

Efficient Syntheses and Anti-Cancer Activity of Xenortides A-D Including *ent/epi*-Stereoisomers

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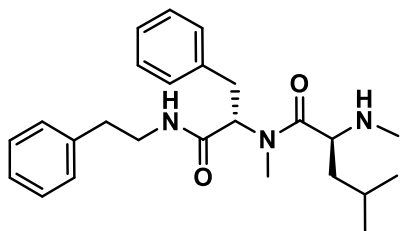
Table of Content

¹H NMR, ¹³C NMR, optical rotation, and mass spectral data for Xenortides A-D and their *ent/epi*-stereoisomers.....**S2-S50**

All reagents and solvents were purchased from commercial sources and used without further purification. Compounds were purified using flash chromatography with Whatman Purasil 60 Å 230-400 mesh silica gel or by preparative TLC using Dynamic Absorbents Inc. silica gel TLC 250 µm w/h F-254, catalog no. 84111. Proton and carbon NMR spectra were recorded using a Bruker Avance III 600 spectrometer. The residual solvent signal in CD₃OD was referenced to 3.31 and 49.0 ppm in proton and carbon spectra respectively. Mass spectral data were taken on a Waters ESI-MS, model LCT premier XE. Methyl isocyanide was prepared as described in: R. E. Schuster, J. E. Scott, J. Casanova, *Organic Syntheses* 1966, **46**, 75. (DOI: 10.15227/orgsyn.046.0075).

(S)-N,4-dimethyl-2-(methylamino)-N-((S)-1-oxo-1-(phenethylamino)-3-phenylpropan-2-yl)pentanamide (5)

The compound was obtained as a white solid; yield: (185.01 mg, 27%); $[\alpha]_D^{20}$ -57 (c 0.2, MeOH); lit¹ -54 (c 0.2, MeOH); R_f:

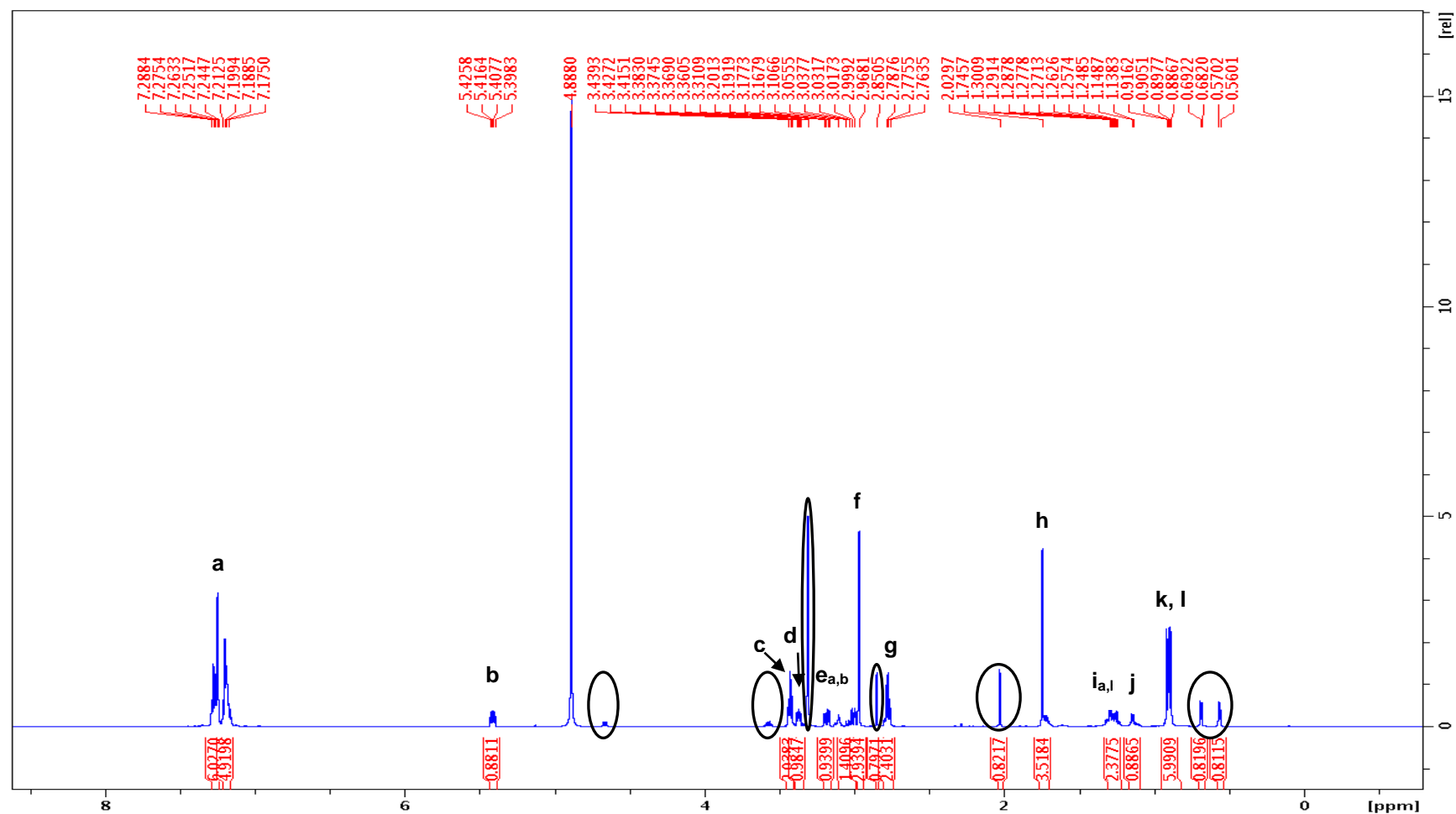
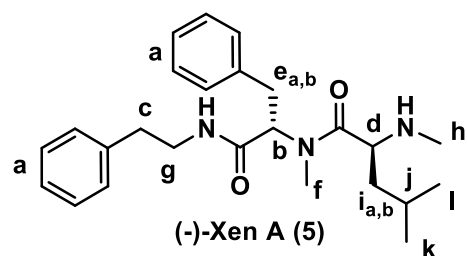


(-)-Xen A (5)

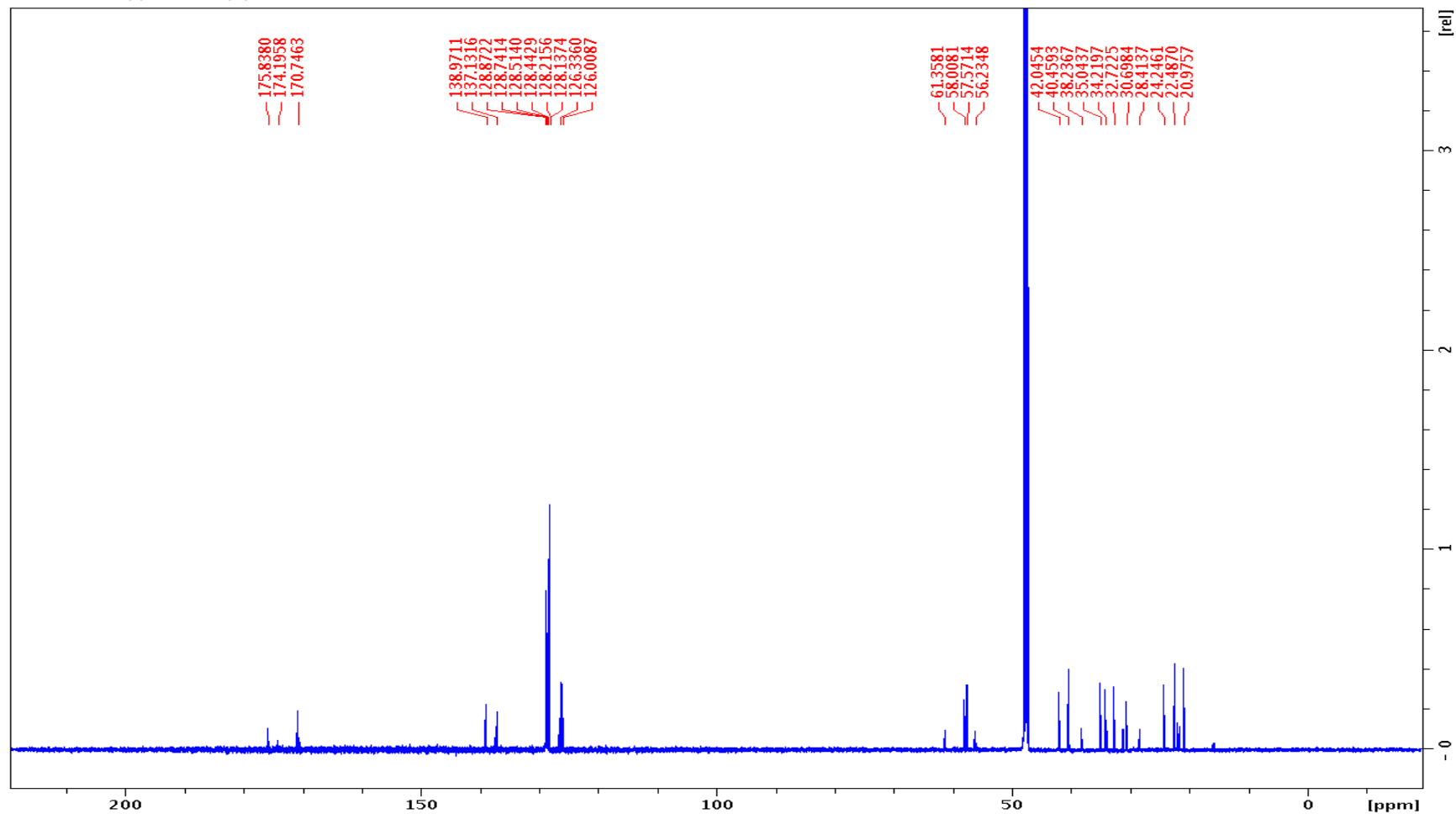
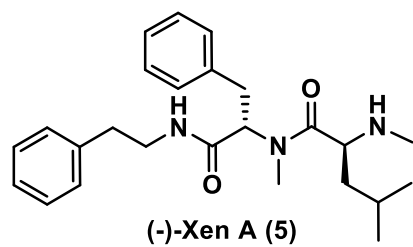
0.5 cm; **¹H NMR** (600 MHz, CD₃OD) showed the presence of two rotamers in a ratio of 4.3/1, major rotamer shown: δ 7.29-7.24 (m, 6H, aryl), 7.21-7.17 (m, 4H, aryl), 5.42-5.39 (dd, J_1 = 6.0 Hz, J_2 = 12.0 Hz, 1H, CH), 3.43-3.41 (t, J = 7.2 Hz, 2H, CH₂), 3.38-3.36 (m, 1H, CH), 3.18-3.03 (dd, J_1 = 5.4 Hz, J_2 = 14.4 Hz, 1H, CH), 3.11-3.00 (m, 1H, CH),

2.97 (s, 3H, CH₃-N), 2.78-2.76 (t, J = 7.2 Hz, 2H, CH₂), 1.74 (s, 3H, CH₃-NH), 1.30-1.25 (m, 2H, CH₂), 1.15-1.14 (m, 1H, CH), 0.92-0.89 (m, 6H, 2CH₃); **¹³C NMR** (600 MHz, CD₃OD) major rotamer shown: δ 175.84, 170.75, 138.97, 137.13, 128.87, 128.74, 128.51, 128.14, 126.34, 126.01, 58.01, 57.57, 42.04, 40.46, 35.04, 34.22, 32.72, 30.70, 24.24, 22.49, 20.97 ppm; **HRMS** (TOF-ESI): [M+H]⁺calculated for C₂₅H₃₆N₃O₂: 410.2808; found: 410.2807.

1. Reimer, D.; Nollmann, F. I.; Schultz, K.; Kaiser, M. Bode, H. B. *Journal of Natural Products*, **2014**, *77*, 1976-1980.



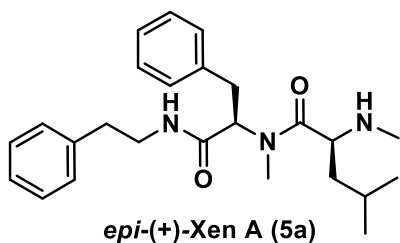
¹H NMR spectrum of compound (-)-5



¹³C NMR spectrum of compound (-)-5

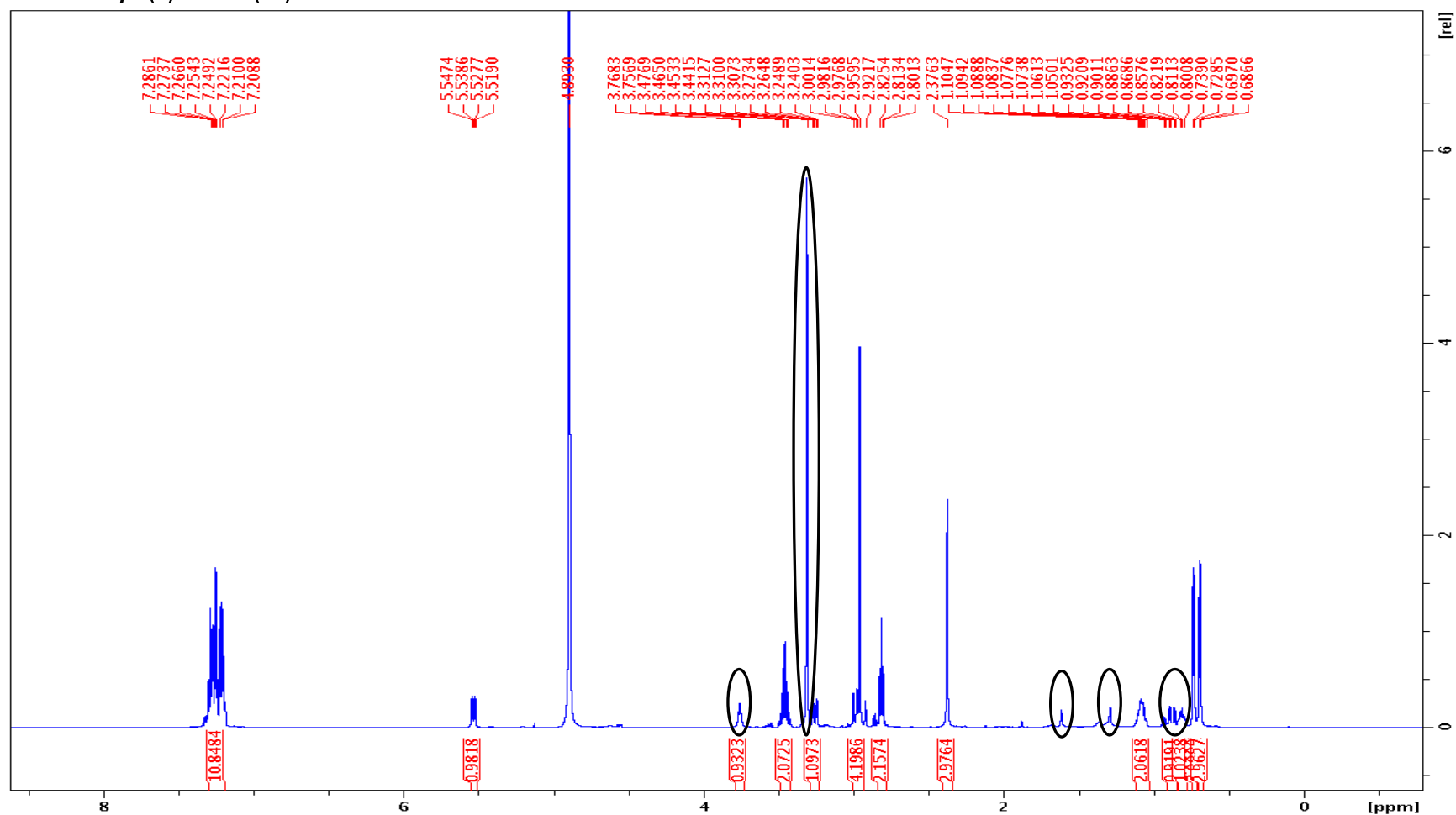
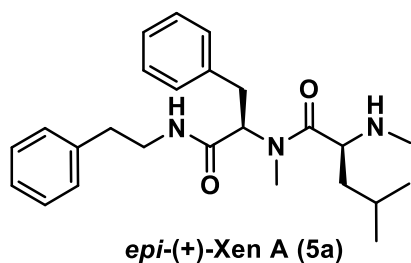
(S)-N,4-dimethyl-2-(methylamino)-N-((R)-1-oxo-1-(phenethylamino)-3-phenylpropan-2-yl)pentanamide (5a)

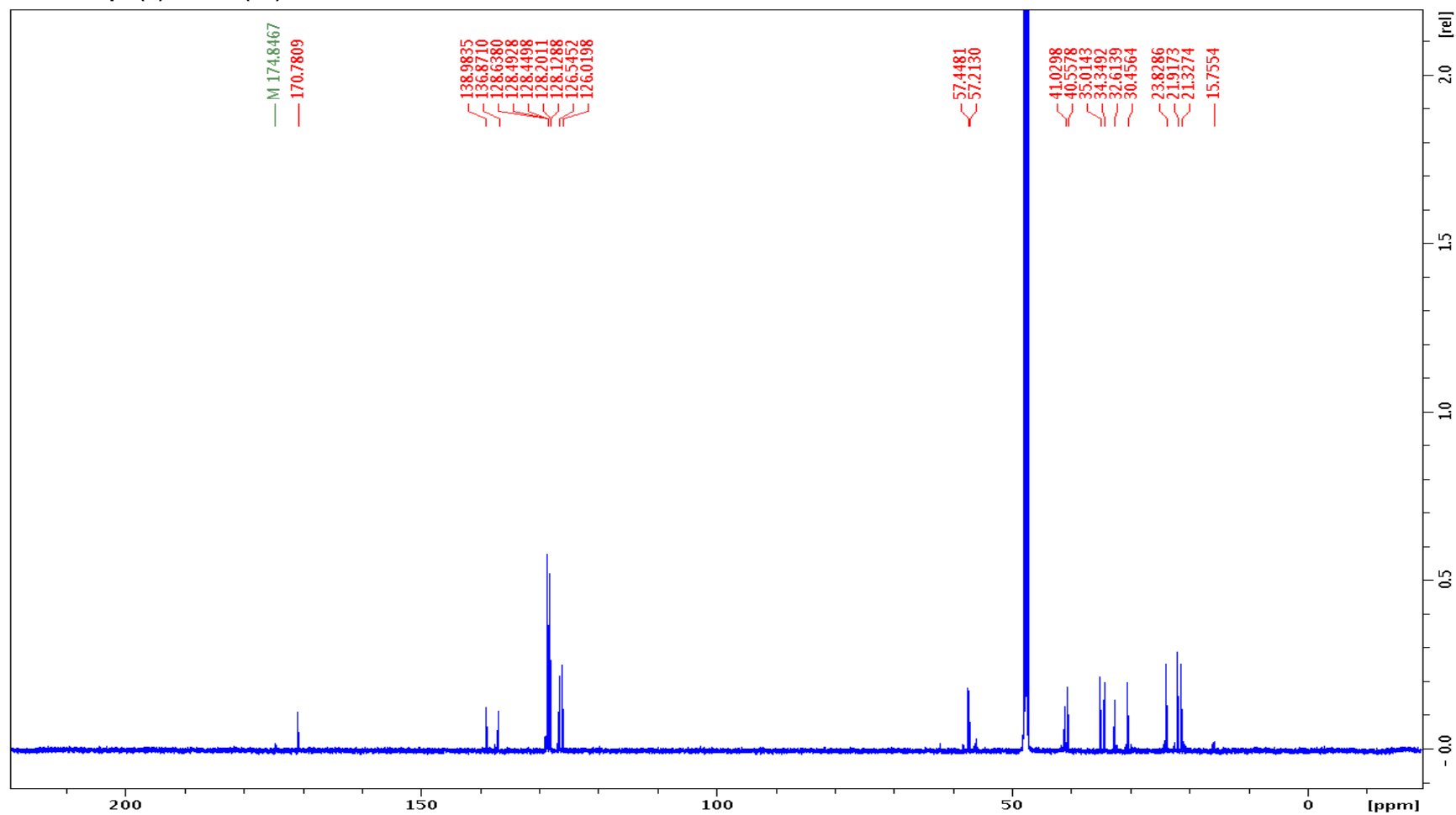
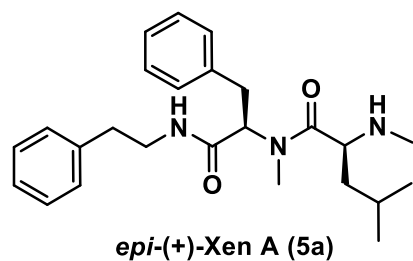
The compound was obtained as a white solid; yield: (127.59 mg, 18%); $[\alpha]_D^{20} +43$ (*c* 0.2, MeOH); *R*_f: 0.8 cm; **¹H NMR**



(600 MHz, CD₃OD); δ 7.28-7.20 (m, 10H, aryl), 5.54-5.51 (dd, $J_1 = 6.0$ Hz, $J_2 = 12.0$ Hz, 1H, aryl), 3.77-3.75 (m, 1H, CH), 3.48-3.44 (m, 2H, CH₂), 3.31-3.25 (dd, $J_1 = 6.0$ Hz, $J_2 = 12.0$ Hz, 1H, CH₂), 3.00-2.92 (m, 4H, CH, CH₃-N), 2.82-2.80 (t, $J = 6.0$ Hz, 2H, CH₂), 2.37 (s, 3H, CH₃-NH), 1.10-1.07 (m, 2H, CH₂), 0.89- 0.85 (m, 1H, CH), 0.74-0.73 (d, $J = 6.0$ Hz, 3H, CH₃), 0.69-0.68 (d, $J = 6.0$ Hz, 3H, CH₃) ppm; **¹³C NMR** (600 MHz,

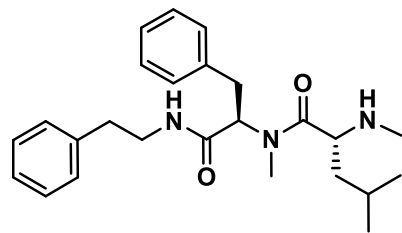
CD₃OD): δ 174.85, 170.78, 138.98, 136.87, 128.49, 128.45, 128.20, 128.13, 126.55, 126.02, 57.45, 57.21, 41.03, 40.56, 35.01, 34.35, 32.61, 30.46, 23.83, 21.92, 21.33 ppm; **HRMS** (TOF-ESI): [M+H]⁺calculated for C₂₅H₃₆N₃O₂: 410.2808; found: 410.2820.





