Asymmetric Synthesis of α-Branched Primary Amines on Solid Support *via* Novel Hydrazine Resins

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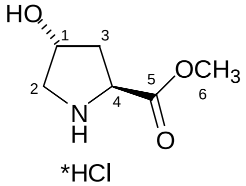
Supporting Informations

General

All chemicals were obtained from commercial suppliers and were of reagent grade. *Merrifield* resin (1-2% cross linked, 200-400 mesh, 0.93 and 0.67 mmol·g^{-1}) was purchased from NovaBioChem and PolymerLabs, *tert*- and *n*-butyllithium from Merck, *n*-hexyllithium from Aldrich, phenyllithium from Acros and BH_3·THF solution (1 M) from Aldrich. *tert*-BuONO[1] and *N,N*-dibenzylleucinol[2] were synthesized according to literature procedures. Solvents were dried and purified by conventional methods prior to use. THF was freshly distilled from sodium/lead alloy under argon, DMF from calcium hydride. Filtration devices with 20 µm pore size were purchased from International Sorbent Technology. Preparative column chromatography was carried out using Merck silica gel 60, particle size 0.040-0.063 mm (230-400 mesh), analytical TLC on silica gel 60 F254 plates, Merck, Darmstadt. Preparative HPLC chromatography was performed on Gilson Abimed, Lichrosorb®-column, Si 60 (7µm), UV detector, analytical chiral HPLC on Hewlett-Packard Daicel AD, UV detector. On-bead IR analysis was carried out using a Perkin-Elmer FT/IR 1750 spectrometer. Micro analyses were obtained with a Heraeus CHN-O-Rapid element analyzer, mass spectra with a Varian MAT 212 (EI 70 eV). ^{1}H-NMR and ^{13}C-NMR analyses (300 and 400 MHz) were performed on Gemini 300 or Varian Inova 400 (solvent $CDCl_3$ or CD_3OD, TMS as internal standard.).

1. Synthesis of the chiral auxiliaries (*S,R*)-4 and (*R*)-6 in liquid phase

1.1 *trans*-4-Hydroxy-(*S*)-prolin-methylester-hydrochloride



1

To $SOCl_2$ (290 mL), carefully dissolved in methanol (1.3 L) at 0°C, *trans*-4-hydroxy-(*S*)-proline (146 g, 1.10 mol) (*S,R*)-**1** was added in small portions. After warming to room temperature, the mixture was stirred for additional 24 h and concentrated in *vacuo*. The residue was taken up in methanol, ether was added and the precipitate collected on a filter. Evaporation of the mother liquor and a second crystallization furnished the product in quantitative yield (199.5 g) as colourless needles.

^{1}H-NMR (300 MHz, CD_3OD):

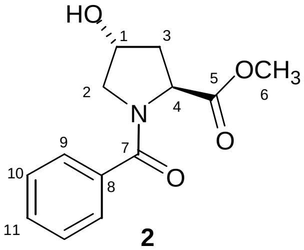
δ = 2.19 (m, 1H, C3-*H*a), 2.41 (m, 1H, C3-*H*b), 3.30 (m, 1H, C2-*H*a), 3.43 (dd, *J* = 12.3 Hz, *J* = 3.5 Hz, 1H, C2-*H*b) , 3.86 (s, 3H, C6-H_3), 4.60 (m, 2H, C1-*H*, C4-*H*) ppm.

^{13}C-NMR (75 MHz, CD_3OD):

δ = 38.55 (C3), 53.98 (C6), 55.01 (C2), 59.42 (C4), 70.61 (C1), 170.62 (C5) ppm.

Other spectroscopic data are in agreement with those reported in the literature.[3]

1.2 (2*S*,4*R*)-4-Hydroxy-1-benzoyl-prolin-methylester



2

Ester **1** (48.6 g, 0.27 mol) was dissolved in dichloromethane (300 mL) at 0°C, triethylamine (93 mL, 2.5 equiv.) was added and the mixture stirred for 1,5 h. After addition of 4-(dimethylamino)pyridine, DMAP (1.6 g, 5 mol%) Benzoylchloride (31.1 mL, 1.0 equiv.) was added dropwise and the mixture was stirred for 12 h at room temperature. The suspension was washed with water (70 mL), hydrochloric acid (5%, 60 mL), 0.5 *N* NaOH (60 mL) and again water (70 mL). The organic phase was dried over $MgSO_4$, concentrated in *vacuo* and the resulting residue taken up in a small amount of dichloromethane. After addition of pentane, a colourless precipitate fell out and was collected on a filter, washed with pentane and dried in *vacuo* to yield 54.8 g (82%) of the desired product.

$[\alpha]_D^{26}$ = –139.8 (*c* = 1.04, $CHCl_3$) **mp:** 139°C

^{1}H-NMR (300 MHz, $CDCl_3$):

δ = 2.11 (ddd, *J* = 13.2 Hz, *J* = 8.5 Hz, *J* = 4.1 Hz, 1H, C3-*H*a), 2.35 (m, 1H, C3-*H*b), 2.66 (br. s, 1H, O*H*), 3.50 (m, 1H, C2-*H*a), 3.77 (s, 3H, C6-H_3), 3.80 (m, 1H, C2-*H*b), 4.46 (m, 1H, C1-*H*), 4.83 (m, 1H, C4-*H*), 7.40 (k.B., 3H, C10-*H*,C11-*H*), 7.55 (m, 2H, C9-*H*) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$):

δ = 37.75 (C3), 52.40 (C6), 57.88 (2 C-atoms, C2, C4), 70.30 (C1), 127.49 (C10), 128.29 (C9), 130.48 (C11), 135.53 (C8), 170.25 (C5), 172.86 (C7) ppm.

IR (KBr):

$\tilde{\nu}$ = 3449 (s), 3062 (w), 3032 (w), 3001 (w), 2956 (m), 2930 (m), 1740 (vs), 1700 (w), 1608 (vs), 1574 (vs), 1500 (m), 1452 (vs), 1437 (vs), 1313 (m), 1276 (vs), 1229 (m), 1211 (m), 1177 (w), 1087 (s), 1055 (w), 1025 (vs), 988 (w), 956 (w), 930 (w), 905 (w), 883 (w), 798 (m), 727 (vs), 703 (s), 672 (w), 647 (w), 611 (w), 588 (w), 495 (w), 467 (w) cm^{-1}.

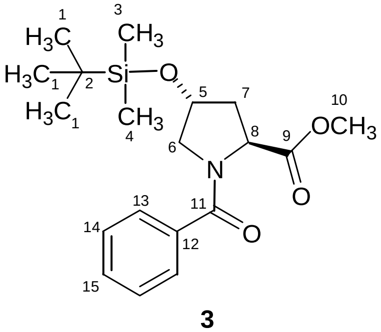
MS (70 eV):

m/z (%) = 250 (5, M^++1), 249 (32, M^+), 231 (2), 218 (2), 192 (1), 191 (13), 190 (100), 144 (1), 106 (6), 105 (85), 78 (2), 77 (24), 76 (1), 56 (4), 55 (1), 51 (9), 50 (2).

CHN-Analysis: $C_{13}H_{15}NO_4$ (249.26 g/mol)

calcd (%):	C 62.64	H 6.07	N 5.62
found (%):	C 62.68	H 6.05	N 5.54

1.3 (2*S*,4*R*)-4-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]-oxy}-1-benzoyl-prolin-methyl-ester (*S*,*R*)-2



3

Amide **2** (209.6 g, 0.84 mol) and imidazol (143 g, 2.5 equiv.) were dissolved in DMF (1.1 l) and stirred for 3 h at room temperature. A solution of *tert*-butyldimethyl-silylchloride (50% in toluene, 317 g, 1.25 equiv.) was added dropwise and the mixture stirred for 40 h. After concentration in *vacuo* (rotary evaporator, 80°C), the residue was taken up in ether, washed with water, deluted acetic acid, $NaHCO_3$ solution and water and dried over $MgSO_4$. After evaporation of the solvent, the obtained colourless residue (300 g, 98%) can be used in the next step without further purification. An analytical sample was obtained by crystallization from dichloromethane/pentane.

