Supporting Information

Synthesis and Anticonvulsant Activities of *N*-(4'-Substituted)benzyl (*R*)-2-Acetamido-3-methoxypropionamides

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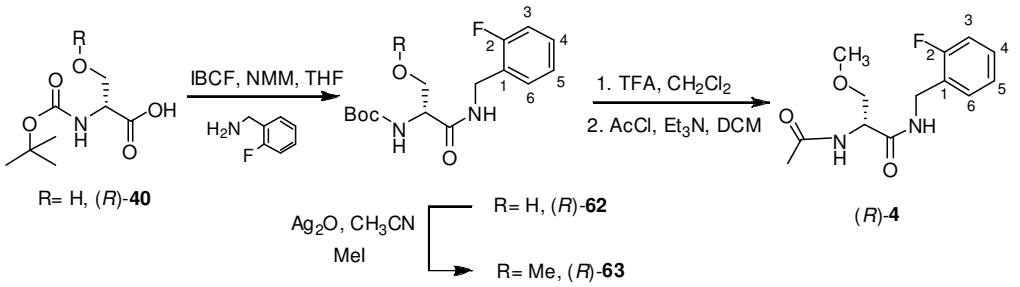
General Methods. Melting points were determined in open capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were run on an ATI Mattson Genesis FT-IR spectrometer. Absorption values are expressed in wavenumbers (cm^{-1}). Optical rotations were obtained on a Jasco P-1030 polarimeter at the sodium D line (589 nm) using a 1 dm path length cell. NMR spectra were obtained at 300 MHz or 400 MHz (^{1}H) and 75 MHz or 100 MHz (^{13}C) using TMS as an internal standard. Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane. Low-resolution mass spectra were obtained with a BioToF-II-Bruker Daltonics spectrometer by Drs. Matt Crowe and S. Habibi at the University of North Carolina Department of Chemistry. The high-resolution mass spectrum was performed on a Bruker Apex-Q 12 Telsa FTICR spectrometer by Drs. Matt Crowe and S. Habibi. Microanalyses were performed by Atlantic Microlab, Inc. (Norcross, GA). Reactions were monitored by analytical thin-layer chromatography (TLC) plates (Aldrich, Cat # Z12272-6) and analyzed with 254 nm light. The reactions were purified by MPLC (CombiFlash Rf) with self-packed columns (silica gel from Dynamic Adsorbents Inc., Cat # 02826-25) or by flash column chromatography using silica gel (Dynamic Adsorbents Inc., Cat # 02826-25). All chemicals and solvents were reagent grade and used as obtained from commercial sources without further purification. THF was distilled from blue sodium benzophenone ketyl. Yields reported are for purified products and were not optimized. Compounds were checked by TLC, ^{1}H and ^{13}C NMR, MS, and elemental analyses. The analytical results are within +0.40% of the theoretical

value. The TLC, NMR and the analytical data confirmed the purity of the products was ≥95%.

1. Preparation of (*R*)-*N*-(2'-Fluoro)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-4).



Preparation of (*R*)-*N*-(2'-Fluoro)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-62). A THF solution (250 mL) of (*R*)-Boc-serine (5.00 g, 24.4 mmol) was stirred and cooled at –78 °C under Ar and then 4-methylmorpholine (NMM) (3.0 mL, 29.2 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (4.0 mL, 29.2 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min and then (2-fluoro)benzylamine (3.66 g, 29.2 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and then the white solid filtered and the organic layer concentrated in vacuo. The residue was purified by flash chromatography on silica gel with EtOAc/hexanes (8/2 to 10/0) as the eluant to obtain (*R*)-*N*-(2'-fluoro)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide (6.50 g, 85%) as a white sticky solid: R_f = 0.86 (hexanes/EtOAc 5/5); mp 87–92 °C; $[\alpha]^{25.9}_D$ +34.0° (*c* 1.0, $CHCl_3$); IR (nujol) 3332, 3242, 2962, 2880, 1655, 1530, 1458, 1375, 1304, 1239, 1165, 1097, 1007, 866, 758 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, (CH_3)$_3$C), 3.38–3.47 (br m, CHH'OH), 3.60–3.71 (br m, CHH'OH), 4.04–4.20 (br m, $CHCH_2$, OH), 4.44–4.53 (m, CH_2N), 5.67 (d, *J* = 7.8 Hz, *tert*-BocNH), 6.99–7.11 (m, 2 ArH), 7.20–7.32 (m, 2 ArH, NH); ^{13}C NMR ($CDCl_3$) δ 28.2 ((CH_3)$_3$C), 37.4 (d, *J* = 4.2 Hz, NCH_2), 54.8 (OCH_2CH), 62.7 (OCH_2CH), 80.6 ((CH_3)$_3$C), 115.4 (d, *J* = 21.1 Hz, C_3), 124.2 (d, *J* = 3.4 Hz, C_5), 124.7 (d, *J* = 14.8 Hz, C_4 or C_6), 129.3 (d, *J* = 7.9 Hz, C_6 or C_4),

129.6–129.7 (br d, **C$_1$**), 156.3 (N**C**(O)), 160.8 (d, *J* = 245.0 Hz, **C**F), 171.4 (**C**(O)); HRMS (M+Na$^+$)(ESI$^+$) 335.1383 [M + Na$^+$] (calcd for $C_{15}H_{21}FN_2O_4Na^+$ 335.1383); Anal. Calcd. for $C_{15}H_{21}FN_2O_4$: C, 57.68; H, 6.78; F, 6.08; N, 8.97. Found: C, 57.63; H, 6.87; F, 5.92; N, 9.01.

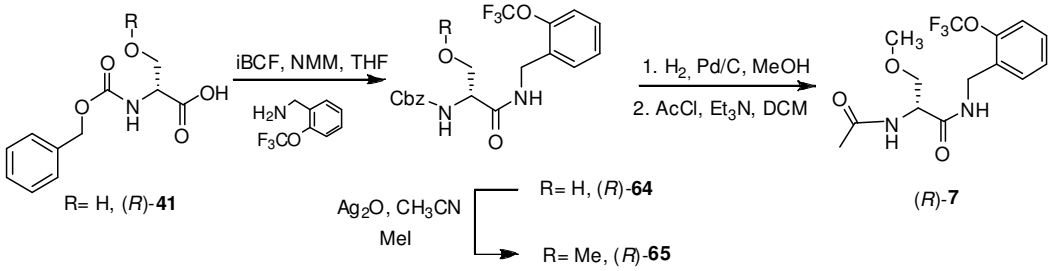
Preparation of (*R*)-*N*-(2'-Fluoro)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-63). Ag_2O (118.5 g, 80.0 mmol) was added to a CH_3CN solution (750 mL) of (*R*)-*N*-(2'-fluoro)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide (5.00 g, 16.0 mmol) and CH_3I (10.0 mL, 160.0 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature in the dark (3 d), filtered through a pad of Celite®, and the filtrate concentrated in vacuo to obtain a white solid. The solid was purified by flash column chromatography on silica gel with EtOAc/hexanes (3/7 to 6/4) as the eluant to obtain (*R*)-*N*-(2'-fluoro)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide as a white solid (3.40 g, 65%): R_f = 0.78 (5/5 EtOAc/hexanes); mp 63–65 °C; $[\alpha]^{25.1}_D$ –12.7° (*c* 1.0, $CHCl_3$); IR (nujol) 3305, 2927, 2861, 1649, 1528, 1457, 1374, 1318, 1250, 1168, 1102, 1048, 913, 867, 761, 650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.43 (s, C(C**H$_3$**)$_3$), 3.36 (s, OC**H$_3$**), 3.46 (dd, *J* = 6.6, 8.7 Hz, C**H**H'), 3.82 (dd, *J* = 3.3, 8.7 Hz, CH**H'**), 4.22–4.30 (br m, C**H**CH$_2$), 4.50–4.60 (br m, C**H$_2$**N), 5.33–5.46 (br m, OC(O)N**H**), 6.78–6.85 (br m, CH$_2$N**H**), 7.00–7.12 (m, 2 Ar**H**), 7.22–7.34 (m, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 28.2 ((**C**H$_3$)$_3$C), 37.5 (d, *J* = 4.6 Hz, N**C**H$_2$), 53.8 (OCH$_2$**C**H), 59.0 (O**C**H$_3$), 71.9 (O**C**H$_2$CH), 80.3 ((CH$_3$)$_3$**C**), 115.3 (d, *J* = 21.1 Hz, **C$_3$**), 124.2 (d, *J* = 3.4 Hz, **C$_5$**), 125.0 (d, *J* = 14.2 Hz, **C$_4$** or **C$_6$**), 129.2 (d, *J* = 7.9 Hz, **C$_6$** or **C$_4$**), 129.6–129.7 (br d, **C$_1$**), 156.5 (N**C**(O)), 160.9 (d, *J* = 244.7 Hz, **C**F), 170.4 (**C**(O)); HRMS (M+Cs$^+$)(ESI$^+$) 459.0696 [M + Cs$^+$] (calcd for $C_{16}H_{23}FN_2O_4Cs^+$ 459.0693); Anal. Calcd. for $C_{16}H_{23}FN_2O_4$: C, 58.88; H, 7.10; F, 5.82; N, 8.58. Found: C, 59.15; H, 7.20; F, 5.78; N, 8.52.

Preparation of (*R*)-*N*-(2'-Fluoro)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-4). TFA (10 mL) was added to a CH_2Cl_2 solution

(200 mL) of (*R*)-*N*-(2'-fluoro)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide (2.90 g, 8.9 mmol), and the solution was stirred at room temperature (1 h). A saturated aqueous $NaHCO_3$ solution was added until pH ~ 9. The layers were separated and the aqueous layer was washed with CH_2Cl_2 (2 x100 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo.

The residue was dissolved in CH_2Cl_2 (100 mL) and then triethylamine (3.7 mL, 26.7 mmol) and acetyl chloride (1.3 mL, 17.8 mmol) were carefully added at 0 °C and the resulting solution was stirred at room temperature (2 h). An aqueous 10% citric acid solution (100 mL) was added and the organic layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, washed with a saturated aqueous $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/MeOH (10/0 to 9/1) as the eluant to obtain (*R*)-*N*-(2'-fluoro)benzyl 2-acetamido-3-methoxypropionamide as a white solid (1.12 g, 88%): R_f = 0.52 (EtOAc); mp 173–175 °C; $[\alpha]^{25.2}_D$ –23.0° (*c* 1 ,$CHCl_3$); IR (nujol) 3289, 2925, 2858, 1638, 1550, 1457, 1376, 1237, 1135, 977, 842, 754, 610 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.00 (s, C**H**$_3$CO), 3.35 (s, OC**H**$_3$), 3.43 (dd, *J* = 7.2, 9.0 Hz, C**H**H'), 3.76 (dd, *J* = 4.5, 9.0 Hz, CH**H'**), 4.46–4.63 (m, C**H**$_2$N, C**H**), 4.84–4.91 (br s, N**H**CH_2), 6.64 (d, *J* = 7.2 Hz, N**H**C(O)CH_3), 7.00–7.13 (m, 2 Ar**H**), 7.23–7.32 (m, 2 Ar**H**), addition of excess of (R)-(–)-mandelic acid to a $CDCl_3$ solution of (R)-*N*-(2'-fluoro)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.0 (**C**H_3C(O)), 37.4 (d, *J* = 4.0 Hz, N**C**H_2), 52.4 (OCH_2**C**H), 58.9 (O**C**H_3), 71.8 (O**C**H_2CH), 115.1 (d, *J* = 21.0 Hz, **C$_3$**), 124.2 (d, *J* = 3.4 Hz, **C$_5$**), 124.8 (d, *J* = 14.5 Hz, **C$_4$** or **C$_6$**), 129.1 (d, *J* = 8.2 Hz, **C$_6$** or **C$_4$**), 129.6–129.7 (br d, **C$_1$**), 160.8 (d, *J* = 244.7 Hz, **C**F), 170.1, 170.4 (2 **C**(O)); HRMS (M+Cs^+)(ESI$^+$) 401.0278 [M + Cs^+] (calcd for $C_{13}H_{17}FN_2O_3Cs^+$ 401.0274); Anal. Calcd. for $C_{13}H_{17}FN_2O_3$: C, 58.20; H, 6.39; F, 7.08; N, 10.44. Found: C, 58.12; H, 6.40; F, 6.96; N, 10.41.

2. Preparation of (*R*)-*N*-(2'-Trifluoromethoxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-7).



Preparation of (*R*)-*N*-(2'-Trifluoromethoxy)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-hydroxypropionamide ((*R*)-64). A THF solution (250 mL) of (*R*)-Cbz-serine (8.00 g, 33.5 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (4.4 mL, 40.2 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (5.3 mL, 40.2 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min and then (2'-trifluoromethoxy)benzylamine (7.67 g, 40.1 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and then the white solid filtered and the organic layer concentrated in vacuo. The residue was purified by flash chromatography on silica gel with EtOAc/hexanes (6/4 to 10/0) as the eluant to obtain (*R*)-*N*-(2'-trifluoromethoxy)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide (5.50 g, 50%) as a white solid: R_f = 0.49 (hexanes/EtOAc 5/5); mp 129–134 °C; $[\alpha]^{24.5}_D$ –11.2° (*c* 1.0, DMSO); IR (nujol) 3296, 3172, 3096, 2944, 2860, 1658, 1544, 1457, 1378, 1271, 1157, 1090, 1026, 919, 758, 695, 634 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.97–3.06 (br m, O**H**), 3.59–3.72 (br m, C**H**), 4.09–4.26 (br m, C**H$_2$**OH), 4.51 (d, *J* = 5.4 Hz, C**H$_2$**N), 5.10 (s, C**H$_2$**O), 5.80–5.91 (br d, N**H**), 6.98–7.07 (br s, N**H**), 7.23–7.34 (m, 9 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 38.2 (N**C**H$_2$), 55.4 (OCH$_2$**C**H), 62.7 (O**C**H$_2$CH), 67.4 (Ph**C**H$_2$O), 120.5 (q, *J* = 256.8 Hz, **C**F$_3$), 120.6, 127.1, 128.0, 128.3, 128.6, 129.0, 129.8, 130.2, 135.9, 147.3 (10 Ar**C**), 156.7 (N**C**(O)O), 170.9 (**C**(O)); HRMS (M+Cs^+)(ESI$^+$) 545.0300 [M + Cs^+] (calcd for $C_{19}H_{19}F_3N_2O_5Cs^+$ 545.0297);

Anal. Calcd. for $C_{19}H_{19}F_3N_2O_5$: C, 55.34; H, 4.64; F, 13.82; N, 6.79. Found: C, 55.27; H, 4.62; F, 13.80; N, 6.74.

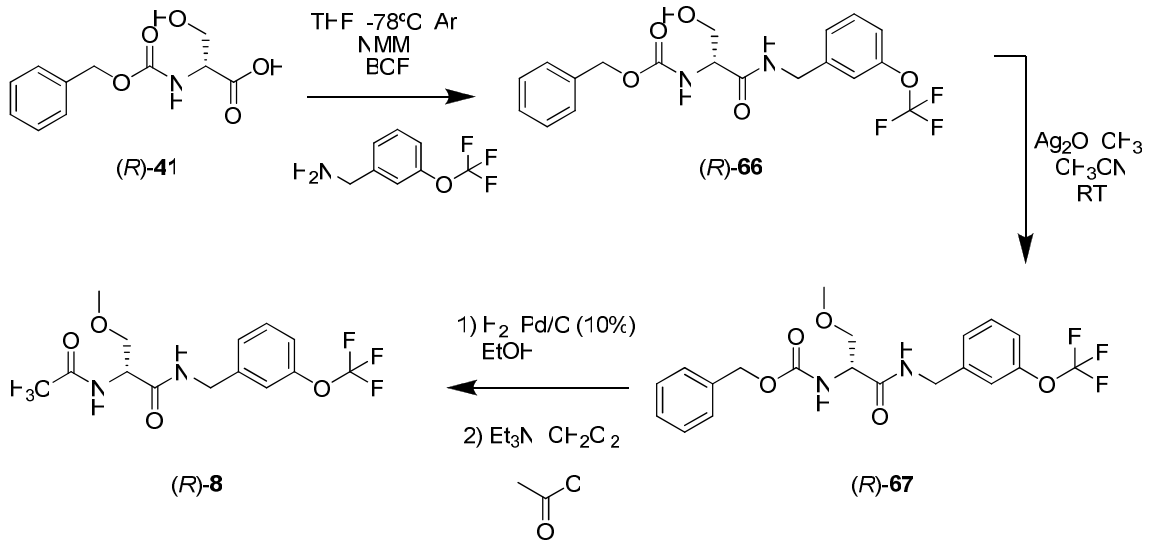
Preparation of (*R*)-*N*-(2'-Trifluoromethoxy)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-methoxypropionamide ((*R*)-65). Ag_2O (13.37 g, 57.9 mmol) was added to a CH_3CN solution (500 mL) of (*R*)-*N*-(2'-trifluoromethoxy)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide (3.80 g, 11.6 mmol) and CH_3I (7.2 mL, 116.0 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature in the dark (3 d), filtered through a pad of Celite®, and the filtrate concentrated in vacuo to obtain a white solid. The solid was purified by flash column chromatography on silica gel with EtOAc/hexanes (50/50) as the eluant to obtain (*R*)-*N*-(2'-trifluoromethyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide as a white solid (3.50 g, 88%): R_f = 0.90 (5/5 EtOAc/hexanes); mp 125–126 °C; $[\alpha]^{25.1}_D$ –13.1° (*c* 1.0, $CHCl_3$); IR (nujol) 3141, 2957, 2728, 1685, 1642, 1540, 1459, 1376, 1277, 1217, 1163, 1046, 959, 843, 756, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.35 (s, OC**H$_3$**), 3.46 (dd, *J* = 6.9, 9.3 Hz, C**H**H'), 3.85 (dd, *J* = 3.9, 9.3 Hz, CH**H'**), 4.27–4.38 (br m, C**H**CH_2), 4.54 (d, *J* = 6.0 Hz, C**H$_2$**N), 5.12 (s, OC**H$_2$**), 5.62–5.71 (br m, OC(O)N**H**), 6.74–6.85 (br m, CH_2N**H**), 7.20–7.40 (m, 9 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 38.7 (N**C**H_2), 54.6 (OCH_2**C**H), 59.2 (O**C**H_3), 67.7 (Ph**C**H_2O), 72.3 (O**C**H_2CH), 120.9 (1 Ar**C**), 121.0 (q, *J* = 256.1 Hz, O**C**F_3), 127.6, 128.6, 128.8, 129.0, 129.4, 130.3, 130.8, 136.4, 147.7 (9 Ar**C**), 156.6 (N**C**(O)O), 170.5 (**C**(O)); HRMS ($M+Cs^+$)(ESI^+) 559.0457 [M + Cs^+] (calcd for $C_{20}H_{21}F_3N_2O_5Cs^+$ 559.0454); Anal. Calcd. for $C_{20}H_{21}F_3N_2O_5$: C, 56.34; H, 4.96; F, 13.37; N, 6.57. Found: C, 56.30; H, 4.98; F, 13.22; N, 6.59.

Preparation of (*R*)-*N*-(2'-Trifluoromethoxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-7). An EtOH solution (200 mL) of (*R*)-*N*-(2'-trifluoromethoxy)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (3.40 g, 8.0 mmol) was treated with H_2 (1 atm) in presence of 10% Pd/C (340 mg) at room temperature (16 h). The mixture was carefully filtered through a bed

of Celite®. The pad was washed with MeOH and CH_2Cl_2, and the washings were collected and evaporated in vacuo.

The residue was dissolved in CH_2Cl_2 (100 mL) and then triethylamine (3.3 mL, 24.0 mmol) and acetyl chloride (1.2 mL, 16.0 mmol) were carefully added at 0 °C and the resulting solution was stirred at room temperature (2 h). An aqueous 10% citric acid solution (100 mL) was added and then washed with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, washed with a saturated aqueous $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/MeOH (10/0 to 9/1) as the eluant to obtain (*R*)-*N*-(2'-trifluoromethoxy)benzyl 2-acetamido-3-methoxypropionamide as a white solid (3.50 g, 88%): R_f = 0.36 (EtOAc); mp 130–131 °C; $[\alpha]^{24.8}_D$ –15.1° (*c* 1 , $CHCl_3$); IR (nujol) 2919, 2858, 1640, 1547, 1458, 1272, 1203, 1164, 767, 712, 606 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.98 (s, C**H**$_3$C(O)), 3.35 (s, OC**H**$_3$), 3.45 (br dd, *J* = 7.2, 9.3 Hz, C**H**H'), 3.76 (dd, *J* = 4.2, 9.3 Hz, CH**H'**), 4.46–4.63 (m, C**H**$_2$N, C**H**), 6.71 (br d, *J* = 6.3 Hz, N**H**C(O)CH_3), 7.22–7.40 (m, CH_2N**H**, 4 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(2'-trifluoromethoxy)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 22.9 (**C**H_3C(O)), 38.1 (**C**H_2N), 52.4 (**C**HCH_2), 58.9 (O**C**H_3), 71.7 (**C**H_2OCH_3), 120.4 (1 Ar**C**), 120.5 (q, *J* = 256.1 Hz, O**C**F_3), 127.0, 128.8, 129.7, 130.3, 147.1 (5 Ar**C**), 170.2, 170.4 (2 **C**(O)); HRMS (M+Na^+)(ESI^+) 357.1038 [M + Na^+] (calcd for $C_{14}H_{17}F_3N_2O_4Na^+$ 357.1038); Anal. Calcd. for $C_{14}H_{17}F_3N_2O_4$: C, 50.30; H, 5.13; F, 17.05; N, 8.38. Found: C, 50.28; H, 5.21; F, 17.30; N, 8.18.

3. Preparation of (*R*)-*N*-(3'-Trifluoromethoxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-8).



Preparation of (*R*)-*N*-(3'-Trifluoromethoxy)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-hydroxypropionamide ((*R*)-66). A THF solution (170 mL) of (*R*)-Cbz-serine (5.00 g, 20.9 mmol) was stirred and cooled at -78 ºC under Ar. Then, 4-methylmorpholine (NMM) (2.8 mL, 25.1 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (3.3 mL, 25.1 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min. Then, 3-trifluoromethoxybenzylamine (4.80 g, 25.1 mmol) was added portionwise at -78 ºC. The mixture was stirred at -78 ºC (5 min) and then at room temperature (2 h). The white solid was removed by filtration and the organic layer was concentrated in vacuo. The residue was recrystallized with EtOAc to obtain (*R*)-*N*-(3'-trifluoromethoxy)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide as a white solid (2.30 g, 27%): R_f = 0.41 (EtOAc/hexanes 7/3); mp 121 ºC; $[\alpha]^{24.2}_D$ –2.7º (*c* 1.0, $CHCl_3$); IR (nujol) 2953, 1687, 1571, 1454, 1372, 1290, 1213, 1164, 1061, 793, 734 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.55–3.67 (m, C**H**$_2$OH), 4.05–4.12 (m, C**H**), 4.34 (d, *J* = 5.8 Hz, C**H**$_2$N), 4.91 (t, *J* = 5.7 Hz, O**H**), 5.01 (½ ABq, *J* = 12.6 Hz, C**H**H'), 5.07 (½ ABq, *J* = 12.6 Hz, CH**H'**), 7.02–7.46 (m, 9 Ar**H**, N**H**), 8.54 (t, *J* = 5.8 Hz, N**H**); ^{13}C NMR ($CDCl_3$) δ 42.0 (N**C**H$_2$), 57.9 (OCH$_2$**C**H), 62.2 (O**C**H$_2$CH), 66.0 (Ph**C**H$_2$O), 120.5 (q, *J* = 254.6 Hz, O**C**F$_3$), 119.5, 119.8, 126.4, 128.2, 128.3, 128.8, 130.5, 137.4, 142.9 (9 Ar**C**), 149.0 (**C**OCF$_3$), 156.5 (N**C**(O)O), 171.0 (**C**(O)); LRMS (M+Na$^+$) (ESI$^+$) 435.1 [M+Na$^+$] (calcd for

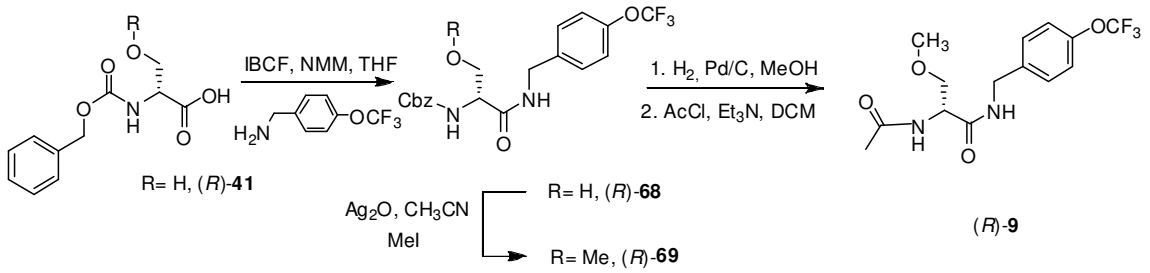
$C_{19}H_{19}F_3N_2O_5Na^+$ 435.1); Anal. Calcd. for $C_{19}H_{19}F_3N_2O_5$: C, 55.34; H, 4.64; F, 13.82; N, 6.79. Found: C, 55.44; H, 4.59; F, 13.66; N, 6.79.

Preparation of (*R*)-*N*-(3'-Trifluoromethoxy)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-methoxypropionamide ((*R*)-67). Ag_2O (5.50 g, 23.6 mmol) was added to a CH_3CN solution (100 mL) of (*R*)-*N*-(3'-trifluoromethoxy)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide (1.95 g, 4.72 mmol) and CH_3I (2.9 mL, 47.2 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature in the dark (3 d), filtered through a Celite® pad, and the filtrate was concentrated in vacuo. The residue was recrystallized with EtOAc to obtain (*R*)-*N*-(3'-trifluoromethoxy)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide as a white solid (2.00 g, quantitative): R_f = 0.74 (EtOAc/hexanes, 7/3); mp 117–118 ºC; $[\alpha]^{25.7}_D$ –20.8º (*c* 1.0, $CHCl_3$); IR (nujol) 2922, 2857, 1685, 1649, 1548, 1457, 1378, 1266, 1161, 1050, 964, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.37 (s, OC**H$_3$**), 3.50 (dd, *J* = 6.5, 9.0 Hz, C**H**H'), 3.88 (dd, *J* = 3.6, 9.0 Hz, CH**H'**), 4.30–4.40 (br m, C**H**CH_2, C**H$_2$**N), 5.13 (s, OC**H$_2$**), 5.62–5.72 (br m, N**H**), 6.71–6.80 (br m, N**H**), 7.11–7.19 (m, 3 Ar**H**), 7.32–7.37 (m, 6 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 42.7 (N**C**H_2), 54.4 (OCH_2**C**H), 59.0 (O**C**H_3), 67.3 (Ar**C**H_2O), 71.9 (O**C**H_2CH), 120.4 (q, *J* = 255.6 Hz, O**C**F_3), 119.7, 125.5, 128.1, 128.3, 128.5, 129.9, 135.9, 140.4 (8 Ar**C**), 149.5 (**C**OCF_3), 156.1 (N**C**(O)O), 170.1 (**C**(O), one signal was not detected and is believed to overlap with nearby peaks; LRMS ($M+Na^+$) (ESI^+) 449.1 [$M+Na^+$] (calcd for $C_{20}H_{21}F_3N_2O_5Na^+$ 449.1); Anal. Calcd. for $C_{20}H_{21}F_3N_2O_5$: C, 56.34; H, 4.96; F, 13.37; N, 6.57. Found: C, 56.15; H, 4.86; F, 13.23; N, 6.48.

Preparation of (*R*)-*N*-(3'-Trifluoromethoxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-8). An EtOH solution (200 mL) of (*R*)-*N*-(3'-trifluoromethoxy)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (1.80 g, 4.2 mmol) was treated with H_2 (1 atm) in presence of 10% Pd/C (180 mg) at room temperature (16 h). The mixture was carefully filtered through a bed of Celite® and the filtrate was evaporated in vacuo to obtain a yellow oil.

The oil was dissolved in CH_2Cl_2 (50 mL) and then triethylamine (0.7 mL, 5.0 mmol) and acetyl chloride (0.35 mL, 5.0 mmol) were carefully added at 0 °C and the resulting solution was stirred at room temperature (2 h). An aqueous 10% citric acid solution (50 mL) was added and the organic layer was washed with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, washed with a saturated $NaHCO_3$ solution (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was recrystallized in EtOAc to obtain (*R*)-*N*-(3'-trifluoromethoxy)benzyl 2-acetamido-3-methoxypropionamide as a white solid (750 mg, 54%): R_f = 0.33 (EtOAc); mp = 147–148 ºC; $[\alpha]^{25.0}_D$ –12.1º (*c* 1.0, $CHCl_3$); IR (nujol) 3287, 3041, 2859, 2355, 1637, 1552, 1456, 1377, 1272, 1214, 1150, 715, 610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, C**H$_3$**CO), 3.39 (s, OC**H$_3$**), 3.44 (dd, *J* = 7.6, 9.0 Hz, C**H**H'), 3.83 (dd, *J* = 4.2, 9.0 Hz, CH**H'**), 4.43–4.60 (m, C**H$_2$**N, C**H**), 6.38–6.46 (br d, N**H**(CO)CH_3), 6.82–6.91 (br t, CH_2N**H**), 7.11–7.15 (m, 2 Ar**H**), 7.19 (d, *J* = 7.8 Hz, 1 Ar**H**), 7.36 (dt, *J* = 1.9, 7.8 Hz, 1 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(3'-trifluoromethoxy)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.1 (**C**H_3CO), 42.8 (**C**H_2N), 52.5 (**C**HCH_2), 59.0 (O**C**H_3), 71.6 (**C**H_2OCH_3), 120.4 (q, *J* = 255.6 Hz, O**C**F_3), 119.7, 119.8, 125.6, 130.0, 140.4 (5 Ar**C**), 149.5 (**C**OCF_3), 170.2, 170.4 (2 **C**(O)); LRMS ($M+Na^+$) (ESI^+) 357.1 [$M+Na^+$] (calcd for $C_{14}H_{17}F_3N_2O_4Na^+$ 357.1); Anal. Calcd. for $C_{14}H_{17}F_3N_2O_4$: C, 50.30; H, 5.13; F, 17.05; N, 8.38. Found: C, 50.25; H, 5.07; F, 16.78; N, 8.17.

4. Preparation of (*R*)-*N*-(4'-Trifluoromethoxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-9).



Preparation of (*R*)-*N*-(4'-Trifluoromethoxy)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-hydroxypropionamide ((*R*)-68). A THF solution (200 mL) of (*R*)-Cbz-serine (6.00 g, 25.1 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (3.3 mL, 30.1 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (3.9 mL, 30.1 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min and then 4-trifluoromethoxybenzylamine (4.6 mL, 30.1 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and then the white solid filtered and the organic layer concentrated in vacuo. The residue was recrystallized in EtOAc to obtain (*R*)-*N*-(4'-trifluoromethoxy)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide as a white solid (6.10 g, 59%): R_f = 0.30 (hexanes/EtOAc 5/5); mp 189–190 °C; $[\alpha]^{27.4}_D$ –6.5° (*c* 1.0, DMSO); IR (nujol) 3278, 3143, 2926, 2866, 1691, 1645, 1539, 1457, 1374, 1278, 1224, 1157, 1025, 963 739, 690 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.56 (m, C**H**H', CH**H'**), 4.05–4.12 (br dd, C**H**), 4.31 (d, *J* = 5.7 Hz, C$\mathbf{H_2}$N), 4.91 (t, *J* = 5.5 Hz, O**H**), 5.04 (s, C$\mathbf{H_2}$O), 7.25–7.38 (m, N**H**, 9 Ar**H**), 8.50 (t, *J* = 5.7 Hz, CH_2N**H**); ^{13}C NMR (DMSO-d_6) δ 41.3 (N**C**H_2), 57.3 (OCH_2**C**H), 61.7 (O**C**H_2CH), 65.5 (Ph**C**H_2O), 120.0 (q, *J* = 254.4 Hz, O**C**F_3), 120.7, 127.6, 127.7, 128.2, 128.7, 136.9, 138.9, (7 Ar**C**), 147.0 (q, *J* = 1.7 Hz, **C**OCF_3), 155.9 (N**C**(O)O), 170.3 (**C**(O)); HRMS (M+H^+)(ESI$^+$) 413.1325 [M + H^+] (calcd for $C_{19}H_{19}F_3N_2O_5H^+$ 413.1324); Anal. Calcd. for $C_{19}H_{19}F_3N_2O_5$: C, 55.34; H, 4.64; F, 13.82; N, 6.79. Found: C, 55.06; H, 4.61; F, 13.70; N, 6.74.

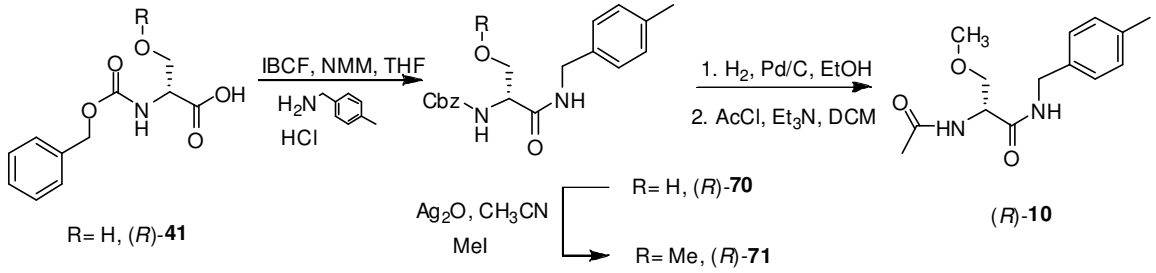
Preparation of (*R*)-*N*-(4'-Trifluoromethoxy)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-methoxypropionamide ((*R*)-69). Ag_2O (15.56 g, 66.7 mmol) was added to a CH_3CN solution (250 mL) of (*R*)-*N*-(4'-trifluoromethoxy)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide (5.50 g, 13.4 mmol) and CH_3I (8.3 mL, 134.0 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature in the dark (3 d), filtered through a pad of Celite®, and the filtrate was concentrated in vacuo. The solid was purified by flash column chromatography on silica gel with EtOAc/hexanes (50/50) as the eluant to obtain (*R*)-*N*-(4'-trifluoromethoxy)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide as a white solid (4.40 g, 97%): R_f = 0.77 (EtOAc/hexanes 5/5); mp 114–115 °C; $[\alpha]^{24.5}_D$ –21.4° (*c* 1.0, $CHCl_3$); IR (nujol) 3279, 3089, 2958, 2858, 1638, 1553, 1456, 1377, 1285, 1221, 1148, 988, 918, 841, 725, 610 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.36 (s, OC**H$_3$**), 3.49 (dd, *J* = 6.3, 9.0 Hz, C**H**H'), 3.86 (dd, *J* = 3.9, 9.0 Hz, CH**H'**), 4.29–4.40 (br m, C**H**CH_2), 4.46 (d, *J* = 6.3 Hz, C**H$_2$**N), 5.12 (s, OC**H$_2$**), 5.53–5.64 (br s, N**H**), 6.74–6.84 (br m, N**H**), 7.15 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.24–7.39 (m, 7 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 42.7 (N**C**H_2), 54.4 (OCH_2**C**H), 59.1 (O**C**H_3), 67.3 (O**C**H_2), 71.9 (O**C**H_2CH), 120.4 (q, *J* = 255.5 Hz, O**C**F_3), 121.2, 128.2, 128.3, 128.6, 128.7, 135.9, 136.7 (7 Ar**C**), 148.5 (**C**OCF_3), 156.1 (N**C**(O)O), 170.0 (**C**(O)); HRMS ($M+H^+$)(ESI$^+$) 427.1481 [M + H^+] (calcd for $C_{20}H_{21}F_3N_2O_5H^+$ 427.1481); Anal. Calcd. for $C_{20}H_{21}F_3N_2O_5$: C, 56.34; H, 4.96; F, 13.37; N, 6.57. Found: C, 56.34; H, 4.97; F, 13.28; N, 6.63.

Preparation of (*R*)-*N*-(4'-Trifluoromethoxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-9). An EtOH solution (400 mL) of (*R*)-*N*-(4'-trifluoromethoxy)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (3.90 g, 9.2 mmol) was treated with H_2 (1 atm) in presence of 10% Pd/C (390 mg) at room temperature (16 h). The mixture was carefully filtered through a bed of Celite® and the filtrate was evaporated in vacuo to obtain a brown oil: ^1H NMR ($CDCl_3$) δ 1.44–1.95 (br s, N**H$_2$**), 3.38 (s, OC**H$_3$**), 3.50–3.67 (br m, C**H$_2$**, C**H**), 4.46

(d, J = 5.7 Hz, NC**H$_2$**), 7.17 (d, J = 8.0 Hz, 2 Ar**H**), 7.31 (d, J = 8.0 Hz, 2 Ar**H**), 7.80–8.00 (br s, N**H**C(O)).

The oil was dissolved in CH_2Cl_2 (100 mL) and then triethylamine (1.5 mL, 11.0 mmol) and acetyl chloride (0.78 mL, 11.0 mmol) were carefully added at 0 °C and the resulting solution was stirred at room temperature (2 h). An aqueous 10% citric acid solution (100 mL) was added and the organic layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, washed with a saturated $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was recrystallized in EtOAc to obtain (*R*)-*N*-(4'-trifluoromethoxy)benzyl 2-acetamido-3-methoxypropionamide as a white solid (2.50 g, 83%): R_f = 0.49 (EtOAc); mp 134–135 °C; $[\alpha]^{24.9}_D$ –17.6° (*c* 0.5, $CHCl_3$); IR (nujol) 3279, 3088, 2958, 2858, 1638, 1553, 1456, 1377, 1285, 1221, 1148, 988, 918, 841, 725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.04 (s, C**H$_3$**CO), 3.39 (s, OC**H$_3$**), 3.44 (dd, J = 7.5, 9.0 Hz, C**H**H'), 3.82 (dd, J = 4.2, 9.0 Hz, CH**H'**), 4.44–4.52 (m, C**H$_2$**N), 4.52–4.59 (m, C**H**), 6.41 (br d, J = 6.6 Hz, N**H**C(O)CH_3), 6.78–6.89 (br t, CH_2N**H**), 7.18 (d, J = 8.1 Hz, 2 Ar**H**), 7.29 (d, J = 8.1 Hz, 2 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-trifluoromethoxy)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) 23.1 (**C**H_3CO), 42.7 (**C**H_2N), 52.5 (**C**HCH_2), 59.1 (O**C**H_3), 71.7 (**C**H_2OCH_3), 120.4 (q, J = 255.5 Hz, **C**F_3), 121.2, 128.7, 136.7 (3 Ar**C**), 148.4 (app d, J = 1.7 Hz, **C**OCF_3), 170.1, 170.4 (2 **C**(O)); HRMS (M+H$^+$)(ESI$^+$) 335.1219 [M + H$^+$] (calcd for $C_{14}H_{17}F_3N_2O_4H^+$ 335.1218); Anal. Calcd. for $C_{14}H_{17}F_3N_2O_4$: C, 50.30; H, 5.13; F, 17.05; N, 8.38. Found: C, 50.45; H, 5.13; F, 17.18; N, 8.39.

5. Preparation of (*R*)-*N*-(4'-Methyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-10).



Preparation of (*R*)-*N*-(4'-Methyl)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-hydroxypropionamide ((*R*)-70). A THF solution (300 mL) of (*R*)-Cbz-serine (10.00 g, 41.8 mmol) was stirred and cooled at -78 °C under Ar and then (4-methyl)morpholine (NMM) (5.5 mL, 50.2 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (6.6 mL, 50.2 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min and then (4-methyl)benzylamine (6.3 mL, 50.2 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and then the white solid filtered and the organic layer concentrated in vacuo. The residue was recrystallized with EtOAc to obtain (*R*)-*N*-(4'-methyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide as a white solid (4.80 g, 32%): R_f = 0.19 (hexanes/EtOAc 5/5); mp 129 °C; $[\alpha]^{25.4}_D$ +14.3° (*c* 1.0, $CHCl_3$); IR (nujol) 2896, 2728, 1712, 1641, 1572, 1522, 1457, 1374, 1314, 1240, 1048, 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.32 (s, C**H**$_3$), 3.67 (dd, *J* = 4.8, 11.1 Hz, C**H**H'), 4.07–4.16 (br dd, CH**H'**), 4.19–4.28 (br m, C**H**), 4.38 (d, *J* = 6.0 Hz, C**H**$_2$N), 5.08 (s, C**H**$_2$O), 5.87 (d, *J* = 6.6 Hz, N**H**), 6.87–6.97 (br s, N**H**), 7.11 (s, 4 Ar**H**), 7.33 (s, 5 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 21.1 (**C**H$_3$), 43.3 (N**C**H$_2$), 55.2 (OCH$_2$**C**H), 62.8 (O**C**H$_2$CH), 67.4 (Ph**C**H$_2$O), 127.5, 128.1, 128.3, 128.6, 129.4, 134.5, 135.9, 137.3 (8 Ar**C**), 156.7 (N**C**(O)O), 170.7 (**C**(O)); HRMS (M+H$^+$)(ESI$^+$) 343.1658 [M + H$^+$] (calcd for $C_{19}H_{22}N_2O_4H^+$ 343.1658); Anal. Calcd. for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.49; H, 6.53; N, 8.07.

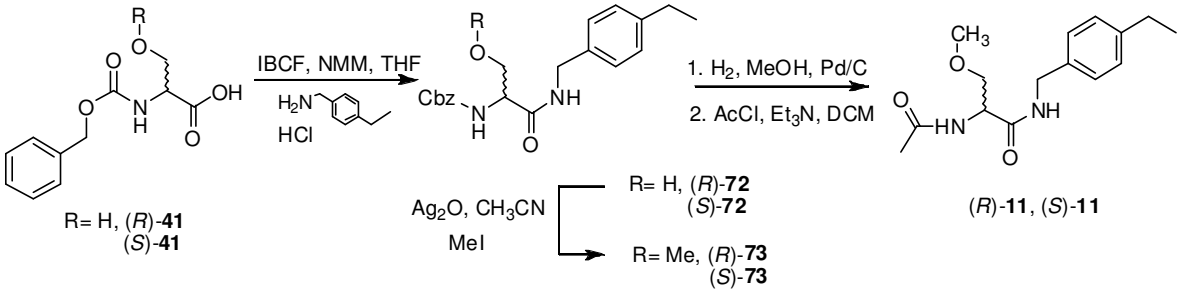
Preparation of (*R*)-*N*-(4'-Methyl)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-methoxypropionamide ((*R*)-71). Ag_2O (15.32 g,

65.8 mmol) was added to a CH_3CN solution (300 mL) of (*R*)-*N*-(4'-methyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide (4.50 g, 13.1 mmol) and CH_3I (8.2 mL, 131.5 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature in the dark (2 d), filtered through a pad of Celite®, and the filtrate concentrated in vacuo to obtain a white solid. The solid was purified by flash column chromatography on silica gel with EtOAc/hexanes (0/100 to 50/50) as the eluant to obtain (*R*)-*N*-(4'-methyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide as a white solid (3.40 g, 73%): R_f = 0.51 (1/1 EtOAc/hexanes); mp 126–127 °C; $[\alpha]^{25.8}_D$ –24.7° (*c* 1.0, $CHCl_3$); IR (nujol) 3253, 2947, 2862, 1693, 1534, 1459, 1375, 1314, 1258, 1125, 1054, 964, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.33 (s, PhC**H$_3$**), 3.35 (s, OC**H$_3$**), 3.49 (dd, *J* = 6.6, 9.0 Hz, C**H**H'), 3.84 (dd, *J* = 3.6, 9.0 Hz, CH**H'**), 4.29–4.38 (br m, C**H**CH_2), 4.41 (d, *J* = 5.7 Hz, C**H$_2$**N), 5.10 (s, OC**H$_2$**), 5.62–5.75 (br m, OC(O)N**H**), 6.61–6.72 (br m, CH_2N**H**), 7.13 (s, 4 Ar**H**), 7.34 (s, 5 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 21.0 (**C**H_3), 43.3 (N**C**H_2), 54.3 (OCH_2**C**H), 59.0 (O**C**H_3), 67.2 (Ph**C**H_2O), 72.0 (O**C**H_2CH), 127.5, 128.1, 128.2, 128.5, 129.3, 134.8, 136.0, 137.2 (8 Ar**C**), 156.1 (N**C**(O)O), 169.7 (**C**(O)); HRMS (M+H^+)(ESI$^+$) 357.1815 [M + H^+] (calcd for $C_{20}H_{24}N_2O_4H^+$ 357.1814); Anal. Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86. Found: C, 67.22; H, 6.82; N, 7.82.

Preparation of (*R*)-*N*-(4'-Methyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-10). An EtOH solution (250 mL) of (*R*)-*N*-(4'-methyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (3.20 g, 9.0 mmol) was treated with H_2 (1 atm) in presence of 10% Pd/C (320 mg) at room temperature (16 h). The mixture was carefully filtered through a bed of Celite® and the filtrate was evaporated in vacuo to obtain a colorless oil: ^1H NMR ($CDCl_3$) δ 1.60–1.65 (br s, N**H$_2$**), 2.33 (s, PhC**H$_3$**), 3.37 (s, OC**H$_3$**), 3.56–3.67 (m, C**H$_2$**, C**H**), 4.34–4.43 (m, NC**H$_2$**), 7.10–7.79 (m, 4 Ar**H**), 7.70–7.77 (br s, N**H**C(O)); ^{13}C NMR ($CDCl_3$) δ 21.0 (Ph**C**H_3), 42.9 (**C**H_2N), 54.8 (**C**H), 58.8 (O**C**H_3), 74.5 (**C**H_2), 127.6, 129.3, 135.3, 137.0 (4 Ar**C**), 172.5 (**C**(O)).

The oil was dissolved in CH_2Cl_2 (100 mL) and then triethylamine (1.5 mL, 10.8 mmol) and acetyl chloride (766 μL, 10.8 mmol) were carefully added at 0 °C and the resulting solution was stirred at room temperature (2 h). An aqueous 10% citric acid solution (100 mL) was added and the organic layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, washed with a saturated $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), and concentrated in vacuo. After 2 recrystallizations from EtOAc, (*R*)-*N*-(4'-methyl)benzyl 2-acetamido-3-methoxypropionamide was obtained as a white solid (1.70 g, 72%): R_f = 0.50 (EtOAc); mp 128–129 °C; $[\alpha]^{25}_D$ –22.4° (*c* 1 , $CHCl_3$); IR (nujol) 3285, 3062, 1637, 1548, 1458, 1375, 1311, 1105, 915, 808, 724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.98 (s, C**H**$_3$CO), 2.32 (PhC**H**$_3$), 3.35 (s, OC**H**$_3$), 3.45 (dd, *J* = 6.9, 9.3 Hz, C**H**H'), 3.75 (dd, *J* = 4.2, 9.3 Hz, CH**H'**), 4.36–4.43 (m, C**H**$_2$N), 4.57–4.62 (m, C**H**), 6.71 (br d, *J* = 6.9 Hz, N**H**C(O)CH_3), 6.98–7.04 (br t, CH_2N**H**), 7.09–7.16 (m, 4 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-methyl)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 21.0 (Ph**C**H_3), 23.1 (**C**H_3CO), 43.3 (**C**H_2N), 52.4 (**C**HCH_2), 59.0 (O**C**H_3), 71.7 (**C**H_2OCH_3), 127.4, 129.3, 134.8, 137.1 (4 Ar**C**), 169.9, 170.3 (2 **C**(O)); HRMS (M+H^+)(ESI$^+$) 265.1552 [M + H^+] (calcd for $C_{14}H_{20}N_2O_3H^+$ 265.1552); Anal. Calcd. for $C_{14}H_{20}N_2O_3$: C, 63.62; H, 7.63; N, 10.60. Found: C, 63.44; H, 7.68; N, 10.60.

6. Preparation of (*R*)- and (*S*)-*N*-(4'-Ethyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)- and (*S*)-11).



Preparation of (*R*)-*N*-(4'-Ethyl)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-hydroxypropionamide ((*R*)-72). A THF solution (200 mL) of (*R*)-Cbz-serine (6.00 g, 25.1 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (3.3 mL, 30.1 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (3.9 mL, 30.1 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min and then (4-ethyl)benzylamine (4.3 mL, 30.1 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and then the white solid filtered and the organic layer concentrated in vacuo. The remaining solid was recrystallized with EtOAc to obtain (*R*)-*N*-(4'-ethyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide as a white solid (5.36 g, 60%): R_f = 0.40; mp 169–170 ºC; $[\alpha]^{25}_D$ –3.2° (*c* 1.0, MeOH); IR (nujol) 3288, 3062, 1689, 1643 cm^{-1}; ^1H NMR (CD_3OD) δ 1.20 (t, *J* = 7.8 Hz, $CH_2C\mathbf{H_3}$), 2.60 (q, *J* = 7.8 Hz, $C\mathbf{H_2}CH_3$), 3.79 (d, *J* = 5.4 Hz, $NC\mathbf{H_2}$), 4.20–4.29 (m, C**H**), 4.30 (d, *J* = 3.0 Hz, C**H**H'OH), 4.39 (d, J = 3.0 Hz, CH**H**'OH), 5.10 (s, $ArC\mathbf{H_2}$), 7.10 (s, $C_6\mathbf{H_4}$), 7.20–7.40 (m, $C_6\mathbf{H_5}$); HRMS ($M+H^+$)(ESI$^+$) 357.1807 [M + H^+] (calcd for $C_{20}H_{24}N_2O_4H^+$ 357.1814); Anal. Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86; Found: C, 67.31; H, 6.81; N, 7.88.

Preparation of (*S*)-*N*-(4'-Ethyl)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-hydroxypropionamide ((*S*)-72). A THF solution (200 mL) of (*S*)-Cbz-serine (6.00 g, 25.1 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (3.3 mL, 30.1 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (3.9 mL, 30.1 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min and then (4-ethyl)benzylamine (4.3 mL, 30.1 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and then the white solid filtered and the organic layer concentrated in vacuo. The remaining solid was recrystallized with EtOAc to obtain (*S*)-*N*-(4'-ethyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide as a white solid (6.81g, 65%): R_f = 0.35 (5%

MeOH/$CHCl_3$); mp 168–169 ºC; $[\alpha]^{25}$ +4.0° (*c* 1.0, MeOH); IR (nujol) 3288, 3061, 1689, 1643 cm^{-1}; ^1H NMR (CD_3OD) δ 1.56 (t, *J* = 7.2 Hz, CH_2CH_3), 2.94 (q, *J* = 7.2 Hz, CH_2CH_3), 3.62 (d, *J* = 1.5 Hz, NCH_2), 4.08–4.11 (m, CH), 4.55 (d, *J* = 3.0 Hz, CHH'OH), 4.75 (d, *J* = 3.0 Hz, CHH'OH), 5.47 (s, $ArCH_2$), 7.50–7.61 (m, C_6H_4), 7.62–7.76 (m, C_6H_5); HRMS ($M+H^+$)(ESI^+) 357.1806 [M + H^+] (calcd for $C_{20}H_{24}N_2O_4H^+$ 357.1814); Anal. Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86; Found: C, 67.40; H, 6.78; N, 7.86.

Preparation of (*R*)-*N*-(4'-Ethyl)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-methoxypropionamide ((*R*)-73). Ag_2O (12.95 g, 55.5 mmol) was added to a CH_3CN solution (400 mL) of (*R*)-*N*-(4'-ethyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide (3.97 g, 11.1 mmol) and CH_3I (6.9 mL, 111.1 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature in the dark (4 d), filtered through a pad of Celite®, and the filtrate concentrated in vacuo to obtain a white solid. The solid was purified by flash column chromatography on silica gel with EtOAc/hexanes (50/50) as the eluant to obtain (*R*)-*N*-(4'-ethyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide as a white solid (2.83 g, 69%): R_f = 0.60 (5% MeOH/$CHCl_3$); mp 114–115 ºC ; IR (nujol) 3292, 3063, 1689, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (t, *J* = 7.5 Hz, CH_2CH_3), 2.62 (q, *J* = 7.5 Hz, CH_2CH_3), 3.34 (s, OCH_3), 3.44 (dd, *J* = 2.9, 9.0 Hz, CHH'OCH_3), 3.85 (dd, *J* = 2.9, 9.0 Hz, CHH'OCH_3), 4.37–4.40 (m, CH), 4.42 (d, *J* = 5.4 Hz, NCH_2), 5.09 (s, $ArCH_2$), 6.65–675 (br t, NH), 7.11–7.21 (m, C_6H_4), 7.26–7.41 (m, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 15.6 (CH_3), 28.5 (CH_2CH_3), 43.3 (CH_2N), 54.5 ($CHCH_2$), 59.0 (OCH_3), 67.1 ($PhCH_2O$), 72.0 (CH_2OCH_3), 127.5, 128.0, 128.1, 127.2, 128.5, 135.0, 136.1, 143.5 (8 Ar**C**), 156.2 (N**C**(O)O), 169.7 (**C**(O)); HRMS ($M+H^+$)(ESI^+) 393.1783 [M + Na^+] (calcd for $C_{21}H_{26}N_2O_4Na^+$ 393.1790); Anal. Calcd. for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56; Found: C, 67.86; H, 7.10; N, 7.59.

Preparation of (*S*)-*N*-(4'-Ethyl)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-methoxypropionamide ((*S*)-73). Ag_2O (12.95 g, 55.5 mmol) was added to a CH_3CN solution (400 mL) of (*S*)-*N*-(4'-ethyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide (3.97 g, 11.1 mmol) and CH_3I (6.9 mL, 111.1 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature in the dark (4 d), filtered through a pad of Celite®, and the filtrate concentrated in vacuo to obtain a white solid. The solid was purified by flash column chromatography on silica gel with EtOAc/hexanes (50/50) as the eluant to obtain (*S*)-*N*-(4'-ethyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide as a white solid (3.95 g, 96%): R_f = 0.60 (5% MeOH in $CHCl_3$); mp 114–115 ºC; IR (nujol) 3295, 3073, 1698, 1648 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, J = 7.5 Hz, $CH_2C\mathbf{H_3}$), 2.62 (q, J = 7.5 Hz, $C\mathbf{H_2}CH_3$), 3.34 (s, $OC\mathbf{H_3}$), 3.44 (dd, J = 2.9, 9.0 Hz, C**H**H'OCH_3), 3.85 (dd, J = 2.9, 9.0 Hz, CH**H'**OCH_3), 4.37–4.40 (m, C**H**), 4.42 (d, J = 5.4 Hz, $NC\mathbf{H_2}$), 5.09 (s, $ArC\mathbf{H_2}$), 6.71 (br t, N**H**), 7.11–7.21 (m, $C_6\mathbf{H_4}$), 7.26–7.41 (m, $C_6\mathbf{H_5}$); HRMS (M+H^+)(ESI$^+$) 393.1783 [M + Na^+] (calcd for $C_{21}H_{26}N_2O_4Na^+$ 393.1790); Anal. Calcd. for $C_{21}H_{26}N_2O_4$•0.05H_2O: C, 67.91; H, 7.08; N, 7.54; Found: C, 67.66; H, 7.18; N, 7.59.

Preparation of (*R*)-*N*-(4'-Ethyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-11). A MeOH solution (250 mL) of (*R*)-*N*-(4'-ethyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (1.20 g, 3.0 mmol) was treated with H_2 (1 atm) in presence of 10% Pd/C (120 mg) at room temperature (3 d). The mixture was carefully filtered through a bed of Celite®. The pad was washed with MeOH and CH_2Cl_2, and the washings were collected and evaporated in vacuo to obtain a yellow solid. The residue was dissolved in CH_2Cl_2 (40 mL) and then triethylamine (0.5 mL, 3.5 mmol) and acetyl chloride (250 μL, 3.5 mmol) were carefully added at 0 °C and the resulting solution was stirred at room temperature (2 h). An aqueous 10% citric acid solution (100 mL) was added and the organic layer was extracted with CH_2Cl_2 (3 x 100 mL). The

organic layers were combined, washed with a saturated aqueous $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), and concentrated in vacuo. After recrystallization of the residue with EtOAc, (*R*)-*N*-(4'-ethyl)benzyl 2-acetamido-3-methoxypropionamide was obtained as a white solid: mp 132-133 °C; IR (nujol) 3413, 3305, 3057, 2968, 2932, 1693, 1528, 1266, 1116 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (t, *J* = 7.5 Hz, **C**H_3CH_2), 2.02 (s, C**H$_3$**CO), 2.63 (q, *J* = 7.5 Hz, CH_3**C**H_2), 3.37 (s, OC**H$_3$**), 3.43 (dd, *J* = 7.2, 9.0 Hz, C**H**H'), 3.79 (dd, *J* = 4.2, 9.0 Hz, CH**H'**), 4.43 (d, *J* = 6.0 Hz, C**H$_2$**N), 4.50–4.58 (m C**H**), 6.47 (br d, *J* = 6.9 Hz, N**H**C(O)CH_3), 6.71–6.82 (br t, CH_2N**H**), 7.15–7.18 (m, 4 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-ethyl)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 15.5 (CH_2**C**H_3), 23.1 (**C**H_3CO), 28.5 (**C**H_2CH_3), 43.3 (**C**H_2N), 52.4 (**C**HCH_2), 59.0 (O**C**H_3), 71.7 (**C**H_2OCH_3), 127.5, 128.1, 135.0, 143.5 (4 Ar**C**), 169.9, 170.3 (2 **C**(O)); HRMS (M+H^+)(ESI$^+$) 279.1708 [M + H^+] (calcd for $C_{15}H_{22}N_2O_3^+$ 279.1705); Anal. Calcd. for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.52; H, 7.98; N, 10.05.

Preparation of (*S*)-*N*-(4'-Ethyl)benzyl 2-Acetamido-3-methoxypropionamide ((*S*)-11). A MeOH solution (250 mL) of (*S*)-*N*-(4'-ethyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (1.20 g, 3.0 mmol) was treated with H_2 (1 atm) in presence of 10% Pd/C (120 mg) at room temperature (3 d). The mixture was carefully filtered through a bed of Celite®. The pad was washed with MeOH and CH_2Cl_2, and the washings were collected and evaporated in vacuo to obtain a yellow solid. The residue was dissolved in CH_2Cl_2 (40 mL) and then triethylamine (0.5 mL, 3.5 mmol) and acetyl chloride (250 μL, 3.5 mmol) were carefully added at 0 °C and the resulting solution was stirred at room temperature (2 h). An aqueous 10% citric acid solution (100 mL) was added and the organic layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, washed with a saturated aqueous $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), and concentrated in vacuo. After recrystallization of the residue with EtOAc, (*S*)-*N*-(4'-ethyl)benzyl 2-acetamido-3-

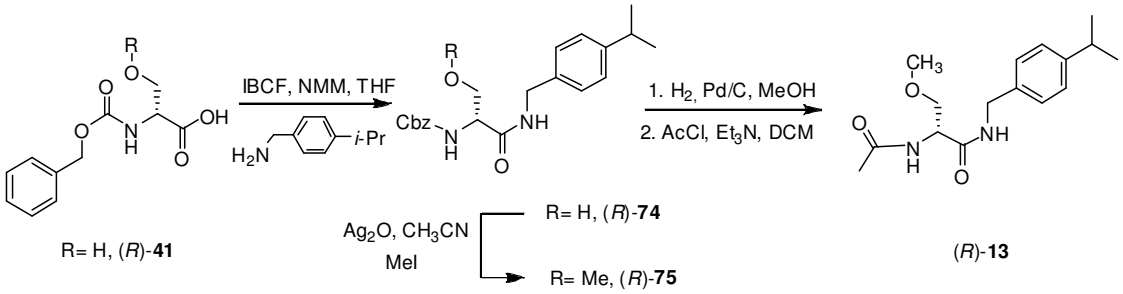
methoxypropionamide was obtained as a white solid: mp 132–133 °C; IR (nujol) 3286, 2932, 2928, 1637, 1554, 1458, 1375, 1311, 1197, 1102, 1051, 909, 821, 724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (t, J = 7.5 Hz, **C**H_3CH_2), 2.02 (s, C**H$_3$**CO), 2.62 (q, J = 7.5 Hz, CH_3**C**H_2), 3.37 (s, OC**H$_3$**), 3.43 (dd, J = 7.2, 9.0 Hz, C**H**H'), 3.79 (dd, J = 4.5, 9.0 Hz, CH**H'**), 4.43 (d, J = 5.7 Hz, C**H$_2$**N), 4.43–4.58 (m C**H**), 6.48 (br d, J = 6.3 Hz, N**H**C(O)CH_3), 6.71–6.82 (br t, CH_2N**H**), 7.15–7.18 (m, 4 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*S*)-*N*-(4'-ethyl)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 15.8 (CH_2**C**H_3), 23.4 (**C**H_3CO), 28.7 (**C**H_2CH_3), 43.5 (**C**H_2N), 52.6 (**C**HCH_2), 59.3 (O**C**H_3), 72.0 (**C**H_2OCH_3), 127.7, 128.4, 135.2, 143.8 (4 Ar**C**) , 170.1, 170.5 (2 **C**(O)); HRMS (M+H^+)(ESI^+) 279.1708 [M + H^+] (calcd for $C_{15}H_{22}N_2O_3^+$ 279.1705); Anal. Calcd. for $C_{15}H_{22}N_2O_3$: C, 64.73; H, 7.97; N, 10.06. Found: C, 64.73; H, 7.98; N, 10.04.

7. Preparation of (*R*)-*N*-(4'-Propyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-12).

Preparation of (*R*)-*N*-(4'-Propyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-12). PtO_2 (100 mg) was added to an EtOH solution of (*R*)-*N*-(4'-(prop-1-ynyl))benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**24**) (700 mg, 2.25 mmol), and the mixture was stirred at room temprerature under H_2 (1 atm) (24 h). The reaction mixture was filtered through a pad of Celite®, and the pad was washed successively with EtOH and CH_2Cl_2. The filtrate was concentrated under vacuum and the residue was purified by flash chromatography on silica gel with EtOAc/hexanes (8/2 to 10/0) as the eluant to obtain (*R*)-*N*-(4'-propyl)benzyl 2-acetamido-3-methoxypropionamide (560 mg, 79%) as a white solid: R_f = 0.37 (EtOAc); mp 126–127 °C; $[\alpha]^{25.4}_D$ = –27.2° (*c* 0.5, $CHCl_3$); IR (nujol) 3439, 3374, 3140, 2949, 2859, 1637, 1548, 1457, 1374, 1305, 1137, 1098, 972, 832, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, J = 7.5 Hz, C**H$_3$**CH_2),

1.57–1.64 (m, $CH_2C\mathbf{H_2}CH_3$), 2.04 (s, $C\mathbf{H_3}C(O)$), 2.57 (t, J = 7.8 Hz, $C\mathbf{H_2}CH_2CH_3$), 3.34–3.45 (m, C**H**H', $OC\mathbf{H_3}$), 3.81 (dd, J = 4.2, 9.0 Hz, CH**H'**), 4.44 (d, J = 5.7 Hz, $C\mathbf{H_2}N$), 4.50–4.57 (m, NC(**H**)CO), 6.38–6.46 (br m, CHN**H**), 6.63–6.73 (br m, $CH_2N\mathbf{H}$), 7.12–7.19 (m, 4 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-propyl)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 13.8 ($CH_2\mathbf{C}H_3$), 23.1 ($\mathbf{C}H_3CO$), 24.5 ($\mathbf{C}H_2CH_3$), 37.6 ($\mathbf{C}H_2CH_2CH_3$), 43.3 ($\mathbf{C}H_2N$), 52.4 ($\mathbf{C}HCH_2$), 59.0 ($O\mathbf{C}H_3$), 71.8 ($\mathbf{C}H_2OCH_3$), 123.4, 128.7, 135.0, 142.0 (4 Ar**C**), 169.9, 170.3 (2 **C**(O)); HRMS ($M+H^+$)(ESI^+) 293.1865 [M + H^+] (calcd for $C_{16}H_{24}N_2O_3H^+$ 293.1865); Anal. Calcd. for $C_{16}H_{24}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 66.01; H, 8.24; N, 9.36.

8. Preparation of (*R*)-*N*-(4'-*iso*-Propyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-13).



Preparation of (*R*)-*N*-(4'-*iso*-Propyl)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-hydroxypropionamide ((*R*)-74). A THF solution (200 mL) of (*R*)-Cbz-serine (5.00 g, 20.9 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (2.8 mL, 25.1 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (3.3 mL, 25.1 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for an additional 2 min. A THF (40 mL) suspension of 4-*iso*-propylbenzylamine hydrochloride (5.42 g, 29.3 mmol)

and NMM (2.8 mL, 25.1 mmol), were added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and then the white solid filtered and the organic layer concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (30/70 to 100/0) as the eluant to obtain (*R*)-*N*-(4'-*iso*-propyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide as a white solid (2.40 g, 31%): R_f = 0.75 (EtOAc); mp 151–152 °C; $[\alpha]^{24.7}_D$ +20.8° (*c* 0.5, $CHCl_3$); IR (nujol) 3289, 3099, 2952, 2861, 1690, 1643, 1537, 1458, 1375, 1313, 1240, 1025, 738, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (d, *J* = 6.9 Hz, CH(C**H**$_3$)$_2$), 2.88 (sept., *J* = 6.9 Hz, C**H**$(CH_3)_2$), 3.12–3.24 (br s, O**H**), 3.61–3.72 (m, C**H**H'), 4.10 (dd, *J* = 2.4, 11.1 Hz, CH**H'**), 4.21–4.27 (br m, C**H**), 4.39 (d, *J* = 5.4 Hz, C**H**$_2$N), 5.08 (s, C**H**$_2$O), 5.90 (br d, *J* = 7.5 Hz, N**H**), 6.89–7.00 (br s, N**H**), 7.16 (s, 4 Ar**H**), 7.33 (s, 5 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 23.9(CH(**C**H$_3$)$_2$), 33.8 (**C**H$(CH_3)_2$), 43.3 (N**C**H$_2$), 55.3 (OCH$_2$**C**H), 62.8 (O**C**H$_2$CH), 67.4 (Ph**C**H$_2$O), 126.8, 127.6, 128.1, 128.3, 128.6, 134.8, 135.9, 148.3 (8 Ar**C**), 156.7 (N**C**(O)O), 170.7 (**C**(O)); HRMS (M+H$^+$)(ESI$^+$) 371.1971 [M + H$^+$] (calcd for $C_{21}H_{26}N_2O_4H^+$ 371.1971); Anal. Calcd. for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 67.82; H, 6.98; N, 7.47.

