Stereoselective Syntheses of the 14-Hydroxy Epimers of Amphotericin B Methyl Ester

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(14*R*)-Hydroxyamphotericin B methyl ester **8** and its (14*S*)-epimer **12** have been obtained by way of *m*-CPBA oxidation of the enol ethers **5** and **6** respectively.

The polyene macrolide antibiotic[1] amphotericin B **1** is widely used to combat severe systemic fungal infections.[2] Amphotericin B was first isolated from *Streptomyces nodusus*[3] and its structure has been determined by X-ray crystallography.[4] Previous chemical manipulation includes its partial[5] and total[6] synthesis, selective degradation,[7] functionalisation at C-16,[8,9] and derivatisation of its amino function.[10] Following our identification of the dehydration at C-13,14 of *N*-acetylamphotericin B methyl ester **2**,[11] we now describe two synthetic sequences (Scheme 1) which yield (14*R*)-hydroxyamphotericin B methyl ester **8** and its (14*S*)-epimer **12**.† These stereoselective hydroxylations are the first reported substitution at C-14 of amphotericin B.

N-(Fmoc)amphotericin B methyl ester **3** was dehydrated by way of the silylated intermediate **4** to give the 13,14-anhydro derivative **5**‡ using our published methodology.[11] Treatment of this ester **5** with *m*-CPBA in THF–H_2O resulted in the chemo- and stereo-selective dihydroxylation of the enol ether, in preference to the conjugated heptaene system, affording the (14*R*)-hydroxy derivative **7** in 54% yield (after column chromatography). It is postulated that the initial attack of the electrophilic peracid at C-14 is directed by the hydroxy group at C-15, yielding the (14*R*)-epimer as the sole product. In contrast, the pertriethylsilyl derivative **6** obtained by silylation of the anhydro ester **5**, gave solely the (14*S*)-hydroxy derivative **10** in 50% yield (after column chromatography) when treated with *m*-CPBA in hexane.§ Presumably blocking the directing effect of the C-15 hydroxy group by silylation results in attack on the enol ether from the less hindered β-face.

The novel hydroxylated derivatives **7** and **10** were converted into their corresponding amphotericin B methyl ester analogues. Treatment of **7** with piperidine[8] in DMSO–MeOH liberated the amine function to give the (14*R*)-hydroxyamphotericin B methyl ester **8** (80%). Desilylation of **10** with HF–pyridine in THF–pyridine resulted in concomitant cleavage of the anomeric benzoyl group to give the fluoride **11** (32%).¶ Hydrolysis of the fluoride **11** (CSA–THF–H_2O) followed by regeneration of the amino group with piperidine in DMSO–MeOH gave (14*S*)-hydroxyamphotericin B methyl ester **12** (87%).

Experimental

(14R)-N-(9-*Fluorenylmethoxycarbonyl*)-14-*hydroxyamphotericin B Methyl Ester* **7**.—To a solution of the polyene **5** (0.372 g, 0.37 mmol) in THF–H_2O (6:1; 3 cm^3), at 0 °C was added solid *m*-CPBA (0.067 g, 0.39 mmol). The coolant was removed and the reaction mixture was stirred at room temperature for 1 h and then diluted with ethyl acetate. The organic solution was washed sequentially with aqueous sodium metabisulfite, aqueous sodium hydrogen carbonate and water, dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography on silica gel with the separated lower phase of chloroform–methanol–ammonium hydroxide (*d* 0.88) (5:1:1) mixture as eluent to give the polyene **7** (0.207 g, 54%) as a yellow amorphous solid; ν_{max}(KBr)/cm^{-1} 3427, 3013, 2972, 2934, 1717, 1636, 1514, 1450, 1376, 1323, 1190, 1071, 1010, 905, 882, 848, 760, 742, 651 and 540; λ_{max}(MeOH)/nm 405, 382, 363 and 344; δ_H [400 MHz; C_5D_5N–CD_3OD, 1:1; Me_4Si] 7.84 (2 H, d, *J* 7.5, ArH), 7.71 (2 H, m, ArH), 7.41 (2 H, t, *J* 7.4, ArH), 7.30 (2 H, t, *J* 7.3, ArH), 6.66–6.32 (13 H, complex, olefinic), 5.63 (1 H, m, 37-H), 5.49 (1 H, dd, *J* 14.7, 10.2, 33-H), 4.88 (1 H, m, 17-H), 4.77–4.67 (4 H, complex, 1'-H, 11-H, 15-H, 19-H), 4.46 (1 H, m, 3-H), 4.37 (2 H, m, $NHCO_2CH_2$), 4.24–4.20 (2 H, complex, $NHCO_2CH_2CH$, 2'-H), 4.07 (1 H, dd, *J* 10.1, 2.6, 3'-H), 3.95 (1 H, m, 5-H), 3.87 (1 H, d, *J* 2.8, 14-H), 3.85 (1 H, complex, 9-H), 3.80 (3 H, s, CO_2CH_3), 3.77 (1 H, t, *J* 9.9, 4'-H), 3.59 (1 H, m, 5'-H), 3.47–3.36 (2 H, complex, 8-H, 35-H), 3.14 (1 H, t, *J* 10.8, 16-H), 2.56 (1 H, complex), 2.49 (1 H, dd, *J* 16.9, 9.7, 2-H), 2.40–2.27 (3 H, complex), 2.13–1.92 (4 H, complex), 1.81–1.45 (7 H, complex), 1.49 (3 H, d, *J* 5.8, 6'-CH_3), 1.35 (3 H, d, *J* 6.4, 38-CH_3), 1.24 (3 H, d, *J* 6.4, 40-CH_3) and 1.17 (3 H, d, *J* 7.1, 39-CH_3); δ_C [100.6 MHz; C_5D_5N–CD_3OD, 1:1; Me_4Si] 174.8, 172.3, 158.1, 145.1, 145.0, 142.1, 137.5, 134.9, 134.8, 134.3, 134.2, 133.9, 133.8, 133.7, 133.6, 133.5, 133.0, 130.5, 128.5, 127.9, 126.14, 126.10, 120.7, 100.4, 98.7, 79.1, 77.1, 76.4, 75.3, 75.0, 72.8, 72.3, 71.8, 71.4, 70.5, 70.3, 69.3, 68.7, 67.4, 66.6, 58.5, 52.3, 52.2, 48.2, 44.9, 44.0, 43.3, 42.9, 41.3, 41.1, 38.5, 36.4, 31.6, 19.1, 18.6, 17.3 and 12.6; *m/z* (FAB–thiodiethanol, sodium matrix) 1199 (MNa^+).

