# Synthesis of Amphotericin B. A Convergent Strategy to the Polyol Segment of the Heptaene Macrolide Antibiotics

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Amphotericin B (**1**) and nystatin A$_1$ (**2**) are prominent representatives of the clinically important heptaene/pseudoheptaene subfamily of the polyene macrolide antibiotics.[1] For more than 30 years, amphotericin B has been the preeminent drug for the treatment of serious systemic fungal infections.[2] The potent activity of these compounds has been attributed to sterol-dependent ion channel formation in membranes, favoring the ergosterol-rich membranes of fungal cells.[3] Unfortunately, the therapeutic value of these agents is attenuated by their accompanying mammalian toxicity, and efforts to gain an understanding of this biological mechanism have been hampered by the structural complexity of this family of compounds. This has spurred synthetic studies on the polyene macrolides,[4] several of which have concluded in successful total syntheses.[5,6] We report herein on the development of a concise synthetic strategy for amphotericin B that offers promising generality for the preparation of structurally related heptaene and pseudoheptaene macrolides.

Amphotericin B (**1**)

Nystatin A$_1$ (**2**)
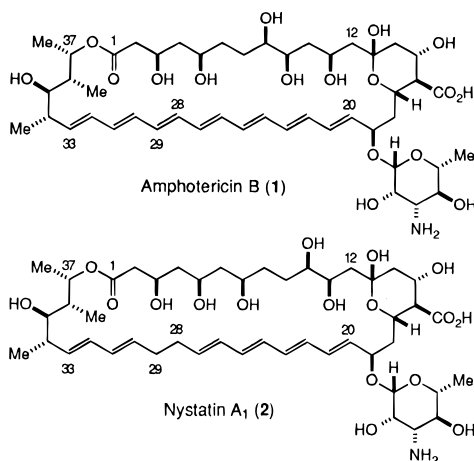
It had been demonstrated that amphotericin B (**1**) may be realized from the protected aglycon **3**,[5a] which, in turn, can be assembled through the fusion of the polyene and polyol fragments **4** and **5**, respectively (Scheme 1). Having efficient access already available to the C21−C37

fragment (**4**),[7] the problem becomes focused on the preparation of the polyol segment **5**. With the demonstration by Nicolaou that phosphonate **5** could be obtained in a single step from the C19 methyl ester,[5a] our synthetic objective is reduced to fragment **6**. We anticipated convergent assemble of this fragment through a stereoselective nitrile oxide cycloaddition of oxime **7** with dipolarophile **8**.[8] This approach conferred several benefits, including the following: segregation of the conserved (C14−C19) and variable (C1−C13) regions in the heptaene/pseudoheptaene macrolides, simultaneous establishment of the C13−C14 bond and the C15 stereocenter, and straightforward differentiation of C1 and C19 for later adjustments leading to **6**. Furthermore, the cycloaddition reaction would lead to the direct placement of the final oxidation state of the C16 side chain and would offer reaction conditions compatible with an unprotected alcohol at C17 to allow subsequent hemiketal formation at C13.

The approach adopted to the C1−C13 fragment **7** took advantage of its inherent symmetry by employing protected epoxy alcohol **9** for both the C2−C7 and C8−C13 segments.[7b] An expedient route to this key intermediate was available from L-malic acid as described in Scheme 2. The previously reported hydroxy acetonide **10**[9] was converted to the monoprotected triol **11** for subsequent dehydration via the secondary mesylate to epoxide **9** (68% yield from **10**). The elaboration of this intermediate to the C1−C13 fragment **12** followed the convergent sequence previously reported.[7b] The nitrile oxide precursor in the form of oxime **7** was realized by routine methods in excellent overall yield (92%). The dipolarophile **8** was prepared in a single step through an Evans asymmetric aldol condensation of the boron enolate derived from the crotyl imidate **13**[10] and the readily available β-(aryloxy)

