Supplementary Material (ESI) for Chemical Communications

–Supporting information

Towards the Stereochemical Assignment of Natural Lydiamycin A

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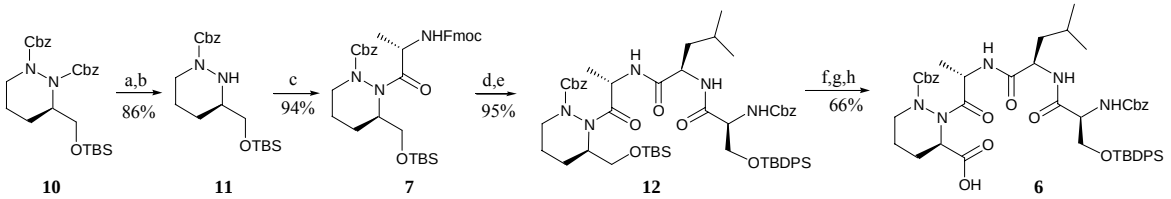
Content

General Methods

Unless otherwise noted, reagents were commercially available and used without further purification. All solvents were distilled prior to use: THF was distilled from Na/benzophenone, dichloromethane, DMF, triethylamine, collidine, acetonitrile and diisopropylethylamine were distilled from CaH_2. All non-aqueous reactions were performed under an atmosphere of nitrogen or argon using oven-dried glassware and standard syringe / septa techniques. ^1H- and ^{13}C-NMR spectra were measured in $CDCl_3$ or CD_3OD on a Bruker Avance AV500 or DPX-300 at 500 MHz (125 MHz) or 300 MHz (75 MHz), respectively. Chemical shifts are reported in ppm and were referenced to either a tetramethylsilane internal standard or the signals due to the solvent residual. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, coupling constant in Hz. Mass spectra were measured on an ABI Q-star Elite. Optical rotations were measured on a Perkin-Elmer 351 polarimeter at 589nm with a 100 mm path length cell at 22°C (reported as follows: concentration (*c* in g/100mL), solvent). The reaction progress was checked on precoated TLC plates. TLC was carried out using pre-coated sheets (Qingdao silica gel 60-F250, 0.2mm) which, after development, were visualized under UV light at 254nm, and/or staining in p-anisole, ninhydrin or phosphomolybdic acid solution followed by heating. Flash column chromatography was performed using the indicated solvents (with Rf = 2.0 – 3.0 for the desired component) on E. Qingdao silica gel 60 (230-400 mesh ASTM). HPLC was performed on Agilent 1200 system. Yields refer to chromatographically purified compounds, unless otherwise stated.

Synthesis of **6**



10 **11** **7** **12** **6**

Reagents and Conditions: (a) H_2, Pd/C; (b) Cbz-Cl, Et_3N, MeOH; (c) Fmoc-*L*-Ala, $(COCl)_2$, DMF (cat.), CH_2Cl_2, then **11**, AgCN, benzene; (d) Et_2NH, MeCN; (e) *L*-Cbz-Ser(OTBDPS)-*D*-Leu-OH, EDCI, HOBt, DIPEA; f) PPTS, MeOH; (g) DMP, $NaHCO_3$, CH_2Cl_2; (h). $NaClO_2$, NaH_2PO_4, *t*-BuOH-H_2O.

To a solution of **10** (1.52 g, 3.1 mmol) in methanol (20 mL) was added Pd/C (0.10 g, catalyst, 10% palladium on charcoal), the suspension was stirred under hydrogen atmosphere for 72 h. Pd/C was removed by filtration. The filtrate was cooled to -20 °C, triethyl amine (0.84 mL, 6.0 mmol) and benzyl chloroformate (0.68 mL, 3.4 mmol) were added. The reaction mixture was stirred at -20°C for 1 h before it was concentrated in *vacuo*. The residue was dissolved in ethyl acetate (150 mL), washed with saturated ammonium chloride (50 mL), brine (50 mL). The organic phase was dried over sodium sulfate (anhydrous), filtered and concentrated. The residue was purified by flash chromatography (ethyl acetate : hexanes = 1 : 9) to afford **11** (0.96 g, 86%). $[\alpha]^{22}_D$ -3.3 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6H), 0.89 (s, 9H), 1.32 (dq, 1H, J = 2.4 Hz, J = 7.5Hz), 1.54 (d, 1H, J = 7.5Hz), 1.61 (d, 1H, J = 7.8Hz), 1.68 (d, 1H, J = 8.4Hz), 2.88 (s, 1H), 3.01 (t, 1H, J = 7.2Hz), 3.47 (t, 1H, J = 5.4Hz), 3.60 (dd, 1H, J = 2.1Hz, J = 6.0Hz), 4.12 (d, 1H, J = 6.9Hz), 5.18 (s, 2H), 7.30-7.37 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ -5.6, -5.5, 18.2, 23.8, 25.8, 26.3, 44.9, 58.3, 65.3, 67.3, 127.9, 128.0, 128.4, 136.5, 154.9 ppm; HR-ESIMS for $C_{19}H_{33}N_2O_3Si$ (M + H): m/z, calculated: 365.2260; found: 365.2275.

To a solution of Fmoc-*L*-Ala (0.10 g, 0.3 mmol) in dichloromethane (5 mL), oxalyl chloride (0.06 mL, 0.6 mmol) was slowly added at 0 °C, followed by DMF (0.01 mL, 0.1 mmol) via a syringe. The reaction mixture was stirred at 0 °C until gas evolution had ceased. Volatiles were removed in *vacuo*. The residue

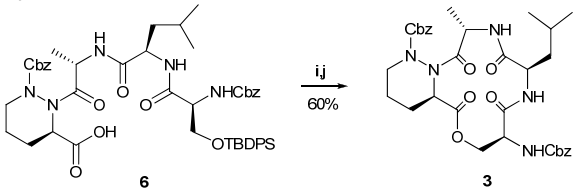
was dissolved dichloromethane (5 mL) and concentrated in *vacuo*, these procedures were repeated twice to produce the acyl chloride. The acyl chloride was dissolved in benzene (5 mL) and dropwise added to the suspension of **11** (0.11 g, 0.3 mmol) and AgCN (0.09 g, 0.6 mmol) in benzene (5 mL) at 0 ^{o}C. The reaction mixture was allowed to warm to 80 ^{o}C and stirred for 40 minutes before it was poured into saturated sodium bicarbonate (50 mL) and extracted with ethyl acetate (50 mL X 3). The combined organic phases were washed with brine (30 mL), dried over sodium sulfate (anhydrous), filtered and concentrated *in vacuo*. Purification of the residue by flash chromatography (ethyl acetate : hexances = 1 : 9) afforded **7** (0.19 g, 94%). $[\alpha]^{22}_{D}$ +10.1 (*c* 1.0, $CHCl_3$) ^{1}H NMR (500 MHz, $CDCl_3$) exists as rotational conformers: δ 0.00 (m, 6H), 0.86-0.91 (m, 9H), 1.27-1.35 (m, 3H), 1.52-1.55 (m, 1H), 1.71-2.10 (m, 3H), 3.00-3.19 (br m, 1H), 3.40-3.46 (m, 1H), 3.54-3.83 (m, 1H), 4.12-4.30 (m, 2H), 4.30-4.40 (m, 2H), 4.59-4.73 (br m, 2H), 4.90-5.25 (m, 2H), 5.61-5.90 (m, 1H), 7.23 (br s, 3H), 7.33 (t, 3H, *J* = 7.5Hz), 7.41 (t, 3H, *J* = 7.5Hz), 7.62 (d, 2H, *J* = 7.5Hz), 7.77 (d, 2H, *J* = 7.5Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.6, -5.5, 18.1, 18.5, 19.6, 22.6, 25.8, 46.6, 47.1, 47.3, 52.1, 60.1, 66.9, 68.9, 119.9(2C), 125.2, 127.1, 127.6, 128.2, 128.4, 128.6, 141.3, 144.0, 155.2, 156.0, 174.9 ppm. HR-ESIMS for $C_{37}H_{48}N_3O_6Si$ (M + H): m/z, calculated: 658.3312; found: 658.3317.

To a solution of **7** (0.99 g, 1.5 mmol) in acetonenitrile (10.0 mL) was added diethylamine (3.0 mL) at 0 ^{o}C. The reaction mixture was stirred at room temperature for 3 h before volatiles were removed in *vacuo*. The residue was dissolved in dichloromethane (5 mL) and concentrated, these procedures were repeated twice. The residue was then dried under high vacuum for 2 h. The above free amine intermediate was dissolved in dichloromethane (5 mL) and transferred to a solution of Cbz-*L*-Ser(OTBDPS)-*D*-Leu-OH (0.91 g 1.5 mmol) in dichloromethane (5 mL) *via* a cannula at 0 ^{o}C. After EDCI (1.15 g, 6.0 mmol), HOBt (0.31 g, 2.3 mmol) and triethylamine (1.0 mL, 6.0 mmol) were added, the reaction mixture was allowed to warm to room temperature and stirred for 20 h before it was poured into saturated sodium bicarbonate (50 mL) and extracted with ethyl acetate (50 mL X 3). The combined organic fractions were washed with brine (50 mL), dried over sodium sulfate (anhydrous), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate : hexanes = 1 : 4) to afford **12** (1.50 g, 95%). $[\alpha]^{22}_{D}$ +27.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) existed as rotational conformers: δ -0.07-0.09 (m, 6H), 0.84-0.92 (m, 15H), 1.06 (s, 9H), 1.28-1.32 (m, 3H), 1.48-1.57 (m, 2H), 1.57-1.70 (m, 4H), 1.85-2.07 (m, 1H), 2.96-3.10 (m, 1H), 3.36-3.75 (m, 2H), 3.83 (br s, 1H), 3.97-4.10 (m, 1H), 4.10-4.40 (m, 2H), 4.54 (br s, 2H), 4.68-4.95 (m, 1H), 4.95-5.31 (m, 4H), 5.62 (br s, 1H), 6.78-6.95 (m, 2H), 7.20-7.42 (m, 16H), 7.62-7.68 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.5, -5.4, 18.1, 18.5, 18.8, 19.2, 22.0, 22.5, 22.9, 24.8, 25.8, 26.9, 42.4, 45.8, 51.9, 52.1, 56.3, 60.1, 64.2, 67.0, 68.9, 127.8, 127.9, 128.0, 128.1, 128.2, 128.5(2C), 128.6, 129.9, 130.0, 135.5, 135.6, 156.0(2C), 169.4, 170.3, 173.5 ppm. HR-ESIMS for $C_{55}H_{78}N_5O_9Si_2$ (M + H): m/z, calculated: 1008.5338; found: 1008.5334.

To a solution of **12** (1.30 g, 1.3 mmol) in methanol (30 mL) was added PPTS (0.10 g, 0.4 mmol). The reaction mixture was refluxed for 3 h before it was concentrated in *vacuo*. The residue was dissolved in ethyl acetate (100 mL), washed with sodium bicarbonate (30 mL) and brine (30 mL). The organic phase was dried over sodium sulfate (anhydrous), filtered and concentrated. The residue was purified by flash chromatography (ethyl acetate : hexanes = 1 : 1) to produce the corresponding alcohol (0.95 g, 82%). $[\alpha]^{22}_{D}$ +16.8 (c 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) existed as rotational conformers: δ 0.88 (d, 3H, *J* = 6.5Hz), 0.91 (d, 3H, *J* = 6.0Hz), 1.06 (s, 9H), 1.22-1.34 (m, 3H), 1.50 (br s, 2H), 1.65-1.74 (m, 5H), 3.00-3.14 (m, 1H), 3.15-3.70 (m, 3H), 3.84 (br s, 1H), 4.00 (br s, 1H), 4.12-4.43 (m, 2H), 4.57 (br s, 1H), 4.65-4.95 (m, 2H), 5.05-5.13 (m, 3H), 5.22-5.34 (m, 1H), 5.62-5.78 (m, 1H), 6.77-7.12 (m, 2H), 7.27-7.45 (m, 16H), 7.44-7.65 (m, 4H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 18.5, 19.2, 19.6, 22.0, 22.9, 23.1, 24.8, 26.9, 42.0, 46.2, 51.8, 53.0, 56.7, 60.1, 64.2, 67.1, 69.6, 127.8(2C), 128.0(2C), 128.5, 128.8, 130.0, 132.6, 133.0, 135.5, 135.6, 136.3, 156.2, 158.0, 169.6, 170.5, 174.0 ppm. HR-ESIMS for $C_{49}H_{64}N_5O_9Si$ (M + H): m/z, calculated: 894.4473; found: 894.4462.
To the above alcohol (0.88 g, 1.0 mmol) in dichloromethane (20 mL), $NaHCO_3$ (0.42 g, 2.0 mmol) and DMP (0.85 g, 2.0 mmol) were added. The reaction mixture was stirred at room temperature for 2 h, and

quenched with saturated sodium thiosulfate (5 mL). Layers were separated. The aqueous phase was extracted with dichloromethane (20 mL). The combined organic phases were concentrated in *vacuo* to give the crude aldehyde. This aldehyde was not further purified, but dissolved in THF-H_2O-*t*-BuOH (20 mL, 2 : 2 : 1) and cooled to 0 ^oC. To the above solution, NaH_2PO_4 (0.62 g, 4.0 mmol) and $NaClO_2$ (0.18 g, 2.0 mmol) were added sequentially. The reaction mixture was stirred at room temperature for 10 h before saturated sodium sulfite (5 mL) was added at 0 ^oC. The solution was stirred for another 1 h., and volatiles were removed under reduced pressure. The residue was extracted with ethyl acetate (50 mL x 3). The combined organic phases were washed with brine (100 mL), dried over sodium sulfate (anhydrous), filtered and concentrated to dryness to produce the corresponding carboxylic acid **6** (0.72g, 80%), which was used in the next reactions without further purification.

Synthesis of **3**

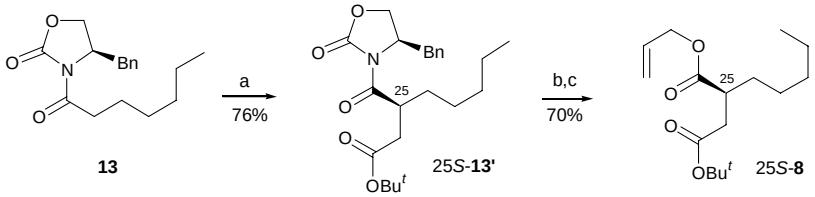


6 **3**

Reagents and reaction conditions: (i) TBAF, THF; (j) DEAD, Ph_3P, THF

To a solution of acid **6** (0.90 g, 1.0 mmol) in THF (20 mL), TBAF (5 mL, 5.0 mmol, 1.0M in THF) was added. The reaction was stirred at room temperature for 3 h and quenched with citric acid (10 mL, 10% in water). Volatiles were removed in *vacuo*, the residue was extracted with ethyl acetate (50 mL x 3). The combined organic fractions were washed with brine (100 mL), dried over sodium sulfate (anhydrous), filtered and concentrated to give the precursor of macrocyclization. This linear precursor, which had been dried under high vacuum for 2 h, was dissolved in THF (50 mL), after PPh_3 (0.52 g, 2.0 mmol) dissolved in THF (50 mL) and DEAD (0.32 mL, 2.0 mmol) were added *via* a syringe. The reaction mixture was stirred at room temperature for 24 h before it was concentrated under reduced pressure. The residue, dissolved in ethyl acetate (200 mL), was successively washed with saturated ammonium chloride (30 mL), sodium bicarbonate (30 mL) and brine (30 mL), dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. Purification with flash chromatography (ethyl acetate : Hexane = 1: 1) gave the desired marcrocycle **3** (0.32 g, 60%). $[\alpha]^{22}_D$ -12.7 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) exists as rotational conformers: δ 0.90-0.96 (d, 6H, *J* = 7.5Hz), 1.20-1.30 (m, 3H) 1.42-1.43 (m, 1H), 1.55-1.65 (m, 3H), 1.74-1.76 (m, 1H), 1.83 (br s, 2H), 3.36-3.45 (m, 1H), 4.03-408 (m, 1H), 4.24 (d, 2H, *J* = 15.0Hz), 4.43 (q, 1H, *J* = 14.5Hz), 4.55 (d, 2H, *J* = 14.5Hz), 4.98-5.10 (m, 2H), 5.12-5.25 (m, 4H), 6.61 (d, 1H, *J* = 13.0Hz), 6.72 (d, 1H, *J* = 9.5Hz), 7.28-7.39 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.1, 17.8, 19.2, 21.0, 22.5, 23.0, 24.9, 37.9(37.7), 43.5, 48.2, 51.1, 54.3(55.2), 65.7, 67.5(67.8), 69.9(69.7), 128.2, 128.4, 128.5, 128.7, 128.9, 134.9, 135.6, 136.4, 156.3, 158.3, 169.5, 169.8, 170.4, 174.3 ppm. HR-ESIMS for $C_{33}H_{42}N_5O_9$ (M+H): m/z, calculated: 652.2983; found: 652.2973.

Synthesis of 25*S*-**8**



13 25*S*-**13'** 25*S*-**8**

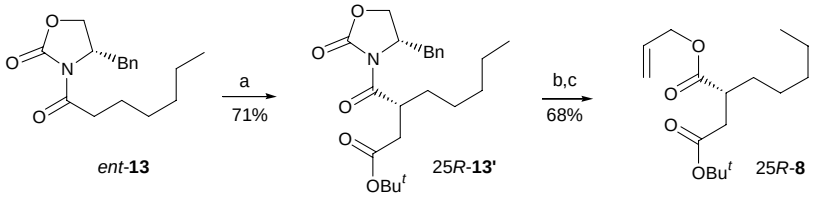
Reagents and reaction conditions: (a) LiHMDS, $BrCH_2CO_2Bu^t$, THF, -78 ^oC; (b) LiOH, H_2O_2, THF-H_2O; (c) allyl bromide, DIPEA, MeCN.

To a solution of **13** (4.13 g, 14.2 mmol) in THF (50 mL) was added LiHMDS (17 mL, 17.0 mmol, 1.0 M in THF) at -78 ^oC. 1 hour later, *tert*-butyl bromoacetate (4.0 mL, 27.0 mmol) was added *via* a syringe. The

reaction mixture was stirred at -78 °C for 2 h, then warmed to 0 °C and quenched with Et_2O (100 mL) and aqueous ammonium chloride (50 mL). Layers were separated, and the aqueous phase was extracted with diethyl ether (50 mL x 2). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. Purification by flush chromatography (ethyl acetate : hexanes = 1 : 8) gave 25*S*-**13'** (4.35 g, 76%). $[\alpha]^{22}_D$ -30.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 7Hz), 1.30-1.40 (m, 6H), 1.44 (m, 10H), 1.67-1.75 (m, 1H), 2.48 (dd, 1H, *J* = 4.5Hz, 17.0Hz), 2.72-2.83 (m, 2H), 3.35 (dd, 1H, *J* = 3.0Hz, 13.5Hz), 4.15-4.20 (m, 3H), 4.20-4.69 (m, 1H), 7.27-7.28 (m, 3H), 7.33-7.36 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 22.5, 26.5, 28.1, 31.7, 31.9, 37.1, 37.5, 39.3, 55.6, 65.9, 80.7, 127.2, 128.9, 129.5, 135.8, 153.0, 171.5, 176.1 ppm. HR-ESIMS for $C_{23}H_{33}NO_5Na$ (M+Na): m/z, calculated: 426.2256; found: 426.2276.

To a solution of 25*S*-**13'** (2.24 g, 5.6 mmol) in H_2O-THF (25 mL, 1 : 1.5) was added LiOH (0.47 g, 11.1 mmol) and H_2O_2 (5 mL, 30% in water). The reaction mixture was stirred at room temperature for 18 h before it was quenched by addition of sodium sulfite at 0 °C. Volatiles were removed under reduced pressure, and the residue was extracted with diethyl ether (50 mL x 2). The organic phases were discarded, while the aqueous layer was acidified to pH 4.0 with citric acid (1.0 N aqueous solution) and then extracted with ethyl acetate (50 mL x 2). The combined organic fractions were washed with brine (50 mL), dried over sodium sulfate (anhydrous), filtered and concentrated to yield crude acid. The acid, without further purification, was dissolved in acetonitrile (20 mL). After allyl bromide (2.4 mL, 27.7 mmol) and diisopropylethylamine (4.6 mL, 27.7 mmol) were added, the reaction mixture was stirred at room temperature for 24 h. Volatiles were removed under reduced pressure, the residue was dissolved in ethyl acetate (100 mL) and washed with saturated sodium bicarbonate (50 mL), brine (50 mL). The organic phase was then dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. Purification by flash chromatography (ethyl acetate : hexanes = 1 : 15) afforded the allyl ester 25*S*-**8** (1.1 g, 70%). $[\alpha]^{22}_D$ -3.6 (*c* 0.3, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 (t, 3H, *J* = 7.0Hz), 1.35-1.34 (m, 6H), 1.43 (s, 9H), 1.45-1.52 (m, 1H), 1.61-1.66 (m, 1H), 2.36 (dd, 1H, *J* = 5.0Hz, 16.5Hz), 2.62 (dd, 1H, *J* = 9.0Hz, 16.5Hz), 2.78-2.83 (m, 1H), 4.55-4.63 (m, 2H), 5.22, (dd, 1H, *J* = 1.5Hz, 10.5Hz), 5.32, (dd, 1H, *J* = 1.5Hz, 17.0Hz), 5.87-5.95 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.4, 26.6, 28.0, 31.6, 31.9, 37.4, 41.5, 65.1, 80.6, 118.1, 132.3, 171.1, 174.7 ppm; HR-ESIMS for $C_{16}H_{28}O_4Na$ (M+Na): m/z, calculated: 307.1885; found: 307.1893.

Synthesis of 25*R*-**8**

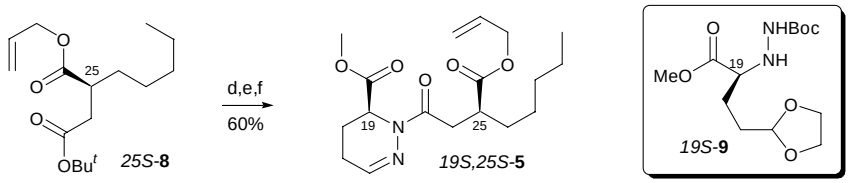


Reagents and reaction conditions: (a) LiHMDS, $BrCH_2CO_2Bu^t$, THF, -78 °C; (b) LiOH, H_2O_2, THF-H_2O; (c) allyl bromide, DIPEA, MeCN.

To a solution of *ent*-**13** (4.21 g, 15.0 mmol) in THF (50 mL) was added LiHMDS (17.3 mL, 17.3 mmol, 1.0 M in THF) at -78 °C. 1 hour later, *tert*-butyl bromoacetate (4.1 mL, 27.5 mmol) was added *via* a syringe. The reaction mixture was stirred at -78 °C for 2 h, then warmed to 0 °C and quenched with Et_2O (100 mL) and aqueous ammonium chloride (50 mL). Layers were separated, and the aqueous phase was extracted with diethyl ether (50 mL x 2). The combined organic layers were washed with brine (100 mL), dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. Purification by flush chromatography (ethyl acetate : hexanes = 1 : 8) gave 25*R*-**13'** (4.3 g, 71%).
To a solution of 25*R*-**13'** (2.51 g, 5.0 mmol) in H_2O-THF(25 mL, 1 : 1.5) was added LiOH (0.53 g, 12.4 mmol) and H_2O_2 (5 mL, 30% in water). The reaction mixture was stirred at room temperature for 18 h before it was quenched by addition of sodium sulfite at 0 °C. Volatiles were removed under reduced

pressure, and the residue was extracted with diethyl ether (50 mL x 2). The organic phases were discarded, while the aqueous layer was acidified to pH 4.0 with citric acid (1.0 N aqueous solution) and extracted with ethyl acetate (50 mL x 2). The combined organic fractions were washed with brine (50 mL), dried over sodium sulfate (anhydrous), filtered and concentrated to yield crude acid. The acid, without further purification, was dissolved in acetonitrile (20 mL). After allyl bromide (3.0 mL, 31.0 mmol) and diisopropylethylamine (5.2 mL, 31.0 mmol) were added, the reaction mixture was stirred at room temperature for 24 h. Volatiles were removed under reduced pressure, the residue was dissolved in ethyl acetate (100 mL) and washed with saturated sodium bicarbonate (50 mL), brine (50 mL). The organic phase was then dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. Purification by flash chromatography (ethyl acetate : hexanes = 1 : 15) afforded the allyl ester 25*R*-**8** (1.2 g, 68%). The analytical data was identical to its enantiomer 25*S*-**8**.

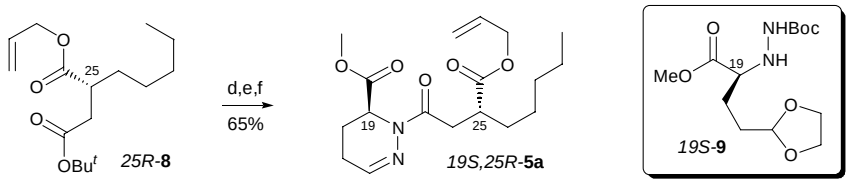
Synthesis of 19*S*,25*S*-**5**



Reagents and reaction conditions: (d) TFA, CH_2Cl_2; (e) $(COCl)_2$, DMF, CH_2Cl_2, then 19*S*-**9**, collidine; (f) TFA-H_2O

To a solution of 25*S*-**8** (0.30 g, 1.0 mmol) in dichloromethane (5 mL) was added TFA (1.0 mL) at 0 ^oC. The reaction mixture was stirred for 3 h before it was concentrated in *vacuo* to produce the carboxylic acid. This acid, without further purification, was dissolved in dichloromethane (5 mL) at 0 ^oC. After oxalyl chloride (0.17 mL, 2.0 mmol), followed by DMF (0.01 mL, 0.1 mmol), were added, the reaction mixture was allowed to warm to room temperature within 1 hour and stirred at room temperature for further 2 h. Volatiles were removed in *vacuo* to afford acyl chloride. After the acyl chloride was dried under high vacuum for 2 h, it was dissolved in dichloromethane (5 mL) and transferred to a solution of 19*S*-**9** (0.16 g, 0.5 mmol) and collidine (0.17 mL, 1.3 mmol) in dichloromethane (10 mL). The reaction mixture was stirred under an argon atmosphere for 20 min then poured into saturated sodium bicarbonate (20 mL). Layers were separated, and the aqueous phase was extracted with dichloromethane (20 mL x 2). The combined organic fractions were washed with brine (20 mL), dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. This intermediate, without further purification, was treated with TFA (10 mL, 90% in water) for 30 min at room temperature. The reaction mixture was then concentrated in *vacuo* and partitioned between dichloromethane (50 mL) and citric acid (20 mL, 10% solution in water). Layers were separated and the organic phase was washed with water (20 mL), saturated sodium bicarbonate (20 mL) and brine (20 mL), dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. The residue, after purification by flash chromatography (ethyl acetate : hexanes = 1 : 2), afforded 19*S*,25*S*-**5** (0.10 g, 60%). HR-ESIMS for $C_{18}H_{28}N_2O_5Na$ (M+Na): m/z, calculated: 375.1896; found: 375.1801. Analytical data for 19*S*,25*S*-**5**: $[\alpha]^{22}_D$ +15.7 (*c* 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ 0.87 (t, 3H, 7.0Hz), 1.26-1.36 (m, 6H), 1.56-1.59 (m, 1H),1.65-1.68 (m, 1H), 1.87-1.90 (m, 1H), 2.07-2.12 (m, 1H), 2.18-2.22 (m, 1H), 2.33-2.37 (m, 1H), 2.90 (dd, 1H, *J* = 4.5Hz, 17.0Hz), 2.95-2.98 (m, 1H), 3.16 (dd, 1H, *J* = 7.0Hz, 10.0Hz), 3.72 (s, 3H), 4.58-4.63 (m, 2H), 5.19-5.22 (m, 2H), 5.32 (dd, 1H, *J* = 1.5Hz, *J* = 17.5Hz), 5.90-5.96 (m, 1H), 6.89 (d, 1H, *J* = 4.5Hz) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 18.8, 20.5, 22.4, 26.7, 31.7, 32.2, 35.0, 41.0, 50.9, 52.6, 65.0, 117.8, 132.6, 141.3, 170.5, 173.0, 175.6 ppm.

