Pergamon

Tetrahedron Letters 39 (1998) 7163–7166

TETRAHEDRON LETTERS

Monamycin Synthetic Studies. Pt 1. An Enantiospecific Total Synthesis of (3*S*,5*S*)-5-Hydroxypiperazic Acid from D-Mannitol

Karl J. Hale,* Neha Jogiya, and Soraya Manaviazar

The Christopher Ingold Laboratories,
Department of Chemistry, University College London,
20 Gordon Street, London WC1H 0AJ, UK.

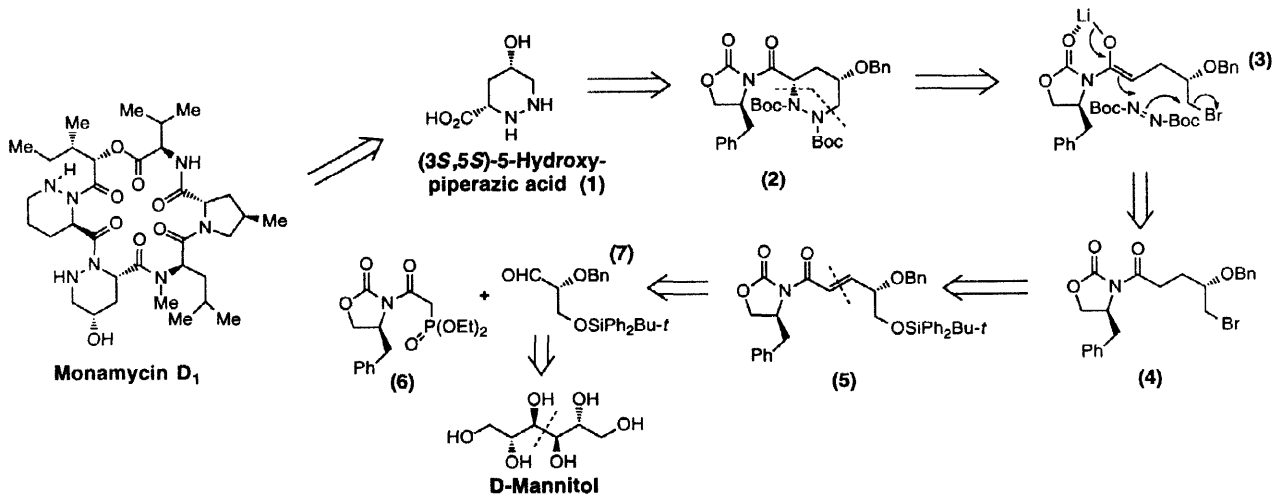
(e-mail: k.j.hale@ucl.ac.uk)

Received 28 May 1998; accepted 20 July 1998

Abstract. The first enantiospecific total synthesis of (3*S*,5*S*)-hydroxypiperazic acid **1** is described. The synthesis begins from D-mannitol and exploits a tandem electrophilic hydrazination/nucleophilic cyclisation reaction to assemble the hexahydropyridazine ring system.

