Supporting Information for: Parallel Synthesis of Glycomimetic Libraries: Targeting a C-Type Lectin

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A. General Procedures:

Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter at room (21-22 °C). Concentrations (c) are reported in g/100 mL. Infrared spectra (IR) were obtained on a Perkin-Elmer Model 781 spectrometer or on a Mattson Polaris FT-IR equipped with a DTGS detector. Signals are reported in wavenumbers (cm^{-1}) with the designation (br) signifying a broad signal. Individual fluorescence measurements were obtained on a Hitachi F-4500 fluorescence spectrophotometer. When 96-well plates were utilized, fluorescent readings were taken on a molecular dynamics BioLumin 960 plate reader (Amersham Pharmacia, Piscataway, NJ). Results are reported as relative fluorescence units (RFU). Mass spectrometry was performed via electrospray ionization on a Finnigan TSQ 700 with a triple quadrupole analyzer. Proton nuclear magnetic resonance (^1H NMR) spectra were recorded in deuterated solvents ($CDCl_3$, CD_3OD, D_2O) on a Bruker AC-300 (300 MHz) a Bruker WP-250 MHz (250 MHz) spectrometer as indicated. Chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS, δ 0.00). Proton NMR splitting patterns are designated as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), sextet (sex), septet (sep), multiplet (m), apparent (ap), and broad (br) with the coupling constants reported in hertz (Hz). Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded in deuterated solvents ($CDCl_3$, CD_3OD, D_2O) on a Bruker AC-300 (75.4 MHz) spectrometer. Chemical shifts are reported in parts per million (ppm, δ) relative to tetramethylsilane (TMS, δ 0.00). Coincidental magnetically equivalent carbons are noted when relative signal intensity allowed assignment.

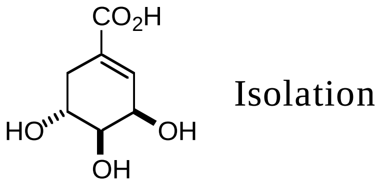
All moisture-sensitive reactions were performed in flame- or oven-dried glassware under a stream of nitrogen unless otherwise noted. External bath temperatures were used to record all reaction temperatures. Concentrated *in vacuo* refers to the removal of volatile solvents via distillation using a Büchi rotary evaporator at water aspirator pressure, followed by residual solvent removal under high vacuum (< 1 torr).

Analytical thin layer chromatography (TLC) was carried out on E. Merck (Darmstadt) TLC plates pre-coated with silica gel 60 F_{254} (250 μ layer thickness). Visualization was accomplished using UV light, iodine vapors, a *p*-anisaldehyde (PAA) charring solution (18 mL *p*-anisaldehyde, 7.5 mL glacial acetic acid, 25 mL 12.0 M H_2SO_4, 675 mL absolute EtOH), ninhydrin solution (200 mg ninhydrin, 95 ml butanol, 5 ml 10% AcOH), permanganate solution (3 g potassium permanganate, 20 g potassium carbonate, 5 ml 5% aqueous NaOH, 300 mL water) and/or phosphomolybdic acid (PMA) solution (10% PMA in EtOH). Flash column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Solvent mixtures for TLC and column chromatography are reported in either v_1/v_2 ratios or V_1/V_{total} x 100%.

Dowex 50Wx8-200 strongly acidic resin was washed and dried before use. The washing procedure involved copious rinsing of the resin with three cycles of water followed by methanol. After the final methanol rinse, the resin was allowed to air-dry and residual solvent was removed under high vacuum (< 1 torr).

Tetrahydrofuran (THF), diethyl ether (Et_2O), and benzene (PhH) were distilled from sodium/benzophenone ketyl immediately prior to use. To reduce the presence of water, *N*,*N*-dimethylformamide (DMF) was distilled under reduced pressure from sodium sulfate and stored over 4 Å molecular sieves. Alternatively, to only reduce the presence of amines, DMF was stored over washed and dried 50Wx8-200 Dowex strongly acidic resin (1 g/1 L) for at least one day prior to use. *tert*-Butanol was distilled from sodium sulfate and stored in a desiccator over 4 Å molecular sieves. Methanol (MeOH) was distilled from magnesium methoxide immediately prior to use. Dichloromethane (CH_2Cl_2), and triethylamine (Et_3N) were distilled from calcium hydride immediately prior to use. *N*-Bromosuccinimide was recrystallized from water and residual solvent was removed under high vacuum (< 1 torr). All other commercially obtained reagents and solvents were used as received without further purification unless otherwise indicated.

B. Solution Phase Synthetic Procedures:



1

Isolation of shikimic acid from Star Anise:

The spice star anise (120 g, Whole Foods Market, Madison, WI) was crushed with a mortar and pestle to a course powder. The resulting powder was subjected to Soxhlet extraction in five equal portions with 95% ethanol. The ethanol volume was maintained at 200 mL and each thimble of powder was extracted for at least 4 h. The organic extract was concentrated under aspiration to yield a thick green slurry that smelled strongly of anise.

The crude oil was dissolved in H_2O (500 mL) and heated to 80 °C. 37% formaldehyde/H_2O (2 mL) was added and the temperature was maintained at 80 °C for 5 min. The aqueous solution was let cool to rt and vacuum filtered. The solution was extracted with ethyl acetate (2 x 200 mL) and the aqueous layer was filtered through a 0.45 µ nylon filter.

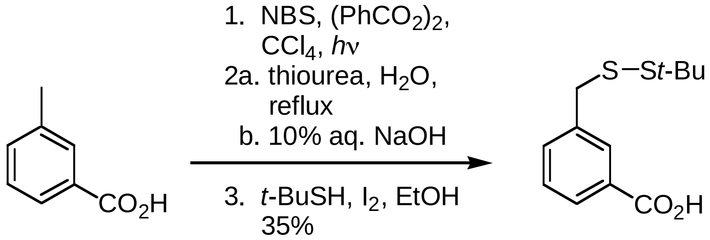
The entire aqueous solution was loaded onto a 13 x 5 cm column of Biorad AG1-X8 anion exchange resin in its acetate form. The column was flushed with H_2O (2 L) and the shikimic acid was then eluted with 25% acetic acid/H_2O (1.2 L). The shikimic acid solution was concentrated under aspiration to yield a dark-amber oil. Azeotrope removal of water with toluene under aspirator pressure resulted in the formation of an amber solid. The solid was crystallized from methanol/toluene at –20 °C to yield shikimic acid (3.89 g, 22.8 mmol), in two crops, as an off-white, amorphous solid.

Isolation of shikimic acid from *E. coli* strain A10807/pkD136/pCl-aroE:

E. coli strain A10807/pkD136/pCl-aroE was generously provided by Prof. John Frost (Department of Chemistry, Michigan State University). Briefly, a 50 mL culture of innoculum from a single colony of *E. coli* strain A10807/pkD136/pCl-aroE was grown overnight with shaking at 37 °C in Luria – Bertani medium (LB) containing ampicillin (50 µg/mL), spectinomycin (50 µg/mL), chloramphenicol (20 µg/mL), and tetracycline (12.5 µg/mL). The culture was transferred to 1 L $LB_{amp/spec/chlor/tet}$ and isopropylthiogalactoside (IPTG) was added (24 µg/mL). After shaking for 10 h at 37 °C, the turbid culture was centrifuged at 7500 rpm (5 °C) for 5 mins. The supernatant was discarded and the cells were suspended in 1 L M9 buffer (6 g Na_2HPO_4, 3 g $KHPO_4$, 1 g NH_4Cl, 0.5 g NaCl in 1 L) and shaken for 24 h at 37 °C. The M9 lysates were centrifuged at 7500 rpm (5 °C) for 10 mins and the cellular debris discarded. The lysate was further purified via filtration through a 0.45 µ nylon filter.

The aqueous solution was loaded onto a 14.5 x 5 cm column of Biorad AG1-X8 anion exchange resin in its acetate form. The column was flushed with H_2O (300 mL) and methanol (1 L) and the shikimic acid was then eluted with 1/1 glacial acetic acid/methanol (800 mL). The shikimic acid solution was concentrated *in vacuo* and residual acetic acid was removed by azeotrope formation with toluene. The oil was dissolved in methanol (250 mL) and activated carbon (2 g) was added. After stirring 1.5 h, the mixture was filtered through a plug of celite and the organics concentrated *in vacuo*. Shikimic acid (2.21 g) was obtained as an off-white, amorphous solid.

Data for compound **1**: Rf 0.38 (5:4:1 $CHCl_3$/MeOH/H_2O); ^1H NMR (D_2O, 300 MHz) δ 6.64 (ddd, 1 H, *J* = 4.0, 1.8, 1.5 Hz), 4.25-4.30 (m, 1 H), 3.83 (ddd, 1 H, *J* = 8.0, 7.4, 6.0 Hz), 3.58 (dd, 1 H, *J* = 8.0, 4.0 Hz), 2.51 (dddd, 1 H, *J* = 18.0, 6.0, 1.5, 1.5 Hz), 2.02 (ddddd, 1 H, *J* = 18.0, 7.4, 2.1, 1.8, 0.3 Hz); ^{13}C NMR (1:1 D_2O/CD_3OD, 75 MHz) δ 170.72, 138.67, 130.81, 72.48, 67.93, 67.10, 31.63; MS (ESI) *m/e* 349.12 (2M + H^+, $2(C_7H_{10}O_5) + H^+$ calcd 349.11)



14 **15**

Synthesis of **15**:

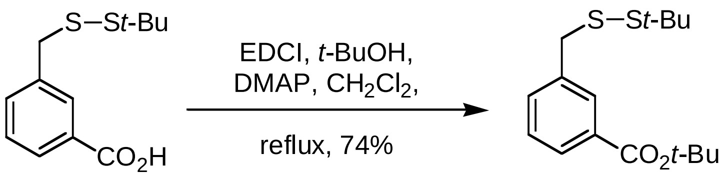
To a solution of *m*-toluic acid (7.50 g, 55.1 mmol) in CCl_4 (55 mL) was added recrystallized *N*-bromosuccinimide (10.3 g, 57.8 mmol) and a catalytic amount of benzoyl peroxide (40.2 mg, 0.166 mmol). A reflux condenser was attached to the flask, and the reaction was irradiated with a

250 W light bulb for 9 h. During its course, the reaction solution turned from yellow to orange and back to white. The reaction mixture was diluted with $CHCl_3$ (200 mL) and was washed with 0.2 M aqueous HCl. (2 x 80 mL). The organics were dried with brine (100 mL) and Na_2SO_4, filtered and concentrated *in vacuo*. The crude bromide (11.6 g) was obtained as a white, amorphous solid.

To a flask containing 11.6 g of the crude bromide was added H_2O (74 mL) and thiourea (4.11 g, 54.0 mmol). The flask was equipped with a condenser, heated to reflux for 1 h, and then allowed to cool to rt. 10 % aqueous NaOH (55 mL) was added and the reaction was refluxed 1 h. The reaction mixture was cooled to 0 °C and 2 M HCl was added until the reaction was slightly acidic. A yellow precipitate formed that was isolated by vacuum filtration providing 7.42 g crude thiol.

Crude thiol (7.206 g) was dissolved in 95% EtOH (30 mL) and 2-methyl-2-propanethiol (29 mL , 257 mmol) was added. The thiol solution was cooled to 0 °C and a solution of iodine (6.57 g, 25.7 mmol) in 95% EtOH (66 mL) was added dropwise over 30 min until the reaction changed from colorless to red. After stirring for 90 min, saturated aqueous $NaHCO_3$ was added until the reaction was neutral. The flask was removed from the ice bath and concentrated *in vacuo* (utilizing a bleach trap) to provide a black syrup. Ethyl acetate (150 mL) was added to the oil and the organics were washed 10% $NaHSO_3$ (3 x 10 mL). The pale yellow organics were dried with brine (80 mL) and Na_2SO_4, filtered and concentrated *in vacuo*. The disulfide was purified by chromatography (1:5:94 glacial acetic acid/ethyl acetate/hexanes). The desired product **15** (4.93 g, 19.2 mmol, 35% over 3 steps) was obtained as a white, crystalline solid.

Data for compound **15**: Rf 0.29 (20% ethyl acetate/hexanes); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.04 (dd, 1 H, J = 1.6, 1.6 Hz), 8.03 (ddd, 1 H, J = 7.0, 1.6, 1.6 Hz), 7.53 (ddd, H, J = 7.0, 1.6,



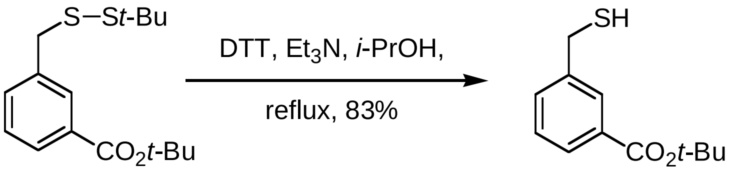
15 **16**

1.6 Hz), 7.44 (dd, 1 H, *J* = 7.0, 7.0 Hz), 3.98 (s, 2 H), 1.36 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.16, 138.11, 134.68, 130.95, 129.53, 129.22, 128.75, 48.20, 44.85, 30.02; MS (ESI) *m/e* 255.0503 (M - H^+ $[C_{12}H_{14}O_2S_2]^-$ calcd 255.0513)

Synthesis of **16**:

To a flask containing **15** (1.94 g, 7.55 mmol) and DMAP (0.952 g, 7.79 mmol) was added CH_2Cl_2 (18 mL) and *tert*-butanol (9 mL, 94.1 mmol). 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.18 g, 11.4 mmol) was added and the solution was heated at reflux for 3 days. After cooling to rt the solvent was removed from the reaction mixture *in vacuo*. Ethyl acetate (100 mL) was added to the residue and the organics were washed with H_2O (20 mL) and saturated aqueous $NaHCO_3$ (2 x 20 mL). The organic layer was washed with brine (20 mL) and dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by chromatography (8% ethyl acetate/hexanes) yielding **16** (1.75 g, 5.61 mmol, 74%) as a clear, colorless oil.

Data for compound **16**: Rf 0.64 (20% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.93 (dd, 1 H, *J* = 1.2, 1.2 Hz), 7.90 (ddd, 1 H, *J* = 7.3, 1.2, 1.2 Hz), 7.48 (ddd, 1 H, *J* = 7.3, 1.2, 1.2 Hz), 7.38 (dd, 1 H, *J* = 7.3, 7.3 Hz), 3.96 (s, 2 H), 1.61 (s, 3 H), 1.46 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.47, 137.54, 133.20, 132.23, 130.16, 128.43, 81.07, 48.14, 45.12, 30.01, 28.16; MS (ESI) *m/e* 313.1283 (M + H^+ $[C_{16}H_{25}O_2S_2]^+$ calcd 313.1296)

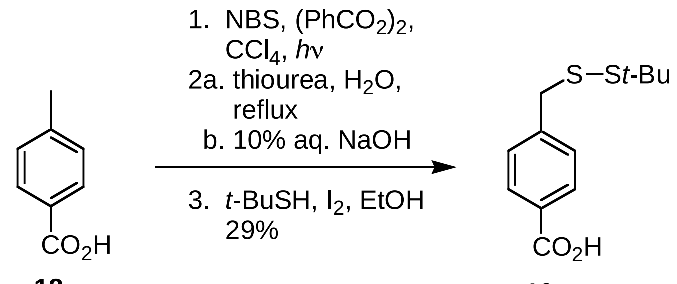


16 **17**

Synthesis of **17**:

To a flask containing **16** (0.445 g, 1.43 mmol) was added DTT (0.650 g, 4.22 mmol) and deoxygenated *iso*-propanol (8 mL). Triethylamine (0.5 mL) was added and the reaction was heated to reflux for 24 h. After cooling to rt, the reaction mixture was concentrated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2 (20 mL) and washed with H_2O (3 x 5 mL). The organic layer was dried with brine (10 mL) and Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by chromatography (5% ethyl acetate/hexanes) to yield **17** (0.265 g, 1.18 mmol 83%) as a colorless, crystalline solid.

Data for compound **17**: Rf 0.61 (20% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.93 (ddd, 1 H, *J* = 2.0, 2.0, 1.0 Hz), 7.87 (ddd, 1 H, *J* = 8.0, 1.8, 2.0 Hz), 7.48 (dddd, 1 H, *J* = 7.5, 2.0, 1.8, 1.0 Hz), 7.36 (t, 1 H, *J* = 7.5 Hz), 3.74 (d, 2 H, *J* = 7.7 Hz), 1.80 (t, 1 H, *J* = 7.7 Hz), 1.61 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.20, 141.14, 132.16, 131.94, 128.74, 128.39, 127.91, 80.86, 42.56, 27.97



18

19

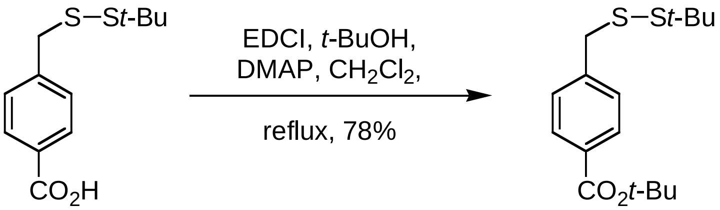
Synthesis of **19**:

To a solution of *p*-toluic acid (7.50 g, 55.1 mmol) in CCl_4 (55 mL) was added recrystallized *N*-bromosuccinimide (10.3 g, 57.8 mmol) and a catalytic amount of benzoyl peroxide (41.3 mg, 0.171 mmol). A reflux condenser was attached to the flask and the reaction was irradiated with a 250 W bulb for 9 h. During its course, the reaction solution turned from yellow to orange and back to white. The reaction mixture was diluted with $CHCl_3$ (500 mL) and washed with 0.2 M aqueous HCl (2 x 100 mL), H_2O (100 mL), 10% $NaHSO_3$ (100 mL), and brine (150 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. 7.55 g of the crude bromide was obtained as a white, amorphous solid.

To a flask containing the crude bromide (7.50 g) was added H_2O (55 mL) and thiourea (2.65 g, 34.9 mmol). The flask was equipped with a condenser, heated to reflux for 1 h, and then allowed to cool to rt. A solution of 10 % aqueous NaOH (40 mL) was added and the reaction was heated at reflux for 1 h. The reaction mixture was cooled to 0 °C and 2 M HCl was added until the reaction was slightly acidic. A yellow precipitate formed that was isolated by vacuum filtration providing crude thiol (5.67 g).

Crude thiol (l5.59 g) was dissolved in 95% EtOH (22 mL) and 2-methyl-2-propanethiol (22 mL, 260 mmol) was added. The resulting solution was cooled to 0 °C and a solution of iodine (5.08 g, 20.0 mmol) in 95% EtOH (44 mL) was added dropwise over 30 min until the color of the reaction changed from colorless to red. After stirring for 90 min, saturated aqueous $NaHCO_3$ was added until the pH of the reaction was neutral. The flask was removed from the ice bath and the solution was concentrated *in vacuo* (utilizing a bleach trap) to provide a yellow solid. Ethyl acetate (400 mL) was added to the oil and the organic layer weas washed with 10% $NaHSO_3$ (3 x 10 mL and brine (80 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The disulfide was purified by chromatography (1:5:94 glacial acetic acid/ethyl acetate/hexanes). The desired product **19** (4.13 g, 16.1 mmol, 29% over 3 steps) was obtained as a white, crystalline solid.

Data for compound **19**: **Rf** 0.18 (20% ethyl acetate/hexanes); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 11.23 (br s, 1 H), 8.04 (ap d, 2 H, *J* = 8.0 Hz), 7.27 (ap d, 2 H, *J* = 8.0 Hz), 3.98 (s, 2 H), 1.18 (s, 9 H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 172.17, 143.82, 130.46, 129.35, 128.27, 48.21, 45.03, 29.99; **MS** (ESI) *m/e* 255.0512 (M - H^+ $[C_{12}H_{14}O_2S_2]^-$ calcd 255.0514)



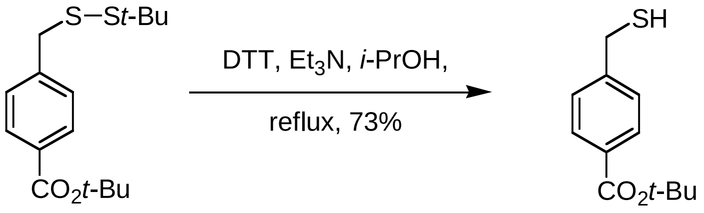
19 **20**

Synthesis of **20**:

To a flask containing **19** (4.13 g, 16.1 mmol) and DMAP (1.97 g, 16.1 mmol) was added CH_2Cl_2 (32 mL) and *tert*-butanol (25.0 mL, 261 mmol). 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.63 g, 24.2 mmol) was added, and the solution was heated to reflux for 3 days. After cooling to rt, the solvent was removed from the reaction mixture *in vacuo*. Ethyl acetate(200 mL) was added to the residue and the organics were washed with H_2O

(60 mL), saturated aqueous $NaHCO_3$ (2 x 75 mL), and brine (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (3% ethyl acetate/hexanes) to afford of **20** (3.91 g, 12.5 mmol, 78%) as a pale-pink, crystalline solid.

Data for compound **20**: Rf 0.66 (20% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.94 (ap d, 2 H, *J* = 7.7 Hz), 7.35 (ap d, 2 H, *J* = 7.7 Hz), 3.94 (s, 2 H), 1.60 (s, 9 H), 1.35 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.47, 142.10, 130.96, 129.62, 129.02, 80.93, 48.14, 45.07, 29.98, 28.16; MS (ESI) *m/e* 313.1293 (M + H^+ $[C_{16}H_{25}O_2S_2]^+$ calcd 313.1296)



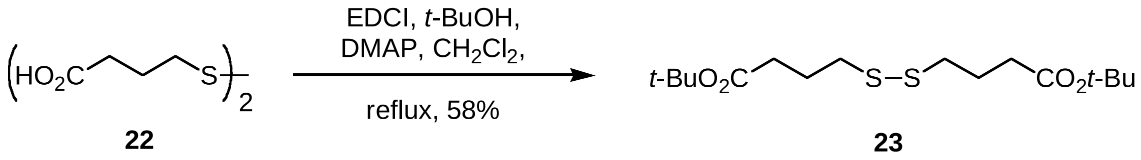
20 **21**

Synthesis of **21**:

To a flask containing **20** (3.10 g, 9.90 mmol) was added (±)-dithiothreitol (2.30 g, 14.9 mmol) and deoxygenated *iso*-propanol. (50 mL). Triethylamine (3 mL) was added and the reaction was heated at reflux for 24 hrs. After cooling to rt, the reaction mixture was concentrated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2 (100 mL) and washed with H_2O (3 x 30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by chromatography (5% ethyl acetate/hexanes) to yield **21** (1.62 g, 7.20 mmol, 73%) as a colorless, crystalline solid.

Data for compound **21**: Rf 0.61 (20% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.94 (ap d, 2 H, *J* = 6.8 Hz), 7.33 (ap d, 2 H, *J* = 6.8 Hz), 3.69 (d, 2 H, *J* = 8.0 Hz), 1.79 (t, 1 H, *J*

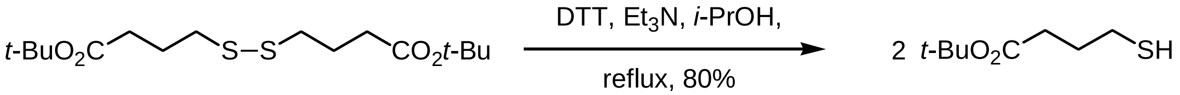
= 8.0 Hz), 1.58 (s, 9H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 164.86, 145.46, 130.28, 129.42, 127.51, 80.38, 42.27, 27.79



Synthesis of **23**:

To a flask containing **22** (0.211 g, 0.839 mmol) and DMAP (0.207 g, 1.68 mmol) was added CH_2Cl_2 (4.2 mL) and *tert*-butanol (2.60 mL, 26.9 mmol). 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.488 g, 2.52 mmol) was added and the solution was heated at reflux for 6 days. After cooling to rt, the solvent was removed from the reaction mixture *in vacuo*. Ethyl acetate (10 mL) was added to the residue and the organics were washed with H_2O (2 mL), saturated aqueous $NaHCO_3$ (2 x 3 mL) and brine (3 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography (7% ethyl acetate/hexanes) to afford of **23** (0.181 g, 0.487 mmol, 58%) as a clear, yellow oil.

Data for compound **23**: Rf 0.46 (10% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.64 (t, 6 H, *J* = 7.0 Hz), 2.28 (t, 6 H, *J* = 7.2 Hz), 1.91 (tt, 6 H, *J* = 7.2, 7.0 Hz), 1.38 (s, 18 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.07, 80.18, 37.77, 3.74, 27.95, 24.27; MS (ESI) *m/e* 351.1647 (M + H^+ $[C_{16}H_{31}O_4S_2]^+$ calcd 351.1664)

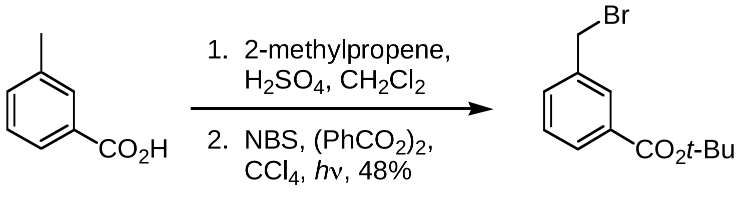


23 **24**

Synthesis of **24**:

To a flask containing **23** (0.896 g, 2.56 mmol) was added DTT (0.475 g, 3.080 mmol) and deoxygenated *iso*-propanol. (12.8 mL). Triethylamine (0.35 mL, 2.5 mmol) was added and the reaction was heated at reflux for 2 days. After cooling to rt, the reaction mixture was concentrated *in vacuo*. The resulting oil was dissolved in CH_2Cl_2 (50 mL) and the mixture was washed with H_2O (3 x 40 mL) and brine (35 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product **24** was isolated a pungent, clear, colorless oil (0.721 g, 4.10 mmol, 80%) that was not purified further.

Data for compound **24**: Rf 0.56 (20% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.57 (ddd, 2 H, *J* = 13.9, 7.5, 6.8 Hz), 2.36 (t, 2 H, *J* = 7.5 Hz), 1.79 (dt, 2 H, *J* = 13.9, 6.8 Hz), 1.46 (s, 9 H), 1.36 (t, 1 H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.27, 80.34, 33.90, 29.18, 28.04, 23.96; MS (ESI) *m/e* 177.0936 (M + H^+ $[C_{16}H_{25}O_2S_2]^+$ calcd 177.0949)



14 **25**

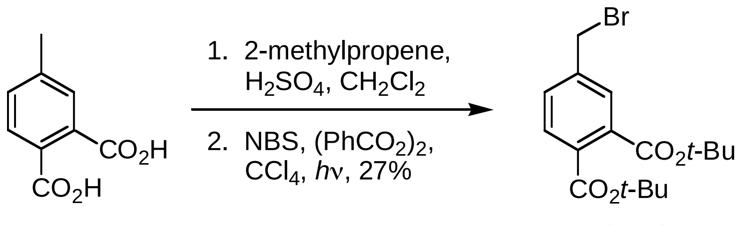
Synthesis of **25**:

To a 100 mL round bottom flask containing *m*-toluic acid (5.11 g, 37.6 mmol) was added CH_2Cl_2 (15 mL). The flask was cooled to $^-$12 °C in a $NaCl_{(s)}/H_2O_{(l)}/H_2O_{(s)}$ bath and 2-

methylpropene (approximately 10 mL) was condensed in the mixture. Concentrated H_2SO_4 (0.5 mL) was carefully added by pipette and the flask was sealed with a glass stopper. The glass stopper was wired to the flask and the reaction was let warm to rt behind a protective shield. After stirring for 2 days, the flask was cooled to ⁻12 °C in a $NaCl_{(s)}/H_2O_{(l)}/H_2O_{(s)}$ bath and the contents of the flask were poured into a beaker containing saturated aqueous $NaHCO_3$ (50 mL). The contents of the beaker were stirred at rt for 1 h, and then CH_2Cl_2 (20 mL) was added. In a separatory funnel, the aqueous layer was partitioned, and the organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 10 mL), H_2O (10 mL), and brine (10 mL). The organic layer was dried Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude ester (7.31 g).

To a solution of the crude ester in CCl_4 (38 mL) was added recrystallized *N*-bromosuccinimide (6.80 g, 38.2 mmol) and a catalytic amount of benzoyl peroxide (20 mg, 0.083 mmol). A reflux condenser was attached to the flask and the mixture was irradiated wth a 250 W bulb for 15 h. During its course, the reaction solution turned orange and then returned to an off-white color. The reaction mixture was diluted with CH_2Cl_2 (300 mL) and the organic layer was washed with H_2O (2 x 100 mL), saturated aqueous $NaHCO_3$ (100 mL), H_2O (100 mL), and brine (100 mL). The resulting solution was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude bromide was recrystallized from hexanes at –20 °C to yield of **25** (4.91 g, 18.1 mmol, 48% over 2 steps) as a white crystalline solid.

Data for compound **25**: **Rf** 0.45 (10% ethyl acetate/hexanes); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 8.03 (dd, 1 H, *J* = 1.5, 1.5 Hz), 7.93 (ddd, 1 H, *J* = 7.5, 1.5, 1.5 Hz), 7.54 (ddd, 1 H, *J* = 7.5, 1.5, 1.5 Hz), 7.39 (dd, 1 H, *J* = 7.5, 7.5 Hz), 4.49 (s, 2 H), 1.59 (s, 9 H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 164.94, 137.84, 132.90, 132.46, 129.74, 129.28, 128.65, 81.17, 32.59, 28.05.



26

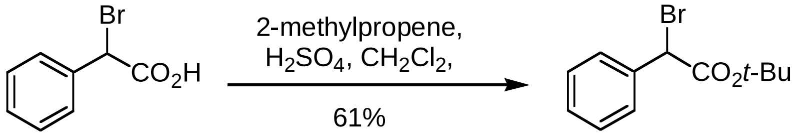
27 (B17)

Synthesis of **27**:

To a 100 mL round bottom flask containing 4-methyphthalic acid (5.0 g, 28 mmol) was added CH_2Cl_2 (9 mL). The flask was cooled to –12 °C in a $NaCl_{(s)}/H_2O_{(l)}/H_2O_{(s)}$ bath and 2-methylpropene (approximately 10 mL) was condensed in the reaction. Concentrated H_2SO_4 (0.5 mL) was carefully added by pipette and the flask was sealed with a glass stopper. The glass stopper was wired to the flask and the reaction was let warm to rt behind a protective shield. After stirring for 4 days, the flask was cooled to –12 °C in a $NaCl_{(s)}/H_2O_{(l)}/H_2O_{(s)}$ bath and the contents of the flask were poured into a beaker containing saturated aqueous $NaHCO_3$ (50 mL). The contents of the beaker were stirred at rt for 1 h and then CH_2Cl_2 (20 mL) was added. In a separatory funnel, the aqueous layer was partitioned, and the organic layer washed with saturated aqueous $NaHCO_3$ (2 x 10 mL), H_2O (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude bis-ester (6.49 g).

To a solution of the crude bis-ester in CCl_4 (22 mL) was added recrystallized N-bromosuccinimide (4.8 g, 27 mmol) and a catalytic amount of benzoyl peroxide (16 mg, 0.066 mmol). A reflux condenser was attached to the flask and the mixture was irradiated with a 250 W bulb for 7 hs. During its course, the reaction solution turned red-orange. The reaction mixture was diluted with CH_2Cl_2 (300 mL) and washed with H_2O (2 x 100 mL), saturated aqueous $NaHCO_3$ (100 mL) and H_2O (100 mL), and brined (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude bromide was purified by flash chromatography using a solvent gradient (1%, 3%, 5%, 7%, and 9% ethyl acetate/hexanes) to provide **27** (2.76 g, 7.41 mmol, 27% over 2 steps) as a crystalline, white solid.

Data for compound **27**: Rf 0.33 (10% ethyl acetate/hexanes); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.62 (d, 1 H, *J* = 1.8 Hz), 7.59 (d, 1 H, *J* = 7.9 Hz), 7.45 (dd, 1 H, *J* = 7.9, 1.8 Hz), 4.46 (s, 2 H), 1.61 (s, 9 H), 1.59 (s, 9 H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 166.10, 166.06, 140.09, 134.23, 133.41, 130.72, 129.19, 129.05, 81.97, 81.83, 31.54, 27.88



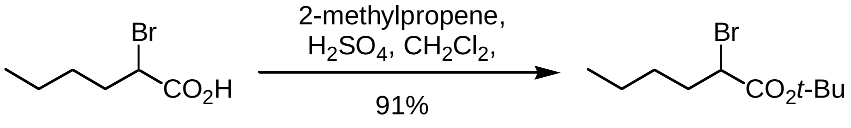
28 **29 (B13)**

Synthesis of **29**:

To a 100 mL round bottom flask containing **28** (5.13 g, 23.9 mmol) was added CH$_2$Cl$_2$ (10 mL). The flask was cooled to –12 °C in a NaCl$_{(s)}$/H$_2$O$_{(l)}$/H$_2$O$_{(s)}$ bath and 2-methylpropene (approximately 10 mL) was condensed in the reaction. Concentrated H$_2$SO$_4$ (0.5 mL) was carefully added by pipette and the flask was sealed with a glass stopper. The glass stopper was wired to the flask and the reaction was let warm to rt behind a protective shield. After stirring for 3 days, the flask was cooled to –12 °C in a NaCl$_{(s)}$/H$_2$O$_{(l)}$/H$_2$O$_{(s)}$ bath and the contents of the flask were poured into a beaker containing saturated aqueous NaHCO$_3$ (50 mL). The contents of the beaker were stirred at rt for 1 h and then CH$_2$Cl$_2$ (20 mL) was added. In a separatory funnel, the aqueous layer was partitione, and the organic layer washed with saturated aqueous NaHCO$_3$ (2 x 10 mL), H$_2$O (10 mL), and brine (10 mL). The organic layer was dried over Na$_2$SO$_4$, filtered and concentrated *in vacuo*. The crude ester was purified by fractional distillation under high vacuum

(< 1 torr). It distilled over at 115 °C., and compound **29** (3.95 g, 14.6 mmol, 61%) was obtained as a clear, colorless oil.

Data for compound **29**: Rf 0.53 (10% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50-7.55 (m, 2 H), 7.30-7.35 (m, 3 H), 5.27 (s, 1 H), 1.46 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.98, 136.12, 128.85, 128.51, 128.44, 82.78, 48.14, 27.53



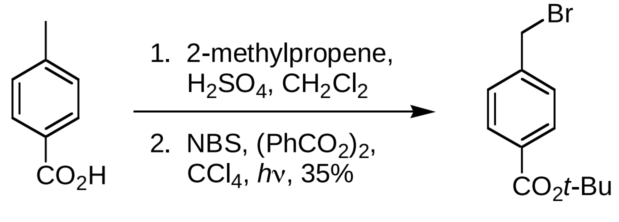
30

31 (B14)

Synthesis of **31**:

To a Schlenk-type sealing tube containing **30** (3.0 mL, 21 mmol) was added CH_2Cl_2 (5 mL). The tube was cooled to –12 °C in a $NaCl_{(s)}/H_2O_{(l)}/H_2O_{(s)}$ bath and 2-methylpropene (approximately 4 mL) was condensed into the reaction. Concentrated H_2SO_4 (0.1 mL) was carefully added by pipette and the flask was sealed with its threaded Teflon stopper. The reaction was let warm to rt behind a protective shield. After stirring for 3 days, the flask was cooled to –12 °C in a $NaCl_{(s)}/H_2O_{(l)}/H_2O_{(s)}$ bath and the contents of the flask were poured into a beaker containing saturated aqueous $NaHCO_3$ (50 mL). The contents of the beaker were stirred at rt for 1 h and then CH_2Cl_2 (20 mL) was added. In a separatory funnel, the aqueous layer was partitioned and the organic layer washed with saturated aqueous $NaHCO_3$ (2 x 10 mL), H_2O (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude ester was purified by flash chromatography (hexanes) to afford of **31** (4.72 g, 18.8 mmol, 91%) as a clear, colorless oil.

Data for compound **31**: Rf 0.76 (10% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.12 (t, 1 H, *J* = 7.0 Hz), 1.92-2.08 (m, 2 H), 1.48 (s, 9 H), 1.30-1.40 (m, 4 H), 0.93 (t, 3 H, *J* = 6.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.86, 82.05, 47.75, 34.61, 29.33, 27.67, 21.96, 13.77



18 **32 (B15)**

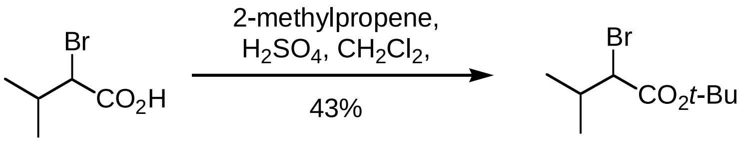
Synthesis of **32**:

To a 100 mL round bottom flask containing *p*-toluic acid (5.20 g, 38.2 mmol) was added CH_2Cl_2 (15 mL). The flask was cooled to –12 °C in a $NaCl_{(s)}/H_2O_{(l)}/H_2O_{(s)}$ bath and 2-methylpropene (approximately 10 mL) was condensed into the reaction. Concentrated H_2SO_4 (0.5 mL) was carefully added by pipette and the flask was sealed with a glass stopper. The glass stopper was wired to the flask and the reaction was let warm to rt behind a protective shield. After stirring for 2 days, the flask was cooled to –12 °C in a $NaCl_{(s)}/H_2O_{(l)}/H_2O_{(s)}$ bath and the contents of the flask were poured into a beaker containing saturated aqueous $NaHCO_3$ (50 mL). The contents of the beaker were stirred at rt for 1 h and then CH_2Cl_2 (20 mL) was added. In a separatory funnel, the aqueous layer was partitioned and the organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 10 mL), H_2O (10 mL), and brine (10 mL). The organic layer was dried using Na_2SO_4, filtered and concentrated *in vacuo* to afford the crude ester (6.51 g).

To a solution of the crude ester in CCl_4 (38 mL) was added recrystallized *N*-bromosuccinimide (6.095 g, 34.2 mmol) and a catalytic amount of benzoyl peroxide (25 mg, 0.10 mmol). A reflux condenser was attached to the flask and the mixture was irradiated with a

250 W bulb for 15 h. During its course, the reaction solution turned orange and then returned to an off-white color. The reaction mixture was diluted with CH_2Cl_2 (300 mL), and the mixture was washed with H_2O (2 x 100 mL), saturated aqueous $NaHCO_3$ (100 mL), H_2O (100 mL), and brine (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude bromide was purified by distillation under high vacuum (< 1 torr) and distilled over at 125 °C .to afford **32** (3.65 g, 13.4 mmol, 35% over 2 steps) as an off-white solid.

