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Tetrahedron Letters 46 (2005) 3327–3330
Tetrahedron Letters

An efficient stereoselective synthesis of (3*S*,4*R*)-4-(hydroxymethyl)pyrrolidin-3-ol from (*S*)-diethylmalate

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Received 16 February 2005; revised 14 March 2005; accepted 15 March 2005
Available online 2 April 2005

Abstract—A concise stereoselective synthesis of an imino sugar, (3*S*,4*R*)-4-(hydroxymethyl)pyrrolidin-3-ol from (*S*)-diethylmalate has been developed in five steps and in overall yield of 28%.

Hydroxy pyrrolidines, also known as imino sugars, are known to have an inhibitory effect on certain enzymes[1–3] and glial GABA uptake.[4] The use of these imino sugars as building blocks for the synthesis of some compounds having antibacterial activity is well documented.[5,6] The very first aza *C*-nucleoside incorporating imino sugar was reported by Sorensen et al.[3] Recently, some highly potent purine nucleoside phosphorylase (PNP) inhibitors (**1a**–**c**, Chart 1) have been reported based upon imino sugars.[7–12] One of these PNP inhibitors, BCX-1777 (**1a**), is one of our clinical candidates for T-cell- and B-cell-mediated malignancies. Another clinical candidate, BCX-4208 (**2**, Chart 1), has evolved from the second generation of PNP inhibitors, where (3*R*,4*R*)-4-(hydroxymethyl)pyrrolidin-3-ol (**3**) is the precursor for its preparation.[13,14]

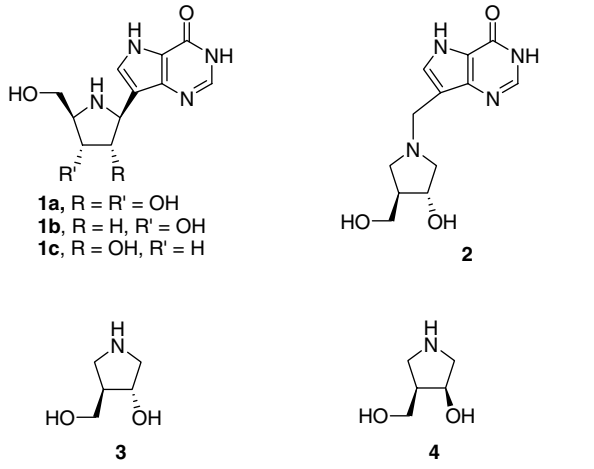

Chart 1.

The very first synthesis of **3** was reported by Jaeger and Biel[15] from *N*-benzylglycinate and ethyl acrylate. This compound was obtained as a mixture of *cis*/*trans*-isomers. The synthesis of the *trans*-racemic compound was first reported by Makino and Ichikawa[16] starting from fumaric acid dimethylester. The pure enantiomer of the *trans*-isomer, (3*R*,4*R*)-4-(hydroxymethyl)pyrrolidin-3-ol (**3**), was prepared by Filichev from glucose and xylose involving a 14–15-step synthesis.[17,18] A shorter synthesis of this isomer was achieved by Karlsson and Hogberg[19,20] via asymmetric 1,3-dipolar cycloaddition using camphor sultam as a chiral auxiliary. This synthesis was recently modified by us[21] and adapted to a practical large-scale preparation of the desired *trans*-isomer, which was used for the preparation of kilo quantities of our clinical candidate, BCX-4208.