$[\alpha]_D^{26}$ = –88.2 (c = 0.99, $CHCl_3$) **mp:** 77°C

^{1}H-NMR (300 MHz, $CDCl_3$):

δ = –0.04 (s, 3H, C3-H_3), 0.03 (s, 3H, C4-H_3), 0.82 (s, 9H, C1-H_3), 2.08 (m, 1H, C7-*H*a), 2.29 (m, 1H, C7-*H*b), 3.39 (m, C6-*H*a) 3.75 (m, 1H, C6-*H*b), 3.79 (s, 3H, C10-H_3), 4.43 (m, 1H, C5-*H*), 4.81 (t, J = 8.0 Hz, 1H, C8-*H*), 7.43 (k.B., 3H, C14-*H*,C15-*H*), 7.56 (m, 2H, C13-*H*) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$):

δ = –4.96 (C3), –4.82 (C4), 17.86 (C2), 25.62 (C1), 38.39 (C7), 52.34 (C10), 57.94 (C8), 58.14 (C6), 70.77 (C5), 127.40 (C14), 128.29 (C13), 130.30 (C15), 135.95 (12), 170.24 (C9), 172.96 (C11) ppm.

IR (KBr):

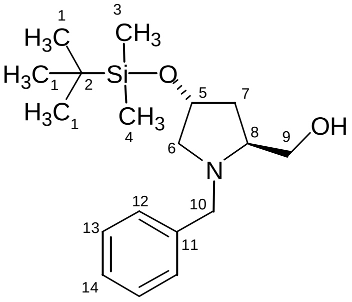
$\tilde{\nu}$ = 3476 (m), 3229 (w), 3070 (m), 2954 (vs), 2931 (vs), 2889 (s), 2856 (s), 1960 (w), 1897 (w), 1754 (vs), 1703 (w), 1617 (vs), 1574 (vs), 1498 (s), 1464 (vs), 1450 (vs), 1418(vs), 1385 (vs), 1358 (vs), 1317 (s), 1292 (m), 1255 (vs), 1233 (s), 1195 (vs), 1167 (vs), 1145 (s), 1097 (vs), 1063 (s), 1025 (vs), 991 (s), 928 (s), 916 (m), 869 (m), 838 (vs), 809 (s) cm^{-1}.

MS (70 eV):

m/z (%) = 348 (2, M^+-CH_3), 332 (1), 308 (6), 307 (22), 306 (100), 305 (2), 304 (4), 246 (1), 220 (2), 179 (1), 149 (1), 142 (2), 106 (6), 105 (81), 101 (1), 89 (2), 78 (1), 77 (15), 75 (5), 73 (5), 69 (1), 59 (2), 57 (1), 51 (1).

CHN-Analysis:		$C_{19}H_{29}NO_4Si$	(363.52 g/mol)
calcd (%):	C 62.78	H 8.04	N 3.85
found (%):	C 62.49	H 8.25	N 3.57

1.4 (2*S*,4*R*)-4-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]-oxy}-1-benzyl-2-hydroxy-methyl-pyrrolidin



4

A suspension of lithiumaluminumhydride (25 g, 0.66 mol, 3.3 equiv.) in THF (400 mL) was heated under reflux for 15 min. Ester **3** (74.0 g, 0.20 mol), dissolved in THF (100 mL), was added at a rate keeping the reaction mixture under gentle reflux. After complete addition, the mixture was heated for 1 h, cooled to room temperature and carefully hydrolyzed with KOH solution (20%, 100 mL). The solid was filtered of and extracted with ether (150 mL) under reflux (1 h). The combined organic filtrates were concentrated and ether was added. After drying over $MgSO_4$ and evaporation of the solvent under reduced pressure (HV), the obtained colourless oil (65.0 g, 99%) can be used in the next step without further purification. An analytical sample was obtained by flash chromatography (pentane/ether 1:1).

R_f: 0.40 (pentane/ether 1:1); $[\alpha]_D^{26}$ = –50.6 (*c* = 1.04, $CHCl_3$); **mp:** 48°C

^{1}H-NMR (300 MHz, $CDCl_3$):

δ = 0.01 (s, 3H, C3-*H*$_3$), 0.03 (s, 3H, C4-*H*$_3$), 0.87 (s, 9H, C1-*H*$_3$), 1.82 (ddd, *J* = 12.7 Hz, *J* = 8.4 Hz, *J* = 4.3 Hz, 1H, C7-*H*a), 2.06 (m, 1H, C7-*Hb*), 2.35 (dd *J* = 10.1 Hz, *J* = 5.7 Hz, 1H, C6-*H*a), 2.74 (br. s, 1H, O*H*), 3.04 (m, 1H, C8-*H*), 3.12 (dd, *J* = 9.7 Hz, *J* = 5.3 Hz, 1H, C6-*H*b), 3.37 (d, *J* = 11.1 Hz, 1H, C9-*H*a), 3.45 (dd, = 13.1 Hz, *J* = 4.4 Hz, 1H, C10-*H*a), 3.63 (dd, *J* = 11.1 Hz, *J* = 10.7 Hz, 1H, C9-*H*b), 3.96 (d, *J* = 13.1 Hz, 1H, C10-*H*b), 4.26 (m, 1H, C5-*H*), 7.22 (k.B., 3H, C13-*H*, C14-*H*), 7.32 (m, 2 H, C12-*H*) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$):

= –4.83 (C3), –4.78 (C4), 17.99 (C2), 25.82 (C1), 37.87 (C7), 58.81 (C10), 61.22 (C6), 62.30 (C9), 63.47 (C8), 70.73 (C5), 127.09 (C13), 128.37 (C12), 128.66 (C14), 139.15 (C11) ppm.

IR (KBr):

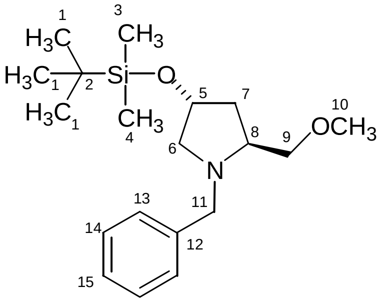
$\tilde{\nu}$ = 3420 (m,br), 3086 (w), 3063 (m), 3029 (m), 2954 (vs), 2929 (vs), 2885 (vs), 2857 (vs), 2803 (s), 2738 (w), 1496 (m), 1472 (s), 1463 (s), 1454 (s), 1385 (s), 1361 (m), 1337(m), 1309 (w), 1255 (vs), 1217 (m), 1130 (vs), 1112 (vs), 1052 (vs), 1007 (m), 963 (w), 938 (w), 915 (s), 882 (m), 837 (vs), 777 (vs), 737 (s), 700 (vs), 669 (w) cm^{-1}.

MS (70 eV):

m/z (%) = 306 (3, M^+-CH_3), 292 (7), 291 (24), 290 (100), 289 (1), 264 (1), 206 (1), 205 (3), 191 (1), 190 (9), 176 (6), 159 (3), 158 (21), 142 (2), 131 (1), 111 (1), 97 (1), 92 (4), 91 (51), 88 (2), 75 (2), 73 (5), 70 (4), 69 (1), 68 (1), 65 (1), 61 (4), 59 (1), 45 (3).

