Supplementary Information (SI) for Organic & Biomolecular Chemistry.

Supporting Information

Non-Catalytic Low-Cost and Sustainable Amidation using a Twisted Amide

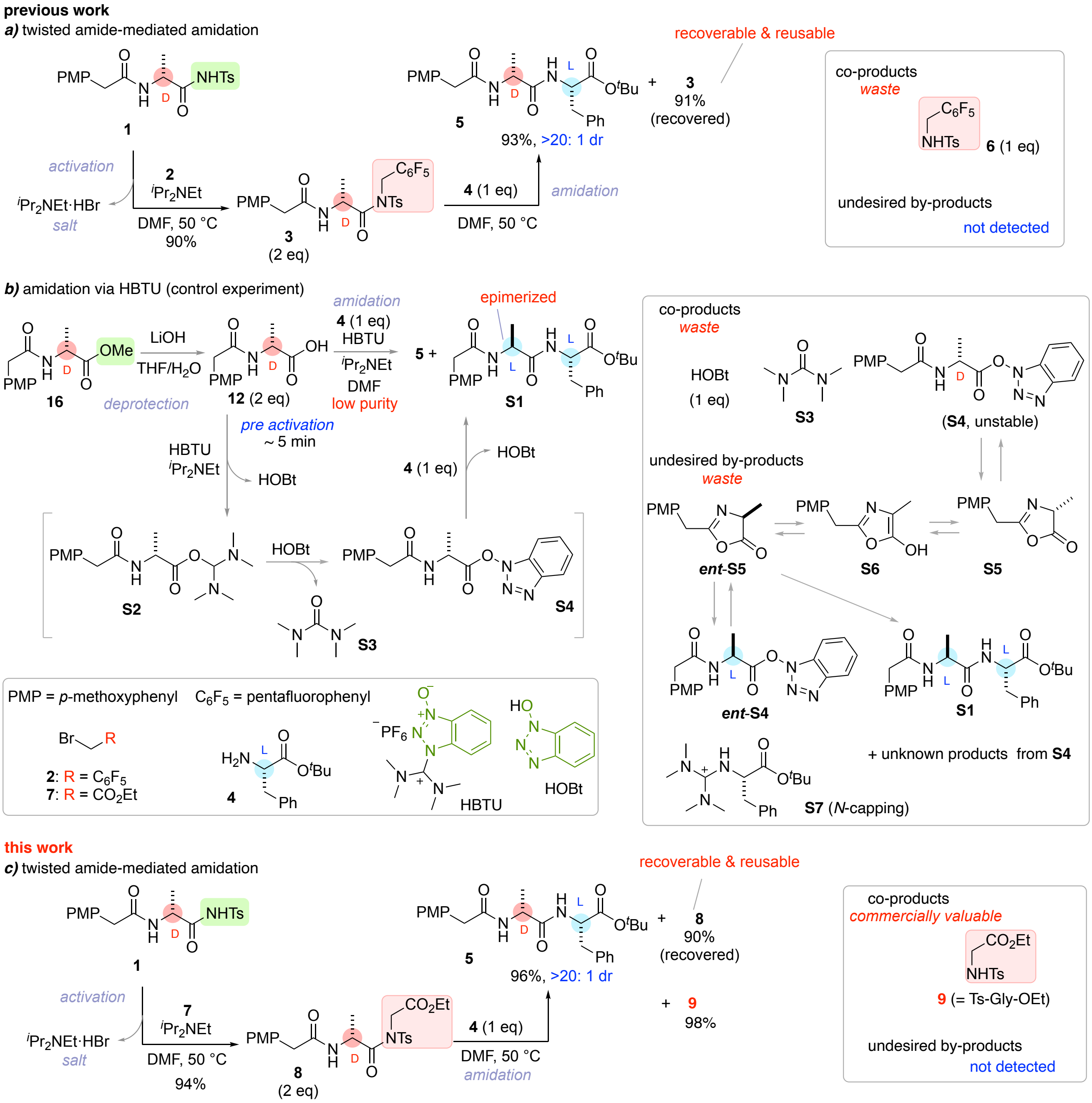
Takefumi Kuranaga,* Ai Koyama, Kosuke Shimizu, Tensei Tokuda, and Hideaki Kakeya*

Department of System Chemotherapy and Molecular Sciences, Division of Medicinal Frontier Sciences, Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

E-mail: *tkuranaga@pharm.kyoto-u.ac.jp*, *scseigyo-hisyo@pharm.kyoto-u.ac.jp*

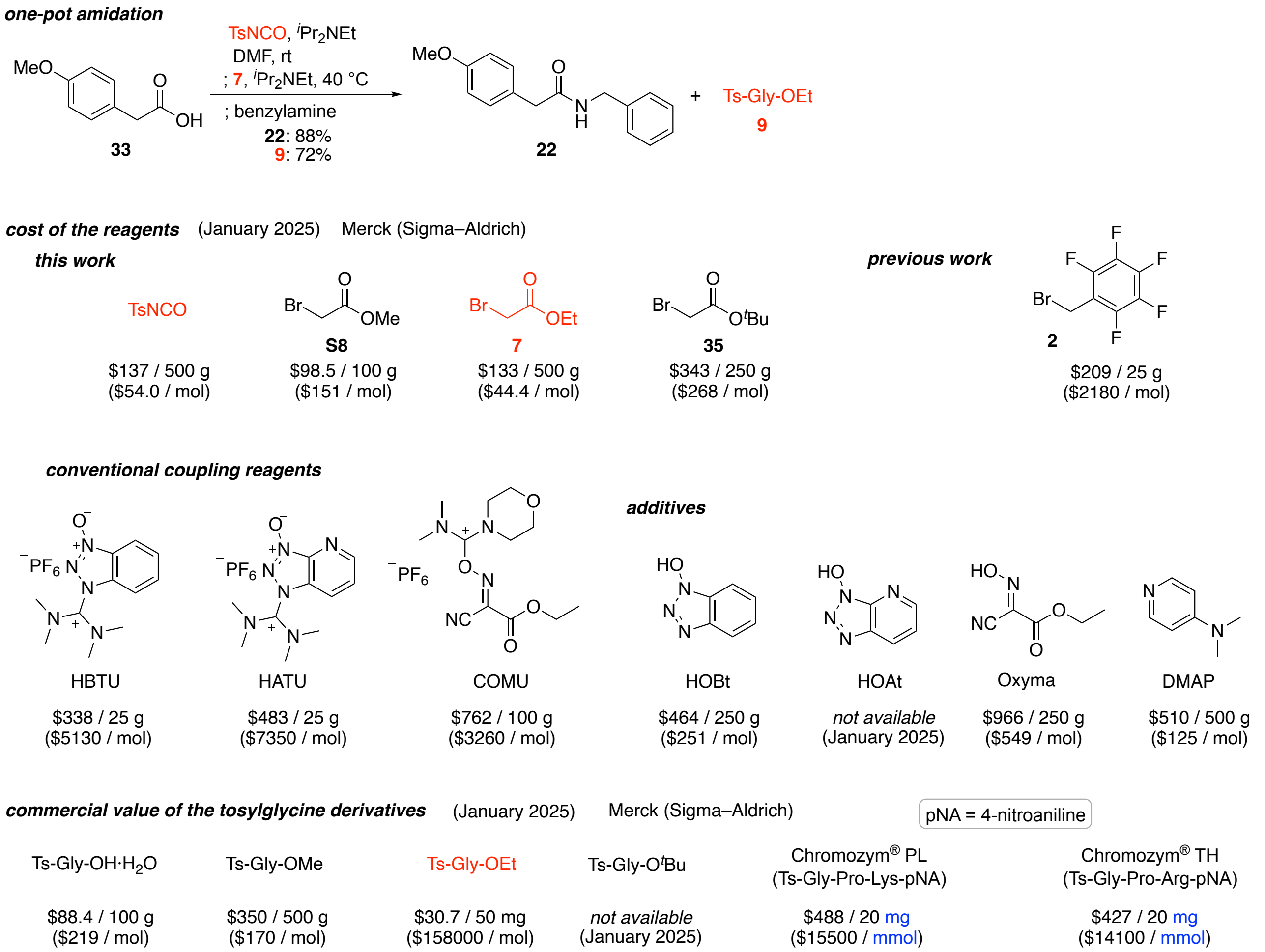
65 pages

Supporting Schemes

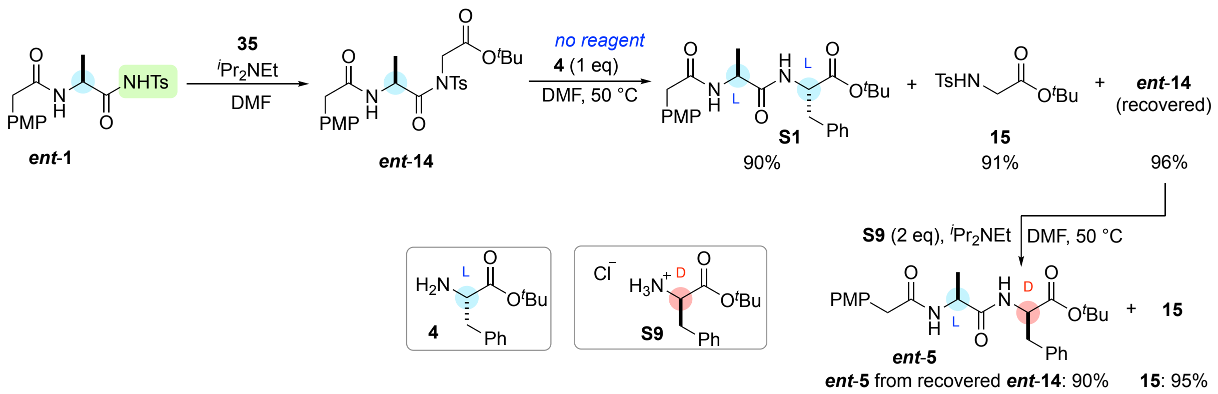


Scheme S1. The details of the amidations.

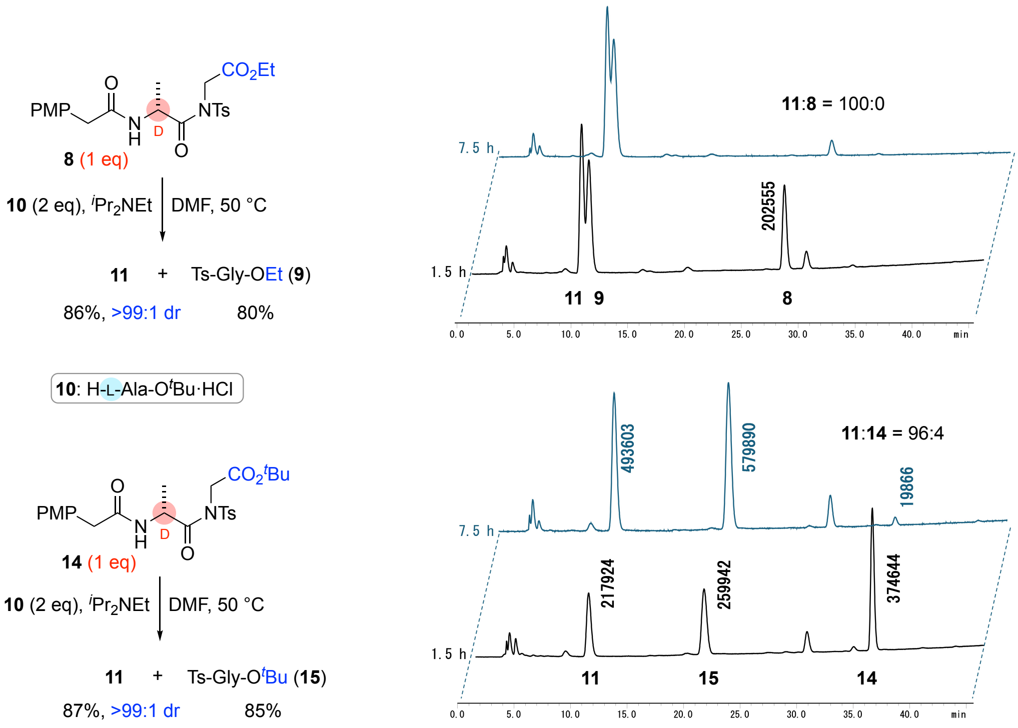
Note: In this study, each intermediate was isolated for detailed analysis of its reactivity. However, amides can be synthesized in a one-pot manner from corresponding carboxylic acids without isolating reactive intermediates (Scheme S2). Cost of the reagents are also summarized in Scheme S2. Ethyl bromoacetate (**7**) is less expensive than Methyl bromoacetate (**S8**), and thus **7** was used in this study instead of **S8**.



Scheme S2. One-pot amidation and cost of the reagents.

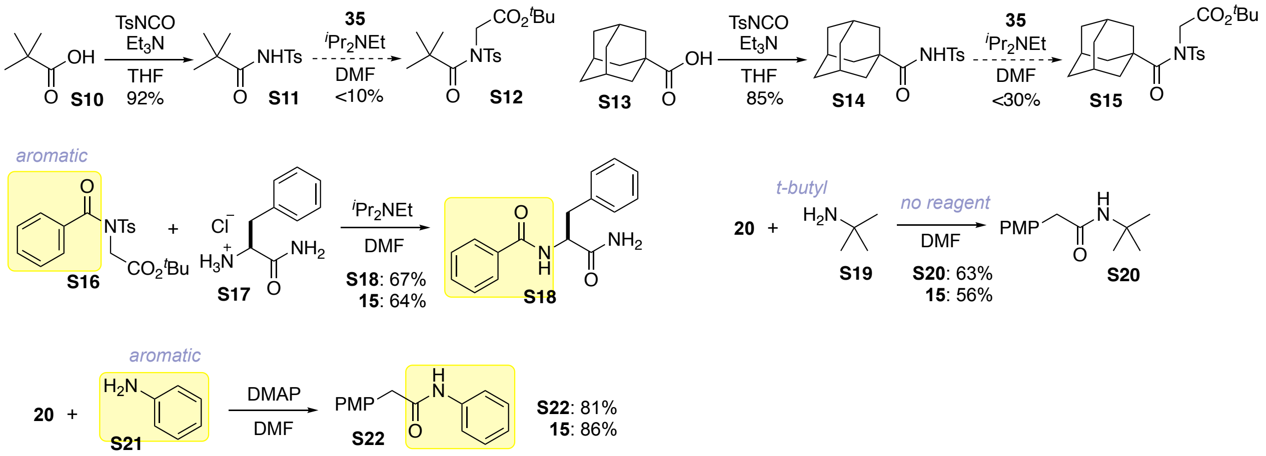


Scheme S3. Investigation of the reusability of recovered ***ent*-14**.

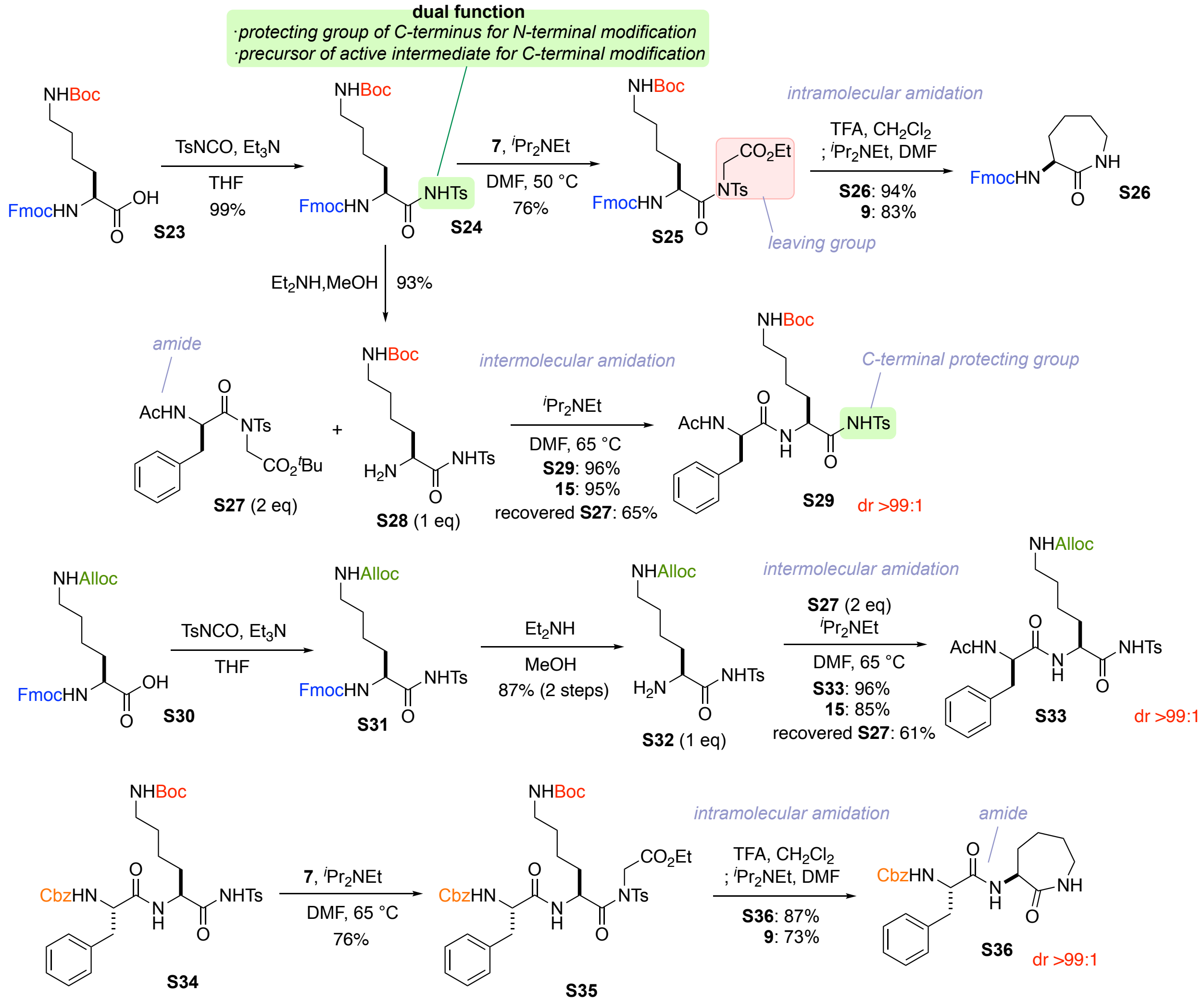


HPLC conditions: COSMOSIL AR-II Φ 2.0 × 250 mm, MeCN/H_2O/TFA (0 to 40 min 40/60/0.05 to 80/20/0.05), 0.2 mL/min, 40 °C

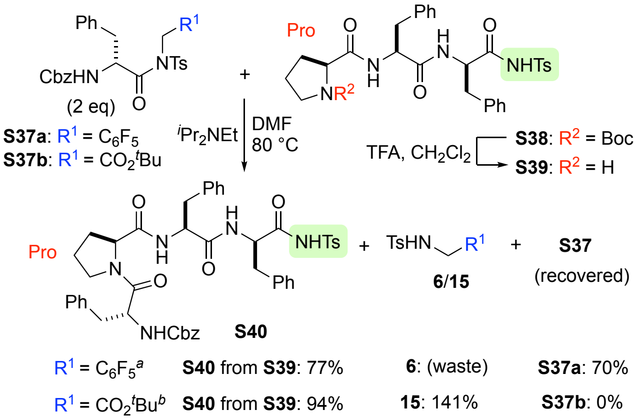
Scheme S4. Reaction rate analysis of the amidations.



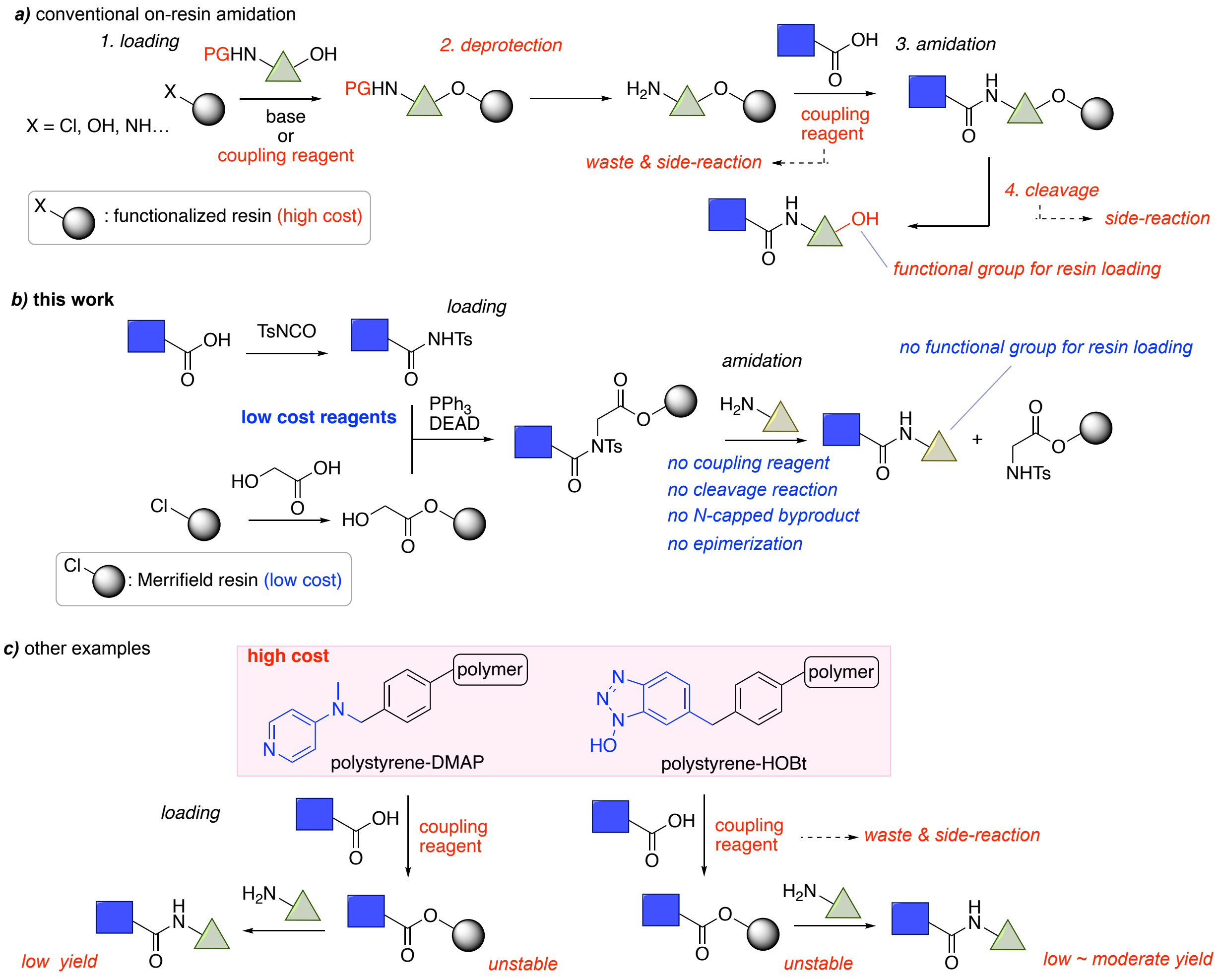
Scheme S5. Investigation of steric and electronic effects.



Scheme S6. Investigation of protecting groups (Boc, Fmoc, Cbz, Alloc).



Scheme S7. Synthesis of tetrapeptide **S40**. [a]Reaction conditions: **29a** (2 eq), **31** (1 eq), ^{i}Pr$_2$NEt (1.2 eq), DMF (0.1 M). [b]Reaction conditions: **29b** (2 eq), **31** (1 eq), ^{i}Pr$_2$NEt (1.1 eq), DMAP (0.1 eq), DMF (0.1 M).



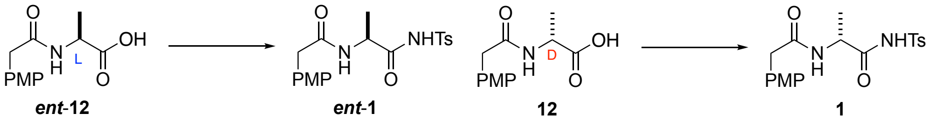
Scheme S8. Summary of on-resin amidations.

General methods

All reactions were carried out under air unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECA500 (500 MHz for ^{1}H NMR) or a JEOL ECZ600 (600 MHz for ^{1}H NMR) spectrometer. ESI-MS and LC-MS experiments were recorded on a Shimadzu LCMS-IT-TOF. Optical rotations were recorded on a JASCO P-2200 polarimeter. High performance liquid chromatography (HPLC) experiments were performed with a SHIMADZU HPLC system equipped with a LC-20AD intelligent pump. Automated flash column chromatography was performed using Biotage Isolera Prime system with Wakogel C-300 (FUJIFILM Wako Chemicals). All reagents were used as supplied unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using E. Merck Silica gel 60 F$_{254}$ pre-coated plates or Silicagel 70 F254 TLC Plate-Wako (FUJIFILM Wako Chemicals). Column chromatography was performed using 40–50 µm Silica Gel 60N (Kanto Chemical Co., Inc.) or 64–210 µm Wakosil 60 (FUJIFILM Wako Chemicals).

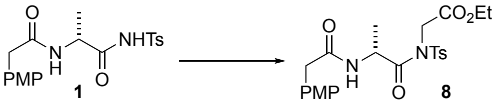
Synthesis and compound characterizations

Scheme 1



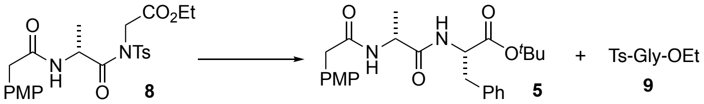
To a solution of ***ent*-12** (501 mg, 2.11 mmol) in THF 10 mL were added Et$_3$N (0.35 mL, 2.5 mmol) and TsNCO (0.35 mL, 2.3 mmol) at room temperature. After being stirred for 15 min, the reaction mixture was treated with 1 M HCl/brine (= 1:4). The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with 1 M HCl/brine (= 1:4), dried over MgSO$_4$, filtered, and concentrated. The residue was recrystallized (EtOAc/hexane) to afford ***ent*-1** (799 mg, 97%) as a white amorphous: $[\alpha]_D^{20}$ –48.8 (*c* 1.00, CHCl$_3$); ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.2 (s, 1H), 8.28 (d, 1H, J = 6.9 Hz), 7.77 (d, 2H, J = 8.3 Hz), 7.40 (d, 2H, J = 7.6 Hz), 7.10 (d, 2H, J = 9.0 Hz), 6.81 (d, 2H, J = 8.3 Hz), 4.17 (dq, 1H, J = 6.9, 6.9 Hz), 3.71 (s, 3H), 3.36–3.30 (m, 2H), 2.39 (s, 3H), 1.12 (d, 6H, J = 7.6 Hz); ^{13}C NMR (150 MHz, DMSO-d_6) δ 171.6, 170.4, 157.8, 144.2, 136.3, 129.9, 129.5, 128.0, 127.4, 113.6, 55.0, 48.5, 40.7, 21.1, 17.0; HRMS (ESI) *m/z*: [M+Na]$^+$ calcd for $C_{19}H_{22}N_2NaO_5S^+$ 413.1142, found 413.1138.

1: $[\alpha]_D^{20}$ +45.3 (*c* 1.00, CHCl$_3$).



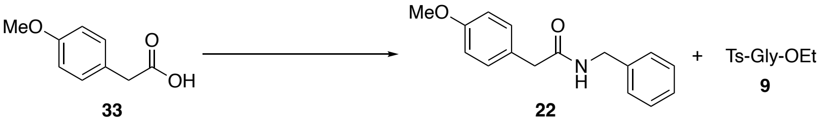
To a solution of **1** (391 mg, 1.0 mmol) in DMF 2 mL were added *i*-Pr$_2$NEt (0.51 mL, 3.0 mmol) and ethyl bromoacetate (**7**) (0.33 mL, 3.0 mmol) at room temperature. After being stirred for 9 h at 50 °C, the reaction mixture was treated with 2% aqueous KHSO$_4$. The resulting solution was extracted with EtOAc (twice). The combined organic layer was washed with 2% aqueous KHSO$_4$, dried over MgSO$_4$, filtered, and concentrated.

The residue was purified by automated silica gel flash chromatography (EtOAc/hexane = 20:80 to 50:50) to afford **8** (450 mg, 94%) as a pale-yellow oil: $[\alpha]_D^{20}$ +8.4 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (d, 2H, *J* = 8.3 Hz), 7.36 (d, 2H, *J* = 8.3 Hz), 7.12 (d, 2H, *J* = 8.3 Hz), 6.86 (d, 2H, *J* = 8.3 Hz), 5.92 (brs, 1H), 5.35 (brs, 1H), 4.52 (d, 1H, *J* = 17.9 Hz), 4.42 (d, 1H, *J* = 17.2 Hz), 4.16 (q, 2H, *J* = 7.1 Hz), 3.79 (s, 3H), 3.45 (dd, 2H, *J* = 21.3, 15.8 Hz), 2.43 (s, 3H), 1.32 (d, 3H, *J* = 6.9 Hz), 1.23 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.6, 171.6, 168.2, 159.5, 146.1, 136.0, 131.1, 130.6, 128.9, 126.9, 115.1, 62.5, 55.9, 49.2, 47.5, 43.1, 22.4, 19.7, 14.7: HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{23}H_{28}N_2NaO_7S^+$ 499.1509, found 499.1505.



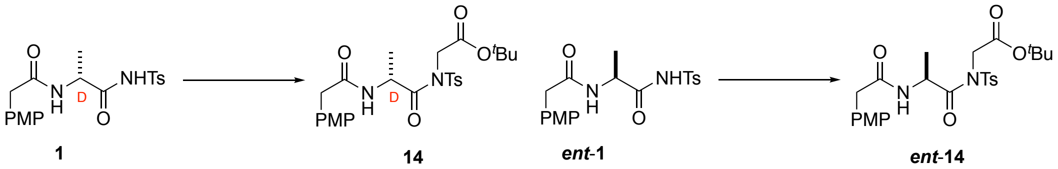
To a solution of L-phenylalanine *t*-butyl ester (**4**) (57.1 mg, 0.258 mmol) in DMF 2.6 mL was added **8** (245 mg, 0.514 mmol) at room temperature. After being stirred for 16 h at 50 °C, the reaction mixture was concentrated. The residue was azeotroped with toluene (three times) and purified by automated silica gel flash chromatography (EtOAc/hexane = 3:97 to 70:30) to afford **9** (65.4 mg, 98%), **8** (110.3 mg, 90% recovered) and **5** (108.7 mg, 96%) as a white amorphous: $[\alpha]_D^{20}$ +23.5 (c 1.00, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29–7.22 (m, 3H), 7.15–7.11 (m, 4H), 6.87 (d, 2H, *J* = 8.3 Hz), 6.38 (br, 1H), 5.90 (br, 1H), 4.69–4.64 (m, 1H), 4.46–4.39 (m, 1H), 3.80 (s, 3H), 3.52–3.44 (m, 2H), 3.11–2.90 (m, 2H), 1.40 (s, 9H), 1.26 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 171.2, 170.2, 158.9, 136.0, 130.4, 129.4, 128.4, 127.0, 126.3, 114.5, 82.4, 55.3, 53.6, 48.7, 42.6, 37.9, 27.9, 18.0; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{25}H_{32}N_2NaO_5^+$ 463.2203, found 463.2204.

Scheme S2 (procedures for one-pot amidation)



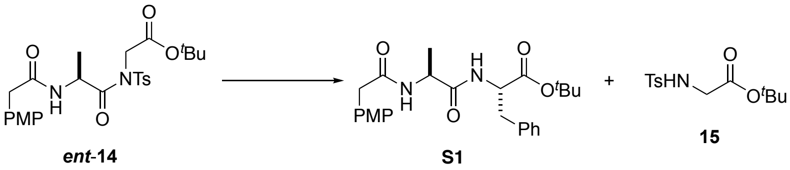
To a solution of **33** (66.8 mg, 0.402 mmol) in DMF 4 mL were added *i*-Pr_2NEt (0.080 mL, 0.47 mmol) and TsNCO (0.070 mL, 0.46 mmol) at room temperature. After being stirred for 25 min, to the reaction mixture were added *i*-Pr_2NEt (0.080 mL, 0.47 mmol) and ethyl bromoacetate (**7**) (0.05 mL, 0.45 mmol) at room temperature. After being stirred for 15 h at 40 °C, to the reaction mixture was added benzylamine (**21**) (0.090 mL, 0.82 mmol). After being stirred for 1.5 h at 40 °C, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with saturated aqueous NH_4Cl, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by automated silica gel flash chromatography (EtOAc/hexane = 5:95 to 60:40) to afford **9** (74.9 mg, 72%) and **22** (CAS: 52532-96-4, 79.9 mg, 88%).

Scheme S3

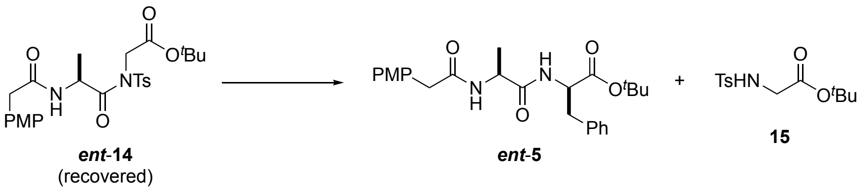


To a solution of **1** (191 mg, 0.489 mmol) in DMF 1.0 mL were added *i*-Pr_2NEt (0.17 mL, 0.98 mmol) and *t*-butyl bromoacetate (**35**) (0.14 mL, 0.95 mmol) at room temperature. After being stirred for 17.5 h at 50 °C, the reaction mixture was treated with 2% aqueous $KHSO_4$. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with 2% aqueous $KHSO_4$, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by automated silica gel flash chromatography (EtOAc/hexane = 30:70 to 40:60) to afford **14** (246 mg, 99%) as a pale-yellow oil: $[\alpha]_D^{20}$ +8.8 (c 1.00, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 7.93 (d, 2H, $J = 8.3$ Hz), 7.34 (d, 2H, $J = 8.3$ Hz), 7.12 (d, 2H, $J = 9.0$ Hz), 6.85 (d, 2H, $J = 8.3$ Hz), 6.00 (s, 1H), 5.30 (s, 1H), 4.44 (d, 1H, $J = 17.2$ Hz), 4.32 (d, 1H, $J = 16.5$ Hz), 3.78 (s, 3H), 3.44 (d, 2H, $J = 4.8$ Hz), 2.42 (s, 3H), 1.41 (s, 9H), 1.32 (d, 3H, $J = 6.9$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.7, 170.8, 166.4, 158.7, 145.2, 135.4, 130.5, 130.4, 130.1, 129.8, 128.2, 126.2, 114.3, 82.6, 55.2, 48.3, 47.4, 42.3, 27.8, 21.6, 19.0: HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{25}H_{32}N_2NaO_7S^+$ 527.1822, found 527.1830.

***ent*-14**: $[\alpha]_D^{20}$ –9.2 (c 1.00, $CHCl_3$).

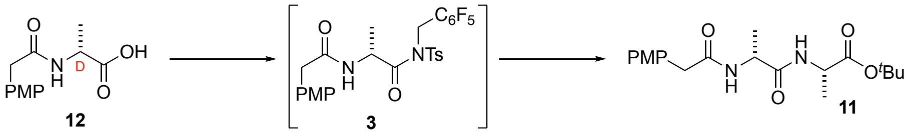


To a solution of L-phenylalanine *t*-butyl ester (**4**) (67.5 mg, 0.305 mmol) in DMF 3 mL was added ***ent*-14** (262 mg, 0.520 mmol) at room temperature. After being stirred for 22 h at 50 °C, the reaction mixture was concentrated. The residue was azeotroped with toluene (twice) and purified by silica gel column chromatography (EtOAc/hexane = 10:90 to 60:40) to afford ***ent*-14** (104 mg, 96% recovered), **15** (79.2 mg, 91%), and **S1** (121 mg, 90%) as a white foam: $[\alpha]_D^{20}$ –36.5 (*c* 1.00, MeOH); ^1H NMR (600 MHz, $CDCl_3$) δ 7.29–7.18 (m, 3H), 7.16–7.10 (m, 4H), 6.84 (d, 2H, $J = 9.0$ Hz), 6.68 (br, 1H), 6.19 (br, 1H), 4.68 (m, 1H), 4.48 (m, 1H), 3,78 (s, 3H), 3.48 (s, 2H), 3.11–3.05 (m, 1H), 3.02–2.96 (m, 3H), 1.40 (s, 9H), 1.20 (d, 3H, $J = 7.6$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 171.1, 170.2, 158.7, 136.0, 130.4, 129.4, 128.3, 126.9, 126.4, 114.3, 82.3, 55.1, 53.5, 48.6, 42.5, 37.9, 27.9, 18.4; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{25}H_{32}N_2NaO_5^+$ 463.2203, found 463.2200.



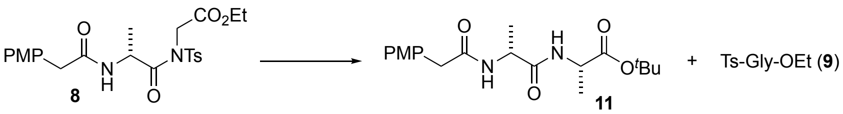
To a solution of the above recovered ***ent*-14** (104 mg, 0.206 mmol) in DMF 2 mL were added D-Phenylalanine *t*-butyl ester hydrochloride (**S9**) (100 mg, 0.388 mmol) and *i*-Pr$_2$NEt (0.07 mL, 0.402 mmol) at room temperature. After being stirred for 23 h at 50 °C, the reaction mixture was treated with saturated aqueous NH$_4$Cl. The resulting solution was extracted with EtOAc (twice). The combined organic layer was washed with brine, dried over MgSO$_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane = 10:90 to 60:40) to afford **15** (55.9 mg, 95%), and ***ent*-5** (81.7 mg, 90%): $[\alpha]_D^{20}$ –24.3 (*c* 1.00, MeOH).

Scheme 2

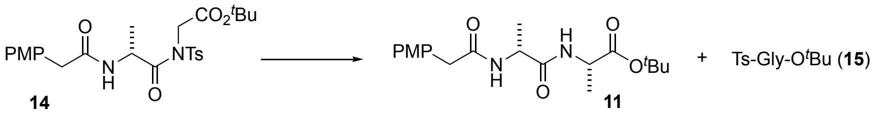


(Procedures for one-pot amidation and characterization of **11**)

To a solution of **12** (129 mg, 0.544 mmol) in DMF 2.7 mL were added *i*-Pr$_2$NEt (0.11 mL, 0.65 mmol) and TsNCO (0.090 mL, 0.60 mmol) at room temperature. After being stirred for 15 min, to the reaction mixture were added *i*-Pr$_2$NEt (0.11 mL, 0.65 mmol) and pentafluorobenzyl bromide (0.090 mL, 0.64 mmol) at room temperature. After being stirred for 7 h at 50 °C, to the reaction mixture were added L-alanine *t*-butyl ester hydrochloride (198 mg, 1.09 mmol) and *i*-Pr$_2$NEt (0.19 mL, 1.1 mmol). After being stirred for 18 h at 50 °C, the reaction mixture was treated with saturated aqueous NH$_4$Cl. The resulting solution was extracted with EtOAc (twice). The combined organic layer was washed with saturated aqueous NH$_4$Cl, dried over MgSO$_4$, filtered, and concentrated. The residue was purified by automated silica gel flash chromatography (EtOAc/hexane = 10:90 to 80:20) to afford **11** (120 mg, 61%) as a white foam: $[\alpha]_D^{20}$ +9.7 (*c* 1.00, CHCl$_3$); ^{1}H NMR (600 MHz, CDCl$_3$) δ 7.18 (d, 2H, *J* = 9.0 Hz), 6.87 (d, 2H, *J* = 9.0 Hz), 6.60 (br, 1H), 6.02 (br, 1H), 4.49 (dq, 1H, *J* = 6.9, 6.9 Hz), 4.37 (dq, 1H, *J* = 7.6, 6.9 Hz), 3.80 (s, 3H), 3.53 (d, 2H, *J* = 2.0 Hz), 1.46 (s, 9H), 1.34 (d, 3H, *J* = 7.6 Hz), 1.28 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (150 MHz, CDCl$_3$) δ 171.8, 171.4, 171.3, 158.9, 130.5, 126.4, 114.4, 82.0, 55.2, 48.8, 48.6, 42.7, 27.9, 18.4, 18.0; HRMS (ESI) *m/z*: [M+Na]$^+$ calcd for $C_{19}H_{28}N_2NaO_5^+$ 387.1890, found 387.1894.

