivatives from amphotericin B, see: Nicolaou, K. C.; Chakraborty, T. K.; Daines, R. A.; Ogawa, Y. *J. Chem. Soc., Chem. Commun.*, in press.

(7) For an excellent recent review on the use of the trichloroimidate group in glycosidation reactions, see: Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212.

(8) For the utilization of the acetate group in controlling stereochemistry in glycosidation reactions, see: Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155. For some recent applications, see: Nicolaou, K. C.; Randall, J. L. *J. Am. Chem. Soc.* **1986**, *107*, 5556. Dolle, R. E.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1985**, *107*, 1695.

(9) A number of unsuccessful attempts were made toward the desired glycosidation, which led, nevertheless, to the rational design of Scheme I and the choice of the groups at C-1–3 of the carbohydrate fragment. These studies will be described in detail in the forthcoming full account of this work.

(10) Eby, R.; Webster, K. T.; Schuerch, C. *Carbohydr. Res.* **1984**, *129*, 111.

(11) Molecular modeling and molecular mechanics calculations (MM-2) suggested stereoselective reduction of this ketone. We thank Prof. W. C. Still, Columbia University, for the MACRO-MODEL computer program.

(12) The initially obtained α:β anomeric mixture (1:1) of lactol was enriched in the α-anomer (α:β ≥ 9:1 ratio) by passing repeatedly (3 times) through a silica gel column. Under the employed trichloroacetimidate forming conditions (see also Scheme II), only the α-lactol anomer reacted, giving exclusively the α-trichloroacetimidate derivative **7**.

(13) The chromatographically faster moving methoxy anomer of **8** was used in this reaction. Subsequent intermediates were, therefore, also single methoxy anomers (unassigned stereochemistry).

(14) We thank Prof. R. R. Schmidt, Fakultat Chemie der Universitat Konstanz, F.R.G., for helpful discussions regarding this coupling reaction.

(15) The β-stereochemistry of glycoside **9** was evident from the coupling constant of the anomeric proton (δ 4.35, J = 7.9 Hz, $CDCl_3$–Me_4Si) 250 MHz.)

(16) In addition to the desired β-glycoside **9**, this reaction also furnished the corresponding ortho ester in approximately equal amounts.

(17) Bayley, H.; Standing, D. N.; Knowles, J. R. *Tetrahedron Lett.* **1978**, 3633.

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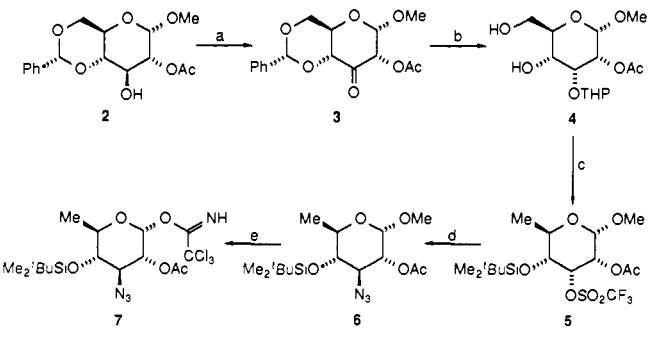
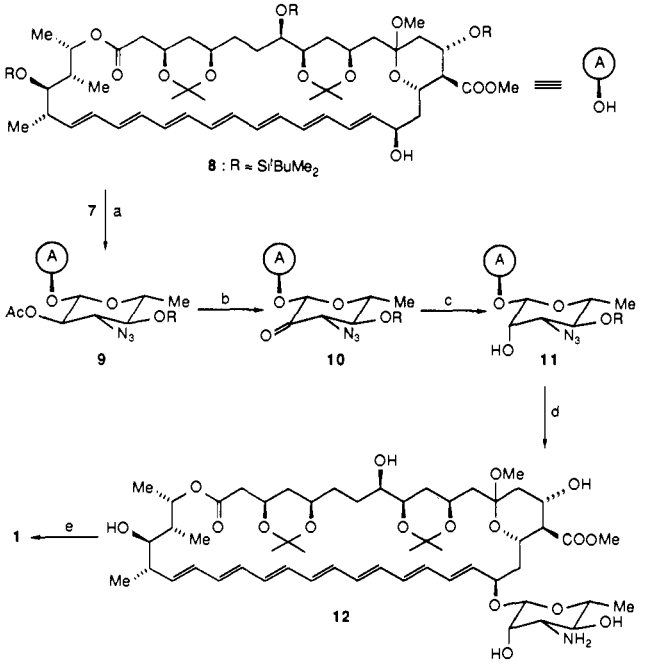
Scheme II[a]



