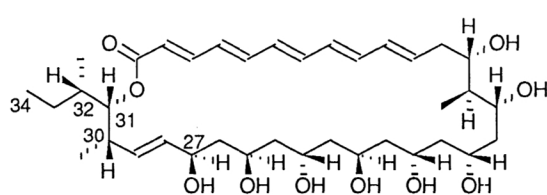


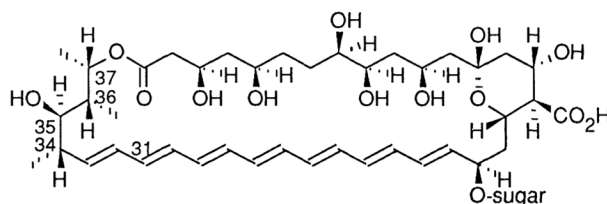
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We wish to report an enantiocontrolled synthesis of key fragments of the polyketide macrolide antibiotics, C₂₇₋₃₄ fragment (**17**) of mycotycin B¹⁾ (**1**) and C₃₁₋₃₇ fragment (**24**) of amphotericin B²⁾ (**2**), using a common building block (**8**) prepared from (S)-O-benzylglycidol³⁾ (**3**).



mycoticin B 1



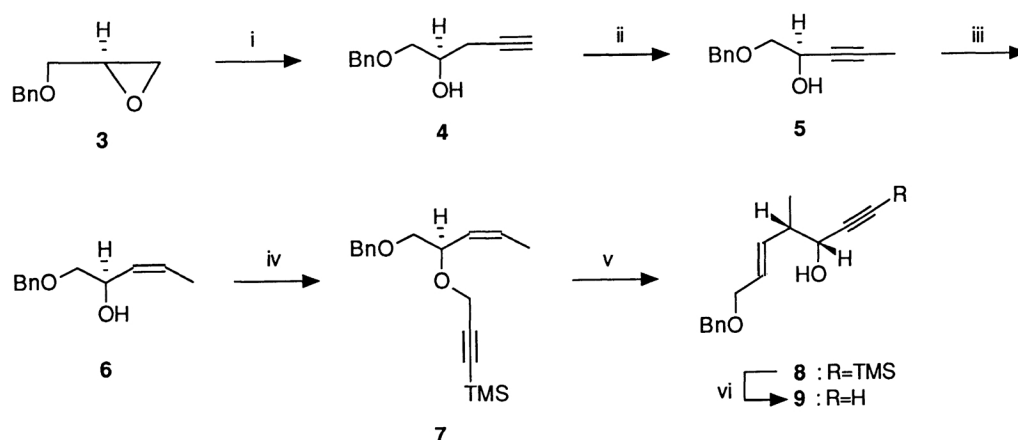
amphotericin B 2

Fig. 1.

As outlined we developed⁴⁾ an efficient stereocontrolled preparation of the eneynol (**9**) from (S)-O-benzylglycidol (**3**) employing highly stereoselective [2,3]-Wittig rearrangement⁵⁾ of the silylpropargyl ether (**7**) as the key step. Thus, the internal acetylene (**5**) obtained in one-step (85%) from **3** via novel acetylene rearrangement of the terminal acetylene⁶⁾ (**4**) was sequentially transformed to the Z-enol (**6**) (100%) and the ether (**7**), $[\alpha]_D^{27} -80.74^\circ$ (c 1.02, CHCl₃), (81%). The latter on treatment with n-butyllithium yielded the erythro-alcohol (**8**), $[\alpha]_D^{24} +18.91^\circ$ (c 0.62, CHCl₃), (90%), stereospecifically as a single product which was desilylated to give **9**, $[\alpha]_D^{26} +18.15^\circ$ (c 1.15, CHCl₃) (Scheme 1).

The silyl ether (10), $[\alpha]_D^{24} +17.61^\circ$ (c 0.99, CHCl_3), derived from 9 in 87% yield, was treated with methyl chloroformate in the presence of n-butyllithium to give the ester (11), $[\alpha]_D^{25} +21.75^\circ$ (c 1.00, CHCl_3), (80%). Partial hydrogenation of 11, followed by exposure of the resulting Z-olefin (12), $[\alpha]_D^{25} -5.39^\circ$ (c 1.04, CHCl_3), to methanolic hydrochloric acid (10:1 v/v) yielded the unsaturated lactone (13), $[\alpha]_D^{26} -99.80^\circ$ (c 1.01, CHCl_3), (83% overall). Conjugate addition of 13 occurred in highly selective manner from the less hindered face of the molecule to

give the saturated lactone (**14**), $[\alpha]_D^{24} -3.03^\circ$ (c 1.32, CHCl_3), (87%) bearing a new chiral center as a single product.



