Synthesis and evaluation of a new polymer–supported pseudoephedrine auxiliary for asymmetric alkylations on solid phase

Andrea M. McGhee, Jean-Claude Kizirian and David J. Procter*

School of Chemistry, Oxford Road, The University of Manchester, Manchester, M13 9PL, UK.

E-mail: david.j.procter@manchester.ac.uk

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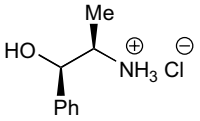
(1*R*, 2*R*)-2-Amino-1-phenyl-propan-1-ol (norpseudoephedrine) hydrochloride 6[1]

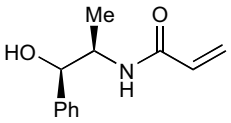


To a stirred solution of (1*S*,2*R*)-norephedrine (20.6 g, 136.1 mmol, 1 eq.) and Et_3N (19.0 mL, 136.1 mmol, 1 eq.) in dry CH_2Cl_2 (100 mL) at 0 °C under argon was added dropwise via syringe a solution of benzoyl chloride (15.8 mL, 136 mmol, 1eq.) in dry CH_2Cl_2 (20 mL). An additional 20 mL CH_2Cl_2 was required to aid stirring of the resulting white emulsion which was stirred at room temperature for 3 h. The white precipitate was collected by Buchner filtration and washed with pet. ether. The filtrate was concentrated under reduced pressure to give a white solid. The solids were combined and recrystallised from EtOAc. The resulting material was dissolved in degassed THF (400 mL) and PPh_3 (39.1 g, 149 mmol, 1.25 eq.) added. The solution was degassed with N_2 for 20 min before addition of degassed diisopropylazadicarboxylate (DIAD) (29.4 mL, 149 mmol, 1.25 eq.) and the reaction stirred for 18 h. The solvent was removed under reduced pressure and the resulting residue treated with 1.1 M HCl (700 mL, 3M in H_2O) and heated to reflux for 120 h. The volume was reduced by half under reduced pressure and the mixture extracted with CH_2Cl_2 (3 × 200 mL). The aqueous phase was concentrated under reduced pressure (azeotroping with EtOH) and the resulting material triturated with EtOAc. The solid was collected by Buchner filtration and washed with acetone to give known

[1] B. Colman, S. E. de Sousa, P. O'Brien, T. D. Towers and W. Watson, *Tetrahedron: Asymmetry*, 1999, **10**, 4175.

compound[1] **6** as a white solid (20.4 g, 109 mmol, 80%). mp 169-172 °C; $[\alpha]_D^{20} = -21.6$ (c = 1.2 in H_2O), (lit[1] $[\alpha]_D^{20} = -41.8$ (c = 7.2 in H_2O)); (lit[2,3] 179-181 °C); ν_{max} (neat) 3362, 2952, 2530, 3036, 1935, 1602, 1467, 1094, 1033 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d*6) δ 0.96 (3H, d, J = 6.7 Hz, CH_3); 3.20-3.27 (1H, m, C*H*CH_3); 4.46 (1H, d, J = 8.6 Hz, C*H*OH); 6.22 (1H, broad s, O*H*); 7.32-7.42 (5H, m, 5 Ar C*H*); 8.09 (3H, broad s, NH_3); ^{13}C NMR (100 MHz, DMSO-*d*6) δ 15.4 (*C*H_3); 52.6 (*C*HCH_3); 74.8 (*C*HOH); 127.4 (2 Ar *C*H); 128.4 (Ar *C*H); 128.7 (2 Ar *C*H); 141.7 (Ar *C*).

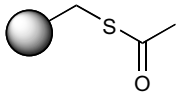
(1*R*,2*R*)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)acrylamide 11



To a stirred suspension of **6** (7.31, 39.0 mmol, 1 eq.) in dry THF (200 mL) at 0 °C under N_2 was added Et_3N (27.0 mL, 195 mmol, 5 eq.) and TMSCl (7.40 mL, 58.5 mmol, 1.5 eq.). After stirring at 0 °C for 1 h, the reaction was warmed to room temperature, a solution of acryloyl chloride (6.34 mL. 78.0 mmol, 2 eq.) in dry THF (20 mL) added and the reaction stirred overnight. The solvent was removed under reduced pressure and the residue partitioned between H_2O and CH_2Cl_2. The layers were separated and the aqueous phase washed with CH_2Cl_2 (2 × 50 mL). The combined organics were concentrated under reduced pressure and the residue treated with excess citric acid in MeOH for 3 h. The solvent was removed under reduced pressure and the residue partitioned between CH_2Cl_2 and H_2O. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (2 × 50

