Asymmetric Synthesis of *trans* 3-Amino-4-alkylazetidin-2-ones from Chiral *N,N*-Dialkylhydrazones

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SUPPORTING INFORMATION

General experimental methods. Solvents were purified and dried by standard procedures. Light petroleum ether used had a bp 40-65 °C. Flash chromatography was carried out using silica-gel (0.063-0.200 mm, 0.040-0.063 mm or 0.015-0.040 mm) or prepacked silica columns. Melting points were recorded in a metal block and are uncorrected. Infrared spectra were recorded for KBr pellets or films. 1H NMR spectra were recorded at 300 MHz or 500 MHz; ^{13}C NMR spectra were recorded at 75 MHz or 125 MHz, with the solvent peak used as the internal reference. Spectra were recorded at 95 °C in DMSO when spectra at lower temperatures showed broad signals due to rotamery. Hydrazones **3b**, **3c** and **3d** were synthesized according to previously described procedures.[1]

General procedure for the synthesis of hydrazones 3a, 3e and 3f. Et_3N (3.5 mL, 25 mmol) was added to a solution of (2*S*, 5*S*)-2,5-hexanediol (10 mmol, 1.2 g) in dry CH_2Cl_2 (20 mL) under an argon atmosphere. The mixture was cooled at -30 °C and methanesulphonyl chloride (2 mL, 25 mmol) was added dropwise. The reaction was stirred at 0 °C for 3 h and then HCl 1 M was added

(20 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layer was washed with saturated $NaHCO_3$ (10 mL), dried (Na_2SO_4) and concentrated. The crude dimesylate was cooled at 0 °C and hydrazine monohydrate (9.7 mL, 200 mmol) was added. The reaction was stirred at room temperature overnight and then saturated $NaHCO_3$ (20 mL) was added. The aqueous layer was extracted with of Et_2O (6 × 10 mL) and the combined organic layer was dried (Na_2SO_4) and filtered. To the ethereal solution were added Na_2SO_4 and the corresponding aldehyde (1.2-1.5 eq). The mixture was stirred until total consumption of starting material (1-3 days), filtered and concentrated. Purification method, yields and spectral and analytical data for compounds **3a**, **3e** and **3f** are as follows:

Synthesis of (2*R*,5*R*)-1-ethylidenamine-2,5-dimethylpyrrolidine 3a. From acetaldehyde (0.85 mL, 15 mmol), purification by distillation (65 °C, 11-15 mmHg) gave 300 mg (25%, over 3 steps) of hydrazone **3a** as a colourless liquid: $[\alpha]^{22}_D$ –6.7 (*c* 1.0, $CHCl_3$); 1H NMR (300 MHz, $CDCl_3$) δ 1.06 (d, 6H, *J* = 6.2 Hz), 1.41-1.52 (m, 2H), 1.92 (d, 3H, *J* = 5.1 Hz), 2.04-2.17 (m, 2H), 3.57-3.65 (m, 2H), 6.68 (q, 1H, *J* = 5.1 Hz); 13C NMR (75 MHz, $CDCl_3$) δ 17.6, 19.1, 29.1, 55.1, 133.6; IR (film) 2965, 2926, 2875, 1722, 1607, 1448, 1174, 1123 cm^{-1}; mass spectrum (EI) *m/z* (rel intensity) 140 (M^+, 10), 139 (100), 125 (11), 98 (13), 83 (66); HRMS calcd for $C_8H_{15}N_2$ [M^+-1] 139.1235, found 139.1235.

Synthesis of (2*R*,5*R*)-1-hexylidenamine-2,5-dimethylpyrrolidine 3e. From hexanal (1.82 mL, 15 mmol), flash chromatography (1:16 Et_2O-petroleum ether) gave 1.32 g (67%, over 3 steps) of hydrazone **3e** as an oil: $[\alpha]^{22}_D$ –16.3 (*c* 1.1, CH_2Cl_2); 1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 6.9 Hz), 1.06 (d, 6H, *J* = 6.2 Hz), 1.26-1.37 (m, 4H), 1.39-1.53 (m, 4H), 2.02-2.17 (m, 2H), 2.18-2.25 (m, 2H), 3.56-3.65 (m, 2H), 6.62 (t, 1H, *J* = 5.6 Hz); 13C NMR (125 MHz, $CDCl_3$) δ 14.2, 17.8, 22.7, 27.8, 29.3, 31.6, 33.5, 55.3, 138.9; IR (film) 2964, 2927, 2866, 1610, 1460, 1371, 1319, 1208,

1171 cm^{-1}; mass spectrum (EI) *m/z* (rel intensity) 196 (M^+, 14), 195 (53), 181 (28), 125 (14), 112 (8), 98 (31); HRMS calcd for $C_{12}H_{23}N_2$ 195.1861, found 195.1868.

Synthesis of (2*R*,5*R*)-1-[(2-benzyloxy)ethylidenamine]-2,5-dimethylpyrrolidine 3f. From benzyloxyacetaldehyde (1.74 mL, 12 mmol), flash chromatography (20:1→8:1 Et_2O-petroleum ether) gave 1.77 g (72%, over 3 steps) of hydrazone **3f** as an oil: $[\alpha]^{22}_D$ –42.8 (*c* 1.0, CH_2Cl_2); 1H NMR (300 MHz, $CDCl_3$) δ 1.10 (d, 6H, *J* = 6.3 Hz), 1.43-1.55 (m, 2H), 2.05-2.19 (m, 2H), 3.64-3.72 (m, 2H), 4.12 (dd, 1H, *J* = 11.7, 5.4 Hz), 4.17 (dd, 1H, *J* = 11.7, 5.4 Hz), 4.53 (s, 2H), 6.54 (br t, 1H, *J* = 5.5 Hz), 7.24-7.38 (m, 5H); 13C NMR (75 MHz, $CDCl_3$) δ 18.1, 29.4, 55.2, 71.3, 71.9, 127.6, 128.1, 128.5, 128.7, 138.6; IR (film) 3023, 2967, 2928, 2872, 1593, 1458, 1371, 1315, 1212, 1077, 846, 735, 703 cm^{-1}; mass spectrum (EI) *m/z* (rel intensity) 246 (M^+, 27), 231 (22), 155 (60), 140 (36), 125 (34), 98 (14), 91 (100); HRMS calcd for $C_{15}H_{22}N_2O$ 246.1732, found 246.1736.

Synthesis of 3-amino-4-alkylazetidin-2-ones 4a-f. $^iPr_2EtN$ (12 mmol, 2.1 mL) was added, under an argon atmosphere, to a solution of hydrazones **3a-f** (1 mmol) in dry toluene (5 mL). The mixture was heated to 80 °C (unless otherwise stated) and a solution of *N*-benzyloxycarbonyl-*N*-benzyl glycine (6 mmol, 1.8 g) in dry toluene (15 mL) was added dropwise (6 portions of 1 mmol each over 5 hours). Also, 6 portions of 2-chloro-*N*-methylpyridinium iodide (1.1 mmol each, 281 mg) were added over the same period of time. The mixture was stirred at 80 °C until TLC indicated total consumption of the starting material. The mixture was then diluted with EtOAc (20 mL), washed with brine (20 mL) and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layer was dried (Na_2SO_4). The organic solvent was evaporated under reduced pressure and the residue purified by flash chromatography. Eluants, yields and spectral and analytical data for compounds **4a-f** are as follows:

(3*R*,4*R*)-*1*-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]-3-(*N*-benzyl-*N*-benzyloxycarbonyl)amino-4-methyl-azetidin-2-one 4a. From hydrazone **3a** (142 mg, 1 mmol), the reaction time was 6h. Flash

chromatography (1:1:12 → 1:1:5 Et_2O-CH_2Cl_2-petroleum ether) gave 312 mg (74%) of **4a** as an oil: $[\alpha]^{22}_D$ –62.8 (*c* 0.97, $CHCl_3$); 1H NMR (300 MHz, DMSO-d_6, 95 °C) δ 0.97 (d, 6H, *J* = 6.3 Hz), 1.05 (d, 3H, *J* = 6.1 Hz), 1.26-1.34 (m, 2H), 1.87-1.94 (m, 2H), 3.52-3.58 (m, 3H), 4.23 (d, 1H, *J* = 2.2 Hz), 4.50 (d, 1H, *J* = 16 Hz), 4.60 (d, 1H, *J* = 16 Hz), 5.15 (s, 2H), 7.21-7.34 (m, 10H); 13C NMR (75 MHz, DMSO-d_6, 95 °C) δ 14.8, 18.0, 29.4, 50.0, 54.9, 56.9, 66.4, 66.9, 126.5, 126.6, 127.0, 127.3, 127.8, 136.0, 137.7, 154.7, 163.5; IR (film) 2965, 2928, 1755, 1707, 1450, 1421, 1371 cm^{-1}; mass spectrum (EI) *m/z* (rel intensity) 421 (M^+, 12), 330 (12), 190 (31), 140 (27), 91 (100). Anal. Calcd for $C_{25}H_{31}N_3O_3$: C, 71.23; H, 7.41; N, 9.97. Found: C, 71.44; H, 7.83; N, 9.89.

(3*R*,4*R*)-1-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]-3-(*N*-benzyl-*N*-benzyloxycarbonyl)amino-4-isopropyl-azetidin-2-one 4b. From hydrazone **3b** (168 mg, 1 mmol), the reaction time was 53h. Flash chromatography (1:1:6 Et_2O-CH_2Cl_2-petroleum ether) gave 297 mg (66%) of **4b** as an oil: $[\alpha]^{22}_D$ –18.4 (*c* 0.9, CH_2Cl_2); 1H NMR (500 MHz, DMSO-d_6, 95 °C) δ 0.83 (d, 3H, *J* = 6.7 Hz), 0.94 (d, 3H, *J* = 6.7 Hz), 1.03 (d, 6H, *J* = 5.7 Hz), 1.31-1.32 (m, 2H), 1.76 (m, 1H, *J* = 6.7 Hz), 1.91-1.94 (m, 2H), 3.35 (dd, 1H, *J* = 2.5, 7.5 Hz), 3.60-3.67 (m, 2H), 4.33 (d, 1H, *J* = 16.4 Hz), 4.57 (d, 1H, *J* = 2.5 Hz), 4.68 (d, 1H, *J* = 16.4 Hz), 5.12 (d, 1H, *J* = 12.7 Hz), 5.16 (d, 1H, *J* = 12.7 Hz), 7.14-7.31 (m, 10H); 13C NMR (75 MHz, DMSO-d_6, 95 °C) δ 17.7, 17.8, 18.5, 28.5, 29.3, 49.4, 54.9, 57.0, 63.1, 66.1, 66.5, 126.2, 126.4, 126.6, 127.3, 127.5, 127.7, 127.8, 128.4, 135.9, 137.5, 154.6, 163.8; IR (film) 2961, 1753, 1707, 1454, 1240, 1137 cm^{-1}; mass spectrum (EI) *m/z* (rel intensity) 449 (M^+, 2), 358 (5), 254 (15), 168 (25), 91 (100); HRMS calcd for $C_{27}H_{35}N_3O_3$ 449.2678, found 449.2658.

(3*R*,4*R*)-1-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]-3-(*N*-benzyl-*N*-benzyloxycarbonyl)amino-4-isobutyl-azetidin-2-one 4c. From hydrazone **3c** (182 mg, 1 mmol), the reaction time was 26h. Flash chromatography (1:1:8 → 1:1:6 Et_2O-CH_2Cl_2-petroleum ether) gave 345 mg (72%) of **4c** as a solid: M.p. 89-90 °C; $[\alpha]^{22}_D$ –36.6 (*c* 1.1, CH_2Cl_2); 1H NMR (500 MHz, DMSO-d_6, 95 °C) δ 0.74 (d, 3H,

J = 6.5 Hz), 0.77 (d, 3H, J = 6.5 Hz), 0.99 (d, 6H, J = 6.3 Hz), 1.21-1.23 (m, 1H), 1.29-1.31 (m, 2H), 1.54-1.61 (m, 2H), 1.90-1.92 (m, 2H), 3.53-3.58 (m, 3H), 4.40 (d, 1H, J = 16.2 Hz), 4.44 (d, 1H, J = 2.3 Hz), 4.64 (d, 1H, J = 16.2 Hz), 5.13 (d, 1H, J = 12.6 Hz), 5.18 (d, 1H, J = 12.6 Hz), 7-13-7.31 (m, 10H); 13C NMR (125 MHz, DMSO-d_6, 95 °C) δ 18.5, 22.3, 22.4, 24.7, 29.8, 50.2, 53.4, 59.8, 66.9, 67.0, 126.9, 127.1, 127.6, 127.9, 128.1, 128.3, 128.9, 136.5, 138.1, 155.2, 164.3; IR (film) 2968, 1758, 1701, 1453, 1421, 1092 cm^{-1}; mass spectrum (EI) *m/z* (rel intensity) 463 (M^+, 10), 232 (20), 182 (25), 91 (100). Anal. Calcd for $C_{28}H_{37}N_3O_3$: C, 72.54; H, 8.04; N, 9.06. Found: C, 72.25; H, 8.07; N, 9.32.

(3*R*,4*R*)-1-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]-3-(*N*-benzyl-*N*-benzyloxycarbonyl)amino-4-(2-phenylethyl)azetidin-2-one 4d. From hydrazone **3d** (230 mg, 1 mmol), the reaction time was 20h. Flash chromatography (1:1:15 → 1:1:5 Et_2O-CH_2Cl_2-petroleum ether) gave 358 mg (70%) of **4d** as an oil: $[\alpha]^{22}_D$ –28.0 (*c* 1.1, $CHCl_3$); 1H NMR (500 MHz, DMSO-d_6, 95 °C) δ 1.00 (d, 6H, J = 6.3 Hz), 1.23-1.35 (m, 2H), 1.67-1.73 (m, 1H), 1.89-1.98 (m, 3H), 2.57-2.61 (m, 2H), 3.55-3.59 (m, 3H), 4.42 (d, 1H, J = 16.1 Hz), 4.45 (d, 1H, J = 2.25 Hz), 4.56 (d, 1H, J = 16.1 Hz), 5.13 (d, 1H, J = 12.6 Hz), 5.17 (d, 1H, J = 12.6 Hz), 7.03-7.38 (m, 15H); 13C NMR (125 MHz, DMSO-d_6, 95 °C) δ 18.4, 29.8, 31.2, 32.2, 50.4, 55.4, 61.0, 66.3, 67.0, 125.7, 126.9, 127.0, 127.5, 127.8, 128.0, 128.2, 128.2, 136.5, 138.0, 141.2, 155.1, 164.1; IR (film) 2960, 2926, 1755, 1707, 1454, 1417 cm^{-1}; mass spectrum (CI) *m/z* (rel intensity) 512 (M^+, 100), 420 (16), 280 (33), 98 (19), 91 (61). Anal. Calcd for $C_{32}H_{37}N_3O_3$: C, 75.12; H, 7.29; N, 8.21. Found: C, 75.26; H, 7.63; N, 8.04.

