Practical Asymmetric Synthesis of Both Enantiomers of 6-(Hydroxymethyl)piperidin-2-one

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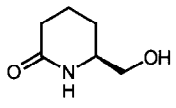
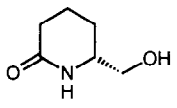
Abstract: A practical asymmetric synthesis of both enantiomers of 6-(hydroxymethyl)piperidin-2-one **1** is described. Asymmetric dihydroxylation (AD) of alkenyl ester **2** using the $(DHQ)_2AQN$ ligand provides diol (5*S*)-**3** in ≥95% ee after recrystallisation. This diol can subsequently be transformed into (*6R*)-**1** using a five step reaction sequence. By employing $(DHQD)_2AQN$ [1,4-bis(dihydroquininyl)anthraquinone] in the initial AD reaction, (6*S*)-**1** can be prepared in an analogous fashion.

Key words: 6-(hydroxymethyl)piperidin-2-one, asymmetric dihydroxylation, 1,4-bis(dihydroquininyl)anthraquinone, 4-methoxyphenylmethyl 5,6-dihydroxyhexanoate, 4-methoxyphenylmethyl hex-5-enoate

As part of a programme directed towards the synthesis of analogues of the azinomycins,[1] an important class of antitumour agents, we required access to both enantiomers of 6-(hydroxymethyl)piperidin-2-one **(1)**. Lactam (6*S*)-**1** has previously been made from (*S*)-2-α-aminoadipic acid,[2] or alternatively from (*S*)-lysine.[3, 4] The (*S*)-enantiomer of this lactam has proven useful in the synthesis of conformationally constrained pipecolic acid derivatives,[5] and some novel acyclic nucleic acid analogues.[6] Furthermore, Moloney et al. have demonstrated that this lactam can be used to make a chiral bicyclic lactam template which can be used to make other functionalised piperidines in a diastereoselective fashion.[3] Unfortunately, in order to access the (*R*)-enantiomer of lactam **1** using the known preparative methods would necessitate the use of the unnatural (*R*)-amino acids. The cost of such starting materials makes these approaches impractical on a preparative scale. In this paper, we disclose an alternative route to 6-(hydroxymethyl)piperidin-2-one **(1)** which allows it to be readily prepared in either enantiomerically enriched form.

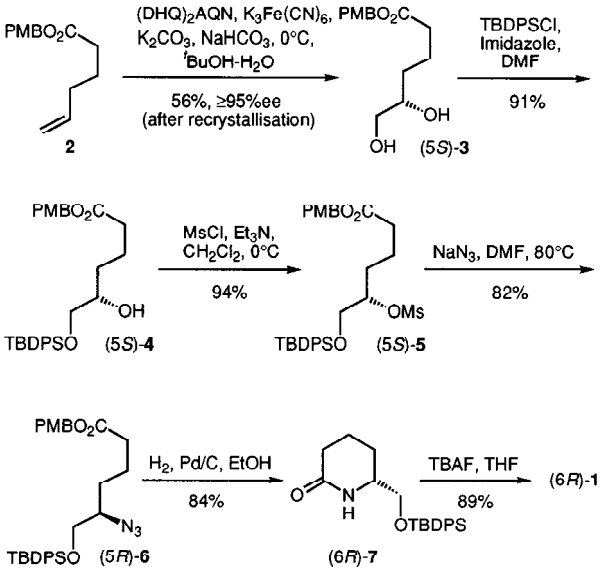


(6*S*)-**1**



(6*R*)-**1**

Our approach to (6*R*)-6-(hydroxymethyl)piperidin-2-one does not rely on a starting material from the chiral pool but instead uses the excellent AD methodology developed by Sharpless to introduce the stereochemistry at C-6.[7, 8] Boger et al. have recently described the asymmetric dihydroxylation of alkenyl ester **2** with the commercially available $(DHQD)_2AQN$ in high yield and enantiomeric excess (88–92% ee).[9] The PMB (4-methoxyphenylmethyl) ester was employed because it imparted crystallinity to the diol product enabling its optical purity to be further enriched by recrystallisation. We have established that asymmetric dihydroxylation of olefin **2** using the pseudo enantiomeric $(DHQ)_2AQN$ ligand under buffered dihydroxylation conditions gives diol **3** in 81% yield and 86% ee as determined by chiral HPLC (see Experimental). On the basis of literature precedent, this diol was assigned the (5*S*)-configuration, which was later confirmed by its conversion into (6*R*)-**1** (*vide infra*). Recrystallisation from diethyl ether gives (5*S*)-**3** in 56% yield from **2** in ≥95% ee (Scheme). While attempts to recycle the chiral ligand by extraction into aqueous acid as described by Sharpless led to extensive decomposition of diol **3**,[7] the successful use of low ligand loading (1 mol%) makes this reaction practical on a preparative (>80 mmol) scale.