mL). The combined organics were washed with brine (2 × 25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (30% EtOAc/ pet. ether to 100% EtOAc/ silica) provided acrylamide **11** (4.45 g, 21.6 mmol, 56%) as a pale yellow viscous oil, which solidified upon standing. $[\alpha]_D^{20}$ = -14.9 (c 2.15, $CHCl_3$); m.pt. 70-71 °C; ν_{max}(neat) 3285, 3065, 2973, 1624, 1655, 1536, 1450, 1410, 1313, 1235, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ major rotamer) δ 1.15 (3H, d, J = 6.8Hz, CH_3CHN); 4.26 (1H, app. sextet, J = 6.4 Hz, C*H*C(O)); 4.65 (1H, d, J = 5.6 Hz, C*H*OH); 5.64 (1H, dd, J = 10.4 and 0.8 Hz, 1H of CH_2CH); 5.97 (1H, ,br d, O*H*); 6.07 (1H, dd, J = 16.8 and 10.4 Hz, CH_2CH); 6.25 (1H, dd, J = 16.8 and 1.2 Hz, 1H of CH_2CH) 7.26-7.36 (5H, m, 5 Ar C*H*); ^{13}C NMR (100 MHz, $CDCl_3$, major rotamer) δ 17.8 (CH_3CHN); 52.0 (CH_3CHN); 77.9 (*C*HOH); 126.8 (Ar *C*H); 127.3 (CH_2CH) 128.3 (Ar *C*H); 128.8 (Ar *C*H); 131.0 ($CHCH_2$) 142.0 (q*C*); 166.6 (*C*=O); *m/z* (EI^+ mode) 206 (4), 188 (8), 98 (100); HRMS calcd for ($M^+ + H^+$) 206.1176, found 206.1180; Anal. calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82; found: C, 69.79; H, 7.54; N, 6.81.

Merrifield based thioacetate resin[2]

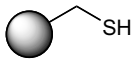


To a slowly stirred suspension of Merrifield resin (5.21 g, 1.20 mmol/g, 1 eq.) in dry DMF (40 mL) at room temperature under N_2 was added a solution of potassium thioacetate (1.96 g, 17.2 mmol, 3 eq.) in DMF (10 mL) via cannula and the reaction

[2] S. Kobayashi, I. Hachiya, S. Suzuki and M. Moriwaki*, Tetrahedron Lett.,* 1996, **37**, 2809.

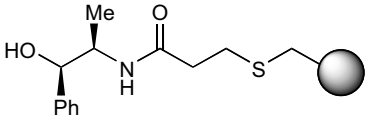
stirred overnight. The reaction was filtered and the resin washed with THF (distilled, 3 × 100 mL), THF/H_2O (2:1, 3 × 50 mL; 1:1, 3 × 50 mL; 1:2, 3 × 50 mL), MeOH then CH_2Cl_2 (3 × 50 mL each) and THF (distilled, 3 × 100 mL) and dried *in vacuo*. ν_{max} (ATR) 2901, 1688 (C=O), 1446, 1096 cm^{-1}.

Merrifield based thiol resin 16[2]



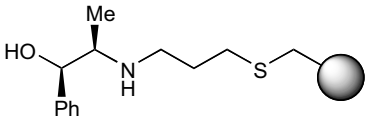
To a slowly stirred suspension of thioacetate resin (5.27 g, 1.15 mmol/g (max.), 1 eq.) in dry THF (25 mL) at room temperature under N_2 was added a $LiBH_4$ (551 mg, 25.3 mmol, 4.2 eq.) and the reaction stirred overnight. The reaction was poured slowly onto MeOH (100 mL), filtered and the resin **16** washed with THF (distilled, 3 × 100 mL), THF/H_2O (2:1, 3 × 50 mL; 1:1, 3 × 50 mL; 1:2, 3 × 50 mL), MeOH then CH_2Cl_2 (3 × 50 mL each) and THF (distilled, 3 × 100 mL) and dried *in vacuo*. ν_{max}(ATR) 2919, 1600, 1442, 1057 cm^{-1}.