(*R*)-N,4-dimethyl-2-(methylamino)-N-((*R*)-1-oxo-1-(phenethylamino)-3-phenylpropan-2-yl)pentanamide (5b)

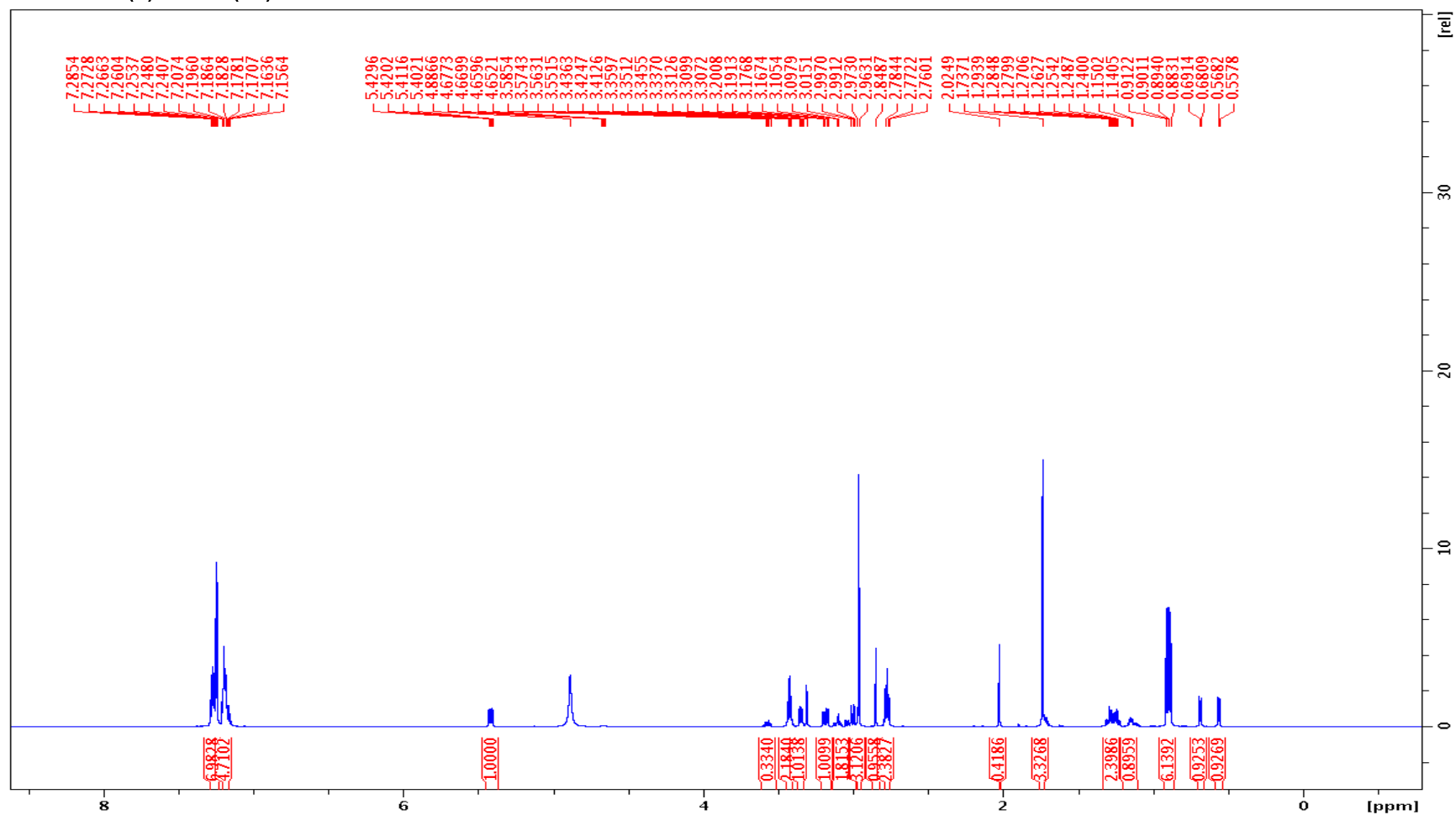
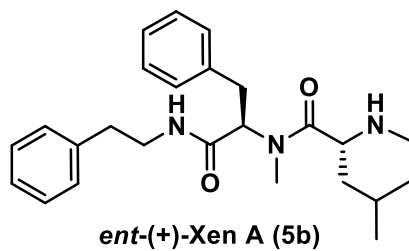
The compound was obtained as a white solid; yield: (102.30 mg, 15%); $[\alpha]_{\text{D}}^{20} +57$ (c 0.2, MeOH); R_f : 0.3 cm; **^1H NMR**

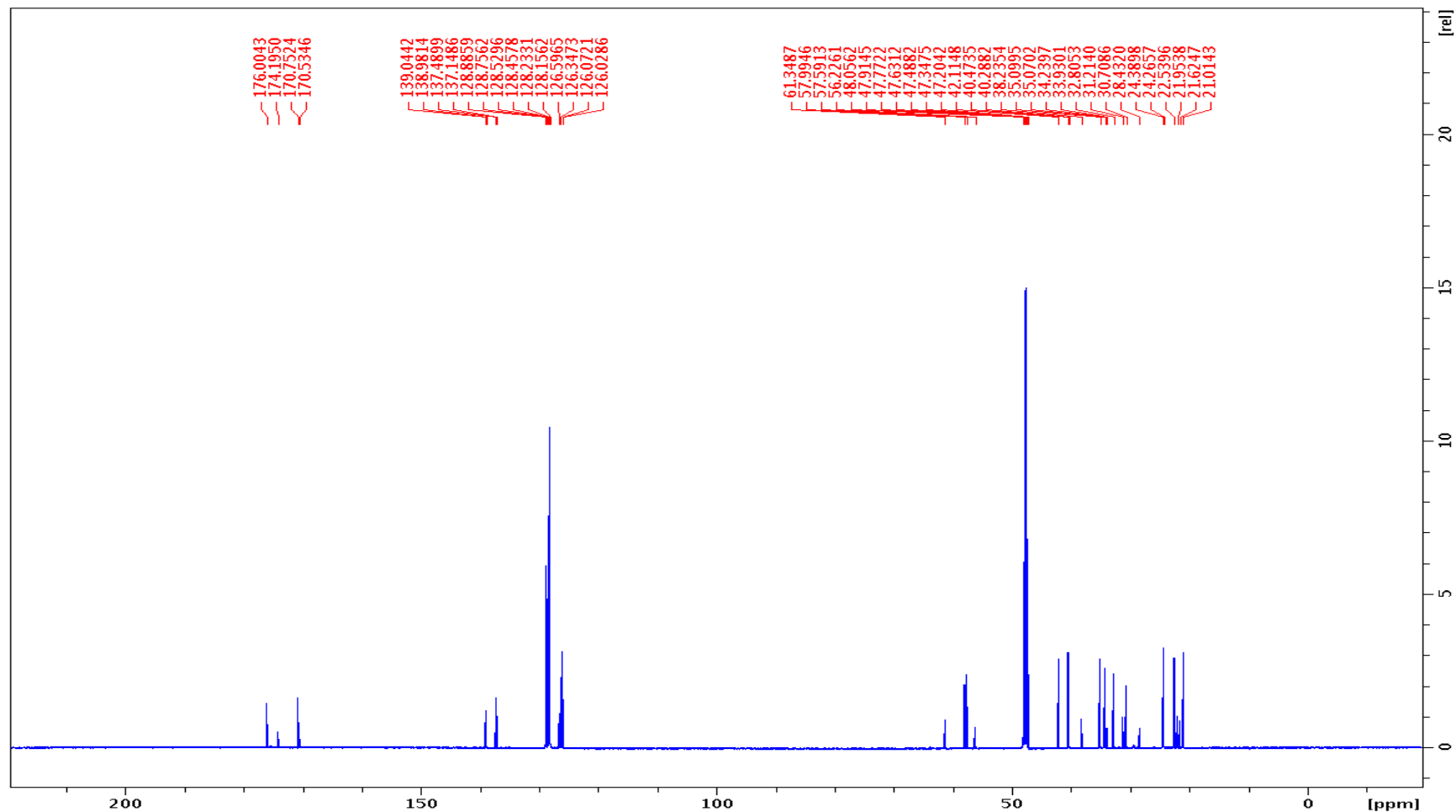
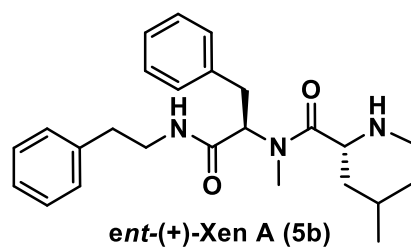


ent-(+)-Xen A (5b)

(600 MHz, CD_3OD) showed the presence of two rotamers in a ratio of 3.5/1, major rotamer shown: δ 7.28-7.21 (m, 6H, aryl), 7.19-7.16 (m, 4H, aryl), 5.43-5.40 (dd, $J_1 = 6.0$ Hz, $J_2 = 12.0$ Hz, 1H, CH), 3.44-3.36 (t, $J = 7.2$ Hz, 2H, CH_2), 3.35-3.33 (m, 1H), 3.20-3.17 (dd, $J_1 = 5.2$ Hz, $J_2 = 14.3$ Hz, 1H), 3.01-2.96 (m, 4H, CH, $\text{CH}_3\text{-N}$), 2.78-2.76 (t, $J = 7.2$ Hz, 2H, CH_2), 1.73 (s, 3H, $\text{CH}_3\text{-NH}$), 1.29-1.24 (m, 2H, CH_2), 1.14-1.13 (m,

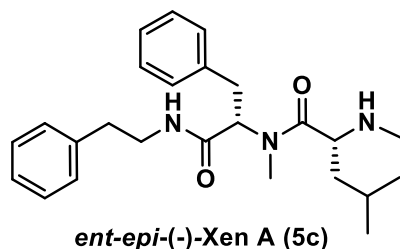
1H, CH), 0.91-0.88 (m, 6H, 2 CH_3); **^{13}C NMR** (600 MHz, CD_3OD) major rotamer shown: δ 176.00, 170.75, 139.04, 137.48, 128.88, 128.74, 128.52, 126.60, 126.34, 126.07, 58.01, 57.99, 56.22, 40.47, 35.09, 34.24, 32.80, 30.71, 24.24, 21.95, 21.01 ppm; **HRMS** (TOF-ESI): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{25}\text{H}_{36}\text{N}_3\text{O}_2$: 410.2808; found: 410.2823.





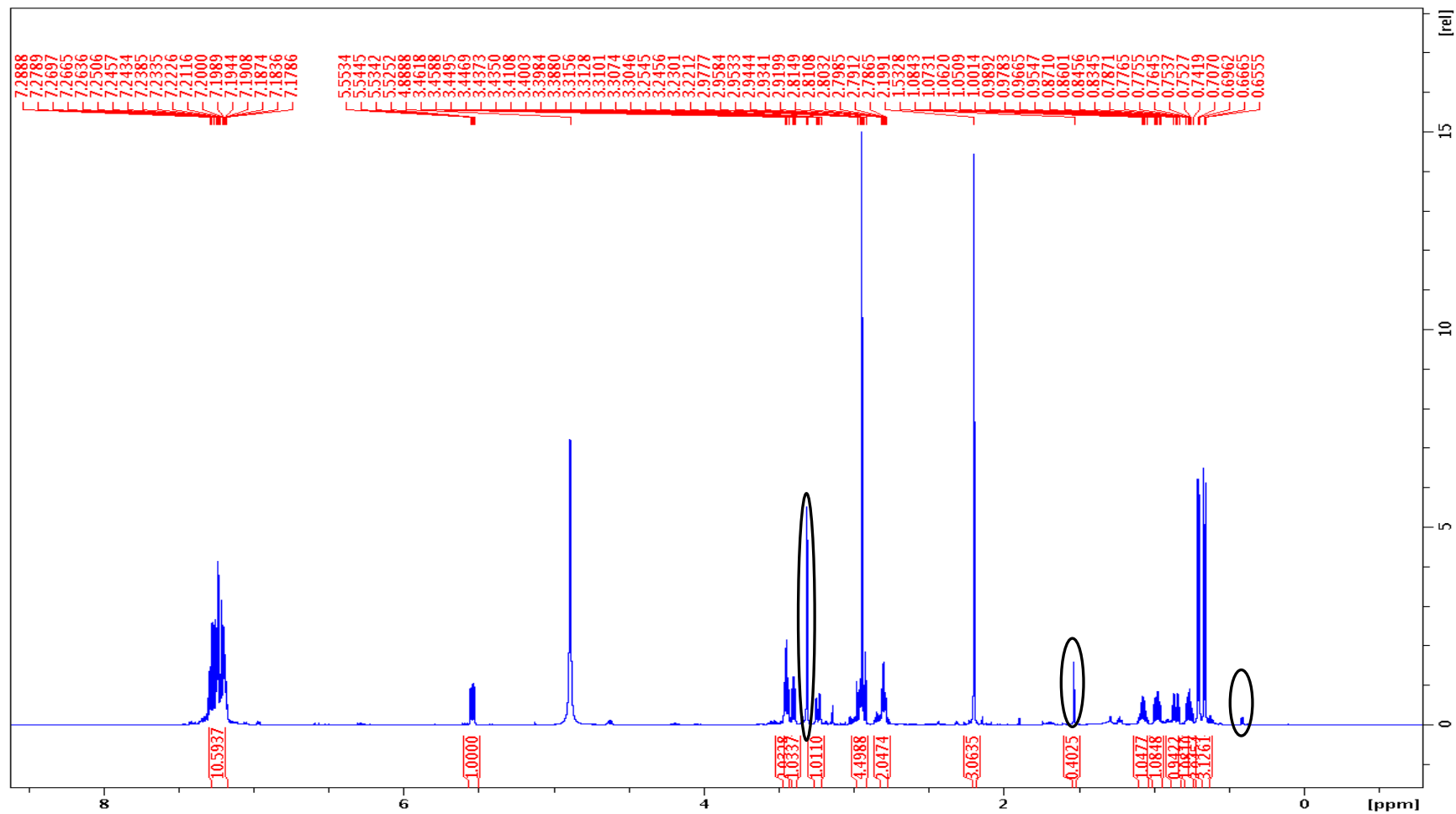
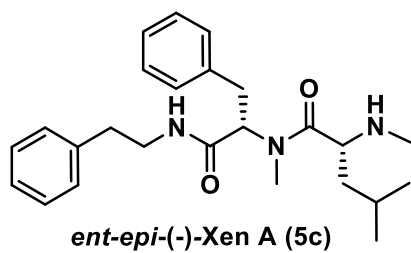
¹³C NMR spectrum of compound (+)-5b

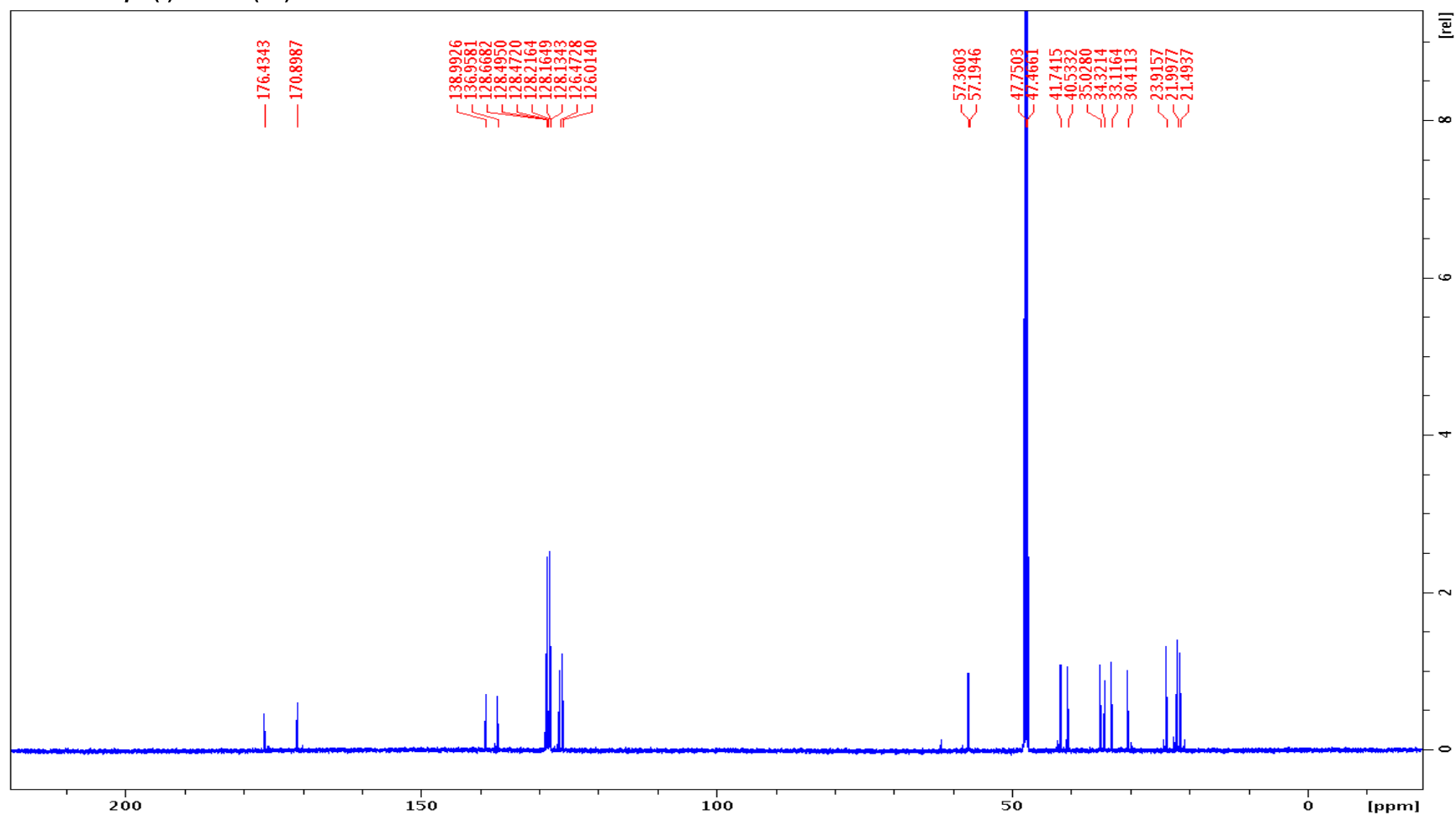
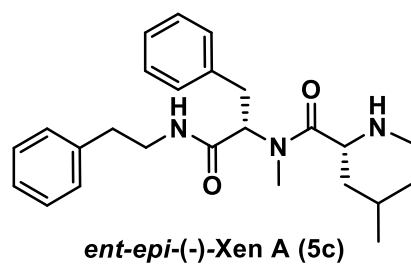
(R)-N,4-dimethyl-2-(methylamino)-N-((S)-1-oxo-1-(phenethylamino)-3-phenylpropan-2-yl)pentanamide (5c)



The compound was obtained as a white solid; yield: (133.02 mg, 19%); $[\alpha]_{\text{D}}^{20}$ -43 (*c* 0.2, MeOH); *R*_f: 0.6 cm; **¹H NMR** (600 MHz, CD₃OD); δ = 7.29-7.17 (m, 10H, aryl), 5.55-5.52 (dd, J_1 = 5.3 Hz, J_2 = 12.0 Hz, 1H, CH), 3.46-3.40 (m, 2H, CH₂), 3.39-3.38 (m, 1H, CH), 3.25-3.22 (dd, J_1 = 5.3 Hz, J_2 = 12.0 Hz, 1H, CH), 2.98-2.93 (m, 4H, CH, CH₃-N), 2.81-

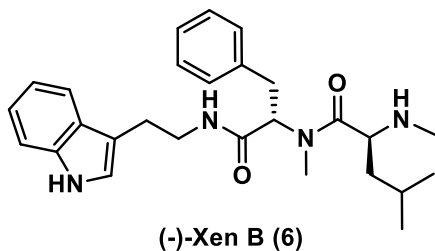
2.78 (m, 2H, CH₂), 2.20 (s, 3H, CH₃-NH), 0.99-0.95 (m, 1H, CH), 0.83-0.78 (m, 1H, CH), 0.77-0.74 (m, 1H, CH), 0.75 (d, J = 6.0 Hz, 3H, CH₃), 0.66 (d, J = 6.0 Hz, 3H, CH₃) ppm; **¹³C NMR** (600 MHz, CD₃OD): δ 176.43, 170.89, 138.99, 136.95, 128.49, 128.47, 128.21, 128.16, 126.47, 126.01, 57.36, 57.19, 41.74, 40.53, 35.03, 34.32, 33.11, 30.41, 23.91, 21.99, 21.49 ppm; **HRMS** (TOF-ESI): $[M+H]^+$ calculated for C₂₅H₃₆N₃O₂: 410.2808; found: 410.2816.