Data for compound **32**: **Rf** 0.59 (10% ethyl acetate/hexanes); **^{1}H NMR** ($CDCl_3$, 300 MHz) δ 7.96 (ap d, 2 H, *J* = 8.4 Hz), 7.42 (ap d, 2 H, *J* = 8.4 Hz), 4.49 (s, 2 H), 1.60 (s, 9H); **^{13}C NMR** ($CDCl_3$, 75 MHz) δ 165.07, 142.01, 131.88, 129.83, 128.78, 81.14, 32.32, 28.10



33

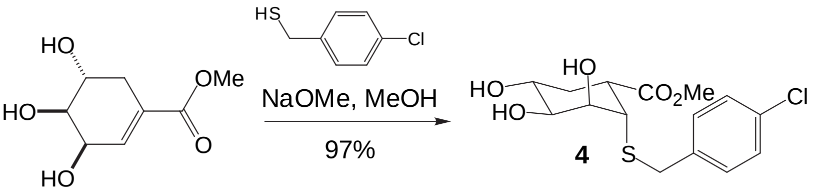
34 (B16)

Synthesis of **34**:

To a 100 mL round bottom flask containing **33** (5.087 g, 28.1 mmol) was added CH_2Cl_2 (10 mL). The flask was cooled to –12 °C in a $NaCl_{(s)}/H_2O_{(l)}/H_2O_{(s)}$ bath and 2-methylpropene (approximately 10 mL) was condensed into the reaction. Concentrated H_2SO_4 (0.5 mL) was carefully added by pipette and the flask was sealed with a glass stopper. The glass stopper was wired to the flask and the reaction was let warm to rt behind a protective shield. After stirring for 3 days, the flask was cooled to –12 °C in a $NaCl_{(s)}/H_2O_{(l)}/H_2O_{(s)}$ bath and the contents of the flask were poured into a beaker containing saturated aqueous $NaHCO_3$ (50 mL). The contents of the beaker were stirred at rt for 1 h and then CH_2Cl_2 (20 mL) was added. In a separatory funnel, the aqueous layer was partitioned and the organic layer washed with saturated aqueous $NaHCO_3$ (2 x

10 mL), H_2O (10 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude ester was purified by fractional distillation under water aspirator vacuum and distilled at 125 °C to afford **34** (2.83 g, 11.9 mmol, 43%) as a clear, colorless oil.

Data for compound **34**: Rf 0.67 (20% ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.94 (d, 1 H, *J* = 7.8 Hz), 2.12-2.27 (m, 1 H), 1.48 (s, 9 H), 1.08 (d, 3H, *J* = 6.4 Hz), 1.04 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.33, 82.01, 56.27, 32.23, 27.63, 19.83, 19.81

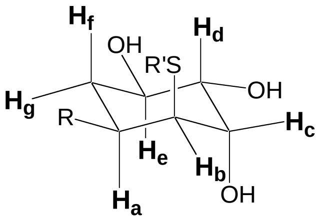


Compound **4**

Shikimic acid methyl ester (200 mg, 1.06 mmol) and 4-chlorobenzene methanethiol (351 μL, 2.66 mmol) were dissolved in 0.21 M NaOMe in methanol (12.5 mL, 2.60 mmol). The reaction was allowed to stir for 2 h at rt and then Amberlite IR-120(plus) acidic resin was added until the solution was neutral. The resin was filtered out and washed with methanol (2 x 10 mL). The resulting solution was concentrated under reduced pressure to give the product as a yellow oil. Purfication by column chromatography (silica gel, 0.5:9.5 MeOH/CH_2Cl_2) gave the product as a clear oil (356 mg, 97%).

Data for thioether **4**: ^{1}H NMR (500 MHz, CD_3OD) δ 7.35-7.10 (4H, m), 3.87 (1H, t, *J* = 2.9 Hz), 3.75 (1H, d, *J* = 13.7 Hz, A of AB), 3.70 (1H, d, *J* = 13.7 Hz, B of AB), 3.65 (1H, ddd, *J* = 11.1, 9.7, 4.6 Hz), 3.61 (1H, dd, *J* = 9.5, 2.9 Hz), 3.58 (3H, s), 3.21 (1H, dt, *J* = 13.0, 4.2 Hz), 3.20 (1H, dd, *J* = 4.5, 2.5 Hz), 2.04 (1H, dddd, *J* = 13.0, 5.0, 3.5, 2.0 Hz), 1.55 (1H, q, *J* = 13.9 Hz);

^{13}C NMR (125 MHz, CD_3OD) δ 173.2, 136.2, 132.9, 130,3, 128.6, 73.3 (2C), 69.2, 51.9, 47.5, 40.1, 36.6, 30.3; ESI-MS $(M+Na)^+$: 369.0



TOCSY1D (500 MHz, CD_3OD) d 3.20 (Ha, bdt, $J_{Ha\text{-}Hf}$ = 13 Hz, $J_{Ha\text{-}Hg}$ = 4-5 Hz, $J_{Ha\text{-}Hb}$ = 4-5 Hz), 3.20 (Hb, dd, $J_{Hb\text{-}Ha}$ = 5 Hz, $J_{Hb\text{-}Hc}$ = 2 Hz). (^1H NMR simulations were performed with an updated version of WinDNMR (http://www.chem.wisc.edu/areas/reich/plt/windnmr.htm).[2]

C. Solid-Phase Synthetic Procedures

General procedures

Solid phase reactions were performed in fritted filter funnels (FFF), in the FlexChem combinatorial block or in vials (as described below). Reactions performed on a FFF required positive N_2 pressure for agitation and aspirator vacuum for removal of liquid from the resin. Reactions performed in the block were agitated with an orbital shaker or the block was left stationary with occasional agitation. Reactions performed in vials were sealed and agitated by placement on an orbital shaker.

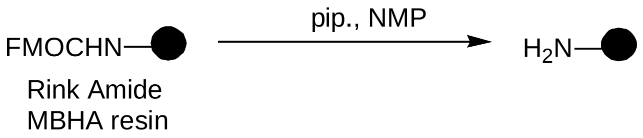
Resin was swelled in the following manner: In a repetitive fashion, *N*-methyl pyrolidine (NMP) or DMF was added to the resin and the solvent was then filtered from the resin. The process was repeated three additional times. In the FFF, the volume of each wash was about 3 mL and in the combinatorial block, the volume of each wash was about 0.7 mL. The shorthand notation for this process used below is “4 x NMP” or “4 x DMF.”

Resin washing was accomplished analogous to the resin swelling procedure. DMF was added to the resin, the resin was filtered, and the process was repeated two additional times. Then methanol was added, the resin was filtered, and the process was repeated two additional times. Then DMF was added to the resin, the resin was filtered, and the process was repeated two additional times. Then methanol was added, the resin was filtered, and the process was repeated two additional times. Finally, diethyl ether (Et_2O) was added and the resin was filtered. In the FFF, the volume of each wash was about 3 mL and in the combinatorial block, the volume of each wash was about 0.7 mL. The shorthand for this procedure is “3 x DMF, 3 x MeOH, 3 x DMF, 3 x MeOH, 1 x Et_2O.”

Amide-bond forming reactions were monitored for completion by use of the Kaiser ninhydrin test for free amines[1]. If the coupling was not complete, the coupling reaction was performed up to a total of three times. For solid-phase reactions, the number of equivalents used for reagents is based on the amount of Rink Amide MBHA resin weighed out initially, prior to the first protecting group removal step, and its loading capacity (0.55 mmol/g).

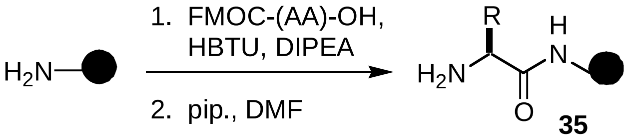
2. Synthesis of the test-library I

a. Fmoc Removal



Rink Amide MBHA (300 mg) resin was weighed into a 15 mL FFF. The resin was swelled 3 x NMP and then a 1:1 piperidine (pip)/NMP solution (4 mL) was added. After 10 min., the solution was filtered from the resin, and the resin was rinsed with 3 x DMF, 3 x MeOH, 3 x DMF, 3 x MeOH, 1 x Et_2O.

b. Amino Acid Couplings

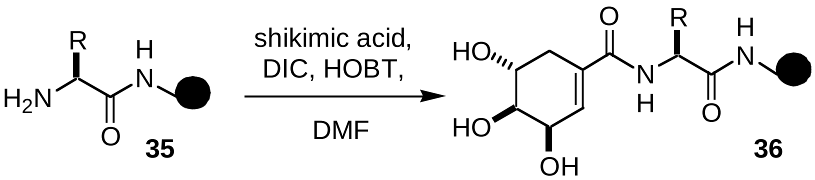


35

After removal of the Fmoc group, the resin was swelled using 3 x NMP. To the resin was then added HBTU (3 eq) dissolved in NMP (1.5 mL), DIPEA (6 eq) and the Fmoc-protected amino acid (3 eq) dissolved in NMP (1 mL). The solution was sparged with N_2 for 2 h and then the resin was isolated by filtration. The resin was washed 3 x DMF, 3 x MeOH, 3 x DMF, 3 x MeOH, 1 x Et_2O and then analyzed by the Kaiser test.

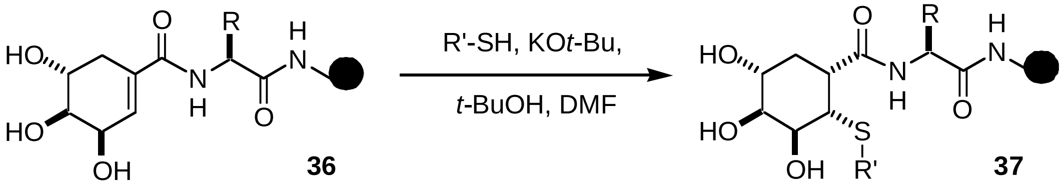
When the amide-bond forming reaction was complete, the Fmoc protecting group was removed. The resin was swelled 3 x NMP and then a 1:1 pip./NMP solution (4 mL) was added. After 10 min. the solution was filtered from the resin and the resin was rinsed with 3 x DMF, 3 x MeOH, 3 x DMF, 3 x MeOH, 1 x Et_2O.

c. Shikimic Acid Coupling



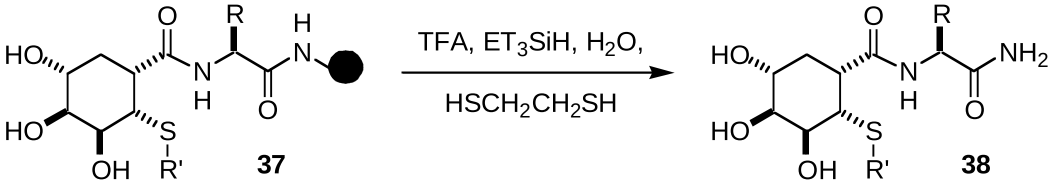
The amino acid-derivatized resin was treated to remove the Fmoc group, and then swelled 4 x NMP. NMP (1 mL) was added followed by HOBT (1 eq). A solution of NMP (1 mL), shikimic acid (2.5 eq), and diisopropyl carbodiimide (2.5 eq), that had been stirring for 10 min., was then added to the resin. The mixture was sparged with N_2 for 4 h and then the solution was removed by filtation. The resin was washed 3 x DMF, 3 x MeOH, 3 x DMF, 3 x MeOH, 1 x Et_2O and then analyzed by the Kaiser test.

d. Conjugate addition reactions

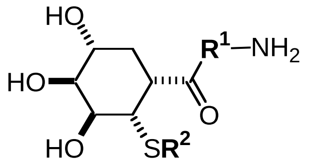


Dry resin (approximately 100 mg) was added to a vial followed by *t*-BuOH (0.3 mL), DMF (1.2 mL), thiol (8 eq) and KO*t*-Bu (3 eq). The vial was sealed and agitated in an orbital shaker at rt for 24 h. The resin was transferred to a 15 mL FFF and rinsed 3 x DMF, 3 x MeOH, 3 x DMF, 3 x $CHCl_3$, 3 x MeOH, 1 x Et_2O.

e. Cleavage of the shikimic acid-derived product



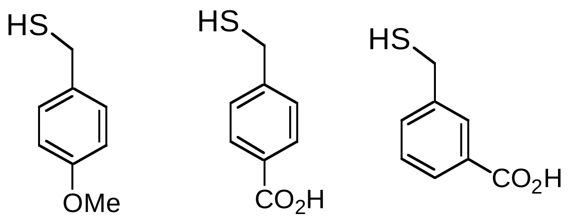
To the resin, **37**, in a 15 mL FFF was added a solution containing $TFA/H_2O/Et_3SiH/HSCH_2CH_2SH$ (92.5:2.5:2.5:2.5). The mixture was sparged with N_2 for 1 h and the solution was filtered into a clean flask. The resin was rinsed with TFA (2 x 1 mL) and the combined acidic filtrates concentrated *in vacuo* to afford the crude products.



2

	R^1 =
A1	Ala
A2	Asp
A3	Glu
A4	Leu
A5	Lys
A6	Trp
A7	Asp-Asp
A8	Asp-Leu
A9	Glu-Leu

R^2SH =



S1 **S2** **S3**

f. Crude Weights for the test-Library I Members

2 (A1,S1) = 28 mg, **2 (A1,S2)** = 33 mg, **2 (A1,S3)** = 29 mg, **2 (A2,S1)** = 19 mg, **2 (A2,S2)** = 28 mg, **2 (A2,S3)** = 30 mg, **2 (A3,S1)** = 24 mg, **2 (A3,S2)** = 31 mg, **2 (A3,S3)** = 33 mg, **2 (A4,S1)** or **4** (number in main text) = 17 mg, **2 (A4,S2)** = 25 mg, **2 (A4,S3)** = 21 mg, **2 (A5,S1)** = 27 mg, **2 (A5,S2)** = 33 mg, **2 (A5,S3)** = 37 mg, **2 (A6,S1)** = 19 mg, **2 (A6,S2)** = 21 mg, **2 (A6,S3)** = 18 mg, **2 (A7,S1)** = 36 mg, **2 (A7,S2)** = 56 mg, **2 (A7,S3)** = 55 mg, **2 (A8,S1)** = 17 mg, **2 (A8,S2)** = 23 mg, **2 (A8,S3)** = 25 mg, **2 (A9,S1)** = 19 mg, **2 (A9,S2)** = 18 mg, **2 (A9,S3)** = 19 mg

3. Synthesis of Library I with the Combinatorial Block

In general, the synthetic methods used in the combinatorial block-based synthesis were the same as those used in the test-library I synthesis. Differences include the time reactions were allowed to proceed and the volumes of solvent used.

a. Loading of resin into the combinatorial block wells

Resin was loaded into the block as an iso-buoyant suspension in CH_2Cl_2/DMF. Specifically, a 5% suspension of Rink Amide MBHA resin in CH_2Cl_2/DMF (1.5:1, 1.4 mL) was added to each well in the block, via Pipetteman, to provide ~70 mg resin/well. Each compound was made in duplicate (i.e., a single product was made in two separate wells on a total of 140 mg resin). Application of aspirator vacuum to the bottom of the block allowed for the removal of solvent from the wells. The resin was then washed 3 x DMF, 3 x MeOH, 3 x DMF, 3 x MeOH, 1 x Et_2O.

b. Fmoc removal

The resin was swelled using 3 x NMP and then a 1:1 pip./NMP solution (0.75 mL) was added. After 20 min. the solution was filtered from the resin and the resin rinsed with 3 x DMF, 3 x MeOH, 3 x DMF, 3 x MeOH, 1 x Et_2O.

c. Amino acid coupling

After removal of the Fmoc group, the resin was swelled using 3 x NMP. To each well containing resin was then added a solution of HATU (3 eq), DIPEA (9 eq) and the Fmoc-protected amino acid (3 eq) dissolved in NMP (0.70 mL). The block was sealed and agitated by occasional shaking over 6 h. The resin was washed with 3 x DMF, 3 x MeOH, 3 x DMF, 3 x

MeOH, 1 x Et_2O and then analyzed by the Kaiser test. Reactions that did not go to completion were performed up to two additional times.

When the amide-bond forming reaction was complete, the Fmoc protecting group was removed. The resin was swelled 3 x NMP and then a 1:1 pip./NMP solution (0.70 mL) was added. After 10 min. the solution was filtered from the resin and the resin was rinsed with 3 x DMF, 3 x MeOH, 3 x DMF, 3 x MeOH, 1 x Et_2O.

d. Shikimic Acid Coupling

After the Fmoc group of the amino acid-derivatized resin was cleaved, the resin was swelled 4 x NMP. To the well containing resin was then added a solution of shikimic acid (3 eq), DIC (3 eq) and HOBt (3 eq) in NMP (0.70 mL. The block was sealed and the mixture was agitated by occasional shaking over 16 h. The resin was washed 3 x DMF, 3 x MeOH, 3 x DMF, 3 x MeOH, 1 x Et_2O and then analyzed by the Kaiser test. No additional couplings were necessary.

e. Conjugate addition reaction

The resin was swelled using 4 x NMP. To each well in the block was added a solution containing *t*-BuOH (0.15 mL), DMF (0.45 mL), thiol (8 eq\) and KO*t*-Bu (3 eq). The block was sealed and agitated by occasional shaking over 43 h. After, the solution was removed by filtration and the resin was rinsed with 3 x DMF, 3 x MeOH, 3 x DMF, 3 x $CHCl_3$, 3 x MeOH, 1 x Et_2O.

f. Cleavage of the product from the solid support

To each well in the block containing resin was added TFA/H_2O (95:5) solution (0.6 mL). The block was sealed and the mixture was agitated by occasional shaking for1 h. The products were collected by filtration of the combinatorial block into a 96-well plate with 1 mL capacity wells. Each well containing resin in the block was then washed with TFA (2 x 200 μL), and these washings were combined with the initial filtrate (same 96-well plate used for all filtrations).

The 96-well plate was placed into a vacuum desiccator and concentrated under aspirator vacuum. After most of the TFA was removed (24-48 h), the desiccator was attached to high vacuum to remove all solvent (ca. 24 h). Compounds were then individually transferred to pre-weighed vials and, finally, aliquoted for biological testing.

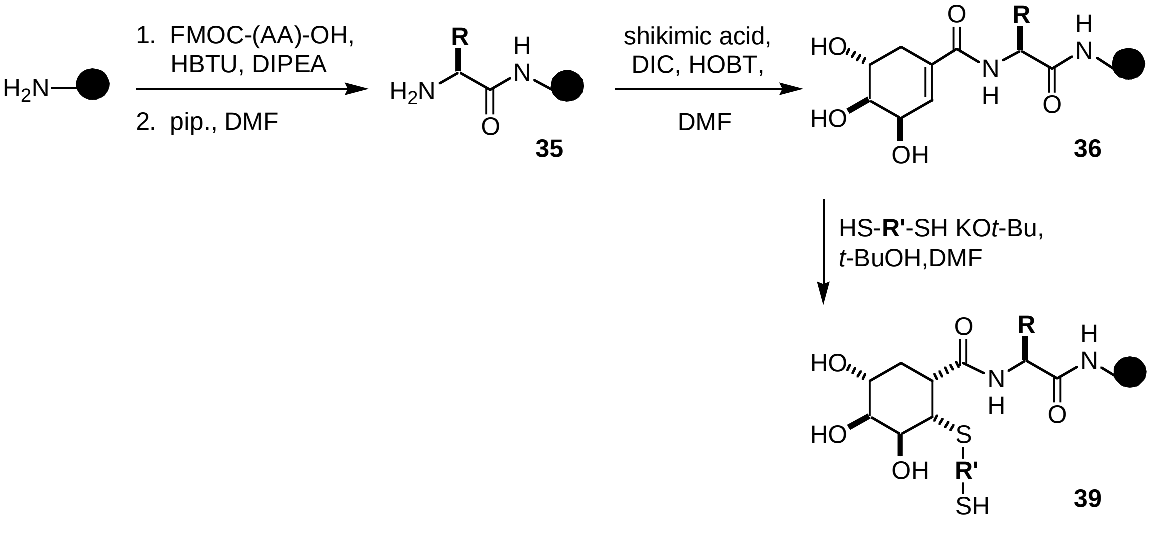
f. Crude Weights for the Library I Members

2 (A1,S1) = 29 mg, **2 (A1,S2)** = 33 mg, **2 (A1,S3)** = 28 mg, **2 (A1,S4)** = 27 mg, **2 (A1,S5)** or **4** (number in main text)= 24 mg, **2 (A1,S6)** = 23 mg, **2 (A2,S1)** = 25 mg, **2 (A2,S2)** = 23 mg, **2 (A2,S3)** = 30 mg, **2 (A2,S4)** = 30 mg, **2 (A2,S5)** = 24 mg, **2 (A2,S6)** = 26 mg, **2 (A3,S1)** = 27 mg, **2 (A3,S2)** = 26 mg, **2 (A3,S3)** = 31 mg, **2 (A3,S4)** = 20 mg, **2 (A3,S5)** = 22 mg, **2 (A3,S6)** = 28 mg, **2 (A4,S1)** or **6** (number in main text) = 27 mg, **2 (A4,S2)** = 23 mg, **2 (A4,S3)** = 26 mg, **2 (A4,S4)** or **5** (number in main text) = 28 mg, **2 (A4,S5)** = 22 mg, **2 (A4,S6)** = 24 mg, **2 (A5,S1)** = 23 mg, **2 (A5,S2)** = 23 mg, **2 (A5,S3)** = 26 mg, **2 (A5,S4)** = 26 mg, **2 (A5,S5)** = 29 mg, **2 (A5,S6)** = 26 mg, **2 (A6,S1)** = 16 mg, **2 (A6,S2)** = 12 mg, **2 (A6,S3)** = 16 mg, **2 (A6,S4)** = 13 mg, **2 (A6,S5)** = 16 mg, **2 (A6,S6)** = 19 mg, **2 (A7,S1)** = 48 mg, **2 (A7,S2)** = 51 mg, **2 (A7,S3)** = 39 mg, **2 (A7,S4)** = 51 mg, **2 (A7,S5)** = 56 mg, **2 (A7,S6)** = 58 mg, **2 (A8,S1)** = 34 mg, **2 (A8,S2)** = 46 mg, **2 (A8,S3)** = 30 mg, **2 (A8,S4)** = 37 mg, **2 (A8,S5)** = 34 mg, **2 (A8,S6)** = 35 mg, **2 (A9,S1)** = 39 mg, **2 (A9,S2)** = 25 mg, **2 (A9,S3)** = 36 mg, **2 (A9,S4)** = 43 mg, **2 (A9,S5)** = 41 mg, **2 (A9,S6)** = 29 mg, **2 (A10,S1)** or **8** (number in main text) = 18 mg, **2 (A10,S2)** = 22 mg, **2 (A10,S3)** = 17 mg, **2 (A10,S4)** or **7** (number in main text) = 18 mg, **2 (A10,S5)** = 17 mg, **2 (A10,S6)** = 17 mg, **2 (A11,S1)** = 40 mg, **2 (A11,S2)** = 35 mg, **2 (A11,S3)** = 34 mg, **2 (A11,S4)** = 35 mg, **2 (A11,S5)** = 33 mg, **2 (A11,S6)** = 28 mg, **2 (A12,S1)** = 59 mg, **2 (A12,S2)** = 62 mg, **2 (A12,S3)** = 64 mg, **2 (A12,S4)** = 54 mg, **2 (A12,S5)** = 43 mg, **2 (A12,S6)** = 54 mg

4. Synthesis of library II with the combinatorial block

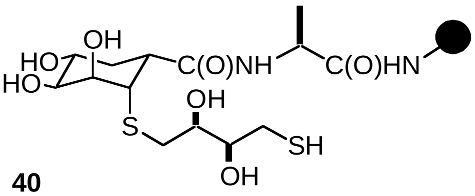
Library II was synthesized both on a FFF (60 mL) and in the combinatorial block. Specifically, the shikimic acid-containing analogs up through the Michael addition were performed using a FFF and subsequent reactions were performed using the combinatorial block.

a. Synthesis of library II through the conjugate addition reaction

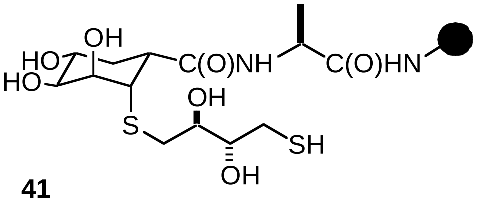


The initial steps in the synthesis, through **39**, were performed as in section *Synthesis of the test-library I*. All compounds were synthesized in parallel. Three amino acids were utilized

(Ala (**A1**), Asp (**A2**), and Glu(**A3**)) and two dithiols (DTT (**L1**) and DTE (**L2**)) were incorporated. As such, six compounds were synthesized: **40**, **41**, **42**, **43**, **44**, **45**, and **46**. For each synthesis, 2.0 g Rink Amide MBHA resin was used.



40



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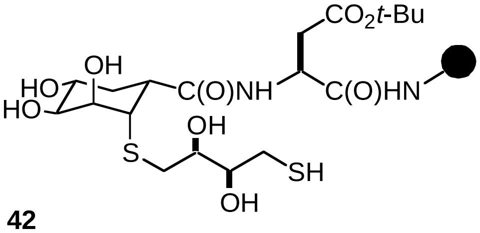

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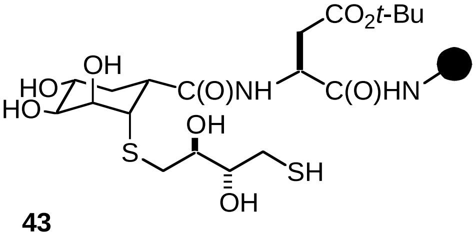

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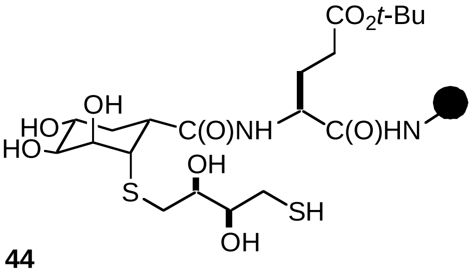
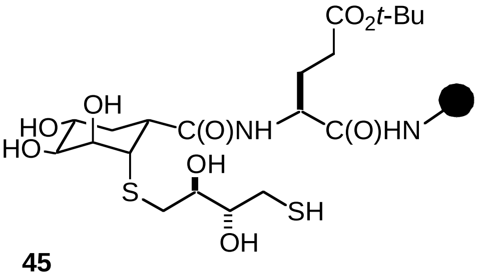


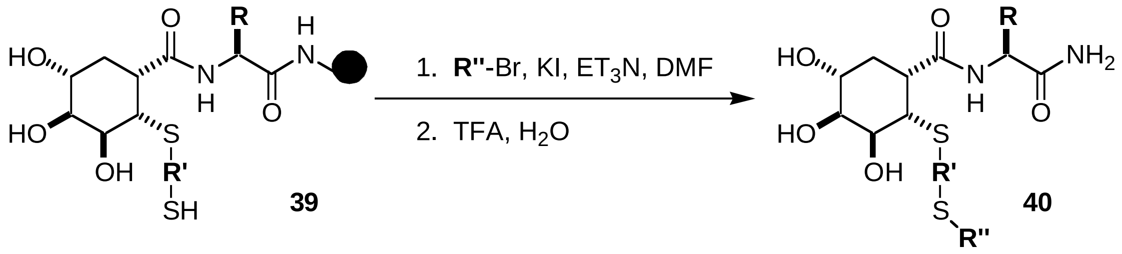
44



45

b. Completion of the Synthesis of Library II

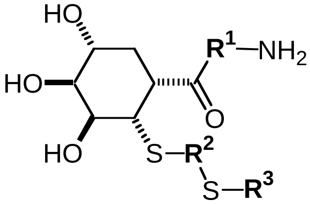
The synthesis of Library II was completed using the combinatorial block. Each of the six compounds was separately aliquoted into 20 wells in the block (0.1 g/well). Specifically, 1.0 mL of a 10% suspension of the derivatized resin in CH_2Cl_2/DMF (1.5:1) was added to each of 20 wells in the block via Pipetteman.



To effect the alkylation, a solution of alkyl bromide (8 eq), Et_3N (8 eq), and KI (1 eq) in DMF (0.7 mL) was added to the resin. The block was sealed and agitated by occasional shaking over 36 h. After, the solution was removed by filtration and the resin was rinsed with 3 x DMF, 3 x MeOH, 3 x DMF, 3 x $CHCl_3$, 3 x MeOH, 1 x Et_2O.

To each well in the block containing resin was added TFA/H_2O (95:5) solution (0.6 mL) The block was sealed and agitated by occasional shaking over 1 h. The products were collected by filtration of the combinatorial block into a 96-well plate with 1 mL capacity wells. Each well containing resin in the block was then washed with TFA (2 x 200 μL), and these washings were combined with the initial filtrate (same 96-well plate used for all filtrations).

The 96-well plate was placed into a vacuum desiccator and concentrated under aspirator vacuum. After most of the TFA was removed (24-48 h), the desiccator was attached to high vacuum and the 96-well plate was maintained under vaccuum until all solvent was removed (about 24 h). Compounds were then individually transferred to pre-weighed vials and aliquoted for biological testing.

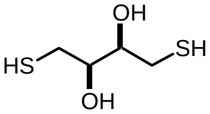


3

R^1 =

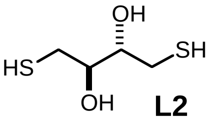
A1	Ala
A2	Asp
A3	Glu

HS-**R^2**-SH =



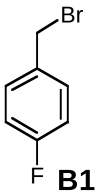
+ enantiomer

L1

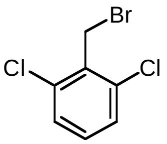


L2

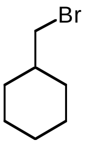
R^3-Br =



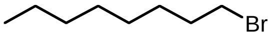
B1



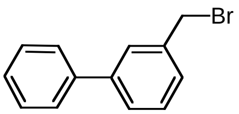
B2



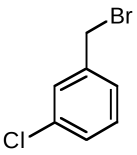
B3



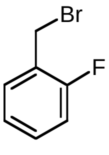
B4



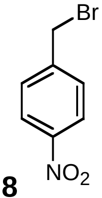
B5



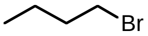
B6



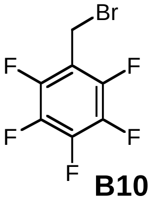
B7



B8



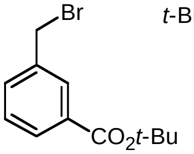
B9



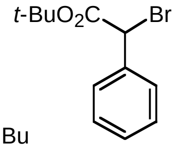
B10

$C_{18}H_{37}Br$

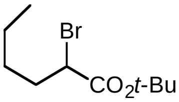
B11



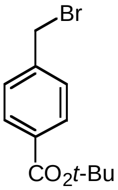
B12



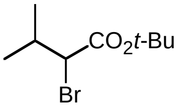
B13



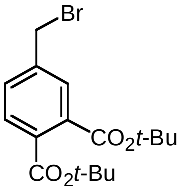
B14



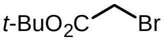
B15



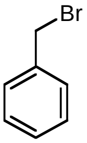
B16



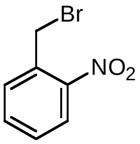
B17



B18



B19



B20

c. Crude Weights for the Library II Members

3 (A1,L1,B1) = 24 mg, **3 (A1,L1,B2)** = 26 mg, **3 (A1,L1,B3)** = 17 mg, **3 (A1,L1,B4)** or **9a** and **9b** (numbers in main text) = 13 mg, **3 (A1,L1,B5)** =14 mg, **3 (A1,L1,B6)** = 9.3 mg, **3 (A1,L1,B7)** = 6.0 mg, **3 (A1,L1,B8)** = 11 mg, **3 (A1,L1,B9)** = 14 mg, **3 (A1,L1,B10)** = 15 mg, **3 (A1,L1,B11)** = 11 mg, **3 (A1,L1,B12)** = 19 mg, **3 (A1,L1,B13)** = 18 mg, **3 (A1,L1,B14)** = 16 mg, **3 (A1,L1,B15)** = 15 mg, **3 (A1,L1,B16)** = 15 mg, **3 (A1,L1,B17)** = 27 mg, **3 (A1,L1,B18)** = 26 mg, **3 (A1,L1,B19)** = 34 mg, **3 (A1,L1,B20)** = 36 mg

3 (A1,L2,B1) = 27 mg, **3 (A1,L2,B2)** = 23 mg, **3 (A1,L2,B3)** = 19 mg, **3 (A1,L2,B4)** = 19 mg, **3 (A1,L2,B5)** = 22 mg, **3 (A1,L2,B6)** = 19 mg, **3 (A1,L2,B7)** = 18 mg, **3 (A1,L2,B8)** = 19 mg, **3 (A1,L2,B9)** = 19 mg, **3 (A1,L2,B10)** = 22 mg, **3 (A1,L2,B11)** = 9.7 mg, **3 (A1,L2,B12)** = 18 mg, **3 (A1,L2,B13)** = 21 mg, **3 (A1,L2,B14)** = 17 mg, **3 (A1,L2,B15)** = 20 mg, **3 (A1,L2,B16)** = 16 mg, **3 (A1,L2,B17)** = 17 mg, **3 (A1,L2,B18)** = 15 mg, **3 (A1,L2,B19)** = 17 mg, **3 (A1,L2,B20)** = 12 mg

3 (A2,L1,B1) = 20 mg, **3 (A2,L1,B2)** = 21 mg, **3 (A2,L1,B3)** or **12a** and **12b** (numbers in main text) = 18 mg, **3 (A2,L1,B4)** or **10a** and **10b** (numbers in main text) = 20 mg, **3 (A2,L1,B5)** = 222 mg, **3 (A2,L1,B6)** = 20 mg, **3 (A2,L1,B7)** = 21 mg, **3 (A2,L1,B8)** = 21 mg, **3 (A2,L1,B9)** = 12 mg, **3 (A2,L1,B10)** = 23 mg, **3 (A2,L1,B11)** = 21 mg, **3 (A2,L1,B12)** = 21 mg, **3 (A2,L1,B13)** = 21 mg, **3 (A2,L1,B14)** = 20 mg, **3 (A2,L1,B15)** = 22 mg, **3 (A2,L1,B16)** = 17 mg, **3 (A2,L1,B17)** = 11 mg, **3 (A2,L1,B18)** = 20 mg, **3 (A2,L1,B19)** =45 mg, **3 (A2,L1,B20)** = 18 mg

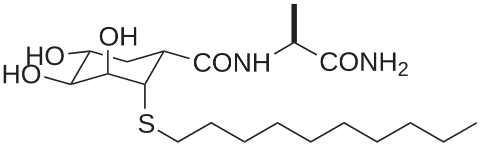
3 (A2,L2,B1) = 7.8 mg, **3 (A2,L2,B2)** = 16 mg, **3 (A2,L2,B3)** or **13a** and **13b** (numbers in main text) = 15 mg, **3 (A2,L2,B4)** = 15 mg, **3 (A2,L2,B5)** = 15 mg, **3 (A2,L2,B6)** = 17 mg, **3 (A2,L2,B7)** = 14 mg, **3 (A2,L2,B8)** = 15 mg, **3 (A2,L2,B9)** = 15 mg, **3 (A2,L2,B10)** = 14 mg, **3**

(A2,L2,B11) = 16 mg, **3 (A2,L2,B12)** = 16 mg, **3 (A2,L2,B13)** = 16 mg, **3 (A2,L2,B14)** = 15 mg, **3 (A2,L2,B15)** = 17 mg, **3 (A2,L2,B16)** = 13 mg, **3 (A2,L2,B17)** = 14 mg, **3 (A2,L2,B18)** = 12 mg, **3 (A2,L2,B19)** = 37 mg, **3 (A2,L2,B20)** =11 mg

3 (A3,L1,B1) = 27 mg, **3 (A3,L1,B2)** = 25 mg, **3 (A3,L1,B3)** = 21 mg, **3 (A3,L1,B4)** = 15 mg, **3 (A3,L1,B5)** = 25 mg, **3 (A3,L1,B6)** = 23 mg, **3 (A3,L1,B7)** = 18 mg, **3 (A3,L1,B8)** = 25 mg, **3 (A3,L1,B9)** = 22 mg, **3 (A3,L1,B10)** = 25 mg, **3 (A3,L1,B11)** = 24 mg, **3 (A3,L1,B12)** = 31 mg, **3 (A3,L1,B13)** = 30 mg, **3 (A3,L1,B14)** = 26 mg, **3 (A3,L1,B15)** = 29 mg, **3 (A3,L1,B16)** = 23 mg, **3 (A3,L1,B17)** = 27 mg, **3 (A3,L1,B18)** = 24 mg, **3 (A3,L1,B19)** = 23 mg, **3 (A3,L1,B20)** = 25 mg

3 (A3,L2,B1) = 23 mg, **3 (A3,L2,B2)** = 22 mg, **3 (A3,L2,B3)** = 21 mg, **3 (A3,L2,B4)** or **11a** and **11b** (numbers in main text) = 20 mg, **3 (A3,L2,B5)** = 25 mg, **3 (A3,L2,B6)** = 21 mg, **3 (A3,L2,B7)** = 23 mg, **3 (A3,L2,B8)** = 23 mg, **3 (A3,L2,B9)** = 21 mg, **3 (A3,L2,B10)** = 23 mg, **3 (A3,L2,B11)** = 27 mg, **3 (A3,L2,B12)** = 28 mg, **3 (A3,L2,B13)** = 26 mg, **3 (A3,L2,B14)** = 25 mg, **3 (A3,L2,B15)** = 27 mg, **3 (A3,L2,B16)** = 17 mg, **3 (A3,L2,B17)** = 22 mg, **3 (A3,L2,B18)** = 21 mg, **3 (A3,L2,B19)** = 17 mg, **3 (A3,L2,B20)** = 17 mg

Mass spectrometry data for a sampling of active and inactive compounds



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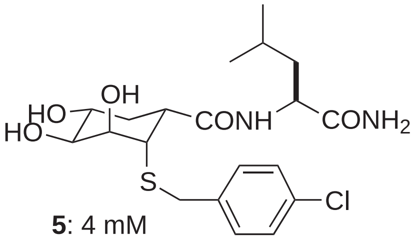

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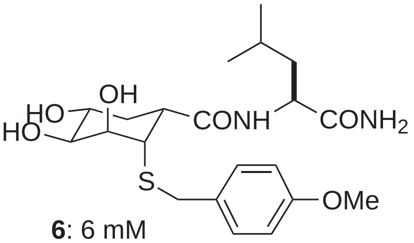

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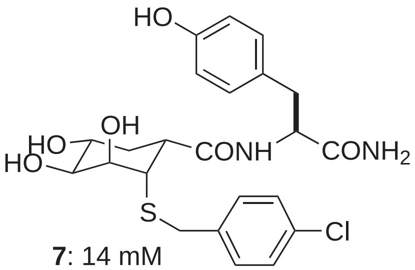
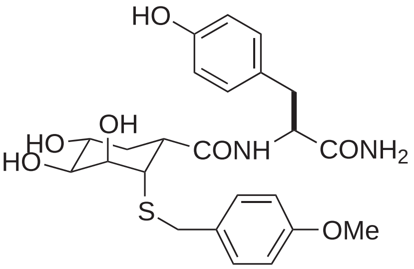
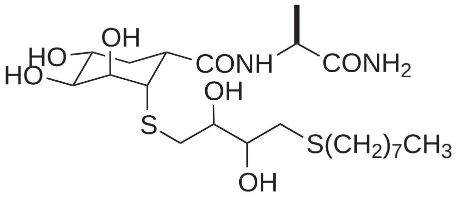


