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SYNTHESIS OF AMPHOTERICIN B. 2. FRAGMENT C-D OF THE AGLYCONE

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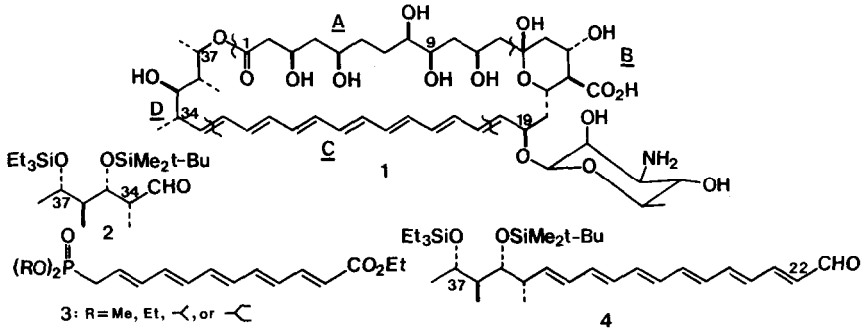
Summary: Fragment C-D, the C(21)-C(37) unit of the aglycone of amphotericin B, has been synthesized.

Amphotericin B (1), a 38-membered polyenemacrolide antibiotic,[1] has been one of our synthetic target molecules. This molecule is retrosynthetically dissected into four fragments A, B, C, and D as indicated, and fragments A and B have already been prepared.[2,3,4] This Note describes syntheses of the remaining fragments D [C(33)-C(37) unit, (2)] and C [C(21)-C(32) unit, (3)] and assembly of the two fragments to provide fragment C-D [C(21)-C(37), (4)] which is suitably functionalized for further transformations.



Synthesis of 2 (Scheme 1). With many chiral reagents[5] and an enriched chiral pool[6] now available, several routes leading to 2 are readily conceivable and have been examined. Of these routes the following has been shown to be the most efficient for preparing multi-gram quantities of 2.

The known alcohol 5[7] was subjected to a series of standard reactions, 1) silylation, 2) debenzylation, and 3) Collins' oxidation, to provide the corresponding primary aldehyde which was in turn converted to the pure Z-olefin 6 with the anion derived from bis(2,2,2,-trifluoroethyl)(methoxycarbonylmethyl)phosphonate [KN(TMS)2 and 18-crown-6 ether][8] (overall yield, ca. 70%). Reduction with diisobutylaluminum hydride (Dibal) followed by treatment with meta-chloroperbenzoic acid provided a 3.5:1

mixture of two readily separable epoxides, the major one (70% yield) being the predicted α-isomer.[9] Regiospecific epoxide opening of the α-isomer with dimethyl cuprate led to the formation of the 1,3-diol 7 with all chiral centers embedded in 2 established (88% yield).[10]

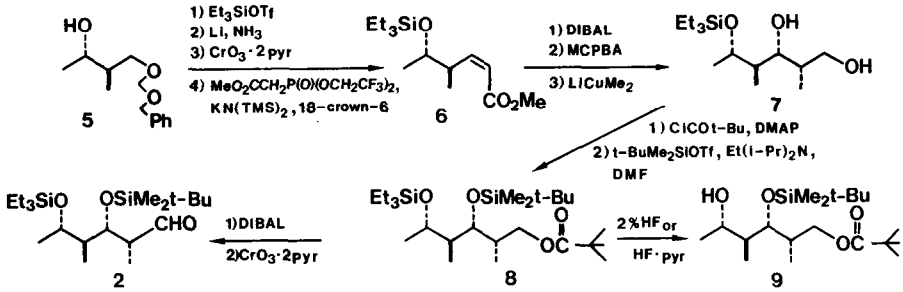
Esterification of the primary alcohol of 7 with pivaloyl chloride followed by silylation with t-butyldimethylsilyl triflate and diisopropylethylamine in N,N-dimethylformamide[11] yielded disilyl ether 8, and subsequent removal of the pivaloyl group of 8 with Dibal followed by Collin's oxidation of the resulting alcohol provided 2. Selective removal of the triethylsilyl group of 8 proceeded smoothly with either 2% HF in acetonitrile or pyridinium hydrogen fluoride in THF. We will require this preferential deprotection later in our amphotericin synthesis.