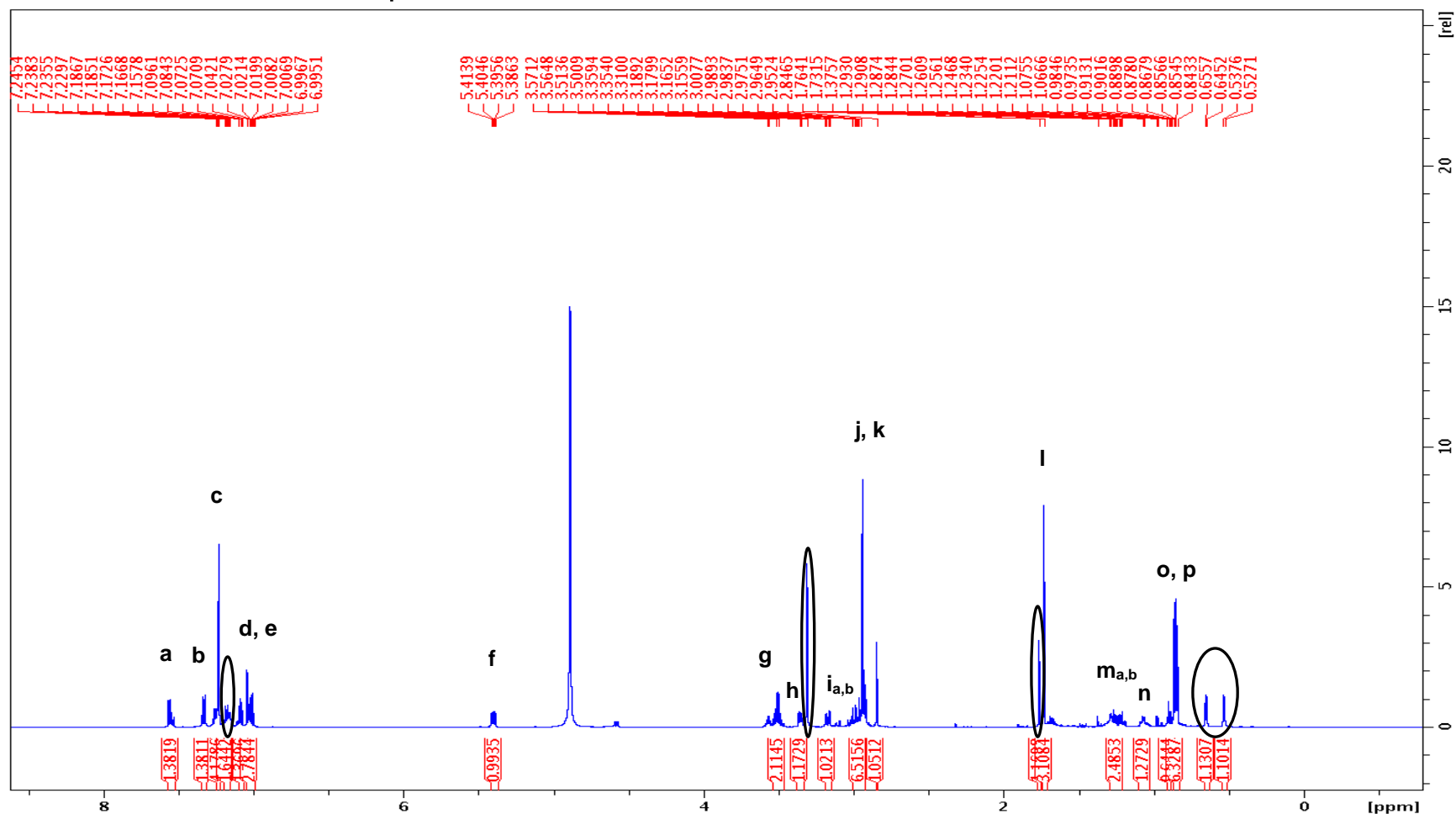
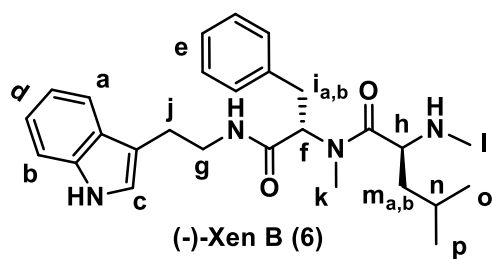
(S)-N-((S)-1-((2-(1H-indol-3-yl)ethyl)amino)-1-oxo-3-phenylpropan-2-yl)-N,4-dimethyl-2-(methylamino)pentanamide

(6)

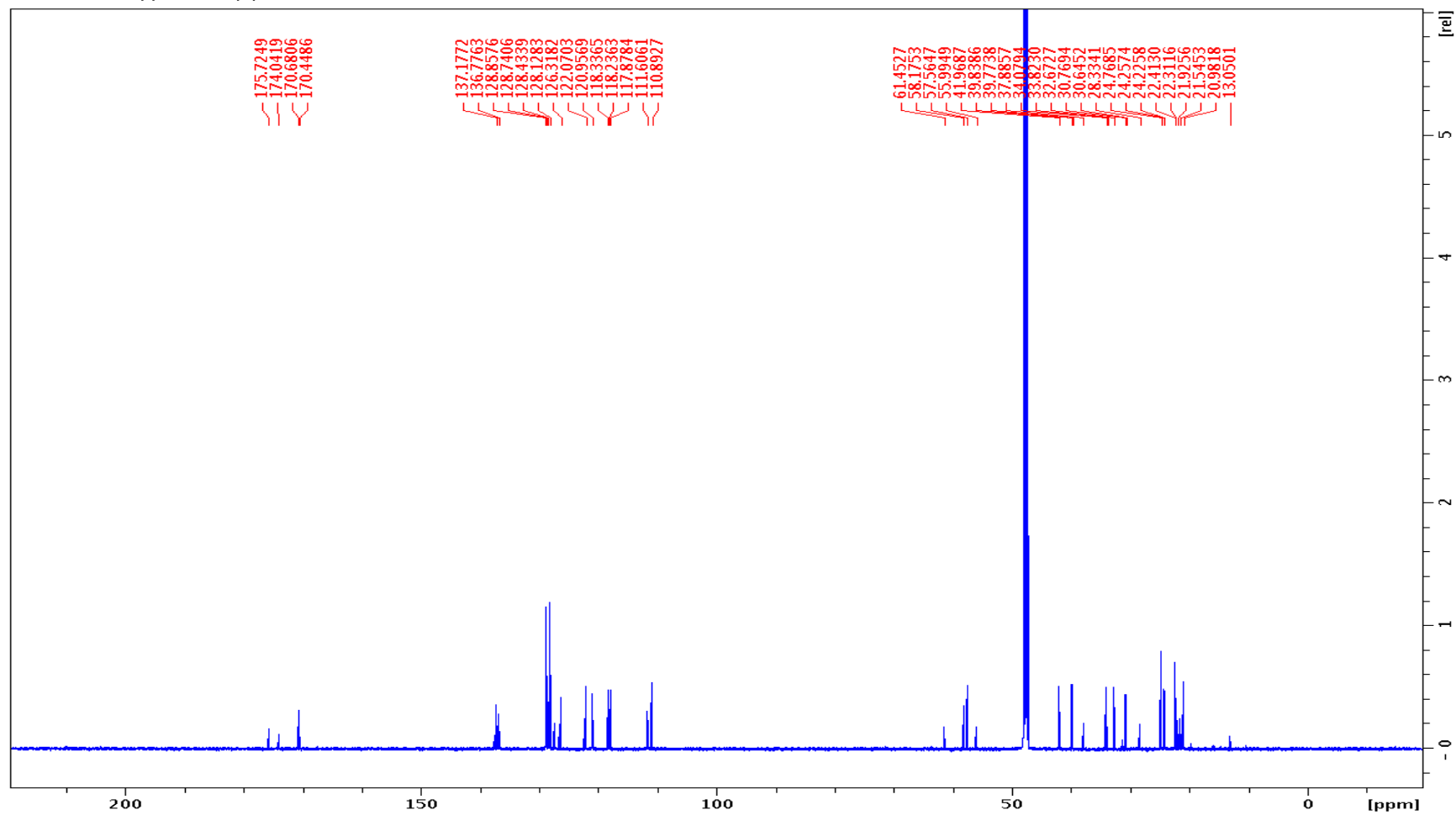
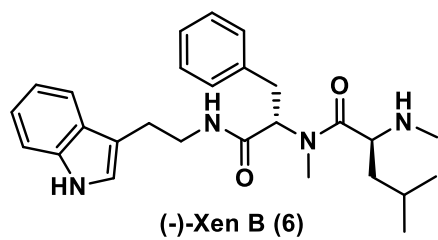


The compound was obtained as a yellowish solid; yield: (215.77 mg, 28%); $[\alpha]_D^{20}$ -56 (c 0.3, MeOH); lit^{1a} -58 (c 0.3, MeOH); R_f: 0.3 cm; **¹H NMR** (600 MHz, CD₃OD) showed the presence of two rotamers in a ratio of 2.8/1, major rotamer shown: δ 7.56-7.55 (d, J = 6.0 Hz, 1H, aryl), 7.33-7.32 (d, J = 6.0Hz, 1H, aryl), 7.26-7.23 (m, 4H, aryl), 7.19-7.16 (m, 1H, aryl), 7.08-7.06 (t, J = 7.2 Hz, 1H, aryl), 7.04-6.99 (m, 2H, aryl), 5.40-5.39 (dd, J_1 = 6.0, J_2 = 12.0 Hz, 1H, CH), 3.57-3.50 (m, 2H, CH₂), 3.36-3.35 (m, 1H, CH), 3.17-3.15 (dd, J_1 = 5.4 Hz, J_2 = 14.4 Hz, 1H, CH), 3.01-2.95 (m, 6H, CH, CH₂, CH₃-N), 1.73 (s, 3H, CH₃-NH), 1.37-1.21 (m, 2H, CH₂), 1.07-1.06 (m, 1H, CH), 0.98-0.84 (m, 6H, 2CH₃) ppm; **¹³C NMR** (600 MHz, CD₃OD) major rotamer shown: δ 175.72, 170.68, 136.78, 128.74, 128.43, 128.13, 127.39, 126.32, 121.05, 120.96, 118.23, 117.88, 111.61, 110.89, 58.17, 57.56, 39.84, 39.77, 32.67, 30.77, 30.64, 24.77, 24.26, 22.41, 20.98 ppm; **HRMS** (TOF-ESI): [M+H]⁺calculated for C₂₇H₃₇N₄O₂:

449.2917 found 449.2933.

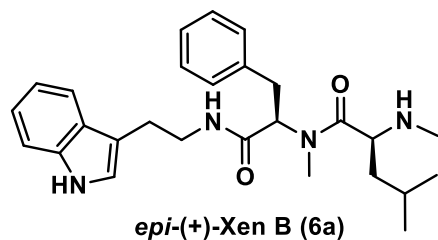


1H NMR spectrum of compound (-)-6



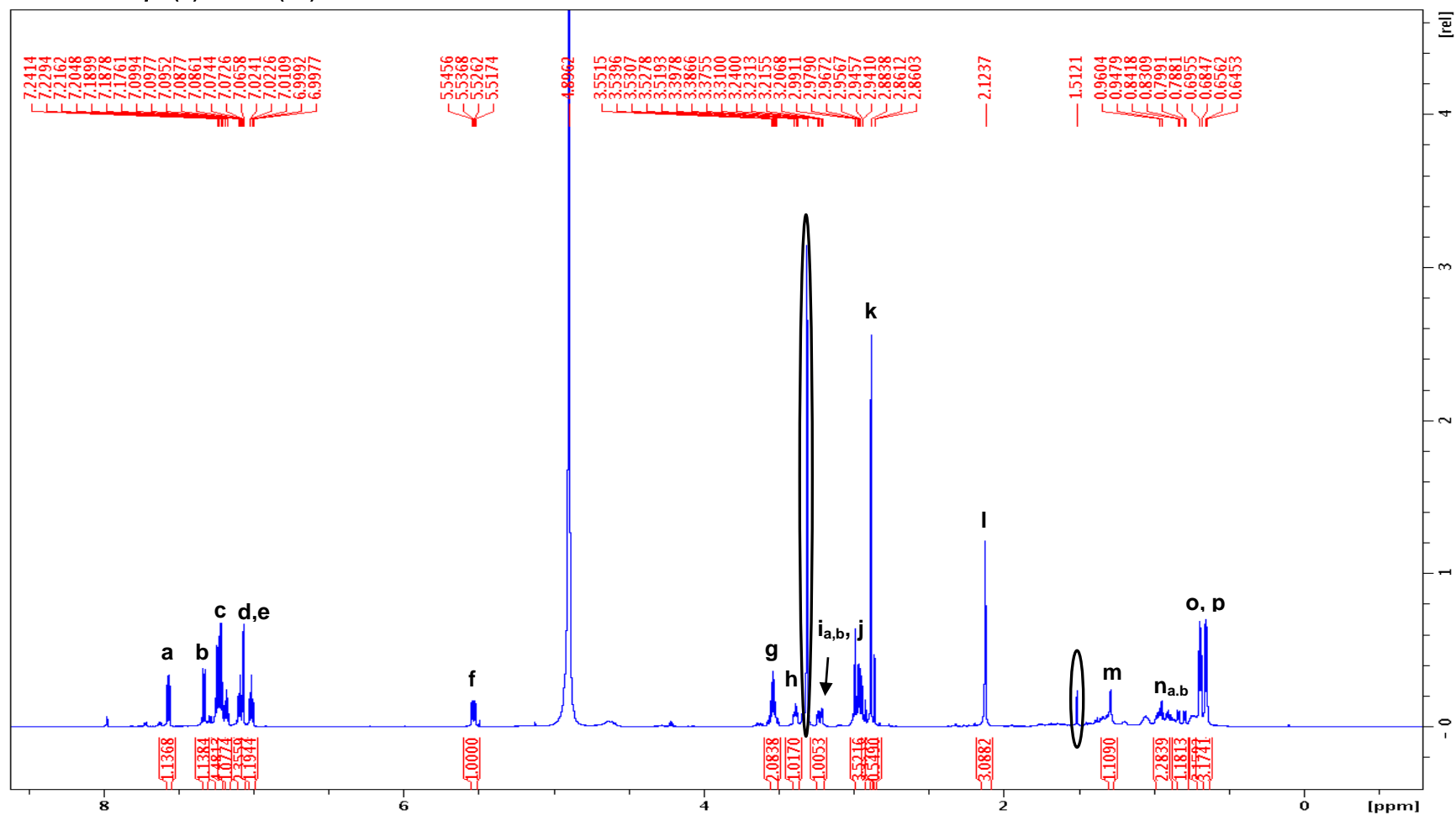
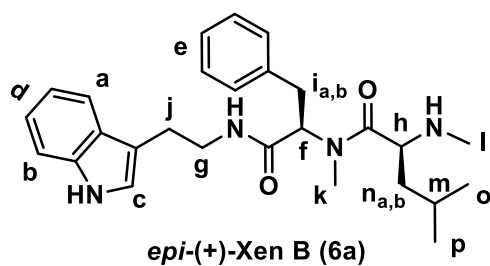
¹³C NMR spectrum of compound (-)-(6)

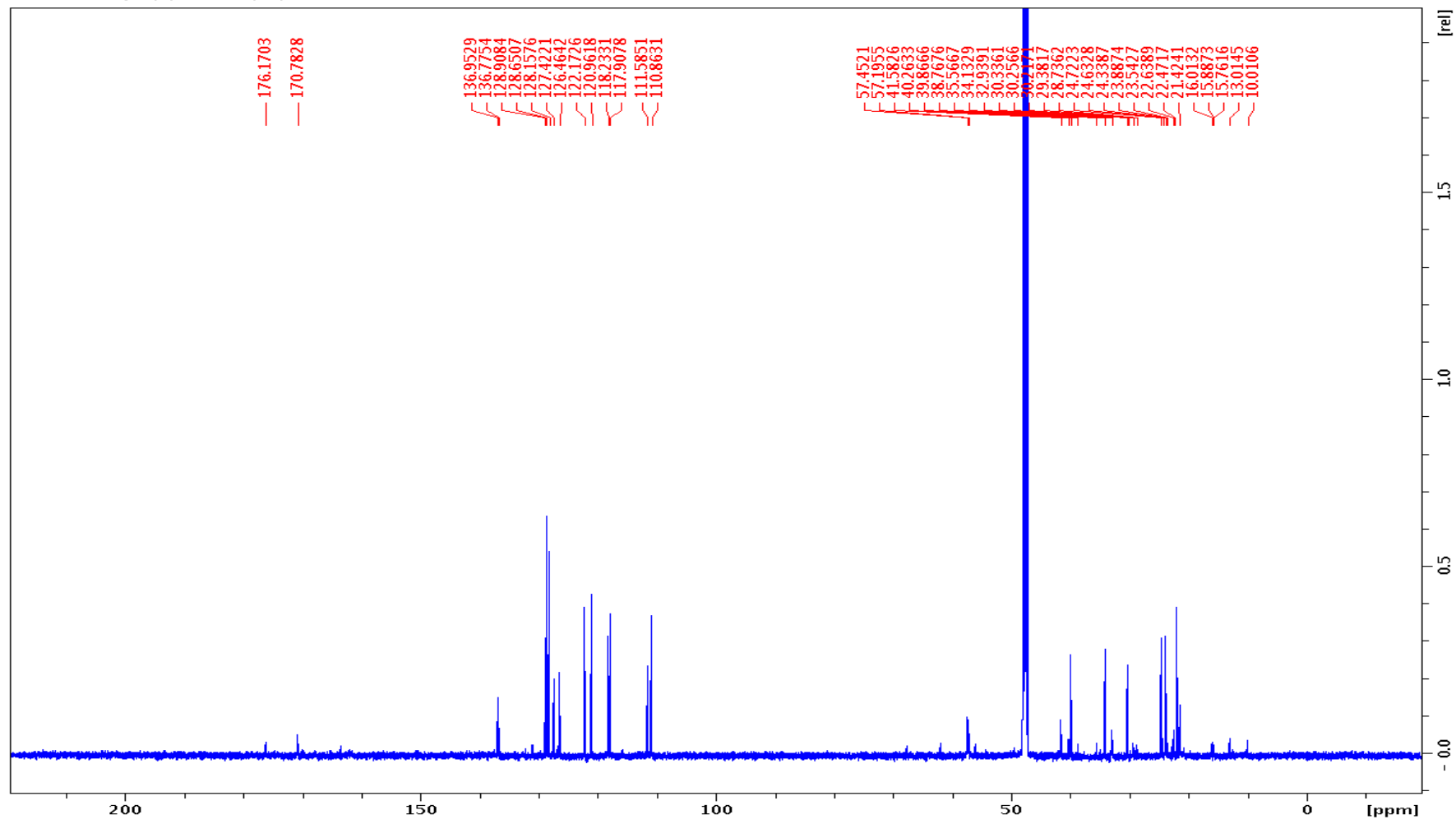
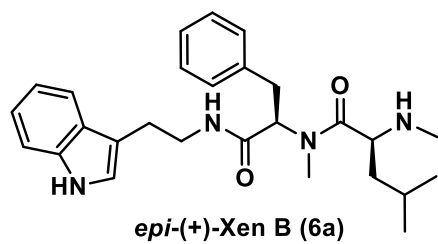
(S)-N-((R)-1-((2-(1H-indol-3-yl)ethyl)amino)-1-oxo-3-phenylpropan-2-yl)-N,4-dimethyl-2-(methylamino)pentanamide (6a)