Scheme

Selective protection of the primary hydroxyl group of diol (5*S*)-**3** as its *tert*-butyldiphenylsilyl ether furnished (5*S*)-**4** in 91% yield. Conversion of the remaining secondary hydroxy group to the corresponding azide was accomplished in two steps via mesylate **5** and involved stereochemical inversion at C-5. Reduction of azide (5*R*)-**6** by hydrogenation resulted in spontaneous lactamisation of the resultant δ-amino ester yielding lactam (6*R*)-**7**. Final deprotection of the *tert*-butyldiphenylsilyl group using tetrabutylammonium fluoride gave lactam (6*R*)-**1** in 29% overall yield from alkenyl ester **2**. The optical rotation of this material, $[\alpha]_D^{20}$ –28.1 (*c* = 1.1, $CHCl_3$) [lit.[2] $[\alpha]_D^{22}$ +22.2 (*c* = 1.0, $CHCl_3$) for (*S*)-enantiomer] confirmed that it possessed the (*R*)-configuration. The enantiomeric excess of our material was determined to be ≥95% ee by conversion into the corresponding MTPA ester and analysis by ^1H NMR according to the method described by Weller et al.[2]

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Performing the asymmetric dihydroxylation of alkenyl ester **2** with $(DHQD)_2AQN$ according to the method previously described by Boger gave diol (5*R*)-**3** in 59% yield and ≥95% ee after recrystallisation.[7] Using the same sequence of reactions as outlined above, this diol was readily converted into lactam (6*S*)-**1** [≥95% ee, $[\alpha]_D^{20}$ +26.7 (*c* = 1.1, $CHCl_3$)]. In summary, we have developed a practical route to both enantiomers of 6-(hydroxymethyl)piperidin-2-one in excellent enantiomeric excess. We believe that this strategy could be used to make other synthetically useful functionalised δ-lactam derivatives.

Reactions requiring anhydrous conditions were performed using oven-dried glassware and conducted under a positive pressure of N_2. Light petroleum (40–60 °C) and EtOAc were distilled from $CaCl_2$. CH_2Cl_2 was distilled from P_2O_5. Anhyd THF was prepared by distillation from sodium-benzophenone ketyl under N_2 immediately prior to use, or alternatively purchased from Aldrich in Sure/Seal™ bottles. All other solvents and reagents were purified by standard means. IR spectra were recorded in the range 4000–600 cm^{-1} on a Nicolet Magna-550 FT-IR spectrometer with internal calibration. Spectra were recorded as thin films or Nujol mulls. NMR spectra were recorded on a Bruker DRX-400 spectrometer with either TMS or residual protic solvent as internal reference. Elemental analyses were carried out on a Perkin–Elmer 2400 CHN elemental analyser. MS were recorded under EI or CI conditions on a VG Analytical ZAB-E instrument, or under EI conditions on a Kratos Profile HV-3 mass spectrometer.

