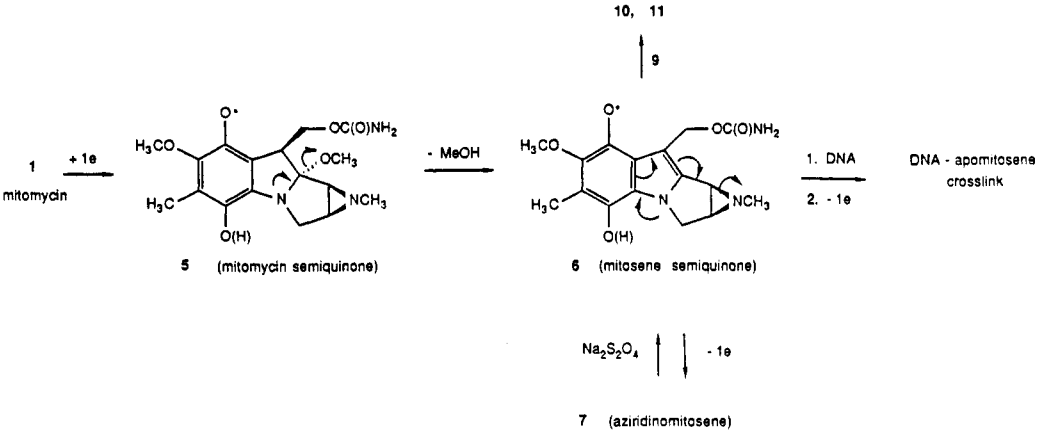
Scheme III. Summary of the Reductive Activation–Alkylation Reactions of *N*-Methylmitomycin A



complicated by uncertainties in the sequence of the various acylations.

Hornemann and Kohn had previously examined the reaction of MMC with potassium ethyl xanthate (**9**) under reductive ($Na_2S_2O_4$) conditions.[14] Apomitosenes, arising from the nonstereospecific ring opening of the aziridine by nucleophile at C_1, were encountered. It was implicitly presumed that reaction had occurred via the MMC derived version of **3a**. In the *N*-MeMMA series, we could evaluate the reactivity of the aziridine-containing compounds **7** and **3a**, generated as discrete entities by our methodology.[3a,b] Reactions were conducted in aqueous pyridine. From this series of reactions, three products could be obtained and identified. These were the C_1 and C_{10} xanthates **10** and **12**, as well as the dixanthate **11**. When reaction was conducted with **3a** (10 min, 0 °C) followed by subsequent air oxidation, a 20% yield of the three products in the indicated ratio was obtained. When reaction was conducted on **7**, a trace of **10** (ca. 5%) could be detected and ca. 95% of **7** was recovered.

Maximum yield was realized from the reaction of **7** with $Na_2S_2O_4$ in the presence of **9**. Oxidation (air) after the 10-min incubation period afforded a 35% yield of **10** and a 25% yield of **11**. Thus the process of reductive priming of **7** with sodium dithionite gave a substantially higher yield than was realized from the two-electron reduction product (**3a**) itself. Furthermore, attempted reduction of **7** with dithionite (aqueous pyridine) in the absence of nucleophile **9** led to very slow reaction and the product was not **3a**, but rather the ene pyrrole **4** (NMR analysis). *The rate of formation of* ***3a*** *is too slow for it to be the primary alkylating agent.* Hence the formulation whereby the two electron reduction product, **3a**, acts as the active alkylating agent, producing **10**, **11**, and **12**, is untenable. The sequence embodied in Scheme III, wherein mitosene semiquinone **6** alkylates nucleophile **9**, accounts very well for the observed result. Further support for the proposal comes from the reaction of aziridinomitosene (**7**) with a catalytic amount (0.3 equiv) of $Na_2S_2O_4$ in the presence of nucleophile **9**. Workup after 35 min yielded an 80% combined yield of xanthate alkylated products.[15] *Thus the extent of alkylation substantially exceeds the availability of reducing agent.* These data in the aggregate point toward the intervention of a steady-state reactive intermediate (cf. semiquinone **6**) as the active electrophile.

A parallelism is noted between the intervention of semiquinone equivalent **6** in the xanthate alkylation reactions and the involvement of species **5** in the C_{9a} methoxy-ejection event (**1** → **7**).[3b] The rough vinylogy between the two processes is indicated (cf. arrows). Our data do not preclude significant alkylation properties for compound **3a**. They also do not define the precise species involved in the remarkable transformation of **3a** → **4**.[16] They do, however, provide a basis for proposing a very concise sequence for bioactivation of mitomycins, as shown in Scheme III. A natural consequence of these findings is that new departures in mitomycin drug development might well center on substitutions which will favor species generically related to **6**. This proposition will now be pursued.