Preparation of (*R*)-*N*-(4'-*iso*-Propyl)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-methoxypropionamide ((*R*)-75). Ag_2O (6.00 g, 25.7 mmol) was added to a CH_3CN solution (100 mL) of (*R*)-*N*-(4'-*iso*-propyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide (1.90 g, 5.1 mmol) and CH_3I (3.2 mL, 51.0 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature in the dark (3 d), filtered through a pad of Celite®, and the filtrate concentrated in vacuo to obtain (*R*)-*N*-(4'-*iso*-propyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide as a white solid (1.90 g, quant.): R_f = 0.66 (EtOAc); mp 79–81 °C; $[\alpha]^{26.8}_D$ –25.2° (*c* 0.5, $CHCl_3$); IR (nujol) 3275, 2888, 1690, 1645, 1548, 1458, 1374, 1315, 1255, 1156, 1091, 1044, 972, 919, 808, 727 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (d, *J* = 6.9 Hz, CH(C**H**$_3$)$_2$), 2.89 (sept. *J* = 6.9 Hz, C**H**$(CH_3)_2$), 3.35 (s, OC**H**$_3$), 3.49 (dd, *J* = 6.3, 9.2 Hz, C**H**H'), 3.85 (dd, *J* = 3.6, 9.2 Hz, CH**H'**), 4.29–4.38 (br m, C**H**CH$_2$), 4.43

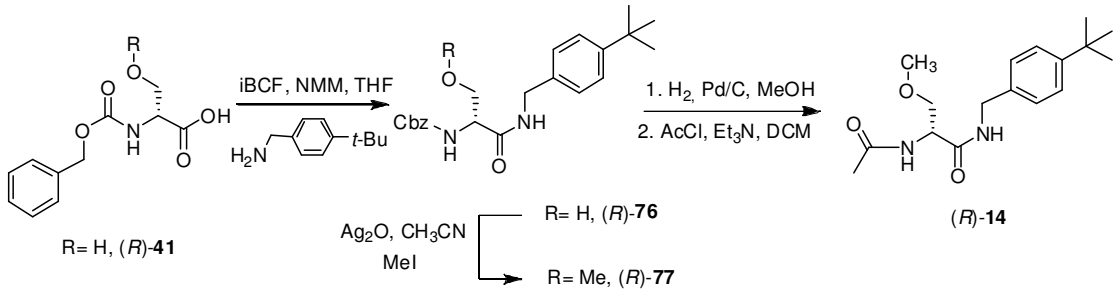
(d, J = 5.7 Hz, C**H**$_2$N), 5.11 (s, OC**H**$_2$), 5.62–5.76 (br d, OC(O)N**H**), 6.61–6.75 (br m, CH$_2$N**H**), 7.18 (s, 4 Ar**H**), 7.34 (s, 5 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 23.9 (CH(**C**H$_3$)$_2$), 33.8 (**C**H(CH$_3$)$_2$), 43.3 (N**C**H$_2$), 54.3 (OCH$_2$**C**H), 59.1 (O**C**H$_3$), 67.2 (Ph**C**H$_2$O), 72.0 (O**C**H$_2$CH), 126.7, 127.5, 128.1, 128.2, 128.5, 135.1, 136.0, 148.2 (8 Ar**C**), 156.1 (N**C**(O)O), 169.8 (**C**(O)); HRMS (M+H$^+$)(ESI$^+$) 385.2128 [M + H$^+$] (calcd for $C_{22}H_{28}N_2O_4H^+$ 385.2127); Anal. Calcd. for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N, 7.29. Found: C, 68.71; H, 7.40; N, 7.29.

Preparation of (*R*)-*N*-(4'-*iso*-Propyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-13). An EtOH solution (250 mL) of (*R*)-*N*-(4'-*iso*-propyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (1.80 g, 4.7 mmol) was treated with H_2 (1 atm) in presence of 10% Pd/C (180 mg) at room temperature (16 h). The mixture was carefully filtered through a bed of Celite® and the filtrate was evaporated in vacuo to obtain a brown oil: ^{1}H NMR ($CDCl_3$) δ 1.24 (d, J = 6.9 Hz, CH(C**H$_3$**)$_2$), 2.89 (sept., J = 6.9 Hz, C**H**(CH$_3$)$_2$), 3.38 (s, OC**H$_3$**), 3.59–3.66 (m, C**H$_2$**, C**H**), 4.35–4.49 (m, NC**H$_2$**), 7.16 (m, 4 Ar**H**), 7.69–7.82 (br s, N**H**C(O)); ^{13}C NMR ($CDCl_3$) δ 23.9 (CH(**C**H$_3$)$_2$), 33.8 (**C**H(CH$_3$)$_2$), 42.9 (**C**H$_2$N), 54.8 (**C**H), 58.8 (O**C**H$_3$), 74.5 (**C**H$_2$), 126.7, 127.7, 135.6, 148.1 (4 Ar**C**), 172.5 (**C**(O)).

The oil was dissolved in CH_2Cl_2 (50 mL) and then triethylamine (0.79 mL, 5.6 mmol) and acetyl chloride (0.40 mL, 5.6 mmol) were carefully added at 0 °C and the resulting solution was stirred at room temperature (2 h). An aqueous 10% citric acid solution (50 mL) was added and the organic layer was extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, washed with a saturated $NaHCO_3$ solution (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/hexanes (80/20 to 100/0) as the eluant to obtain (*R*)-*N*-(4'-*iso*-propyl)benzyl 2-acetamido-3-methoxypropionamide as a white solid (2.40 g, 62%): R_f = 0.39 (EtOAc/hexanes 80/20); mp 95–97 °C; $[\alpha]^{27.0}_D$ –10.5° (*c* 0.5, $CHCl_3$); IR (nujol) 3289, 2921, 2858, 1635, 1550, 1457, 1376, 1312, 1193, 1101, 1048, 913, 811, 723 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.24 (d, J = 6.9 Hz, CH(C**H$_3$**)$_2$), 2.03

(s, C**H**$_3$CO), 2.90 (sept., J = 6.9 Hz, C**H**(CH$_3$)$_2$), 3.38 (s, OC**H**$_3$), 3.43 (dd, J = 7.8, 9.0 Hz, C**H**H'), 3.81 (dd, J = 4.2, 9.0 Hz, CH**H'**), 4.44 (d, J = 5.7 Hz, C**H**$_2$N), 4.50–4.56 (m, C**H**), 6.44 (br d, J = 6.3 Hz, N**H**C(O)CH$_3$), 6.65–6.74 (br t, CH$_2$N**H**), 7.19 (s, 4 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-*iso*-propyl)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.2 (**C**H$_3$CO), 24.0 (CH(**C**H$_3$)$_2$), 33.8 (**C**H(CH$_3$)$_2$), 43.3 (**C**H$_2$N), 52.4 (**C**HCH$_2$), 59.0 (O**C**H$_3$), 71.7 (**C**H$_2$OCH$_3$), 126.7, 127.5, 135.1, 148.2 (4 Ar**C**), 169.9, 170.3 (2 **C**(O)); MS (M+Na$^+$)(ESI$^+$) 315.2 [M + H$^+$] (calcd for $C_{16}H_{22}N_2O_3Na^+$ 315.2); Anal. Calcd. for $C_{16}H_{22}N_2O_3$: C, 65.73; H, 8.27; N, 9.58. Found: C, 65.46; H, 8.21; N, 9.48.

9. Preparation of (*R*)-*N*-(4'-*tert*-Butyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-14).



Preparation of (*R*)-*N*-(4'-*tert*-Butyl)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-hydroxypropionamide ((*R*)-76). A THF solution (200 mL) of (*R*)-Cbz-serine (6.10 g, 25.5 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (3.4 mL, 30.6 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (4.0 mL, 30.6 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min and then 4-*tert*-butylbenzylamine (5.00 g, 30.6 mmol) was added portionwise at -78 °C. The

mixture was allowed to stir at room temperature (2 h), and then the white solid filtered and the organic layer concentrated in vacuo. The residue was recrystallized with EtOAc to obtain (*R*)-*N*-(4'-*tert*-butyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide as a white solid (6.10 g, 62%): R_f = 0.15 (hexanes/EtOAc 5/5); mp 137–139 °C; $[\alpha]^{26.0}_D$ +16.8° (*c* 1.0, $CHCl_3$); IR (nujol) 3239, 3062, 2861, 1681, 1569, 1457, 1374, 1290, 1061, 798, 737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.28 (s, C(C**H**$_3$)$_3$), 3.42–3.56 (br s, O**H**), 3.61–3.72 (m, C**H**H'), 3.99–4.08 (m, CH**H'**), 4.23–4.31 (br m, C**H**), 4.37 (d, *J* = 5.7 Hz, C**H**$_2$N), 5.05 (s, C**H**$_2$O), 6.01 (d, *J* = 6.9 Hz, N**H**), 7.01–7.10 (br s, N**H**), 7.15 (d, *J* = 8.1 Hz, 2 Ar**H**), 7.31 (s, 7 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 31.3(C(**C**H$_3$)$_3$), 34.4 (**C**(CH$_3$)$_3$), 43.2 (N**C**H$_2$), 55.3 (OCH$_2$**C**H), 62.8 (O**C**H$_2$CH), 67.3 (Ph**C**H$_2$O), 125.6, 127.2, 128.0, 128.5, 134.4, 135.9, 150.5 (7 Ar**C**), 156.7 (N**C**(O)O), 170.7 (**C**(O)), one signal was not detected and is believed to overlap with nearby peaks; HRMS (M+H$^+$)(ESI$^+$) 385.2128 [M + H$^+$] (calcd for $C_{22}H_{28}N_2O_4H^+$ 385.2127); Anal. Calcd. for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N, 7.29. Found: C, 68.60; H, 7.36; N, 7.26.

Preparation of (*R*)-*N*-(4'-*tert*-Butyl)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-methoxypropionamide ((*R*)-77). Ag_2O (13.64 g, 58.5 mmol) was added to a CH_3CN solution (300 mL) of (*R*)-*N*-(4'-*tert*-butyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide (4.50 g, 11.7 mmol) and CH_3I (7.3 mL, 117.0 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature in the dark (2 d), filtered through a pad of Celite®, and the filtrate concentrated in vacuo to obtain a white solid. The solid was purified by flash column chromatography on silica gel with EtOAc/hexanes (0/100 to 50/50) as the eluant to obtain (*R*)-*N*-(4'-*tert*-butyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide as a white solid (4.40 g, 97%): R_f = 0.59 (1/1 EtOAc/hexanes); mp 74–76 °C; $[\alpha]^{26.0}_D$ –25.6° (*c* 1.0, $CHCl_3$); IR (nujol) 3291, 2958, 2860, 1687, 1645, 1533, 1458, 1374, 1314, 1243, 969, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (s, C(C**H**$_3$)$_3$), 3.36 (s, OC**H**$_3$), 3.50 (dd, *J* = 6.6, 9.0 Hz, C**H**H'), 3.85 (dd, *J* = 3.3, 9.0 Hz, CH**H'**), 4.31–4.38 (br m, C**H**CH$_2$), 4.44 (d, *J* = 5.7 Hz, C**H**$_2$N), 5.11 (s, OC**H**$_2$), 5.70–5.80 (br m,

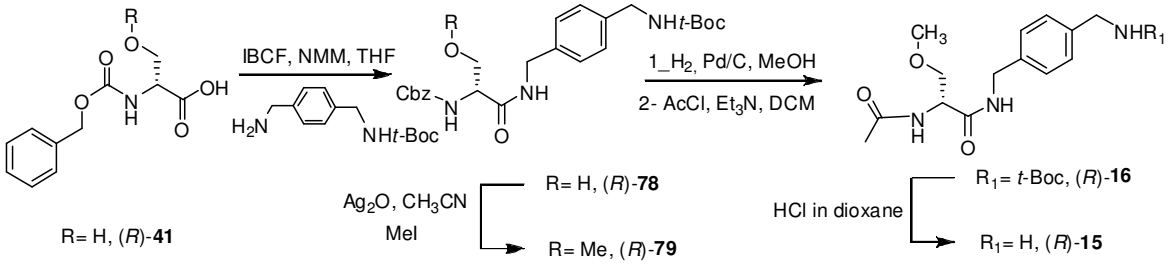
OC(O)N**H**), 6.69–6.80 (br m, CH_2N**H**), 7.19 (d, *J* = 7.5 Hz, 2 Ar**H**), 7.34 (s, 7 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 31.0 (C(**C**H_3)$_3$), 34.4 (**C**(CH_3)$_3$), 43.2 (N**C**H_2), 54.3 (OCH_2**C**H), 59.0 (O**C**H_3), 67.1 (Ph**C**H_2O), 72.0 (O**C**H_2CH), 125.5, 127.2, 128.1, 128.2, 128.5, 134.7, 136.0, 150.4 (8 Ar**C**), 156.1 (N**C**(O)O), 169.8 (**C**(O)); HRMS (M+H^+)(ESI$^+$) 399.2284 [M + H^+] (calcd for $C_{23}H_{30}N_2O_4H^+$ 399.2284); Anal. Calcd. for $C_{23}H_{30}N_2O_4$: C, 69.32; H, 7.59; N, 7.03. Found: C, 69.15; H, 7.64; N, 7.03.

Preparation of (*R*)-*N*-(4'-*tert*-Butyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-14). An EtOH solution (250 mL) of (*R*)-*N*-(4'-*tert*-butyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide. (4.00 g, 10.0 mmol) was treated with H_2 (1 atm) in presence of 10% Pd/C (400 mg) at room temperature (16 h). The mixture was carefully filtered through a bed of Celite® and the filtrate was evaporated in vacuo to obtain a brown oil: ^{1}H NMR ($CDCl_3$) δ 1.31 (s, C(C**H$_3$**)$_3$), 1.58–1.62 (br s, N**H$_2$**), 3.38 (s, OC**H$_3$**), 3.59–3.66 (m, C**H$_2$**, C**H**), 4.36–4.49 (m, NC**H$_2$**), 7.21 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.36 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.69–7.81 (br s, N**H**C(O)); ^{13}C NMR ($CDCl_3$) δ 31.3 (C(**C**H_3)$_3$), 34.5 (**C**(CH_3)$_3$), 42.8 (**C**H_2N), 54.9 (**C**H), 58.8 (O**C**H_3), 74.5 (**C**H_2), 125.5, 127.4, 135.2, 150.3 (4 Ar**C**), 172.5 (**C**(O)); HRMS (M+H^+)(ESI$^+$) 265.1916 [M + H^+] (calcd for $C_{15}H_{24}N_2O_2H^+$ 265.1916).

The oil was dissolved in CH_2Cl_2 (100 mL) and then triethylamine (1.7 mL, 12.0 mmol) and acetyl chloride (856 μL, 12.0 mmol) were carefully added at 0 °C and the resulting solution was stirred at room temperature (2 h). An aqueous 10% citric acid solution (100 mL) was added and the organic layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, washed with a saturated $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), and concentrated in vacuo. After recrystallization of the residue with EtOAc (*R*)-*N*-(4'-*tert*-butyl)benzyl 2-acetamido-3-methoxypropionamide was obtained as a white solid (1.70 g, 55%): R_f = 0.73 (EtOAc); mp 125–126 °C; $[\alpha]^{26.8}_D$ –26.0° (*c* 1 , $CHCl_3$); IR (nujol) 3280, 2920, 2860, 1636, 1544, 1456, 1374, 1301, 1247, 1197, 1119, 966, 815, 725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, C(C**H$_3$**)$_3$), 1.99 (s, C**H$_3$**CO), 3.37 (s, OC**H$_3$**), 3.46 (dd, *J* = 7.2, 9.0 Hz, C**H**H'), 3.77 (dd, *J* = 4.2, 9.0 Hz, CH**H'**), 4.36–4.44 (m,

C**H**$_2$N), 4.56–4.62 (m, C**H**), 6.63 (br d, J = 6.6 Hz, N**H**C(O)CH$_3$), 6.89–6.98 (br t, CH$_2$N**H**), 7.18 (d, J = 8.1 Hz, 2 Ar**H**), 7.35 (d, J = 8.1 Hz, 2 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-*tert*-butyl)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.1 (**C**H$_3$CO), 31.3 (C(**C**H$_3$)$_3$), 34.4 (**C**(CH$_3$)$_3$), 43.2 (**C**H$_2$N), 52.4 (**C**HCH$_2$), 59.0 (O**C**H$_3$), 71.8 (**C**H$_2$OCH$_3$), 125.5, 127.2, 134.7, 150.4 (4 Ar**C**), 169.9, 170.3 (2 **C**(O)); HRMS (M+H$^+$)(ESI$^+$) 307.2022 [M + H$^+$] (calcd for $C_{17}H_{26}N_2O_3H^+$ 307.2021); Anal. Calcd. for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14. Found: C, 66.61; H, 8.49; N, 9.09.

10. Preparation of (*R*)-*N*-(4'-(Aminomethyl))benzyl 2-Acetamido-3-methoxypropionamide Hydrochloride ((*R*)-15).



Preparation of (*R*)-*N*-(4'-(*tert*-Butoxycarbonyl)aminomethyl)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-hydroxypropionamide ((*R*)-78). A THF solution (200 mL) of (*R*)-Cbz-serine (7.00 g, 29.3 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (3.9 mL, 35.1 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (4.6 mL, 35.1 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min and then 1-(*N*-Boc-aminomethyl)-4-(aminomethyl)benzene

(8.30 g, 35.1 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and then the white solid filtered and the organic layer concentrated in vacuo. The residue was recrystallized with EtOAc to obtain (*R*)-*N*-(4'-(*tert*-butoxycarbonyl)aminomethyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide as a white solid (5.10 g), and the filtrate was purified by flash column chromatography on silica gel with EtOAc/hexanes (50/50) as the eluant to obtain (*R*)-*N*-(4'-(*tert*-butoxycarbonyl)aminomethyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide as a white solid (2.40 g) (total yield: 7.50 g (56%)): R_f = 0.16 (hexanes/EtOAc 5/5); mp 150–151 °C; $[\alpha]^{26.9}_D$ +8.7° (*c* 1.0, $CHCl_3$); IR (nujol) 3320, 3099, 2953, 2916, 1689, 1648, 1534, 1456, 1366, 1282, 1241, 1173, 1027, 926, 863, 741, 664 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.38 (s, C(C**H**$_3$)$_3$), 3.52–3.66 (m, C**H**$_2$OH), 4.05–4.11 (m, C**H**$_2$NH, C**H**), 4.26 (d, *J* = 5.4 Hz, C**H**$_2$N), 4.89 (t, *J* = 5.7 Hz, O**H**), 5.04 (s, C**H**$_2$O), 7.13–7.24 (m, N**H**, 4 Ar**H**), 7.31–7.38 (m, N**H**, 5 Ar**H**), 8.39 (t, *J* = 5.7 Hz, CH_2N**H**); ^{13}C NMR (DMSO-d_6) δ 28.2 (C(**C**H_3)$_3$), 41.8, 43.0 (2 N**C**H_2), 57.3 (OCH_2**C**H), 61.7 (O**C**H_2CH), 65.4 (Ph**C**H_2O), 77.6 (**C**$(CH_3)_3$), 126.7, 126.8, 127.6, 127.7, 128.3, 136.9, 137.6, 138.5 (8 Ar**C**), 155.7, 155.7 (2 N**C**(O)O), 170.0 (**C**(O)); HRMS (M+H$^+$)(ESI$^+$) 458.2291 [M + H$^+$] (calcd for $C_{24}H_{31}N_3O_6H^+$ 458.2291); Anal. Calcd. for $C_{24}H_{31}N_3O_6$: C, 63.00; H, 6.83; N, 9.18. Found: C, 62.99; H, 6.70; N, 9.16.

Preparation of (*R*)-*N*-(4'-(*tert*-Butoxycarbonyl)aminomethyl)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-methoxypropionamide ((*R*)-79). Ag_2O (15.30 g, 65.6 mmol) was added to a CH_3CN solution (250 mL) of (*R*)-*N*-(4-(*tert*-butoxycarbonyl)aminomethyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide (6.00 g, 13.1 mmol) and CH_3I (8.2 mL, 131.0 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature in the dark (5 d), filtered through a pad of Celite®, and the filtrate concentrated in vacuo. The solid was purified by flash column chromatography on silica gel with EtOAc/hexanes (0/100 to 20/80) as the eluant to obtain (*R*)-*N*-(4'-(*tert*-butoxycarbonyl)aminomethyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-

methoxypropionamide as a white solid (5.60 g, 91%): R_f = 0.30 (EtOAc/hexanes 2/8); mp 120–121 °C; $[\alpha]^{26.0}_D$ –16.2° (*c* 1.0, $CHCl_3$); IR (nujol) 3321, 2929, 2857, 1684, 1648, 1529, 1457, 1375, 1308, 1251, 1164, 1052, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, C(C**H**$_3$)$_3$), 3.35 (s, OC**H**$_3$), 3.49 (dd, *J* = 6.6, 9.0 Hz, C**H**H'), 3.84 (dd, *J* = 3.6, 9.0 Hz, CH**H'**), 4.24–4.38 (br m, C**H**CH_2, C**H**$_2$N), 4.43 (d, *J* = 5.4 Hz, C**H**$_2$N), 4.83–4.95 (br s, *t*-BocN**H**), 5.10 (s, OC**H**$_2$), 5.67–5.76 (br s, N**H**), 6.69–6.78 (br m, N**H**), 7.17–725 (m, 4 Ar**H**), 7.34 (s, 5 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 28.4 (s, C(**C**H_3)$_3$), 41.2, 44.3 (2 N**C**H_2), 54.3 (OCH_2**C**H), 59.1 (O**C**H_3), 67.2 (O**C**H_2), 72.0 (O**C**H_2CH), 79.5 (**C**$(CH_3)_3$), 127.7, 128.1, 128.3, 128.5, 136.0, 136.9, 138.2 (7 Ar**C**), 155.8, 156.1 (2 N**C**(O)O), 169.8 (**C**(O)), one signal was not detected and is believed to overlap with nearby peaks; HRMS ($M+H^+$)(ESI^+) 472.2448 [M + H^+] (calcd for $C_{25}H_{33}N_3O_6H^+$ 472.2447); Anal. Calcd. for $C_{25}H_{33}N_3O_6$: C, 63.68; H, 7.05; N, 8.91. Found: C, 63.61; H, 7.12; N, 8.88.

Preparation of (*R*)-*N*-(4'-(*tert*-Butoxycarbonyl)aminomethyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-16). An EtOH solution (400 mL) of (*R*)-*N*-(4'-(*tert*-butoxycarbonyl)aminomethyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (5.30 g, 11.2 mmol) was treated with H_2 (1 atm) in presence of 10% Pd/C (530 mg) at room temperature (24 h) and then an additional 470 mg of Pd/C was added and then the mixture was allowed to stir at room temperature (12 h). The mixture was carefully filtered through a bed of Celite® and the filtrate was evaporated in vacuo to obtain a brown oil.

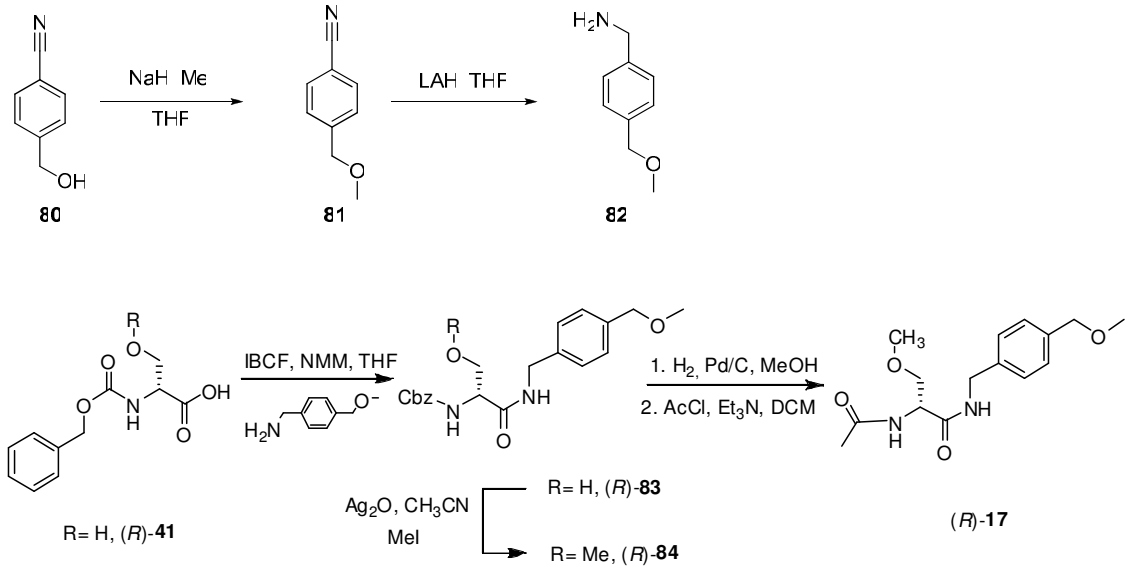
The oil was dissolved in CH_2Cl_2 (100 mL) and then triethylamine (1.9 mL, 13.5 mmol) and acetyl chloride (0.96 mL, 13.5 mmol) were carefully added at 0 °C and the resulting solution was stirred at room temperature (2 h). An aqueous 10% citric acid solution (100 mL) was added and the organic layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, washed with a saturated $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was recrystallized from EtOAc to obtain (*R*)-*N*-(4'-(*tert*-butoxycarbonyl)aminomethyl)lbenzyl 2-acetamido-3-methoxypropionamide as a

white solid (2.50 g, 60%): R_f = 0.47 (EtOAc); mp 153–154 °C; $[\alpha]^{24.9}_D$ –15.9° (*c* 1.0, $CHCl_3$); IR (nujol) 3318, 2919, 2861, 1675, 1639, 1530, 1458, 1374, 1260, 1167, 1127, 1057, 835, 724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, C(C**H**$_3$)$_3$), 2.01 (s, C**H**$_3$CO), 3.37 (s, OC**H**$_3$), 3.44 (dd, *J* = 7.2, 9.0 Hz, C**H**H'), 3.79 (dd, *J* = 4.2, 9.0 Hz, CH**H'**), 4.28 (d, *J* = 5.7 Hz, C**H**$_2$N), 4.43 (d, *J* = 5.7 Hz, C**H**$_2$N), 4.51–4.57 (m, C**H**), 4.86–4.95 (br s, *t*-BocN**H**), 6.49–6.57 (br d, N**H**C(O)CH_3), 6.83–6.93 (br m, CH_2N**H**), 7.17–7.26 (m, 4 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-(*tert*-butoxycarbonyl)aminomethyl)lbenzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.1 (**C**H_3CO), 28.4 (C(**C**H_3)$_3$), 43.2, 44.3 (2 **C**H_2N), 52.4 (**C**HCH$_2$), 59.0 (O**C**H_3), 71.7 (**C**H_2OCH_3), 79.5 (**C**$(CH_3)_3$), 127.7, 136.9, 138.3 (3 Ar**C**), 155.9 (N**C**(O)O), 170.0, 170.4 (2 **C**(O)), one signal was not detected and is believed to overlap with nearby peaks; HRMS (M+H^+)(ESI^+) 380.2186 [M + H^+] (calcd for $C_{19}H_{29}N_3O_5H^+$ 380.2185); Anal. Calcd. for $C_{19}H_{29}N_3O_5$: C, 60.14; H, 7.70; N, 11.07. Found: C, 60.11; H, 7.83; N, 11.02.

Preparation of (*R*)-*N*-(4'-Aminomethyl)benzyl 2-Acetamido-3-methoxypropionamide Hydrochloride ((*R*)-15). A saturated HCl solution in dioxane (11.25 mL, 45.0 mL) was added to (*R*)-*N*-(4'-(*tert*-butoxycarbonyl)aminomethyl)lbenzyl 2-acetamido-3-methoxypropionamide (1.70 g, 4.5 mmol) at 0 °C and the solution was stirred at room temperature (4 h). The reaction solution was concentrated in vacuo and dried (30 min). The residue was triturated with Et_2O and the white solid was filtered to obtain (*R*)-*N*-(4'-aminomethyl)lbenzyl 2-acetamido-3-methoxypropionamide hydrochloride (1.20 g, quant.): R_f = 0.00 (EtOAc); mp > 210 °C; $[\alpha]^{26.2}_D$ –1.6° (*c* 1.0, DMSO); IR (nujol) 3124, 2919, 2860, 1635, 1639, 1457, 1374, 1281, 1195, 1121, 974, 728 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.87 (s, C**H**$_3$CO), 3.25 (s, OC**H**$_3$), 3.44–3.56 (m, C**H**$_2$OH), 3.97 (q, *J* = 5.7 Hz, C**H**$_2$$NH_3$Cl), 4.28 (d, *J* = 6.0 Hz, C**H**$_2$N), 4.36–4.50 (m, C**H**), 7.26 (d, *J* = 7.9 Hz, 2 Ar**H**), 7.43 (d, *J* = 7.9 Hz, 2 Ar**H**), 8.15 (br d, *J* = 7.8 Hz, N**H**C(O)CH_3), 8.38–8.55 (br m, N**H**$_3$Cl), 8.58 (br t, *J* = 6.0 Hz, CH_2N**H**); ^{13}C NMR

(DMSO-d_6) δ 22.5 (**C**H_3CO), 41.6, 41.8 (2 **C**H_2N), 52.6 (**C**HCH$_2$), 58.1 (O**C**H_3), 72.0 (**C**H_2OCH$_3$), 127.0, 128.7, 132.2, 139.6 (4 Ar**C**), 169.3, 169.7 (2 **C**(O)); HRMS (M+H$^+$)(ESI$^+$) 280.1661 [M + H$^+$] (calcd for $C_{14}H_{21}N_3O_3H^+$ 280.1661); Anal. Calcd. for $C_{14}H_{22}ClN_3O_3$•0.49 HCl: C, 50.38; H, 6.79; N, 12.59. Found: C, 50.15; H, 6.90; N, 12.29.

11. Preparation of (*R*)-*N*-(4'-(Methoxymethyl))benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-17).



Preparation of 4-(Methoxymethyl)benzonitrile (81).[1] A THF solution (250 mL) of 4-(hydroxymethyl)benzonitrile (**80**) (10.00 g, 75.0 mmol) was added dropwise at 0 °C to a NaH (60% in mineral oil suspension, 11.50 g, 300.0 mmol) suspension in THF (600 mL). The mixture was stirred (10 min) and MeI (11.7 mL, 187.5 mmol) was added dropwise. The mixture was stirred at room temperature (3 h) and then a saturated aqueous NH_4Cl solution (100 mL) was added. The reaction mixture was extrated with CH_2Cl_2 (3 x 250 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo. The residue was distilled in vacuo (125 °C, 5 torr) to obtain a colorless oil (10.50 g, 95%): R_f = 0.59 (hexanes/EtOAc 9/1); ^{1}H NMR ($CDCl_3$) δ 3.43 (s, OC**H$_3$**), 4.51 (s, C**H$_2$**O), 7.44 (d,

J = 8.3 Hz, 2 Ar**H**), 7.63 (d, *J* = 8.3 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 58.4 (**C**H_3O), 73.5 (**C**H_2OCH_3), 111.1 (**C**CN), 118.7 (**C**N), 127.6, 132.0, 143.8 (3 Ar**C**); HRMS (M– CH_3^+)(ESI$^+$) 132.0443 [M – CH_3^+] (calcd for $C_8H_6NO^+$ 132.0443).

Preparation of 4-(Methoxymethyl)benzylamine (82).[2] To a $LiAlH_4$ (7.36 g, 193.7 mmol) suspension in THF (400 mL) was added dropwise a THF (30 mL) solution of 4-(methoxymethyl)benzonitrile (**81**) (9.50 g, 64.6 mmol) at 0 °C. The mixture was stirred at room temperature (16 h) and then H_2O (6 mL) was added dropwise at 0 °C followed by an aqueous NaOH solution (3 mL, 15% w/w), and then H_2O (6 mL). The mixture was stirred at room temperature (2 h) and the precipitate was filtered, and the pad was washed with CH_2Cl_2. The filtrate was concentrated in vacuo to give 8.20 g of a colorless oil (84%): R_f = 0.00 (hexanes/EtOAc 9/1); ^{1}H NMR ($CDCl_3$) δ 1.41 (br s, N**H$_2$**), 3.88 (s, OC**H$_3$**), 3.86 (s, C**H$_2$**NH_2), 4.47 (s, C**H$_2$**O), 7.20–7.40 (br m, 4 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 46.2 (**C**H_2NH_2), 58.0 (**C**H_3O), 74.4 (**C**H_2OCH_3), 127.1, 128.0, 136.7, 142.8 (4 Ar**C**); HRMS (M+H^+)(ESI$^+$) 152.1073 [M + H^+] (calcd for $C_9H_{13}NOH^+$ 152.1075).

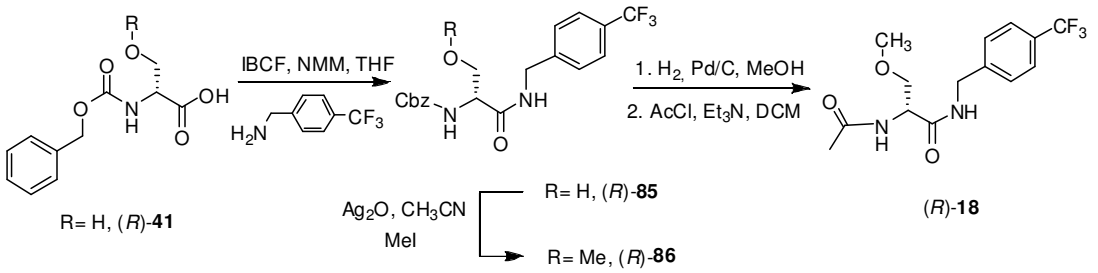
Preparation of (*R*)-*N*-(4'-(Methoxymethyl))benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-hydroxypropionamide ((*R*)-83). A THF solution (75 mL) of *(R)*-Cbz-serine (5.30 g, 22.0 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (2.9 mL, 26.4 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (3.5 mL, 26.4 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min. 4-Methoxymethylbenzylamine (4.00 g, 26.4 mmol) was added portionwise at -78 °C and the mixture was stirred at room temperature (2 h). The white solid was filtered and the organic layer was concentrated in vacuo. The residue was triturated with EtOAc resulting in a solid that was filtered and recrystallized with EtOAc to give (*R*)-*N*-(4'-(methoxymethyl))benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide as a white solid (7.20 g, 88%): R_f = 0.63 (EtOAc); mp 138–140 °C; $[\alpha]^{25.8}_D$ –34.0° (*c* 1.0, DMSO); IR (nujol) 3385, 3294, 3106, 2923,

2859, 1690, 1646, 1544, 1458, 1373, 1307, 1243, 1098, 1028, 919, 738, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.36 (s, OC**H**$_3$), 3.64 (dd, *J* = 5.1, 10.8 Hz C**H**H'OH), 3.88–4.06 (br d, CH**H'**OH), 4.19–4.29 (m, C**H**), 4.34–4.45 (m, C**H**$_2$OCH$_3$, NC**H**$_2$), 5.06 (s, C**H**$_2$O), 6.96 (d, *J* = 7.2 Hz, OC(O)N**H**), 7.02–7.14 (br s, N**H**), 7.19 (d, *J* = 7.8 Hz, 2 Ar**H**), 7.27 (d, *J* = 7.8 Hz, 2 Ar**H**), 7.30–7.38 (m, 5 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 43.2 (N**C**H$_2$), 55.5 (OCH$_2$**C**H), 58.1 (**C**H$_3$O), 62.7 (O**C**H$_2$CH), 67.3 (**C**H$_2$O), 74.3 (**C**H$_2$OCH$_3$), 127.6, 128.0, 128.1, 128.3, 128.5, 135.9, 137.0, 137.5 (8 Ar**C**), 156.7 (O**C**(O)N), 170.7 (C(O)); HRMS (M+H$^+$)(ESI$^+$) 373.1764 [M + H$^+$] (calcd for $C_{20}H_{24}N_2O_5H^+$ 373.1763); Anal. Calcd. for $C_{20}H_{24}N_2O_5$•0.25H_2O: C, 63.73; H, 6.55; N, 7.43. Found: C, 63.35; H, 6.43; N, 7.29.

Preparation of (*R*)-*N*-(4'-(Methoxymethyl))benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-methoxypropionamide ((*R*)-84). Ag_2O (12.40 g, 53.7 mmol) was added to a CH_3CN solution (100 mL) of (*R*)-*N*-(4'-(methoxymethyl))benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide (4.00 g, 10.7 mmol) and CH_3I (6.71 mL, 107.5 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature (2 d), filtered through a pad of Celite®, and the filtrate concentrated in vacuo to obtain 3.90 g of the desired compound as a white solid (94%): R_f = 0.79 (EtOAc); mp 107–108 °C; $[\alpha]^{24.6}_D$ –22.1° (*c* 1.0, $CHCl_3$); IR (nujol) 3285, 2958, 2732, 2681, 1688, 1645, 1545, 1458, 1376, 1305, 1240, 1112, 1048, 966, 815, 729, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.36, 3.38 (2 s, 2 OC**H**$_3$), 3.49 (dd, *J* = 6.6, 9.3 Hz, C**H**H'), 3.85 (dd, *J* = 3.3, 9.3 Hz, CH**H'**), 4.28–4.38 (br m, C**H**CH$_2$), 4.43 (s, C**H**$_2$OCH$_3$), 4.46 (d, *J* = 6.3 Hz, C**H**$_2$N), 5.11 (s, OC**H**$_2$), 5.64–5.72 (br m, OC(O)N**H**), 6.66–6.74 (br m, CH$_2$N**H**), 7.23 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.29 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.31–7.38 (m, 5 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 43.2 (N**C**H$_2$), 54.3 (OCH$_2$**C**H), 58.0 (CH$_2$O**C**H$_3$) 59.0 (O**C**H$_3$), 67.2 (Ph**C**H$_2$O), 72.0 (O**C**H$_2$CH), 74.3 (**C**H$_2$OCH$_3$), 127.5, 128.0, 128.1, 128.2, 128.5, 136.0, 137.2, 137.6 (8 Ar**C**), 156.1 (O**C**(O)), 169.8 (C(O)); HRMS (M+H$^+$)(ESI$^+$) 387.1920 [M + H$^+$] (calcd for $C_{21}H_{26}N_2O_5H^+$ 387.1920); Anal. Calcd. for $C_{21}H_{26}N_2O_5$: C, 65.27; H, 6.78; N, 7.25. Found: C, 65.27; H, 6.79; N, 7.38.

Preparation of (*R*)-*N*-(4'-(Methoxymethyl))benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-17). A MeOH solution (400 mL) of (*R*)-*N*-(4'-(methoxymethyl))benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (3.50 g, 9.1 mmol) was treated with H_2 (1 atm) in presence of 10% Pd/C (350 mg) at room temperature (16 h). The mixture was carefully filtered through a bed of Celite® and the filtrate was evaporated in vacuo to obtain a colorless oil. The oil was dissolved in CH_2Cl_2 (150 mL) and then triethylamine (1.52 mL, 10.9 mmol) and acetyl chloride (772 μL, 10.9 mmol) were carefully added at 0 °C and the resulting solution was stirred at room temperature (2 h). An aqueous 10% citric acid solution (150 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, washed with an aqueous saturated $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was triturated with EtOAc to give (*R*)-*N*-(4'-(methoxymethyl))benzyl 2-acetamido-3-methoxypropionamide as a white solid (1.50 g, 56%): R_f = 0.35 (EtOAc); mp 119–120 °C; $[\alpha]^{25}_D$ –25.4° (*c* 0.5 , $CHCl_3$); IR (nujol) 3266, 3069, 2935, 2863, 1635, 1550, 1458, 1457, 1382, 1282, 1226, 1194, 1125, 948, 836, 792, 726 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.03 (s, C**H**$_3$CO), 3.37, 3.38 (2 s, 2 OC**H**$_3$), 3.43 (dd, *J* = 7.5, 9.1 Hz, C**H**H'), 3.80 (dd, *J* = 4.2, 9.1 Hz, CH**H'**), 4.41–4.49 (m, C**H**$_2$OCH$_3$, C**H**$_2$N), 4.51–4.58 (m, C**H**), 6.42–6.52 (br d, N**H**C(O)CH$_3$), 6.75–6.84 (br t, CH$_2$N**H**), 7.24 (d, *J* = 7.9 Hz, 2 Ar**H**), 7.30 (d, *J* = 7.9 Hz, 2 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-(methoxymethyl))benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.2 (**C**H$_3$CO), 43.3 (**C**H$_2$N), 52.5 (**C**HCH$_2$), 58.1 (O**C**H$_3$), 59.1 (O**C**H$_3$), 71.8 (**C**H$_2$OCH$_3$), 74.3 (**C**H$_2$OMe), 127.5, 128.1, 137.3, 137.5 (4 Ar**C**), 170.0, 170.3 (2 **C**(O)); HRMS (M+H$^+$)(ESI$^+$) 295.1658 [M + H$^+$] (calcd for $C_{15}H_{22}N_2O_4H^+$ 295.1658); Anal. Calcd. for $C_{15}H_{22}N_2O_4$: C, 61.21; H, 7.45; N, 9.52. Found: C, 60.88; H, 7.45; N, 9.35.

12. Preparation of (*R*)-*N*-(4'-Trifluoromethyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-18).



Preparation of (*R*)-*N*-(4'-Trifluoromethyl)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-hydroxypropionamide ((*R*)-85). A THF solution (200 mL) of (*R*)-Cbz-serine (6.00 g, 25.1 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (3.3 mL, 30.1 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (3.9 mL, 30.1 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min and then 4-trifluoromethybenzylamine (4.3 mL, 30.1 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and then the white solid filtered and the organic layer concentrated in vacuo. The residue was recrystallized with EtOAc to obtain (*R*)-*N*-(4'-trifluoromethyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide as a white solid (1.50 g). The solid obtained during the first filtration was washed with H_2O and $CHCl_3$. The remaining solid was recrystallized with EtOAc to obtain (*R*)-*N*-(4'-trifluoromethyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide as a white solid (4.80 g, m_T = 6.30 g, 63%): R_f = 0.17 (hexanes/EtOAc 5/5); mp 160-161 °C; $[\alpha]^{25.9}_D$ –12.0° (*c* 0.5, DMSO); IR (nujol) 3119, 2945, 2862, 1689, 1645, 1565, 1530, 1458, 1375, 1334, 1243, 1165, 1113, 1024, 964, 738 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.57–3.66 (m, C**H**H', CH**H'**), 4.04–4.12 (br m, C**H**), 4.37 (d, *J* = 6.0 Hz, C$\mathbf{H_2}$N), 4.92 (t, *J* = 5.7 Hz, O**H**), 5.05 (s, C$\mathbf{H_2}$O), 7.27–7.38 (m, N**H**, 5 Ar**H**), 7.47 (d, *J* = 8.1 Hz, 2 Ar**H**), 7.65 (d, *J* = 8.1 Hz, 2 Ar**H**), 8.55 (t, *J* = 5.7 Hz, $CH_2N\mathbf{H}$); ^{13}C NMR (DMSO-d_6) δ 41.7 (N**C**H_2), 57.3 (OCH_2**C**H), 61.6 (O**C**H_2CH),

65.5 (Ph**C**H_2O), 124.3 (q, J = 269.8 Hz, **C**F_3), 124.9 (br q, J = 3.4 Hz, **C**CF_3), 127.5, 127.7, 128.2, 136.9, 144.3 (5 Ar**C**), 155.9 (N**C**(O)O), 170.4 (**C**(O)), 2 signals were not detected and are believed to overlap with nearby peaks; Anal. Calcd. for $C_{19}H_{19}F_3N_2O_4$•0.08$C_4H_8O_2$: C, 57.52; H, 4.91; F, 14.11; N, 6.93. Found: C, 57.14; H, 4.82; F, 13.71; N, 6.99.

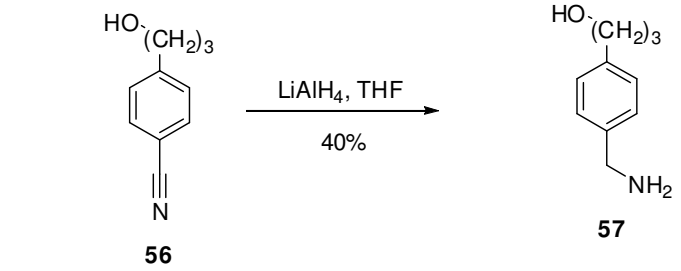
Preparation of (*R*)-*N*-(4'-Trifluoromethyl)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-methoxypropionamide ((*R*)-86). Ag_2O (12.95 g, 55.5 mmol) was added to a CH_3CN solution (400 mL) of (*R*)-*N*-(4'-trifluoromethyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide (4.40 g, 11.1 mmol) and CH_3I (6.9 mL, 111.1 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature in the dark (4 d), filtered through a pad of Celite®, and the filtrate concentrated in vacuo to obtain a white solid. The solid was purified by flash column chromatography on silica gel with EtOAc/hexanes (50/50) as the eluant to obtain (*R*)-*N*-(4'-trifluoromethyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide as a white solid (1.30 g, 29%): R_f = 0.37 (1/1 EtOAc/hexanes); mp 120–124 °C; $[\alpha]^{24.6}_D$ +16.0° (*c* 0.5, DMSO); IR (nujol) 3297, 2957, 2728, 1687, 1650, 1537, 1457, 1373, 1329, 1240, 1164, 1116, 1063, 958, 845, 733 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.38 (s, OC**H$_3$**), 3.51 (dd, J = 6.3, 9.0 Hz, C**H**H'), 3.88 (dd, J = 3.6, 9.0 Hz, CH**H'**), 4.31–4.42 (br m, C**H**CH_2), 4.53 (d, J = 6.3 Hz, C**H$_2$**N), 5.13 (s, OC**H$_2$**), 5.61–5.70 (br m, OC(O)N**H**), 6.73–6.85 (br m, CH_2N**H**), 7.29–7.40 (s, 7 Ar**H**), 7.57 (d, J = 8.1 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 42.9 (N**C**H_2), 54.4 (OCH_2**C**H), 59.1 (O**C**H_3), 67.3 (Ph**C**H_2O), 71.9 (O**C**H_2CH), 124.0 (q, J = 270.4 Hz, **C**F_3), 125.6 (q, J = 4.0 Hz, **C$_3$**), 127.5, 128.1, 128.3, 128.6 (4 Ar**C**), 129.7 (q, J = 31.9 Hz, **C$_4$**), 135.9, 142.0 (2 Ar**C**), 156.1 (N**C**(O)O), 170.2 (**C**(O)); HRMS (M+H$^+$)(ESI$^+$) 411.1538 [M + H$^+$] (calcd for $C_{20}H_{21}F_3N_2O_4H^+$ 411.1531).

Preparation of (*R*)-*N*-(4'-Trifluoromethyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-18). An EtOH solution (250 mL) of (*R*)-*N*-(4'-trifluoromethyl)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide

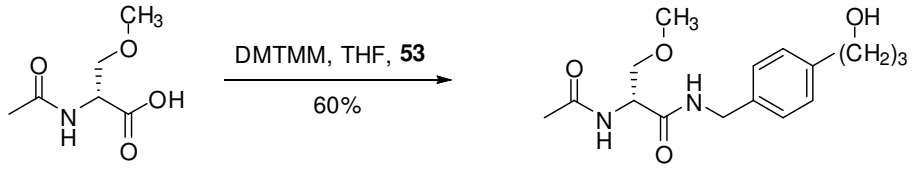
(1.20 g, 3.0 mmol) was treated with H_2 (1 atm) in presence of 10% Pd/C (120 mg) at room temperature (16 h). The mixture was carefully filtered through a bed of Celite®. The pad was washed with MeOH and CH_2Cl_2, and the washings were collected and evaporated in vacuo to obtain a yellow solid: ^{1}H NMR ($CDCl_3$) δ 1.62–1.67 (br d, N**H$_2$**), 3.39 (s, OC**H$_3$**), 3.58–3.72 (m, C**H$_2$**, C**H**), 4.52 (d, *J* = 6.0 Hz, NC**H$_2$**), 7.39 (d, *J* = 8.2 Hz, 2 Ar**H**), 7.58 (d, *J* = 8.2 Hz, 2 Ar**H**), 7.88–7.89 (br s, N**H**C(O)).

The residue was dissolved in CH_2Cl_2 (40 mL) and then triethylamine (0.5 mL, 3.5 mmol) and acetyl chloride (250 μL, 3.5 mmol) were carefully added at 0 °C and the resulting solution was stirred at room temperature (2 h). An aqueous 10% citric acid solution (100 mL) was added and the organic layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, washed with a saturated aqueous $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), and concentrated in vacuo. After recrystallization of the residue with EtOAc (*R*)-*N*-(4'-trifluoromethyl)benzyl 2-acetamido-3-methoxypropionamide was obtained as a white solid (495 mg, 55%): R_f = 0.45 (EtOAc); mp 160–161 °C; $[\alpha]^{26.7}_D$ +2.6° (*c* 0.5 , DMSO); IR (nujol) 3393, 3278, 3145, 2923, 2834, 2723, 2673, 1638, 1552, 1456, 1374, 1157, 1111, 965, 840, 726 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.05 (s, C**H$_3$**CO), 3.40 (s, OC**H$_3$**), 3.45 (dd, *J* = 7.8, 9.3 Hz, C**H**H'), 3.83 (dd, *J* = 4.2, 9.3 Hz, CH**H'**), 4.50–4.61 (m, C**H$_2$**N, C**H**), 6.37–6.44 (br d, N**H**C(O)CH_3), 6.85–6.94 (br t, CH_2N**H**), 7.38 (d, *J* = 8.2 Hz, 2 Ar**H**), 7.58 (d, *J* = 8.2 Hz, 2 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-trifluoromethyl)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.1 (**C**H_3CO), 42.9 (**C**H_2N), 52.5 (**C**HCH_2), 59.1 (O**C**H_3), 71.6 (**C**H_2OCH_3), 124.0 (q, *J* = 270.4 Hz, **C**F_3), 125.6 (q, *J* = 3.4 Hz, **C$_3$**), 127.5 (**C$_2$**), 129.7 (q, *J* = 31.9 Hz, **C$_4$**), 142.0 (**C$_1$**), 170.3, 170.5 (2 **C**(O)); HRMS (M+H$^+$)(ESI$^+$) 319.1270 [M + H$^+$] (calcd for $C_{14}H_{17}F_3N_2O_3H^+$ 307.1269); Anal. Calcd. for $C_{14}H_{17}F_3N_2O_3$: C, 52.83; H, 5.38; F, 17.91; N, 8.80. Found: C, 52.84; H, 5.30; F, 17.67; N, 8.78.

13. Preparation of (*R*)-*N*-(4'-(3-hydroxypropyl))benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-19).



56 **57**



(*R*)-**58** (*R*)-**19**

Preparation of 4-(3-Hydroxypropyl)benzylamine (57). To a $LiAlH_4$ (1.41 g, 37.2 mmol) suspension in THF (120 mL) was added dropwise a THF (10 mL) solution of 4-(3-hydroxypropyl)benzonitrile (**56**)[3] (2.00 g, 12.4 mmol) at 0 °C. The mixture was stirred at room temperature (16 h) and then H_2O (1.2 mL) was added dropwise at 0 °C followed by an aqueous NaOH solution (0.65 mL, 15% w/w), and then H_2O (1.2 mL). The mixture was stirred at room temperature (2 h) and the precipitate was filtered, and the pad was washed with CH_2Cl_2. The filtrate was concentrated in vacuo to give 610 mg of a colorless oil (84%): R_f = 0.00 (hexanes/EtOAc 5/5); ^{1}H NMR (DMSO-d_6) δ 1.62–1.73 (m, N**H$_2$**, CH_2C**H$_2$**CH_2), 2.56 (t, J = 7.8 Hz, C**H$_2$**Ar), 3.36–3.44 (br m, HOC**H$_2$**), 3.65 (s, C**H$_2$**NH_2), 4.41–4.49 (br m, **H**O), 7.10 (d, J = 8.1 Hz, 2 Ar**H**), 7.21 (d, J = 8.1 Hz, 2 Ar**H**); HRMS (M+H$^+$)(ESI$^+$) 166.1632 [M + H$^+$] (calcd for $C_{10}H_{15}NOH^+$ 166.1231); Anal. Calcd. for $C_{10}H_{15}NO$•0.12THF: C, 72.38; H, 9.25; N, 8.04. Found: C, 72.78; H, 9.25; N, 7.65.

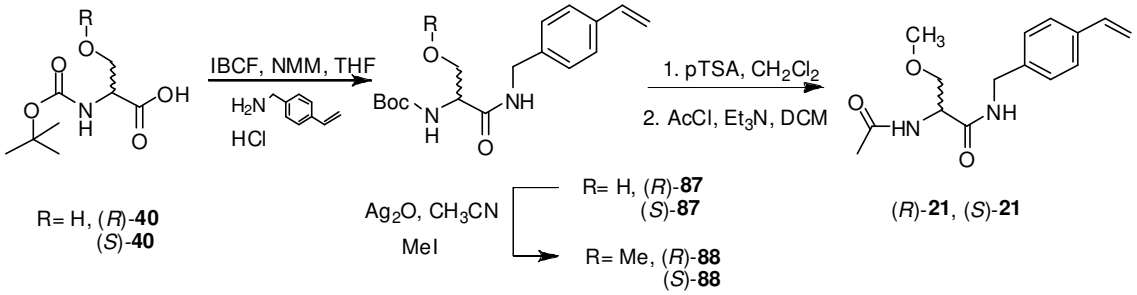
Preparation of (*R*)-*N*-(4'-(3-Hydroxypropyl))benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-19). 4-(3-Hydroxypropyl)benzylamine (600 mg, 3.6 mmol) was added to a THF (33 mL) solution of the (*R*)-2-acetamido-3-methoxypropionoic acid ((*R*)-**58**)[4] (532 mg, 3.3 mmol) and the mixture was stirred at room temperature (5 min). DMTMM[5] (1.10 mg, 4.0 mmol) was added, and the reaction was stirred at room temperature (16 h). The white precipitate was filtered and the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc to EtOAc/acetone (5/5) as the eluant to obtain after recrystallisation with EtOAc a white solid (560 mg, 55%): R_f = 0.26 (8/2 EtOAc/acetone); mp 118 °C; $[\alpha]^{26.9}_D$ –25.0° (*c* 0.5, $CHCl_3$); IR (nujol) 3339, 3279, 2951, 2862, 1630, 1552, 1456, 1376, 1304, 1195, 1140, 1097, 1038, 909, 820, 724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34–1.45 (br m, O**H**), 1.83–1.93 (br m, $CH_2C\mathbf{H_2}CH_2$), 2.03 (s, $C\mathbf{H_3}CO$), 2.70 (t, *J* = 7.8 Hz, $C\mathbf{H_2}Ar$), 3.38 (s, $OC\mathbf{H_3}$), 3.43 (dd, *J* = 7.5, 9.0 Hz, C**H**H'), 3.63–3.72 (br m, $C\mathbf{H_2}OH$), 3.80 (dd, *J* = 3.9, 9.0 Hz, CH**H'**), 4.44 (d, *J* = 6.0 Hz, $C\mathbf{H_2}N$), 6.41–4.50 (br d, $CH_3C(O)N\mathbf{H}$), 6.69–6.79 (m, N**H**), 7.12–7.23 (m, 4 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-(3-hydroxypropyl))benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.0 ($C(O)\mathbf{C}H_3$), 31.7, 34.2 (2 $\mathbf{C}H_2$), 43.2 ($N\mathbf{C}H_2$), 52.6 ($\mathbf{C}HCH_2$), 59.0 ($O\mathbf{C}H_3$), 61.9 ($\mathbf{C}H_2OH$), 72.1 ($\mathbf{C}H_2O$), 127.5, 128.7, 135.3, 141.2 (4 Ar**C**), 170.1, 170.6 (2 **C**(O)); HRMS ($M+H^+$)(ESI^+) 309.1815 [M + H^+] (calcd for $C_{16}H_{24}N_2O_4H^+$ 319.1814); Anal. Calcd. for $C_{16}H_{24}N_2O_4$: C , 62.32; H, 7.84; N, 9.08. Found: C, 62.33; H, 7.69; N, 9.12.

14. Preparation of (*R*)-*N*-(4'-(3-Methoxypropyl))benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-20).

Preparation of (*R*)-*N*-(4'-(3-Methoxypropyl))benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-20). An EtOH solution (30 mL) of (*R*)-*N*-(4'-(3-methoxyprop-1-ynyl))benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**27**) (1.00 g, 3.1 mmol) was treated with H_2 (1 atm) in the presence of 10% PtO_2 (50 mg) at

room temperature (16 h). The mixture was carefully filtered through a bed of Celite®. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography on silica gel with EtOAc as the eluant to obtain (*R*)-*N*-(4'-(3-methoxypropyl))benzyl 2-acetamido-3-methoxypropionamide (510 mg, 51%) as a white solid: R_f = 0.27 (EtOAc); mp 105–107 °C; $[\alpha]^{25}_D$ +3.0° (*c* 0.5 , DMSO); IR (nujol) 3283, 3085, 1638, 1550, 1457, 1379, 1299, 1122, 979, 725, 605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.81–1.92 (m, C**H**$_2$), 2.03 (s, C**H**$_3$CO), 2.67 (t, *J* = 7.8 Hz, C**H**$_2$Ph), 3.33–3.46 (m, C**H**H'O, C**H**$_2$O, 2 OC**H**$_3$), 3.80 (dd, *J* = 4.0, 9.1 Hz, CH**H'**O), 4.44 (d, *J* = 5.7 Hz, C**H**$_2$N), 4.50–4.57 (m, C**H**), 6.45 (br d, *J* = 6.6 Hz, N**H**C(O)CH_3), 6.70–6.75 (br t, CH_2N**H**), 7.15–7.20 (m, 4 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-(3-methoxypropyl))benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.2 (**C**H_3CO), 31.2, 31.9 (2 **C**H_2), 43.3 (**C**H_2N), 52.4 (**C**HCH_2), 58.6, 59.1 (2 O**C**H_3), 71.7, 71.9 (2 **C**H_2OMe), 127.5, 128.8, 135.3, 141.4 (4 Ar**C**), 169.9, 170.2 (2 **C**(O)); HRMS (M+Na^+)(ESI^+) 345.1784 [M + Na^+] (calcd for $C_{17}H_{26}N_2O_4Na^+$ 345.1790); Anal. Calcd. for $C_{17}H_{26}N_2O_4$: C , 63.33; H, 8.13; N, 8.69. Found: C, 63.12; H, 8.13; N, 8.64.

15. Preparation of (*R*)- and (*S*)-*N*-(4'-Vinyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)- and (*S*)-21).



Preparation of (*R*)-*N*-(4'-Vinyl)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-87). A THF solution (140 mL) of *(R)-tert*-Boc-serine (1.00 g, 4.87 mmol) was stirred and cooled at -78 °C under Ar and then 4-

methylmorpholine (NMM) (607 μL, 5.85 mmol) was added dropwise. The reaction was stirred at this temperature (2 min) and then isobutylchloroformate (IBCF) (765 μL, 5.85 mmol) was added dropwise leading to the precipitation of a white solid. The reaction was allowed to proceed for additional 2 min. A heterogenous THF (10 mL) mixture of 4-aminomethylstyrene hydrochloride (911 mg, 5.40 mmol) and NMM (593 μL, 5.40 mmol) was added portionwise at –78 °C. The mixture was allowed to stir at room temperature (2 h) and the white solid was filtered and the organic layer was concentrated in vacuo. The residue was purified by flash chromatography on silica gel with EtOAc/hexanes (50/50 to 100/0) as the eluant to obtain (*R*)-*N*-(4'-vinyl)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide (950 mg, 60%) as a white solid: R_f = 0.43 (7/3 EtOAc/hexanes); mp 109 °C; $[\alpha]^{24}_D$ +1.7° (*c* 2.8, CH_2Cl_2); IR (nujol) 3317, 1657, 1532, 1458, 1376, 1305, 1242, 1170, 1008, 1005, 900, 850, 631 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, ($C\mathbf{H_3}$)$_3$C), 3.65–3.70 (m, HOC**H**H'), 4.03–4.09 (br m, HOCH**H'**), 4.20 (br s, C**H**CH_2), 4.36–4.47 (m, C$\mathbf{H_2}$N), 5.24 (d, J_{cis} = 10.5 Hz, CH=C**H**H'), 5.71 (d, J_{trans} = 17.4 Hz, CH=CH**H'**), 5.72 (br s, 1H, *tert*-BocN**H**), 6.68 (dd, J_{cis} = 10.5 Hz, J_{trans} = 17.4 Hz, C**H**=CH_2), 7.19 (d, *J* = 8.2 Hz, 2 Ar**H**), 7.34 (d, J = 8.2 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 28.3 (($\mathbf{C}H_3$)$_3$C), 43.2 (N$\mathbf{C}H_2$), 55.1 ($OCH_2\mathbf{C}H$), 62.8 (O$\mathbf{C}H_2$CH), 80.6 ($(CH_3)_3\mathbf{C}$), 114.0 (CH=$\mathbf{C}H_2$), 126.5, 127.7, 136.3, 136.9, 137.3 (4 Ar**C**, **C**H=CH_2), 156.3 (N**C**(O)O), 171.3 (**C**(O)); HRMS (M+Na^+)(ESI^+) 343.1624 [M + Na^+] (calcd for $C_{17}H_{24}N_2O_4Na^+$ 343.1628). Anal. Calcd. For $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74. Found: C, 63.45; H, 7.60; N, 8.70.

Preparation of (*S*)-*N*-(4'-Vinyl)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*S*)-87). Employing the same procedure for (*R*)-*N*-(4'-vinyl)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide and using (*S*) *tert*-Boc-serine (1.00 g, 4.87 mmol), NMM (1.24 mL, 11.25 mmol), IBCF (765 μL, 5.85 mmol), and 4-aminomethylstyrene hydrochloride (911 mg, 5.40 mmol) in THF (150 mL) gave 700 mg (45%) of a white solid: R_f = 0.43 (7/3 EtOAc/hexanes); mp 109 °C; $[\alpha]^{24}_D$ –1.7° (*c* 2.8, CH_2Cl_2); IR (nujol) 3316, 1656,

1530, 1458, 1375, 1305, 1241, 1167, 1004 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, (CH_3)$_3$C), 3.46–3.49 (br m, CHH'OH), 3.67–3.70 (br m, CHH'OH), 4.09 (br d, *J* = 11.4 Hz, OH or CHCH$_2$), 4.17–4.21 (br m, OH or CHCH$_2$), 4.35–4.45 (m, CH$_2$N), 5.24 (d, J_{cis} = 10.5 Hz, CH=CHH'), 5.67 (br s, *tert*-BocNH), 5.71 (d, J_{trans} = 17.4 Hz, CH=CHH'), 6.68 (dd, J_{cis} = 10.5 Hz, J_{trans} = 17.4 Hz, CH=CH$_2$), 7.15 (br s, CH$_2$NH), 7.19 (d, *J* = 8.2 Hz, 2 ArH), 7.34 (d, J = 8.2 Hz, 2 ArH); ^{13}C NMR ($CDCl_3$) δ 28.3 ((CH$_3$)$_3$C), 43.1 (NCH$_2$), 55.0 (OCH$_2$CH), 62.9 (OCH$_2$CH), 80.7 ((CH$_3$)$_3$C), 114.0 (CH=CH$_2$), 126.5, 127.7, 136.4, 136.9, 137.3 (4 ArC, CH=CH$_2$), 156.3 (NC(O)O), 171.4 (C(O)); HRMS (M+Na$^+$)(ESI$^+$) 343.1624 [M + Na$^+$] (calcd for $C_{17}H_{24}N_2O_4Na^+$ 343.1629); Anal. Calcd. For $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74. Found: C, 63.55; H, 7.63; N, 8.57.

