Electronic Supplementary Material (ESI) for RSC Advances

Chiral phosphoric acid catalyzed enantioselective sulfamination of amino−alkenes

Lijun Li,[a] Zequan Li,[a] Deshun Huang,[a] Haining Wang[a] and Yian Shi*[a,b]

[a] *Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China.*

[b] *Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523,USA*

Supporting Information

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General Methods. All commercially available reagents were used without further purification. Toluene, tetrahydrofuran, and ethyl ether were distilled from sodium-benzophenone. CH_3CN and CH_2Cl_2 were distilled from CaH_2. $CHCl_3$ was distilled from P_2O_5. CH_3CCl_3 was dried by $CaCl_2$ and used directly. Column chromatography was performed on silica gel (200-300 mesh). ^1H NMR spectra were recorded on a 400 MHz NMR spectrometer and ^{13}C NMR spectra were recorded on a 100 MHz NMR spectrometer. IR spectra were recorded on a FT-IR spectrometer. Melting points were uncorrected.

Compounds **1a-c**, **1j** were prepared from commercially available alcohols by Mitsunobu reaction with 4-nitrobenzenesulfonamide.[1] Compounds **1d**, **1e**, **1h**, and **1i** were prepared by Wittig reaction of the corresponding aldehydes and {4-[(*tert*-butyldiphenylsilyl)oxy]butyl}triphenylphosphonium iodide,[2] desilylation with TBAF, and Mitsunobu reaction with 4-nitrobenzenesulfonamide.[1] Compounds **1f** and **1g** were prepared by Wittig reaction of 4-oxobutyl acetate and the above phosphonium salt,[2] followed by deacetylation with K_2CO_3 in MeOH, or desilylation with TBAF and subsequent Mitsunobu reaction with 4-nitrobenzenesulfonamide.[1] Compounds **1k** and **1l** were prepared by Johnson-Claisen rearrangement,[3-5] reduction with $LiAlH_4$, and Mitsunobu reaction 4-nitrobenzenesulfonamide.[1] Phosphoric acids **3a** and **3b** were prepared according to the reported procedure.[6] Phosphoric acid **3c** was prepared according to the reported procedure and recrystallized from dichloromethane/hexane.[7]

(1) H. H. Jung and P. E. Floreancig, *J. Org. Chem.*, 2007, **72**, 7359.

(2) S. H. Kang, S. B. Lee and C. M. Park, *J. Am. Chem. Soc.*, 2003, **125**, 15748.

(3) C. U. Grünanger and B. Breit, *Angew. Chem., Int. Ed.*, 2010, **49**, 967.

(4) W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner and M. R. Petersen, *J. Am. Chem. Soc.*, 1970, **92**, 741.

(5) W. S. Johnson, M. B. Gravestock and B. E. McCarry, *J. Am. Chem. Soc.*, 1971, **93**, 4332.

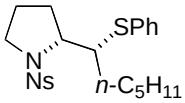
(6) (a) T. Akiyama, H. Morita, J. Itoh and K. Fuchibe, *Org. Lett.*, 2005, **7**, 2583; (b) R. Ian Storer, D. E. Carrera, Y. Ni and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2006, **128**, 84.

(7) (a) S. Hoffmann, A. M. Seayad and B. List, *Angew. Chem., Int. Ed.*, 2005, **44**, 7424; (b) W.-J. Liu, X.-H. Chen and L.-Z. Gong, *Org. Lett.*, 2008, **10**, 5357; (c) C. H. Cheon and H. Yamamoto, *J. Am. Chem. Soc.*, 2008, **130**, 9246; (d) M. Klussmann, L. Ratjen, S. Hoffmann, V. Wakchaure, R. Goddard and B. List, *Synlett*, 2010, 2189.

Representative procedure for asymmetric sulfamination (Table 2, entry 1).

To a stirred solution of alkene **1a** (0.102 g, 0.30 mmol) and chiral phosphoric acid **3c** (0.023 g, 0.030 mmol) in CH_3CCl_3 (15.0 mL) was added PhSOMe (**2**) (0.051 g, 0.36 mmol) at 35 ^oC. Upon stirring at 35 ^oC for 72 h, the reaction mixture was quenched with Et_3N (0.6 mL), concentrated, and purified by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate/dichloromethane = 50:1:0 to 20:1:1) to give pyrrolidine **4a** as yellow solid (0.108 g, 80%).

(*R*)-1-(4-nitrophenylsulfonyl)-2-[(*R*)-1-(phenylthio)hexyl]pyrrolidine (Table 2, entry 1)

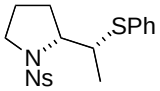


4a

Yellow solid; mp. 133-135 ^oC; $[\alpha]_D^{20}$ = +205.1 (*c* 1.00, $CHCl_3$) (86% ee); IR (film) 1522, 1159 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.60-7.49 (m, 4H), 7.46-7.33 (m, 3H), 3.89 (dt, *J* = 11.6, 3.2 Hz, 1H) 3.58-3.44 (m, 2H), 3.25-3.16 (m, 1H), 2.05-1.92 (m, 1H), 1.90-1.65 (m, 4H), 1.58-1.45 (m, 1H), 1.45-1.20 (m, 6H), 0.93 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 142.1, 135.2, 132.2, 129.4, 128.9, 127.3, 124.3, 62.5, 52.1, 51.4, 31.9, 27.7, 27.4, 26.8, 24.6, 22.8, 14.3; Anal. Calcd for $C_{22}H_{28}N_2O_4S_2$: C, 58.90; H, 6.29; N, 6.24; Found: C, 58.74; H, 6.35; N, 6.15.

L. Li, H. Wang, D. Huang and Y. Shi, *Tetrahedron*, 2012, **68**, 9853.

(*R*)-1-(4-nitrophenylsulfonyl)-2-[(*R*)-1-(phenylthio)ethyl]pyrrolidine (Table 2, entry 2)

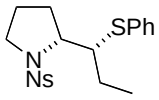


4b

White solid; mp. 139-141 ^oC; $[\alpha]_D^{20}$ = +208.5 (*c* 1.04, $CHCl_3$) (78% ee); IR (film) 1530,

1351 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.62 (d, *J* = 8.8 Hz, 2H), 7.56-7.49 (m, 2H), 7.45-7.33 (m, 3H), 4.12-4.02 (m, 1H), 3.57-3.46 (m, 2H), 3.22-3.12 (m, 1H), 2.05-1.94 (m, 1H), 1.83-1.71 (m, 1H), 1.70-1.57 (m, 1H), 1.47-1.33 (m, 1H), 1.30 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 142.1, 134.6, 132.3, 129.4, 128.9, 127.5, 124.3, 62.1, 51.1, 45.8, 26.0, 24.7, 13.3; HRMS (ESI) Calcd for $C_{18}H_{21}N_2O_4S_2$ (M+H): 393.0937; Found: 393.0932.

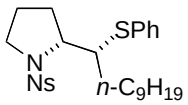
(*R*)-1-(4-nitrophenylsulfonyl)-2-[(*R*)-1-(phenylthio)propyl]pyrrolidine (Table 2, entry 3)



4c

Pale yellow solid; mp. 148-149 °C; $[\alpha]_D^{20}$ = +211.1 (*c* 0.95, $CHCl_3$) (84% ee); IR (film) 1534, 1350 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.4 Hz, 2H), 7.63-7.48 (m, 4H), 7.45-7.32 (m, 3H), 3.84-3.74 (m, 1H), 3.59-3.44 (m, 2H), 3.27-3.15 (m, 1H), 2.07-1.88 (m, 2H), 1.83-1.62 (m, 2H), 1.42-1.24 (m, 2H), 1.20 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 142.1, 135.2, 132.2，129.4，128.8，127.2，124.3, 62.6, 54.3，51.3, 26.8，24.5，20.8, 12.9; HRMS (ESI) Calcd for $C_{19}H_{23}N_2O_4S_2$ (M+H): 407.1094; Found: 407.1094.

(*R*)-1-(4-nitrophenylsulfonyl)-2-[(*R*)-1-(phenylthio)decyl]pyrrolidine (Table 2, entry 4)

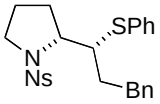


4d

White solid; mp. 92-94 °C; $[\alpha]_D^{20}$ = +177.8 (*c* 1.02, $CHCl_3$) (85% ee); IR (film) 1519, 1350 , 1161 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.60-7.50 (m, 4H), 7.45-7.33 (m, 3H), 3.95-3.83 (m, 1H), 3.58-3.43 (m, 2H), 3.27-3.16 (m, 1H), 2.05-1.91 (m, 1H), 1.90-1.64 (m, 4H), 1.58-1.20 (m, 15H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 142.1, 135.2, 132.2, 129.4, 128.9, 127.3, 124.3, 62.5, 52.1, 51.4, 32.1, 29.7, 29.5, 28.0, 27.5, 26.7, 24.5, 22.9, 14.3; HRMS (ESI) Calcd for $C_{26}H_{37}N_2O_4S_2$ (M+H): 505.2189; Found: 505.2185.

(*R*)-1-(4-nitrophenylsulfonyl)-2-[(*R*)-3-phenyl-1-(phenylthio)propyl]pyrrolidine (Table 2,

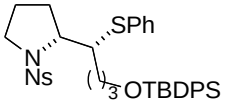
entry 5)



4e

Yellow solid; mp. 140-142 °C; $[\alpha]_D^{20}$ = +179.0 (*c* 1.04, $CHCl_3$) (83% ee); IR (film) 1530, 1351 , 1164 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.58-7.49 (m, 4H), 7.45-7.37 (m, 3H), 7.33 (t, *J* = 7.2 Hz, 2H), 7.29-7.20 (m, 3H), 3.92 (dt, *J* = 11.6, 3.2 Hz, 1H), 3.58-3.43 (m, 2H), 3.25-3.08 (m, 2H), 2.87-2.75 (m, 1H), 2.27-2.13 (m, 1H), 2.07-1.91 (m, 1H), 1.80-1.67 (m, 2H), 1.66-1.52 (m, 1H), 1.40-1.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 142.1, 141.7, 134.9, 132.2, 129.4, 128.9, 128.73, 128.67, 127.4, 126.3, 124.3, 62.5, 51.8, 51.3, 34.2, 29.6, 26.8, 24.5; HRMS (ESI) Calcd for $C_{25}H_{27}N_2O_4S_2$ (M+H): 483.1407; Found: 483.1405.

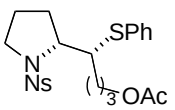
(*R*)-2-[(*R*)-4-(*tert*-butyldiphenylsilyloxy)-1-(phenylthio)butyl]-1-(4-nitrophenylsulfonyl)-pyrrolidine (Table 2, entry 6)



4f

White solid; mp. 102-104 °C; $[\alpha]_D^{20}$ = +133.2 (*c* 1.03, $CHCl_3$) (83% ee); IR (film) 1559, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.74-7.66 (m, 4H), 7.60-7.50 (m, 4H), 7.48-7.34 (m, 9H), 3.92-3.83 (m, 1H), 3.78 (t, *J* = 6.0 Hz, 2H) 3.57-3.44 (m, 2H), 3.26-3.14 (m, 1H), 2.13-1.92 (m, 3H), 1.83-1.62 (m, 3H), 1.45-1.20 (m, 2H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 142.2, 135.83, 135.81, 135.1, 134.2, 132.3, 129.8, 129.4, 128.9, 127.9, 127.4, 124.3, 63.8, 62.5, 52.3, 51.3, 31.3, 27.1, 26.7, 24.5, 24.2, 19.5; HRMS (ESI) Calcd for $C_{36}H_{43}N_2O_5S_2Si$(M+H): 675.2377; Found: 675.2360.

(*R*)-4-[(*R*)-1-(4-nitrophenylsulfonyl)pyrrolidin-2-yl]-4-(phenylthio)butyl acetate (Table 2, entry 7)

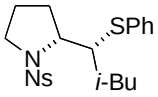


4g

Pale yellow solid; mp. 106-108 °C; $[\alpha]_D^{20}$ = +177.5 (*c* 1.05, $CHCl_3$) (80% ee); IR (film)

1734, 1530, 1350 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.8 Hz, 2H), 7.59-7.51 (m, 4H), 7.46-7.36 (m, 3H), 4.17 (t, *J* = 6.0 Hz, 2H), 3.94-3.85 (m, 1H), 3.60-3.44 (m, 2H), 3.25-3.15 (m, 1H), 2.19-2.06 (m, 1H), 2.09 (s, 3H), 2.05-1.68 (m, 5H), 1.44-1.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 150.2, 141.8, 134.7, 132.4, 129.4, 128.9, 127.5, 124.3, 64.2, 62.4, 51.8, 51.4, 27.1, 26.7, 24.4, 24.1, 21.2; HRMS (ESI) Calcd for $C_{22}H_{27}N_2O_6S_2$(M+H): 479.1305; Found: 479.1300.

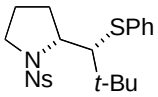
(*R*)-2-[(*R*)-3-methyl-1-(phenylthio)butyl]-1-(4-nitrophenylsulfonyl)pyrrolidine (Table 2, entry 8)



4h

Pale yellow solid; mp. 99-102 °C; $[\alpha]_D^{20}$ = +231.6 (*c* 1.05, $CHCl_3$) (85% ee); IR (film) 1531, 1351 , 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.8 Hz, 2H), 7.58-7.51 (m，4H)，7.45-7.34 (m, 3H), 4.00 (dt, *J* = 11.6, 3.2 Hz, 1H), 3.57-3.43 (m, 2H), 3.24-3.14 (m, 1H), 2.10-1.94 (m, 2H), 1.81-1.65 (m, 2H), 1.62-1.53 (m, 1H), 1.39-1.25 (m, 2H), 1.05 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 142.1, 135.1, 132.3, 129.4, 128.9, 127.3, 124.3, 62.4, 51.5, 49.9, 36.2, 26.7, 25.8, 24.5, 24.2, 21.5; HRMS (ESI) Calcd for $C_{21}H_{27}N_2O_4S_2$ (M+H): 435.1407; Found: 435.1404.

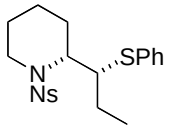
(*R*)-2-[(*R*)-2,2-dimethyl-1-(phenylthio)propyl]-1-(4-nitrophenylsulfonyl)pyrrolidine (Table 2, entry 9)



4i

Yellow solid; mp. 105-107 °C; $[\alpha]_D^{20}$ = +218.9 (*c* 0.78, $CHCl_3$) (85% ee); IR (film) 1529, 1350 , 1163 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.8 Hz, 2H), 7.60 (d，*J* = 8.0 Hz, 2H)，7.51 (d，*J* = 6.8 Hz, 2H), 7.42-7.28（m, 3H）, 3.95-3.83 (m, 1H), 3.57-3.44 (m, 1H), 3.32-3.13 (m, 2H), 2.04-1.91 (m, 1H), 1.88-1.75 (m, 1H), 1.69-1.55 (m, 1H), 1.37-1.17 (m, 1H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 143.0, 137.0, 132.6, 129.3, 128.9, 127.2, 124.2, 65.4, 63.4, 50.3, 35.9, 30.7, 29.7, 24.2; HRMS (ESI) Calcd for $C_{21}H_{27}N_2O_4S_2$ (M+H): 435.1407; Found: 435.1405.

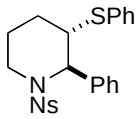
(*R*)-1-(4-nitrophenylsulfonyl)-2-[(*R*)-1-(phenylthio)propyl]piperidine (Table 2, entry 10)



4j

Yellow oil; $[\alpha]_D^{20}$ = +72.9 (*c* 1.01, $CHCl_3$) (71% ee); IR (film) 1529, 1348, 1188 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.8 Hz, 2H), 8.02 (d, *J* = 8.8 Hz, 2H), 7.38-7.32 (m, 2H), 7.31-7.20 (m, 3H), 4.13-4.03 (m, 1H), 3.74 (dd, *J* = 14.8, 4.4 Hz, 1H), 3.63-3.53 (m, 1H), 3.08-2.95 (m, 1H), 1.85-1.30 (m, 8H), 1.05 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 147.1, 135.5, 132.5, 129.2, 128.7, 127.3, 124.3, 55.9, 51.3, 42.0, 25.7, 24.3, 23.8, 18.8, 9.8; HRMS (ESI) Calcd for $C_{20}H_{25}N_2O_4S_2$(M+H): 421.1250; Found: 421.1249.

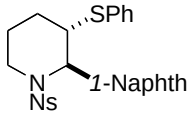
(2*R*,3*S*)-1-(4-nitrophenylsulfonyl)-2-phenyl-3-(phenylthio)piperidine (Table 2, entry 11)



5k

Yellow syrup; $[\alpha]_D^{20}$ = -45.3 (*c* 0.76, $CHCl_3$) (44% ee); IR (film) 1529, 1349, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.8 Hz, 2H), 8.04 (d, *J* = 8.8 Hz, 2H), 7.47-7.16 (m, 10H), 5.39 (s, 1H), 3.99-3.81 (m, 2H), 3.38-3.22 (m, 1H), 1.95-1.76 (m, 3H), 1.54-1.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 146.6, 138.2, 134.8, 132.1, 129.6, 129.1, 128.9, 127.9, 127.8, 126.9, 124.1, 60.8, 49.4, 42.5, 24.1, 20.1; HRMS (ESI) Calcd for $C_{23}H_{23}N_2O_4S_2$(M+H): 455.1094; Found: 455.1091.

(2*R*,3*S*)-2-(naphthalen-1-yl)-1-(4-nitrophenylsulfonyl)-3-(phenylthio)piperidine (Table 2, entry 12)

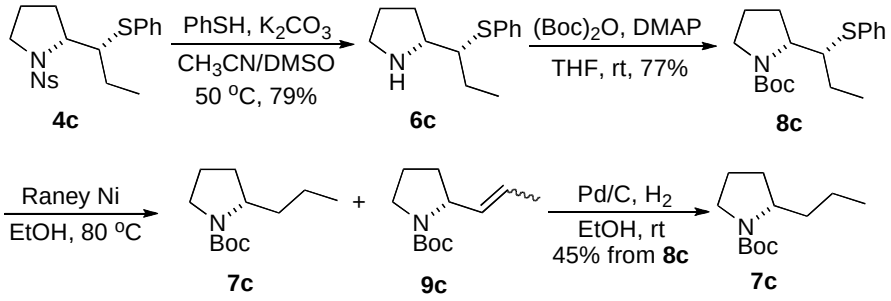


5l

Pale yellow solid; mp. 160-162 °C; $[\alpha]_D^{20}$ = +4.1 (*c* 0.93, $CHCl_3$) (55% ee); IR (film) 1528, 1348, 1164 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.4 Hz, 2H), 7.80-7.72 (m, 3H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.61-7.52 (m, 2H), 7.46-7.33 (m, 4H), 7.33-7.20 (m, 3H),

7.14 (t, *J* = 7.6 Hz, 1H), 5.98 (s, 1H), 4.15-4.03 (m, 1H), 3.86-3.70 (m, 2H), 2.24-2.07 (m, 1H), 1.92-1.62 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 145.9, 134.9, 134.8, 134.1, 133.7, 130.5, 129.6, 129.3, 128.8, 128.7, 128.5, 127.0, 126.0, 125.0, 124.6, 123.8, 122.7, 58.4, 50.3, 44.5, 24.2, 20.4; HRMS (ESI) Calcd for $C_{27}H_{24}N_2NaO_4S_2$(M+Na): 527.1070; Found: 527.1060.

The determination of the absolute configuration of pyrrolidine 4c (Scheme 2)



To a stirred mixture of pyrrolidine **4c** (0.315 g, 0.77 mmol), K_2CO_3 (0.428 g, 3.10 mmol), CH_3CN (14.7 mL), and DMSO (0.3 mL) was added PhSH (0.342 g, 3.10 mmol) at 50 °C. Upon stirring at 50 °C for 7 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution, concentrated to remove CH_3CN, extracted with CH_2Cl_2 (3×50 mL), washed with brine, dried over $MgSO_4$, filtered, concentrated, and purified by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate = 10:1 to 5:1 to 2:1) to afford pyrrolidine **6c** as yellow oil (0.134 g, 79%).

(*R*)-2-[(*R*)-1-(phenylthio)propyl]pyrrolidine (6c) (Scheme 2). $[\alpha]_D^{20}$ = +17.8 (*c* 1.03, $CHCl_3$); IR (film) 1583, 1479, 1438 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.2 Hz, 2H), 7.26 (t, *J* = 7.6 Hz, 2H), 7.23-7.17 (m, 1H), 3.22-3.14 (m, 1H), 3.07-2.93 (m, 2H), 2.91-2.82 (m, 1H), 2.01 (br s, 1H), 1.92-1.67 (m, 4H), 1.62-1.48 (m, 2H), 1.07 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.2, 132.1, 129.0, 126.8, 61.8, 57.7, 46.6, 29.7, 26.0, 25.7, 11.8; HRMS (ESI) Calcd for $C_{13}H_{20}NS$(M+H): 222.1311; Found: 222.1308.

A. B. Pulipaka and S. C. Bergmeier, *J. Org. Chem.*, 2008, **73**, 1462.

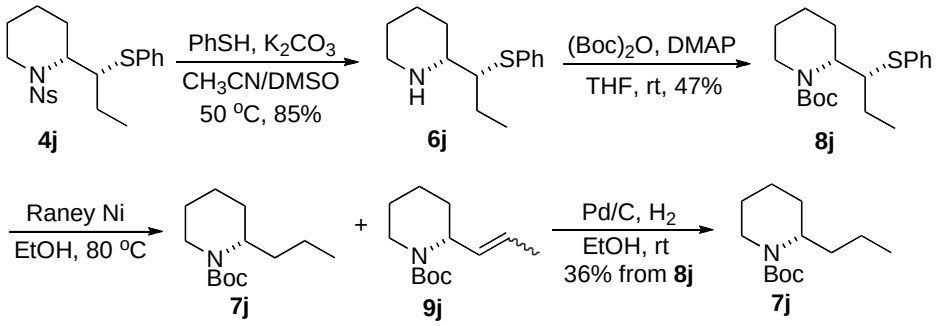
A solution of pyrrolidine **6c** (0.134 g, 0.61 mmol), DMAP (0.037 g, 0.31 mmol), and $(Boc)_2O$ (0.266 g, 1.22 mmol) in THF (5 mL) was stirred at room temperature for 12 h, concentrated, and purified by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate = 20:1) to afford pyrrolidine **8c** as colorless oil (0.151 g, 77%). $[\alpha]_D^{20}$ = -31.5 (*c* 1.10, $CHCl_3$).