Acknowledgements

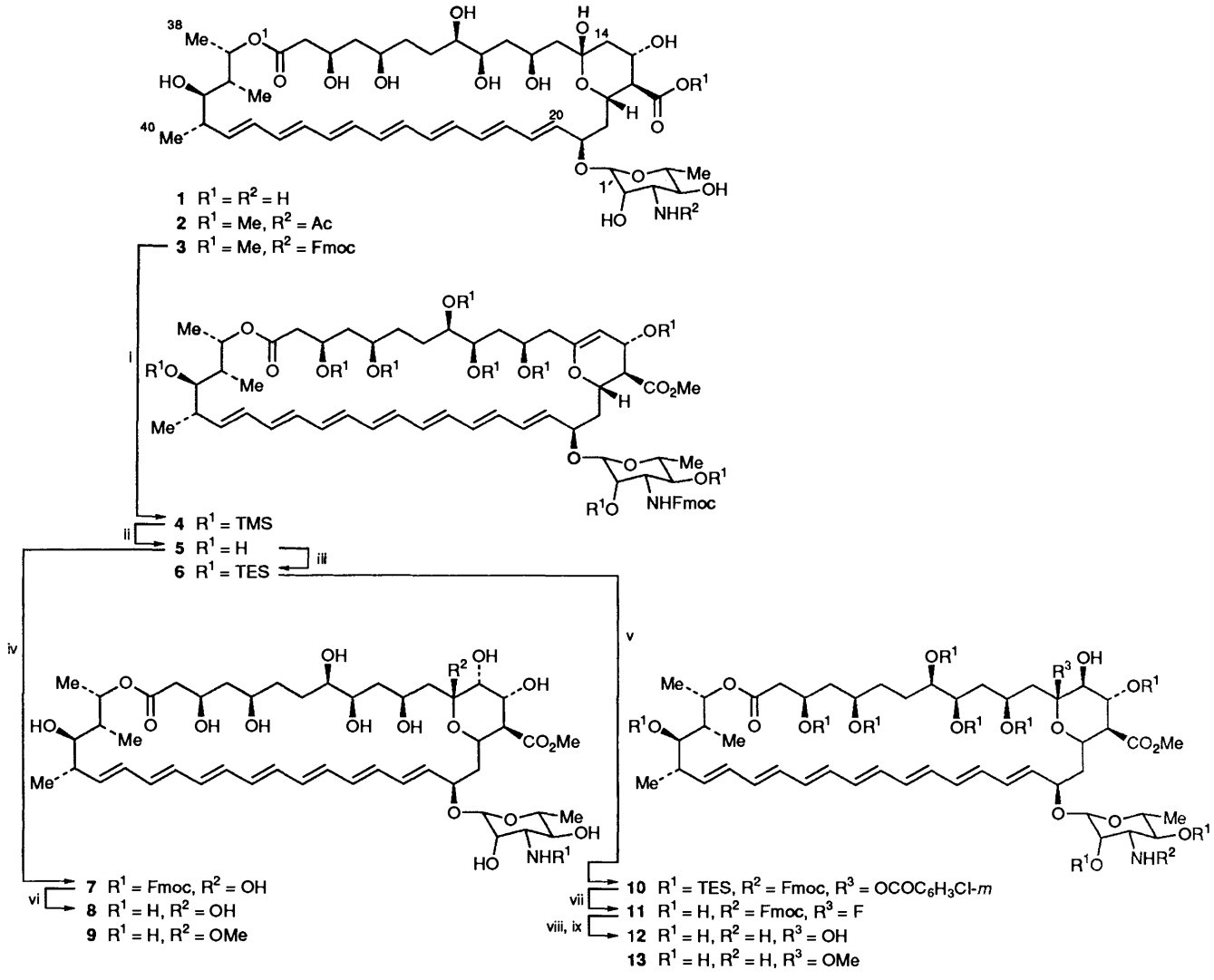
We thank Dr D. F. Corbett for his encouragement during this work and Dr S. A. Readshaw for 2 D NMR assignments.