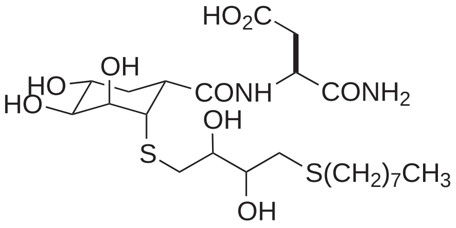
7: 14 mM



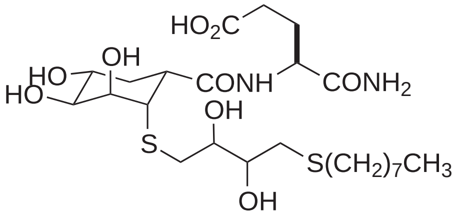
8: 7 mM



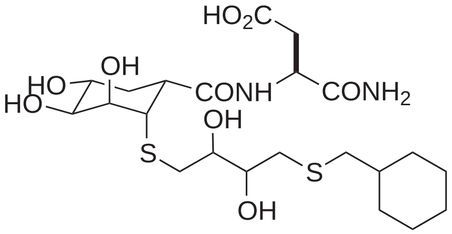
9a (R,R) **9b** (S,S)*: 11 mM



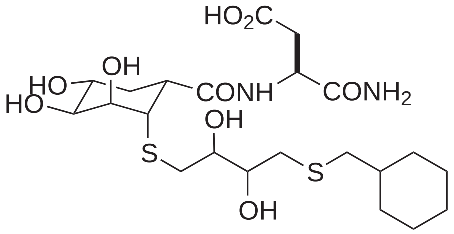
10a (R,S), **10b** (S,R)*: 8 mM



11a (R,S) **11b** (S.R)*: 6 mM



12a (R,R) **12b** (S,S)*: 4 mM



13a (R,S) **13b** (S,R)*: 10 mM

Active Compounds

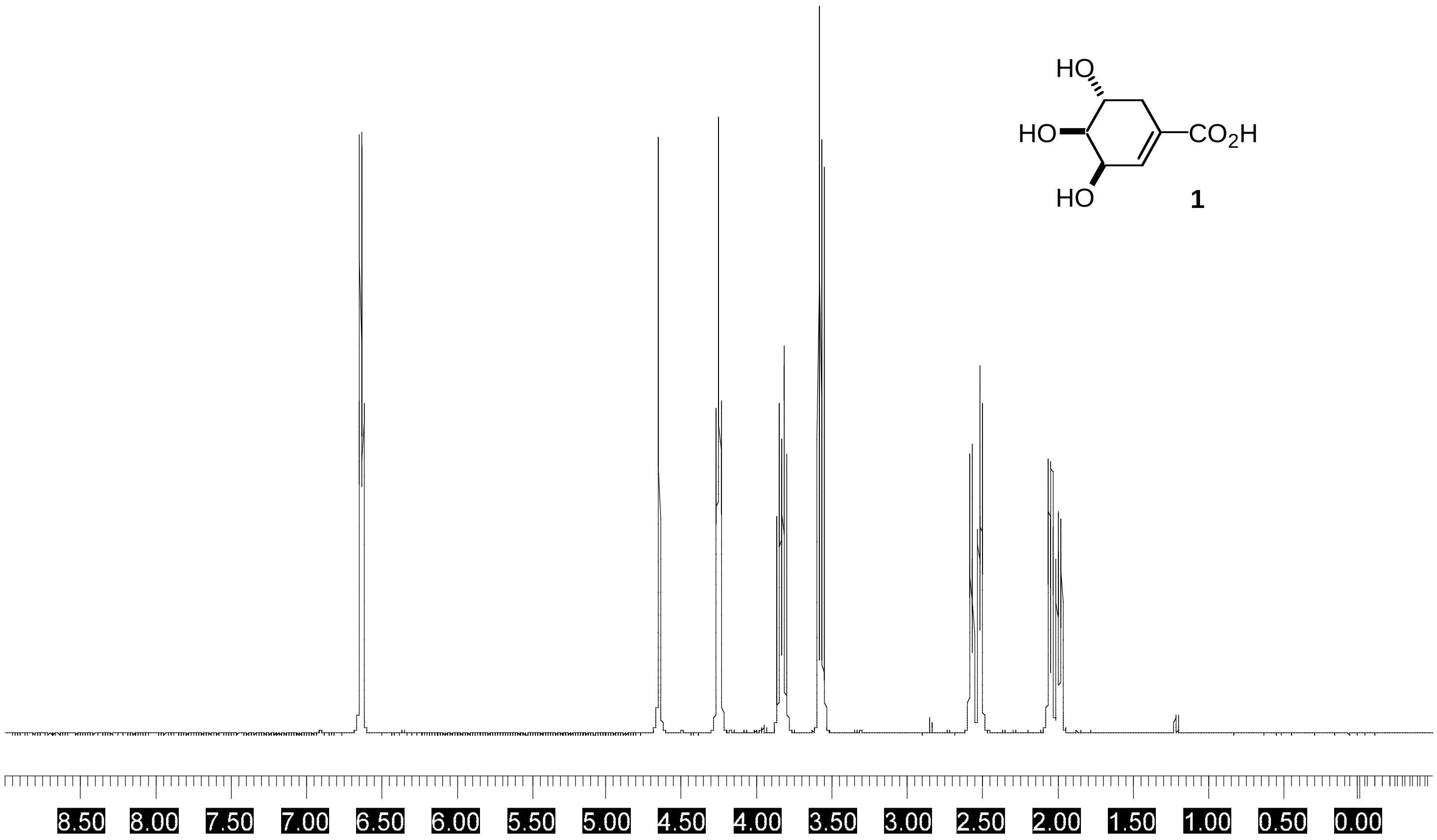
5: (ESI) *m/e* 445.1573 (M + H$^+$ $[C_{20}H_{30}O_5N_2SCl]^+$ calcd 445.1564); **6**: (ESI) *m/e* 441.2080 (M + H$^+$ $[C_{21}H_{33}O_6N_2S]^+$ calcd 441.2059); **7**: (ESI) *m/e* 495.1342 (M + H$^+$ $[C_{23}H_{28}O_6N_2SCl]^+$ calcd 495.1356); **9a**/**9b**: (ESI) *m/e* 511.2486 (M + H$^+$ $[C_{22}H_{43}O_7S_2N_2]^+$ calcd 511.2511); **10a**/**10b**: (ESI) *m/e* 553.2241 (M - H$^+$ $[C_{23}H_{41}O_9S_2N_2]^-$ calcd 553.2253); **11a/11b**: (ESI) *m/e* 567.2390 (M - H$^+$ $[C_{22}H_{43}O_9S_2N_2]^-$ calcd 567.2410); **13a**/**13b**: (ESI) *m/e* 537.1951 (M - H$^+$ $[C_{22}H_{37}O_9S_2N_2]^-$ calcd 537.1941)

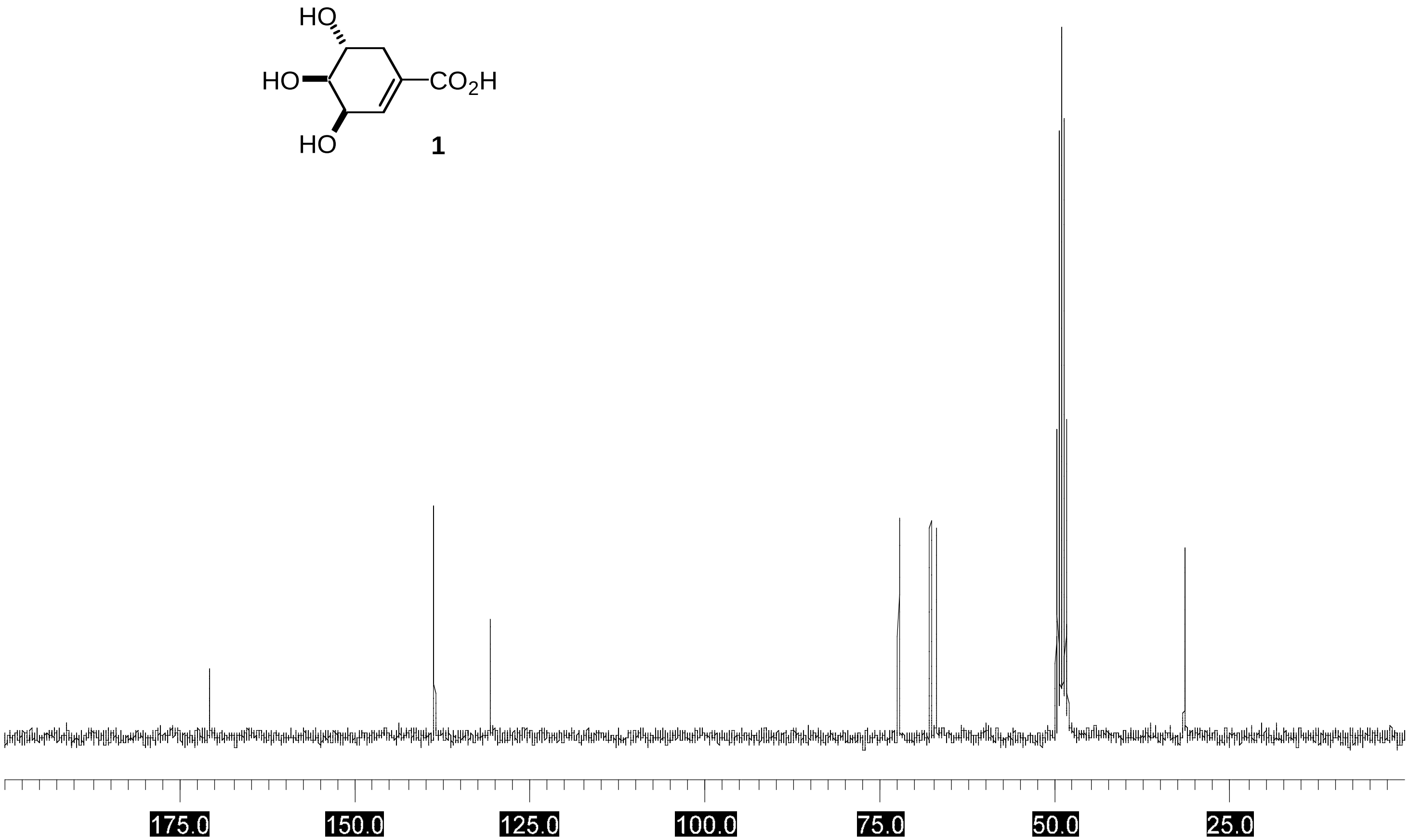
Inactive Compounds

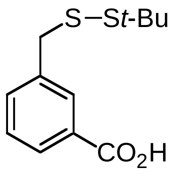
2 (A$_2$, S$_5$): (ESI) *m/e* 461.2312 (M + H$^+$ $[C_{21}H_{38}O_7N_2S]^+$ calcd 461.2321); **2 (A$_2$, S$_1$):** (ESI) *m/e* 485.2292 (M + Na$^+$ $[C_{21}H_{38}O_7N_2SNa]^+$ calcd 485.2297); **2 (A$_3$, S$_1$):** (ESI) *m/e* 479.1469 (M + Na$^+$ $[C_{20}H_{28}O_8N_2SNa]^+$ calcd 479.1464)

(1) Kaiser, E. C., R. L., Bossinger, C. D., Cook, P. I. *Analytical Biochemistry* **1970**, *34*, 595-598.

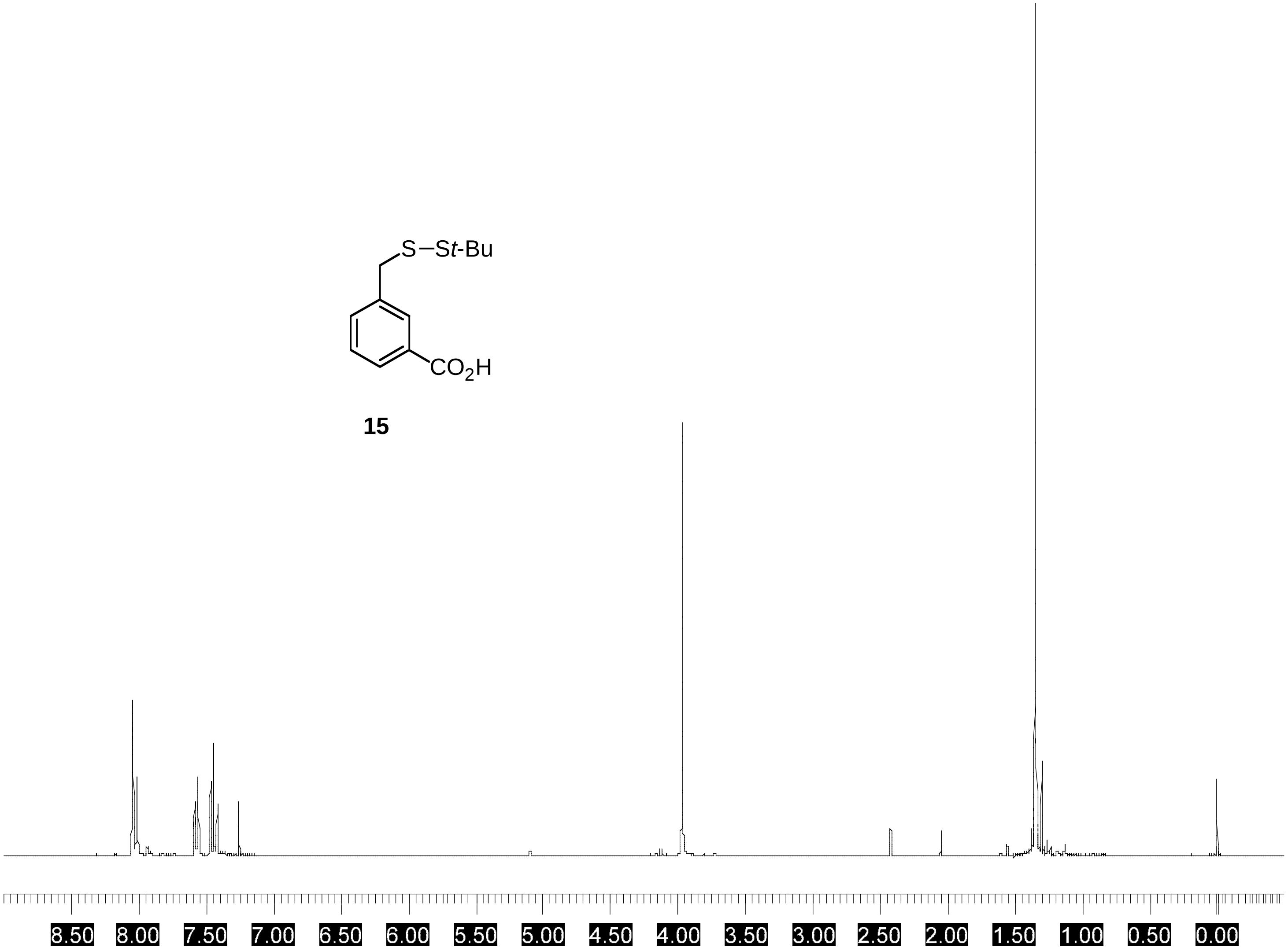
(2) Reich, H. J, *J. Chem. Ed. Software*, Series D, **1996** *Vol. 3D*, No. 2.