4-Methoxyphenylmethyl (5*S*)-5,6-Dihydroxyhexanoate [(5*S*)-3]:
A stirred solution of 1,4-bis(dihydroquininyl)anthraquinone (700 mg, 0.817 mmol), $K_3Fe(CN)_6$ (80.61 g, 0.245 mol), K_2CO_3 (33.81 g, 0.245 mol), $NaHCO_3$ (20.58 g, 0.245 mol) and potassium osmate(VI) dihydrate (120 mg, 0.326 mmol) in *t*-BuOH (350 mL) and water (350 mL) was prepared at r.t. The mixture was cooled to 0 °C whereupon some of the dissolved salts precipitated. 4-Methoxyphenylmethyl hex-5-enoate **(2)** (19.11 g, 81.7 mmol) was added in one portion and the orange heterogeneous slurry was stirred at 0 °C for 12 h. Anhyd Na_2SO_3 (122.50 g, 0.972 mol) was added at 0 °C and the mixture allowed to warm to r.t. and stirred for 1 h. EtOAc (200 mL) was added to the resulting green-brown mixture and, after separation of the layers, the aqueous phase was further extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give a yellow oil. Column chromatography (30% EtOAc/light petroleum) provided 4-methoxybenzyl alcohol (1.79 g, 16%) as a colourless liquid. Further elution (100% EtOAc) gave (5*S*)-**3** as a white solid (17.72 g, 81%) which was found to be 86% ee by HPLC analysis using a Chiralpak AD column (8% i-PrOH/hexane; 0.7 mL min^{-1}) [33.6 min (major); 36.1 min (minor)]. Recrystallisation (Et_2O) provided (5*S*)-**3** (12.36 g, 56%) in ≥95% ee as white plates, mp 61–63 °C; $[\alpha]_D^{20}$ –11.1 (*c* = 1.1, EtOH).
IR (thin film): ν_{max} = 3364 (OH), 1734 (C=O), 1614, 1587, 1518 cm^{-1} (aromatic C=C).
^1H NMR (400 MHz, $CDCl_3$): δ= 7.27 (2H, d, *J* = 8.8 Hz, ArH), 6.88 (2H, d, *J* = 8.8 Hz, ArH), 5.04 (2H, s, CO_2CH_2Ar), 3.79 (3H, s, OCH_3), 3.66 (1H, m, H-5), 3.59 (1H, m, H-6), 3.40 (1H, m, H-6), 3.18 (1H, br s, OH), 3.01 (1H, br s, OH), 2.36 (2H, t, *J* = 7.3 Hz, H-2), 1.74 (2H, m), 1.43 (2H, m).
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.8 (s, C-1), 159.7 (s, ArC), 130.1 (d, ArCH), 128.1 (s, ArC), 114.0 (d, ArCH), 71.8 (d, C-5), 66.6 (t), 66.1 (t), 55.3 (q, OCH_3), 34.1 (t), 32.4 (t), 20.9 (t, C-3).
MS (EI^+): *m/z* (%) = 268 (M^+, 5), 121 (100).
Anal. Found: C: 62.96; H: 7.63; $C_{14}H_{20}O_5$ requires C: 62.67; H: 7.51.
HRMS Observed (M^+): 268.1310; $C_{14}H_{20}O_5$ requires 268.1311.

4-Methoxyphenylmethyl (5*R*)-5,6-Dihydroxyhexanoate [(5*R*)-3]:
A stirred solution of 1,4-bis(dihydroquinidinyl)anthraquinone (565 mg, 0.659 mmol), $k_3Fe(CN)_6$ (65.08 g, 0.198 mol), K_2CO_3 (27.30 g, 0.198 mol), $NaHCO_3$ (16.62 g, 0.198 mol) and potassium osmate(VI) dihydrate (97.1 mg, 0.264 mmol) in *t*-BuOH (300 mL) and water (300 mL) was prepared at r.t. The mixture was cooled to 0 °C whereupon some of the dissolved salts precipitated. 4-Methoxyphenylmethyl hex-5-enoate **(2)** (15.43 g, 65.9 mmol) was added in one portion and the orange heterogeneous slurry was stirred at 0 °C for 12 h. Workup and purification as described above gave (5*R*)-**3** (14.67 g, 83%) as a white solid (91% ee). Recrystallisation (Et_2O) provided (5*R*)-**3** (10.42 g, 59%) in ≥95% ee as white plates, mp 61–63 °C (lit.[9] mp 57–59 °C); $[\alpha]_D^{20}$ +11.7 (*c* = 1.1, EtOH) [lit.[9] $[\alpha]_D^{22}$ +2.1 (*c* = 0.06, $CHCl_3$)]. Spectroscopic data were identical with the corresponding (5*S*)-enantiomer and those reported by Boger et al.[9] 4-Methoxybenzyl alcohol (1.21 g, 13%) was also isolated as a colourless liquid.