Acknowledgment. This work was supported by PHS Grant CA 28824. NMR spectra were obtained through the auspices of the Northeast Regional NSF/NMR Facility at Yale University, which was supported by NSF Chemistry Division Grant CHE 7916210. We also thank Dr. Terry Doyle of the Bristol Pharmaceutical Co. for supplying us with mitomycin C.

Supplementary Material Available: Experimental data for compounds **2a,b**, **3a,b**, **4**, **7**, **8a,c** and **10–12** (3 pages). Ordering information is given on any current masthead page.

(13) (a) Tomasz, M.; Lipman, R. *Biochemistry* **1986**, *25*, 4337. (b) Compounds **8a** and **8b** are briefly alluded to (stereochemistry not defined) by the following patent: Matsui, M.; Yamada, Y.; Uzu, K.; Hirata, T.; Wakaki, S. U.S. Patent 3 429 894, Feb. 25, 1969.

(14) Hornemann, U.; Iguchi, K.; Keller, P. J.; Huynh, M. V.; Kozlowski, J. F.; Kohn, H. *J. Org. Chem.* **1983**, *48*, 5026.

(15) Compounds **10**, **11**, and **12** were obtained in yields of 8%, 23%, and 33%, respectively. Twelve percent of the starting material (**7**) was recovered. Reaction of **7** and **9** for a similar time period resulted in a 15% yield of **10** and an 85% recovery of starting material.

(16) The similarities of "electron flow" inherent in the formation of xanthate adducts **10**, **11**, **12**, and of ene pyrrole **4** make tempting the possibility that semiquinone **6** is intervening in the formation of **4**.

Stereocontrolled Construction of Key Building Blocks for the Total Synthesis of Amphoteronolide B and Amphotericin B

K. C. Nicolaou,* R. A. Daines, J. Uenishi, W. S. Li, D. P. Papahatjis, and T. K. Chakraborty

Department of Chemistry, University of Pennsylvania Philadelphia, Pennsylvania 19104

Received October 6, 1986

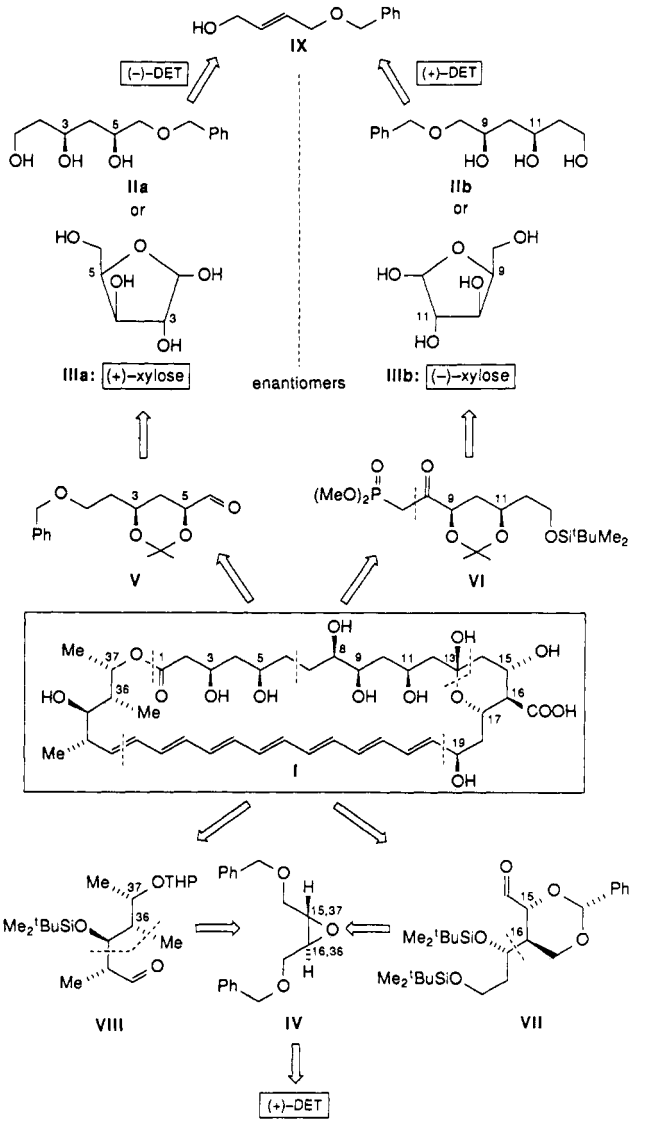
Amphotericin B[1] (I, Scheme I, with β-linked mycosamine at the C-19 hydroxyl), a clinically used antifungal agent isolated from *Streptomyces nodosus*, and its aglycon, amphoteronolide B[2] (I, Scheme I), are important synthetic targets of considerable current interest.[3] In this paper we describe stereocontrolled constructions

(1) Isolation: Vandeputte, J.; Watchtel, J. L.; Stiller, E. T. *Antibiot. Annu.* **1956**, 587. X-ray structural determination: 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.