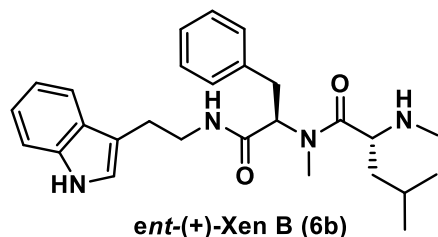
The compound was obtained as a yellowish solid; yield: (142.97 mg, 19%); $[\alpha]_D^{20} +26^\circ$ (c 0.3, MeOH); R_f : 0.6 cm; $^1\text{H NMR}$ (600 MHz, CD_3OD) showed the presence of two rotamers in a ratio of 2.68/1, major rotamer shown: δ 7.57-7.56 (d, $J = 7.8$ Hz, 1H, aryl), 7.33-7.31 (d, $J = 7.8$ Hz, 1H, aryl), 7.25-7.20 (m, 4H, aryl), 7.19-7.17 (t, $J = 7.2$ Hz, 1H, aryl), 7.09-7.06 (m, 2H, aryl), 7.02-7.01 (t, $J = 7.8$ Hz, 1H, aryl), 5.54-5.51

(dd, $J_1 = 5.4$ Hz, $J_2 = 11.4$ Hz, 1H, CH), 3.55-3.52 (m, 2H, CH_2), 3.40-3.37 (m, 1H, CH), 3.17-3.15 (dd, $J_1 = 5.4$, $J_2 = 15.0$ Hz, 1H, CH), 2.99-2.94 (m, 3H, CH, CH_2), 2.88 (s, 3H, $\text{CH}_3\text{-N}$), 2.21 (s, 3H, $\text{CH}_3\text{-NH}$), 0.96-0.95 (m, 2H, CH_2), 0.84-0.79 (m, 1H, CH_2), 0.80-0.69 (d, $J = 6.0$ Hz, 3H, CH_3), 0.65-0.64 (d, $J = 6.0$ Hz, 3H, CH_3) ppm; $^{13}\text{C NMR}$ (600 MHz, CD_3OD) major rotamer shown: δ 176.17, 170.78, 136.95, 136.77, 128.65, 128.16, 127.42, 126.46, 122.17, 120.96, 118.23, 117.91, 111.58, 110.86, 57.45, 57.19, 41.58, 39.87, 34.13, 30.34, 30.25, 24.63, 24.34, 22.47, 21.42 ppm; **HRMS** (TOF-ESI): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{27}\text{H}_{37}\text{N}_4\text{O}_2$: 449.2917 found 449.2931.



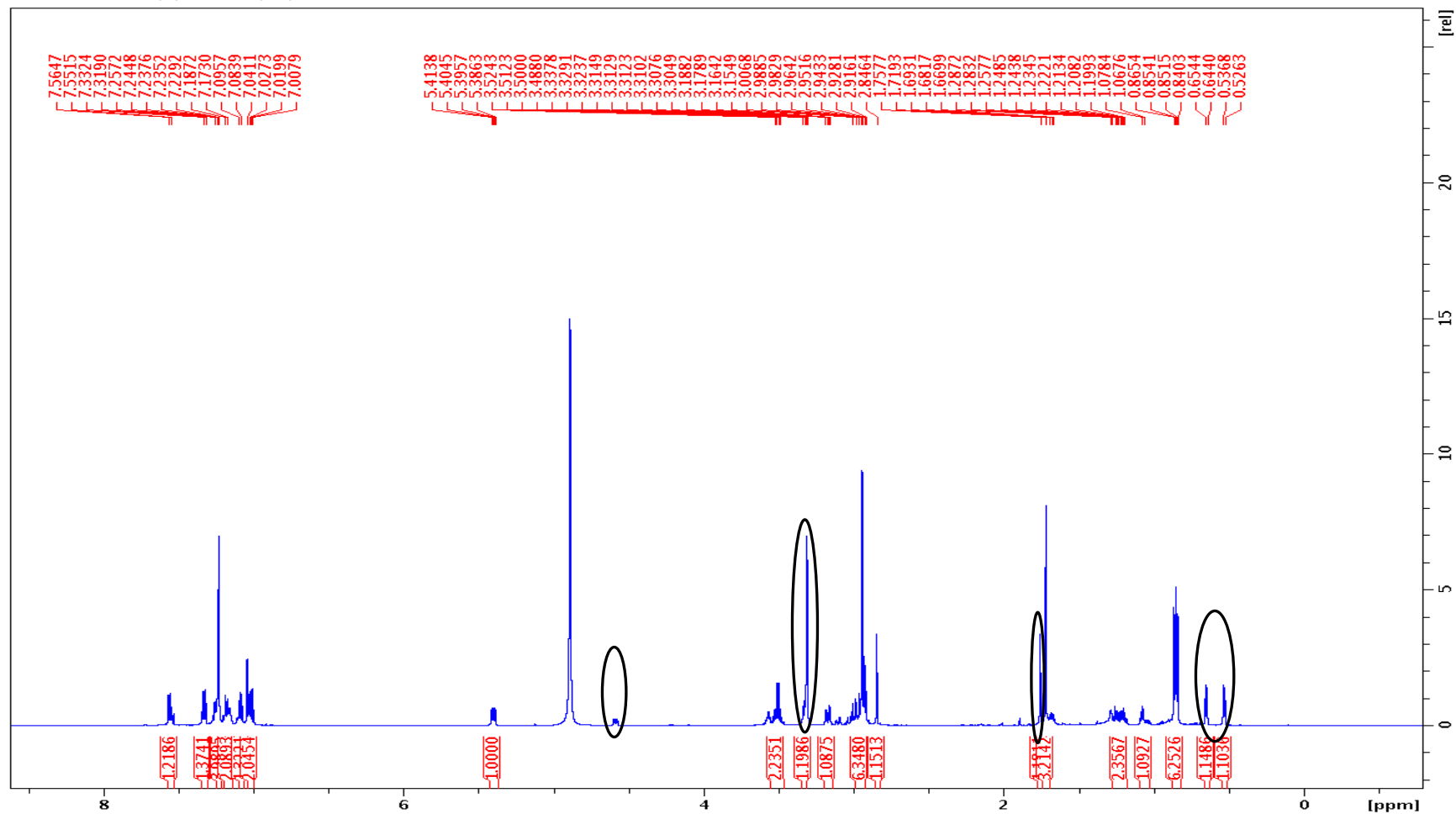
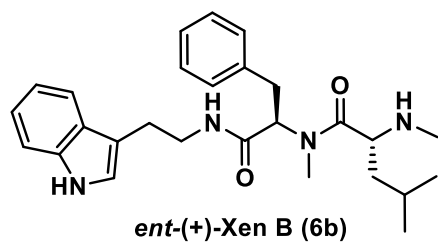


(*R*)-N-((*R*)-1-((2-(1H-indol-3-yl)ethyl)amino)-1-oxo-3-phenylpropan-2-yl)-N,4-dimethyl-2-(methylamino)pentanamide
(6b)

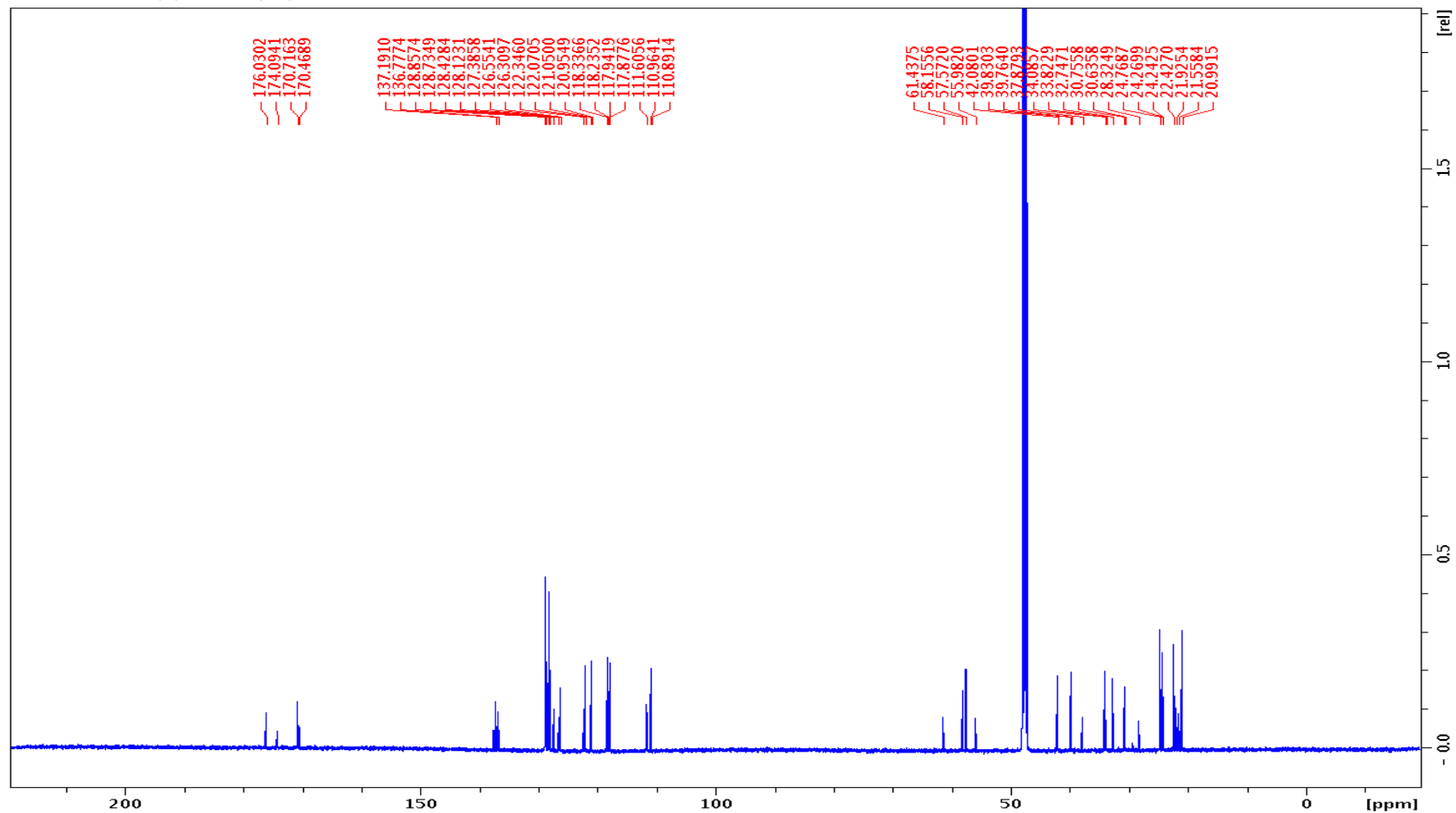
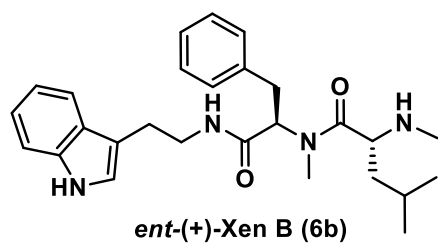


The compound was obtained as a yellowish solid; yield: (151.63 mg, 20%); $[\alpha]_D^{20} +56$ (c 0.3, MeOH); R_f: 0.5 cm; **¹H NMR** (600 MHz, CD₃OD) showed the presence of two rotamers in a ratio of 2.7/1, major rotamer shown: δ 7.56-7.55 (m, 1H, aryl), 7.33-7.17 (m, 4H, aryl), 7.09-7.00 (m, 5H, aryl), 5.41-5.39 (dd, $J_1 = 5.6$, $J_2 = 11.0$ Hz, 1H, CH), 3.52-3.50 (m, 2H, CH₂), 3.34-3.32 (m, 1H, CH), 3.19-3.15 (dd, $J_1 = 5.6$ Hz, $J_2 =$

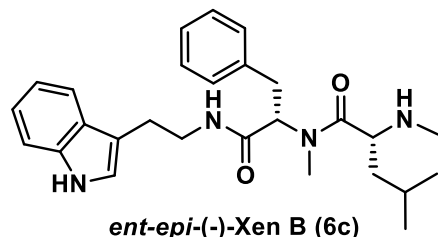
14.4 Hz, 1H, CH), 3.00-2.91 (m, 6H, CH, CH₂, CH₃-N), 1.69 (s, 3H, CH₃-NH), 1.29-1.20 (m, 2H), 1.07-1.06 (m, 1H, CH), 0.86-0.84 (m, 6H, 2CH₃) ppm; **¹³C NMR** (600 MHz, CD₃OD) major rotamer shown: δ 176.03, 170.71, 137.19, 128.85, 128.42, 128.12, 127.38, 126.31, 122.07, 120.95, 118.23, 117.87, 110.96, 110.89, 61.43, 57.57, 43.08, 39.83, 34.08, 32.74, 30.63, 24.77, 24.27, 22.42, 20.99 ppm; **HRMS** (TOF-ESI): [M+H]⁺ calculated for C₂₇H₃₇N₄O₂: 449.2917 found 449.2914.



¹H NMR spectrum of compound (+)-6b

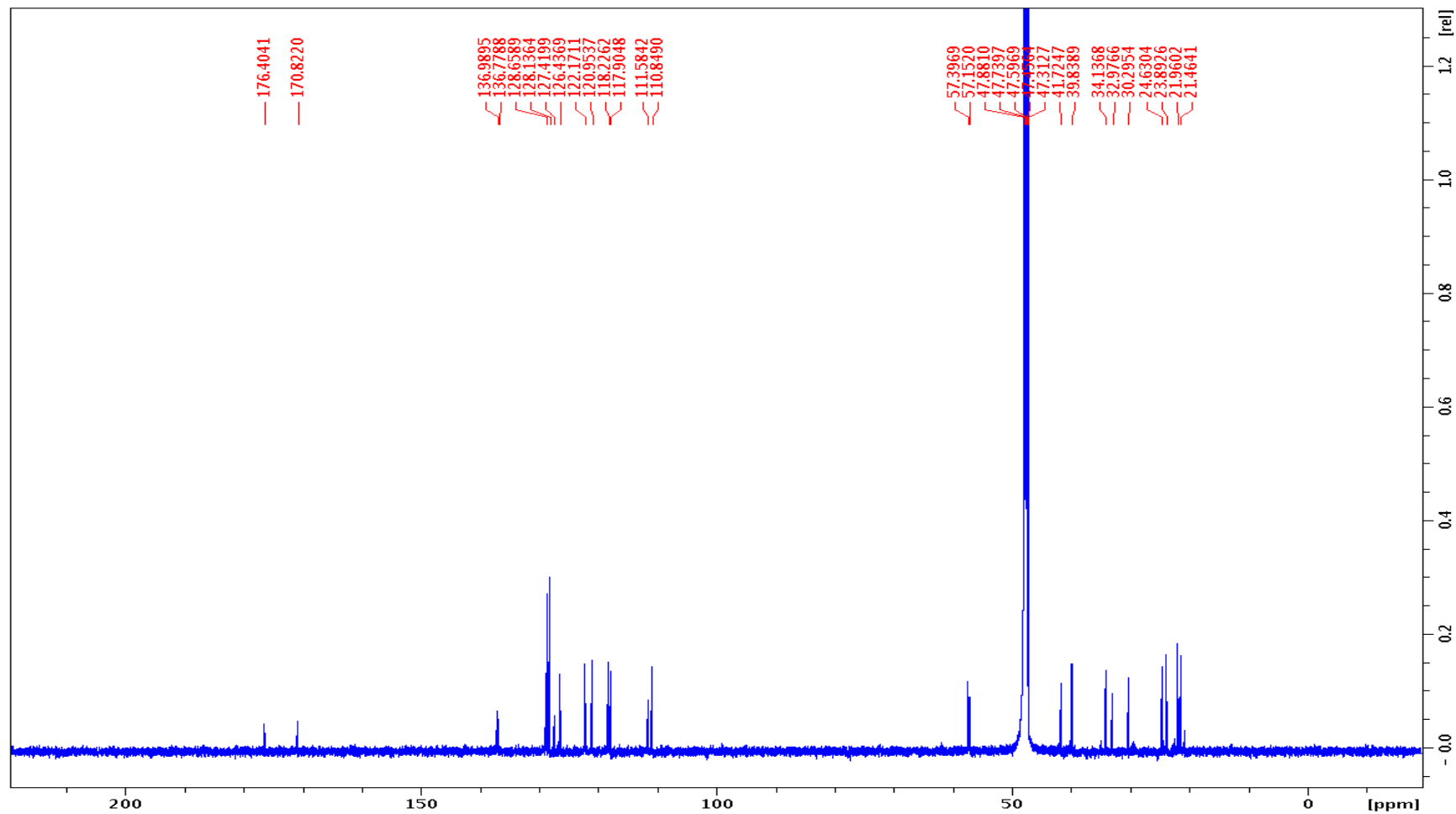
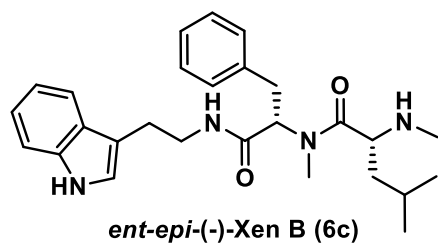


(R)-N-((S)-1-((2-(1H-indol-3-yl)ethyl)amino)-1-oxo-3-phenylpropan-2-yl)-N,4-dimethyl-2-(methylamino)pentanamide
(6c)



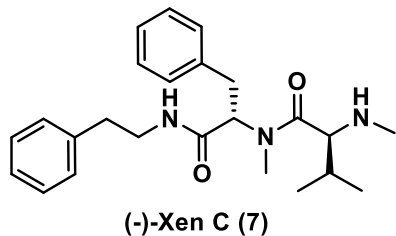
The compound was obtained as a yellowish solid; yield: (212.30 mg, 28%); $[\alpha]_D^{20}$ -26 (c 0.3, MeOH); R_f: 0.8 cm; **¹H NMR** (600 MHz, CD₃OD) showed the presence of two rotamers in a ratio of 6.0/1, major rotamer shown: δ = 7.57-7.56 (d, J = 7.8 Hz, 1H, aryl), 7.33-7.31 (d, J = 7.8 Hz, 1H, aryl), 7.25-7.17 (m, 5H, aryl), 7.10-7.07 (m, 2H, aryl), 7.02-7.01 (t, J = 7.8 Hz, 1H, aryl), 5.54-5.52 (dd, J_1 = 4.32 Hz, J_2 = 11.0 Hz, 1H,

CH), 3.54-3.36 (m, 2H, CH₂), 3.35-3.31 (m, 1H), 3.23-3.20 (dd, J_1 = 5.4, J_2 = 15.0 Hz, 1H, CH), 2.99-2.94 (m, 3H, CH, CH₂), 2.88 (s, 3H, CH₃-N), 2.21 (s, 3H, CH₃-NH), 0.96-0.93 (m, 2H, CH₂), 0.84-0.79 (m, 1H, CH), 0.80-0.69 (d, J = 6.0 Hz, 3H, CH₃), 0.65-0.64 (d, J = 6.0 Hz, 3H, CH₃) ppm; **¹³C NMR** (600 MHz, CD₃OD) major rotamer shown: δ 176.40, 170.82, 136.99, 136.78, 128.66, 128.14, 127.42, 126.44, 122.17, 120.95, 118.22, 117.90, 111.58, 110.85, 57.40, 57.15, 41.72, 39.84, 34.14, 32.98, 30.29, 24.63, 23.89, 21.96, 21.46; **HRMS** (TOF-ESI): [M+H]⁺ calculated for C₂₇H₃₇N₄O₂: 449.2917 found 449.2931.