U. Jacquemard, V. Bénéteau, M. Lefoix, S. Routier, J.-Y. Mérour and G. Coudert, *Tetrahedron*, 2004, **60**, 10039.

A solution of pyrrolidine **8c** (0.170 g, 0.53 mmol) in ethanol (7 mL) was added Raney Ni (1.1 g) at room temperature.[1] Upon stirring at 80 ^oC for 2 h, the reaction mixture was filtered through a plug of silica gel with ethanol as eluent, concentrated, and purified by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate = 30:1) to afford *N*-Boc-pyrrolidine **7c** along with small amounts of **9c** as colorless oil. The mixture was hydrogenated[2] with Pd/C (0.018 g) in ethanol (10 mL) under hydrogen (1 atm) at rt for 24 h to give pyrrolidine **7c** as colorless oil (0.050 g, 45% from **8c**) after purification by column chromatography (silica gel, eluent: petroleum ether/ethyl acetate = 30:1). $[\alpha]_D^{20}$ = +40.2 (*c* 0.99, $CHCl_3$) (84% ee) {lit.[3] for *S*-**7c**; $[\alpha]_D^{21}$ = +45.6 (c 0.46, $CHCl_3$)}; IR (film) 1697, 1395, 1173 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.85-3.64 (m, 1H), 3.50-3.22 (m, 2H), 2.01-1.71 (m, 4H), 1.70-1.57 (m, 1H), 1.45 (s, 9H), 1.39-1.17 (m, 3H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 79.0, 57.2, 46.6 and 46.2, 37.1 and 36.5, 30.8 and 30.1, 28.8, 23.9 and 23.3, 19.7, 14.3; HRMS (ESI) Calcd for $C_{12}H_{23}NNaO_2$(M+Na): 236.1621; Found: 236.1617.

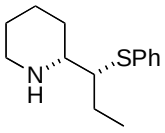
(1) T. Ohsawa, M. Ihara and K. Fukumoto, *J. Org. Chem.*, 1983, **48**, 3644.
(2) M. Hiersemann, *Eur. J. Org. Chem.*, 2001,483.
(3) I. Coldham and D. Leonori, *J. Org. Chem.*, 2010, **75**, 4069.

The determination of the absolute configuration of piperidine 4j (Scheme 2)



Piperidine **4j** was converted to **7j** in a manner similar to transformation of pyrrolidine **4c** to **7c**.

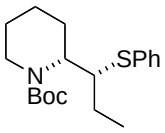
(*R*)-2-[(*R*)-1-(phenylthio)propyl]piperidine (Scheme 2)



6j

Pale yellow oil; $[\alpha]_D^{20}$ = +7.4 (*c* 0.91, $CHCl_3$); IR (film) 3316, 1479, 1438 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 7.6 Hz, 2H), 7.30-7.23 (m, 2H), 7.23-7.17 (m, 1H), 3.16-3.07 (m, 1H), 2.94-2.85 (m, 1H), 2.62 (td, *J* = 12.0, 2.8 Hz, 1H), 2.57-2.50 (m, 1H), 2.20 (br s, 1H), 1.88-1.69 (m, 3H), 1.63-1.19 (m, 5H), 1.06 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.1, 132.1, 129.0, 126.8, 59.4, 58.3, 47.5, 30.3, 26.5, 25.1, 24.5, 11.6; HRMS (ESI) Calcd for $C_{14}H_{22}NS$(M+H): 236.1468; Found: 236.1468.

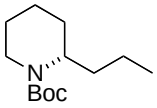
(*R*)-*tert*-butyl 2-[(*R*)-1-(phenylthio)propyl]piperidine-1-carboxylate



8j

Pale yellow oil; $[\alpha]_D^{20}$ = +54.3 (*c* 1.03, $CHCl_3$); IR (film) 1690, 1142 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.2 Hz, 2H), 7.30-7.23 (m, 2H), 7.23-7.17 (m, 1H), 4.37-4.24 (m, 1H), 4.04-3.90 (m, 1H), 3.63-3.54 (m, 1H), 2.71-2.57 (m, 1H), 1.82-1.35 (m, 8H), 1.50 (s, 9H), 1.06 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 136.6, 132.7, 129.0, 126.9, 79.7, 52.4, 51.4, 39.4, 28.7, 26.3, 25.5, 24.3, 19.3, 9.4; HRMS (ESI) Calcd for $C_{19}H_{30}NO_2S$ (M+H): 336.1992; Found: 336.1995.

Scheme 2

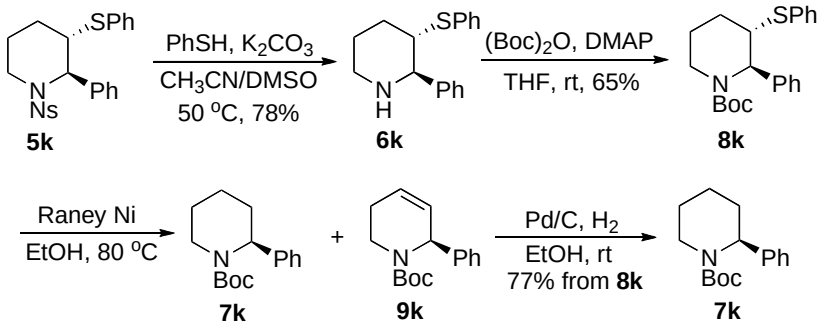


7j

Colorless oil; $[\alpha]_D^{20}$ = +22.0 (*c* 1.15, $CHCl_3$) (70% ee) {lit. for *R*-**7j**; $[\alpha]_D$ = -39.8 (c 0.60, $CHCl_3$)}; IR (film) 1692, 1416, 1148 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.28-4.13 (m, 1H), 4.02-3.87 (m, 1H), 2.74 (t, *J* = 13.2 Hz, 1H), 1.71-1.49 (m, 6H), 1.44 (s, 9H), 1.42-1.17 (m, 4H), 0.91 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 79.1, 50.3, 38.8, 32.1, 28.7, 25.9, 19.7, 19.2, 14.2; HRMS (ESI) Calcd for $C_{13}H_{25}NNaO_2$ (M+Na): 250.1778; Found: 250.1780.

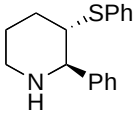
D. Passarella, A. Barilli, F. Belinghieri, P. Fassi, S. Riva, A. Sacchetti, A. Silvani and B. Danieli, *Tetrahedron: Asymmetry*, 2005, **16**, 2225.

The determination of the absolute configuration of piperidine 5k (Scheme2)



Piperidine **5k** was converted to **7k** in a manner similar to transformation of pyrrolidine **4c** to **7c**.

(2*R*,3*S*)-2-phenyl-3-(phenylthio)piperidine (Scheme 2)

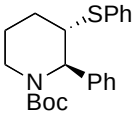


6k

Colorless oil; $[\alpha]_D^{20}$ = -28.0 (*c* 1.03, $CHCl_3$); IR (film) 3325, 1474, 1438 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 7.2 Hz, 2H), 7.30-7.19 (m, 3H), 7.17-7.09 (m, 5H), 3.52 (d,

J = 10.0 Hz, 1H), 3.20 (td, *J* = 10.4, 3.6 Hz, 1H), 3.13-3.05 (m, 1H), 2.74 (td, *J* = 11.6, 3.2 Hz, 1H), 2.28-2.18 (m, 1H), 1.82-1.48 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5, 134.6, 133.0, 128.7, 128.4, 128.2, 127.9, 126.9, 68.0, 52.0, 47.3, 33.9, 27.3; HRMS (ESI) Calcd for $C_{17}H_{20}NS$(M+H): 270.1311; Found: 270.1310.

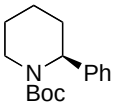
(2*R*,3*S*)-*tert*-butyl 2-phenyl-3-(phenylthio)piperidine-1-carboxylate



8k

Colorless oil; $[\alpha]_D^{20}$ = -23.7 (*c* 0.97, $CHCl_3$); IR (film) 1692, 1415 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.6 Hz, 2H), 7.36-7.27 (m, 4H), 7.26-7.15 (m, 4H), 5.51 (s, 1H), 4.20 (dd, *J* = 13.6, 3.2 Hz, 1H), 4.10 (s, 1H), 2.81 (td, *J* = 13.2, 3.2 Hz, 1H), 2.11-1.96 (m, 1H), 1.95-1.80 (m, 2H), 1.55-1.30 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 139.5, 135.7, 132.1, 129.3, 128.9, 127.3, 127.0, 126.5, 80.0, 57.1, 47.9, 39.7, 28.5, 24.6, 20.5; HRMS (ESI) Calcd for $C_{22}H_{28}NO_2S$ (M+H): 370.1835; Found: 370.1845.

Scheme 2



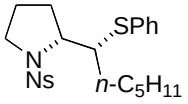
7k

White solid; mp 71-73 °C; $[\alpha]_D^{20}$ = -43.6 (*c* 1.06, $CHCl_3$) (42% ee) {lit. for *R*-**7k**; $[\alpha]_D^{22}$ = +76.2 (c 1.00, $CHCl_3$)}; IR (film) 1691, 1157 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.6 Hz, 2H), 7.25-7.18 (m, 3H), 5.42 (s, 1H), 4.05 (d, *J* = 13.6 Hz, 1H), 2.83-2.70 (m, 1H), 2.36-2.24 (m, 1H), 1.94-1.82 (m, 1H), 1.64-1.35 (m, 4H), 1.46 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 140.7, 128.7, 126.7, 126.5, 79.7, 53.5, 40.3, 28.7, 28.3, 25.7, 19.6; HRMS (ESI) Calcd for $C_{16}H_{24}NO_2$ (M+H): 262.1802; Found: 262.1803.

T. K. Beng and R. E. Gawley, *Org. Lett.*, 2011, **13**, 394.

The determination of enantiomeric excess

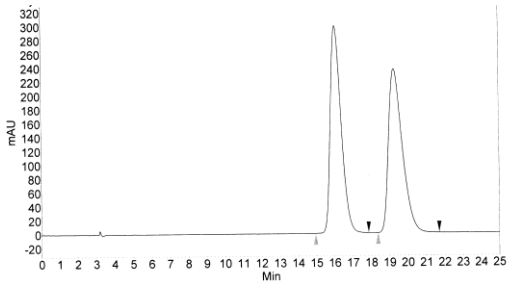
Table 2, entry 1



4a

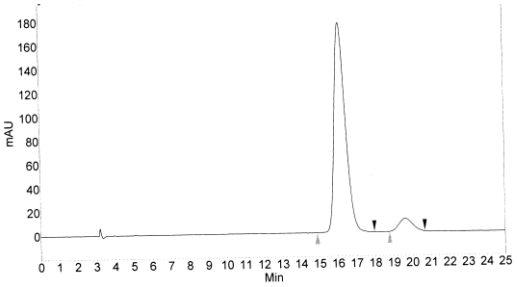
HPLC Condition: Column: Chiralpak OD-H, Daicel Chemical Industries, Ltd.; **Eluent:** Hexanes/IPA (95/5); **Flow rate:** 1.0 mL/min; **Detection:** UV256 nm.

Racemic



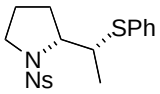
Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	16.08	50.006	14.96	17.85
2	19.29	49.994	18.37	21.70
Total		100.000		

Chiral



Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	16.15	93.090	14.89	17.96
2	19.63	6.910	18.78	20.67
Total		100.000		

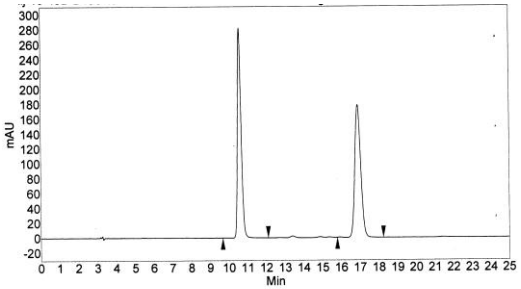
Table 2, entry 2



4b

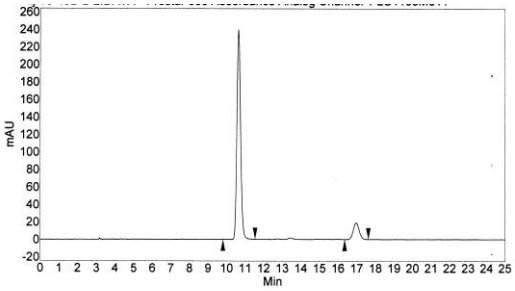
HPLC Condition: Column: Chiralpak AD-H, Daicel Chemical Industries, Ltd.; **Eluent:** Hexanes/IPA (90/10); **Flow rate:** 1.0 mL/min; **Detection:** UV256 nm.

Racemic



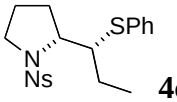
Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	10.59	49.998	9.67	12.10
2	16.91	50.002	15.79	18.24
Total		100.000		

Chiral



Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	10.65	88.897	9.80	11.53
2	16.97	11.103	16.36	17.62
Total		100.000		

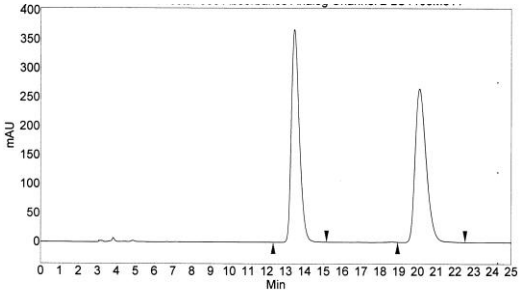
Table 2, entry 3



4c

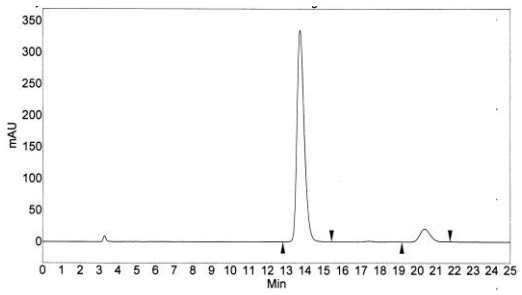
HPLC Condition: Column: Chiralpak OD-H, Daicel Chemical Industries, Ltd.; **Eluent:** Hexanes/IPA (90/10); **Flow rate:** 1.0 mL/min; **Detection:** UV252 nm.

Racemic



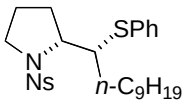
Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	13.47	50.047	12.33	15.17
2	20.09	49.953	18.94	22.52
Total		100.000		

Chiral



Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	13.75	92.135	12.82	15.43
2	20.39	7.865	19.17	21.75
Total		100.000		

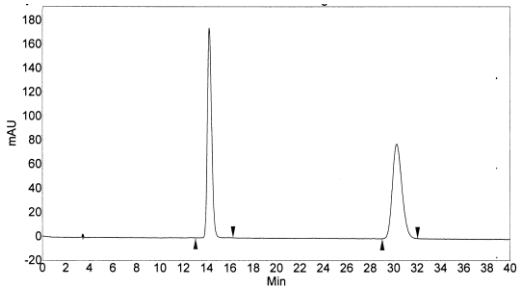
Table 2, entry 4



4d

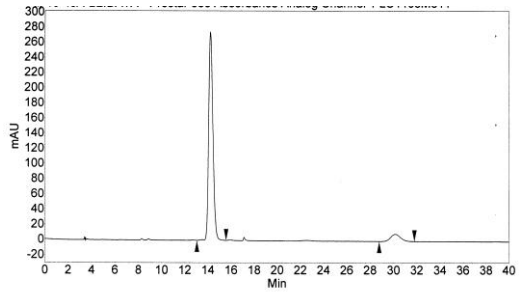
HPLC Condition: Column: Chiralpak IC-H, Daicel Chemical Industries, Ltd.; **Eluent:** Hexanes/IPA (95/5); **Flow rate:** 1.0 mL/min; **Detection:** UV256 nm.

Racemic



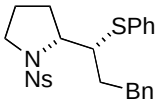
Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	14.23	49.906	13.04	16.26
2	30.25	50.094	29.02	32.03
Total		100.000		

Chiral



Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	14.23	92.542	13.04	15.56
2	30.13	7.458	28.77	31.79
Total		100.000		

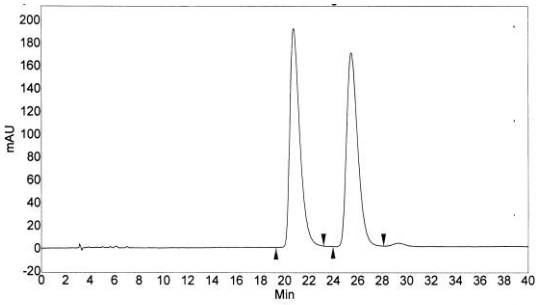
Table 2, entry 5



4e

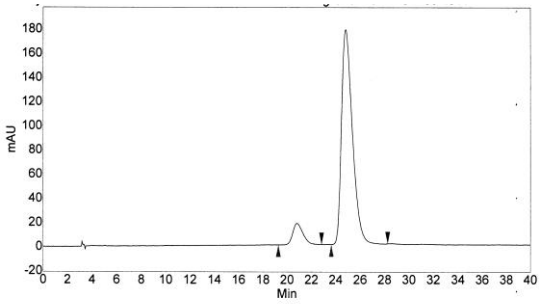
HPLC Condition: Column: Chiralpak OD-H, Daicel Chemical Industries, Ltd.; **Eluent:** Hexanes/IPA (90/10); **Flow rate:** 1.0 mL/min; **Detection:** UV252 nm.

Racemic



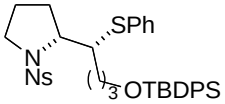
Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	20.69	50.183	19.28	23.20
2	25.44	49.817	23.98	28.11
Total		100.000		

Chiral



Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	20.81	8.518	19.28	22.83
2	24.81	91.482	23.61	28.24
Total		100.000		

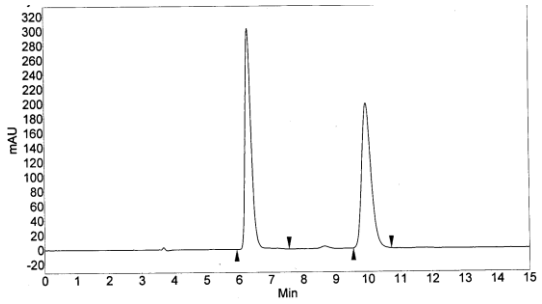
Table 2, entry 6



4f

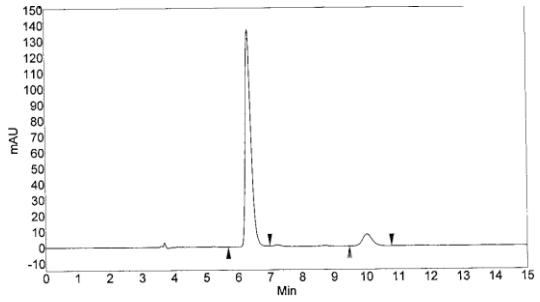
HPLC Condition: Column: Chiralpak AD-H, Daicel Chemical Industries, Ltd.; **Eluent:** Hexanes/IPA (95/5); **Flow rate:** 1.0 mL/min; **Detection:** UV258 nm.

Racemic



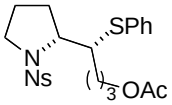
Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	6.29	50.015	5.93	7.55
2	9.95	49.985	9.55	10.73
Total		100.000		

Chiral



Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	6.32	91.383	5.68	6.98
2	10.03	8.617	9.47	10.79
Total		100.000		

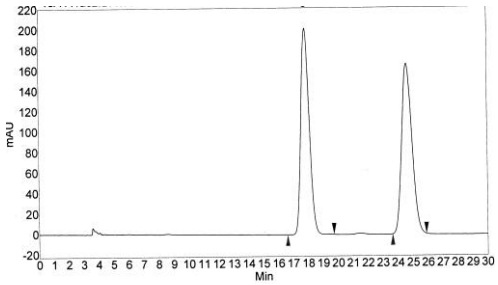
Table 2, entry 7



4g

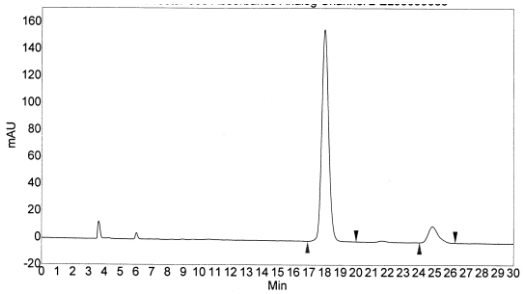
HPLC Condition: Column: Chiralpak AD-H, Daicel Chemical Industries, Ltd.; **Eluent:** Hexanes/IPA (90/10); **Flow rate:** 1.0 mL/min; **Detection:** UV230 nm.

Racemic



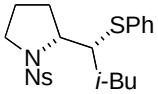
Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	17.83	50.013	16.63	19.72
2	24.61	49.987	23.65	25.88
Total		100.000		

Chiral



Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	18.01	90.063	16.90	20.00
2	24.84	9.937	24.03	26.29
Total		100.000		

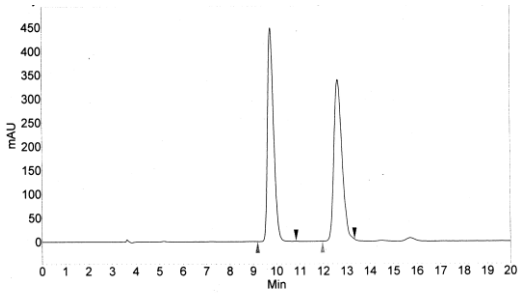
Table 2, entry 8



4h

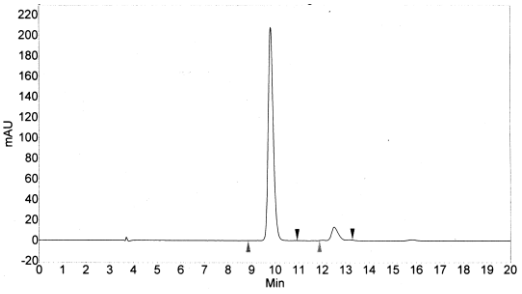
HPLC Condition: Column: Chiralpak AD-H, Daicel Chemical Industries, Ltd.; **Eluent:** Hexanes/IPA (95/5); **Flow rate:** 1.0 mL/min; **Detection:** UV258 nm.

