Supplementary Information (SI) for Organic & Biomolecular Chemistry.

Straightforward Syntheses of Bottromycin Derivatives via Ugi-Reactions and Matteson Homologations

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Supporting Information

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General Information

Chemicals and **solvents** were obtained from the central chemical storage of Saarland University or are already stock chemicals of AK Kazmaier (pentane and EtOAc were redistilled before use).

Anhydrous solvents were dried with standard methods (THF over sodium/benzophenone and DIPA over CaH_2) or purchased already in an anhydrous state from *Acros Organics* and *Thermo Scientific* (DMF, MeCN, MeOH, DCM, toluene).

General working methods: Reaction flasks requiring anhydrous conditions were flame dried under vacuum, flushed with protection gas (nitrogen, argon), and kept under an inert atmosphere.

NMR-spectra were measured on a *Bruker* spectrometer at 400 or 500 MHz (*Bruker AVII 400*, *AVI 500,* and *AV Neo 500*). Spectra were calibrated on the solvent signals: $CDCl_3$ (^{1}H 7.26 ppm, ^{13}C 77.00 ppm) or DMSO-d_6 (^{1}H 2.50 ppm, ^{13}C 39.52 ppm). Unless otherwise specified, the spectra were recorded at 298 K. The spectral data were analyzed with ACD/NMR Processor Academic Edition (Version 12.01). Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. Multiplicities in ^{1}H-NMR spectra are reported as singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m). ^{13}C-NMR spectra were measured broadband decoupled, theoretical multiplicity of the carbon is given as s (quaternary C-atom), d (tertiary C-Atom, t (secondary C-Atom) and q (primary C-Atom). Protons and carbons were assigned by 2D-NMR spectra *H*,*H*-COSY, HSQC (multiplicity-edited) and HMBC.

Thin-layer chromatography (TLC) was used for reaction monitoring on ready to use *Macherey-Nagel* Polygram® SIL G/UV254 silica 60 TLC-PET-plates (UV-light at 254 nm, Cerium(IV)/ammonium molybdate-, ninhydrin- and $KMnO_4$-solution).

For reaction control with liquid chromatography coupled with mass spectrometry and UV-Vis (**LC-MS**), a *Shimadzu Prominence-i* LC-2030C 3D Plus system with *Shimadzu* LCMS-2020 spectrometer was used with a *Phenomenex Onyx*® column (monolithic C-18, 4.6 mm x 50 mm). All runs were performed at a flow rate of 4 mL/min with a column temperature of 40 °C and 0.1% $HCOOH_{aq}$/MeCN as mobile phase.

Table 1: LC time program

solvent mixture	time [min]
90:10	0
1:99	1.5
90:10	2.5
90:10	2.51
90:10	3.2

Automated flash column chromatography was done on a *Büchi* Pure C815 Flash with *Teledyne Isco RediSep*® *Rf* cartridges (4-220 g). Automated reversed phase column chromatography was done on a *Büchi Reveleris*® *Prep* with *Büchi* FlashPure Select C18 (spherical, 4-80 g) cartridges.

Preparative HPLC was done with a *Büchi Reveleris*® *Prep* with a *Phenomenex Luna*® (C18, 5 µm, 21.2 x 250 mm).

Specific optical rotation ($[\alpha]_D^{20}$) was measured on a *Krüss* polarimeter *P8000-T* with *Krüss* thermostat *PT80* at 20 °C, given concentration (g/100 mL) and at the sodium D-line (λ = 589 nm).

High-resolution mass spectra (HRMS) were recorded at the Helmholtz-Institute for Pharmaceutical Research Saarland (HIPS) by Christine Walt or Alexander Volz on a *Bruker Daltonics maXis 4G* (ESI, ToF).

Synthesis of the Compounds

(4*S*,5*S*)-4,5-Dicyclohexyl-2-methyl-1,3,2-dioxaborolane (1)

Preparation according to Kazmaier and Kinsinger.[1]

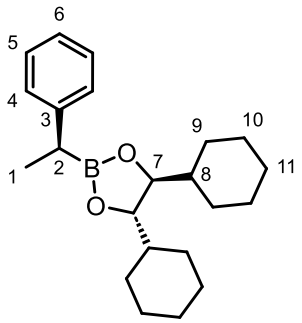
(4*S*,5*S*)-4,5-Dicyclohexyl-2-((*S*)-1-phenylethyl)-1,3,2-dioxaborolane (3)[2]

LDA solution: In a dried Schlenk flask under nitrogen atmosphere, 3.7 ml diisopropylamine (26.1 mmol, 1.35 eq.) was dissolved in 4.0 ml anhydrous THF and cooled to –40 °C. A solution of 15.0 ml *n*-BuLi (1.6 M in hexane, 24.2 mmol, 1.25 eq.) was added dropwise over 5 min and the resulting mixture was stirred at –40 °C for 10 min. After removing the cooling bath, the mixture was stirred for another 30 min at room temperature.

Homologisation: In a second flame-dried Schlenk flask under nitrogen atmosphere, 4.84 g boronic acid ester **1**[1] (19.4 mmol, 1.0 eq.) and 3.7 ml DCM (58.0 mmol, 3.0 eq.) were dissolved in 28 ml anhydrous THF and cooled to –40 °C. The freshly prepared LDA solution was slowly added to the solution via the cooled inside of the flask. After stirring for 10 min, a solution of 5.27 g previously dried zinc chloride (38.7 mmol, 2.0 eq.) in 26 ml anhydrous THF was added to the reaction mixture. The cooling bath was removed and the reaction was stirred for 2 h at room temperature. After complete conversion (^{1}H-NMR control), the reaction was quenched with sat. NH_4Cl solution and extracted three times with pentane. The combined organic phases were dried over Na_2SO_4, the solvent was removed under reduced pressure and the residue was used for the substition step.

Substitution:. In a Schlenk flask under nitrogen atmosphere, the previously prepared α-chloroboronic acid ester was dissolved in 52 ml anhydrous THF and a suspension of 2.64 g zinc chloride (19.4 mmol, 1.0 eq.) in 12 ml anhydrous THF was added. The reaction mixture was cooled to 0 °C and 16.1 ml phenylmagnesium bromide solution (3 M in THF, 48.4 mmol, 2.5 eq.) was added dropwise. After complete addition, the mixture was stirred for 16 h and warmed to room temperature. After complete conversion (1H-NMR control), the reaction was quenched with sat. NH_4Cl solution and extracted three times with pentane. The combined organic phases were dried over Na_2SO_4, the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, pentane/Et_2O 99:1) to obtain 5.38 g of the boronic acid ester **3** (14.9 mmol, 77 % + 5 % phenylboronic acid ester as by-product) as a colourless amorphous solid.

TLC: t_R (**3**) = 0.21 (pentane/Et_2O 99:1)



3

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.22-7.28 (m, 4 H, 4-H, 5-H), 7.13 (m, 1 H, 6-H), 3.85 (m, 2 H, 7-H), 2.50 (q, $^3J_{2,1}$ = 7.6 Hz, 1 H, 2-H), 1.51-1.79 (m, 10 H, 9-H‘, 10-H‘, 11-H), 1.37 (d, $^3J_{1,2}$ = 7.6 Hz, 3 H, 1-H), 1.29 (m, 2 H, 8-H), 0.82-1.22 (m, 10 H, 9-H‘, 10-H‘).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 145.1 (s, C-3), 128.2 (d, C-4), 127.8 (d, C-5), 125.1 (d, C-6), 83.4 (d, C-7), 42.9 (d, C-8), 28.1 (t, C-9‘), 27.2 (t, C-10‘), 26.4 (t, C-11), 26.0 (t, C-9), 25.9 (t, C-10), 24.8 (d, C-2), 17.1 (q, C-1).

optical rotation:	$[\alpha]_D^{20}$ = –27.3 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{22}H_{34}BO_2$ $[M+H]^+$	341.2646	341.2645

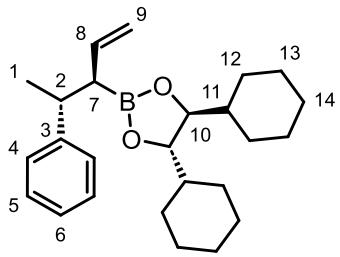
(4*S*,5*S*)-4,5-Dicyclohexyl-2-((3*R*,4*R*)-4-phenylpent-1-en-3-yl)-1,3,2-dioxaborolane (4)

LDA solution: In a flame-dried Schlenk flask under nitrogen atmosphere, 3.0 ml diisopropylamine (21.1 mmol, 1.35 eq.) was dissolved in 5.0 ml anhydrous THF and cooled to –40 °C. A solution of 12.2 ml *n*-BuLi (1.6 M in hexane, 19.6 mmol, 1.25 eq.) was added dropwise over 5 min and the resulting mixture was stirred at –40 °C for 10 min. After removing the cooling bath, the mixture was stirred for another 30 min at room temperature.

Homologisation: In a second flame-dried Schlenk flask under nitrogen atmosphere, 5.33 g boronic acid ester **3** (15.7 mmol, 1.0 eq.) and 3.0 ml DCM (47.0 mmol, 3.0 eq.) were dissolved in 22 ml anhydrous THF and cooled to –40 °C. The freshly prepared LDA solution was slowly added to the solution via the cooled inside of the flask. After stirring for 10 min, a solution of 4.27 g previously dried zinc chloride (31.3 mmol, 2.0 eq.) in 20 ml anhydrous THF was added to the reaction mixture. The cooling bath was removed and the reaction was stirred for 4.5 h at room temperature. After complete conversion (^{1}H-NMR control), the reaction was quenched with sat. NH_4Cl solution and extracted three times with pentane. The combined organic phases were dried over Na_2SO_4, the solvent was removed under reduced pressure and the residue was used for the substition step.

Substitution:[1] In a flame-dried Schlenk flask under nitrogen atmosphere, the previously prepared α-chloroboronic acid ester was dissolved in 35 ml anhydrous THF and a suspension of 2.13 g zinc chloride (15.7 mmol, 1.0 eq.) in 20 ml anhydrous THF was added. The reaction mixture was cooled to –78 °C and 39.2 ml vinylmagnesium bromide solution (1 M in THF, 39.2 mmol, 2.5 eq.) was added dropwise. After complete addition, the mixture was slowly warmed to 0 °C and stirred for two days. After complete conversion (1H-NMR control), the reaction was quenched with sat. NH_4Cl solution and extracted three times with pentane. The combined organic phases were dried over Na_2SO_4, the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, pentane/Et_2O 98:2) to obtain 4.91 g of the boronic acid ester **4** (10.9 mmol, 74 % + 12 % vinylboronic acid ester as by-product) as a colourless amorphous solid.

TLC: t_R (**4**) = 0.09 (pentane/Et_2O 99:1)



4

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.19-7.25 (m, 4 H, 4-H, 5-H), 7.14 (m, 1 H, 6-H), 5.79 (dt, $^3J_{8,9}$ = $^3J_{8,7}$ = 9.9 Hz, $^3J_{8,9'}$ = 17.0 Hz, 1 H, 8-H), 5.11 (ddd, $^3J_{9,8}$ = 17.1 Hz, $^2J_{9,9'}$ = 1.8 Hz, $^4J_{9,7}$ = 0.9 Hz, 1 H, 9-H), 5.03 (dd, $^3J_{9,8}$ = 10.2 Hz, $^2J_{9,9}$ = 1.8 Hz, 1 H, 9-H‘), 3.63 (m, 2 H, 10-H),

2.92 (dq, $^3J_{2,7}$ = 10.8 Hz, $^3J_{2,1}$ = 6.9 Hz, 1 H, 2-H), 2.24 (dd, $^3J_{7,2}$ = $^3J_{7,8}$ = 10.0 Hz, 1 H, 7-H), 1.50-1.81 (m, 10 H, 12-H‘, 13-H‘, 14-H), 1.34 (m, 2 H, 11-H), 1.20 (d, $^3J_{1,2}$ = 7.0 Hz, 3 H, 1-H), 0.60-1.13 (m, 10 H, 12-H‘, 13-H‘).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 147.7 (s, C-3), 138.6 (d, C-8), 128.2 (d, C-4), 127.2 (d, C-5), 125.8 (d, C-6), 115.4 (t, C-9), 83.2 (d, C-10), 42.8 (d, C-11), 40.9 (d, C-2), 28.0 (t, C-12‘), 27.2 (t, C-13‘), 26.3 (t, C-14), 26.0 (t, C-12), 25.8 (t, C-13), 22.5 (q, C-1).

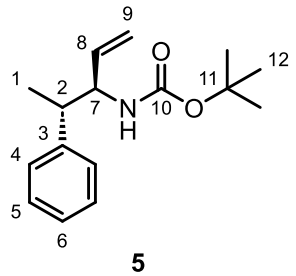
optical rotation:	$[\alpha]_D^{20}$ = –16.6 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{25}H_{38}BO_2$ $[M+H]^+$	381.2959	381.2961

***tert*-Butyl((3*R*,4*S*)-4-phenylpent-1-en-3-yl)carbamate (5)**

Preparation of *O*-methylhydroxylamine solution: 7.50 g *O*-methylhydroxylamine hydrochloride (90.0 mmol, 1.0 eq.) and 3.59 g sodium hydroxide (90.0 mmol, 1.0 eq.) were dissolved under nitrogen atmosphere in 15 ml anhydrous THF and one drop of water were added. The white suspension was stirred vigorously for 23 h at room temperature. The supernatant solution was transferred with a syringe into another flame-dried, round bottom flask containing 24.5 g calcium sulphate (180 mmol, 2.0 eq.). After allowing to stand for 16 h at room temperature, the supernatant solution was transferred to a flame-dried Schlenk flask under nitrogen atmosphere. The desiccant was rinsed twice with 5.0 ml anhydrous THF and also transferred to the Schlenk flask. Using NMR control with toluene as an internal standard, the concentration of the solution was determined (2.76 M).

Amination:[3] 143 µl of the prepared *O*-methylhydroxylamine solution (2.76 M in THF, 35.0 µmol, 3.0 eq.) was dissolved in a flame-dried crimp vial and diluted with 1.3 ml anhydrous THF. The solution was cooled to –78 °C and 246 µl *n*-BuLi solution (1.6 M in hexane, 39.0 µmol, 3.0 eq.) was added dropwise. After stirring at –78 °C for 30 min, 50.0 mg boronic acid ester **4** (13.0 µmol, 1.0 eq.), dissolved in 0.3 ml anhydrous THF, was added dropwise. The reaction mixture was warmed to room temperature and stirred for 23 h. After complete conversion (TLC control), 98 µl Boc_2O (92.0 mg, 42.0 µmol, 3.2 eq.) was added and stirred for another 2 h at room temperature. Water was added to quench the reaction, the phases were separated and the aqueous phase was extracted twice with EtOAc. The combined organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, pentane/Et_2O 10 to 50 %). To separate the product from the diol formed as a by-product, it was purified again by reversed-phase column chromatography (C18 spherical, H_2O/MeCN 10 to 100 %) to obtain 20.0 mg of the Boc-protected amine **5** (51.0 µmol, 46 %) as a colourless amorphous solid.

TLC: t_R (**5**) = 0.27 (pentane/Et_2O 8:2)



5

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.31 (m, 2 H, 5-H), 7.20-7.23 (m, 3 H, 4-H, 6-H), 5.73 (ddd, $^3J_{8,9‘}$ = 16.7 Hz, $^3J_{8,9}$ = 10.7 Hz, $^3J_{8,7}$ = 6.0 Hz, 1 H, 8-H), 5.10 (ddd, $^3J_{9,8}$ = 10.4 Hz, $^2J_{9,9‘}$ = $^3J_{9,7}$ = 1.3 Hz, 1 H, 9-H), 5.08 (ddd, $^3J_{9‘,8}$ = 17.0 Hz, $^2J_{9‘,9}$ = $^3J_{9‘,7}$ = 1.3 Hz, 1 H, 9-H‘), 4.38 (m, 1 H,

NH), 4.31 (m, 1 H, 7-H), 2.95 (dq, $^3J_{2,7}$ = $^3J_{2,1}$ = 6.6 Hz, 1 H, 2-H), 1.39 (s, 9 H, 12-H), 1.30 (d, $^3J_{1,2}$ = 7.3 Hz, 3 H, 1-H).

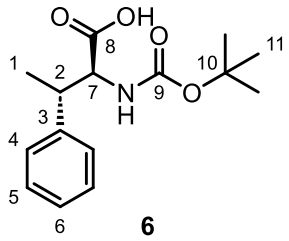
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 155.4 (s, C-10), 142.4 (s, C-3), 137.1 (d, C-8), 128.3 (d, C-4), 128.0 (d, C-5), 126.6 (d, C-6), 115.4 (t, C-9), 79.3 (d, C-11), 57.8 (d, C-7), 43.8 (d, C-2), 28.3 (q, C-12), 17.2 (q, C-1).

optical rotation:	$[\alpha]_D^{20}$ = +64.9 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{16}H_{24}NO_2$ $[M+H]^+$	262.1802	262.1803

(*2S,3S*)-2-((*tert*-Butoxycarbonyl)amino)-3-phenylbutanoic acid (6)

557 mg of alkene **5** (2.13 mmol, 1.0 eq.) was dissolved in 40 ml DCM and cooled to −78 °C using an acetone/nitrogen cooling bath. Using an ozone generator, ozone was passed through the reaction solution for 10 min (until the solution turned blue) and excess ozone was removed from the solution by passing through oxygen. Subsequently, 15.7 ml dimethyl sulphide (213 mmol, 100 eq.) was added and warmed to room temperature. After stirring for 1 h at room temperature, the solvent was removed under reduced pressure and the residue was taken up in 57 ml *tert*-butanol/water (4:1). After addition of 1.53 g sodium dihydrogen phosphate monohydrate (11.1 mmol, 5.2 eq.), 1.25 g sodium chlorite (11.1 mmol, 5.2 eq.) and 1.0 ml 2-methyl-2-butene (9.31 mmol, 4.4 eq.), stirring was continued for 17 h at room temperature. For work-up, the solvent was concentrated under reduced pressure and the residue was acidified with 10 % citric acid solution to a pH of 3. The aqueous phase was extracted three times with Et_2O and the combined organic phases were washed with sat. $Na_2S_2O_3$ solution. After drying over $MgSO_4$, the solvent was removed and the residue was purified by column chromatography (C18 spherical, H_2O/MeCN 10 to 100 %) to obtain 290 mg of acid **6** (1.04 mmol, 49 %) as a colourless resin.

LC-MS: t_R (**6**) = 1.09 min



6

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.32 (m, 2 H, 5-H), 7.26 (m, 1 H, 6-H), 7.21 (m, 2 H, 4-H), 4.76 (d, $^3J_{NH,7}$ = 8.8 Hz, 1 H, NH), 4.51 (dd, $^3J_{7,2}$ = 5.4 Hz, $^3J_{7,NH}$ = 8.2 Hz, 1 H, 7-H), 3.41 (m, 1 H, 2-H), 1.41 (s, 12 H, 11-H, 1-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 176.3 (s, C-8), 155.9 (s, C-9), 140.6 (s, C-3), 128.7 (d, C-5), 127.7 (d, C-4), 127.3 (d, C-6), 80.3 (d, C-10), 58.8 (d, C-7), 41.5 (d, C-2), 28.2 (q, C-11), 17.8 (q, C-1).

selected rotamer signals:

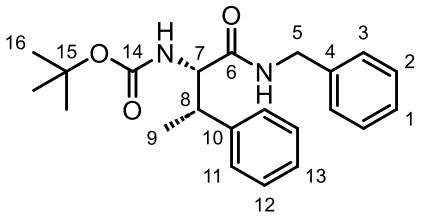
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.34 (m, 1 H, NH), 4.30 (m, 1 H, 7-H), 3.21 (m, 1 H, 2-H).

optical rotation:	$[\alpha]_D^{20}$ = +22.5 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{15}H_{22}NO_4$ $[M+H]^+$	280.1543	280.1546

***tert*-Butyl((*2S,3S*)-1-(benzylamino)-1-oxo-3-phenylbutan-2-yl)carbamate (7)**

Under nitrogen atmosphere, 290 mg of acid **6** (1.04 mmol, 1.0 eq.) and 137 µl NMM (126 mg, 1.25 mmol, 1.2 eq.) were dissolved in 5.2 ml DCM and cooled to −20 °C. Subsequently, 164 µl IBCF (170 mg, 1.25 mmol, 1.2 eq.) was added and stirred for 10 min. After the addition of 172 µl benzylamine (169 mg, 1.56 mmol, 1.5 eq.), the cooling bath was removed and the reaction was stirred for 2 h at room temperature. The reaction mixture was diluted with EtOAc and quenched with the addition of water. The phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed successively with 1 M $KHSO_4$ solution, sat. $NaHCO_3$ solution and brine. After drying over $MgSO_4$, the solvent was removed under reduced pressure and the residue was purified by column chromatography (C18 spherical, H_2O/MeCN 10 to 100 %) to obtain 314 mg of amide **7** (0.85 mmol, 82 %) as a colourless amorphous solid.

LC-MS: t_R (**7**) = 1.28 min



7

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.21-7.32 (m, 8 H, 1-H, 2-H, 11-H, 12-H, 13-H), 7.14-7.16 (m, 2 H, 3-H), 6.09 (bs, 1 H, NH_b), 5.02 (bs, 1 H, NH_a), 4.37 (d, $^3J_{5,NHa}$ = 5.8 Hz, 2 H, 5-H), 4.32 (m, 1 H, 7-H), 3.52 (m, 1 H, 8-H), 1.39 (s, 9 H, 16-H), 1.33 (d, $^3J_{9,8}$ = 7.0 Hz, 3 H, 9-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.6 (s, C-6), 155.5 (s, C-14), 141.5 (s, C-10), 137.7 (s, C-4), 128.6 (d, C-3), 128.6 (d, C-11), 127.8 (d, C-2), 127.7 (d, C-12), 127.5 (d, C-13), 127.0 (d, C-1), 80.0 (s, C-15), 60.1 (d, C-7), 43.4 (t, C-5), 41.0 (d, C-8), 28.2 (q, C-16), 16.8 (q, C-9).

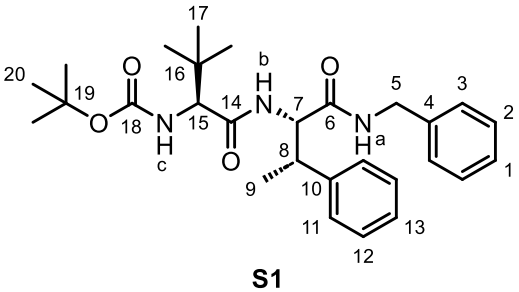
optical rotation:	$[\alpha]_D^{20}$ = +19.0 [$CHCl_3$, c = 0.5]	
HRMS (ESI):	calculated:	found:
$C_{22}H_{29}N_2O_3$ $[M+H]^+$	369.2173	369.2177

***tert*-Butyl((*S*)-1-(((*2S,3S*)-1-(benzylamino)-1-oxo-3-phenylbutan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamate (S1)**

308 mg of Boc-protected amine **7** (836 µmol, 1.0 eq.) was added to 2.0 ml DCM (2.5 ml/mmol) under nitrogen atmosphere and cooled to 0 °C. Subsequently, 4.2 ml HCl solution (4 M in dioxane, 16.7 mmol, 20 eq.) was added and the ice bath was removed. After 2 h of stirring at room temperature, the LC-MS control showed complete conversion and the solvent was removed under reduced pressure.

The residue was dissolved under nitrogen atmosphere in 8.4 ml DCM (10 ml/mmol). After addition of 290 mg Boc-*tert*-leucine (1.25 mmol, 1.5 eq.) and 414 µl NMM (381 mg, 3.76 mmol, 4.5 eq.), the reaction mixture was cooled to 0 °C. Then 476 mg HATU (1.25 mmol, 1.5 eq.) was added, the ice bath removed and stirred for 4 h at room temperature. For work-up, the reaction solution was washed with 1 M $KHSO_4$ solution, sat. $NaHCO_3$ solution and brine. After drying over $MgSO_4$, the solvent was removed under reduced pressure and the residue was purified by column chromatography (C18 spherical, H_2O/MeCN 10 to 100 %) to obtain 370 mg of the peptide **S1** (763 µmol, 91 %) as a colourless foam.

LC-MS: t_R (**S1**) = 1.37 min



S1

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.17-7.32 (m, 10 H**,** 1-H, 2-H, 3-H, 11-H, 12-H, 13-H**),** 6.49 (bs, 1 H, NH_a), 6.40 (d, $^3J_{NHb,7}$ = 7.6 Hz, 1 H, NH_b), 5.00 (d, $^3J_{NHc,15}$ = 6.3 Hz, 1 H, NH_c), 4.62 (dd, $^3J_{7,NHb}$ = 8.2 Hz, $^3J_{7,8}$ = 5.7 Hz, 1 H, 7-H), 4.34 (m, 2 H, 5-H), 3.72 (d, $^3J_{15,NHc}$ = 6.6 Hz, 1 H, 15-H), 3.63 (m, 1 H, 8-H), 1.32 (d, $^3J_{9,8}$ = 7.3 Hz, 3 H, 9-H), 1.28 (s, 9 H, 20-H), 0.94 (s, 9 H, 17-H).

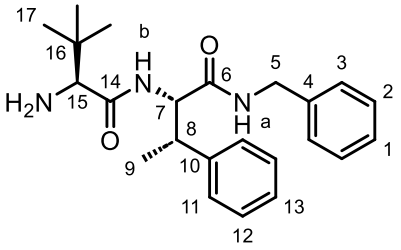
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 170.7 (s, C-14), 170.0 (s, C-6), 155.8 (s, C-18), 141.1 (s, C-10), 137.8 (s, C-4), 128.7 (d, C-3), 128.5 (d, C-11), 127.9 (d, C-2), 127.7 (d, C-12), 127.3 (d, C-13), 127.1 (d, C-1), 80.1 (s, C-19), 63.4 (d, C-15), 58.4 (d, C-7), 43.5 (t, C-5), 40.3 (d, C-8), 33.7 (s, C-16), 28.1 (q, C-20), 26.7 (q, C-17), 16.9 (q, C-9).

optical rotation:	$[\alpha]_D^{20}$ = –26.4 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{28}H_{40}N_3O_4$ $[M+H]^+$	482.3013	482.3011

(*S*)-2-Amino-*N*-((2*S*,3*S*)-1-(benzylamino)-1-oxo-3-phenylbutane-2-yl)-3,3-dimethylbutanamide (8)

363 mg of the protected amine **S1** (754 µmol, 1.0 eq.) was added to 1.90 ml DCM and cooled to 0 °C. Subsequently, 3.8 ml HCl solution (4 M in dioxane, 15.1 mmol, 20.0 eq.) was added and stirred at room temperature for 2 h. After complete deprotection (LC-MS control), the solvent was removed under reduced pressure. The residue was dissolved in EtOAc and neutralised with 30% aqueous NH_3 solution at 0°C. The phases were separated and the aqueous phase was extracted twice with EtOAc. The combined organic phases were washed with brine and dried over $MgSO_4$. After removal of the solvent under reduced pressure, 287 mg of the free amine **8** (0.75 mmol, quant.) was obtained as a colourless foam.

LC-MS: t_R (**8**) = 0.80 min



8

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, $^3J_{NHb,7}$ = 8.4 Hz, 1 H, NH_b), 7.17-7.32 (m, 10 H, 1-H, 2-H, 3-H, 11-H, 12-H, 13-H), 6.85 (t, $^3J_{NHa,5}$ = 8.4 Hz, 1 H, NH_a), 4.62 (dd, $^3J_{7,8}$ = $^3J_{7,NHb}$ = 8.8 Hz, 1 H, 7-H), 4.48 (dd, $^2J_{5,5'}$ = 14.8 Hz, $^3J_{5,NHa}$ = 6.1 Hz, 1 H, 5-H), 4.32 (dd, $^2J_{5',5}$ = 14.8 Hz, $^3J_{5,NHa}$ = 5.5 Hz, 1 H, 5'-H), 3.37 (dq, $^3J_{8,9}$ = 7.0 Hz, $^3J_{8,7}$ = 9.0 Hz, 1 H, 8-H), 2.89 (s, 1 H, 15-H), 1.91 (bs, 2 H, NH_2), 1.30 (d, $^3J_{9,8}$ = 7.0 Hz, 3 H, 9-H), 0.70 (s, 9 H, 17-H).

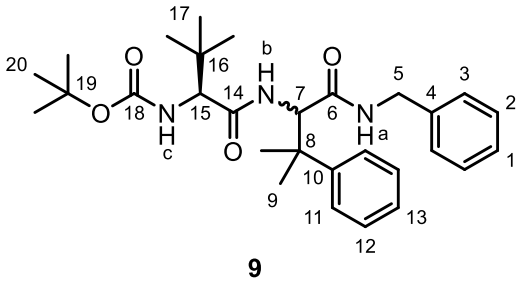
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.6 (s, C-14), 170.7 (s, C-6), 142.5 (s, C-10), 137.9 (s, C-4), 128.7 (d, C-12), 128.6 (d, C-2), 127.8 (d, C-3), 127.7 (d, C-11), 127.4 (d, C-1), 126.9 (d, C-13), 64.0 (d, C-15), 58.4 (d, C-7), 43.5 (t, C-5), 41.2 (d, C-8), 33.8 (s, C-16), 26.4 (q, C-17), 18.4 (q, C-9).

optical rotation:	$[\alpha]_D^{20}$ = –19.2 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{23}H_{32}N_3O_2$ $[M+H]^+$	382.2489	382.2489

tert-Butyl ((*S*)-1-(((*S*)-1-(benzylamino)-3-methyl-1-oxo-3-phenylbutan-2-yl)amino)-3,3-dimethyl-1-oxobutan-2-yl)carbamat (9)

1.30 ml 2-methyl-2-phenylpropanal[4] (1.28 g, 8.65 mmol, 1.0 eq.) was dissolved in 4.3 ml NH_3 solution (2 M in methanol, 8.65 mmol, 1.0 eq.) at 0 °C and stirred for 15 min. Then 1.05 ml benzyl isocyanide[5] (1.01 g, 8.65 mmol, 1.0 eq.) and 2.00 g Boc-*t*Le-OH (8.65 mmol, 1.0 eq.), each dissolved in 6.5 ml trifluoroethanol, were added. The reaction solution was allowed to warm to room temperature and stirred for 15 h. For work-up, the reaction volume was doubled with DCM and the organic phase was washed with sat. $NaHCO_3$ solution and 1 M $KHSO_4$ solution. After drying over $MgSO_4$, the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, cyclohexane/EtOAc 0 to 35 %) to give 2.56 g of the major diastereomers (5.16 mmol, 60 %) as a white solid and 976 mg (1.97 mmol, 23 %) of the minor diastereomer as a white solid and a mixture of rotamers. This resulted in an overall yield of 83 %.

LC-MS: t_R (**9**) = 1.42 min



9

Major diastereomer 1:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.42 (m, 2 H, 11-H), 7.21-7.32 (m, 7 H, 2-H, 3-H, 12-H, 13-H), 6.93-6.99 (m, 2 H, 1-H, NH_b), 5.74 (m, 1 H, NH_a), 5.45 (d, $^3J_{NHc,15}$ = 7.7 Hz, 1 H, NH_c), 4.89 (d, $^3J_{7,NHb}$ = 8.4 Hz, 1 H, 7-H), 4.19 (d, $^3J_{5,NHa}$ = 5.1 Hz, 2 H, 5-H), 4.03 (d, $^3J_{15,NHc}$ = 8.7 Hz, 1 H, 15-H), 1.47 (s, 9 H, 20-H), 1.46 (s, 3 H, 9-H), 1.39 (s, 3 H, 9‘-H), 1.02 (s, 9 H, 17-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.4 (s, C-14), 169.3 (s, C-6), 155.9 (s, C-18), 146.1 (s, C-10), 137.5 (s, C-4), 128.7 (d, C-2), 128.4 (d, C-12), 127.8 (d, C-3), 127.4 (d, C-1), 126.7 (d, C-13), 126.2 (d, C-11), 79.7 (s, C-19), 63.2 (d, C-15), 61.2 (d, C-7), 43.4 (t, C-5), 42.3 (s, C-8), 34.2 (s, C-16), 29.7 (q, C-9), 28.3 (q, C-20), 27.1 (q, C-9‘), 26.7 (q, C-17).

Minor diastereomer:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.42 (m, 2 H, 11-H), 7.21-7.32 (m, 5 H, 2-H, 12-H, 13-H), 6.93-6.99 (m, 3 H, 1-H, 3-H), 6.55 (d, $^3J_{NHb,7}$ = 7.7 Hz, 1 H, NH_b), 5.27 (d, $^3J_{NHc,15}$ = 8.6 Hz, 1 H, NH_c), 5.12 (m, 1 H, NH_a), 4.82 (d, $^3J_{7,NHb}$ = 8.7 Hz, 1 H, 7-H), 4.09 (d, $^3J_{5,NHa}$ = 5.5 Hz, 2 H, 5-H), 3.89 (d, $^3J_{15,NHc}$ = 8.2 Hz, 1 H, 15-H), 1.46 (s, 12 H, 20-H, 9-H), 1.37 (s, 3 H, 9‘-H), 1.00 (s, 9 H, 17-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.2 (s, C-14), 169.1 (s, C-6), 155.7 (s, C-18), 146.1 (s, C-10), 137.3 (s, C-4), 128.7 (d, C-2), 128.4 (d, C-12), 127.7 (d, C-3), 127.3 (d, C-1), 126.7 (d, C-13), 126.2 (d, C-11), 79.7 (s, C-19), 62.9 (d, C-15), 60.9 (d, C-7), 43.4 (t, C-5), 42.1 (s, C-8), 34.1 (s, C-16), 28.3 (q, C-20), 26.6 (q, C-17), 23.3 (q, C-9), 21.8 (q, C-9‘).

rotamer 1:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, $^{3}J_{11,12}$ = 7.6 Hz, 2 H, 11-H), 7.09-7.30 (m, 8 H, 1-H, 2-H, 3-H, 12-H, 13-H), 6.97 (m, 1 H, NH_a), 5.32 (s, 1 H, 7-H), 4.94 (d, $^{3}J_{NHc,15}$ = 7.5 Hz, 1 H, NH_c), 4.65 (dd, $^{3}J_{5,NHa}$ = 7.5 Hz, $^{2}J_{5,5‘}$ = 14.9 Hz, 1 H, 5-H), 4.06 (dd, $^{3}J_{5‘,NHa}$ = 4.4 Hz, $^{2}J_{5‘,5}$ = 14.9 Hz, 1 H, 5‘-H), 3.80 (d, $^{3}J_{15,NHc}$ = 7.6 Hz, 1 H, 15-H), 1.50 (s, 3 H, 9-H), 1.50 (s, 3 H, 9‘-H), 1.36 (s, 9 H, 20-H), 0.83 (s, 9 H, 17-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 171.7 (s, C-14), 167.8 (s, C-6), 156.2 (s, C-18), 145.7 (s, C-10), 138.3 (s, C-4), 128.4 (d, C-2), 128.4 (d, C-12), 127.9 (d, C-3), 127.2 (d, C-1), 126.5 (d, C-13), 126.3 (d, C-11), 81.7 (d, C-7), 80.4 (s, C-19), 62.6 (d, C-15), 43.2 (t, C-5), 40.8 (s, C-8), 33.8 (s, C-16), 28.2 (q, C-20), 27.4 (q, C-9), 26.5 (q, C-17), 24.3 (q, C-9‘).

rotamer 2:

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, $^{3}J_{11,12}$ = 7.6 Hz, 2 H, 11-H), 7.09-7.30 (m, 8 H, 1-H, 2-H, 3-H, 12-H, 13-H), 6.30 (m, 1 H, NH_a), 5.16 (s, 1 H, 7-H), 4.86 (d, $^{3}J_{NHc,15}$ = 7.8 Hz, 1 H, NH_c), 4.37 (dd, $^{3}J_{5,NHa}$ = 6.1 Hz, $^{2}J_{5,5‘}$ = 14.7 Hz, 1 H, 5-H), 4.19 (dd, $^{3}J_{5‘,NHa}$ = 5.5 Hz, $^{2}J_{5‘,5}$ = 14.6 Hz, 1 H, 5‘-H), 3.93 (d, $^{3}J_{15,NHc}$ = 8.1 Hz, 1 H, 15-H), 1.50 (s, 3 H, 9-H), 1.47 (s, 3 H, 9‘-H), 1.34 (s, 9 H, 20-H), 0.72 (s, 9 H, 17-H).

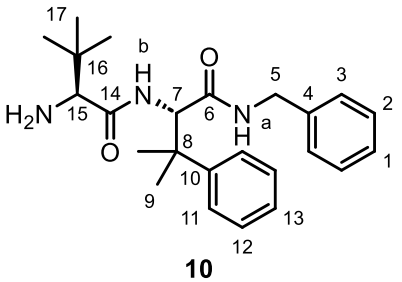
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.3 (s, C-14), 167.5 (s, C-6), 156.2 (s, C-18), 145.3 (s, C-10), 137.9 (s, C-4), 128.4 (d, C-2), 128.3 (d, C-12), 127.4 (d, C-3), 126.9 (d, C-1), 126.4 (d, C-13), 126.3 (d, C-11), 81.5 (d, C-7), 80.3 (s, C-19), 62.4 (d, C-15), 42.9 (t, C-5), 40.8 (s, C-8), 32.8 (s, C-16), 28.2 (q, C-20), 26.1 (q, C-17), 25.6 (q, C-9), 23.5 (q, C-9‘).

HRMS (ESI):	calculated:	found:
$C_{29}H_{42}N_3O_4$ $[M+H]^+$	496.3170	496.3170

(*S*)-2-Amino-*N*-((*S*)-1-(benzylamino)-3-methyl-1-oxo-3-phenylbutan-2-yl)-3,3-dimethyl-butanamide [(*S*,*S*)-10] and **(*S*)-2-Amino-*N*-((*R*)-1-(benzylamino)-3-methyl-1-oxo-3-phenylbutan-2-yl)-3,3-dimethyl-butanamide [(*S*,*R*)-10]**

1.16 g of the protected amine **9** (2.33 mmol, 1.0 eq.) was dissolved in 5.8 ml DCM (2.5 ml/mmol) and cooled to 0 °C. Subsequently, 11.6 ml HCl solution (4 M in dioxane, 46.6 mmol, 20.0 eq.) was added and stirred at room temperature for 1 h. After complete deprotection (LC-MS control), the solvent was removed under reduced pressure. The two diastereomers were then separated by preparative HPLC (Luna, 0.1 % $HCOOH_{aq}$/MeCN 0 to 40 %). The two product fractions obtained were each dissolved in EtOAc and neutralised with 30% aqueous NH_3 solution. The phases were then separated and the aqueous phase was extracted twice with EtOAc. The combined organic layers were washed with brine and dried over $MgSO_4$. After concentration in vacuo, 427 mg amine **(*S*,*S*)-10** (1.08 mmol, 46 %) and 429 mg amine **(*S*,*R*)-10** (1.09 mmol, 47 %) were obtained.

LC-MS: t_R (**(*S*,*S*)-10**) = 0.85 min



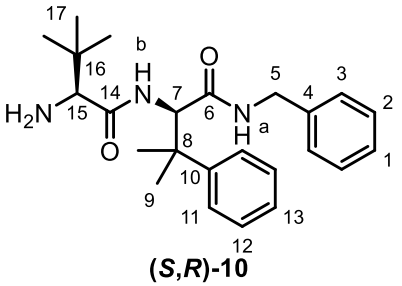
10

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, $^3J_{NHb,7}$ = 8.9 Hz, 1 H, NH_b), 7.42 (m, 2 H, 11-H), 7.17-7.29 (m, 6 H, 1-H, 2-H, 12-H, 13-H), 6.91 (m, 2 H, 3-H), 5.20 (t, $^3J_{NHa,5}$ = 5.0 Hz, 1 H, NH_a), 4.79 (d, $^3J_{7,NHb}$ = 8.9 Hz, 1 H, 7-H), 4.14 (dd, $^2J_{5,5'}$ = 14.6 Hz, $^3J_{5,NHa}$ = 5.8 Hz, 1 H, 5-H), 4.06 (dd, $^2J_{5',5}$ = 14.6 Hz, $^3J_{5',NHa}$ = 5.4 Hz, 1 H, 5'-H), 3.10 (s, 1 H, 15-H), 1.68 (bs, 2 H, NH_2), 1.40 (s, 3 H, 9-H), 1.38 (s, 3 H, 9'-H), 0.97 (s, 9 H, 17-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.0 (s, C-14), 169.7 (s, C-6), 146.4 (s, C-10), 137.3 (s, C-4), 128.7 (d, C-2), 128.5 (d, C-12), 127.8 (d, C-3), 127.4 (d, C-13), 126.7 (d, C-1), 126.3 (d, C-11), 64.7 (d, C-15), 60.8 (d, C-7), 43.5 (t, C-5), 42.0 (d, C-8), 34.1 (s, C-16), 27.3 (q, C-17), 26.8 (q, C-9), 22.3 (q, C-9').

optical rotation:	$[\alpha]_D^{20}$ = +2.4 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{24}H_{34}N_3O_2$ $[M+H]^+$	396.2646	396.2645

LC-MS: t_R (**(*S*,*R*)-10**) = 0.90 min



(*S*,*R*)-10

^{1}H-NMR (500 MHz, DMSO-d_6): δ = 8.46 (t, $^3J_{NHa,5}$ = 6.0 Hz, 1 H, NH_a), 7.69 (d, $^3J_{NHb,7}$ = 9.1 Hz, 1 H, NH_b), 7.39 (d, $^3J_{11,12}$ = 7.6 Hz, 2 H, 11-H), 7.14-7.27 (m, 6 H, 1-H, 2-H, 12-H, 13-H), 7.09 (d, $^3J_{3,2}$ = 7.0 Hz, 2 H, 3-H), 4.83 (d, $^3J_{7,NHb}$ = 8.8 Hz, 1 H, 7-H), 4.23 (dd, $^2J_{5,5'}$ = 15.5 Hz, $^3J_{5,NHa}$ = 6.0 Hz, 1 H, 5-H), 4.17 (dd, $^2J_{5',5}$ = 15.1 Hz, $^3J_{5',NHa}$ = 5.7 Hz, 1 H, 5'-H), 3.02 (s, 1 H, 15-H), 1.36 (s, 3 H, 9-H), 1.31 (s, 3 H, 9'-H), 0.65 (s, 9 H, 17-H).

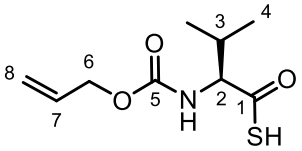
^{13}C-NMR (125 MHz, DMSO-d_6): δ = 172.7 (s, C-14), 169.8 (s, C-6), 146.7 (s, C-10), 139.1 (s, C-4), 128.1 (d, C-2), 127.8 (d, C-12), 127.3 (d, C-3), 126.7 (d, C-13), 126.4 (d, C-1), 125.9 (d, C-11), 62.1 (d, C-15), 59.9 (d, C-7), 42.0 (t, C-5), 40.8 (d, C-8), 33.5 (s, C-16), 26.7 (q, C-9), 26.3 (q, C-17), 23.9 (q, C-9').

optical rotation:	$[\alpha]_D^{20}$ = –11.3 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{24}H_{34}N_3O_2$ $[M+H]^+$	396.2646	396.2647

Alloc-Val-SH (11)[6]

1.75 g Alloc-Val-OH (8.68 mmol, 1.0 eq.) was dissolved under nitrogen atmosphere in 26 ml anhydrous THF. Subsequently, 1.83 g CDI (11.3 mmol, 1.3 eq.) was added. After stirring for 1 h at room temperature, H_2S was passed through the reaction solution for further 60 min. After

complete conversion (TLC control), the reaction was diluted with 50 ml EtOAc and cooled to 0 °C. To quench the reaction, the pH was slowly adjusted to a value of 4 within 15 min using cooled 1 M $HCl_{aq.}$ solution. The phases were separated and the organic phase was washed with brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the thioacid **11** was immediately used in the following Ugi-reaction.



11

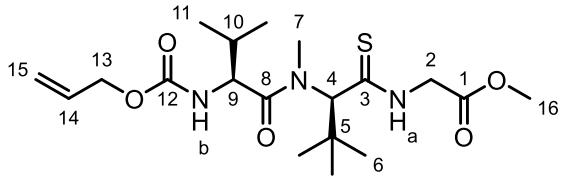
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.92 (m, 1 H, 7-H), 5.33 (d, $^3J_{8,7}$ = 17.4 Hz, 1 H, 8-H), 5.24 (d, $^3J_{8',7}$ = 10.4 Hz, 1 H, 8'-H), 5.19 (d, $^3J_{NH,2}$ = 7.8 Hz, 1 H, NH), 4.62 (m, 2 H, 6-H), 4.33 (dd, $^3J_{2,3}$ = 4.4 Hz, $^3J_{2,NH}$ = 9.0 Hz, 1 H, 2-H), 2.30 (m, 1 H, 3-H), 1.02 (d, $^3J_{4,3}$ = 6.9 Hz, 3 H, 4-H), 0.91 (d, $^3J_{4',3}$ = 6.9 Hz, 3 H, 4'-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 199.4 (s, C-1), 156.0 (s, C-5), 132.4 (d, C-7), 118.1 (t, C-8), 66.6 (d, C-2), 66.2 (d, C-6), 30.7 (d, C-3), 19.4 (q, C-4), 16.7 (q, C-4').

Methyl((*R*)-2-((*S*)-2-(((allyloxy)carbonyl)amino)-*N*,3-dimethylbutanamido)-3,3-dimethyl-butanthioyl)glycinat [(S,*R*)-12][7] and **Methyl((*S*)-2-((*S*)-2-(((allyloxy)carbonyl)amino)-*N*,3-dimethylbutanamido)-3,3-dimethyl-butanthioyl)glycinat [(*S*,*S*)-12]**[7]

943 µl pivalaldehyde (748 mg, 8.68 mmol, 1.0 eq.) and 1.08 ml methylamine (817 mg, 8.68 mmol, 1.0 eq.) were dissolved in 8.6 ml trifluoroethanol at 0 °C. After stirring at 0 °C for 30 min, 789 µl methyl-2-isocyanoacetate[5] (860 mg, 8.68 mmol, 1.0 eq.) and 1.89 g Alloc-Val-SH **11** (8.68 mmol, 1.0 eq.), each dissolved in 4.3 ml trifluoroethanol, were added. The reaction was warmed to room temperature and stirred for 15 h. After full conversion the reaction was diluted with DCM and the organic phase was washed with sat. $NaHCO_3$ solution and 1 M $KHSO_4$ solution. After drying over MgSO4, the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, cyclohexane/EtOAc 0 to 40 %) to obtain 1.18 g thioamide **(*S*,*R*)-12** (2.83 mmol, 33 %) as a yellow resin and 1.09 g thioamide **(*S*.S)-12** (2.63 mmol, 30 %) also as a yellow resin. This resulted in a total yield of 63 %.

LC-MS: t_R (**12**) = 1.27 min and 1.31 min



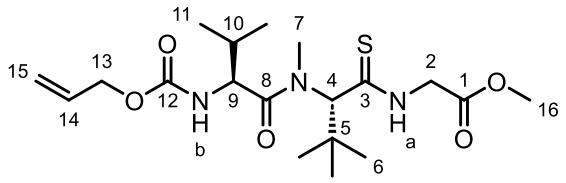
(*S*,*R*)-12

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.54 (bs, 1 H, NH_a), 5.90 (ddt, $^3J_{14,15'}$ = 17.1 Hz, $^3J_{14,15}$ = 10.5 Hz, $^3J_{14,13}$ = 5.6 Hz, 1 H, 14-H), 5.54 (d, $^3J_{NHb,9}$ = 7.8 Hz, 1 H, NH_b), 5.29 (dd, $^3J_{15,14}$ = 17.2 Hz, $^2J_{15,15'}$ = 1.1 Hz, 1 H, 15-H), 5.29 (s, 1 H, 4-H), 5.20 (dd, $^3J_{15',14}$ = 10.4 Hz, $^2J_{15',15}$ = 1.2 Hz, 1 H, 15'-H), 4.49-4.60 (m, 3 H, 13-H, 9-H), 4.40 (dd, $^2J_{2,2'}$ = 18.5 Hz, $^3J_{2,NHa}$ = 5.3 Hz, 1 H, 2-H), 4.28 (m, 1H, 2'-H), 3.75 (s, 3 H, 16-H), 3.37 (s, 3 H, 7-H), 2.02 (dsept, $^3J_{10,11}$ = $^3J_{10,9}$ = 6.4 Hz, 1 H, 10-H), 1.18 (s, 9 H, 6-H), 1.00 (d, $^3J_{11,10}$ = 6.7 Hz, 3 H, 11-H), 0,90 (d, $^3J_{11',10}$ = 6.7 Hz, 3 H, 11'-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 200.7 (s, C-3), 174.6 (s, C-8), 168.8 (s, C-1), 156.3 (s, C-12), 132.7 (d, C-14), 117.7 (t, C-15), 67.1 (d, C-4), 65.8 (t, C-13), 56.1 (d, C-9), 52.4 (q, C-16), 46.3 (t, C-2), 35.9 (s, C-5), 33.7 (q, C-7), 31.1 (d, C-10), 28.3 (q, C-6), 19.8 (q, C-11), 16.8 (q, C-11‘).

optical rotation: $[\alpha]_D^{20}$ = +93.3 [$CHCl_3$, c = 1.0]

HRMS (ESI):	calculated:	found:
$C_{19}H_{34}N_3O_5S$ $[M+H]^+$	416.2214	416.2213



(*S*,*S*)-12

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.95 (bs, 1 H, NH_a), 5.89 (ddt, $^3J_{14,15‘}$ = 17.0 Hz, $^3J_{14,15}$ = 10.8 Hz, $^3J_{14,13}$ = 5.7 Hz, 1 H, 14-H), 5.71 (d, $^3J_{NHb,9}$ = 5.7 Hz, 1 H, NH_b), 5.28 (dd, $^3J_{15,14}$ = 17.1 Hz, $^2J_{15,15‘}$ = 1.5 Hz, 1 H, 15-H), 5.18 (d, $^3J_{15‘,14}$ = 9.6 Hz, 1 H, 15‘-H), 4.54-4.45 (m, 4 H, 2-H, 9-H, 13-H), 4.28 (m, 1 H, 2‘-H), 3.74 (s, 3 H, 16-H), 3.41 (s, 3 H, 7-H), 1.97 (dsept, $^3J_{10,11}$ = $^3J_{10,9}$ = 6.7 Hz, 1 H, 10-H), 1.14 (s, 9 H, 6-H), 0.94 (d, $^3J_{11,10}$ = 6.7 Hz, 3 H, 11-H), 0.90 (d, $^3J_{11‘,10}$ = 6.7 Hz, 3 H, 11‘-H). 4-H was not found

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 201.2 (s, C-3), 174.4 (s, C-8), 168.9 (s, C-1), 156.3 (s, C-12), 132.7 (d, C-14), 117.5 (t, C-15), 67.5 (d, C-4), 65.7 (t, C-13), 56.0 (d, C-9), 52.4 (q, C-16), 46.3 (t, C-2), 36.0 (s, C-5), 33.9 (q, C-7), 31.0 (d, C-10), 28.4 (q, C-6), 19.5 (q, C-11), 17.4 (q, C-11‘).

optical rotation: $[\alpha]_D^{20}$ = –89.5 [$CHCl_3$, c = 1.0]

HRMS (ESI):	calculated:	found:
$C_{19}H_{34}N_3O_5S$ $[M+H]^+$	416.2214	416.2212

Methyl((*R*)-2-((*S*)-2-(((allyloxy)carbonyl)amino)-*N*,3-dimethylbutanamido)-3,3-dimethylbutanoyl)glycinate [(*S*.*R*)-13]:

Conversion of thioamide **(S,*R*)-12** into amide **(*S*,*R*)-13**:

30.0 mg thioamide **(*S*,*R*)-12** (72.0 µmol, 1.0 eq.), 43.2 mg $Hg(OTf)_2$ (87.0 µmol, 1.2 eq.) and 34 µl 2,6-lutidine (30.9 mg, 289 µmol, 4.0 eq.) were dissolved in 720 µl MeCN. After stirring for 15 min at room temperature, the reaction was quenched by adding 5 % $Na_2S_2O_3$ solution. To separate the mercury salts, the reaction was filtered through a pad of Celite and rinsed with EtOAc. The solvent was removed under reduced pressure and the residue was purified by column chromatography (C18 spherical, H_2O/MeCN 10 to 100 %) to obtain 17.0 mg of the amide **(S,*R*)-13** (43.0 µmol, 59 %) as a colourless resin.

optical rotation: $[\alpha]_D^{20}$ = +79.2 [$CHCl_3$, c = 1.0]

Via linear peptide coupling with D-*tert*-leucine:

100 mg Boc-(*R*)-*tert*-leucine (432 µmol, 1.0 eq.) was dissolved in 0.8 ml DMF under nitrogen atmosphere and cooled to 0 °C. Subsequently, 86.0 mg NaH (60 % in mineral oil, 2.16 mmol, 5.0 eq.) was added, the reaction mixture was heated to room temperature and stirred for 20 min. After the addition of 270 µl methyl iodide (614 mg, 4.32 mmol, 10.0 eq.), stirring was continued for a further 22 h. The reaction was quenched by adding 10 ml water. The aqueous

phase was extracted three times with Et_2O. The combined organic phases were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the *N*-methylated methyl ester was immediately used in the following step.

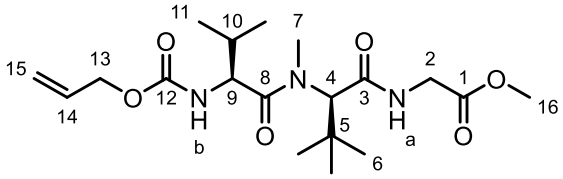
112 mg of the above-prepared methyl ester (432 µmol, 1.0 eq.) was dissolved in 2.1 ml of a THF/water/MeOH mixture (1:1:1, v:v:v) and 92.0 mg LiOH (2.16 mmol, 5.0 eq.) was added. After stirring for 17 h at room temperature, the solvent was removed under reduced pressure. The aqueous phase was acidified with acetic acid to a pH of 5 and extracted three times with EtOAc. The combined organic phase was washed with brine and dried over $MgSO_4$. After removal of solvent under reduced pressure, the free acid was used without further purification.

106 mg of the above-prepared free acid (432 µmol, 1.0 eq.), 65.0 mg H-Gly-OMe·HCl (518 µmol, 1.2 eq.) and 195 µl NMM (179 mg, 1.77 mmol, 4.1 eq.) were dissolved in 4.3 ml DCM and cooled to 0 °C. Subsequently, 180 mg HATU (485 µmol, 1.1 eq.) was added. The ice bath was removed and the reaction was stirred for 3.5 h at room temperature. After full conversion the organic phase was washed with 1 M $KHSO_4$ solution, sat. $NaHCO_3$ solution and brine. After drying over $MgSO_4$, the solvent was removed under reduced pressure and the residue was immediately used in the following step.

137 mg of the above-prepared dipeptide (432 µmol, 1.0 eq.) was dissolved under nitrogen atmosphere in 8.5 ml DCM and 2.1 ml HCl solution (4 M in dioxane, 8.64 mmol, 20.0 eq.) was added and stirred for 2 h at room temperature. After full conversion, the solvent was removed under reduced pressure.

The residue was dissolved in 8.5 ml DCM and 96.0 mg Alloc-Val-OH (475 µmol, 1.1 eq.) and 152 µl NMM (140 mg, 1.38 mmol, 3.2 eq.) was added and cooled to –20 °C. After the addition of 130 mg BEP (475 µmol, 1.1 eq.), the reaction was warmed to room temperature and stirred for 16 h (cold bath was left underneath). After dilution with DCM, the organic phase was washed successively with water, sat. $NaHCO_3$ solution and brine and dried over $MgSO_4$. Column chromatographic purification (C18 spherical, 0.1 % $HCOOH_{aq}$/MeCN, 10 to 90 %) obtained 36.0 mg peptide **(S,*R*)-13** (90.0 µmol, 21 % over 5 steps) as a colourless resin.