(2) Preparation from amphotericin B: Nicolaou, K. C.; Chakraborty, T. K.; Daines, R. A.; Ogawa, Y. *J. Chem. Soc., Chem. Commun.*, in press.

0002-7863/87/1509-2205$01.50/0

Scheme I[a]

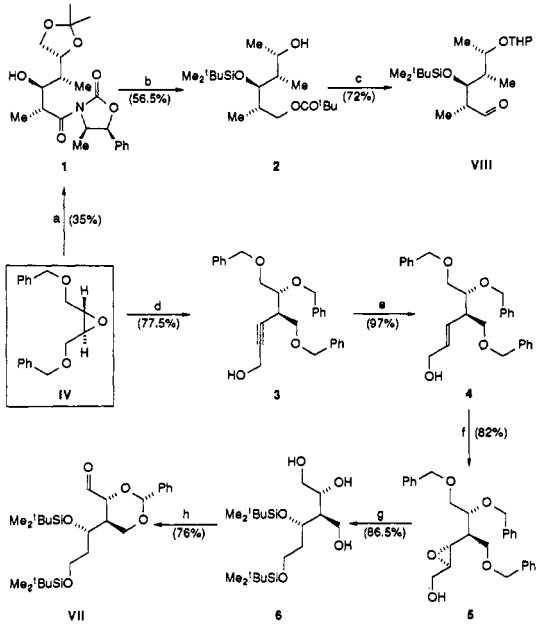


[a] Retrosynthetic analysis and key building blocks of amphoteronolide B (I).

of all requisite building blocks (V–VIII, Scheme I) for these polyene macrolide targets. The reported strategies were based on the recognition of important subtle symmetry elements in these complex molecules that simplified considerably the overall synthetic plan and made it possible to adopt the same or enantiomerically related materials as starting points for all four syntheses.

Scheme I presents the retrosynthetic analysis and strategic bond disconnections defining the key compounds V–VIII as the four requisite building blocks for an eventual total synthesis of amphoteronolide B and amphotericin B. This analysis uncovered certain stereochemical and symmetry elements allowing the design of a synthetic strategy that utilizes the readily available enantiomers of xylose and tartaric acid as starting materials and/or

Scheme II[a]



[a] Reagents and conditions. (a) See: ref 6, ca. 35% overall. (b) (i) 1.0 equiv of $LiBH_4$, THF, 0 °C, 0.5 h, then 1.1 equiv of *t*-BuCOCl, pyr, 3 h, 90% overall, (ii) 1.2 equiv of Me_2-*t*-BuSiOTf, 2.0 equiv of 2,6-lutidine, CH_2Cl_2, 0 °C, 1 h, 97%, then AcOH–THF–H_2O (3:1:1), 50 °C, 2 h, 72%, (iii) 1.2 equiv of PhSSPh, 1.2 equiv of *n*-Bu_3P, THF, 0–25 °C, 3 h then Raney Ni, EtOH, 12 h, 90% overall. (c) (i) 1.2 equiv of dihydropyran, CSA catalyst, CH_2Cl_2, 0–25 °C, 3 h, 96%, (ii) 2.5 equiv of DIBAL, CH_2Cl_2, −78 °C, 0.5 h, then 1.5 equiv of CrO_3·HCl·pyr, 1.5 equiv of NaOAc, CH_2Cl_2, 25 °C, 4 h, 75% overall. (d) (i) 2.5 equiv of $Et_2AlC{\equiv}CCH_2OSi$-*t*-$BuPh_2$, hexane–toluene (1:1), −78 → 0 °C, 0.5 h, 85%, (ii) 1.2 equiv of NaH, 1.2 equiv of $PhCH_2Br$, THF, 0–25 °C, 14 h, 91%, (iii) 1.5 equiv of *n*-Bu_4NF, THF, 0–25 °C, 95%. (e) 3.5 equiv of REDAL, Et_2O, 0–25 °C, 3 h, 97%. (f) 1.5 equiv of (−)-DET, 2.2 equiv of *t*-BuOOH, 1.2 equiv of $Ti(iPrO)_4$, CH_2Cl_2, −20 °C, 16 h, 82%. (g) (i) 4.0 equiv of REDAL, THF, 0 °C, 4 h, 97%, (ii) 2.6 equiv of *t*-$BuMe_2SiCl$, 3.0 equiv of imidazole, DMF, 0–25 °C, 12 h, 89%, (iii) H_2, 10% $Pd(OH)_2$–C, EtOH, 25 °C, 1 h, 95%. (h) (i) 1.2 equiv of $PhCH(OMe)_2$, CSA catalyst, benzene, 25 °C, 1 h, 80%, (ii) 6.0 equiv of SO_3·pyr, 10.0 equiv of Et_3N, 20 equiv of Me_2SO, CH_2Cl_2, 25 °C, 2 h, 95%.