† Stereochemical assignments were made by correlation with 2D NMR of the corresponding 13-*O*-methyl acetals **9** and **13**.

‡ Compounds **5**–**13** were characterised by ^{13}C NMR, ^1H NMR, IR, UV and FAB MS.

§ In hexane the peroxyacid adds across the enol ether[12] introducing the (14*S*)-hydroxy substituent and the axial[7b] 3-chlorobenzoyloxy group at the anomeric centre.[13]

¶ The stereochemistry at C-13 is evident[14] from the large *trans* diaxial vicinal coupling obtained ($^3J_{14\text{-H},13\text{-F}}$ = 23.3 Hz) from the ^1H NMR spectrum of **11**: δ_H [400 MHz; C_5D_5N/CD_3OD, 1:1; Me_4Si] 7.84 (2 H, d, *J* 7.5, ArH), 7.71 (2 H, t, *J* 7.8, ArH), 7.42 (2 H, t, *J* 7.5, ArH), 7.30 (2 H, t, *J* 7.5, ArH), 6.62–6.33 (12 H, complex, olefinic), 6.27 (1 H, dd, *J* 15.4, 8.3, 20-H), 5.56 (1 H, m, 37-H), 5.53 (1 H, dd, *J* 14.0, 9.8, 33-H), 4.77–4.75 (3 H, complex, 1'-H, 17-H, 19-H), 4.55 (1 H, m, 11-H), 4.51–4.46 (1 H, complex, 3-H), 4.48 (1 H, t, *J* 9.7, 15-H), 4.37 (2 H, d, *J* 9.7, $NHCO_2CH_2$), 4.24–4.21 (2 H, complex, 2'-H, $NHCO_2CH_2CH$), 4.04 (1 H, dd, *J* 10.2, 2.9, 3'-H), 3.98 (1 H, m, 5-H), 3.89 (1 H, m, 9-H), 3.80 (3 H, s, CO_2CH_3), 3.77 (1 H, t, *J* 9.9, 4'-H), 3.58 (1 H, dd, *J* 23.3, 9.4, 14-H), 3.57 (1 H, m, 5'-H), 3.45 (1 H, m, 8-H), 3.40 (1 H, m, 35-H), 2.91 (1 H, t, *J* 10.8, 16-H), 2.59–2.45 (3 H, complex), 2.35 (1 H, dd, *J* 16.8, 2.9, 2-H), 2.27 (1 H, m, 18-H), 2.13–1.92 (5 H, complex), 1.79–1.51 (6 H, complex), 1.48 (3 H, d, *J* 6.1, 6'-CH_3), 1.35 (3 H, d, *J* 6.4, 38-CH_3), 1.24 (3 H, d, *J* 6.4, 40-CH_3) and 1.16 (3 H, d, *J* 7.2, 39-CH_3).



Scheme 1 *Reagents and conditions*: i, $Me_3SiOSO_2CF_3$ (13 equiv.), 2,6-lutidine (16 equiv.), CH_2Cl_2, 0–25 °C, 1 h; ii, HF–pyridine (80 equiv.), THF, pyridine, 25 °C, 4 h, 46% from **3**; iii, $Et_3SiOSO_2CF_3$ (13 equiv.), 2,6-lutidine (18 equiv.), CH_2Cl_2, 0 °C 0.5 h, 25 °C 20 h, 61%; iv, *m*-CPBA (1.2 equiv.), THF, H_2O, 0–25 °C, 2 h, 54%; v, *m*-CPBA (1.2 equiv.), hexane, 0–25 °C, 1 h, 50%; vi, piperidine (2 equiv.), DMSO, MeOH, 2 h, 80%; vii, HF–pyridine (80 equiv.), THF, pyridine, 25 °C, 24 h, 32%; viii, CSA (1 equiv.), THF, H_2O, 25 °C, 4 h; ix, piperidine (2 equiv.); DMSO, MeOH, 3 h, 87%.

Abbreviations used here and in text: THF = tetrahydrofuran, Fmoc = fluoren-9-ylmethoxycarbonyl, TMS = trimethylsilyl, TES = triethylsilyl, DMSO = dimethyl sulfoxide, *m*-CPBA = *m*-chloroperbenzoic acid, CSA = camphor-10-sulfonic acid.

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Paper 3/03272H
Received 8*th June* 1993
Accepted 22*nd June* 1993