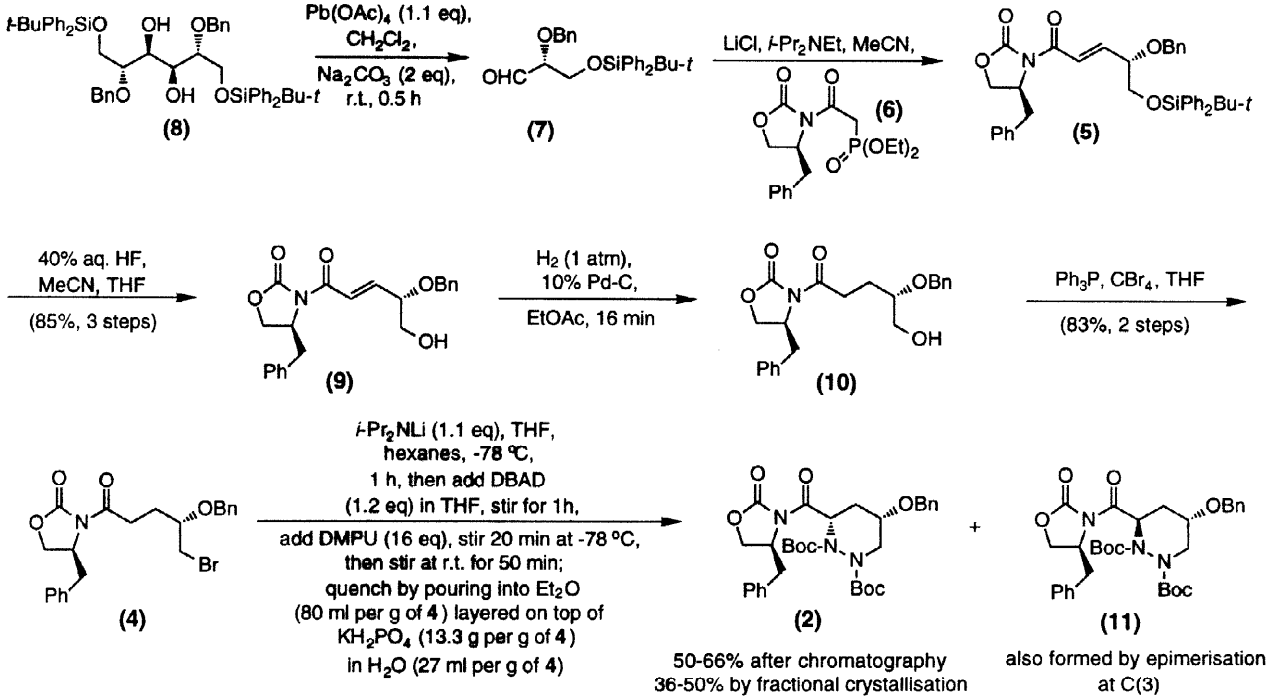
The monamycins are structurally unique cyclohexadepsipeptides that show pronounced antibiotic effects against resistant strains of Gram-positive bacteria at low drug concentrations. First characterised in the early 1970s by Hassall and coworkers,[1] the family currently consists of fifteen members, each of which contains the rare hexahydropyridazine, (3*S*,5*S*)-5-hydroxypiperazic acid **1**. So far, asymmetric approaches to optically pure **1** have been lacking. The current method for obtaining **1** involves an optical resolution of the racemate with quinine,[2] which is very uneconomical to perform on large scale. In this Letter, we now describe a convenient enantiospecific synthesis of **1** from D-mannitol that exploits a *tandem* electrophilic hydrazination and nucleophilic cyclisation reaction to build the homochiral hexahydropyridazine ring system.[3] The essence of our strategy is depicted in retrosynthetic form in Scheme 1.

