Supporting Info for

Racemization-free synthesis of *S*-alkylated cysteines *via* thiol-ene reaction

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Supporting Information

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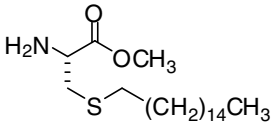
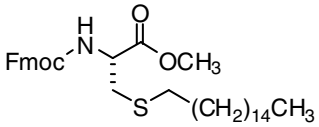
General considerations. NMR spectra were calibrated to the solvent signals of $CDCl_3$ (δ=7.26 and 77.00 ppm) or CD_3OD (δ=3.31 and 49.05 ppm). The following abbreviations are used to indicate signal multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), sept (septet), br (broad), ap (apparent). LCMS was performed using a gradient of 60% acetonitrile to 100% acetonitrile in 10 min. Chiral HPLC analysis was performed with a Chiralcel OD-R column.

General procedure for the alkylation of cysteine by means of the thiol-ene reaction.
The solvent was degassed under an Argon stream in a sonicator bath for 15 min. prior to use. To a solution of cysteine in solvent (0.26 M), 3 equivalents of alkene and 0.5 equivalents of AIBN were added and the mixture was brought to reflux at 90 ºC until TLC analysis of the crude reaction mixture indicated that the cysteine had been completely consumed. The solution was allowed to cool to room temperature and the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography to provide the desired product (0.1 eq of AIBN has been also used, giving similar reaction yields).

Experimental procedures and characterization of products



(L)-2-Amino-3-hexadecylsulfanyl-propionic acid methyl ester (2). Radical alkylation was performed with L-cysteine methyl ester hydrochloride (0.58 g; 3.37 mmol) and hexadecene in dichloroethane (DCE) (12 mL). The reaction was complete after refluxing at 90 ºC for 3 h, then the solution was cooled to r.t. and the solvent was removed under reduced pressure. Compound **2** (1.1 g; 91%) was obtained after purification of the residue by flash column chromatography using a CH_2Cl_2:MeOH mixture (9:1) as a eluent. Analytical data: ^{1}H-NMR (400 MHz, CD_3OD): 0.86 (t, 3H, *J*= 6.8 Hz), 1.2-1.4 (m, 22H), 1.39 (t, 2H, *J*= 6.8 Hz), 1,60 (q, 2H, *J*= 7.2 Hz), 2.56 (t, 2H, *J*= 7.2 Hz), 3.05 (dd, 1H *J*= 7.2, 14.4 Hz), 3.10 (dd, 1H, *J*= 4.4, 14.4 Hz), 3.84 (s, 3H), 4.19 (dd, 1H, *J*= 4.4, 6.8 Hz), 4.73 (bs, 2H); ^{13}C-NMR (100 MHz, CD_3OD): 14.1, 22.6, 28.7, 29.2, 29.31, 29.35, 29.50, 29.55, 29.60, 29.63, 29.65, 29.68, 29.7, 31.9, 32.7, 33.4, 53.0, 170.0; LC-MS (ESI): calcd for $C_{20}H_{42}O_2N_1{}^{32}S_1$: 360.29308 $[M+H]^+$, found 360.15 $[M+H]^+$, R_t 1.35 min; ES MS: *m/z*: calcd for $C_{20}H_{42}O_2N_1{}^{32}S_1$: 360.29308 $[M+H]^+$; found: 360.29321 $[M+H]^+$.

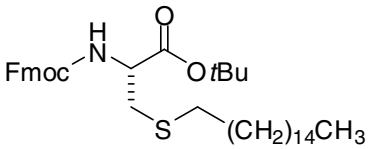


(L)-(9H-Fluoren-9-ylmethoxycarbonylamino)-3-hexadecylsulfanyl-propionic acid methyl ester (3)

- **Radical alkylation method using AIBN as initiator.** Radical alkylation was performed with L-cysteine methyl ester hydrochloride (0.58 g; 3.37 mmol) and hexadecene in DCE (12 mL). The reaction was complete after refluxing at 90 ºC for 3 h. Then the solution was cooled to r.t. and the solvent was removed under reduced pressure. The residue was dissolved in dioxane:H_2O 1:1 (100 mL) and Na_2CO_3 (0.91 g; 8.73 mmol) and Fmoc-OSu (1.17 g; 3.48 mmol) were added at 0 ºC. The mixture was stirred at this temperature for 10 min and 3 h at r.t. after which it was poured into water (50 mL) and washed 3 times with ethyl acetate. The combined organic phases were dried with Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography using a mixture

cyclohexane:ethyl acetate (9:1) and giving compound **3** in 71% overall yield (1.24 g) after two steps.

- **Using UV light as a initiator.** L-cysteine methyl ester hydrochloride (0.5 g; 2.91 mmol) and hexadecene (2.50 mL; 8.73 mmol) in DMF (3 mL, 0.97 M) were shaken in a light reactor (UV light, 254 nm) at 40 ºC for 24h. The solvent was removed under reduced pressure and Fmoc protection was performed in the mentioned conditions. After column chromatography compound **3** was isolated (0.25 g; 15%). Analytical data: ^{1}H-NMR (400 MHz, $CDCl_3$): 0.88 (t, 3H, *J*= 6.8 Hz), 1.2-1.4 (m, 24H), 1.57 (q, 2H, *J*= 7.2 Hz), 2.52 (t, 2H, *J*= 7.6 Hz), 2.99 (d, *J*= 4.4 Hz), 3.78 (t, 3H), 4.24 (t, 2H, *J*= 7.2 Hz), 4.39 (d, 1H, *J*= 7.2 Hz), 4.61 (dd, 1H, *J*= 5.2, 12.8 Hz), 5.62 (d, 1H, *J*= 8 Hz), 7.32 (t, 2H, *J*= 7.2 Hz), 7.40 (t, 2H, *J*= 7.2 Hz), 7.60 (d, 2H, *J*=6.4 Hz), 7.76 (d, 2H, *J*= 7.2 Hz). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.1, 22.6, 28.7, 29.2, 29.3, 29.51, 29.55, 29.59, 29.64, 19.66, 29.68, 31.9, 32.8, 34.4, 47.1, 52.6, 53.6, 67.2, 119.9, 125.1, 127.0, 127.7, 141.2, 143.7, 156.6, 171.3; $[\alpha]_D^{20}$ +6.71 (*c* 0.65, CH_2Cl_2); LC-MS (ESI): calcd for $C_{35}H_{52}O_4N_1{}^{32}S_1$: 582.36116 $[M+H]^+$, found 582.24 $[M+H]^+$, R_t 10.77 min; ES MS: *m/z*: calcd for $C_{35}H_{52}O_4N_1{}^{32}S_1$: 582.36116 $[M+H]^+$; found: 582.36083 $[M+H]^+$.

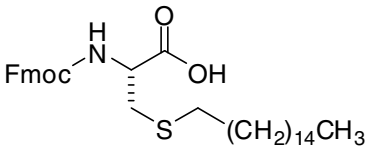


(L)-9H-Fluoren-9-ylmethoxycarbonylamino)-3-hexadecylsulfanyl-propionic acid *tert*-butyl ester (5)

- **From Cystine-O*t*Bu.** NEt_3 (0,42 mL; 3 mmol) was slowly added to a solution of cystine-O*t*Bu hydrochloride (0.63 g, 1.5 mmol) and DTT (0.92 g, 6 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred overnight at r.t. and subsequently poured into H_2O (15 mL). After washing two times with H_2O (15 mL), the organic phase was dried with Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The residue was solved in 10 mL DCE and the radical alkylation was performed under the general described conditions. After removing the solvent under reduced pressure the residue was dissolved in a 1:1 dioxane:H_2O mixture (100 mL) and Na_2CO_3 (0.95 g; 9 mmol). Subsequently, Fmoc-OSu (1.21 g; 3.6 mmol) was added and the mixture was stirred at r.t. for 3h. After this time, ethyl acetate (50 mL) was added and the combined organic phase was washed with H_2O (50 mL). The residue was purified by flash

chromatography using a mixture of cyclohexane:ethyl acetate (9:1) as eluent to obtain **5** (1.05 g; 57%).