(1*R*,2*R*)-*S*-Merrifield bound-3-sulfanyl-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-propionamide 17



To a slowly stirred suspension of resin **16** (3.02 g, 1.21 mmol/g (max.), 1 eq.) in dry THF (60 mL) at room temperature under N_2 was added NaH (175 mg, 7.31 mmol, 2 eq.) followed by a solution of acrylamide **11** (2.00 g, 9.13 mmol, 2.5 eq.) in dry THF (10 mL). The reaction was stirred slowly for 24 h then filtered and the resin **17** washed with THF (distilled, 3 × 100 mL), THF/H_2O (2:1, 3 × 100 mL; 1:1, 3 × 100 mL; 1:2, 3 × 100 mL), MeOH then CH_2Cl_2 (3 × 100 mL each) and THF (distilled, 3 × 100 mL) and dried *in vacuo*. ν_{max}(ATR) 3300 (OH), 2909, 1643 (C=O), 1495, 1450, 1026 cm^{-1}.

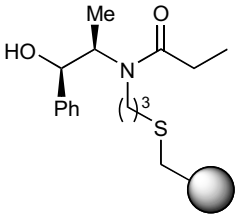
(1*R*,2*R*)-*S*-Merrifield bound-2-(3-sulfanylpropylamino)-1-phenyl-propan-1-ol 18



To a slowly stirred suspension of amide resin **17** (3.80 g, 0.93 mmol/g (max.), 1 eq.) in dry THF (25 mL) at room temperature under N_2 was added BH_3•THF (35 mL, 1M in THF, 10 eq.) and the reaction stirred for 3 h. The reaction was poured slowly onto MeOH (200 mL), filtered and the resin washed with THF (distilled, 3 × 100 mL), MeOH then CH_2Cl_2 (3 × 50 mL each) and THF (distilled, 3 × 100 mL). The resin **18** was then treated with a solution of $EtNH_2$ (35 mL, 2M in THF, 20 eq.) for 1 h, filtered and washed as before and dried *in vacuo*. ν_{max}(ATR) 2901, 1599, 1446, 1036 cm^{-1}.

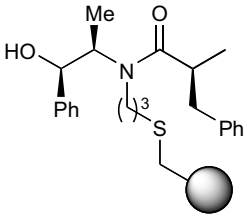
Representative procedures for the synthesis of carboxylic acids, alcohols and ketones using pseudoephedrine resin 18

(1*R*,2*R*)-*S*-Merrifield bound-*N*-(3-sulfanyl-propyl)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)propionamide 19 (R= Me)



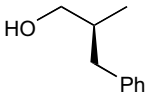
To a slowly stirred suspension of resin **18** (1.89 g, 0.90 mmol/g (max.), 1 eq.) in dry THF (40 mL) at 0 °C under N_2 was added Et_3N (1.19 mL, 8.50 mmol, 5 eq.) and TMSCl (0.32 mL, 2.55 mmol, 1.5 eq.) and the reaction stirred for 3 h. Propionic anhydride (1.09 mL, 8.50 mmol, 5 eq.) was added and the reaction allowed to warm to room temperature and stirred for 17 h. The reaction filtered and the resin washed with THF (distilled, 3 × 50 mL), MeOH then CH_2Cl_2 (3 × 50 mL each) and THF (distilled, 3 × 50 mL). The resin **19 (R= Me)** was then treated with a solution of TBAF (5.1 mL, 1M in THF, 3 eq.) for 17 h, filtered and washed as before and dried *in vacuo*. ν_{max}(ATR) 3251 (OH), 2920, 1638 (C=O), 1606, 1442, 1025 cm^{-1}.

(1*R*,2*R*)-*S*-Merrifield bound-*N*-(3-sulfanylpropyl)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-(2*S*)-2-methyl-3-phenyl-propionamide 20 (R= Me)



To a stirred solution of LiCl (662 mg, 15.9 mmol, 18 eq.) and *i*-Pr_2NH (0.82 mL, 5.92 mmol, 6.7 eq.) in dry THF (18 mL) at –78 °C under N_2 was added *n*-BuLi (2.16 mL, 2.54 M in hexanes, 6.2 eq.). The solution was warmed briefly to 0 °C then cooled to –78 °C again and added to a slowly stirred suspension of resin **19 (R= Me)** (1.03 g, 0.86 mmol/g (max.), 1 eq.) and LiCl (662 mg, 15.9 mmol, 18 eq.) in dry THF (18 mL) at –78 °C under N_2. The reaction was stirred slowly for 3 h, warmed to 0 °C for 10 min, to room temperature for 10 min and cooled to 0 °C again before addition of BnBr (0.47 mL, 3.97 mmol, 4.5 eq.). The reaction was allowed to warm to r.t. and stirred for 48 h. The reaction was filtered and the resin **20 (R= Me)** washed with THF (distilled, 3 × 50 mL), MeOH then CH_2Cl_2 (3 × 50 mL each) and THF (distilled, 3 × 50 mL) and dried *in vacuo*. ν_{max}(ATR) 3360 (OH), 2920, 1620 (C=O), 1422, 1026 cm^{-1}.