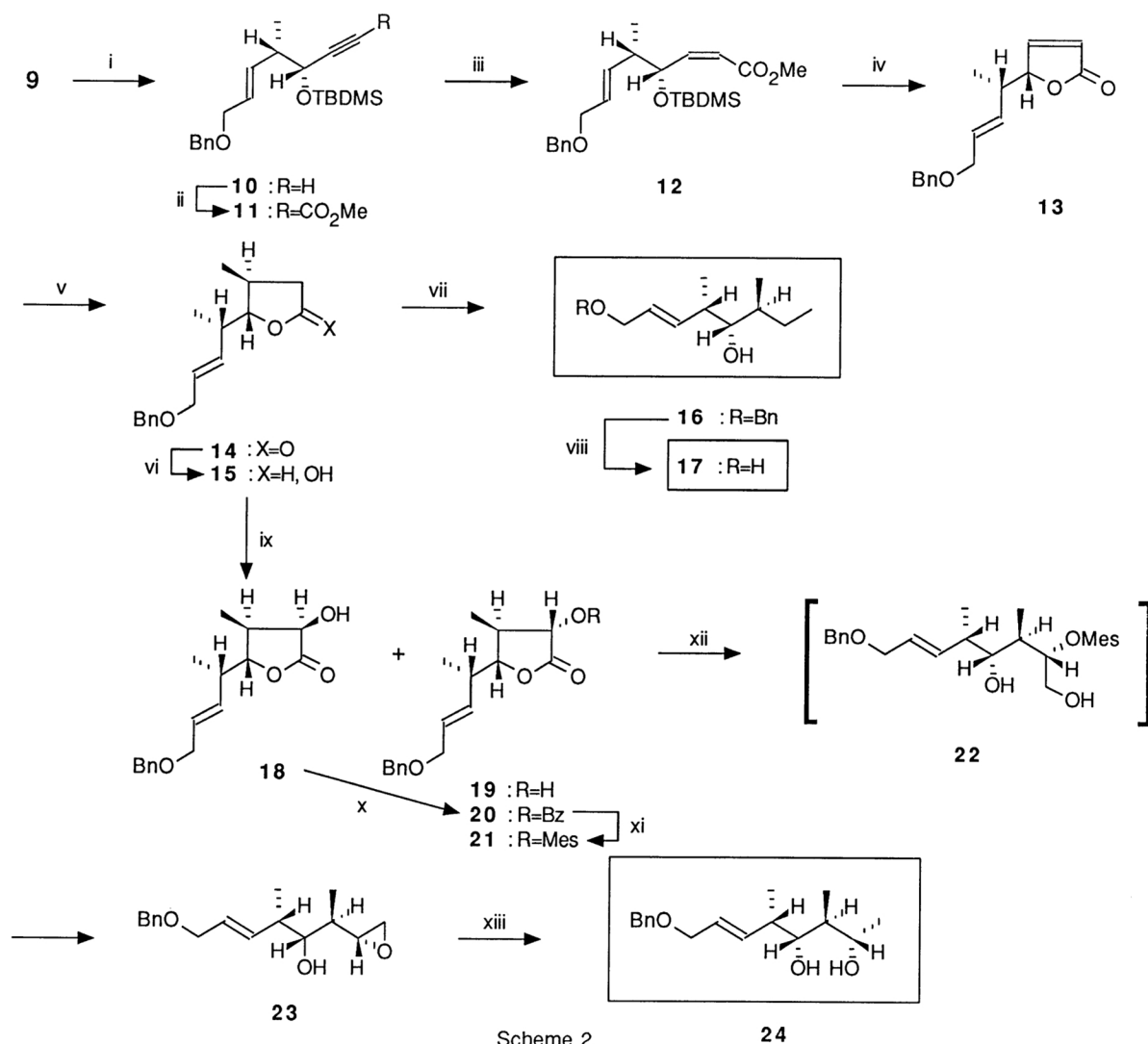
Scheme 1.

