Tetrahedron: *Asymmetry* 19 (2008) 2330–2333

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

An efficient synthesis of (*R*)- and (*S*)-2-(aminomethyl)piperidine dihydrochloride

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ARTICLE INFO

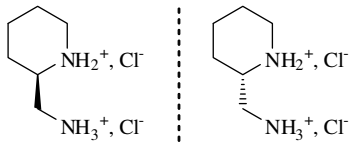
Article history:
Received 10 September 2008
Accepted 17 September 2008
Available online 22 October 2008

ABSTRACT

The synthesis of the dihydrochloride salts of (*R*)-**1** and (*S*)-**1** 2-(aminomethyl)piperidine is reported starting from either (*S*) or (*R*) lysine, respectively. A key step in the synthetic protocol involves the in situ formation of aziridinium **8**, which then undergoes an intramolecular ring opening with concomitant piperidinium ring formation, in a stereoselective manner. The route offers a practical synthesis of (*R*)-**1** and (*S*)-**1**, and it should make them more accessible for exploration in asymmetric catalysis or as building blocks in pharmaceutical research.

1. Introduction

Chiral diamines form an important class of compounds that have found a wide range of applications in chemistry, particularly as bidentate ligands for the design of asymmetric catalysts.[1,2] The enantiomers of 2-(aminomethyl)piperidine (*R*)-**1** and (*S*)-**1** are attractive structural motifs; however, they have not been widely used in the design of chiral ligands, most probably, due to their limited availability.[3,4] Indeed, (*R*)-**1** and (*S*)-**1** are not commercially available, although these enantiomers have been prepared by the resolution of the racemate,[4] or from the enantiomers of pipecolic acid by a sequential amidation and reduction protocol.[5,6] These methods do not constitute a practical route to (*R*)-**1** and (*S*)-**1** in reasonable quantities, and consequently the exploration of these stereoisomers in bidentate ligand design has been limited. Beyond asymmetric catalysis, enantiopure amines continue to find an important role as building blocks in pharmaceutical development, and a ready source of (*R*)-**1** and (*S*)-**1** would also contribute to that activity (see Fig. 1).[7,8]



(*R*)-**1** (*S*)-**1**

Figure 1. (*R*)- and (*S*)-2-(aminomethyl)piperidine dihydrochloride.

2. Results and discussion

Herein, we report an efficient synthesis of the enantiomers of 2-(aminomethyl)piperidine dihydrochloride (*R*)-**1** and (*S*)-**1** from the amino acids (*S*)-L- and (*R*)-D-lysine (see Scheme 1).

(*S*)-L-Lysine monohydrochloride (*S*)-**2** was perbenzylated by treatment with benzyl bromide in ethanol using K_2CO_3 as a base, following the protocol of Beaulieu and Wernic.[9] This resulted in an efficient conversion to the pentabenzyl amino acid derivative (*S*)-**3** in almost quantitative yield. Reduction of (*S*)-**3** with $LiAlH_4$ gave the corresponding alcohol (*S*)-**4** in 89% yield. With (*S*)-**4** in hand, two routes to the 1,1-dibenzyl-2-((dibenzylamino)methyl)-piperidinium chloride **5** were explored. The first attempt involved the use of fluorinating reagent Et_2NSF_3 (DAST). It is known that the treatment of *N*,*N*-dibenzyl-α-aminoalcohols with DAST produces an aziridinium intermediate in situ, which then undergoes ring opening by fluoride ion attack (paths b and c) to predominantly form the most substituted alkyl fluorine (path b).[10] In our case, (Scheme 2), it was anticipated that the peripheral dibenzylamine moiety of (*S*)-**4** would compete with the fluoride ions to open the aziridinium intermediate (*S*)-**8** by a 6-*exo*-*tet* ring closure process (path a) to produce piperidinium (*R*)-**5**. It was also expected that the stereochemical course of aziridinium ring opening (paths a and b) would occur with an inversion of configuration as illustrated in Scheme 2.