Racemic



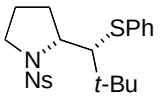
Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	9.76	50.034	9.18	10.84
2	12.64	49.966	11.97	13.33
Total		100.000		

Chiral



Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	9.81	92.628	8.85	10.94
2	12.52	7.372	11.89	13.29
Total		100.000		

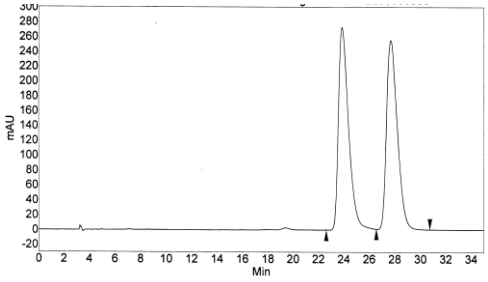
Table 2, entry 9



4i

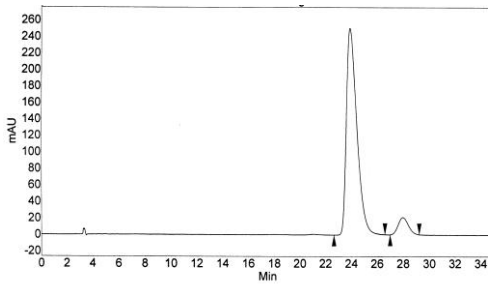
HPLC Condition: **Column:** Chiralpak OD-H, Daicel Chemical Industries, Ltd.; **Eluent:** Hexanes/IPA (95/5); **Flow rate:** 1.0 mL/min; **Detection:** UV256 nm.

Racemic



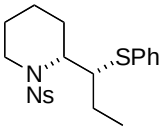
Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	23.87	50.091	22.61	26.55
2	27.69	49.909	26.55	30.74
Total		100.000		

Chiral



Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	23.89	92.501	22.65	26.58
2	27.96	7.499	26.98	29.22
Total		100.000		

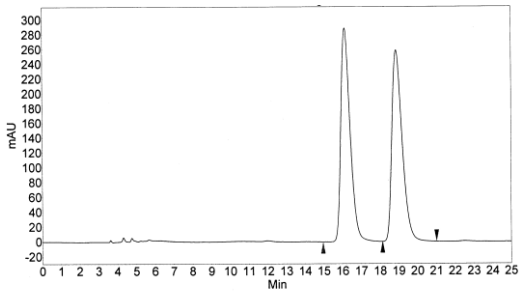
Table 2, entry 10



4j

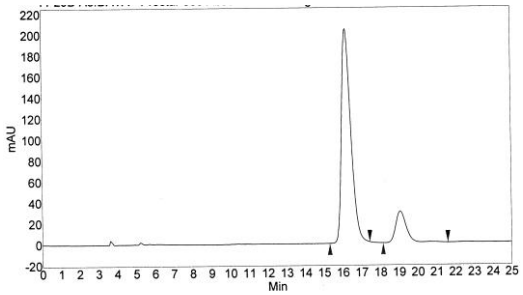
HPLC Condition: **Column:** Chiralpak OD-H, Daicel Chemical Industries, Ltd.; **Eluent:** Hexanes/IPA (90/10); **Flow rate:** 1.0 mL/min; **Detection:** UV256 nm.

Racemic



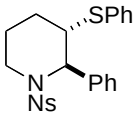
Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	16.15	50.108	14.96	18.14
2	18.88	49.892	18.14	21.00
Total		100.000		

Chiral



Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	16.20	85.610	15.31	17.44
2	19.07	14.390	18.15	21.59
Total		100.000		

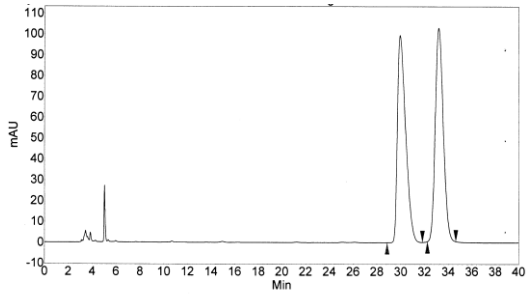
Table 2, entry 11



5k

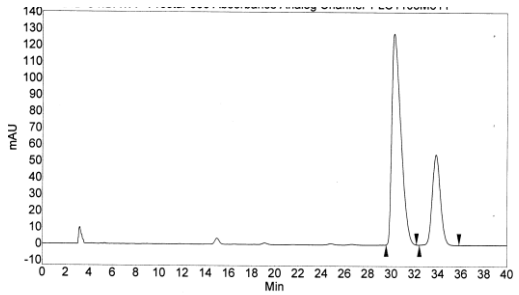
HPLC Condition: Column: Chiralpak AD-H, Daicel Chemical Industries, Ltd.; **Eluent:** Hexanes/IPA (90/10); **Flow rate:** 1.0 mL/min; **Detection:** UV256 nm.

Racemic



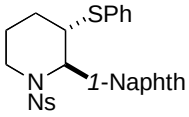
Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	29.95	49.882	28.85	31.83
2	33.20	50.118	32.24	34.63
Total		100.000		

Chiral



Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	30.25	72.103	29.56	32.16
2	33.83	27.897	32.41	35.83
Total		100.000		

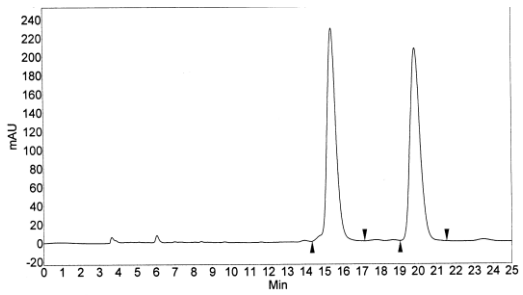
Table 2, entry 12



5l

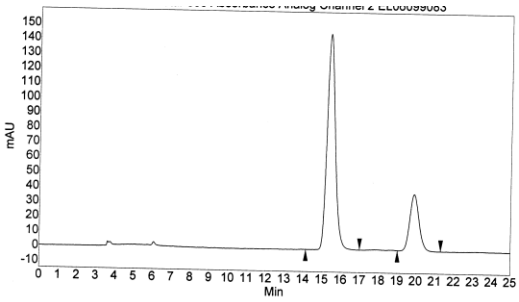
HPLC Condition: Column: Chiralpak AD-H, Daicel Chemical Industries, Ltd.; **Eluent:** Hexanes/IPA (90/10); **Flow rate:** 1.0 mL/min; **Detection:** UV230 nm.

Racemic



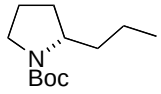
Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	15.39	49.914	14.34	17.16
2	19.84	50.086	19.04	21.52
Total		100.000		

Chiral



Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	15.40	77.355	14.14	17.00
2	19.88	22.645	19.01	21.29
Total		100.000		

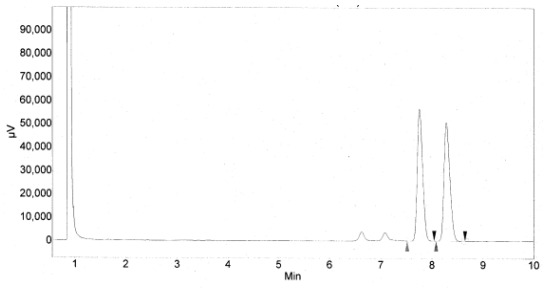
Scheme 2



7c

GC Condition: Column: Chiraldex CP-7495, Advanced Separation Technologies Inc. Oven: 120 ^{o}C; Carrier: Helium, head pressure: 25 psi; Detection: FID 250 ^{o}C.

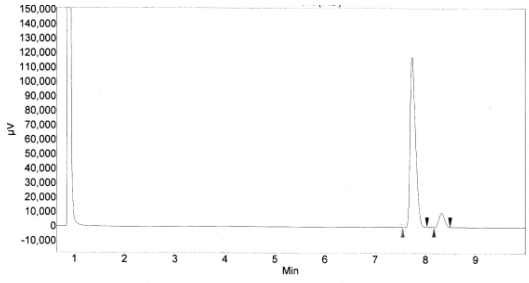
Racemic



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [µV]	Area [µV.Min]	Area % [%]
1	UNKNOWN	7.76	50.04	56485.9	6787.5	50.044
2	UNKNOWN	8.28	49.96	50643.8	6775.7	49.956
Total			100.00	107129.6	13563.1	100.000

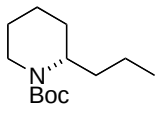
Chiral



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [µV]	Area [µV.Min]	Area % [%]
1	UNKNOWN	7.73	91.95	117732.7	14575.4	91.951
2	UNKNOWN	8.32	8.05	9812.1	1275.8	8.049
Total			100.00	127544.8	15851.2	100.000

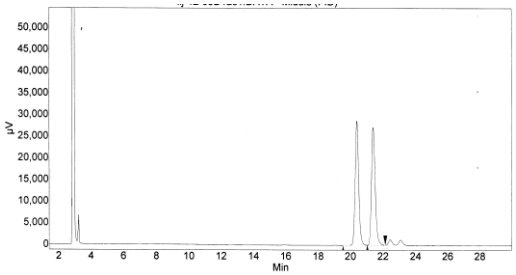
Scheme 2



7j

GC Condition: Column: Chiraldex B-DM, Advanced Separation Technologies Inc. Oven: 120 ^{o}C; Carrier: Helium, head pressure: 10 psi; Detection: FID 250 ^{o}C.

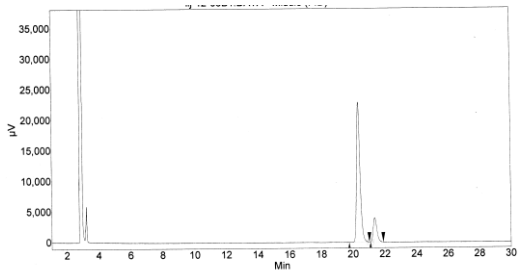
Racemic



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [µV]	Area [µV.Min]	Area % [%]
1	UNKNOWN	20.41	49.90	28714.5	7162.6	49.896
2	UNKNOWN	21.39	50.10	27228.1	7192.5	50.104
Total			100.00	55942.6	14355.1	100.000

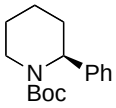
Chiral



Peak results :

Index	Name	Time [Min]	Quantity [% Area]	Height [µV]	Area [µV.Min]	Area % [%]
1	UNKNOWN	20.37	84.96	22967.8	5801.0	84.962
2	UNKNOWN	21.36	15.04	3950.6	1026.7	15.038
Total			100.00	26918.4	6827.8	100.000

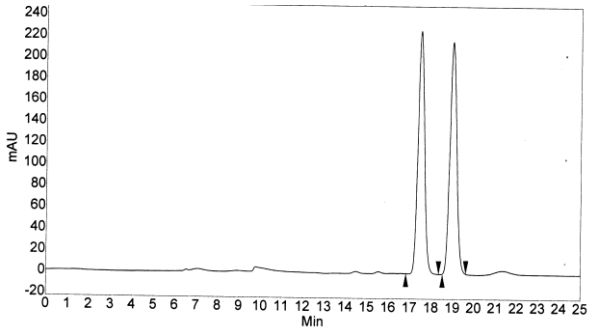
Scheme 2



7k

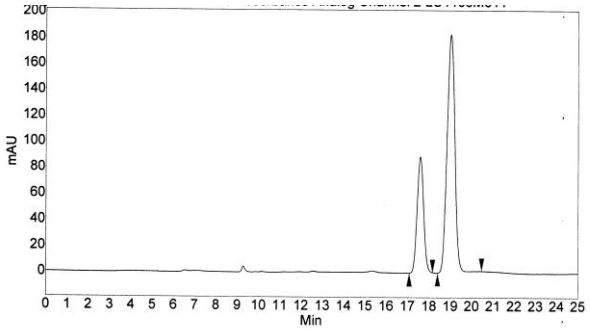
HPLC Condition: Column: Chiralpak AD-H, Daicel Chemical Industries, Ltd.; **Eluent:** Hexanes/IPA (99/1); **Flow rate:** 0.5 mL/min; **Detection:** UV206 nm.

Racemic

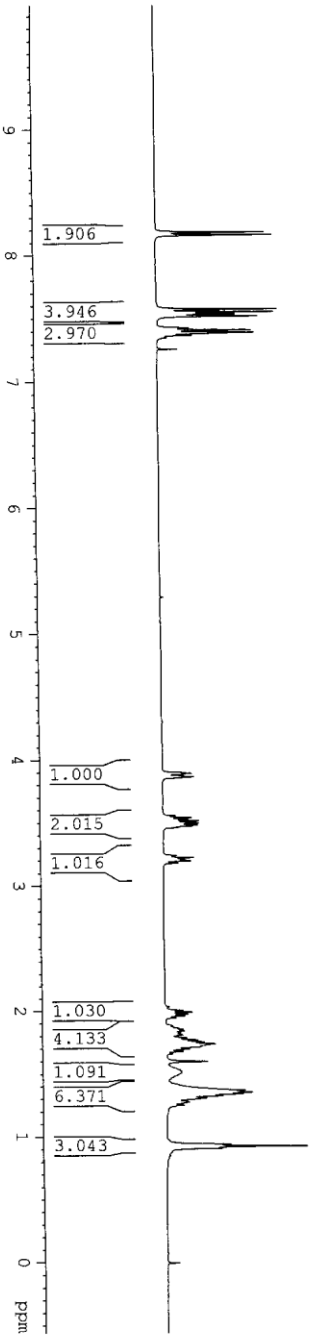


Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	17.49	49.908	16.82	18.34
2	18.99	50.092	18.52	19.61
Total		100.000		

Chiral



Index	Time [Min]	Area % [%]	Start [Min]	End [Min]
1	17.59	29.027	17.08	18.16
2	18.99	70.973	18.40	20.46
Total		100.000		



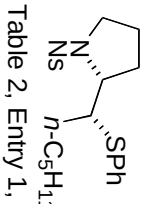
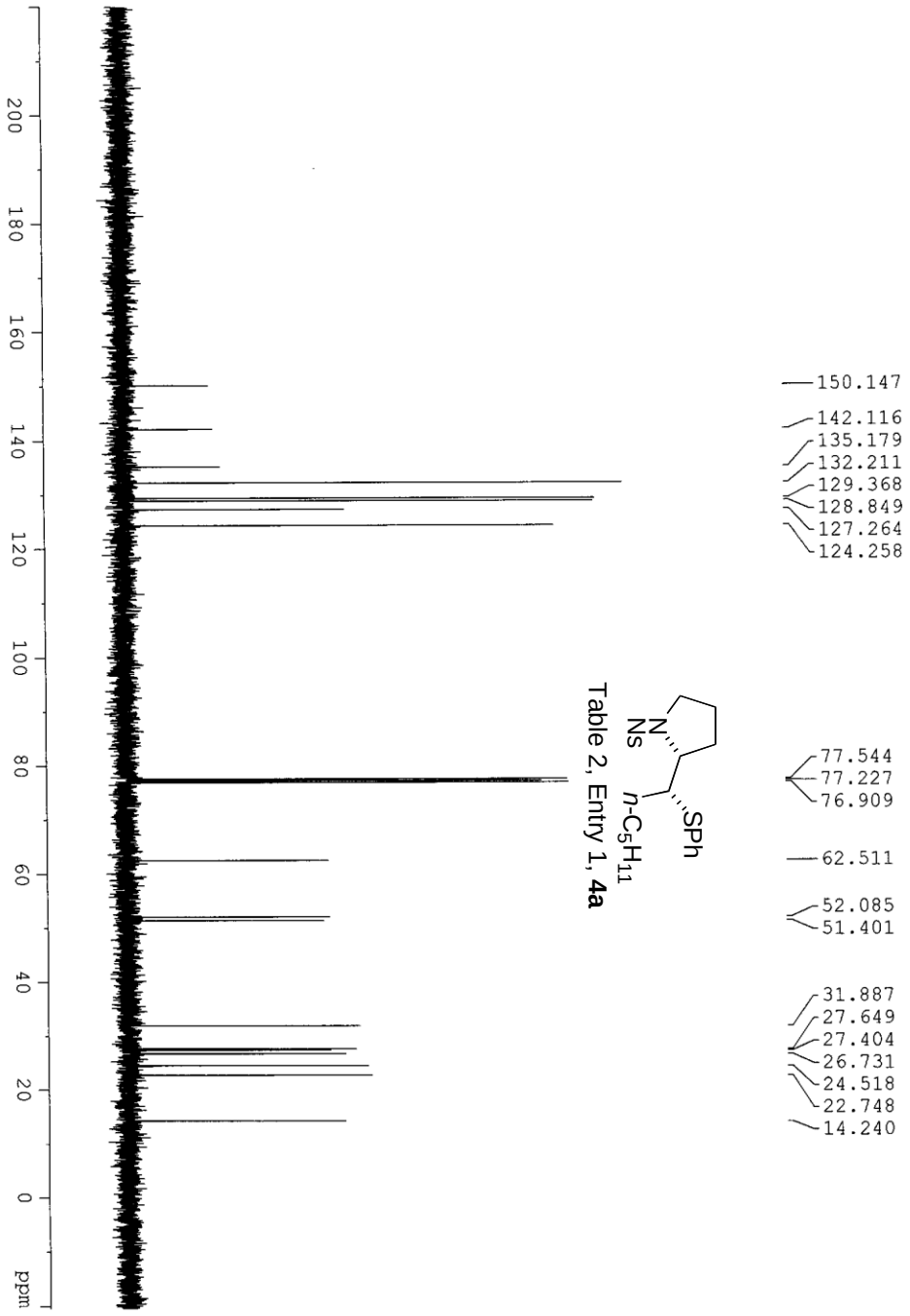
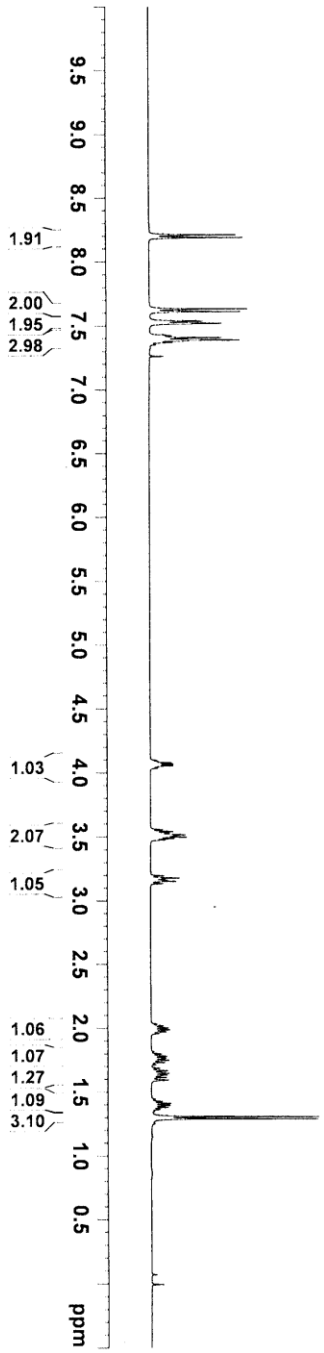