Preparation of (*R*)-*N*-(4'-Vinyl)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-88). Ag_2O (3.15 g, 13.6 mmol) was added to a CH_3CN solution (40 mL) of (*R*)-*N*-(4'-vinyl)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide (0.87 g, 2.7 mmol) and then CH_3I (1.7 mL, 27.2 mmol) was added at room temperature under Ar. The reaction mixture was stirred at room temperature (3 d), filtered through a pad of Celite®, and the filtrate concentrated in vacuo. The residue was purified by column chromatography (SiO_2; 2/3 EtOAc/hexanes) to obtain 700 mg (77%) of an oil that crystallized after a few days: R_f = 0.67 (1/1 EtOAc/hexanes); mp 67 °C; $[\alpha]^{22}_D$ +11.2° (*c* 1.0, MeOH); IR (nujol) 3322, 1658, 1525, 1458, 1375, 1302, 1246, 1164, 1047, 955, 900, 719 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (s, (CH$_3$)$_3$C), 3.29 (s, OCH$_3$), 3.45 (dd, *J* = 6.0, 9.3 Hz, CHH'), 3.75 (dd, *J* = 3.9, 9.3 Hz, CHH'), 4.25–4.31 (br m, CHCH$_2$), 4.32–4.45 (m, CH$_2$N), 5.17 (d, J_{cis} = 10.8 Hz, CH=CHH'), 5.53 (br d, *J* = 5.7 Hz, *tert*-BocNH), 5.68 (d, J_{trans} = 17.7 Hz, CH=CHH'), 6.64 (dd, J_{cis} = 10.8 Hz, J_{trans} = 17.7 Hz, CH=CH$_2$), 6.95 (br t, *J* = 5.1 Hz, CH$_2$NH), 7.16 (d, *J* = 8.1 Hz, 2 ArH), 7.30 (d, *J* = 8.1 Hz, 2 ArH); ^{13}C NMR ($CDCl_3$) δ 28.1 ((CH$_3$)$_3$C), 42.9 (NCH$_2$), 53.9 (OCH$_2$CH), 58.8 (OCH$_3$) 72.0 (OCH$_2$CH), 80.0 ((CH$_3$)$_3$C), 113.6 (CH=CH$_2$), 126.2, 127.4, 136.2, 136.6, 137.5 (4 ArC, CH=CH$_2$), 155.4 (NC(O)O), 170.2

(**C**(O)). Anal. Calcd. For $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.51; H, 7.88; N, 8.33.

Preparation of (*S*)-*N*-(4'-Vinyl)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxypropionamide ((*S*)-88). Employing the same procedure for (*R*)-*N*-(4'-vinyl)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide and using (*S)-N*-(4'-vinyl)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide (2.50 g, 7.8 mmol), Ag_2O (9.00 g, 39.1 mmol), and MeI (4.9 mL, 78.0 mmol) gave 2.05 g (77%) of (*S*)-*N*-(4'-vinyl)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide after silica gel column chromatography: R_f = 0.67 (1/1 EtOAc/hexanes); mp 67 °C; $[\alpha]^{22}_D$ –11.0° (*c* 1.0, MeOH); IR (nujol) 3349, 2727, 1659, 1525, 1458, 1374, 1302, 1246, 1164, 1115, 1048, 722 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, (C**H**$_3$)$_3$C), 3.34 (s, OC**H**$_3$), 3.50 (dd, *J* = 6.0, 9.1 Hz, C**H**H'), 3.79 (dd, *J* = 3.9, 9.1 Hz, CH**H'**), 4.24–4.36 (br m, C**H**CH_2), 4.37–4.48 (m, C**H**$_2$N), 5.22 (d, J_{cis} = 10.7 Hz, CH=C**H**H'), 5.50–5.55 (br m, *tert*-BocN**H**), 5.71 (d, J_{trans} = 17.7 Hz, CH=CH**H'**), 6.68 (dd, J_{cis} = 10.7 Hz, J_{trans} = 17.7 Hz, C**H**=CH_2), 6.91–6.98 (br m, CH_2N**H**), 7.19 (d, *J* = 8.1 Hz, 2 Ar**H**), 7.34 (d, *J* = 8.1 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 28.1 ((**C**H_3)$_3$C), 42.9 (N**C**H_2), 54.0 (OCH_2**C**H), 58.9 (O**C**H_3), 72.0 (O**C**H_2CH), 80.1 ((CH_3)$_3$**C**), 113.7 (CH=**C**H_2), 126.3, 127.5, 136.2, 136.6, 137.5 (4 Ar**C**, **C**H=CH_2), 155.4 (N**C**(O)O), 170.2 (**C**(O)); HRMS (M+Na^+)(ESI^+) 357.1784 [M + Na^+] (calcd for $C_{18}H_{26}N_2O_4Na^+$ 357.1790); Anal. Calcd. For $C_{18}H_{26}N_2O_4$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.73; H, 7.98; N, 8.25.

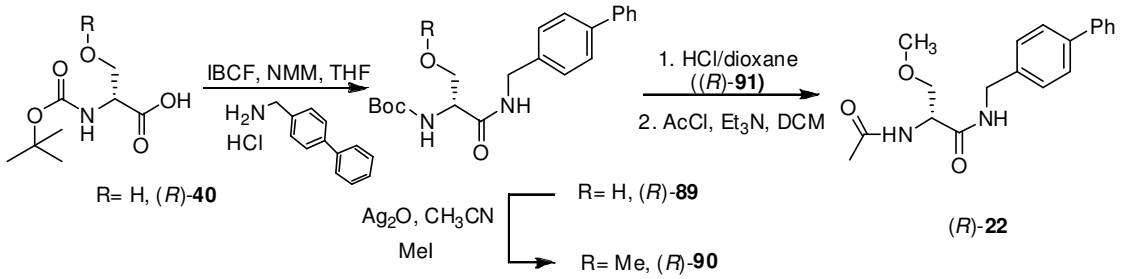
Preparation of (*R*)-*N*-(4'-Vinyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-21). pTSA (769 mg, 4.04 mmol) was added to a CH_2Cl_2 (6 mL) solution of (*R*)-*N*-(4'-vinyl)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide (900 mg, 2.7 mmol). The reaction was stirred at room temperature (24 h). Et_3N (2.3 mL, 16.2 mmol) follow by AcCl (574 μL, 8.1 mmol) were added at 0 °C. The solution was stirred at room temperature (30 min). Aqueous 10% citric acid was added and then the organic layer was separated. The aqueous layer was washed with CH_2Cl_2 (2 x 30 mL). The organic layers were

combined, washed with aqueous saturated $NaHCO_3$ and H_2O, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (SiO_2; EtOAc) to obtain 700 mg (77%) of white solid. R_f = 0.49 (5/5 EtOAc/acetone); mp = 148–149 °C; $[\alpha]^{26}_D$ = +3.5° (*c* 1.0, DMSO); IR (nujol) 3281, 3093, 1638, 1552, 1456, 1381, 1298, 1246, 1125, 1043, 986, 917, 825, 722, 604 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.03 (s, C**H**$_3$CO), 3.38 (s, OC**H**$_3$), 3.43 (dd, *J* = 7.2, 9.0, Hz, C**H**H'), 3.80 (dd, *J* = 4.2, 9.0, Hz, CH**H'**), 4.43–4.52 (m, C**H**$_2$N), 4.53–4.58 (m, NC(**H**)CO), 5.24 (d, J_{cis} = 10.8 Hz, CH=C**H**H'), 5.75 (d, J_{trans} = 17.7 Hz, CH=CH**H**'), 6.46 (br d, *J* = 6.6 Hz, N**H**C(O)CH_3), 6.70 (dd, J_{cis} = 10.8 Hz, J_{trans} = 17.7 Hz, C**H**=CH_2), 6.75–6.82 (br m, CH_2N**H**), 7.24 (d, *J* = 8.1 Hz, 2 Ar**H**), 7.35 (d, *J* = 8.1 Hz, 2 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-vinyl)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.3 (**C**H_3CO), 43.4 (**C**H_2N), 52.6 (**C**HCH_2), 59.2 (O**C**H_3), 72.0 (**C**H_2OCH_3), 114.1 (CH=**C**H_2), 126.7, 127.8, 136.6, 137.0, 137.6 (4 Ar**C**, **C**H=CH_2), 170.2, 170.6 (2 **C**(O)). HRMS (M+K^+)(ESI$^+$) 315.1115 [M + K^+] (calcd for $C_{15}H_{20}N_2O_3K^+$ 315.1111); Anal. Calcd. for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14. Found: C, 65.17; H, 7.33; N, 10.02.

Preparation of (*S*)-*N*-(4'-Vinyl)benzyl 2-Acetamido-3-methoxypropionamide ((*S*)-21). Employing the same procedure for (*R*)-*N*-(4'-vinyl)benzyl 2-acetamido-3-methoxypropionamide and using (*S*)-*N*-(4'-vinyl)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide (900 mg, 2.7 mmol), Et_3N (2.3 mL, 16.2 mmol) and AcCl (574 μL, 8.1 mmol) gave 690 mg (76%) of (*S*)-*N*-(4'-vinyl)benzyl 2-acetamido-3-methoxypropionamide after silica gel column chromatography: R_f = 0.45 (1/9 MeOH/EtOAc); mp 140–142 °C; $[\alpha]^{26}_D$ = –3.1° (*c* 1.0, DMSO); IR (nujol) 3284, 3087, 1640, 1548, 1457, 1378, 1298, 1244, 1198, 1127, 1046, 985, 912, 826, 721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (s, C**H**$_3$CO), 3.38 (s, OC**H**$_3$), 3.44 (dd, *J* = 7.5, 9.0, Hz, C**H**H'), 3.80 (dd, *J* = 4.2, 9.0, Hz, CH**H'**), 4.39–4.48 (m, C**H**$_2$N), 4.53–4.59 (m, NC(**H**)CO), 5.24 (d, J_{cis} = 11.1 Hz, CH=C**H**H'), 5.75 (d, J_{trans} = 17.4 Hz, CH=CH**H**'), 6.48 (br d, *J* = 6.6 Hz,

N**H**C(O)CH_3), 6.70 (dd, J_{cis} = 11.1 Hz, J_{trans} = 17.4 Hz, C**H**=CH_2), 6.82–6.85 (br m, CH_2N**H**), 7.22 (d, J = 8.1 Hz, 2 Ar**H**), 7.34 (d, J = 8.1 Hz, 2 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*S*)-*N*-(4'-vinyl)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.4 (**C**H_3CO), 43.5 (**C**H_2N), 52.6 (**C**HCH_2), 59.3 (O**C**H_3), 71.9 (**C**H_2OCH_3), 114.2 (CH=**C**H_2), 126.7, 127.8, 136.5, 137.1, 137.6 (4 Ar**C**, **C**H=CH_2), 170.2, 170.5 (2 **C**(O)); HRMS (M+K^+)(ESI$^+$) [M + K^+] 315.1114 (calcd for $C_{15}H_{20}N_2O_3K^+$ 315.1111); Anal. Calcd. for $C_{15}H_{20}N_2O_3$•0.10H_2O: C, 64.78; H, 7.32; N, 10.07. Found: C, 64.83; H, 7.31; N, 10.00.

16. Preparation of (*R*)-*N*-(Biphenyl-4-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-22).



Preparation of (*R*)-*N*-(Biphenyl-4-yl)methyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-89). A THF solution (300 mL) of (*R*)-*t*-Boc-serine (4.66 g, 22.8 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (3.0 mL, 27.3 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (3.6 mL, 27.3 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min before adding 4-phenylbenzylamine (5.00 g, 27.3 mmol) portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and then the white solid was filtered and the organic layer concentrated in vacuo. The residue was recrystallized with EtOAc to obtain (*R*)-*N*-(biphenyl-4-yl)methyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-

hydroxypropionamide as white needles (4.30 g, 51%): R_f = 0.20 (hexanes/EtOAc 5/5); mp 132–134 °C; $[\alpha]^{25.9}_D$ +14.6° (*c* 1.0, $CHCl_3$); IR (nujol) 3312, 2960, 2912, 2859, 1658, 1535, 1458, 1378, 1305, 1242, 1171, 1109, 1007, 846, 696 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, ($C\mathbf{H_3}$)$_3$C), 3.57–3.75 (m, C**H**H', CH**H'**), 4.04–4.25 (br m, O**H**, C**H**), 4.40–4.59 (m, C$\mathbf{H_2}$N), 5.62–5.78 (br m, N**H**), 7.28–7.45 (m, 5 Ar**H**), 7.53 (m, 4 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 28.2 (($\mathbf{C}H_3$)$_3$C), 43.1 (N$\mathbf{C}H_2$), 54.9 (OCH$_2$**C**H), 62.8 (O$\mathbf{C}H_2$CH), 80.6 ((CH$_3$)$_3$**C**), 127.0, 127.3, 127.4, 127.9, 128.8, 136.7, 140.5, 140.7 (8 Ar**C**), 156.3 (N**C**(O)O), 171.4 (**C**(O)), MS (M+H$^+$)(ESI$^+$) 371.1 [M + H$^+$] (calcd for $C_{21}H_{26}N_2O_4H^+$ 371.2); Anal. Calcd. for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.07; N, 7.56. Found: C, 68.09; H, 7.14; N, 7.48.

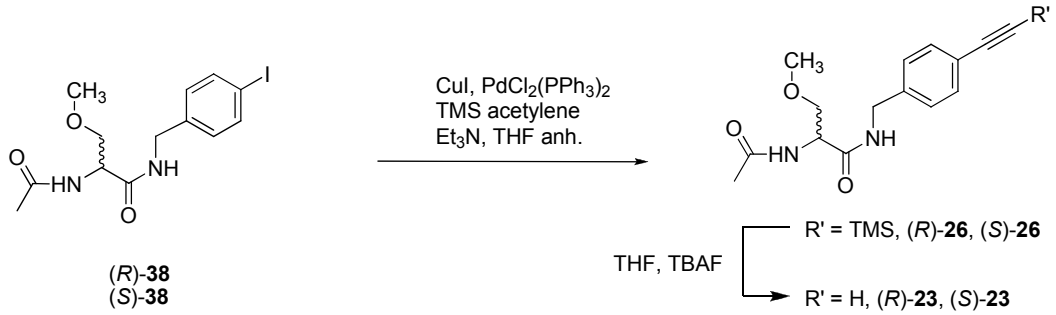
Preparation of (*R*)-*N*-(Biphenyl-4-yl)methyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-90). Ag_2O (12.60 g, 54.0 mmol) was added to a CH_3CN solution (300 mL) of (*R*)-*N*-(biphenyl-4-yl)methyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide (4.00 g, 10.8 mmol) and CH_3I (6.7 mL, 108.1 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature in the dark (4 d), filtered through a pad of Celite®, and the filtrate concentrated in vacuo to obtain a white solid. The solid was purified by flash column chromatography on silica gel with EtOAc/hexanes (70/30 to 50/50) as the eluant to obtain (*R*)-*N*-(biphenyl-4-yl)methyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide as a white solid (3.70 g, 89%): R_f = 0.42 (1/1 EtOAc/hexanes); mp 105–106 °C; $[\alpha]^{26.7}_D$ –12.6° (*c* 1.0, $CHCl_3$); IR (nujol) 3208, 2957, 2728, 1657, 1534, 1458, 1375, 1303, 1243, 1172, 1108, 1054, 961, 729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, ($C\mathbf{H_3}$)$_3$C), 3.38 (s, OC$\mathbf{H_3}$), 3.51 (dd, *J* = 6.3, 9.0 Hz, C**H**H'), 3.87 (dd, *J* = 3.9, 9.0 Hz, CH**H'**), 4.24–4.35 (br m, C**H**CH$_2$), 4.53 (d, *J* = 5.1 Hz, C$\mathbf{H_2}$N), 5.36–5.47 (br m, OC(O)N**H**), 6.73–6.82 (br t, CH$_2$N**H**), 7.30–7.38 (s, 3 Ar**H**), 7.41–7.47 (m, 2 Ar**H**), 7.54–7.59 (m, 4 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 28.2 (($\mathbf{C}H_3$)$_3$C), 43.2 (N$\mathbf{C}H_2$), 54.0 (OCH$_2$**C**H), 59.1 (O$\mathbf{C}H_3$), 72.0 (O$\mathbf{C}H_2$CH), 80.4 ((CH$_3$)$_3$**C**), 127.0, 127.3, 127.4, 127.9, 128.8, 137.0, 140.4, 140.7 (8 Ar**C**), 155.5 (N**C**(O)O), 170.3 (**C**(O)); Anal. Calcd. for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N, 7.29. Found: C, 68.52; H, 7.48; N, 7.24.

Preparation of (*R*)-*N*-(Biphenyl-4-yl)methyl 2-Amino 3-methoxypropionamide Hydrochloride ((*R*)-91). A saturated HCl solution in dioxane (1 mmol/2 mL, 11.5 mL) was added to (*R*)-*N*-(biphenyl-4-yl)methyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide (2.20 g, 5.7 mmol) at 0 °C and the solution was stirred at room temperature (12 h). A second saturated HCl solution in dioxane (1 mmol/2 mL, 11.5 mL) was added to the reaction solution and the solution was stirred at room temperature (6 h). The white solid was filtered to obtain 1.25 g (70%) of (*R*)-*N*-(biphenyl-4-yl)methyl 2-amino 3-methoxypropionamide hydrochloride: mp 145–148 °C; $[\alpha]^{27.0}_{D}$ +33.2° (*c* 0.5, H_2O); IR (nujol) 3253, 3212, 2917, 2860, 1660, 1563, 1459, 1375, 1253, 1182, 1105, 1013, 962, 760 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.32 (s, OC**H**$_3$), 3.75 (d, *J* = 4.6 Hz, OC**H**$_2$), 4.09 (t, *J* = 4.6 Hz, C**H**CH_2), 4.36–4.44 (m, C**H**$_2$N), 7.34–7.41 (s, 3 Ar**H**), 7.43–7.90 (m, 2 Ar**H**), 7.61–7.68 (m, 4 Ar**H**), 8.31–8.44 (br s, N**H**$_3$Cl), 9.22 (t, *J* = 5.7 Hz, C(O)N**H**; ^{13}C NMR (DMSO-d_6) δ 41.9 (N**C**H_2), 52.1 (OCH_2**C**H), 59.4 (O**C**H_3), 70.3 (O**C**H_2CH), 126.5, 126.5, 127.3, 127.7, 128.8, 137.7, 138.8, 139.8 (8 Ar**C**), 166.2 (**C**(O)); Anal. Calcd. for $C_{17}H_{21}ClN_2O_2$: C, 63.64; H, 6.60; Cl, 11.05; N, 8.73. Found: C, 63.42; H, 6.65; Cl, 11.04; N, 8.64.

Preparation of (*R*)-*N*-(Biphenyl-4-yl)methyl 2-Acetamido-3-methoxypropionamide ((*R*)-22). Triethylamine (0.79 mL, 5.7 mmol) and acetyl chloride (561 μL, 2.8 mmol) were carefully added at 0 °C to a CH_2Cl_2 solution of (*R*)-*N*-(biphenyl-4-yl)methyl 2-amino 3-methoxypropionamide hydrochloride (600 mg, 1.9 mmol) and the resulting solution was stirred at room temperature (2 h). An aqueous 10% citric acid solution (100 mL) was added and the organic layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, washed with a saturated $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with EtOAc/MeOH (100/0 to 80/20) as the eluant to obtain (*R*)-*N*-(biphenyl-4-yl)methy) 2-acetamido-3-methoxypropionamide. The solid was recrystallized (EtOAc) to obtain 380 mg (55%) of the desired product as a white

solid: R_f = 0.20 (EtOAc); mp 178–180 °C; $[\alpha]^{26.9}_D$ –8.8° (*c* 0.5, $CHCl_3$); IR (nujol) 3293, 3087, 2870, 1642, 1547, 1457, 1376, 1298, 1127, 727 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, C**H**$_3$CO), 3.40 (s, OC**H**$_3$), 3.45 (dd, *J* = 7.5, 9.2 Hz, C**H**H'), 3.83 (dd, *J* = 3.9, 9.2 Hz, CH**H'**), 4.50–4.61 (m, C**H**$_2$N, C**H**), 6.45 (br d, *J* = 5.7 Hz, N**H**C(O)CH_3), 6.76–6.84 (br t, CH_2N**H**), 7.31–7.38 (m, 3 Ar**H**), 7.41–7.48 (m, 2 Ar**H**), 7.55–7.60 (m, 4 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(biphenyl-4-yl)methyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.2 (**C**H_3CO), 43.2 (**C**H_2N), 52.4 (**C**HCH_2), 59.1 (O**C**H_3), 71.6 (**C**H_2OCH_3), 127.0, 127.3, 127.4, 127.8, 128.8, 136.9, 140.5 (7 Ar**C**), 170.0, 170.3 (2 **C**(O)), 1 signal was not detected and is believed to overlap with nearby peaks; HRMS (M+H^+)(ESI^+) 327.1709 [M + H^+] (calcd for $C_{19}H_{22}N_2O_3H^+$ 327.1708); Anal. Calcd. for $C_{19}H_{22}N_2O_3$•0.1H_2O: C, 69.54; H, 6.82; N, 8.54. Found: C, 69.23; H, 6.76; N, 8.42.

17. Preparation of (*R*)- and (*S*)-*N*-(4'-Ethynyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)- and (S)-23).



Preparation of (*R*)-*N*-(4'-(Trimethylsilyl)ethynylbenzyl 2-Acetamido-3-methoxypropionamide ((*R*)-26). To an anhydrous THF (70 mL) solution of (*R*)-*N*-(4'-iodo)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**38**) (2.40 g, 6.4 mmol), triethylamine (1.79 mL, 12.8 mmol), trimethylsilylacetylene (1.35 ml, 9.6

mmol), dichlorobis(triphenylphosphine)palladium (II) (224 mg, 0.32 mmol), and CuI (121 mg, 0.64 mmol) were sequentially added under Ar. The mixture was stirred at room temperature (4 h), and then Et_2O added and the precipitate filtered through a Celite pad. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography on silica gel with EtOAc/MeOH (9/1) as the eluant to obtain (*R*)-*N*-(4'-(trimethylsilyl)ethynylbenzyl 2-acetamido-3-methoxypropionamide (1.50 g, 68%). The desired product (1.50 g) was purified with 7.50 g of resin scavenger (PhosPhonics, cat# SPM32) to remove the traces of palladium to obtain 1.20 mg (55%) of as a brown solid: R_f = 0.41 (EtOAc); mp 126–127 °C; $[\alpha]^{24}_D$ = +6.1° (*c* 1.0, DMSO); IR (nujol) 3285, 2157, 1641, 1546, 1457, 1375, 1302, 1248, 1130, 975, 862, 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.24 (s, (C**H**$_3$)$_3$Si), 1.99 (s, C**H**$_3$CO), 3.35 (s, OC**H**$_3$), 3.45 (dd, *J* = 7.2, 9.0 Hz, C**H**H'), 3.75 (dd, *J* = 4.2, 9.0 Hz, CH**H'**), 4.33–4.47 (m, C**H**$_2$N), 4.57–4.62 (m, NC(**H**)CO), 6.66 (br d, *J* = 6.9 Hz, N**H**C(O)CH$_3$), 7.07–7.13 (br t, CH$_2$N**H**), 7.17 (d, *J* = 7.9 Hz, 2 Ar**H**), 7.40 (d, *J* = 7.9 Hz, 2 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-(trimethylsilyl)ethynylbenzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ –0.1 (**C**H$_3$)$_3$Si), 23.2 (**C**H$_3$CO), 43.2 (**C**H$_2$N), 52.4 (**C**HCH$_2$), 59.1 (O**C**H$_3$), 71.6 (**C**H$_2$OCH$_3$), 94.4 (**C**≡C), 104.7 (C≡**C**), 122.4, 127.2, 132.3, 138.3 (4 Ar**C**), 170.0, 170.3 (2 **C**(O)); HRMS (M+Na$^+$)(ESI$^+$) 369.1605 [M + Na$^+$] (calcd for $C_{18}H_{26}N_2O_3SiNa^+$ 369.01610); Anal. Calcd. for $C_{18}H_{26}N_2O_3Si$: C, 62.39; H, 7.56; N, 8.08; Found: C, 62.41; H, 7.60; N, 7.99.

Preparation of (*S*)-*N*-(4'-(Trimethylsilyl)ethynylbenzyl 2-Acetamido-3-methoxypropionamide ((*S*)-26). Employing the preceding procedure and using (*S*)-*N*-(4'-iodo)benzyl 2-acetamido-3-methoxypropionamide (2.40 g, 6.4 mmol), triethylamine (1.79 mL, 12.8 mmol), CuI (121 mg, 0.64 mmol), dichlorobis(triphenylphosphine)palladium (II) (224 mg, 0.32 mmol), and trimethylsilylacetylene (1.35 mL, 9.6 mmol) gave 1.97 g (91%) of (*S*)-*N*-(4'-(trimethylsilyl)ethynylbenzyl 2-acetamido-3-methoxypropionamide as a brown

solid: R_f = 0.41 (EtOAc); mp 126–127 °C; $[\alpha]^{24}_D$ = –6.2° (*c* 1.0, DMSO); IR (nujol) 3285, 2727, 2157, 1641, 1546, 1457, 1374, 1304, 1250, 1137, 862, 725 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.22 (s, $(CH_3)_3Si$), 1.87 (s, C**H**$_3$CO), 3.25 (s, OC**H**$_3$), 3.44–3.55 (m, C**H**H', CH**H'**), 4.29 (d, *J* = 5.7 Hz, C**H**$_2$N), 4.43–4.51 (m, NC(**H**)CO), 7.24 (d, *J* = 8.2 Hz, 2 Ar**H**), 7.40 (d, *J* = 8.2 Hz, 2 Ar**H**), 8.10 (br d, *J* = 8.1 Hz, N**H**C(O)CH_3), 8.53 (br t, *J* = 6.0 Hz, CH_2N**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*S*)-*N*-(4'-(trimethylsilyl)ethynylbenzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR (DMSO-d_6) δ –0.2 (**C**$H_3)_3$Si), 22.4 (**C**H_3CO), 41.7 (**C**H_2N), 52.6 (**C**HCH_2), 58.1 (O**C**H_3), 71.9 (**C**H_2OCH_3), 93.6 (**C**≡C), 105.1(C≡**C**), 120.0, 127.1, 131.4, 140.4 (4 Ar**C**), 169.3, 169.8 (2 **C**(O)); HRMS (M+Na^+)(ESI^+) 369.1603 [M + Na^+] (calcd for $C_{18}H_{26}N_2O_3SiNa^+$ 369.01610); Anal. Calcd. for $C_{18}H_{26}N_2O_3Si$: C, 62.39; H, 7.56; N, 8.08. Found: C, 62.10; H, 7.67; N, 7.93.

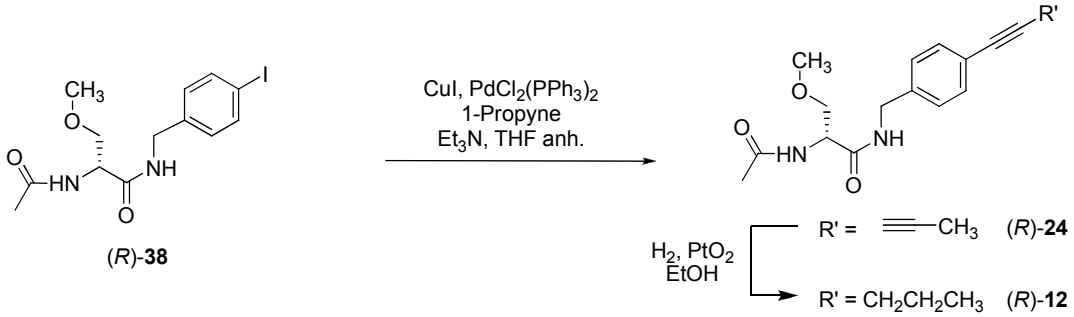
Preparation of (*R*)-*N*-(4'-Ethynyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-23). A 1 M THF solution of TBAF (8.66 mL, 8.66 mmol) was added to a THF (60 mL) solution (*R*)-*N*-(4'-(trimethylsilyl)ethynylbenzyl 2-acetamido-3-methoxypropionamide (1.50 g, 4.33 mmol) and then the solution was stirred at room temperature (4 h). CH_2Cl_2 and an aqueous 10% citric acid solution were added and the organic layer was separated. The aqueous layer was washed with CH_2Cl_2 (2 x 30 mL). The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography on silica gel with EtOAc as the eluant to obtain (*R*)-*N*-(4'-ethynyl)benzyl 2-acetamido-3-methoxypropionamide (0.81 g, 68%) as a white solid: R_f = 0.41 (EtOAc); mp 161–162 °C; $[\alpha]^{24}_D$ = +4.2° (*c* 0.5, DMSO); IR (nujol) 3290, 1634, 1544, 1458, 1375, 1311, 1240, 1197, 1104, 1041, 714 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (s, C**H**$_3$CO), 3.07 (s, C≡C**H**), 3.37 (s, OC**H**$_3$), 3.45 (dd, *J* = 7.2, 9.3 Hz, C**H**H'), 3.77 (dd, *J* = 4.5, 9.3 Hz, CH**H'**), 4.36–4.49 (m, C**H**$_2$N), 4.56–4.63 (m, NC(**H**)CO), 6.60 (br d, *J* = 6.9 Hz, N**H**C(O)CH_3), 7.01–7.10 (br t, CH_2N**H**), 7.20 (d, *J* = 8.2 Hz, 2 Ar**H**), 7.44 (d, *J* = 8.2 Hz, 2 Ar**H**), addition of

excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-ethynyl)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.1 (**C**H_3CO), 43.1 (**C**H_2N), 52.5 (**C**HCH_2), 59.0 (O**C**H_3), 71.7 (**C**H_2OCH_3), 77.3 (**C**≡C), 82.2(C≡**C**), 121.2, 127.3, 132.4, 138.7 (4 Ar**C**), 170.1, 170.4 (2 **C**(O)); HRMS (M+Na^+)(ESI^+) 297.1210 [M + Na^+] (calcd for $C_{15}H_{18}N_2O_3Na^+$ 297.1215); Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.39; H, 6.58; N, 10.08.

Preparation of (*S*)-*N*-(4'-ethynyl)benzyl 2-Acetamido-3-methoxypropionamide ((*S*)-23). Employing the preceding procedure and using (*S*)-*N*-(4'- (trimethylsilyl)ethynylbenzyl 2-acetamido-3-methoxypropionamide (50 mg, 0.145 mmol), and TBAF (290 μL, 0.290 mmol) gave 753 mg (91%) of (*S*)-*N*-(4'-ethynyl)benzyl 2-acetamido-3-methoxypropionamide as a white solid: R_f = 0.41 (EtOAc); mp 159–160 °C; $[\alpha]^{24}_D$ = –4.4° (*c* 0.5, DMSO); IR (nujol) 3289, 2728, 1635, 1544, 1458, 1375, 1304, 1234, 975, 724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.03 (s, C**H**$_3$CO), 3.07 (s, C≡C**H**), 3.38 (s, OC**H**$_3$), 3.44 (dd, *J* = 7.5, 9.0 Hz, C**H**H'), 3.80 (dd, *J* = 4.2, 9.0 Hz, CH**H'**), 4.41–4.51 (m, C**H**$_2$N), 4.52–4.57 (m, NC(**H**)CO), 6.46 (br d, *J* = 5.4 Hz, N**H**C(O)CH_3), 6.80–6.92 (br t, CH_2N**H**), 7.21 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.45 (d, *J* = 8.4 Hz, 2 Ar**H**); ^1H NMR (DMSO-d_6) δ 1.87 (s, C**H**$_3$CO), 3.25 (s, OC**H**$_3$), 3.44–3.55 (m, C**H**H', CH**H'**), 4.14 (s, C≡C**H**), 4.29 (d, *J* = 6.0 Hz, C**H**$_2$N), 4.43–4.48 (m, NC(**H**)CO), 7.25 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.42 (d, *J* = 8.4 Hz, 2 Ar**H**), 8.11 (br d, *J* = 7.8 Hz, N**H**C(O)CH_3), 8.52 (br t, *J* = 6.0 Hz CH_2N**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*S*)-*N*-(4'-ethynyl)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.2 (**C**H_3C(O)), 43.2 (**C**H_2N), 52.5 (**C**HCH_2), 59.1 (O**C**H_3), 71.7 (**C**H_2OCH_3), 77.3 (**C**≡C), 83.3 (C≡**C**), 121.2, 127.3, 132.4, 138.8 (4 Ar**C**), 170.1, 170.4 (2 **C**(O)), HMQC experiment showed a correlation between the δ 3.07 signal in the ^1H NMR and the δ 77.3 peak in the ^{13}C NMR; ^{13}C NMR (DMSO-d_6) δ 22.3

(**C**H_3C(O)), 41.6 (**C**H_2N), 52.4 (**C**HCH_2), 58.0 (O**C**H_3), 71.8 (**C**H_2OCH_3), 80.2 (**C**≡C), 83.2 (C≡**C**), 119.8, 126.9, 131.3, 140.2 (4 Ar**C**), 169.2, 169.6 (2 **C**(O)), HMQC experiment showed a correlation between the δ 4.14 signal in the ^{1}H NMR and the δ 80.2 peak in the ^{13}C NMR; HRMS (M+Na^+)(ESI^+) 297.1212 [M + Na^+] (calcd for $C_{15}H_{18}N_2O_3Na^+$ 297.1215); Anal. Calcd. for $C_{15}H_{18}N_2O_3$•0.25 H_2O: C, 64.62; H, 6.69; N, 10.05. Found: C, 64.60; H, 6.57; N, 9.99.

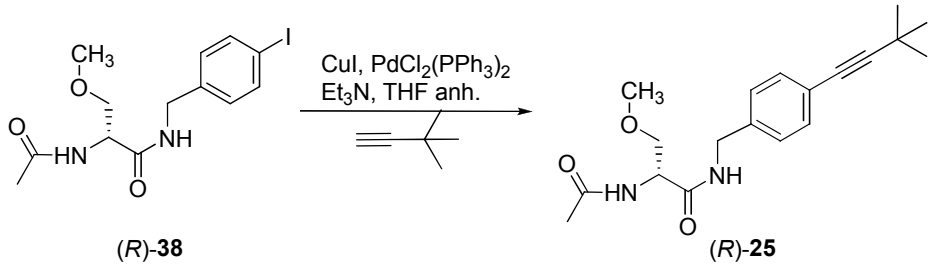
18. Preparation of (*R*)-*N*-(4'-(Prop-1-ynyl))benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-24).



Preparation of (*R*)-*N*-(4'-(Prop-1-ynyl))benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-24). To an anhydrous triethylamine solution (0.1 M, 2.66 mL) of (*R*)-*N*-(4'-iodo)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**38**) (100 mg, 0.266 mmol), dichlorobis(triphenylphosphine)palladium (II) (19 mg, 0.026 mmol), and CuI (2.5 mg, 0.013 mmol) were sequentially added to a flame-dried Schlenk tube under Ar. The mixture was cooled down to -78 °C, and then the reaction vessel was evacuated and propyne was bubbled into the triethylamine solution until the solution reached ~ 1 atm. The mixture was stirred at room temperature (16 h). The mixture was cooled to -78 °C and re-evacuated. A balloon of propyne was bubbled into the mixture and the reaction was stirred at room temperature (24 h). The reaction mixture was concentrated in vacuo and the residue was purified by flash chromatography on silica gel with

EtOAc/hexanes (5/5 to 10/0) as the eluant to obtain (*R*)-*N*-(4'-(prop-1-ynyl))benzyl 2-acetamido-3-methoxypropionamide (70 mg, 92%) as a white solid. The desired product (60 mg) was purified with 340 mg of resin scavenger (PhosPhonics, cat# SPM32) to remove the traces of palladium to obtain 50 mg (66%)of (*R*)-*N*-(4'-(prop-1-ynyl))benzyl 2-acetamido-3-methoxypropionamide: R_f = 0.37 (EtOAc); mp 178–180 °C; $[\alpha]^{24.3}_D$ = –18.0° (*c* 0.5, $CHCl_3$); IR (nujol) 3474, 3273, 2960, 2856, 1683, 1550, 1457, 1375, 1299, 1125, 978, 811, 724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, C**H**$_3$CO), 2.05 (s, C**H**$_3$), 3.38–3.45 (m, C**H**H', OC**H**$_3$), 3.81 (dd, *J* = 4.2, 9.3 Hz, CH**H'**), 4.39–4.50 (m, C**H**$_2$N), 4.51–4.57 (m, NC(**H**)CO), 6.39–6.45 (br d, CHN**H**), 6.71–6.79 (br t, CH_2N**H**), 7.17 (d, *J* = 8.1 Hz, 2 Ar**H**), 7.35 (d, *J* = 8.1 Hz, 2 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-(prop-1-ynyl))benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 4.33 (**C**H$_3$), 23.2 (**C**H$_3$CO), 43.3 (**C**H$_2$N), 52.4 (**C**HCH$_2$), 59.1 (O**C**H$_3$), 71.7 (**C**H$_2$OCH$_3$), 79.4 (**C**≡C), 86.1 (C≡**C**), 123.2, 127.3, 131.8, 137.3 (4 Ar**C**), 170.0, 170.3 (2 **C**(O)); HRMS (M+H$^+$)(ESI$^+$) 311.1372 [M + H$^+$] (calcd for $C_{16}H_{20}N_2O_3H^+$ 311.1372); Anal. Calcd. for $C_{16}H_{20}N_2O_3$•0.2H_2O: C, 65.62; H, 7.06; N, 9.57. Found: C, 65.98; H, 7.02; N, 9.17.

19. Preparation of (*R*)-*N*-(4'-(3,3-Dimethylbut-1-ynyl))benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-25).

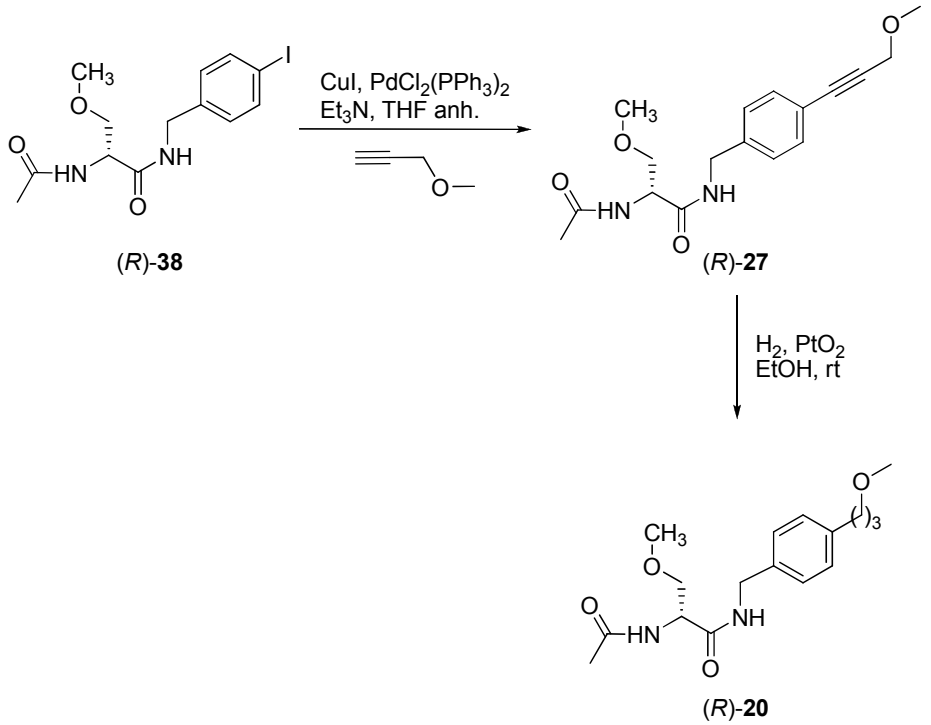


(*R*)-**38** (*R*)-**25**

Preparation of (*R*)-*N*-(4'-(3,3-Dimethylbut-1-ynyl))benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-25). To an anhydrous THF (10 mL) solution of

(*R*)-*N*-(4'-iodo)benzyl 2-acetamido-3-methoxypropionamide ((*R*)-**38**) (376 mg, 1.0 mmol), triethylamine (280 μL, 2.0 mmol), 3,3-dimethylbut-1-yne (182 μl, 1.5 mmol), dichlorobis(triphenylphosphine)palladium (II) (35 mg, 0.05 mmol), and CuI (19 mg, 0.1 mmol) were sequentially added under Ar. The mixture was stirred at room temperature (4 h), and then Et_2O (10 mL) added and the precipitate filtered through a Celite pad. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography on silica gel with EtOAc/MeOH (9/1) as the eluant to obtain (*R*)-*N*-(4'-(3,3-dimethylbut-1-ynyl))benzyl 2-acetamido-3-methoxypropionamide (220 mg, 66%) as a brown solid: R_f = 0.22 (EtOAc); mp 120–121 °C; $[\alpha]^{25}_D$ = +4.8° (*c* 1.0, DMSO); IR (nujol) 3287, 2727, 2364, 1641, 1547, 1458, 1375, 1297, 1132, 972, 816, 724 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (s, ($C\mathbf{H_3}$)$_3$C), 2.00 (s, $C\mathbf{H_3}CO$), 3.35 (s, $OC\mathbf{H_3}$), 3.42 (dd, *J* = 7.5, 9.0 Hz, C**H**H'), 3.76 (dd, *J* = 4.2, 9.0 Hz, CH**H'**), 4.33–4.50 (m, $C\mathbf{H_2}N$), 4.50–4.61 (m, NC(**H**)CO), 6.60 (d, *J* = 6.3 Hz, CHN**H**), 6.91–6.99 (br t, $CH_2N\mathbf{H}$), 7.14 (d, *J* = 8.1 Hz, 2 Ar**H**), 7.33 (d, *J* = 8.1 Hz, 2 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-(3,3-dimethylbut-1-ynyl))benzyl 2-acetamido-3-methoxy-propionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.2 (**C**H_3CO), 27.9 (**C**$(CH_3)_3$), 31.0 ($C(\mathbf{C}H_3)_3$), 43.3 ($\mathbf{C}H_2N$), 52.5 ($\mathbf{C}HCH_2$), 59.1 ($O\mathbf{C}H_3$), 71.8 ($\mathbf{C}H_2OCH_3$), 78.6 (**C**≡C), 98.8 (C≡**C**), 123.3, 127.2, 131.8, 137.1 (4 Ar**C**), 170.2, 170.6 (2 **C**(O)); HRMS (M+H$^+$)(ESI$^+$) 331.2019 [M + H$^+$] (calcd for $C_{19}H_{26}N_2O_3H^+$ 331.2021); Anal. Calcd. for $C_{19}H_{26}N_2O_3$•0.2 H_2O: C, 68.32; H, 7.97; N, 8.39. Found: C, 68.25; H, 7.96; N, 8.33.

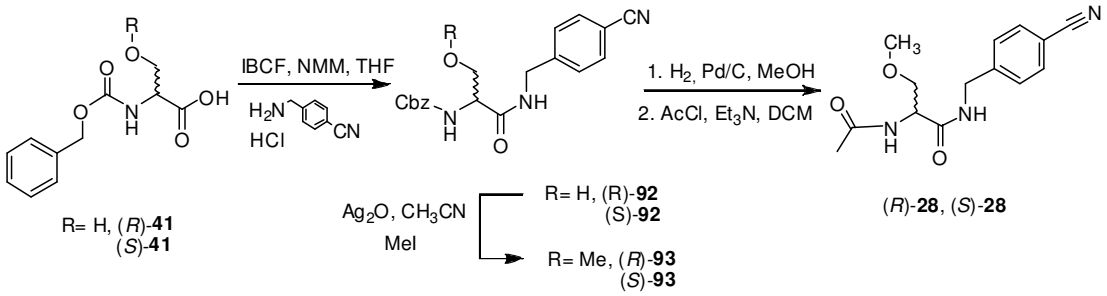
20. Preparation of (*R*)-*N*-(4'-(3-Methoxyprop-1-ynyl))benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-27).



Preparation of (*R*)-*N*-(4'-(3-Methoxyprop-1-ynyl))benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-27). To an anhydrous THF (10 mL) solution (*R*)-*N*-(4'-iodo)benzyl 2-acetamido-3-methoxypropionamide (376 mg, 1.0 mmol), triethylamine (280 μL, 2.0 mmol), 3-methoxyprop-1-yne (125 μl, 1.5 mmol), dichlorobis(triphenylphosphine)palladium (II) (70 mg, 0.1 mmol), and CuI (38 mg, 0.2 mmol) were sequentially added under Ar. The mixture was stirred at room temperature (4 h), and then Et_2O (10 mL) was added and the precipitate filtered through a Celite pad. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography on silica gel with EtOAc/MeOH (9/1) as the eluant to obtain (*R*)-*N*-(4'-(3-methoxyprop-1-ynyl))benzyl 2-acetamido-3-methoxypropionamide (260 mg, 82%) as a beige solid: R_f = 0.27 (EtOAc); mp 141–142 °C; $[\alpha]^{27}_D$ = +4.4° (*c* 1.0, DMSO); IR (nujol) 3278, 3096, 1640, 1554, 1458, 1370, 1304, 1257, 1192, 1099, 966, 903, 810, 732 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02 (s, C**H**$_3$CO), 3.37 (s, OC**H**$_3$), 3.45–3.47 (m, C**H**H', OC**H**$_3$), 3.78 (dd, *J* = 4.2, 9.0 Hz, CH**H'**), 4.32 (s, C≡CC**H**$_2$OCH$_3$), 4.38–4.52 (m, C**H**$_2$N), 4.54–4.61 (m, NC(**H**)CO), 6.52 (d, *J* = 6.6 Hz, CHN**H**), 6.91–6.99 (br t, CH_2N**H**), 7.19 (d, *J* = 7.9 Hz, 2 Ar**H**), 7.41 (d, *J* = 7.9 Hz, 2 Ar**H**), addition of excess (*R*)-(–)-mandelic acid

to a $CDCl_3$ solution of (*R*)-*N*-(4'-(3-methoxyprop-1-ynyl))benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.2 (**C**H_3CO), 43.2 (**C**H_2N), 52.5 (**C**HCH_2), 57.7 (C≡CCH_2O**C**H_3), 59.1 (O**C**H_3), 60.4 (C≡**C**CH_2OCH_3), 71.7 (**C**H_2OCH_3), 85.2 (**C**≡C), 86.0 (C≡**C**), 121.8, 127.3, 132.1, 138.4 (**C**$_6H_4$), 170.4 (br d, 2 **C**(O)); HRMS (M+H^+)(ESI^+) 319.1652 [M + H^+] (calcd for $C_{17}H_{22}N_2O_4H^+$ 319.1658); Anal. Calcd. for $C_{17}H_{22}N_2O_4$•0.33 H_2O: C, 62.95; H, 7.04; N, 8.64. Found: C, 62.98; H, 6.78; N, 8.47.

21. Preparation of (R)- and (*S*)-*N*-(4'-Cyano)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)- and (*S*)-28).



Preparation of (*R*)-*N*-(4'-Cyano)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-hydroxypropionamide ((*R*)-92). A THF solution (150 mL) of (*R*)-Cbz-serine (4.71 g, 19.7 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (2.6 mL, 23.6 mmol) was added dropwise. After 2 min of stirring at this temperature, the isobutylchloroformate (IBCF) (3.1 mL, 23.6 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min. A heterogenous THF (75 mL) mixture of 4-aminomethylbenzonitrile hydrochloride (3.55 g, 22.0 mmol), NMM (2.6 mL, 23.6 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h). The white solid was filtrated and the organic layer was concentrated in vacuo. The residue was triturated with EtOAc resulting in a white solid that was filtered and recrystalized with EtOAc to give (*R*)-*N*-(4'-cyano)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-

hydroxypropionamide as a white solid (4.03 g, 56%): R_f = 0.25 (EtOAc); mp 146–147 °C; $[\alpha]^{24}_D$ –3.9° (*c* 4, DMSO); IR (nujol) 3283, 2229, 1638, 1643, 1567, 1521, 1458, 1375, 1311, 1242, 1025, 747 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.60-3.66 (m, C**H**$_2$OH), 4.11 (q, *J* = 7.5 Hz, NC**H**), 4.38 (d, *J* = 5.6 Hz, NC**H**$_2$), 4.93-4.96 (br m, O**H**), 5.06 (s, C**H**$_2$O), 7.29–7.37 (m, N**H**, 5 Ar**H**), 7.45 (d, *J* = 8.1 Hz, 2 Ar**H**), 7.76 (d, *J* = 8.1 Hz, 2 Ar**H**), 8.58 (t, *J* = 5.6 Hz, N**H**); ^{13}C NMR (DMSO-d_6) δ 41.8 (N**C**H$_2$), 57.3 (OCH$_2$**C**H), 61.5 (O**C**H$_2$CH), 65.5 (**C**H$_2$O), 109.3 (**C**CN), 118.9 (**C**N), 127.7, 128.2, 132.0, 136.9, 145.4 (5 Ar**C**), 155.9 (N**C**(O)O), 170.5 (**C**(O)), the remaining aromatic peaks were not detected and are believed to overlap with the observed signals; HRMS (M+Na$^+$)(ESI$^+$) 354.1451 [M + H$^+$] (calcd for $C_{19}H_{19}N_3O_4H^+$ 354.1454); Anal. Calcd. for $C_{19}H_{19}N_3O_4$•0.25H_2O: C, 63.77; H, 5.49; N, 11.74. Found: C, 64.01; H, 5.37; N, 11.73.

Preparation of (*S*)-*N*-(4'-Cyano)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-hydroxypropionamide ((*S*)-92). Employing the preceding procedure and using (*S*)-Cbz-serine (4.71 g, 19.7 mmol), NMM (5.2 mL, 47.2 mmol), IBCF (3.1 mL, 23.6 mmol), 4-aminomethylbenzonitrile hydrochloride (3.55 g, 22.0 mmol), and THF (225 mL) gave 4.05 g (56%) of (*S*)-*N*-(4'-cyano)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide as a white solid: R_f = 0.25 (EtOAc); mp 146–147 °C; $[\alpha]^{21}_D$ +3.9° (c 4, DMSO); IR (nujol) 3283, 2229, 1639, 1643, 1567, 1521, 1458, 1375, 1311, 1243, 1025 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.57–3.67 (m, C**HH'**OH), 4.10 (q, *J* = 7.5 Hz, NC**H**), 4.38 (d, *J* = 5.9 Hz, NC**H**$_2$), 4.95 (br t, *J* = 5.4 Hz, O**H**), 5.05 (d, *J* = 12.6 Hz, C**H**H'O), 5.07 (d, *J* = 12.6 Hz, CH**H'**O), 7.29–7.37 (m, N**H**, 5 Ar**H**), 7.45 (d, *J* = 8.1 Hz, 2 Ar**H**), 7.76 (d, *J* = 8.1 Hz, 2 Ar**H**), 8.58 (br t, *J* = 5.9 Hz, N**H**); ^{13}C NMR (DMSO-d_6) δ 42.5 (N**C**H$_2$), 58.0 (OCH$_2$**C**H), 62.3 (O**C**H$_2$CH), 66.2 (**C**H$_2$O), 110.0 (**C**CN), 119.5 (**C**N), 128.4, 128.9, 132.7, 137.5, 146.0 (5 **Ar**), 156.6 (N**C**(O)O), 171.2 (**C**(O)), the remaining aromatic peaks were not detected and are believed to overlap with the observed signals; HRMS (M+Na$^+$)(ESI$^+$) 354.1449 [M + H$^+$] (calcd for $C_{19}H_{19}N_3O_4H^+$ 354.1454); Anal. Calcd. for $C_{19}H_{19}N_3O_4$: C, 64.58; H, 5.42; N, 11.89. Found: C, 64.20; H, 5.38; N, 11.70.

Preparation of (*R*)-*N*-(4'-Cyano)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-methoxypropionamide ((*R*)-93). Ag_2O (6.36 g, 27.55 mmol) was added to a CH_3CN solution (100 mL) of (*R*)-*N*-(4'-cyano)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide (2.00 g, 5.51 mmol) and then CH_3I (3.5 mL, 55.1 mmol) was added at room temperature under Ar. The reaction mixture was stirred at room temperature (3 d), filtered through a pad of Celite®, and the filtrate concentrated in vacuo. The residue was purified by trituration with Et_2O to obtain 1.63 g (78%) of (*R*)-*N*-(4'-cyano)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide as a white solid: R_f = 0.82 (EtOAc); mp 143–144 °C; $[\alpha]^{25}_D$ – 6.1° (*c* 4, DMSO); IR (nujol) 3288, 2229, 1687, 1645, 1539, 1458, 1375, 1303,1245, 1123, 1041 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.33 (s, OC**H**$_3$), 3.48 (dd, *J* = 6.0, 9.1 Hz, C**H**H'), 3.82 (dd, *J* = 3.9, 9.1 Hz, CH**H'**), 4.34–4.37 (br m, C**H**CH_2), 4.47 (d, *J* = 6.0 Hz, C**H**$_2$N), 5.08 (s, OC**H**$_2$), 5.73 (br d, *J* = 6.3 Hz, Cbz-N**H**), 6.98 (t, *J* = 6.0 Hz, CH_2N**H**), 7.28–7.32 (m, 7 Ar**H**), 7.53 (d, *J* = 8.1 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 42.8 (N**C**H_2), 54.3 (OCH_2**C**H), 59.0 (O**C**H_3), 67.2 (Ph**C**H_2O), 71.8 (O**C**H_2CH), 111.0 (**C**CN), 118.6 (**C**N), 127.7, 128.0, 128.3, 128.5 132.3, 135.8, 143.5 (7 Ar**C**), 156.0 (N**C**(O)O), 170.3 (**C**(O)); HRMS (M+H$^+$)(ESI$^+$) 368.1610 [M + H$^+$] (calcd for $C_{20}H_{21}N_3O_4H^+$ 368.1610); Anal. Calcd. for $C_{20}H_{21}N_3O_4$•0.25H_2O: 64.59; H, 5.83; N, 11.30. Found: C, 64.61; H, 5.79; N, 11.01.

Preparation of (*S*)-*N*-(4'-Cyano)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-methoxypropionamide ((*S*)-93). Employing the preceding procedure and using (*S*)-*N*-(4'-cyano)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide (2.00 g, 5.51 mmol), Ag_2O (6.36 g, 27.55 mmol), and MeI (3.5 mL, 55.1 mmol) gave 1.58 g (77%) of (*S*)-*N*-(4'-cyano)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide as a white solid after trituration with Et_2O: R_f = 0.82 (EtOAc); mp 142–143 °C; $[\alpha]^{25}_D$ +6.0° (*c* 4, DMSO); IR (nujol) 3288, 2228, 1648, 1534, 1459, 1376, 1303,1243, 1123, 1041 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.35 (s, OC**H**$_3$), 3.50 (dd, *J* = 6.0, 9.1 Hz, C**H**H'), 3.83 (dd, *J* = 3.9, 9.1 Hz, CH**H'**), 4.34–4.37 (br m, C**H**CH_2), 4.48 (d, *J* =

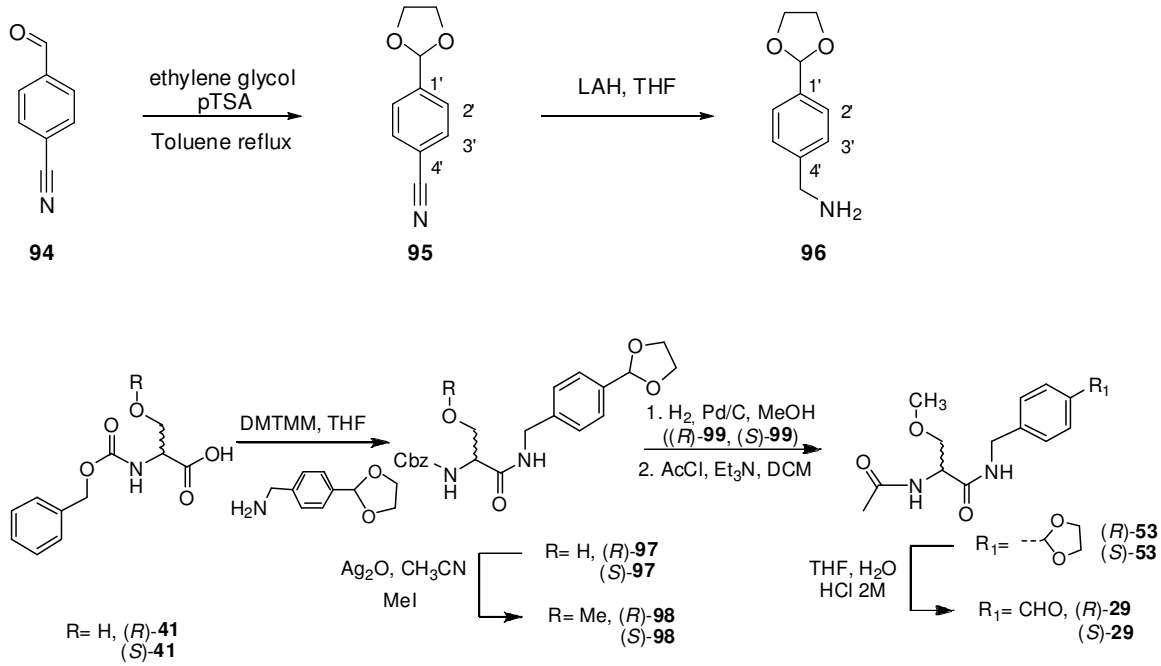
6.0 Hz, C**H**$_2$N), 5.09 (s, OC**H**$_2$), 5.76 (d, J = 6.0 Hz, Cbz-N**H**), 7.03 (t, J = 6.0 Hz, CH$_2$N**H**), 7.30–7.37 (m, 7 Ar**H**), 7.55 (d, J = 8.1 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 42.8 (N**C**H$_2$), 54.5 (OCH$_2$**C**H), 59.0 (O**C**H$_3$), 67.2 (Ph**C**H$_2$O), 71.8 (O**C**H$_2$CH), 111.0 (**C**CN), 118.6 (**C**N), 127.7, 128.0, 128.3, 128.5, 132.3, 135.8, 143.5 (7 Ar**C**), 156.1 (N**C**(O)O), 170.3 (**C**(O)); HRMS (M+H$^+$)(ESI$^+$) 368.1607 [M + H$^+$] (calcd for $C_{20}H_{21}N_3O_4H^+$ 368.1610); Anal. Calcd. for $C_{20}H_{21}N_3O_4$•0.25H_2O: 64.59; H, 5.83; N, 11.30. Found: C, 64.63; H, 5.70; N, 11.51.

Preparation of (*R*)-*N*-(4'-Cyano)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-28). A MeOH solution (150 mL) of (*R*)-*N*-(4'-cyano)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (1.80 g, 4.8 mmol) was treated with H_2 (1 atm) in presence of 10% Pd/C (250 mg) at room temperature (36 h). The mixture was carefully filtered through a bed of Celite® and the filtrate was evaporated in vacuo to obtain a colorless oil. The oil was dissolved in CH_2Cl_2 (50 mL) and then triethylamine (810 μL, 5.8 mmol) and acetyl chloride (410 μL, 5.8 mmol) were carefully added at 0°C and the resulting solution was stirred at room temperature (2 h). H_2O was added and the organic layer was extracted (3 x 100 mL) with CH_2Cl_2. The organic layers were combined, dried ($MgSO_4$), and concentrated in vacuo. After trituration of the residue with EtOAc, 320 mg of (*R*)-*N*-(4'-cyano)benzyl 2-acetamido-3-methoxypropionamide was obtained as a white solid (42%): R_f = 0.54 (9/1 EtOAc/MeOH); mp 168–169 °C; $[\alpha]^{24}_D$ +4.9° (*c* 1 , DMSO); IR (nujol) 3273, 2725, 2226, 1635, 1547, 1458, 1374, 1309, 1191, 1093, 907, 727 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.87 (s, C**H**$_3$CO), 3.26 (s, OC**H**$_3$), 3.45–3.57 (m, C**H**$_2$OCH$_3$), 4.36 (d, J = 6.0 Hz, C**H**$_2$N), 4.43–4.49 (m, NC(**H**)CO), 7.42 (d, J = 8.6 Hz, 2 Ar**H**), 7.34 (d, J = 8.6 Hz, 2 Ar**H**), 8.14 (d, J = 7.8 Hz, N**H**C(O)CH$_3$), 8.61 (t, J = 6.0 Hz, CH$_2$N**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-cyano)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR (DMSO-d_6) δ 22.4 (**C**H$_3$CO), 41.7 (**C**H$_2$N), 52.6 (**C**HCH$_2$), 58.1 (O**C**H$_3$), 71.9 (**C**H$_2$OMe), 109.3 (**C**CN), 118.8 (**C**N), 127.6, 132.1, 145.3 (3 Ar**C**), 169.4, 170.0 (2 **C**(O));

HRMS (M+Na^+)(ESI^+) 298.1163 [M + Na^+] (calcd for $C_{14}H_{17}N_3O_3Na^+$ 298.1168); Anal. Calcd. for $C_{14}H_{17}N_3O_3$•0.25 H_2O: , C, 60.09; H, 6.30; N, 15.02. Found: C, 60.17; H, 6.22; N, 14.66.

Preparation of (*S*)-*N*-(4'-Cyano)benzyl 2-Acetamido-3-methoxypropionamide ((*S*)-28). Employing the preceding procedure and using (*S*)-*N*-(4'-cyano)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (1.20 g, 3.2 mmol), 10% Pd/C (250 mg), triethylamine (539 μL, 3.8 mmol), and acetyl chloride (273 μL, 3.8 mmol) gave 620 mg (70%) of (*S*)-*N*-(4'-cyano)benzyl 2-acetamido-3-methoxypropionamide as a white solid after trituration with EtOAc: R_f = 0.54 (9/1 EtOAc/MeOH); mp 168–169 °C; $[\alpha]^{25}_D$ –4.9° (*c* 1 , DMSO); IR (nujol) 3271, 2726, 2228, 1630, 1552, 1458, 1374, 1312, 1194, 1095, 908, 729 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, C**H**$_3$CO), 3.40 (s, OC**H**$_3$), 3.45 (dd, *J* = 7.2, 9.6 Hz, C**H**H'), 3.81 (dd, *J* = 3.9, 9.6 Hz, CH**H'**), 4.49–4.61 (m, C**H**$_2$N, NC**H**CO), 6.48 (br d, *J* = 5.7 Hz, N**H**C(O)CH_3), 7.06–7.08 (br m, CH_2N**H**), 7.36 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.34 (d, *J* = 8.4 Hz, 2 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*S*)-*N*-(4'-cyano)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.1 (**C**H_3CO), 43.0 (**C**H_2N), 52.5 (**C**HCH_2), 59.1 (O**C**H_3), 71.5 (**C**H_2OCH_3), 111.2 (**C**CN), 118.6 (**C**N), 127.8, 132.4, 143.5 (3 Ar**C**), 170.3, 170.4 (2 **C**(O)); HRMS (M+Na^+)(ESI^+) 298.1163 [M + Na^+] (calcd for $C_{14}H_{17}N_3O_3Na^+$ 298.1168); Anal. Calcd. for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.16. Found: C, 61.02; H, 6.35; N, 15.08.

22. Preparation of (*R*)- and (S)-*N*-(4'-Formy)lbenzyl 2-Acetamido-3-methoxypropionamide ((*R*)-and (*S*)-29).



Preparation of 4-(1,3-Dioxolan-2-yl)benzonitrile (95).[6] To a toluene solution (150 mL) of (4-cyano)benzaldehyde (**94**) (15.00 g, 108.8 mmol) was added ethylene glycol (23.9 mL, 435.1 mmol) and pTSA (20.7 mg, 0.11 mmol). The reaction solution was heated to reflux with a Dean Stark apparatus (16 h) after which the formation of H_2O ceased. The reaction solution was cooled to room temperature and successively washed with aqueous saturated $NaHCO_3$ (150 mL) and brine (2 x 75 mL). The organic layer was concentrated in vacuo to give a pale yellow residue that was recrystallized (Et_2O/hexanes) to provide four crops of pure 4-(1,3-dioxolan-2-yl)benzonitrile as white flakes (17.20 g, 90%): R_f = 0.55 ($CHCl_3$); mp 44–45 °C (lit.[6] mp = 39–40 °C); ^{1}H NMR ($CDCl_3$) δ 4.02–4.14 (m, OC**H**$_2$C**H**$_2$O), 5.84 (s, OC**H**O), 7.58 (d, J = 9.0 Hz, 2 $C_{3'}$**H**), 7.66 (d, J = 9.0 Hz, 2 $C_{2'}$**H**); ^{13}C NMR ($CDCl_3$) δ 65.6 (O**C**H$_2$**C**H$_2$O), 102.6 (O**C**HO), 113.0 (**C**$_4$,C≡N), 118.7 (**C**≡N), 127.3 (2 **C**$_{3'}$), 132.4 (2 **C**$_{2'}$), 143.3 (**C**$_1$,CH(O)O).

Preparation of (4-(1,3-Dioxolan-2-yl)phenyl)methanamine (96).[6] A THF solution (60 mL) of 4-(1,3-dioxolan-2-yl)benzonitrile (23.12 g, 132 mmol) was

added dropwise to a stirred THF solution of 1.0 M $LiAlH_4$ (400 mL, 400 mmol) at 0 °C. The reaction solution was stirred at 0 °C (15 min) during which time the solution progressively turned yellow and then warmed to room temperature (15 h). The excess $LiAlH_4$ was quenched by cooling the reaction (0 °C) and successively adding H_2O (12 mL), aqueous (15 %) NaOH (6 mL), and H_2O (12 mL), and then the mixture was stirred at room temperature (2 h) and filtered. The solid residue was rinsed with CH_2Cl_2 and the combined organic layers were evaporated to give 21.80 g (92%) of (4-(1,3-dioxolan-2-yl)phenyl)methanamine as a slightly yellow residue and the amine was not further purified: R_f = 0.20–0.44 (5/95 MeOH/$CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.43 (s, N**H$_2$**), 3.85 (s, C**H$_2$**NH_2), 3.96–4.16 (m, OC**H$_2$**C**H$_2$**O), 5.79 (s, OC(**H**)O), 7.31 (d, *J* = 8.1 Hz, 2 Ar**H**), 7.43 (d, *J* = 8.1 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 46.4 (NH_2**C**$H_2C_6H_4$), 65.6 (O**C**H_2**C**H_2O), 103.7 (O**C**(H)O), 126.8 (2 **C$_2$**, or 2 **C$_3$**), 127.3 (2 **C$_3$**, or 2 **C**$_{2'}$), 136.5 (NH_2CH_2**C$_4$**), 144.6 (**C$_1$**,CH(O)O).