The DAST reaction at room temperature gave a mixture of compounds **5**, **6** and **7** in a ratio of 83:15:2, but with a moderate overall conversion. When silica gel (SiO_2) was added as a suspension in DCM to the reaction mixture (SiO_2–DAST, 6.0:1.5 equiv), the conversion to piperidinium **5** increased to 80% with only very minor traces of the fluorinated products **6** and **7**. The silica is clearly sequestering fluoride ions from solution, and is rendering the reaction cleaner and more efficient overall. Other reagents were then

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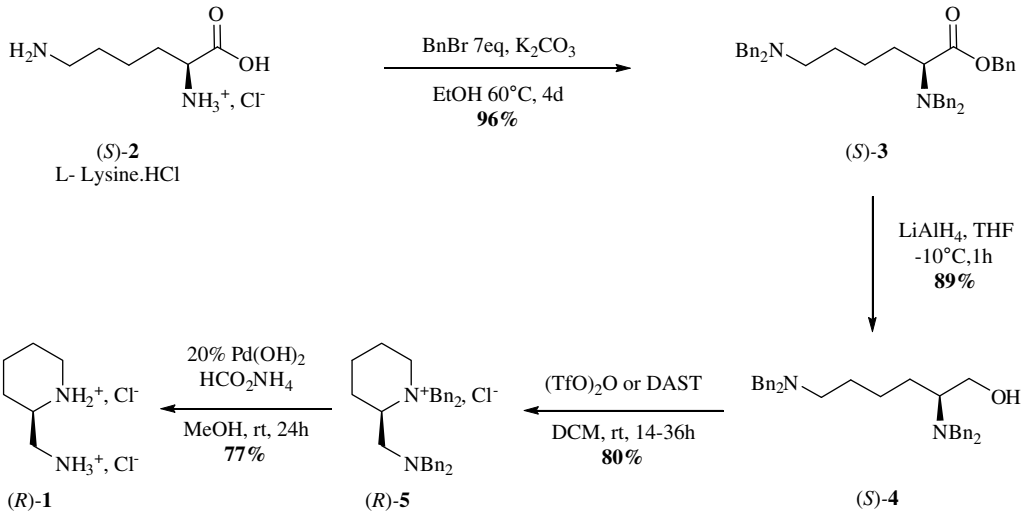
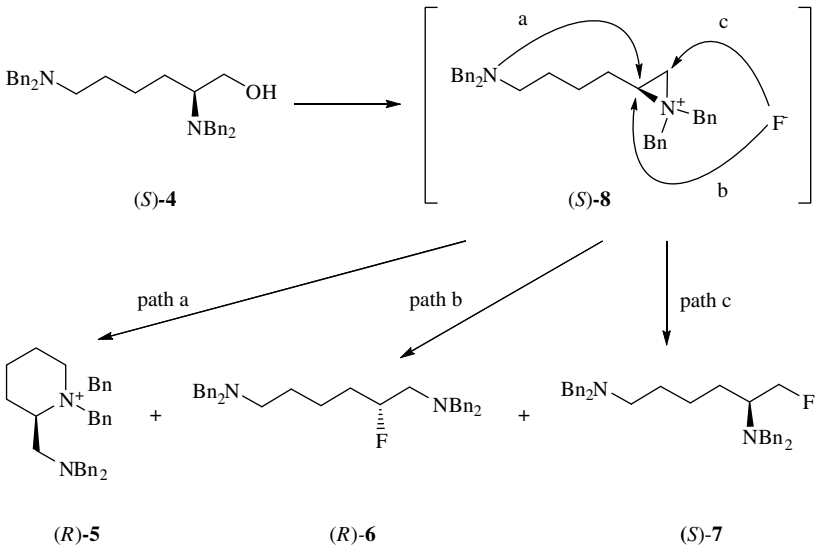
doi:10.1016/j.tetasy.2008.09.015



Scheme 1. The synthetic route from (*S*)-L-lysine (*S*)-**2** to (*R*)-**1**.