Table 2, Entry 1, **4a**





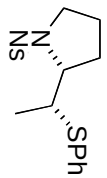


Table 2, Entry 2, **4b**

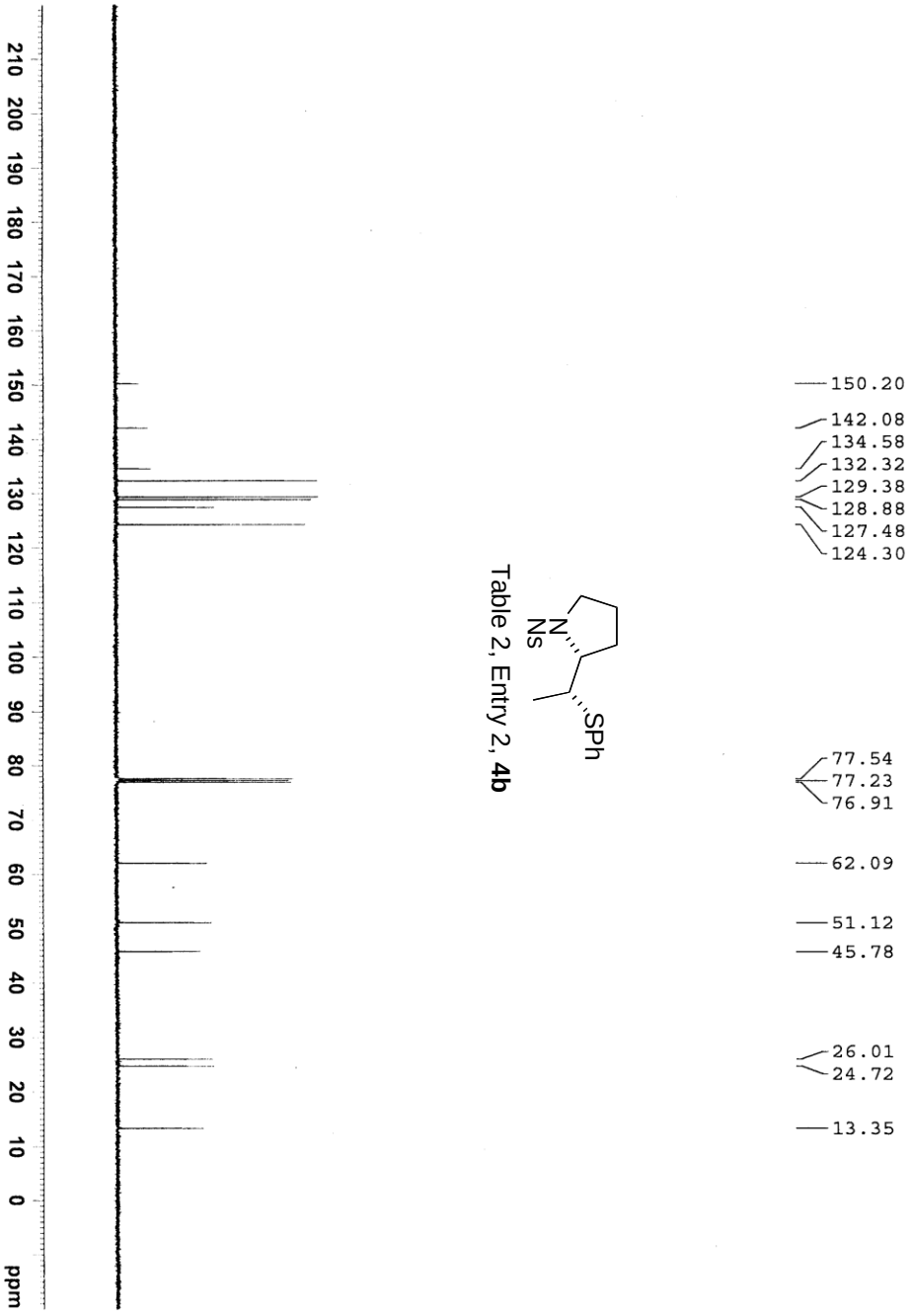


Table 2, Entry 2, **4b**

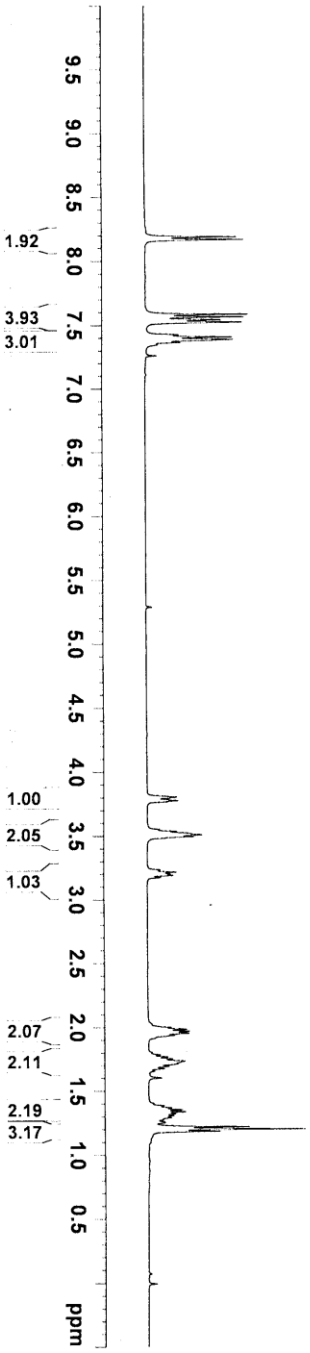
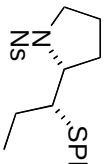
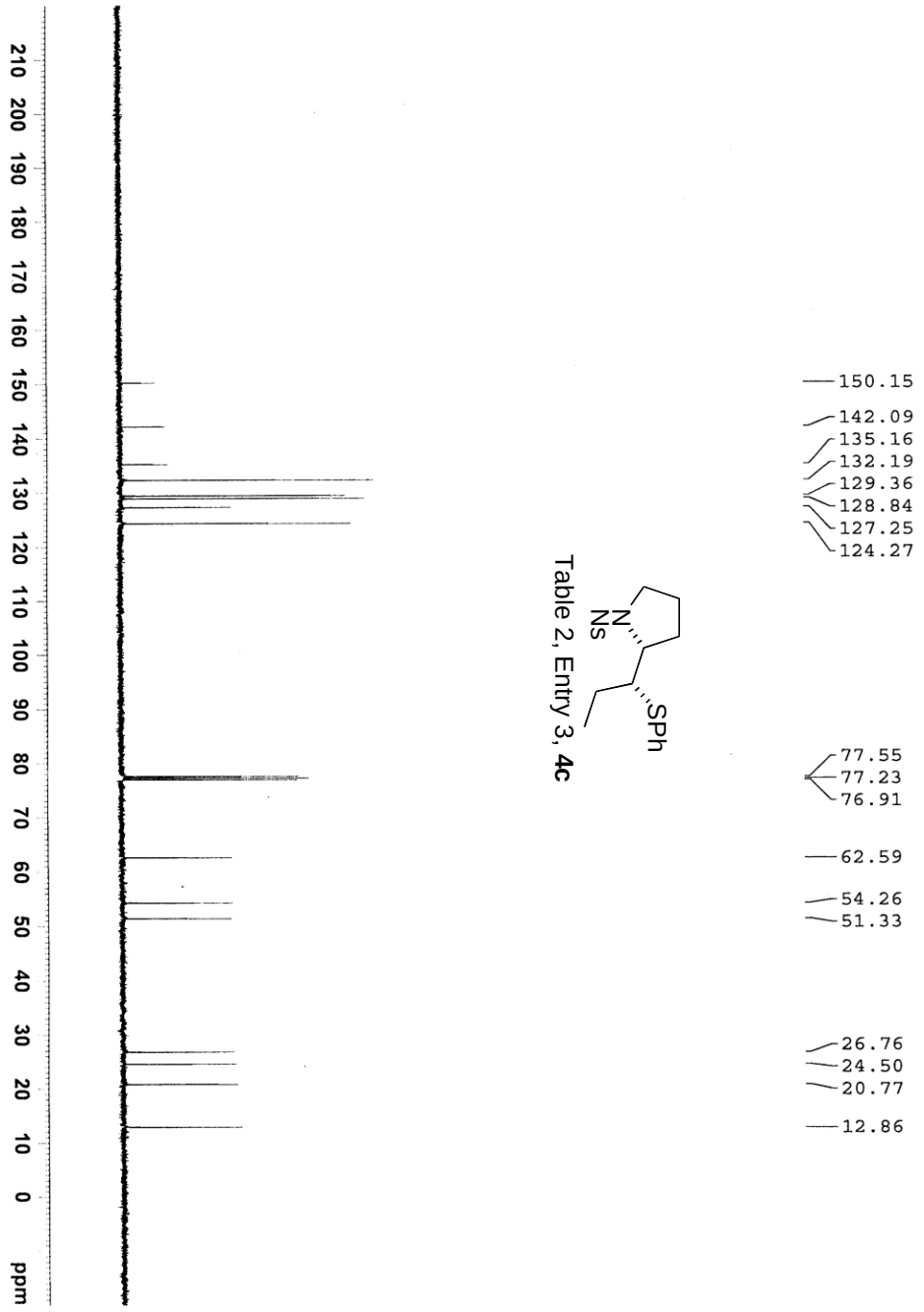
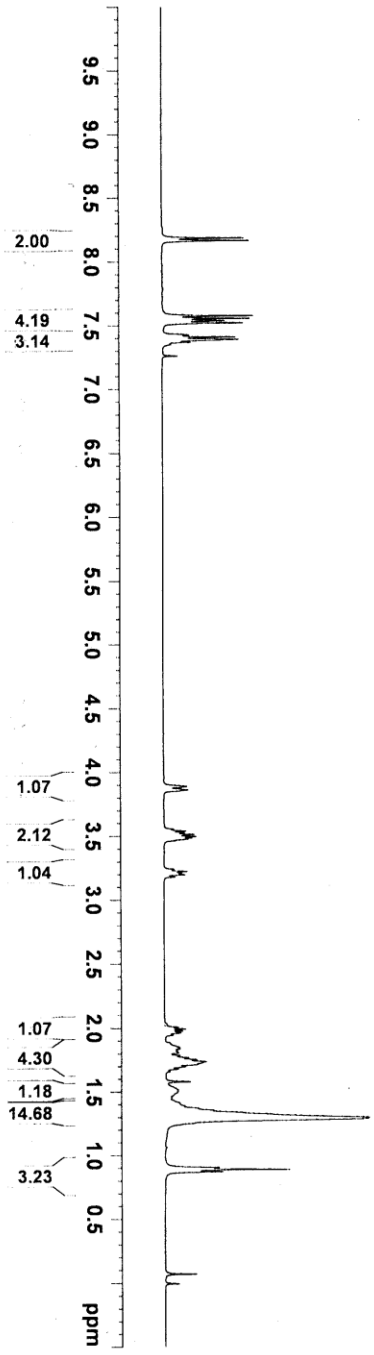


Table 2, Entry 3, **4c**




210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
150.15
142.09
135.16
132.19
129.36
128.84
127.25
124.27
77.55
77.23
76.91
62.59
54.26
51.33
26.76
24.50
20.77
12.86
N
Ns
SPh
Table 2, Entry 3, 4c



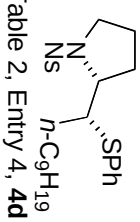


Table 2, Entry 4, **4d**

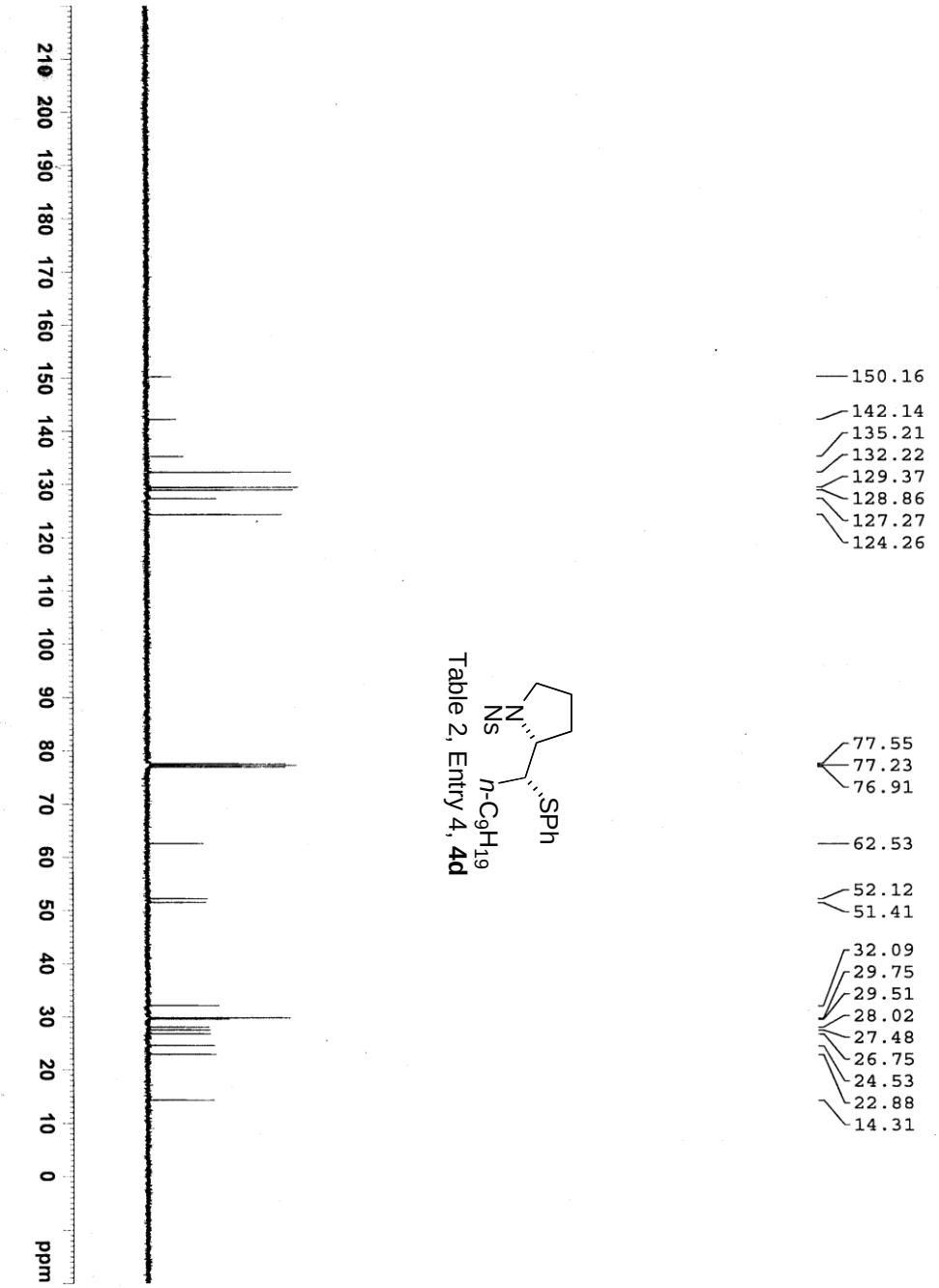
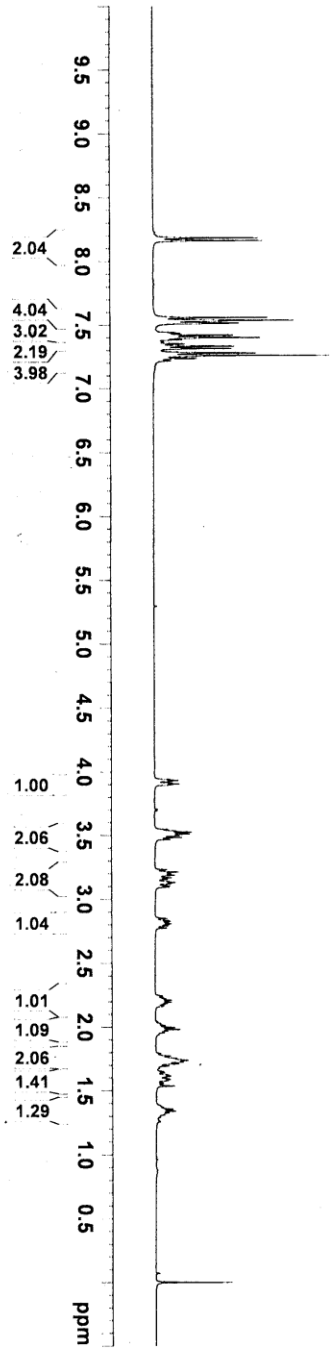
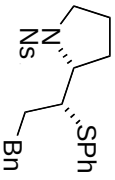


Table 2, Entry 4, **4d**





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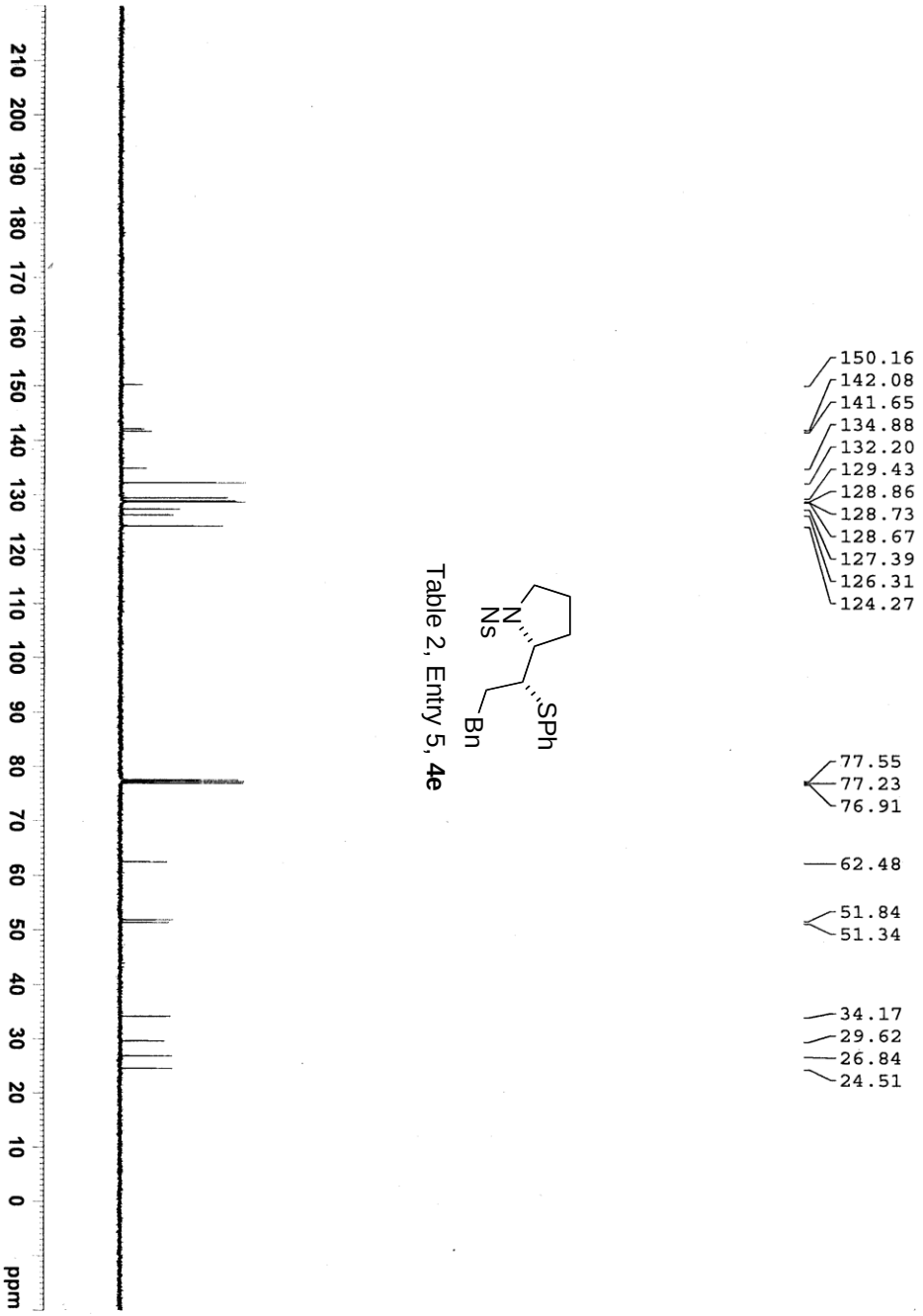

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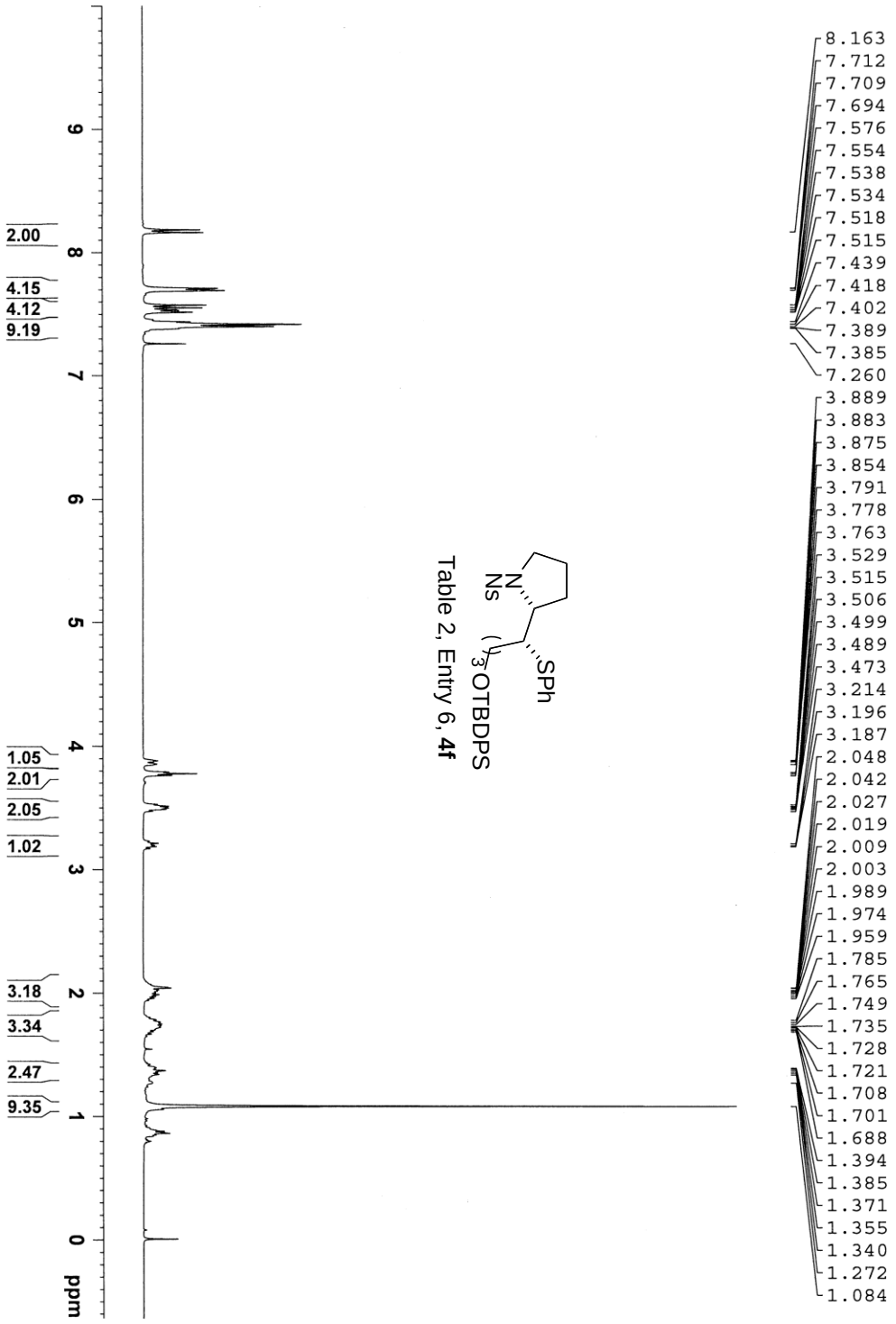