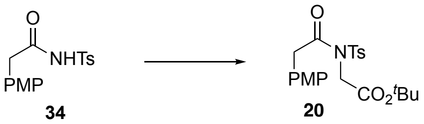


To a solution of **8** (85.5 mg, 0.18 mmol) in DMF 1.8 mL were added *i*-Pr_2NEt (0.060 mL, 0.35 mmol) and L-alanine *t*-butyl ester hydrochloride (65 mg, 0.36 mmol) at room temperature. After being stirred for 25 h at 50 °C, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by automated silica gel flash chromatography (EtOAc/hexane = 20:80 to 80:20) to afford **9** (36.8 mg, 80%), and **11** (56.6 mg, 86%).

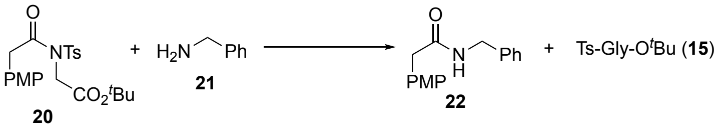


To a solution of **14** (158 mg, 0.31 mmol) in DMF 3 mL were added *i*-Pr_2NEt (0.11 mL, 0.63 mmol) and L-alanine *t*-butyl ester hydrochloride (114 mg, 0.63 mmol) at room temperature. After being stirred for 4 h at 65 °C, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (twice). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by automated silica gel flash chromatography (EtOAc/hexane = 20:80 to 80:20) to afford **15** (76.3 mg, 85%), and **11** (99.0 mg, 87%).

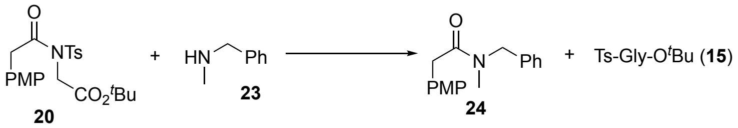
Scheme 3



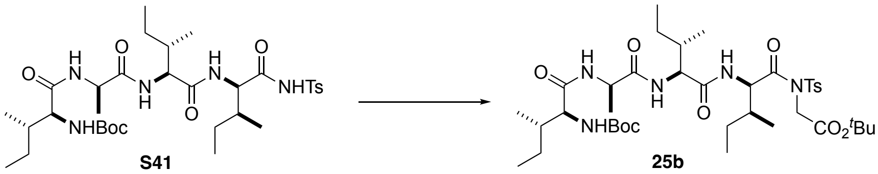
To a solution of **34** (CAS: 161184-90-3, 139 mg, 0.44 mmol) in DMF 2 mL were added *i*-Pr_2NEt (0.15 mL, 0.86 mmol) and **35** (0.13 mL, 0.89 mmol) at room temperature. After being stirred for 13.5 h at 50 °C, the reaction mixture was treated with 2% aqueous $KHSO_4$. The resulting solution was extracted with EtOAc (twice). The combined organic layer was washed with 2% aqueous $KHSO_4$, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane = 20:80) to afford **20** (180 mg, 96%) as a pale-yellow oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (d, 2H, J = 8.3 Hz), 7.34 (d, 2H, J = 8.3 Hz), 7.00 (d, 2H, J = 8.3 Hz), 6.80 (d, 2H, J = 9.0 Hz), 4.51 (s, 2H), 3.85 (s, 2H), 3.77 (s, 3H), 2.45 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.8, 167.6, 159.4, 145.8, 137.0, 131.2, 130.5, 128.9, 125.7, 114.6, 83.3, 55.9, 48.3, 42.2, 28.6, 22.3; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{22}H_{27}NNaO_6S^+$ 456.1451, found 456.1463.



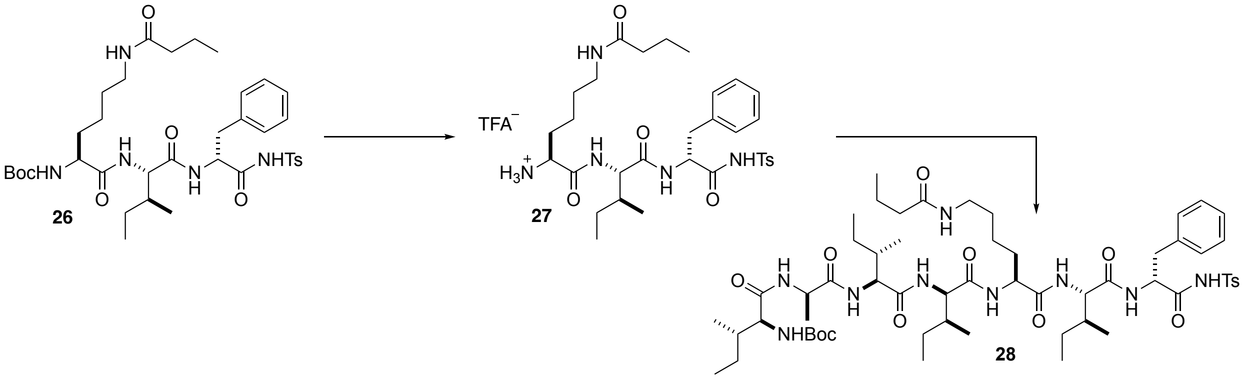
To a solution of **20** (95.0 mg, 0.219 mmol) in DMF 2.2 mL was added **21** (0.048 mL, 0.439 mmol) at room temperature. After being stirred for 90 min at 50 °C, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (twice). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by automated silica gel flash chromatography (EtOAc/hexane =10:90 to 90:10) to afford **22** (CAS:52532-96-4, 46.2 mg, 83%) and **15** (51.0 mg, 82%).



To a solution of **20** (100 mg, 0.231 mmol) in DMF 2.3 mL was added **23** (0.06 mL, 0.465 mmol) at room temperature. After being stirred for 19 h at 50 °C, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (twice). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by automated silica gel flash chromatography (EtOAc/hexane =10:90 to 80:20) to afford **24** (CAS: 135181-98-5, 55.2 mg, 89%), and **15** (58.2 mg, 88%).



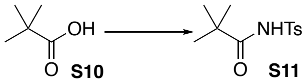
To a solution of **S41** (142 mg, 0.208 mmol) in DMF (1.0 mL) were added *i*-Pr_2NEt (0.040 mL, 0.235 mmol) and **35** (0.060 mL, 0.41 mmol) at room temperature. After being stirred for 16 h at 65 °C, the reaction mixture was treated with aqueous 2% $KHSO_4$. The resulting solution was extracted with EtOAc (twice). The combined organic layer was washed with aqueous 2% $KHSO_4$, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by automated silica gel flash chromatography (EtOAc/hexane = 3:97 to 70:30) to afford **25b**, which was immediately used in the next reaction.



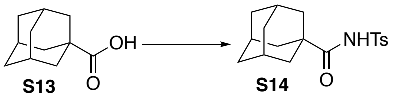
To a solution of **26** (53.9 mg, 0.0738 mmol) in CH_2Cl_2 (1 mL) was added TFA (1 mL) at room temperature. After being stirred for 1 h, the solution was concentrated and azeotroped with toluene (twice) to afford **27**, which was used in the next reaction without further purification.

To a solution of the above **25b** and **27** was added *i*-Pr_2NEt (25 μL, 0.147 mmol) in DMF (0.4 mL) at room temperature. After being stirred for 38 h at 65 °C, the reaction mixture was concentrated. The residue was purified by reversed-phase HPLC [COSMOSIL AR-II Φ20 × 250 mm, MeOH/H_2O/TFA (84/16/0.05), 15.2 mL/min, 40 °C] to afford recovered **25b** (56.7 mg, 0.0713 mmol) and **28** (37.3 mg, 0.0327 mmol, 44% for 2 steps) as a white powder: $[\alpha]_D^{20}$ –4.8 (*c* 0.50, MeOH); ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 12.36 (brs, 1H), 8.26 (d, 1H, *J* = 8.3 Hz), 8.04 (d, 1H, *J* = 7.6 Hz), 8.00 (d, 1H, *J* = 8.3 Hz), 7.88 (d, 1H, *J* = 8.9 Hz), 7.79 (d, 2H, *J* = 8.3 Hz), 7.75–7.66 (m, 3H), 7.41 (d, 2H, *J* = 8.3 Hz), 7.22–7.12 (m, 5H), 6.67 (d, 1H, *J* = 8.3 Hz), 4.55–4.47 (m, 1H), 4.43–4.32 (m, 3H), 4.30–4.23 (m, 1H), 4.10 (dd, 1H, *J* = 8.3, 6.2 Hz), 3.84 (t, 1H, *J* = 7.6 Hz), 3.04–2.86 (m, 3H), 2.57 (dd, 1H, *J* = 13.1, 11.0 Hz), 2.40 (s, 3H), 2.01 (t, 2H, *J* = 7.6 Hz), 1.81–1.70 (m, 2H), 1.70–1.60 (m, 1H), 1.59–0.97 (m, 30H), 0.86–0.70 (m, 24H), 0.58 (t, 3H, *J* = 6.9 Hz), 0.45 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (150 MHz, DMSO-*d*$_6$) δ 172.1, 171.7, 171.4, 171.14, 171.10. 170.9, 170.8, 170.3, 155.3, 144.3, 136.8, 136.2, 129.6, 129.1, 128.0, 127.5, 126.5, 78.0, 58.7, 56.8, 56.6, 55.3, 54.3, 52.0, 48.3, 40.1, 38.3, 37.4, 37.2, 37.1, 36.8, 36.6, 36.4, 31.0, 28.7, 28.1, 23.8, 23.7, 22.7, 21.1, 18.8, 18.7, 15.34, 15.31, 14.9, 14.5, 13.7, 11.5, 11.3, 11.1, 11.0; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{58}H_{93}N_9NaO_{12}S^+$ 1162.6557, found 1162.6556.

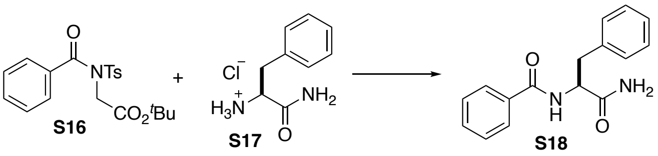
Scheme S5



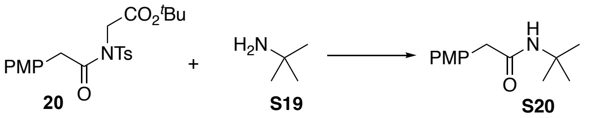
To a solution of **S10** (1.1 mL, 10 mmol) in THF 50 mL were added Et_3N (1.5 mL, 10.8 mmol) and TsNCO (1.6 mL, 10.5 mmol) at room temperature. After being stirred for 45 min, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with saturated aqueous NH_4Cl, dried over $MgSO_4$, filtered, and concentrated. The residue was recrystallized (EtOAc/hexane) to afford **S11** (CAS:81005-27-8, 2.34 g, 92%).



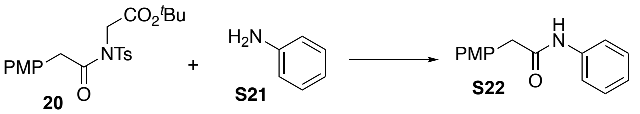
To a solution of **S13** (1.8 g, 10 mmol) in THF 50 mL were added Et_3N (1.5 mL, 10.8 mmol) and TsNCO (1.6 mL, 10.5 mmol) at room temperature. After being stirred for 60 min, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with saturated aqueous NH_4Cl, dried over $MgSO_4$, filtered, and concentrated. The residue was recrystallized (EtOAc/hexane) to afford **S14** (CAS:2130389-36-3, 2.84 g, 85%).



To a solution of **S16** (122 mg, 0.313 mmol) in DMF 3.1 mL were added *i*-Pr_2NEt (0.11 mL, 0.63 mmol) and **S17** (126 mg, 0.627 mmol) at room temperature. After being stirred for 13 h at 65 °C and 24 h at 80 °C, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (twice). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane = 5:95 to 100:0) to afford **S18** (CAS: 72150-35-7, 56.3 mg, 67%) and **15** (57.4 mg, 64%).

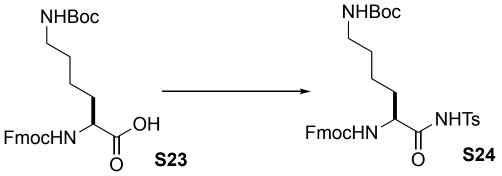


To a solution of **20** (120 mg, 0.277 mmol) in DMF 2.8 mL was added **S19** (0.060 mL, 0.57 mmol) at room temperature. After being stirred for 21 h at 65 °C, the reaction mixture was treated with 2% aqueous $KHSO_4$. The resulting solution was extracted with EtOAc (twice). The combined organic layer was washed with 2% aqueous $KHSO_4$, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by automated silica gel flash chromatography (EtOAc/hexane =5:95 to 40:60) to afford **S20** (CAS: 330467-50-5, 38.7 mg, 63%) and **15** (44.2 mg, 56%).

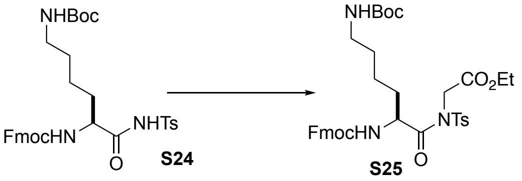


To a solution of **20** (68.3 mg, 0.154 mmol) in DMF 1.5 mL were added **S21** (0.03 mL, 0.3 mmol) and DMAP (1.9 mg, 0.015 mmol) at room temperature. After being stirred for 15 h at 65 °C, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with 1 M HCl, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane =15:85 to 20:80) to afford **S22** (CAS: 85274-97-1, 30.1 mg, 81%) and **15** (37.6 mg, 86%).

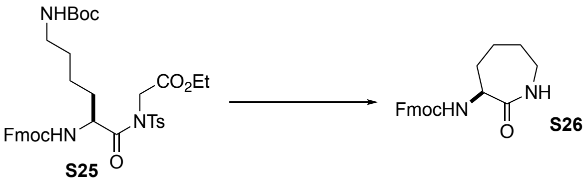
Scheme S6



To a solution of **S23** (470 mg, 1.00 mmol) in THF 5 mL were added Et_3N (0.17 mL, 1.2 mmol) and TsNCO (0.17 mL, 1.1 mmol) at room temperature. After being stirred for 30 min, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with saturated aqueous NH_4Cl, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography ($MeOH/CHCl_3$ = 0.5:99.5 to 5:95) to afford **S24** (620 mg, 99%) as a white foam: $[\alpha]_D^{20}$ –6.9 (*c* 1.00, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 9.96 (s, 1H), 7.89 (d, 2H, *J* = 8.4 Hz), 7.76 (d, 2H, *J* = 7.8 Hz), 7.56 (t, 2H, *J* = 7.8 Hz), 7.39 (t, 2H, *J* = 7.2 Hz), 7.33–7.22 (m, 4H), 5.57 (d, 1H, *J* = 7.8 Hz), 4.69 (s, 1H), 4.45–4.30 (m, 2H), 4.23–4.10 (m, 2H), 3.17–2.97 (m, 2H), 2.45–2.31 (m, 3H), 1.85 (s, 2H), 1.65–1.53 (m, 1H), 1.43 (s, 9H), 1.36–1.22 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ170.3, 156.8, 156.7, 145.2, 143.8, 143.6, 141.4, 135.7, 129.7, 128.5, 127.9, 127.3, 125.2, 120.1, 79.8, 67.6, 54.9, 47.1, 39.4, 30.8, 29.3, 28.6, 22.1, 21.8; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{33}H_{39}N_3NaO_7S^+$ 644.2401, found 644.2401.

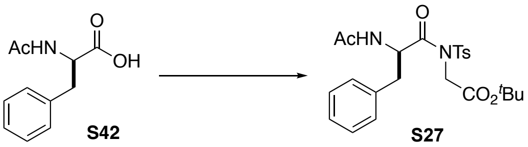


To a solution of **S24** (62.2 mg, 0.100 mmol) in DMF 1 mL were added *i*-Pr_2NEt (0.021 mL, 0.12 mmol) and **7** (0.022 mL, 0.2 mmol) at room temperature. After being stirred for 15.5 h at 50 °C, the reaction mixture was treated with 2% aqueous $KHSO_4$. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with 2% aqueous $KHSO_4$, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane = 20:80 to 100:0) to afford **S25** (108 mg, 76%) as a pale-yellow oil: $[\alpha]_D^{20}$ –15.0 (*c* 1.00, $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$) δ 7.94 (d, 2H, *J* = 8.4 Hz), 7.76 (d, 2H, *J* = 7.2 Hz), 7.57 (t, 2H, *J* = 8.1 Hz), 7.43–7.28 (m, 6H), 5.40 (d, 2H, *J* = 7.2 Hz), 4.66 (s, 1H), 4.53 (d, 1H, *J* = 17.4 Hz), 4.44–4.29 (m, 3H), 4.21–4.14 (m, 3H), 3.12 (d, 2H, *J* = 4.2 Hz), 2.39 (s, 3H), 1.95 (s, 1H), 1.67–1.8 (m, 5H), 1.43 (s, 9H), 1.24 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.8, 167.6, 156.2, 156.2, 145.7, 143.9, 143.8, 141.4, 135.5, 130.1, 128.2, 127.9, 127.2, 125.2, 120.1, 79.2, 67.3, 62.0, 54.4, 47.2, 46.9, 40.1, 33.3, 29.5, 28.6, 22.6, 21.8, 14.2; HRMS (ESI) m/z: [M+Na]$^+$ calcd for $C_{37}H_{45}N_3NaO_9S^+$ 730.2769, found 730.2770.

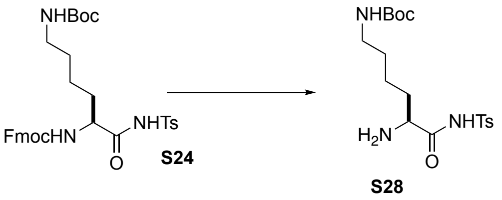


To a solution of **S25** (111 mg, 0.139 mmol) in CH_2Cl_2 1 mL was added TFA 1 mL at room temperature. After being stirred for 1 h, the reaction mixture was concentrated. The residue was azeotroped with toluene (twice) to afford crude amine, which was used in the next reaction without further purification.

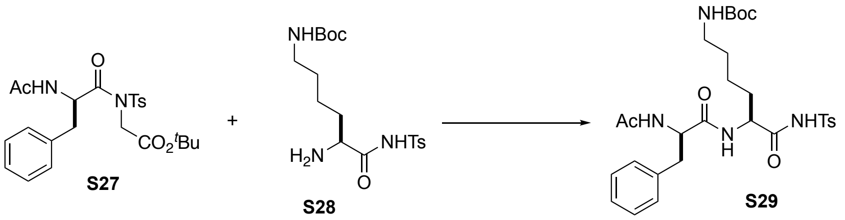
To the solution of the above amine in DMF 5 mL was added *i*-Pr_2NEt (0.032 mL, 0.13 mmol) at room temperature. After being stirred for 2 h, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by automated silica gel flash chromatography (EtOAc/$CHCl_3$ = 5:95 to 60:40) to afford **9** (24.6 mg, 83%) and **S26** (CAS: 181181-94-2, 37.8 mg, 94%).



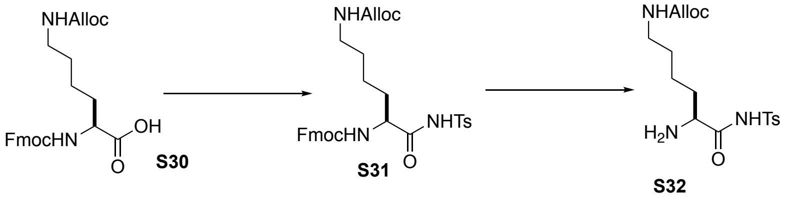
To a solution of **S42** (51.0 mg, 0.246 mmol) in DMF 2.5 mL were added *i*-Pr_2NEt (0.050 mL, 0.29 mmol) and TsNCO (0.045 mL, 0.30 mmol) at room temperature. After being stirred for 15 min, the reaction mixture was added *i*-Pr_2NEt (0.050 mL, 0.29 mmol) and **35** (0.072 mL, 0.49 mmol) at room temperature. After being stirred for 15.5 h at 65 °C, the reaction mixture was treated with 2% aqueous $KHSO_4$. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with 2% aqueous $KHSO_4$, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane = 30:70 to 100:0) to afford **S27** (79.1 mg, 68%) as a pale-yellow oil: $[\alpha]_D^{20}$ +7.2 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.98 (d, 2H, *J* = 8.3 Hz), 7.36 (d, 2H, *J* = 7.6 Hz), 7.32–7.15 (m, 5H), 5.83 (d, 1H, *J* = 8.3 Hz), 4.46–4.21 (m, 2H), 3.37 (d, 1H, *J* = 12.4 Hz), 2.83 (dd, 1H, *J* = 8.3 Hz, 13.8 Hz), 2.44 (s, 3H), 1.85 (s, 3H), 1.45 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.7, 169.6, 166.5, 145.4, 135.7, 135.5, 129.8, 129.4, 128.5, 128.4, 127.1, 82.8, 53.2, 47.5, 38.7, 27.9, 22.9, 21.7; HRMS (ESI) *m/z*: [M+Na]$^+$ calcd for $C_{24}H_{30}N_2NaO_6S^+$ 497.1717, found 497.1712.



To a solution of **S24** (354 mg, 0.569 mmol) in MeOH 3 mL was added Et_2NH (0.59 mL, 5.7 mmol) at room temperature. After being stirred for 19 h, the reaction mixture was concentrated and purified by silica gel column chromatography ($MeOH/CHCl_3/Et_3N$ = 5:95:0.5 to 50:50:0.5) to afford **S28** (211 mg, 93%) as a white amorphous: $[\alpha]_D^{20}$ +18.9 (*c* 0.10, MeOH); ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 7.71–7.65 (m, 4H), 7.18 (d, 2H, *J* = 7.6 Hz), 6.73 (t, 1H, *J* = 5.5 Hz), 3.30 (dt, 1H, *J* = 6.5, 5.2 Hz), 2.82 (dt, 2H, *J* = 6.9, 6.9 Hz), 2.31 (s, 3H), 1.70–1.61 (m, 1H), 1.60–1.54 (m, 1H), 1.37 (s, 9H), 1.29–1.27 (m, 2H), 1.24–1.15 (m, 1H), 1.13–1.08 (m, 1H); ^{13}C NMR (150 MHz, DMSO-*d*$_6$) δ 172.1, 155.6, 142.7, 139.8, 128.1, 127.0, 77.4, 54.7, 30.9, 29.2, 28.3, 21.7, 20.9; HRMS (ESI) *m/z*: $[M+Na]^+$ calcd. for $C_{18}H_{29}N_3NaO_5S^+$ 422.1720, found 422.1715.

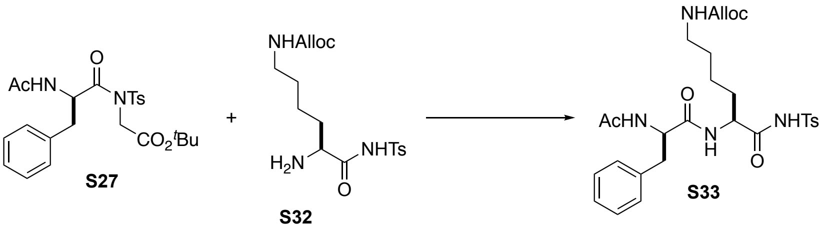


To a solution of **S28** (141 mg, 0.352 mmol) in DMF 3.5 mL were added *i*-Pr_2NEt (0.12 mL, 0.13 mmol) and **S27** (334 mg, 0.704 mmol) at room temperature. After being stirred for 18 h at 65 °C, the reaction mixture was treated with 2% aqueous $KHSO_4$. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with 2% aqueous $KHSO_4$, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (1st: $MeOH/CHCl_3$ = 1:99 to 8:92; 2nd: EtOAc/hexane = 30:70 to 60:40) to afford **S27** (109 mg, 65% recovered), **15** (95.0 mg, 95%), and **S29** (199 mg, 96%) as a white foam: $[\alpha]_D^{20}$ –35.4 (*c* 1.00, MeOH); ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 12.08 (s, 1H), 8.22 (d, 1H, *J* = 8.4 Hz), 8.08 (d, 1H, *J* = 7.8 Hz), 7.82 (d, 2H, *J* = 8.4 Hz), 7.41 (d, 2H, *J* = 8.4 Hz), 7.25–7.14 (m, 5H), 6.72 (t, 1H, *J* = 5.4 Hz), 4.59–4.52 (m, 1H), 4.17–4.10 (m, 1H), 2.88–2.69 (m, 4H), 2.39 (s, 3H), 1.75 (s, 3H), 1.47–1.28 (m, 2H), 1.36 (s, 9H), 1.26–1.16 (m, 2H), 0.95–0.87 (m, 2H); ^{13}C NMR (150 MHz, DMSO-*d*$_6$) δ 171.3, 170.9, 169.0, 155.5, 144.3, 137.6, 136.3, 129.6, 129.2, 128.0, 127.5, 126.3, 77.4, 53.7, 52.6, 40.1, 38.3, 30.8, 28.9, 28.3, 22.4, 22.2, 21.1; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{29}H_{40}N_4NaO_7S^+$ 611.2510, found 611.2508.

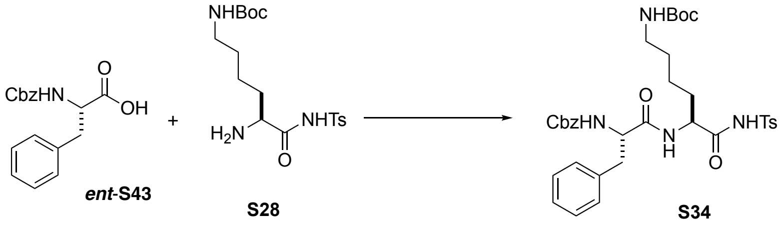


To a solution of **S30** (1.36 g, 3.00 mmol) in THF 15 mL were added Et_3N (0.50 mL, 3.6 mmol) and TsNCO (0.50 mL, 3.3 mmol) at room temperature. After being stirred for 60 min, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with saturated aqueous NH_4Cl, dried over $MgSO_4$, filtered, and concentrated. The residue was roughly purified by silica gel column chromatography (MeOH/$CHCl_3$ = 0.5:99.5 to 5:95) to afford crude **S31**, which was used in the next reaction without further purification.

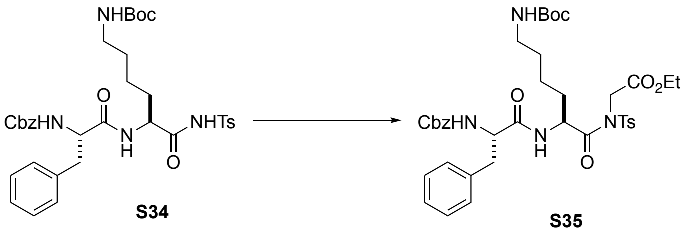
To a solution of the above **S31** in MeOH 30 mL was added Et_2N (3.1 mL, 30 mmol) at room temperature. After being stirred for 13.5 h, the reaction mixture was concentrated. The residue was recrystallized (MeOH/Et_2O) to afford **S32** (1.00 g, 87% for 2 steps) as a white amorphous: $[\alpha]_D^{20}$ +16.3 (*c* 0.50, MeOH); ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.66 (d, 4H, *J* = 6.6 Hz), 7.18 (d, 2H, *J* = 7.8 Hz), 7.16–7.10 (m, 1H), 5.96–5.86 (m, 1H), 5.27 (d, 1H, *J* = 17.4 Hz), 5.16 (d, 1H, *J* = 10.2 Hz), 4.45 (d, 2H, *J* = 5.4 Hz), 3.39–3.29 (m, 2H), 2.92–2.86 (m, 2H), 2.31 (s, 3H), 1.71–1.63 (m, 1H), 1.62–1.54 (m, 1H), 1.37–1.28 (m, 2H), 1.27–1.18 (m, 1H), 1.17–1.07 (m, 1 H); ^{13}C NMR (150 MHz, DMSO-d_6) δ172.0, 155.9, 142.7, 139.8, 133.9, 128.0, 127.0, 116.9, 64.2, 54.7, 40.1, 30.9, 29.2, 21.6, 20.9; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{26}N_3O_5S^+$ 384.1588, found 384.1587.



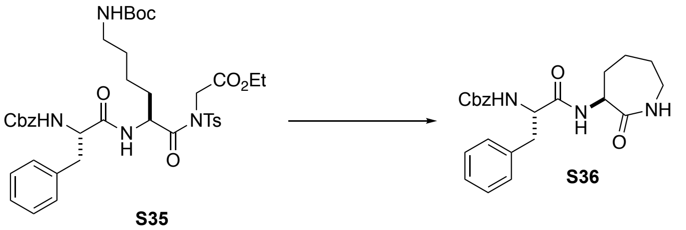
To a solution of **S32** (43.3 mg, 0.113 mmol) in DMF 1.1 mL were added *i*-Pr_2NEt (0.040 mL, 0.22 mmol) and **S27** (107 mg, 0.226 mmol) at room temperature. After being stirred for 15 h at 65 °C, the reaction mixture was treated with 2% aqueous $KHSO_4$. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with 2% aqueous $KHSO_4$, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (1st: MeOH/$CHCl_3$ = 1:99 to 30:70; 2nd: EtOAc/hexane = 30:70 to 50:50) to afford **S27** (32.9 mg, 61% recovered), **15** (27.4 mg, 85%), and **S33** (62.3 mg, 96%) as a white foam: $[\alpha]_D^{20}$ –33.9 (*c* 0.67, MeOH); ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.10 (s, 1H), 8.09 (d, 2H, *J* = 7.8 Hz), 7.76 (d, 2H, *J* = 8.4 Hz), 7.39 (d, 2H, *J* = 8.4 Hz), 7.26–7.11 (m, 6H), 5.92–5.83 (m, 1H), 5.25 (dd, 1H, *J* = 17.4, 1.8 Hz), 5.15 (d, 1H, *J* = 10.2 Hz), 4.57–4.51 (m, 1H), 4.43 (d, 2H, *J* = 5.4 Hz), 4.15–4.08 (m, 1H), 2.90–2.80 (m, 3H), 2.74–2.68 (m, 1H), 2.38 (s, 3H), 1.75 (s, 3H), 1.47–1.39 (m, 1H), 1.38–1.29 (m, 1H), 1.28–1.19 (m, 2H), 0.96–0.88 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ171.2, 169.0, 155.9, 137.7, 133.9, 129.4, 129.2, 128.0, 127.5, 126.2, 116.9, 64.1, 53.8, 52.7, 40.1, 38.2, 30.9, 28.9, 22.4, 22.1, 21.1; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{28}H_{37}N_4O_7S^+$ 573.2377, found 573.2377.



To a solution of ***ent*-S43** (165 mg, 0.412 mmol) in THF (2 mL) were added NMM (0.05 mL, 0.455 mmol) and isobutyl chloroformate (0.06 mL, 0.456 mmol) at 0 °C. After being stirred for 15 min, the mixture was treated with the solution of the above **S28** in DMF (2 mL). After being stirred for 18 h at room temperature, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NH_4Cl, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$ = 2:98) to afford **S34** (226 mg, 81%) as a white amorphous: $[\alpha]_D^{20}$ –11.6 (*c* 1.0, MeOH); ^{1}H NMR (600 MHz, DMSO-d_6) δ 12.23 (s, 1H), 8.19 (d, 1H, *J* = 6.9 Hz), 7.79 (d, 2H, *J* = 8.3 Hz), 7.46 (d, 1H, *J* = 9.0 Hz), 7.42 (d, 2H, *J* = 7.6 Hz), 7.33–7.18 (m, 10H), 6.76 (s, 1H), 4.92 (s, 2H), 4.26–4.19 (m, 2H), 2.90 (dd, 1H, *J* = 13.4, 3.1 Hz), 2.83–2.78 (m, 2H), 2.64 (t, 1H, *J* = 12.7 Hz), 2.38 (s, 3H), 1.54 (t, 1H, *J* = 6.5 Hz), 1.46–1.42 (m, 1H), 1.37 (s, 9H), 1.31–1.25 (m, 2H), 1.14–1.08 (m, 2H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 171.8, 170.9, 155.8, 155.5, 144.3, 138.0, 137.0, 136.3, 129.5, 129.2, 128.3, 128.0, 127.7, 127.5, 127.4, 126.8, 126.2, 77.4, 65.2, 55.7, 52.9, 37.3, 30.7, 29.1, 28.3, 22.5, 21.1; HRMS (ESI) *m/z*: [M+Na]$^+$ calcd. for $C_{35}H_{44}N_4NaO_8S^+$ 703.2772, found 703.2781.



To a solution of **S34** (139 mg, 0.205 mmol) in DMF 1 mL were added *i*-Pr_2NEt (0.07 mL, 0.412 mmol) and ethyl bromoacetate (**7**) (0.05 mL, 0.452 mmol) at room temperature. After being stirred for 19.5 h at 50 °C, the reaction mixture was treated with 2% aqueous $KHSO_4$. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with 2% aqueous $KHSO_4$, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by automated silica gel flash chromatography (EtOAc/hexane = 5:95 to 60:40) to afford **S35** (121 mg, 76%) as a pale-yellow oil: $[\alpha]_D^{20}$ –17.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (d, 2H, *J* = 8.3 Hz), 7.37 (d, 2H, *J* = 8.3 Hz), 7.34–7.29 (m, 5H), 7.18 (d, 3H, *J* = 5.5 Hz), 7.08 (t, 2H, *J* = 3.8 Hz), 6.46 (brs, 1H), 5.42 (brs, 1H), 5.07 (d, 2H, *J* = 13.1 Hz), 4.83 (brs, 1H), 4.49 (d, 1H, *J* = 17.2 Hz), 4.41 (brs, 1H), 4.17 (q, 2H, *J* = 7.1 Hz), 3.04–3.01 (m, 4H), 2.44 (s, 3H), 1.86 (brs, 1H), 1.52–1.35 (m, 12H), 1.29–1.23 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 1 172.6, 170.8, 167.5, 156.0, 155.9, 145.5, 136.1, 135.4, 130.0, 129.3, 128.6, 128.5, 128.2, 128.1, 126.9, 79.0, 67.0, 61.8, 55.9, 52.2, 46.6, 39.9, 38.2, 32.9, 29.0, 28.4, 22.3, 21.7, 14.0; HRMS (ESI) *m/z*: [M+Na]$^+$ calcd. for $C_{39}H_{50}N_4NaO_{10}S^+$ 789.3140, found 789.3143.

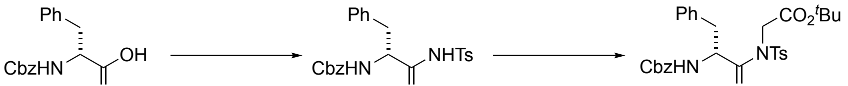


S35 **S36**

To a solution of **S35** (41.1 mg, 0.0535 mmol) in CH_2Cl_2 (1 mL) was added TFA (1 mL) at room temperature. After being stirred for 1 h, the solution was concentrated and azeotroped with toluene (× 2) to afford crude amine, which was used in the next reaction without further purification.

To the solution of the above amine in DMF (5 mL) was added *i*-Pr_2NEt (10 µL, 0.0588 mmol) at room temperature. After being stirred for 18.5 h at room temperature, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with saturated aqueous NH_4Cl, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by automated silica gel flash chromatography (EtOAc/hexane = 3:97 to 100:0) to afford **9** (10.1 mg, 73%) and **S36** (76.3 mg, 87%) as a white foam: $[\alpha]_D^{20}$ +15.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37–7.15 (m, 10H), 6.30 (s, 1H), 5.45 (s, 1H), 5.08 (d, 1H, *J* = 12.4 Hz), 5.03 (d, 1H, *J* = 12.4 Hz), 4.56 (s, 1H), 4.43 (q, 1H, *J* = 5.5 Hz), 3.27–3.18 (m, 2H), 3.07 (dd, 2H, *J* = 21.7, 15.5 Hz), 2.05 (d, 1H, *J* = 11.0 Hz), 1.98 (d, 1H, *J* = 14.5 Hz), 1.80 (q, 2H, *J* = 13.5 Hz), 1.45–1.31 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 175.6, 170.7, 156.4, 136.9, 130.0, 129.2, 129.2, 128.8, 128.6, 127.6, 67.6, 56.5, 53.0, 42.7, 39.5, 32.0, 29.5, 28.5; HRMS (ESI) *m/z*: [M+Na]$^+$ calcd. for $C_{23}H_{27}N_3NaO_4S^+$ 432.1894, found 432.1898.

Scheme S7

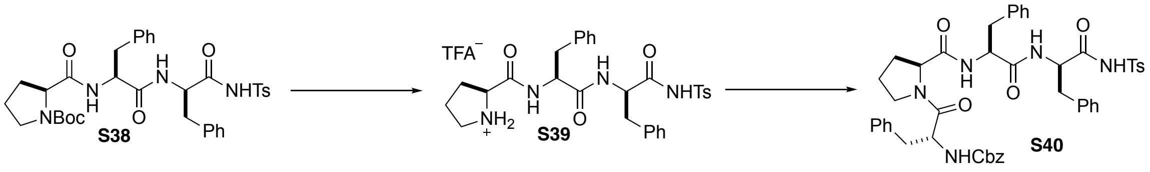


***ent*-S43** **S44** **S37b**

To a solution of Cbz-D-Phe-OH (**S43**) (307 mg, 1.03 mmol) in DMF 5 mL were added *i*-Pr_2NEt (0.18 mL, 1.24 mmol) and TsNCO (0.19 mL, 1.24 mmol) at room temperature. After being stirred for 50 min, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The residue was roughly purified by silica gel column chromatography (MeOH/$CHCl_3$ = 0:100 to 5:95) to afford **S44**, which was used in the next reaction without further purification.

To a solution of the above **S44** in DMF 5 mL were added *i*-Pr_2NEt (0.34 mL, 2.0 mmol) and **35** (0.34 mL, 2.3 mmol) at room temperature. After being stirred for 25 h at 65 °C, the reaction mixture was treated with 2%

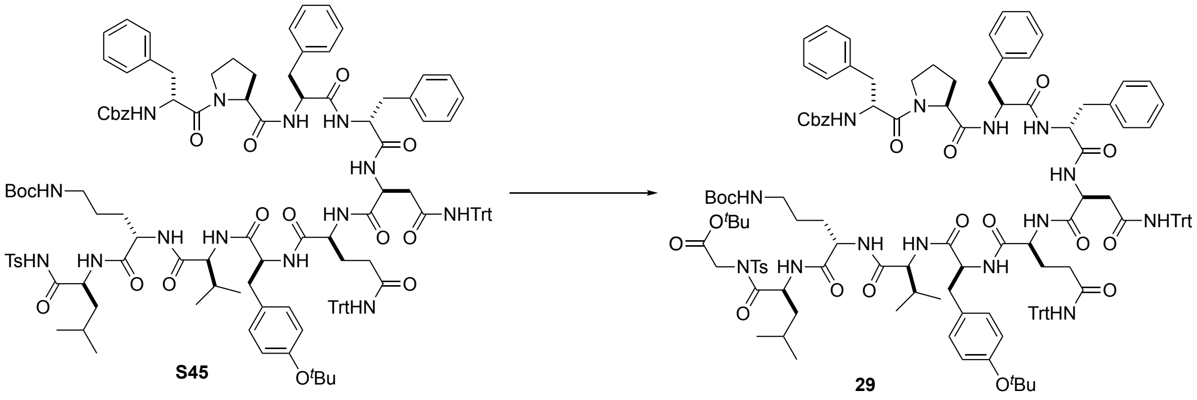
aqueous $KHSO_4$. The resulting solution was extracted with EtOAc (twice). The combined organic layer was washed with 2% aqueous $KHSO_4$, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane = 20:80) to afford **S37b** (484 mg, 85%, 2 steps) as a white foam: $[\alpha]_D^{20}$ +28.5 (*c* 1.00, $CHCl_3$);^{1}H NMR (600 MHz, $CDCl_3$) δ 7.96 (d, 2H, *J* = 6.9 Hz), 7.35–7.22 (m, 12H), 5.44 (brs, 1H), 5.20 (d, 1H, *J* = 8.3 Hz), 5.00 (d, 1H, *J* = 12.4 Hz), 4.95 (d, 1H, *J* = 12.4 Hz), 4.40 (d, 1H, *J* = 17.2 Hz), 4.30 (d, 1H, *J* = 17.9 Hz), 3.37 (dd, 1H, *J* = 13.8, 4.1 Hz), 2.80 (dd, 1H, *J* = 13.4, 8.6 Hz), 2.44 (s, 3H), 1.44 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.2, 167.7, 156.9, 146.6, 137.6, 137.1, 137.0, 131.3, 130.9, 129.9, 129.82, 129.79, 129.6, 129.4, 129.2, 128.4, 84.1, 68.2, 56.6, 48.9, 40.7, 29.3, 23.0: HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{31}H_{25}F_5N_2NaO_5S^+$ 589.1979, found 589.1988.