LC-MS: t_R (**(S,*R*)-13**) = 1.15 min



(*S*,*R*)-13

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.75 (bs, 1 H, NH_a), 5.89 (ddt, $^3J_{14,15'}$ = 17.2 Hz, $^3J_{14,15}$ = 10.5 Hz, $^3J_{14,13}$ = 5.6 Hz, 1 H, 14-H), 5.52 (d, $^3J_{NHb,9}$ = 8.3 Hz, 1 H, NH_b), 5.29 (dd, $^3J_{15,14}$ = 17.2 Hz, $^2J_{15,15'}$ = 1.3 Hz, 1 H, 15-H), 5.20 (dd, $^3J_{15',14}$ = 10.4 Hz, $^2J_{15',15}$ = 1.2 Hz, 1 H, 15'-H), 5.06 (s, 1 H, 4-H), 4.50-4.58 (m, 3 H, 13-H, 9-H), 3.99 (dd, $^2J_{2,2'}$ = 17.9 Hz, $^3J_{2,NHa}$ = 5.3 Hz, 1 H, 2-H), 3.95 (dd, $^2J_{2',2}$ = 17.5 Hz, $^3J_{2,NHa}$ = 5.3 Hz, 1 H, 2'-H), 3.72 (s, 3 H, 16-H), 3.24 (s, 3 H, 7-H), 2.02 (dsept, $^3J_{10,11}$ = $^3J_{10,9}$ = 6.4 Hz, 1 H, 10-H), 1.10 (s, 9 H, 6-H), 1.00 (d, $^3J_{11,10}$ = 6.7 Hz, 3 H, 11-H), 0.94 (d, $^3J_{11',10}$ = 6.7 Hz, 3 H, 11'-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.1 (s, C-8), 170.2 (s, C-1), 169.6 (s, C-3), 156.6 (s, C-12), 132.6 (d, C-14), 117.8 (t, C-15), 65.9 (d, C-13), 62.7 (t, C-4), 56.0 (d, C-9), 52.2 (q, C-16), 40.8 (t, C-2), 35.1 (s, C-5), 34.0 (q, C-7), 30.9 (d, C-10), 28.0 (q, C-6), 19.8 (q, C-11), 17.2 (q, C-11').

optical rotation:	$[\alpha]_D^{20}$ = +79.8 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{19}H_{34}N_3O_6$ $[M+H]^+$	400.2442	400.2443

Methyl((*S*)-2-((*S*)-2-(((allyloxy)carbonyl)amino)-*N*,3-dimethylbutanamido)-3,3-dimethyl-butanoyl)glycinat [(*S*,*S*)-13]

Conversion of thioamide **(*S*,*S*)-12** to amide **(*S*,*S*)-13**:

36.0 mg thioamide **(*S*,*S*)-12** (87.0 µmol, 1.0 eq.), 51.8 mg $Hg(OTf)_2$ (104 µmol, 1.2 eq.) and 40 µl 2,6-lutidine (37.1 mg, 347 µmol, 4.0 eq.) was dissolved in 0.860 µl MeCN. After stirring for 15 min at room temperature, the reaction was quenched by adding 5 % $Na_2S_2O_3$ solution. To separate the mercury salts, the reaction was filtered through a pad of Celite and rinsed with EtOAc. The solvent was removed under reduced pressure and the residue was purified by column chromatography (C18 spherical, H_2O/MeCN 10 to 100 %) to obtain 25.0 mg of the amide **(*S*,*S*)-13** (63.0 µmol, 72 %) as a colourless resin.

optical rotation: $[\alpha]_D^{20}$ = –96.1 [$CHCl_3$, c = 1.0]

Via linear peptide coupling with L-*tert*-leucine:

100 mg Boc-(*S*)-*tert*-leucine (432 µmol, 1.0 eq.) was dissolved in 800 µl DMF under nitrogen atmosphere and cooled to 0 °C. Subsequently, 86.0 mg NaH (60 % in mineral oil, 2.16 mmol, 5.0 eq.) was added, the reaction mixture was heated to room temperature and stirred for 20 min. After the addition of 270 µl methyl iodide (614 mg, 4.32 mmol, 10.0 eq.), stirring was continued for a further 22 h. The reaction was quenched by adding 10 ml water. The aqueous phase was extracted three times with Et_2O. The combined organic phases were washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the *N*-methylated methyl ester was immediately used in the following step.

112 mg of the above-prepared methyl ester (432 µmol, 1.0 eq.) was dissolved in 2.1 ml of a THF/water/MeOH mixture (1:1:1, v:v:v) and 92 mg LiOH (2.16 mmol, 5.0 eq.) was added. After stirring for 17 h at room temperature, the solvent was removed under reduced pressure. The aqueous phase was acidified with acetic acid to a pH of 5 and extracted three times with EtOAc. The combined organic phase was washed with brine and dried over $MgSO_4$. After removal of solvent under reduced pressure, the free acid was used without further purification.

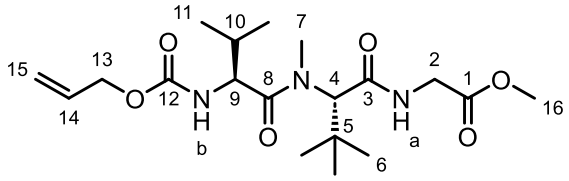
106 mg of the above-prepared free acid (432 µmol, 1.0 eq.), 65.0 mg HCl-Gly-OMe (518 µmol, 1.2 eq.) and 195 µl NMM (179 mg, 1.77 mmol, 4.1 eq.) were dissolved in 4.3 ml DCM and cooled to 0 °C. Subsequently, 180 mg HATU (482 µmol, 1.1 eq.) was added. The ice bath was removed and the reaction was stirred for 3.5 h at room temperature. After full conversion the organic phase was washed with 1 M $KHSO_4$ solution, sat. $NaHCO_3$ solution and brine. After drying over $MgSO_4$, the solvent was removed under reduced pressure and the residue was immediately used in the following step.

137 mg of the above-prepared dipeptide (432 µmol, 1.0 eq.) was dissolved under nitrogen atmosphere in 8.5 ml DCM and 2.1 ml HCl solution (4 M in dioxane, 8.64 mmol, 20.0 eq.) was added and stirred for 2 h at room temperature. After full conversion, the solvent was removed under reduced pressure.

The residue was dissolved in 8.5 ml DCM and 96.0 mg Alloc-Val-OH (475 µmol, 1.1 eq.) and 152 µl NMM (140 mg, 1.38 mmol, 3.2 eq.) was added and cooled to –20 °C. After the addition of 130 mg BEP (0.475 µmol, 1.1 eq.), the reaction was warmed to room temperature and stirred for 16 h (cold bath was left underneath). After dilution with DCM, the organic

phase was washed successively with water, sat. $NaHCO_3$ solution and brine and dried over $MgSO_4$. Column chromatographic purification (C18 spherical, 0.1 % $HCOOH_{aq}$/MeCN, 10 to 90 %) obtained 15.0 mg peptide **(S,S)-13** (38.0 µmol, 9 % over 5 steps) as a colourless resin.

LC-MS: t_R (**(*S*,S)-13**) = 1.16 min



(***S*,*S*)-13**

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.60 (bs, $^3J_{NHa,2}$ = 5.1 Hz, 1 H, NH_a), 5.90 (ddt, $^3J_{14,15'}$ = 17.1 Hz, $^3J_{14,15}$ = 10.6 Hz, $^3J_{14,13}$ = 5.6 Hz, 1 H, 14-H), 5.57 (d, $^3J_{NHb,9}$ = 9.4 Hz, 1 H, NH_b), 5.28 (dd, $^3J_{15,14}$ = 17.2 Hz, $^2J_{15,15'}$ = 1.2 Hz, 1 H, 15-H), 5.19 (d, $^3J_{15',14}$ = 10.4 Hz, 1 H, 15'-H), 5.02 (s, 1 H, 4-H), 4.51-4.56 (m, 3 H, 9-H, 13-H), 4.04 (dd, $^2J_{2,2'}$ = 18.0 Hz, $^3J_{2,NHa}$ = 5.9 Hz, 1 H, 2-H), 3.94 (dd, $^2J_{2',2}$ = 17.9 Hz, $^3J_{2',NHa}$ = 5.4 Hz, 1 H, 2'-H), 3.72 (s, 3 H, 16-H), 3.28 (s, 3 H, 7-H), 2.01 (dsept, $^3J_{10,11}$ = $^3J_{10,9}$ = 6.7 Hz, 1 H, 10-H), 1.06 (s, 9 H, 6-H), 0.96 (d, $^3J_{11,10}$ = 7.2 Hz, 3 H, 11-H), 0.94 (d, $^3J_{11',10}$ = 7.0 Hz, 3 H, 11'-H).

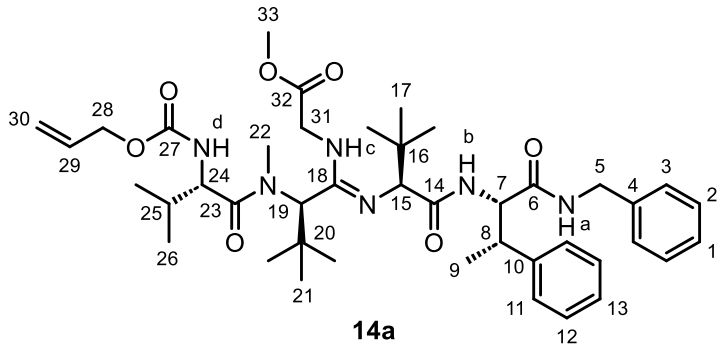
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 174.1 (s, C-8), 170.1 (s, C-1), 169.7 (s, C-3), 156.3 (s, C-12), 132.7 (d, C-14), 117.6 (t, C-15), 65.7 (d, C-13), 62.4 (t, C-4), 55.9 (d, C-9), 52.2 (q, C-16), 40.8 (t, C-2), 35.5 (s, C-5), 33.6 (q, C-7), 31.0 (d, C-10), 27.7 (q, C-6), 19.4 (q, C-11), 17.6 (q, C-11').

optical rotation:	$[\alpha]_D^{20}$ = –91.8 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{19}H_{34}N_3O_6$ $[M+H]^+$	400.2442	400.2444

Methyl((*R,Z*)-2-((*S*)-2-(((allyloxy)carbonyl)amino)-*N*,3-dimethylbutanamido)-1-(((*S*)-1-(((2*S*,3*S*)-1-(benzylamino)-1-oxo-3-phenylbutane-2-yl)amino)-3,3-dimethyl-1-oxobutane-2-yl)imino)-3,3-dimethylbutyl)glycinate (14a)[8]

In a flame-dried Schlenk flask under argon, 118 mg thioamide **(*R*)-12** (283 µmol, 1.0 eq.) and 125 mg amine **8** (328 µmol, 1.2 eq.) were dissolved in 2.8 ml MeCN. Then 127 µl 2,6-lutidine (117 mg, 1.09 mmol, 3.9 eq.) and 163 mg $Hg(OTf)_2$ (328 µmol, 1.2 eq.) were added and stirred for 35 min at room temperature. After full conversion, the reaction was quenched by adding 5 % $Na_2S_2O_3$ solution. To remove the mercury salts, the reaction was filtered through a pad of Celite and rinsed with EtOAc. The filtrate was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by column chromatography (C18 spherical, H_2O/MeCN 10 to 100 %) to obtain 47.0 mg of amidine **14a** (62.0 µmol, 22 %) as a colourless amorphous solid. In addition, 80.0 mg of the amine **8** (210 µmol, 62 % of the starting material) could be recovered.

LC-MS: t_R (**14a**) = 1.06 min



14a

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.67 (bs, 1 H, NH_c), 7.32-7.15 (m, 10 H, 1-H, 2-H, 3-H, 11-H, 12-H, 13-H), 6.68 (m, 1 H, NH_d), 6.45 (m, 1 H, NH_b), 5.84 (m, 1 H, 29-H), 5.63 (s, 1 H, 15-H), 5.30 (bs, 1 H, NH_a), 5.25 (m, 1 H, 30-H), 5.18 (m, 1 H, 30'-H), 4.64-4.40 (m, 4 H, 5-H, 7-H, 28-H), 4.22-4.17 (m, 2 H, 5'-H, 24-H), 4.06 (dd, $^2J_{31,31'}$ = 17.5 Hz, $^3J_{31,NHc}$ = 6.2 Hz, 1 H, 31-H), 3.99 (s, 1 H, 19-H), 3.78 (dd, $^2J_{31',31}$ = 17.6 Hz, $^3J_{31',NHc}$ = 5.6 Hz, 1 H, 31'-H), 3.68 (s, 3 H, 33-H), 3.22 (m, 1 H, 8-H), 3.16 (s, 3 H, 22-H), 1.86 (m, 1 H, 25-H), 1.32-1.24 (m, 12 H, 9-H, 17-H), 0.92 (m, 3 H, 26-H), 0.80 (d, $^3J_{26'25}$ = 6.6 Hz, 3-H, 26-H'), 0.48 (s, 9 H, 21-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.2 (s, C-6), 171.3 (s, C-14), 170.5 (s, C-32), 169.6 (s, C-23), 159.4 (s, C-18), 156.1 (s, C-27), 142.5 (s, C-10), 138.0 (s, C-4), 132.2 (d, C-29), 128.9 (d, C-12), 128.6 (d, C-2), 127.7 (d, C-13), 127.5 (d, C-3), 127.5 (d, C-11), 127.4 (d, C-1), 118.4 (t, C-30), 69.4 (s, C-19), 66.1 (t, C-28), 65.1 (d, C-15), 58.3 (d, C-7), 55.8 (d, C-24), 51.9 (q, C-33), 43.3 (t, C-5), 41.3 (d, C-8), 40.8 (t, C-31), 36.1 (q, C-22), 35.1 (s, C-20), 35.1 (s, C-16), 30.4 (d, C-25), 29.5 (q, C-17), 26.1 (q, C-21), 20.8 (q, C-26), 19.4 (q, C-26'), 19.3 (q, C-9).

Amidine tautomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 6.57 (m, 1 H, NH_b), 4.50 (m, 1 H, 24-H), 3.75 (m, 1 H, 5-H), 3.63 (s, 3 H, 33-H), 3.60 (s, 3 H, 33-H), 3.39 (m, 1 H, 8-H), 3.11 (s, 3 H, 22-H), 1.99 (m, 1 H, 25-H), 1.02-0.73 (m, 15 H, 17-H, 26-H), 0.75 (s, 9 H, 21-H), 0.73 (s, 9 H, 21-H) 0.60 (d, $^3J_{26'25}$ = 7.7 Hz, 3-H, 26-H').

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 127.1 (d, C-1), 65.6 (t, C-28), 55.9 (d, C-24), 52.2 (q, C-33), 44.3 (t, C-5), 40.9 (t, C-31), 33.1 (q, C-22), 28.2 (q, C-17), 27.0 (q, C-21).

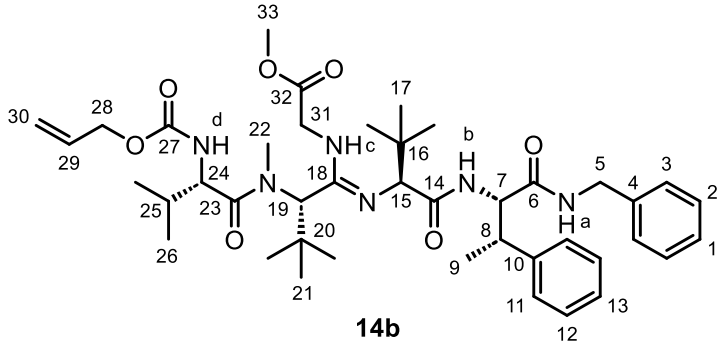
optical rotation:	$[\alpha]_D^{20}$ = +8.6 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{42}H_{63}N_6O_7$ $[M+H]^+$	763.4753	763.4752

Methyl((*S,Z*)-2-((*S*)-2-(((allyloxy)carbonyl)amino)-*N*,3-dimethylbutanamido)-1-(((*S*)-1-(((2*S*,3*S*)-1-(benzylamino)-1-oxo-3-phenylbutane-2-yl)amino)-3,3-dimethyl-1-oxobutane-2-yl)imino)-3,3-dimethylbutyl)glycinate (14b)[8]

In a flame-dried Schlenk flask under argon, 163 mg thioamide **(*S*)-12** (393 µmol, 1.0 eq.) and 180 mg amine **8** (472 µmol, 1.2 eq.) were dissolved in 3.9 ml MeCN. Then 183 µl 2,6-lutidine (169 mg, 1.57 mmol, 4.0 eq.) and 235 mg $Hg(OTf)_2$ (472 µmol, 1.2 eq.) were added and stirred for 35 min at room temperature. After full conversion, the reaction was quenched by adding 5 % $Na_2S_2O_3$ solution. To remove the mercury salts, the reaction was filtered through a pad of Celite and rinsed with EtOAc. The filtrate was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by column chromatography (C18 spherical, H_2O/MeCN 10 to 100 %) to obtain 82.0 mg of amidine **14b** (107 µmol, 27 %) as a colourless amorphous solid.

In addition, 114 mg of the amine **8** (299 µmol, 63 % of the starting material) could be recovered.

LC-MS: t_R (**14b**) = 1.15 min



14b

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.16-7.33 (m, 10 H, 1-H, 2-H, 3-H, 11-H, 12-H, 13-H), 6.78 (d, $^3J_{7,NHb}$ = 7.6 Hz, 1 H, NH_b), 6.38 (bs, 1 H, NH_a), 5.84 (ddt, $^3J_{29,30}$ = 17.1 Hz, $^3J_{29,30'}$ = 10.5 Hz, $^3J_{29,28}$ = 5.6 Hz, 1 H, 29-H), 5.46 (m, 1 H, 15-H), 5.25 (dd, $^3J_{30,29}$ = 17.1 Hz, $^2J_{30,30'}$ = 1.2 Hz, 1 H, 30-H), 5.18 (dd, $^3J_{30,29}$ = 10.4 Hz, $^2J_{30,30'}$ = 0.9 Hz, 1 H, 30'-H), 4.63 (m, 1 H, 7-H), 4.51 (m, 2H, 28-H), 4.39 (dd, $^2J_{5,5'}$ = 14.9 Hz, $^3J_{5,NHa}$ = 6.4 Hz, 1 H, 5'-H), 4.05-4.18 (m, 2 H , 5-H, 31-H), 3.89 (m, 1 H, 19-H), 3.80 (m, 1 H, 31'-H), 3.69 (m, 1 H, 24-H), 3.64 (s, 3 H, 33-H), 3.05-3.30 (m, 4 H, 8-H, 22-H), 1.94 (m, 1 H, 25-H), 1.16 (s, 9 H, 17-H), 1.26 (d, $^3J_{9,8}$ = 6.6 Hz, 3 H, 9-H), 0.95 (d, $^3J_{26,25}$ = 6.2 Hz, 3 H, 26-H), 0.75 (m, 3 H, 26'-H), 0.71 (s, 9 H, 21-H).

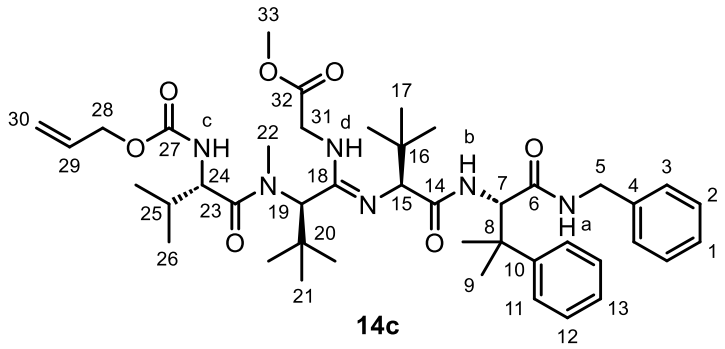
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 173.0 (s, C-18), 171.3 (s, C-14), 170.8 (s, C-32), 170.5 (s, C-6), 159.7 (s, C-23), 155.6 (s, C-27), 141.9 (s, C-10), 137.6 (s, C-4), 132.6 (d, C-29), 128.8 (d, C-12), 128.7 (d, C-2), 127.6 (d, C-3, C-11, C-13), 127.2 (d, C-1), 117.8 (t, C-30), 70.4 (s, C-19), 65.7 (t, C-28), 63.3 (d, C-15), 57.7 (d, C-7), 51.8 (q, C-33), 51.8 (d, C-24), 43.3 (t, C-5), 42.0 (d, C-8), 41.0 (t, C-31), 35.7 (s, C-20), 35.6 (s, C-16), 35.4 (q, C-22), 31.9 (d, C-25), 28.6 (q, C-17), 26.7 (q, C-21), 20.7 (q, C-26), 18.7 (q, C-26'), 17.5 (q, C-9).

optical rotation:	$[\alpha]_D^{20}$ = –81.6 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{42}H_{63}N_6O_7$ $[M+H]^+$	763.4753	763.4750

Methyl((*R*,*Z*)-2-((*S*)-2-(((allyloxy)carbonyl)amino)-*N*,3-dimethylbutanamido)-1-(((*S*)-1-(((*S*)-1-(benzylamino)-3-methyl-1-oxo-3-phenylbutane-2-yl)amino)-3,3-dimethyl-1-oxobutane-2-yl)imino)-3,3-dimethylbutyl)glycinate (14c)[8]

In a flame-dried Schlenk flask under argon, 226 mg thioamide **(*R*)-12** (544 µmol, 1.0 eq.) and 257 mg amine **10** (650 µmol, 1.2 eq.) were dissolved in 5.4 ml MeCN. Then 252 µl 2,6-lutidine (232 mg, 2.16 mmol, 4.0 eq.) and 324 mg $Hg(OTf)_2$ (650 µmol, 1.2 eq.) were added and stirred for 35 min at room temperature. After full conversion, the reaction was quenched by adding 5 % $Na_2S_2O_3$ solution. To remove the mercury salts, the reaction was filtered through a pad of Celite and rinsed with EtOAc. The filtrate was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by column chromatography (C18 spherical, H_2O/MeCN 10 to 100 %) to obtain 92.0 mg of amidine **14c** (118 mmol, 22 %) as a colourless amorphous solid. In addition, 96 mg of the amine **10** (243 mmol, 38 % of the starting material) could be recovered.

LC-MS: t_R (**14c**) = 1.17 min



14c

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.69 (bs, 1 H, NH_d), 7.39 (m, 2 H, 11-H), 7.29-7.15 (m, 7 H, 1-H, 2-H, 12-H, 13-H, NH_a), 6.90 (m, 1 H, NH_b), 6.81 (m, 2 H, 3-H), 5.86 (m, 1 H, 29-H), 5.52 (m, 1 H, NH_c), 5.51 (m, 1 H, 15-H), 5.27 (m, 1 H, 30-H), 5.20 (d, $^3J_{30,29}$ = 10.3 Hz , 1 H, 30-H‘), 4.69 (d, $^3J_{7,NHb}$ = 9.2 Hz, 1 H, 7-H), 4.50 (m, 2 H, 28-H), 4.25 (m, 1 H, 24-H), 4.11 (s, 1 H, 19-H), 4.10 (dd, $^2J_{31,31‘}$ = 17.4 Hz, $^3J_{31,NH}$ = 6.1 Hz, 1 H, 31-H), 3.97 (m, , 5-H), 3.82 (dd, $^2J_{31‘,31}$ = 17.7 Hz, $^3J_{31‘,NH}$ = 5.6 Hz, 1H, 31-H‘), 3.70 (s, 3 H, 33-H), 3.22 (s, 3 H, 22-H), 1.95 (m, 1 H, 25-H), 1.42 (s, 3 H, 9-H), 1.39 (s, 3 H, 9-H‘), 1.28 (s, 9 H, 17-H), 0.95 (m, 3 H, 26-H), 0.88 (s, 9 H, 21-H), 0.74 (d, $^3J_{26‘,25}$ = 6.6 Hz, 3 H, 26-H‘).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.3 (s, C-18), 171.6 (s, C-14), 170.5 (s, C-32), 169.0 (s, C-6), 160.1 (s, C-23), 156.2 (s, C-27), 146.2 (s, C-10), 137.4 (s, C-4), 132.4 (d, C-29), 128.6 (d, C-12), 128.4 (d, C-2), 127.5 (d, C-3), 127.3 (d, C-1), 126.6 (d, C-13), 126.3 (d, C-11), 118.3 (t, C-30), 70.3 (d, C-19), 66.1 (t, C-28), 65.9 (d, C-15), 60.9 (d, C-7), 56.2 (d, C-24), 51.9 (q, C-33), 43.2 (t, C-5), 41.9 (s, C-8), 40.9 (t, C-31), 36.0 (q, C-22), 35.6 (s, C-20), 35.2 (s, C-16), 30.7 (d, C-25), 29.5 (q, C-17), 27.1 (q, C-9), 26.8 (q, C-21), 22.3 (q, C-9), 20.8 (q, C-26), 19.2 (q, C-26‘).

Amidine tautomer (selected signals):

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.78 (d, $^3J_{7,NHb}$ = 9.0 Hz, 1 H, 7-H), 3.59 (s, 3 H, 33-H), 3.16 (s, 3 H, 22-H), 1.19 (s, 9 H, 17-H), 0.99 (s, 9 H, 21-H).

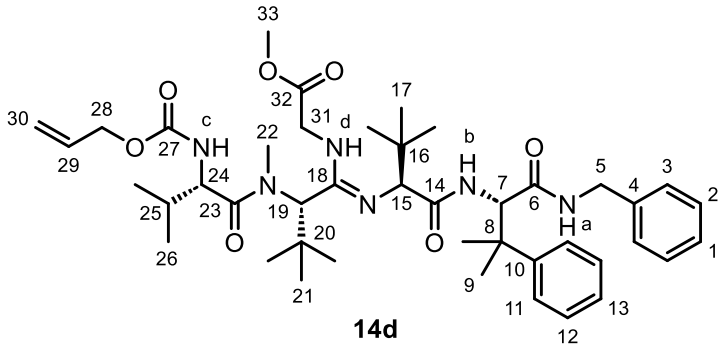
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 128.7 (d, C-2), 128.6 (d, C-12), 127.8 (d, C-3), 64.7 (d, C-15), 29.7 (q, C-17), 27.2 (q, C-9), 26.8 (q, C-21).

optical rotation:	$[\alpha]_D^{20}$ = +35.3 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{43}H_{65}N_6O_7$ $[M+H]^+$	777.4909	777.4908

Methyl((*S*,*Z*)-2-((*S*)-2-(((allyloxy)carbonyl)amino)-*N*,3-dimethylbutanamido)-1-(((*S*)-1-(((*S*)-1-(benzylamino)-3-methyl-1-oxo-3-phenylbutane-2-yl)amino)-3,3-dimethyl-1-oxobutane-2-yl)imino)-3,3-dimethylbutyl)glycinate (14d)[8]

In a flame-dried Schlenk flask under argon, 207 mg thioamide **(*S*)-12** (498 µmol, 1.0 eq.) and 228 mg amine **10** (576 µmol, 1.2 eq.) were dissolved in 5.0 ml MeCN. Then 232 µl 2,6-lutidine (214 mg, 1.99 mmol, 4.0 eq.) and 288 mg $Hg(OTf)_2$ (576 µmol, 1.2 eq.) were added and stirred for 35 min at room temperature. After full conversion, the reaction was quenched by adding 5 % $Na_2S_2O_3$ solution. To remove the mercury salts, the reaction was filtered through a pad of Celite and rinsed with EtOAc. The filtrate was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by column chromatography (C18 spherical, H_2O/MeCN 10 to 100 %) to obtain 78.0 mg of amidine **14c** (100 µmol, 20 %) as a colourless amorphous solid. In addition, 151 mg of the amine **10** (382 µmol, 64 % of the starting material) could be recovered.

LC-MS: t_R (**14d**) = 1.26 min



14d

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.34 (, 2 H, 12-H), 7.16-7.35 (m, 10 H, 1-H, 3-H, 11-H, 13-H, NH_c, NH_d), 7.07 (m, 1 H, NH_b), 6.81 (m, 2 H, 2-H), 5.89 (ddt, $^3J_{29,30}$ = 17.0 Hz, $^3J_{29,30'}$ = 10.5 Hz, $^3J_{29,28}$ = 5.6 Hz, 1 H, 29-H), 5.40-5.55 (m, 2 H, NH_a, 19-H), 5.28 (d, $^3J_{30,29}$ = 16.5 Hz, 1 H, 30-H), 5.21 (d, $^3J_{30,29}$ = 10.4 Hz , 1 H, 30'-H), 4.83 (d, $^3J_{7,NHb}$ = 8.3 Hz, 1 H, 7-H), 4.57 (dd, $^2J_{28,28'}$ = 13.5 Hz, $^3J_{28,29}$ = 5.8 Hz , 1 H, 28-H), 4.54 (m, 1 H, 24-H), 4.51 (dd, $^2J_{28',28}$ = 13.2 Hz, $^3J_{28',29}$ = 5.8 Hz, 1 H, 28-H'), 4.17 (m, 1 H, 31-H), 4.04 (s, 1 H, 15-H), 3.96 (dd, $^2J_{31',31}$ = 14.8 Hz, $^3J_{31',NH}$ = 6.1 Hz, , 5-H), 3.75-3.92 (m, 2H, 5-H', 31-H'), 3.57 (s, 3 H, 33-H), 3.23 (s, 3 H, 22-H), 2.00 (m, 1 H, 25-H), 1.34 (s, 6 H, 9-H), 1.18 (s, 9 H, 17-H), 0.98 (m, 12 H, 21-H, 26-H), 0.74 (d, $^3J_{26',25}$ = 6.6 Hz, 3 H, 26-H').

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.4 (s, C-14), 171.4 (s, C-23), 170.7 (s, C-32), 169.9 (s, C-6), 160.7 (s, C-18), 155.7 (s, C-27), 145.9 (s, C-10), 137.1 (s, C-4), 132.7 (d, C-29), 128.6 (d, C-3), 128.5 (d, C-11), 127.5 (d, *C-13),* 127.4 (d, C-2), 126.7 (d, C-1), 126.3 (d, C-12), 117.8 (t, C-30), 70.8 (d, C-15), 65.7 (t, C-28), 63.5 (d, C-19), 60.1 (d, C-7), 55.8 (d, C-24), 51.6 (q, C-33), 43.2 (t, C-5), 41.9 (s, C-8), 41.1 (t, C-31), 35.8 (s, C-20), 35.8 (s, C-16), 35.8 (q, C-22), 31.6 (d, C-25), 28.6 (q, C-17), 27.6 (q, C-9), 27.2 (q, C-21), 22.1 (q, C-9'), 20.8 (q, C-26), 18.5 (q, C-26').

optical rotation:	$[\alpha]_D^{20}$ = –53.1 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{43}H_{65}N_6O_7$ $[M+H]^+$	777.4909	777.4908

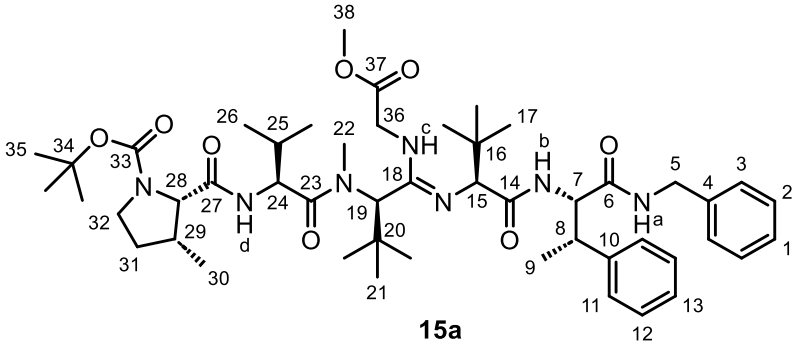
tert-Butyl(2*S*,3*R*)-2-(((4*S*,7*S*,10*R*,13*S*,*Z*)-7,10-di-*tert*-butyl-9-((2-methoxy-2-oxoethyl)-amino)-11,14-dimethyl-3,6,12-trioxo-1-phenyl-4-((*S*)-1-phenylethyl)-2,5,8,11-tetraaza-pentadec-8-en-13-yl)carbamoyl)-3-methylpyrrolidine-1-carboxylate (15a)

40.0 mg of the Alloc-protected amine **14a** (52.0 µmol, 1.0 eq.) was dissolved in 1.0 ml of an H_2O/MeCN mixture (1:1, v:v) and 55 µl diethylamine (38.3 mg, 524 µmol, 10.0 eq.), 2.4 mg TPPTS (4.2 µmol, 0.08 eq.) and 105 µl $Pd(OAc)_2$ solution (0.02 M in MeCN, 2.1 µmol, 0.04 eq.) were added. After stirring for 15 min at room temperature, the solvent was removed under reduced pressure and the free amine was immediately used in the following coupling reaction.

In a round bottom flask, the above-prepared free amine was dissolved in 0.5 ml DCM and 14.3 mg Boc-MePro-OH[9] (62.0 µmol, 1.2 eq.) and 17.2 µl NMM (15.8 mg, 156 µmol, 3.0 eq.) were added. After cooling the reaction solution to 0 °C, 24.7 mg HATU (65.0 µmol, 1.25 eq.) was added and the reaction was warmed to room temperature within 16 h. After full conversion, the organic phase was washed with 1 M HCl solution, sat. $NaHCO_3$ solution and brine. After drying over $MgSO_4$, the solvent was removed under reduced pressure and the

crude product was purified by column chromatography (C-18 spherical, H_2O/MeCN 10 to 100 %) to obtain 24.0 mg of the linear peptide **15a** (27.0 µmol, 52 %) as a colourless resin.

LC-MS: t_R (**15a**) = 1.24 min



15a

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.78 (bs, 1 H, NH_c), 7.32 (m, 2 H, 2-H), 7.15-7.27 (m, 9 H, 1-H, 3-H, 11-H, 12-H, 13-H, NH_d), 6.56 (bs, 1 H, NH_a), 6.46 (bs, 1 H, NH_b), 5.56 (bs, 1 H, 15-H), 4.58 (dd, $^2J_{5',5}$ = 14.5 Hz, $^3J_{5',NHa}$ = 5.5 Hz, 1 H, 5-H'), 4.49 (dd, $^3J_{7,NHb}$ = $^3J_{7,8}$ = 9.0 Hz, 1 H, 7-H), 4.28 (d, $^3J_{24,NHd}$ = 7.8 Hz, 1 H, 24-H), 4.19 (dd, $^2J_{5,5'}$ = 14.8 Hz, $^3J_{5,NHa}$ = 4.7 Hz, 1 H, 5-H), 4.09 (d, $^3J_{28,29}$ = 7.0 Hz, 1 H, 28-H), 4.05-4.15 (m, 1 H, 36-H'), 3.97 (m, 1 H, 19-H), 3.78 (m, 1 H, 36-H), 3.68 (s, 3 H, 38-H), 3.39 (t, $^3J_{32,31}$ = 9.5 Hz, 1 H, 32-H), 3.26 (m, 2 H, 8-H, 32-H'), 3.18 (s, 3 H, 22-H), 2.17 (m, 1 H, 29-H), 1.90-2.00 (m, 2 H, 25-H, 31-H'), 1.85 (m, 1 H, 31-H), 1.43 (s, 9 H, 35-H), 1.25-1.27 (m, 12 H, 9-H, 17-H), 1.01 (d, $^3J_{30,29}$ = 6.7 Hz, 3 H, 30-H), 0.94 (d, $^3J_{26',25}$ = 6.3 Hz, 3 H, 26'-H), 0.76 (d, $^3J_{26,25}$ = 6.4 Hz, 3 H, 26-H), 0.51 (s, 9 H, 21-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 173.1 (s, C-18), 171.7 (s, C-14), 171.3 (s, C-27), 170.5 (s, C-37), 169.6 (s, C-6), 159.6 (s, C-23), 155.4 (s, C-33), 142.5 (s, C-10), 137.9 (s, C-4), 128.9 (d, C-12), 128.7 (d, C-2), 127.6 (d, C-3), 127.6 (d, C-11), 127.4 (d, C-13), 127.1 (d, C-1), 80.4 (s, C-34), 69.7 (d, C-19), 65.2 (d, C-15), 61.4 (d, C-28), 58.3 (d, C-7), 55.3 (d, C-24), 51.9 (q, C-38), 46.3 (t, C-32), 43.4 (t, C-5), 41.0 (d, C-8), 40.9 (t, C-36), 36.4 (d, C-29), 36.2 (q, C-22), 35.5 (s, C-20), 35.3 (s, C-16), 32.1 (t, C-31), 30.3 (d, C-25), 29.5 (q, C-17), 28.4 (q, C-35), 26.6 (q, C-21), 20.5 (q, C-26'), 19.6 (q, C-9), 19.4 (q, C-26), 13.4 (q, C-30).

optical rotation:	$[\alpha]_D^{20}$ = –9.0 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{49}H_{76}N_7O_8$ $[M+H]^+$	890.5750	890.5744

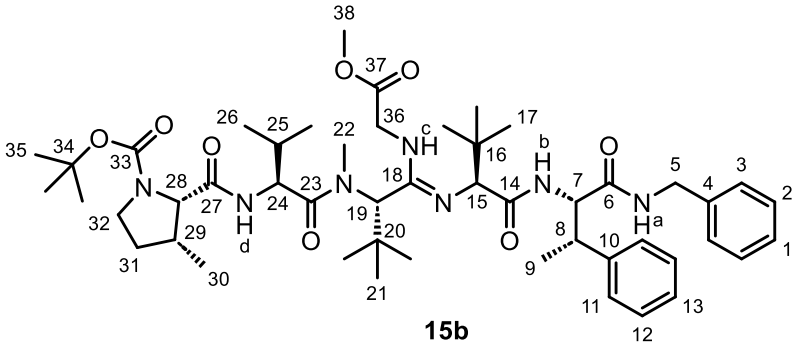
tert-Butyl(2*S*,3*R*)-2-(((4*S*,7*S*,10*S*,13*S*,*Z*)-7,10-di-*tert*-butyl-9-((2-methoxy-2-oxoethyl)-amino)-11,14-dimethyl-3,6,12-trioxo-1-phenyl-4-((*S*)-1-phenylethyl)-2,5,8,11-tetraaza-pentadec-8-en-13-yl)carbamoyl)-3-methylpyrrolidine-1-carboxylate (15b)

79.0 mg of the Alloc-protected amine **14b** (104 µmol, 1.0 eq.) was dissolved in 2.0 ml of an H_2O/MeCN mixture (1:1, v:v) and 108 µl diethylamine (76.0 mg, 1.04 mmol, 10.0 eq.), 4.7 mg TPPTS (8.3 µmol, 0.08 eq.) and 207 µl $Pd(OAc)_2$ solution (0.02 M in MeCN, 4.1 µmol, 0.04 eq.) were added. After stirring for 25 min at room temperature, the solvent was removed under reduced pressure and the free amine was immediately used in the following coupling reaction.

In a round bottom flask, the above-prepared free amine was dissolved in 1.0 ml DCM and 28.8 mg Boc-MePro-OH[9] (125 µmol, 1.2 eq.) and 34.5 µl NMM (31.7 mg, 314 µmol, 3.0 eq.) were added. After cooling the reaction solution to 0 °C, 49.6 mg HATU (131 µmol, 1.25 eq.) was added, and the reaction was warmed to room temperature within 16 h. After full

conversion, the organic phase was washed with 1 M HCl solution, sat. $NaHCO_3$ solution and brine. After drying over $MgSO_4$, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (C-18 spherical, H_2O/MeCN 10 to 100 %) to obtain 56.0 mg of the linear peptide **15b** (63.0 µmol, 60 %) as a colourless resin.

LC-MS: t_R (**15b**) = 1.26 min



15b

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.15-7.31 (m, 10 H, 1-H, 2-H, 3-H, 11-H, 12-H, 13-H), 6.87 (bs, 1 H, NH_d), 6.79 (bs, 2 H, NH_a, NH_c), 6.67 (bs, 1 H, NH_b), 5.58 (bs, 1 H, 15-H), 4.85 (m, 1 H, 24-H), 4.66 (m, 1 H, 7-H), 4.39 (dd, $^2J_{5,5'}$ = 14.3 Hz, $^3J_{5,NHa}$ = 5.8 Hz, 1 H, 5-H), 4.19 (m, 1 H, 36-H), 4.11 (m, 2 H, 5-H', 28-H), 3.91 (s, 1 H, 19-H), 3.86 (dd, $^2J_{36,36'}$ = 17.2 Hz, $^3J_{36,NHc}$ = 4.1 Hz, 1 H, 36-H), 3.63 (s, 3 H, 38-H), 3.51 (m, 1 H, 32-H), 3.30 (dt, $^2J_{32',32}$ = 17.2 Hz, $^3J_{32',31}$ = 4.1 Hz, 1 H, 32-H'), 3.22 (s, 3 H, 22-H), 3.15 (m, 1 H, 8-H), 2.26 (m, 1 H, 29-H), 2.05 (m, 2 H, 25-H, 31-H), 1.89 (m, 1 H, 31-H'), 1.37 (s, 9 H, 35-H), 1.22 (m, 3 H, 9-H), 1.13 (s, 9 H, 17-H), 0.98 (d, $^3J_{30,29}$ = 6.6 Hz, 3 H, 30-H), 0.92 (d, $^3J_{26',25}$ = 6.2 Hz, 3 H, 26'-H), 0.71-0.78 (m, 12 H, 21-H, 26-H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 172.7 (s, C-18), 171.5 (s, C-14), 170.9 (s, C-37), 170.6 (s, C-27), 170.6 (s, C-6), 160.1 (s, C-23), 154.8 (s, C-33), 142.1 (s, C-10), 137.8 (s, C-4), 128.8 (d, C-12), 128.6 (d, C-2), 127.8 (d, C-3), 127.6 (d, C-11), 127.5 (d, C-13), 127.1 (d, C-1), 79.9 (s, C-34), 70.6 (d, C-19), 63.1 (d, C-15), 63.0 (d, C-28), 57.5 (d, C-7), 53.4 (d, C-24), 51.7 (q, C-38), 46.4 (t, C-32), 43.4 (t, C-5), 42.1 (d, C-8), 41.0 (t, C-36), 36.5 (d, C-29), 35.6 (q, C-22), 35.6 (s, C-16), 35.6 (s, C-20), 32.0 (t, C-25), 31.8 (d, C-31), 28.6 (q, C-17), 28.3 (q, C-35), 27.1 (q, C-21), 20.2 (q, C-26'), 19.1 (q, C-26), 18.1 (q, C-9), 14.0 (q, C-30).

optical rotation:	$[\alpha]_D^{20}$ = –96.0 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{49}H_{76}N_7O_8$ $[M+H]^+$	890.5750	890.5750

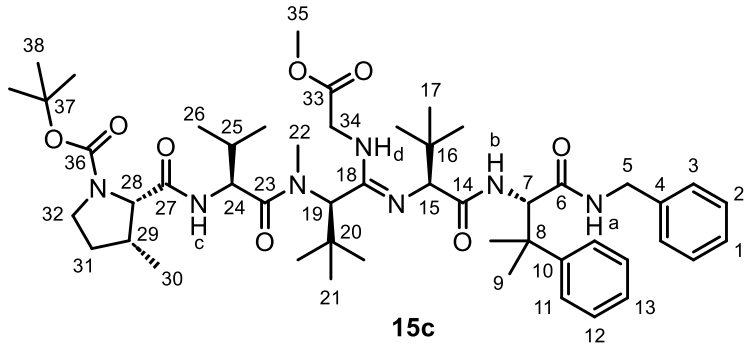
tert-Butyl(2*S*,3*R*)-2-(((4*S*,7*S*,10*R*,13*S*,*Z*)-7,10-di-*tert*-butyl-9-((2-methoxy-2-oxoethyl) amino)-11,14-dimethyl-3,6,12-trioxo-1-phenyl-4-(2-phenylpropan-2-yl)-2,5,8,11-tetraaza-pentadec-8-en-13-yl)carbamoyl)-3-methylpyrrolidin-1-carboxylate (15c)

85.0 mg of the Alloc-protected amine **14c** (109 µmol, 1.0 eq.) was dissolved in 2.0 ml of an H_2O/MeCN mixture (1:1, v:v) and 114 µl diethylamine (80 mg, 1.09 mmol, 10.0 eq.), 5.0 mg TPPTS (8.75 µmol, 0.08 eq.) and 219 µl $Pd(OAc)_2$ solution (0.02 M in MeCN, 4.38 µmol, 0.04 eq.) were added. After stirring for 25 min at room temperature, the solvent was removed under reduced pressure and the free amine was immediately used in the following coupling reaction.

In a round bottom flask, the above-prepared free amine was dissolved in 1.0 ml DCM and 30.0 mg Boc-MePro-OH[9] (131 µmol, 1.2 eq.) and 36 µl NMM (33.1 mg, 327 µmol, 3.0 eq.) were added. After cooling the reaction solution to 0 °C, 51.7 mg HATU (136 µmol, 1.25 eq.)

was added and the reaction was warmed to room temperature within 16 h. After full conversion, the organic phase was washed with 1 M HCl solution, sat. $NaHCO_3$ solution and brine. After drying over $MgSO_4$, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (C-18 spherical, H_2O/MeCN 10 to 100 %) to obtain 36.0 mg of the linear peptide **15c** (40.0 µmol, 37 %) as a colourless resin.

LC-MS: t_R (**15c**) = 1.27 min



15c

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.66 (bs, 1 H, NH_a), 7.39 (d, $^3J_{11,12}$ = 7.5 Hz, 2 H, 11-H), 7.25 (m, 2 H, 12-H), 7.17-7.14 (m, 4 H, 1-H, 2-H, 13-H), 7.10 (bs, 1 H, NH_c), 6.93 (bs, 1 H, NH_b), 6.80 (m, 2 H, 3-H), 5.31 (m, 1 H, 15-H), 5.05 (m, 1 H, NH_a), 4.65 (d, $^3J_{7,NHb}$ = 9.0 Hz, 1 H, 7-H), 4.34 (m, 1 H, 24-H), 4.08 (d, $^3J_{28,29}$ = 7.3 Hz, 1 H, 28-H), 4.06 (m, 1 H, 34-H), 4.01 (m, 1 H, 19-H), 3.99 (dd, $^2J_{5,5'}$ = 14.7 Hz, $^3J_{5,NHa}$ = 5.2 Hz, 1 H, 5-H), 3.93 (dd, $^2J_{5',5}$ = 14.8 Hz, $^3J_{5',NHa}$ = 5.2 Hz, 1 H, 5-H'), 3.82 (m, 1 H, 34-H'), 3.66 (s, 3 H, 35-H), 3.40 (t, $^3J_{32,31}$= 9.3 Hz, 1 H, 32-H), 3.25 (m, 1 H, 32-H'), 3.17 (s, 3 H, 22-H), 2.20 (m, 1 H, 29-H), 2.00-1.93 (m, 2 H, 25-H, 31-H), 1.87 (m, 1 H, 31-H'), 1.41 (s, 9 H, 38-H), 1.39 (m, 6 H, 9-H), 1.21 (s, 9 H, 17-H), 1.03 (d, $^3J_{30,29}$ = 6.9 Hz, 3 H, 30-H), 0.90 (s, 9 H, 21-H), 0.89 (d, $^3J_{26,25}$ = 6.4 Hz, 3 H, 26-H), 0.66 (d, $^3J_{26',25}$ = 6.1 Hz, 3 H, 26-H').

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 173.0 (s, C-6), 171.9 (s, C-14), 171.1 (s, C-27), 170.4 (s, C-33), 169.1 (s, C-18), 160.6 (s, C-23), 155.2 (s, C-36), 146.3 (s, C-10), 137.3 (s, C-4), 128.6 (d, C-12), 128.4 (d, C-2), 127.5 (d, C-3), 127.3 (d, C-1), 126.6 (d, C-13), 126.2 (d, C-11), 80.4 (s, C-37), 70.7 (d, C-19), 66.1 (d, C-15), 62.0 (d, C-28), 60.9 (d, C-7), 55.6 (d, C-24), 51.9 (q, C-35), 46.4 (t, C-32), 43.3 (t, C-5), 41.9 (s, C-8), 40.9 (t, C-34), 36.5 (d, C-29), 35.9 (q, C-22), 35.9 (s, C-20), 35.6 (s, C-16), 32.0 (t, C-31), 31.0 (d, C-25), 29.4 (q, C-17), 28.4 (q, C-38), 27.2 (q, C-9, C-21), 22.4 (q, C-9'), 20.3 (q, C-26), 19.3 (q, C-26'), 13.6 (q, C-30).

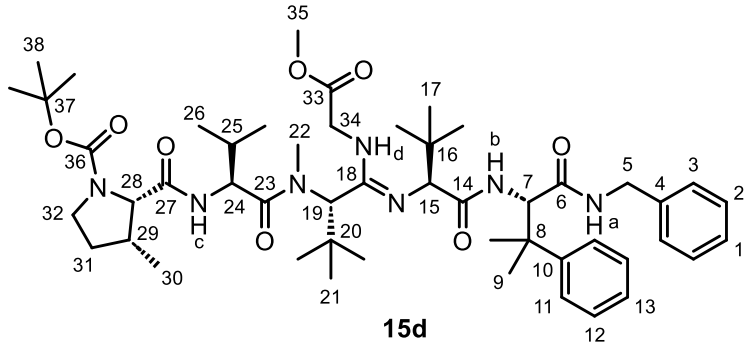
optical rotation:	$[\alpha]_D^{20}$ = +38.5 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{50}H_{78}N_7O_8$ $[M+H]^+$	904.5906	904.5908

tert-Butyl(2*S*,3*R*)-2-(((4*S*,7*S*,10*S*,13*S*,*Z*)-7,10-di-*tert*-butyl-9-((2-methoxy-2-oxoethyl) amino)-11,14-dimethyl-3,6,12-trioxo-1-phenyl-4-(2-phenylpropan-2-yl)-2,5,8,11-tetraaza-pentadec-8-en-13-yl)carbamoyl)-3-methylpyrrolidin-1-carboxylate (15d)

27.0 mg of the Alloc-protected amine **14d** (35.0 µmol, 1.0 eq.) was dissolved in 0.7 ml of an H_2O/MeCN mixture (1:1, v:v) and 36.0 µl diethylamine (25.4 mg, 347 µmol, 10.0 eq.), 1.6 mg TPPTS (2.78 µmol, 0.08 Äq.) and 70 µl $Pd(OAc)_2$ solution (0.02 M in MeCN, 1.39 µmol, 0.04 eq.) were added. After stirring for 25 min at room temperature, the solvent was removed under reduced pressure and the free amine was immediately used in the following coupling reaction.

In a round bottom flask, the above-prepared free amine was dissolved in 0.4 ml DCM and 11.0 mg Boc-MePro-OH[9] (48.0 µmol, 1.2 eq.) and 13 µl NMM (12.1 mg, 120 µmol, 3.0 eq.) were added. After cooling the reaction solution to 0 °C, 19.0 mg HATU (50.0 µmol, 1.25 eq.) was added and the reaction was warmed to room temperature within 16 h. After full conversion, the organic phase was washed with 1 M HCl solution, sat. $NaHCO_3$ solution and brine. After drying over $MgSO_4$, the solvent was removed under reduced pressure and the crude product was purified by column chromatography (C-18 spherical, H_2O/MeCN 10 to 100 %) to obtain 25.5 mg of the linear peptide **15d** (28.0 µmol, 70 %) as a colourless resin.

LC-MS: t_R (**15d**) = 1.26 min



15d

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, $^3J_{11,12}$ = 7.6 Hz, 2 H, 11-H), 7.26 (m, 2 H, 12-H), 7.21-7.16 (m, 4 H, 1-H, 2-H, 13-H, NH_d), 6.98 (d, $^3J_{11,12}$ = 10.5 Hz, 1 H, NH_b), 6.81 (m, 2 H, 3-H), 6.64 (bs, 1 H, NH_c), 5.56 (m, 1 H, 15-H), 5.02 (s, 1 H, NH_a), 4.91 (m, 1 H, 24-H), 4.77 (d, $^3J_{7,NHb}$ = 9.3 Hz, 1 H, 7-H), 4.20 (m, 1 H, 34-H), 4.02 (d, $^3J_{28,29}$ = 6.6 Hz, 1 H, 28-H), 3.96 (s, 1 H, 19-H), 3.90 (d, $^3J_{5,NHa}$ = 4.9 Hz, 2 H, 5-H), 3.83 (m, 1 H, 34-H‘), 3.56 (s, 3 H, 35-H), 3.50 (t, $^3J_{32,31}$= 9.3 Hz, 1 H, 32-H), 3.28 (m, 1 H, 32-H‘), 3.23 (s, 3 H, 22-H), 2.26 (m, 1 H, 29-H), 2.17-2.00 (m, 2 H, 25-H, 31-H), 1.90 (m, 1 H, 31-H‘), 1.42 (s, 9 H, 38-H), 1.40 (s, 3 H, 9-H), 1.33 (s, 3 H, 9-H), 1.15 (s, 9 H, 17-H), 1.04-1.03 (m, 12 H, 21-H, 30-H), 0.93 (d, $^3J_{26,25}$ = 6.0 Hz, 3 H, 26-H), 0.69 (d, $^3J_{26',25}$ = 6.5 Hz, 3 H, 26-H‘).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.1 (s, C-18), 171.4 (s, C-14), 170.8 (s, C-33), 170.4 (s, C-27), 169.8 (s, C-6), 160.7 (s, C-23), 154.9 (s, C-36), 146.0 (s, C-10), 136.9 (s, C-4), 128.7 (d, C-12), 128.5 (d, C-2), 127.5 (d, C-1, C-3), 126.8 (d, C-13), 126.2 (d, C-11), 79.9 (s, C-37), 71.3 (d, C-19), 63.2 (d, C-15), 63.1 (d, C-28), 60.3 (d, C-7), 53.5 (d, C-24), 51.6 (q, C-35), 46.4 (t, C-32), 43.3 (t, C-5), 42.0 (s, C-8), 41.1 (t, C-34), 36.6 (d, C-29), 36.1 (s, C-20), 35.9 (q, C-22), 35.9 (s, C-16), 32.0 (t, C-31), 31.7 (d, C-25), 28.6 (q, C-17), 28.4 (q, C-38), 27.5 (q, C-9, C-21), 22.2 (q, C-9‘), 20.0 (q, C-26), 18.7 (q, C-26‘), 13.8 (q, C-30).

optical rotation:	$[\alpha]_D^{20}$ = –73.6 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{50}H_{78}N_7O_8$ $[M+H]^+$	904.5906	904.5905

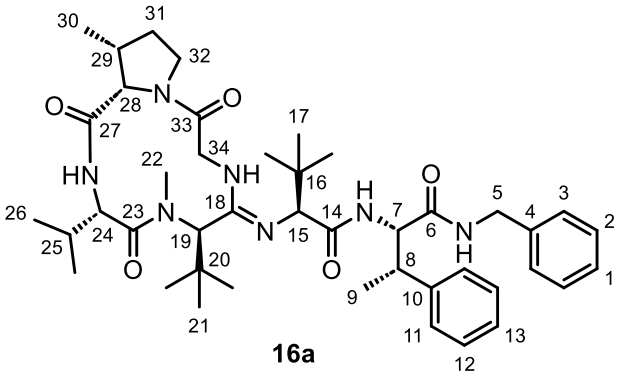
(*S*)-*N*-((2*S*,3*S*)-1-(Benzylamino)-1-oxo-3-phenylbutane-2-yl)-2-(((3*S*,6*R*,14*R*,14a*S*,*Z*)-6-(*tert*-butyl)-3-isopropyl-5,14-dimethyl-1,4,10-trioxododecahydropyrrolo[1,2-*a*]-[1,4,7,10]-tetraazacyclododecin-7(8*H*)-ylidene)amino)-3,3-dimethylbutanamide (16a)

21.7 mg of the linear peptide **15a** (24.0 µmol, 1.0 eq.) was dissolved in 250 µl anhydrous THF and 36 µl LiOH solution (1 M in H_2O, 36.0 µmol, 1.5 eq.) was added and stirred for 3 h at room temperature. After complete conversion (LC-MS control), the solvent was removed under reduced pressure.

The residue was dissolved under nitrogen atmosphere in 250 µl DCM and 125 µl HCl solution (4 M in dioxane, 488 µmol, 20.0 eq.) was added. The reaction mixture was stirred for 50 min at room temperature. After complete conversion (LC-MS control), the solvent was removed under reduced pressure and the deprotected peptide was immediately used in the following cyclisation reaction.

For macrocyclisation, 32.4 mg HATU (85.0 µmol, 3.5 eq.) was dissolved in 23 ml DCM and 19 µl DIPEA (14.2 mg, 110 µmol, 4.5 eq.) was added. The previously deprotected peptide, dissolved in 1.6 ml DMF, was then dripped into the suspension over a period of 8 h using a syringe pump. After complete addition, stirring was continued for further 9 h at room temperature. After full conversion, the solvent was concentrated and the residue was diluted with 30 ml EtOAc. The organic phase was washed with 1 M $KHSO_4$ solution, H_2O, sat. $NaHCO_3$ solution and brine. After drying over $MgSO_4$, the crude product was first purified by column chromatography (C18 spherical, H_2O/MeCN 10 to 100 %) and afterwards by preparative HPLC (Luna, 0.1 % $HCOOH_{aq}$/(MeCN + 0.1 % HCOOH) 10 to 100 %) to obtain 14.5 mg of the cyclic bottromycin derivative **16a** (19.0 µmol, 78 % over 3 steps) as a colourless lyophilisate.