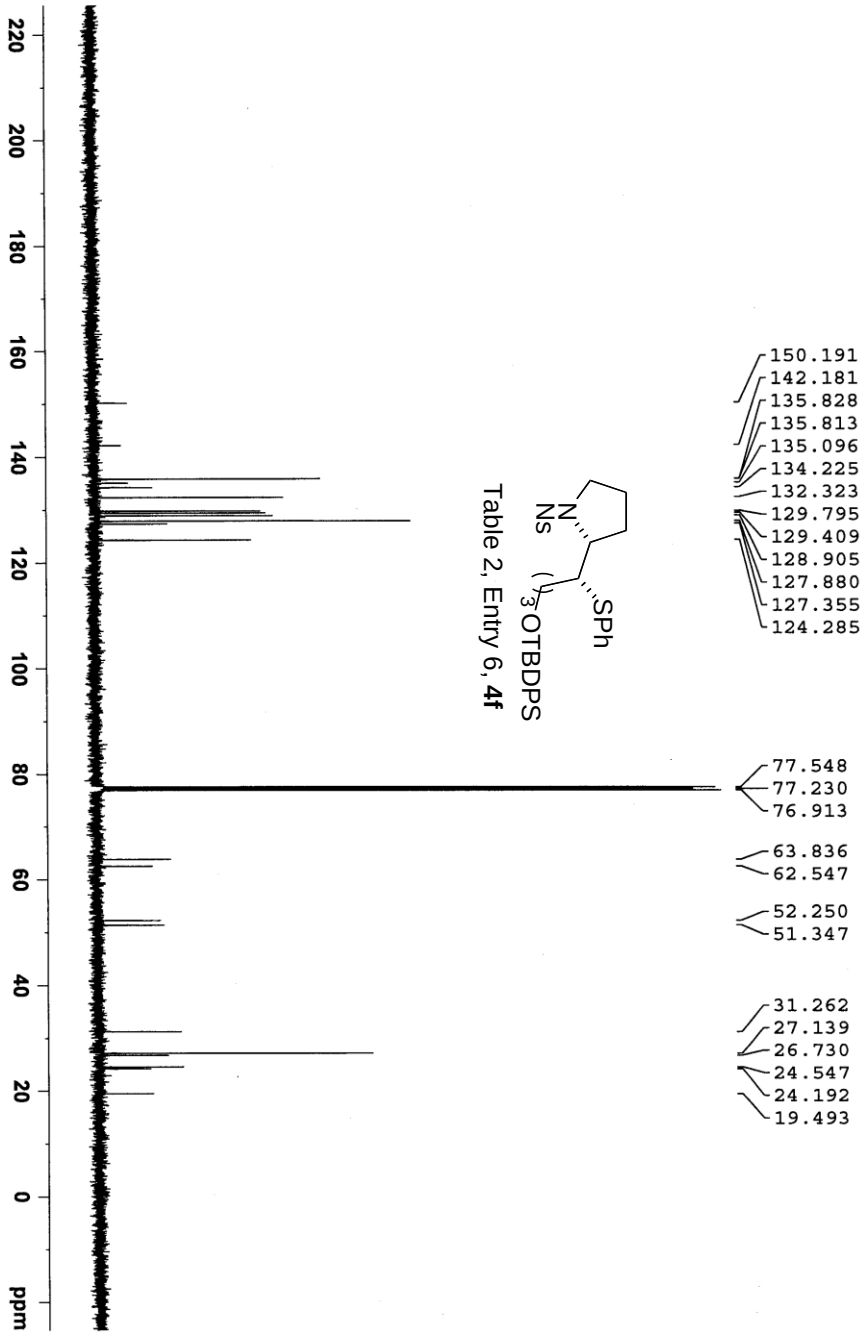

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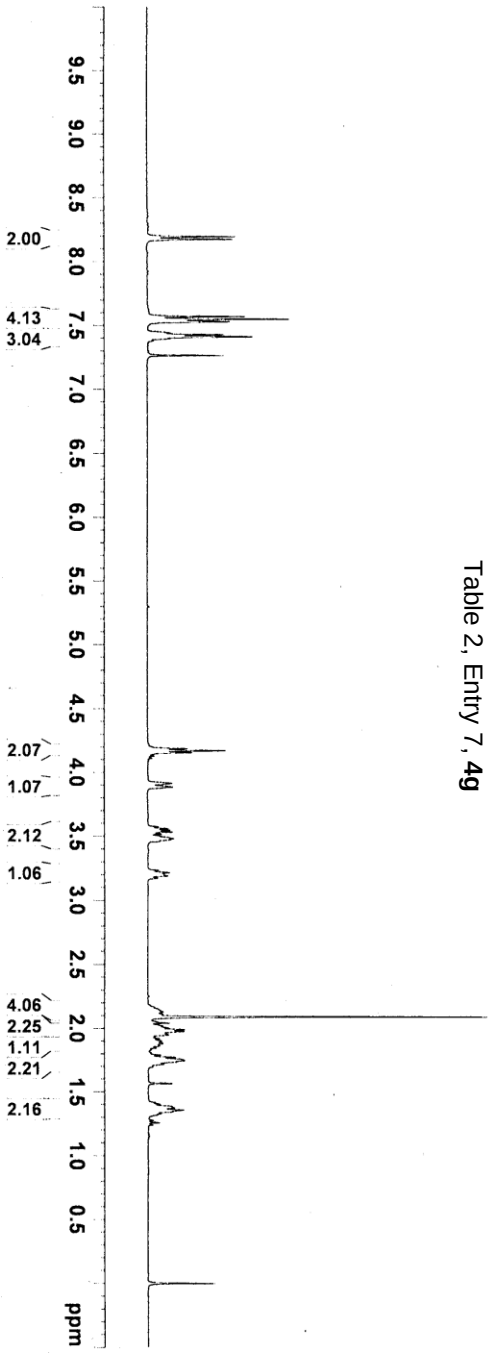

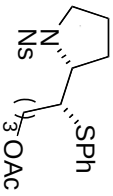

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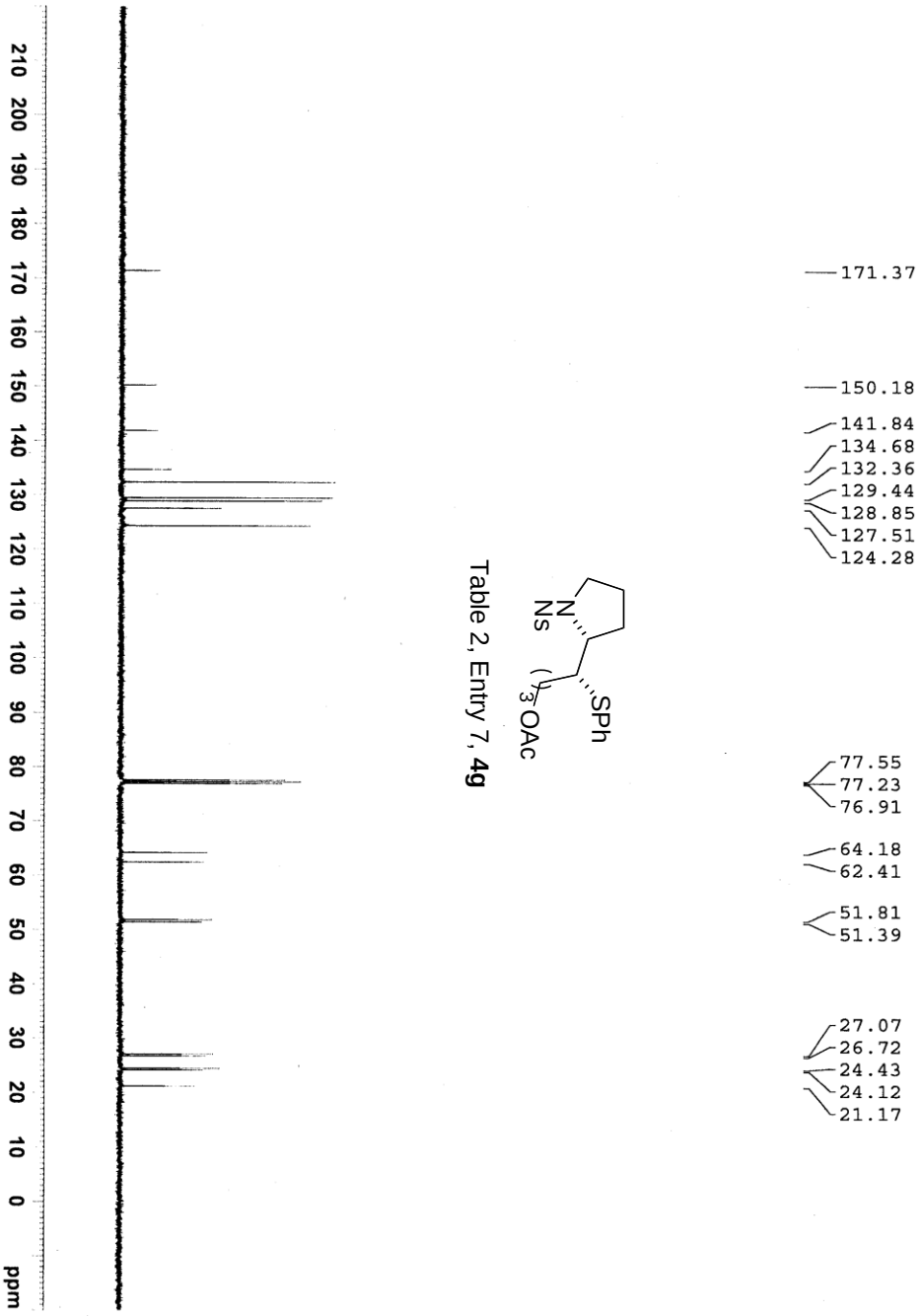

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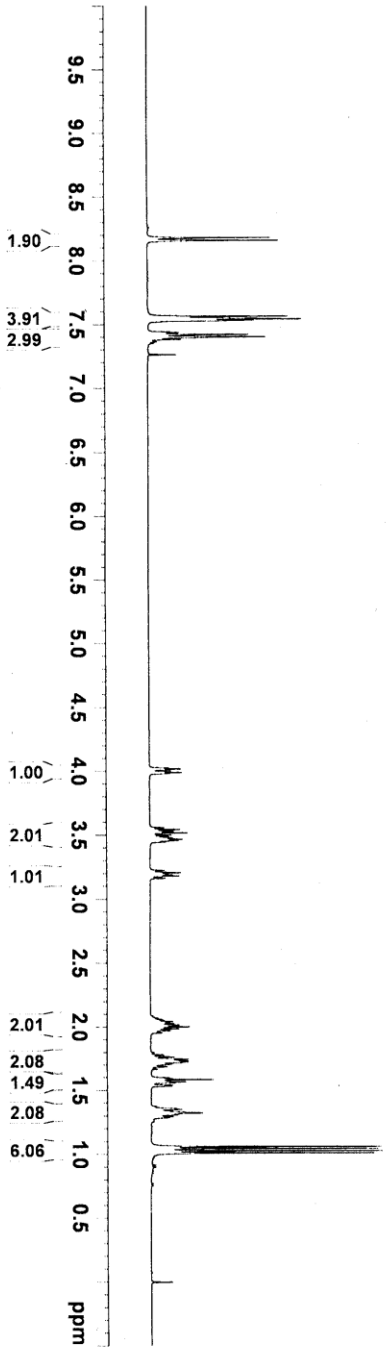

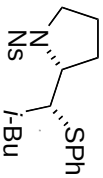

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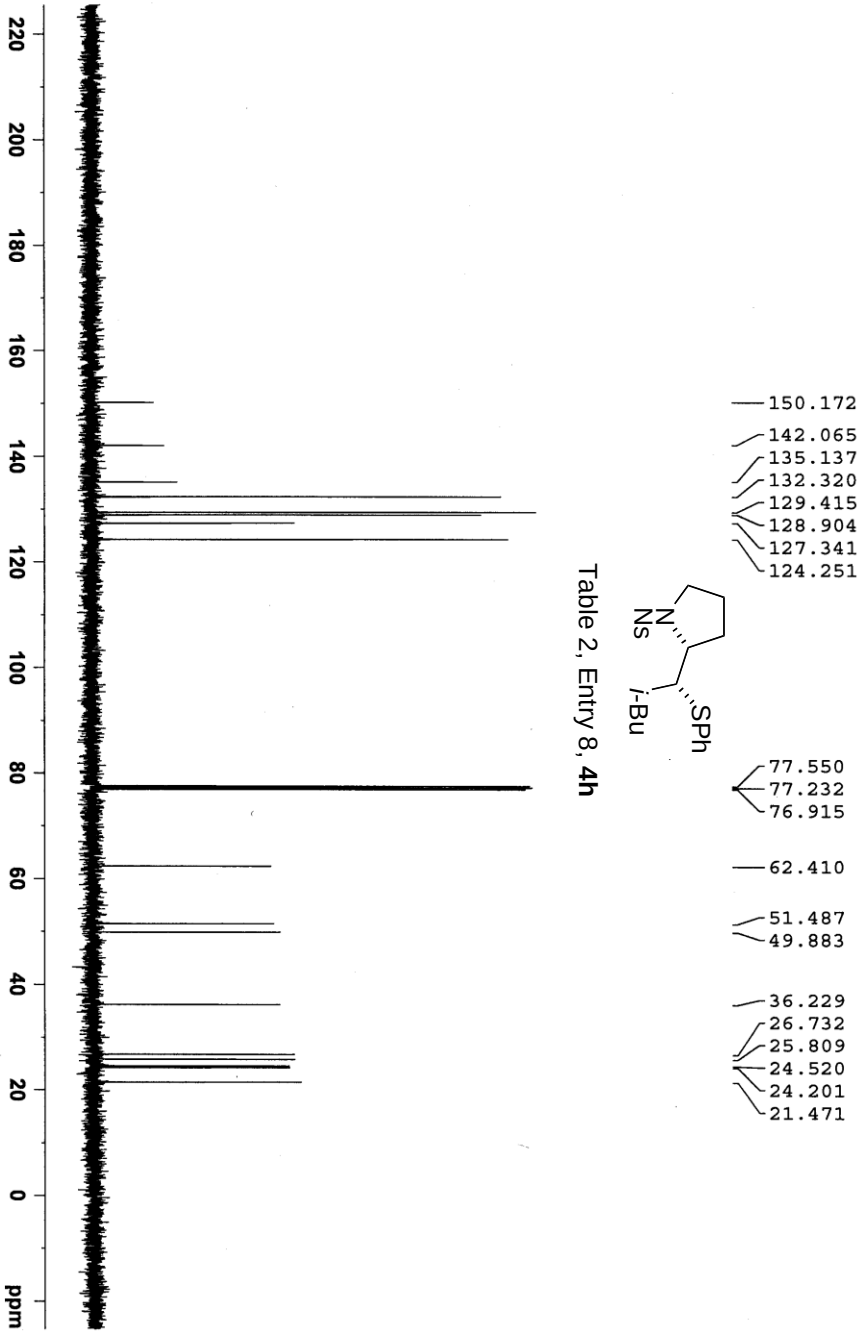

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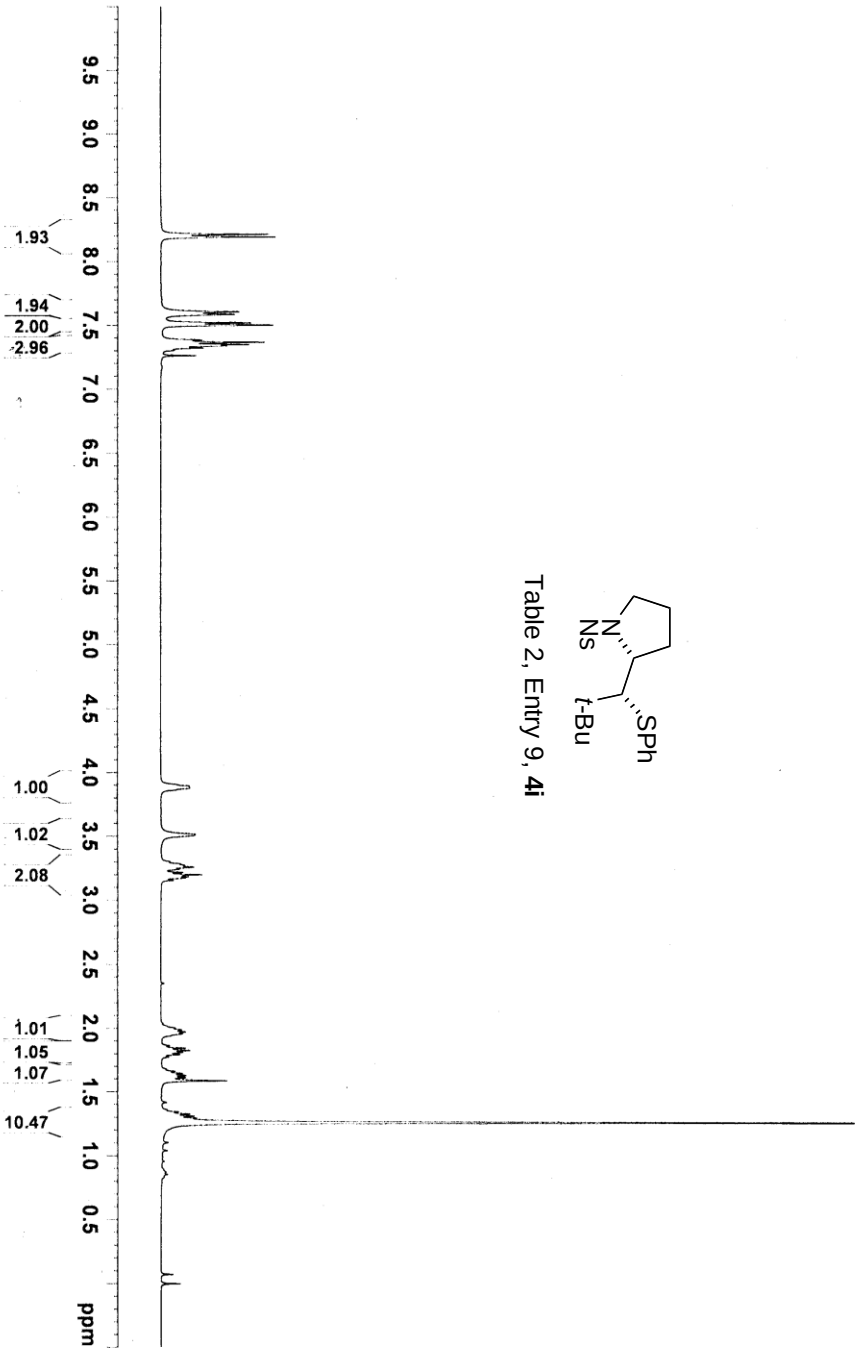
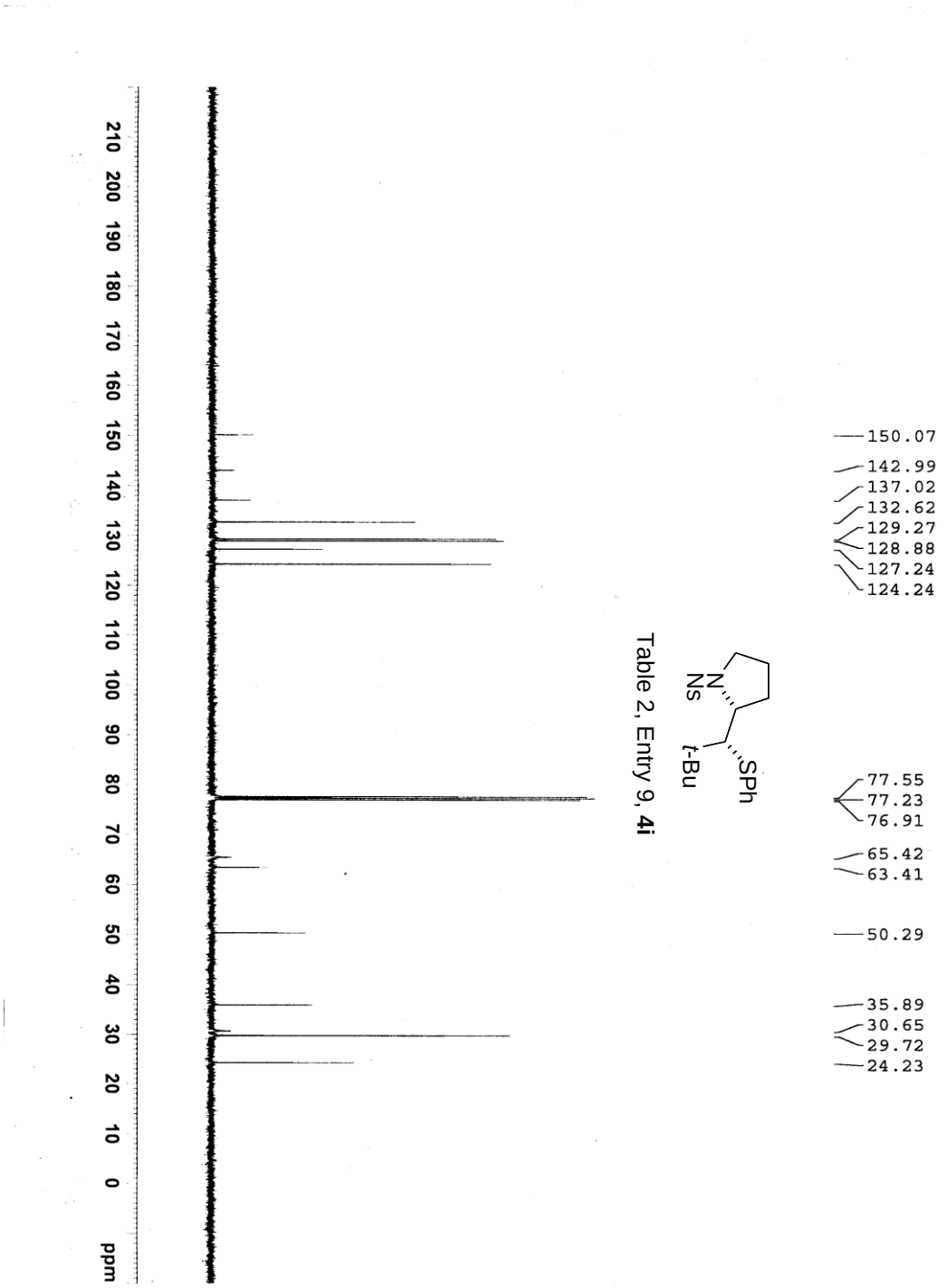