[a] (a) 5.0 equiv of PDC, 4-Å MS, CH_2Cl_2, 25 °C, 16 h, 98%; (b) (i) 1.0 equiv of $NaBH_4$, THF:MeOH (9:1), -10 °C, 1 min, 96%, (ii) 1.2 equiv of dihydropyran, TsOH catalyst, CH_2Cl_2, 0 °C, 0.5 h, 91%, (iii) $Pd(OH)_2$ catalyst, H_2, EtOAc, 25 °C, 16 h, 90%; (c) (i) 3.0 equiv of PPh_3, 3.0 equiv of imidazole, 2.0 equiv of I_2, benzene, 45 °C, 4 h, 89%, (ii) 1.1 equiv of t-$BuMe_2SiOSO_2CF_3$, 1.5 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, 94%, (iii) 2.0 equiv of n-Bu_3SnH, AIBN catalyst, toluene, Δ, 2 h, 99%, (iv) 0.1 equiv of PPTS, MeOH, 50 °C, 3 h, 86%, (v) 1.1 equiv of $(CF_3SO_2)_2O$, 1.5 equiv of pyridine, CH_2Cl_2, 25 °C, 2 h, 100%; (d) 1.1 equiv of NaN_3, 1.1 equiv of 15-crown-5, DMF, 25 °C, 0.5 h, 83%; (e) (i) Ac_2O, H_2SO_4 catalyst, 0-25 °C, 2 h, 90%, (ii) 10 equiv of Cl_2CHOMe, $ZnCl_2$ catalyst, CH_2Cl_2, 25 °C, 2 h, 80%, (iii) 1.0 equiv of $HgBr_2$, MeCN:H_2O (9:1), $CaCO_3$, 25 °C, 0.5 h, and then silica gel, 100% (α:β ca. 9:1), (iv) 1.1 equiv of NaH, 10 equiv Cl_3CCN, CH_2Cl_2, 0 °C, 0.5 h, 90%.

Scheme III[a]



[a] (a) **7** (3.0 equiv), PPTS catalyst, hexane (0.007 M), 25 °C, 4 h, 40% (based on aglycon, 50% conversion); (b) (i) 1.5 equiv of K_2CO_3, MeOH-THF (3:2), 25 °C, 6 h, 90%, (ii) 2.5 equiv of $(CF_3CO)_2O$, 5.0 equiv of Me_2SO, 5.0 equiv of tetramethylurea, 5.0 equiv of Et_3N, CH_2Cl_2, -78 °C, 2 h; (c) 1.5 equiv of $NaBH_4$, MeOH-THF (3:2), 25 °C, 5 min, 80% overall from **9**; (d) (i) excess HF·pyr, MeOH, 50 °C, 48 h, 50%; (ii) 10.0 equiv of $HS(CH_2)_3SH$, 10.0 equiv of Et_3N, MeOH, 25 °C, 24 h, 90%; (e) (i) 1.2 equiv of CSA, MeOH, 25 °C, 2 h, and then H_2O, 25 °C, 4 h, 60%, (ii) 10 equiv of LiOH, THF-H_2O (1:1), 25 °C, 1 h, 80%.