(3*R*,4*R*)-1-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]-3-(*N*-benzyl-*N*-benzyloxycarbonyl)amino-4-pentyl-azetidin-2-one 4e. From hydrazone **3e** (196 mg, 1mmol), the reaction time was 10h. Flash chromatography (1:1:12 → 1:1:5 Et_2O-CH_2Cl_2-petroleum ether) gave 277 mg (58%) of a 92:8 mixture of *trans:cis* adduct **4e** as an oil: $[\alpha]^{22}_D$ –39.7 (*c* 1, $CHCl_3$); NMR data of *trans* isomer: 1H

NMR (300 MHz, DMSO-d_6, 95 °C) δ 0.82 (t, 3H, J = 7.0 Hz), 0.99 (d, 6H, J = 6.3 Hz), 1.13-1.39 (m, 9H), 1.59-1.66 (m, 1H), 1.87-1.97 (m, 2H), 3.46-3.51 (m, 1H), 3.54-3.60 (m, 2H), 4.42 (d, 1H, J = 2.3 Hz), 4.44 (d, 1H, J = 15.9 Hz), 4.61 (d, 1H, J = 15.9 Hz), 5.13 (d, 1H, J = 12.6 Hz), 5.18 (d, 1H, J = 12.6 Hz), 7.21-7.35 (m, 10H); 13C NMR (75 MHz, DMSO-d_6, 95 °C) δ 12.9, 17.8, 21.1, 23.9, 29.3, 29.8, 30.5, 49.6, 54.9, 60.8, 65.7, 66.4, 126.3, 126.4, 127.0, 127.2, 127.6, 135.9, 137.5, 154.6, 163.6; IR (film) 2961, 1753, 1707 cm^{-1}; mass spectrum (CI) *m/z* (rel intensity) 478 (M^+ + 1, 100), 477 (25), 245 (37), 98 (39), 91 (32). Anal. Calcd for $C_{29}H_{39}N_3O_3$: C, 72.92; H, 8.23; N, 8.68. Found: C, 73.05; H, 8.38; N, 8.68.

(3*R*,4*R*)- and (3*R*,4*S*)-1-[(2*R*,5*R*)-2,5-dimethylpyrrolidin-1-yl]-3-(*N*-benzyl-*N*-benzyloxycarbonyl)amino-4-benzyloxymethylazetidin-2-one 4f. Method A. Following general procedure described above, from hydrazone **3f**, the reaction time was 38h. Flash chromatography (10:1 toluene-EtOAc) gave **4f** as a 46:54 mixture of *cis:trans* adduct (348 mg, 66%). Medium pressure liquid chromatography (6:1 toluene-EtOAc) allowed the isolation of both isomers *cis*-**(3*R*,4*R*)-4f** and *trans*-**(3*R*,4*S*)-4f** as single enantiomers, both oils. Data of *cis* adduct: $[\alpha]^{22}_D$ –32.3 (*c* 1, CH_2Cl_2); 1H NMR (300 MHz, DMSO-d_6, 95 °C) δ 1.01 (d, 6H, J = 6.3 Hz), 1.21-1.36 (m, 2H), 1.83-1.97 (m, 2H), 3.45 (dd, 1H, J = 10.7, 5.3 Hz), 3.51-3.66 (m, 3H), 3.90 (q, 1H, J = 5.3 Hz), 4.37 (s, 2H), 4.41 (d, 1H, J = 15.9 Hz), 4.51 (d, 1H, J = 15.9 Hz), 4.93 (d, 1H, J = 5.3 Hz), 5.08 (s, 2H), 7.14-7.37 (m, 15H); 13C NMR (125 MHz, DMSO-d_6, 95 °C) δ 18.1, 29.2, 50.8, 55.1, 61.5, 63.5, 66.4, 67.6, 72.2, 126.5, 126.9, 127.1, 127.3, 127.6, 136.0, 137.5, 137.6, 154.8, 164.1; IR (film) 1759, 1704, 1379, 1244, 1101, 708 cm^{-1}; mass spectrum (FAB) *m/z* (rel intensity) 550 (M^++Na, 17), 528 (M^++1, 29), 436 (19), 139 (100); HRMS calcd for $C_{32}H_{38}N_3O_4$ 528.2862, found 528.2860.

Data of *trans* adduct: $[\alpha]^{22}_D$ –41.1 (*c* 0.87, CH_2Cl_2); 1H NMR (300 MHz, DMSO-d_6, 95 °C) δ 0.99 (d, 6H, J = 6.4 Hz), 1.25-1.37 (m, 2H), 1.87-1.98 (m, 2H), 3.42 (dd, 1H, J = 10.8, 3.3 Hz), 3.53-3.64 (m, 2H), 3.62 (dd, 1H, J = 10.8, 3.3 Hz), 3.75-3.78 (m, 1H), 4.36 (d, 1H, J = 12.0 Hz), 4.43 (d, 1H, J

= 12.0 Hz), 4.59-4.78 (m, 2H), 4.68 (d, 1H, J = 2.4 Hz), 5.15 (s, 2H), 7.23-7.35 (m, 15H); 13C NMR (125 MHz, DMSO-d_6, 95 °C) δ 17.9, 29.6, 50.3, 55.6, 60.5, 61.5, 65.5, 66.6, 72.1, 126.6, 126.7, 126.9, 127.0, 127.1, 127.4, 127.8, 127.9, 128.0, 136.1, 137.5, 137.7, 154.8, 164.1; IR (film) 1757, 1718, 1376, 1241, 1114, 748, 709 cm^{-1}; mass spectrum (EI) *m/z* (rel intensity) 527 (M^+, 8), 436 (6), 91 (100); HRMS calcd for $C_{32}H_{37}N_3O_4$ 527.2784, found 527.2795.

Method B. When the reaction was performed at 40 °C, only *cis*-**4f** adduct was observed (501 mg, 95%), with spectral and analytical data as described above.

Oxidative cleavage of N-N bonds. Synthesis of compounds 5a-f. To a solution of β-lactams **4a-f** (1 mmol) in CH_3OH (0.4 mL) was added MMPP•6 H_2O (730 mg, 1.25 mmol) and the mixture was stirred at room temperature until total consumption of the starting material (ca. 1 h). The mixture was then diluted with CH_2Cl_2 (10 mL) and washed with saturated $NaHCO_3$ (2 × 10 mL) and H_2O (2 × 10 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL) and the combined organic layer was dried (Na_2SO_4), concentrated and the residue purified by flash chromatography. Eluants, yields, and spectral and analytical data for compounds **5a-f** are as follows:

(3*R*,4*R*)-3-(*N*-benzyl-*N*-benzyloxycarbonyl)amino-4-methylazetidin-2-one 5a. From (3*R*,4*R*)-**4a**, flash chromatography (1:1:1 Et_2O-CH_2Cl_2-petroleum ether) and further purification using medium pressure liquid chromatography (1:1 toluene-AcOEt) gave 292 mg (90%) of (3*R*,4*R*)-**5a** as an oil: $[\alpha]^{22}_D$ +18.3 (*c* 1, $CHCl_3$); 1H NMR (500 MHz, DMSO-d_6, 95 °C) δ 1.06 (d, 3H, J = 6.1 Hz), 3.51-3.53 (m, 1H), 4.25 (d, 1H, J = 2.3 Hz), 4.49 (d, 1H, J = 15.8 Hz), 4.56 (d, 1H, J = 15.8 Hz), 5.13 (s, 2H), 7.23-7.35 (m, 10H), 7.82 (br s, 1H); 13C NMR (125 MHz, DMSO-d_6, 95 °C) δ 18.3, 50.1, 66.5, 70.3, 126.6,126.7, 127.0, 127.3, 127.8, 127.8, 136.0, 137.8, 154.7, 164.8; IR (film) 3255 br, 1767, 1701, 1454, 1417, 1369 cm^{-1}; mass spectrum (EI) *m/z* (rel intensity) 324 M^+ (1), 281 (24), 190 (63), 146 (42), 91 (100); HRMS calcd for $C_{19}H_{20}N_2O_3$ 324.1474, found 324.1457.

(3*R*,4*R*)-3-(*N*-benzyl-*N*-benzyloxycarbonyl)amino-4-isopropylazetidin-2-one 5b. From (3*R*,4*R*)-**4b**, flash chromatography (1:1 → 5:1 Et_2O-petroleum ether) gave 253 mg (72%) of (3*R*,4*R*)-**5b** as an oil: $[\alpha]^{22}_D$ +24.4 (*c* 1.1, CH_2Cl_2); 1H NMR (300 MHz, DMSO-d_6, 95 °C) δ 0.77 (d, 3H, *J* = 7.2 Hz), 0.79 (d, 3H, *J* = 7.2 Hz), 1.53-1.65 (m, 1H), 3.21 (dd, 1H, *J* = 2.7, 7.5 Hz), 4.36 (d, 1H, *J* = 16.2 Hz), 4.52 (d, 1H, *J* = 2.7 Hz), 4.65 (d, 1H, *J* = 16.2 Hz), 5.13 (s, 2H), 7.23-7.32 (m, 10H), 8.02 (br s, 1H); 13C NMR (75 MHz, DMSO-d_6, 95 °C) δ 17.5, 17.8, 30.4, 49.6, 59.9, 66.5, 67.0, 126.6, 127.0, 127.3, 127.8, 135.9, 137.7, 154.7, 165.4; IR (film) 3277, 2967, 1776, 1704, 1426,1100, 743 cm^{-1}; mass spectrum (CI) *m/z* (rel intensity) 353 (M^+, 20), 325 (20), 218 (40), 91 (100); HRMS calcd for $C_{21}H_{25}N_2O_3$ 353.1865, found 353.1865.

(3*R*,4*R*)-3-(*N*-benzyl-*N*-benzyloxycarbonyl)amino-4-isobutylazetidin-2-one 5c. From (3*R*,4*R*)-**4c**, flash chromatography (1:1 → 4:1 Et_2O-petroleum ether) gave 311 mg (85%) of (3*R*,4*R*)-**5c** as an oil: $[\alpha]^{22}_D$ +32.5 (*c* 1.3, CH_2Cl_2); 1H NMR (300 MHz, DMSO-d_6, 95 °C) δ 0.73 (d, 3H, *J* = 7.0 Hz), 0.75 (d, 3H, *J* = 7.0 Hz), 1.13-1.36 (m, 2H), 1.42-1.51 (m, 1H), 3.42-3.47 (m, 1H), 4.38 (d, 1H, *J* = 2.5 Hz), 4.44 (d, 1H, *J* = 15.9 Hz), 4.59 (d, 1H, *J* = 15.9 Hz), 5.12 (d, 1H, *J* = 12.6 Hz), 5.16 (d, 1H, *J* = 12.6 Hz), 7.21-7.37 (m, 10H), 7.93 (br, 1H); 13C NMR (75 MHz, DMSO-d_6, 95 °C) δ 21.9, 22.6, 25.2, 42.6, 50.4, 53.2, 67.0, 69.9, 127.1, 127.6, 127.8, 128.3, 136.5, 138.3, 155.2, 165.8; IR (film) 3293, 2959, 1776, 1704, 1458, 1428, 1243, 743, 703 cm^{-1}; mass spectrum (EI) *m/z* (rel intensity) 366 (M^+, 1), 323 (10), 236 (20), 91 (100). Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 72.32; H, 7.02; N, 7.45.

(3*R*,4*R*)-3-(*N*-benzyl-*N*-benzyloxycarbonyl)amino-4-(2-phenylethyl)azetidin-2-one 5d. From (3*R*,4*R*)-**4d**, flash chromatography (1:1:2 Et_2O-CH_2Cl_2-petroleum ether) gave 302 mg (73%) of (3*R*,4*R*)-**5d** as an oil: $[\alpha]^{22}_D$ +26.4 (*c* 0.92, $CHCl_3$); 1H NMR (300 MHz, DMSO-d_6, 95 °C) δ 1.66-1.73 (m, 2H), 2.41-2.58 (m, 2H), 3.45 (td, 1H, *J* = 6.3, 2.3 Hz), 4.42 (d, 1H, *J* = 2.4 Hz), 4.45 (d, 1H,

J = 15.9 Hz), 4.55 (d, 1H, J = 15.9 Hz), 5.13 (s, 2H), 7.04-7.35 (m, 10H), 7.98 (s br, 1H); 13C NMR (75 MHz, DMSO-d_6, 95 °C) δ 31.0, 34.4, 50.0, 53.7, 66.5, 68.9, 125.2, 126.6, 126.7, 127.0, 127.3, 127.5, 127.7, 127.8, 135.9, 137.6, 140.6, 154.6, 165.1; IR (film) 3240 br, 1767, 1699, 1454, 1420 cm^{-1}; mass spectrum (EI) *m/z* (rel intensity) 414 M^+ (1), 371 (4), 280 (21), 236 (15), 91 (100). Anal. Calcd for $C_{26}H_{26}N_2O_3$: C, 75.34; H, 6.32; N, 6.76. Found: C, 74.98; H, 5.77; N, 6.54.

(3*R*,4*R*)-3-(*N*-benzyl-*N*-benzyloxycarbonyl)amino-4-pentylazetidin-2-one 5e. From (3*R*,4*R*)-**4e**, flash chromatography (1:1:2 Et_2O-CH_2Cl_2-petroleum ether) gave 281 mg (74%) of (3*R*,4*R*)-**5e** as an oil: $[\alpha]^{22}_D$ +27.6 (*c* 0.9, $CHCl_3$); 1H NMR (500 MHz, DMSO-d_6, 95 °C) δ 0.82 (t, 3H, J = 7.1 Hz), 1.13-1.23 (m, 6H), 1.34-1.37 (m, 2H), 3.39-3.41 (m, 1H), 4.37 (d, 1H, J = 2.4 Hz), 4.47 (d, 1H, J = 15.9 Hz), 4.57 (d, 1H, J = 15.9 Hz), 5.09-5.16 (m, 2H), 7.23-7.34 (m, 10H), 7.94 (s br, 1H); 13C NMR (125 MHz, DMSO-d_6, 95 °C) δ 14.0, 22.2, 25.4, 31.3, 33.6, 50.8, 55.1, 67.5, 69.8, 127.6, 127.6, 128.0, 128.3, 128.6, 128.7, 136.9, 138.7, 155.6, 166.2; IR (film) 3293 br, 2930, 1767, 1705,1456, 1421 cm^{-1}; mass spectrum (EI) *m/z* (rel intensity) 380 M^+ (1), 337 (12), 246 (42), 236 (28), 190 (18), 91 (100). Anal. Calcd for $C_{23}H_{28}N_2O_3$: C, 72.61; H, 7.42; N, 7.36. Found: C, 71.07; H, 7.86; N, 6.97.

(3*R*,4*R*)-3-(*N*-benzyl-*N*-benzyloxycarbonyl)amino-4-benzyloxymethylazetidin-2-one 5f. From (3*R*,4*R*)-**4f**, flash chromatography (1:1 → 4:1 Et_2O-petroleum ether) gave 318 mg (74%) of (3*R*,4*R*)-**5f** as an oil: $[\alpha]^{22}_D$ –29.5 (*c* 0.9, CH_2Cl_2); 1H NMR (300 MHz, DMSO-d_6, 95 °C) δ 3.33-3.42 (m, 2H), 3.83 (dt, 1H, J = 6.2, 5.3 Hz), 4.35 (s, 2H), 4.45 (d, 1H, J = 15.6 Hz), 4.52 (d, 1H, J = 15.6 Hz), 4.93 (dd, 1H, J = 5.1, 1.3 Hz), 5.07 (s, 2H), 7.21-7.37 (m, 15H), 8.12 (s br, 1H); 13C NMR (125 MHz, DMSO-d_6, 95 °C) δ 50.6, 52.8, 65.5, 66.4, 69.3, 72.1, 126.5, 126.8, 126.9, 127.1, 127.3, 127.6, 127.6, 127.7, 135.9, 137.7, 154.8, 164.9; IR (film) 1767, 1701, 1370, 1251, 1094 cm^{-1}; mass spectrum (EI) *m/z* (rel intensity) 453 (M^++Na, 100), 431(M^++1, 18), 339 (2), 295 (3), 240 (4); HRMS calcd for $C_{26}H_{27}N_2O_4$ 431.1971, found 431.1971.