Table 2, Entry 9, **4i**



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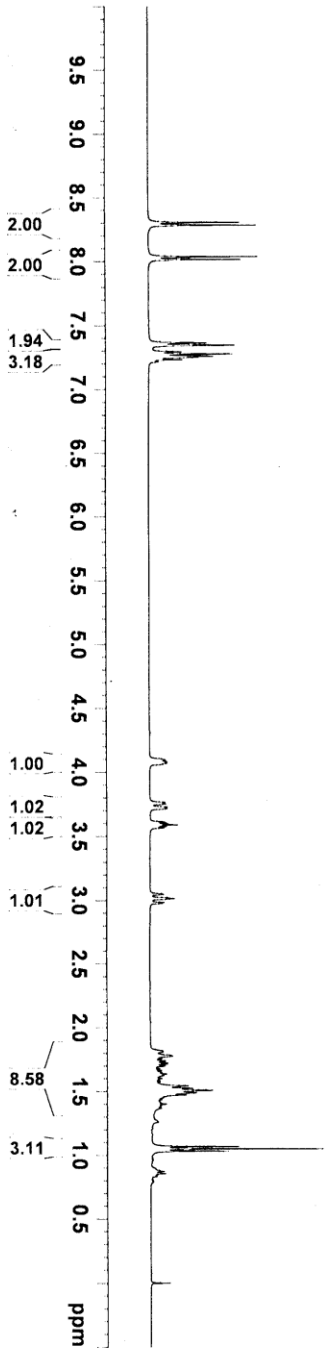

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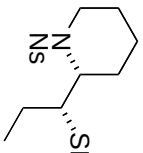
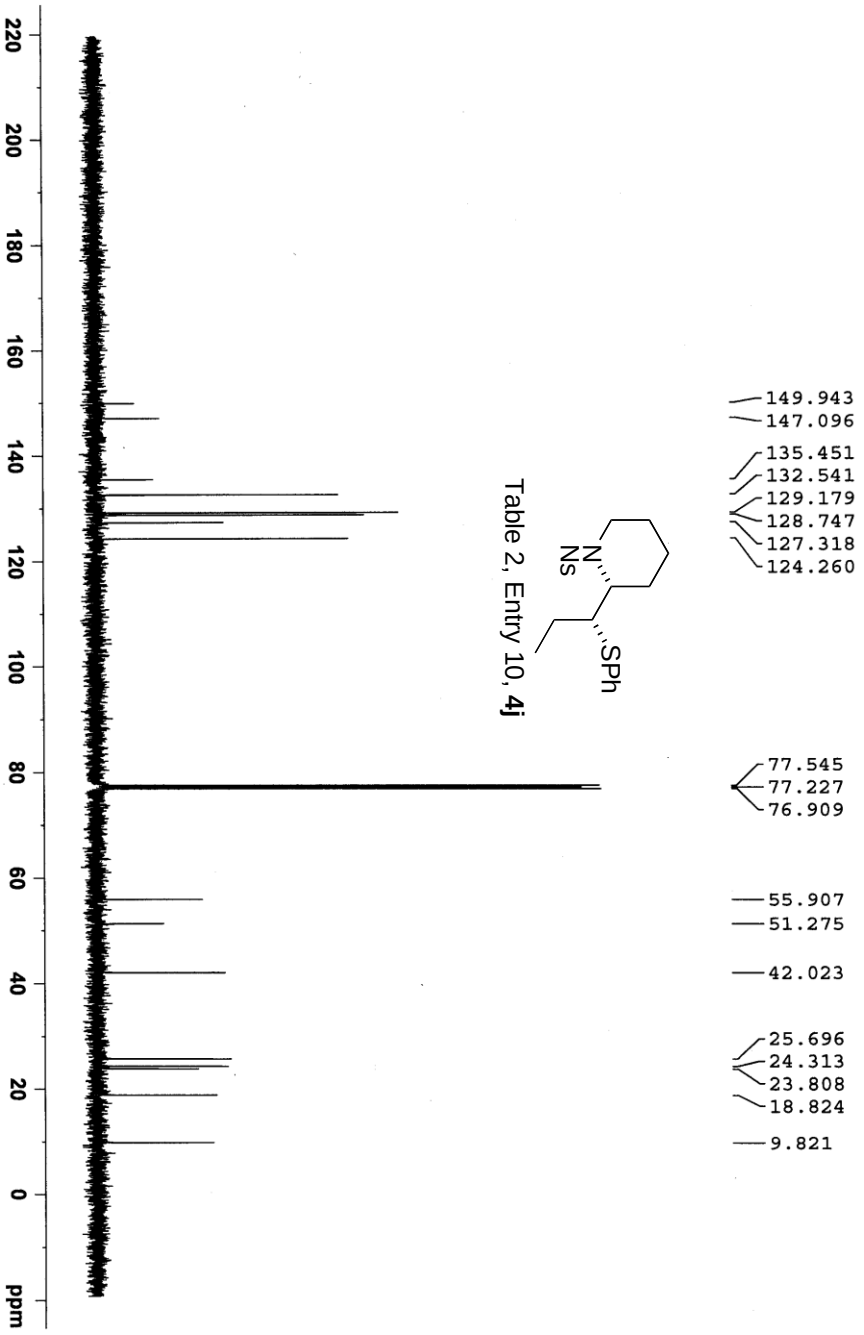
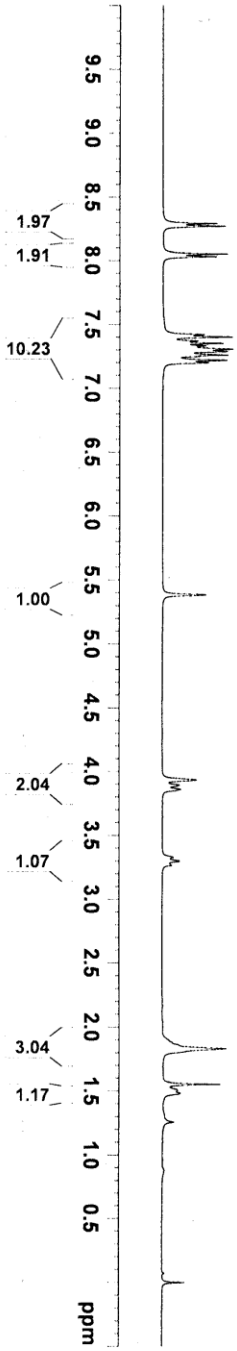






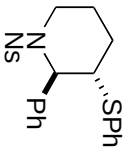
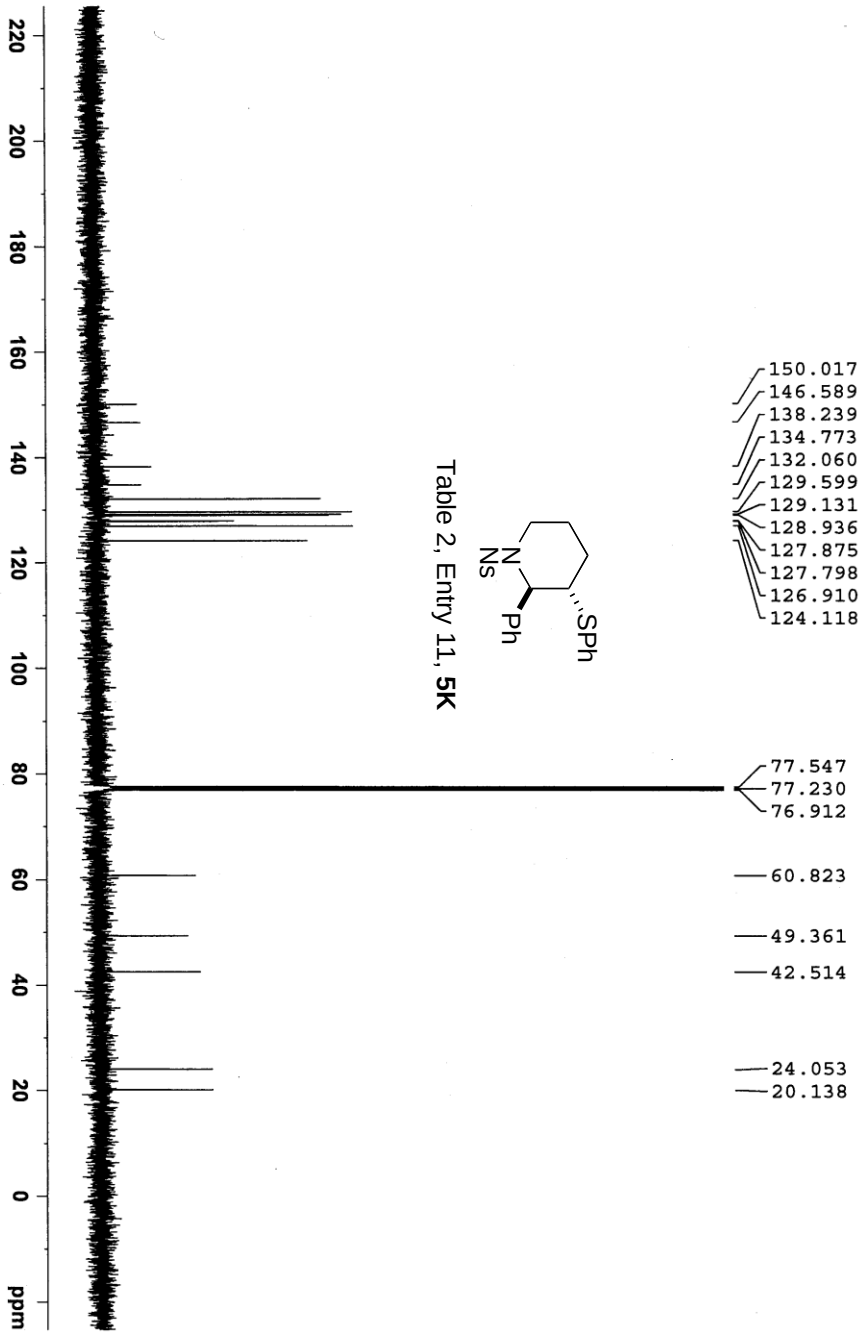
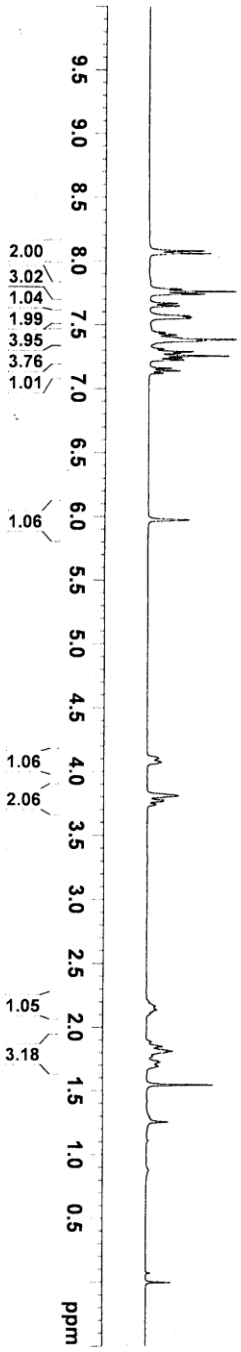


Table 2, Entry 11, **5K**





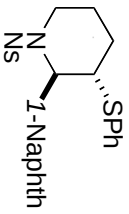
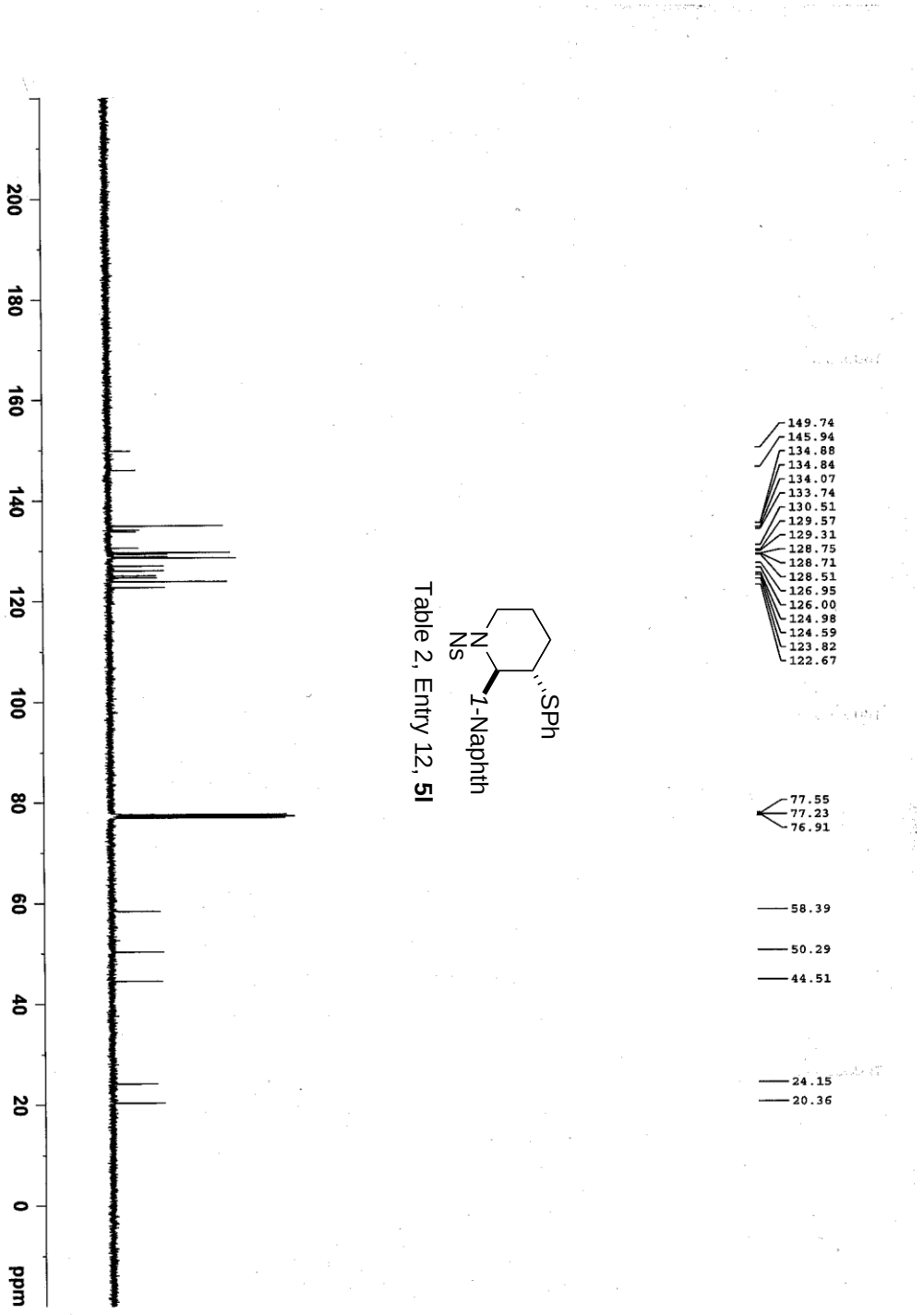


Table 2, Entry 12, **5l**



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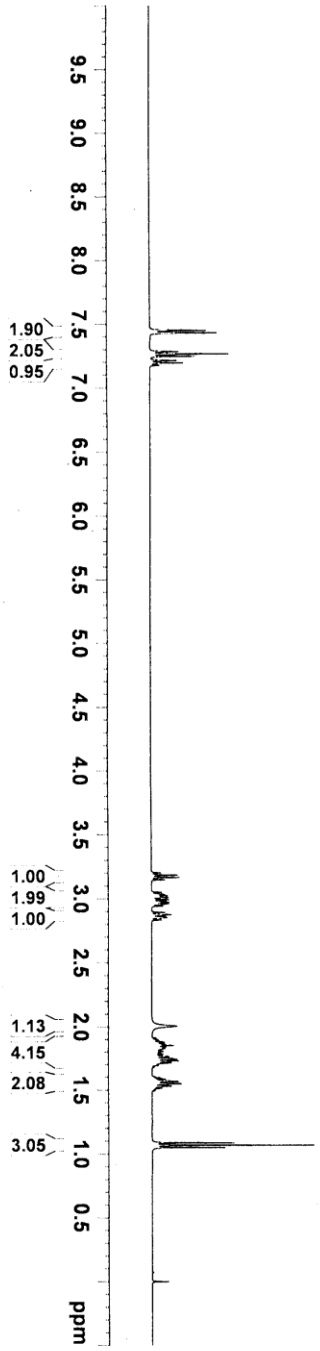
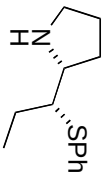
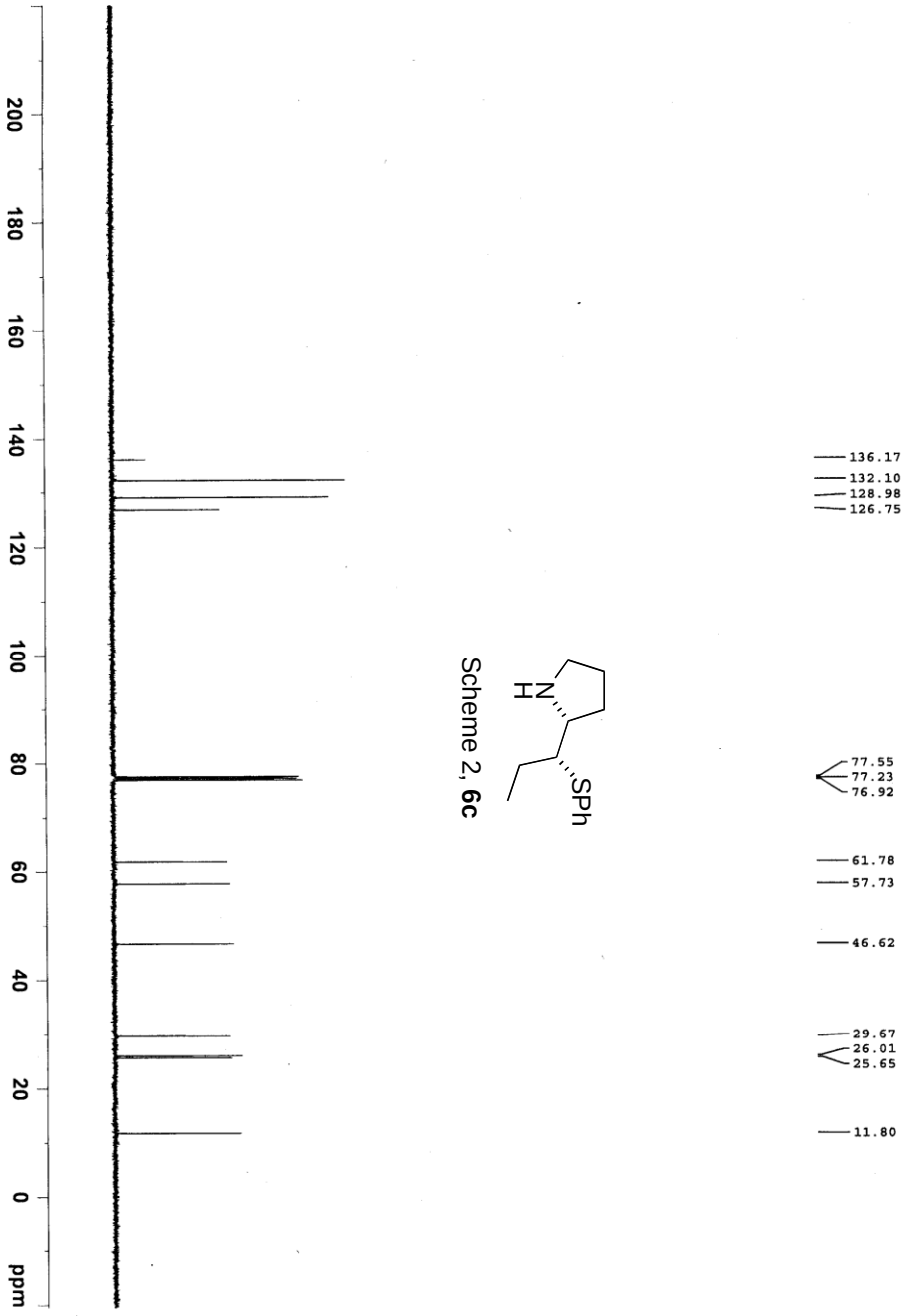
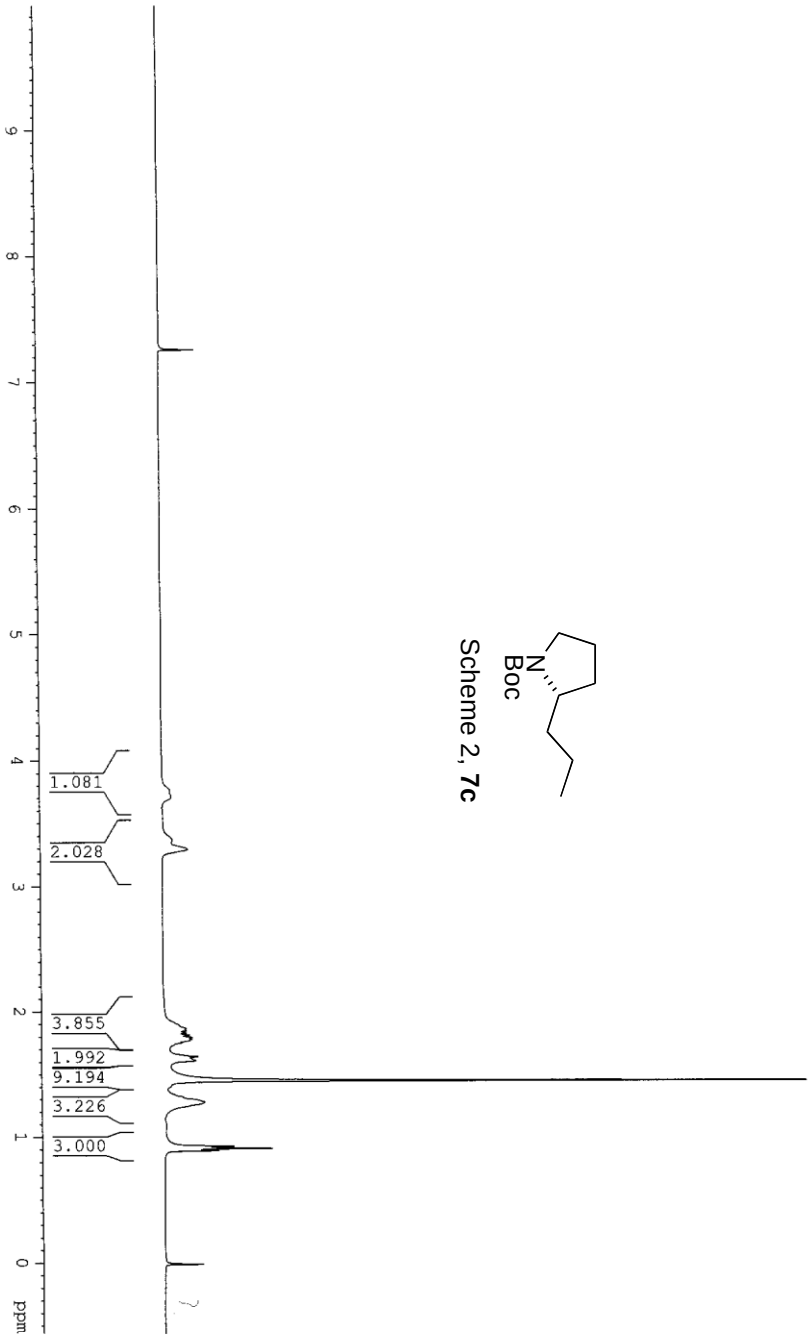