Preparation of (*R*)-*N*-(4'-(1,3-Dioxolan-2-yl))benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-hydroxypropionamide ((*R*)-97). To a THF solution (200 mL) of (4-(1,3-dioxolan-2-yl)phenyl)methanamine (5.09 g, 28.44 mmol) was added (*R*)-Cbz-serine (6.18 g, 25.85 mmol) in portions. After 5 min a white solid precipitated and additional THF (200 mL) was added to allow efficient stirring. DMTMM (7.86 g, 28.44 mmol) was added to the suspension and the reaction was stirred at room temperature (3 h). The reaction mixture was filtered and the cake was rinsed with THF. The filtrate was evaporated to dryness and dissolved in minimal amount of hot $CHCl_3$, cooled to 0 °C, and then hexanes added to give a white precipitate. The solid was filtered, triturated with ice-cold $CHCl_3$, and filtered. The last two steps were repeated twice. The workup procedure gave 5.46 g (54%) of (*R*)-*N*-(4'-(1,3-dioxolan-2-yl))benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide. The filtrate was concentrated *in vacuo* and purified using flash chromatography (6/93.5/0.5 MeOH/$CHCl_3$/NEt_3) to yield another 1.86 g (18%) of (*R*)-*N*-(4'-(1,3-dioxolan-2-yl))benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide (total yield: 7.42 g, 72%): R_f =

0.37 (5/95 MeOH/$CHCl_3$); mp 129–131 °C; $[\alpha]^{25}_D$ –2.9° (*c* 1.0, MeOH); IR (nujol) 3288, 1689, 1642, 1540, 1459 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.53–3.59 (m, CHC**H$_2$**O), 3.88–4.13 (m, OC**H$_2$**C**H$_2$**O, C**H**CH_2O), 4.30 (d, *J* = 5.7 Hz, NHC**H$_2$**C$_6$H$_4$), 4.82–4.97 (br s, CH_2O**H**). 5.04 (s, C$_6$H$_5$C**H$_2$**O), 5.69 (s, OC(**H**)O), 7.19–7.42 (m, 9 Ar**C**), 8.44 (t, *J* = 5.7 Hz, N**H**CH_2C$_6$H$_4$), the carbamate NH was not detected; ^{13}C NMR (CD_3OD) δ 44.0 (NH**C**H_2C$_6$H$_4$), 58.9 (**C**HCH_2OH), 63.4 (C$_6$H$_5$**C**H_2O), 66.4 (O**C**H_2**C**H_2O), 68.0 (CH**C**H_2OH), 104.9 (O**C**(H)O), 128.0, 128.4, 129.1, 129.2, 129.6, 138.2, 138.5, 141.0 (8 Ar**C**), 158.6 (O**C**(O)NH), 173.2 (CH**C**(O)NH); HRMS (M+Na^+) (ESI^+) 423.1525 (calcd for $C_{21}H_{24}N_2O_6Na^+$ 423.1532); Anal. Calcd. for $C_{21}H_{24}N_2O_6$:C, 62.99; H, 6.04; N, 7.00. Found: C, 62.86; H, 6.05; N, 7.06.

Preparation of (*S*)-*N*-(4'-(1,3-Dioxolan-2-yl))benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-hydroxypropionamide ((*S*)-97). Using the preceding procedure, Cbz-L-serine (6.18 g, 25.8 mmol), (4-(1,3-dioxolan-2-yl)phenyl)methanamine (5.09 g, 28.4 mmol) and DMTMM (7.86 g, 28.4 mmol) in THF (2 x 200 mL) gave 5.66 g (55%) of (*S*)-*N*-(4'-(1,3-dioxolan-2-yl))benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide and another 1.78 g (17%) after flash chromatography (6/93.5/0.5 MeOH/$CHCl_3$/NEt_3) (total yield: 7.44 g, 72%): R_f = 0.37 (5/95 MeOH/$CHCl_3$); mp 129–131 °C; $[\alpha]^{25}_D$ +2.9° (*c* 1.0, MeOH); IR (nujol) 3288, 1689, 1642, 1540, 1459 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.53–3.59 (m, CHC**H$_2$**O), 3.88–4.13 (m, OC**H$_2$**C**H$_2$**O, C**H**CH_2O), 4.30 (d, *J* = 5.7 Hz, NHC**H$_2$**C$_6$H$_4$), 4.90 (t, *J* = 5.4 Hz, CH_2O**H**), 5.04 (s, C$_6$H$_5$C**H$_2$**O), 5.69 (s, OC(**H**)O), 7.19–7.42 (m, 9 Ar**H**), 8.44 (t, *J* = 5.7 Hz, N**H**CH_2C$_6$H$_4$), the carbamate NH was not detected; ^{13}C NMR (DMSO-d_6) δ 41.9 (NH**C**H_2C$_6$H$_4$), 57.4 (**C**HCH_2OH), 61.7 (C$_6$H$_5$**C**H_2O), 64.8 (O**C**H_2**C**H_2O), 65.5 (CH**C**H_2OH), 102.7 (O**C**(H)O), 126.2, 126.8, 127.7, 127.8, 128.3, 136.5, 137.0, 140.4, (8 Ar**C**) 155.9 (O**C**(O)NH), 170.2 (CH**C**(O)NH); HRMS (M+Na^+) (ESI^+) 423.1531 (calcd for $C_{21}H_{24}N_2O_6Na^+$ 423.1532); Anal. Calcd. for $C_{21}H_{24}N_2O_6$: C, 62.99; H, 6.04; N, 7.00. Found: C, 63.00; H, 6.03; N, 6.97.

Preparation of (*R*)-*N*-(4'-(1,3-Dioxolan-2-yl))benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-methoxypropionamide ((*R*)-98). To a CH_3CN solution (100 mL) of (*R*)-*N*-(4'-(1,3-dioxolan-2-yl))benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide (5.56 g 13.9 mmol) were successively added Ag_2O (16.19 g, 69.5 mmol) and MeI (8.66 mL, 139 mmol) and the suspension was stirred at room temperature (3 d) in the dark. The reaction mixture was filtered through a Celite bed and the residue rinsed with $CHCl_3$. The combined organic layer was evaporated to give an oily residue (~ 5 mL). Ice-cold Et_2O (150 mL) was added to the residue and a white solid precipitated. The solid was filtered, rinsed with ice-cold Et_2O and dried to give 3.95 g (69%) of (*R*)-*N*-(4'-(1,3-dioxolan-2-yl))benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide as a white powder: R_f = 0.57 (5/95 MeOH/$CHCl_3$); mp 118–119 °C; $[\alpha]^{25}_D$ –1.5° (*c* 1.0, MeOH); IR (film) 3424, 3055, 2986, 1723, 1678 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.36 (s, $CH_2OC\mathbf{H_3}$), 3.47 (dd, *J* = 6.6, 9.3 Hz, C**H**H'OCH_3), 3.87 (dd *J* = 3.8, 9.3 Hz, CH**H'**OCH_3), 4.01–4.15 (m, $OC\mathbf{H_2}C\mathbf{H_2}O$), 4.28–4.38 (br m, C**H**CH'H), 4.48 (d, *J* = 5.7 Hz, $NHC\mathbf{H_2}C_6H_4$), 5.12 (s, $C_6H_5C\mathbf{H_2}O$), 5.61–5.70 (br m, OC(O)N**H**), 5.80 (s, OC**H**O), 6.61–6.74 (br m, N**H**$CH_2C_6H_4$), 7.22–7.48 (m, 9 Ar**H**), 8.44 (t, *J* = 5.7 Hz, N**H**$CH_2C_6H_4$); ^{13}C NMR ($CDCl_3$) δ 43.5 ($NH_2\mathbf{C}H_2C_6H_4$), 54.5 (**C**HCH_2OCH_3), 59.3 ($CH_2O\mathbf{C}H_3$), 65.5 ($O\mathbf{C}H_2\mathbf{C}H_2O$), 67.5 ($C_6H_5\mathbf{C}H_2O$), 72.2 ($\mathbf{C}H_2OCH_3$), 103.7 (O**C**(H)O), 127.1, 127.7, 128.4, 128.5, 128.8, 136.2, 137.5, 139.1 (8 Ar**C**), 156.3 (O**C**(O)NH), 170.1 (CH**C**(O)NH); HRMS (M+Na^+) (ESI^+) 437.1681 (calcd for $C_{22}H_{26}N_2O_6Na^+$ 437.1689); Anal. Calcd. for $C_{22}H_{26}N_2O_6 \cdot 0.25H_2O$: C, 63.07; H, 6.38; N, 6.69. Found. C, 63.09; H, 6.37; N, 6.64.

Preparation (*S*)-*N*-(4'-(1,3-Dioxolan-2-yl))benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-methoxypropionamide ((*S*)-98). Using the preceding procedure, (*S*)-*N*-(4'-(1,3-dioxolan-2-yl))benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide (5.66 g, 14.2 mmol), Ag_2O (16.54 g, 71.0 mmol) and MeI (8.84 mL, 142.0 mmol) gave 3.91 g (67%) of (*S*)-*N*-(4'-(1,3-dioxolan-2-yl))benzyl 2-*N*-(benzyloxycarbonyl)amino-3-

methoxypropionamide after precipitation from Et_2O: R_f = 0.57 (5% MeOH/$CHCl_3$); mp 118–119 °C; $[\alpha]^{25}_D$ +1.5° (*c* 1.0, MeOH); IR (nujol) 3298, 1690, 1645, 1542 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.34 (s, $CH_2OC\mathbf{H_3}$), 3.47 (dd, *J* = 6.6, 9.3 Hz, C**H**H'OCH_3), 3.82 (dd *J* = 3.8, 9.3 Hz, CH**H'**OCH_3), 4.01–4.15 (m, $OC\mathbf{H_2}C\mathbf{H_2}O$), 4.08–4.18 (br m, C**H**CH'H), 4.45 (d, *J* = 5.7 Hz, $NHC\mathbf{H_2}C_6H_4$), 5.10 (s, $C_6H_5C\mathbf{H_2}O$), 5.73 (br d, *J* = 5.7 Hz, OC(O)N**H**), 5.78 (s, OC(**H**)O), 6.61–6.74 (br m, N**H**$CH_2C_6H_4$), 7.26 (d, *J* = 7.8 Hz, 2 Ar**H**), 7.31–7.39 (m, $C_6\mathbf{H_5}$), 7.42 (d, *J* = 7.8 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 43.4 ($NH_2\mathbf{C}H_2C_6H_4$), 54.5 (**C**HCH_2OH), 59.3 ($CH_2O\mathbf{C}H_3$), 65.5 ($O\mathbf{C}H_2\mathbf{C}H_2O$), 67.4 ($C_6H_5\mathbf{C}H_2O$), 72.2 (**C**$H_2OCH_3$), 103.6 (O**C**(H)O), 127.0, 127.7, 128.3, 128.4, 128.7, 136.2, 137.4, 139.1 (9 Ar**C**), 156.3 (O**C**(O)NH), 170.0 (CH**C**(O)NH); HRMS ($M+Na^+$) (ESI^+) 437.1687 (calcd for $C_{22}H_{26}N_2O_6Na^+$ 437.1689); Anal. Calcd. for $C_{22}H_{26}N_2O_6 \bullet 0.25H_2O$: C, 63.07; H, 6.38; N, 6.69. Found: C, 63.18; H, 6.38; N, 6.70.

Preparation of (*R*)-*N*-(4'-(1,3-Dioxolan-2-yl))benzyl 2-Amino-3-methoxypropionamide ((*R*)-99). (*R*)-*N*-(4'-(1,3-Dioxolan-2-yl))benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (3.75 g, 9.1 mmol) was dissolved in MeOH (50 mL) and 10% Pd/C catalyst (700 mg) was added. The reaction mixture was vigorously stirred under H_2 (1 atm) overnight. The catalyst was removed by filtration over a bed of Celite and the filtrate was evaporated to give 2.57 g (100%) of of (*R*)-*N*-(4'-(1,3-dioxolan-2-yl))benzyl 2-amino-3-methoxypropionamide as a yellow oily residue that was directly used for next step without purification: R_f = 0.24 (1/9 MeOH/$CHCl_3$); $[\alpha]^{25}_D$ –1.3° (*c* 1.0, MeOH); IR (neat) 3325, 1662, 1523 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.69 (br s, $N\mathbf{H_2}CH$), 3.34 (s, $CH_2OC\mathbf{H_3}$), 3.58–3.64 (m, $C\mathbf{H_2}OCH_3$, C**H**CH_2OCH_3), 4.01–4.15 (m, $OC\mathbf{H_2}C\mathbf{H_2}O$), 4.45 (dd, *J* = 2.1, 6.0 Hz, $NHC\mathbf{H_2}C_6H_4$), 5.80 (s, OC(**H**)O), 7.28 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.42 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.76–7.84 (br m, N**H**$CH_2C_6H_4$); ^{13}C NMR ($CDCl_3$) δ 43.1 ($NH_2\mathbf{C}H_2C_6H_4$), 54.9 (**C**HCH_2OH), 59.1 ($CH_2O\mathbf{C}H_3$), 65.5 ($O\mathbf{C}H_2\mathbf{C}H_2O$), 74.4 (**C**$H_2OCH_3$), 103.7 (O**C**(H)O), 127.0, 127.9, 137.3, 139.6 (4 Ar**C**), 172.5 (CH**C**(O)NH); HRMS ($M+H^+$) (ESI^+) 281.1496 (calcd for

$C_{14}H_{20}N_2O_4H^+$ 281.1501).); Anal. Calcd. for $C_{14}H_{20}N_2O_4$•0.25CH_3OH: C, 59.36; H, 7.34; N, 9.72. Found: C, 59.33; H, 7.14; N, 9.45.

Preparation of (*S*)-*N*-(4'-(1,3-Dioxolan-2-yl))benzyl 2-Amino-3-methoxypropionamide ((*S*)-99). Using the preceding procedure, (*S*)-*N*-(4'-(1,3-dioxolan-2-yl))benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (3.81 g, 9.2 mmol) and 10% Pd/C catalyst (700 mg) gave 2.54 g (100%) of a yellow oily residue that was directly acetylated without purification: R_f = 0.24 (10% MeOH/$CHCl_3$); $[\alpha]^{25}_D$ +1.2° (*c* 1.0, MeOH); IR (neat) 3325, 1662, 1523 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.72 (br s, N**H**$_2$CH), 3.37 (s, CHH'OC**H**$_3$), 3.59–3.65 (m, C**H**$_2$OCH_3, C**H**CH_2OCH_3), 4.01–4.16 (m, OC**H**$_2$C**H**$_2$O), 4.45 (dd, *J* = 2.4, 6.0 Hz , NHC**H**$_2C_6H_4$), 5.80 (s, OC(**H**)O), 7.29 (d, *J* = 8.1 Hz, 2 Ar**H**), 7.44 (d, *J* = 8.1 Hz, 2 Ar**H**), 7.76–7.84 (br m, N**H**$CH_2C_6H_4$); ^{13}C NMR ($CDCl_3$) δ 43.1 (NH_2**C**$H_2C_6H_4$), 54.9 (**C**HCHH'OH), 59.1 (CH_2O**C**H_3), 65.5 (O**C**H_2**C**H_2O), 74.4 (**C**H_2OCH_3), 103.7 (O**C**(H)O), 127.0, 127.9, 137.3, 139.6 (4 Ar**C**), 172.5 (CH**C**(O)NH); HRMS ($M+H^+$) (ESI^+) 281.1498 (calcd for $C_{14}H_{20}N_2O_4H^+$ 281.1501). Anal. Calcd. for $C_{14}H_{20}N_2O_4$•0.25 CH_3OH: C, 59.36; H, 7.34; N, 9.72. Found: C, 59.28; H, 7.14; N, 9.52.

Preparation of (*R*)-*N*-(4'-(1,3-Dioxolan-2-yl))benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-53). (*R*)-*N*-(4'-(1,3-Dioxolan-2-yl))benzyl 2-amino-3-methoxypropionamide (2.54 g, 9.07 mmol) was dissolved in THF (100 mL) and cooled (0 °C). Triethylamine (1.26 mL, 9.07 mmol) was added dropwise to the reaction followed by the slow addition of acetyl chloride (0.644 mL, 9.07 mmol). After the reaction was stirred at 0 °C (1 h), the white precipitate was filtered and the filtrate was evaporated. The crude residue was recrystallized from EtOAc and hexanes to give 1.67 g (57%) of (*R*)-*N*-(4'-(1,3-dioxolan-2-yl))benzyl 2-acetamido-3-methoxypropionamide as a light brown solid. The product was not further purified and directly used in the next step: R_f = 0.39 (5/95 MeOH/$CHCl_3$); mp 138–139 °C; $[\alpha]^{25}_D$ –13.0° (*c* 1.0, MeOH); IR (nujol) 3281, 3084, 1638, 1546, 1458 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.03 (s, C**H**$_3$C(O)), 3.38 (s, CHH'OC**H**$_3$), 3.43 (dd,

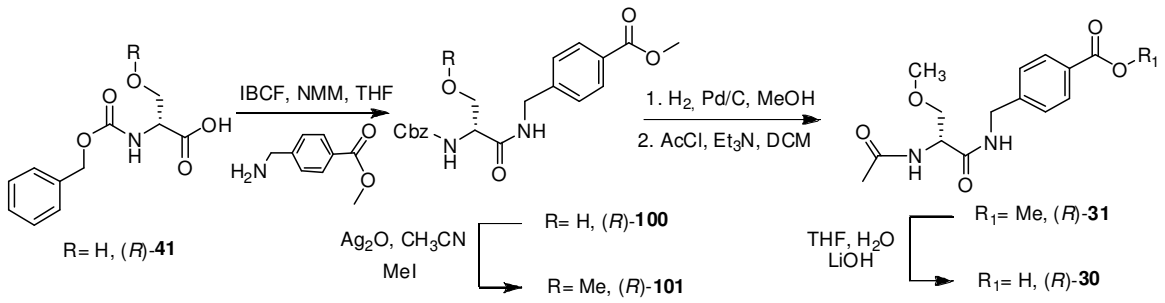
J = 7.5, 9.0 Hz, C**H**H'OCH_3), 3.80 (dd J = 3.7, 9.0 Hz, CH**H'**OCH_3), 4.01–4.15 (m, O**CH_2CH_2**O), 4.40–4.50 (m, NHC**H_2**C_6H_4), 4.54 (app. dt, J = 3.7, 7.5 Hz, C**H**CH'H), 5.80 (s, OC(**H**)O), 6.45 (d, J = 6.6 Hz, CH_3C(O)N**H**), 6.78–6.82 (m, N(**H**)$CH_2C_6H_4$), 7.27 (d, J = 7.8 Hz, 2 Ar**H**), 7.45 (d, J = 7.8 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 23.4 (**C**H_3C(O)), 43.5 (NH_2**C**$H_2C_6H_4$), 52.6 (**C**HCH_2OH), 59.3 (CH_2O**C**H_3), 65.5 (O**C**H_2**C**H_2O), 71.8 (**C**H_2OCH_3), 103.7 (O**C**(H)O), 127.0, 127.7, 137.5, 139.1 (4 Ar**C**), 170.2, 170.5 (2 **C**(O)); HRMS (M+Na^+) (ESI^+) 345.1421 (calcd for $C_{16}H_{22}N_2O_5Na^+$ 345.1426); Anal. Calcd. for $C_{16}H_{22}N_2O_5$: C, 59.61; H, 6.88; N, 8.69. Found: C, 59.50; H, 6.90; N, 8.56.

Preparation of (*S*)-*N*-(4'-(1,3-Dioxolan-2-yl))benzyl 2-Acetamido-3-methoxypropionamide ((*S*)-53). Using the preceding procedure, (*S*)-*N*-(4'-(1,3-dioxolan-2-yl))benzyl 2-amino-3-methoxypropionamide (2.57g, 9.18 mmol), triethylamine (1.28 mL, 9.18 mmol), and acetyl chloride (0.65 mL, 9.18 mmol) gave 1.70 g (57%) of (*S*)-*N*-(4'-(1,3-dioxolan-2-yl))benzyl 2-acetamido-3-methoxypropionamide as a light brown solid after precipitation from EtOAc and hexanes: R_f = 0.39 (5/95 MeOH/$CHCl_3$); mp 138–139 °C; $[\alpha]^{25}_D$ +13.0 ° (c 1.0, MeOH); IR (nujol) 3281, 3090, 1638, 1546, 1458 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.97 (s, C**H_3**C(O)), 3.35 (s, CH_2OC**H_3**), 3.45 (dd, J = 6.9, 9.0 Hz, C**H**H'OCH_3), 3.73 (dd J = 4.2, 9.0 Hz, CH**H'**OCH_3), 4.01–4.15 (m, O**CH_2CH_2**O), 4.38 (dd, J = 5.6, 15.0 Hz, NHC**H**H'C_6H_4), 4.47 (dd, J = 5.6, 15.0 Hz, NHCH**H'**C_6H_4), 4.56–4.64 (app. dt, J = 4.2, 6.9 Hz, C**H**CH'H), 5.80 (s, OC(**H**)O), 6.76 (d, J = 6.9 Hz, CH_3C(O)N**H**), 7.14 (t, J = 5.6 Hz, N**H**$CH_2C_6H_4$), 7.25 (d, J = 7.8 Hz, 2 Ar**H**), 7.42 (d, J = 7.8 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 23.2 (**C**H_3C(O)), 43.3 (NH_2**C**$H_2C_6H_4$), 52.7 (**C**HCH_2OH), 59.2 (CH_2O**C**H_3), 65.4 (O**C**H_2**C**H_2O), 72.0 (**C**H_2OCH_3), 103.6 (O**C**(H)O), 126.9, 127.6 (2 Ar**C**), 137.2 (NHCH_2**C**), 139.2 (**C**C(H)O(O)), 170.2, 170.6 (2 **C**(O)): HRMS (M+Na^+) (ESI^+) 345.1424 (calcd for $C_{16}H_{22}N_2O_5Na^+$ 345.1426). Anal. Calcd. for $C_{16}H_{22}N_2O_5$: C, 59.61; H, 6.88; N, 8.69. Found: C, 59.51; H, 6.90; N, 8.58.

Preparation of (*R*)-*N*-(4'-Formyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-29). (*R*)-*N*-(4'-(1,3-dioxolan-2-yl))benzyl 2-acetamido-3-methoxypropionamide (1.62 g, 5.03 mmol) was dissolved in a 2:1 THF:H_2O mixture (30 mL) and 2 M HCl (10 drops) was added. The reaction was stirred at room temperature overnight and diluted with H_2O (20 mL). The solution was neutralized with the dropwise addition of a saturated aqueous $NaHCO_3$ solution at 0 °C. The THF was removed in vacuo and the remaining aqueous layer was extracted with $CHCl_3$ (5 x 25 mL). The organic layers were combined, dried (Na_2SO_4), concentrated in vacuo, and the residue recrystallized from EtOAc to give 930 mg (66%) of (*R*)-*N*-(4'-formyl)benzyl 2-acetamido-3-methoxypropionamide as a white solid. The mother liquor was concentrated and purified by flash chromatography (5/95 MeOH/$CHCl_3$) to yield of product 336 mg (24%) (total yield: 1.27 g (90%)): R_f = 0.40 (5/95 MeOH/$CHCl_3$); mp 132–133 °C; $[\alpha]^{25}_D$ +10.4 ° (*c* 1.0, $CHCl_3$); IR (nujol) 3288, 1687, 1642, 1549, 1458, 1375 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.96 (s, C**H**$_3$C(O)), 3.36 (s, CH_2OC**H**$_3$), 3.53 (dd, *J* = 6.0, 9.3 Hz, C**H**H'OCH_3), 3.75 (dd *J* = 4.8, 9.3 Hz, CH**H'**OCH_3), 4.38–4.58 (m, NHC**H**$_2$$C_6H_4$), 4.71 (app. dt, *J* = 5.4, 6.0 Hz, C**H**CH'H), 7.03 (d, *J* = 7.8 Hz, N**H**$CH_2C_6H_4$), 7.38 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.68 (t, *J* = 5.4 Hz, $CH_3C(O)$N**H**), 7.77 (d, *J* = 8.4 Hz, 2 Ar**H**), 9.93 (s, C(O)**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-formyl)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the methoxy protons and the acetyl peak protons, addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*S*)-*N*-(4'-formyl)benzyl 2-acetamido-3-methoxypropionamide and (*R*)-*N*-(4'-formyl)benzyl 2-acetamido-3-methoxypropionamide (1:2 ratio) gave two signals for the acetyl methyl protons (δ 2.037 (*S*) and 2.023 (*R*) (Δppm = 0.014)) and two signals for the methoxy protons (δ 3.346 (*S*) and 3.377 (*R*) (Δppm = 0.031)); ^{13}C NMR ($CDCl_3$) δ 23.0 (**C**$H_3C(O)$), 43.1 (NH_2**C**$H_2C_6H_4$), 52.8 (**C**HCHH'OH), 59.1 (CH_2O**C**H_3), 72.0 (**C**HH'OCH_3), 127.7, 130.0, 135.5, 145.3 (4 Ar**C**), 170.5, 170.7 (2 **C**(O)), 192.0 (**C**(O)H); HRMS (M+Na^+) (ESI^+) 301.1158 [M+Na^+] (calcd for $C_{14}H_{18}N_2O_4Na^+$ 301.1164); Anal. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.40; H, 6.57; N, 9.90.

Preparation of (*S*)-*N*-(4'-Formyl)benzyl 2-Acetamido-3-methoxypropionamide ((*S*)-29). Using the preceding procedure, (*S*)-*N*-(4'-(1,3-dioxolan-2-yl))benzyl 2-acetamido-3-methoxypropionamide (1.65 g, 5.12 mmol) gave 900 mg (63%) of (*S*)-*N*-(4'-formyl)benzyl 2-acetamido-3-methoxypropionamide after recrystallization from EtOAc and another 268 mg (19%) after flash chromatography (total yield: 1.17 g, 82%): R_f = 0.40 (5/95 MeOH/$CHCl_3$); mp 132–133 °C; $[\alpha]^{25}_D$ –10.4 ° (*c* 1.0, $CHCl_3$); IR (nujol) 3288, 3073, 1687, 1637, 1551, 1458, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, C**H**$_3$C(O)), 3.40 (s, CH_2OC**H**$_3$), 3.46 (dd, *J* = 7.5, 9.6 Hz, C**H**H'OCH_3), 3.83 (dd *J* = 4.2 Hz, 9.6 Hz, CH**H'**OCH_3), 4.48–4.64 (m, NHC**H**$_2C_6H_4$, C**H**CH'H), 6.45 (d, *J* = 6.6 Hz, $CH_3C(O)N$**H**), 6.99–7.15 (m, N**H**$CH_2C_6H_4$), 7.42 (d, *J* = 8.1 Hz, 2 Ar**H**), 7.85 (d, *J* = 8.1 Hz, 2 Ar**H**), 9.99 (s, C(O)**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*S*)-*N*-(4'-formyl)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the the acetyl peak protons and the methoxy protons, addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*S*)-*N*-(4'-formyl)benzyl 2-acetamido-3-methoxypropionamide and (*R*)-*N*-(4'-formyl)benzyl 2-acetamido-3-methoxypropionamide (1:2 ratio) gave two signals for the acetyl methyl protons (δ 2.037 (*S*) and 2.023 (*R*) (Δppm = 0.014)) and two signals for the methoxy protons (δ 3.317 (*S*) and 3.351 (*R*) (Δppm = 0.034)); ^{13}C NMR ($CDCl_3$) δ 23.4 (**C**$H_3C(O)$), 43.4 (NH_2**C**$H_2C_6H_4$), 52.7 (**C**HCH_2OH), 59.4 (CH_2O**C**H_3), 71.7 (**C**H_2OCH_3), 128.0, 130.3, 135.9, 145.2 (4 Ar**C**), 170.5, 170.6 (2 **C**(O)), 192.0 (**C**(O)H); HRMS (M+Na^+) (ESI^+) 301.1161 [M+Na^+] (calcd for $C_{14}H_{18}N_2O_4Na^+$ 301.1164); Anal. Calcd. for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.13; H, 6.49; N, 9.91.

23. Preparation of (*R*)-*N*-(4'-Carboxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-30).



Preparation of (*R*)-*N*-(4'-(Methyloxycarbonyl))benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-hydroxypropionamide ((*R*)-100). To an anhydrous THF solution (150 mL) of (*R*)-Cbz-serine (5.09 g, 21.3 mmol) at –78 °C was added 4-methylmorpholine (NMM) (5.70 mL, 51.8 mmol). The solution was stirred (5 min), followed by the addition of isobutyl chloroformate (3.43 mL, 26.2 mmol). This mixture was stirred (5 min) and then methyl 4-(aminomethyl)benzoate hydrochloride (5.01 g, 24.8 mmol) was added. The reaction mixture was stirred at room temperature (1.5 h), and filtered. The filtrate was concentrated in vacuo, and purified by flash column chromatography (9:1 $CHCl_3$:MeOH) yielding (*R*)-*N*-(4'-(methyloxycarbonyl))benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide as a white powder (3.36 g, 66%): R_f = 0.75 (9/1 $CHCl_3$/MeOH); mp 155–156 °C; ^{1}H NMR (DMSO-d_6) δ 3.56–3.69 (m, C**H**$_2$OH), 3.84 (s, C**H**$_3$), 4.07–4.14 (m, C**H**), 4.37 (d, J = 6.0 Hz, NHC**H**$_2$), 4.93 (t, J = 5.7 Hz, O**H**), 5.05 (s, C**H**$_2$O), 7.28–7.41 (m, N**H**, 7 Ar**H**), 7.89 (d, J = 8.1 Hz, 2 Ar**H**), 8.55 (t, J = 6.0 Hz, N**H**CH$_2$); ^{13}C NMR (DMSO-d_6) δ 41.9 (HN**C**H$_2$Ph), 52.0 (**C**H), 57.4 ((O)CO**C**H$_3$), 61.7 (**C**H$_2$OH), 65.5 (Ph**C**H$_2$O), 127.1, 127.7, 128.0, 128.3, 129.1, 137.0, 145.2 (7 Ar**C**), 156.0 (O**C**N(H)), 166.1, 170.4 (2 **C**(O)), the remaining aromatic resonance was not detected and is believed to overlap with nearby signals; Anal. Calcd. for $C_{20}H_{22}N_2O_6$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.02; H, 5.78; N, 7.22.

Preparation of (*R*)-*N*-(4'-(Methyloxycarbonyl))benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-methoxypropionamide ((*R*)-101). Dry (*R*)-*N*-(4'-(methyloxycarbonyl))benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide (0.42 g, 1.1 mmol) was dissolved in CH_3CN (20 mL), and then Ag_2O (1.21 g, 5.2 mmol) and CH_3I (0.65 mL, 10.4 mmol) were added. The solution was stirred in the dark at room temperature (72 h). The solution was filtered through Celite®, and then washed with CH_3CN. The filtrate was evaporated, and the crude product was purified by column chromatography using a 15/1 $CHCl_3$/MeOH solvent system to yield (*R*)-*N*-(4'-(methyloxycarbonyl))benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (0.32 g, 77%) as a white solid: R_f = 0.76 (9/1 $CHCl_3$/MeOH); ^{1}H NMR ($CDCl_3$) δ 3.37 (s, C**H**$_3$OCH$_2$), 3.45 (dd, J = 3.0, 9.0 Hz, C**H**H'OCH$_3$), 3.87 (dd, J = 5.4, 9.0 Hz, CH**H'**OCH$_3$), 3.91 (s, C**H**$_3$OC(O)), 4.32–4.40 (m, C**H**), 4.53 (d, J = 6.0 Hz, NHC**H**$_2$), 5.12 (s, PhC**H**$_2$O), 5.68 (br s, N**H**CH), 6.76–6.84 (br t, N**H**CH$_2$), 7.27–7.41 (m, 7 Ar**H**), 7.99 (d, J = 8.1 Hz, 2 Ar**H**).

Preparation of (*R*)-*N*-(4'-(Methyloxycarbonyl))benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-31). Pd/C (10%, 400 mg) was added to a solution of (*R*)-*N*-(4'-(methyloxycarbonyl))benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (1.28 g, 3.20 mmol) in anhydrous MeOH (35 mL). The mixture was hydrogenated (45 psi, 24 h), and then filtered through Celite®. The filtrate was evaporated in vacuo leaving a mixture (0.80 g) of a white solid (impurities, minor) and an oil of the desired amine (TLC analysis using ninhydrin indicated the presence of a primary amine).

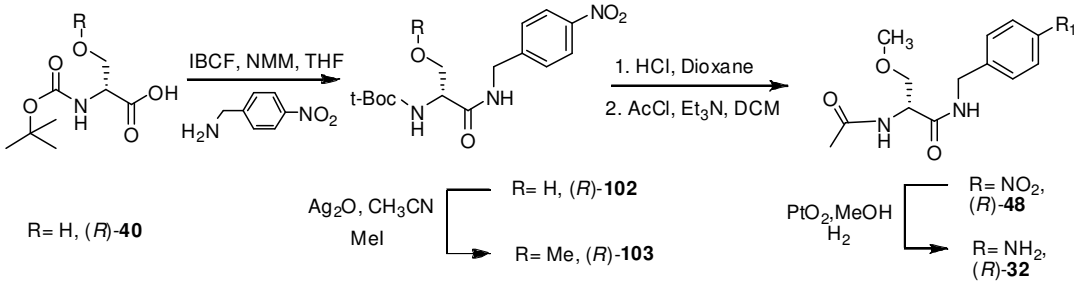
The amine mixture was dissolved in anhydrous CH_2Cl_2 (50 mL), and triethylamine (1.25 mL, 9 mmol) and acetyl chloride (0.32 mL, 4.5 mmol) were added sequentially and stirred at room temperature (30 min). The reaction solution was combined with CH_2Cl_2 (100 mL) and washed with H_2O (3 x 100 mL), and saturated aqueous NaCl (1 x 100 mL). The desired product was recrystallized from EtOAc to yield 0.43 g of a white solid (47% from (*R*)-*N*-(4'-(methyloxycarbonyl))benzyl 2-*N*-(benzyloxycarbonyl)amino-3-

methoxypropionamide): R_f = 0.62 (9/1 $CHCl_3$/MeOH); mp 167–168 °C; $[\alpha]^{25}_D$ –11.4° (*c* 2.2, $CHCl_3$); IR (nujol) 3279, 2927, 1712, 1639, 1550, 1457 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, C**H**$_3$C(O)), 3.39 (s, C**H**$_3$OCH_2), 3.45 (dd, *J* = 7.5, 9.0 Hz, C**H**H'OCH_3), 3.82 (dd, *J* = 4.2, 9.0 Hz, CH**H'**OCH_3), 3.91 (s, C**H**$_3$OC(O)), 4.51–4.55 (m, C**H**, C**H**$_2$NH), 6.45 (d, *J* = 6.6 Hz, N**H**CH), 6.85–6.95 (br m, N**H**CH_2), 7.32 (d, *J* = 8.4 Hz, 2 Ar**H**), 8.00 (d, *J* = 8.4 Hz, 2 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-(methyloxycarbonyl))benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl protons and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.3 (**C**H_3C(O)), 43.3 (**C**H_2N), 52.3 (**C**H_3OC(O)), 52.7 (**C**H), 59.2 (**C**H_3OCH_2), 72.0 (**C**H_2O), 127.3, 129.4, 130.1, 143.4 (4 Ar**C**), 167.0 (O**C**(O)), 170.4, 170.6 (2 **C**(O)); HRMS (ESI) 309.1451 [M + H^+] (calcd. for $C_{15}H_{20}N_2O_5$ 309.1450); Anal. Calcd. for $C_{15}H_{20}N_2O_5$: C, 58.43; H, 6.54; N, 9.09. Found: C, 58.40; H, 6.43; N, 8.91.

Preparation of (*R*)-*N*-(4'-Carboxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-30). To a solution of (*R*)-*N*-(4'-(methyloxycarbonyl))benzyl 2-acetamido-3-methoxypropionamide (0.75 g, 2.6 mmol) in THF:H_2O (1:1, 50 mL) at 0 °C, was added LiOH•H_2O (66 mg, 2.8 mmol). The resulting solution was stirred for 36 h. The solvent was removed in vacuo, washed with Et_2O (4x, 100 mL), acidified to a pH of ~2 (1 N HCl), extracted with EtOAc (8 x 50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to yield 472 mg of a white powder (66%): R_f = 0.51 (9/1 $CHCl_3$/MeOH); mp 197–198 °C; $[\alpha]^{25}_D$ +6.0° (*c* 0.8, MeOH); IR (nujol) 3163, 2923, 2856, 1692, 1637, 1533, 1457, 1376, 1291, 1122, 939 cm^{-1}; ^1H NMR (CD_3OD) δ 2.03 (s, C**H**$_3$C(O)), 3.37 (s, C**H**$_3$OCH_2), 3.60 (dd, *J* = 5.1, 9.7 Hz, C**H**H'OCH_3), 3.72 (dd, *J* = 5.1, 9.7 Hz, CH**H'**OCH_3), 4.48 (d, *J* = 6.0 Hz, C**H**$_2$NH), 4.53 (t, *J* = 9.7 Hz, C**H**), 7.39 (d, *J* = 8.3 Hz, 2 Ar**H**), 7.97 (d, *J* = 8.3 Hz, 2 Ar**H**), 8.57 – 8.66 (br t, N**H**CH_2), one amide proton and the carboxylic acid proton were not observed; ^{13}C NMR (CD_3OD) δ 21.4 (**C**H_3C(O)), 42.7 (**C**H_2N), 54.2 (**C**H), 58.2 (**C**H_3O), 72.0 (**C**H_2O), 127.1, 129.6, 129.8, 144.3 (4 Ar**C**), 168.8 (HO**C**(O)), 171.6, 172.6 (2 **C**(O));

LRMS (ESI) 295.1 [M + H^+] (calcd. for $C_{14}H_{18}N_2O_5H^+$: 295.1); Anal. Calcd. for $C_{14}H_{18}N_2O_5$: C, 57.13; H, 6.16; N, 9.52. Found: C, 57.10; H, 6.18; N, 9.30.

24. Preparation of (*R*)-*N*-(4'-Amino)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-32).



Preparation of (*R*)-*N*-(4'-Nitro)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-102). A THF solution (140 mL) of *(S)-tert*-Boc-serine (1.00 g, 4.9 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (607 μL, 5.9 mmol) was added dropwise. The reaction was stirred at this temperature (2 min) and then isobutylchloroformate (IBCF) (765 μL, 5.9 mmol) was added dropwise leading to the precipitation of a white solid. The reaction was allowed to proceed for additional 2 min. A heterogeneous THF (10 mL) mixture of 4-nitrobenzylamine hydrochloride (1.02 g, 5.40 mmol) and NMM (593 μL, 5.4 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), the white solid was filtered, and the organic layer was concentrated in vacuo. The residue was purified by flash chromatography on silica gel with EtOAc/hexanes (50/50 to 100/0) as the eluant to obtain (*R*)-*N*-(4'-nitro)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide (843 mg, 51%) as a white solid: R_f = 0.29 (5/5 EtOAc/hexanes); mp 128–129 °C; $[\alpha]^{25}_D$ +10.1° (*c* 1.0, MeOH); IR (nujol) 3313, 3061, 1662, 1602, 1449, 1348, 1304, 1252, 1164, 1068, 1006, 855, 792, 738,

656 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.40 (s, (C**H**$_3$)$_3$C), 3.56–3.62 (m, O**H**, C**H**H'OH), 3.97–4.04 (dd, *J* = 5.4, 13.0 Hz, CH**H'**OH), 4.34–4.50 (m, C**H**$_2$N), 4.90 (t, *J* = 5.9 Hz, C**H**CHH'), 6.76 (d, *J* = 7.5 Hz, N**H**C(O)C(CH$_3$)$_3$), 7.53 (d, *J* = 8.7 Hz, 2 Ar**H**), 8.15 (d, *J* = 8.7 Hz, 2 Ar**H**), 8.55 (t, *J* = 5.9 Hz, CH$_2$N**H**); ^{13}C NMR (DMSO-d_6) δ 28.2 ((**C**H$_3$)$_3$C), 41.7 (N**C**H$_2$), 57.0 (OCH$_2$**C**H), 61.7 (O**C**H$_2$CH), 78.2 ((CH$_3$)$_3$**C**), 123.2, 127.9, 146.3, 147.7 (4 Ar**C**), 155.3 (N**C**(O)O), 170.9 (**C**(O)); HRMS (M+Na$^+$)(ESI$^+$) 362.1324 [M + Na$^+$] (calcd for $C_{15}H_{21}N_3O_6Na^+$ 362.1322); Anal. Calcd. For $C_{15}H_{21}N_3O_6$: C, 53.09; H, 6.24; N, 12.38. Found: C, 52.99; H, 6.35; N, 11.98.

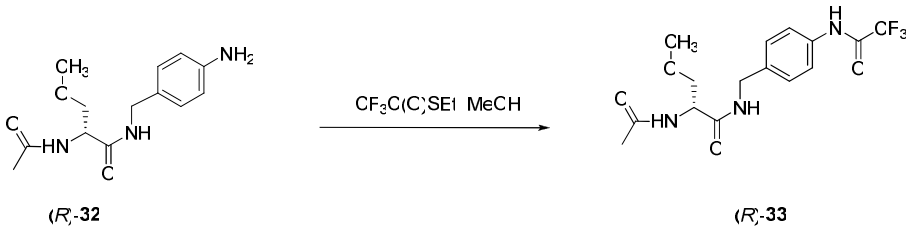
Preparation of (*R*)-*N*-(4'-Nitro)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-103). Ag_2O (9.00 g, 39.1 mmol) was added to a CH_3CN solution (100 mL) of (*R*)-*N*-(4'-nitro)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide (2.65 g, 7.8 mmol) and then CH_3I (4.9 mL, 78.0 mmol) was added at room temperature under Ar. The reaction mixture was stirred at room temperature (3 d), filtered through a pad of Celite®, and the filtrate concentrated in vacuo. The residue was purified by column chromatography (SiO_2; 1/1 EtOAc/hexanes) to obtain 2.21 g (80%) of (*R*)-*N*-(4'-nitro)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide as an oil that crystallized after a few days: R_f = 0.73 (1/1 EtOAc/hexanes); mp 96–97 °C; $[\alpha]^{26}_D$ –1.5° (*c* 1.0, DMSO); IR (nujol) 3330, 1659, 1528, 1459, 1353, 1297, 1243, 1166, 1126, 1037, 947, 859, 778, 730, 645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.45 (s, (C**H**$_3$)$_3$C), 3.40 (s, OC**H**$_3$), 3.52 (dd, *J* = 6.0, 9.2 Hz, C**H**H'OCH$_3$), 3.88 (dd, *J* = 3.6, 9.2 Hz, CH**H'**OCH$_3$), 4.25–4.35 (m, C**H**CHH'), 4.59 (d, *J* = 6.1 Hz, C**H**$_2$N), 5.30–5.40 (br m, N**H**), 6.86–6.96 (br m, N**H**), 7.43 (d, *J* = 8.7 Hz, 2 Ar**H**), 8.19 (d, *J* = 8.7 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 28.2 ((**C**H$_3$)$_3$C), 41.7 (N**C**H$_2$), 54.2 (OCH$_2$**C**H), 59.1 (O**C**H$_3$), 71.9 (O**C**H$_2$CH), 80.6 ((CH$_3$)$_3$**C**), 123.8, 127.8, 145.7, 147.3 (4 Ar**C**), 155.5 (N**C**(O)O), 170.8 (**C**(O)); HRMS (M+H$^+$)(ESI$^+$) 353.1583 [M + H$^+$] (calcd for $C_{16}H_{23}N_3O_6H^+$ 353.1587); Anal. Calcd. For $C_{16}H_{23}N_3O_6$: C, 54.38; H, 6.56; N, 11.89. Found: C, 54.54; H, 6.60; N, 11.70.

Preparation of (*R*)-*N*-(4'-Nitro)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-48).[7] A saturated HCl solution in dioxane (1 mmol/2 mL, 17 mL) was added to (*R*)-*N*-(4'-nitro)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide (3.00 g, 8.5 mmol) at 0 °C and the solution was stirred at room temperature (2 h). The reaction solution was concentrated in vacuo and dried (30 min). CH_2Cl_2 (30 mL) was added to the residue followed by the successive additions of Et_3N (3.6 mL, 25.6 mmol) and AcCl (906 μL, 12.3 mmol) at 0 °C. The mixture was stirred at room temperature (18 h), and then aqueous 10% citric acid was added and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The organic layers were combined, washed with aqueous saturated $NaHCO_3$ (30 mL) and H_2O (30 mL), dried ($MgSO_4$), and concentrated in vacuo. The solid was recrystallized with EtOAc to obtain (*R*)-*N*-(4'-nitro)benzyl 2-acetamido-3-methoxypropionamide (2.43 g, 76%) as a white solid: R_f = 0.64 (9/1 CH_2Cl_2/MeOH); mp 162 °C (lit.[7] mp 163–164 °C); $[\alpha]^{25}_D$ +9.5 (c 1.33, MeOH) (lit.[7] $[\alpha]^{27}_D$ +9.6 (c 1.33, MeOH)); ^{1}H NMR ($CDCl_3$) δ 2.05 (s, C**H**$_3$CO), 3.41 (s, OC**H**$_3$), 3.48 (dd, J = 7.2, 9.2 Hz, C**H**H'), 3.83 (dd, J = 4.2, 9.2 Hz, CH**H'**), 4.49–4.64 (m, C**H**$_2$N, NC(**H**)CO), 6.48 (br d, J = 6.6 Hz, N**H**C(O)CH_3), 7.08–7.19 (br t, CH_2N**H**), 7.42 (d, J = 8.6 Hz, 2 Ar**H**), 8.18 (d, J = 8.6 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 23.2 (**C**H_3CO), 42.7 (**C**H_2N), 52.6 (**C**HCH_2), 59.1 (O**C**H_3), 71.5 (**C**H_2OCH_3), 123.9, 127.9, 145.5, 147.2 (4 Ar**C**), 170.4, 170.5 (2 **C**(O)).

Preparation of (*R*)-*N*-(4'-Amino)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-32).[7] A MeOH solution (150 mL) of (*R*)-*N*-(4'-nitro)benzyl 2-acetamido-3-methoxypropionamide (2.00 g, 6.8 mmol) was treated with H_2 (1 atm) in presence of PtO_2 (160 mg) at room temperature (16 h). The mixture was carefully filtered through a bed of Celite® and the filtrate was evaporated in vacuo to obtain a colorless oil that was triturated with EtOAc to give 1.67 g of (*R*)-*N*-(4'-amino)benzyl 2-acetamido-3-methoxypropionamide as a white solid (90%): R_f = 0.39 (9/1 $CHCl_3$/MeOH); mp 151–152 °C (lit.[7] mp 183–184 °C); ^{1}H NMR ($CDCl_3$) δ 2.02 (s, C**H**$_3$CO), 3.36 (s, OC**H**$_3$), 3.42 (dd, J = 7.8,

9.3 Hz, C**H**H'), 3.78 (dd, *J* = 4.5, 9.3 Hz, CH**H'**), 4.34 (d, *J* = 5.4 Hz, C**H**$_2$N), 4.48–4.55 (m, NC(**H**)CO), 6.48 (br d, *J* = 6.0 Hz, N**H**C(O)CH$_3$), 6.60–6.67 (m, CH$_2$N**H**, 2 Ar**H**), 7.05 (d, *J* = 8.1 Hz, 2 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-amino)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons.

25. Preparation of (*R*)-*N*-(4'-(2,2,2-Trifluoroacetamido))benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-33).

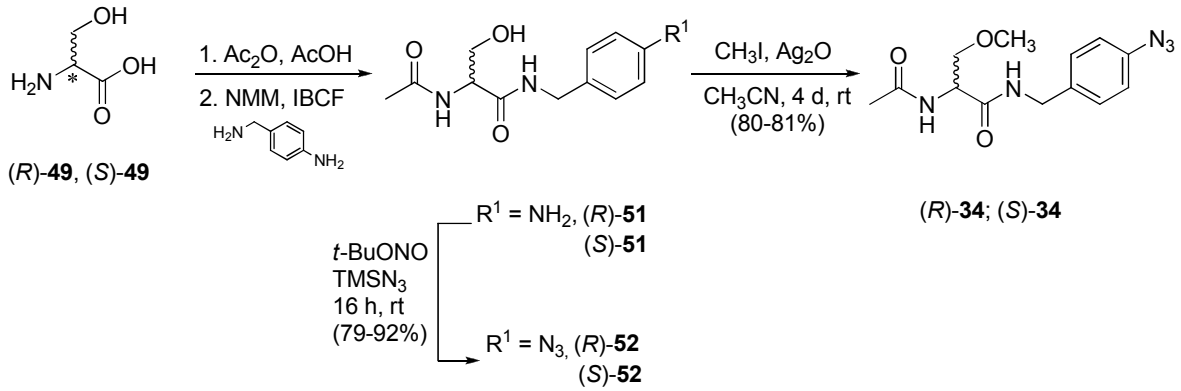


(*R*)-32 (*R*)-33

Preparation of (*R*)-*N*-(4'-(2,2,2-Trifluoroacetamido))benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-33). (*S*)-Ethyltrifluorothioacetate (2.99 g, 18.9 mmol) was added to a MeOH (10 mL) solution of (*R*)-*N*-(4'-amino)benzyl 2-acetamido-3-methoxypropionamide (1.00 g, 3.8 mmol) at room temperature and then the reaction was maintained at this temperature (3 h). Addition of EtOAc (10 mL) led to the precipitation of (*R*)-*N*-(4'-(2,2,2-trifluoroacetamido))benzyl 2-acetamido-3-methoxypropionamide as a white solid (600 mg) after filtration. The filtrate was concentrated in vacuum and the residue purified by flash chromatography on silica gel with EtOAc as the eluant to obtain an additional 350 mg of (*R*)-*N*-(4'-(2,2,2-trifluoroacetamido))benzyl 2-acetamido-3-methoxypropionamide as a white solid. The solids were combined to obtain 950 mg (70%) of (*R*)-*N*-(4'-(2,2,2-trifluoroacetamido))benzyl 2-acetamido-3-methoxypropionamide: R_f = 0.24 (EtOAc); mp 202–204 °C; $[\alpha]^{26}_D$ –1.2° (*c* 0.5,

DMSO); IR (nujol) 3389, 3282, 1721, 1653, 1536, 1459, 1375, 1294, 1249, 1206, 1150, 1066, 974, 896, 838, 727, 653 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.87 (s, C**H**$_3$CO), 3.25 (s, OC**H**$_3$), 3.45–3.55 (m, C**HH**'O), 4.27 (d, J = 5.8 Hz, C**H**$_2$N), 4.44–4.50 (m, C**H**), 7.27 (d, J = 8.7 Hz, 2 Ar**H**), 7.58 (d, J = 8.7 Hz, 2 Ar**H**), 8.11 (d, J = 7.8 Hz, $CH_3C(O)N$**H**), 8.51 (t, J = 5.8 Hz, CH_2N**H**), 11.23 (s, $CF_3C(O)N$**H**); ^{13}C NMR (DMSO-d_6) δ 22.4 (**C**$H_3C(O)$), 41.5 (N**C**H_2), 52.6 (OCH_2**C**H), 58.1 (O**C**H_3), 71.9 (O**C**H_2CH), 115.7 (q, J = 284.6 Hz, **C**F_3), 120.1, 127.4, 134.7, 136.7 (4 Ar**C**), 154.3 (q, J = 37.5 Hz, N**C**(O)CF_3), 169.3, 169.7 (2 **C**(O)); HRMS (M+H$^+$)(ESI$^+$) 362.1321 [M + H$^+$] (calcd for $C_{15}H_{18}F_3N_3O_4H^+$ 362.1328); Anal. Calcd. For $C_{15}H_{18}F_3N_3O_4$: C, 49.86; H, 5.02; F, 15.77; N, 11.63. Found: C, 49.79; H, 4.91; F, 15.66; N, 11.56.

26. Preparation of (*R*)- and (S)-*N*-(4'-Azido)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)- and (*S*)-34).



Preparation of (*R*)-*N*-(4'-(Amino))benzyl 2-Acetamido-3-hydroxypropionamide ((*R*)-51). To a stirred AcOH (80 mL) suspension of (*R*)-serine (10.00 g, 95.24 mmol) was added Ac_2O (9.44 mL, 100.00 mmol), and then the reaction suspension was stirred at room temperature (24 h). The AcOH was removed in vacuo to give an oily residue, and then THF (600 mL) was added to the residue. The solution was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (15.7 mL, 142.9 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (15.7 mL, 120.1

mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min and then 4-aminobenzylamine (12.9 mL, 114.3 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and then the white solid filtered and the organic layer concentrated in vacuo. The residue was purified by flash column chromatography on silica gel with MeOH/$CHCl_3$ (10/70) as the eluant to obtain (*R*)-*N*-(4'-(amino))benzyl 2-acetamido-3-hydroxypropionamide (3.35 g, 14%) as a white: R_f = 0.30 (1/7 MeOH/$CHCl_3$); mp 158–160 °C; $[\alpha]^{26}_D$ +18.3° (*c* 1.0, MeOH); IR (nujol) 3302, 2924, 2359, 1630, 1551, 1458 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.86 (s, C**H**$_3$C(O)), 3.55 (t, *J* = 5.6 Hz, C**H**$_2$OH), 4.06 (1/2**H**H'$_q$, *J* = 5.9, 14.7 Hz, C**H**H'Ar), 4.12 (1/2H**H'**$_q$, *J* = 5.9, 14.7 Hz, CH**H'**Ar), 4.24–4.30 (m, C**H**), 4.85 (t, *J* = 5.6 Hz, O**H**), 4.94 (s, N**H**$_2$), 6.46–6.50 (m, 2 Ar**H**), 6.88–6.91 (m, 2 Ar**H**), 7.88 (d, *J* = 7.8 Hz, N**H**CH), 8.14 (t, *J* = 5.9 Hz, N**H**CH$_2$); ^{13}C NMR (DMSO-d_6) δ 22.7 (**C**H$_3$C(O)), 41.8 (**C**H$_2$Ph), 55.2 (**C**H), 61.8 (**C**H$_2$OH), 113.6, 126.1, 128.0, 147.4 (4 Ar**C**), 169.3, 169.8 (2 **C**(O)); HRMS (M+H$^+$)(ESI$^+$) 252.1344 [M + H$^+$] (calcd. for $C_{12}H_{18}N_3O_3$ 252.1348); Anal. Calcd. for $C_{12}H_{17}N_3O_3$: C, 57.36; H, 6.82; N, 16.72. Found: C, 57.13; H, 6.87; N, 16.55.

Preparation of (*S*)-*N*-(4'-(Amino))benzyl 2-Acetamido-3-hydroxypropionamide ((*S*)-51). Using L-serine (10.00 g, 95.24 mmol), Ac_2O (9.44 mL, 100.00 mmol), and the preceding procedure gave 3.30 g (14%) of (*S*)-*N*-(4'-(amino))benzyl 2-acetamido-3-hydroxypropionamide as a white solid: R_f = 0.30 (1/7 MeOH/$CHCl_3$); mp 158–160 °C; $[\alpha]^{26}_D$ –18.7° (*c* 1.0, MeOH); IR (nujol) 3280, 2923, 1628, 1551, 1458 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.86 (s, C**H**$_3$C(O)), 3.55 (t, *J* = 5.6 Hz, C**H**$_2$OH), 4.06 (1/2**H**H'$_q$, *J* = 5.9, 14.7 Hz, C**H**H'Ar), 4.12 (1/2H**H'**$_q$, *J* = 5.9, 14.7 Hz, CH**H'**Ar), 4.24–4.30 (m, C**H**), 4.86 (t, *J* = 5.6 Hz, O**H**), 4.94 (s, N**H**$_2$), 6.46–6.51 (m, 2 Ar**H**), 6.88–6.91 (m, 2 Ar**H**), 7.88 (d, *J* = 7.8 Hz, N**H**CH), 8.14 (t, *J* = 5.9 Hz, N**H**CH$_2$); ^{13}C NMR (DMSO-d_6) δ 22.7 (**C**H$_3$C(O)), 41.8 (**C**H$_2$Ph), 55.2 (**C**H), 61.8 (**C**H$_2$OH), 113.7, 126.1, 128.1, 147.4 (4 Ar**C**), 169.3, 169.9 (2 **C**(O)); HRMS (M+H$^+$)(ESI$^+$) 252.1344 [M + H$^+$] (calcd. for

$C_{12}H_{18}N_3O_3$ 252.1348); Anal. Calcd. for $C_{12}H_{17}N_3O_3$: C, 57.36; H, 6.82; N, 16.72. Found: C, 57.12; H, 6.84; N, 16.43.

Preparation of (*R*)-*N*-(4'-Azido)benzyl 2-Acetamido-3-hydroxypropionamide ((*R*)-52). To a cooled (0 °C) CH_3CN solution (70 mL) of (*R*)-*N*-(4'-(amino))benzyl 2-acetamido-3-hydroxypropionamide (2.40 g, 9.56 mmol) maintained under Ar, *t*-BuONO (3.41 mL, 28.68 mmol) followed by $TMSN_3$ (3.02 mL, 22.94 mmol) were slowly added. The resulting solution was allowed to stir at room temperature (16 h) under Ar. The solvent was removed in vacuo, and the product was purified by column chromatography (SiO_2; 1/9 MeOH/$CHCl_3$) to give 2.10 g (79%) of (*R*)-*N*-(4'-azido)benzyl 2-acetamido-3-hydroxypropionamide as a white solid: R_f = 0.35 (1/9 MeOH/$CHCl_3$); mp 161–163 °C; $[\alpha]^{26}_D$ +13.2° (*c* 1.0, MeOH); IR (nujol) 3268, 2924, 2128, 1649, 1553, 1459 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.87 (s, C**H**$_3$C(O)), 3.58 (t, *J* = 5.7 Hz, C**H**$_2$OH), 4.26–4.32 (m, C**H**$_2$Ar, C**H**), 4.91 (t, *J* = 5.7 Hz, O**H**), 7.03–7.08 (m, 2 Ar**H**), 7.28–7.31 (m, 2 Ar**H**), 7.94 (d, *J* = 8.1 Hz, N**H**CH), 8.40 (t, *J* = 6.0 Hz, N**H**CH_2); ^{13}C NMR (DMSO-d_6) δ 22.7 (**C**H_3C(O)), 41.5 (**C**H_2Ph), 55.3 (**C**H), 61.7 (**C**H_2OH), 118.9, 128.7, 136.5, 137.7 (4 Ar**C**), 169.4, 170.3 (2 **C**(O)); HRMS (M+H^+)(ESI^+) 278.1249 [M + H^+] (calcd. for $C_{12}H_{16}N_5O_3$ 278.1253); Anal. Calcd. for $C_{12}H_{15}N_5O_3$: C, 51.98; H, 5.45; N, 25.26. Found: C, 51.93; H, 5.47; N, 24.98.

Preparation of (*S*)-*N*-(4'-Azido)benzyl 2-Acetamido-3-hydroxypropionamide ((*S*)-52). Using (*S*)-*N*-(4'-(amino))benzyl 2-acetamido-3-hydroxypropionamide (2.80 g, 11.16 mmol), t-BuONO (3.98 mL, 33.48 mmol), $TMSN_3$ (3.52 mL, 26.78 mmol), and the preceding procedure gave 2.85 g (92%) of (*S*)-*N*-(4'-azido)benzyl 2-acetamido-3-hydroxypropionamide as a white solid: R_f = 0.35 (1/9 MeOH/$CHCl_3$); mp 161–162 °C; $[\alpha]^{26}_D$ –13.6° (*c* 1.0, MeOH); IR (nujol) 3267, 2924, 2129, 1648, 1552, 1459 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.87 (s, C**H**$_3$C(O)), 3.58 (t, *J* = 5.6 Hz, C**H**$_2$OH), 4.26–4.31 (m, C**H**$_2$Ar, C**H**), 4.91 (t, *J* = 5.6 Hz, O**H**), 7.03–7.08 (m, 2 Ar**H**), 7.27–7.32 (m, 2 Ar**H**), 7.94 (d, *J* = 7.8 Hz, N**H**CH), 8.40 (t, *J* = 6.0 Hz, N**H**CH_2); ^{13}C NMR (DMSO-d_6) δ 22.6 (**C**H_3C(O)),

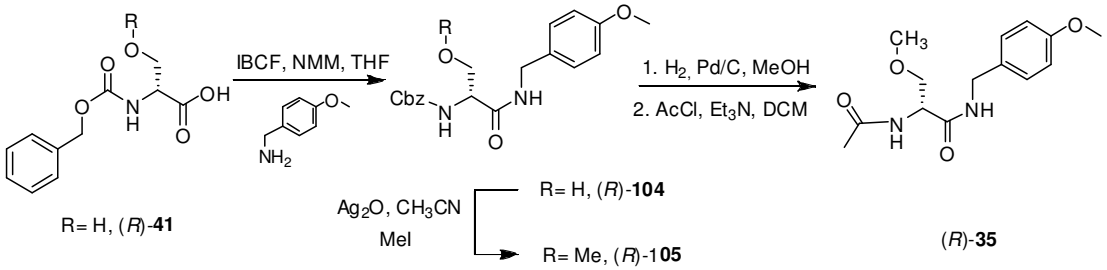
41.5 (**C**H_2Ph), 55.3 (**C**H), 61.7 (**C**H_2OH), 118.9, 128.7, 136.5, 137.7 (4 Ar**C**), 169.4, 170.3 (2 **C**(O)); HRMS (M+H^+)(ESI^+) 278.1248 [M + H^+] (calcd. for $C_{12}H_{16}N_5O_3$ 278.1253); Anal. Calcd. for $C_{12}H_{15}N_5O_3$: C, 51.98; H, 5.45; N, 25.26. Found: C, 52.08; H, 5.51; N, 25.00.

Preparation of (*R*)-*N*-(4'-Azido)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-34). Ag_2O (4.85 g, 20.94 mmol) was added to a CH_3CN solution (100 mL) of (*R*)-*N*-(4'-azido)benzyl 2-acetamido-3-hydroxypropionamide (1.16 g, 4.19 mmol) and CH_3I (2.61 mL, 41.89 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature in the dark (5 d), filtered through a pad of Celite®, and the filtrate concentrated in vacuo. The solid was purified by flash column chromatography on silica gel (1/9 MeOH/$CHCl_3$) to obtain 0.98 g (80%) of (*R*)-*N*-(4'-azido)benzyl 2-acetamido-3-methoxypropionamide as a white solid: R_f = 0.5 (1/9 MeOH/$CHCl_3$); mp 149-150 °C; $[\alpha]^{26}_D$ −15.2° (*c* 1.0, MeOH); IR (nujol) 3285, 2931, 2113, 1635, 1560, 1456 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.03 (s, C**H**$_3$C(O)), 3.38 (s, OC**H**$_3$), 3.44 (dd, *J* = 7.5, 9.3 Hz, C**H**H'OCH_3), 3.80 (dd, *J* = 4.2, 9.3 Hz, CH**H'**OCH_3), 4.40 (1/2**H**H'$_q$, *J* = 6.2, 15.0 Hz, C**H**H'Ar), 4.46 (1/2H**H'**$_q$, *J* = 6.2, 15.0 Hz, CH**H'**Ar), 4.52–4.58 (m, C**H**), 6.48 (br d, *J* = 6.3 Hz, N**H**CH), 6.82–6.85 (br m, N**H**CH_2), 6.96–7.01 (m, 2 Ar**H**), 7.23–7.28 (m, 2 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-azido)benzyl 2-acetamido-3-methoxypropionamide gave only a single signal for the acetyl methyl protons and the ether methyl protons, addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-azido)benzyl 2-acetamido-3-methoxypropionamide and (*S*)-*N*-(4'-azido)benzyl 2-acetamido-3-methoxypropionamide (1:2 ratio) gave two signals for the acetyl methyl protons (δ 1.995 (*R*) and 2.010 (*S*) (Δppm = 0.015)), and two signals for the ether methyl protons (δ 3.302 (*S*) and 3.342 (*R*) (Δppm = 0.040)); ^{13}C NMR ($CDCl_3$) δ 23.4 (**C**H_3C(O)), 43.1 (**C**H_2Ph), 52.7 (**C**H), 59.3 (CH_2O**C**H_3), 71.8 (**C**H_2OCH_3), 119.5, 129.1, 134.9, 139.5 (4 Ar**C**), 170.2, 170.5 (2 **C**(O)); HRMS (ESI) 292.1406 [M + H^+] (calcd. for $C_{13}H_{18}N_5O_3$ 292.1410); Anal.

Calcd. for $C_{13}H_{17}N_5O_3$: C, 53.60; H, 5.88; N, 24.04. Found: C, 53.72; H, 5.91; N, 23.84.