- **From Fmoc-Cystine-O*t*Bu.** Fmoc-cystine-O*t*Bu was obtained by Fmoc protection of cystine-O*t*Bu following conditions reported in the literature.[1] After reduction of the disulfide bond of Fmoc-cystine-O*t*Bu (0.5 g; 0.62 mmol) under the conditions reported above, radical alkylation was performed under the general conditions described using DCE as solvent. After purification by column chromatography (cyclohexane:ethyl acetate (9:1)) compound **5** was isolated pure (0.3 g; 42%). Analytical data: ^{1}H-NMR (400 MHz, $CDCl_3$): 0.90 (t, 3H, *J*= 6.8 Hz), 1.4-1.2 (m, 24H), 1.44 (s, 4.5 H), 1.51 (s, 4.5 H), 1.58 (t, 2H, *J*= 7.2 Hz), 2.56 (t, 2H, *J*= 7.6 Hz), 2.98 (dd, *J*= 5.6, 13.6 Hz), 3.03 (dd, *J*= 5.2, 12.4 Hz), 4.24 (t, 2H, *J*= 7.2 Hz), 4.53 (q, 1H, *J*= 4.8 Hz), 5.70 (d, 1H, *J*= 7.6 Hz), 7.30 (dt, 2H, *J*= 1.2, 7.6 Hz), 7.40 (t, 2H, *J*= 7.2 Hz), 7.61 (d, 2H, *J*= 7.2 Hz), 7.75 (d, 2H, *J*= 7,6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): 14.0, 22.6, 26.8, 27.9, 28.7, 29.1, 29.3, 29.4, 29.5, 20.60, 29.61, 29.63, 31.8, 33.0, 34.6, 47.0, 54.2, 67.1, 82.6, 119.8, 125.0, 126.9, 127.6, 141.2, 143.7, 143.8, 155.6, 169.7; $[\alpha]_D^{20}$ -2.4 (*c* 2, CH_2Cl_2); LC-MS (ESI): calcd for $C_{38}H_{58}O_4N_1{}^{32}S_1$: 568.35 $[M+H\text{-}t\text{Bu}]^+$, found 568.23 $[M+H\text{-}t\text{Bu}]^+$, R_t 11.79 min; ES MS: *m/z*: calcd for $C_{38}H_{58}O_4N_1{}^{32}S_1$ $[M+H]^+$: 624.40811; found: 624.40808 $[M+H]^+$.

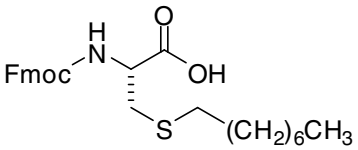


(L)-9H-Fluoren-9-ylmethoxycarbonylamino)-3-hexadecylsulfanyl-propionic acid (4)

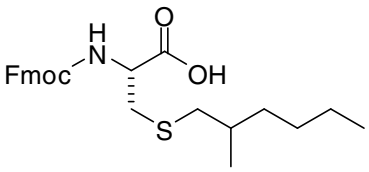
- **By Hydrolysis of 3 methyl ester.** $AlCl_3$ (0.5 g; 3.80 mmol) was added to a solution of **3** (0.32 g; 0.54 mmol) in CH_2Cl_2 (4 mL), after 2 min dimethylaniline (DMA) (0.756 mL; 5.94 mmol) was added and the reaction mixture was refluxed at 55 ºC for 2 h and cooled to r.t. A solution of HCl 1N was slowly added till pH 2 after which CH_2Cl_2 was added and the mixture was washed with brine. The organic phase was dried with Na_2SO_4, filtered, and solvent was removed under reduced pressure. The residue was purified by flash chromatography giving compound **4** in 55% yield (0.17 g).
- **From Fmoc Cysteine-O*t*Bu (5).** Compound **4** (0.11 g; 0.18 mmol) was dissolved in 6 mL CH_2Cl_2 after which 2 mL of TFA were slowly added at r.t. The mixture was stirred overnight at r.t. and then toluene was added and the solvent was removed under

reduced pressure. The residue was coevaporated two times more with toluene to obtain **4** (0.1 g, quant.).

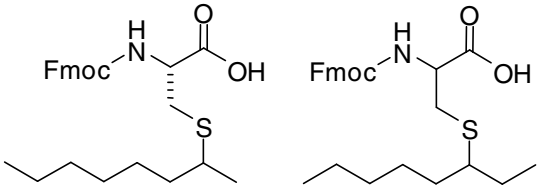
- **From Fmoc-Cysteine(Trt)-OH.** Fmoc-cysteine(Trt)-OH (4 g; 6.8 mmol) was deprotected following reported conditions.[2] The residue was dissolved in 30 mL DCE and the radical alkylation was performed under the general conditions described, yielding **4** (2.0 g, 53%) after purification by column chromatography using CH_2Cl_2:MeOH (95:5). Analytical data: ^{1}H-NMR (400 MHz, $CDCl_3$): 0.87 (t, 3H, *J*= 6.8 Hz), 1.24 (s, 26H), 1.51 (m, 2H), 2.52 (m, 2H), 3.02 (m, 2H), 4.20 (t, 1H, *J*= 6.8 Hz), 4.38 (s, 2H), 4.37 (s, 1H), 5.76 (bs, 1H), 7.27 (t, 2H, *J*= 7.2 Hz), 7.36 (t, 2H, *J*= 7.3 Hz), 7.55 (s, 2H), 7.73 (d, 2H, *J*= 7.59 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): 14.0, 22.6, 28.7, 29.1, 29.2, 29.47, 29.49, 29.55, 29.59, 29.60, 29.63, 31.8, 32.8, 34.1, 47.0, 53,4, 67.3, 119.9, 125.0, 127.0, 127.6, 130.3, 141.2, 143.5, 143.7, 155.8, 175.0; $[\alpha]_D^{20}$ -8.9 (*c* 0.22, CH_2Cl_2); LC-MS (ESI): calcd for $C_{34}H_{50}NO_4{}^{32}S$: 568.35 $[M+H]^+$, found 568.23 $[M+H]^+$, R_t 9.76 min; calcd for $C_{34}H_{50}O_4N_1{}^{32}S_1$: 568.3455 $[M+H]^+$, 590.3275 $[M+Na]^+$, found: 568.3451 $[M+H]^+$, 590.3270 $[M+Na]^+$.



(L)-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-3-octylsulfanyl-propionic acid (6) (Table 2, entry 1). After deprotection of Fmoc-cysteine(Trt)-OH (1.33 g; 2.28 mmol) under acidic conditions, the radical reaction was performed in DCE with 1-octene (1.16 mL; 6.8 mmol) under the general conditions described. After purification by column chromatography using CH_2Cl_2:MeOH (95:5), compound **6** was isolated as a white foam (0.59 g; 57%). Analytical data: ^{1}H-NMR (400 MHz, CD_3OD): 0.86 (t, 3H, *J*= 6.8 Hz), 1.2-1.4 (m, 8H), 1.37 (t, 2H, *J*= 6.8 Hz), 1.58 (q, 2H, *J*= 7.6 Hz), 2.56 (t, 2H, *J*= 7.2 Hz), 2.84 (dd, 1H, *J*= 8.4, 13.6 Hz) , 2.87 (dd, 1H *J*= 3.6, 14 Hz), 4.24 (q, 1H, *J*= 6.8 Hz), 4.33 (m, 2H), 4.38 (dd, 1H, *J*= 6.8, 10.4 Hz), 7.30 (dt, 2H, *J*= 1.2, 7.6 Hz), 7.38 (t, 2H, *J*= 7.2 Hz), 7.69 (d, 2H *J*= 7.6 Hz), 7.78 (d, 2H, *J*= 7.6 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): 14.0, 22.6, 28.8, 29.1, 29.5, 31.7, 32.8, 47.0, 53.9, 67.4, 119.9, 125.13, 127.0, 127.6, 143.6, 156.2, 175.9; $[\alpha]_D^{20}$ -5.6 (*c* 1, CH_2Cl_2); LC-MS (ESI): calcd for $C_{26}H_{34}O_4N_1{}^{32}S_1$: 456.22 $[M+H]^+$; found 456.16 $[M+H]^+$, R_t 6.07 min; ES MS: *m/z*: calcd for $C_{26}H_{34}O_4N_1{}^{32}S_1$: 456.22031 $[M+H]^+$; found: 456.22003 $[M+H]^+$.

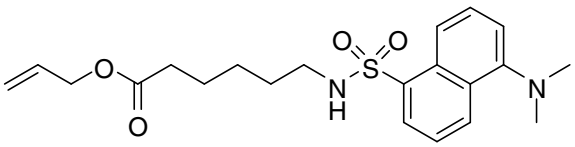


(L)-2-(9H-Fluoren-9-ylmethoxycarbonylamino)-3-(2-methyl-hexylsulfanyl)-propionic acid (7) (Table 2, entry 2). After deprotection of Fmoc-cysteine(Trt)-OH (1.33 g; 2.28 mmol) and radical alkylation using 2-methyl-1-hexene as alkene, compound **7** was isolated after column chromatography using CH_2Cl_2:MeOH (95:5) (0.79 g; 91%). Analytical data: ^{1}H-NMR (400 MHz, $CDCl_3$): 0.78 (t, 3H, *J*= 6.8 Hz), 0.86 (dd, 3H, *J*= 6.8 Hz), 1.1 (dd, 2H, *J*= 7.6, 17.2 Hz), 1.66 (m, 4H), 1.52 (m, 1H), 2.29 (m, 1H), 2.34 (m, 1H), 2.93 (bs, 2H), 4.14 (t, 1H, *J*= 7.2 Hz), 4.29 (d, 2H, *J*= 7.2 Hz), 4.43 (m, 1H), 5.67 (d, NH, *J*= 7.6 Hz), 7.16 (t, 2H, *J*= 7.6 Hz), 7.22 (t, 2H, *J*= 7.2 Hz), 7.31 (d, 2H, *J*= 7,6 Hz), 7.52 (d, 2H, *J*= 7.6 Hz), 8.51 (bs, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$): 14.0, 19.1, 19.2, 22.7, 27.1, 29.0, 29.1, 33.2, 33.28, 34.7, 34.8, 35.6, 35.7, 40.5, 40.6, 47.0, 57.6, 67.3, 119.9, 120.2, 124.9, 127.0, 127.6, 141.2, 143.6. 156.0, 175.2; $[\alpha]_D^{20}$ +4.6 (*c* 0.11, CH_2Cl_2); LC-MS (ESI): calcd for $C_{25}H_{32}O_4N_1{}^{32}S_1$: 442.21 $[M+H]^+$; found 442.11 $[M+H]^+$, R_t 5.44 min; ES MS: *m/z*: calcd for $C_{25}H_{32}O_4N_1{}^{32}S_1$: 442.20466 $[M+H]^+$; found: 442.20443 $[M+H]^+$.