We are now interested in the preparation of the optically pure *cis*-isomer of 4-(hydroxymethyl)pyrrolidin-3-ol (**4**), which has been used for the preparation of one of the isomers of BCX-4208 (**2**), and it could also become the precursor for other bioactive molecules. A literature search revealed only one reference for the preparation of the *cis*-isomer starting from D-xylose in 12 steps.[22] We envisioned the synthesis of this compound from diethylmalate, in which the hydroxyl group is already present; hydroxymethyl could be introduced stereoselectively at the active methylene position; and

Keywords: Diethylmalate; Imino sugar.
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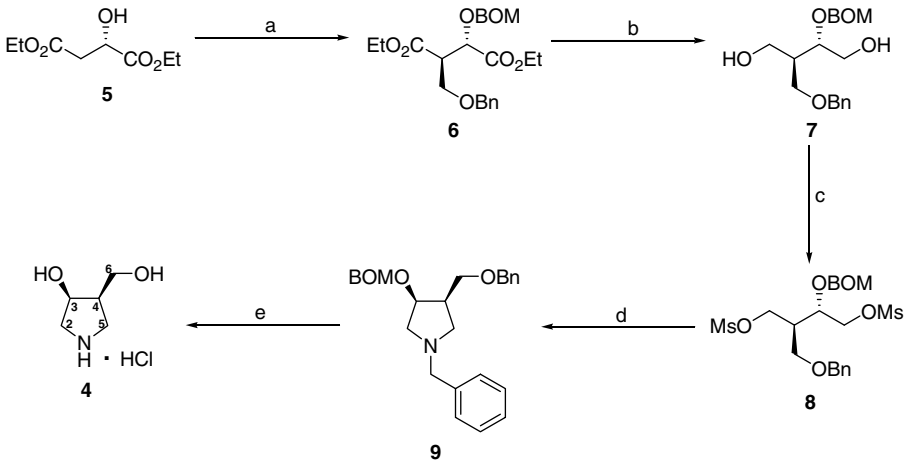
0040-4039/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2005.03.077



Scheme 1. Reagents and conditions: (a) LDA, $ClCH_2OCH_2Ph$, HMPA, THF, −78 °C to rt; (b) $LiAlH_4$, Et_2O; (c) MsCl, pyridine; (d) $BnNH_2$, 60 °C; (e) H_2, Pd/C (10%), HCl.

the diester groups would give dialcohol on reduction and the cyclization of dialcohol with amine through mesylate would result in the desired imino sugar. The search of the literature showed that diethylmalate has been used for the introduction of hydroxymethyl functionality by Kinoshita and co-workers[23] for the preparation of one natural product and the reported synthesis in this paper has indeed given the isomer we needed for this work.

(*S*)-Diethylmalate (**5**) (Scheme 1) was obtained from commercially available (*S*)-malic acid as reported in the literature[24] through acid catalyzed esterification with ethanol. The chemical and the optical purity were compared with literature [^{1}H NMR and optical rotation $[\alpha]_D^{25}$ −15.53 (*c* 12.08, acetone), lit.[24] $[\alpha]_D^{25}$ 15.12 (*c* 5.65, acetone)]. (*S*)-Diethylmalate was subjected to alkylation under the same conditions as reported by Kinoshita and co-workers. The alkylation was done with 3.0 equiv of benzyl chloromethyl ether (BOM–Cl) in THF using 2.2 equiv of freshly prepared LDA as base at −78 °C. The reaction resulted into exclusive formation of one isomer, which was characterized as diethyl (2*S*,3*R*)-3-benzyloxymethyl-2-benzyloxymethoxysuccinate (**6**).[25] The characterization was based upon Kinoshita and co-workers report[23] (experimental details and ^{1}H NMR data were obtained from Kinoshita), where this compound was used for the preparation of a natural product. The desired compound **6** was isolated in 69% yield (lit.[23] 70% in the provided experimental details) after chromatographic purification. It appears that the reaction is very stereospecific, since we did not isolate any product corresponding to other isomer. The only other product isolated was nonalkylated diethyl (2*S*)-2-benzyloxymethoxysuccinate in 16.5% yield. Reduction of **6** was achieved with 2.0 equiv of LAH in THF at reflux temperature and dialcohol **7** was obtained in 76% yield with complete retention of stereochemistry.[26] Since methanesulfonyloxy groups have been successfully used for the formation of pyrrolidine ring through the reaction with benzylamine, we chose the same group for our synthesis. Therefore, dialcohol **7** was reacted with 3.0 equiv of methanesulfonyl chloride in pyridine at 0 °C for 1 h to furnish dimesylated product **8** in 62% isolated yield.[27] Cyclization of dimesyl derivative **8** was accomplished in excess of benzylamine at 60 °C, yielding 88% isolated pyrrolidine **9**.[28] Hydrogenolysis of the benzyl derivative **9** was done in the presence of 10% Pd/C in ethanol at 70 psi using 2.0 equiv of concd HCl, which resulted into quantitative yield of debenzylated product **4** as hydrochloride.[29] The structure of **4** was confirmed by NOE experiments. Since compound **4** is reported in the literature as *p*-nitrobenzoate, we decided to convert hydrochloride into *p*-nitrobenzoate by first making it as free base then reacting with an equivalent amount of *p*-nitrobenzoic acid.[30] Again, the structure was confirmed by NOE experiments and the optical purity was compared with literature reports $[\alpha]_D^{25}$ −12.8 (*c* 0.62, methanol), lit.[22] $[\alpha]_D^{25}$ −10.2 (*c* 0.6, methanol). ^{1}H NMR, ^{13}C NMR, and mp are comparable to the literature report.