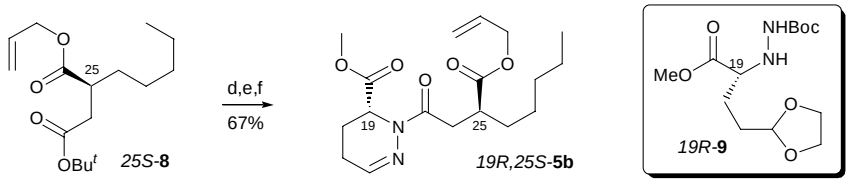
Synthesis of 19*S*,25*R*-**5a**



Reagents and reaction conditions: (d) TFA, CH_2Cl_2; (e) $(COCl)_2$, DMF, CH_2Cl_2, then 19*S*-**9**, collidine; (f) TFA-H_2O

To a solution of 25*R*-**8** (0.21 g, 0.7 mmol) in dichloromethane (5 mL) was added TFA (0.7 mL) at 0 ^oC. The reaction mixture was stirred for 3 hour before it was concentrated in *vacuo* to produce the carboxylic acid. This acid, without further purification, was dissolved in dichloromethane (5 mL) at 0 ^oC. After oxalyl chloride (0.12 mL, 1.4 mmol), followed by DMF (0.002 mL, 0.07 mmol), were added, the reaction mixture was allowed to warm to room temperature within 1 hour and stirred at room temperature for further 2 h. Volatiles were removed in *vacuo* to afford acyl chloride. After the acyl chloride was dried under high vacuum for 2 h, it was dissolved in dichloromethane (5 mL) and transferred to a solution of 19*S*-**9** (0.11 g, 0.35 mmol) and collidine (0.12 mL, 0.9 mmol) in dichloromethane (10 mL). The reaction mixture was stirred under an argon atmosphere for 20 min and then poured into saturated sodium bicarbonate (20 mL). Layers were separated, and the aqueous phase was extracted with dichloromethane (20 mL x 2). The combined organic fractions were washed with brine (20 mL), dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. This intermediate, without further purification, was treated with TFA (7 mL, 90% in water) for 30 min at room temperature. The reaction mixture was then concentrated in *vacuo* and partitioned between dichloromethane (50 mL) and citric acid (20 mL, 10% solution in water). Layers were separated and the organic phase was washed with water (20 mL), saturated sodium bicarbonate (20 mL) and brine (20 mL), dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. The residue, after purification by flash chromatography (ethyl acetate : hexanes = 1 : 2), afforded 19*S*,25*R*-**5a** (0.11 g, 65%). Analytical data for 19*S*,25*R*-**5a**: $[\alpha]^{22}_D$ -12.6 (*c* 1.0, $CHCl_3$) ^1H NMR (500 MHz, $CDCl_3$): δ 0.87 (t, 3H, *J* = 4.0Hz), 1.28-1.31 (m, 6H), 1.57-1.60 (m, 1H), 1.67-1.69 (m, 1H), 1.88-1.90 (m, 1H), 2.05-2.09 (m, 1H), 2.17-2.23 (m, 1H), 2.22-2.28 (m, 1H), 2.87-2.91 (m, 1H), 2.93-2.96 (m, 1H), 3.17 (q, 1H, *J* = 8.0Hz), 3.72 (s, 3H), 4.59-4.62 (m, 2H), 5.19-5.24 (m, 2H), 5.31-5.35 (dd, 1H, *J* = 1.5Hz, 17.5Hz), 5.90-5.96 (m, 1H), 6.89 (d, 1H, *J* = 4.0Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 18.8, 20.5, 22.4, 26.7. 31.7, 32.0, 35.1, 41.2, 50.9, 52.5, 65.0, 117.7, 132.6, 141.4, 170.4, 172.9, 175.1 ppm.

Synthesis of 19*R*,25*S*-**5b**

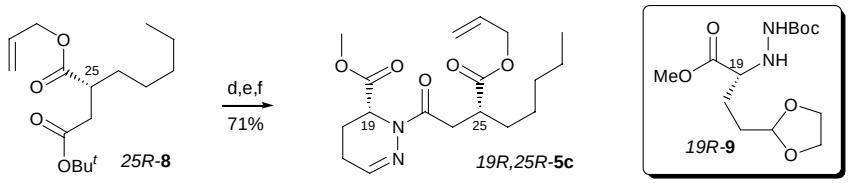


Reagents and reaction conditions: (d) TFA, CH_2Cl_2; (e) $(COCl)_2$, DMF, CH_2Cl_2, then 19*R*-**9**, collidine; (f) TFA-H_2O

To a solution of 25*S*-**8** (0.24 g, 0.8 mmol) in dichloromethane (5 mL) was added TFA (0.8 mL) at 0 ^oC. The reaction mixture was stirred for 3 h before it was concentrated in *vacuo* to produce the carboxylic acid. This acid, without further purification, was dissolved in dichloromethane (5 mL) at 0 ^oC. After oxalyl chloride (0.14 mL, 1.6 mmol), followed by DMF (0.01 mL, 0.1 mmol), were added, the reaction mixture was allowed to warm to room temperature within 1 hour and stirred at room temperature for 2 hour. Volatiles were removed in *vacuo* to afford acyl chloride. After the acyl chloride was dried under high vacuum for 2 hour, it was dissolved in dichloromethane (5 mL) and transferred to a solution of 19*R*-**9** (0.13 g, 0.4 mmol) and collidine (0.14 mL, 1.0 mmol) in dichloromethane (10 mL). The reaction

mixture was stirred under an argon atmosphere for 20 min and then poured into saturated sodium bicarbonate (20 mL). Layers were separated, and the aqueous phase was extracted with dichloromethane (20 mL x 2). The combined organic fractions were washed with brine (20 mL), dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. This intermediate, without further purification, was treated with TFA (8 mL, 90% in water) for 30 min at room temperature. The reaction mixture was then concentrated in *vacuo* and partitioned between dichloromethane (50 mL) and citric acid (20 mL, 10% solution in water). Layers were separated and the organic phase was washed with water (20 mL), saturated sodium bicarbonate (20 mL) and brine (20 mL), dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. The residue, after purification by flash chromatography (ethyl acetate : hexanes = 1 : 2), afforded 19*R*,25*S*-**5b** (0.09 g, 67%). Its analytical data was identical to 19*S*,25*R*-**5a**.

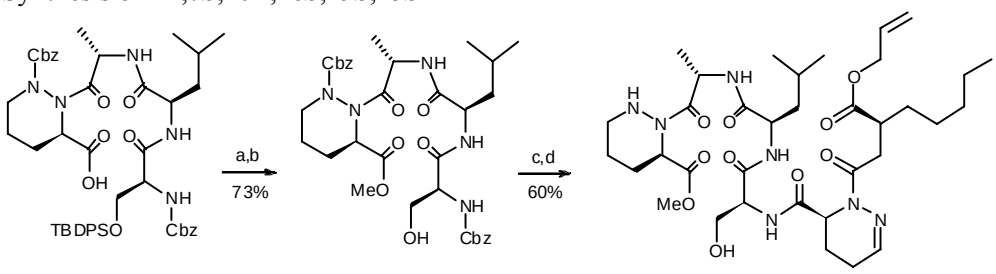
Synthesis of 19*R*,25*R*-**5c**



Reagents and reaction conditions: (d) TFA, CH_2Cl_2; (e) $(COCl)_2$, DMF, CH_2Cl_2, then 19*R*-**9**, collidine; (f) TFA-H_2O

To a solution of 25*R*-**8** (0.27 g, 0.9 mmol) in dichloromethane (5 mL) was added TFA (0.9 mL) at 0 ^oC. The reaction mixture was stirred for 3 h before it was concentrated in *vacuo* to produce the carboxylic acid. This acid, without further purification, was dissolved in dichloromethane (5 mL) at 0 ^oC. After oxalyl chloride (0.15 mL, 1.8 mmol), followed by DMF (0.01 mL, 0.1 mmol), was added, the reaction mixture was allowed to warm to room temperature within 1 hour and stirred at room temperature for 2 hours. Volatiles were removed in *vacuo* to afford acyl chloride. After the acyl chloride was dried under high vacuum for 2 hours, it was dissolved in dichloromethane (5 mL) and transferred to a solution of 19*R*-**9** (0.14 g, 0.45 mmol) and collidine (0.15 mL, 1.2 mmol) in dichloromethane (10 mL). The reaction mixture was stirred under an argon atmosphere for 20 min and then poured into saturated sodium bicarbonate (20 mL). Layers were separated, and the aqueous phase was extracted with dichloromethane (20 mL x 2). The combined organic fractions were washed with brine (20 mL), dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. The intermediate, without further purification, was treated with TFA (9 mL, 90% in water) for 30 min at room temperature. The reaction mixture was then concentrated in *vacuo* and partitioned between dichloromethane (50 mL) and citric acid (20 mL, 10% solution in water). Layers were separated and the organic phase was washed with water (20 mL), saturated sodium bicarbonate (20 mL) and brine (20 mL), dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. The residue, after purification by flash chromatography (ethyl acetate : hexanes = 1 : 2), afforded 19*R*,25*R*-**5c** (0.11 g, 71%). Its analytical data was identical to 19*S*,25*S*-**5**.

Synthesis of 2*R*,7*S*,10*R*,16*S*,19*S*,25*S*-**14**

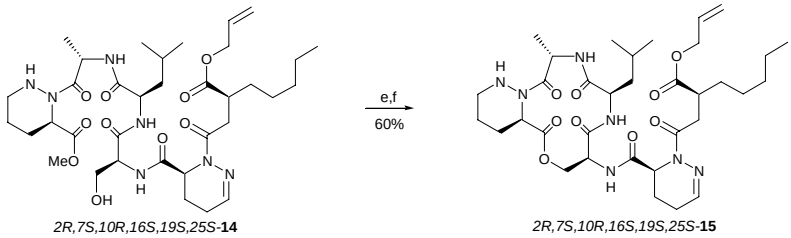


Reagents and reaction conditions: (a) CH_2N_2, Ether; (b) TBAF, THF; (c) H_2, Pd/C, MeOH; (d) 19*S*,25*S*-**16**, HATU, HOAt, DIPEA, DMF;

To 2*R*,7*S*,10*R*,16*S*-**6** (0.54 g, 0.6 mmol) in THF (30 mL) was added freshly prepared CH_2N_2 (10.0 mmol) in ether at 0 ^oC. The solution was stirred for 3h before glacial acetic acid (5 mL) was added. The reaction mixture was stirred for further 1h, was then poured into saturated sodium bicarbonate (50 mL) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. The residue was purified by flash chromatography (ethyl acetate : hexanes = 1 : 1) to give the corresponding ester. The resulting methyl ester was dissolved in dry THF (40 mL), TBAF (3.0 mL, 3.0 mmol, 1M in THF,) was added at 0 ^oC. The reaction solution was stirred at room temperature for 3 h. Volatiles were removed under reduced pressure, the residue was dissolved in ethyl acetate (150 mL) and washed with critic acid (30 mL, 15 % solution in water), saturated ammonium chloride (30 mL) and brine (30 mL). The organic phase was dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. The residue was purified by flash chromatography (ethyl acetate : hexanes = 3 : 1) to afford 2*R*,7*S*,10*R*,16*S*-**6'** (0.30g, 73%). Analytical data: ^1H NMR (500 MHz, $CDCl_3$) exists as rotational conformers: δ 0.90 (br s, 6H), 1.21-1.29 (m, 3H), 1.39-1.47 (m, 1H), 1.52-1.64 (m, 2H), 1.71-1.78 (m, 2H), 2.04-2.14 (m, 2H), 2.99-3.04 (m, 1H), 3.32-3.44 (m, 2H), 3.59-3.70 (m, 3H), 4.20-4.27 (m, 3H), 4.43-4.50 (m, 1H), 4.77-4.92 (m, 1H), 5.11-5.23 (m, 5H), 5.96-6.07 (m, 1H), 6.65 (br s, 1H), 7.19 (br s, 1H), 7.31-7.35 (br m, 10H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.6, 14.5, 18.6, 21.6, 23.7, 24.4, 24.8, 39.5, 45.7(45.5), 50.7, 51.4, 52.3, 57.0, 62.8, 67.3, 69.1, 128.0, 128.1, 128.2, 128.5(2C), 128.6, 135.2, 136.0, 155.7, 156.2, 169.7, 170.6, 171.5(172.1), 174.4(175.7) ppm.

2*R*,7*S*,10*R*,16*S*-**6'** (0.07 g, 0.1 mmol) was dissolved in methanol (10 mL), after a catalytic amount of Pd/C (10%) was added, the reaction mixture was exposed to hydrogen atmosphere. The reaction was monitored by thin layer chromatography until all the starting material was consumed (ca 3 h). Then it was filtered through a pad of Celite to remove the catalyst. The filtrate was concentrated in *vacuo* to afford the corresponding free amine. The amine, freshly prepared acid 19*S*,25*S*-**16** (0.04 g, 0.1 mmol) and HOAt (0.03 g, 0.22 mmol) were dissolved in DMF (5 mL) at 0 ^oC. To the above solution, HATU (0.09 g, 0.22 mmol) and diisopropylethylamine (0.1 mL, 0.55 mmol) were added. The reaction solution was stirred at room temperature for 20 h, then poured into saturated sodium bicarbonate (50 mL) and extracted with ethyl acetate (50mL x 3). The combined organic layers were washed with brine (50 mL), dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. The residue was purified by flash chromatography (ethyl acetate) to afford 2*R*,7*S*,10*R*,16*S*,19*S*,25*S*-**14** (0.04 g, 60%). $[\alpha]^{22}_D$ +16.0 (*c* 0.3 $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, 3H, *J* = 7.0Hz), 0.91 (d, 3H, *J* = 5.5Hz), 0.94 (d, 3H, *J* = 6.0Hz), 1.26-1.36 (m, 9H), 1.44-1.49 (m, 1H), 1.58-1.67 (m, 6H), 1.76-1.84 (m, 1H), 1.86-1.89 (m, 1H), 2.21-2.26 (m, 3H), 2.41 (d, 1H, *J* = 15.0Hz), 2.75 (q, 1H, *J* = 13.0Hz), 2.93-3.00 (m, 2H), 3.07-3.13 (m, 2H), 3.62 (d, 1H, *J* = 8.5Hz), 3.75 (s, 3H), 3.89 (br s, 1H), 4.15 (d, 1H, *J* = 12.0Hz), 4.29 (d, 1H, *J* = 11.5Hz), 4.38-4.43 (m, 2H), 4.52-4.64 (m, 2H), 5.02 (d, 1H, *J* = 4.5Hz), 5.15 (d, 1H, *J* = 4.5Hz), 5.20-5.34 (m, 3H), 5.88-5.94 (m, 1H), 6.79 (d, 1H, *J* = 8.0Hz), 6.96-7.00 (m, 2H), 7.08 (d, 1H, *J* = 7.0Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 18.1, 18.5, 20.4, 21.6, 21.8, 22.5, 23.0, 24.8, 25.7, 26.6, 31.6, 32.1, 35.2, 39.4, 41.0, 46.1, 47.0, 51.2, 51.9, 52.6, 52.8, 55.8, 62.4, 65.2, 117.9, 132.3, 143.8, 170.1, 171.2, 171.3(2C), 174.5, 174.9, 175.7 ppm. HR-ESIMS for $C_{35}H_{58}N_7O_{10}$ (M+H): m/z, calculated: 736.4245; found: 736.4258.

Synthesis of 2*R*,7*S*,10*R*,16*S*,19*S*,25*S*-**15** from 2*R*,7*S*,10*R*,16*S*,19*S*,25*S*-**14**

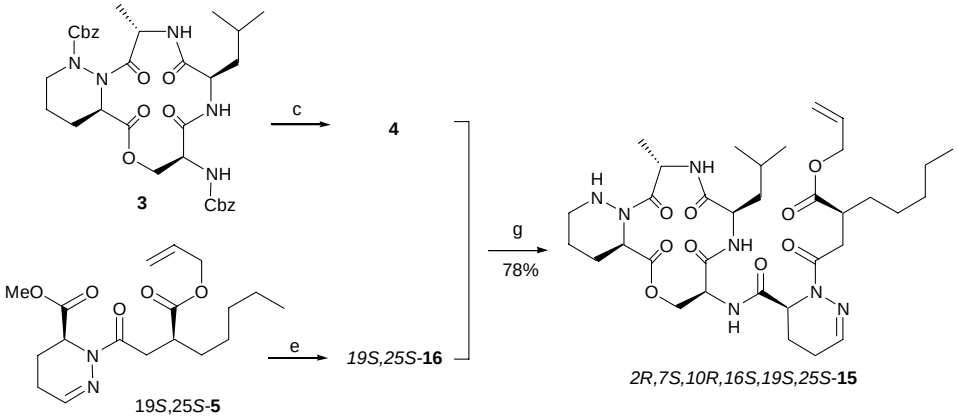


2R,7S,10R,16S,19S,25S-**14** *2R,7S,10R,16S,19S,25S*-**15**

Reagents and reaction conditions: (e) LiOH, THF-MeOH-H_2O; (f) DEAD, PPh_3, THF;

2*R*,7*S*,10*R*,16*S*,19*S*,25*S*-**14** (0.04 g, 0.05 mmol) was dissolved in THF-H_2O (4 ml, 1 : 1). LiOH (0.004 g, 0.1 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 1 hour before it was concentrated in *vacuo*. The aqueous residue was acidified with 1 N HCl to pH 3. Layers were separated, and the aqueous layer was extracted with ethyl acetate (20 mL x 2). The combined organic phases were washed with brine (20 mL), dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo* to give the corresponding acid. The crude acid, without further purification, was dissolved in THF (5 mL) and chilled in an ice-water bath. After DEAD (15 μL 0.1 mmol) and PPh_3 (0.03 g, 0.1 mmol) were added, the solution was stirred at room temperature for 24 h. Volatiles were removed in *vacuo*, the residue was purified by flash chromatography (ethyl acetate : hexanes = 2 : 1) to afford *2R,7S,10R,16S,19S,25S*-**15** (0.02 g, 60%). $[\alpha]^{22}_D$ +2.0 (*c* 0.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88-0.90 (m, 6H), 0.93 (d, 3H, *J* = 6.5Hz), 1.27 (d, 3H, *J* = 7.5Hz), 1.31-1.38 (m, 6H), 1.49-1.52 (m, 2H), 1.62-1.65 (m, 2H), 1.74-1.87 (m, 5H), 2.24-2.28 (m, 3H), 2.51-2.58 (m, 2H), 2.73-2.78 (m, 1H), 2.97-3.03 (m, 2H), 3.39 (dd, 1H, *J* = 11.5Hz, 15.5Hz), 3.94 (d, 1H, *J* = 11.0Hz), 4.33-4.37 (m, 1H), 4.50-4.52 (m, 2H), 4.60-4.62 (m, 2H), 4.74 (q, 1H, *J* = 4.0Hz), 5.18 (d, 1H, *J* = 4.0Hz), 5.24-5.27 (m, 2H), 5.38 (dd, 1H, *J* = 1.5Hz, 17.0Hz), 5.50 (dd, 1H, *J* = 6.5Hz, 9.5Hz), 5.89-5.96 (m, 1H), 6.54 (d, 1H, *J* = 9.5Hz), 6.76 (d, 1H, *J* = 8.0Hz), 7.03 (s, 1H), 7.38 (d, 1H, *J* = 8.0Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 16.8, 17.8, 20.6, 21.8, 21.9, 22.4, 23.0, 24.7, 24.8, 26.7, 31.6, 31.7, 34.6, 37.1, 42.1, 43.6, 47.0, 51.7(3C), 52.9, 65.7, 65.9, 118.1, 132.0, 144.9, 169.0, 170.3, 170.4, 170.6, 173.5, 174.6, 176.0 ppm. HR-ESIMS m/z calcd for $C_{34}H_{54}N_7O_9$ (M+H), 704.3983; Found 704.3971.

Synthesis of 2*R*,7*S*,10*R*,16*S*,19*S*,25*S*-**15** from **3** and 19*S*,25*S*-**5**

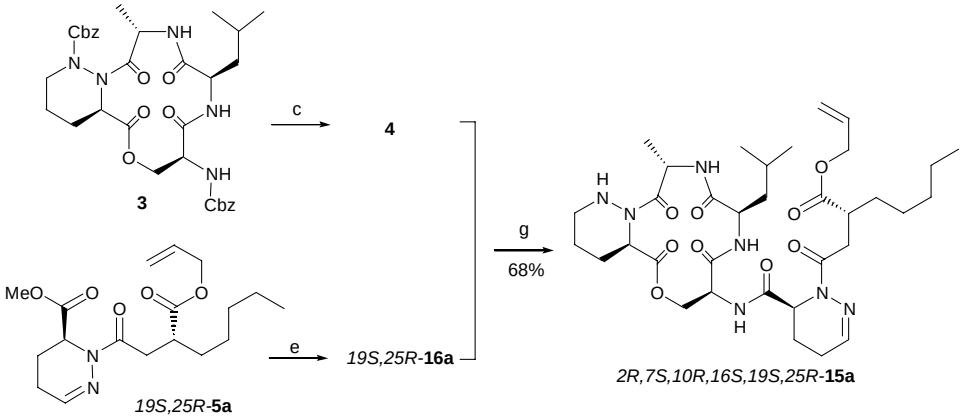


Reagents and reaction conditions: (c) H_2, Pd/C, MeOH; (e) LiOH, THF-MeOH-H_2O; (g) HATU, HOAt, DIPEA, DMF;

Compound **3** (0.13 g, 0.2 mmol) was dissolved in methanol (20 mL). After a catalytic amount of Pd/C (10%) was added, the reaction mixture was exposed to hydrogen atmosphere. The reaction was monitored by thin layer chromatography until all the starting material was consumed (ca 3 h). It was then filtered through a pad of Celite to remove the catalyst. The filtrate was concentrated in *vacuo* to afford the free amine **4**. While 19*S*,25*S*-**5** (0.08 g, 0.22 mmol) was dissolved in THF-H_2O (ca 5 mL, 1 : 1) at 0 ^oC and lithium hydroxide (0.02 g, 0.44 mmol) was added to the solution. The reaction mixture was stirred at room temperature and monitored by thin layer chromatography until starting ester was consumed (ca. 3 h). Volatiles were removed under reduced pressure and the residue was diluted with brine (5 mL) and extracted with diethyl ether (20 mL x 2). The organic phase was discarded; and the aqueous phase was acidified to pH 3 with citric acid (30mL, 15% solution in water) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo* to give the corresponding acid 19*S*,25*S*-**16**. Acid 19*S*,25*S*-**16** and free amine **4** were dissolved in DMF (30 mL) and chilled with an ice - water bath. HOAt (0.25 g, 0.66 mmol), followed by HATU (0.09 g, 0.66 mmol), were added, and diisopropylethylamine (0.58 mL, 3.3 mmol)

was added 10 min later. The reaction mixture was then stirred at room temperature for 24 h, before it was concentrated in *vacuo*. The residue was dissolved in ethyl acetate – benzene (200 mL, 3 : 1) and washed with water (50 mL), saturated sodium bicarbonate (50 mL) and brine (50 mL). The organic phase was dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. The residue was purified by flash chromatography (ethyl acetate : hexanes = 2 : 1) to produce 2*R*,7*S*,10*R*,16*S*,19*S*,25*S*-**15** (0.12 g, 78%). HR-ESIMS m/z calcd for $C_{34}H_{54}N_7O_9$ (M+H), 704.3983; Found 704.3970. Analytical data was identical to the product obtained from linear precusor **14**.

Synthesis of 2*R*,7*S*,10*R*,16*S*,19*S*,25*R*-**15a** from **3** and 19*S*,25*R*-**5a**

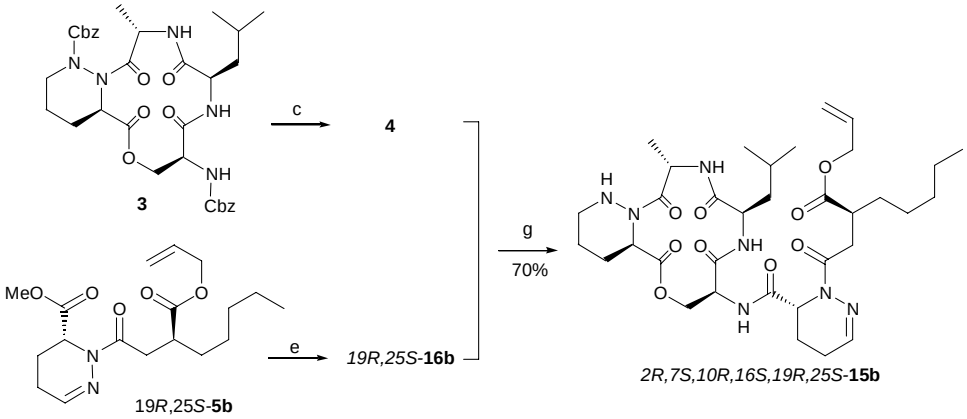


Reagents and reaction conditions: (c) H_2, Pd/C, MeOH; (e) LiOH, THF-MeOH-H_2O; (g) HATU, HOAt, DIPEA, DMF;

Compound **3** (0.19 g, 0.3 mmol) was dissolved in methanol (20 mL). After a catalytic amount of Pd/C (10%) was added, the reaction mixture was exposed to hydrogen atmosphere. The reaction was monitored by thin layer chromatography until all the starting material was consumed (ca 3 h). It was then filtered through a pad of Celite to remove the catalyst, and the filtrate was concentrated in *vacuo* to afford the free amine **4**. While 19*S*,25*R*-**5a** (0.12 g, 0.33 mmol) was dissolved in THF-H_2O (ca 5 mL, 1 : 1) at 0 ^oC, lithium hydroxide (0.03 g, 0.66 mmol) was added to the solution. The reaction mixture was stirred at room temperature and monitored by thin layer chromatography until all starting ester was consumed (ca. 3 h). Volatiles were removed under reduced pressure and the residue was diluted with brine (5 mL) and extracted with diethyl ether (20 mL x 2). The organic phase was discarded, and the aqueous phase was acidified to pH 3 with citric acid (30mL, 15% solution in water) and extracted with ethyl acetate (30 mL x 3). The combined organic layers were washed with brine (30 mL), dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo* to give the corresponding acid 19*S*,25*R*-**16a**. The above acid 19*S*,25*R*-**16a** and free amine **4** were dissolved in DMF (30 mL) and chilled with an ice - water bath. HOAt (0.38 g, 0.99 mmol), followed by HATU (0.13 g, 0.99 mmol) were added, and diisopropylethylamine (0.87 mL, 5.0 mmol) was added 10 min later. The reaction mixture was stirred at room temperature for 24 h, before it was concentrated in *vacuo*. The residue was dissolved in ethyl acetate – benzene (200 mL, 3 : 1) and washed with water (50 mL), saturated sodium bicarbonate (50 mL) and brine (50 mL). The organic phase was dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. The residue was purified by flash chromatography (ethyl acetate : hexanes = 2 : 1) to produce 2*R*,7*S*,10*R*,16*S*,19*S*,25*R*-**15a** (0.16 g, 68%). Analytical data: $[\alpha]^{22}_D$ +27.0 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 0.87-0.90 (m, 6H), 0.92 (d, 3H, *J* = 6.5Hz), 1.26 (d, 3H, *J* = 6.5Hz), 1.30-1.35 (m, 6H), 1.60-1.86 (m, 9H), 2.19 (d, 1H, *J* = 17.5Hz), 2.30 (d, 1H, *J* = 13.5Hz), 2.39-2.42 (m, 2H), 2.71-2.78 (m, 1H), 2.83-2.88 (m, 1H), 2.94-2.97 (m, 1H), 3.04-3.14 (m, 2H), 3.91 (d, 1H, *J* = 11.5Hz), 4.28-4.32 (m, 1H), 4.41 (d, 1H, *J* = 8.5Hz), 4.55-4.60 (m, 3H), 4.70 (d, 1H, *J* = 7.0Hz), 5.12 (d, 1H, *J* = 5.0Hz), 5.20-5.23 (m, 2H), 5.32 (d, 1H, *J* = 17.0Hz), 5.47-5.50 (m, 1H), 5.87-5.91 (m, 1H), 6.64 (d, 1H, *J* = 9.0Hz), 7.01 (d, 1H, *J* = 3.5Hz), 7.27 (br s, 1H), 7.36 (d, 1H, *J* = 7.5Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 16.9, 17.5, 20.4, 22.0(2C), 22.4, 22.9, 24.8(2C), 26.7, 31.6, 32.1, 35.7, 37.2, 41.7,

43.5, 47.1, 51.4, 51.6, 51.9, 52.7, 65.4, 66.4, 118.0, 132.2, 145.0, 169.0, 170.2, 170.3, 170.7, 173.1, 175.1, 175.5 ppm.