Synthesis of (3*R*,4*R*)-3-amino-4-methylazetidin-2-one 6. Compound (3*R*,4*R*)-**5a** (324 mg, 1 mmol) was solved in dioxane:H_2O 20:1 (25 mL) and catalytic $Pd(OH)_2/C$ was added. The mixture was stirred under H_2 (6 atm) until total deprotection was observed by TLC (ca. 6 h). The mixture was then filtered through a pad of Celite and concentrated. Purification of the residue by flash chromatography (15:1 → 8:1 CH_2Cl_2-CH_3OH) gave 75 mg (75%) of (3*R*,4*R*)-**6** as an oil: $[\alpha]^{22}_D$ +63.5 (*c* 0.72, $CHCl_3$); 1H NMR (300 MHz, CD_3OD) δ 1.33 (d, 3H, *J* = 6.1 Hz), 3.42 (qd, 1H, *J* = 6.0, 2.1 Hz), 3.55 (d, 1H, *J* = 2.0 Hz); 13C NMR (75 MHz, CD_3OD) δ 19.2, 55.9, 67.5, 172.9; IR (film) 3283, 2874, 1748, 1377, 1352 cm^{-1}.

Synthesis of (3*R*,4*R*)-3-(*terc*-butoxycarbonyl)amino-4-methylazetidin-2-one 7. (3*R*,4*R*)-3-amino-4-methylazetidin-2-one **6** (100 mg, 1 mmol) was solved in CH_3OH (2 mL) and Et_3N (0.28 mL, 2 mmol) was added. Then, a solution of Boc_2O (436 mg, 2 mmol) in CH_3OH (2 mL) was added dropwise and the mixture stirred at room temperature until TLC indicated total consumption of starting material. The mixture was concentrated and then diluted with CH_2Cl_2 and washed with water and saturated NaCl. The organic layer was dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (15:1 CH_2Cl_2-MeOH) gave 144 mg (72%) of (3*R*,4*R*)-**7** as a white solid: M.p. 132-133 °C; $[\alpha]^{22}_D$ +59.0 (*c* 1.85, CH_3OH) [lit.[2] (3*S*,4*S*) $[\alpha]^{22}_D$ –64.2 (*c* 0.85, CH_3OH)]; 1H NMR (500 MHz, $CDCl_3$) δ 1.38 (d, 3H, *J* = 6.1 Hz), 1.41 (s, 9H), 3.67 (qd, 1H, *J* = 6.1, 2.1 Hz), 4.23 (br d, 1H, *J* = 7.0 Hz), 5.50 (br d, 1H, *J* = 7.0 Hz), 6.59 (br s, 1H); 13C NMR (125 MHz, $CDCl_3$) δ 19.2, 28.2, 54.1, 64.6, 80.2, 155.0, 167.4; IR (film) 3260, 3246, 2982, 2920, 1726, 1695, 1530, 1449, 1385, 1371, 1072, 880; mass spectrum (CI) *m/z* (rel intensity) 201 (M^+ + 1, 28), 173 (27), 145 (100), 127 (9), 117 (89), 101 (36), 73 (38), 57 (66); *m/z* calcd for $C_9H_{17}N_2O_3$ 201.1239, found 201.1249.

Synthesis of (3*R*,4*R*)-3-(*N*-benzyloxycarbonyl)amino-4-hydroxymethylazetidin-2-one 9. Compound (3*R*,4*R*)-**5f** (430 mg, 1 mmol) was solved in CH_3OH (20 mL) and ammonium formiate

(780 mg, 12 mmol) and Pd/C (1.5 g) were added. The reaction was stirred under reflux until TLC indicated total consumption of starting material. The mixture was filtered through a pad of celite and concentrated. The crude residue was solved in CH_3OH (2 mL) and Et_3N (280 μL, 2 mmol) and benzyl chloroformiate (300 μL, 2 mmol) were added. The mixture was stirred at room temperature until TLC indicated total consumption of starting material. The mixture was concentrated and the residue was solved in EtOAc and washed with H_2O (2 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (EtOAc) gave 138 mg (55%, two steps) of (3*R*,4*R*)-**9** as a white solid: M.p. 125-127 °C; $[\alpha]^{22}_D$ –7.4 (*c* 1, $CHCl_3$) [lit.[3] (3*S*,4*S*) $[\alpha]^{22}_D$ +8.6 (*c* 0.9, $CHCl_3$); lit.[4] (3*S*,4*S*) $[\alpha]^{22}_D$ +8.7 (*c* 0.55, $CHCl_3$); lit.[5] (3*S*,4*S*) $[\alpha]^{22}_D$ +9.0 (*c* 0.93, $CHCl_3$)]; 1H NMR (300 MHz, DMSO-d_6, 95 °C) δ 3.56 (m, 2H), 3.69 (ddd, 1H, *J* = 6.1, 5.1, 4.4 Hz), 4.49 (br t, 1H, *J* = 5.1 Hz), 4.88 (ddd, 1H, *J* = 6.2, 5.2, 1.1 Hz), 5.06 (d, 1H, *J* = 12.6 Hz), 5.10 (d, 1H, *J* = 12.6 Hz), 7.28-7.40 (m, 5H, Ph), 7.87 (br s, 1H); 13C NMR (75 MHz, DMSO-d_6, 95 °C) δ 53.7, 59.1, 60.3, 65.4, 127.1, 127.3, 127.8, 136.5, 155.2, 167.0; mass spectrum (EI) *m/z* (rel intensity) 250(M^+, 1), 116 (16), 107 (4), 91 (100), 60 (14); HRMS calcd for $C_{12}H_{14}N_2O_4$ 250.0954, found 250.0954.

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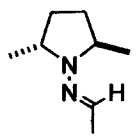

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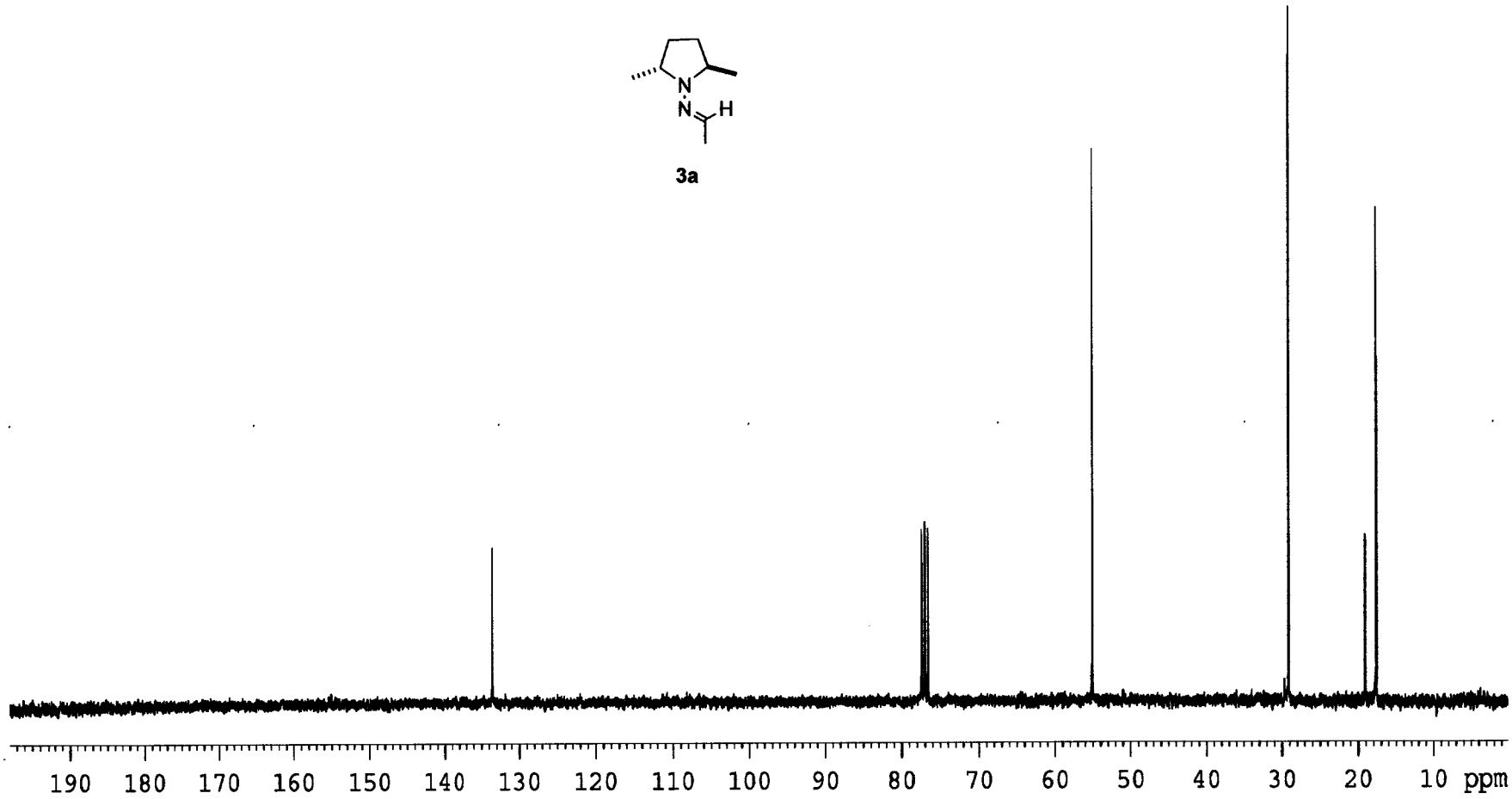
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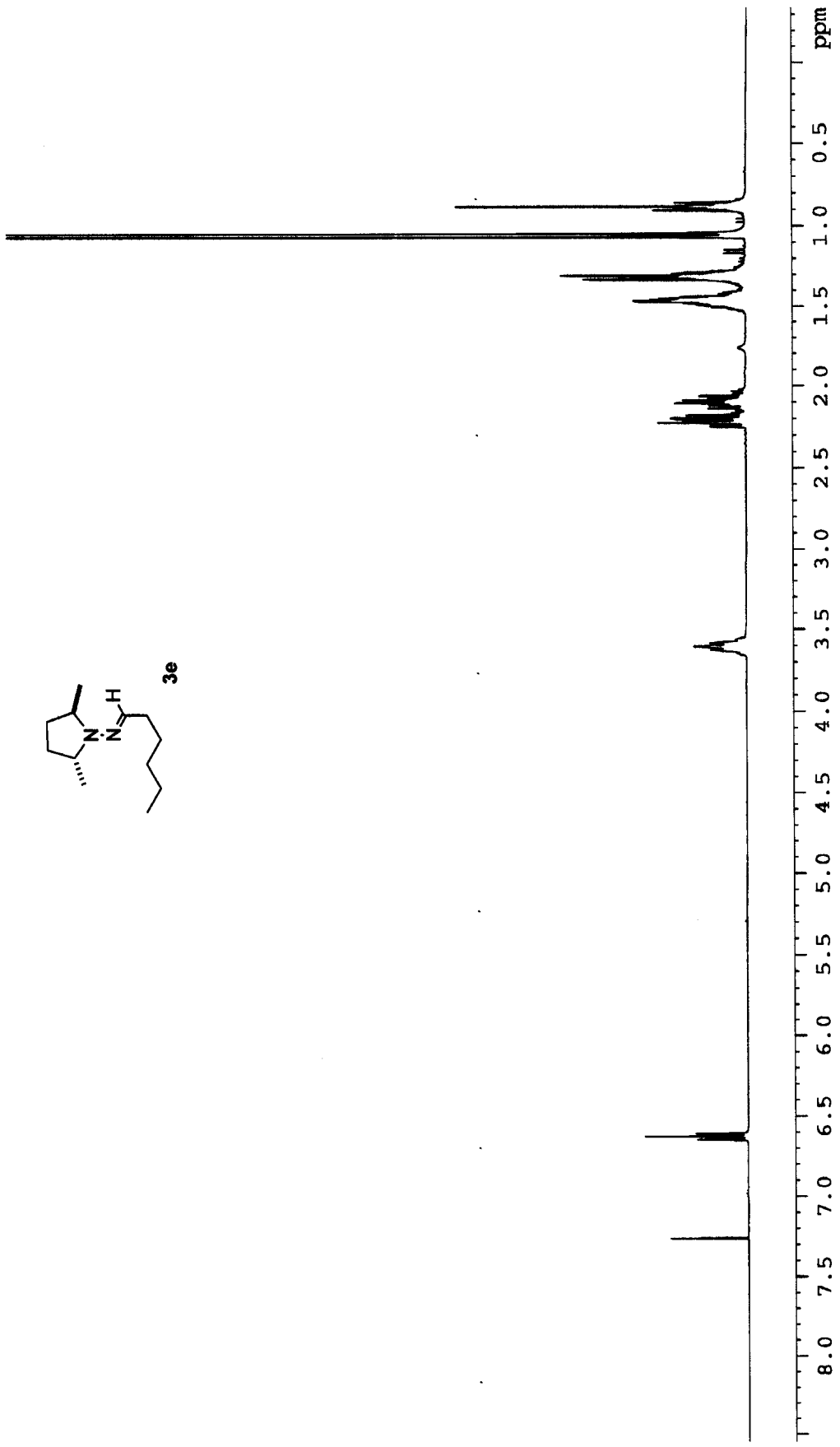
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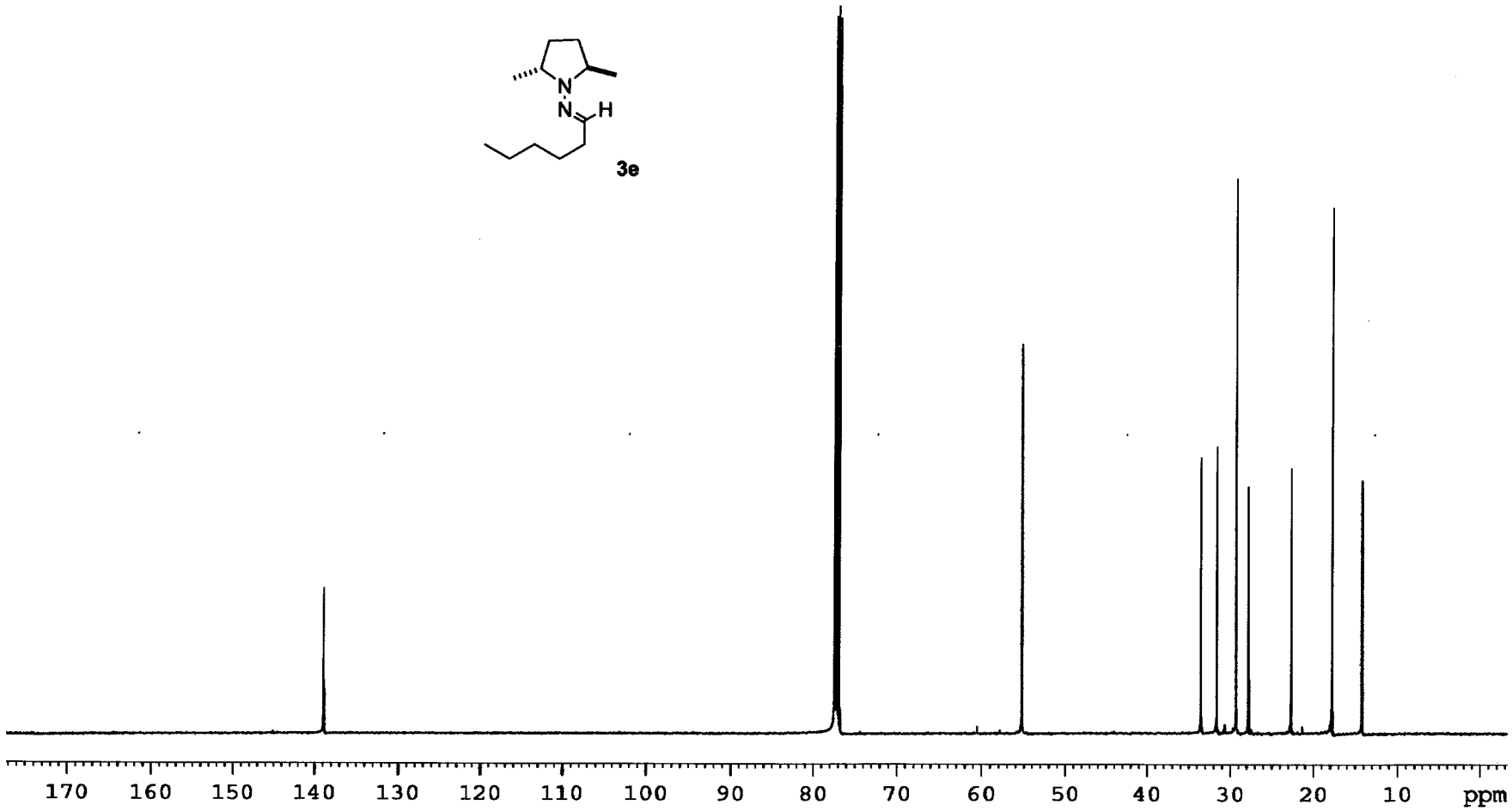
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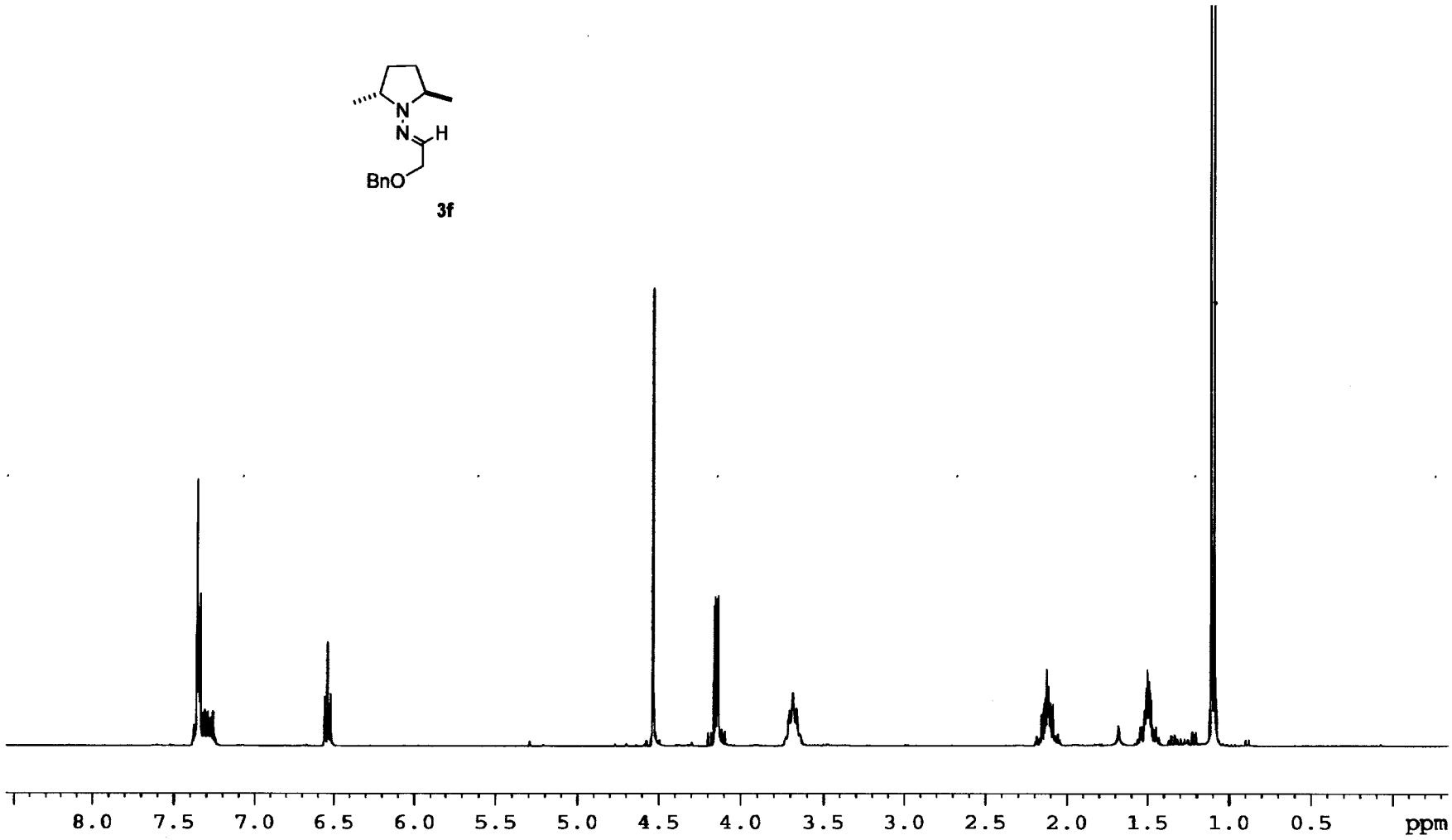
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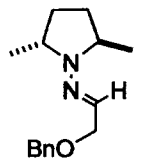