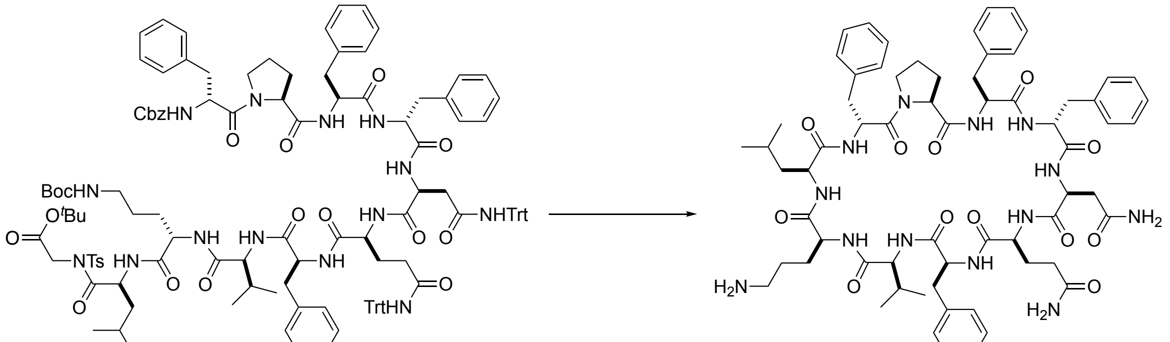
To the solution of **S38** (55.3 mg, 0.083 mmol) in CH_2Cl_2 1 mL was added TFA 1 mL at room temperature. After being stirred for 1 h, the reaction mixture was concentrated. The residue was azeotroped with toluene (twice) to give **S39**, which was used in the next reaction without further purification.

To a solution of the above **S39** and **S37b** (91.1 mg, 0.16 mmol) were added *i*-Pr_2NEt (0.015 mL, 0.086 mmol) and DMAP (5.6 mg, 0.046 mmol) in DMF 0.8 mL at room temperature. After being stirred for 18 h at 65 °C, and 6 h at 80 °C, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography ($MeOH/CHCl_3$ = 0:100 to 2:98) to afford **15** (33.3 mg, 141%) and **S40** (65.8 mg, 94% for 2 steps) a white foam: $[\alpha]_D^{20}$ –39.1 (*c* 1.00, MeOH); ^{1}H NMR (600 MHz, CD_3CN) δ 10.1 (brs, 1H), 7.81 (d, 2H, *J* = 7.6 Hz), 7.46 (t, 1H, *J* = 6.9 Hz), 7.36–7.08 (m, 22H), 6.41 (brs, 1H), 5.13 (d, 1H, *J* = 12.4 Hz), 4.97 (d, 1H, *J* = 12.4 Hz), 4.47–4.37 (m, 2H), 4.29 (brs, 1H), 4.11 (brs, 1H), 3.55 (brs, 1H), 3.19 (d, 1H, *J* = 14.1 Hz), 3.13–2.87 (m, 5H), 2.77 (t, 1H, *J* = 13.7 Hz), 2.35 (s, 3H), 1.81–1.71 (m, 1H), 1.50 (brs, 2H), 1.35 (brs, 1H); ^{13}C NMR (150 MHz, CD_3CN) δ 173.3, 172.6, 172.1, 170.9, 158.0, 146.0, 139.1, 137.6, 137.6, 137.5, 137.3, 136.9, 130.4, 129.9, 129.4, 129.3, 129.2, 129.0, 128.9, 128.7, 127.9, 127.6, 127.4, 67.8, 62.2, 57.0, 55.9, 55.6, 48.4, 37.8, 36.9, 29.7, 24.8, 21.5; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{47}H_{49}N_5O_8S^+$ 844.3375, found 844.3350.

Scheme 4



To a solution of **S45** (37.0 mg, 0.0167 mmol) in DMF 0.8 mL were added *i*-Pr_2NEt (0.028 mL, 0.16 mmol) and **35** (0.025 mL, 0.17 mmol) at room temperature. After being stirred for 18.5 h at 65 °C, to the solution were added *i*-Pr_2NEt (0.014 mL, 0.084 mmol) and **35** (0.013 mL, 0.065 mmol). After being stirred for 26 h at 65 °C, the mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with saturated aqueous NH_4Cl, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by reversed-phase HPLC [COSMOSIL AR-II Φ 10 × 250 mm, $MeCN/H_2O/TFA$ (= 92:8:0.05), 19 mL/min, 40 °C] to afford **29** (17.6 mg, 45%) and **S45** (12.9 mg, 35% recovered). After confirmation of its purity and structure by HPLC, ^1H NMR, and HRMS, the reactive intermediate **29** was immediately used in the next reaction. HPLC (Figure S6); ^1H NMR (Figure S52); HRMS *m/z*: $[M+2Na]^{2+}$ calcd for $C_{134}H_{156}N_{14}Na_2O_{21}S^+$ 1187.5558, found 1187.5595.

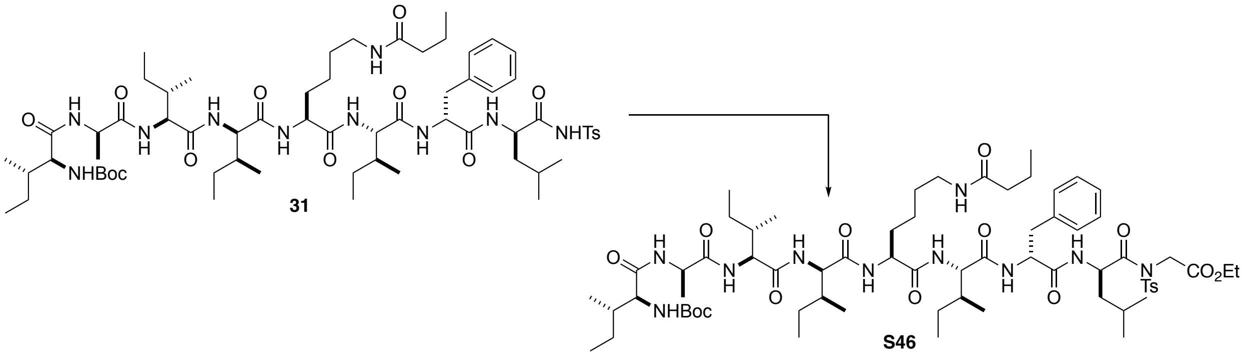


To a solution of **29** (6.02 mg, 2.58 μmol) in THF/AcOH (= 20:1) 1 mL under N_2 was added $Pd(OH)_2/C$ (10 mg) at room temperature. The reaction mixture was exposed to an atmosphere of H_2. After being stirred for 6 h, the reaction mixture was filtered through a membrane filter (SHIMADZU, TORAST^{TM} DISC, PTFE 0.22 μm). The filtrate was concentrated. The residue was azeotroped with toluene (three times), and then used in the next reaction without further purification.

To the solution of the above crude peptide in DMF 2.6 mL was added *i*-Pr_2NEt (4.4 μL, 26 μmol) at room temperature. After being stirred for 15 h at 65 °C, the reaction mixture was concentrated. The residue was azeotroped with toluene (three times) to afford a crude peptide, which was used in the next reaction without further purification.

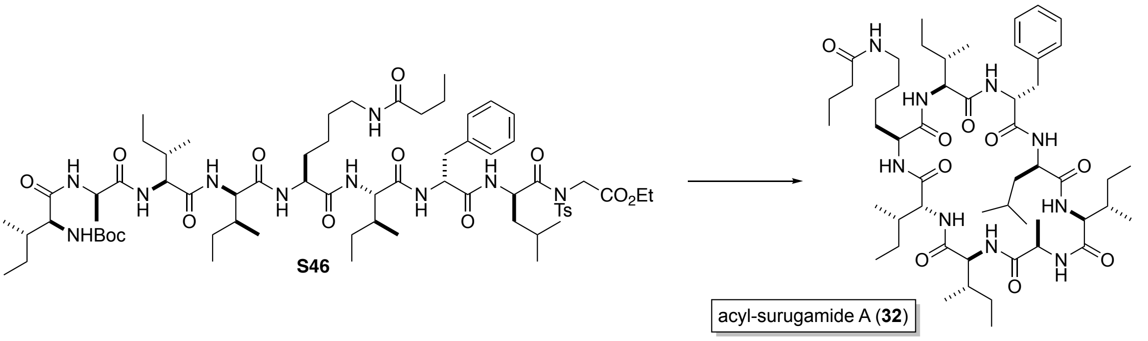
To the above crude peptide was added a solution of TFA/*i*-Pr_3SiH/H_2O (= 90:5:5, 2 mL) at room temperature. After being stirred for 2 h, the reaction mixture was concentrated. The residue was purified by reversed-phase HPLC [COSMOSIL AR-II Φ 20 × 250 mm, $MeCN/H_2O/TFA$ (= 50:50:0.05), 19 mL/min, 40 °C] to afford **30** (3.1 mg, 93%): ^1H NMR (600 MHz, DMSO-d_6) see Figure S53; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{66}H_{87}N_{13}O_{13}^+$ 1270.6619, found 1270.6631. The data were consistent with those of reported.

Scheme 5



To a solution of **31** (38.8 mg, 0.0309 mmol) in DMF 1 mL were added *i*-Pr_2NEt (0.026 mL, 0.15 mmol) and **7** (0.034 mL, 0.31 mmol) at room temperature. After being stirred for 15 h at 65 °C, the reaction mixture was treated with 2% aqueous $KHSO_4$. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with 2% aqueous $KHSO_4$, dried over $MgSO_4$, filtered, and concentrated.

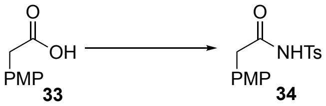
The residue was purified by silica gel column chromatography ($MeOH/CHCl_3$ = 1:99 to 5:95) to afford **S46** (38.4 mg, 93%). After confirmation of its purity and structure by ^1H NMR and HRMS, the reactive intermediate **S46** was immediately used in the next reaction. ^1H NMR (Figure S54); HRMS *m/z*: $[M+Na]^+$ calcd for $C_{68}H_{110}N_{10}NaO_{15}S^+$ 1361.7765, found 1361.7763.



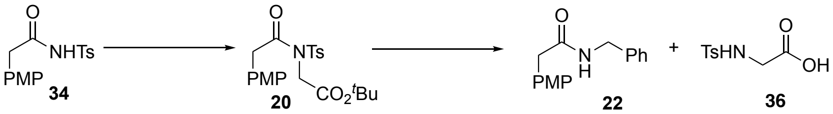
To a solution of **S46** (14.8 mg, 0.0110 mmol) in CH_2Cl_2 1 mL was added TFA 1 mL at room temperature. After being stirred for 1 h, the reaction mixture was concentrated. The residue was azeotroped with toluene (twice) to afford crude amine, which was used in the next reaction without further purification.

To the solution of the above amine in DMF 11 mL was added *i*-Pr_2NEt (0.004 mL, 0.02 mmol) at room temperature. After being stirred at 65 °C for 14 h, the reaction mixture was concentrated and azeotroped with toluene (twice) to afford crude **32**. The crude **32** was purified by reversed-phase HPLC [COSMOSIL π-NAP Φ 10 × 250 mm,1-PrOH/H_2O/TFA (= 55:45:0.05), 2.35 mL/min, 45 °C] to afford **32** (9.8 mg, 91%): ^{1}H NMR (600 MHz, DMSO-d_6) see Figure S55; HRMS (ESI) *m/z*: $[M+H]^+$ calcd for $C_{52}H_{87}N_9NaO_9^+$ 1004.6519, found 1004.6510. The data were consistent with those of reported.

Scheme 6



To a solution of **33** (333 mg, 2.0 mmol) in THF 10 mL were added Et_3N (0.29 mL, 2.1 mmol) and TsNCO (0.32 mL, 2.1 mmol) at room temperature. After being stirred for 60 min, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was recrystallized (EtOAc/hexane) to afford **34** (CAS: 161184-90-3, 570 mg, 89%).

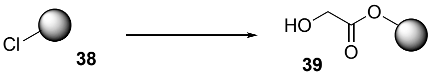


To a solution of **34** (313 mg, 0.98 mmol) in DMF 3 mL were added *i*-Pr_2NEt (0.32 mL, 1.9 mmol) and **35** (0.27 mL, 1.80 mmol) at room temperature. After being stirred for 18.5 h at 50 °C, the reaction mixture was treated with 2% aqueous $KHSO_4$. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with 2% aqueous $KHSO_4$, dried over $MgSO_4$, filtered, and concentrated to give **20**, which was used in the next reaction without further purification.

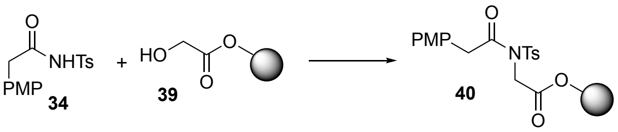
To a solution of the above **20** (0.98 mmol) in DMF 9.8 mL was added benzyl amine (0.21 mL, 1.92 mmol) at room temperature. After being stirred for 2.5 h at 50 °C, the reaction mixture was treared with 0.2 M aqueous HCl. The resulting solution was extracted with EtOAc. The combined organic layer was washed with 0.2 M aqueous HCl, dried over $MgSO_4$, filtered, and concentrated. to give the crude mixture of **22** and **15**, which was used in the next reaction without further purification.

To a solution of the above crude mixture of **22** and **15** in CH_2Cl_2 (6 mL) were added TFA (3 mL), H_2O (1 mL) at room temperature. After being stirred for 1.5 h, the solution was concentrated and treated with 0.2 M aqueous NaOH (to pH 9). The resulting solution was extracted with EtOAc. The combined organic layer was washed with saturated aqueous 0.2 M aqueous NaOH, dried over $MgSO_4$, filtered, and concentrated. The residue was recrystallized (CH_2Cl_2/hexane) to afford **22** (CAS: 52532-96-4, 152 mg, 61% for 3 steps).

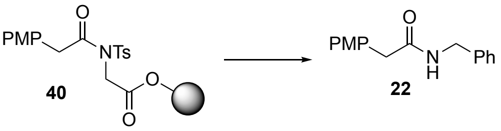
The above aqueous layer was treated with 4 M aqueous HCl aq (to pH 1). The resulting solution was extracted with EtOAc (twice). The combined organic layer was washed with saturated aqueous satisfied aqueous NH_4Cl, dried over $MgSO_4$, filtered, and concentrated. The residue was recrystallized (EtOAc/hexane) to afford **36** (CAS: 1080-44-0, 142 mg, 63% for 3 steps).



To Merrifield resin (2.0 mmol/g, 601 mg, 1.2 mmol) were added DMF (20 mL), glycolic acid (185 mg, 2.4 mmol), Cs_2CO_3 (780 mg, 2.4 mmol), and KI (40 mg, 0.24 mmol). After being stirred overnight at 50 °C, the reaction mixture was filtered. The resin was washed with DMF/H_2O (= 4:1, × 3), MeOH (× 5) and CH_2Cl_2 (× 3) to afford **39**.

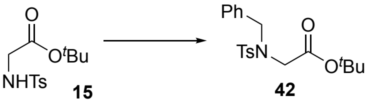


To **39** in Agilent Bond Elut Reservoir (20 mL tube) were added **34** (256 mg, 0.801 mmol), PPh_3 (320 mg, 1.22 mmol), THF (8 mL), and DEAD (2.2 M in toluene, 0.55 mL, 1.2 mmol, dropwise). After shaking 6 h at room temperature, the reaction mixture was filtered. The resin was washed with CH_2Cl_2 (× 3) and DMF (× 3) to afford **40**.

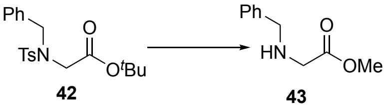


To the above **40** in Agilent Bond Elut Reservoir (20 mL tube) were added DMF (8 mL) and **21** (0.11 mL, 1.0 mmol). After shaking overnight at room temperature, the reaction mixture was filtered. The resin was washed with CH_2Cl_2 (× 3). The filtrate was washed with 1 M HCl/brine (= 1:2), dried over $MgSO_4$, and concentrated. The residue was recrystallized (EtOH/hexane) to afford **22** (190 mg, 93% for 2 steps).

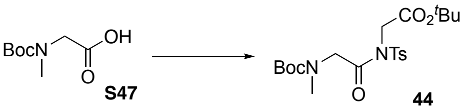
Scheme 7



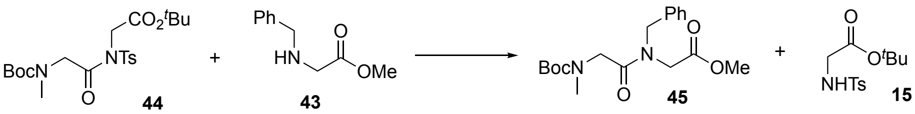
To a solution of **15** (286 mg, 1.0 mmol) in DMF 5 mL were added K_2CO_3 (276 mg, 2.0 mmol), BnCl (0.14 mL, 1.2 mmol) and TBAI (36.9 mg, 0.10 mmol) at room temperature. After being stirred for 5.5 h at 50 °C, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (twice). The combined organic layer was washed with saturated aqueous $Na_2S_2O_3$, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane = 20:80) to afford **42** (CAS: 245364-68-5, 370 mg, 99%).



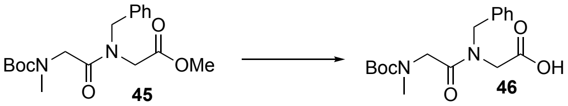
To a solution of **42** (110 mg, 0.293 mmol) in MeOH 6 mL under N_2 were added Mg turnings (170 mg, 7.0 mmol) at 0 °C. After being sonicated for 1 h at 0 °C and stirred for 13.5 h at room temperature, the reaction mixture was treated with Mg turnings (170 mg, 7.0 mmol). After being sonicated for 9 h at 0 °C, the reaction mixture was treated with Mg turnings (42.5 mg, 1.75 mmol). After being sonicated for 80 min at 0 °C and stirred for 13.5 h at room temperature, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (twice). The combined organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/$CHCl_3$ = 30:70) to afford **43** (CAS: 53386-64-4, 30.7 mg, 58%).



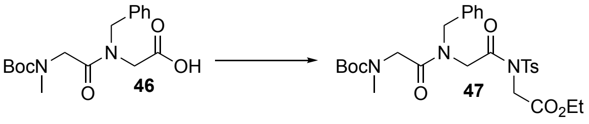
To a solution of **S47** (389 mg, 2.0 mmol) in DMF 10 mL were added *i*-Pr_2NEt (0.41 mL, 2.4 mmol) and TsNCO (0.34 mL, 2.2 mmol) at room temperature. After being stirred for 15 min, the reaction mixture was added *i*-Pr_2NEt (0.41 mL, 2.4 mmol) and **35** (0.35 mL, 2.4 mmol) at room temperature. After being stirred for 16 h at 50 °C, the reaction mixture was treated with 2% aqueous $KHSO_4$. The resulting solution was extracted with EtOAc (twice). The combined organic layer was washed with 2% aqueous $KHSO_4$, dried over MgSO4, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane = 20:80) to afford **44** (910 mg, 99%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 7.85 (m, 2H), 7.35 (d, 2H, *J* = 8.3 Hz), 4.43–4.27 (m, 4H), 2.88–2.82 (m, 3H), 2.44–2.40 (m, 3H), 1.42–1.26 (m, 18H); ^{13}C NMR (150 MHz, $CDCl_3$, mixture of rotamers) δ 169.8, 169.6, 167.1, 166.9, 156.8, 156.2, 146.1, 146.0, 136.5, 136.5, 130.7, 130.6, 128.7, 128.5, 83.2, 83.1, 80.7, 80.7, 54.3, 53.5, 48.4, 48.3, 36.3, 36.2, 29.0, 28.8, 28.6, 28.6, 28.5, 28.3, 22.3, 22.3, 22.2: HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{21}H_{32}N_2NaO_7S^+$ 479.1822, found 479.1818.



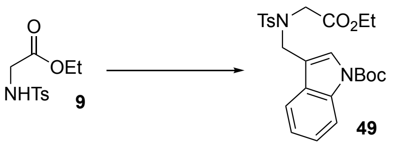
To a solution of **44** (121.8 mg, 0.262 mmol) were added **43** (163.7 mg, 0.759 mmol) in DMF 1.1 mL, *i*-Pr_2NEt (0.14 mL, 0.804 mmol), DMAP (9.5 mg, 0.078 mmol) at room temperature. After being stirred for 24.5 h at 80 °C, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (twice). The combined organic layer was washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane = 20:80) to afford recovered **43** (97.5 mg, 95%), **15** (50.5 mg, 68%), and **45** (82.8 mg, 90%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 7.37–7.19 (m, 5H), 4.68–4.57 (m, 2H), 4.22–3.91 (m, 4H), 3.71–3.67 (m, 3H), 2.96–2.93 (m, 3H), 1.47–1.42 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$, mixture of rotamers) δ 170.4, 170.3, 170.1, 169.8, 156.7, 156.3, 136.8, 136.2, 130.0, 129.9, 129.8, 129.7, 129.3, 129.2, 129.2, 129.0, 128.8, 128.6, 128.5, 128.4, 127.7, 127.3, 127.3, 127.1, 80.8, 80.7, 80.6, 53.6, 53.1, 52.8, 52.2, 51.9, 51.6, 51.4, 50.8, 50.8, 50.1, 48.4, 48.1, 47.8, 47.5, 47.4, 36.3, 36.1, 29.0, 28.9, 28.6; HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{18}H_{26}N_2NaO_5^+$ 373.1734, found 373.1734.



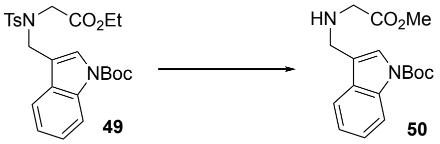
To a solution of **45** (486 mg, 1.39 mmol) in THF/H_2O (= 1:1) 10 mL was added LiOH·H_2O (71.1 mg, 1.69 mmol) at room temperature. After being stirred for 20 min, the reaction mixture was treated with 2% aqueous $KHSO_4$. The resulting solution was extracted with EtOAc (three times), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (MeOH/$CHCl_3$ = 2:98 to 10:90) to afford **46** (CAS: 1837313-58-2, 427 mg, 91%).



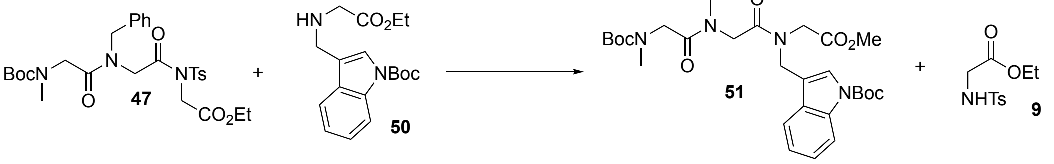
To a solution of **46** (324 mg, 0.96 mmol) in DMF 5 mL were added *i*-Pr_2NEt (0.20 mL, 1.14 mmol) and TsNCO (0.16 mL, 1.05 mmol) at room temperature. After being stirred for 20 min, the reaction mixture was added *i*-Pr_2NEt (0.20 mL, 1.14 mmol) and **7** (0.13 mL, 1.18 mmol) at room temperature. After being stirred for 18 h at 50 °C, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (twice). The combined organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane = 20:80 to 80:20) to afford **47** (412 mg, 75%) as a white foam: ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 7.88–7.66 (m, 2H), 7.38–7.20 (m, 5H), 7.15–7.05 (m, 2H), 4.55–3.70 (m, 10H), 2.98–2.85 (m, 3H), 2.50–2.40 (m, 3H), 1.50–1.36 (m, 9H), 1.30–1.20 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, mixture of rotamers) δ 170.4, 170.2, 170.1, 169.5, 169.3, 169.2, 168.1, 168.0 (x2), 167.9, 156.8, 156.7, 156.4, 156.3, 146.6, 146.5, 146.2, 146.1, 137.1, 136.8, 136.2, 136.1, 135.8, 130.9, 130.8, 130.7, 129.7, 129.6, 129.3, 129.2, 128.7, 128.5, 128.4, 128.3, 128.2, 127.9, 127.4, 80.7, 80.6, 80.6, 62.6, 62.4, 52.0, 51.9, 51.3, 50.8, 50.7, 50.5, 50.4, 50.3, 49.8, 47.9, 47.7, 36.4, 36.2, 36.0, 29.0, 29.0, 28.9, 22.4, 22.4, 14.7(x2); HRMS (ESI) m/z: $[M+Br]^-$ calcd for $BrC_{28}H_{37}N_3O_8S^-$ 654.1490, found 654.1472.



To a solution of **9** (101.6 mg, 0.395 mmol) in DMF 2 mL were added K_2CO_3 (110.6 mg, 0.800 mmol) and **48** (CAS:96551-21-2, 150.7 mg, 0.486 mmol) at room temperature. After being stirred for 3 h, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc/hexane (= 1:9) (twice). The combined organic layer was washed with saturated aqueous $Na_2S_2O_3$, dried over MgSO4, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane = 10:90 to 20:80) to afford **49** (175 mg, 90%) as a white foam: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.79 (d, 2H, *J* = 8.3 Hz), 7.63 (d, 1H, *J* = 7.6 Hz), 7.43 (s, 1H), 7.34–7.31 (m, 3H), 7.23 (t, 1H, *J* = 7.6 Hz), 4.66 (s, 2H), 3.98–3.93 (m, 4H), 2.45 (s, 3H), 1.65 (s, 10H), 1.11 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.4, 150.1, 144.2, 137.3, 136.3, 130.2, 129.9, 128.1, 126.5, 125.6, 123.6, 120.4, 115.8, 114.7, 84.7, 61.7, 47.0, 43.2, 28.8, 22.3, 14.6 : HRMS (ESI) m/z: $[M+Na]^+$ calcd for $C_{25}H_{30}N_2NaO_6S^+$ 509.1717, found 509.1717.

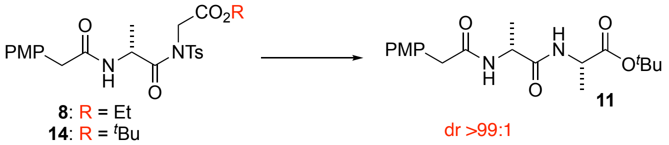


To a solution of **49** (75.7 mg, 0.155 mmol) in MeOH 2 mL under N_2 was added Mg turnings (74.9 mg, 3.08 mmol) and sonicated at room temperature. After being sonicated for 5 h at room temperature, the reaction mixture was treated with Mg turnings (75.3 mg, 3.10 mmol). After being sonicated for 3 h at room temperature, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (three times). The combined organic layer was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (EtOAc/hexane = 20:80 to 30:70) to afford **50** (25.9 mg, 53%) as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.64 (d, 1H, *J* = 7.6 Hz), 7.52 (s, 1H), 7.31 (t, 1H, *J* = 8.3 Hz), 7.23 (t, 1H, *J* = 7.9 Hz), 3.93 (s, 2H), 3.73 (s, 3H), 3.48 (s, 2H), 1.65 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.6, 150.4, 136.4, 130.5, 125.2, 124.5, 123.2, 119.9, 119.3, 115.9, 84.2, 52.5, 50.6, 44.7, 28.9; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{17}H_{23}N_2O_4^+$ 319.1652, found 319.1648.



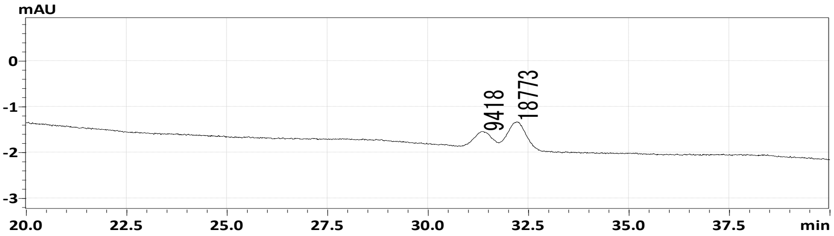
To a solution of **47** (75.2 mg, 0.131 mmol) were added **50** (113 mg, 0.356 mmol) in DMF 1 mL, *i*-Pr_2NEt (0.070 mL, 0.40 mmol), DMAP (2.0 mg, 0.016 mmol) at room temperature. After being stirred for 5.5 h at 80 °C, the reaction mixture was treated with saturated aqueous NH_4Cl. The resulting solution was extracted with EtOAc (twice). The combined organic layer was washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated. The residue was purified by silica gel column chromatography (1st: EtOAc/hexane = 30:70 to 50:50; 2nd: EtOAc/hexane/AcOH = 30:70:1 to EtOAc/hexane/Et_3N = 60:40:1) to afford recovered **50** (76.7 mg, 92%), **9** (18.6 mg, 55%), and **51** (53.3 mg, 64%) as a white foam: ^{1}H NMR (600 MHz, $CDCl_3$, mixture of rotamers) δ 8.11 (brs, 1H), 7.60–7.15 (m, 10H), 4.80–3.84 (m, 10H), 3.75–3.50 (m, 3H), 3.00–2.89 (m, 3H), 1.66 (brs, 9H), 1.45–1.36 (m, 9H); ^{13}C NMR (150 MHz, $CDCl_3$, mixture of rotamers) δ 170.3, 169.7, 169.6, 169.5, 169.3, 169.1, 168.9, 168.8, 168.3, 156.4, 156.1, 155.8, 149.6, 149.5, 136.8, 136.0, 135.8, 135.7, 129.4, 129.0, 128.7, 128.0, 127.9, 127.6, 127.4, 126.9, 125.8, 125.7, 125.3, 125.1, 124.9, 124.6, 123.1, 119.9, 119.7, 118.8, 118.6, 115.7, 115.5, 115.4, 115.3, 114.9, 84.3, 84.2, 84.1, 80.1, 79.9, 52.7, 52.4, 52.3, 51.4, 51.3, 51.2, 51.1, 50.8, 50.5, 50.3, 50.3, 50.1, 50.0, 49.9, 47.5, 47.4, 47.3, 46.8, 46.4, 46.1, 46.0, 43.8, 43.7, 41.5, 41.2, 36.0, 35.9, 35.8, 35.6, 35.6, 35.5, 28.4, 28.3; HRMS (ESI) m/z: $[M+H]^+$ calcd for $C_{34}H_{45}N_4O_8^+$ 637.3232, found 637.3216

HPLC charts

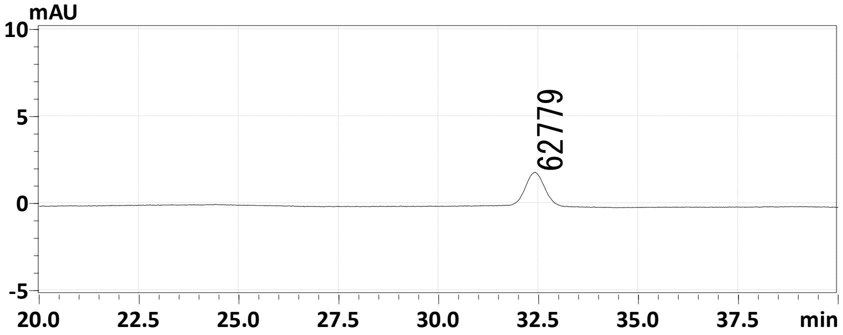


8: R = Et
14: R = ^{t}Bu
11
dr >99:1

Standard samples (**11** + ***epi*-11**)



11 synthesized from **8**



11 synthesized from **14**

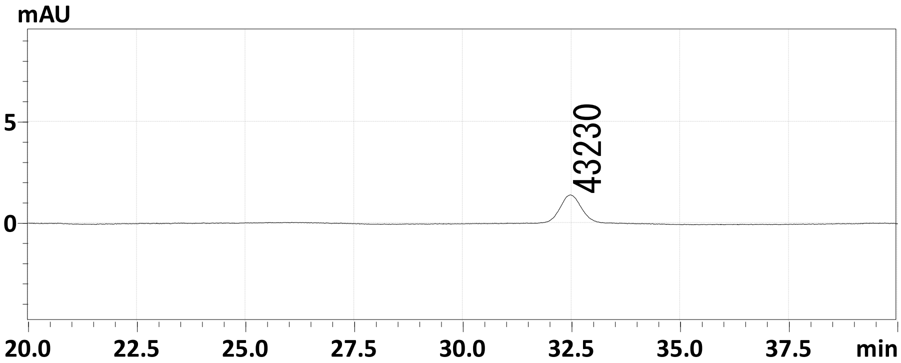
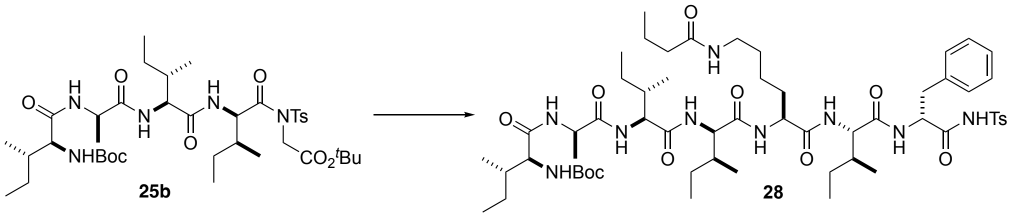
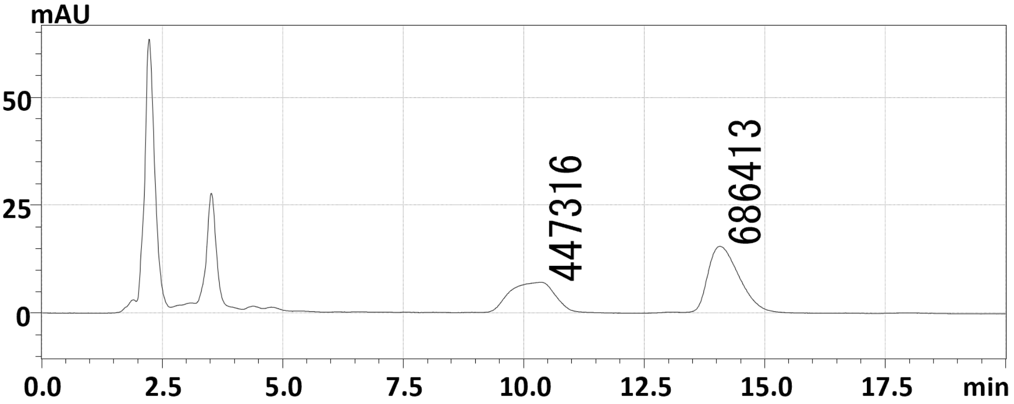


Figure S1. HPLC analysis of **11**. HPLC conditions: COSMOSIL AR-II Φ 4.6 × 250 mm, MeCN/H_2O/TFA (= 29/71/0.05), 1.0 mL/min, 40 °C, UV 254 nm.



Standard samples (**28** + ***epi*-28**)



28 synthesized in study

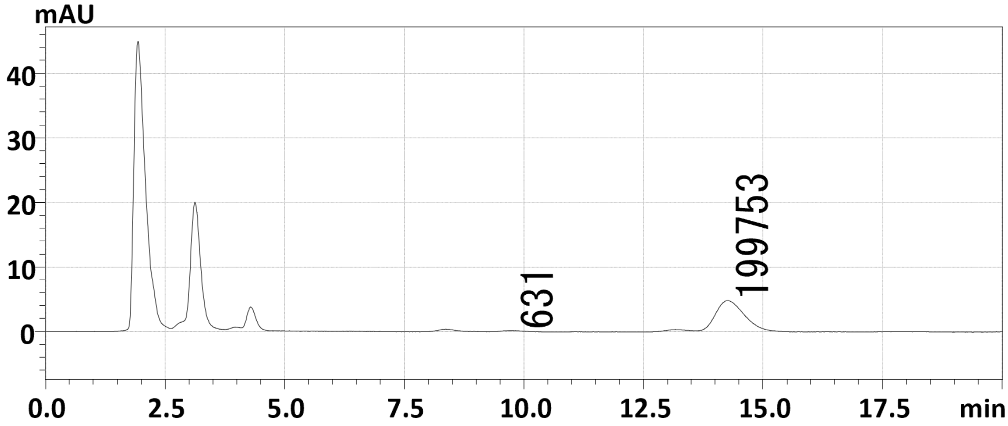
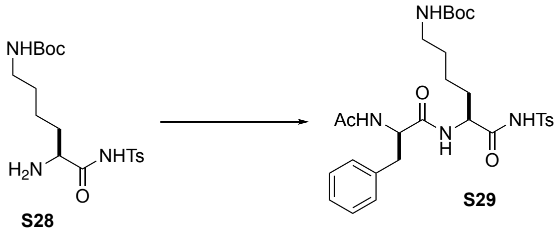
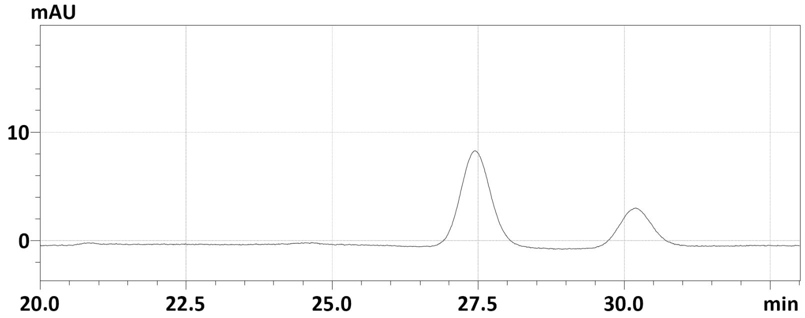


Figure S2. HPLC analysis of **28**. HPLC conditions: COSMOSIL AR-II Φ 2.0 × 250 mm, MeOH/H_2O/TFA (= 80/20/0.05), 0.3 mL/min, 40 °C, UV 254 nm.