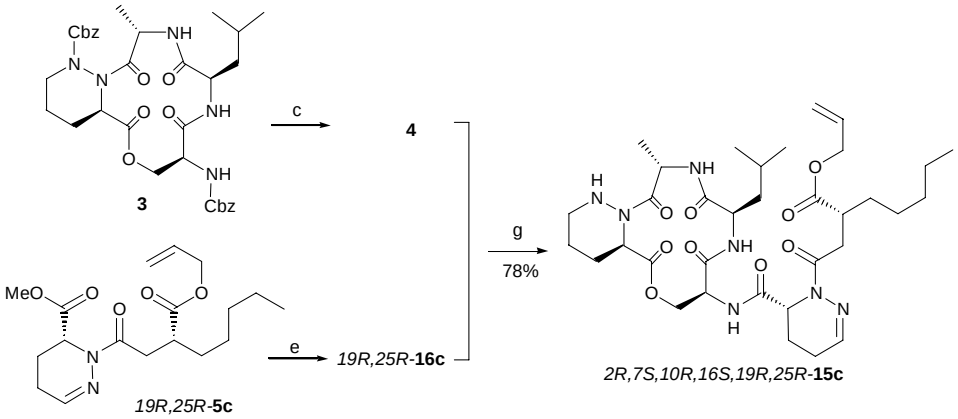
Synthesis of 2*R*,7*S*,10*R*,16*S*,19*R*,25*S*-**15b** from **3** and 19*R*,25*S*-**5b**



Reagents and reaction conditions: (c) H_2, Pd/C, MeOH; (e) LiOH, THF-MeOH-H_2O; (g) HATU, HOAt, DIPEA, DMF;

Compound **3** (0.19 g, 0.3 mmol) was dissolved in methanol (20 mL). After a catalytic amount of Pd/C (10%) was added, the reaction mixture was exposed to hydrogen atmosphere. The reaction was monitored by thin layer chromatography until all the starting material was consumed (ca 3 h). It was then filtered through a pad of Celite to remove the catalyst. The filtrate was concentrated in *vacuo* to afford the free amine **4**. While 19*R*,25*S*-**5b** (0.12 g, 0.33 mmol) was dissolved in THF-H_2O (ca 5 mL, 1 : 1) at 0 ^oC. After lithium hydroxide (0.03 g, 0.66 mmol) was added to the solution, the reaction mixture was stirred at room temperature and monitored by thin layer chromatography until all starting ester was consumed (ca. 3 h). Volatiles were removed under reduced pressure and the residue was diluted with brine (5 mL) and extracted with diethyl ether (20 mL x 2). The organic phase was discarded, and the aqueous phase was acidified to pH 3 with citric acid (30mL, 15% solution in water) and extracted with ethyl acetate (30 mL x 3). The combined organic fractions were washed with brine (30 mL), dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo* to give the corresponding acid 19*R*,25*S*-**16b**. The above acid 19*R*,25*S*-**16b** and free amine **4** were dissolved in DMF (30 mL) and chilled with an ice - water bath. HOAt (0.38 g, 0.99 mmol), followed by HATU (0.13 g, 0.99 mmol), was added, and diisopropylethylamine (0.87 mL, 5.0 mmol) was added 10 min later. The reaction mixture was then stirred at room temperature for 24 h, before it was concentrated in *vacuo*. The residue was dissolved in ethyl acetate – benzene (200 mL, 3 : 1) and washed with water (50 mL), saturated sodium bicarbonate (50 mL) and brine (50 mL). The organic phase was dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. The residue was purified by flash chromatography (ethyl acetate : hexanes = 2 : 1) to produce 2*R*,7*S*,10*R*,16*S*,19*R*,25*S*-**15b** (0.16 g, 70%). Analytical data: $[\alpha]^{22}_D$ +4.3 (c 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 0.87 (d, 3H, J = 6.0Hz), 0.88-0.91 (m, 6H), 1.28 (d, 3H, J = 7.0 Hz), 1.32-1.34 (m, 4H), 1.39-1.42 (m, 2H), 1.44-1.53 (m, 3H), 1.61-1.67 (m, 2H), 1.72-1.91 (m, 4H), 2.20-2.33 (m, 3H), 2.57-2.65 (m, 1H), 2.77 (q, 1H, J = 11.0Hz), 2.88 (dd, 1H, J = 4.0Hz, 17.0Hz), 3.02-3.05 (m, 1H), 3.26- 3.32 (m, 2H), 3.97 (d, 1H, J = 11.5Hz), 4.36-4.39 (m, 1H), 4.55-4.64 (m, 4H), 4.77 (dd, 1H, J = 2.5Hz, 9.0Hz), 4.94 (d, 1H, J = 4.5Hz), 5.22-5.25 (m, 2H), 5.32 (dd, 1H, J = 2.0Hz, 17.5Hz), 5.57-5.60 (m, 1H), 5.89-5.94 (m, 1H), 6.31 (d, 1H, J = 9.5Hz), 6.42 (d, 1H, J = 8.5Hz), 7.06 (d, 1H, J = 4.0Hz), 7.46 (d, 1H, J = 9.0Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 17.0, 17.4, 20.3, 22.0, 22.2, 22.5, 23.0, 24.7(2C), 26.6, 31.6, 32.2, 35.6, 37.4, 41.1, 43.3, 46.9, 51.1, 51.3, 51.9, 52.0, 65.2, 66.3, 118.0, 132.3, 145.3, 168.8, 169.6, 170.0, 170.9, 173.4, 175.4, 176.0 ppm.

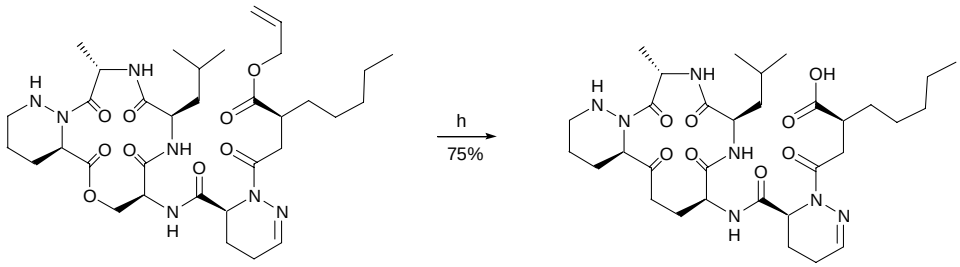
Synthesis of 2*R*,7*S*,10*R*,16*S*,19*R*,25*R*-**15c** from **3** and 19*R*,25*R*-**5c**



Reagents and reaction conditions: (c) H_2, Pd/C, MeOH; (e) LiOH, THF-MeOH-H_2O; (g) HATU, HOAt, DIPEA, DMF;

Compound **3** (0.26 g, 0.4 mmol) was dissolved in methanol (20 mL). After a catalytic amount of Pd/C (10%) was added, the reaction mixture was exposed to hydrogen atmosphere. The reaction was monitored by thin layer chromatography until all the starting material was consumed (ca 3 h). Then it was filtered through a pad of Celite to remove the catalyst, the filtrate was concentrated in *vacuo* to afford the free amine **4**. While 19*R*,25*R*-**5c** (0.16 g, 0.44 mmol) was dissolved in THF-H_2O (ca 5 mL, 1 : 1) at 0 ^oC. After lithium hydroxide (0.04 g, 0.88 mmol) was added, the reaction mixture was stirred at room temperature and monitored by thin layer chromatography until all starting ester was consumed (ca. 3 h). Volatiles were removed under reduced pressure and the residue was diluted with brine (5 mL) and extracted with diethyl ether (20 mL x 2). The organic phase was discarded, while the aqueous phase was acidified to pH 3 with citric acid (30mL, 15% solution in water) and extracted with ethyl acetate (30 mL x 3). The combined organic fractions were washed with brine (30 mL), dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo* to give the corresponding acid 19*R*,25*R*-**16c**. The above acid 19*R*,25*R*-**16c** and free amine **4** were dissolved in DMF (30 mL) and chilled with an ice - water bath. HOAt (0.50 g, 1.32 mmol), followed by HATU (0.18 g, 1.32 mmol), were added, and diisopropylethylamine (1.16 mL, 6.6 mmol) was added 10 min later. The reaction mixture was then stirred at room temperature for 24 h, before it was concentrated in *vacuo*. The residue was dissolved in ethyl acetate – benzene (200 mL, 3 : 1) and washed with water (50 mL), saturated sodium bicarbonate (50 mL) and brine (50 mL). The organic phase was dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. The residue was purified by flash chromatography (ethyl acetate : hexanes = 2 : 1) to produce 2*R*,7*S*,10*R*,16*S*,19*R*,25*R*-**15c** (0.21 g, 68%). Analytical data: $[\alpha]^{22}_D$ +45.0 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86-0.89 (m, 6H), 0.91 (d, 3H, *J* = 7.0Hz), 1.26 (d, 3H, *J* = 6.5 Hz), 1.31-1.35 (m, 6H), 1.53-1.61(m, 5H), 1.73-1.81 (m, 4H), 2.24-2.32 (m, 3H), 2.46-2.49 (m, 1H), 2.56 (dd, 1H, *J* = 4.5Hz, 15.0Hz), 2.69-2.78 (m, 1H), 3.05-3.07 (m, 2H), 3.40-3.42 (m, 1H), 4.13 (d, 1H, *J* = 11.5Hz), 4.30 (d, 1H, *J* = 6.5Hz), 4.47-4.49 (m, 1H), 4.56-4.58 (m, 2H), 4.62-4.64 (m, 2H), 5.15 (s, 1H), 5.23-5.25 (m, 2H), 5.34 (dd, 1H, *J* = 1.5Hz, 17.0Hz), 5.49-5.53 (m, 1H), 5.86-5.94 (m, 1H), 6.55 (d, 1H, *J* = 9.0Hz), 6.90 (d, 1H, *J* = 3.0Hz), 7.01 (s, 1H), 7.38 (d, 1H, *J* = 7.0Hz) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 16.9, 17.8, 20.6, 21.8(2C), 22.4, 23.0, 24.6, 24.8, 26.7, 29.6, 31.6(2C), 34.3, 37.2, 42.4, 43.5, 47.0, 51.5, 51.7, 53.1, 65.8(2C), 118.1, 131.9, 144.8, 168.8, 170.0(2C), 170.6, 173.3, 174.7, 175.9 ppm.

Synthesis of 2*R*,7*S*,10*R*,16*S*,19*S*,25*S*-**1**

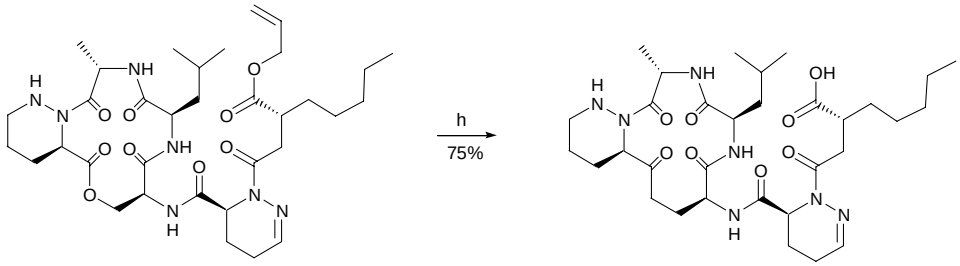


2R,7S,10R,16S,19S,25S-**15** *2R,7S,10R,16S,19S,25S*-**1**

Reagents and reaction conditions: (h) Pd_2dba_3, Ph_3P, Et_2NH.

To 2*R*,7*S*,10*R*,16*S*,19*S*,25*S*-**15** (0.028 g, 0.04 mmol), Pd_2dba_3 (0.003 g, 0.004 mmol), PPh_3 (0.002 g, 0.008 mmol) in dry THF under N_2 atmosphere was added diethylamine (0.04 mL, 0.4 mmol). The reaction solution was stirred at room temperature for 2h. Volatiles were removed under reduced pressure. The residue was dissolved in ethyl acetate (100 mL) and washed with HCl (20 mL, 1N solution in water), brine (20 mL). The organic layer was dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. Purification was performed with semi-preparative HPLC (Agilent 1200 system, using a reversed-phase C18 SG300 column (S-5uM, 10.0 mm i.d. x 150 mm length, from Fine Chemicals, Shiseido CAPCELL PAK), eluting with a gradient consisting of water / MeCN from 98 : 2 to 30 : 70 within 10min, flow rate was 10 mL min^{-1}, temperature was 25 ^oC and the DAD detector was set at 220 nm wave length), to afford 2*R*,7*S*,10*R*,16*S*,19*S*,25*S*-**1** (0.02 g, 75%, Retention time for HPLC: 8.495 min). Analytical data: $[\alpha]^{22}_D$ +16.1 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 0.85-0.95 (m, 9H), 1.28 (d, 3H, *J* = 7.0Hz), 1.34 (br, 5H), 1.41-1.42 (m, 3H), 1.59-1.62 (m, 3H), 1.67-1.75 (m, 3H), 1.85-1.88 (m, 2H), 2.02-2.09 (m, 1H), 2.20-2.27 (m, 3H), 2.63-2.71 (m, 3H), 3.32 (br s, 1H), 3.58-3.63 (m, 1H), 4.36 (d, 1H, *J* = 11.0Hz), 4.52-4.57 (m, 2H), 5.11 (d, 1H, *J* = 4.5Hz), 5.24 (d, 1H, *J* = 9.5Hz), 5.43 (s, 1H), 5.64-5.67 (m, 1H), 6.72 (d, 1H, *J* = 7.5Hz), 6.79 (d, 1H, *J* = 10.0Hz), 6.98-7.01 (m, 2H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 16.9, 18.8, 21.2, 22.2, 22.5, 22.7, 22.9, 24.9, 25.0, 27.1, 31.5, 31.8, 32.4, 37.5, 41.6, 43.9, 46.2, 50.5, 51.9, 52.1(2C), 68.8, 145.0, 168.9, 170.2, 171.4, 172.5, 172.7, 174.5, 181.4 ppm; HR-ESIMS for $C_{31}H_{49}N_7O_9Na$ (M+Na): m/z, calculated: 686.3489; found: 686.3485.

Synthesis of 2*R*,7*S*,10*R*,16*S*,19*S*,25*R*-**1a**



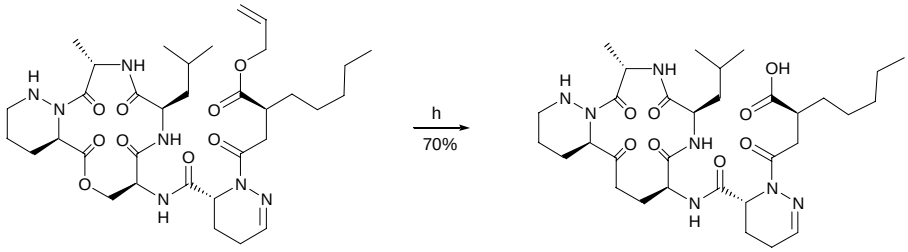
2R,7S,10R,16S,19S,25R-**15a** *2R,7S,10R,16S,19S,25R*-**1a**

Reagents and reaction conditions: (h) Pd_2dba_3, Ph_3P, Et_2NH.

To 2*R*,7*S*,10*R*,16*S*,19*S*,25*R*-**15a** (0.028 g, 0.04 mmol), Pd_2dba_3 (0.003 g, 0.004 mmol), PPh_3 (0.002 g, 0.008 mmol) in dry THF under N_2 atmosphere was added diethylamine (0.04 mL, 0.4 mmol). The reaction solution was stirred at room temperature for 2h. Volatiles were removed under reduced pressure. The residue was dissolved in ethyl acetate (100 mL) and washed with HCl (20 mL, 1N solution in water), brine (20 mL). The organic layer was dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. Purification was performed with semi-preparative HPLC (Agilent 1200 system, using a reversed-phase C18 SG300 column (S-5uM, 10.0 mm i.d. x 150 mm length, from Fine Chemicals, Shiseido CAPCELL PAK), eluting with a gradient consisting of water / MeCN from 98 : 2 to 30 : 70

within 10 min, flow rate was 10 mL min^{-1}, temperature was 25 °C and the DAD detector was set at 220 nm wave length), to afford 2*R*,7*S*,10*R*,16*S*,19*S*,25*S*-**1a** (0.02 g, 75%, Retention time for HPLC: 8.423 min). Analytical data: $[\alpha]^{22}_D$ +32.9 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 0.88-0.90 (m, 6H), 0.94 (d, 3H, *J* = 4.0Hz), 1.28-1.33 (m, 9H), 1.42 (br s, 2H), 1.55-1.58 (m, 2H), 1.65 (br s, 2H), 1.76-1.83 (m, 3H), 1.94-2.05 (m, 2H), 2.22-2.29 (m, 3H), 2.61 (d, 1H, *J* = 11.0Hz), 2.70 (d, 1H, *J* = 12.0Hz), 2.76 (br s, 1H), 2.88-2.91 (m, 1H), 3.54 (dd, 1H, *J* = 5.0Hz, 13.0Hz), 4.35 (d, 1H, *J* = 11.5Hz), 4.49 (d, 1H, *J* = 5.5Hz), 4.59 (dd, 1H, *J* = 4.0Hz, 11.5Hz), 5.15 (d, 2H, *J* = 4.0Hz), 5.27 (d, 1H, *J* = 6.5Hz), 5.70 (br s, 1H), 6.87 (br s, 1H), 7.04 (s, 1H), 7.27 (d, 1H, *J* = 2.0Hz), 7.39 (br s, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 16.8, 18.8, 20.8, 22.1(2C), 22.5, 22.8, 24.6, 25.0, 27.5, 31.2, 31.6, 37.1(2C), 43.4, 43.5, 46.1, 50.7, 51.7, 51.8, 52.9, 68.5, 144.6, 168.8, 170.1, 171.4, 172.1, 172.6, 174.2, 180.7 ppm.

Synthesis of 2*R*,7*S*,10*R*,16*S*,19*R*,25*S*-**1b**

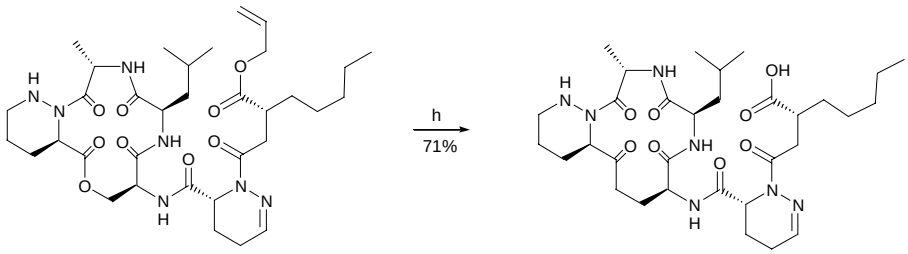


2R,7S,10R,16S,19R,25S-**15b** *2R,7S,10R,16S,19R,25S*-**1b**

Reagents and reaction conditions: (h) Pd_2dba_3, Ph_3P, Et_2NH.

To 2*R*,7*S*,10*R*,16*S*,19*R*,25*S*-**15b** (0.028 g, 0.04 mmol), Pd_2dba_3 (0.003 g, 0.004 mmol), PPh_3 (0.002 g, 0.008 mmol) in dry THF under N_2 atmosphere was added diethylamine (0.04 mL, 0.4 mmol). The reaction solution was stirred at room temperature for 2h. Volatiles were removed under reduced pressure, the residue was dissolved in ethyl acetate (100 mL) and washed with HCl (20 mL, 1N solution in water), brine (20 mL). The organic layer was dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. Purification was performed with semi-preparative HPLC (Agilent 1200 system, using a reversed-phase C18 SG300 column (S-5uM, 10.0 mm i.d. x 150 mm length, from Fine Chemicals, Shiseido CAPCELL PAK), eluting with a gradient consisting of water / MeCN from 98 : 2 to 30 : 70 within 10min, flow rate was 10 mL min^{-1}, temperature was 25 °C and the DAD detector was set at 220 nm wave length), to afford 2*R*,7*S*,10*R*,16*S*,19*R*,25*S*-**1b** (0.019 g, 70%, Retention time for HPLC: 8.392 min). Analytical data: $[\alpha]^{22}_D$ +109.0 (*c* 0.3, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$), δ 0.87 (br s, 6H), 0.92 (br s, 3H), 1.26-1.28 (m, 4H), 1.34 (br s, 4H), 1.42 (br s, 3H), 1.55-1.64 (m, 6H), 1.90 (br s, 2H), 2.20 (d, 1H, J = 7.0Hz), 2.31 (d, 2H, *J* = 13.5Hz), 2.40-2.47 (m, 1H), 2.54 (br, 1H), 2.69-2.74 (m, 1H), 2.93 (d, 1H, *J* = 12.5Hz), 3.24-3.32 (m, 1H), 3.41 (br s, 1H), 4.55-4.59 (m, 3H), 4.98 (d, 1H, *J* = 8.0Hz), 5.16 (s, 1H), 5.21 (s, 1H), 5.61 (br s, 1H), 6.73 (d, 1H, *J* = 10.0Hz), 6.98 (s, 1H), 7.59 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 16.7, 16.9, 20.5, 21.7, 22.2, 22.5, 22.9, 24.6, 25.0, 26.9, 29.7, 31.6(2C), 37.1, 41.8, 43.8, 46.6, 50.2, 51.1, 51.7, 52.4, 67.7, 144.4, 169.2, 170.3, 171.0, 172.6 (2C), 175.3, 179.2 ppm.

Synthesis of 2*R*,7*S*,10*R*,16*S*,19*R*,25*R*-**1c**



2R,7S,10R,16S,19R,25R-**15c** *2R,7S,10R,16S,19R,25R*-**1c**

Reagents and reaction conditions: (h) Pd_2dba_3, Ph_3P, Et_2NH.

To 2*R*,7*S*,10*R*,16*S*,19*R*,25*R*-**15c** (0.028 g, 0.04 mmol), Pd_2dba_3 (0.003 g, 0.004 mmol), PPh_3 (0.002 g, 0.008 mmol) in dry THF under N_2 atmosphere was added diethylamine (0.04 mL, 0.4 mmol). The reaction solution was stirred at room temperature for 2h. Volatiles were removed under reduced pressure. The residue was dissolved in ethyl acetate (100 mL) and washed with HCl (20 mL, 1N solution in water), brine (20 mL). The organic layer was dried over sodium sulfate (anhydrous), filtered and concentrated in *vacuo*. Purification was performed with semi-preparative HPLC (Agilent 1200 system, using a reversed-phase C18 SG300 column (S-5uM, 10.0 mm i.d. x 150 mm length, from Fine Chemicals, Shiseido CAPCELL PAK), eluting with a gradient consisting of water / MeCN from 98 : 2 to 30 : 70 within 10min, flow rate was 10 mL min^{-1}, temperature was 25 ^oC and the DAD detector was set at 220 nm wave length), to afford 2*R*,7*S*,10*R*,16*S*,19*R*,25*R*-**1c** (0.019 g, 71%, Retention time for HPLC: 8.547 min). Analytical data: $[\alpha]^{22}_D$ +178.6 (*c* 0.5, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 0.87-0.93 (m, 9H), 1.28 (d, 3H, *J* = 7.0 Hz), 1.34 (br s, 4H), 1.43 (br, 2H), 1.57-1.66 (m, 6H), 1.74-1.80 (m, 1H), 1.86-1.90 (m, 2H), 2.19-2.26 (m, 2H), 2.30 (d, 1H, *J* = 14.0Hz), 2.50-2.56 (m, 2H), 2.76-2.79 (m, 1H), 3.03-3.05 (m, 1H), 3.15 (d, 1H, *J* = 13.5Hz), 3.42 (d, 1H, *J* = 13.0Hz), 3.71 (dd, 1H, *J* = 12.5Hz, 16.5Hz), 4.54-4.57 (m, 2H), 4.68-4.70 (m, 1H), 5.07 (d, 1H, *J* = 10.5Hz), 5.21 (d, 1H, *J* = 5.0Hz), 5.25 (s, 1H), 5.52-5.56 (m, 1H), 6.79 (d, 1H, *J* = 9.5Hz), 7.04 (d, 1H, *J* = 4.0Hz), 7.12 (d, 1H, *J* = 10.0Hz), 7.70 (d, 1H, *J* = 9.0Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0, 16.7, 16.8, 20.7, 22.0, 22.2, 22.4, 22.8, 24.6, 24.8, 26.7, 30.7, 31.7, 32.8, 36.4, 40.9, 43.9, 47.4, 50.5, 50.6, 51.8, 52.4, 68.1, 145.1, 169.1, 170.7, 171.1, 172.4, 173.2, 176.4, 178.7 ppm.