CHN-Analysis:		$C_{18}H_{31}NO_2Si$ (321.53 g/mol)	
calcd (%):	C 67.24	H 9.72	N 4.36
found (%):	C 66.89	H 10.20	N 4.25

1.5 (2*S*,4*R*)-4-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]-oxy}-1-benzyl-2-methoxy-methyl-pyrrolidin (*S*,*R*)-3



5

To a mixture of NaH (60% in paraffin oil, 43.2 g, 1.08 mol, 1.5 equiv.) and methyliodide (66.4 mL, 1.08 mol, 1.5 equiv.) in THF (1.2 L) was added a solution of alcohol **4** (232 g, 0.72 mol) in THF (400 mL), during which the reaction mixture starts to reflux. After complete addition, the mixture was heated for 1 h, cooled to ambient temperature and hydrolyzed with pH-7-buffer (300 mL). After addition of brine (100 mL), the mixture was extracted with ether (3×400 mL) and the combined organic layers were washed with water (3×100 mL) and brine (100 mL). After evaporation of the solvent in *vacuo*, the obtained yellow oil (223.5 g, 93%) can be used in the next step without further purification. An analytical sample was obtained by flash chromatography (pentane/ether 4:1).

R_f: 0.13 (pentane/ether 4:1); $[\alpha]_D^{25}$ = –57.6 (*c* = 1.04, $CHCl_3$)

^{1}H-NMR (300 MHz, $CDCl_3$):

δ = 0.00 (s, 3H, C3-H_3), 0.02 (s, 3H, C4-H_3), 0.86 (s, 9H, C1-H_3), 1.83-1.93 (k.B., 2H, C7-H_2), 2.25 (dd, *J* = 9.6 Hz, *J* = 6.0 Hz, 1H, C6-*H*a), 3.00 (m, 1H, C8-*H*), 3.11 (m, 1H, C6-*H*b), 3.28-3.40 (k.B., 2H, C9-H_2), 3.33 (s, 3H, C10-H_3), 3.45 (m, 1H, C11-*H*a), 4.06 (d, *J* = 13.2 Hz, 1H, C11-*H*b), 4.29 (p, *J* = 6.0 Hz, 1H, C5-*H*), 7.22-7.32 (k.B., 5H, C14-*H*, C15-*H*, C13-*H*) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$):

δ = –4.83 (C3, C4), 18.02 (C2), 25.83 (C1), 38.85 (C7), 59.10 (C10), 59.75 (C11), 61.89 (C8), 62.56 (C6), 70.29 (C5), 76.01 (C9), 126.80 (C15), 128.16 (C14), 128.89 (C13), 139.46 (12) ppm.

IR (film):

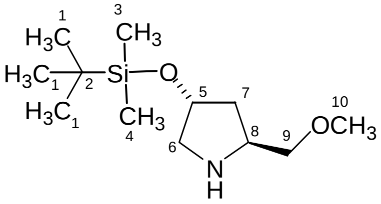
$\tilde{\nu}$ = 3086 (w), 3063 (w), 3028 (m), 2954 (vs), 2928 (vs), 2885 (vs), 2857 (vs), 2828 (s), 2808 (s), 2737 (w), 1495 (m), 1472 (s), 1463 (s), 1454 (s), 1381 (s), 1361 (m), 1345 (m), 1313 (w), 1255 (vs), 1221 (m), 1190 (m), 1118 (vs), 1103 (vs), 1058 (s), 1031 (s), 1007 (m), 964 (m), 939 (w), 913 (s), 886 (m), 837 (vs), 811 (m), 776 (vs), 738 (s), 699 (vs), 669 (w) cm^{-1}.

MS (70 eV):

m/z (%) = 334 (1, M^+ –1), 320 (2), 292 (24), 290 (100), 159 (3), 158 (18), 142 (1), 111 (1), 92 (4), 91 (46), 88 (4), 85 (1), 83 (1), 75 (3), 73 (6), 71 (2), 70 (7), 69 (1), 65 (1), 61 (7), 59 (2), 57 (2), 55 (2), 45 (6).

CHN-Analysis:		$C_{19}H_{33}NO_2Si$ (335.56 g/mol)	
calcd (%):	C 68.01	H 9.91	N 4.17
found (%):	C 67.73	H 10.22	N 4.43

1.6 (2*S*,4*R*)-4-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]-oxy}-2-methoxymethyl-pyrrolidin



6

Benzylamine **5** (110 g) was dissolved in ethanol (200 mL), Pd/C (10%, 1.0 g) was added and the mixture hydrogenolyzed (4.5 bar of hydrogen) at 60°C for 2 d. After complete conversion (TLC control), the catalyst was filtered off, the solvent evaporated and the green residue was purified by distillation (76-78°C, 0.05 torr) to yield the product as a colourless liquid (68.8 g, 86%).

$[\alpha]_D^{26}$ = +15.1 (*c* = 0.98, $CHCl_3$)

^{1}H-NMR (300 MHz, $CDCl_3$):

δ = 0.04 (s, 3H, C3-H_3), 0.05 (s, 3H, C4-H_3), 0.88 (s, 9H, C1-H_3), 1.56 (m, 1H, C7-*H*a), 1.76 (m, 1H, C7-*H*b), 2.23 (s, 1H, N*H*), 2.80 (ddd, *J* = 11.5 Hz, *J* = 2.8 Hz, *J* = 1.3 Hz, 1H, C6-*H*a), 2.98 (dd, *J* = 11.5 Hz, *J* = 4.4 Hz, 1H, C6-*H*b), 3.26-3.40 (k.B., 2H, C9-H_2), 3.36 (s, 3H, C10-H_3), 3.54 (m, 1H, C8-*H*), 4.34 (m, 1H, C5-*H*) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$):

δ = –4.77 (C3), –4.74 (C4), 18.07 (C2), 25.85 (C1), 38.54 (C7), 55.77 (C6), 56.44 (C8), 59.00 (C10), 73.28 (C5), 76.35 (C9) ppm.

IR (film):

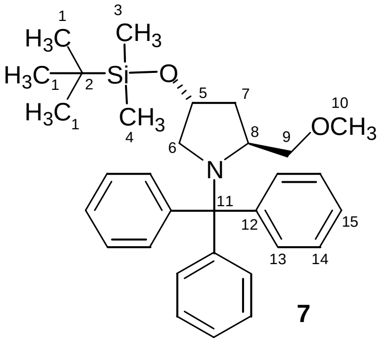
$\tilde{\nu}$ = 3343 (w), 2954 (vs), 2928 (vs), 2868 (vs), 2857 (vs), 2826 (s), 2739 (w), 1472 (s), 1463 (s), 1434 (m), 1408 (m), 1388 (m), 1362 (s), 1326 (w), 1255 (vs), 1213 (m), 1198 (m), 1186 (m), 1131 (vs), 1102 (vs), 1023 (s), 1007 (s), 972 (w), 939 (m), 910 (s), 837 (vs), 809 (s), 776 (vs), 700 (w), 669 (w) cm^{-1}.

MS (70 eV):

m/z (%) = 246 (1, M$^+$+1), 230 (3), 202 (4), 201 (16), 200 (89), 188 (13), 116 (15), 115 (4), 100 (4), 89 (4), 82 (5), 80 (4), 75 (17), 73 (23), 71 (5), 69 (6), 68 (100), 59 (10), 57 (9), 56 (5), 55 (21), 47 (4), 45 (10).

CHN-Analysis:		$C_{12}H_{27}NO_2Si$ (245.43 g/mol)	
calcd (%):	C 58.72	H 11.09	N 5.71
found (%):	C 58.87	H 11.11	N 6.01

1.7 (2S,4R)-4-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]-oxy}-2-methoxymethyl-1-trityl-pyrrolidin



7

Amine **6** (19.5 g, 0.08 mol) was dissolved in dichloromethane (500 mL) under argon, treated with tritylbromide (32.2 g, 1.25 equiv.) and triethylamine (20.2 g, 2.5 equiv.) and stirred for 24 h at room temperature. The mixture was washed with water (3×50 mL), brine (50 mL) and dried over Na_2SO_4. After evaporation of the solvent in *vacuo*, the obtained orange oil (38.9 g, 99%) can be used in the next step without further purification. An analytical sample was obtained by dry-flash chromatography (pentane→pentane/ether 1:1, 1% triethylamine).