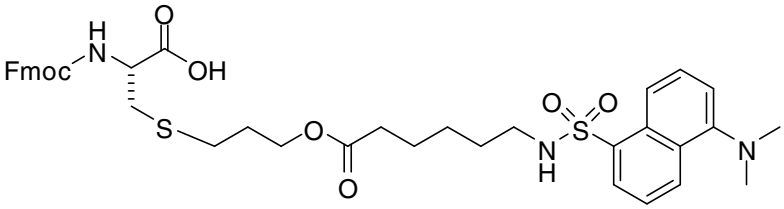


(**9H-Fluoren-9-ylmethoxycarbonylamino)-3-(1-methyl-heptylsulfanyl)-propionic acid, (9H-Fluoren-9-ylmethoxycarbonylamino)-3-(1-ethyl-hexylsulfanyl)-propionic acid (8a/8b) (Table 2, entry 3).** After deprotection Fmoc-cysteine(Trt)-OH (1.33 g, 2.28 mmol) and radical alkylation using *trans*-2-octene as alkene, compound **8** was isolated after column chromatography in silica gel using CH_2Cl_2:MeOH (95:5) (0.3 g, 28%) as a mixture of regioisomers (3.3:1). Analytical data: ^{1}H-NMR (400 MHz, CD_3OD): 0.82 (m, 3H), 0.98 (dt, 3H, *J*= 3.2, 7.2 Hz), 1.09 (d, 3H, *J*= 6.8 Hz), 1.12 (d, 3H, *J*= 6.4 Hz), 1.24 (m, 8H), 1.57 (m, 1H), 2.62 (q, 1H, *J*= 4.8 Hz), 2.83 (m, 1H), 3.00 (m, 1H), 4.23 (q, 1H, *J*= 6.4 Hz), 4.33 (m, 3H), 7.04 (t, 2H, *J*= 7.2 Hz), 7.13 (t, 2H, *J*= 7.2Hz), 7.36 (dd, 2H, *J*= 7.2 Hz), 7.49 (d, 2H, *J*= 7.2 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$:CD_3OD): 13.3, 18.3, 22.0, 25.9, 25.97, 26.0, 28.7, 28.8, 29.1, 31.2, 31.3, 33.4, 36.6, 36.63, 37.4, 39.2, 40.3, 40.4, 41.1, 42.0, 46.6, 65.6, 119.4, 124.63, 126.6, 127.0, 129.0, 140.8, 143.3, 155.8, 167.4, 172.5; $[\alpha]_D^{20}$ -10.21 (*c* 0.95, CH_2Cl_2);

LC-MS (ESI): calcd for $C_{26}H_{34}NO_4{}^{32}S$: 456.22 $[M+H]^+$; found 456.07 $[M+H]^+$, R_t 10.41 min; ES MS: *m/z*: calcd for $C_{26}H_{34}NO_4{}^{32}S$: 456.2203$[M+H]^+$, 478.2023 $[M+Na]^+$; found: 456.2200 $[M+H]^+$, 478.2018 $[M+Na]^+$.

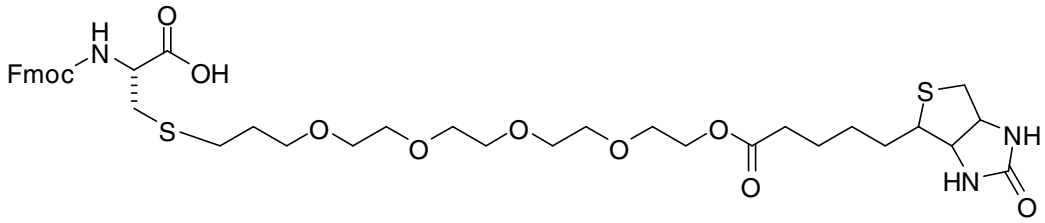


6-(5-Dimethylamino-naphtalene-1-sulfonylamino-hexanoic acid allyl ester (9). O-Allyl aminocaproic ester *p*-TsOH salt (0.40 g; 1.18 mmol) and DIPEA (1 mL; 5.93 mmol) were dissolved in 10 mL CH_2Cl_2 and a solution of dansyl chloride (0.32 g, 1.18 mmol) in CH_2Cl_2 (5 mL) was slowly added. The mixture was stirred at r.t. for 20 h, the solvent was removed under reduced pressure and the residue was purified by flash chromatography in silica gel using a mixture of CH_2Cl_2:MeOH 99.6:0.4 as eluent. Compound **9** (0.33 g; 70%) was isolated. Analytical data: ^{1}H-NMR (400 MHz, $CDCl_3$): 1.15 (m, 2H), 1.36 (q, 2H, *J*= 7.2 Hz), 1.40 (q, 2H, *J*= 7.2 Hz), 2.14 (t, 2H, *J*= 7.6 Hz), 2.87 (s, 6H), 2.87 (q, 2H, *J*= 6.8 Hz), 4.52 (td, 2H, *J*=1.4, 5.7 Hz), 4.94 (t, 1H, *J*= 6.1 Hz), 5.23 (qdd, 2H, *J*= 1.4, 10.4, 23.8 Hz), 5.87 (tdd, 1H, *J*= 5.7, 10.4, 17.2, Hz), 7.52 (ddd, 2H, *J*= 7.4, 13.2 Hz), 8.23 (dd, *J*= 1.2, 7.3 Hz), 8.30 (d, 1H, *J*= 8.6 Hz), 8.53 (d, 1H, *J*= 8,8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$): 24.0, 5.7, 29.0, 33.7, 42.9, 45.3, 64.9, 115.1, 118.0, 118.7, 123.1, 128.2, 129.5, 129.55, 129.8, 130.3, 132.1, 134.7, 151.9, 173. LC-MS (ESI): calcd for $C_{21}H_{29}N_2O_4{}^{32}S$: 405.18 $[M+H]^+$; found 405.17 $[M+H]^+$, R_t 4.01 min; ES MS: *m/z*: calcd for $C_{21}H_{29}N_2O_4{}^{32}S$: 405.18426 $[M+H]^+$; found: 405.18381 $[M+H]^+$.



2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-3-(3-(6-(5-(dimethylamino)naphthalene-1-sulfonamido) hexanoyloxy)propylthio)propanoic acid (10) (Table 2, entry 4). After deprotection of Fmoc-cysteine(Trt)-OH under acidic conditions (0.35 mmol), alkene **9** (0.14 g; 0.34 mmol) and AIBN (28 mg; 0.17 mmol) were added to the solution. Radical alkylation was performed under the general conditions using 1 equivalent of alkene and compound **10** was purified by column chromatography using CH_2Cl_2:MeOH (95:5) as eluent (90 mg, 35%).

Analytical data:^{1}H-NMR (400 MHz, $CDCl_3$): 1.17 (t, 2H, *J*= 8 Hz), 1.34 (t, 2H, *J*= 7.2 Hz), 1.43 (t, 2H, *J*= 7.6 Hz), 1.84 (m, 2H), 2.11 (t, 2H, *J*= 7.2 Hz), 2.58 (m, 2H), 2.86 (m, 8H), 3.05 (m, 2H), 4.08 (t, 2H, *J*= 6.8 Hz), 4.18 (t, 1H, *J*= 7.2 Hz), 4.36 (t, 2H, *J*= 9.2 Hz), 4.57 (bs, 1H), 5.22 (bs, 1H), 5.90 (bs, 1H), 7.17 (d, 1H, *J*= 8 Hz), 7.26 (t, 2H, *J*= 7.6 Hz), 7.35 (2H, *J*= 7.2 Hz), 7.50 (m, 2H), 7.56 (t, 2H, *J*= 6.8 Hz), 7.77 (d, 2H *J*= 7.6 Hz), 7.73 (d, 2H, *J*= 7.6 Hz), 8.21 (dd, 1H, *J*= 0.8, 7.2 Hz), 8.30 (d, 1H, *J*= 8.8 Hz), 8.52 (d, 1H, J= 8.8 Hz); ^{13}C-NMR (100 MHz, CD_3OD): 24.3, 26.0, 28.7, 20.3, 34.0, 42.9, 45.5, 47.32, 47.39, 63.1, 67.3, 115.4, 119.1, 120.1, 123.4, 125.3, 127.2, 127.3, 127.9, 128.3, 129.5, 129.8, 130.4, 141.4, 144.0, 152.0, 171.2, 174.2. $[\alpha]_D^{20}$ +5.83 (*c* 0.24, CH_2Cl_2); LC-MS (ESI): calcd for $C_{39}H_{46}O_8N_3{}^{32}S_2$ 748.27 $[M+H]^+$; found 748.22 $[M+H]^+$, R_t 13.51 min; ES MS: m/z: calcd for $C_{39}H_{46}O_8N_3{}^{32}S_2$: 748.27209 $[M+H]^+$; found: 748.27207 $[M+H]^+$.