Scheme 2. Reaction pathways on treatment of (*S*)-**4** with DAST.

investigated to promote the activation of the primary alcohol **4**, and Ms_2O, MsCl and Tf_2O were all explored. Such reagents had previously been used to generate aziridinium rings from *N*,*N*-dibenzyl-α-aminoalcohols.[11] Reactions involving Ms_2O/Et_3N (1.5 equiv) and MsCl failed; however treatment with triflic anhydride (Tf_2O) promoted an efficient cyclisation and generated piperidine (*R*)-**5** in a good 88% yield. It appears from our experiments that DAST and particularly Tf_2O are suitable reagents to promote the conversion of (*S*)-**4** to (*R*)-**5**. Several attempts at debenzylation with hydrogen using 10% Pd/C at high pressure (30 bar/2 d) gave only poor results, however, a transfer hydrogenation using ammonium formate (5 equiv) with 20% $Pd(OH)_2$ as the catalyst gave piperidine (*R*)-**1** in good yield. The stereochemistry of this process was unambiguously established by X-ray structure analysis of the debenzylated product (*R*)-**1** after hydrogenation (Fig. 2). Samples of each enantiomer of **1** were prepared starting with the appropriate enantiomer of the amino acid lysine. Enantiopurity was established by titration of racemic and enantiopure samples of **1** with (*S*)-*O*-methylmandelic acid. In the case of racemic **1**, the 1:1 ratio of the diastereoisomeric salts was easily resolvable and observed in solution by ^1H NMR (400 MHz, [$^2H_4$]-MeOD), whereas no such signal resolution was observed in the case of the enantiopure material. This method allowed us to be confident of an enantiopurity of >95% ee.

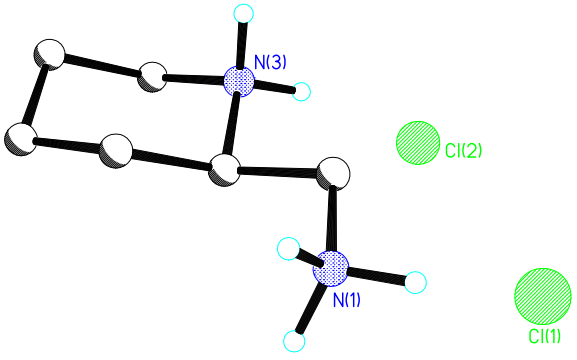


Figure 2. X-ray structure determination of (*R*)-**1** was used to assign absolute configuration.

Crystal data for (*R*)-**1** $C_6H_{16}Cl_2N_2$, $M = 187.11$, Monoclinic, space group *P*2(1), $a = 7.036(2)$, $b = 9.112(2)$, $c = 7.702(2)$ Å,

$\beta = 106.010(7)°$, $V = 474.6(2)$ Å^3, $F(000) = 200$, $Z = 2$, $D_c = 1.309$ Mg m^{-3}, $\mu = 0.621$ mm^{-1} (Mo Kα, $\lambda = 0.71073$ Å). The data were collected at $T = 93(2)$ K, 3060 reflections ($2.75 < \theta < 25.35°$) were measured on a Rigaku Saturn 92 detector with 007 generator yielding 1638 unique data ($R_{merg} = 0.0170$). Conventional $R = 0.0194$ for 1638 reflections with $I > 2\sigma$, GOF = 1.053; 112 refined parameters, Flack parameter = 0.00(5). The largest peak in the residual map is 0.156 e Å^{-3}. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 701754.

3. Conclusion

In conclusion, we have described a straightforward four step synthesis of (*R*)-**1** and (*S*)-**1** 2-(aminomethyl)piperidine·HCl from either D- or L-lysine. The key step involves the cyclisation of **4** via the aziridinium intermediate **8**. The overall yield of **1** from lysine is 53%, and this should allow (*R*)-**1** and (*S*)-**1** to be prepared on a sufficient scale for consideration as building blocks for the development of ligands for catalysis or for their inclusion in novel bioactive discovery in pharmaceuticals research.