Synthesis of 3 (Scheme 2). The synthesis began with the known conversion of cyclooctatetraene to the trienedialdehyde 10.[12] Horner-Emmons reaction of 10 with triethyl phosphonoacetate in THF provided the (trans)^5-pentaene diester 11, which showed 1) J=15.2 Hz of the vinyl protons α,β to the carboxyl groups and 2) two-fold symmetry in its ^{13}C NMR spectrum. Partial hydrolysis (ca. 80% yield on recycling recovered 11) and reduction of the resulting half-ester [1) EtOCOCl and 2) $NaBH_4$] afforded the allylic alcohol 12 (77% yield). Reaction of 12 in THF with thionyl bromide (1.3 equiv) in the presence of lutidine or 2,6-di-t-butylpyridine at -20°C for 25 min[13] led to the formation of the corresponding highly labile bromide which without purification was converted to the phosphonates 3a-3d (60-70% yield).

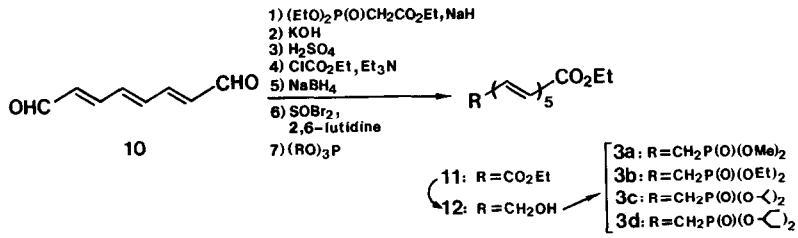
Assembly of 2 and 3 (Scheme 3). The selection of proper conditions for the Horner-Emmons reaction of 2 with 3 turned out to be extremely critical. Thus, while anion generation from 3a or 3b with lithium diisopropylamide in THF followed by the addition of isobutyraldehyde provided preferentially the corresponding (trans)^6-hexaene, the aldehyde 2, under identical conditions with 3a and 3b, led to the formation of both the (trans)^6- (13) and cis,(trans)^5- (13a) isomers, the ratios being 1:1.2 and 1.75:1, respectively.[14] With the aid of the "bulkier" phosphonates 3c[15] and 3d the exclusive formation of the (trans)^6-isomer 13 was realized, but in a yield of only 20%. After exhaustive efforts, it was found that the use of lithium tetramethylpiperidide in THF (ca. 0.3 M) at -30° ~ -35°C for 1 h did raise the yield to an acceptable 68% with retention of the stereoselectivity.

The alcohol resulting from Dibal reduction of 13 was very labile to acid and air and had to be immediately dehydrogenated with DDQ to the corresponding aldehyde 4[14] (65% yield). While this aldehyde, even in crystalline form, deteriorated upon long exposure to air, it underwent a smooth Horner-Emmons reaction with a model β-ketophosphonate under the conditions specified earlier[16] to provide the (trans)^7-heptaene 14, thus ensuring the planned coupling of 4 with fragment A-B.[17]

