Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Supporting Information

The stereoselective synthesis of cis- and trans-fused pyrrolidine containing bicyclic azepine and oxepine derivatives using aza-Cope rearrangement-Mannich cyclization as a key step

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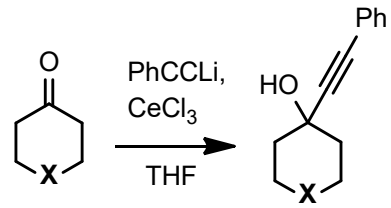
I. General information

All materials were obtained from commercial suppliers and used without further purification. NMR spectra were recorded on Bruker Avance 400 (400 MHz for ^{1}H and 100 MHz for ^{13}C) spectrometer at room temperature if not specified otherwise; the chemical shifts δ were measured in ppm with respect to solvent ($CDCl_3$: ^{1}H: δ = 7.26 ppm, ^{13}C: δ = 77.0 ppm; DMSO-d_6: ^{1}H: δ = 2.50 ppm, ^{13}C: δ = 39.5 ppm). ^{19}F NMR spectra were recorded at 470 MHz with fluorobenzene as an internal reference (δ = −112.96 ppm in $CDCl_3$). Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublets), and br (broad). Coupling constants (*J*) are given in Hz. The structures of synthesized compounds were elucidated with the aid of 1D NMR (^{1}H, and ^{13}C) and 2D NMR (COSY ^{1}H-^{1}H, HSQC and HMBC ^{1}H-^{13}C, and NOESY ^{1}H-^{1}H) spectroscopies. IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer. Registration of spectra was carried out at a resolution of 4 cm^{-1}, and the number of scans was 10. Samples were placed on the working surface of the internal reflection (ATR) element from ZnSe with the angle of incidence of 45°. High-resolution mass spectra were recorded on a Bruker microTOF-Q spectrometer with electrospray ionization (ESI). The specific rotation was measured on Perkin-Elmer 241 and Jasco DIP-360 polarimeters at 589 nm in cells with path length 5 and 10 cm. Methylene chloride, chloroform, and methanol were used as the solvent for measurement of the specific rotation. The GC/MS study was carried out using an Agilent 1200 gas-liquid chromatograph with fluorimetric and diode-matrix detectors, a 4.6x250 mm Chiralcel OD-H or Chiralpak AD-RH columns, detection at UV 250 nm, and water–acetonitrile in various ratios as the mobile phase. The flow rate was 1 ml/min. Analytical thin-layer chromatography (TLC) was carried out using percolated aluminum sheets of silica gel 60 (F_{254}). The visualization of the TLC plates was done by a UV lamp (365 nm). Column chromatography was performed on a silica gel 60 (230−400 mesh). Melting points (mp) were determined using Electrothermal 9100 and SMP-20 capillary melting point apparatus. All the reactions were carried out using freshly distilled and dry solvents from solvent stills. All reactions were performed on a gram-scale.

II. General procedures

General procedure for the synthesis of products **9-10 (GP 1)**

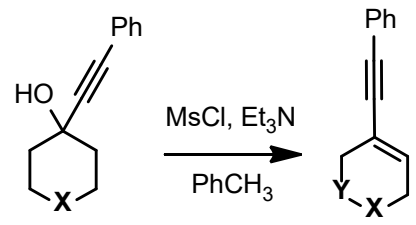


To the solution of phenylacetylene (0.16 mol, 1.6 eq) in THF (150 ml) at -78°C 2.5 M BuLi in hexane (0.15 mol, 1.5 equiv.) was added dropwise over 10 min, the reaction mixture was stirred at -78°C for 30 min and warmed to complete dissolution of the precipitate. Then, using a cannula, the solution was transferred to cooled to -78°C suspension of $CeCl_3$ (81.3 mmol, 0.81 eq) in THF (170 ml), the mixture was stirred for 1 h at -78°C and a solution of ketone (0.10 mmol) in THF (60 ml) was added. The reaction mixture was stirred 1.5 h at -78°C, poured into 0.15 M CH_3CO_2H (1 L) and extracted with hexane-DCM 4:1 mixture (2 x 500 mL). The combined organic extracts were dried with Na_2SO_4, the solvents were evaporated in vacuo. Removing the excess of phenylacetylene in an oil pump vacuum (40-50°C, 0.05 mm Hg) and used in the next stage without purification.

Analytically pure sample of **9** was obtained by chromatographic purification (SiO_2, hexane-DCM-EtOAc gradient from 4: 1: 0.5 to 4: 1: 2.5). Rf 0.5 (hexane - EtOAc 2: 1).

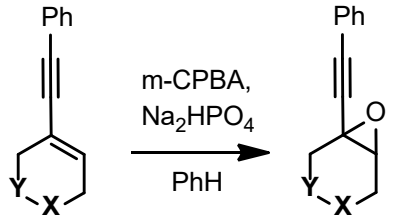
Analytically pure sample of **10** was obtained by chromatographic purification (SiO_2, hexane-DCM-EtOAc gradient from 2: 1: 0.3 to 2: 1: 1.5). Rf 0.45 (hexane - EtOAc 2: 1).

General procedure for the synthesis of products **11-12 (GP 2)**



To a solution of the alcohol (~ 0.10 mol) in toluene (250 ml) at -30°C Et_3N (0.30 mol, 3 eq) was added and then MsCl (0.12 mol, 1.2 eq) was added dropwise over 5 min. The mixture was stirred for 30 min at -30°C, the cooling bath was removed and the reaction was stirred at room temperature for an additional 24 h. The mixture was then treated with 5% H_2SO_4 (350 ml), the organic layer was separated and the aqueous was extracted with a hexane-DCM 10: 1 mixture (200 ml). Organic extracts were combined, dried with Na_2SO_4, the solvents were evaporated in vacuo. The residue was purified by using chromatography (SiO_2, hexane-DCM-EtOAc 10: 1: 1) to afford the desired products.

General procedure for the synthesis of products **14-16 (GP 3)**



To a solution of alkene (49.5 mmol) in benzene (500 ml) Na_2HPO_4 (296 mmol, 6 eq) and 70% m-CPBA (60 mmol, 1.2 eq) were added and the mixture was vigorously stirred for 1 h. Then additional portion of 70% m-CPBA (25 mmol, 0.5 eq) was added and the reaction was stirred for an additional 2 h

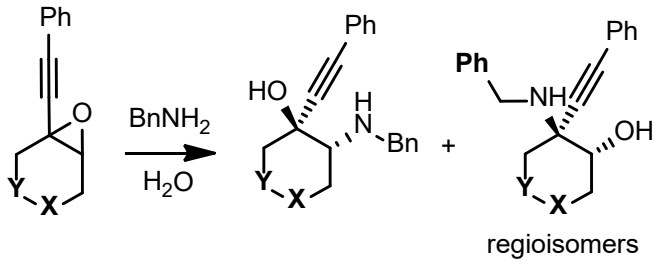
and left overnight. The mixture was then thoroughly washed twice with a solution of K_2CO_3 (30 g) and Na_2SO_3 (15 g) in water (500 ml), the organic layer was separated and the aqueous was combined and extracted with hexane-DCM 4: 1 mixture (250 ml). The combined organic extracts were dried with Na_2SO_4, the solvents were evaporated in vacuo to afford the desired products which were used without further purification on the next step.

Analytically pure sample of **14** was obtained by chromatographic purification (SiO_2, hexane-DCM-EtOAc 10: 1: 1).

Analytically pure sample of **15** was obtained by chromatographic purification (SiO_2, hexane-DCM-EtOAc 10: 1: 1.5). Rf 0.40 (hexane - EtOAc 4: 1).

Analytically pure sample of **16** was obtained by chromatographic purification (SiO_2, hexane-DCM-EtOAc 10: 1: 1). Rf 0.4 (hexane - EtOAc 4: 1)

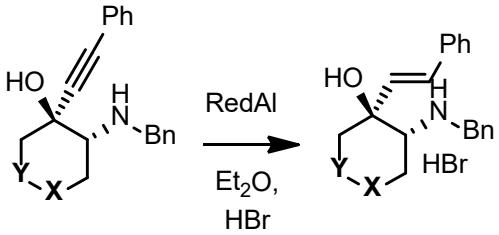
General procedure for the synthesis of products **17-19 (GP 4)**



The emulsion of epoxide (**14-16**) (50 mmol) and amine (150 mmol, 3 eq) in water (35 mL) was vigorously stirred at 45°C for 72 h. Then water (200 ml) was added and the reaction was extracted with hexane-DCM 4:1 mixture (2 x 200 ml). The organic extracts were combined, dried with Na_2SO_4, the solvents were evaporated in vacuo. Chromatographic purification of the residue (SiO_2, hexane-DCM-EtOAc 10: 1: 2) to afford amino propargylic alcohols **17-19** as bright to dark yellow/orange oils. Amino propargylic alcohols **17** and **18** contained a small amount of regioisomers **17a** and **18a** in 8 to 13% yields.

Analytically pure sample of **17** was obtained by crystallization of the hydrobromide salt from EtOH – Et_2O mixture. **17**: Rf (free base) 0.4 (hexane - EtOAc 4: 1)

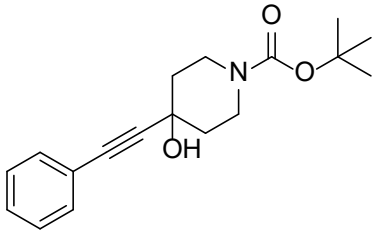
General procedure for the synthesis of products **20-22 (GP 5)**



RedAl (30 ml of 70% solution in toluene, 105 mmol, 3.5 eq) was dissolved in Et_2O (100 ml), the mixture was cooled to -10^{O}C and a solution of amino propargylic (29.6 mmol) in Et_2O (100 ml) was added dropwise in a 10 min period of time. The reaction was stirred at -10°C - 0°C for 2 h, cooled to -20°C and water (4 ml), 15% aq. KOH (6 ml) and water (4 ml) were added dropwise successively under vigorous stirring. Cooling bath was removed and the mixture was allowed to warm to room temperature. The clear solution was decanted and the pasty precipitate was thoroughly washed with Et_2O (100 ml) with vigorous stirring. The organic solutions were combined, washed with water (100 ml), dried with Na_2SO_4, the solvents were evaporated in vacuo. The residue was dissolved in EtOH-Et_2O (1 : 4) mixture (100 ml), the solution was cooled to 0°C, and 7 M aq. HBr (4.5 ml) was added dropwise under vigorous stirring until pH = 5. After initial precipitation had completed, Et_2O (100 ml) was added and the mixture was left at -30°C overnight. The precipitate was filtered off, washed with Et_2O and dried to afford hydrobromides **20, 21**, and **22**.

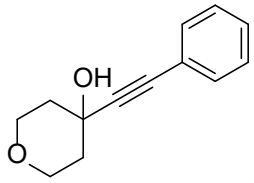
III. Analytical data of the synthesized derivatives

Tert-butyl 4-hydroxy-4-(phenylethynyl)piperidine-1-carboxylate (9)



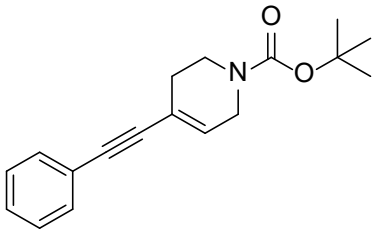
Compound **9** was synthesized according to the **GP 1** from ketone **3** (20 g, 0.10 mol) affording 29.54 g (98%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm):1.47 (s, 9 H), 1.74 - 1.85 (m, 2 H), 1.95 - 2.05 (m, 2 H), 2.39 (br. s., 1 H), 3.33 (ddd, *J* = 13.4, 9.7, 3.3 Hz, 2 H), 3.84 (br. s., 2 H), 7.28 - 7.37 (m, 3 H), 7.40 - 7.48 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 28.4 (3 C), 39.1 (2 C), 40.7 (br.), 41.2 (br.), 67.2, 79.7, 85.3, 91.0, 122.2, 128.3 (2 C), 128.6, 131.7 (2 C), 154.7. IR υ_{max}, (KBr): 3207 (br.), 2960, 2931, 2856, 2216 (w.), 1697, 1421, 1365, 1277, 1248, 1173, 1144, 1068, 754, 690 cm^{-1}. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{18}H_{23}NO_3Na^+$: 324.1570, found: 324.1570.

4-(Phenylethynyl)tetrahydro-2*H*-pyran-4-ol (10)



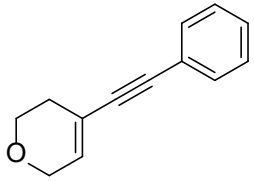
Compound **10** was synthesized according to the **GP 1** from ketone **4** (20 g, 100.0 mmol) affording 20.85 g (97%) as a yellow solid; m. p. 54 - 56^{O}C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.91 (ddd, *J* = 12.9, 9.3, 4.0 Hz, 2 H), 2.00 - 2.09 (m, 2 H), 3.74 (ddd, *J* = 11.9, 9.2, 2.8 Hz, 2 H), 3.97 (dt, *J* = 11.9, 4.5 Hz, 2 H), 7.29 - 7.37 (m, 3 H), 7.41 - 7.48 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm):40.0 (2 C), 64.9 (2 C), 66.2, 85.1, 91.2, 122.3, 128.3 (2 C), 128.5, 131.6 (2 C). IR υ_{max}, (KBr): 3356, 2962, 2933, 2870, 2218 (w.), 1338, 1290, 1230, 1153, 1095, 1084, 987, 842, 760, 696 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{15}O_2^+$: 203.1067, found: 203.1054.

Tert-butyl 4-(phenylethynyl)-5,6-dihydropyridine-1(2H)-carboxylate (11)



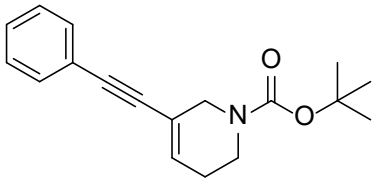
Compound **11** was synthesized according to the **GP 2** from alcohol **9** (30.14 g, 100.0 mmol) affording 26.06 g (92%) as a yellow oil; Rf 0.6 (hexane - EtOAc 4: 1). ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.48 (s, 9 H), 2.34 (br. s., 2 H), 3.54 (t, *J* = 5.4 Hz, 2 H), 4.02 (d, *J* = 2.5 Hz, 2 H), 6.10 (br. s., 1 H), 7.28 - 7.34 (m, 3 H), 7.39 - 7.47 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 28.4 (3 C), 29.2, (39.3 (br.), 40.6 (br.)), (43.3 (br.), 43.8 (br.)), 79.8, 88.5, 89.2, 119.4 (br.), 123.1, 128.1, 128.2 (2 C), (130.3 (br.), 130.8 (br.)), 131.4 (2 C), 154.7. IR υ_{max}, (KBr): 2976, 2931, 2249 (w.), 1697, 1419, 1365, 1273, 1240, 1169, 957, 912, 756, 733, 690 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{22}NO_2$: 284.1645, found: 284.1649.

4-(Phenylethynyl)-3,6-dihydro-2*H*-pyran (12)



Compound **12** was synthesized according to the **GP 2** from alcohol **10** (20.22 g, 100.0 mmol) affording 17.13 g (93%) as a yellow oil; Rf 0.55 (hexane - EtOAc 4: 1). ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 2.32 - 2.39 (m, 2 H), 3.84 (t, *J* = 5.3 Hz, 2 H), 4.26 (q, *J* = 2.8 Hz, 2 H), 6.15 - 6.20 (m, 1 H), 7.28 - 7.36 (m, 3 H), 7.41 - 7.48 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 29.1, 63.9, 65.5, 88.4, 89.1, 118.5, 123.2, 128.1, 128.3 (2 C), 131.5 (2 C), 132.4. IR υ_{max}, (KBr): 3057, 2966, 2858, 2249 (w.), 2202 (w.), 1720, 1491, 1383, 1132, 1070, 910, 758, 733, 690 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{11}O$: 183.0804, found: 183.0804.

***Tert*-butyl 3-(phenylethynyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (13)**



A solution of tert-butyl 3-bromo-5,6-dihydropyridine-1(2H)-carboxylate[1] **(5)** (15.7 g, 57.3 mmol), phenylacetylene (9.2 g, 90 mmol, 1.5 eq), pyrrolidine (12.8 g, 180 mmol, 3 eq), CuI (1.15 g, 6.05 mmol, 0.1 eq) and $Pd(PPh_3)_4$ (1.73 g, 1.50 mmol, 0.025 eq) in CH_3CN (150 ml) was stirred for 2 h at 70°C. Then additional portion of phenylacetylene (3 g, 29.4 mmol, 0.5 eq) was added and the reaction was stirred 2 h at 70^{O}C. The mixture was cooled to room temperature, poured into 2% aq HCl (500 ml) and extracted with hexane-DCM 3: 1 mixture (2 x 200 ml). Organic extracts were combined, dried with Na_2SO_4, the solvents were evaporated in vacuo. The residue was purified by column chromatography (SiO_2, hexane-DCM-EtOAc 10: 1: 1) to afford **13** (16.3 g, 96%). Rf 0.45 (hexane-EtOAc 10: 1), m. p. 58 – 61^{O}C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.49 (s, 9 H), 2.26 (br. s., 2 H), 3.50 (t, J = 5.6 Hz, 2 H), 4.03 (br. s., 2 H), 6.29 (br. s., 1 H), 7.25 - 7.36 (m, 3 H), 7.39 - 7.50 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 25.4, 28.4 (3 C), (38.8 (br.), 40.2 (br.)), (45.7 (br.), 46.0 (br.)), 79.9, 87.6, 88.6 (br.), 118.9 (br.), 123.0, 128.2, 128.3 (2 C), 131.5 (2 C), 132.8 (br.), 154.5. IR υ_{max}, (KBr): 2978, 2929, 2249 (w.), 1697, 1419, 1365, 1242, 1169, 1122, 910, 756, 733, 690 cm^{-1}. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{18}H_{21}NO_2Na$: 306.1465, found: 306.1463.

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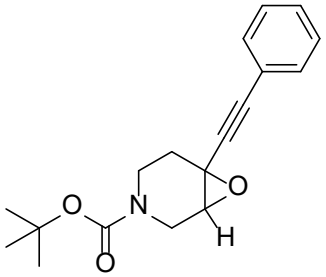
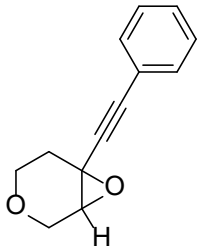
[1] Bromide **5** was prepared from 3-bromopyridine by a method described in: O.O. Grygorenko, O.V. Hryshchuk, Y.O. Kuchkovska, A.V. Tymtsunik, A.O. Varenyk, Y. Yurov, *Eur. J. Org. Chem.,* 2020, 2020, 2217 - 2224. Bromide **5** was commercially available. All physical and spectral characteristics for Bromide **5** were in accordance with: O.O. Grygorenko, O.V. Hryshchuk, Y.O. Kuchkovska, A.V. Tymtsunik, A.O. Varenyk, Y. Yurov, *Eur. J. Org. Chem.,* 2020, 2020, 2217 - 2224..

***Tert*-butyl 6-(phenylethynyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (14).**



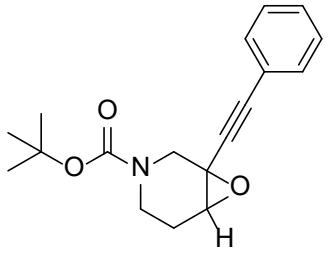
Compound **14** was synthesized according to the **GP 3** from alkene **11** (15.15 g, 53.5 mmol) affording 15.85 g (98%) as a yellow oil; Rf 0.45 (hexane - EtOAc 4: 1), which was used without further purification on the next step. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.47 (s, 9 H), 2.13 - 2.44 (m + br. s., 2 H), 3.03 - 3.16 (m, 1 H), 3.43 - 3.79 (br. m., 3 H), 3.85 - 4.20 (br. m., 1 H), 7.28 - 7.30 (m, 3 H), 7.40 - 7.50 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 28.3 (3 C), (29.4 (br.), 29.5 (br.)), (36.7 (br.), 37.8 (br.)), (41.4 (br.), 42.1 (br.)), 49.7 (br.), (57.8 (br.), 58.1 (br.)), 80.0, 83.2, 87.3, 121.7, 128.2 (2 C), 128.8, 131.8 (2 C), 154.6. IR υ_{max}, (KBr): 2978, 2931, 2251 (w.), 1697, 1691, 1425, 1367, 1248, 1171, 1161, 1119, 912, 733 cm^{-1}. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{18}H_{22}NO_3$: 322.1414, found: 322.1417.

6-(Phenylethynyl)-3,7-dioxabicyclo[4.1.0]heptane (15)



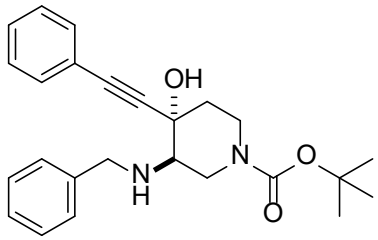
Compound **15** was synthesized according to the **GP 3** from alkene **12** (15.02 g, 81.5 mmol) affording 16.0 g (98%) as a yellow oil; Rf 0.40 (hexane - EtOAc 4: 1), which was used without further purification on the next step. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 2.20 - 2.36 (m, 2 H), 3.50 (d, *J* = 2.5 Hz, 1 H), 3.54 (d, *J* = 5.1 Hz, 1 H), 3.55 (d, *J* = 5.0 Hz, 1 H), 3.96 (d, *J* = 13.5 Hz, 1 H), 4.11 (dd, *J* = 13.5, 2.9 Hz, 1 H), 7.28 - 7.38 (m, 3 H), 7.41 - 7.49 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 39.9, 48.7, 58.2, 61.1, 64.4, 83.2, 87.4, 121.8, 128.3 (2 C), 128.8, 131.8 (2 C). IR υ_{max}, (KBr): 2958, 2850, 2231 (w.), 1491, 1298, 1242, 1128, 870, 758, 733, 692 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$calcd for $C_{13}H_{13}O_2$: 210.0910, found: 210.0909.

***Tert*-butyl 1-(phenylethynyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (16).**



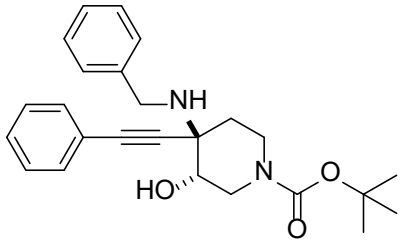
Compound **16** was synthesized according to the **GP 3** from alkene **13** (15.02 g, 38.9 mmol) affording 11.4 g (99%) as a yellow oil; Rf 0.40 (hexane - EtOAc 4: 1), which was used without further purification on the next step.^{1}H NMR ($CDCl_3$, 400 MHz, 50^{O}C), δ (ppm): 1.49 (s, 9 H), 1.92 - 2.02 (m, 1 H), 2.04 - 2.16 (m, 1 H), 3.20 - 3.30 (m, 1 H), 3.36 (br. s., 1 H), 3.55 (s, 1 H), 3.92 (br. d., *J* = 13.8 Hz, 1 H), 4.07 (d, *J* = 15.0 Hz, 1 H), 7.26 - 7.38 (m, 3 H), 7.40 - 7.50 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz, 50^{O}C), δ (ppm):23.7 (br.), 28.4 (3 C), 37.6 (br.), 46.6 (br.), 49.3, 59.0, 80.2, 84.2, 86.5, 122.0, 128.3 (2 C), 128.8, 131.9 (2 C), 154.8. IR υ_{max}, (KBr): 2976, 2927, 2231 (w.), 1697, 1421, 1367, 1248, 1171, 1155, 758, 692 cm^{-1}. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{18}H_{21}NO_3Na$: 322.1414, found: 322.1424.

(3*RS*,4*SR*)-*Tert*-butyl 3-(benzylamino)-4-hydroxy-4-(phenylethynyl)piperidine-1-carboxylate (17).



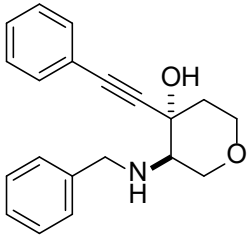
Compound **17** was synthesized according to the **GP 4** from epoxide **14** (14.92 g, 49.9 mmol) affording 15.2 g (75%) as a yellow oil; Rf (free base) 0.4 (hexane - EtOAc 4: 1). Hydrobromide: m. p. 198 – 201^{O}C (EtOH – Et_2O). ^{1}H NMR (DMSO-d_6, 400 MHz), δ (ppm): 1.40 (s, 9 H), 1.59 (td, *J* = 12.9, 4.0 Hz, 1 H), 2.08 (d, *J* = 13.1 Hz, 1 H), 2.79 (br. s., 1 H), 2.86 - 3.14 (br. m., 2 H), 3.94 (br. d., *J* = 10.2 Hz, 1 H), 4.08 – 4.55 (br. m., 3 H), 6.69 (s, 1 H), 7.38 - 7.54 (m, 6 H), 7.56 - 7.71 (m, 4 H), 9.04 (br. s., 1 H), 9.38 (br. s., 1 H). ^{13}C NMR (DMSO-d_6, 100 MHz), δ (ppm): 27.9 (3 C), 40.6 (br.), 41.8 (br.), 49.0, 59.5, 68.4, 79.9, 86.0, 88.4, 121.3, 128.6 (2 C), 128.8 (2 C), 129.3, 129.4, 130.5 (2 C), 130.7, 131.9 (2 C), 153.4 (br.). One aliphatic signal was lost because of broadening or overlapping with the signals of the solvent. IR υ_{max}, (KBr): 3247 (br.) 2974, 2931, 2816, 2227 (w.), 1697, 1566, 1458, 1444, 1423, 1412, 1275, 1248, 1189, 1151, 1066, 1057, 761, 748, 694 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{31}N_2O_3$: 407.2329, found: 407.2324.

(3*SR*,4*RS*)-*tert*-Butyl 4-(benzylamino)-3-hydroxy-4-(phenylethynyl)piperidine-1-carboxylate (17a).



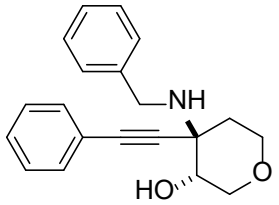
Yellow solid; 1.6 g, yield 8%; m. p. 106 – 108°C; Rf 0.25 (hexane - EtOAc 4: 1). ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.47 (s, 9 H), 1.62 (td, *J* = 13.3, 4.0 Hz, 1 H), 1.85 – 2.50 (m + br. s., 3 H), 2.95 – 3.25 (br. m., 2 H), 3.49 – 3.62 (m, 1 H), 3.89 (d, *J* = 12.1 Hz, 1 H), 3.92 – 4.30 (br. s. + d, *J* = 12.5 Hz, 3 H), 7.24 – 7.30 (m, 1 H), 7.31 – 7.42 (m, 7 H), 7.47 – 7.53 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 28.3 (3 C), (34.8 (br.), 34.9 (br.)), (40.2 (br.), 41.2 (br.)), (46.3 (br.), 47.1 (br.)), 47.9, 60.4 (br.), 72.6 (br.), 79.9, 87.3 (br.), 88.6 (br.), 122.4 (br.), 127.0, 128.30 (2 C), 128.34 (2 C), 128.4 (2 C), 128.5 (br.), 131.8 (2 C), 140.3 (br.), 154.6. IR υ_{max}, (ZnSe): 3379 (br.), 2974, 2929, 2868, 2233 (w.), 1693, 1672, 1425, 1365, 1275, 1248, 1171, 1149, 1070, 881, 756, 692 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{31}N_2O_3$: 407.2329, found: 407.2324.

(3*RS*,4*SR*)-3-(Benzylamino)-4-(phenylethynyl)tetrahydro-2*H*-pyran-4-ol (18)



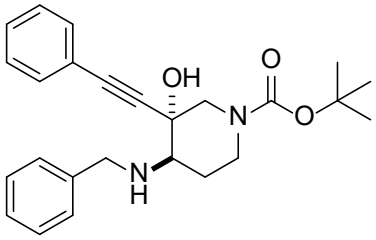
Compound **18** was synthesized according to the **GP 4** from epoxide **15** (16.23 g, 81.7 mmol) affording 16.2 g (65%) as a yellow solid; m. p. 115 - 117°C; Rf 0.45 (hexane - EtOAc 7: 3). ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 0.90 - 2.20 (br. s., 1 H), 1.94 (td, *J* = 12.6, 4.7 Hz, 1 H), 2.15 (dt, *J* = 13.0, 2.0 Hz, 1 H), 2.76 (dd, *J* = 10.5, 4.4 Hz, 1 H), 3.32 (t, *J* = 10.9 Hz, 1 H), 3.30 - 4.31 (br. s., 1 H), 3.77 (td, *J* = 12.1, 2.0 Hz, 1 H), 3.84 (d, *J* = 13.2 Hz, 1 H), 3.93 - 4.00 (m, 1 H), 4.01 (d, *J* = 13.5 Hz, 1 H), 4.12 (dd, *J* = 11.3, 4.4 Hz, 1 H), 7.25 - 7.41 (m, 8 H), 7.42 - 7.49 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 38.8, 51.1, 62.6, 65.6, 68.3, 70.6, 87.2, 88.4, 122.2, 127.3, 128.0 (2 C), 128.3 (2 C), 128.5 (2 C), 128.6, 131.7 (2 C), 140.1. IR υ_{max}, (KBr): 3406 (br.), 3060, 2972, 2868, 2844, 2220 (w.), 1491, 1444, 1340, 1119, 1090, 976, 752, 733, 704, 692, 557 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{22}NO_2$: 308.1645, found: 308.1639.

(3*RS*,4*RS*)-4-(benzylamino)-4-(phenylethynyl)tetrahydro-2*H*-pyran-3-ol (18a)



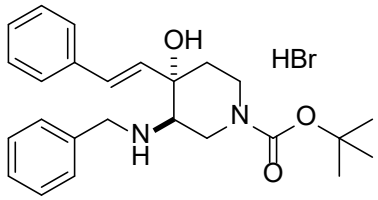
Yellow solid; 3.2 g, yield 13%; mp 122 – 124°C; Rf 0.25 (hexane - EtOAc 7: 3). ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.82 (ddd, *J* = 13.2, 11.5, 4.4 Hz, 1 H), 2.01 (br. s., 2 H), 2.18 (dt, *J* = 13.5, 2.4 Hz, 1 H), 3.52 (t, *J* = 9.9 Hz, 1 H), 3.67 (dd, *J* = 9.7, 4.5 Hz, 1 H), 3.76 (td, *J* = 11.8, 2.1 Hz, 1 H), 3.87 – 3.97 (m, 3 H), 4.06 (d, *J* = 12.3 Hz, 1 H), 7.24 – 7.30 (m, 1 H), 7.31 – 7.44 (m, 7 H), 7.47 – 7.55 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 36.1, 47.8, 59.9, 64.8, 68.8, 72.4, 87.6, 88.8, 122.3, 127.1, 128.4 (4 C), 128.5 (2 C), 128.6, 131.8 (2 C), 140.3. IR υ_{max}, (ZnSe): 3159, 2968, 2904, 2854, 2360, 2328, 1689, 1489, 1450, 1429, 1128, 1088, 1020, 982, 883, 752, 692 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{22}NO_2$: 308.1645, found: 308.1649.

(3*SR*,4*SR*)-*Tert*-butyl 4-(benzylamino)-3-hydroxy-3-(phenylethynyl)piperidine-1-carboxylate (19)



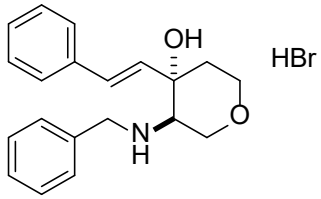
The reaction was performed according to slightly modified conditions of the GP 4. A solution of epoxide **16** (9.88 g, 33 mmol), benzylamine (7 g, 65.4 mmol, 2 eq) and $LiClO_4$ (5.3 g, 50 mmol, 1.5 eq) in CH_3CN (25 ml) was stirred at 45°C for 24 h. Then the solution was cooled to room temperature, poured into water (100 ml) and extracted with hexane-DCM 3: 1 mixture (2 x 100 ml). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. After purification of the residue by column chromatography (SiO_2, hexane-DCM-EtOAc 3: 1: 1.5) **16** (6.70 g, 50%) was obtained. Rf 0.45 (hexane-EtOAc 7: 3), mp 118 – 120°C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.40 (s + br. s., 10 H), 1.58 (qd, *J* = 7.9, 4.3 Hz, 1 H), 2.00 - 2.17 (m, 1 H), 2.58 (d, *J* = 11.0 Hz, 1 H), 2.69 (t, *J* = 11.7 Hz, 1 H), 2.80 (d, *J* = 12.6 Hz, 1 H), 3.78 (d, *J* = 12.9 Hz, 1 H), 4.05 (d, *J* = 13.2 Hz, 1 H), 4.14 (br. s., 1 H), 4.38 (d, *J* = 13.0 Hz, 0.75 H), 4.50 (d, *J* = 12.5 Hz, 0.75 H), 4.58 (br. s., 0.5 H), 7.23 - 7.46 (m, 10 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 28.3 (3 C), 28.4, 42.7, 50.4, 53.1, 63.9, 70.1, 79.8, 86.3, 88.2, 122.3, 127.2, 128.06 (2 C), 128.14 (2 C), 128.4, 128.5 (2 C), 131.7 (2 C), 139.9, 154.5. IR υ_{max}, (KBr): 3425 (br.), 2976, 2920, 2891, 2852, 1676, 1460, 1435, 1363, 1236, 1153, 760, 700 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{31}N_2O_3$: 407.2329, found: 407.2325.

(3*RS*,4*SR*)-*Tert*-butyl 3-(benzylamino)-4-hydroxy-4-((*E*)-styryl)piperidine-1-carboxylate hydrobromide (20)



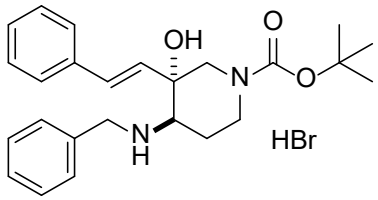
20 was prepared from **17** (12 g, 29.6 mmol) according to the **GP 5** procedure. White solid; 12.3 g, yield 85%; mp 219 – 223°C (EtOH); Rf (base) 0.3 (hexane - EtOAc 4: 1). ^{1}H NMR (DMSO-d_6, 400 MHz), δ (ppm): 1.43 (s, 9 H), 1.64 (td, *J* = 12.3, 3.8 Hz, 1 H), 1.85 (br. d., *J* = 12.7 Hz, 1 H), 2.84 (br. s., 1 H), 3.22 (br. s., 2 H), 3.76 (br. s., 1 H), 4.00 – 4.40 (br. s. + s, 3 H), 5.83 (s, 1 H), 6.76 (d, *J* = 15.7 Hz, 1 H), 6.93 (d, *J* = 15.5 Hz, 1 H), 7.29 (t, *J* = 7.0 Hz, 1 H), 7.38 (t, *J* = 7.4 Hz, 2 H), 7.44 (s, 3 H), 7.53 - 7.66 (m, 4 H), 8.47 (br. s., 1 H), 9.09 (br. s., 1 H). ^{13}C NMR (DMSO-d_6, 100 MHz), δ (ppm): 28.0 (3 C), 38.2, 40.7 (br.), 48.5, 59.9, 70.9, 79.7, 126.7, 127.1 (2 C), 127.8, 128.5 (2 C), 128.7 (2 C), 129.2, 130.4 (br., 2 C), 130.8, 132.0, 136.4, 153.6 (br.). One aliphatic signal was lost because of broadening or overlapping with the signals of the solvent. IR υ_{max}, (KBr): 3340 (br.), 2966, 2922, 2798, 1684, 1452, 1421, 1248, 1163, 974, 748, 698 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{25}H_{33}NO_2$: 409.2486, found: 409.2487.

(3*RS*,4*SR*)-3-(Benzylamino)-4-((*E*)-styryl)tetrahydro-2*H*-pyran-4-ol hydrobromide (21)



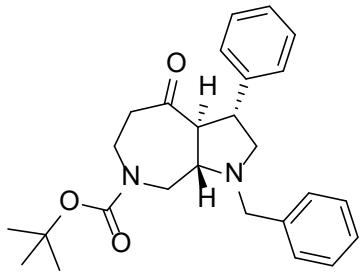
White solid; 10.4 g, yield 82%; mp 213 – 217°C (EtOH-Et_2O); Rf (base) 0.5 (hexane - EtOAc 6: 4). **21** was prepared from **18** (10 g, 32.6 mmol) according to the **GP 5** procedure with minor modifications. **18** was added to the reaction mixture as undissolved powder portionwise and **21** was precipitated from EtOH-Et_2O 1: 6 mixture. ^{1}H NMR (DMSO-d_6, 400 MHz), δ (ppm): 1.70 - 1.83 (m, 1 H), 1.88 - 2.01 (m, 1 H), 2.94 (br. s., 1 H), 3.64 - 3.82 (m, 3 H), 4.06 (dd, *J* = 11.9, 3.5 Hz, 1 H), 4.25 (br. s., 2 H), 5.79 (s, 1 H), 6.69 (d, *J* = 15.9 Hz, 1 H), 6.88 (d, *J* = 15.9 Hz, 1 H), 7.29 (t, *J* = 7.2 Hz, 1 H) 7.34 - 7.47 (m, 5 H), 7.57 (d, *J* = 6.7 Hz, 4 H), 8.45 (br. s., 1 H), 9.13 (br. s., 1 H). ^{13}C NMR (DMSO-d_6, 100 MHz), δ (ppm): 37.8 (br.), 48.9, 60.0, 62.7, 64.0, 69.7, 127.0 (2 C), 127.9 (n. + br. 2 C), 128.5 (2 C), 128.8 (2 C), 129.1, 130.4 (2 C), 131.1, 131.7, 136.3. IR υ_{max}, (KBr): 3315, 2958, 2924, 2871, 2794, 1566, 1417, 1398, 1130, 1051, 980, 748, 692 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{24}NO_2$: 310.1802, found: 310.1799.

(3*SR*,4*SR*)-*Tert*-butyl 4-(benzylamino)-3-hydroxy-3-((*E*)-styryl)piperidine-1-carboxylate hydrobromide (22)



White solid; 5.18 g, yield 86%; mp 240 – 250°C (dec.); Rf (base) 0.55 (hexane-EtOAc 1: 1). **22** was prepared from **19** (5 g, 12.3 mmol) according to the **GP 5** procedure with minor modifications. **19** was added as undissolved powder portionwise and **22** was precipitated from EtOH-Et_2O 1: 10 mixture. ^{1}H NMR (DMSO-d_6, 400 MHz), δ (ppm): 1.35 (s, 9 H), 1.74 (qd, *J* = 8.3, 4.6 Hz, 1 H), 2.15 (br. d., *J* = 12.1 Hz, 1 H), 2.68 - 2.90 (br. m., 2 H), 3.06 - 3.17 (m, 1 H), 4.00 (d, *J* = 12.9 Hz, 1 H), 4.10 (d, *J* = 12.1 Hz, 1 H), 4.27 (s, 2 H), 5.98 (s, 1 H), 6.34 (d, *J* = 15.7 Hz, 1 H), 6.95 (d, *J* = 16.4 Hz, 1 H), 7.29 (t, *J* = 7.1 Hz, 1 H), 7.38 (t, *J* = 7.1 Hz, 2 H), 7.41 - 7.50 (m, 5 H), 7.56 – 7.65 (m, 2 H), 8.39 (br. s., 1 H), 8.99 (br. s., 1 H). ^{13}C NMR (DMSO-d_6, 100 MHz), δ (ppm): 24.2, 27.7 (3 C), 41.3 (br.), 48.2, 53.3 (br.), 62.0, 70.7, 79.1, 125.9, 126.4 (2 C), 127.7, 128.3 (2 C), 128.5 (2 C), 128.8, 130.1 (2 C), 131.0, 131.5, 136.2, 153.1. IR υ_{max}, (KBr): 3294 (br.), 2968, 2800, 2703, 1685, 1571, 1458, 1433, 1365, 1248, 1159, 744, 688 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{33}N_2O_3$: 409.2486, found: 409.2485.

(3RS,3aSR,8aSR)-*Tert*-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-c]azepine-7(1H)-carboxylate (23a)

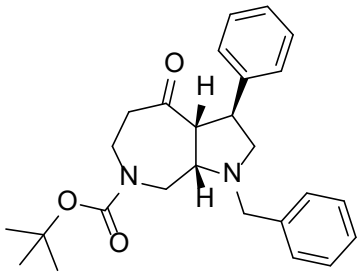


To a solution of **20** (10.0 g, 24.5 mmol) in DMSO (120 ml) 37% formaldehyde solution (3.6 mL, 48.8 mmol, 2 eq) and (+)-10-camphorsulfonic acid (2.8 g, 12.1 mmol, 0.5 eq) were added and the reaction was stirred for 24 h at 40°C. Then the solution was poured into 10% aq K_2CO_3 (400 ml) and extracted with hexane-DCM 3:1 mixture (2 x 300 ml). The organic layers were combined, dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane-DCM-Et_2O 3: 1: 0.6) to afford **23a** (7.4 g, 62%). Rf 0.3 (EtOAc), white solid, mp 110 – 112°C.

^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.48 (s, 9H), 2.41 (d, *J* = 18.8 Hz, 1H), 2.50 (td, *J* = 10.0, 3.3 Hz, 1H), 2.67-2.98 (m, 3H), 3.05-3.20 (m, 1.5H), 3.23-3.44 (m, 2.5H), 3.87-3.97 (m, 1H), 4.04 (d, *J* = 13.4 Hz, 1H), 4.17 (d, *J* = 13.4 Hz, 1H), 4.51 (d, *J* = 12.6 Hz, 0.4H), 4.74 (dd, *J* = 13.5, 2.8 Hz,

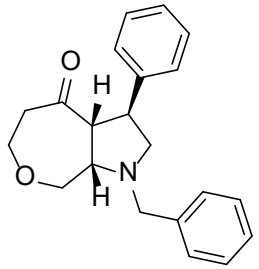
0.6H), 7.17 (t, *J* = 6.8 Hz, 1H), 7.21-7.41 (м, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 28.3 (3C), 40.6, (42.4, 42.8), (43.09, 43.13), (52.0, 53.1), (58.0, 58.1), (60.8, 61.0), (67.1, 67.3), (67.7, 67.9), (80.27, 80.30), 126.3, (127.0, 127.2), 127.4 (2C), (128.26, 128.3) (2C), (128.45, 128.48) (2C), 128.52 (2C), 138.4, 145.7, (154.1, 154.4), (207.4, 207.5). IR υ_{max}, (ZnSe): 2970, 2922, 1695, 1464, 1410, 1367, 1340, 1257, 1217, 1167, 1142, 1078, 700 см$^{-1}$. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{33}N_2O_3$: 421.2486, found: 421.2486.