4. Experimental

4.1. General

All reagents were of synthetic grade, and used without further purification. Solvents were dried on a M Braun SPS-800 column system. All moisture-sensitive reactions were carried out under a positive pressure of nitrogen in oven-dried glassware (140 °C). Column chromatography was performed using silica gel 60 (40–63 μm) from Apollo Scientific Ltd. GC–MS analyses were obtained using an Agilent 5890 gas chromatograph equipped with an Agilent 5973N mass-selective detector. High-resolution mass spectrometry was performed on a Waters LCT or GCT time-of-flight mass spectrometer. NMR spectra were recorded on either Bruker AV-300 (^{1}H at 300.06 MHz, ^{13}C at 75.45 MHz, ^{19}F at 282.34 MHz), or Bruker AV-400 (^{1}H at 400 MHz, ^{13}C at 100 MHz), or Bruker AV-500 (^{1}H at 499.90 MHz, ^{19}F at 470.33 MHz). Chemical shifts δ are reported in parts per million (ppm), and quoted relative to internal standard Me_4Si for ^{1}H and ^{13}C NMR and to external standard $CFCl_3$ for ^{19}F NMR. ^{1}H, ^{13}C and ^{19}F NMR data were assigned on a routine basis by a combination of one- and two-dimensional experiments (COSY, HSQC, HMBC, NOESY). Melting points were measured using a GallenKamp Griffin MPA350·BM2.5 melting point apparatus, and are uncorrected. Optical rotations were determined using a Perkin Elmer Model 341 polarimeter. $[\alpha]_D^{20}$ values are measured at 589 nm and given in 10^{-1} deg cm^2 g^{-1}. Elemental analyses were carried out on a CE instrument EA 1110 CHNS analyser. IR spectra were recorded on a Perkin Elmer Spectrum GX FT-IR system as KBr disc or as thin film on NaCl plates.

4.2. (*S*)-Benzyl 2,6-bis(dibenzylamino)hexanoate (*S*)-3

Anhydrous K_2CO_3 (242.14 g, 1.752 mol) and benzyl bromide (182 mL, 1.53 mol) were added to a solution of (*S*)-L-lysine (40 g, 0.219 mol) in EtOH (400 mL). After stirring at 60 °C for 4 days, the resulting white slurry was filtered over Celite®, and the solids were washed with EtOAc. After evaporation of solvents, the residue was re-dissolved in EtOAc and washed with saturated NaCl solution. EtOAc was removed under reduced pressure, and the residue was distillated (100 °C, 0.01 mbar) to give (*S*)-**3** as a light yellow oil (125.5 g, 96%). $[\alpha]_D^{20} = -46.9$ (*c* 1.6, $CHCl_3$), {lit. $[\alpha]_D^{20} = -52.5$ (*c* 2.8, $CHCl_3$)}; IR (film, cm^{-1}) 3029, 2942, 2798, 1731, 1494, 1454, 1365, 1138, 1028, 969, 745, 698; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17–7.40 (25H, m, Ar–*H*), 5.23 (1H, d, *J* = 12.3 Hz, PhC*H*$_A$H$_B$O), 5.11 (1H, d, *J* = 12.3 Hz, PhCH$_A$*H*$_B$O), 3.89 (2H, d, *J* = 13.9 Hz, 2 × PhC*H*$_A$H$_B$N), 3.49 (2H, d, *J* = 13.9 Hz, 2 × PhCH$_A$*H*$_B$N), 3.42–3.52 (4H, dd, PhC*H*$_2$N′), 3.32 (1H, dd, *J* = 6.2 Hz, *J* = 8.7 Hz, CHN), 2.33 (2H, t, *J* = 6.8 Hz, C*H*$_2$N′), 1.14–1.76 (6H, m, C*H*$_2$); ^{13}C (75 MHz, $CDCl_3$): 172.9 (CO_2), 140.0 (2 × C, Ar), 139.6 (2 × C, Ar), 136.1 (Ar), 128.8 (4 × C, Ar), 128.7 (4 × C, Ar), 128.5 (2 × C, Ar), 128.4 (2 × C, Ar), 128.3 (Ar), 128.2 (4 × C, Ar), 128.1 (4 × C, Ar), 126.9 (2 × C, Ar), 126.7 (2 × C, Ar), 65.8 (PhC*H*$_2$O), 60.6 (*C*HN), 58.2 (2 × PhC*H*$_2$N′), 54.4 (2 × PhCH$_2$ N), 53.0 (*C*H$_2$N′), 29.3 (*C*H$_2$), 26.6 (*C*H$_2$), 23.7 (*C*H$_2$); HRMS (+EI) calcd for $C_{41}H_{45}N_2O_2$ ([MH]$^+$): 597.3481. Found: 597.3477 (−0.6 ppm).