Towards the Stereochemical Assignment of Natural Lydiamycin A

Bo Chen,[a] Lu Dai, [a] Hui Zhang,[a] Wenfei Tan,[a] Zhengshuang Xu,* [a,b] and Tao Ye*[a,b]

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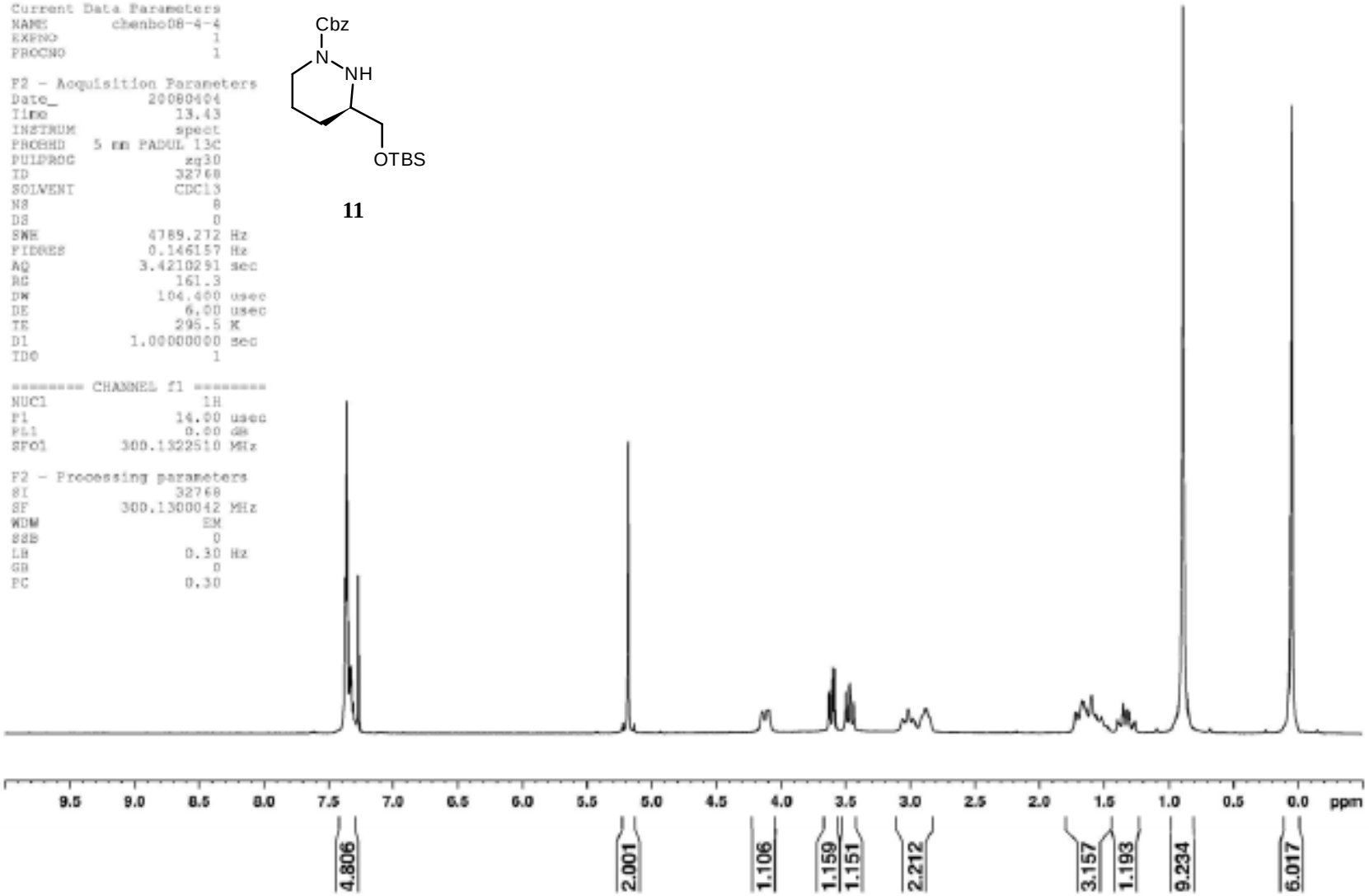
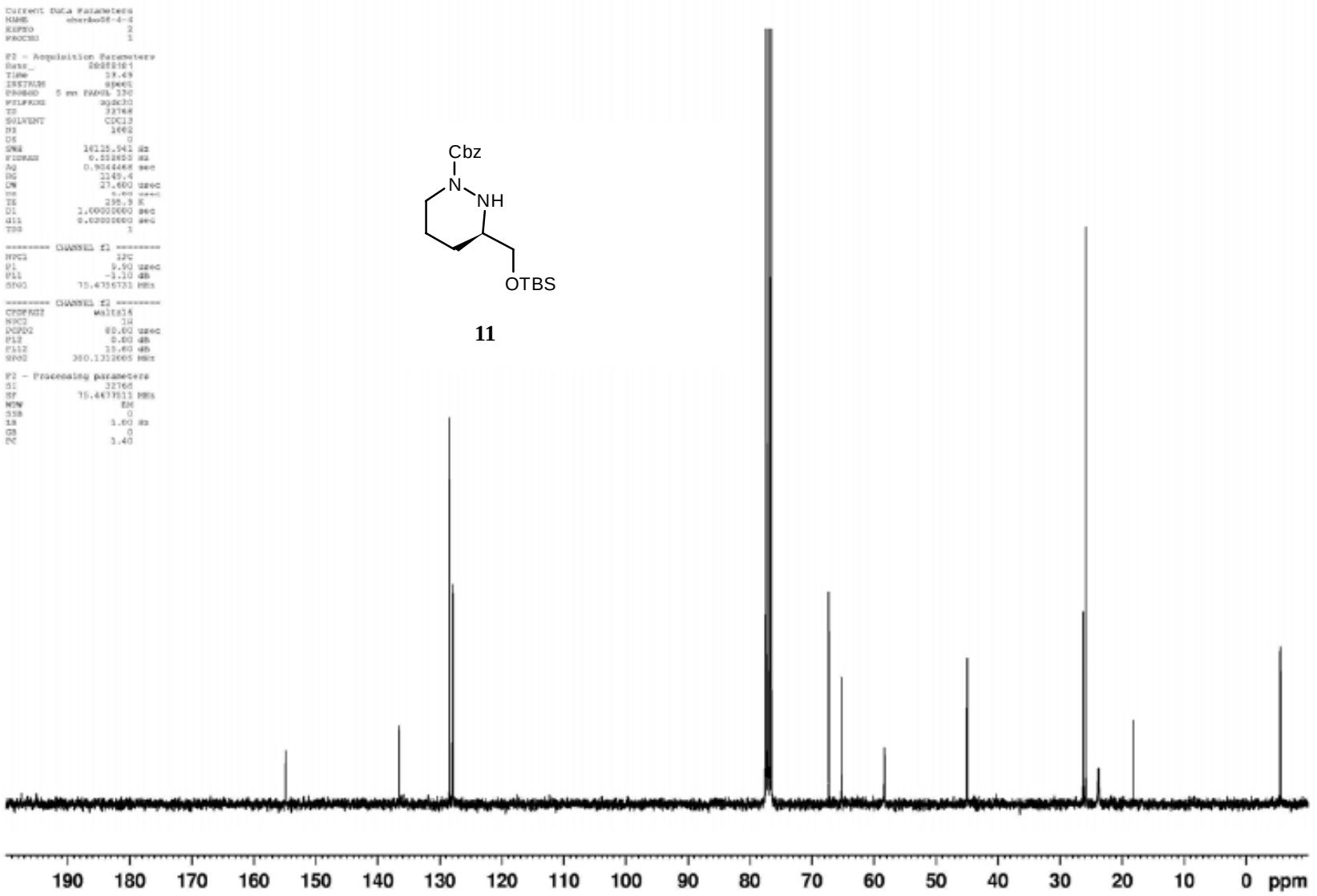
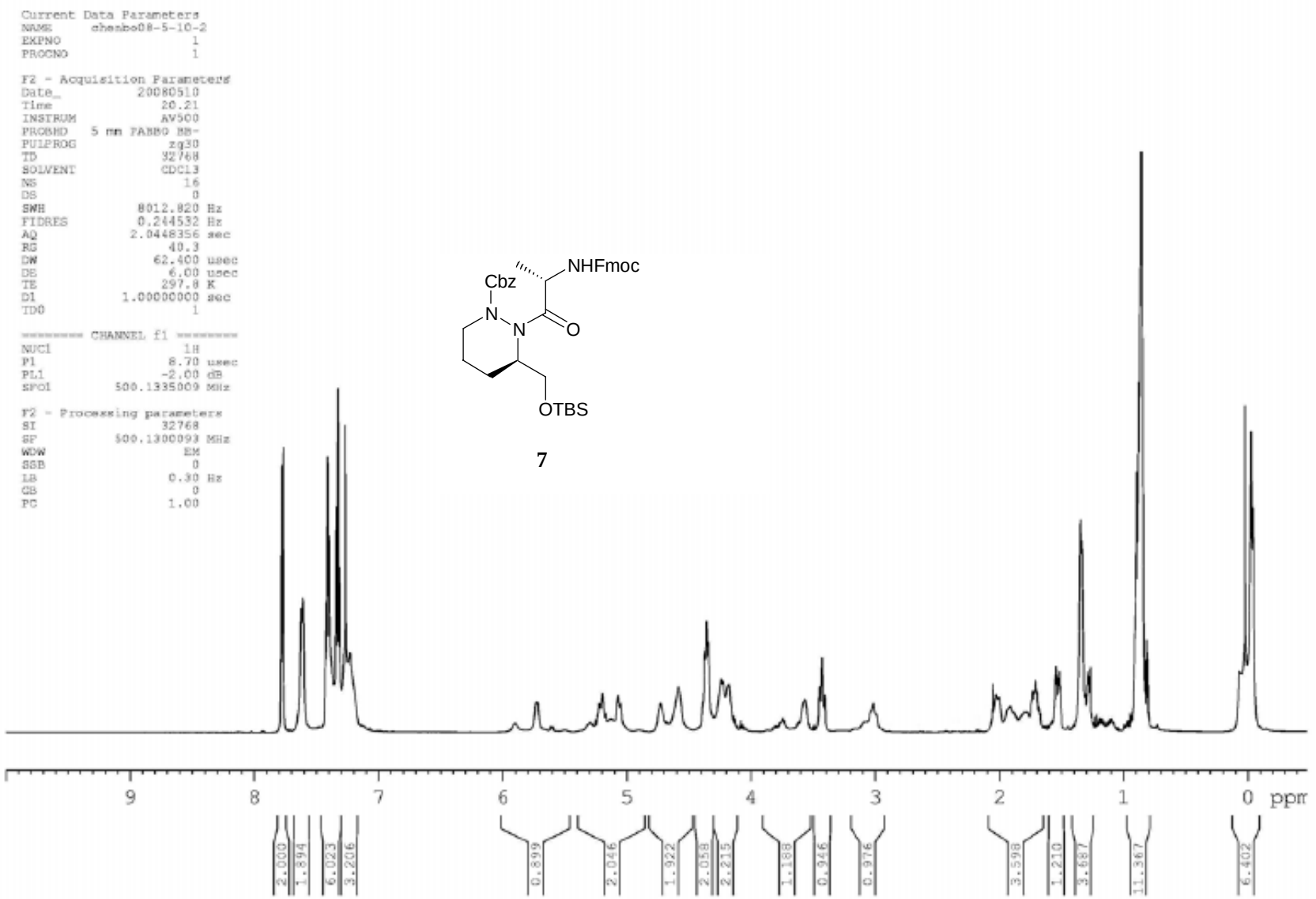
^{1}H spectrum of **11**



^{13}C spectrum of **11**



^{1}H spectrum of **7**



7

^{13}C spectrum of **7**

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EXPNO                   2
PROCNO                  1

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Time              20.26
INSTRUM           AV500
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PULPROG          zgdc30
TD                32768
SOLVENT           CDCl3
NS                 1540
DS                    0
SWH           30030.029 Hz
FIDRES        0.916444 Hz
AQ            0.5456530 sec
RG                645.1
DW               16.650 usec
DE                6.00 usec
TE               297.9 K
D1           1.00000000 sec
d11          0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 7.00 usec
PL1                0.00 dB
SFO1        125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2         waltz16
NUC2                1H
PCPD2             80.00 usec
PL2               -2.00 dB
PL12              17.00 dB
SFO2        500.1320005 MHz

F2 - Processing parameters
SI                32768
SF          125.7577890 MHz
WDW                 EM
SSB                   0
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GB                    0
PC                 1.40
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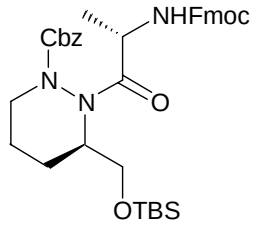
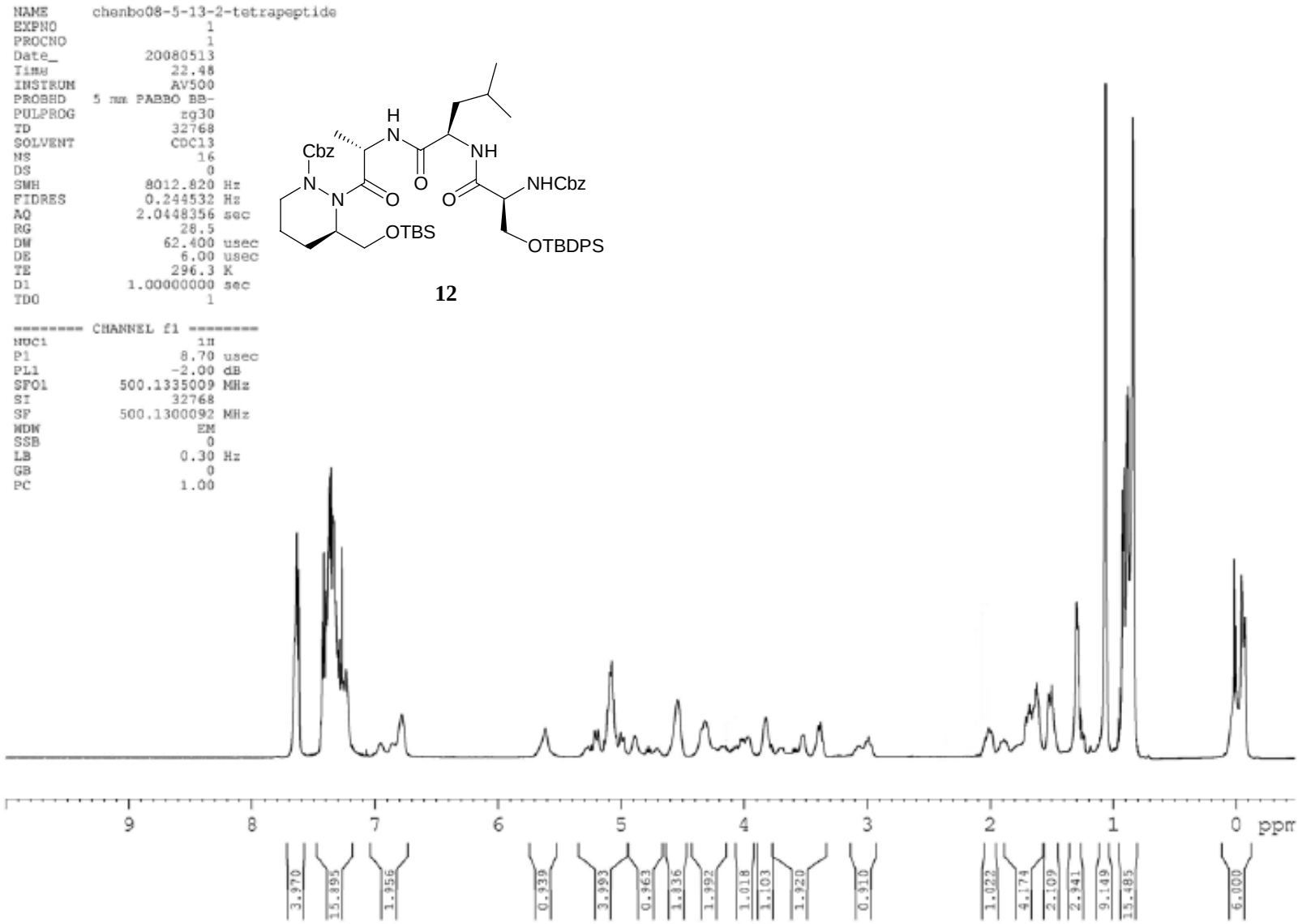
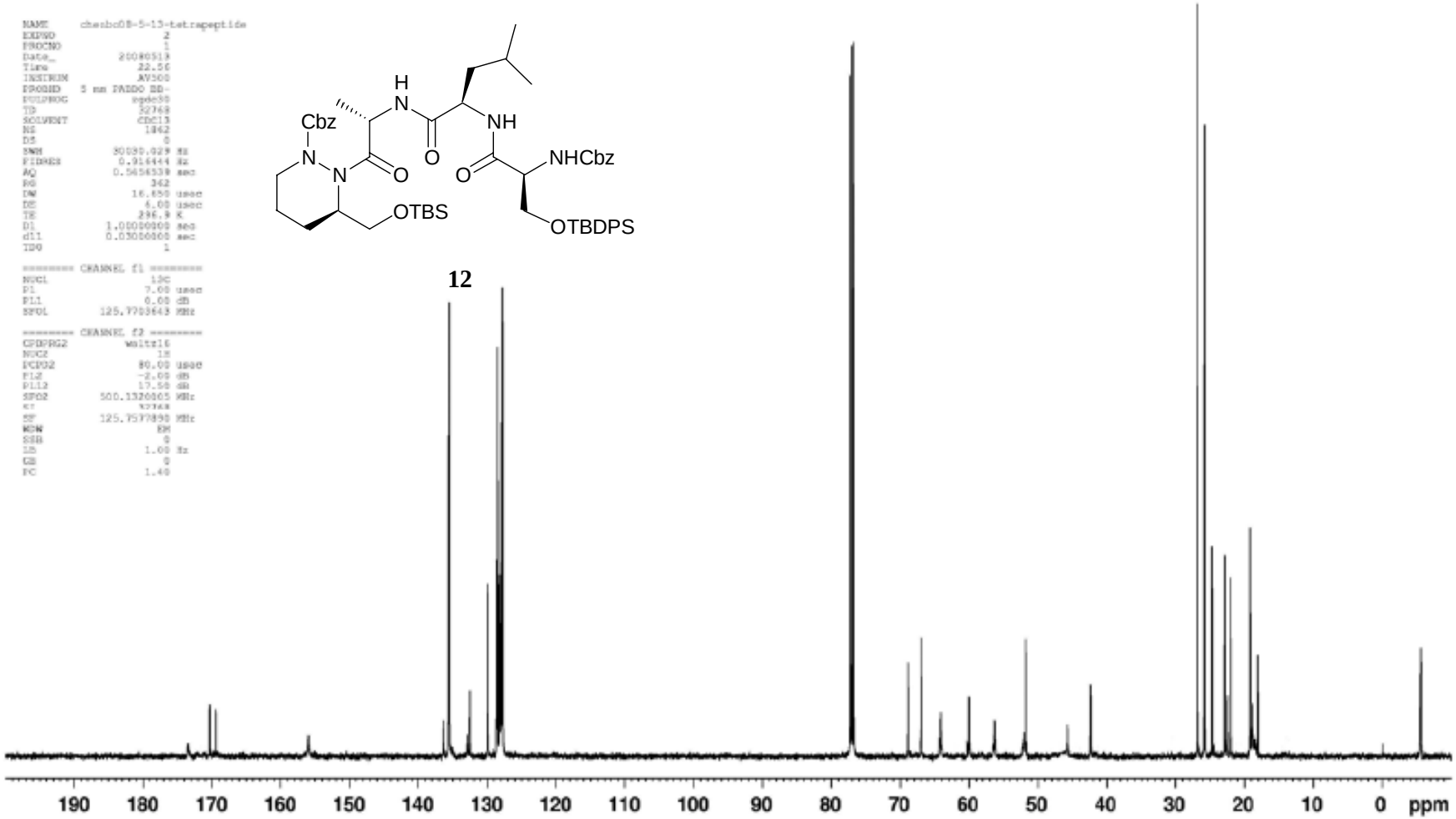