chiral auxiliaries to secure optically active materials. Thus, following the indicated disconnections (dotted lines) in Scheme I the initially generated key intermediates V–VIII were further traced back to epoxide IV (VII and VIII), (+)-xylose (IIIa) and (−)-xylose (IIIb) (V and VI, respectively), or compounds IIa and IIb (V and VI, respectively). Enantiomerically pure epoxide IV is readily available from (+)-DET (diethyl tartrate), whereas (−)- and (+)-DET can be used as chiral inducers to build the requisite absolute stereochemistry in intermediates IIa and IIb, respectively, from the prochiral starting material IX via a Sharpless asymmetric epoxidation.[4] The numbering in Scheme I traces the origin of selected carbon centers of amphoteronolide B, clarifying the choice of starting materials.

Scheme II outlines the construction of building blocks VIII and VII from epoxide IV.[5] Thus, IV was expeditiously converted to intermediate **1** by the Evans aldol methodology[6] (35% overall

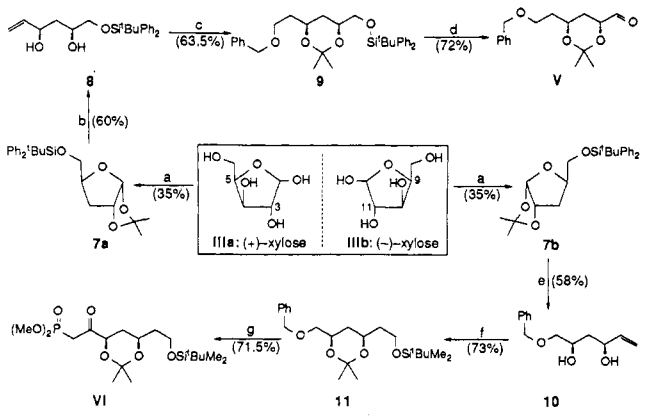
(3) Synthetic studies: (a) McGarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matsubara, Y.; Taeboem, O. *J. Am. Chem. Soc.* **1986**, *108*, 4943. (b) Boscheli, D.; Takemasa, T.; Nishitani, Y.; Masamune, S. *Tetrahedron Lett.* **1985**, 5239. (c) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfield, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, 2183. (d) Masamune, S.; Ma, P.; Okumoto, H.; Ellingboe, J. W. *J. Org. Chem.* **1984**, *49*, 2843. (e) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378. (f) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521. (g) Liang, D.; Pauls, H. W.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1984**, 1123. (h) Lipshutz, B. H.; Koslowski, J. A. *J. Org. Chem.* **1984**, *49*, 1147. (i) Hirama, M.; Vie, M. *Tetrahedron Lett.* **1982**, 5307. (j) Brooks, D. W.; Kellogg, R. P. *Tetrahedron Lett.* **1982**, 4991. (k) Floyd, D. M.; Fritz, A. W. *Tetrahedron Lett.* **1981**, 2847. Hanessian, S.; Sahoo, S. P.; Murray, P. J. *Tetrahedron Lett.* **1985**, *26*, 5631.

(4) For excellent recent reviews of this reaction see: Rossiter, B. E. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1985; Vol. 5, p 193. Finn, M. G.; Sharpless, K. B. *Ibid.*; p 247.

(5) Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Magolda, R. L.; Dolle, R. E. *J. Org. Chem.* **1985**, *50*, 1440.

(6) This conversion, which features a stereoselective Evans aldol condensation (for an excellent review of this reaction, see: Evans, D. A.; Nelson, J. V.; Taber, T. R. In *Topics in Stereochemistry*; Allinger, N. L, Eliel, E. L., Wilen, S. H., Eds.; 1982; Vol. 13, p 1) was first reported at the 1st Cyprus Conference on New Methods in Drug Research, Cyprus, 1983; see: Nicolaou, K. C.; Petasis, N. A.; Dolle, R. E.; Li, W. S.; Papahatjis, D. P.; Uenishi, J.; Zipkin, R. E. In *New Methods in Drug Research*; Makriyannis, A., Ed.; Prous Science: Barcelona, Spain, 1985; p 179.