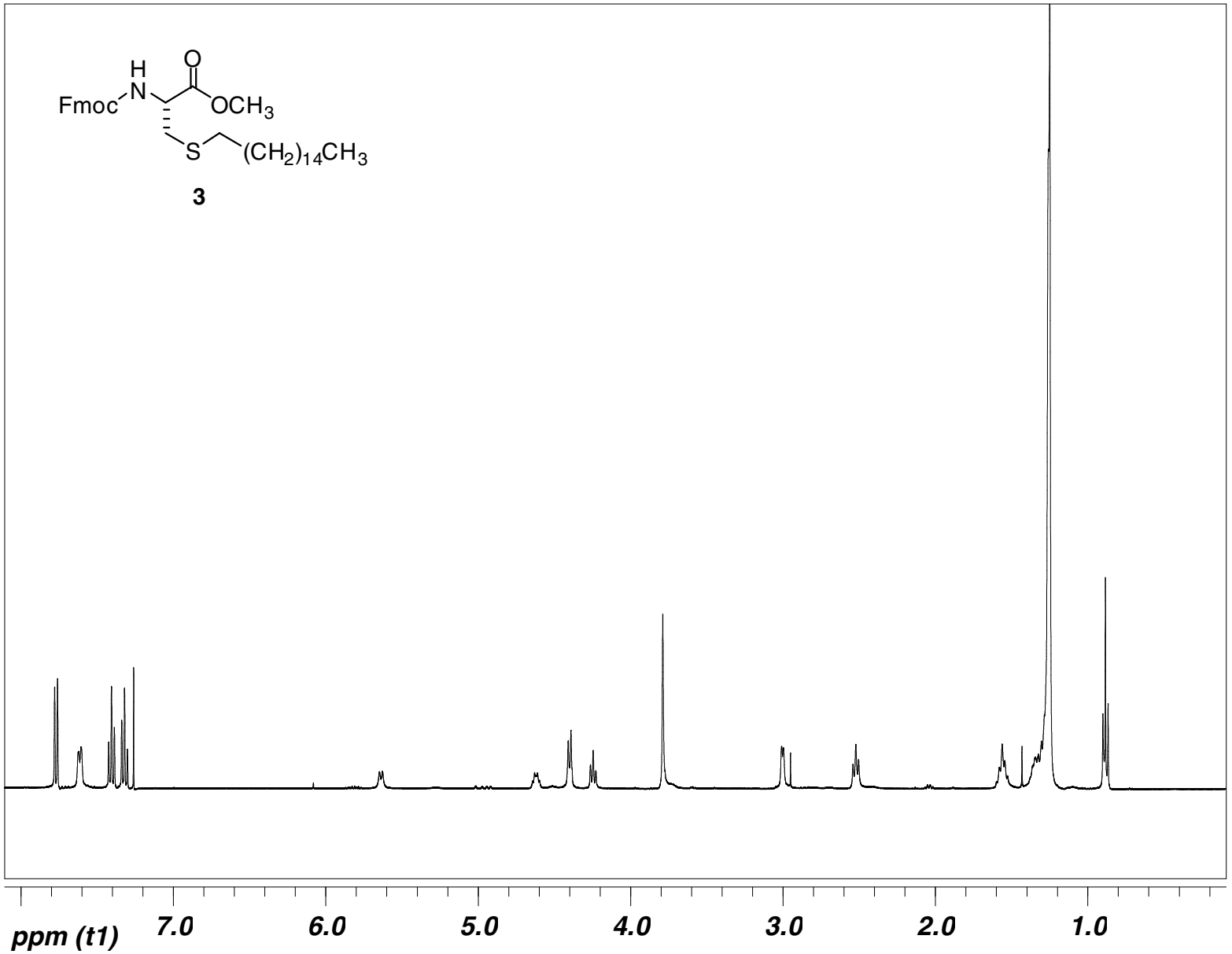


2-(((9H-fluoren-9-yl)methoxy)carbonylamino)-21-oxo-25-(2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-8,11,14,17,20-pentaoxa-4-thiapentacosan-1-oic acid (12) (Table 2, entry 5). After deprotection of Fmoc-cysteine(Trt)-OH under acidic conditions (30 mg, 0.05 mmol), radical alkytion was performed using equimolar conditions of alkene **11** (22 mg, 0.05 mmol) and AIBN (4 mg, 0,02 mmol) in 1 mL DCE. After purification by flash chromatography using CH_2Cl_2:MeOH (95:5), compound **12** was isolated (16 mg; 0,020 mmol) 42%. Analytical data: ^{1}H-NMR (500 MHz, $CDCl_3$;CD_3OD,): 1.18 (qn, 2H, *J*= 8 Hz, 2H), 1.41 (m, 4H), 1.60 (qn, 2H, *J*= 6.5 Hz, 2H), 2.13 (t, 2H, *J*= 7.5 Hz), 2.40 (m, 2H), 2.50 (d, 1H, *J*= 13 Hz), 2.67 (dd, 1H, *J*= 5, 13 Hz), 2.73 (dd, 1H, *J*= 6.5, 13 Hz), 2.83 (dd, 1H, *J*= 4.5, 14 Hz), 2.92 (m, 1H), 3.30 (t , 2H, *J*= 6 Hz), 3.33-3.42 (m, 12H), 3.54 (t, 2H, *J*= 4.5 Hz), 3.97 (t, 2H, *J*= 5 Hz), 3.97 (t, 1H, *J*= 7 Hz), 4.06 (dd, 1H, *J*= 4.5, 8 Hz), 4.12-4.30 (m, 4H), 7.07 (t, 2H *J*= 7 Hz), 7.15 (t, 2H *J*= 7.5 Hz), 7.40 (d, 2H, *J*= 7 Hz), 7.53 (d, 2H, *J*= 7.5 Hz); $[\alpha]_D^{20}$ +7.5 (*c* 0.12, CH_2Cl_2); LC-MS (ESI): calcd for $C_{39}H_{54}O_{11}N_3{}^{32}S_2$: 804.31 $[M+H]^+$; found 804.30 $[M+H]^+$, R_t 2.23 min; ES MS: *m/z*: calcd for $C_{39}H_{54}O_{11}N_3{}^{32}S_2$: 804.31942$[M+H]^+$; found: 804.31985 $[M+H]^+$.

References

(1)Swali, V.; Matteucci, M.; Elliot, R.; Bradley, M. *Tetrahedron* **2002**, *58*, 9101-9109.

