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A Route to Key Fragments of Mycoticin B and Amphotericin B from (S)-O-Benzylglycidol

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A concise enantioselective synthesis of C_{27-34} fragment of mycoticin B and C_{31-37} fragment of amphotericin B is described using a common building block prepared from (S)-O-benzylglycidol.

We wish to report an enantiocontrolled synthesis of key fragments of the polyketide macrolide antibiotics, C_{27-34} fragment (**17**) of mycoticin B[1] (**1**) and C_{31-37} fragment (**24**) of amphotericin B[2] (**2**), using a common building block (**8**) prepared from (S)-O-benzylglycidol[3] (**3**).

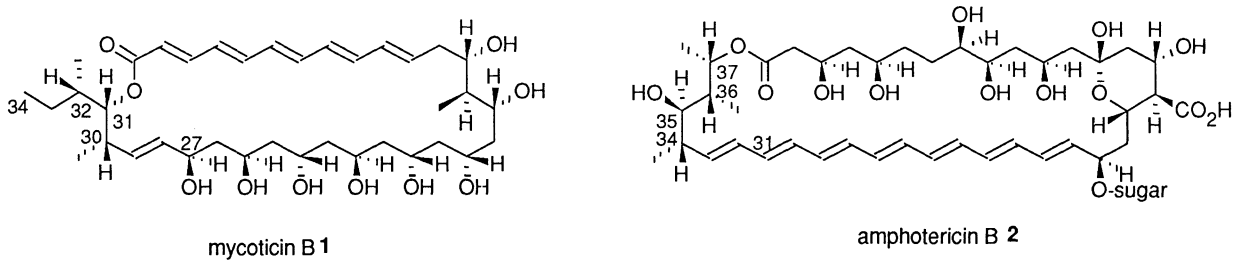
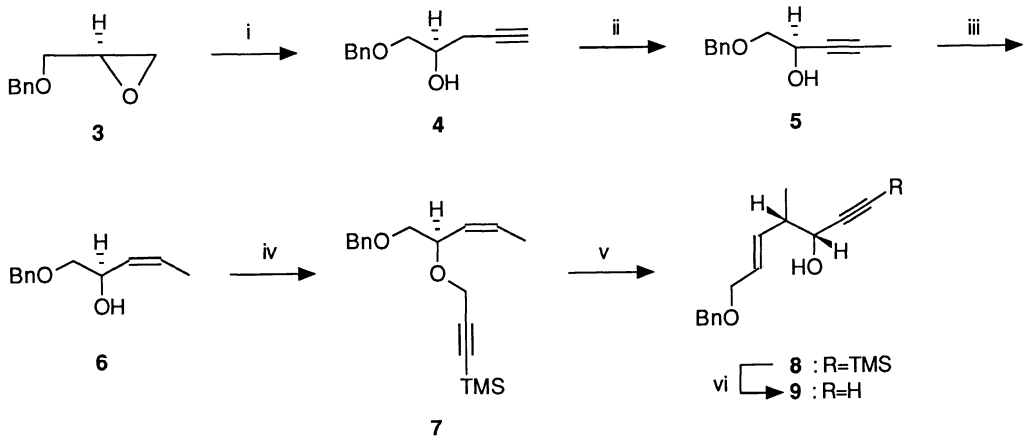


Fig. 1.

As outlined we developed[4] an efficient stereocontrolled preparation of the eneynol (**9**) from (S)-O-benzylglycidol (**3**) employing highly stereoselective [2,3]-Wittig rearrangement[5] 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 acetylene[6] (**4**) was sequentially transformed to the Z-enol (**6**) (100%) and the ether (**7**), $[\alpha]_D^{27}$ -80.74° (c 1.02, $CHCl_3$), (81%). The latter on treatment with n-butyllithium yielded the erythro-alcohol (**8**), $[\alpha]_D^{24}$ +18.91° (c 0.62, $CHCl_3$), (90%), stereospecifically as a single product which was desilylated to give **9**, $[\alpha]_D^{26}$ +18.15° (c 1.15, $CHCl_3$) (Scheme 1).