4-Methoxyphenylmethyl (5*S*)-6-[(*tert*-Butyldiphenylsilyl)oxy]-5-hydroxyhexanoate [(5*S*)-4]:
To a stirred solution of (5*S*)-**3** (12.11 g, 45.2 mmol) and imidazole (6.76 g, 99.4 mmol) in anhyd DMF (50 mL) at r.t. under N_2 was added TBDPSCl (13.64 g, 49.7 mmol) in DMF (50 mL). The mixture was stirred for 12 h at r.t., quenched with water (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with water (5 × 100 mL), dried (Na_2SO_4) and concentrated in vacuo to give a pale yellow oil. Column chromatography (5 → 30% EtOAc/light petroleum) gave (5*S*)-**4** as a colourless oil (20.81 g, 91%); $[\alpha]_D^{20}$ +1.19 (*c* = 2.2, $CHCl_3$).
IR (thin film): ν_{max} = 3505 (OH), 1734 (C=O), 1614, 1587, 1516 cm^{-1} (aromatic C=C).
^1H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.64 (4H, m, ArH), 7.44–7.35 (6H, m, ArH), 7.26 (2H, d, *J* = 8.7 Hz, ArH), 6.86 (2H, d, *J* = 8.7 Hz, ArH), 5.02 (2H, s, CO_2CH_2Ar), 3.77 (3H, s, OCH_3), 3.69 (1H, m, H-5), 3.63 (1H, dd, *J* = 10.1, 3.5 Hz, H-6), 3.48 (1H, dd, *J* = 10.1, 7.3 Hz, H-6), 2.50 (1H, br d, *J* = 3.4 Hz, OH), 2.32 (2H, t, *J* = 7.4 Hz, H-2), 1.71 (2H, m), 1.41 (2H, m), 1.06 [9H, s, $C(CH_3)_3$].
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.4 (s, C-1), 159.7 (s, ArC), 135.58 (d, ArCH), 135.56 (d, ArCH), 133.22 (s, ArC), 133.20 (s, ArC), 130.1 (d, ArCH), 129.9 (d, ArCH), 128.3 (s, ArC), 127.8 (d, ArCH), 114.0 (d, ArCH), 71.6 (d, C-5), 68.0 (t), 66.0 (t), 55.3 (q, OCH_3), 34.2 (t), 32.2 (t), 26.9 [q, $C(\underline{C}H_3)_3$], 21.1 (t, C-3), 19.3 [s, $\underline{C}(CH_3)_3$].
MS (EI^+): *m/z* (%) = 506 (M^+, 0.1), 121 (100).
HRMS Observed (M^+): 506.2500; $C_{30}H_{38}O_5Si$ requires 506.2489.

4-Methoxyphenylmethyl (5*R*)-6-[(*tert*-Butyldiphenylsilyl)oxy]-5-hydroxyhexanoate [(5*R*)-4]:
To a stirred solution of (5*R*)-**3** (10.20 g, 38.1 mmol) and imidazole (5.69 g, 83.7 mmol) in anhyd DMF (40 mL) at r.t. under N_2 was added TBDPSCl (11.49 g, 41.9 mmol) in DMF (50 mL). The mixture was stirred for 12 h at r.t. then quenched with water (100 mL). Workup and purification as described above gave (5*R*)-**4** (17.52 g, 91%) as a colourless oil; $[\alpha]_D^{20}$ –0.90 (*c* = 2.2, $CHCl_3$) [lit.[9] $[\alpha]_D^{22}$ –0.92 (*c* = 2.1, $CHCl_3$)]. Spectroscopic data were identical with the (5*S*)-enantiomer and those reported by Boger et al.[9]

4-Methoxyphenylmethyl (5*S*)-6-[(*tert*-Butyldiphenylsilyl)oxy]-5-(methylsulfonyloxy)hexanoate [(5*S*)-5]:
To a stirred solution of (5*S*)-**4** (20.64 g, 40.8 mmol) and Et_3N (8.51 mL, 61.2 mmol) in anhyd CH_2Cl_2 (100 mL) at 0 °C under N_2 was added MsCl (3.36 mL, 42.8 mmol) dropwise. The mixture was stirred at 0 °C for 1 hour and then sat. aq $NaHCO_3$ (100 mL) was added. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give a dark yellow oil. Column chromatography (100% CH_2Cl_2) provided (5*S*)-**5** as a pale yellow oil (22.45 g, 94%); $[\alpha]_D^{20}$ –6.38 (*c* = 1.0, EtOH).