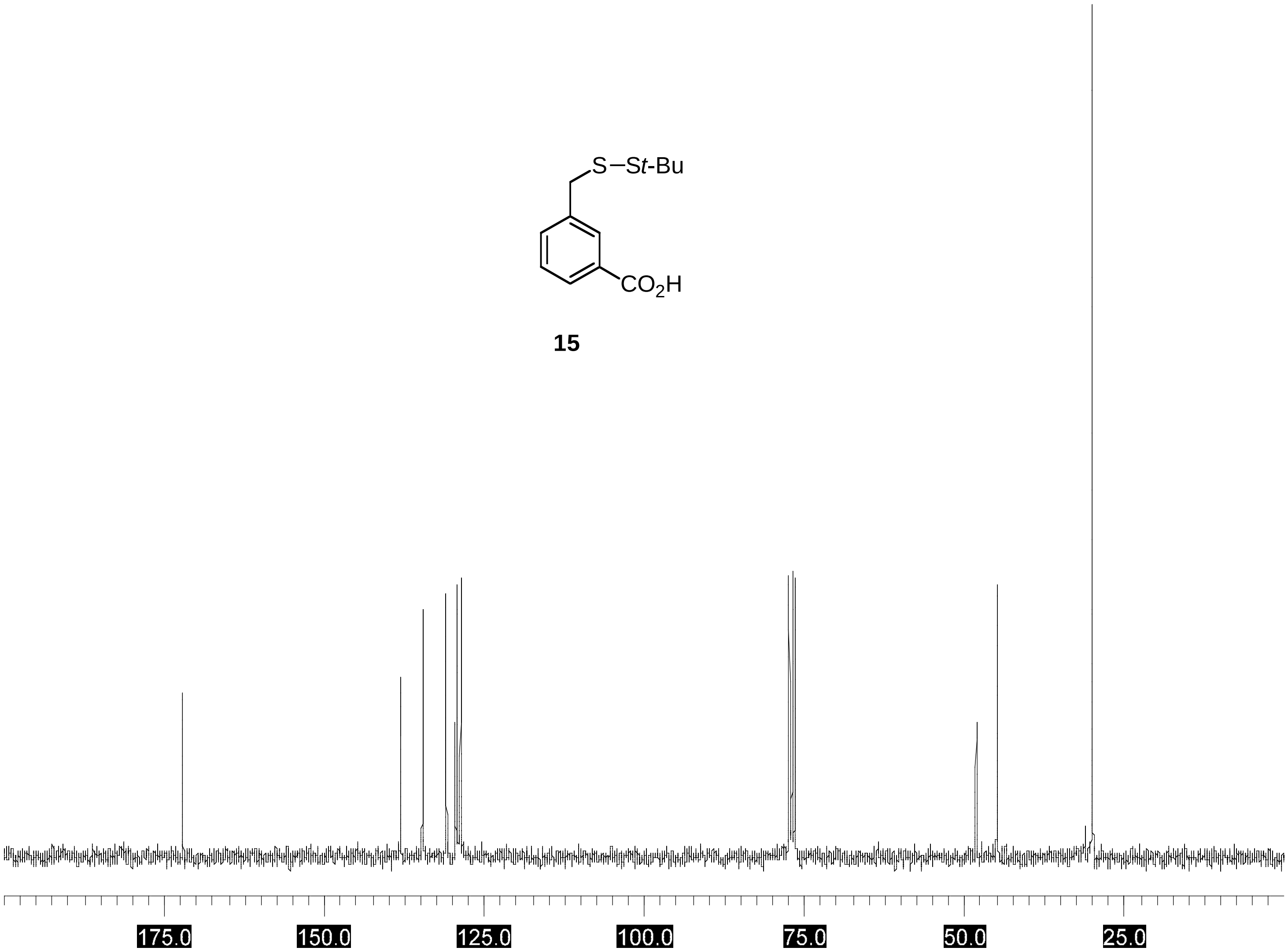

HO
HO
CO$_2$H
HO
1
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00


1


S−St-Bu
CO2H

15

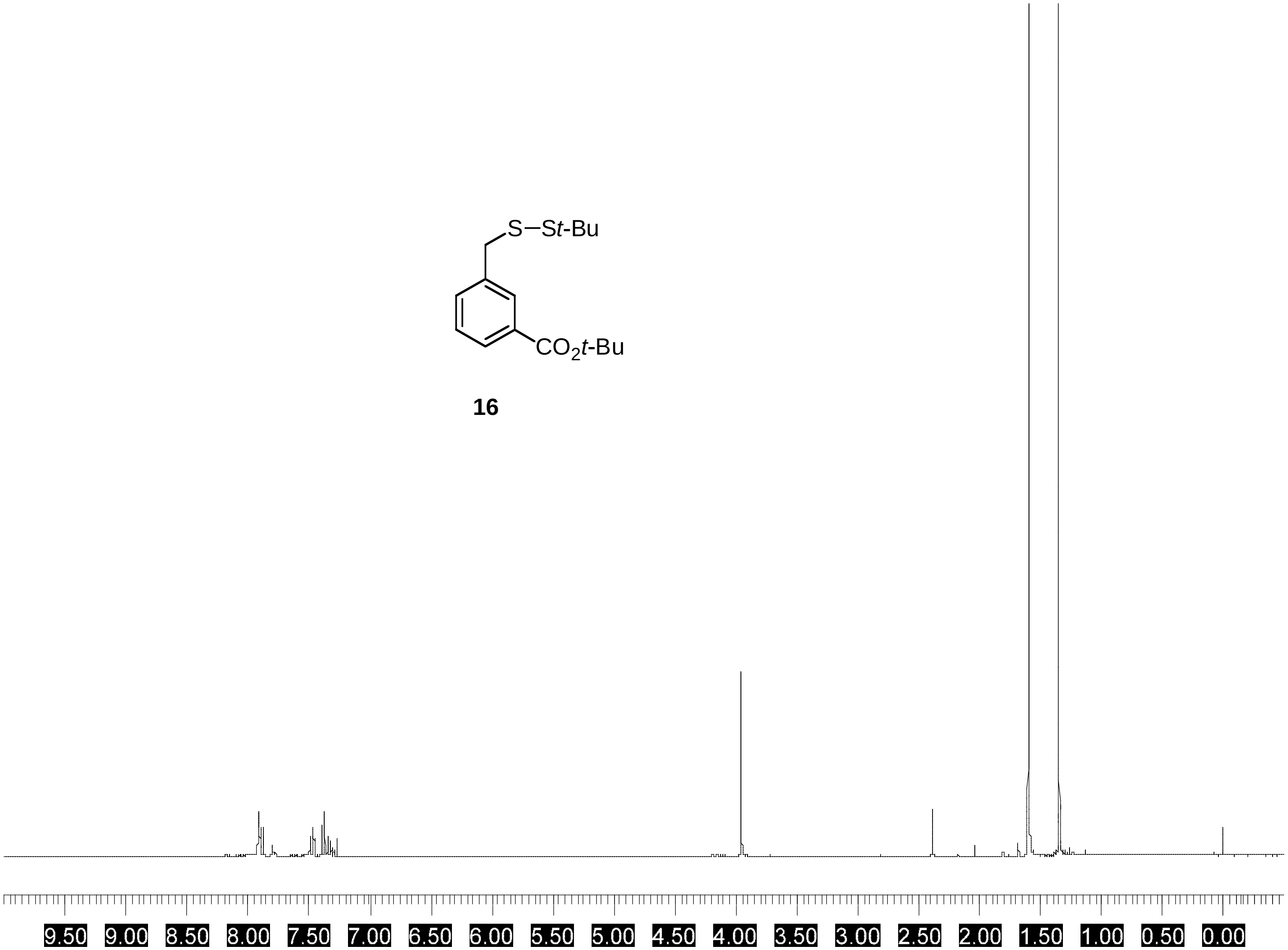

8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00



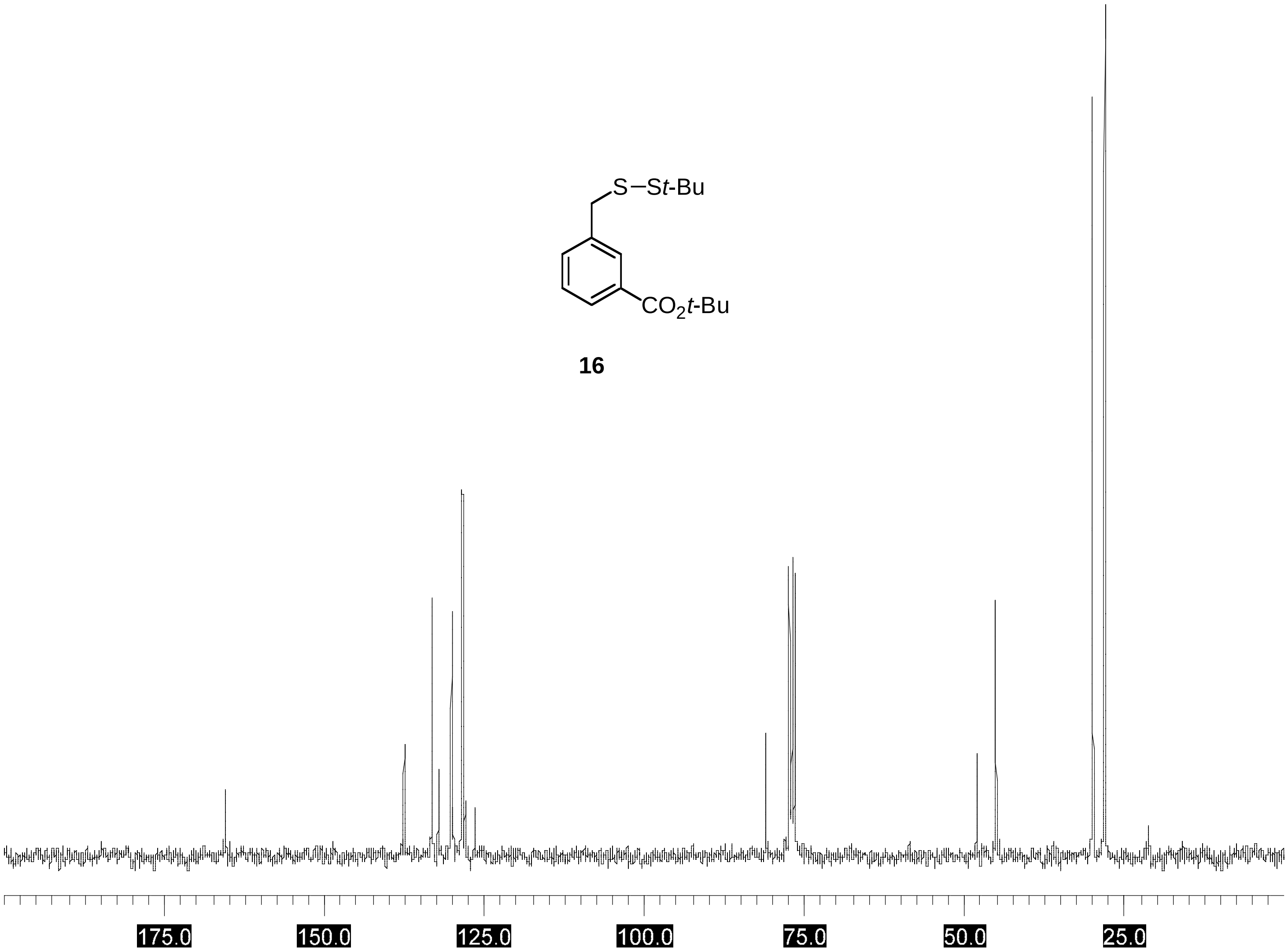
15

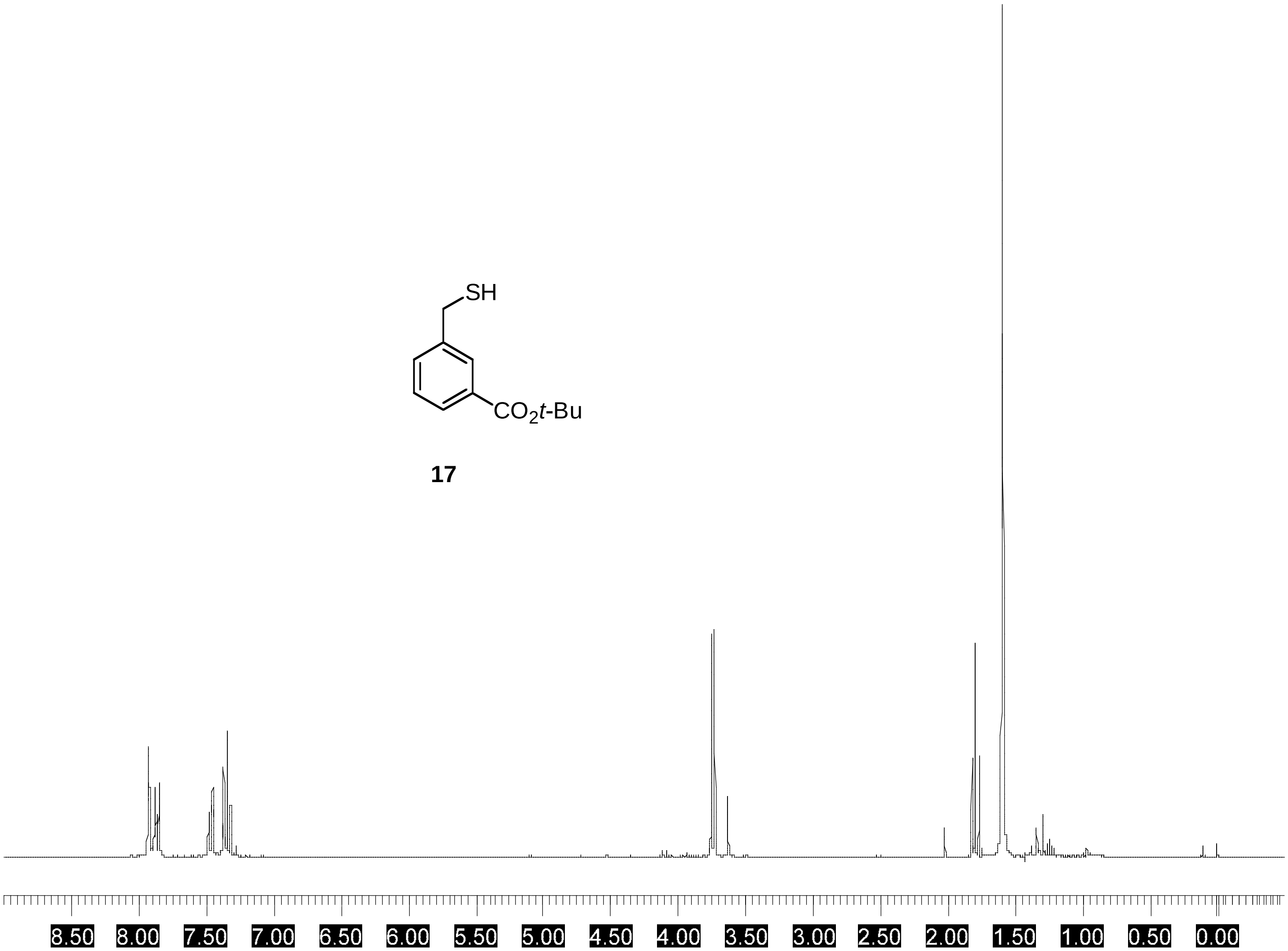
S−St-Bu
CO2t-Bu

16

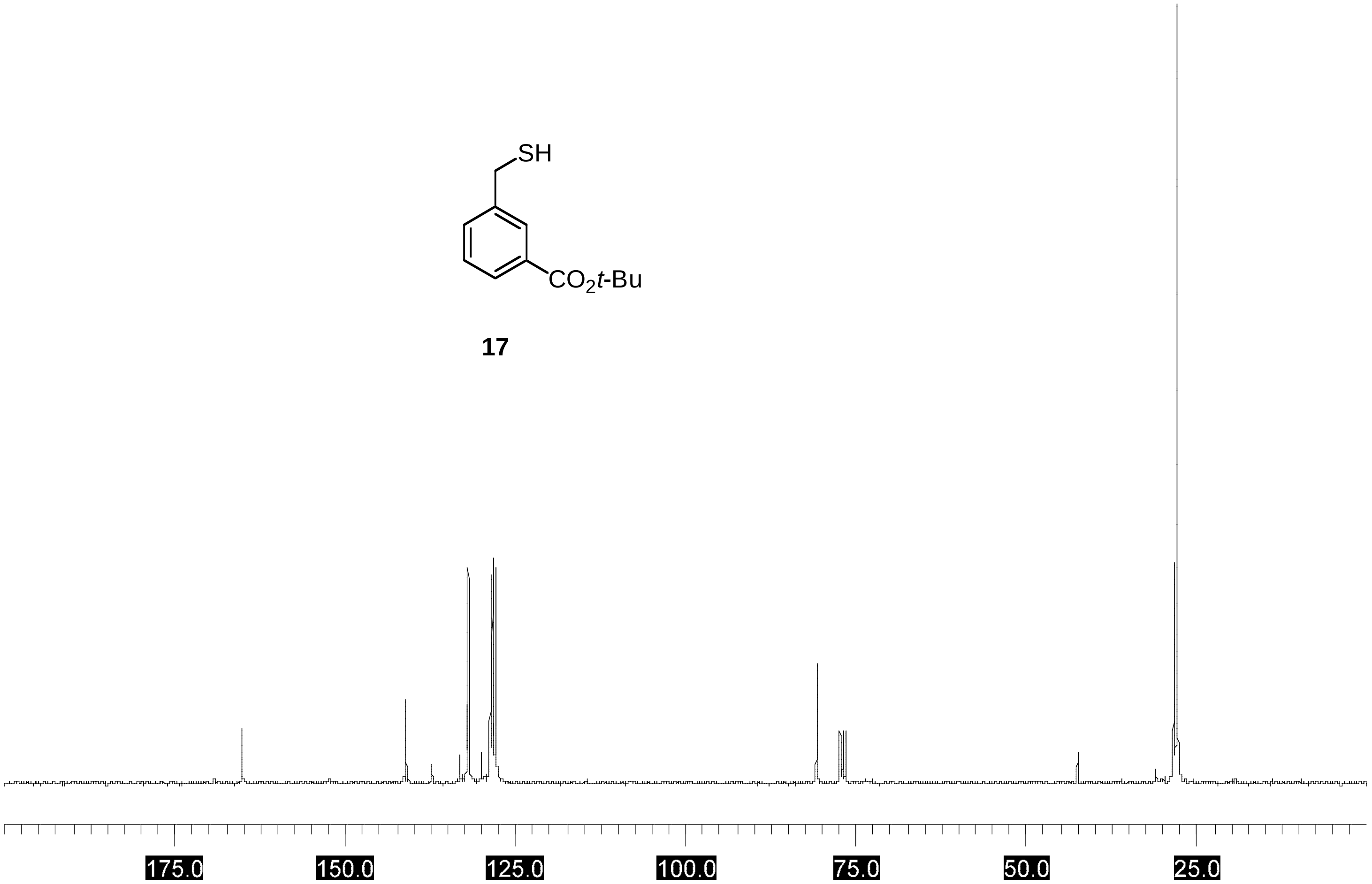

9.50
9.00
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

16

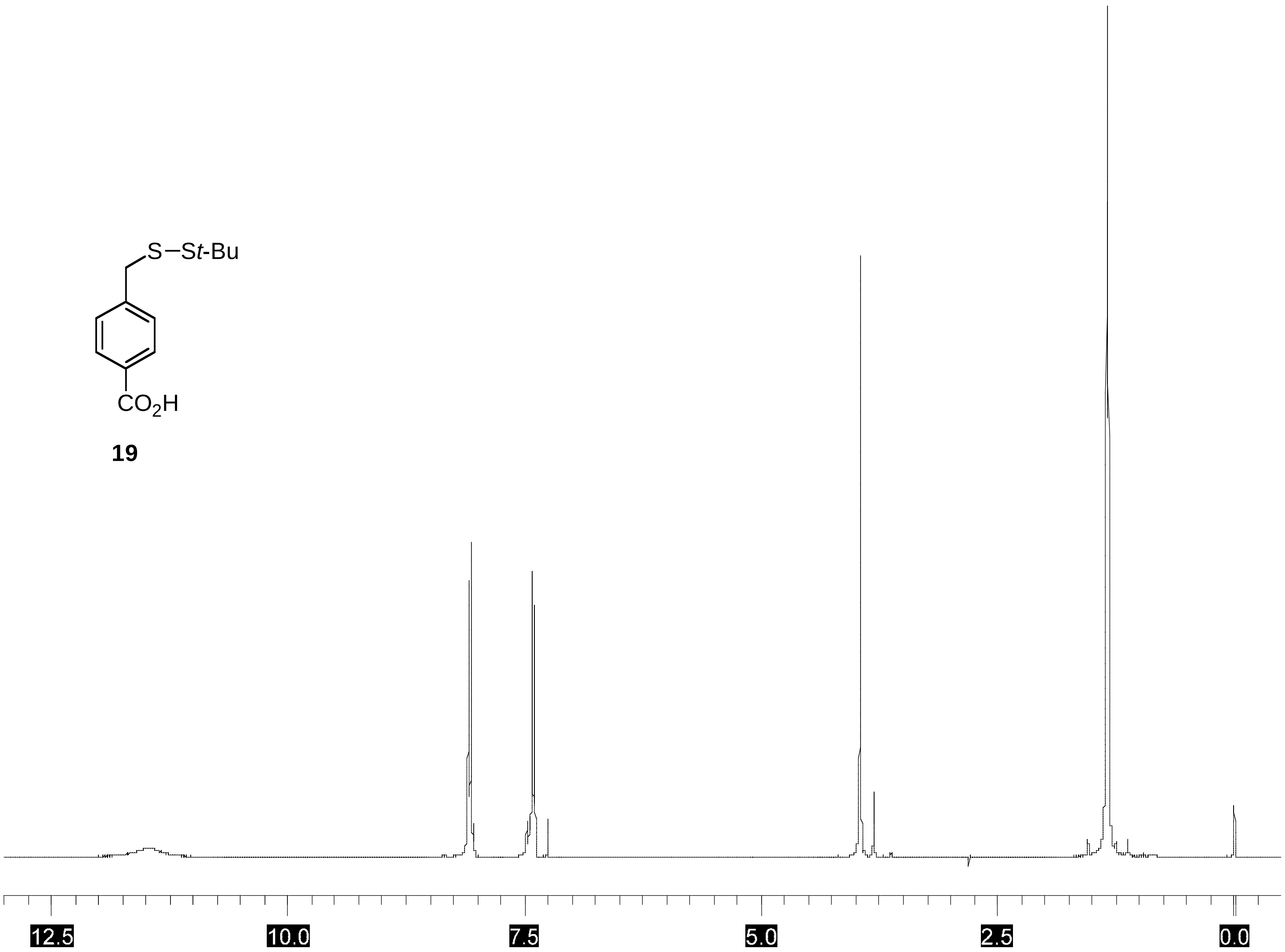



SH
CO$_2$*t*-Bu
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

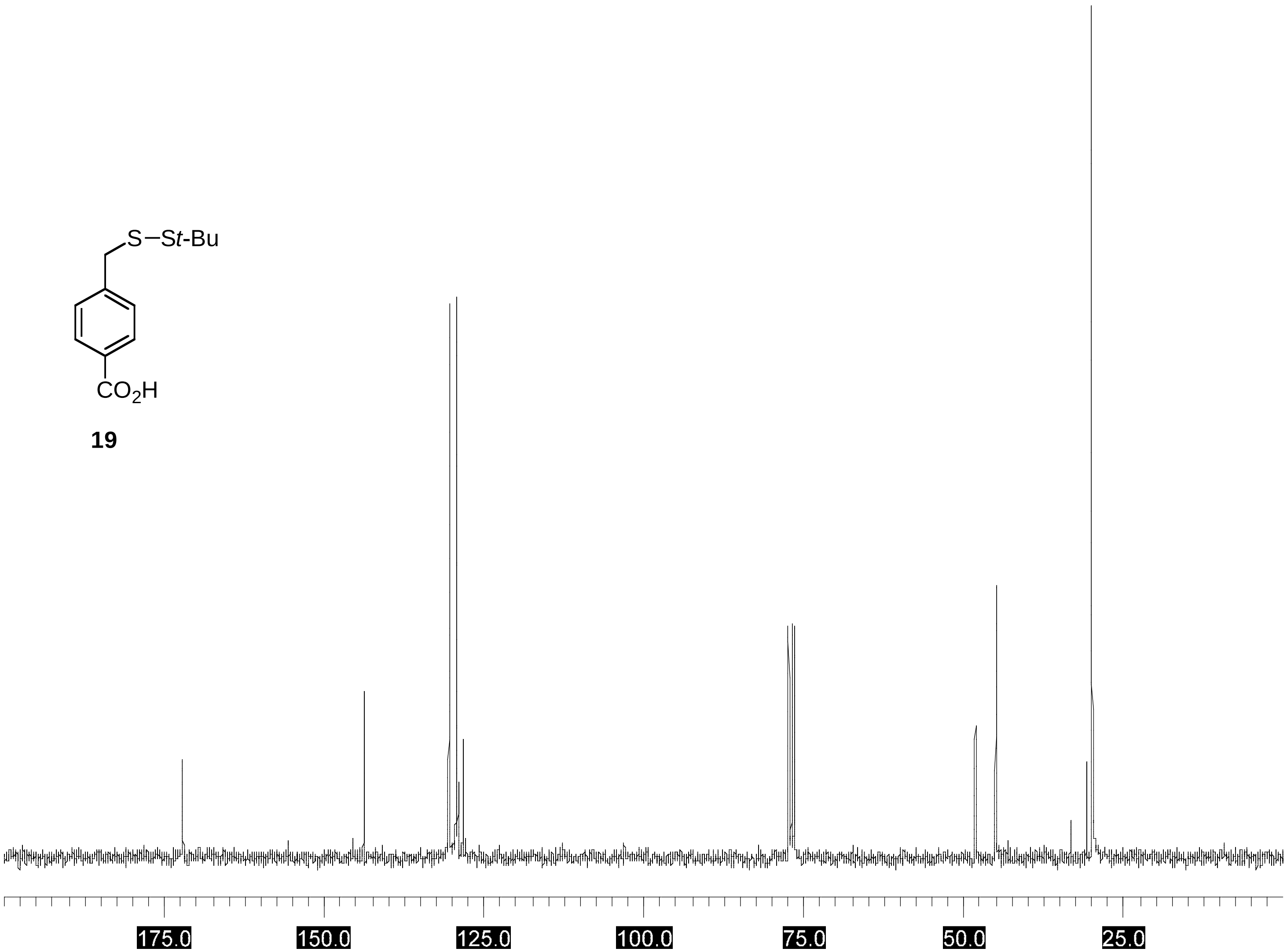
17



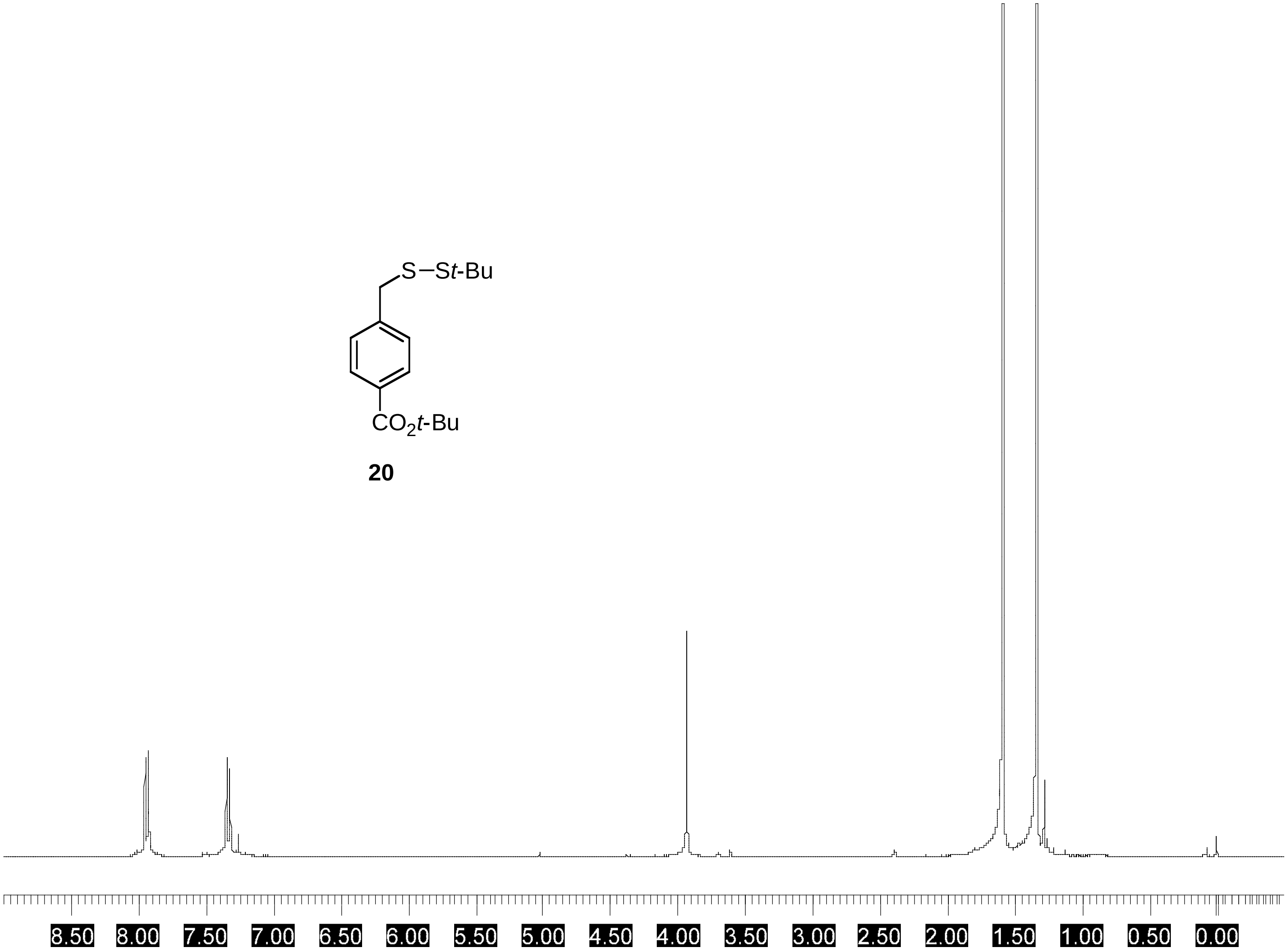
17



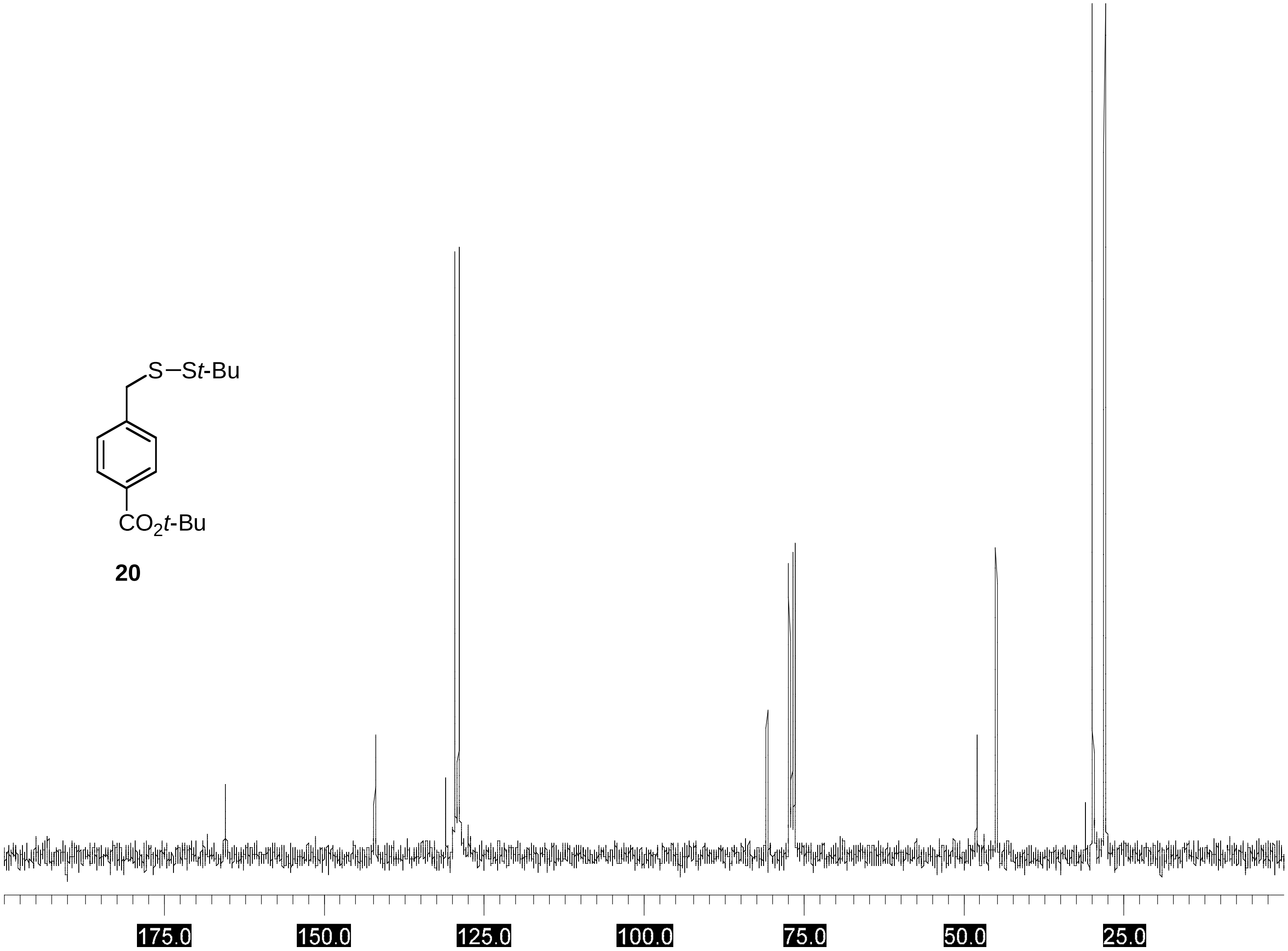
19



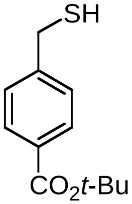
19


S−St-Bu
CO$_2$t-Bu
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

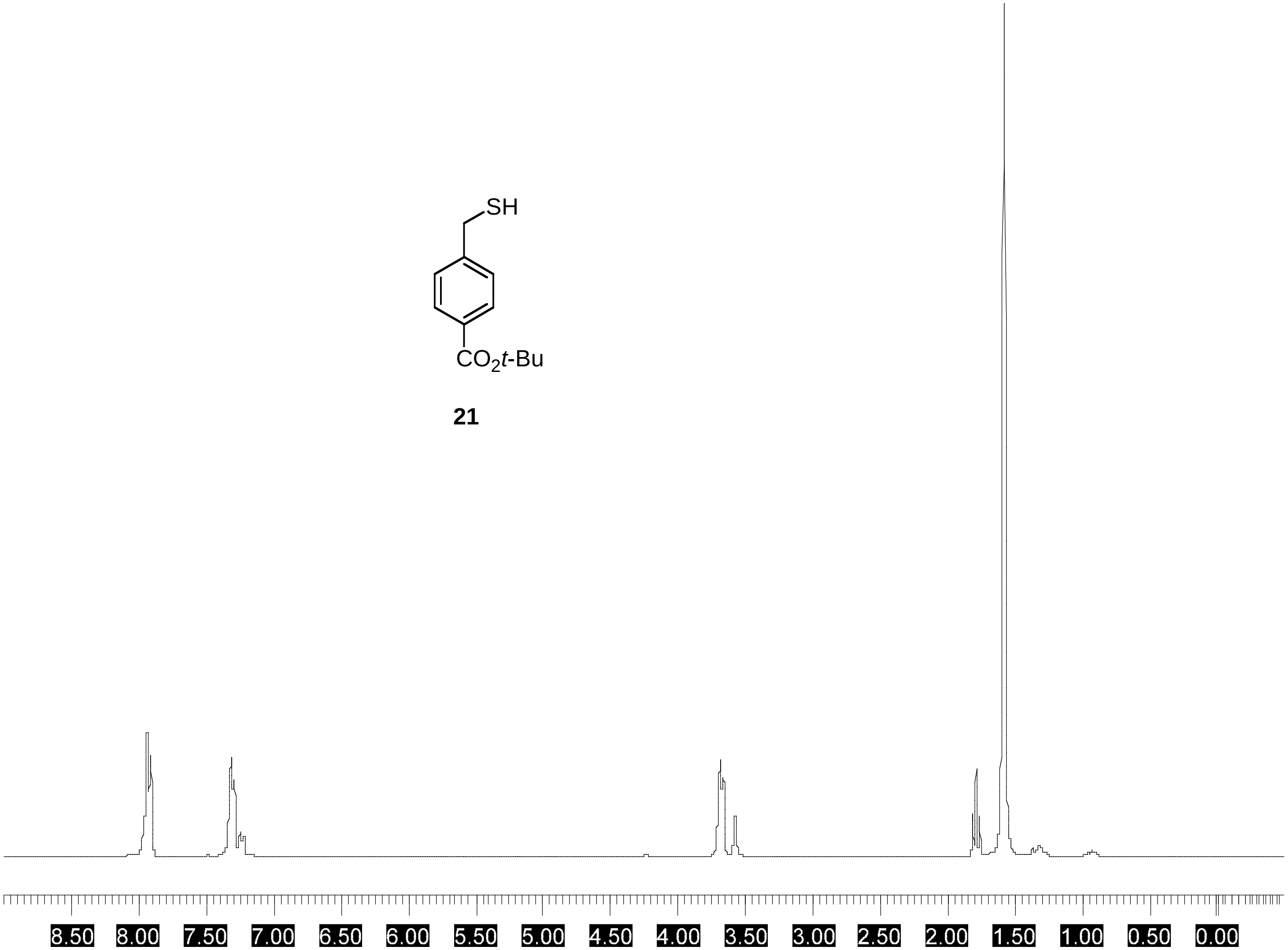
20

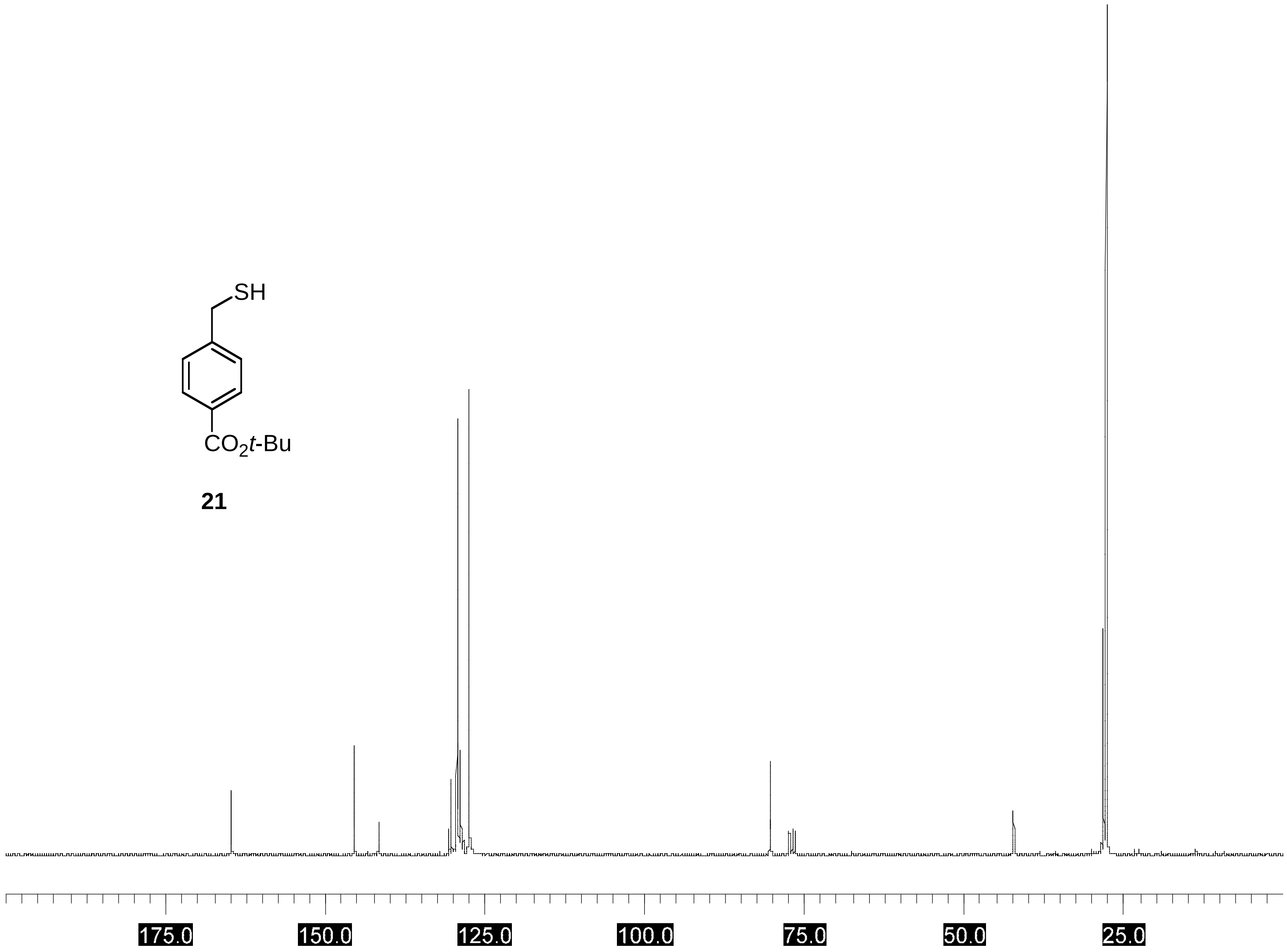


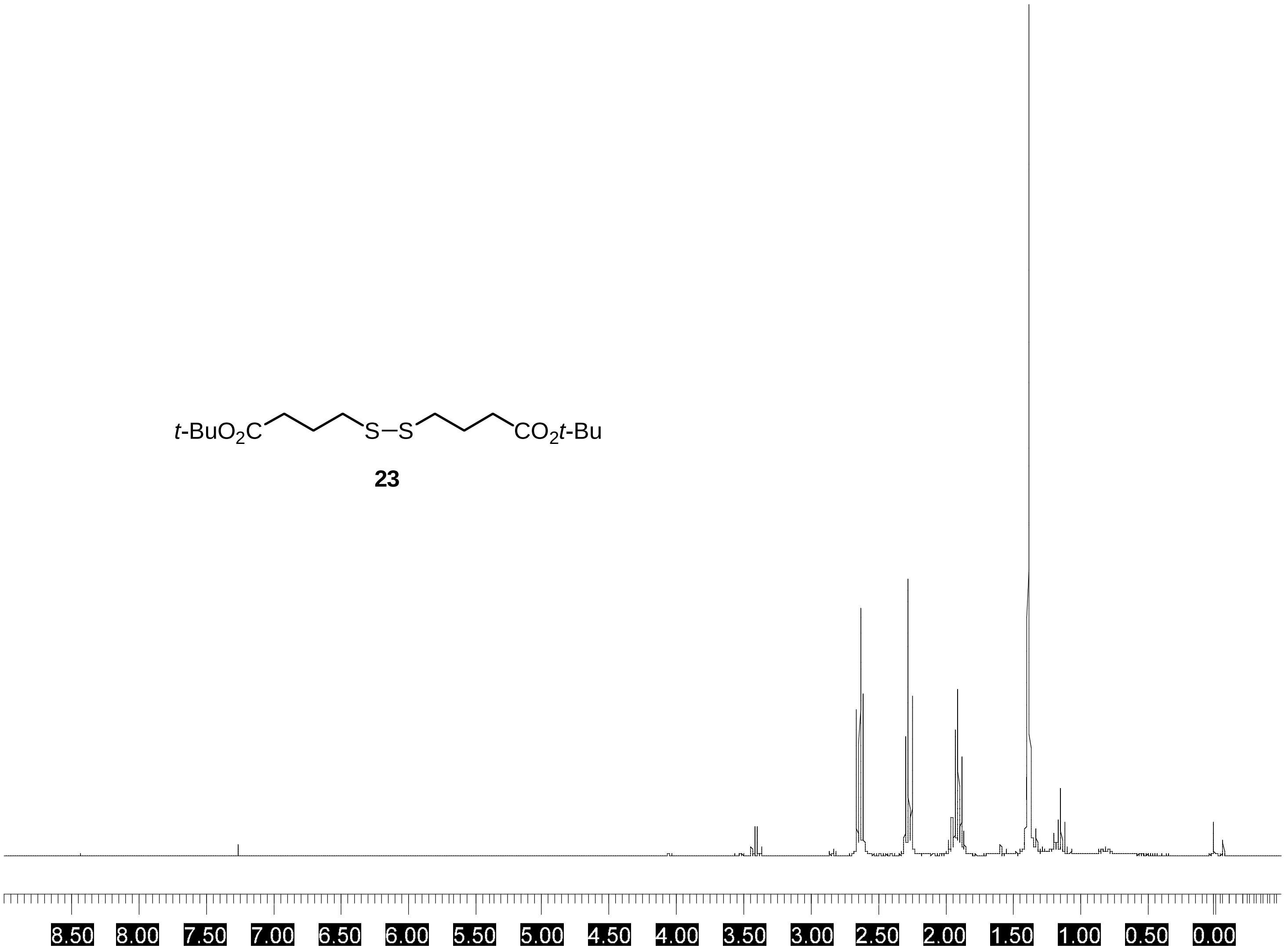
20


SH
CO2t-Bu

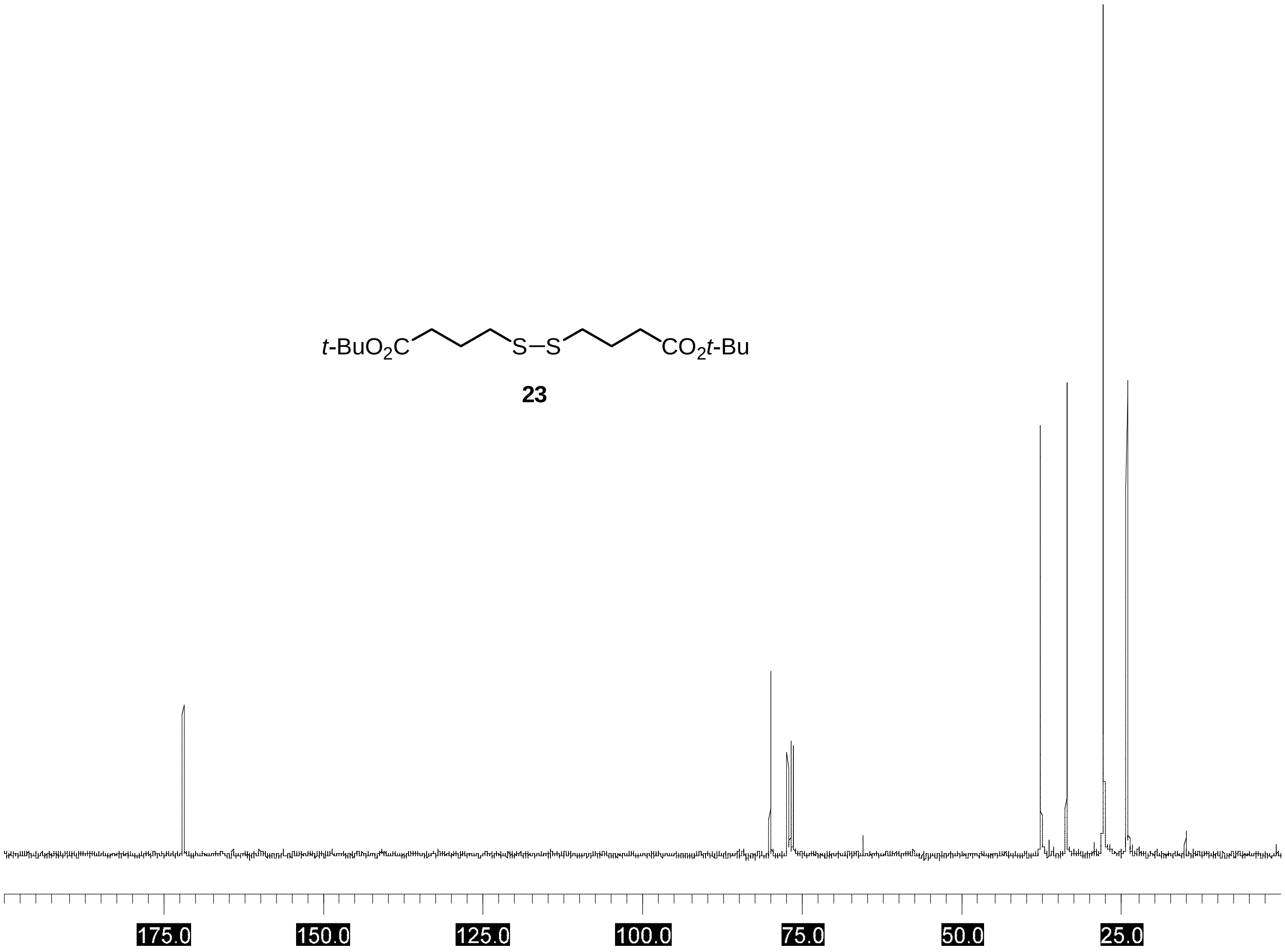
21


8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

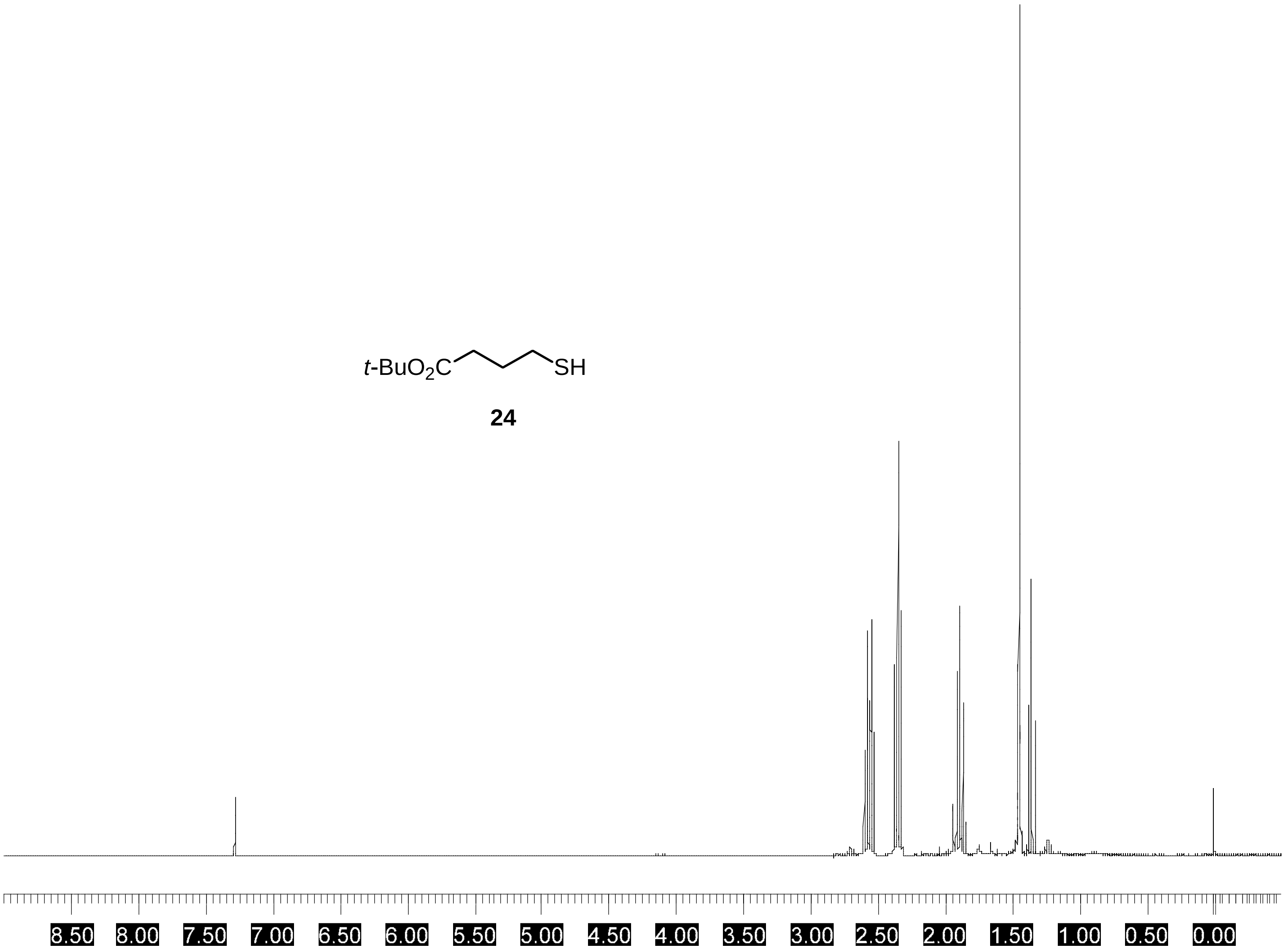

SH
CO2t-Bu
21
175.0
150.0
125.0
100.0
