Observations on the deprotection of pinanediol and pinacol boronate esters via fluorinated intermediates

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SUPPORTING INFORMATION

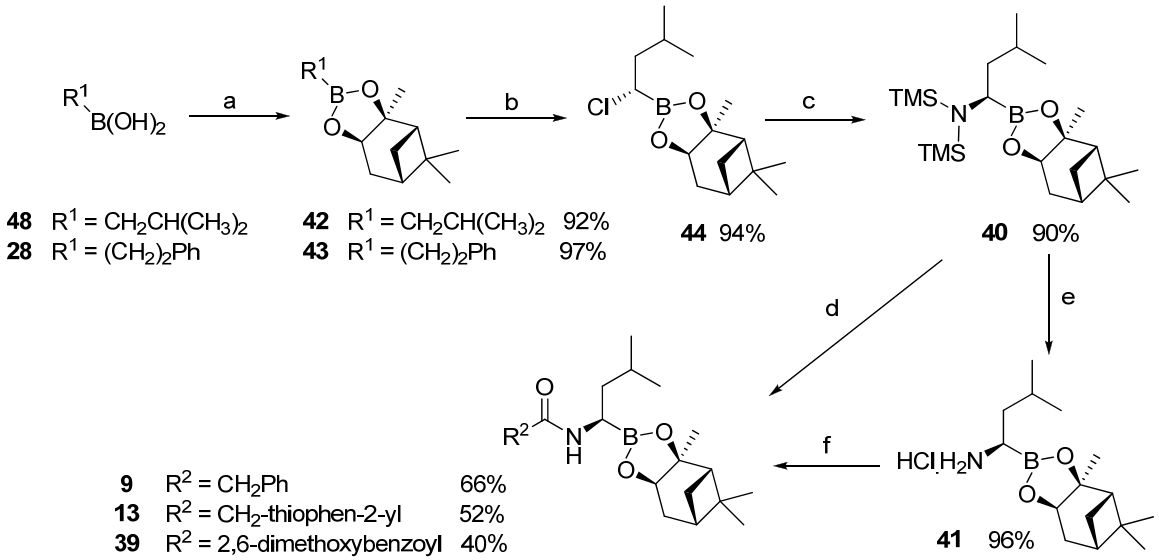
Contents

Full experimental section

General synthetic considerations. Precursors **40** and **41** for preparation of α-amido pinanediol boronates **9**, **13** and **39** (Scheme S-1) were prepared according to a reported method;[1,2] complete characterisations for known compounds **40-44** in Scheme S-1 are included as only partial characterisations have been reported previously.[1,3] **9** and **13** were prepared from **40** by adapting a reported method.[4] α-Amido pinacol ester **14**, was prepared by the same method used to prepare the corresponding α-amido pinanediol ester **13** as illustrated in Scheme S-2. Pinacol boronate precursor **45**, for preparation of **14**, was prepared by similar methods used for preparation of pinanediol boronate **40**;[1] the identity of **45** (and intermediates) was confirmed by comparison with reported data.[5] Pinanediol boronate **10** was prepared as reported.[6] Aniline precursor **46** for the preparation of phenylboronic acid pinacol ester **19** was prepared from **47** using a reported method (Scheme S-3).[7] Pinacol ester **3** was prepared as reported.[8] The identities of starting materials prepared according to reported procedures were confirmed by comparison of $^{1}H/^{13}C$ NMR and mp data with that reported, and were further confirmed by mass spectrometry. ^{1}H and ^{13}C NMR assignments for new compounds, particularly for (+)-pinanediol boronate esters were made from 2D NMR experiments; example 2D spectra for **42** are provided.

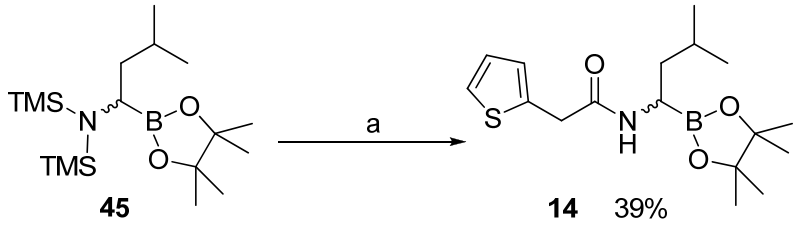
Starting materials **20**, **25**, **28**, **47**, **48**, (+)-pinanediol and other commonly used reagents were obtained from commercial sources. Other general synthetic considerations have been provided previously.[8]

Scheme S-1: Synthesis of α-amido pinanediol boronate esters.[a]



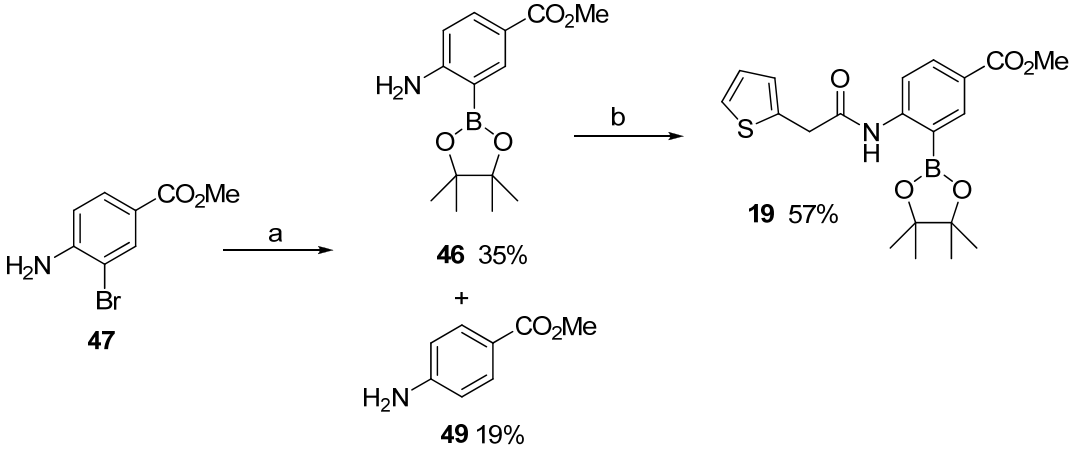
[a] Reagents and conditions; (a) (+)-pinanediol/THF/rt; (b) LDA/CH_2Cl_2/$ZnCl_2$/THF/–78°C to rt; (c) $LiN(TMS)_2$/THF/–78°C to rt; (d) R^2CO_2H/R^2COCl/THF/–78°C to rt; (e) HCl/ether/dioxane/0°C to rt; (f) R^2COCl/Et_3N/DMAP/THF/DMF/0°C to rt.

Scheme S-2: Synthesis of α-amido pinacol ester **14**.[a]



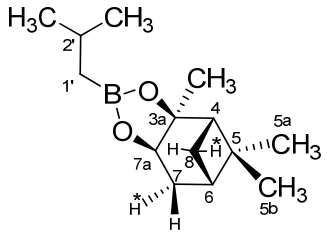
[a] Reagents and conditions; (a) 2-thiopheneacetic acid/2-thiopheneacetyl chloride /THF/–78°C to rt.

Scheme S-3: Synthesis of phenyl boronic acid pinacol ester **19**. [a]

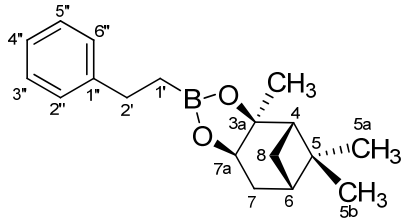


[a] Reagents and conditions; (a) Pinacolborane/$PdCl_2$.dppf/triethylamine/dioxane/Δ 5h; (b) 2-thiopheneacetyl chloride/Et_3N/THF/0°C to rt, overnight.

Synthetic procedures and compound characterisations

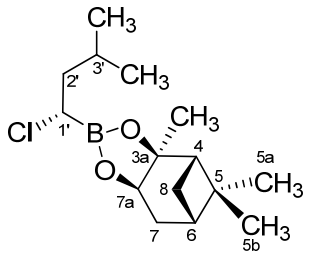


(3a*S*,4*S*,6*S*,7a*R*)-2-Isobutyl-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborole 42: A mixture of isobutylboronic acid **48** (3.32 g, 0.033 mol) and (+)-pinanediol (5.27 g, 0.031 mol) in THF (40 mL) was stirred overnight at room temp. The mixture was concentrated, and the residue purified by filtration through silica gel using 9:1 hexane/ethyl acetate as eluant to afford 7.10 g (92%) of the title **42** compound as a colourless liquid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.78 (2H, dd, *J* = 2.1, 7.1 Hz, H1'), 0.85 (3H, s, $CH_3$5a), 0.95 (6H, d, *J* = 6.8 Hz, ($C\underline{H}_3$)$_2$C2'), 1.14 (1H, d, *J* = 10.9 Hz, H8), 1.29 (3H, s, $CH_3$5b), 1.38 (3H, s, $C\underline{H}_3$C3a), 1.82-1.93 (3H, m, H2', H7 and H6), 2.05 (1H, t, *J* = 5.5 Hz, H4), 2.19-2.24 (1H, m, H8*), 2.31-2.37 (1H, m, H7*), 4.26 (1H, dd, *J* = 2.1, 8.9 Hz, H7a). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 21.2 (br, C1'), 24.0 ($CH_3$5a), 24.9 (C2'), 25.2 ($\underline{C}H_3$C2'), 25.3 ($\underline{C}H_3$*C2'), 26.5 (C8), 27.0 ($CH_3$5b), 28.7 ($\underline{C}H_3$C3a), 33.6 (C7), 38.1 (C5), 39.6 (C6), 51.2 (C4), 77.6 (C7a), 85.2 (C3a). IR (neat) 2952, 2921, 1376 cm^{-1}. MS (ESI, negative ion) *m/z* 267 (M+MeO[^{11}B], 80%), 266 (M+MeO[^{10}B], 25), 123 (100). Anal. Calcd for $C_{14}H_{25}BO_2$: C, 71.20; H, 10.67. Found: C, 71.09; H, 10.58. $[\alpha]_D^{25}$ +26.9 (*c* 1.75, $CHCl_3$).



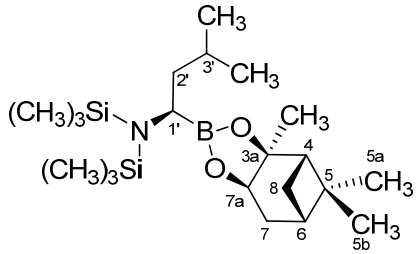
(3a*S*,4*S*,6*S*,7a*R*)-3a,5,5-Trimethyl-2-(2-phenylethyl)hexahydro-4,6-methano-1,3,2-benzodioxaborole 43: A mixture of (2-phenylethyl)boronic acid **28** (0.900 g, 6.00 mmol) and (+)-pinanediol (1.123 g, 6.60 mmol) in THF (12 mL) was stirred at room temp overnight. The mixture was concentrated, and the residue purified by filtration through silica gel using 9:1 hexane/ethyl acetate as eluant to afford 1.647 g

(97%) of the title **43** compound as a colourless liquid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.86 (3H, s, $CH_3$5a), 1.10 (1H, d, *J* = 11.1 Hz, H8), 1.21 (2H, t, *J* = 8.2 Hz, 2×H1'), 1.30 (3H, s, $CH_3$5b), 1.39 (3H, s, C$\underline{H}_3$C3a), 1.84 (1H, br d, *J* = 14.7 Hz, H7), 1.89-1.92 (1H, m, H6), 2.06 (1H, t, *J* = 5.4 Hz, H4), 2.16-2.21 (1H, m, H8*), 2.31-2.37 (1H, m, H7*), 2.79 (2H, t, *J* = 8.2 Hz, 2×H2'), 4.27 (1H, dd, *J* = 2.1, 9.0 Hz, H7a), 7.17 (1H, br t, *J* = 7.0 Hz,, H4''), 7.23-7.30 (4H, m, H2'', H3'', H5'' and H6''). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 12.4 (br, C1'), 24.0 ($CH_3$5a), 26.4 (C8), 27.1 ($CH_3$5b), 28.6 (C$\underline{H}_3$C3a), 30.1 (C2'), 35.4 (C7), 38.1 (C5), 39.5 (C6), 51.2 (C4), 77.7 (C7a), 85.5 (C3a), 125.5 (C4''), 128.0 ([C2'' and C6''] or [C3'' and C5'']), 128.2 ([C3'' and C5''] or [C2'' and C6'']), 144.4 (C1''). IR (neat) 2918, 1603, 1496, 1475, 1452, 1382 cm^{-1}. MS (ESI, positive ion) *m/z* 493 (30), 492 (100), 308 (8), 307 (M+Na[^{11}B], 40), 306 (M+Na[^{10}B], 12). HRMS (FI, positive ion) *m/z* found 284.1953, $C_{18}H_{25}{}^{11}BO_2$ ($M^{+\bullet}$) requires 284.1948. Anal. Calcd for $C_{18}H_{25}BO_2$: C, 76.07; H, 8.87. Found C. 76.12; H, 8.90. $[\alpha]_D{}^{25}$ +18.0 (*c* 1.51, $CHCl_3$).



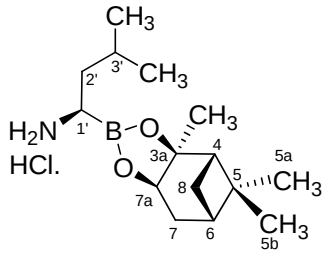
(3a*S*,4*S*,6*S*,7a*R*)-2-[(1*S*)-1-Chloro-3-methylbutyl]-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborole 44: Lithium diisopropylamide (LDA) was prepared fresh by addition of 2.5 M *n*-butyllithium in hexane (6.62 mL, 16.6 mmol) to a solution of diisopropylamine (1.68 g, 16.6 mmol) in THF (7 mL) at –78°C under a nitrogen atmosphere. The mixture was stirred at –78°C for 10 min before warming to ca. –20°C. In a separate flask, a mixture of the boronate **42** (3.26 g, 13.8 mmol) and dichloromethane (4.68 g, 55.2 mmol) in THF (45 mL) was stirred at –78°C under nitrogen, to which the freshly prepared LDA solution was added over 30 min. Stirring was continued at –78°C for 30 min before addition of a 1M $ZnCl_2$ solution in ether (22.2 mL, 22.2 mmol). The resulting mixture was left to warm to room temperature overnight. The mixture was concentrated and saturated ammonium chloride

solution was added (100 mL) and the resulting mixture stirred for 10 min. The mixture was extracted with hexane and the combined extracts were washed with brine, dried (Na_2SO_4) and the solvent was removed to afford the title compound **44** (3.68 g, 94%) as a pale brown oil. ^{1}H NMR analysis indicated the product contained ca. 10% unreacted starting material, consistent with the reported procedure;[1] the product was used in the next step without purification. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.85 (3H, s, $CH_3$5a), 0.90 (3H, d, *J* = 6.6 Hz, CH_3C3'), 0.93 (3H, d, *J* = 6.6 Hz, CH_3*C3'), 1.19 (1H, d, *J* = 11.2 Hz, H8), 1.29 (3H, s, $CH_3$5b), 1.41 (3H, s, C$\underline{H}_3$C3a), 1.59-1.65 (1H, m, H2'a), 1.77-1.83 (1H, m, H2'b), 1.84-1.94 (3H, m, H3', H7 and H6), 2.09 (1H, t, *J* = 5.6 Hz, H4), 2.23-2.27 (1H, m, H8*), 2.33-2.39 (1H, m, H7*), 3.53 (1H, dd, *J* = 5.9, 10.2 Hz, H1'), 4.36 (1H, dd, *J* = 1.4, 9.1 Hz, H7a). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 21.2 (C$\underline{H}_3$C3'), 22.9 (C$\underline{H}_3$*C3'), 23.9 ($CH_3$5a), 25.5 (C3'), 26.3 (C8), 27.0 ($CH_3$5b), 28.4 (C$\underline{H}_3$C3a), 35.3 (C7), 38.2 (C5), 39.3 (C6), 41.5 (br, C1'), 42.7 (C2'), 51.1 (C4), 78.5 (C7a), 86.6 (C3a). IR (neat) 2956, 2927, 1468, 1377, 1342 cm^{-1}. MS (ESI, negative ion) *m/z* 318 (5%), 317 (M+MeO[^{11}B,^{37}Cl], 40), 316 (M+MeO[^{10}B,^{37}Cl], 30), 315 (M+MeO[^{11}B,^{35}Cl], 100), 314 (M+MeO[^{10}B,^{35}Cl], 35), 304 (15), 303 (M+OH[^{11}B,^{37}Cl], 65), 302 (M+OH[^{10}B,^{37}Cl], 35), 301 (M+OH[^{11}B,^{35}Cl], 95), 300 (M+OH[^{10}B,^{35}Cl], 35). HRMS (ESI, positive ion) *m/z* found 307.1600, $C_{15}H_{26}{}^{11}B^{35}ClNaO_2^+$ (M+Na$^+$) requires 307.1607. $[\alpha]_D^{25}$ +32.7 (*c* 1.10, $CHCl_3$).



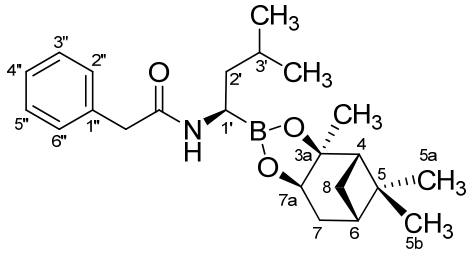
***N*,*N*-Bis(trimethylsilyl)-{(1*R*)-3-methyl-1-[(3a*S*,4*S*,6*S*,7a*R*)-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl]butyl}amine 40:** To a stirred solution of boronate **44** (3.50 g, 12.3 mmol) in THF (35 mL) at −78°C under nitrogen was added a solution of lithium hexamethyldisilazide (2.26 g, 13.5 mmol) in THF (14 mL) over 30 min. The resulting mixture was left to warm to room temp overnight. The mixture was concentrated and suspended in hexane (60 mL) and stirred for 1h. This suspension was filtered through celite and the celite pad washed with further hexane (100 mL). The

filtrate was concentrated to afford the title compound **40** (4.55 g, 90%) as a dense pale brown oil which was used in subsequent reactions without purification. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.12 (18H, s, 2 × $(CH_3)_3Si$), 0.84 (3H, s, $CH_3$5a), 0.88 (3H, d, *J* = 7.3 Hz, CH_3C3'), 0.90 (3H, d, *J* = 7.3 Hz, CH_3*C3'), 1.12 (1H, d, *J* = 10.9 Hz, H8), 1.23-1.30 (1H, m, H2'b), 1.29 (3H, s, $CH_3$5b), 1.37 (3H, s, C$\underline{H}_3$C3a), 1.60-1.66 (1H, m, H2'a), 1.76-1.92 (3H, m, H3', H7 and H6), 2.03 (1H, t, *J* = 5.2 Hz, H4), 2.18-2.23 (1H, m, H8*), 2.29-2.34 (1H, m, H7*), 2.65 (1H, dd, *J* = 7.3, 8.0 Hz, H1'), 4.28 (1H, dd, *J* = 1.9, 8.6 Hz, H7a). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 3.1 [$(CH_3)_3Si$], 22.8 ($\underline{C}H_3$C3'), 23.5 ($\underline{C}H_3$*C3'), 24.0 ($CH_3$5a), 25.3 (C3'), 26.4 (C8), 27.1 ($CH_3$5b), 28.4 ($\underline{C}H_3$C3a), 35.5 (C7), 38.1 (C5), 39.5 (C6), 40.1 (br, C1'), 45.2 (C2'), 51.4 (C4), 78.1 (C7a), 85.2 (C3a). IR (neat) 2954, 1451, 1375 cm^{-1}. MS (ESI, negative ion) *m/z* 418 (25%), 417 (100), 416 (25); anticipated molecular species not observed. $[\alpha]_D^{25}$ +5.5 (*c* 0.85, $CHCl_3$).



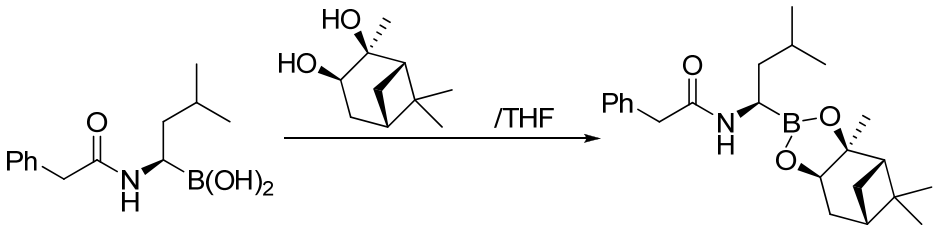
(1*R*)-3-Methyl-1-[(3a*S*,4*S*,6*S*,7a*R*)-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl]butan-1-amine hydrochloride 41: Hexamethyldisilazide **40** (1.023 g, 2.50 mmol) was stirred in dioxane (7.5 mL) and ether (2.5 mL) under nitrogen with ice cooling before addition of 2M HCl in ether (5.5 mL, 11.0 mmol) over 10 min. The mixture was brought to room temp and stirred for 4h, before concentrating and resuspending in hexane (10 mL), and stirring for a further 30 min, This mixture was then concentrated to dryness to afford the title compound **41** (0.724 g, 96%) as a pale brown sticky solid, that was used in the next step without purification. ^{1}H NMR (d_6-Acetone, 500 MHz) δ: 0.89 (3H, s, $CH_3$5a), 0.96 (6H, d, *J* = 6.6 Hz, $(CH_3)_2$C3'), 1.30 (3H, s, $CH_3$5b), 1.34 (1H, d, *J* = 9.7 Hz, H8), 1.45 (3H, s, C$\underline{H}_3$C3a), 1.63-1.69 (1H, m, H2'a), 1.86-1.94 (3H, m, H2'b and H6 and H7), 1.99 (1H, sept, *J* = 6.6 Hz, H3'), 2.05-2.11 (1H, m, H4 [overlaps with d_6-acetone]), 2.18-2.26 (1H, m, H8*), 2.35-2.42 (1H, m, H7*), 3.02 (1H, br s, H1'), 4.47 (1H, br d, *J* = 8.3 Hz, H7a), 8.52 (3H, br s, NH_3). ^{13}C NMR (d_6-

Acetone, 125 MHz) δ: 22.8 ($\underline{C}H_3C3'$), 22.9 ($\underline{C}H_3$*C3'), 24.2 ($CH_3$5a), 25.7 (C3'), 27.1 (C8), 27.4 ($CH_3$5b), 28.8 ($\underline{C}H_3$C3a), 35.7 (C7), 36.0 (br, C1'), 38.0 (C5), 39.3 (C2'), 40.3 (C6), 52.1 (C4), 79.1 (C7a), 84.3 (C3a). IR (nujol) 3417 (NH), 1634 cm^{-1}. MS (ESI, positive ion) *m/z* 267 (15), 266 (M–Cl[^{11}B], 100), 265 (M–Cl[^{10}B], 25). HRMS (ESI, positive ion) *m/z* found 266.2286, $C_{15}H_{29}{}^{11}BNO_2^+$ ($M–Cl^–$) requires 266.2286. $[\alpha]_D^{25}$ +12.7 (*c* 1.02, MeOH).

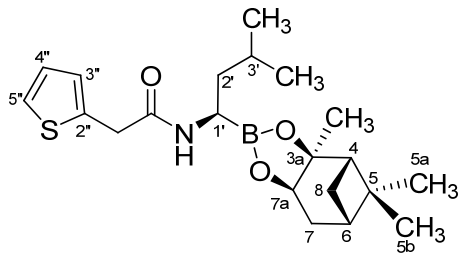


***N*-{(1*R*)-3-Methyl-1-[(3a*S*,4*S*,6*S*,7a*R*)-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl]butyl}-2-phenylacetamide 9:** To a solution of disilazide **40** (1.00 g, 2.44 mmol) in THF (20 mL) at −78°C under nitrogen, was added a prepared mixture of phenylacetic acid (0.366 g, 2.69 mmol) and phenylacetyl chloride (0.414 g, 2.69 mmol) in THF (5 mL) over 20 min. The resulting mixture was allowed to warm to room temp overnight. The mixture was concentrated, resuspended in ether, and washed with $NaHCO_3$ solution (2×), and brine, before drying (Na_2SO_4) and concentrating to afford a sticky solid (0.620 g, 66%). ^{1}H NMR and mass spectrometric analysis of this material revealed it consisted of a mixture of **9** and a phenylacetate-boronate adduct. The material was purified by chromatography on silica gel with a gradient of 7-60% ethyl acetate/hexane as eluant. The material isolated (R_f 0.18 in 7:3 hexane/ethyl acetate) was crystallised from hot hexane to afford the pure title compound **9** (0.250 g, 25%) as colourless prisms, mp 115-118°C. (A further 0.180 g of less pure material was recovered from the mother liquor). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.84 (3H, d, *J* = 5.0 Hz, CH_3C3'), 0.85 (3H, d, *J* = 5.0 Hz, CH_3*C3'), 0.86 (3H, s, $CH_3$5a), 1.28 (3H, s, $CH_3$5b), 1.31-1.47 (2H, m, H2'a and H2'b), 1.35 (1H, d, *J* = 10.7 Hz, H8), 1.43 (3H, s, $C\underline{H}_3$C3a), 1.47-1.56 (1H, m, H3'), 1.80-1.91 (2H, m, H7 and H6), 2.03 (1H, t, *J* = 5.4 Hz, H4), 2.11-2.19 (1H, m, H8*), 2.30-2.37 (1H, m, H7*), 2.86-2.92 (1H, m, H1'), 3.67 (2H, br s, $C\underline{H}_2$Ph), 4.28 (1H, dd, *J* = 2.1, 8.8 Hz, H7a), 6.21 (1H, br s, NH), 7.22-7.27 (2H, m, [H2'' and H6''] or [H3'' and H5'']), 7.29-7.39 (3H, m, [H3'' and H5''] or

[H2'' and H6''] and H4''). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 22.2 (<u>C</u>H_3C3'), 23.0 (<u>C</u>H_3*C3'), 24.1 ($CH_3$5a), 25.8 (C3'), 26.4 (C8), 27.2 ($CH_3$5b), 28.8 (<u>C</u>H_3C3a), 36.1 (C7), 38.2 (C5), 39.0 (br, C1'), 39.9 (C6), 40.2 (C2'), 40.4 (br, <u>C</u>H_2Ph), 51.8 (C4), 76.8 (C7a), 84.6 (C3a), 127.8 (C4''), 129.2 ([C2'' and C6''] or [C3'' and C5'']), 129.5 ([C3'' and C5''] or [C2'' and C6'']), 133.2 (C1''), 174.3 (CON). IR (KBr) 3185 (NH), 3068 (NH), 1599 (CON), 1558 cm^{-1}. IR ($CHCl_3$) 3423 (NH), 1651 (CON), 1594 cm^{-1}. MS (ESI, negative ion) *m/z* 766 ({2×M}–H, 40%), 765 ({2×M}–H, 70), 764 ({2×M}–H, 45), 420 (M+Cl[^{11}B,^{37}Cl], 15), 419 (M+Cl[^{10}B,^{37}Cl], 10), 418 (M+Cl[^{11}B,^{35}Cl], 50), 417 (M+Cl[^{10}B,^{35}Cl], 8), 383 (60), 382 (M–H[^{11}B], 100), 381 (M–H[^{10}B], 60). HRMS (ESI, positive ion) *m/z* found 406.2525, $C_{23}H_{34}{}^{11}BNNaO_3^+$ ($M+Na^+$) requires 406.2524. Anal. Calcd for $C_{23}H_{34}BNO_3$: C, 72.06; H, 8.94; N, 3.65. Found C, 72.07; H, 8.97; N, 3.58. $[\alpha]_D^{25}$ –22.9 (*c* 0.70, $CHCl_3$).

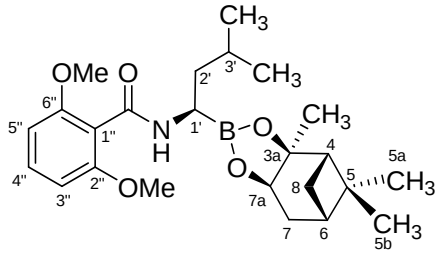


***N*-{(1*R*)-3-Methyl-1-[(3a*S*,4*S*,6*S*,7a*R*)-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl]butyl}-2-phenylacetamide 9:** (**Reformation from corresponding free boronic acid.**) A mixture of the boronic acid **31** (as obtained below) (65 mg, 0.26 mmol) and (+)-pinanediol (49 mg, 0.29 mmol) was stirred in THF (5 mL) overnight. The solution was concentrated, and the residue was crystallised from hot hexane to afford the title compound **9** (58 mg, 58%) as white needles, mp 115-118°C. $[\alpha]_D^{25}$ –22.8 (*c* 1.12, $CHCl_3$). Other characterisation data as given above.



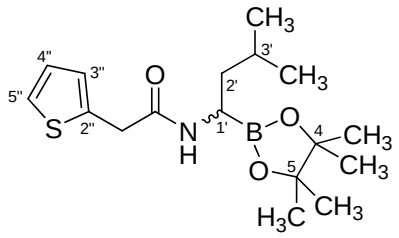
***N*-{(1*R*)-3-Methyl-1-[(3a*S*,4*S*,6*S*,7a*R*)-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl]butyl}-2-(2-thienyl)acetamide 13:** To a solution of disilazide **40** (2.256 g, 5.51 mmol) in THF (25 mL) at −78°C under nitrogen, was added a prepared mixture of 2-thiopheneacetic acid (0.861 g, 6.06 mmol) and 2-thiopheneacetyl chloride (0.970 g, 6.06 mmol) in THF (12 mL) over 30 min. The resulting mixture was allowed to warm to room temp overnight. The mixture was concentrated, and resuspended in ether, washed with 5% $NaHCO_3$ solution (3×) and brine, before drying (Na_2SO_4) and concentrating to afford 2.350 g of a sticky residue that was partially purified by chromatography on silica gel using a gradient of 10-80% ethyl acetate/hexane, to afford a mixture of the title compound **13** (R_f 0.37 in 40% ethyl acetate/hexane) and 2-thiophene acetic acid (co-eluted). The mixture was redissolved in ether and washed with 5% $NaHCO_3$ solution (3×) and brine, before drying (Na_2SO_4) and removing the solvent to afford the pure title compound **13** (1.108 g, 52%) as a pale yellow solid, mp 96-100 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.84 (3H, d, *J* = 6.6 Hz, CH_3C3'), 0.85 (3H, s, $CH_3$5a), 0.87 (3H, d, *J* = 6.6 Hz, CH_3*C3'), 1.28 (3H, s, $CH_3$5b), 1.32 (1H, d, *J* = 10.9 Hz, H8), 1.35-1.46 (2H, m, H2'a and H2'b), 1.41 (3H, s, C$\underline{H}_3$C3a), 1.54 (1H, sept, *J* = 6.6 Hz, H3'), 1.81-1.91 (2H, m, H7 and H6), 2.02 (1H, t, *J* = 5.4 Hz, H4), 2.14-2.19 (1H, m, H8*), 2.30-2.36 (1H, m, H7*), 2.95-3.00 (1H, m, H1'), 3.83 (2H, s, C$\underline{H}_2$Ar), 4.28 (1H, dd, *J* = 2.1, 8.9 Hz, H7a), 6.08 (1H, br s, NH), 6.94-6.96 (1H, m, H3''), 7.00 (1H, dd, *J* = 3.5, 5.3 Hz, H4''), 7.26 (1H, dd, *J* = 1.4, 5.3 Hz, H5''). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 22.1 (C$\underline{H}_3$C3'), 23.0 (C$\underline{H}_3$*C3'), 24.1 ($CH_3$5a), 25.7 (C3'), 26.4 (C8), 27.2 ($CH_3$5b), 28.7 (C$\underline{H}_3$C3a), 35.2 (C$\underline{H}_2$Ar), 35.9 (C7), 37.7 (br, C1'), 38.1 (C5), 39.7 (C6), 40.1 (C2'), 51.7 (C4), 77.2 (C7a), 84.8 (C3a), 125.8 (C5''), 127.4 (C4''), 127.7 (C3''), 134.9 (C2''), 172.1 (CON). IR (nujol) 3176 (NH), 3065 (NH), 1603 (CON), 1557, 1464 cm^{-1}. MS (ESI, negative ion) *m/z* 778 ({2×M}−H, 10%), 777 ({2×M}−H, 25), 776 ({2×M}−H, 10), 426 (M+Cl[^{11}B,^{37}Cl], 20), 425 (M+Cl[^{10}B,^{37}Cl], 15), 424

(M+Cl[^{11}B,^{35}Cl], 70), 423 (M+Cl[^{10}B,^{35}Cl], 10), 389 (80), 388 (M–H[^{11}B], 100), 387 (M–H[^{10}B], 85). HRMS (ESI, positive ion) *m/z* found 412.2073, $C_{21}H_{32}BNNaO_3S^+$ (M+Na^+) requires 412.2088. Anal. Calcd for $C_{21}H_{32}BNO_3S$: C, 64.78; H, 8.28; N, 3.60. Found C, 64.83; H, 8.18; N, 3.47. $[\alpha]_D^{25}$ –12.7 (*c* 0.99, $CHCl_3$).