The silyl ether (**10**), $[\alpha]_D^{24}$ +17.61° (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° (c 1.00, $CHCl_3$), (80%). Partial hydrogenation of **11**, followed by exposure of the resulting Z-olefin (**12**), $[\alpha]_D^{25}$ -5.39° (c 1.04, $CHCl_3$), to methanolic hydrochloric acid (10:1 v/v) yielded the unsaturated lactone (**13**), $[\alpha]_D^{26}$ -99.80° (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° (c 1.32, $CHCl_3$), (87%) bearing a new chiral center as a single product.



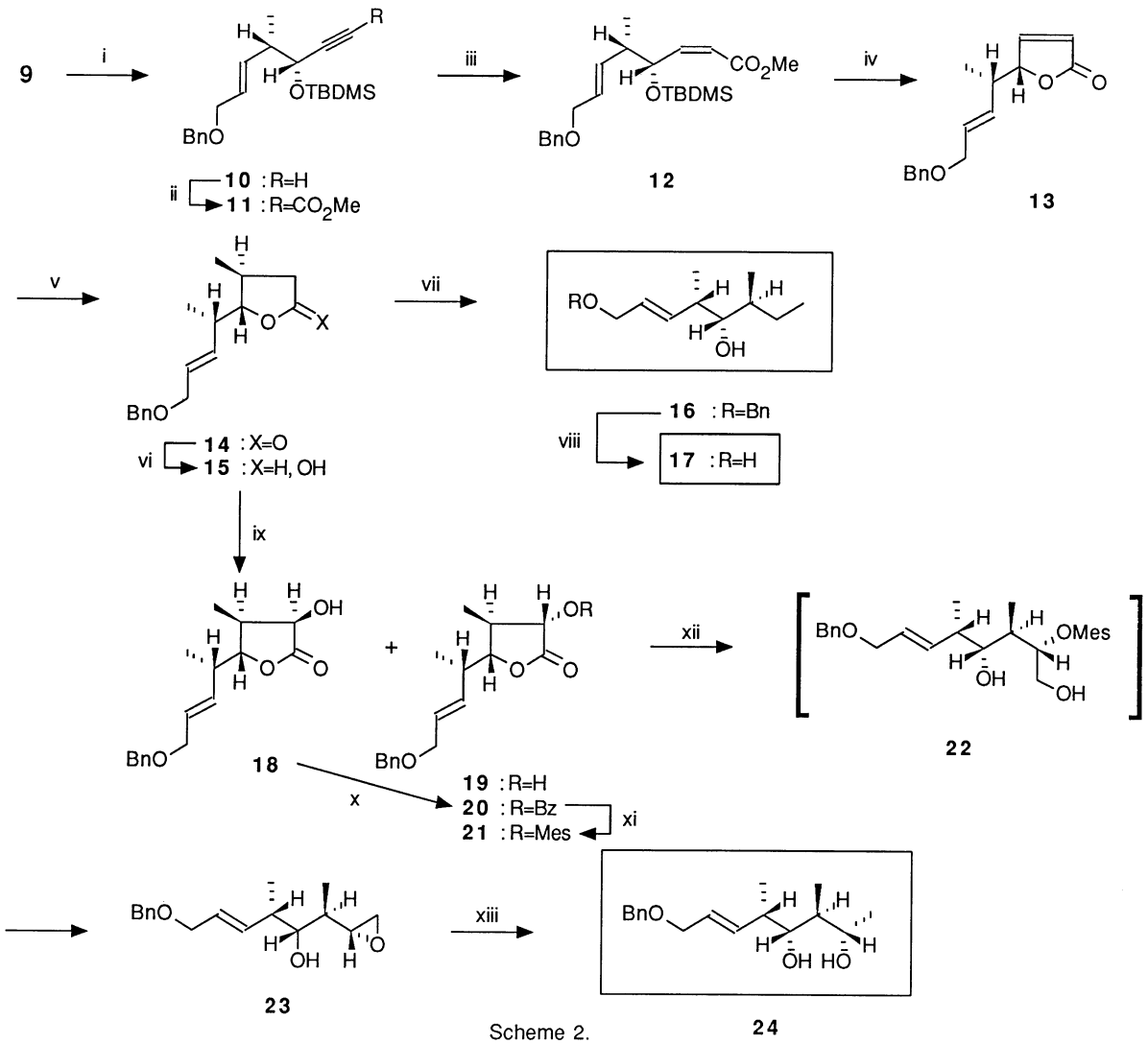
Scheme 1.