Scheme 1



0040-4039/98/$ - see front matter
PII: S0040-4039(98)01533-0

Scheme 2

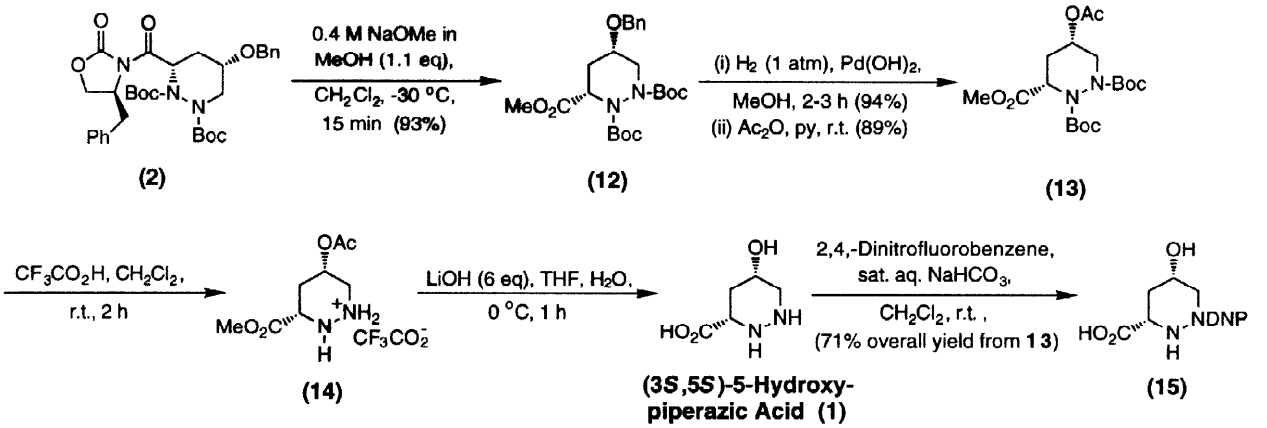


Bromide **4** was prepared in five steps (71% overall yield) from the known D-mannitol derivative **8**[4] via the route outlined in Scheme 2. Oxidative cleavage of diol **8**[4] with $Pb(OAc)_4$ in buffered CH_2Cl_2 furnished aldehyde **7** which readily participated in a Wittig-Horner olefination with known phosphonate **6**[5] under the Roush-Masamune conditions.[6] This produced the crystalline alkene **5** as a single geometrical isomer. The silyl group was detached from **5** by treatment with 40% aq. HF in THF/MeCN (2:1); the product alcohol **9** was isolated in 85% overall yield from **8**. Hydrogenation of **9** in EtOAc with 10% palladium on carbon (Aldrich, Wet Degussa Type) chemoselectively reduced the olefin, without disturbing the *O*-benzyl ether, to provide the alcohol **10** in good yield. Compound **10** was then brominated with Ph_3P (2 eq) and carbon tetrabromide (2 eq) (Aldrich) in dry THF at room temperature to furnish **4** as an oil in 83% yield from **9**.

Treatment of bromide **4** with LDA (1.1 eq) in dry THF and hexanes at -78 °C produced an enolate **3** that underwent a highly stereoselective hydrazination[7] with di-*tert*-butylazodicarboxylate (DBAD) (1.2 eq). Tandem cyclisation[3] of the resulting aza anion occurred after dry DMPU (16 eq) was added to the reaction mixture and it was stirred at room temperature for 50 min. After extractive work up with Et_2O and sat. aq. KH_2PO_4, product **2** was obtained in 50-66% yield after chromatographic purification and crystallisation. Unlike our previous synthesis of (3*R*)- and (3*S*)-piperazic acids,[3] where the tandem cyclisation was complete after warming to 0 °C, cyclisation of the aza anion derived from **4** was slower. It required an extended period at room temperature to reach completion, which led to some epimerisation at the newly-installed C(3) stereocentre, as judged by TLC analysis. The diastereoisomeric product **11** moved slightly faster than **2** on TLC; it also had a mobility very similar to the hydrazinated bromide. As yet, we have been unable to obtain an accurate yield for **11**, since extensive preparative TLC is needed to obtain it pure.

The most convenient procedure for cleaving the chiral auxiliary from **2** reacted it with sodium methoxide in CH_2Cl_2 and methanol at -30 °C for 15 min (Scheme 3). Typically, this regime delivered **12** as an oil in 93% yield after chromatography. To complete the synthesis of **1** the following sequence of reactions was investigated. The *O*-benzyl ether was cleaved from **12** by catalytic hydrogenolysis with $Pd(OH)_2$ in methanol,

Scheme 3

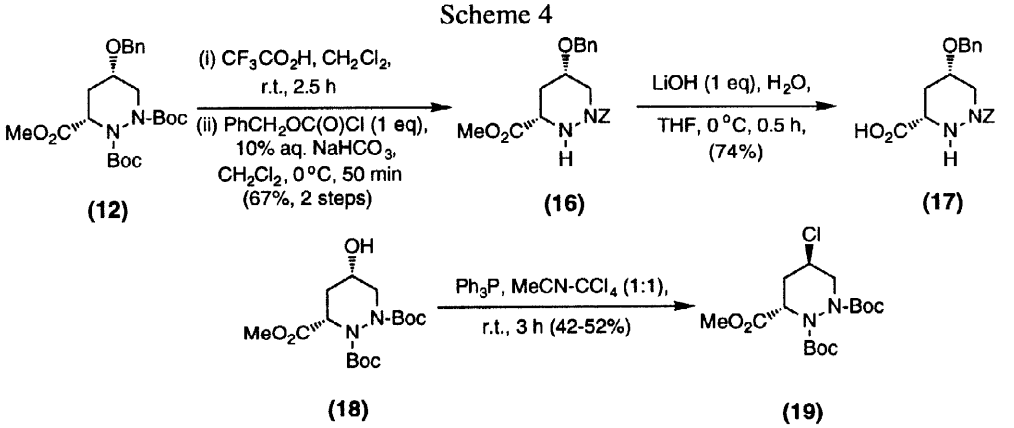


and the resulting alcohol temporarily *O*-acetylated to obtain **13**. This permitted a clean and high yielding deprotection of the two Boc groups with trifluoroacetic acid. Crude **14** was then reacted with excess LiOH (6 eq) in THF and H_2O for 1 h at 0 °C to obtain **1**. To isolate **1** the reaction mixture was acidified to pH 4 with aq. HCl and the solvents removed *in vacuo*. After concentration of the residue from H_2O several times, the product was then purified by SiO_2 flash chromatography with 6:1 CH_2Cl_2/MeOH as eluent. Reverse-phase chromatography on a C(18)-column with H_2O as eluent then led to **1** as a hygroscopic gum.