(3*SR*,3a*RS*,8a*SR*)-*Tert*-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate (23b)



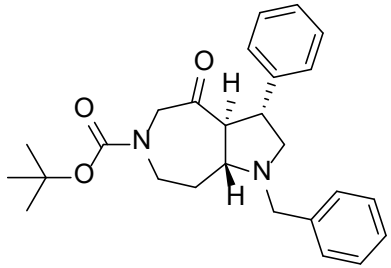
To a solution of **20** (5.0 g, 12.3 mmol) in THF (100 ml) 37% formaldehyde solution (2 g, 24.5 mmol, 2 eq) and (+)-10-camphorsulfonic acid (1.4 g, 6.0 mmol, 0.5 eq) were added and the reaction mixture was stirred for 24 h. Then the solution was evaporated in vacuo and the residue was treated with 5% aq K_2CO_3 (50 ml) and extracted with DCM (2 x 50 ml). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo to a volume of ~ 15 ml. Then MTBE (75 ml) was added and the solvents were removed in vacuo to a volume of ~40 ml. To the remaining solution an additional portion of MTBE (70 ml) was added and the mixture was maintained at room temperature until the initial crystallization was completed and then at -30°C overnight. The precipitate was filtered off, washed with Et_2O-hexane 1:1 mixture and dried to afford **23b** (2.84 g, 55%). Rf 0.45 (hexane-EtOAc 4: 1), white solid, mp 176 – 178°C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.52 + 1.53 (s + s, 9 H), 2.43 - 2.57 (m, 2 H), 2.64 (dd, *J* = 14.7, 10.3 Hz, 1.3 H), 2.73 (td, *J* = 11.7, 4.2 Hz, 0.7 H), 3.00 (t, *J* = 13.0 Hz, 0.6 H), 3.09 - 3.24 (m, 1.4 H), 3.25 - 3.55 (m, 3 H), 3.79 – 3.89 (m, 1 H), 4.08 (d, *J* = 14.7 Hz, 1 H), 4.14 (d, *J* = 13.2 Hz, 0.7 H), 4.19 - 4.35 (m, 1.3 H), 7.15 - 7.38 (m, 10 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 28.5 (3 C), 42.4, (44.8, 45.3), (45.6, 45.7), (49.5, 50.4), (57.8, 58.2), 60.3, 61.5, 62.7, 80.3, 126.6, (126.9, 127.2), 127.8 (2 C), 128.1, 128.3, 128.4 (2 C), 128.6, 128.9, (138.3, 138.6), 140.9, 154.6, (207.9, 208.0). IR υ_{max}, (ZnSe): 2974, 2927, 2860, 2812, 1699, 1454, 1417, 1367, 1240, 1161, 1113, 1097, 754, 700 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{33}N_2O_3$: 421.2486, found: 421.2485.

(3*SR*,3a*RS*,8a*SR*)-1-Benzyl-3-phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (24b).



24b (5.10 g, 82%) was prepared from **21** (6.0 g, 19.4 mmol) according to the procedure for **23b**. Rf 0.4 hexane-EtOAc 2: 1), mp 167 – 168°C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 2.55 (dd, *J* = 11.4, 9.0 Hz, 1 H), 2.61 (ddd, *J* = 11.9, 4.9, 2.5 Hz, 1 H), 2.86 (ddd, *J* = 11.4, 11.0, 4.3 Hz, 1 H), 3.22 - 3.32 (m, 2 H), 3.37 (td, *J* = 9.9, 2.5 Hz, 1 H), 3.53 (d, *J* = 13.1 Гц, 1 H), 3.55 (t, *J* = 10.2 Hz, 1 H), 3.69 (ddd, *J* = 12.0, 10.6, 2.5 Hz, 1 H), 3.79 (td, *J* = 10.6, 6.5 Hz, 1 H), 3.97 (dd, *J* = 12.9, 2.5 Hz, 1 H), 3.99 - 4.07 (m, 2 H), 7.17 - 7.24 (m, 1 H), 7.24 - 7.40 (m, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 42.9, 47.1, 58.7, 60.8, 61.7, 62.9, 69.2, 73.0, 126.6, 127.2, 127.7 (2 C), 128.3 (2 C), 128.4 (2 C), 128.7 (2 C), 138.4, 140.8, 207.9. IR υ_{max}, (KBr): 3028, 2964, 2927, 2854, 2812, 1699, 1495, 1454, 1377, 1246, 1142, 1126, 758, 750, 700 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{24}NO_2$: 322.1802, found: 322.1808.

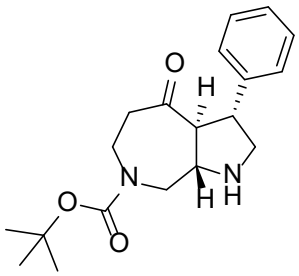
(3*RS*,3a*SR*,8a*RS*)-*Tert*-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate (25a)



To a solution of **22** (5.0 g, 12.3 mmol) in DCM (60 ml) Na_2SO_4 (12 g, 84.5 mmol, 7 eq) and (+)-10-camphorsulfonic acid (1.4 g, 6.0 mmol, 0.5 eq) were added and then 37% formaldehyde solution (2 g, 24.5 mmol, 2 eq) was added in one portion under vigorous stirring. The reaction mixture was stirred for 24 h, then solids were filtered off and washed with DCM (50 ml). The organic solutions were combined and evaporated in vacuo. The residue was treated with 5% aq K_2CO_3 (50 ml) and extracted with DCM (2 x 50 ml). The combined organic extracts were dried with Na_2SO_4 and concentr ated in vacuo to a volume of ~ 15 ml. Then hexane (75 ml) was added and the solvents were removed in vacuo to a volume of ~50 ml. The mixture was maintained at room temperature until the initial crystallization was completed and then at 0°C overnight. The precipitate was filtered off, washed with hexane and dried to afford **25a** (4.64 g, 90%). Rf 0.65 (hexane-EtOAc 2: 1), white solid, m p. 147 – 148°C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.25 (s, 5 H), 1.49 (s, 4 H), 1.88 - 2.03 (m, 0.5 H), 2.05 - 2.28 (m, 1.5 H), 2.28 - 2.43 (m, 1 H), 2.53 – 2.65 (m, 1 H), 2.72 (q, *J* = 13.0 Hz, 1 H), 3.04 (t, *J* = 9.6 Hz, 1 H), 3.11 - 3.30 (m, 2 H), 3.45 (dd, *J* = 18.6, 16.6 Hz, 1 H), 3.88 (t, *J* = 6.8 Hz, 1 H), 4.14 (d, *J* = 13.0 Hz, 1 H), 4.22 (d, *J* = 15.1

Hz, 0.5 H), 4.36 (d, *J* = 15.0 Hz, 0.5 H), 4.47 (d, *J* = 19.0 Hz, 0.5 H), 4.75 (d, *J* = 18.6 Hz, 0.5 H), 7.10 - 7.10 (m, 1 H), 7.19 - 7.42 (m, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): (28.0 (3 C), 28.3 (3 C)), (33.0, 33.8), (40.0, 40.3), (46.8, 47.2), (58.0, 58.1), (58.2, 58.8), (60.3, 60.9), (65.5, 66.3), (67.4, 68.0), (80.6, 80.8), (126.0, 126.2), 127.0 (2 C), 127.2, 128.3 (2 C), 128.4 (2 C), 128.5 (2 C), (138.7, 138.8), (146.0, 146.6), (154.4, 155.1), (207.9, 208.2). IR υ_{max}, (KBr): 2979, 2958, 2800, 1714, 1695, 1454, 1415, 1392, 1365, 1246, 1165, 758, 704 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calc. for $C_{26}H_{33}N_2O_3$: 421.2486, found: 421.2482.

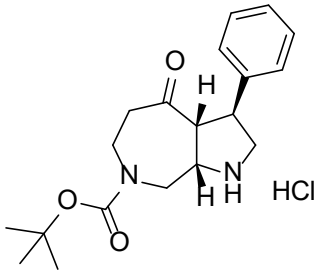
(3*RS*,3a*SR*,8a*SR*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate (26a)



To a solution of **20** (6.0 g, 14.7 mmol) in DMSO (75 ml) 37% formaldehyde solution (2.4 g, 29.6 mmol, 2 eq) and (+)-10-camphorsulfonic acid (1.7 g, 7.35 mmol, 0.5 eq) were added and the reaction was stirred for 24 h at 40^{O}C. Then the solution was poured into 2% aq K_2CO_3 (200 ml) and extracted with hexane-DCM 3:1 mixture (2 x 200 ml). The organic layers were combined, dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane-DCM-Et_2O 3: 1: 0.6) to afford 9: 1 mixture of **23a** and **23b** (4.45 g, 72%, d.e. **23a** 80%). The mixture was dissolved in MeOH (50 ml) and hydrogenated with 5% Pd/C (0.45 g, 10% by weight) under H_2 atmosphere (1 bar) until the reaction was completed (~ 24 h). Pd/C was filtered off through celites, MeOH was evaporated in vacuo. The residue was subjected to chromatographic separation (SiO_2, hexane-DCM-Et_2O gradient from 3: 1: 4 to 0: 0: 1) to afford **26a** (2.9 g, 84% from the mixture of **23a** and **23b**, 60% for 2 steps from **20**). Also **26b** (0.31 g, 9% from the mixture of **23a** and **23b,** 6.4% for 2 steps from **20**) was obtained. **26a**: Rf 0.3 (EtOAc), mp 105 – 107°C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.46 (s, 9 H), 2.03 (br. s., 1 H), 2.37 (t, *J* = 2.7 Hz, 0.45 H), 2.42 (t, *J* = 2.5 Hz, 0.55 H), 2.63 – 3.37 (m, 6 H), 3.49 (t, *J* = 9.5 Hz, 1 H), 3.88 – 4.08 (m, 1.6 H), 4.16 (d, *J* = 14.3 Hz, 0.4 H), 4.36 (d, *J* = 12.2 Hz, 0.4 H), 4.50 (dd, *J* = 13.4, 3.4 Hz, 0.6 H), 7.16 – 7.24 (m, 1 H), 7.25 – 7.35 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 28.3 (3 C), (42.7, 42.8), (43.2, 43.3), (44.8, 45.1), (53.4, 54.1), 53.5, (62.2, 62.8), (66.0, 66.3), 80.4, 126.5, 127.5 (2 C),

128.6 (2 C), (143.2, 143.5), 154.4, 207.4. IR υ_{max}, (KBr): 3423 (br.), 3244 (br.), 2979, 2856, 1697, 1457, 1417, 1365, 1250, 1221, 1169, 756, 700 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{27}N_2O_3$: 331.2016, found: 331.2020.

(3*SR*,3a*RS*,8a*SR*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate hydrochloride (26b)

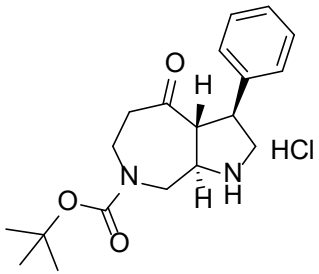


(A) From 23b: 23b (2.4 g, 5.7 mmol) was dissolved in MeOH (30 ml), the solution was acidified with 2 M HCl in MeOH to pH~5, 5% Pd/C (0.24 g, 10% by weight) was added and the mixture was stirred under H_2 atmosphere (1 bar) until the reaction was completed (~ 24 h). Pd/C was filtered off through celites, MeOH was evaporated in vacuo. The residue was crystallized from EtOH – Et_2O mixture to afford **26b** (1.89 g, 90%). Rf (base) 0.4 (EtOAc). White solid, mp 102 – 105°C.

(**B) From 35:** To a solution of **35** (3.5 g, 11 mmol) in DCM (60 ml) (+)-10-camphorsulfonic acid (2.3 g, 9.9 mmol, 0.9 eq) and Na_2SO_4 (11 g, 77 mmol, 7 eq) were added and then under vigorous stirring 37% formaldehyde solution (0.94 g, 11.6 mmol, 1.05 eq.) was added in one portion. The reaction mixture was stirred for 24 h, solids were filtered off and washed with DCM (50 ml). The organic solutions were combined and washed with 5% aq K_2CO_3 (50 ml). The organic layer was separated and the aq. layer was extracted with DCM (50 ml). The organic extracts were combined, dried with Na_2SO_4 and concentrated in vacuo. The residue was subjected to chromatographic separation (SiO_2, hexane-DCM-Et_2O gradient from 3: 1: 4 to 0: 0: 1) to afford **26b** (2.6 g, 72%). Also **26a** (0.22 g, 6%) was obtained.

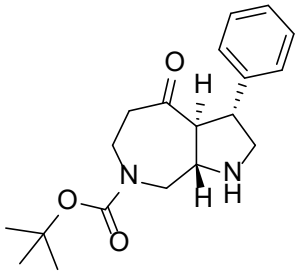
^1H NMR ($CDCl_3$, 400 MHz), δ (ppm):1.50 (s, 9 H), 2.10 (br. s., 1 H), 2.44 - 2.56 (m, 1 H), 2.57 - 2.82 (m., 2 H), 2.97 (t, *J* = 10.6 Hz, 1 H), 3.03 - 3.26 (m, 1 H), 3.31 - 3.57 (m, 2 H), 3.75 - 4.03 (m, 2.4 H), 4.04 - 4.22 (m, 1.6 H), 7.15 - 7.37 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 28.4 (3 C), (44.4, 45.0), (46.5, 47.0), (50.5, 50.7), (55.1, 55.5), (57.3, 58.4), (63.7, 63.9), 80.4, 126.6, 127.6 (2 C), 128.6 (2 C), 141.9, (154.5, 154.6), (208.6, 208.8). IR υ_{max}, (KBr): 3444 (br.), 3182, 2978, 2931, 2854, 1691, 1415, 1365, 1225, 1169, 945, 754, 702 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{27}N_2O_3$: 331.2016, found: 331.2018.

(3*S*,3a*R*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate hydrochloride ((+)-26a)



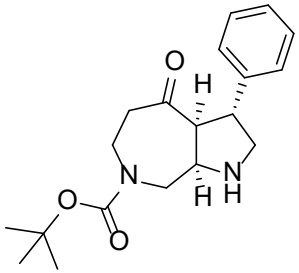
(+)-26a (4.85 g, 91%) was prepared from **52a** (7 g, 16.1 mmol) according to the procedure for **26a**. Rf 0.3 (EtOAc), $[\alpha]_D^{23}$ = + 57.9 (c 1, $CHCl_3$). White solid, mp 133 – 135°C. ^{1}H NMR (DMSO-d_6, 400 MHz), δ (ppm): 1.39 (s, 9H), 2.51 - 2.64 (m, 2H), 3.22 (t, *J* = 10.9 Hz, 1H), 3.28 - 3.66 (m, 3H), 3.70 (t, *J* = 10.5 Hz, 1H), 3.79 - 3.93 (m, 2H), 3.95 - 4.09 (m, 1H), 4.27 - 4.43 (m, 1H), 7.20 - 7.27 (m, 1H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.43 (d, *J* = 7.3 Hz, 2H), 10.18 (br.s., 2H). ^{13}C NMR (DMSO-d_6, 100 MHz), δ (ppm): 27.9 (3C), 42.3, (41.9, 43.1), 43.4, (47.4, 48.5), (49.5, 49.7), (58.5, 59.0), (60.0, 60.3), (79.8, 79.9), 127.2, 128.1 (2C), 128.5 (2C), (138.8, 139.0), (153.2, 153.6), 205.3. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{27}N_2O_3$: 331.2016, found: 331.2015.

(3*R*,3a*S*,8a*S*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((-)-26a)



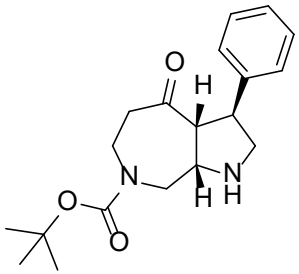
(-)-26a (5.5 g, 90%) was prepared from **55a** (8.0 g, 18.4 mmol) according to the procedure for **26a**. Rf 0.3 (EtOAc), a light-yellow solid with mp 140 – 144°C, $[\alpha]_D^{23}$ = - 57.1 (c 1, $CHCl_3$). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{27}N_2O_3$: 331.2016, found: 331.2014.

(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((-)-26b)



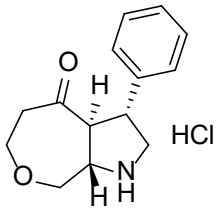
To a solution of **46** (7.5 g, 17.8 mmol) in DCM (90 ml) Na_2SO_4 (17.5 g, 123 mmol, 7 eq) and (+)-10-camphorsulfonic acid (2.0 g, 8.62 mmol, 0.5 eq) were added and then 37% formaldehyde solution (2.9 g, 35.8 mmol, 2 eq) was added in one portion under vigorous stirring. The reaction mixture was stirred for 24 h at 40^{O}C, cooled to room temperature, solids were filtered off and washed with DCM (50 ml). The organic solutions were combined, washed with 5% aq K_2CO_3 (100 ml), dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane-DCM-Et_2O 3: 1: 0.6) to afford 3: 1 mixture of **52a** and **52b** (6.8 g, 88%). The mixture was dissolved in MeOH (80 ml) and hydrogenated with 5% Pd/C (0.68 g, 10% by weight) under H_2 atmosphere (1 bar) until the reaction was completed (~ 24 h). Pd/C was filtered off through celites, MeOH was evaporated in vacuo. The residue was subjected to chromatographic separation (SiO_2, hexane-DCM-Et_2O gradient from 3: 1: 4 to 0: 0: 1) to afford (-)-**26b** (1.15 g, 22%). Also (+)-**26a** (3.25 g, 63%) was isolated. (-)-**26b**: Rf 0.4 (EtOAc), mp 90 – 92°C, $[\alpha]_D^{23}$ = - 59.7 (c 0.6, $CHCl_3$). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{27}N_2O_3$: 331.2016, found: 331.2015.

(3*S*,3a*R*,8a*S*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((+)-26b)



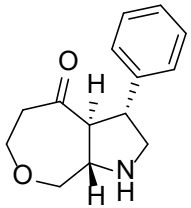
According to the procedure for (-)-**26b** 1: 1.3 mixture of **55a** and **55b** (8.7 g, 85%) was obtained from **49** (10.0 g, 23.7 mmol). The mixture was dissolved in MeOH (80 ml) and hydrogenated with 5% Pd/C (0.68 g, 10% by weight) under H_2 atmosphere (1 bar) until the reaction was completed (~ 24 h). Pd/C was filtered off through celites, MeOH was evaporated in vacuo. The residue was subjected to chromatographic separation (SiO_2, hexane-DCM-Et_2O gradient from 3: 1: 4 to 0: 0: 1) to afford (+)-**26b** (3.2 g, 48%) as a light-yellow solid with mp 85 – 87°C, $[\alpha]_D^{23}$ = + 93.7 (c 1, $CHCl_3$). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{27}N_2O_3$: 331.2016, found: 331.2016.

(3*RS*,3a*SR*,8a*SR*)-3-phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one hydrochloride (27a)



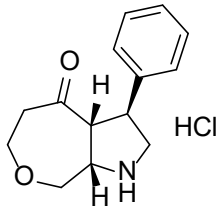
39a (0.50 g, 1.26 mmol, contained ~ 12% **39b** - d.e. **39a** 76%) was dissolved in MeOH (6 ml), 5% Pd/C (0.05 g, 10% by weight) was added and the mixture was stirred under H_2 atmosphere (1 bar) until the reaction was completed (~ 24 h). Pd/C was filtered off through celites, the solution was acidified with 2 M HCl in MeOH to pH ~ 5, MeOH was evaporated in vacuo. The residue was crystallized from EtOH – Et_2O mixture to afford **27a** (0.30 g, 82%, contained ~15.4% of **27b** – d.e. **27a** 69%). Rf (base) 0.4 (Et_2O-MeOH 10: 1). Chemical shifts of the signals of major isomer in ^1H and ^{13}C NMR spectra coincide with the signals of **(-)-27a**. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{18}NO_2$: 232.1332, found: 232.1332.

(3*R*,3a*S*,8a*S*)-3-phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one ((-)-27a)



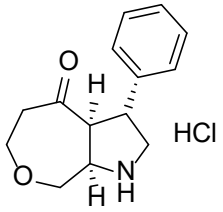
56a (1.4 g, 4.18 mmol) was dissolved in MeOH (20 ml), 5% Pd/C (0.14 g, 10% by weight) was added and the mixture was stirred under H_2 atmosphere (1 bar) until the reaction was completed (~ 24 h). Pd/C was filtered off through celites, the solution was evaporated in vacuo and the residue was purified by column chromatography (SiO_2, Et_2O-MeOH 15: 1) to afford **(-)-27a** (0.87 g, 90%) as a light-yellow solid with mp. 60 – 62°C. Rf 0.4 (Et_2O-MeOH 10: 1), $[\alpha]_D^{23}$ - 22.5 (c = 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz), δ (ppm): 2.13 (br. s., 1 H), 2.45 (dt, *J* = 19.0, 2.3 Hz, 1 H), 2.74 (ddd, *J* = 19.0, 11.9, 4.5 Hz, 1 H), 3.11 - 3.24 (m, 2 H), 3.30 (t, *J* = 9.2 Hz, 1 H), 3.47 (dd, *J* = 10.4, 9.3 Hz, 1 H), 3.54 (dd, *J* = 11.8, 9.9 Hz, 1 H), 3.78 - 3.94 (m, 2 H), 4.11 (ddd, *J* = 13.3, 4.4, 2.9 Hz, 1 H), 4.28 (dd, *J* = 11.7, 3.9 Hz, 1 H), 7.16 - 7.23 (m, 1 H), 7.25 - 7.36 (m, 4 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 44.8, 45.2, 53.6, 62.2, 66.2, 66.5, 77.0, 126.5, 127.4 (2 C), 128.5 (2 C), 143.3, 207.1. IR υ_{max}, (KBr): 3328 (br.), 2947, 2875, 1701, 1250, 1159, 1134, 914, 843, 758, 702 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{14}H_{18}NO_2$: 232.1332, found: 232.1333.

(3*SR*,3a*RS*,8a*SR*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one hydrochloride (27b)



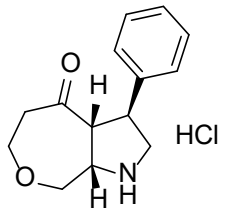
27b(3.55 g, 95%) was prepared from **24b** (4.5 g, 14 mmol) according to the procedure for **27**. Rf (base) 0.4 (Et_2O-MeOH 10: 1), white solid, mp 106 - 108°C. ^1H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.99 (br. s., 1 H), 2.67 (ddd, *J* = 11.9, 5.3, 3.5 Hz, 1 H), 2.83 (ddd, *J* = 11.8, 9.6, 4.7 Hz, 1 H), 2.99 (t, *J* = 10.3 Hz, 1 H), 3.42 (dd, *J* = 9.6, 8.3 Hz, 1 H), 3.45 - 3.57 (m, 2 H), 3.68 - 3.82 (m, 3 H), 3.92 (dt, *J* = 11.8, 5.0 Hz, 1 H), 3.98 (dd, *J* = 13.1, 3.2 Hz, 1 H), 7.18 - 7.35 (m, 5 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 45.9, 47.6, 55.2, 58.5, 64.2, 68.8, 72.9, 126.7, 127.5 (2 C), 128.6 (2 C), 141.6, 208.1. Hydrochloride: m. p. 210 – 220^{O}C (dec.). ^1H NMR (DMSO-d_6, 400 MHz), δ (ppm): 2.61 (dt, *J* = 8.4, 4.1 Hz, 1 H), 2.97 (ddd, *J* = 12.5, 9.8, 4.8 Hz, 1 H), 3.20 (t, *J* = 11.2 Hz, 1 H), 3.59 (dd, *J* = 10.7, 7.5 Hz, 1 H), 3.66 (td, *J* = 12.5, 3.6 Hz, 1 H), 3.72 - 3.82 (m, 2 H), 3.82 - 3.93 (m, 2 H), 4.07 (dd, *J* = 13.5, 2.5 Hz, 1 H), 4.24 (ddd, *J* = 10.1, 7.7, 2.5 Hz, 1 H), 7.22 - 7.29 (m, 1 H), 7.30 - 7.42 (m, 4 H), 10.00 (br. s., 2 H). ^{13}C NMR (DMSO-d_6, 100 MHz), δ (ppm): 43.2, 44.3, 49.7, 56.7, 59.3, 67.2, 67.7, 127.2, 127.9 (2C), 128.6 (2C), 138.8, 206.0. IR υ_{max}, (KBr): 3423 (br., w.), 2858, 2740, 2611, 1705, 1140, 756, 698 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{18}NO_2$: 232.1332, found: 232.1332.

(3*R*,3a*S*,8a*R*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one hydrochloride ((+)-27b)



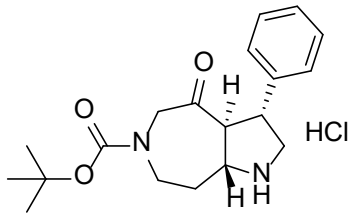
(+)-27b (1.82 g, 91%) was prepared from **53b** (2.5 g, 7.46 mmol) according to the procedure for **27a**. White solid, mp 217 – 223°C, $[\alpha]_D^{23}$ + 5.0 (c = 1, MeOH). Rf (base) 0.4 (Et_2O-MeOH 10: 1). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{18}NO_2$: 232.1332, found: 232.1335.

(3*S*,3a*R*,8a*S*)-3-phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one hydrochloride ((-)-27b)



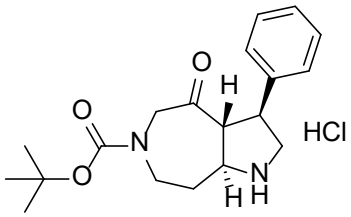
(-)-27b (1.88 g, 94%) was prepared from 5**6b** (2.5 g, 7.46 mmol) according to the procedure for **27a**. White solid, mp 225 – 230°C, $[\alpha]_D^{23}$ – 9.0 (c = 1, MeOH). Rf (base) 0.4 (Et_2O-MeOH 10: 1). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{14}H_{18}NO_2$: 232.1332, found: 232.1334.

(3*RS*,3a*SR*,8a*RS*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate hydrochloride (28a)



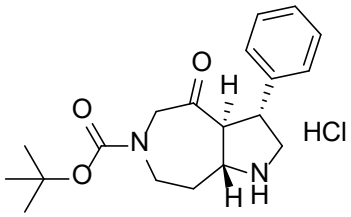
28a (3.1 g, 89%) was prepared from **25a** (4.0 g, 9.52 mmol) according to the procedure for **27a**. Rf (base) 0.25 (EtOAc). White solid, mp 155 – 157°C (dec.) ^{1}H NMR (DMSO-d_6, 400 MHz), δ (ppm): 1.27 (s, 4 H), 1.47 (s., 5 H), 2.13 (t, *J* = 14.1 Hz, 1 H), 2.40 - 2.67 (m, 1 H), 2.94 - 3.12 (m, 1 H), 3.16 – 3.35 (m, 2 H), 3.59 - 3.90 (m, 4 H), 3.94 (d, *J* = 14.7 Hz, 0.6 H), 4.04 (d, *J* = 15.4 Hz, 0.4 H), 4.17 (d, *J* = 19.0 Hz, 0.4 H), 4.29 (d, *J* = 18.7 Hz, 0.6 H), 7.19 - 7.27 (m, 1 H), 7.31 (t, *J* = 7.4 Hz, 2 H), 7.39 (d, *J* = 7.0 Hz, 2 H), 10.18 (br. s., 2 H). ^{13}C NMR (DMSO-d_6, 100 MHz), δ (ppm): (27.8, 27.9) (3 C), (30.2, 30.6), (43.0, 43.1), 45.3, (49.0, 49.1), (57.6, 58.3), (58.5, 58.8), 61.1, (79.9, 80.2), 127.1, (127.7, 127.9) (2 C), (128.4, 128.5) (2 C), (139.9, 140.2) (153.5, 154.7), (205.2, 205.3). IR υ_{max}, (KBr): 3361 (br.), 2974, 2922, 2792, 2760, 2721, 1718, 1703, 1460, 1419, 1367, 1246, 1167, 700 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{27}N_2O_3$: 331.2016, found: 331.2019.

(3*S*,3a*R*,8a*S*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate ((+)-28a)



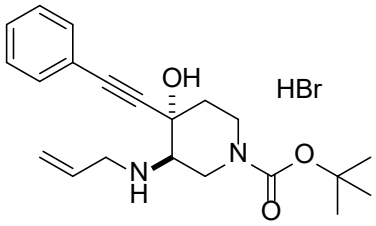
(+)-28a (1.84 g, 87%) was prepared from **54a** (2.5 g, 5.76 mmol) according to the procedure for **27a**. Rf (base) 0.25 (EtOAc). White solid, mp 220 – 227°C (dec.), $[\alpha]_D^{23}$ + 39.8 (c = 1, MeOH). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{27}N_2O_3$: 331.2016, found: 331.2017.

(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate ((-)-28a)



(-)-28a (1.58 g, 85%) was prepared from **57a** (2.2 g, 5.07 mmol) according to the procedure for **27a**. Rf (base) 0.25 (EtOAc). White solid, mp 210 – 214°C (dec.), $[\alpha]_D^{23}$ - 39.3 (c = 1, MeOH). HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{19}H_{27}N_2O_3$: 331.2016, found: 331.2022.

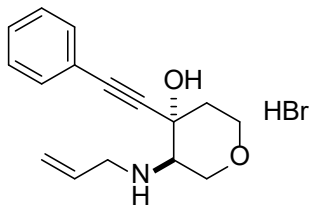
(3*RS*,4*SR*)-*Tert*-butyl 3-(allylamino)-4-hydroxy-4-(phenylethynyl)piperidine-1-carboxylate hydrobromide (31)



31 (10.9 g, 61% for 2 steps) was prepared from epoxide **14** (~50 mmol) and allylamine (8.5 g, 149 mmol, 3. eq) according to the procedure **GP-4** with minor modifications. The reaction was carried out at 50°C for 216 h, and chromatographic purification of the product on silica gel was run using hexane-DCM-EtOAc 10: 3: 3 mixture. Analytically pure sample of **31** was prepared according to the procedure for **20**. Rf (base) 0.25 (hexane-EtOAc 4: 1). White solid, mp 155 – 160°C.

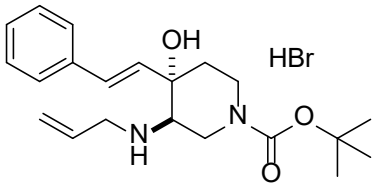
^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 1.42 (s, 9 H), 1.71 (td, *J* = 12.8, 4.4 Hz, 1 H), 2.12 (d, *J* = 12.9 Hz, 1 H), 3.01 (br. s., 3 H), 3.75 (br. d., *J* = 4.7 Hz, 2 H), 3.97 (br. d., *J* = 12.8 Hz, 1 H), 4.29 (br. s., 1 H), 5.49 (d, *J* = 10.4 Hz, 1 H), 5.57 (d, *J* = 17.2 Hz, 1 H), 5.87 – 5.98 (m, 1 H), 6.75 (s, 1 H), 7.40 - 7.48 (m, 3 H), 7.54 - 7.61 (m, 2 H), 8.93 + 9.00 (br. s. + br. s., 2 H). 13C NMR (100 MHz, DMSO-d_6), δ (ppm): 28.0 (3 C), 39.0, 41.2 (br.), 41.9 (br.), 48.7, 60.1, 68.6, 79.9, 86.0, 88.3, 121.3, 123.7, 128.6 (2 C), 128.7, 129.3, 131.9 (2 C), 153.5. IR υ_{max}, (KBr): 3280 (br.), 2902, 2775, 2670, 2233 (w.), 1697, 1691, 1570, 1425, 1390, 1246, 1149, 877, 760, 690 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{29}N_2O_3$: 357.2173, found: 357.2173.

(3*RS*,4*SR*)-3-(Allylamino)-4-(phenylethynyl)tetrahydro-2*H*-pyran-4-ol hydrobromide (32)



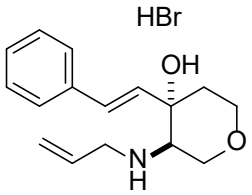
32 (8.1 g, 63% for 2 steps) was prepared from epoxide **15** (~50 mmol) and allylamine (8.5 g, 149 mmol, 3. eq) according to the procedure **GP-4** with minor modifications. The reaction was carried out at 40°C for 72 h, and chromatographic purification of the product on silica gel was run using hexane-EtOAc 2: 1 mixture. Analytically pure sample of **32** was obtained by crystallization from EtOH – Et2O mixture. R_f (base) 0.35 (hexane - EtOAc 1: 1). White solid, mp 198-203°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 1.88 (td, *J* = 13.2, 4.6 Hz, 1 H), 2.14 (d, *J* = 13.3 Hz, 1 H), 3.04 - 3.13 (m, 1 H), 3.52 (t, *J* = 11.2 Hz, 1 H), 3.59 (td, *J* = 11.7, 1.8 Hz, 1 H), 3.74 (d, *J* = 5.2 Hz, 2 H), 3.90 (dt, *J* = 11.6, 2.9 Hz, 1 H), 4.20 (dd, *J* = 11.5, 4.1 Hz, 1 H), 5.47 (d, *J* = 10.7 Hz, 1 H), 5.57 (d, *J* = 17.1 Hz, 1 H), 5.85 - 5.98 (m, 1 H), 6.71 (s, 1 H), 7.40 - 7.48 (m, 3 H), 7.53 - 7.60 (m, 2 H), 8.89 (br. s., 2 H). ^{13}C NMR (100 MHz, DMSO-d_6), δ (ppm): 39.8 (overlaps with the signal of the solvent),48.6, 60.0, 63.9, 64.9, 67.3, 86.6, 88.0, 121.3, 123.7, 128.6 (2 C), 128.9, 129.2, 131.8 (2 C). IR υ_{max}, (KBr): 3222(br.), 2991, 2868, 2767, 2679, 2632, 2522, 2424, 2237, 2222,1595, 1489, 1435, 1419, 1128, 1107, 1063, 987, 883, 843, 769, 600cm^{-1}.HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{20}NO_2$: 258.1489, found: 258.1493.

(3*RS*,4*SR*)-*Tert*-butyl 3-(allylamino)-4-hydroxy-4-((*E*)-styryl)piperidine-1-carboxylate hydrobromide (33)



33 (8.30 g, 84%) was prepared from **31** (8.0 g, 22.5 mmol) according to the procedure **GP-5** with minor modifications. The reaction was carried out for 1 h at -5 - +5°C and **33** was precipitated from EtOH-Et_2O 1: 4 mixture. R_f (base) 0.5 (hexane-Et_2O 7: 3). White solid, mp 210 – 215°C. ^{1}H NMR (DMSO-*d*$_6$, 400 MHz), δ (ppm): 1.43 (s, 9 H), 1.72 (td, *J* = 11.7, 4.3 Hz, 1 H), 1.90 (d, *J* = 13.3 Hz, 1 H), 3.02 (br. s., 1 H), 3.27 (br. s., 2 H), 3.67 (br. s., 2 H), 3.75 (br. d., *J* = 13.5 Hz, 1 H), 4.10 (br. s., 1 H), 5.46 (d, *J* = 10.0 Hz, 1 H), 5.52 (d, *J* = 17.1 Hz, 1 H), 5.81 - 5.96 (m, 2 H), 6.71 (d, *J* = 15.7 Hz, 1 H), 6.87 (d, *J* = 15.7 Hz, 1 H), 7.28 (t, *J* = 7.1 Hz, 1 H), 7.37 (t, *J* = 7.7 Hz, 2 H), 7.57 (d, *J* = 7.4 Hz, 2 H), 8.42 (br. s., 1 H), 8.77 (br. s., 1 H). ^{13}C NMR (DMSO-*d*$_6$, 100 MHz), δ (ppm): 28.0 (3 C), 37.7, 40.4 (br., 2 C), 47.9, 60.1, 70.8, 79.7, 123.5, 126.9, 127.1 (2 C), 127.9, 128.5 (2 C), 128.7, 131.9, 136.4, 153.8. IR υ_{max}, (KBr): 3319 (br.), 2974, 2787, 1697, 1572, 1427, 1365, 1248, 1155, 1092, 983, 867, 746, 690 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{31}N_2O_3$: 359.2329, found: 359.2324.

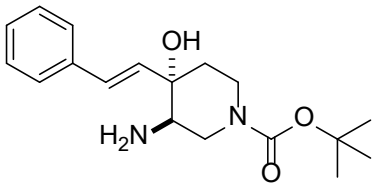
(3*RS*,4*SR*)-3-(Allylamino)-4-((*E*)-styryl)tetrahydro-2*H*-pyran-4-ol hydrobromide (34)



34 (8.5 g, 86%) was prepared from **32** (7.5 g, 29.2 mmol) according to the procedure **GP-5** with minor modifications. The reaction was carried out for 75 min at -5 - 0°C. After the reaction was worked up the product was purified by chromatography (SiO2, hexane – DCM – EtOAc mixture, gradient from 10: 1: 2.2 to 10: 1: 11) and then **34** was precipitated from EtOH-Et_2O 1: 4 mixture. R_f (base) 0.2 (hexane-EtOAc 1: 1). White solid, mp 199-204^{v}C. ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 1.76 - 1.86 (m, 1 H), 1.93 - 2.03 (m, 1 H), 3.06 (br. s., 1 H), 3.60 – 3.71 (m, 3 H), 3.72 - 3.85 (m, 2 H), 4.07 (dd, *J* = 12.0, 3.3 Hz, 1 H), 5.43 (d, *J* = 10.1 Hz, 1 H), 5.52 (d, *J* = 17.0 Hz, 1 H), 5.80 – 5.94 (m, 2 H), 6.66 (d, *J* = 15.8 Hz, 1 H), 6.85 (d, *J* = 15.8 Hz, 1 H), 7.29 (t, *J* = 7.3 Hz, 1 H), 7.38 (t, *J* = 7.5 Hz, 1 H), 7.55 (d, *J* = 7.5 Hz, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6), δ (ppm): 37.4, 48.0, 60.1, 62.5, 64.0, 69.6, 123.5, 126.9 (2 C), 127.9, 128.1, 128.5 (2 C), 128.9, 131.6, 136.3.

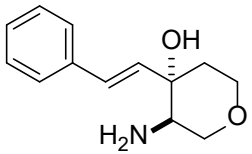
IR υ_{max}, (KBr): 3313(br.), 2954, 2879, 2785, 2679, 1566, 1437, 1400, 1174, 1130, 1101, 1055, 985, 974, 748, 692, 633cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{16}H_{22}NO_2$: 260.1645, found: 260.1644.

(3*RS*,4*SR*)-*Tert*-butyl 3-amino-4-hydroxy-4-((*E*)-styryl)piperidine-1-carboxylate (35)



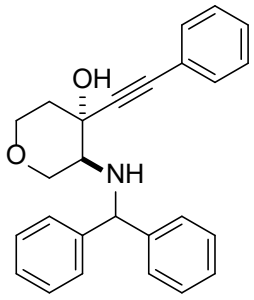
To a solution of **33** (5.0 g, 14 mmol) in DCM (70 ml) DMBA (6.5 g, 41.7 mmol, 3 eq) and $Pd(PPh_3)_4$ (0.33 g, 0.285 mmol, 0.02 eq) were added and the mixture was stirred at 40°C until the reaction was completed (~1 h). Then the reaction mixture was treated with 10% aq. K_2CO_3 (100 ml), the organic layer was separated and the aq. layer was extracted with DCM (2 x 100 ml). The combined organic extracts were dried with Na_2SO_4, the solvents were removed in vacuo. After purification of the residue by column chromatography (SiO_2, Et_2O-MeOH 10: 1) **35** (4.0 g, 90%) was obtained. Analytically pure sample of **35** was obtained by crystallization from MTBE. R_f 0.25 (Et_2O). White solid, mp 99 – 101°C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.47 (s, 9 H), 1.68 (ddd, *J* = 13.3, 9.2, 4.1 Hz, 1 H), 1.95 - 2.07 (m, 1 H), 2.79 (dd, *J* = 7.5, 3.4 Hz, 1 H), 3.08 (br. s., 1 H), 3.37 (br. s., 1 H), 3.77 (dt, *J* = 13.9, 4.8 Hz, 1 H), 3.84 (br. s., 1 H), 6.48 (d, *J* = 15.8 Hz, 1 H), 6.79 (d, *J* = 16.2 Hz, 1 H), 7.22 – 7.29 (m, 1 H), 7.33 (t, *J* = 7.9 Hz, 2 H), 7.40 (d, *J* = 7.1 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 28.5 (3C), (35.3 (br.), 36.0 (br.)), (40.2 (br.), 41.1 (br.)), 47.9, 56.3, 73.3, 80.0, 126.7 (2C), 128.0, 128.8 (2C), 129.9 (br.) 131.5, 136.6. 155.2. IR υ_{max}, (ZnSe): 3359, 3292, 2974, 2912, 1689, 1406, 1365, 1275, 1250, 1155, 1076, 1001, 968, 960, 754, 694 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{18}H_{27}N_2O_3$: 319.2016, found: 319.2019.