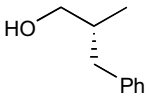
(2*S*)-(+)-2-Methyl-3-phenyl propanol (*S*)–5[3] (from **18**)



[3] A. G. Myers, B. H. Yang, H. Chen, L. McKinstry, D. J. Kopecky, J. L. Gleason, *J. Am. Chem. Soc.*, 1997, **119**, 6496.

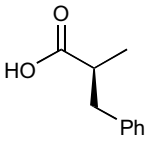
To a stirred solution of *i*-Pr_2NH (0.49 mL, 3.50 mmol, 8.4 eq) in dry THF (9.5 mL) at –78 °C under N_2 was added *n*-BuLi (1.31mL, 2.50 M in hexanes, 7.8 eq.) and the mixture stirred at –78 °C for 10 min and at 0 °C for 10 min. BH_3•NH_3 (104 mg, 3.38 mmol, 8.0 eq.) was added and the resulting mixture stirred at 0 °C for 15 min and at room temperature for 15 min. After cooling to 0 °C again the mixture was added via cannula to a suspension of the resin bound amide **20 (R= Me)** (528 mg, 0.80 mmol/g (max.), 1 eq.) in dry THF (5 mL) at 0 °C under N_2. The reaction was stirred slowly for 24 h after which the resin was filtered and washed with distilled THF (300 mL). The filtrate was concentrated under reduced pressure and the resulting organic residue quenched with 3M HCl (5 mL) and extracted with Et_2O (2 × 10 mL). The combined organics were washed with 3M HCl (2 mL), 2M NaOH (2 mL) and brine (2 mL), dried over Na_2SO_4 and concentrated to give *(S)*–**5** (36 mg, 0.240 mmol, 56%) as a clear oil in 86% enantiomeric excess, determined by chiral GC analysis using a β-cyclodextrin column (50-100 °C @ 5°C/min, 3 min hold, 100-109 °C @ 0.1°C/min, 15 min hold, 109-112 °C @ 0.1°C/min, 1 min hold, major enantiomer eluted at 109.08 min). $[\alpha]_D^{20}$ = -9.9 (c = 0.9 in $CHCl_3$), (lit[3] $[\alpha]_D^{20}$ = +10.0 (c = 0.84 in $CHCl_3$) for opposite enantiomer); ν_{max}(neat, ATR) 3327 (OH), 2919, 1453, 1260, 1033 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (3H, d, J = 5.5 Hz, C*H*$_3$); 1.95-1.98 (1H, m, C*H*CH_3); 2.44 (1H, dd, J = 8.0 and 13.5 Hz, 1H of C*H*$_2$Ph); 2.77 (1H, dd, J = 6.5 and 13.5 Hz, 1H of C*H*$_2$Ph); 3.49 (1H, dd, J = 6.0 and 10.6 Hz, 1H of C*H*$_2$OH); 3.56 (1H, dd, J = 5.9 and 10.6 Hz, 1H of C*H*$_2$OH); 7.18-7.31 (5H, m, 5 Ar C*H*).

(2*S*)-(+)-2-Methyl-3-phenyl propanol (*R*)-5[3] (from *ent*-**18**)