75.0
50.0
25.0


t-BuO2C
S–S
CO2t-Bu
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

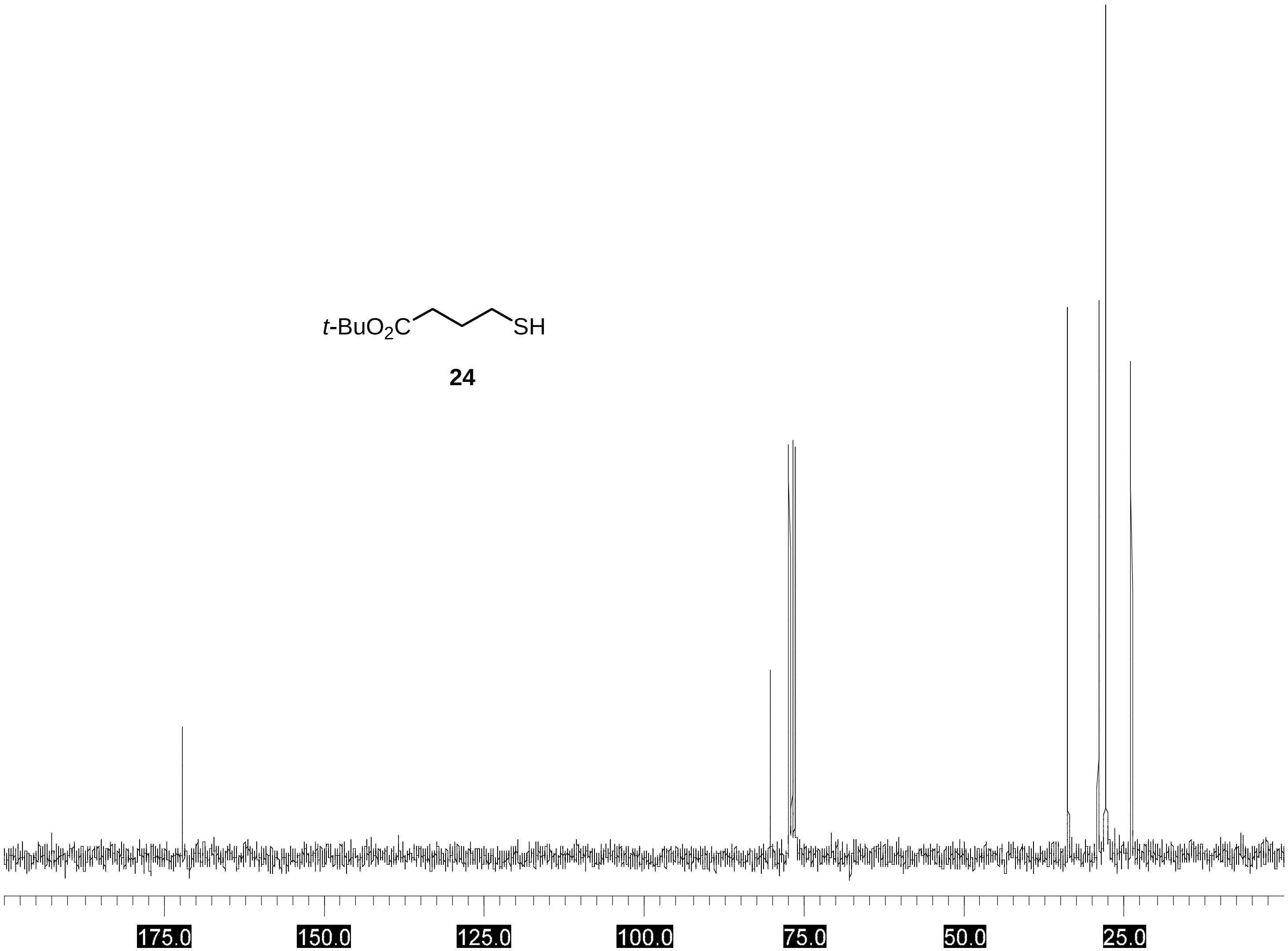
23



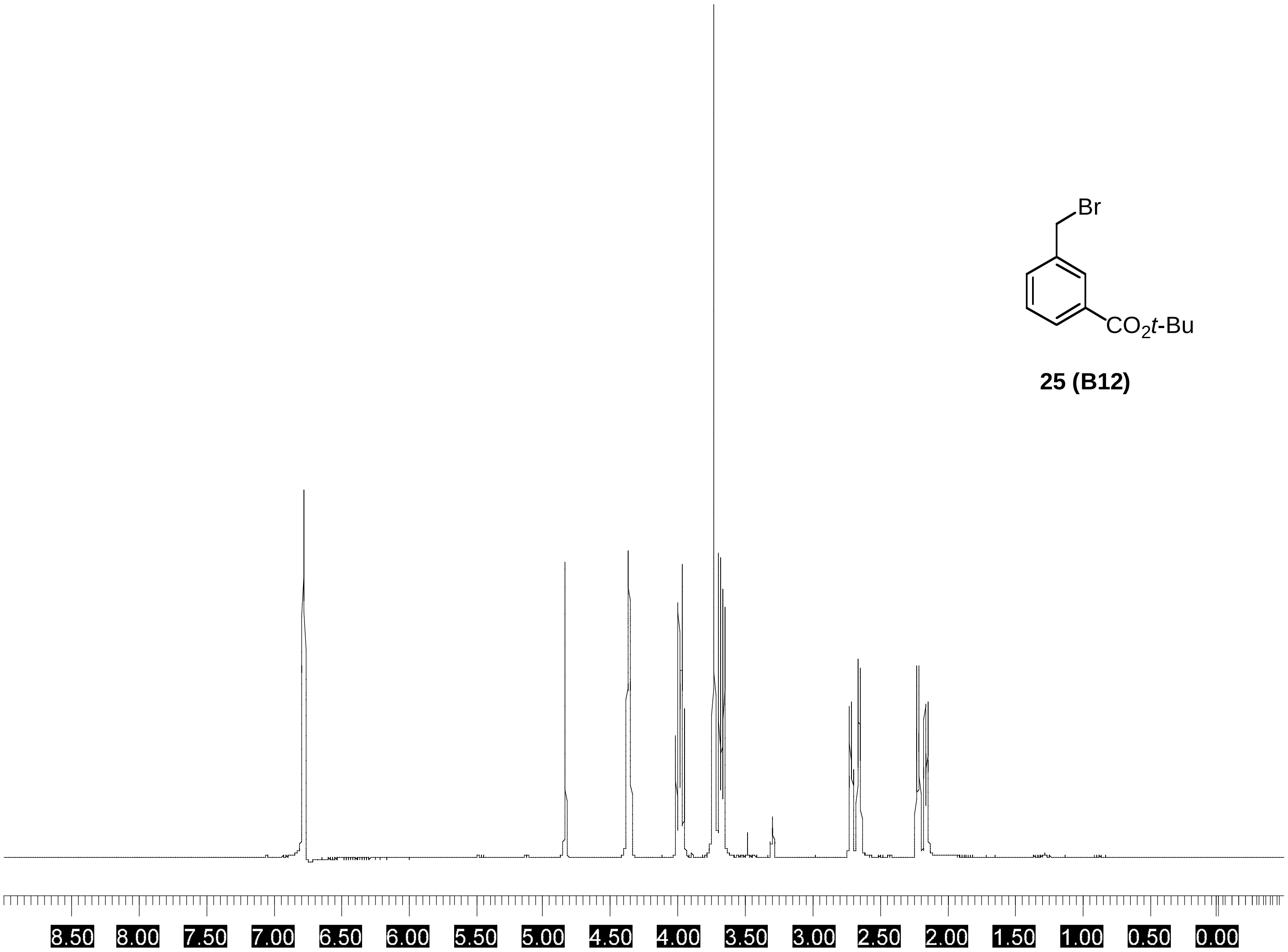
23


t-BuO2C
SH
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

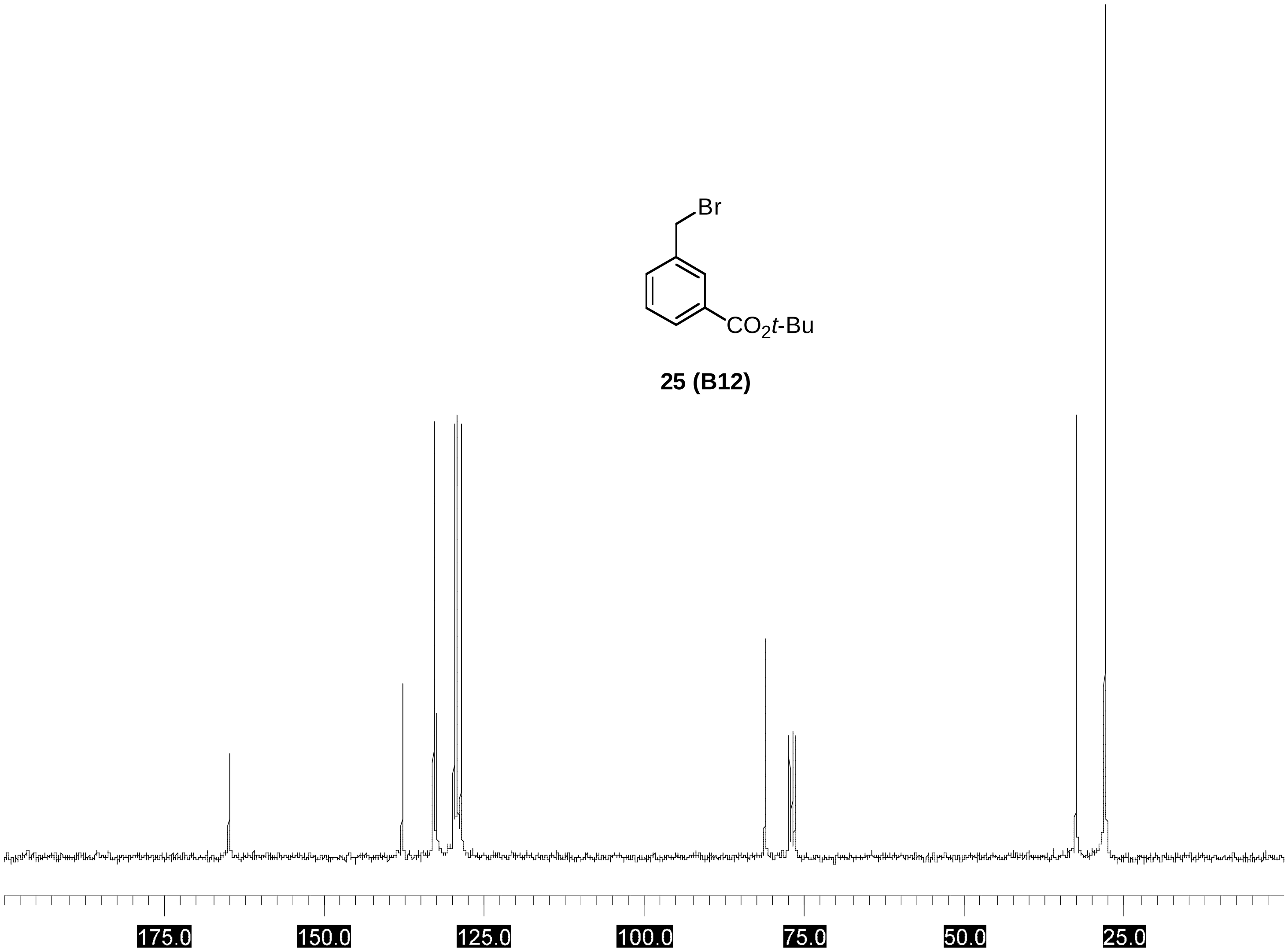
24



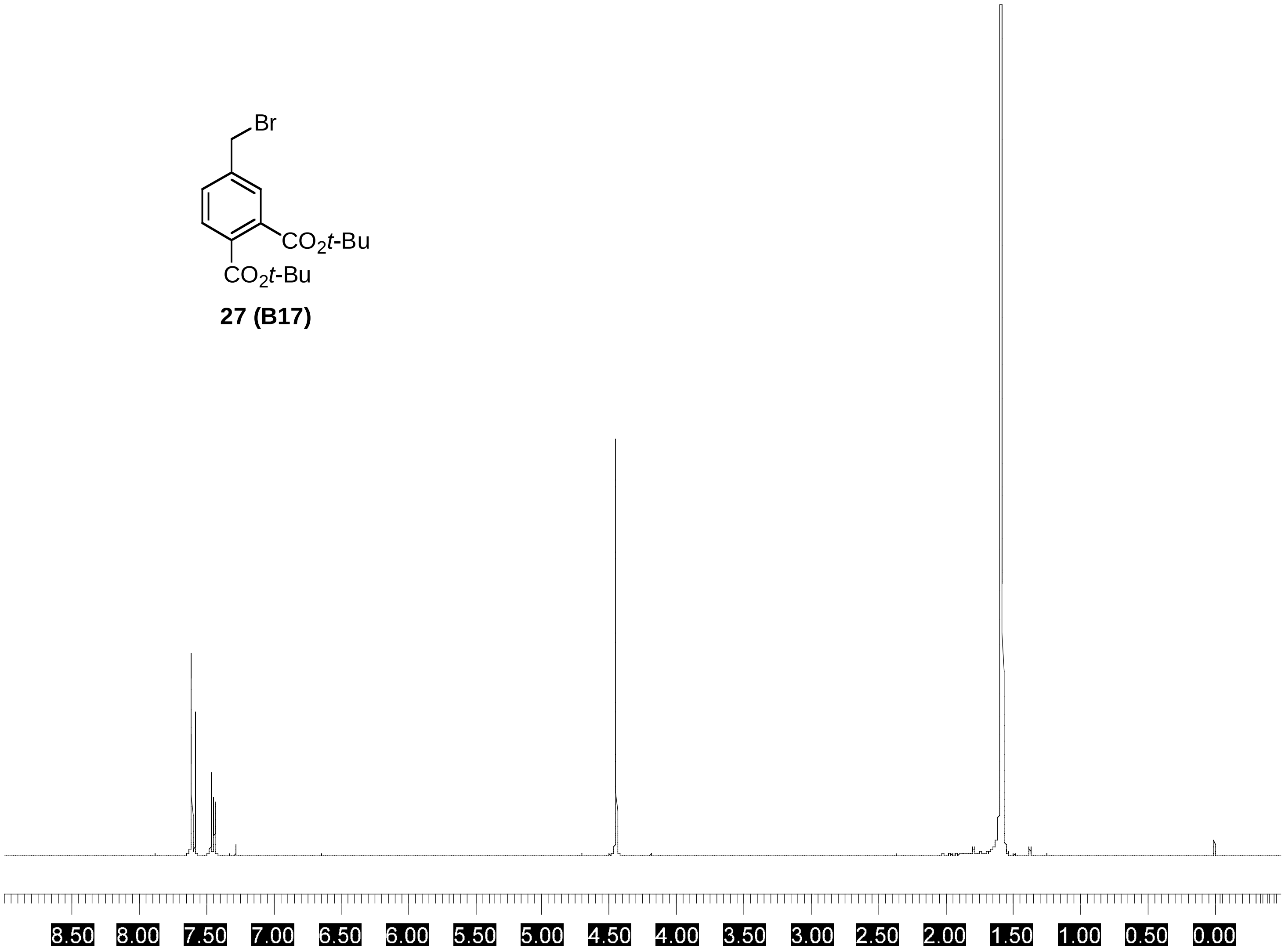
24


Br
CO2t-Bu
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

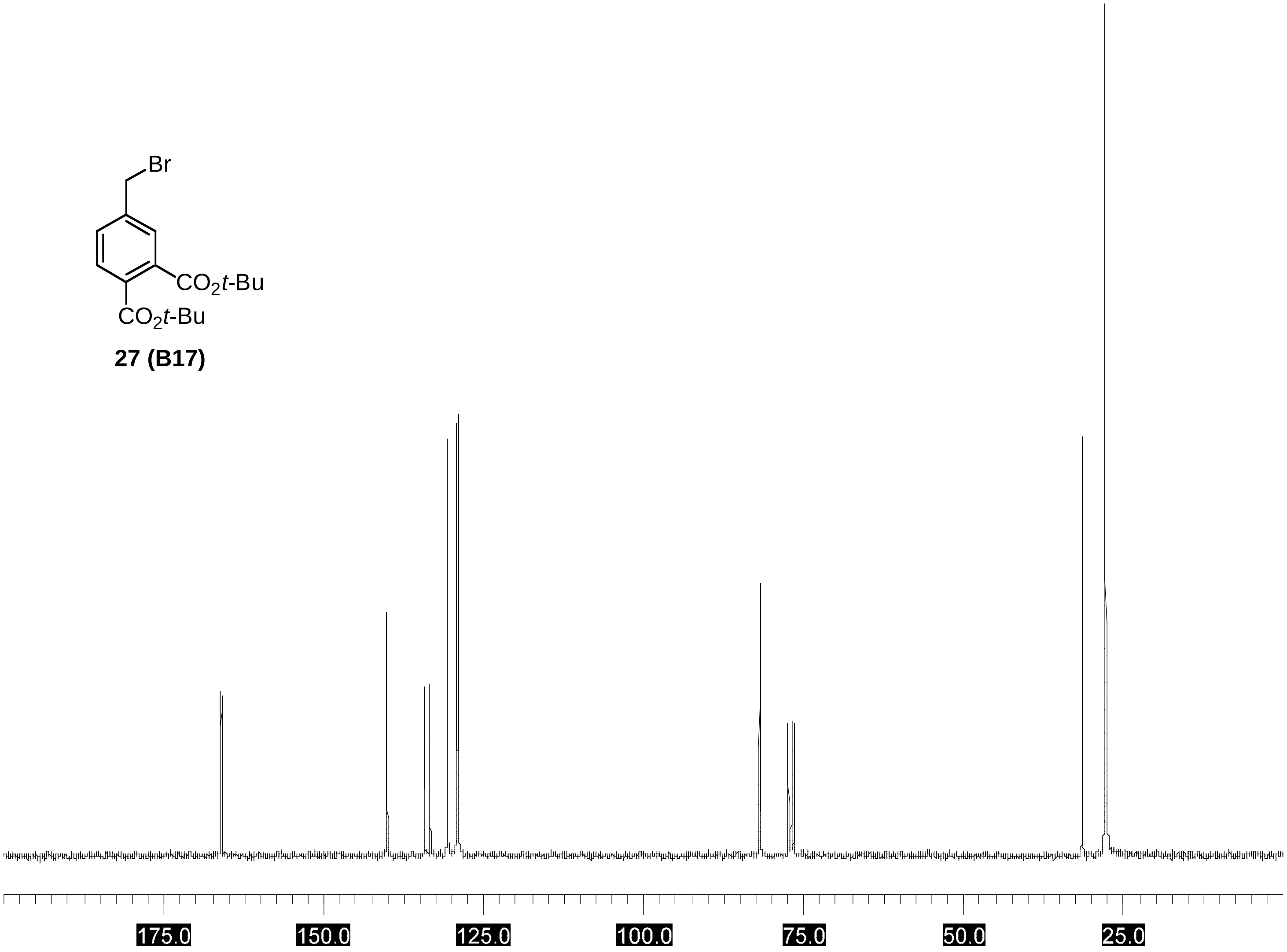
25 (B12)



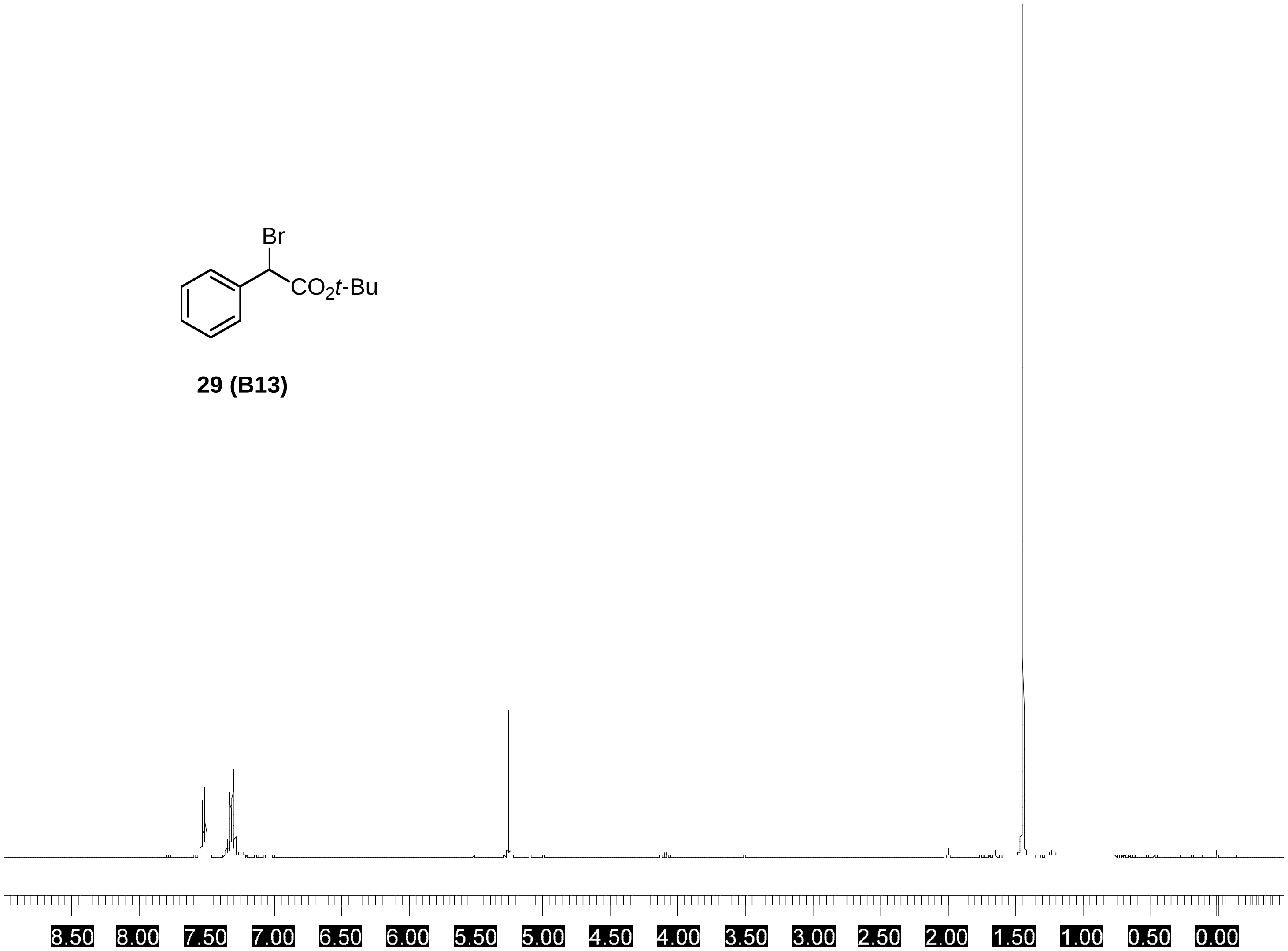
25 (B12)


Br
CO2t-Bu
CO2t-Bu
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

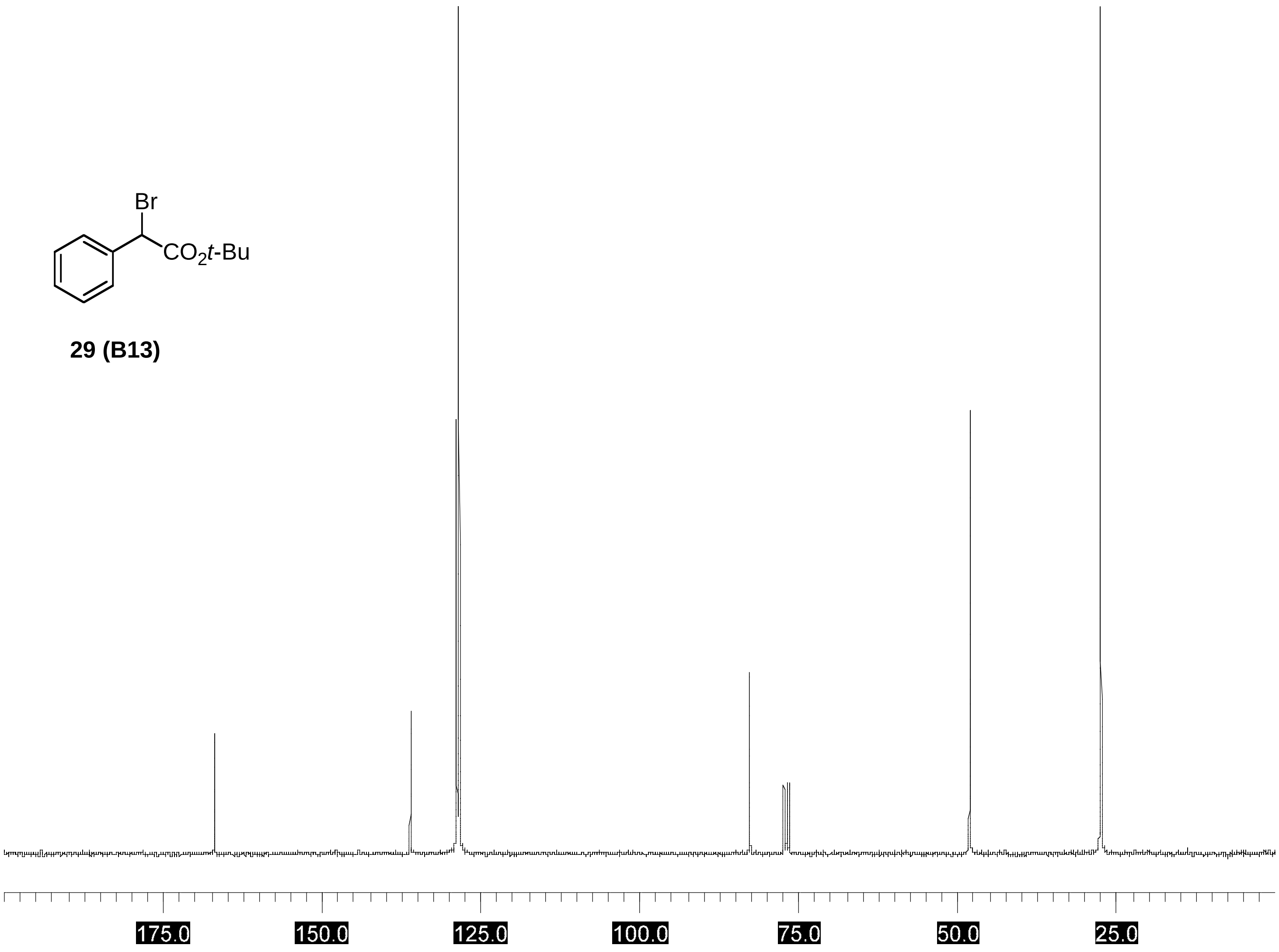
27 (B17)



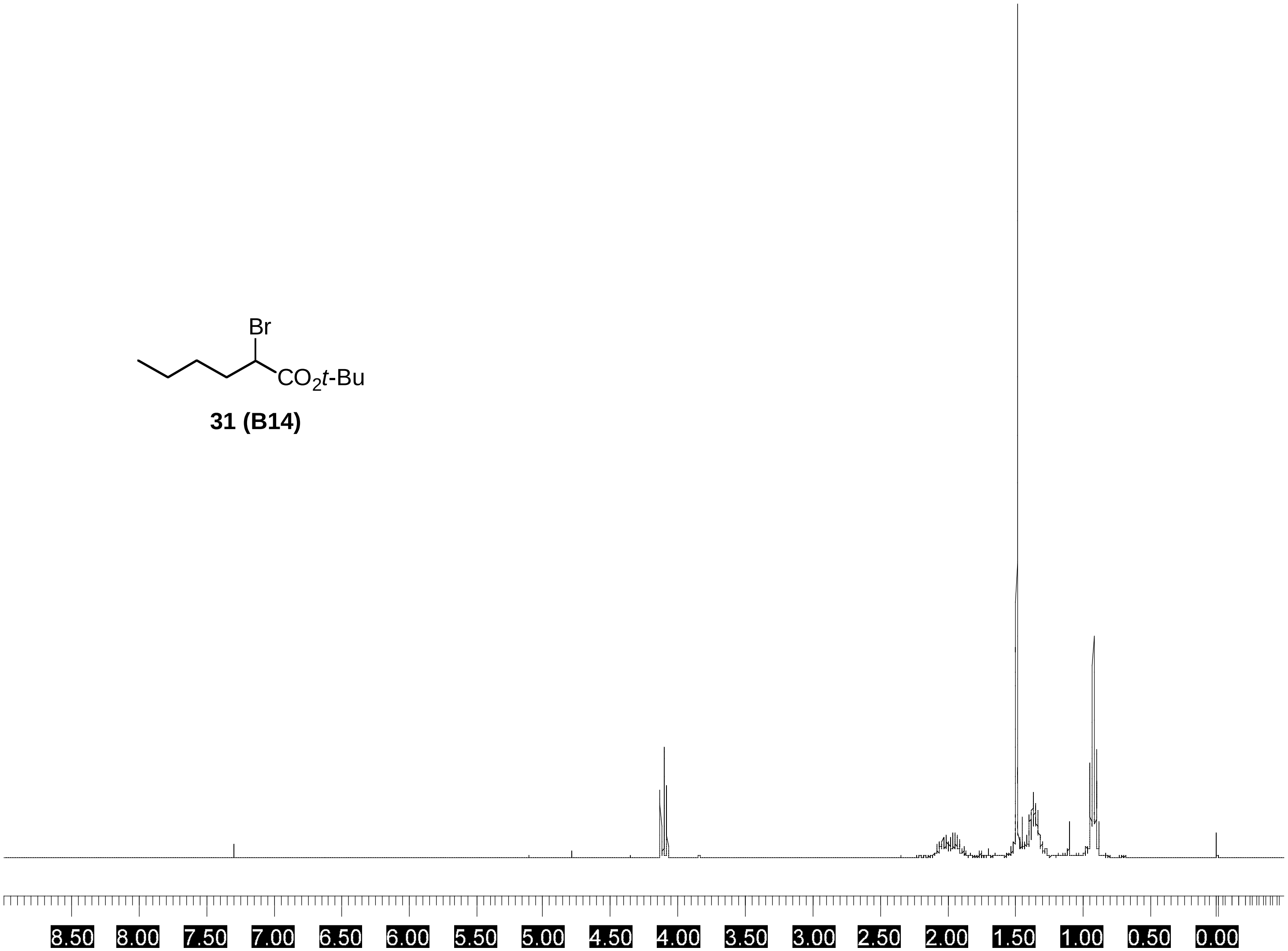
27 (B17)


Br
CO2t-Bu
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

29 (B13)

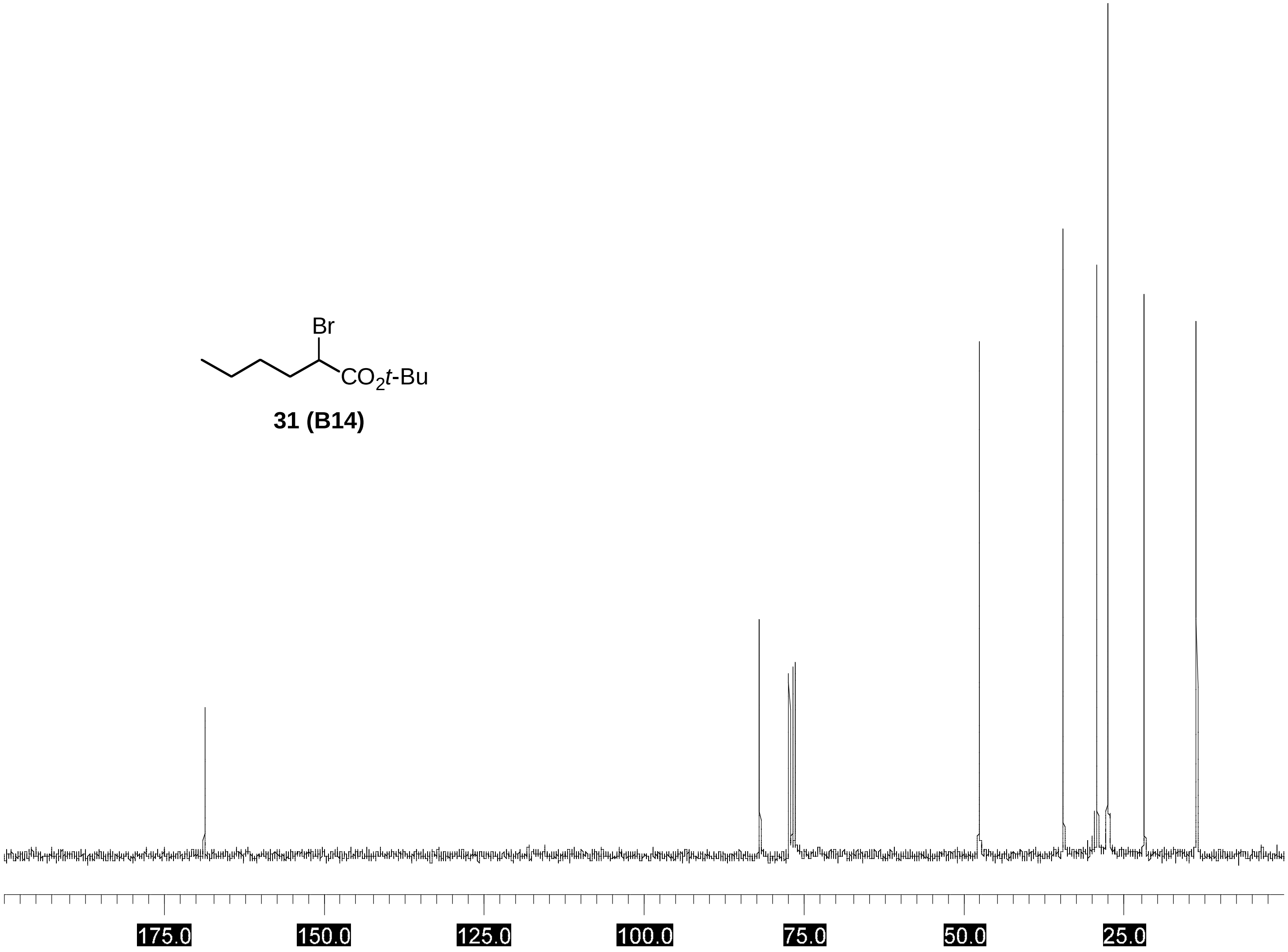


29 (B13)

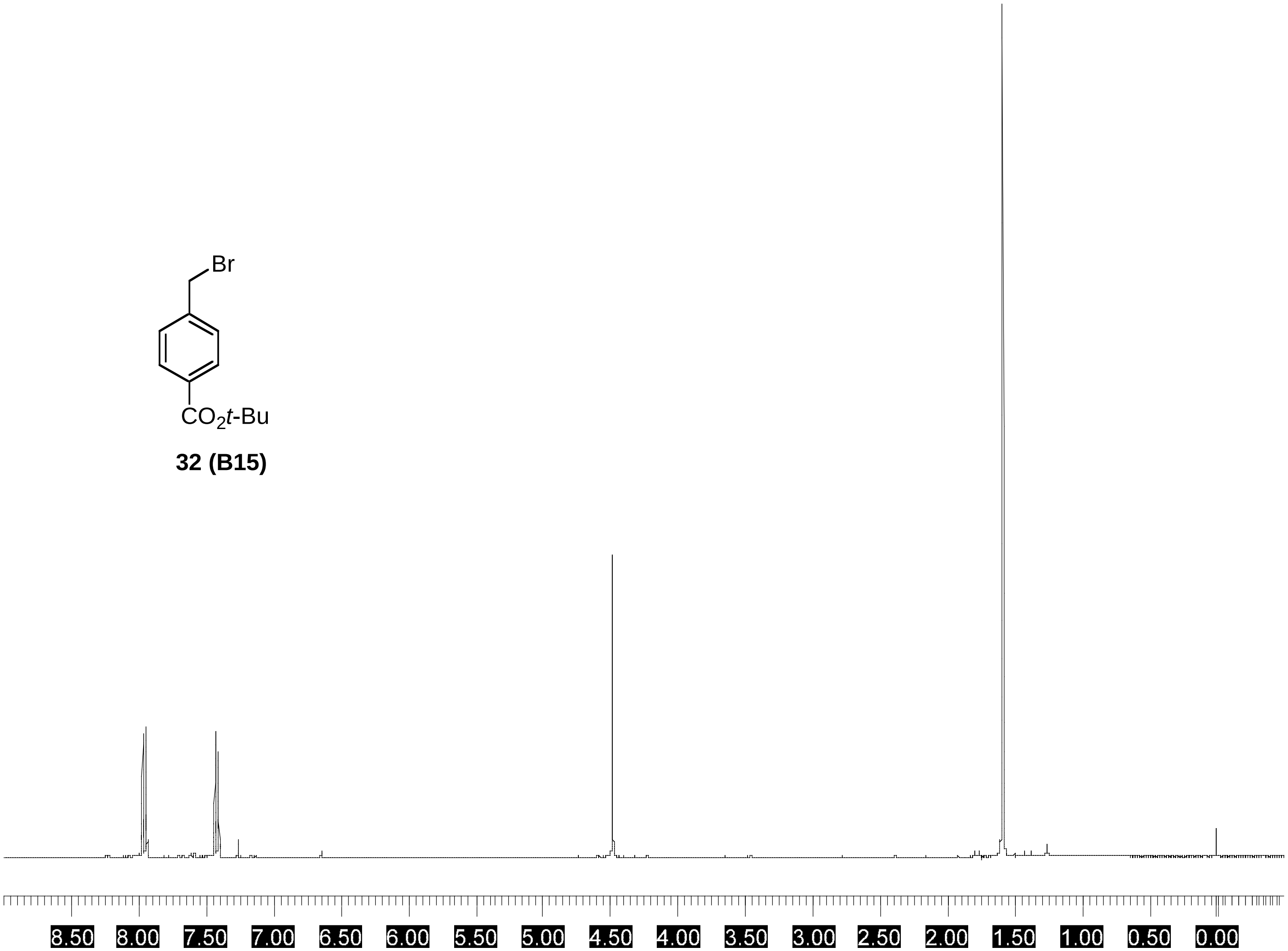

Br
CO2t-Bu

31 (B14)

8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

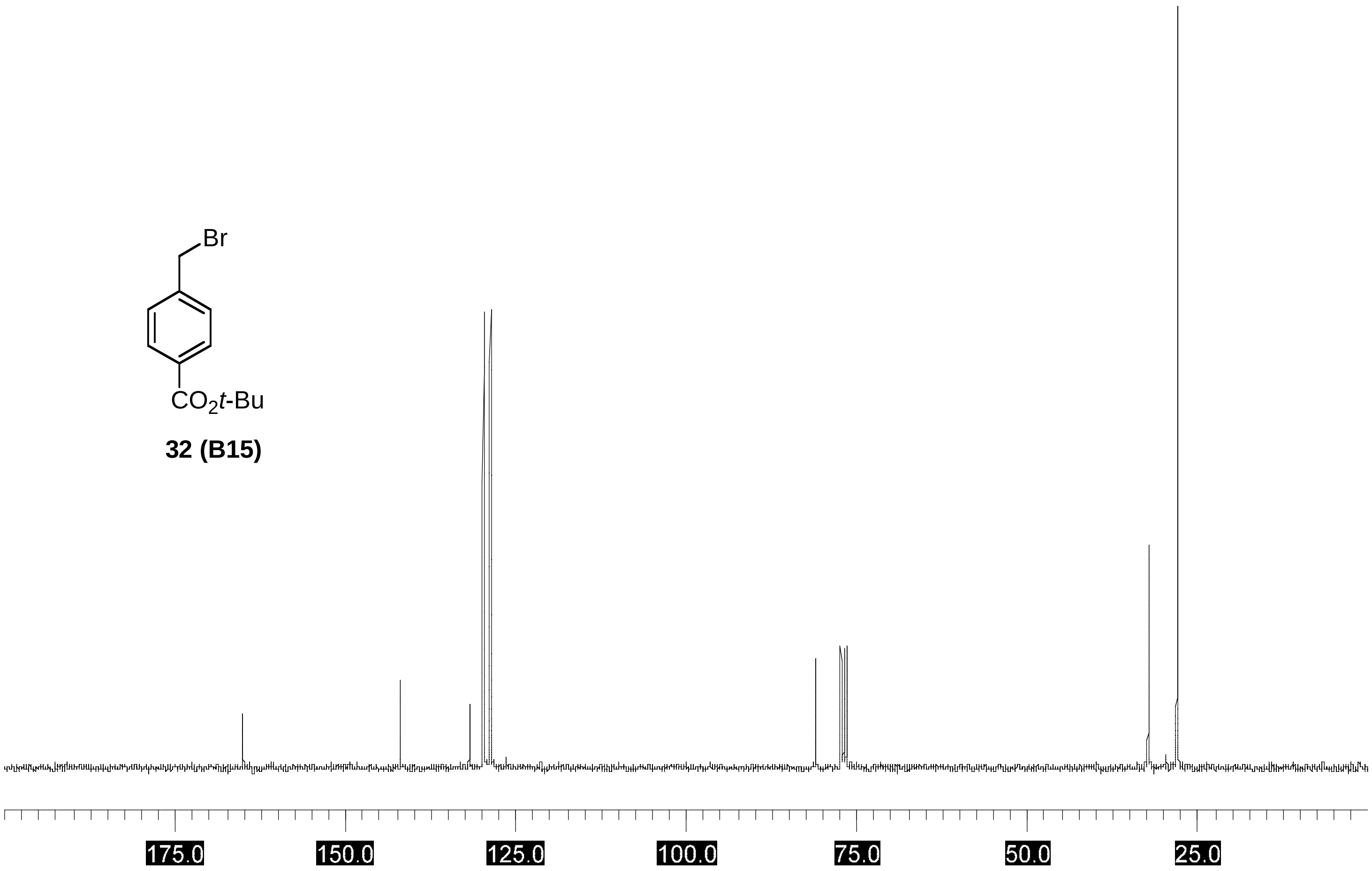


31 (B14)

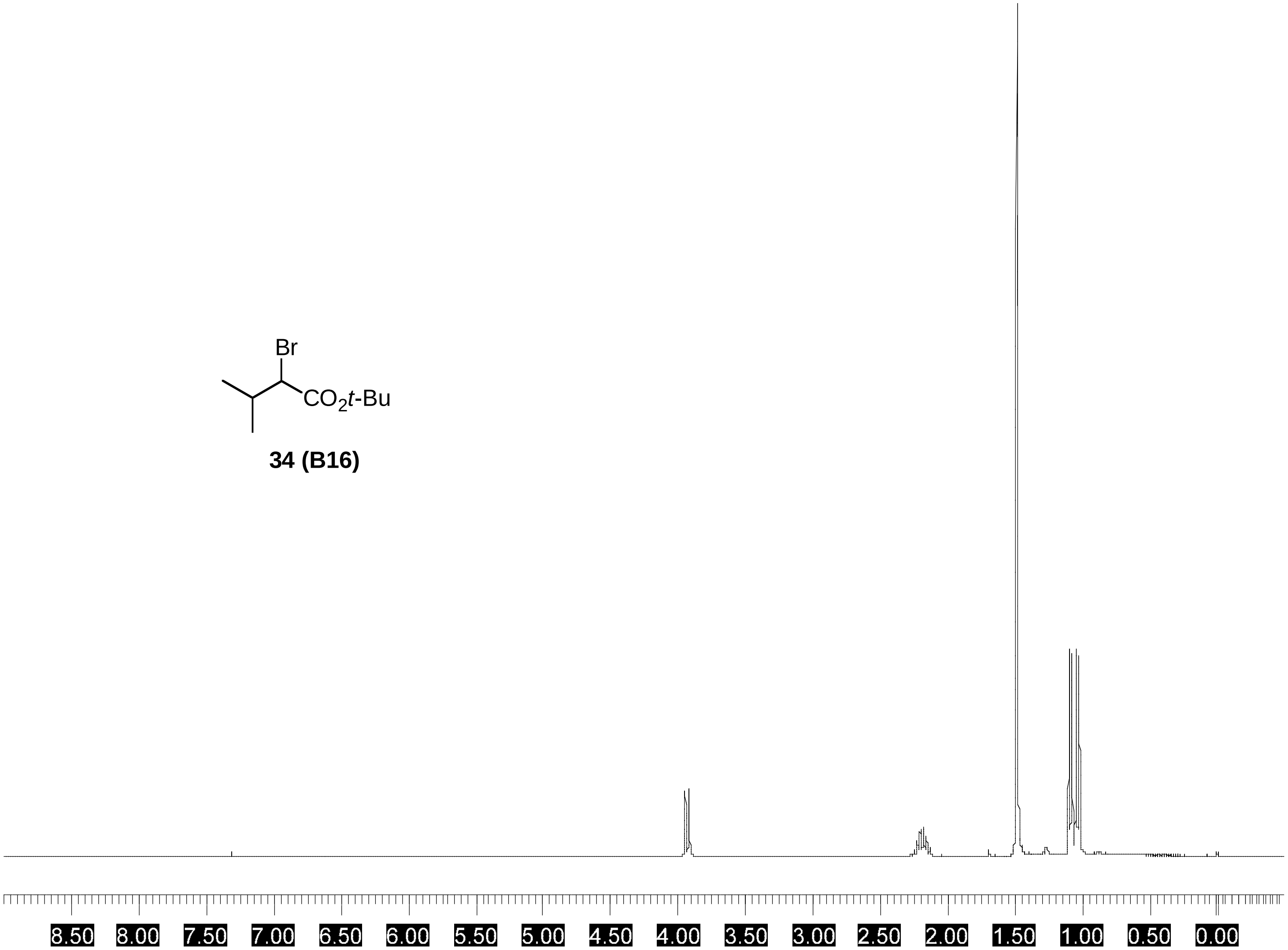

Br
CO2t-Bu

32 (B15)

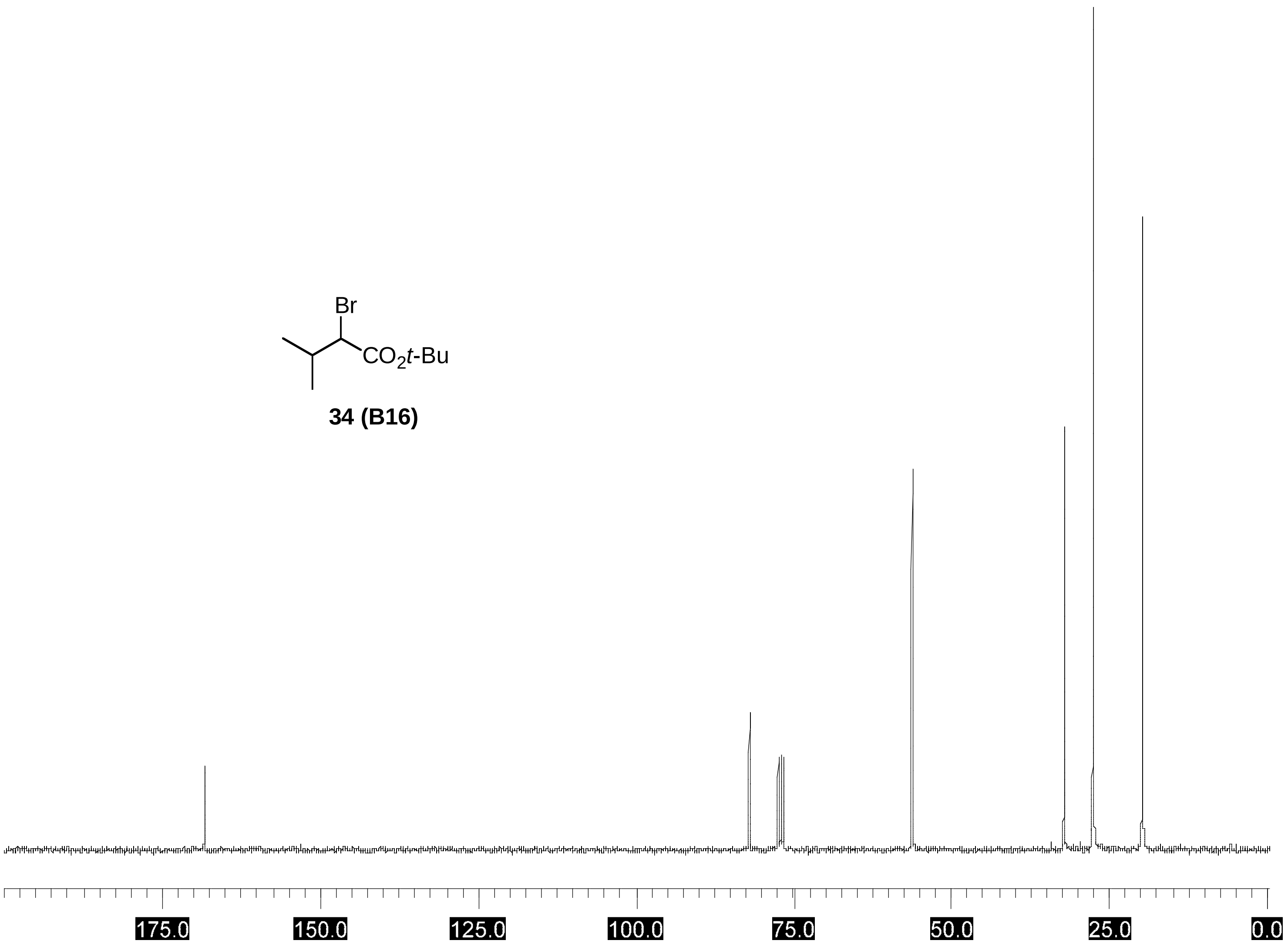
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00