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IR (thin film): ν_{max} = 1734 (C=O), 1614, 1587, 1516 cm^{-1} (aromatic C=C).
^1H NMR (400 MHz, $CDCl_3$): δ= 7.67–7.62 (4H, m, ArH), 7.46–7.36 (6H, m, ArH), 7.26 (2H, d, *J* = 8.8 Hz, ArH), 6.86 (2H, d, *J* = 8.8 Hz, ArH), 5.03 (2H, s, CO_2CH_2Ar), 4.72 (1H, m, H-5), 3.80 (1H, dd, *J* = 11.5, 6.1 Hz, H-6), 3.78 (3H, s, OCH_3), 3.72 (1H, dd, *J* = 11.5, 3.9 Hz, H-6), 2.95 (3H, s, OSO_2CH_3), 2.34 (2H, t, *J* = 6.9 Hz, H-2), 1.74–1.67 (4H, m, H-3, H-4), 1.06 [9H, s, $C(CH_3)_3$].
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 172.9 (s, C-1), 159.7 (s, ArC), 135.6 (d, ArCH), 135.5 (d, ArCH), 132.9 (s, ArC), 132.7 (s, ArC), 130.11 (d, ArCH), 130.06 (d, ArCH), 130.0 (d, ArCH), 128.1 (s, ArC), 127.9 (d, ArCH), 114.0 (d, ArCH), 83.1 (d, C-5), 66.1 (t), 65.3 (t), 55.3 (q, $O\underline{C}H_3$), 38.6 (q, OSO_2CH_3), 33.8 (t, C-2), 30.8 (t, C-4), 26.9 [q, $C(\underline{C}H_3)_3$], 20.3 (t, C-3), 19.3 [s, $\underline{C}(CH_3)_3$].
MS (CI): *m/z* (%) = 602 (MNH_4^+, 79), 121 (100).
HRMS Observed (MNH_4^+): 602.2610; $C_{31}H_{44}NO_7SSi$ requires 602.2610.

4-Methoxyphenylmethyl (5*R*)-6-[(*tert*-Butyldiphenylsilyl)oxy]-5-(methylsulfonyloxy)hexanoate [(5*R*)-5]:
To a stirred solution of (5*R*)-**4** (17.45 g, 34.5 mmol) and Et_3N (7.20 mL, 51.7 mmol) in anhyd CH_2Cl_2 (100 mL) at 0 °C under N_2 was added MsCl (2.80 mL, 36.2 mmol) dropwise. The mixture was stirred at 0 °C for 1 h and then sat. aq $NaHCO_3$ (100 mL) was added. Workup and purification as described above gave (5*R*)-**5** (19.18 g, 95%) as a pale yellow oil; $[\alpha]_D^{20}$ +7.77 (*c* = 1.0, EtOH). Spectroscopic data were identical with the (5*S*)-enantiomer.