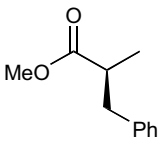
To a stirred solution of *i*-Pr_2NH (0.48 mL, 3.40 mmol, 8.4 eq) in dry THF (7 mL) at –78 °C under N_2 was added *n*-BuLi (1.40 mL, 2.25 M in hexanes, 7.8 eq.) and the mixture stirred at –78 °C for 10 min and at 0 °C for 10 min. BH_3•NH_3 (100 mg, 3.24 mmol, 8.0 eq.) was added and the resulting mixture stirred at 0 °C for 15 min and at room temperature for 15 min. After cooling to 0 °C again the mixture was added via cannula to a suspension of the resin bound amide *ent*-**20 (R= Me)** (507 mg, 0.80 mmol/g (max.), 1 eq.) in dry THF (5 mL) at 0 °C under N_2. The reaction was stirred slowly for 24 h after which the resin was filtered and washed with distilled THF (300 mL). The filtrate was concentrated *in vacuo* and the resulting organic residue quenched with 3M HCl (5 mL) and extracted with Et_2O (2 × 10 mL). The combined organics were washed with 3M HCl (2 mL), 2M NaOH (2 mL) and brine (2 mL), dried over Na_2SO_4 and concentrated. Purification by column chromatography (15% EtOAc/ pet. ether/ silica provided chiral alcohol (*R*)–**5** (35 mg, 0.233 mmol, 58%) as a clear oil in 92% enantiomeric excess as determined by chiral GC analysis using a β-cyclodextrin column (50-100 °C @ 5°C/min, 3 min hold, 100-109 °C @ 0.1°C/min, 15 min hold, 109-112 °C @ 0.1°C/min, 1 min hold, major enantiomer eluted at 112.00 min). $[\alpha]_D^{20}$ = +10.4 (c = 2.3 in $CHCl_3$), (lit[3] $[\alpha]_D^{20}$ = +10.0 (c = 0.84 in $CHCl_3$)). See **(*S*)-5** for data.

(2*S*)-(+)-2-Methyl-3-phenyl propanoic acid 21[3]



A slowly stirred suspension of resin **20 (R= Me)** (1.95 g, 0.80 mmol/g (max.), 1 eq.) and *n*-Bu_4NOH (10.4 mL, 40% w/w, 10 eq.) in *t*-BuOH (10 mL), H_2O (10 mL) and THF (30 mL) was heated to reflux for 6 h. The reaction was cooled to room temperature, filtered and the resin washed with distilled THF (200 mL) and THF/H_2O (1:1, 200 mL). The filtrate was concentrated under reduced pressure and partitioned between 0.5 M NaOH and Et_2O. The aqueous phase was extracted with Et_2O (2 × 40 mL) and acidified to pH ≤ 2 with 3 M HCl. The acidic aqueous phase was extracted with Et_2O (2 × 50 mL), the organics, washed with water, dried over Na_2SO_4 and concentrated under reduced pressure to **21** (90 mg, 0.55 mmol, 35% for 3 steps) as a pale yellow oil. $[\alpha]_D^{20} = 22.8$ (c = 0.5 in $CHCl_3$) (lit[3] $[\alpha]_D^{20} = 25.5$ (c = 1.0 in $CHCl_3$)); ν_{max}(neat, ATR) 2931 (br, OH), 1693 (C=O), 1463, 1230, 1095 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.22 (3H, d, J = 6.9 Hz, C*H*$_3$); 2.70 (1H, dd, J = 8.0 and 13.5 Hz, 1H of C*H*$_2$Ph); 2.77-2.84 (1H, m, C*H*CH_3); 3.12 (1H, dd, J = 6.5 and 13.5 Hz, 1H of C*H*$_2$Ph); 7.21-7.34 (5H, m, 5 Ar C*H*).

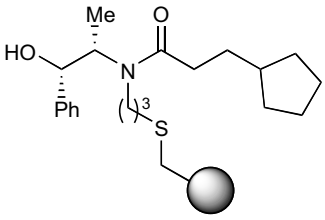
Methyl-(2*S*)-(+)-2-methyl-3-phenyl propanoate 15[4] (from **21**)



[4] D. Kato, K. Miyamoto, H. Ohta, *Tetrahedron: Asymmetry,* 2004, **15**, 2975.

To a stirred solution of acid **21** (15 mg, 0.09 mmol, 1 eq.) in dry MeOH (1.5 mL) at room temperature under N_2 was added $TMSCHN_2$ (0.27 mL, 2 M in hexanes, 6 eq.) and the reaction stirred for 0.5 h. The reaction was quenched with a few drops of formic acid, diluted with EtOAc, washed with aq. sat. $NaHCO_3$ and concentrated under reduced pressure to give methyl ester **15** (10 mg, 0.056 mmol, 62%) as a pale oil in 85% enantiomeric excess, determined by chiral GC analysis using a β-cyclodextrin column (80 °C, 45 min hold, 80-92 °C @ 0.1°C/min, 0 min hold, 92-150 °C @ 5.0°C/min, 5 min hold; major enantiomer eluted at 158.55 min). ν_{max}(neat) 2928, 1725, 1662, 1453, 1367, 1245, 1175, 1095 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.09 (3H, d, J = 6.9 Hz, C*H*$_3$); 2.59 (1H, dd, J = 7.8 and 13.3 Hz, 1H of C*H*$_2$Ph); 2.65-2.69 (1H, m, C*H*CH_3); 2.96 (1H, dd, J = 6.7 and 13.3 Hz, 1H of C*H*$_2$Ph); 3.57 (3H, s, OC*H*$_3$); 7.10-7.23 (5H, m, 5 Ar C*H*).