^{1}H-NMR (300 MHz, $CDCl_3$):

δ =0.00 (s, 3H, C3-H_3), 0.03 (s, 3H, C4-H_3), 0.77 (m, 1H, C7-*H*a), 0.87 (s, 9*H*, C1-H_3), 1.88 (ddd, 1H, J= 12 Hz, J= 8 Hz, C7-*H*b), 2.60 (dd, 1H, J= 11 Hz, J= 6 Hz, C6-*H*b), 3.33 (s, 3H, C10-H_3), 3.48 (dd, 1H, J= 9 Hz, J= 3 Hz, C6-*H*a), 3.60 (m, 3H, C9-H_2, C8-*H*), 4.49 (q, 1H, J= 7 Hz, C5-*H*), 7.26 (m, 3H, C15-*H*), 7.36 (m, 6H, C13-*H*), 7.68 (d, 6H, J= 7 Hz, C14-*H*) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$):

δ = –5.2 (C3), –5.0 (C4), 17.6 (C2), 25.4 (C1), 36.8 (C7), 57.4 (C6), 58.2 (C10), 58.4 (C8), 70.9 (C9), 74.9 (C5), 77.14 (C11), 125.7 (C15), 127.0 (C14), 129.3 (C13), 143.9 (C12) ppm.

IR (kapillar):

$\tilde{\nu}$ = 3087 (m), 3057(m), 3034(m), 2954(s), 2928(s), 2888(s), 2856(s), 2824(m), 2739(w), 2708(w), 2323(w), 1958(w), 1912(w), 1815(w), 1666(w), 1596(m), 1512(m), 1488(s), 1480(s), 1472(s), 1462(s), 1448(s), 1406(w), 1385(m), 1361(m), 1334(w), 1319(w), 1252(s), 1203(m), 1186(m), 1113(s), 1051(m), 1034(s), 1016(m), 968(m), 936(m), 914(m), 898(m), 836(s), 775(s), 744(s), 733(m), 710(s), 678(s), 645(w), 631(m), 572(w), 527(w), 473(w) cm^{-1}.

MS (70 eV):

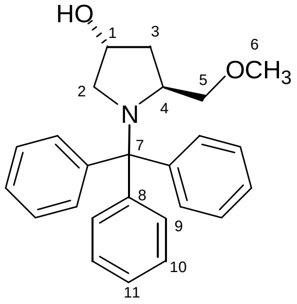
m/z (%) = 487 (1, M^+), 442 (4), 243 (100), 228 (4), 165 (24), 115 (1), 73 (2).

CHN-Analysis: $C_{31}H_{41}NO_2Si$ (487.75 g/mol)

calcd (%): C 76.34 H 8.47 N 2.87

found (%): C 75.97 H 8.57 N 2.86

1.8 (2*S*,4*R*)-4-Hydroxy-2-methoxymethyl-1-trityl-pyrrolidin (*S*,*R*)-4



8

To a solution of silylether **7** (38.9 g, 0.08 mmol) in THF (300 mL) was added tetra-*n*-butylammonium fluoride (1 M in THF, 120 mL, 1.5 equiv.) and the mixture stirred for 48 h at room temperature. Ether (500 mL) was added and the mixture washed with water (3×100 mL) and brine (100 mL). After drying over Na_2SO_4 and evaporation of the solvent, the obtained residue was purified by dry flash chromatography (pentane→ether, 1% triethylamine) to yield the product (30 g, 99%) as a colourless foam.

^{1}H-NMR (300 MHz, $CDCl_3$):

δ = 0.64 (m, 1H, C3-*H*a), 1.93 (ddd, *J* = 12.9 Hz, *J* = 7.7 Hz, *J* = 2.4 Hz, 1H, C3-*H*b), 2.68 (m, 1H, C2-*H*a), 3.24 (s, 3H, C6-H_3),3.27 (m, 1H, C2-*H*b), 3.30-3.45 (k.B., 2H, C5-H_2), 3.63 (m, C4-*H*), 4.29 (m, 1H, C1-*H*), 7.17 (t, *J* = 6.0 Hz, 3H C11-*H*), 7.27 (t, *J* = 6.0 Hz, 6H, C10-*H*), 7.60 (d, *J* = 6.0 Hz, 6H, C9-*H*) ppm.

^{13}C-NMR (75 MHz, $CDCl_3$):

δ = 38.12 (C3), 58.40 (C2), 58.85 (C4), 59.22 (C6), 72.71 (C1), 75.45 (C5), 126.36 (C11), 127.60 (C10), 129.55 (C9), 144.85 (C8), not detected (C7) ppm.

IR (KBr):

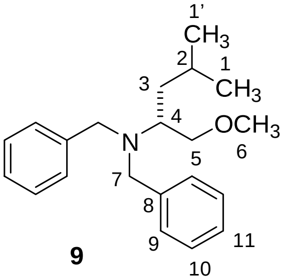
$\tilde{\nu}$ = 3421(s), 3084(m), 3055(m), 3030(m), 2968(s), 2925(s), 2873(s), 2824(s), 1595(m), 1488(vs), 1448(vs), 1384(m), 1351(m), 1319(m), 1264(m), 1205(s), 1186(s), 1104(vs), 1031(vs), 967(m), 934(m), 901(s), 823(w), 774(s), 745(vs), 711(vs), 644(w), 630(s), 519(w) cm^{-1}.

MS (70 eV):

m/z (%) = 329 (2), 328 (7), 245 (2), 244 (22), 243 (100), 241 (3), 239 (3), 228 (4), 215 (2), 165 (25), 164 (2), 115 (1), 91 (1).

CHN-Analysis:		$C_{25}H_{27}NO_2$ (373.49 g/mol)	
calcd (%):	C 80.40	H 7.29	N 3.75
found (%):	C 80.73	H 7.23	N 4.12

1.9 (1*R*)-(–)-*N,N*-Dibenzyl-(1-methoxymethyl-3-methylbutyl)amine



9

To a mixture of NaH (60% in paraffin oil, 5.63 g, 140 mmol, 1.3 equiv.) and methyliodide (8.72 mL, 140 mmol, 1.3 equiv.) in THF (150 mL) was added a solution of (*R*)-*N,N*-Dibenzylleucinol[2] (31.9 g, 108 mmol) in THF (40 mL), while the reaction mixture starts to reflux. After complete addition, the mixture was heated for 3 h, cooled to ambient temperature and hydrolyzed with pH-7-buffer (20 mL). After evaporation of the solvents in *vacuo*, the residue was taken up in ether and dried over $MgSO_4$. After removal of the solvent the product was obtained as a yellow oil (33.49 g, quant.) and could be used without further purification in the next step. An analytical sample was obtained by flash chromatography (pentane/ether 20:1).

R_f = 0.64 (pentane/ether 20:1); $[\alpha]_D^{25}$ = –43.0, (*c* =1.0, $CHCl_3$)

^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 0.59 (d, *J* = 6.59 Hz, 3 H, $CH(CH_3)_2$); 0.82 (d, *J* = 6.59 Hz, 3 H, $CH(CH_3)_2$); 1.11 (m, 1 H, C*H*HCH($CH_3)_2$); 1.45 (m, 1 H, CH*H*CH($CH_3)_2$); 1.80 (m, 1 H, C*H*($CH_3)_2$); 2.85 (m, 1 H, NC*H*); 3.32 (s, 3 H, OCH_3); 3.35 (d/d, *J* = 9.89/5.22 Hz, 1 H, C*H*HOCH_3); 3.58 (m, 1 H, CH*H*OCH_3); 3.60 (d, *J* = 13.46 Hz, 2 H, NCH_2); 3.74 (d, *J* = 13.46 Hz, 2 H, NCH_2); 7.16-7.39 (kB, 10 H, H_{arom}) ppm.