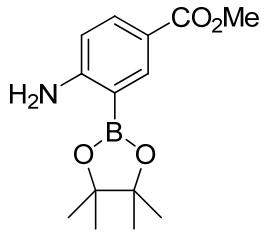
***N*-{(1*R*)-3-Methyl-1-[(3a*S*,4*S*,6*S*,7a*R*)-3a,5,5-trimethylhexahydro-4,6-methano-1,3,2-benzodioxaborol-2-yl]butyl}-2,6-dimethoxybenzamide 39:** To an ice-cooled stirred mixture of 4-(dimethylamino)pyridine (0.012 g, 0.099 mmol) and triethylamine (0.148 g, 1.46 mmol) in THF (3 mL) under nitrogen, was added a solution of 2,6-dimethoxybenzoyl chloride (0.146 g, 0.730 mmol) in THF (3 mL) over 10 min, during which a white precipitate formed. This suspension was stirred for 30 min before addition of a solution of amine hydrochloride **41** (0.200 g, 0.664 mmol) in DMF (2 mL), over 10 min. The resulting mixture was stirred on ice for a further 30 min, and then at room temp overnight. The mixture was concentrated, and resuspended in ethyl acetate, washed with 2% citric acid (2×), 5% $NaHCO_3$ (2×), brine, then dried (Na_2SO_4) and concentrated to afford a dense yellow glass that was purified by chromatography on silica gel using a gradient of 12-100% ethyl acetate/hexane to afford the title compound **39** (0.115 g, 40%) as dense colourless oil (R_f 0.24 in 1:1 hexane/ethyl acetate) that eventually solidified under high-vacuum to furnish a white solid, mp 48-53°C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.86 (3H, s, $CH_3$5a), 0.95 (3H, d, *J* = 6.6 Hz, CH_3C3'), 0.96 (3H, d, *J* = 6.6 Hz, CH_3*C3'), 1.28 (3H, s, $CH_3$5b), 1.42 (3H, s, C$\underline{H}_3$C3a), 1.49 (1H, d, *J* = 10.8 Hz, H8), 1.51-1.56 (2H, m, H2'a and H2'b), 1.75 (1H, sept, *J* = 6.6 Hz, H3'), 1.86-1.91 (2H, m, H7 and H6), 2.03-2.06 (1H, m, H4), 2.13-2.18 (1H, m, H8*), 2.30-2.37 (1H, m, H7*), 3.12-3.17 (1H, m, H1'), 3.80 (6H, s, 2×CH_3O), 4.30 (1H, dd, *J* = 2.1, 8.7 Hz, H7a), 6.55 (2H, d, *J* = 8.5 Hz, H3'' and H5''), 6.72 (1H, br s, NH), 7.30 (1H, t, *J* =

8.5 Hz, H4''). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 22.1 ($\underline{C}H_3$C3'), 23.2 ($\underline{C}H_3$*C3'), 24.1 ($CH_3$5a), 25.9 (C3'), 26.4 (C8), 27.3 ($CH_3$5b), 28.9 ($\underline{C}H_3$C3a), 36.1 (C7), 38.2 (C5), 38.4 (br, C1'), 39.9 (C6), 40.3 (C2'), 51.9 (C4), 56.1 (2×CH_3O), 76.9 (C7a), 84.3 (C3a), 104.3 (C3'' and C5''), 111.2 (C1''), 132.0 (C4''), 158.6 (C2'' and C6''), 167.6 (CON). IR (nujol) 3433 (NH), 3214 (NH), 1597 (CON), 1537 cm^{-1}. MS (ESI, negative ion) *m/z* 466 (M+Cl[^{11}B,^{37}Cl], 5%), 465 (M+Cl[^{10}B,^{37}Cl], 5), 464 (M+Cl[^{11}B,^{35}Cl], 12), 463 (M+Cl[^{10}B,^{35}Cl], 5), 461 (10), 460 (M+MeO[^{11}B], 50), 459 (M+MeO[^{10}B], 10), 429 (80), 428 (M–H[^{11}B], 100), 427 (M–H[^{10}B], 60). Anal. Calcd for $C_{24}H_{36}BNO_5$: C, 67.14; H, 8.45; N, 3.26. Found C, 67.09; H, 8.56; N, 3.17. $[\alpha]_D^{25}$ –31.5 (*c* 0.65, $CHCl_3$).



***N*-[3-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butyl]-2-(2-thienyl)acetamide 14:** To a solution of disilazide **45** (2.460 g, 6.88 mmol) in THF (25 mL) at –78°C under nitrogen, was added a prepared mixture of 2-thiopheneacetic acid (1.075 g, 7.57 mmol) and 2-thiopheneacetyl chloride (1.211 g, 7.57 mmol) in THF (14 mL) over 20 min. The resulting mixture was allowed to warm to room temp overnight. The mixture was concentrated, and resuspended in dichloromethane (70 mL), washed with 5% $NaHCO_3$ solution (3×) and brine, before drying (Na_2SO_4) and concentrating to afford 2.121 g of a pale brown sticky solid. Recrystallisation from ethyl acetate afforded the title compound **14** (0.898 g, 39%) as a white fluffy solid, mp 145-147 °C. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.85 (3H, d, *J* = 6.5 Hz, CH_3C3'), 0.86 (3H, d, *J* = 6.5 Hz, CH_3*C3'), 1.24 (12H, s, 4 × CH_3[pinacolyl]), 1.33-1.43 (2H, m, H2'a and H2'b), 1.54 (1H, sept, *J* = 6.5 Hz, H3'), 2.79-2.83 (1H, m, H1'), 3.87 (2H, s, $C\underline{H}_2$Ar), 6.32 (1H, br s, NH), 6.95 (1H, br d, *J* = 3.5 Hz, H3''), 7.01 (1H, dd, *J* = 3.5, 5.0 Hz, H4''), 7.28 (1H, d, *J* = 5.0 Hz, H5''). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 22.0 ($\underline{C}H_3$C3'), 23.2 ($\underline{C}H_3$*C3'), 25.0 [($\underline{C}H_3)_2$C4], 25.1 [($\underline{C}H_3)_2$C5], 26.0 (C3'), 34.1 ($\underline{C}H_2$Ar), 39.8 (C2'), 40.1 (br, C1'), 81.7 (C4 and C5), 126.1 (C5''), 127.5 (C4''), 128.0 (C3''), 133.9 (C2''), 173.5 (CON). IR (nujol) 3165 (NH), 1616 (CON), 1546 cm^{-1}. MS

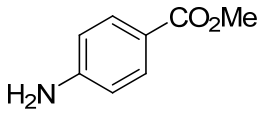
(ESI, negative ion) *m/z* 374 (M+Cl[^{11}B,^{37}Cl], 10%), 373 (M+Cl[^{10}B,^{37}Cl], 10), 372 (M+Cl[^{11}B,^{35}Cl], 25), 371 (M+Cl[^{10}B,^{35}Cl], 10), 337 (30), 336 (M–H[^{11}B], 100), 325 (M–H[^{10}B], 40). Anal. Calcd for $C_{17}H_{28}BNO_3S$: C, 60.54; H, 8.37; N, 4.15. Found C, 60.59; H, 8.32; N, 4.10.



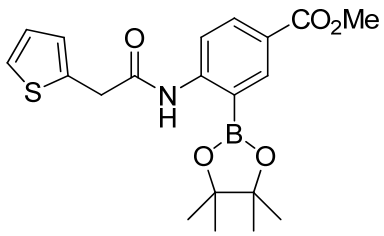
Methyl 4-amino-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate 46: A mixture of methyl 3-bromo-4-aminobenzoate **47** (1.500 g, 2.18 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) chloride (complex with dichloromethane) (0.090 g, 0.11 mmol) was stirred in dioxane (8 mL) under nitrogen before addition of triethylamine (0.883 g, 1.22 mL, 8.73 mmol) followed by pinacolborane (0.838 g, 0.950 mL, 6.55 mmol) over 10 min. The resultant mixture was heated at reflux for 5h. After cooling, the mixture was carefully quenched by addition of saturated NH_4Cl. The resultant mixture was concentrated and extracted with ethyl acetate (3×) and washed with brine (1×), dried (Na_2SO_4) and concentrated to afford a brown residue that was purified by chromatography on silica gel using a gradient of 7-60% ethyl acetate/hexane to afford the title compound **46** (0.639 g, 35%) (R_f 0.44 in 7:3 hexane/ethyl acetate) as a white solid, accompanied by the by-product methyl 4-aminobenzoate **49** (0.064 g, 19%) (R_f 0.27 in 7:3 hexane/ethyl acetate) as a white solid.

46: mp 189-191°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.35 (12H, s, 4×CH_3[pinacolyl]), 3.85 (3H, s, CH_3O), 5.20 (2H, br s, NH_2), 6.55 (1H, d, *J* = 8.6 Hz, H5), 7.88 (1H, dd, *J* = 2.2, 8.6 Hz, H6), 8.31 (1H, d, *J* = 2.2 Hz, H2). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.9 (4×CH_3[pinacolyl]), 51.4 (CH_3O), 83.8 (C4' and C5'), 113.9 (C5), 118.1 (C1), 134.4 (C6), 139.5 (C2), 157.3 (C4), 167.2 (CO_2), C3 not observed. IR (nujol) 3469 (NH), 3365 (NH), 3241 (NH), 1697 (CO_2), 1635, 1603 cm^{-1}. MS (ESI, positive ion) *m/z* 855 ({3×M}+H, 20%), 854 ({3×M}+H, 40), 853 ({3×M}+H, 25), 578 ({2×M}+Na, 30), 577 ({2×M}+Na, 65), 576 ({2×M}+Na, 45), 556 ({2×M}+H, 80), 555 ({2×M}+H, 100), 554 ({2×M}+H,

80), 553 ({2×M}+H, 25), 279 (30), 278 (M+H[^{11}B], 75), 277 (M+H[^{10}B], 50). HRMS (ESI, positive ion) *m/z* found 278.1568, $C_{14}H_{21}{}^{11}BNO_4^+$ ($M+H^+$) requires 278.1558. Anal. Calcd for $C_{14}H_{20}BNO_4$: C, 60.68; H, 7.27; N, 5.05. Found C, 60.68; H, 7.36; N, 4.83.

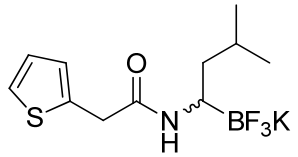


49: mp 108-112°C (lit.[9] 110-111°C). ^{1}H NMR (400 MHz, $CDCl_3$) consistent with the commercially available material.[9] IR (nujol) 3410 (NH), 3332 (NH), 3226 (NH), 1684 (CO_2), 1637, 1601 cm^{-1}. MS (ESI, negative ion) *m*/*z* 308 (100%), 151 (5), 150 (M–H, 30).

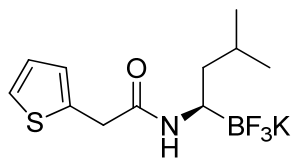


Methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-4-[(2-thienylacetyl)amino]benzoate 19: A mixture of aniline **46** (0.250 g, 0.902 mmol) and triethylamine (0.163 mL, 0.118 g, 1.17 mmol) in THF (6 mL) was stirred under nitrogen with ice-cooling before addition of a solution of 2-thiopheneacetyl choride (0.525 g, 3.3 mmol) in THF (2 mL) over 20 min. The mixture was stirred on ice for a further 45 min and then at room temp overnight. The mixture was filtered and the filtrate was concentrated. The residue was purified by chromatography on silica gel using a gradient of 7-60% ethyl acetate/hexane to afford the title compound **19** (0.187 g, 52%) as a white solid, mp 130-135°C. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.33 (12H, s, 4×CH_3[pinacolyl]), 3.90 (3H, s, CH_3O), 3.94 (2H, s, CH_2), 7.02 (1H, dd, *J* = 3.5, 5.0 Hz, H4''), 7.04-7.05 (1H, m, H3''), 7.27 (1H, dd, *J* = 1.0, 5.0 Hz, H5''), 8.11 (1H, dd, *J* = 2.0, 8.7 Hz, H6), 8.44 (1H, d, *J* = 2.0 Hz, H2), 8.60 (1H, d, *J* = 8.7 Hz, H5), 9.59 (1H, br s, NH). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.8 (4×CH_3[pinacolyl]), 39.7 (CH_2), 52.0 (CH_3O), 84.7 (C4' and C5'), 118.8 (C5), 124.5 (C1), 125.5 (C5''), 127.2 (C3'' and C4''), 134.3 (C6), 135.5 (C2''), 138.1 (C2), 148.2 (C4), 166.6 (CO_2), 168.5 (CON), C3 not observed. IR (nujol) 3312 (NH), 3105 (NH), 1717 (CO_2), 1690 (CON), 1608, 1586 cm^{-1}. IR ($CHCl_3$) 3354 (NH), 1715 (CO_2), 1702 (CON), 1615 (weak), 1588 cm^{-1}.

MS (ESI, positive ion) *m/z* 804 ({2×M}+H, 50%), 803 ({2×M}+H, 95), 802 ({2×M}+H, 70), 403 (25), 402 (M+H[^{11}B], 100), 401 (M+H[^{10}B], 40). HRMS (ESI, positive ion) *m/z* found 424.1362, $C_{20}H_{24}BNNaO_5S^+$ $(M+Na)^+$ requires 424.1360. Anal. Calcd for $C_{20}H_{24}BNO_5S$: C, 59.86; H, 6.03; N, 3.49. Found C, 59.82; H, 6.05; N, 3.43.

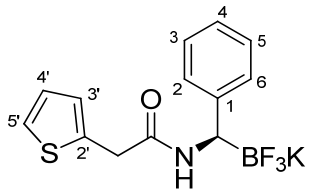


Potassium trifluoro{3-methyl-1-[(2-thienylacetyl)amino]butyl}borate 18: To a solution of pinacol ester **14** (0.270 g, 0.80 mmol) in methanol (9 mL) was added 4.5 M $KHF_{2(aq)}$ (1.7 mL, 7.7 mmol) {NOTE: KHF_2 is corrosive and discolours glassware after prolonged exposure.} The resulting mixture was stirred for 1h, and concentrated to dryness. The residue, a white solid, was extracted with hot acetone (2×), and the combined filtered extracts were concentrated to a volume of ca. 2 mL. Ether (50 mL) was added and the resultant precipitate was collected and dried to afford the title compound **18** (0.231 g, 91%) as a white solid, mp 230-245 °C (dec). ^{1}H NMR (d_6-acetone/few drops d_6-DMSO, 500 MHz) δ: 0.82 (3H, d, *J* = 6.5 Hz, CH_3C3), 0.84 (3H, d, *J* = 6.5 Hz, CH_3*C3), 1.20-1.29 (2H, m, H2a and H2b), 1.63 (1H, sept, *J* = 6.5 Hz, H3), 3.00-3.06 (1H, m, H1), 3.64 (1H, d, *J* = 15.5 Hz, C<u>H</u>aHbAr), 3.72 (1H, d, *J* = 15.5 Hz, CHa<u>H</u>bAr), 6.24 (1H, br d, *J* = 9.5 Hz, NH), 6.92-6.95 (2H, m, H3' and H5'), 7.25 (1H, dd, *J* = 1.0, 5.0 Hz, H5'). ^{13}C NMR (d_6-acetone/few drops d_6-DMSO, 125 MHz) δ: 22.8 (<u>C</u>H_3C3), 24.5 (<u>C</u>H_3*C3), 26.0 (C3), 38.5 (<u>C</u>H_2Ar), 42.0 (br, C1), 42.6 (C2), 125.0 (C5'), 126.7 (C3' or C4'), 127.3 (C4' or C3'), 140.1 (C2'), 169.1 (CON). ^{19}F NMR (d_6-acetone/few drops d_6-DMSO, 376 MHz) δ: – 148.5 (3F, s, BF_3). IR (nujol) 3282 (NH), 3091 (NH), 1644 (CON), 1613, 1563 cm^{-1}. MS (ESI, negative ion) *m/z* 279 (20%), 278 (M–K[^{11}B], 100), 277 (M–K[^{10}B], 40). Anal. Calcd for $C_{11}H_{16}BF_3KNOS$: C, 41.65; H, 5.08; N, 4.42. Found C, 41.59; H, 5.16; N, 4.51.



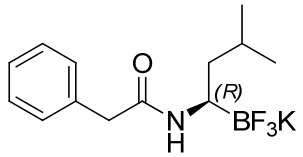
Potassium trifluoro{(1*R*)-3-methyl-1-[(2-thienylacetyl)amino]butyl}borate 17: Pinanediol boronate ester **13** (0.300 g, 0.77 mmol) was dissolved in methanol (9 mL) before addition of 4.5 M $KHF_{2(aq)}$ (1.7 mL, 7.7 mmol) {NOTE: KHF_2 is corrosive and discolours glassware after prolonged exposure.} The resulting mixture was stirred for 1h, and concentrated to dryness. The residue, a white solid, was extracted with hot acetone (2×), during which, only low solubility was apparent. The combined filtered extracts were concentrated to a volume of ca. 3 mL. Ether (50 mL) was added and the resultant small precipitate was collected and dried to afford the title compound **17** (0.060 g, 25%) as an off-white solid. The remaining residue was extracted with further portions of hot acetone, and the combined filtered extracts were concentrated to afford additional **17** (0.047 g, 19%) as a white solid. (Total yield; 0.107 g, 44%).* mp 235-245 °C dec. $[\alpha]_D^{25}$ –11.7 (*c* 0.52, MeOH). Other characterisation data consistent with that reported above for racemic compound **18**.

* The remaining residue was extracted with hot methanol, and the combined filtered extracts were concentrated to afford additional material (0.211 g, 86%). The ^{1}H NMR spectrum of this material supported the structure **17**, but its composition was assumed to contain significant inorganic impurity, as indicated by the quantity isolated.

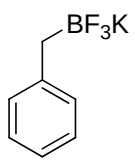


Potassium trifluoro{(*R*)-phenyl[(2-thienylacetyl)amino]methyl}borate 30: To a stirred solution of boronate **10**[6] (0.59 g, 1.4 mmol) in methanol (5 mL) was added 4.5 M $KHF_{2(aq)}$ (1.9 mL, 8.7 mmol) and the resulting suspension was stirred at room temperature for 30 min. {NOTE: KHF_2 is corrosive and discolours glassware after prolonged exposure.} The mixture was then concentrated to dryness and extracted with hot acetone. The extracts were filtered and concentrated and the residue recrystallised from acetone/ether to afford the title compound **30** (85 mg, 17 %) as an off-white solid, mp 128-129°C. ^{1}H NMR (500 MHz, CD_3OD) δ: 3.78 (1H, br s, CHB), 4.39 (2H, br s, CH_2), 6.97 (1H, d, *J* = 3.6 Hz, H4'), 7.23-7.34 (7H, m, 5×Ph[H], H3' and H5'). ^{13}C NMR (500 MHz, CD_3OD) δ: 37.9 (CB), 44.3

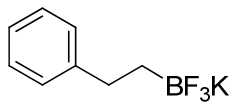
(CH_2), 125.8 (C1), 126.5 (C4), 127.7 (C5'), 128.3 (C2 and C6), 128.6 (C3'), 129.5 (C4'), 138.1 (C3 and C5), 139.8 (C2'), 172.8 (CON). ^{19}F NMR (376 MHz, CD_3OD) δ: −152.7 (3F, s, BF_3). IR (nujol) 3292 (NH), 1650 (CON) cm^{-1}. HRMS (ESI, negative ion) *m/z* found 298.0690, $C_{13}H_{12}BF_3NOS^-$ [M–K^+] requires 298.0693. $[\alpha]_D^{25}$ −4.3 (*c* 0.5, MeOH).



Potassium trifluoro{(1*R*)-3-methyl-1-[(phenylacetyl)amino]butyl}borate 11: Pure boronate **9** (0.150 g, 0.39 mmol) was dissolved with stirring in methanol (4 mL) before addition of 4.5 M $KHF_{2(aq)}$ (0.8 mL, 3.60 mmol). {NOTE: KHF_2 is corrosive and discolours glassware after prolonged exposure.} The resulting mixture was stirred at room temp for 1h, before concentrating to dryness. The resulting white solid was collected by filtration and washed several times with hot ether, followed by a small amount of water. The residue was dried to afford the title compound **11** (0.078 g, 64%) as white powder, mp 279-285°C. ^{1}H NMR (d_6-DMSO, 500 MHz) δ: 0.76 (6H, d, *J* = 6.5 Hz, 2×CH_3), 1.02-1.13 (2H, m, 2×H2), 1.47 (1H, sept, *J* = 6.5 Hz, H3), 2.74-2.83 (1H, m, H1), 3.30-3.39 (2H, m, C<u>H</u>$_2$Ph [overlaps with H_2O peak]), 6.44 (1H, br d, *J* = 9.5 Hz, NH), 7.17-7.19 (1H, m, H4'), 7.20-7.28 (4H, m, H2', H3', H5' and H6'). ^{13}C NMR (d_6-DMSO, 125 MHz) δ: 22.5 (CH_3), 23.9 (CH_3*), 24.7 (C3), 39.2-40.1 (m, C1, [overlaps with d_6-DMSO peak]), 42.2 (C2), 43.0 (<u>C</u>H_2Ph), 125.8 (C4'), 127.9 ([C2'' and C6''] or [C3'' and C5'']), 129.0 ([C3'' and C5''] or [C2'' and C6'']), 137.7 (C1'), 168.7 (CON). ^{19}F NMR (d_6-DMSO, 376 MHz) δ: −114.9 (3F, s, BF_3). IR (nujol) 3323 (NH), 1612 (CON), 1547 cm^{-1}. MS (ESI, negative ion) *m/z* 273 (55%), 272 (M–K[^{11}B], 100), 271 (M–K[^{10}B], 65). HRMS (ESI, negative ion) *m/z* found 272.1444, $C_{13}H_{18}{}^{11}BF_3NO^-$ (M–K^+) requires 272.1439. $[\alpha]_D^{25}$ −9.6 (*c* 0.47, MeOH).



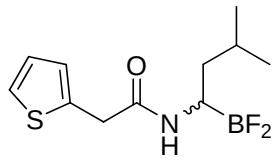
Potassium benzyl(trifluoro)borate 27: Benzylboronic acid pinacol ester **25** (1.000 g, 4.60 mmol) was dissolved with stirring in methanol (15 mL) before addition of 4.5 M $KHF_{2(aq)}$ (9.2 mL, 41.4 mmol). {NOTE: KHF_2 is corrosive and discolours glassware after prolonged exposure.} The resulting mixture was stirred at room temp for 1h, before concentrating to dryness. The resulting white solid was collected by filtration and washed several times with hot ether, followed by small amounts of water to furnish the title compound **27** (0.338 g, 37%) as a white solid. The aqueous filtrate was concentrated and suspended in water (6 mL) and a further 90 mg (10%) of **27** was collected by filtration. The filtrate was re-concentrated to dryness and extracted with hot acetone; the acetone extract was filtered and concentrated to dryness to afford a further 0.149 g (16%) of pure **27**. (Total yield, 0.577 g, 64%). mp 204-212°C. ^{1}H NMR (400 MHz, d_6-Acetone) δ: 1.65 (2H, br s, CH_2), 6.88 (1H, br t, J = 7.3 Hz, H4), 7.02-7.06 (2H, m, H3 and H5), 7.10-7.12 (2H, m, H2 and H6). ^{13}C NMR (125 MHz, d_6-Acetone) δ: 30.0-30.4 (m, CH_2, [overlaps with d_6-acetone peak]), 122.9 (C4), 127.8 ([C2 and C6] or [C3 and C5]), 129.7 ([C3 and C5] or [C2 and C6]), 148.0 (C1). IR (nujol) 1494, 1455 cm^{-1}. MS (ESI, negative ion) *m*/*z* 160 (10%), 159 (M–K[^{11}B], 100), 158 (M–K[^{10}B], 40). Anal. Calcd for $C_7H_7BF_3K$: C, 42.45; H, 3.56. Found C, 42.36; H, 3.39.



Potassium trifluoro(2-phenylethyl)borate 26: Boronate **43** (0.862 g, 3.03 mmol) was stirred in methanol (10 mL) before addition of 4.5 M $KHF_{2(aq)}$ (6.0 mL, 27.0 mmol). {NOTE: KHF_2 is corrosive and discolours glassware after prolonged exposure.} The resulting mixture was stirred at room temp for 1h, before concentrating to dryness. The resulting white solid was collected by filtration and washed several times with hot ether. The remaining white solid was extracted several times with hot acetone; the extracts were filtered and concentrated to dryness to afford the title compound **26** (0.274 g, 43%) as a white solid, mp 305-312°C. ^{1}H NMR (500 MHz, d_6-Acetone) δ: 0.46-0.52 (2H, m, CH_2B), 2.55-2.59 (2H, m, C$\underline{H}_2$Ph), 7.04-7.06 (1H, m, H4), 7.17-7.20 (4H, m, H2, H3, H4, H5). ^{13}C NMR (125 MHz, d_6-Acetone) δ: 22.5 (v br, CH_2B), 33.0 (Ph$\underline{C}H_2$), 125.1 (C4), 128.6 ([C2 and C6] or [C3 and C5]), 128.7

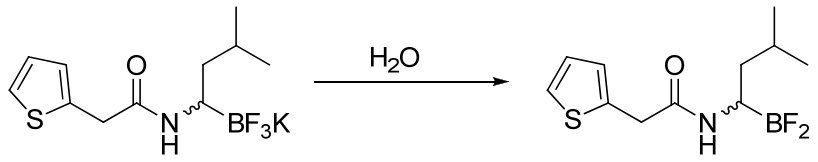
([C3 and C5] or [C2 and C6]), 149.4 (C1). ^{19}F NMR (d_6-Acetone, 376 MHz) δ: –141.9 to – 141.8 (3F, m, BF_3). IR (nujol) 1455 cm^{-1}. MS (FI, positive ion) *m/z* 155 (10%), 154 ({M–KF}$^{+\bullet}$[^{11}B], 100), 153 ({M–KF}$^{+\bullet}$[^{10}B], 30). Anal. Calcd for $C_8H_9BF_3K$: C, 45.31; H, 4.28. Found C, 45.36; H, 4.31.

General procedure for the preparation of difluorboranes. The boronate (1 equiv) was dissolved and stirred in methanol and THF as indicated before addition of 4.5 M $KHF_{2(aq)}$ (ca. 9 equiv) and the resulting suspension was stirred at room temp for 1h. {NOTE: KHF_2 is corrosive and discolours glassware after prolonged exposure.} The mixture was concentrated to dryness and the solid residue was collected by filtration and washed several times with hot ether. The remaining solid was suspended in water (~ 20 mL/mmol starting material) and stirred overnight. The material was collected by filtration and washed with a little water, and dried to afford the difluoroborane.

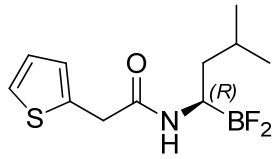


***N*-[1-(Difluoroboryl)-3-methylbutyl]-2-(2-thienyl)acetamide 16:** To a solution of pinacol ester **14** (0.300 g, 0.89 mmol) in methanol (9 mL) was added 4.5 M $KHF_{2(aq)}$ (1.9 mL, 8.6 mmol) as described in the general procedure. {NOTE: KHF_2 is corrosive and discolours glassware after prolonged exposure.} Following the ether washes, the remaining residue was stirred overnight in water (15 mL), and the resulting solid was collected by filtration and washed with a little water, and dried to afford the title compound **16** (0.176 g, 77%) as a fine white powder, mp 145-148 °C. ^{1}H NMR (d_6-Acetone, 500 MHz) δ: 0.90 (6H, d, *J* = 6.6 Hz, 2×CH_3), 1.36 (2H, t, *J* = 7.4 Hz, 2×H2), 1.69 (1H, sept, *J* = 6.6 Hz, H3), 2.63-2.69 (1H, m, H1), 4.20 (2H, s, C$\underline{H}_2$Ar), 7.03 (1H, dd, *J* = 3.6, 5.1 Hz, H4'), 7.09-7.11 (1H, m, H3'), 7.44 (1H, d, *J* = 1.3, 5.1 Hz, H5'), 9.64 (1H, br s, NH). ^{13}C NMR (d_6-Acetone, 125 MHz) δ: 22.5 (CH_3), 23.3 (CH_3*), 26.7 (C3), 31.5 (br, $\underline{C}H_2$Ar), 40.1 (C2), 46.9 (v br, C1), 126.9 (C5'), 128.1 (C4'), 128.9 (C3'), 133.9 (C2'), 178.2 (CON). ^{19}F NMR (d_6-Acetone, 376 MHz) δ: –150.3 (1F, br s, BF), –142.5 (1F, br s, BF). IR (nujol) 3354 (NH), 1636 (CON), 1525 cm^{-1}. IR ($CHCl_3$) 3398 (NH), 1607 (CON), 1538 cm^{-1}. MS (FI, positive ion) *m/z* 260 (10%), 259 (M$^{+\bullet}$[^{11}B], 100), 258 (M$^{+\bullet}$[^{10}B], 25).

HRMS (FI, positive ion) *m/z* found 259.1009, $C_{11}H_{16}{}^{11}BF_2NOS$ ($M^{+\bullet}$) requires 259.1014. Anal. Calcd for $C_{11}H_{16}BF_2NOS$: C, 50.99; H, 6.22; N, 5.41. Found C, 50.91; H, 6.18; N, 5.39.