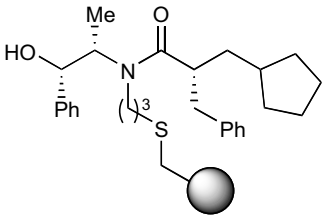
(1*S*,2*S*)-*S*-Merrifield bound-*N*-(3-sulfanylpropyl)-3-cyclopentyl-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-propionamide



To a slowly stirred suspension of resin *ent*-**18** (834 mg, 0.902 mmol/g (max.), 1 eq.) in dry THF (15 mL) at 0 °C under N_2 was added Et_3N (0.29 mL, 2.06 mmol, 5 eq.) and TMSCl (0.10 mL, 0.83 mmol, 1.5 eq.) and the reaction stirred for 3 h. To a stirred solution of 3-cyclopentyl propionic acid (0.54 mL, 3.75 mmol, 5 eq.) in dry THF (5 mL)

at room temperature under N_2 was added Et_3N (0.52 mL, 3.76 mmol, 5 eq.). The mixture was stirred for 20 min then cooled to 0 °C and pivaloyl chloride (0.463 mL, 3.76 mmol, 5 eq.) added and the mixture stirred for a further 3 h. The resulting solution was added to the suspension of resin and the reaction allowed to warm to room temperature and stirred for 20 h. Water (10 mL) was added, the reaction filtered and the resin washed with THF (distilled, 3 × 50 mL), MeOH then CH_2Cl_2 (3 × 50 mL each) and THF (distilled, 3 × 50 mL). The resin was then treated with a solution of TBAF (2.26 mL, 1M in THF, 3 eq.) in THF (5 mL) for 20 h, filtered and washed as before and dried *in vacuo*. ν_{max}(ATR) 3402 (OH), 2920, 1608 (C=O), 1442, 1024 cm^{-1}.

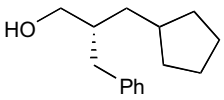
(1*S*,2*S*)-*S*-Merrifield bound-(2*R*)-2-benzyl-*N*-(3-sulfanylpropyl)-3-cyclopentyl-*N*-(2-hydroxy-1-methyl-2-phenylethyl)propionamide



To a stirred solution of LiCl (339 mg, 8.01 mmol, 18 eq.) and *i*-Pr_2NH (0.42 mL, 2.99 mmol, 6.7 eq.) in dry THF (6 mL) at –78 °C under N_2 was added *n*-BuLi (1.28 mL, 2.25 M in hexanes, 6.2 eq.). The solution was warmed briefly to 0 °C then cooled to –78 °C again and added to a slowly stirred suspension of (1*S*,2*S*)-*S*-Merrifield bound-*N*-(3-sulfanylpropyl)-3-cyclopentyl-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-propionamide (518 mg, 0.86 mmol/g (max.), 1 eq.) and LiCl (339 g, 8.01 mmol, 18 eq.) in dry THF (4 mL) at –78 °C under N_2. The reaction was stirred slowly for 3 h, warmed to 0 °C for 10 min, to room temperature for 10 min and cooled to 0 °C again before addition of BnBr (0.24

mL, 2.00 mmol, 4.5 eq.). The reaction was allowed to warm to room temperature and stirred for 48 h. The reaction was filtered and the resin washed with THF (distilled, 3 × 30 mL), MeOH then CH_2Cl_2 (3 × 30 mL each) and THF (distilled, 3 × 30 mL) and dried *in vacuo*. ν_{max}(ATR) 3404 (OH), 2921, 1607 (C=O), 1605, 1442, 1056 cm^{-1}.