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 22.02 (C-1); 23.41 (C-1‘); 24.54 (C-2); 38.44 (C-3); 54.05 (2 C-atoms, C-4, C-7); 58.77 (C-6); 62.74 (C-3); 73.62 (C-5); 126.4, 127.8, 128.7 (C-9, C-10, C-11); 140.6 (C-8) ppm.

IR (film):

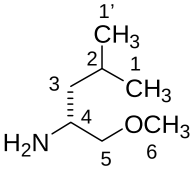
ν = 3085, 30622, 3027 (m, C_{ar}-H); 2952, 2928, 2890, 2867, 2829, 2804 (vs, C-H); 1946, 1873, 1806, 1747 (w); 1603 (m); 1494 (m); 1453 (s); 1385, 1365 (m); 1324, 1249, 1196, 1153 (m); 1112 (vs); 1075, 1029, 1013, 975, 950, 909 (m); 874, 819 (w); 746, 730, 699 (vs) cm^{-1}.

MS: (70 eV)

m/z (%) = 311 (0.2, M^+); 266 (100, $M^+–CH_2OCH_3$); 181 (13); 91 (93, $C_7H_7^+$).

CHN-Analysis:	$C_{21}H_{29}NO$ (311.47 g/mol)		
calcd.	C 80.98	H 9.39	N 4.50
found.	C 80.76	H 9.03	N 4.88

1.10 (1*R*)-(+)-1-Methoxymethyl-3-methylbutylamine (*R*)-6



10

N,N-Dibenzylamine **9** (30.06 g, 98.8 mmol) was dissolved in methanol (300 mL), $Pd(OH)_2/C$ (20%, 5.3 g) was added and the mixture hydrogenolyzed (4 bar of hydrogen) at room temperature for 3 d. After complete conversion (TLC control), the catalyst was filtered off, the solvent evaporated and the residue was purified by distillation (65°C/34 mbar) to yield the product as a colourless liquid (10.54 g, 81%).

^{1}H-NMR (400 MHz, CD_3OD):

δ = 0.89 (d, *J* = 6.59 Hz, 3 H, $CHCH_3$); 0.92 (d, *J* = 6.59 Hz, 3 H, $CHCH_3$); 1.19 (t, *J* = 7.0 Hz, 2 H, $CH_2CH(CH_3)_2$); 1.72 (quin, *J* = 6.59 Hz, 1 H, $CH(CH_3)_2$); 2.95 (m, 1 H, NC*H*); 3.12 (d/d, *J* = 9.07/7.69 Hz, 1 H, $CHHOCH_3$); 3.31 (m, 1 H, $CHHOCH_3$) 3.33 (s, 3 H, OCH_3); 4.61 (br s, 2 H, NH_2) ppm.

^{13}C-NMR (100 MHz, CD_3OD):

δ = 21.71 (C-1); 22.73 (C-1‘); 24.62 (C-2); 42.90 (C-3); 48.44 (C-4); 58.12 (C-6); 77.70 (C-5) ppm.

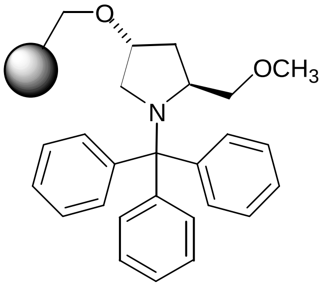
Other spectroscopic data are in agreement with those reported in the literature.[4]

2. Synthesis of the chiral linkers (*S*,*R*)-12 and (*R*)-13

2.1 General procedure for the work-up of the resin (GP 1)

The resin was washed on a glass or plastic frit alternately with THF and methanol (three times with each approx. 40 mL for each per 1.00 g resin). Subsequently the resin was dried *in vacuo*.

2.2 (2S,4R)-4-(Polystyrene-methyloxy)-2-methoxymethyl-1-trityl-pyrrolidin



11

In a dry 500 mL three necked round-bottom flask, fitted with a mechanical stirrer and a gas inlet, *Merrifield*-resin (15.0 g, 13.95 mmol, loading 0.93 mmol·g^{-1}) was swollen under argon in dry DMF (200 mL). A solution of alcohol **8** (13.0 g, 34.9 mmol, 2.5 equiv.) in DMF (20 mL) was added, followed by KH (1.39 g, 34.9 mmol, 2.5 equiv.). The suspension was stirred for 40 h at 50°C. Dry methanol (5 mL) was added and the mixture stirred for additional 18 h at that temperature. After cooling to ambient temperature methanol (50 mL) was added the obtained resin was purified according to GP 1.

<u>CHN-Analysis</u>:

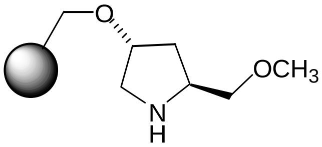
100% Conversion:	$C_{105}H_{106}NO_2$ calcd (%):	C 89.19	H 7.56	N 0.99
66% Conversion:	$C_{145}H_{146}NO_2$ calcd (%):	C 90.01	H 7.61	N 0.72
	found (%):	C 86.89	H 7.59	N 0.72

<u>Loading of the resin</u>: 0.62 mmol N/g calcd from CHN analysis.

IR (KBr):

ν = 3437(m, br), 3080(s), 3057(s), 3023(s), 2908(s), 2209(w, br), 1946(m), 1872(m), 1806(m), 1744(m), 1656(m), 1598(s), 1545(m), 1489(s), 1444(s), 1356(s), 1324(s), 1181(s), 1152(s), 1090(s), 1022(s), 901(s), 843(m), 821(m), 745(s), 691(s), 662(s), 624(s), 523(s) cm^{-1}.

2.3 (2*S*,4*R*)-4-(Polystyrene-methyloxy)-2-methoxymethyl-pyrrolidin (*S,R*)-8



12

Resin **11** (15.0 g) was stirred in a mixture of TFA and dichloromethane (1:10) (3×200 mL) for 15 min. The resin was collected on a frit and washed with methanol and afterwards dichloromethane until a colourless filtrate was obtained. This cleavage procedure was repeated three times (until no further yellow cleavage products were observed). The free, polymer bound amine can be liberated by treatment of the resin with Et_3N/DCM, Et_3N/MeOH, followed by dichloromethane, ether and methanol (3 times each).

CHN-Analysis:

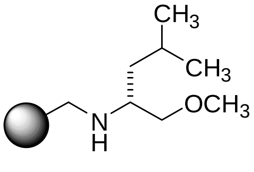
$C_{126}H_{132}NO_2$ calcd (%): C 89.42 H 7.86 N 0.82

found (%): C 88.71 H 8.03 N 0.81

IR (KBr):

$\tilde{\nu}$ = 3363 (m), 3161 (w), 3081 (s), 3058 (s), 3022 (vs), 2913 (vs), 2311 (m), 1943 (s), 1871 (m), 1803 (m), 1746 (m), 1648 (w), 1600 (vs), 1583 (s), 1543 (w), 1511 (m), 1491 (vs), 1449 (vs), 1358 (vs), 1265 (s), 1181 (s), 1154 (s), 1071 (vs), 1027 (vs), 964 (s), 905 (s), 841 (m), 819 (s), 747 (vs) cm^{-1}.