7

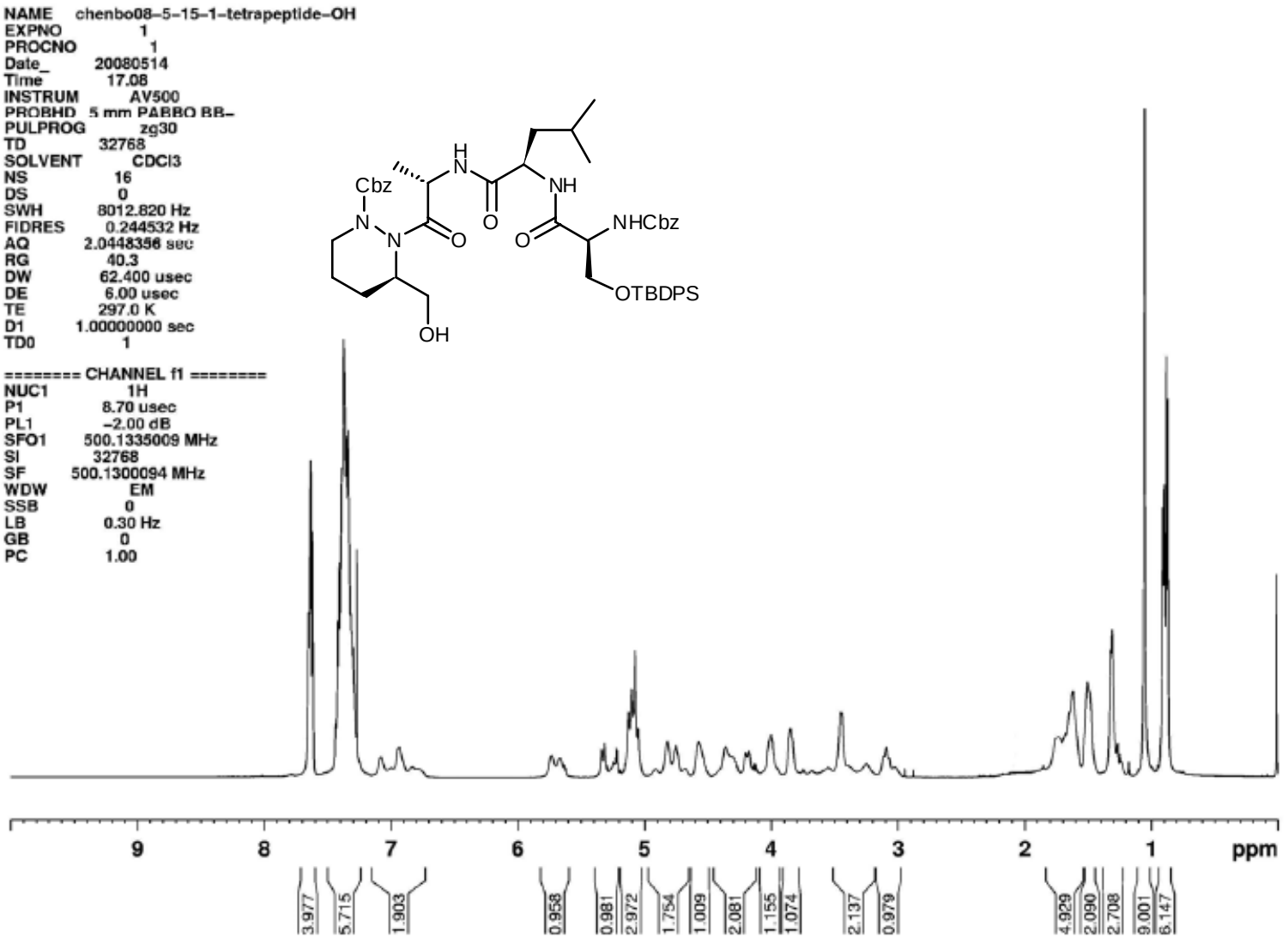
^{1}H spectrum of **12**



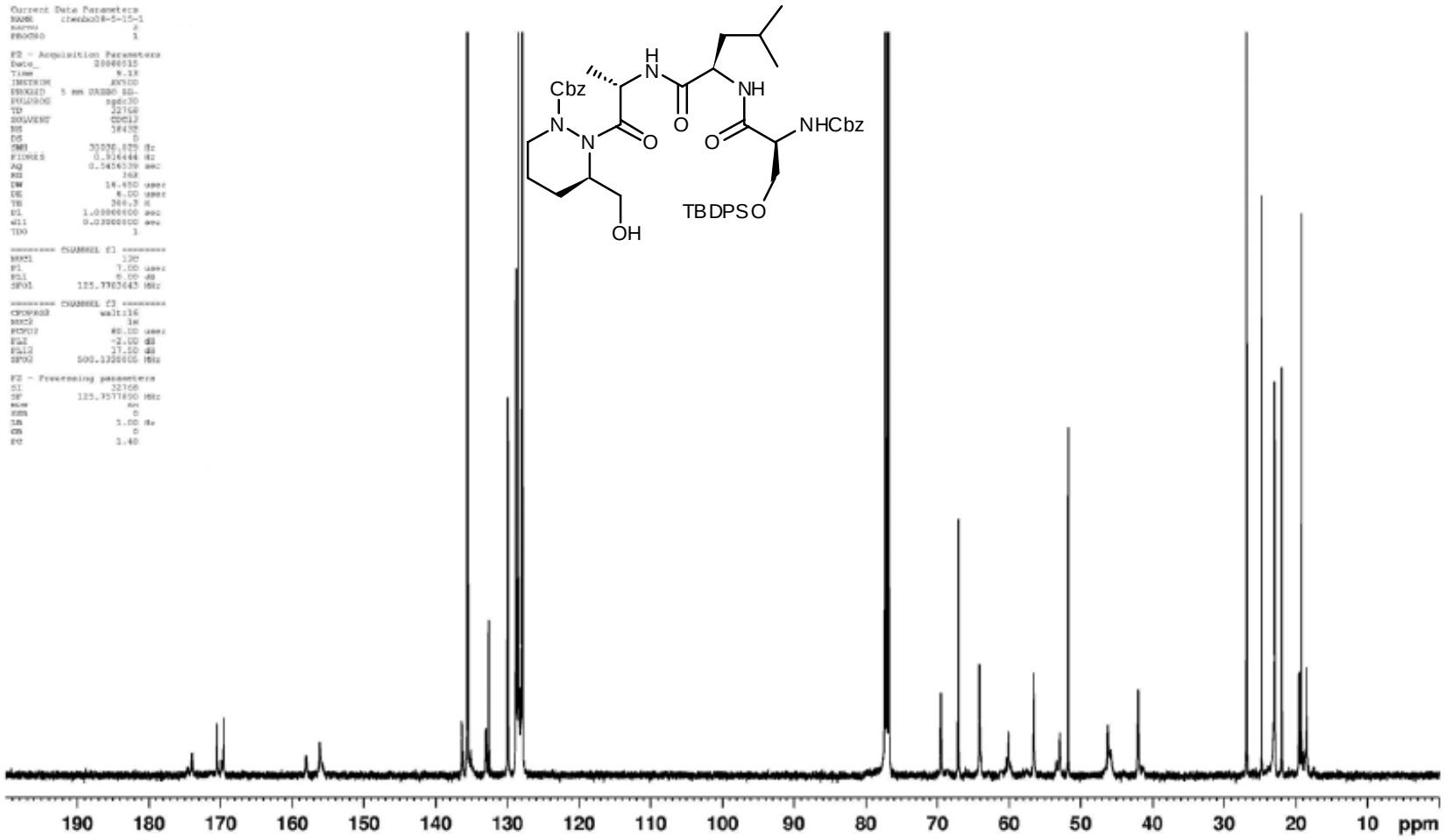
^{13}C spectrum of **12**



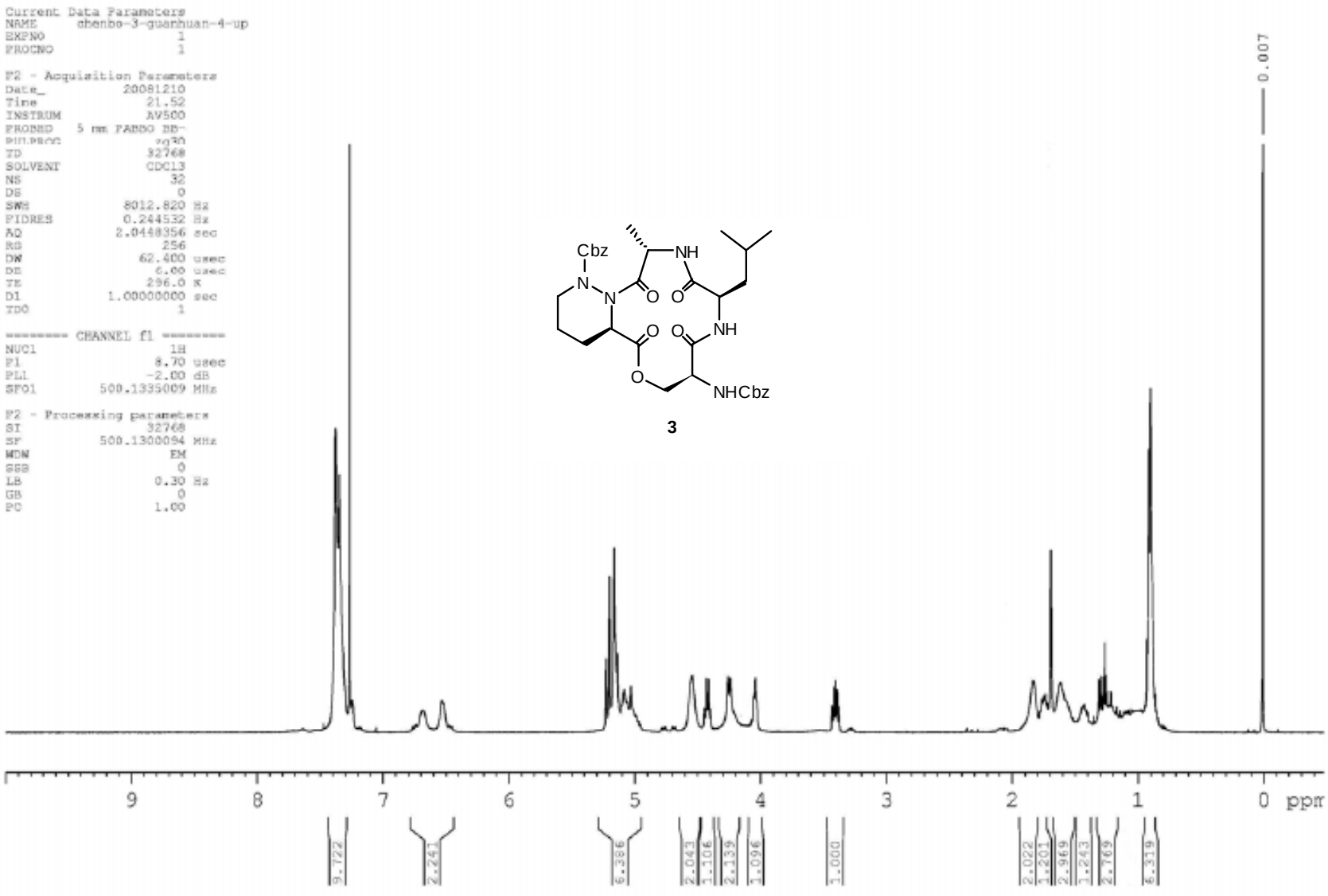
^{1}H spectrum of alcohol from **12**



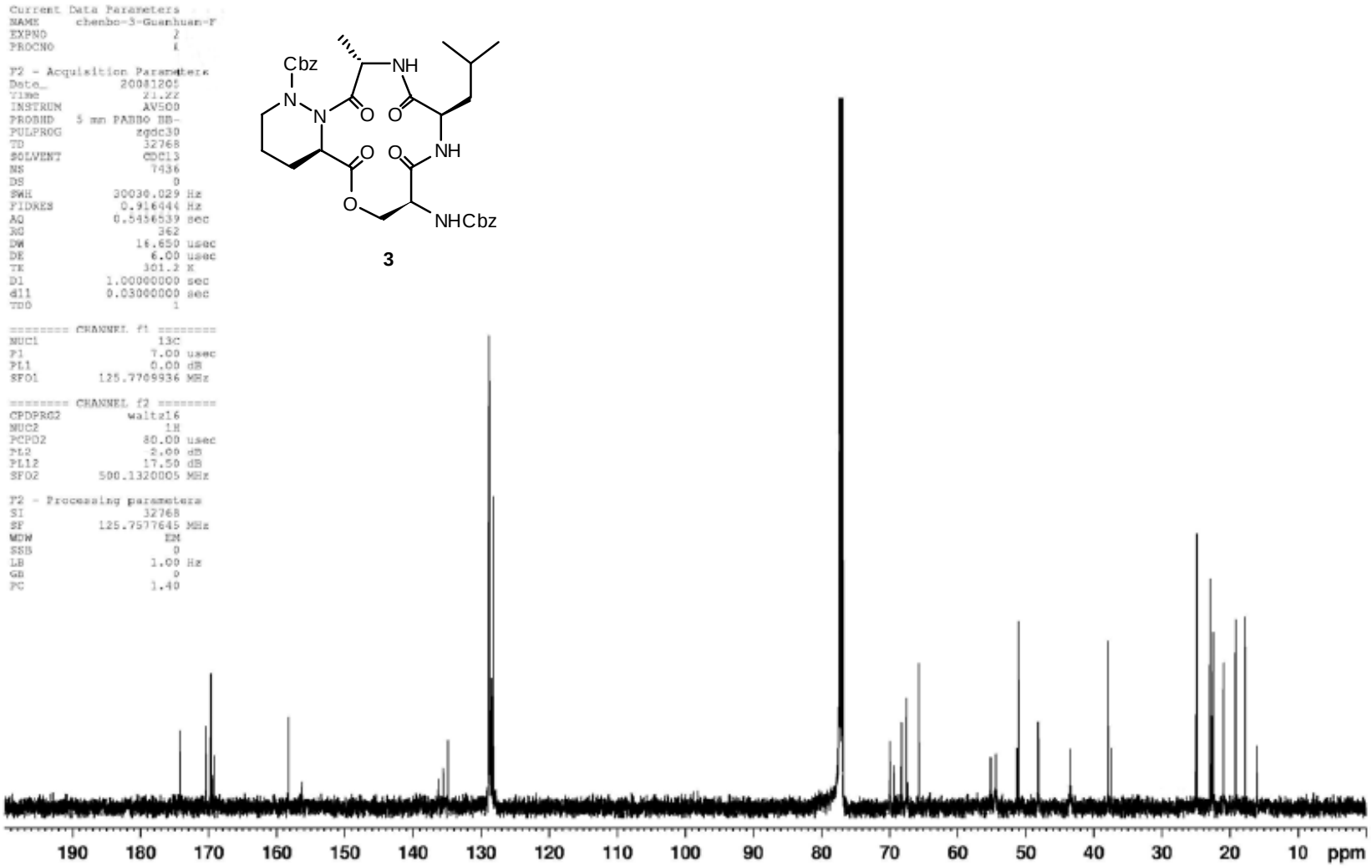
^{13}C spectrum of alcohol from **12**



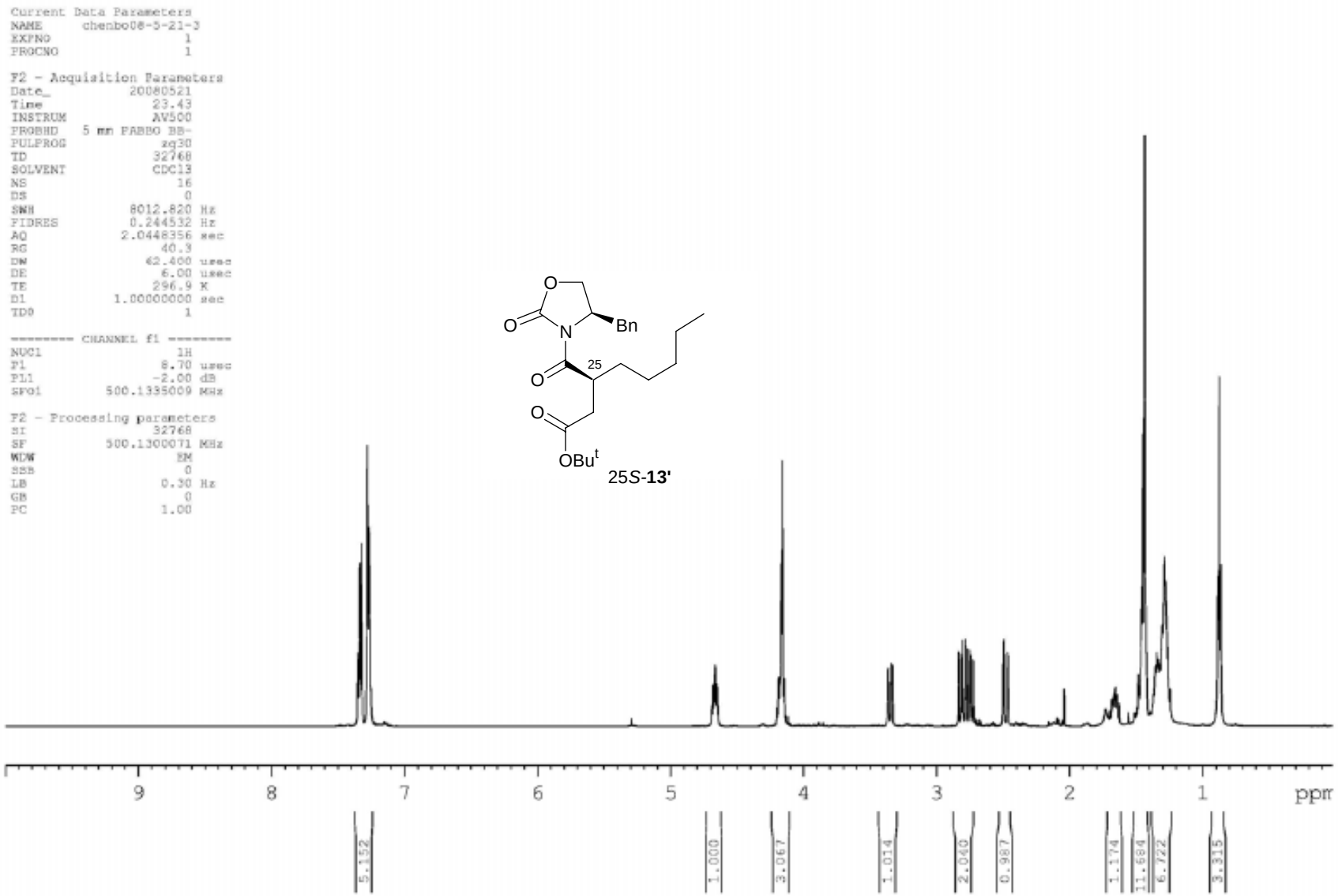
^{1}H spectrum of **3**



^{13}C spectrum of **3**



^{1}H spectrum of 25S-**13'**



^{13}C spectrum of 25S-**13'**

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EXPNO                   2
PROCNO                  1

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PULPROG           zgdc30
TD                 32768
SOLVENT            CDCl3
NS                    85
DS                     0
SWH              30030.030 Hz
FIDRES           0.916444 Hz
AQ               0.5456539 sec
RG                   362
DW                16.650 usec
DE                 6.00 usec
TE                297.1 K
D1           1.00000000 sec
d11          0.03000000 sec
TD0                    1

======== CHANNEL f1 ========
NUC1                  13C
P1                   7.00 usec
PL1                  0.00 dB
SFO1         125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2               80.00 usec
PL2                 -2.00 dB
PL12                17.50 dB
SFO2         500.1320005 MHz

F2 - Processing parameters
SI                 32768
SF          125.7577950 MHz
WDW                   EM
SSB                    0
LB                  1.00 Hz
GB                     0
PC                  1.40
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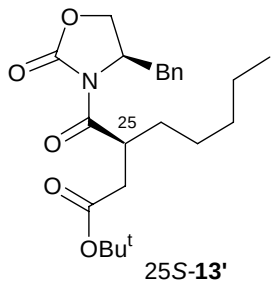
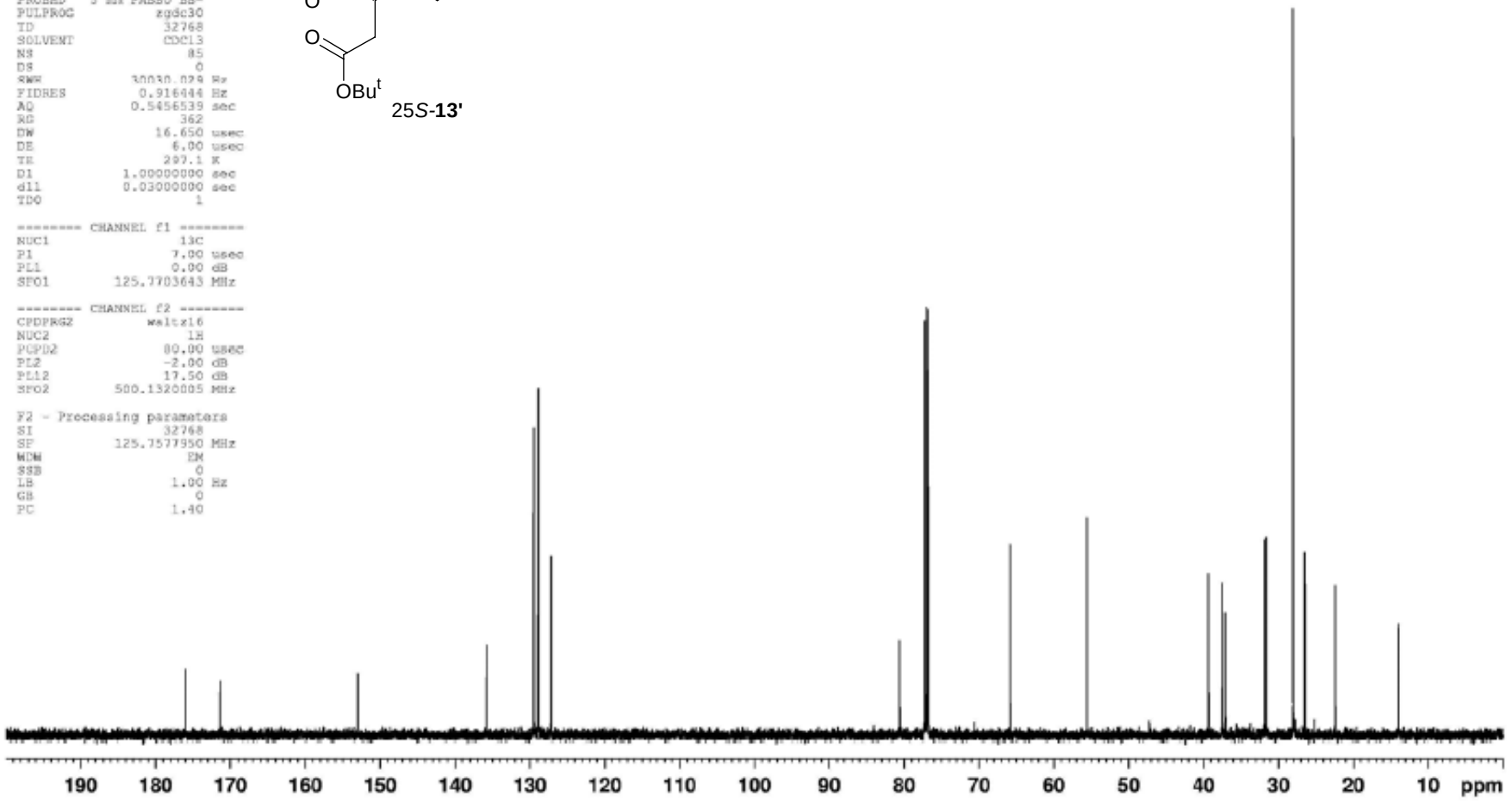
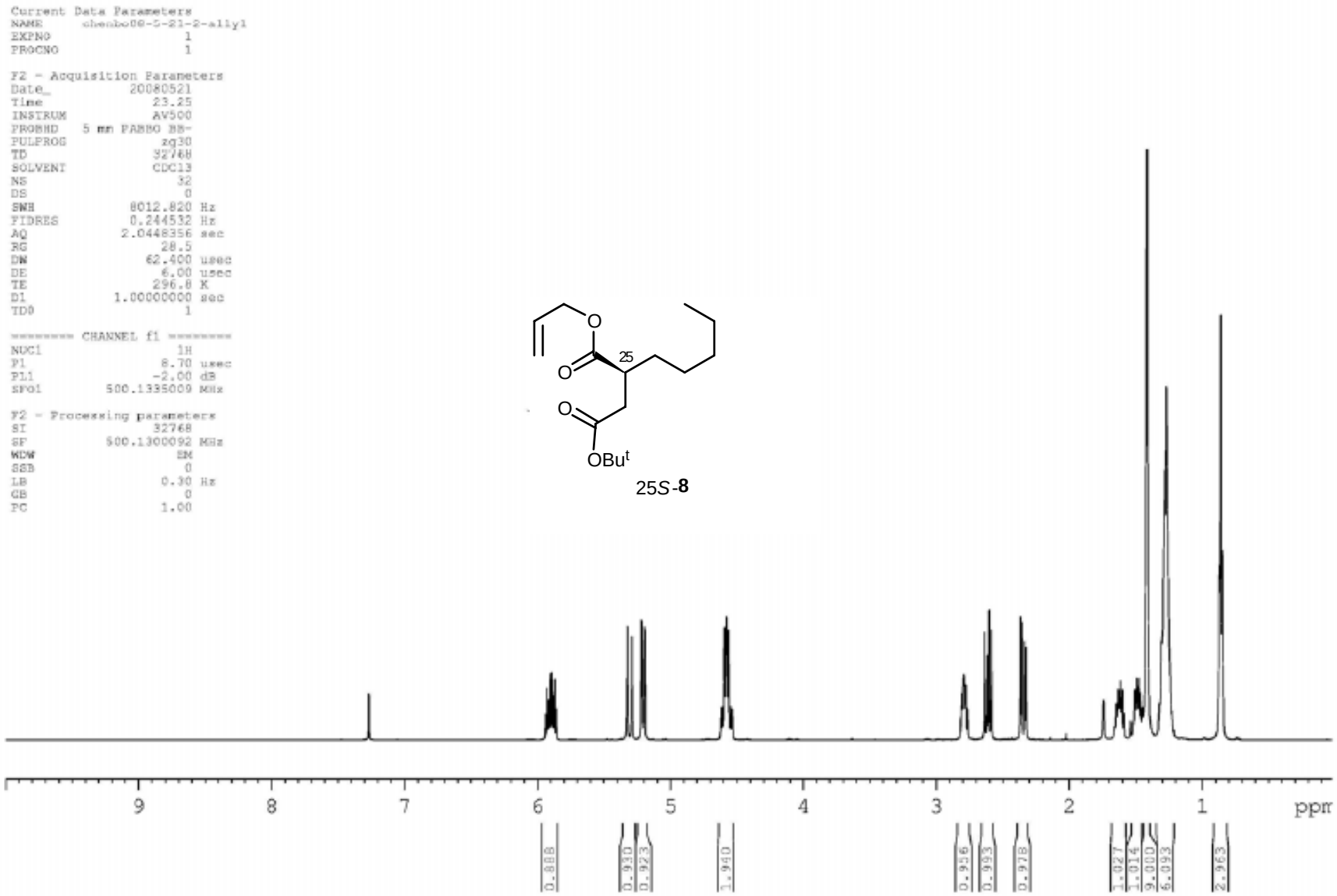