LC-MS: t_R (**16a**) = 1.04 min



16a

rotamer 1:

^{1}H-NMR (500 MHz, 373 K, DMSO-d_6): δ = 8.62 (m, 1 H, NH_a), 7.40-7.12 (m, 11 H, 1-H, 2-H, 3-H, 11-H, 12-H, 13-H, NH_c), 6.69 (bs, 1 H, NH_b), 6.64 (t, $^3J_{NHd,34}$ = 5.0 Hz, 1 H, NH_d), 4.46 (dd, $^2J_{5,5'}$ = 15.2 Hz, $^3J_{5,NHa}$ = 6.2 Hz, 1 H, 5-H), 4.44 (s, 1 H, 19-H), 4.32 (dd, $^2J_{5',5}$ = 15.1 Hz, $^3J_{5',NHa}$ = 5.1 Hz, 1 H, 5'-H), 4.25 (m, 1 H, 28-H), 4.18 (dd, $^3J_{7,8}$ = 10.0 Hz, $^3J_{7,NHb}$ = 4.6 Hz, 1 H, 7-H), 4.00 (dd, $^3J_{24,25}$ = 11.7 Hz, $^3J_{24,NHc}$ = 5.0 Hz, 1 H, 24-H), 3.75 (dd, $^2J_{34,34'}$ = 15.0 Hz, $^3J_{34,15}$ = 4.8 Hz, 1 H, 34-H), 3.69 (s, 1 H, 15-H), 3.57 (m, 1 H, 32-H), 3.50 (m, 1-H, 34-H'), 3.36 (m, 1-H, 32-H'), 3.23 (dq, $^3J_{8,7}$ = 9.2 Hz, $^3J_{8,9}$ = 7.4 Hz, 1-H, 8-H), 2.77 (dsept, $^3J_{25,26}$ = 6.0 Hz, $^3J_{25,24}$ = 6.0 Hz, 1-H, 25-H), 2.54 (s, 3-H, 22-H), 2.15 (m, 1 H, 29-H), 2.03 (m, 1 H, 31-H), 1.61 (m, 1 H, 31-H'), 1.18 (d, $^3J_{9,8}$ = 5.6 Hz, 3 H, 9-H), 1.07 (s, 9 H, 21-H), 1.04 (d, $^3J_{26,25}$ = 7.2 Hz, 3 H, 26-H), 0.95 (d, $^3J_{26',25}$ = 7.0 Hz, 3 H, 26-H'), 0.92 (s, 9 H, 17-H), 0.86 (d, $^3J_{9,8}$ = 7.0 Hz, 3 H, 30-H).

^{13}C-NMR (125 MHz, 373 K, DMSO-d_6): δ = 171.4 (s, C-14), 171.3 (s, C-6), 169.9 (s, C-27), 169.5 (s, C-18), 159.7 (s, C-23), 167.7 (s, C-33), 143.5 (s, C-10), 138.5 (s, C-4), 127.8 (d, C-12), 127.5 (d, C-2), 127.2 (d, C-3), 126.7 (d, C-11), 126.5 (d, C-1), 126.1 (d, C-13), 70.5 (d, C-15), 66.8 (d, C-19), 63.7 (d, C-28), 59.0 (d, C-7), 58.0 (d, C-24), 45.8 (t, C-32), 45.2 (t, C-34), 42.0 (t, C-5), 39.2 (d, C-8), 37.3 (d, C-29), 35.7 (q, C-22), 33.9 (s, C-20), 34.3 (s, C-16), 29.1 (t, C-31), 28.5 (q, C-21), 28.3 (d, C-25), 26.5 (q, C-17), 21.4 (q, C-26), 20.7 (q, C-26'), 18.3 (q, C-9), 13.9 (q, C-30).

rotamer 2:

^{1}H-NMR (500 MHz, 373 K, DMSO-d_6): δ = 8.90 (m, 1 H, NH_a), 8.71 (d, $^3J_{NHd,34}$ = 9.0 Hz, 1 H, NH_d), 7.42-7.12 (m, 11 H, 1-H, 2-H, 3-H, 11-H, 12-H, 13-H, NH_c), 5.97 (d, $^3J_{NHb,7}$ = 8.6 Hz, 1 H, NH_b), 4.75 (dd, $^2J_{34,34'}$ = 13.5 Hz, $^3J_{34,NHd}$ = 9.5 Hz, 1 H, 34-H), 4.67 (dd, $^3J_{7,NHb}$ = 8.9 Hz, $^3J_{7,8}$ = 5.3 Hz, 1 H, 7-H), 4.40 (d, $^3J_{28,29}$ = 9.1 Hz, 1 H, 28-H), 4.38 (m, 1 H, 5-H), 4.25 (m, 1 H, 24-H), 3.96 (s, 1 H, 15-H), 3.39 (m, 1 H, 32-H), 3.34 (m, 1-H, 8-H), 3.29 (m, 1-H, 32-H'), 3.13 (dd, $^2J_{34',34}$ = 13.7 Hz, $^3J_{34,NHd}$ = 1.6 Hz, 1-H, 34-H'), 2.88 (s, 3-H, 22-H), 2.82 (s, 1 H, 19-H), 2.38-2.47 (m, 2-H, 25-H, 29-H), 1.80 (m, 1 H, 31-H), 1.55 (m, 1 H, 31-H'), 1.33 (d, $^3J_{9,8}$ = 7.2 Hz, 3 H, 9-H), 1.21 (d, $^3J_{9,8}$ = 6.1 Hz, 3 H, 30-H), 1.06 (s, 9 H, 21-H), 0.94 (d, $^3J_{26,25}$ = 6.7 Hz, 3 H, 26-H), 0.89 (d, $^3J_{26',25}$ = 6.6 Hz, 3 H, 26-H'), 0.66 (s, 9 H, 17-H).

^{13}C-NMR (125 MHz, 373 K, DMSO-d_6): δ = 172.2 (s, C-6), 170.1 (s, C-14), 168.7 (s, C-23), 168.1 (s, C-27), 168.1 (s, C-33), 162.6 (s, C-18), 140.5 (s, C-10), 137.7 (s, C-4), 127.7 (d, C-12), 127.7 (d, C-2), 127.1 (d, C-11), 126.8 (d, C-3), 126.3 (d, C-1), 125.9 (d, C-13), 69.4 (d, C-19), 68.9 (d, C-15), 64.1 (d, C-28), 56.5 (d, C-7), 55.7 (d, C-24), 45.0 (t, C-32), 42.5 (t, C-5), 42.2 (t, C-34), 40.9 (d, C-8), 37.6 (d, C-29), 35.2 (s, C-20), 34.5 (s, C-16), 33.6 (q, C-22), 29.8 (t, C-31), 28.5 (q, C-21), 27.8 (d, C-25), 26.1 (q, C-17), 21.2 (q, C-26), 19.0 (q, C-26'), 17.7 (q, C-9), 14.5 (q, C-30).

optical rotation:	$[\alpha]_D^{20}$ = –8.0 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{43}H_{63}N_7O_5$ $[M+H]^+$	758.4963	758.4963

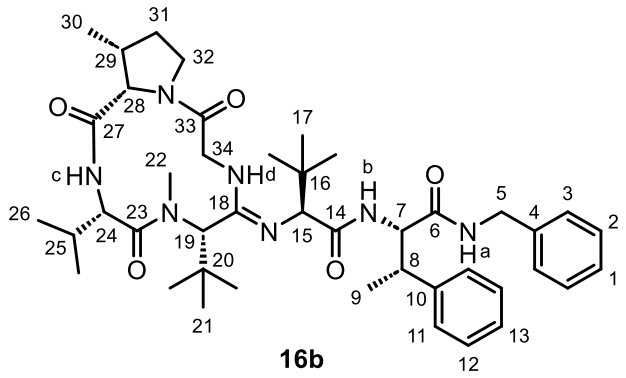
(*S*)-*N*-((2*S*,3*S*)-1-(Benzylamino)-1-oxo-3-phenylbutane-2-yl)-2-(((3*S*,6*S*,14*R*,14a*S*,*Z*)-6-(tert-butyl)-3-isopropyl-5,14-dimethyl-1,4,10-trioxododecahydropyrrolo[1,2-*a*]-[1,4,7,10]tetraazacyclododecine-7(8*H*)-ylidene)amino)-3,3-dimethylbutanamide (16b)

54.0 mg of the linear peptide **15b** (61.0 µmol, 1.0 eq.) was dissolved in 610 µl anhydrous THF and 91 µl LiOH solution (1 M in H_2O, 91.0 µmol, 1.5 eq.) was added and stirred for 4 h at room temperature. After complete conversion (LC-MS control), the solvent was removed under reduced pressure.

The residue was dissolved under nitrogen atmosphere in 300 µl DCM and 300 µl HCl solution (4 M in dioxane, 1.21 mmol, 20.0 eq.) was added. The reaction mixture was stirred for 50 min at room temperature. After complete conversion (LC-MS control), the solvent was removed under reduced pressure and the deprotected peptide was immediately used in the following cyclisation reaction.

For macrocyclisation, 81.0 mg HATU (212 µmol, 3.5 eq.) was dissolved in 56 ml DCM and 48 µl DIPEA (35.2 mg, 272 µmol, 4.5 eq.) was added. The previously deprotected peptide, dissolved in 3.9 ml DMF, was then dripped into the suspension over a period of 12 h using a syringe pump. After complete addition, stirring was continued for further 2 h at room temperature. After full conversion, the solvent was concentrated and the residue was diluted with 30 ml EtOAc. The organic phase was washed with 1 M $KHSO_4$ solution, H_2O, sat. $NaHCO_3$ solution and brine. After drying over $MgSO_4$, the crude product was first purified by column chromatography (C18 spherical, H_2O/MeCN 10 to 100 %) and afterwards by preparative HPLC (Luna, 0.1 % $HCOOH_{aq}$/(MeCN + 0.1 % HCOOH) 10 to 100 %) to obtain 20.0 mg of the cyclic bottromycin derivative **16b** (26.0 µmol, 44 % over 3 steps) as a colourless lyophilisate.

LC-MS: t_R (**16b**) = 0.92 min



16b

^{1}H-NMR (500 MHz, DMSO-d_6): δ = 8.60 (t, $^3J_{NHa,5}$ = 5.8 Hz, 1 H, NH_a), 7.88 (bs, 1 H, NH_c), 7.53 (bs, 1 H, NH_d), 7.31 (m, 2 H, 2-H), 7.24 (m, 5 H, 11-H, 12-H, 13-H), 7.19 (m, 2 H, 3-H), 7.15 (m, 1 H, 1-H), 6.97 (d, $^3J_{NHb,7}$ = 8.9 Hz, 1 H, NH_b), 4.62 (t, $^3J_{7,8}$ = 9.2 Hz, 1 H, 7-H), 4.21 (m, 4 H, 5-H, 28-H, 34-H), 4.10 (dd, $^3J_{24,25}$ = 10.4 Hz, $^3J_{24,NHc}$ = 4.7 Hz, 1 H, 24-H), 3.77 (s, 1 H, 19-H), 3.61 (dd, $^2J_{34',34}$ = 15.9 Hz, $^3J_{34',NHd}$ = 3.4 Hz, 1 H, 34-H'), 3.45 (s, 1 H, 15-H), 3.33 (m, 2 H, 32-H), 2.96 (dq, $^3J_{8,7}$ = 9.1 Hz, $^3J_{8,9}$ = 6.9 Hz, 1 H, 8-H), 2.91 (s, 3 H, 22-H), 2.31 (m, 1 H, 29-H), 1.84 (m, 1 H, 25-H), 1.78 (m, 1 H, 31-H), 1.55 (m, 1 H, 31-H), 1.11 (d, $^3J_{9,8}$ = 7.0 Hz, 3 H, 9-H), 1.02 (s, 9 H, 21-H), 0.97 (d, $^3J_{26,25}$ = 6.3 Hz, 3 H, 26-H), 0.92 (d, $^3J_{30,29}$ = 6.7 Hz, 3 H, 30-H), 0.66 (d, $^3J_{26',25}$ = 6.9 Hz, 3 H, 26'-H), 0.62 (s, 9 H, 17-H).

^{13}C-NMR (125 MHz, DMSO-d_6): δ = 171.1 (s, C-14), 170.2 (s, C-6), 169.7 (s, C-18), 169.3 (s, C-27), 167.3 (s, C-33), 158.0 (s, C-23), 143.2 (s, C-10), 139.2 (s, C-4), 128.2 (d, C-2), 128.1 (d, C-12), 127.7 (d, C-3), 127.5 (d, C-11), 126.8 (d, C-13), 126.3 (d, C-1), 71.3 (d, C-15), 67.0 (d, C-19), 63.0 (d, C-28), 56.3 (d, C-7), 53.3 (d, C-24), 47.1 (t, C-32), 44.4 (t, C-34), 42.7 (d, C-8), 42.0 (t, C-5), 37.4 (d, C-29), 36.2 (s, C-20), 35.8 (q, C-22), 35.4 (s, C-16), 30.8 (d, C-25), 29.1 (q, C-21), 28.5 (t, C-31), 27.3 (q, C-17), 21.1 (q, C-26), 19.6 (q, C-9), 18.6 (q, C-26'), 14.9 (q, C-30).

optical rotation:	$[\alpha]_D^{20}$ = –46.9 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{43}H_{63}N_7O_5$ $[M+H]^+$	758.4963	758.4962

(*S*)-*N*-Benzyl-2-((*S*)-2-(((3*S*,6*R*,14*R*,14a*S*,*Z*)-6-(*tert*-butyl)-3-isopropyl-5,14-dimethyl-1,4,10-trioxododecahydropyrrolo[1,2-*a*][1,4,7,10]tetraazacyclododecine-7(8*H*)-ylidene) amino)-3,3-dimethylbutanamido)-3-methyl-3-phenylbutanamide (16c)

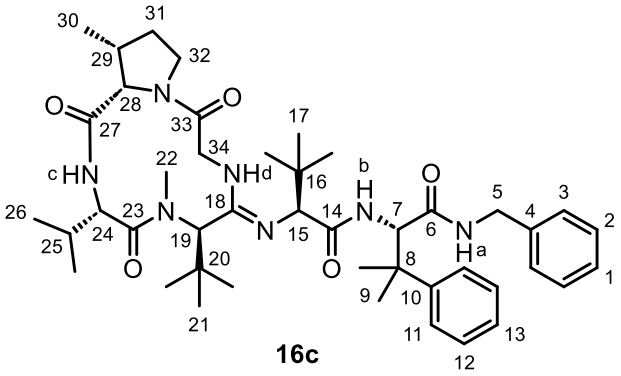
35.0 mg of the linear peptide **15c** (39.0 µmol, 1.0 eq.) was dissolved in 400 µl anhydrous THF and 58 µl LiOH solution (1 M in H_2O, 58.0 µmol, 1.5 eq.) was added and stirred for 3 h at room temperature. After complete conversion (LC-MS control), the solvent was removed under reduced pressure.

The residue was dissolved under nitrogen atmosphere in 400 µl DCM and 200 µl HCl solution (4 M in dioxane, 800 µmol, 20.0 eq.) was added. The reaction mixture was stirred for 25 min at room temperature. After complete conversion (LC-MS control), the solvent was removed under reduced pressure and the deprotected peptide was immediately used in the following cyclisation reaction.

For macrocyclisation, 51.5 mg HATU (136 µmol, 3.5 eq.) was dissolved in 36 ml DCM and 30 µl DIPEA (22.5 mg, 174 µmol, 4.5 eq.) was added. The previously deprotected peptide, dissolved in 2.5 ml DMF, was then dripped into the suspension over a period of 8 h using a syringe pump. After complete addition, stirring was continued for further 9 h at room

temperature. After full conversion, the solvent was concentrated and the residue was diluted with 30 ml EtOAc. The organic phase was washed with 1 M $KHSO_4$ solution, H_2O, sat. $NaHCO_3$ solution and brine. After drying over $MgSO_4$, the crude product was first purified by column chromatography (C18 spherical, H_2O/MeCN 10 to 100 %) and afterwards by preparative HPLC (Luna, 0.1 % $HCOOH_{aq}$/(MeCN + 0.1 % HCOOH) 10 to 100 %) to obtain 20.3 mg of the cyclic bottromycin derivative **16c** (26.0 µmol, 68 % over 3 steps) as a colourless lyophilisate.

LC-MS: t_R (**16c**) = 1.07 min



16c

^{1}H-NMR (500 MHz, DMSO-d_6): δ = 8.96 (bs, 1 H, NH_a), 7.41 (bs, 1 H, NH_c), 7.37 (m, 1 H, 13-H), 7.35-7.25 (m, 8 H, 2-H, 3-H, 11-H, 12-H), 7.20 (m, 1 H, 1-H), 6.88 (bs, 1 H, NH_d), 5.98 (bs, 1 H, NH_b), 4.64 (d, $^3J_{7,NHb}$ = 8.4 Hz, 1 H, 7-H), 4.50 (s, 1 H, 19-H), 4.42 (dd, $^2J_{5,5'}$ = 15.3 Hz, $^3J_{5,NHa}$ = 5.5 Hz, 1 H, 5-H), 4.32-4.38 (m, 2 H, 28-H, 5-H‘), 3.89-3.93 (m, 1 H, 24-H), 3.77 (dd, $^2J_{34,34'}$= 15.4 Hz, $^3J_{34,NHd}$ = 5.0 Hz, 1 H, 34-H), 3.70 (dd, $^2J_{34,34'}$ = 15.6 Hz, $^3J_{34,NHd}$ = 7.0 Hz, 1 H, 34-H‘), 3.61 (s, 1 H, 15-H), 3.28 (m, 2 H, 32-H), 2.76 (m, 1-H, 25-H), 2.56 (s, 3-H, 22-H), 2.21 (m, 1 H, 29-H), 1.79 (m, 1 H, 31-H), 1.53 (m, 1 H, 31-H‘), 1.37 (s, 3 H, 9-H), 1.36 (s, 3 H, 9-H‘), 1.04 (s, 9 H, 21-H), 1.03 (d, $^3J_{26,25}$ = 8.4 Hz, 3 H, 26-H), 0.91 (d, $^3J_{26',25}$ = 6.7 Hz, 3 H, 26-H‘), 0.82 (d, $^3J_{30,29}$ = 6.7 Hz, 3 H, 30-H), 0.72 (s, 9 H, 17-H).

^{13}C-NMR (125 MHz, DMSO-d_6): δ = 171.5 (s, C-14, C-6), 170.6 (s, C-27), 170.0 (s, C-18), 168.3 (s, C-33), 160.0 (s, C-23), 144.9 (s, C-10), 138.0 (s, C-4), 128.4 (d, C-2), 128.2 (d, C-12), 127.7 (d, C-13), 127.3 (d, C-11), 126.5 (d, C-1), 126.3 (d, C-3), 70.3 (d, C-15), 66.9 (d, C-19), 64.1 (d, C-28), 60.0 (d, C-7), 58.6 (d, C-24), 46.6 (t, C-32), 45.6 (t, C-34), 42.8 (t, C-5), 40.1 (d, C-8), 37.8 (d, C-29), 36.8 (q, C-22), 35.8 (s, C-20), 34.7 (s, C-16), 29.5 (t, C-31), 28.9 (q, C-21), 28.9 (d, C-25), 27.6 (q, C-9), 26.7 (q, C-17), 24.0 (q, C-9‘), 22.0 (q, C-26), 20.5 (q, C-26‘), 14.4 (q, C-30).

rotamer (selected signals):

^{1}H-NMR (500 MHz, DMSO-d_6): δ = 8.82 (bs, 1 H, NH_a), 3.92 (s, 1 H, 15-H), 2.84 (s, 1 H, 22-H), 1.01 (s, 9 H, 21-H), 0.48 (s, 9 H, 17-H).

^{13}C-NMR (125 MHz, DMSO-d_6): δ = 128.1 (d, C-12), 127.1 (d, C-11), 69.3 (d, C-15), 34.6 (s, C-20), 33.9 (q, C-22), 26.3 (q, C-17).

optical rotation:	$[\alpha]_D^{20}$ = +54.0 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{44}H_{65}N_7O_5$ $[M+H]^+$	772.5120	772.5119

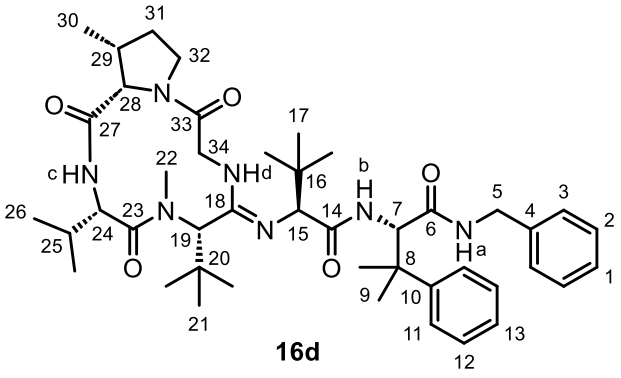
(*S*)-*N*-Benzyl-2-((*S*)-2-(((3*S*,6*S*,14*R*,14a*S*,*Z*)-6-(*tert*-butyl)-3-isopropyl-5,14-dimethyl-1,4,10-trioxododecahydropyrrolo[1,2-*a*][1,4,7,10]tetraazacyclododecine-7(8*H*)-ylidene) amino)-3,3-dimethylbutanamido)-3-methyl-3-phenylbutanamide (16d)

34.0 mg of the linear peptide **15d** (38.0 µmol, 1.0 eq.) was dissolved in 375 µl anhydrous THF and 56 µl LiOH solution (1 M in H_2O, 56.0 µmol, 1.5 eq.) was added and stirred for 5 h at room temperature. After complete conversion (LC-MS control), the solvent was removed under reduced pressure.

The residue was dissolved under nitrogen atmosphere in 400 µl DCM and 200 µl HCl solution (4 M in dioxane, 800 mmol, 21.0 eq.) was added. The reaction mixture was stirred for 25 min at room temperature. After complete conversion (LC-MS control), the solvent was removed under reduced pressure and the deprotected peptide was immediately used in the following cyclisation reaction.

For macrocyclisation, 50.1 mg HATU (132 µmol, 3.5 eq.) was dissolved in 35 ml DCM and 30 µl DIPEA (22.5 mg, 169 µmol, 4.5 eq.) was added. The previously deprotected peptide, dissolved in 2.4 ml DMF, was then dripped into the suspension over a period of 8 h using a syringe pump. After complete addition, stirring was continued for further 9 h at room temperature. After full conversion, the solvent was concentrated and the residue was diluted with 30 ml EtOAc. The organic phase was washed with 1 M $KHSO_4$ solution, H_2O, sat. $NaHCO_3$ solution and brine. After drying over $MgSO_4$, the crude product was first purified by column chromatography (C18 spherical, H_2O/MeCN 10 to 100 %) and afterwards by preparative HPLC (Luna, 0.1 % $HCOOH_{aq}$/(MeCN + 0.1 % HCOOH) 10 to 100 %) to obtain 13.2 mg of the cyclic bottromycin derivative **16d** (17.0 µmol, 45 % over 3 steps) as a colourless lyophilisate.

LC-MS: t_R (**16d**) = 1.01 min



16d

^{1}H-NMR (500 MHz, DMSO-d_6): δ = 8.32 (bs, 1 H, NH_a), 7.92 (bs, 1 H, NH_c), 7.67 (bs, 1 H, NH_d), 7.41 (m, 2 H, 11-H), 7.27-7.17 (m, 7 H, 1-H, 2-H, 12-H, 13-H NH_b), 6.94 (m, 2 H, 3-H), 4.76 (d, $^3J_{7,NHb}$ = 9.3 Hz, 1 H, 7-H), 4.25 (m, 1 H, 28-H), 4.10-4.18 (m, 2 H, 24-H, 34-H), 4.06 (m, 2 H, 5-H), 3.80 (s, 1 H, 19-H), 3.65 (m, 1 H, 34-H‘), 3.52 (m, 1 H, 15-H), 3.35 (m, 2 H, 32-H), 3.00 (s, 3-H, 22-H), 2.32 (m, 1 H, 29-H), 1.85 (m, 1 H, 25-H), 1.78 (m, 1 H, 31-H), 1.58 (m, 1 H, 31-H‘), 1.33 (s, 3 H, 9-H‘), 1.31 (s, 3 H, 9-H), 1.02 (s, 9 H, 21-H), 1.00 (m, 3 H, 26-H), 0.93 (d, $^3J_{30,29}$ = 6.3 Hz, 3 H, 30-H), 0.80 (s, 9 H, 17-H), 0.66 (d, $^3J_{26',25}$ = 6.1 Hz, 3 H, 26-H‘).

^{13}C-NMR (125 MHz, DMSO-d_6): δ = 171.3 (s, C-14), 169.6 (s, C-18), 169.2 (s, C-6), 167.4 (s, C-33), 163.8 (s, C-27), 157.9 (s, C-23), 146.2 (s, C-10), 139.0 (s, C-4), 128.0 (d, C-2), 127.7 (d, C-12), 127.1 (d, C-3), 126.5 (d, C-11), 126.5 (d, C-1), 125.9 (d, C-13), 71.5 (d, C-15), 66.9 (d, C-19), 62.9 (d, C-28), 58.9 (d, C-7), 53.2 (d, C-24), 47.1 (t, C-32), 44.3 (t, C-34), 41.7 (t, C-5), 41.1 (d, C-8), 37.4 (d, C-29), 36.1 (s, C-20), 35.8 (s, C-16), 35.7 (q, C-22), 30.7 (t,

C-25), 29.1 (q, C-21), 28.5 (d, C-31), 27.6 (q, C-17), 25.5 (q, C-9), 24.6 (q, C-9‘), 21.2 (q, C-26), 18.5 (q, C-26‘), 14.8 (q, C-30).

optical rotation:	$[\alpha]_D^{20}$ = –77.3 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{44}H_{65}N_7O_5$ $[M+H]^+$	772.5120	772.5120

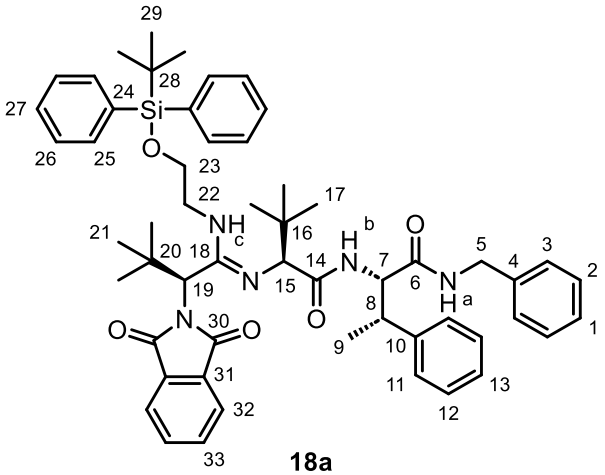
(*S*)-*N*-(2-((*tert*-Butyldiphenylsilyl)oxy)ethyl)-2-(1,3-dioxoisoindolin-2-yl)-3,3-dimethyl-butanethioamid (17)

Preparation according to Sunazuka and Omura *et al*.[8]

(*S*,*Z*)-*N*-((2*S*,3*S*)-1-(Benzylamino)-1-oxo-3-phenylbutane-2-yl)-10-(*tert*-butyl)-8-((*S*)-1-(1,3-dioxoisoindoline-2-yl)-2,2-dimethylpropyl)-2,2-dimethyl-3,3-diphenyl-4-oxa-7,9-diaza-3-silaundec-8-en-11-amide (18a)[8]

In a flame-dried Schlenk flask under nitrogen atmosphere, 250 mg of the thioamide **17** (447 µmol, 1.0 eq.) was dissolved in 4.5 ml MeCN and 205 mg amine **8** (537 µmol, 1.2 eq.), 208 µl 2,6-lutidine (192 mg, 1.79 mmol, 4.0 eq.) and 268 mg $Hg(OTf)_2$ (537 µmol, 1.2 eq.) were added. After stirring for 30 min at room temperature, the reaction was quenched by adding 5 % $Na_2S_2O_3$ solution. To remove the mercury salts, the reaction mixture was filtered over a pad of Celite, the solvent was removed and the residue was taken up in EtOAc. The organic phase was washed with 10 % citric acid solution, sat. $NaHCO_3$ solution and brine. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by column chromatography (C18 spherical, H_2O/MeCN 10 to 100 %) to obtain 295 mg amidine **18a** (326 µmol, 73 %) as a colourless foam.

LC-MS: t_R (**18a**) = 1.49 min



18a

^{1}H-NMR (500 MHz, 373 K, DMSO-d_6): δ = 7.90-7.76 (m, 4 H, 32-H, 33-H), 7.75 (m, 1 H, NH_a), 7.73-7.56 (m, 4 H, 25-H), 7.48-7.37 (m, 6 H, 26-H, 27-H), 6.73 (t, $^3J_{NH,5}$ = 5.0 Hz, 1 H, NH_c), 7.29-7.10 (m, 4 H, 2-H, 11-H), 7.06-6.91 (m, 6 H, 1-H, 3-H, 12-H, 13-H), 6.41 (d, $^3J_{NHb,7}$ = 8.7 Hz, 1 H, NH_b), 5.10 (s, 1 H, 19-H), 4.37 (dd, $^3J_{7,NHb}$ = 9.0 Hz, $^3J_{7,8}$ = 6.4 Hz, 1 H, 7-H), 3.86 (m, 2 H, 23-H), 3.64 (s, 1 H, 15-H), 3.60 (m, 1 H, 5-H), 3.60 (m, 1 H, 22-H), 3.32 (dd, $^2J_{5,5'}$ = 14.8 Hz, $^3J_{5,NHa}$ = 5.1 Hz, 1 H, 5-H‘), 3.18 (m, 1 H, 22-H‘), 2.94 (dq, $^3J_{8,9}$ = $^3J_{8,7}$ = 6.9 Hz, 1 H, 8-H), 1.07 (d, $^3J_{9,8}$ = 6.6 Hz, 3 H, 9-H), 1.10 (s, 9 H, 29-H), 1.06 (s, 9 H, 21-H), 0.84 (s, 9 H, 17-H).

^{13}C-NMR (125 MHz, 373 K, DMSO-d_6): δ = 170.4 (s, C-14), 169.1 (s, C-6), 168.0 (s, C-30), 154.2 (s, C-18), 142.1 (s, C-10), 138.4 (s, C-4), 134.6 (d, C-25), 133.8 (d, C-33), 133.4 (s, C-31), 133.1 (s, C-24), 129.1 (d, C-27), 127.6-126.5 (d, C-2, C-3, C-11, C-12, C-26), 125.9 (d, C-13), 125.7 (d, C-1), 122.7 (d, C-32), 69.6 (d, C-15), 62.4 (t, C-23), 55.5 (d, C-7), 53.8 (d, C-19), 42.5 (t, C-22), 41.7 (d, C-8), 41.4 (t, C-5), 35.8 (s, C-20), 34.6 (s, C-16), 27.7 (q, C-21), 26.7 (q, C-17), 26.2 (q, C-29), 18.3 (s, C-28), 17.9 (q, C-9).

rotamer (selected signals):

^{1}H-NMR (500 MHz, 373 K, DMSO-d_6): δ = 7.90-7.76 (m, 4 H, 32-H, 33-H), 7.73-7.56 (m, 4 H, 25-H), 7.48-7.37 (m, 6 H, 26-H, 27-H), 7.29-7.10 (m, 4 H, 2-H, 11-H), 7.06-6.91 (m, 6 H, 1-H, 3-H, 12-H, 13-H), 6.50 (d, $^{3}J_{NHb,7}$ = 9.0 Hz, 1 H, NH_b), 5.38 (s, 1 H, 19-H), 4.42 (m, 1 H, 7-H), 4.05 (m, 1 H, 5-H), 3.92 (dd, $^{2}J_{5',5}$ = 14.8 Hz, $^{3}J_{5,NHa}$ = 5.5 Hz, 1 H, 5-H‘), 3.72 (m, 2 H, 23-H), 3.50 (m, 1 H, 22-H), 3.47 (s, 1 H, 15-H), 3.36 (m, 1 H, 22-H‘), 2.80 (dq, $^{3}J_{8,9}$ = $^{3}J_{8,7}$ = 7.2 Hz, 1 H, 8-H), 1.09 (s, 9 H, 21-H), 1.04 (s, 9 H, 29-H), 0.88 (d, $^{3}J_{9,8}$ = 7.0 Hz, 3 H, 9-H), 0.70 (s, 9 H, 17-H).

^{13}C-NMR (125 MHz, 373 K, DMSO-d_6): δ = 170.8 (s, C-14), 169.5 (s, C-6), 168.8 (s, C-30), 152.5 (s, C-18), 141.7 (s, C-10), 138.3 (s, C-4), 134.6 (d, C-25), 134.0 (d, C-33), 133.4 (s, C-31), 133.0 (s, C-24), 129.1 (d, C-27), 127.6-126.5 (d, C-2, C-3, C-11, C-12, C-26), 126.1 (d, C-13), 125.6 (d, C-1), 122.7 (d, C-32), 69.4 (d, C-15), 64.7 (t, C-23), 56.3 (d, C-7), 54.1 (d, C-19), 50.6 (t, C-22), 41.4 (d, C-8), 35.4 (s, C-20), 34.4 (s, C-16), 27.6 (q, C-21), 26.4 (q, C-17), 26.2 (q, C-29), 17.6 (q, C-9).

amidine tautomer (selected signals):

^{1}H-NMR (500 MHz, 373 K, DMSO-d_6): δ = 7.90-7.76 (m, 4 H, 32-H, 33-H), 7.75 (m, 1 H, NH_a), 7.73-7.56 (m, 4 H, 25-H), 7.48-7.37 (m, 6 H, 26-H, 27-H), 6.73 (t, $^{3}J_{NHc,5}$ = 5.0 Hz, 1 H, NH_c), 7.29-7.10 (m, 4 H, 2-H, 11-H), 7.06-6.91 (m, 6 H, 1-H, 3-H, 12-H, 13-H), 6.42 (m, 1 H, NH_c), 5.10 (s, 1 H, 19-H), 4.72 (s, 1 H, 19-H), 4.43 (m, 1 H, 7-H), 4.15 (dd, $^{2}J_{5,5'}$ = 15.1 Hz, $^{3}J_{5,NHa}$ = 6.1 Hz, 1 H, 5-H), 4.05 (m, 2 H, 5-H‘), 4.02 (d, $^{3}J_{15,NHc}$ = 6.0 Hz, 1 H, 15-H), 3.51 (t, $^{3}J_{23,22}$ = 5.1 Hz, 2 H, 23-H), 3.18 (m, 1 H, 22-H), 2.88 (m, 1 H, 22-H‘), 1.20 (d, $^{3}J_{9,8}$ = 7.0 Hz, 3 H, 9-H), 1.00 (s, 9 H, 29-H), 0.90 (s, 9 H, 17-H).

^{13}C-NMR (125 MHz, 373 K, DMSO-d_6): δ = 170.1 (s, C-14), 168.0 (s, C-30), 153.2 (s, C-18), 138.5 (s, C-4), 134.5 (d, C-25), 134.0 (d, C-33), 130.6 (s, C-31), 129.0 (d, C-27), 127.6-126.5 (d, C-2, C-3, C-11, C-12, C-26), 126.1 (d, C-13), 125.4 (d, C-1), 122.6 (d, C-32), 62.4 (d, C-15), 63.0 (t, C-23), 58.3 (d, C-7), 57.4 (d, C-19), 44.3 (t, C-22), 41.7 (d, C-8), 41.8 (t, C-5), 36.1 (s, C-20), 32.3 (s, C-16), 26.6 (q, C-17), 18.8 (q, C-9).

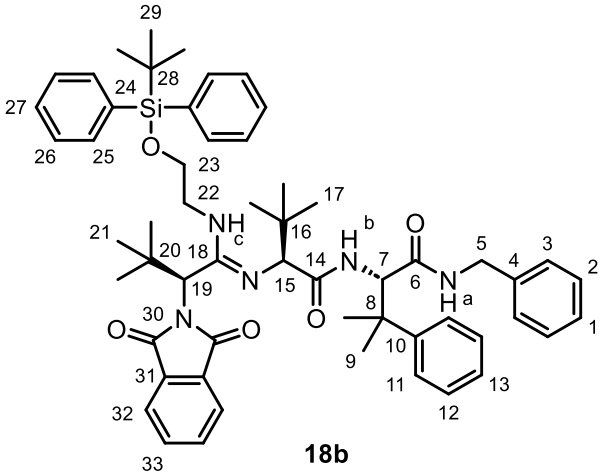
optical rotation:	$[\alpha]_D^{20}$ = –37.7 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{55}H_{68}N_5O_5Si$ $[M+H]^+$	906.4984	906.4984

(*S*,*Z*)-*N*-((*S*)-1-(Benzylamino)-3-methyl-1-oxo-3-phenylbutane-2-yl)-10-(*tert*-butyl)-8-((*R*)-1-(1,3-dioxoisoindoline-2-yl)-2,2-dimethylpropyl)-2,2-dimethyl-3,3-diphenyl-4-oxa-7,9-diaza-3-silaundec-8-en-11-amide (18b)[8]

In a flame-dried Schlenk flask under nitrogen atmosphere, 250 mg of the thioamide **17** (447 µmol, 1.0 eq.) was dissolved in 4.5 ml MeCN and 212 mg amine **10** (537 µmol, 1.2 eq.), 208 µl 2,6-lutidine (192 mg, 1.79 mmol, 4.0 eq.) and 268 mg $Hg(OTf)_2$ (537 µmol, 1.2 eq.) were added. After stirring for 30 min at room temperature, the reaction was quenched by adding 5 % $Na_2S_2O_3$ solution. To remove the mercury salts, the reaction mixture was filtered over a pad of Celite, the solvent was removed and the residue was taken up in EtOAc. The organic

phase was washed with 10 % citric acid solution, sat. $NaHCO_3$ solution and brine. The organic phase was dried over $MgSO_4$ and concentrated in vacuo. The crude was purified by column chromatography (C18 spherical, H_2O/MeCN 10 to 100 %) to obtain 302 mg amidine **18b** (328 µmol, 74 %) as a colourless foam.

LC-MS: t_R (**18b**) = 1.51 min



18b

^{1}H-NMR (500 MHz, 373 K, DMSO-d_6): δ = 7.86-7.90 (m, 4 H, 32-H, 33-H), 7.70 (m, 4 H, 25-H), 7.52 (m, 1 H, NH_a), 7.41-7.46 (m, 6 H, 26-H, 27-H), 7.21 (m, 4 H, 2-H, 11-H), 7.11-7.15 (m, 3 H, 1-H, 12-H), 6.96-7.07 (m, 1 H, 13-H), 6.88 (d, $^3J_{3,2}$ = 7.0 Hz, 1 H, 3-H), 6.75 (t, $^3J_{NHc,22}$ = 5.0 Hz, 1 H, NH_c), 6.55 (d, $^3J_{NHb,7}$ = 9.2 Hz, 1 H, NH_b), 5.43 (s, 1 H, 19-H), 4.49 (d, $^3J_{7,NHb}$ = 9.5 Hz, 1 H, 7-H), 3.93 (dd, $^2J_{5,5'}$ = 13.3 Hz, $^3J_{5,NHa}$ = 6.3 Hz, 1 H, 5-H), 3.92 (t, $^3J_{23,22}$ = 5.5 Hz, 2 H, 23-H), 3.74 (m, 1 H, 5-H'), 3.66 (m, 1 H, 22-H), 3.63 (s, 1 H, 15-H), 3.30 (m, 1 H, 22-H'), 1.11 (s, 9 H, 21-H), 1.04 (s, 9 H, 29-H), 0.95 (s, 3 H, 9-H), 0.94 (s, 9 H, 17-H), 0.91 (s, 3 H, 9-H').

^{13}C-NMR (125 MHz, 373 K, DMSO-d_6): δ = 170.0 (s, C-14), 168.8 (s, C-6), 169.1 (s, C-30), 154.0 (s, C-18), 145.8 (s, C-10), 138.3 (s, C-4), 134.6 (d, C-25), 134.5 (d, C-25'), 134.0 (d, C-33), 133.5 (s, C-24), 133.1 (s, C-24'), 130.8 (s, C-31), 129.1 (d, C-26), 129.0 (d, C-26'), 127.4 (d, C-11), 127.1 (d, C-27), 127.0 (d, C-27'), 126.9 (d, C-12), 126.8 (d, C-3), 126.0 (d, C-1), 125.7 (d, C-2), 125.1 (d, C-13), 122.8 (d, C-32), 62.9 (d, C-15), 62.4 (t, C-23), 58.8 (d, C-7), 54.1 (d, C-19), 42.6 (t, C-22), 41.6 (t, C-5), 40.6 (s, C-8), 35.5 (s, C-20), 32.0 (s, C-16), 27.6 (q, C-21), 26.7 (q, C-17), 26.3 (q, C-29), 24.3 (q, C-9), 24.2 (q, C-9'), 18.3 (s, C-28).

amidine tautomer (selected signals):

^{1}H-NMR (500 MHz, 373 K, DMSO-d_6): δ = 7.78-7.80 (m, 2 H, 32-H, 33-H), 7.66-7.73 (m, 4 H, 25-H), 7.41-7.46 (m, 6 H, 26-H, 27-H), 7.37 (t, 1 H, NH_a), 7.11-7.15 (m, 5 H, 1-H, 2-H, 11-H), 6.96-7.07 (m, 3 H, 12-H, 13-H), 6.86 (m, 2 H, 3-H), 6.62 (d, $^3J_{NHb,7}$ = 9.3 Hz, 1 H, NH_b), 6.55 (d, $^3J_{NHb,7}$ = 9.2 Hz, 1 H, $NH_{c'}$), 5.11 (s, 1 H, 19-H), 4.53 (d, $^3J_{7,NHb}$ = 9.5 Hz, 1 H, 7-H), 4.00 (d, $^3J_{15,NHc}$ = 8.4 Hz, 1 H, 15-H), 3.77 (m, 2 H, 23-H), 3.57 (dd, $^2J_{5,5'}$ = 15.0 Hz, $^3J_{5,NHa}$ = 6.7 Hz, 1 H, 5-H), 3.52 (m, 1 H, 22-H), 3.40 (m, 1 H, 22-H'), 3.15 (dd, $^2J_{5',5}$ = 15.0 Hz, $^3J_{5',NHa}$ = 4.9 Hz, 1 H, 5-H'), 1.15 (s, 3 H, 9-H), 1.12 (s, 3 H, 9-H'), 1.10 (s, 9 H, 29-H), 1.07 (s, 9 H, 21-H), 0.80 (s, 9 H, 17-H).

^{13}C-NMR (125 MHz, 373 K, DMSO-d_6): δ = 168.6 (s, C-6), 167.9 (s, C-30), 152.6 (s, C-18), 145.7 (s, C-10), 138.2 (s, C-4), 134.6 (d, C-25), 134.6 (d, C-25'), 133.9 (d, C-33), 133.4 (s, C-24), 133.1 (s, C-24'), 130.6 (s, C-31), 129.1 (d, C-26), 127.3 (d, C-11), 171.1 (d, C-27'), 127.2 (d, C-12), 126.9 (d, C-3), 125.9 (d, C-1), 125.6 (d, C-2), 125.0 (d, C-13), 122.7 (d, C-32), 69.7 (d, C-15), 64.7 (t, C-23), 58.3 (d, C-7), 53.6 (d, C-19), 50.6 (t, C-22), 41.3 (t, C-5),

40.5 (s, C-8), 36.0 (s, C-20), 34.6 (s, C-16), 27.8 (q, C-21), 26.8 (q, C-17), 24.0 (q, C-9), 25.7 (q, C-9‘).

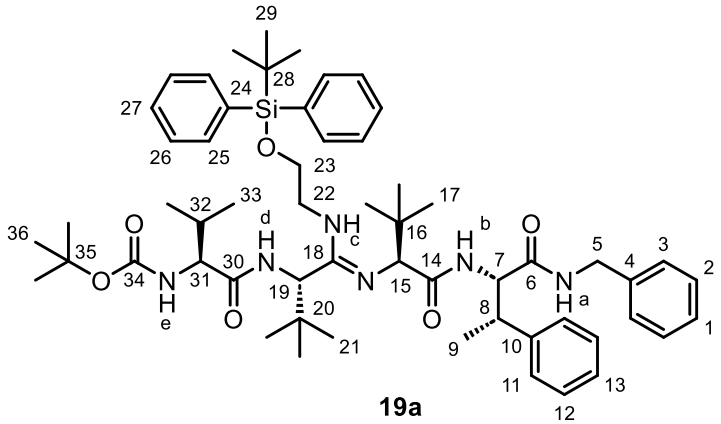
optical rotation:	$[\alpha]_D^{20}$ = +11.2 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{56}H_{70}N_5O_5Si$ $[M+H]^+$	920.5141	920.5142

***tert*-Butyl((4*S*,7*S*,10*S*,13*S*,*Z*)-7,10-di-*tert*-butyl-9-((2-((*tert*-butyldiphenylsilyl)oxy)ethyl) amino)-14-methyl-3,6,12-trioxo-1-phenyl-4-((*S*)-1-phenylethyl)-2,5,8,11-tetraaza-pentadec-8-en-13-yl)carbamate (19a)**[8]

272 mg phthaloyl protected amine **18a** (0.30 mmol, 1.0 eq.) was dissolved in 3.0 ml EtOH. After addition of 58 µl hydrazine hydrate (60.1 mg, 1.20 mmol, 4.0 eq.), the reaction was stirred for 2 h at 70 °C. After complete conversion (LC-MS control), the reaction mixture was cooled to 0 °C and the precipitated solid was filtered off. The filtrate was concentrated and the resulting residue was dissolved in EtOAc. The organic phase was washed twice with 10 % ammonia solution and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure to give the free amine which was used without further purification.

The above-prepared free amine was dissolved in 2.7 ml DCM and 72.0 mg Boc-Val-OH (330 µmol, 1.1 eq.) and 157 µl DIPEA (116 mg, 900 µmol, 3.0 eq.) were added. After cooling to 0 °C, 148 mg HBTU (390 µmol, 1.3 eq.) in 1.4 ml DMF was added and the reaction was stirred for 30 min at 0 °C and a further 4.5 h at room temperature. After full conversion, the solvent was concentrated, the residue was diluted with Et_2O and the resulting organic phase was washed successively with 10 % citric acid, sat. $NaHCO_3$ solution and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, cyclohexane/EtOAc 0 to 50 %) to obtain 256 mg peptide **19a** (262 µmol, 87 %) as a colourless solid.

LC-MS: t_R (**19a**) = 1.49 min



19a

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.27 (d, $^3J_{NHb,7}$ = 8.1 Hz, 1 H, NH_b), 7.63 (m, 4 H, 25-H), 7.43-7.36 (m, 6 H, 26-H, 27-H), 7.32-7.22 (m, 5 H, 2-H, 11-H, 12-H, 13-H), 7.20-7.15 (m, 3 H, 1-H, 3-H), 7.11 (d, $^3J_{NHd,19}$ = 9.8 Hz, 1 H, NH_d), 5.53 (bs, 1 H, NH_a), 5.44 (d, $^3J_{NHe,31}$ = 8.5 Hz, 1 H, NH_e), 4.89 (bs, 1 H, NH_c), 4.71 (m, 1 H, 7-H), 4.65 (m, 1 H, 19-H), 4.63 (dd, $^2J_{5,5'}$ = 14.6 Hz, $^3J_{5,NHa}$ = 6.4 Hz, 1 H, 5-H), 4.23 (m, 1 H, 5-H‘), 4.04 (t, $^3J_{31,32}$ = $^3J_{31,NHe}$ = 7.6 Hz, 1 H, 31-H), 3.70 (m, 1 H, 23-H), 3.67 (m, 1 H, 23-H‘), 3.50 (s, 1 H, 15-H), 3.41 (m, 1 H, 22-H), 3.35 (quint, $^3J_{8,9}$ = $^3J_{8,7}$ = 6.4 Hz, 1 H, 8-H), 3.30 (m, 1 H, 22-H‘), 1.86 (m, 1 H, 32-H), 1.38 (s, 9 H, 36-H), 1.29 (d, $^3J_{9,8}$ = 7.2 Hz, 3 H, 9-H), 1.11 (s, 9 H, 21-H), 1.06 (s, 9 H, 29-H), 0.94 (s, 9 H, 17-H), 0.78 (m, 6 H, 33-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 172.4 (s, C-14), 171.9 (s, C-30), 170.3 (s, C-6), 157.5 (s, C-18), 155.6 (s, C-34), 141.8 (s, C-10), 137.4 (s, C-4), 135.5 (d, C-25), 135.5 (d, C-25‘), 133.0 (s, C-24), 132.8 (s, C-24‘), 129.9 (d, C-27), 129.9 (d, C-27‘), 128.7 (d, C-12), 128.6 (d, C-13), 128.1 (d, C-3), 127.8 (d, C-26, C-11), 127.8 (d, C-26‘, C-2), 127.0 (d, C-1), 79.1 (s, C-35), 69.2 (d, C-15), 63.1 (t, C-23), 59.9 (d, C-31), 57.8 (d, C-7), 54.6 (d, C-19), 45.4 (t, C-22), 43.9 (t, C-5), 42.2 (s, C-8), 36.3 (s, C-16), 35.9 (s, C-20), 31.1 (d, C-32), 28.3 (q, C-36), 27.6 (q, C-17), 27.0 (q, C-21), 26.8 (q, C-29), 19.2 (q, C-33), 19.1 (s, C-28), 18.4 (q, C-33‘), 15.2 (q, C-9).

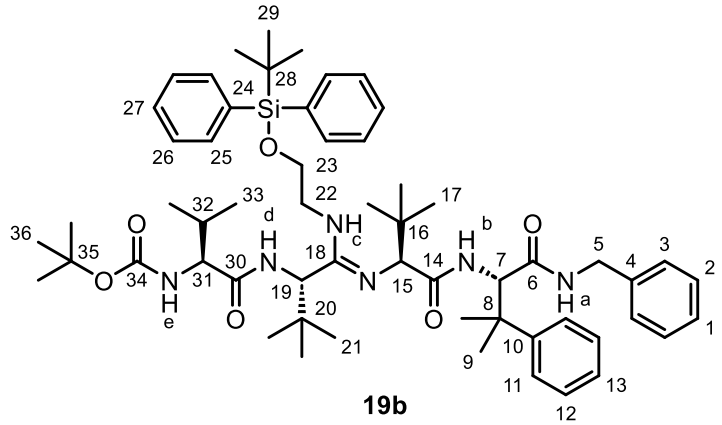
optical rotation:	$[\alpha]_D^{20}$ = –50.8 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{57}H_{83}N_6O_6Si$ $[M+H]^+$	975.6138	975.6143

***tert*-Butyl((4*S*,7*S*,10*S*,13*S*,*Z*)-7,10-di-*tert*-butyl-9-((2-((*tert*-butyldiphenylsilyl)oxy)ethyl) amino)-14-methyl-3,6,12-trioxo-1-phenyl-4-(2-phenylpropane-2-yl)-2,5,8,11-tetraaza-pentadec-8-en-13-yl)carbamate (19b)**[8]

278 mg phthaloyl protected amine **18b** (0.30 mmol, 1.0 eq.) was dissolved in 6.0 ml EtOH. After addition of 58 µl hydrazine hydrate (60.5 mg, 1.21 mmol, 4.0 eq.), the reaction was stirred for 3 h at 70 °C. After complete conversion (LC-MS control), the reaction mixture was cooled to 0 °C and the precipitated solid was filtered off. The filtrate was concentrated and the resulting residue was dissolved in EtOAc. The organic phase was washed twice with 10 % ammonia solution and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure to give the free amine which was used without further purification.

The above-prepared free amine was dissolved in 2.70 ml DCM and 72.0 mg Boc-Val-OH (332 µmol, 1.1 eq.) and 158 µl DIPEA (117 mg, 906 µmol, 3.0 eq.) were added. After cooling to 0 °C, 149 mg HBTU (393 µmol, 1.3 eq.) in 1.36 ml DMF was added and the reaction was stirred for 30 min at 0 °C and a further 4.5 h at room temperature. After full conversion, the solvent was concentrated, the residue was diluted with Et_2O and the resulting organic phase was washed successively with 10 % citric acid, sat. $NaHCO_3$ solution and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, cyclohexane/EtOAc 0 to 50 %) to obtain 252 mg peptide **19b** (255 µmol, 84 %) as a colourless solid.

LC-MS: t_R (**19b**) = 1.51 min



19b

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.55 (d, $^3J_{NHb,7}$ = 9.2 Hz, 1 H, NH_b), 7.63 (m, 4 H, 25-H), 7.43-7.37 (m, 8 H, 11-H, 26-H, 27-H), 7.33 (d, $^3J_{NHd,19}$ = 9.8 Hz, 1 H, NH_d), 7.26 (m, 2 H, 12-H), 7.19-7.23 (m, 3 H, 1-H, 2-H), 7.16 (m, 1 H, 13-H), 6.86 (m, 2 H, 3-H), 5.52 (d, $^3J_{NHe,31}$ =

8.9 Hz, 1 H, NH_e), 4.92 (t, $^3J_{NHc,22}$ = 4.9 Hz, 1 H, NH_c), 4.89 (d, $^3J_{7,NHb}$ = 9.3 Hz, 1 H, 7-H), 4.68 (d, $^3J_{19,NHd}$ = 9.8 Hz, 1 H, 19-H), 4.64 (t, $^3J_{NHa,5}$ = 5.0 Hz, 1 H, NH_a), 4.36 (dd, $^2J_{5,5'}$ = 14.5 Hz, $^3J_{5,NHa}$ = 5.6Hz, 1 H, 5-H), 4.14-4.07 (m, 2 H, 5-H', 31-H), 3.71 (m, 1 H, 23-H) 3.67 (m, 1 H, 23-H'), 3.57 (s, 1 H, 15-H), 3.43 (m, 1 H, 22-H), 3.29 (m, 1 H, 22-H'), 1.82 (m, 1 H, 32-H), 1.38 (s, 3 H, 9-H), 1.34 (s, 9 H, 36-H), 1.27 (s, 3 H, 9-H'), 1.18 (s, 9 H, 21-H), 1.08 (s, 9 H, 17-H), 1.06 (s, 9 H, 29-H), 0.75 (d, $^3J_{33,32}$ = 6.6 Hz, 6 H, 33-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 173.1 (s, C-14), 171.9 (s, C-30), 170.3 (s, C-6), 157.4 (s, C-18), 155.4 (s, C-34), 146.9 (s, C-10), 136.7 (s, C-4), 135.5 (d, C-25), 135.4 (d, C-25'), 133.0 (s, C-24), 132.8 (s, C-24'), 129.8 (d, C-27), 129.8 (d, C-27'), 129.0 (d, C-12), 128.4 (d, C-2), 127.9 (d, C-3), 127.8 (d, C-26), 127.8 (d, C-26'), 127.4 (d, C-1), 126.7 (d, C-13), 126.2 (d, C-11), 78.9 (s, C-35), 69.7 (d, C-15), 63.2 (t, C-23), 60.1 (d, C-7), 59.7 (d, C-31), 54.7 (d, C-19), 45.3 (t, C-22), 44.0 (t, C-5), 42.7 (s, C-8), 36.6 (s, C-16), 35.9 (s, C-20), 31.5 (d, C-32), 28.8 (q, C-9), 28.3 (q, C-36), 28.0 (q, C-17), 27.0 (q, C-21), 26.8 (q, C-29), 21.0 (q, C-9'), 19.1 (q, C-33), 19.0 (q, C-33'), 18.5 (s, C-28).

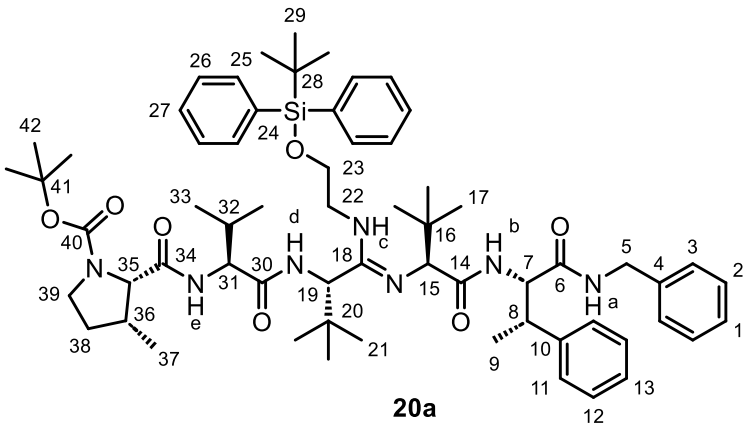
optical rotation:	$[\alpha]_D^{20}$ = –27.5 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{58}H_{85}N_6O_6Si$ $[M+H]^+$	989.6294	989.6291

***tert*-Butyl(2*S*,3*R*)-2-(((4*S*,7*S*,10*S*,13*S*,*Z*)-7,10-di-*tert*-butyl-9-((2-((*tert*-butyldiphenylsilyl)-oxy)ethyl)amino)-14-methyl-3,6,12-trioxo-1-phenyl-4-((*S*)-1-phenylethyl)-2,5,8,11-tetra-azapentadec-8-en-13-yl)carbamoyl)-3-methylpyrrolidine-1-carboxylate (20a)**

228 mg Boc-protected amine **19a** (234 µmol, 1.0 eq.) was dissolved in 1.85 ml DCM and cooled to 0 °C. Subsequently, 1.2 ml TFA was added and the reaction was stirred for 6 h at 0 °C. After complete conversion, the solvent was removed under reduced pressure and the residue was used without further purification.