2.4 (1*R*)-*N*-Methylpolystyrene-*N*-(1-methoxymethyl-3-methylbutyl)amine (*R*)-9



13

In a dry 500 mL three necked round-bottom flask, fitted with a mechanical stirrer, gas inlet and a reflux condenser, *Merrifield*-resin (8.74 g, 5.85 mmol, loading 0.67 mmol·g^{-1}) was swollen under argon in dry DMF (90 mL), methoxyamine **10** (3.07 g, 23.4 mmol, 4.0 equiv.) and tetra-*n*-butylammonium iodide (216 mg, 0.59 mmol, 10mol%) were added and the mixture stirred for three days at 80°C. After cooling to ambient temperature the obtained resin was purified according to GP 1.

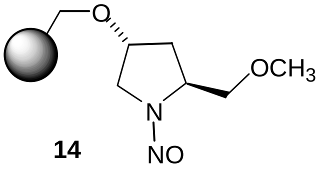
CHN-Analysis: $C_{119}H_{128}NO$ (1592)

calcd.	C 90.0	H 8.12	N 0.88
found.	C 88.0	H 8.10	N 0.881

IR (KBr):

ν = 3446 (br m); 3080, 3059, 3024, 2920, 2849 (s); 2339, 2309, 2253, 1944, 1872, 1799 (m); 1721, 1674, 1640 (m); 1600 (vs); 1545 (m); 1491, 1448 (vs); 1355, 1315, 1270, 1185, 1155, 1093, 1069, 1024, 980, 905 (s); 841 (w); 748, 696 (vs) cm^{-1}.

2.5 (2S,4R)-4-(Polystyrene-methyloxy)-2-methoxymethyl-1-nitroso-pyrrolidin (*S,R*)-10



14

A 500 mL three necked round-bottom flask, equiped with a mechanical stirrer and a reflux condenser, was charged with resin **12** (15.0 g, 9.3 mmol) and THF (200 mL). *tert*-BuONO (5.2 g, 50 mmol, 5 equiv.) was added and the reaction mixture heated under reflux for 24 h. After cooling to ambient temperature, the resin was purified according to GP 1.

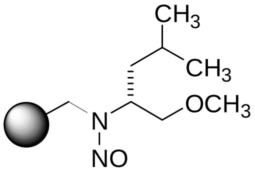
CHN-Analysis:

$C_{126}H_{131}N_2O_3$	calcd (%):	C 87.91	H 7.67	N 1.63
	found (%):	C 86.16	H 7.31	N 1.78

IR (KBr):

ν = 3905 (w), 3856 (w), 3841 (w), 3805 (w), 3753 (w), 3676 (m), 3651 (m), 3438 (m), 3162 (m), 3081 (s), 3058 (s), 3023 (vs), 2909 (vs), 2848 (vs), 2372 (m), 2339 (m), 2309 (m), 1943 (m), 1872 (m), 1803 (m), 1745 (m), 1702 (w), 1673 (m), 1600 (s), 1584 (m), 1546 (m), 1492 (vs), 1449 (vs), 1423 (s), 1351 (s), 1296 (s), 1275 (s), 1196 (s), 1154 (m), 1068 (vs), 1026 (vs), 963 (s), 905 (s), 842 (m), 821 (m), 748 (vs), 684 (vs), 531 (vs) cm^{-1}.

2.6 (1*R*)-*N*-Methylpolystyrene-*N*-(1-methoxymethyl-3-methylbutyl)-*N*-nitroso-amin (*R*)-11



15

A 250 mL three necked round-bottom flask, equiped with a mechanical stirrer and a reflux condenser, was charged with resin **13** (9.13 g, 6.09 mmol) and THF (100 mL). *tert*-BuONO (6.3 g, 61 mmol, 10 equiv.) was added and the reaction mixture heated under reflux for 24 h. After cooling to ambient temperature, the resin was purified according to GP 1.

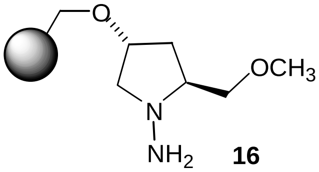
CHN-Analysis: $C_{119}H_{127}N_2O_2$ (1621)

calcd.	C 88.4	H 7.91	N 1.73
found.	C 86.7	H 8.00	N 1.72

IR (KBr):

ν = 3448 (br m); 3082, 3059, 3024, 3001, 2907 (vs); 2734, 2633, 2604 (m); 2311 (w); 1944, 1872, 1803, 1775, 1719 (m); 1701 (s); 1658, 1638 (m); 1601 (vs); 1584 (s); 1561, 1544, 1509 (m); 1493, 1441 (vs); 1366, 1313, 1271, 1182, 1153, 1107, 1069, 1026, 975, 935, 906 (s); 842 (m); 746, 696, 527 (vs) cm^{-1}.

2.7 (2S,4R)-4-(Polystyrene-methyloxy)-2-methoxymethyl-1-amino-pyrrolidin (*S,R*)-12



16

A dry 250 mL three necked round-bottom flask was fitted with a mechanical stirrer, gas inlet and a reflux condenser. The apparatus was purged with argon and charged with dry dichloromethane (100 mL) and resin **14** (10.0 g, 6.2 mmol). Diisobutylaluminumhydride-solution (1 M in dichloromethane, 50 mL, 50 mmol, 8 equiv.) was added carefully and the mixture was stirred for 5 h under reflux. After cooling to ambient temperature, the resin was separated from the reaction solution by filtration under inert gas. The resin was washed with dry dichloromethane and excess diisobutylaluminiumhydride was destroyed with a mixture of 80 ml THF and 20 ml of a sodium methoxide solution (30%) in methanol. The resin was washed with methanol and dichloromethane. Subsequent work up was conducted according to GP 1.

Conversion: 93% (0.52 mmol/g) (determined by elemental analysis of the *p*-nitrobenzaldehyde-hydrazone)

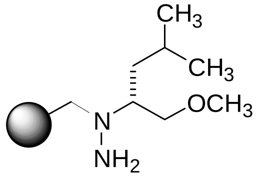
CHN-Analysis:

$C_{126}H_{133}N_2O_2$:	calcd (%):	C 88.63	H 7.85	N 1.64
	found (%):	C 87.79	H 8.37	N 1.53

IR (KBr):

ν = 3905 (w), 3856 (w), 3840 (w), 3821 (w), 3804 (w), 3751 (w), 3735 (w), 3675 (m), 3650 (m), 3424 (vs), 3081 (vs), 3059 (vs), 3023 (vs), 2907 (vs), 1944 (m), 1872 (m), 1802 (m), 1740 (m), 1669 (vs), 1600 (vs), 1544 (m), 1512 (m), 1492 (s), 1449 (vs), 1365 (s), 1179 (vs), 1130 (vs), 1068 (vs), 1026 (vs), 964 (s), 906 (s), 834 (m), 800 (m), 748 (vs), 681 (vs), 529 (vs) cm^{-1}.

2.8 (1*R*)-*N*-Amino-*N*-methylpolystyrene-*N*-(1-methoxymethyl-3-methylbutyl)-amine (*R*)-13



17

A dry 250 mL three necked round-bottom flask was fitted with a mechanical stirrer, gas inlet and a reflux condenser. The apparatus was purged with argon and charged with dry THF (70 mL) and resin **15** (5.61 g, 3.93 mmol). Diisobutylaluminumhydride-solution (1 M in dichloromethane, 39 mL, 39 mmol, 10 equiv.) was added carefully and the mixture was stirred for 5 h at 50°C. After cooling to ambient temperature, the resin was separated from the reaction solution by filtration and excess diisobutyl-aluminiumhydride was carefully destroyed with ethanol. The resin was washed with THF and a THF/water mixture (1:1) (hydrogen formation!). Subsequent work up was conducted according to GP 1.