i, NaH, acetylene, DMSO, 0 °C to room temp ; ii, ^tBuOK, DMSO, room temp ; iii, H_2, Lindlar catalyst, AcOEt, room temp ; iv, (a) propargyl bromide, KF-Al_2O_3, CH_3CN, room temp , (b) EtMgBr (2.5 equiv.), Et_2O, 0 °C, then TMSCl; v, ^nBuLi, THF, -78 °C; vi, $^nBu_4NF$ (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° (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° (c 0.80, $CHCl_3$), (60%), corresponding to the C_{27-34} fragment of mycoticin 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° (c 0.95, $CHCl_3$), (40%) and the α-hydroxy lactone (**19**), $[\alpha]_D^{25}$ +5.80° (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 reaction[8] 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 methanesulfonate (**21**) (92%) with sodium borohydride furnished the epoxide (**23**), $[\alpha]_D^{28}$ -20.83° (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 regioselective ring-cleavage to give the diol (**24**), $[\alpha]_D^{24}$ +4.41° (c 1.13, $CHCl_3$), (79%), bearing four contiguous chiral centers corresponding to the C_{31-37} fragment of amphotericin B (**1**).



Scheme 2.

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, $H_2NNH_2 \cdot H_2O$, diethyleneglycol, 130 °C to 200 °C; viii, Na, liq. NH_3; ix, LDA, MoOPH, THF, -78 °C; x, $(NCO_2Pr^i)_2$, 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.

References

1) S. L. Schreiber and M. T. Goulet, Tetrahedron Lett., 28, 6001 (1987); S. L. Schreiber, M. T. Goulet, and T. Sammakia, ibid., 28, 6005 (1987); S. L. Schreiber and M. T. Gowlet, J. Am. Chem. Soc., 109, 8120 (1987).

2) K. C. Nicolaou, T. K. Chakraborty, Y. Ogawa, R. A. Daines, N. S. Simpkins, and G. T. Furst, J. Am. Chem. Soc., 110, 4660 (1988); K. C. Nicolaou, R. A. Daines, J. Uenishi, W. S. Li, D. P. Papahatjis, and T. K. Chakraborty, ibid., 110, 4672 (1988); K. C. Nicolaou, R. A. Daines, T. K. Chakraborty, and Y. Ogawa, ibid., 110, 4685 (1988); K. C. Nicolaou, R. A. Daines, Y. Ogawa, and T. K.

Chakraborty, ibid., 110, 4696 (1988), and references cited therein.

3) S. Takano, M. Akiyama, and K. Ogasawara, Synthesis, 1985, 503.

4) S. Takano, Y. Sekiguchi, and K. Ogasawara, J. Chem. Soc., Chem. Commun., 1987, 555.

5) T. Nakai and K. Mikami, Chem. Rev., 86, 885 (1986).

6) S. Takano, Y. Sekiguchi, N. Sato, and K. Ogasawara, Synthesis, 1987, 139.

7) S. Takano, M. Morimoto, and K. Ogasawara, J. Chem. Soc., Chem. Commun., 1984, 82.

8) O. Mitsunobu, Synthesis, 1981, 1.

9) Construction of fragment of amphotericin B (**2**) bearing four contiguous chiral centers: see, Ref. 2b; D. W. Brooks and R. P. Kellogg, Tetrahedron Lett., 23, 4991 (1982); D. Boschelli, T. Takemasa, Y. Nishitani, and S. Masamune, ibid., 26, 5239 (1985); G. J. McGarvey, J. M. Williams, R. N. Hiner, Y. Matsubara, and T. Oh, J. Am. Chem. Soc., 104, 4943 (1986); S. Hanessian, S. P. Sahoo, and B. Botta, Tetrahedron Lett., 28, 1147 (1987); M. Kinoshita, H. Takami, M. Taniguchi, and T. Tamai, Bull. Chem. Soc. Jpn., 60, 2151 (1987).

10) All the products obtained gave satisfactory spectral data as follows:
13: IR (film) ν 1790, 1760 cm^{-1}; ^{1}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}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}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}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}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}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}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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