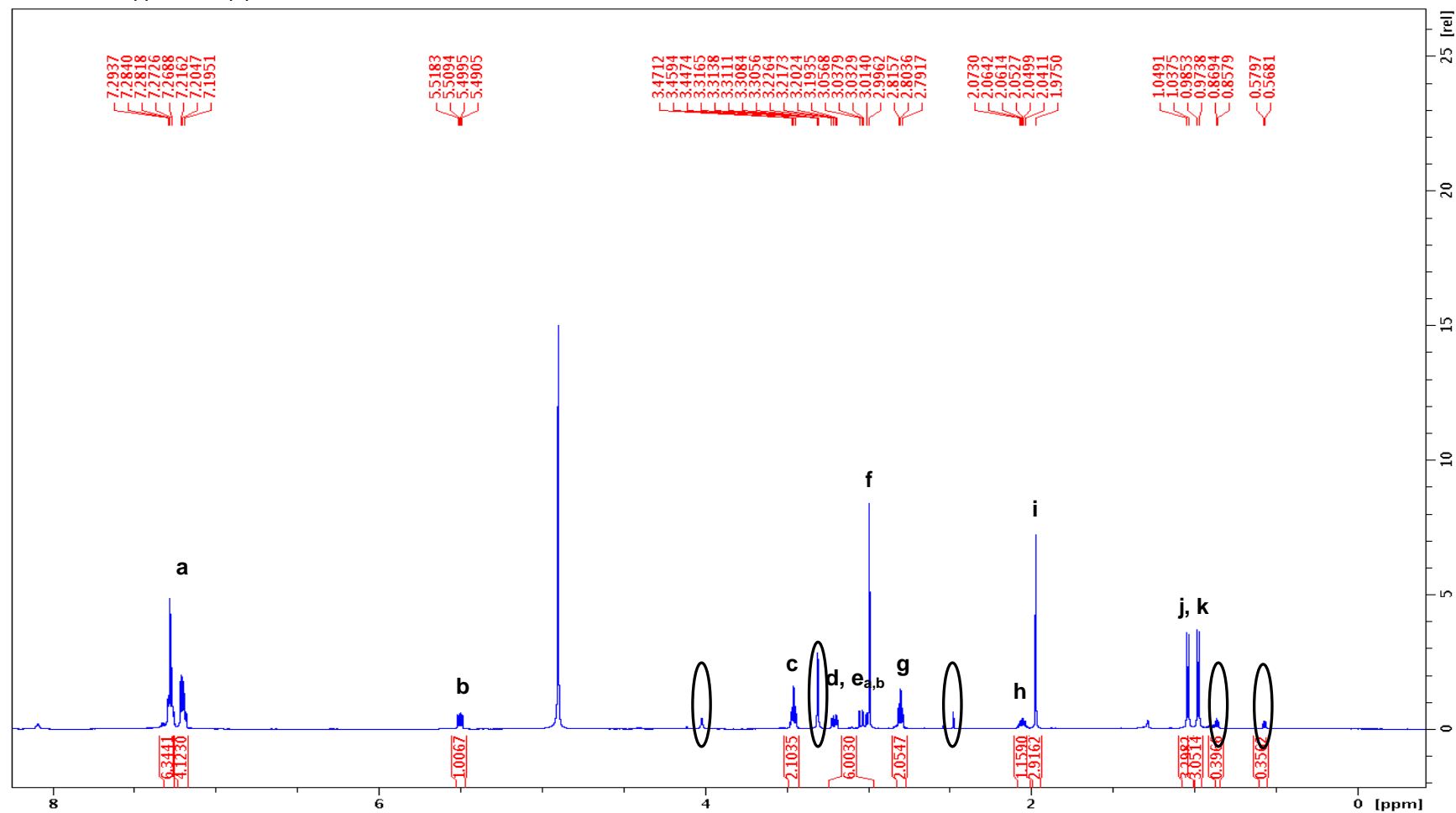
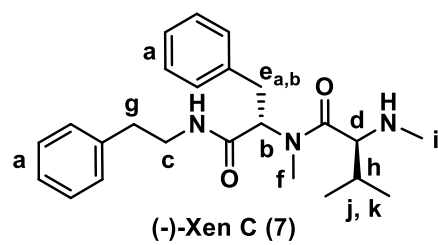
¹³C NMR spectrum of compound (-)-6c

(S)-N,3-dimethyl-2-(methylamino)-N-((S)-1-oxo-1-(phenethylamino)-3-phenylpropan-2-yl)butanamide (7)

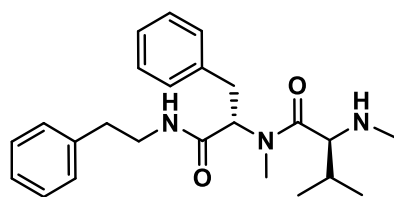


The compound was obtained as a white solid; yield: (166.99 mg, 25%); $[\alpha]_{\text{D}}^{20}$ -54 (c 0.2, MeOH); R_f: 0.5 cm; **¹H NMR** (600 MHz, CD₃OD) showed the presence of two rotamers in a ratio of 7.70/1, major rotamer shown: δ 7.29-7.27 (m, 6H, aryl), 7.22-7.7.19 (m, 4H, aryl), 5.51-5.49 (dd, $J_1 = 5.4$ Hz, $J_2 = 11.4$ Hz, 1H, CH), 3.50-3.44 (t, $J = 7.2$ Hz, 2H, CH₂), 3.22-2.99 (m, 6H, CH, CH₂, CH₃-N), 2.07-2.04 (m, 1H, CH), 1.97

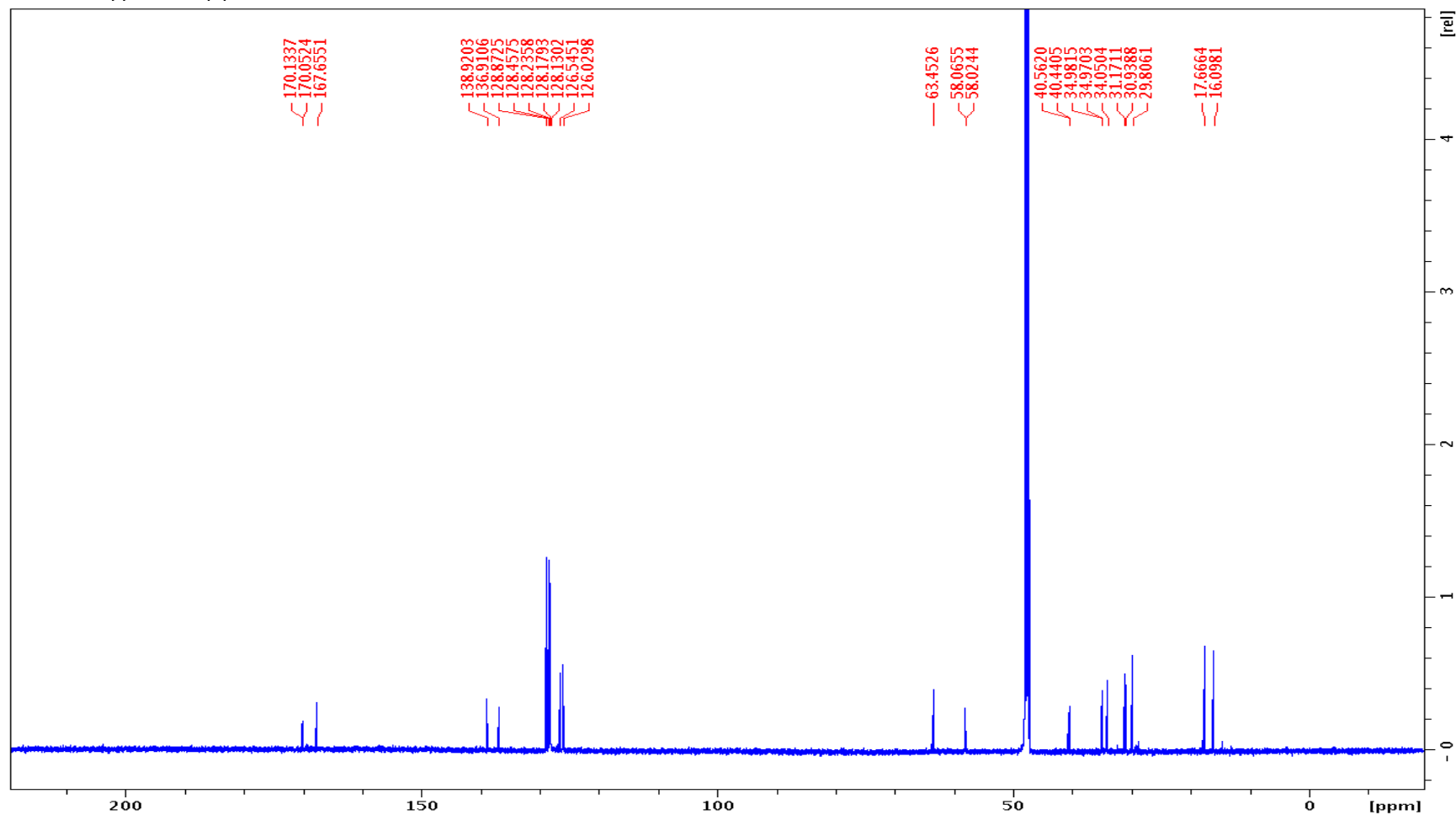
(s, 3H, CH₃-NH), 1.04-1.03 (d, $J = 6.6$ Hz, 3H, CH₃), 0.98-0.97 (d, $J = 6.6$ Hz, 3H, CH₃) ppm; **¹³C NMR** (600 MHz, CD₃OD) major rotamer shown: δ 170.13, 167.65, 138.92, 136.91, 128.46, 128.23, 128.18, 128.13, 126.54, 126.03, 63.45, 58.06, 40.44, 34.98, 34.97, 34.05, 31.17, 29.81, 17.67, 16.10 ppm; **HRMS** (TOF-ESI): [M+H]⁺calculated for C₂₄H₃₄N₃O₂: 396.2651; found: 396.2645.



¹H NMR spectrum of compound (-)-7

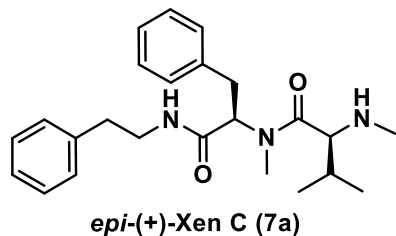


(-)-Xen C (7)

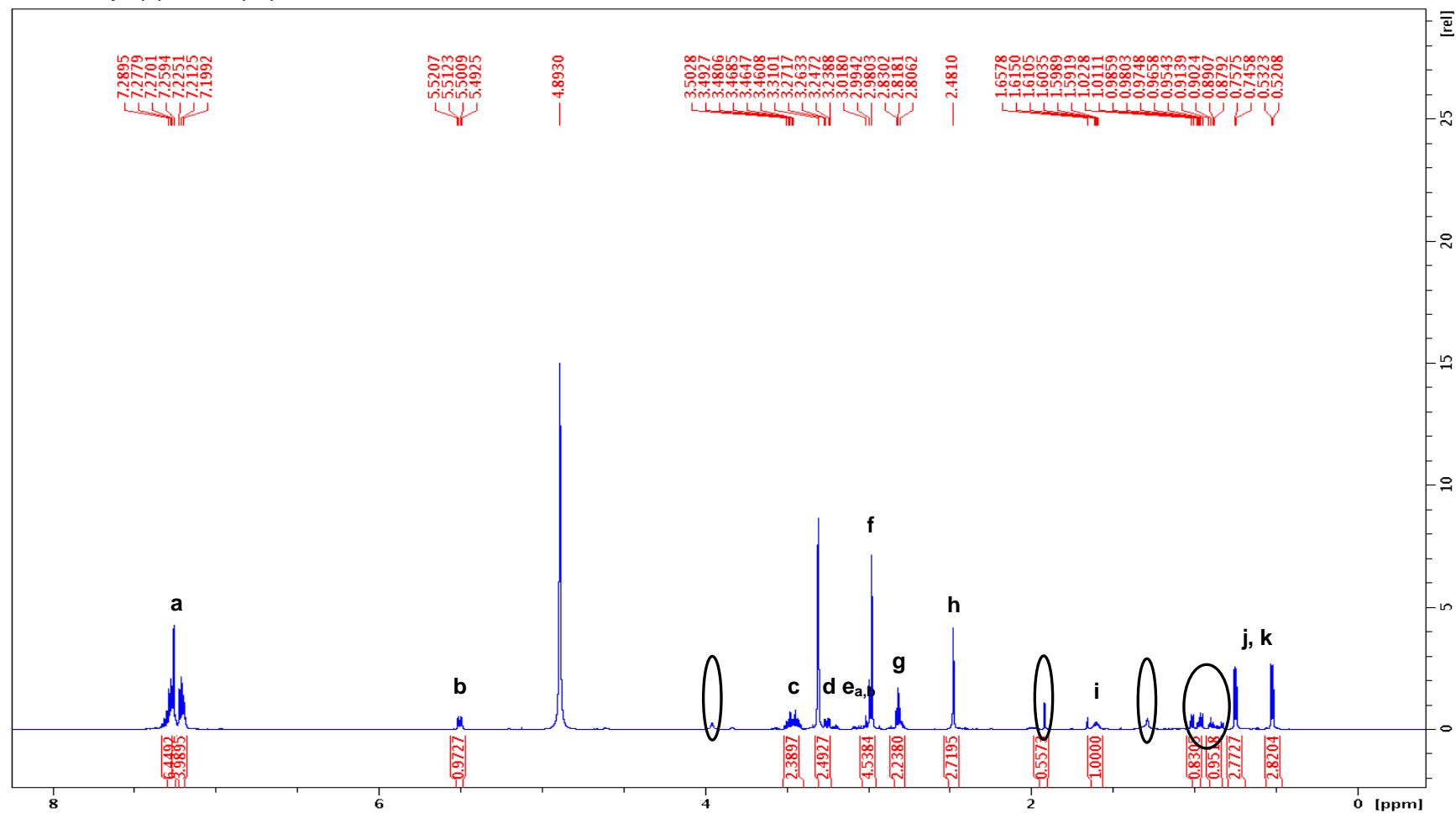
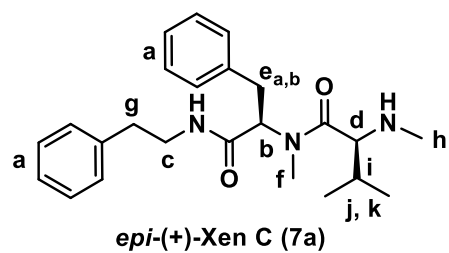


¹³C NMR spectrum of compound (-)-7

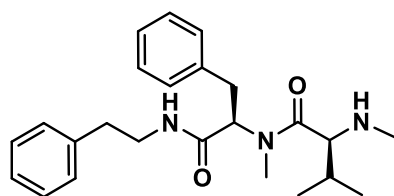
(S)-N,3-dimethyl-2-(methylamino)-N-((R)-1-oxo-1-(phenethylamino)-3-phenylpropan-2-yl)butanamide (7a)



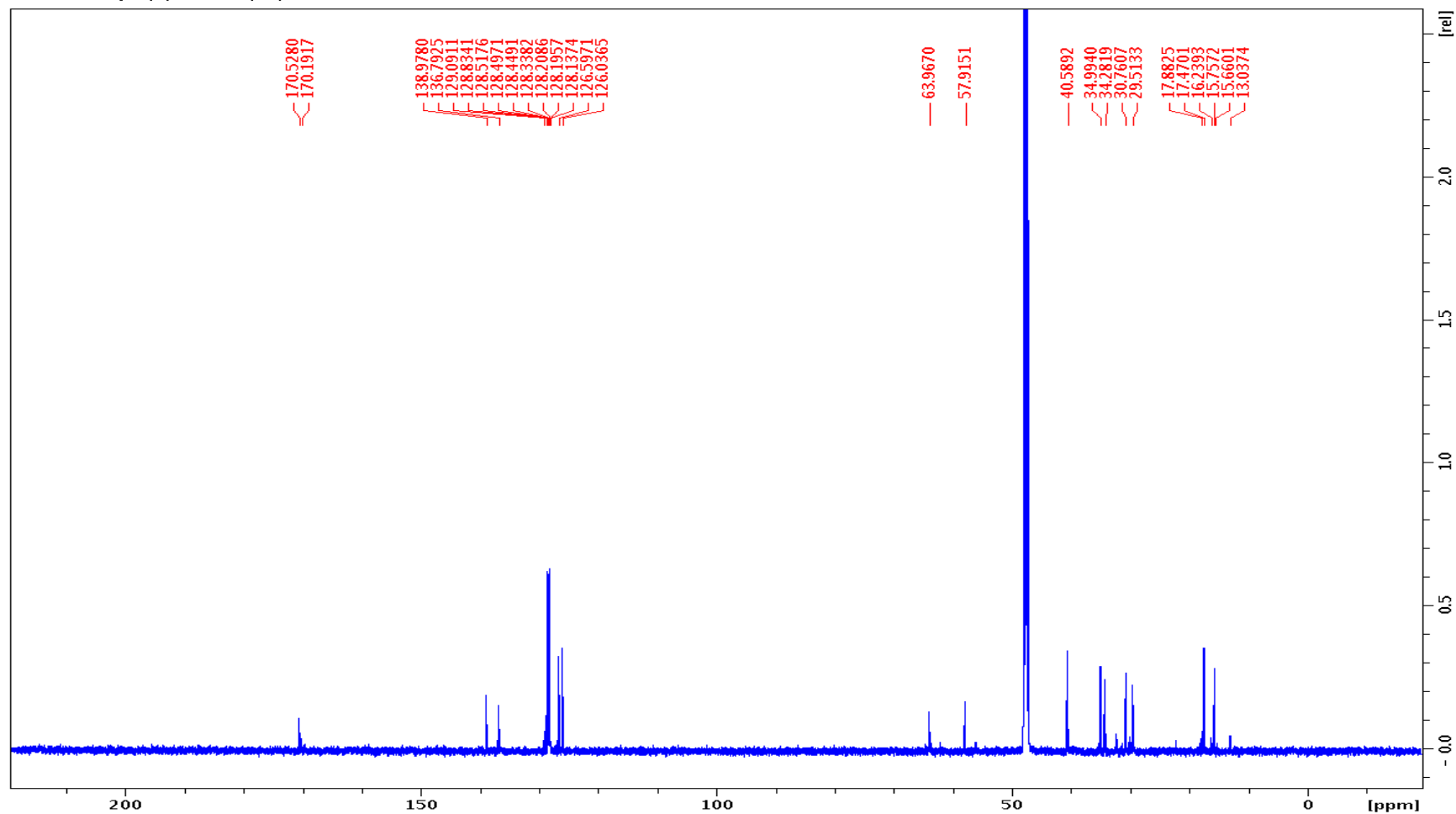
The compound was obtained as a white solid; yield: (129.45 mg, 19%); $[\alpha]_D^{20} +29$ (c 0.2, MeOH); R_f : 0.7 cm; **^1H NMR** (600 MHz, CD_3OD) showed the presence of two rotamers in a ratio of 2.96/1, major rotamer shown: δ 7.29-7.26 (m, 6H, aryl), 7.22-7.20 (m, 4H, aryl), 5.55-5.49 (dd, $J_1 = 5.4\text{ Hz}$, $J_2 = 12.0\text{ Hz}$, 1H, CH), 3.50-3.46 (m, 2H, CH_2), 3.27-3.23 (m, 2H, CH_2), 3.02-2.98 (m, 4H, CH, $\text{CH}_3\text{-N}$), 2.83-2.81 (t, $J = 7.2\text{ Hz}$, 2H, CH_2), 2.48 (s, 3H, $\text{CH}_3\text{-NH}$), 1.66-1.59 (m, 1H, CH), 0.75-0.74 (d, $J = 6.6\text{ Hz}$, 3H, CH_3), 0.53-0.52 (d, $J = 6.6\text{ Hz}$, 3H, CH_3) ppm; **^{13}C NMR** (600 MHz, CD_3OD) major rotamer shown: δ 170.53, 170.19, 138.98, 136.79, 128.52, 128.50, 128.34, 128.14, 126.60, 126.04, 63.97, 57.91, 40.59, 34.99, 34.28, 30.76, 29.51, 17.47, 15.66, 13.04 ppm; **HRMS** (TOF-ESI): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{24}\text{H}_{34}\text{N}_3\text{O}_2$: 396.2651; found: 396.2640.