The above-prepared amine was dissolved in 2.2 ml DCM and 54.0 mg Boc-MePro-OH[9] (234 µmol, 1.0 eq.) and 123 µl DIPEA (91.0 mg, 702 µmol, 3.0 eq.) were added. After cooling the solution to 0 °C, 115 mg HBTU (304 µmol, 1.3 eq.) in 1.1 ml DMF was added. The reaction was slowly warmed to room temperature for 16 h. After full conversion, the solvent was concentrated, the residue was diluted with Et_2O and the resulting organic phase was washed successively with 10 % citric acid, sat. $NaHCO_3$ solution and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, cyclohexane/EtOAc 0 to 60 %) to obtain 222 mg peptide **20a** (204 µmol, 87 %) as a colourless amorphous solid.

LC-MS: t_R (**20a**) = 1.49 min



20a

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.46 (bs, 1 H, NH_b), 7.63 (d, $^3J_{25,26}$ = 7.9 Hz, 4 H, 25-H), 7.43-7.36 (m, 6 H, 26-H, 27-H), 7.29-7.16 (m, 10 H, 1-H, 2-H, 3-H, 11-H, 12-H, 13-H), 6.45 (m, 1 H, NH_e), 5.73 (bs, 1 H, NH_a), 5.42 (bs, 1 H, NH_d), 4.87 (bs, 1 H, NH_c), 4.67 (d, $^3J_{19,NHd}$ = 9.9 Hz, 1 H, 19-H), 4.73-4.60 (m, 2 H, 5-H, 7-H), 4.38 (m, 1 H, 31-H), 4.27 (m, 1 H, 5-H‘), 4.03 (d, $^3J_{35,36}$ = 8.4 Hz, 1 H, 35-H), 3.71 (m, 1 H, 23-H), 3.65 (m, 1 H, 23-H‘), 3.58 (t, $^3J_{39,38}$ = 9.2 Hz, 1 H, 39-H), 3.51 (m, 1 H, 15-H), 3.41 (m, 1 H, 22-H), 3.36-3.27 (m, 3 H, 8-H, 22-H‘, 39-H‘), 2.37 (m, 1 H, 36 H), 1.89 (m, 1 H, 32-H), 1.82-1.63 (m, 2 H, 38-H), 1.38 (s, 9 H, 42-H), 1.27 (d, $^3J_{9,8}$ = 7.2 Hz, 3 H, 9-H), 1.08 (s, 9 H, 21-H), 1.06 (s, 9 H, 29-H), 0.99-0.92 (m, 12 H, 17-H, 37-H), 0.70 (m, 6 H, 33-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 172.5 (s, C-14), 171.0 (s, C-30), 170.3 (s, C-6), 170.3 (s, C-34), 157.3 (s, C-18), 154.3 (s, C-40), 141.5 (s, C-10), 137.8 (s, C-4), 135.5 (d, C-25), 135.5 (d, C-25‘), 133.0 (s, C-24), 132.8 (s, C-24‘), 129.9 (d, C-27), 129.9 (d, C-27‘), 128.7 (d, C-12), 128.5 (d, C-13), 128.2 (d, C-3), 127.8 (d, C-26, C-11), 127.8 (d, C-26‘, C-2), 127.0 (d, C-1), 79.9 (s, C-41), 69.3 (d, C-15), 64.4 (d, C-35), 63.1 (t, C-23), 57.6 (d, C-7), 57.0 (d, C-31), 54.6 (d, C-19), 46.0 (t, C-39), 45.5 (t, C-22), 44.0 (t, C-5), 42.2 (s, C-8), 36.2 (d, C-36), 35.7 (s, C-20), 33.8 (s, C-16), 32.3 (d, C-38), 31.2 (t, C-32), 28.3 (q, C-42), 27.6 (q, C-17), 27.0 (q, C-21), 26.8 (q, C-29), 19.1 (q, C-33), 19.1 (s, C-28), 18.1 (q, C-33‘), 14.8 (q, C-37), 14.5 (q, C-9).

rotamer (selected signals):

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.19 (bs, 1 H, NH_b), 7.67 (d, $^3J_{25,26}$ = 7.6 Hz, 4 H, 25-H), 5.91 (bs, 1 H, NH_a), 5.04 (bs, 1 H, NH_d), 4.56 (m, 1 H, 31-H), 1.44 (s, 9 H, 42-H), 0.69 (m, 6 H, 33-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 81.2 (d, C-41), 69.6 (d, C-15), 41.1 (s, C-8), 37.3 (d, C-36), 32.5 (d, C-38), 19.5 (q, C-33), 17.0 (q, C-33‘).

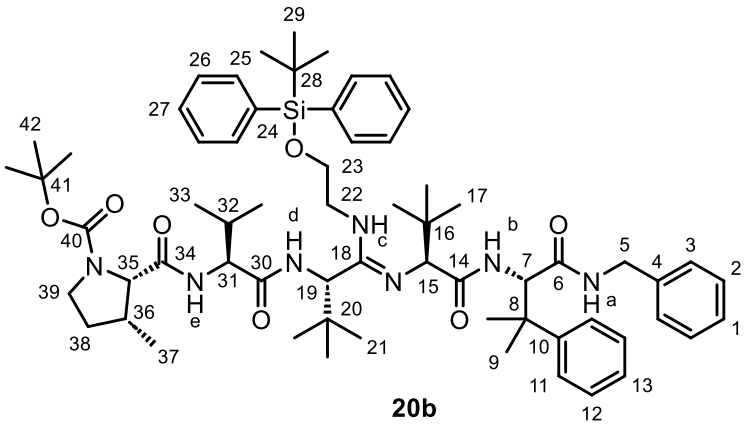
optical rotation:	$[\alpha]_D^{20}$ = –45.0 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{63}H_{92}N_7O_7Si$ $[M+H]^+$	1086.6822	1086.6825

tert-Butyl(2*S*,3*R*)-2-(((4*S*,7*S*,10*S*,13*S*,*Z*)-7,10-di-*tert*-butyl-9-((2-((*tert*-butyldiphenylsilyl) oxy)ethyl)amino)-14-methyl-3,6,12-trioxo-1-phenyl-4-(2-phenylpropane-2-yl)-2,5,8,11-tetraazapentadec-8-en-13-yl)carbamoyl)-3-methylpyrrolidine-1-carboxylate (20b)

192 mg Boc-protected amine **19a** (190 µmol, 1.0 eq.) was dissolved in 1.5 ml DCM and cooled to 0 °C. Subsequently, 1.0 ml TFA was added and the reaction was stirred for 4.5 h at 0 °C. After complete conversion, the solvent was removed under reduced pressure and the residue was used without further purification.

The above-prepared amine was dissolved in 1.9 ml DCM and 44.5 mg Boc-MePro-OH[9] (194 µmol, 1.0 eq.) and 102 µl DIPEA (75.0 mg, 582 µmol, 3.0 eq.) were added. After cooling the solution to 0 °C, 96.0 mg HBTU (252 µmol, 1.3 eq.) in 0.9 ml DMF was added. The reaction was slowly warmed to room temperature for 16 h. After full conversion, the solvent was concentrated, the residue was diluted with Et_2O and the resulting organic phase was washed successively with 10 % citric acid, sat. $NaHCO_3$ solution and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, cyclohexane/EtOAc 0 to 60 %) to obtain 162 mg peptide **20b** (147 µmol, 76 %) as a colourless amorphous solid.

LC-MS: t_R (**20b**) = 1.53 min



20b

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 8.65 (m, 1 H, NH_b), 7.64-7.62 (m, 5 H, 25-H, NH_d), 7.45-7.37 (m, 8 H, 11-H, 26-H, 27-H), 7.26 (m, 2 H, 12-H), 7.20-7.18 (m, 3 H, 1-H, 2-H), 7.16 (m, 1 H, 13-H), 6.87 (m, 2 H, 3-H), 6.52-6.42 (m, 1 H, NH_e), 4.91 (m, 1 H, NH_c), 4.87 (d, $^3J_{7,NHb}$ = 9.0 Hz, 1 H, 7-H), 4.70 (d, $^3J_{19,NHd}$ = 9.9 Hz, 1 H, 19-H), 4.61 (m, 2 H, 31-H, NH_a), 4.43 (dd, $^2J_{5,5'}$ = 14.7 Hz, $^3J_{5,NHa}$ = 5.7 Hz, 1 H, 5-H), 4.18 (m, 1 H, 5-H‘), 4.00 (d, $^3J_{35,36}$ = 8.4 Hz, 1 H, 35-H), 3.71 (m, 1 H, 23-H), 3.65 (m, 1 H, 23-H‘), 3.59 (s, 1 H, 15-H), 3.57 (t, $^3J_{39,38}$ = 9.2 Hz, 1 H, 39-H), 3.45 (m, 1 H, 22-H), 3.35-3.20 (m, 2 H, 22-H‘, 39-H‘), 2.36 (m, 1 H, 36-H), 1.87 (m, 1 H, 38-H), 1.75 (m, 1 H, 32-H), 1.66 (m, 1 H, 38-H‘), 1.37 (s, 3 H, 9-H), 1.36 (s, 9 H, 42-H), 1.25 (s, 3 H, 9-H‘), 1.16 (s, 9 H, 21-H), 1.09 (s, 9 H, 17-H), 1.06 (s, 9 H, 29-H), 0.95 (d, $^3J_{37,36}$ = 6.9 Hz, 3 H, 37-H), 0.66 (m, 6 H, 33-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 173.3 (s, C-14), 171.1 (s, C-30), 170.2 (s, C-6, C-34), 157.2 (s, C-18), 154.3 (s, C-40), 146.9 (s, C-10), 137.0 (s, C-4), 135.5 (d, C-25), 135.5 (d, C-25‘), 133.0 (s, C-24), 132.8 (s, C-24‘), 129.9 (d, C-27), 129.9 (d, C-27‘), 129.1 (d, C-12), 128.3 (d, C-2), 128.1 (d, C-3), 127.9 (d, C-26), 127.8 (d, C-26‘), 127.3 (d, C-1), 126.8 (d, C-13), 126.3 (d, C-11), 79.9 (s, C-41), 69.8 (d, C-15), 64.5 (d, C-35), 63.2 (t, C-23), 60.1 (d, C-7), 56.9 (d, C-31), 54.8 (d, C-19), 46.0 (t, C-39), 45.5 (t, C-22), 44.1 (t, C-5), 42.8 (s, C-8), 37.3 (d, C-36), 36.6 (s, C-16), 35.6 (s, C-20), 32.4 (d, C-32), 31.5 (t, C-38), 29.1 (q, C-9), 28.4 (q, C-42), 28.1 (q, C-17), 27.1 (q, C-21), 26.9 (q, C-29), 20.8 (q, C-9‘), 19.2 (s, C-28), 18.8 (q, C-33), 18.4 (q, C-33‘), 14.9 (q, C-37).

rotamer (selected signals):

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 64.3 (d, C-35), 57.3 (d, C-31), 46.4 (t, C-39).

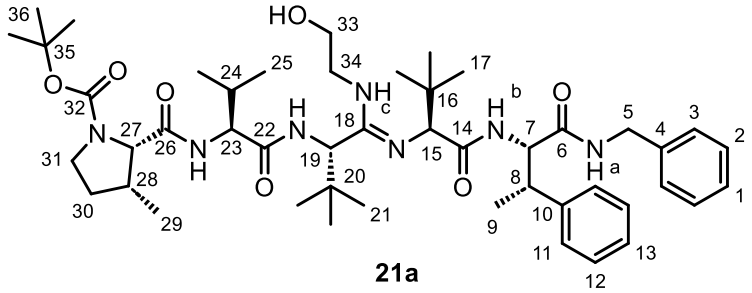
optical rotation:	$[\alpha]_D^{20}$ = –25.1 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{64}H_{94}N_7O_7Si$ $[M+H]^+$	1100.6979	1100.6980

tert-Butyl(2*S*,3*R*)-2-(((4*S*,7*S*,10*S*,13*S*,*Z*)-7,10-di-*tert*-butyl-9-((2-hydroxyethyl)amino)-14-methyl-3,6,12-trioxo-1-phenyl-4-((*S*)-1-phenylethyl)-2,5,8,11-tetraazapentadec-8-en-13-yl)carbamoyl)-3-methylpyrrolidine-1-carboxylate (21a)

210 mg of the protected alcohol **20a** (193 µmol, 1.0 eq.) was dissolved in 1.9 ml anhydrous THF. After adding 201 µl TBAF solution (1.0 M in THF, 201 µmol, 1.04 eq.), the reaction solution was stirred at room temperature for 15 h. After full conversion, the reaction was quenched by addition sat. NH_4Cl solution, the phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed successively with sat. NH_4Cl solution and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure and the residue was purified by column chromatography

(silica gel, DCM/MeOH 0 to 10 %) to obtain 154 mg free alcohol **21a** (182 µmol, 94 %) as a colourless solid.

LC-MS: t_R (**21a**) = 1.06 min



21a

^{1}H-NMR (500 MHz, 373 K, DMSO-d_6): δ = 9.23 (bs, 1 H, OH), 8.51 (m, 1 H, NH_a), 8.24 (m, 1 H, NH_d, NH_e), 7.90 (m, 1 H, NH_c), 7.64 (m, 1 H, NH_b), 7.30-7.16 (m, 10 H, 1-H, 2-H, 3-H, 11-H, 12-H, 13-H), 5.08-4.70 (m, 2 H, 15-H, 19-H), 4.58 (m, 1 H, 7-H), 4.36 (m, 1 H, 5-H), 4.30-4.15 (m, 3 H, 5-H‘, 23-H, 27-H), 3.65-3.35 (m, 4 H, 33-H, 34-H), 3.46 (m, 1 H, 31-H), 3.24 (m, 1 H, 31-H‘), 3.16 (m, 1 H, 8-H), 2.35 (m, 1 H, 28-H), 1.99 (m, 1 H, 24-H), 1.85 (m, 1 H, 30-H), 1.62 (m, 1 H, 30-H‘), 1.38 (s, 9 H, 36-H), 1.21 (m, 3 H, 9-H), 1.03-0.75 (m, 27 H, 17-H, 21-H, 25-H, 29-H).

^{13}C-NMR (125 MHz, 373 K, DMSO-d_6): δ = 171.1 (s**,** C-6), 170.2 (s, C-26), 170.2 (s, C-14), 168.5 (s, C-22), 152.9 (s, C-32), 141.9 (s, C-10), 138.5 (s, C-4), 127.5 (d, C-2), 127.4 (d, C-12), 127.1 (d, C-3), 126.9 (d, C-1), 126.2 (d, C-11), 125.7 (d, C-13), 77.9 (s, C-35), 62.5 (d, C-27), 60.3 (t, C-33), 58.3 (t, C-34), 57.5 (d, C-23), 57.5 (d, C-7), 57.4 (d, C-19), 54.6 (d, C-15), 45.4 (t, C-31), 41.9 (t, C-5), 40.9 (s, C-8), 35.9 (d, C-28), 33.5 (s, C-16), 30.5 (t, C-30), 30.4 (s, C-20), 29.6 (d, C-24), 27.7 (q, C-36), 26.1 (q, C-17), 25.7 (q, C-21), 18.7 (q, C-25), 17.9 (q, C-25‘), 17.6 (q, C-9), 14.1 (q, C-29).

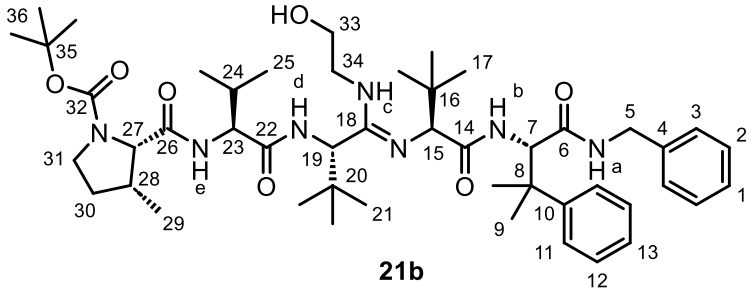
C-18 disappears in the noise of the spectrum.

optical rotation:	$[\alpha]_D^{20}$ = –36.6 [$CHCl_3$, c = 1.0]	
HRMS (ESI):	calculated:	found:
$C_{47}H_{74}N_7O_7$ $[M+H]^+$	848.5644	848.5645

***tert*-butyl-(2*S*,3*R*)-2-(((4*S*,7*S*,10*S*,13*S*,*Z*)-7,10-di-*tert*-butyl-9-((2-hydroxyethyl)amino)-14-methyl-3,6,12-trioxo-1-phenyl-4-(2-phenylpropane-2-yl)-2,5,8,11-tetraazapentadec-8-en-13-yl)carbamoyl)-3-methylpyrrolidine-1-carboxylate (21b)**

145 mg of the protected alcohol **20b** (132 µmol, 1.0 eq.) was dissolved in 1.3 ml anhydrous THF. After adding 137 µl TBAF solution (1.0 M in THF, 137 µmol, 1.04 eq.), the reaction solution was stirred at room temperature for 15 h. After full conversion, the reaction was quenched by addition sat. NH_4Cl solution, the phases were separated and the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed successively with sat. NH_4Cl solution and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, DCM/MeOH 0 to 10 %) to obtain 106 mg free alcohol **21b** (123 µmol, 93 %) as a colourless solid.

LC-MS: t_R (**21b**) = 1.09 min



21b

^{1}H-NMR (500 MHz, 373 K, DMSO-d_6): δ = 9.50 (bs, 1 H, OH), 8.63 (m, 1 H, NH_c), 7.88 (m, 1 H, NH_b), 7.76 (m, 1 H, NH_a), 7.67 (bs, 1 H, NH_e), 7.40 (m, 2 H, 11-H), 7.26-7.15 (m, 6 H, 1-H, 2-H, 12-H, 13-H), 7.06 (m, 2 H, 3-H), 5.38 (m, 1 H, 19-H), 5.02 (m, 1 H, 15-H), 4.83 (m, 1 H, NH_d), 4.65 (d, 1 H, 7-H), 4.25-4.15 (m, 3 H, 5-H, 23-H, 27-H), 4.02 (m, 1 H, 5-H‘), 3.72-3.53 (m, 4 H, 33-H, 34-H), 3.46 (t, $^3J_{39,38}$ = 9.1 Hz, 1 H, 31-H), 3.24 (td, $^3J_{31,30}$ = 9.8 Hz, $^2J_{31,31‘}$ = 7.2 Hz, 1 H, 31-H‘), 2.36 (m, 1 H, 28-H), 1.99 (m, 1 H, 24-H), 1.86 (m, 1 H, 30-H), 1.62 (m, 1 H, 30-H‘), 1.41 (s, 3 H, 9-H), 1.39 (s, 9 H, 36-H), 1.34 (s, 3 H, 9-H‘), 1.05 (s, 9 H, 17-H), 1.00 (s, 9 H, 21-H), 0.90 (m, 6 H, 25-H, 29-H), 0.80 (m, 3 H, 25-H‘).

^{13}C-NMR (125 MHz, 373 K, DMSO-d_6): δ = 171.2 (s**,** C-6), 170.2 (s, C-26), 166.6 (s, C-14), 166.3 (s, C-22), 164.6 (s, C-18), 152.9 (s, C-32), 145.6 (s, C-10), 138.4 (s, C-4), 127.4 (d, C-2), 127.2 (d, C-12), 126.7 (d, C-3), 126.0 (d, C-1), 125.8 (d, C-11), 125.3 (d, C-13), 77.9 (s, C-35), 62.4 (d, C-27), 61.3 (d, C-19), 60.3 (d, C-7), 58.3 (t, C-33), 57.5 (d, C-23), 54.6 (d, C-15), 47.5 (t, C-34), 45.4 (t, C-31), 41.7 (t, C-5), 40.6 (s, C-8), 35.9 (d, C-28), 35.1 (s, C-16), 34.7 (s, C-20), 30.5 (t, C-30), 29.6 (d, C-24), 27.7 (q, C-36), 26.2 (q, C-17), 25.7 (q, C-9), 25.6 (q, C-21), 23.8 (q, C-9‘), 18.8 (q, C-25), 17.9 (q, C-25‘), 14.1 (q, C-29).

optical rotation:	$[\alpha]_D^{20}$ = +64.3 [$CHCl_3$, c = 0.93]	
HRMS (ESI):	calculated:	found:
$C_{48}H_{76}N_7O_7$ $[M+H]^+$	862.5801	862.5805

(*S*)-*N*-((2*S*,3*S*)-1-(Benzylamino)-1-oxo-3-phenylbutane-2-yl)-2-(((3*S*,6*S*,14*R*,14a*S*,*Z*)-6-(*tert*-butyl)-3-isopropyl-14-methyl-1,4,10-trioxododecahydropyrrolo[1,2-*a*][1,4,7,10]tetra-azacyclododecine-7(8*H*)-ylidene)amino)-3,3-dimethylbutanamide (23a)

85.0 mg of the Boc-protected amine **21a** (100 µmol, 1.0 eq.) was dissolved in 2.0 ml DCM and 1.0 ml HCl solution (4 M in dioxane, 4.00 mmol, 40.0 eq.) was added and the reaction mixture was stirred for 1 h at room temperature. After complete conversion (LC-MS control), the solvent was removed in a nitrogen countercurrent.

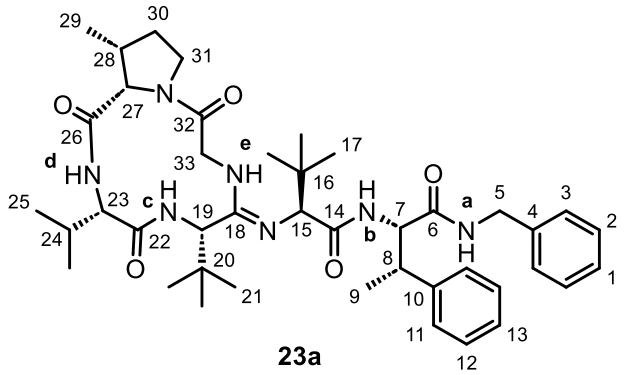
[Jones reagent (2.67 M): 100 mg CrO_3, 291 µl H_2O, 84 µl H_2SO_4]

The above-prepared hydrochloride was dissolved in 2.0 ml acetone and 1.1 ml Jones reagent (2.67 M) was added at room temperature. After stirring for 2.5 h, the reaction mixture was diluted with isopropanol and adsorbed on isolute and purified by column chromatography (C18 spherical, 0.1 % $HCOOH_{aq.}$/MeCN 10 to 100 %) to give 53.0 mg of acid **22a** (70 µmol, 70 %) with slight impurities.

For macrocyclisation, 93.0 mg HATU (243 µmol, 3.5 eq.) was suspended in 65 ml DCM and 55 µl DIPEA (40.5 mg, 313 µmol, 4.5 eq.) was added. After 53.0 mg acid **22a** (70 µmol, 1.0 eq.), dissolved in 4.5 ml DMF, was added using a syringe pump over a period of 9 h, the reaction was stirred for further 5 h at room temperature. After full conversion, the solvent was concentrated and the residue diluted with EtOAc. The organic phase was washed successively with 1 M $KHSO_4$ solution, H_2O, sat. $NaHCO_3$ solution and brine. The organic

layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was first purified by column chromatography (C18 spherical, H_2O/MeCN 10 to 100 %) and afterwards by preparative HPLC (Luna, 0.1 % $HCOOH_{aq}$/(MeCN + 0.1 % HCOOH) 10 to 100 %) to obtain 4.5 mg of the bottromycin derivative **23a** (6.1 µmol, 6 % over 3 steps) as a colourless lyophilisate.

LC-MS: t_R (**23a**) = 0.98 min



23a

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.78 (m, 1 H, NH_d), 7.34-7.15 (m, 10 H, 1-H, 2-H, 3-H, 11-H, 12-H, 13-H), 7.03 (d, $^3J_{NHc,19}$ = 10.8 Hz, 1 H, NH_c), 6.88 (d, $^3J_{NHb,7}$ = 8.4 Hz, 1 H, NH_b), 6.48 (bs, 1 H, NH_a), 4.90 (m, 1 H, 7-H), 4.62 (d, $^3J_{19,NHc}$ = 10.7 Hz, 1 H, 19-H), 4.39 (dd, $^2J_{5,5'}$ = 14.8 Hz, $^3J_{5,NHa}$ = 6.4 Hz, 1 H, 5-H), 4.25 (dd, $^2J_{5',5}$ = 14.8 Hz, $^3J_{5',NHa}$ = 5.0 Hz, 1 H, 5-H‘), 4.19 (d, $^3J_{27,28}$ = 7.9 Hz, 1 H, 27-H), 3.94 (m, 1 H, NH_e), 3.87 (s, 1 H, 15-H), 3.81-3.74 (m, 3 H, 33-H, 31-H), 3.58 (td, $^2J_{31',31}$ = 11.4 Hz, $^3J_{31,30}$ = 7.2 Hz, 1 H, 31-H‘), 3.28 (m, 1 H, 8-H), 2.87 (m, 1 H, 24-H), 2.57 (m, 1 H, 23-H), 2.53 (m, 1 H, 28-H), 2.03 (m, 1 H, 30-H‘), 1.69 (m, 1 H, 30-H), 1.28 (d, $^3J_{9,8}$ = 7.2 Hz, 3 H, 9-H), 1.15 (d, $^3J_{29,28}$ = 6.9 Hz, 3 H, 29-H), 0.98 (s, 9 H, 21-H), 0.90 (s, 9 H, 17-H), 0.82 (d, $^3J_{25,24}$ = 6.3 Hz, 3 H, 25-H), 0.78 (d, $^3J_{25',24}$ = 6.4 Hz, 3 H, 25‘-H).

^{13}C-NMR (125 MHz, $CDCl_3$): δ = 174.5 (s, C-26), 172.7 (s, C-14), 172.2 (s, C-6), 171.5 (s, C-22), 169.2 (s, C-32), 157.1 (s, C-18), 141.5 (s, C-10), 137.0 (s, C-4), 128.9 (d, C-2), 128.5 (d, C-12), 128.1 (d, C-11), 127.8 (d, C-1), 127.5 (d, C-3), 127.0 (d, C-13), 70.4 (d, C-15), 69.4 (d, C-23), 65.7 (d, C-27), 57.3 (d, C-7), 54.0 (d, C-19), 48.0 (t, C-33), 47.0 (t, C-31), 43.3 (t, C-5), 42.3 (d, C-8), 38.5 (d, C-28), 35.3 (s, C-16), 32.9 (s, C-20), 30.3 (t, C-30), 27.6 (q, C-17), 27.5 (q, C-21), 26.9 (d, C-24), 20.2 (q, C-25), 19.6 (q, C-25‘), 15.9 (q, C-9), 15.6 (q, C-29).

optical rotation: $[\alpha]_D^{20}$ = –4.3 [$CHCl_3$, c = 0.3] Lit.: $[\alpha]_D^{20}$ = –3.8 [$CHCl_3$, c = 0.3][10]

HRMS (ESI):	calculated:	found:
$C_{42}H_{62}N_7O_5$ $[M+H]^+$	744.4807	744.4798

(*S*)-*N*-Benzyl-2-((*S*)-2-(((3*S*,6*S*,14*R*,14a*S*,*Z*)-6-(*tert*-butyl)-3-isopropyl-14-methyl-1,4,10-trioxododecahydropyrrolo[1,2-*a*][1,4,7,10]tetraazacyclododecine-7(8*H*)-ylidene)amino)-3,3-dimethylbutanamido)-3-methyl-3-phenylbutanamide (23b)

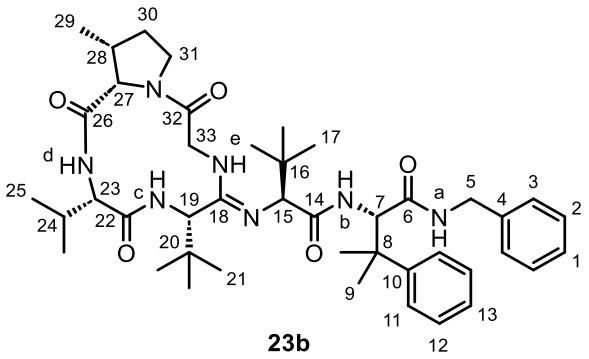
49.0 mg of the Boc-protected amine **21b** (57.0 µmol, 1.0 eq.) was dissolved in 1.1 ml DCM and 0.6 ml HCl solution (4 M in dioxane, 2.27 mmol, 40.0 eq.) was added and the reaction mixture was stirred for 1 h at room temperature. After complete conversion (LC-MS control), the solvent was removed in a nitrogen countercurrent.

[Jones reagent (2.67 M): 100 mg CrO_3, 291 µl H_2O, 84 µl H_2SO_4]

The above-prepared hydrochloride was dissolved in 1.1 ml acetone and 0.64 ml Jones reagent (2.67 M) was added at room temperature. After stirring for 2 h, the reaction mixture was diluted with isopropanol and adsorbed on isolute, and purified by column chromatography (C18 spherical, 0.1 % $HCOOH_{aq.}$/MeCN 10 to 100 %) to give 28.0 mg of acid **22b** (36.0 µmol, 64 %) with slight impurities.

For macrocyclisation, 42.3 mg HATU (111 µmol, 3.5 eq.) was suspended in 30 ml DCM and 25 µl DIPEA (18.5 mg, 143 µmol, 4.5 eq.) was added. After 24.0 mg acid **22b** (31.0 µmol, 1.0 eq.), dissolved in 2.0 ml DMF, was added using a syringe pump over a period of 9 h, the reaction was stirred for a further 5 h at room temperature. After full conversion, the solvent was concentrated and the residue diluted with EtOAc. The organic phase was washed successively with 1 M $KHSO_4$ solution, H_2O, sat. $NaHCO_3$ solution and brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The crude product was first purified by column chromatography (C18 spherical, H_2O/MeCN 10 to 100 %) and afterwards by preparative HPLC (Luna, 0.1 % $HCOOH_{aq}$/(MeCN + 0.1 % HCOOH) 10 to 100 %) to obtain 3.0 mg of the bottromycin derivative **23b** (4.0 µmol, 8 % over 3 steps) as a colourless lyophilisate.

LC-MS: t_R (**23b**) = 0.99 min



23b

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 7.83 (d, $^3J_{NHd,23}$ = 5.4 Hz, 1 H, NH_d), 7.42 (m, 2 H, 11-H), 7.28 (m, 3 H, 1-H, 2-H), 7.24 (dd, $^3J_{12,11}$ = $^3J_{12,13}$ = 7.6 Hz, 2 H, 12-H), 7.13 (m, 1 H, 13-H), 7.02 (m, 2 H, 3-H), 6.94 (d, $^3J_{NHc,19}$ = 10.6 Hz, 1 H, NH_c), 6.89 (d, $^3J_{NHb,7}$ = 9.2 Hz, 1 H, NH_b), 5.58 (m, 1 H, NH_a), 4.88 (d, $^3J_{7,NHb}$ = 9.2 Hz, 1 H, 7-H), 4.64 (d, $^3J_{19,NHc}$ = 10.7 Hz, 1 H, 19-H), 4.19 (d, $^3J_{27,28}$ = 8.2 Hz, 1 H, 27-H), 4.17 (dd, $^2J_{5,5'}$ = 14.6 Hz, $^3J_{5,NHa}$ = 5.6 Hz, 1 H, 5-H), 4.09 (dd, $^2J_{5',5}$ = 14.5 Hz, $^3J_{5',NHa}$ = 5.4 Hz, 1 H, 5-H‘), 3.93 (s, 1 H, 15-H), 3.91 (m, 1H, NH_e), 3.71-3.84 (m, 3 H, 31-H‘, 33-H), 3.57 (dt, $^3J_{31,30}$ = 7.0 Hz, $^2J_{31,31'}$ = 11.5 Hz, 1 H, 31-H), 2.87 (dsept, $^3J_{24,23}$ = 12.0 Hz, $^3J_{34,25}$ = 6.0 Hz, 1 H, 24-H), 2.61 (dd, $^3J_{23,24}$ = 12.0 Hz, $^3J_{23,NHd}$ = 5.4 Hz, 1 H, 23-H), 2.55 (m, 1 H, 28-H), 1.98-2.06 (m, 1 H, 30-H‘), 1.71 (m, 1 H, 30-H), 1.43 (s, 3 H, 9-H), 1.32 (s, 3 H, 9‘-H), 1.15 (d, $^3J_{29,28}$ = 7.0 Hz, 3 H, 29-H), 1.03 (s, 9 H, 17-H), 1.00 (s, 9 H, 21-H), 0.81 (d, $^3J_{25',24}$ = 6.5 Hz, 3 H, 25‘-H), 0.78 (d, $^3J_{25,24}$ = 6.7 Hz, 3 H, 25-H).

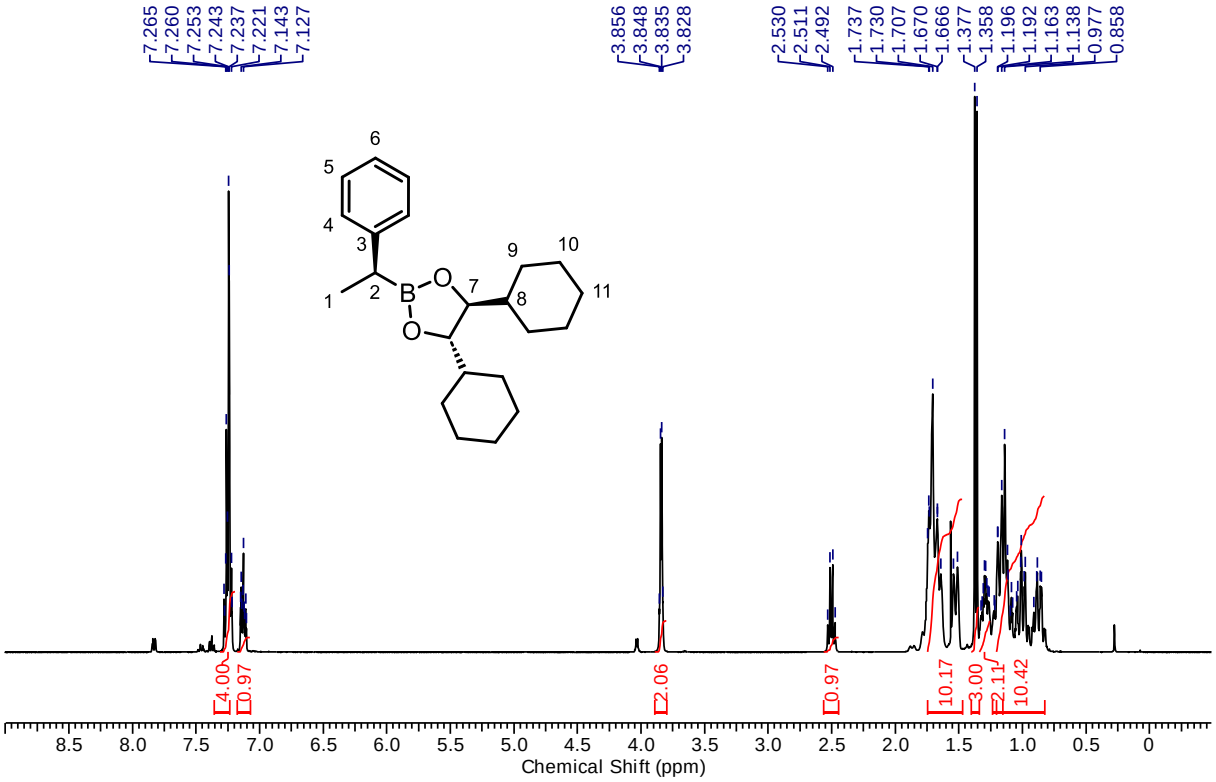
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 174.6 (s, C-26), 173.0 (s, C-14), 171.9 (s, C-6), 171.1 (s, C-22), 169.3 (s, C-32), 156.9 (s, C-18), 145.9 (s, C-10), 136.3 (s, C-4), 128.8 (d, C-2), 128.4 (d, C-12), 127.8 (d, C-1), 127.5 (d, C-3), 126.8 (d, C-11), 126.5 (d, C-13), 70.9 (d, C-15), 69.5 (d, C-23), 65.7 (d, C-27), 60.2 (d, C-7), 54.0 (d, C-19), 48.1 (d, C-33), 47.0 (t, C-31), 43.3 (t, C-5), 42.1 (s, C-8), 38.5 (d, C-28), 35.5 (s, C-16), 32.9 (s, C-20), 30.3 (t, C-30), 27.9 (q, C-17), 27.8 (q, C-9), 27.7 (q, C-21), 26.8 (d, C-24), 23.4 (q, C-9‘), 20.2 (q, C-25), 19.6 (q, C-25‘), 15.7 (q, C-29).

optical rotation:	$[\alpha]_D^{20}$ = +23.3 [$CHCl_3$, c = 0.3]	
HRMS (ESI):	calculated:	found:
$C_{43}H_{64}N_7O_5$ $[M+H]^+$	758.4963	758.4962

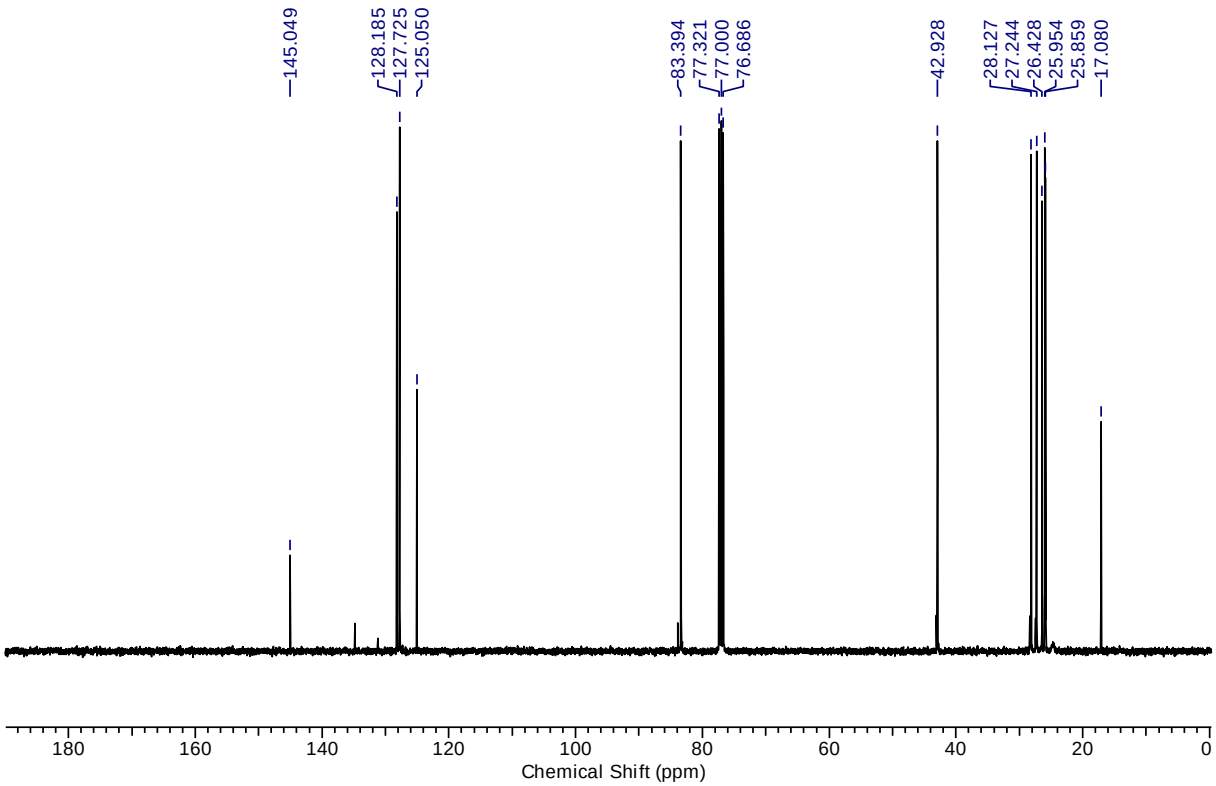
NMR-Spectra of the compounds

(4*S*,5*S*)-4,5-Dicyclohexyl-2-((*S*)-1-phenylethyl)-1,3,2-dioxaborolane (3)

^{1}H-NMR (400 MHz, $CDCl_3$):

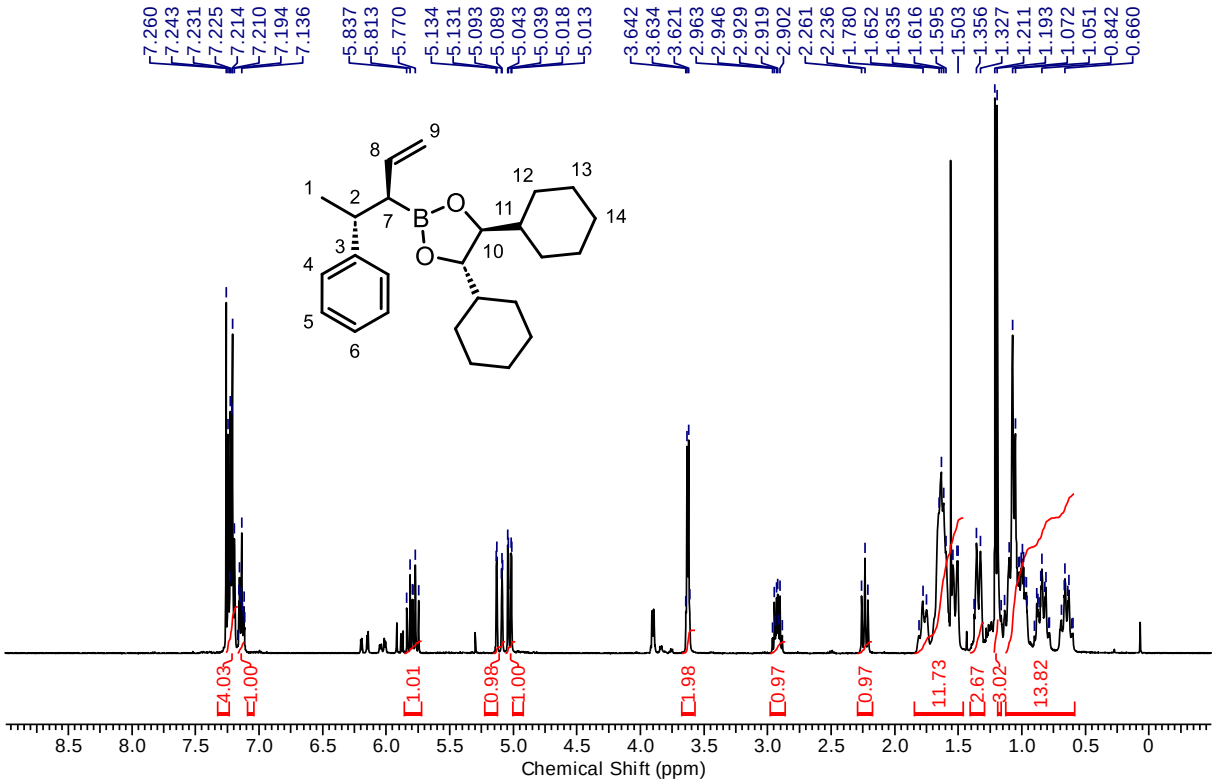


^{13}C-NMR (100 MHz, $CDCl_3$):

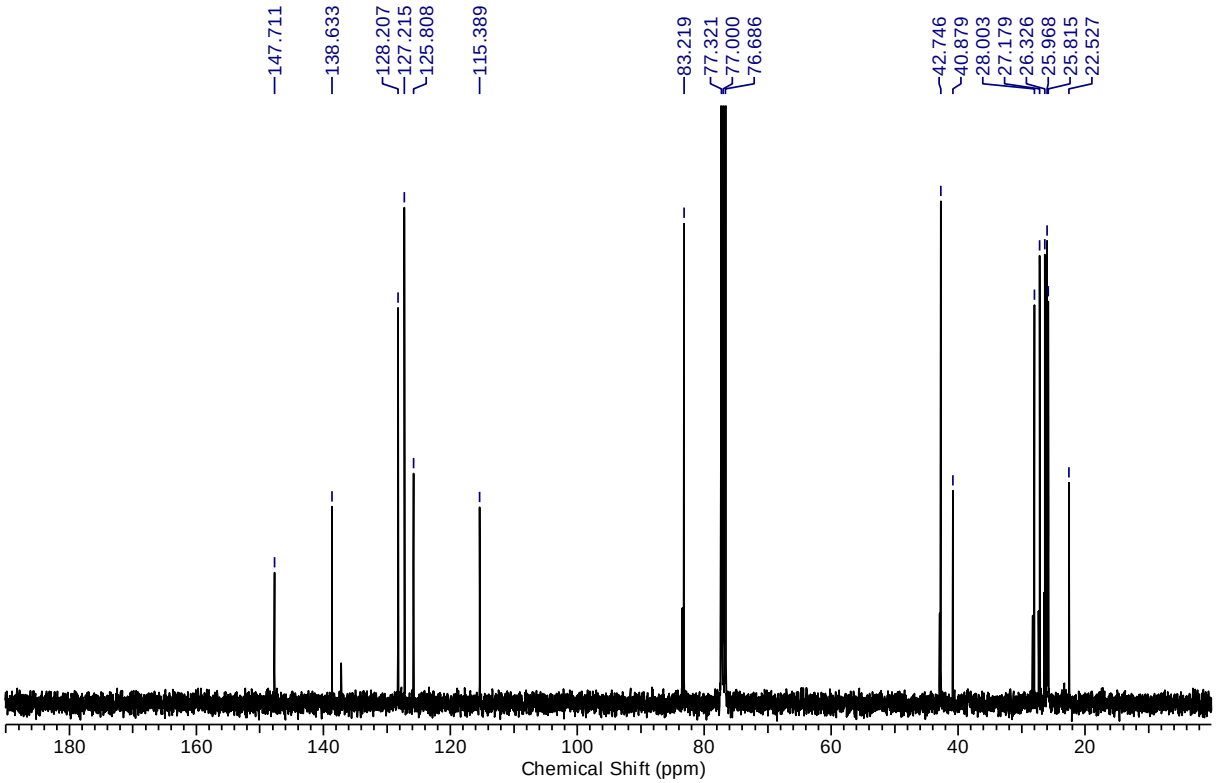


(4*S*,5*S*)-4,5-Dicyclohexyl-2-((3*R*,4*R*)-4-phenylpent-1-en-3-yl)-1,3,2-dioxa-borolane (4)

^{1}H-NMR (400 MHz, $CDCl_3$):

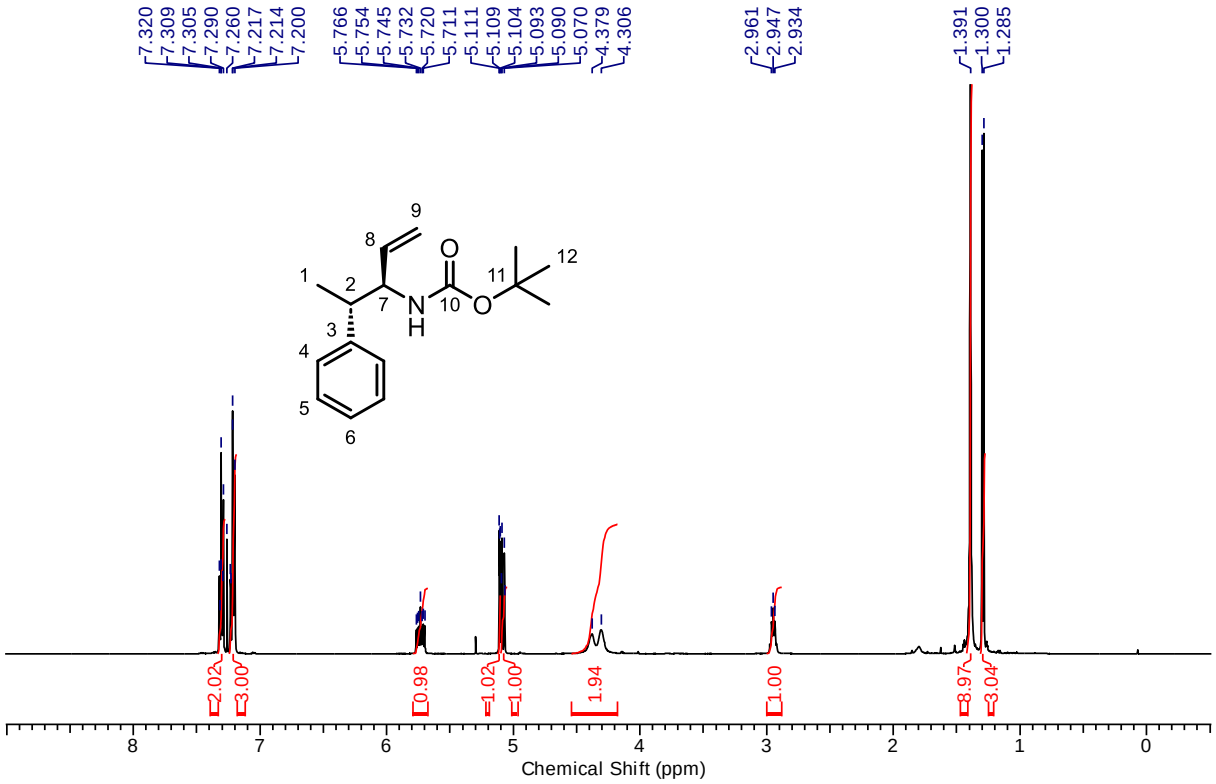


^{13}C-NMR (100 MHz, $CDCl_3$):

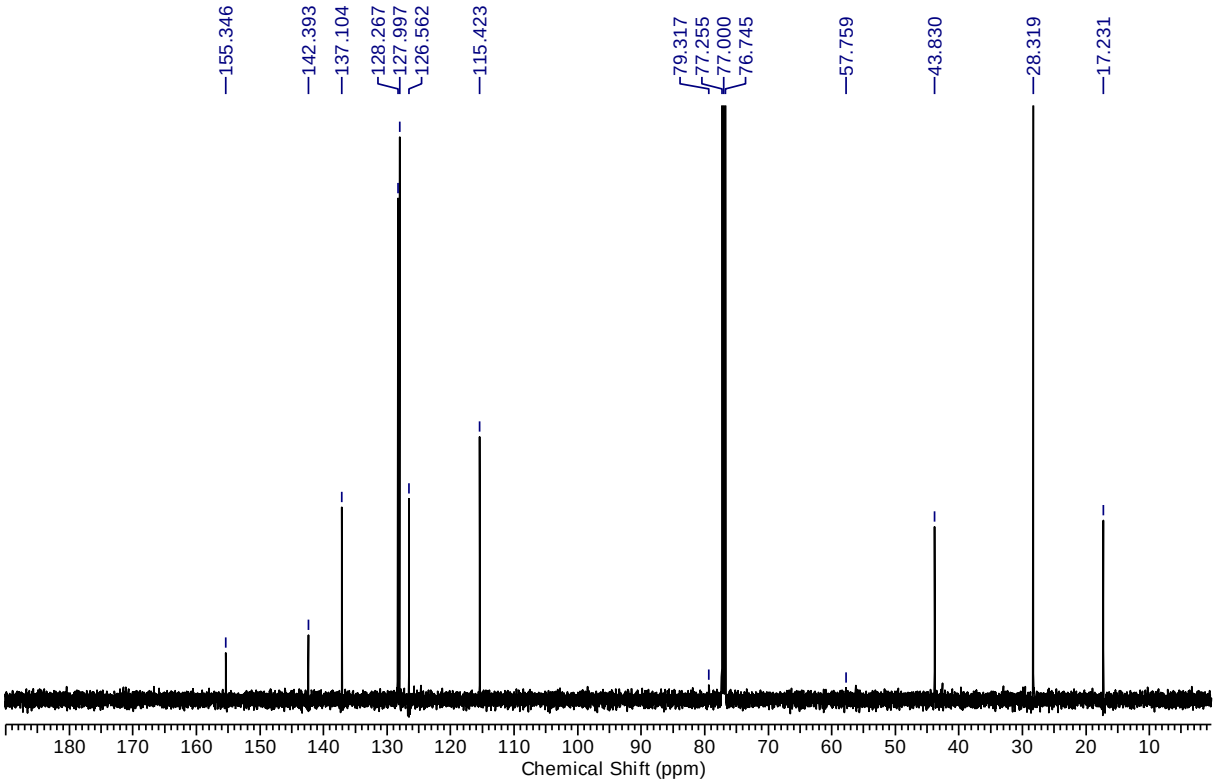


***tert*-Butyl((3*R*,4*S*)-4-phenylpent-1-en-3-yl)carbamate (5)**

^{1}H-NMR (500 MHz, $CDCl_3$):

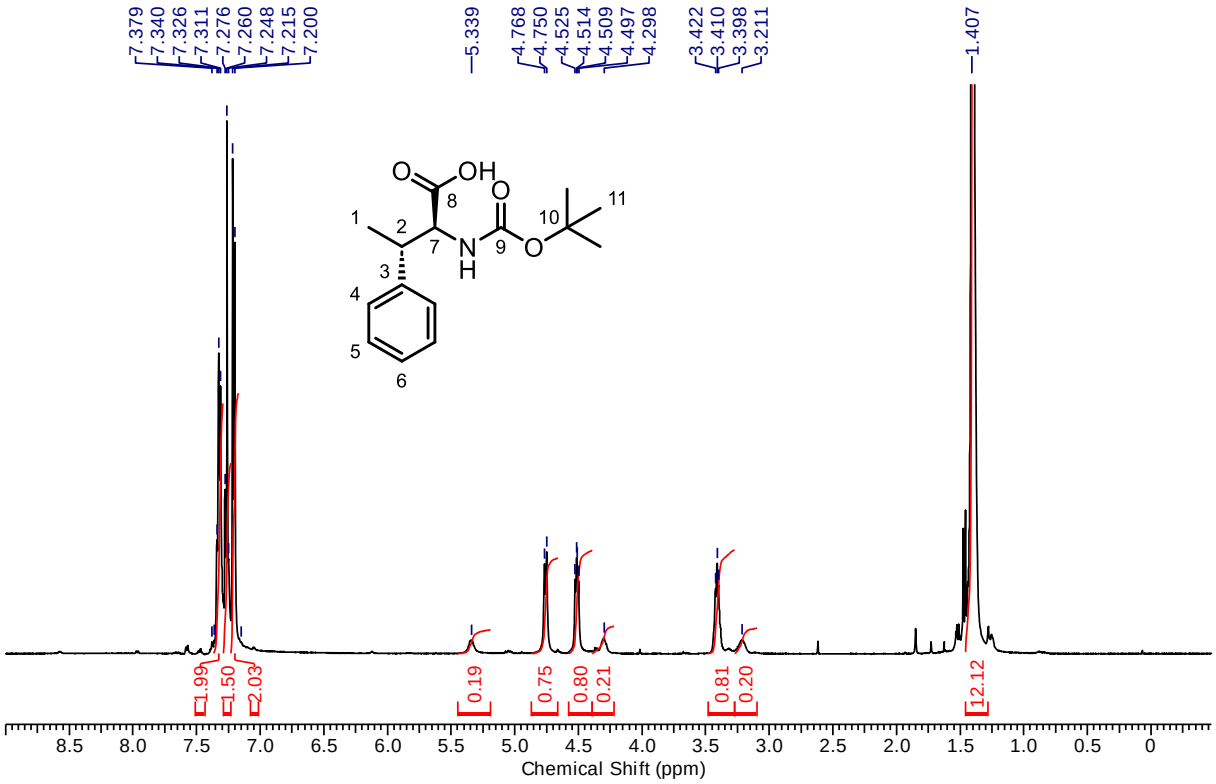


^{13}C-NMR (125 MHz, $CDCl_3$):