In conclusion, we have developed a short and efficient synthesis of (3*S*,4*R*)-4-(hydroxymethyl)pyrrolidin-3-ol, which could be a valuable starting material for bioactive molecules.

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25. Compound **6**: To a solution of diisopropylamine (9.05 mL, 64.6 mmol) in THF (100 mL) was added dropwise *n*-BuLi (1.6 M in hexanes, 36.5 mL, 58.3 mmol) at 0 °C over a period of 10 min under nitrogen atmosphere. The LDA formed was stirred further at 0 °C for 30 min and cooled to −78 °C and to this was added dropwise (*S*)-diethyl malate (5.04 g, 26.5 mmol, $[\alpha]_D^{25}$ −15.53 (*c* 12.08, acetone) over a period of 10 min. The reaction mixture was further stirred at −78 °C for 30 min and warmed to −20 °C and maintained at −20 °C for 1 h. After cooling to −78 °C again, BOM–Cl (11 mL, 79.5 mmol) was added over a period of 10 min and was stirred at this temperature for 6 h and at room temperature for 24 h. The reaction mixture was quenched with glacial acetic acid (7.5 mL) in ether (10 mL) and poured into 100 mL water. The mixture was extracted with ether (4 × 100 mL) and the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated to furnish oily residue. Purification of the crude by flash column chromatography (300 g, silica gel) eluting with ethyl acetate in hexanes (0–30%) furnished 7.92 g (69%) of **6** as an oil; ^{1}H NMR (DMSO-d_6): δ 7.37–7.23 (m, 10H), 4.76 (s, 2H), 4.54 (s, 2H), 4.46–4.45 (m, 3H), 4.13–4.01 (m, 4H), 3.74–3.58 (m, 2H), 3.17 (dd, *J* = 7 and 12 Hz, 1H), 1.16 (t, *J* = 7 Hz, 3H), 1.15 (t, *J* = 7 Hz, 3H); IR (KBr) 3019, 2901, 1735, 1455, 1374, 1215, 1040 cm^{-1}; MS (ES$^+$) 453.39 [100% (M+Na)$^+$]. Anal. ($C_{24}H_{30}O_7$) C, H. $[\alpha]_D^{25}$ −38.15 (*c* 1.28, acetone).
26. Compound **7**: A solution of **6**[23] (9 g, 21.12 mmol) in THF (20 mL) was added to a mixture of LAH (1.61 g, 42.23 mmol) in THF (20 mL) at 0 °C over a period of 30 min. The reaction mixture was heated at reflux for 4 h and quenched by drop-wise addition of water (3 mL) after cooling to 0 °C. The reaction mixture was filtered through a pad of Celite and $MgSO_4$ and the cake washed with 1000 mL ethyl acetate. The filtrate was concentrated under vacuum and the residue purified by flash column chromatography (275 g silica gel, eluting with 0–25% chloroform–methanol–ammonium hydroxide [80:18:2] in chloroform) to furnish 5.56 g (76%) of **7** as an oil; ^{1}H NMR ($CDCl_3$): δ 7.41–7.29 (m, 10H), 4.89 (d, *J* = 7.0 Hz, 1H), 4.77 (d, *J* = 7.0 Hz, 1H), 4.72–4.59 (dd, *J* = 12.0 and 25.0 Hz, 2H), 4.50 (s, 2H), 3.92–3.85 (m, 1H), 3.81–3.78 (d, *J* = 4.5 Hz, 2H), 3.75 (br s, 1H), 3.67 (d, *J* = 5.0 Hz, 1H), 3.62 (d, *J* = 6.0 Hz, 2H), 3.16 (br s, 1H), 2.76 (br s, 1H), 2.12–2.03 (m, 1H); IR (KBr): 3432, 3014, 2886, 1454, 1365, 1216, 1026 cm^{-1}; MS (ES$^+$) 369.41 [(M+Na)$^+$]. Anal. ($C_{20}H_{26}O_5 \cdot 0.25H_2O$) C, H. $[\alpha]_D^{25}$ −7.5 (*c* 1.45, acetone).