4-Methoxyphenylmethyl (5*R*)-5-Azido-6-[(*tert*-butyldiphenylsilyl)oxy)]hexanoate [(5*R*)-6]:
A stirred solution of (5*S*)-**5** (22.31 g, 38.2 mmol) and NaN_3 (24.83 g, 0.382 mol) in anhyd DMF (150 mL) under N_2 was heated at 80 °C for 18 h. The resulting white heterogeneous mixture was quenched with water (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with water (5 × 100 mL), dried (Na_2SO_4) and concentrated in vacuo to give a yellow oil. Column chromatography (10% EtOAc/light petroleum) provided (5*R*)-**6** as a colourless oil (16.72 g, 82%); $[\alpha]_D^{20}$ +13.5 (*c* = 1.1, EtOH).
IR (thin film): ν_{max} = 2106 (N_3), 1734 (C=O), 1614, 1587, 1516 cm^{-1} (aromatic C=C).
^1H NMR (400 MHz, $CDCl_3$): δ= 7.68–7.66 (4H, m, ArH), 7.45–7.36 (6H, m, ArH), 7.27 (2H, d, *J* = 8.6 Hz, ArH), 6.86 (2H, d, *J* = 8.6 Hz, ArH), 5.03 (2H, s, CO_2CH_2Ar), 3.78 (3H, s, OCH_3), 3.70 (1H, dd, *J* = 10.7, 3.9 Hz, H-6), 3.62 (1H, dd, *J* = 10.7, 6.9 Hz, H-6), 3.37 (1H, m, H-5), 2.31 (2H, t, *J* = 7.4 Hz, H-2), 1.69 (2H, m), 1.42 (2H, m), 1.07 [9H, s, $C(CH_3)_3$].
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.0 (s, C-1), 159.7 (s, ArC), 135.67 (d, ArCH), 135.65 (d, ArCH), 133.12 (s, ArC), 133.06 (s, ArC), 130.1 (d, ArCH), 129.9 (d, ArCH), 128.2 (s, ArC), 127.9 (d, ArCH), 114.0 (d, ArCH), 67.0 (t), 66.1 (t), 63.6 (d, C-5), 55.3 (q, OCH_3), 34.0 (t), 29.8 (t), 26.8 [q, $C(\underline{C}H_3)_3$], 21.6 (t, C-3), 19.2 [s, $\underline{C}(CH_3)_3$].
MS (CI): *m/z* (%) = 549 (MNH_4^+, 72), 504 (100).
HRMS Observed (MNH_4^+): 549.2900; $C_{30}H_{41}N_4O_4Si$ requires 549.2900.

4-Methoxyphenylmethyl (5*S*)-5-Azido-6-[(*tert*-butyldiphenylsilyl)oxy]hexanoate [(5*S*)-6]:
A stirred solution of (5*R*)-**5** (19.68 g, 33.7 mmol) and NaN_3 (21.90 g, 0.337 mol) in anhyd DMF (150 mL) under N_2 was heated at 80 °C for 18 h. The resulting white heterogeneous mixture was quenched with water (100 mL). Workup and purification as described above gave (5*S*)-**6** (14.89 g, 83%) as a colourless oil; $[\alpha]_D^{20}$ –13.8 (*c* = 1.1, EtOH). Spectroscopic data were identical with the (5*R*)-enantiomer.

(6*R*)-6-[(*tert*-Butyldiphenylsilyl)oxymethyl]piperidin-2-one [(6*R*)-7]:
To a stirred solution of (5*R*)-**6** (16.62 g, 31.3 mmol) in abs EtOH (120 mL) was added 10% Pd/C (1.66 g, 10% w/w) and the suspension stirred under H_2 (1 atm) for 18 h at r.t. The black heterogeneous mixture was filtered through a pad of Celite and the filtrate concentrated in vacuo to give a pale yellow oil. Column chromatography (20% EtOAc/light petroleum) provided a colourless liquid which was identified as 4-methoxybenzyl alcohol (3.81 g, 88%). Further elution (50% EtOAc/light petroleum) gave (6*R*)-**7** (9.62 g, 84%) as a white crystalline solid, mp 91–93 °C; $[\alpha]_D^{20}$+6.74 (*c* = 1.1, $CHCl_3$).
IR (Nujol): ν_{max} = 3192 (NH), 1665 (C=O), 1587, 1506 cm^{-1} (aromatic C=C).
^1H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.63 (4H, m, ArH), 7.44–7.37 (6H, m, ArH), 6.23 (1H, br s, NH), 3.61 (1H, dd, *J* = 9.3, 3.7 Hz, H-7), 3.55 (1H, m, H-6), 3.47 (1H, dd, *J* = 9.3, 8.6 Hz, H-7), 2.40 (1H, m, H-3), 2.26 (1H, m, H-3), 1.84 (1H, m), 1.76–1.62 (2H, m), 1.27 (1H, m), 1.06 [9H, s, $C(CH_3)_3$].
^{13}C NMR (100.6 MHz, $CDCl_3$): δ= 171.9 (s, C-2), 135.5 (d, ArCH), 132.92 (s, ArC), 132.85 (s, ArC), 130.0 (d, ArCH), 127.9 (d, ArCH), 67.7 (t, C-7), 54.5 (d, C-6), 31.6 (t, C-3), 26.8 [q, $C(\underline{C}H_3)_3$], 24.4 (t), 19.6 (t), 19.2 [s, $\underline{C}(CH_3)_3$].
MS (CI): *m/z* (%) = 385 (MNH_4^+, 2), 368 (MH^+, 100).
Anal. Found: C: 71.67; H: 7.96; N: 3.76; $C_{22}H_{29}NO_2Si$ requires C: 71.89; H: 7.95; N: 3.81.