(2*R*)-2-Benzyl-3-cyclopentyl-propan-1-ol 22[5] (from *ent*-**18**)

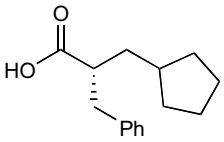


To a stirred solution of *i*-Pr_2NH (0.32 mL, 2.29 mmol, 8.4 eq) in dry THF (5 mL) at –78 °C under N_2 was added *n*-BuLi (0.94 mL, 2.25 M in hexanes, 7.8 eq.) and the mixture stirred at –78 °C for 10 min and at 0 °C for 10 min. $BH_3.NH_3$ (67 mg, 2.176 mmol, 8.0 eq.) was added and the resulting mixture stirred at 0 °C for 15 min and at room temperature for 15 min. After cooling to 0 °C again the mixture was added via cannula to a suspension of (1*S*,2*S*)-*S*-Merrifield bound-(2*R*)-2-benzyl-*N*-(3-sulfanylpropyl)-3-cyclopentyl-*N*-(2-hydroxy-1-methyl-2-phenylethyl)propionamide (360 mg, 0.76 mmol/g (max.), 1 eq.) in dry THF (4 mL) at 0 °C under N_2. The reaction was allowed to warm slowly to room temperature and slowly stirred for 24 h after which the resin was filtered and washed with distilled THF (300 mL). The filtrate was concentrated *in vacuo* and the resulting organic residue quenched with 3M HCl (5 mL) and extracted with Et_2O (2 x 10 mL). The combined organics were washed with 3M HCl (2 mL), 2M NaOH (2 mL) and brine (2 mL), dried over Na_2SO_4 and concentrated to give alcohol **22** (30 mg, 0.137

[5] P. C Hutchison, T. D. Heightman, D. J. Procter, *J. Org. Chem.,* 2004, **69**, 790.

mmol, 51%) as a clear oil in 87% enantiomeric excess as determined by chiral GC analysis using a β-cyclodextrin column (100 °C, 5 min hold, 100-155 °C @ 0.1°C/min, 70 min hold, 155-200 °C at 5.0 °C/min, 10 min hold; major enantiomer eluted at 77.37 min, see appendix 3). $[\alpha]_D^{20}$ = +5.90 (c = 2.7 in $CHCl_3$); (lit[5] $[\alpha]_D^{20}$ = -6.22 (c = 1.19 in $CHCl_3$) for opposite enantiomer); ν_{max}(neat) 3324 (OH), 2916, 1450, 1025 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.92-0.99 (2H, m, C*H*$_2$); 1.18-1.26 (1H, m, 1H of C*H*$_2$CHBn); 1.32-1.37 (1H, m, 1H of C*H*$_2$CHBn); 1.43-1.53 (4H, m, 2 × C*H*$_2$); 1.70-1.85 (4H, m, C*H*Bn, C*H*, C*H*$_2$); 2.54-2.59 (2H, m, C*H*$_2$Ph); 3.43-3.48 (2H, m, C*H*$_2$OH); 7.11-7.23 (5H, m, 5 Ar C*H*).

(2*R*)-2-Benzyl-3-cyclopentyl-propionic acid 23 (from *ent*-**18**)

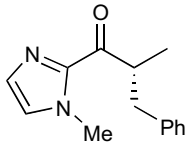


A slowly stirred suspension of (1*S*,2*S*)-*S*-Merrifield bound-(2*R*)-2-benzyl-*N*-(3-sulfanyl-propyl)-3-cyclopentyl-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-propionamide (431 mg, 0.82 mmol/g (max.), 1 eq.) and *n*-Bu_4NOH (2.0 mL, 40% w/w, 20eq.) in *t*-BuOH (2.0 mL), H_2O (2.0 mL) and THF (8 mL) was heated to reflux for 16 h. The reaction was cooled to room temperature, filtered and the resin washed with distilled THF (300 mL). The filtrate was concentrated under reduced pressure and partitioned between 0.5 M NaOH and Et_2O. The aqueous phase was extracted with Et_2O (2 × 20 mL) and acidified to pH ≤ 2 with 3N HCl. The acidic aqueous phase was extracted with Et_2O (2 × 25 mL), the organics washed with water, dried over Na_2SO_4 and concentrated under reduced