Scheme III[a]

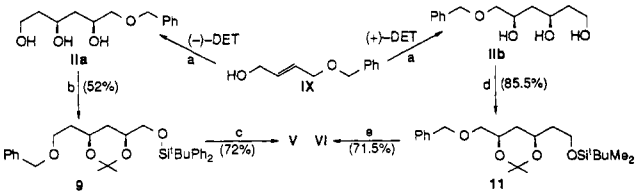


[a] Reagents and conditions. (a) (i) Me_2CO, concentrated H_2SO_4 catalyst, 25 °C, 6 h, then dilute H_2SO_4 catalyst MeOH, 25 °C, 2 h, 50% overall, (ii) 1.1 equiv of t-$BuPh_2SiCl$, 4.0 equiv of imidazole, DMF, 0–25 °C, 2 h, 96%, (iii) 1.5 equiv of PhOC(S)Cl, 2.5 equiv of pyr, DMAP catalyst, CH_2Cl_2, 0–25 °C, 15 h, 94% then 1.1 equiv of n-Bu_3SnH, AIBN catalyst, toluene, 80 °C, 1 h, 77%. (b) (i) 1.0 equiv of BCl_3, CH_2Cl_2–hexane (1:2), −78 °C, 10 min, 90%, (ii) 1.0 equiv of NaH then 3.2 equiv of $Ph_3P{=}CH_2$ (from $CH_3PPh_3^+Br^-$ and n-BuLi in THF), THF, −30 → 25 °C, 4 h, 67%. (c) (i) $Me_2C(OMe)_2$, CSA catalyst, 25 °C, 1 h, 90%, (ii) 2.1 equiv of Sia_2BH, THF, 0 °C, 1.5 h then NaOH–H_2O_2 workup, 88%, (iii) 1.2 equiv of KH, 1.2 equiv of $PhCH_2Br$, THF, 0–25 °C, 14 h, 85%. (d) (i) 1.2 equiv of n-Bu_4NF, THF, 0–25 °C, 4 h, 96%, (ii) 6.0 equiv of SO_3·pyr, 10.0 equiv of Et_3N, 20.0 equiv of Me_2SO, CH_2Cl_2, 25 °C, 3 h, 75%. (e) (i) same as (d) (i) above, (ii) 1.1 equiv of NaH, 1.1 equiv of $PhCH_2Br$, THF, 0–25 °C, 2 h, 95%, (iii) dil HCl, DME–H_2O (2:1), reflux, 1 h, 95%, then same as b part ii, above. (f) same as c parts i and ii, above, then 1.1 equiv of t-$BuMe_2SiCl$, 4.0 equiv of imidazole, DMF, 0–25 °C, 1 h, 92%. (g) (i) H_2, 10% Pd–C, EtOH, 25 °C, 98%, (ii) 5.0 equiv of $NaIO_4$, RuO_4 catalyst, CH_3CN–CCl_4–H_2O (2:2:3), 25 °C, 6 h, then CH_2N_2, 76% overall, (iii) 2.2 equiv of $(MeO)_2P(O)CH_2Li$, THF, −78 to 0 °C, 1 h, 96%.

yield), which was reduced ($LiBH_4$) to the corresponding primary alcohol, protected as a pivalate ester, silylated at the free secondary hydroxyl, deacetonated, and deoxygenated at the liberated primary position to afford compound **2** (56.5% overall yield). Protection of the hydroxyl group in **2** as a THP ether followed by DIBAL cleavage of the pivalate ester and PCC oxidation led to the desired key intermediate VIII (72% overall) in optically active form. The synthesis of VII began with attack on epoxide IV by [[(*tert*-butyldiphenylsilyl)oxy]propargyl]diethylalane ($Et_2AlC{\equiv}CCH_2OSi$-t-$BuPh_2$),[7] affording, after benzylation and desilylation, hydroxy acetylene **3** in 77.5% overall yield. REDAL reduction of **3** gave allylic alcohol **4** (97%), which underwent smooth Sharpless asymmetric epoxidation [(−)-DET] furnishing hydroxy epoxide **5** (82%). Regioselective epoxide opening of **5** (REDAL)[8] followed by silylation and debenzylation then gave **6** (86.5% overall), which was selectively protected as a six-membered benzylidene[9] and oxidized with SO_3·pyr complex to afford fragment VII (76% overall yield), optically pure and suitably protected for further elaboration.