Preparation of (*S*)-*N*-(4'-Azido)benzyl 2-Acetamido-3-methoxypropionamide ((*S*)-34). Utilizing the preceding procedure, (*S*)-*N*-(4'-azido)benzyl 2-acetamido-3-hydroxypropionamide (2.40 g, 8.66 mmol), Ag_2O (10.04 g, 43.30 mmol), and MeI (5.40 mL, 86.60 mmol) gave crude (*S*)-*N*-(4'-azido)benzyl 2-acetamido-3-methoxypropionamide after 4 d. The product was purified by column chromatography (SiO_2; 1/9 MeOH/$CHCl_3$) to obtain 2.05 g (81%) of (*S*)-*N*-(4'-azido)benzyl 2-acetamido-3-methoxypropionamide as a white solid: R_f = 0.50 (1/9 MeOH/$CHCl_3$); mp 149–150 °C; $[\alpha]^{26}_D$ +15.4° (*c* 1.0, MeOH); IR (nujol) 3285, 2927, 2112, 1635, 1565, 1457 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.03 (s, C**H**$_3$C(O)), 3.38 (s, OC**H**$_3$), 3.43 (dd, *J* = 7.5, 9.0 Hz, C**H**H'OCH$_3$), 3.81 (dd, *J* = 4.2, 9.0 Hz, CH**H'**OCH$_3$), 4.40 (1/2**H**H'$_q$, *J* = 6.0, 15.0 Hz, C**H**H'Ar), 4.46 (1/2H**H'**$_q$, *J* = 6.0, 15.0 Hz, CH**H'**Ar), 4.51–4.57 (m, C**H**), 6.43 (br d, *J* = 6.3 Hz, N**H**CH), 6.78–6.83 (br m, N**H**CH$_2$), 6.96–7.01 (m, 2 Ar**H**), 7.23–7.27 (m, 2 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*S*)-*N*-(4'-azido)benzyl 2-acetamido-3-methoxypropionamide gave only a single signal for the acetyl methyl protons and the ether methyl protons, addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-azido)benzyl 2-acetamido-3-methoxypropionamide and (*S*)-*N*-(4'-azido)benzyl 2-acetamido-3-methoxypropionamide (1:2 ratio) gave two signals for the acetyl methyl protons (δ 1.995 (*R*) and 2.010 (*S*) (Δppm = 0.015)), and the ether methyl protons (δ 3.302 (*S*) and 3.342 (*R*) (Δppm = 0.040)); ^{13}C NMR ($CDCl_3$) δ 23.3 (**C**H$_3$C(O)), 43.1 (**C**H$_2$Ph), 52.7 (**C**H), 59.2 (CH$_2$O**C**H$_3$), 72.0 (**C**H$_2$OCH$_3$), 119.4, 129.1, 135.0, 139.4 (4 Ar**C**), 170.3, 170.6 (2 **C**(O)); HRMS (M+H$^+$)(ESI$^+$) 292.1405 [M + H$^+$] (calcd. for $C_{13}H_{18}N_5O_3$ 292.1410); Anal. Calcd. for $C_{13}H_{17}N_5O_3$: C, 53.60; H, 5.88; N, 24.04. Found: C, 53.76; H, 5.97; N, 24.22.

27. Preparation of (*R*)-*N*-(4'-Methoxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-35).



Preparation of (*R*)-*N*-(4'-Methoxy)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-hydroxypropionamide ((*R*)-104). A THF solution (100 mL) of *(R)*-Cbz-serine (7.00 g, 29.3 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (3.9 mL, 35.1 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (4.6 mL, 35.1 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was stirred (2 min). 4-Methoxybenzylamine (4.84 g, 35.1 mmol) was added portionwise at -78 °C, and the mixture was stirred at room temperature (2 h). The white solid was filtered and the organic layer was concentrated in vacuo. The residue was triturated with EtOAc resulting in a solid that was filtered and recrystallized with EtOAc to give (*R*)-*N*-(4'-methoxy)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide as a white solid (5.05 g, 48%): R_f = 0.62 (EtOAc); mp 134–135 °C; $[\alpha]^{24}_D$ –9.3° (*c* 1.0, DMSO); IR (nujol) 3336, 3255, 3107, 1710, 1645, 1577, 1519, 1457, 1377, 1313, 1245, 1174, 1045, 917 cm^{-1};^{1}H NMR (DMSO-d_6) δ 3.53–3.64 (m, C**H$_2$**OH), 3.72 (s, OC**H$_3$**), 4.03–4.11 (m, NC**H**), 4.21 (d, *J* = 5.4 Hz, NC**H$_2$**), 4.88 (t, *J* = 5.7 Hz, O**H**), 5.04 (s, C**H$_2$**O), 6.85 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.17 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.22 (d, *J* = 7.8 Hz, OC(O)N**H**), 7.28–7.38 (m, 5 Ar**H**), 8.30–8.38 (br t, CH_2N**H**); ^{13}C NMR (DMSO-d_6) δ 41.4 (N**C**H_2), 54.9 (**C**H_3O), 57.3 (OCH_2**C**H), 61.7 (O**C**H_2CH), 65.4 (**C**H_2O), 113.5, 127.6, 128.2, 131.1, 136.9 (5 Ar**C**), 155.8 (C(O)), 158.0 (**C**OMe), 169.9 (C(O)), the remaining aromatic peaks were not detected and are believed to overlap with the observed signals; HRMS (M+H$^+$)(ESI$^+$) 359.1602 [M + H$^+$]

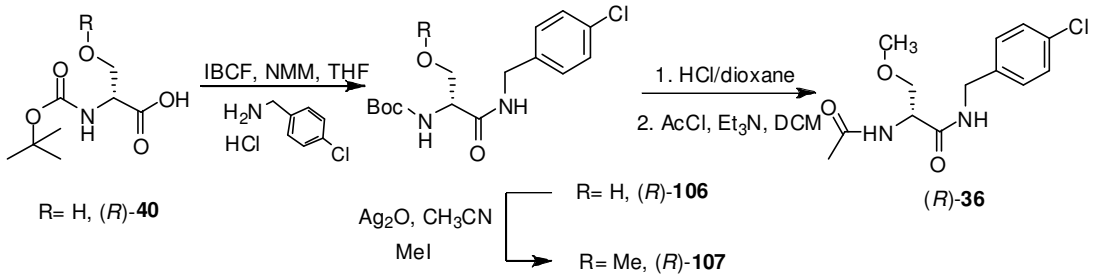
(calcd for $C_{19}H_{22}N_2O_5H^+$ 359.1607); Anal. Calcd. for $C_{19}H_{22}N_2O_5 \cdot 0.05H_2O$: C, 63.51; H, 6.20; N, 7.80. Found: C, 63.24; H, 6.26; N, 7.72.

Preparation of (*R*)-*N*-(4'-Methoxy)benzyl 2-*N*-(Benzyloxycarbonyl)amino-3-methoxypropionamide ((*R*)-105). Ag_2O (11.60 g, 50.2 mmol) was added to a CH_3CN solution (100 mL) of (*R*)-*N*-(4'-methoxy)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-hydroxypropionamide (3.60 g, 10.1 mmol) and CH_3I (6.3 mL, 101.0 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature (2 d), filtered through a pad of Celite®, and the filtrate concentrated in vacuo. The residue was dissolved in EtOAc (20 mL) and passed through a pad of silica gel (Dynamic Adsorbents Inc., Cat # 02826-25) using EtOAc (500 mL). The filtrate was concentrated in vacuo, and the solid was recrystallized with MeOH to obtain 2.61 g (70%) of (*R*)-*N*-(4'-methoxy)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide as a white solid: R_f = 0.89 (EtOAc); mp 128–130 °C; $[\alpha]^{25}_D$ –14.7° (*c* 1.0, DMSO); IR (nujol) 3294, 3086, 2860, 1649, 1548, 1458, 1380, 1304, 1243, 1171, 1128, 1047, 963, 821, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.35 (s, OC**H$_3$**), 3.48 (dd, *J* = 6.9, 9.3 Hz, C**H**H'), 3.79 (s, C_6H_4OC**H$_3$**), 3.85 (dd, *J* = 3.9, 9.3 Hz, CH**H'**), 4.28–4.36 (br m, C**H**CH_2), 4.40 (d, *J* = 5.7 Hz, C**H$_2$**N), 5.11 (s, OC**H$_2$**), 5.60–5.72 (br s, OC(O)N**H**), 6.58–6.68 (br s, CH_2N**H**), 6.85 (d, *J* = 8.6 Hz, 2 Ar**H**), 7.17 (d, *J* = 8.6 Hz, 2 Ar**H**), 7.31–7.36 (m, 5 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 43.1 (N**C**H_2), 54.3 (OCH_2**C**H), 55.3 (ArO**C**H_3), 59.1 (O**C**H_3), 67.2 (Ph**C**H_2O), 72.0 (O**C**H_2CH), 114.1, 128.2, 128.3, 128.6, 128.9, 129.9, 136.1 (7 Ar**C**), 159.1 (O**C**(O)), 169.7 (C(O)), the remaining aromatic peak was not detected and is believed to overlap with the observed signals; HRMS (M+H^+)(ESI$^+$) 373.1765 [M + H^+] (calcd for $C_{20}H_{24}N_2O_5H^+$ 373.1763); Anal. Calcd. for $C_{20}H_{24}N_2O_5$: 64.50; H, 6.50; N, 7.52. Found: C, 64.25; H, 6.50; N, 7.52.

Preparation of (*R*)-*N*-(4'-Methoxy)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-35). A MeOH solution (300 mL) of (*R*)-*N*-(4'-methoxy)benzyl 2-*N*-(benzyloxycarbonyl)amino-3-methoxypropionamide (2.40 g,

6.4 mmol) was treated with H_2 (1 atm) in presence of 10% Pd/C (480 mg) at room temperature (16 h). The mixture was carefully filtered through a bed of Celite® and the filtrate was evaporated in vacuo to obtain a colorless oil. The oil was dissolved in CH_2Cl_2 (100 mL) and then triethylamine (1.1 mL, 7.74 mmol) and acetyl chloride (550 μL, 7.74 mmol) were carefully added at 0 °C and the resulting solution was stirred at room temperature (2 h). An aqueous 10% citric acid solution (100 mL) was added and the organic layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, washed with a saturated $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), and concentrated in vacuo. After trituration of the residue with EtOAc, (*R*)-*N*-(4'-methoxy)benzyl 2-acetamido-3-methoxypropionamide was obtained as a white solid (900 mg, 70%): R_f = 0.82 (EtOAc); mp 146–147 °C; $[\alpha]^{25}_D$ –26.0° (*c* 0.5 , $CHCl_3$); IR (nujol) 3283, 2861, 1642, 1520, 1458, 1377, 1299, 1255, 1176, 1127, 1031, 978, 719 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.02 (s, C**H**$_3$CO), 3.37 (s, OC**H**$_3$), 3.43 (dd, *J* = 7.8, 9.3 Hz, C**H**H'), 3.76–3.81 (m, C**H**$_3$OC$_6$H$_4$, CH**H'**), 4.39 (d, *J* = 6.0 Hz, C**H**$_2$N), 4.50–4.57 (m, C**H**), 6.49 (br d, *J* = 6.0 Hz, N**H**C(O)CH$_3$), 6.71–6.82 (br t, CH$_2$N**H**), 6.86 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.18 (d, *J* = 8.4 Hz, 2 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-methoxy)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.2 (**C**H$_3$CO), 43.0 (**C**H$_2$N), 52.4 (**C**HCH$_2$), 55.3 (C$_6$H$_4$O**C**H$_3$), 59.0 (O**C**H$_3$), 71.7 (**C**H$_2$OCH$_3$), 114.1, 128.8, 129.9, 159.0 (4 Ar**C**), 169.8, 170.3 (2 **C**(O)); HRMS (M+Na$^+$)(ESI$^+$) 303.1320 [M + Na$^+$] (calcd for $C_{14}H_{20}N_2O_4Na^+$ 303.1321); Anal. Calcd. for $C_{14}H_{20}N_2O_4$: C, 59.99; H, 7.19; N, 9.99. Found: C, 60.04; H, 7.32; N, 9.86.

28. Preparation of (*R*)-*N*-(4'-Chloro)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-36).



Preparation of (*R*)-*N*-(4'-Chloro)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-106). A THF solution (400 mL) of (*R*)-*t*-Boc-serine (10.00 g, 48.8 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (6.4 mL, 58.5 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (7.6 mL, 58.5 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min and then 4-chlorobenzylamine (8.28 g, 58.5 mmol) was added portionwise at -78 °C. The mixture was allowed to stir at room temperature (2 h), and then the white solid filtered and the organic layer concentrated in vacuo The residue was recrystallized with EtOAc to obtain (*R*)-*N*-(4'-chloro)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide as a white solid (8.30 g, 52%): R_f = 0.76 (EtOAc); mp 130–131 °C; $[\alpha]^{26.2}_D$ +32.0° (*c* 1.0, $CHCl_3$); IR (nujol) 3293, 2861, 1652, 1519, 1458, 1374, 1303, 1246, 1163, 1090, 1012, 848, 783 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, C(C**H**$_3$)$_3$), 3.31–3.42 (br s, O**H**), 3.61–3.74 (m, C**H**H'), 4.05–4.19 (m, CH**H'**, C**H**), 4.30–4.49 (br m, C**H**$_2$N), 5.66 (br d, *J* = 7.2 Hz, *t*-BocN**H**), 7.15–7.22 (br s, CH_2N**H**, 2 Ar**H**), 7.27 (d, *J* = 8.7 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 28.2(C(**C**H$_3$)$_3$), 42.6 (N**C**H$_2$), 54.8 (OCH$_2$**C**H), 62.7 (O**C**H$_2$CH), 80.7 (O**C**H(CH$_3$)$_3$), 128.7, 128.8, 133.3, 136.3 (4 Ar**C**), 156.3 (N**C**(O)O), 171.4 (**C**(O)); HRMS (M+H$^+$)(ESI$^+$) 323.1267 [M + H$^+$] (calcd for $C_{15}H_{21}ClN_2O_4H^+$ 323.1267); Anal. Calcd. for $C_{15}H_{21}ClN_2O_4$: C, 54.79; H, 6.44; Cl, 10.78; N, 8.52. Found: C, 54.96; H, 6.28; Cl, 10.91; N, 8.66.

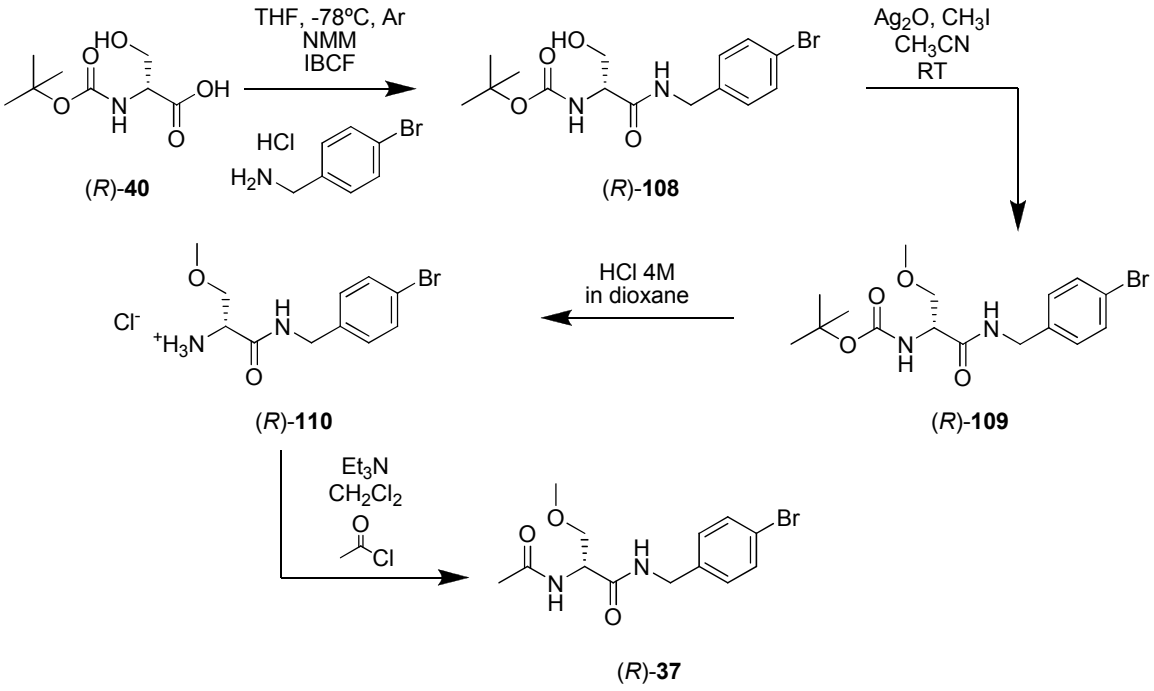
Preparation of (*R*)-*N*-(4'-Chloro)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-107). Ag_2O (28.50 g, 122.0 mmol) was added to a CH_3CN solution (450 mL) of (*R*)-*N*-(4'-chloro)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide (8.00 g, 24.4 mmol) and CH_3I (15.2 mL, 244.0 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature in the dark (2 d), filtered through a pad of Celite®, and the filtrate concentrated in vacuo. The residue was recrystallized in EtOAc to obtain (*R*)-*N*-(4'-chloro)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide as a white solid (4.70 g, 56%): R_f = 0.77 (EtOAc/hexanes 5/5); mp 74–75 °C; $[\alpha]^{24.5}_D$ –20.1° (*c* 1.0, $CHCl_3$); IR (nujol) 3327, 3255, 3181, 2966, 2903, 2728, 1660, 1529, 1458, 1374, 1301, 1245, 1162, 1093, 1018, 944, 862, 808, 777 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, C(C**H**$_3$)$_3$), 3.37 (s, OC**H**$_3$), 3.49 (dd, *J* = 6.3, 9.3 Hz, C**H**H'), 3.83 (dd, *J* = 3.9, 9.3 Hz, CH**H'**), 4.22–4.33 (br m, C**H**CH_2), 4.38–4.51 (m, C**H**$_2$N), 5.36–5.48 (br s, OC(O)N**H**), 6.82 (t, *J* = 5.4 Hz, CH_2N**H**), 7.19 (d, *J* = 8.2 Hz, 2 Ar**H**), 7.28 (d, *J* = 8.2 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 28.2 (C(**C**H_3)$_3$), 42.7 (N**C**H_2), 54.0 (OCH_2**C**H), 59.1 (O**C**H_3), 72.0 (O**C**H_2CH), 80.4 (O**C**(CH_3)$_3$), 128.7, 133.2, 136.6 (3 Ar**C**), 155.5 (N**C**(O)O), 170.4 (**C**(O)), one signal was not detected and is believed to overlap with nearby peaks; HRMS (M+H$^+$)(ESI$^+$) 343.1424 [M + H$^+$] (calcd for $C_{16}H_{23}ClN_2O_4H^+$ 343.1424); Anal. Calcd. for $C_{16}H_{23}ClN_2O_4$: C, 56.06; H, 6.77; Cl, 10.34; N, 8.17. Found: C, 56.19; H, 6.77; Cl, 10.07; N, 8.17.

Preparation of (*R*)-*N*-(4'-Chloro)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-36). A saturated HCl solution in dioxane (1 mmol/2 mL, 24.0 mL) was added to (*R*)-*N*-(4'-chloro)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide (4.10 g, 12.0 mmol) at 0 °C and the solution was stirred at room temperature (2 h). The reaction solution was concentrated in vacuo and dried (30 min).

The oil was dissolved in CH_2Cl_2 (50 mL) and then triethylamine (5.0 mL, 36.00 mmol) and acetyl chloride (1.3 mL, 18.0 mmol) were carefully added at 0 °C and the resulting solution was stirred at room temperature (2 h). An aqueous

10% citric acid solution (50 mL) was added and the organic layer was extracted with CH_2Cl_2 (3 x 50 mL). The organic layers were combined, washed with a saturated $NaHCO_3$ solution (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The solid was recrystallized with EtOAc to obtain (*R*)-*N*-(4'-chloro)benzyl 2-acetamido-3-methoxypropionamide (3.10 g, 80%) as a white solid: R_f = 0.42 (EtOAc); mp 155 °C; $[\alpha]^{27.0}_D$ –20.5° (*c* 1 , $CHCl_3$); IR (nujol) 3288, 3277, 3162, 2900, 1634, 1556, 1457, 1375, 1306, 1259, 1193, 1137, 1098, 1045, 964, 909, 801, 732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.01 (s, C**H$_3$**CO), 3.37 (s, OC**H$_3$**), 3.43 (dd, *J* = 7.8, 9.2 Hz, C**H**H'), 3.78 (dd, *J* = 4.2, 9.2 Hz, CH**H'**), 4.34–4.49 (m, C**H$_2$**N), 4.54–4.61 (m, C**H**), 6.54 (br d, *J* = 6.6 Hz, N**H**C(O)CH_3), 6.94–7.03 (br t, CH_2N**H**), 7.19 (d, *J* = 8.8 Hz, 2 Ar**H**), 7.29 (d, *J* = 8.8 Hz, 2 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-chloro)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.1 (**C**H_3CO), 42.8 (**C**H_2N), 52.5 (**C**HCH_2), 59.1 (O**C**H_3), 71.7 (**C**H_2OCH_3), 128.7, 133.2, 136.4, (3 Ar**C**), 170.1, 170.4 (2 **C**(O)), one signal was not detected and is believed to overlap with nearby peaks; HRMS (M+H$^+$)(ESI$^+$) 285.1006 [M + H$^+$] (calcd for $C_{13}H_{17}ClN_2O_3H^+$ 285.1006); Anal. Calcd. for $C_{13}H_{17}ClN_2O_3$: C, 54.84; H, 6.02; Cl, 12.45; N, 9.84. Found: C, 54.71; H, 5.95; Cl, 12.37; N, 9.76.

29. Preparation of (*R*)-*N*-(4'-Bromo)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-37).



Preparation of (*R*)-*N*-(4'-Bromo)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-108). A THF solution (180 mL) of (*R*)-Boc-serine (4.61 g, 22.47 mmol) was stirred and cooled at -78 ºC under Ar, and then 4-methylmorpholine (NMM) (3.0 mL, 26.96 mmol) was added dropwise. After 2 minutes of stirring at this temperature, isobutylchloroformate (IBCF) (3.5 mL, 26.96 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 minutes. Then a THF (50 mL) solution of 4-bromobenzylamine hydrochloride (6.00 g, 26.96 mmol) and NMM (3.2 mL, 29.21 mmol) was added portionwise at -78 ºC. The mixture was stirred at -78 ºC (5 min) and then at room temperature (2 h). The white solid was filtered and the organic layer was concentrated in vacuo. The residue was recrystallized with EtOAc to obtain (*R*)-*N*-(4'-bromo)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide as a white solid (6.19 g, 74%): R_f = 0.50 (7/3, EtOAc/hexanes); mp 132–133 ºC; $[\alpha]^{25}_D$ +30.5º (*c* 1.0, $CHCl_3$); IR (nujol) 3319, 2955, 2912, 2861, 1653, 1522, 1458, 1374, 1304, 1249, 1165, 1073, 1014, 781, 658, 591, 552, 468 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.39 (s, C(C**H**$_3$)$_3$), 3.45–3.64 (m, C**H**$_2$OH), 3.95–4.00 (m, C**H**), 4.18–4.32 (m, C**H**$_2$N), 4.80–4.86 (br s, O**H**), 6.69 (d, *J* = 8.1 Hz, C(O)N**H**), 7.22 (d, *J* = 8.4 Hz, 2 Ar**H**),

7.47 (d, J = 8.4 Hz, 2 Ar**H**), 8.38 (t, J = 6.0 Hz, CH_2N**H**); ^{13}C NMR ($CDCl_3$) δ 28.2 ($C(\mathbf{C}H_3)_3$), 42.7 ($N\mathbf{C}H_2$), 54.7 ($OCH_2\mathbf{C}H$), 62.7 ($O\mathbf{C}H_2CH$), 80.8 ($\mathbf{C}(CH_3)_3$), 121.4, 129.1, 131.8, 136.8 (4 Ar**C**), 156.4 (N**C**(O)O), 171.5 (**C**(O)); HRMS (+ESI) 395.08 $[M+Na]^+$ (100%), 397.03 $[M+2+Na]^+$ (100%) (calcd for $C_{15}H_{21}BrN_2O_4Na^+$ 395.06 $[M+Na]^+$); Anal. Calcd for $C_{15}H_{21}BrN_2O_4$: C, 48.27; H, 5.67; Br, 21.41; N, 7.51. Found: C, 48.08, H, 5.63; Br, 21.41; N, 7.44.

Preparation of (*R*)-*N*-(4'-Bromo)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-109). Ag_2O (18.60 g, 80.4 mmol) was added to a CH_3CN solution (300 mL) of (*R*)-*N*-(4'-bromo)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide (6.00 g, 16.0 mmol) and CH_3I (10.0 mL, 160.8 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature in the dark (2 d), filtered through a Celite® pad, and the filtrate was concentrated in vacuo. The residue was purified by liquid chromatography on silica gel with EtOAc/hexanes (3/7 to 5/5) as the eluant to obtain (*R*)-*N*-(4'-bromo)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide as a white solid (2.34 g, 38%): R_f = 0.69 (7/3, EtOAc/hexanes); mp 84–85 ºC; $[\alpha]^{25}_D$ –12.7º (c 1.0, $CHCl_3$); IR (nujol) 3426, 3258, 3055, 2978, 2932, 1672, 1527, 1372, 1260, 1166, 1122, 1018, 948, 864, 740, 641, 479 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.44 (s, $C(C\mathbf{H_3})_3$), 3.37 (s, $OC\mathbf{H_3}$), 3.49 (dd, J = 6.3, 9.2 Hz, C**H**H'), 3.84 (dd, J = 3.6, 9.2 Hz, CH**H'**), 4.20–4.32 (br s, C**H**), 4.43 (d, J = 4.2 Hz, $C\mathbf{H_2}N$), 5.35–5.43 (br s, C(O)N**H**), 6.72–6.82 (br t, CH_2N**H**), 7.14 (d, J = 8.6 Hz, 2 Ar**H**), 7.44 (d, J = 8.6 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 28.2 ($C(\mathbf{C}H_3)_3$), 42.7 ($N\mathbf{C}H_2$), 54.0 ($OCH_2\mathbf{C}H$), 59.1 ($O\mathbf{C}H_3$), 72.0 ($O\mathbf{C}H_2CH$), 80.4 ($\mathbf{C}(CH_3)_3$), 121.2, 129.1, 131.7, 137.1 (4 Ar**C**), 155.6 (N**C**(O)O), 170.4 (**C**(O)); HRMS (+ESI) 409.2 $[M+Na]^+$ (100%), 411.1 $[M+2+Na]^+$ (100%) (calcd for $C_{16}H_{23}BrN_2O_4Na^+$ 409.1 $[M+Na]^+$); Anal. Calcd for $C_{16}H_{23}BrN_2O_4$: C, 49.62; H, 5.99; Br, 20.63; N, 7.23. Found: C, 49.82, H, 6.09; Br, 20.60; N, 7.15.

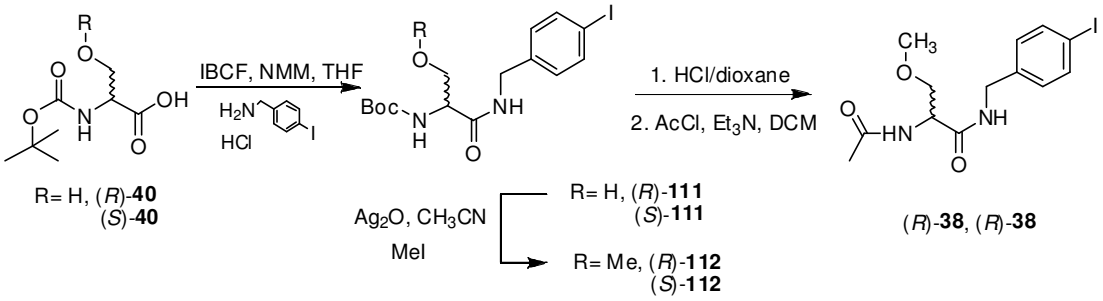
Preparation of (*R*)-*N*-(4'-Bromo)benzyl 2-Amino-3-methoxypropionamide Hydrochloride ((*R*)-110). HCl (4M in dioxane, 16 mL)

was added at 0ºC to (*R*)-*N*-(4'-bromo)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide (2.24 g, 5.78 mmol). The solution was stirred at room temperature overnight. The reaction was concentrated in vacuo, and triturated in Et_2O to obtain (*R*)-*N*-(4'-bromo)benzyl 2-amino-3-methoxypropionamide hydrochloride as a white solid (1.18 g, 63%): R_f = 0.13 (EtOAc); mp 165–167 ºC; $[\alpha]^{25}_D$ +1.2º (*c* 1.0, MeOH); IR (nujol) 3323, 2964, 2861, 2716, 1617, 2467, 1965, 1660, 1567, 14.61, 1374, 1265, 1133, 1017, 955, 798, 726, 648, 476, 432 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.30 (s, OC**H$_3$**), 3.67–3.77 (m, CHC**H$_2$**), 4.07 (t, *J* = 4.8 Hz, C**H**), 4.25–4.39 (m, NC**H$_2$**), 7.25 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.53 (d, *J* = 8.4 Hz, 2 Ar**H**), 8.26–8.42 (br s, N**H$_3^+$**), 9.20 (t, *J* = 5.7 Hz, N**H**); ^{13}C NMR (DMSO-d_6) δ 41.1 (N**C**H$_2$), 51.6 (OCH$_2$**C**H), 58.0 (O**C**H$_3$), 69.9 (O**C**H$_2$CH), 119.4, 128.9, 130.6, 137.7 (4 Ar**C**), 166.0 (**C**(O)); HRMS (+ESI) 287.0 $[M+H]^+$ (100%), 289.1 $[M+2+H]^+$ (100%) (calcd for $C_{11}H_{15}BrN_2O_2H^+$ 287.0 $[M+H]^+$); Anal. Calcd for $C_{11}H_{16}BrClN_2O_2$: C, 40.83; H, 4.98; Br, 24.69; Cl, 10.96; N, 8.66. Found: C, 40.71; H, 4.97; Br, 24.74; Cl, 11.06; N, 8.71.

Preparation of (*R*)-*N*-(4'-Bromo)benzyl 2-Acetamido-3-methoxy-propionamide ((*R*)-37). (*R*)-*N*-(4'-Bromo)benzyl 2-amino-3-methoxypropionamide hydrochloride (1.00 g, 3.09 mmol) was dissolved in CH_2Cl_2 (30 mL) and then Et_3N (1.3 mL, 9.27 mmol) and acetyl chloride (0.3 mL, 3.71 mmol) were carefully added at 0 °C and the resulting solution was stirred at room temperature (2 h). An aqueous 10% citric acid solution (30 mL) was added and the organic layer was extracted with CH_2Cl_2 (3 x 30 mL). The organic layers were combined, washed with an aqueous saturated $NaHCO_3$ solution (30 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was recrystallized with EtOAc to obtain (*R*)-*N*-(4'-bromo)benzyl 2-acetamido-3-methoxypropionamide as a white solid (690 mg, 68%): R_f = 0.08 (7/3, EtOAc/hexanes); mp 159–161 ºC; $[\alpha]^{25}_D$ –15.9º (*c* 1.0, $CHCl_3$); IR (nujol) 3272, 3093, 2919, 2860, 1634, 1555, 1457, 1375, 1306, 1254, 1197, 1135, 1046, 964, 907, 795, 740, 606, 550, 468 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (C(O)C**H$_3$**), 3.39 (s, OC**H$_3$**), 3.43 (dd, *J* = 7.5, 9.0 Hz, C**H**H'), 3.81 (dd, *J* = 4.2, 9.0 Hz, CH**H'**), 4.37–4.48 (m, NC**H$_2$**), 4.51–4.57 (m,

C**H**), 6.40–6.42 (br d, C(O)N**H**), 6.76–6.84 (br t, CH_2N**H**), 7.14 (d, *J* = 8.6 Hz, 2 Ar**H**), 7.45 (d, *J* = 8.6 Hz, 2 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-bromo)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl protons and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.1 (C(O)**C**H_3), 42.8 (N**C**H_2), 52.4 (OCH_2**C**H), 59.1 (O**C**H_3), 71.6 (O**C**H_2CH), 121.3, 129.1, 131.7, 137.0 (4 Ar**C**), 170.1, 170.4 (2 **C**(O)); LRMS (+ESI) 351.0 $[M+Na]^+$ (100%), 353.0 $[M+2+Na]^+$ (100%) (calcd for $C_{13}H_{17}BrN_2O_3Na^+$ 351.0 $[M+Na]^+$); Anal. Calcd for $C_{13}H_{17}BrN_2O_3$: C, 47.43; H, 5.21; Br, 24.27; N, 8.51. Found: C, 47.47; H, 5.31; Br, 24.11; N, 8.41.

30. Preparation of (*R*)- and (*S*)-*N*-(4'-Iodo)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)- and (*S*)-38).



Preparation of (*R*)-*N*-(4'-Iodo)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-111). A THF solution (240 mL) of (*R*)-*tert*-Boc-serine (6.00 g, 29.2 mmol) was stirred and cooled at -78 °C under Ar and then 4-methylmorpholine (NMM) (3.80 mL, 35.04 mmol) was added dropwise. The reaction was stirred at this temperature (2 min) and then isobutylchloroformate (IBCF) (4.6 mL, 35.04 mmol) was added dropwise leading to the precipitation of a white solid. The reaction was allowed to proceed for additional 2 min. A heterogeneous THF (10 mL) mixture of 4-iodobenzylamine hydrochloride (8.65 g, 32.60 mmol) and NMM (3.80 mL, 35.04 mmol) was added portionwise at –78 °C. The mixture was allowed to stir at room temperature (2 h) and the white solid

was filtered and the organic layer was concentrated in vacuum. The solid was recrystallized in EtOAc to obtain (*R*)-*N*-(4'-iodo)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide (8.97 g, 73%) as a white solid: R_f = 0.60 (EtOAc); mp 129–130 °C; $[\alpha]^{24}_D$ +0.97° (*c* 2.8, DMSO); IR (nujol) 3327, 1656, 1521, 1458, 1375, 1302, 1244, 1164, 1009 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.39 (s, (C**H**$_3$)$_3$C), 3.49-3.60 (br m, C**H**H'OH, CH**H'**OH), 3.95-4.01 (br m, C**H**CH_2), 4.18-4.31 (m, C**H**$_2$N), 4.86 (br s, O**H**), 6.68 (d, *J* = 7.8 Hz, *tert*-BocN**H**), 7.08 (d, *J* = 8.1 Hz, 2 Ar**H**), 7.64 (d, *J* = 8.1 Hz, 2 Ar**H**), 8.37 (br s, CH_2N**H**); ^{13}C NMR ($CDCl_3$) δ 28.2 ((**C**H_3)$_3$C), 42.8 (N**C**H_2), 54.7 (OCH_2**C**H), 62.7 (O**C**H_2CH), 80.8 ((CH_3)$_3$**C**), 92.8 (**C**I), 129.3, 137.5, 137.7 (3 Ar**C**), 156.4 (N**C**(O)O), 171.5 (**C**(O)); HRMS (M+Na^+)(ESI^+) 443.0435 [M + Na^+] (calcd for $C_{15}H_{21}IN_2O_4Na^+$ 443.0444); Anal. Calcd. for $C_{15}H_{21}IN_2O_4$: C, 42.87; H, 5.04; I, 30.20; N, 6.67. Found: C, 43.13; H, 5.14; I, 29.96; N, 6.71.

Preparation of (*S*)-*N*-(4'-Iodo)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*S*)-111). Employing the same procedure for (*R*)-*N*-(4'-iodo)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide and using (*S*)-*tert*-Boc-serine (1.72 g, 8.42 mmol), NMM (1.1 mL, 10.10 mmol), IBCF (1.3 mL, 10.10 mmol) and 4-iodobenzylamine hydrochloride (2.5 g, 9.26 mmol) in THF (400 mL) gave 2.51 g (71%) of the desired product as a white solid: R_f = 0.60 (EtOAc); mp 129–130 °C; $[\alpha]^{24}_D$ –0.93° (*c* 2.8, DMSO); IR (nujol) 3324, 1652, 1520, 1373, 1301, 1246, 1163, 1008, 850, 779 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.39 (s, (C**H**$_3$)$_3$C), 3.50–3.60 (br m, C**H**H'OH, CH**H'**OH), 3.94–4.02 (br m, C**H**CH_2), 4.16–4.30 (m, C**H**$_2$N), 4.83–4.87 (br s, O**H**), 6.68 (d, *J* = 8.1 Hz, *tert*-BocN**H**), 7.07 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.64 (d, *J* = 8.4 Hz, 2 Ar**H**), 8.37 (t, *J* = 5.7 Hz, CH_2N**H**); ^{13}C NMR (DMSO-d_6) δ 28.1 ((**C**H_3)$_3$C), 41.4 (N**C**H_2), 56.9 (OCH_2**C**H), 61.7 (O**C**H_2CH), 78.1 ((CH_3)$_3$**C**), 92.1 (**C**I), 129.3, 136.7, 139.3 (3 Ar**C**), 155.1 (N**C**(O)O), 170.5 (**C**(O)); HRMS (M+Na^+)(ESI^+) 443.0445 [M + Na^+] (calcd for $C_{15}H_{21}IN_2O_4Na^+$ 443.0444); Anal. Calcd. for $C_{15}H_{21}IN_2O_4$: C, 42.87; H, 5.04; ; I, 30.20; N, 6.67. Found: C, 43.08; H, 5.10; I, 29.94; N, 6.62.

Preparation of (*R*)-*N*-(4'-Iodo)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-112). Ag_2O (20.63 g, 89.29 mmol) was added to a CH_3CN solution (300 mL) of (*R*)-*N*-(4'-iodo)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide (7.50 g, 17.86 mmol) and then CH_3I (11.12 mL, 178.57 mmol) was added at room temperature under Ar. The reaction mixture was stirred at room temperature (3 d), filtered through a pad of Celite®, and the filtrate concentrated in vacuo. The residue was purified by column chromatography (SiO_2; 2/3 EtOAc/hexanes) to obtain 5.80 g (75%) of a white solid: R_f = 0.53 (1/1 EtOAc/hexanes); mp 86–87 °C; $[\alpha]^{23}_D$ –3.4° (*c* 1.0, DMSO); IR (nujol) 3334, 1659, 1528, 1461, 1376, 1303, 1245, 1165, 1110, 1049, 954, 870, 788, 619 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, $(CH_3)_3C$), 3.37 (s, OCH_3) 3.48 (dd, *J* = 6.3, 9.3 Hz, C**H**H'OH), 3.84 (dd, *J* = 3.9, 9.3 Hz, CH**H'**OH), 4.20–4.28 (br m, C**H**CH_2), 4.41 (d, *J* = 5.4 Hz, CH_2N), 5.39 (br s, *tert*-BocN**H**), 6.75–6.80 (br t, CH_2N**H**), 7.01 (d, *J* = 8.2 Hz, 2 Ar**H**), 7.64 (d, *J* = 8.2 Hz, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 28.2 ((**C**$H_3)_3$C), 42.8 (N**C**H_2), 54.0 (OCH_2**C**H), 59.1 (O**C**H_3), 71.9 (O**C**H_2CH), 80.5 ($(CH_3)_3$**C**), 92.7 (**C**I), 129.3, 137.7, 137.8 (3 Ar**C**), 155.5 (N**C**(O)O), 170.4 (N**C**(O)O); HRMS (M+H^+)(ESI$^+$) 435.0777 [M + H^+] (calcd for $C_{16}H_{23}IN_2O_4H^+$ 435.0781); Anal. Calcd. for $C_{16}H_{23}IN_2O_4$: C, 44.25; H, 5.34; I, 29.22; N, 6.45;. Found: C, 44.51; H, 5.34; I, 28.99; N, 6.41.

Preparation of (*S*)-*N*-(4'-Iodo)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxypropionamide ((S)-112). Employing the preceding procedure and using (S)-*N*-(4'-iodo)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide (8.50 g, 20.24 mmol), Ag_2O (23.40 g, 101.20 mmol) and MeI (12.60 mL, 202.4 mmol) gave 7.56 g (85%) of (*S*)-*N*-(4'-iodo)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide as a white solid after trituration with Et_2O: R_f = 0.53 (1/1 EtOAc/hexanes); mp 87 °C; $[\alpha]^{23}_D$ +3.3° (*c* 1.0, DMSO); IR (nujol) 3337, 2728, 1657, 1527, 1461, 1376, 1303, 1244, 1164, 1109, 1048, 953, 869, 787, 617 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.39 (s, $(CH_3)_3C$), 3.24 (s, OCH_3) 3.47 (d, *J* = 6.0 Hz, C**H**H'OH, CH**H'**OH), 4.14–4.18 (br m, C**H**CH_2), 4.20–4.25 (m, CH_2N), 6.88 (d, *J* = 7.5 Hz, *tert*-BocN**H**), 7.05 (d, *J* = 8.2

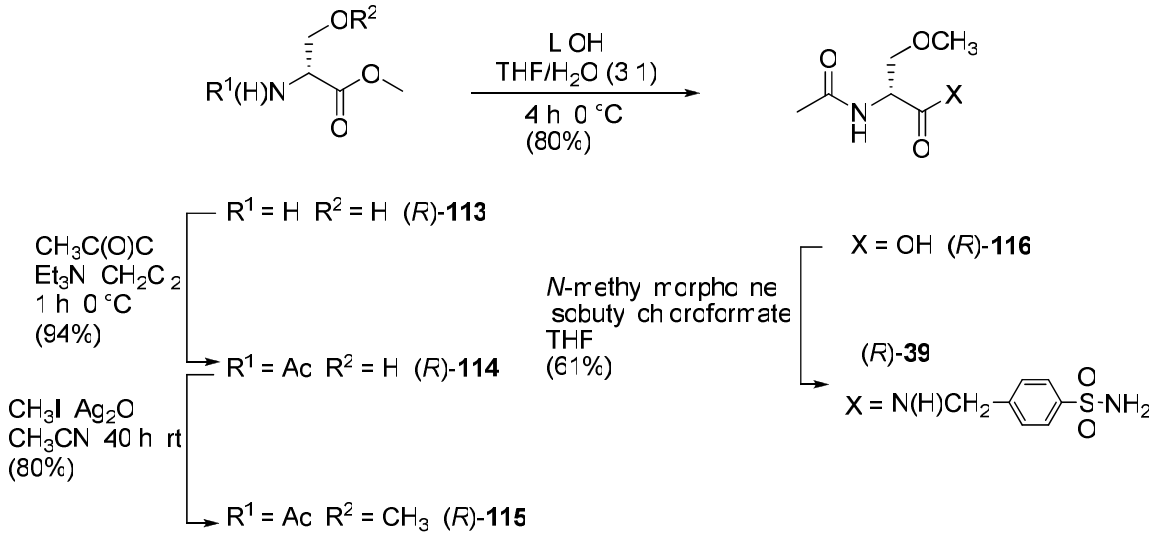
Hz, 2 Ar**H**), 7.64 (d, *J* = 8.2 Hz, 2 Ar**H**), 8.45 (t, *J* = 6.0 Hz, CH_2N**H**); ^{13}C NMR (DMSO-d_6) δ 28.0 (($\mathbf{C}H_3)_3C$), 41.4 ($N\mathbf{C}H_2$), 54.2 ($OCH_2\mathbf{C}H$), 58.0 ($O\mathbf{C}H_3$), 71.8 ($O\mathbf{C}H_2CH$), 78.1 ($(CH_3)_3\mathbf{C}$), 92.2 (**C**I), 129.3, 136.7, 139.2 (3 Ar**C**), 155.1 (N**C**(O)O), 170.0 (**C**(O)); HRMS (M+H$^+$)(ESI$^+$) 435.0775 [M + H$^+$] (calcd for $C_{16}H_{23}IN_2O_4H^+$ 435.0781); Anal. Calcd. for $C_{16}H_{23}IN_2O_4$: C, 44.25; H, 5.34; I, 29.22; N, 6.45;. Found: C, 44.54; H, 5.38; I, 28.92; N, 6.35.

Preparation of (*R*)-*N*-(4'-Iodo)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-38). A saturated HCl solution in dioxane (1 mmol/2 mL, 25.00 mL) was added to (*R*)-*N*-(4'-iodo)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide (5.50 g, 12.67 mmol) at 0 °C and the solution was stirred at room temperature (2 h). The reaction solution was concentrated in vacuo and dried (30 min). CH_2Cl_2 (50 mL) was added to the residue followed by the successive additions of Et_3N (10.66 mL, 76.02 mmol) and AcCl (2.70 mL, 38.01 mmol) at 0 °C. The mixture was stirred at room temperature (2 h), aqueous 10% citric acid was added, and then the organic layer was separated. The aqueous layer was washed with CH_2Cl_2 (2 x 50 mL). The organic layers were combined, washed with aqueous saturated $NaHCO_3$ (50 mL) and H_2O (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The solid was recrystallized with EtOAc to obtain (*R*)-*N*-(4'-iodo)benzyl 2-acetamido-3-methoxypropionamide (3.40 g, 71%) as a white solid: R_f = 0.76 (5/5 acetone/EtOAc); mp 159–160 °C; $[\alpha]^{25}_D$ = +3.3° (*c* 1.0, DMSO); IR (nujol) 3279, 1636, 1552, 1457, 1375, 1305, 1139, 725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.02 (s, C**H$_3$**CO), 3.38 (s, OC**H$_3$**), 3.44 (dd, *J* = 7.2, 9.0 Hz, C**H**H'), 3.79 (dd, *J* = 4.2, 9.0 Hz, CH**H'**), 4.38–4.41 (m, C**H$_2$**N), 4.52–4.59 (m, NC(**H**)CO), 6.46 (br d, *J* = 6.6 Hz, N**H**C(O)CH_3), 6.85–6.93 (br t, CH_2N**H**), 7.00 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.64 (d, *J* = 8.4 Hz, 2 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(4'-iodo)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.1 (**C**H_3CO), 42.9 (**C**H_2N), 52.4 (**C**HCH_2), 59.1 ($O\mathbf{C}H_3$), 71.6 (**C**H_2OCH_3), 92.7 (**C**I), 129.3, 137.7, 139.1 (3 Ar**C**), 170.1, 170.3 (2 **C**(O)); HRMS

(M+Na$^+$)(ESI$^+$) 399.0177 [M + Na$^+$] (calcd for $C_{13}H_{17}IN_2O_3Na^+$ 399.0182); Anal. Calcd. for $C_{13}H_{17}IN_2O_3$: C, 41.51; H, 4.55; I, 33.73; N, 7.45. Found: C, 41.70; H, 4.49; I, 33.69; N, 7.39.

Preparation of (*S*)-*N*-(4'-Iodo)benzyl 2-Acetamido-3-methoxypropionamide ((*S*)-38). Employing the preceding procedure and using (*S*)-2-*N*-(4'-iodo)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide (3.70 g, 8.52 mmol), saturated dioxane solution of HCl (1 mmol/2 mL, 17 mL), Et_3N (3.6 mL, 25.60 mmol) and AcCl (906 μL, 12.30 mmol) gave 2.43 g (76%) of (*S*)-*N*-(4'-iodo)benzyl 2-acetamido-3-methoxypropionamide as a white solid after recrystallization with EtOAc: R_f = 0.76 (5/5 acetone/EtOAc); mp 159–160 °C; $[\alpha]^{24}_D$ = –3.2° (*c* 1.0, DMSO); IR (nujol) 3278, 1636, 1552, 1458, 1375, 1305, 1138, 725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.02 (s, C**H$_3$**CO), 3.38 (s, OC**H$_3$**), 3.43 (dd, *J* = 7.2, 9.0 Hz, C**H**H'), 3.79 (dd, *J* = 4.2, 9.0 Hz, CH**H'**), 4.38–4.42 (m, C**H$_2$**N), 4.53–4.59 (m, NC(**H**)CO), 6.47 (br d, *J* = 6.0 Hz, N**H**C(O)CH_3), 6.85–6.93 (br t, CH_2N**H**), 7.00 (d, *J* = 8.4 Hz, 2 Ar**H**), 7.64 (d, *J* = 8.4 Hz, 2 Ar**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*S*)-*N*-(4'-Iodo)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl and one signal for the ether methyl protons; ^{13}C NMR (DMSO-d_6) δ 22.4 (**C**H_3CO), 41.4 (**C**H_2N), 52.5 (**C**HCH_2), 58.1 (O**C**H_3), 71.9 (**C**H_2OCH_3), 92.2 (**C**I), 129.3, 136.8, 139.1 (3 Ar**C**), 169.3, 169.7 (2 **C**(O)); HRMS (M+Na$^+$)(ESI$^+$) 399.0177 [M + Na$^+$] (calcd for $C_{13}H_{17}IN_2O_3Na^+$ 399.0182); Anal. Calcd. for $C_{13}H_{17}IN_2O_3$: C, 41.51; H, 4.55; I, 33.73; N, 7.45. Found: C, 41.37; H, 4.52; I, 33.47; N, 7.37.

31. Preparation of (*R*)-*N*-(4'-Sulfamoyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-39).



Preparation of (*R*)-Methyl 2-Acetamido-3-hydroxypropionate ((*R*)-114).[8] To a solution of D-serine methyl ester hydrochloride ((*R*)-**113**)(10.00 g, 64.27 mmol) and Et_3N (18.81 mL,134.97 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added acetyl chloride (4.77 mL, 67.48 mmol). After the mixture was allowed to stir at 0 °C (1 h) under Ar, the solvent was evaporated in vacuo and EtOAc (150 mL) was added. The mixture was filtered and the filtrate evaporated in vacuo. The residue was purified by column chromatography (SiO_2; 1/9 MeOH/$CHCl_3$) to yield 9.73 g (94%) of (*R*)-methyl 2-acetamido-3-hydroxypropionate as a yellow oil: R_f = 0.35 (1/9 MeOH/$CHCl_3$); $[\alpha]^{25}_D$ –10.1° (*c* 1.9, MeOH); ^{1}H NMR (DMSO-d_6) δ 1.86 (s, C**H**$_3$C(O)), 3.55–3.71 (m, C**H**$_2$OH, OC**H**$_3$), 4.29–4.35 (m, C**H**), 5.08 (t, *J* = 5.7 Hz, O**H**), 8.19 (d, *J* = 7.5 Hz, N**H**); ^{13}C NMR (DMSO-d_6) δ 22.3 (**C**H$_3$C(O)), 51.8 (C(O)O**C**H$_3$), 54.7 (**C**H), 61.3 (**C**H$_2$OH), 169.5, 171.3 (2 **C**(O)).

Preparation of (*R*)-Methyl 2-Acetamido-3-methoxypropionate ((*R*)-115).[9] Ag_2O (45.34 g, 195.65 mmol) was added to a CH_3CN solution (500 mL) of (*R*)-methyl 2-acetamido-3-hydroxypropionate (9.00 g, 55.90 mmol) and CH_3I (24.41 mL, 391.30 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature in the dark (5 d), filtered through a pad of Celite®, and the filtrate concentrated in vacuo. The product was purified by column chromatography (1/15 MeOH/$CHCl_3$) to obtain 7.86 g (80%) of (*R*)-methyl 2-acetamido-3-methoxypropionate as a white solid: R_f = 0.50 (1/15

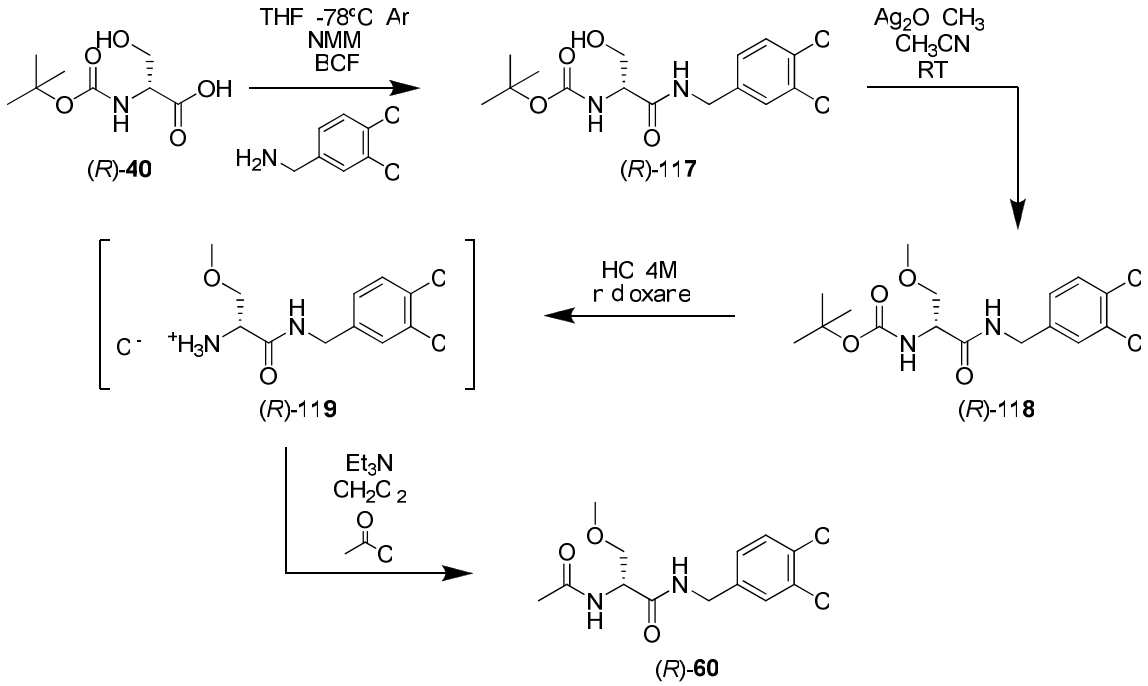
MeOH/$CHCl_3$); mp 75–77 °C (lit.[9] mp 76–78 °C); $[\alpha]^{25}_D$ +7.2° (*c* 1.0, MeOH) (lit.[9] $[\alpha]^{23}_D$ +7.8 (*c* 1.0, MeOH)); ^{1}H NMR ($CDCl_3$) δ 2.06 (s, C**H**$_3$C(O)), 3.35 (s, CH_2O**C**H_3), 3.61 (dd, *J* = 3.3, 9.3 Hz, C**H**H'OCH_3), 3.78 (s, C(O)OC**H**$_3$), 3.82 (dd, *J* = 3.0, 9.3 Hz, CH**H'**OCH_3), 4.72–4.77 (m, C**H**), 6.40 (d, *J* = 6.6 Hz, N**H**), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-methyl 2-acetamido-3-methoxypropanoate gave two signals each for the acetyl methyl protons and the ether methyl protons in a ratio of 93:7; ^{13}C NMR ($CDCl_3$) δ 23.3 (**C**H_3C(O)), 52.7 (**C**H, C(O)O**C**H_3), 59.4 (CH_2O**C**H_3), 72.4 (**C**H_2OCH_3), 170.1, 171.0 (2 **C**(O)); HRMS (M+H$^+$)(ESI$^+$) 176.0918 [M + H$^+$] (calcd. for $C_7H_{14}NO_4$ 176.0923).

Preparation of (*R*)-2-Acetamido-3-methoxypropionoic Acid ((*R*)-116).[9] (*R*)-Methyl 2-acetamido-3-methoxypropionoate (3.50 g, 20.00 mmol) was dissolved in THF (60 mL) and cooled to 0 °C, and an aqueous 1 M solution (20 mL) of LiOH (20.00 mmol) was added. The reaction solution was stirred at 0 °C (4 h) and then concentrated in vacuo. The resulting aqueous phase was diluted with H_2O (50 mL) and washed with Et_2O (2 × 50 mL). The aqueous layer was acidified to pH 1-2 with aqueous 1 M HCl, and extracted with EtOAc (6 × 50 mL). The combined organic phases was dried (Na_2SO_4), evaporated in vacuo, and then recrystallized (EtOAc/hexanes) to yield 1.30 g of (*R*)-2-acetamido-3-methoxypropionoic acid (40%) as a white solid: R_f = 0.10 (1/4 MeOH/$CHCl_3$); mp 136–138 °C; $[\alpha]^{25}_D$ –21.0° (*c* 1.0, MeOH) (lit.[9] $[\alpha]^{23}_D$ –16.9 (*c* 1.2, MeOH) for an 85:15 mixture of (*R*)- and (*S*)-acids); ^{1}H NMR (DMSO-d_6) δ 1.86 (s, C**H**$_3$C(O)), 3.25 (s, CH_2O**C**H_3), 3.49 (dd, *J* = 4.1, 9.8 Hz, C**H**H'OCH_3), 3.63 (dd, *J* = 5.9, 9.8 Hz, CH**H'**OCH_3), 4.38–4.44 (m, C**H**), 8.19 (d, *J* = 8.1 Hz, N**H**); ^{13}C NMR (DMSO-d_6) δ 22.3 (**C**H_3C(O)), 52.1 (**C**H), 58.3 (CH_2O**C**H_3), 71.8 (**C**H_2OCH_3), 169.3, 171.6 (2 **C**(O)); Anal. Calcd. for $C_6H_{11}NO_4$: C, 44.72%; H, 6.88%; N, 8.69%. Found: C, 44.71%; H, 6.74%; N, 8.66%. Concentration of the recrystallization mother liquid led to an additional 1.28 g of (*R*)- and (*S*)-2-acetamido-3-methoxypropanoic acid

(40%, 92:8 enantiomer mixture) as a white sticky foam: $[\alpha]^{25}_{D}$ –18.7° (*c* 1.0, MeOH).

Preparation of (*R*)-*N*-(4'-Sulfamoyl)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-39). To an anhydrous THF solution (30 mL) of (*R*)- and (*S*)-2-acetamido-3-methoxypropionoic acid (92:8 enantiomer mixture) (1.00 g, 6.21 mmol) at –78 °C was added 4-methylmorpholine (NMM) (1.50 mL, 13.66 mmol). The solution was stirred (5 min), followed by the addition of isobutyl chloroformate (1.03 mL, 7.89 mmol). This mixture was stirred (5 min) and then methyl 4-(aminomethyl)benzenesulfonamide hydrochloride (2.07 g, 9.32 mmol) was added. The reaction mixture was stirred at room temperature (1.5 h), and filtered. The product was purified by column chromatography (1/7 MeOH/$CHCl_3$) and then recrystallized (MeOH/$CHCl_3$) to yield 1.25 g (61%) of (*R*)-*N*-(4'-sulfamoyl)benzyl 2-acetamido-3-methoxypropionamide as a white solid: R_f = 0.35 (1/7 MeOH/$CHCl_3$); mp 177–179 °C; $[\alpha]^{25}_{D}$ +10.7° (*c* 1.0, MeOH); IR (nujol) 3293, 2935, 1623, 1557, 1459 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.87 (s, C**H**$_3$(O)), 3.26 (s, CH_2O**C**H_3), 3.46–3.56 (m, C**H**$_2$OCH_3), 4.34 (d, *J* = 6.1 Hz, C**H**$_2$Ar), 4.43–4.50 (m, C**H**), 7.31 (s, N**H**$_2$), 7.41 (d, *J* = 8.6 Hz, 2 Ar**H**), 7.75 (d, *J* = 8.6 Hz, 2 Ar**H**), 8.13 (d, *J* = 7.8 Hz, N**H**CH), 8.59 (t, *J* = 6.1 Hz, N**H**CH_2); ^{13}C NMR (DMSO-d_6) δ 22.5 (**C**H_3(O)), 41.7 (**C**H_2Ar), 52.7 (**C**H), 58.2 (CH_2O**C**H_3), 72.0 (**C**H_2OCH_3), 125.5, 127.2, 142.5, 143.5 (4 Ar**C**), 169.5, 169.9 (2 **C**(O)); HRMS (M+H$^+$)(ESI$^+$) 330.1117 [M + H$^+$] (calcd. for $C_{13}H_{20}N_3O_5S$ 330.1124); Anal. Calcd. for $C_{13}H_{19}N_3O_5S$: C, 47.71; H, 5.81; N, 12.76; S, 9.74. Found: C, 47.43; H, 5.95; N, 12.77; S, 9.77.

32. Preparation of (*R*)-*N*-(3',4'-Dichloro)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-60).



Preparation of (*R*)-*N*-(3',4'-Dichloro)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-117). A THF solution (250 mL) of (*R*)-Boc-serine (6.00 g, 29.2 mmol) was stirred and cooled at -78 ºC under Ar, and then 4-methylmorpholine (NMM) (3.8 mL, 35.1 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (4.6 mL, 35.1 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for an additional 2 min. Then, 3,4-dichlorobenzylamine (4.8 mL, 35.1 mmol) was added portionwise at -78 ºC. The mixture was stirred at -78 ºC (5 min) and then at room temperature (2 h). The white solid was filtered and the organic layer was concentrated in vacuo. The residue was recrystallized with EtOAc to obtain (*R*)-*N*-(3',4'-dichloro)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide as a white solid (5.84 g, 55%): R_f = 0.25 (EtOAc/hexanes, 7/3); mp = 130 ºC; $[\alpha]^{24.6}_D$ +39.3º (*c* 1.0, $CHCl_3$); IR (nujol) 2934, 1656, 1517, 1458, 1375, 1303, 1247, 1159, 1031, 867, 720, 660, 572, 464 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.40 (s, C(C**H**$_3$)$_3$), 3.56–3.59 (m, C**H**$_2$OH), 3.94–4.00 (m, C**H**), 4.28 (d, *J* = 6.3 Hz, C**H**$_2$N), 4.88 (t, *J* = 5.9 Hz, O**H**), 6.75 (d, *J* = 7.8 Hz, C(O)N**H**), 7.25 (dd, *J* = 1.8, 8.4 Hz, 1 Ar**H**), 7.52–7.56 (m, 2 Ar**H**), 8.44 (t, *J* = 6.3 Hz, CH_2N**H**); ^{13}C NMR ($CDCl_3$) δ 28.4 (C(**C**H$_3$)$_3$), 42.3

(N**C**H_2), 55.0 (OCH_2**C**H), 62.8 (O**C**H_2CH), 81.0 (**C**$(CH_3)_3$), 126.9, 129.4, 130.7, 131.7, 132.9, 138.3 (6 Ar**C**), 156.5 (N**C**(O)O), 171.7 (**C**(O)); LRMS (ESI$^+$) 385.04 [M+Na$^+$, 100%], 387.04 [M+2+Na$^+$, 63%], 389.04 [M+4+Na$^+$, 14%], (calcd for $C_{15}H_{20}Cl_2N_2O_4$ Na$^+$ 385.07); Anal. Calcd. for $C_{15}H_{20}Cl_2N_2O_4$: C, 49.60; H, 5.55; Cl, 19.52; N, 7.71. Found: C, 49.62, H, 5.54; Cl, 19.65; N, 7.70.

Preparation of (*R*)-*N*-(3',4'-Dichloro)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-118). Ag_2O (16.00 g, 68.8 mmol) was added to a CH_3CN solution (250 mL) of (*R*)-*N*-(3',4'-dichloro)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide (5.00 g, 13.8 mmol) and CH_3I (8.6 mL, 137.3 mmol) at room temperature under Ar. The reaction mixture was stirred at room temperature in the dark (2 d), filtered through a Celite® pad, and the filtrate was concentrated in vacuo to obtain (*R*)-*N*-(3',4'-dichloro)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide as a white foam (5.10 g, 98%): R_f = 0.73 (EtOAc/hexanes, 7/3); mp = 71 ºC; $[\alpha]^{24.7}_D$ –18.4º (*c* 1.0, $CHCl_3$); IR (nujol) 3295, 2958, 2912, 2728, 2359, 1658, 1525, 1458, 1374, 1305, 1247, 1159, 1030, 950, 864, 812, 719, 649, 542, 440 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.44 (s, C(C**H$_3$**)$_3$), 3.39 (s, OC**H$_3$**), 3.48–3.53 (m, C**H**H'), 3.82–3.86 (m, CH**H'**), 4.28 (br s, C**H**), 4.43 (d, *J* = 5.7 Hz, C**H$_2$**N), 5.43 (br s, N**H**), 6.91 (br s, N**H**), 7.09 (br d, *J* = 8.1 Hz, 1 Ar**H**), 7.36–7.39 (m, 2 Ar**H**); ^{13}C NMR ($CDCl_3$) δ 28.2 (C(**C**H_3)$_3$), 42.2 (N**C**H_2), 54.2 (OCH_2**C**H), 59.1 (O**C**H_3), 72.0 (O**C**H_2CH), 80.5 (**C**$(CH_3)_3$), 126.6, 129.1, 130.5, 131.3, 132.7, 138.4 (6 Ar**C**), 155.5 (N**C**(O)O), 170.6 (**C**(O)); HRMS (ESI$^+$) 377.1035 [M+H$^+$, 100%], 379.1004 [M+2+H$^+$, 63%], 381.0973 [M+4+H$^+$, 19%] (calcd for $C_{16}H_{22}Cl_2N_2O_4$ H$^+$ 377.1029); Anal. Calcd. for $C_{16}H_{22}Cl_2N_2O_4$•0.05EtOAc: C, 50.98; H, 5.92; Cl, 18.57; N, 7.34. Found: C, 51.36, H, 5.95; Cl, 18.20; N, 7.35.