(3*RS*,4*SR*)-3-Amino-4-((*E*)-styryl)tetrahydro-2*H*-pyran-4-ol hydrochloride (36)



36 (4.65 g, 92%) was prepared from **34** (6 g, 23.2 mmol) according to the procedure for **35** with minor modifications. After work up of reaction mixture with 10% aq. K_2CO_3 (100 ml) product was extracted with DCM (3 x 600 ml). Chromatographic purification of the product was run using silica gel pre-treated with DCM/NH3 and DCM/NH_3 – MeOH 100: 1 mixture as eluent. Analytically pure sample of **36** was obtained by crystallization of hydrochloride salt from EtOH – Et2O mixture. R_f (base) 0.25 (DCM/NH_3 – MeOH 20: 1). White solid, mp 164-167°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ (ppm): 1.64 (dt, *J* = 14.1, 4.4 Hz, 1 H), 2.07 - 2.20 (m, 1 H), 3.02 (br. s., 1 H), 3.67 - 3.81 (m, 2 H), 3.92 (dd, *J* = 11.8, 2.3 Hz, 1 H), 5.68 (s, 1 H), 6.53 (d, *J* = 15.9 Hz, 1 H), 6.74 (d, *J* = 15.9 Hz, 1 H), 7.26 (t, *J* = 6.9 Hz, 1 H), 7.35 (t, *J* = 7.5 Hz, 2 H), 7.53 (d, *J* = 7.7 Hz, 2 H), 8.32 (br. s., 3H). ^{13}C NMR (100 MHz, DMSO-d_6), δ (ppm): 34.3 (br.), 54.2, 63.6, 64.6, 68.8, 126.9 (2 C), 127.7, 128.5 (2 C), 130.57, 130.63 (br.), 136.5. IR υ_{max}, (KBr): 3257 (br.), 3005, 2858, 1618, 1574, 1508, 1346, 1146, 1066, 976, 750, 696 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{13}H_{18}NO_2$: 220.1332, found: 220.1332.

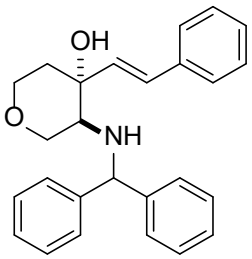
(3*RS*,4*SR*)-3-(Benzhydrylamino)-4-(phenylethynyl)tetrahydro-2*H*-pyran-4-ol (37)



37 (2.3 g, 60%) was prepared from epoxide **15** (~10 mmol) and diphenylmethanamine (5.5 g, 30 mmol, 3 eq) according to the procedure **GP-4** with minor modifications. The reaction was carried out at 85°C for 16 h, and after chromatographic purification of the product (SiO_2, hexane-DCM-EtOAc 10: 1: 0.6) it was additionally purified via crystallization by dissolution in MTBE (10 ml), then addition of hexane (30 ml) and maintaining overnight at -30°C. R_f 0.4 (hexane-EtOAc 3: 1). White solid, mp 130 - 135°C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.70 – 1.92 (td + br. s., *J* = 12.6, 4.8 Hz, 2 H), 2.12 (d, *J* = 13.1 Hz, 1 H), 2.74 (d, *J* = 7.7 Hz, 1 H), 3.33 (t, *J* = 11.1 Hz, 1 H), 3.62 – 3.79 (td + br. s., *J* = 12.1, 2.0 Hz, 2 H), 3.93 (dd, *J* = 11.6, 3.4 Hz, 1 H), 4.13 (dd, *J* = 11.1, 3.9 Hz, 1 H), 5.09 (s, 1 H), 7.20 – 7.28 (m, 2 H), 7.29 - 7.38 (m, 7 H), 7.30 - 7.50 (m, 6 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 38.8, 60.3, 64.1, 65.4, 68.2, 71.0, 87.5, 88.5, 122.1, 126.8 (2 C), 127.28, 127.31 (2 C), 127.4, 128.3 (2 C), 128.61, 128.67 (2 C), 128.70 (2 C), 131.7 (2 C), 142.9, 144.2.

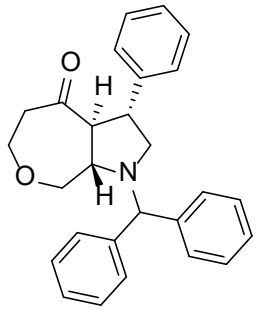
IR υ_{max}, (KBr): 3350 (br.), 2924, 2858, 2218, 1597, 1491, 1450, 1333, 1109, 972, 889, 758, 704 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{26}NO_2$: 384.1958, found: 384.1964.

(3*RS*,4*SR*)-3-(Benzhydrylamino)-4-((*E*)-styryl)tetrahydro-2*H*-pyran-4-ol (38)



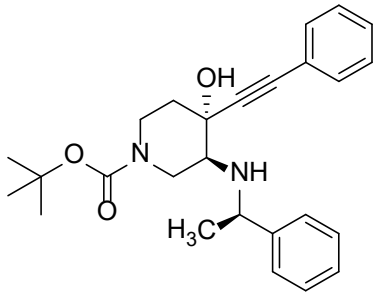
38 (1.9 g, 90%) was prepared from **37** (2.1 g, 5.5 mmol) according to the procedure **GP-5** with minor modifications. **37** was added to the reaction mixture as undissolved powder portionwise, the reaction was carried out at -5 - 0°C for 1 h and after purification by column chromatography (SiO_2, hexane-DCM-EtOAc 10: 1: 2) **38** was additionally purified via crystallization by dissolution in MTBE (5 ml), then addition of hexane (20 ml) and maintaining overnight at -30°C . R_f 0.25 (hexane-EtOAc 3: 1). White solid, mp 112 - 114°C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.72 (br. s., 1 H), 1.82 (br. s., 1 H), 2.05 (ddd, *J* = 12.9, 6.1, 3.7 Hz, 1 H), 2.23 (br. s., 1 H), 2.61 (br. s., 1 H), 3.56 (br. s., 1 H), 3.66 – 3.77 (m, 1 H), 3.87 (ddd, *J* = 11.9, 6.1, 3.9 Hz, 1 H), 3.99 (dd, *J* = 11.4, 2.9 Hz, 1 H), 4.99 (br. s., 1 H), 6.72 (d, *J* = 16.3 Hz, 1 H), 6.79 (d, *J* = 15.8 Hz, 1 H), 7.14 – 7.51 (m, 15 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 36.5 (br.), 59.9 (br.), 64.3, 64.9, 66.4, 72.2, 126.5 (2 C), 127.1 (2 C), 127.18, 127.22, 127.7 (3 C), 128.5 (2 C), 128.59 (2 C), 128.62 (2 C), 129.7, 132.2, 136.8, 143.2, 144.6. IR υ_{max}, (KBr): 3371 (br.), 2937, 1597, 1581, 1464, 1450, 1377, 1170, 1107, 1063, 971, 746, 704, 694 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{28}NO_2$: 386.2115, found: 386.2120.

(3*RS*,3a*SR*,8a*SR*)-1-benzhydryl-3-phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (39a)



To a solution of **38** (1.0 g, 2.60 mmol) in DMSO (25 ml) 37% formaldehyde solution (0.42 g, 5.18 mmol, 2 eq) and (+)-10-camphorsulfonic acid (0.55 g, 2.37 mmol, 0.9 eq) were added and the reaction was stirred for 24 h at 45°C. Then the solution was poured into 2% aq K_2CO_3 (100 ml) and extracted with hexane-DCM 3:1 mixture (2 x 50 ml). The organic layers were combined, dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane-DCM-EtOAc 20: 1: 1) to afford ~7 : 1 mixture of **39a** and **39b** (0.74 g, 72%, d.e. **39a** 75%). R_f 0.35 (hexane-EtOAc 3: 1). White solid, mp 125 – 127°C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm) (major isomer): 2.43 (d, *J* = 18.8 Hz, 1 H), 2.70 (ddd, *J* = 18.3, 11.6, 4.9 Hz, 1 H), 2.85 (td, *J* = 10.1, 3.8 Hz, 1 H), 2.96 (t, *J* = 10.3 Hz, 1 H), 3.18 (dd, *J* = 10.7, 6.7 Hz, 1 H), 3.40 (t, *J* = 11.6 Hz, 1 H), 3.56 (t, *J* = 9.3 Hz, 1 H), 3.69 (dd, *J* = 11.8, 3.6 Hz, 1 H), 3.73 – 3.84 (m, 2 H), 4.00 (dt, *J* = 13.5, 3.8 Hz, 1 H), 4.83 (s, 1 H), 7.17 – 7.42 (m, 13 H), 7.46 (d, *J* = 7.4 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm) (major isomer): 41.1, 44.9, 59.4, 66.1, 66.3, 66.7, 72.6, 77.1, 126.4, 127.1, 127.4, 127.5 (2 C), 128.3 (4 C), 128.37 (2 C), 128.40 (2 C), 128.5 (2 C), 141.6, 142.5, 143.7, 207.5. IR υ_{max}, (KBr): 2922, 2854, 1714, 1600, 1456, 1377, 1068, 931, 846, 741, 702 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{28}NO_2$: 398.2115, found: 398.2121.

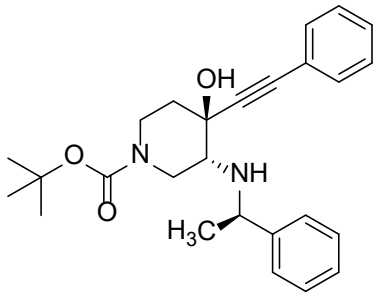
(3*S*,4*R*)-*Tert*-butyl 4-hydroxy-3-(((*R*)-1-phenylethyl)amino)-4-(phenylethynyl)piperidine-1-carboxylate (40)



40 (15.3 g, 38%) was prepared from epoxide **14** (~96 mmol) and (R)-1-phenylethylamine (29 g, 240 mmol, 2.5 eq) according to the procedure **GP-4** with minor modifications. The reaction was carried out at 55°C for 120 h, and chromatographic separation of **40** and **43** on silica gel was run using hexane-DCM-EtOAc 10: 1: 1 mixture. **40**: R_f 0.6 (hexane-EtOAc 5: 1), $[\alpha]_D^{23}$ = + 72.0 (c 1, $CHCl_3$). White solid, mp 83 – 85°C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.41 (d, *J* = 6.3 Hz, 3 H), 1.47 (s, 9 H), 1.59 (td, *J* = 12.5, 4.4 Hz, 1 H), 2.07 (d, *J* = 12.9 Hz, 1 H), 2.30 (br. s., 1 H), 2.70 (br. s., 1 H), 3.07 (br. s., 1 H), 3.90 (s, 1 H), 3.94 – 4.22 (m, 2 H), 4.27 – 4.60 (br. m., 1 H), 7.24 – 7.41 (m, 8 H), 7.45 –

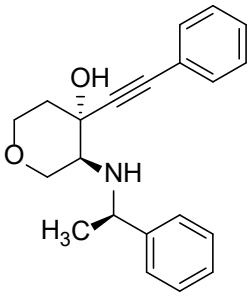
7.51 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 25.4, 28.3 (3 C), 37.1, (40.8 (br.), 41.6 (br.)), (44.8 (br.), 45.3 (br.)), 54.4, 59.8, 71.0, 79.8, 87.1, 88.4, 122.2, 126.8 (2 C), 127.4 (br.), 128.3 (2 C), 128.6 (2 C), 131.7 (2 C), 144.3 (br.), 144.6 (br.), 154.3. IR υ_{max}, (KBr): 3480, 3400, 3250, 2940, 2870, 1707, 1475 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{33}N_2O_3$: 421.2486, found: 421.2482.

(3*R*,4*S*)-*Tert*-butyl 4-hydroxy-3-(((*R*)-1-phenylethyl)amino)-4-(phenylethynyl)piperidine-1-carboxylate (43)



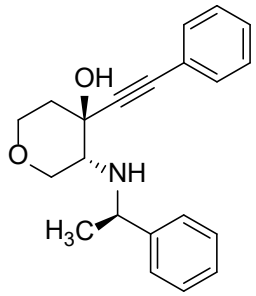
43 (14.5 g, 36%) was prepared from epoxide **14** (~96 mmol) and (R)-1-phenylethylamine (29 g, 240 mmol, 2.5 eq) according to the procedure **GP-4** with minor modifications. The reaction was carried out at 55°C for 120 h, and chromatographic separation of **40** and **43** on silica gel was run using hexane-DCM-EtOAc 10: 1: 1 mixture. **43**: R_f 0.5 (hexane-EtOAc 5:1). White solid, mp 164 – 165°C, $[\alpha]_D^{23}$ = + 52.8 (c 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz, 50°C), δ (ppm):1.40 (d, *J* = 6.5 Hz, 3 H), 1.47 (s, 9 H), 1.50 – 1.62 (m, 1 H), 1.79 (td, *J* = 12.7, 4.5 Hz, 1 H), 2.17 (dt, *J* = 12.9, 2.9 Hz, 1 H), 2.63 (q, *J* = 11.1 Hz, 1 H), 2.68 (dd, *J* = 10.9, 3.2 Hz, 1 H), 3.09 (t, *J* = 13.1 Hz, 1 H), 3.91 (br. s., 1 H), 4.05 (q, *J* = 6.6 Hz, 1 H), 4.13 (d, *J* = 13.2 Hz, 1 H), 4.20 (br. s., 1 H), 7.23 - 7.46 (m, 10 H). ^{13}C NMR ($CDCl_3$, 100 MHz, 50°C), δ (ppm): 23.9, 28.4 (3 C), 37.7, 41.6 (br.), 46.3 (br.), 55.6 (br.), 61.5 (br.) 71.6, 79.8, 87.3, 88.7, 122.4, 126.3 (2 C), 127.2, 128.3 (2 C), 128.5, 128.6 (2 C), 131.8, 146.4, 154.6. IR υ_{max}, (KBr): 3400 (br.), 2940, 2885, 1668, 1475, 1160, 780, 710 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{33}N_2O_3$: 421.2486, found: 421.2482.

(3*S*,4*R*)-3-(((*R*)-1-Phenylethyl)amino)-4-(phenylethynyl)tetrahydro-2*H*-pyran-4-ol (41)



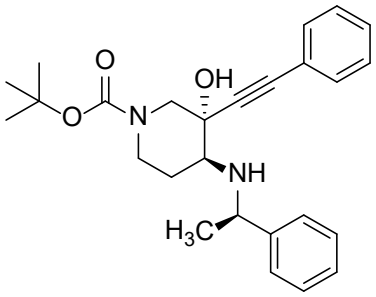
The emulsion of the epoxide **15** (~70 mmol) and (R)-1-phenylethylamine (21 g, 174 mmol, 2.5 eq) in water (50 mL) was vigorously stirred at 55°C for 96 h. Then water (200 ml) was added and the reaction was extracted with DCM (2 x 200 ml). The organic extracts were combined, dried with Na_2SO_4 and concentrated in vacuo. Chromatographic purification of the residue (SiO_2, hexane-DCM-EtOAc 10: 3: 2) yielded a mixture of **41** and **44** which was dissolved in MTBE (60 ml), hexane (120 ml) was added and the solution was concentrated in vacuo to a vol. ~60 ml. Then hexane (150 ml) was added and the solution was maintained overnight at -20°C. The precipitate was separated, washed with hexane and crystallized again as described to afford **41** (6.3 g, 28%). Rf 0.5 (hexane-EtOAc 4: 1). White solid, mp 130 – 131°C, $[\alpha]_D^{23}$ = - 25.6 (c 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.39 (d + br. s., *J* = 6.5 Hz, 4 H), 1.79 (dt, *J* = 12.7, 4.7 Hz, 1 H), 2.07 (d, *J* = 12.9 Hz, 1 H), 2.52 (dd, *J* = 10.5, 4.2 Hz, 1 H), 3.32 (t, *J* = 10.8 Hz, 1 H), 3.69 - 3.81 (m, 2 H), 3.91 (dd, *J* = 11.7, 3.5 Hz, 1 H), 3.99 (q, *J* = 6.5 Hz, 1 H), 4.14 (dd, *J* = 11.2, 4.2 Hz, 1 H), 7.23 - 7.45 (m, 8 H), 7.46 - 7.59 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 25.4, 38.5, 54.6, 59.8, 65.5, 68.1, 70.4, 87.2, 88.7, 122.3, 126.7 (2 C), 127.4, 128.4 (2 C), 128.6, 128.7 (2 C), 131.7 (2 C), 144.7. IR υ_{max}, (KBr): 3400, 2966, 2929, 2864, 1597 (w.), 1489, 1394, 1336, 1281, 1124, 1101, 1070, 1055, 1022, 980, 758, 732, 698, 690, 665, 552 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{24}NO_2$: 322.1802, found: 322.1801.

(3*R*,4*S*)-3-(((*R*)-1-Phenylethyl)amino)-4-(phenylethynyl)tetrahydro-2*H*-pyran-4-ol (44)



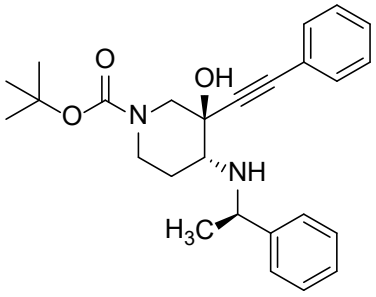
The emulsion of the epoxide **15** (~70 mmol) and (R)-1-phenylethylamine (21 g, 174 mmol, 2.5 eq) in water (50 mL) was vigorously stirred at 55°C for 96 h. Then water (200 ml) was added and the reaction was extracted with DCM (2 x 200 ml). The organic extracts were combined, dried with Na_2SO_4 and concentrated in vacuo. Chromatographic purification of the residue (SiO_2, hexane-DCM-EtOAc 10: 3: 2) yielded a mixture of **41** and **44** which was dissolved in MTBE (60 ml), hexane (120 ml) was added and the solution was concentrated in vacuo to a vol. ~60 ml. Then hexane (150 ml) was added and the solution was maintained overnight at -20°C. The precipitate was separated, washed with hexane and crystallized again as described to afford **41** (6.3 g, 28%). Mother liquors from crystallizations were combined and the solvents were evaporated in vacuo to yield **44** (7.2 g, 32%), which contained ~12.5% of the residual **41** (d.e. **32** 75%). R_f 0.5 (hexane-EtOAc 4: 1), $[\alpha]_D^{23}$ = + 14.0 (c 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm) (major product): 1.41 (d, *J* = 6.5 Hz, 3 H), 1.97 (td, *J* = 12.6, 4.7 Hz, 1 H), 2.16 (d, *J* = 12.9 Hz, 1 H), 2.81 (dd, *J* = 10.6, 4.3 Hz, 1 H), 3.17 (t, *J* = 10.9 Hz, 1 H), 3.66 - 3.80 (m, 2 H), 3.93 (dd, *J* = 11.7, 3.1 Hz, 1 H), 4.00 (q, *J* = 6.5 Hz, 1 H), 7.21 - 7.52 (m, 10 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm) (major product): 24.0, 39.0, 56.3, 61.5, 65.5, 68.8, 71.0, 87.4, 88.5, 122.2, 126.3 (2 C), 127.4, 128.3 (2 C), 128.6, 128.7 (2 C), 131.7 (2 C), 146.1 (br.). IR υ_{max}, (KBr): 3388 (br.), 3060, 3027, 2962, 2925, 2860, 2245 (w.), 2225 (w.), 1647, 1599, 1491, 1450, 1373, 1333, 1122, 1099, 1066, 75, 702, 692 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{24}NO_2$: 322.1802, found: 322.1798.

(3*S*,4*S*)-*Tert*-butyl 3-hydroxy-4-(((*R*)-1-phenylethyl)amino)-3-(phenylethynyl)piperidine-1-carboxylate (42)



42 (4.4 g, 35%) wase prepared from epoxide **16** (~30 mmol) and (R)-1-phenylethylamine (7.5 g, 62 mmol, ~2 eq) according to the procedure **GP-4** with minor modifications. The reaction was carried out at 35°C for 96 h and chromatographic separation of **42** and **45** on silica gel was run using hexane-DCM-EtOAc mixture with gradient from 10: 1: 1.3 to 10: 1: 2.6. **42**: R_f 0.5 (hexane-EtOAc 4: 1), $[\alpha]_D^{23}$ + 48.0 (c = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz, 55^{O}C), δ (ppm): 1.41 (s, 12 H), 1.50 - 1.66 (m, 1 H), 2.07 (d, *J* = 11.9 Hz, 1 H), 2.35 (d, *J* = 11.0 Hz, 1 H), 2.50 - 2.70 (m, 2 H), 1.60 - 3.00 (br. s., 1 H), 4.05 (q, *J* = 6.5 Hz, 1 H), 4.27 (br. s., 1 H), 4.44 (d, *J* = 11.7 Hz, 1 H), 7.23 - 7.51 (m, 10 H). ^{13}C NMR ($CDCl_3$, 100 MHz, 55^{O}C), δ (ppm): 25.5, 28.4 (3 C), 28.5, 43.0 (br.), 53.0 (br.), 54.2, 61.5, 70.3, 79.7, 86.4, 88.7, (122.8, 126.3), 126.8 (2 C), 127.3, 128.2 (2 C), 128.4, 128.7 (2 C), 131.9 (2 C), 144.9, 154.6. IR υ_{max}, (KBr): 3354 (br.), 2976, 2927, 2864, 2247 (w.), 1691, 1429, 1365, 1279, 1238, 1155, 908, 897, 758, 733, 702, 694 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{33}N_2O_3$: 421.2486, found: 421.2484.

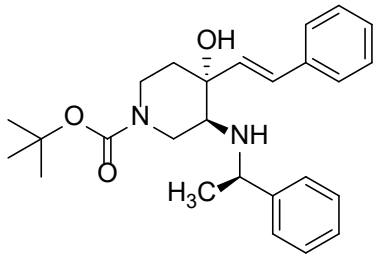
(3*R*,4*R*)-*Tert*-butyl 3-hydroxy-4-(((*R*)-1-phenylethyl)amino)-3-(phenylethynyl)piperidine-1-carboxylate (45)



45 (3.4 g, 27%) was prepared from epoxide **16** (~30 mmol) and (R)-1-phenylethylamine (7.5 g, 62 mmol, ~2 eq) according to the procedure for **19** with minor modifications. The reaction was carried out at 35°C for 96 h and chromatographic separation of **42** and **45** on silica gel was run using hexane-DCM-EtOAc mixture with gradient from 10: 1: 1.3 to 10: 1: 2.6. **45**: R_f 0.45 (hexane-EtOAc 4: 1), $[\alpha]_D^{23}$ – 52.4 (c = 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.25 - 1.61 (m, 13 H), 1.65 – 1.87 (m, 1 H), 2.66 (dd, *J* = 11.5, 3.7 Hz, 2 H), 2.84 (d, *J* = 12.2 Hz, 1 H), 2.00 - 3.50 (br. s., 2 H), 3.98 (q, *J* = 6.3 Hz, 1 H), 4.30 (d, *J* = 11.3 Hz, 1 H), 4.42 – 4.67 (m, 1 H), 7.20 – 7.44 (m, 10 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 23.6, 28.5 (3 C), 29.3, 42.9, 53.3, 55.3, 62.9, 70.3, 79.8, 86.3, 88.3, 122.4, 126.3 (2 C), 127.3, 128.1 (2 C), 128.3, 128.6 (2 C), 131.8, 146.3

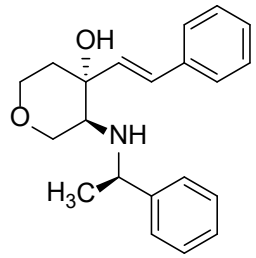
(br.), 154.5. IR υ_{max}, (KBr): 3386 (br.), 2974, 2927, 2864, 2247 (w.), 1681, 1491, 1431, 1365, 1242, 1155, 910, 758, 733, 702, 694 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{33}N_2O_3$: 421.2486, found: 421.2479.

(3*S*,4*R*)-*Tert*-butyl 4-hydroxy-3-(((*R*)-1-phenylethyl)amino)-4-((*E*)-styryl)piperidine-1-carboxylate (46)



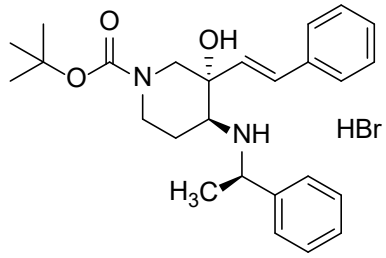
46 (10.3 g, 85%) was prepared from **40** (12 g, 28.6 mmol) according to the procedure **GP-5** with minor modifications. **40** was added to the reaction mixture as undissolved powder portionwise, the reaction was carried out at -5°C for 1 h and **46** was purified by column chromatography (SiO_2, hexane-DCM-Et_2O 1: 1: 0.5). R_f 0.5 (hexane-EtOAc 7: 3), $[\alpha]_D^{23}$ = - 59.9 (c 1, $CHCl_3$). White solid, mp 155 – 157°C. ^{1}H NMR ($CDCl_3$, 400 MHz, 50^{O}C), δ (ppm): 1.27 (br. s., 1 H), 1.35 (d, *J* = 6.6 Hz, 3 H), 1.53 (s, 9 H), 1.55 - 1.66 (m, 1 H), 1.95 (ddd, *J* = 13.6, 7.3, 4.5 Hz, 1 H), 2.27 (br. s., 1 H), 2.37 (dd, *J* = 6.6, 3.2 Hz, 1 H), 3.42 (dd, *J* = 13.3, 6.7 Hz, 1 H), 3.49 - 3.65 (m, 2 H), 3.82 (d, *J* = 13.8 Hz, 1 H), 3.98 (q, *J* = 6.5 Hz, 1 H), 6.55 (d, *J* = 16.1 Hz, 1 H), 6.72 (d, *J* = 16.1 Hz, 1 H), 7.15 - 7.45 (m, 10 H).^{13}C NMR ($CDCl_3$, 100 MHz, 50^{O}C), δ (ppm): 25.3, 28.5 (3 C), 35.2, 40.2 (br.), 43.2, 55.3, 59.4, 72.4, 79.6, 126.6 (2 C), 127.0 (2 C), 127.1, 127.6, 128.4 (2 C), 128.6 (2 C), 130.0, 132.3, 137.1, 145.3, 155.1. IR υ_{max}, (KBr): 3483 (br.), 2978, 2922, 1662, 1475, 1430, 1365, 1265, 1250, 1161, 1115, 1055, 980, 752, 694 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{35}N_2O_3$: 423.2642, found: 423.2643.

(3*S*,4*R*)-3-(((*R*)-1-Phenylethyl)amino)-4-((*E*)-styryl)tetrahydro-2*H*-pyran-4-ol (47)



47 (5.55 g, 92%) was prepared from **41** (6 g, 18.7 mmol) according to the procedure **GP-5** with minor modifications. **41** was added to the reaction mixture as undissolved powder portionwise, the reaction was carried out at -5 - 0°C for 1.5 h and **47** was purified by column chromatography (SiO_2, hexane-DCM-EtOAc 2: 1: 0.5). R_f 0.3 (hexane-EtOAc 7: 3). White solid, mp 91 – 92°C, $[\alpha]_D^{23}$ = – 121.5 (c 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.34 (d, *J* = 6.5 Hz, 3 H), 1.42 (br. s, 1 H), 1.66 (ddd, *J* = 13.3, 7.5, 3.7 Hz, 1 H), 2.00 (ddd, *J* = 13.5, 6.7, 3.5 Hz, 1 H), 2.33 - 2.58 (m, 2 H), 3.54 (dd, *J* = 11.2, 6.9 Hz, 1 H), 3.73 (ddd, *J* = 11.4, 7.6, 3.5 Hz, 1 H), 3.82 - 3.96 (m, 2 H), 4.02 (dd, *J* = 11.4, 2.9 Hz, 1 H), 6.63 (d, *J* = 16.0 Hz, 1 H), 6.73 (d, *J* = 16.0 Hz, 1 H), 7.17 - 7.52 (m, 10 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 25.3, 36.4 (br.), 55.4, 59.4, 64.3, 66.2, 71.6, 126.5 (2 C), 126.9 (2 C), 127.1, 127.5, 128.4 (2 C), 128.5 (2 C), 129.6, 132.0 (br.), 136.9, 145.1. IR υ_{max}, (KBr): 3543, 3313, 2962, 2864, 1597 (w.), 1490, 1448, 1232, 1134, 1111, 1092, 1028, 1001, 978, 841, 761, 746, 700 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{26}NO_2$: 324.1958, found: 324.1961.

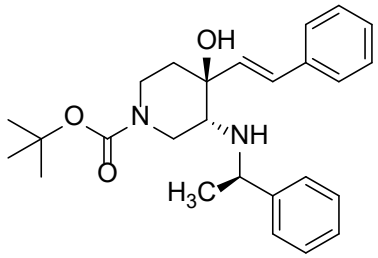
(3*S*,4*S*)-*Tert*-butyl 3-hydroxy-4-(((*R*)-1-phenylethyl)amino)-3-((*E*)-styryl)piperidine-1-carboxylate hydrobromide (48)



48 (3.58 g, 89%) was prepared from **42** (4.0 g, 9.52 mmol) according to the procedure **GP-5** with minor modifications. The reaction was carried out at -2 - +2°C for 2 h and **48** was purified by column chromatography (SiO_2, hexane-DCM-EtOAc 3: 1: 0.8). R_f (base) 0.5 (hexane-EtOAc 3: 1). White solid, mp 230 - 231°C (dec.), $[\alpha]_D^{23}$ – 72.5 (c = 0.5, MeOH). ^{1}H NMR (DMSO-d_6, 400 MHz), δ (ppm): 1.14 - 1.52 (m, 9 H), 1.63 (d, *J* = 6.6 Hz, 3 H), 1.74 (d, *J* = 10.0 Hz, 1 H), 2.02 - 2.22 (m, 1 H), 2.55 - 2.90 (m, 3 H), 3.80 - 4.20 (br. m., 2 H), 4.65 (br. s., 1 H), 6.03 (s, 1 H), 6.20 - 6.47 (m, 1 H), 6.96 (d, *J* = 15.9 Hz, 1 H), 7.30 (t, *J* = 7.0 Hz, 1 H), 7.35 - 7.52 (m, 7 H), 7.60 (d, *J* = 6.8 Hz, 2 H), 8.30 (t, *J* = 8.8 Hz, 1 H), 8.72 (br. s., 1 H). ^{13}C NMR (DMSO-d_6, 100 MHz), δ (ppm): 19.6, 24.1 (br.), 27.8 (3 C), 41.1 (br.), 54.0 (br.), 55.1, 61.5, 70.8, 79.2, 126.3, 126.6 (2 C), 127.8 (2 C), 127.9, 128.5 (2

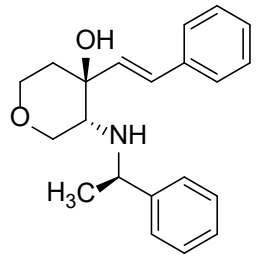
C), 129.0 (3 C), 131.5 (br.), 136.3, 136.7, 153.1 (br.). IR υ_{max}, (KBr): 3369, 2976, 2933, 2819, 1689, 1568, 1454, 1427, 1365, 1279, 1248, 1159, 768, 756, 704 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{35}N_2O_3$: 423.2642, found: 423.2647.

(3*R*,4*S*)-*Tert*-butyl 4-hydroxy-3-(((*R*)-1-phenylethyl)amino)-4-((*E*)-styryl)piperidine-1-carboxylate (49)



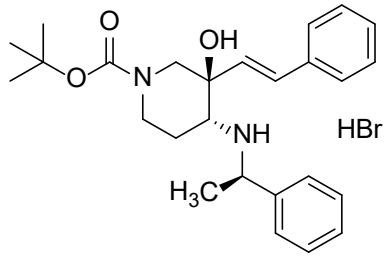
49 (12.2 g, 93%) was prepared from **43** (13 g, 31 mmol) according to the procedure **GP-5** with minor modifications. **43** was added to the reaction mixture as undissolved powder portionwise, the reaction was carried out at -5°C for 1 h and product **49** was purified by column chromatography (SiO_2, hexane-DCM-Et_2O 1: 1: 0.5). R_f 0.5 (hexane-EtOAc 7: 3), $[\alpha]_D^{23}$ = + 47.1 (c 0.6, $CHCl_3$). White solid, mp 100 – 105°C. ^{1}H NMR ($CDCl_3$, 400 MHz, 40^{O}C), δ (ppm): 1.25 – 1.39 (br. s. + d, *J* = 6.5 Hz, 4 H), 1.47 (s, 9 H), 1.70 (ddd, *J* = 13.4, 9.2, 4.4 Hz, 1 H), 2.02 (ddd, *J* = 13.3, 6.2, 3.7 Hz, 1 H), 2.40 - 2.89 (m + br. s., 2 H), 2.99 (dd, *J* = 13.3, 8.3 Hz, 1 H), 3.33 (ddd, *J* = 13.2, 9.5, 3.4 Hz, 1 H), 3.76 (dt, *J* = 13.8 Hz, 4.7 Hz ,1 H), 3.93 (q, *J* = 6.0 Hz, 1 H), 3.60 – 4.05 (br. s., 1 H), 6.60 (d, *J* = 16.0 Hz, 1 H), 6.83 (d, *J* = 16.0 Hz, 1 H), 7.19 - 7.37 (m, 8 H), 7.38 - 7.44 (d, *J* = 7.6 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz, 40^{O}C), δ (ppm): 23.7 (br.), 28.4 (3 C), 36.3, 40.5 (br.), 45.2 (br.), 56.4 (br.), 60.7, 72.9, 79.8, 126.4 (2 C), 126.5 (2 C), 127.1, 127.7, 128.5 (2 C), 128.6 (2 C), 130.5, 131.0 (br.), 137.0, 146.4, 155.1. IR υ_{max}, (KBr): 3388 (br.), 2970, 2927, 2870, 1666, 1429, 1275, 1149, 1068, 764, 700 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{35}N_2O_3$: 423.2642, found: 423.2639.

(3*R*,4*S*)-3-(((*R*)-1-Phenylethyl)amino)-4-((*E*)-styryl)tetrahydro-2*H*-pyran-4-ol (50)



50 (6.35 g, 90%, d.e. 75%) was prepared from **43** (7 g, 21.8 mmol, d.e. 75%) according to the procedure **GP-5** with minor modifications. The reaction was carried out at -5 - 0°C for 1.5 h and **50** was purified by column chromatography (SiO_2, hexane-DCM-EtOAc 2: 1: 0.5). R_f 0.3 (hexane-EtOAc 7: 3), $[\alpha]_D^{23}$ = + 1.0 (c1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm) (major product): 1.36 (d, *J* = 6.5 Hz, 3 H), 1.50 - 3.00 (br. s., 2 H), 1.81 (ddd, *J* = 12.9, 9.1, 4.2 Hz, 1 H), 2.05 (ddd, *J* = 13.5, 5.3, 3.3 Hz, 1 H), 2.72 (dd, *J* = 7.8, 3.5 Hz, 1 H), 3.22 (dd, *J* = 11.4, 8.1 Hz, 1 H), 3.68 (ddd, *J* = 11.8, 9.0, 3.1 Hz, 1 H), 3.77 (dd, *J* = 11.5, 3.5 Hz, 1 H), 3.83 - 3.95 (m, 2 H), 6.69 (d, *J* = 16.0 Hz, 1 H), 6.85 (d, *J* = 16.0 Hz, 1 H), 7.20 - 7.52 (m, 10 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm) (major product): 24.0, 37.5, 56.9, 61.0, 64.4, 68.1, 72.4, 126.4 (2 C), 126.5 (2 C), 127.1, 127.6, 128.5 (2 C), 128.6 (2 C), 130.2, 131.0 (br.), 136.9, 146.3. IR υ_{max}, (KBr): 3411 (br.), 3026, 2962, 2925, 2866, 2247 (w.), 1492, 1448, 1120, 1097, 1066, 972, 910, 748, 733, 700 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{21}H_{26}NO_2$: 324.1958, found: 324.1957.

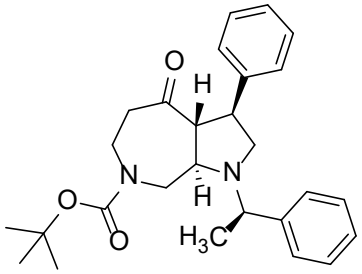
(3*R*,4*R*)-*Tert*-butyl 3-hydroxy-4-(((*R*)-1-phenylethyl)amino)-3-((*E*)-styryl)piperidine-1-carboxylate hydrobromide (51)



51 (2.8 g, 93%) was prepared from **45** (3.0 g, 7.14 mmol) according to the procedure **GP-5** with minor modifications. The reaction was carried out at -10 - -5°C for 2 h and **51** was purified by column chromatography (SiO_2, hexane-DCM-EtOAc 3: 1: 0.8). R_f (base) 0.5 (hexane-EtOAc 3: 1). White solid, mp 245 - 247°C (dec.), $[\alpha]_D^{23}$ + 35.1 (c = 1, MeOH). ^{1}H NMR (DMSO-d_6, 400 MHz), δ (ppm): 1.10 – 1.55 (br. m., 9 H), 1.66 (d, *J* = 6.6 Hz, 3 H), 1.69 – 1.85 (m, 1 H), 2.02 (d, *J* = 9.8 Hz, 1 H), 2.65 - 3.12 (br. m., 2 H), 3.30 - 3.46 (m, 1 H), 4.04 (br. s., 2 H), 4.55 - 4.70 (m, 1 H), 6.08 (s, 1 H), 6.35 (d, *J* = 11.2 Hz, 1 H), 6.94 (d, *J* = 15.9 Hz, 1 H), 7.26 (t, *J* = 7.1 Hz, 1 H), 7.30 - 7.50 (m, 7 H), 7.70 (d, *J* = 7.0 Hz, 2 H), 8.38 (br. s., 1 H), 8.84 (br. s., 1 H). ^{13}C NMR (DMSO-d_6, 100 MHz), δ (ppm): 19.2, 25.2 (br.), 27.9 (3 C), 41.2 (br.), 53.9 (br.), 57.1, 63.2, 71.1, 79.1, 126.3, 126.5 (2 C), 127.8,

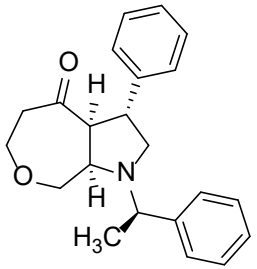
128.3 (2 C), 128.5 (2 C), 128.7 (2 C), 128.8, 131.4 (br.), 136.5, 137.7, 153.1 (br.). IR υ_{max}, (KBr): 3259, 2978, 2935, 2677, 1668, 1585, 1444, 1365, 1250, 1153, 968, 758, 694 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{26}H_{35}N_2O_3$: 423.2642, found: 423.2642.

(3*S*,3a*R*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyl-1-((*R*)-1-phenylethyl)octahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate (52a)



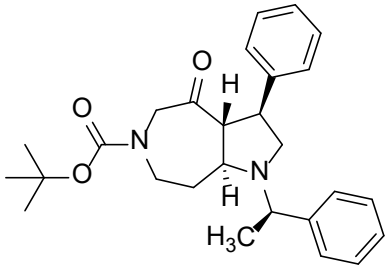
52a (7.5 g, 73%) was prepared from **46** (10 g, 23.7 mmol) according to the procedure for 9: 1 mixture of **23a** and **23b**. R_f 0.4 (hexane-EtOAc 4: 1), $[\alpha]_D^{23}$ = + 68.2 (c 1, $CHCl_3$). White solid, mp 115 – 117°C. ^1H NMR ($CDCl_3$, 400 MHz), δ (ppm):1.48 (s, 4.5 H), 1.50 – 1.60 (s + m, 7.5 H), 2.31 (s, 0.45 H), 2.36 (s, 0.55 H), 2.43 – 2.59 (m, 1 H), 2.60 – 3.04 (m, 3 H), 3.05 – 3.40 (m, 3 H), 3.57 – 3.75 (m, 1 H), 3.94 – 4.24 (m, 2 H), 4.64 (dd, *J* = 14.0, 3.0 Hz, 0.5 H), 4.86 (dd, *J* = 13.4, 3.0 Hz, 0.5 H), 7.10 – 7.44 (m, 10 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): (19.4, 19.7), (28.3, 28.5 (3C)), (40.9, 41.0), (42.3, 42.9), (43.1, 43.2), (52.8 (br.), 53.6 (br.)), (55.0 (br.), 55.6 (br.)), (58.5 (br.), 58.7), (63.9, 64.2), 66.2 (br.), (80.2, 80.5), 126.4, 127.3 (br.), 127.5 (2 C), 127.9, 128.1 (2 C), 128.4, 128.5 (2 C), (139.5 (br.), 140.4 (br.)), (144.1 (br.), 144.6 (br.)), (154.1, 154.3), (207.7, 207.9). IR υ_{max}, (ZnSe): 2983, 2964, 2931, 2885, 1693, 1454, 1414, 1369, 1246, 1165, 760, 702 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{34}N_2O_3$: 435.2642, found: 435.2638.

(3*R*,3a*S*,8a*R*)-3-Phenyl-1-((*R*)-1-phenylethyl)hexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (53b)



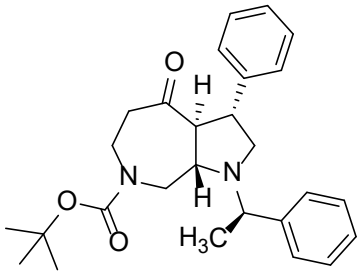
To a solution of **47** (5.0 g, 15.5 mmol) in THF (80 ml) 37% formaldehyde solution (2.5 g, 31 mmol, 2 eq) and (+)-10-camphorsulfonic acid (1.8 g, 7.76 mmol, 0.5 eq) were added and the reaction mixture was stirred for 24 h at 45°C. Then the solution was cooled to room temperature, evaporated in vacuo and the residue was treated with 5% aq K_2CO_3 (50 ml) and extracted with DCM (2 x 50 ml). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2, hexane-DCM-EtOAc 3: 1: 0.75) yielded 1: 3 mixture of **53a** and **53b** (4.95 g, 95%). The mixture was dissolved in MTBE (50 ml), hexane (100 ml) was added, then the solution was concentrated in vacuo to a vol. ~50 ml and maintained for 3 h at room temperature and overnight at -20°C. The precipitate was filtered off, washed with precooled to 0°C hexane and dried to afford **53b** (2.9 g, 56%). R_f 0.5 (hexane-EtOAc 7: 3). White solid, mp 134 – 135^{O}C, $[\alpha]_D^{23}$ = – 16.6 (c 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.51 (d, *J* = 6.3 Hz, 3 H), 2.45 - 2.61 (m, 2 H), 2.84 (td, *J* = 11.1, 4.1 Hz, 1 H), 3.19 (t, *J* = 6.8 Hz, 1 H), 3.27 (dd, *J* = 12.2, 9.5 Hz, 1 H), 3.37 (t, *J* = 10.2 Hz, 1 H), 3.47 (t, *J* = 9.2 Hz, 1 H), 3.57 - 3.74 (m, 2 H), 3.81 - 3.92 (m, 1 H), 3.93 - 4.08 (m, 2 H), 7.12 - 7.43 (m, 10 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 21.8, 43.0, 46.9, 57.8, 58.8, 61.5, 62.3, 69.5, 74.1, 126.6, 127.2, 127.7 (2 C), 127.8 (2 C), 128.29 (2 C), 128.34 (2 C), 140.6, 141.8, 208.3. IR υ_{max}, (KBr): 3427 (br.), 2972, 2960, 2871, 2846, 2800, 1702, 1495, 1454, 1243, 1134, 843, 768, 702 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{26}N_2O_3$: 336.1958, found: 336.1961.