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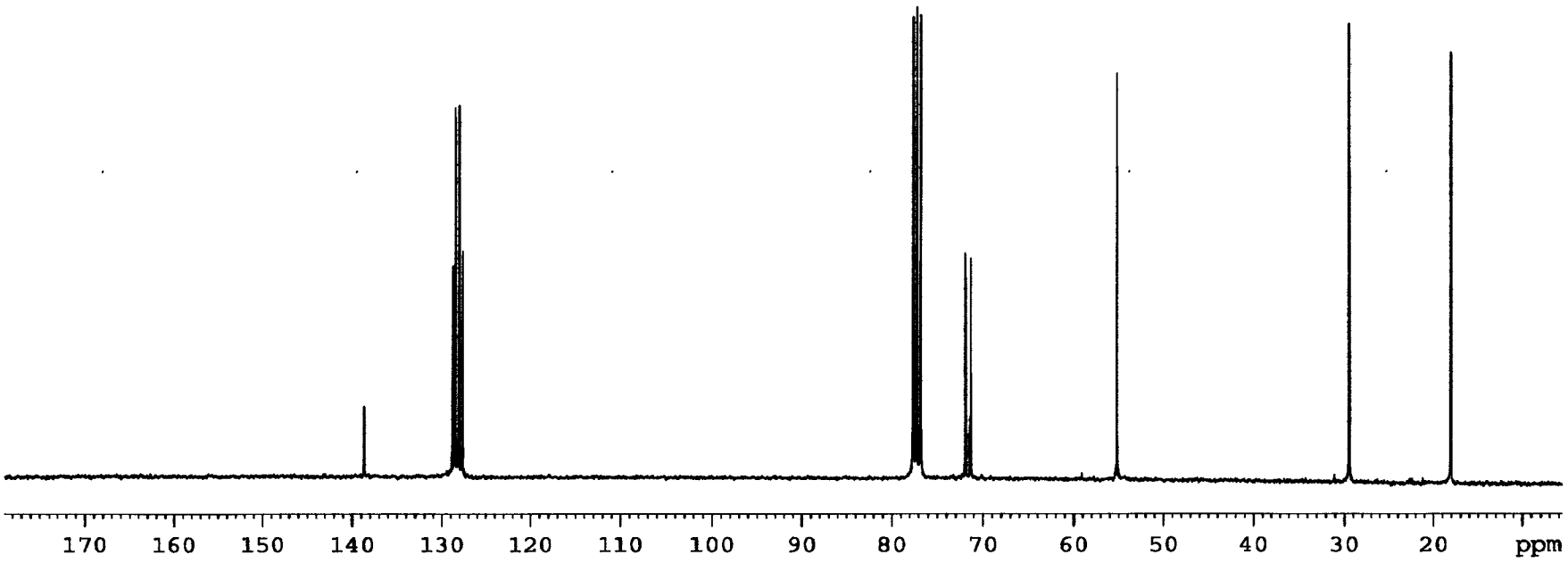