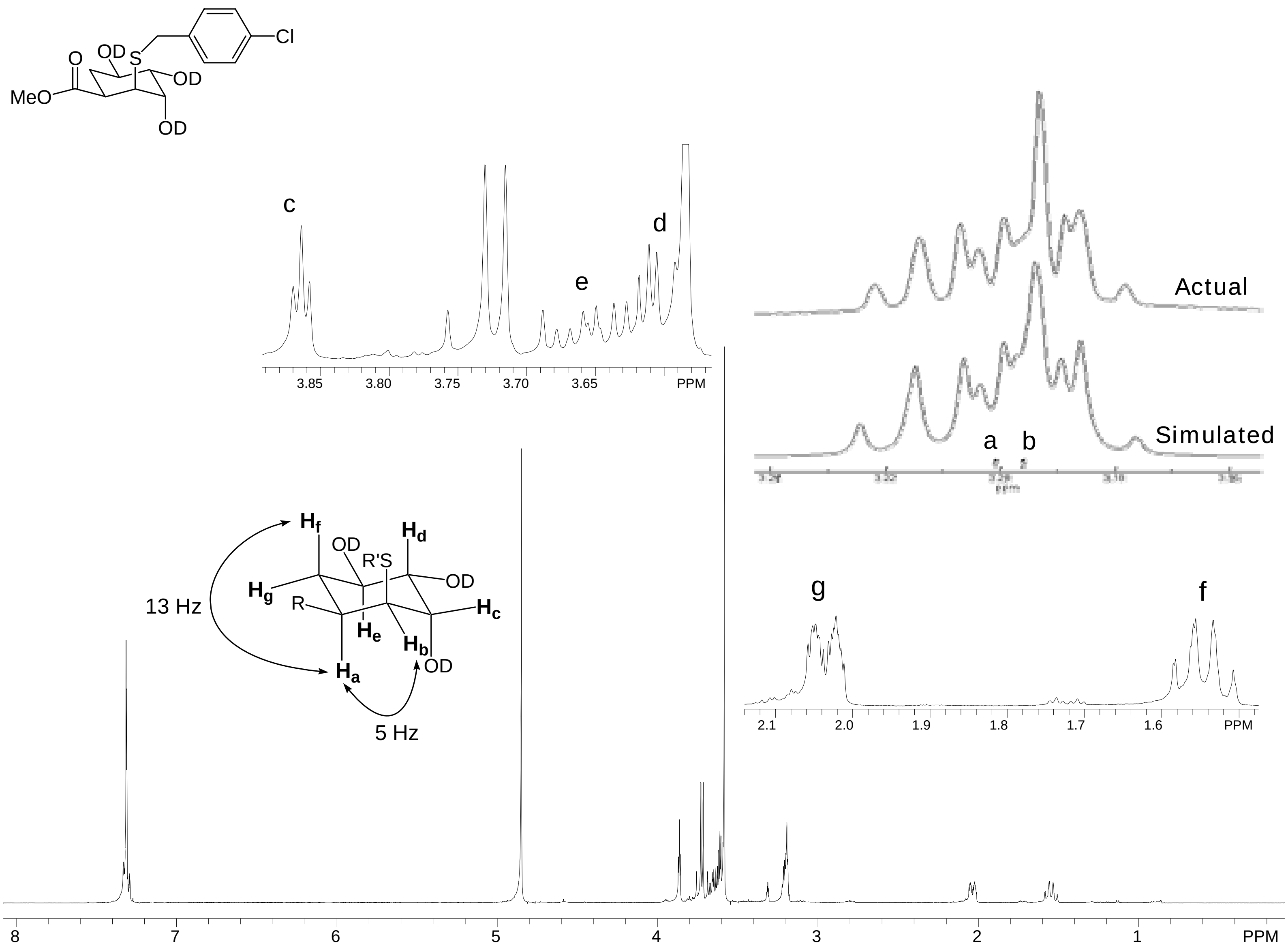
32 (B15)

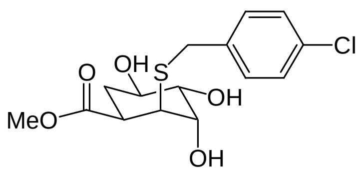

Br
CO2t-Bu
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

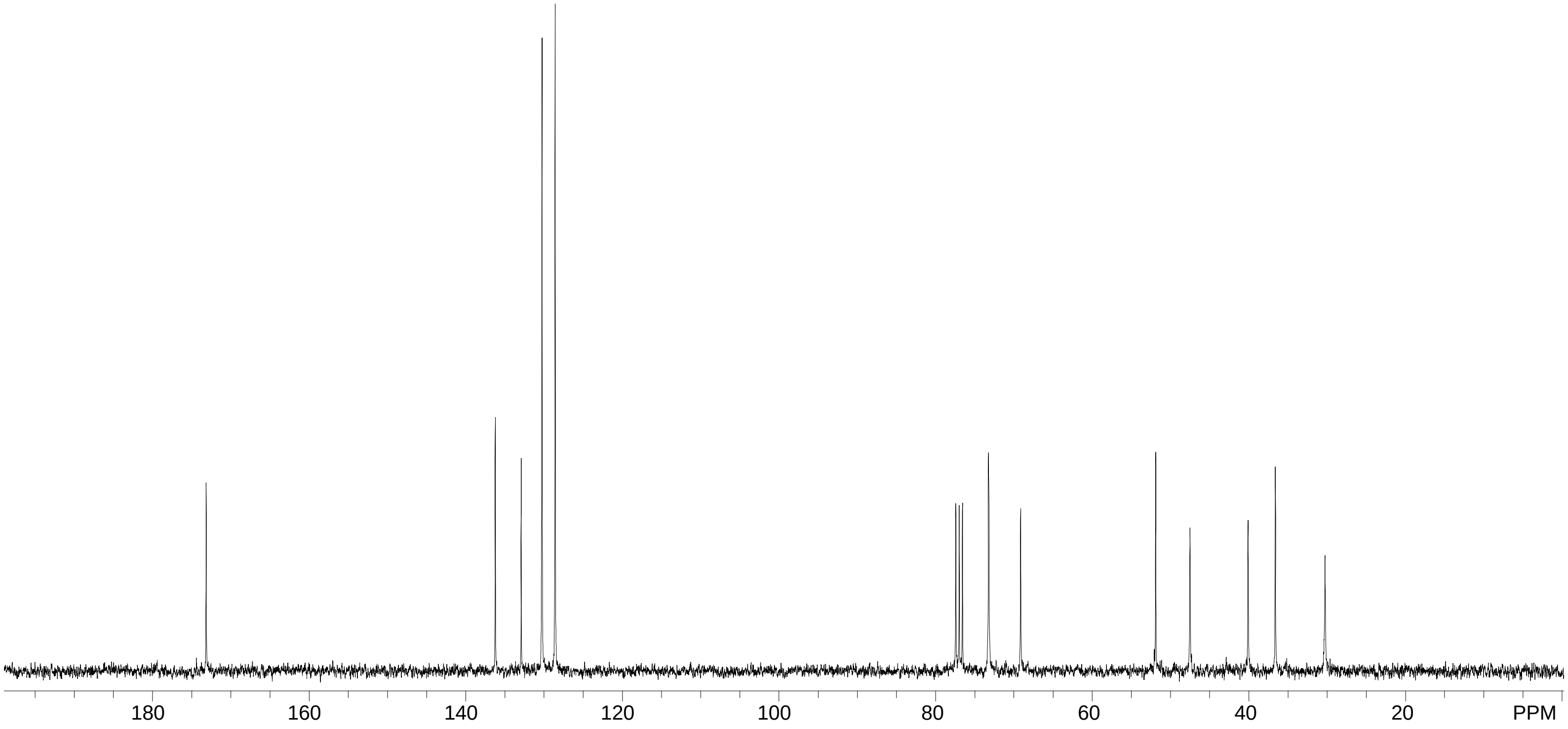
34 (B16)

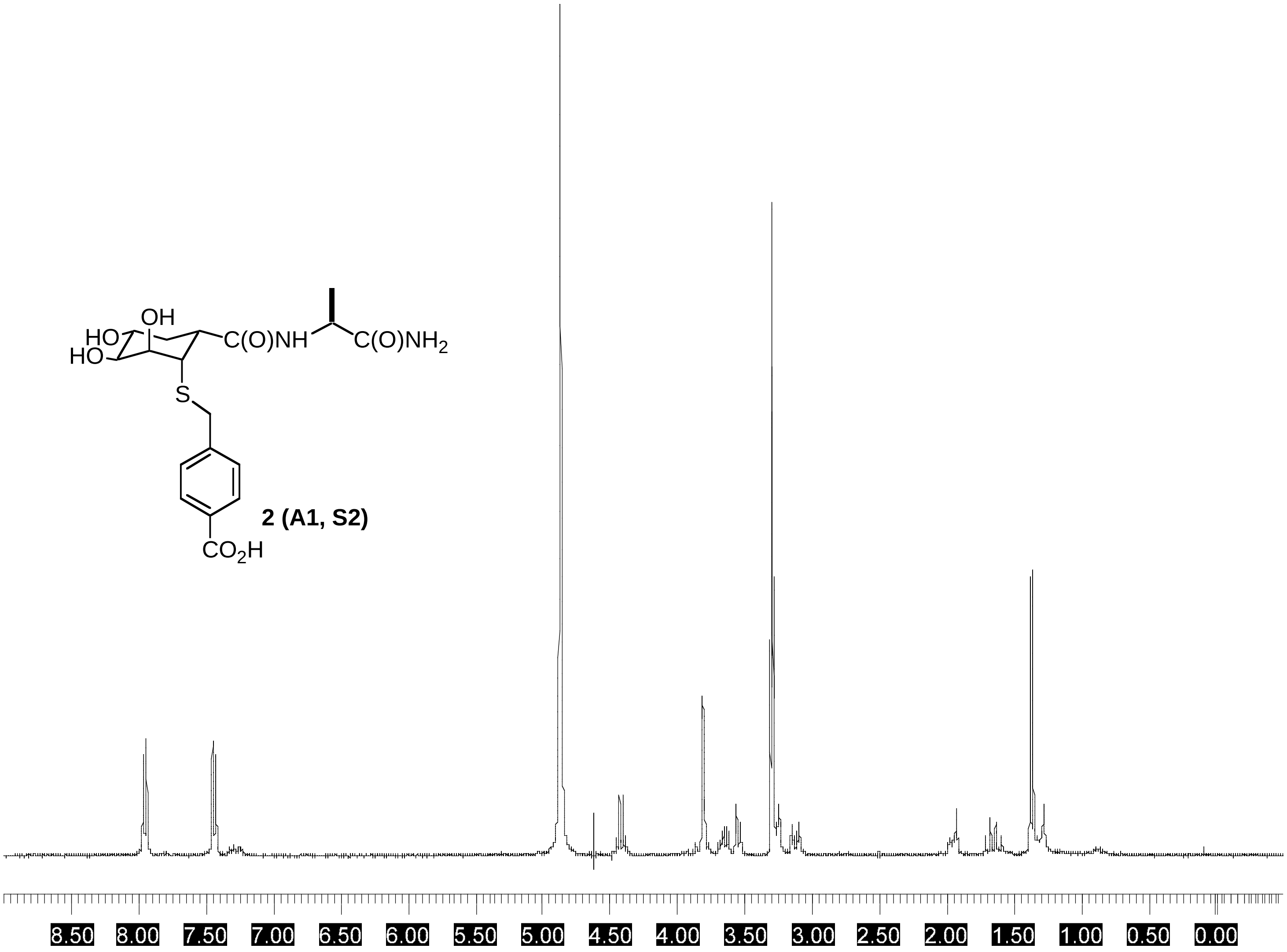


34 (B16)

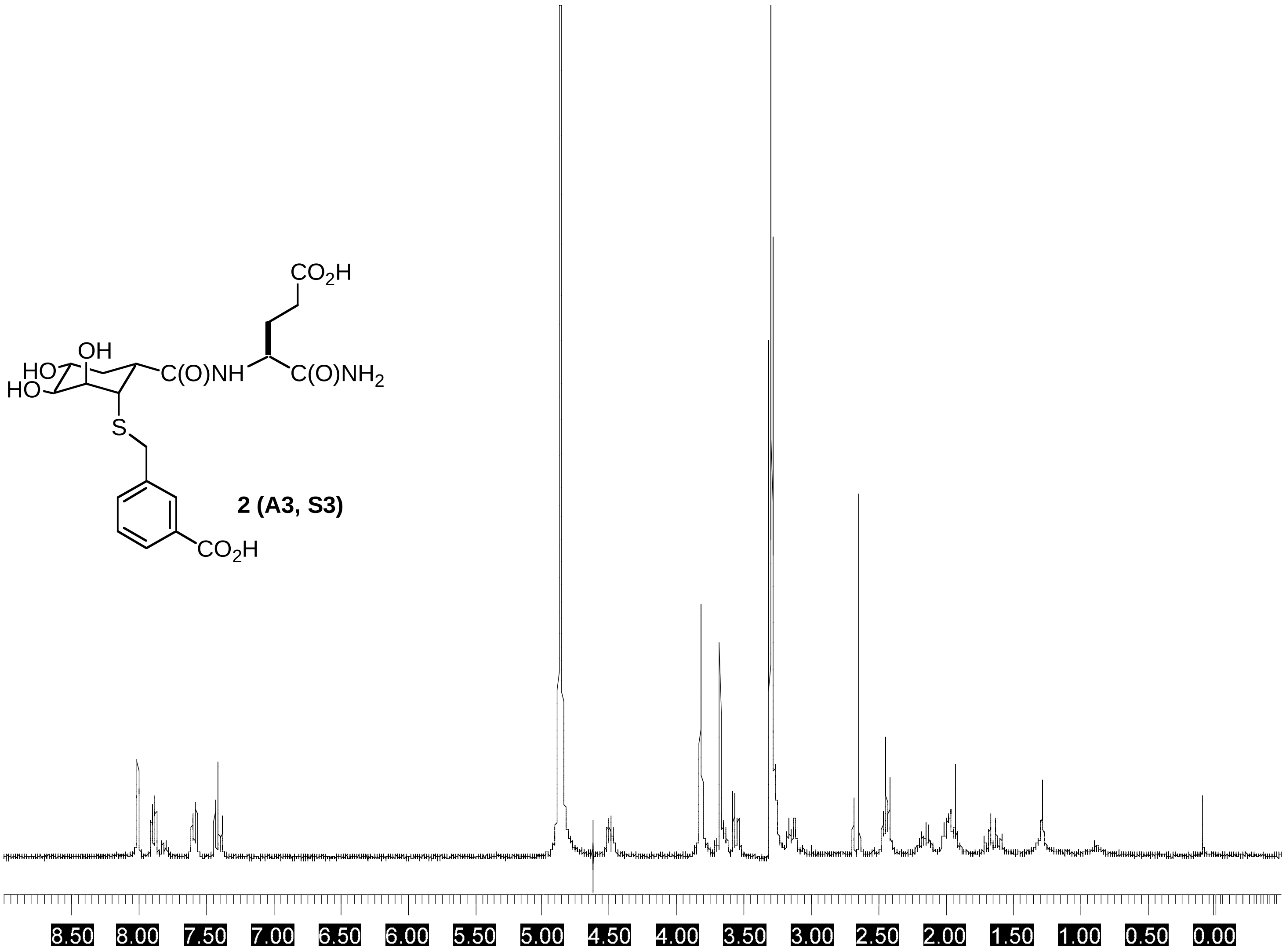

MeO
O
OD
S
Cl
OD
OD
c
e
d
3.85
3.80
3.75
3.70
3.65
PPM
Actual
Simulated
a
b
g
f
2.1
2.0
1.9
1.8
1.7
1.6
PPM
13 Hz
H_f
OD
R'S
H_d
OD
H_g
R
H_c
H_e
H_b
H_a
OD
5 Hz
8
7
6
5
4
3
2
1
PPM


O
OH
S
Cl
MeO
OH
OH

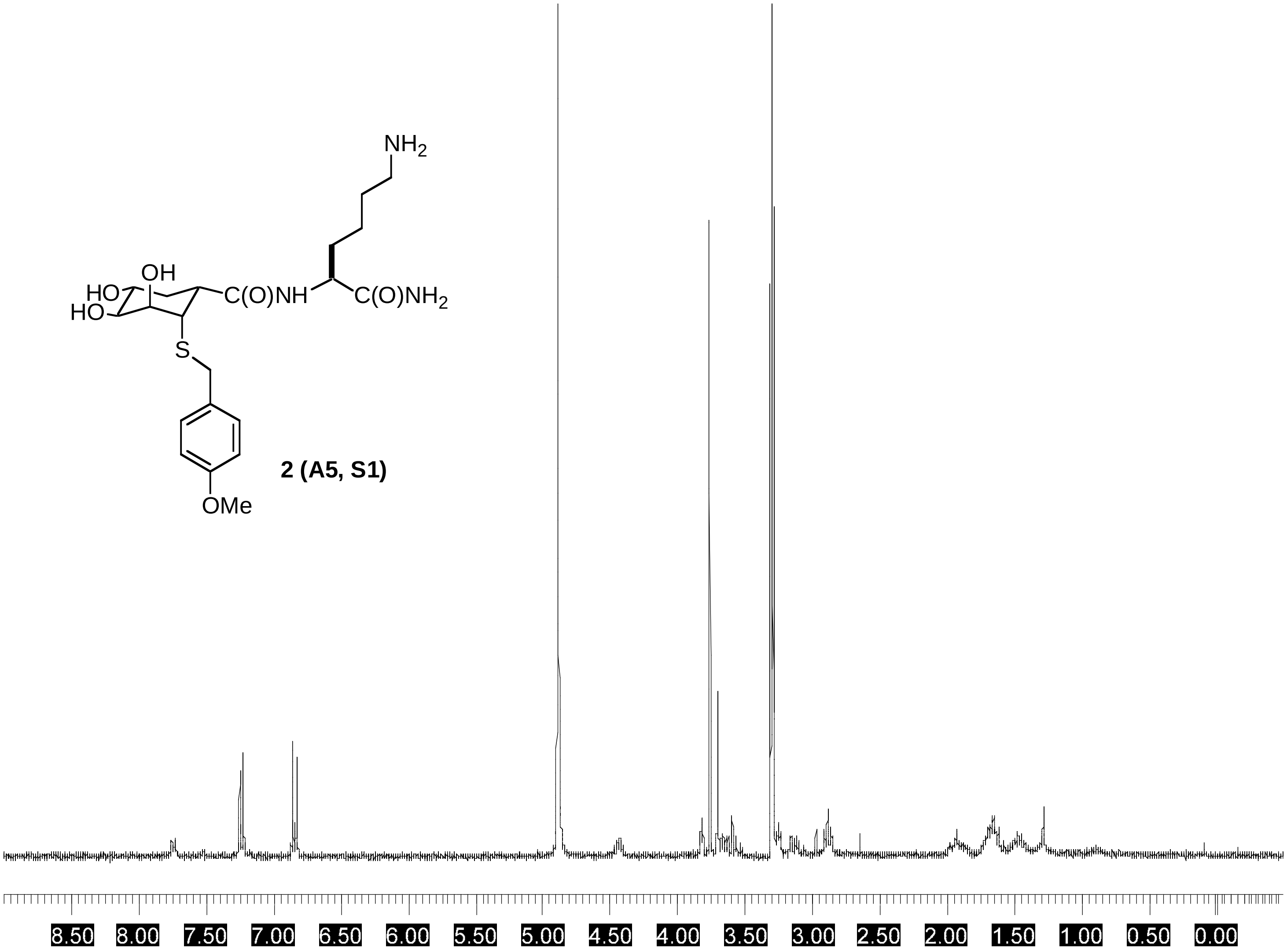

180
160
140
120
100
80
60
40
20
PPM


OH
HO
HO
C(O)NH
C(O)NH2
S
CO2H
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

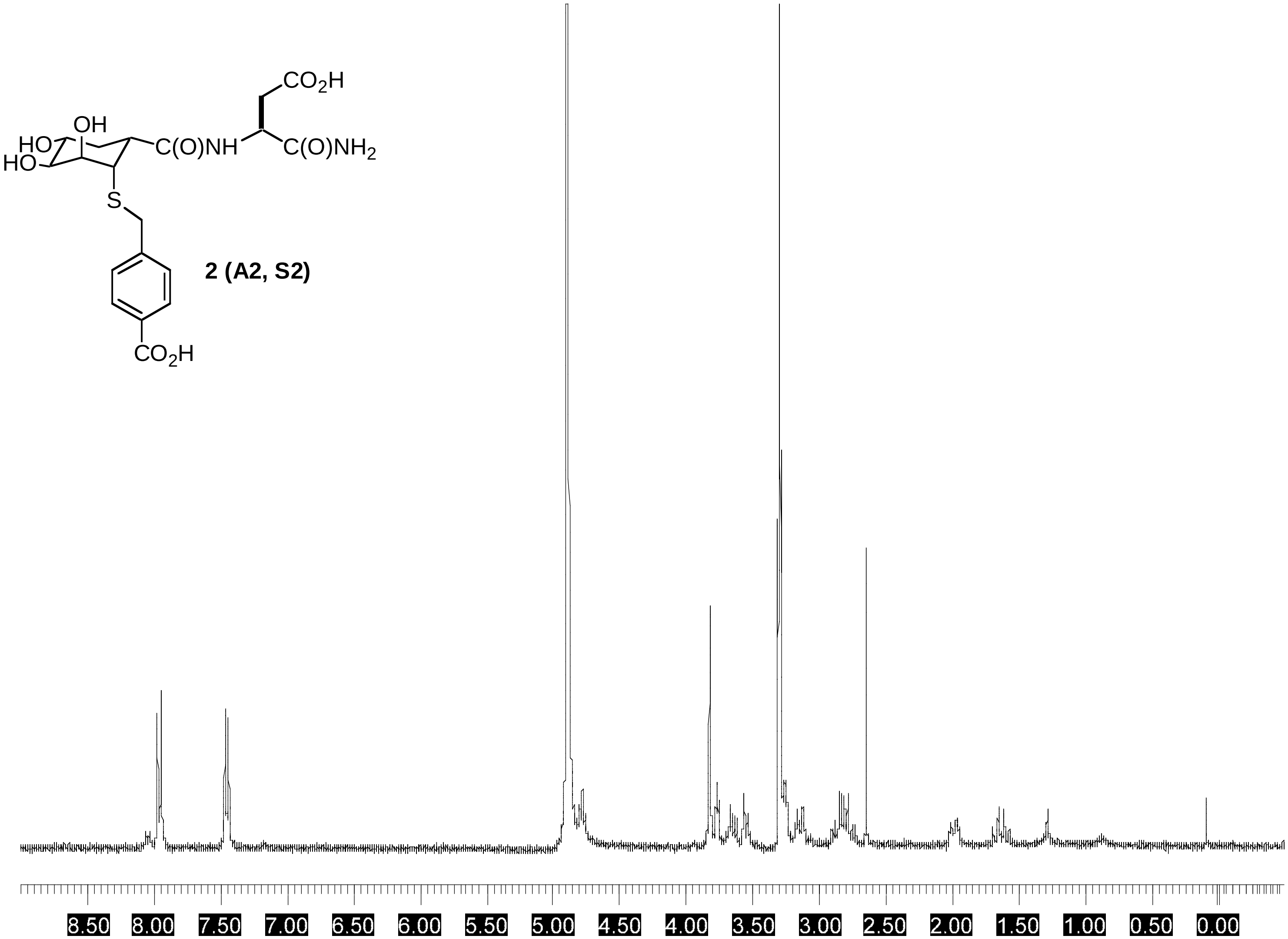
2 (A1, S2)


CO2H
OH
HO
HO
C(O)NH
C(O)NH2
S
CO2H
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

2 (A3, S3)

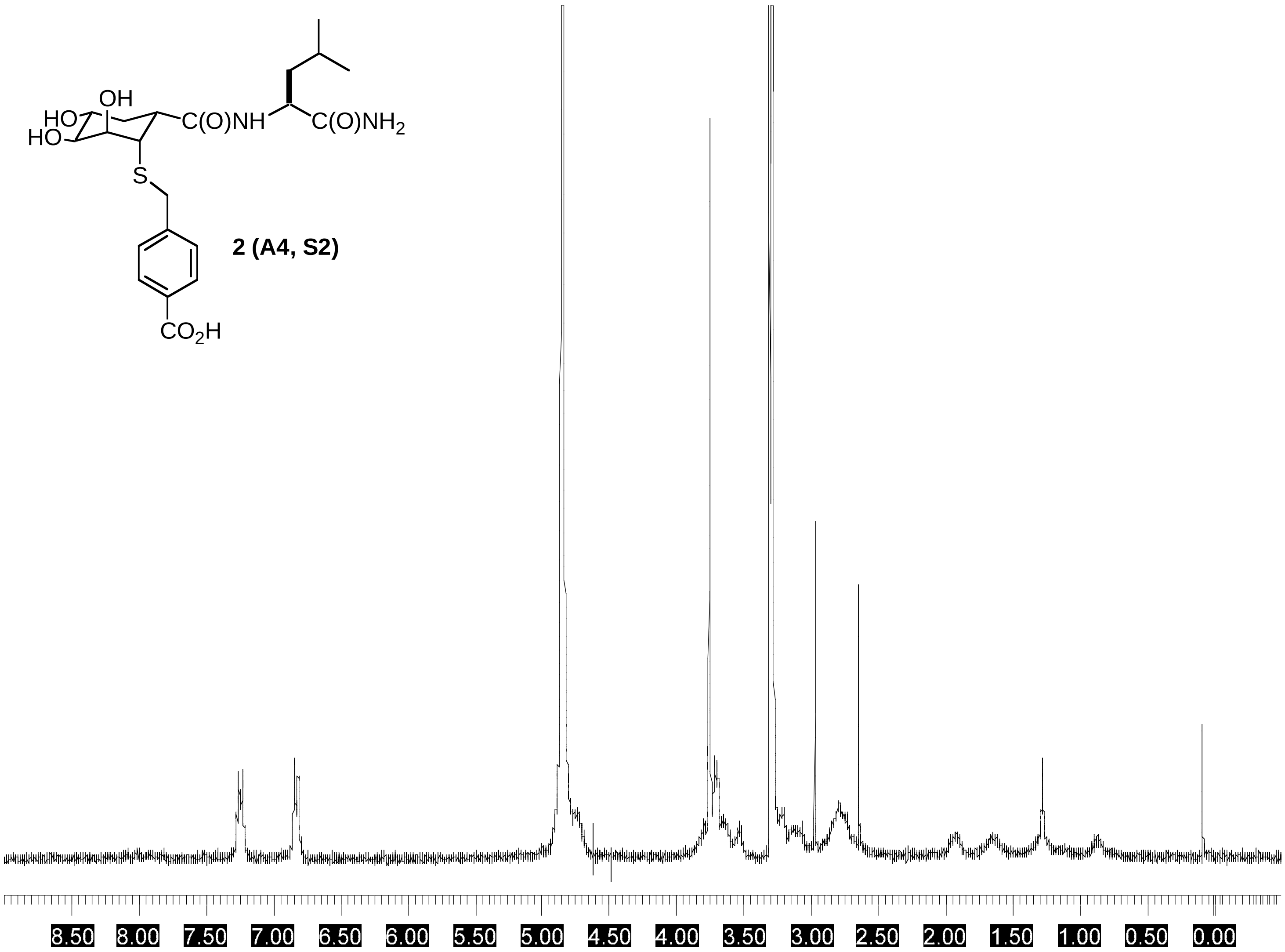

2 (A5, S1)

NH$_2$
OH
HO
HO
C(O)NH
C(O)NH$_2$
S
OMe
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

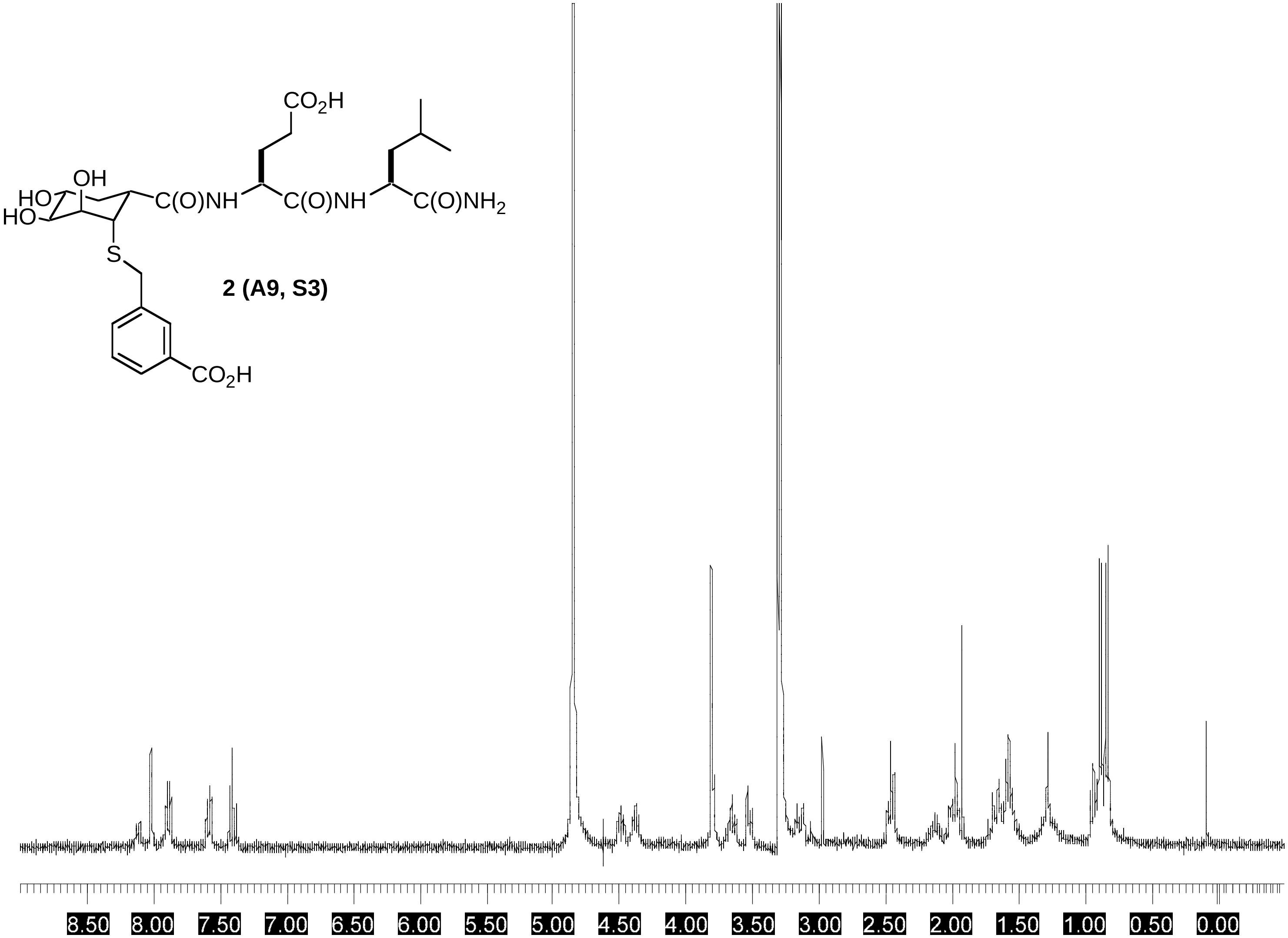


2 (A2, S2)

8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

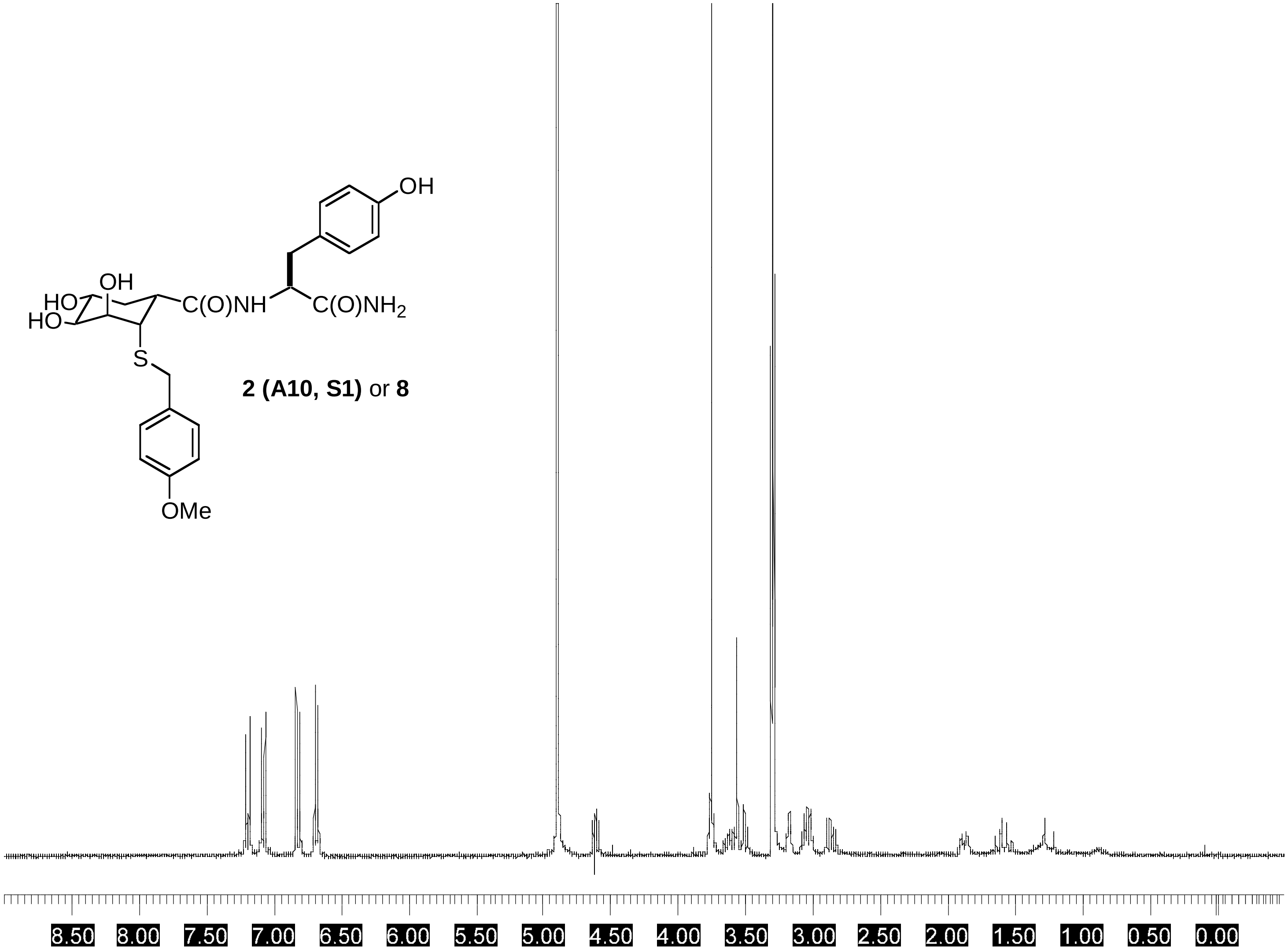

HO
HO
OH
C(O)NH
C(O)NH$_2$
S
CO$_2$H
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

2 (A4, S2)

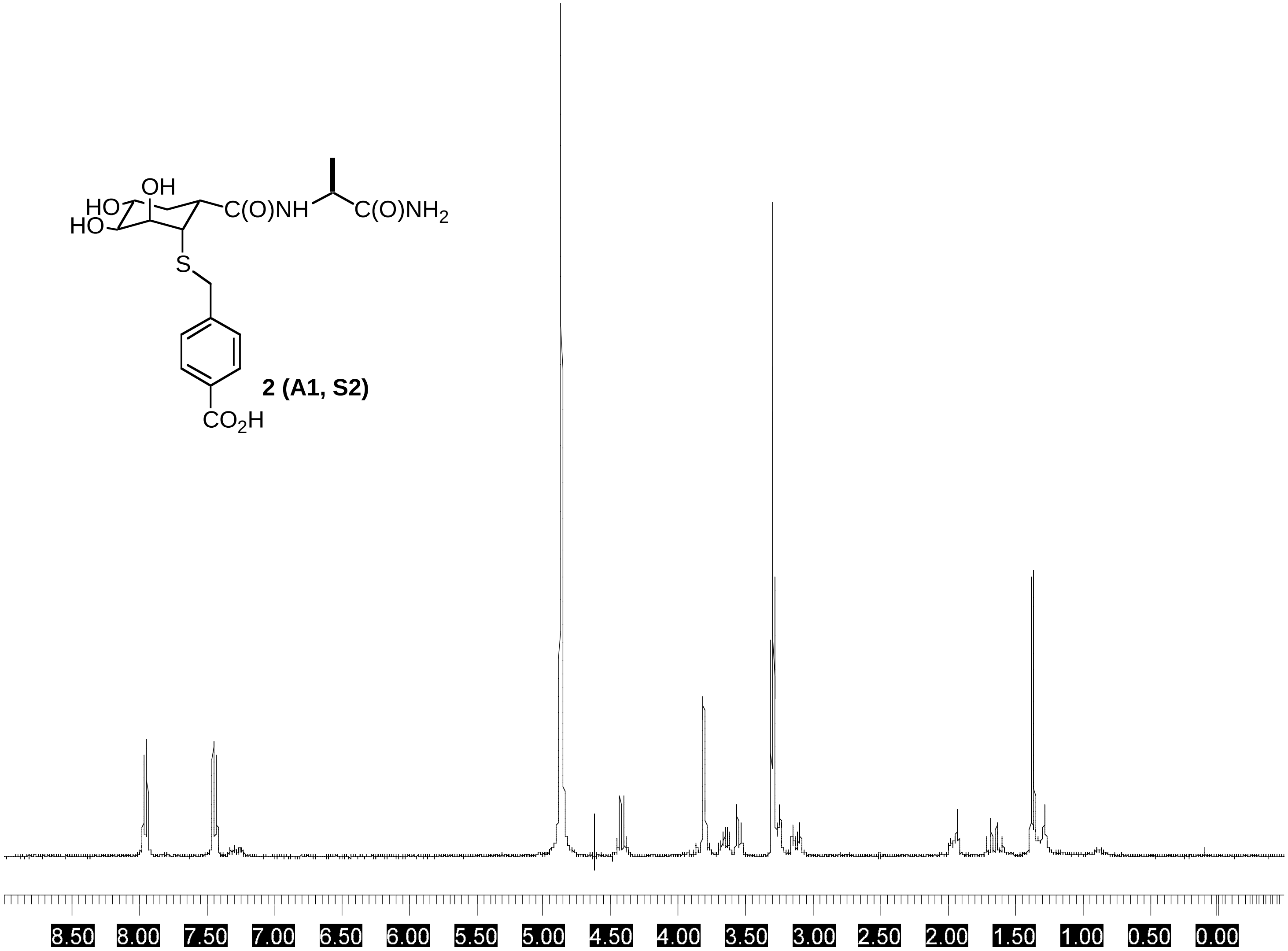

CO2H
OH
HO
HO
C(O)NH
C(O)NH
C(O)NH2
S
CO2H

2 (A9, S3)