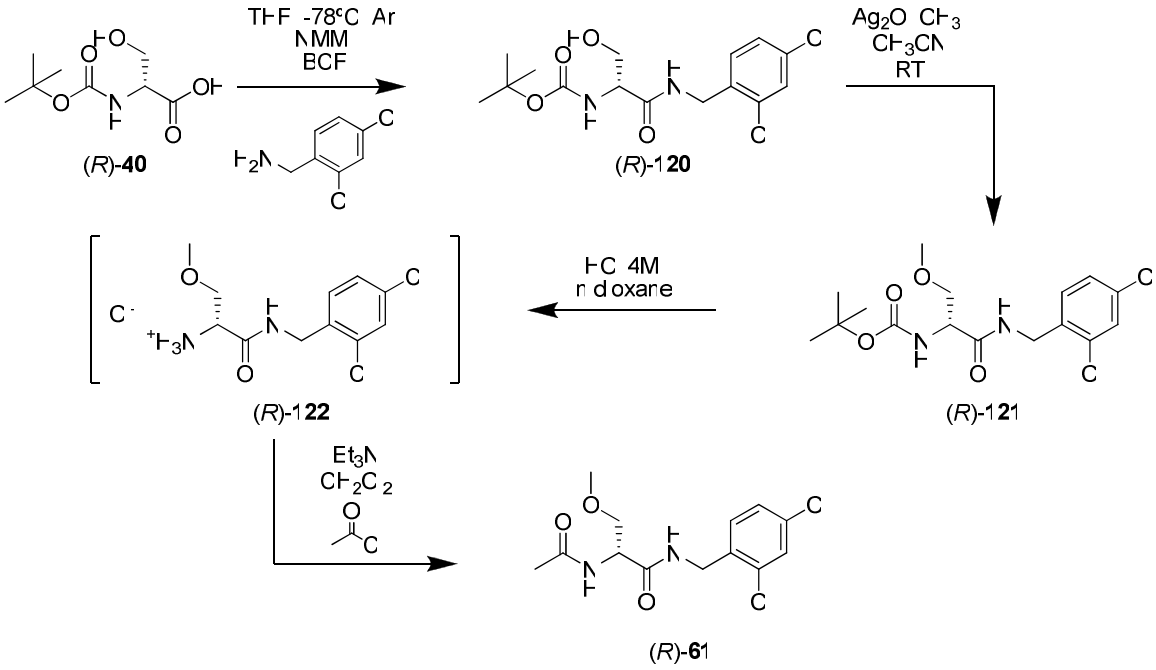
Preparation of (*R*)-*N*-(3',4'-dichloro)benzyl 2-Amino-3-methoxy-propionamide Hydrochloride ((*R*)-119). HCl (4 M in dioxane, 24 mL) was added at 0 ºC to (*R*)-*N*-(3',4'-dichloro)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide (4.58 g, 12.1 mmol). The solution was stirred at room

temperature overnight. The reaction was concentrated in vacuo to obtain (*R*)-*N*-(3',4'-dichloro)benzyl 2-amino-3-methoxypropionamide hydrochloride as a light brown foam: R_f = 0.13 (EtOAc); ^{1}H NMR (DMSO-d_6) δ 3.57 (s, OC**H$_3$**), 3.71 (½ AB$_q$, *J* = 4.1, 10.5 Hz, CHC**H**H'), 3.79 (½ AB$_q$, *J* = 5.3, 10.5 Hz, CHCH**H'**), 4.10 (br s, C**H**), 4.32 (½ AB$_q$, *J* = 6.0, 15.9 Hz, NC**H**H'), 4.40 (½ AB$_q$, *J* = 5.6, 15.9 Hz, NCH**H'**), 7.29 (dd, *J* = 1.8, 8.1 Hz, 1 Ar**H**), 7.54 (d, 1.8 Hz, 1 Ar**H**), 7.61 (d, *J* = 8.1 Hz, 1 Ar**H**), 8.36 (br s, N**H**), 9.25–9.29 (app t, N**H**); LRMS (ESI$^+$) 277.08 [M+H$^+$, 100%], 279.08 [M+2+H$^+$, 66%], 281.08 [M+4+H$^+$, 12%] (calcd for $C_{11}H_{14}Cl_2N_2O_2$ H$^+$ 277.05).

Preparation of (*R*)-*N*-(3',4'-Dichloro)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-60). (*R*)-*N*-(3',4'-dichloro)benzyl 2-amino-3-methoxypropionamide hydrochloride (3.50 g, 11.2 mmol) was dissolved in CH_2Cl_2 (100 mL) and then Et_3N (4.6 mL, 33.5 mmol) and acetyl chloride (0.95 mL, 13.4 mmol) were carefully added at 0 °C and the resulting solution was stirred at room temperature (2 h). An aqueous 10% citric acid solution (100 mL) was added and the organic layer was extracted with CH_2Cl_2 (3 x 100 mL). The organic layers were combined, washed with a saturated aqueous $NaHCO_3$ solution (100 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was recrystallized with EtOAc to obtain (*R*)-*N*-(3',4'-dichloro)benzyl 2-acetamido-3-methoxypropionamide as a white solid (1.60 g, 45%): R_f = 0.16 (EtOAc/hexanes, 7/3); mp = 165 ºC; $[\alpha]^{24.9}_D$ –10.5º (*c* 1.0, $CHCl_3$); IR (nujol) 3292, 3096, 2927, 2859, 1636, 1555, 1459, 1379, 1256, 1135, 1034, 815, 724, 604, 491 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.05 (C(O)C**H$_3$**), 3.41 (s, OC**H$_3$**), 3.45 (dd, *J* = 7.5, 9.3 Hz, C**H**H'), 3.82 (dd, *J* = 4.1, 9.3 Hz, CH**H'**), 4.39–4.49 (m, NC**H$_2$**), 4.52–4.59 (m, C**H**), 6.39–6.41 (br d, C(O)N**H**), 6.80–6.90 (br t, CH_2N**H**), 7.10 (dd, *J* = 2.1, 8.1 Hz, 1 Ar**H**), 7.36 (d, *J* = 2.1 Hz, 1 Ar**H**), 7.40 (d, *J* = 8.1 Hz, 1 Ar**H**)), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(3',4'-dichloro)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl protons and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.1 (C(O)**C**H$_3$), 42.2 (N**C**H$_2$), 52.6 (OCH$_2$**C**H), 59.1 (O**C**H$_3$), 71.7 (O**C**H$_2$CH), 126.6,

129.1, 130.5, 131.3, 132.6, 138.3 (6 Ar**C**), 170.2, 170.4 (2 **C**(O)); LRMS (ESI$^+$) 341.05 [M+Na$^+$, 100%], 343.05 [M+2+Na$^+$, 64%], 345.05 [M+4+Na$^+$, 11%] (calcd for $C_{13}H_{16}Cl_2N_2O_3$ Na$^+$ 341.04); Anal. Calcd. for $C_{13}H_{16}Cl_2N_2O_3$: C, 48.92; H, 5.05; Cl, 22.21; N, 8.78. Found: C, 49.14, H, 5.01; Cl, 22.12; N, 8.80.

33. Preparation of (*R*)-*N*-(2',4'-Dichloro)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-61).



Preparation of (*R*)-*N*-(2',4'-Dichloro)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-hydroxypropionamide ((*R*)-120). A THF solution (180 mL) of (*R*)-Boc-serine (4.30g, 21.0 mmol) was stirred and cooled at -78 ºC under Ar, and then 4-methylmorpholine (NMM) (2.8 mL, 25.1 mmol) was added dropwise. After 2 min of stirring at this temperature, isobutylchloroformate (IBCF) (3.3 mL, 25.1 mmol) was added dropwise leading to the precipitation of a white solid, and the reaction was allowed to proceed for additional 2 min. Then, 2,4-dichlorobenzylamine (3.3 mL, 25.1 mmol) and was added portionwise at -78 ºC. The mixture was stirred at -78 ºC (5 min) and then at room temperature (2 h). The white solid was filtered and the organic layer was concentrated in vacuo. The residue was purified by flash liquid chromatography with EtOAc/hexanes

(3/7 to 7/3) as the eluant to obtain (*R*)-*N*-(2',4'-dichloro)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide as a white solid (4.94 g, 65%): R_f = 0.47 (EtOAc/hexanes, 7/3); mp = 123 ºC; $[\alpha]^{24.8}_D$ +46.6º (*c* 1.0, $CHCl_3$); IR (nujol) 2953, 2955, 2724, 1696, 1638, 1520, 1457, 1374, 1289, 1160, 1076, 827, 725, 634, 515 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, C(C**H**$_3$)$_3$), 2.91–3.05 (m, C**H**H'OH), 3.63–3.71 (m, CH**H'**OH), 4.11–4.16 (m, C**H**, O**H**), 4.45–4.58 (m, C**H**$_2$N), 5.05–5.15 (m, N**H**), 7.19–7.38 (m, 3 Ar**H**, N**H**); ^{13}C NMR ($CDCl_3$) δ 28.2 (C(**C**H$_3$)$_3$), 40.8 (N**C**H$_2$), 54.7 (OCH$_2$**C**H), 62.6 (O**C**H$_2$CH), 80.8 (**C**(CH$_3$)$_3$), 127.3, 129.4, 130.4, 133.8, 134.0, 134.1 (6 Ar**C**), 156.3 (N**C**(O)O), 171.6 (**C**(O)); LRMS (ESI^+) 385.08 [M+Na^+, 100%], 387.08 [M+2+Na^+, 66%], 389.08 [M+4+Na^+, 12%] (calcd for $C_{15}H_{20}Cl_2N_2O_4$ Na^+ 385.07); Anal. Calcd. for $C_{15}H_{20}Cl_2N_2O_4$: C, 49.60; H, 5.55; Cl, 19.52; N, 7.71. Found: C, 49.63, H, 5.62; Cl, 19.65; N, 7.64.

Preparation of (*R*)-*N*-(2',4'-Dichloro)benzyl 2-*N*-(*tert*-Butoxycarbonyl)amino-3-methoxypropionamide ((*R*)-121). Ag_2O (14.80 g, 63.9 mmol, 5 equiv) was added to a CH_3CN solution (230 mL) of (*R*)-*N*-(2',4'-dichloro)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-hydroxypropionamide (4.64 g, 12.8 mmol, 1 equiv) and CH_3I (8.0 mL, 127.7 mmol, 10 equiv) at room temperature under Ar. The reaction mixture was stirred at room temperature in the dark (2 d), filtered through a Celite® pad, and the filtrate was concentrated in vacuo. The residue was purified by flash liquid chromatography on silica gel with EtOAc/hexanes (3/7 to 5/5) as the eluant to obtain (*R*)-*N*-(2',4'-dichloro)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide as a white oil (4.60 g, 95%): R_f = 0.85 (EtOAc/hexanes, 7/3); $[\alpha]^{23.6}_D$ –9.5º (*c* 1.0, $CHCl_3$); IR (nujol) 3055, 2982, 2929, 2358, 1681, 1483, 1371, 1265, 1165, 1112, 1055, 866, 832, 739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.44 (s, C(C**H**$_3$)$_3$), 3.37 (s, OC**H**$_3$), 3.47 (dd, *J* = 6.3, 9.0 Hz, C**H**H'), 3.83 (dd, *J* = 3.6, 9.0 Hz, CH**H'**), 4.26 (br s, C**H**), 4.47–4.53 (m, C**H**$_2$N), 5.38 (br s, N**H**), 6.91 (br s, N**H**), 7.21 (br dd, *J* = 2.1, 8.4 Hz, 1 Ar**H**), 7.31 (br d, *J* = 8.4 Hz, 1 Ar**H**), 7.38 (br d, *J* = 2.1 Hz, 1 Ar**H**), ^{13}C NMR ($CDCl_3$) δ 28.2 (C(**C**H$_3$)$_3$), 40.8 (N**C**H$_2$), 53.9 (OCH$_2$**C**H), 59.0 (O**C**H$_3$), 71.8 (O**C**H$_2$CH), 80.3 (**C**(CH$_3$)$_3$), 127.2, 129.2, 130.3, 133.8, 133.9, 134.0 (6 Ar**C**), 155.4 (N**C**(O)O),

170.4 (**C**(O)); LRMS [M] (ESI$^+$) 399.09 [M+Na$^+$, 100%], 401.09 [M+2+Na$^+$, 65%], 403.08 [M+4+Na$^+$, 12%] (calcd for $C_{16}H_{22}Cl_2N_2O_4$ Na$^+$ 399.08); Anal. Calcd. for $C_{16}H_{22}Cl_2N_2O_4$: C, 50.94; H, 5.88; Cl, 18.79; N, 7.43. Found: C, 51.15, H, 6.02; Cl, 18.92; N, 7.35.

Preparation of (*R*)-*N*-(2',4'-Dichloro)benzyl 2-Amino-3-methoxypropionamide Hydrochloride ((*R*)-122). HCl (4 M in dioxane, 24 mL) was added at 0 ºC to (*R*)-*N*-(2',4'-dichloro)benzyl 2-*N*-(*tert*-butoxycarbonyl)amino-3-methoxypropionamide (4.58 g, 12.1 mmol), and the solution was stirred at room temperature overnight. The reaction was concentrated in vacuo. The residue was triturated with Et_2O to obtain (*R*)-*N*-(2',4'-dichloro)benzyl 2-amino-3-methoxypropionamide hydrochloride as a beige solid: 142–144 ºC; $[\alpha]^{25}_D$ +1.1º (*c* 0.5, MeOH); R_f = 0.13 (EtOAc); IR (nujol) 3452, 3334, 2873, 2731, 1680, 1591, 1459, 1376, 1281, 1239, 1196, 1141, 1101, 1026, 963, 910, 808, 726, 679, 582, 523 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.32 (s, OC**H$_3$**), 3.71 (½ AB$_q$, *J* = 3.9, 10.5 Hz, CHC**H**H'), 3.75 (½ AB$_q$, *J* = 5.4, 10.5 Hz, CHCH**H'**), 4.04–4.13 (br s, C**H**), 4.28–4.44 (m, NC**H$_2$**), 7.28 (dd, *J* = 1.8, 8.1 Hz, 1 Ar**H**), 7.53 (d, 1.8 Hz, 1 Ar**H**), 7.61 (d, *J* = 8.1 Hz, 1 Ar**H**), 8.23–8.38 (br s, N**H$_3^+$**), 9.13–9.17 (app t, N**H**); ^{13}C NMR (DMSO-d_6) δ 40.6 (N**C**H$_2$), 51.7 (OCH$_2$**C**H), 58.0 (O**C**H$_3$), 69.8 (O**C**H$_2$CH), 127.0, 128.4, 128.9, 129.9, 130.4, 139.5 (**C$_6$**H$_4$), 166.2 (**C**(O)); LRMS (+ESI) 277.08 [M+H]$^+$ (100%), 279.08 [M+2+H]$^+$ (66%), 281.08 [M+4+H]$^+$ (12%) (calcd for $C_{11}H_{14}Cl_2N_2O_2$ H$^+$ 277.05 [M+H]$^+$). Anal. Calcd for $C_{11}H_{15}Cl_2N_2O_2$•0.08H_2O: C, 41.95; H, 4.85; Cl, 33.77; N, 8.89. Found: C, 41.72; H, 4.76; Cl, 33.39; N, 8.74.

Preparation of (*R*)-*N*-(2',4'-Dichloro)benzyl 2-Acetamido-3-methoxypropionamide ((*R*)-61). (*R*)-*N*-(2',4'-dichloro)benzyl 2-amino-3-methoxypropionamide hydrochloride (2.70 g, 7.16 mmol) was dissolved in CH_2Cl_2 (60 mL) and then Et_3N (3.0 mL, 21.48 mmol) and acetyl chloride (0.6 mL, 8.59 mmol) were carefully added at 0 °C and the resulting solution was stirred at room temperature (2 h). An aqueous 10% citric acid solution (60 mL) was added and the organic layer was extracted with CH_2Cl_2 (3 x 60 mL). The organic layers

were combined, washed with a saturated $NaHCO_3$ solution (60 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was recrystallized with EtOAc to obtain (*R*)-*N*-(2',4'-dichloro)benzyl 2-acetamido-3-methoxypropionamide as a white solid (1.45 g, 63%): R_f = 0.26 (EtOAc); mp = 149 ºC; $[\alpha]^{23.7}_D$ –11.0º (*c* 1.0, $CHCl_3$); IR (nujol) 3477, 3399, 3276, 2919, 2854, 2725, 2363, 1637, 1552, 1458, 1376, 1304, 1251, 1135, 1102, 1050, 974, 821, 724, 606, 505 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (C(O)C**H$_3$**), 3.37–3.43 (m, OC**H$_3$**, C**H**H'), 3.80 (dd, *J* = 4.1, 9.2 Hz, CH**H'**), 4.43–4.57 (m, NC**H$_2$**, C**H**), 6.36–6.40 (br d, C(O)N**H**), 6.90–7.02 (br t, CH_2N**H**), 7.22 (dd, *J* = 2.1, 8.3 Hz, 1 Ar**H**), 7.30 (d, *J* = 8.3 Hz, 1 Ar**H**), 7.39 (d, *J* = 2.1 Hz, 1 Ar**H**)), addition of excess (*R*)-(–)-mandelic acid to a $CDCl_3$ solution of (*R*)-*N*-(2',4'-dichloro)benzyl 2-acetamido-3-methoxypropionamide gave only one signal for the acetyl methyl protons and one signal for the ether methyl protons; ^{13}C NMR ($CDCl_3$) δ 23.1 (C(O)**C**H_3), 40.9 (N**C**H_2), 52.4 (OCH_2**C**H), 59.0 (O**C**H_3), 71.7 (O**C**H_2CH), 127.2, 129.2, 130.3, 133.8, 133.9 (5 Ar**C**), 170.2, 170.4 (2 **C**(O)), one signal was not detected and is believed to overlap with nearby peaks; LRMS (ESI^+) 341.08 [M+Na^+, 100%], 343.08 [M+2+Na^+, 66%], 345.07 [M+4+Na^+, 13%] (calcd for $C_{13}H_{16}Cl_2N_2O_3$ Na^+ 341.04); Anal. Calcd. for $C_{13}H_{16}Cl_2N_2O_3$: C, 48.92; H, 5.05; Cl, 22.21; N, 8.78. Found: C, 48.99, H, 4.98; Cl, 22.36; N, 8.69.

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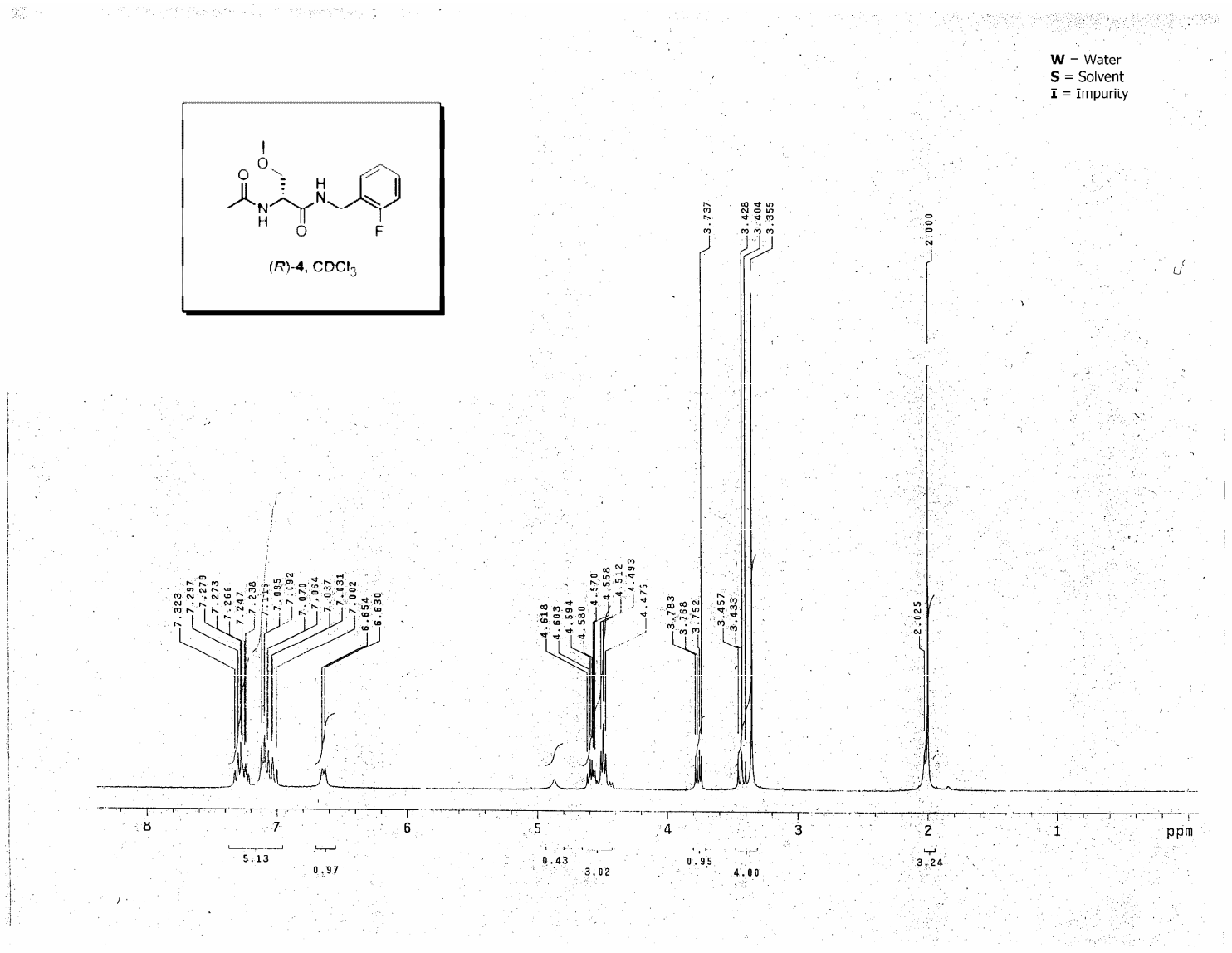
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S = Solvent
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3.768
3.752
3.737
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3.433
3.428
3.404
3.355
2.025
2.000
8
7
6
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4
3
2
1
ppm
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0.95
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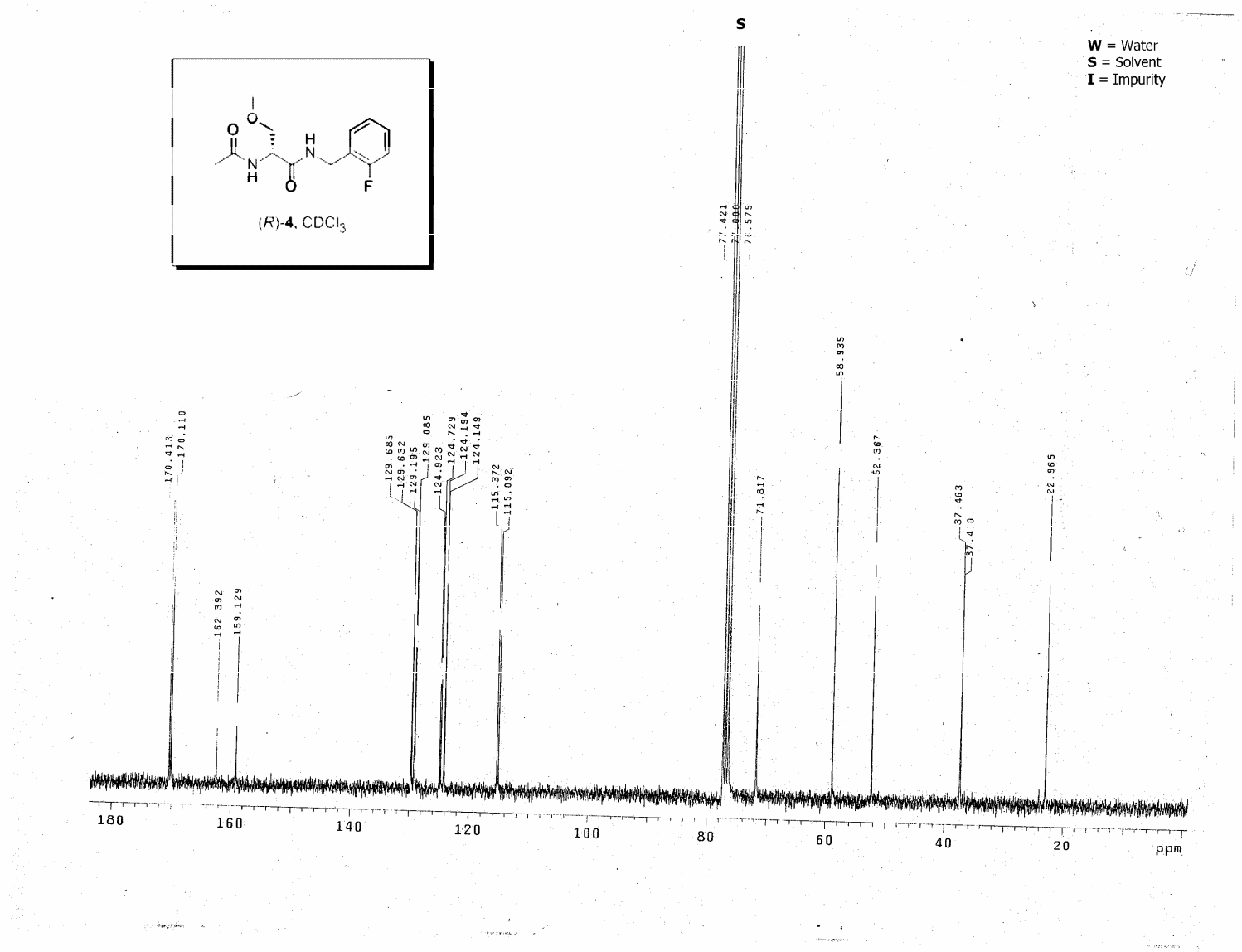
3.24


S
W = Water
S = Solvent
I = Impurity
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129.685
129.632
129.195
129.085
124.923
124.729
124.194
124.149
115.372
115.092
77.421
77.000
76.575
71.817
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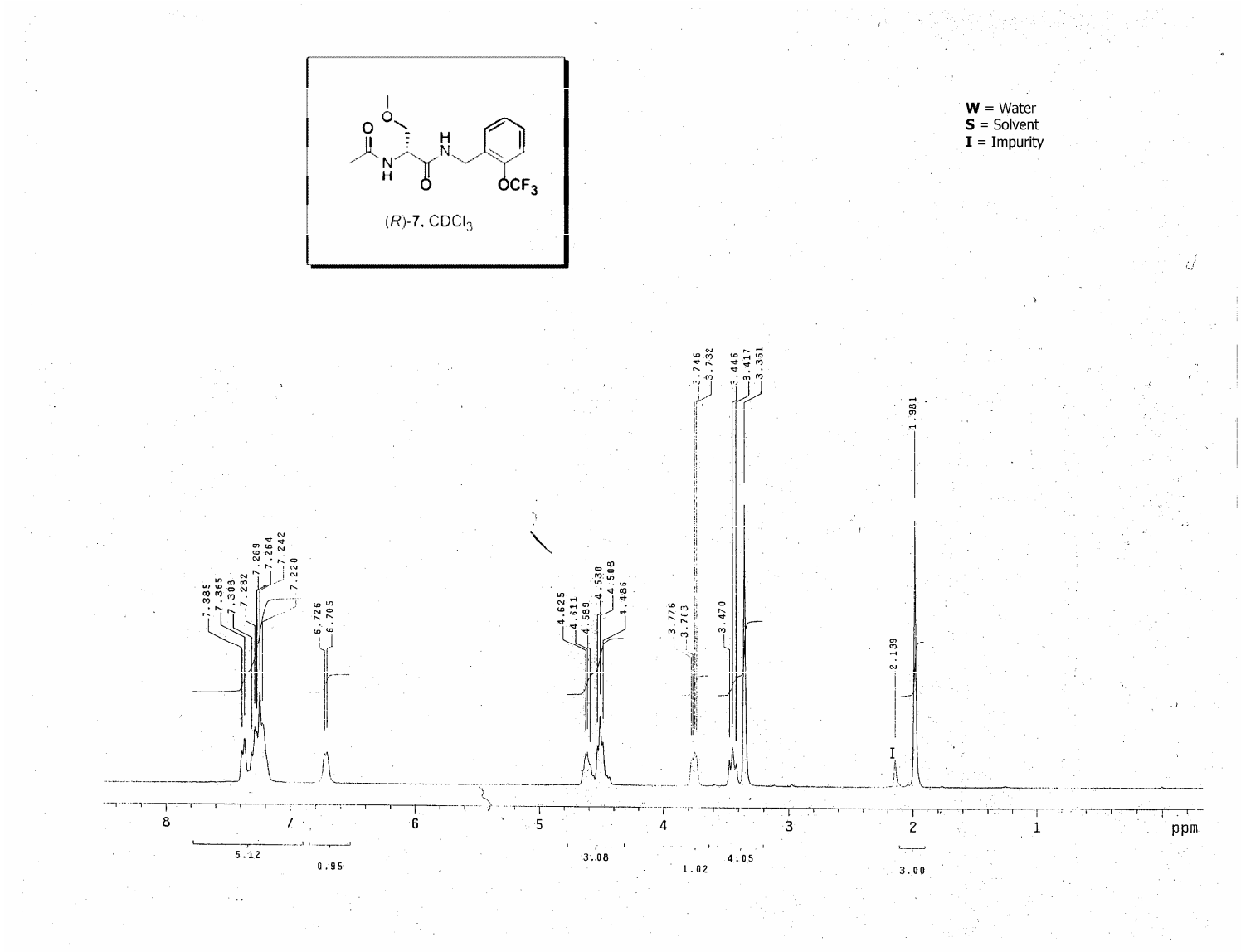
80
60
40
20
ppm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7.242
7.220
6.726
6.705
4.625
4.611
4.589
4.530
4.508
4.486
3.776
3.763
3.746
3.732
3.470
3.446
3.417
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2.139
1.981
I
ppm
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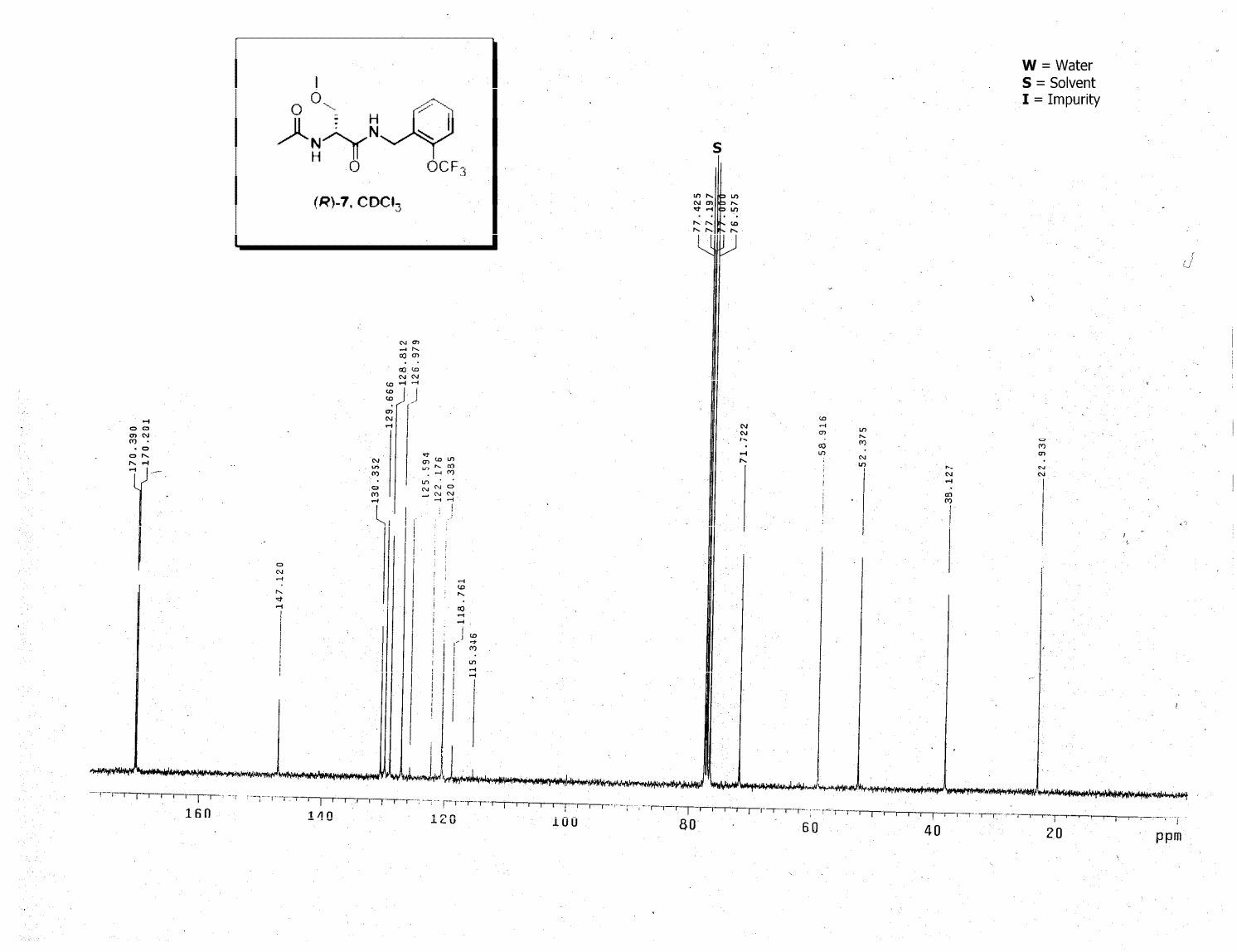
3.00


(R)-7, CDCl3
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I = Impurity
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77.000
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170.201
147.120
130.352
129.666
128.812
126.979
125.594
122.176
120.385
118.761
115.346
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22.930
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140
120
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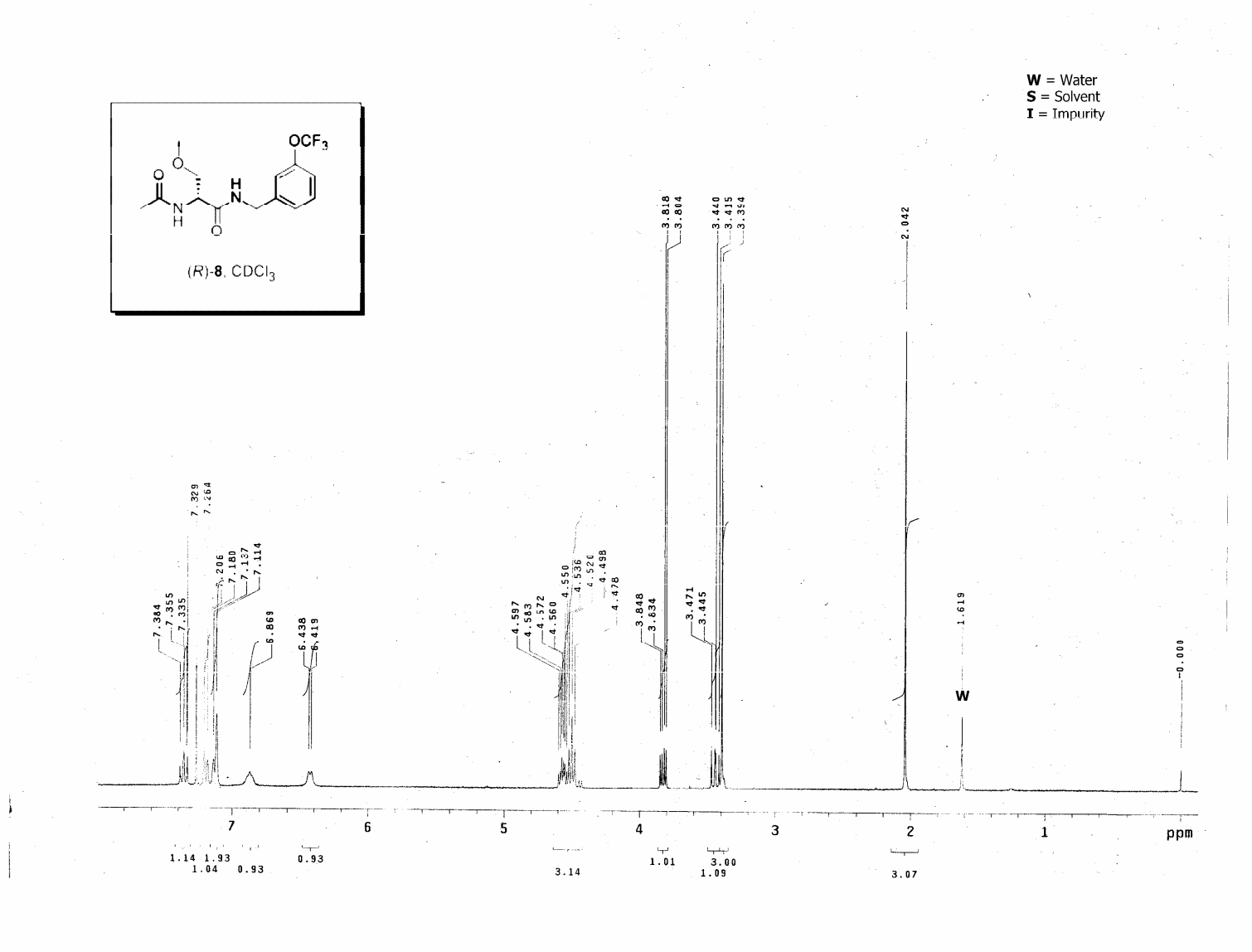
80
60
40
20
ppm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S = Solvent
I = Impurity
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7.335
7.329
7.264
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7.180
7.137
7.114
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6.438
6.419
4.597
4.583
4.572
4.560
4.550
4.536
4.520
4.498
4.478
3.848
3.834
3.818
3.804
3.471
3.445
3.440
3.415
3.354
2.042
1.619
W
0.000
7
6
5
4
3
2
1
ppm
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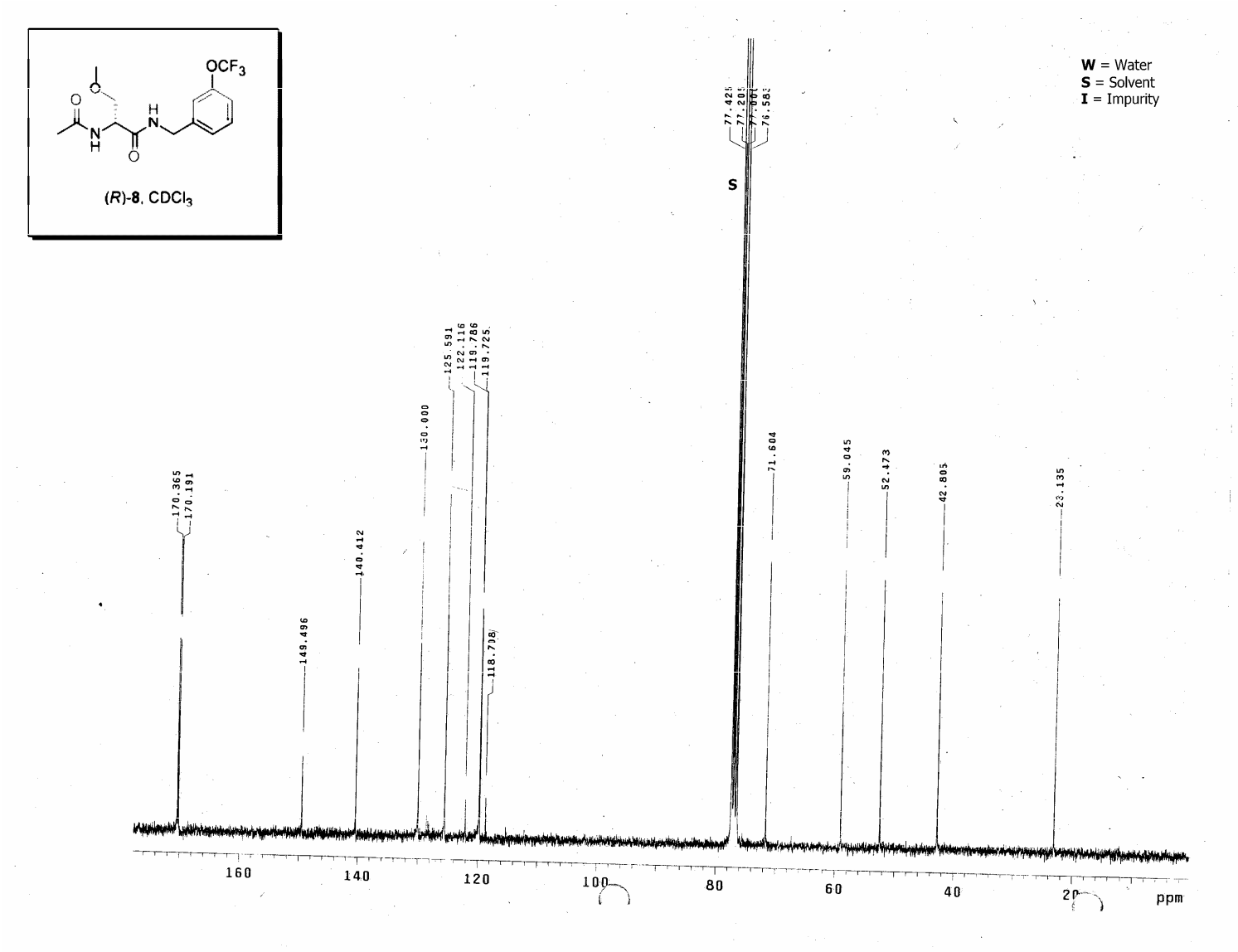
1.93
1.04
0.93
0.93
3.14
1.01
3.00
1.09
3.07


OCF3
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I = Impurity
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170.191
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140.412
130.000
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119.786
119.725
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140
120
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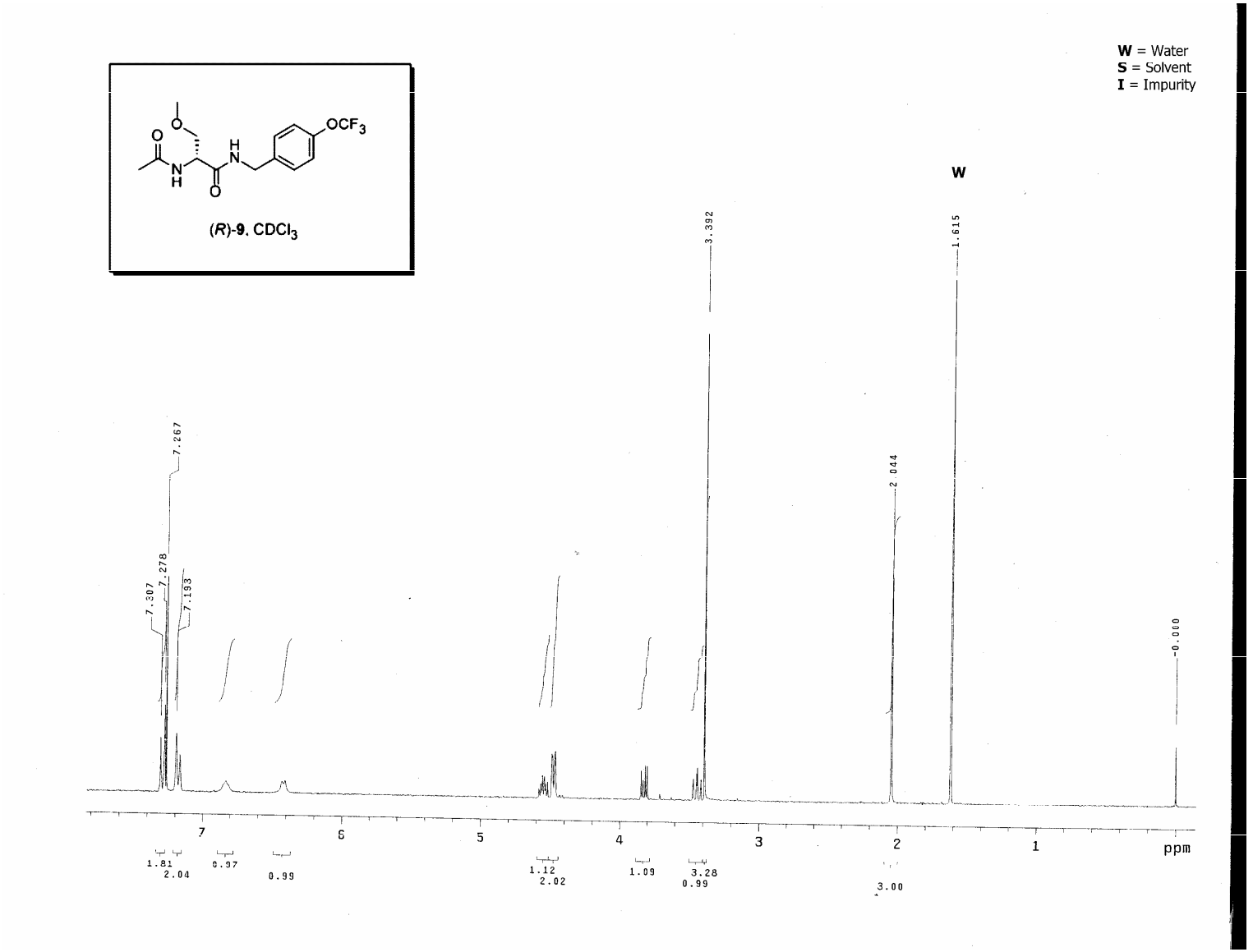
80
60
40
20
ppm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S = Solvent
I = Impurity
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7.307
7.278
7.193
0.000
7
6
5
4
3
2
1
ppm
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0.99
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2.02
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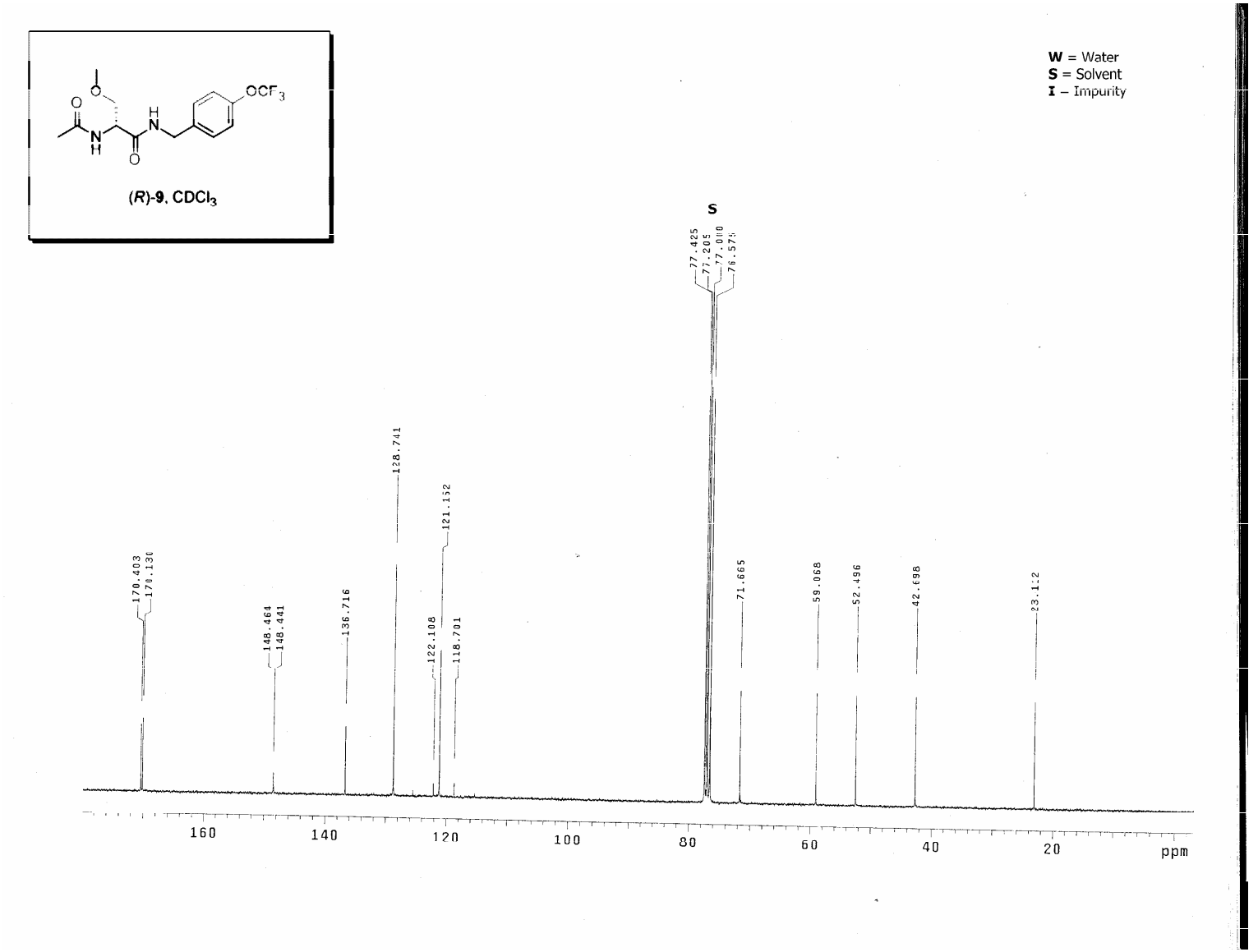
3.00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170.130
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121.132
118.701
71.665
59.068
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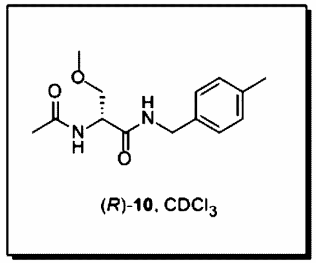
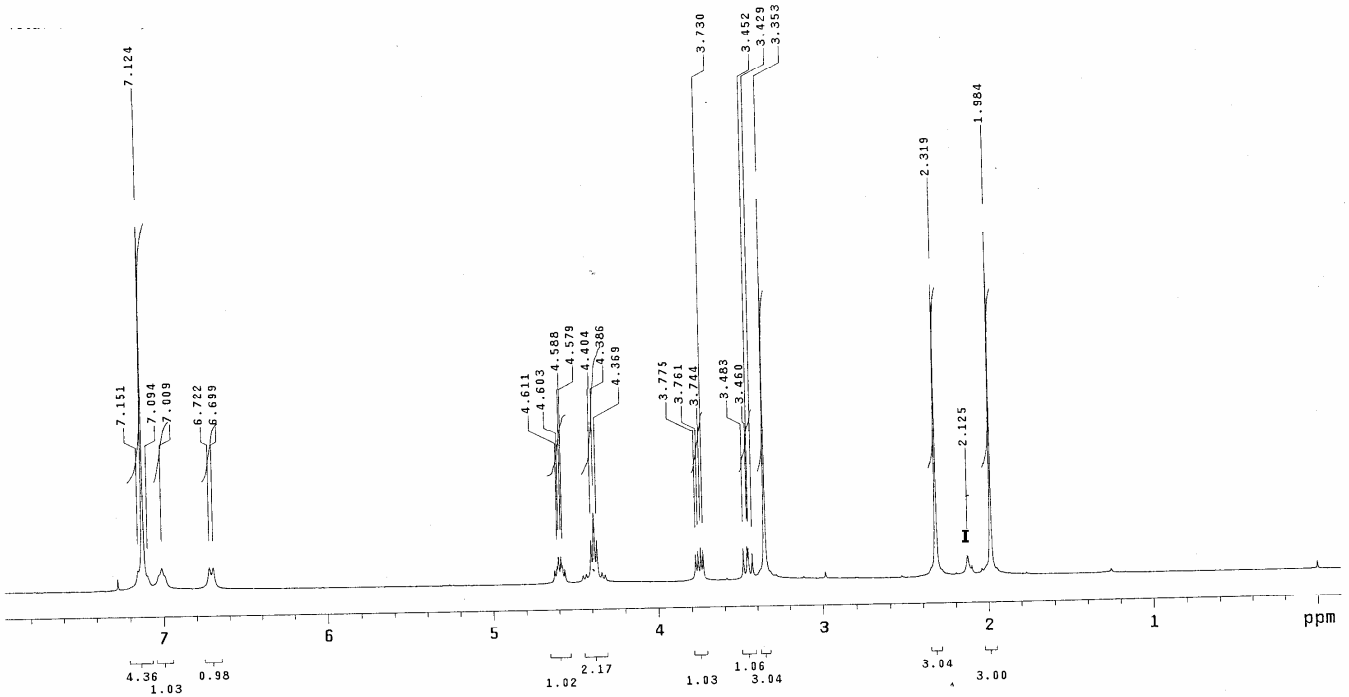
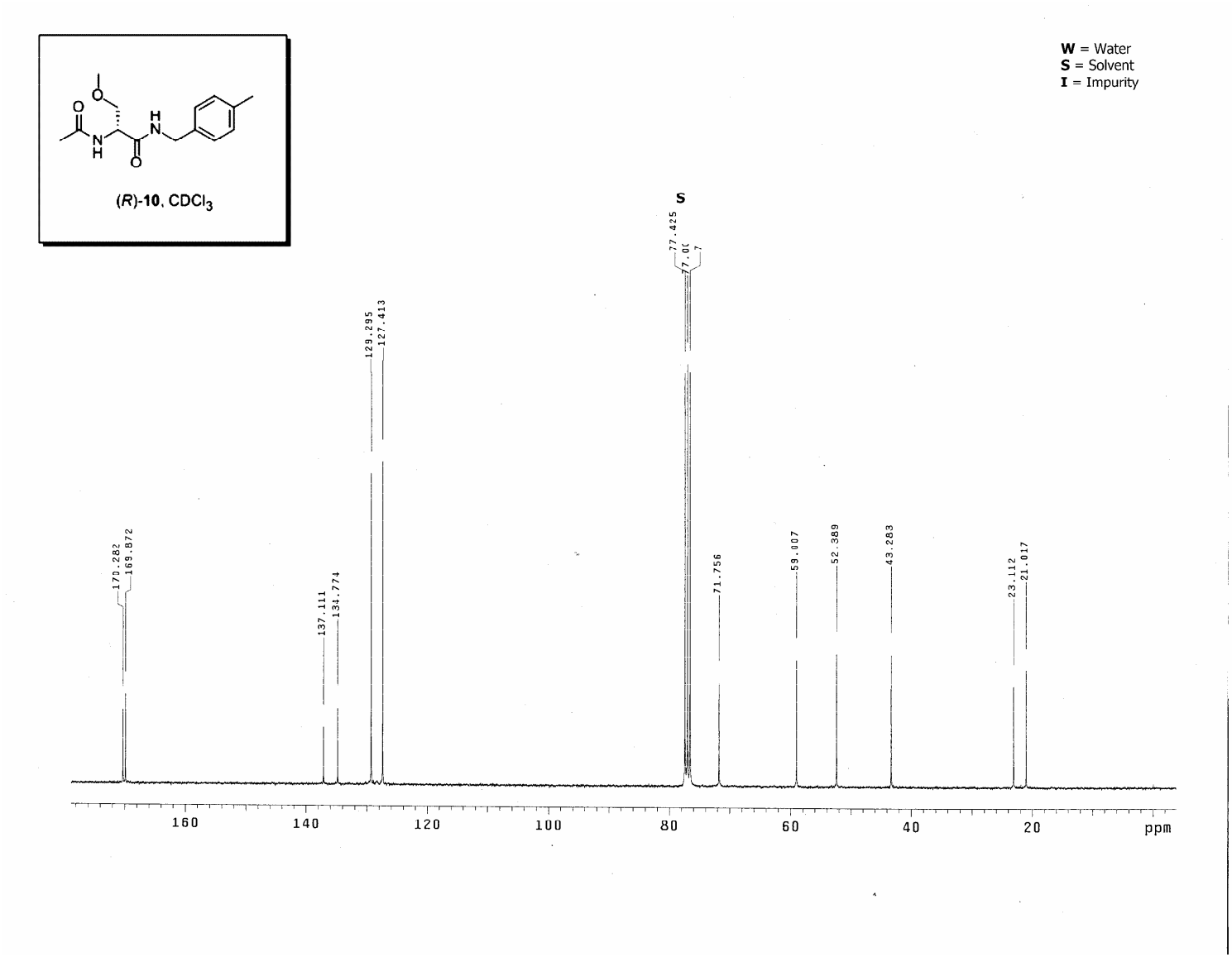
160
140
120
100
80
60
40
20
ppm