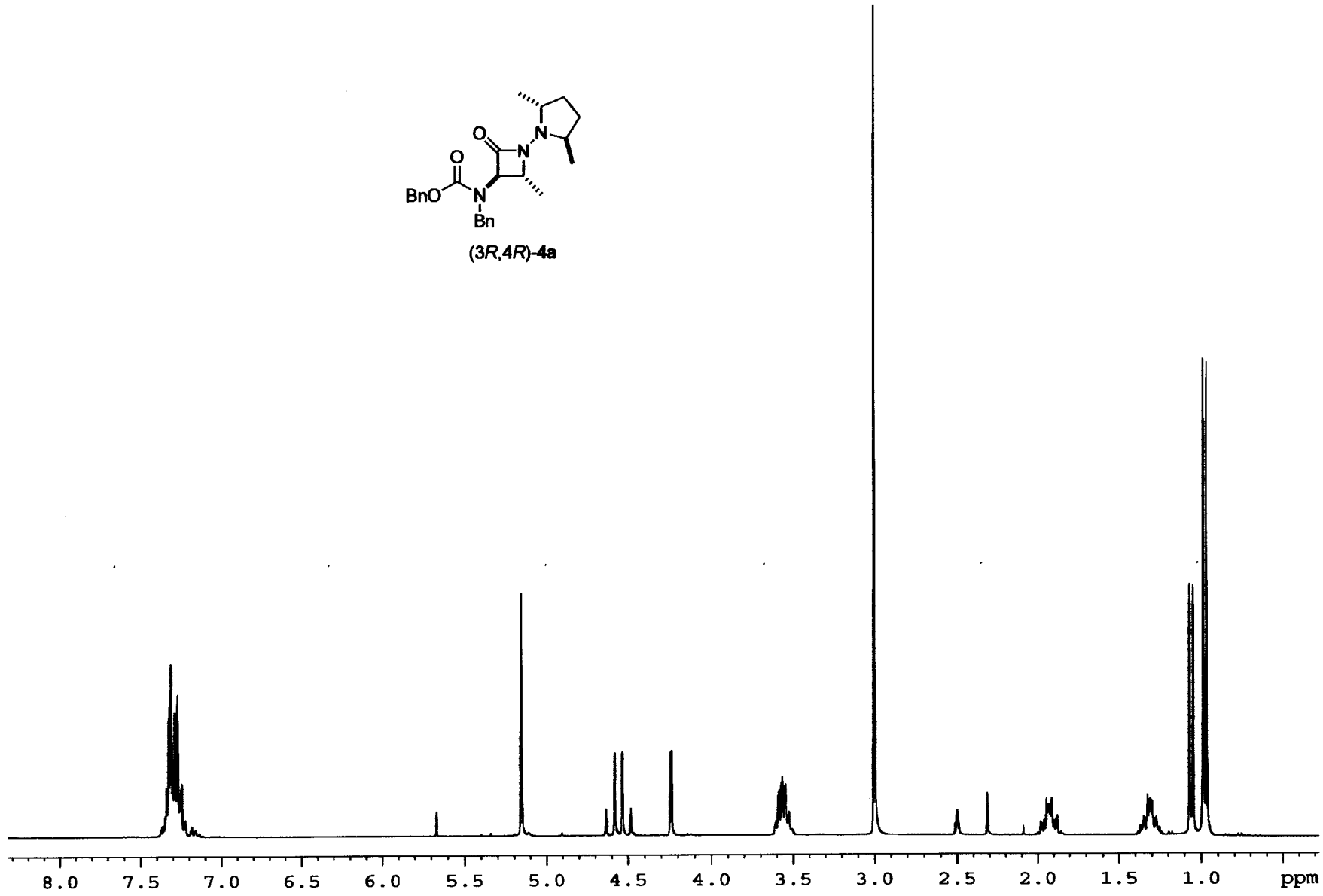

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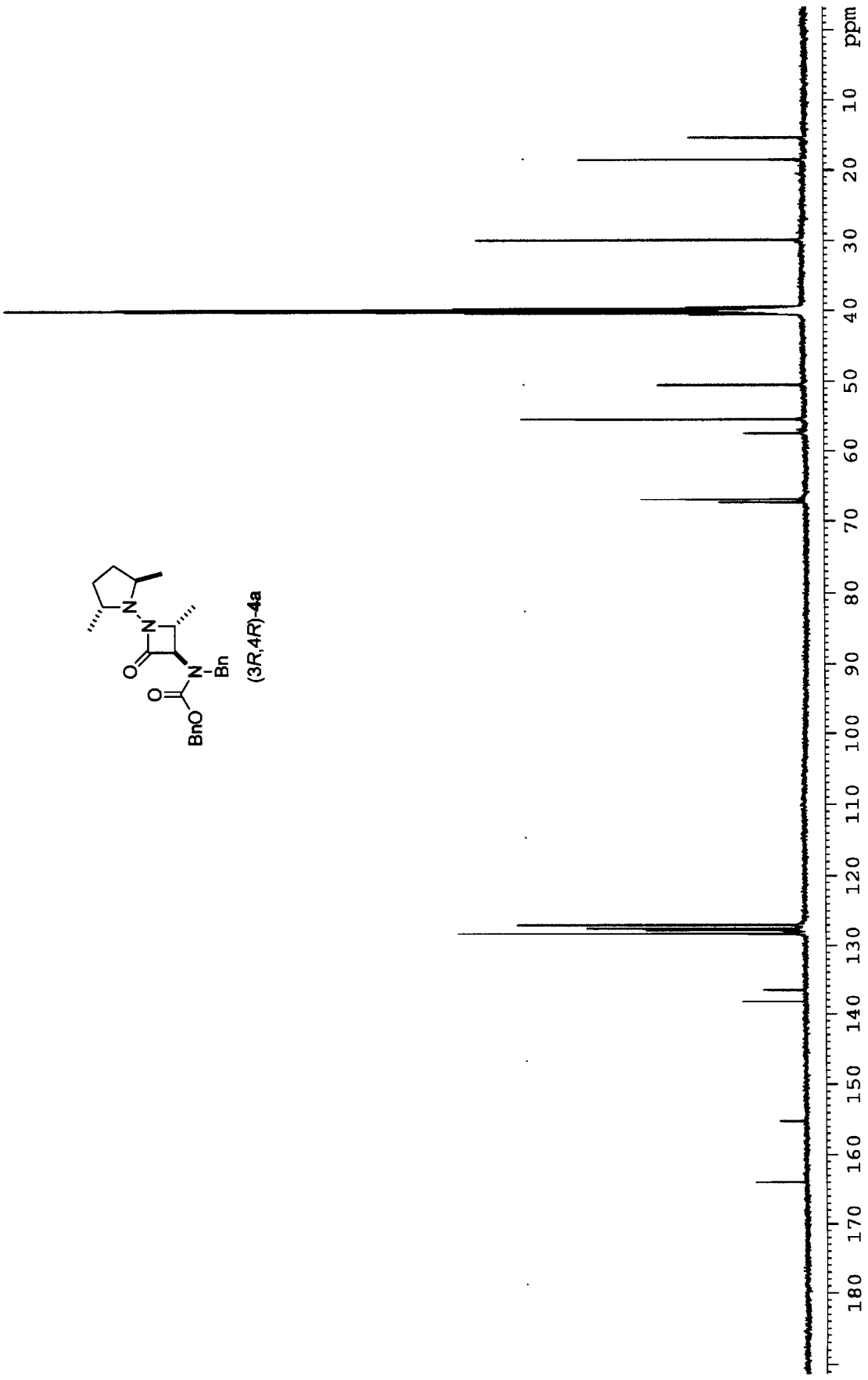
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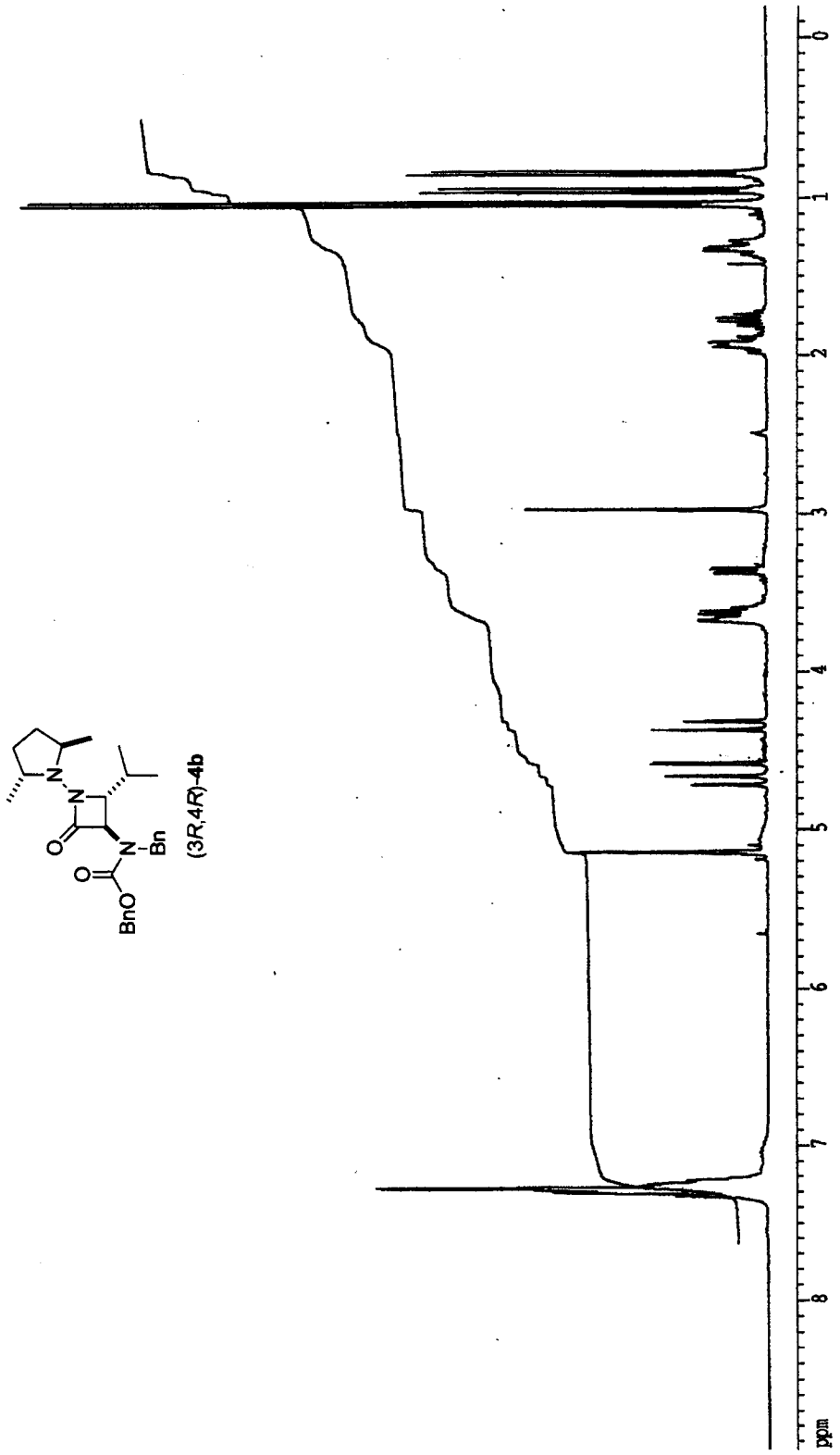
Bn
O
BnO

(3*R*,4*R*)-**4a**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Bn
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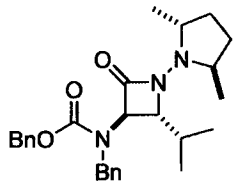

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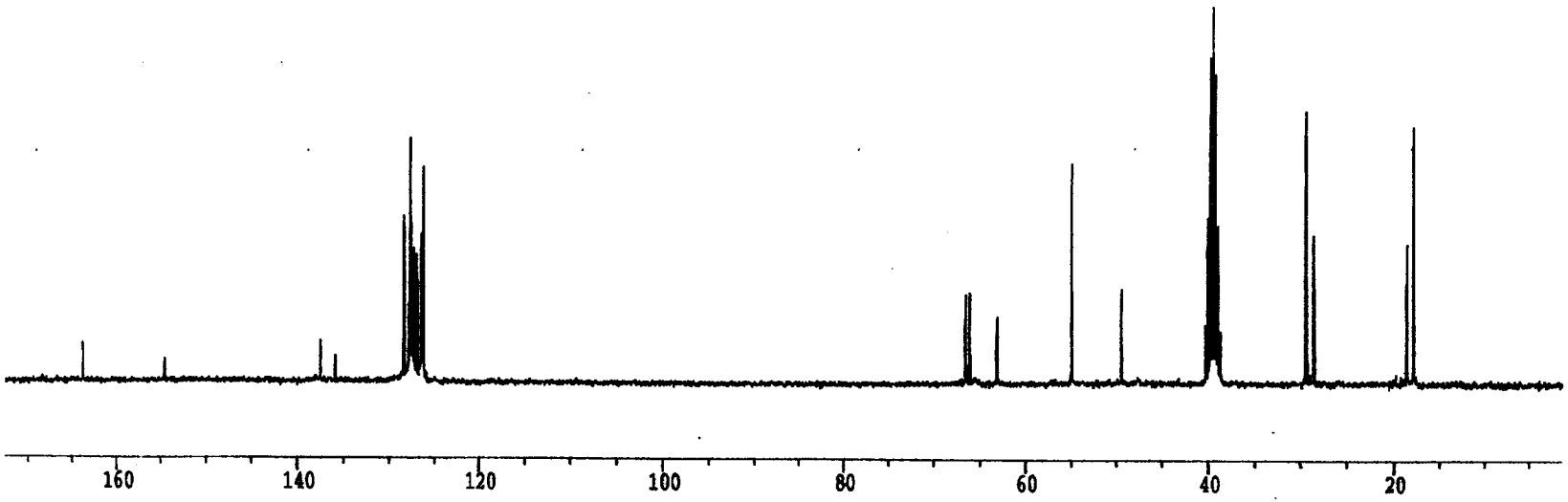

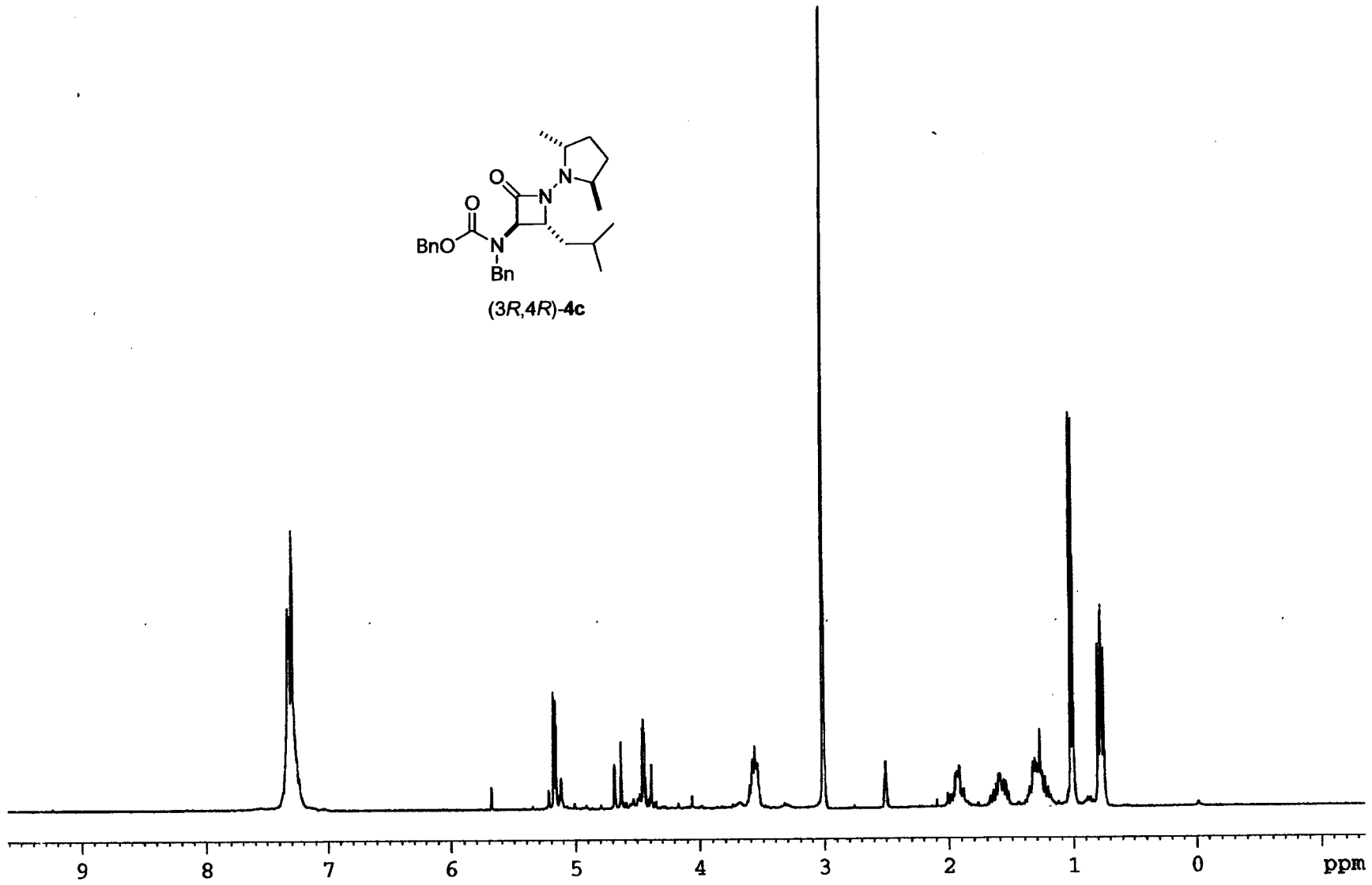

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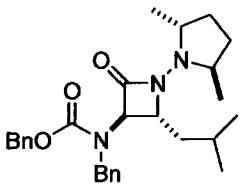

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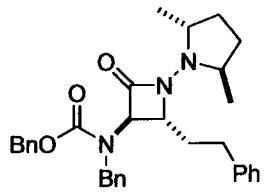

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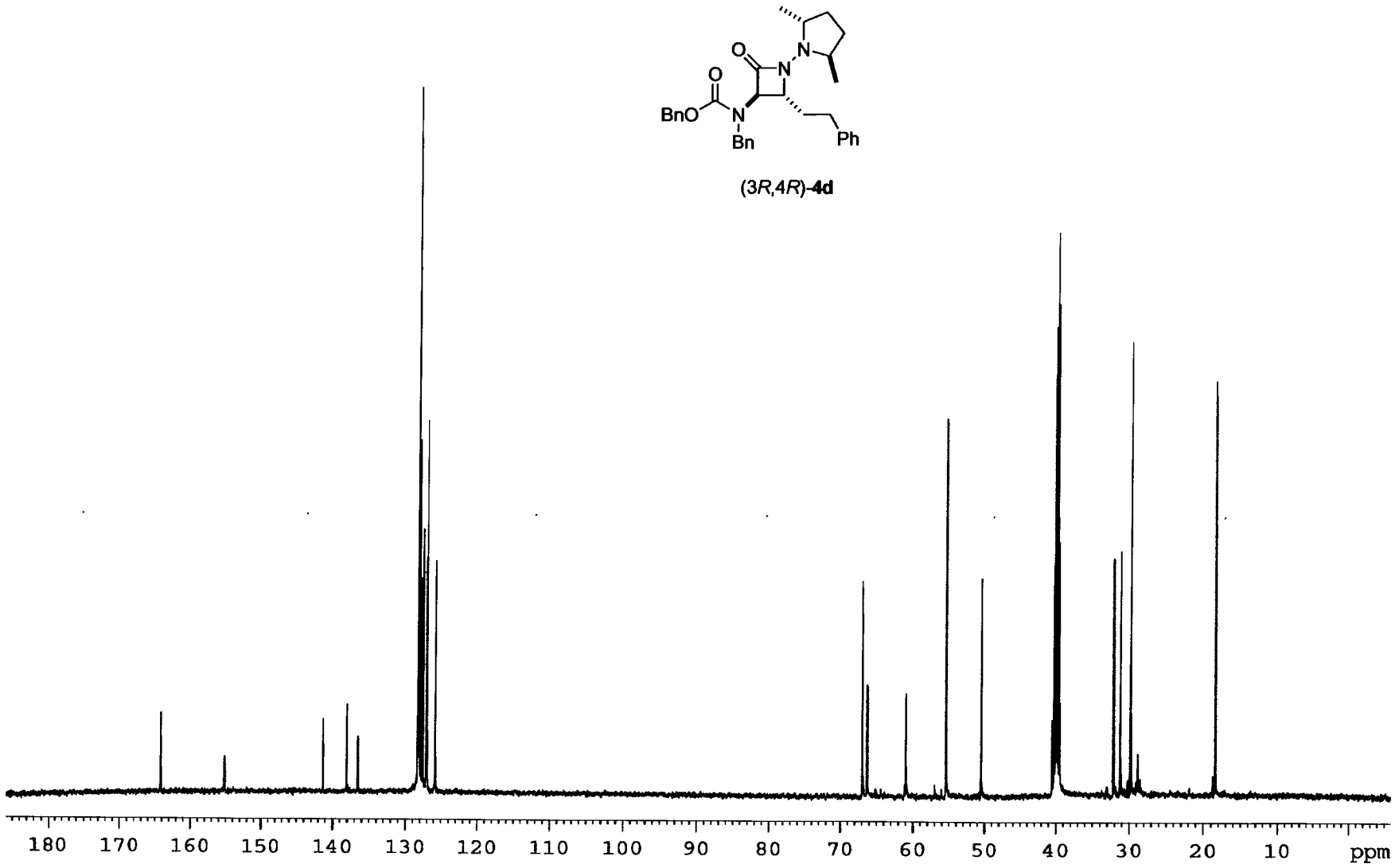
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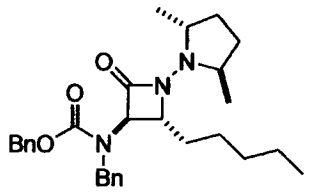