Since the ^1H NMR spectrum for **1** has not been reported, we elected to convert synthetic **1** into the known DNP derivative **15**,[8] for which ^1H NMR data and other physical constants have been published.[1b] Compound **15** prepared by us had a 400 MHz ^1H NMR spectrum in DMSO-d_6 that was fully consistent with the data reported for **15** by Hassall.[1b] Our totally synthetic sample of **15** also gave rise to an $(M+H)^+$ ion at *m/e* 313.0774 in its high resolution mass spectrum.

Delighted at having secured the *first* enantiospecific total synthesis of **1**, we next set out to prepare the partially-protected derivatives **16** and **17** (see Scheme 4). We also investigated the chlorination of **18** with Ph_3P (1.5 eq) in an excess of CCl_4 and MeCN (1:1) at r.t. (Scheme 4). In addition to **19**, an elimination product was

Scheme 4

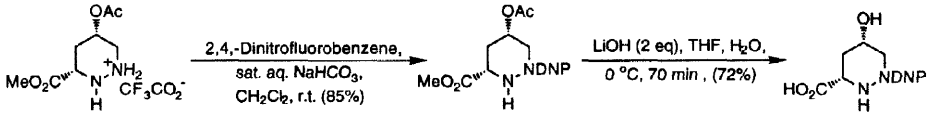


encountered in this reaction, although its precise structure still awaits determination. Clearly, the aforementioned chlorination protocol may prove useful for an eventual synthesis of (3*R*,5*S*)-5-chloropiperazic acid, which like **1**, is a key constituent of monamycins G_1 to I. Further details of the synthetic chemistry described in this Letter will be given in our full account.[9]

Acknowledgements. We thank the EPSRC (GR/L09899), Pfizer, and Zeneca for generous financial support, and the ULIRS MS Service at the London School of Pharmacy for HRMS measurements.

References and Notes

1. (a) K. Bevan, J.S. Davies, C.H. Hassall, R.B. Morton, and D.A.S. Phillips, *J. Chem. Soc. (C)*, **1971**, 514; (b) C.H. Hassall, Y. Ogihara, and W.A. Thomas, *J. Chem. Soc. (C)*, **1971**, 522; (c) C.H. Hassall, R.B. Morton, Y. Ogihara, and D.A.S. Phillips, *J. Chem. Soc. (C)*, **1971**, 526; (d) C.H. Hassall, W.A. Thomas, and (in part) M.C. Moschidis, *J.C.S. Perkin Trans. 1*, **1977**, 2369.
2. C.H. Hassall and K.L. Ramachandran, *Heterocycles*, **1977**, *7*, 119.
3. K.J. Hale, J. Cai, V. Delisser, S. Manaviazar, S.A. Peak, G.S. Bhatia, T.C. Collins, and (in part) N. Jogiya, *Tetrahedron*, **1996**, 52, 1047.
4. U. Peters, W. Bankova, and P. Welzel, *Tetrahedron*, **1987**, *43*, 3803.
5. C.A. Broka and J. Ehler, *Tetrahedron Lett.*, **1991**, *32*, 5907.
6. M.A. Blanchette, W. Choy, J.T. Davis, A.P. Essenfield, S. Masamune, W.R. Roush, and T. Sakai, *Tetrahedron Lett.*, **1984**, *25*, 2183.
7. D.A. Evans, T.C. Britton, R.L. Dorow, and J.F. Dellaria, *Tetrahedron*, **1988**, *44*, 5525.
8. Crude **14** has also been converted to **15** as shown below. The product is best purified on a C(18)-column, eluting with 2:1 H_2O/MeOH to remove impurities, and 4:1 MeOH/H_2O going to 15:1 MeOH/H_2O to obtain **15** as a golden solid: m.p. 188-190 °C; $[\alpha]_D$ -245 ° (*c*. 0.04 Me_2CO), Lit.[1b] $[\alpha]_D$ -240 ° (*c*. 0.15 Me_2CO).