(2)Lumbierres, M.; Palomo, J.; Kragol, G.; S., R.; Müller, O.; Waldmann, H. *Chem. Eur. J.* **2005**, *11*, 7405-7415.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N
O
OCH3
S
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ppm (t1)
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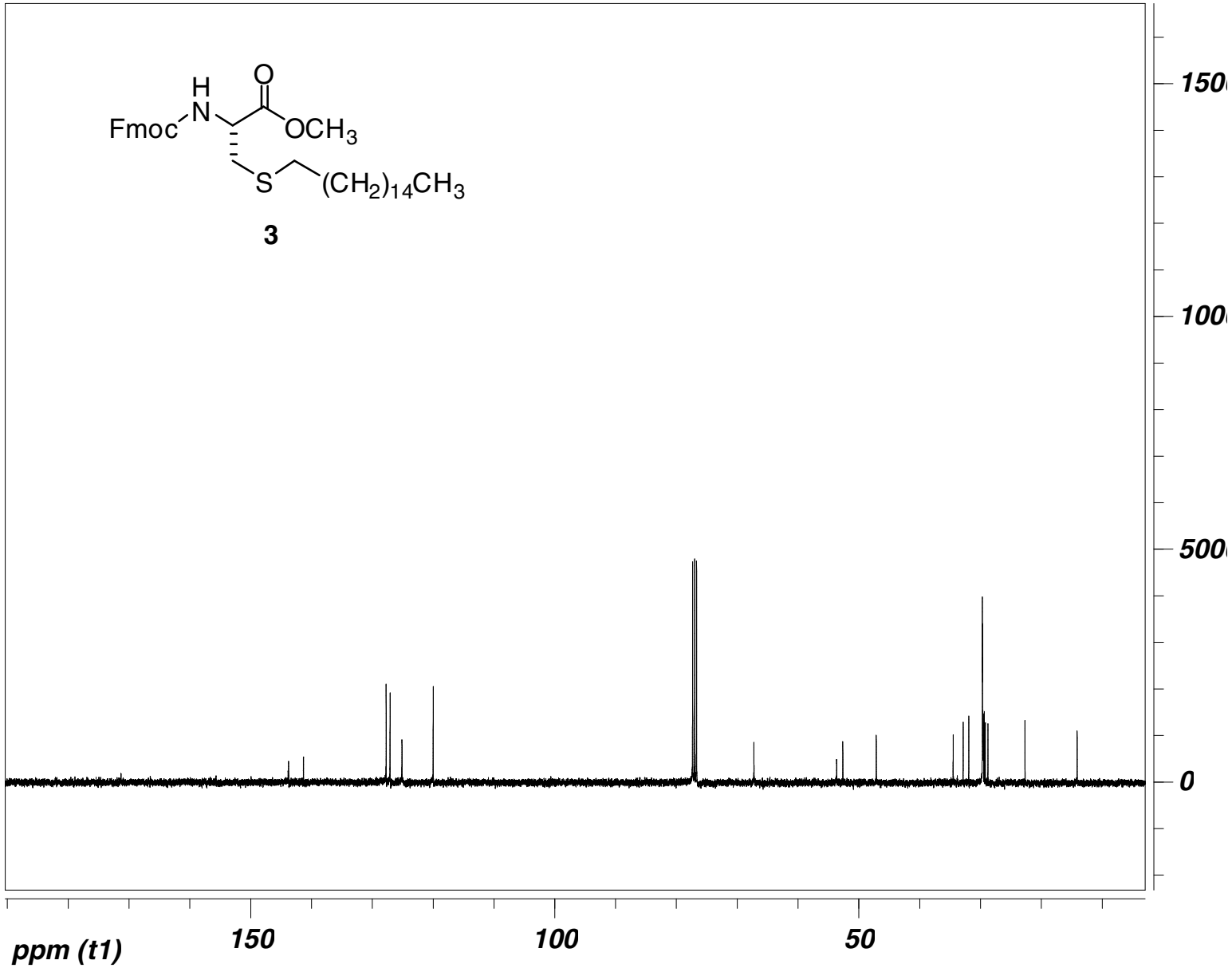
6.0
5.0
4.0
3.0
2.0
1.0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O
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S
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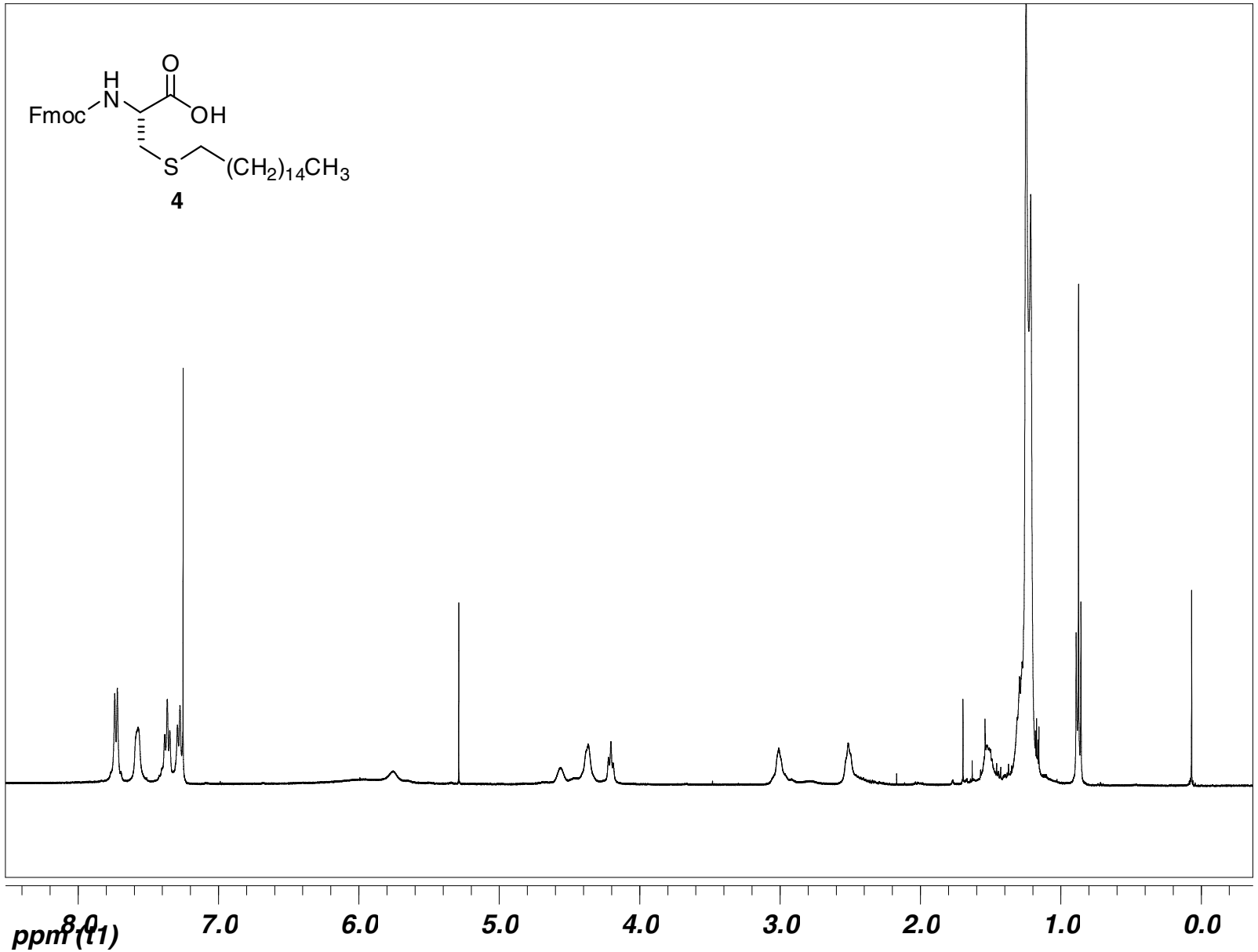
150
100
500
0
ppm (t1)
150
100