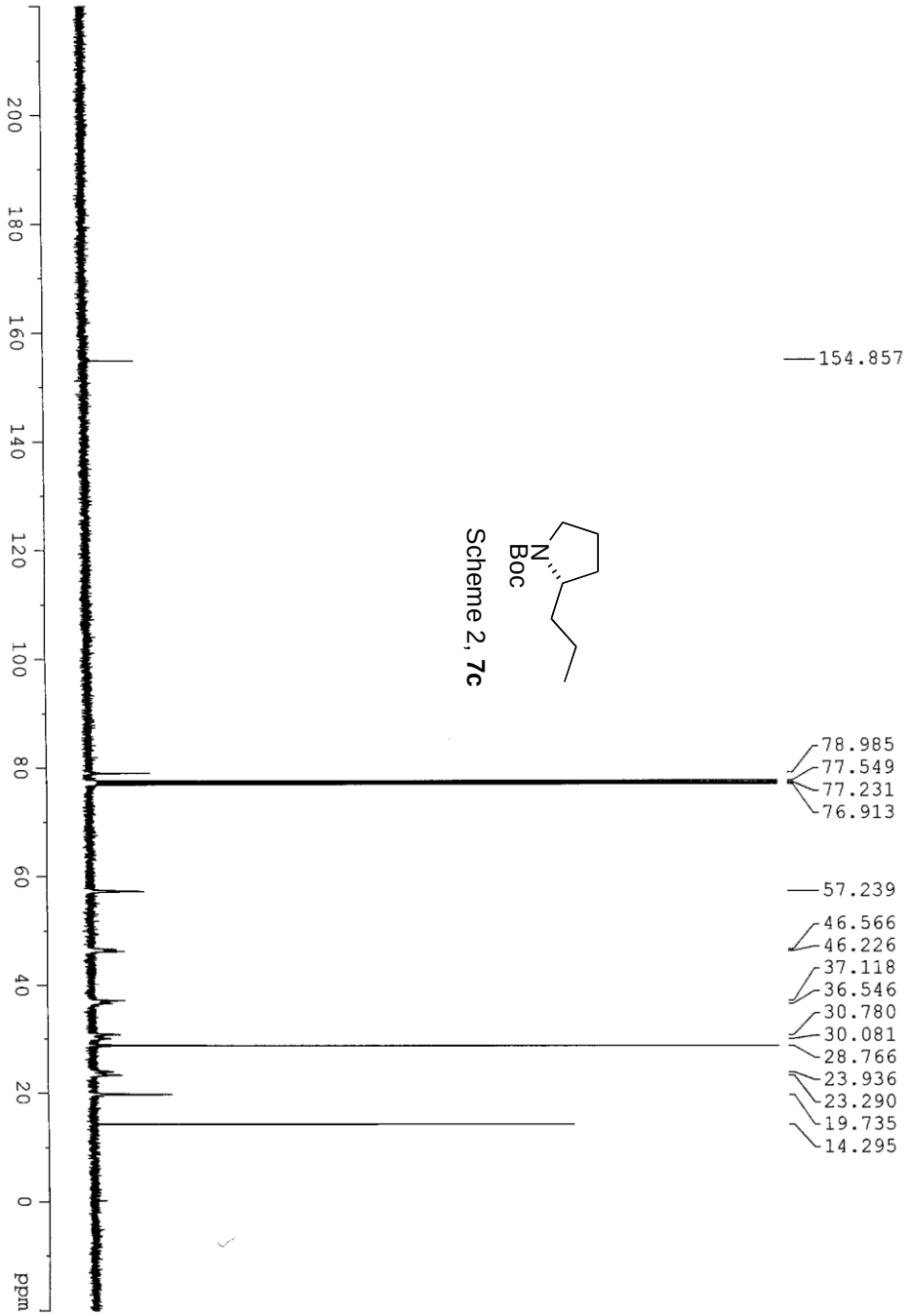
Scheme 2, **6c**

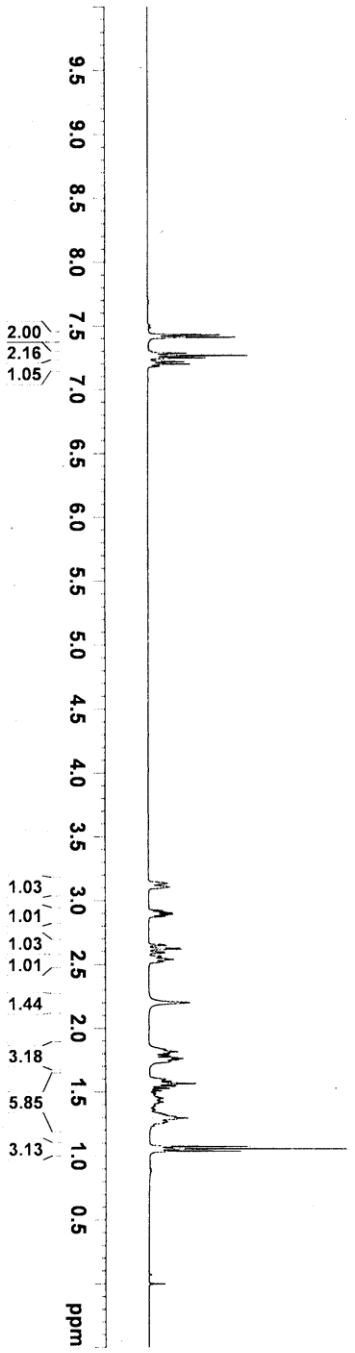


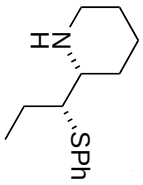
Scheme 2, **6c**



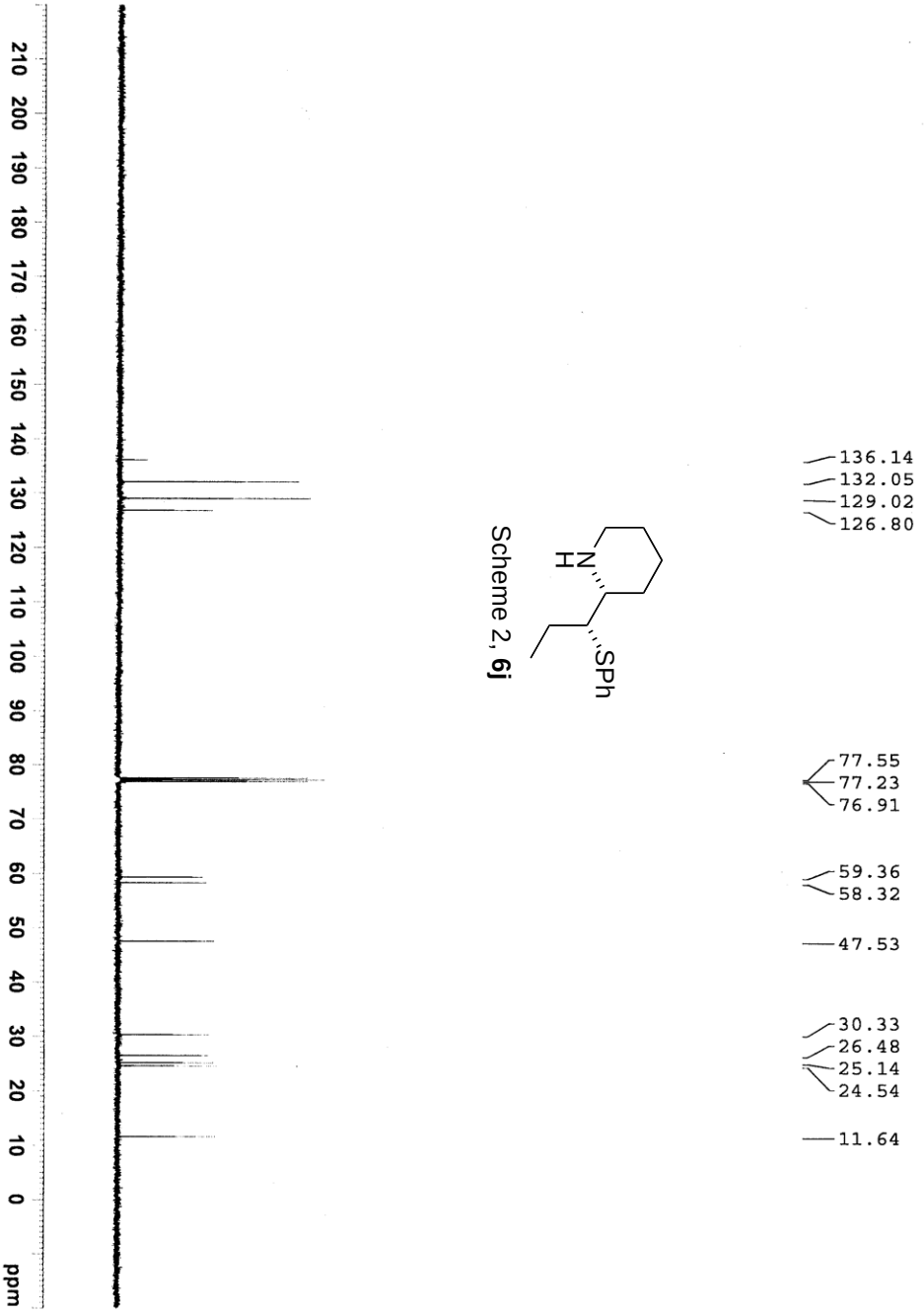
Scheme 2, **7c**



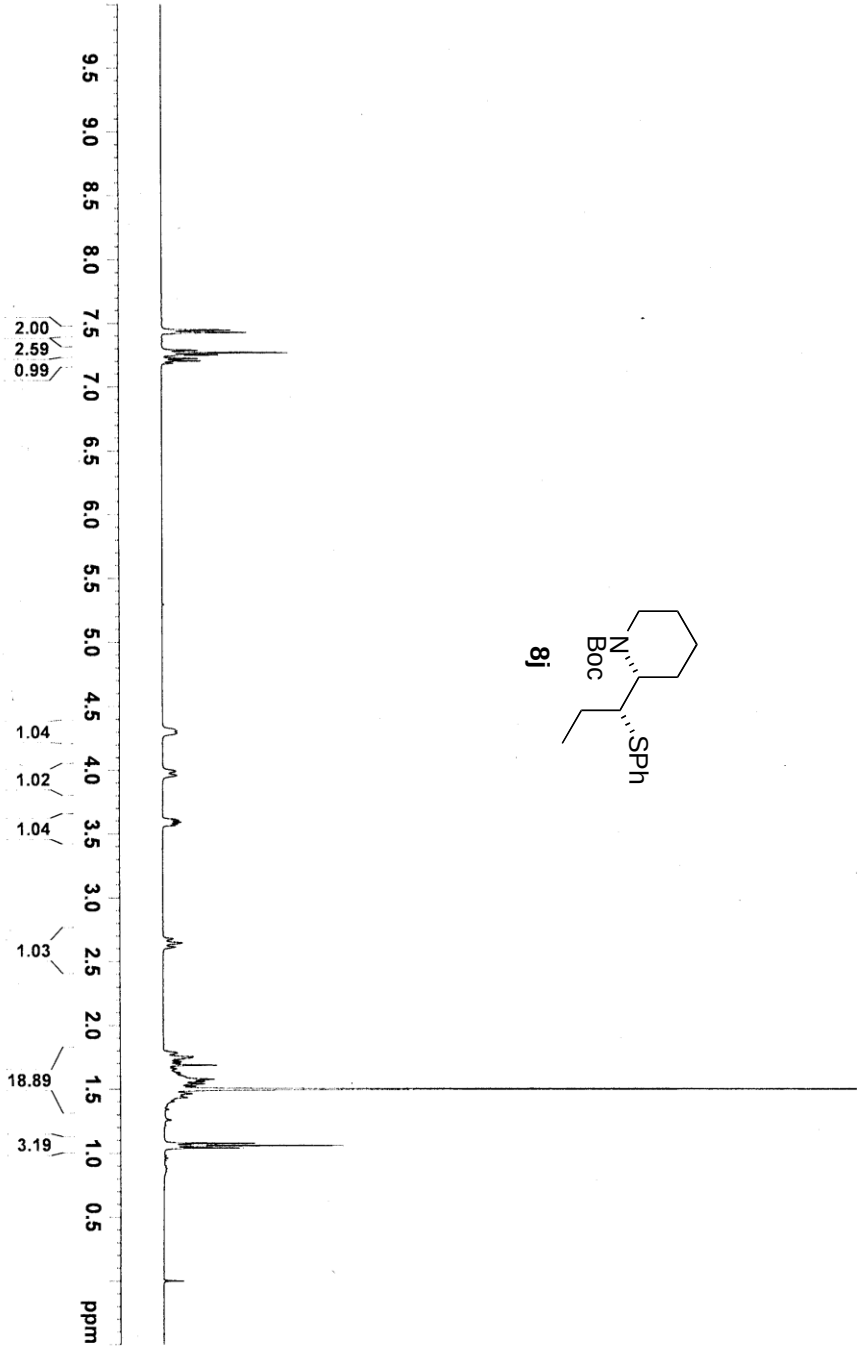


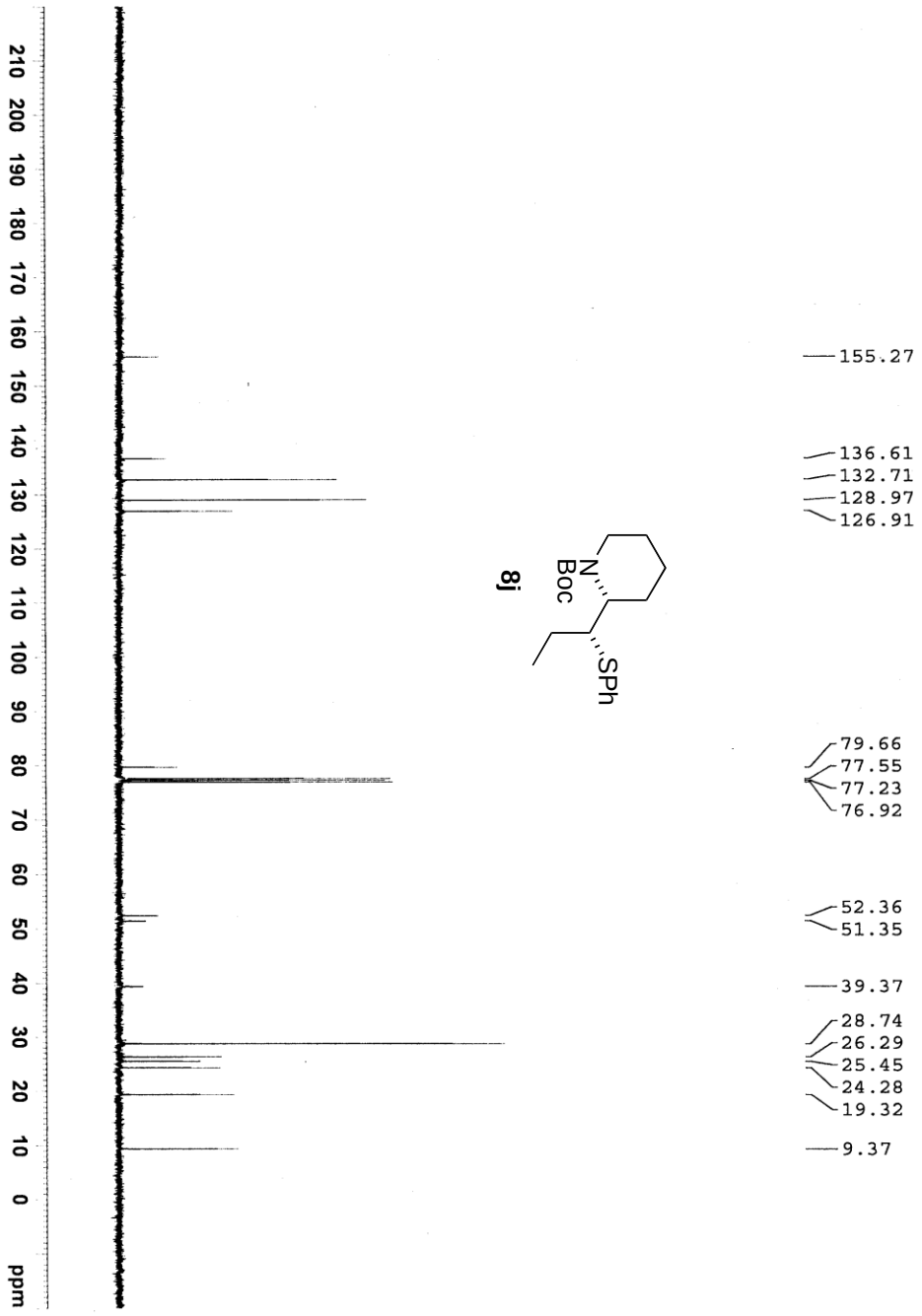


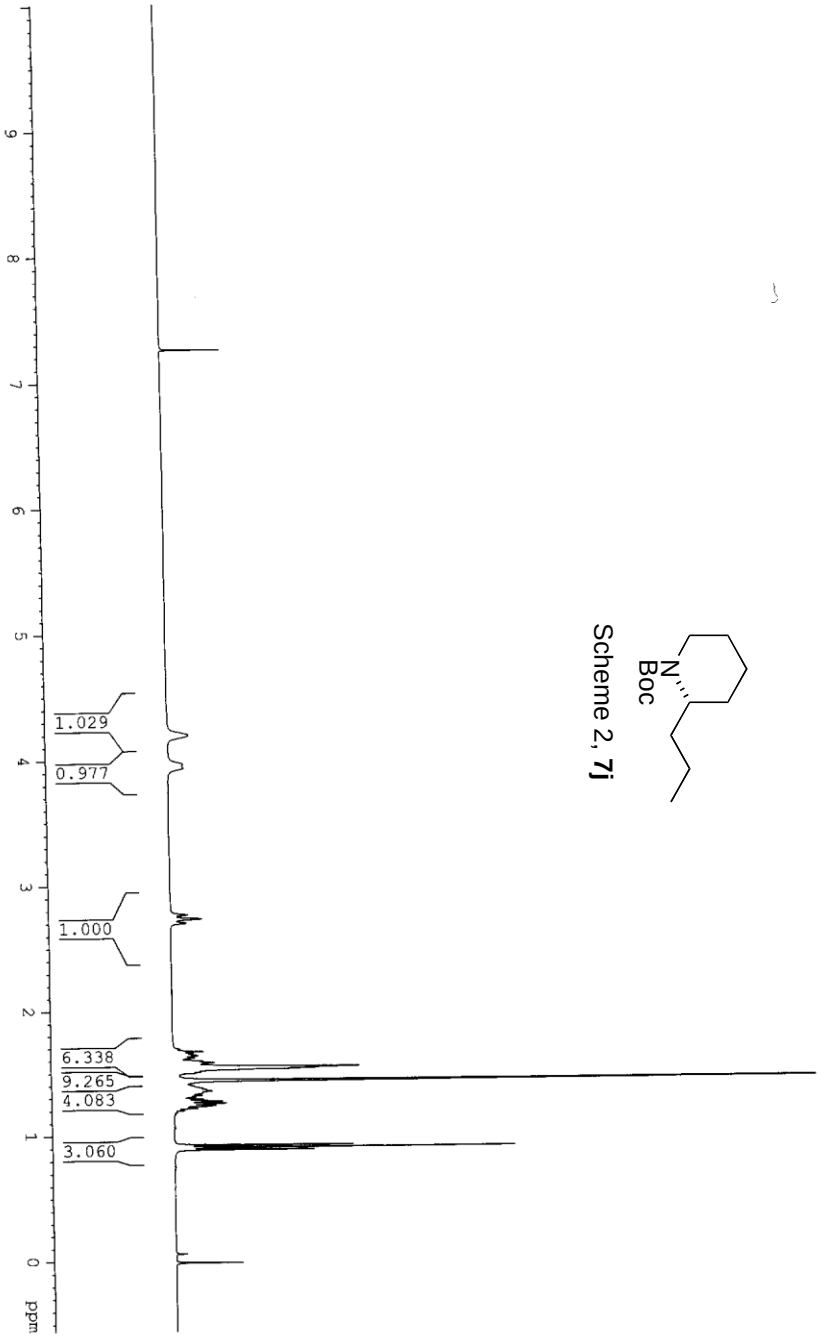
Scheme 2, **6j**



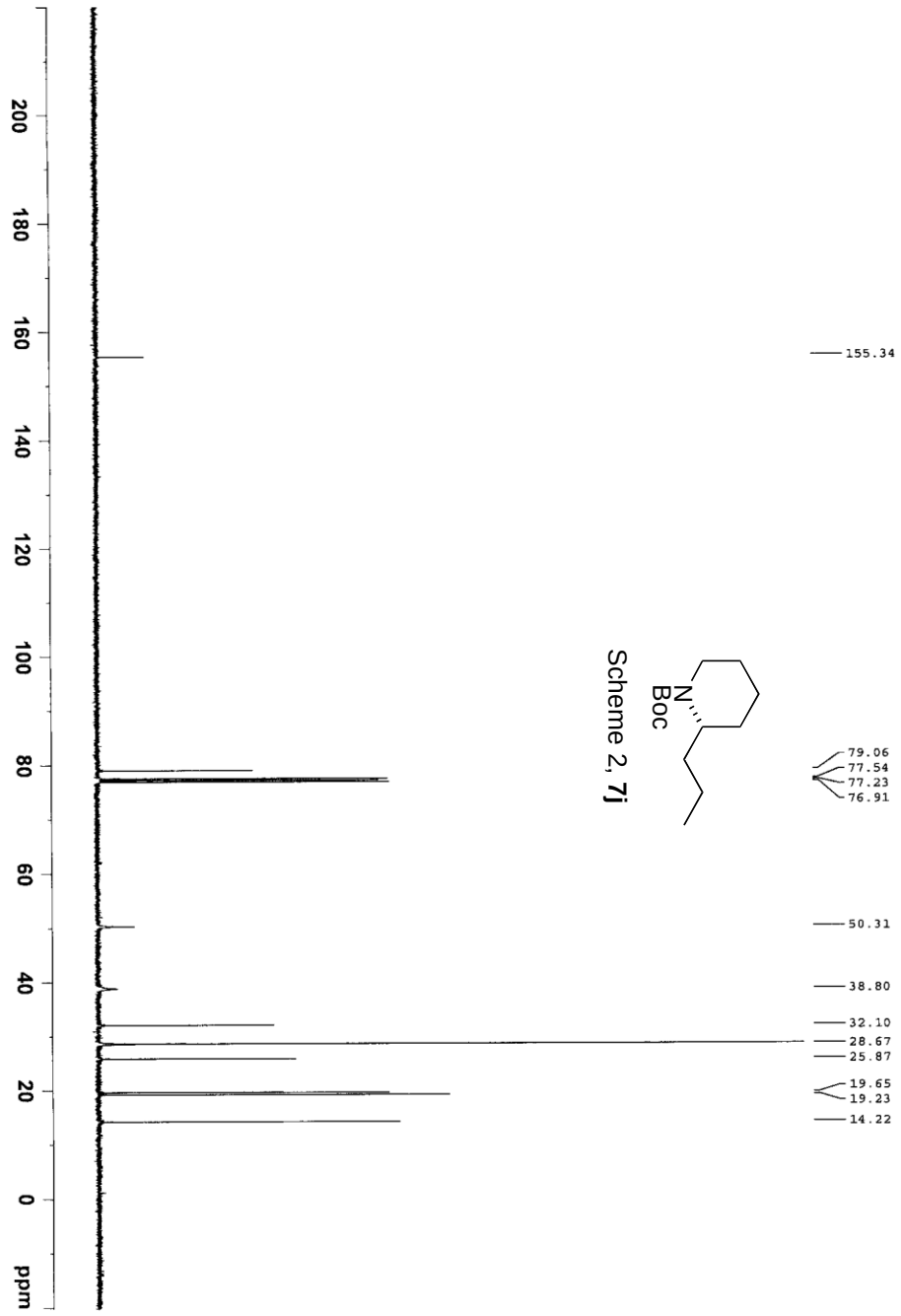