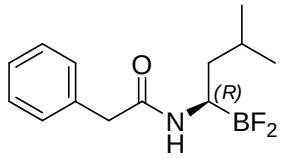
***N*-[1-(Difluoroboryl)-3-methylbutyl]-2-(2-thienyl)acetamide 16 (from pure trifluoroborate):** Potassium trifluoroborate **18** (60 mg, 0.19 mmol) was suspended in water (10 mL). The material was largely solubilised after a few minutes, before gradual precipitation was observed. The mixture was stirred overnight. The resultant precipitate was collected by filtration and dried to afford the title compound **16** (38 mg, 78%) as a white powder. Characterisation data consistent with that given above.



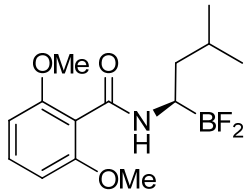
***N*-[(1*R*)-1-(Difluoroboryl)-3-methylbutyl]-2-(2-thienyl)acetamide 15:** To a stirred solution of boronate **13** (0.336 g, 0.863 mmol) in methanol (9 mL) was added 4.5 M $KHF_{2(aq)}$ (1.8 mL, 8.10 mmol) as described in the general procedure. {NOTE: KHF_2 is corrosive and discolours glassware after prolonged exposure.} Following the ether washes, the remaining residue was stirred overnight in water (25 mL), and the resulting solid was collected by filtration and washed with a little water, and dried to afford the title compound **15** (0.126 g, 56%) as a white powder. The mother liquor was concentrated to a volume of ca. 10 mL, from which, upon standing for a few hours, a second crop of material crystallised, which was collected and dried to furnish the trifluoroborate **17** (0.028 g, 10%) as fine white needles.

15: mp 125-135°C. Anal. Calcd for $C_{11}H_{16}BF_2NOS$: C, 50.99; H, 6.22; N, 5.41. Found C, 50.91; H, 6.15; N, 5.39. $[\alpha]_D^{25}$ −55.7 (*c* 0.82, Acetone). Other characterisation data consistent with that reported above for racemic compound **16**.

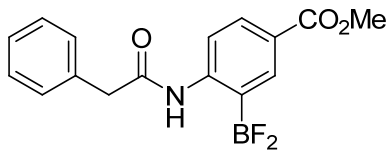
17: mp 235-245 °C dec. Other characterisation data consistent with that reported above.



***N*-[(1*R*)-1-(Difluoroboryl)-3-methylbutyl]-2-phenylacetamide 12:** Crude boronate **9** obtained above (contaminated with phenylacetate adduct, 1.296 g, 3.38 mmol) was dissolved and stirred in methanol (15 mL) and THF (5 mL) before addition of 4.5 M $KHF_{2(aq)}$ (7 mL, 31.5 mmol) as described in the general procedure. Following workup the title compound **12** (0.335 g, 39% [assumes 100% purity of starting material]) was obtained as a white powder, mp 157-160°C. ^{1}H NMR (d_6-Acetone, 500 MHz) δ: 0.90 (6H, d, J = 6.7 Hz, 2×CH_3), 1.35 (2H, t, J = 7.5 Hz, 2×H2), 1.69 (1H, sept, J = 6.7 Hz, H3), 2.62-2.68 (1H, m, H1), 3.93 (2H, s, C$\underline{H}_2$Ph), 7.32-7.41 (5H, m, Ph[H]), 9.7 (1H, br s, NH). ^{13}C NMR (d_6-Acetone, 125 MHz) δ: 22.3 (CH_3), 22.6 (CH_3*), 26.7 (C3), 37.2 ($\underline{C}H_2$Ph), 40.2 (br, C2), 46.5 (br, C1), 128.6 (C4'), 129.7 ([C2' and C6'] or [C3' and C5']), 130.2 ([C3' and C5'] or [C2' and C6']), 133.6 (C1'), 179.1 (CON). ^{19}F NMR (d_6-Acetone, 376 MHz) δ: −150.4 (1F, br s, BF), −142.7 (1F, br s, BF*). IR (nujol) 3364 (NH), 3340 (NH), 1636 (CON), 1524 cm^{-1}. IR ($CHCl_3$) 3623 (NH), 1606 (CON), 1536 cm^{-1}. MS (FI, positive ion) *m/z* 254 (20%), 253 ($M^{+\bullet}$[^{11}B], 100), 252 ($M^{+\bullet}$[^{10}B], 30). HRMS (FI, positive ion) *m/z* found 253.1452, $C_{13}H_{18}{}^{11}BF_2NO$ ($M^{+\bullet}$) requires 253.1450. Anal. Calcd for $C_{13}H_{18}BF_2NO$: C, 61.69; H, 7.17; N, 5.53. Found C, 61.70; H, 7.12; N, 5.33. $[\alpha]_D^{25}$ −53.1 (*c* 0.89, Acetone).

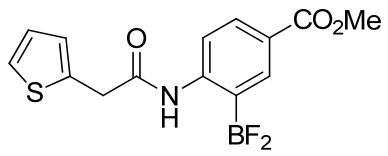


***N*-[(1*R*)-1-(Difluoroboryl)-3-methylbutyl]-2,6-dimethoxybenzamide 35:** Boronate **39** (0.279 g, 0.65 mmol) was treated with 4.5 M $KHF_{2(aq)}$ (1.3 mL, 5.85 mmol) in methanol (7 mL) and THF (2 mL) as described in the general procedure. Following workup the title compound **35** (0.117 g, 60%) was furnished as a white powder, mp 129-134°C. ^{1}H NMR (d_6-Acetone, 500 MHz) δ: 0.96 (6H, d, *J* = 6.6 Hz, 2×CH_3), 1.47 (2H, t, *J* = 7.3 Hz, 2×H2), 1.79 (1H, sept, *J* = 6.6 Hz, H3), 2.74-2.80 (1H, m, H1), 3.87 (6H, s, 2×CH_3O), 6.79 (2H, d, *J* = 8.7 Hz, H3' and H5'), 7.52 (1H, t, *J* = 8.7 Hz, H4'), 9.66 (1H, br s, NH). ^{13}C NMR (d_6-Acetone, 125 MHz) δ: 22.7 (CH_3), 23.4 (CH_3*), 26.8 (C3), 40.5 (C2), 46.5 (v br, C1), 56.7 (2×CH_3O), 105.1 (C3' and C5'), 106.7 (C1'), 134.9 (C4'), 159.7 (C2' and C6'), 172.4 (CON). IR (nujol) 3375 (NH), 1601 (CON), 1576, 1509, 1459 cm^{-1}. MS (FI, positive ion) *m/z* 300 (20%), 299 ($M^{+\bullet}$[^{11}B], 100), 298 ($M^{+\bullet}$[^{10}B], 25). HRMS (FI, positive ion) *m/z* found 299.1530, $C_{14}H_{20}{}^{11}BF_2NO_3$ ($M^{+\bullet}$) requires 299.1504. $[\alpha]_D^{25}$ –43.0 (*c* 0.64, Acetone).

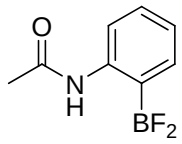


Methyl 3-(difluoroboryl)-4-[(phenylacetyl)amino]benzoate 21: Boronate **3**[8] (0.640 g, 1.62 mmol) was treated with 4.5 M $KHF_{2(aq)}$ (3.3 mL, 14.9 mmol) in methanol (10 mL) and THF (7 mL) as described in the general procedure. Following workup the title compound **21** (0.345 g, 67%) was furnished as a white powder, mp 262-267°C. ^{1}H NMR (500 MHz, d_6-Acetone) δ: 3.87 (3H, s, CH_3), 4.18 (2H, s, CH_2), 7.25 (1H, d, *J* = 8.4 Hz, H5), 7.32-7.36 (1H, m, H4'), 7.38-7.41 (2H, m, H3' and H5'), 7.46-7.48 (2H, m, H2' and H6'), 7.95 (1H, dd, *J* = 2.0, 8.4 Hz, H6), 8.20 (1H, br d, *J* = 2.0 Hz, H2), 12.14 (1H, br s, NH). ^{13}C NMR (125 MHz, d_6-Acetone) δ: 41.9 (CH_2), 52.3 (CH_3O), 117.3 (C5), 128.8 (C4'), 129.6 (C1), 129.8 (C3' and C5'), 130.31 (C6), 130.33 (C2' and C6'), 133.5 (C1'), 133.8 (C2), 140.6 (C4), 166.9 (CO_2), 173.7 (CON), C3 not observed. IR (nujol) 3306 (NH), 3259 (NH), 3187

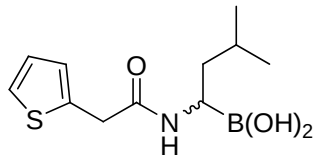
(NH), 1721 (CO_2), 1648 (CON), 1613 cm^{-1}. MS (ESI, negative ion, CH_3CN) *m/z* 634 (15%), 633 ({2×M}–H, 50), 632 ({2×M}–H, 30), 349 (15), 348 (M+MeO[^{11}B], 55), 347 (M+MeO[^{10}B], 30), 341 (30), 340 (M–HF–F+{2×MeO}[^{11}B], 100), 339 (M–HF–F+{2×MeO}[^{10}B], 50), 327 (10), 326 (M–HF–F+OH+MeO[^{11}B], 60), 325 (M–HF–F+OH+MeO[^{10}B], 30), 317 (45), 316 (M–H[^{11}B], 95), 315 (M–H[^{10}B], 70). Anal. Calcd for $C_{16}H_{14}BF_2NO_3$: C, 60.60; H, 4.45; N, 4.42. Found C, 60.52; H, 4.39; N, 4.38.



Methyl 3-(difluoroboryl)-4-[(2-thienylacetyl)amino]benzoate 22: Boronate **19** (0.396 g, 0.98 mmol) was treated with 4.5 M $KHF_{2(aq)}$ (2.0 mL, 9.00 mmol) in methanol (7 mL) and THF (4.5 mL) as described in the general procedure. Following workup the title compound **22** (0.259 g, 81%), was obtained as an off-white solid, mp 235-244°C. ^{1}H NMR (500 MHz, d_6-Acetone) δ: 3.88 (3H, s, CH_3), 4.42 (2H, s, CH_2), 7.04 (1H, dd, *J* = 3.5, 5.0 Hz, H4'), 7.18 (1H, dd, *J* = 1.0, 3.5 Hz, H3'), 7.27 (1H, d, *J* = 8.3 Hz, H5), 7.49 (1H, dd, *J* = 1.0, 5.0 Hz, H5'), 7.96 (1H, dd, *J* = 1.7, 8.3 Hz, H6), 8.21 (1H, d, *J* = 1.7 Hz, H2), 12.24 (1H, br s, NH). ^{13}C NMR (125 MHz, d_6-Acetone) δ: 36.1 (CH_2), 52.3 (CH_3O), 117.3 (C5), 127.2 (C5'), 128.2 (C4'), 129.2 (C3'), 129.6 (C1), 130.3 (C6), 133.79 (C2), 133.81 (C2'), 140.6 (C4), 166.9 (CO_2), 172.6 (CON), C3 not observed. ^{19}F NMR (d_6-Acetone, 376 MHz) δ: –130.9 (2F, br s, BF_2). IR (nujol) 3309 (NH), 3260 (NH), 3184 (NH), 1718 (CO_2), 1649 (CON), 1614 cm^{-1}. IR (CH_3CN) 3626 (NH), 3539 (NH), 1721 (CO_2), 1634 (CON), 1616, 1588 (weak) cm^{-1}. MS (ESI, negative ion, CH_3CN) *m/z* 355 (20%), 354 (M+MeO[^{11}B], 70), 353 (M+MeO[^{10}B], 35), 347 (35), 346 (M–HF–F+{2×MeO}[^{11}B], 95), 345 (M–HF–F+{2×MeO}[^{10}B], 50), 333 (20), 332 (M–HF–F+OH+MeO[^{11}B], 80), 331 (M–HF–F+OH+MeO[^{10}B], 50), 323 (40), 322 (M–H[^{11}B], 100), 321 (M–H[^{10}B], 80). Anal. Calcd for $C_{14}H_{12}BF_2NO_3S$: C, 52.04; H, 3.74; N, 4.33. Found C, 51.91; H, 3.72; N, 4.24.

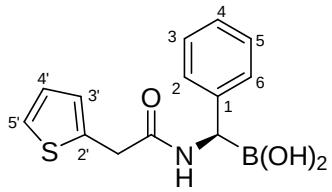


***N*-[2-(Difluoroboryl)phenyl]acetamide 23:** Boronate **20** (0.440 g, 1.69 mmol) was treated with 4.5 M $KHF_{2(aq)}$ (3.6 mL, 16.2 mmol) in methanol (10 mL) and THF (7 mL) as described in the general procedure. Following workup the title compound **23** (0.194 g, 63%), was obtained as a white solid, mp 245-250°C. ^{1}H NMR (500 MHz, d_6-Acetone) δ: 2.50 (3H, s, CH_3), 7.08 (1H, br d, *J* = 7.6 Hz, H6), 7.27 (1H, dt, *J* = 1.3, 7.6 Hz, H4), 7.31 (1H, dt, *J* = 1.7, 7.6 Hz, H5), 7.53 (1H, br d, *J* = 7.6 Hz, H3), 11.67 (1H, br s, NH). ^{13}C NMR (125 MHz, d_6-Acetone) δ: 21.7 (CH_3), 116.5 (C6), 127.8 (C4), 128.9 (C5), 132.2 (C3), 137.3 (C1), 171.6 (CON), C2 not observed. IR (nujol) 3334 (NH), 1642 (CON), 1606, 1586 cm^{-1}. IR (CH_3CN) 3624 (NH), 3541 (NH), 1640 (CON), 1606, 1586 cm^{-1}. MS (ESI, negative ion, CH_3CN) *m/z* 207 (10%), 206 (M–HF–F+{2×MeO}[^{11}B], 50), 205 (M–HF–F+{2×MeO}[^{10}B], 20), 183 (40), 182 (M–H[^{11}B], 100), 181 (M–H[^{10}B], 60). Anal. Calcd for $C_8H_8BF_2NO$: C, 52.52; H, 4.41; N, 7.66. Found C, 52.48; H, 4.48; N, 7.54.

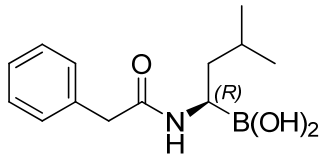


{3-Methyl-1-[(2-thienylacetyl)amino]butyl}boronic acid 33 (from trifluoroborate, TMSCl method): Potassium trifluoroborate **18** (60 mg, 0.19 mmol) was dissolved in acetonitrile (2.5 mL) and water (1.0 mL) before addition of trimethylsilylchloride (71 mg, 84 μL, 0.66 mmol). The resultant mixture was stirred for 1h, before concentrating to a volume of ca. 1 mL. Saturated sodium bicarbonate solution (0.5 mL) and water (1.5 mL) were added to the residue, before extraction with ethyl acetate (2 ×). The combined extracts were washed with near saturated brine, dried (Na_2SO_4), and the solvent was removed to afford the title compound **33** (37 mg, 77%) as a white powder, mp 119-126 °C. ^{1}H NMR (d_6-Acetone, 500 MHz) δ: 0.86 (3H, d, *J* = 6.7 Hz, CH_3), 0.87 (3H, d, *J* = 6.7 Hz, CH_3*), 1.29-1.34 (1H, m, H2a), 1.44-1.49 (1H, m, H2b), 1.69 (1H, sept, *J* = 6.7 Hz, H3), 2.76-2.79 (1H, m, H1), 3.86 (2H, s,

C<u>H</u>$_2$Ar), 6.97 (1H, dd, *J* = 3.5, 5.1 Hz, H4'), 7.01-7.03 (1H, m, H3'), 7.34 (1H, d, *J* = 1.0, 5.1 Hz, H5'), 7.99 (1H, br s, NH). ^{13}C NMR (d$_6$-Acetone, 125 MHz) δ: 23.3 (CH_3), 23.6 (CH_3*), 26.5 (C3), 34.4 (br, <u>C</u>H$_2$Ar), 41.3 (C2), 44.6 (v br, C1), 126.0 (C5'), 127.8 (C4'), 127.9 (C3'), 136.7 (C2'), 173.3 (CON). IR (nujol) 3402 (NH), 3186 (NH), 1647 (CON), 1615, 1547 cm^{-1}. MS (ESI, negative ion, H_2O) *m/z* 492 ({2×M}–H_2O–H, 25%), 491 ({2×M}–H_2O–H), 90), 490 ({2×M}–H_2O–H, 50), 269 (15), 268 (M+MeO–H_2O[^{11}B], 65), 267 (M+MeO–H_2O[^{10}B], 20), 255 (25), 254 (M–H[^{11}B], 100), 253 (M–H[^{10}B], 40), 237 (5), 236 (M–H_2O–H[^{11}B], 35), 235 (M–H_2O–H[^{10}B], 10). Anal. Calcd for $C_{11}H_{18}BNO_3S$: C, 51.78; H, 7.11; N, 5.49. Found C, 51.90; H, 7.02; N, 5.42.

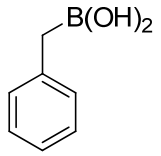


{(*R*)-Phenyl[(2-thienylacetyl)amino]methyl}boronic acid 32: To a solution of trifluoroborate **30** (0.81 g, 2.4 mmol) in CH_3CN/ H_2O (1:1, 8 mL), was added trimethylsilylchloride (0.91 mL, 7.2 mmol). The resulting suspension was stirred at room temperature for 1h, after which the mixture was concentrated *in vacuo* and the product recrystallised from water. This gave the title compound **32** as an off-white solid (0.34 g, 52 %), mp 90-100°C (lit.[6] 90-100°C). ^{1}H and ^{13}C NMR (CD_3OD) consistent with that reported.[6] IR (nujol) 3201 (NH and OH), 1671 (CON) cm^{-1}. HRMS (ESI, positive ion) $C_{13}H_{14}BNNaO_3S$ [M+Na$^+$] requires 298.0706; Found 298.0680. $[\alpha]_D^{25}$ –4.2 (*c* 0.4, MeOH) (lit.[6] –3.1 (*c* 2.1, CD_3OD).

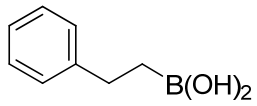


{(1*R*)-3-Methyl-1-[(phenylacetyl)amino]butyl}boronic acid 31: Trifluoroborate **11** (50 mg, 0.16 mmol) was dissolved in CH_3CN (4 mL) and water (0.5 mL) before addition of trimethylsilyl chloride (61 mg, 0.071 mL, 0.56 mmol). The mixture was stirred at room temp for 1h, before addition of saturated $NaHCO_{3(aq)}$ (0.5 mL), drying (Na_2SO_4) and concentrating to afford a white solid that was

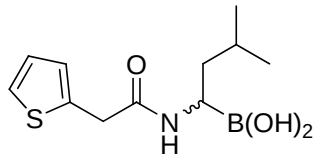
resuspended in acetone and filtered. The filtrate was concentrated to afford the title compound **31** (21 mg, 53%) as a white solid. (Characterisation given below for material prepared by an alternative synthetic route.)



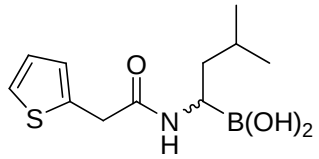
Benzylboronic acid 29: Trifluoroborate **27** (300 mg, 1.52 mmol) was dissolved in CH_3CN (12 mL) and water (3 mL) before addition of trimethylsilyl chloride (626 mg, 0.726 mL, 5.76 mmol). The mixture was stirred at room temp for 1h. The resultant solution was concentrated to a volume of ~ 2 mL, and the resultant precipitate was collected to furnish the title compound **29** (94 mg, 46%) as a fluffy white solid, that degraded to a sticky material with a complex NMR spectrum within a few days at –20°C and immediately when placed under high-vacuum. The product was stable in d_6-acetone solution for at least 6 weeks at room temperature. mp and IR not obtained due degradation. ^{1}H NMR (500 MHz, d_6-Acetone) δ: 2.22-2.24 (2H, m, CH_2), 6.80 (2H, s, 2×BOH), 7.07 (1H, br t, J = 6.7 Hz, H4), 7.14-7.22 (4H, m, H2, H3, H5, H6). ^{13}C NMR (125 MHz, d_6-Acetone) δ: 25.2 (v br, CH_2), 125.1 (C4), 128.9 ([C2 and C6] or [C3 and C5]), 129.7 ([C3 and C5] or [C2 and C6]), 141.5 (C1). MS (ESI, negative ion) *m/z* 207 ({4×M}–{3×H_2O}–H, 25%), 489 ({4×M}–{3×H_2O}–H, 95), 488 ({4×M}–{3×H_2O}–H, 85), 487 ({4×M}–{3×H_2O}–H, 35), 300 ({2×M}–H_2O–H+{2×MeO}, 50), 299 ({2×M}–H_2O–H+{2×MeO}, 95), 298 ({2×M}–H_2O–H+{2×MeO}, 50), 268 ({2×M}–{2×H_2O)+MeO, 20), 267 ({2×M}–{2×H_2O)+MeO, 100), 266 ({2×M}–{2×H_2O)+MeO, 50), 254 ({2×M}–H_2O–H, 15), 253 ({2×M}–H_2O–H, 70), 252 ({2×M}–H_2O–H, 40), 150 (5), 149 (M–H_2O+MeO[^{11}B], 30), 148 (M–H_2O+MeO[^{10}B], 8).



(2-Phenylethyl)boronic acid 28: Trifluoroborate **26** (100 mg, 0.47 mmol) was dissolved in CH_3CN (2.5 mL) and water (1.5 mL) before addition of trimethylsilyl chloride (252 mg, 0.726 mL, 5.76 mmol). The mixture was stirred at room temp for 1h. The resultant solution was concentrated to a volume of ~ 0.5 mL, and the resultant precipitate was collected to furnish the title compound **28** (45 mg, 64%) as a fluffy white solid, mp 58-63°C (lit.[9] 76-81°C). ^{1}H NMR (d_6-Acetone) identical with that of the commercially available material. IR (nujol) 3301 (OH), 1496, 1456 cm^{-1}. MS (ESI, negative ion, H_2O) *m*/*z* 282 ({2×M}–H_2O–H, 15%), 281 ({2×M}–H_2O–H, 50) 280 ({2×M}–H_2O–H, 25), 164 (5), 163 (M–H_2O+MeO[^{11}B], 35), 162 (M–H_2O+MeO[^{10}B], 10), 150 (15), 149 (M–H[^{11}B], 100), 148 (M–H[^{10}B], 40).

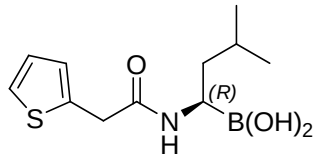


{3-Methyl-1-[(2-thienylacetyl)amino]butyl}boronic acid 33 (from difluroborane): Difluoroborane **16** (60.0 mg, 0.23 mmol) was dissolved in acetonitrile (4.0 mL) and water (3.1 mL) before addition of 8% $NH_{3(aq)}$ solution (0.9 mL). The mixture was stirred for 2h at room temp before concentrating carefully to a volume of ca. 1.5 mL at which point substantial precipitation was observed. The mixture was extracted with ethyl acetate (2×). The combined extracts were washed with near saturated brine, dried (Na_2SO_4) and the solvent was removed to afford the title compound **33** (47.7 mg, 81%) as a white solid. Characterisation data consistent with that given above.

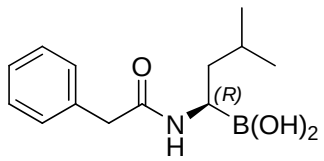


{3-Methyl-1-[(2-thienylacetyl)amino]butyl}boronic acid 33 (from trifluoroborate, aqueous ammonia method): Potassium trifluoroborate **18** (30.0 mg, 0.095 mmol) was dissolved in acetonitrile (2 mL) and water (1.4 mL) before addition of 8% $NH_{3(aq)}$ solution (0.4 mL). The mixture was stirred

overnight at room temp before concentrating carefully to a volume of ca. 1.5 mL at which point substantial precipitation was observed. The mixture was extracted with ethyl acetate (2×). The combined extracts were washed with near saturated brine, dried (Na_2SO_4) and the solvent was removed to afford the title compound **33** (18.7 mg, 78%) as a white solid. Characterisation data consistent with that given above.

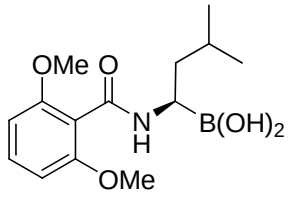


{(1*R*)-3-Methyl-1-[(2-thienylacetyl)amino]butyl}boronic acid 34: The difluoroborane **15** (50 mg, 0.19 mmol) was stirred in CH_3CN (4 mL) and water (3 mL) before addition of an 8% $NH_{3(aq)}$ solution (0.75 mL). The mixture was stirred at room temp for 2h before concentrating carefully under vacuum to a volume of ~ 2 mL, at which point substantial precipitation was observed. The mixture was extracted with ethyl acetate and the combined extracts washed with brine, dried (Na_2SO_4), and the solvent was removed to afford the title compound **34** (42 mg, 85%) as a pale yellow solid, mp 83-89°C. Anal. Calcd for $C_{11}H_{18}BNO_3S$: C, 51.78; H, 7.11; N, 5.49. Found C, 51.79; H, 7.08; N, 5.48. $[\alpha]_D^{25}$ –29.2 (*c* 1.05, Acetone). Other characterisation data consistent with that reported above for racemic compound **33**.



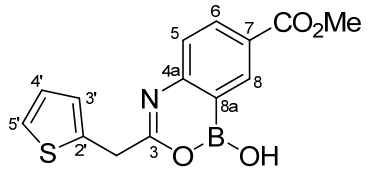
{(1*R*)-3-Methyl-1-[(phenylacetyl)amino]butyl}boronic acid 31: The difluoroborane **12** (100 mg, 0.39 mmol) was stirred in CH_3CN (7.5 mL) and water (5 mL) before addition of an 8% $NH_{3(aq)}$ solution (1.5 mL). The mixture was stirred at room temp for 2h before concentrating carefully under vacuum to a volume of ~ 3 mL, at which point substantial precipitation was observed. The mixture was extracted with ethyl acetate and the combined extracts washed with brine, dried (Na_2SO_4), and the solvent was removed to afford the title compound **31** (80 mg, 81%) as a white solid, mp 85-100°C. (Compound was stable under high-vacuum at room temp for several hours. Some degradation was evident (by ^1H NMR)

after storage at room temp for a few weeks.) ^{1}H NMR (d_6-Acetone, 500 MHz) δ: 0.84 (3H, d, *J* = 6.6 Hz, CH_3), 0.85 (3H, d, *J* = 6.6 Hz, CH_3*), 1.26-1.31 (1H, m, H2a), 1.41-1.47 (1H, m, H2b), 1.67 (1H, sept, *J* = 6.6 Hz, H3), 2.70-2.75 (1H, m, H1), 3.64 (2H, s, C<u>H</u>$_2$Ph), 7.23-7.39 (5H, m, Ph[H]), 7.92 (1H, br s, NH). ^{13}C NMR (d_6-Acetone, 125 MHz) δ: 23.3 (CH_3), 23.5 (CH_3*), 26.5 (C3), 40.2 (br, <u>C</u>H_2Ph), 41.5 (C2), 44.7 (v br, C1), 127.8 (C4'), 129.4 ([C2' and C6'] or [C3' and C5']), 130.1 ([C3' and C5'] or [C2' and C6']), 135.8 (C1'), 174.4 (br, CON). IR (nujol) 3408 (NH), 3203 (NH), 1643 (CON), 1614, 1602, 1546 cm^{-1}. MS (ESI, negative ion, H_2O) *m/z* 480 ({2×M}–H_2O–H, 20%), 479 ({2×M}–H_2O–H), 70), 478 ({2×M}–H_2O–H, 35), 263 (15), 262 (M+MeO–H_2O[^{11}B], 80), 261 (M+MeO–H_2O[^{10}B], 25), 249 (25), 248 (M–H[^{11}B], 100), 247 (M–H[^{10}B], 60), 231 (5), 230 (M–H_2O–H[^{11}B], 40), 229 (M–H_2O–H[^{10}B], 15). Anal. Calcd for $C_{13}H_{20}BNO_3$: C, 62.68; H, 8.09; N, 5.62. Found C, 62.72; H, 8.03; N, 5.49. $[\alpha]_D^{25}$ –34.6 (*c* 0.87, Acetone).



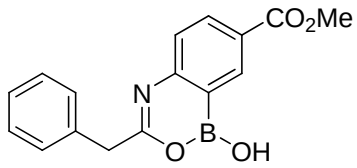
{(1*R*)-1-[(2,6-Dimethoxybenzoyl)amino]-3-methylbutyl}boronic acid 36: The difluoroborane **35** (40 mg, 0.13 mmol) was stirred in CH_3CN (1.5 mL) and water (1.5 mL) before addition of an 8% $NH_{3(aq)}$ solution (0.5 mL). The mixture was stirred at room temp for 2h before concentrating carefully under vacuum to a volume of ~ 1 mL, at which point substantial precipitation was observed. The mixture was extracted with ethyl acetate and the combined extracts washed with brine, dried (Na_2SO_4), and the solvent was removed to afford the title compound **36** (16 mg, 41%) as a white solid, mp 90-100°C. ^{1}H NMR (d_6-Acetone, 500 MHz) δ: 0.95 (6H, d, *J* = 6.7 Hz, 2×CH_3), 1.47-1.52 (1H, m, H2a), 1.65-1.71 (1H, m, H2b), 1.91 (1H, sept, *J* = 6.7 Hz, H3), 2.97-3.01 (1H, m, H1), 3.75 (6H, s, 2×CH_3O), 6.66 (2H, d, *J* = 8.7 Hz, H3' and H5'), 7.33 (1H, t, *J* = 8.7 Hz, H4'), 7.86 (1H, br s, NH). ^{13}C NMR (d_6-Acetone, 125 MHz) δ: 23.6 (CH_3), 23.7 (CH_3*), 26.5 (C3), 41.7 (C2), 44.6 (v br, C1), 56.5 (2×CH_3O), 105.1 (C3' and C5'), 113.3 (br, C1'), 132.3 (C4'), 159.0 (C2' and C6'), 168.5 (CON). IR (nujol) 3420

(NH), 3214 (NH), 1643 (CON), 1596, 1514, 1464 cm^{-1}. MS (ESI, negative ion, H_2O) *m/z* 586 ({2×M}–H_2O–H, 10%), 585 ({2×M}–H_2O–H), 20), 584 ({2×M}–H_2O–H, 10), 572 (15), 571 (60), 570 (30), 309 (5), 308 (M+MeO–H_2O[^{11}B], 45), 307 (M+MeO–H_2O[^{10}B], 10), 295 (20), 294 (M–H[^{11}B], 100), 293 (M–H[^{10}B], 40), 277 (5), 276 (M–H_2O–H[^{11}B], 15), 275 (M–H_2O–H[^{10}B], 5). HRMS (ESI, negative ion, H_2O) *m/z* found 294.1522, $C_{14}H_{21}{}^{11}BNO_5^-$ ($M–H^+$) requires 294.1518. Anal. Calcd for $C_{14}H_{22}BNO_5$: C, 56.97; H, 7.51; N, 4.75. Found C, 56.92; H, 7.45; N, 4.67. $[\alpha]_D^{25}$ –22.9 (*c* 0.34, Acetone).