Conversion:	81% (0.54 mmol/g)	(determined by elemental analysis of the *p*-nitrobenzaldehyde-hydrazone)

CHN-Analysis: $C_{119}H_{129}N_2O$ (1607)

calcd..	C 89.2	H 8.11	N 1.74
found.	C 80.5	H 7.14	N 1.28

IR (KBr):

ν = 3759-2000 (br vs); 1943, 1871, 1803 (m); 1746 (w); 1666 (m); 1601 (vs); 1543 (m); 1492, 1450 (vs); 1365 (s); 1182, 1154, 1109, 1068, 1027, 905, 844, 757, 696, 482 (m) cm^{-1}.

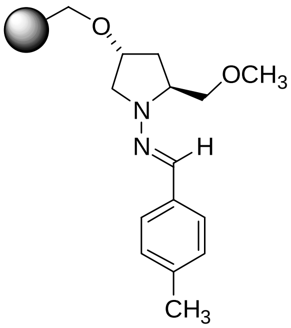
3. Synthesis of polymer-bound hydrazones

3.1 General procedure for the preparation of hydrazone resins 14 and 15 (GP 2)

In a glass or plastic frit hydrazine resins (*R*,*S*)-**12** or (*R*)-**13** were swollen in dry THF (15 mL/g resin), treated with aldehyde (30-40 equiv.) and agitated for 3 d at room temperature. Subsequent work up was conducted according to GP 1.

3.2 Analytical data

3.2.1 (2*S*,4*R*)-[4-(Polystyrene-methyloxy)-2-methoxymethyl-pyrrolidin-1-yl]-(4-methyl-benzylidene)-hydrazone



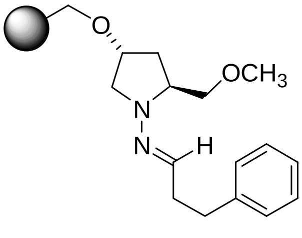
IR (KBr):

ν = 3449 (br m); 3081 (m); 3059, 3024, 3001(s); 2921 (vs); 2849 (s); 2311 (w); 1943 (m); 1871, 1802, 1744, 1702, 1671 (w); 1601 (s); 1585, 1559, 1511 (m); 1493, 1451 (vs); 1358 (m); 1328 (s); 1240, 1181, 1154 (m); 1097, 1070, 1027 (s); 965, 905, 842, 813 (m); 756, 695, 535 (vs) cm^{-1}.

CHN-Analysis: $C_{159}H_{164}N_2O_2$ (2138)

calcd	C 89.5	H 7.74	N 1.31
found	C 85.7	H 7.69	N 1.36

3.2.2 (2*S*,4*R*)-[4-(Polystyrene-methyloxy)-2-methoxymethyl-pyrrolidin-1-yl]-(3-phenyl-propylidene)-hydrazone



IR (KBr):

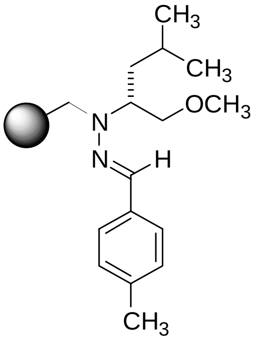
ν = 3450 (br m); 3082 (s); 3059, 3024, 3001, 2918, 2849 (vs); 2311 (w); 1943, 1871, 1803 (m); 1745, 1670 (w); 1601 (vs); 1584 (s); 1543 (w); 1492, 1451 (vs); 1359, 1328, 1181, 1154 (s); 1096, 1070, 1027 (vs); 964, 906 (s); 842 (m); 820 (w); 749, 696, 535 (vs) cm^{-1}.

CHN-Analysis: $C_{160}H_{166}N_2O_2$ (2151)

calcd	C 89.4	H 7.79	N 1.30

found	C 84.8	H 7.34	N 1.24

3.2.3 (1*R*)-*N*-Methylpolystyrene-*N*-(1-methoxymethyl-3-methylbutyl)-*p*-methylbenzaldehyde-hydrazone



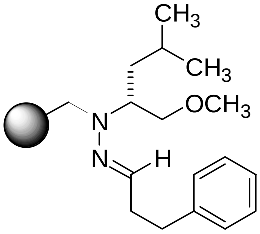
IR (KBr):

ν = 3740-3130 (br vs); 3081, 3059, 3024, 2921 (vs); 2303 (m); 1944, 1872, 1804, 1720 (m); 1667 (w); 1601 (vs); 1549, 1512 (m); 1493, 1450 (vs); 1367 (s); 1271, 1182, 1153 (m); 1104, 1067, 1026 (s); 976, 937, 905, 843 (m); 755, 696 (s); 524 (vs) cm^{-1}.

CHN-Analysis: $C_{155}H_{163}N_2O$ (2066)

calcd	C 88.9	H 7.94	N 1.37
found	C 82.0	H 7.62	N 1.59

3.2.4 (1*R*)-[*N*-Methylpolystyrene-*N*-(1-methoxymethyl-3-methylbutyl)-3-phenyl]propanal-hydrazone



IR (KBr):

ν = 3790-3120 (br vs); 3081, 3059, 3024, 2921 (vs); 1943, 1871, 1803 (m); 1745 (w); 1701 (m); 1601, 1493, 1451 (vs); 1367 (s); 1244, 1181, 1154 (m); 1111, 1067, 1028 (s); 961, 906 (m); 843 (w); 757 (m); 698 (s); 534 (m) cm^{-1}.

4. Synthesis of α-branched amides 19

4.1 General Procedures

General procedure for the preparation of hydrazine resins 16 and 17 *via* 1,2-addition (GP 3)

In a Schlenk flask, equiped with a stirring bar, resins **14** or **15** obtained from GP 2 were swollen under argon in dry THF (15 mL/g resin) and then cooled by means of a cold bath (ethanol/dry ice/liquid nitrogen) to –100°C. The organolithium solution (7 equiv. for aliphatic nucleophiles, 10 equiv. for PhLi) was added dropwise (4 mL/h) and the reaction was allowed to warm to room temperature over night. Water (3 mL/g resin) was added and the mixture collected in a plastic frit, filtered and washed with THF/water 5:1 (3×20 mL/g resin). The further transformations were conducted according to GP 1.

General procedure for the cleavage of the resins 16 and 17 (GP 4)

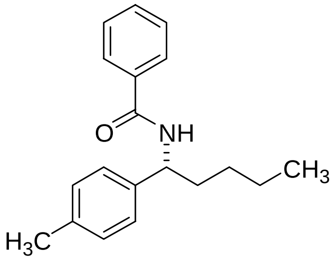
A Schlenk flask, equiped with a stirring bar and a reflux condenser, was purged with argon and charged with resins **16** or **17** obtained from GP 3. The resins were swollen in THF (15 mL/g resin), borane-tetrahydrofuran-complex (1 M in THF, 20 equiv.) was added and the mixture heated under reflux for 4 to 5 h. After cooling to ambient temperature, 3 M aqueous hydrochloric acid (4 mL/g resin) was added, the mixture stirred for 2 h and then collected in a plastic frit, filtered and washed alternately with THF and methanol (3×3 mL/g resin of each). The combined filtrates were concentrated *in vacuo*, 1 M HCl was added (10 mL/g resin) and the aqueous phase extracted with pentane (5 mL/g resin). The aqueous phase was basified with saturated KOH solution and extracted with dichloromethane (4×20 mL/g resin). The combined organic phases were dried with $MgSO_4$ and concentrated *in vacuo* to yield the crude primary amines (*R*/*S*)-**18**.