pressure. Purification by column chromatography (20% EtOAc/ pet. ether/ silica) provided **23** (43 mg, 0.19 mmol, 53%) as a pale yellow oil. $[\alpha]_D^{20}$ = +2.60 (c = 0.9 in $CHCl_3$). ν_{max}(neat) 2938, 1681 (C=O), 1440, 1290, 941 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.02-1.16 (2H, m, C*H*$_2$ of C_5H_9); 1.45-1.66 (5H, m, 1H of C*H*$_2$CHC(O), and 2 × C*H*$_2$ of C_5H_9); 1.78-1.91 (4H, m, 1H of C*H*$_2$ of C_5H_9, C*H*$_2$ of C_5H_9 and C*H* of C_5H_9); 2.73-2.84 (2H, m, 1H of C*H*$_2$Ph and CHC(O)); 2.96-3.04 (1H, dd, J = 12.9 and 7.2 Hz, 1H of C*H*$_2$Ph); 7.21-7.35 (5H, m, 5 Ar C*H*). ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7 (2 × *C*H$_2$ of C_5H_9); 33.0 (*C*H$_2$ of C_5H_9); 33.6 (*C*H$_2$ of C_5H_9); 38.8 (*C*H of C_5H_9); 39.0 (*C*H$_2$CHC(O)); 39.3 (*C*H$_2$Ph); 47.6 (CH$_2$*C*HC(O)); 127.0 (Ar *C*H); 129.1 (Ar *C*H); 129.5 (Ar *C*H); 139.8 (q*C*); 182.8 (C=O); *m/z* (EI^+ mode) 150 (31), 131 (29), 91 (100); HRMS calcd for (M^+ + H^+) 250.1802, found 250.1799.

To a stirred solution of **23** (6 mg, 0.026 mmol, 1 eq.) in dry Et_2O (1 mL) at 0 °C under N_2 was added $LiAlH_4$ (2 mg, 0.052 mmol, 2 eq.) and the reaction stirred for 3 h. The reaction was quenched with ice water and extracted with Et_2O (3 × 2 mL). The combined organics were washed with brine (2 mL), dried over Na_2SO_4 and concentrated under reduced pressure to provide **22** (4 mg, 0.018 mmol, 71 %) as a pale yellow oil in 87% enantiomeric excess determined by chiral GC analysis using a β-cyclodextrin column (100 °C, 5 min hold, 100-155 °C @ 0.1°C/min, 70 min hold, 155-200 °C at 5.0 °C/min, 10 min hold; major enantiomer eluted at 78.01 min).

(2*R*)-2-Methyl-1-(1-methyl-1*H*-imidazol-2-yl)-3-phenyl-propan-1-one 24[5] (from *ent*–**18**)



To a stirred solution of 1-methylimidazole (0.18 mL, 2.20 mmol, 6 eq.) and TMEDA (0.33 mL, 2.20 mmol, 6 eq.) in dry THF (2 mL) at –78 °C under N_2 was added *n*-BuLi (1.10 mL, 2.0 M in hexanes, 6 eq.) and the solution stirred for 3 h. The resulting 1-methyl-2-imidazoyllithium solution was added, via cannula, to a suspension of *ent*–**20** (R= Me) (532 mg, 0.399 mmol, 1 eq.) in dry THF (8 mL) at –78 °C under N_2. The reaction was stirred for 18h while being allowed to warm slowly to room temperature. *i*-Pr_2NH (0.11 mL) was added and the reaction stirred for a further 15 min. The resin was then filtered and washed with distilled THF (250 mL). The filtrate was concentrated under reduced pressure and the residue partitioned between EtOAc and water. The layers were separated and the aqueous phase extracted with EtOAc. The combined organics were washed with water, dried over Na_2SO_4 and concentrated under reduced pressure. Purification by column chromatography (30% EtOAc/pet. ether/silica) provided **24** (30 mg, 0.131 mmol, 33%) as a colourless oil in 78% enantiomeric excess determined by chiral HPLC analysis. $[\alpha]_D^{20} = -58.0$ (c = 1.8 in $CHCl_3$); ν_{max}(neat) 2936, 1668 (C=O), 1452, 1406 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.22 (3H. d. J = 6.9 Hz, CH_3); 2.71 (1H, dd, J = 13.6 and 8.2 Hz, 1H of CH_2Ph); 3.19 (1H, dd, J = 13.5 and 6.4 Hz, 1H of CH_2Ph); 4.01 (3H, s, NCH_3); 4.21-4.27 (1H, m, CHCH_3); 7.04 (1H, s, Ar CH); 7.17-7.30 (6H, m, 6 × Ar CH).

X–ray structure of 4

CCDC reference number 632894