50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O
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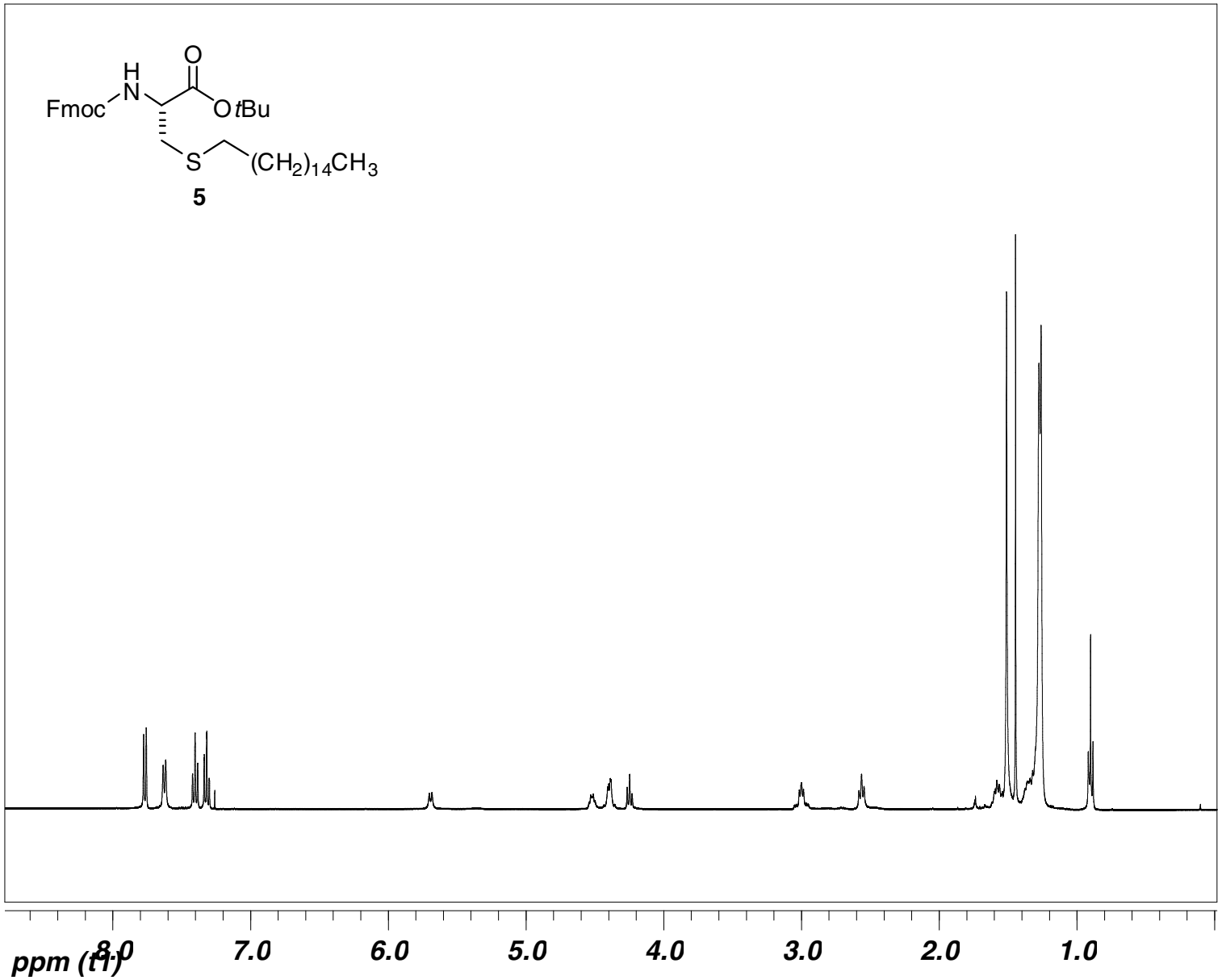
2.0
1.0
0.0
ppm (t1)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N
O
O
tBu
S
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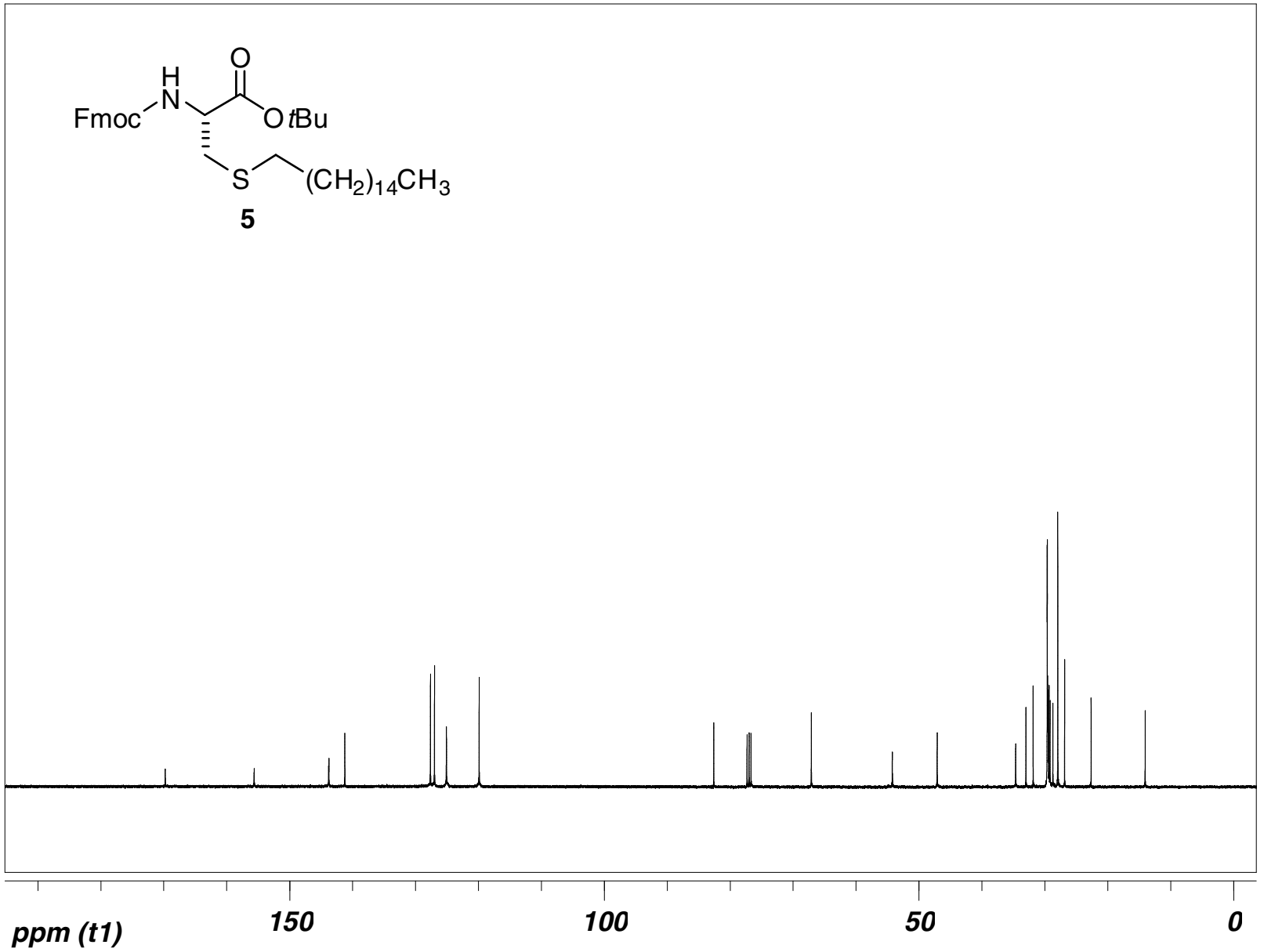
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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N
O
O tBu
S
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5
ppm (t1)
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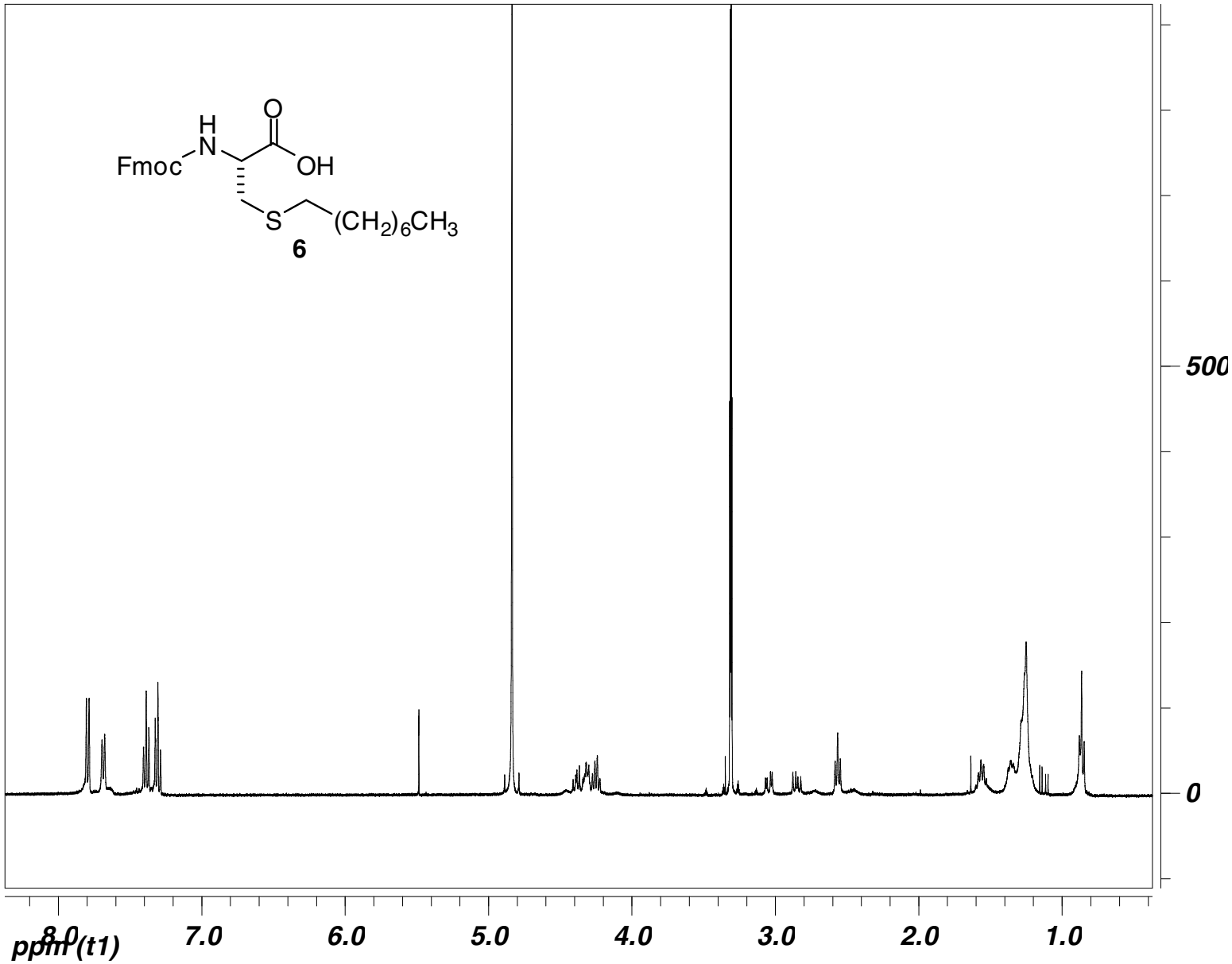
100
50