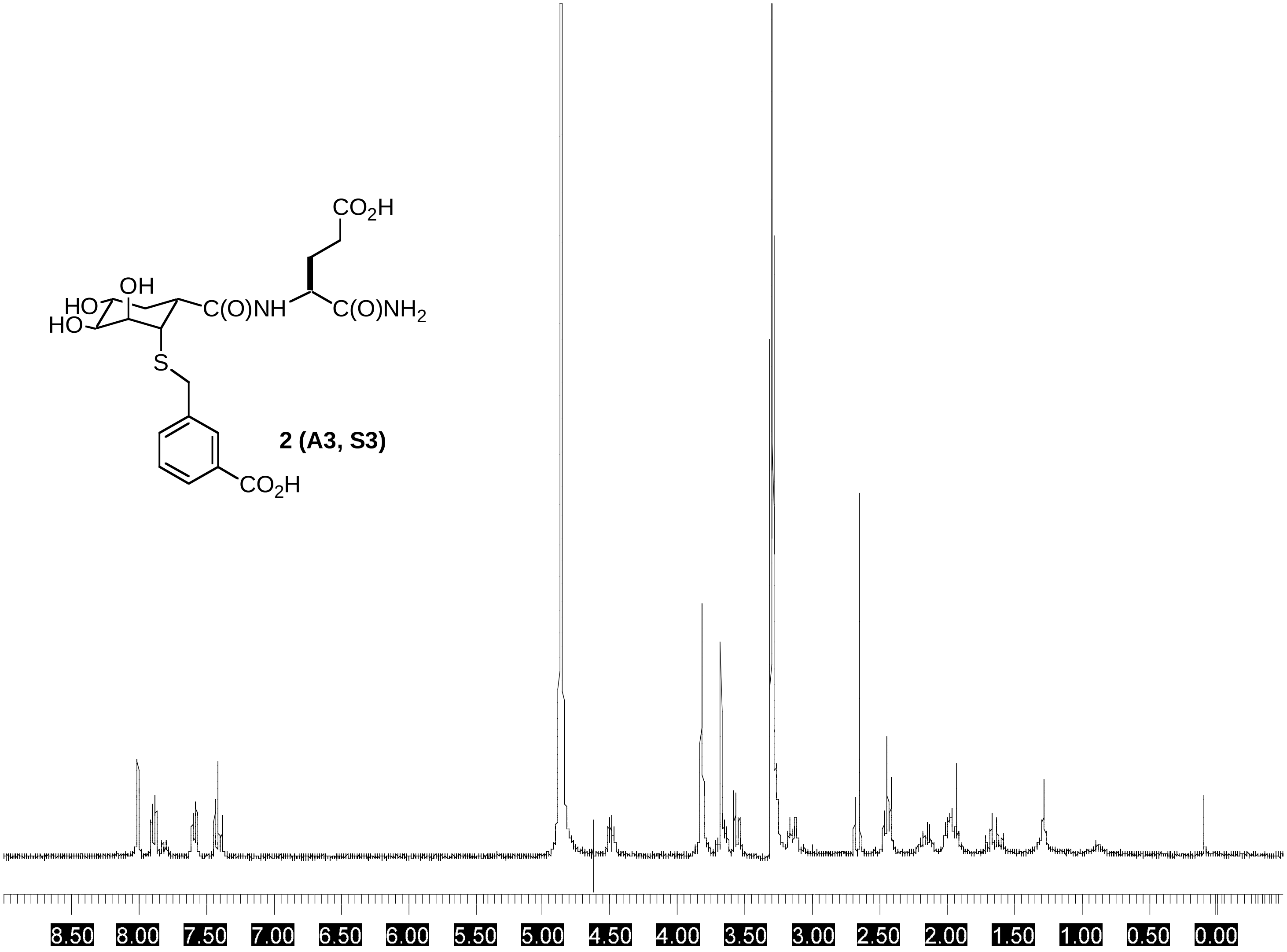
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00


OH
OH
HO
HO
C(O)NH
C(O)NH2
S
OMe
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

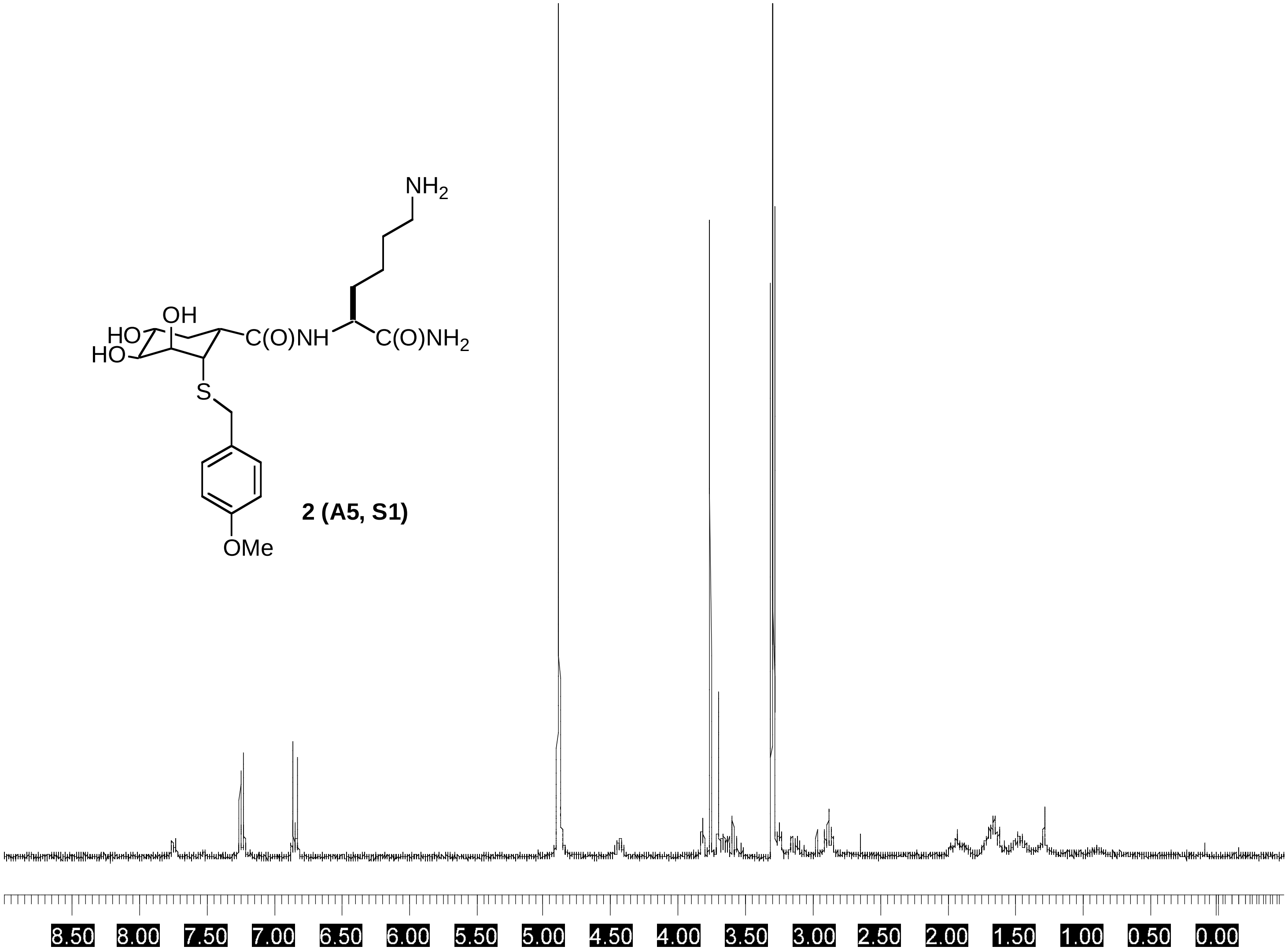
2 (A10, S1) or **8**


2 (A1, S2)

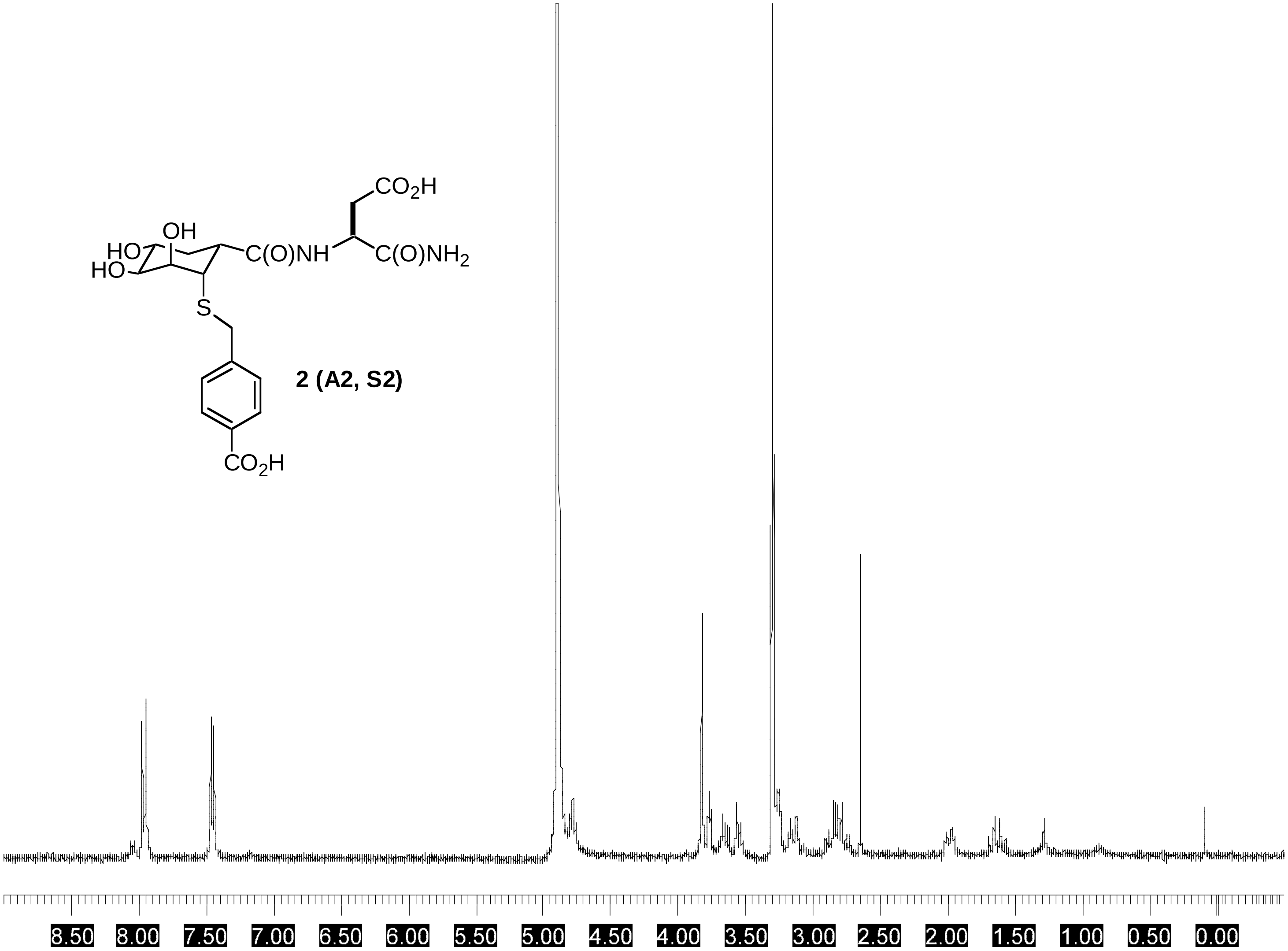
OH
HO
HO
C(O)NH
C(O)NH$_2$
S
CO$_2$H
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00


HO
HO
OH
C(O)NH
CO$_2$H
C(O)NH$_2$
S
CO$_2$H
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

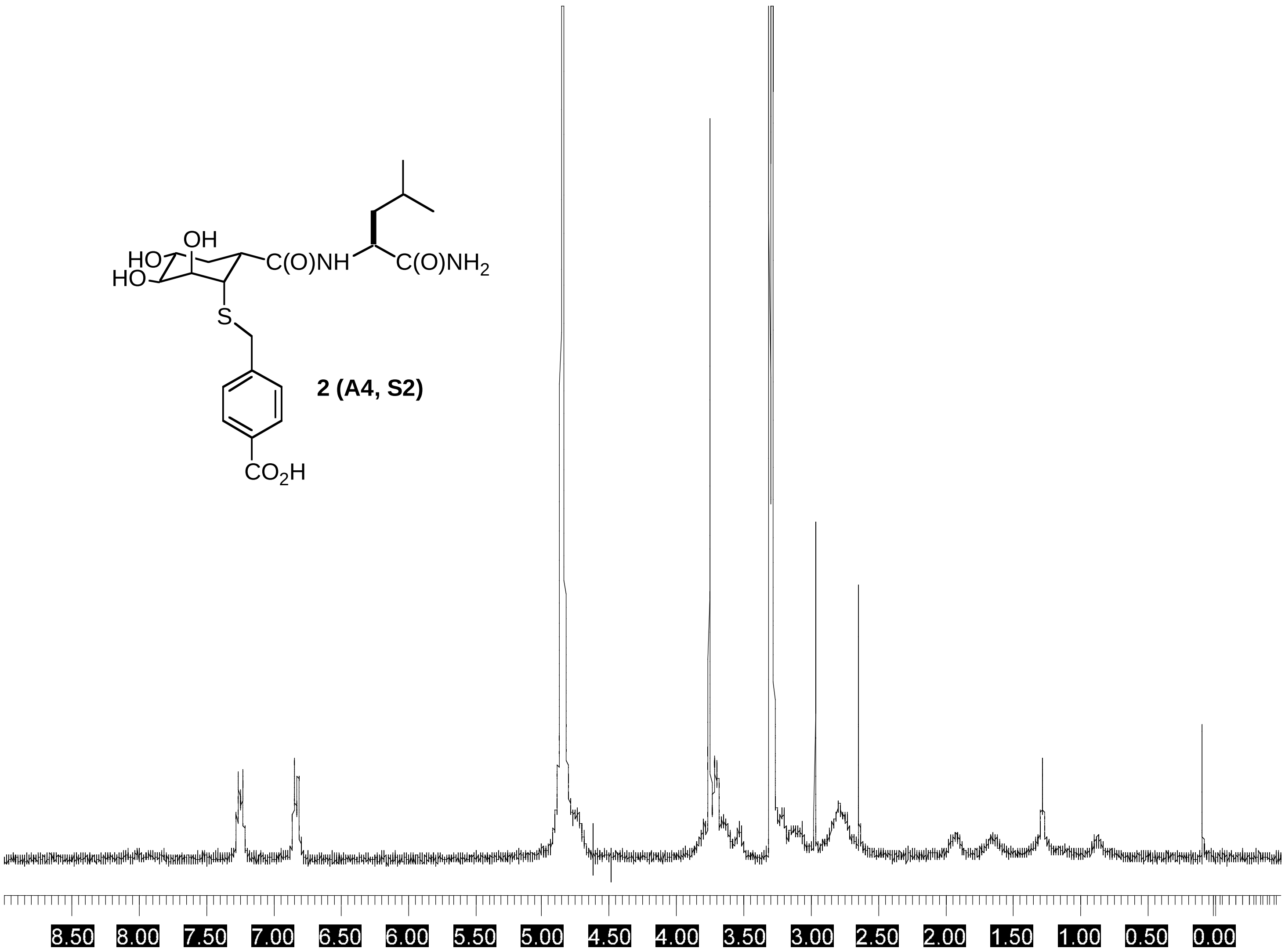
2 (A3, S3)


NH$_2$
OH
HO
HO
C(O)NH
C(O)NH$_2$
S
OMe
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

2 (A5, S1)

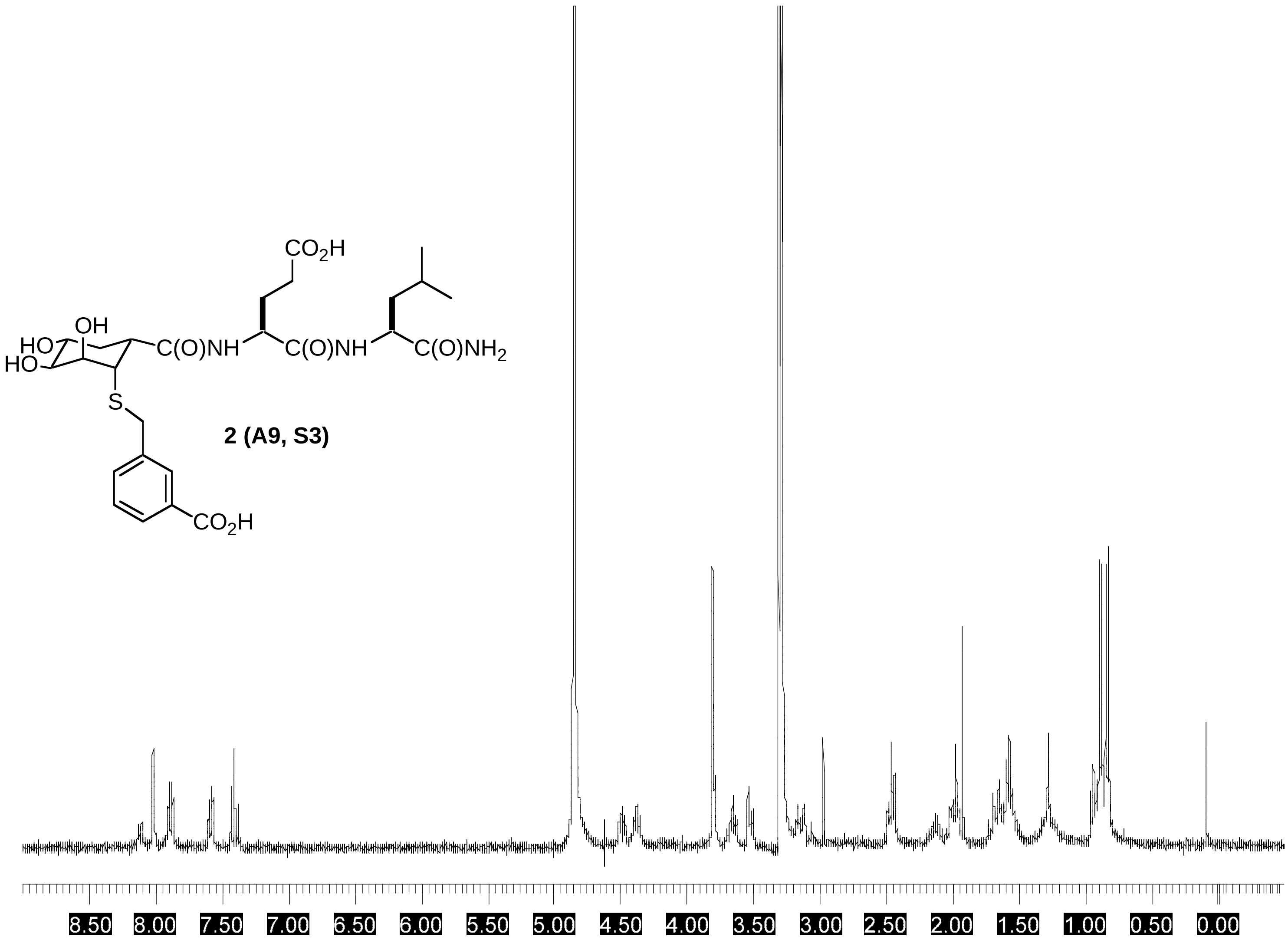

HO
HO
OH
C(O)NH
CO2H
C(O)NH2
S
CO2H
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

2 (A2, S2)

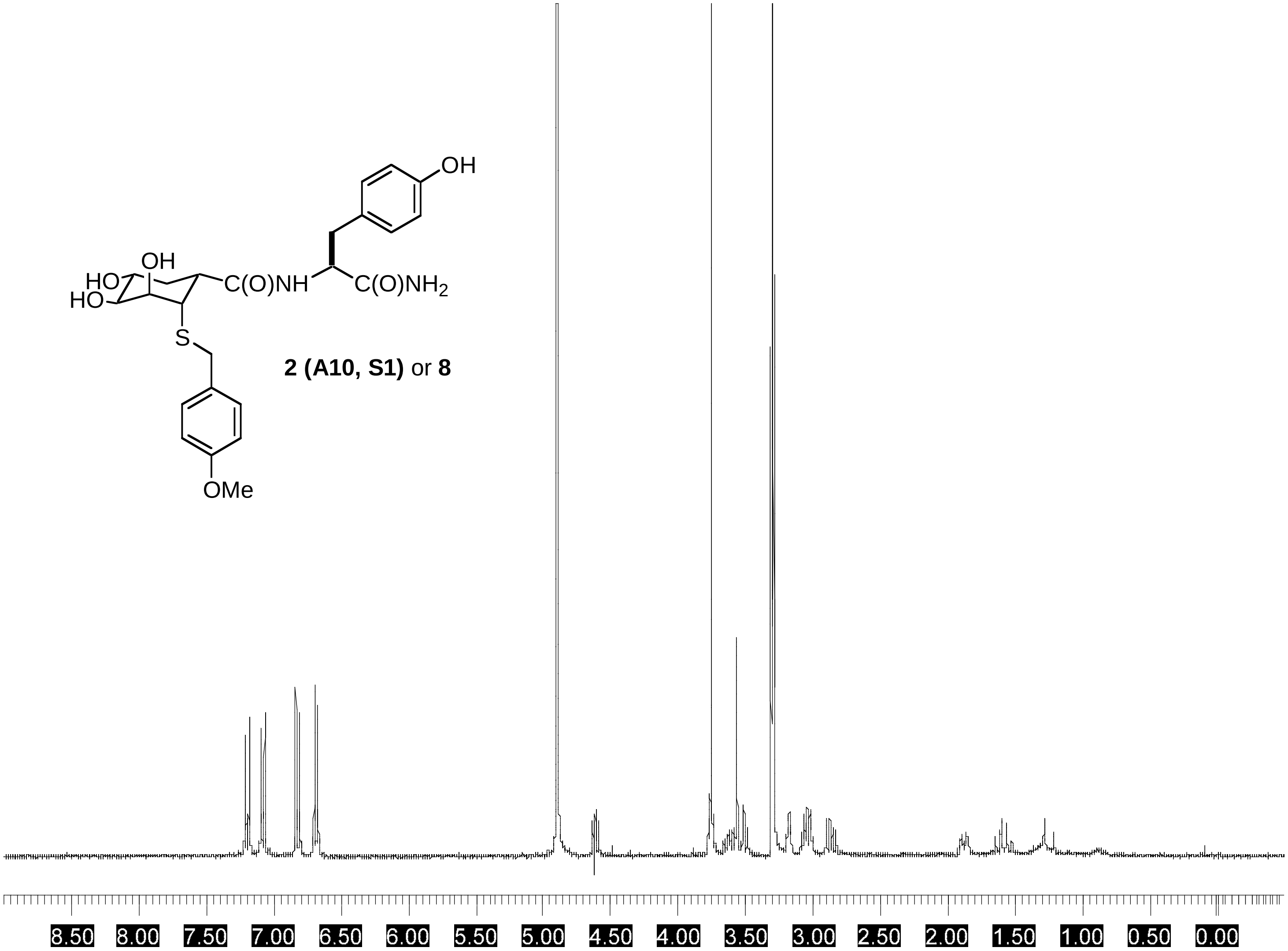


HO
HO
OH
C(O)NH
C(O)NH$_2$
S
CO$_2$H
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

2 (A4, S2)

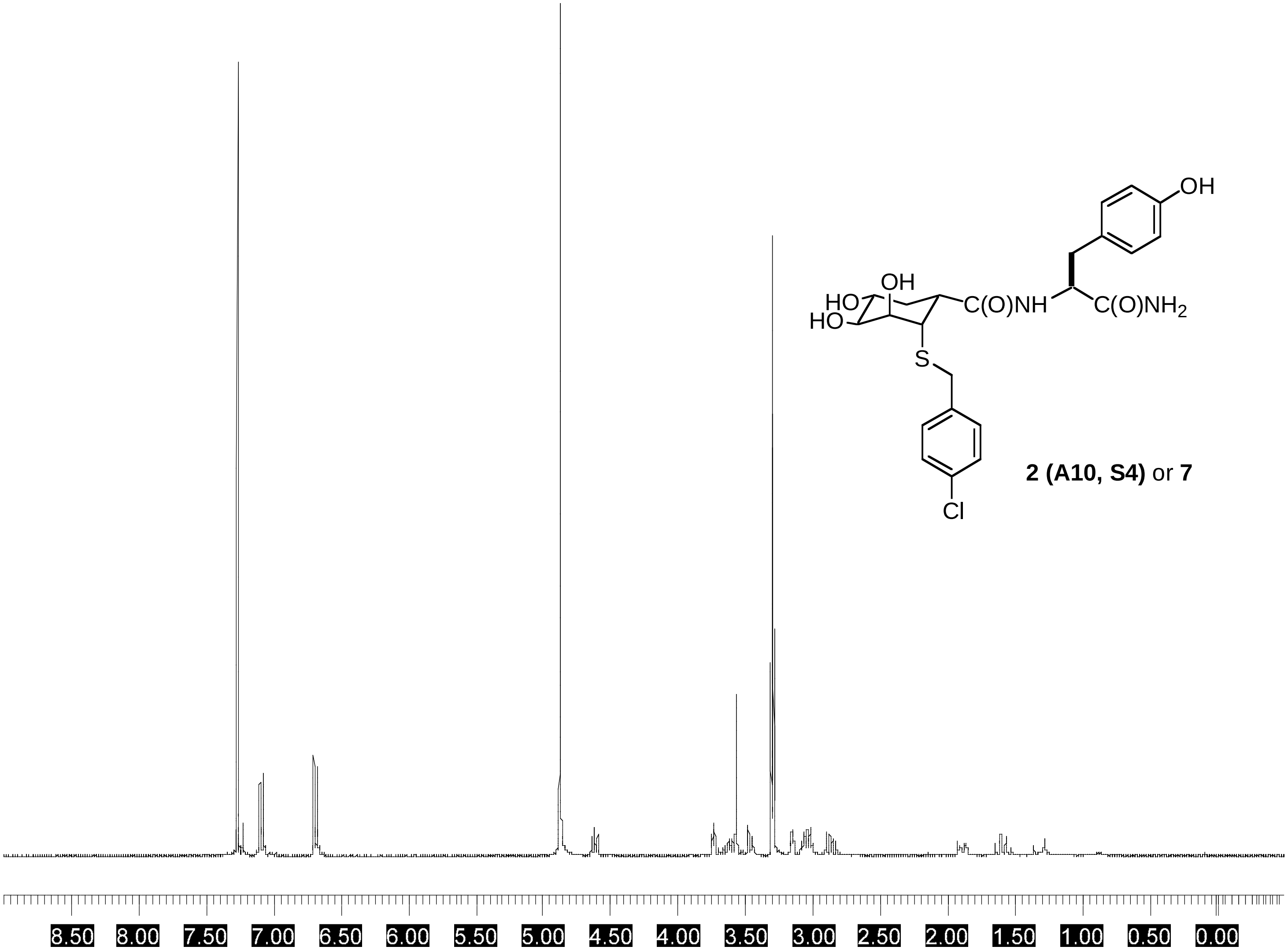

CO2H
OH
HO
HO
C(O)NH
C(O)NH
C(O)NH2
S
CO2H
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

2 (A9, S3)

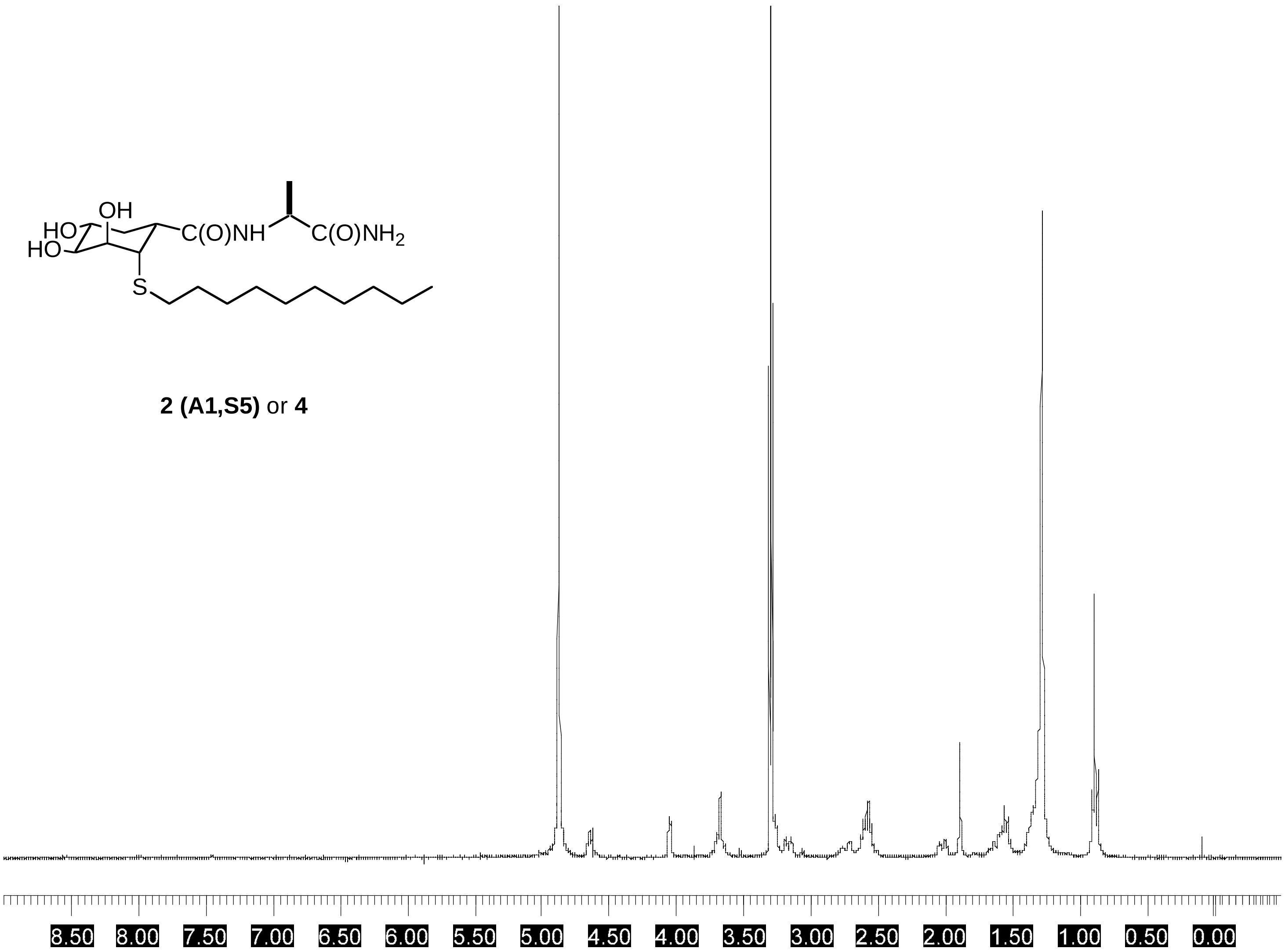

OH
OH
HO
HO
C(O)NH
C(O)NH2
S
OMe

2 (A10, S1) or **8**

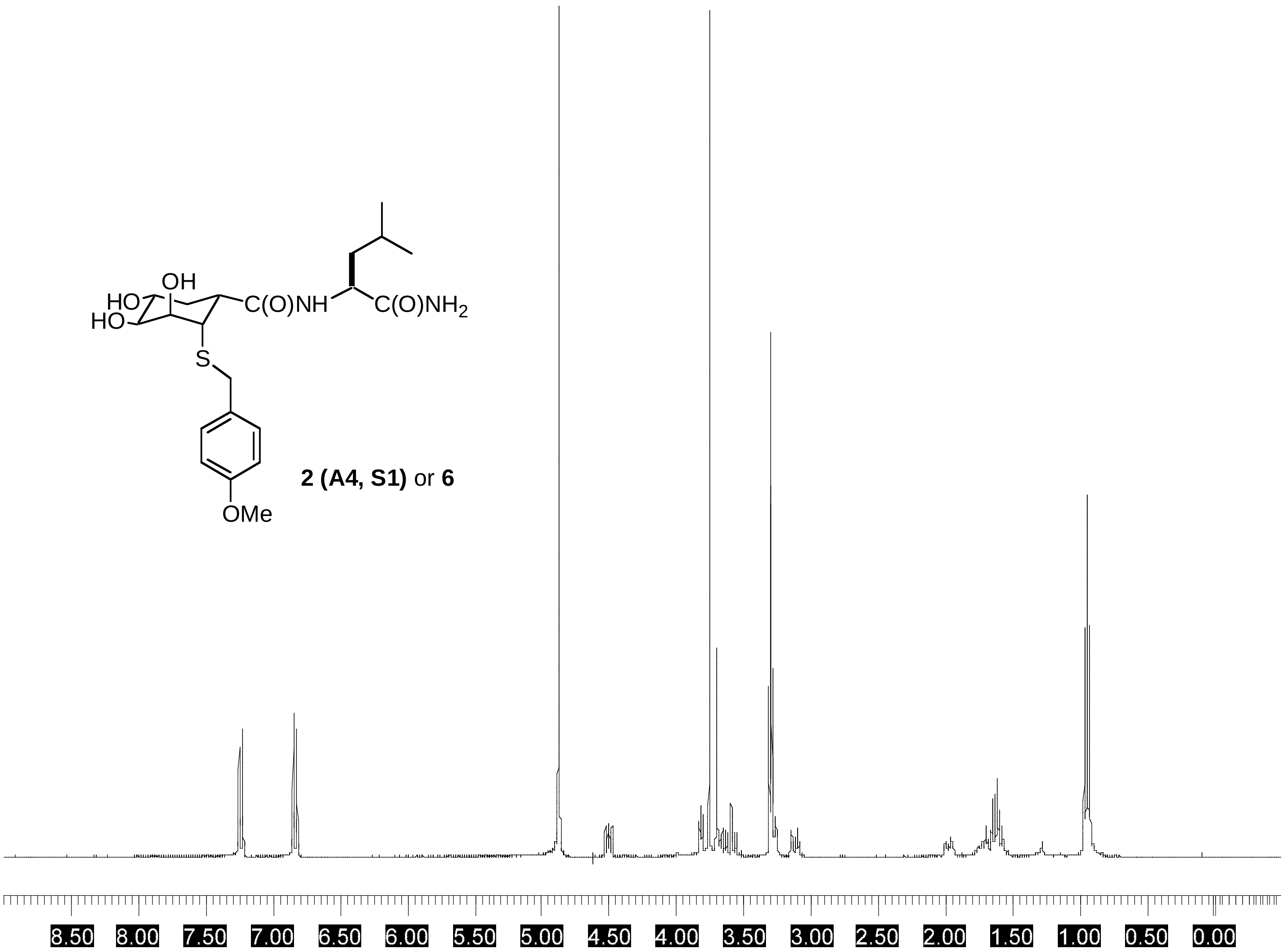
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00


OH
OH
HO
HO
C(O)NH
C(O)NH$_2$
S
Cl
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

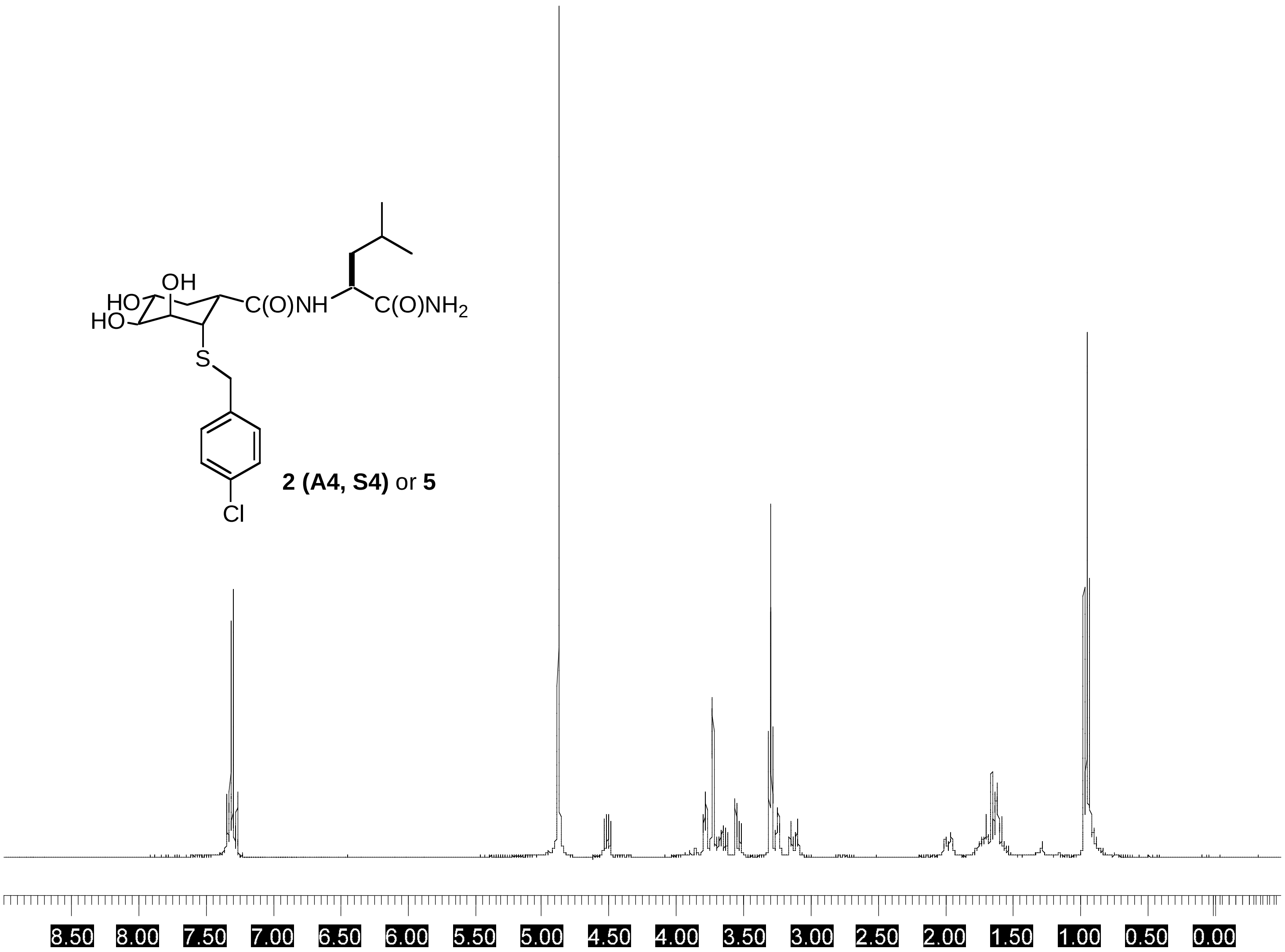
2 (A10, S4) or **7**


OH
HO
HO
C(O)NH
C(O)NH2
S
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

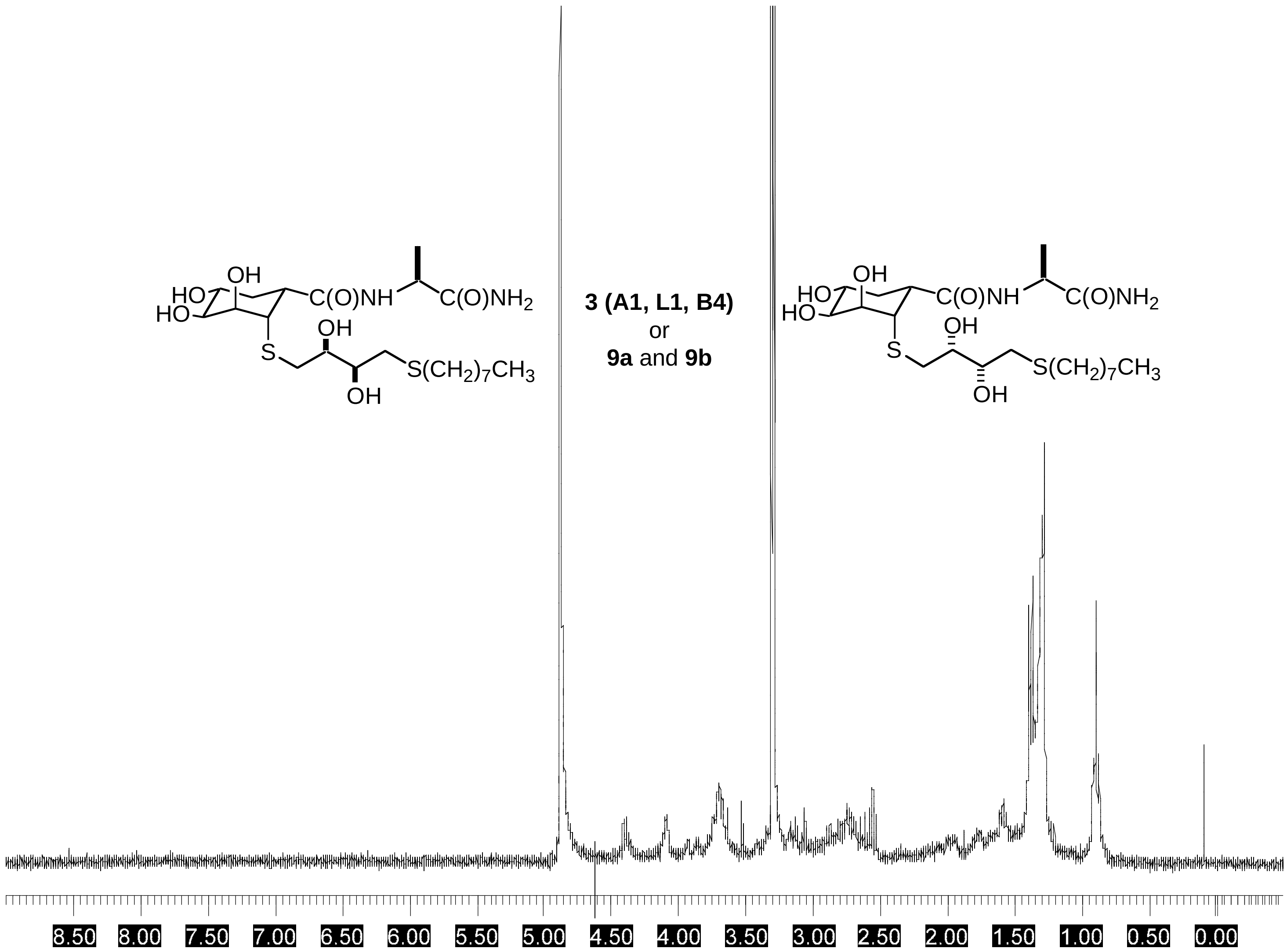
2 (A1,S5) or **4**


OH
HO
HO
C(O)NH
C(O)NH$_2$
S
OMe
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