¹H NMR spectrum of compound (+)-7a

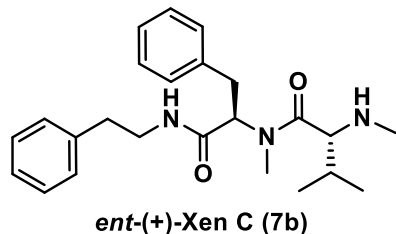


epi-(+)-Xen C (7a)



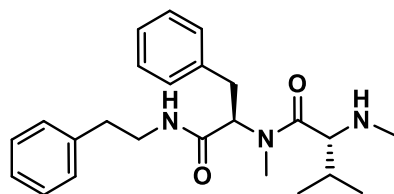
^{13}C NMR spectrum of compound (+)-7a

(*R*)-N,3-dimethyl-2-(methylamino)-N-((*R*)-1-oxo-1-(phenethylamino)-3-phenylpropan-2-yl)butanamide (7b)

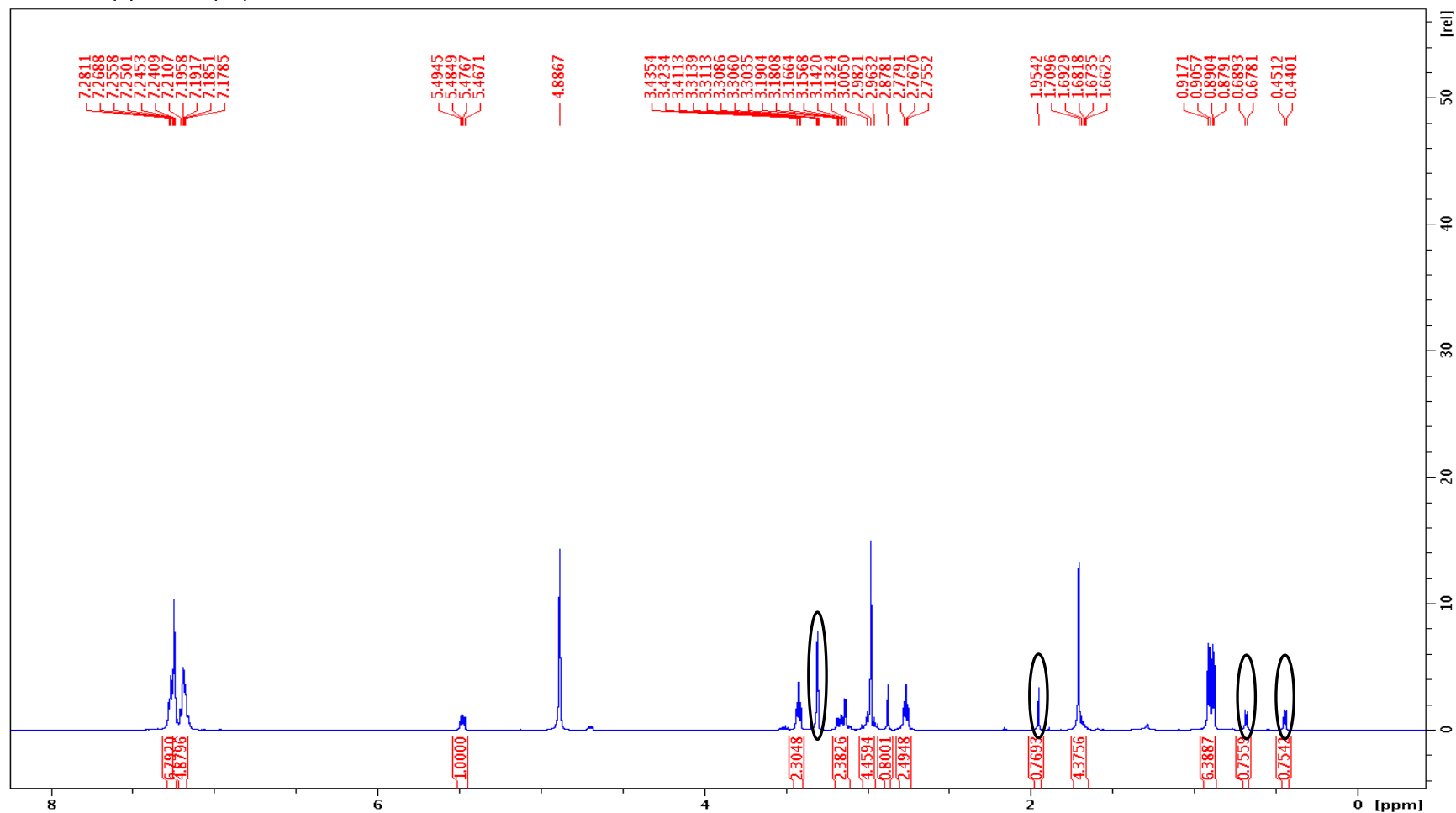


The compound was obtained as a white solid; yield: (142.68 mg, 21%); $[\alpha]_{\text{D}}^{20} +54$ (c 0.2, MeOH); R_f : 0.5 cm; **^1H NMR** (600 MHz, CD_3OD) showed the presence of two rotamers in a ratio of 4.2/1, major rotamer shown: δ 7.29-7.23 (m, 6H, aryl), 7.20-7.17 (m, 4H, aryl), 5.51 (d.d, $J_1 = 5.4$, $J_2 = 10.8$ Hz, 1H, CH), 3.44 (t, $J = 6.6$ Hz, 2H, CH_2), 3.22-3.21 (m, 2H, 2CH), 3.00-2.96 (m, 4H, CH, $\text{CH}_3\text{-N}$), 2.78-2.75 (m, 2H, CH_2), 1.71-

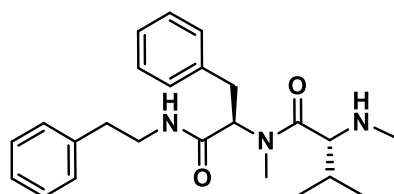
1.66 (m, 4H, CH, $\text{CH}_3\text{-NH}$), 0.92-0.88 (m, 6H, 2 CH_3); **^{13}C NMR** (600 MHz, CD_3OD) major rotamer shown: δ 175.55, 170.46, 138.98, 137.03, 128.97, 128.63, 128.48, 128.19, 128.13, 126.38, 64.42, 57.52, 40.51, 35.03, 34.31, 33.65, 30.50, 30.28, 18.37, 16.24; **HRMS** (TOF-ESI): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{24}\text{H}_{34}\text{N}_3\text{O}_2$: 396.2651; found: 396.2644.



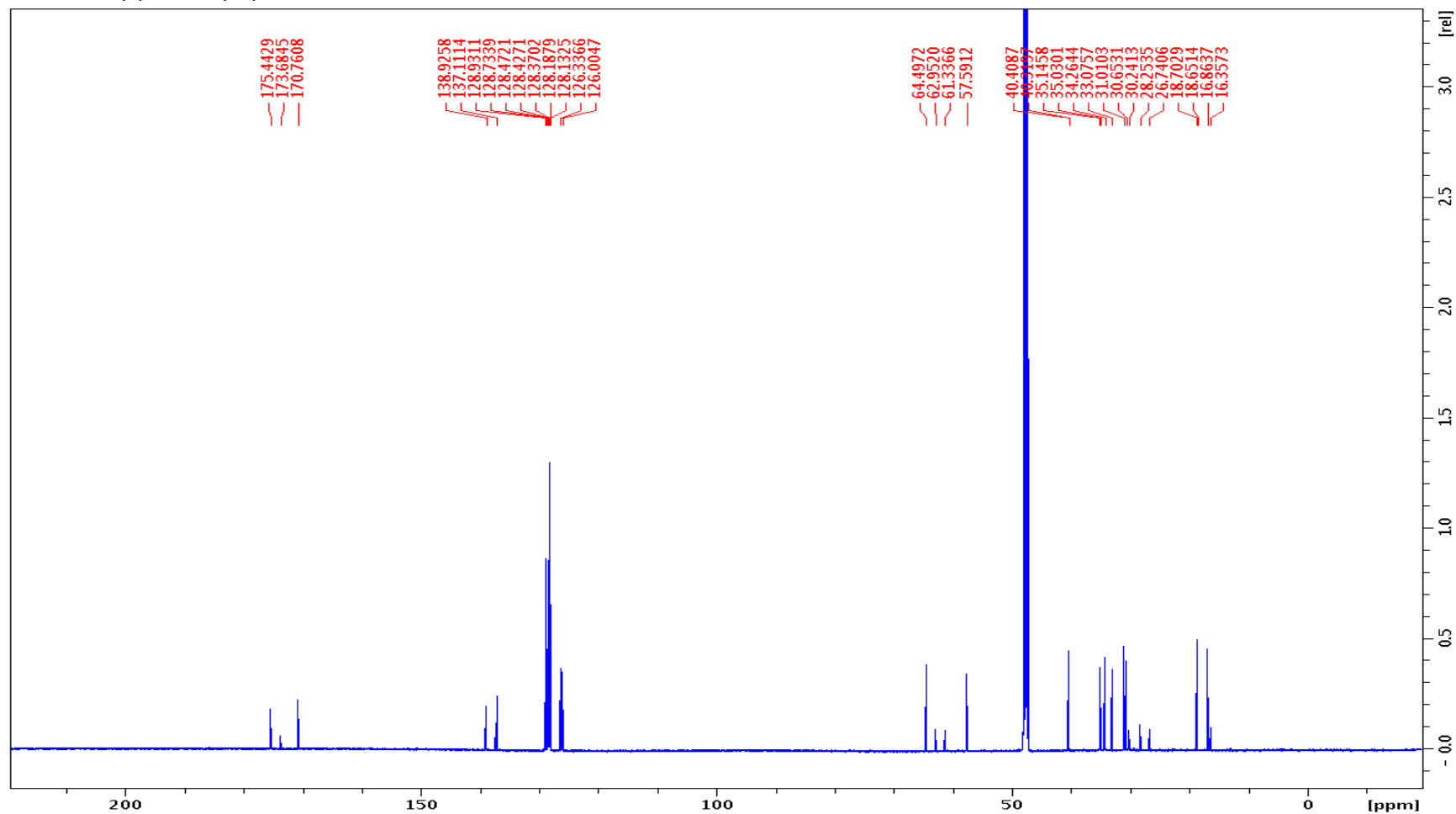
ent-(+)-Xen C (7b)



¹H NMR spectrum of compound (+)-7b

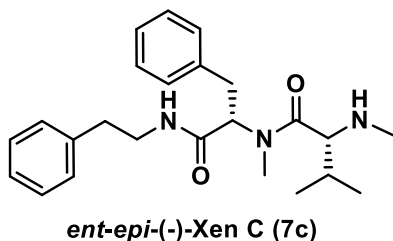


ent-(+)-Xen C (7b)



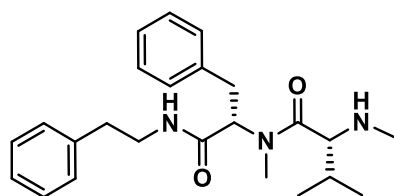
¹³C NMR spectrum of compound (+)-7b

(*R*)-N,3-dimethyl-2-(methylamino)-N-((*S*)-1-oxo-1-(phenethylamino)-3-phenylpropan-2-yl)butanamide (7c)

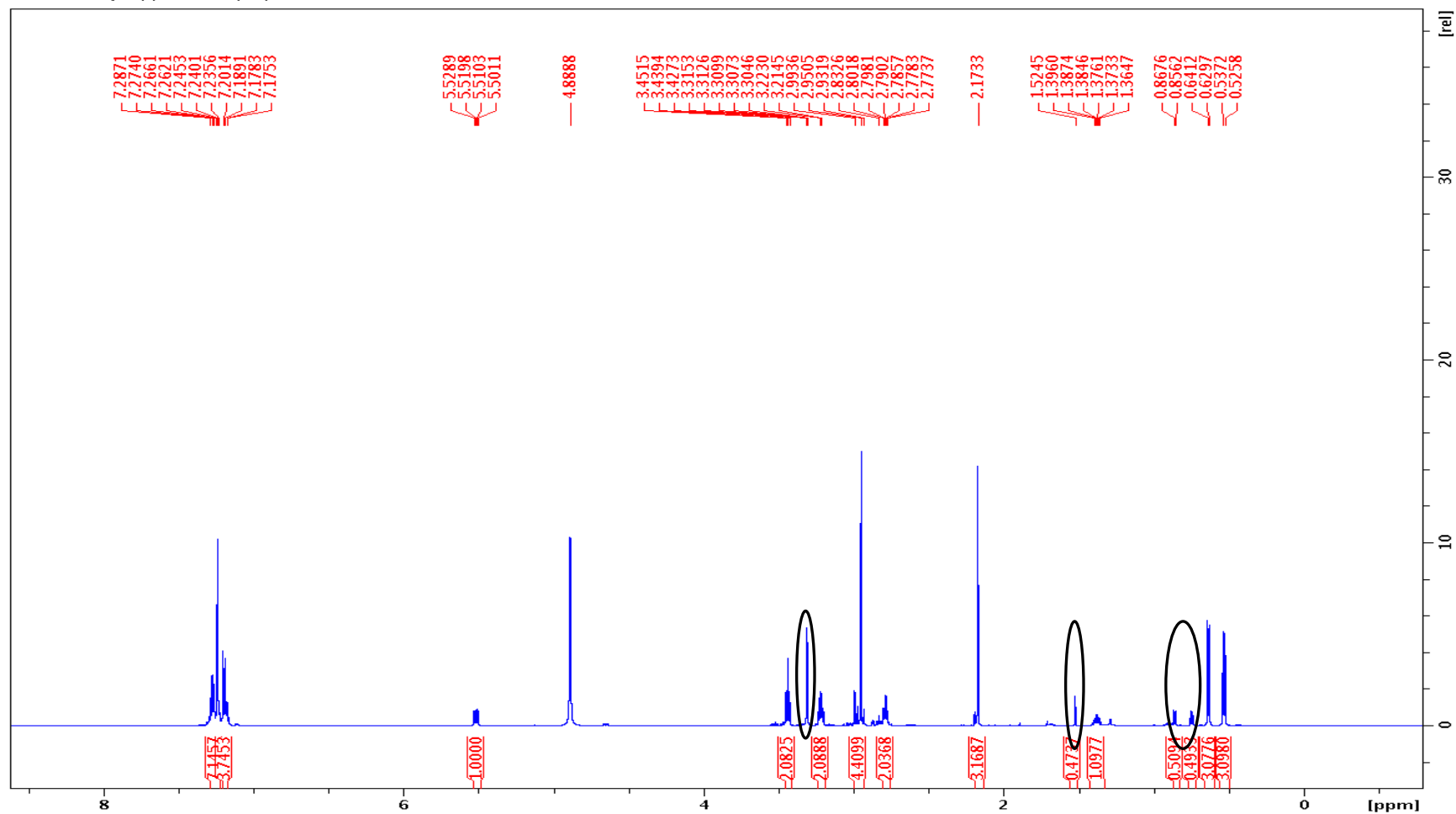


The compound was obtained as a white solid; yield: (156.95 mg, 23%); $[\alpha]_D^{20}$ -29 (*c* 0.2, MeOH); R_f : 0.8 cm; **$^1\text{H NMR}$** (600 MHz, CD_3OD) showed the presence of two rotamers in a ratio of 6.3/1, major rotamer shown: δ 7.29-7.23 (m, 7H, aryl), 7.20-7.17 (m, 3H, aryl), 5.51 (d.d, $J_1 = 5.4$, $J_2 = 10.8$ Hz, 1H, CH), 3.44 (t, $J = 6.6$ Hz, 2H, CH_2), 3.22-3.21 (m, 2H, CH_2), 2.99-2.93 (m, 4H, CH, $\text{CH}_3\text{-N}$), 2.83-2.77 (m, 2H, CH_2), 2.17 (s, 3H, $\text{CH}_3\text{-NH}$), 1.40-

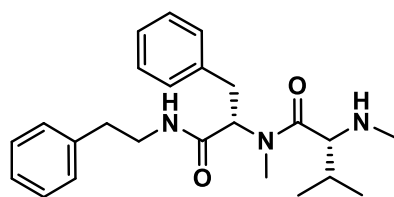
1.36 (1H, m, CH), 0.63 (d, $J = 6.6$ Hz, 3H, CH_3), 0.53 (d, $J = 6.6$ Hz, 3H, CH_3); **$^{13}\text{C NMR}$** (600 MHz, CD_3OD) major rotamer shown: δ 175.55, 170.46, 138.98, 137.03, 128.97, 128.63, 128.48, 128.19, 128.13, 126.38, 64.42, 57.52, 40.51, 35.03, 34.31, 33.65, 30.50, 30.28, 18.37, 16.24; **HRMS** (TOF-ESI): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{24}\text{H}_{34}\text{N}_3\text{O}_2$: 396.2651; found: 396.2644.