(3*S*,3a*R*,8a*S*)-*Tert*-butyl 4-oxo-3-phenyl-1-((*R*)-1-phenylethyl)octahydropyrrolo[2,3-d]azepine-6(2*H*)-carboxylate (54a)



54a (2.7 g, 88%) was prepared from **48** (3.0 g, 7.11 mmol) according to the procedure for **25a** with minor modifications. The reaction was carried out at 40°C and purification of the product **54a** was carried out using column chromatography (SiO_2, hexane-DCM-EtOAc 3: 1: 0.7). R_f 0.5 (hexane-EtOAc 4: 1), $[\alpha]_D^{23}$ - 9.3 (c = 1, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.29 (s, 5 H), 1.52 (s, 4 H), 1.55 (d, *J* = 6.8 Hz, 3 H), 1.82 - 2.17 (m, 1 H), 2.27 - 2.44 (m, 2 H), 2.58 - 2.74 (m, 1 H), 2.88 (dt, *J* = 15.6, 9.0 Hz, 1 H), 3.07 - 3.27 (m, 2 H), 3.36 (dd, *J* = 18.1, 15.6 Hz, 1 H), 3.62 - 3.74 (m, 1 H), 4.12 - 4.27 (m, 1.5 H), 4.29 - 4.49 (m, 1 H), 4.69 (d, *J* = 18.8 Hz, 0.5 H), 7.11 - 7.49 (m, 10 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): (19.60, 19.63), (28.0, 28.2) (3 C), (33.1, 34.1), (39.9, 40.3), (46.5, 46.9), (53.4, 53.9), (56.6, 56.9), (57.8, 58.6), (62.9, 63.5), (64.4, 65.1), (80.5, 80.6), (126.05, 126.13), (127.05, 127.14) (2 C), (127.18, 127.21) (2 C), 127.97 (2 C), 128.03 (2 C), 128.4 (2 C), (138.9, 139.0), (145.1, 145.9), (154.3, 155.0), (208.0, 208.3). IR υ_{max}, (KBr): 2950, 1700, 1460, 1425, 1375, 1260, 1170, 925, 710 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{35}N_2O_3$: 435.2642, found: 435.2639.

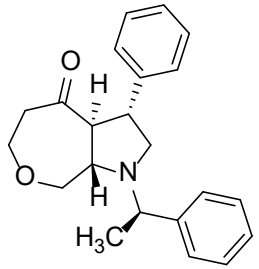
(3*R*,3a*S*,8a*S*)-Tert-butyl 4-oxo-3-phenyl-1-((*R*)-1-phenylethyl)octahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate (55a)



55a (8.6 g, 70%) was prepared from **49** (12 g, 28.4 mmol) according to the procedure for 9: 1 mixture of **23a** and **23b**. R_f 0.5 (hexane-EtOAc 4: 1), $[\alpha]_D^{23}$ = -43.2 (c 1, $CHCl_3$). White solid, mp 111 – 114°C. ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.41 (d, *J* = 6.6 Hz, 3 H), 1.47 (s, 9 H), 2.35 (s, 0.45 H), 2.39 (s, 0.55 H), 2.61 – 2.93 (m, 4 H), 2.99 – 3.19 (m. 1.5 H), 3.21 – 3.42 (m, 1.5 H), 3.75 – 3.87 (m, 1 H), 3.95 – 4.05 (m, 1 H), 4.06 – 4.19 (m, 1 H), 4.29 (dd, *J* = 13.5, 2.8 Hz, 0.5 H), 4.57 (q, *J* = 9.3 Hz, 0.5 H), 7.13 – 7.39 (m, 8 H), 7.45 (d, *J* = 7.3 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): (12.2, 13.4), 28.3, (40.9, 41.3), (42.3, 42.8), (43.1, 43.2), (52.5, 53.4), (53.6, 54.4), (56.7, 57.6), (64.6, 65.8), (66.3, 67.0), (80.15, 80.19), 126.3, (126.8, 126.9), (127.2, 127.3) (2 C), (127.39, 127.43) (2 C), (128.16, 128.20) (2 C), 128.5 (2 C), (143.9, 144.2), (144.7, 145.2), (154.0, 154.3),

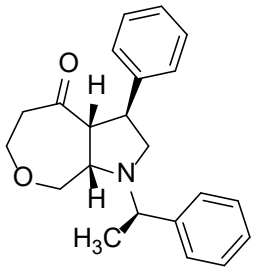
(207.8, 207.9). IR υ_{max}, (ZnSe): 2964, 2802, 1699, 1452, 1415, 1367, 1325, 1244, 1163, 762, 702 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{27}H_{34}N_2O_3$: 435.2642, found: 435.2634.

(3*R*,3a*S*,8a*S*)-3-Phenyl-1-((*R*)-1-phenylethyl)hexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (56a)



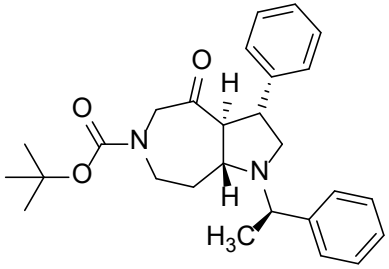
To a solution of **50** (5 g, 15.5 mmol, d.e. 75%) and (+)-10-camphorsulfonic acid (1.8 g, 7.76 mmol, 0.5 eq) in TFE (75 ml) $LiClO_4$ (12 g, 113 mmol, 7.3 eq) was added followed by 37% formaldehyde solution (2.5 g, 31 mmol, 2 eq). The reaction mixture was stirred for 24 h at 70°C. Then the solution was cooled to room temperature, poured into 5% aq K_2CO_3 (150 ml) and extracted with hexane-DCM 3: 1 mixture (2 x 150 ml). The combined organic layers were dried with Na_2SO_4 and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane-DCM-EtOAc 3: 1: 0.75) to afford a mixture of **56a** and **56b** contaminated with small amounts of **53a** and **53b** (4.15 g, 80% totally). The mixture was dissolved in MTBE (20 ml), hexane (100 ml) was added and the solution was concentrated in vacuo to a vol. ~25 ml. Then the solution was diluted with additional portion of hexane (25 ml) and maintained for 5 h at room temperature and overnight at -20°C. The precipitate was filtered off, washed with precooled to 0°C hexane and dried to afford **56a** (1.6 g, 31%). R_f 0.5 (hexane-EtOAc 7: 3). White solid, mp 115 – 118°C, $[\alpha]_D^{23}$ = – 32.7 (c 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.40 (d, *J* = 6.5 Hz, 3 H), 2.44 (d, *J* = 19.0 Hz, 1 H), 2.74 (ddd, *J* = 18.7, 11.7, 4.6 Hz, 1 H), 2.84 (td, *J* = 9.8, 3.6 Hz, 1 H), 2.96 (dd, *J* = 10.0, 5.5 Hz, 1 H), 3.07 (t, *J* = 9.6 Hz, 1 H), 3.41 (q, *J* = 11.3 Hz, 2 H), 3.72 - 3.83 (m, 2 H), 3.87 (q, *J* = 6.4 Hz, 1 H), 3.99 - 4.11 (m, 2 H), 7.18 (t, *J* = 6.7 Hz, 1 H), 7.21 - 7.46 (m, 9 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 14.9, 41.1, 45.0, 55.3, 59.0, 65.6, 66.4, 66.6, 76.9, 126.4, 127.0, 127.3 (2 C), 127.5 (2 C), 128.3 (2 C), 128.5 (2 C), 144.4, 144.7, 207.5. IR υ_{max}, (KBr): 3465 (br.), 2970, 2806, 1705, 1495, 1205, 1155, 1114, 1070, 764,758, 702 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{26}N_2O_3$: 336.1958, found: 336.1955.

(3*S*,3a*R*,8a*S*)-3-Phenyl-1-((*R*)-1-phenylethyl)hexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (56b)



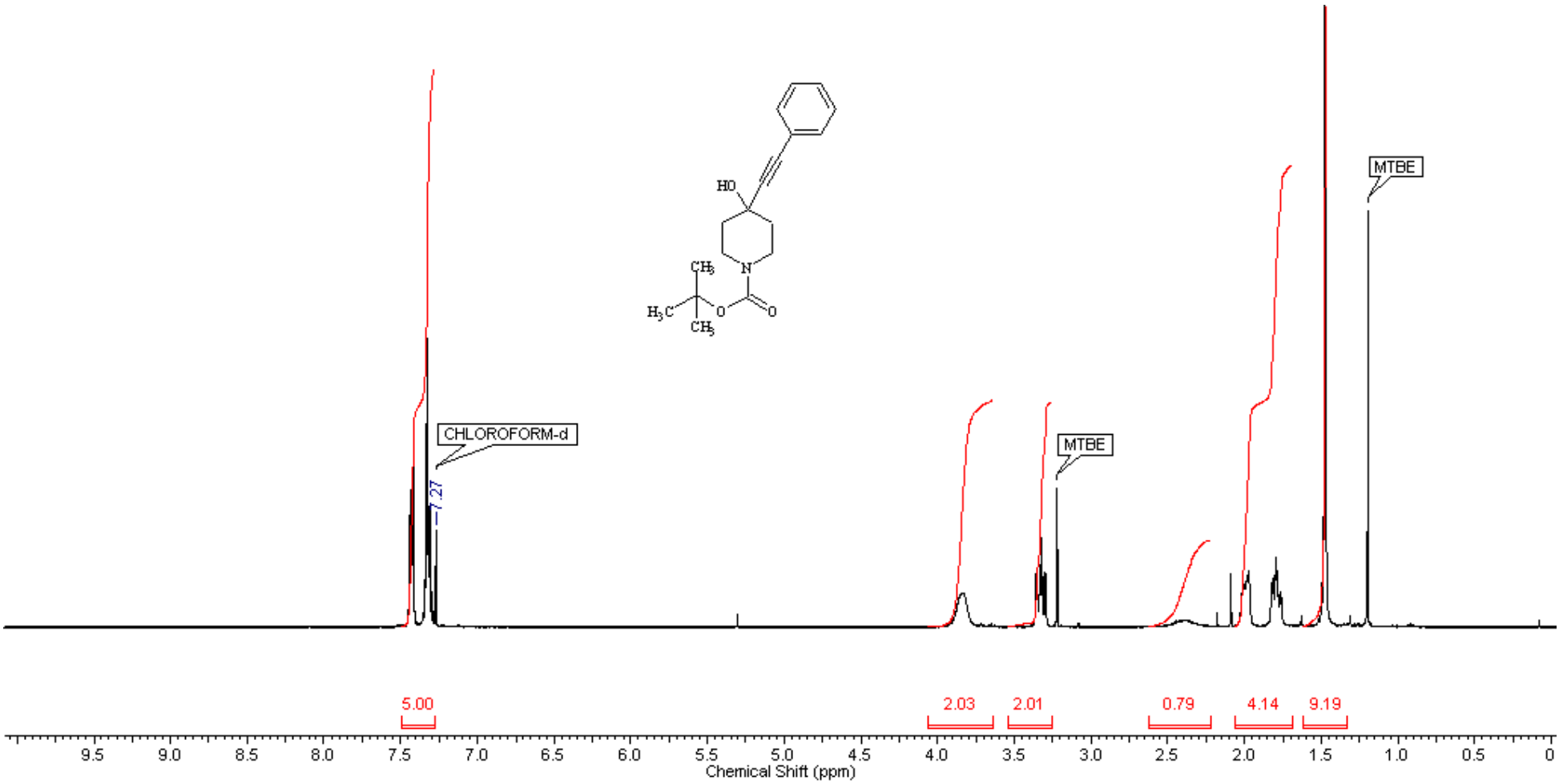
To a solution of **50** (5 g, 15.5 mmol, 75% d.e.) in THF (80 ml) 37% formaldehyde solution (2.5 g, 31 mmol, 2 eq) and (+)-10-camphorsulfonic acid (1.8 g, 7.76 mmol, 0.5 eq) were added and the reaction mixture was stirred for 24 h at 45°C. Then the solution was cooled to room temperature, evaporated in vacuo and the residue was treated with 5% aq K_2CO_3 (50 ml) and extracted with DCM (2 x 50 ml). The combined organic extracts were dried with Na_2SO_4 and concentrated in vacuo. Purification of the residue by column chromatography (SiO_2, hexane-DCM-EtOAc 3: 1: 0.75) yielded a mixture of **56a** and **56b** contaminated with small amounts of **53a** and **53b** (4.45 g, 86% totally). The mixture was dissolved in anhydrous EtOH (50 ml), the solution was cooled to 0°C and acidified with 8 M aq HBr to pH ~ 5. The solution was concentrated in vacuo to a vol. ~25 ml, Et_2O (25 ml) was added and the mixture was maintained for 1 h at -20°C. The precipitate was filtered off, washed with Et_2O and dried to afford **56b** x HBr contaminated with ~5% **56a** x HBr. The salt was transformed into free base by treating with 5% aq K_2CO_3 (50 ml) and extracting with DCM (2 x 50 ml). And then hydrobromide was obtained repeatedly as above to afford **56b** x HBr (3.1 g, 48%) in which contamination with **56a** x HBr was reduced to ~1.7%. This product was used in the next step without additional purification. White solid, mp 205 – 211°C, $[\alpha]_D^{23}$ = + 2.5 (c 1, MeOH). Base: R_f 0.5 (hexane-EtOAc 7: 3). ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.49 (d, *J* = 6.8 Hz, 3 H), 2.57 (ddd, *J* = 11.6, 5.1, 2.5 Hz, 1 H), 2.75 (dd, *J* = 11.1, 8.8 Hz, 1 H), 2.83 (ddd, *J* = 11.4, 10.3, 4.3 Hz, 1 H), 3.03 - 3.12 (m, 1 H), 3.23 (dd, *J* = 8.7, 6.5, 1 H), 3.48 - 3.65 (m, 4 H), 3.67 - 3.77 (m, 1 H), 3.84 - 3.94 (m, 2 H), 7.19 - 7.45 (m, 10 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 16.6, 43.2, 46.8, 56.7, 60.2, 60.4, 62.3, 69.2, 73.6, 126.6, 127.2, 127.5 (2C), 127.6 (2C), 128.3 (2C), 128.4 (2C), 140.6, 143.9, 208.3. IR υ_{max}, (KBr): 3427 (br.), 2613, 2571, 1714, 1456, 1392, 1124, 985, 763, 704, 522 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{22}H_{26}N_2O_3$: 336.1958, found: 336.1953.

(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyl-1-((*R*)-1-phenylethyl)octahydropyrrolo[2,3-d]azepine-6(2*H*)-carboxylate (57a)

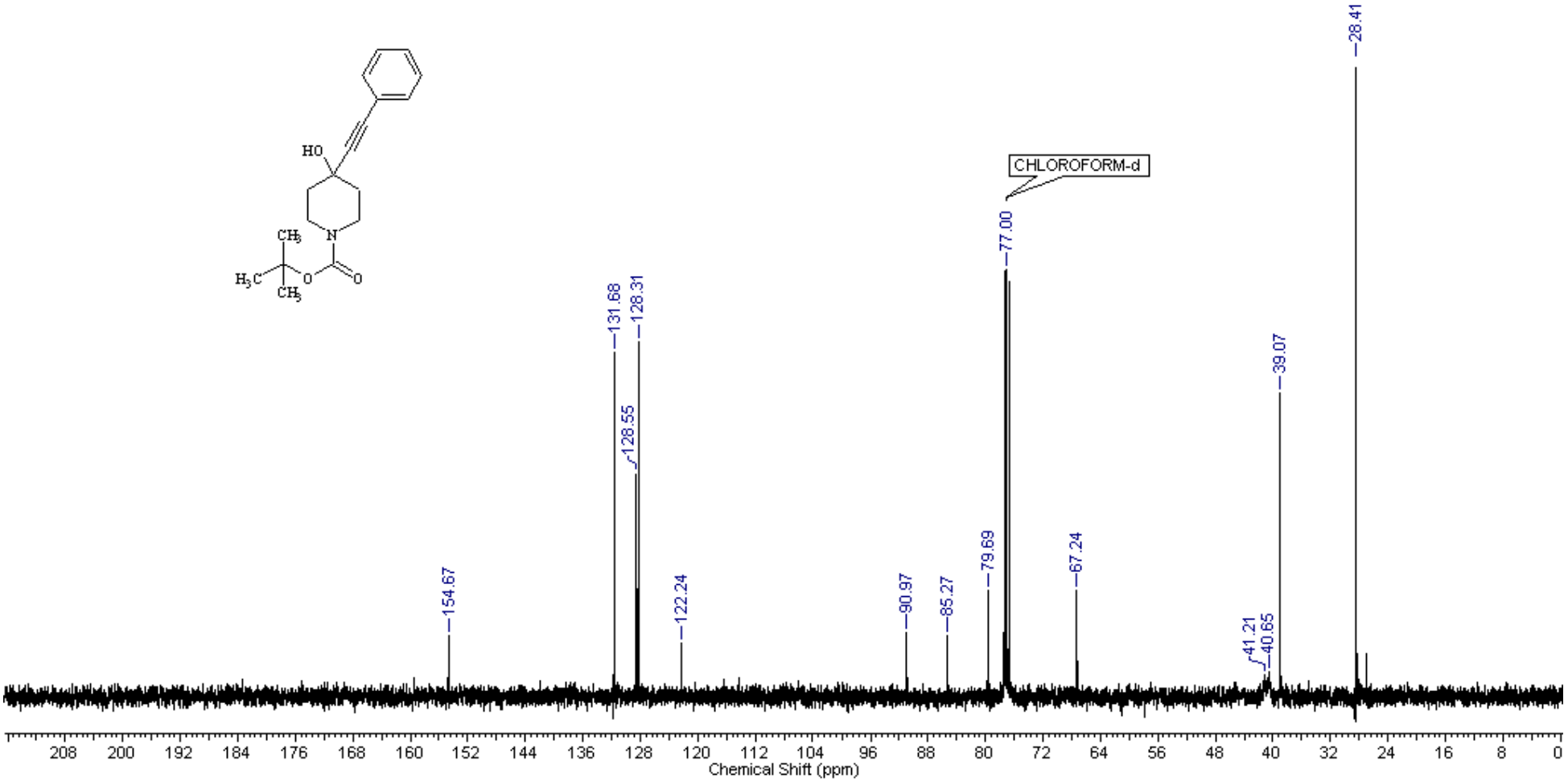


57a (2.45 g, 92%) was prepared from **51** (2.6 g, 6.16 mmol) according to the procedure for **25a** with minor modifications. The reaction was carried out at 40°C and **57a** was purified by column chromatography (SiO_2, hexane-DCM-EtOAc 3: 1: 0.7). R_f 0.5 (hexane-EtOAc 4: 1), $[\alpha]_D^{23}$ - 7.3 (c = 1, MeOH).^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 1.31 (s, 4.5 H), 1.37 (d, *J* = 6.1 Hz, 3 H), 1.51 (s, 4.5 H), 1.78 - 1.93 (m, 0.5 H), 1.95 - 2.11 (m, 1.5 H), 2.58 - 2.74 (m, 2 H), 2.76 - 2.86 (m, 1 H), 2.98 (t, *J* = 9.3 Hz, 0.5 H), 3.04 (t, *J* = 9.3 Hz, 0.5 H), 3.21 (t, *J* = 7.6 Hz, 0.5 H), 3.28 (t, *J* = 8.6 Hz, 0.5 H), 3.46 (t, *J* = 19.1 Hz, 1 H), 3.76 - 3.87 (m, 1 H), 4.03 - 4.20 (m, 1.5 H), 4.31 (d, *J* = 14.5 Hz, 0.5 H), 4.48 (d, *J* = 18.9 Hz, 0.5 H), 4.75 (d, *J* = 18.8 Hz, 0.5 H), 7.11 - 7.19 (m, 1 H), 7.20 - 7.30 (m, 5 H), 7.35 (t, *J* = 7.4 Hz, 2 H), 7.47 (d, *J* = 7.6 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): (11.8, 12.4), (28.0, 28.3) (3 C), (33.5, 34.4), (40.3, 40.8), (46.6, 47.0), (53.2, 53.8), (56.3, 56.8), (58.0, 58.8), 64.6, (65.3, 65.5), (80.5, 80.6), (126.0, 126.1), 126.7, (127.0, 127.2) (2 C), 127.3 (2 C), 128.0 (2 C), (128.28, 128.32) (2 C), (144.05, 144.14), (144.8, 145.8), (154.3, 155.0), (208.1, 208.4). IR υ_{max}, (KBr): 2990, 1705, 1460, 1425, 1375, 1352, 1275, 800, 775, 707 cm^{-1}. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{27}H_{35}N_2O_3$: 435.2642, found: 435.2639.

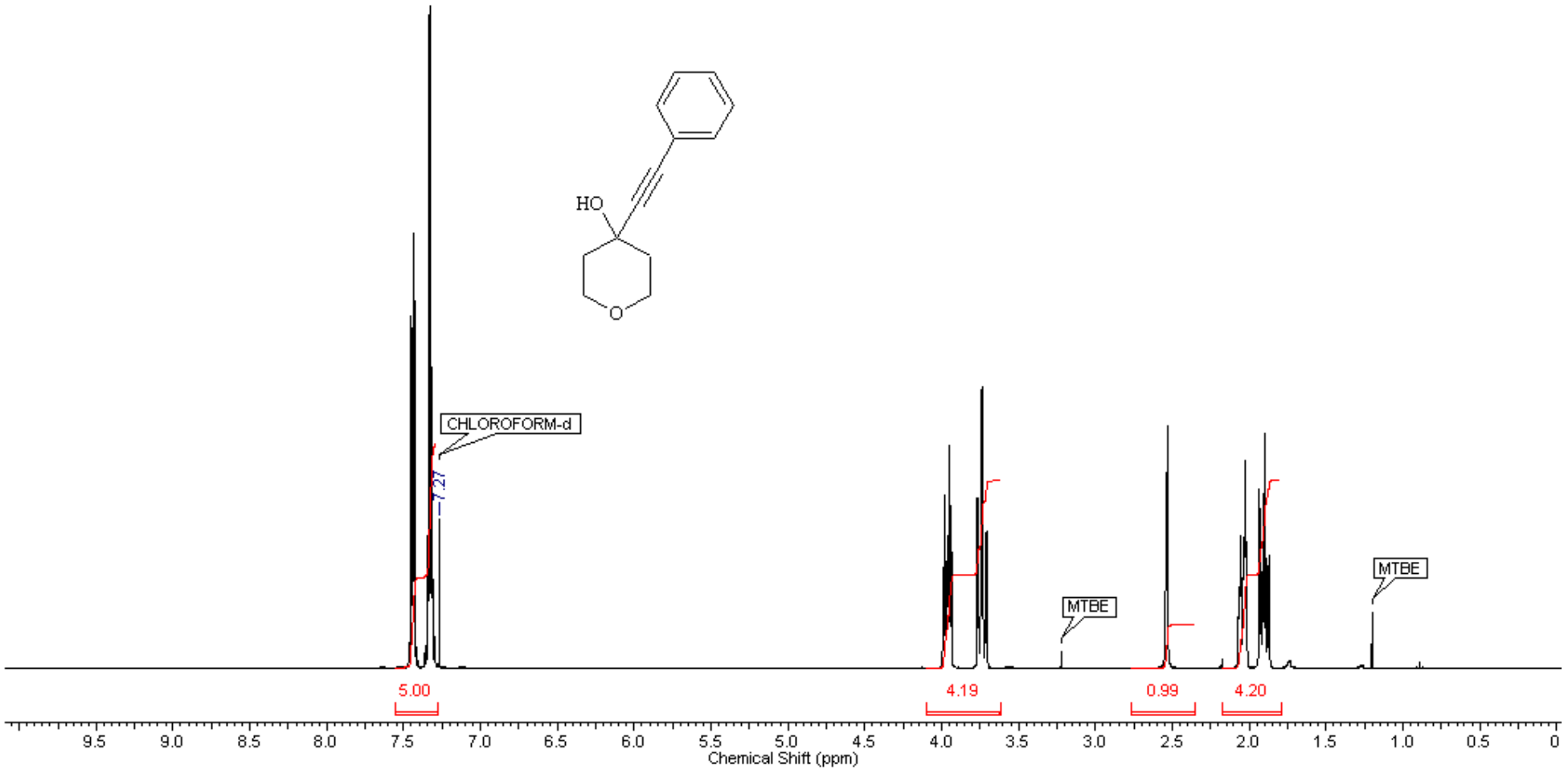
***Tert*-butyl 4-hydroxy-4-(phenylethynyl)piperidine-1-carboxylate (9). ^{1}H NMR ($CDCl_3$, 400 MHz)**



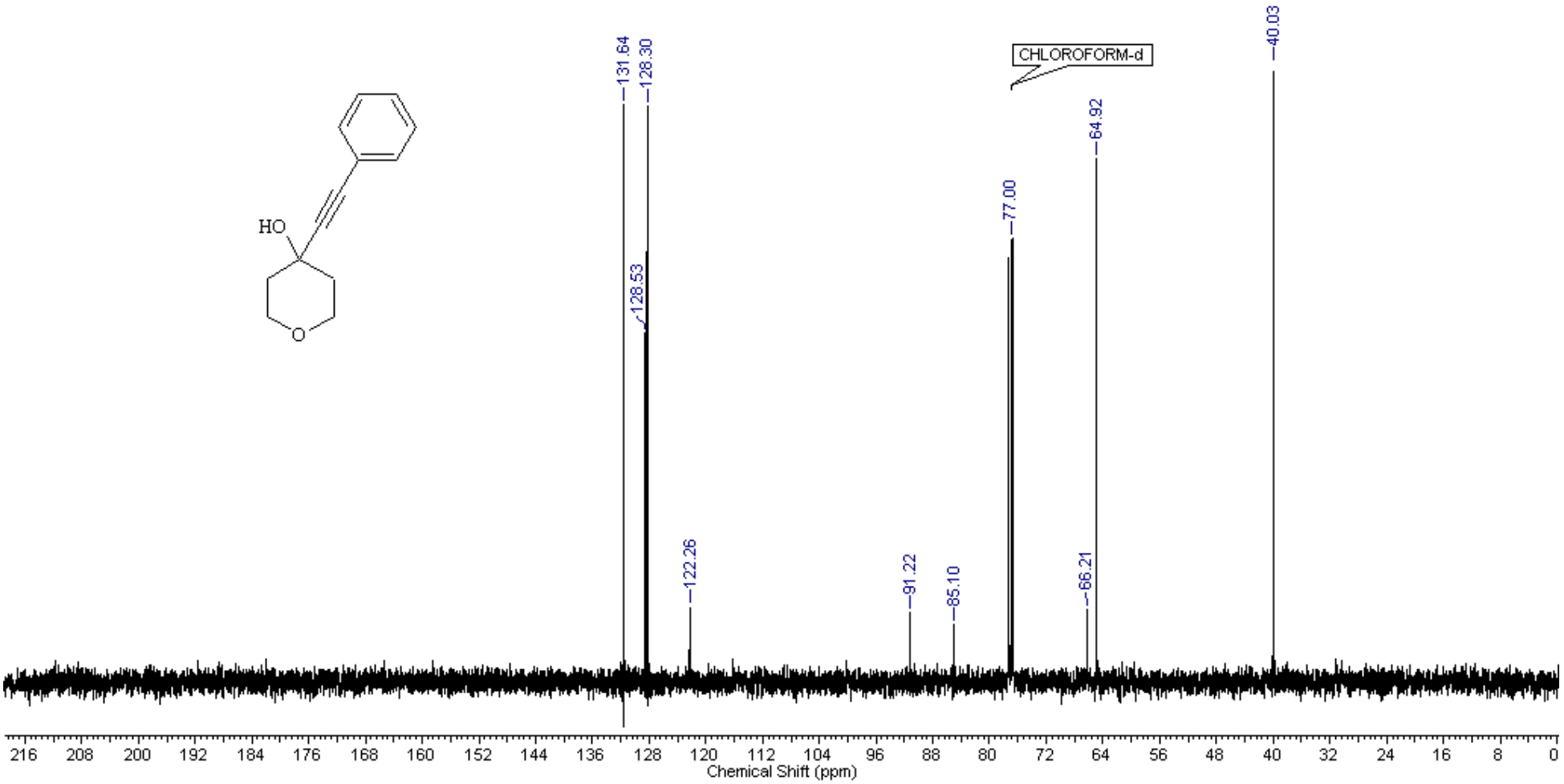
***Tert*-butyl 4-hydroxy-4-(phenylethynyl)piperidine-1-carboxylate (9). ^{13}C NMR ($CDCl_3$, 100 MHz)**



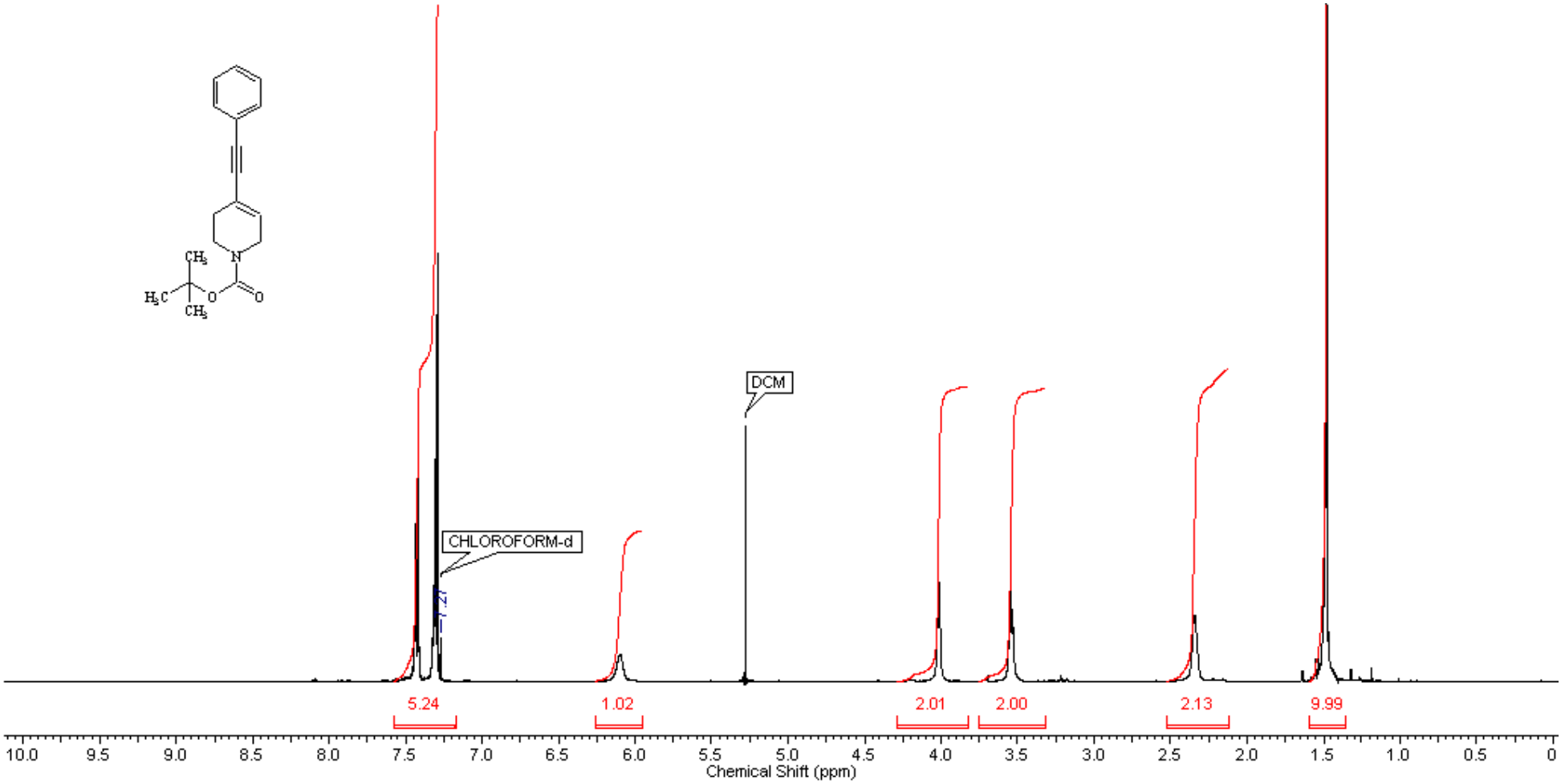
4-(Phenylethynyl)tetrahydro-2*H*-pyran-4-ol (10). ^{1}H NMR ($CDCl_3$, 400 MHz)



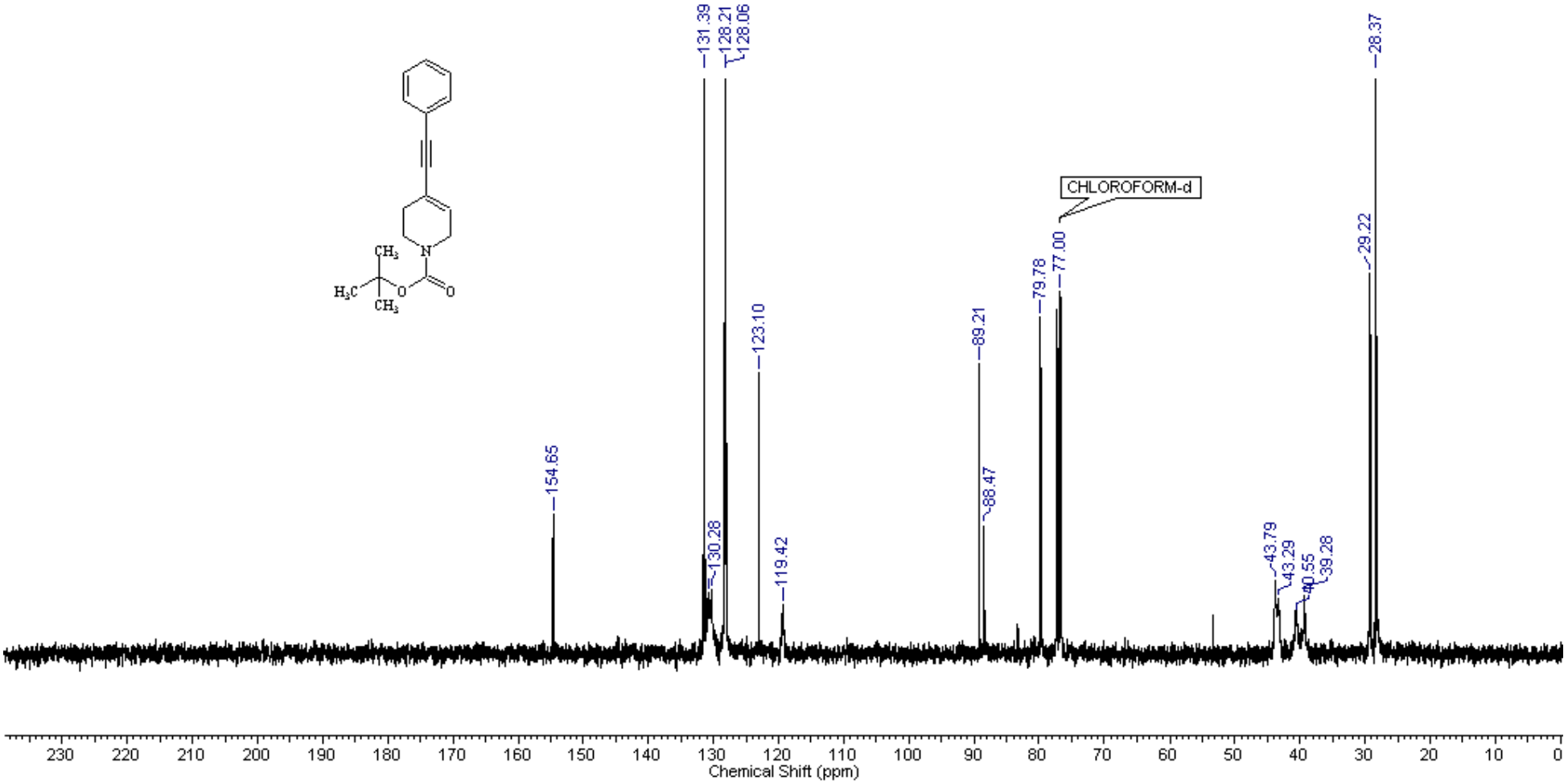
4-(Phenylethynyl)tetrahydro-2*H*-pyran-4-ol (10). ^{13}C NMR ($CDCl_3$, 100 MHz)



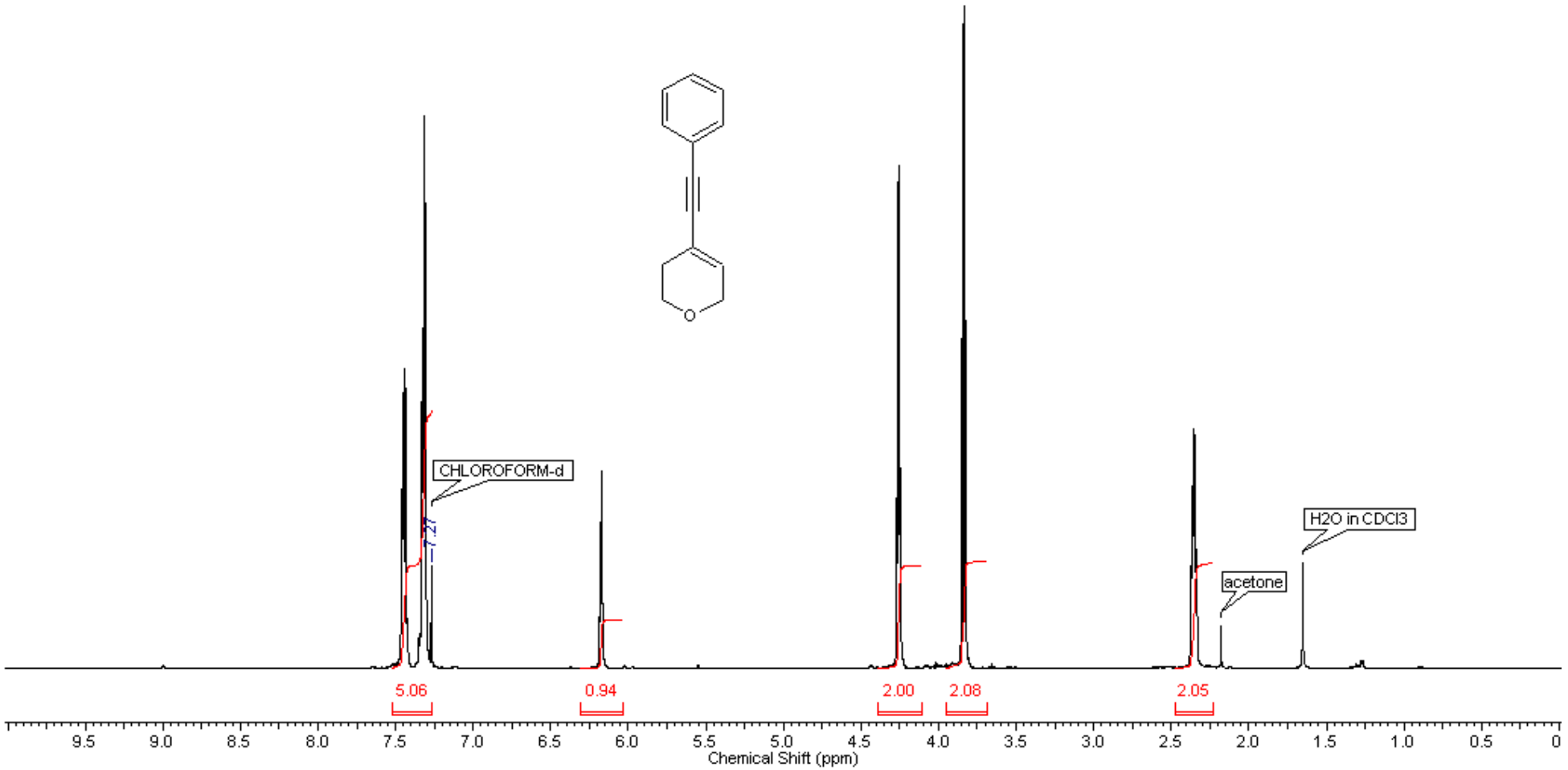
***Tert*-butyl 4-(phenylethynyl)-5,6-dihydropyridine-1(2H)-carboxylate (11). ^{1}H NMR ($CDCl_3$, 400 MHz)**