Scheme III presents the construction of the remaining building blocks V and VI in enantiomerically pure form starting with the two enantiomers of xylose. Thus, (+)-xylose (IIIa) was converted to its 1,2-monoacetonide, selectively silylated at the primary position, and deoxygenated by the Robins and Wilson method[10]

Scheme IV[a]



[a] Reagents and conditions. (a) See: ref 13. (b) (i) 1.1 equiv of t-BuCOCl, pyr, 0 °C, 6 h, 88%, (ii) $Me_2C(OMe)_2$, CSA catalyst, 25 °C, 1 h, 93%, (iii) H_2, 10% Pd–C, EtOH, 12 h, 94%, (iv) 1.1 equiv of t-$BuPh_2$ SiCl, 4.0 equiv of imidazole, DMF, 0–25 °C, 2 h, 88%, (v) 2.5 equiv of DIBAL, CH_2Cl_2, −78 °C, 0.5 h, 91%, (vi) 1.1 equiv of NaH, 1.1 equiv of $PhCH_2Br$, THF, 0–25 °C, 3 h, 85%. (c) As in Scheme III. (d) (i) 1.1 equiv of t-$BuMe_2SiCl$, 4.0 equiv of imidazole, DMF, 0–25 °C, 2 h, 90%, (ii) as in b part ii, above, 95%. (e) As in Scheme III.

to afford derivative **7a** (35% overall yield). Removal of the acetonide group from **7a** required the use of BCl_3[11] and led, after Wittig methylenation, to diol **8** (60% overall). Acetonide formation followed by hydroboration and benzylation of the resulting primary alcohol gave compound **9** (63.5% overall), which was then desilylated and oxidized to afford the targeted aldehyde V (72% overall yield). The route to building block VI started from (−)-xylose (IIIb) and proceeded through derivative **7b**, obtained as described above for its enantiomer (**7a**). The silyl protecting group in **7b** was then exchanged with a benzyl group, the acetonide was removed (aqueous HCl), and the resulting lactol was converted to olefin **10** by a Wittig reaction (58% overall). Engagement of the 1,3-diol system of **10** as an acetonide, followed by hydroboration and silylation, led to compound **11** in 73% overall yield. Finally, debenzylation, oxidation of the liberated hydroxyl group to the carboxylic acid (RuO_4 catalyst–$NaIO_4$),[12] methyl ester formation, and nucleophilic attack by $LiCH_2P(O)(OMe)_2$ furnished the desired keto phosphonate VI in 71.5% overall yield.

Alternative syntheses of fragments V and VI starting with the prochiral allylic alcohol IX are summarized in Scheme IV. As mentioned above, (−)- and (+)-DET were utilized in conjunction with the Sharpless asymmetric epoxidation reaction[4] to induce the desired asymmetry. Thus, according to our previously reported general method for building 1, 3, 5, ..., $(2n + 1)$ polyols,[13] IX was converted to the enantiomeric triols IIa and IIb. Protecting group manipulation of IIa as detailed in Scheme IV then led to intermediate **9** (52% overall yield), which was converted to V as already described above. In parallel, IIb was transformed to the protected derivative **11** by selective silylation and acetonide formation (85.5% overall yield) and thence to VI as described above.

In conclusion, focusing on subtle and repeated structural units, the described retrosynthetic analysis allows the utilization of readily available enantiomeric structures as starting points for an eventual total synthesis of both amphoteronolide B and amphotericin B. Thus, four major building blocks (V–VIII) have been synthesized in optically active forms and by highly efficient and concise sequences using (+)- and (−)-xylose and (+)- and (−)-DET as sources of chirality. The stage is now set for a highly convergent total synthesis of both amphoteronolide B and amphotericin B. The following paper describes the accomplishment of the former goal.[14,15]

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

(7) This reagent was prepared from the corresponding acetylene (hexane, −78 °C) by sequential addition of 1.0 equiv of n-BuLi (1.55 M in hexane) and 1.0 equiv of Et_2AlCl (1.8 M in toluene), see: Suzuki, T.; Saimoto, H. I.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597.

(8) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1169. Kishi, Y.; Finan, J. M. *Tetrahedron Lett.* **1982**, *23*, 2719.

(9) For previous selective six-membered ring benzylidene formations, see: (a) Sinclair, H. B. *Carbohydr. Res.* **1969**, *12*, 150. (b) Ziegler, F. E.; Gilligan, P. J. *Tetrahedron Lett.* **1979**, 3371. (c) Schubert, T.; Welzel, P. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 137.

(10) Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932.

(11) Tewson, T. J.; Welch, M. J. *J. Org. Chem.* **1978**, *43*, 1090.

(12) Carlsen, H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3938.