Standard samples (**S29** + ***epi*-S29**)



S29 synthesized in study

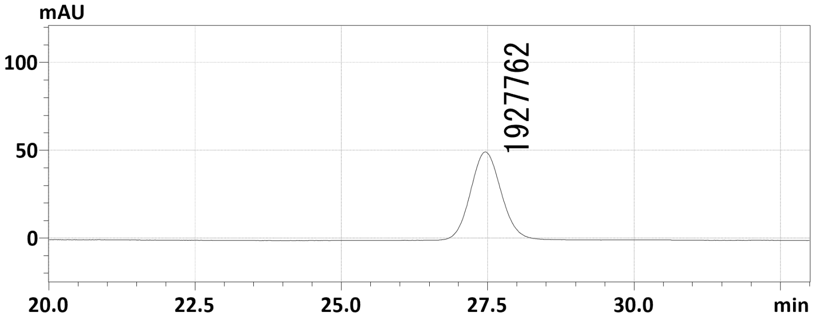
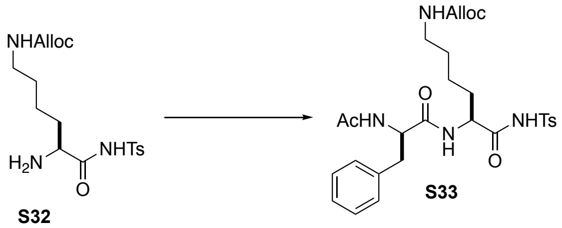
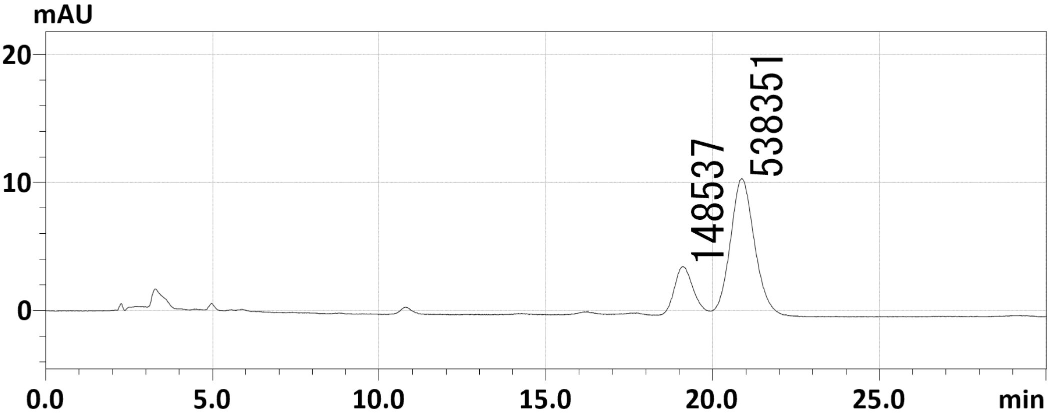


Figure S3. HPLC analysis of **S29**. HPLC conditions: COSMOSIL AR-II Φ 4.6 × 250 mm, MeOH/H_2O/TFA (= 55/45/0.05), 1.2 mL/min, 40 °C, UV 254 nm.



Standard samples (**S33** + ***epi*-S33**)



S33 synthesized in study

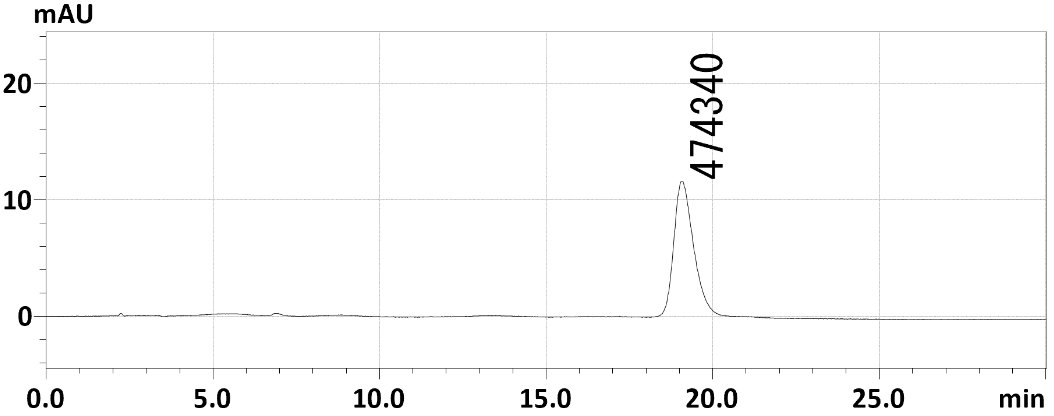
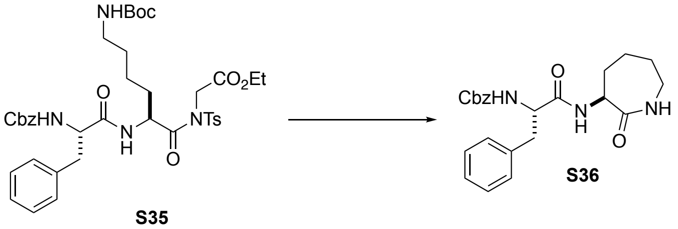
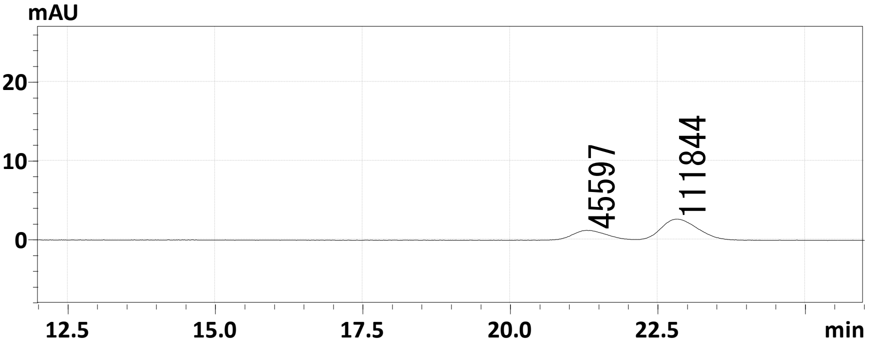


Figure S4. HPLC analysis of **S33**. HPLC conditions: COSMOSIL AR-II Φ 2.0 × 250 mm, MeOH/H_2O/TFA (= 60/40/0.05), 0.3 mL/min, 40 °C, UV 254 nm.



Standard samples (**S36** + ***epi*-S36**)



S36 synthesized in study

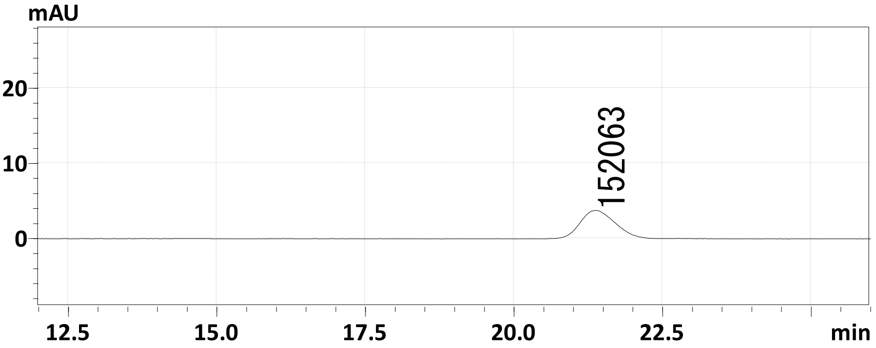
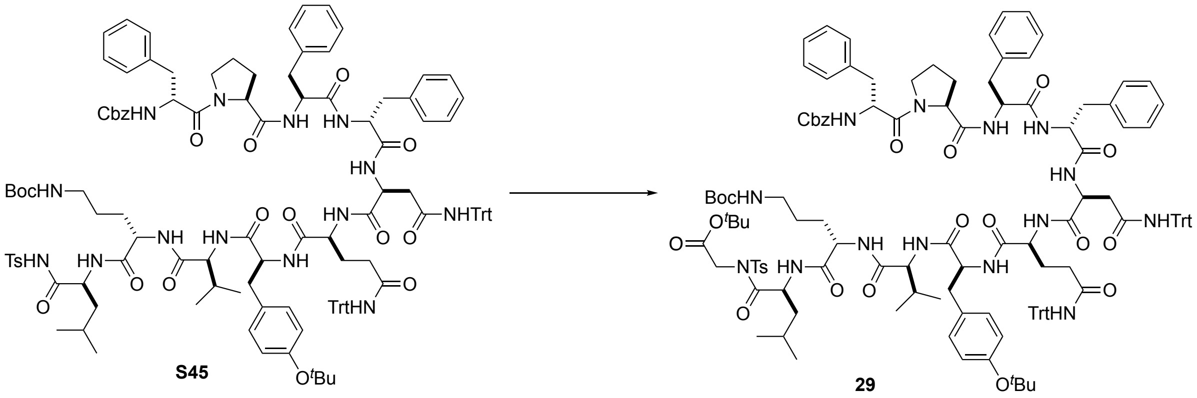


Figure S5. HPLC analysis of **S36**. HPLC conditions: COSMOSIL AR-II Φ 2.0 × 250 mm, MeCN/H_2O/TFA (= 35/65/0.05), 0.2 mL/min, 40 °C, UV 254 nm.



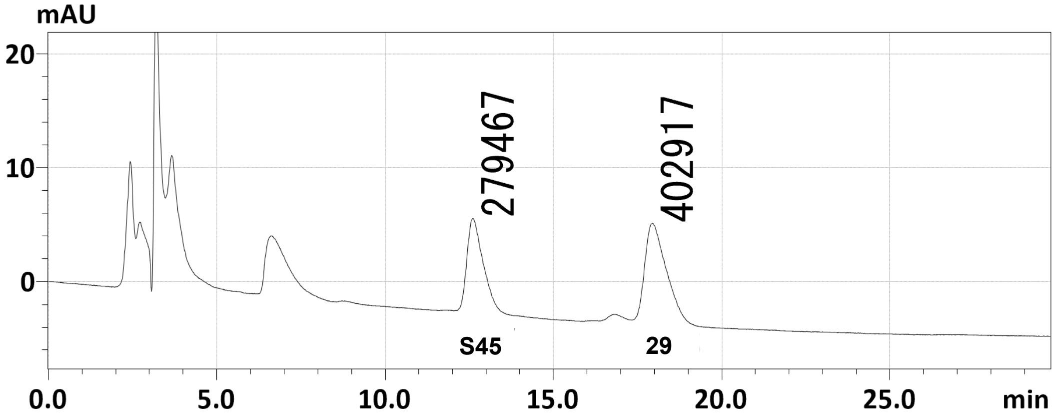


Figure S6. HPLC analysis of **29**. HPLC conditions: COSMOSIL AR-II Φ 2.0 × 250 mm, MeCN/H_2O/TFA (= 92/8/0.05), 0.2 mL/min, 40 °C, UV 254 nm.

NMR spectra

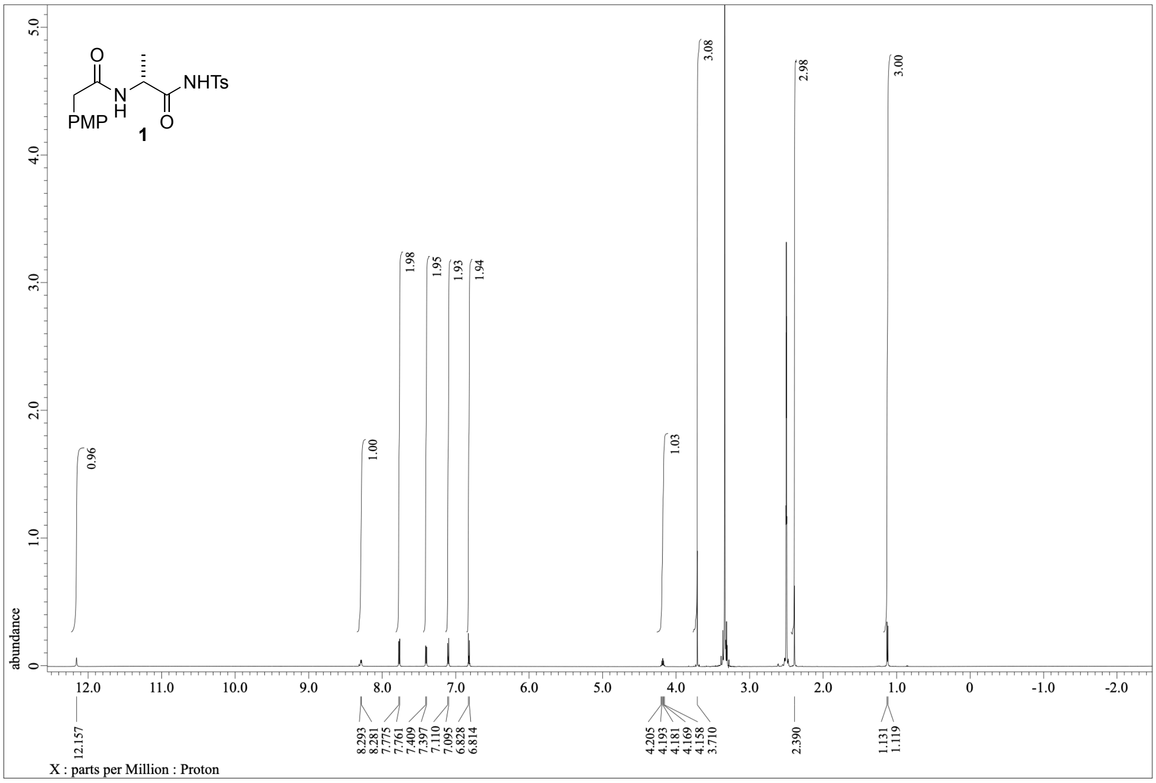


Figure S7. ^{1}H NMR spectrum (600 MHz) of **1** in DMSO-d_6.

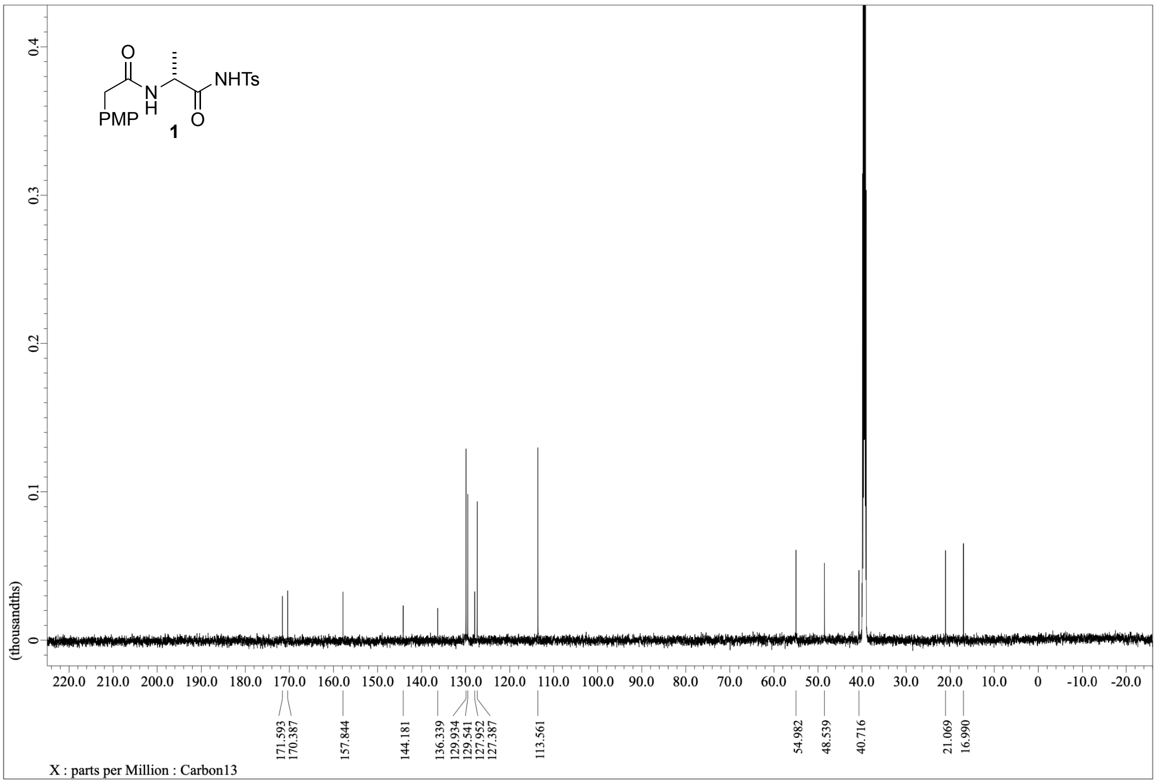


Figure S8. ^{13}C NMR spectrum (150 MHz) of **1** in DMSO-d_6.

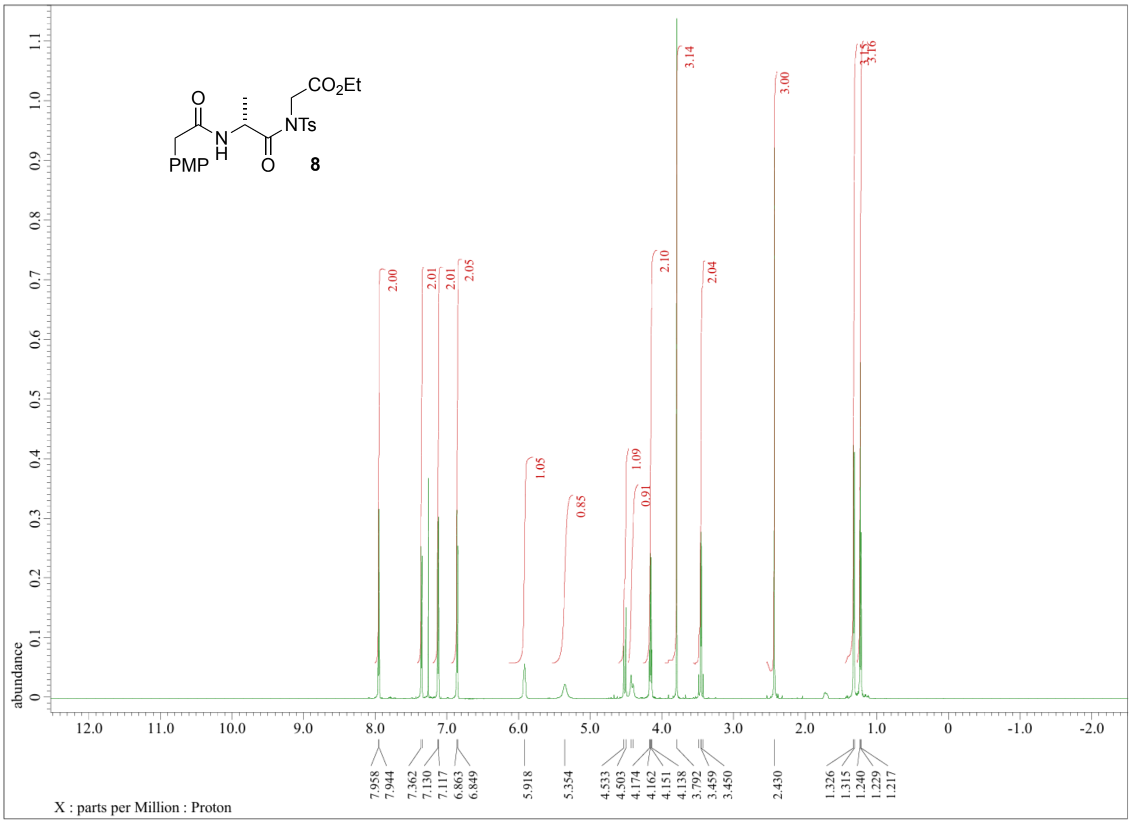


Figure S9. ^{1}H NMR spectrum (600 MHz) of **8** in $CDCl_3$.

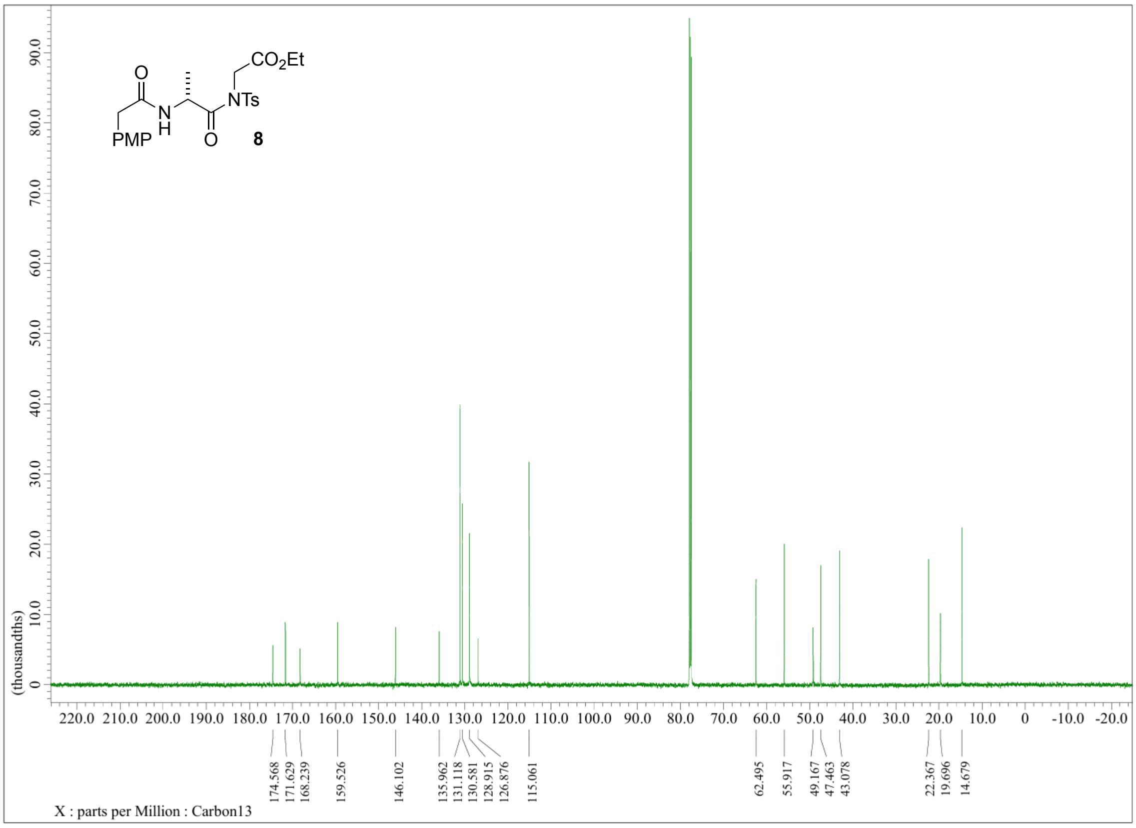


Figure S10. ^{13}C NMR spectrum (150 MHz) of **8** in $CDCl_3$.

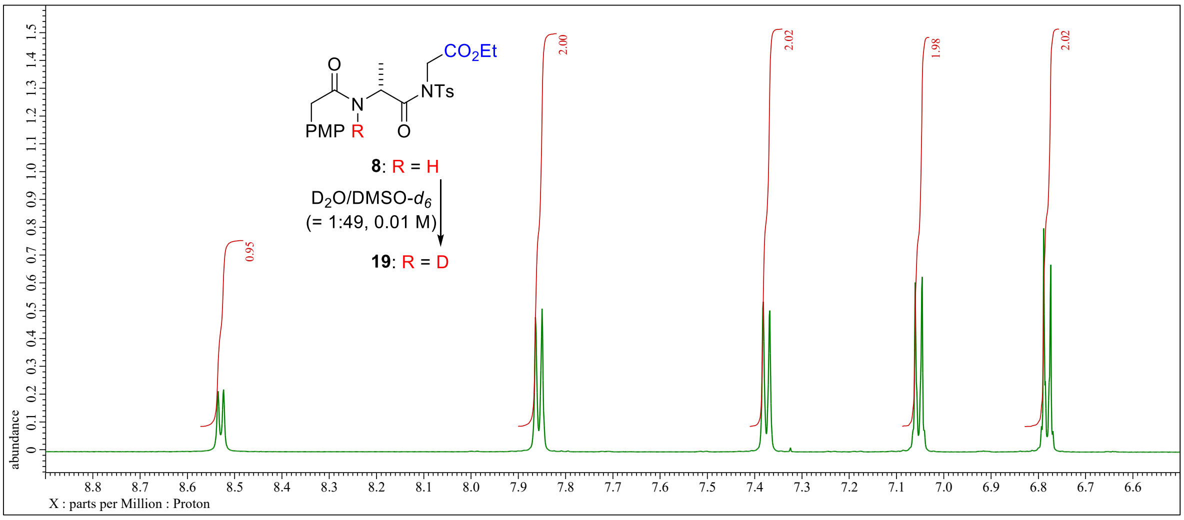


Figure S11. ^{1}H NMR experiments (600 MHz) of **8** to **19** (5 min).

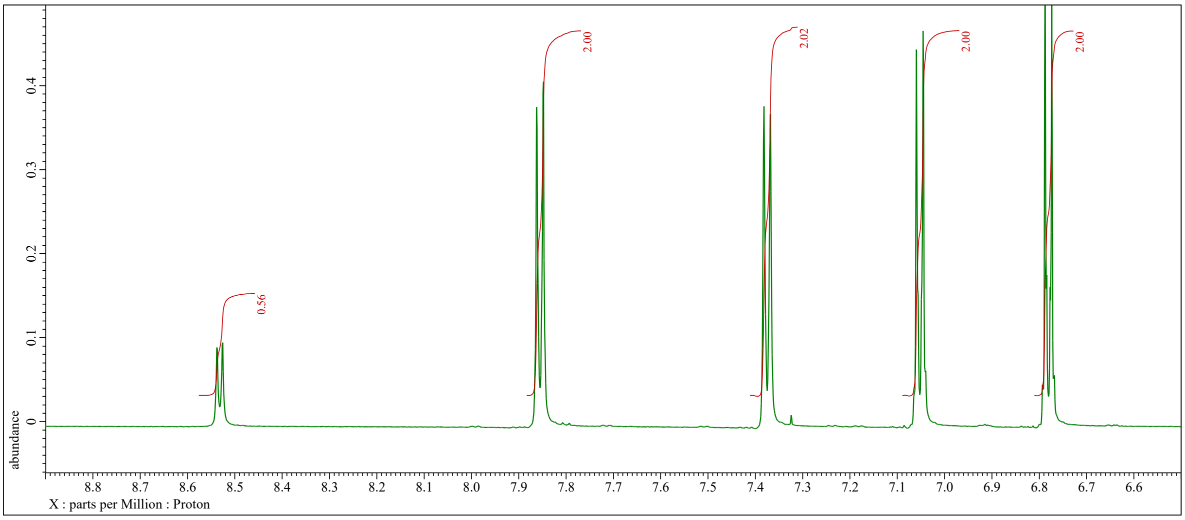


Figure S12. ^{1}H NMR experiments (600 MHz) of **8** to **19** (4 h).

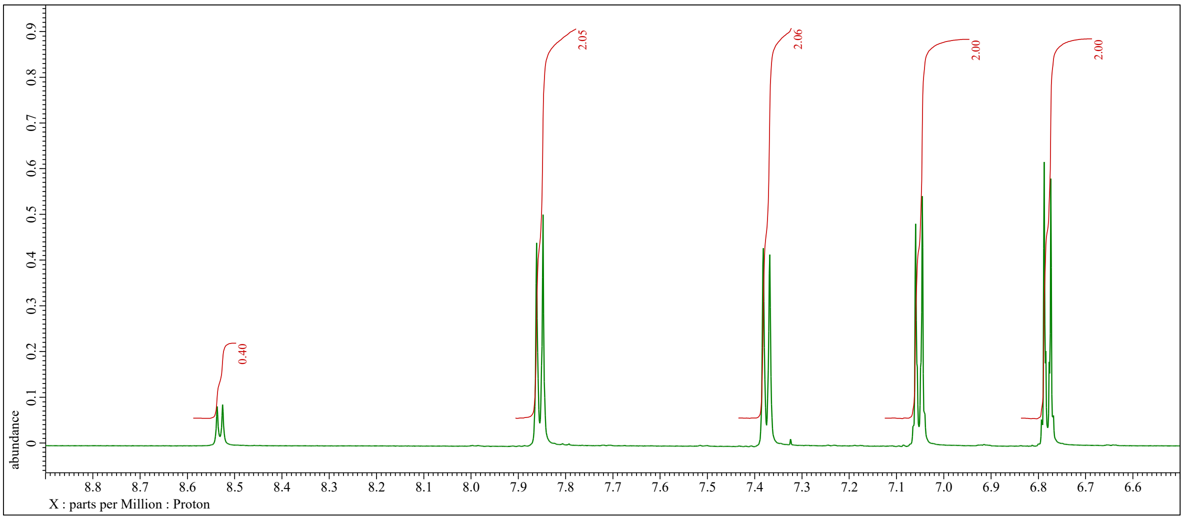


Figure S13. ^{1}H NMR experiments (600 MHz) of **8** to **19** (16.5 h).

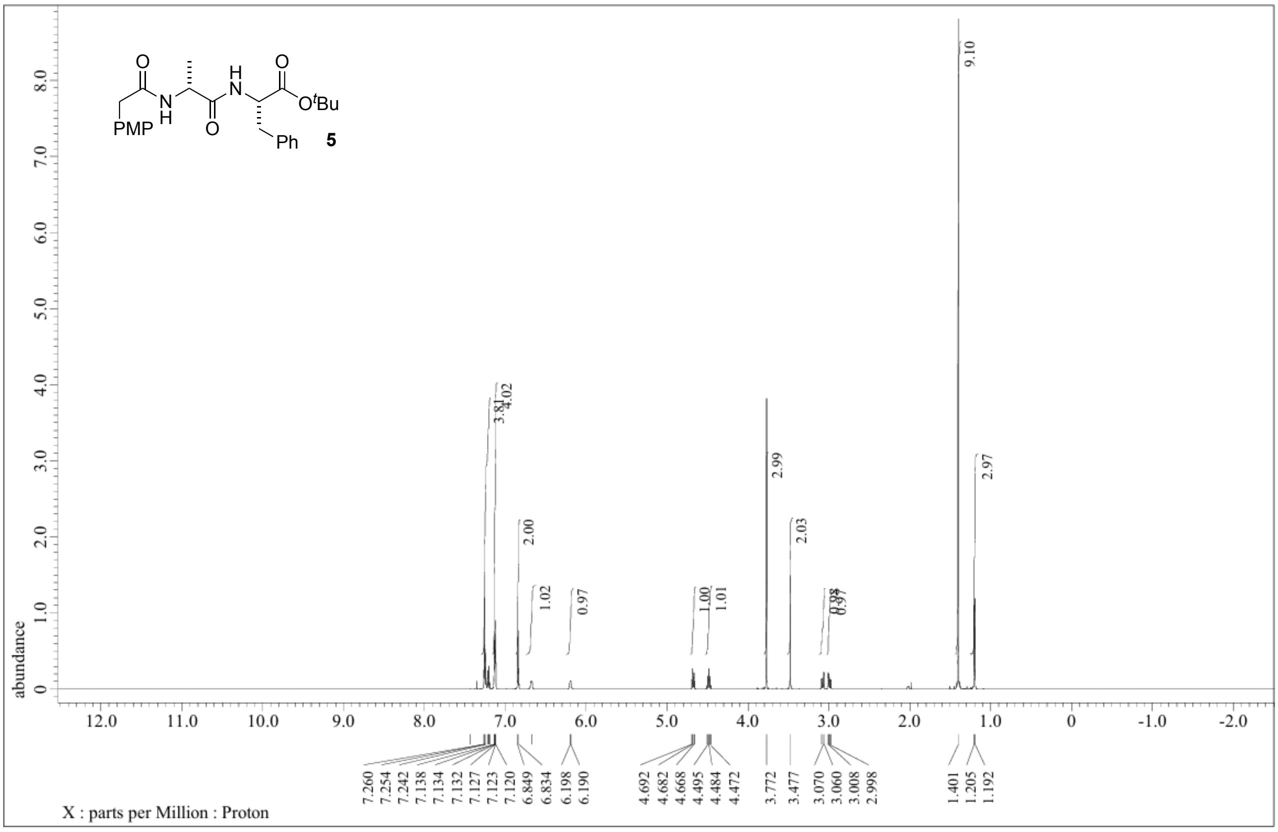


Figure S14. ^{1}H NMR spectrum (600 MHz) of **5** in CDCl$_3$.

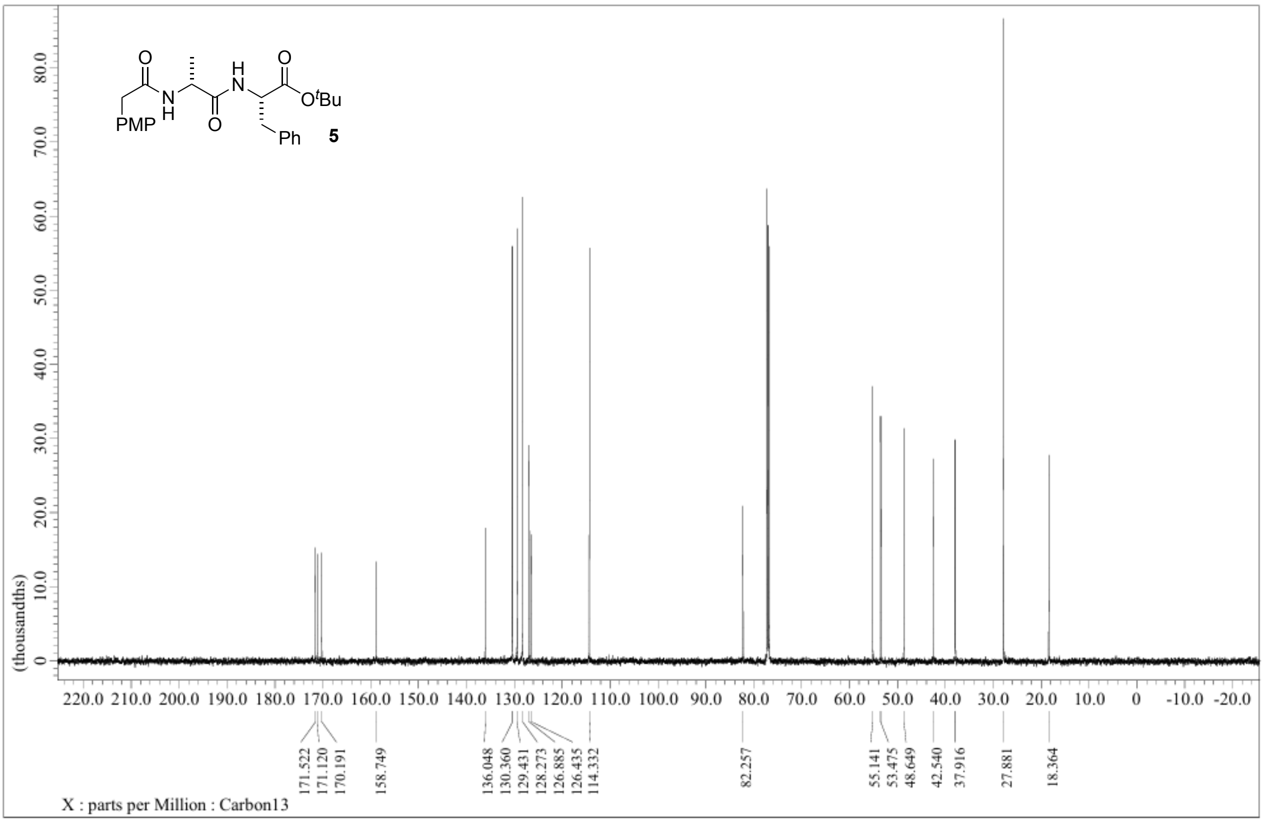
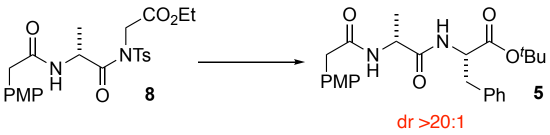


Figure S15. ^{13}C NMR spectrum (150 MHz) of **5** in CDCl$_3$.



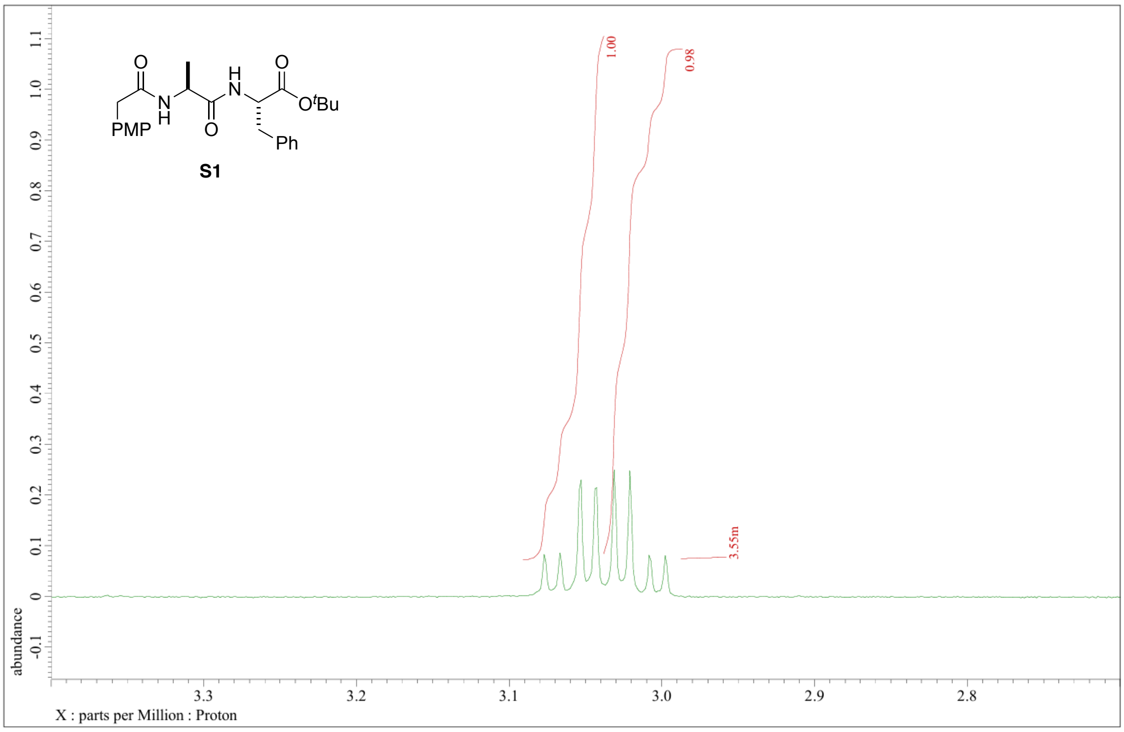


Figure S16. Standard epimerized sample of **5** (= **S1**) (in CDCl$_3$, 600 MHz).

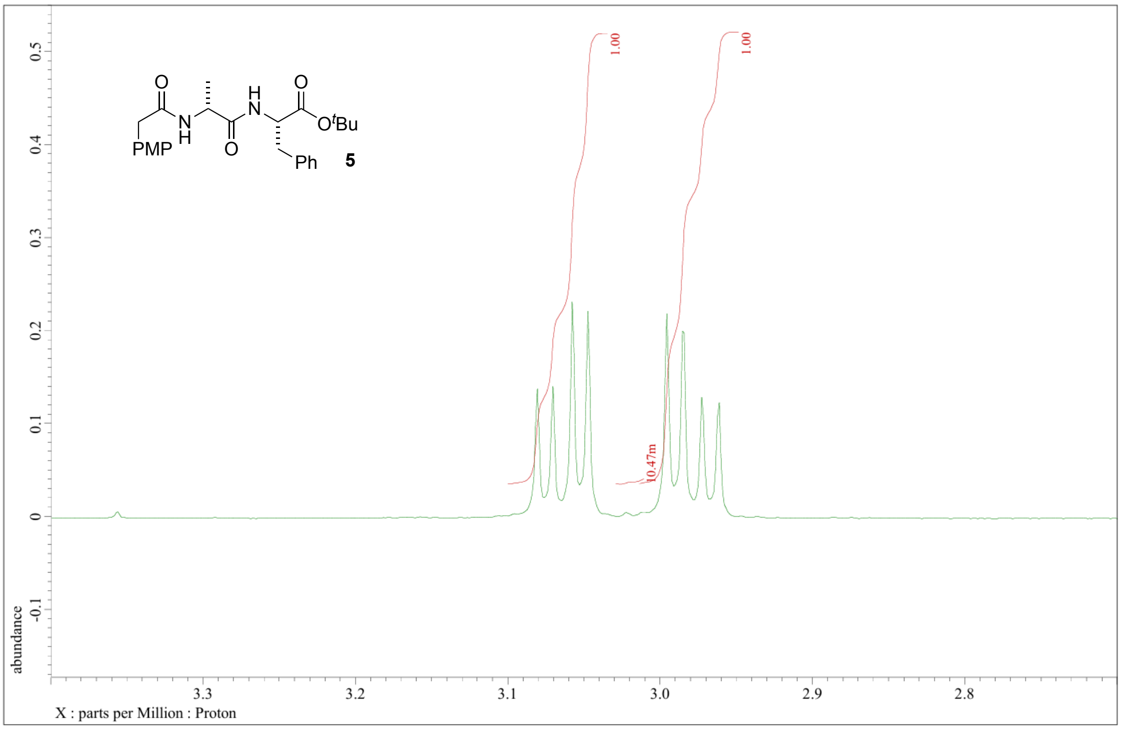


Figure S17. **5** synthesized in study (in CDCl$_3$, 600 MHz).