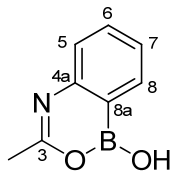


Methyl 1-hydroxy-3-(2-thienylmethyl)-1*H*-2,4,1-benzoxazaborinine-7-carboxylate 37: Difluoroborane **22** (50 mg, 0.16 mmol), was stirred in CH_3CN (4 mL) and water (2 mL) before addition of an 8% $NH_{3(aq)}$ solution (0.45 mL). The resulting mixture was stirred overnight, at which point substantial precipitation was observed. The mixture was concentrated carefully under vacuum to a volume of ~ 1 mL, and the material was collected by filtration and washed with a little water and dried to afford the title compound **37** (41 mg, 88%) as an off-white fine powder, mp 218-222°C. ^{1}H NMR (500 MHz, d_6-DMSO) δ: 3.81 (3H, s, CH_3), 3.87 (2H, br s, CH_2), 6.81-6.83 (2H, m, H3' and H4'), 7.33 (1H, dd, *J* = 1.6, 4.8 Hz, H5'), 7.61 (1H, br d, *J* = 8.4 Hz, H5), 7.91 (1H, dd, *J* = 2.1, 8.4 Hz, H6), 8.30 (1H, d, *J* = 2.1 Hz, H8), 12.34 (1H, br s, OH). ^{13}C NMR (125 MHz, d_6-DMSO) δ: 36.4 (CH_2), 51.8 (CH_3), 116.5 (C5), 125.8 (C5' and C7), 126.8 (C3' and C4'), 129.8 (C6), 134.6 (C2' or C8), 134.8 (C8 or C2'), 142.9 (br, C4a), 166.2 (CO_2), 169.4 (C3). IR (nujol) 3567 (OH), 1674 (CO_2), 1638 (C=N), 1613, 1591 cm^{-1}. MS (ESI, negative ion, CH_3CN) *m/z* 634 (15%), 633 (80), 632 (40), 347 (80), 346 (M–OH+{2×MeO}[^{11}B], 100), 345 (M–OH+{2×MeO}[^{10}B], 90), 333 (20), 332 (M+MeO[^{11}B], 80), 331 (M+MeO[^{10}B], 30), 319 (10), 318 (M+OH[^{11}B], 50), 317 (M+OH[^{10}B], 20), 301 (5), 300 (M–H[^{11}B],

15), 299 (M–H[^{10}B], 5). Anal. Calcd for $C_{14}H_{12}BNO_4S$: C, 55.84; H, 4.02; N, 4.65. Found C, 55.83; H, 4.05; N, 4.59.



Methyl 3-benzyl-1-hydroxy-1*H*-2,4,1-benzoxazaborinine-7-carboxylate 7: Difluoroborane **21** (100 mg, 0.34 mmol), was stirred in CH_3CN (6 mL) and water (2.5 mL) before addition of an 8% $NH_{3(aq)}$ solution (1.0 mL). The resulting mixture was stirred overnight, at which point substantial precipitation was observed. The mixture was concentrated carefully under vacuum to a volume of ~ 2 mL, and the material was collected by filtration and washed with a little water and dried to afford the title compound **7** (89 mg, 97%) as a fine white powder, mp 178-183°C (lit.[8] mp 187-192°C). $^1H/^{13}C$ NMR and MS data consistent with that reported.[8] IR (nujol) 3589 (OH), 1681 (CO_2), 1638 (C=N), 1610, 1586 cm^{-1}. Anal. Calcd for $C_{16}H_{14}BNO_4$: C, 65.12; H, 4.78; N, 4.75. Found C, 64.22; H, 4.92; N, 4.36.



3-Methyl-1*H*-2,4,1-benzoxazaborinin-1-ol 38: Difluoroborane **23** (75 mg, 0.41 mmol), was stirred in CH_3CN (3 mL) before addition of an 8% $NH_{3(aq)}$ solution (1.0 mL). The resulting mixture was stirred overnight, at which point substantial precipitation was observed. The mixture was concentrated carefully under vacuum to a volume of ~ 0.5 mL, and the material was collected by filtration and washed with a little water and dried to afford the title compound **38** (45 mg, 68%) as a white powder. A portion was dissolved in ~ 5 mL of a hot methanol/water mixture, filtered, and the filtrate was concentrated to dryness to afford an analytical sample as a white powder, mp 293-300°C (lit.[10] 293-294°C). (Material precipitates from d_6-DMSO solution after a few hours). ^1H NMR (d_6-DMSO) consistent with that reported.[10] ^{13}C NMR (125 MHz, d_6-DMSO) δ: 139.4 (C4a),* otherwise as reported.[10] IR (nujol) 3274 (OH), 3194 (OH), 1647 (C=N), 1603, 1583 cm^{-1}. MS (ESI, negative ion,

CH_3CN) *m*/*z* 483 ({3×M}–H, 25%), 482 ({3×M}–H, 100), 481 ({3×M}–H, 95), 480 ({3×M}–H, 30), 207 (25), 206 (M–OH+{2×MeO}[^{11}B], 80), 205 (M–OH+{2×MeO}[^{10}B], 50), 161 (5), 160 (M–H[^{11}B], 25), 159 (M–H[^{10}B], 10). MS (ESI, negative ion, H_2O) *m*/*z* 322 ({2×M}–H, 10%), 321 ({2×M}–H, 50), 320 ({2×M}–H, 30), 207 (10), 206 (M–OH+{2×MeO}[^{11}B], 80), 205 (M–OH+{2×MeO}[^{10}B], 30), 179 (10), 178 (M+OH[^{11}B], 70), 177 (M+OH[^{10}B], 25), 161 (20), 160 (M–H[^{11}B], 100), 159 (M–H[^{10}B], 50). Anal. Calcd for $C_8H_8BNO_2$: C, 59.69; H, 5.01; N, 8.70. Found C, 59.62; H, 4.91; N, 8.62.

* not reported.

NMR Spectra of new compounds

Figure S-1: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra ($CDCl_3$) of **42.**

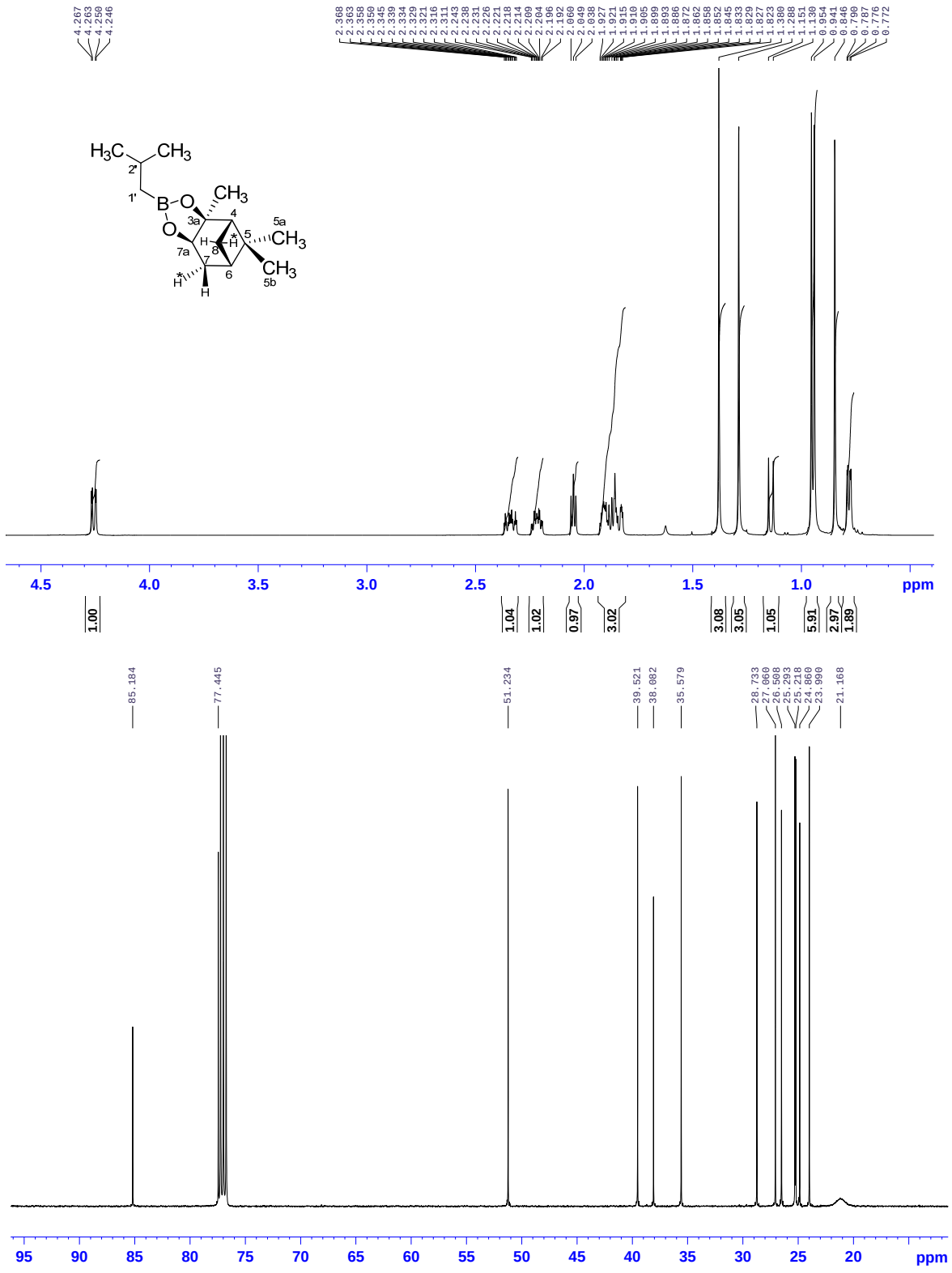
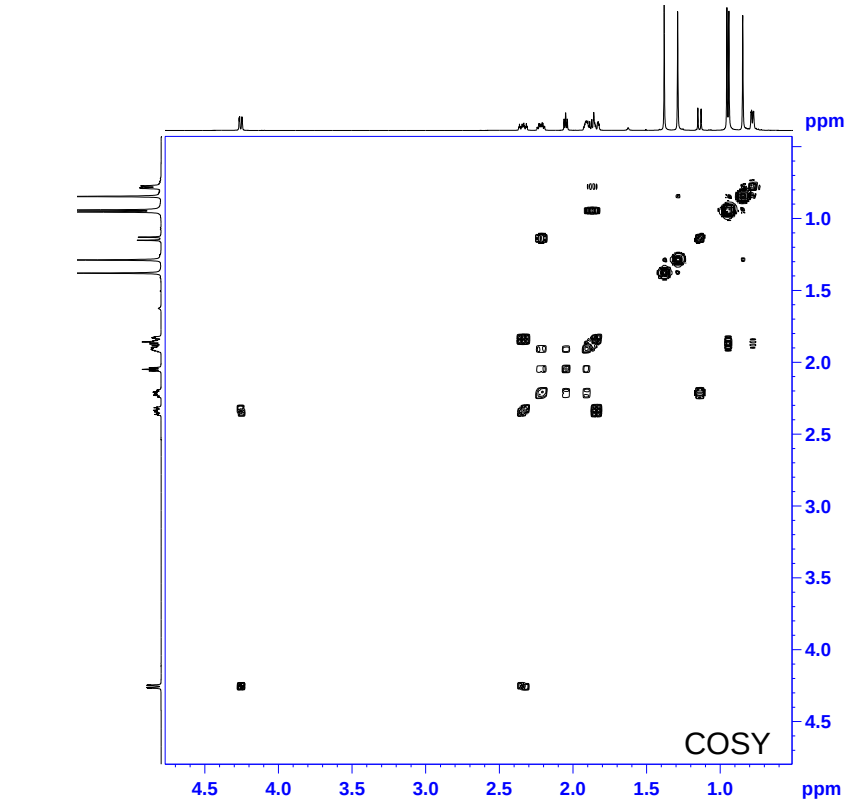


Figure S-2: 500 MHz [^{1}H,^{1}H] COSY (top) and NOESY (bottom) spectra ($CDCl_3$) for **42**. (Representative 2D spectra included for assignment of ^{1}H and ^{13}C spectra for pinanediol esters).



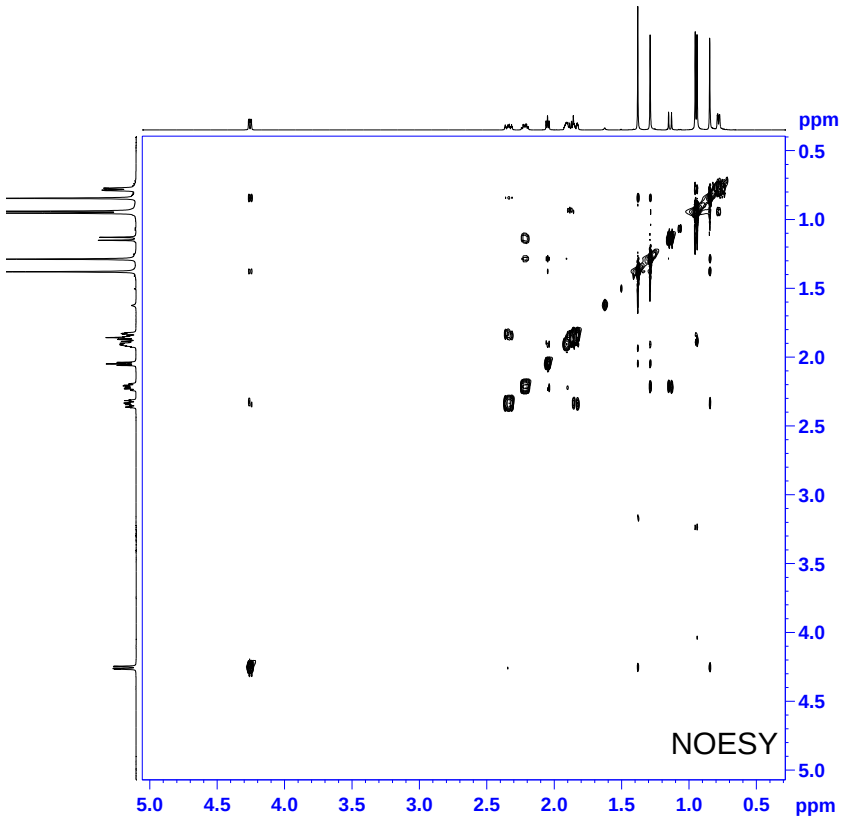


Figure S-3: [^{1}H,^{13}C] HSQC (500 MHz for ^{1}H) spectrum ($CDCl_3$) for **42.**
(Representative 2D spectrum included for assignment of ^{1}H and ^{13}C spectra for pinanediol esters).

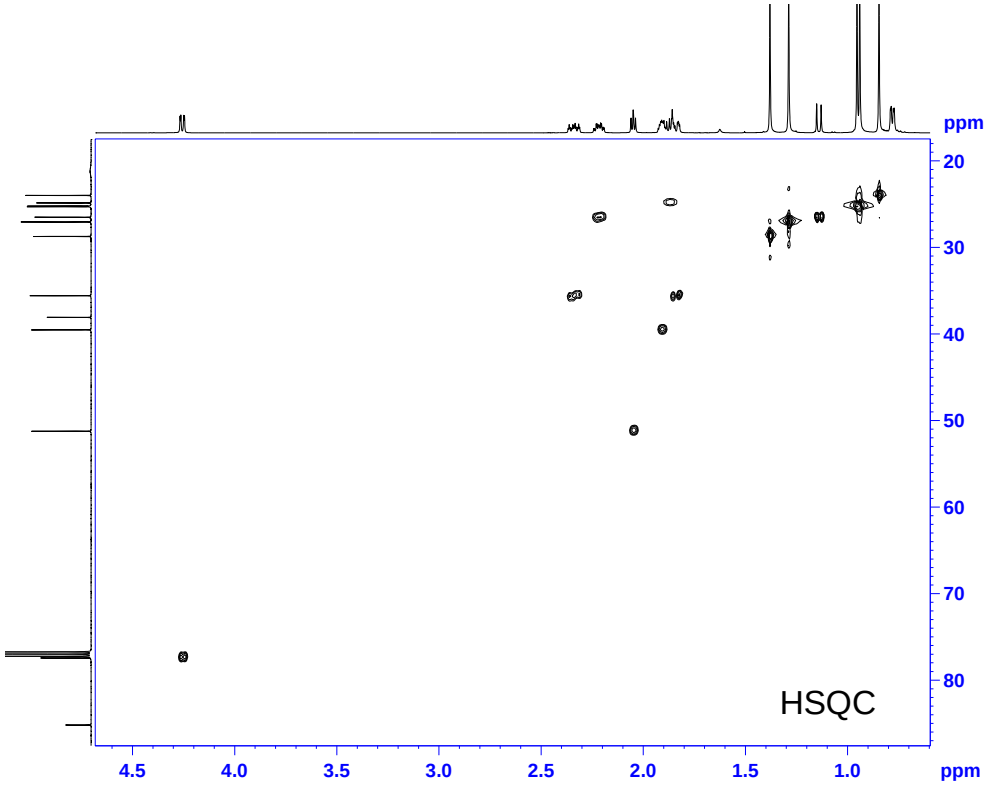


Figure S-4: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra ($CDCl_3$) of **9.**

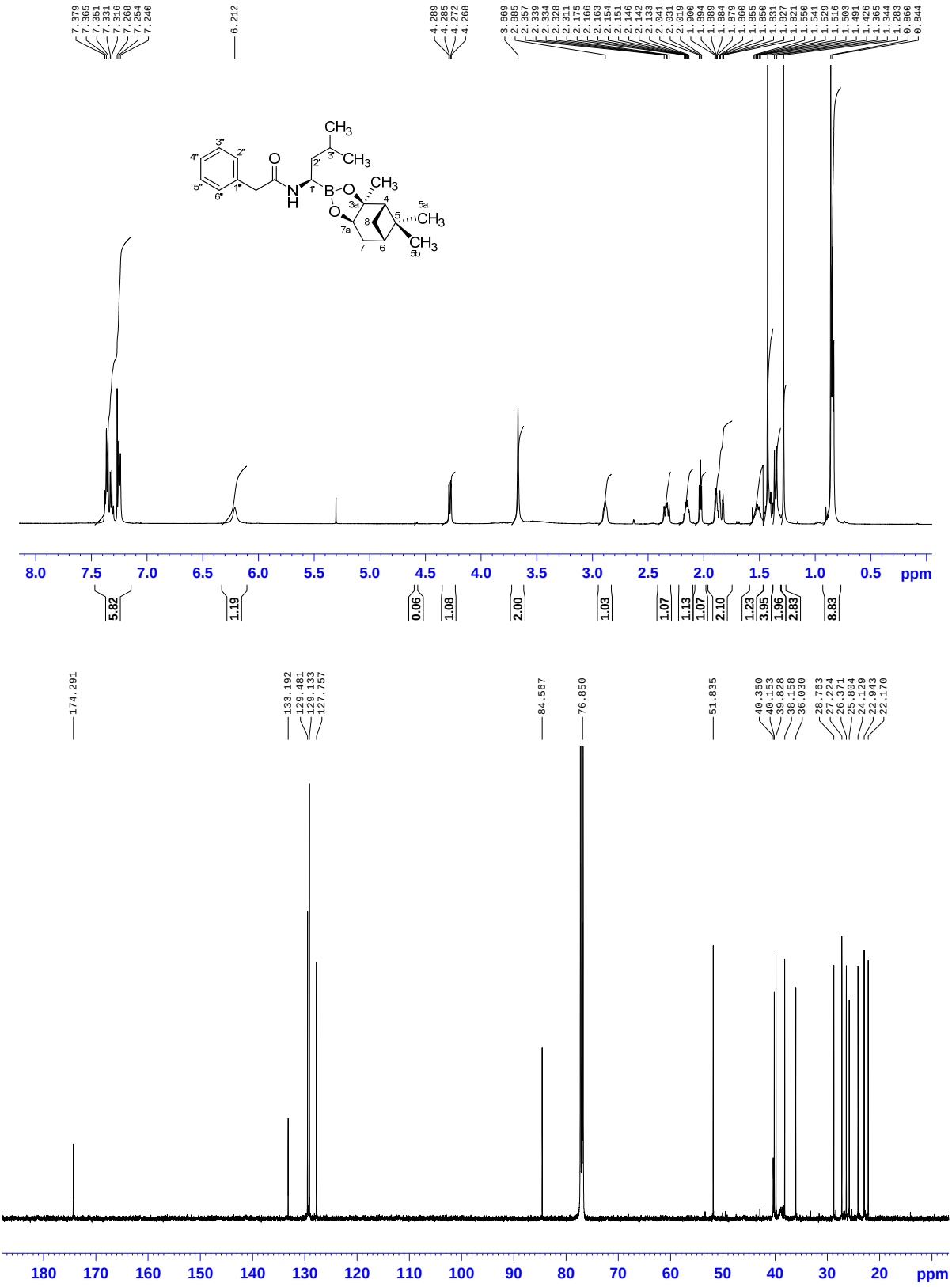


Figure S-5: [^{1}H,^{13}C] HSQC (500 MHz for ^{1}H) spectrum ($CDCl_3$) for **9.**

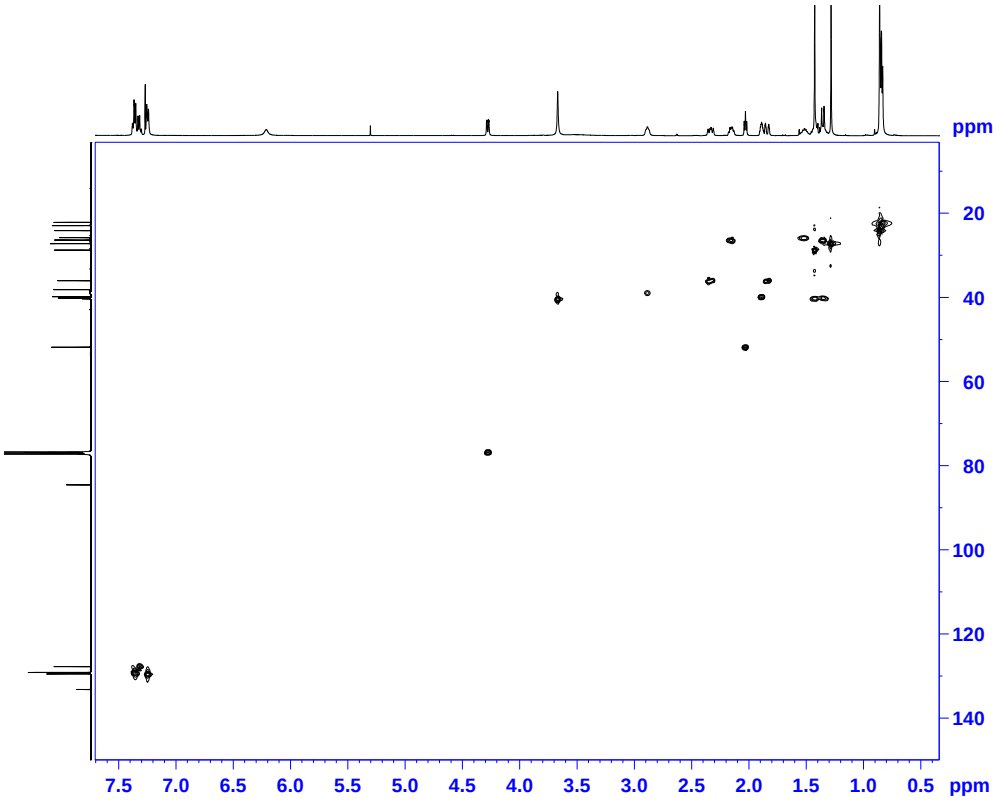


Figure S-6: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra ($CDCl_3$) of **13.**

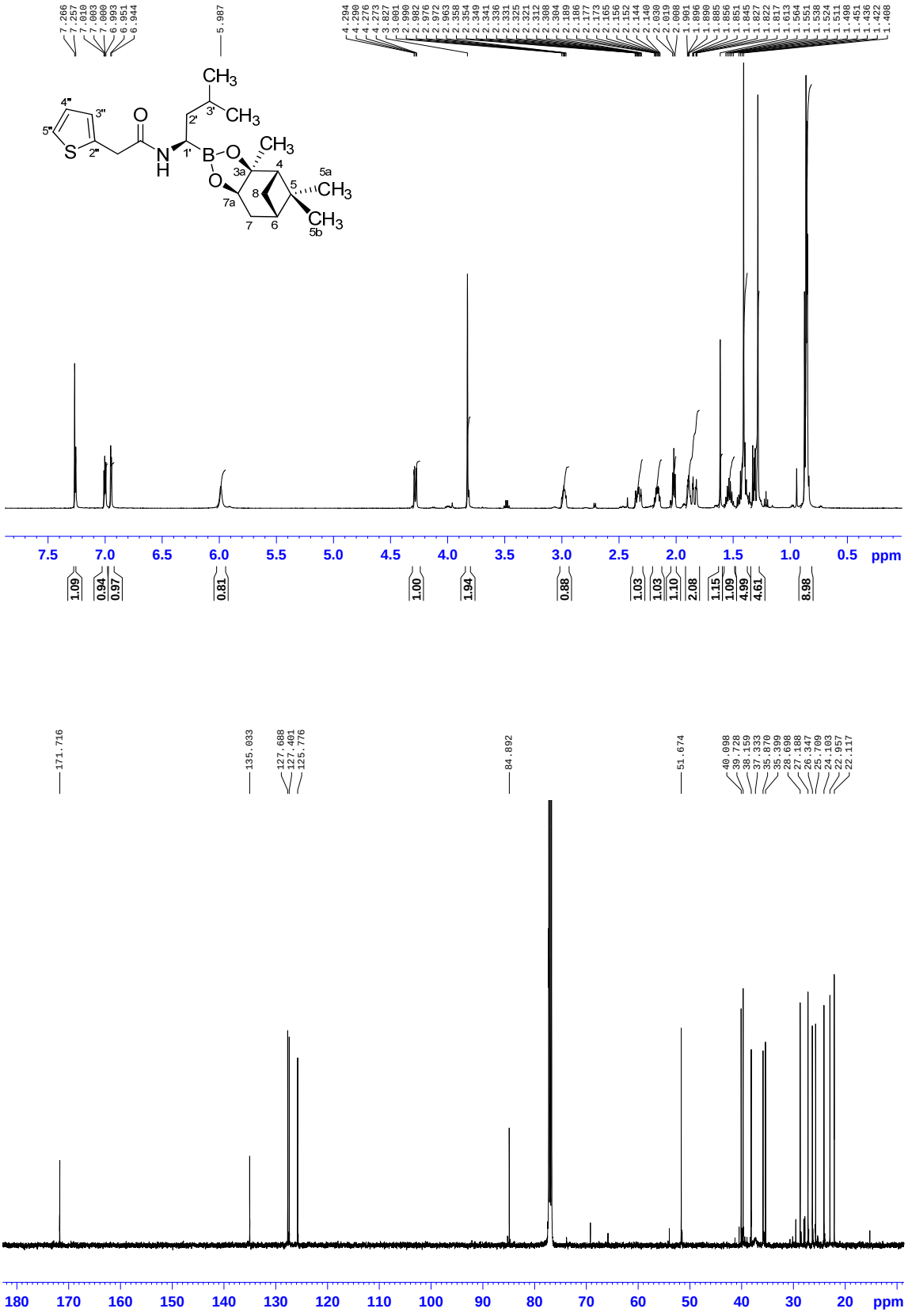


Figure S-7: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra ($CDCl_3$) of **39.**

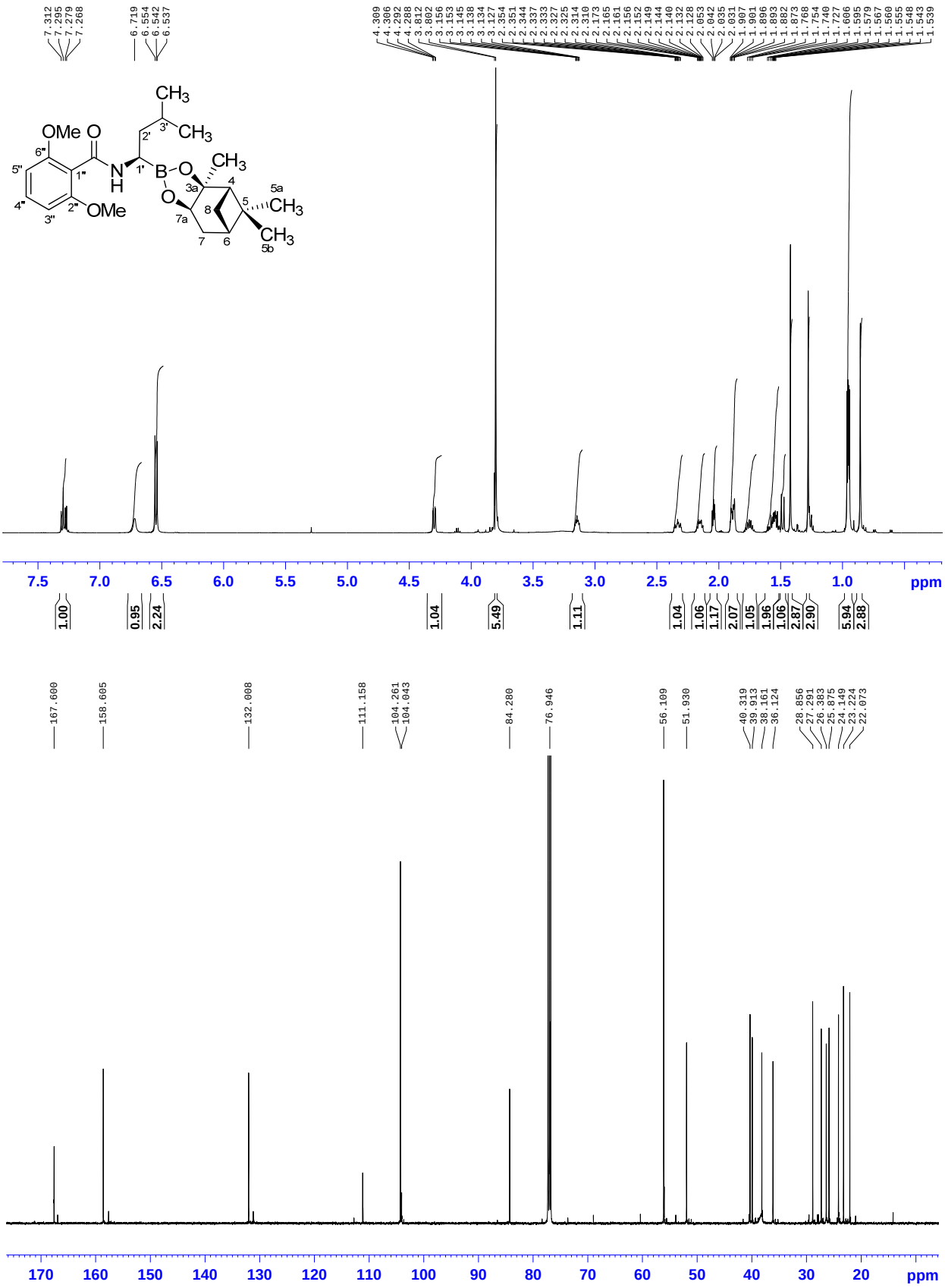


Figure S-8: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra ($CDCl_3$) of **14.**