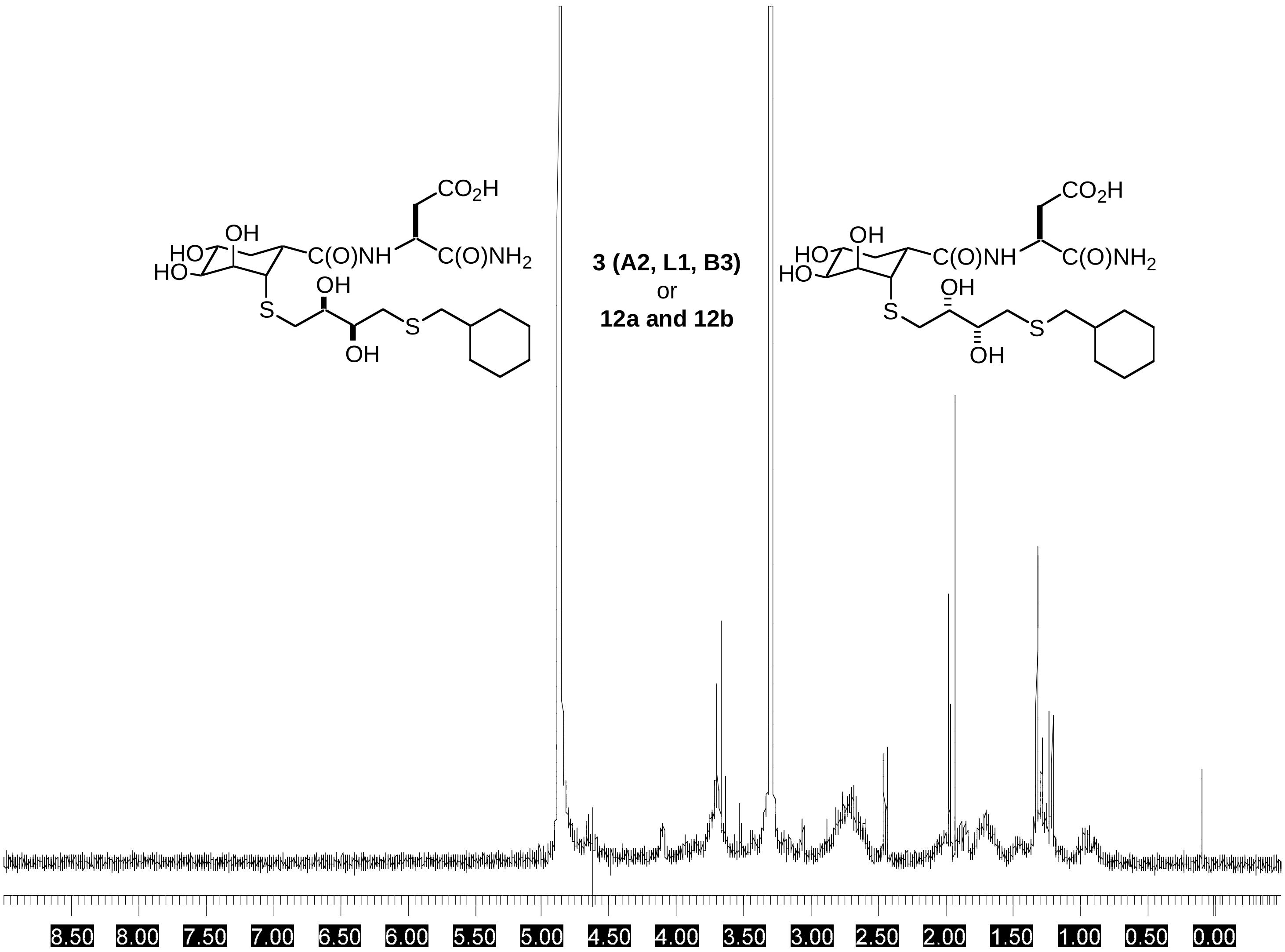
2 (A4, S1) or **6**


OH
HO
HO
C(O)NH
C(O)NH$_2$
S
Cl
8.50
8.00
7.50
7.00
6.50
6.00
5.50
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00

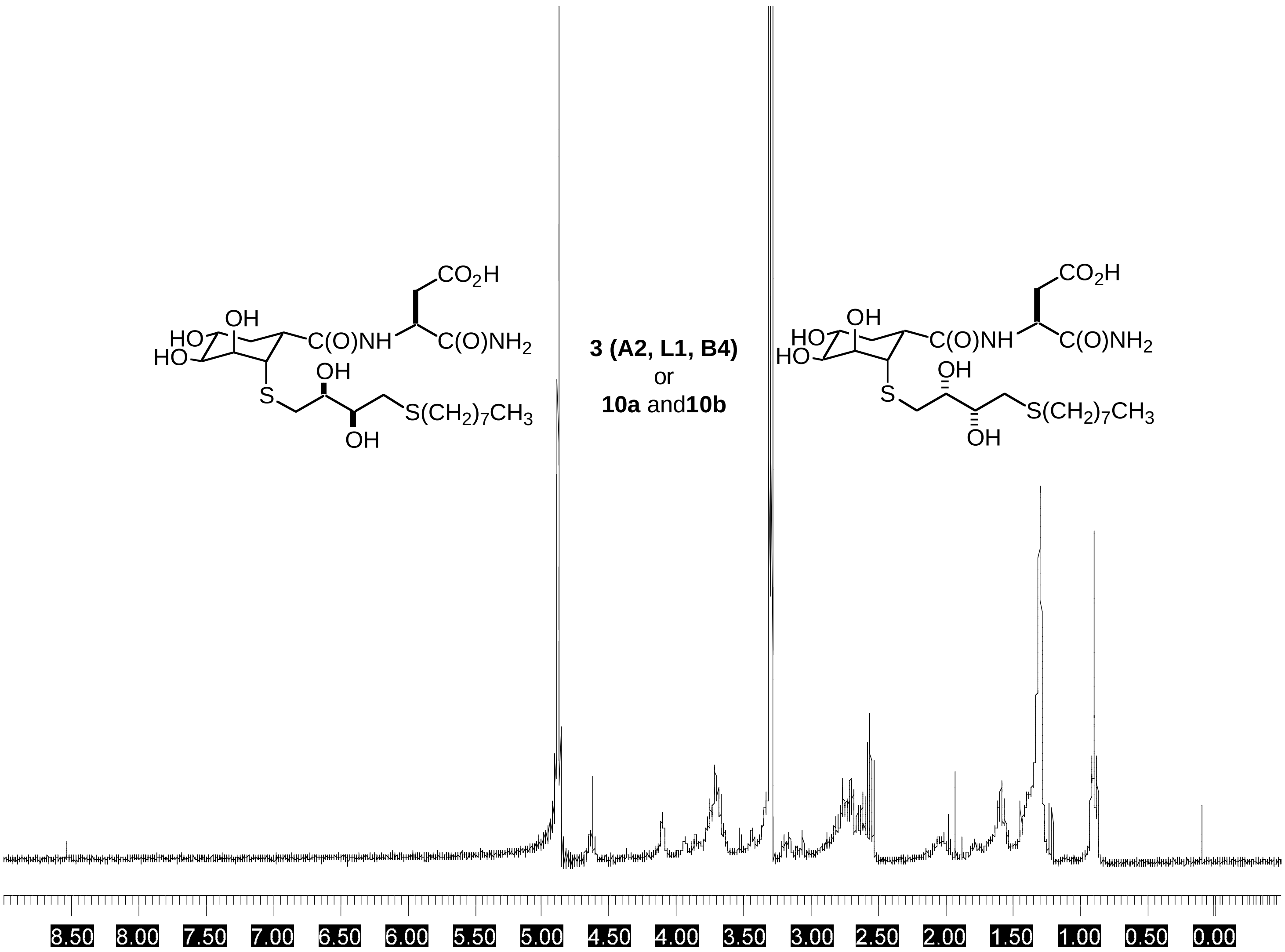
2 (A4, S4) or **5**



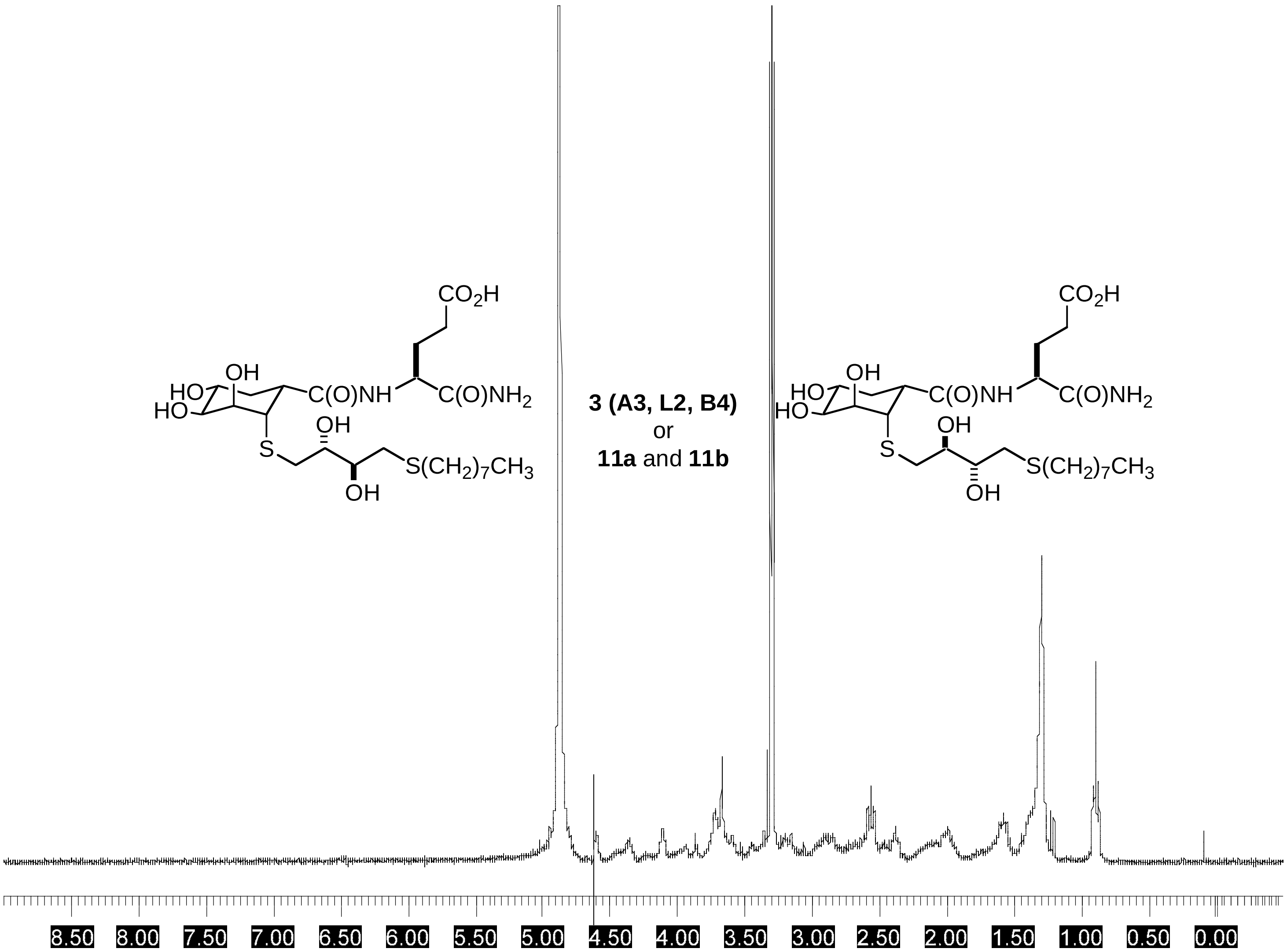
3 (A1, L1, B4)
or
9a and **9b**



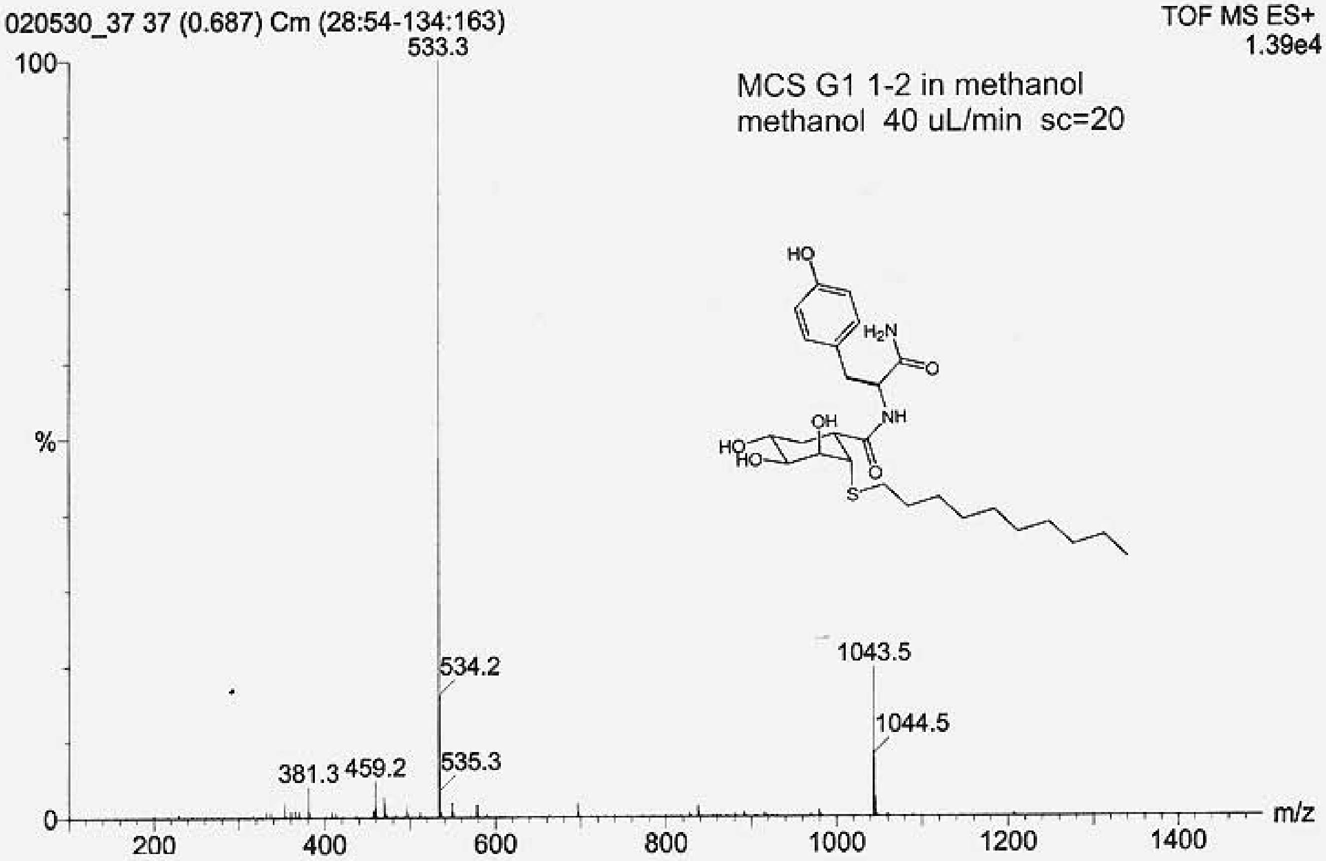
3 (A2, L1, B3)
or
12a and 12b

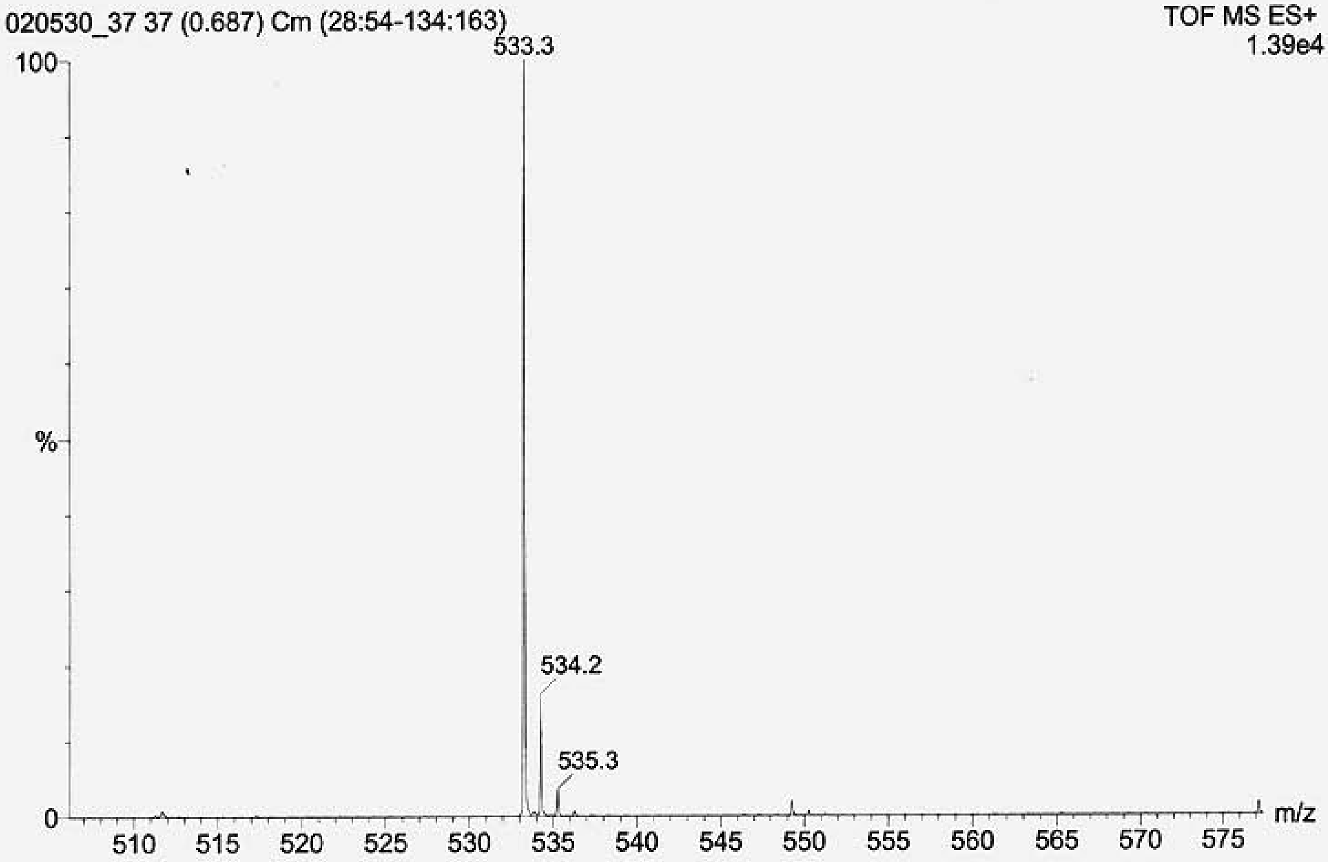


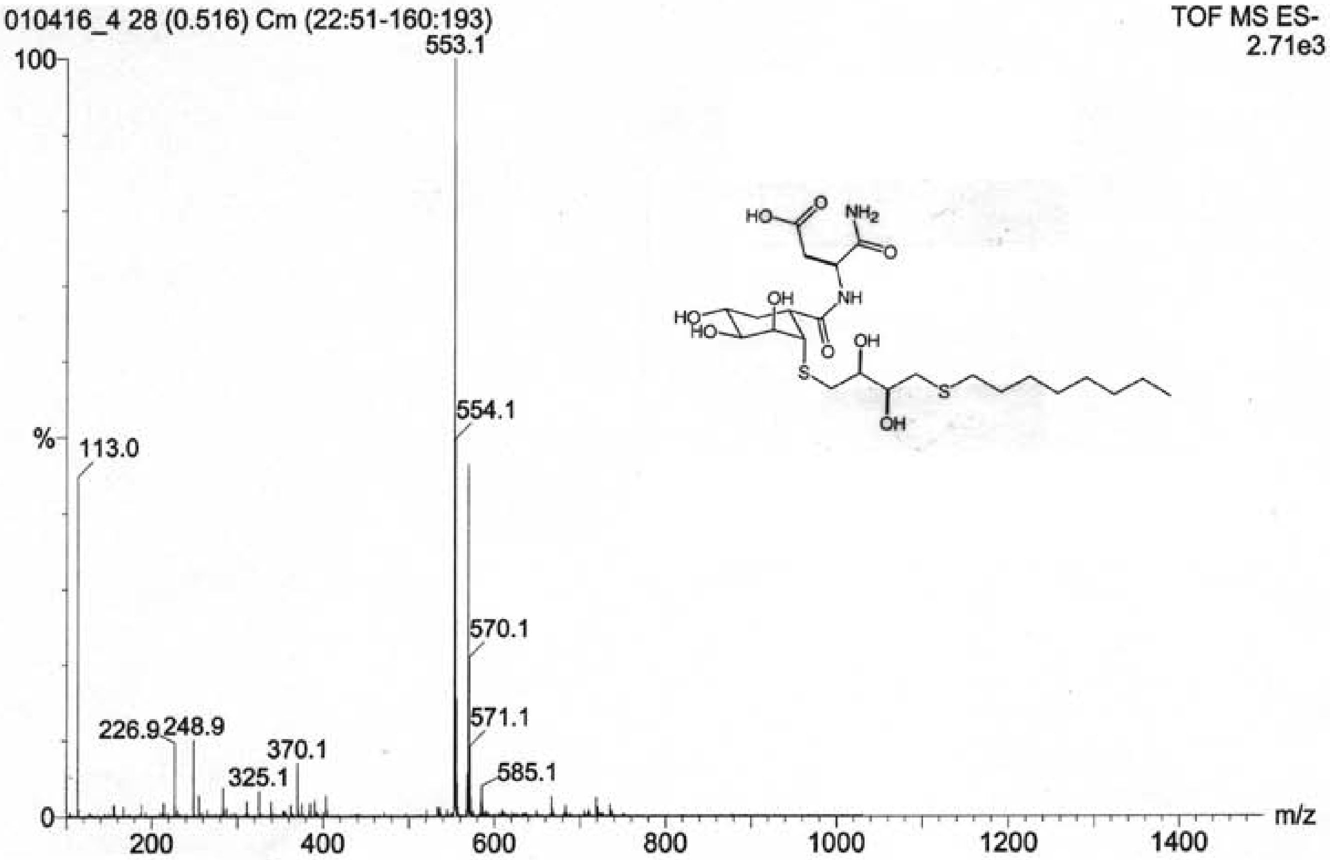
3 (A2, L1, B4)
or
10a and**10b**

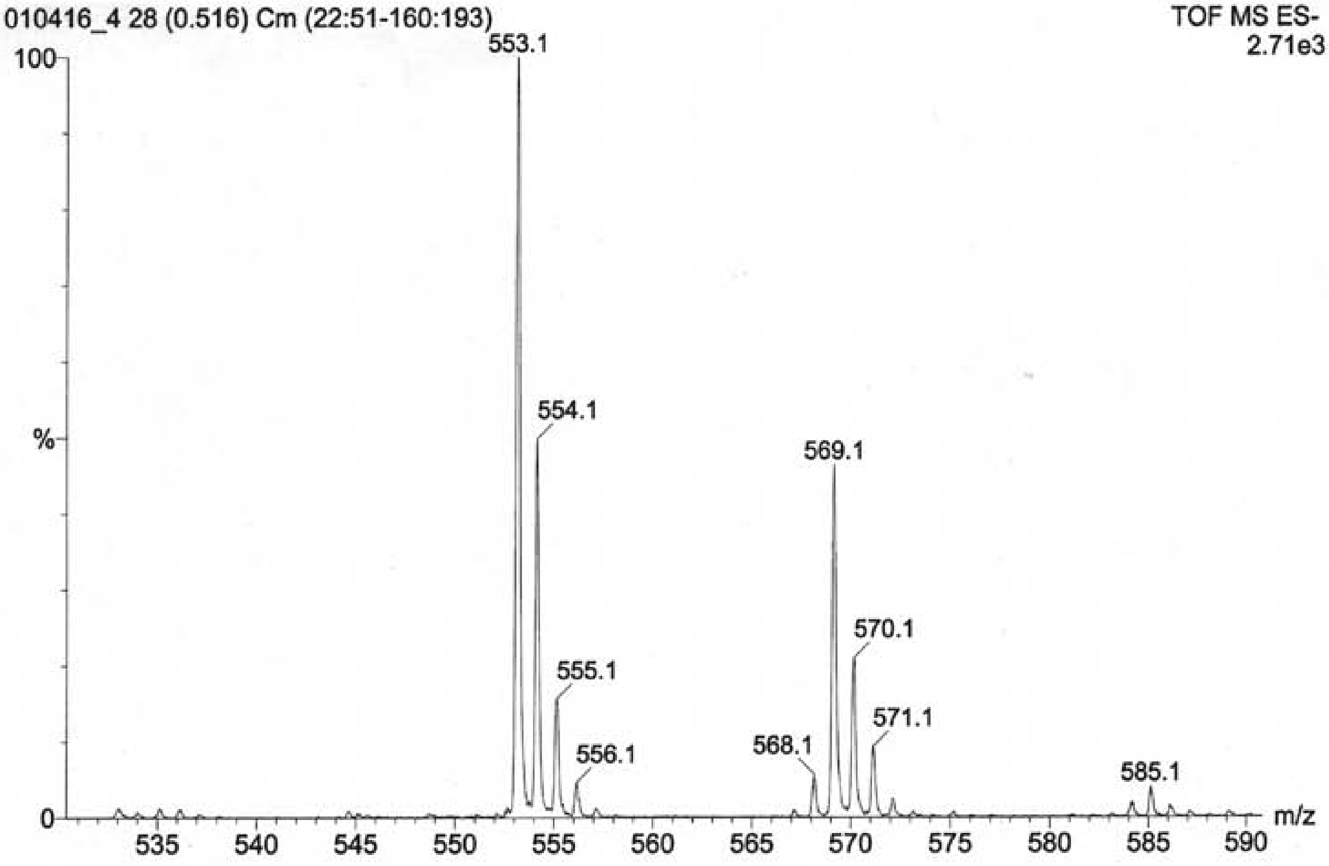


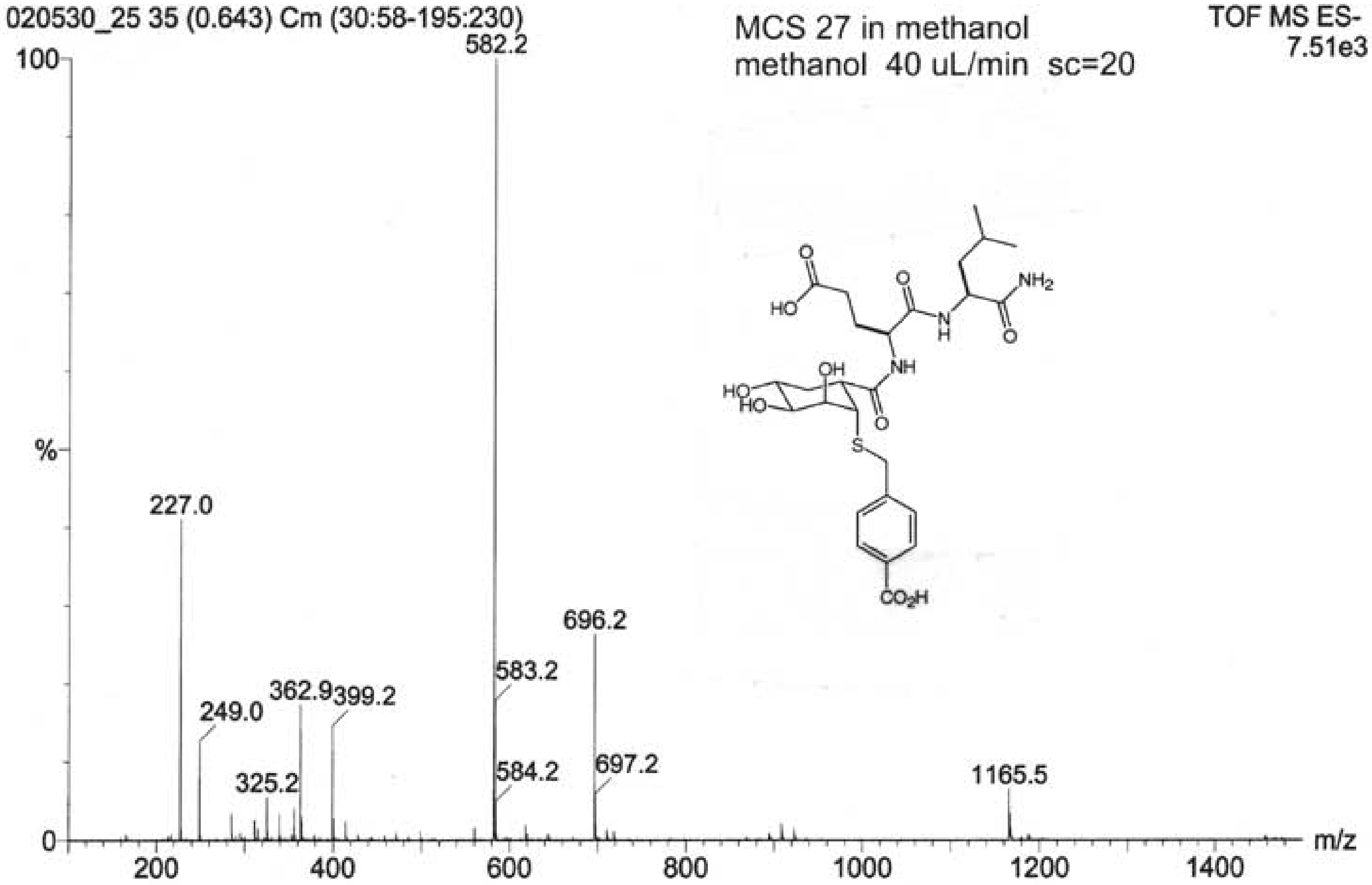
3 (A3, L2, B4)
or
11a and **11b**

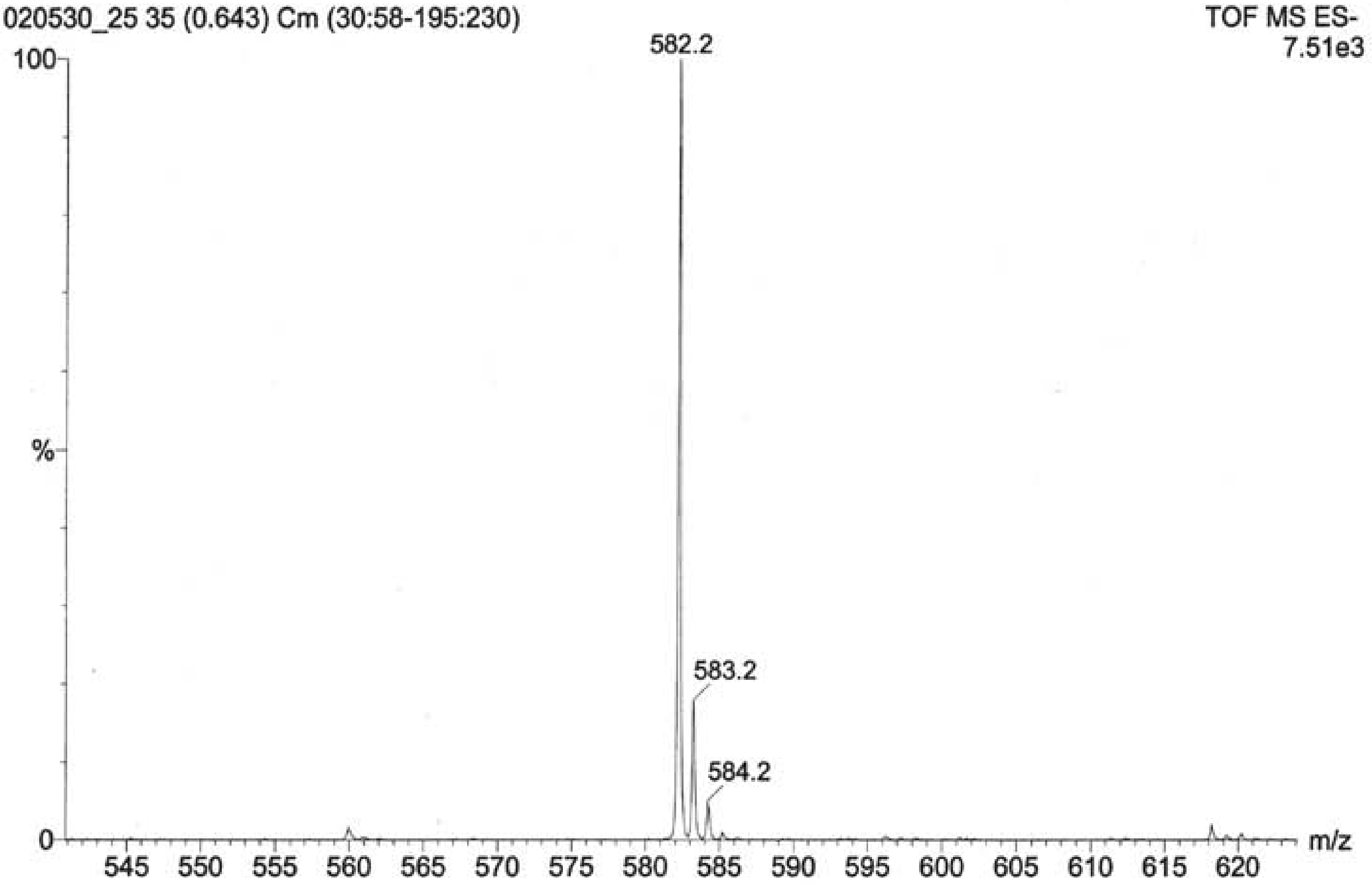

020530_37 37 (0.687) Cm (28:54-134:163)
TOF MS ES+
1.39e4
MCS G1 1-2 in methanol
methanol 40 uL/min sc=20
HO
H2N
O
NH
OH
HO
HO
O
S
100
%
0
533.3
534.2
535.3
381.3
459.2
1043.5
1044.5
200
400
600
800
1000
1200
1400
m/z


020530_37 37 (0.687) Cm (28:54-134:163)
TOF MS ES+
1.39e4
100
%
0
533.3
534.2
535.3
510
515
520
525
530
535
540
545
550
555
560
565
570
575
m/z


010416_4 28 (0.516) Cm (22:51-160:193)
TOF MS ES-
2.71e3
100
%
0
553.1
554.1
113.0
570.1
571.1
226.9
248.9
370.1
325.1
585.1
200
400
600
800
1000
1200
1400
m/z
HO
O
NH2
O
NH
OH
HO
HO
O
S
OH
S
OH


010416_4 28 (0.516) Cm (22:51-160:193)
TOF MS ES-
2.71e3
100
%
0
553.1
554.1
569.1
570.1
555.1
571.1
556.1
568.1
585.1
535
540
545
550
555
560
565
570
575
580
585
590
m/z


020530_25 35 (0.643) Cm (30:58-195:230)
MCS 27 in methanol
methanol 40 uL/min sc=20
TOF MS ES-
7.51e3
100
%
0
582.2
227.0
696.2
583.2
249.0
362.9
399.2
325.2
584.2
697.2
1165.5
200
400
600
800
1000
1200
1400
m/z
HO
O
O
N
H
NH₂
O
OH
NH
HO
HO
O
S
CO₂H


020530_25 35 (0.643) Cm (30:58-195:230)
TOF MS ES-
7.51e3
100
%
0
582.2
583.2
584.2
545
550
555
560
565
570
575
580
585
590
595
600
605
610
615
620
m/z