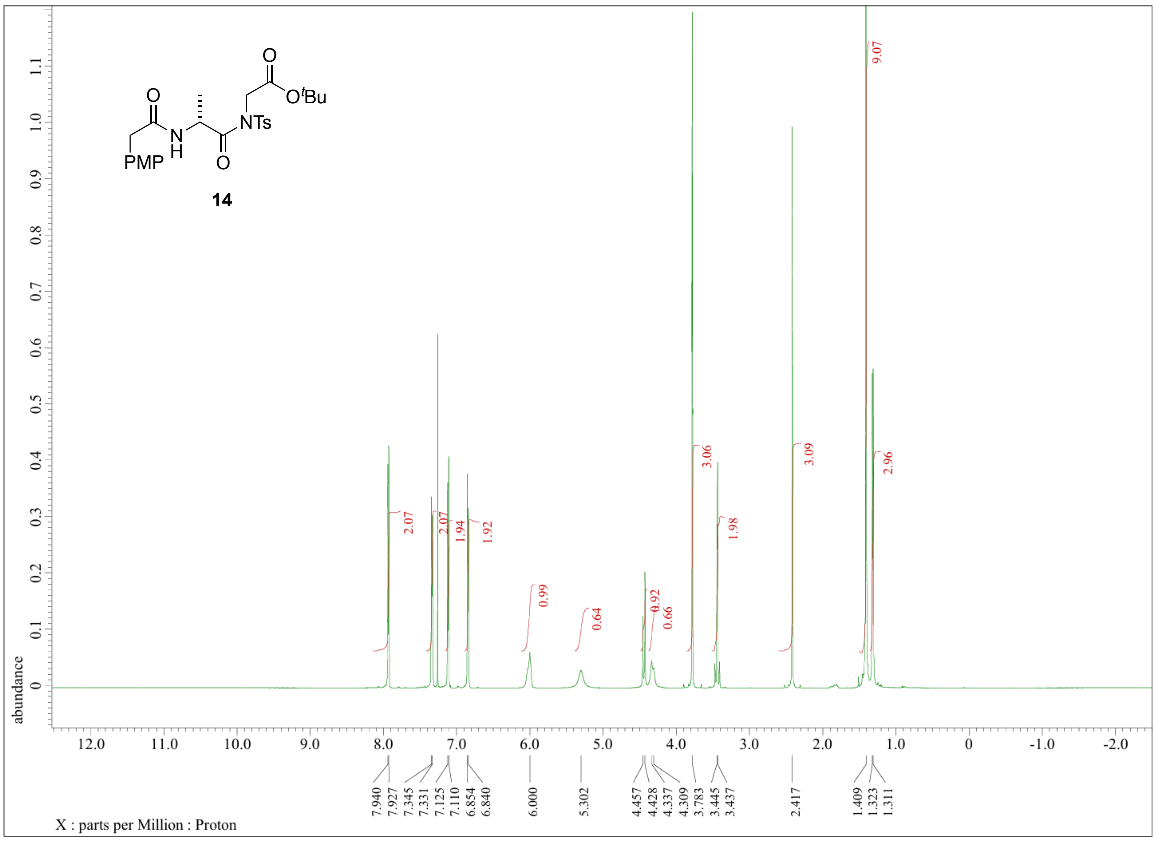


Figure S18. ^{1}H NMR spectrum (600 MHz) of **14** in CDCl$_3$.

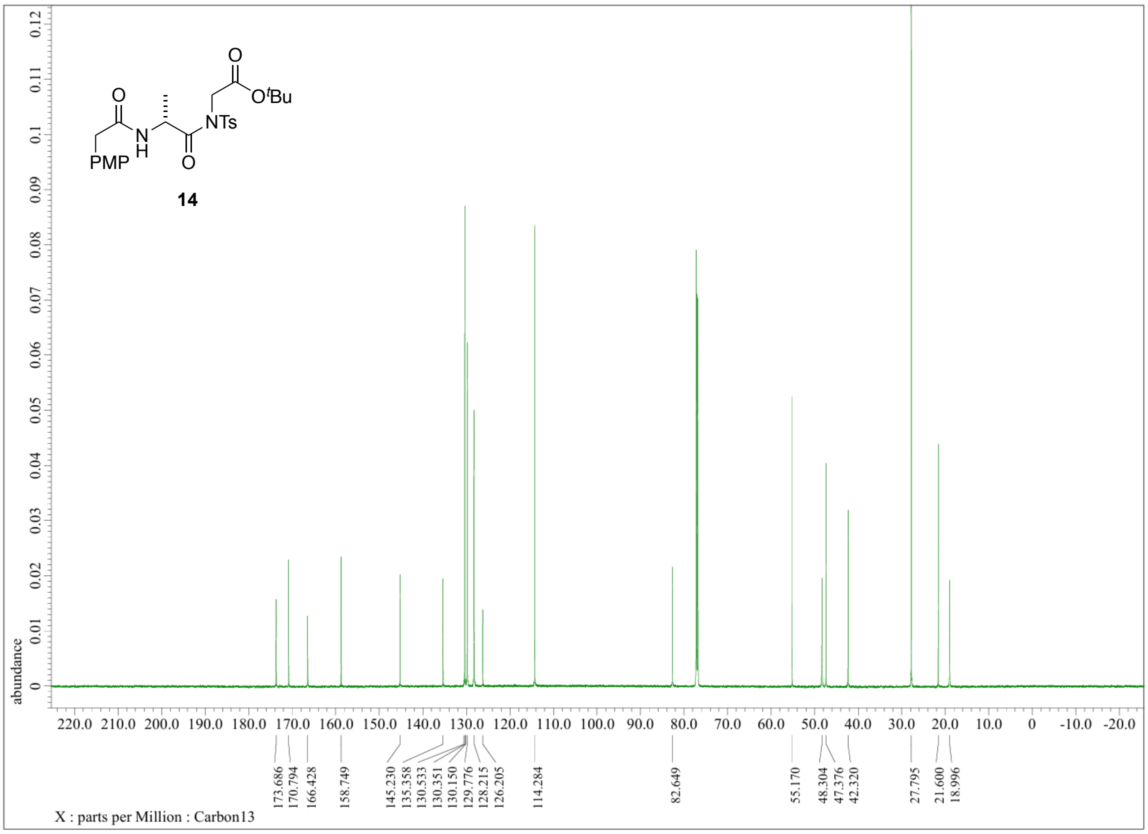


Figure S19. ^{13}C NMR spectrum (150 MHz) of **14** in CDCl$_3$.

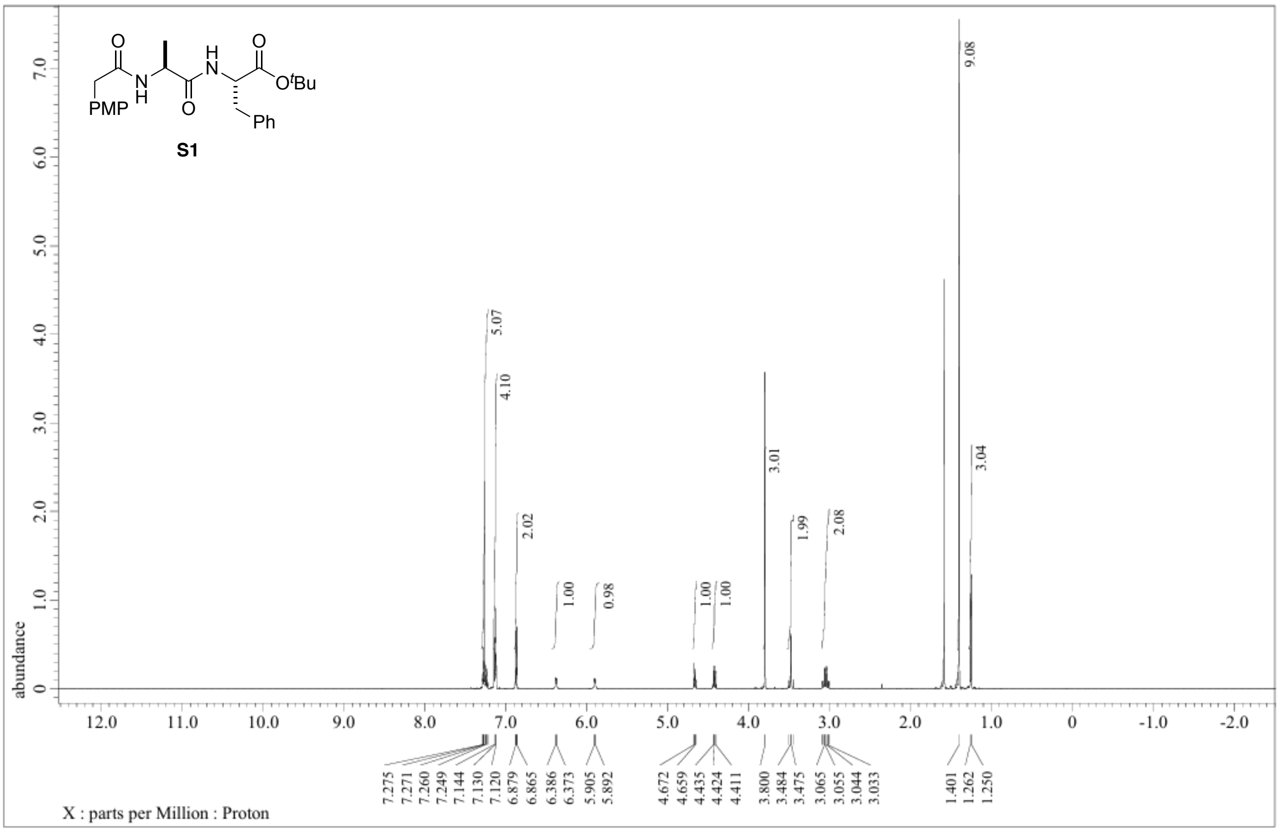


Figure S20. ^{1}H NMR spectrum (600 MHz) of **S1** in CDCl$_3$.

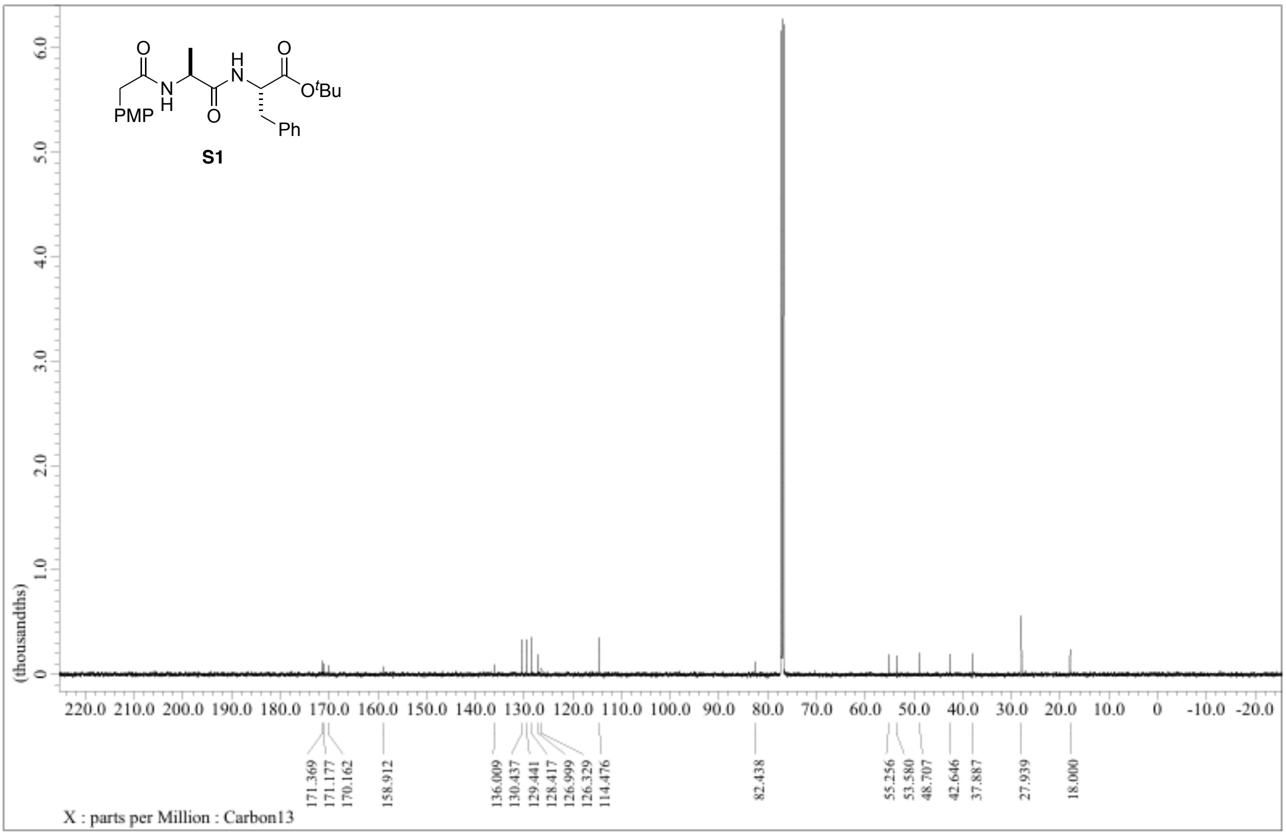


Figure S21. ^{13}C NMR spectrum (150 MHz) of **S1** in CDCl$_3$.

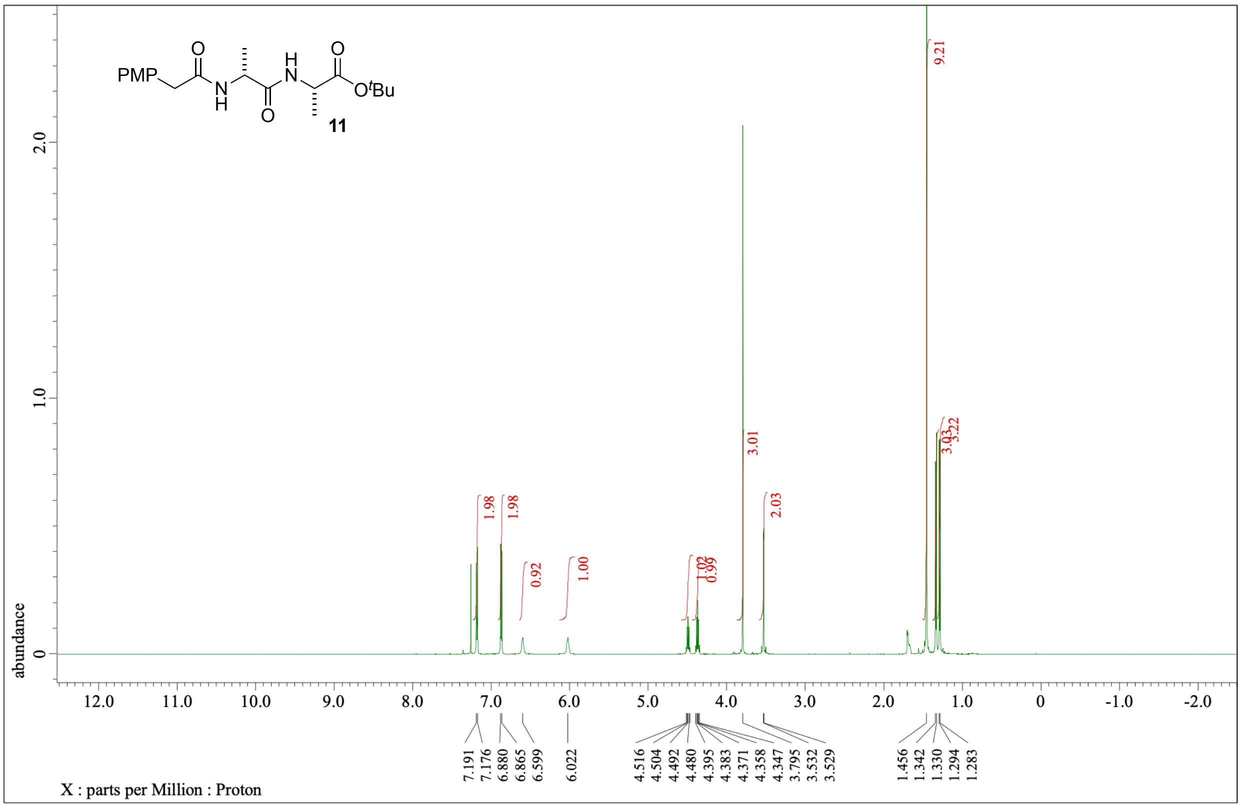


Figure S22. ^{1}H NMR spectrum (600 MHz) of **11** in $CDCl_3$.

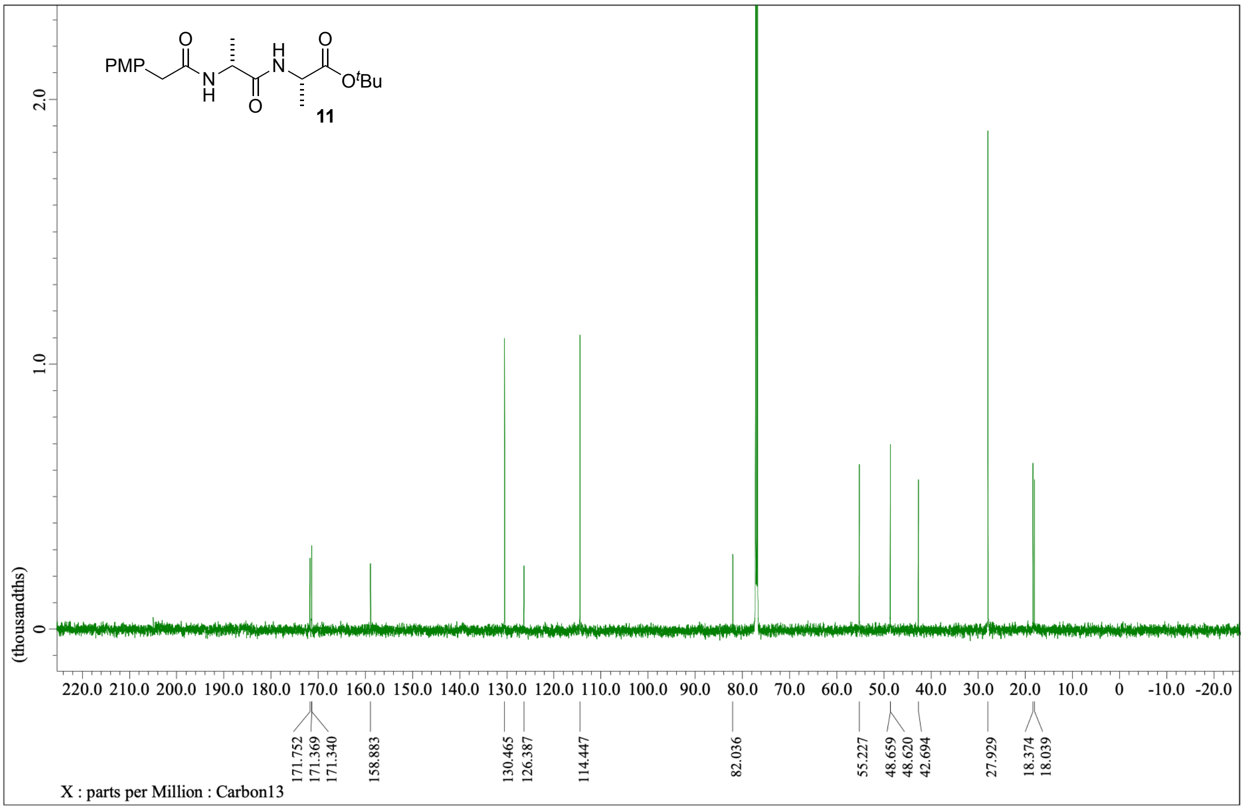


Figure S23. ^{13}C NMR spectrum (150 MHz) of **11** in $CDCl_3$.

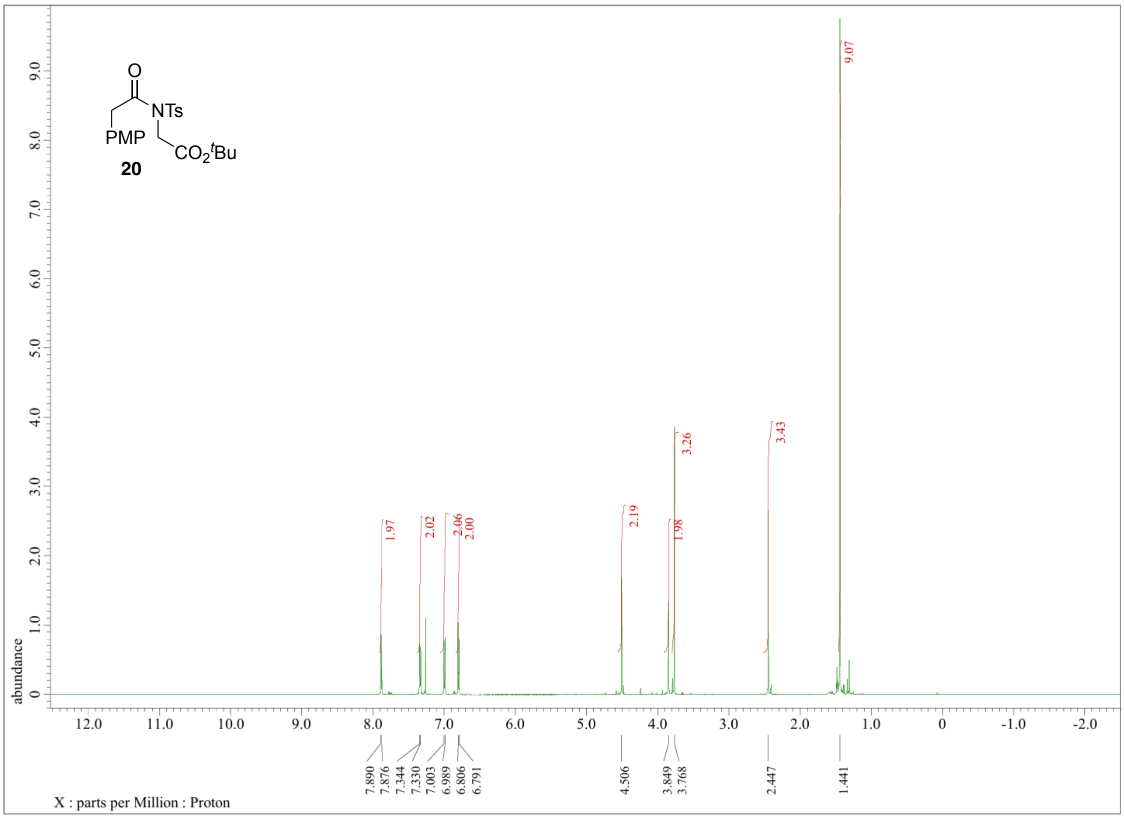


Figure S24. ^{1}H NMR spectrum (600 MHz) of **20** in CDCl$_3$.

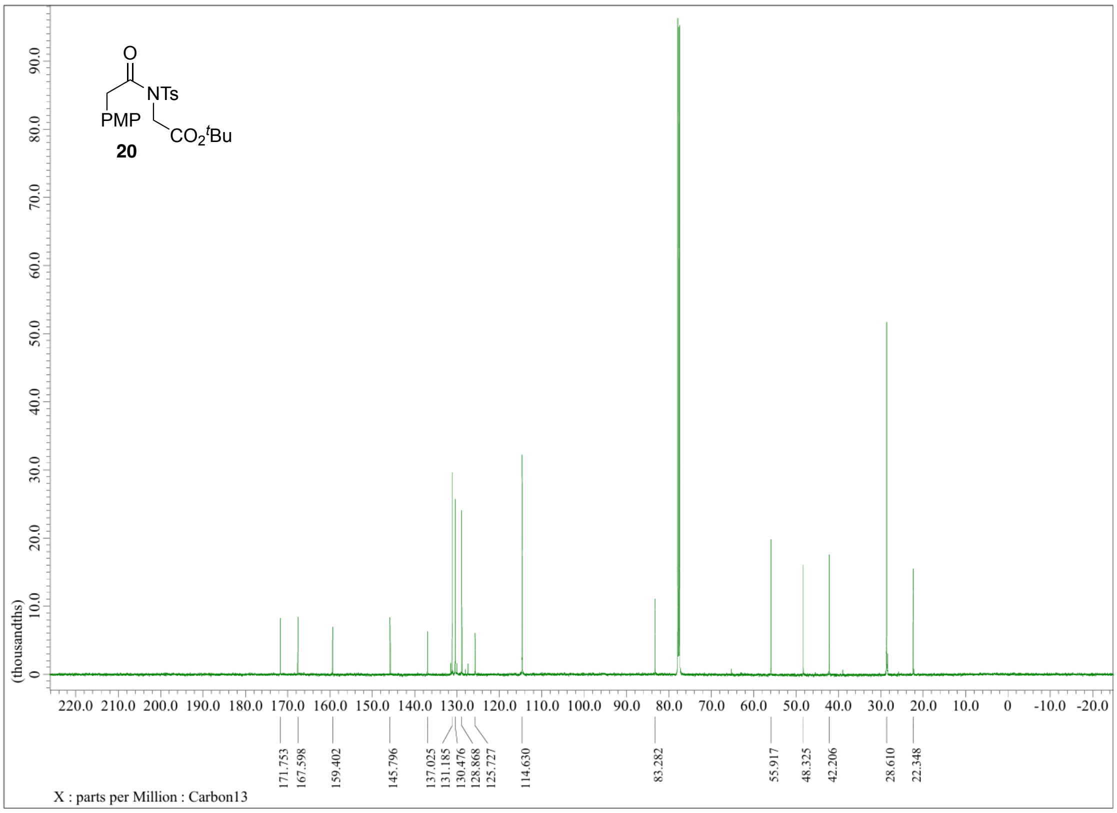


Figure S25. ^{13}C NMR spectrum (150 MHz) of **20** in CDCl$_3$.

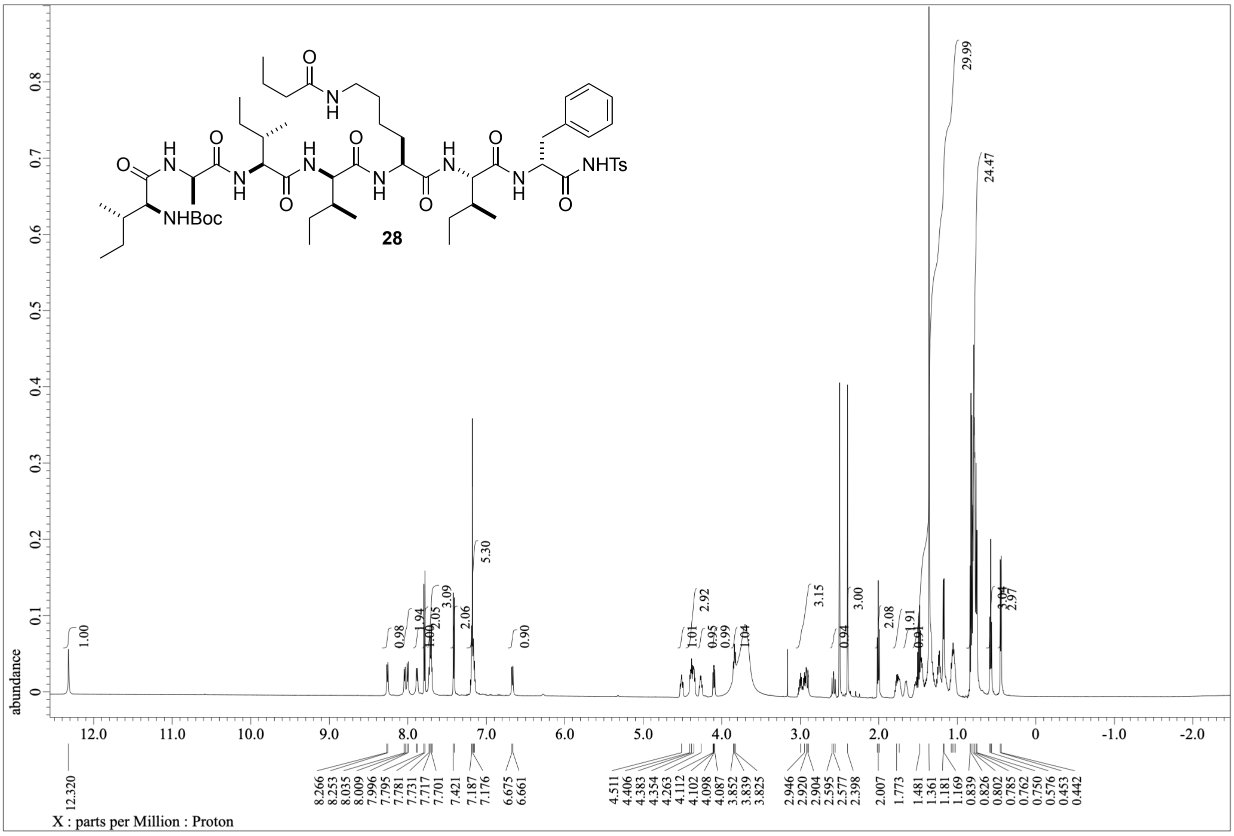


Figure S26. ^{1}H NMR spectrum (600 MHz) of **28** in DMSO-d_6.

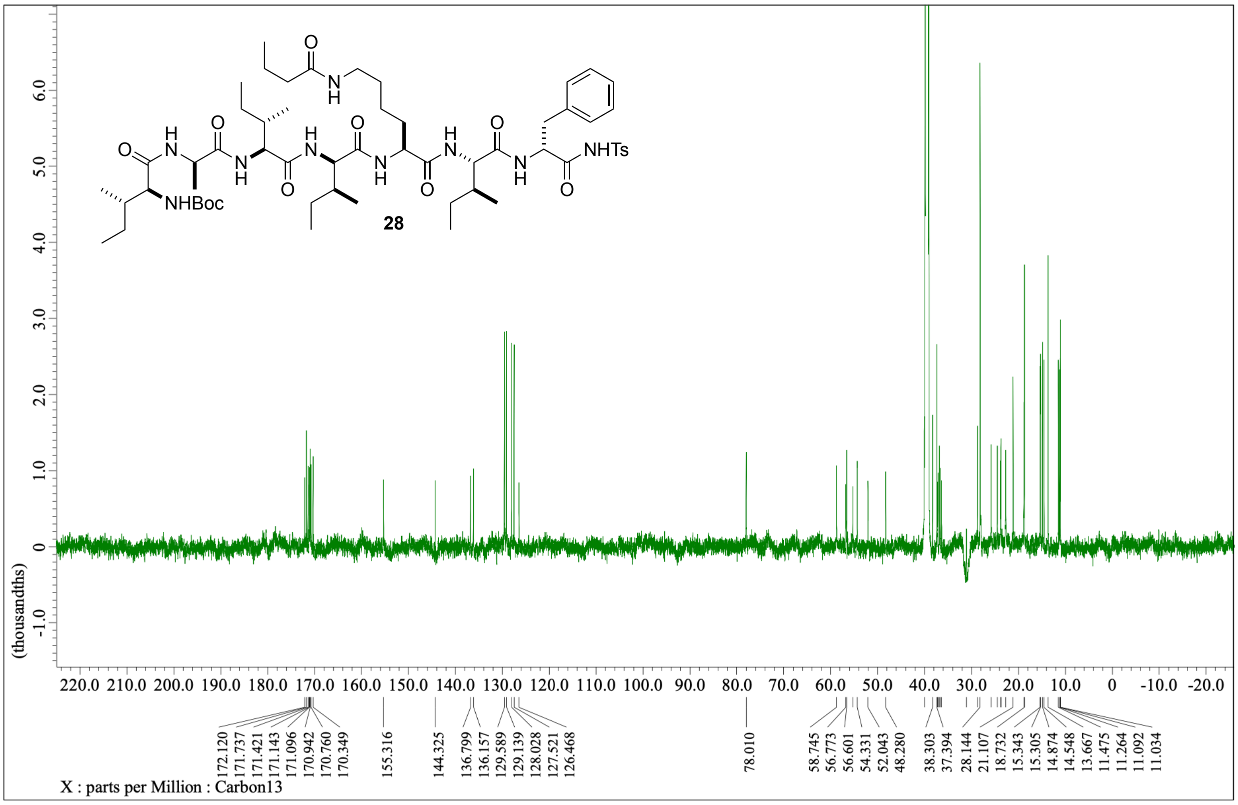


Figure S27. ^{13}C NMR spectrum (150 MHz) of **28** in DMSO-d_6.

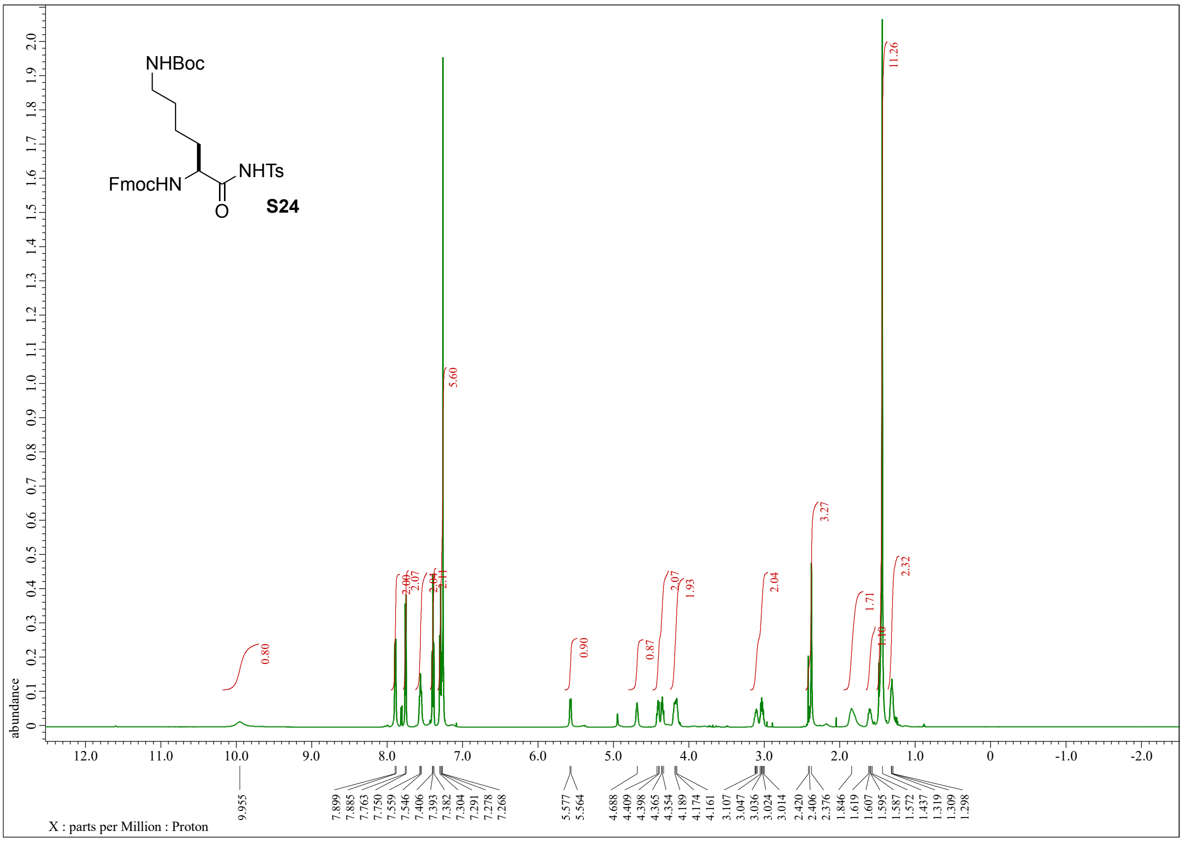


Figure S28. ^{1}H NMR spectrum (600 MHz) of **S24** in $CDCl_3$.

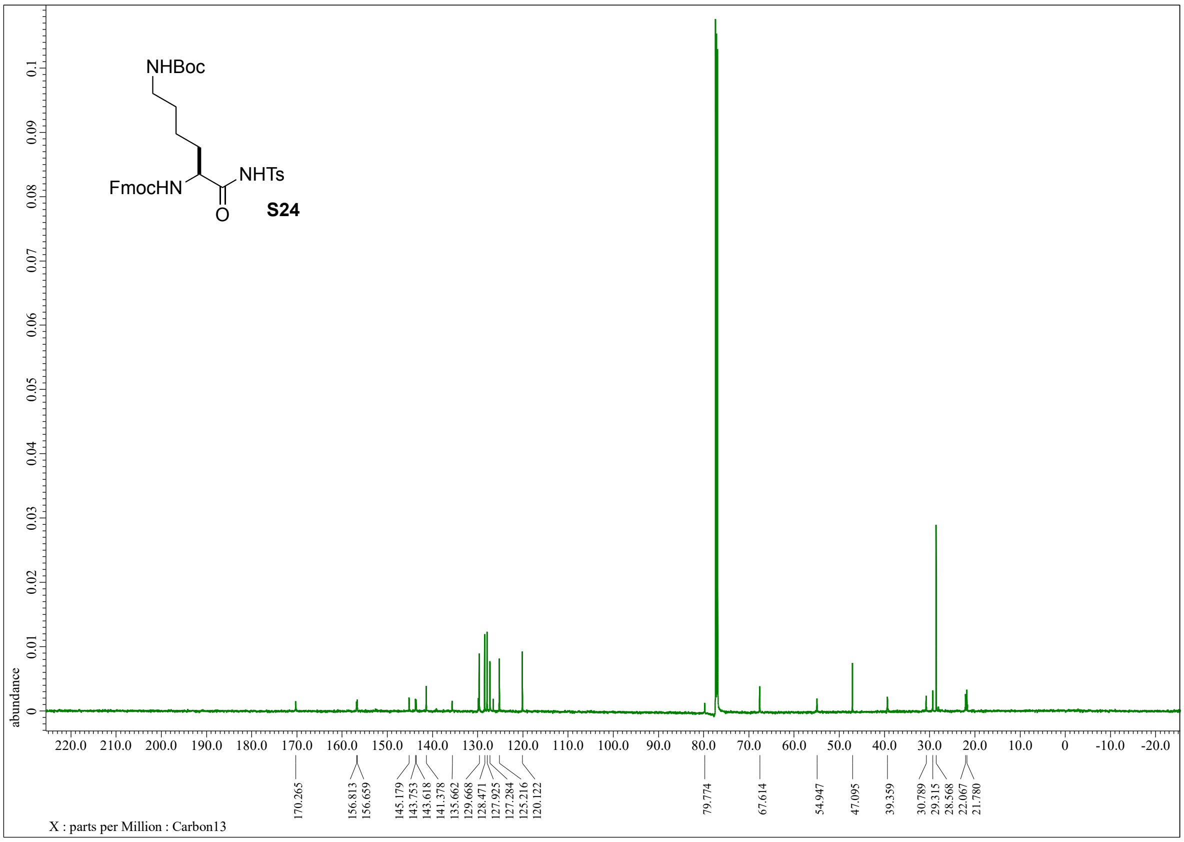


Figure S29. ^{13}C NMR spectrum (150 MHz) of **S24** in $CDCl_3$.