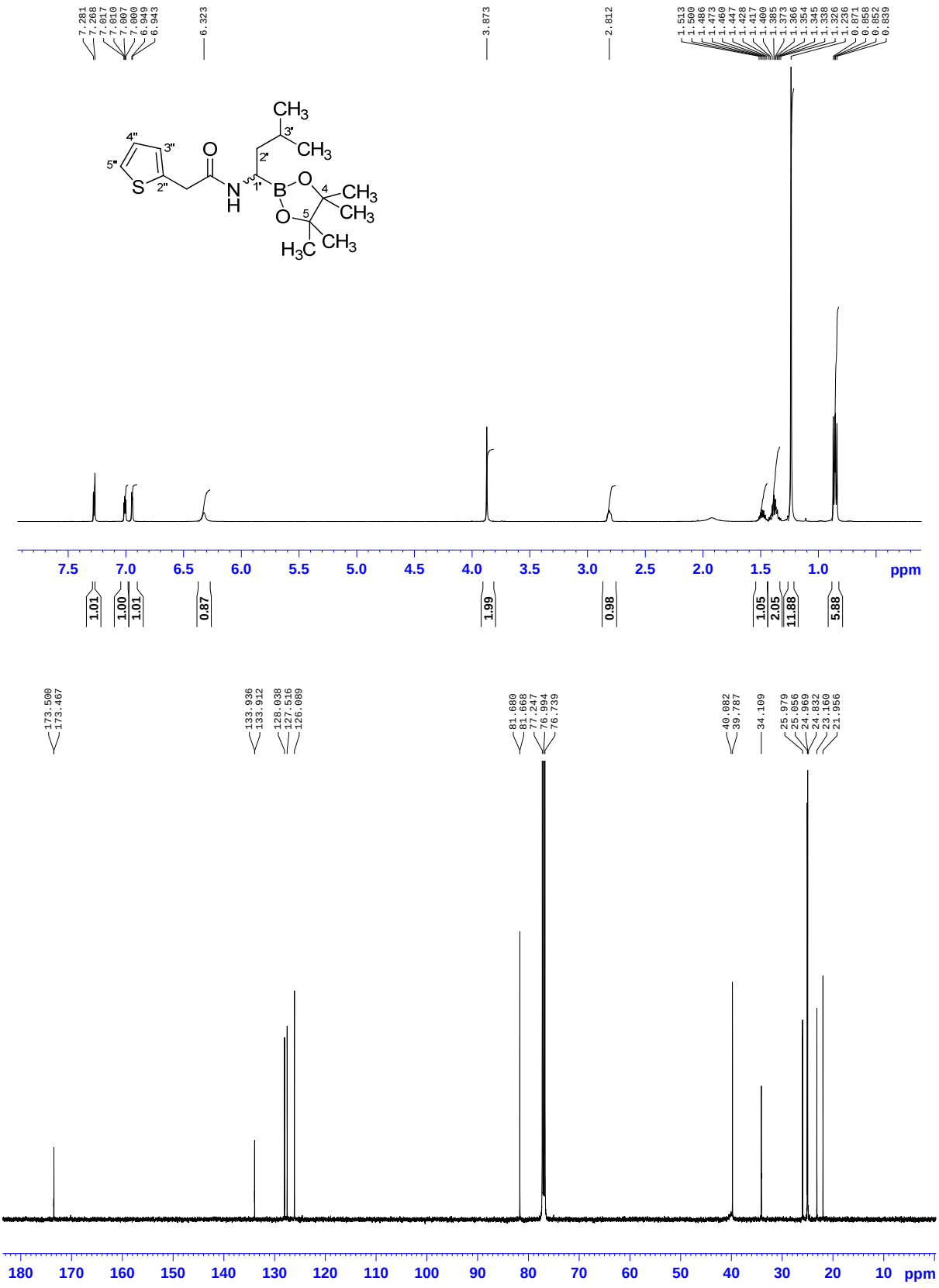


Figure S-9: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra ($CDCl_3$) of **46.**

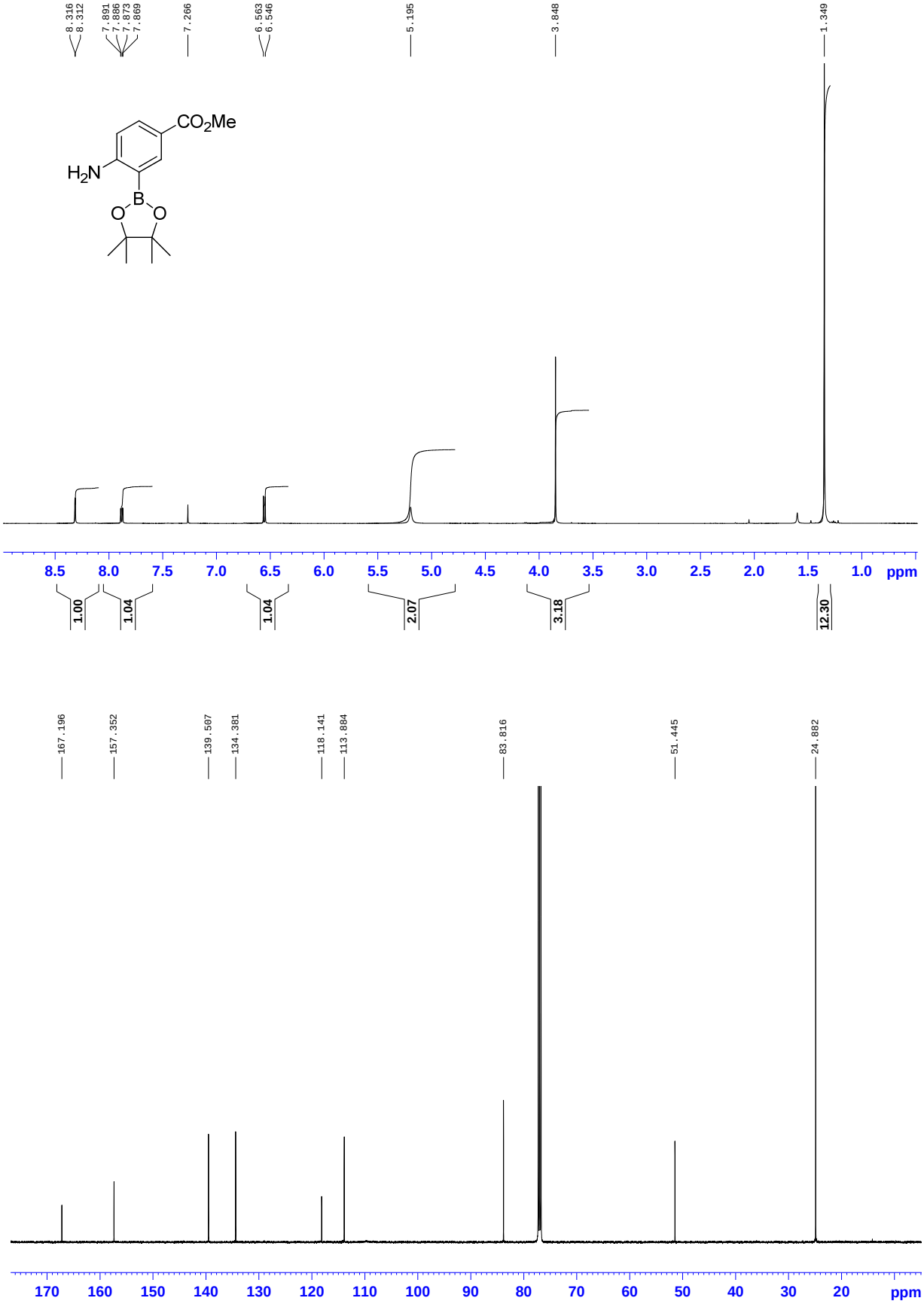


Figure S-10: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra ($CDCl_3$) of **19.**

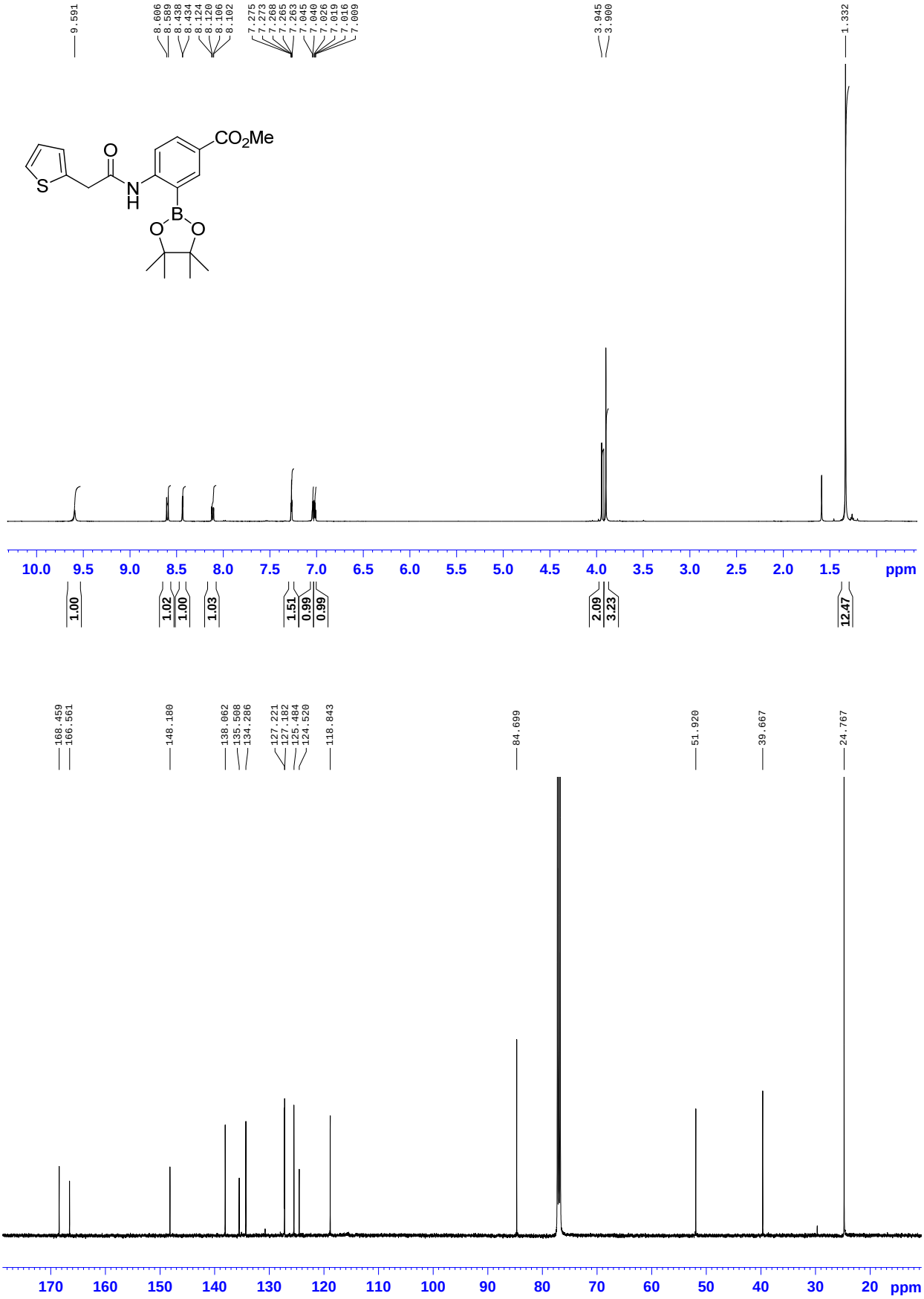


Figure S-11: 500 MHz [^{1}H,^{1}H] NOESY (top) and [^{1}H,^{13}C] HMBC (500 MHz for ^{1}H) (bottom) spectra ($CDCl_3$) for **19**.

(Representative 2D spectra included for assignment of ^{1}H and ^{13}C *ortho*-amido phenylboronic acids).

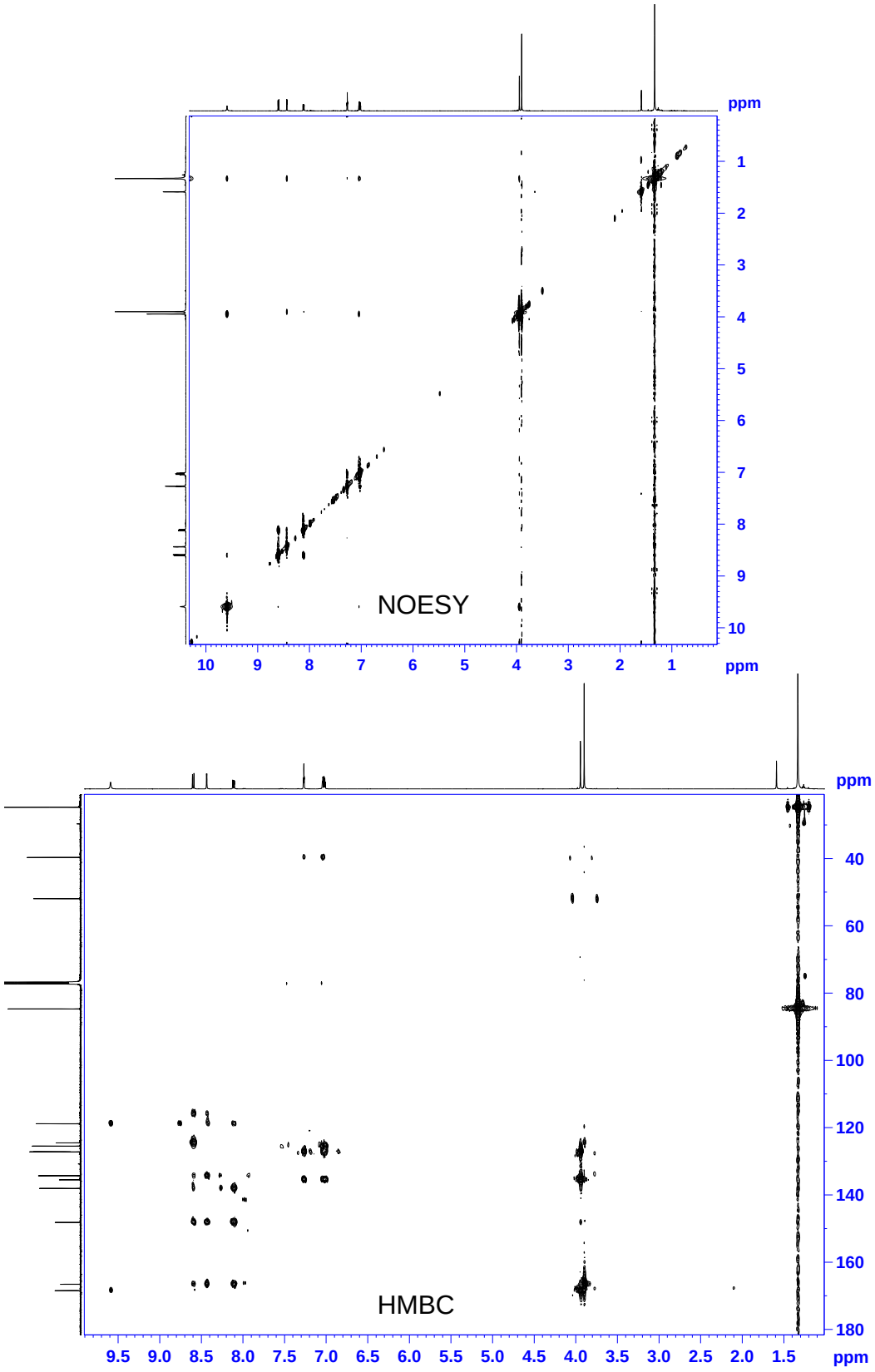


Figure S-12: [^{1}H,^{13}C] HSQC (500 MHz for ^{1}H) spectrum ($CDCl_3$) for **19**.
(Representative 2D spectrum included for assignment of ^{1}H and ^{13}C of *ortho*-amido phenylboronic acids).

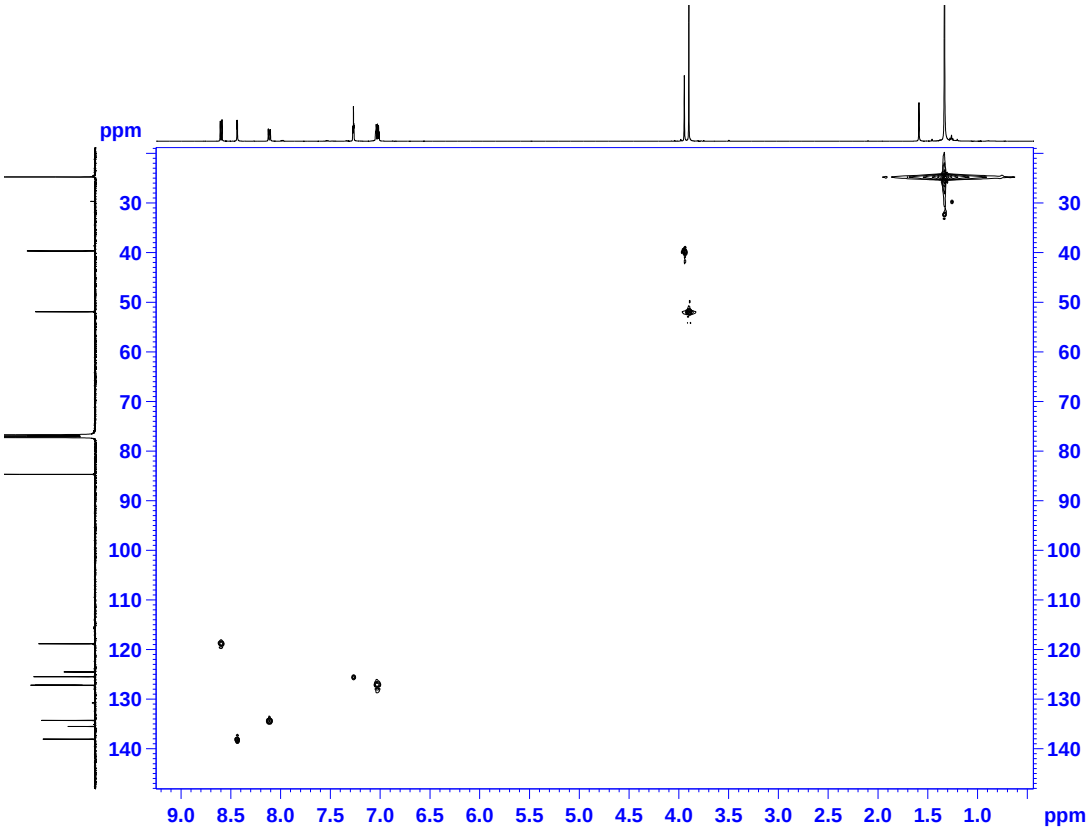


Figure S-13: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra (d_6-acetone/few drops d_6-DMSO) of **18.**

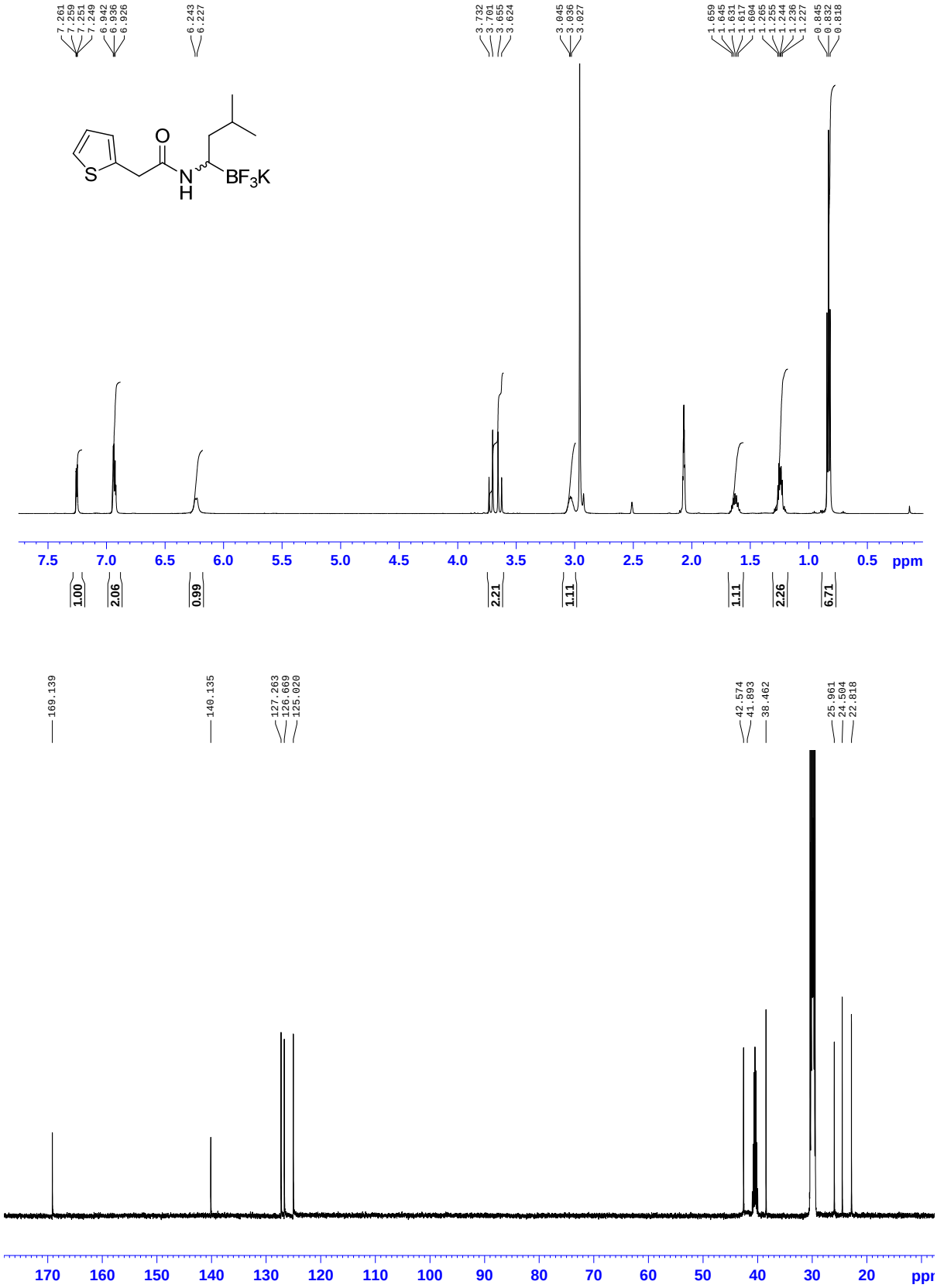


Figure S-14: ^{19}F (376 MHz) NMR spectrum (d_6-acetone/few drops d_6-DMSO) of **18.**

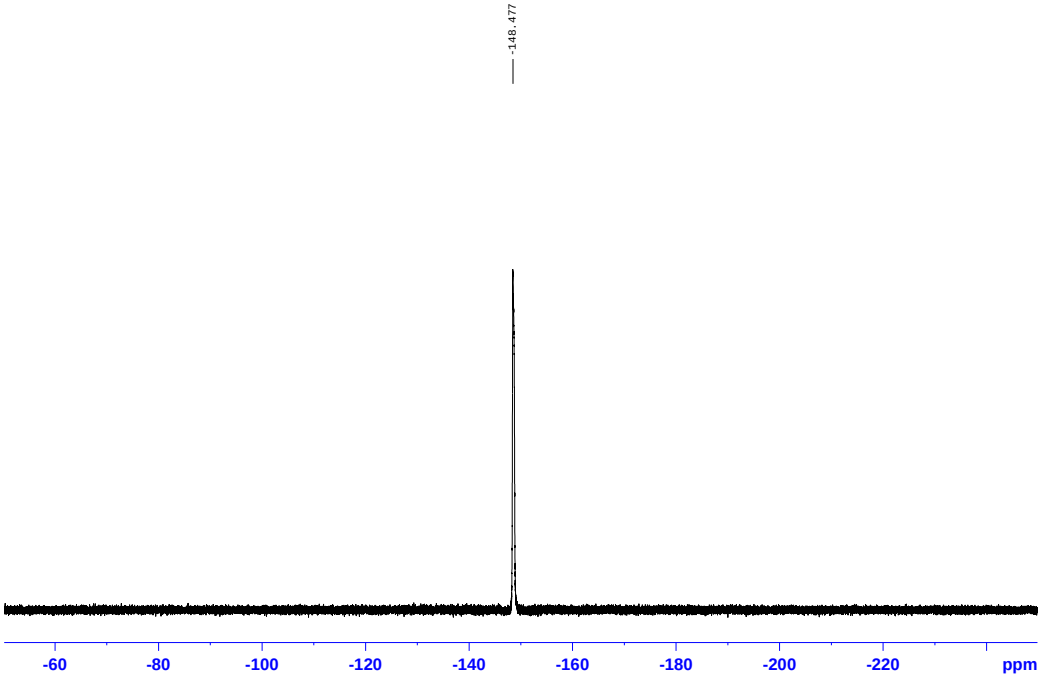


Figure S-15: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra (CD_3OD) of **30**.

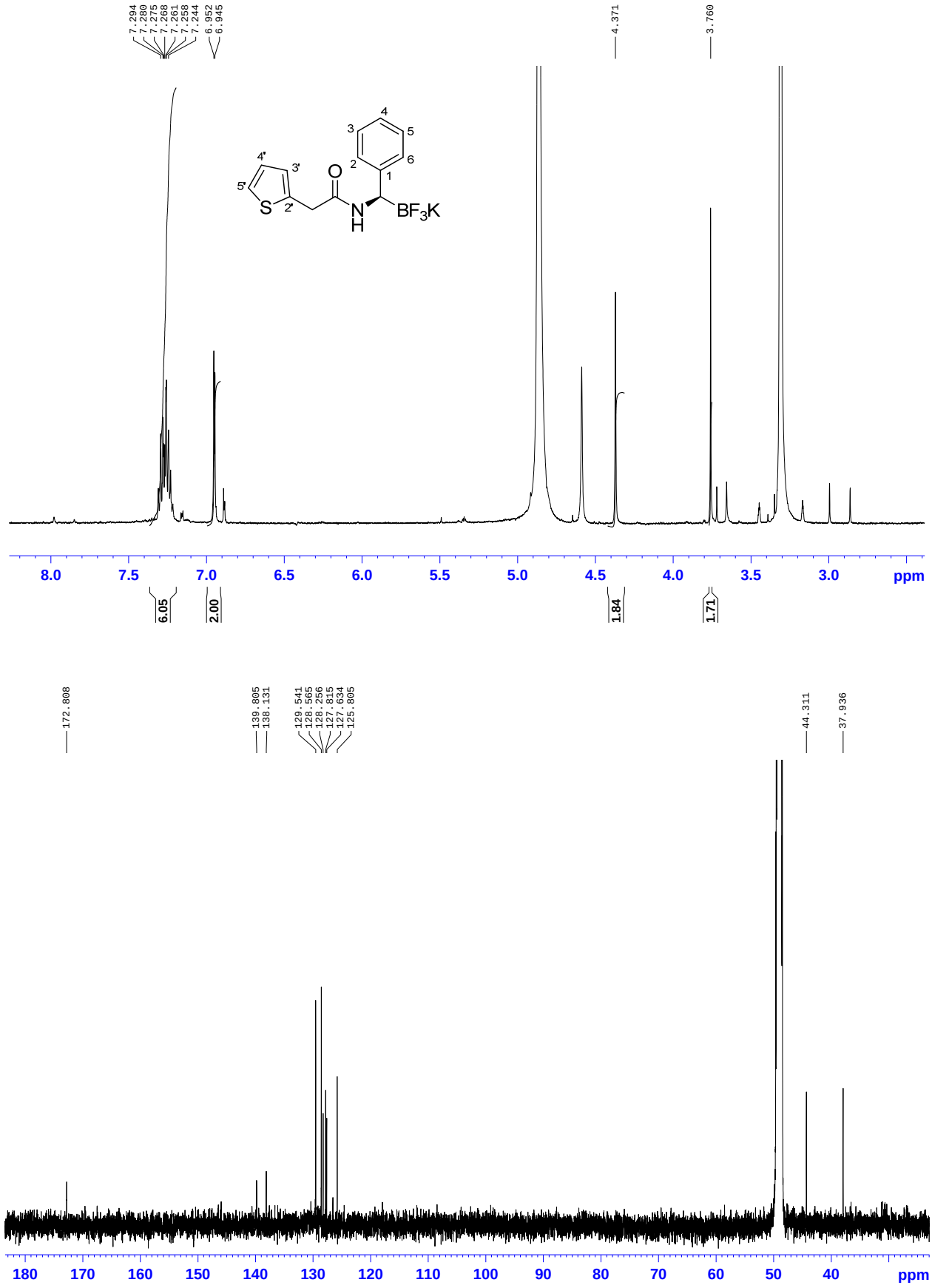


Figure S-16: [^{1}H,^{13}C] HSQC (500 MHz for ^{1}H) spectrum (CD_3OD) for **30**.

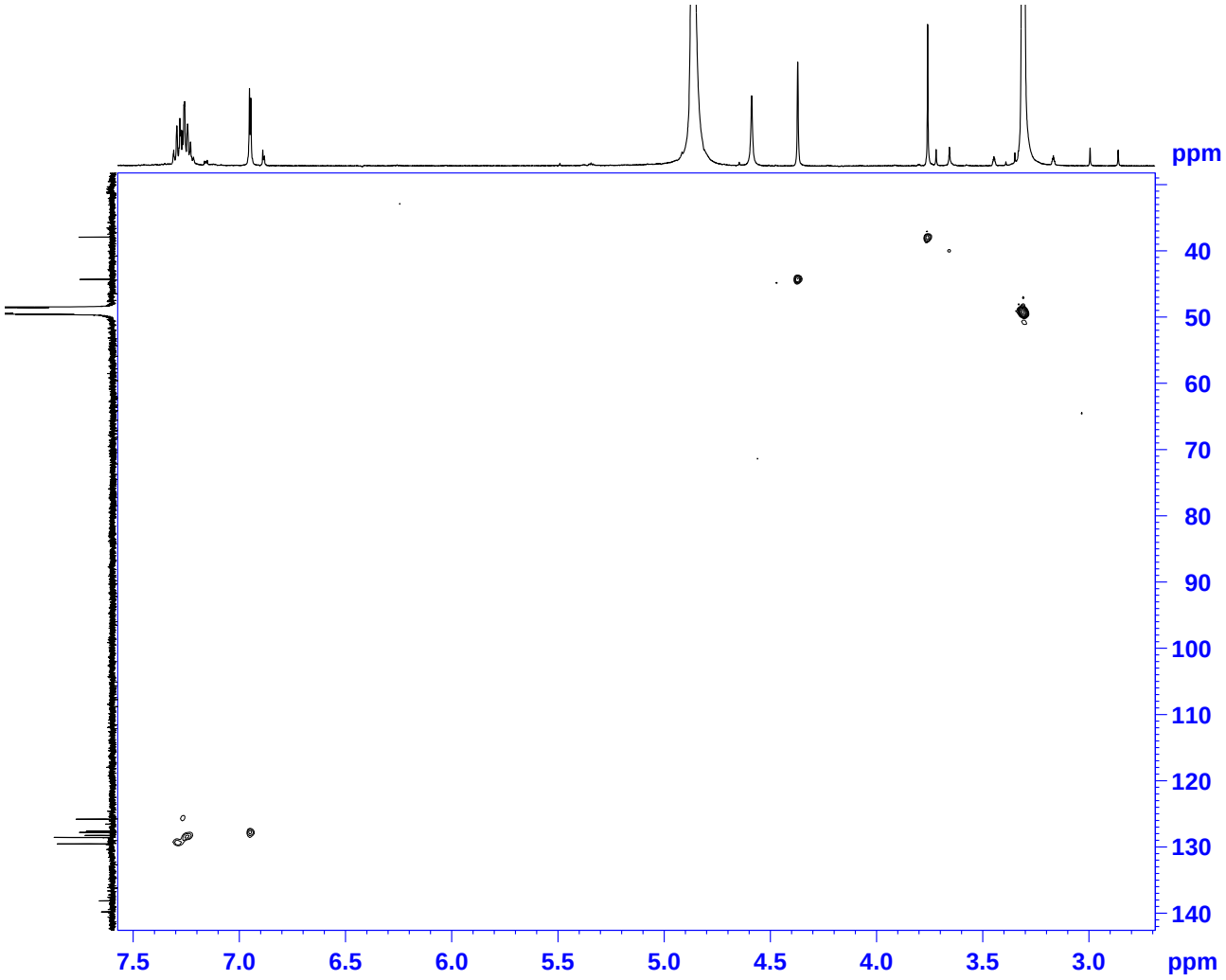


Figure S-17: ^{1}H (400 MHz) and ^{13}C (125 MHz) NMR spectra (d_6-DMSO) of **11**. The additional peaks in the ^{13}C spectrum at ca. 17 and 65 ppm arise from residual diethyl ether from workup; the multiplet at ca. 30 ppm arises from contaminating d_6-acetone in the d_6-DMSO bottle.