0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O
OH
S
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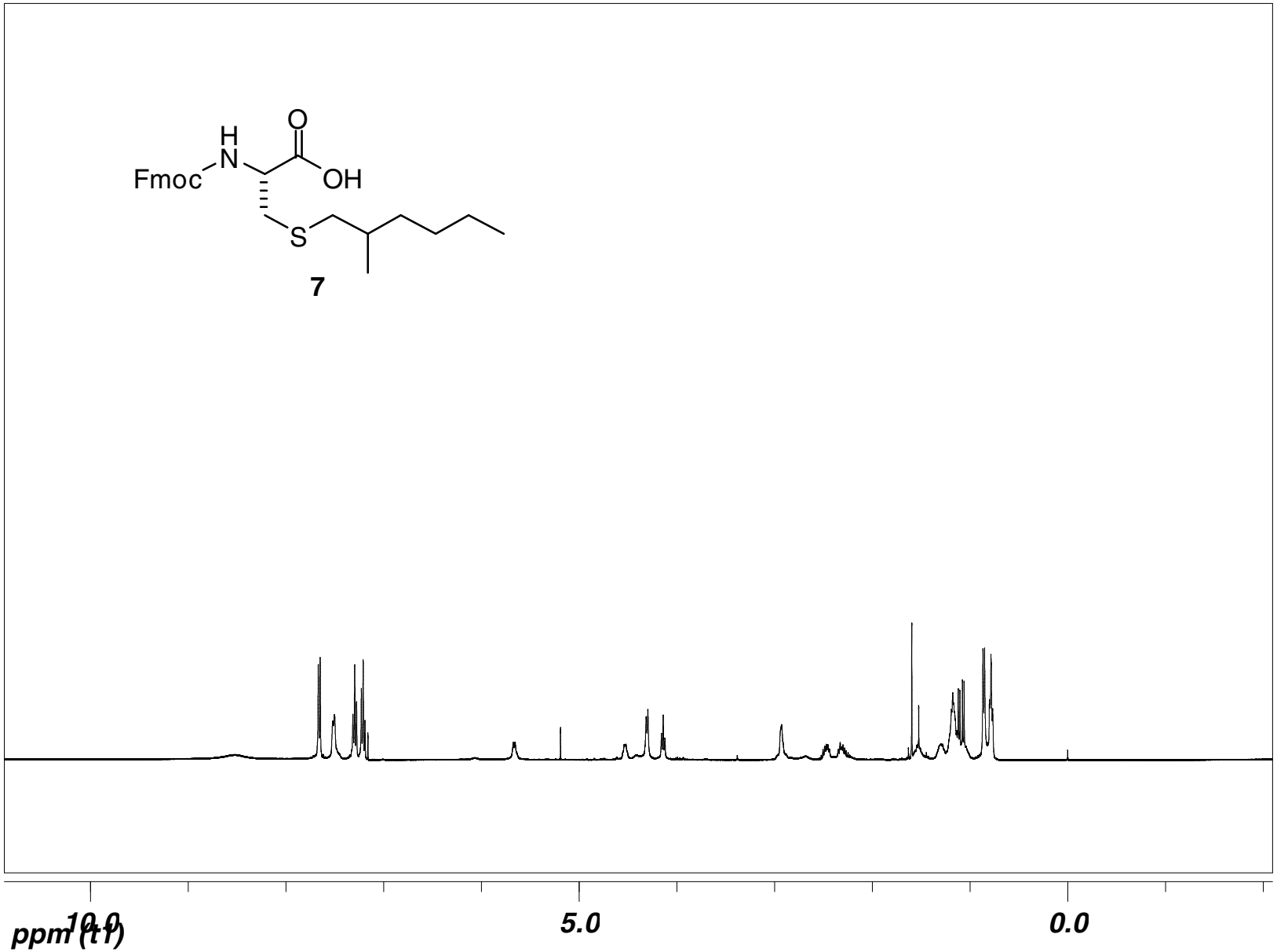
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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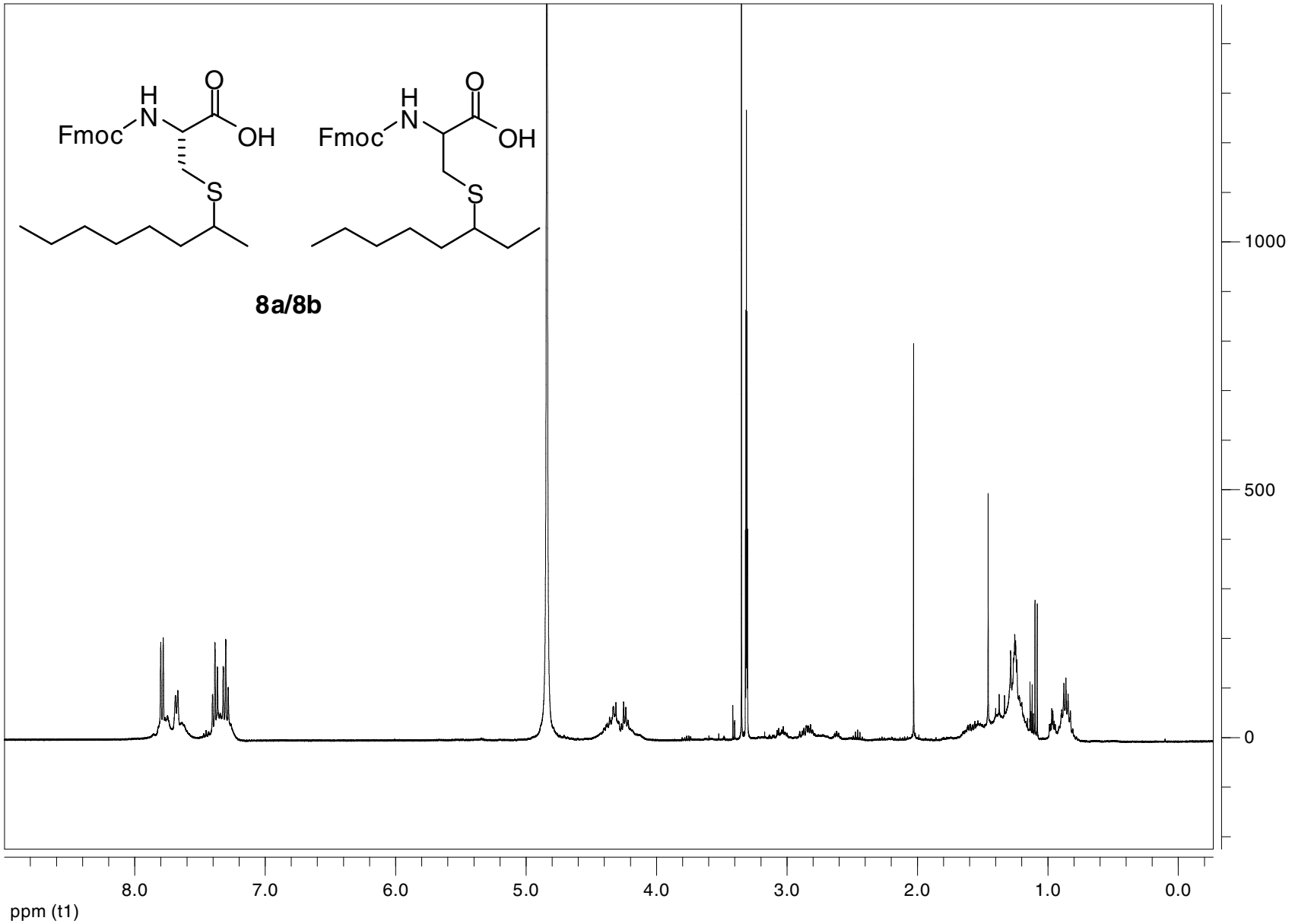
N
O
OH
S
7
10.0
5.0
0.0
ppm (t1)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O
OH
S
Fmoc
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N
O
OH
S
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500
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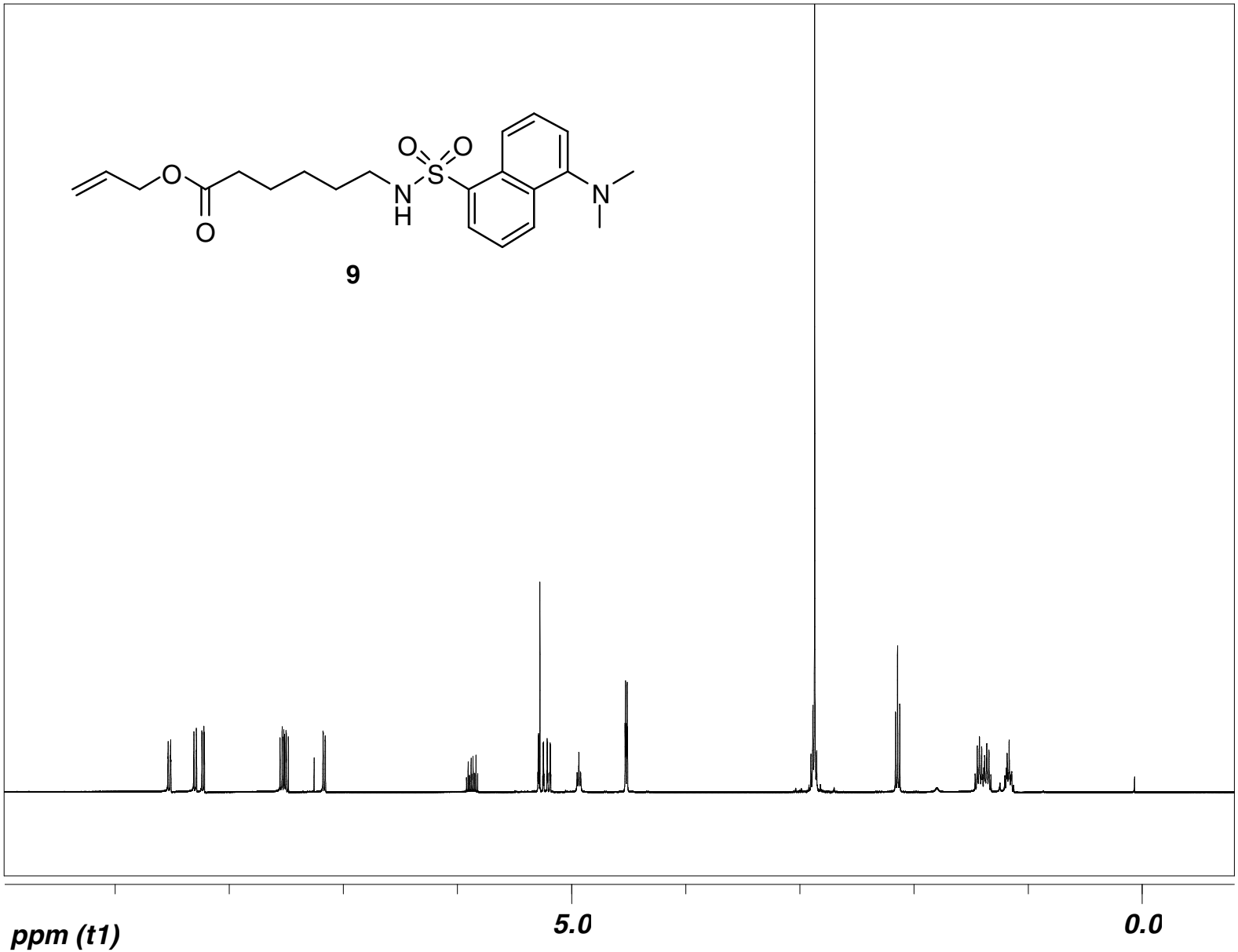