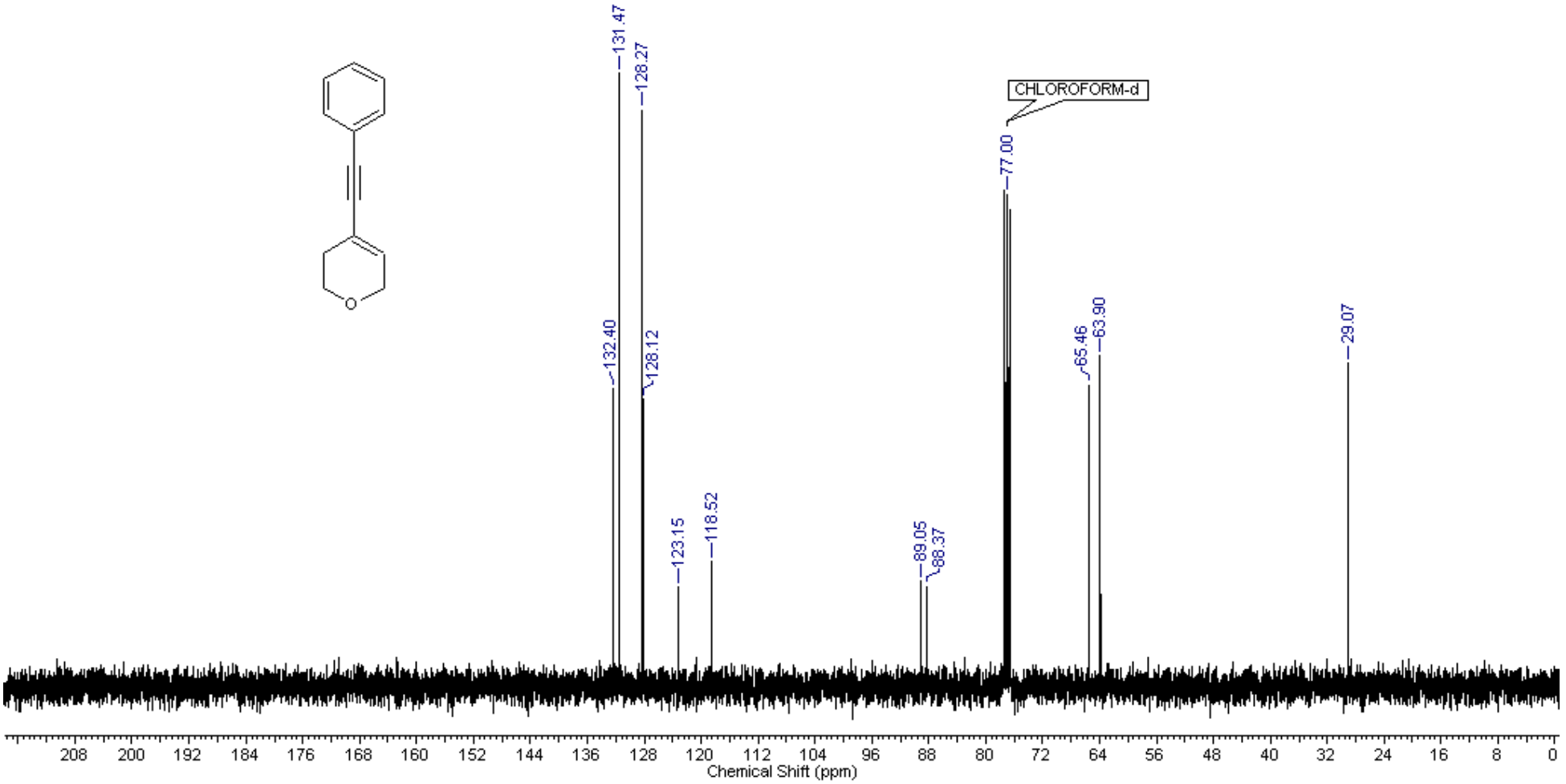
***Tert*-butyl 4-(phenylethynyl)-5,6-dihydropyridine-1(2H)-carboxylate (11). ^{13}C NMR ($CDCl_3$, 100 MHz)**



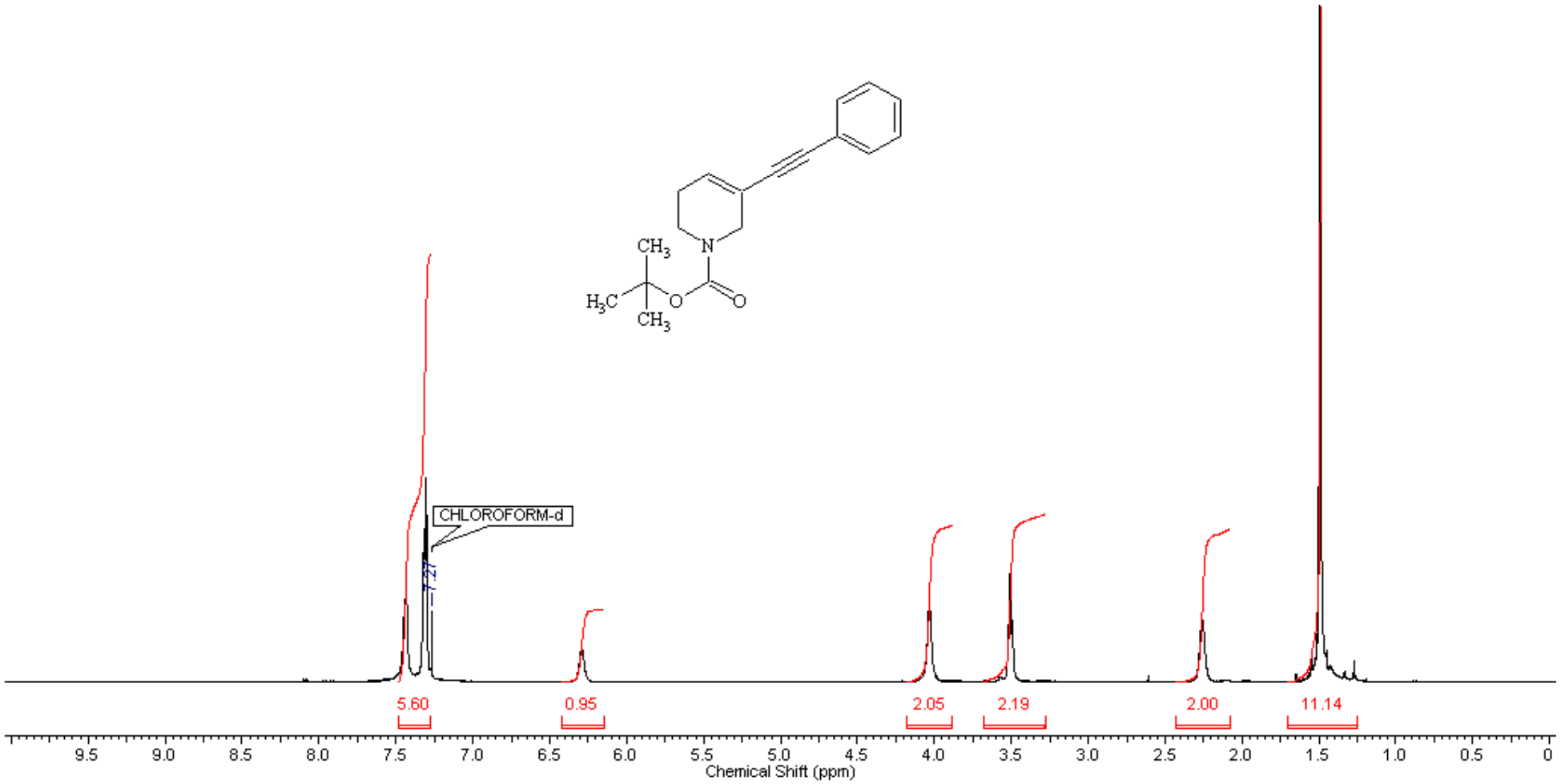
4-(Phenylethynyl)-3,6-dihydro-2*H*-pyran (12). ^{1}H NMR ($CDCl_3$, 400 MHz)



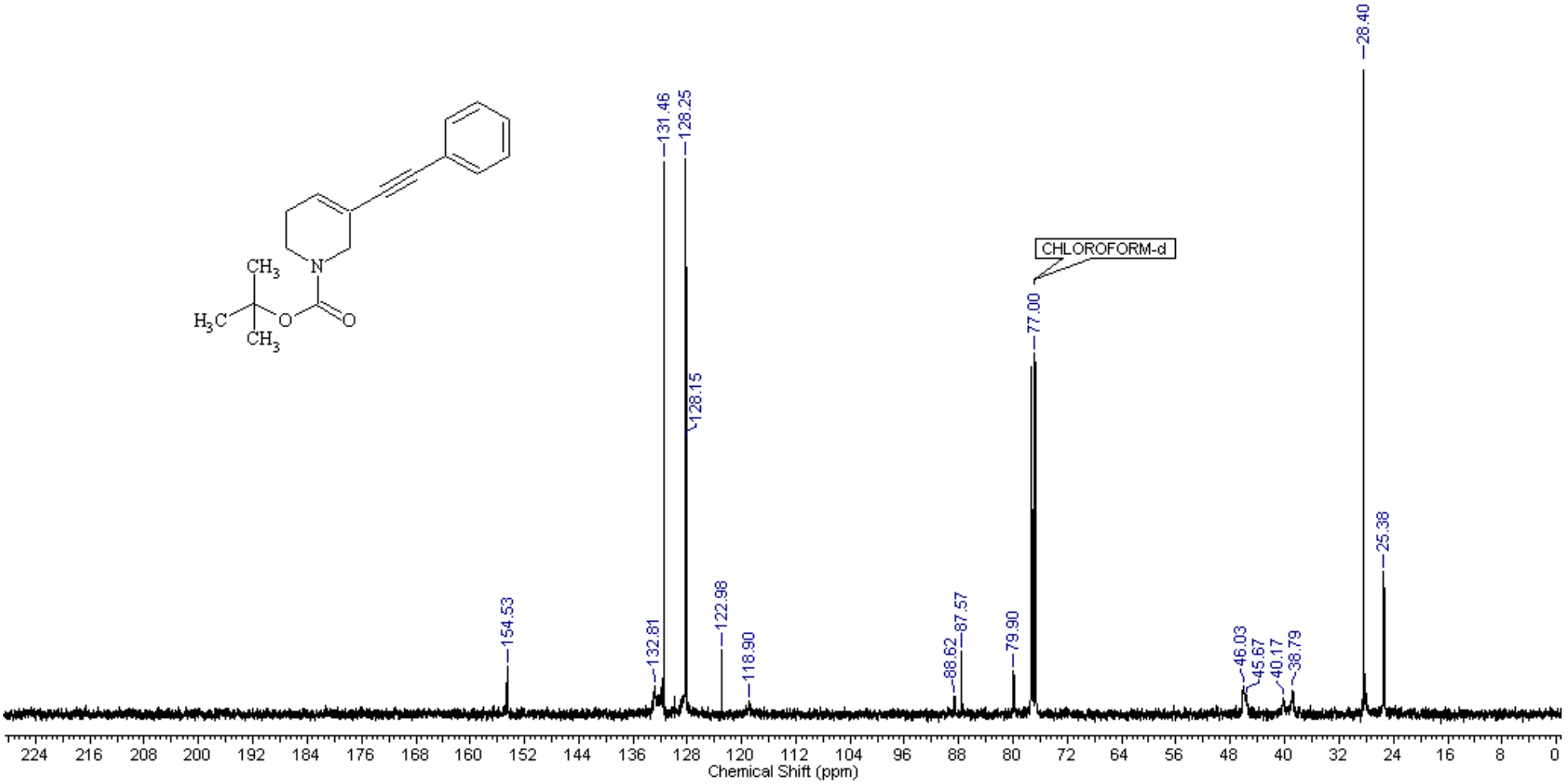
4-(Phenylethynyl)-3,6-dihydro-2*H*-pyran (12). ^{13}C NMR ($CDCl_3$, 100 MHz)



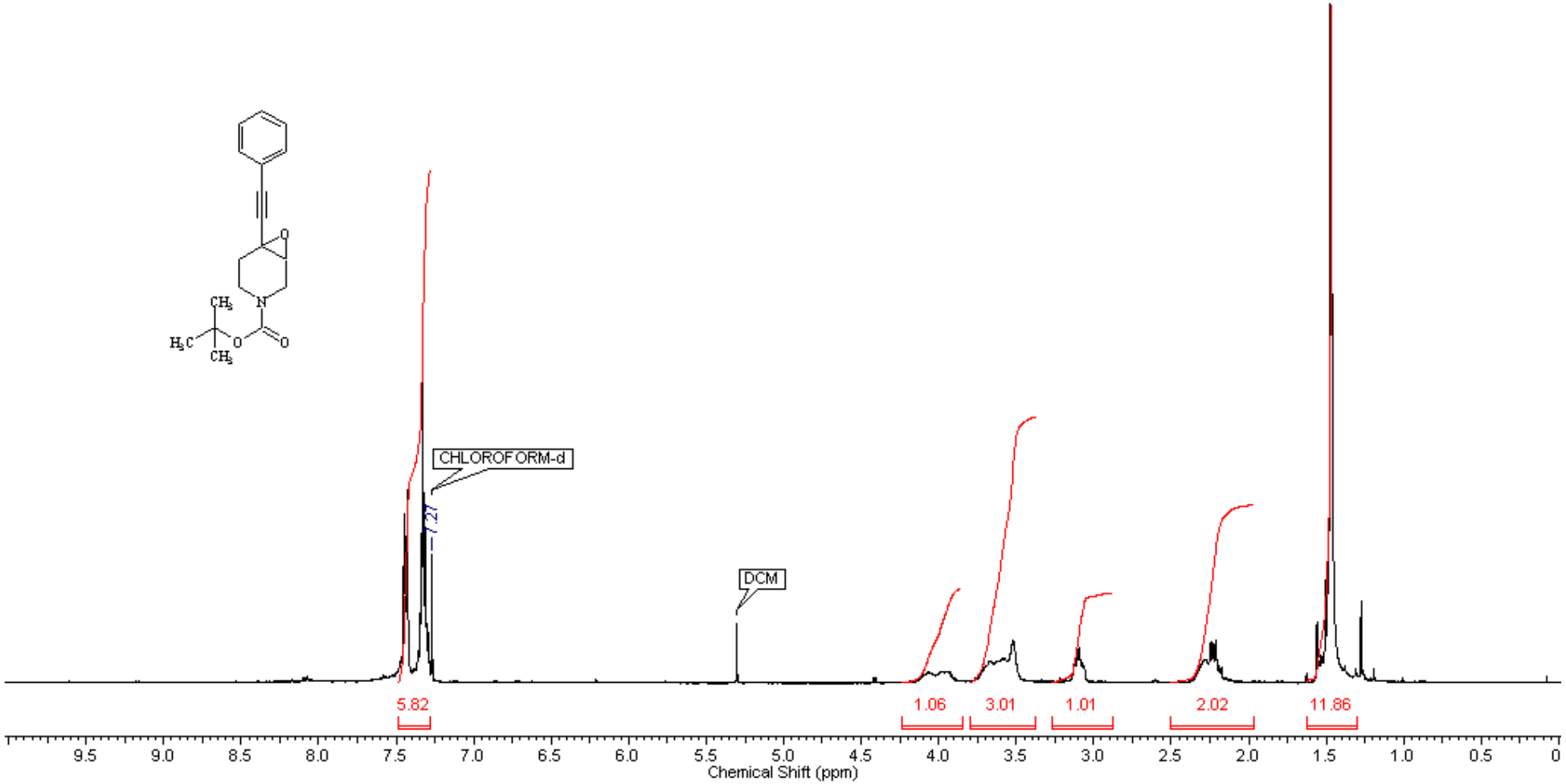
***Tert*-butyl 3-(phenylethynyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (13). ^{1}H NMR ($CDCl_3$, 400 MHz)**



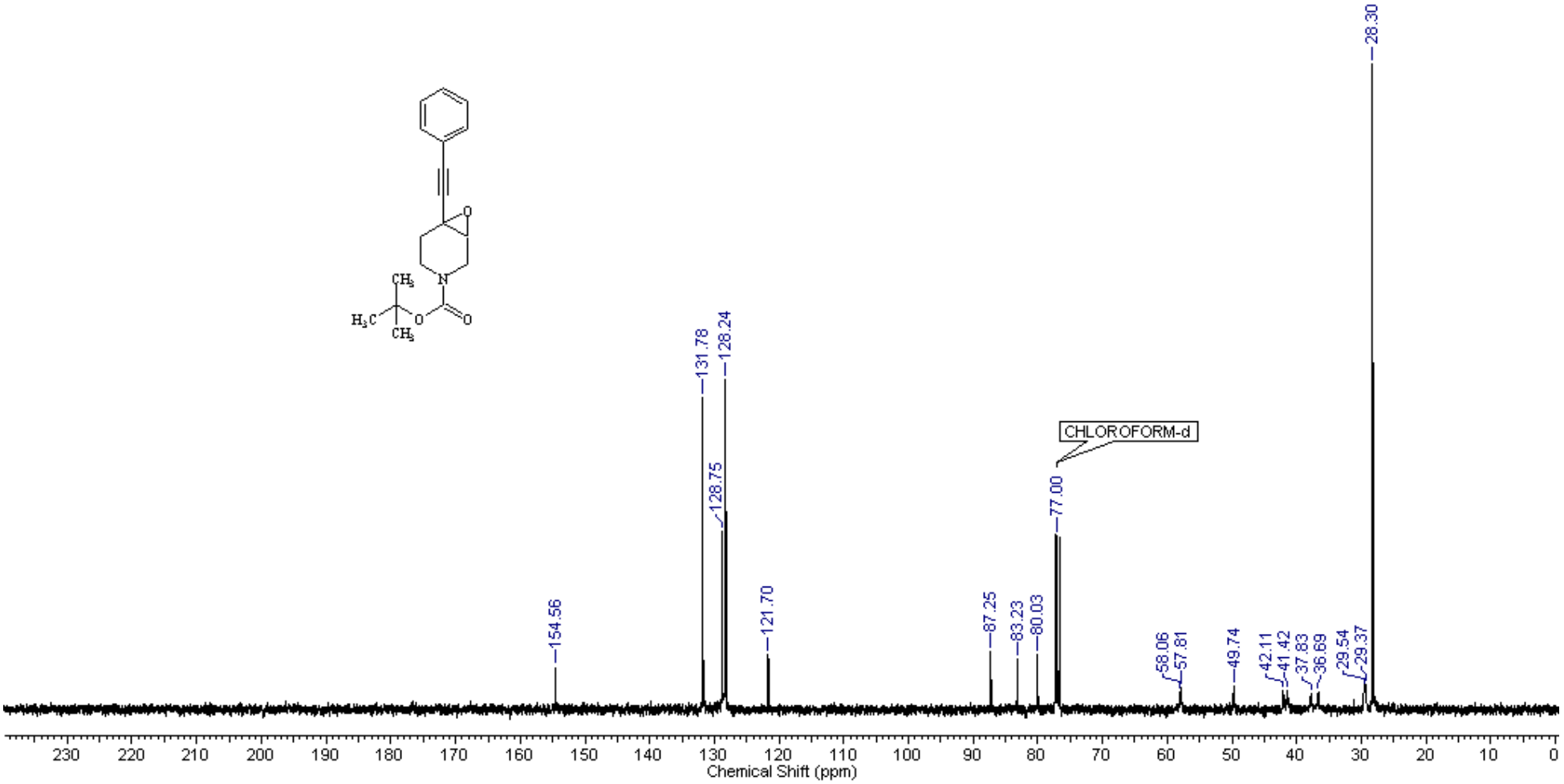
***Tert*-butyl 3-(phenylethynyl)-5,6-dihydropyridine-1(2*H*)-carboxylate (13). ^{13}C NMR ($CDCl_3$, 100 MHz)**



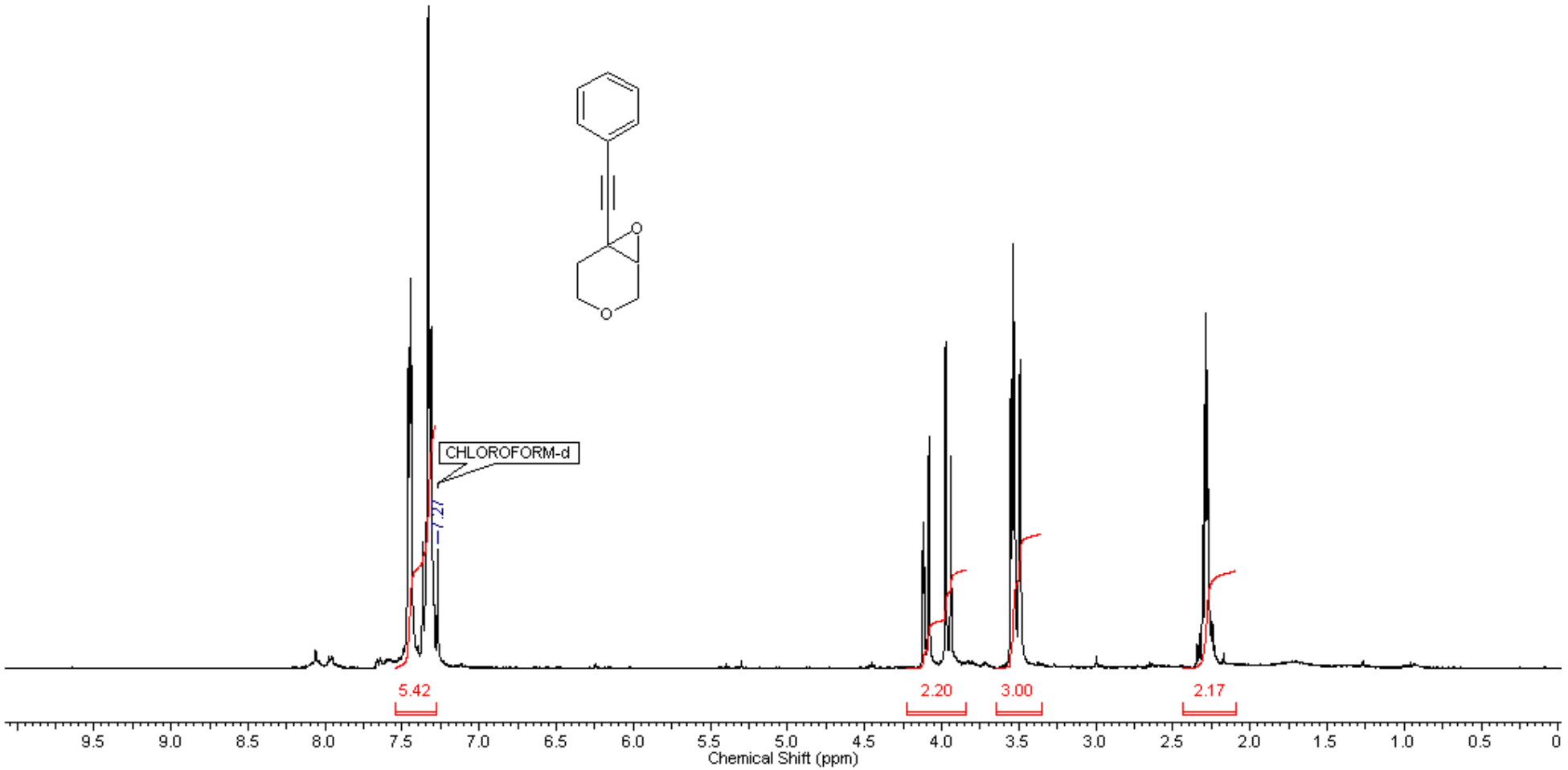
***Tert*-butyl 6-(phenylethynyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (14). ^{1}H NMR ($CDCl_3$, 400 MHz).**



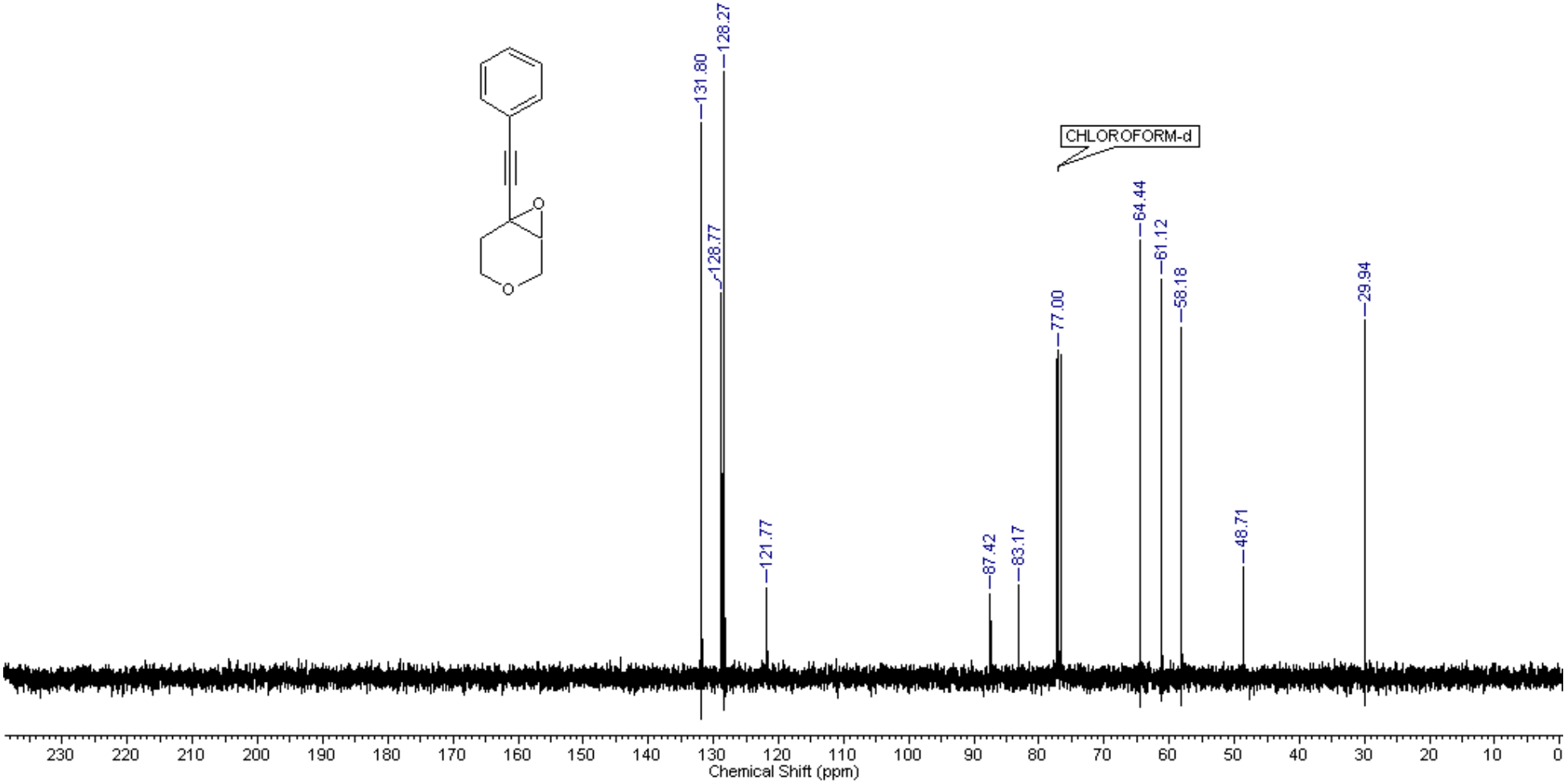
***Tert*-butyl 6-(phenylethynyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (14). ^{13}C NMR ($CDCl_3$, 100 MHz).**



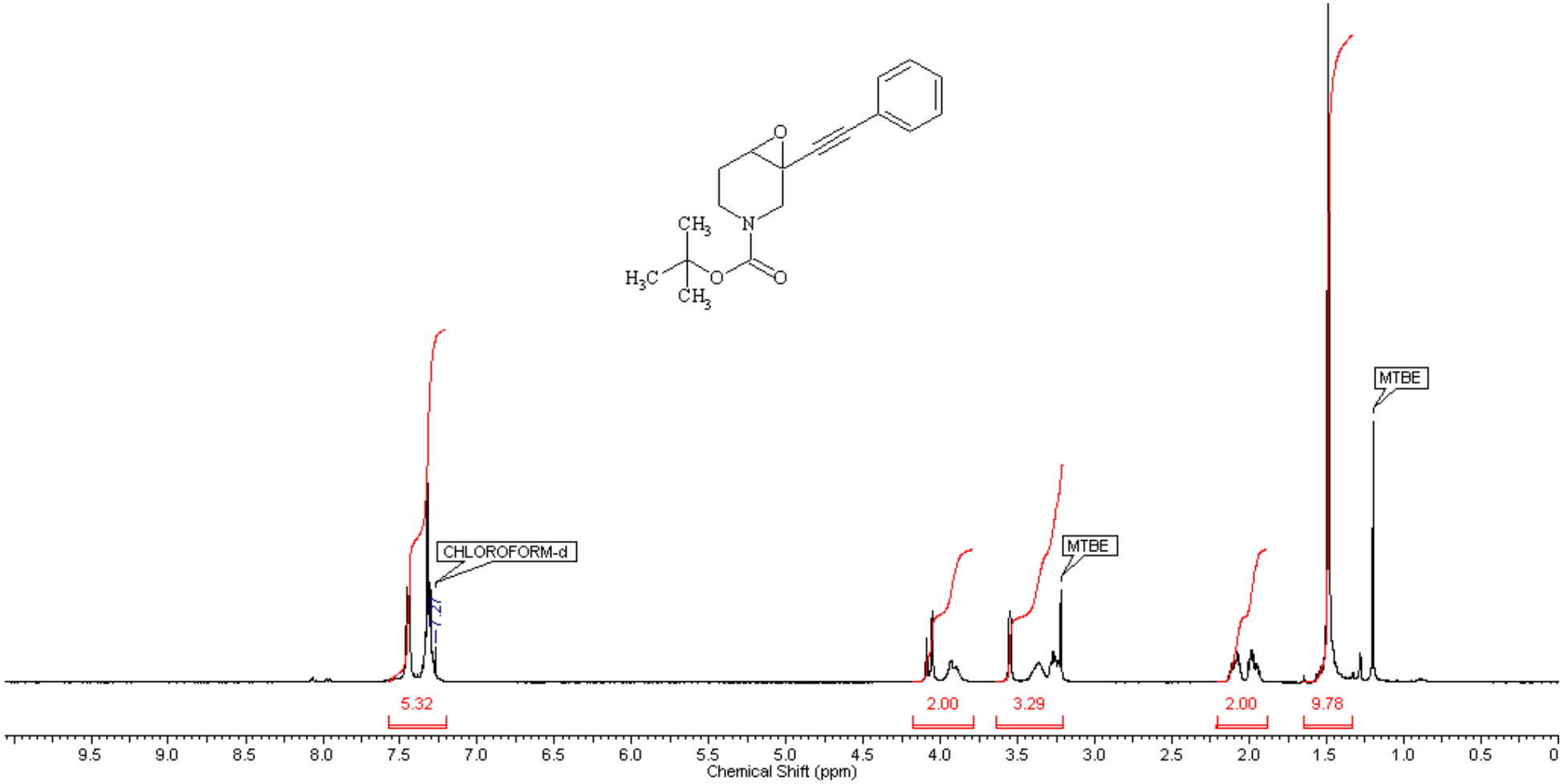
6-(Phenylethynyl)-3,7-dioxabicyclo[4.1.0]heptane (15). ^{1}H NMR ($CDCl_3$, 400 MHz)



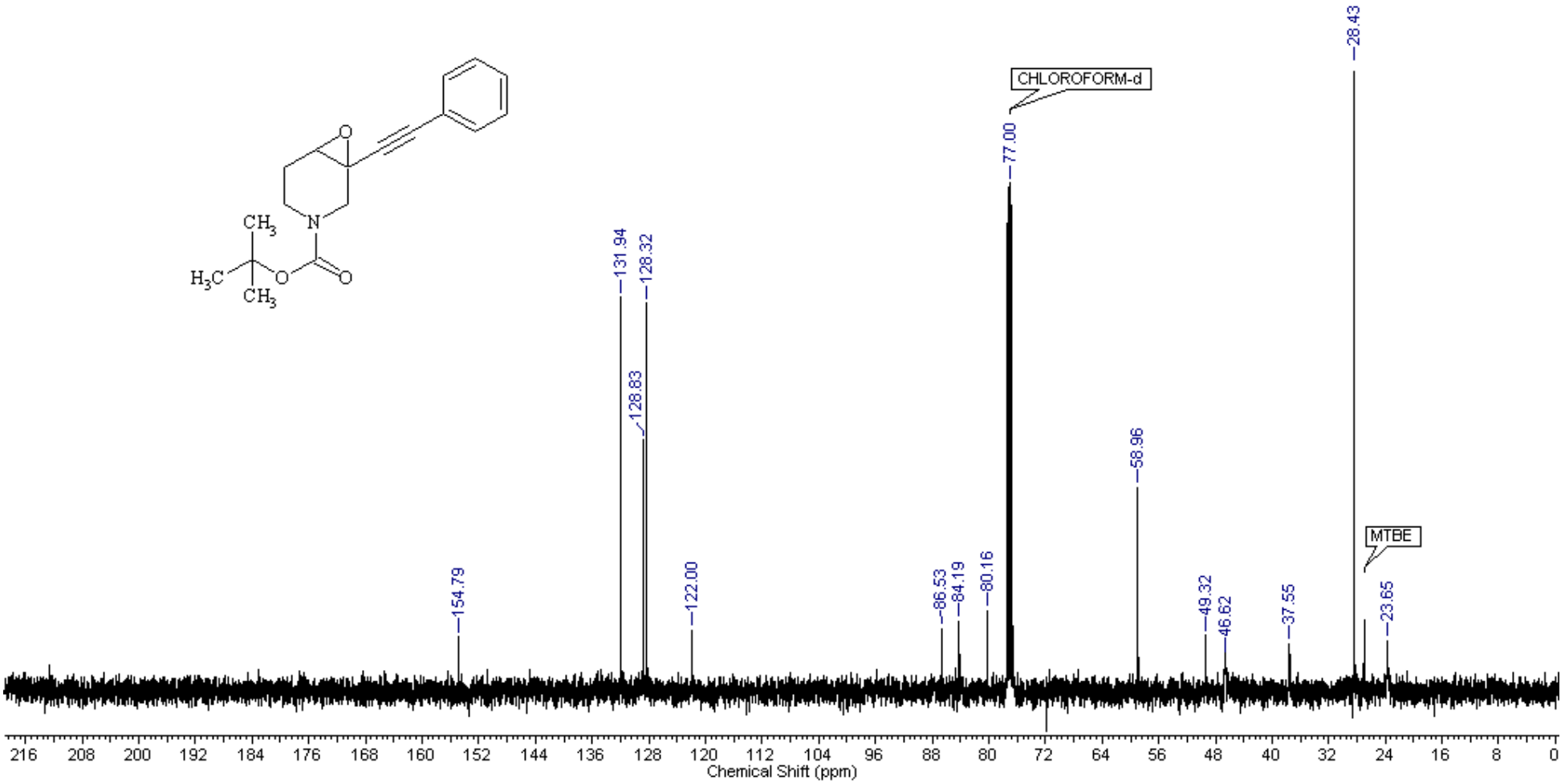
6-(Phenylethynyl)-3,7-dioxabicyclo[4.1.0]heptane (15). ^{13}C NMR ($CDCl_3$, 100 MHz)



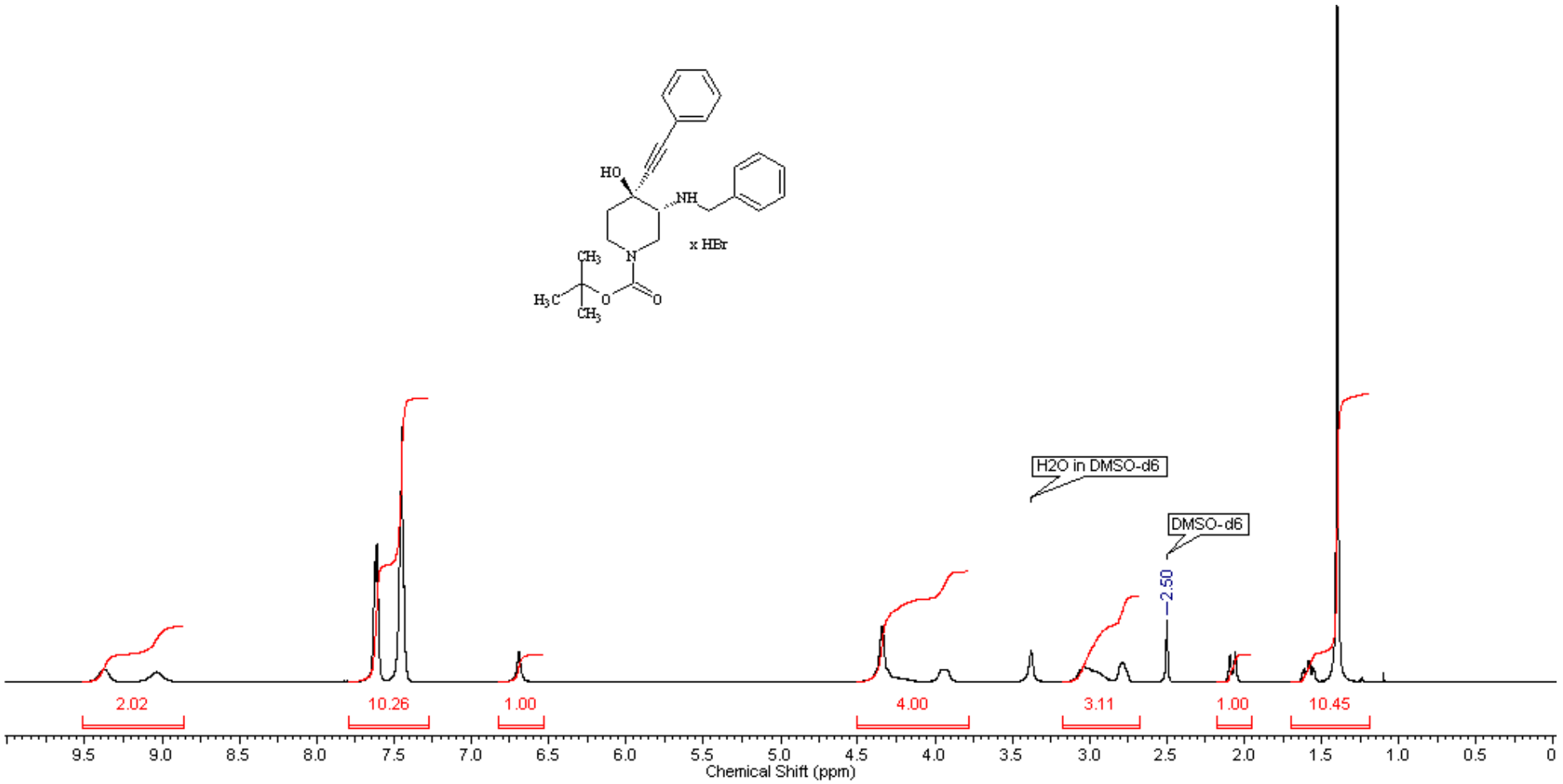
***Tert*-butyl 1-(phenylethynyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (16). ^{1}H NMR ($CDCl_3$, 400 MHz, 50^{O}C)**



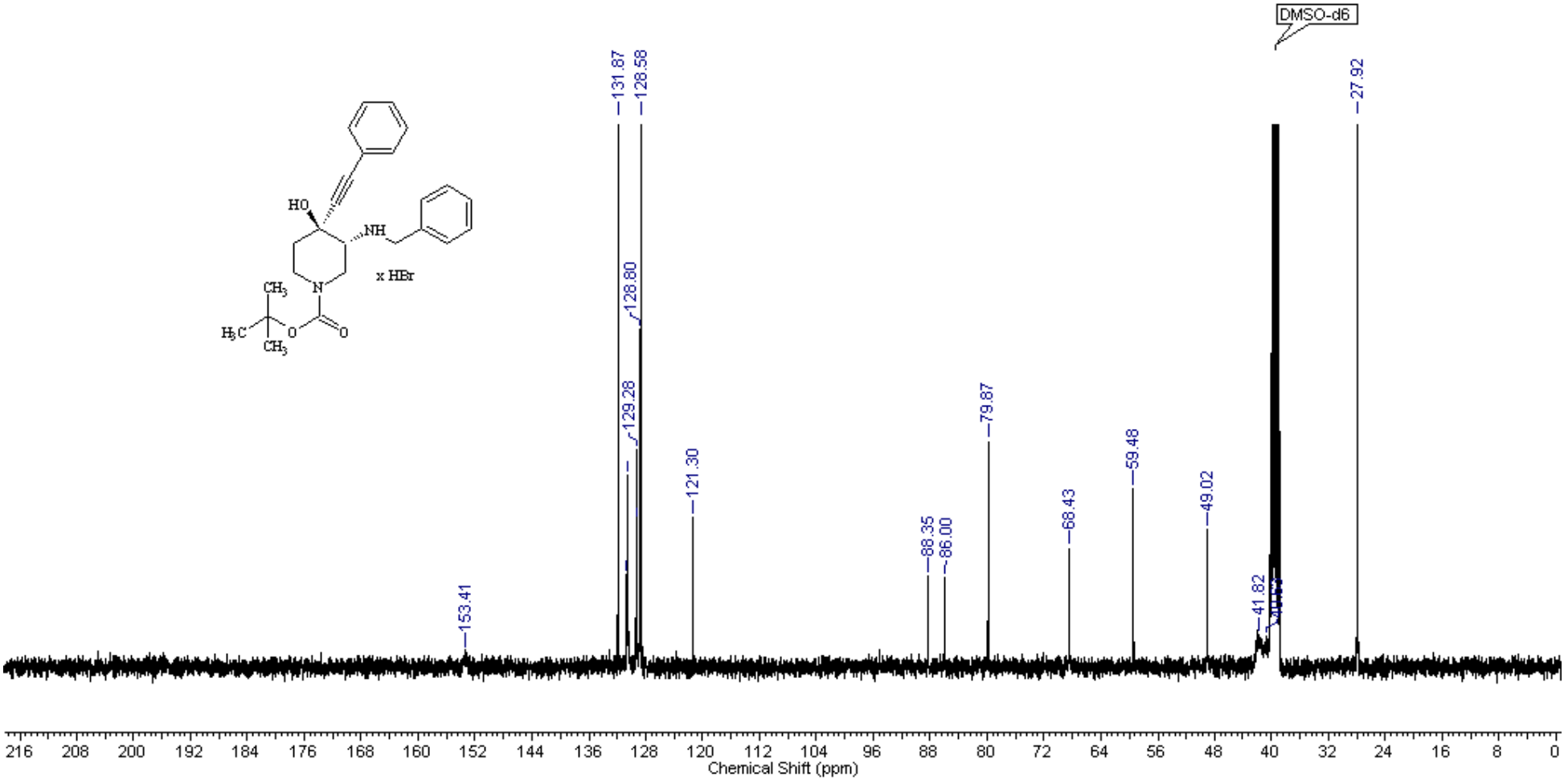
***Tert*-butyl 1-(phenylethynyl)-7-oxa-3-azabicyclo[4.1.0]heptane-3-carboxylate (16). ^{13}C NMR ($CDCl_3$, 100 MHz, 50^{O}C)**