i, NaH, acetylene, DMSO, 0°C to room temp; ii, $t\text{BuOK}$, DMSO, room temp; iii, H_2 , Lindlar catalyst, AcOEt , room temp; iv, (a) propargyl bromide, $\text{KF-Al}_2\text{O}_3$, CH_3CN , room temp, (b) EtMgBr (2.5 equiv.), Et_2O , 0°C , then TMSCl ; v, $n\text{BuLi}$, THF, -78°C ; vi, $n\text{Bu}_4\text{NF}$ (3 equiv.), THF, room temp.

First, **14** was reduced with diisobutylaluminum hydride to give the lactol (**15**) which was immediately treated with hydrazine hydrate and potassium hydroxide in hot diethyleneglycol to afford the secondary alcohol (**16**), $[\alpha]_D^{26} -17.03^\circ$ (c 1.00, CHCl_3), (78%), bearing three contiguous chiral centers. The benzyl group could be removed by Birch reduction to give the diol (**17**), $[\alpha]_D^{26} -27.38^\circ$ (c 0.80, CHCl_3), (60%), corresponding to the C_{27-34} fragment of mycotycin B (**1**).

Second, **14** was oxidized with molybdenum peroxide pyridine hexamethylphosphoric triamide complex (MoOPH) in the presence of lithium diisopropylamide (LDA).⁷⁾ The reaction did not proceed in a stereoselective manner, however, the product mixture could be readily separated by column chromatography (SiO_2) to afford the β -hydroxy lactone (**18**), $[\alpha]_D^{24} -7.82^\circ$ (c 0.95, CHCl_3), (40%) and the α -hydroxy lactone (**19**), $[\alpha]_D^{25} +5.80^\circ$ (c 1.00, CHCl_3), (42%). Stereochemistry of the hydroxy group could be easily determined by nuclear Overhauser effect difference spectroscopy (NOEDS) (500 MHz) which only showed distinct enhancement in C_3 -proton signal of the latter isomer when C_4 -methyl protons of the both isomers were irradiated. Employing the Mitsunobu reaction⁸⁾ the former was cleanly converted into the latter in an excellent yield (88% overall) via the benzoate (**20**).

Methanesulfonylation of **19** followed by reduction of the resulting methane-sulfonate (**21**) (92%) with sodium borohydride furnished the epoxide (**23**), $[\alpha]_D^{28} -20.83^\circ$ (c 0.67, MeOH), (70%), in one-stage without isolation of the diol (**22**). Finally the epoxide (**23**) was treated with lithium aluminum hydride to allow regio-selective ring-cleavage to give the diol (**24**), $[\alpha]_D^{24} +4.41^\circ$ (c 1.13, CHCl_3), (79%), bearing four contiguous chiral centers corresponding to the C_{31-37} fragment of amphotericin B (**1**).



i, TBDMSCl, imidazole, DMF, room temp; ii, n BuLi, THF, -72°C , then ClCO_2Me , -45°C ; iii, H_2 , Lindlar catalyst, benzene, room temp; iv, concd HCl-methanol (1:10 v/v), room temp; v, MeLi, CuI, ether 0°C ; vi, DIBAL, THF, 0°C ; vii, KOH, $\text{H}_2\text{NNH}_2\cdot\text{H}_2\text{O}$, diethyleneglycol, 130°C to 200°C ; viii, Na, liq. NH_3 ; ix, LDA, MoOPH, THF, -78°C ; x, $(\text{NCO}_2\text{Pr}^1)_2$, Ph_3P , benzoic acid, THF, 0°C ; xi, (a) K_2CO_3 , MeOH, room temp, (b) MsCl , Et_3N , CH_2Cl_2 , 0°C ; xii, NaBH_4 , EtOH, room temp; xiii, LiAlH_4 , THF, -30°C .