(6*S*)-6-[(*tert*-Butyldiphenylsilyl)oxymethyl]piperidin-2-one [(6*S*)-7]:
To a stirred solution of (5*S*)-**6** (14.82 g, 27.9 mmol) in abs EtOH (120 mL) was added 10% Pd/C (1.48 g, 10% w/w) and the suspension stirred under H_2 (1 atm) for 18 h at r.t. Workup and purification as described above gave (6*S*)-**7** (8.61 g, 84%) as a white crystalline solid, mp 90–92 °C; $[\alpha]_D^{20}$ –6.41 (*c* = 1.1, EtOH). Spectroscopic data were identical with the (6*R*)-enantiomer. 4-Methoxybenzyl alcohol (3.41 g, 89%) was also isolated as a colourless liquid.

(6*R*)-6-(Hydroxymethyl)piperidin-2-one [(6*R*)-1]:
To a stirred solution of (6*R*)-**7** (500 mg, 1.36 mmol) in anhyd THF (20 mL) at 0 °C under N_2 was added 1.0 M TBAF in THF (1.49 mL, 1.49 mmol), the mixture was allowed to warm to r.t. and stirred for 18 h. The resulting red-brown solution was quenched with glacial HOAc (0.16 mL, 2.80 mmol) and concentrated in vacuo to give a brown semi-solid. Column chromatography (100% EtOAc → 10% MeOH/CH_2Cl_2) gave (6*R*)-**1** (157 mg, 89%) as a white crystalline solid, mp 92–94 °C; $[\alpha]_D^{20}$ –28.1 (*c* = 1.1, $CHCl_3$); preparation of the MTPA ester according to the method of Weller et al.[2] and subsequent ^1H NMR analysis of the crude product determined it to be ≥95% ee.
IR (Nujol): ν_{max} = 3443 (OH), 3242 (NH), 1661 cm^{-1} (C=O).
^1H NMR (400 MHz, $CDCl_3$): δ = 7.33 (1H, br s, NH), 4.87 (1H, br s, OH), 3.65–3.41 (3H, m, 1 × H-6, 2 × H-7), 2.30 (2H, m, H-3), 1.87 (2H, m), 1.71 (1H, m), 1.38 (1H, m).
^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.2 (s, C-2), 65.7 (t, C-7), 54.6 (d, C-6), 31.1 (t, C-3), 24.2 (t), 19.3 (t).
MS (EI^+): *m/z* (%) = 130 (MH^+, 28), 129 (M^+, 9), 55 (100).
Anal. Found: C: 55.67; H: 8.69; N: 10.63; $C_6H_{11}NO_2$ requires C: 55.80; H: 8.58; N: 10.84.
HRMS Observed (M^+): 129.0791; $C_6H_{11}NO_2$ requires 129.0790.

(6*S*)-6-(Hydroxymethyl)piperidin-2-one [(6*S*)-1]:
To a stirred solution of (6*S*)-**7** (500 mg, 1.36 mmol) in anhyd THF (20 mL) at 0 °C under N_2 was added 1.0 M TBAF in THF (1.49 mL, 1.49 mmol), the mixture was allowed to warm to r.t. and stirred for 18 h. Workup and purification as described above gave (6*S*)-**1** (156 mg, 89%) as a white crystalline solid, mp 89.5–91.5 °C (lit.[2] mp

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74°C); $[\alpha]_D^{20}$ +26.7 (*c* = 1.1, $CHCl_3$) (lit.[2] $[\alpha]_D^{22}$ +22.2 (*c* = 1.0, $CHCl_3$); preparation of the MTPA ester according to the method of Weller et al.[2] and subsequent ^1H NMR analysis of the crude product determined it to be ≥95% ee. Spectroscopic data were identical with the (6*R*)-enantiomer and those reported by Weller.

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