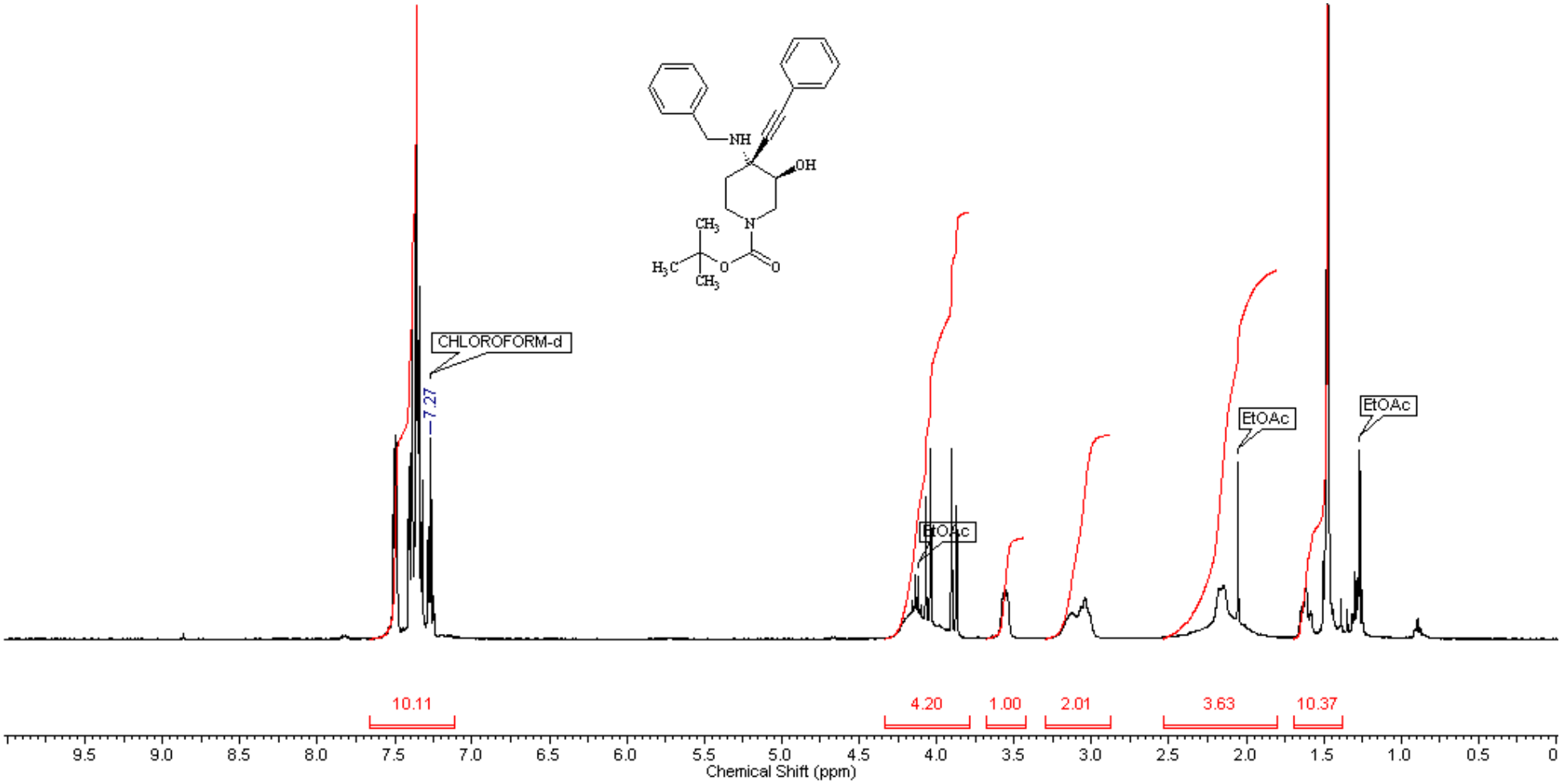
(3*RS*,4*SR*)-*Tert*-butyl 3-(benzylamino)-4-hydroxy-4-(phenylethynyl)piperidine-1-carboxylate hydrobromide (17). ^{1}H NMR (DMSO-d_6, 400 MHz)



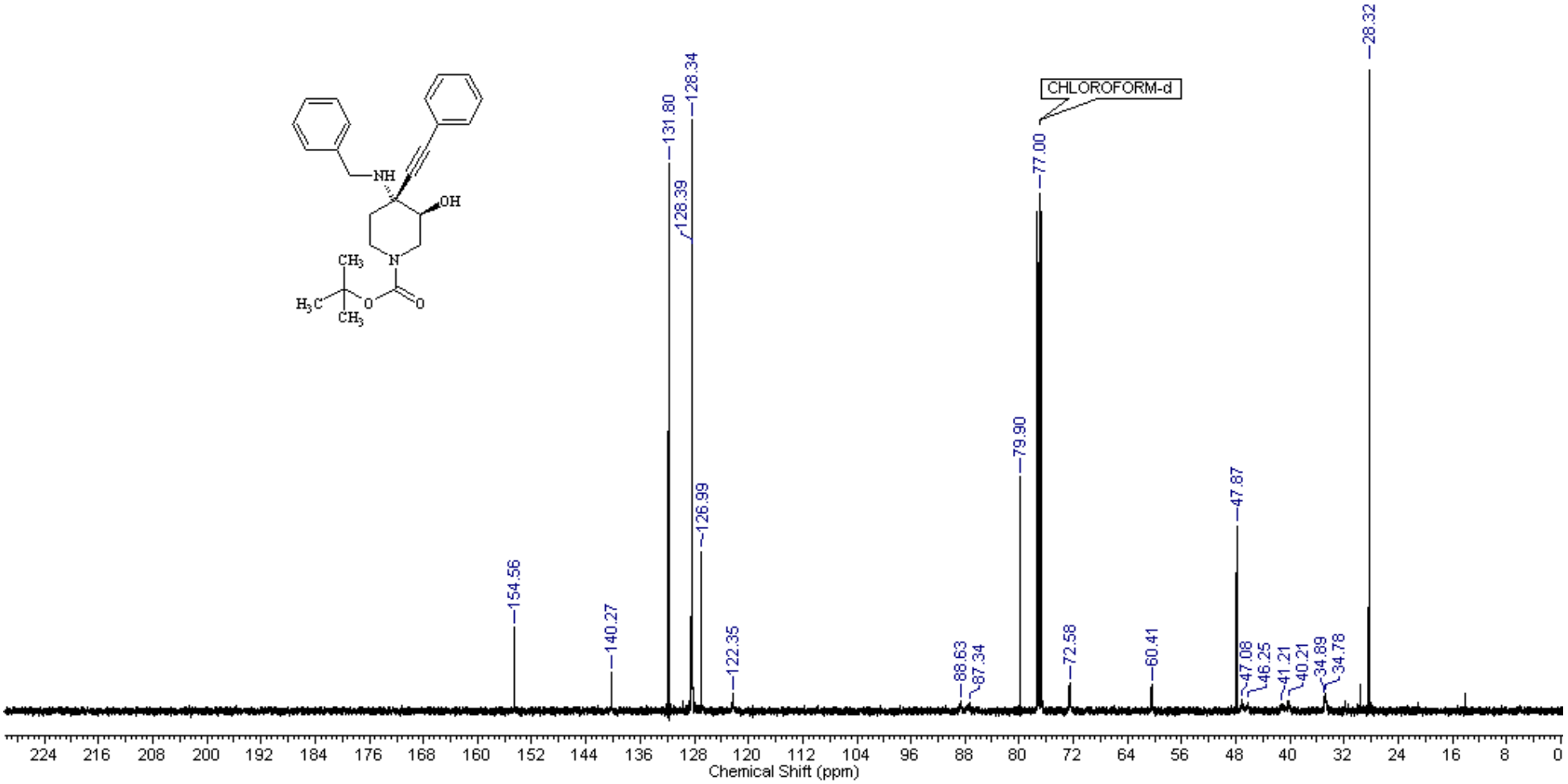
(3*RS*,4*SR*)-*Tert*-butyl 3-(benzylamino)-4-hydroxy-4-(phenylethynyl)piperidine-1-carboxylate hydrobromide (17). ^{13}C NMR (DMSO-d_6, 100 MHz)



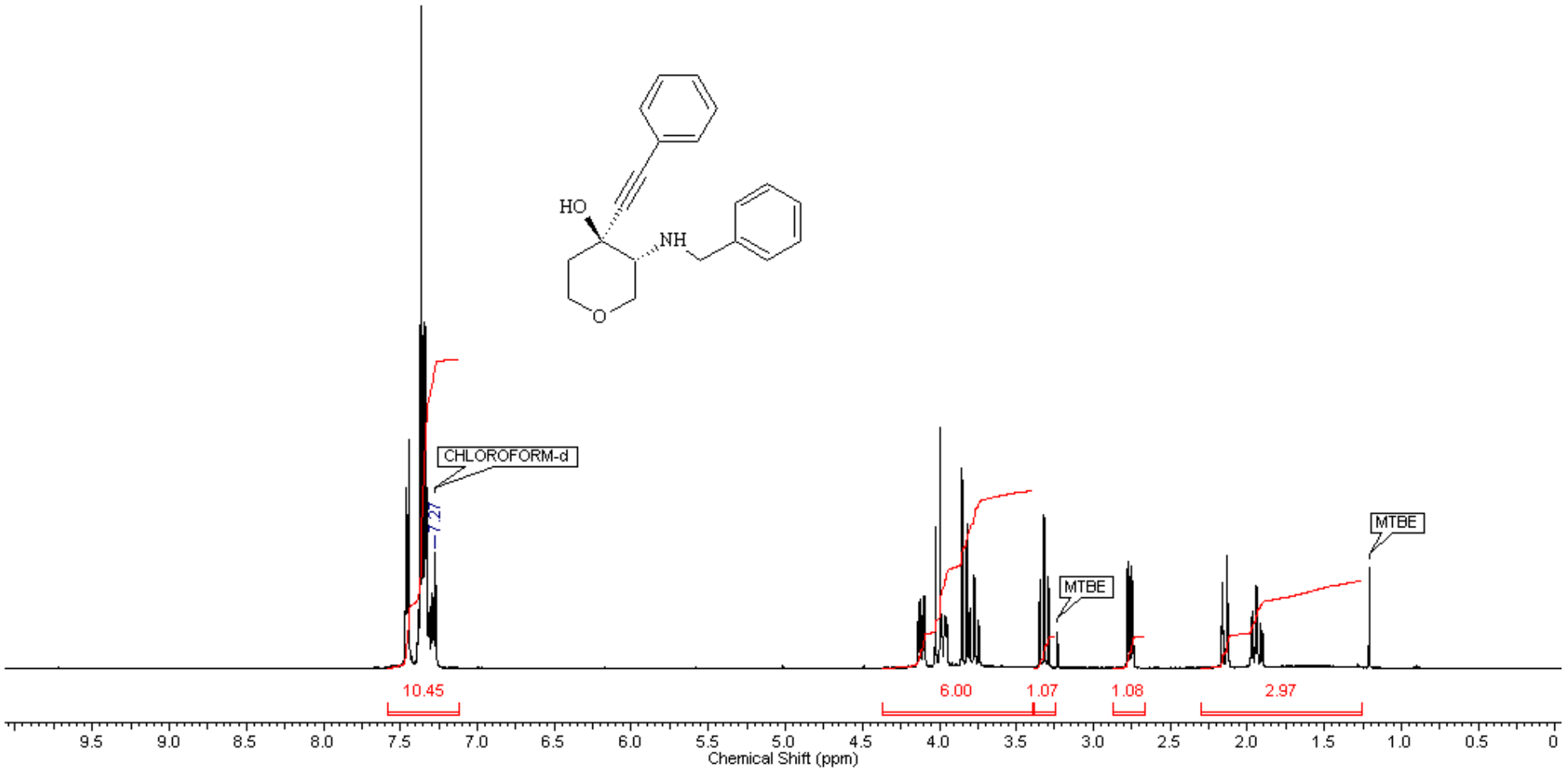
(3*SR*,4*RS*)-*tert*-Butyl 4-(benzylamino)-3-hydroxy-4-(phenylethynyl)piperidine-1-carboxylate (17a). ^{1}H NMR ($CDCl_3$, 400 MHz)



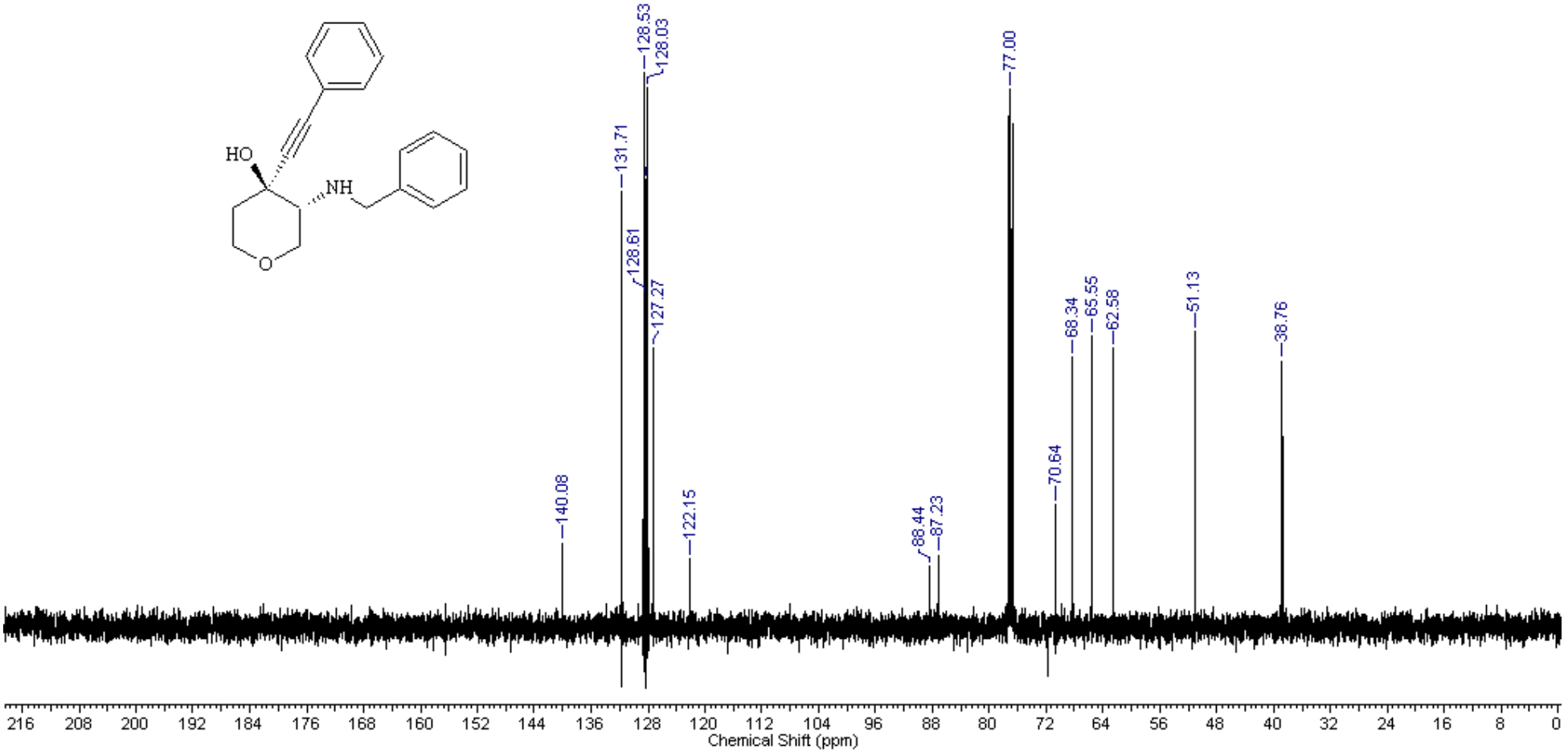
(3*SR*,4*RS*)-*tert*-Butyl 4-(benzylamino)-3-hydroxy-4-(phenylethynyl)piperidine-1-carboxylate (17a). ^{13}C NMR ($CDCl_3$, 100 MHz)



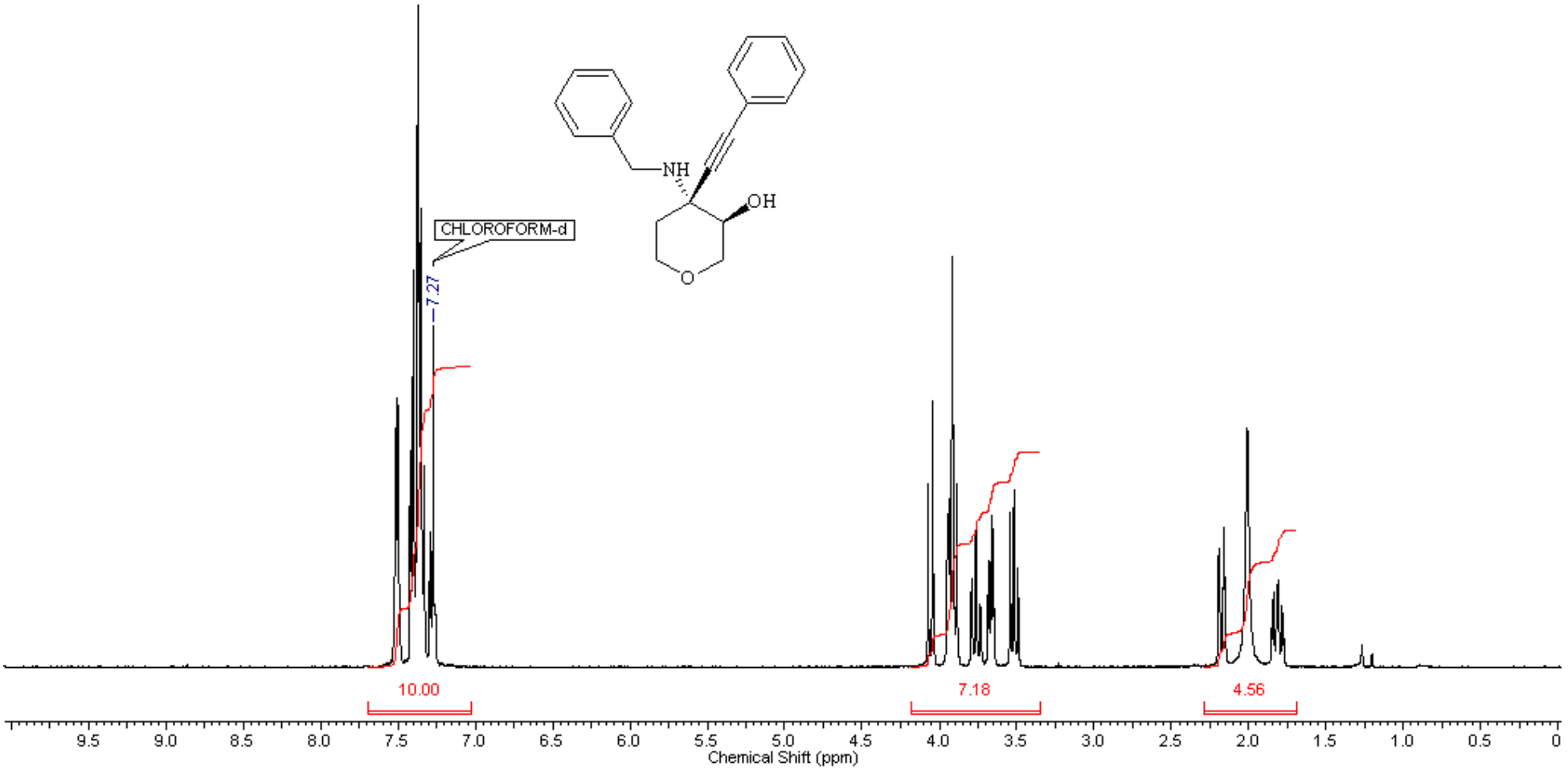
(3*RS*,4*SR*)-3-(Benzylamino)-4-(phenylethynyl)tetrahydro-2*H*-pyran-4-ol (18). ^{1}H NMR ($CDCl_3$, 400 MHz)



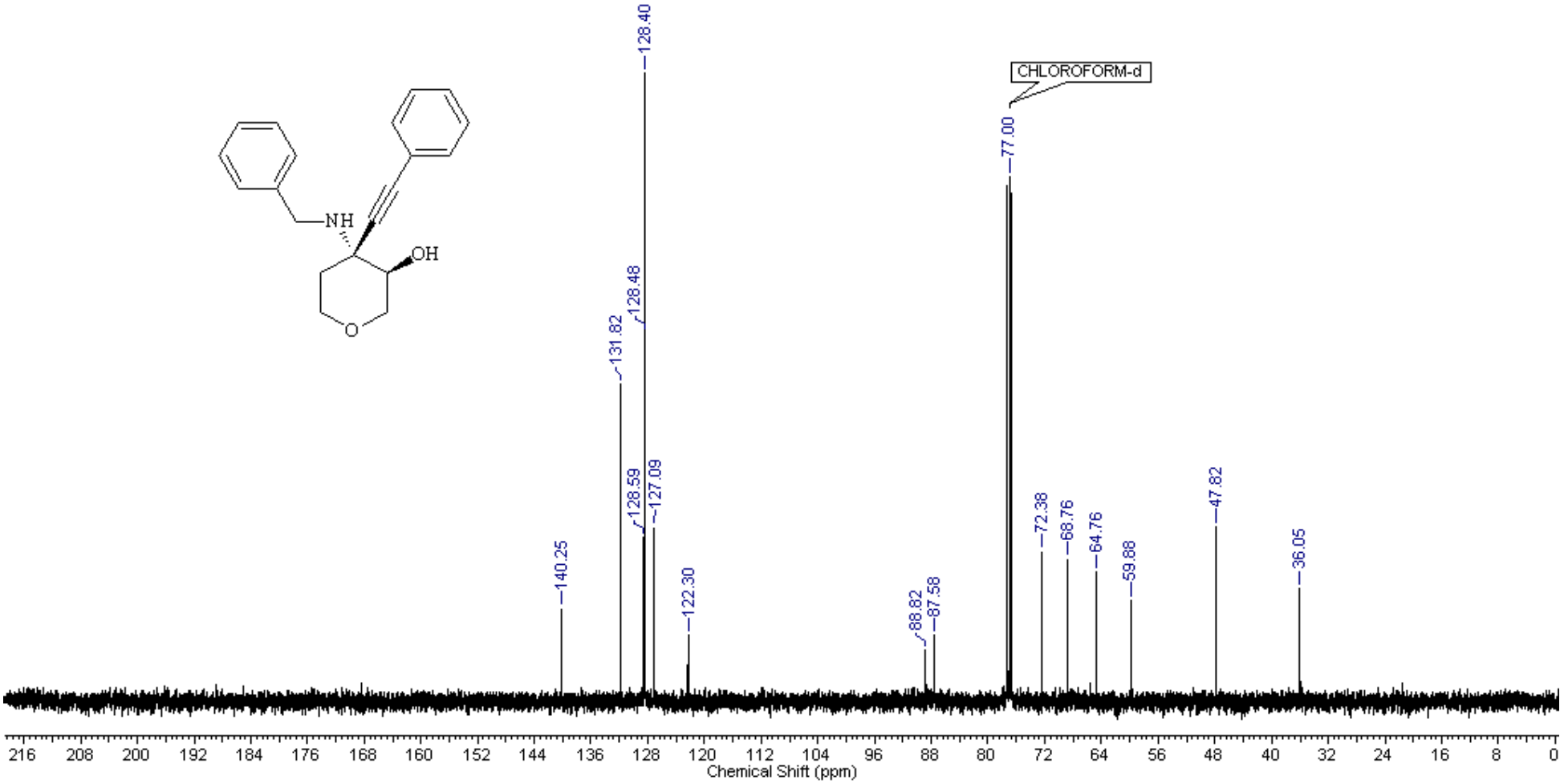
(3*RS*,4*SR*)-3-(Benzylamino)-4-(phenylethynyl)tetrahydro-2*H*-pyran-4-ol (18). ^{13}C NMR ($CDCl_3$, 100 MHz)



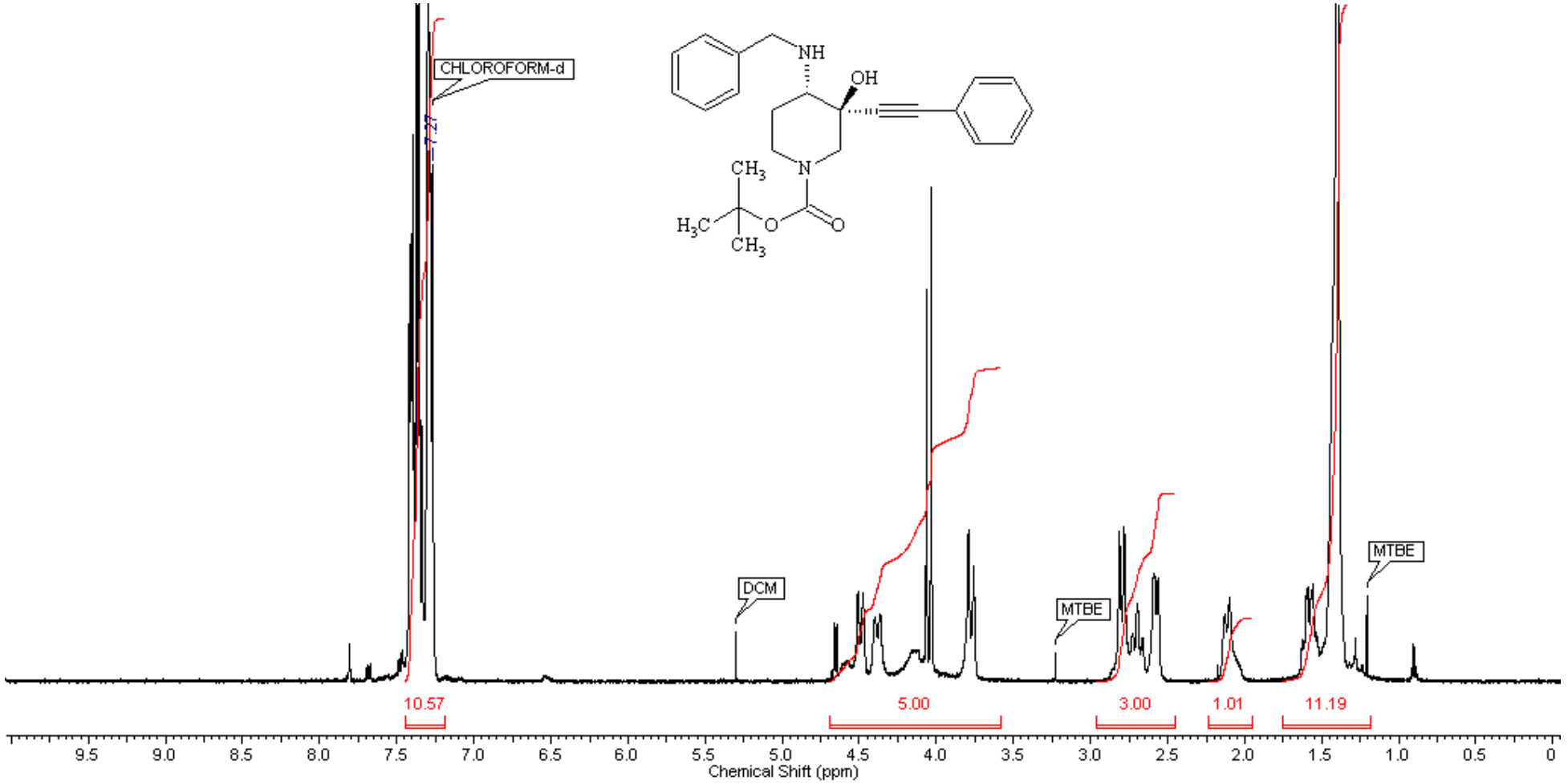
(3*RS*,4*RS*)-4-(benzylamino)-4-(phenylethynyl)tetrahydro-2*H*-pyran-3-ol (18a). ^{1}H NMR ($CDCl_3$, 400 MHz)



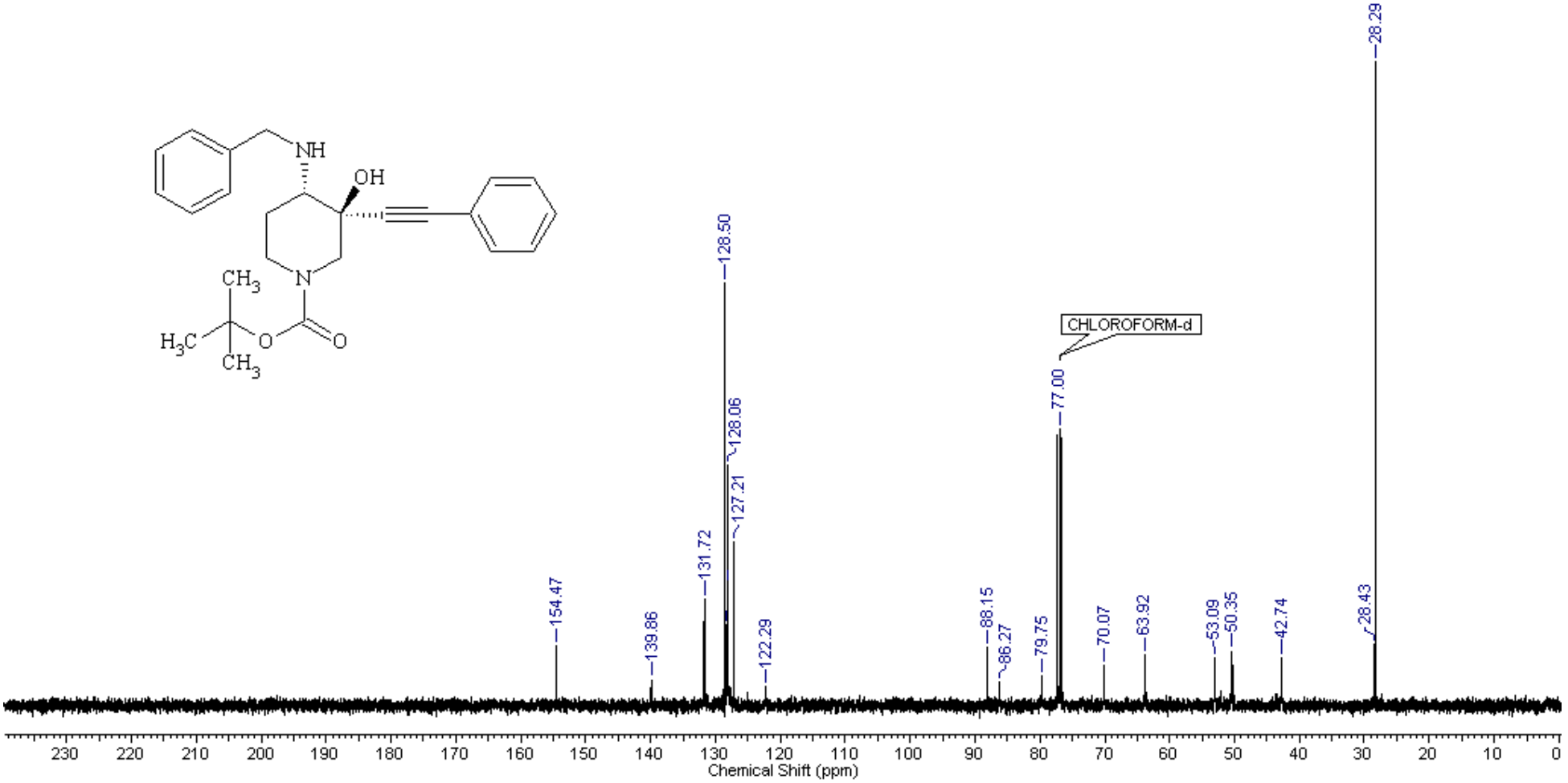
(3*RS*,4*RS*)-4-(benzylamino)-4-(phenylethynyl)tetrahydro-2*H*-pyran-3-ol (18a). ^{13}C NMR ($CDCl_3$, 100 MHz)



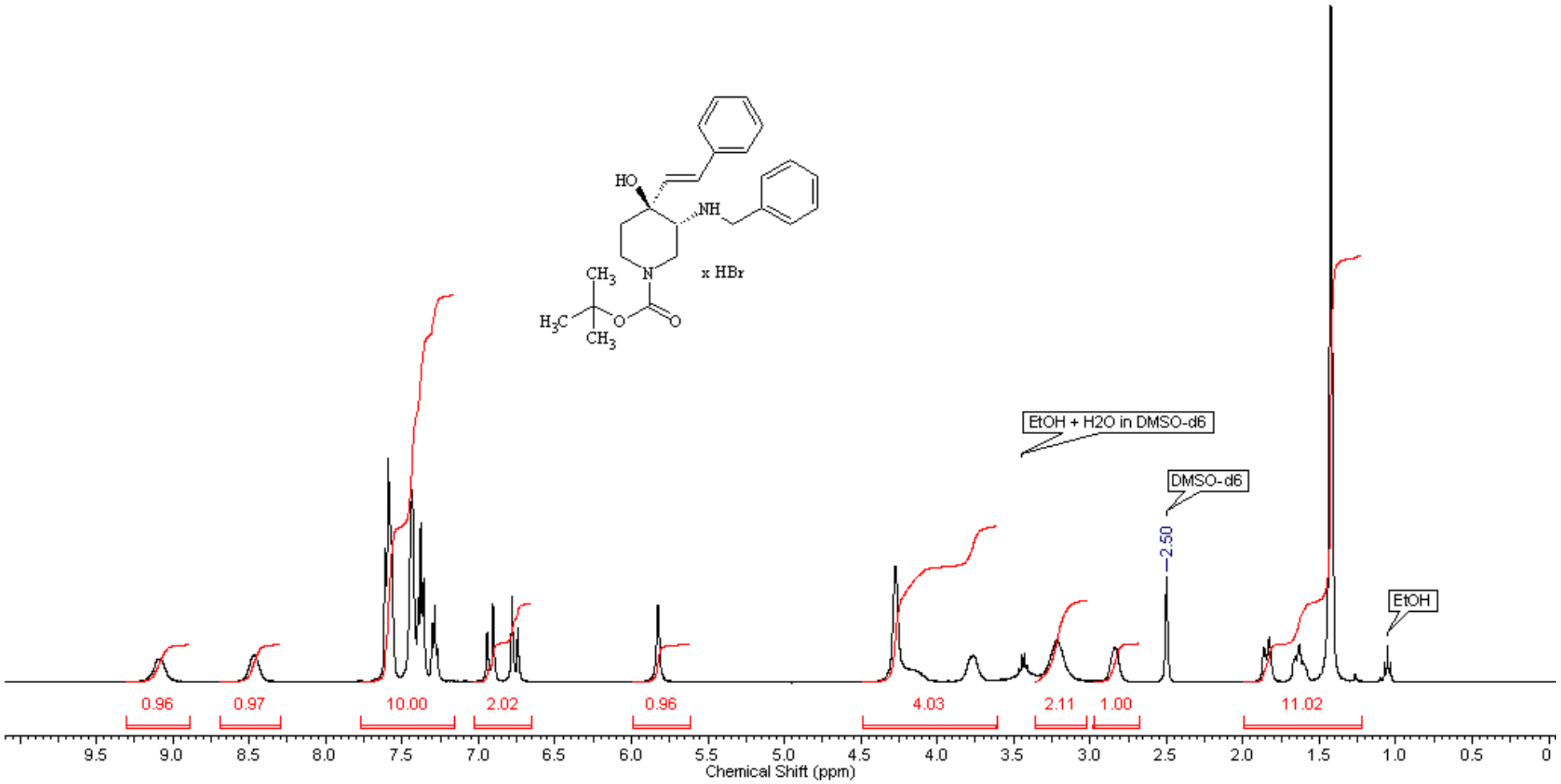
(3*SR*,4*SR*)-*Tert*-butyl 4-(benzylamino)-3-hydroxy-3-(phenylethynyl)piperidine-1-carboxylate (19). ^{1}H NMR ($CDCl_3$, 400 MHz)



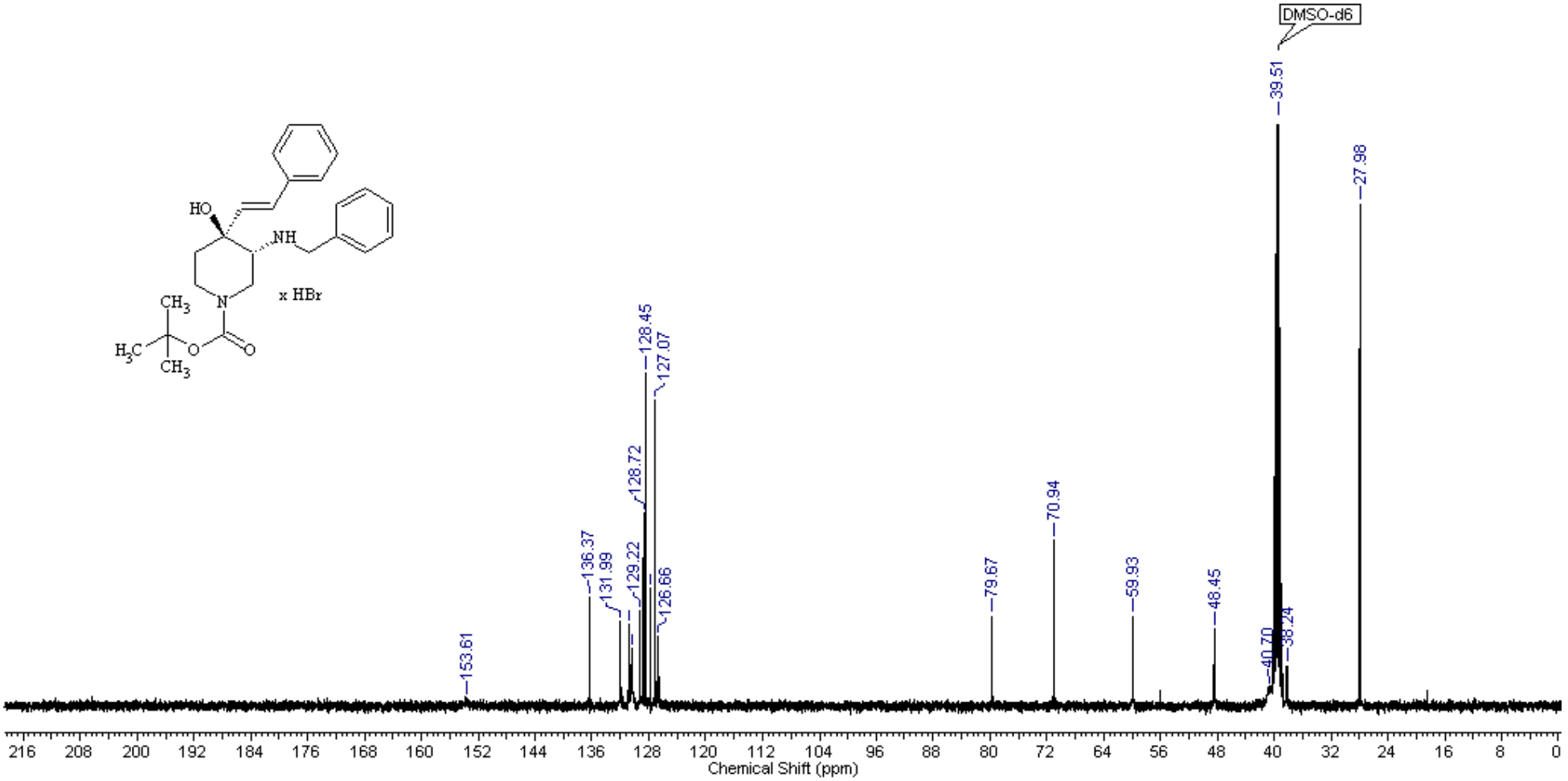
(3*SR*,4*SR*)-*Tert*-butyl 4-(benzylamino)-3-hydroxy-3-(phenylethynyl)piperidine-1-carboxylate (19). ^{13}C NMR ($CDCl_3$, 100 MHz)



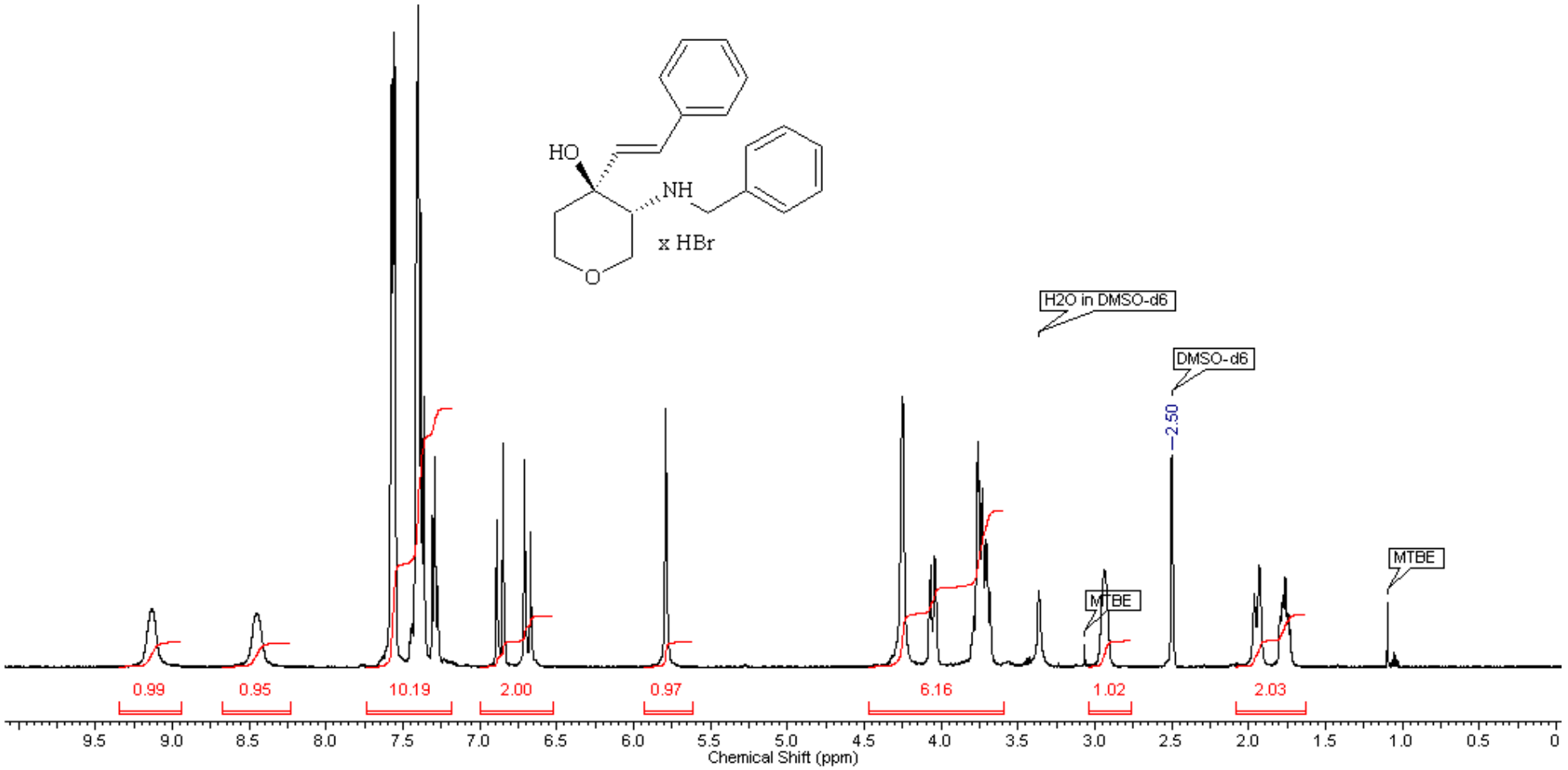
(3*RS*,4*SR*)-*Tert*-butyl 3-(benzylamino)-4-hydroxy-4-((*E*)-styryl)piperidine-1-carboxylate hydrobromide (20). ^{1}H NMR (DMSO-d_6, 400 MHz)