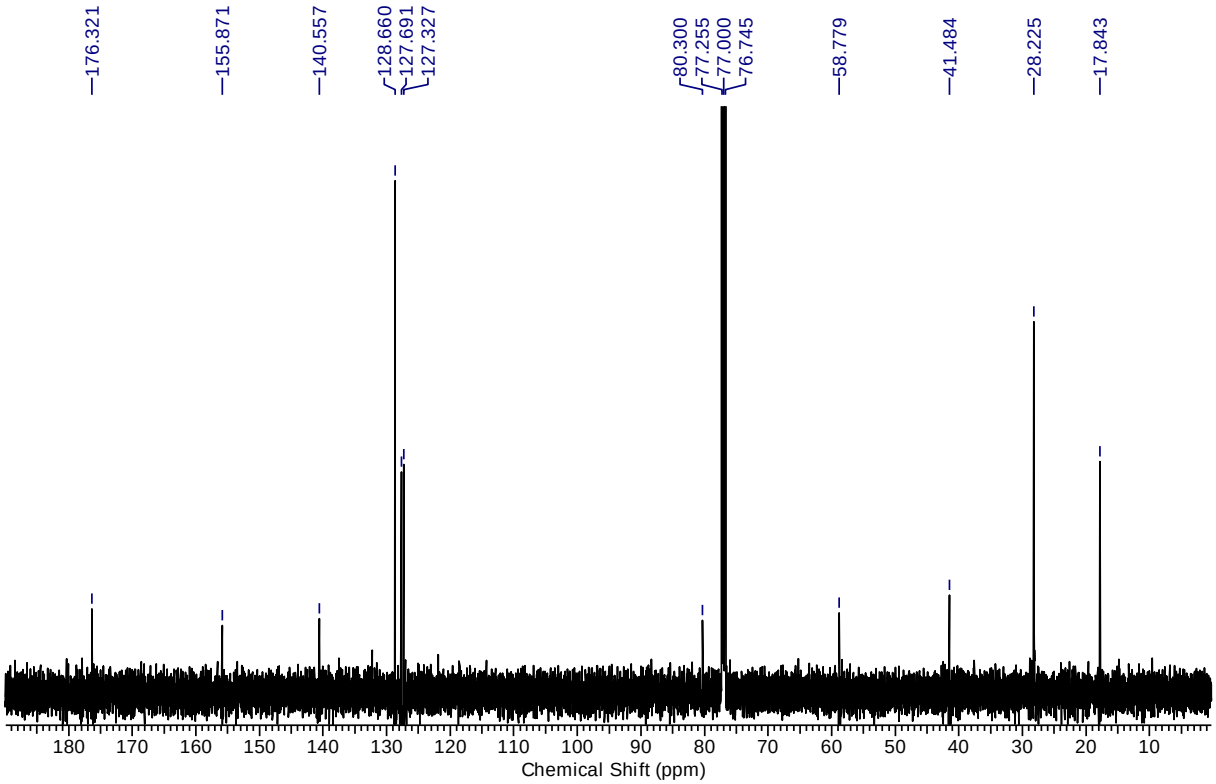


(*2S,3S*)-2-((*tert*-Butoxycarbonyl)amino)-3-phenylbutanoic acid (6)

^{1}H-NMR (500 MHz, $CDCl_3$):

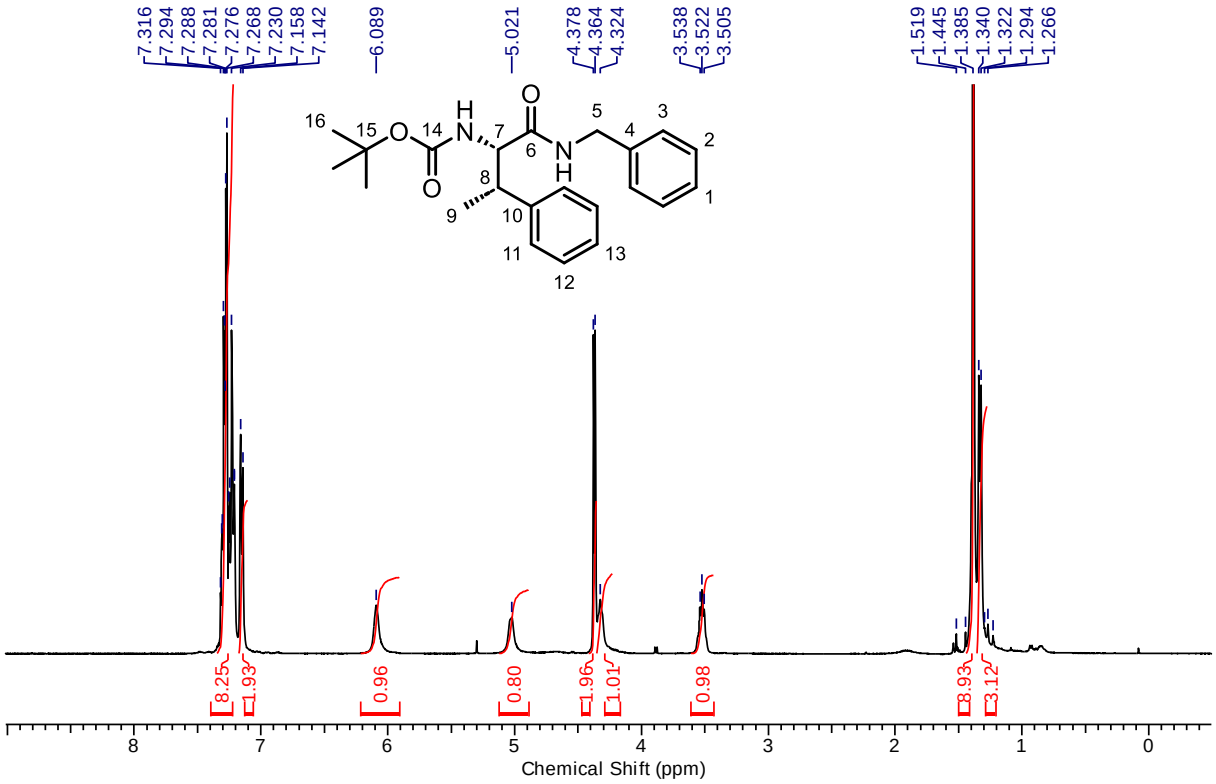


^{13}C-NMR (125 MHz, $CDCl_3$):

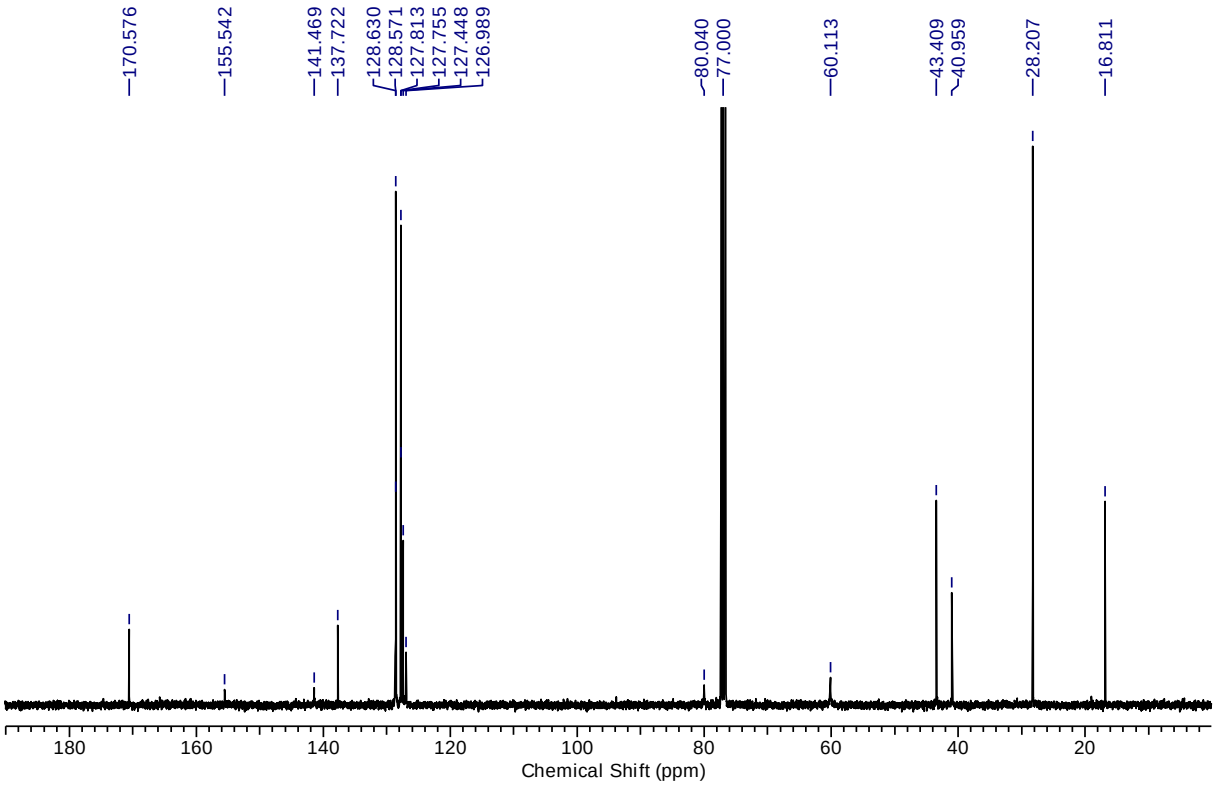


***tert*-Butyl ((*2S,3S*)-1-(benzylamino)-1-oxo-3-phenylbutane-2-yl)carbamate (7)**

^{1}H-NMR (400 MHz, $CDCl_3$):

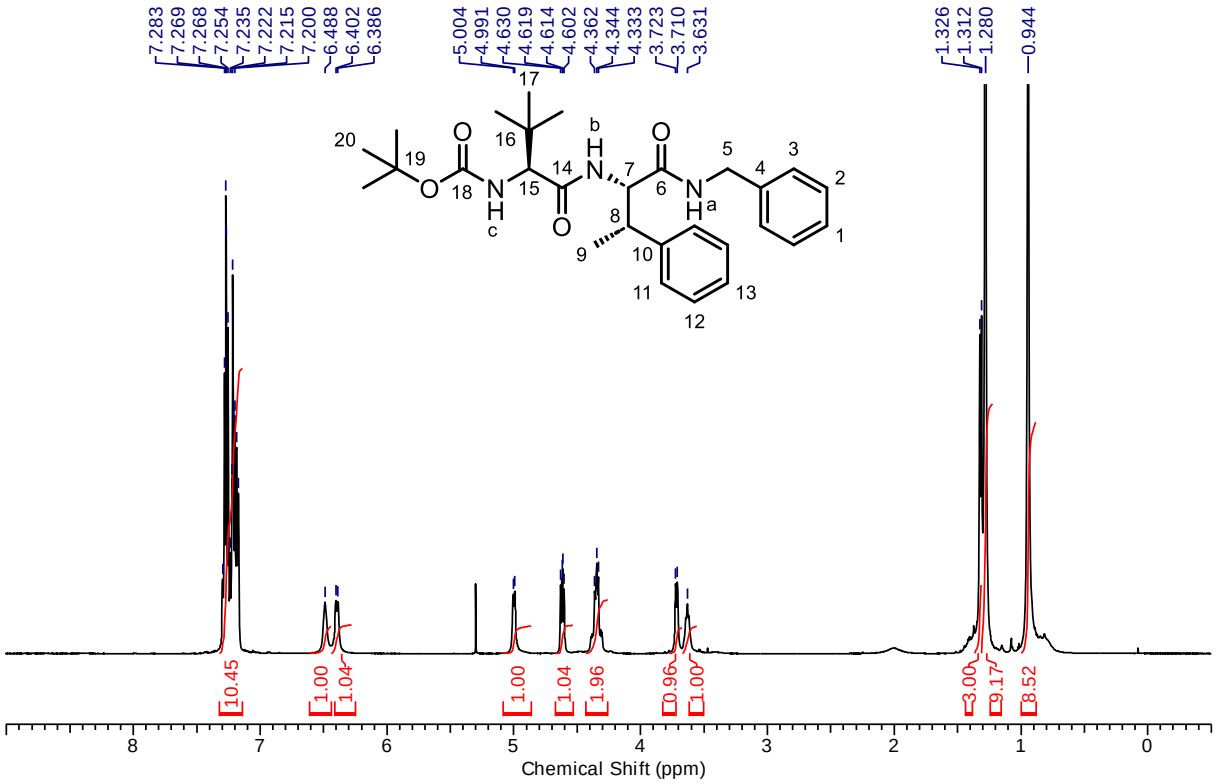


^{13}C-NMR (100 MHz, $CDCl_3$):

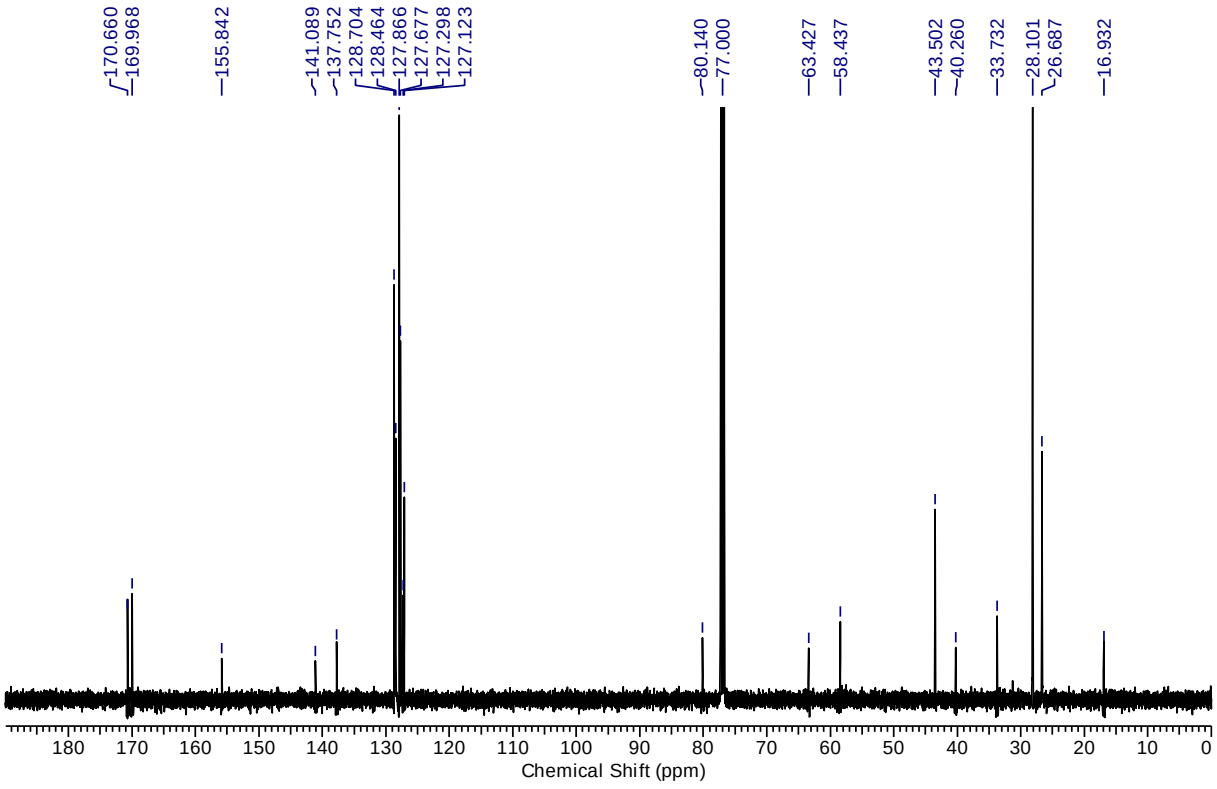


***tert*-Butyl((*S*)-1-(((*2S,3S*)-1-(benzylamino)-1-oxo-3-phenylbutane-2-yl)amino)-3,3-dimethyl-1-oxobutane-2-yl)carbamate (S1)**

^{1}H-NMR (500 MHz, $CDCl_3$):

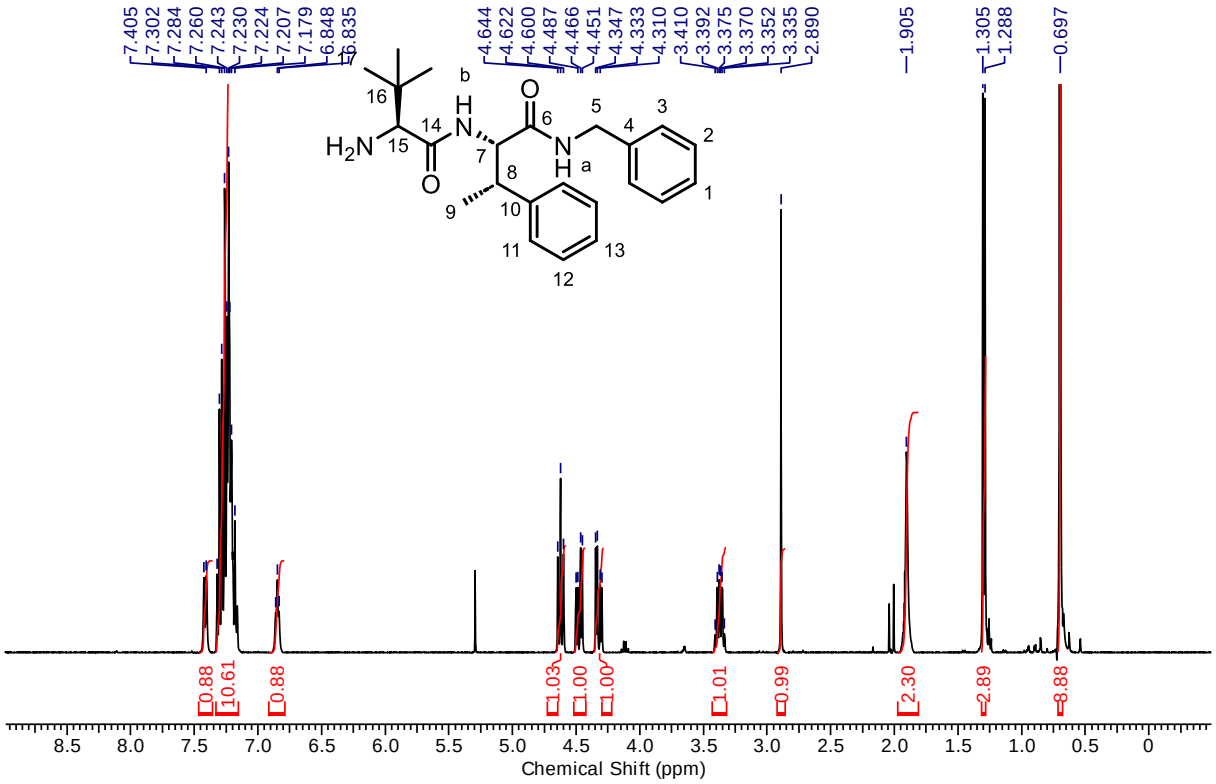


^{13}C-NMR (125 MHz, $CDCl_3$):

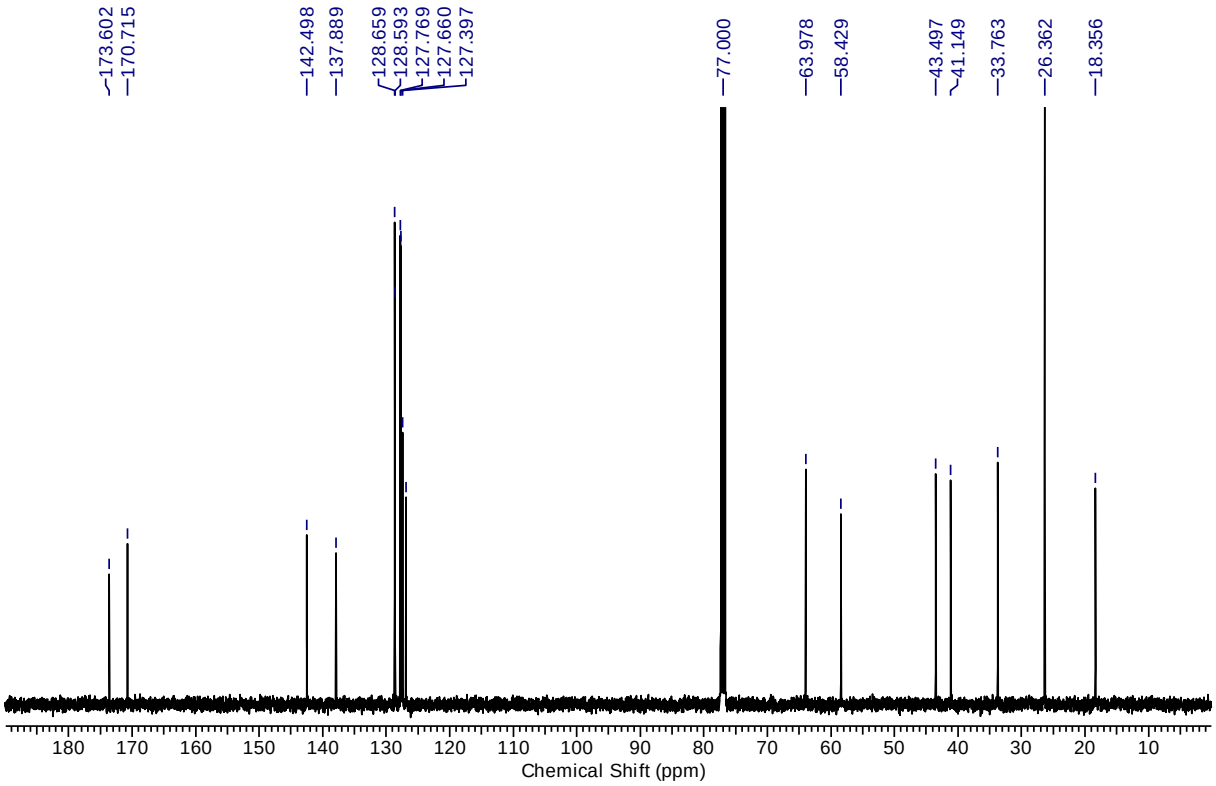


(*S*)-2-Amino-*N*-((2*S*,3*S*)-1-(benzylamino)-1-oxo-3-phenylbutane-2-yl)-3,3-dimethyl-butane-amide (8)

^{1}H-NMR (400 MHz, $CDCl_3$):

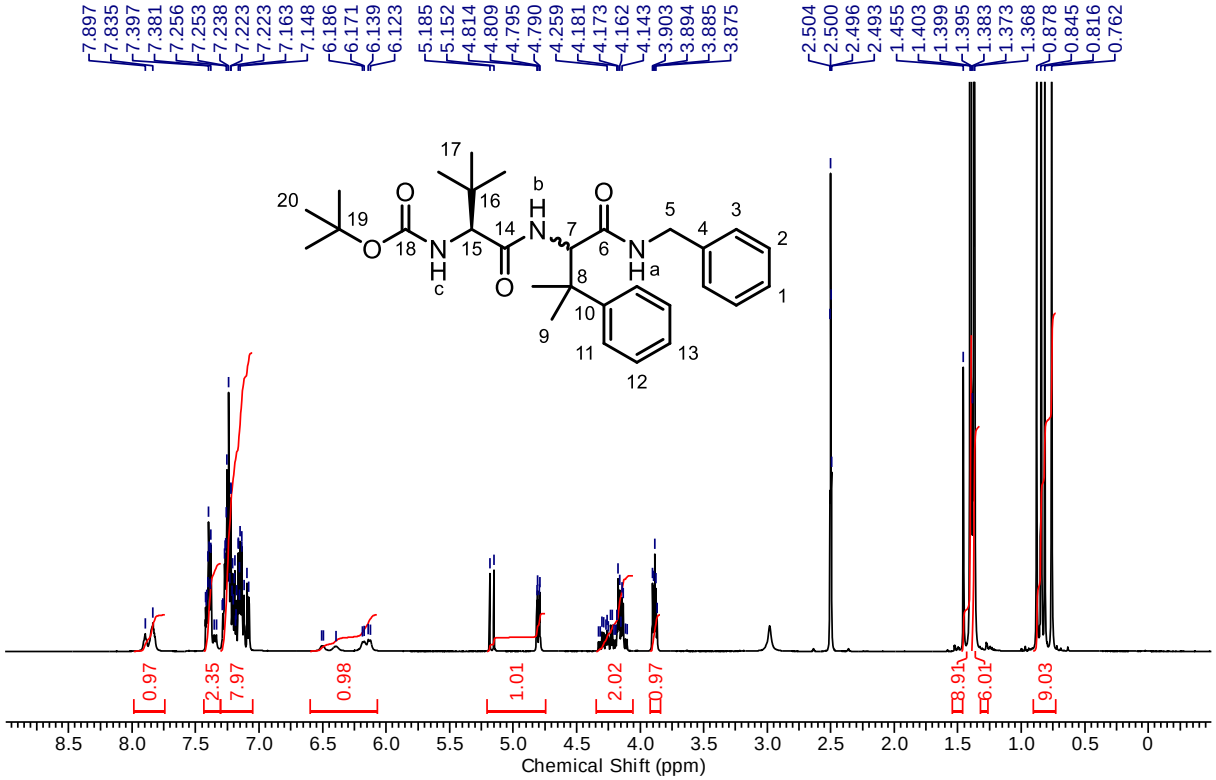


^{13}C-NMR (100 MHz, $CDCl_3$):

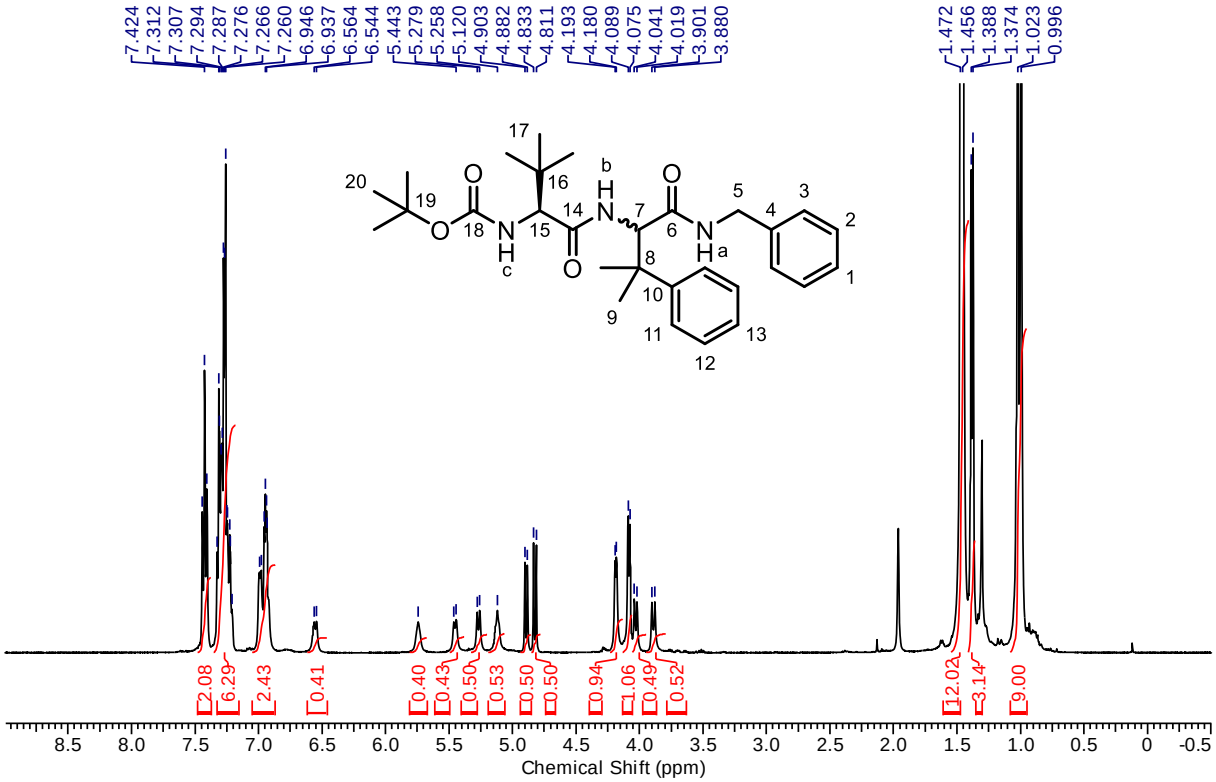


***tert*-Butyl((*S*)-1-(((*S*)-1-(benzylamino)-3-methyl-1-oxo-3-phenylbutane-2-yl)amino)-3,3-dimethyl-1-oxobutane-2-yl)carbamate (9)**

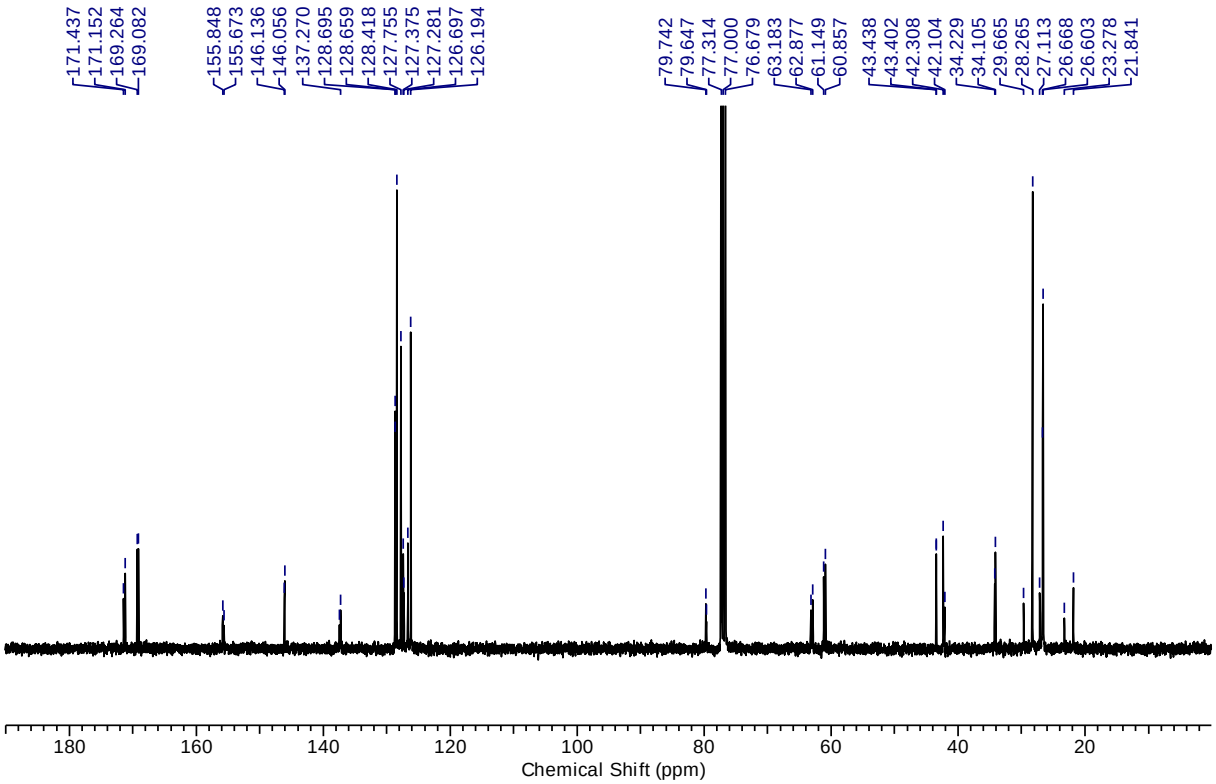
^{1}H-NMR (400 MHz, $CDCl_3$): **mixture of 4 isomers (diastereomers and rotamers)**



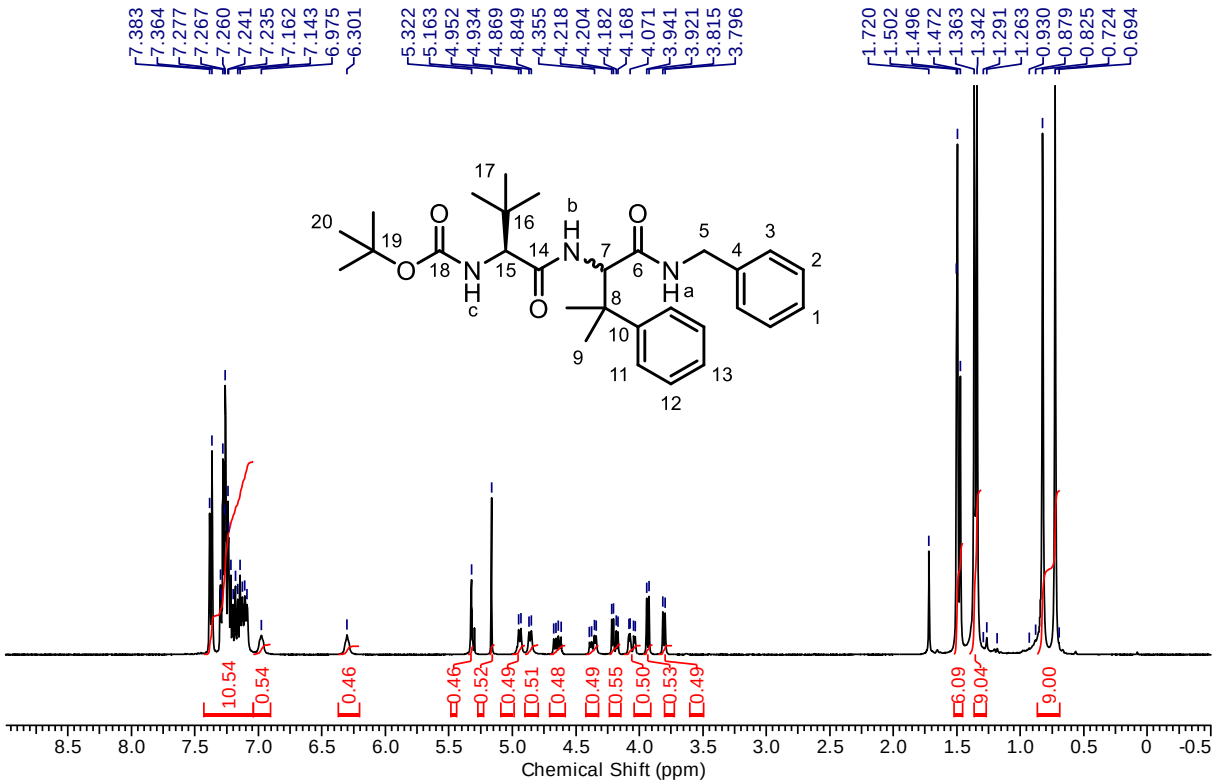
^{1}H-NMR (400 MHz, $CDCl_3$): **major diastereomer (mixture of rotamers)**



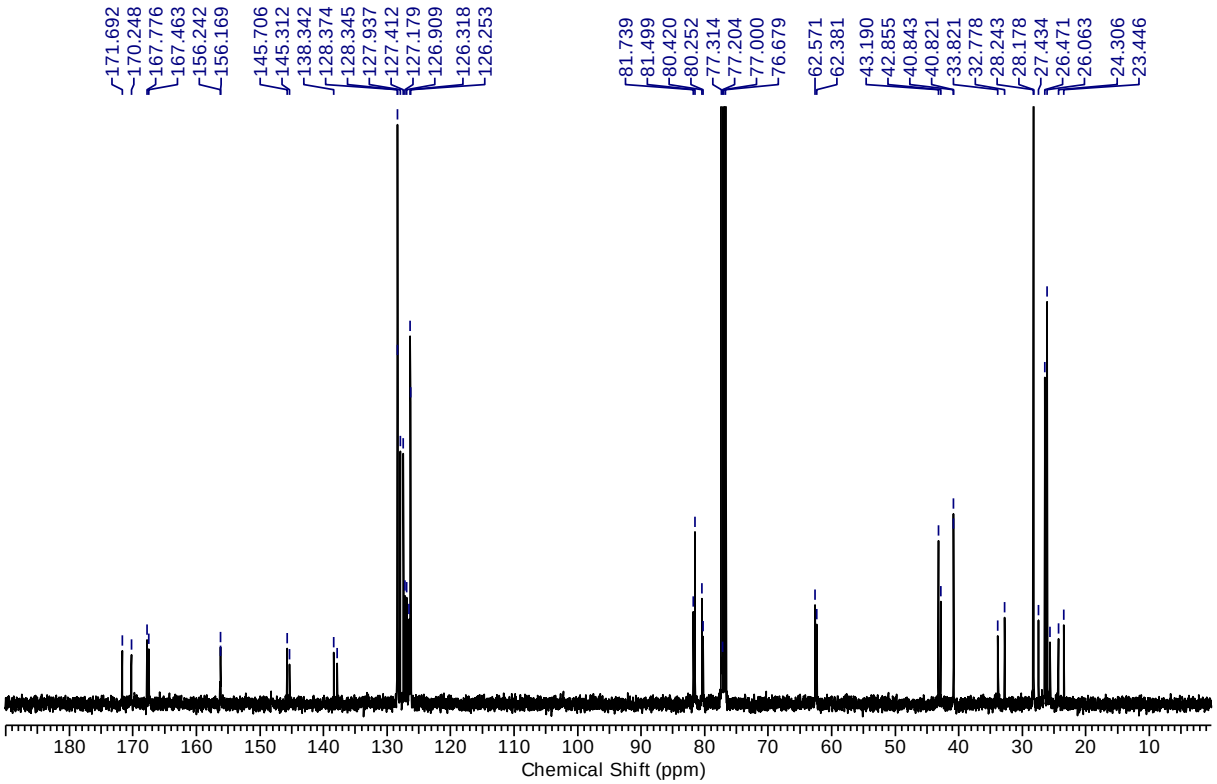
^{13}C-NMR(100 MHz, $CDCl_3$):



^{1}H-NMR(400 MHz, $CDCl_3$): **minor diastereomer (mixture of rotamers)**

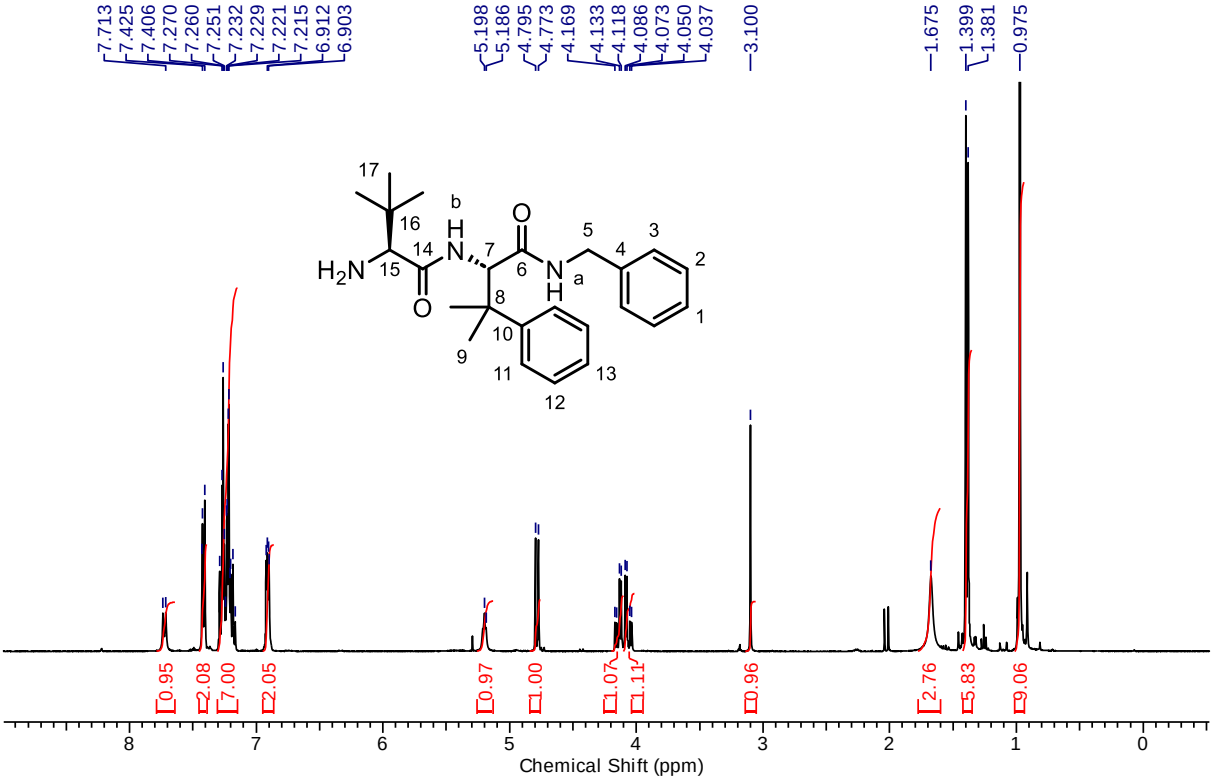


^{13}C-NMR(100 MHz, $CDCl_3$): **side isomers**

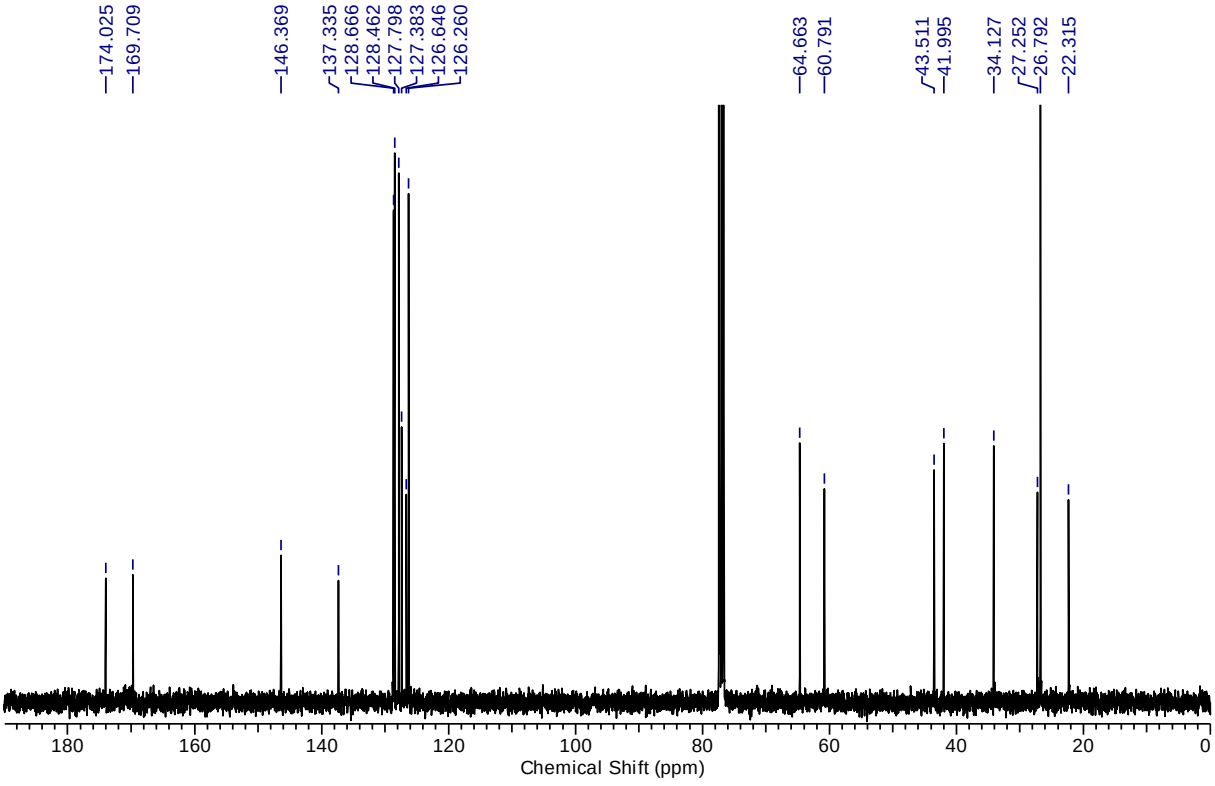


(*S*)-2-Amino-*N*-((*S*)-1-(benzylamino)-3-methyl-1-oxo-3-phenylbutane-2-yl)-3,3-dimethyl-butanamide [(*S*,*S*)-10]

^{1}H-NMR(400 MHz, $CDCl_3$):

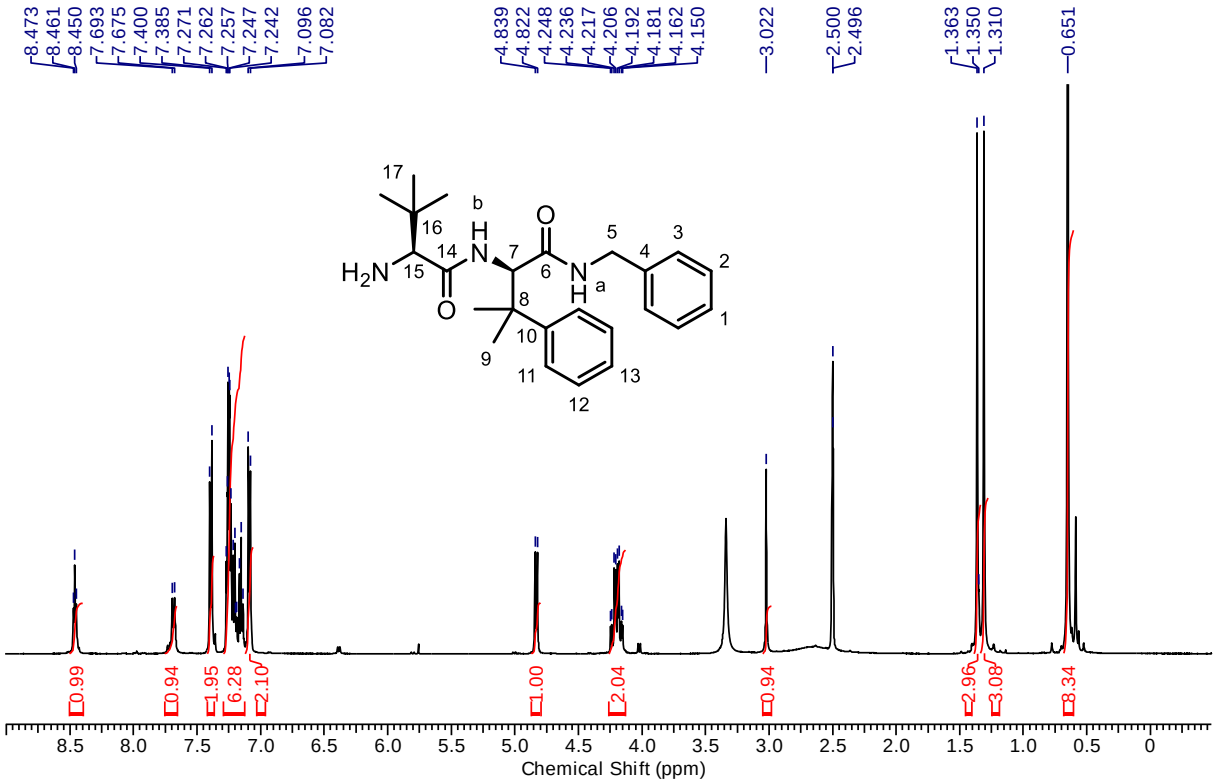


^{13}C-NMR(100 MHz, $CDCl_3$):

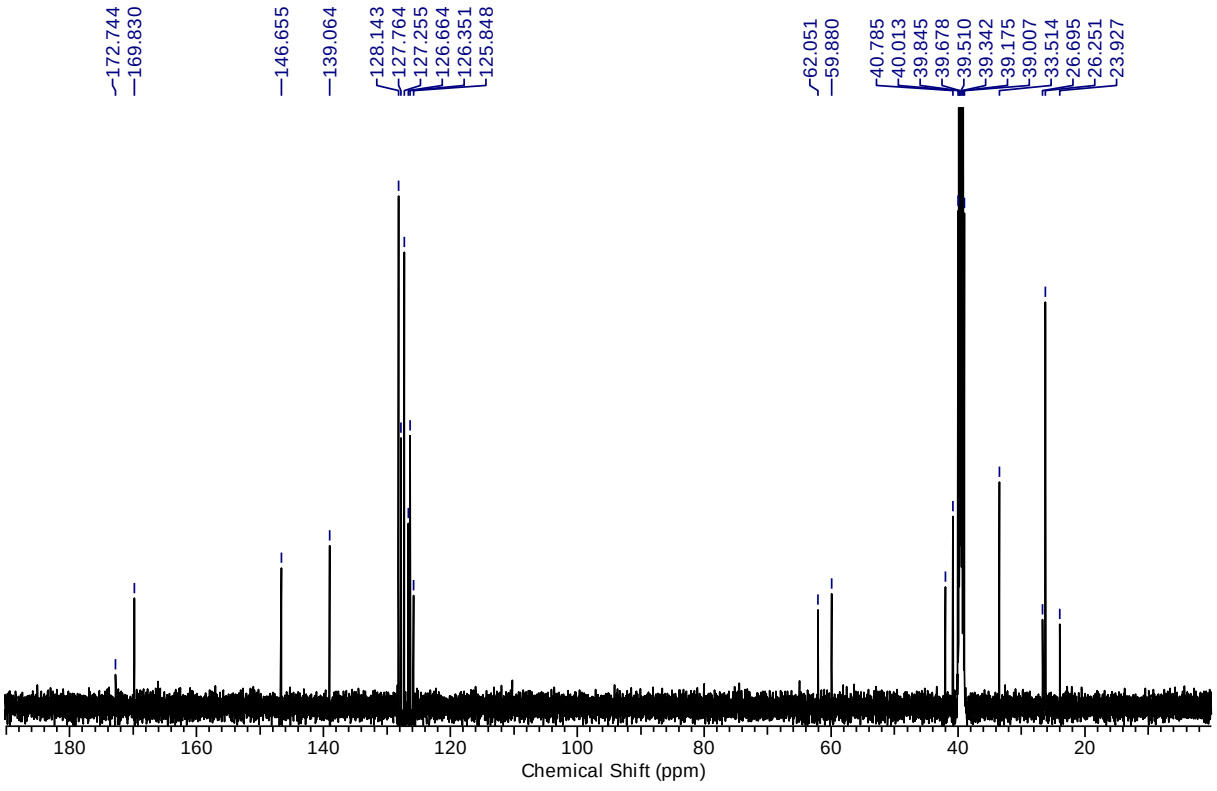


(*S*)-2-Amino-*N*-((*R*)-1-(benzylamino)-3-methyl-1-oxo-3-phenylbutane-2-yl)-3,3-dimethyl-butanamide [(*S*,*R*)-10]

^{1}H-NMR(500 MHz, DMSO-d_6):

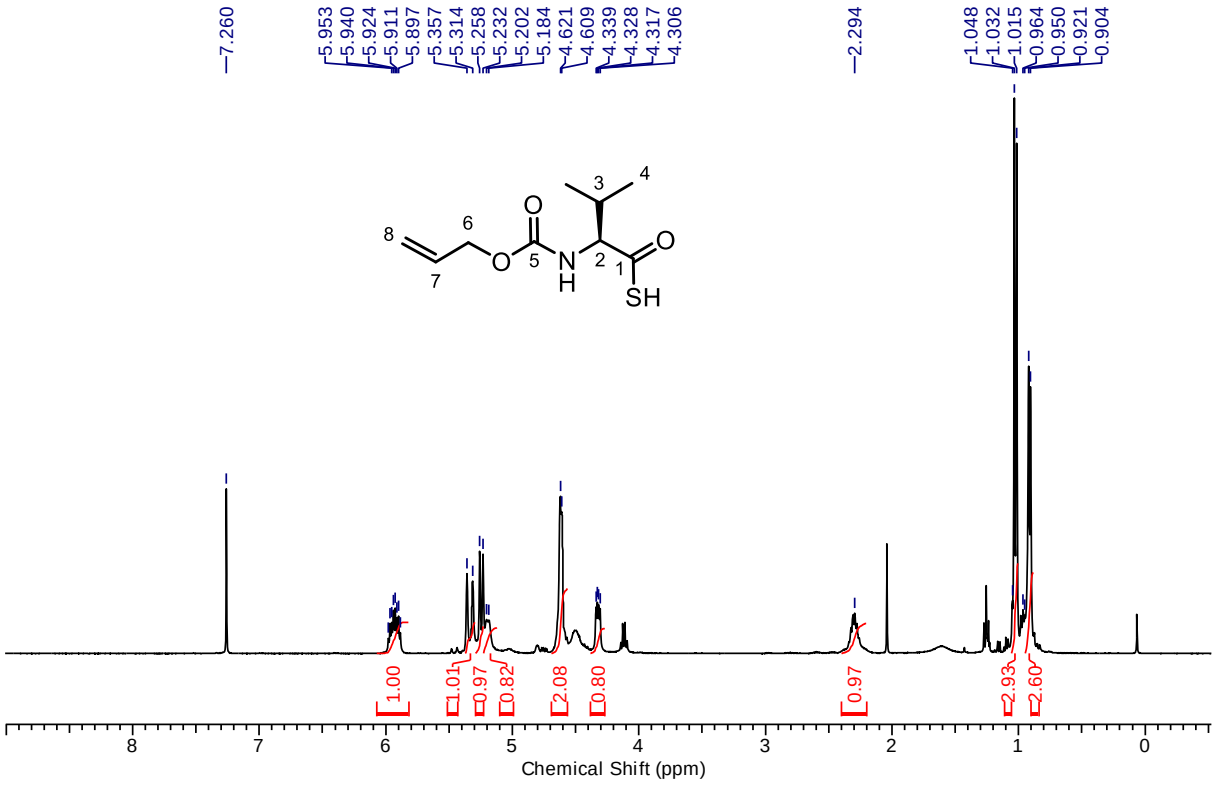


^{13}C-NMR(125 MHz, DMSO-d_6):

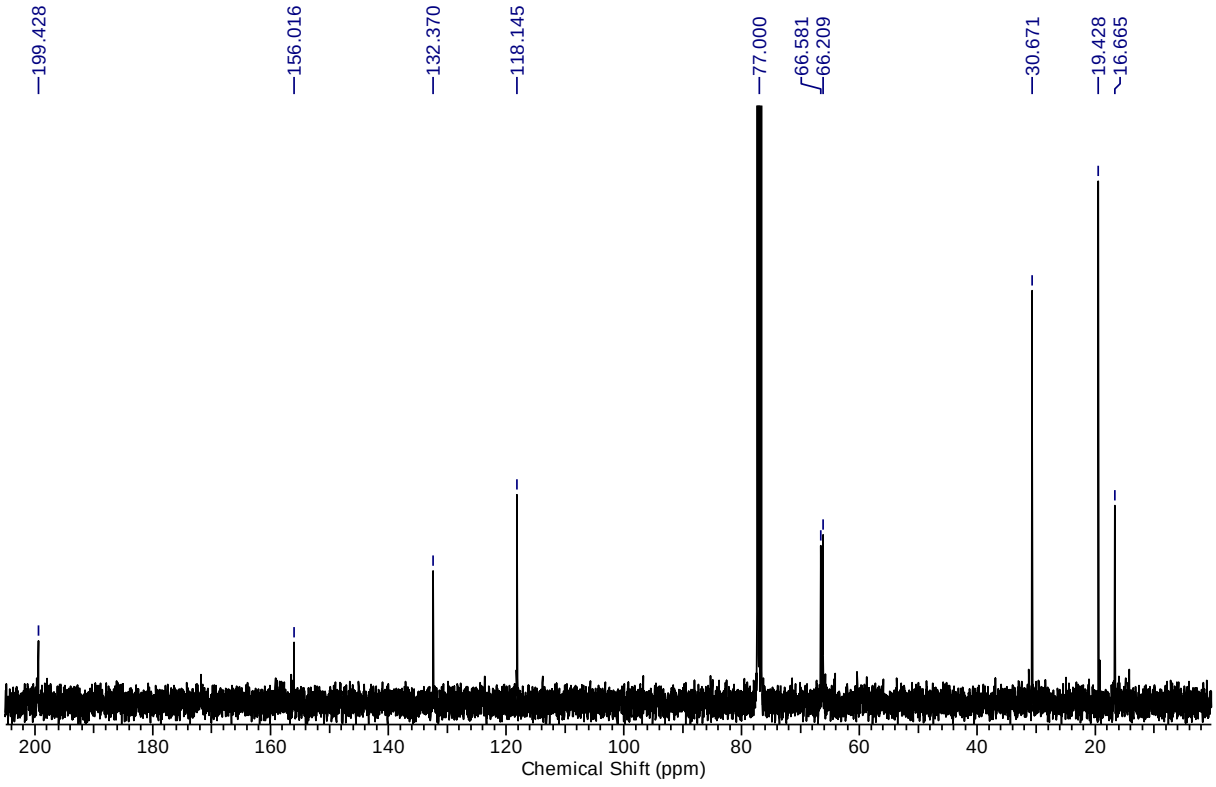


Alloc-Val-SH (11)

^{1}H-NMR(400 MHz, $CDCl_3$):