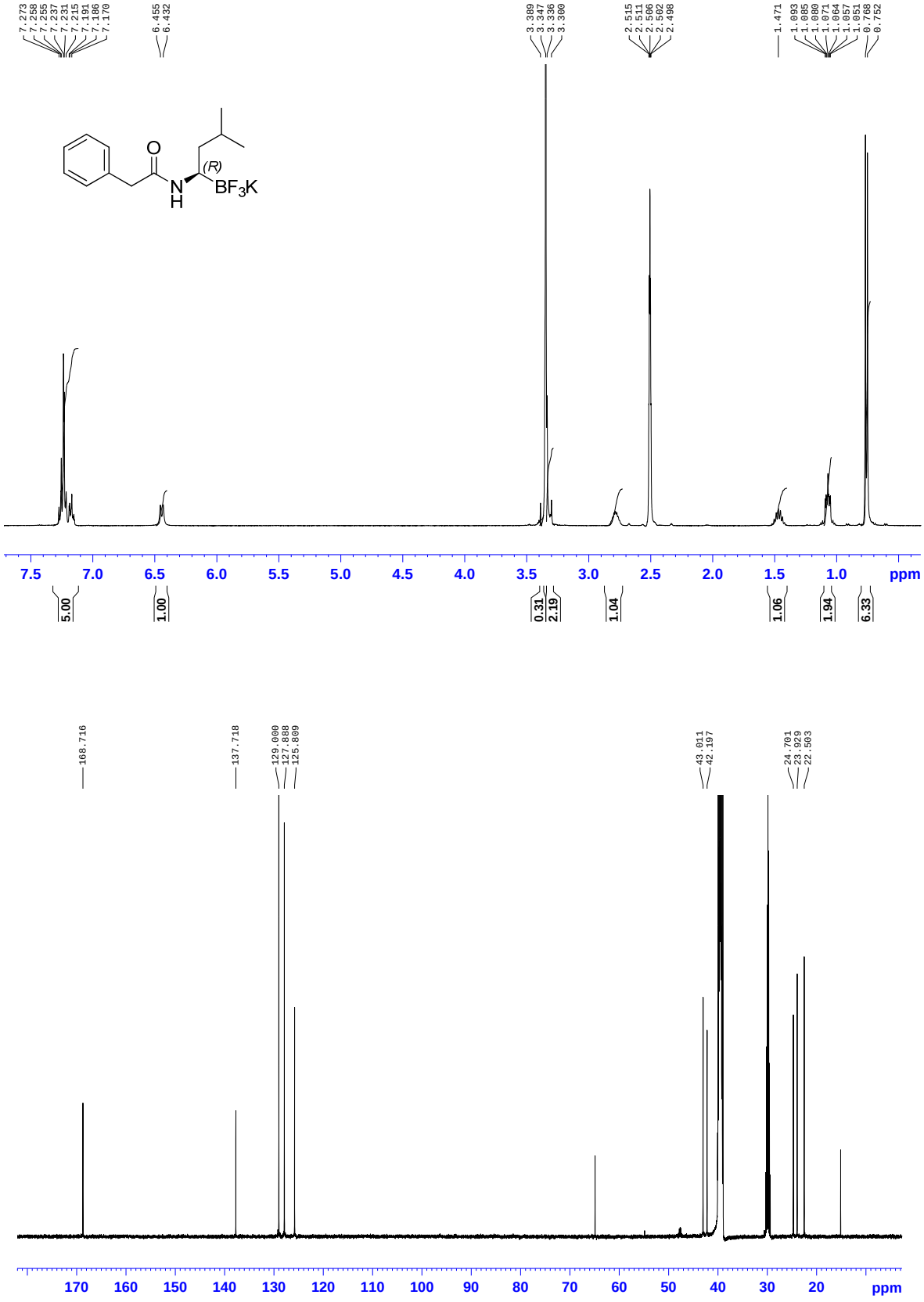


Figure S-18: ^{19}F (376 MHz) NMR spectrum (d_6-DMSO) of **11.**

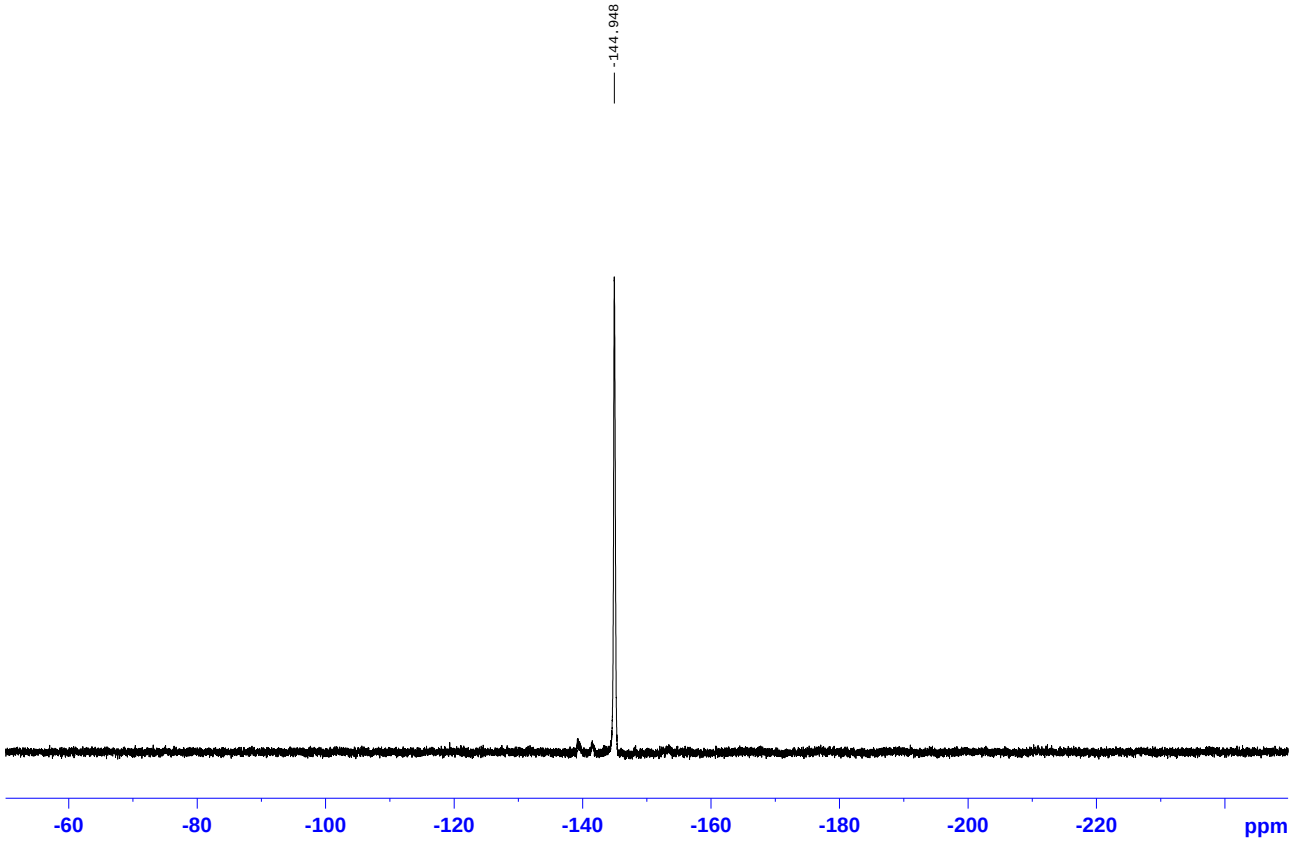


Figure S-19: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra of **27**.

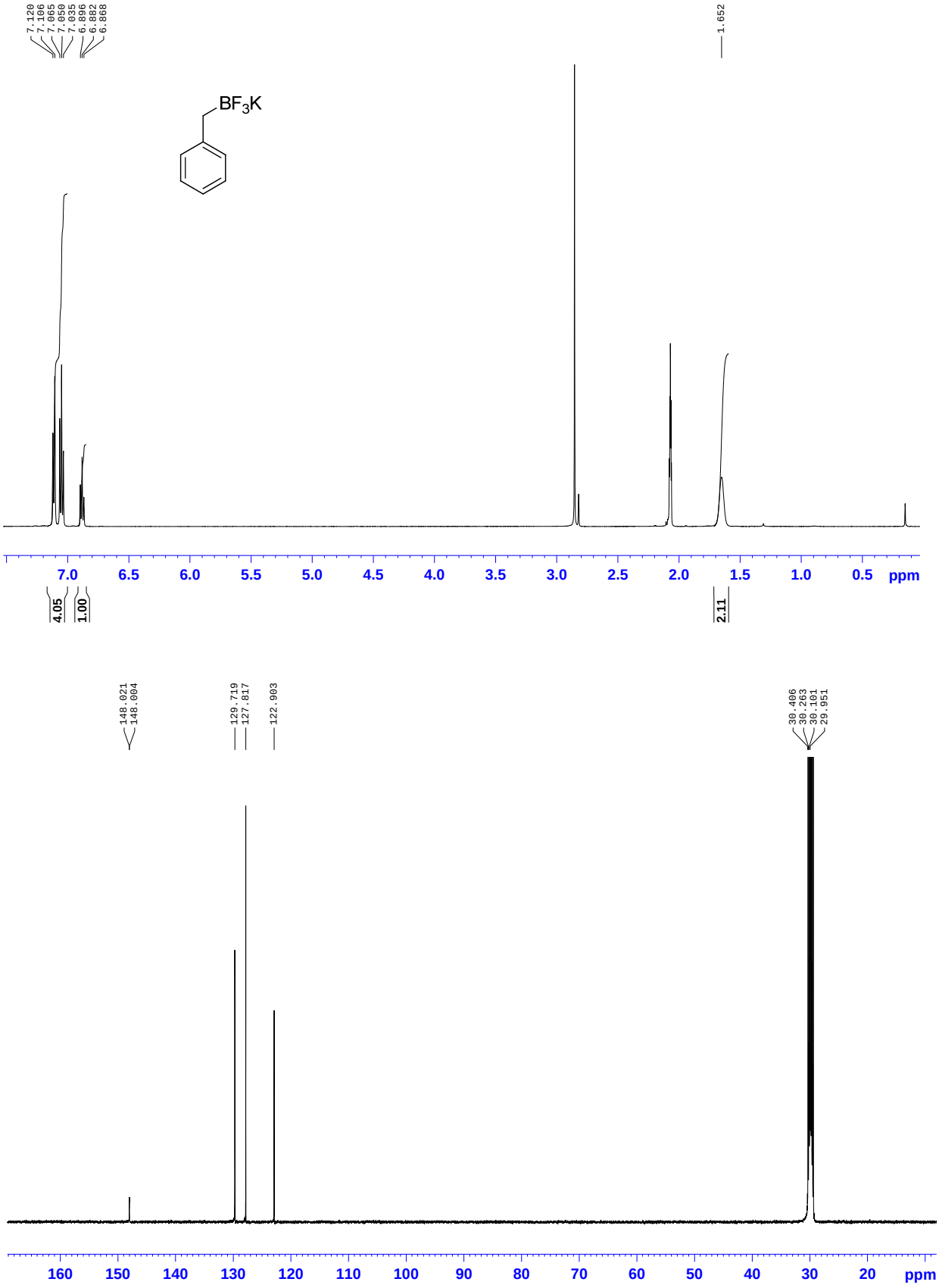


Figure S-20: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra of **26.**

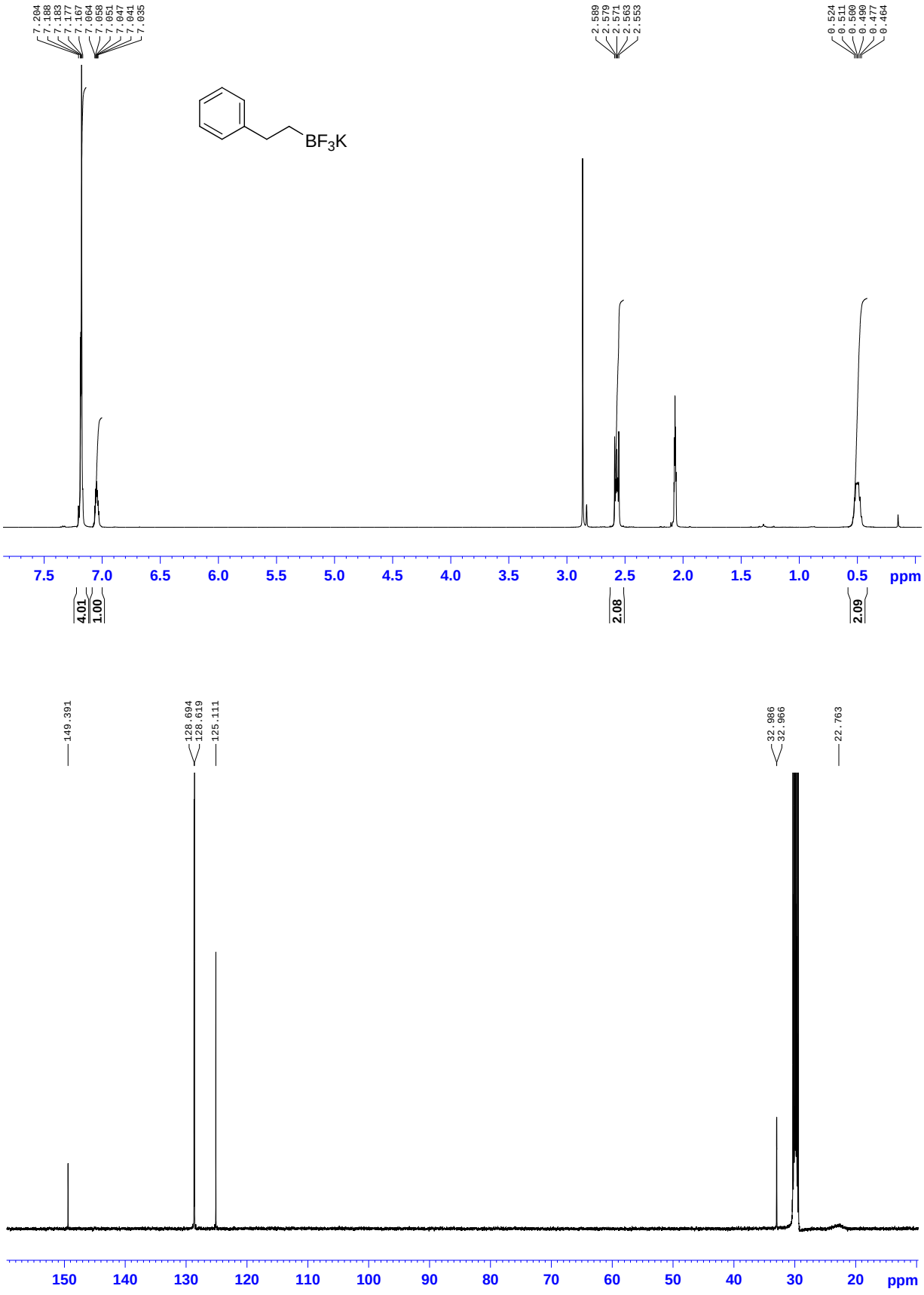


Figure S-21: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra (d_6-acetone) of **16.**

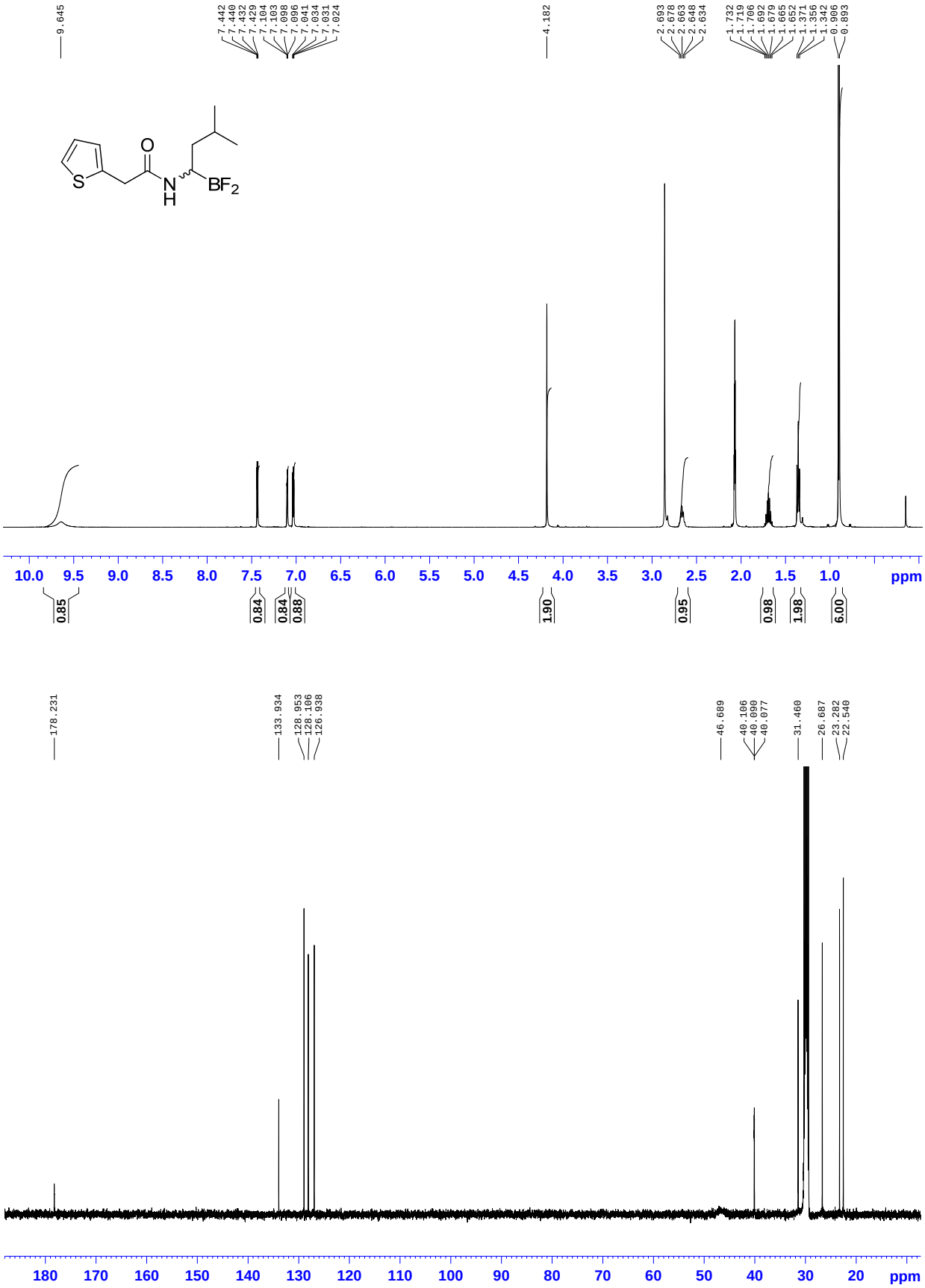


Figure S-22: ^{19}F (376 MHz) NMR spectrum (d_6-acetone) of **16**.

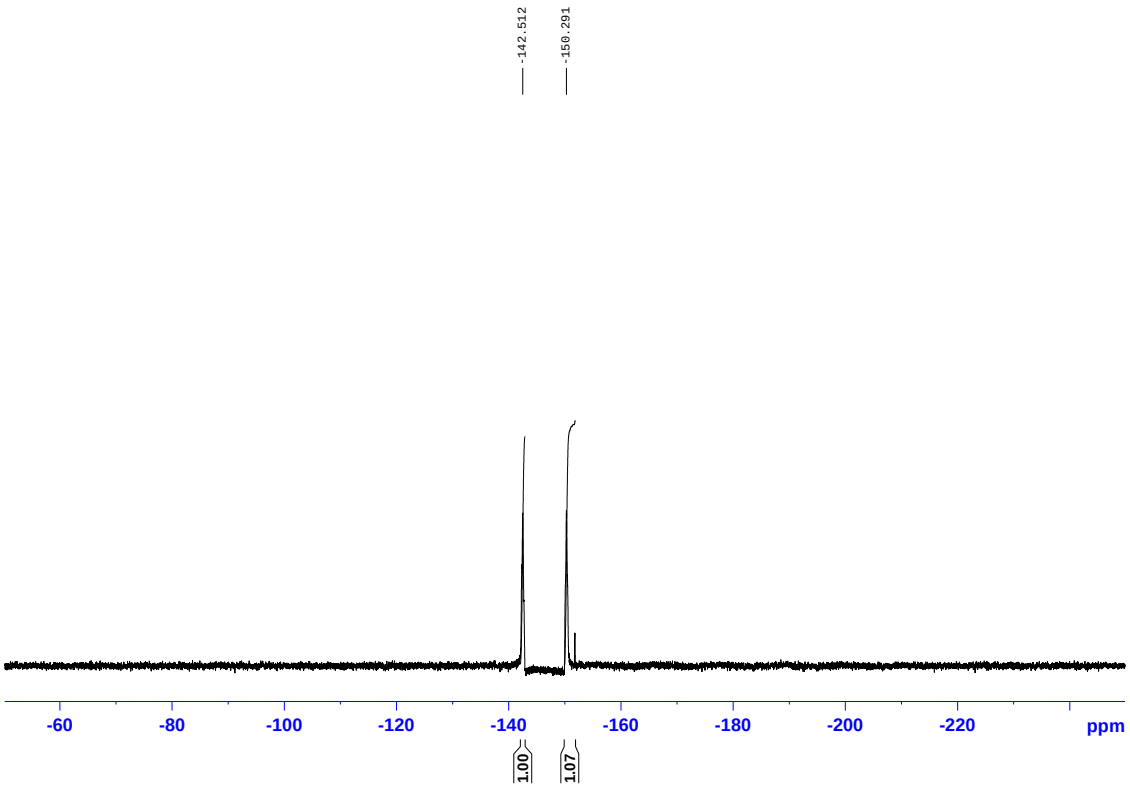


Figure S-23: ^{1}H (400 MHz) NMR spectrum (d_6-acetone) of **15.**

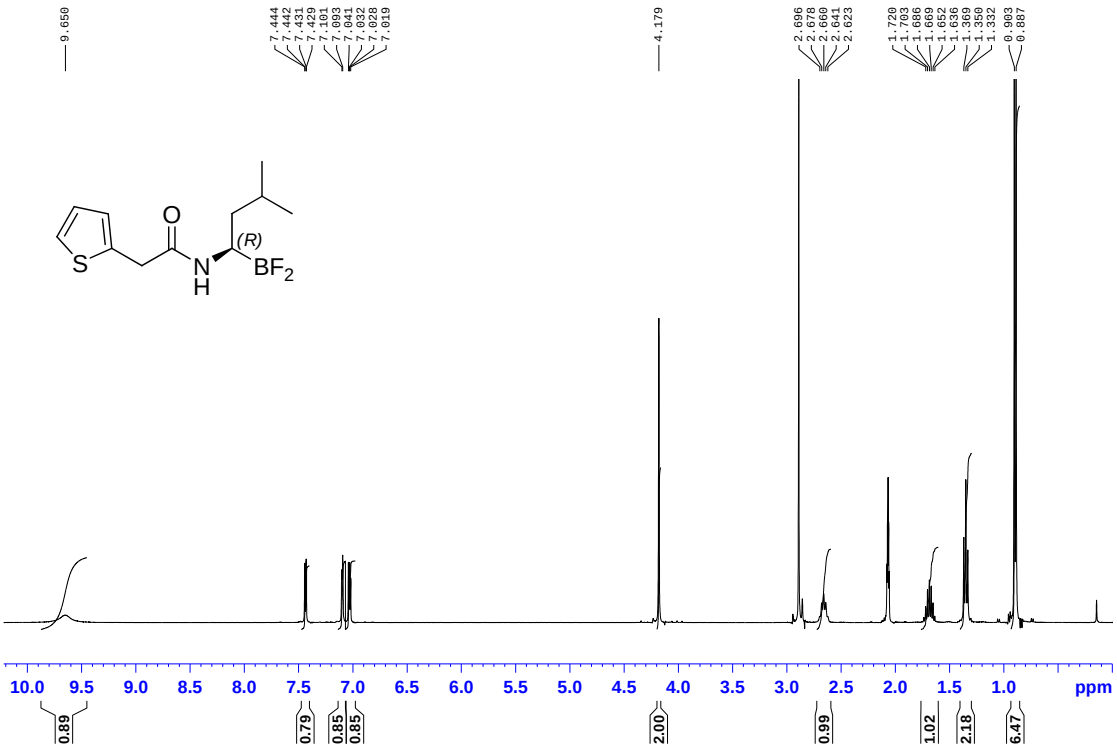


Figure S-24: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra (d_6-acetone) of **12.**

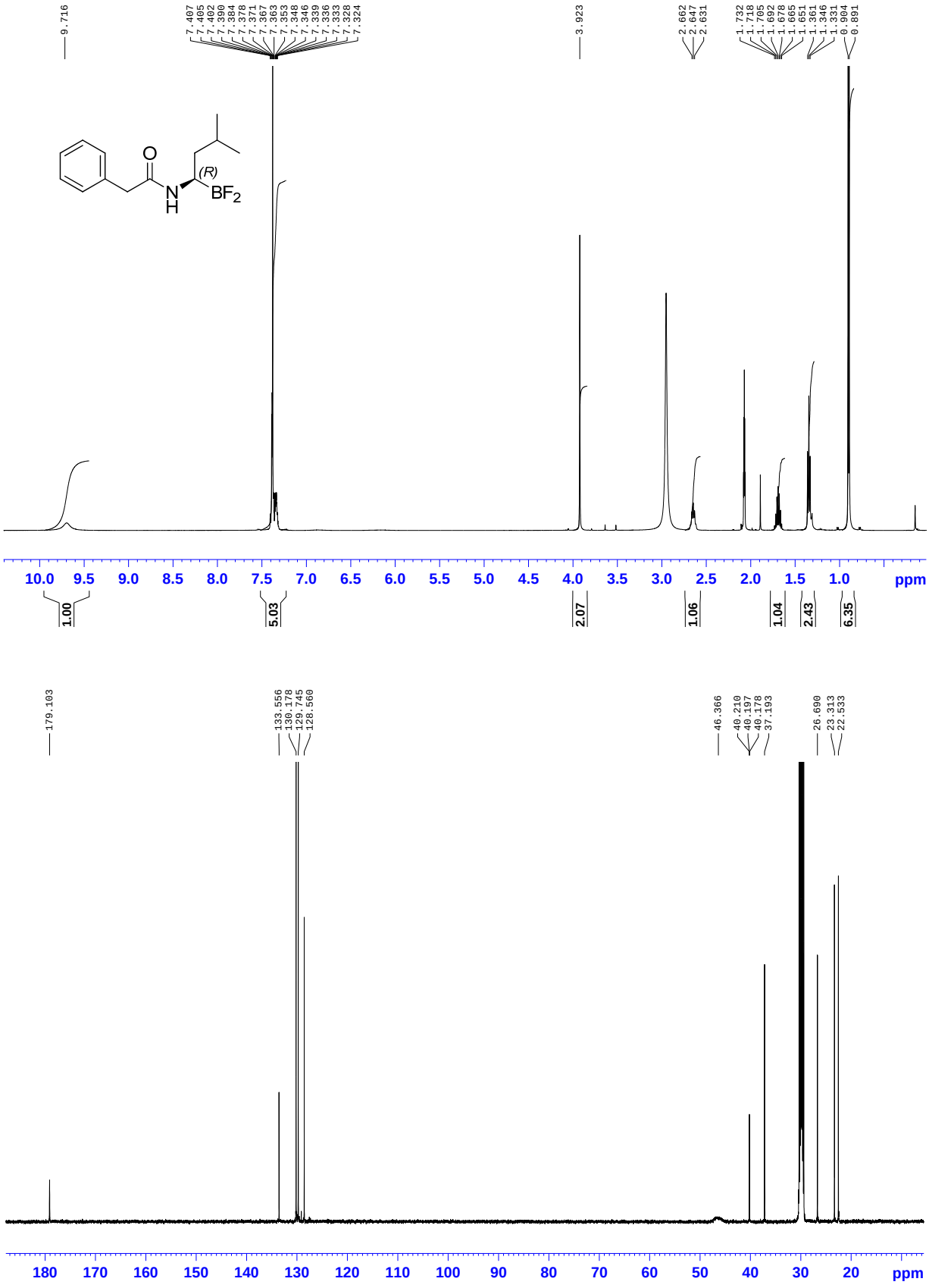


Figure S-25: ^{19}F (376 MHz) NMR spectrum (d_6-acetone) of **12.**

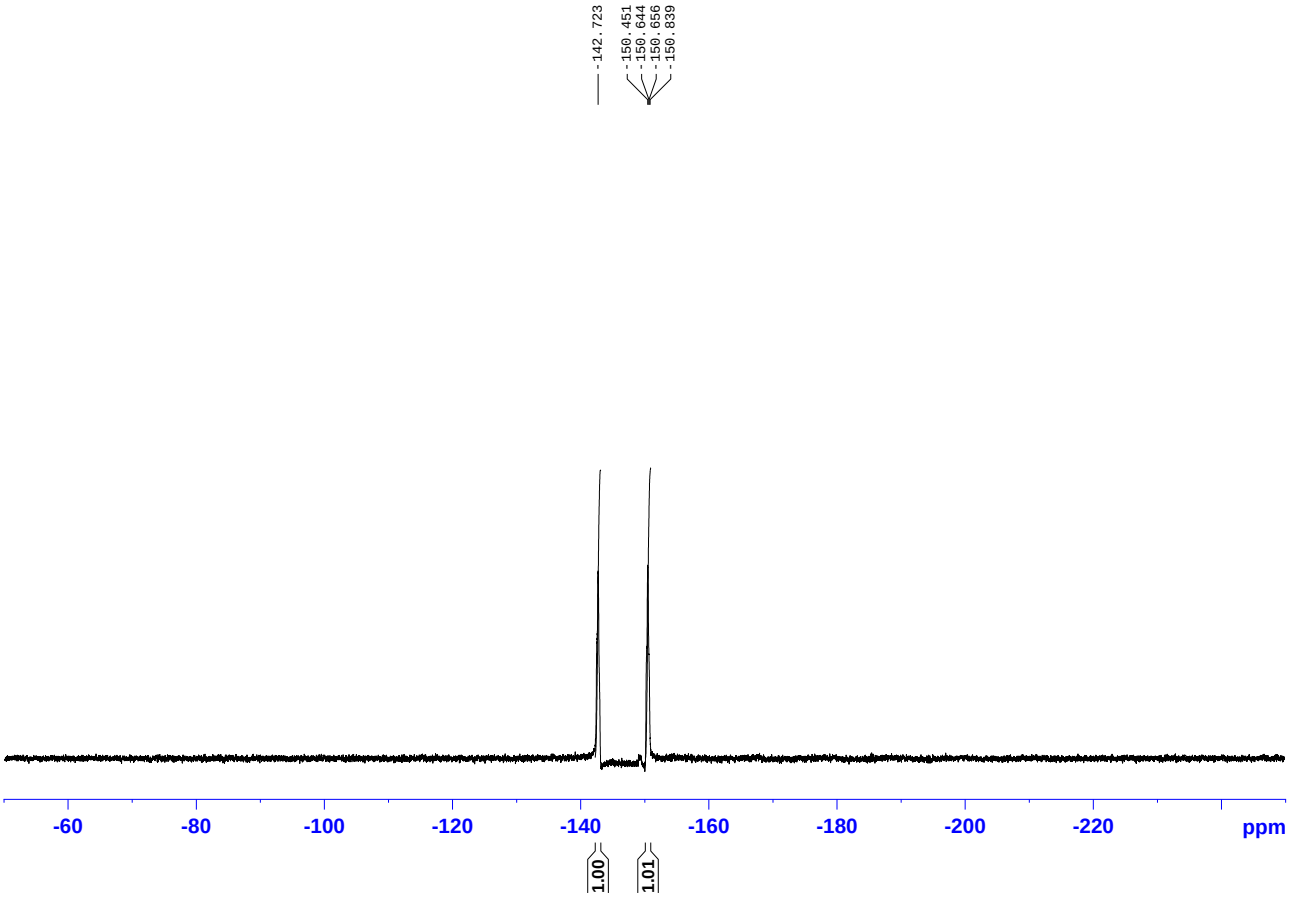


Figure S-26: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra (d_6-acetone) of **35**.