4.3. (*S*)-2,6-Bis(dibenzylamino)hexan-1-ol (*S*)-4

A solution of the benzyl ester **3** (125.5 g, 210 mmol) in THF (600 mL) was added dropwise over 45 min at −10 °C to a suspension of $LiAlH_4$ (11.97 g, 0.315 mmol, 1.5 equiv) in dry THF (300 mL). The mixture was stirred for 3 h at this temperature, and the excess of hydride was quenched by successive addition of EtOAc and 1 M aq NaOH. The mixture was extracted into EtOAc, the organic extracts were combined and the solvent was removed under reduced pressure. The product was distilled (120 °C, 0.01 mbar) to give the aminoalcohol (*S*)-**4** as a viscous clear oil (92.1 g, 89%). $[\alpha]_D^{20} = +49.5$ (*c* 0.8, $CHCl_3$); IR (film, cm^{-1}) 3443, 3027, 2935, 2799, 2360, 1602, 1494, 1453, 1365, 1129, 1028, 747, 698; ^{1}H NMR (300 MHz, $CDCl_3$): 7.19–7.38 (20H, m, Ar–H), 3.75 (2H, d, *J* = 13.3 Hz, PhC*H*$_A$H$_B$N), 3.57 (2H, d, *J* = 13.6 Hz, PhC*H*$_A$H$_B$N′), 3.48 (2H, d, *J* = 13.6 Hz, PhCH$_A$*H*$_B$N′), 3.31–3.45 (2H, m, C*H*$_2$OH), 3.32 (2H, d, *J* = 13.3 Hz, PhCH$_A$*H*$_B$N), 3.14 (1H, br s, *OH*), 2.67–2.77 (1H, m, *C*HN), 2.34–2.47 (2H, m, C*H*$_2$N′), 1.40–1.63 (3H, m), 1.00–1.37 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$): 139.9 (2 × C, Ar), 139.3 (2 × C, Ar), 129.0 (4 × C, Ar), 128.7 (4 × C, Ar), 128.4 (4 × C, Ar), 128.1 (4 × C, Ar), 127.1 (2 × C, Ar), 126.7 (2 × C, Ar), 60.8 (*C*H$_2$OH), 58.9 (*C*HN), 58.4 (2 × PhC*H*$_2$N′), 53.1 (2 × PhCH$_2$ N), 52.8 (*C*H$_2$N′), 27.3 (*C*H$_2$), 24.7 (*C*H$_2$), 24.5 (*C*H$_2$); HRMS (+EI) calcd for $C_{34}H_{41}N_2O$ ([MH]$^+$): 493.3221. Found: 493.3219 (+0.4 ppm).

4.4. (*R*)-1,1-Dibenzyl-2 ((dibenzylamino)methyl)piperidinium chloride (*R*)-5

4.4.1. Cyclisation with DAST

Silica gel (3.46 g, 0.12 mmol) and then DAST (3.8 mL, 28.8 mmol) were added to a solution of (*S*)-**4** (9.45 g, 19.2 mmol) in DCM (200 mL) at 0 °C. The mixture was stirred at 20 °C for 24 h, and the reaction mixture was quenched with saturated NaCl solution, before extraction into DCM. The organic layers were evaporated to dryness to provide a solid amorphous material. The material was resuspended and stirred as a powder in Et_2O to wash off any organic soluble residues. Filtration gave product (*R*)-**5** (7.76 g, 80%) as an off white powder. Mp: 96–97 °C; $[\alpha]_D^{20} = -73.5$ (*c* 1.1, $CHCl_3$); IR (film, cm^{-1}) 2348, 2283, 1187, 1128, 929, 751, 744, 591, 545; ^{1}H NMR (300 MHz, $CDCl_3$): 7.23–7.75 (20H, m, Ar-H), 4.91 (2H, m), 4.27 (1H, d, *J* = 38.5 Hz), 4.23 (1H, d, *J* = 38.8 Hz), 3.72–3.42 (3H, m), 3.21 (1H, m), 2.93 (2H, dd, *J* = 12.7 Hz, *J* = 9.8 Hz), 2.51 (1H, d, *J* = 2.5 Hz), 2.21–2.28 (2H, m), 1.23–1.90 (6H, m, C*H*$_2$); ^{13}C NMR (75 MHz, $CDCl_3$): 138.5 (4 × C, Ar), 133.8 (2 × C, Ar), 133.7 (2 × C, Ar), 130.7 (Ar), 130.5 (Ar), 129.3 (2 × C, Ar), 129.2 (4 × C, Ar), 129.1 (2 × C, Ar), 128.4 (4 × C, Ar), 127.1 (2 × C, Ar), 67.0 (*C*HN), 63.7 (PhCH$_2$ N), 59.0 (2 × PhC*H*$_2$N′), 57.7 (PhC*H*$_2$N), 57.3 (CH$_2$N), 52.7 (C*H*$_2$N′), 25.9 (*C*H$_2$), 22.1 (*C*H$_2$), 20.8 (*C*H$_2$); HRMS (ES+) calcd for $C_{34}H_{39}N_2$ ([M]$^+$): 475.3113. Found: 475.3113 (−0.1 ppm).