27. Compound **8**: Compound **7** (10.5 g, 30.3 mmol) was added to a solution of methanesulfonyl chloride (7 mL, 90.9 mmol) in pyridine (30 mL) at 0 °C over a period of 1 h and allowed to warm to room temperature overnight. The reaction mixture was concentrated under vacuum and to the residue added 0.5 N aqueous HCl (100 mL) and ether (100 mL). The organic layer was separated and washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash column chromatography (400 g silica gel, eluting with 0–50% ethyl acetate in hexanes) to furnish 9.45 g (62%) of **8** as an oil; ^{1}H NMR (DMSO-d_6): δ 7.36–7.28 (m, 10H), 4.82 (q, *J* = 7.0 Hz, 2H), 4.59 (dd, *J* = 12.0 and 16.0 Hz, 2H), 4.47 (s, 2H), 4.45–4.37 (m, 2H), 4.31–4.24 (m, 2H), 4.02 (m, 1H), 3.55 (d, *J* = 5.0 Hz, 2H), 3.16 (s, 6H), 2.14–2.31 (m, 1H); IR (KBr): 3546, 3026, 2940, 2881, 1734, 1455, 1360 cm^{-1}; MS (ES$^+$) 525.31 [(M+Na)$^+$]. Anal. ($C_{22}H_{30}O_9S_2$) C, H. $[\alpha]_D^{25}$ −4.37 (*c* 1.15, ethanol).
28. Compound **9**: A mixture of **8** (8.78 g, 17.5 mmol) and benzylamine (90 mL) was heated at 60 °C for 16 h. The reaction mixture was concentrated to remove most of benzyl amine and to the residue added ethyl acetate (100 mL) and hexanes (100 mL). The mixture was filtered to remove solids and the filtrate concentrated. The residue was purified by flash column chromatography (250 g silica gel, eluting with 0–50% ethyl acetate in hexanes) to furnish 6.41 g (88%) of **9** as an oil: ^{1}H NMR ($CDCl_3$): δ 7.24–7.26 (m, 15H), 4.73 (q, *J* = 7.0 Hz, 2H), 4.54 (dd, *J* = 12.0 and 17.0 Hz, 2H), 4.50 (s, 2H), 4.34 (m, 1H), 3.75–3.58 (m, 3H), 3.50 (dd, *J* = 7.5 and 9.0 Hz, 1H), 2.99 (dd, *J* = 5.5 and 10.0 Hz, 1H), 2.86 (dd, *J* = 7.0 and 8.0 Hz, 1H), 2.58 (m, 2H), 2.46 (t, *J* = 9.0 Hz, 1H); IR (KBr): 3013, 2942, 2864, 2797, 1495, 1454 cm^{-1}; MS (ES$^+$) 418.41 [M+1]. Anal. ($C_{27}H_{31}NO_3$) C, H, N. $[\alpha]_D^{25}$ −8.6 (*c* 1.17, ethanol).
29. Compound **4** as hydrochloride: To a mixture of **9** (1.04 g, 2.5 mmol) and Pd/C (10%, 1 g) in ethanol (25 mL) was added concd HCl (0.41 mL, 5 mmol) and hydrogenated at 70 psi for 4 days. The reaction mixture was filtered through Celite to remove catalyst and concentrated under vacuum to dryness to furnish 0.38 g (100%) of **4** as a semisolid. An analytical sample was prepared by crystallization from ethanol/ether to furnish **4** as a white solid: mp 94–96 °C; ^{1}H NMR (DMSO-d_6): δ 9.21 (br s, 2H, NH_2^+), 5.39 (d, *J* = 4.0 Hz, 1H, 3-OH), 4.72 (t, *J* = 5.0 Hz, 1H, 6-OH), 4.26 (dd, *J* = 7.5 and 3.5 Hz, 1H, H-3), 3.65–3.55 (m, 1H, H-6), 3.48–3.38 (m, 1H, H-6), 3.29–3.12 (m, 2H, H-2α, H-5α), 3.04 (d, *J* = 12.0 Hz, 1H, H-2β), 2.84 (t, *J* = 11.0 Hz, 1H, H-5β), 2.29–2.12 (m, 1H, H-4); ^{13}CNMR (DMSO-d_6): δ 45.59, 46.35, 53.02, 58.33, 69.03; IR (KBr) 3370, 3012, 2921, 1590, 1398, 1317 cm^{-1}; MS (ES$^+$) 118.72 [M+1]. Anal. ($C_5H_{11}NO_2 \cdot HCl$) C, H, N. $[\alpha]_D^{25}$ −19.8 (*c* 0.61, methanol).