(14) (20) (15)

9. All new compounds gave satisfactory IR, 400 MHz ^1H and 100 MHz ^{13}C spectra, as well as HRMS and/or combustion microanalytical data. Selected data: **(15)** 100 MHz ^{13}C NMR (CD_3OD) (shifts relative to MeOH septet at δ 49.0) δ 173.9, 148.8, 139.9, 139.2, 128.2, 122.9, 116.5, 65.7, 57.6, 54.1, 38.3, 400 MHz ^1H NMR (DMSO-d_6) (shifts relative to Me_2SO quintet at δ 2.49) δ 8.31 (d, *J* = 2.7 Hz, H-3'), 8.17 (dd, *J* = 2.7, 9.5 Hz, H-5'), 7.19 (d, *J* = 9.5 Hz, H-6'), 5.06 (d, *J* = 11.8 Hz, NH), 3.95 (dd, *J* = 4.7, 11.8 Hz, H-6eq), 3.73 (m, H-5), 3.31 (m, H-3), 2.79 (apparent t, *J* = 11.0 Hz, H-6ax), 2.18 (m, H-4eq), 1.29 (apparent dd, H-4ax) [Hassall's values and assignments for **(15)**[1b] 100 MHz ^1H NMR (DMSO-d_6) δ 8.30 (H-3'), 8.17 (H-5'), 7.20 (H-6'), 5.02 (NH, *J* = 12 Hz), 3.88 (H-5), 3.70 (H-6eq), 3.34 (H-3), 2.80 (H-6ax), 2.19 (H-4eq), 1.30 (H-4ax)]; **(1)** 400 MHz ^1H NMR (D_2O) (shifts relative to TSP at δ 0 and HOD at δ 4.79; sample pre-exchanged with D_2O) δ 3.81 (m, H-5), 3.39 (m, H-3), 3.12 (m, H-6), 2.51 (m, H-6), 2.33 (m, H-4eq), 1.46 (m, H-4ax); **(20)** 400 MHz ^1H NMR ($CDCl_3$) δ 8.39 (d, *J* = 2.6 Hz, H-3'), 8.20 (dd, *J* = 2.6, 9.3 Hz, H-5'), 7.02 (d, *J* = 9.3 Hz, H-6'), 5.03 (m, H-5), 4.07 (dd, *J* = 4.5, 12.4 Hz, H-6eq), 3.79 (d, *J* = 11.2 Hz, NH), 3.70 (m, H-3), 3.70 (s, 3H, OMe), 3.02 (m, H-6ax), 2.41 (m, H-4eq), 2.07 (s, 3H, OAc), 1.69 (apparent dd, H-4ax); **(16)** $[\alpha]_D$ +18.5 ° (*c*. 0.2, CH_2Cl_2), 400 MHz ^1H NMR at 100 °C (DMSO-d_6) δ 7.35-7.24 (m, 10H), 5.10 (s, 2H), 4.88 (d, *J* = 8.4 Hz, 1H), 4.55 (s, 2H), 4.09 (m, 1H), 3.65 (s, 3H), 3.64-3.48 (m, 2H), 2.95 (m, 1H), 2.31 (m, 1H), 1.57 (m, 1H); **(2)** 400 MHz ^1H NMR ($CDCl_3$) δ 7.33-7.06 (complex m), 5.84 (br), 4.71 (d, *J* = 10.1 Hz), 4.63 (br d, *J* = 14.0 Hz), 4.54-4.28 (very br m), 4.23 (d, *J* = 10.1 Hz), 4.06-3.87 (complex br m), 3.78 (br), 3.70 (br s), 3.53-3.38 (very br m), 3.34 (br d, *J* = 13.5 Hz), 2.90 (br d), 2.58 (br m), 2.21 (br d), 2.07 (br), 1.57 (large s), 1.52 (small s), 1.49 (large s), 1.47 (small s), 1.43 (small s); **(4)** 100 MHz ^{13}C NMR ($CDCl_3$) δ 172.7, 153.4, 137.8, 135.2, 129.3, 128.9, 128.4, 127.8, 127.3, 77.2, 71.8, 66.1, 55.1, 37.8, 34.1, 31.3, 27.9; **(5)** 100 MHz ^{13}C NMR ($CDCl_3$) δ 164.5, 153.2, 147.5, 138.0, 135.6, 135.3, 133.2, 129.7, 129.4, 129.0, 128.4, 127.8, 127.7, 127.6, 127.3, 122.2, 79.2, 71.6, 66.1, 66.0, 55.3, 37.8, 26.8, 19.2.