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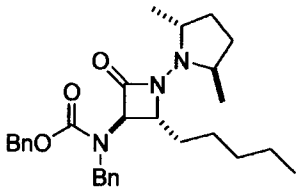
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Bn

(3*R*,4*R*)-**4e**

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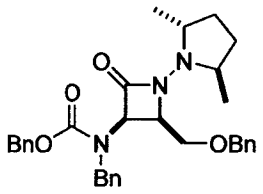

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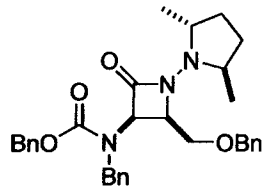
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(3*R*,4*R*)-**4f**

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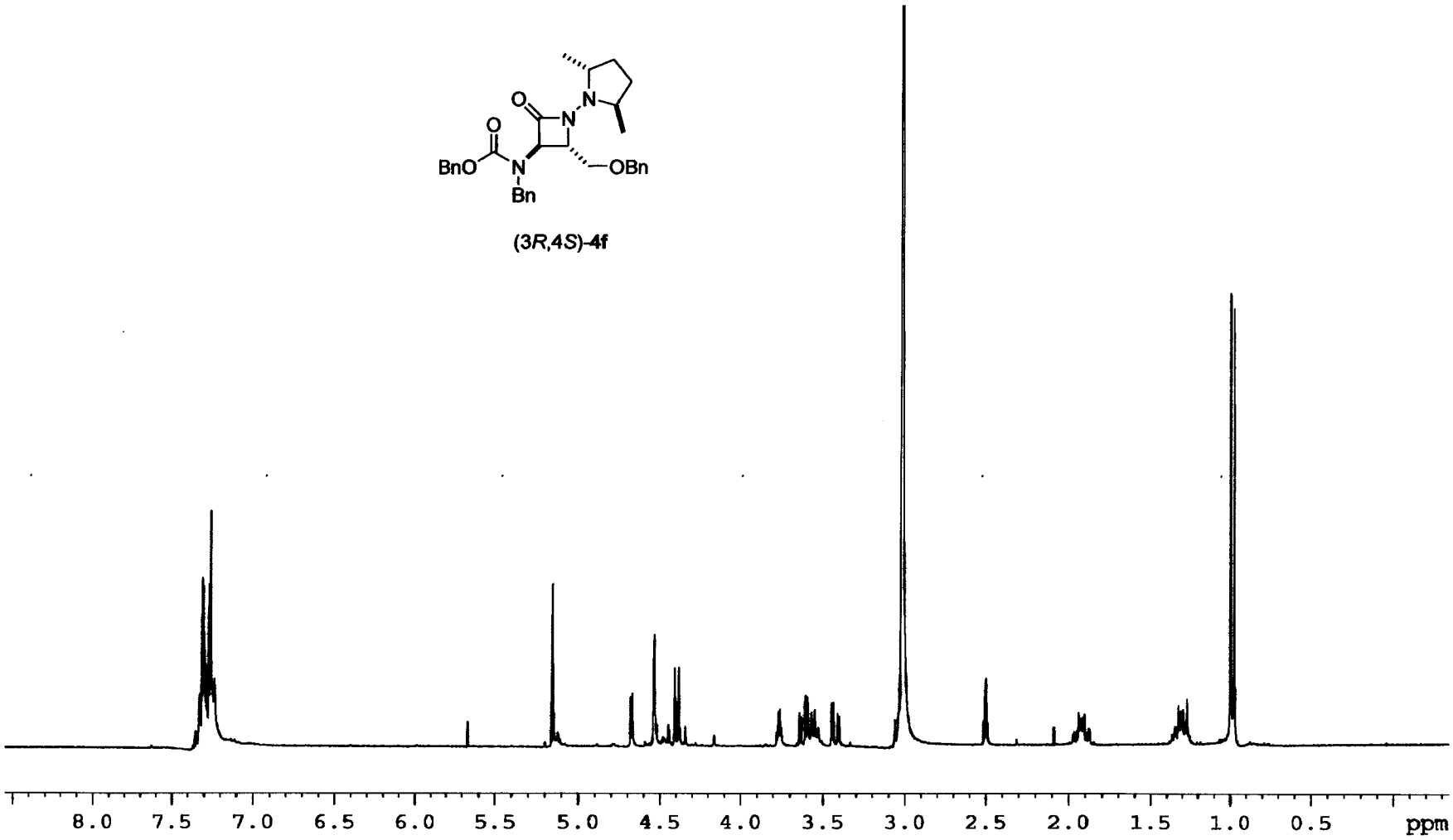

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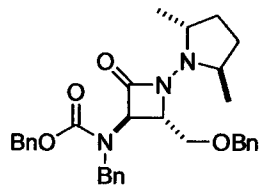
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(3*R*,4*S*)-**4f**

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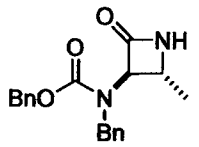
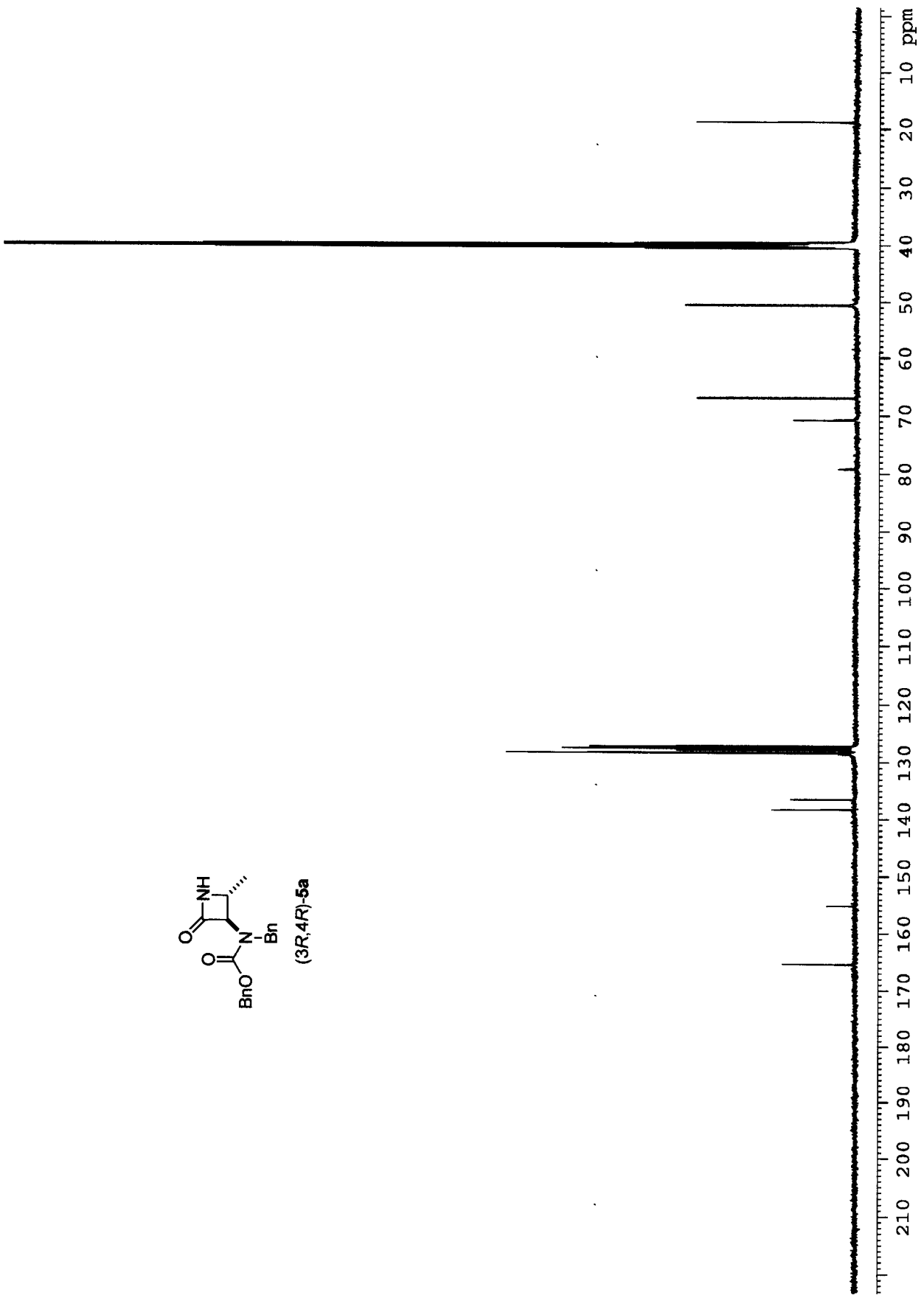


(3*R*,4*R*)-**5a**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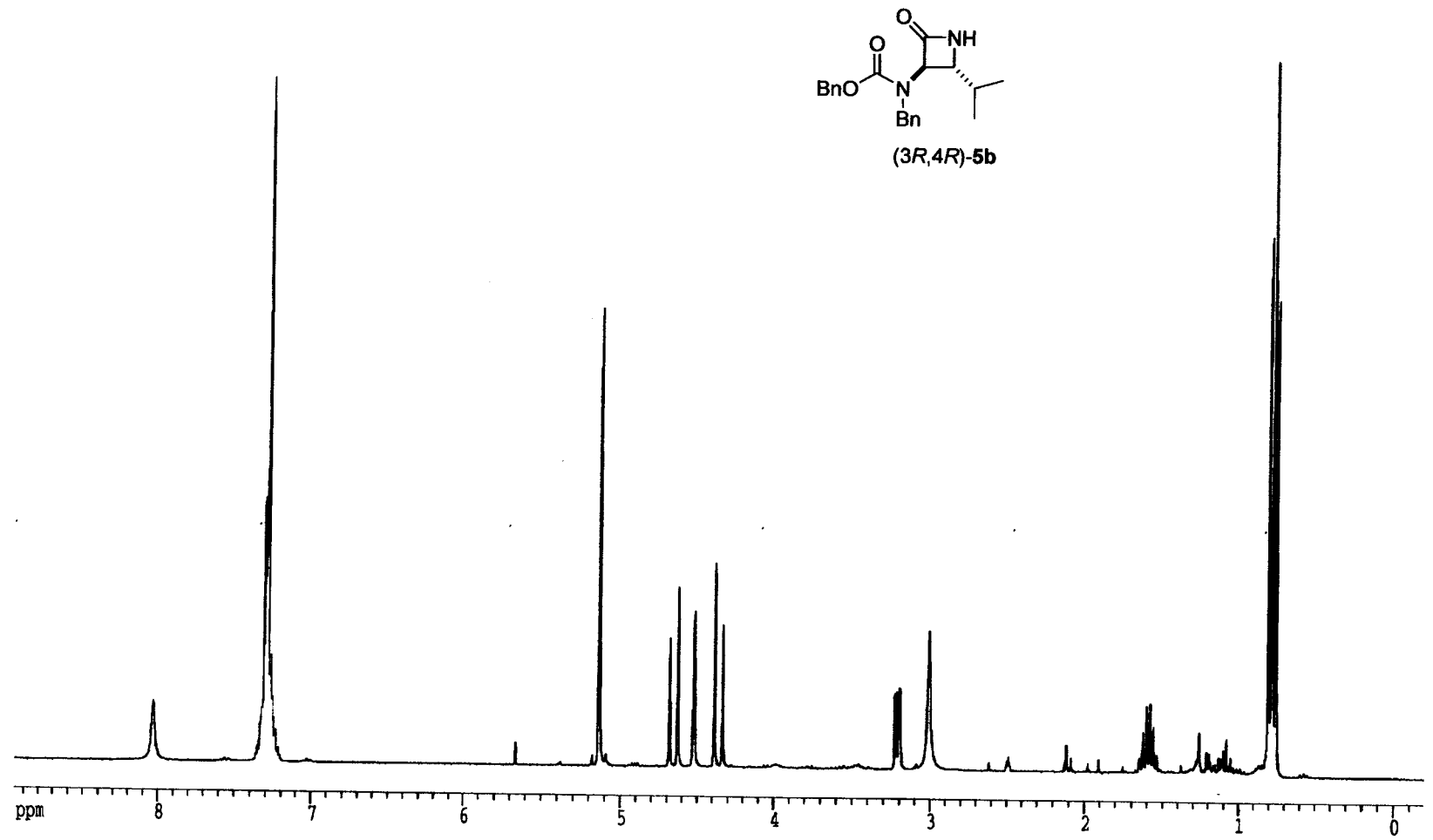
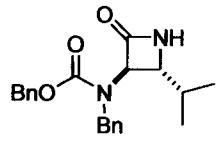
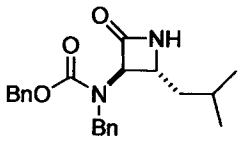
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