90%), to produce the pentakis(*tert*-butyldimethylsilyl)-*N*-acetyl derivative of compound **12**, which was identical (^1H NMR, IR, UV-vis, MS, TLC, HPLC, optical rotation) with an authentic sample, prepared[6] from natural amphotericin B (**1**). The total synthesis of amphotericin B (**1**) from intermediate **11** was then completed by (a) desilylation (HF·pyr, MeOH, 50% based on ca. 50% recovery)[18] followed by reduction of the azido group as described above (90%) leading to compound **12** and (b) sequential deprotection to amphotericin B (**1**) methyl ester (CSA, MeOH, and then H_2O, 55% based on ca. 50% conversion) and finally to amphotericin B (**1**) itself (LiOH, THF-H_2O, 80%). Synthetic amphotericin B (**1**) and its methyl ester were proven to be identical with authentic samples by the usual criteria [^1H NMR, IR, UV-vis, MS, TLC, HPLC, optical rotation]. Thus, the total synthesis of amphotericin B (**1**) was accomplished.

The total synthesis of amphotericin B (**1**) demonstrates the power of modern organic synthesis. With the described strategy and synthetic technology available, attention may now focus on other members of the polyene macrolide class.[19] Accelerated advances in further total syntheses and structural elucidations in this field should be forthcoming.[20]

Acknowledgment. We express our many thanks to Dr. C. Cimarusti, the Squibb Institute for Medical Research for generous samples of amphotericin B, and Dr. M. Weigele, Hoffmann-La Roche, for high-resolution FAB mass spectra. Our thanks are also due to Drs. George Furst, Patrick Carroll, and John Dykins of this department for their superb NMR, X-ray crystallographic, and mass spectroscopic assistance. This work was financially supported by the National Institutes of Health, Merck Sharp & Dohme, and Hoffmann-La Roche, USA.

Supplementary Material Available: Listing of R_f, $[\alpha]_D$, IR, UV, and ^1H NMR data for compounds **7-9**, **11**, pentakis(*tert*-butyldimethylsilyl)-*N*-acetyl derivative of **12**, and methyl ester of amphotericin B (**1**) (4 pages). Ordering information is given on any current masthead page.

(18) Optimum results were obtained when this reaction was allowed to proceed to a mixture of the fully desilylated product and a monosilyl derivative (as yet unassigned isomeric structure, ca. 1:1 ratio). This monosilyl ether could be recycled to the fully desilylated material.

(19) For reviews on this subject see: (a) Omura, S., Ed. *Macrolide Antibiotics Chemistry, Biology and Practice*; 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.

(20) New compounds exhibited satisfactory spectral and analytical and/or exact mass spectral data. Yields refer to spectroscopically and chromatographically homogenous materials.

Synthesis and Electrocyclic Ring Opening of 1,3,2λ³,4λ⁵-Diazadiphosphetines

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Of the three possible types of N-P-N-P four-membered rings, the saturated diazadiphosphetidines A have been widely studied,[1] an example of the fully unsaturated 1,3,2λ⁵,4λ⁵-diazadiphosphete B has been recently isolated,[2] but there is a lack of information

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(1) Grapov, A. F.; Razvodovskaya, L. V.; Mel'nikov, N. N. *Russ. Chem. Rev. (Engl. Tranl.)* **1981**, *50*, 324. Chen, H. J.; Haltiwanger, R. C.; Hill, T. G.; Thompson, M. L.; Coons, D. E.; Norman, A. D. *Inorg. Chem.* **1985**, *24*, 4725 and references therein.

(2) Baceiredo, A.; Bertrand, G.; Majoral, J. P.; Sicard, G.; Jaud, J.; Galy, J. *J. Am. Chem. Soc.* **1984**, *106*, 6088. Baceiredo, A.; Bertrand, G.; Majoral, J. P.; El Anba, F.; Manuel, G. *J. Am. Chem. Soc.* **1985**, *107*, 3945.

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