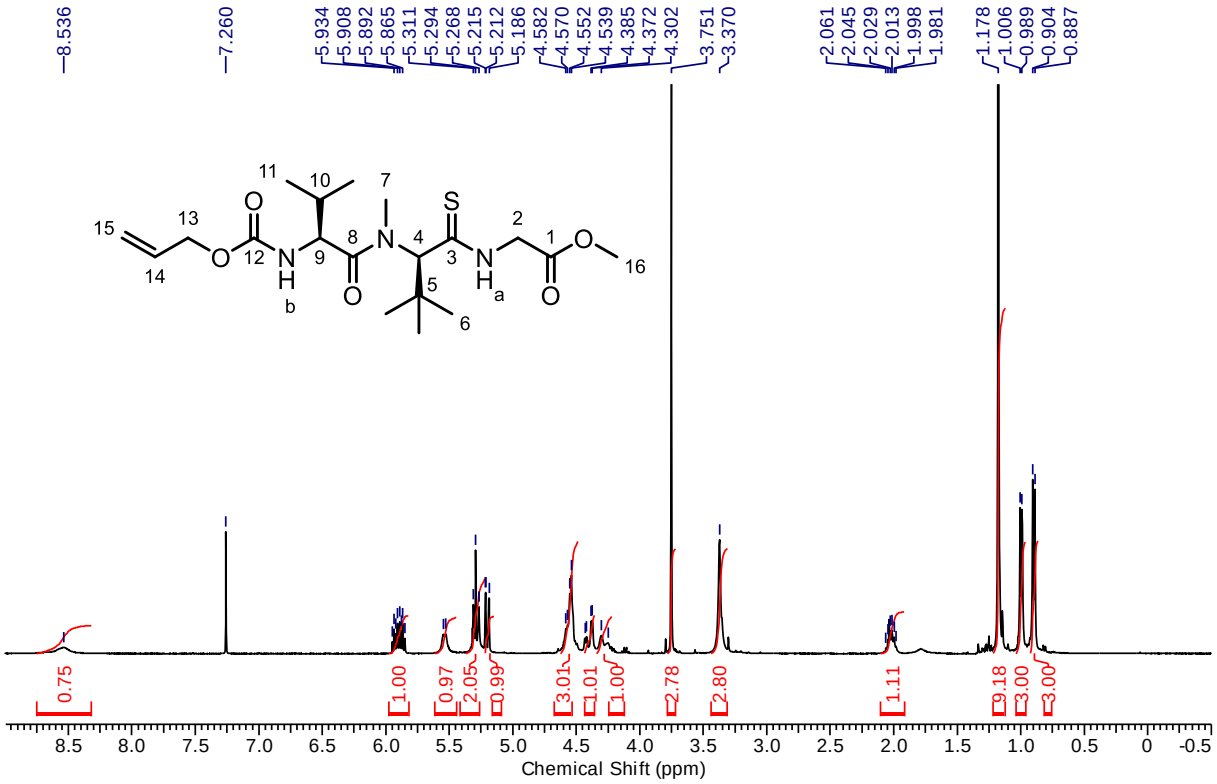


^{13}C-NMR(100 MHz, $CDCl_3$):

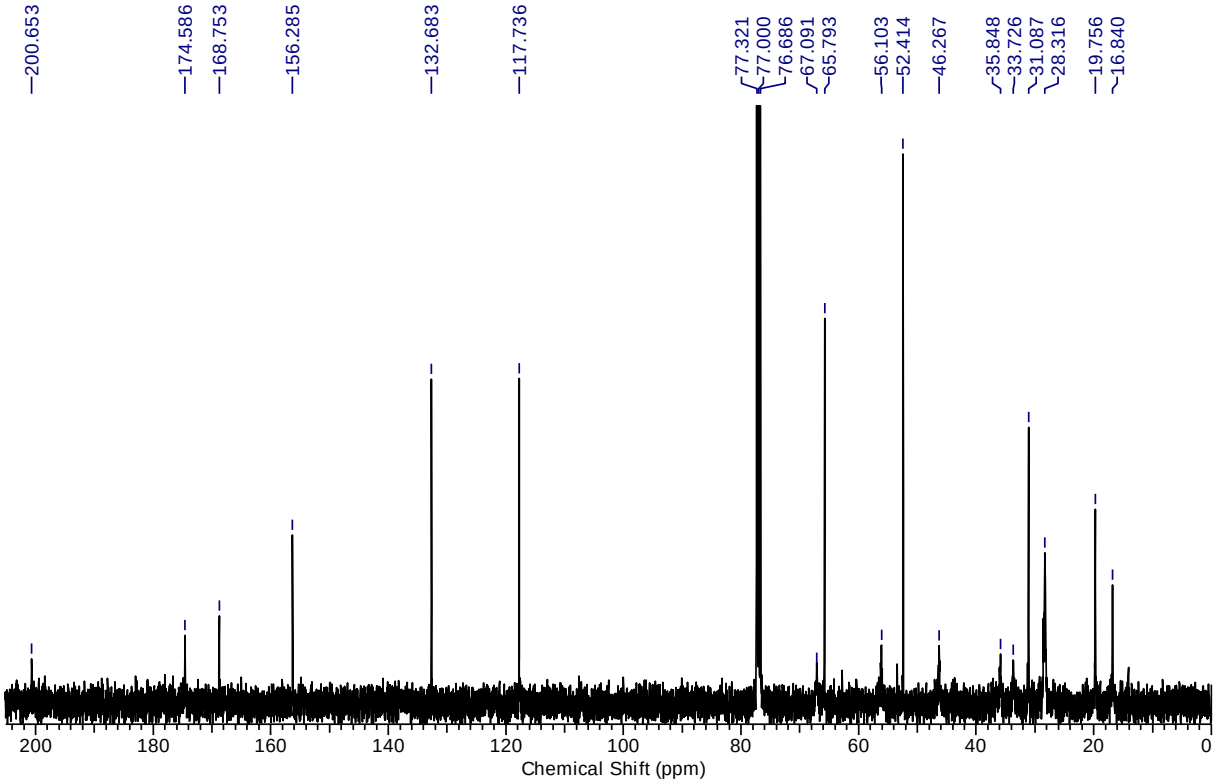


Methyl((*R*)-2-((*S*)-2-(((allyloxy)carbonyl)amino)-*N*,3-dimethylbutanamido)-3,3-dimethylbutanthioyl)glycinate [(*S*,*R*)-12)

^{1}H-NMR(400 MHz, $CDCl_3$):

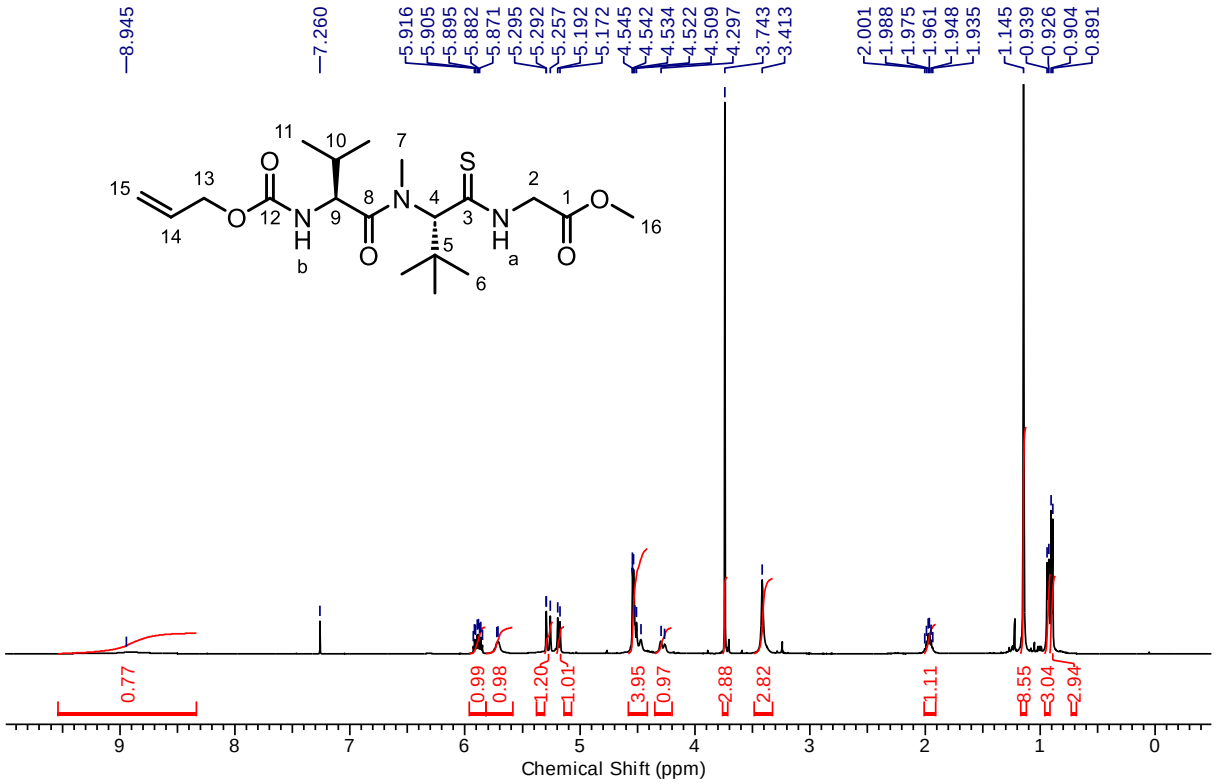


^{13}C-NMR(100 MHz, $CDCl_3$):

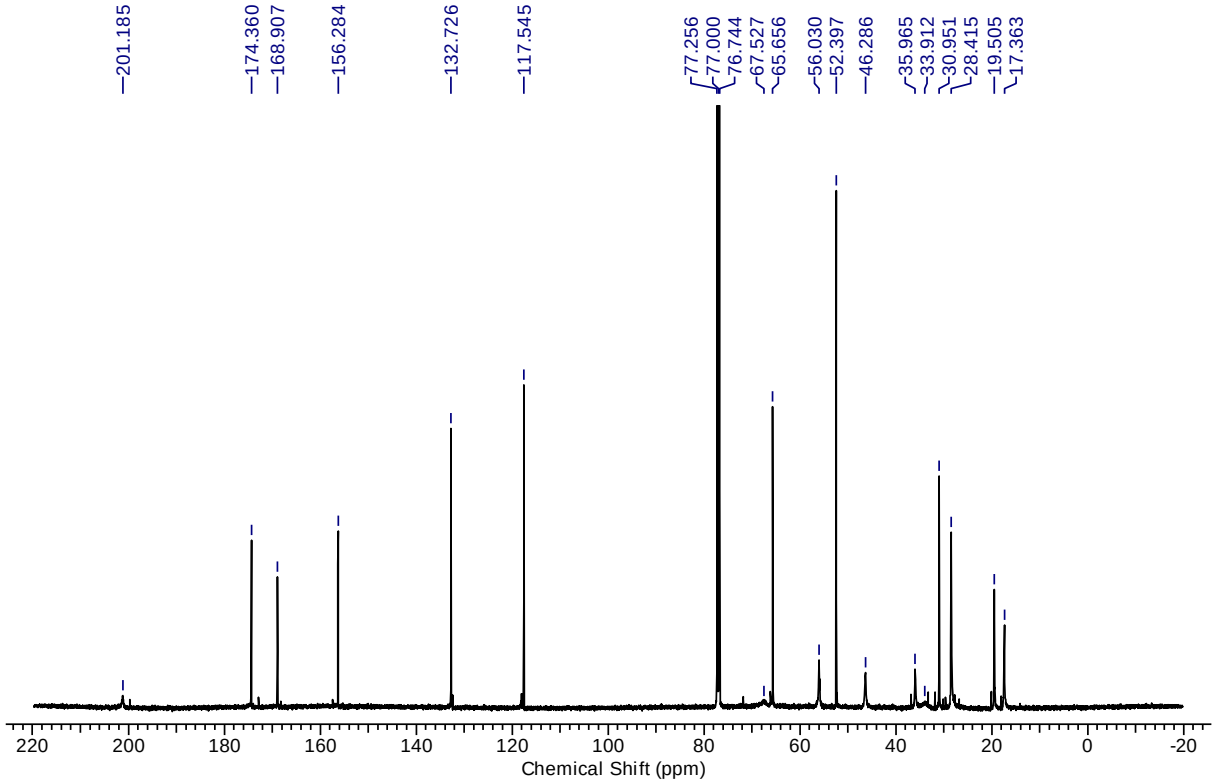


Methyl((*S*)-2-((*S*)-2-(((allyloxy)carbonyl)amino)-*N*,3-dimethylbutanamido)-3,3-dimethylbutanthioyl)glycinate [(S,S)-12]

^{1}H-NMR(500 MHz, $CDCl_3$):

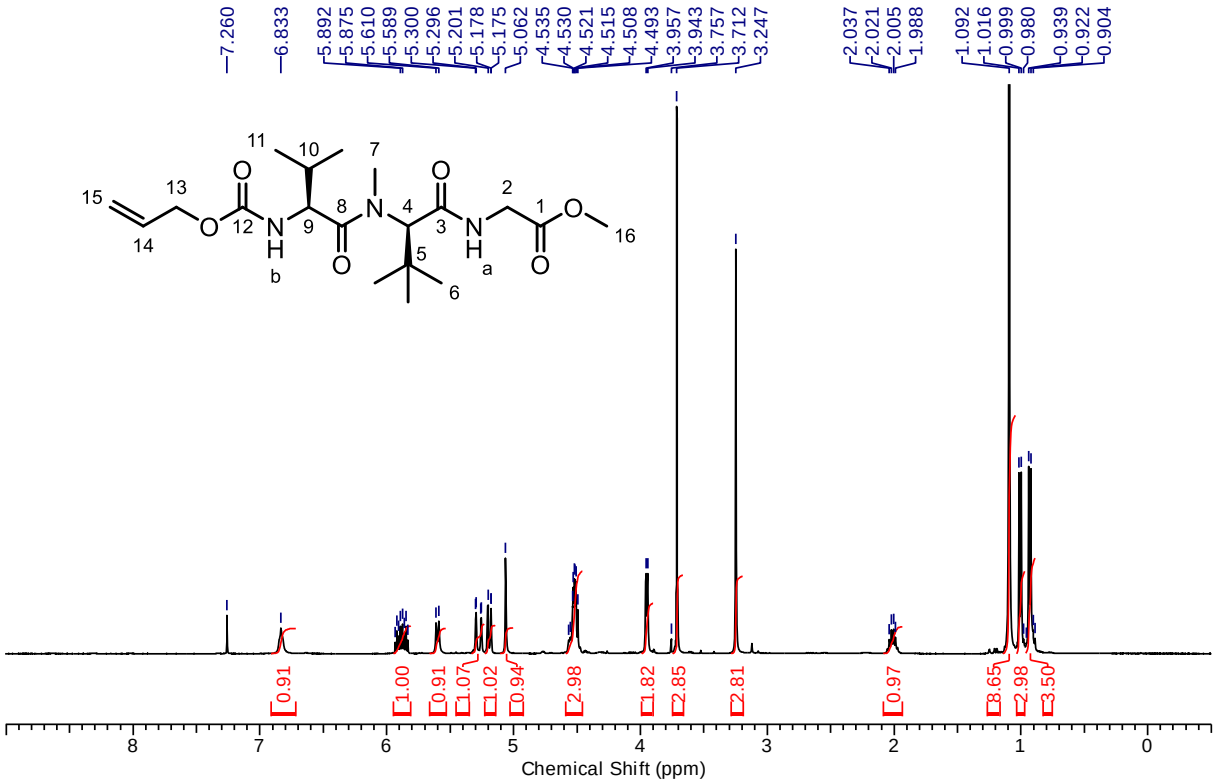


^{13}C-NMR(125 MHz, $CDCl_3$):

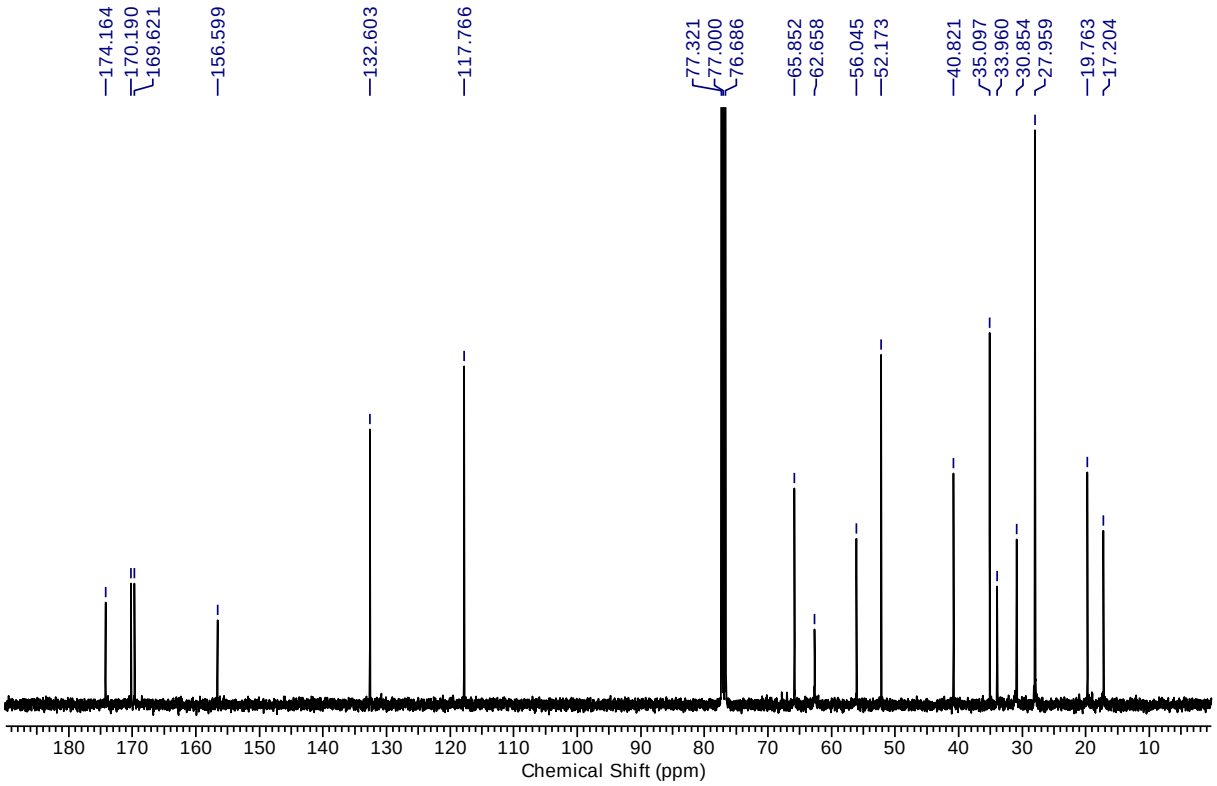


Methyl((*R*)-2-((*S*)-2-(((allyloxy)carbonyl)amino)-*N*,3-dimethylbutanamido)-3,3-dimethylbutanoyl)glycinate [(S,*R*)-13]

^{1}H-NMR(400 MHz, $CDCl_3$):

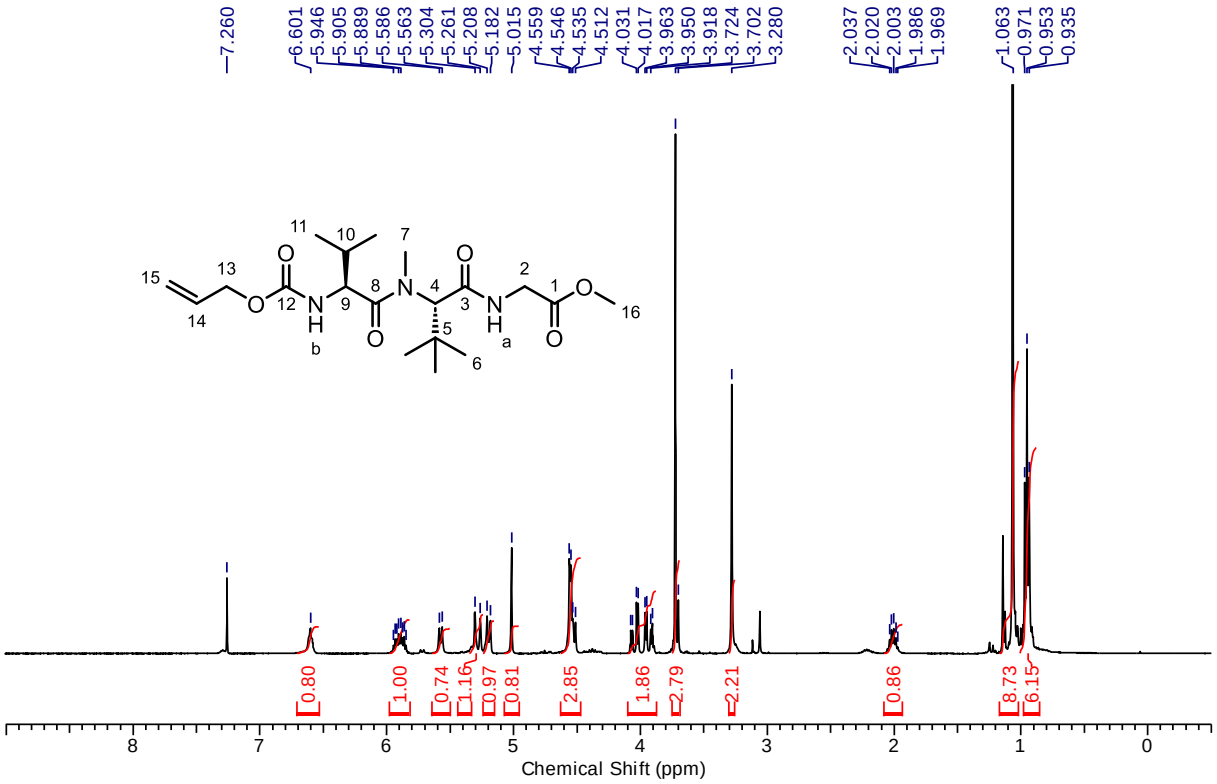


^{13}C-NMR(100 MHz, $CDCl_3$):

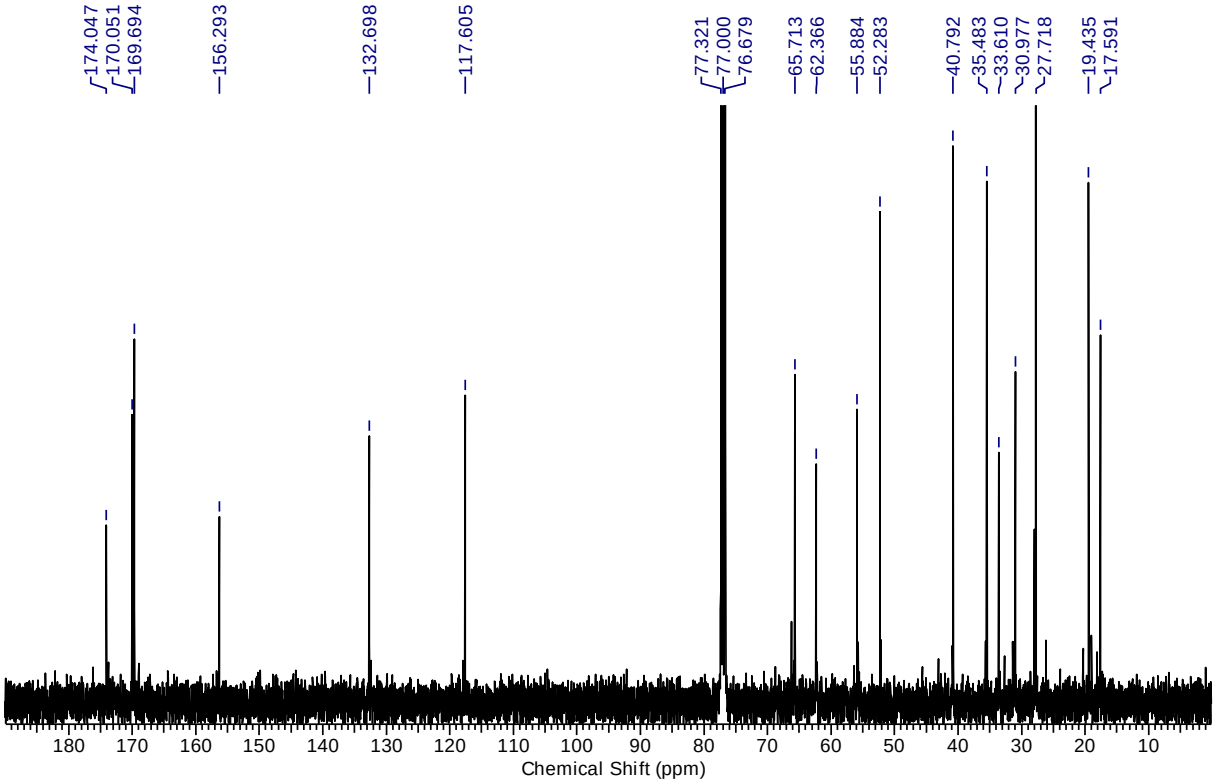


Methyl((*S*)-2-((*S*)-2-(((allyloxy)carbonyl)amino)-*N*,3-dimethylbutanamido)-3,3-dimethylbutanoyl)glycinate [(*S*,*S*)-13]

^{1}H-NMR(400 MHz, $CDCl_3$):

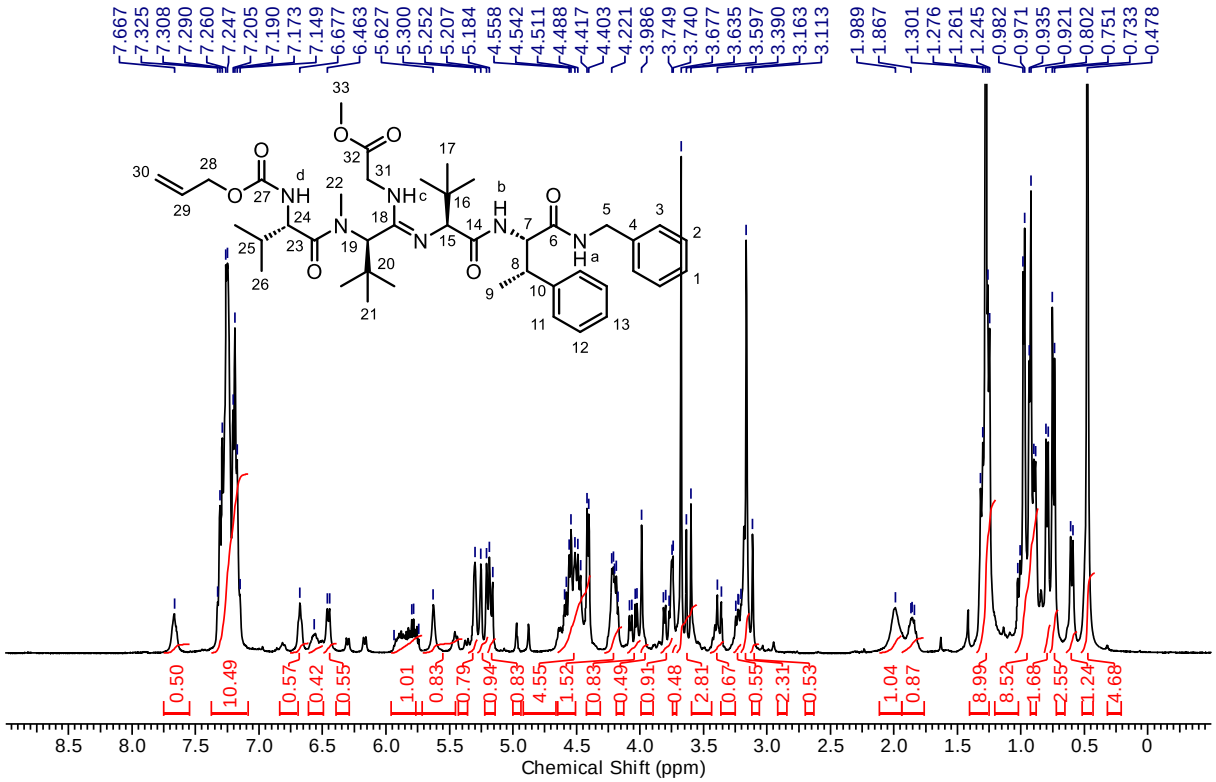


^{13}C-NMR(100 MHz, $CDCl_3$):

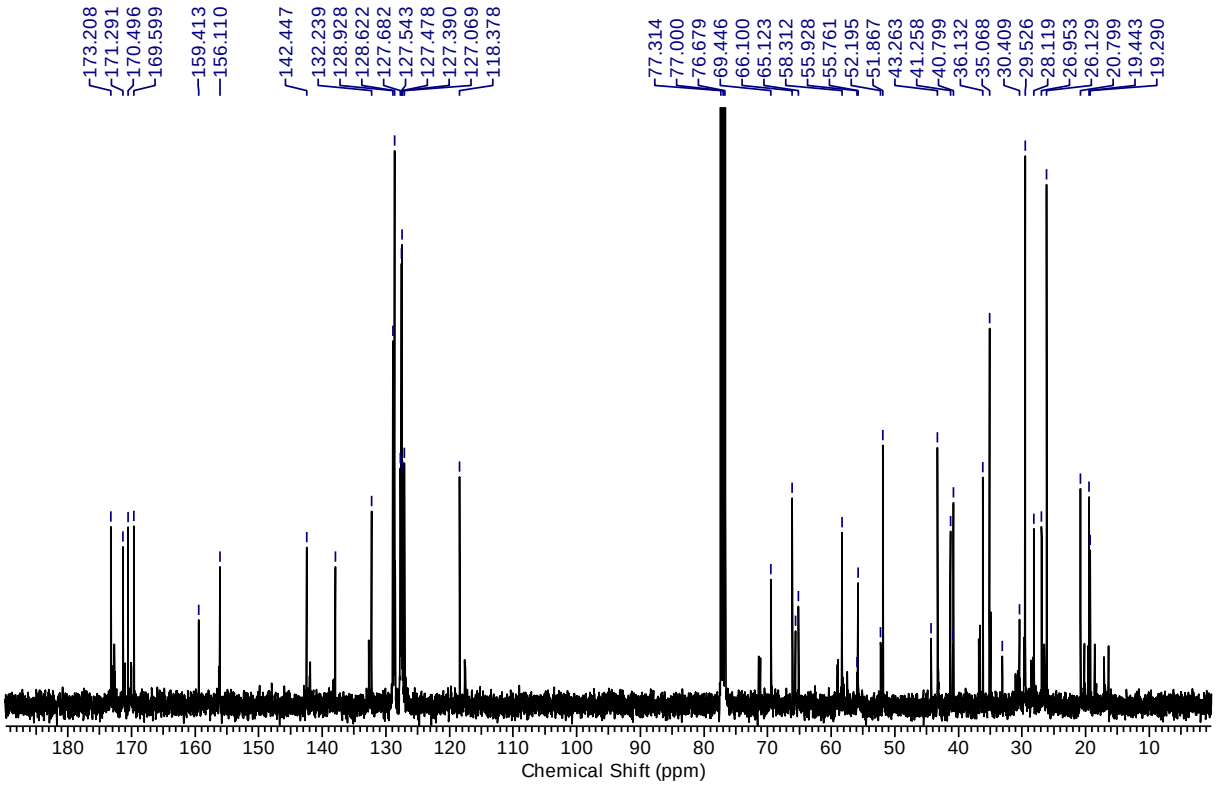


Methyl((*R*,*Z*)-2-((*S*)-2-(((allyloxy)carbonyl)amino)-*N*,3-dimethylbutanamido)-1-(((*S*)-1-(((2*S*,3*S*)-1-(benzylamino)-1-oxo-3-phenylbutane-2-yl)amino)-3,3-dimethyl-1-oxobutane-2-yl)imino)-3,3-dimethylbutyl)glycinate (14a)

^{1}H-NMR(400 MHz, $CDCl_3$):

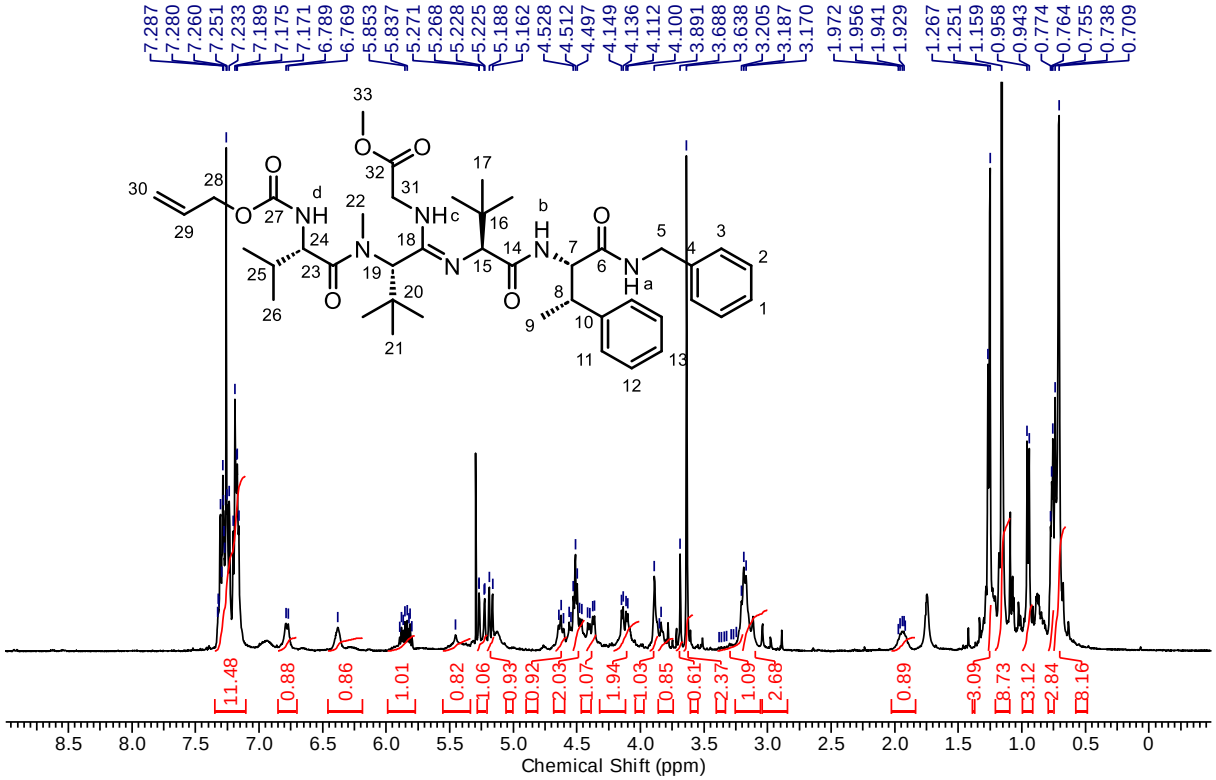


^{13}C-NMR(100 MHz, $CDCl_3$):

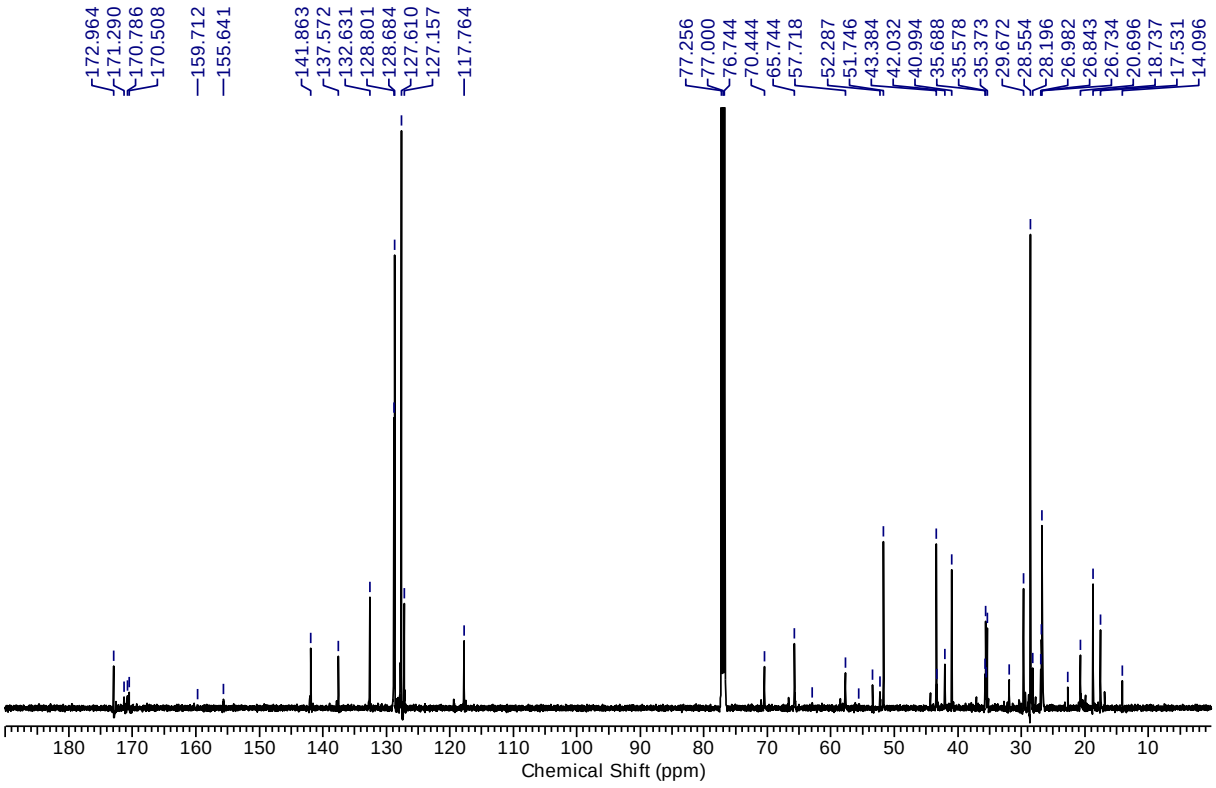


Methyl((*S*,*Z*)-2-((*S*)-2-(((allyloxy)carbonyl)amino)-*N*,3-dimethylbutanamido)-1-(((*S*)-1-(((2*S*,3*S*)-1-(benzylamino)-1-oxo-3-phenylbutane-2-yl)amino)-3,3-dimethyl-1-oxobutane-2-yl)imino)-3,3-dimethylbutyl)glycinate (14b)

^{1}H-NMR(400 MHz, $CDCl_3$):

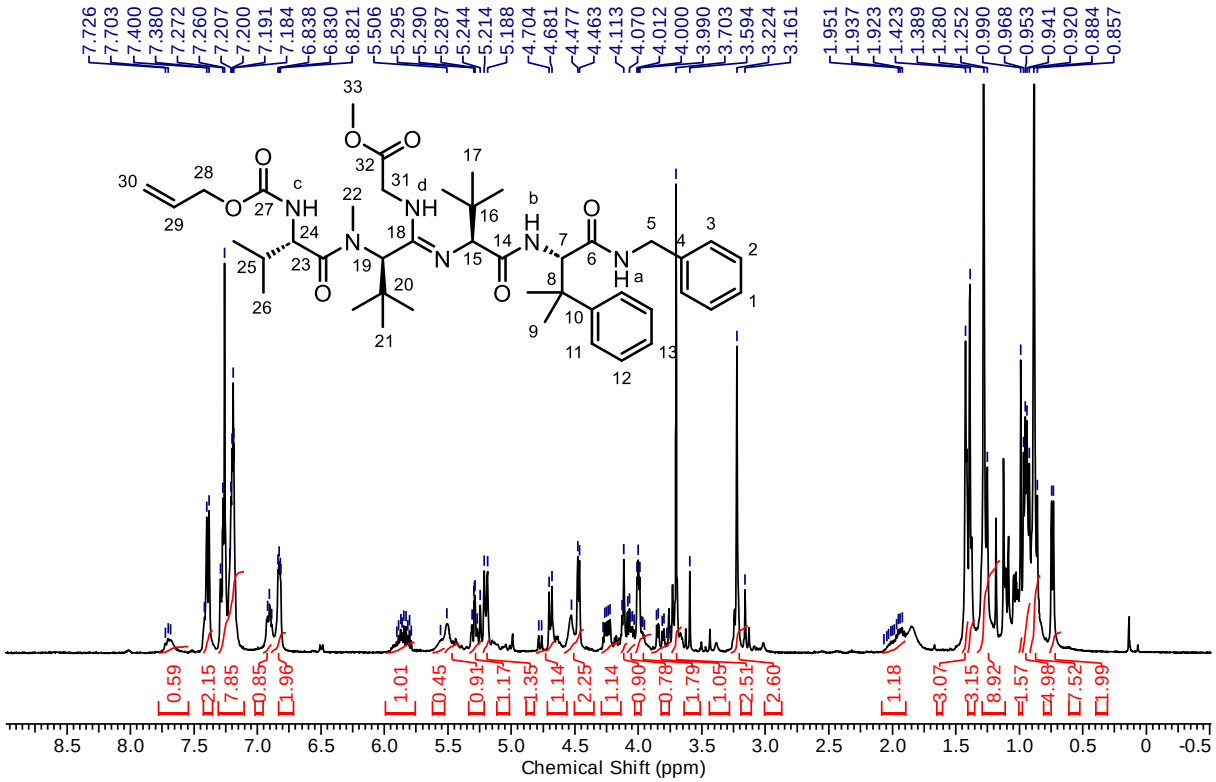


^{13}C-NMR(125 MHz, $CDCl_3$):

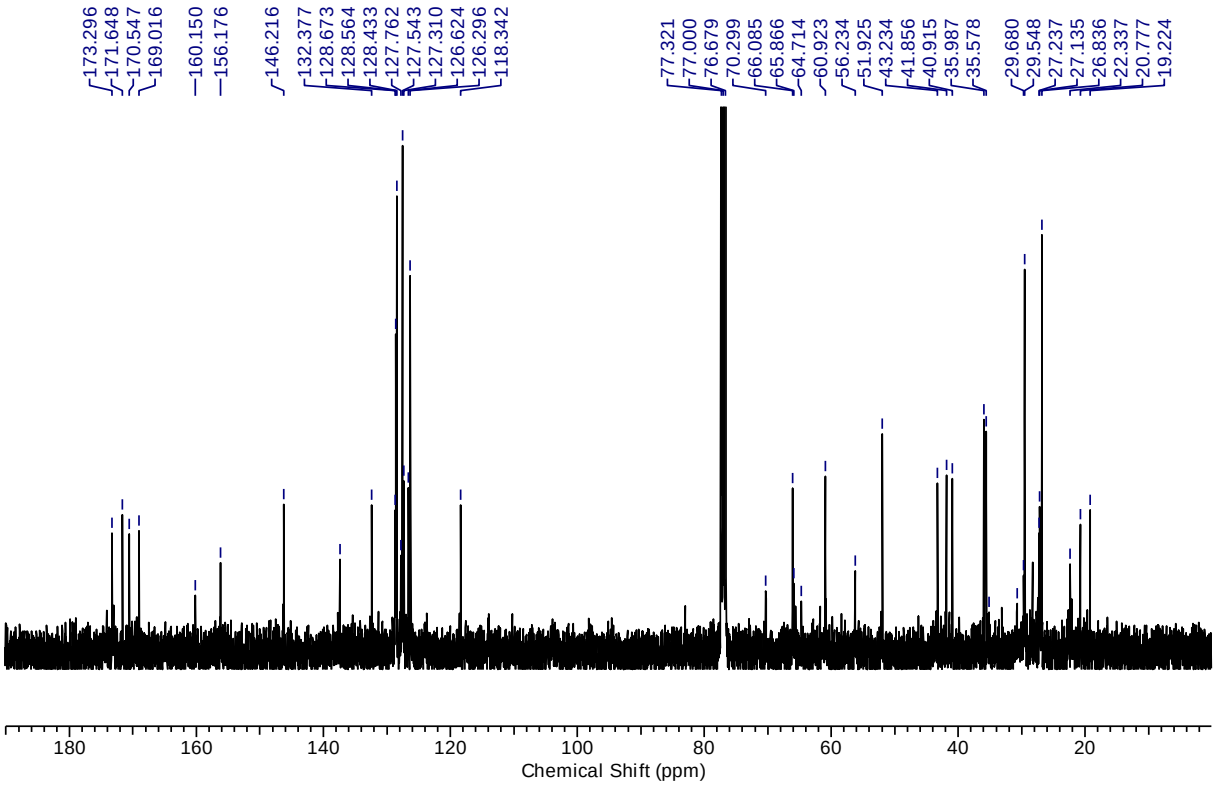


Methyl((*R*,*Z*)-2-((*S*)-2-(((allyloxy)carbonyl)amino)-*N*,3-dimethylbutanamido)-1-(((*S*)-1-(((*S*)-1-(benzylamino)-3-methyl-1-oxo-3-phenylbutane-2-yl)amino)-3,3-dimethyl-1-oxobutane-2-yl)imino)-3,3-dimethylbutyl)glycinate (14c)

^{1}H-NMR(400 MHz, $CDCl_3$):

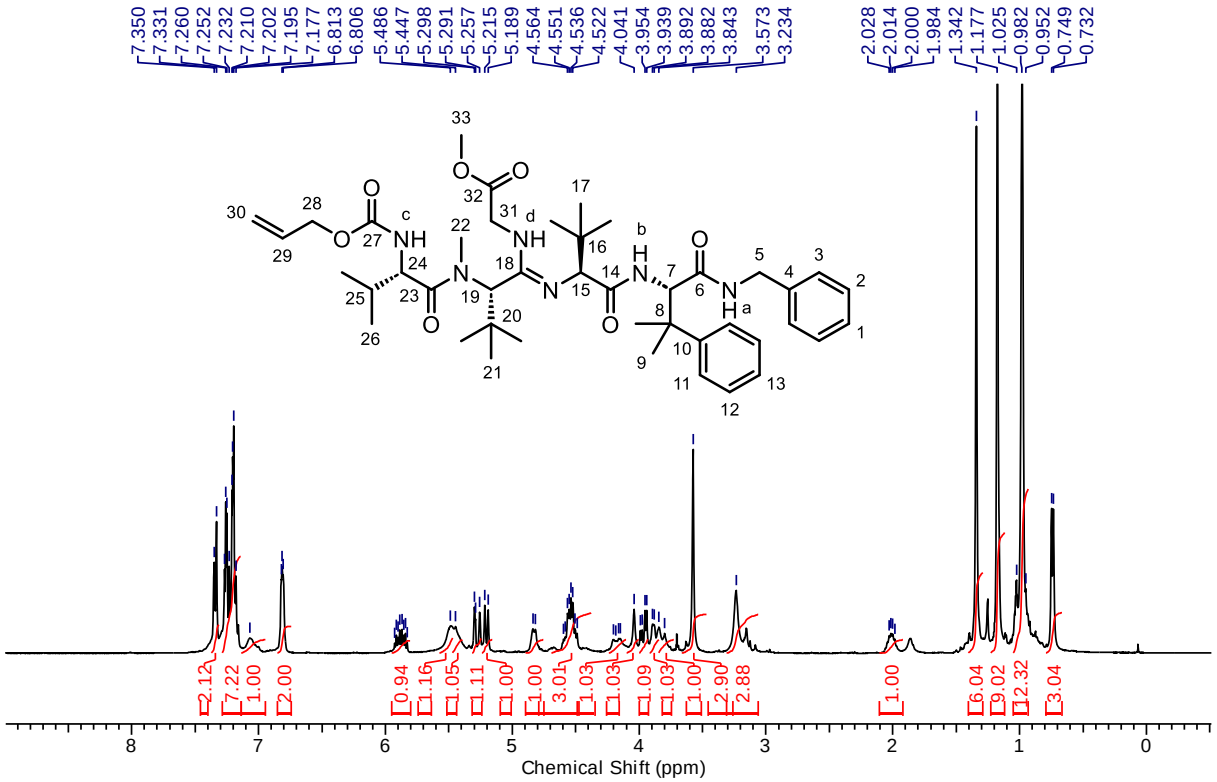


^{13}C-NMR(100 MHz, $CDCl_3$):

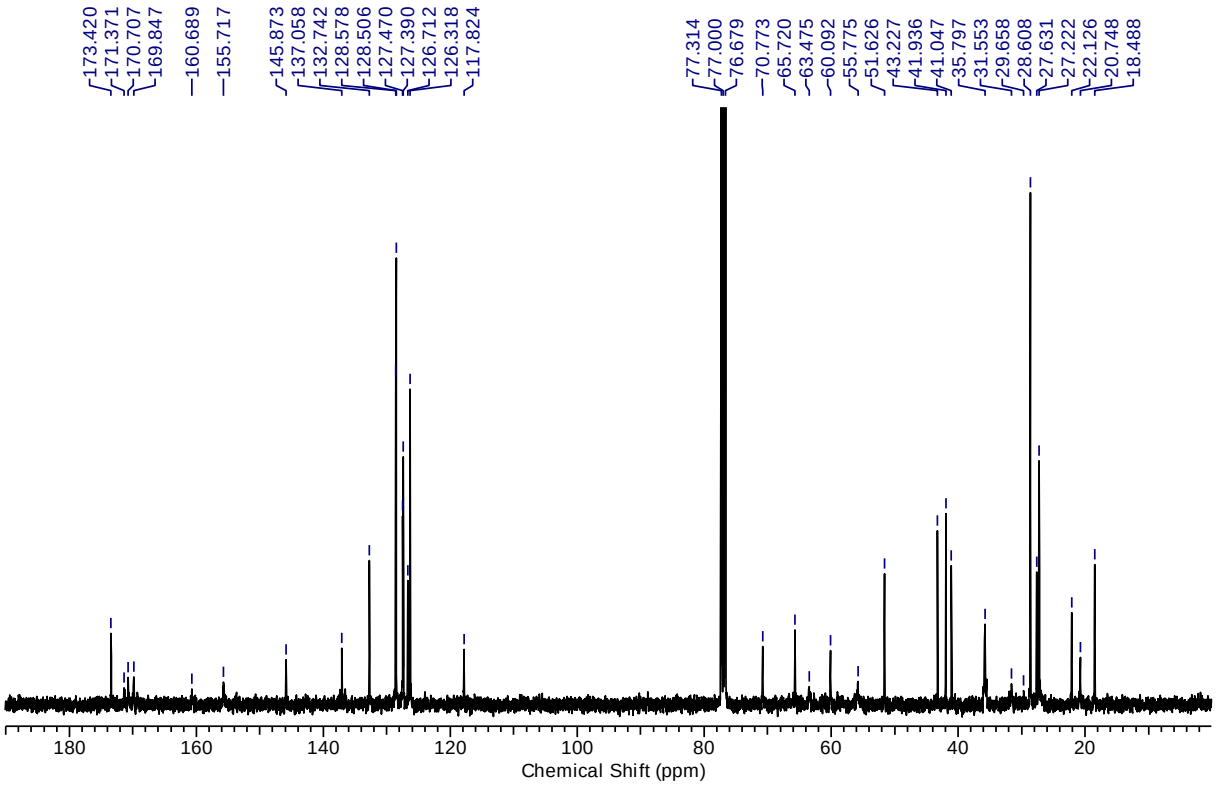


Methyl((*S*,*Z*)-2-((*S*)-2-(((allyloxy)carbonyl)amino)-*N*,3-dimethylbutanamido)-1-(((*S*)-1-(((*S*)-1-(benzylamino)-3-methyl-1-oxo-3-phenylbutane-2-yl)amino)-3,3-dimethyl-1-oxobutane-2-yl)imino)-3,3-dimethylbutyl)glycinate (14d)

^{1}H-NMR(400 MHz, $CDCl_3$):

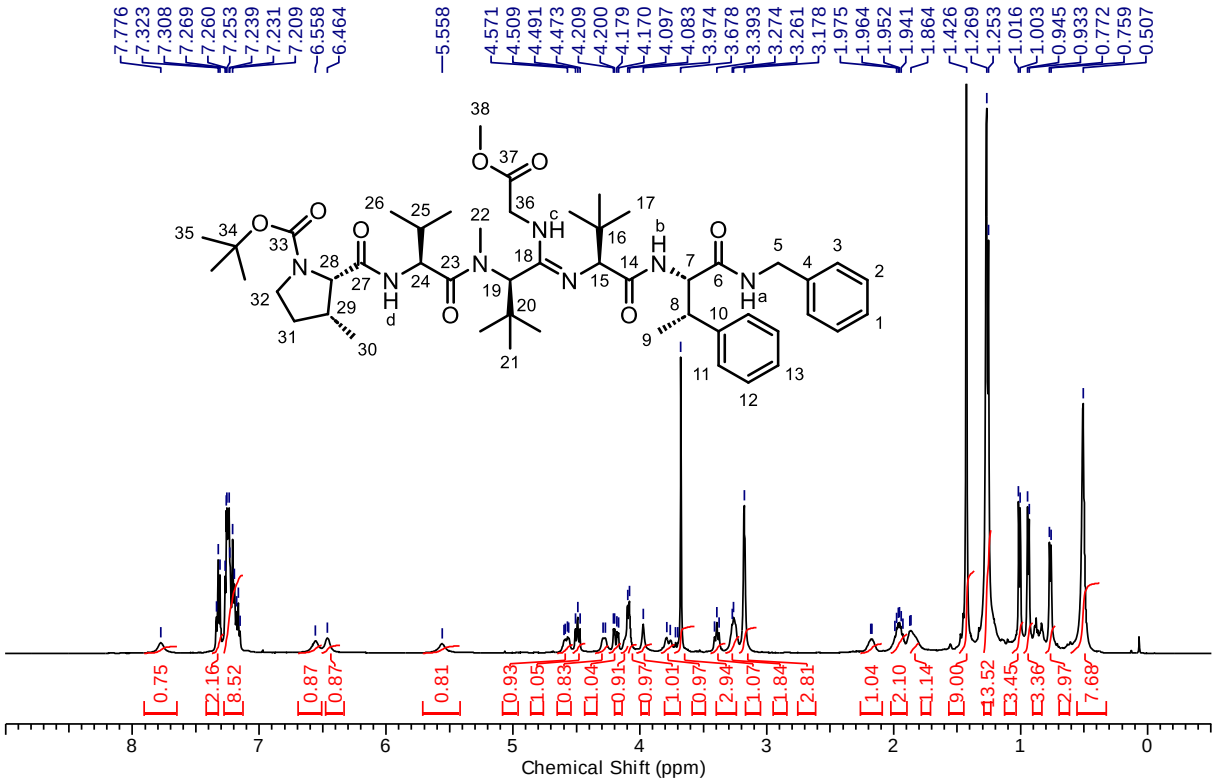


^{13}C-NMR(100 MHz, $CDCl_3$):

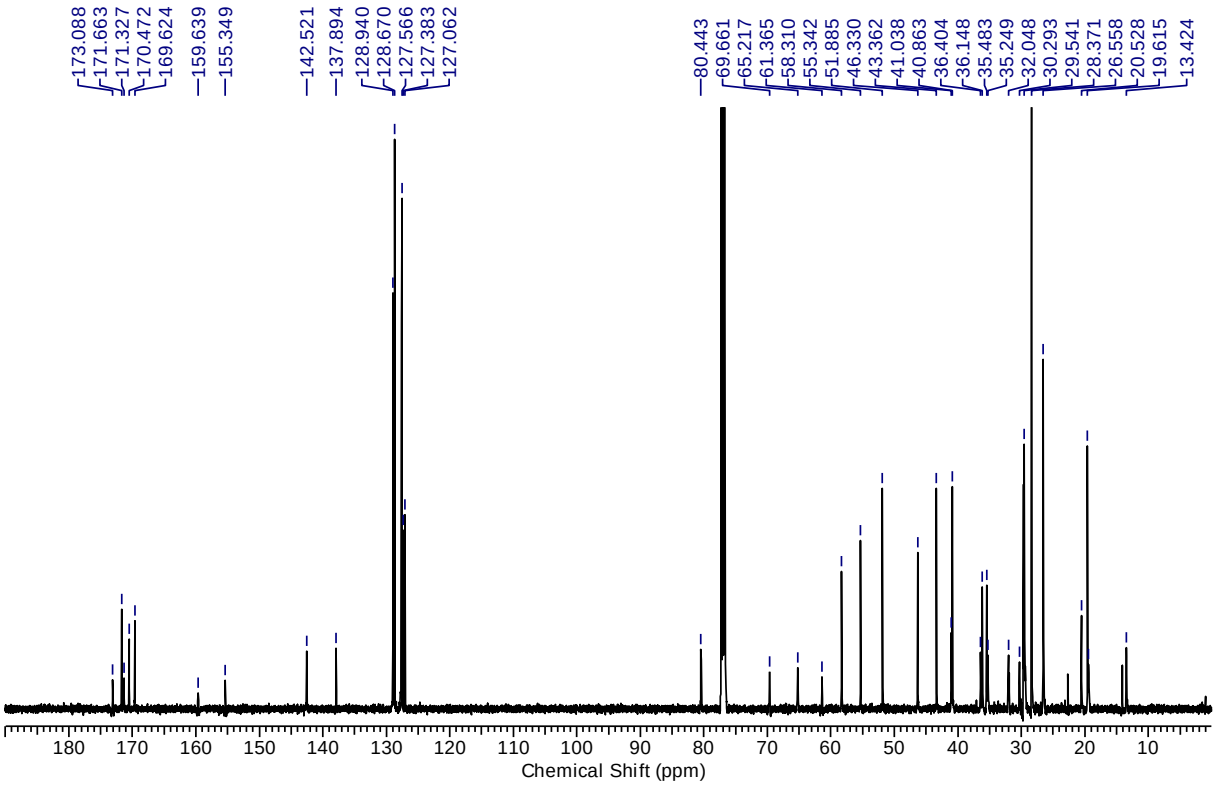


***tert*-Butyl(2*S*,3*R*)-2-(((4*S*,7*S*,10*R*,13*S*,*Z*)-7,10-di-*tert*-butyl-9-((2-methoxy-2-oxoethyl)-amino)-11,14-dimethyl-3,6,12-trioxo-1-phenyl-4-((*S*)-1-phenylethyl)-2,5,8,11-tetraaza-pentadec-8-en-13-yl)carbamoyl)-3-methylpyrrolidine-1-carboxylate (15a)**