(6) For syntheses of nonheptaene macrolide antibiotics see the following. Mycoticin A: (a) Poss, C. S.; Rychnovsky, S. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 3360−3361. (+)-Roxaticin (natural): (b) Mori, Y.; Asai, M.; Okumura, A.; Furukawa, H. *Tetrahedron* **1995**, *51*, 5299−5314. (c) Mori, Y.; Asai. M.; Kawade, J.-i.; Furukawa, H. *Tetrahedron* **1995**, *51*, 5315−5330. (−)-Roxaticin (unnatural): (d) Rychnovsky, S. D.; Hoye, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 1753−1765. Pimarolide: (e) Duplantier, A. J.; Masamune, S. *J. Am. Chem. Soc.* **1990**, *112*, 7079−7081.

(7) For previous studies in these laboratories: (a) McGarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matsubara, Y.; Oh, T. *J. Am. Chem. Soc.* **1986**, *108*, 4943−4952. (b) McGarvey, G. J.; Mathys, J. A.; Wilson, K. J.; Overly, K. R.; Buonora, P. T.; Spoors, P. G. *J. Org. Chem.* **1995**, *60*, 7778−7790.

(8) For a recent review: Easton, C. J.; Hughes, C. M. M.; Savage, G. P.; Simpson, G. W. *Adv. Heterocycl. Chem.* **1994**, *60*, 261−327.

(9) Merifield, E.; Steele, P. G.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1826−1828.

(10) Evans, D. A.; Sjogren, E. B.; Bartroli, J.; Dow, R. L. *Tetrahedron Lett.* **1986**, *27*, 4957−4960.

(11) This was conveniently prepared in multigram quantities from 1,3-propanediol through the following sequence: (a) *p*-anisaldehyde, PhH (− H$_2$O), 100%; (b) DIBAL, CH$_2$Cl$_2$, 84%; (c) PCC, CH$_2$Cl$_2$, 53%.

(12) Moriya, O.; Tanenaka, H.; Iyoda, M.; Urata, Y.; Endo, T. *J. Chem. Soc., Perkin Trans. 1* **1994**, 413−417.

(13) The relative rates of these two methods of nitrile oxide formation were qualitatively assessed by monitoring the rates of disappearance of the hydroximoyl chloride and tributylstannyl oxime by thin layer chromatography (SiO$_2$, 1:1, Et$_2$O:petroleum ether). The hydroximoyl chloride was consumed in approximately 1 h upon treatment with Et$_3$N, whereas the tributylstannyl oxime persisted after 4−6 h when treated with ^{t}BuOCl.

(14) The furoxan product resulting from the dimerization of the nitrile oxide could be isolated and identified by ^{1}H NMR.

(15) Baraldi, P.; Barco, A.; Benetti, S.; Manfredini, S.; Simoni, D. *Synthesis* **1987**, 276−278.

(16) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 1475−1478.

(17) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156−4156.

(18) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091−2096.

(1) Omura, S.; Tanaka, H. In *Macrolide Antibiotics: Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic Press: New York, 1984; pp 351−404. We refer to those structures that differ from a heptaene macrolide antibiotic (e.g., **1**) by saturation at C28−C29 as pseudoheptaene macrolide antibiotics (e.g., **2**).

(2) Gallis, H. A.; Drew, R. H.; Pickard, W. W. *Rev. Infect. Dis.* **1990**, *12*, 308−329.

(3) Brajtburg, J.; Powderly, W. G.; Kobayashi, G. S.; Medoff, G. *Antimicrob. Agents Chemother.* **1990**, *34*, 183−188.

(4) For a review: Beau, J.-M. In *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer-Verlag: Berlin, 1990; pp 135−182.

(5) Total synthesis of amphotericin B: (a) Nicolaou, K. C.; Ogilvie, W. W. *Chemtracts-Org. Chem.* **1990**, *3*, 327−349. 19-Dehydroamphoteronolide B: (b) Kennedy, R. M.; Abiko, A.; Takenasa, T.; Okumoto, H.; Masamune, S. *Tetrahedron Lett.* **1988**, *29*, 451−454.