25*S*-**13'**



^{1}H spectrum of 25S-**8**



^{13}C spectrum of 25S-**8**

```
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PROCNO                1

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Time              23.34
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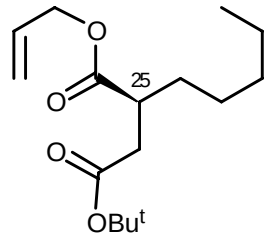
PULPROG          zgdc30
TD                32768
SOLVENT           CDCl3
NS                   90
DS                    0
SWH           30030.029 Hz
FIDRES        0.916444 Hz
AQ            0.5456539 sec
RG                  256
DW               16.650 usec
DE                6.00 usec
TE               297.0 K
D1            1.00000000 sec
d11           0.03000000 sec
TD0                   1

======== CHANNEL f1 ========
NUC1                13C
P1                 7.00 usec
PL1                0.00 dB
SFO1        125.7703643 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                1H
PCPD2             80.00 usec
PL2               -2.00 dB
PL12              17.50 dB
SFO2        500.1320005 MHz

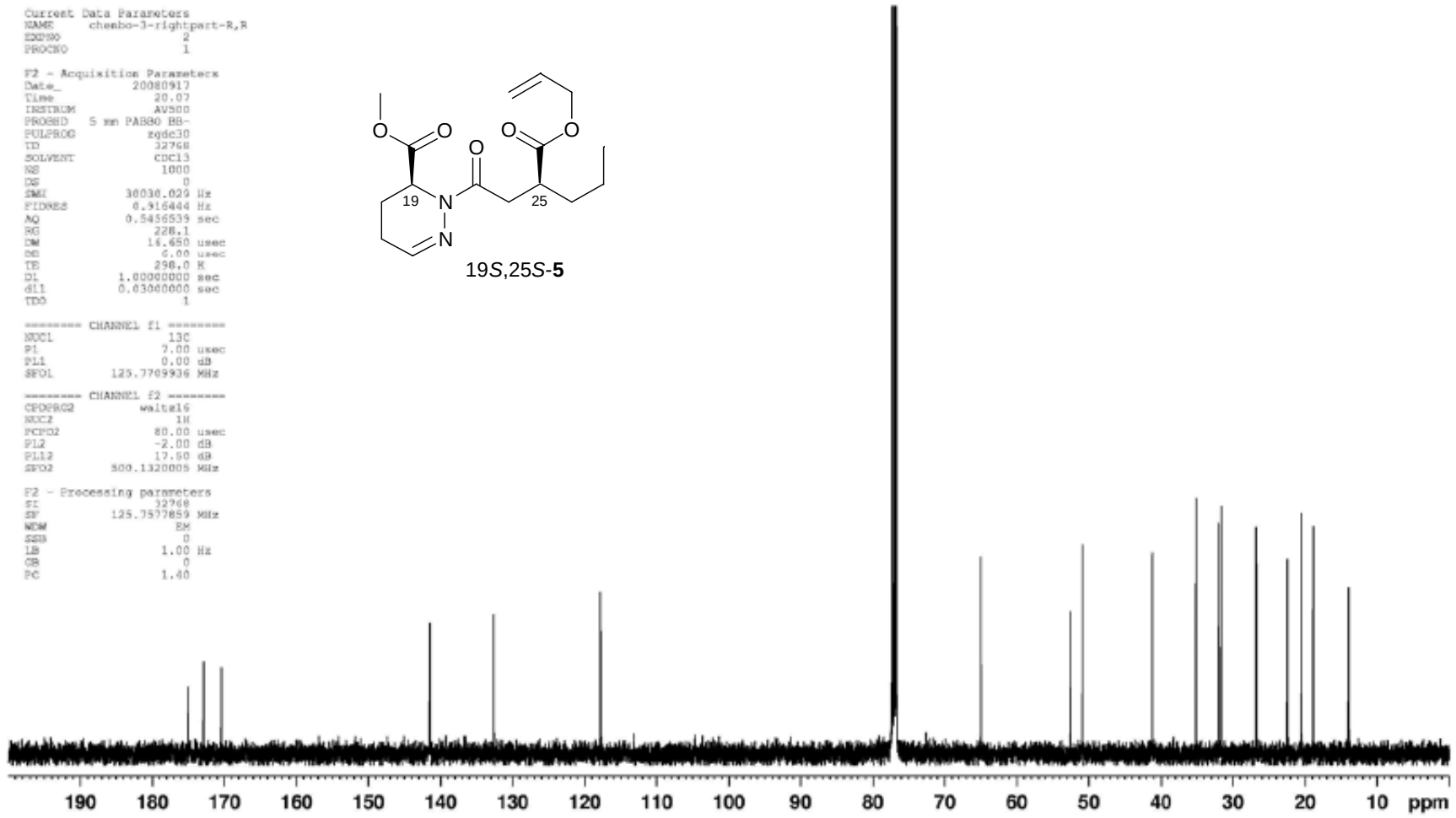
F2 - Processing parameters
SI                32768
SF          125.7577917 MHz
WDW                 EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```



25*S*-**8**

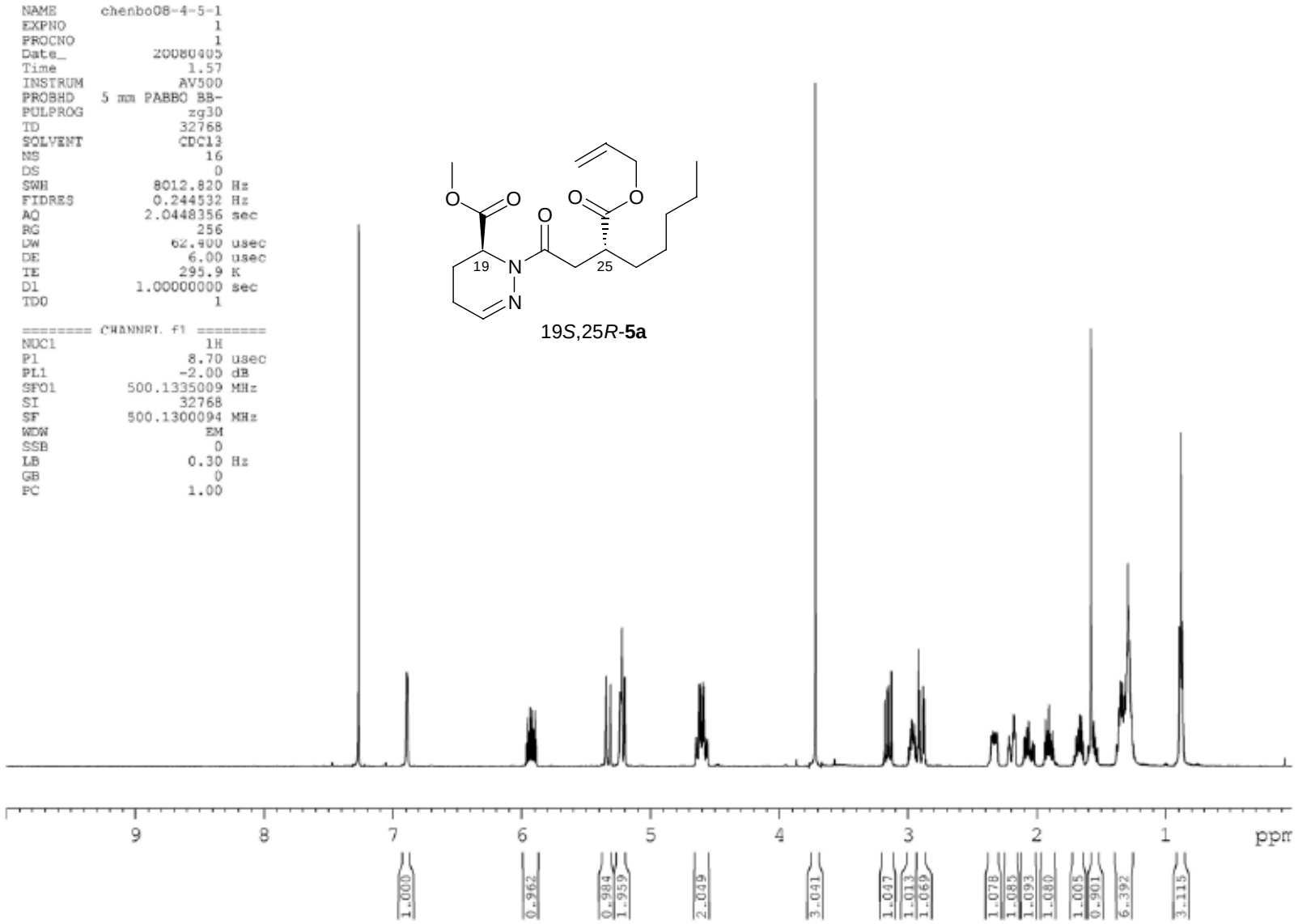
^{1}H spectrum of 19*S*,25*S*-**5**

^{13}C spectrum of 19*S*,25*S*-**5**

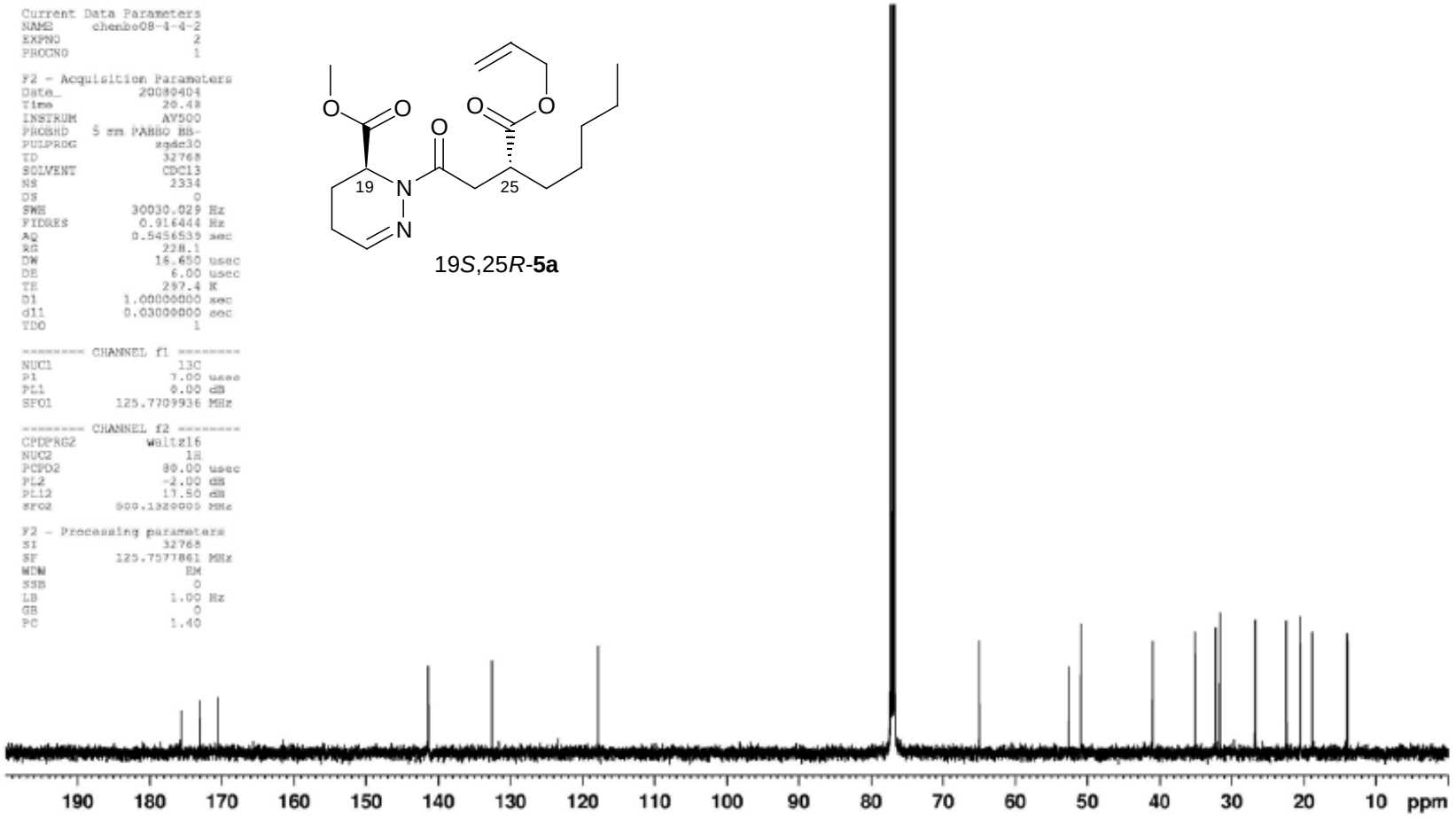


19*S*,25*S*-**5**

^{1}H spectrum of 19*S*,25*R*-**5a**

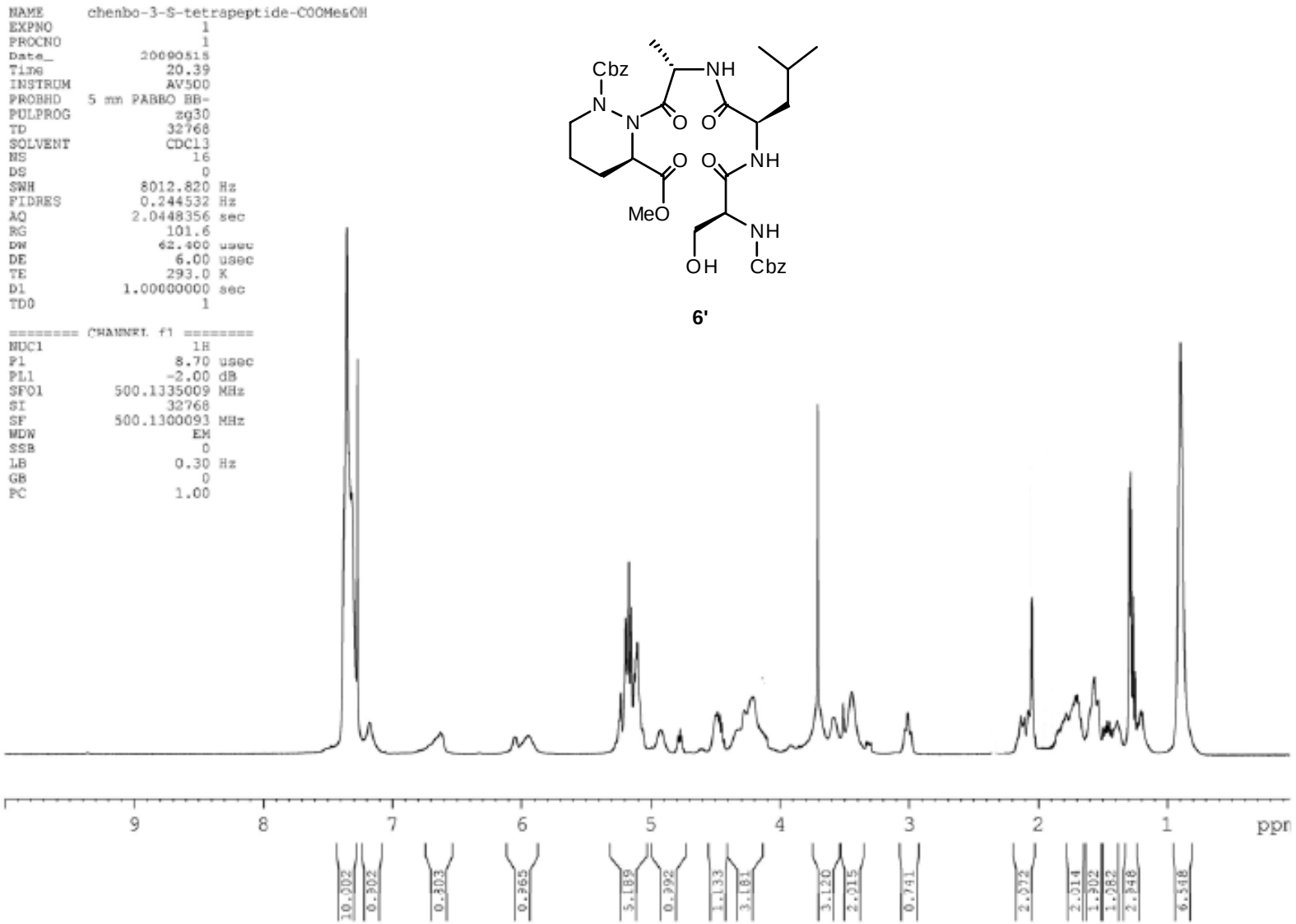


^{13}C spectrum of 19*S*,25*R*-**5a**

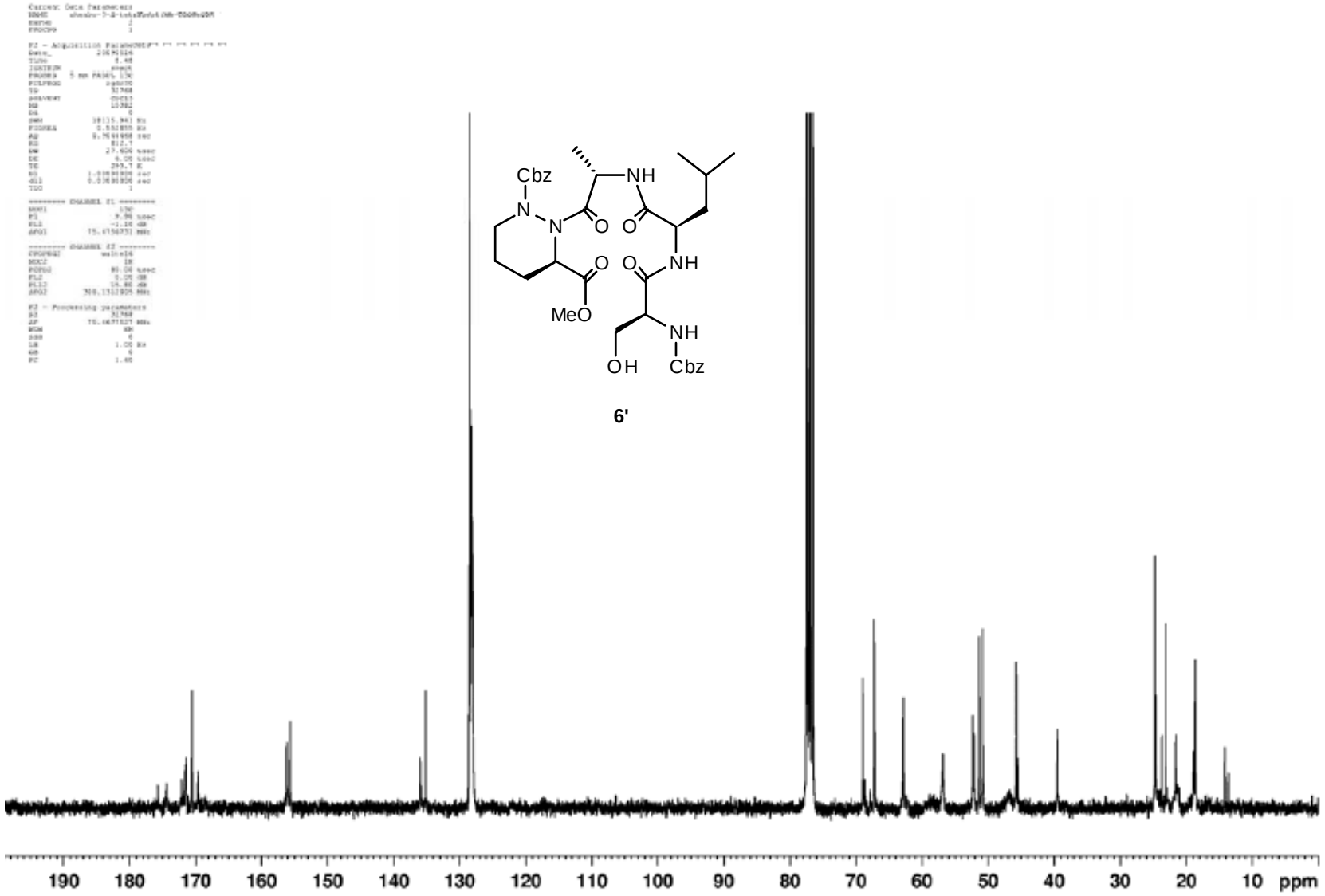


19*S*,25*R*-**5a**

^{1}H spectrum of **6'**

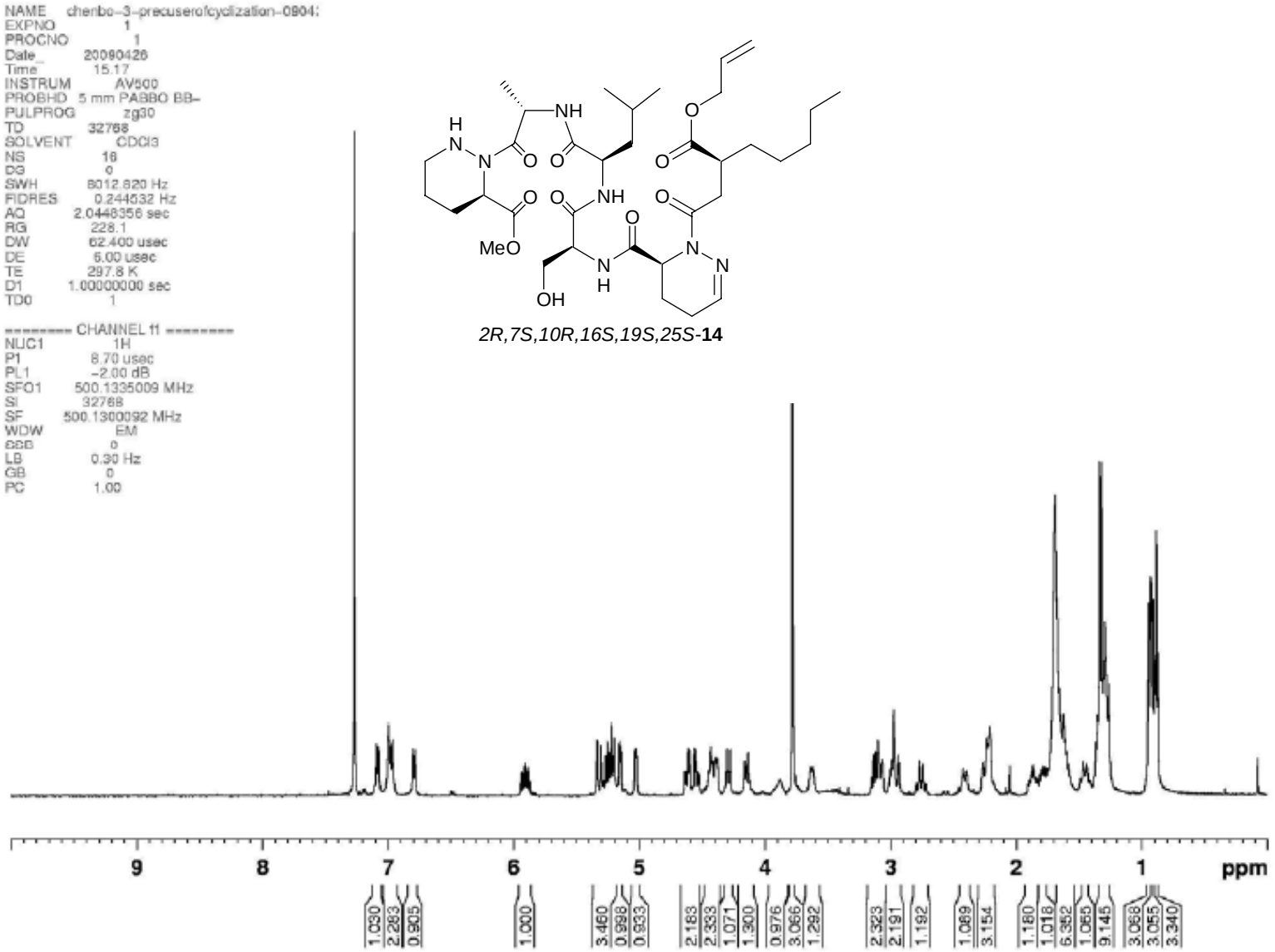


^{13}C spectrum of **6'**



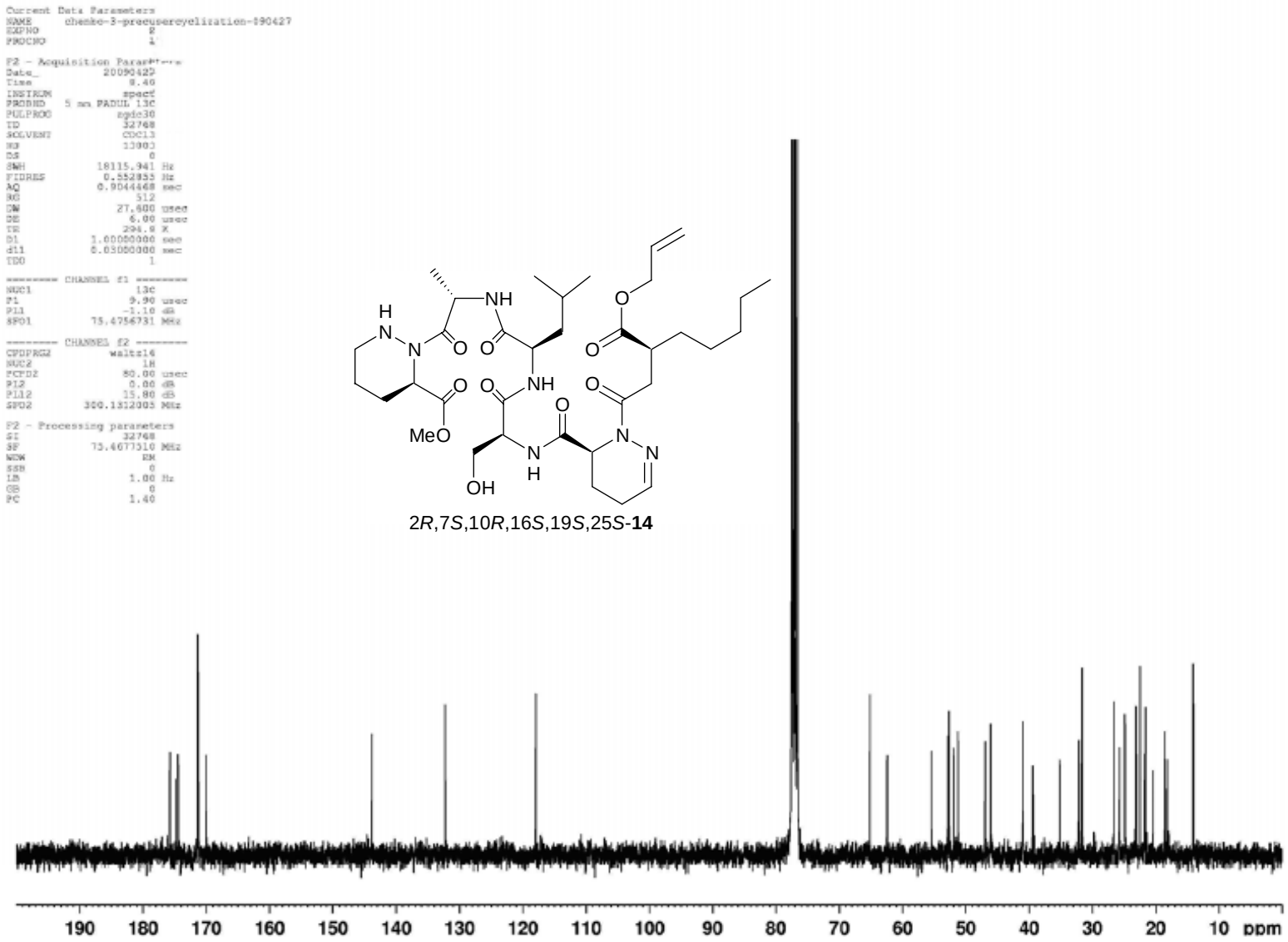
6'

^{1}H spectrum of 2*R*,7*S*,10*R*,16*S*,19*S*,25*S*-**14**



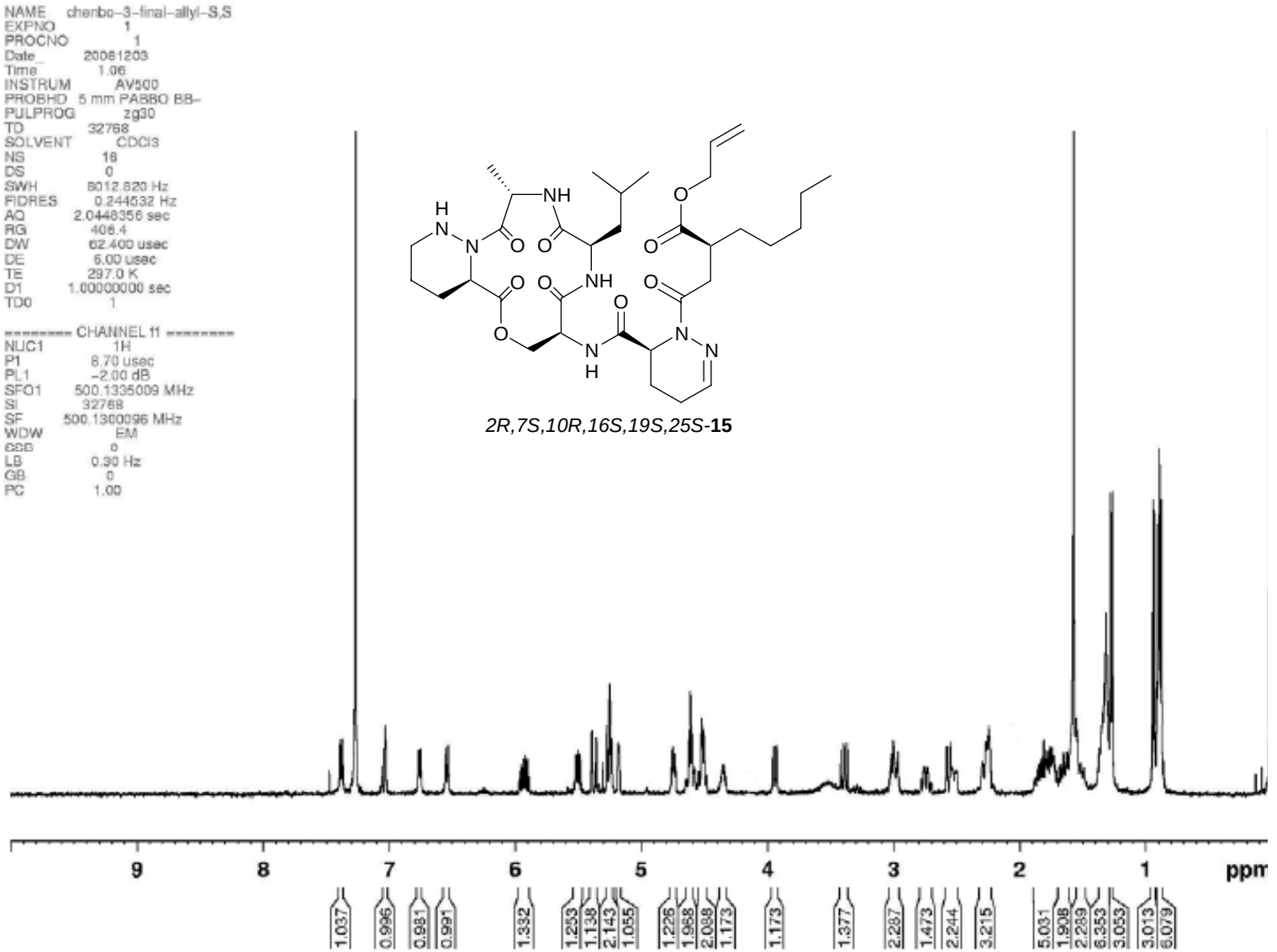
2R,7S,10R,16S,19S,25S-**14**