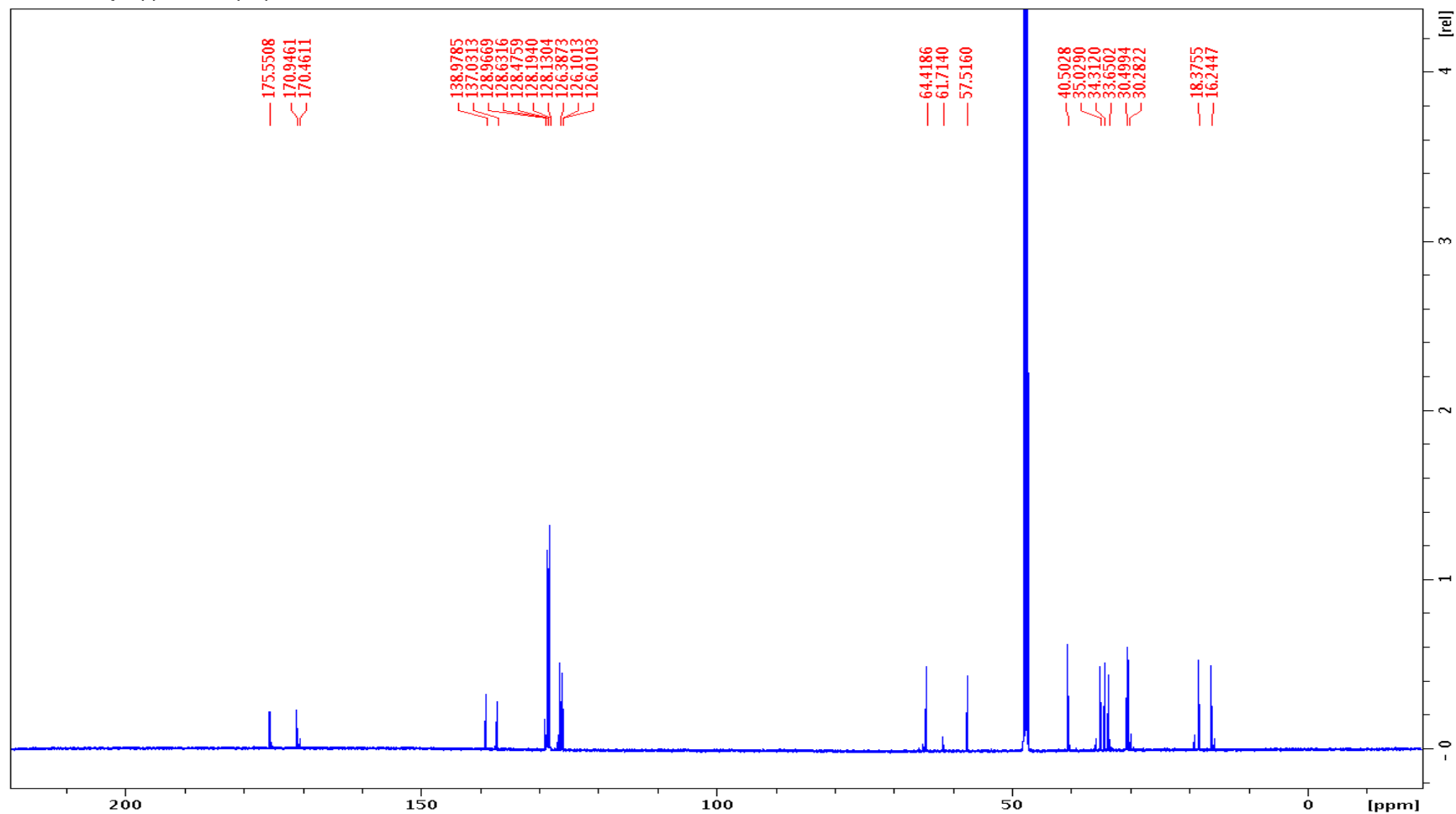
ent-epi-(-)-Xen C (7c)



^1H NMR spectrum of compound (-)-7c

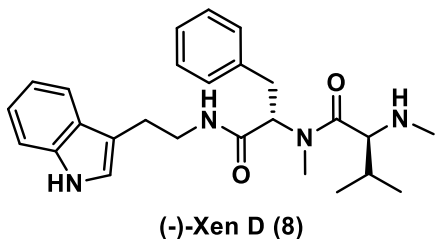


ent-epi-(-)-Xen C (7c)

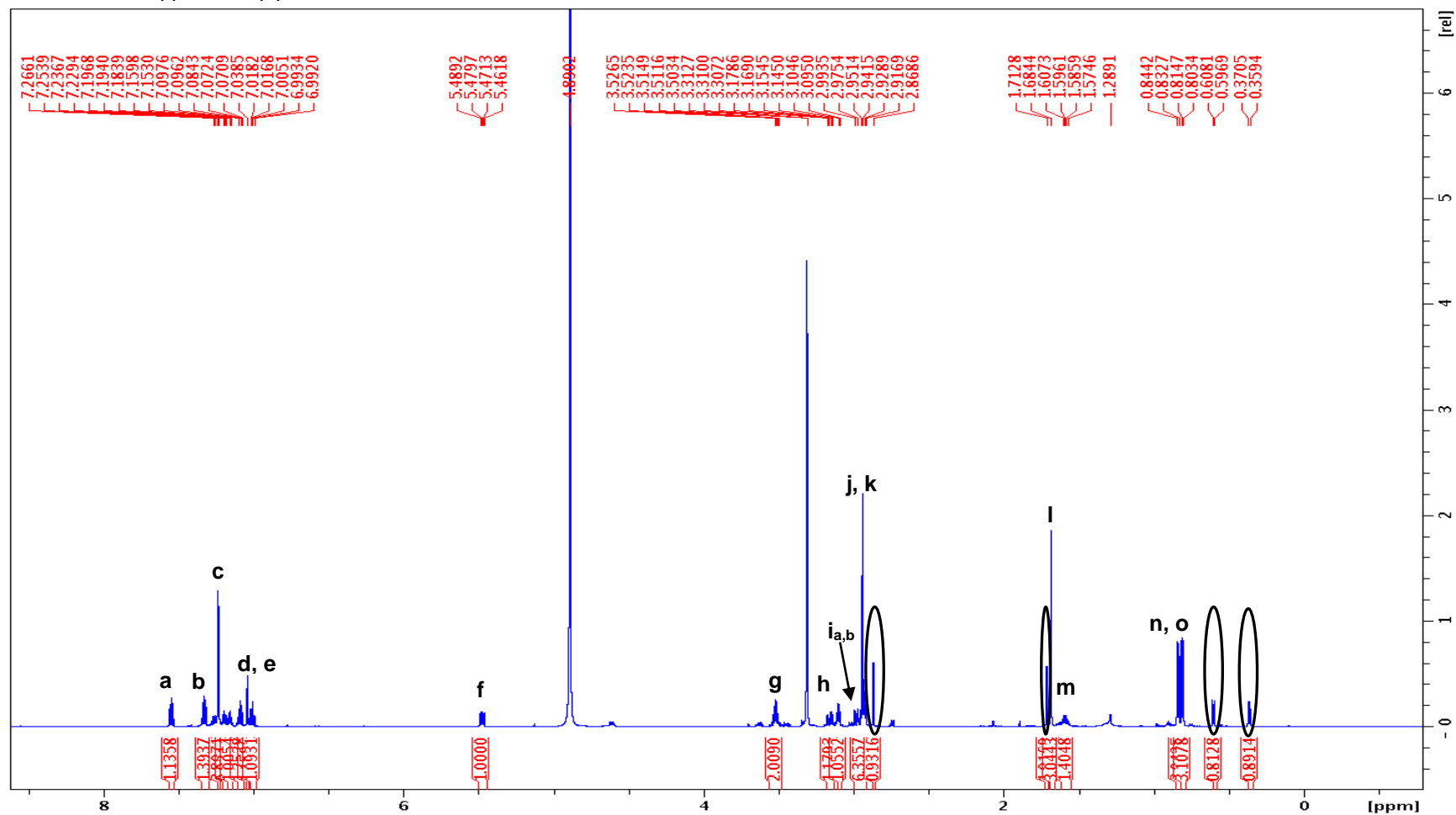
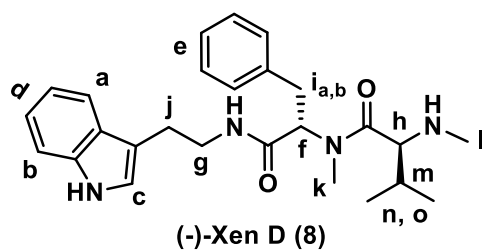


¹³C NMR spectrum of compound (-)-7c

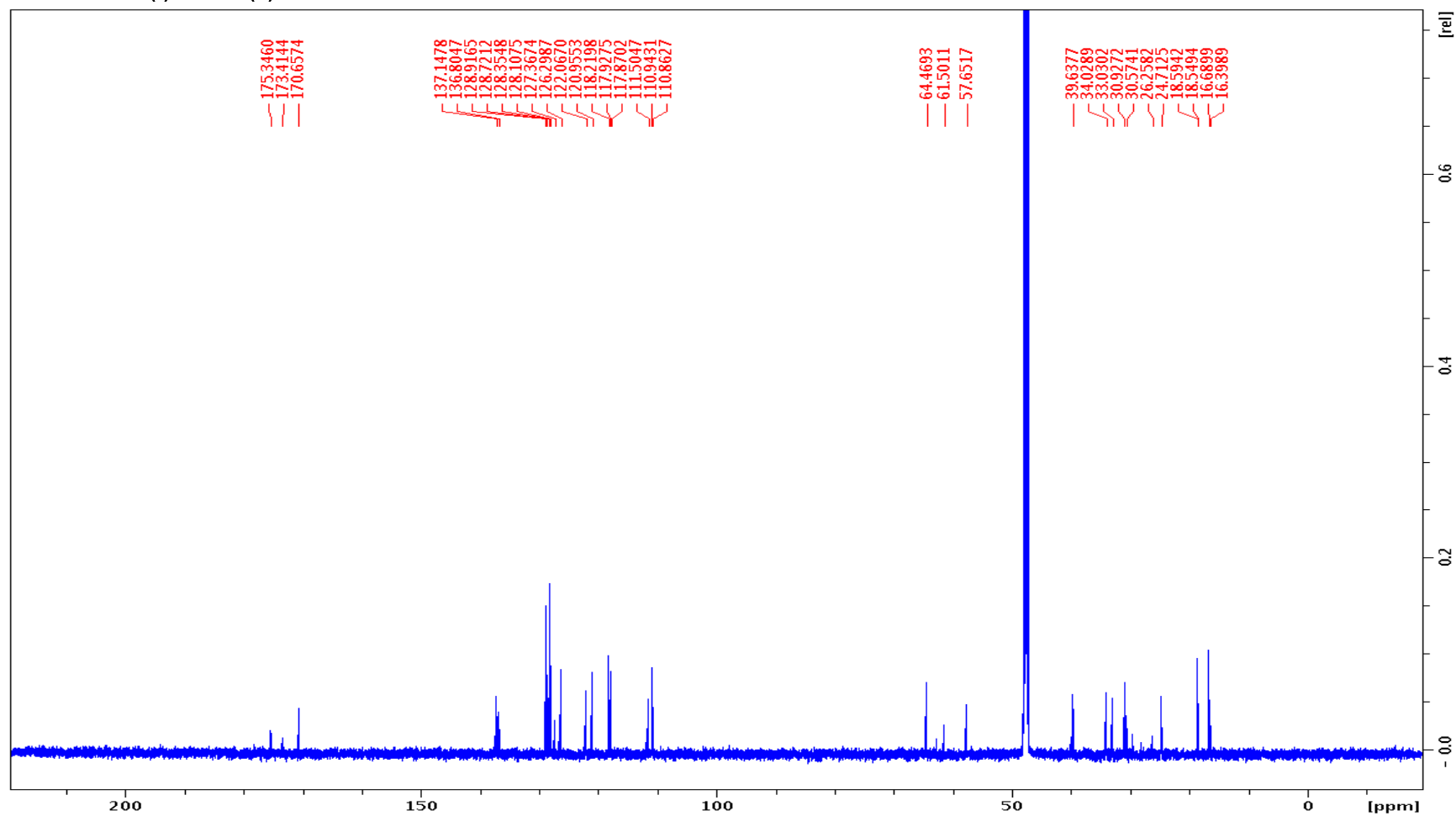
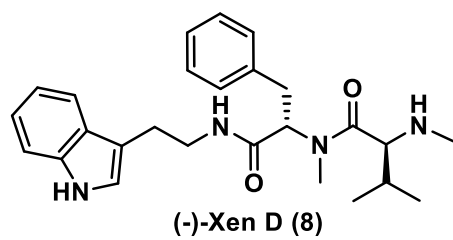
(S)-N-((S)-1-((2-(1H-indol-3-yl)ethyl)amino)-1-oxo-3-phenylpropan-2-yl)-N,3-dimethyl-2-(methylamino)butanamide
(8).



The compound was obtained as a yellowish solid; yield: (142.02 mg, 20%); $[\alpha]_D^{20}$ -58 (c 0.3, MeOH); R_f: 0.4 cm; **¹H NMR** (600 MHz, CD₃OD) showed the presence of two rotamers in a ratio of 3.8/1, major rotamer shown: δ 7.55-7.54 (d, J = 7.8 Hz, 1H, aryl), 7.33-7.31 (d, J = 7.8 Hz, 1H, aryl), 7.23-7.18 (m, 4H, aryl), 7.16-7.15 (m, 1H, aryl), 7.09-7.08 (t, J = 7.2 Hz, 1H, aryl), 7.04 (s, 1H, aryl), 6.99 (t, J = 7.2 Hz, 1H, aryl), 5.47 (dd, J_1 = 6.0 Hz, J_2 = 10.8 Hz, 1H, CH), 3.52-3.50 (m, 2H, CH₂), 3.18-3.14 (m, 1H, CH), 3.10-3.08 (d, J = 6.0 Hz, 1H, CH), 2.99-2.91 (m, 6H, CH, CH₂, CH₃-N), 1.68 (s, 3H, CH₃-NH), 1.60-1.57 (m, 1H, CH), 0.84-0.83 (d, J = 6.6 Hz, 3H, CH₃), 0.81 (d, J = 6.6 Hz, 3H, CH₃) ppm; **¹³C NMR** (600 MHz, CD₃OD) major rotamer shown: δ 175.35, 170.66, 137.15, 136.80, 128.72, 128.35, 128.11, 126.30, 122.07, 120.95, 118.22, 117.87, 111.50, 110.86, 64.47, 57.65, 39.64, 34.03, 33.03, 30.93, 30.57, 24.79, 18.55, 16.40 ppm; **HRMS** (TOF-ESI): [M+H]⁺calculated for C₂₆H₃₅N₄O₂: 435.2760; found: 435.2754.

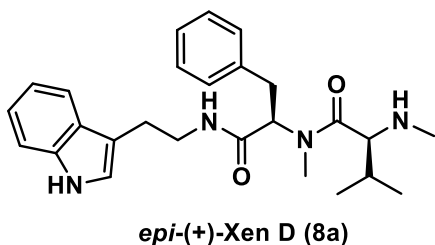


¹H NMR spectrum of compound (-)-8



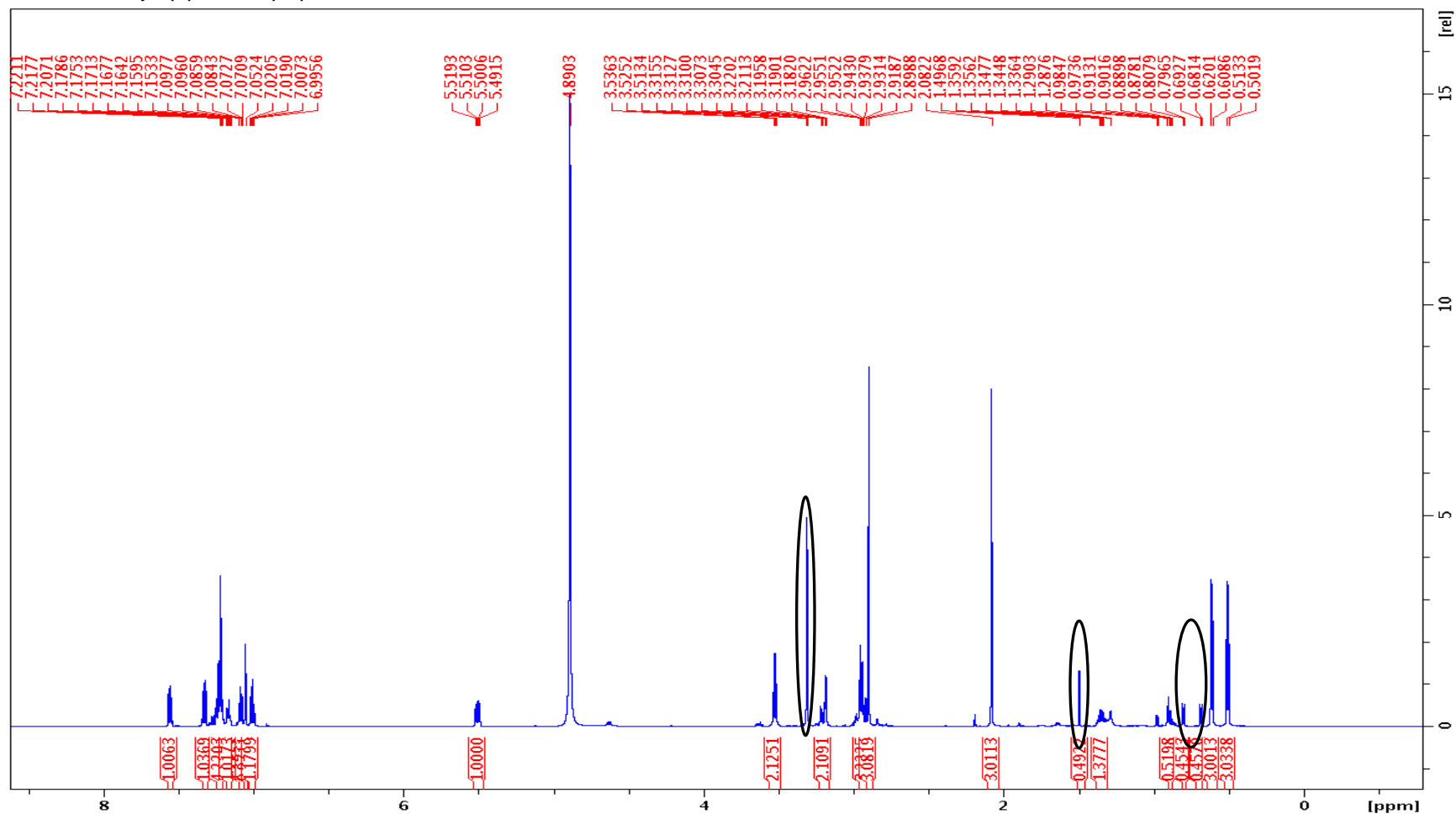
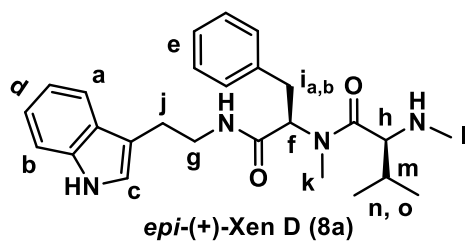
^{13}C NMR spectrum of compound (-)-8

(S)-N-((R)-1-((2-(1H-indol-3-yl)ethyl)amino)-1-oxo-3-phenylpropan-2-yl)-N,3-dimethyl-2-(methylamino)butanamide (8a).

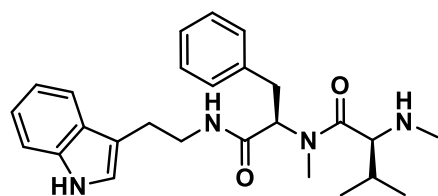


The compound was obtained as a white solid; yield: (109.67 mg, 15%); $[\alpha]_{\text{D}}^{20} +28$ (c 0.3, MeOH); R_f : 0.7 cm; **^1H NMR** (600 MHz, CD_3OD) showed the presence of two rotamers in a ratio of 6.6/1, major rotamer shown: δ 7.56-7.55 (d, $J = 7.8$ Hz, 1H, aryl), 7.33-7.32 (d, $J = 7.8$, 1H, aryl), 7.24-7.21 (m, 4H, aryl), 7.17-7.7.15 (m, 1H, aryl), 7.09-7.08 (t, $J = 7.2$ Hz, 1H, aryl), 7.05 (s, 1H, aryl), 7.01-6.99 (t, $J = 7.2$ Hz, 1H, aryl),

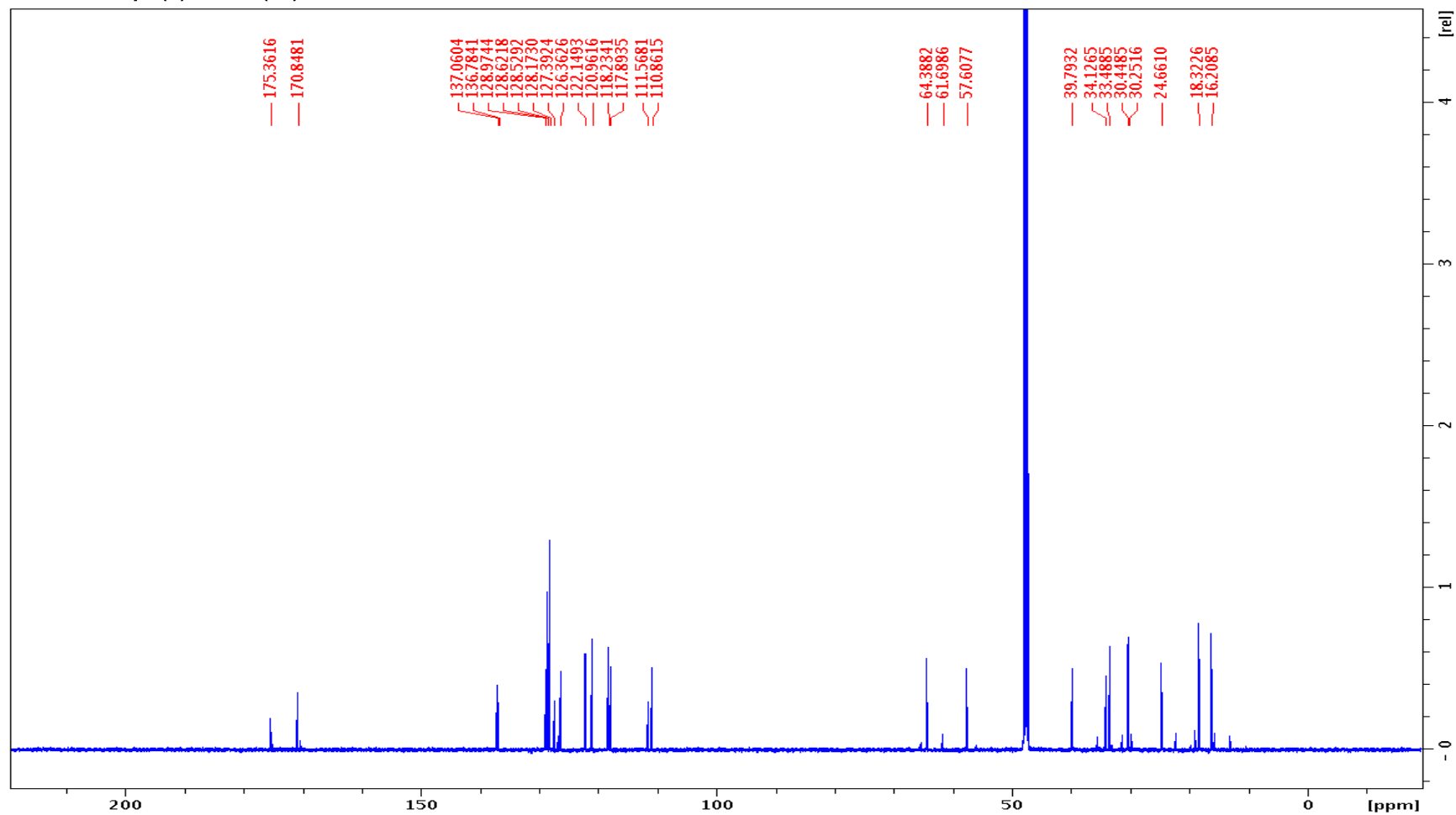
5.52-5.49 (dd, $J_1 = 5.4$ Hz, $J_2 = 11.4$ Hz, 1H, CH), 3.53-3.51 (t, $J = 6.6$ Hz, 2H, CH_2), 3.22-3.18 (m, 2H, CH_2), 2.96-2.90 (m, 6H, CH, CH_2 , $\text{CH}_3\text{-N}$), 2.08 (s, 3H, $\text{CH}_3\text{-NH}$), 1.36-1.29 (m, 1H, CH), 0.62-0.60 (d, $J = 6.6$ Hz, 3H, CH_3), 0.51-0.50 (d, $J = 6.6$ Hz, 3H, CH_3) ppm; **^{13}C NMR** (600 MHz, CD_3OD) major rotamer shown: δ 175.36, 170.85, 137.06, 136.78, 128.62, 128.17, 127.39, 126.36, 122.15, 120.96, 118.23, 117.89, 110.43, 110.86, 64.38, 57.60, 39.79, 33.38, 33.49, 30.49, 30.25, 24.66, 18.32, 16.21 ppm; **HRMS** (TOF-ESI): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{26}\text{H}_{35}\text{N}_4\text{O}_2$: 435.2760 found 435.2775.