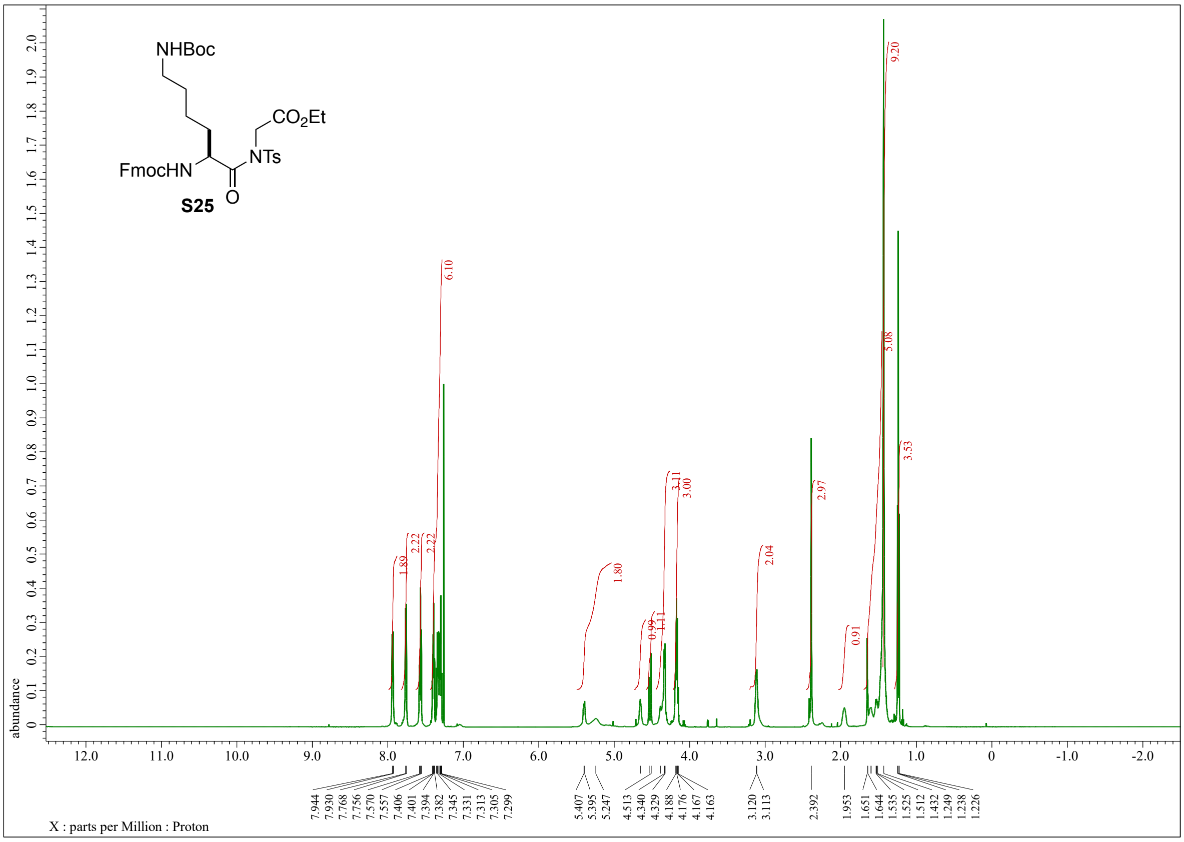


Figure S30. ^{1}H NMR spectrum (600 MHz) of **S25** in $CDCl_3$.

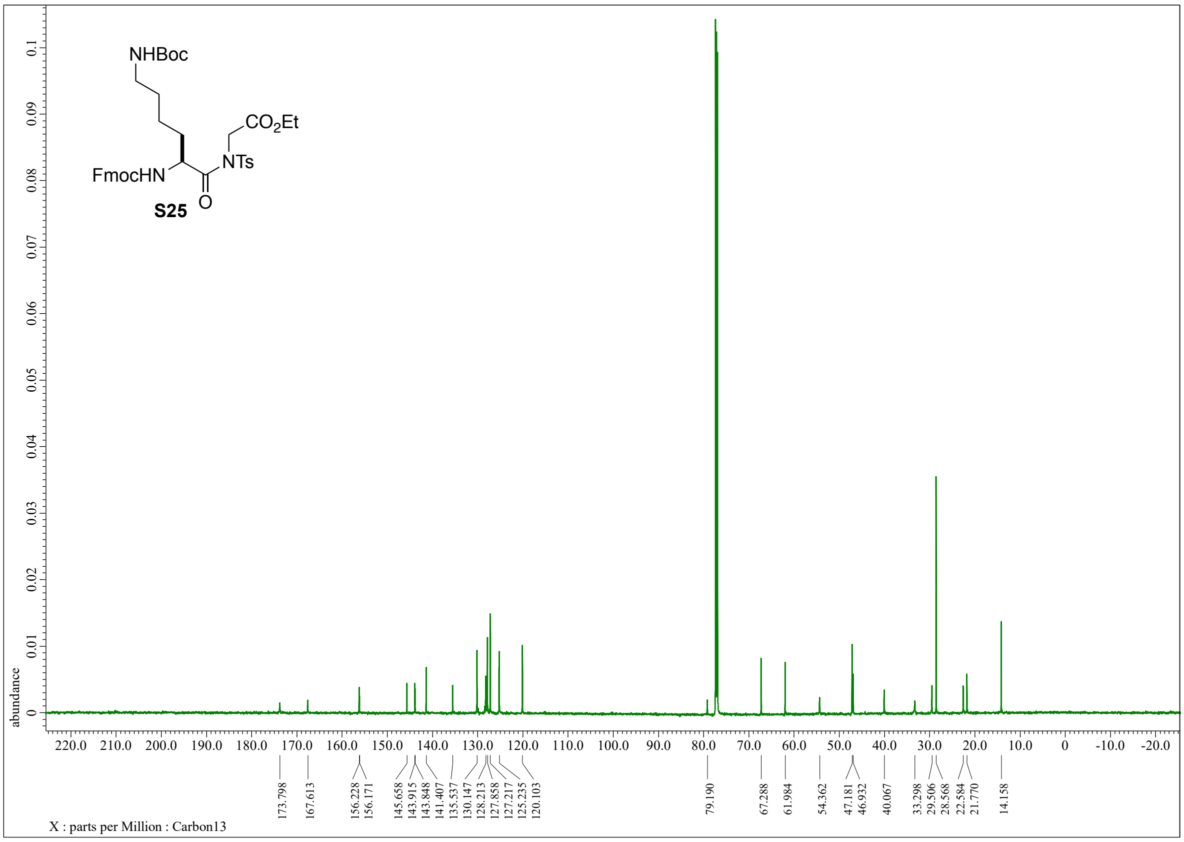


Figure S31. ^{13}C NMR spectrum (150 MHz) of **S25** in $CDCl_3$.

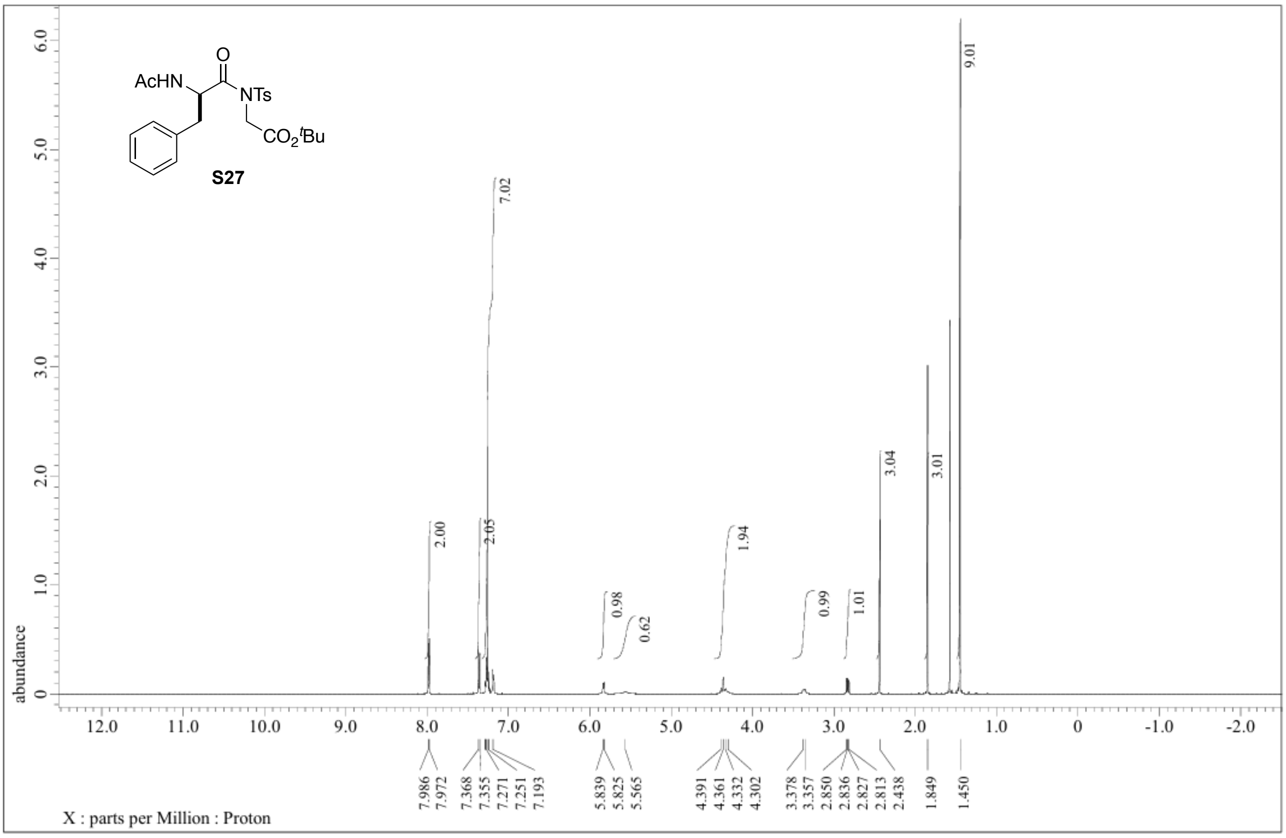


Figure S32. ^{1}H NMR spectrum (600 MHz) of **S27** in $CDCl_3$.

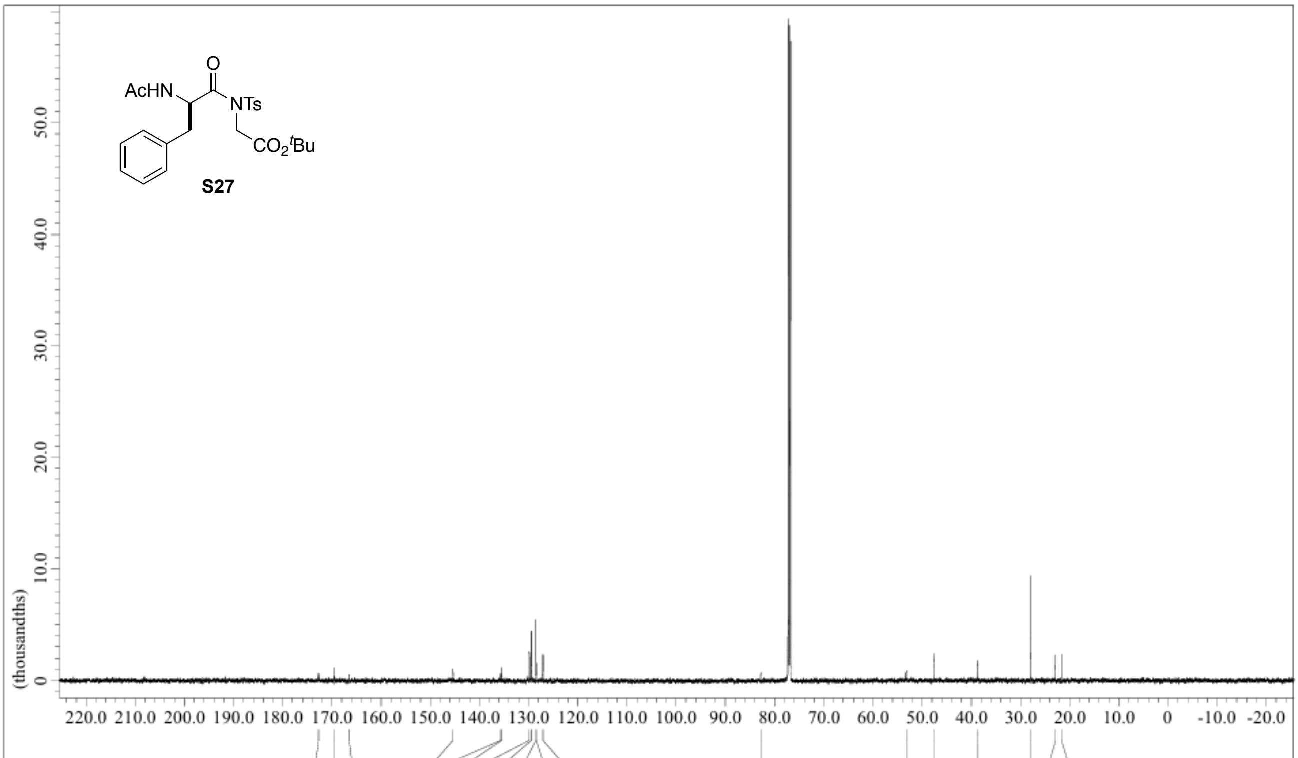


Figure S33. ^{13}C NMR spectrum (150 MHz) of **S27** in $CDCl_3$.

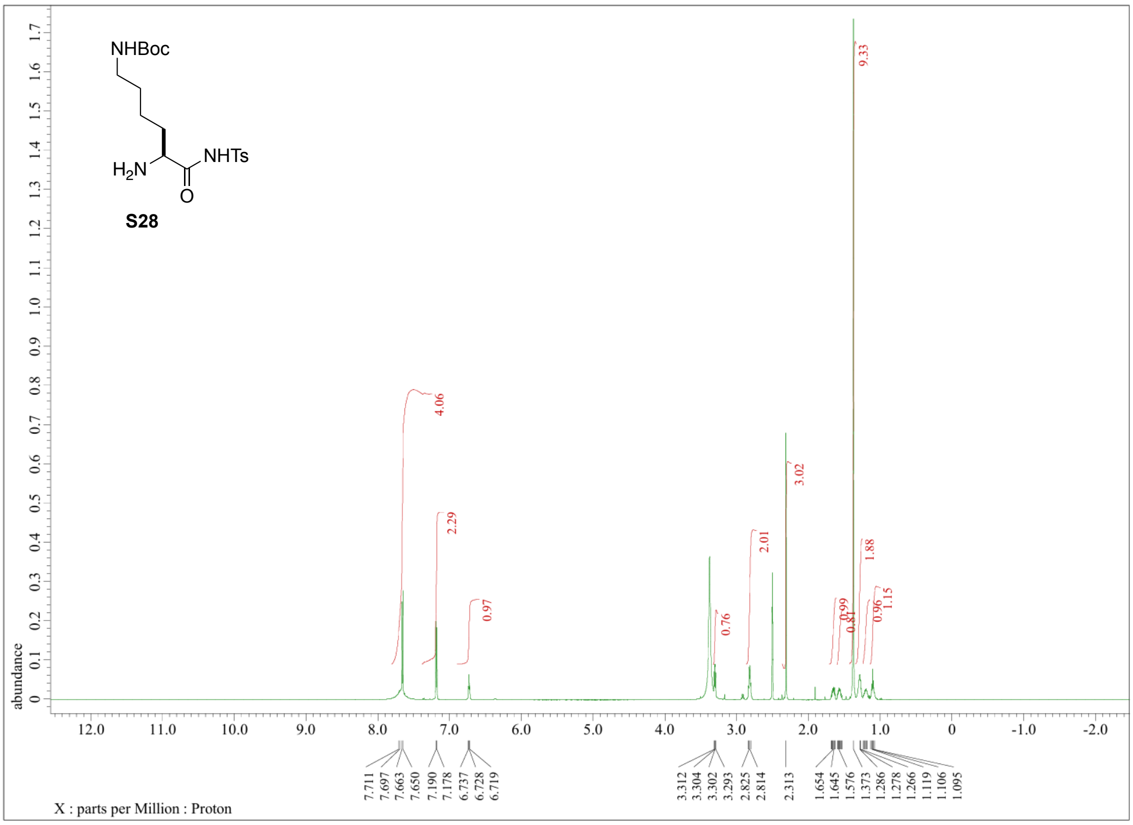


Figure S34. ^{1}H NMR spectrum (600 MHz) of **S28** in DMSO-d_6.

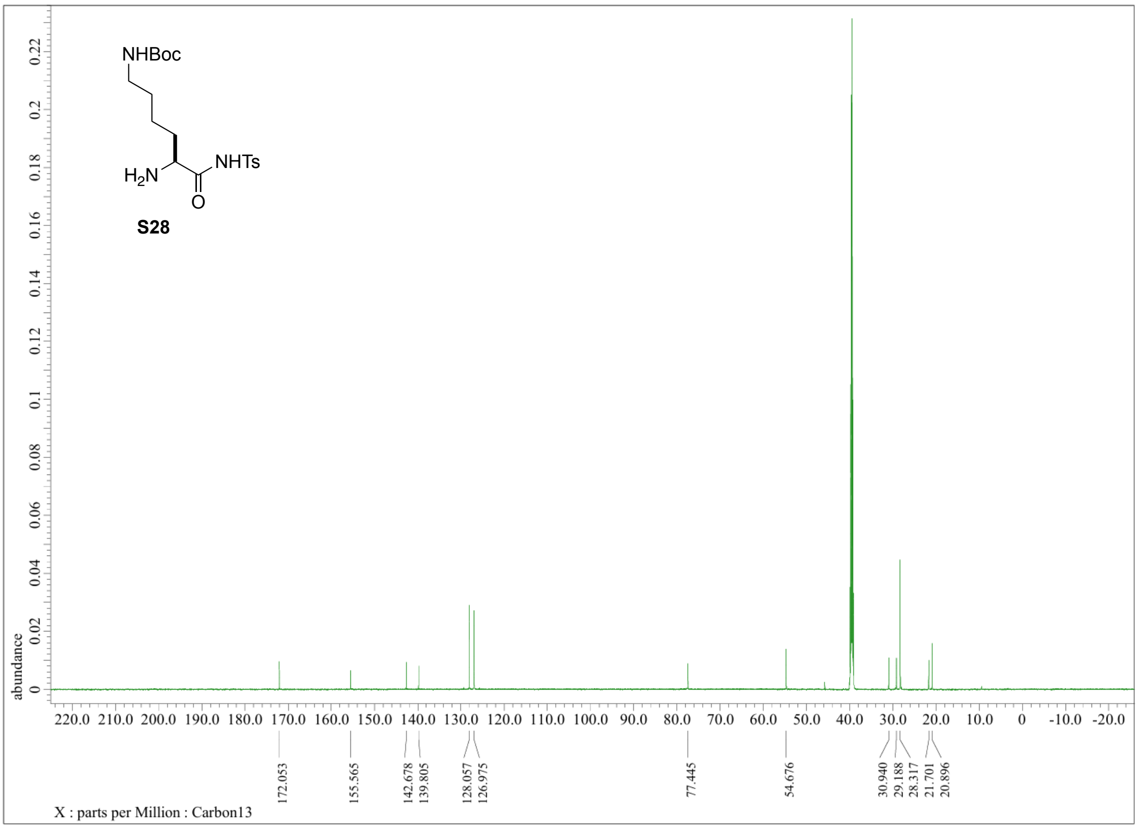


Figure S35. ^{13}C NMR spectrum (150 MHz) of **S28** in DMSO-d_6.

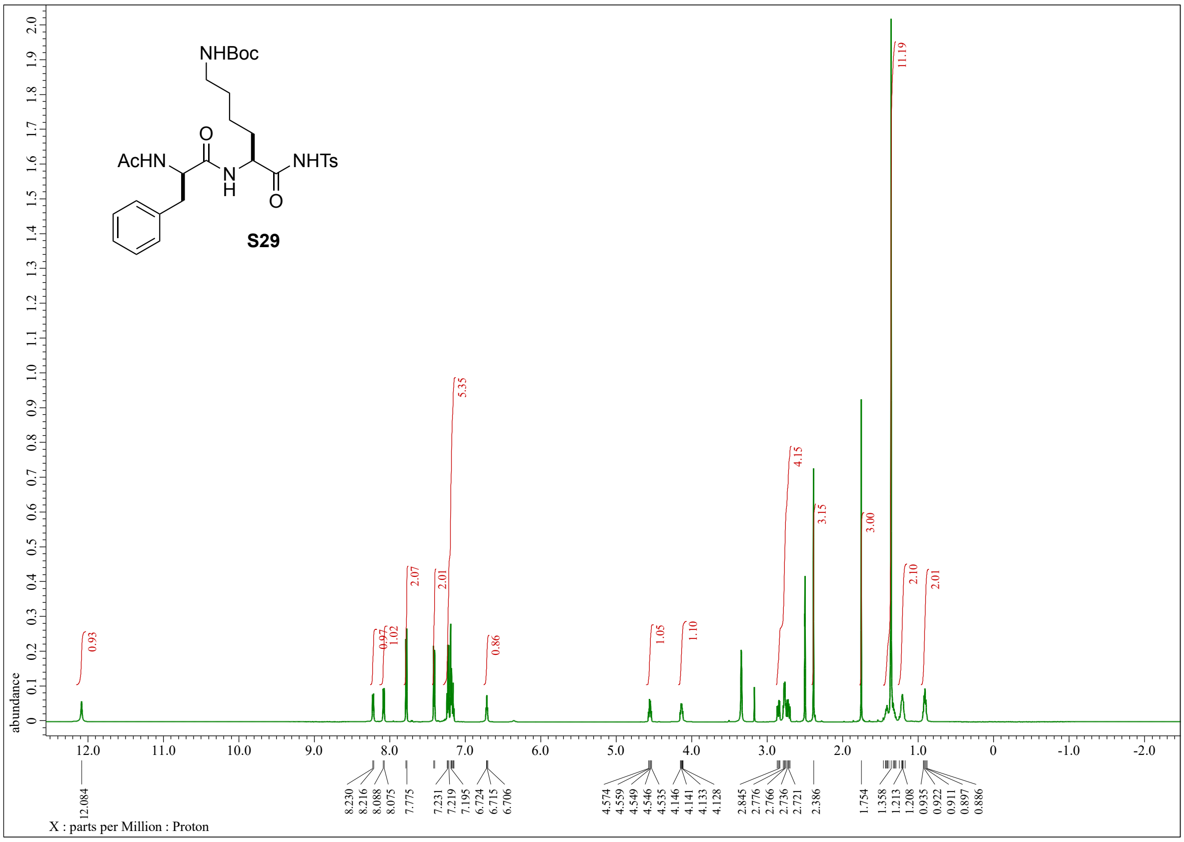


Figure S36. ^{1}H NMR spectrum (600 MHz) of **S29** in DMSO-d_6.

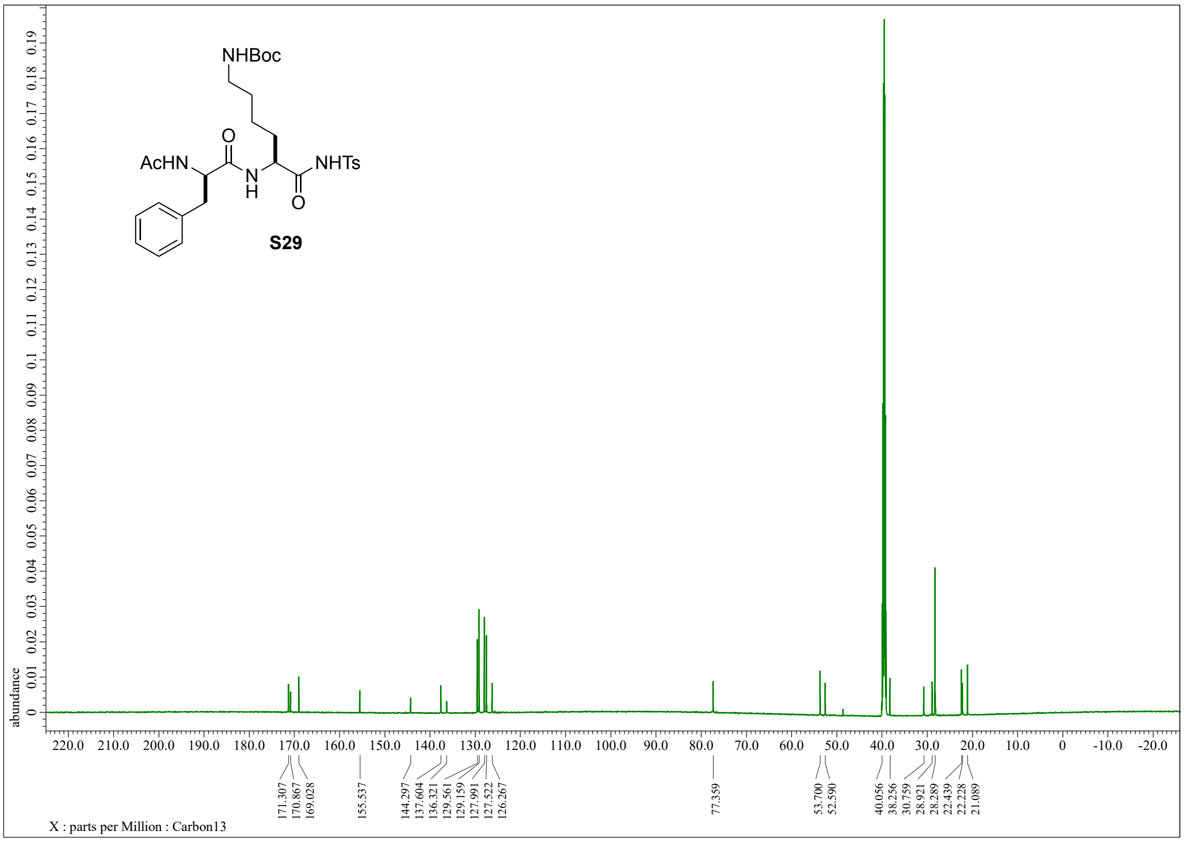


Figure S37. ^{13}C NMR spectrum (150 MHz) of **S29** in DMSO-d_6.

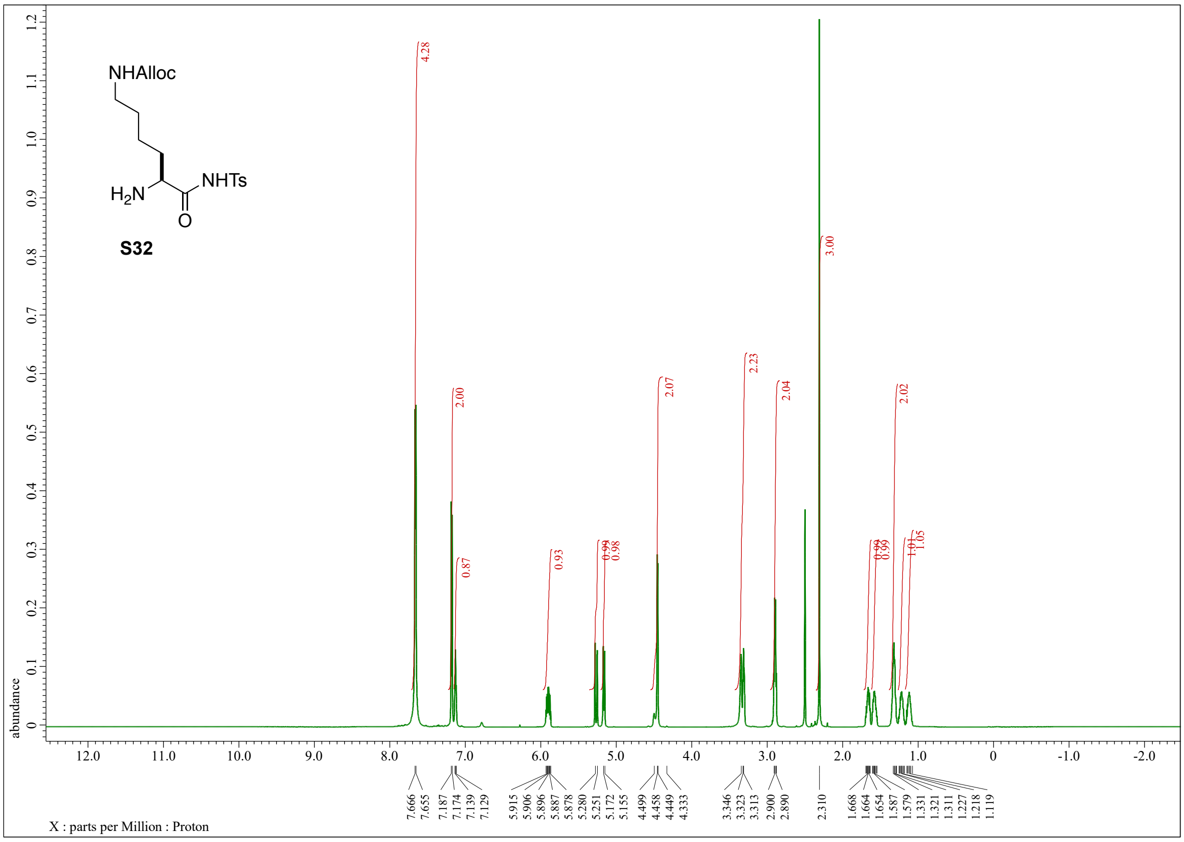


Figure S38. ^{1}H NMR spectrum (600 MHz) of **S32** in DMSO-d_6.

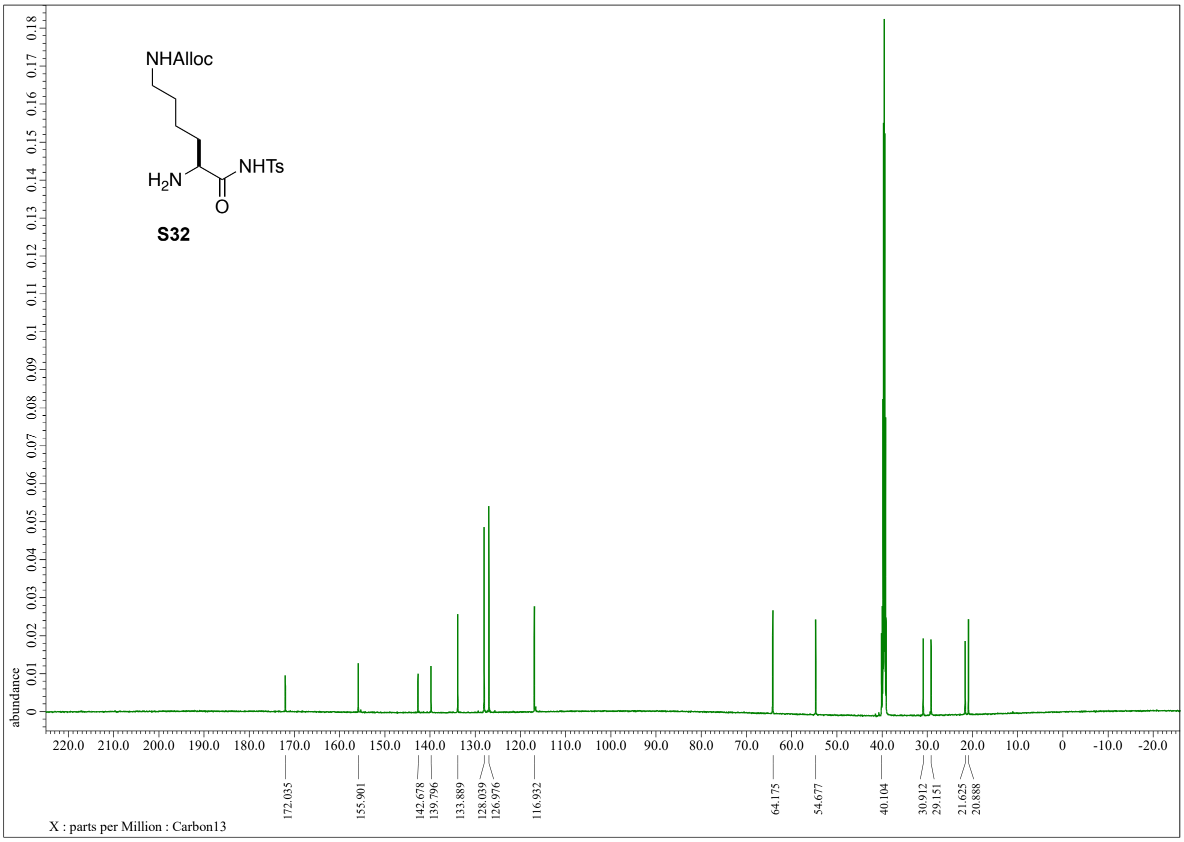


Figure S39. ^{13}C NMR spectrum (150 MHz) of **S32** in DMSO-d_6.

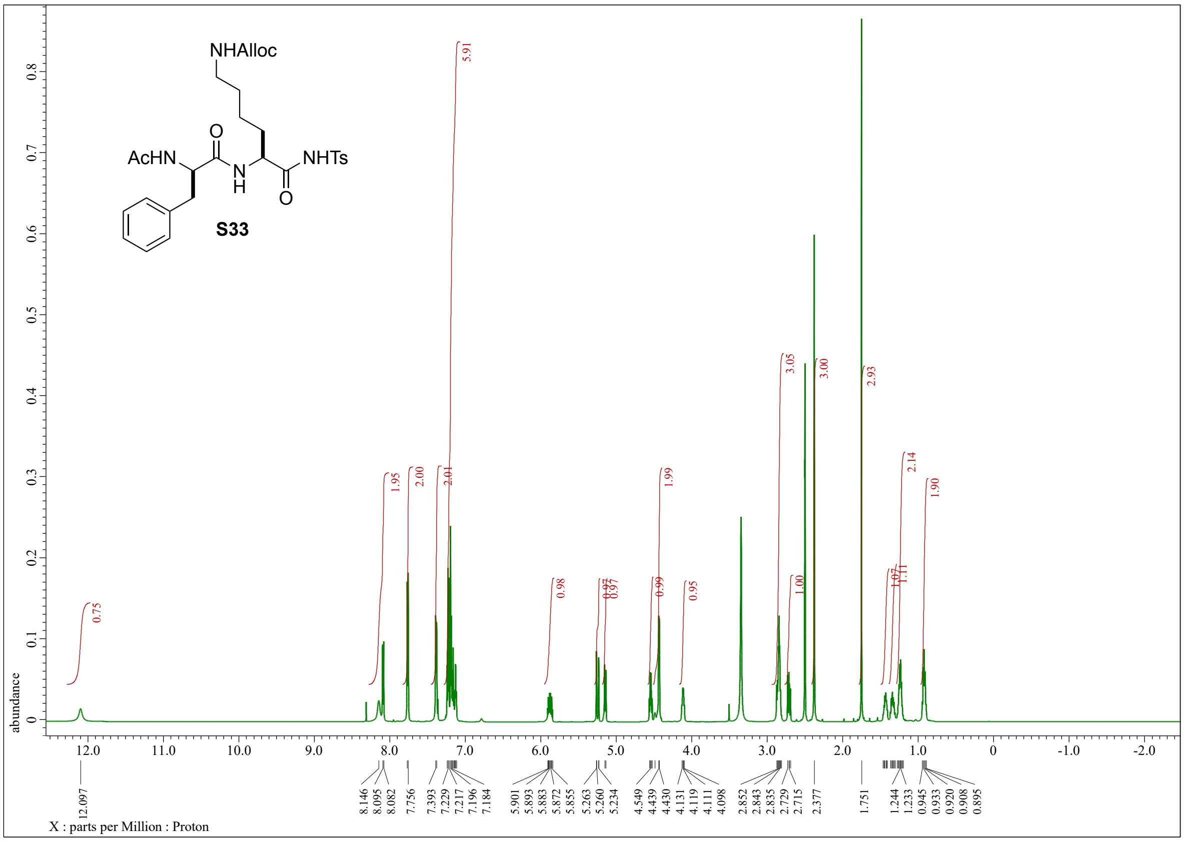


Figure S40. ^{1}H NMR spectrum (600 MHz) of **S33** in DMSO-d_6.

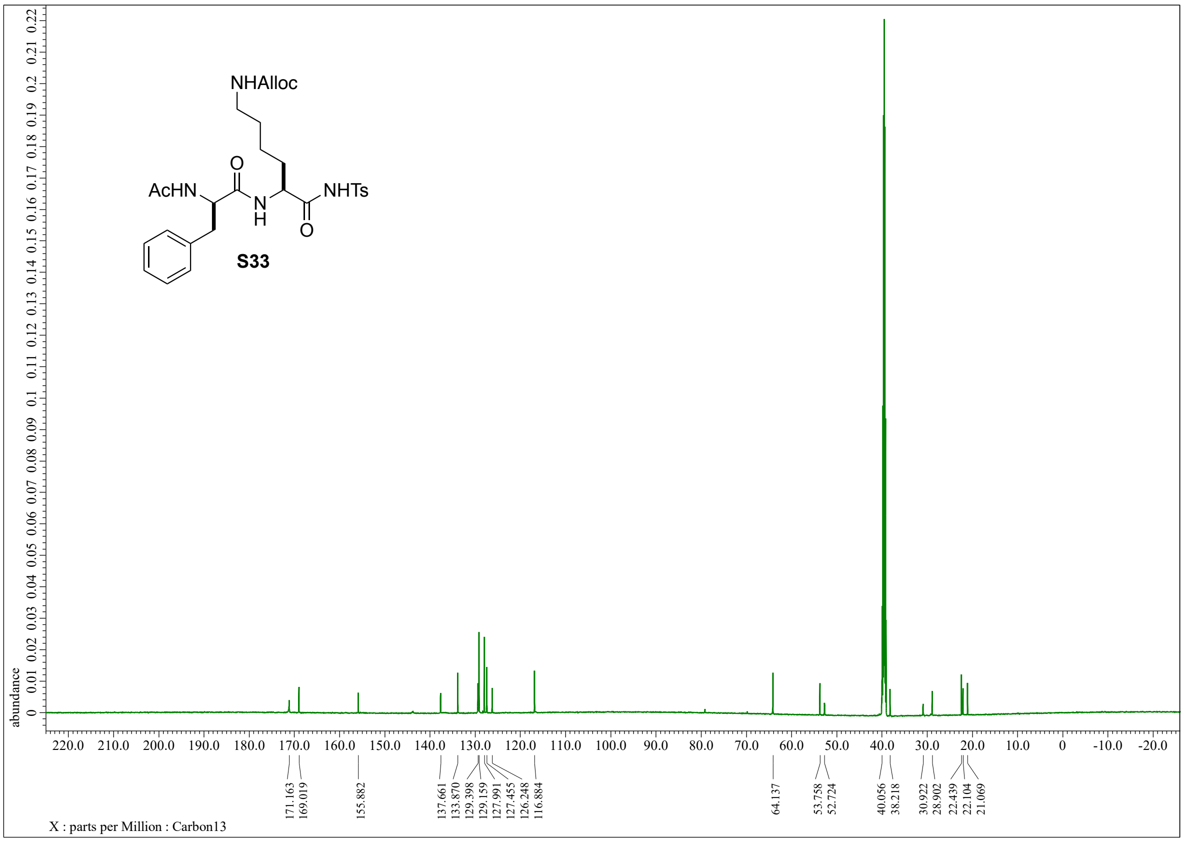


Figure S41. ^{13}C NMR spectrum (150 MHz) of **S33** in DMSO-d_6.