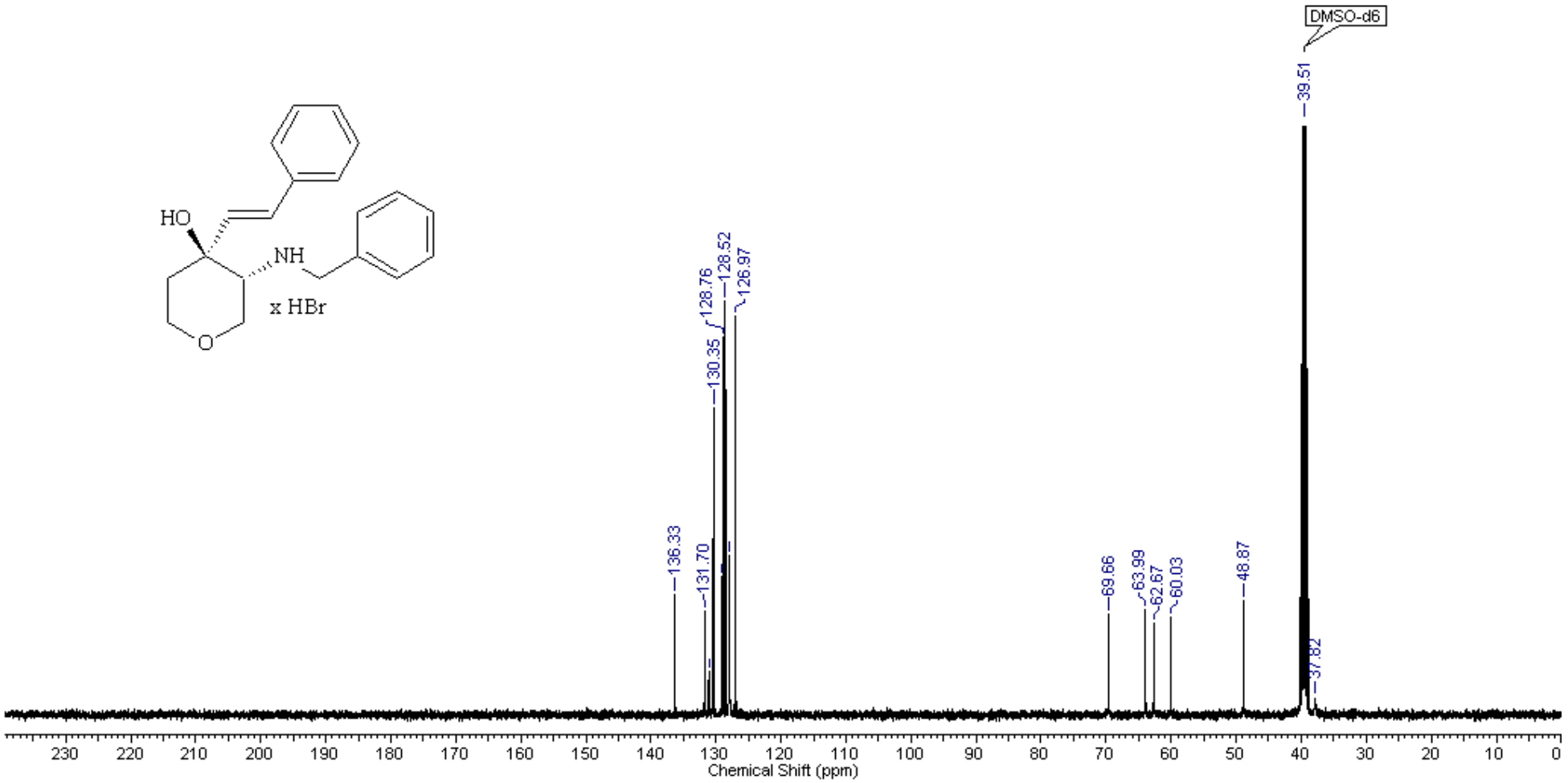
(3*RS*,4*SR*)-*Tert*-butyl 3-(benzylamino)-4-hydroxy-4-((*E*)-styryl)piperidine-1-carboxylate hydrobromide (20). ^{13}C NMR (DMSO-d_6, 100 MHz)



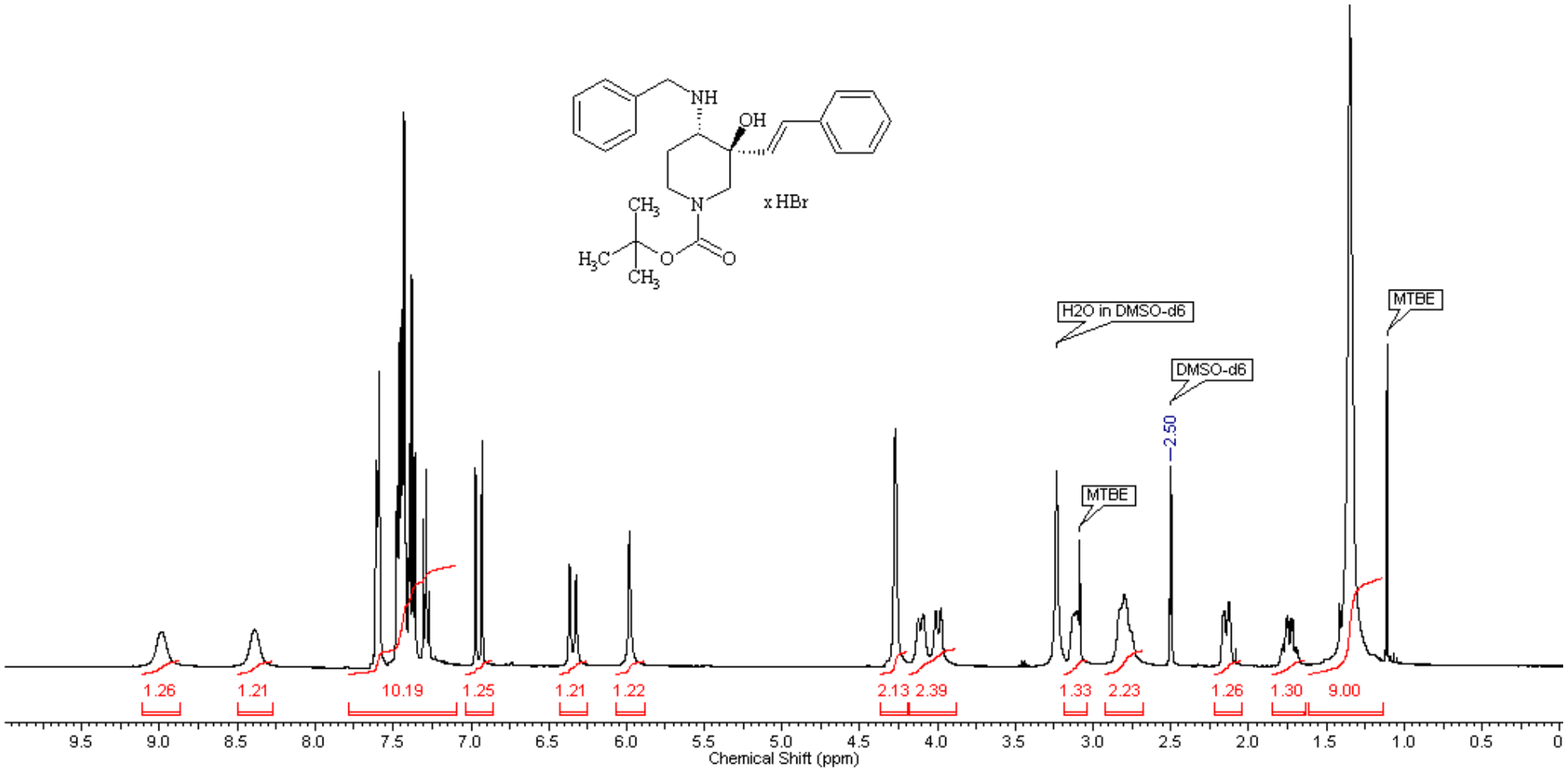
(3*RS*,4*SR*)-3-(Benzylamino)-4-((*E*)-styryl)tetrahydro-2*H*-pyran-4-ol hydrobromide (21). ^{1}H NMR (DMSO-d_6, 400 MHz)



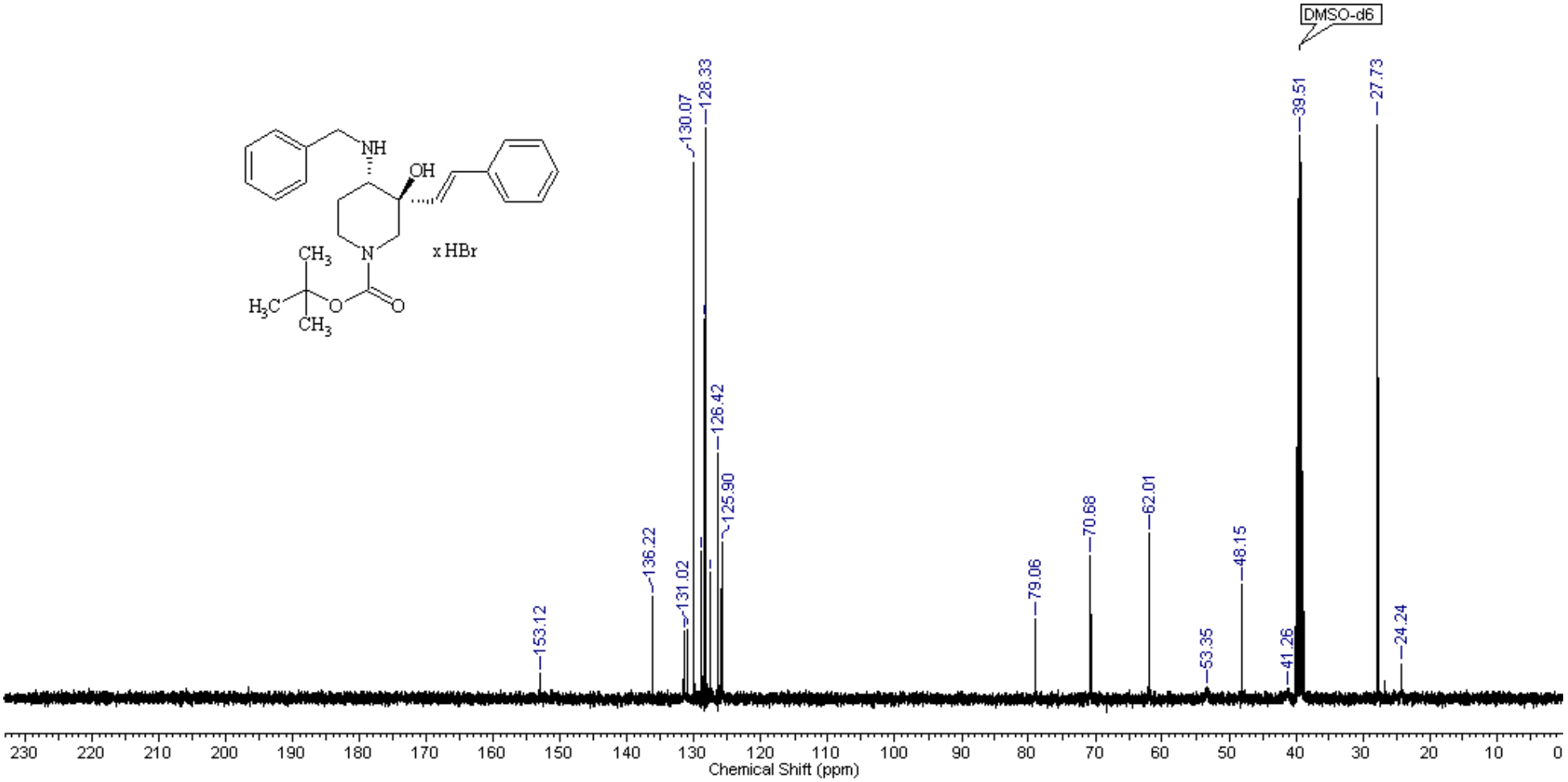
(3*RS*,4*SR*)-3-(Benzylamino)-4-((*E*)-styryl)tetrahydro-2*H*-pyran-4-ol hydrobromide (21). ^{13}C NMR (DMSO-d_6, 100 MHz)



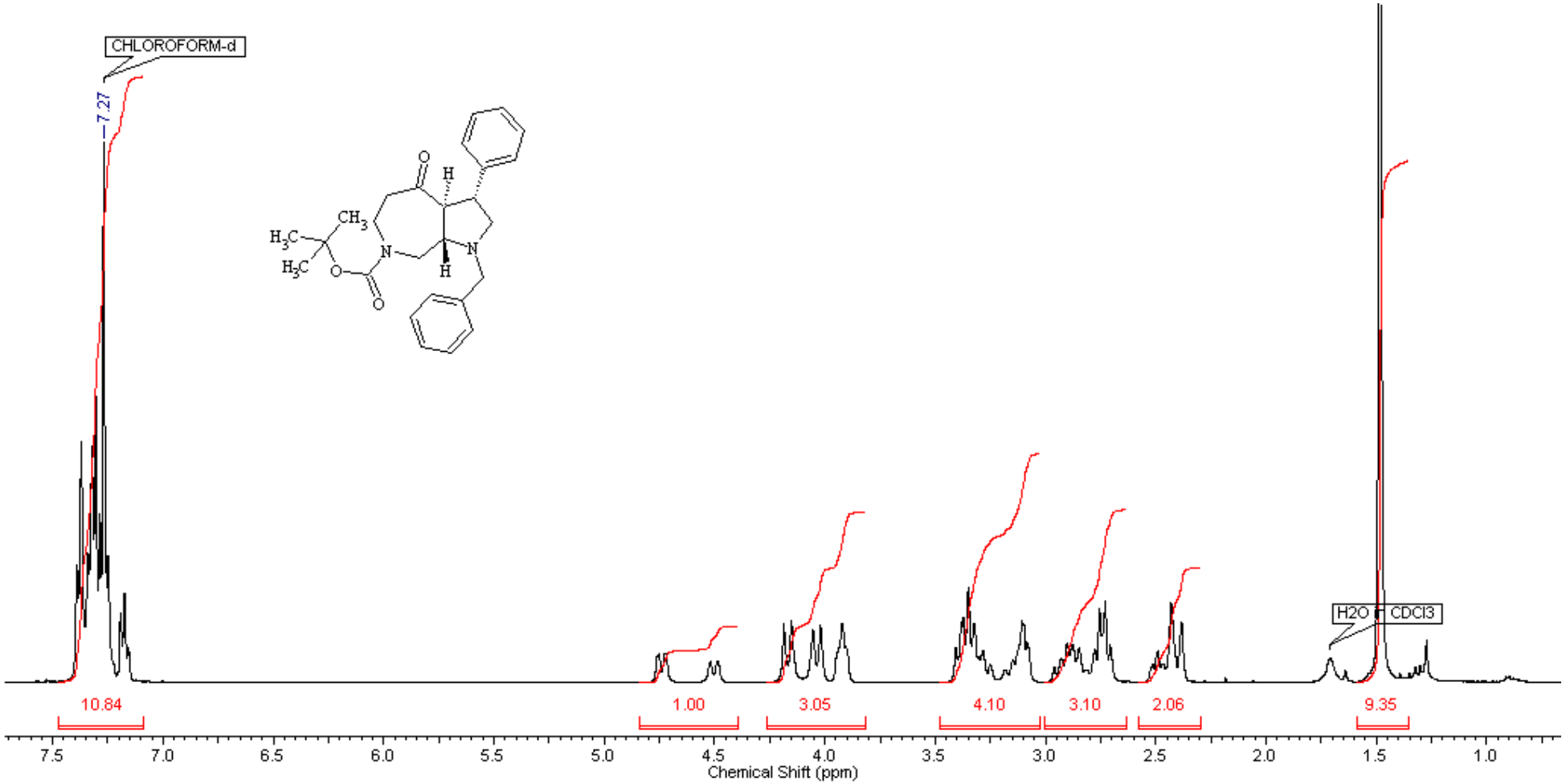
(3*SR*,4*SR*)-*Tert*-butyl 4-(benzylamino)-3-hydroxy-3-((*E*)-styryl)piperidine-1-carboxylate hydrobromide (22). ^{1}H NMR (DMSO-d_6, 400 MHz)



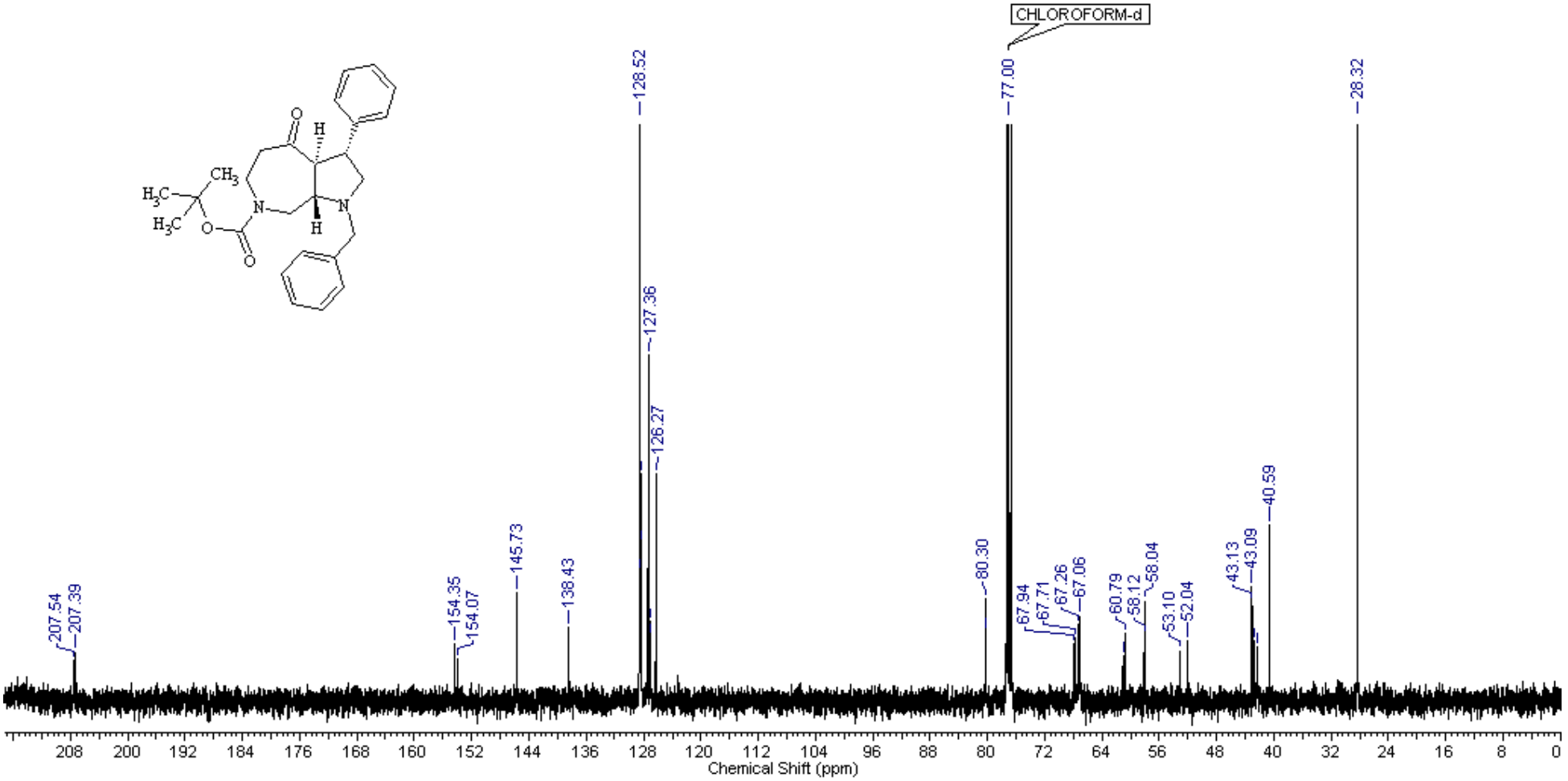
(3*SR*,4*SR*)-*Tert*-butyl 4-(benzylamino)-3-hydroxy-3-((*E*)-styryl)piperidine-1-carboxylate hydrobromide (22). ^{13}C NMR (DMSO-d_6, 100 MHz)



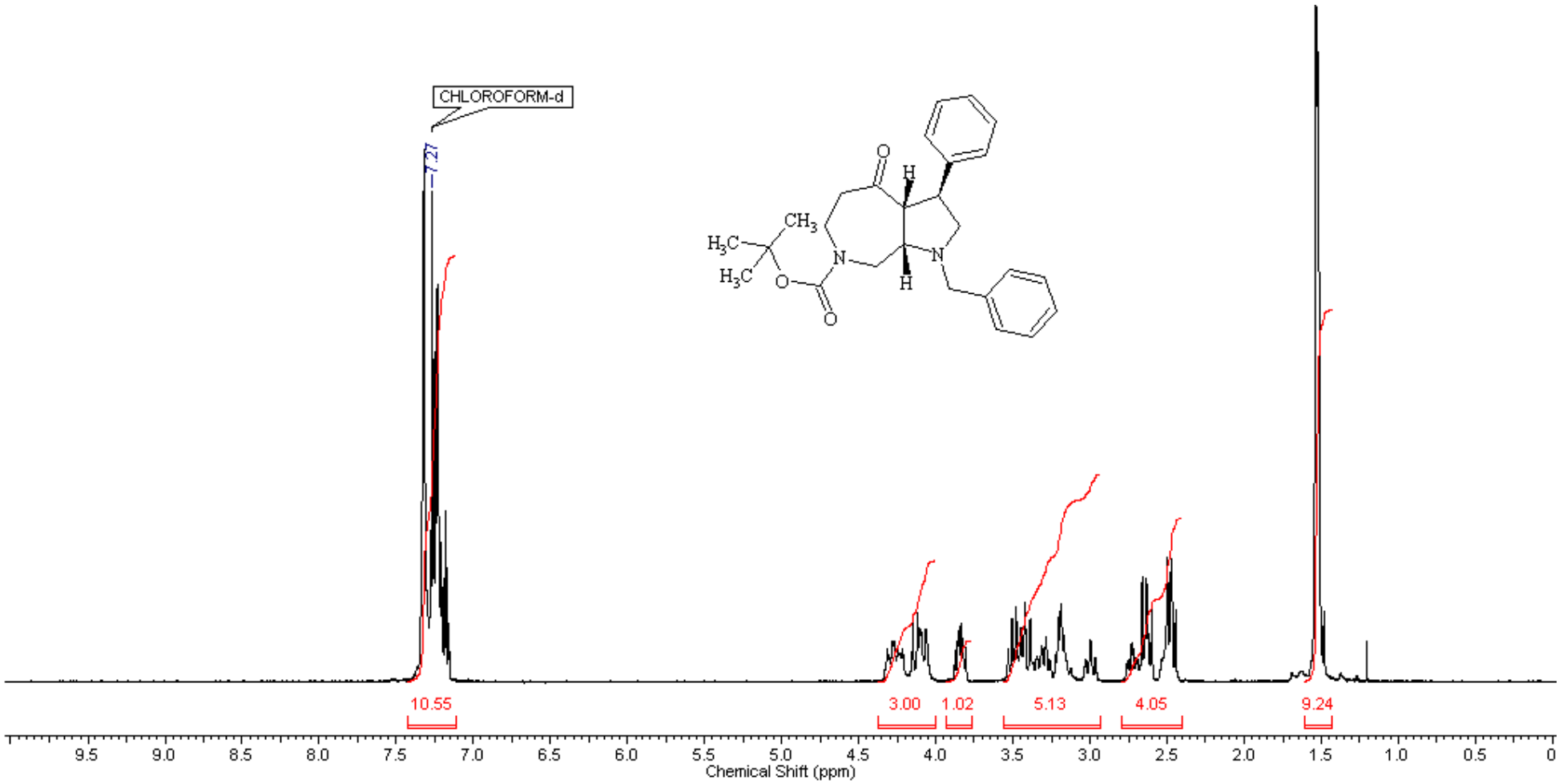
(3RS,3aSR,8aSR)-Tert-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-c]azepine-7(1H)-carboxylate (23a). ^{1}H NMR ($CDCl_3$, 400 MHz).



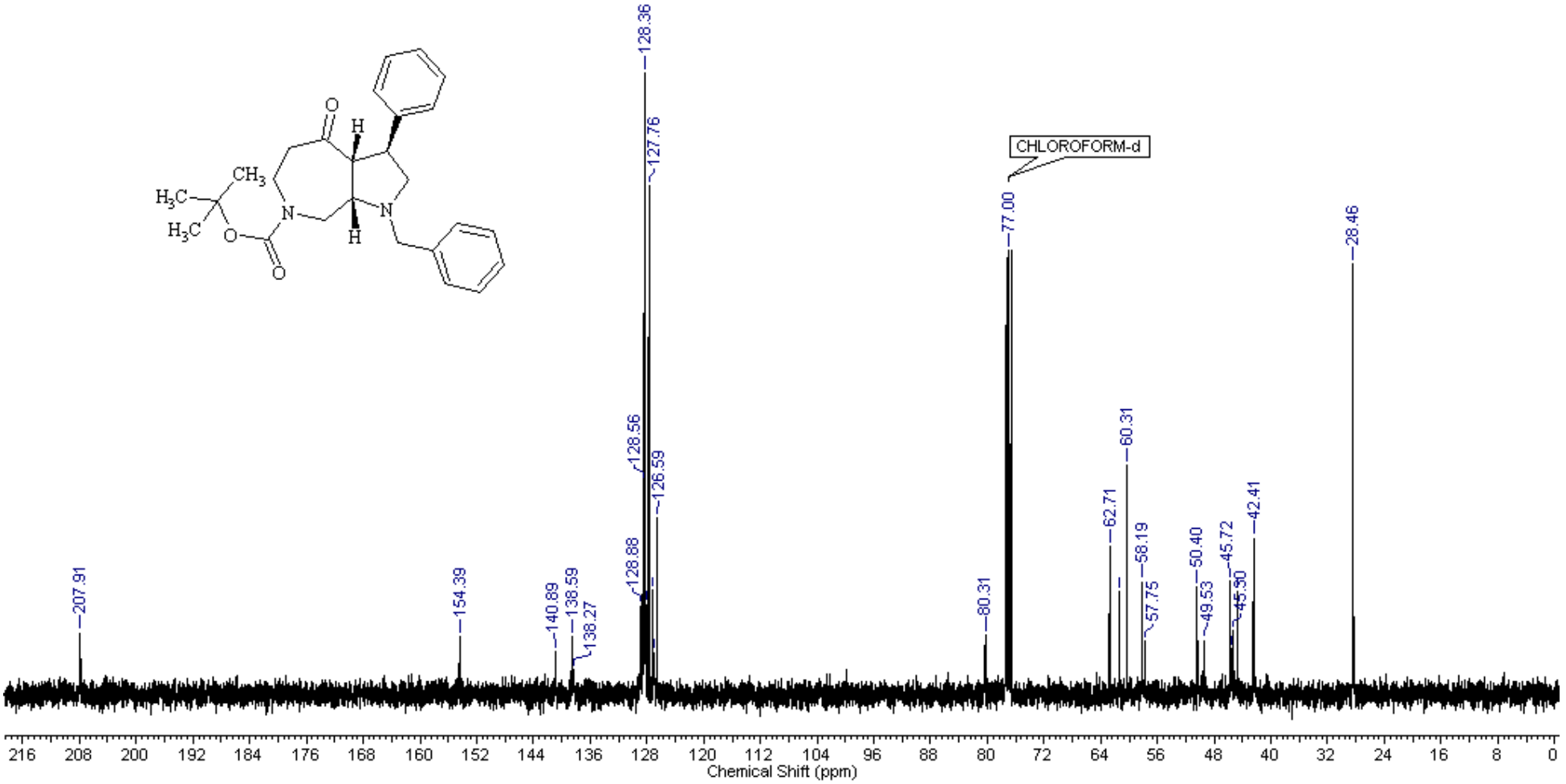
(3RS,3aSR,8aSR)-Tert-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-c]azepine-7(1H)-carboxylate (23a). ^{13}C NMR ($CDCl_3$, 100 MHz)



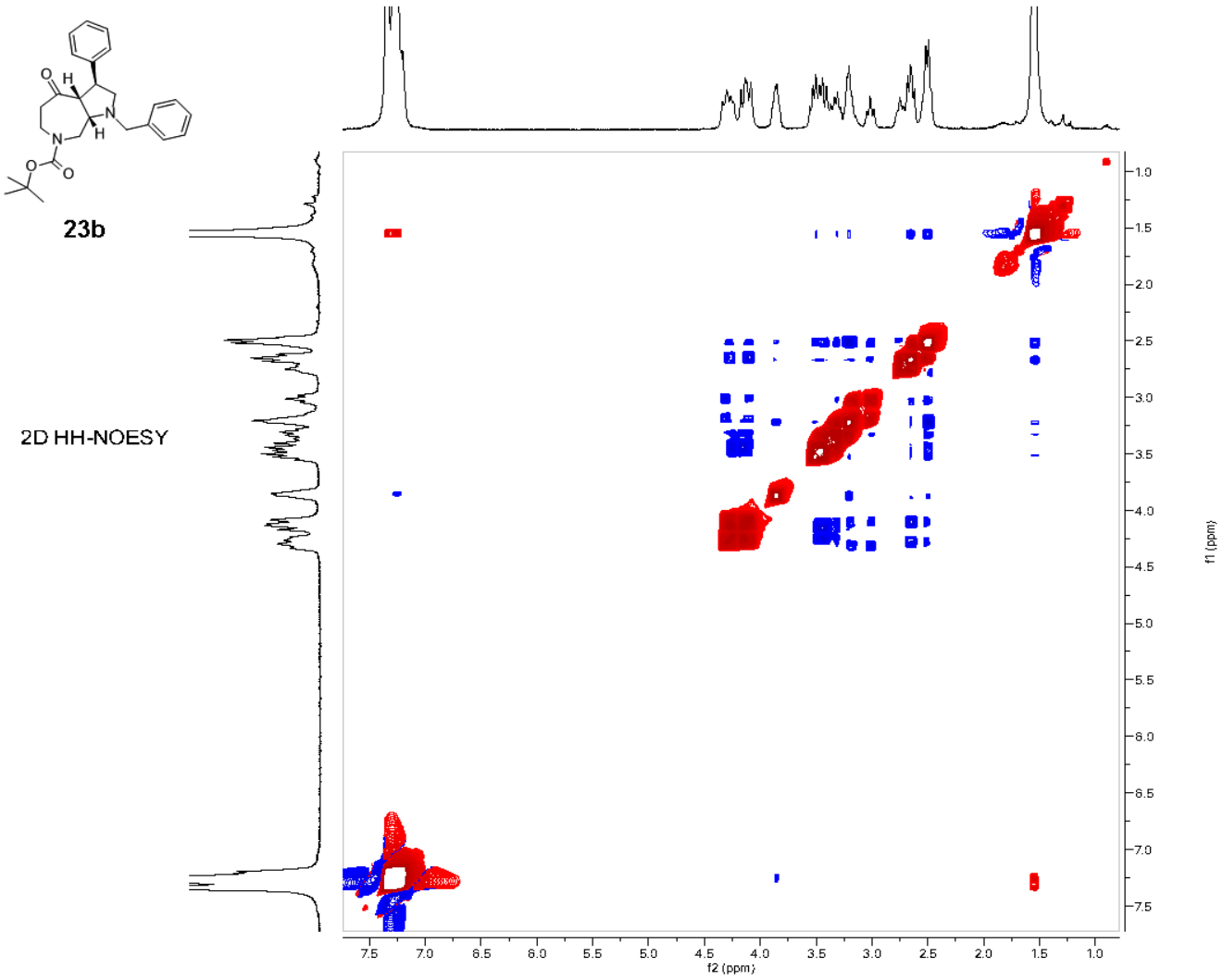
(3*SR*,3a*RS*,8a*SR*)-*Tert*-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate (23b). ^{1}H NMR ($CDCl_3$, 400 MHz).



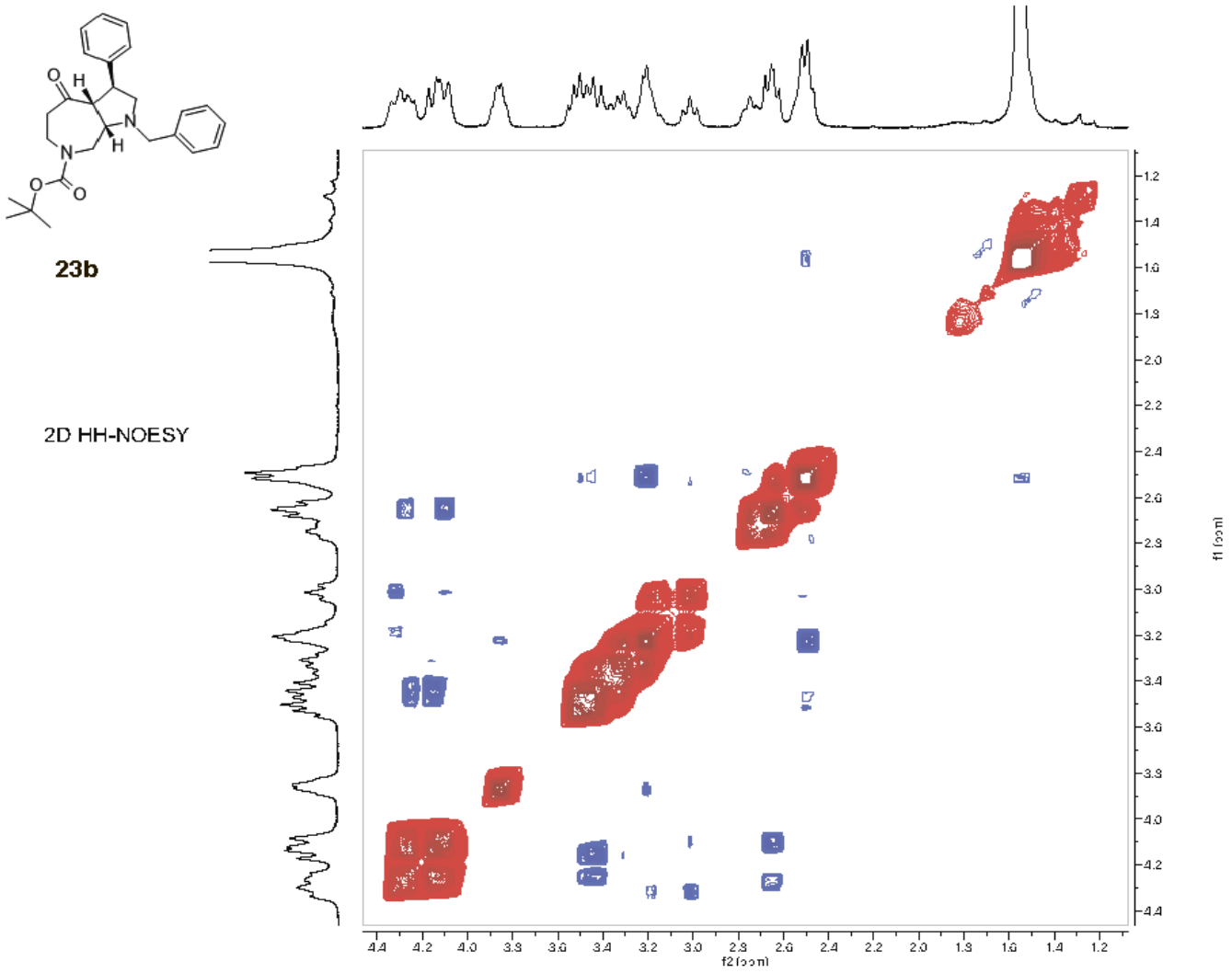
(3*SR*,3a*RS*,8a*SR*)-*Tert*-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate (23b). ^{13}C NMR ($CDCl_3$, 100 MHz).