^{13}C spectrum of 2*R*,7*S*,10*R*,16*S*,19*S*,25*S*-**14**

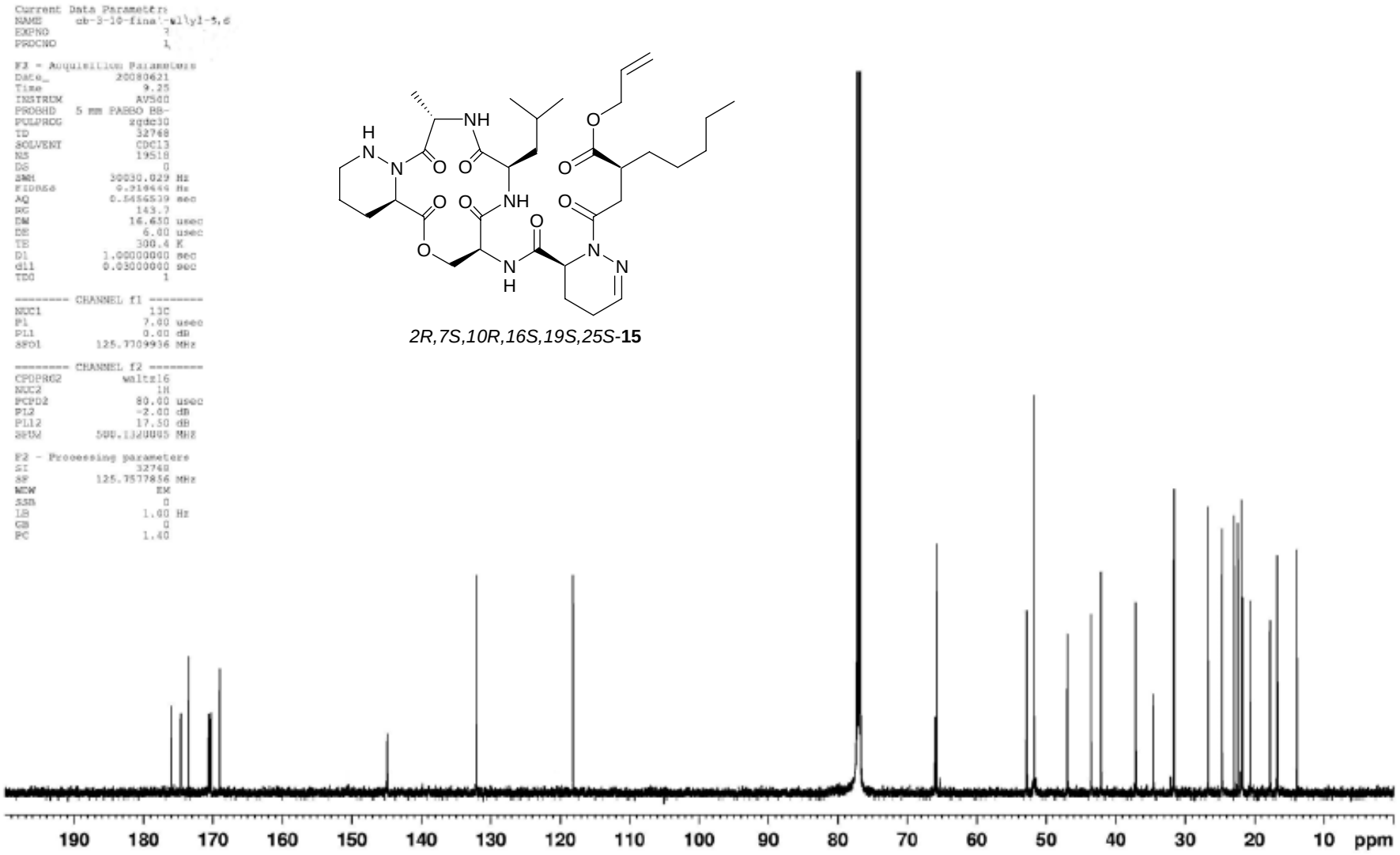


2*R*,7*S*,10*R*,16*S*,19*S*,25*S*-**14**

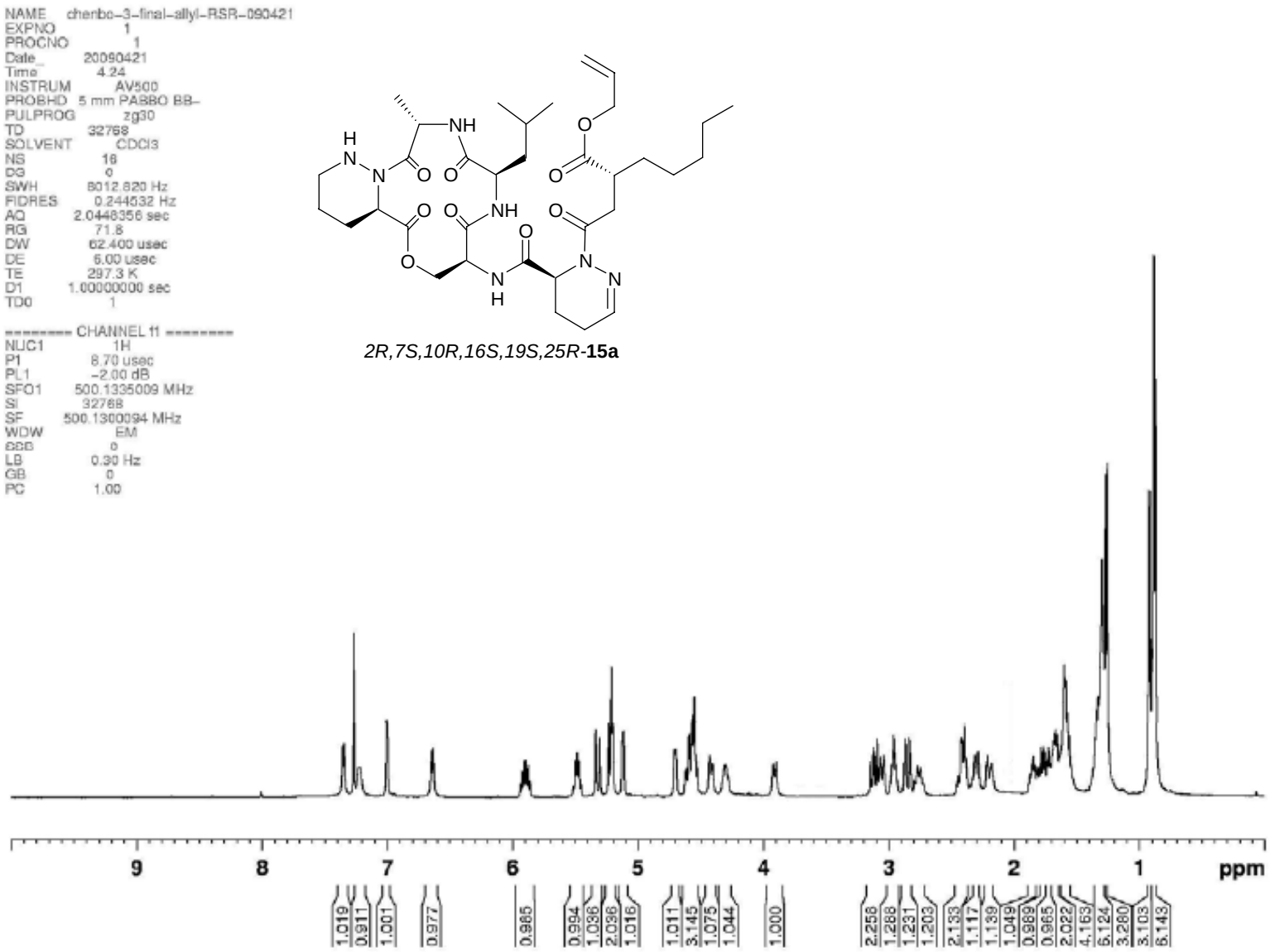
^{1}H spectrum of 2*R*,7*S*,10*R*,16*S*,19S,25S-**15**



^{13}C spectrum of *2R,7S,10R,16S,19S,25S*-**15**

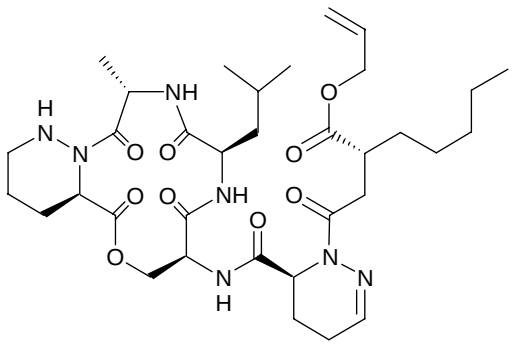


[1]H spectrum of 2*R*,7*S*,10*R*,16*S*,19*S*,25*R*-**15a**



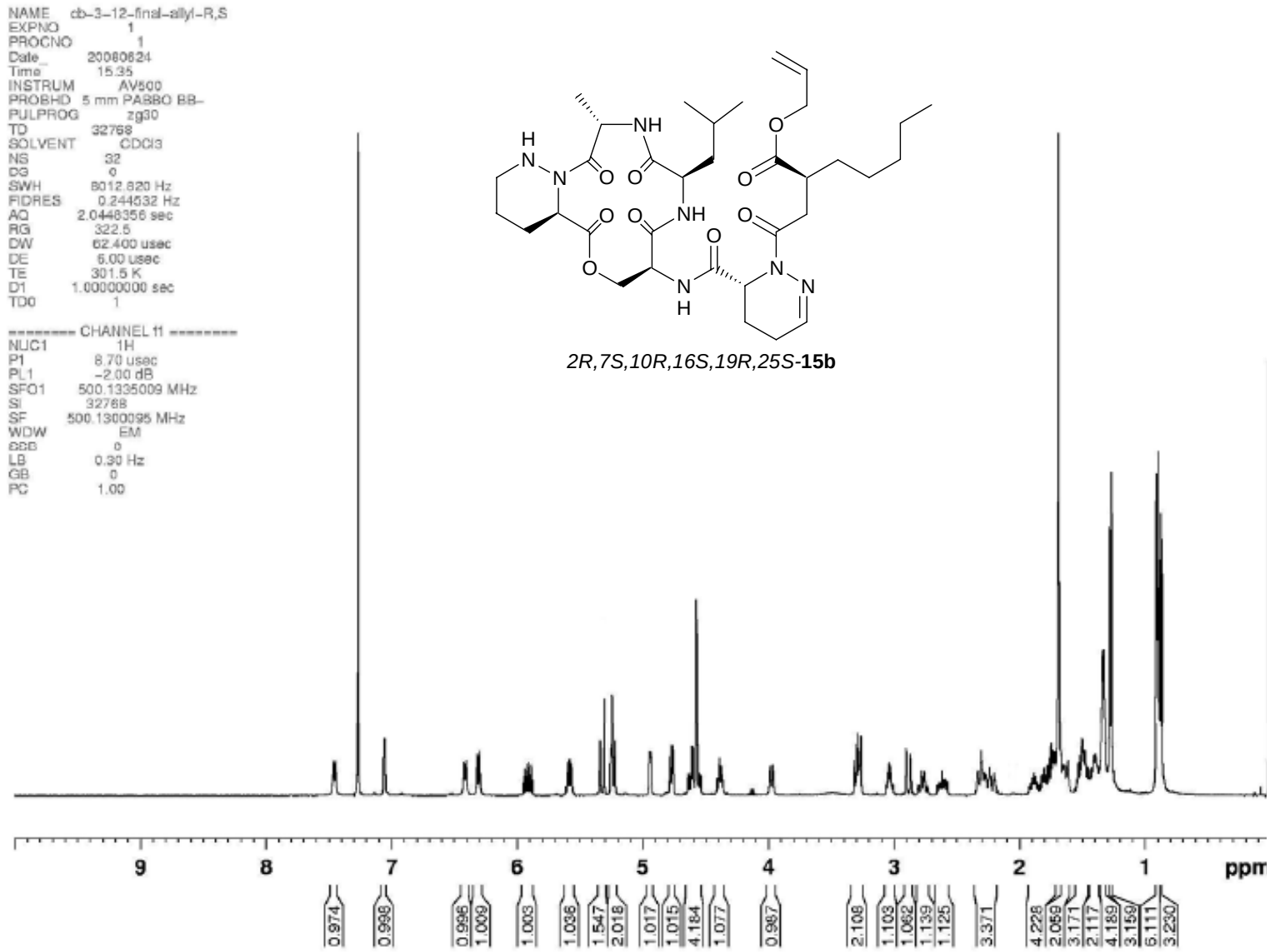
2R,7S,10R,16S,19S,25R-**15a**

^{13}C spectrum of 2*R*,7*S*,10*R*,16*S*,19*S*,25*R*-**15a**



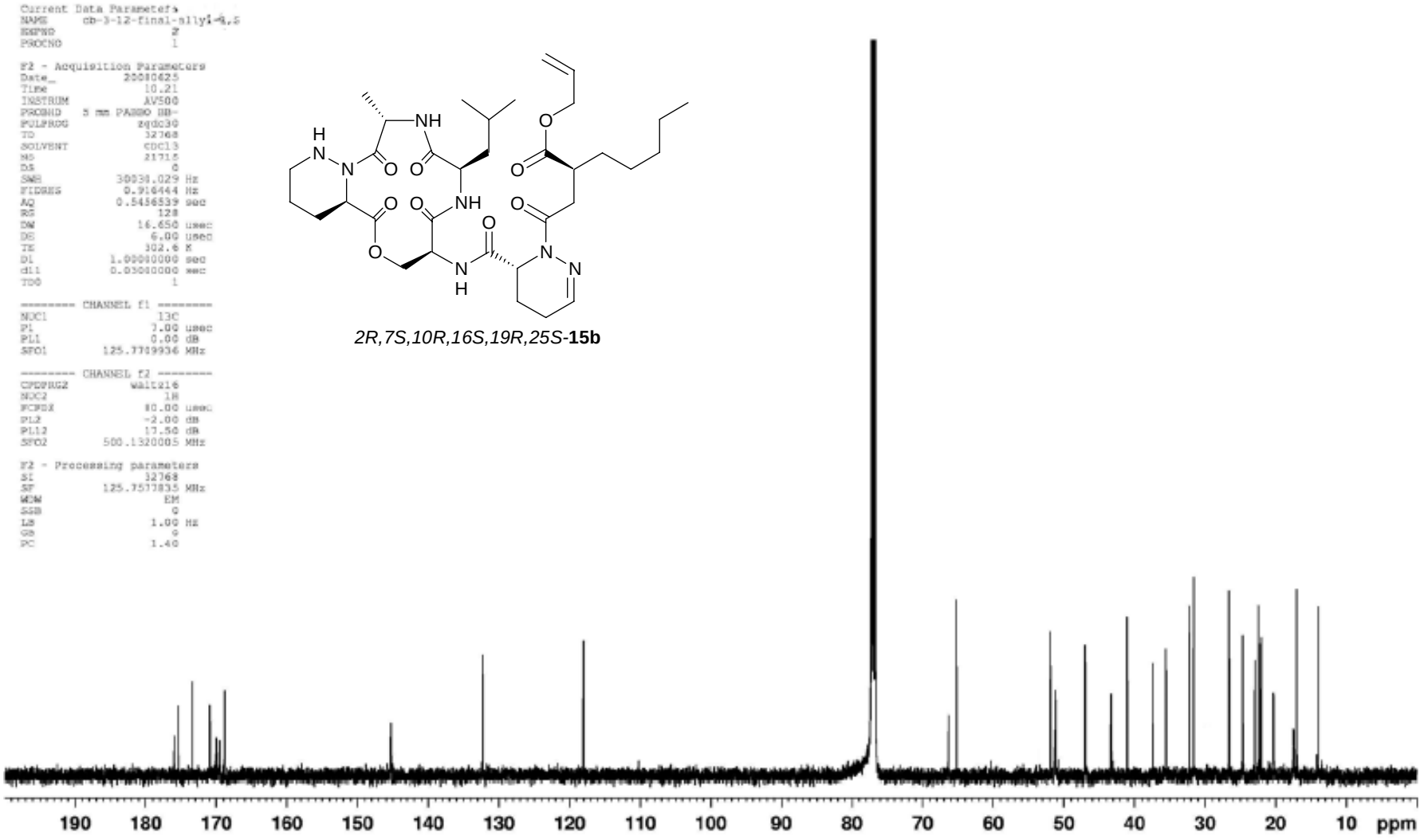
2R,7S,10R,16S,19S,25R-**15a**

^{1}H spectrum of 2*R*,7*S*,10*R*,16*S*,19*R*,25*S*-**15b**



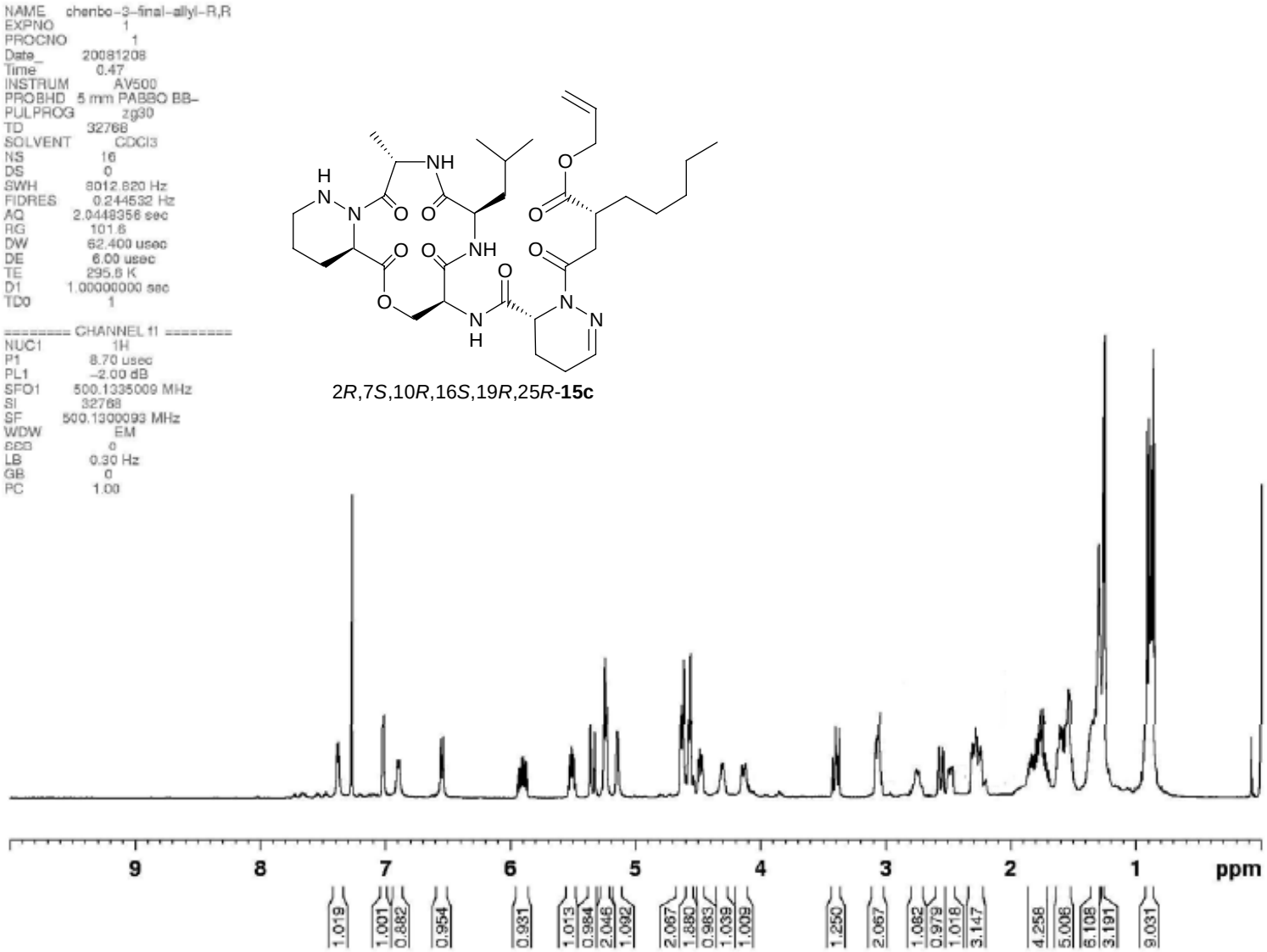
2R,7S,10R,16S,19R,25S-**15b**

^{13}C spectrum of 2*R*,7*S*,10*R*,16*S*,19*R*,25*S*-**15b**

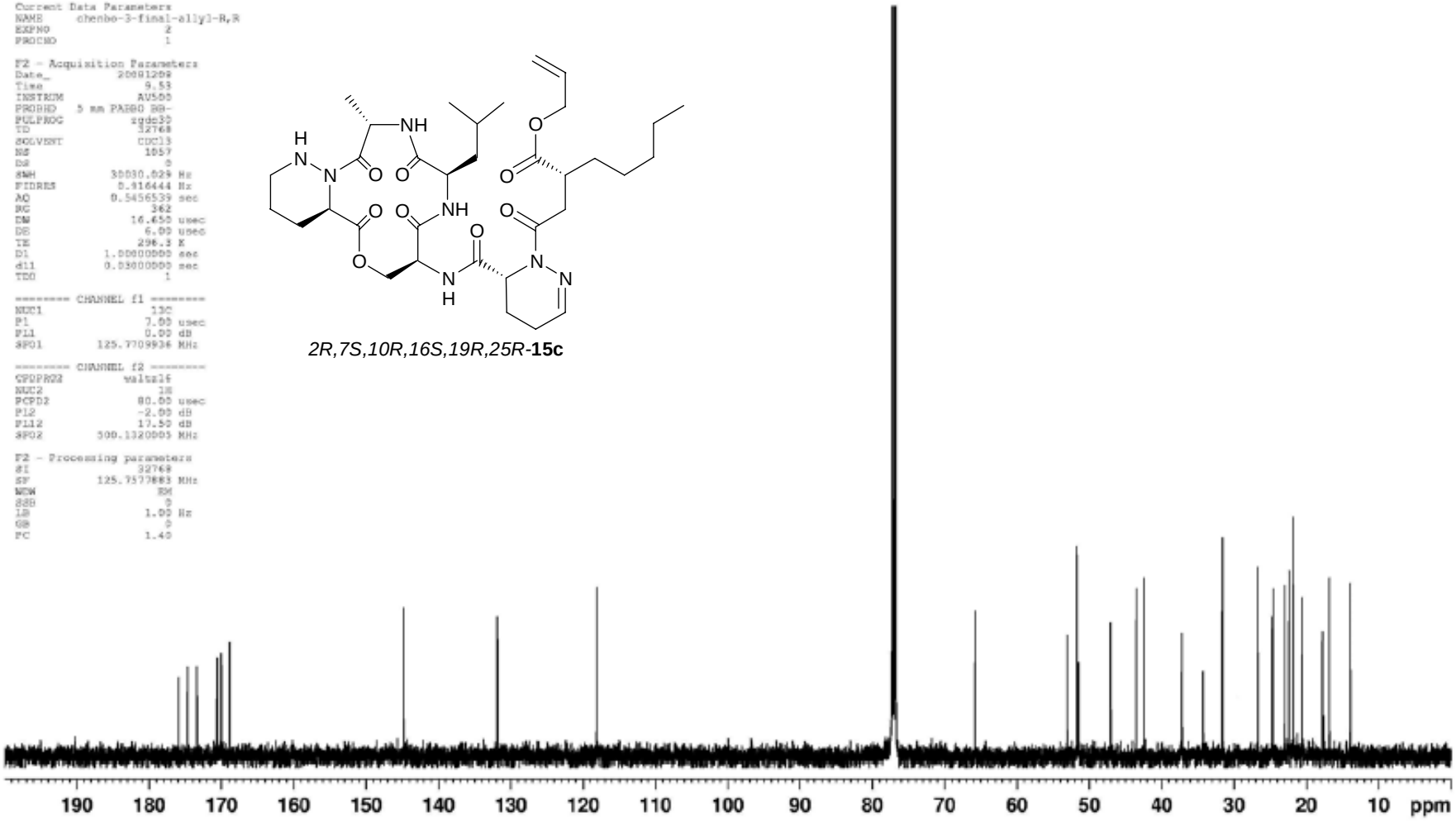


2R,7S,10R,16S,19R,25S-**15b**

^{1}H spectrum of 2*R*, 7*S*,10*R*,16*S*,19*R*,25*R*-**15c**



^{13}C spectrum of 2*R*,7*S*,10*R*,16*S*,19*R*,25*R*-**15c**



^{1}H spectrum of 2*R*,7*S*,10*R*,16*S*,19*S*,25*S*-**1**

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PROCNO      1
Date_       20090408
Time        3.32
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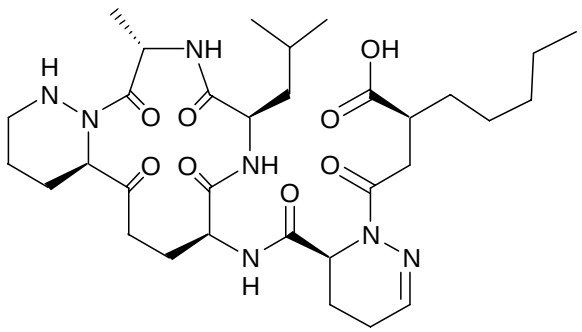
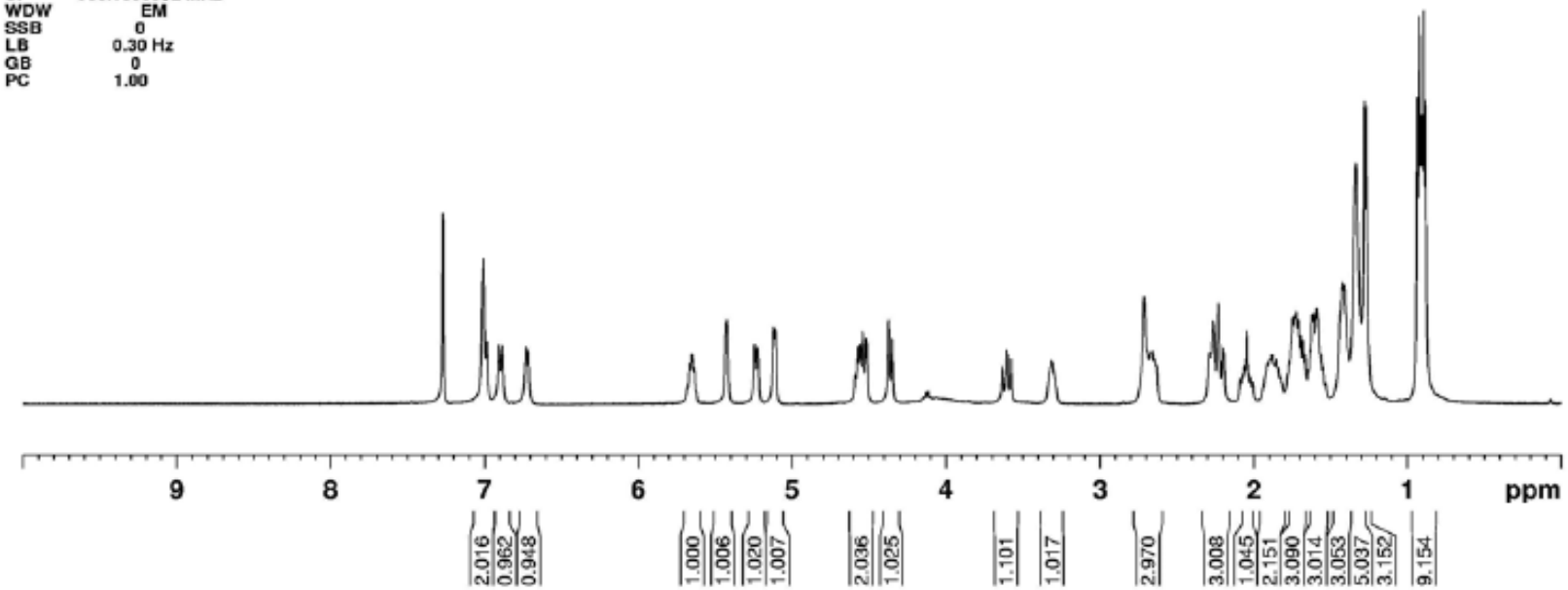
PROBHD      5 mm PABBO BB-
PULPROG     zg30
TD          32768
SOLVENT     CDCl3
NS          16
DS          0
SWH         8012.820 Hz
FIDRES      0.244532 Hz
AQ          2.0448356 sec
RG          114
DW          62.400 usec
DE          6.00 usec
TE          297.3 K
D1          1.00000000 sec
TD0         1

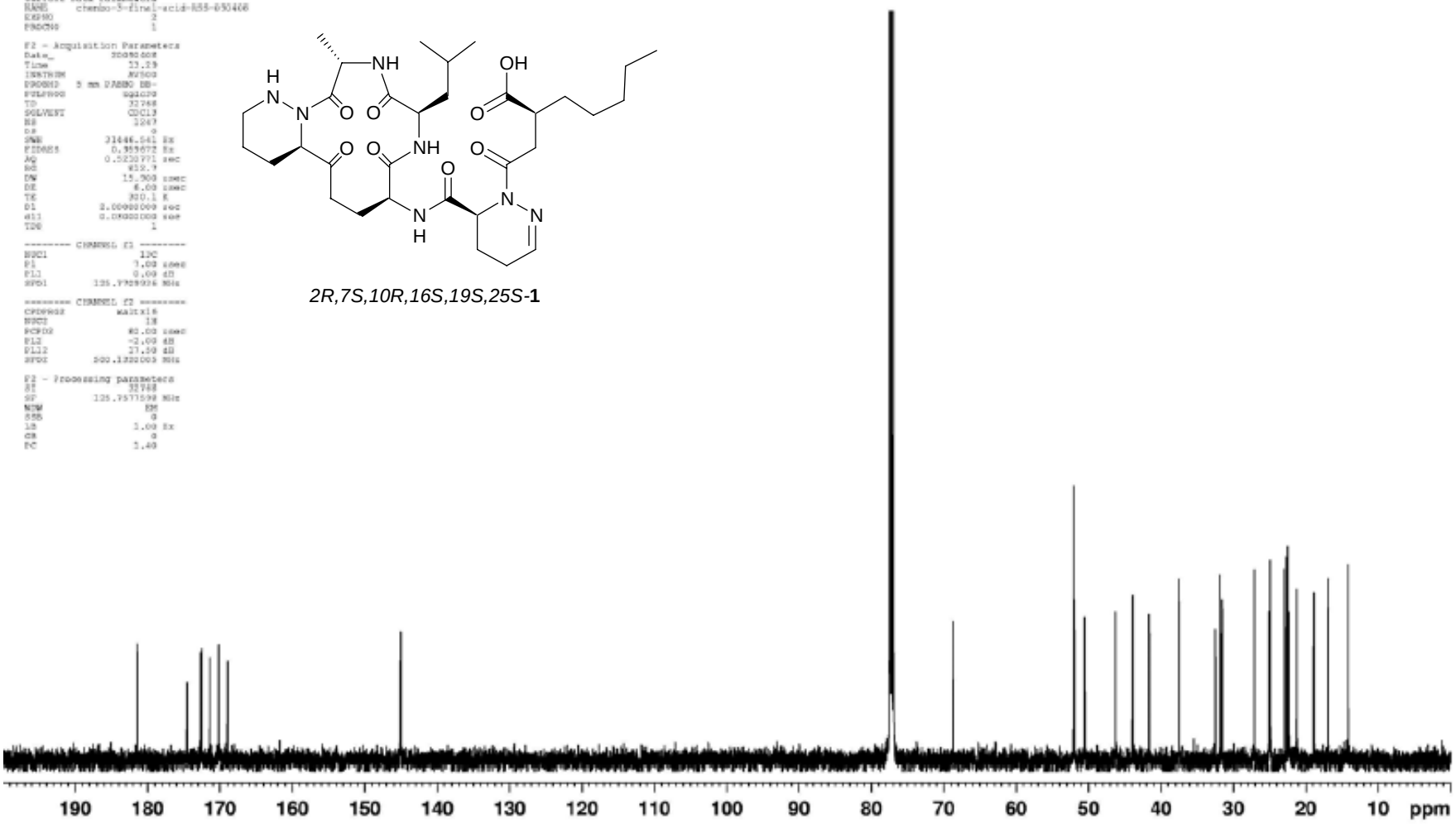
======== CHANNEL f1 ========
NUC1        1H
P1          8.70 usec
PL1         -2.00 dB
SFO1        500.1335009 MHz
SI          32768
SF          500.1300092 MHz
WDW         EM
SSB         0
LB          0.30 Hz
GB          0
PC          1.00
```