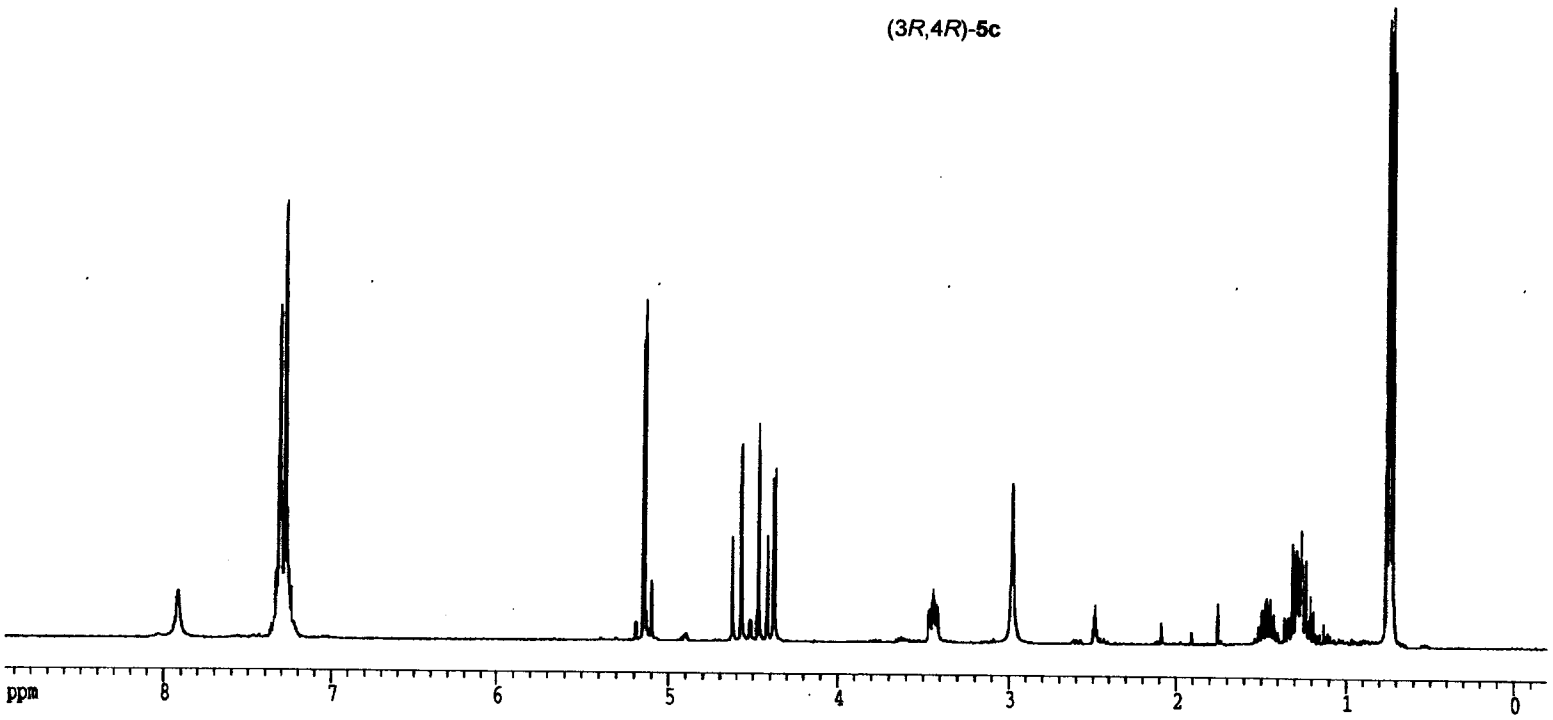

O
NH
O
BnO
N
Bn
(3R,4R)-5b
ppm
8
7
6
5
4
3
2
1
0

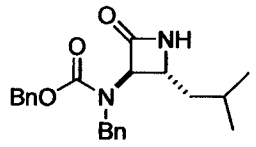


(3*R*,4*R*)-**5b**

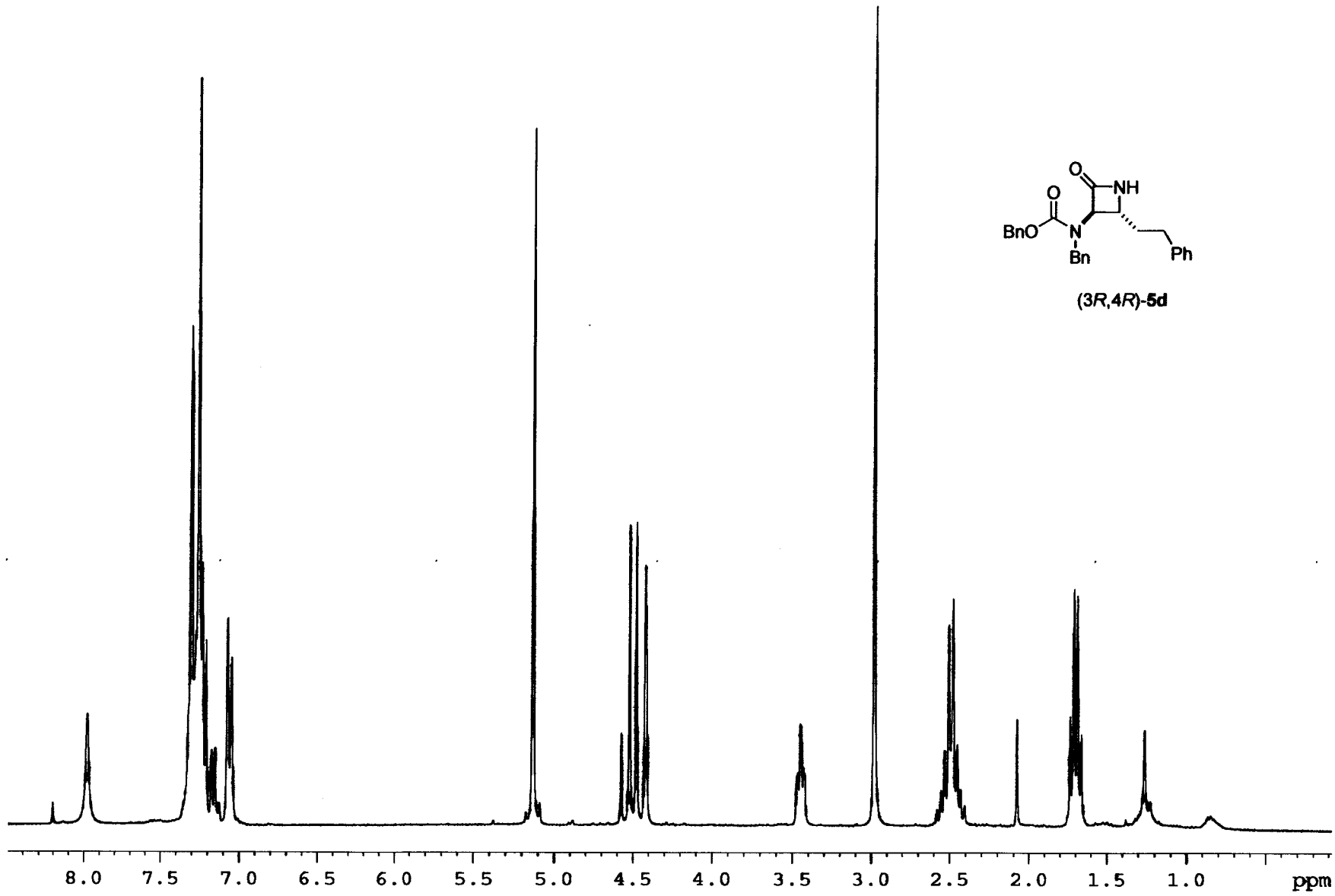


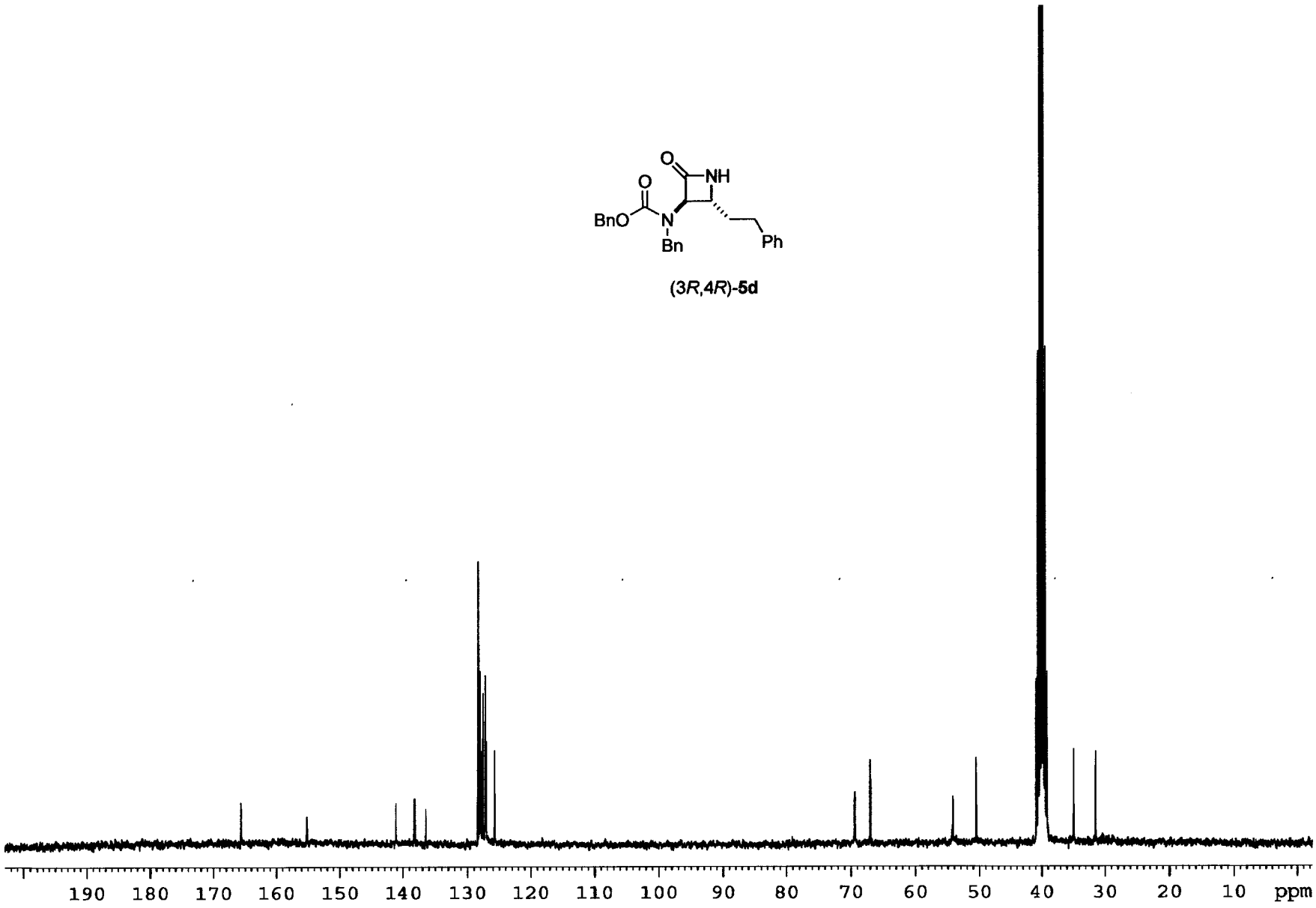
(3*R*,4*R*)-**5c**



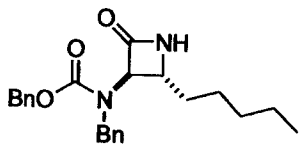


(3*R*,4*R*)-**5c**

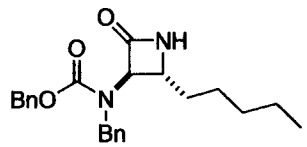

O
NH
O
BnO
N
Bn
Ph
(3R,4R)-5d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