Scheme 1

Scheme 2[a]

[a] Reagents: (a) TBDPSCl, imidazole, DMF, DMAP, 45 °C, 97%; (b) PPTs, MeOH, 93%; (c) ᵗBuCOCl, pyridine, 85%; (d) MeSO₂Cl, pyridine, 24 h; then K₂CO₃ (5 equiv), MeOH, 88%; (e) OsO₄, NMO, ᵗBuOH/H₂O; NaIO₄, EtOH (aq); (f) NH₂OH·HCl, Na₂CO₃, Et₂O: H₂O, 92% from **12**.

aldehyde **14**[11] (eq 1, 71% yield, 94% ds). It was antici-

pated that the chiral auxiliary (X_N) would not only guide the stereochemical course of this aldol reaction, but also act as an acyl protecting group for later conversion to the C16 methyl ester.

With fragments **7** and **8** in hand, the stage was set for the crucial nitrile oxide cycloaddition. The generation of the nitrile oxide through halogenation of oxime to the corresponding hydroximoyl chloride (NCS or ᵗBuOCl) followed by dehydrohalogenation (Et₃N)[8] gave the cycloadduct in only modest yields (<30%). However, formation of the nitrile oxide through halogenation (ᵗBuOCl) of the derived O-stannylated oxime[12] led to the desired product **15** in a gratifying 88% yield and 7.6:1

selectivity favoring the desired C15 stereochemistry (Scheme 3). This significant improvement in yield has been attributed to a slower rate of nitrile oxide formation via the stannyl oxime as compared to the dehydrohalogenation of the hydroximoyl chloride.[13] As a consequence, the nitrile oxide is maintained at a low concentration, suppressing the formation of the undesirable nitrile oxide dimer.[14] The desired hydroxy ketone was revealed through Mo(CO)₆-mediated cleavage of the isoxazoline[15] to directly afford hemiketal (**16**, R = H), which was methylated to afford the desired mixed ketal **16** (R = Me) in excellent overall yield (73% from **15**). The completion of the synthesis of **4** is realized through routine protection of the exposed C15 alcohol, methylation of the C16 side chain, and sequential manipulation of C19 and C1. Compound **4** intersects with the Nicolaou route as previously described and thus completes the formal synthesis of amphotericin B.

The strategy described in this study has potential broad application to the synthesis of the biomedically important heptaene/pseudoheptaene macrolide antibiotics. It is very efficient, affording the polyol fragment **4** in 11% overall yield in only 11 steps from **7**, and allows the convergent fusion of the region that is highly conserved in this subgroup of compounds (C14−C19) with the structurally variable segments (C1−C13). Further application of this concise synthetic approach to the polyene macrolide antibiotics will be reported in due course.

Supporting Information Available: Experimental procedures, characterization data, and selected 500 MHz NMR spectra (18 pages).

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Scheme 3[a]

[a] Reagents: (a) (ⁿBu₃Sn)₂O, CH₂Cl₂, room temperature → −46 °C; then sequentially add olefin **8** and ᵗBuOCl, −46 °C → room temperature, 8 h, 88% (7.6:1 ds); (b) Mo(CO)₆, CH₃CN:H₂O, 70 °C, 81%; (c) MeC(OMe)₃, PPTs, MeOH, room temperature, 90%; (d) TBSOTf, Et₃N, CH₂Cl₂, 99%; (e) DDQ, CH₂Cl₂, 98%; (f) LiOH, dioxane, H₂O; then Me₃SiCH₂N₂,[16] MeOH/PhH, 65%; (g) PDC, DMF, then Me₃SiCH₂N₂,[16] MeOH/PhH, 45%; (h) H₂, Pd(OH)₂, MeOH; (i) Dess−Martin periodinane,[17] CH₂Cl₂; then NaClO₂, Na₂HPO₄, 2-methyl-2-butene, ᵗBuOH,[18] 63% from the benzyl ether.