General procedure for the protection of primary amines 18 (GP 5)

The crude amines (*R*/*S*)-**18** obtained from GP 4 were dissolved in dry dichloromethane (10 mL/mmol), triethylamine (10 equiv.) and catalytic amounts of DMAP were added and the solution cooled to 0°C. The requisite acid chloride was added (5 equiv.), the reaction mixture allowed to warm to room temperature and stirred for 1-3 days. The solvent was evaporated by a stream of argon, the residue taken up in ether and filtered through a glass pipette filled with a plug of glass wool and Florisil™. The filtrate was concentrated *in vacuo* and the residue purified by flash chromatography (silica gel, pentane/ether mixtures, 1% triethylamine) or preparative HPLC to yield the amides (*R*/*S*)-**19**.

4.2 Analytical Data

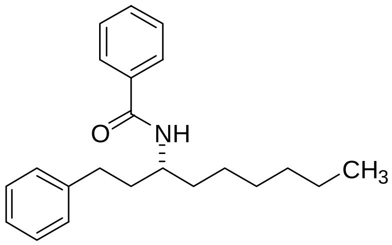
4.2.1 (1*R*)-(+)-*N*-(1-Pentyl-*para*-methylphenyl)benzylamide (*R*)-19d



Yield:	*m* = 7.8 mg	31% starting from 200 mg of resin (*S,R*)-**12**
ee:	66%	(HPLC)
	$[\alpha]_D^{26}$ = +2.6	(c = 0.57, $CHCl_3$)

R_f : 0.32 (pentane/ ether 2:1). — ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, *J* 6.87 Hz, 3H, CH_3), 1.22-1.41 (m, 4H, CH_2), 1.90 (m, 2H, CH_2), 2.33 (s, 3H, CH_3), 5.13 (d/t *J* 7.70/7.42 Hz, 1H, CH), 6.36 (d, *J* 7.70 Hz, 1H, NH), 7.17 (d, *J* 7.96 Hz, 2H, H_{ar}), 7.25 (d, *J* 7.96 Hz, 2H, H_{ar}), 7.36-7.50 (m, 3H, H_{ar}), 7.74 (m, 1H, H_{ar}), 7.76 (m, 1H, H_{ar}) ppm. — MS (EI, 70 eV) *m/z* 281 (11.3, M^+); 224 (49.8, $M^+–C_4H_9$); 105 (100, $C_7H_5O^+$).

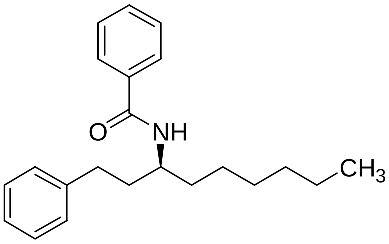
4.2.2 (1*R*)-(+)-*N*-[1-Hexyl-(3-phenylpropyl)]benzylamide (*R*)-19a



Yield:	*m* = 13.4 mg	(43% starting from 200 mg of resin (*S,R*)-**12**)

***ee*:**	83%	(HPLC)
	$[\alpha]_D^{26} = +1.3$	(c = 0.32, $CHCl_3$)

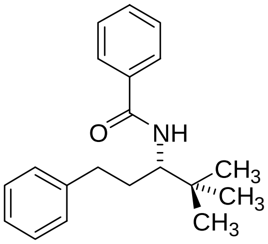
4.2.3 (1*S*)-(–)-*N*-[1-Hexyl-(3-phenylpropyl)]benzylamide (*S*)-19a



Yield:	m = 25 mg	(51% starting from 300 mg of resin (*R*)-**13**)
***ee*:**	78%	(HPLC)
	$[\alpha]_D^{26} = -1.5$	(c = 0.31, $CHCl_3$)

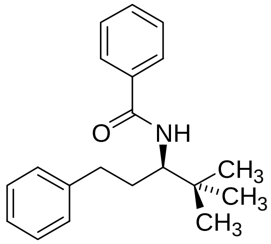
HPLC: 11.0 min (pentane/ether 3:2, 3% NEt_3, 18 mL/min). — ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, *J* 6.8 Hz, 3H, CH_3), 1.20-1.43 (m, 8H, CH_2), 1.45-1.65 (m, 2H, CH_2), 1.82 (m, 1H, CH_2), 1.95 (m, 1H, CH_2), 2.72 (t, *J* 8.1 Hz, 2H, CH_2), 4.25 (m, 1H, CH), 5.81 (d, *J* 8.79 Hz, 1H, NH), 7.15-7.30 (m, 5H, H_{ar}), 7.40-7.52 (m, 3H, H_{ar}), 7.68 (m, 1H, H_{ar}), 7.71 (m, 1H, H_{ar}) ppm. — MS (EI, 70 eV) *m/z* 323 (19.8, M^+); 219 (28.6, $M^+-C_8H_8$); 105 (100, $C_7H_5O^+$).

4.2.4 (1*S*)-(+)-*N*-[1-*tert*-Butyl-(3-phenylpropyl)]benzylamide (*S*)-19b



Yield:	m = 9.9 mg	(37% starting from 200 mg of resin (*S*,*R*)-**12**)
***ee*:**	82%	(HPLC)
	$[\alpha]_D^{26} = +1.1$	(c = 0.035, $CHCl_3$)

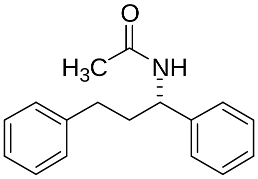
4.2.5 (1*R*)-(–)-*N*-[1-*tert*-Butyl-(3-phenylpropyl)]benzylamide (*R*)-19b



Yield:	*m* = 16.3 mg	(35% starting from 300 mg of resin (*R*)-**13**)
***ee*:**	86%	(HPLC)
	$[\alpha]_D^{26} = -1.5$	($c = 0.07$, $CHCl_3$)

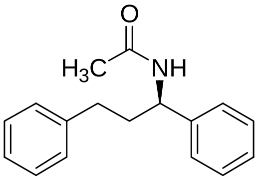
R_f : 0.34 (pentane/ether 2:1). — ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 9H, CH_3), 1.56 (m, 1H, CH_2), 2.06 (m, 1H, CH_2), 2.69 (m, 2H, CH_2), 4.09 (d/t, *J* 10.72/2.48 Hz, 1H, CH), 5.83 (d, *J* 10.72 Hz, 1H, NH), 7.13-7.20 (m, 3H, H_{ar}), 7.23-7.30 (m, 2H, H_{ar}), 7.42-7.56 (m, 3H, H_{ar}), 7.75 (m, 1H, H_{ar}), 7.78 (m, 1H, H_{ar}) ppm. — MS (EI, 70 eV) *m/z* 295 (6.13, M^+); 238 (26.7, $M^+–C_4H_9$); 105 (100, $C_7H_5O^+$)

4.2.6 (1*S*)-(–)-*N*-[1-Phenyl-(3-phenylpropyl)]acetamide (*S*)-19c



Yield:	*m* = 5.4 mg	(24% starting from 200 mg of resin (*S,R*)-**12**)
***ee*:**	81%	(HPLC)
	$[\alpha]_D^{26} = -4.4$	($c = 0.24$, $CHCl_3$)

4.2.7 (1*R*)-(+)-*N*-[1-Phenyl-(3-phenylpropyl)]acetamide (*R*)-19c



Yield:	*m* = 7.1 mg	(28% starting from 200 mg of resin (*R*)-**13**)
***ee*:**	50%	(HPLC)
	$[\alpha]_D^{26}$ = +5.0	(*c* = 0.30, $CHCl_3$)

R_f : 0.56 (ether). — ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96 (s, 3H, H_3CCO), 2.14 (m, 2H, CH_2), 2.60 (m, 2H, CH_2), 5.03 (d/t, *J* 8.79/7.69 Hz, 1H, CH), 5.62 (d, *J* 8.79 Hz, 1H, NH), 7.15-7.38 (m, 10H, H_{ar}) ppm. — MS (EI, 70 eV) *m/z* 253 (22.2, M^+); 149 (51.6, $M^+–C_8H_8$); 106 (100, $C_7H_6N^+$).

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