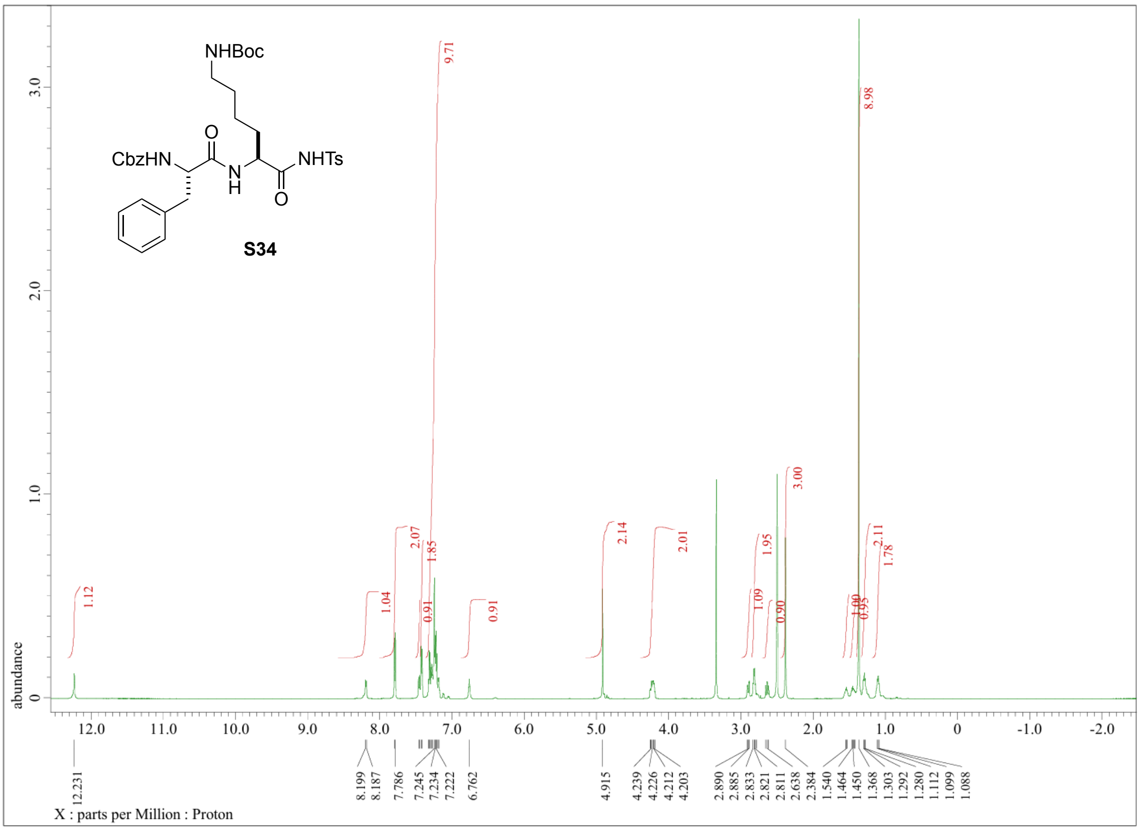


Figure S42. ^{1}H NMR spectrum (600 MHz) of **S34** in DMSO-d_6.

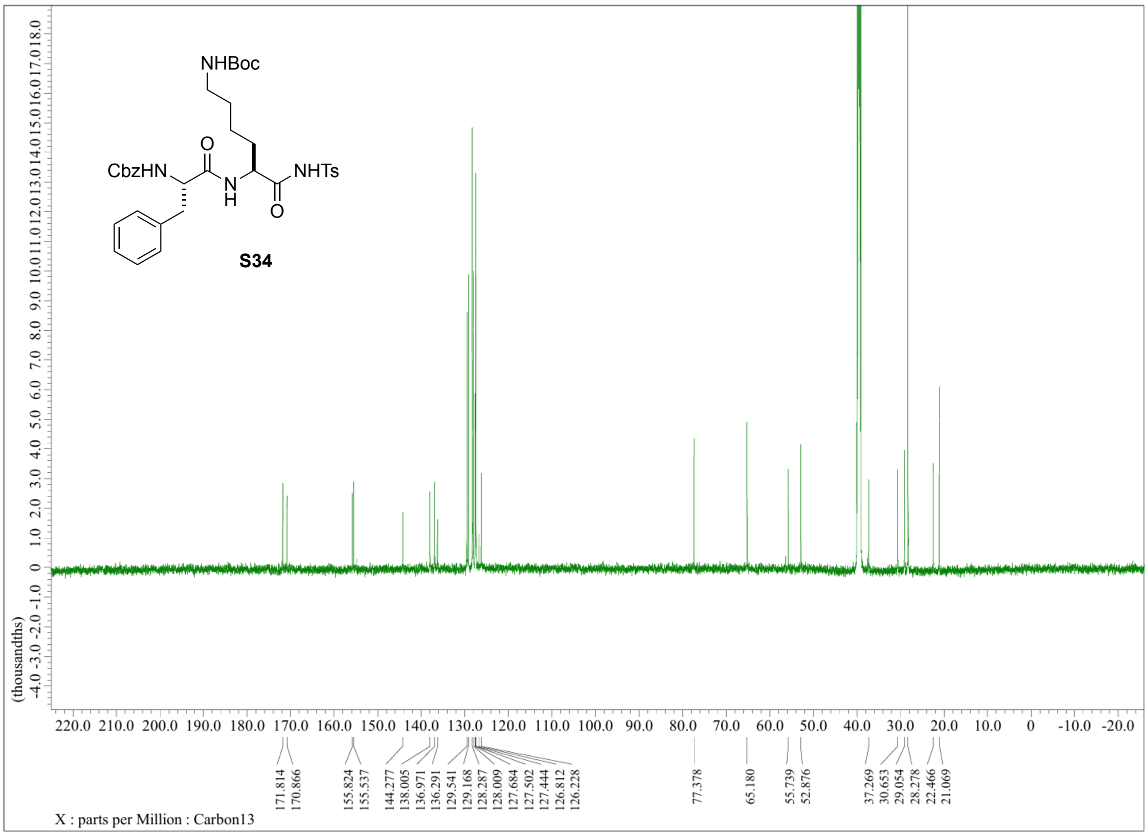


Figure S43. ^{13}C NMR spectrum (150 MHz) of **S34** in DMSO-d_6.

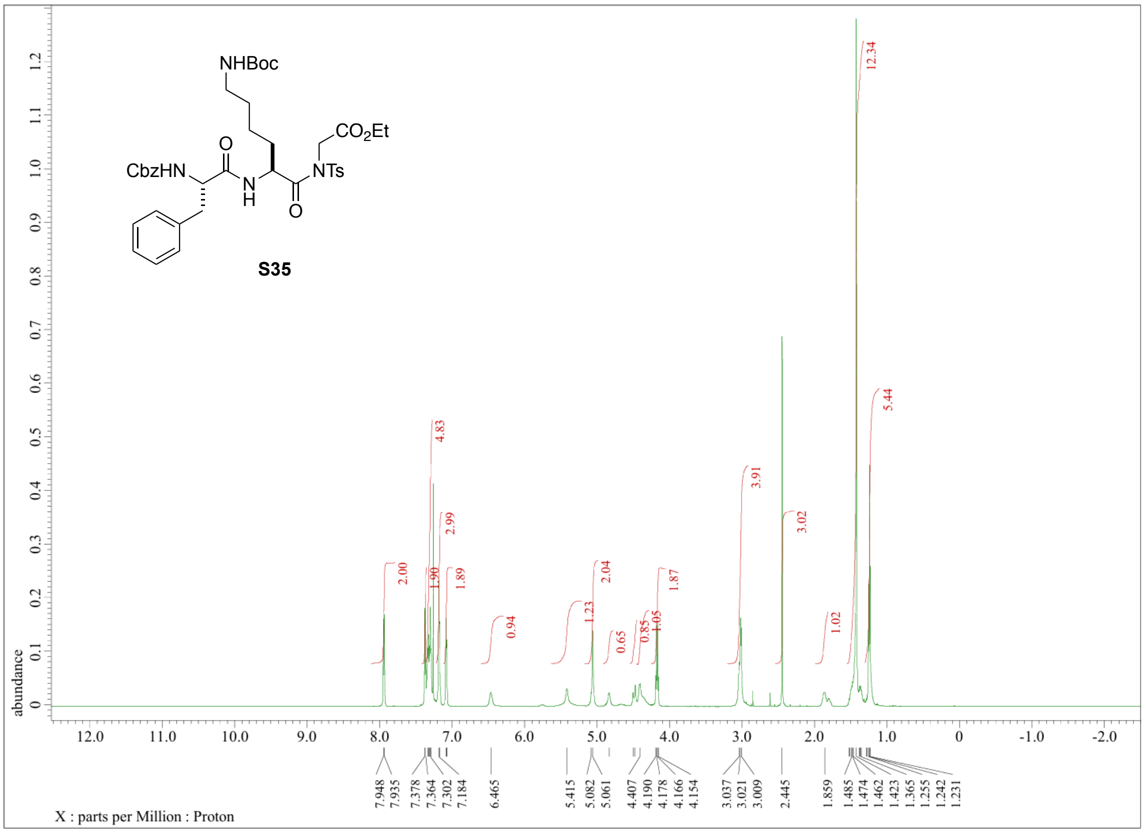


Figure S44. ^{1}H NMR spectrum (600 MHz) of **S35** in CDCl$_3$.

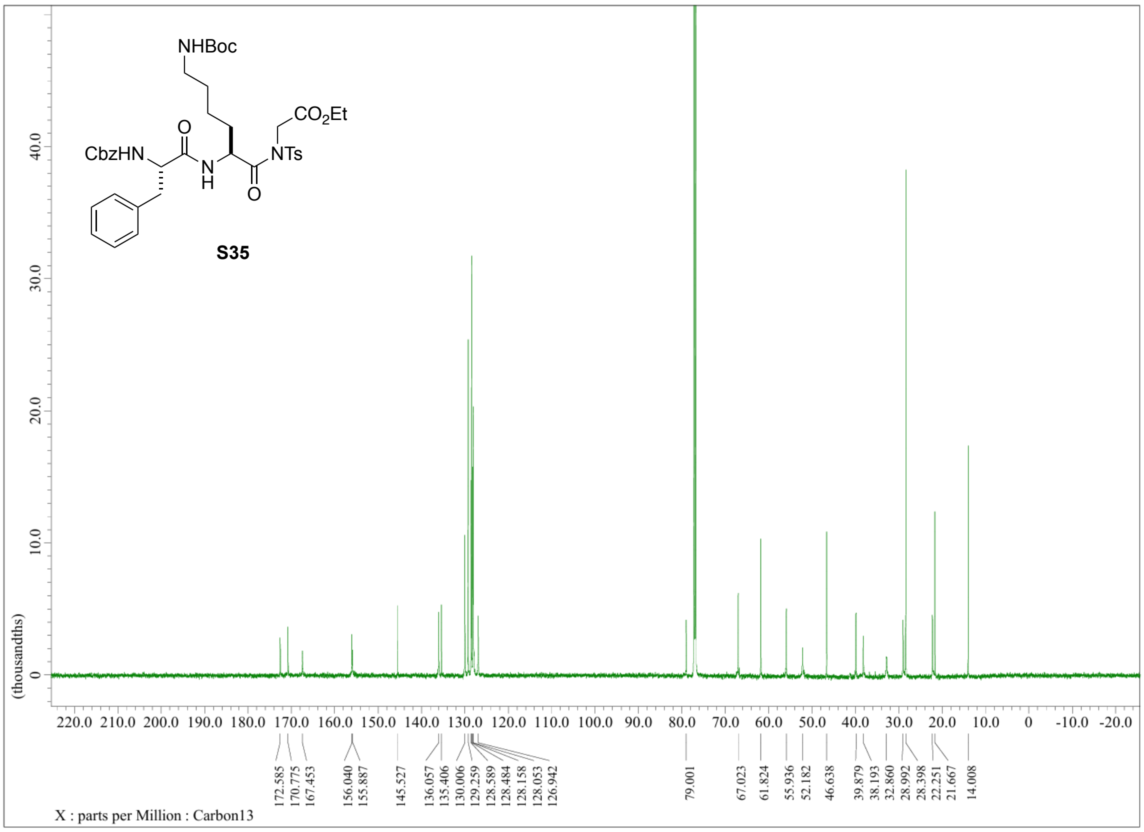


Figure S45. ^{13}C NMR spectrum (150 MHz) of **S35** in CDCl$_3$.

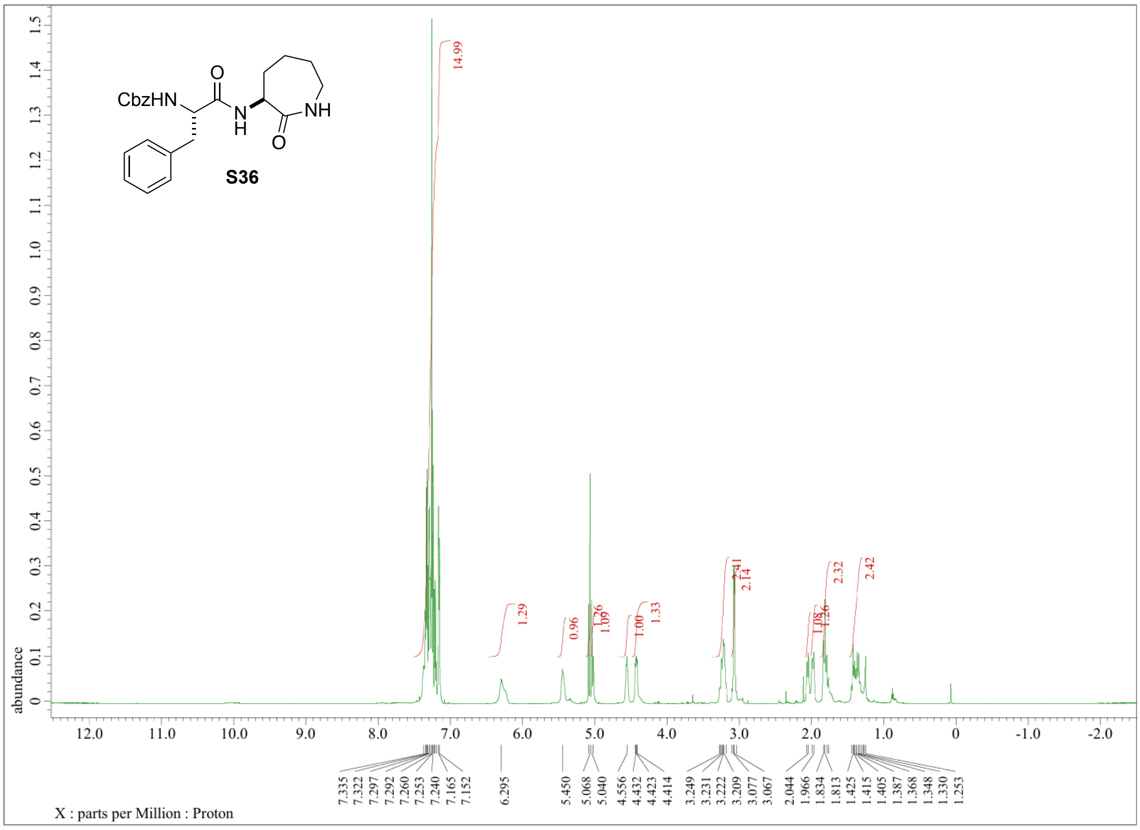


Figure S46. ^{1}H NMR spectrum (600 MHz) of **S36** in $CDCl_3$.

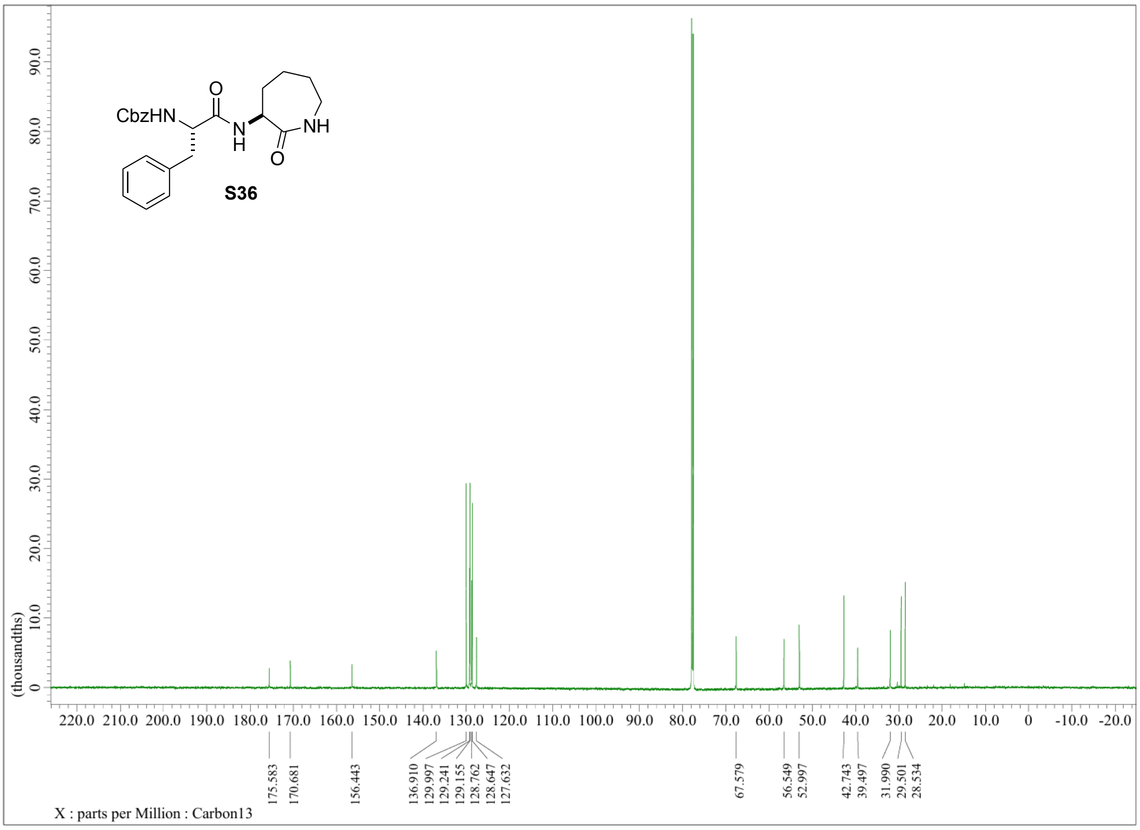


Figure S47. ^{13}C NMR spectrum (150 MHz) of **S36** in $CDCl_3$.

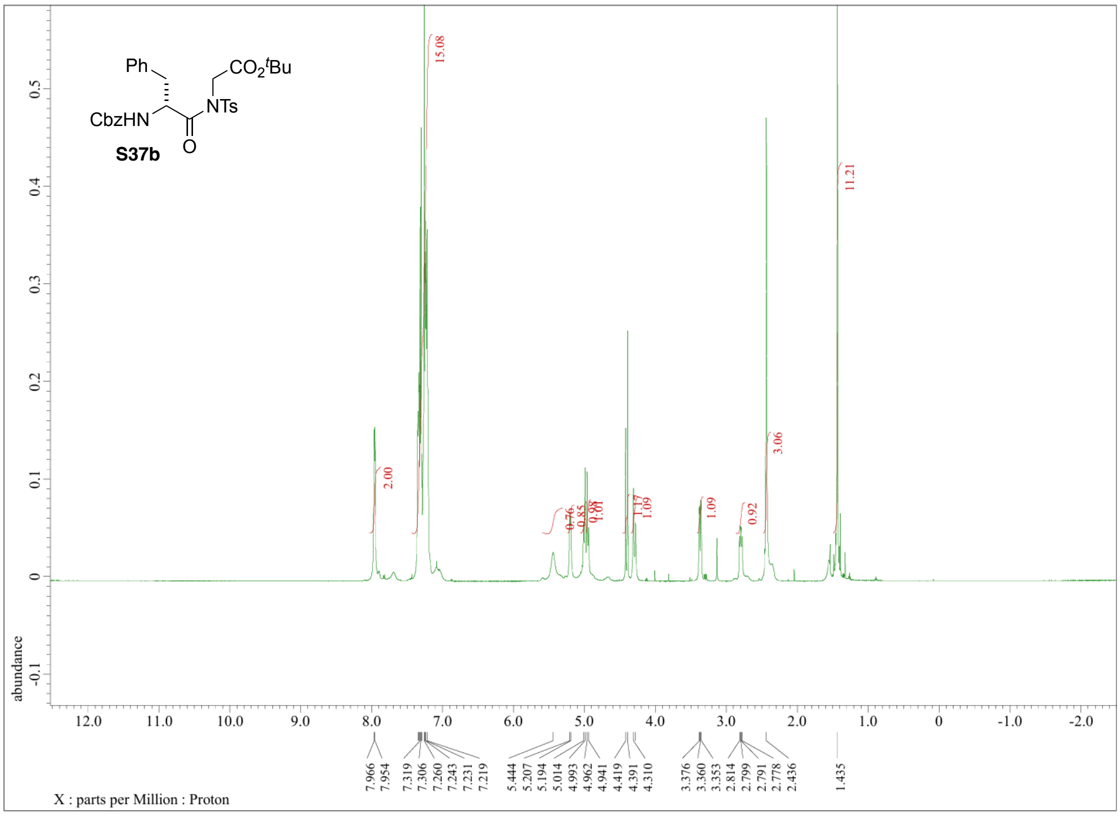


Figure S48. ^{1}H NMR spectrum (600 MHz) of **S37b** in CDCl$_3$.

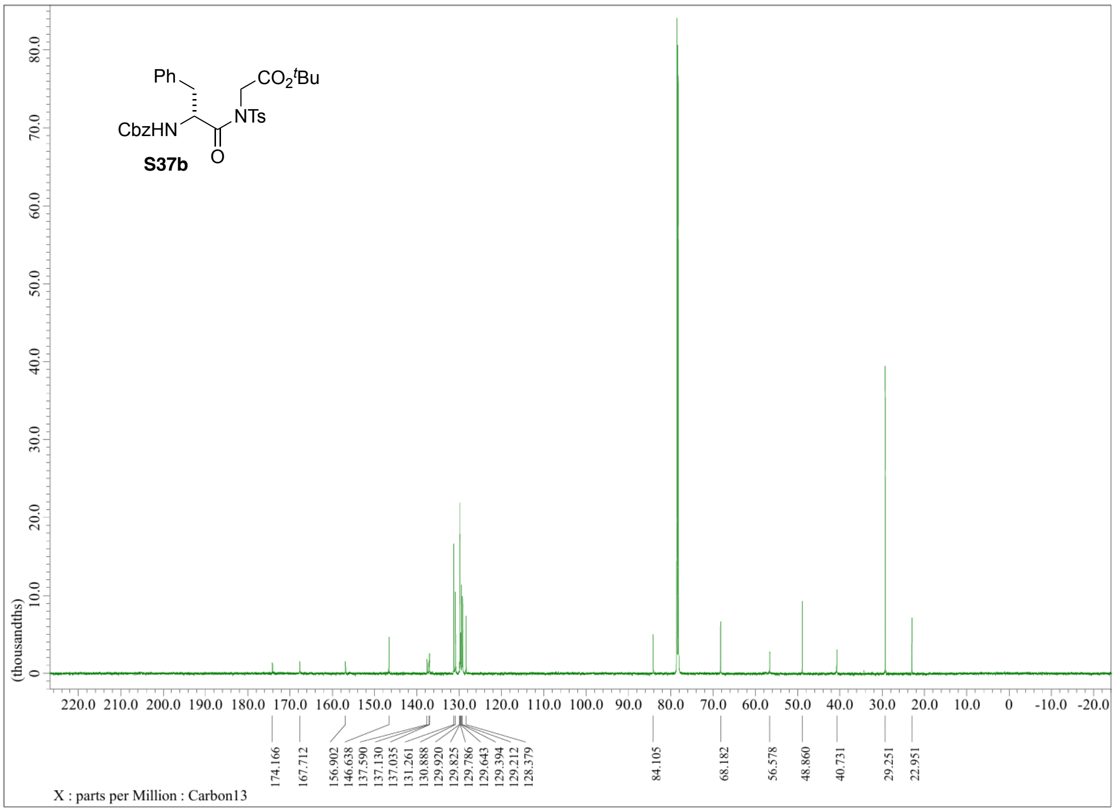


Figure S49. ^{13}C NMR spectrum (150 MHz) of **S37b** in CDCl$_3$.

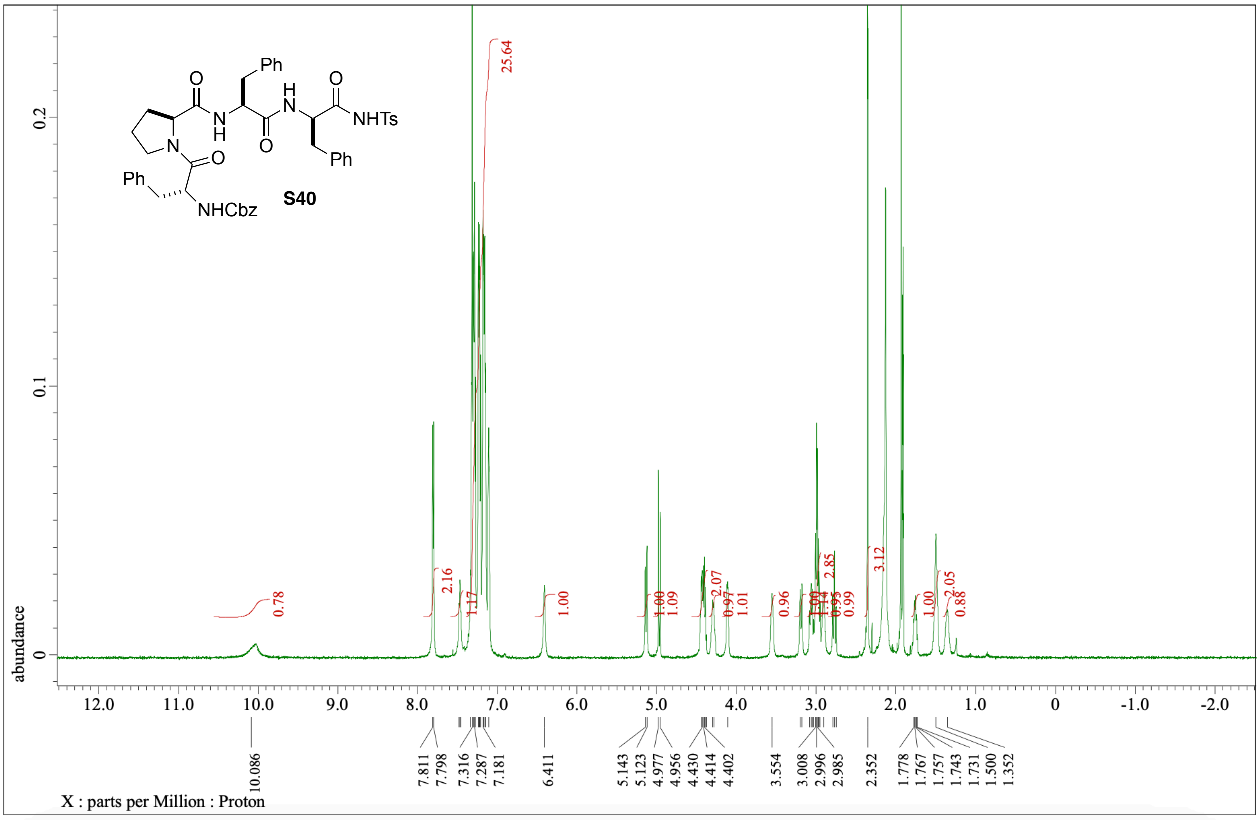


Figure S50. ^{1}H NMR spectrum (600 MHz) of **S40** in CD_3CN.

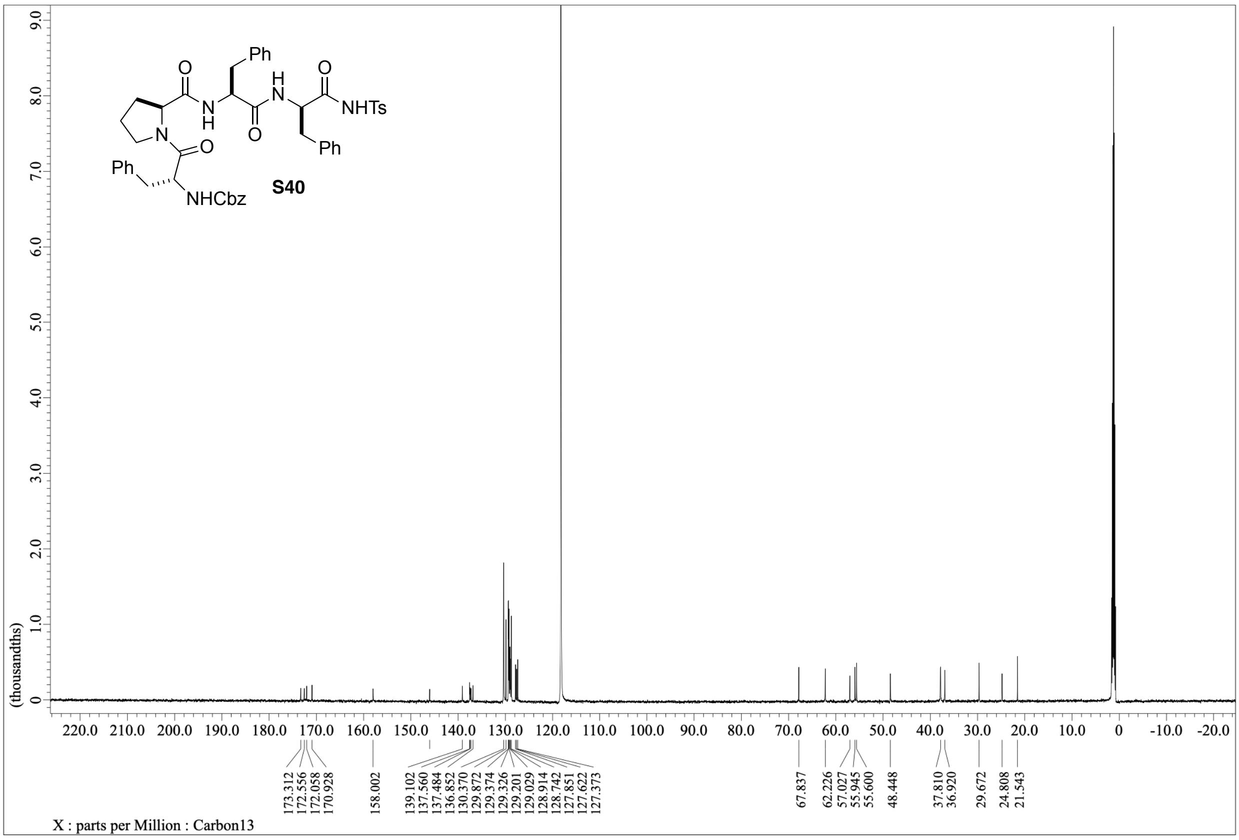


Figure S51. ^{13}C NMR spectrum (150 MHz) of **S40** in CD_3CN.

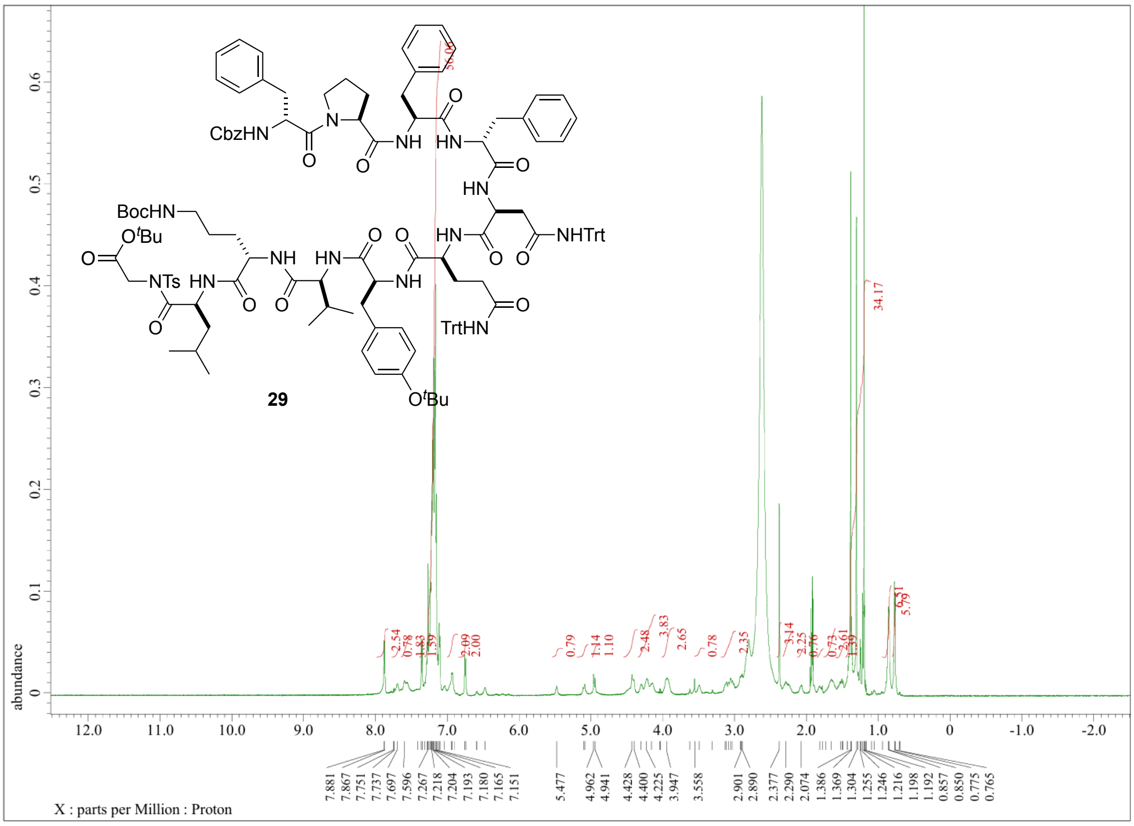


Figure S52. ^{1}H NMR spectrum (600 MHz) of **29** in CD_3CN.

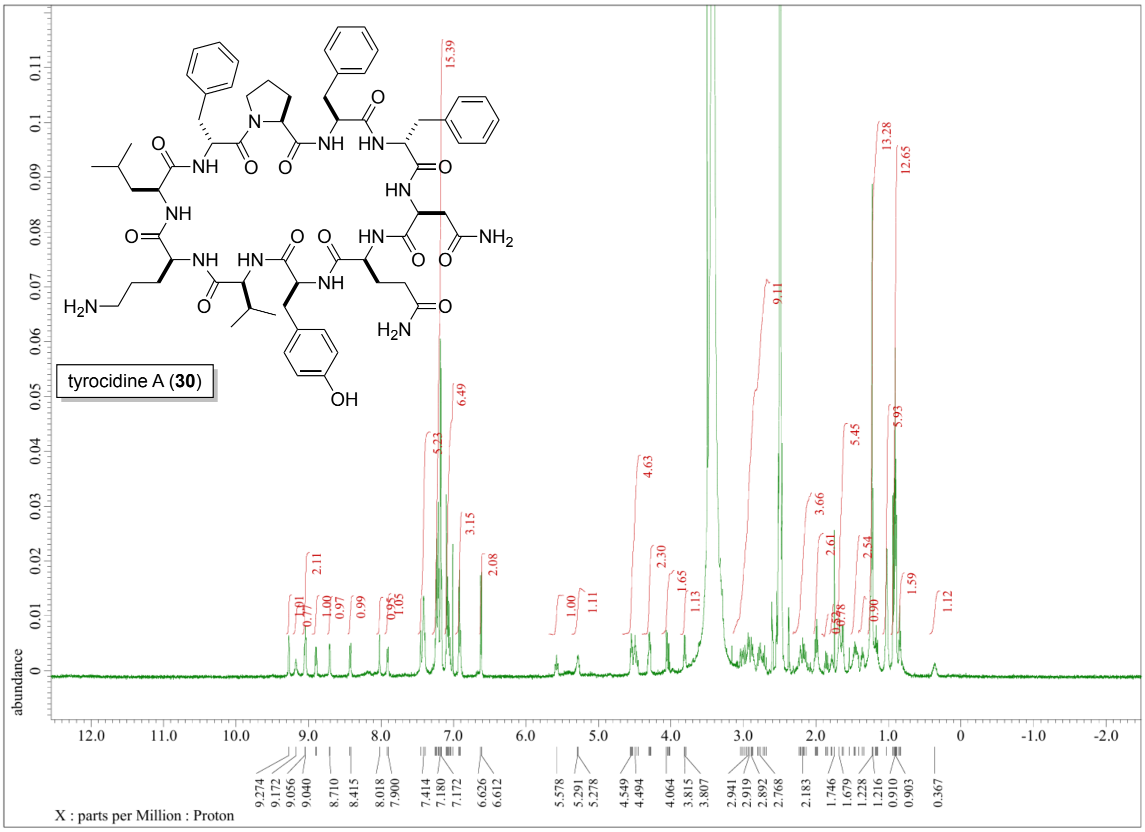


Figure S53. ^{1}H NMR spectrum (600 MHz) of **30** in DMSO-d_6.

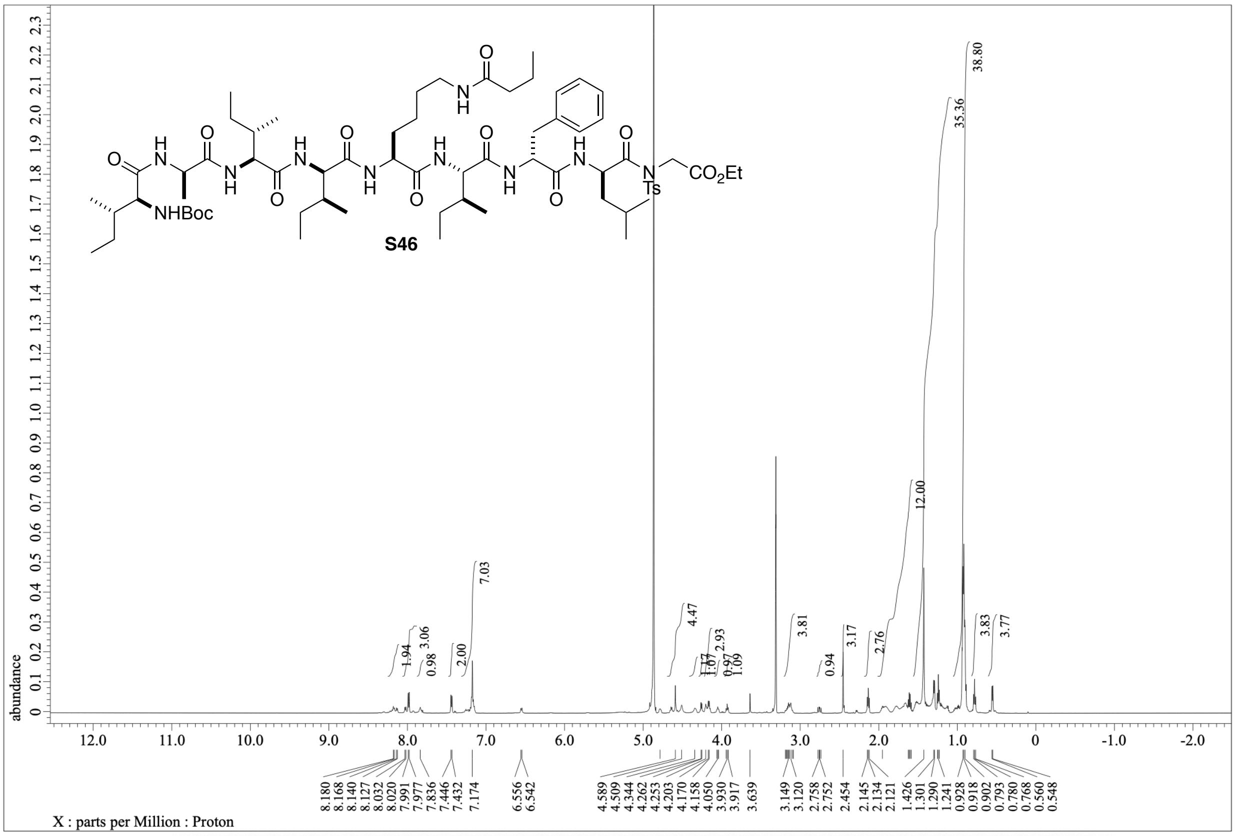


Figure S54. ^{1}H NMR spectrum (600 MHz) of **S46** in CD_3OD.