Scheme 2, **6j**



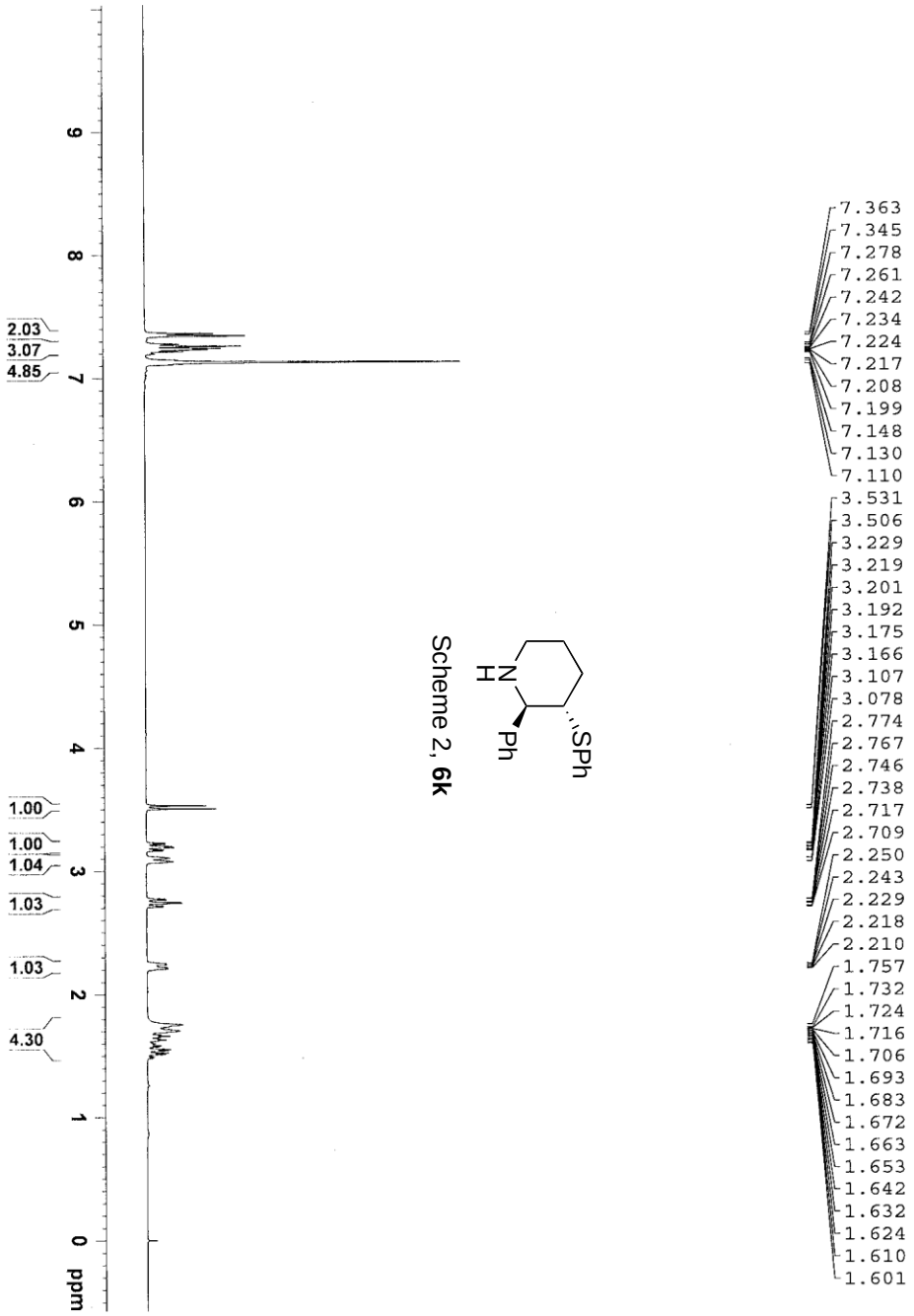




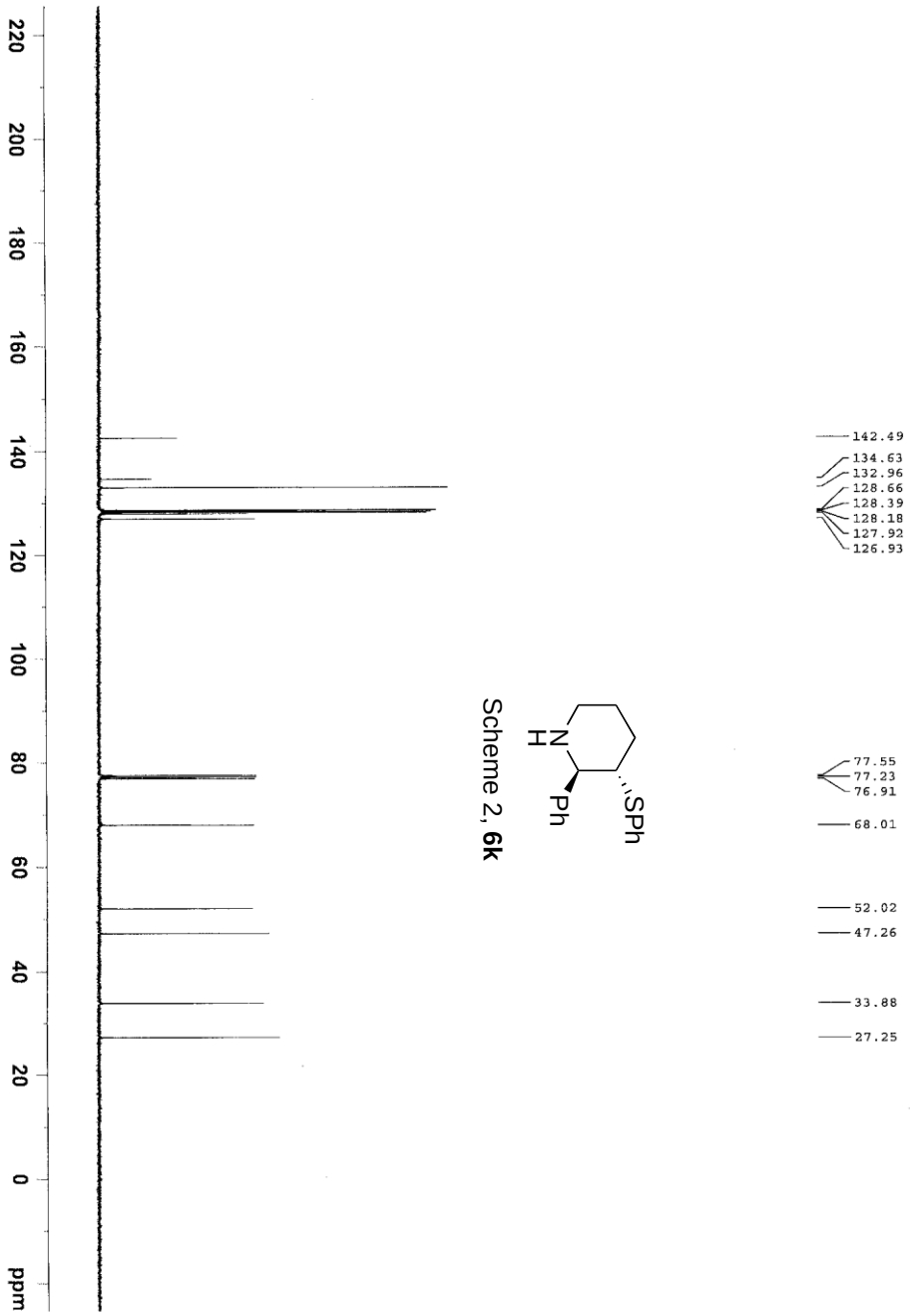
Scheme 2, **7j**



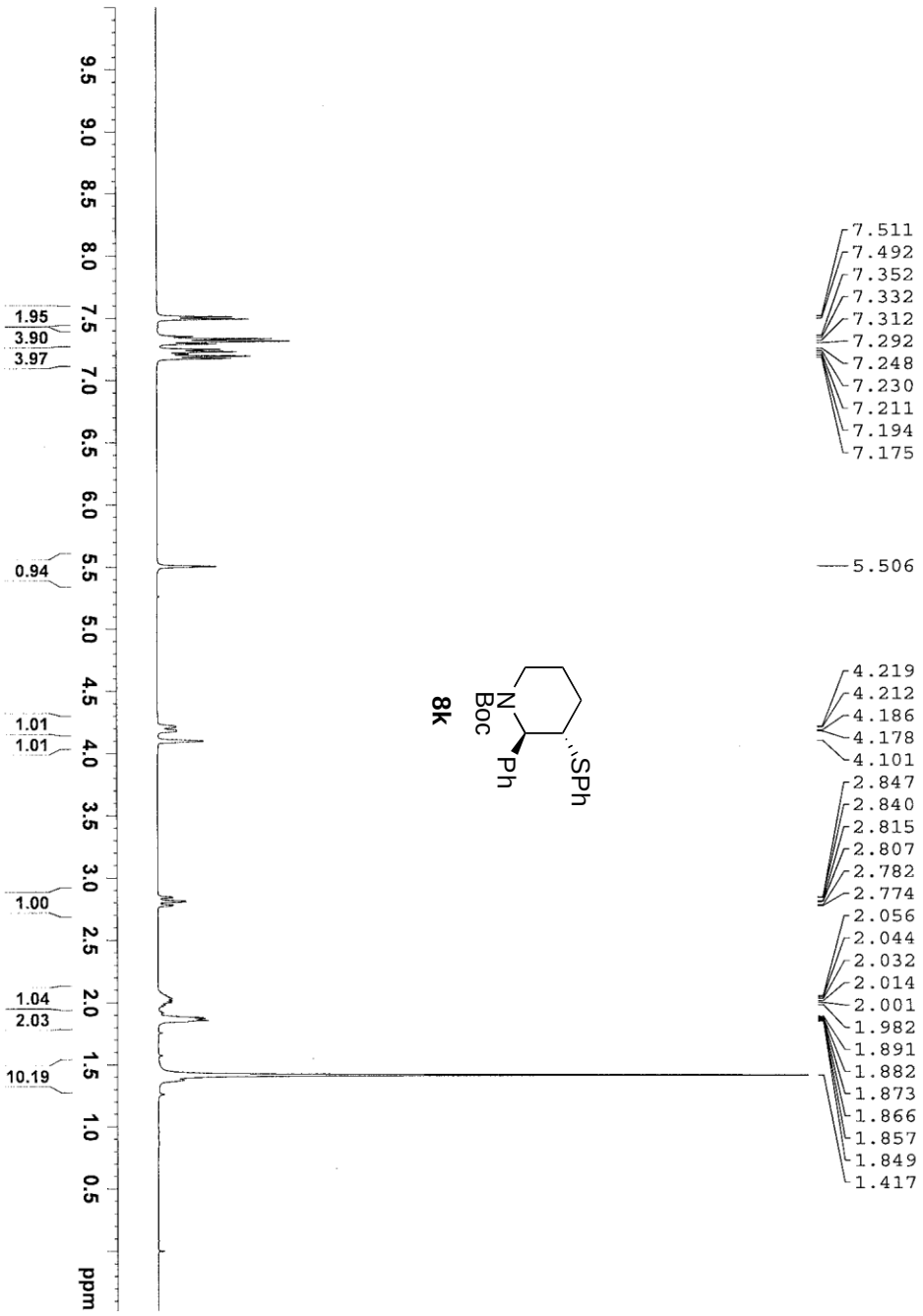
Scheme 2, **7j**

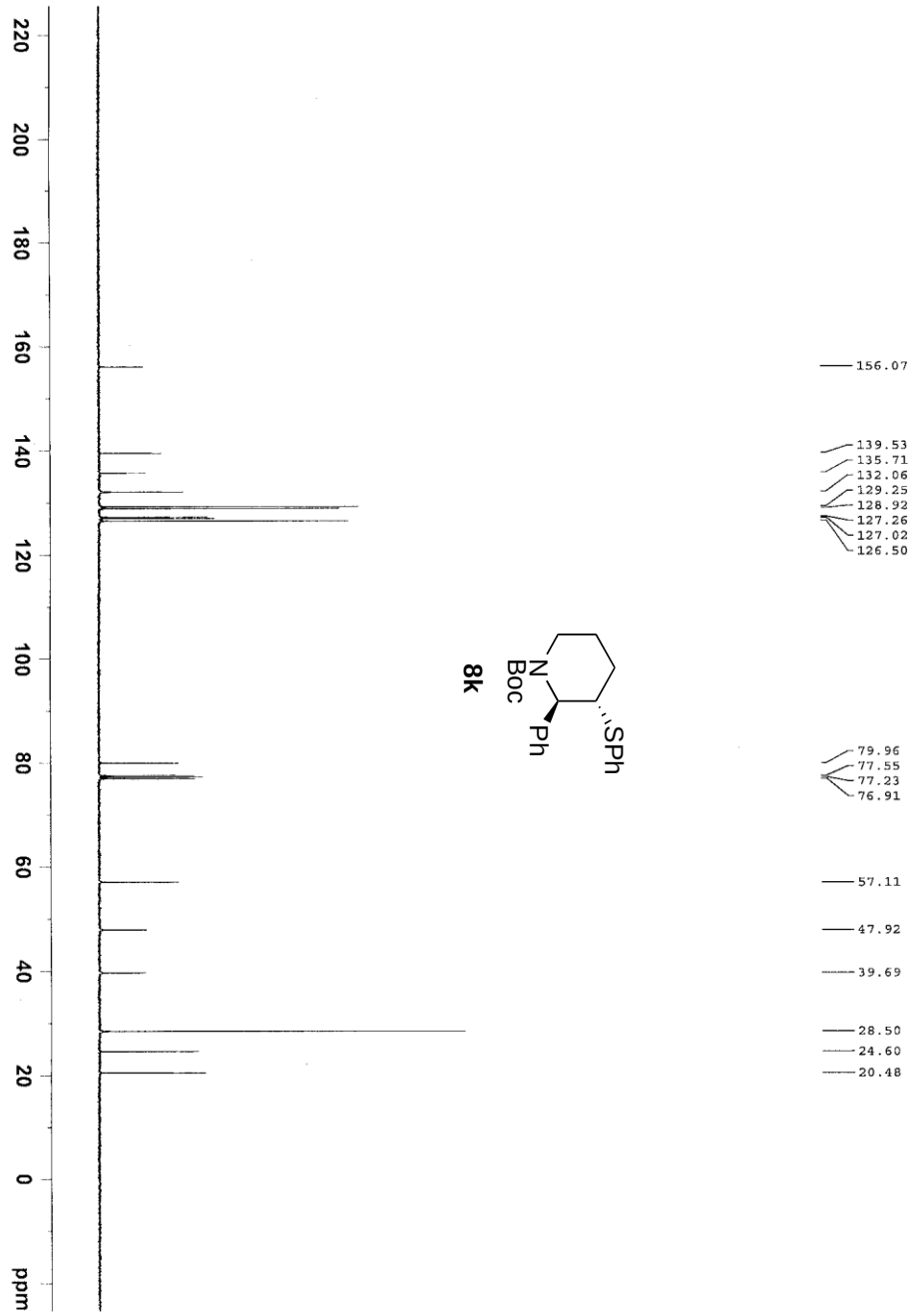


Scheme 2, **6k**



Scheme 2, **6k**

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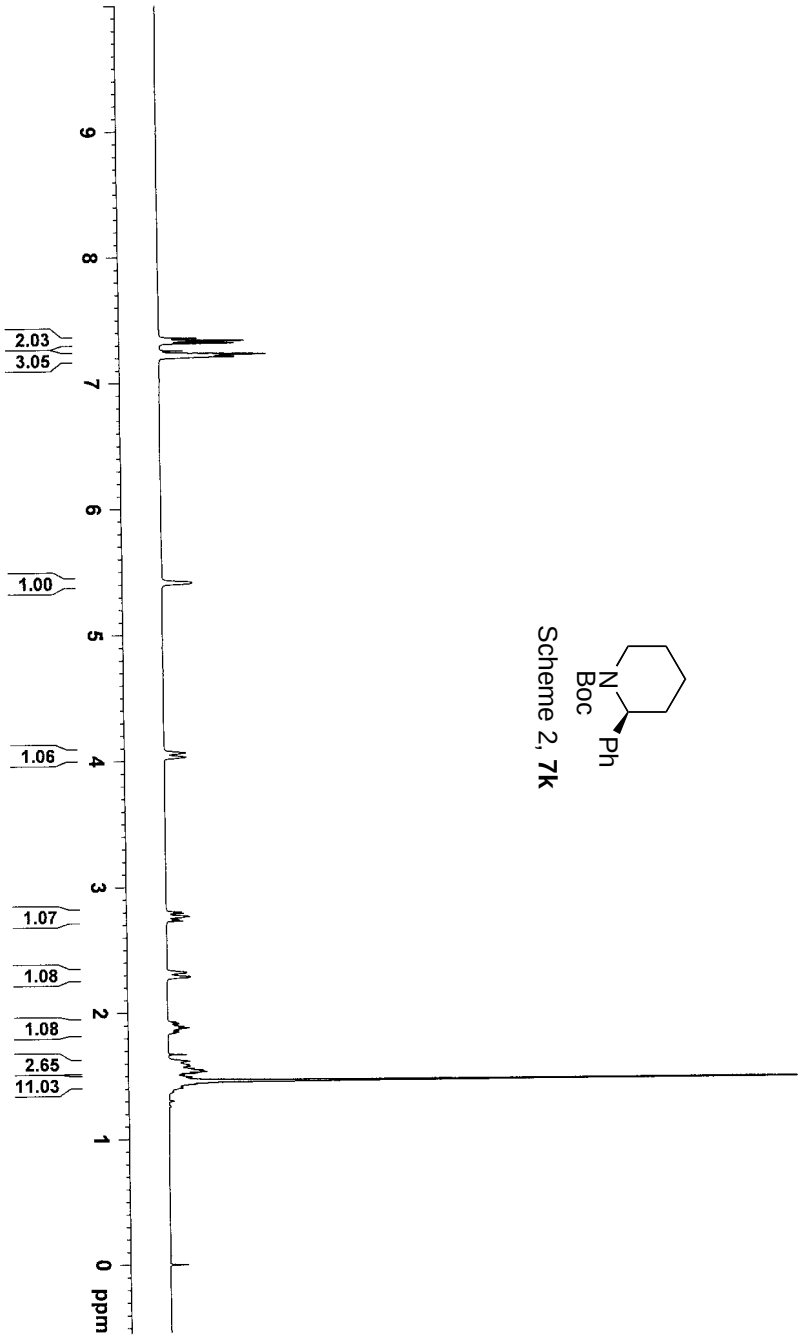

Scheme 2, **7k**