O
NH
O
BnO
N
Bn
Ph
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

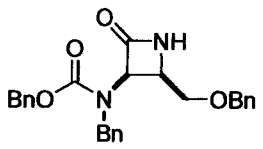
(3*R*,4*R*)-**5d**



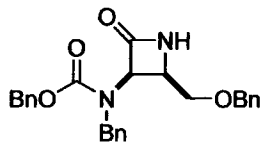
(3*R*,4*R*)-**5e**



(3*R*,4*R*)-**5e**

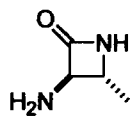


(3*R*,4*R*)-**5f**

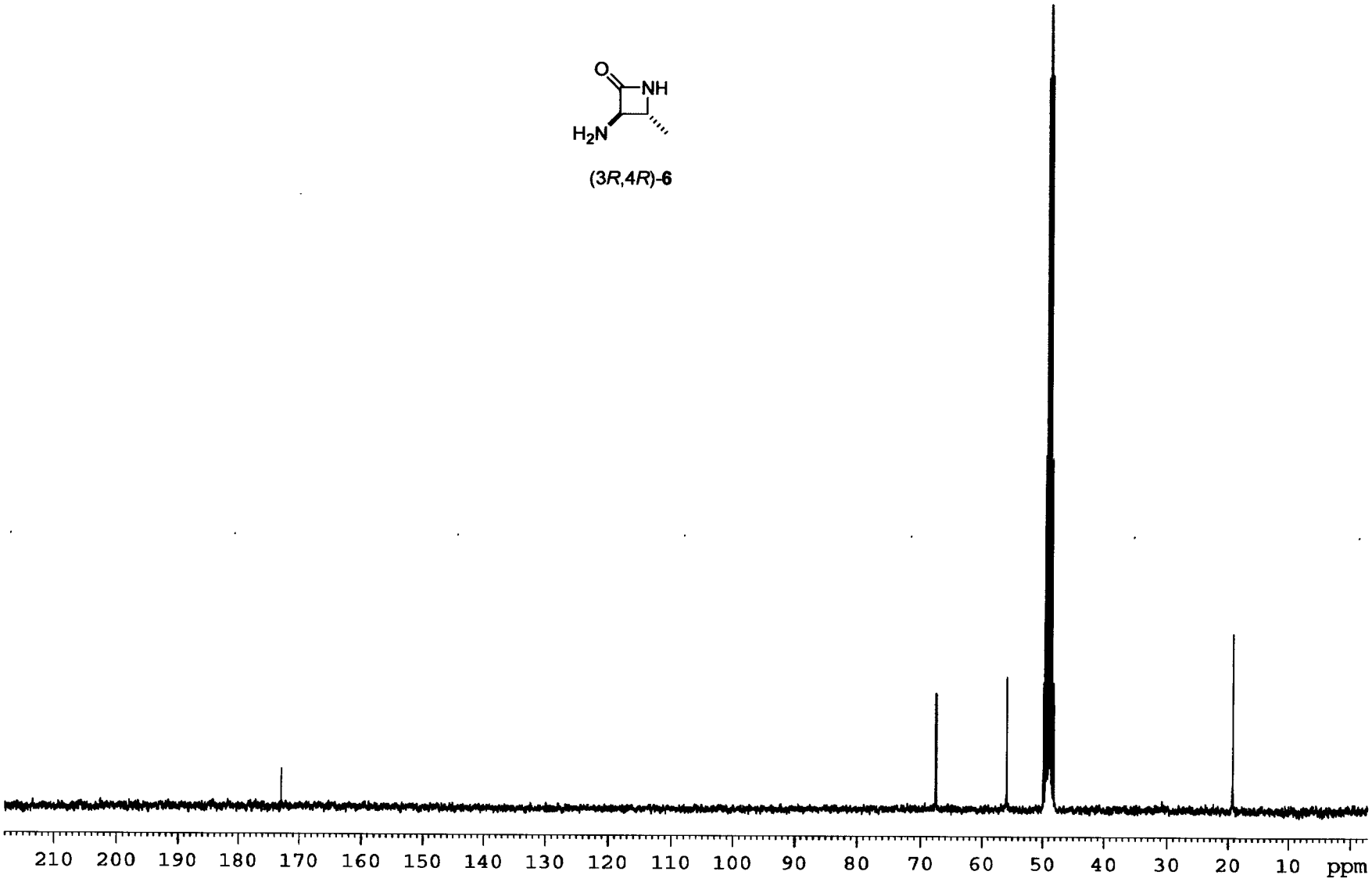

O
NH
O
BnO
N
Bn
OBn

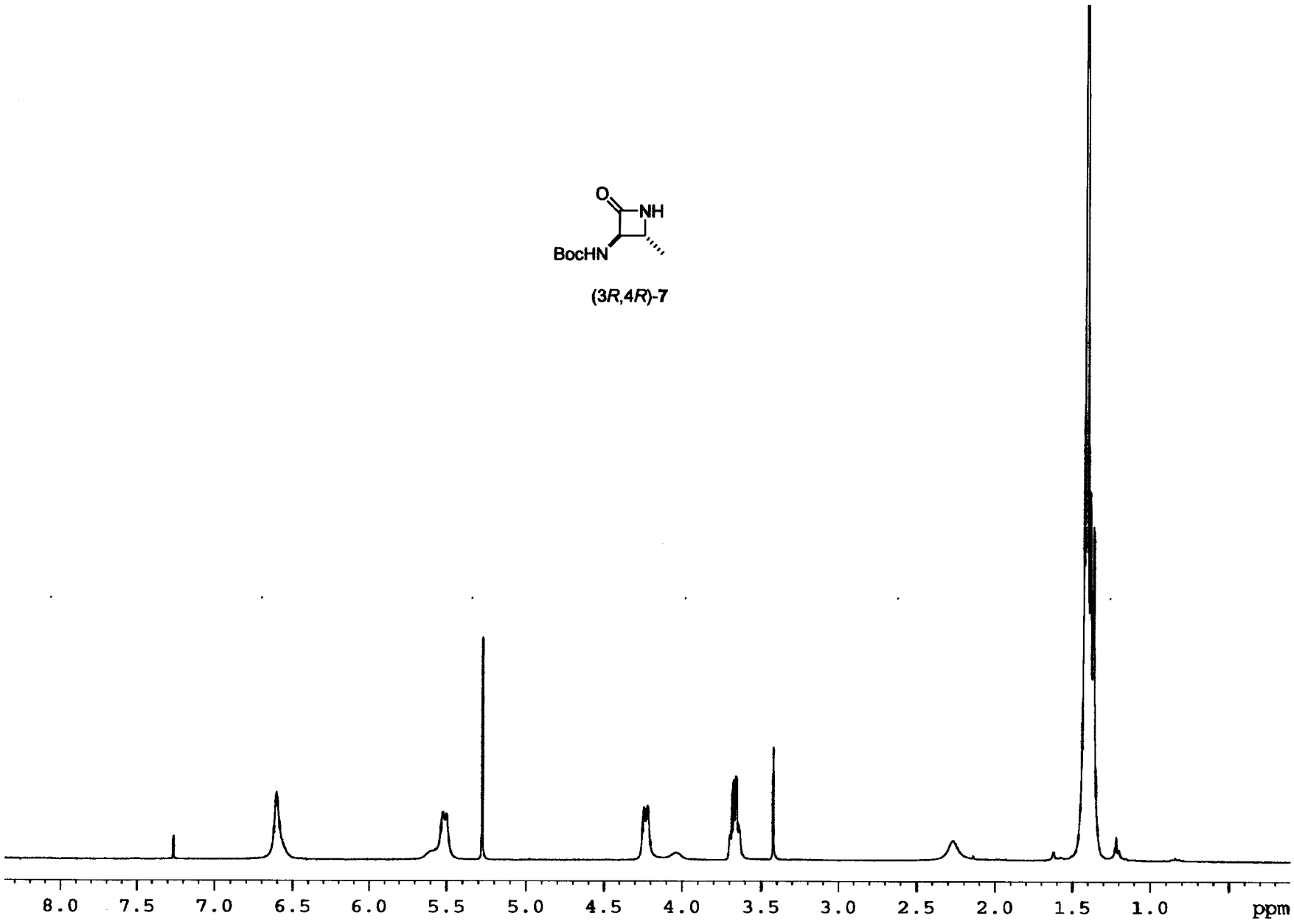
(3*R*,4*R*)-**5f**

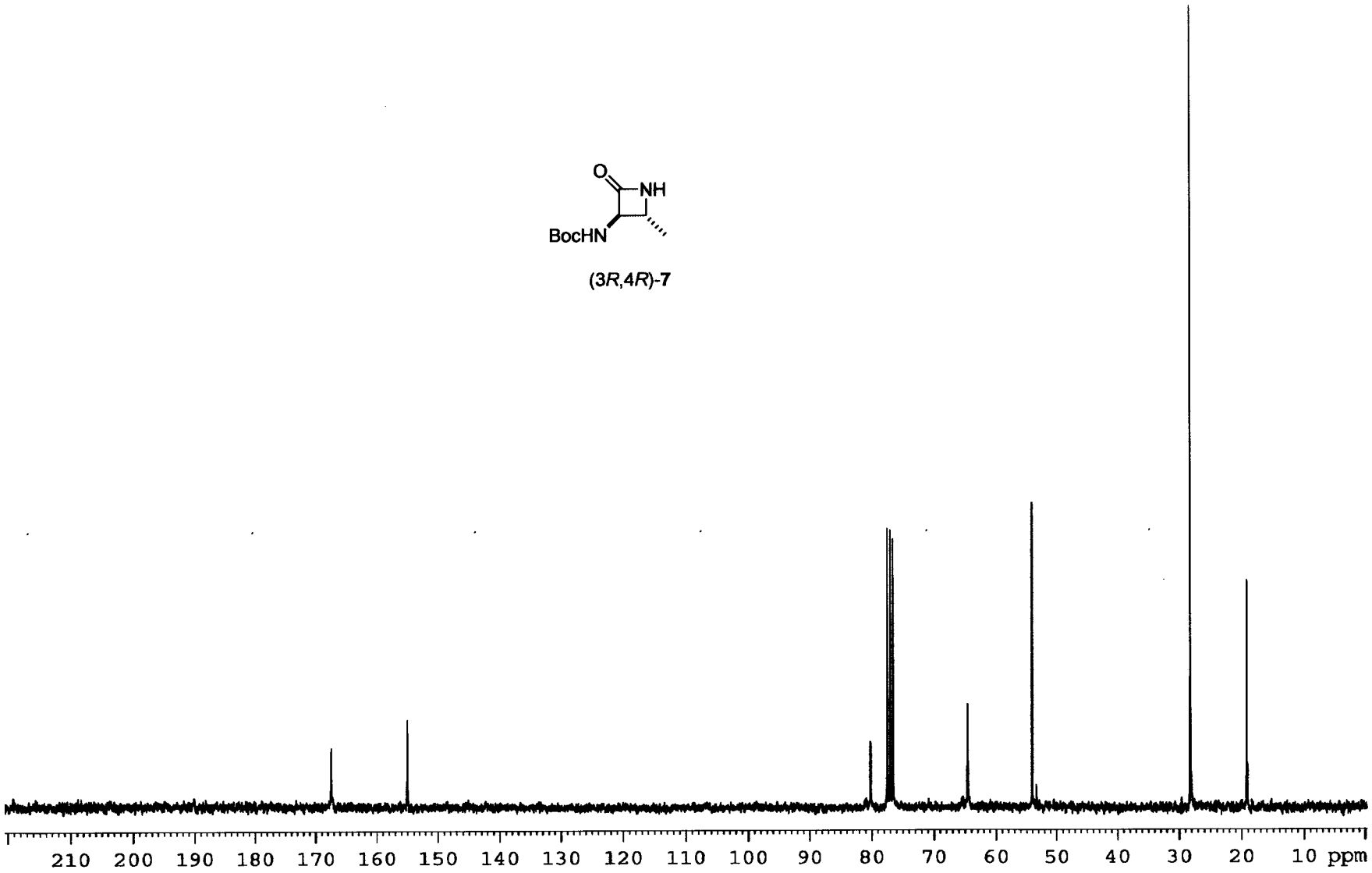
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

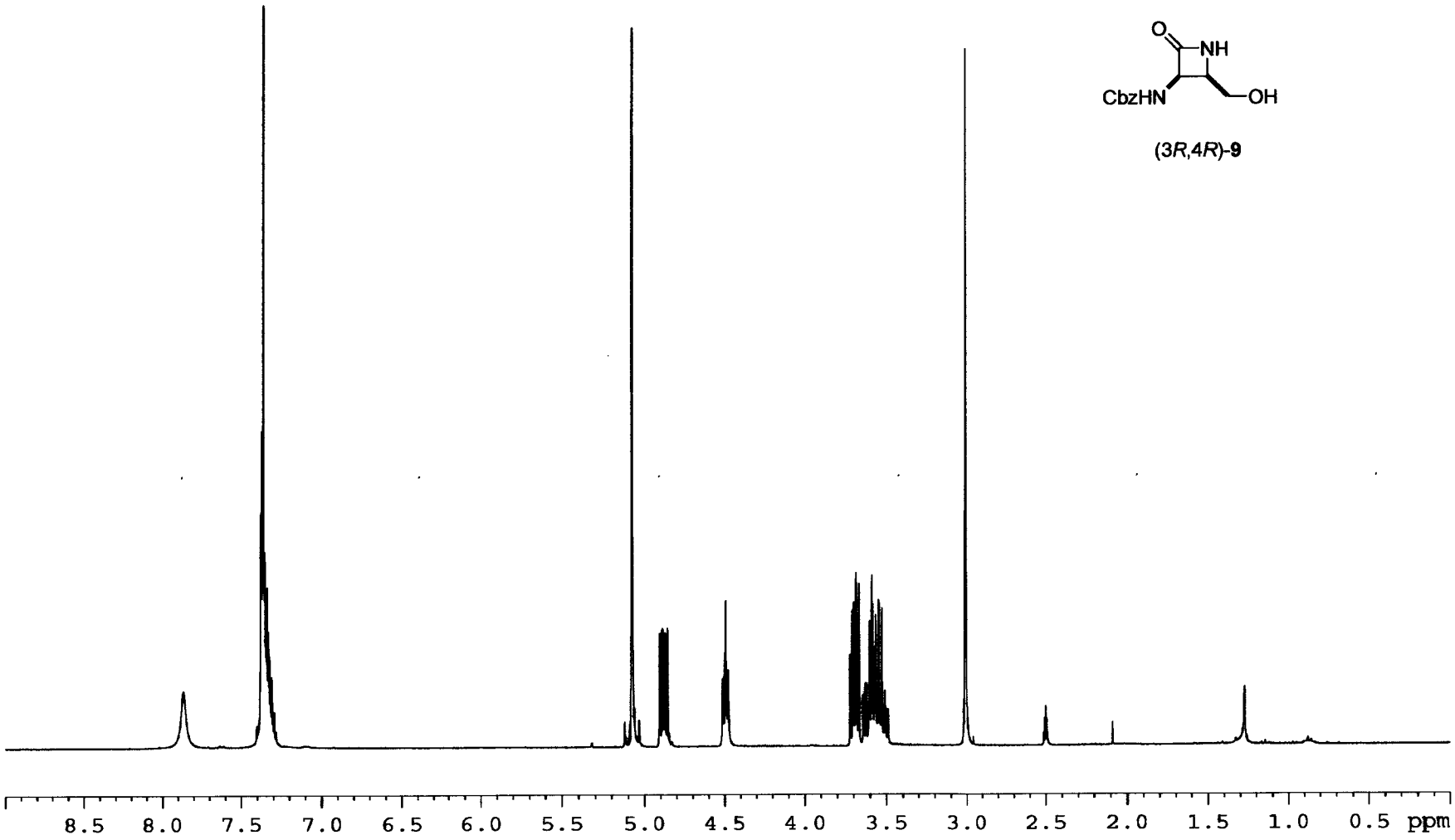


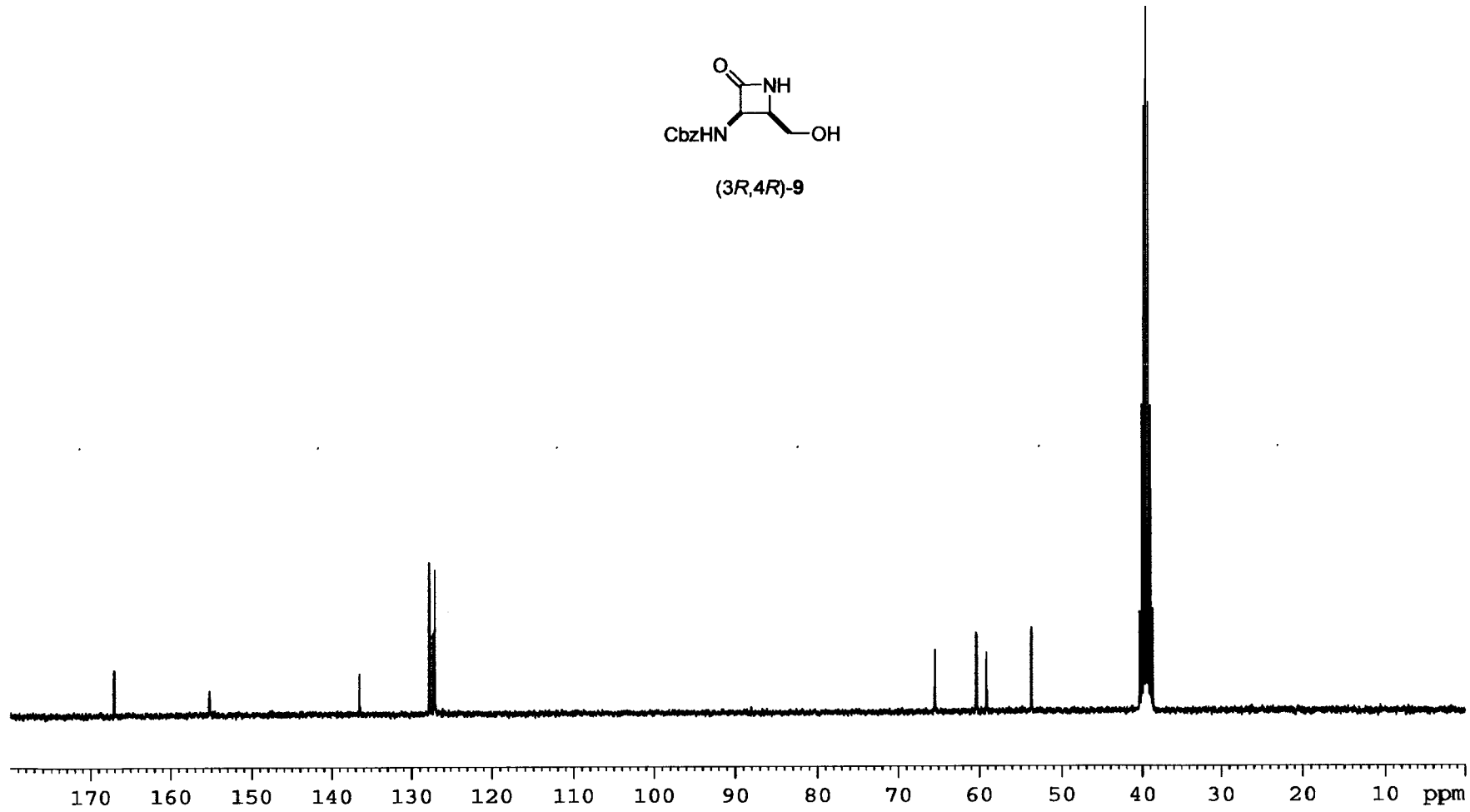
(3*R*,4*R*)-**6**


O
NH
H_2N
(3*R*,4*R*)-**6**
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


O
NH
BocHN
(3R,4R)-7
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm


O
NH
BocHN
(3R,4R)-7
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


O
NH
CbzHN
OH
(3R,4R)-9
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


O
NH
CbzHN
OH
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

(3*R*,4*R*)-**9**