^{1}H-NMR(500 MHz, $CDCl_3$):

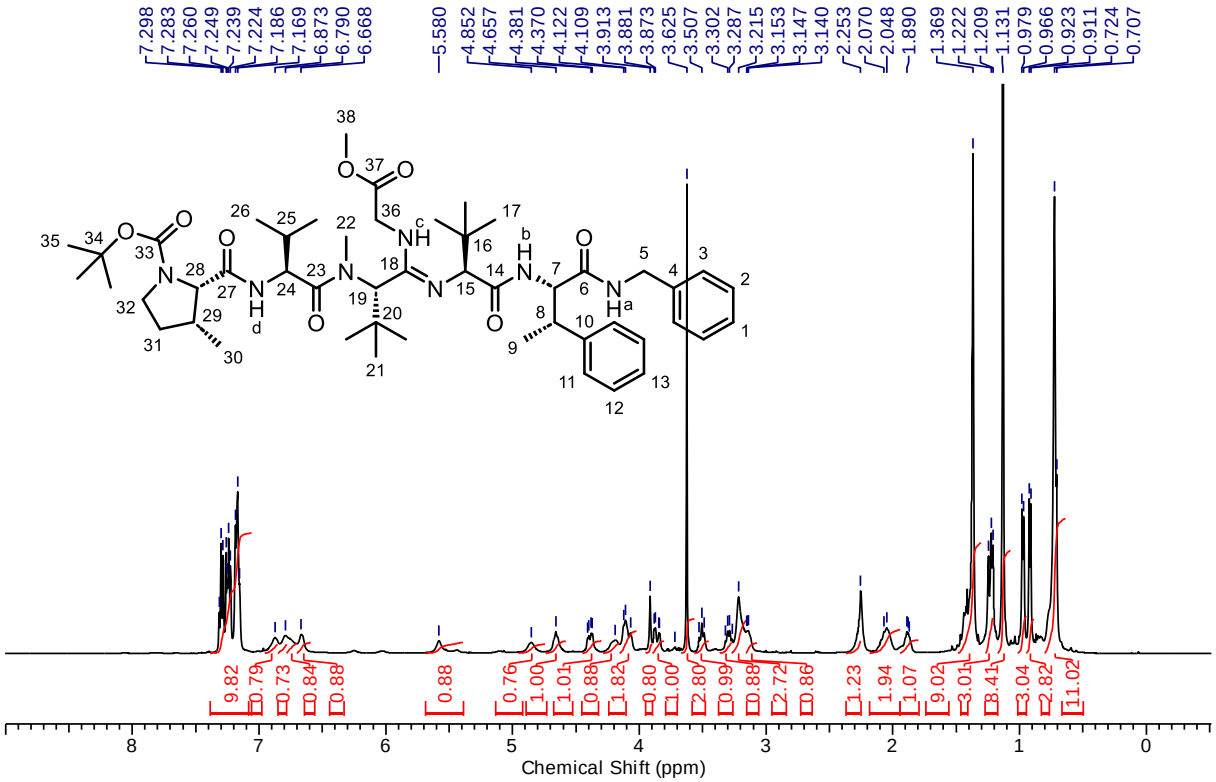


^{13}C-NMR(125 MHz, $CDCl_3$):

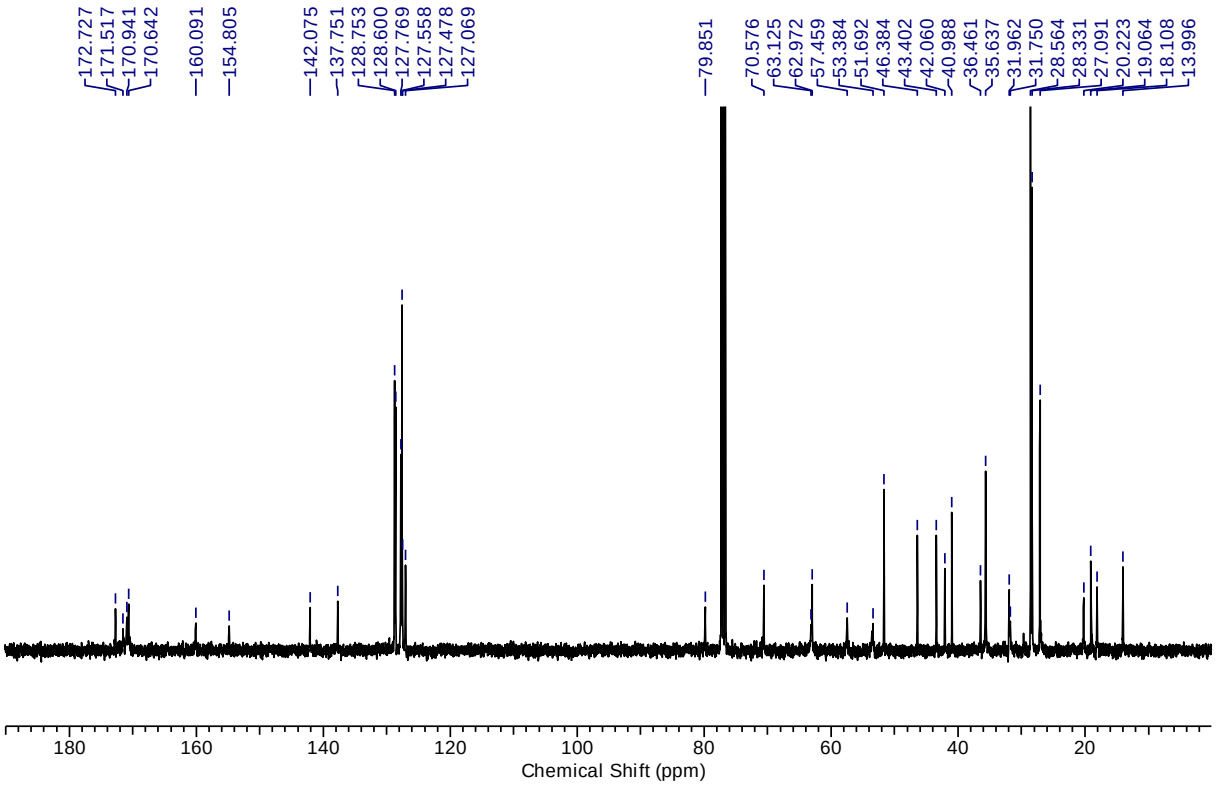


***tert*-Butyl(2*S*,3*R*)-2-(((4*S*,7*S*,10*S*,13*S*,*Z*)-7,10-di-*tert*-butyl-9-((2-methoxy-2-oxoethyl)-amino)-11,14-dimethyl-3,6,12-trioxo-1-phenyl-4-((*S*)-1-phenylethyl)-2,5,8,11-tetraaza-pentadec-8-en-13-yl)carbamoyl)-3-methylpyrrolidine-1-carboxylate (15b)**

^{1}H-NMR(500 MHz, $CDCl_3$):

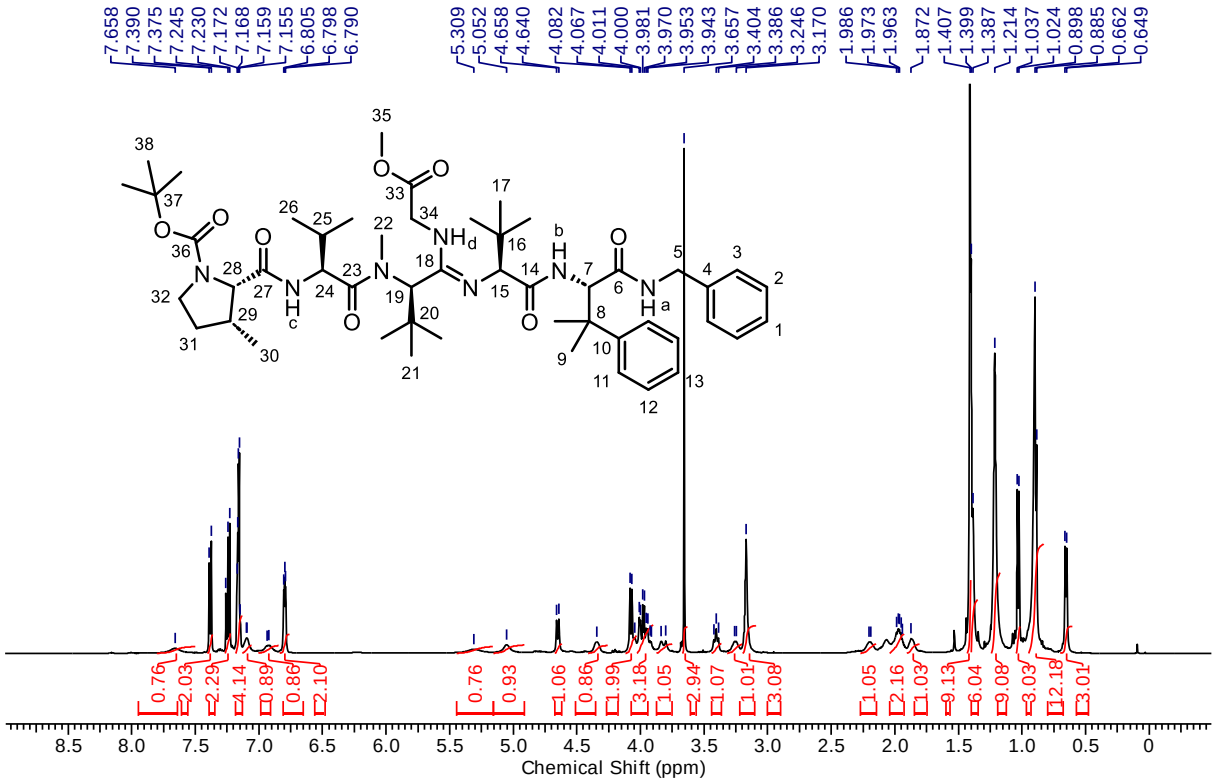


^{13}C-NMR(100 MHz, $CDCl_3$):

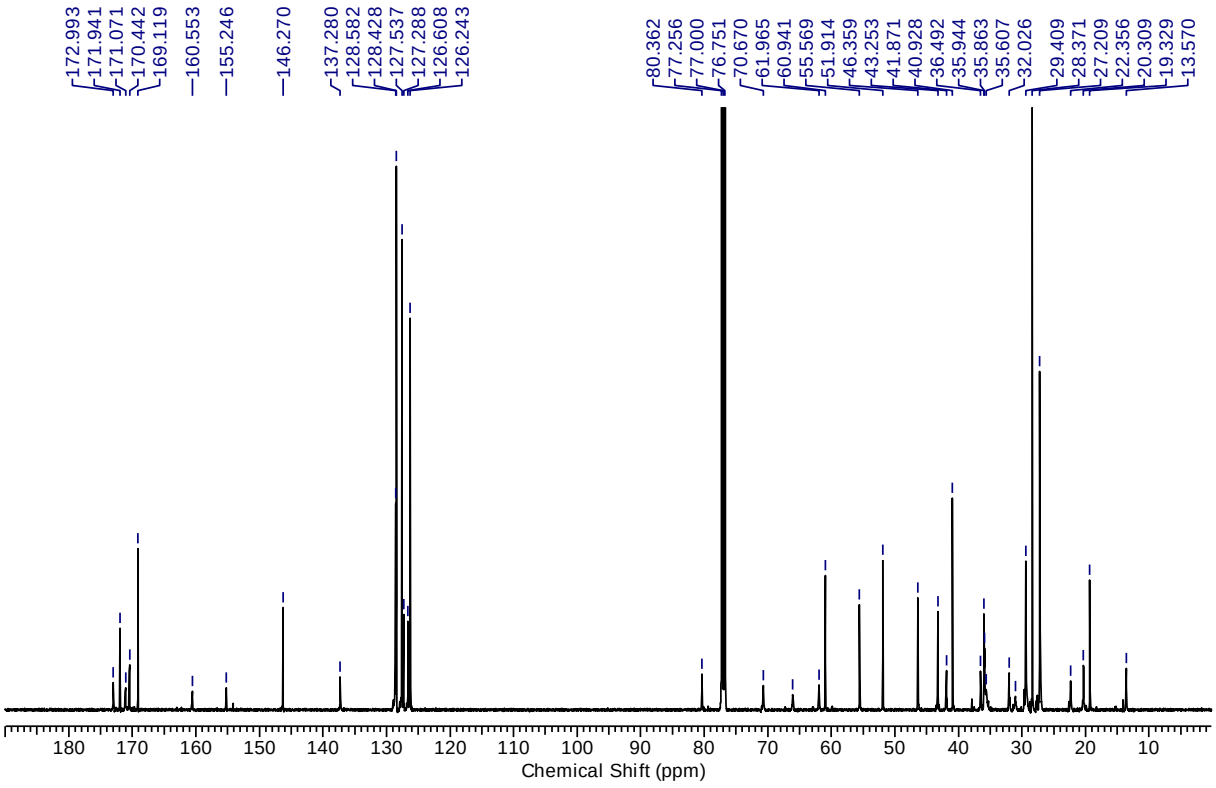


***tert*-Butyl(2*S*,3*R*)-2-(((4*S*,7*S*,10*R*,13*S*,*Z*)-7,10-di-*tert*-butyl-9-((2-methoxy-2-oxo-ethyl)amino)-11,14-dimethyl-3,6,12-trioxo-1-phenyl-4-(2-phenylpropane-2-yl)-2,5,8,11-tetraaza-pentadec-8-en-13-yl)carbamoyl)-3-methylpyrrolidine-1-carboxylate (15c)**

^{1}H-NMR(500 MHz, $CDCl_3$):

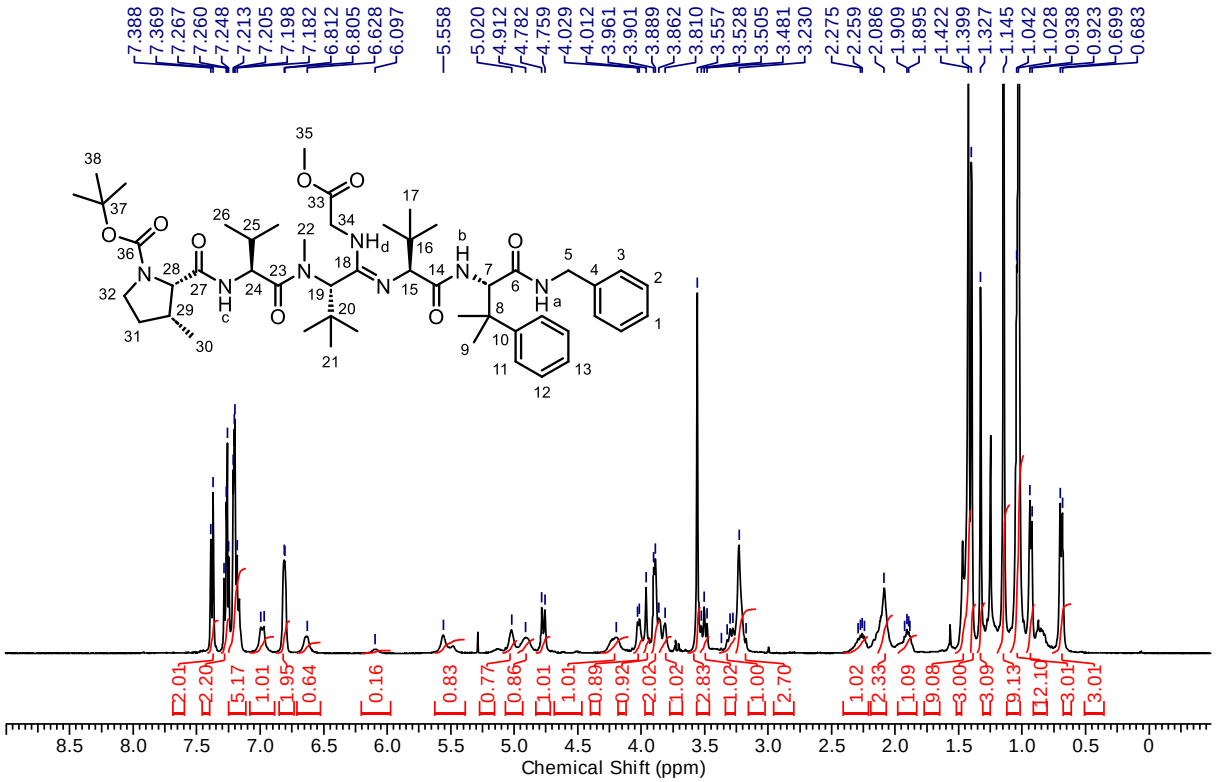


^{13}C-NMR(125 MHz, $CDCl_3$):

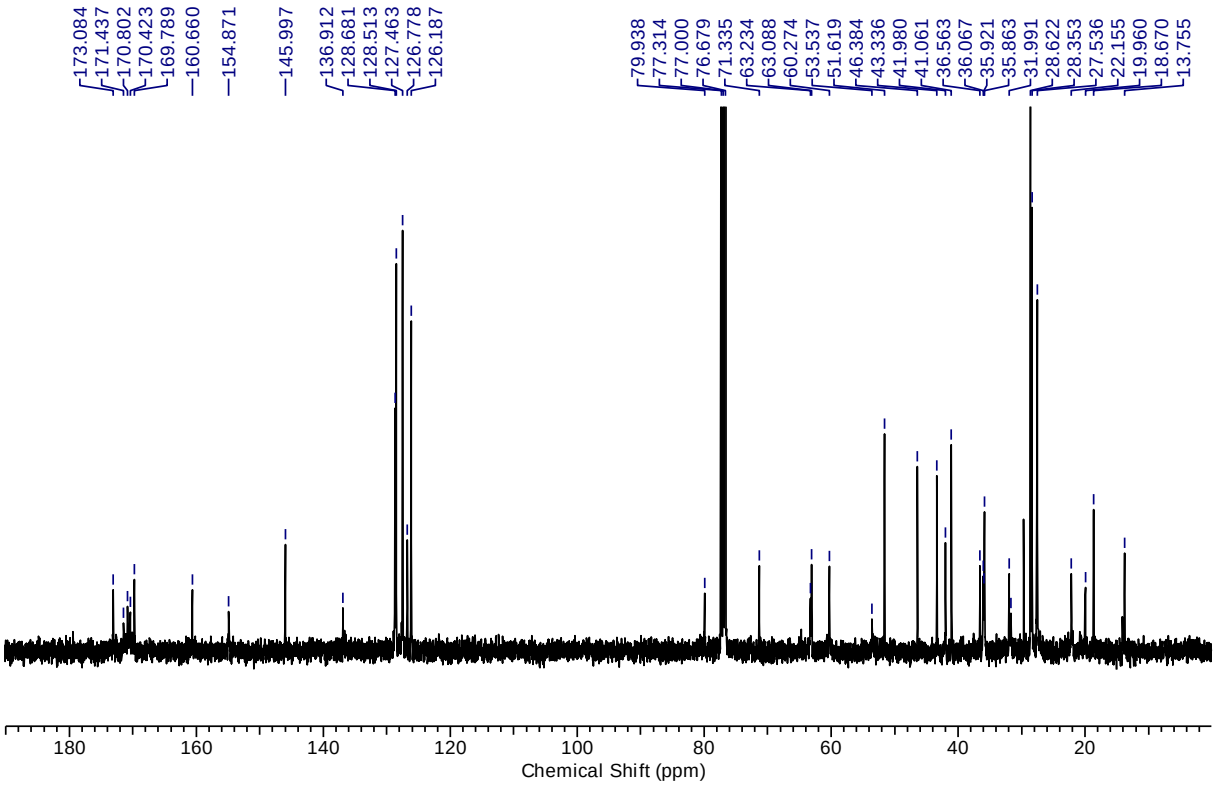


***tert*-Butyl(2*S*,3*R*)-2-(((4*S*,7*S*,10*S*,13*S*,*Z*)-7,10-di-*tert*-butyl-9-((2-methoxy-2-oxo-ethyl) amino)-11,14-dimethyl-3,6,12-trioxo-1-phenyl-4-(2-phenylpropan-2-yl)-2,5,8,11-tetraaza-pentadec-8-en-13-yl)carbamoyl)-3-methylpyrrolidine-1-carboxylate (15d)**

^{1}H-NMR(400 MHz, $CDCl_3$):

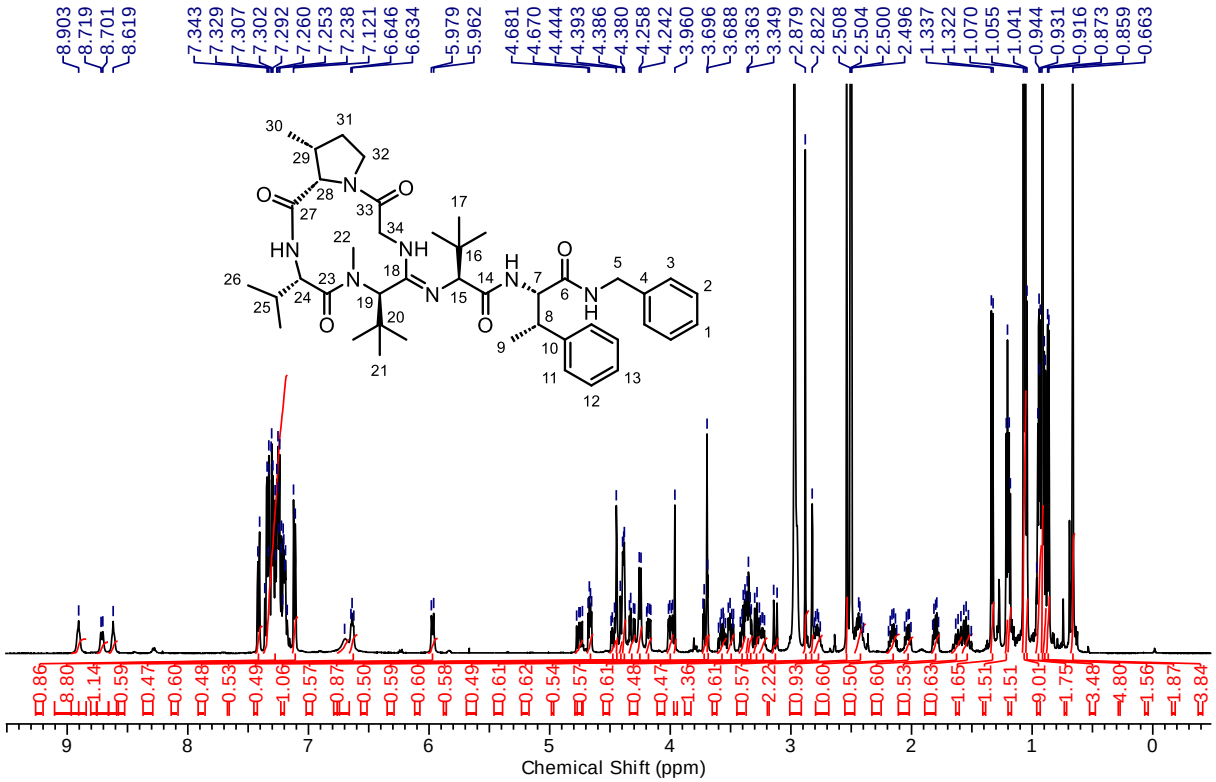


^{13}C-NMR(100 MHz, $CDCl_3$):

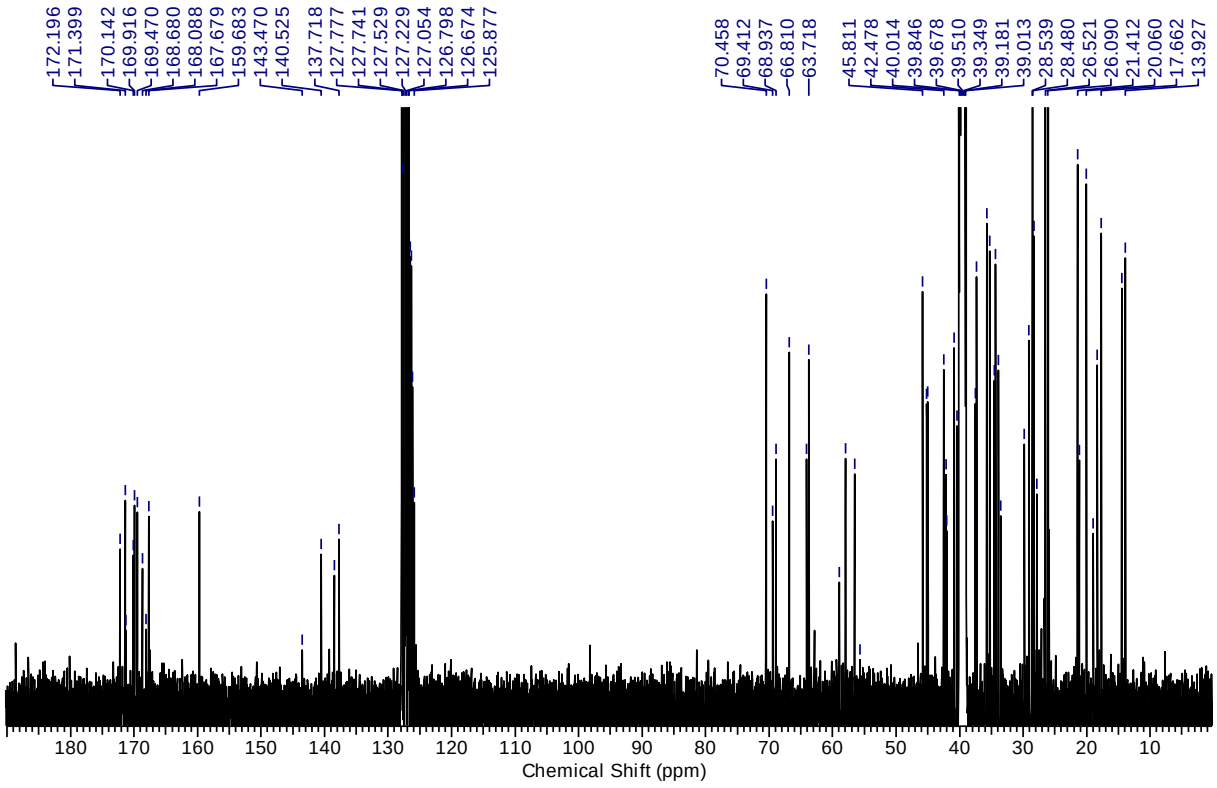


(*S*)-*N*-((2*S*,3*S*)-1-(Benzylamino)-1-oxo-3-phenylbutane-2-yl)-2-(((3*S*,6*R*,14*R*,14a*S*,*Z*)-6-(tert-butyl)-3-isopropyl-5,14-dimethyl-1,4,10-trioxododecahydropyrrolo[1,2-*a*]-[1,4,7,10]tetraazacyclododecine-7(8*H*)-ylidene)amino)-3,3-dimethylbutanamide (16a)

^{1}H-NMR(500 MHz, 373 K, DMSO-d_6):

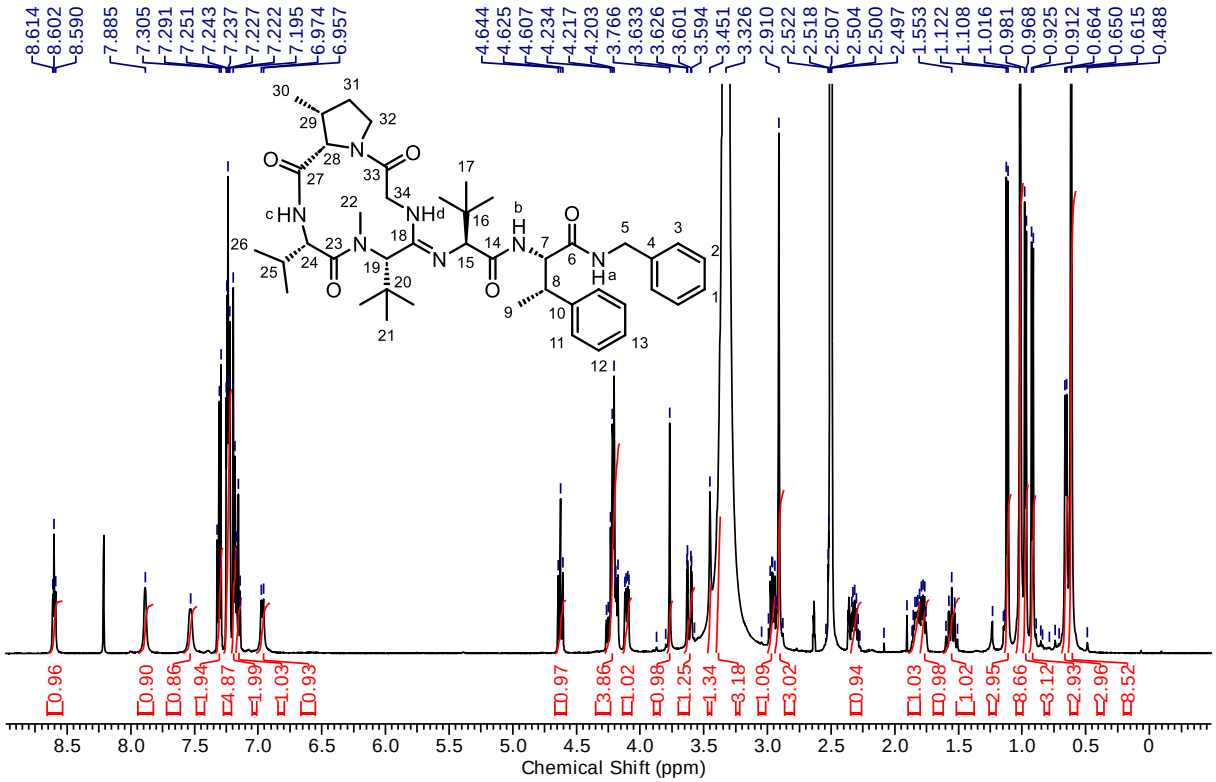


^{13}C-NMR(125 MHz, 373 K, DMSO-d_6):

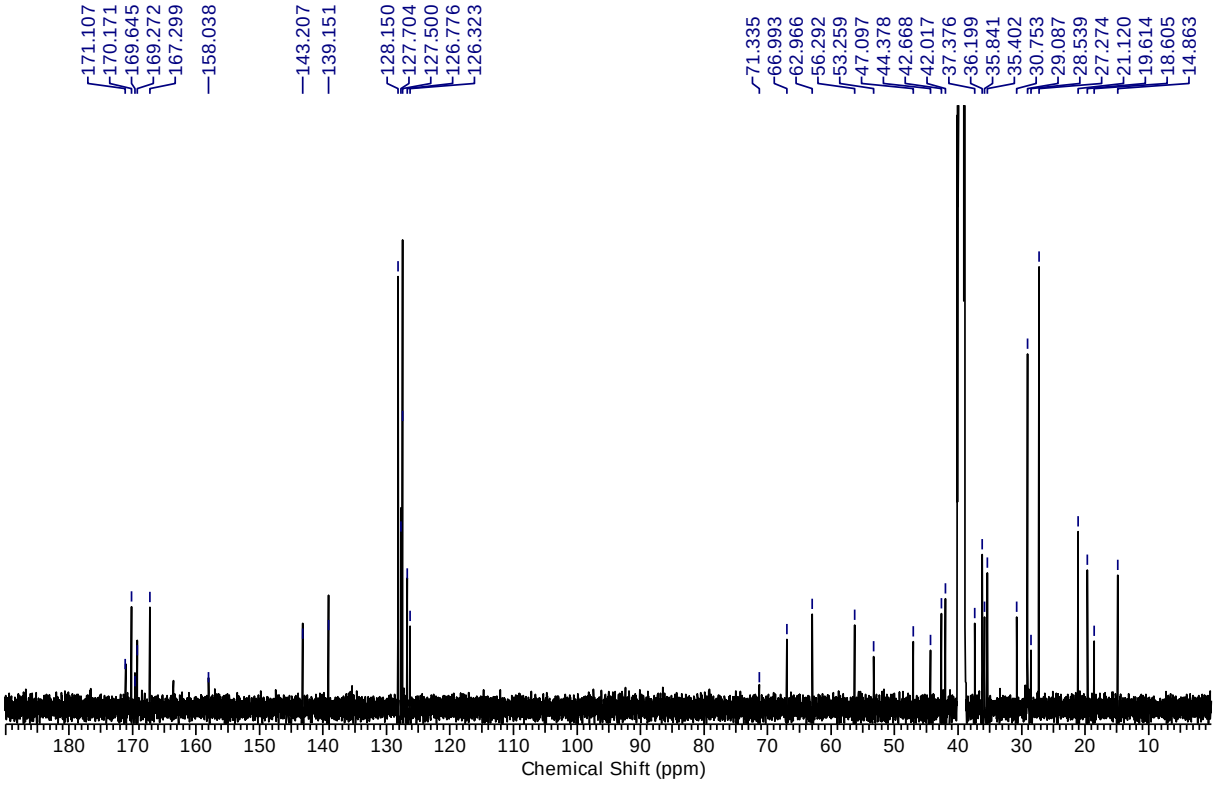


(*S*)-*N*-((2*S*,3*S*)-1-(Benzylamino)-1-oxo-3-phenylbutane-2-yl)-2-(((3*S*,6*S*,14*R*,14a*S*,*Z*)-6-(*tert*-butyl)-3-isopropyl-5,14-dimethyl-1,4,10-trioxododecahydropyrrolo[1,2-*a*]-[1,4,7,10]tetraazacyclododecine-7(8*H*)-ylidene)amino)-3,3-dimethylbutanamide (16b)

^{1}H-NMR(500 MHz, DMSO-d_6):

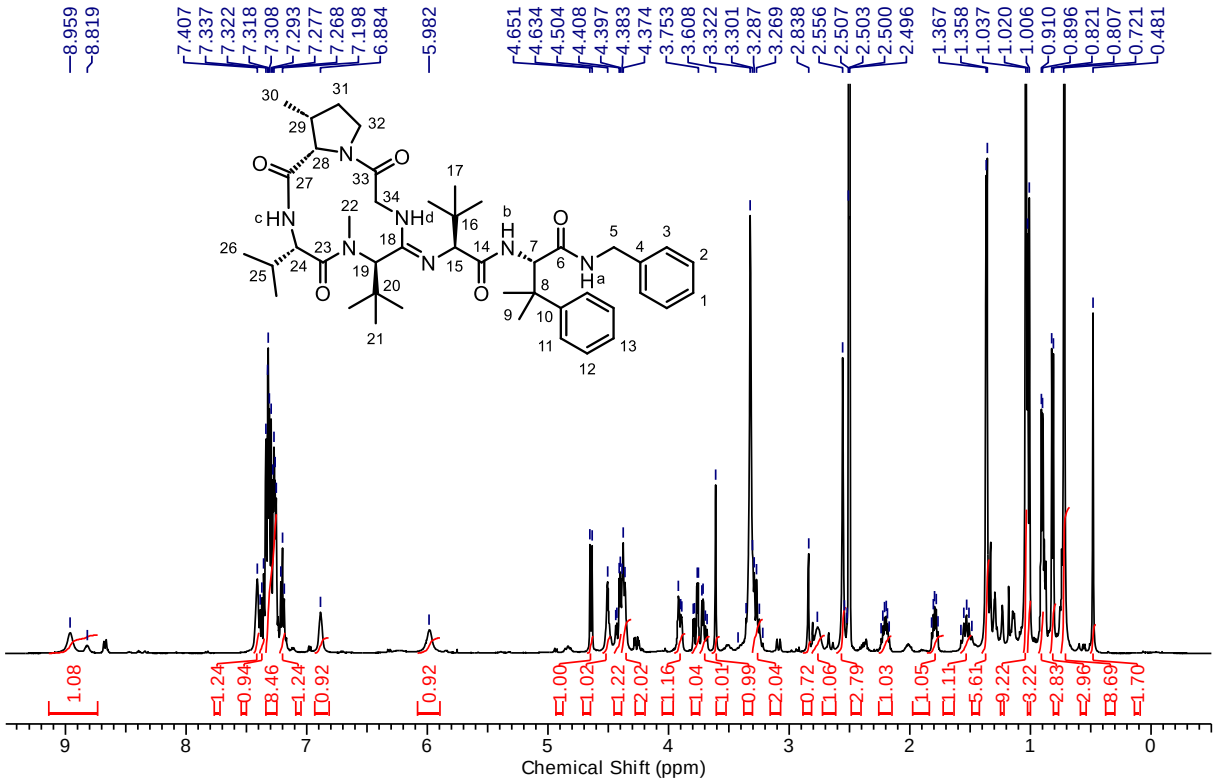


^{13}C-NMR(125 MHz, DMSO-d_6):

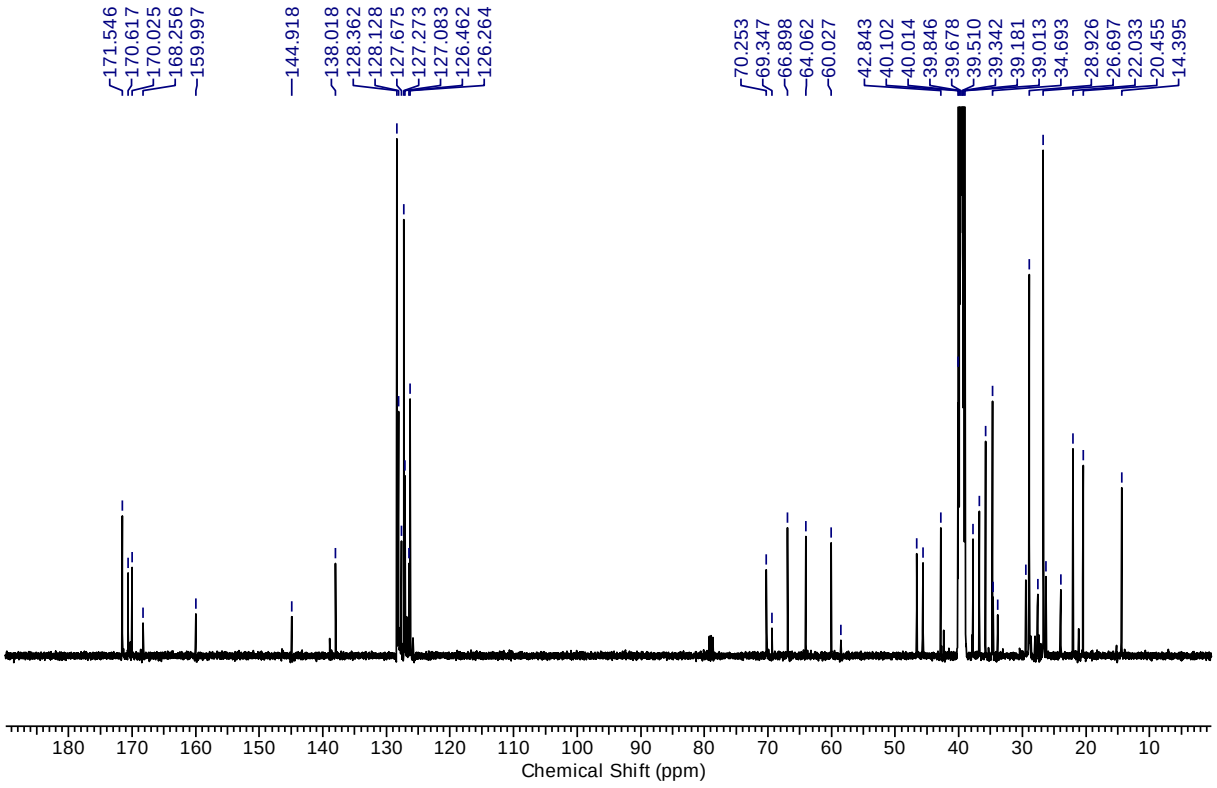


(*S*)-*N*-Benzyl-2-((*S*)-2-(((3*S*,6*R*,14*R*,14a*S*,*Z*)-6-(*tert*-butyl)-3-isopropyl-5,14-di-methyl-1,4,10-trioxododecahydropyrrolo[1,2-*a*][1,4,7,10]tetraazacyclododecine-7(8*H*)-yliden) amino)-3,3-dimethylbutanamido)-3-methyl-3-phenylbutanamide (16c)

^{1}H-NMR(500 MHz, DMSO-d_6):

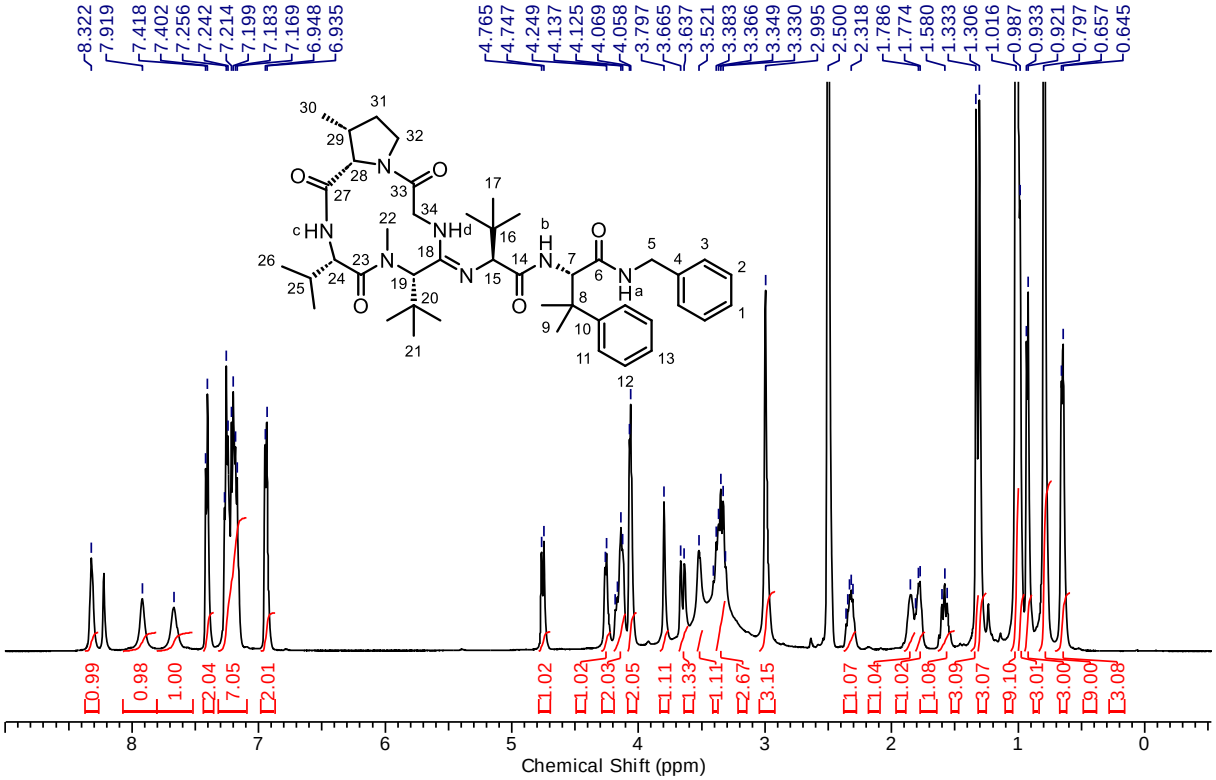


^{13}C-NMR(125 MHz, DMSO-d_6):

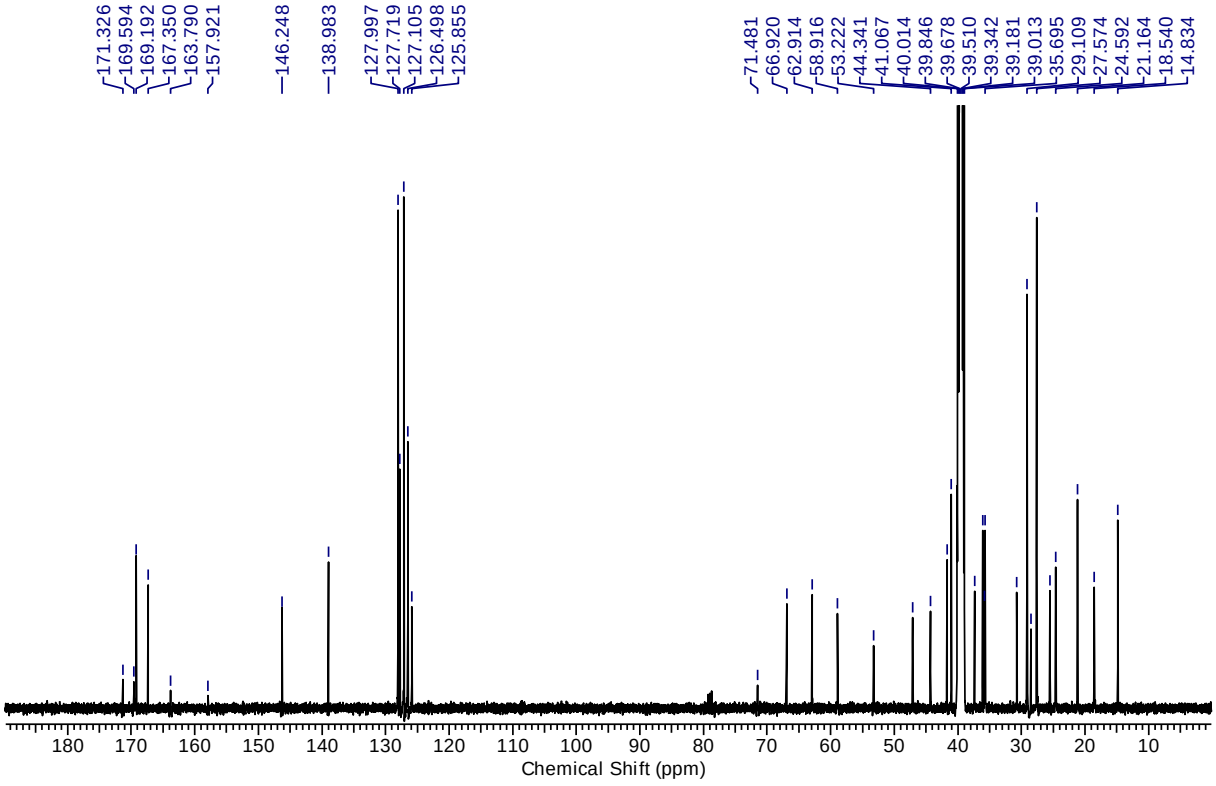


(*S*)-*N*-Benzyl-2-((*S*)-2-(((3*S*,6*S*,14*R*,14a*S*,*Z*)-6-(*tert*-butyl)-3-isopropyl-5,14-di-methyl-1,4,10-trioxododecahydropyrrolo[1,2-*a*][1,4,7,10]tetraazacyclododecine-7(8*H*)-yliden) amino)-3,3-dimethylbutanamido)-3-methyl-3-phenylbutanamide (16d)

^{1}H-NMR(500 MHz, DMSO-d_6):

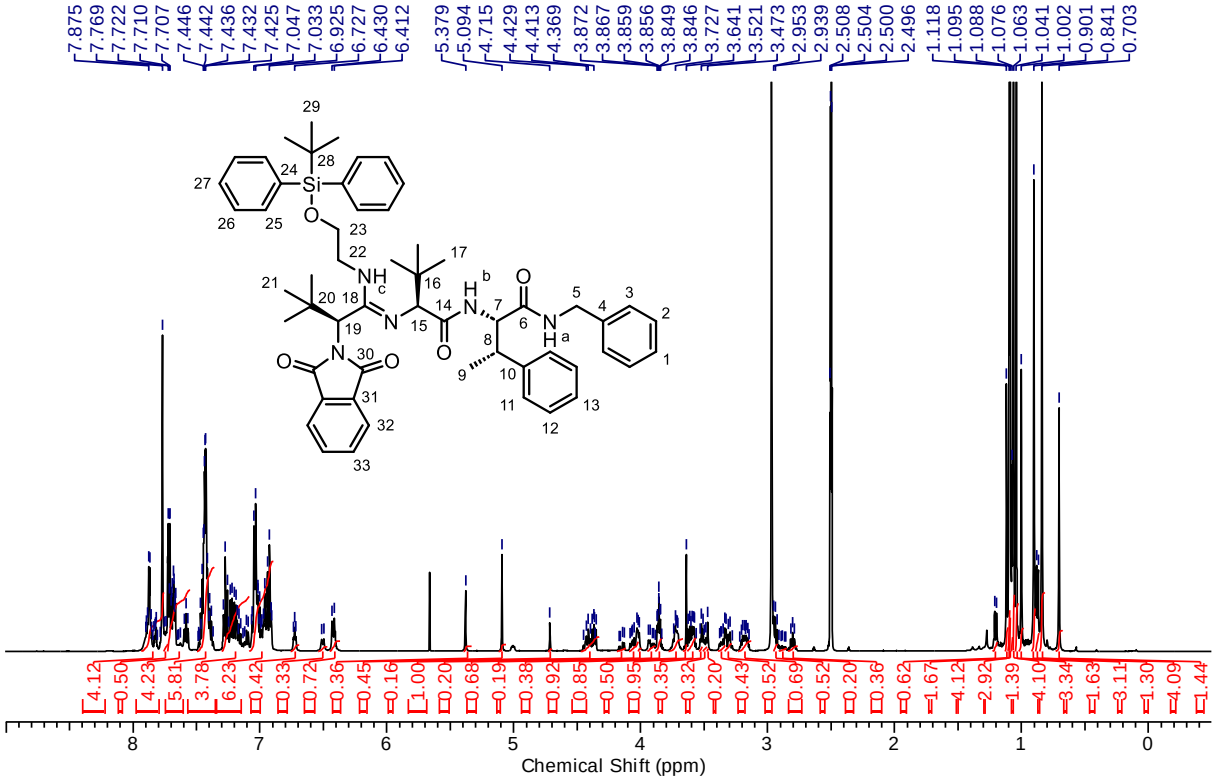


^{13}C-NMR(125 MHz, DMSO-d_6):

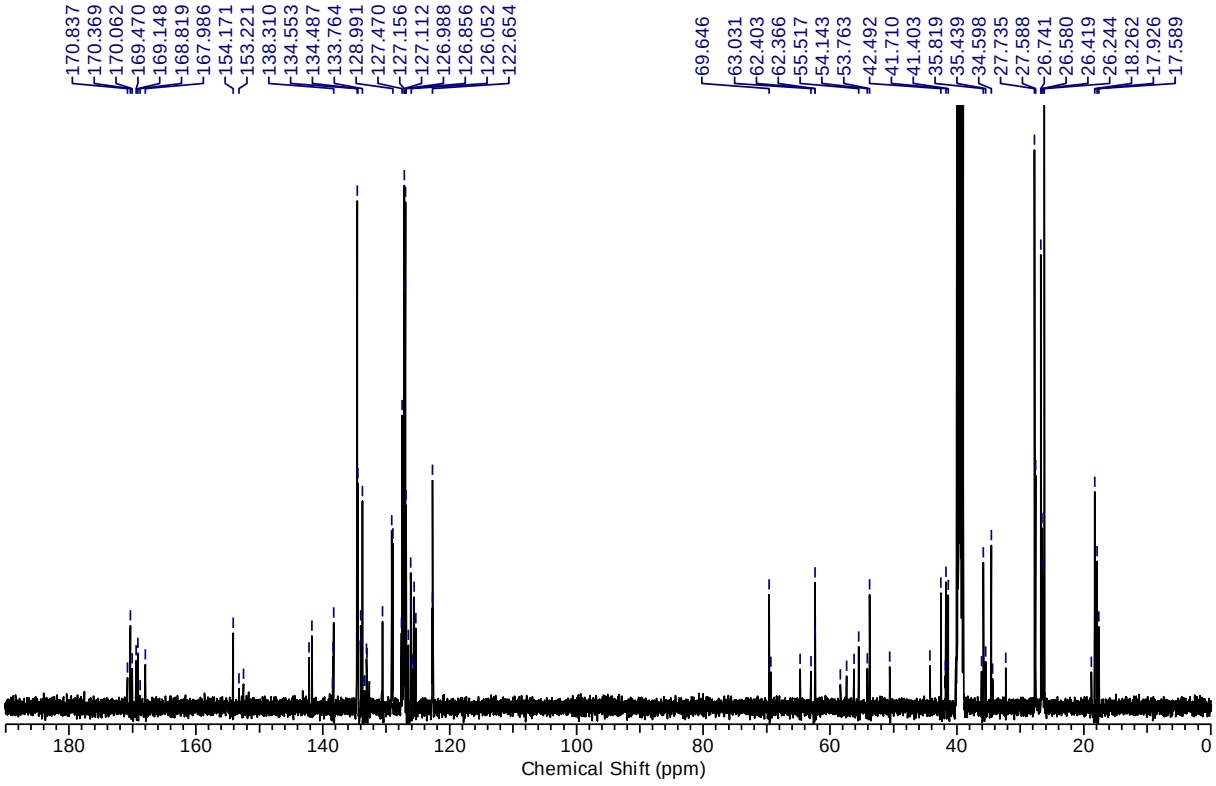


(*S*,*Z*)-*N*-((2*S*,3*S*)-1-(Benzylamino)-1-oxo-3-phenylbutane-2-yl)-10-(*tert*-butyl)-8-((*S*)-1-(1,3-dioxoisoindoline-2-yl)-2,2-dimethylpropyl)-2,2-dimethyl-3,3-diphenyl-4-oxa-7,9-diaza-3-silaundec-8-en-11-amide (18a)

^{1}H-NMR(500 MHz, 373 K, DMSO-d_6):

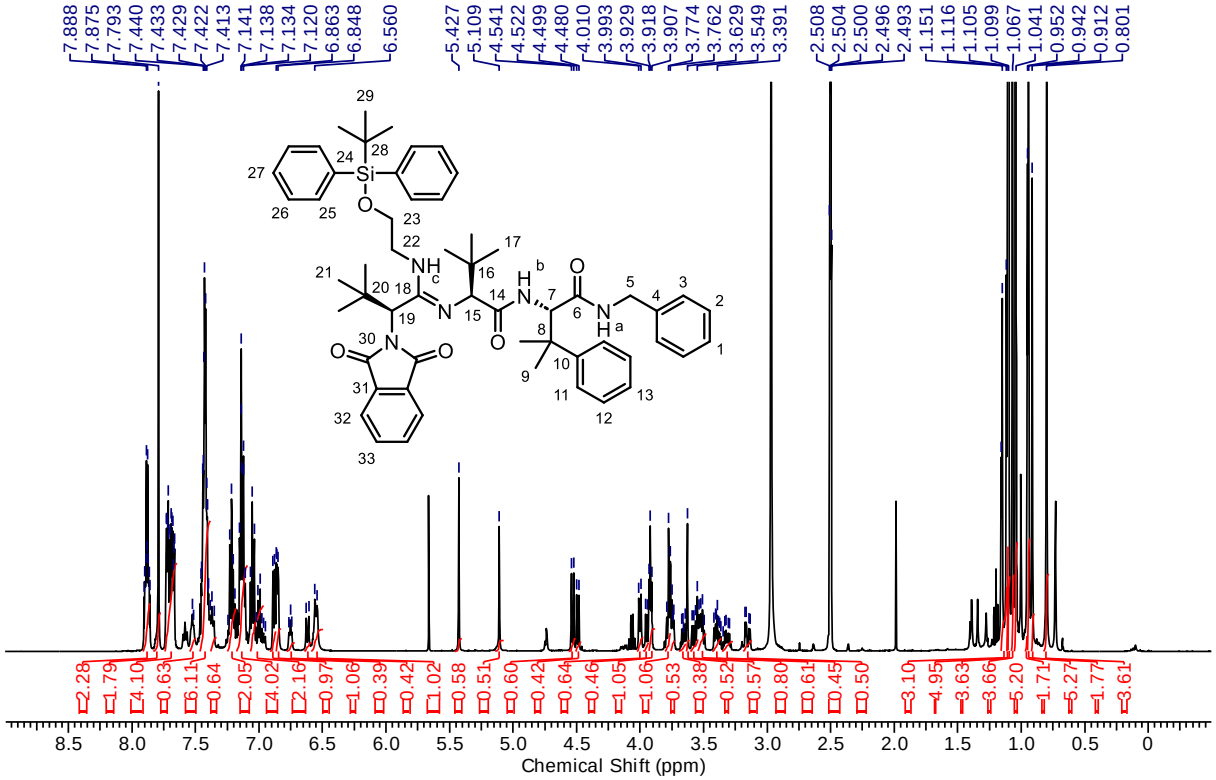


^{13}C-NMR(125 MHz, 373 K, DMSO-d_6):