(13) Nicolaou, K. C.; Uenishi, J. *J. Chem. Soc., Chem. Commun.* **1982**, 1292.

(14) Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K., following paper in this issue.

(15) All new compounds exhibited satisfactory spectral and analytical/exact mass spectral data. Yields refer to spectroscopically and chromatographically homogenous materials.

Dohme, and Hoffmann-La Roche.

Registry No. 1, 106799-08-0; **2**, 101417-56-5; **3**, 106799-09-1; **4**, 106820-43-3; **5**, 106799-10-4; **6**, 106799-11-5; **7a**, 106799-13-7; **7b**, 106799-16-0; **8**, 106862-35-5; **9**, 106799-14-8; **10**, 106799-17-1; **11**, 106799-18-2; IIa, 81120-67-4; IIb, 106862-36-6; IIIa, 58-86-6; IIIb, 609-06-3; IV, 81177-24-4; V, 106799-15-9; VI, 106799-19-3; VII, 106799-12-6; VIII, 105172-28-9; IX, 69152-88-1; $Et_2AlC{\equiv}CCH_2OSi$-t-$BuPh_2$, 106799-20-6; $CH_3PPh_3^+Br^-$, 1779-49-3; $(MeO)_2P(O)CH_2Li$, 34939-91-8; amphoteronolide B, 106799-07-9; amphotericin B, 1397-89-3.

Supplementary Material Available: List of R_f, $[\alpha]_D$, IR, and ^1H NMR data for compounds V-VIII (2 pages). Ordering information is given on any current masthead page.

Total Synthesis of Amphoteronolide B

K. C. Nicolaou,* R. A. Daines, and T. K. Chakraborty

Department of Chemistry, University of Pennsylvania Philadelphia, Pennsylvania 19104

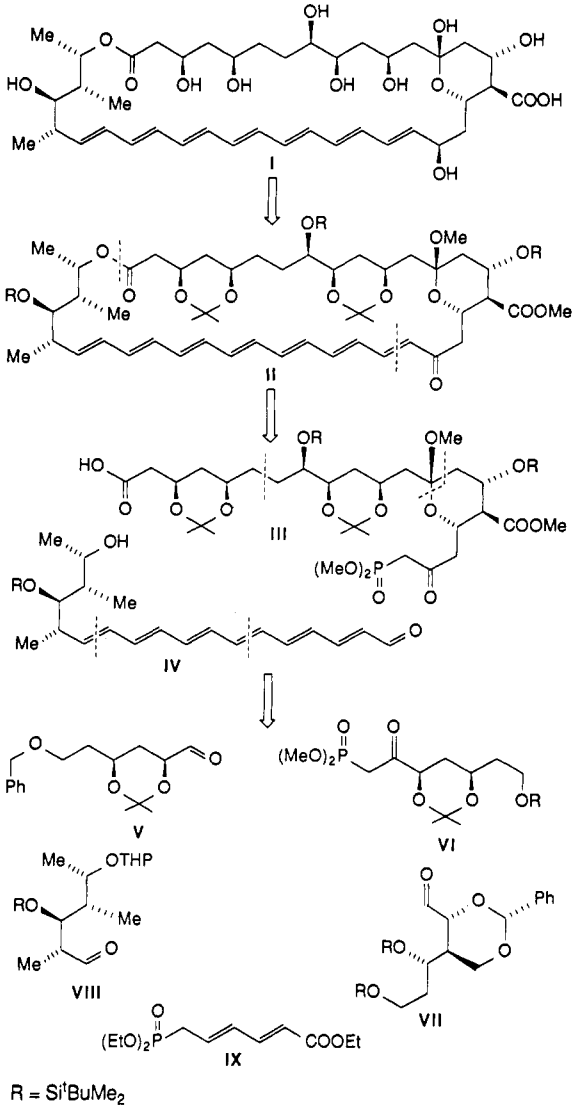
Received October 6, 1986

Amphoteronolide B (I, Scheme I), the aglycon of amphotericin B, has recently been obtained from naturally derived amphotericin B and fully characterized by spectroscopic means.[1] We now report the first total synthesis of this important and long sought target in its optically active form from readily available starting materials and in a highly stereocontrolled manner.[2]

Scheme I outlines a retrosynthetic analysis of the titled molecule. Thus, it was envisioned that amphoteronolide B (I) could be derived from the protected heptaenone II by stereoselective carbonyl reduction and deprotection. This maneuver then allowed disconnection of this precursor at the lactone and unsaturated sites as indicated in structure II. The chosen strategic bond disconnections leading to advanced intermediates III and IV pointed to a highly convergent synthesis and also to two powerful coupling reactions, an esterification and a keto phosphonate-aldehyde condensation, in the synthetic plan to construct II. Finally, subtargets keto phosphonate carboxylic acid III and hydroxy aldehyde IV were retrosynthetically disassembled as indicated in Scheme I, revealing building blocks V-IX as potential starting points for the total synthesis.