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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O
O
S
O
N
H
N
9
ppm (t1)
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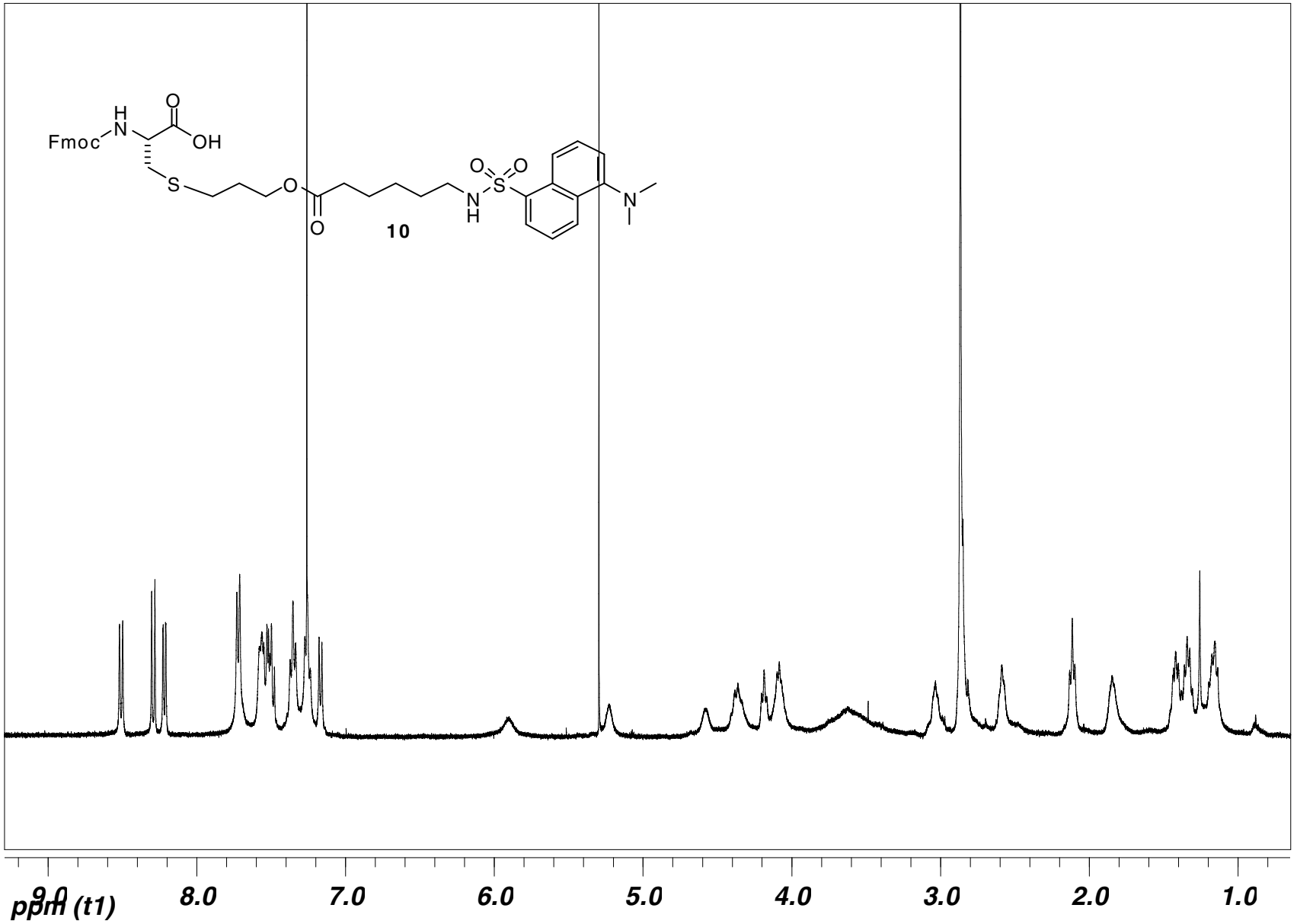
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OH
S
O
O
O
O
H
N
S
O
O
N
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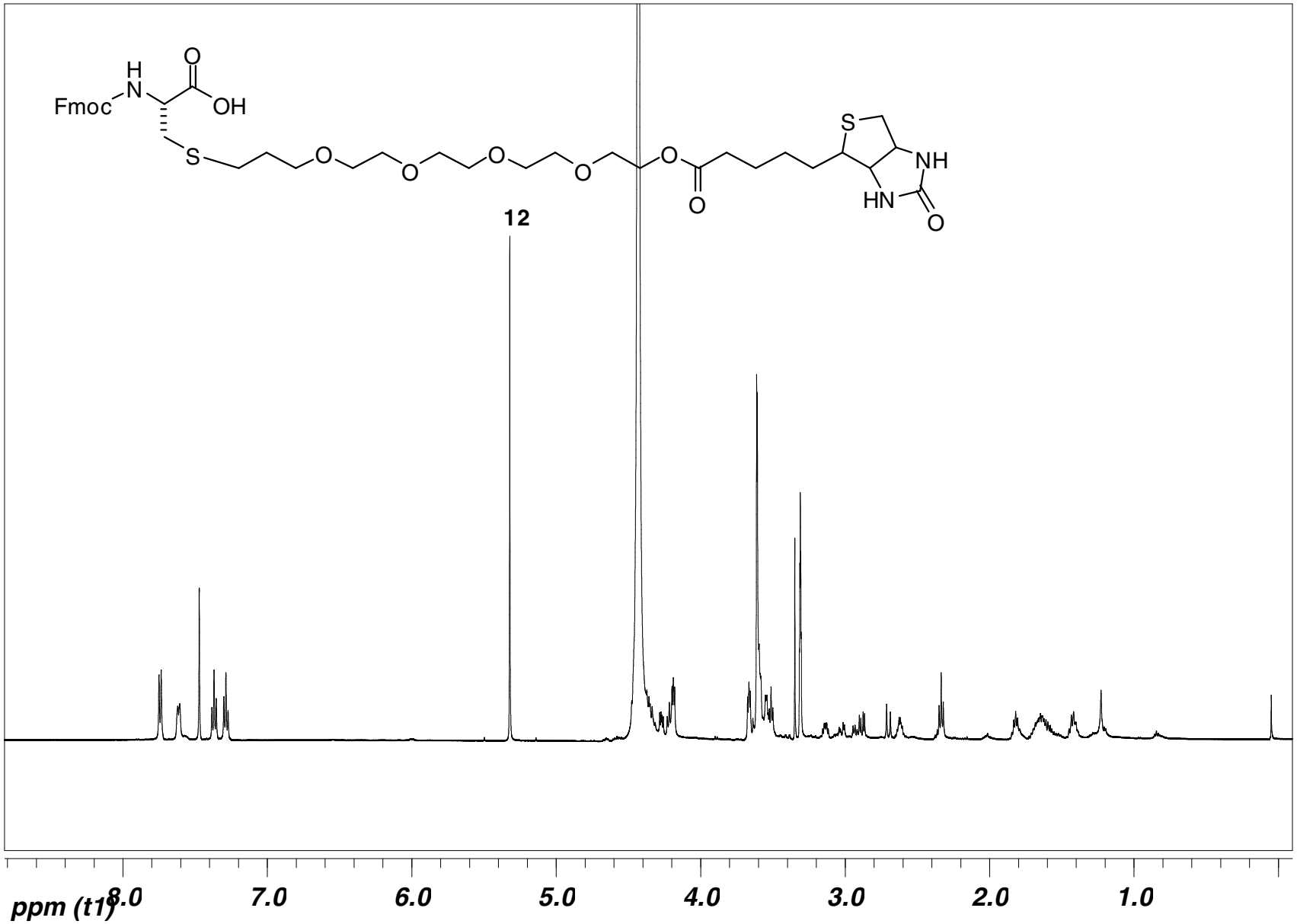
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)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O
OH
S
O
O
O
O
O
O
S
NH
HN
O
O
12
ppm (t1)
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7.0
6.0
5.0
4.0
3.0
2.0
1.0