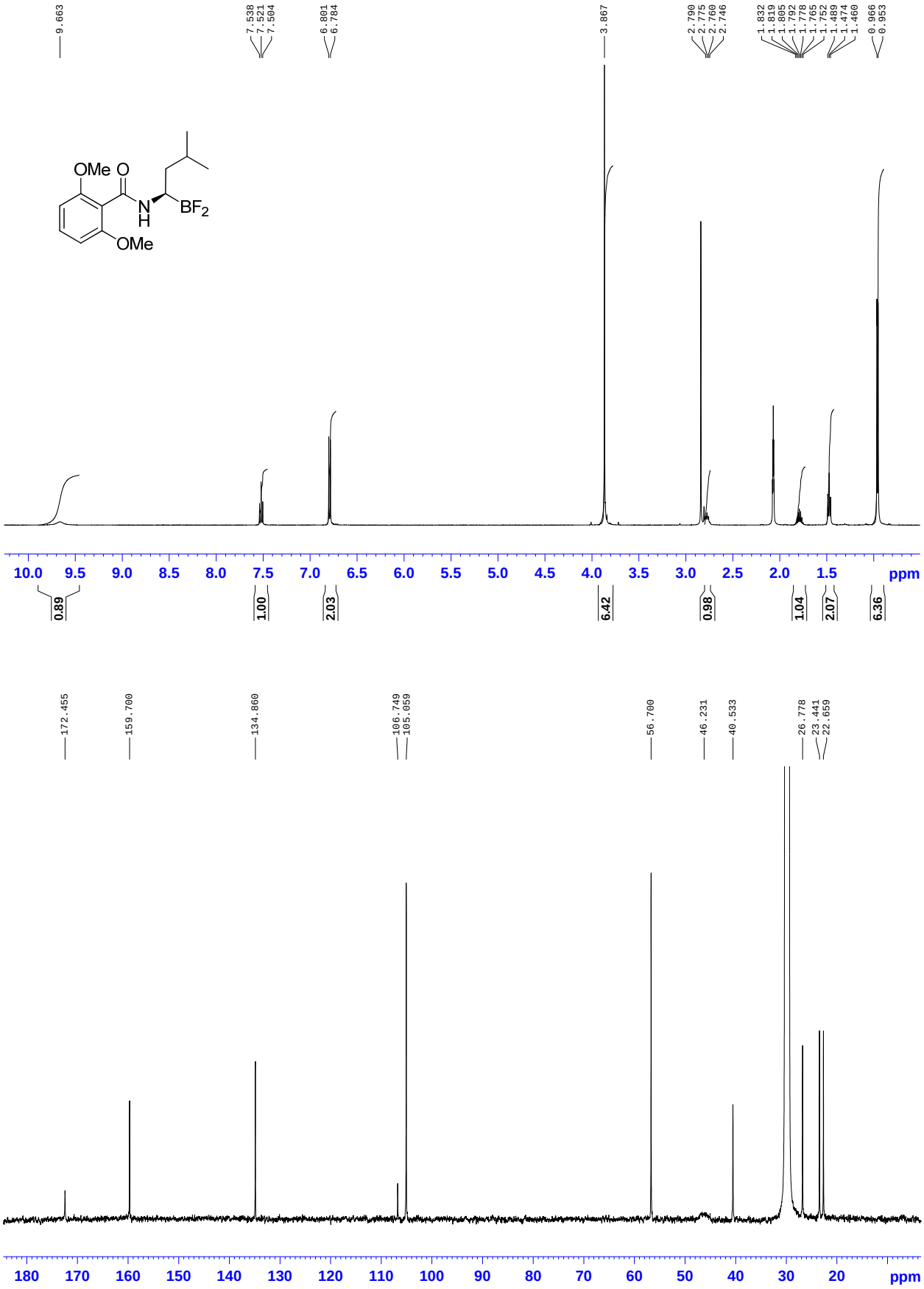


Figure S-27: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra (d_6-acetone) of **21.**

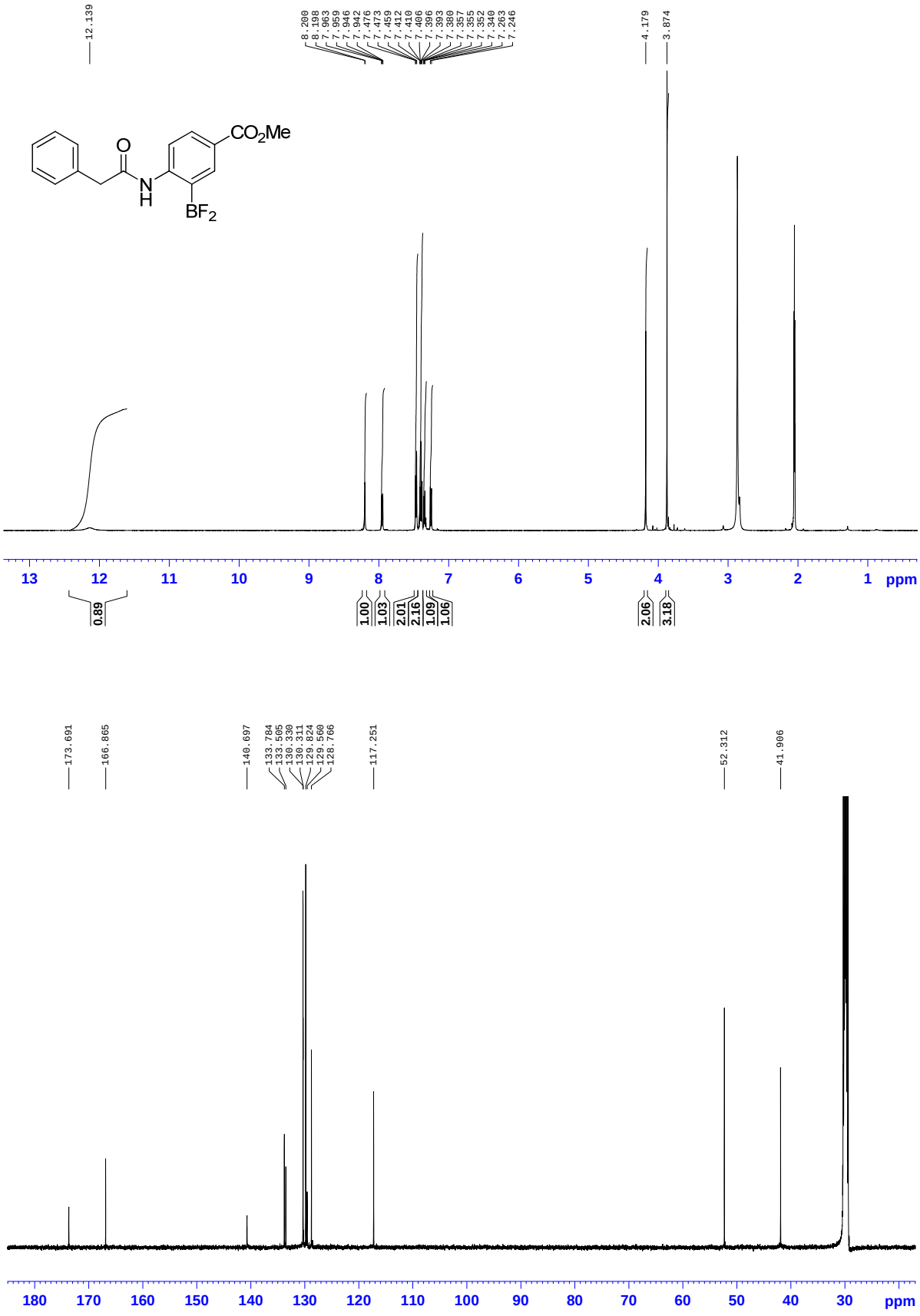


Figure S-28: ^{19}F (376 MHz) NMR spectrum (d_6-acetone) of **21.**

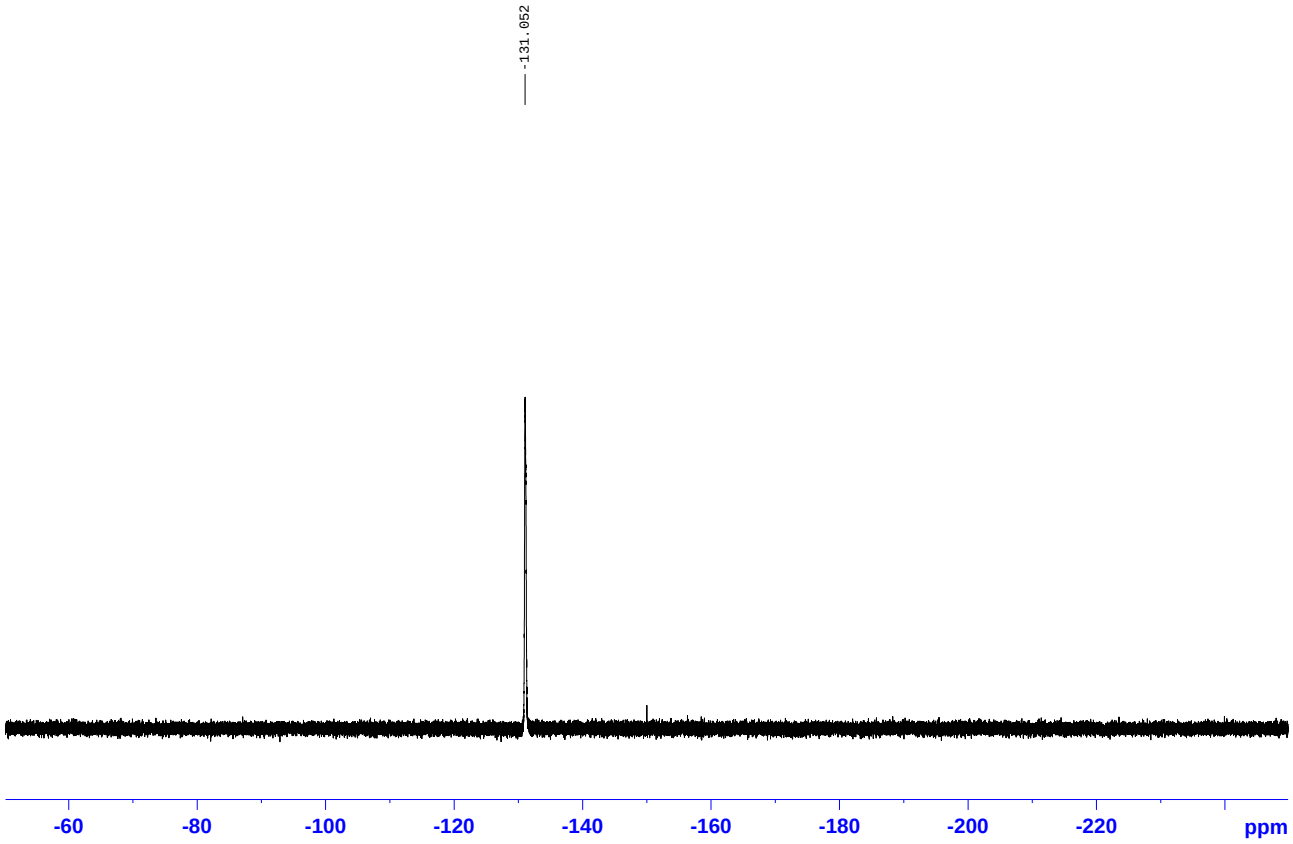


Figure S-29: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra (d_6-acetone) of **22.**

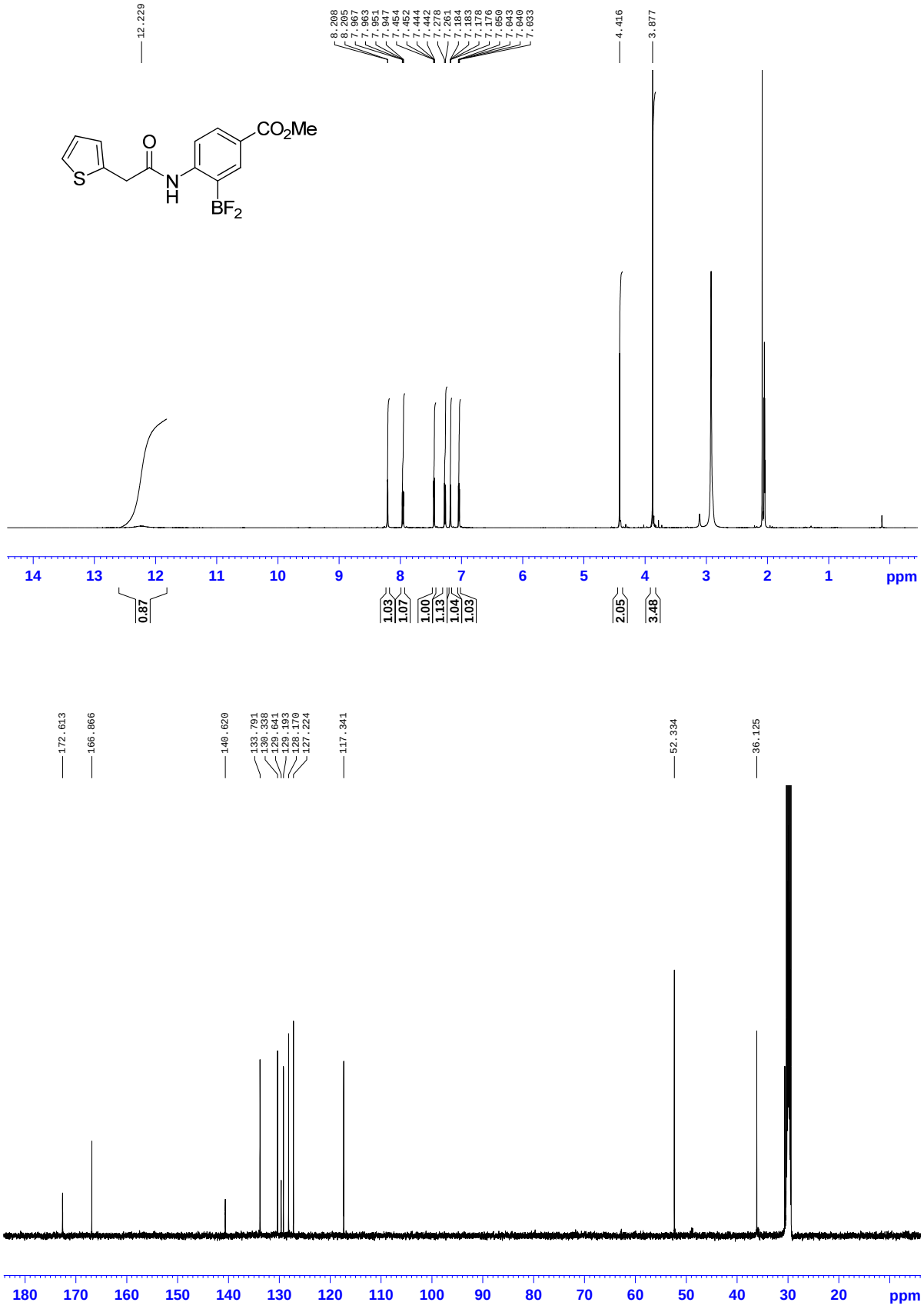


Figure S-30: ^{19}F (376 MHz) NMR spectrum (d_6-acetone) of **22.**

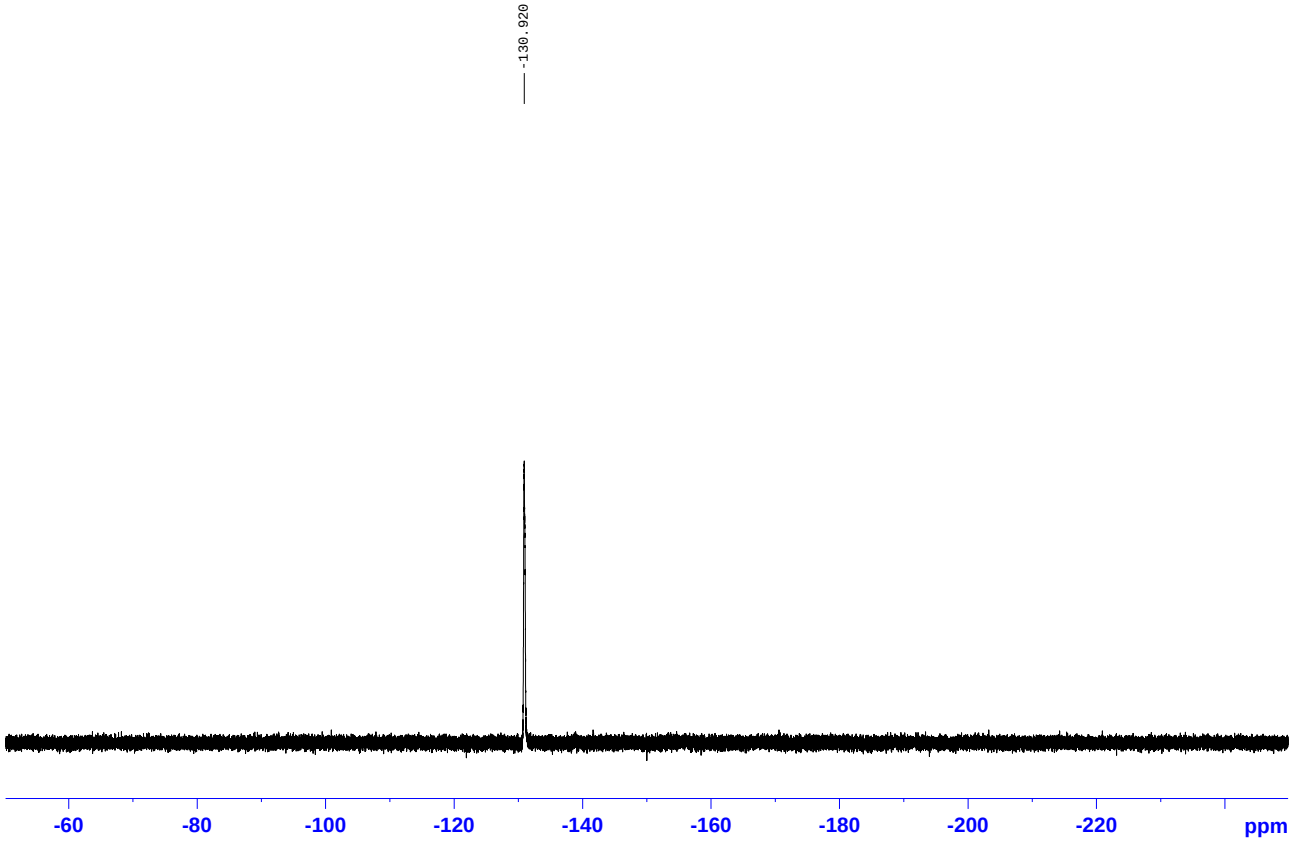


Figure S-31: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra (d_6-acetone) of **23.**

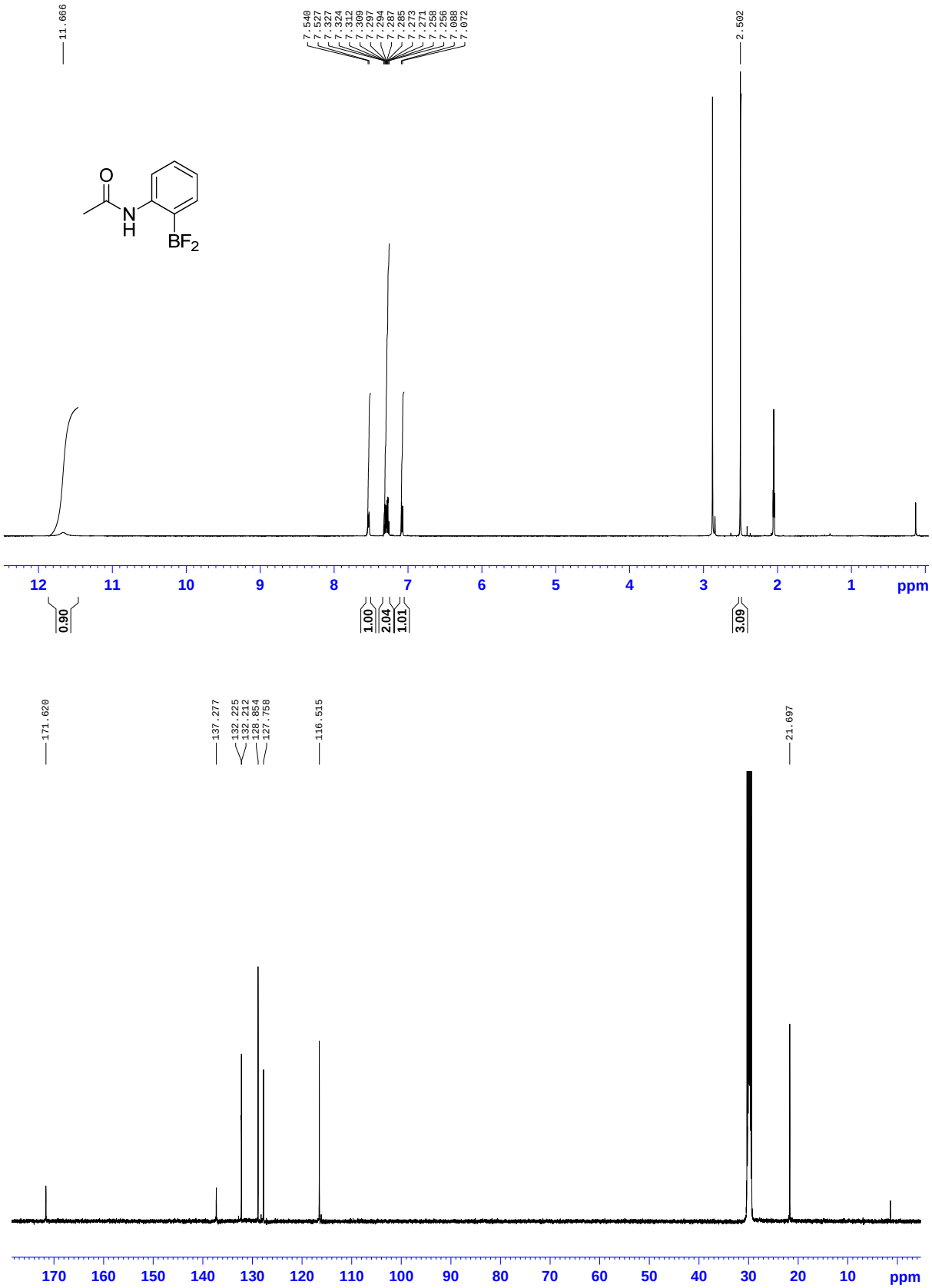


Figure S-32: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra (d_6-acetone) of **33.**

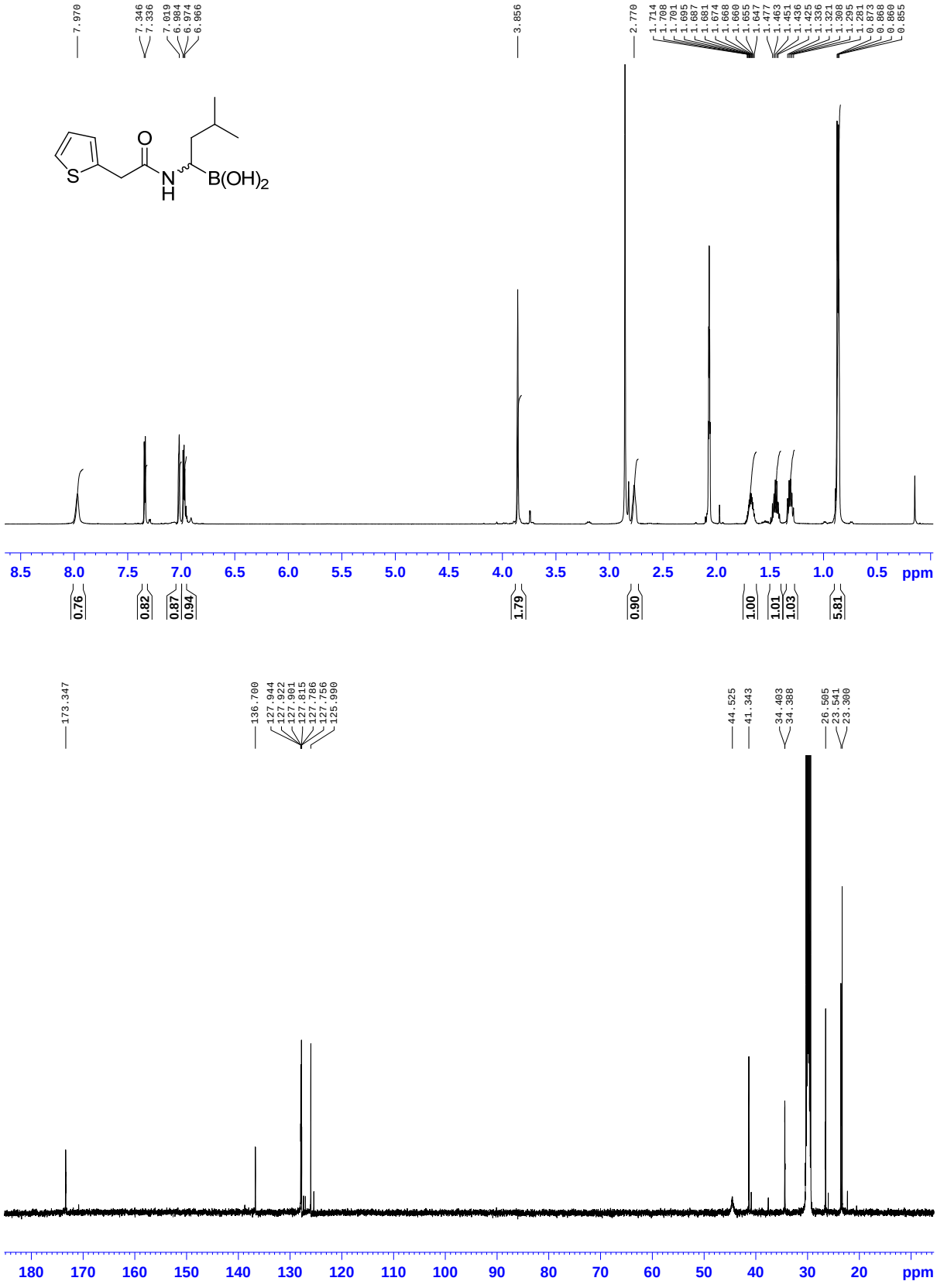


Figure S-33: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra (CD_3OD) of **32.**

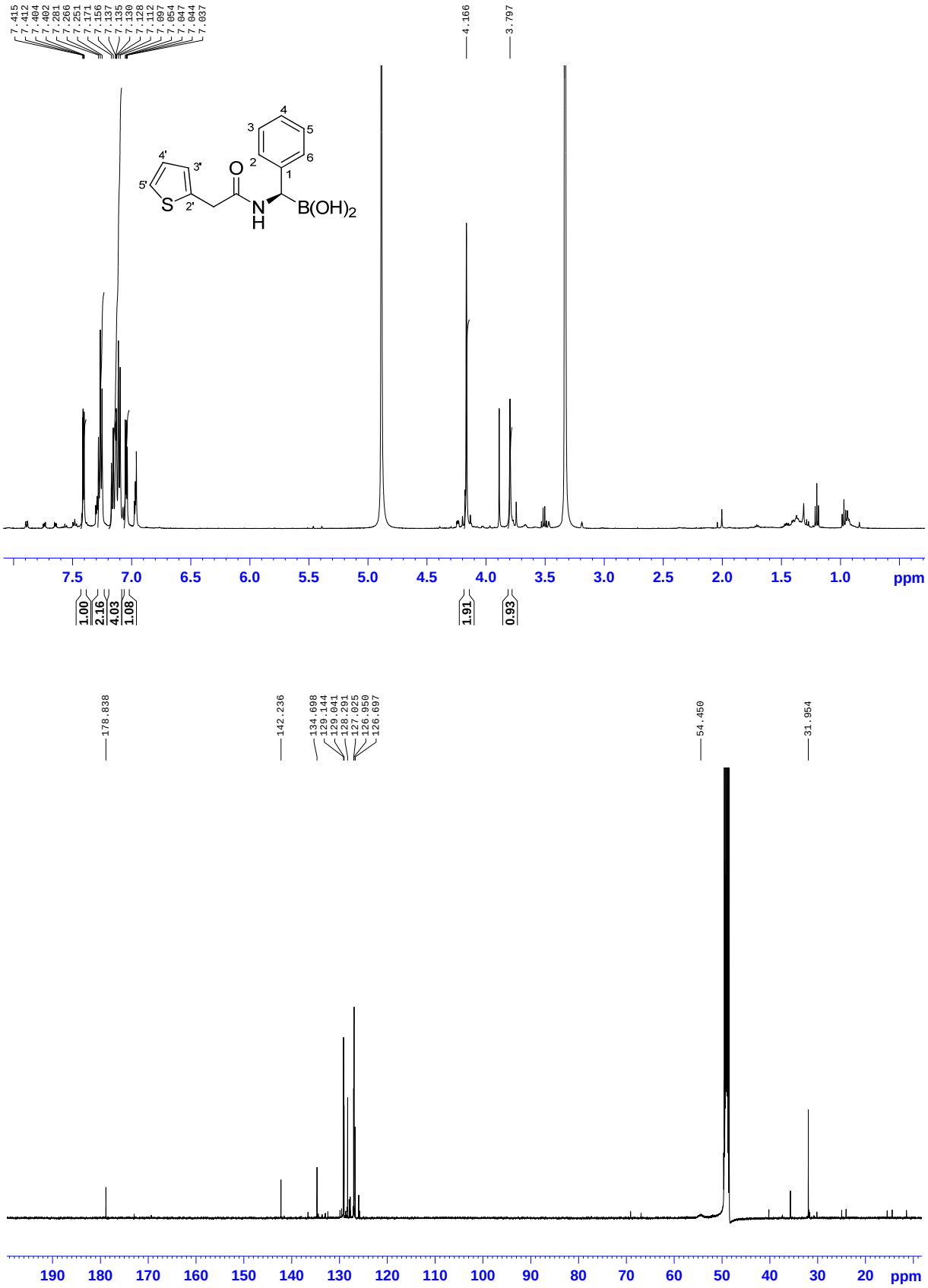


Figure S-34: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra (d_6-acetone) of **29.**