30. Compound **4** as *p*-nitrobenzoate: A solution of **4** hydrochloride (85 mg, 0.56 mmol) in water (3 mL) was loaded on a ion exchange resin (IR-120, H^+, 8 mL) and washed with water (80 mL) followed by concd ammonium hydroxide (50 mL). The relevant fractions were pooled and concentrated under vacuum to furnish 0.038 g (0.35 mmol) of free base of **4**. The free base was dissolved in ethanol (1 mL) and to this added an ethanolic solution of *p*-nitrobenzoic acid (0.04 N, 8.75 mL, 0.35 mmol) and concentrated under vacuum to dryness. The residue was crystallized from ethanol/ether to furnish 0.04 g of *p*-nitrobenzoate **4** as a white solid: mp 158 °C (lit.[22] mp 147–148 °C); ^{1}H NMR (D_2O): δ 8.14 (d, J = 8.8 Hz, 2H, aromatic), 7.84 (d, J = 8.8 Hz, 2H, aromatic), 4.45 (t, J = 3.4 Hz, 1H, H-3), 3.70 (dd, J = 11.3 and 7.4 Hz, 1H, H-6), 3.61 (dd, J = 11.3 and 7.4 Hz, 1H, H-6), 3.40 (dd, J = 11.7 and 8.7 Hz, 1H, H-5α), 3.30 (dd, J = 12.7 and 3.5 Hz, 1H, H-2α), 3.24 (d, J = 13.0 Hz, 1H, H-2β), 3.03 (t, J = 11.5 Hz, 1H, H-5β), 2.41 (m, 1H, H-4); ^{13}C NMR (D_2O): δ 45.28, 45.91, 53.77, 58.70, 69.78, 123.83, 129.90, 143.08, 149.24, 173.98; IR (KBr) 3453, 3391, 3291, 2951, 1644, 1589, 1511, 1388 cm^{-1}; MS (ES^+) 118.69 [M+1]. Anal. ($C_{12}H_{16}N_2O_6$) C, H, N. $[\alpha]_D^{25}$ −12.8 (*c* 0.62, methanol), lit.[22] $[\alpha]_D^{25}$ −10.2 (*c* 0.6, methanol).