W = Water
S = Solvent
I = Impurity



(*R*)-**10**, $CDCl_3$

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80
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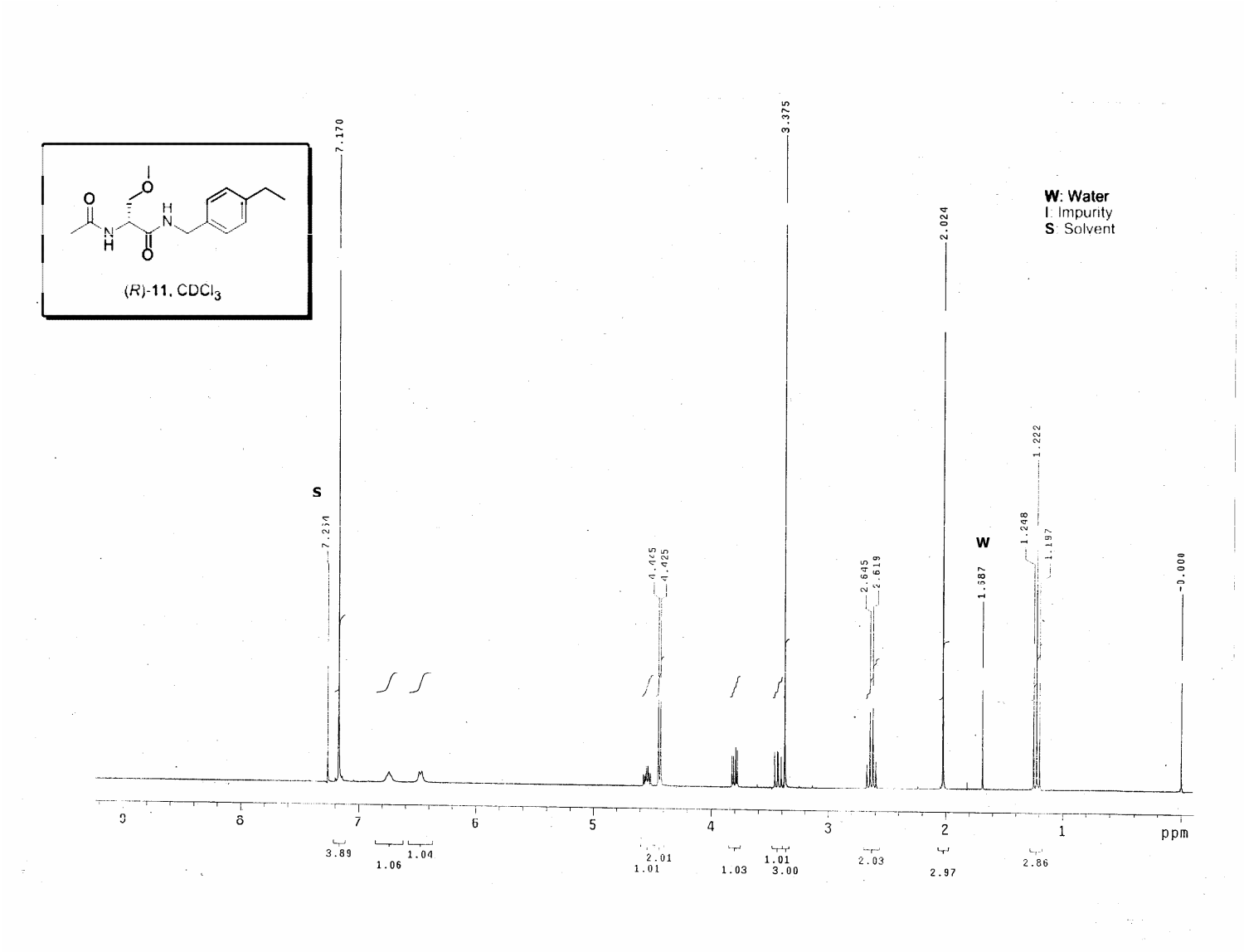
20
ppm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W: Water
I: Impurity
S: Solvent
S
W
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2.024
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1.222
1.248
1.197
2.645
2.619
1.425
1.415
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3.00
2.03
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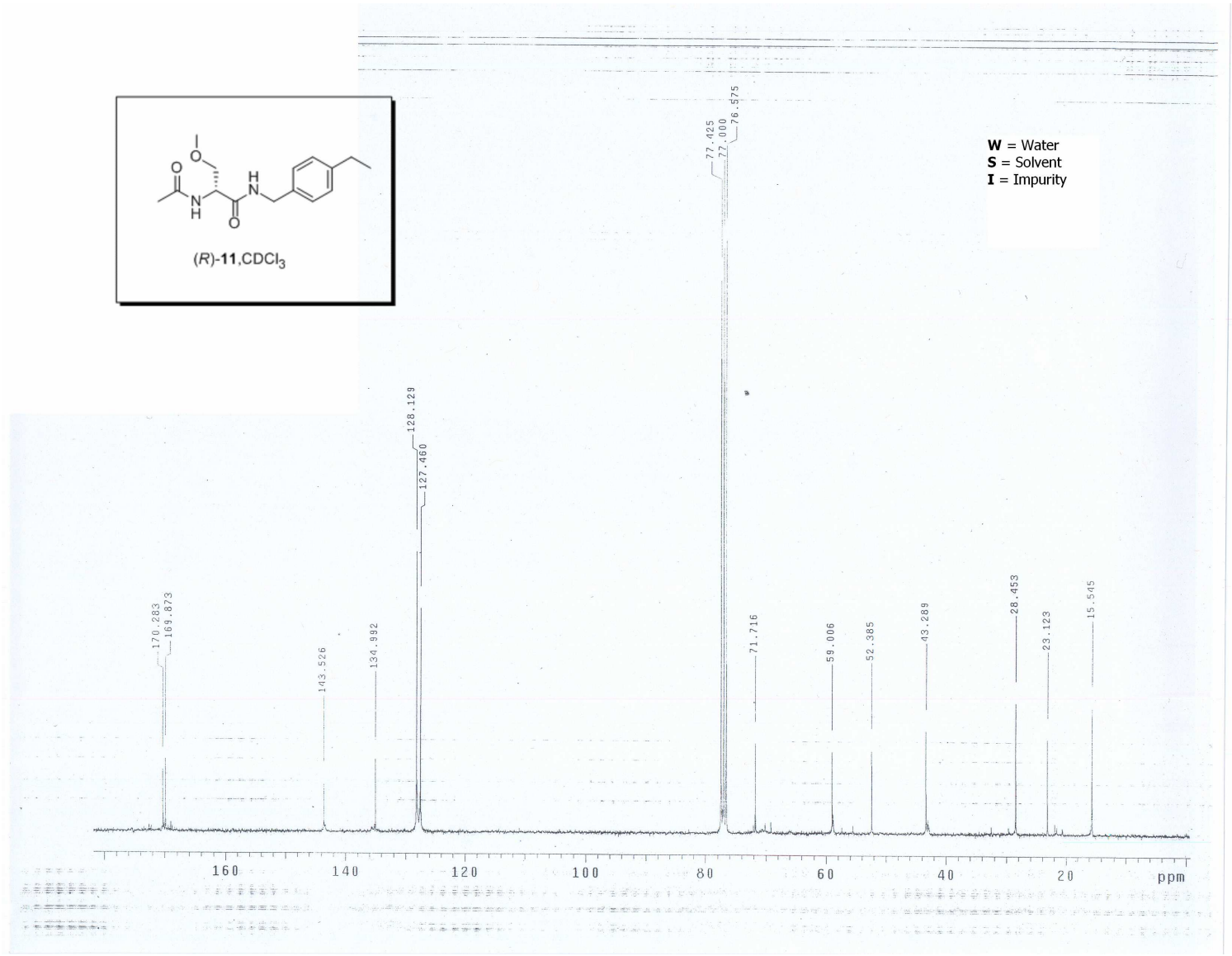
ppm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76.575
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59.006
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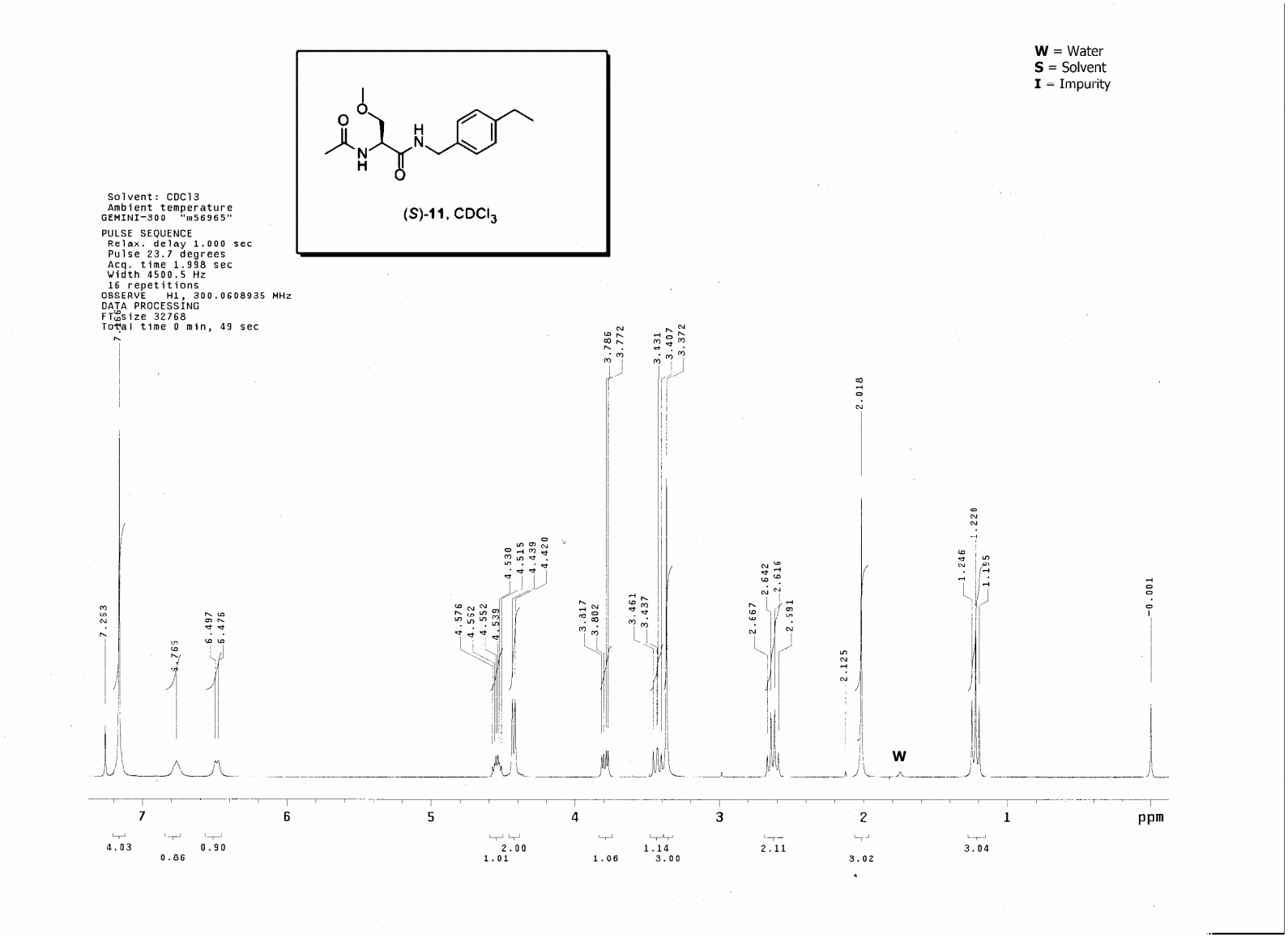
43.289
28.453
23.123
15.545
160
140
120
100
80
60
40
20
ppm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S = Solvent
I = Impurity
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Solvent: CDCl3
Ambient temperature
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Relax. delay 1.000 sec
Pulse 23.7 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 300.0608935 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 49 sec
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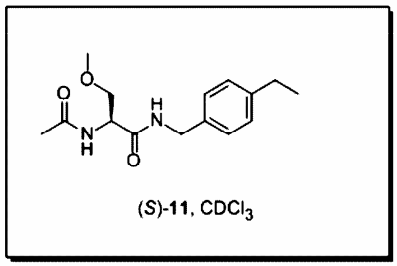
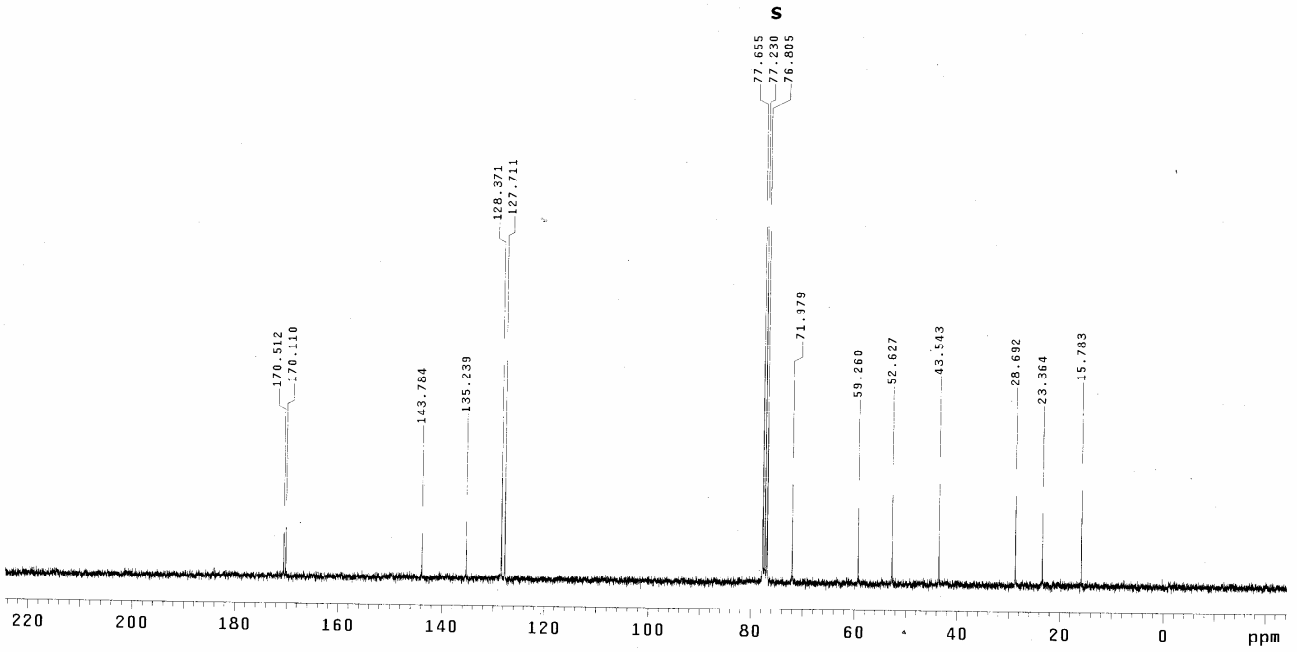
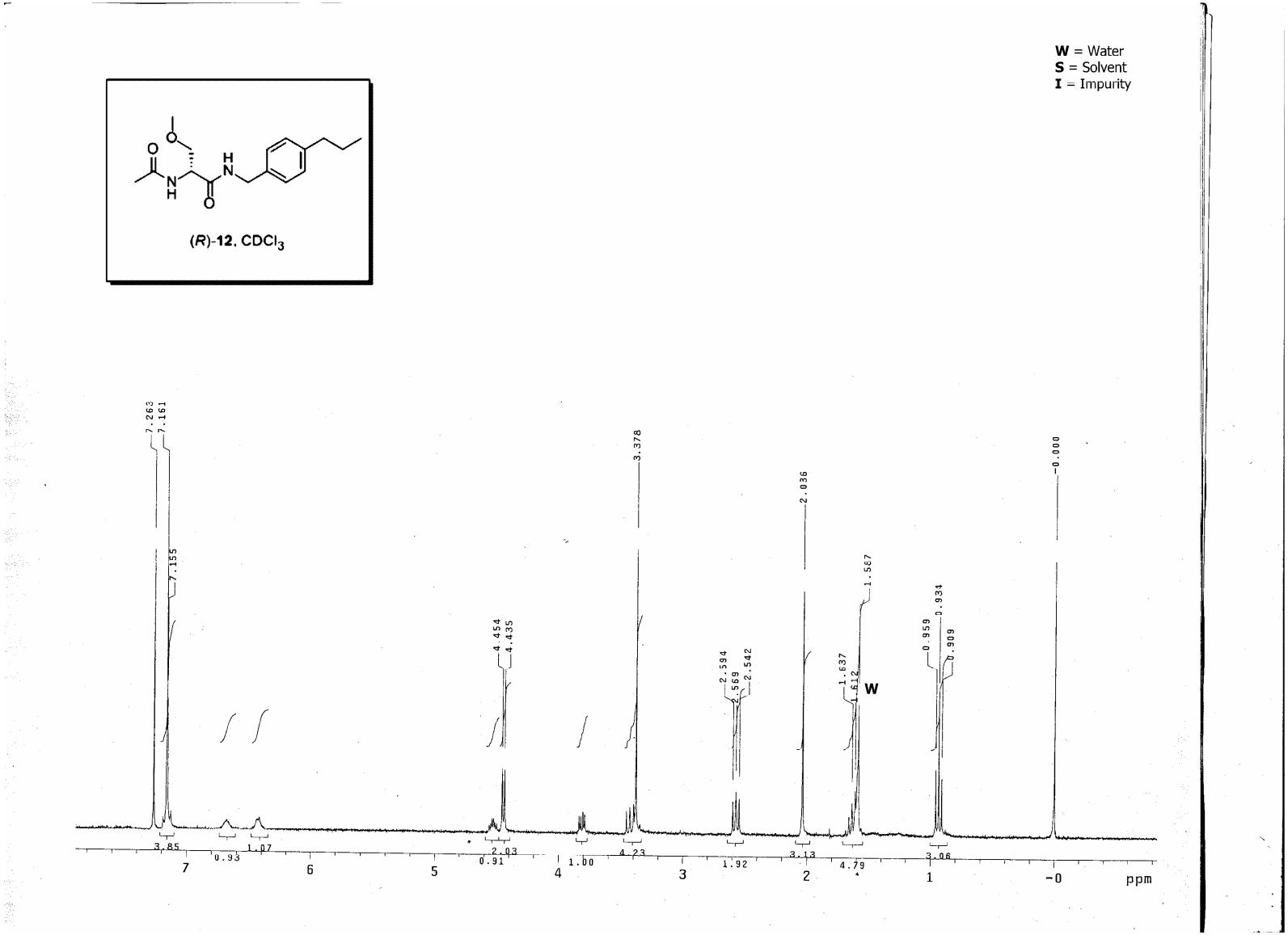
6.765
6.497
6.476
4.576
4.552
4.539
4.530
4.515
4.439
4.420
3.817
3.802
3.786
3.772
3.461
3.437
3.431
3.407
3.372
2.667
2.642
2.616
2.591
2.125
2.018
1.246
1.220
1.195
0.001
W
7
6
5
4
3
2
1
ppm
4.03
0.86
0.90
2.00
1.01
1.06
1.14
3.00
2.11
3.02
3.04

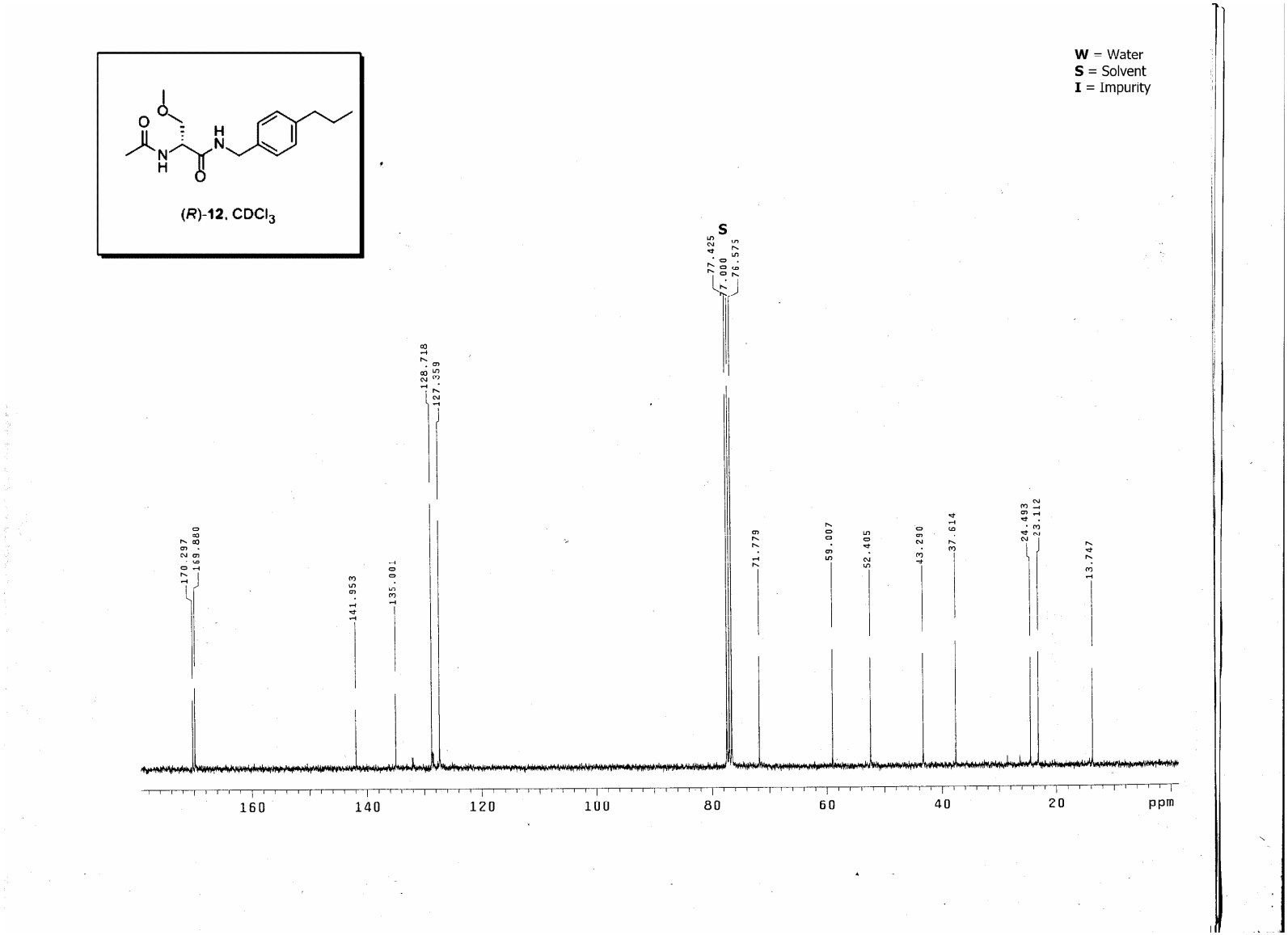


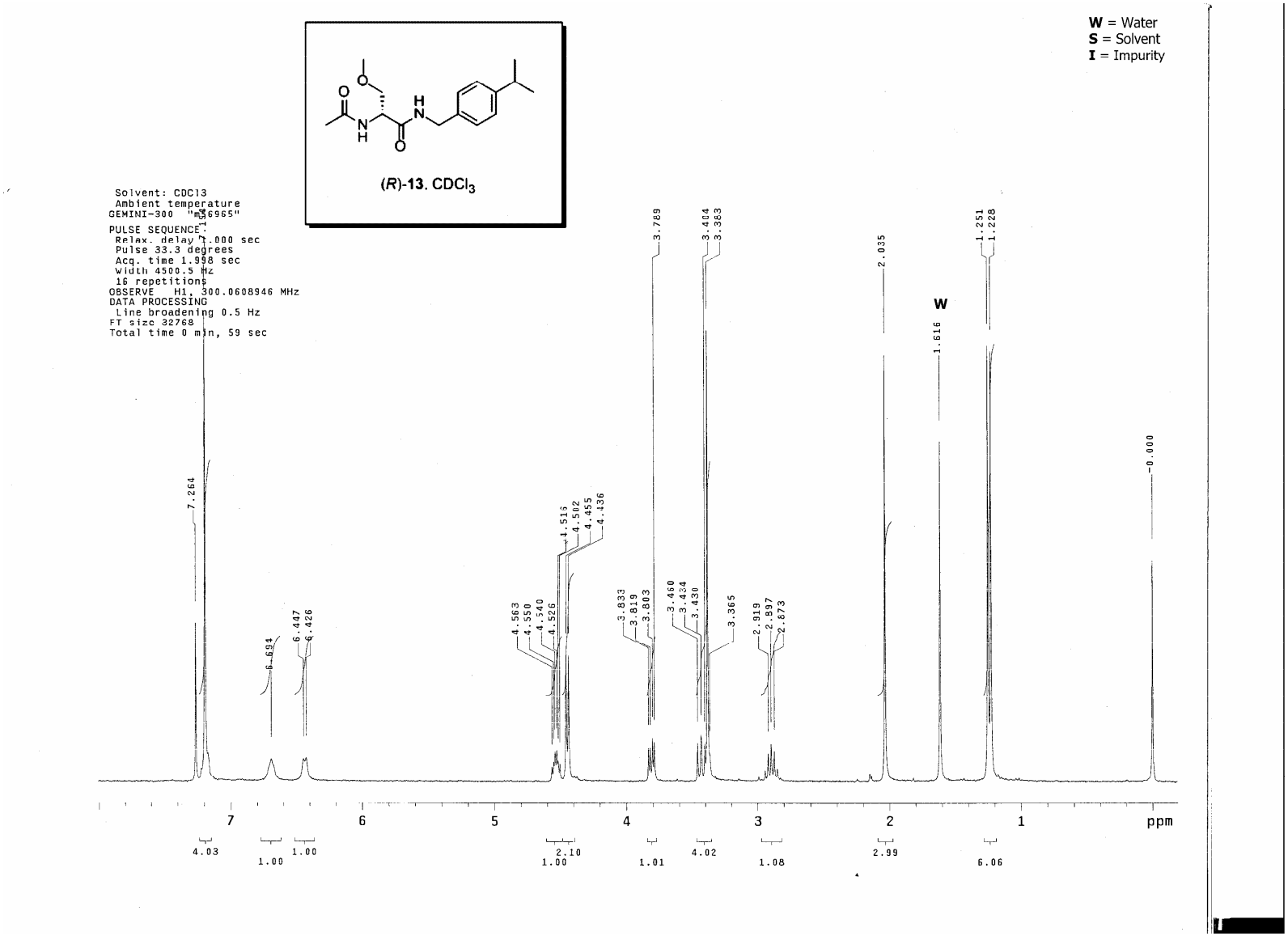
(*S*)-**11**, $CDCl_3$

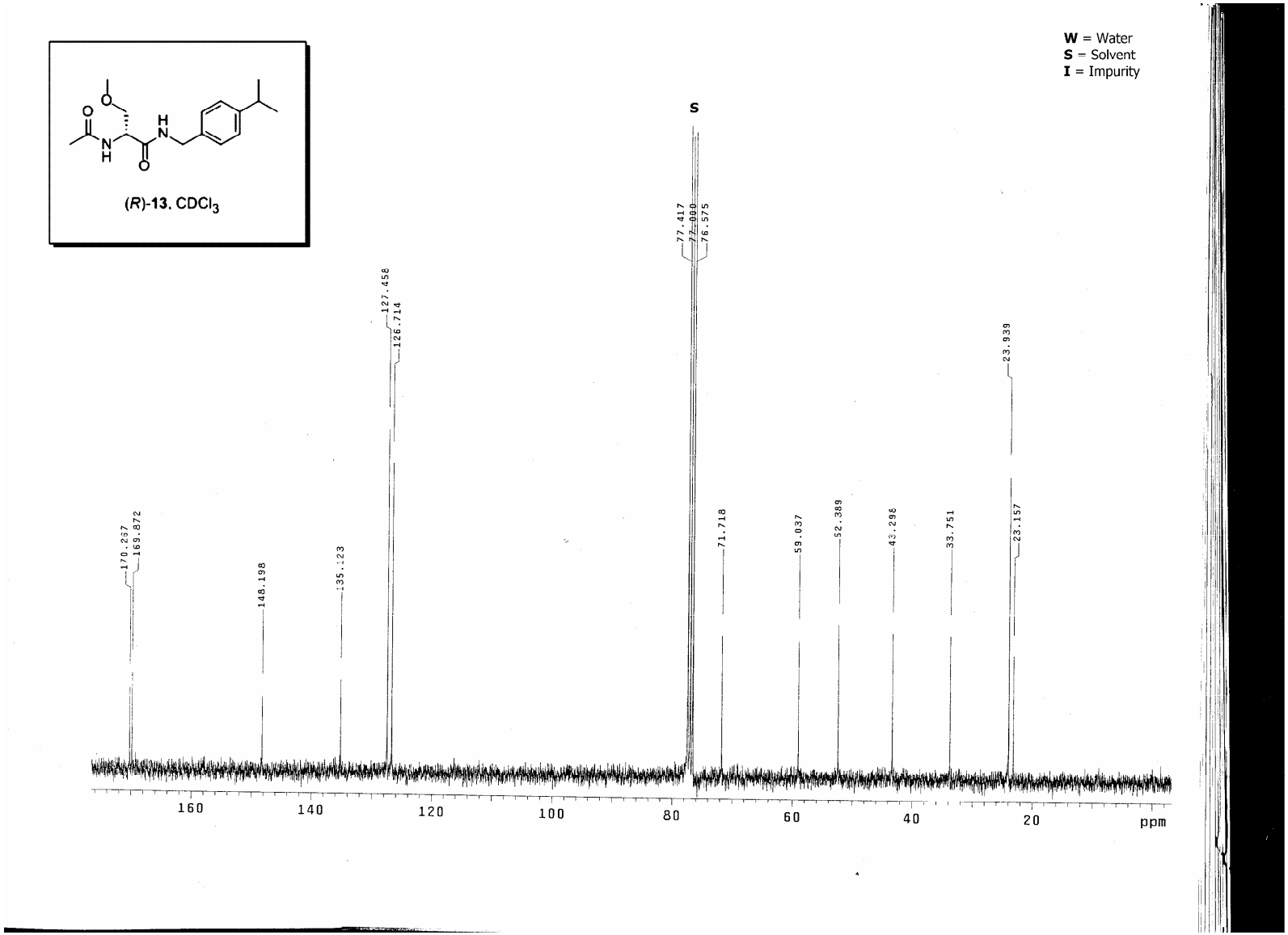
W = Water
S = Solvent
I = Impurity

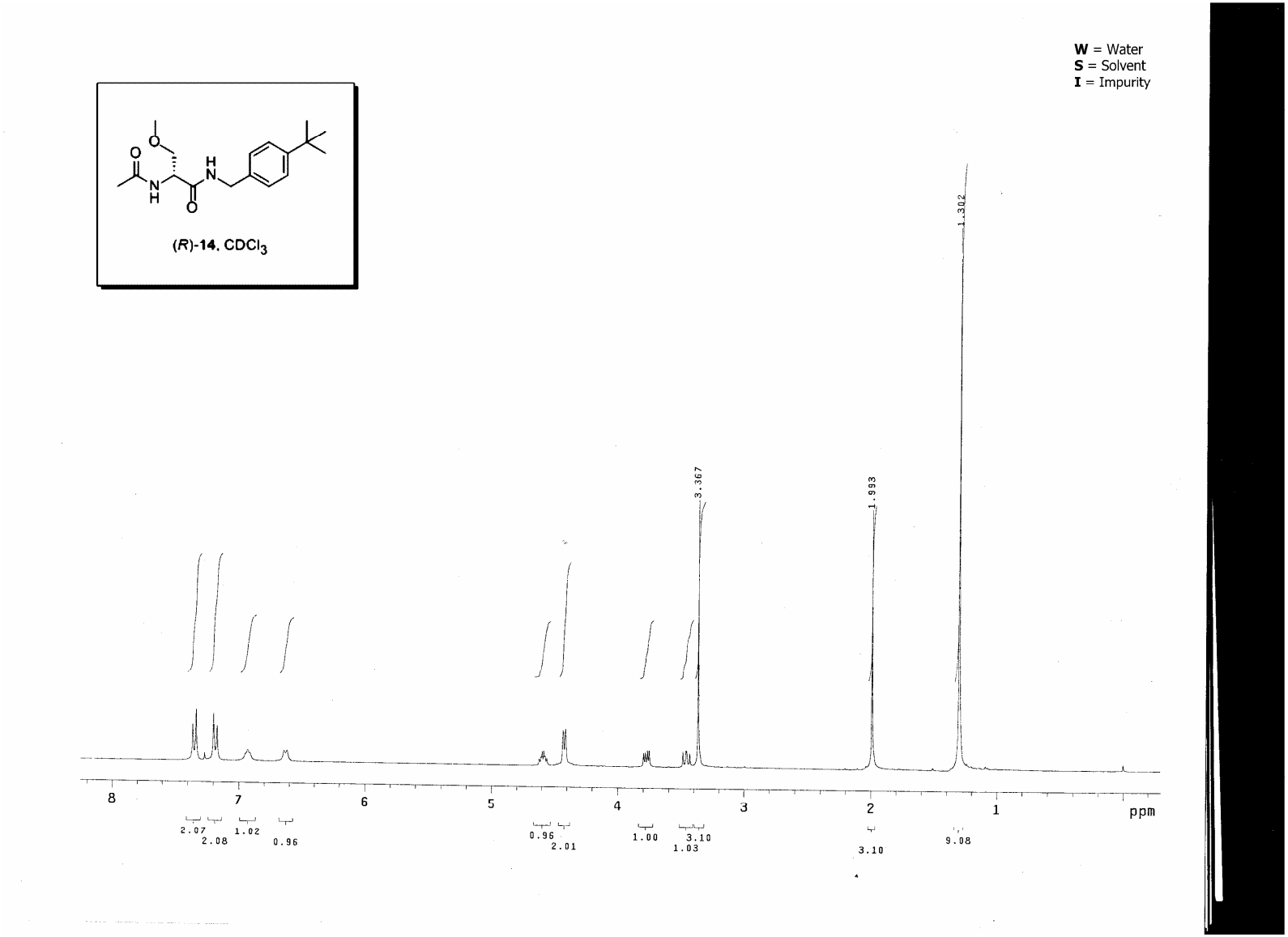


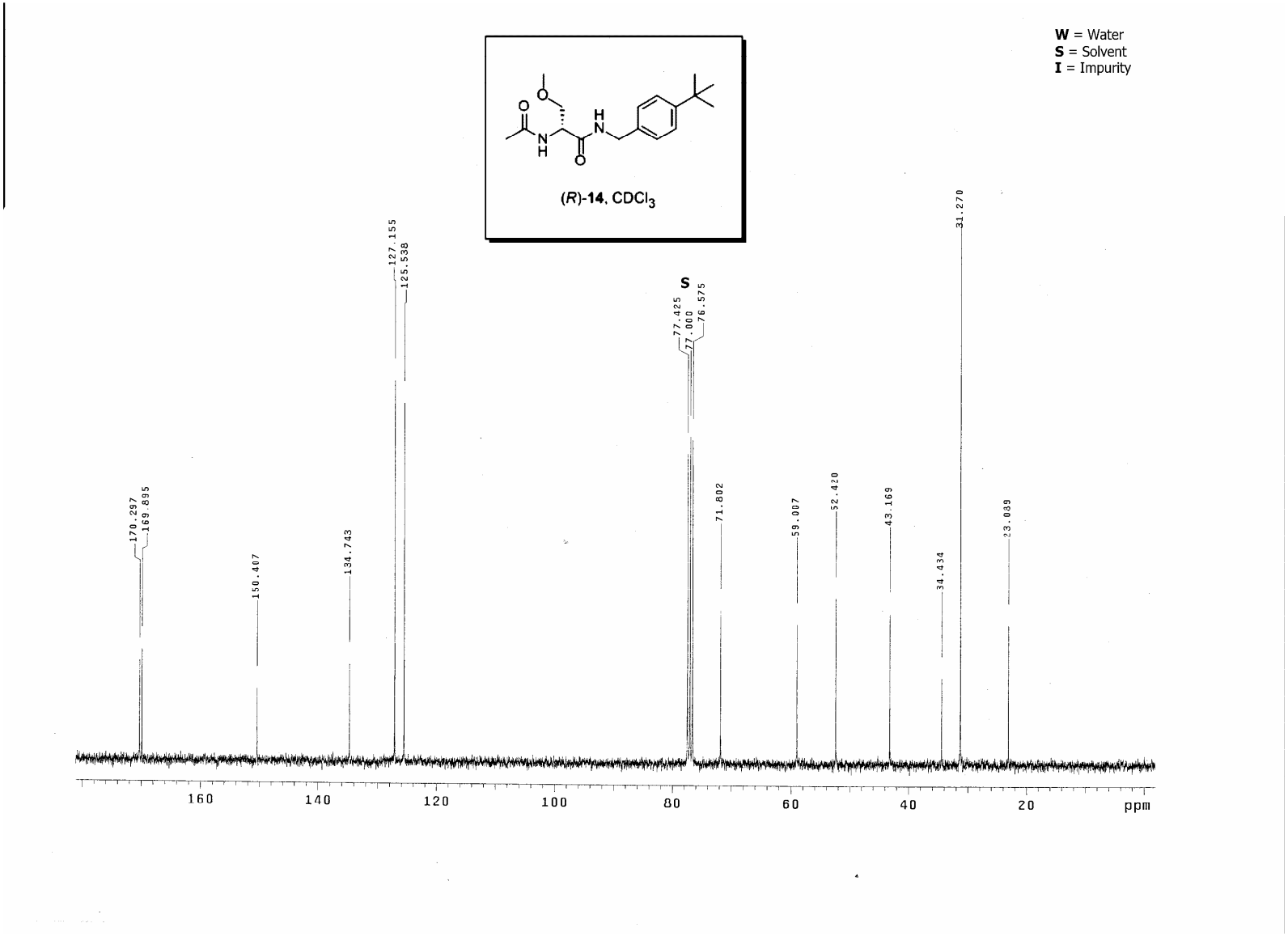

W = Water
S = Solvent
I = Impurity
(R)-12, CDCl3
7.263
7.161
7.155
4.454
4.435
3.378
2.594
2.569
2.542
2.036
1.637
1.612
1.587
W
0.959
0.934
0.909
-0.000
3.85
0.93
1.07
2.03
0.91
1.00
4.23
1.92
3.13
4.79
3.06
7
6
5
4
3
2
1
-0
ppm

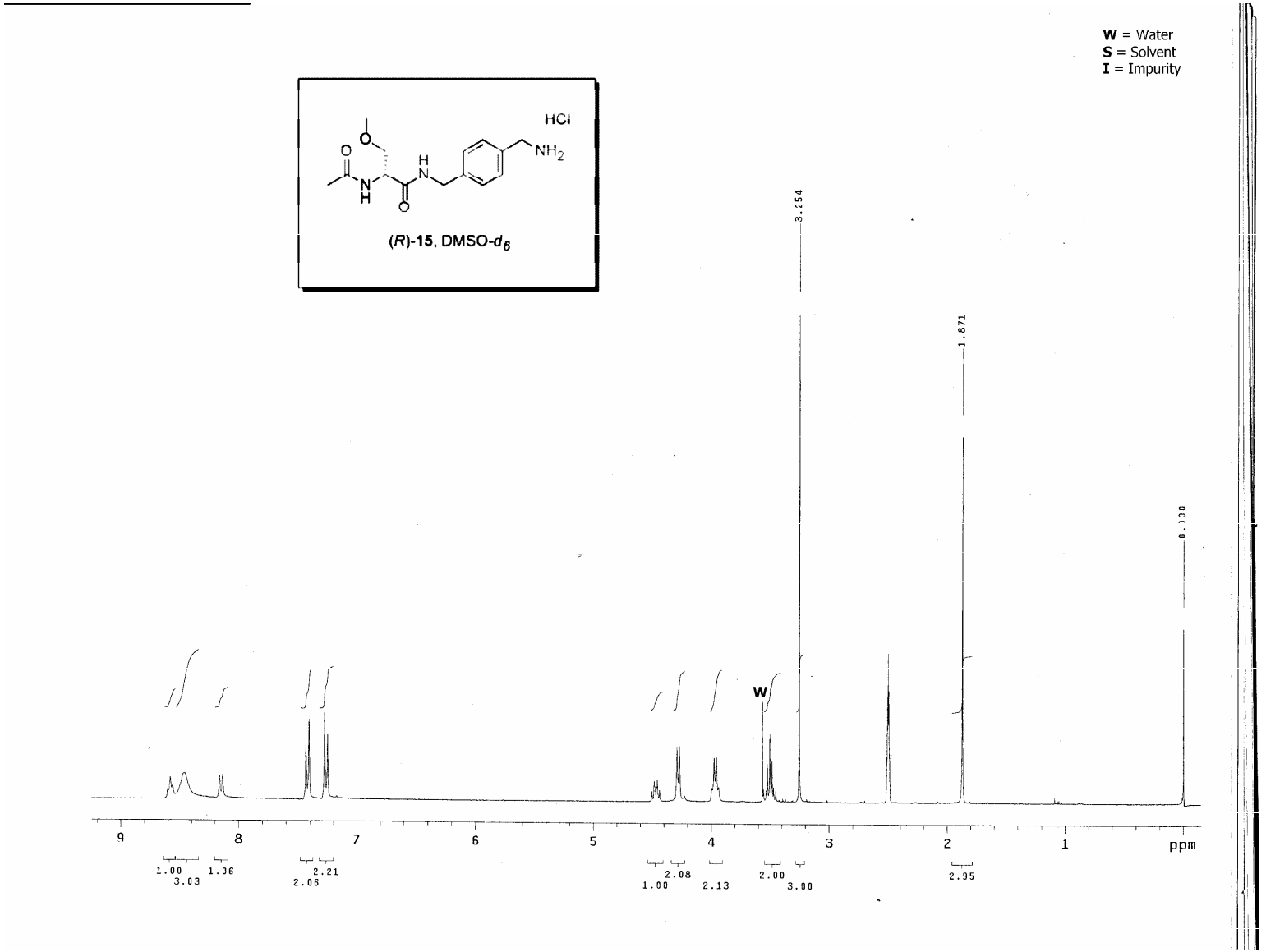

(R)-12, CDCl3
W = Water
S = Solvent
I = Impurity
S
77.425
77.000
76.575
128.718
127.359
170.297
169.880
141.953
135.001
71.779
59.007
52.405
43.290
37.614
24.493
23.112
13.747
160
140
120
100
80
60
40
20
ppm

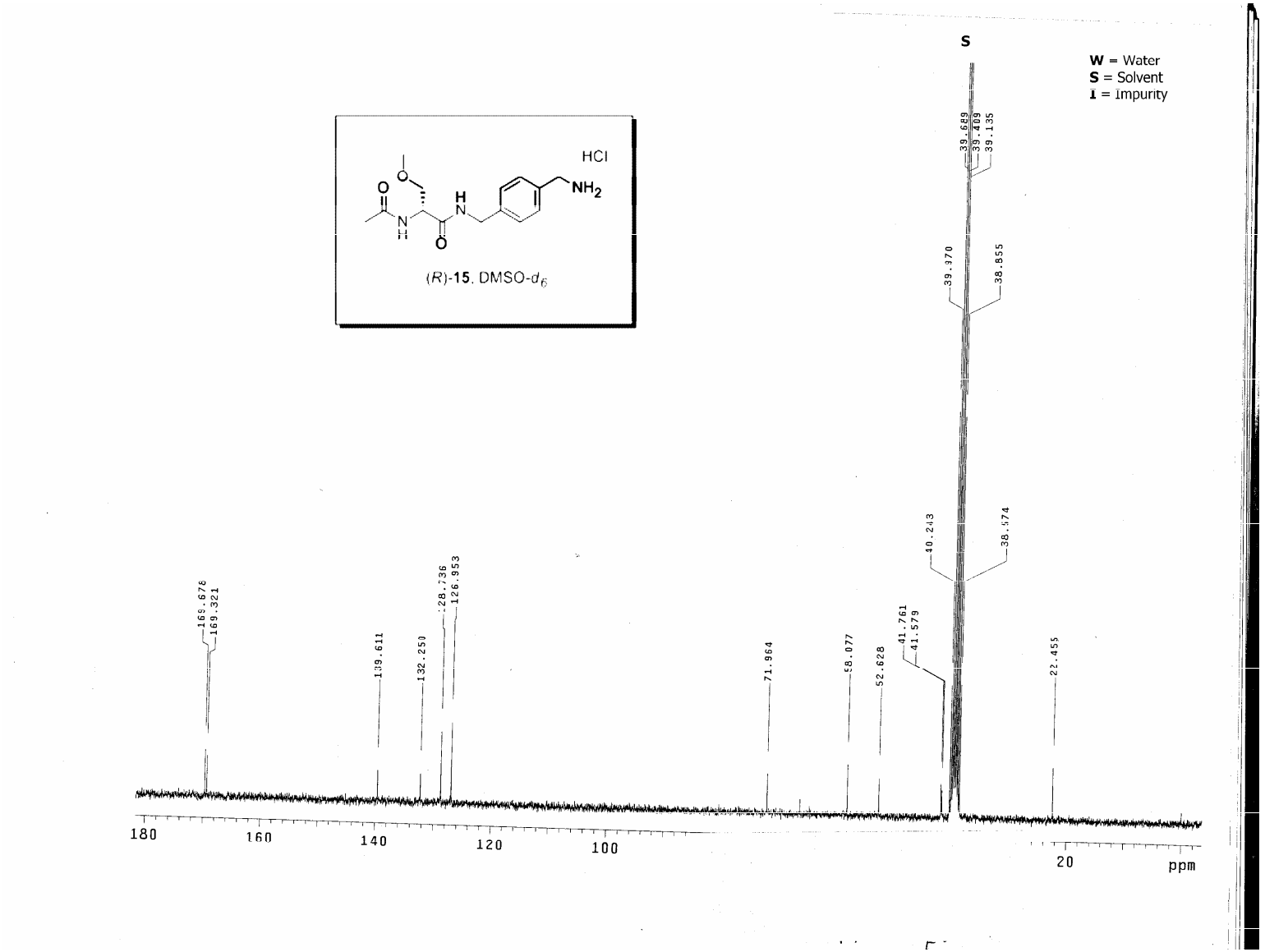

(R)-13. CDCl3
W = Water
S = Solvent
I = Impurity
Solvent: CDCl3
Ambient temperature
GEMINI-300 "m36965"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 33.3 degrees
Acq. time 1.998 sec
width 4500.5 Hz
16 repetitions
OBSERVE H1, 300.0608946 MHz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 32768
Total time 0 min, 59 sec
7.264
6.434
6.447
6.426
4.563
4.550
4.540
4.526
4.516
4.502
4.455
4.436
3.833
3.819
3.803
3.769
3.460
3.434
3.430
3.404
3.383
3.365
2.919
2.897
2.873
2.035
W
1.616
1.251
1.228
0.000
7
6
5
4
3
2
1
ppm
4.03
1.00
1.00
2.10
1.00
1.01
4.02
1.08
2.99
6.06

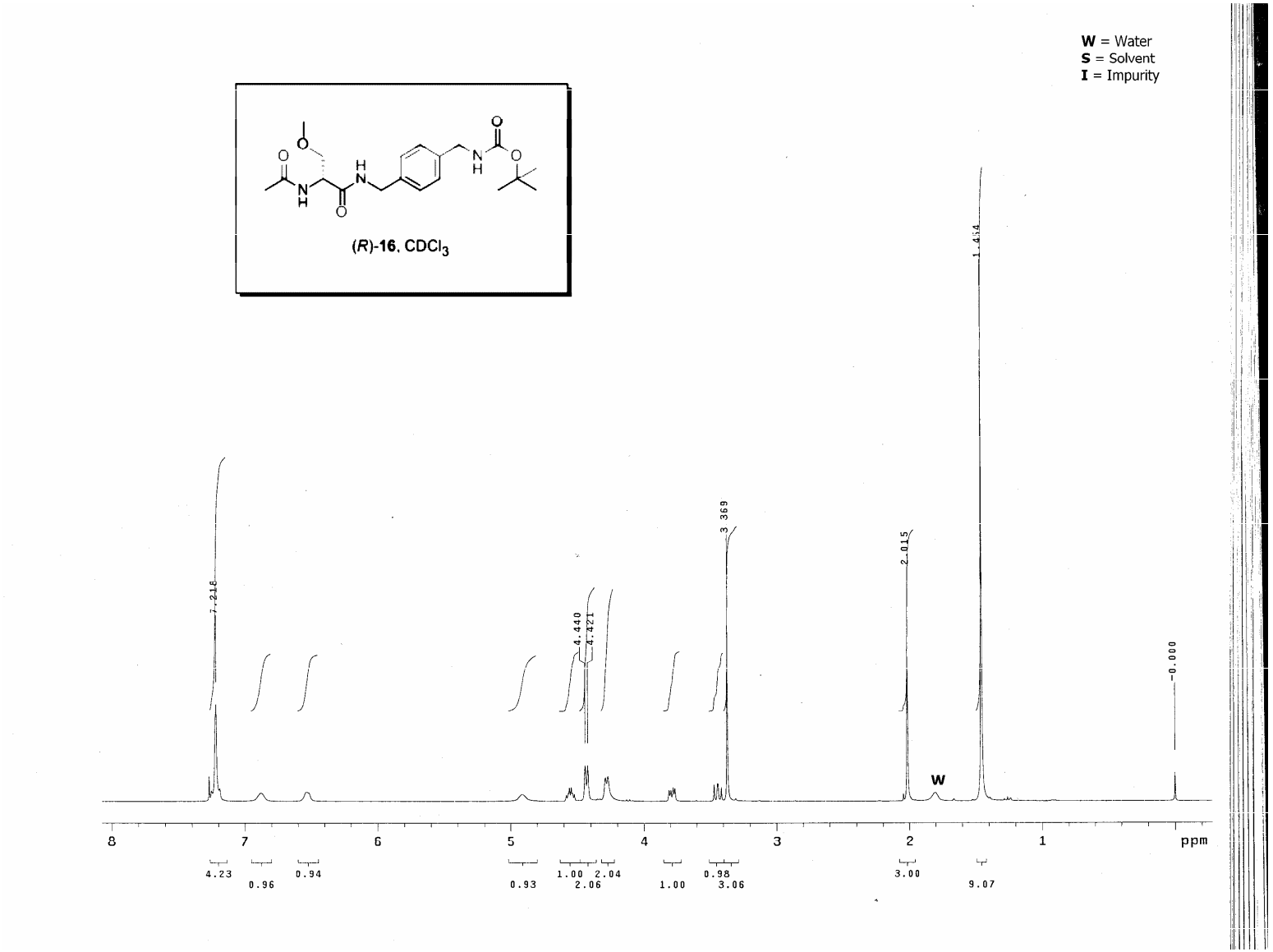

(R)-13, CDCl3
W = Water
S = Solvent
I = Impurity
S
77.417
77.000
76.575
127.458
126.714
170.237
169.872
148.198
135.123
71.718
59.037
52.389
43.298
33.751
23.939
23.157
160
140
120
100
80
60
40
20
ppm

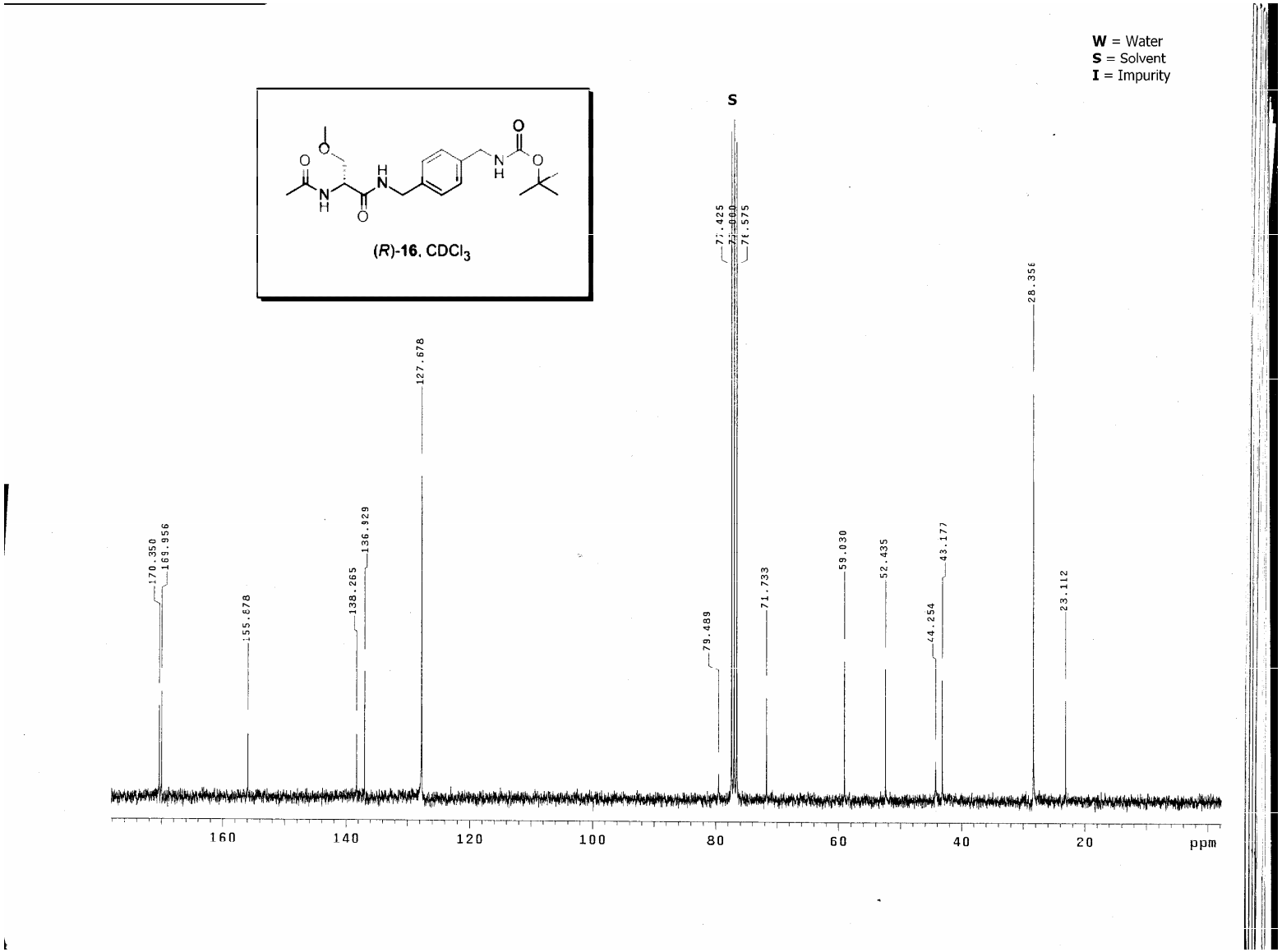

W = Water
S = Solvent
I = Impurity
(R)-14, CDCl3
1.302
3.367
1.993
8
7
6
5
4
3
2
1
ppm
2.07
2.08
1.02
0.96
0.96
2.01
1.00
3.10
1.03
3.10
9.08

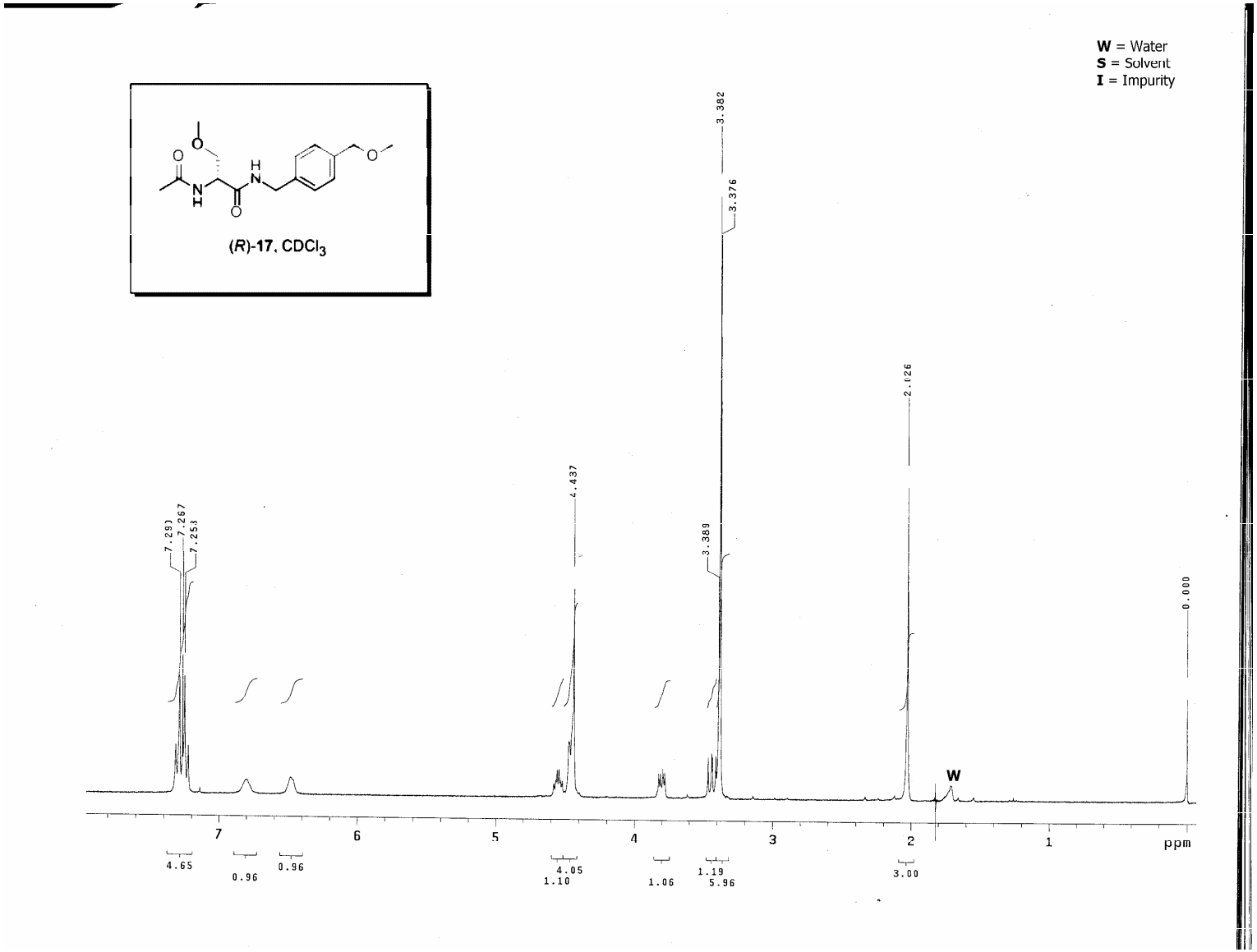

W = Water
S = Solvent
I = Impurity
(R)-14, CDCl3
S
170.297
169.895
150.407
134.743
127.155
125.538
77.425
77.000
76.575
71.802
59.007
52.420
43.169
34.434
31.270
23.089
160
140
120
100
80
60
40
20
ppm

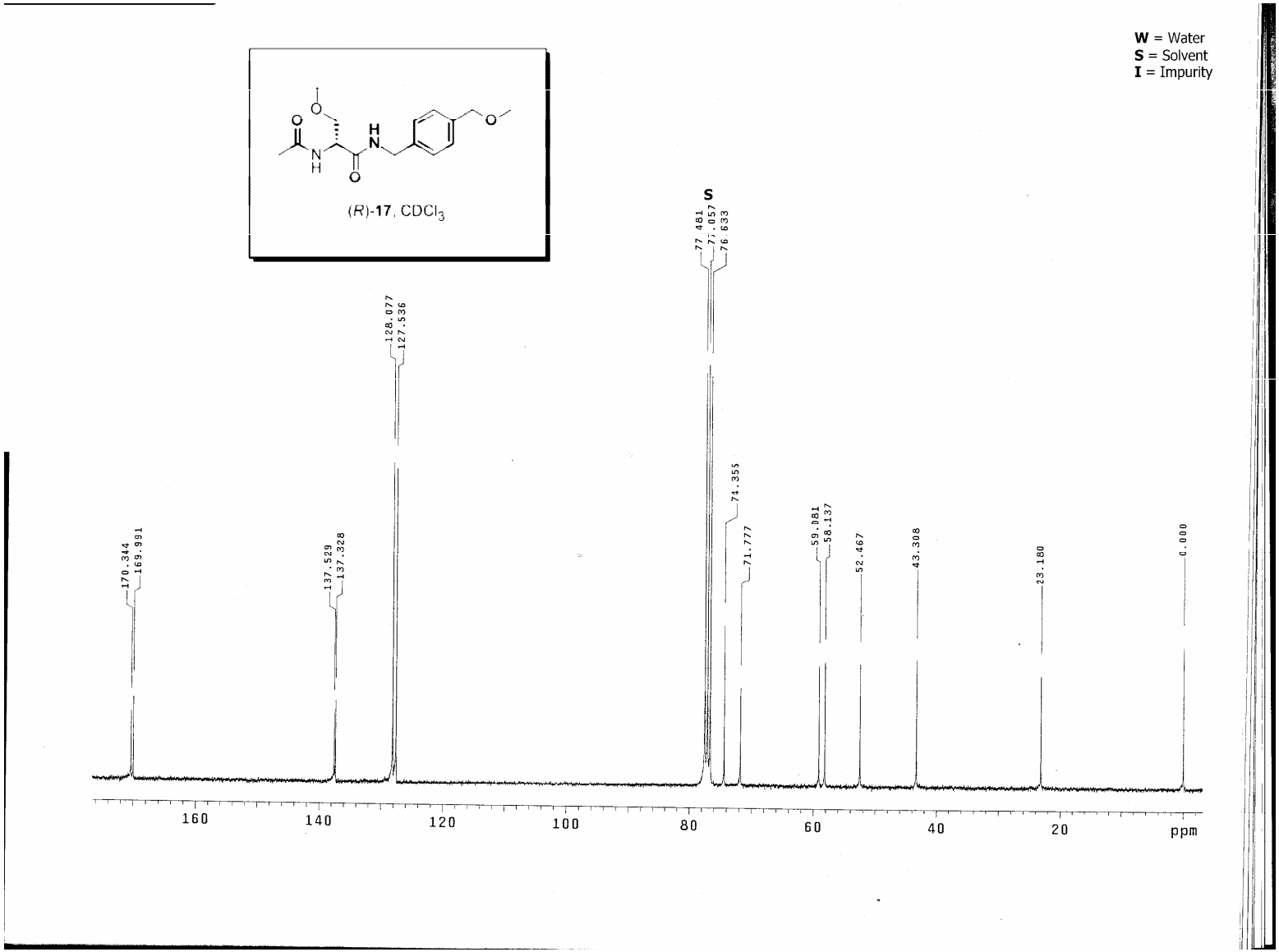

W = Water
S = Solvent
I = Impurity
HCl
NH2
(R)-15, DMSO-d6
3.254
1.871
0.100
W
9
8
7
6
5
4
3
2
1
ppm
1.00
3.03
1.06
2.21
2.06
1.00
2.08
2.13
2.00
3.00
2.95

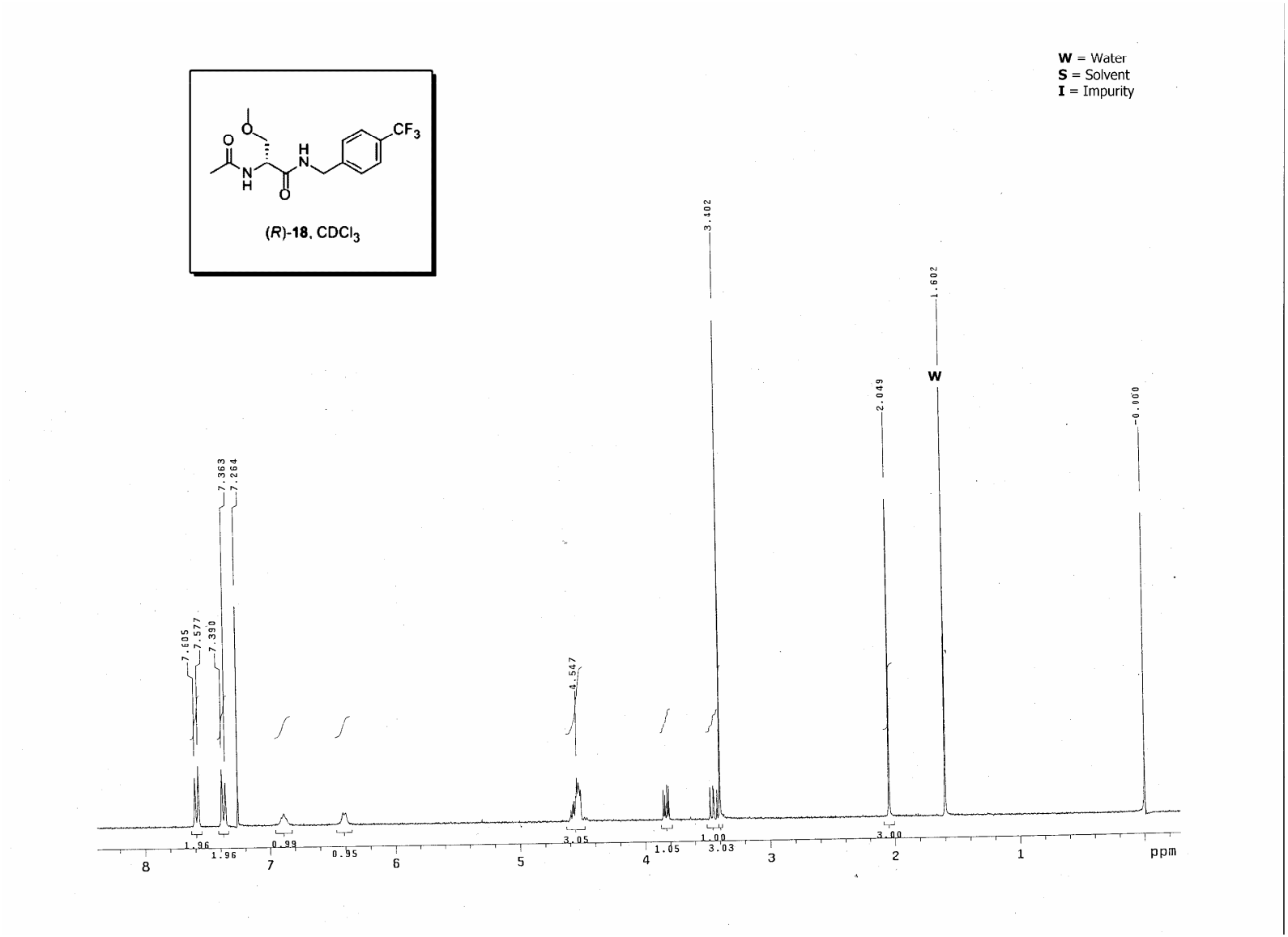

S
W = Water
S = Solvent
I = Impurity
HCl
NH2
(R)-15, DMSO-d6
39.629
39.409
39.135
39.370
38.855
40.243
38.474
169.678
169.321
139.611
132.253
128.736
126.953
71.964
58.077
52.628
41.761
41.579
22.455
180
160
140
120
100
20
ppm

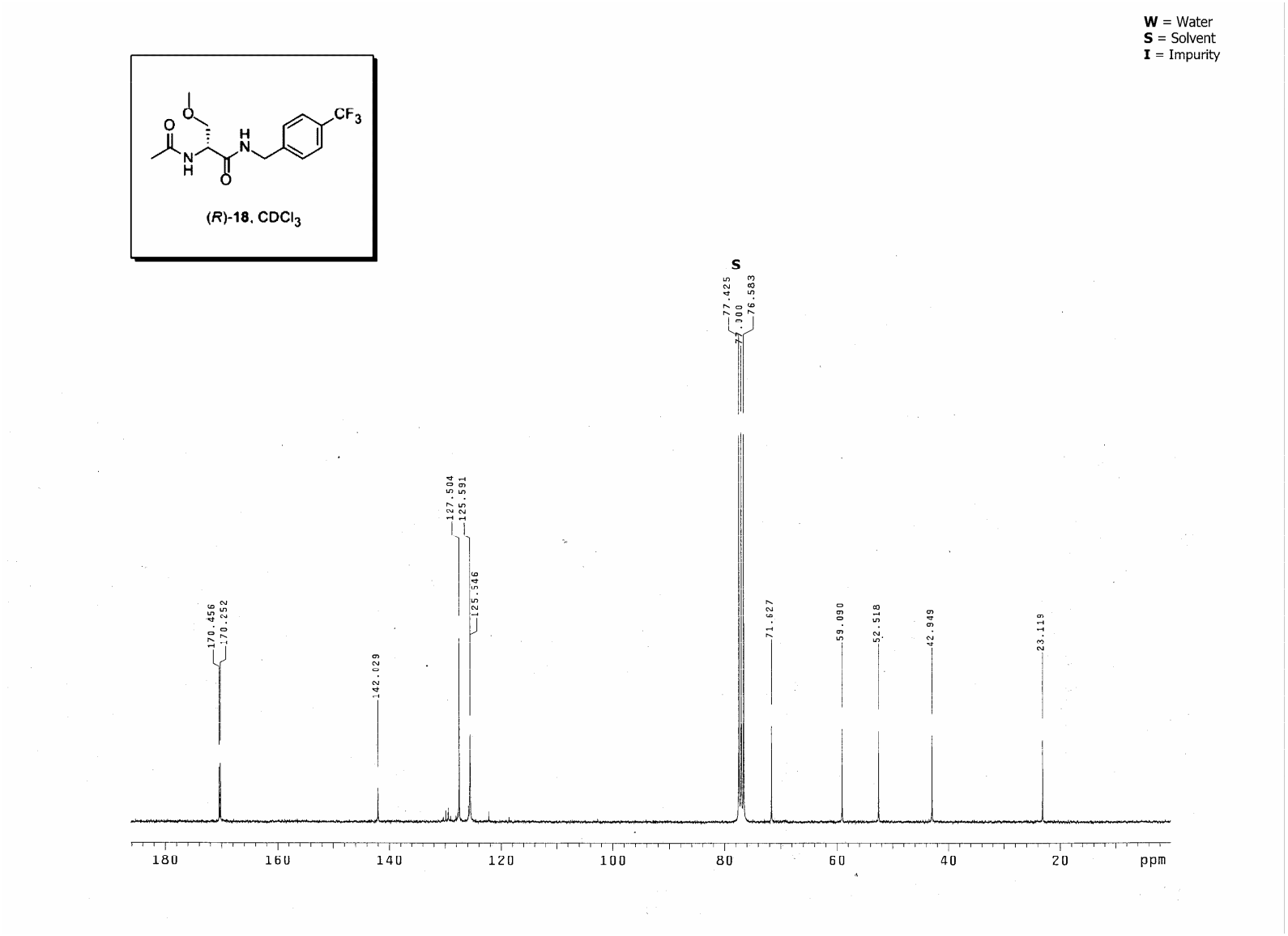

W = Water
S = Solvent
I = Impurity
(R)-16, CDCl3
7.218
4.440
4.421
3.369
2.015
1.414
0.000
W
8
7
6
5
4
3
2
1
ppm
4.23
0.96
0.94
0.93
1.00
2.06
2.04
1.00
0.98
3.06
3.00
9.07

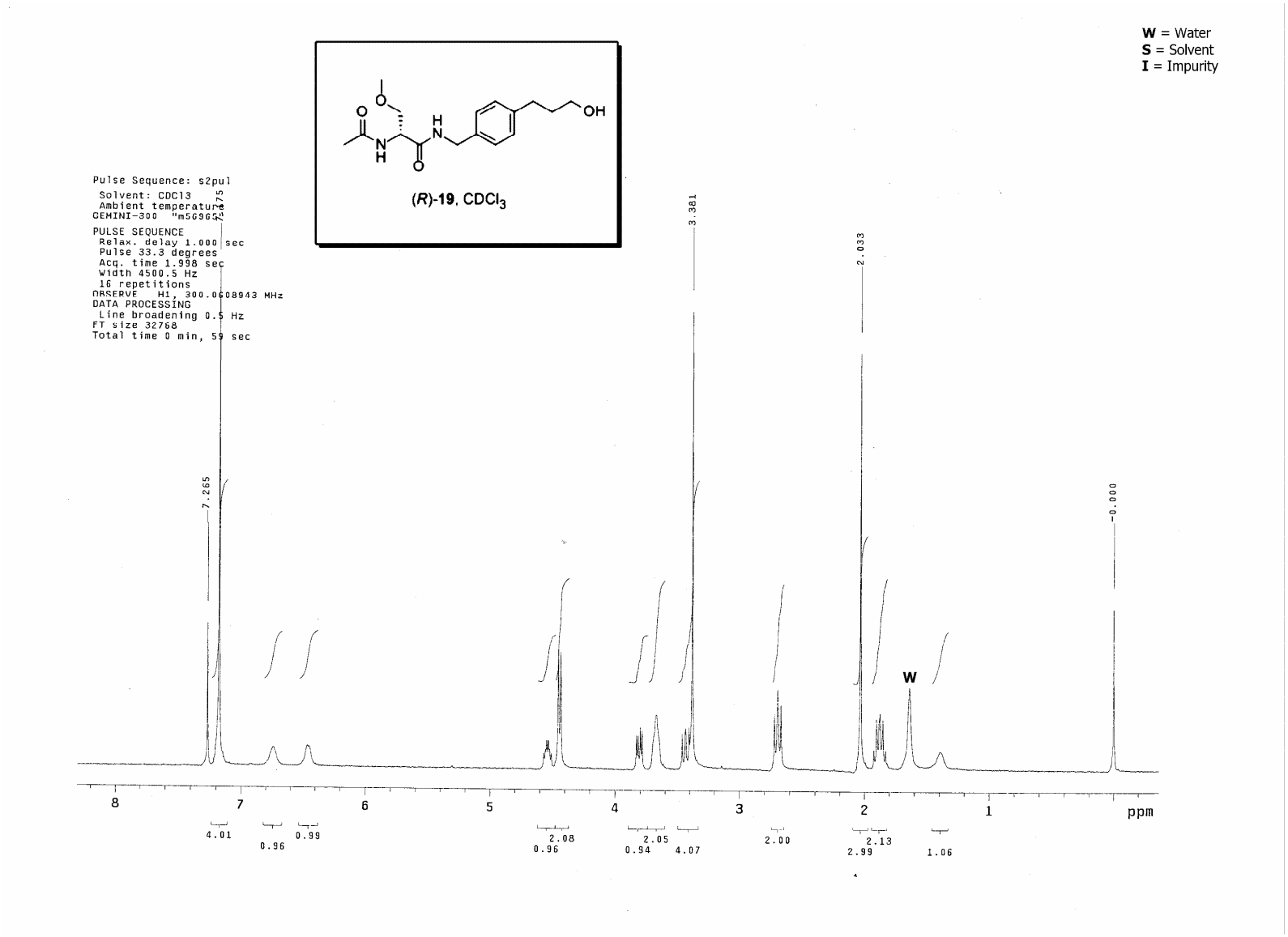

W = Water
S = Solvent
I = Impurity
S
(R)-16, CDCl3
170.350
169.956
155.678
138.265
136.929
127.678
79.489
77.425
77.060
76.575
71.733
59.030
52.435
44.254
43.177
28.356
23.112
160
140
120
100
80
60
40
20
ppm