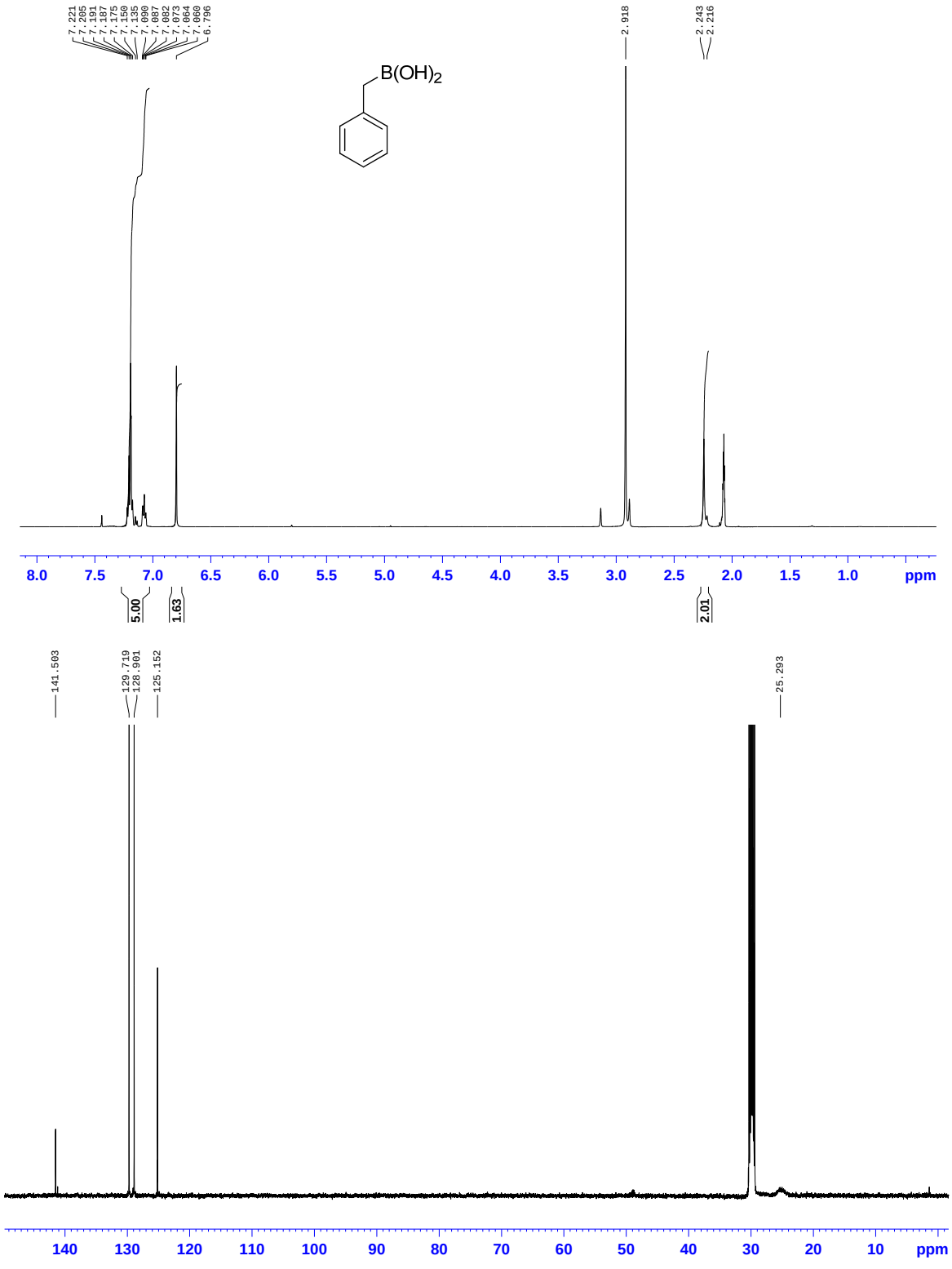


Figure S-35: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra (d_6-acetone) of **34.**

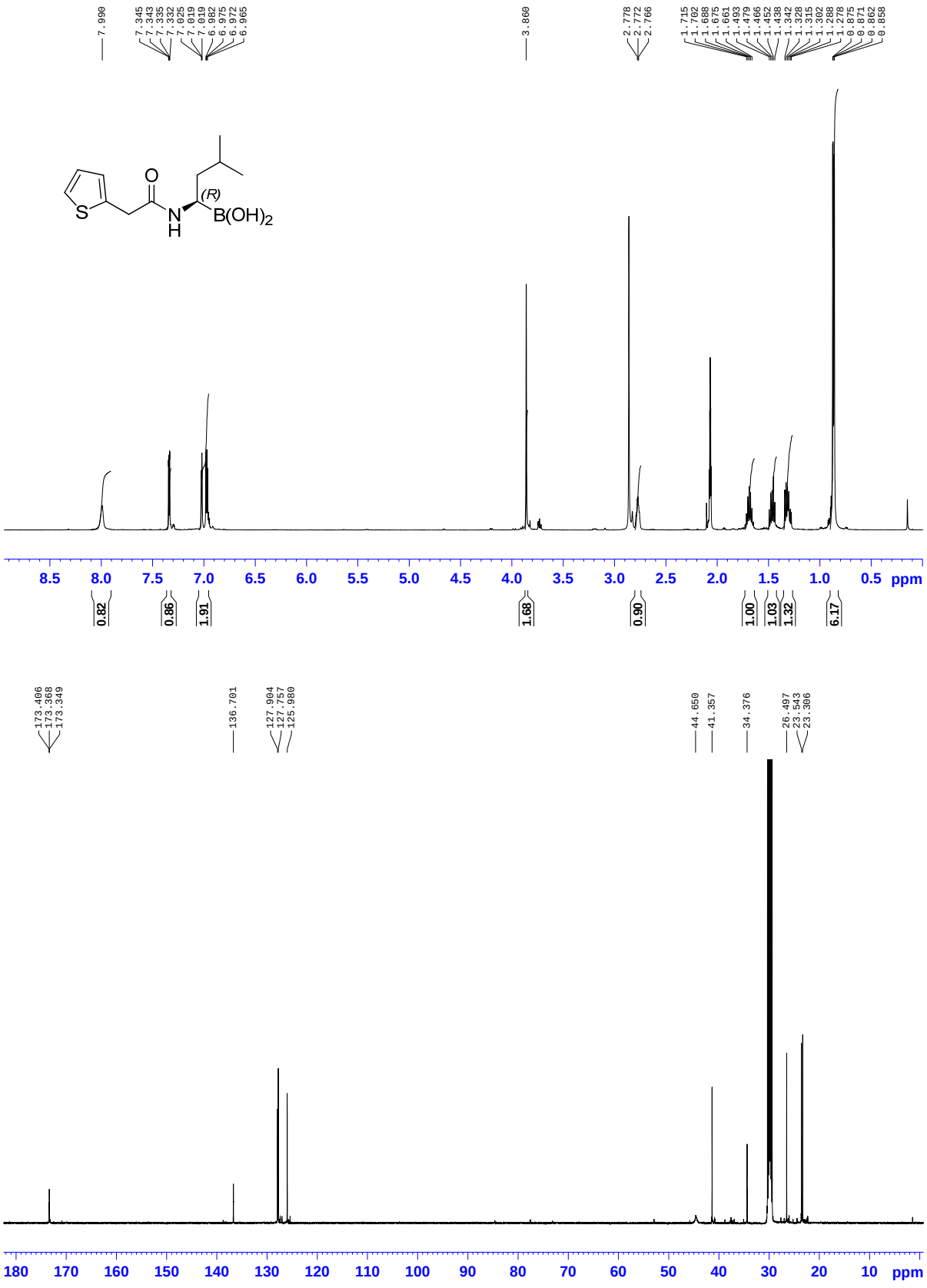


Figure S-36: ^{1}H (400 MHz) and ^{13}C (125 MHz) NMR spectra (d_6-acetone) of **31.**

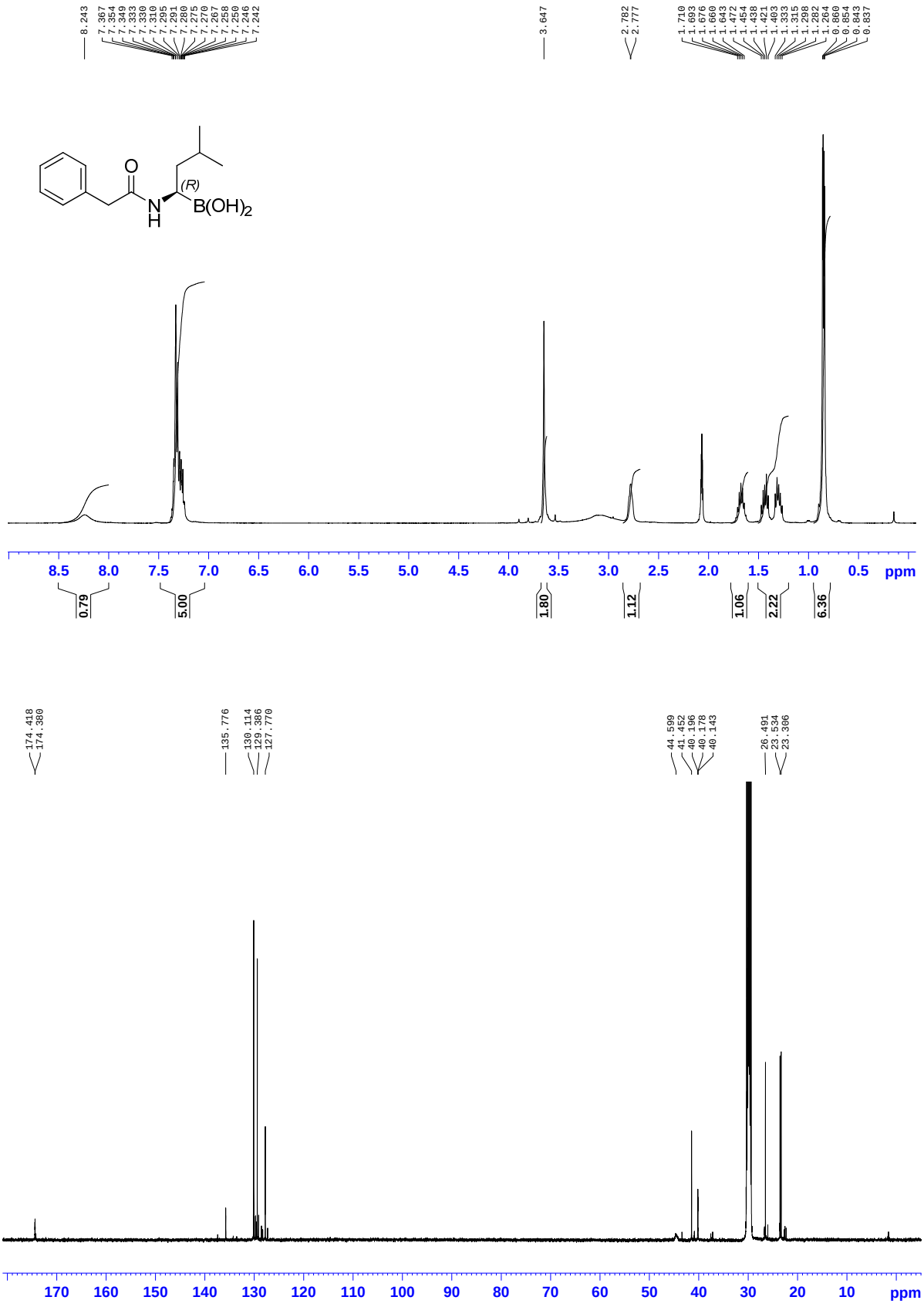


Figure S-37: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra (d_6-acetone) of **36.**

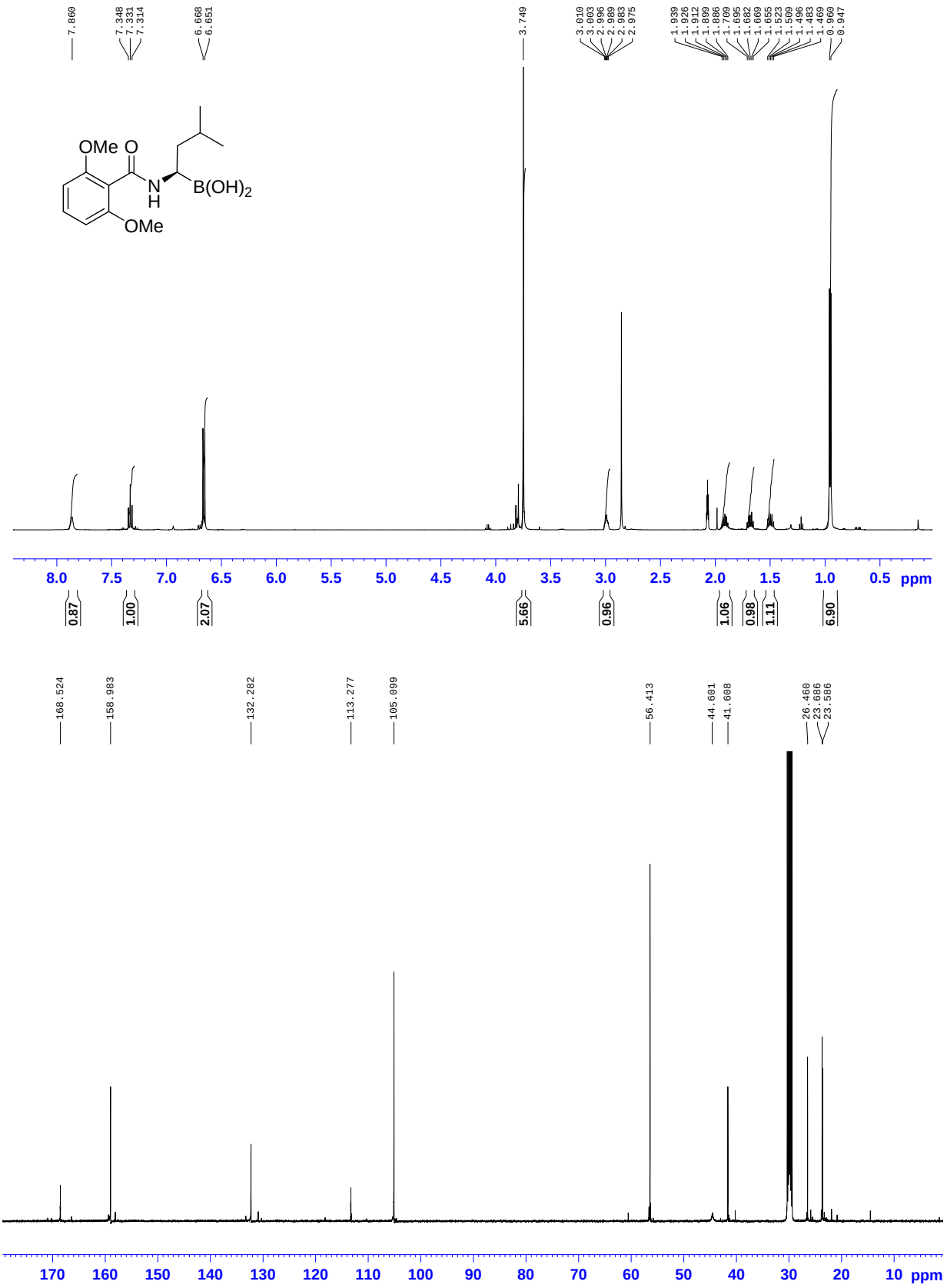


Figure S-38: ^{1}H (400 MHz) and ^{13}C (125 MHz) NMR spectra (d_6-DMSO) of **37.**

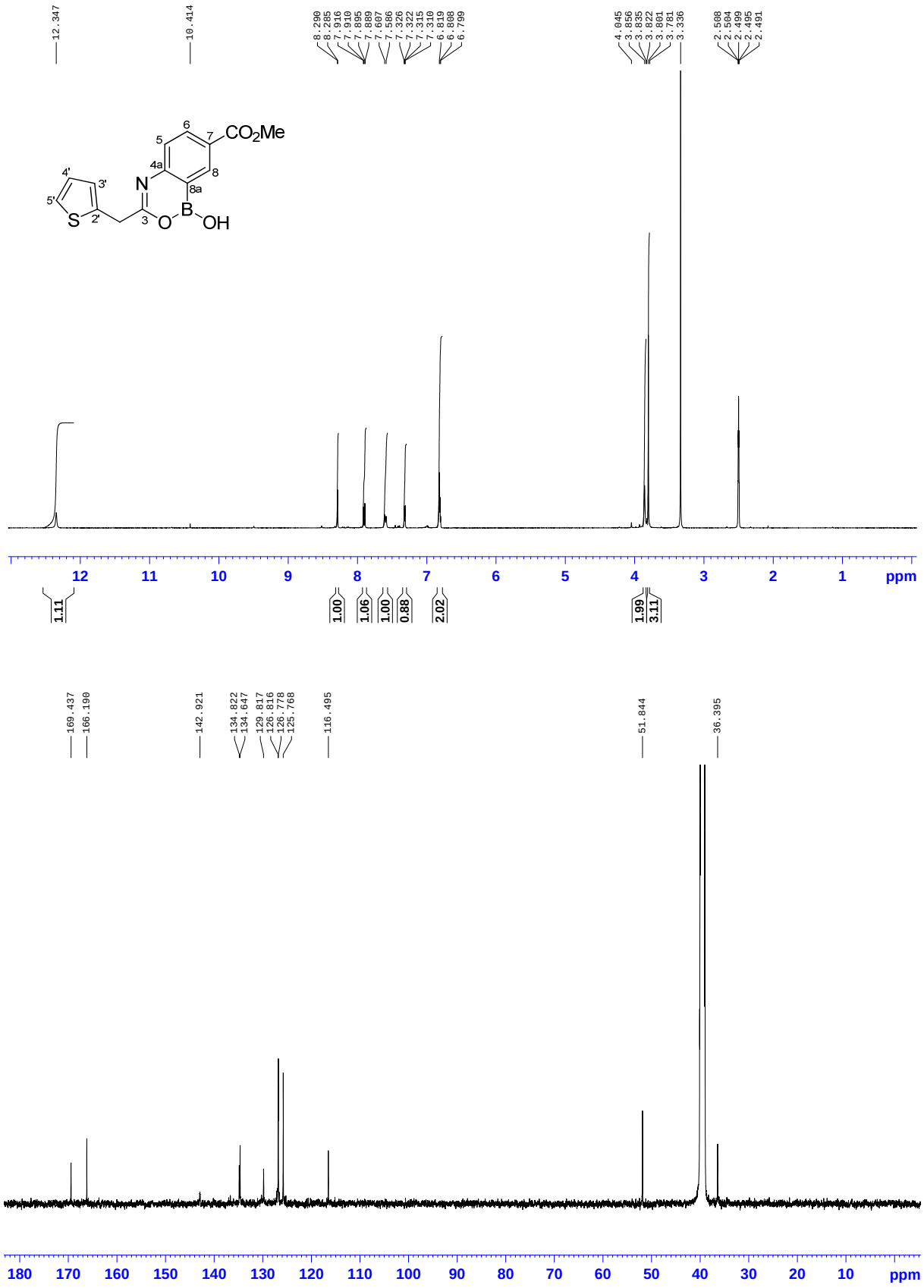


Figure S-39: ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra (d_6-DMSO) of **7.**

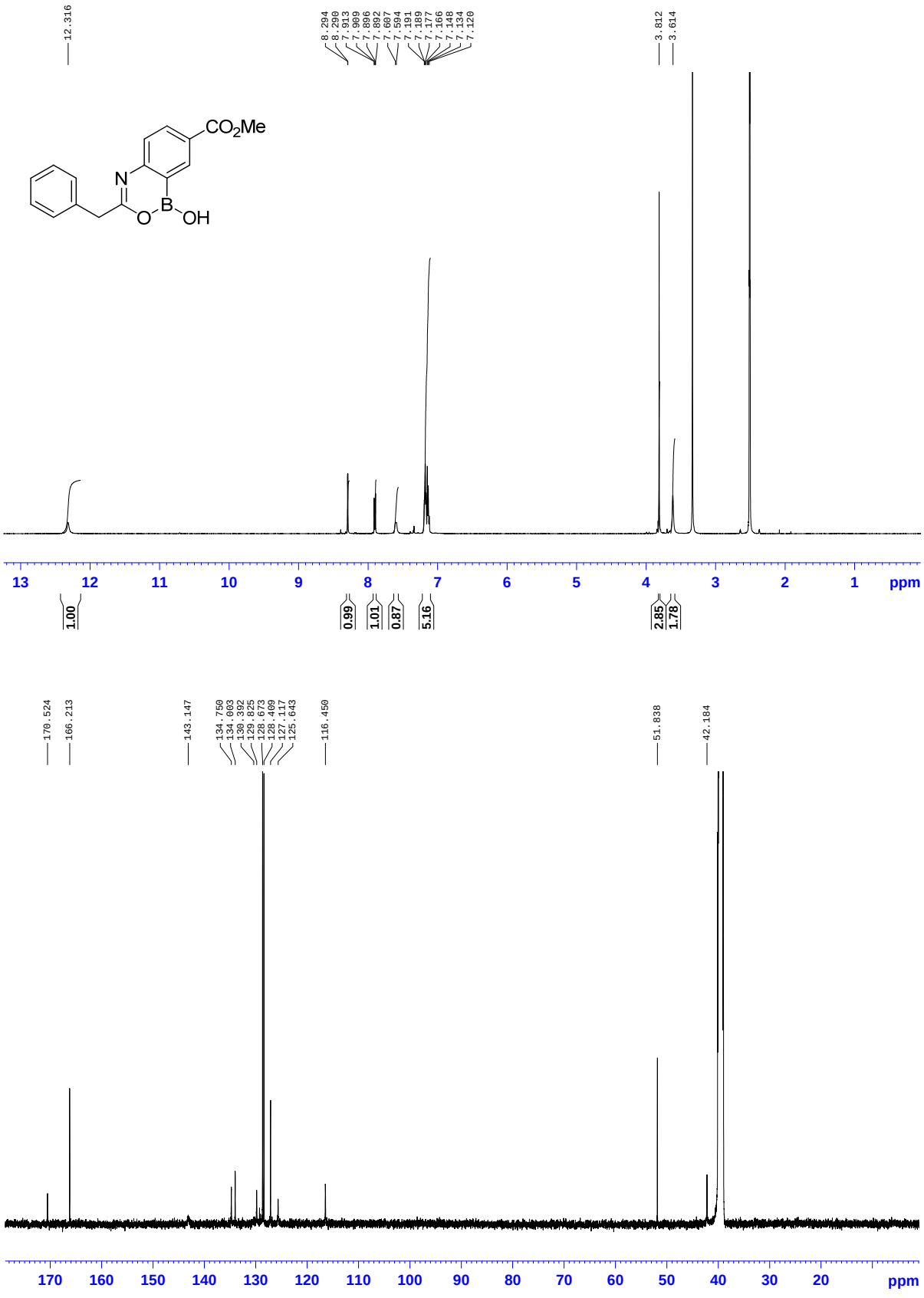
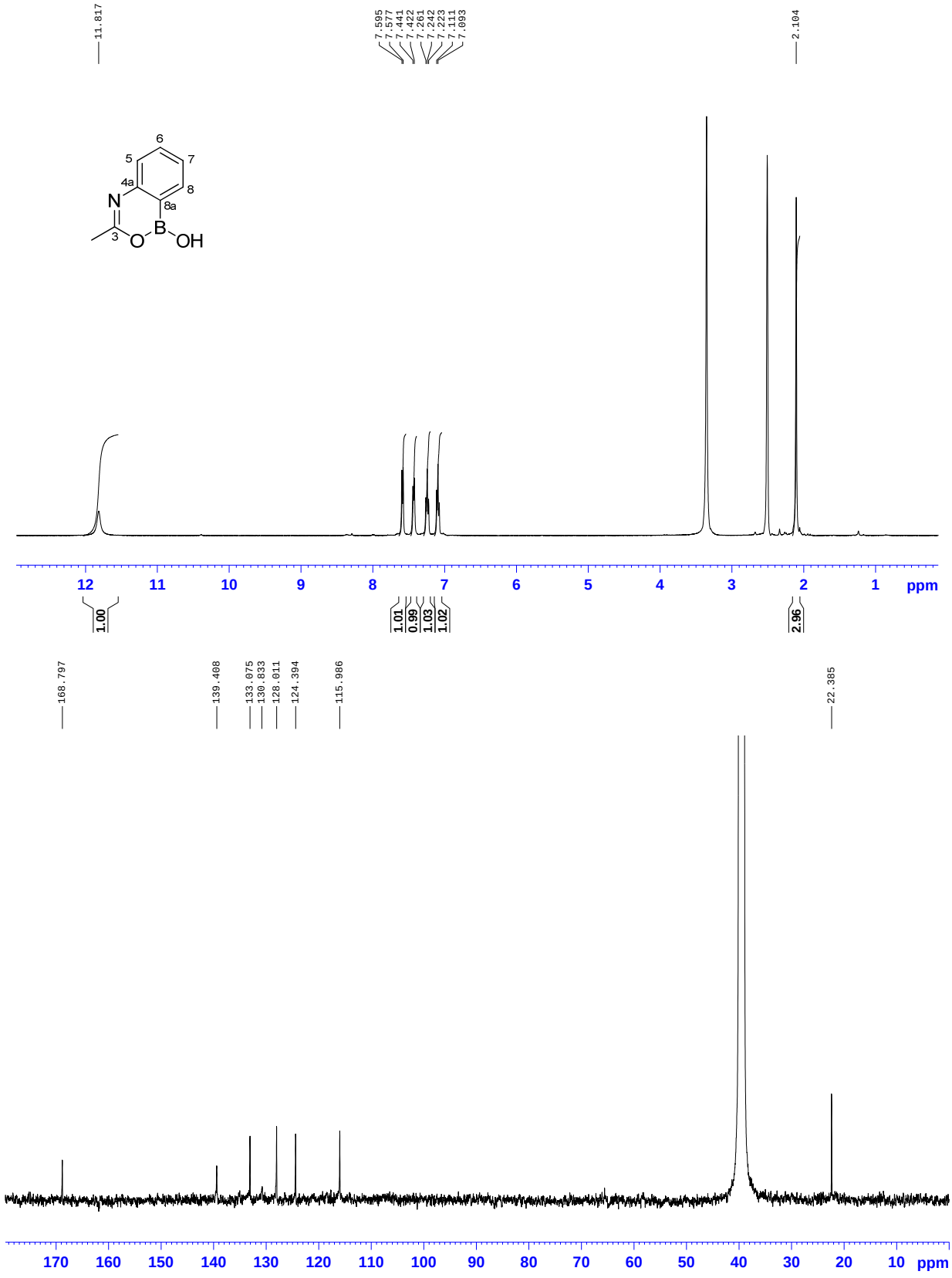


Figure S-40: ^{1}H (400 MHz) and ^{13}C (125 MHz) NMR spectra (d_6-DMSO) of **38.**



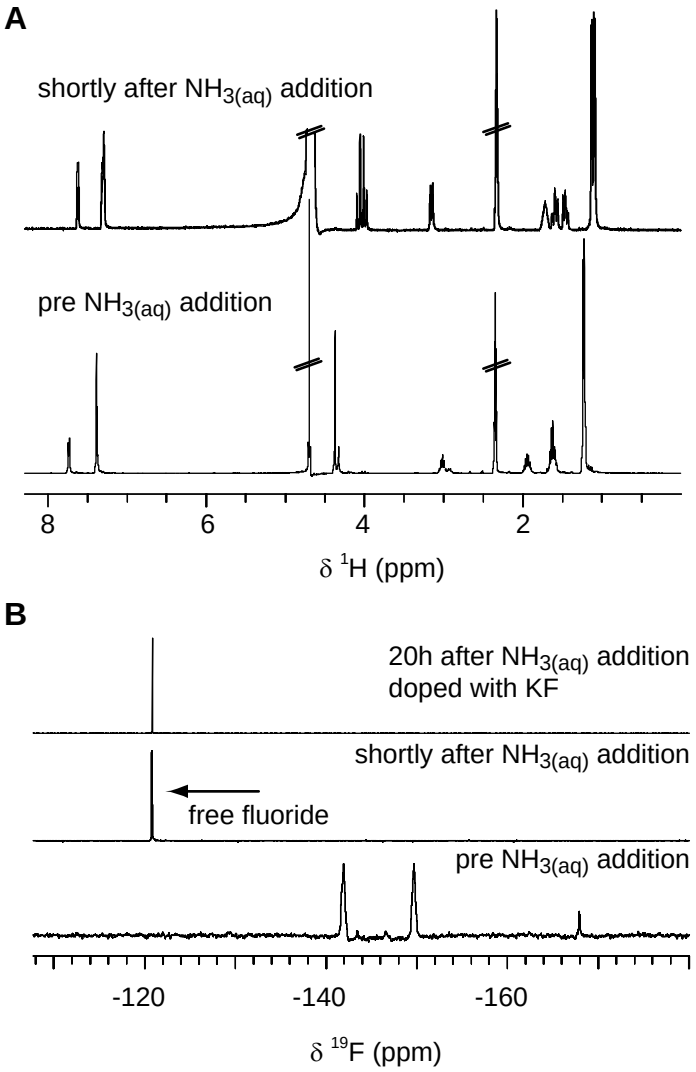


Figure S-41: NMR studies of the hydrolysis of difluoroborane **15** (3 mg in 600 μL of 1:1 CD_3CN/D_2O) to form boronic acid **34.** (A) Stack plot of 400 MHz ^1H spectra of **15** prior (bottom) to addition of 8% NH_3/D_2O and the resultant hydrolysis product shortly after (top). Residual solvent peaks are indicated with diagonal lines; (B) Stack plot of 377 MHz ^{19}F spectra of **15** prior (bottom) to addition of 8% NH_3/D_2O and the hydrolysis product shortly after (middle) revealing only free fluoride is present, confirmed by doping with KF (top).

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