¹H NMR spectrum of compound (+)-8a

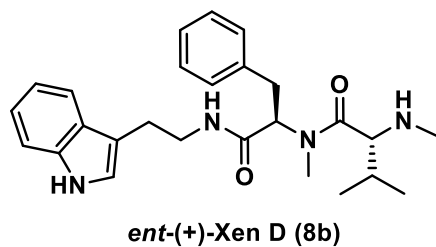


epi-(+)-Xen D (8a)



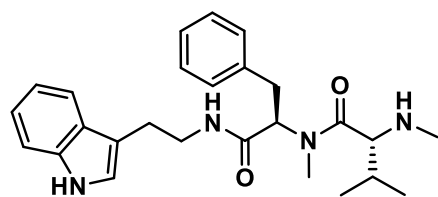
^{13}C NMR spectrum of compound (+)-8a

(*R*)-N-((*R*)-1-((2-(1H-indol-3-yl)ethyl)amino)-1-oxo-3-phenylpropan-2-yl)-N,3-dimethyl-2-(methylamino)butanamide (8b).

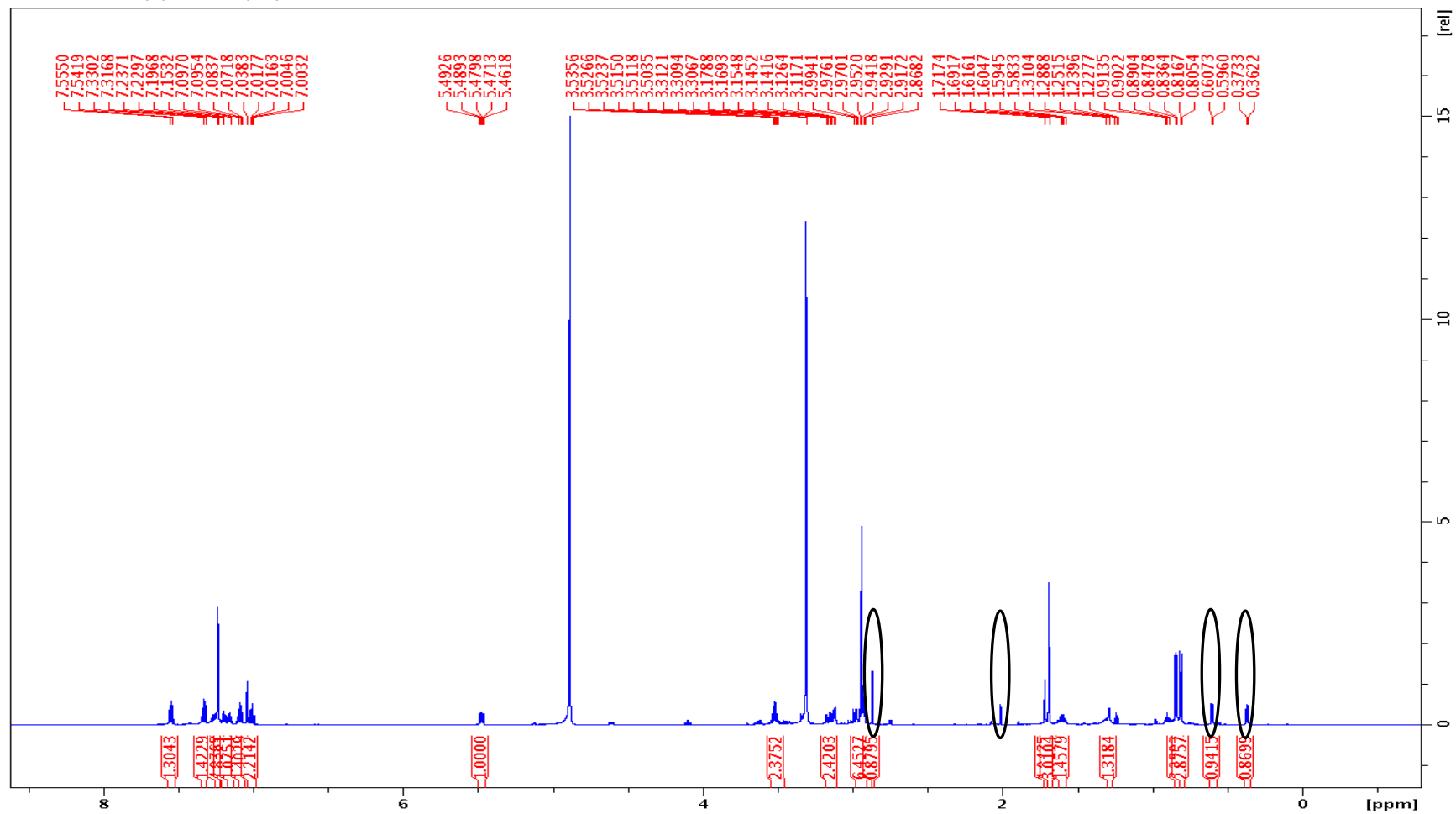


The compound was obtained as a yellowish solid; yield: (121.13 mg, 17%); $[\alpha]_D^{20}$ +58 (c 0.3, MeOH); R_f: 0.4 cm; **¹H NMR** (600 MHz, CD₃OD) showed the presence of two rotamers in a ratio of 3.2/1, major rotamer shown: δ 7.55 (d, J = 7.8 Hz, 1H, aryl), 7.32 (d, J = 7.8 Hz, 1H, aryl), 7.24-7.22 (m, 1H, aryl), 7.18-7.15 (m, 1H, aryl), 7.08 (t, J = 7.8 Hz, 1H, aryl), 7.04-7.00 (m, 1H, aryl), 5.48 (d.d, J_1 = 5.4, J_2 = 11.4

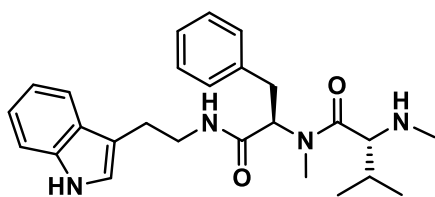
Hz, 1H, CH), 3.53-3.50 (m, 2H, CH₂), 3.17-3.12 (m, 2H, CH₂), 2.99-2.92 (m, 6H, CH, CH₂, CH₃-N), 1.70 (s, 3H, CH₃-NH), 1.62-1.58 (m, 1H, CH), 0.90 (d, J = 7.2 Hz, 3H, CH₃), 0.82 (d, J = 7.2 Hz, 3H, CH₃); **¹³C NMR** (600 MHz, CD₃OD) major rotamer shown: δ 171.43, 170.64, 137.15, 136.80, 128.73, 128.11, 127.37, 126.30, 121.05, 120.95, 118.22, 117.87, 111.51, 110.86, 64.45, 57.66, 39.64, 34.09, 32.99, 30.89, 30.58, 24.79, 18.57, 16.67; **HRMS** (TOF-ESI): [M+H]⁺calculated for C₂₆H₃₅N₄O₂: 435.2760; found: 435.2755.



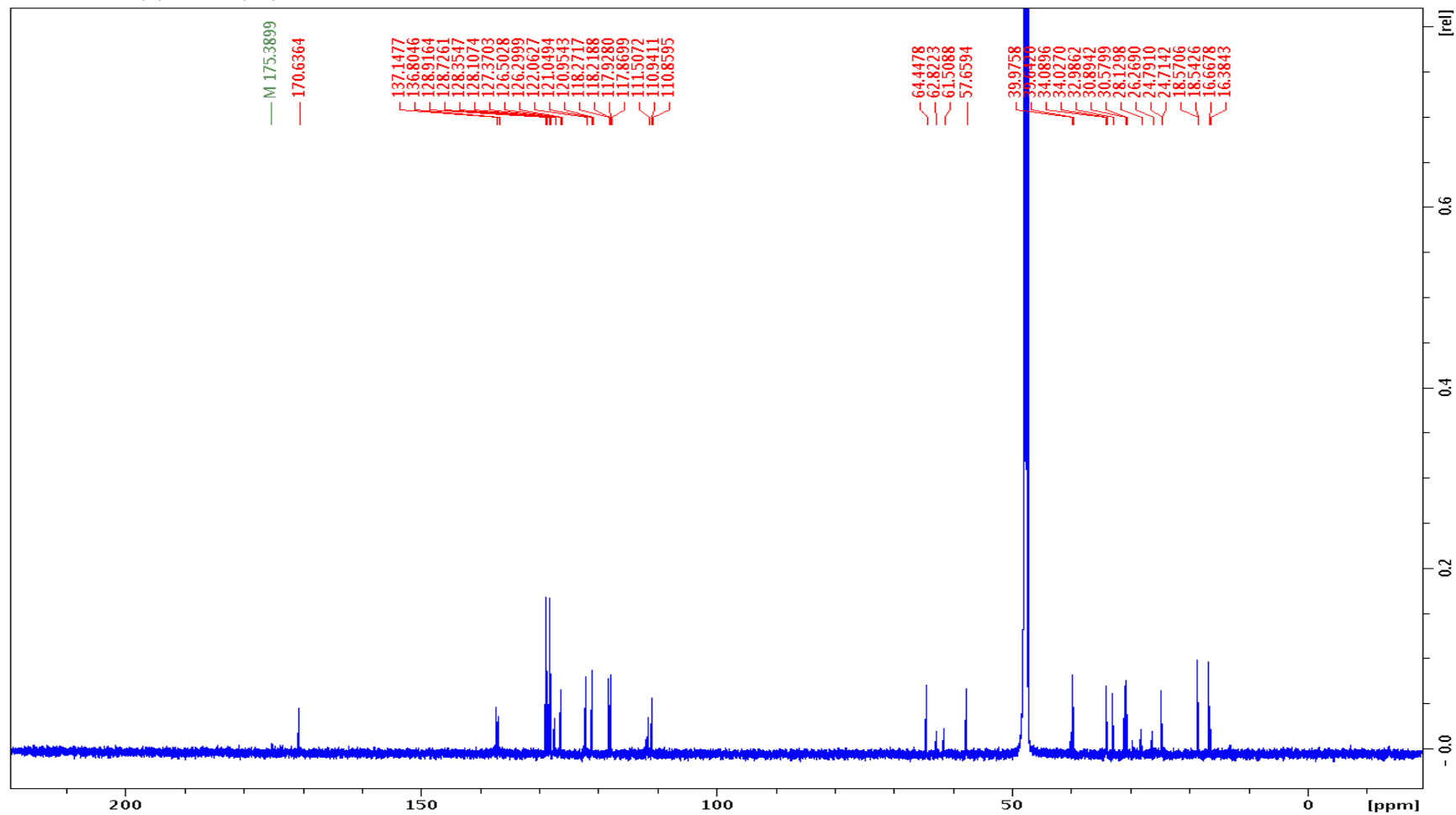
ent-(+)-Xen D (**8b**)



^1H NMR spectrum of compound (+)-**8b**

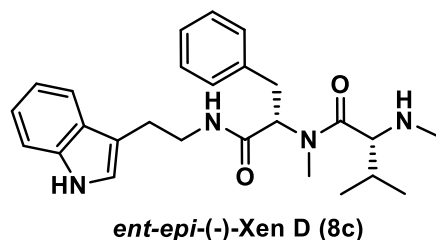


ent-(+)-Xen D (**8b**)



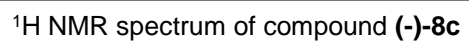
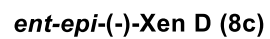
13C NMR spectrum of compound (+)-**8b**

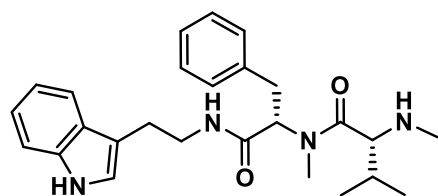
(*R*-N-((*S*)-1-((2-(1*H*-indol-3-yl)ethyl)amino)-1-oxo-3-phenylpropan-2-yl)-*N*,3-dimethyl-2-(methylamino)butanamide (8c).



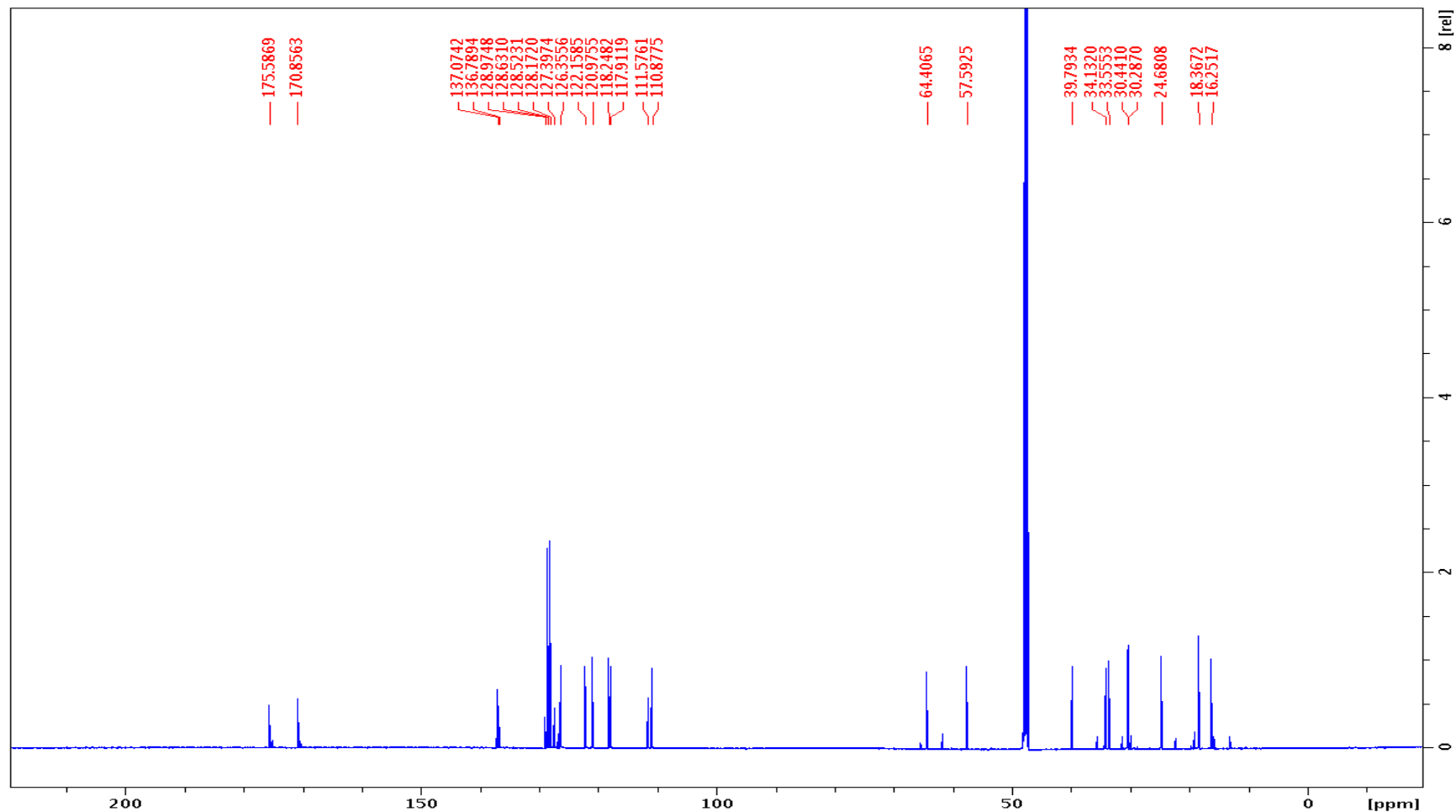
The compound was obtained as a white solid; yield: (182.30 mg, 25%); $[\alpha]_{\text{D}}^{20}$ -28 (*c* 0.3, MeOH); R_f : 0.6 cm; **$^1\text{H NMR}$** (600 MHz, CD_3OD) showed the presence of two rotamers in a ratio of 5.9/1, major rotamer shown: δ 7.56-7.54 (d, $J = 7.8$ Hz, 1H, aryl), 7.33-7.31 (d, $J = 7.8$ Hz, 1H, aryl), 7.22-7.20 (m, 4H, aryl), 7.17-7.15 (m, 1H, aryl), 7.08-7.07 (t, $J = 7.8$ Hz, 1H, aryl), 7.05 (s, 1H, aryl), 7.02-7.01 (m, 1H, aryl),

5.52-5.49 (d.d, $J_1 = 6.0$, $J_2 = 12.0$ Hz, 1H, CH), 3.53-3.51 (t, $J = 7.2$ Hz, 2H, CH_2), 3.21-3.18 (d.d, $J_1 = 3.6$, $J_2 = 15.0$ Hz, 1H, CH), 3.15-3.14 (d, $J = 5.4$, 1H, CH), 2.96-2.93 (m, 3H, CH, CH_2), 2.88 (s, 3H, $\text{CH}_3\text{-N}$), 2.07 (s, 3H, $\text{CH}_3\text{-NH}$), 1.34-1.33 (m, 1H, CH), 0.60 (d, $J = 6.6$ Hz, 3H, CH_3), 0.50 (d, $J = 6.6$ Hz, 3H, CH_3); **$^{13}\text{C NMR}$** (600 MHz, CD_3OD) major rotamer shown: δ 175.59, 170.86, 137.79, 128.63, 128.52, 128.17, 127.40, 126.35, 122.16, 120.97, 118.25, 117.91, 111.58, 110.88, 64.41, 57.60, 39.80, 34.13, 33.55, 30.44, 30.29, 24.68, 18.37, 16.25; **HRMS** (TOF-ESI): $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{26}\text{H}_{35}\text{N}_4\text{O}_2$: 435.2760; found: 435.2726.





ent-epi-(-)-Xen D (8c)



^{13}C NMR spectrum of compound **(-)-8c**