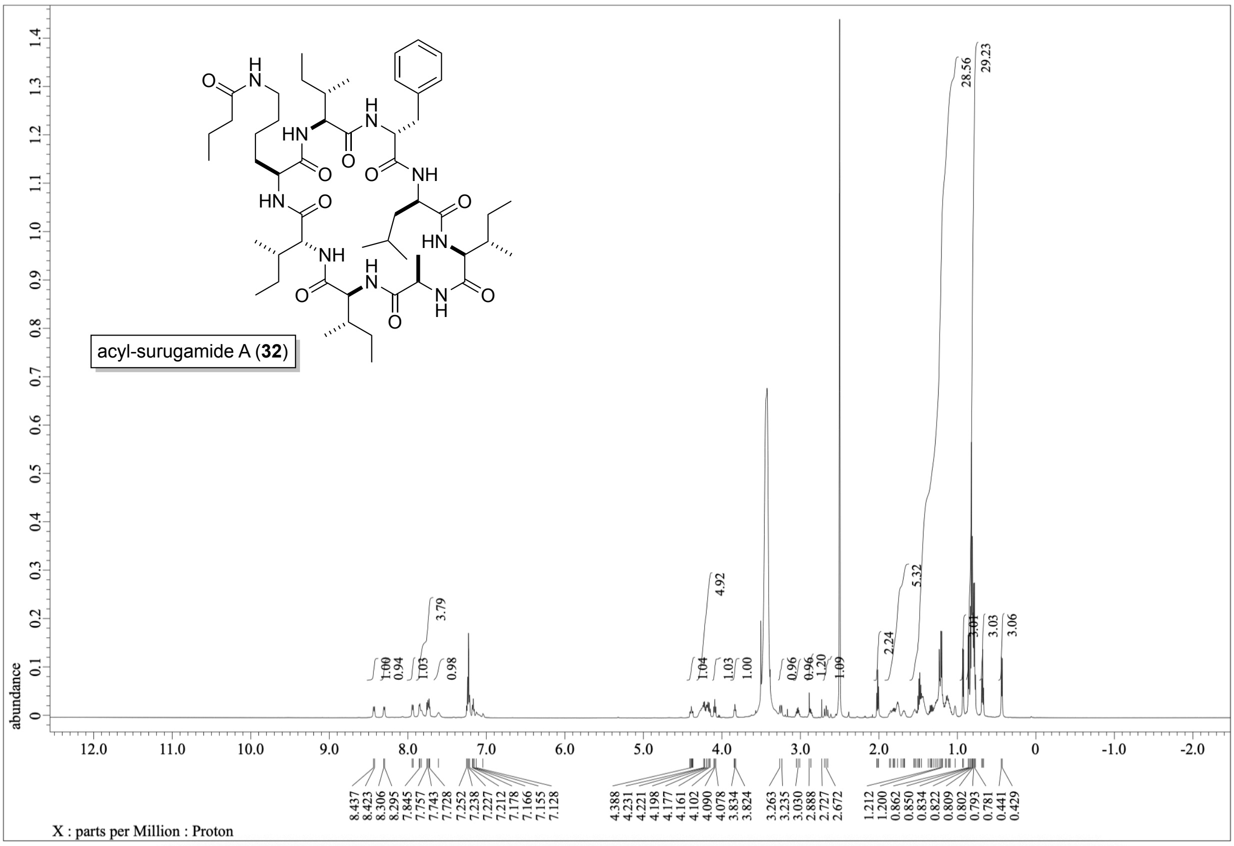


Figure S55. ^{1}H NMR spectrum (600 MHz) of **32** in DMSO-d_6.

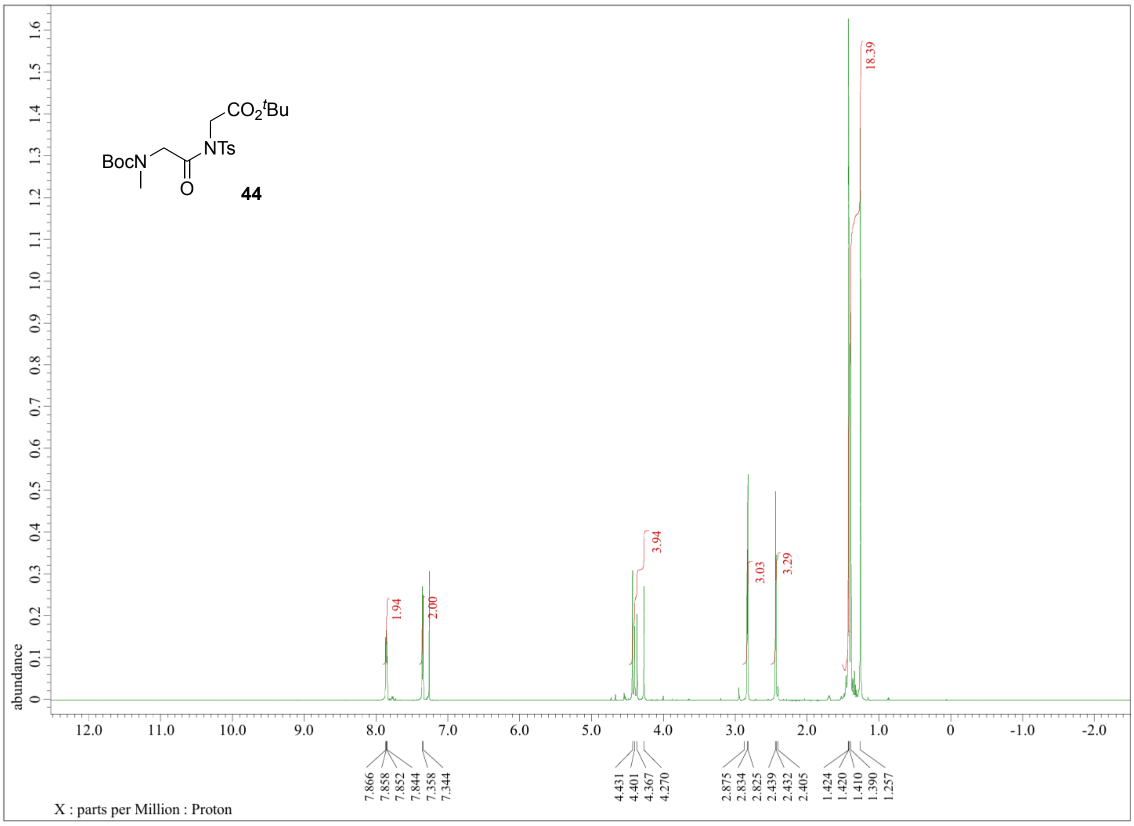


Figure S56. ^{1}H NMR spectrum (600 MHz) of **44** in $CDCl_3$.

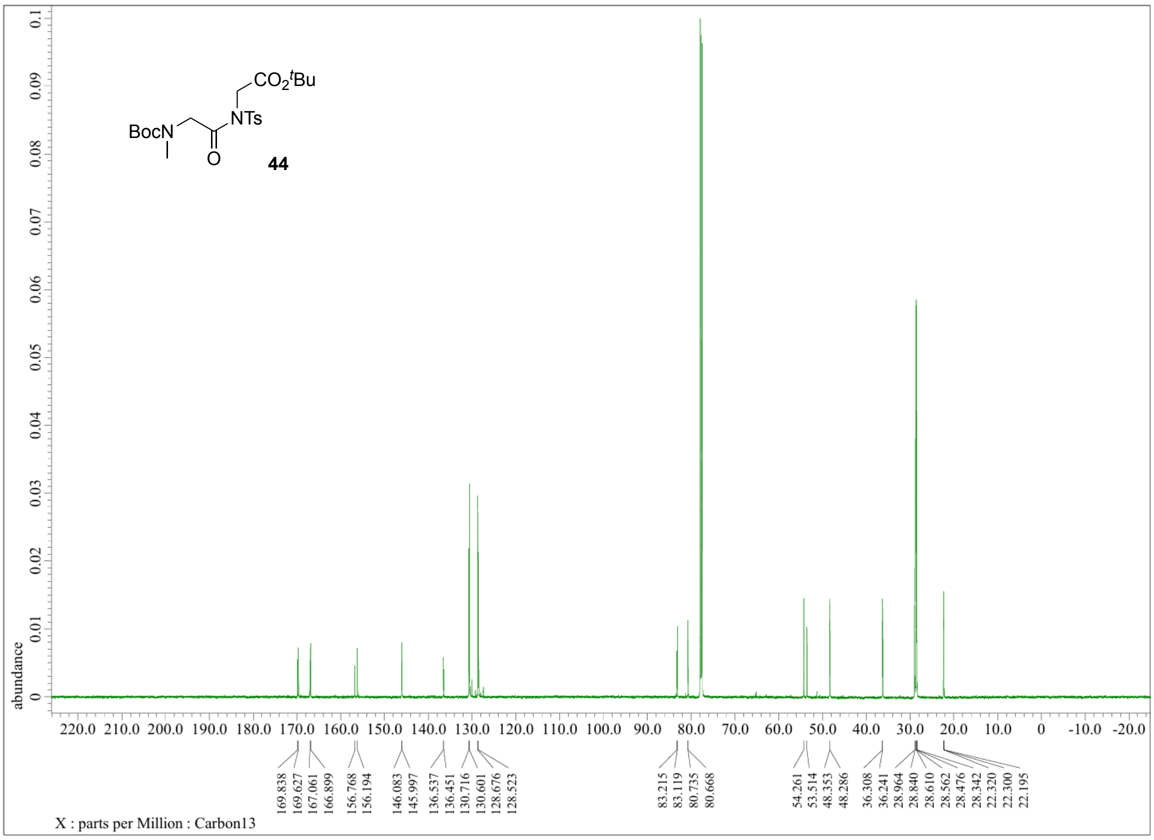


Figure S57. ^{13}C NMR spectrum (150 MHz) of **44** in $CDCl_3$.

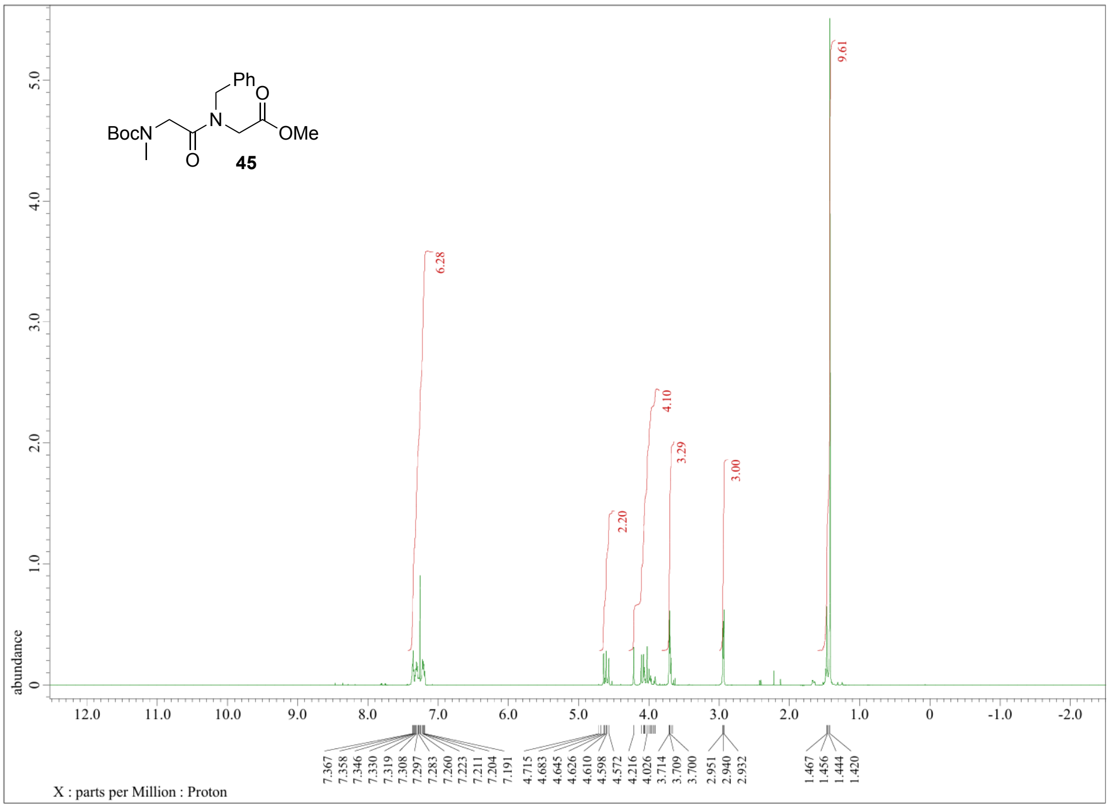


Figure S58. ^{1}H NMR spectrum (600 MHz) of **45** in CDCl$_3$.

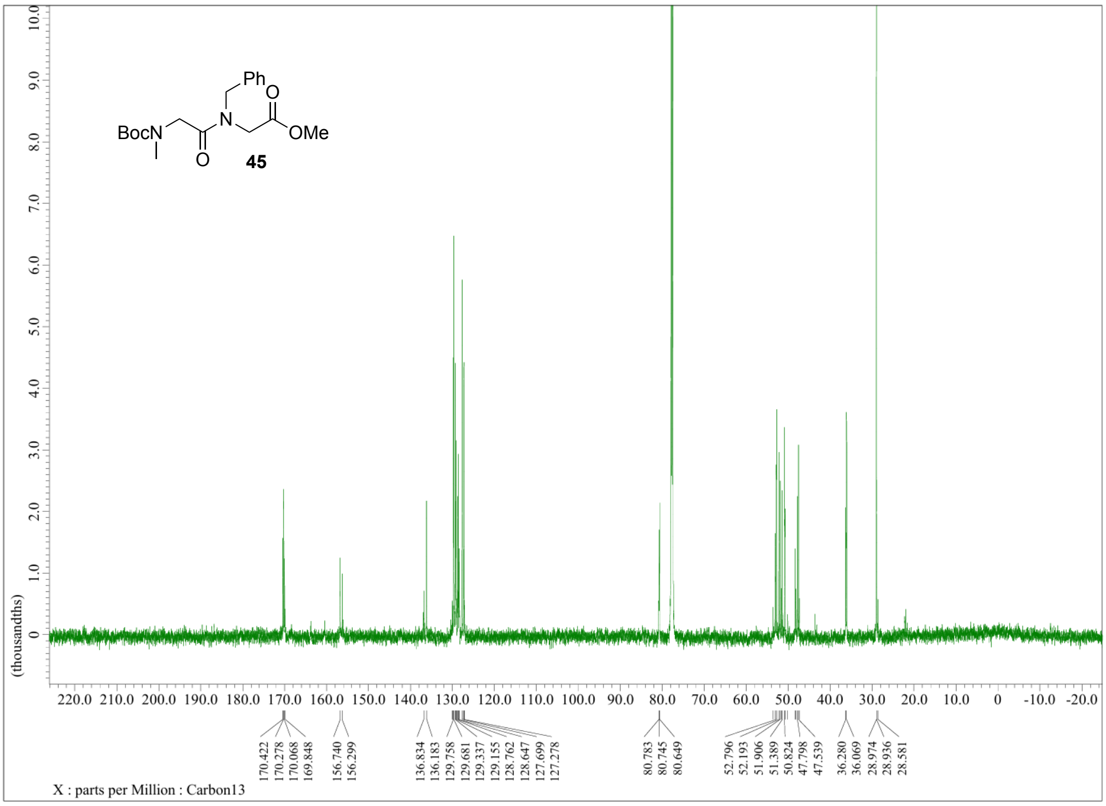


Figure S59. ^{13}C NMR spectrum (150 MHz) of **45** in CDCl$_3$.

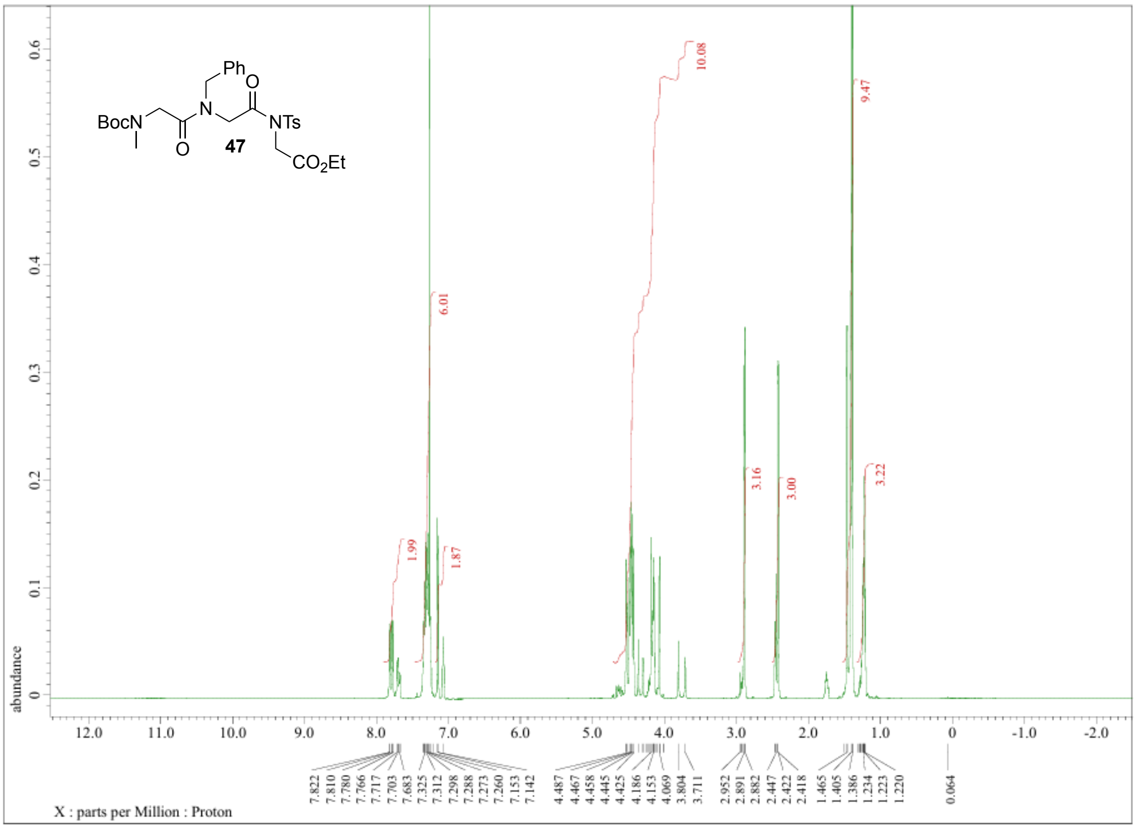


Figure S60. ^{1}H NMR spectrum (600 MHz) of **47** in CDCl$_3$.

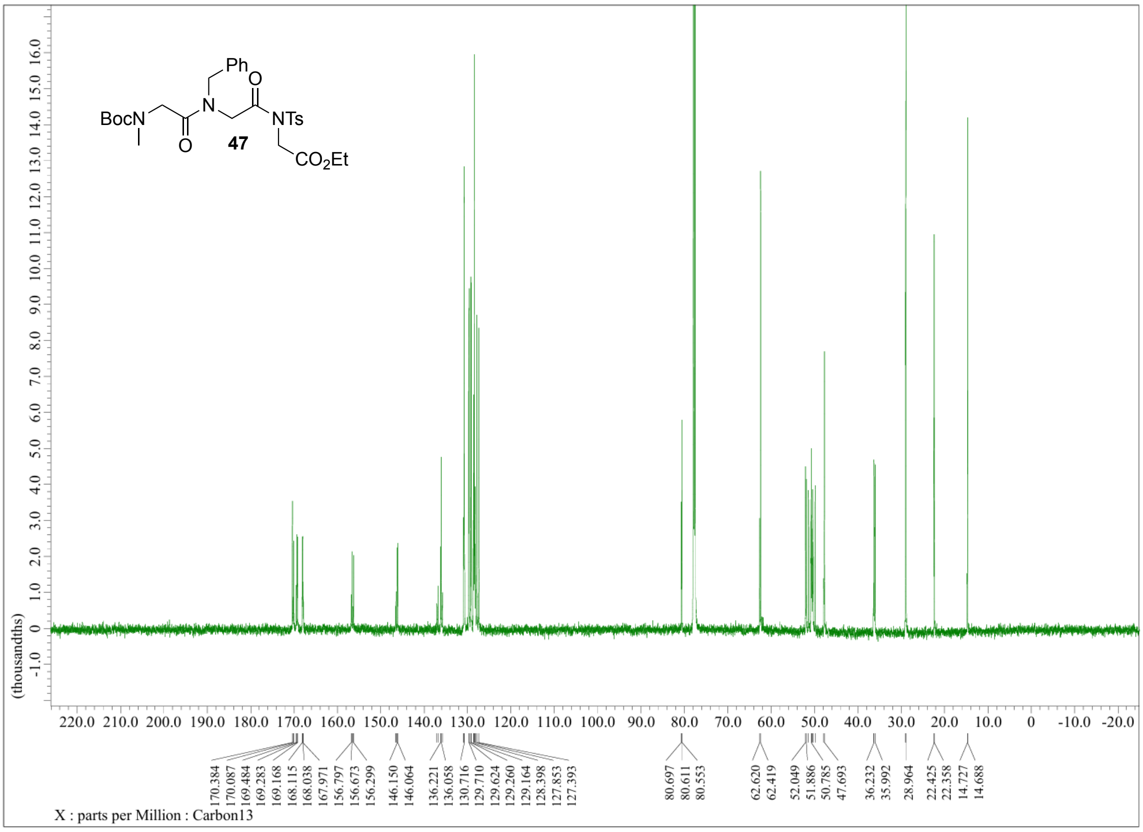


Figure S61. ^{13}C NMR spectrum (150 MHz) of **47** in CDCl$_3$.

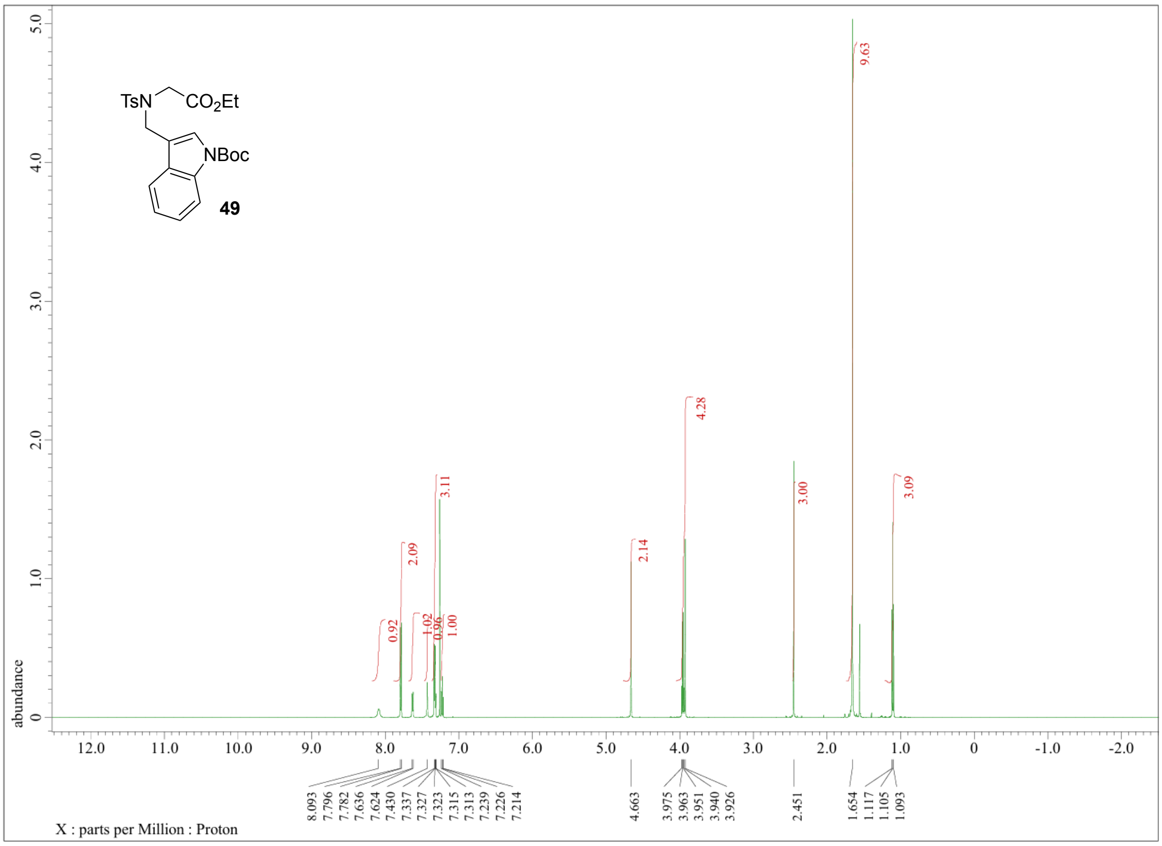


Figure S62. ^{1}H NMR spectrum (600 MHz) of **49** in CDCl$_3$.

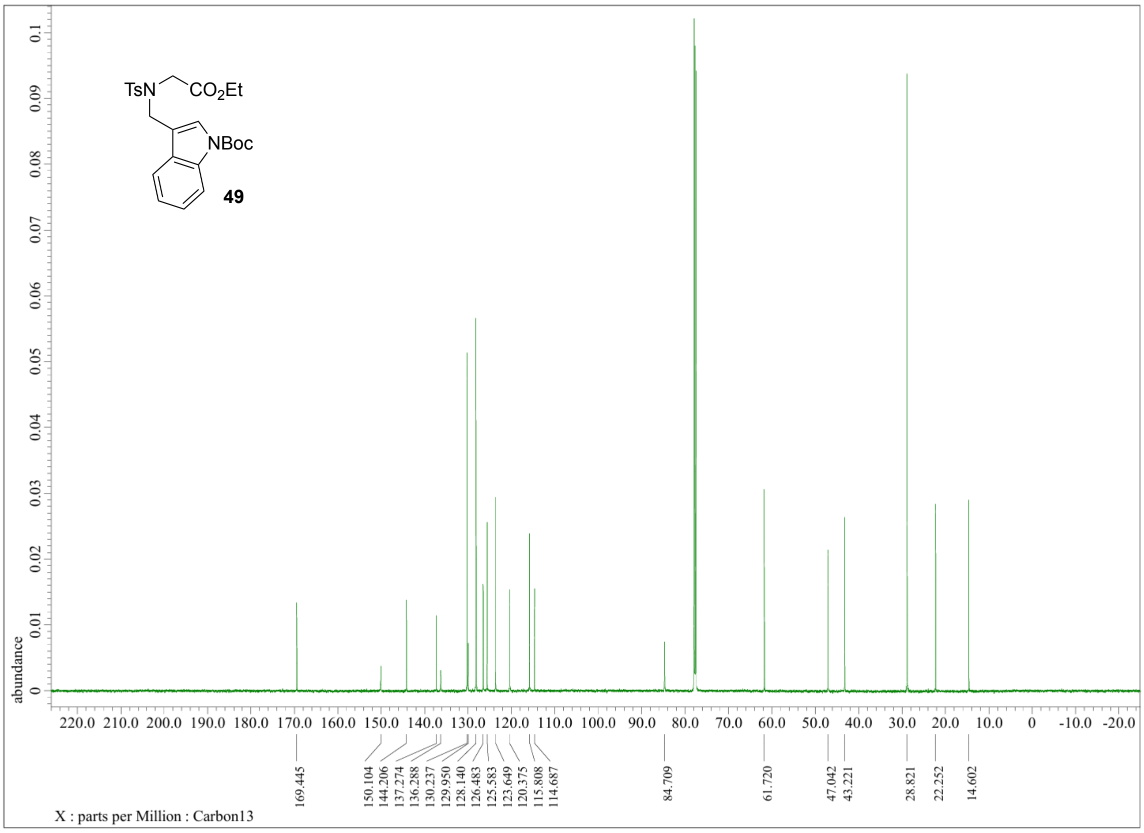


Figure S63. ^{13}C NMR spectrum (150 MHz) of **49** in CDCl$_3$.

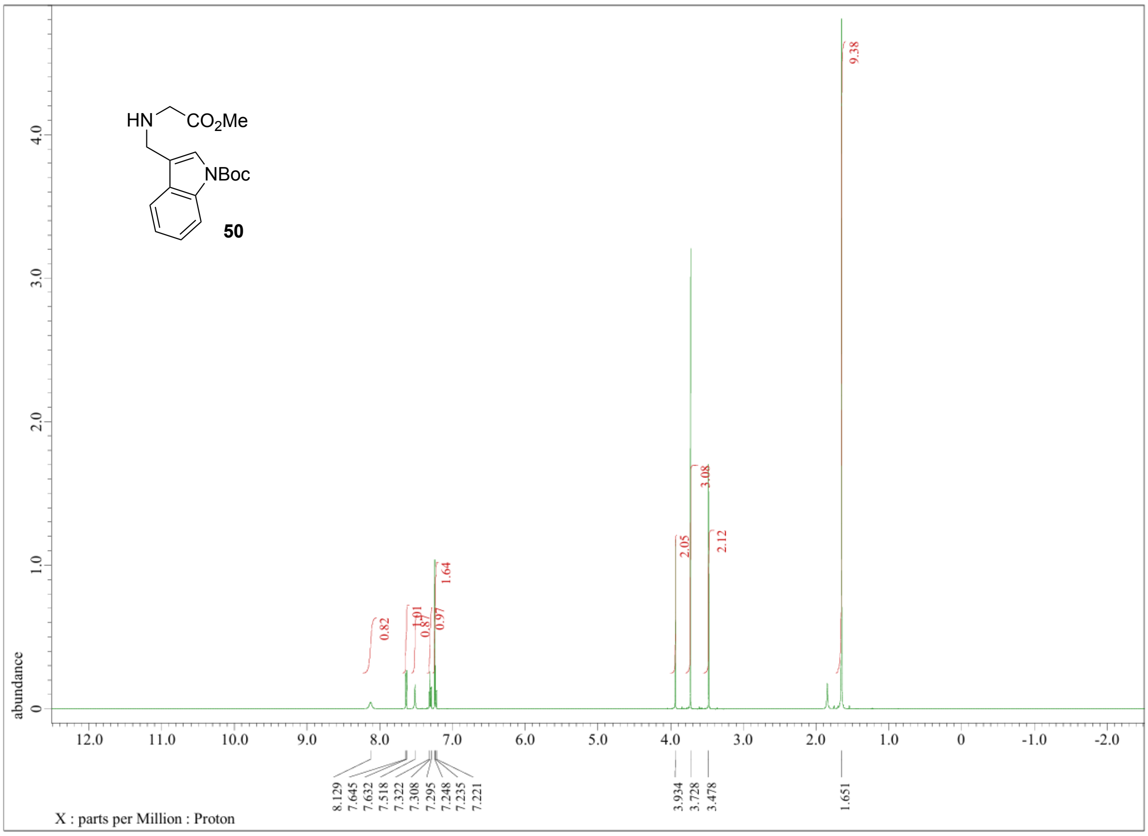


Figure S64. ^{1}H NMR spectrum (600 MHz) of **50** in $CDCl_3$.

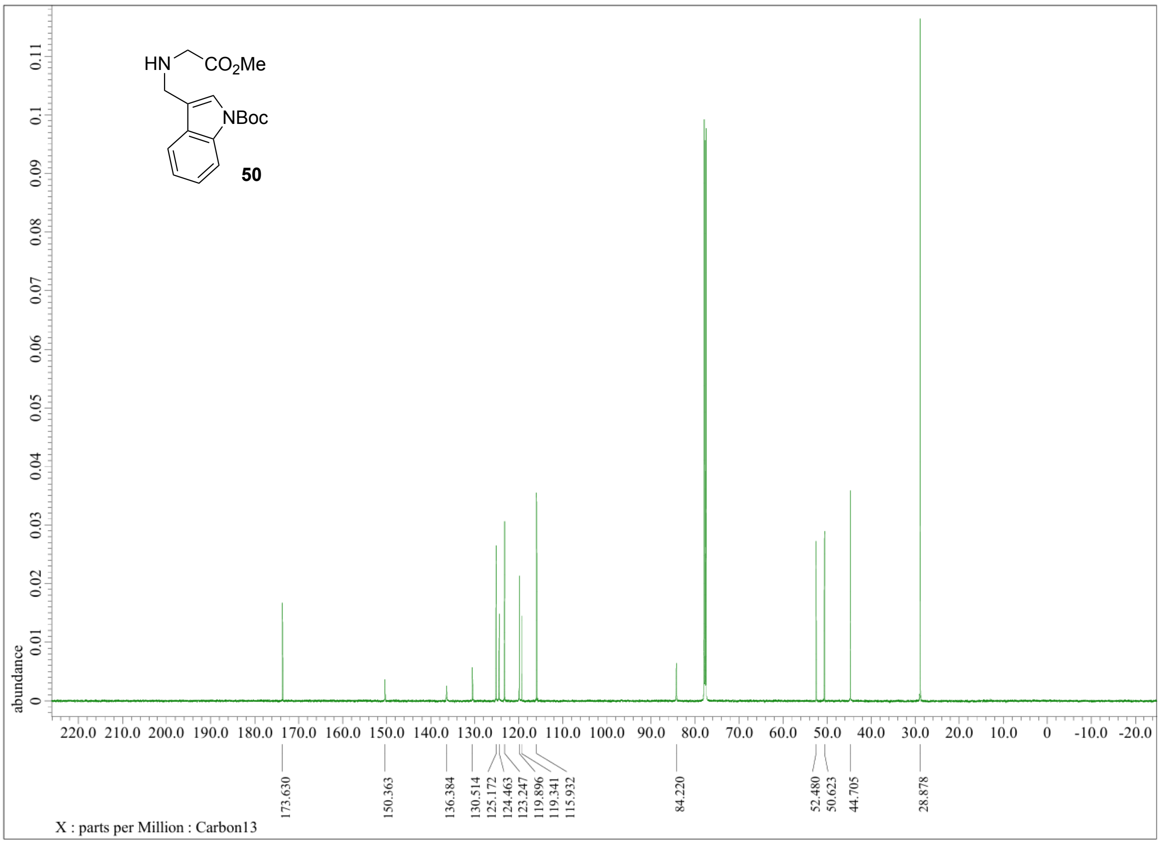


Figure S65. ^{13}C NMR spectrum (150 MHz) of **50** in $CDCl_3$.

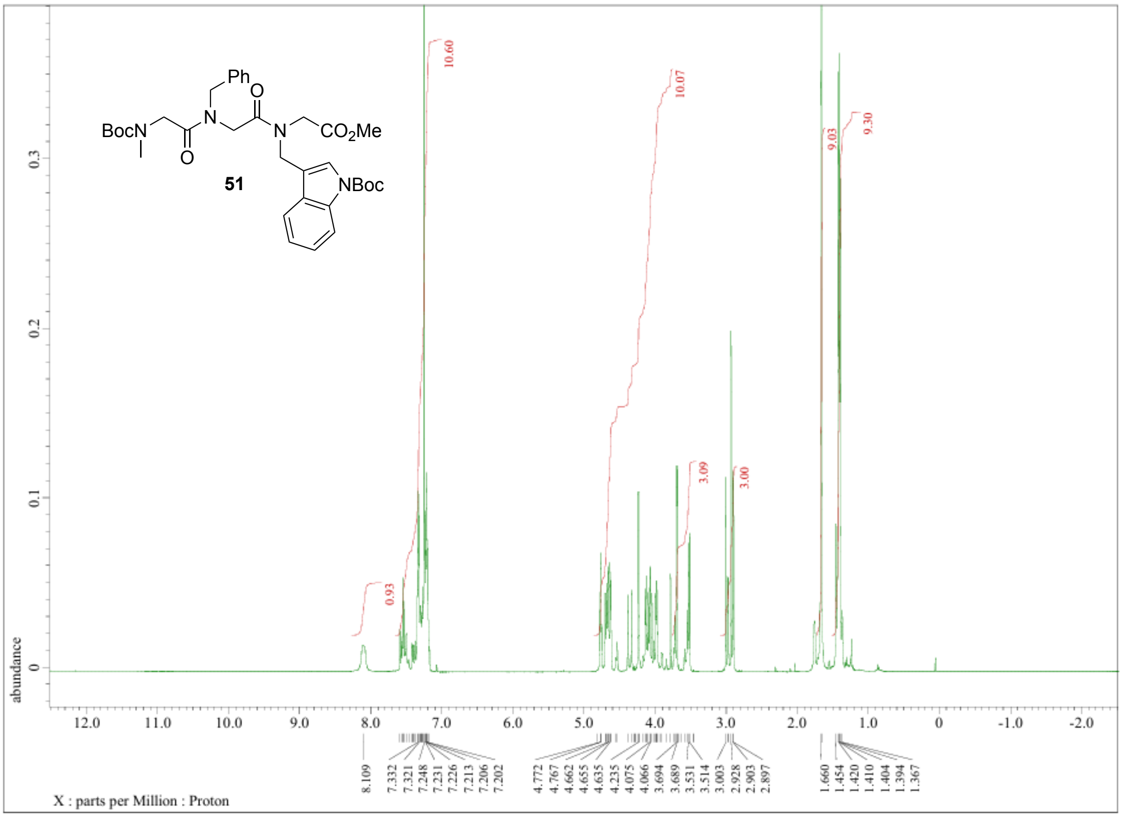


Figure S66. ^{1}H NMR spectrum (600 MHz) of **51** in CDCl$_3$.

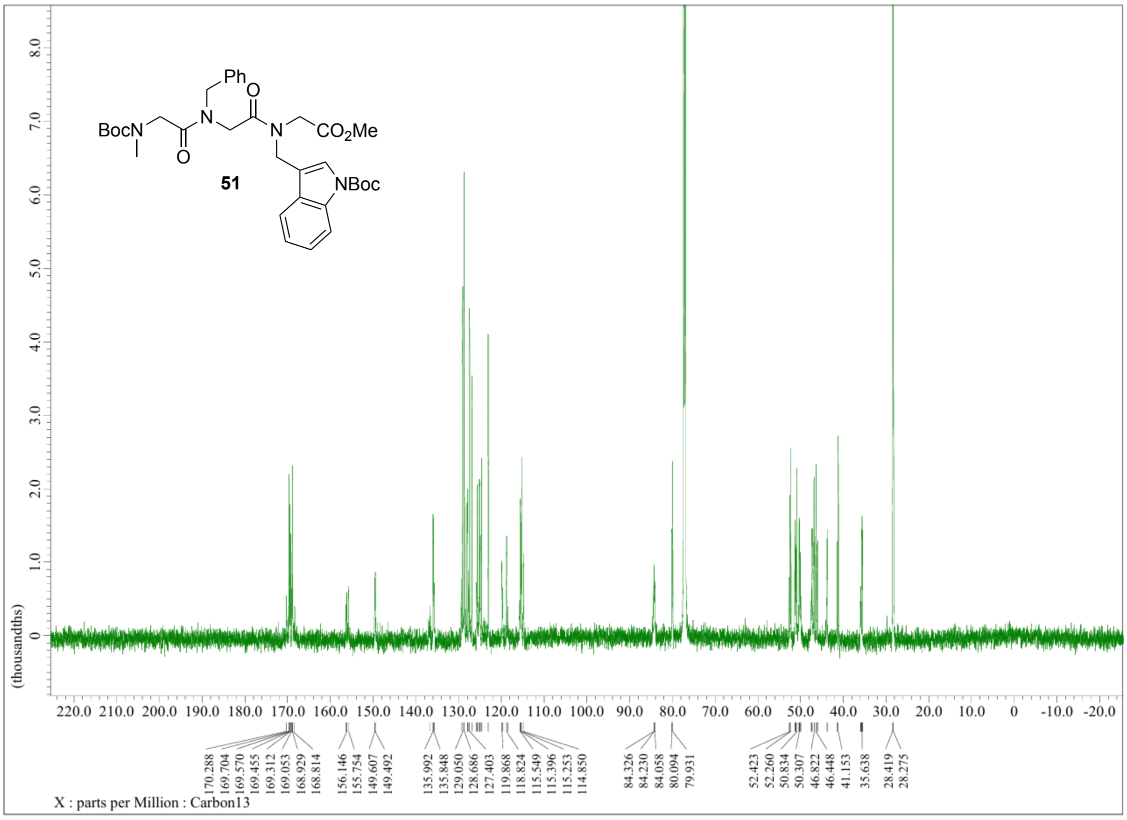


Figure S67. ^{13}C NMR spectrum (150 MHz) of **51** in CDCl$_3$.