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 - 10) All the products obtained gave satisfactory spectral data as follows:
13: IR (film) ν 1790, 1760 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ 7.42 (dd, 1H, $J=5.7, 1.4$ Hz), 7.33 (s, 5H), 6.12 (dd, 1H, $J=5.7, 2.0$ Hz), 5.79-5.58 (m, 2H), 4.50 (s, 2H), 3.98 (d, 2H, $J=4.9$ Hz), 2.78-2.30 (m, 1H), 1.14 (d, 3H, $J=7.1$ Hz); MS (m/z) 259 (M^++1), 91 (100%).
14: IR (film) ν 1780 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ 7.32 (s, 5H), 5.77-5.56 (m, 2H), 4.53 (s, 2H), 4.07-3.80 (m, 3H), 2.85-1.94 (m, 4H), 1.14 (d, 3H, $J=5.8$ Hz), 1.13 (d, 3H, $J=6.5$ Hz); MS (m/z) 274 (M^+), 91 (100%).
16: IR (film) ν 3300 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ 7.35 (m, 5H), 5.73 (dd, 1H, $J=15.6, 6.9$ Hz), 5.65 (dt, 1H, $J=15.6, 6.0$ Hz), 4.51 (s, 2H), 4.01 (d, 2H, $J=6$ Hz), 3.25 (dd, 1H, $J=6.9, 5$ Hz), 2.44 (sext, 1H, $J=6.9$ Hz), 1.68 (m, 2H), 1.51 (m, 3H), 1.02 (d, 3H, $J=6.9$ Hz), 0.89 (t, 3H, $J=6.9$ Hz), 0.88 (d, 3H, $J=6.9$ Hz); MS (m/z) 262 (M^+), 68 (100%).
17: IR (film) ν 3300 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ 5.69 (m, 2H), 4.12 (m, 2H), 3.24 (dd, 1H, $J=6.8, 4.6$ Hz), 2.40 (m, 1H), 1.71 (s, 2H, exchangeable), 1.7-1.1 (m, 3H), 1.1 (d, 3H, $J=6.8$ Hz), 0.89 (t, 3H, $J=6.3$ Hz), 0.88 (d, 3H, $J=6.6$ Hz); MS (m/z) 173 (M^++1), 68 (100%).
18: IR (film) ν 3300, 1760 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ 7.28 (m, 5H), 5.66 (dt, 1H, $J=15.0, 6.0$ Hz), 5.52 (ddt, 1H, $J=15.0, 6.9, 1.3$ Hz), 4.48 (s, 2H), 4.36 (d, 1H, $J=7.0$ Hz), 3.92 (m, 3H), 2.51 (quint, 1H, $J=7.0, 3.0$ Hz), 2.38 (sext, 1H, $J=6.9$ Hz), 1.55 (br.s, 1H, exchangeable with D_2O), 1.04 (d, 3H, $J=6.9$ Hz), 1.02 (d, 3H, $J=7.0$ Hz); MS (m/z) 290 (M^+), 91 (100%).
19: IR (film) ν 3300, 1760 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ 7.28 (m, 5H), 5.71 (m, 2H), 4.52 (s, 2H), 4.04 (d, 1H, $J=10.5$ Hz), 4.00 (d, 2H, $J=4.75$ Hz), 3.91 (dd, 1H, $J=9.3, 6.8$ Hz), 2.52 (sext, 1H, $J=6.8$ Hz), 2.22 (m, 1H), 1.23 (d, 3H, $J=6.4$ Hz), 1.13 (d, 3H, $J=6.8$ Hz); MS (m/z) 290 (M^+), 91 (100%).
24: IR (film) ν 3275 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ 7.34 (m, 5H), 5.81 (dd, 1H, $J=15.9, 6.1$ Hz), 5.69 (dtd, 1H, $J=15.9, 6.1, 1.22$ Hz), 4.52 (s, 2H), 4.02 (d, 2H, $J=6.1$ Hz), 3.81 (dq, 1H, $J=7.9, 6.1$ Hz), 3.53 (dd, 1H, $J=9.2, 2.5$ Hz), 2.67 (br.s, 2H, exchangeable), 2.50 (m, 1H), 1.60 (ddq, 1H, $J=9.2, 7.9, 6.7$ Hz), 1.20 (d, 3H, $J=6.1$ Hz), 1.10 (d, 3H, $J=7.3$ Hz), 0.79 (d, 3H, $J=6.7$ Hz); MS (m/z) 279 (M^++1), 91 (100%).

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