The construction of building blocks V-VIII is reported in the preceeding paper.[3] Their coupling and elaboration to amphoteronolide B is detailed in Scheme II. Thus, coupling of aldehyde V and keto phosphonate VI under basic conditions led to the expected conjugated enone in 94% yield, which was cleanly hydrogenated to the saturated ketone **1** (98%). Molecular models of this ketone suggested that reduction should occur from the opposite side of the adjacent acetonide, particularly by a sterically demanding reagent attacking a frozen conformation of **1**. Indeed, L-selectride at −120 °C produced the single diastereoisomer **2** in 98% yield.[4] The stereochemical outcome of this reduction was

Scheme I[a]



[a] Retrosynthetic analysis of amphoteronolide B (I).

confirmed by X-ray crystallographic analysis (see the ORTEP drawing in Scheme II) of the crystalline *p*-chlorobenzenesulfonate **3** prepared from **2** as outlined in Scheme II. Compound **2** was then functionalized appropriately so as to allow its coupling to the third building block VII as follows. Protection of the secondary hydroxyl of **2** with the more stable t-$BuPh_2Si$ group[5] (91%) followed by selective removal of the t-$BuMe_2Si$ group (84%) from the primary hydroxyl led to compound **5** via **4**. Intermediate **5** was then sequentially converted to iodide **6** (97%) via its mesylate and then to dimethyl phosphonate **7** by displacement with sodium dimethylphosphite.[6] Sulfenation of the anion of **7** then led to a diastereomeric mixture of the α-methylthio phosphonate **8** (73%; ca. 1:1 by ^1H NMR). Condensation of the anion of **8** with aldehyde VII proceeded smoothly, leading to coupling product **9** (84%; mixture of geometrical isomers, ca. 1:1 by ^1H NMR). Desilylation of **9** to the triol **10** (96%) followed by an acid-induced cyclization led to mixed cyclic ketal **11** (64%; ca. 1:1 mixture of anomers by ^1H NMR), which was converted to the methoxy compound **12** by exposure to NBS-MeOH (95%; ca. 1:1 mixture

(1) Nicolaou, K. C.; Chakraborty, T. K.; Daines, R. A.; Ogawa, Y. *J. Chem. Soc., Chem. Commun.*, in press.

(2) For synthetic studies in this area by other groups, see: (a) McGarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matsubara, Y.; Taeboem, O. *J. Am. Chem. Soc.* **1986**, *108*, 4943. (b) Boscheli, D.; Takemasa, T.; Nishitani, Y.; Masamune, S. *Tetrahedron Lett.* **1985**, 5239. (c) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfield, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, 2183. (d) Masamune, S.; Ma, P.; Okumoto, H.; Ellingboe, J. W. *J. Org. Chem.* **1984**, *49*, 2843. (e) Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Viti, S. M. *J. Org. Chem.* **1982**, *47*, 1378. (f) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521. (g) Liang, D.; Pauls, H. W.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1984**, 1123. (h) Lipshutz, B. H.; Koslowski, J. A. *J. Org. Chem.* **1984**, *49*, 1147. (i) Hirama, M.; Vie, M. *Tetrahedron Lett.* **1982**, 5307. (j) Brooks, D. W.; Kellogg, R. P. *Tetrahedron Lett.* **1982**, 4991. (k) Floyd, D. M.; Fritz, A. W. *Tetrahedron Lett.* **1981**, 2847.

(3) Nicolaou, K. C.; Daines, R. A.; Uenishi, J.; Li, W.-S.; Papahatjis, D. P.; Chakraborty, T. K., preceeding paper in this issue.

(4) At least 98% pure, as checked by ^1H NMR spectroscopy (250 MHz). A variety of other reduction conditions gave mixtures of **2** and its epimer (e.g., L-selectride, THF, −78 °C, ca. 5:1 ratio; L-selectride, Et_2O, −78 °C, ca. 1.3:1 ratio; $Zn(BH_4)_2$, Et_2O, 0 or −78 °C, ca. 1:1 ratio; DIBAL, CH_2Cl_2, −78 °C, ca. 2.7:1 ratio; t-$BuNH_2{\cdot}BH_3$, THF, −40 °C, ca. 1.2:1 ratio).

(5) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.

(6) Sturtz, G. *Bull. Chim. Fr.* **1964**, 2340.

0002-7863/87/1509-2208$01.50/0