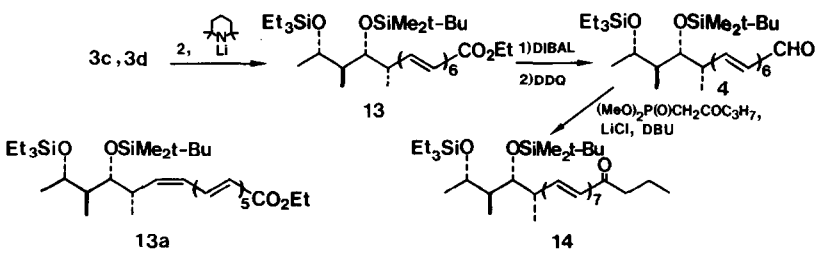
Scheme 1



Scheme 2



Scheme 3



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9. Proof of the major epoxide as α was obtained as follows: The E-allylic alcohol corresponding to the Dibal reduction product of 6 was subjected to Sharpless' asymmetric oxidation and Redal reduction of the resulting epoxide provided a diol (with the established stereochemistry) which was compared with that obtained through Redal reduction of the α-epoxide. See: (a) Ma, P.; Martin, V.S.; Masamune, S.; Sharpless, K.B.; Viti, S.M. J. Org. Chem. 1982, 47, 1378. (b) Katsuki, T.; Lee, A.W.M.; Ma, P.; Martin, V.S.; Masamune, S.; Sharpless, K.B.; Tuddenham, D.; Walker, F.J. Ibid. 1982, 47, 1373.
10. This regiochemistry was verified by decoupling experiments on the ^{1}H NMR spectra of the primary and secondary acetate derivatives of 7.
11. Under more common silylation condition, i.e., 1) TBDMSCl, imidazole or 2) TBDMS(OTf), Hunig's base in CH_2Cl_2, the migration of the triethylsilyl group of 7 occurred.
12. Anet, R. Tetrahedron Lett. 1961, 720. The second step of this two-step conversion is lithium aluminum hydride reduction of diacetoxybicyclo[4.2.0]-octadiene. A solution of the direct reduction product in an organic solvent, e.g., ethyl acetate, must be stirred in air to maximize the yield of 10.
13. These conditions must be strictly followed, or virtually none of the desired bromide results.
14. Compounds 13 and 13a are readily distinguished by the inspection of the δ 5.3-6.0 region of their ^{1}H NMR spectra. The ^{1}H NMR spectrum of 13 (250 MHz, $CDCl_3$). δ -0.02(s, 3 H), 0.01(s, 3 H), 0.55[q (quartet), J=7.9 Hz, 6 H], 0.80(d, J=7.1 Hz, 3 H), 0.88(s, 9 H), 0.93(t, J=7.9 Hz, 9 H), 0.99(d, J=6.8 Hz, 3 H), 1.00(d, J=6.1 Hz, 3 H), 1.27(t, J=7.2 Hz, 3H), 1.68 ~ 1.82(m, 1 H), 2.35 ~ 2.51(m, 1 H), 3.53(dd, J=7.2, 3.7 Hz, 1 H), 4.00(dq, J=7.0, 5.7 Hz, 1 H), 4.18(q, J=7.1 Hz, 2 H), 5.78(dd, J=15.0, 7.5 Hz, 1 H), 5.83(d, J=15.3 Hz, 1 H), 5.96 ~ 6.65(m, 9 H), 7.30(dd, J=15.2, 11.5 Hz, 1 H). Spectral data of 4. UV (EtOH); λ_{max} 289 nm (log ε 3.97), 399 (4.70). IR ($CHCl_3$): 1668, 1605, 1555 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ -0.02(s, 3 H), 0.01(s, 3 H), 0.55(q, J=7.9 Hz, 6 H), 0.80(d, J=7.0 Hz, 3 H), 0.88(s, 9 H), 0.93(t, J=8.0 Hz, 9 H), 1.00(d, J=5.9 Hz, 6 H), 1.68 ~ 1.83(m, 1 H), 3.37 ~ 3.56(m, 1 H), 3.53(dd, J=7.1, 3.6 Hz, 1 H), 4.00(dq, J=7.0, 5.6 Hz, 1 H), 5.81(dd, J=15.0, 7.4 Hz, 1 H), 6.00 ~ 6.79(m, 10 H), 7.15(dd, J=15.0, 11.3 Hz, 1 H), 9.54(d, J=8.0 Hz, 1 H).
15. Cf. Minami, N.; Ko, S.S.; Kishi, Y. J. Am. Chem. Soc. 1982, 104, 1109.
16. Blanchette, M.A.; Choy, W.; Davis, J.T.; Essenfeld, A.P.; Masamune, S.; Roush, W.R.; Sakai, T. Tetrahedron Lett. 1984, 25, 2183.
17. All new compounds showed physical properties consistent with the assigned structures.

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