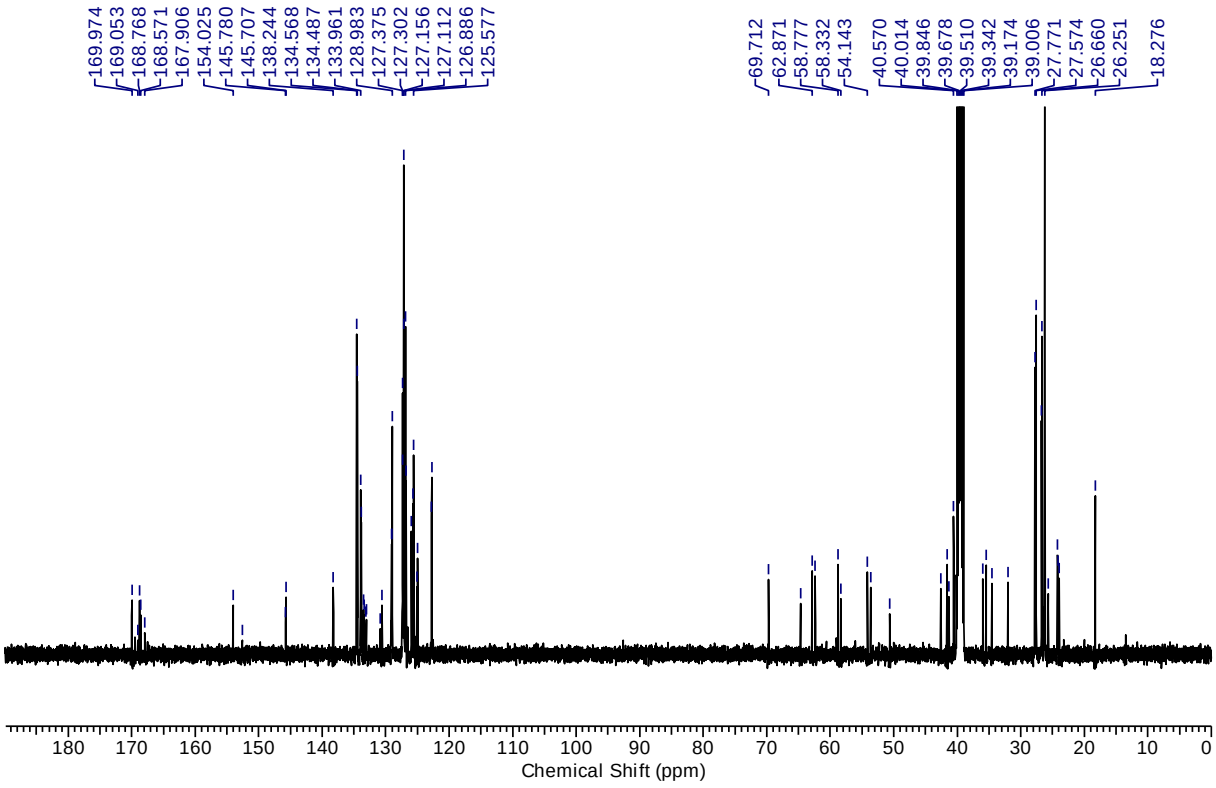


(*S*,*Z*)-*N*-((*S*)-1-(Benzylamino)-3-methyl-1-oxo-3-phenylbutane-2-yl)-10-(*tert*-butyl)-8-((*R*)-1-(1,3-dioxoisoindoline-2-yl)-2,2-dimethylpropyl)-2,2-dimethyl-3,3-diphenyl-4-oxa-7,9-diaza-3-silaundec-8-en-11-amide (18b)

^{1}H-NMR(500 MHz, 373 K, DMSO-d_6):

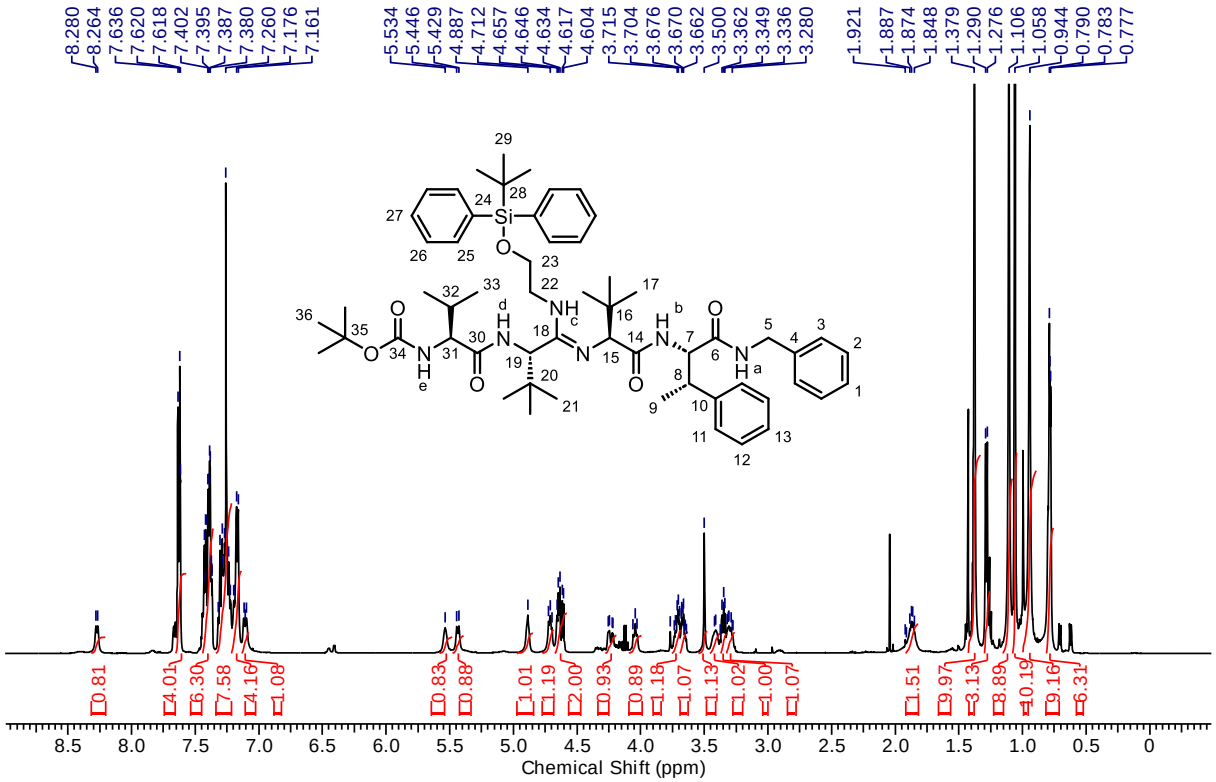


^{13}C-NMR(125 MHz, 373 K, DMSO-d_6):

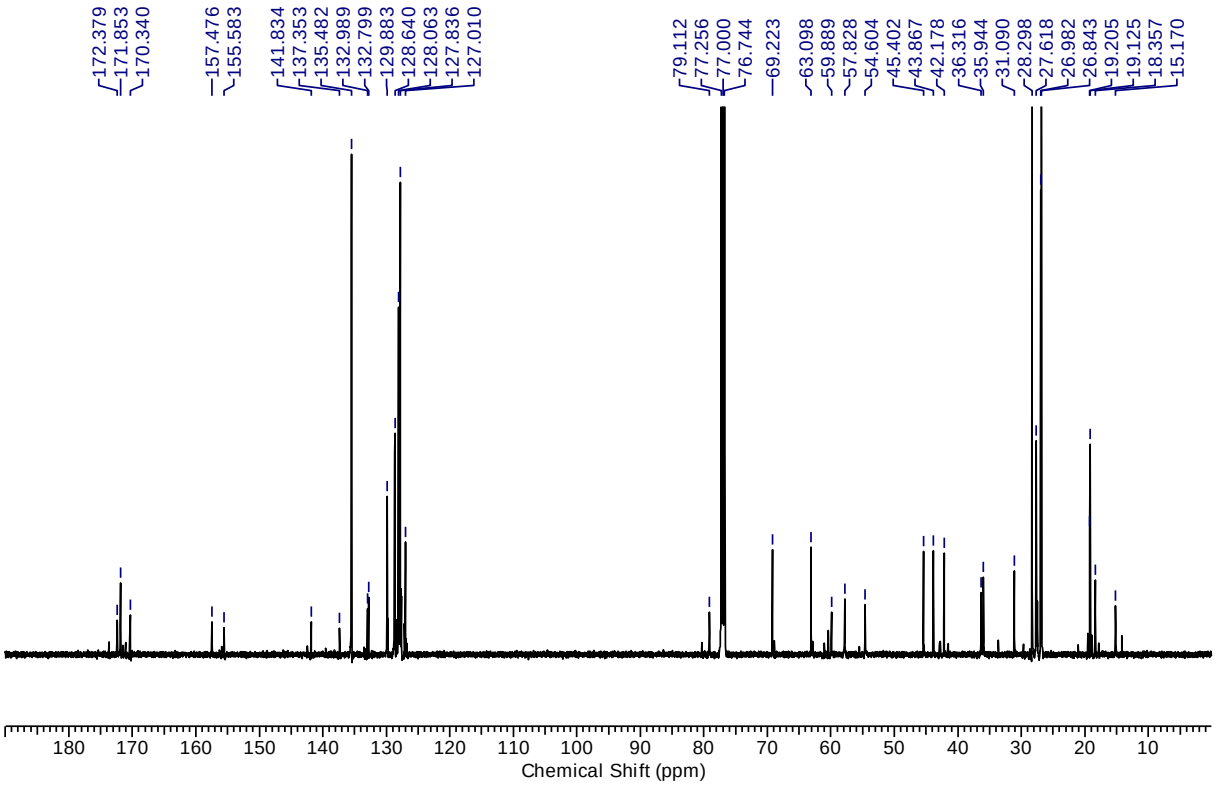


***tert*-Butyl((4*S*,7*S*,10*S*,13*S*,*Z*)-7,10-di-*tert*-butyl-9-((2-((*tert*-butyldiphenylsilyl) oxy)ethyl)-amino)-14-methyl-3,6,12-trioxo-1-phenyl-4-((*S*)-1-phenylethyl)-2,5,8,11-tetra-aza-pentadec-8-en-13-yl)carbamate (19a)**

^{1}H-NMR(500 MHz, $CDCl_3$):

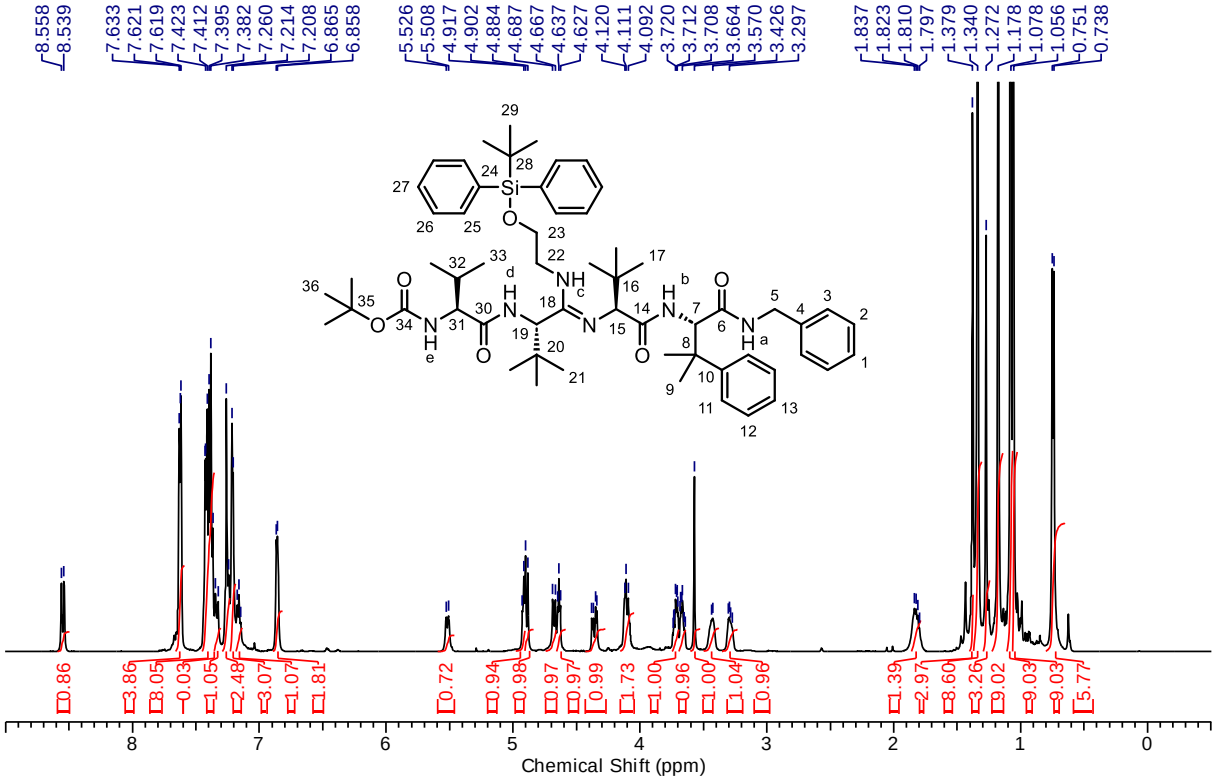


^{13}C-NMR(125 MHz, $CDCl_3$):

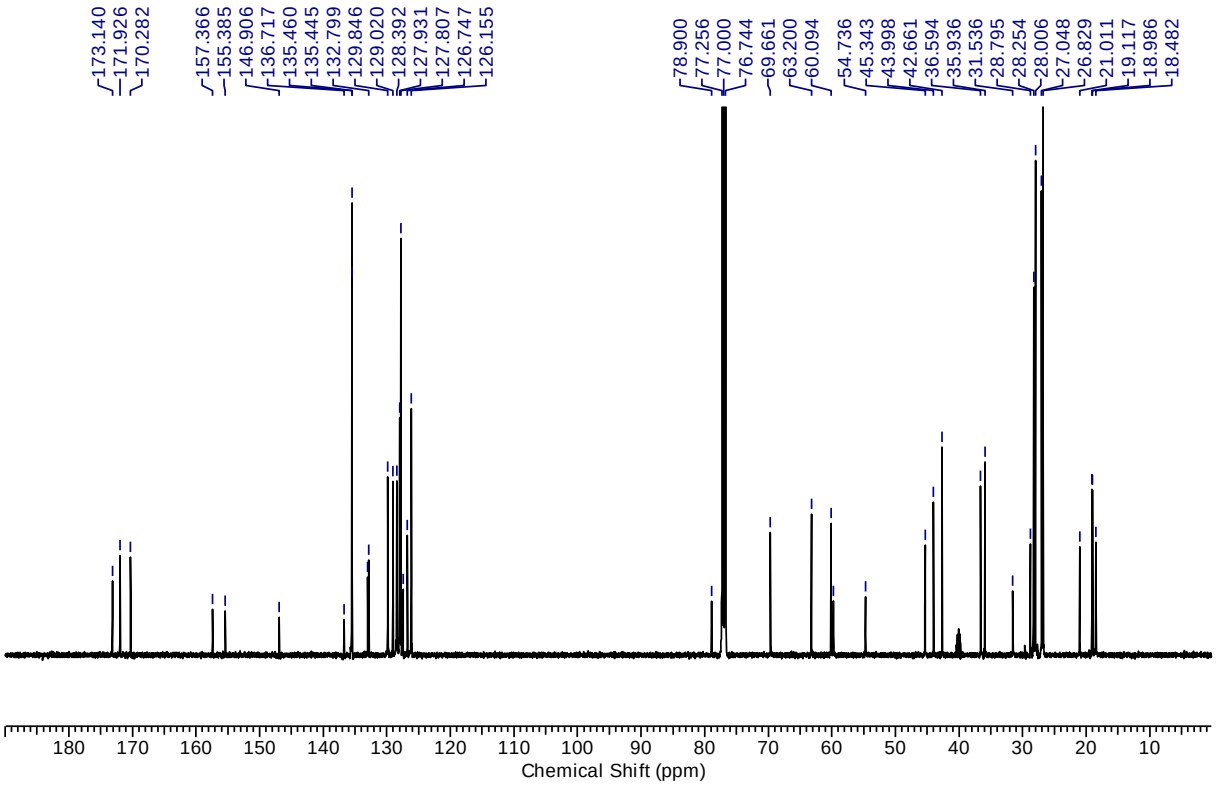


***tert*-Butyl((4*S*,7*S*,10*S*,13*S*,*Z*)-7,10-di-*tert*-butyl-9-((2-((*tert*-butyldiphenylsilyl)-oxy)ethyl) amino)-14-methyl-3,6,12-trioxo-1-phenyl-4-(2-phenylpropane-2-yl)-2,5,8,11-tetraaza-pentadec-8-en-13-yl)carbamate (19b)**

^{1}H-NMR(500 MHz, $CDCl_3$):

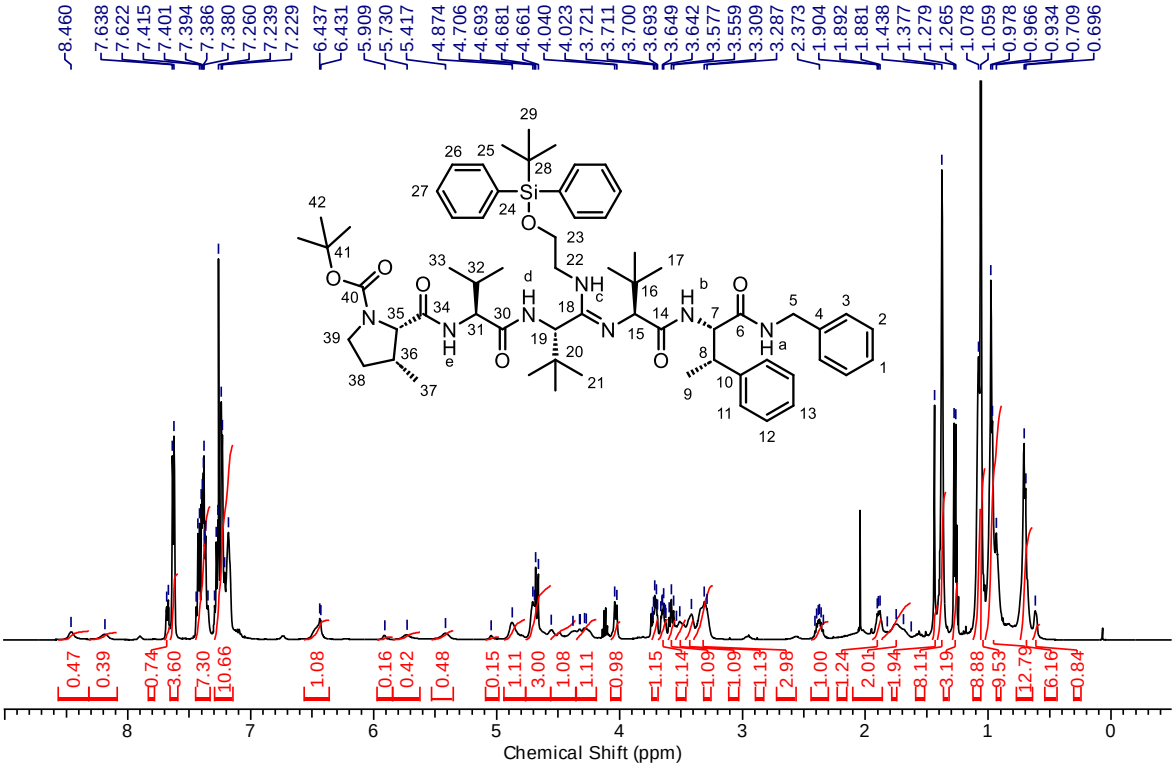


^{13}C-NMR(125 MHz, $CDCl_3$):

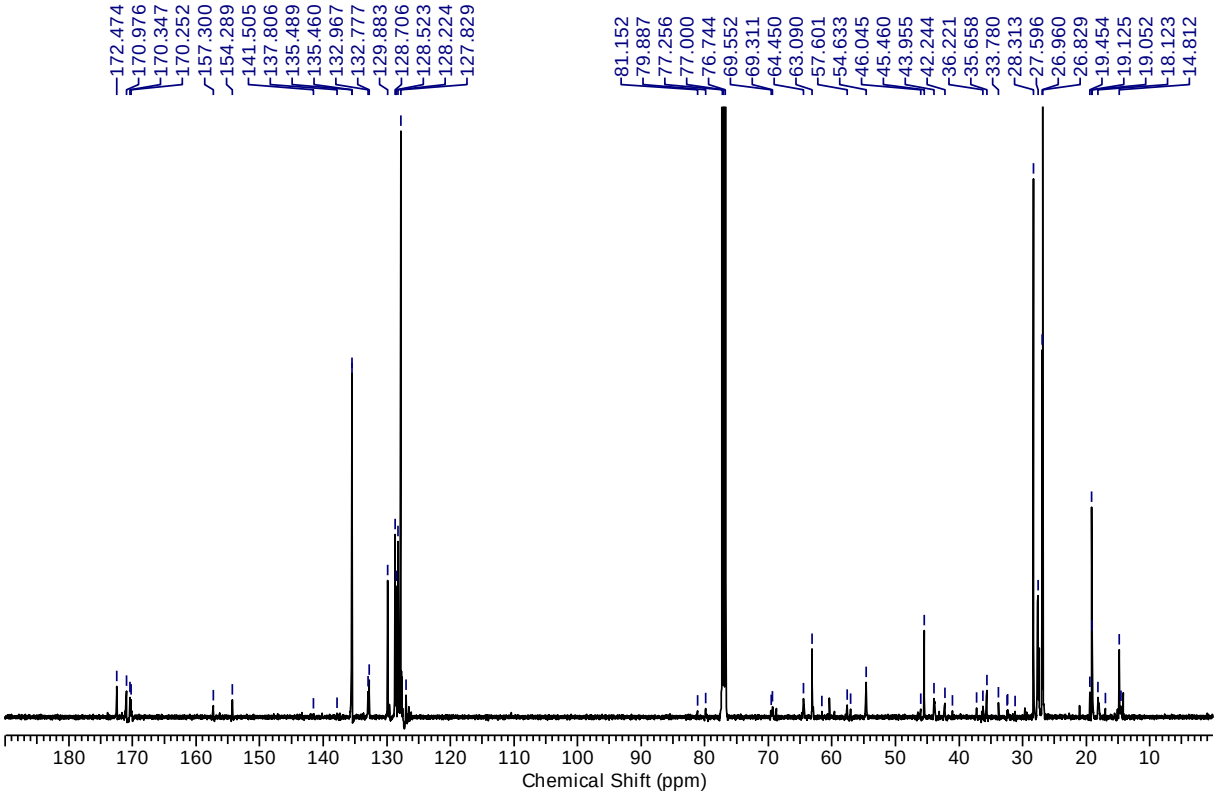


***tert*-Butyl(2*S*,3*R*)-2-(((4*S*,7*S*,10*S*,13*S*,*Z*)-7,10-di-*tert*-butyl-9-((2-((*tert*-butyldi-phenylsilyl)-oxy)ethyl)amino)-14-methyl-3,6,12-trioxo-1-phenyl-4-((*S*)-1-phenylethyl)-2,5,8,11-tetra-azapentadec-8-en-13-yl)carbamoyl)-3-methylpyrrolidine-1-carboxylate (20a)**

^{1}H-NMR(500 MHz, $CDCl_3$):

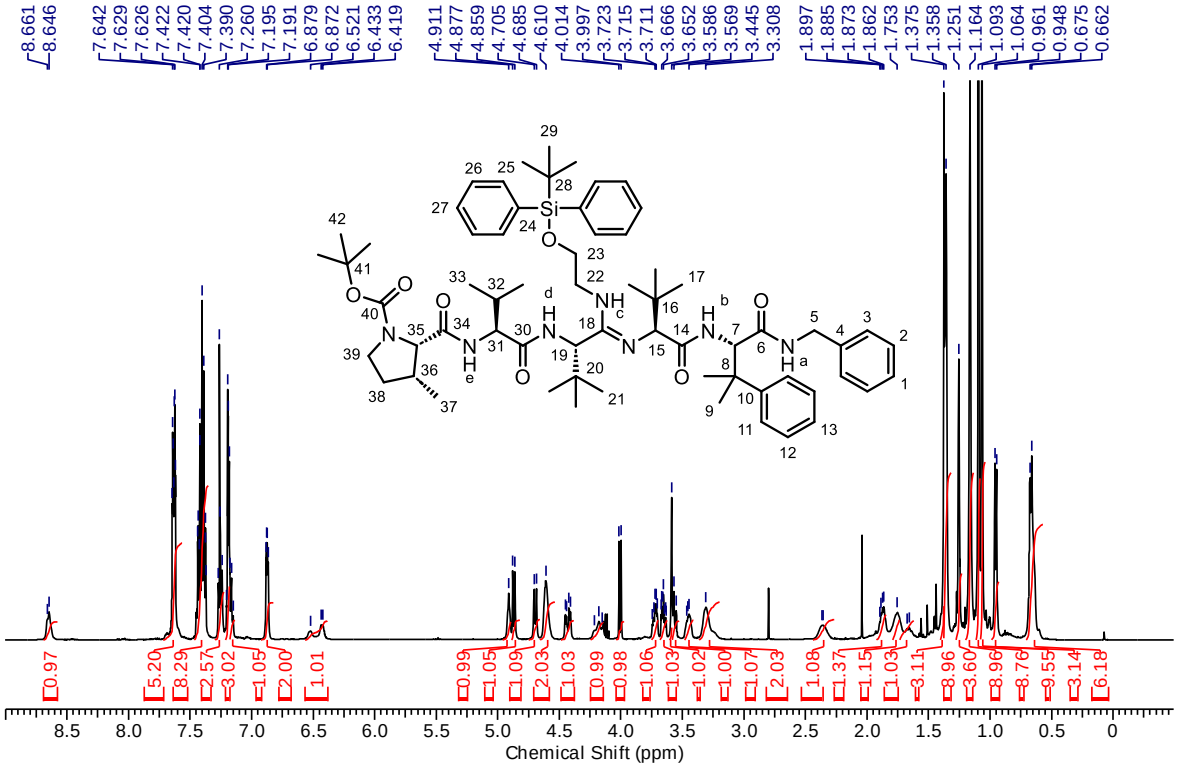


^{13}C-NMR(125 MHz, $CDCl_3$):

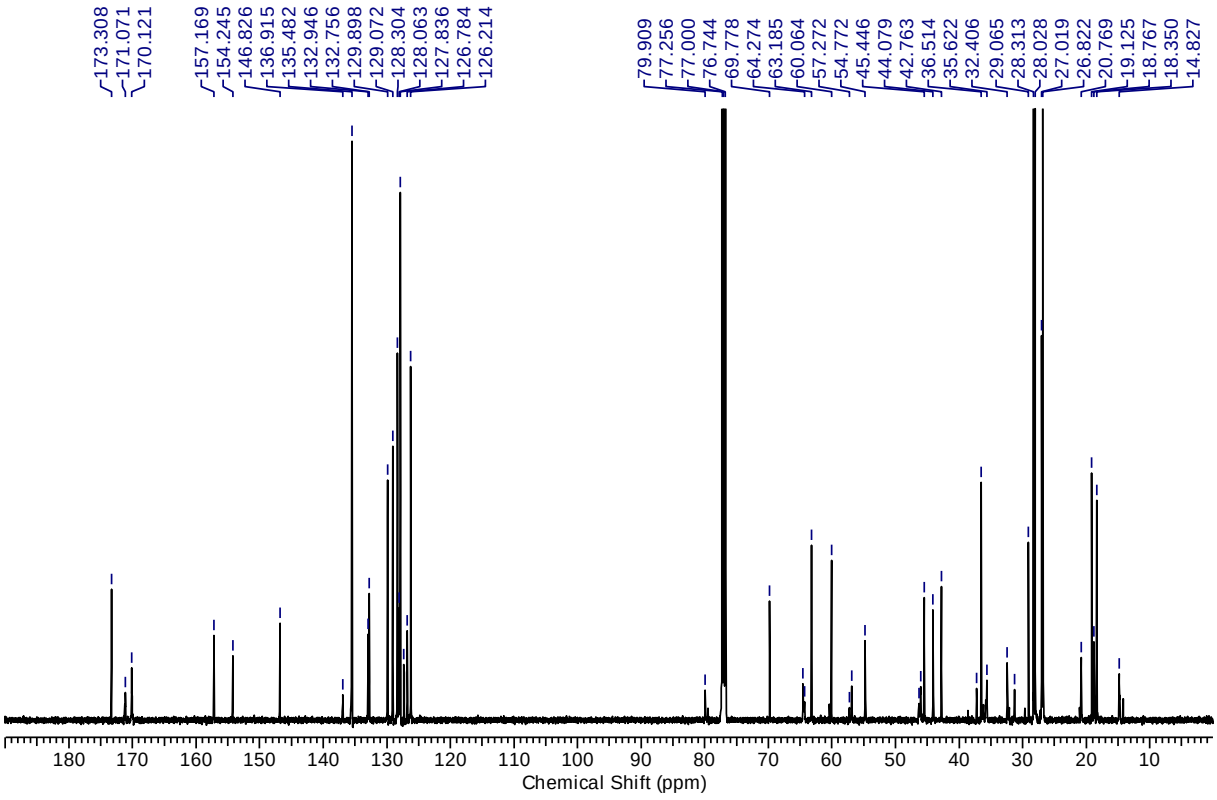


***tert*-Butyl(2*S*,3*R*)-2-(((4*S*,7*S*,10*S*,13*S*,*Z*)-7,10-di-*tert*-butyl-9-((2-((*tert*-butyldiphenylsilyl)oxy)ethyl)amino)-14-methyl-3,6,12-trioxo-1-phenyl-4-(2-phenylpropane-2-yl)-2,5,8,11-tetraazapentadec-8-en-13-yl)carbamoyl)-3-methylpyrrolidine-1-carboxylate (20b)**

^{1}H-NMR(500 MHz, $CDCl_3$):

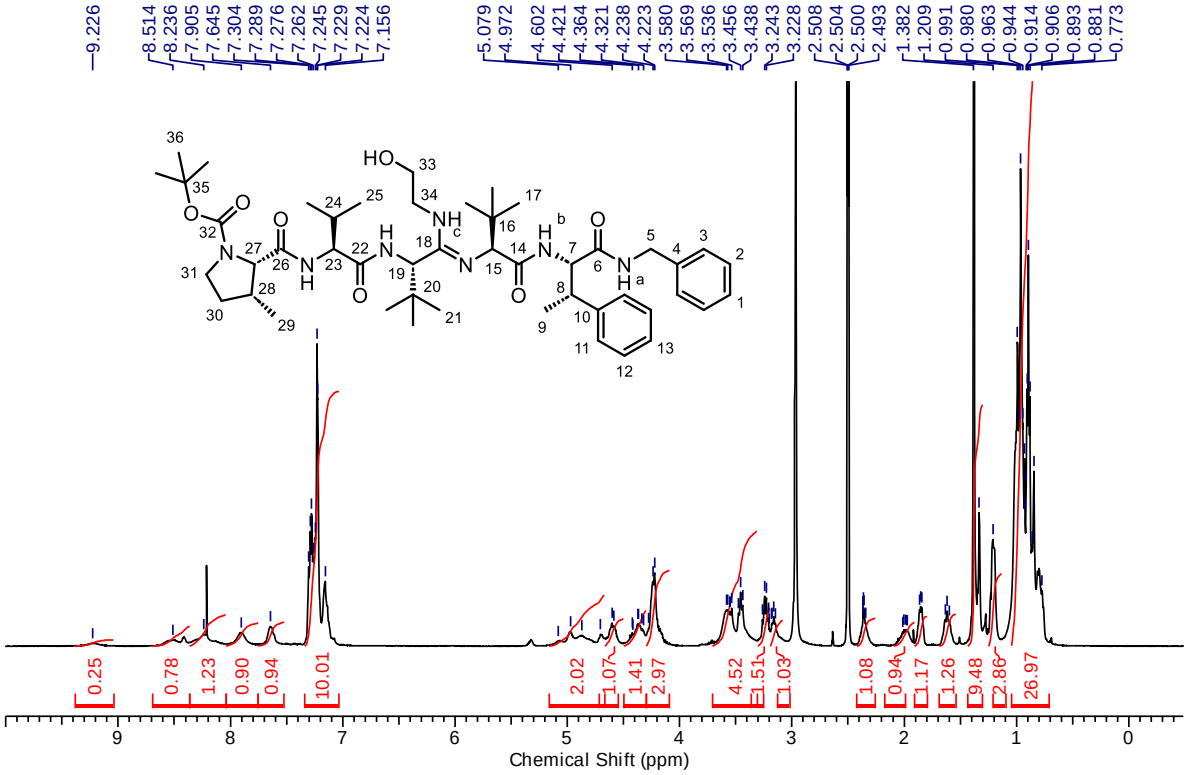


^{13}C-NMR(125 MHz, $CDCl_3$):

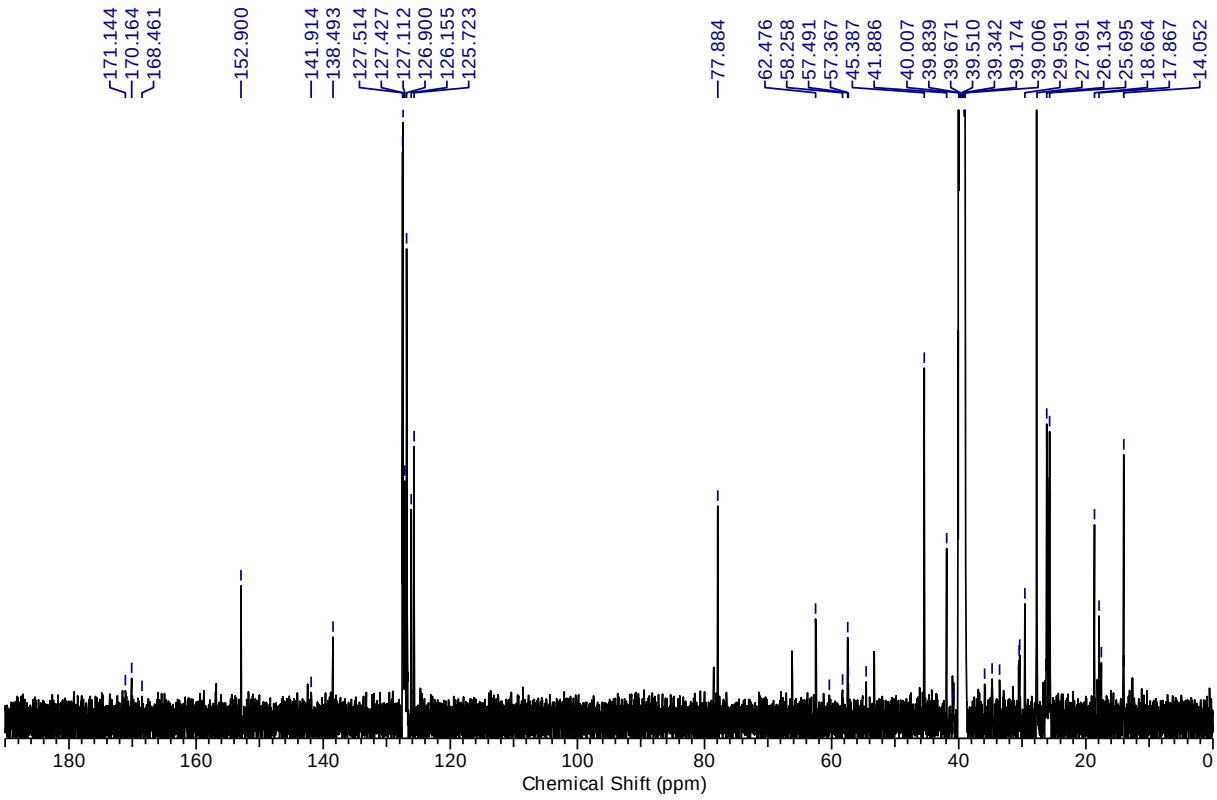


***tert*-Butyl(2*S*,3*R*)-2-(((4*S*,7*S*,10*S*,13*S*,*Z*)-7,10-di-*tert*-butyl-9-((2-hydroxyethyl)amino)-14-methyl-3,6,12-trioxo-1-phenyl-4-((*S*)-1-phenylethyl)-2,5,8,11-tetraazapentadec-8-en-13-yl)carbamoyl)-3-methylpyrrolidine-1-carboxylate (21a)**

^{1}H-NMR(500 MHz, 373 K, DMSO-d_6):

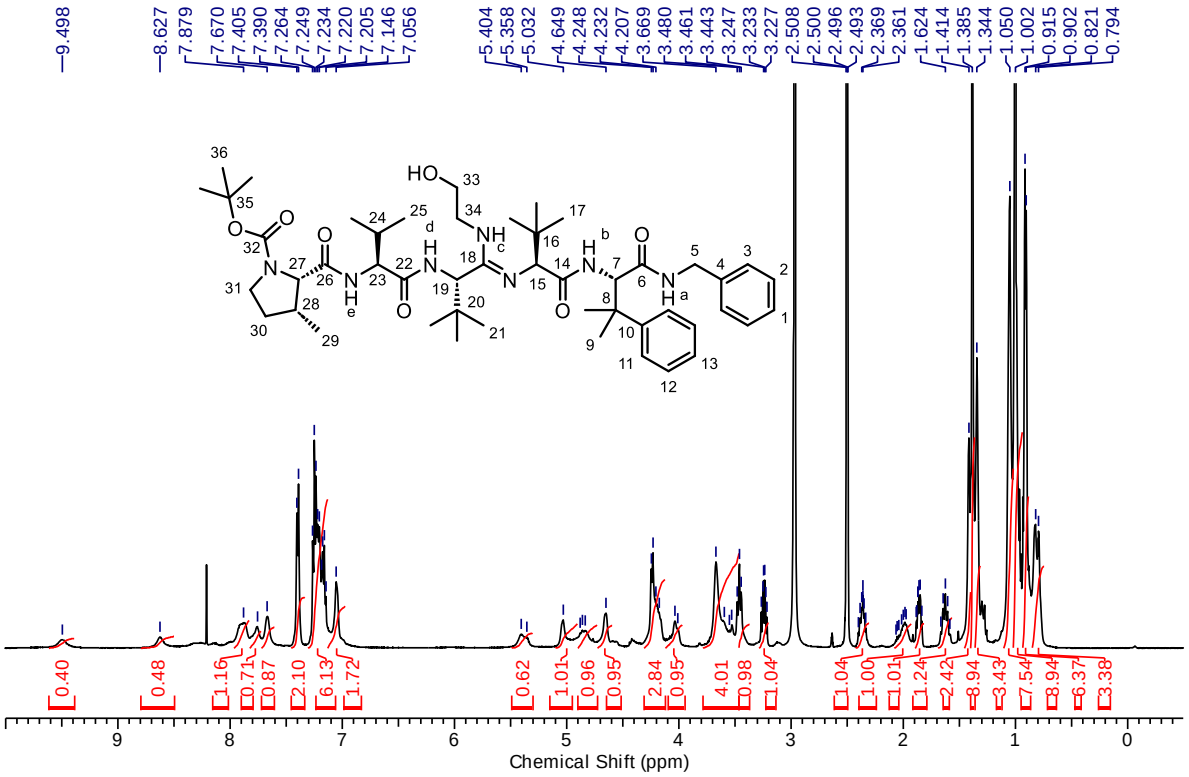


^{13}C-NMR(125 MHz, 373 K, DMSO-d_6):

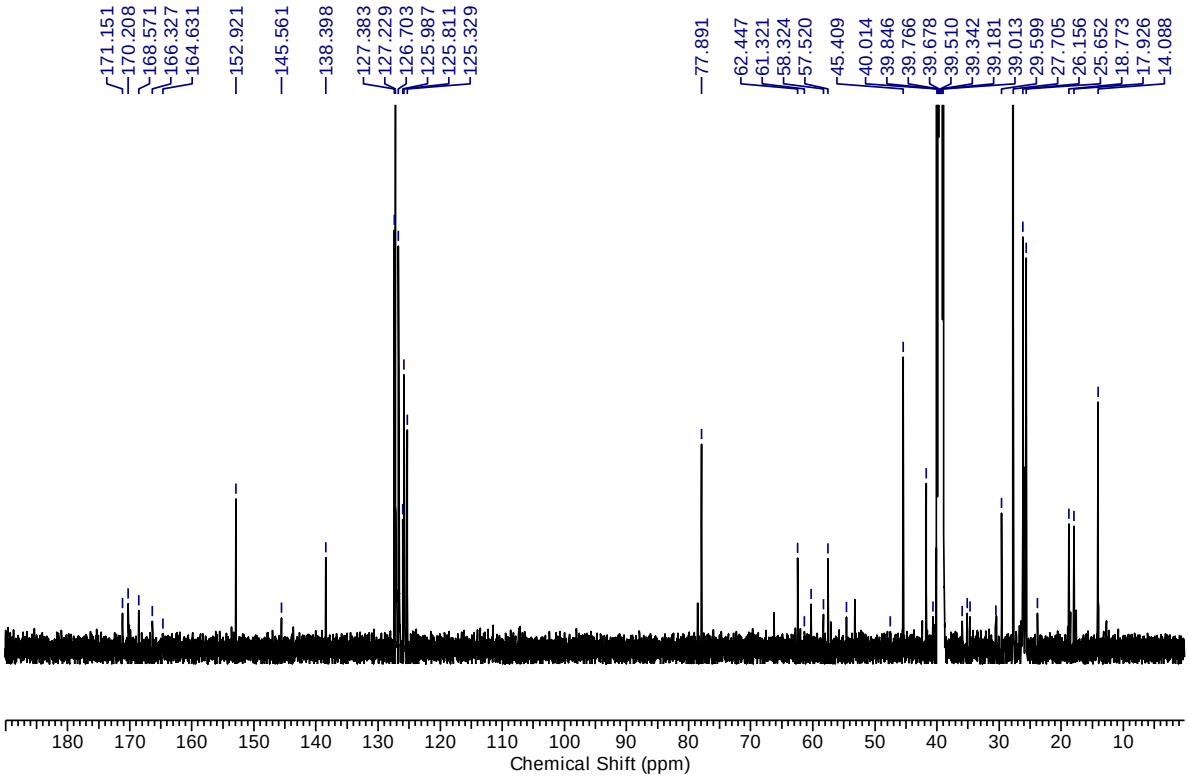


***tert*-Butyl(2*S*,3*R*)-2-(((4*S*,7*S*,10*S*,13*S*,*Z*)-7,10-di-*tert*-butyl-9-((2-hydroxyethyl)amino)-14-methyl-3,6,12-trioxo-1-phenyl-4-(2-phenylpropane-2-yl)-2,5,8,11-tetraazapentadec-8-en-13-yl)carbamoyl)-3-methylpyrrolidine-1-carboxylate (21b)**

^{1}H-NMR(500 MHz, 373 K, DMSO-d_6):

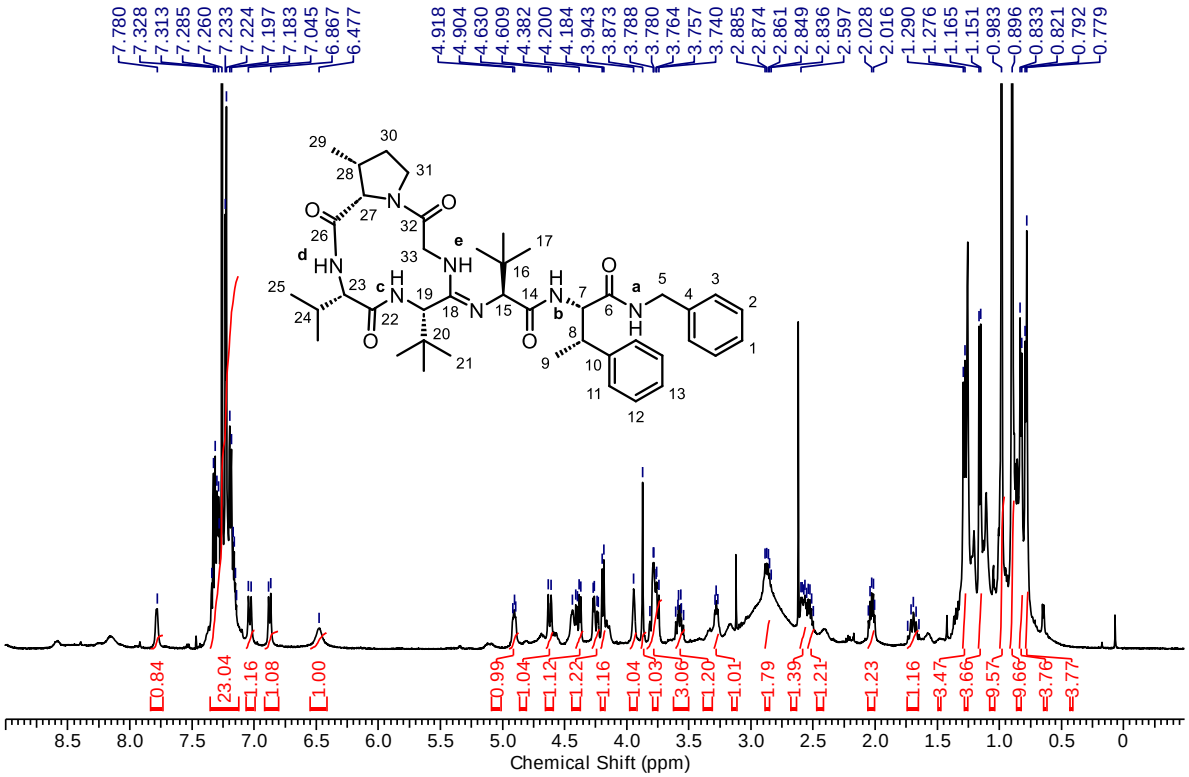


^{13}C-NMR(125 MHz, 373 K, DMSO-d_6):

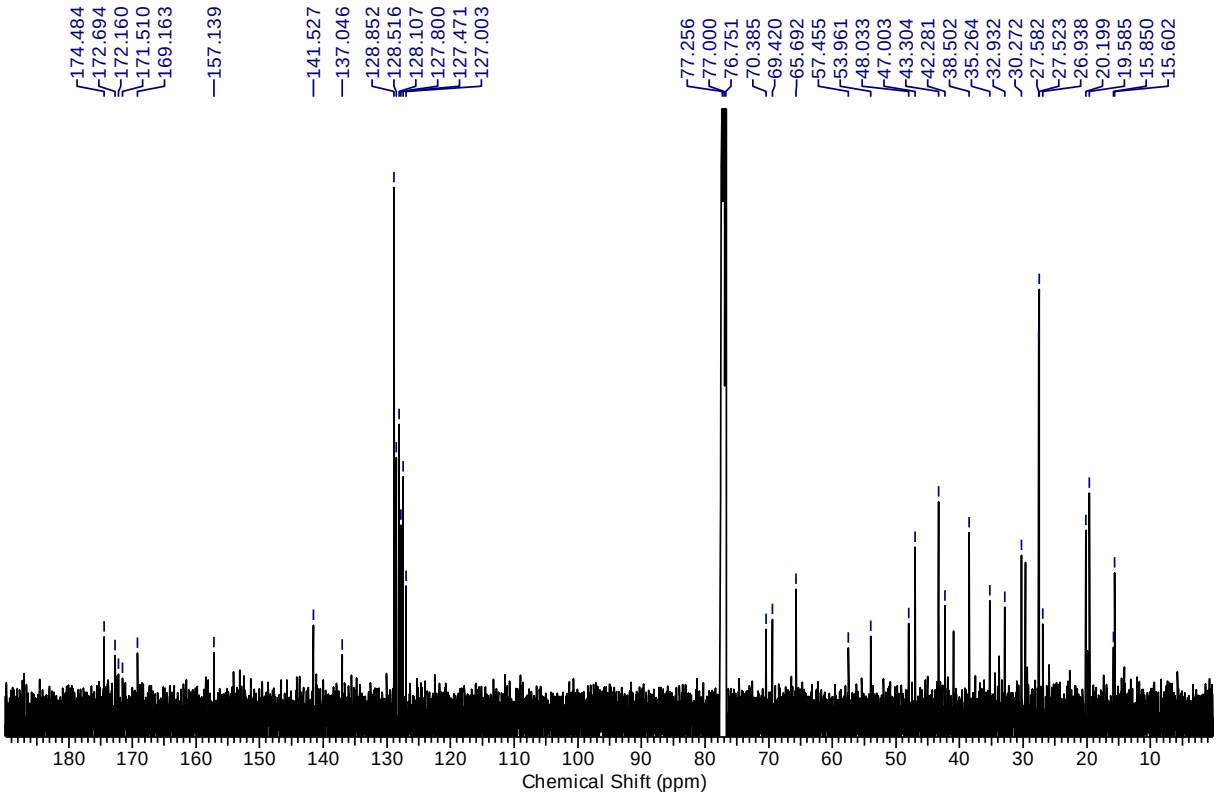


(*S*)-*N*-((2*S*,3*S*)-1-(Benzylamino)-1-oxo-3-phenylbutane-2-yl)-2-(((3*S*,6*S*,14*R*,14a*S*,*Z*)-6-(*tert*-butyl)-3-isopropyl-14-methyl-1,4,10-trioxododecahydropyrrolo[1,2-*a*][1,4,7,10]-tetraazacyclododecine-7(8*H*)-yliden)amino)-3,3-dimethylbutanamide (23a)

^{1}H-NMR(500 MHz, $CDCl_3$):

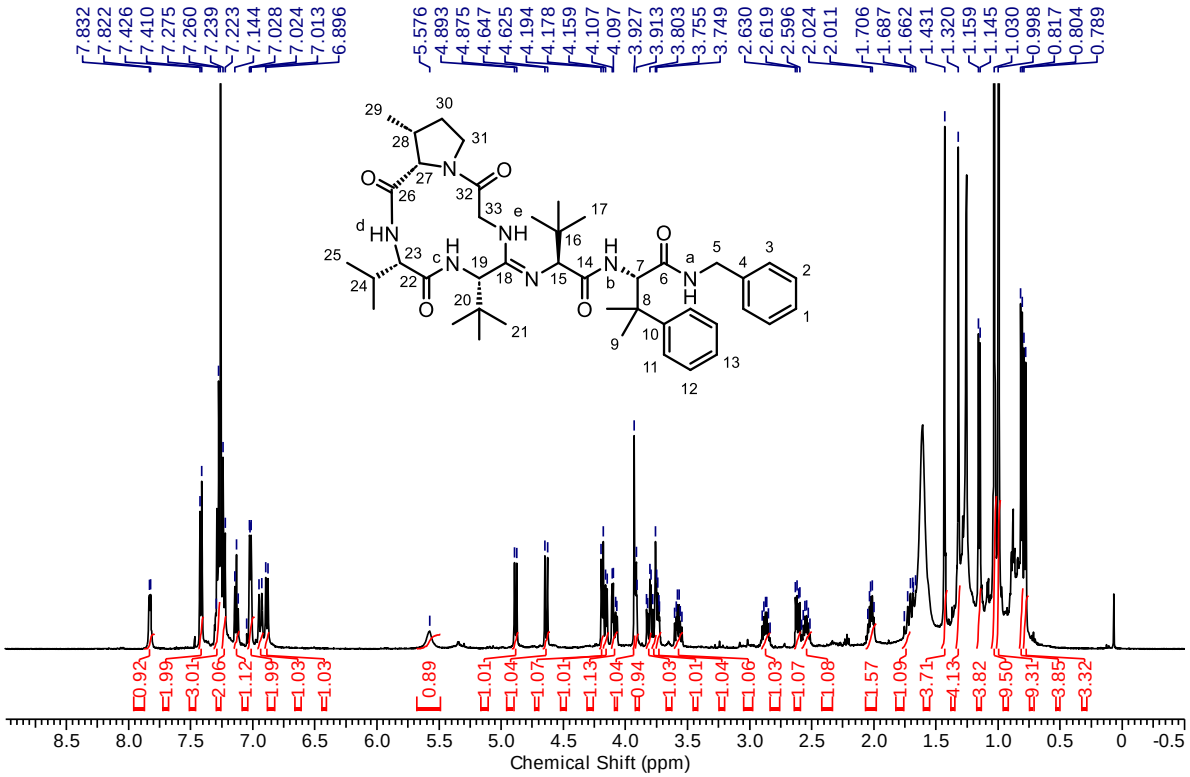


^{13}C-NMR(125 MHz, $CDCl_3$):

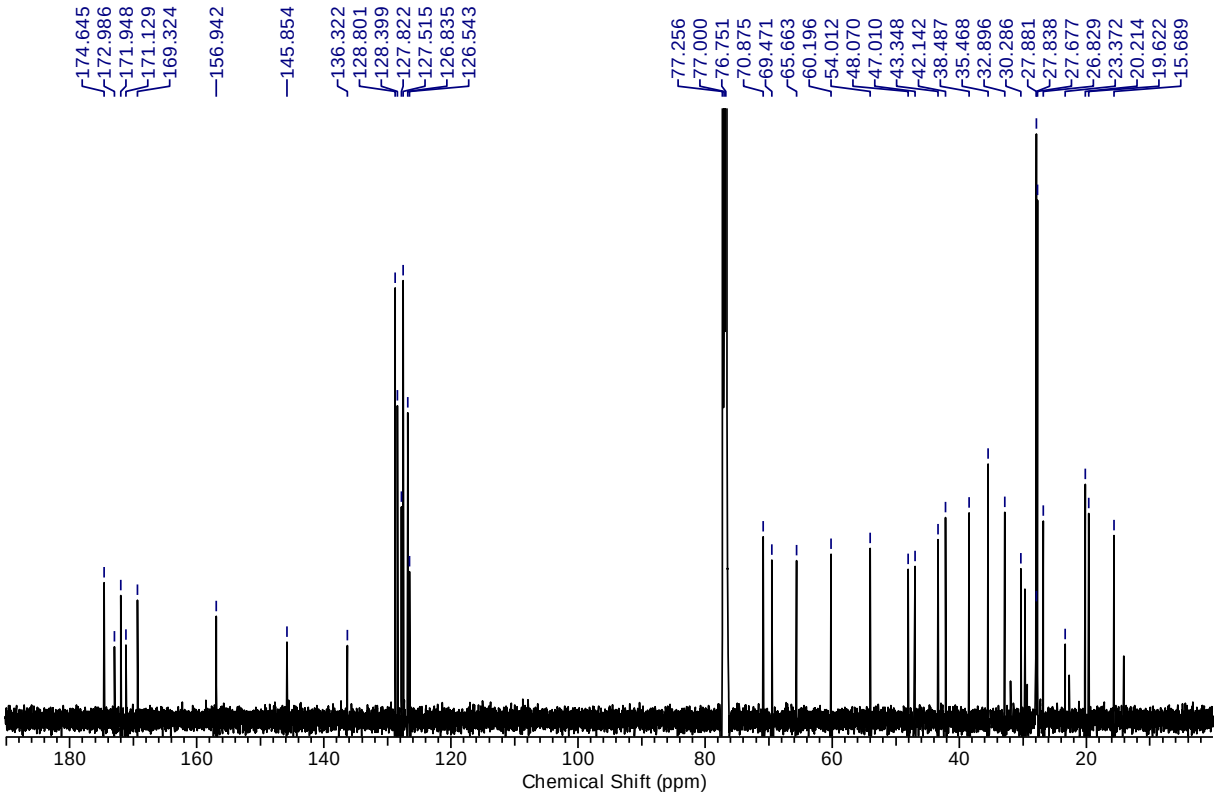


(*S*)-*N*-Benzyl-2-((*S*)-2-(((3*S*,6*S*,14*R*,14a*S*,*Z*)-6-(*tert*-butyl)-3-isopropyl-14-methyl-1,4,10-trioxododecahydropyrrolo[1,2-*a*][1,4,7,10]tetraazacyclododecine-7(8*H*)-ylidene)amino)-3,3-dimethylbutanamido)-3-methyl-3-phenylbutanamide (23b)

^{1}H-NMR(500 MHz, $CDCl_3$):



^{13}C-NMR(125 MHz, $CDCl_3$):



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