4.4.2. Cyclisation with trifluoromethanesulfonic anhydride

At first, Et_3N (0.85 mL, 6.09 mmol) and a catalytic amount of DMAP (50 mg, 0.41 mmol) were added to a solution of (*S*)-**4** (1 g, 2.03 mmol) in DCM (25 mL). The mixture was cooled to 0 °C and the triflic anhydride (0.68 mL, 4.06 mmol) was added. The reaction mixture was stirred for 2 h at 0 °C and at ambient temperature for another 12 h. The reaction was then quenched with saturated NaCl solution and the products were extracted into DCM. The organic extracts were then washed with saturated $NaHCO_3$ solution, dried and evaporated. Resuspension in Et_2O as described above (4.4.1) gave (*R*)-**5** (0.92 g, 88%) as an off-white powder. Spectroscopic analyses were identical to that described in Section 4.4.1.

4.5. (*R*)-2-(Aminomethyl)piperidine dihydrochloride (*R*)-1

Ammonium formate (315.3 mg, 5 mmol) and a suspension of 20% $Pd(OH)_2$ (250 mg) were added to a solution of (*R*)-**5a** (510 mg, 1 mmol) in MeOH (25 mL). The mixture was stirred for 24 h at ambient temperature. The black suspension was then filtered through Celite®, and 1 M HCl in Et_2O (4 mL) was added to the filtrate. Solvents were removed under reduced pressure and the crude product was re-crystallised from MeOH/Et_2O to yield (*R*)-2-(aminomethyl)-piperidine dihydrochloride **1** (144 mg, 77%) as a colourless crystalline solid.

Mp: 213–215 °C; $[\alpha]_D^{20} = +2.3$ (*c* 1.4, MeOH); IR (KBr, cm^{-1}) 3416, 2955 (br), 2842 (br), 1584, 1514, 1484, 1476, 1440, 1407, 1133, 1022, 1008; ^1H NMR (300 MHz, CD_3OD): 4.77 (5 H, s, 5 × N*H*), 3.38–3.48 (1H, m, C*H*N), 3.34–3.42 (1H, m, CH_AH_BN), 3.28 (1H, dd, $J = 5.8$ Hz, $J = 13.6$ Hz, CH_AH_BN'), 3.14 (1H, dd, $J = 6.5$ Hz, $J = 13.6$ Hz, CH_AH_BN'), 3.00 (1H, dt, $J = 3.3$ Hz, $J = 12.5$ Hz, CH_AH_BN), 1.46–2.04 (6H, m, 3 × CH_2); ^{13}C NMR (75 MHz, CD_3OD): 55.8 (*C*HN), 46.5 (CH_2N), 42.9 (CH_2N'), 27.8 (CH_2), 23.3 (CH_2), 23.0 (CH_2); Anal. Calcd for $C_6H_{16}N_2Cl_2$: C, 38.51; H, 8.62; N, 14.97. Found: C, 38.86; H, 8.31; N, 14.66; HRMS (+CI) calcd for $C_6H_{15}N_2$ ($[M]^+$): 115.1235. Found: 115.1236 (+0.4 ppm).

4.6. (*S*)-(2-(Aminomethyl)piperidine dihydrochloride (*S*)-1

$[\alpha]_D^{20} = -2.9$ (*c* 1.4, MeOH). Lit.[12] −5.7 (*c* 0.42, MeOH); lit.[13] −4.7 (*c* 2.8, MeOH). Analytical data were otherwise identical to (*R*)-**1**.

Acknowledgements

We thank the University of St. Andrews for an Interdisciplinary Studentship (G.D.) and the EPSRC for a DTA Studentship (T.M.).

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