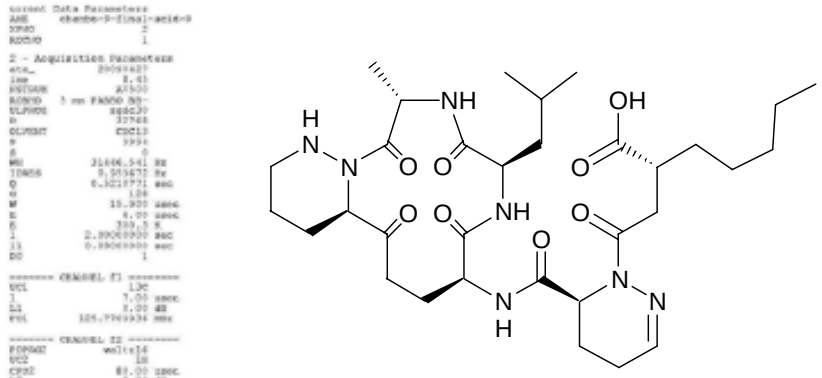
2R,7S,10R,16S,19S,25S-**1**



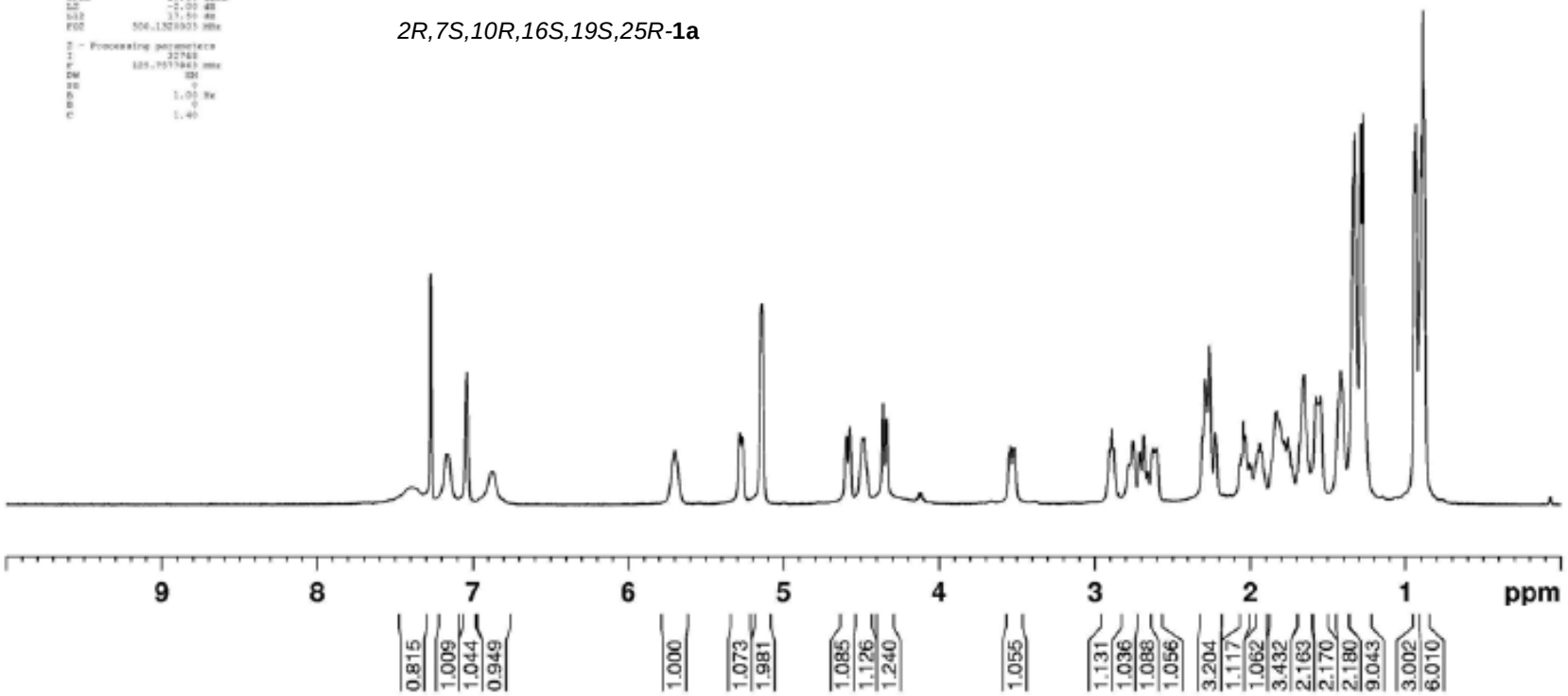
^{1}H spectrum of 2*R*,7*S*,10*R*,16*S*,19*S*,25*S*-**1**



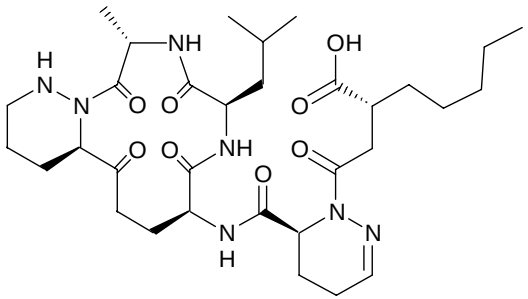
^{1}H spectrum of 2*R*,7*S*,10*R*,16*S*,19*S*,25*R*-**1a**



2R,7S,10R,16S,19S,25R-**1a**

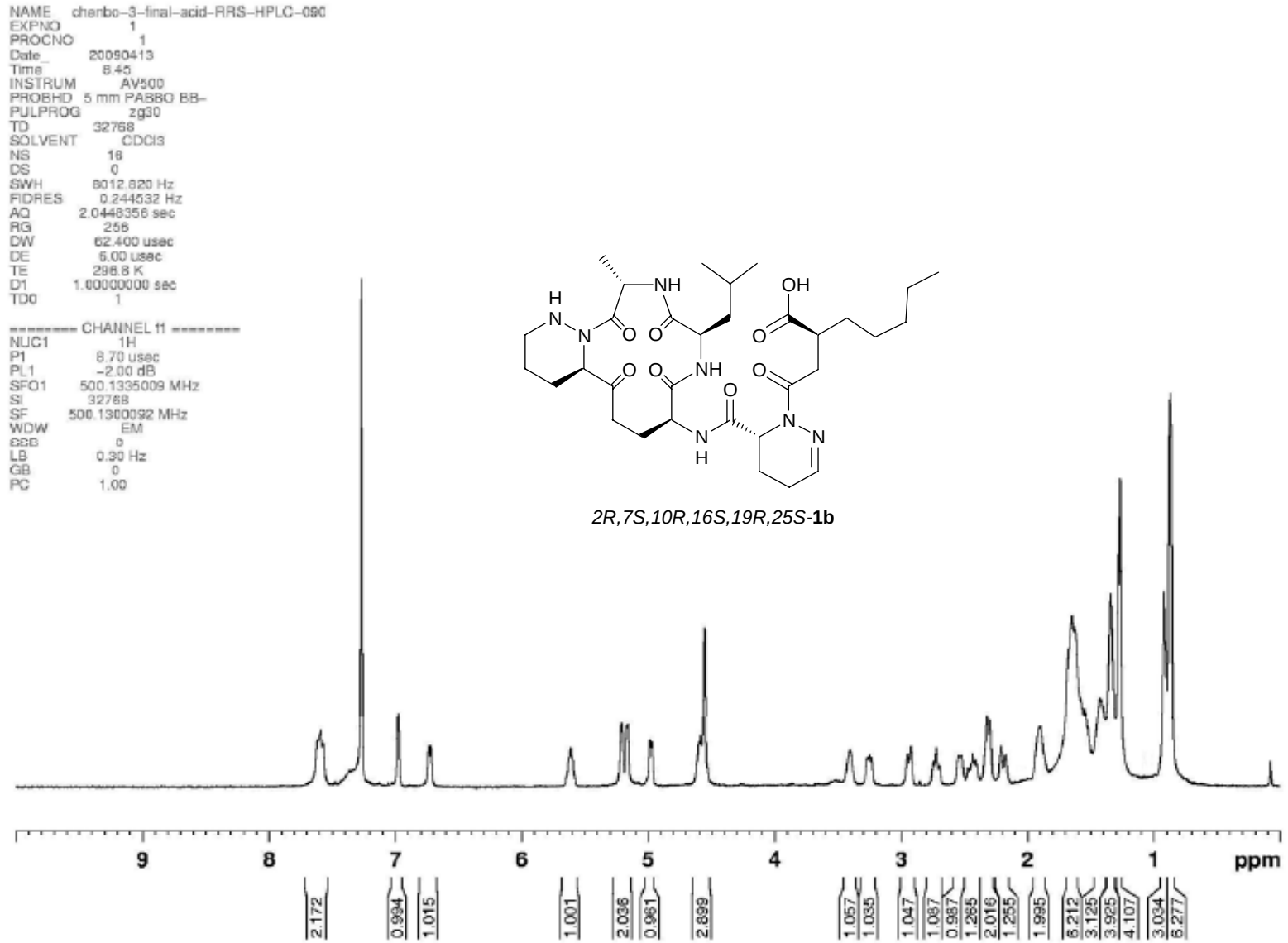


^{13}C spectrum of 2*R*,7*S*,10*R*,16*S*,19*S*,25*R*-**1a**

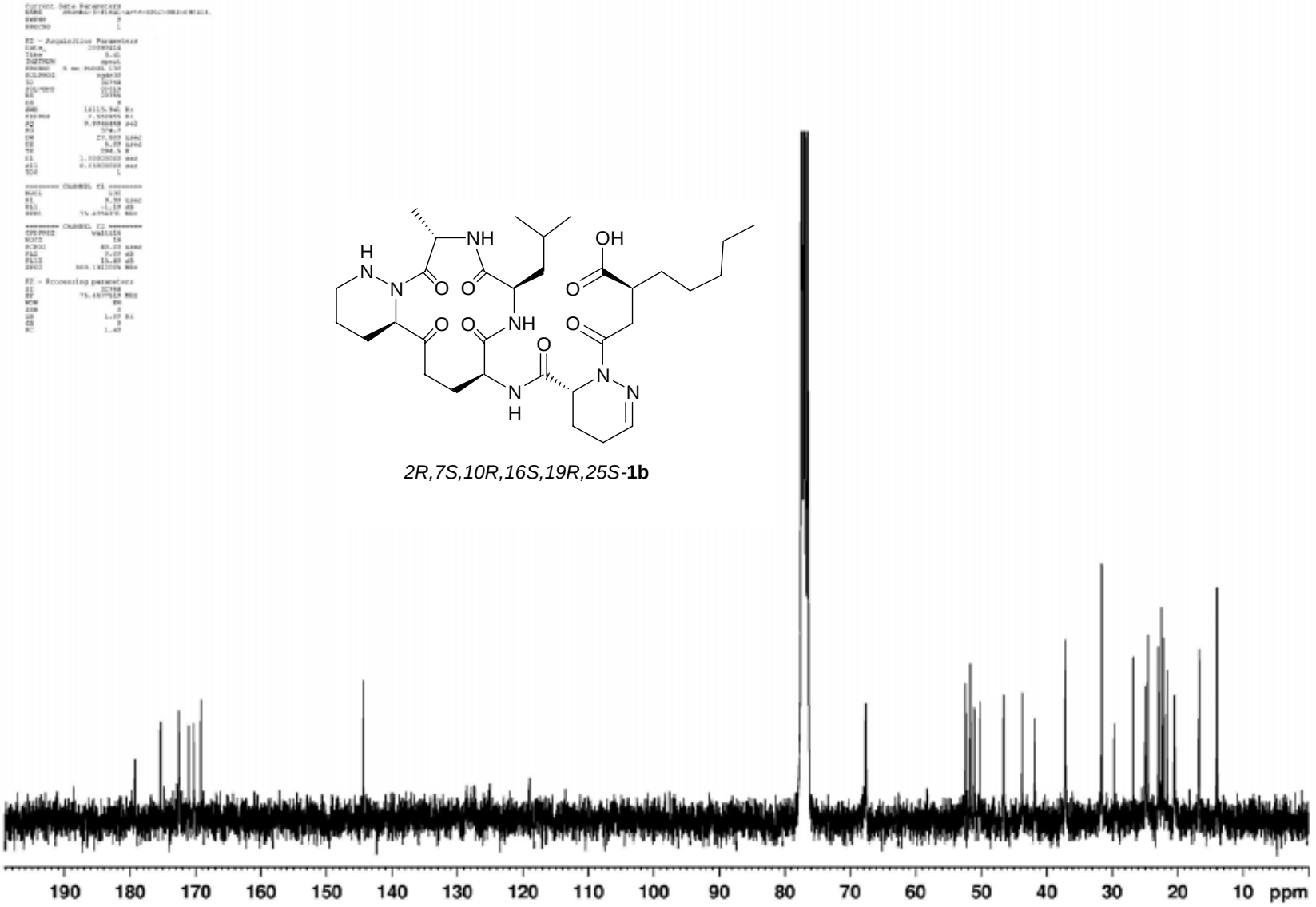


2R,7S,10R,16S,19S,25R-**1a**

^{1}H spectrum of 2*R*,7*S*,10*R*,16*S*,19*R*,25*S*-**1b**

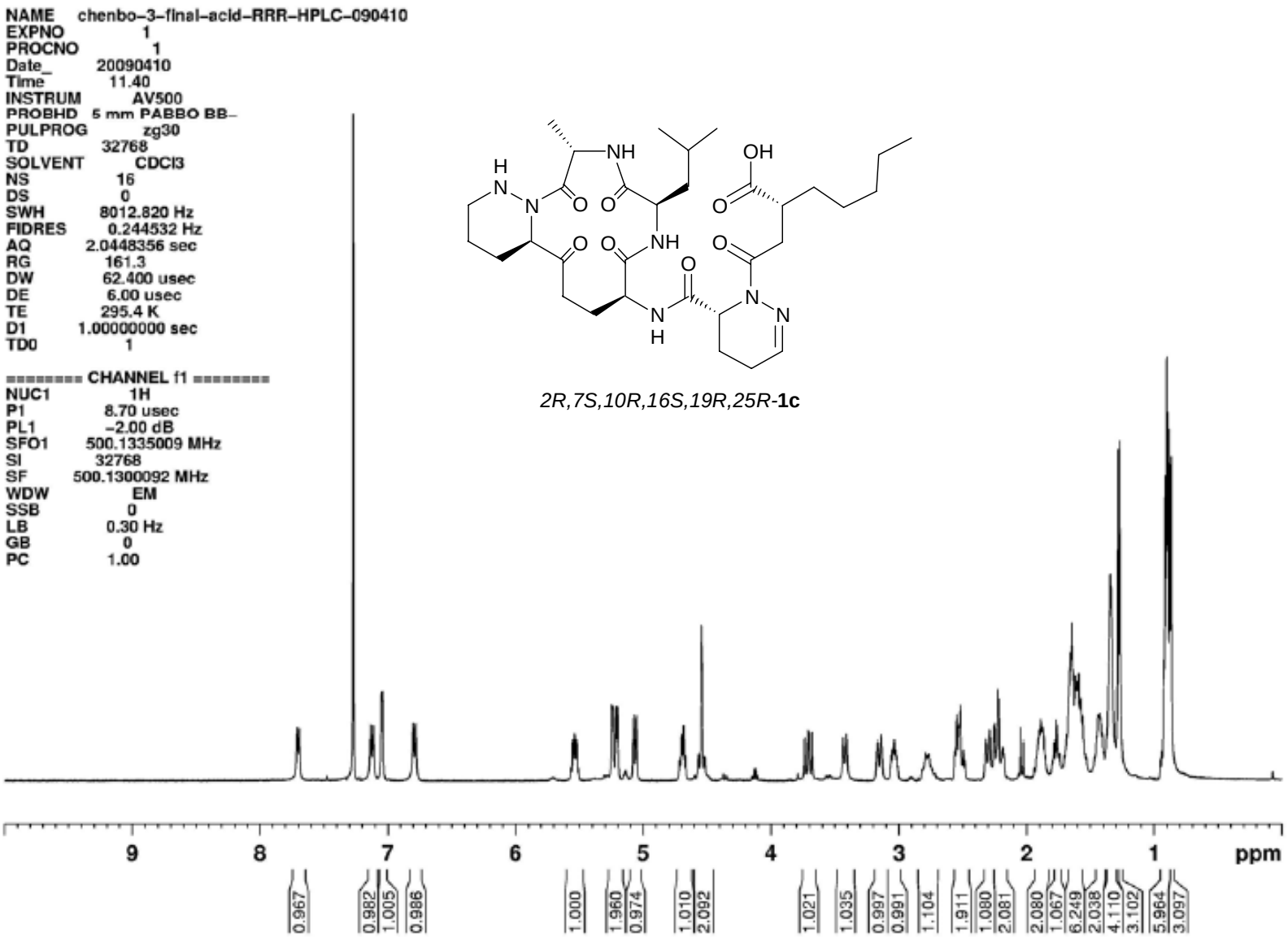


^{13}C spectrum of 2*R*,7*S*,10*R*,16*S*,19*R*,25*S*-**1b**



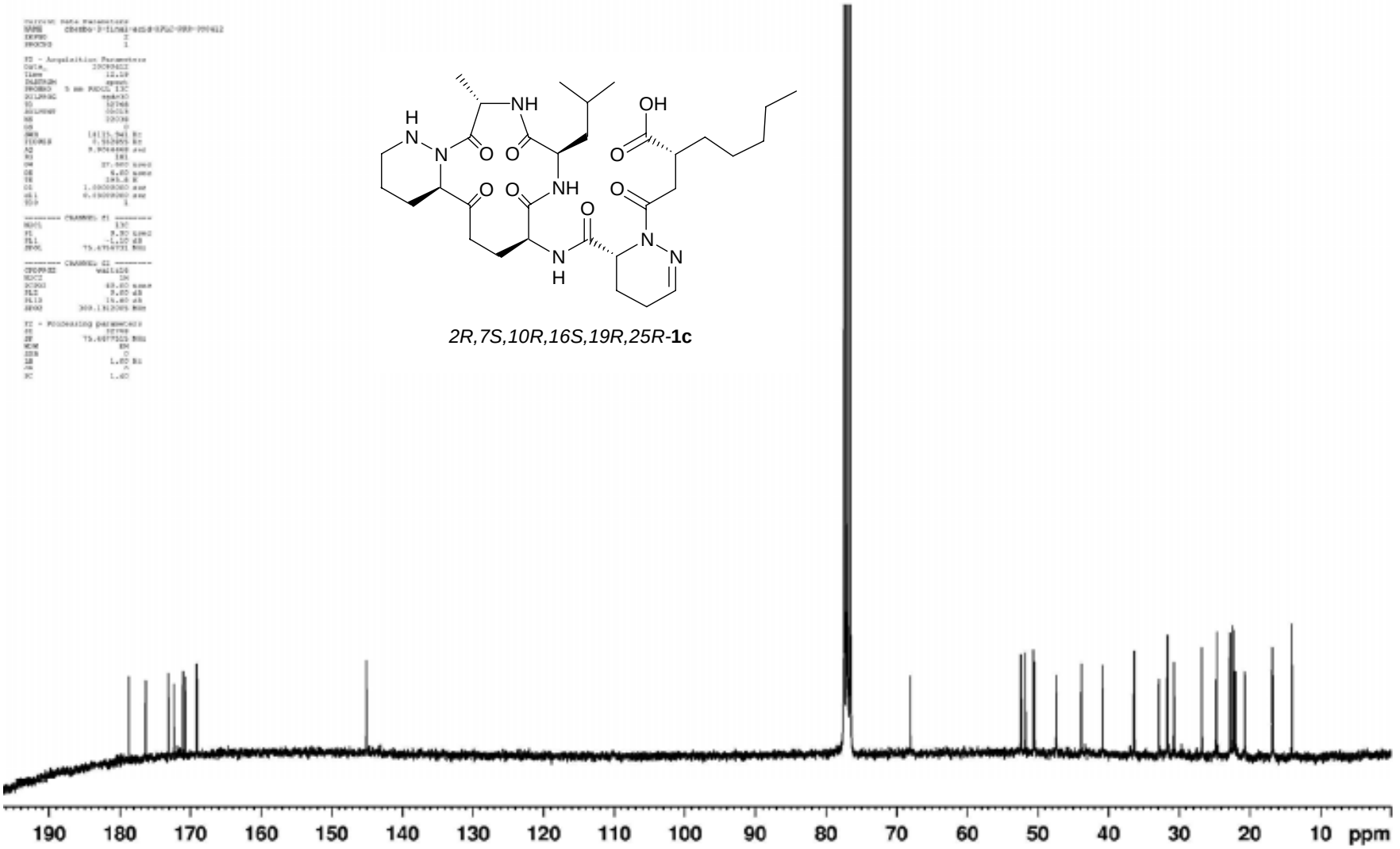
2R,7S,10R,16S,19R,25S-**1b**

^{1}H spectrum of 2*R*, 7*S*,10*R*,16*S*,19*R*,25*R*-**1c**



2R,7S,10R,16S,19R,25R-**1c**

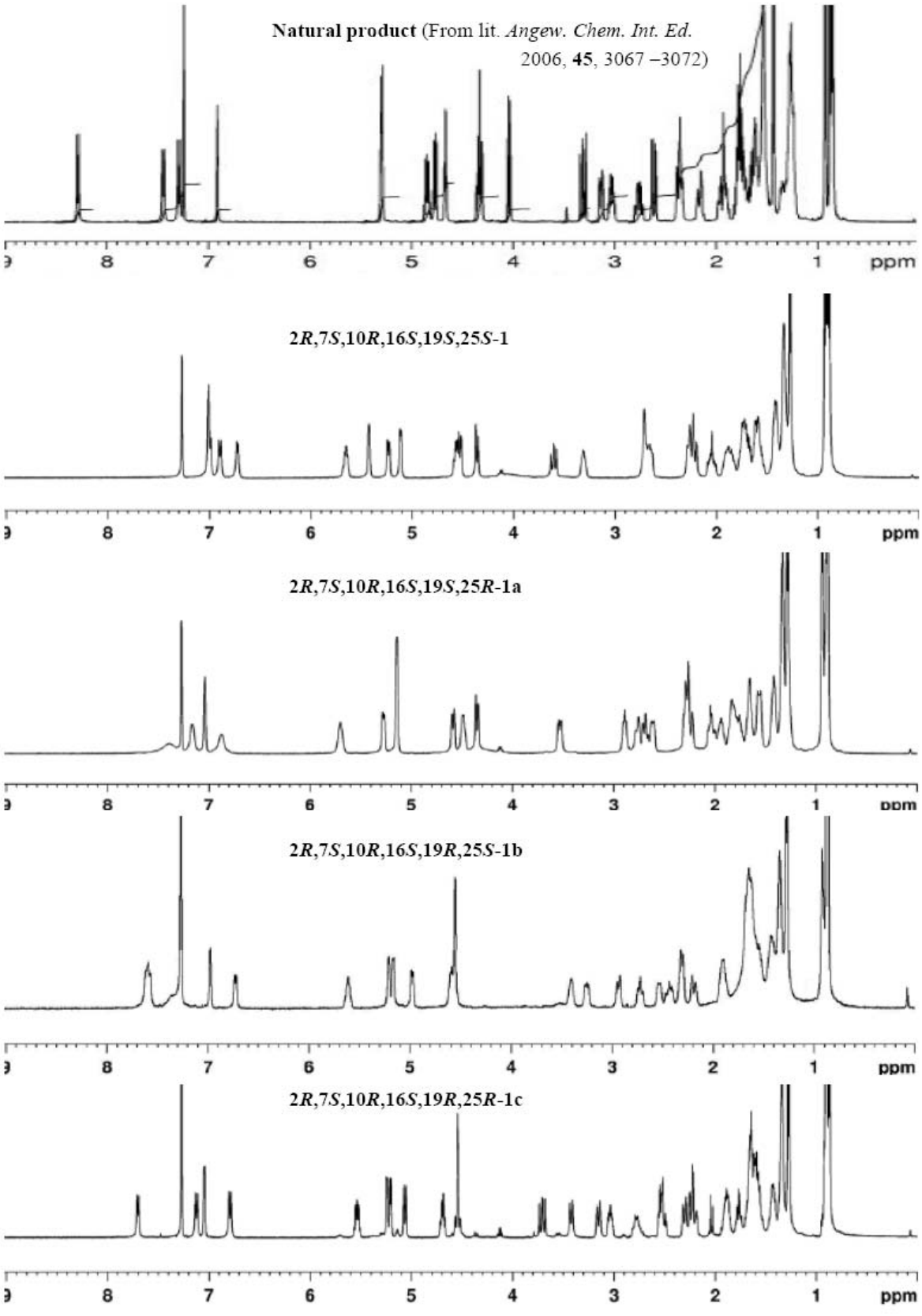
^{13}C spectrum of 2*R*,7*S*,10*R*,16*S*,19*R*,25*R*-**1c**



2R,7S,10R,16S,19R,25R-**1c**

Supplementary Material (ESI) for Chemical Communications

Comparison of ^{1}H NMR of natural product and synthetic samples


Natural product (From lit. Angew. Chem. Int. Ed. 2006, 45, 3067 –3072)
9 8 7 6 5 4 3 2 1 ppm
2R,7S,10R,16S,19S,25S-1
9 8 7 6 5 4 3 2 1 ppm
2R,7S,10R,16S,19S,25R-1a
9 8 7 6 5 4 3 2 1 ppm
2R,7S,10R,16S,19R,25S-1b
9 8 7 6 5 4 3 2 1 ppm
2R,7S,10R,16S,19R,25R-1c
9 8 7 6 5 4 3 2 1 ppm

Comparison of ^{13}C NMR of natural product and synthetic samples