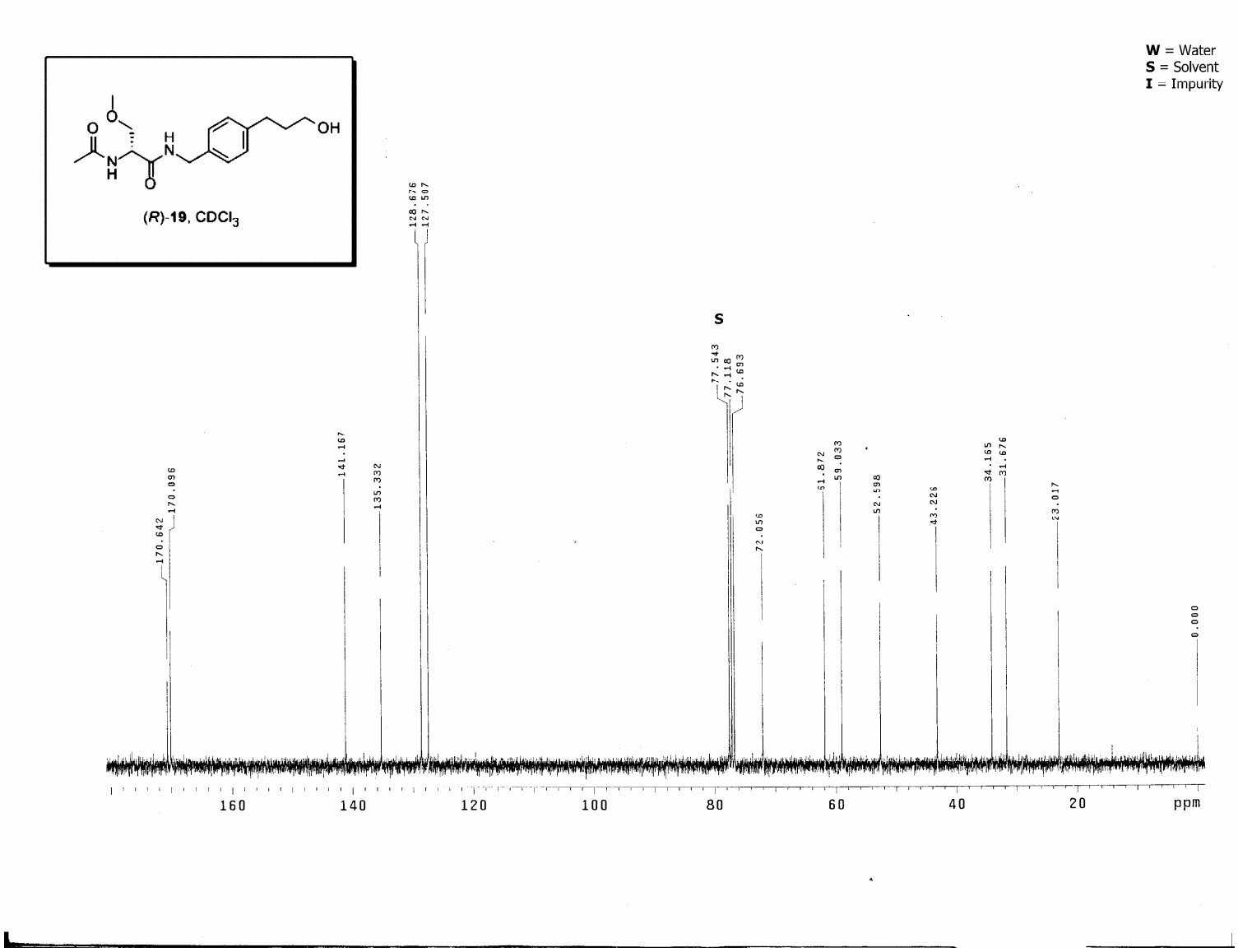

W = Water
S = Solvent
I = Impurity
(R)-17, CDCl3
3.382
3.376
2.126
4.437
3.389
7.291
7.267
7.253
0.000
W
7
6
5
4
3
2
1
ppm
4.65
0.96
0.96
4.05
1.10
1.06
1.19
5.96
3.00

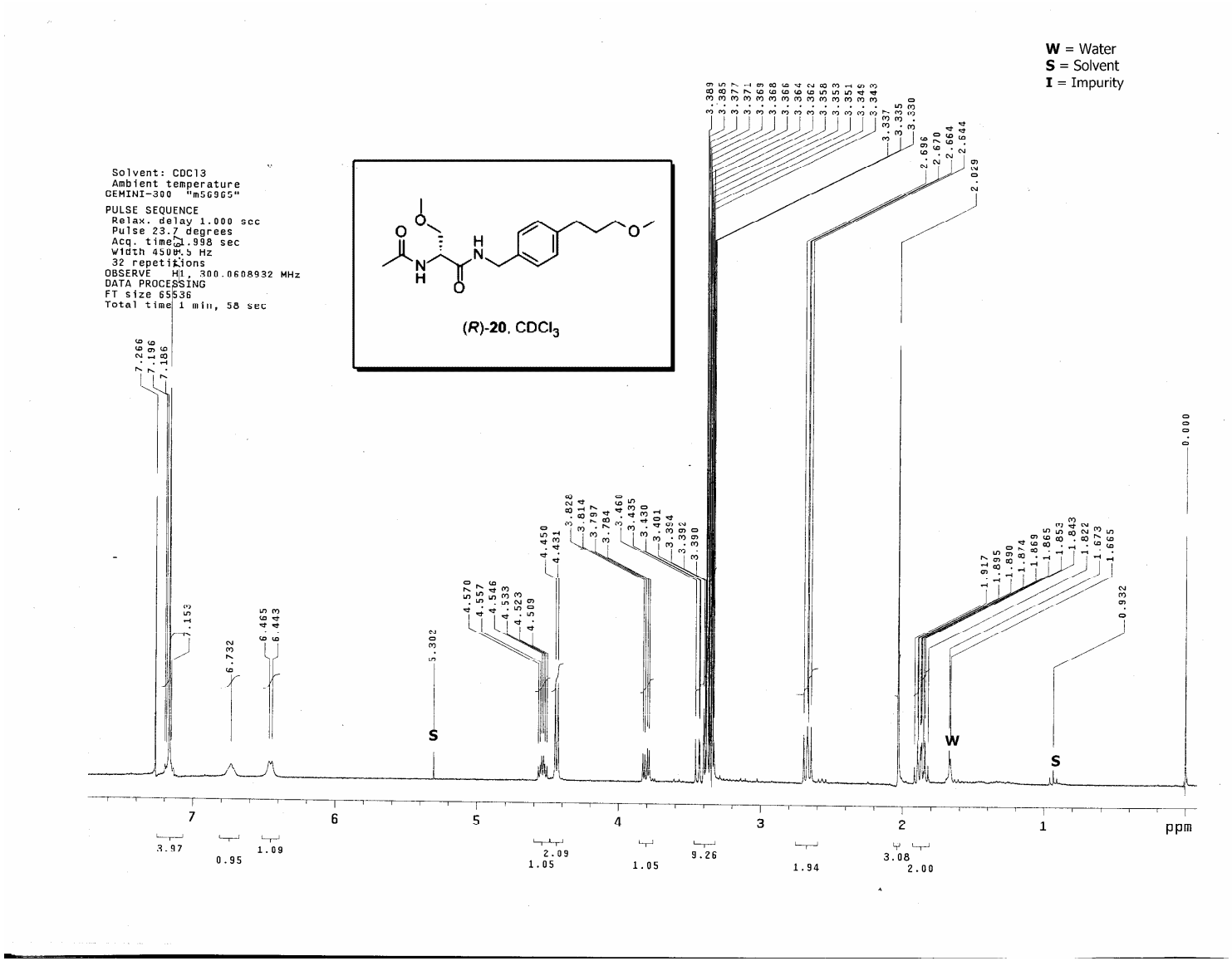

W = Water
S = Solvent
I = Impurity
(R)-17, CDCl3
S
77.481
77.057
76.833
128.077
127.536
74.355
71.777
59.081
58.137
52.467
43.308
23.180
0.000
170.344
169.991
137.529
137.328
160
140
120
100
80
60
40
20
ppm

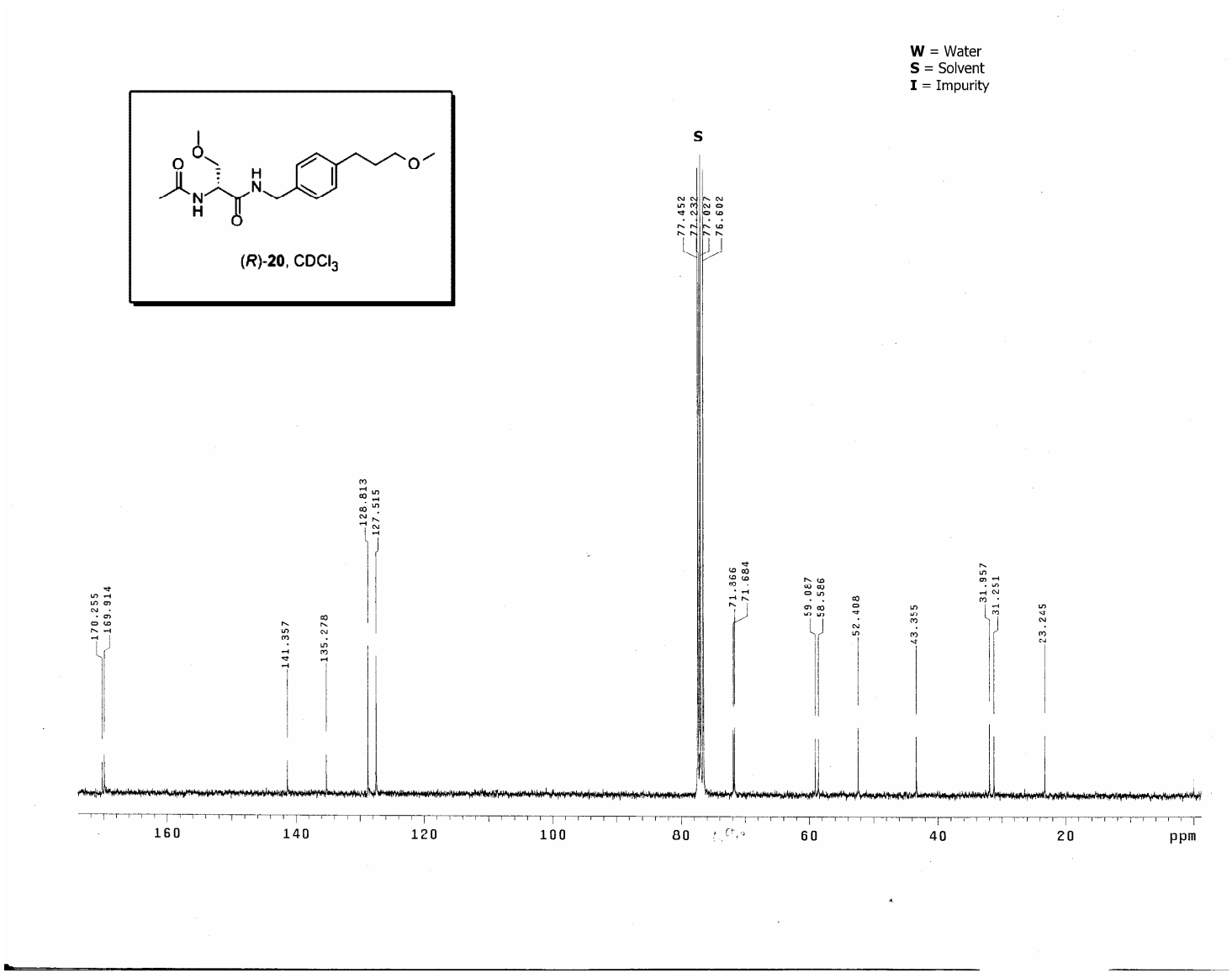

W = Water
S = Solvent
I = Impurity
(R)-18, CDCl3
7.605
7.577
7.390
7.363
7.264
4.547
3.402
2.049
1.602
W
0.000
1.96
1.96
0.99
0.95
3.05
1.05
1.00
3.03
3.00
8
7
6
5
4
3
2
1
ppm

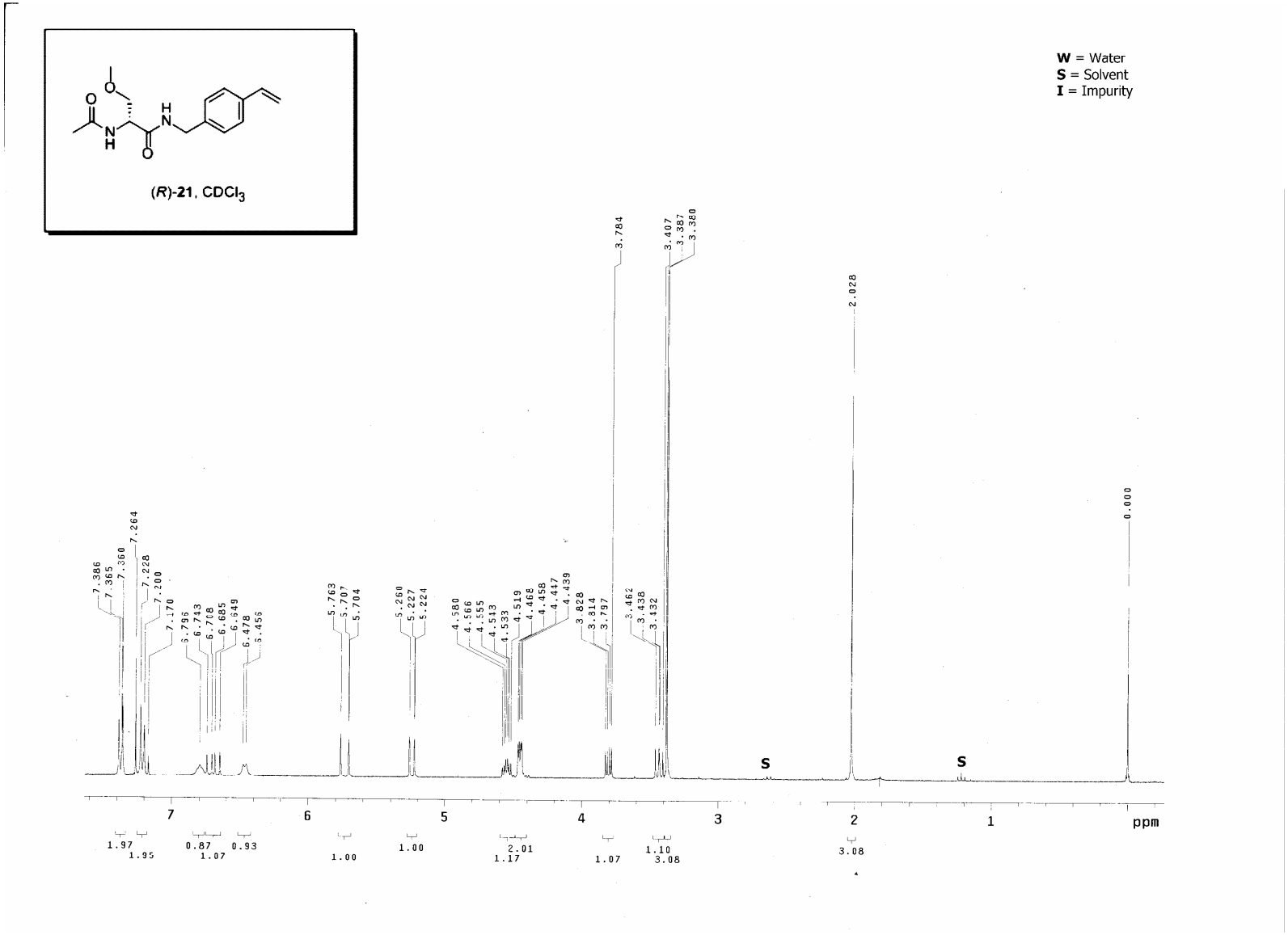

W = Water
S = Solvent
I = Impurity
(R)-18, CDCl3
S
77.425
77.000
76.583
127.504
125.591
125.546
170.456
170.252
142.029
71.627
59.090
52.518
42.949
23.119
180
160
140
120
100
80
60
40
20
ppm

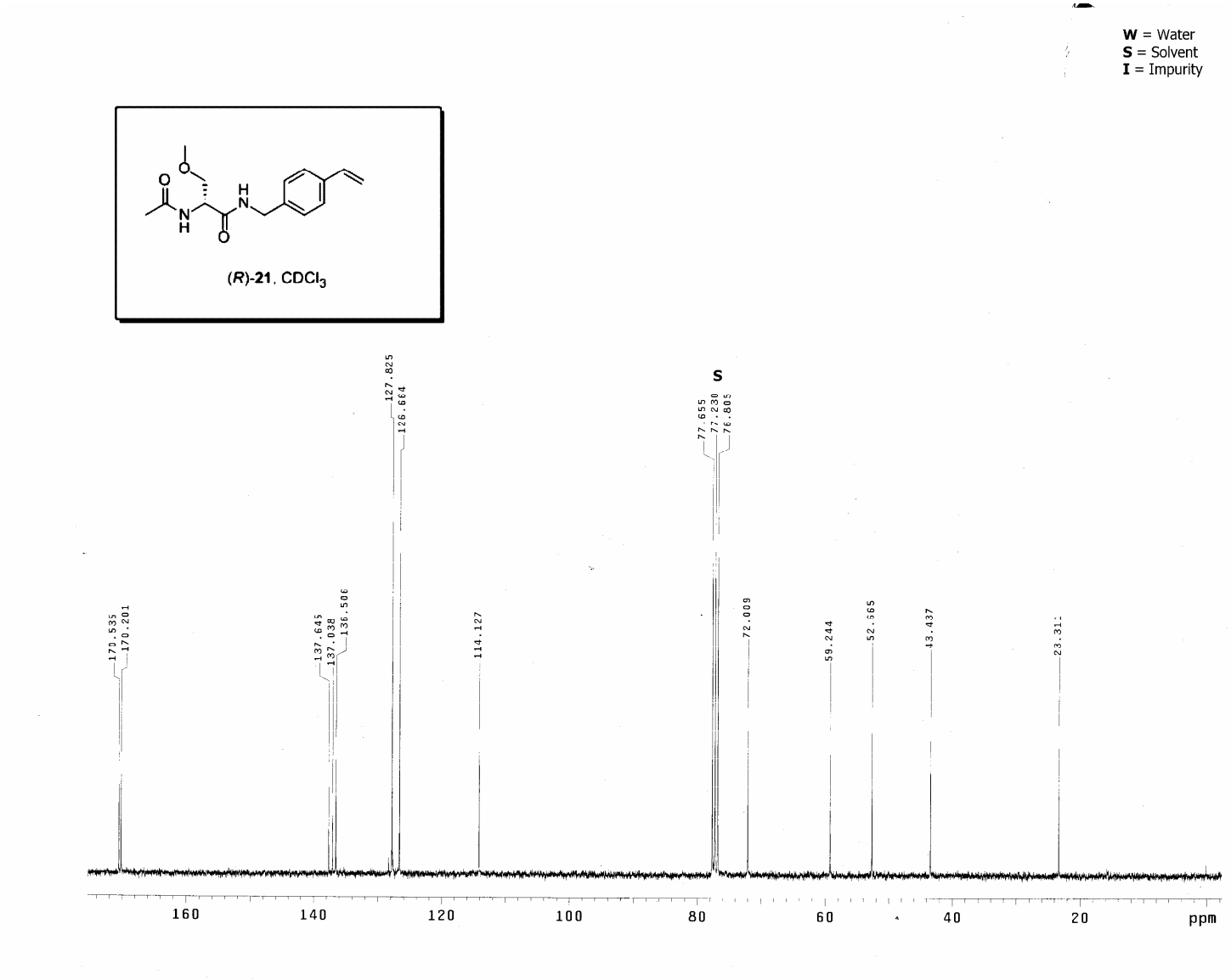

W = Water
S = Solvent
I = Impurity
(R)-19, CDCl3
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
GEMINI-300 "m5G9G5"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 33.3 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 300.0608943 MHz
DATA PROCESSING
Line broadening 0.5 Hz
FT size 32768
Total time 0 min, 59 sec
7.265
3.381
2.033
0.000
W
8
7
6
5
4
3
2
1
ppm
4.01
0.96
0.99
2.08
0.96
2.05
0.94
4.07
2.00
2.99
2.13
1.06

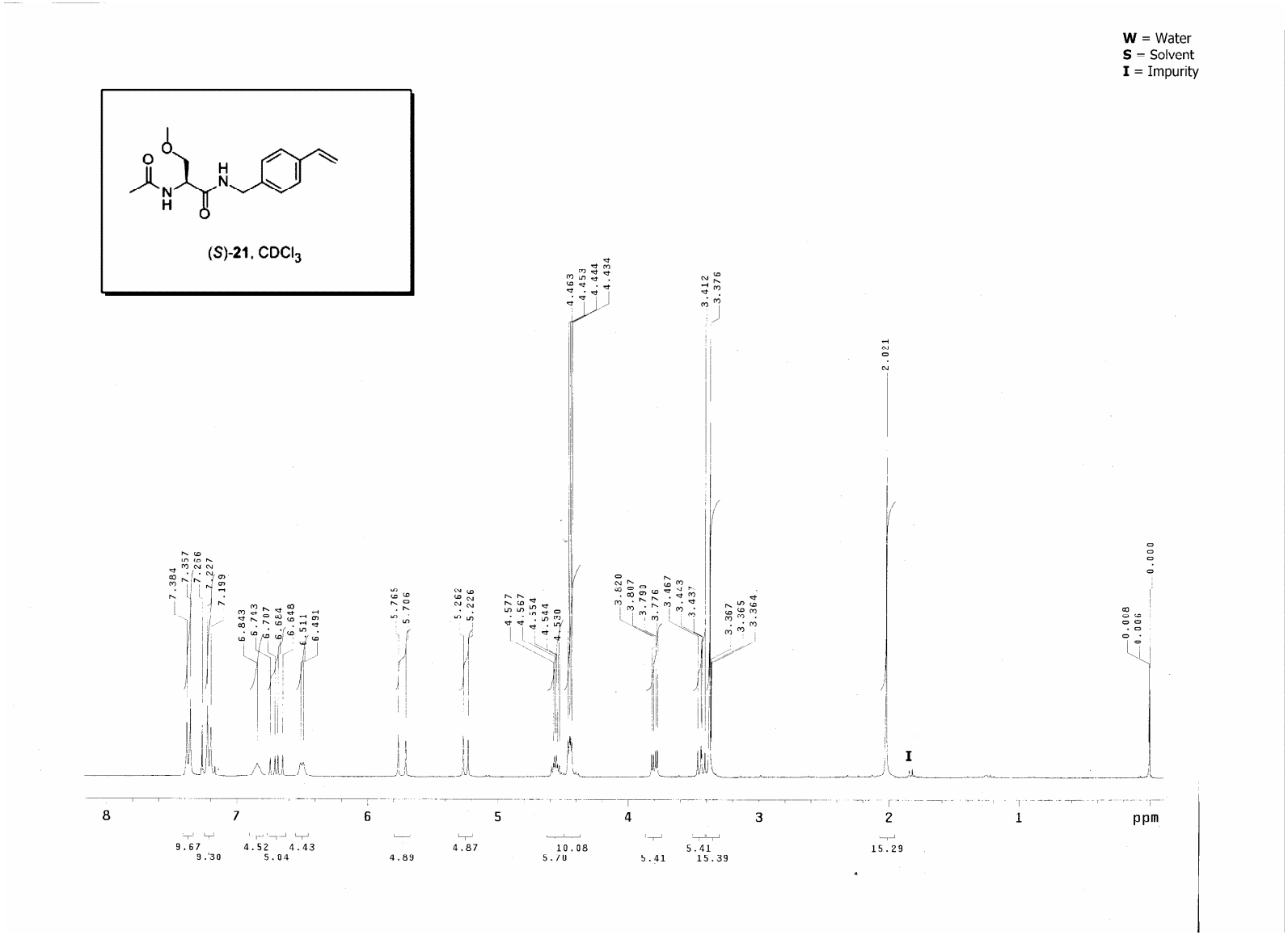

W = Water
S = Solvent
I = Impurity
(R)-19, CDCl3
OH
S
128.676
127.507
141.167
135.332
170.642
170.096
77.543
77.118
76.693
72.056
61.872
59.033
52.598
43.226
34.165
31.676
23.017
0.000
160
140
120
100
80
60
40
20
ppm

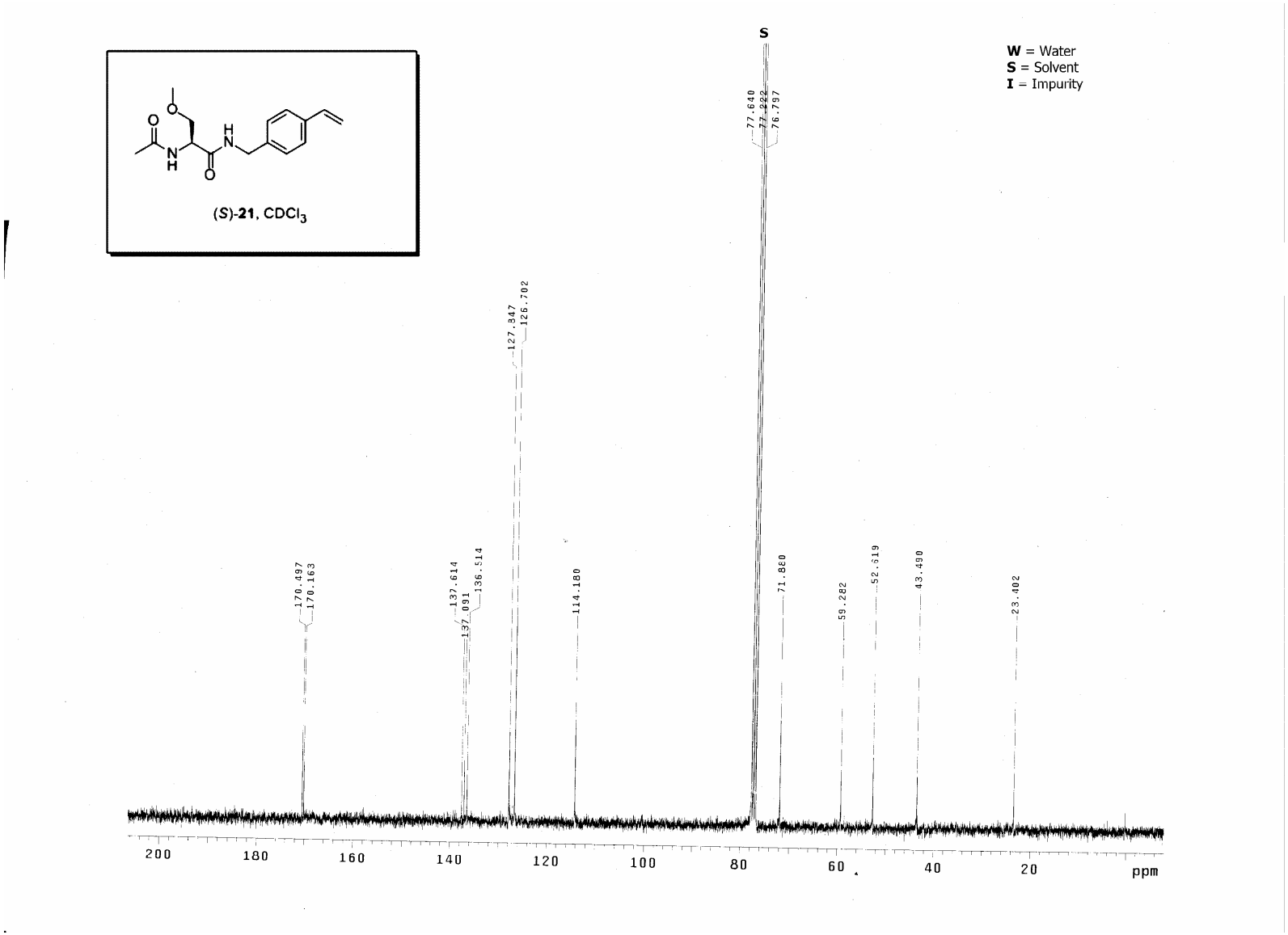

W = Water
S = Solvent
I = Impurity
Solvent: CDCl3
Ambient temperature
GEMINI-300 "m5G9G5"
PULSE SEQUENCE
Relax. delay 1.000 scc
Pulse 23.7 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
32 repetitions
OBSERVE H1, 300.0608932 MHz
DATA PROCESSING
FT size 65536
Total time 1 min, 58 sec
(R)-20, CDCl3
7.266
7.196
7.186
7.153
6.732
6.465
6.443
5.302
4.570
4.557
4.546
4.533
4.523
4.509
4.450
4.431
3.828
3.814
3.797
3.784
3.460
3.435
3.430
3.401
3.364
3.392
3.390
3.389
3.385
3.377
3.371
3.369
3.368
3.366
3.364
3.362
3.356
3.353
3.351
3.345
3.343
3.337
3.335
3.330
2.696
2.670
2.664
2.644
2.029
1.917
1.895
1.890
1.874
1.869
1.865
1.853
1.843
1.822
1.673
1.665
0.932
0.000
S
W
S
7
6
5
4
3
2
1
ppm
3.97
0.95
1.09
2.09
1.05
1.05
9.26
1.94
3.08
2.00

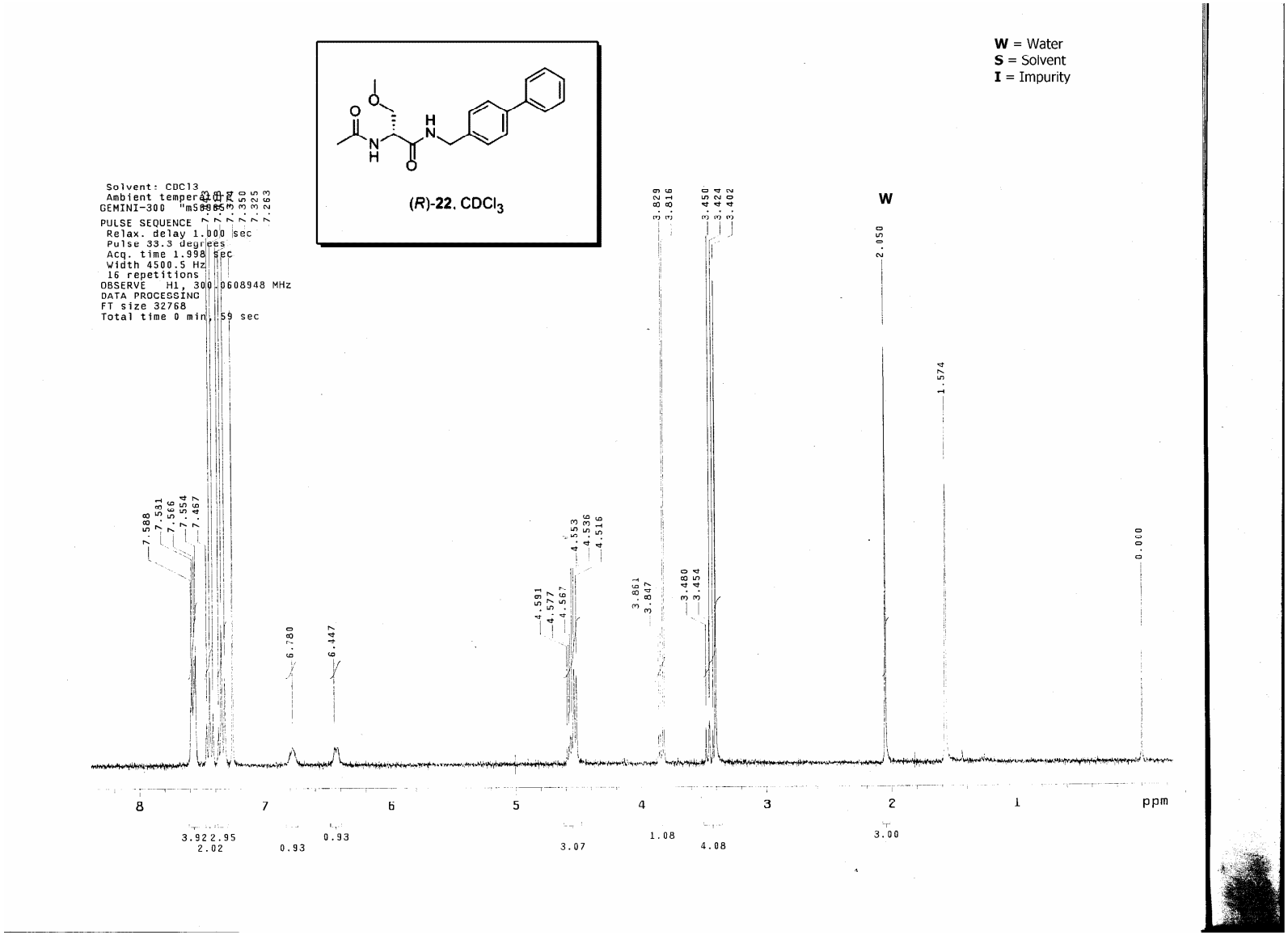

W = Water
S = Solvent
I = Impurity
(R)-20, CDCl3
S
77.452
77.232
77.027
76.602
170.255
169.914
141.357
135.278
128.813
127.515
71.866
71.684
59.087
58.586
52.408
43.355
31.957
31.251
23.245
160
140
120
100
80
60
40
20
ppm

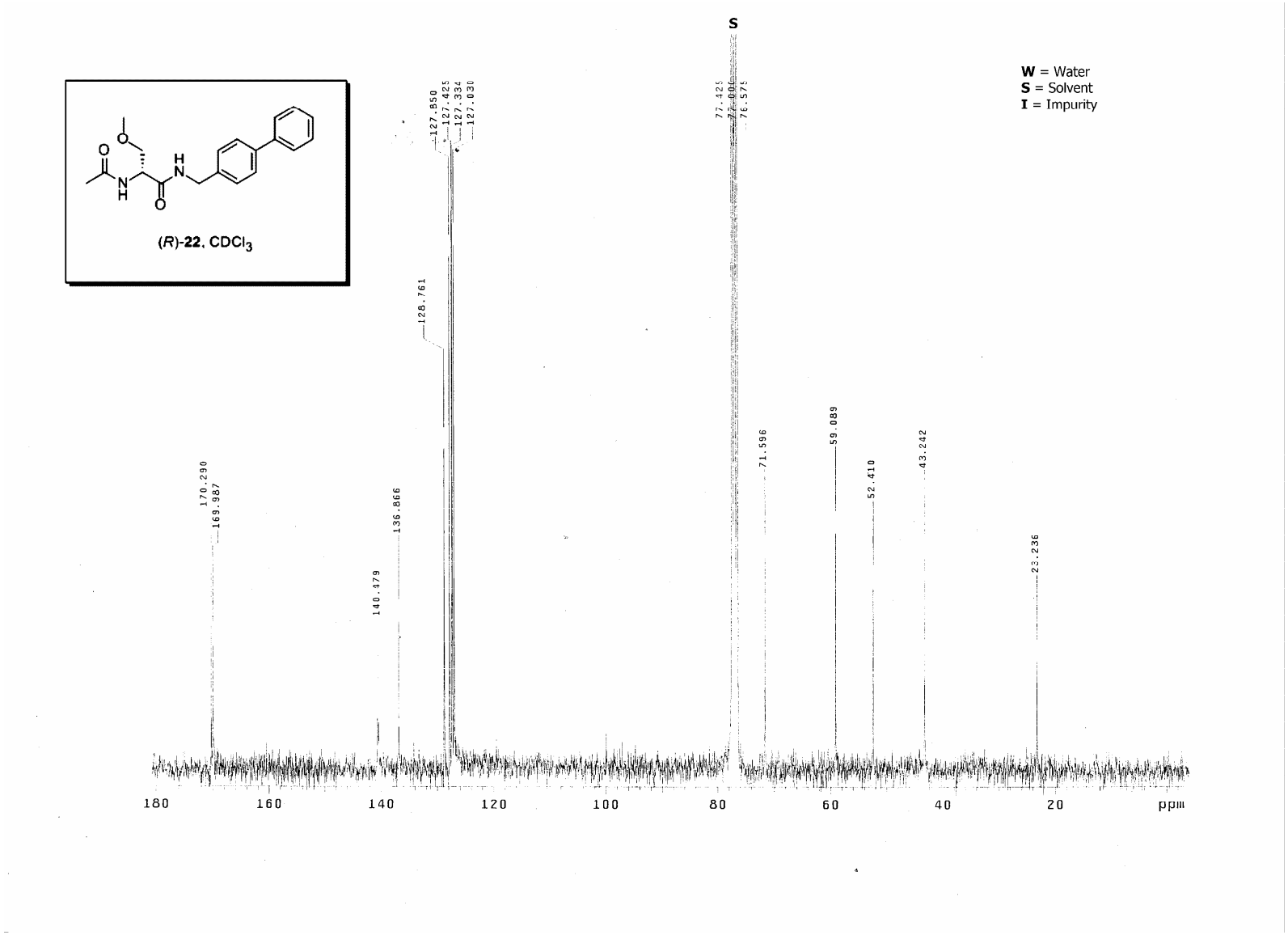

(R)-21, CDCl3
W = Water
S = Solvent
I = Impurity
7.386
7.365
7.360
7.264
7.228
7.200
7.170
6.795
6.743
6.708
6.685
6.649
6.478
6.455
5.763
5.707
5.704
5.260
5.227
5.224
4.580
4.566
4.555
4.513
4.533
4.519
4.468
4.458
4.447
4.439
3.828
3.814
3.797
3.462
3.438
3.432
3.784
3.407
3.387
3.380
2.028
0.000
S
S
7
6
5
4
3
2
1
ppm
1.97
1.95
0.87
1.07
0.93
1.00
1.00
2.01
1.17
1.07
1.10
3.08
3.08

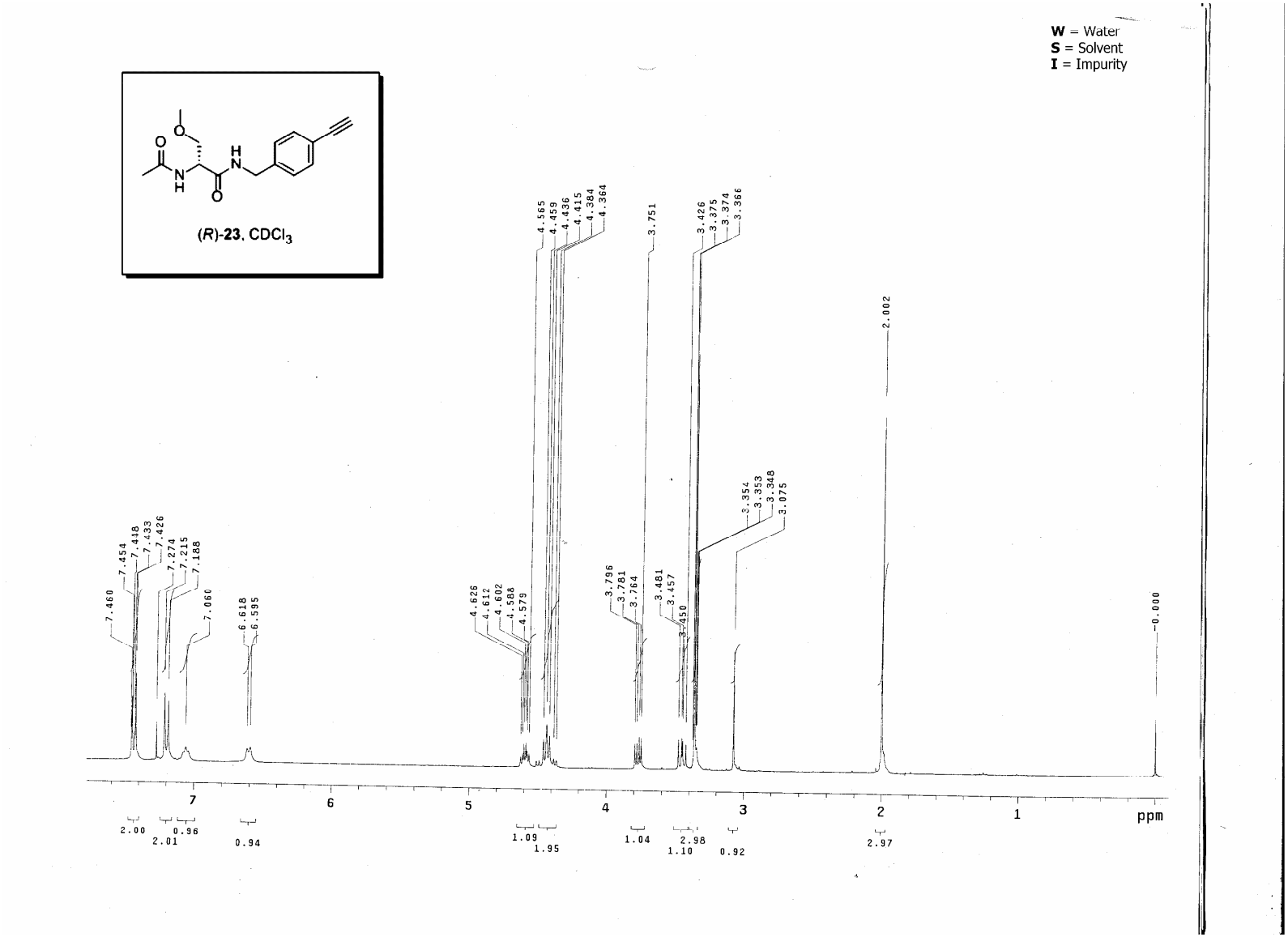

W = Water
S = Solvent
I = Impurity
(R)-21, CDCl3
S
127.825
126.664
77.655
77.230
76.805
170.535
170.201
137.645
137.038
136.506
114.127
72.009
59.244
52.565
43.437
23.31
160
140
120
100
80
60
40
20
ppm

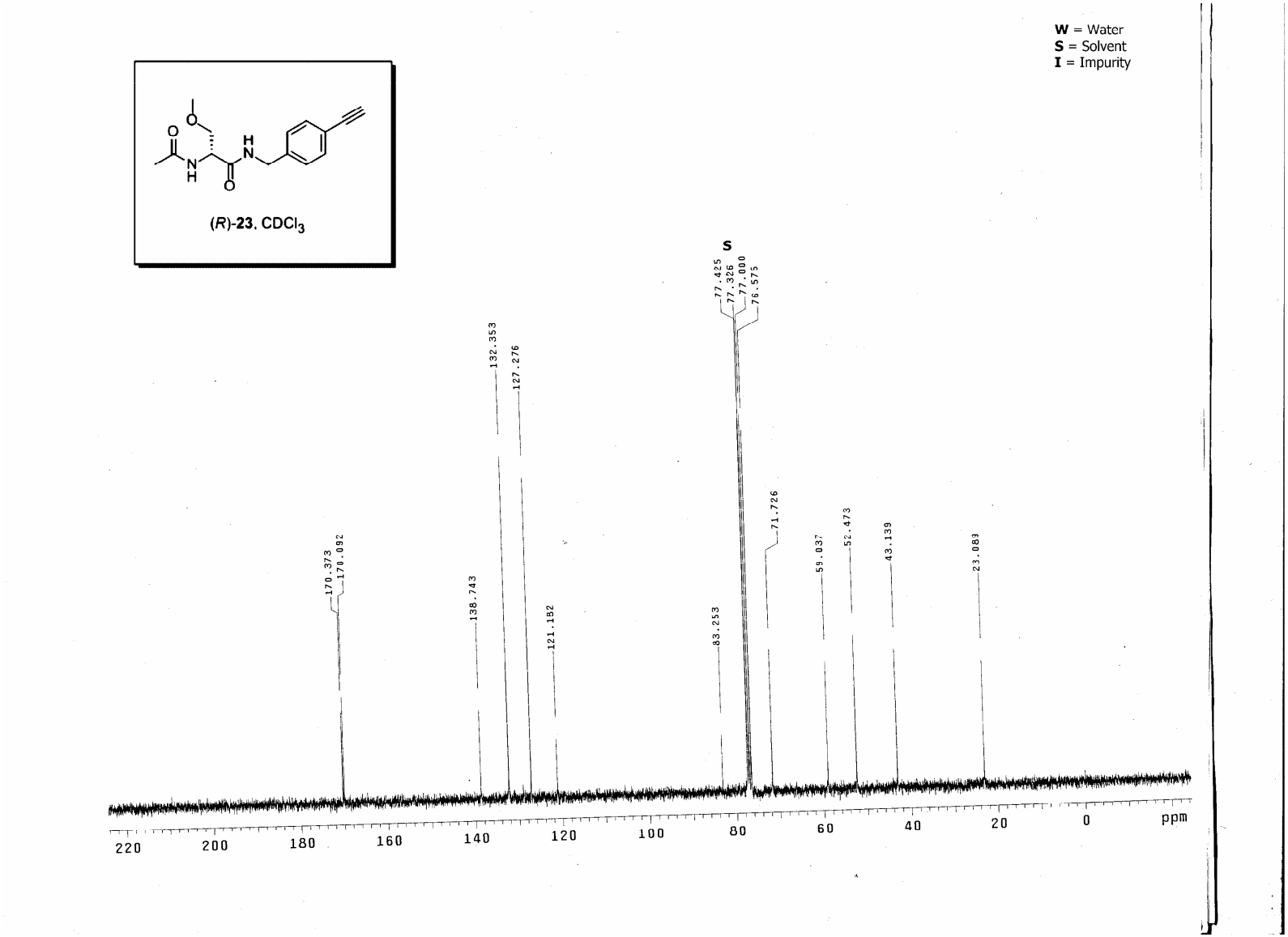

W = Water
S = Solvent
I = Impurity
(S)-21, CDCl3
7.384
7.357
7.266
7.227
7.199
6.843
6.743
6.707
6.684
6.648
6.511
6.491
5.765
5.706
5.262
5.226
4.577
4.567
4.554
4.544
4.530
4.463
4.453
4.444
4.434
3.620
3.807
3.790
3.776
3.467
3.443
3.437
3.412
3.376
3.367
3.365
3.364
2.021
0.008
0.006
0.000
I
8
7
6
5
4
3
2
1
ppm
9.67
9.30
4.52
5.04
4.43
4.89
4.87
10.08
5.70
5.41
5.41
15.39
15.29

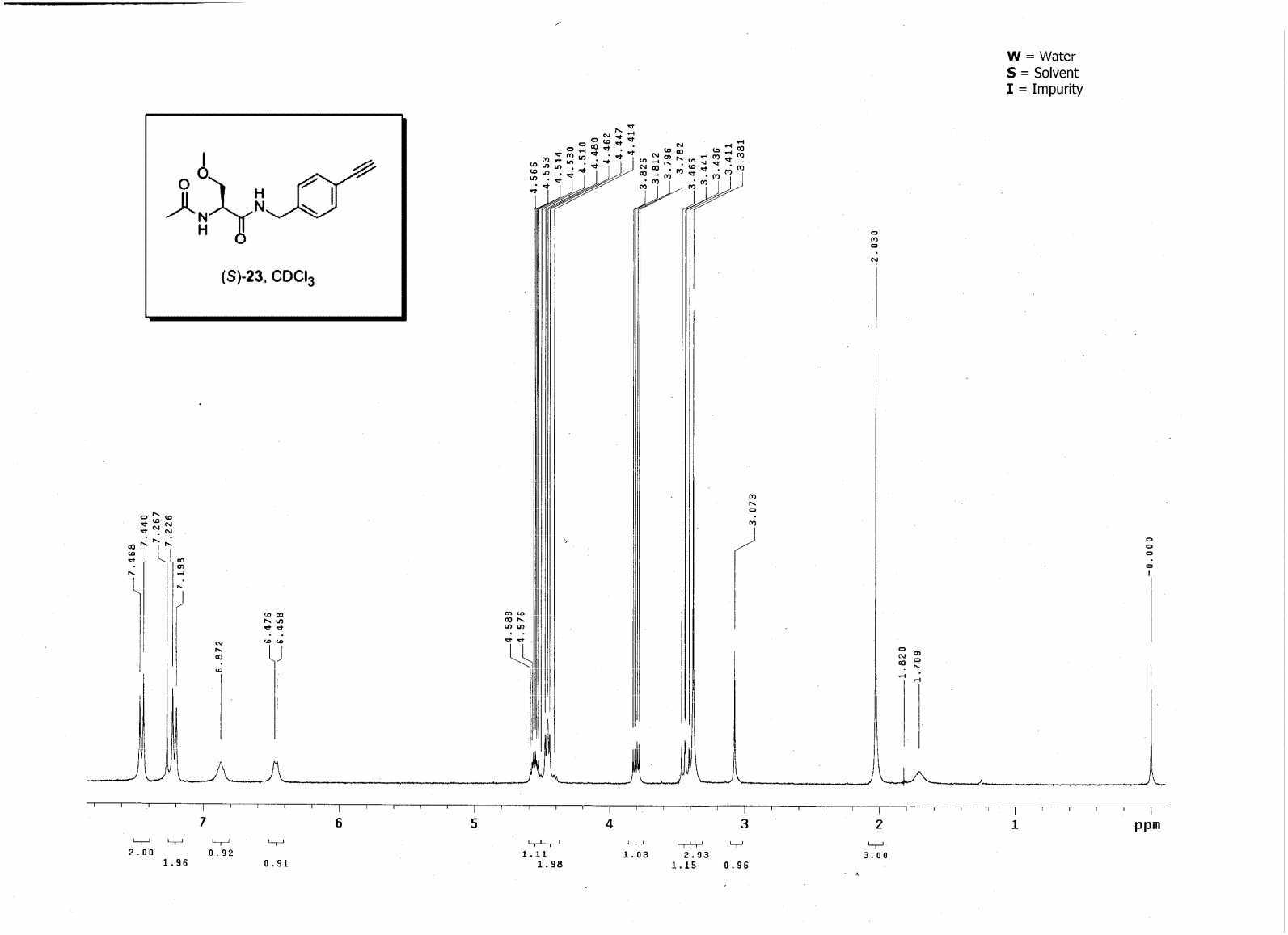

(S)-21, CDCl3
W = Water
S = Solvent
I = Impurity
S
77.640
77.222
76.797
170.497
170.163
137.614
137.091
136.514
127.847
126.702
114.180
71.860
59.282
52.619
43.490
23.402
200
180
160
140
120
100
80
60
40
20
ppm

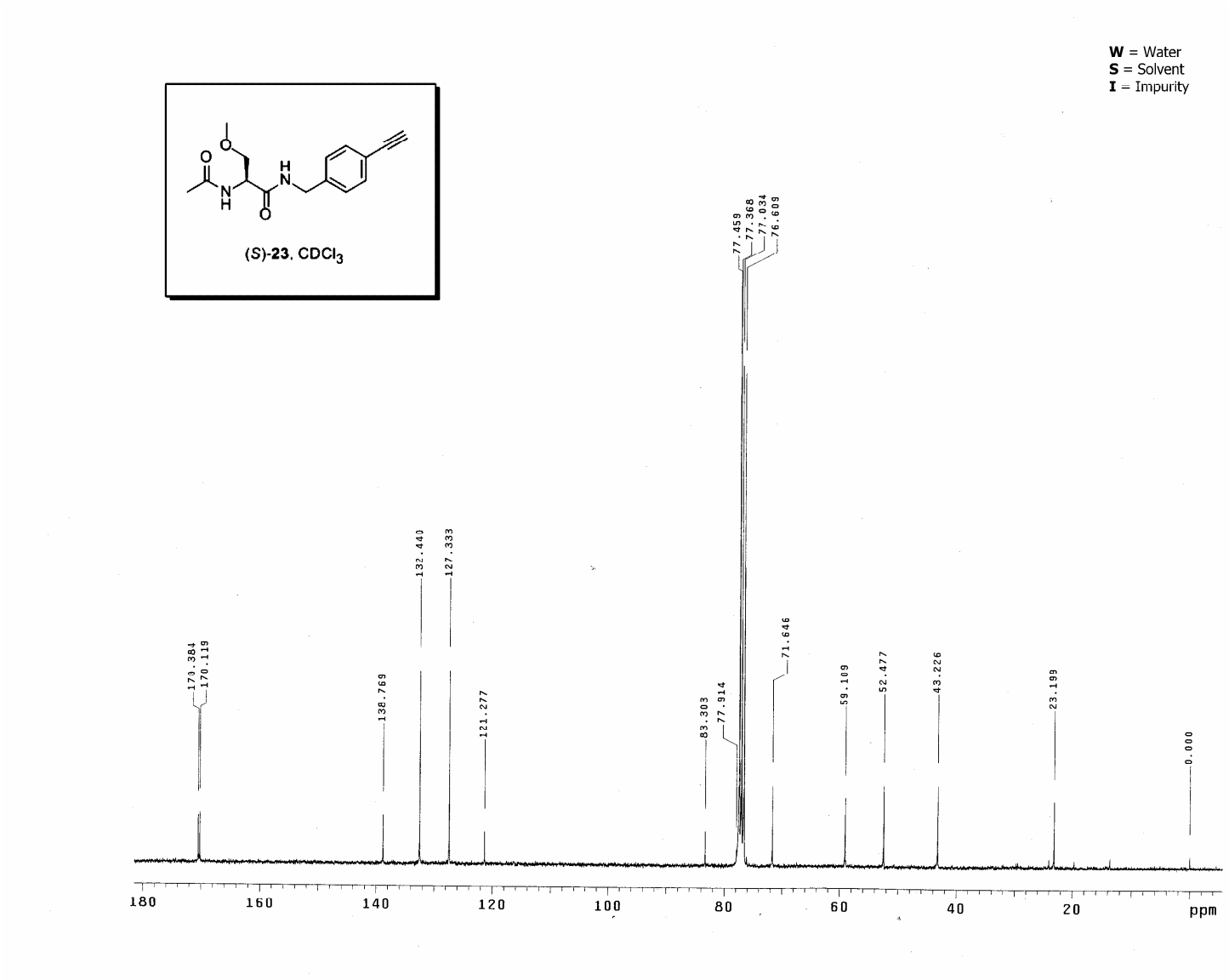

W = Water
S = Solvent
I = Impurity
(R)-22, CDCl3
Solvent: CDCl3
Ambient temperature
GEMINI-300 "m588"
PULSE SEQUENCE
Relax. delay 1.000 sec
Pulse 33.3 degrees
Acq. time 1.998 sec
Width 4500.5 Hz
16 repetitions
OBSERVE H1, 300.0608948 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 59 sec
7.588
7.531
7.566
7.554
7.467
6.780
6.447
4.591
4.577
4.567
4.553
4.536
4.516
3.861
3.847
3.829
3.816
3.480
3.454
3.450
3.424
3.402
W
2.050
1.574
0.000
8
7
6
5
4
3
2
1
ppm
3.92
2.95
2.02
0.93
0.93
3.07
1.08
4.08
3.00

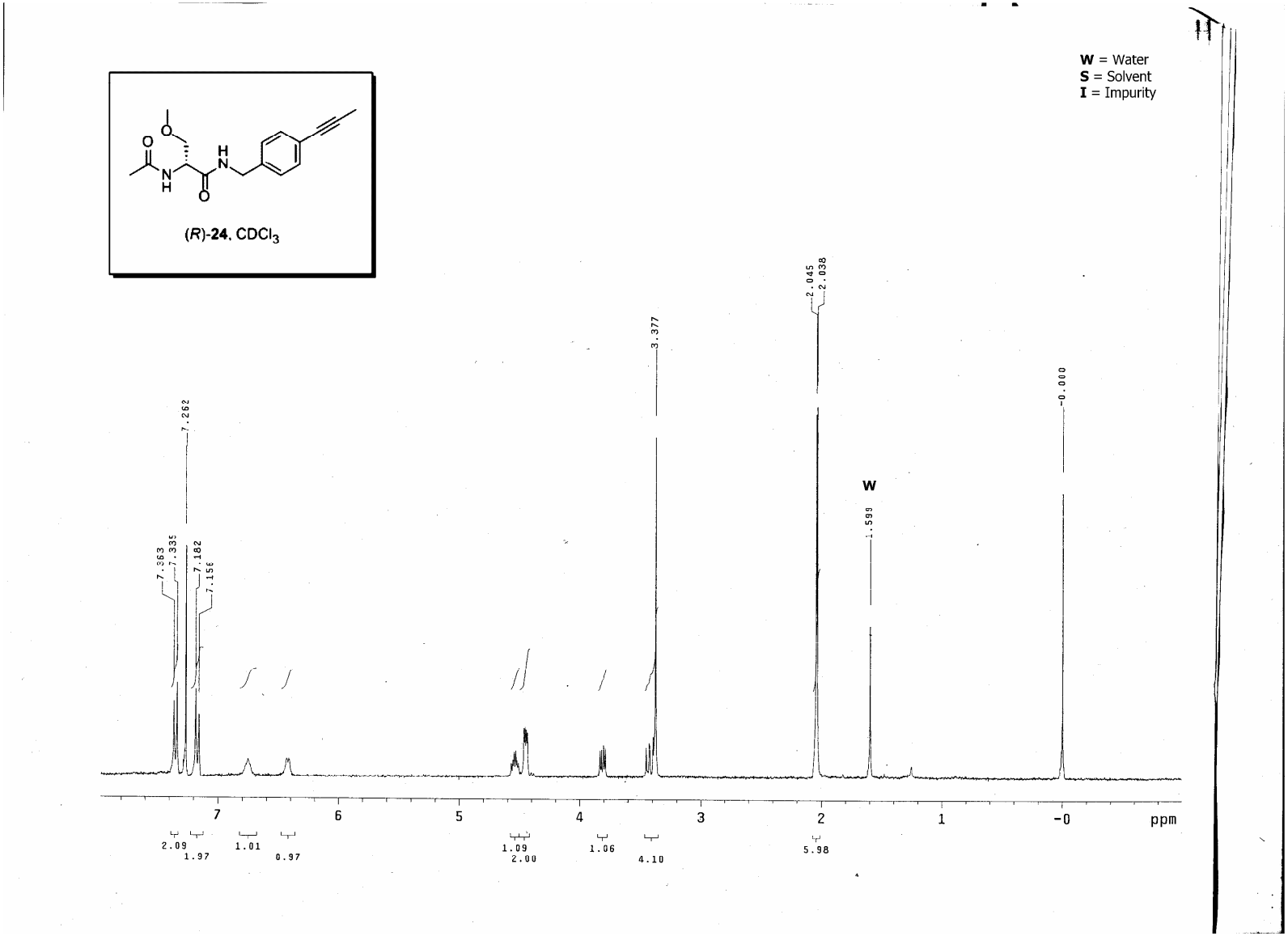

(R)-22, CDCl3
S
W = Water
S = Solvent
I = Impurity
170.290
169.987
140.479
136.866
128.761
127.850
127.425
127.334
127.030
77.425
77.000
76.575
71.596
59.089
52.410
43.242
23.236
180
160
140
120
100
80
60
40
20
ppm

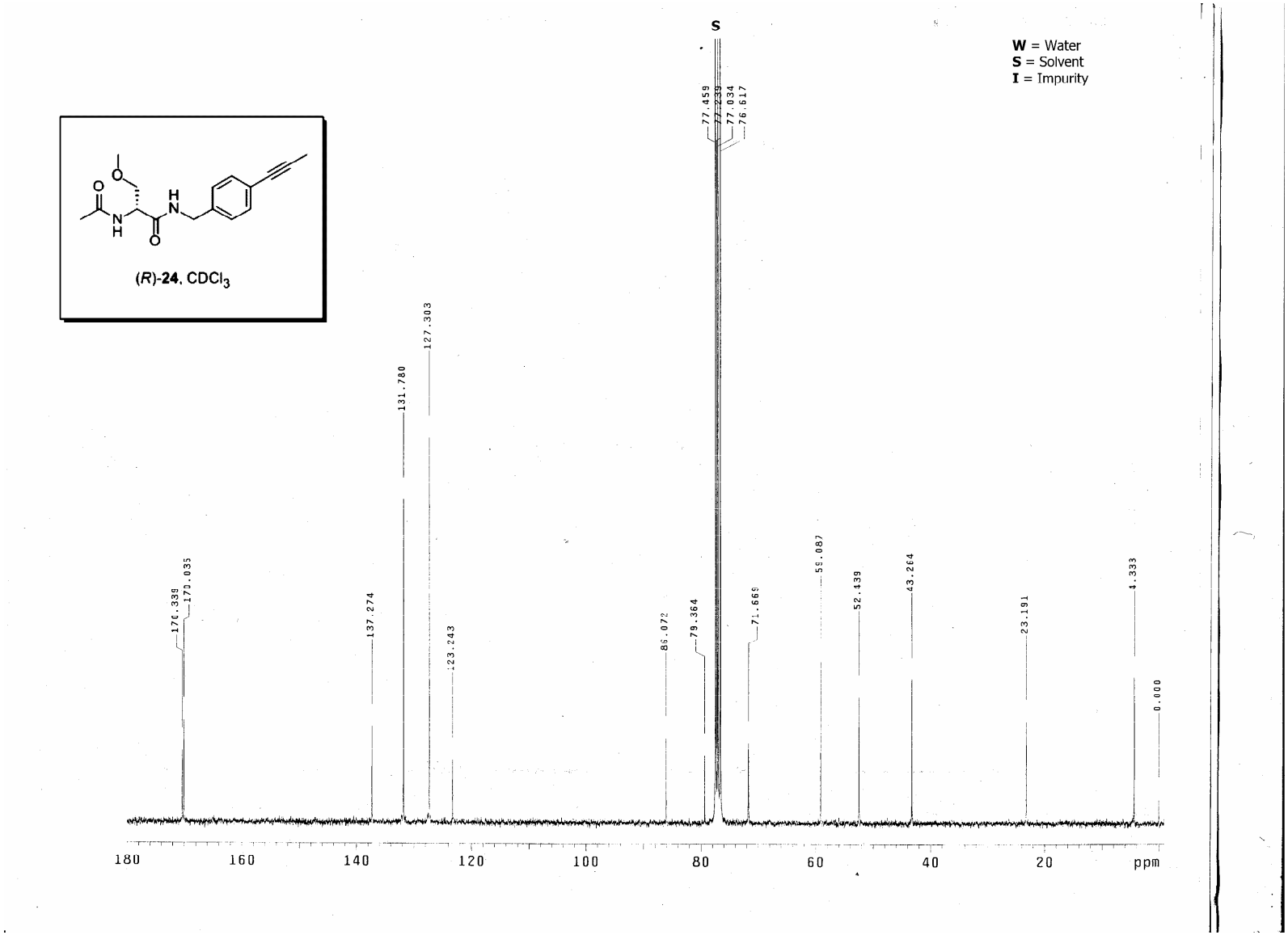

W = Water
S = Solvent
I = Impurity
(R)-23, CDCl3
7.460
7.454
7.418
7.433
7.426
7.274
7.215
7.188
7.060
6.618
6.595
4.626
4.612
4.602
4.588
4.579
4.565
4.459
4.436
4.415
4.384
4.364
3.796
3.781
3.764
3.751
3.481
3.457
3.450
3.426
3.375
3.374
3.366
3.354
3.353
3.348
3.075
2.002
0.000
ppm
2.00
2.01
0.96
0.94
1.09
1.95
1.04
2.98
1.10
0.92
2.97


W = Water
S = Solvent
I = Impurity
(R)-23, CDCl3
S
77.425
77.326
77.000
76.575
132.353
127.276
170.373
170.092
138.743
121.182
83.253
71.726
59.037
52.473
43.139
23.083
220
200
180
160
140
120
100
80
60
40
20
0
ppm


W = Water
S = Solvent
I = Impurity
(S)-23, CDCl3
7.468
7.440
7.267
7.226
7.193
6.872
6.475
6.458
4.589
4.575
4.566
4.553
4.544
4.530
4.510
4.480
4.462
4.447
4.414
3.826
3.812
3.796
3.782
3.466
3.441
3.436
3.411
3.381
3.073
2.030
1.820
1.709
-0.000
7
6
5
4
3
2
1
ppm
2.00
1.96
0.92
0.91
1.11
1.98
1.03
2.93
1.15
0.96
3.00


W = Water
S = Solvent
I = Impurity
(S)-23, CDCl3
170.384
170.119
138.769
132.440
127.333
121.277
83.303
77.914
77.459
77.368
77.034
76.609
71.646
59.109
52.477
43.226
23.199
0.000
180
160
140
120
100
80
60
40
20
ppm


(R)-24, CDCl3
W = Water
S = Solvent
I = Impurity
7.363
7.335
7.262
7.182
7.156
3.377
2.045
2.038
1.599
W
0.000
7
6
5
4
3
2
1
-0
ppm
2.09
1.97
1.01
0.97
1.09
2.00
1.06
4.10
5.98


(R)-24, CDCl3
W = Water
S = Solvent
I = Impurity
S
77.459
77.239
77.034
76.617
131.780
127.303
123.243
137.274
170.339
170.035
86.072
79.364
71.669
55.087
52.439
43.264
23.191
1.333
0.000
180
160
140
120
100
80
60
40
20
ppm