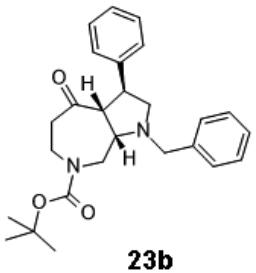
(3*SR*,3a*RS*,8a*SR*)-*Tert*-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate (23b). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms)



(3*SR*,3a*RS*,8a*SR*)-*Tert*-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate (23b). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms)

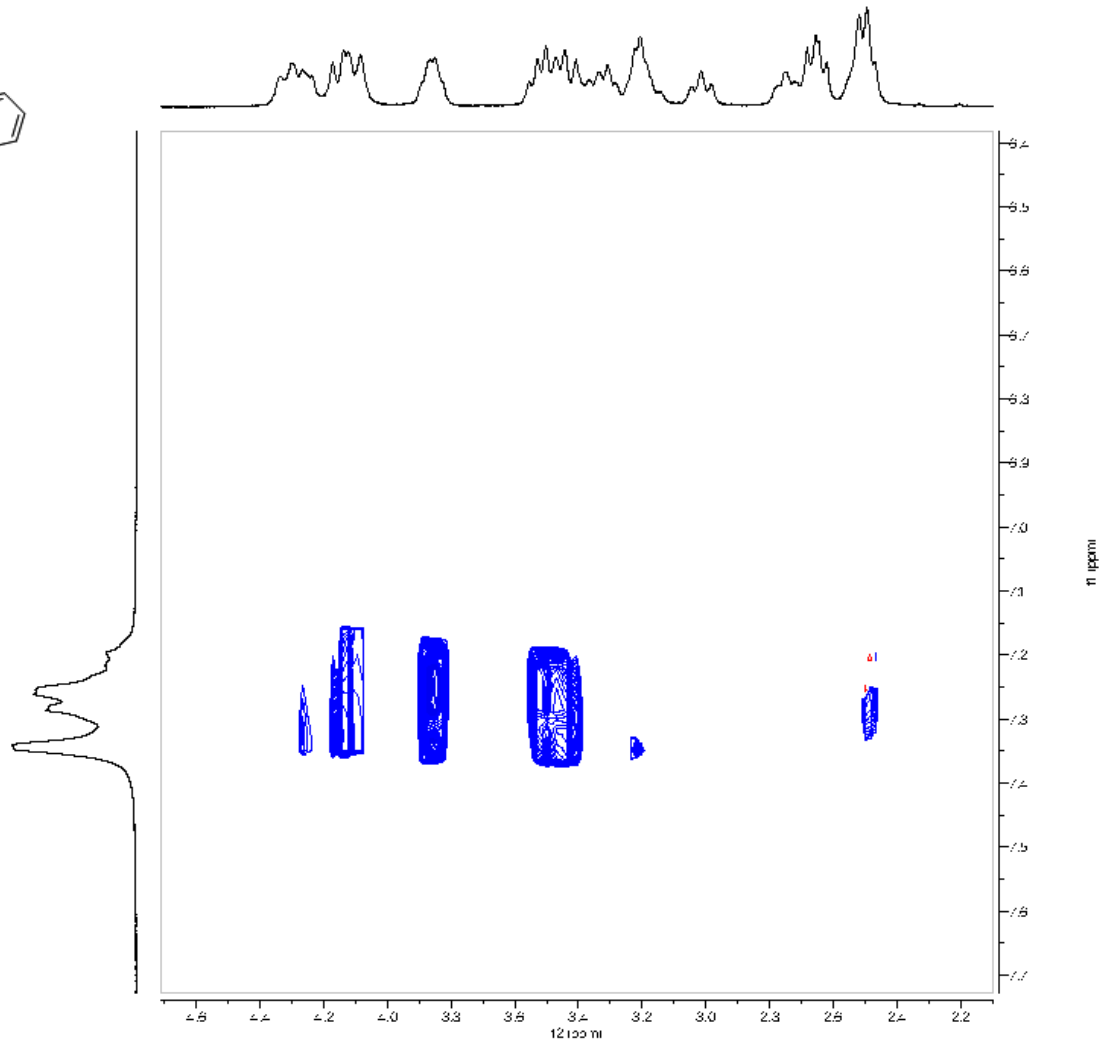


(3*SR*,3a*RS*,8a*SR*)-*Tert*-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate (23b). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms)

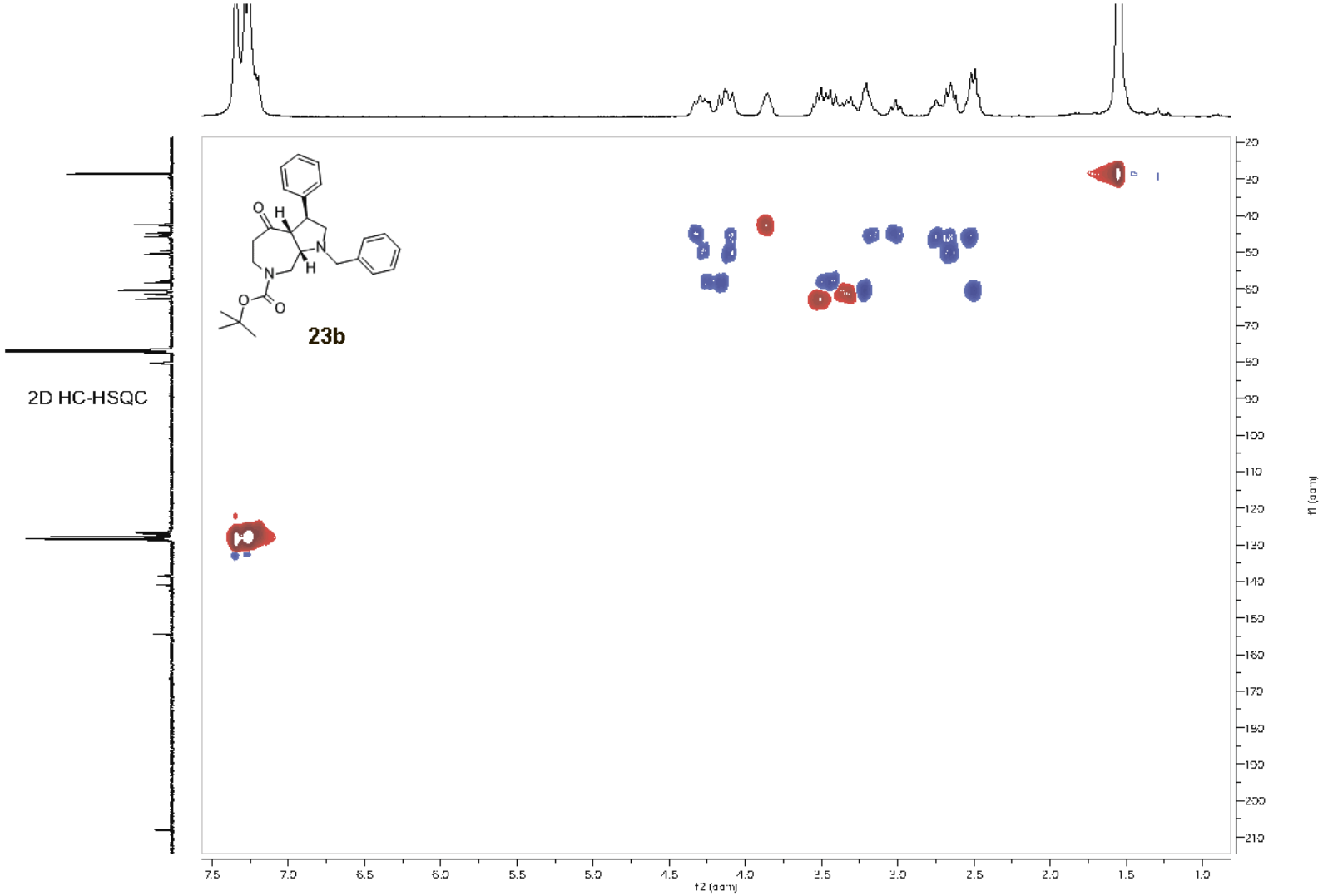


23b

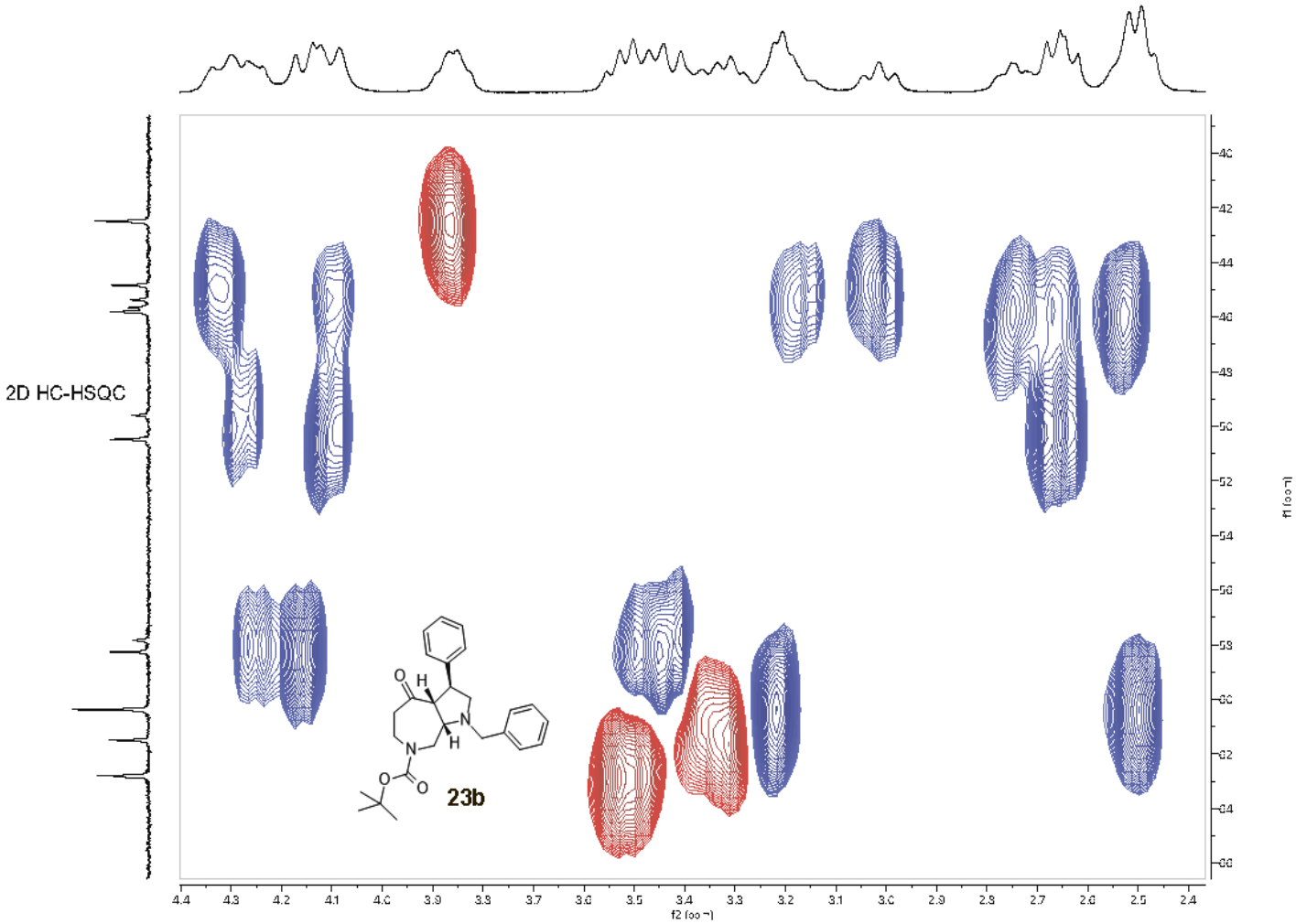
2D HH-NOESY



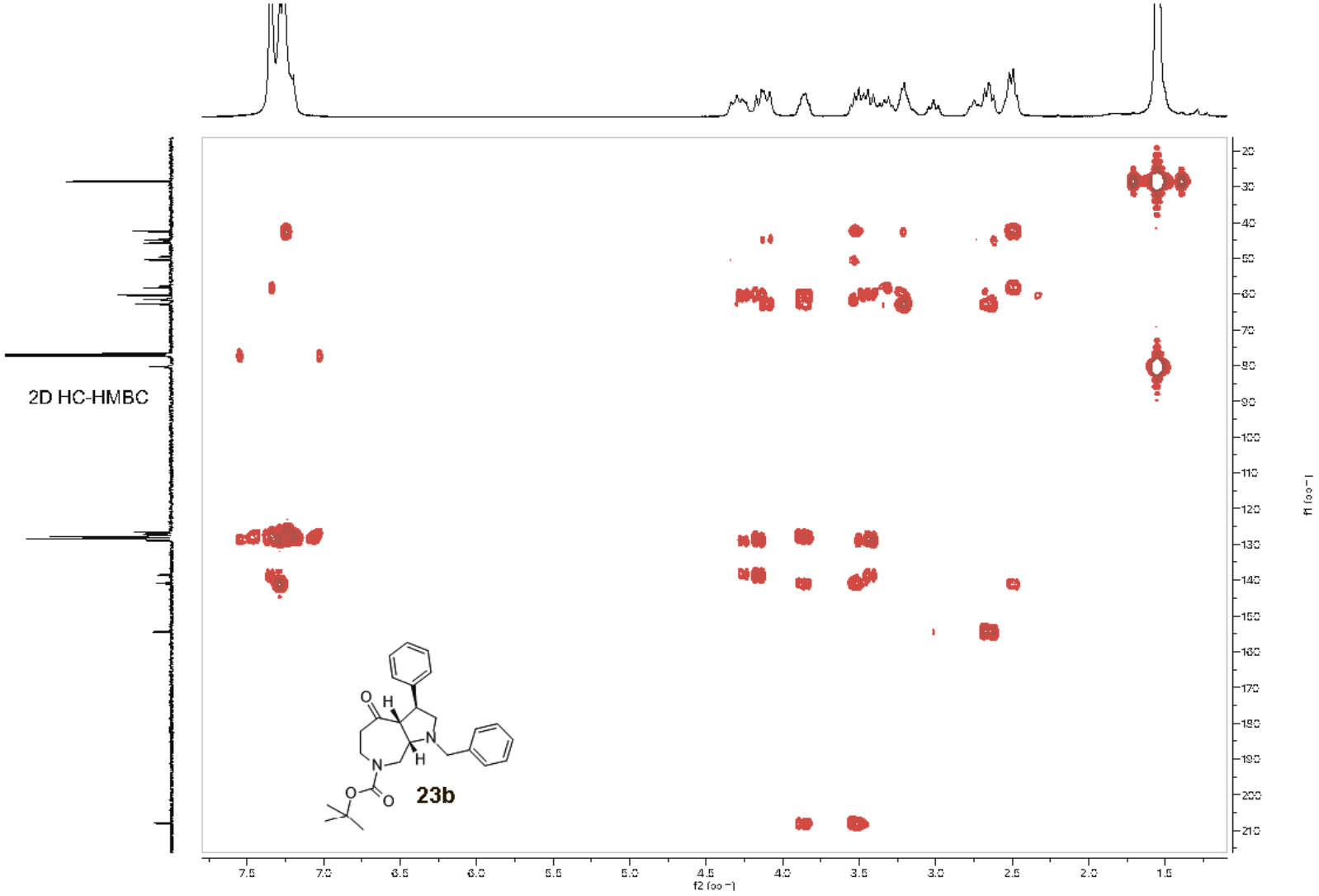
(3*SR*,3a*RS*,8a*SR*)-*Tert*-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate (23b). 2D ^{1}H-^{13}C-HSQC (qphase sensitive J1 (HC)=145Hz).



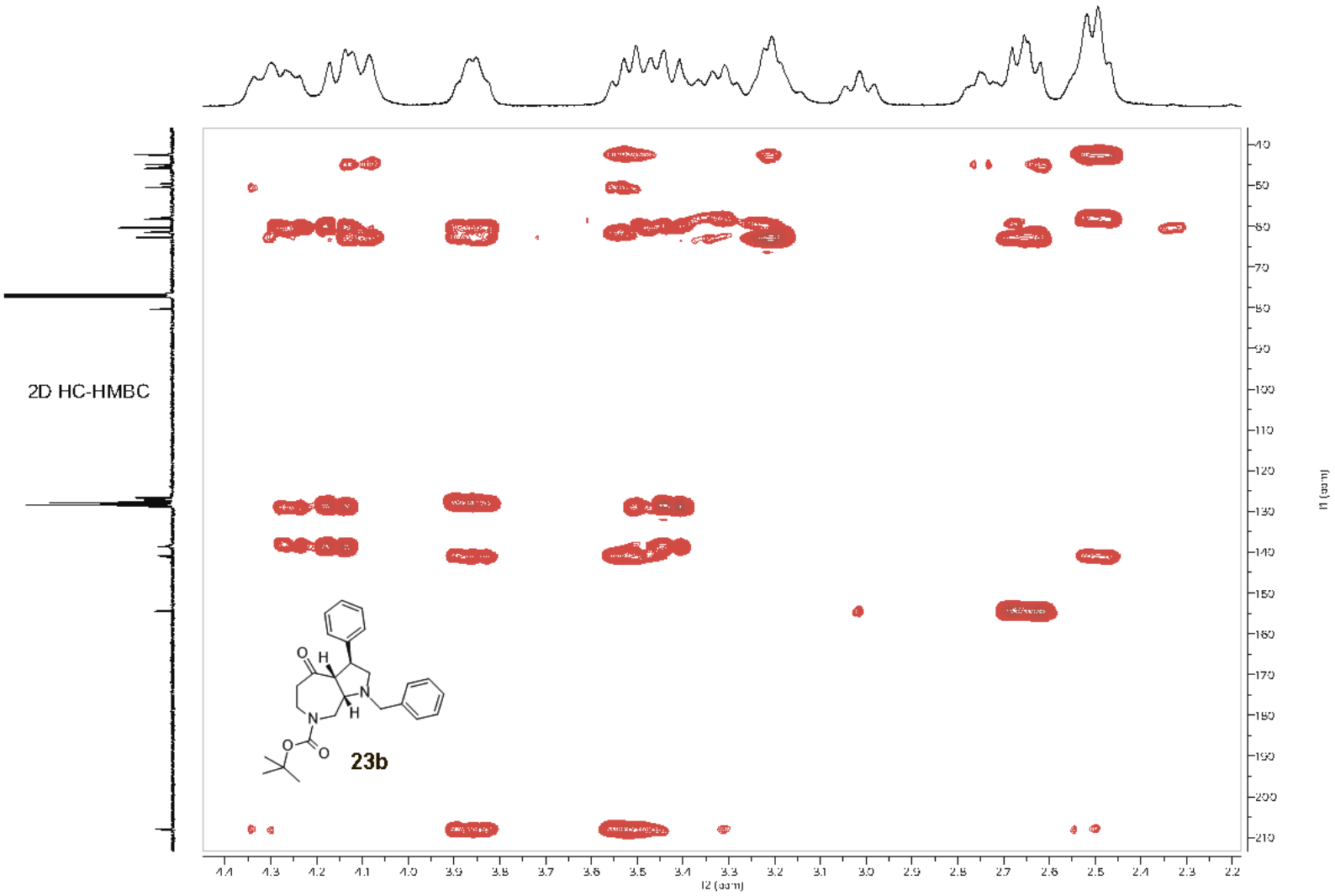
(3*SR*,3a*RS*,8a*SR*)-*Tert*-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate (23b). 2D ^{1}H-^{13}C-HSQC (qphase sensitive J1 (HC)=145Hz).



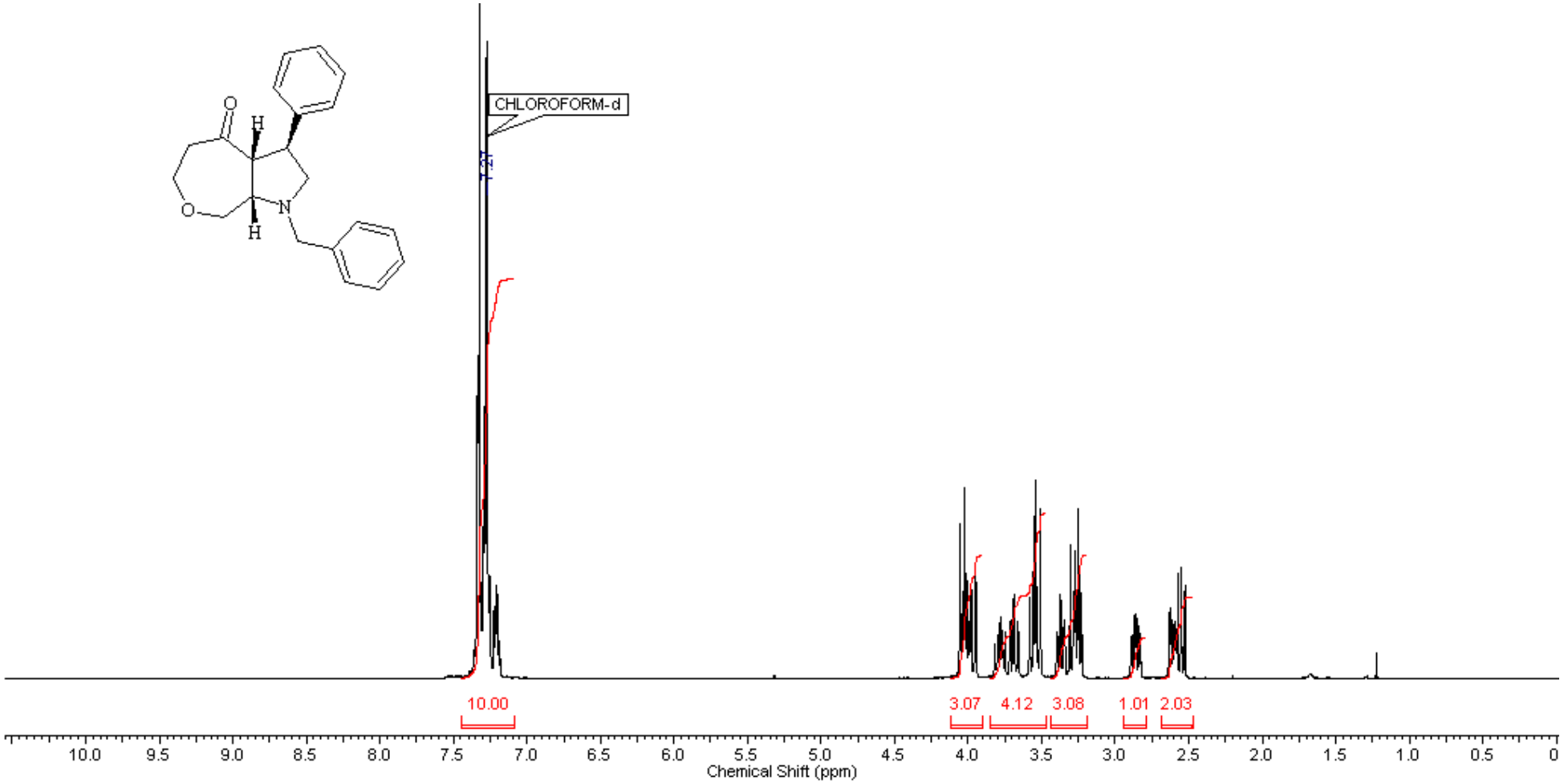
(3*SR*,3a*RS*,8a*SR*)-*Tert*-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate (23b). 2D ^{1}H-^{13}C-HMBC (longrange, J1(HC)=145Hz, J2(HC-long)=10Hz)



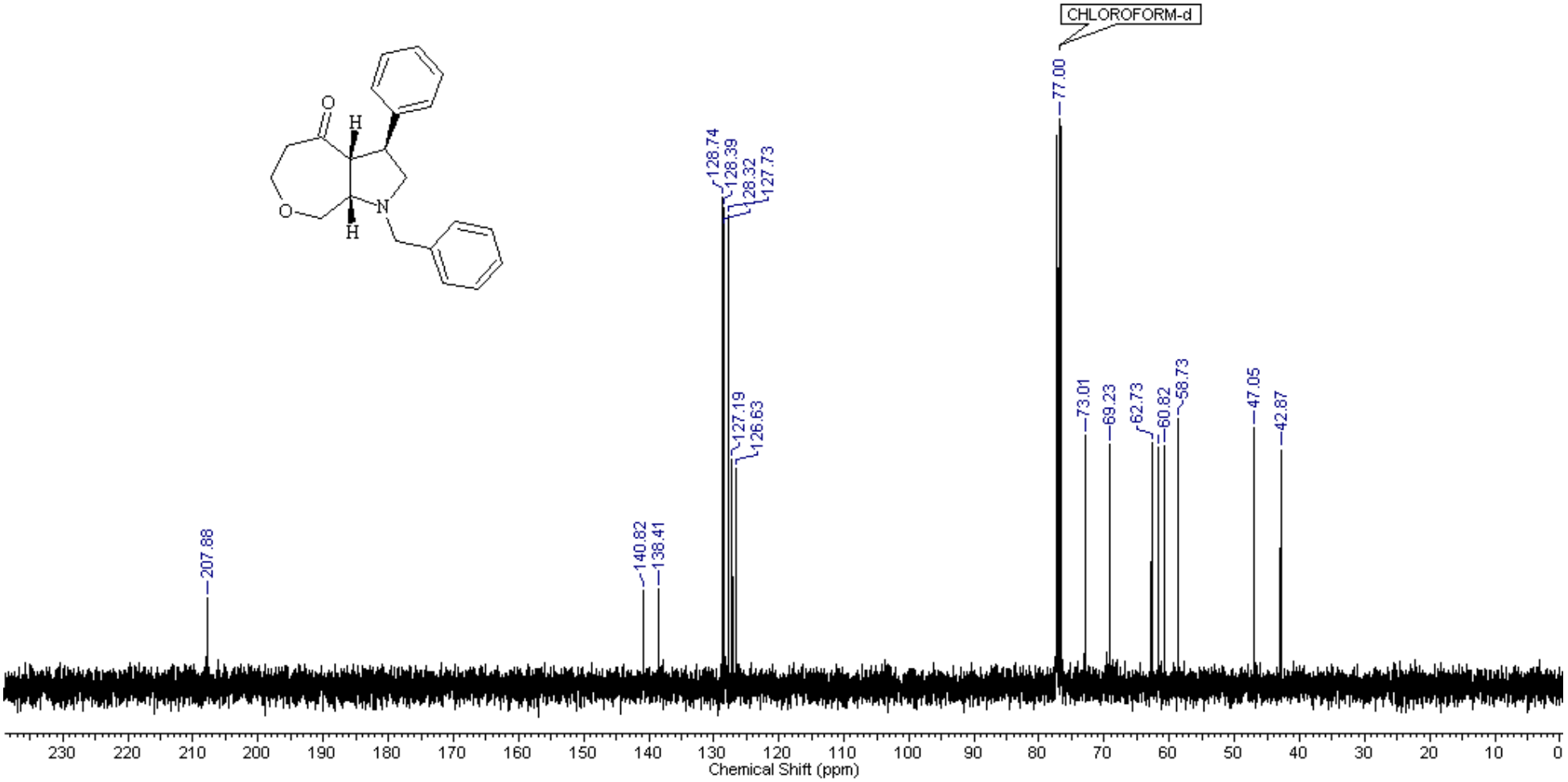
(3*SR*,3a*RS*,8a*SR*)-*Tert*-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate (23b). 2D ^{1}H-^{13}C-HMBC (longrange, J1(HC)=145Hz, J2(HC-long)=10Hz)



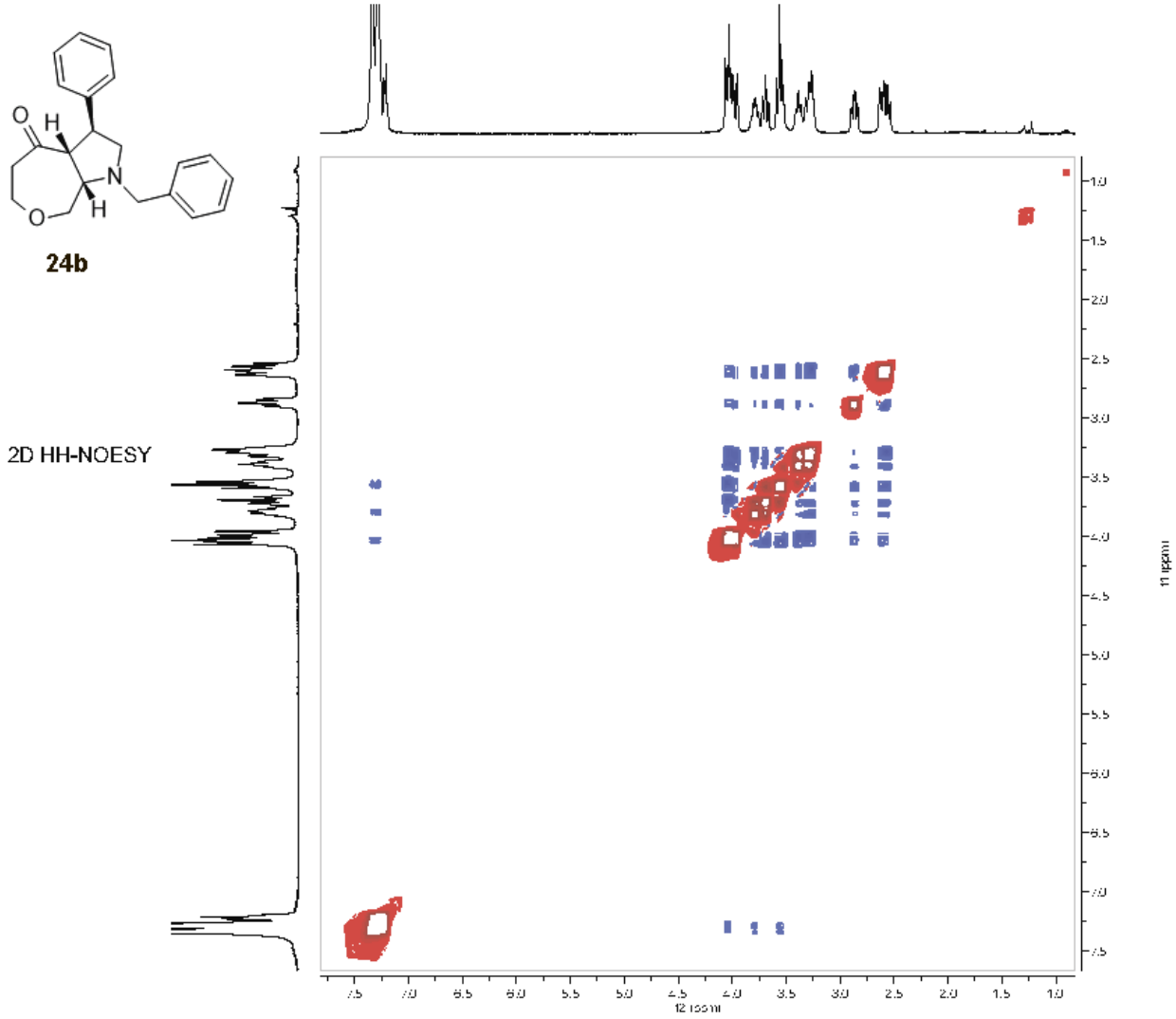
(3*SR*,3a*RS*,8a*SR*)-1-Benzyl-3-phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (24b). ^{1}H NMR ($CDCl_3$, 400 MHz).



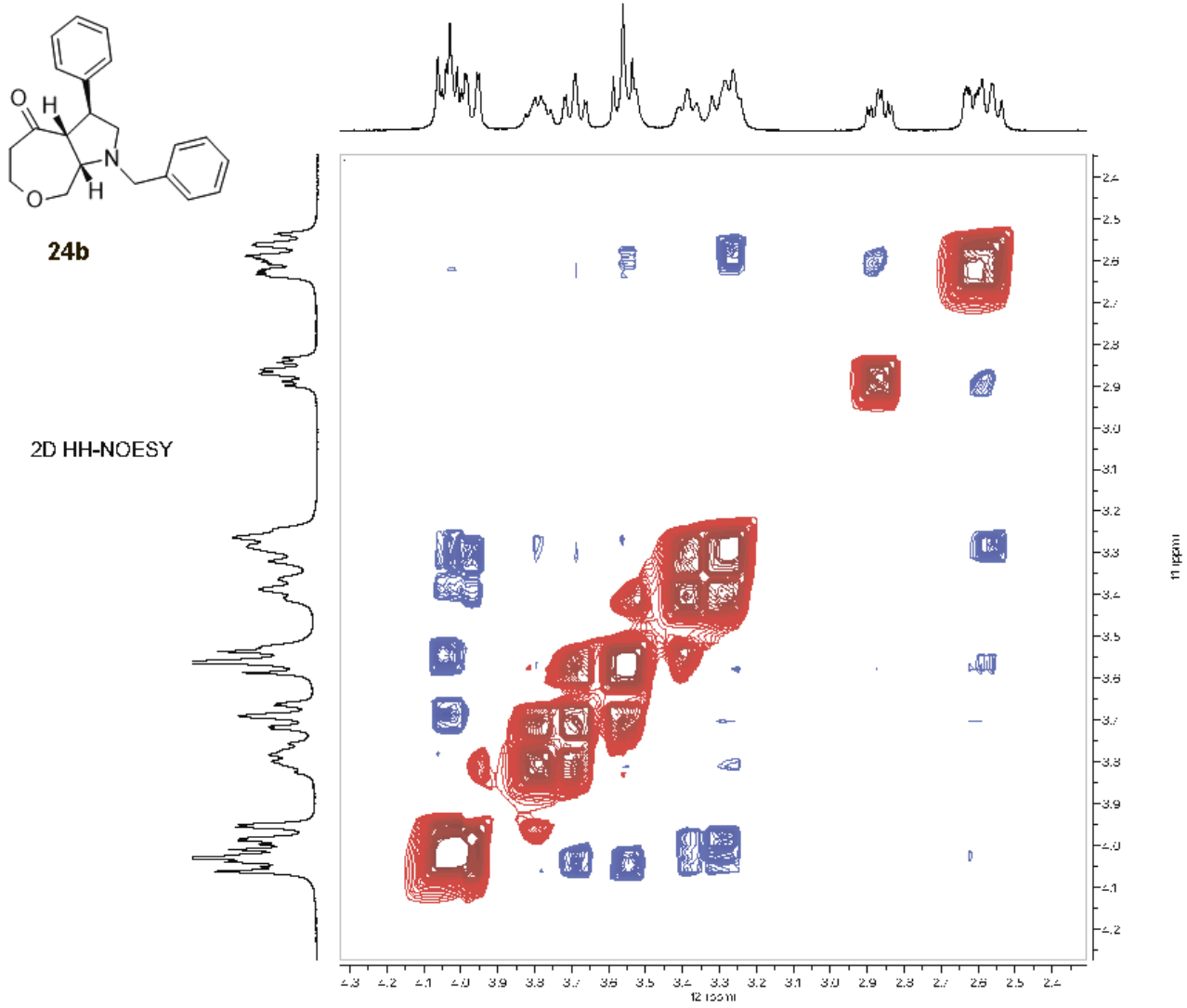
(3*SR*,3a*RS*,8a*SR*)-1-Benzyl-3-phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (24b). ^{13}C NMR ($CDCl_3$, 100 MHz).



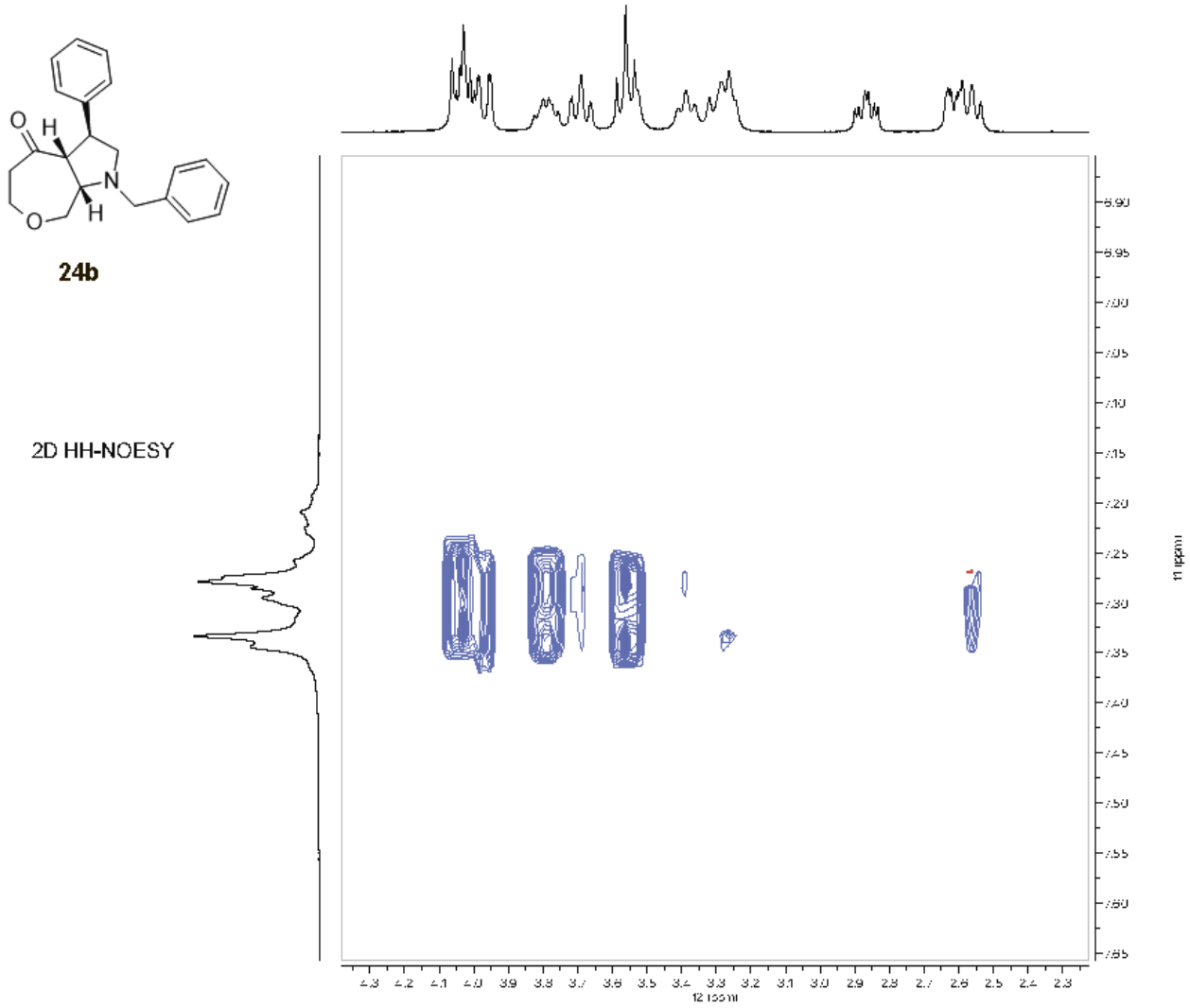
(3*SR*,3a*RS*,8a*SR*)-1-Benzyl-3-phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (24b). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms)



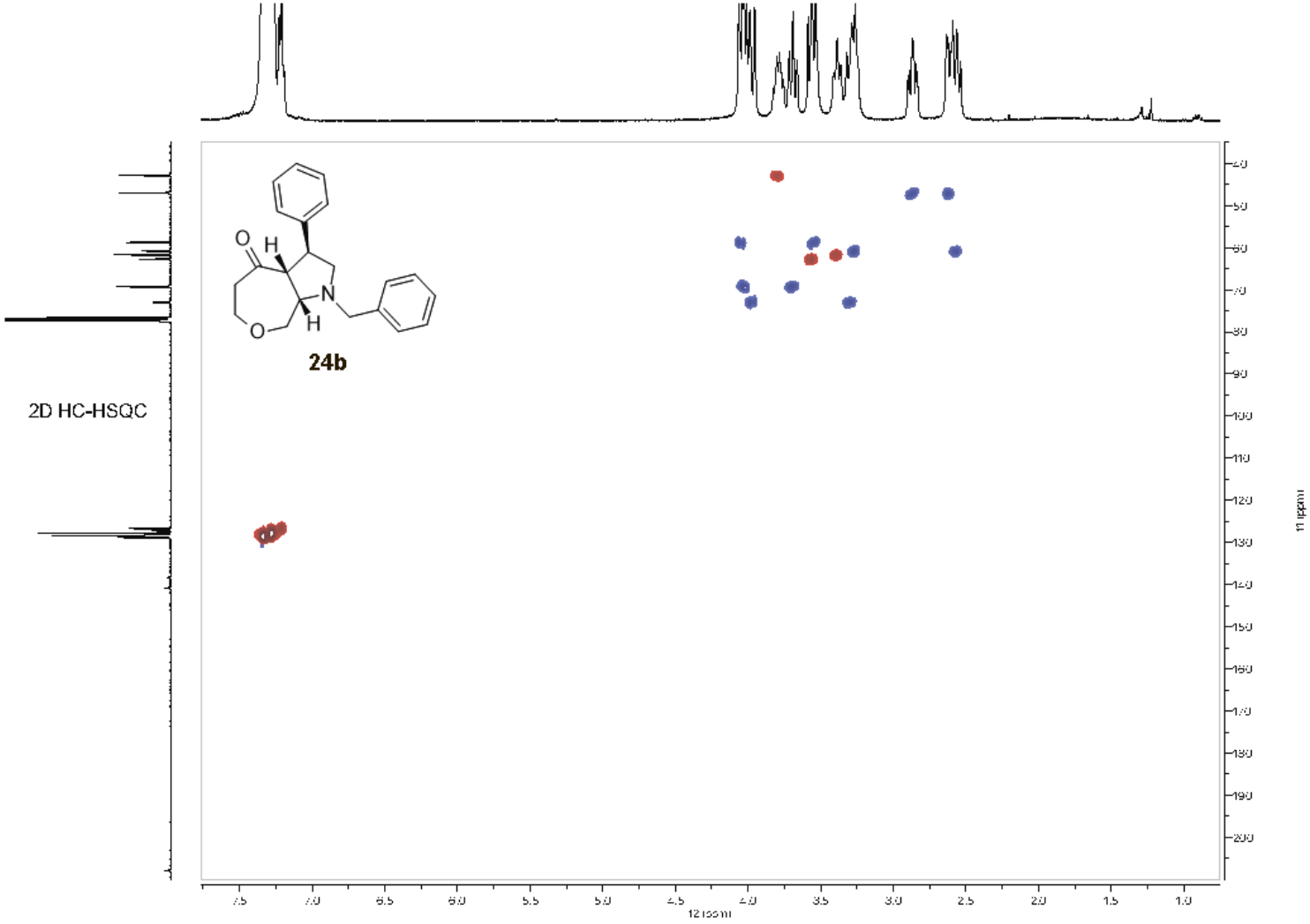
(3*SR*,3a*RS*,8a*SR*)-1-Benzyl-3-phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (24b). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms)



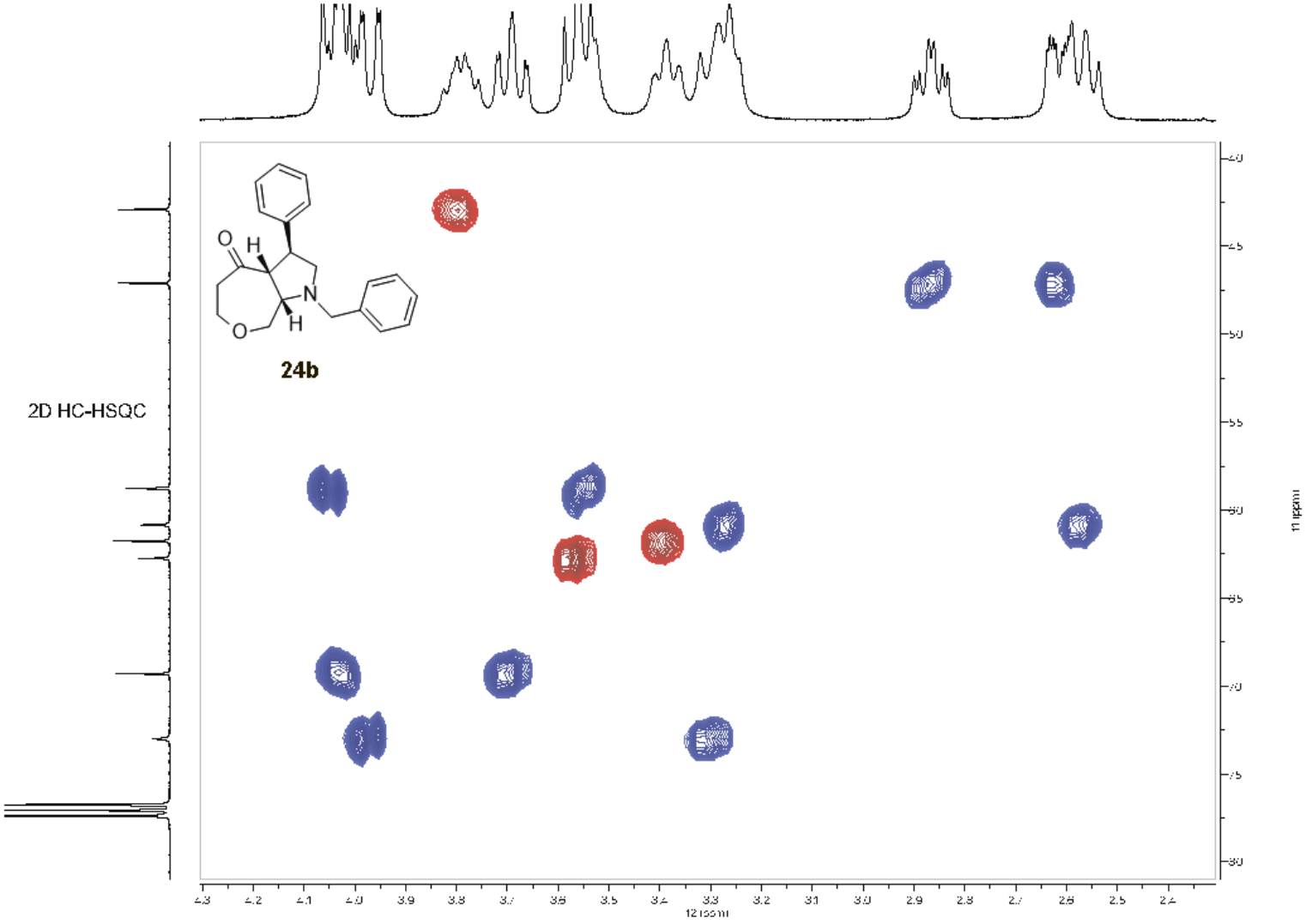
(3*SR*,3a*RS*,8a*SR*)-1-Benzyl-3-phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (24b). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms)



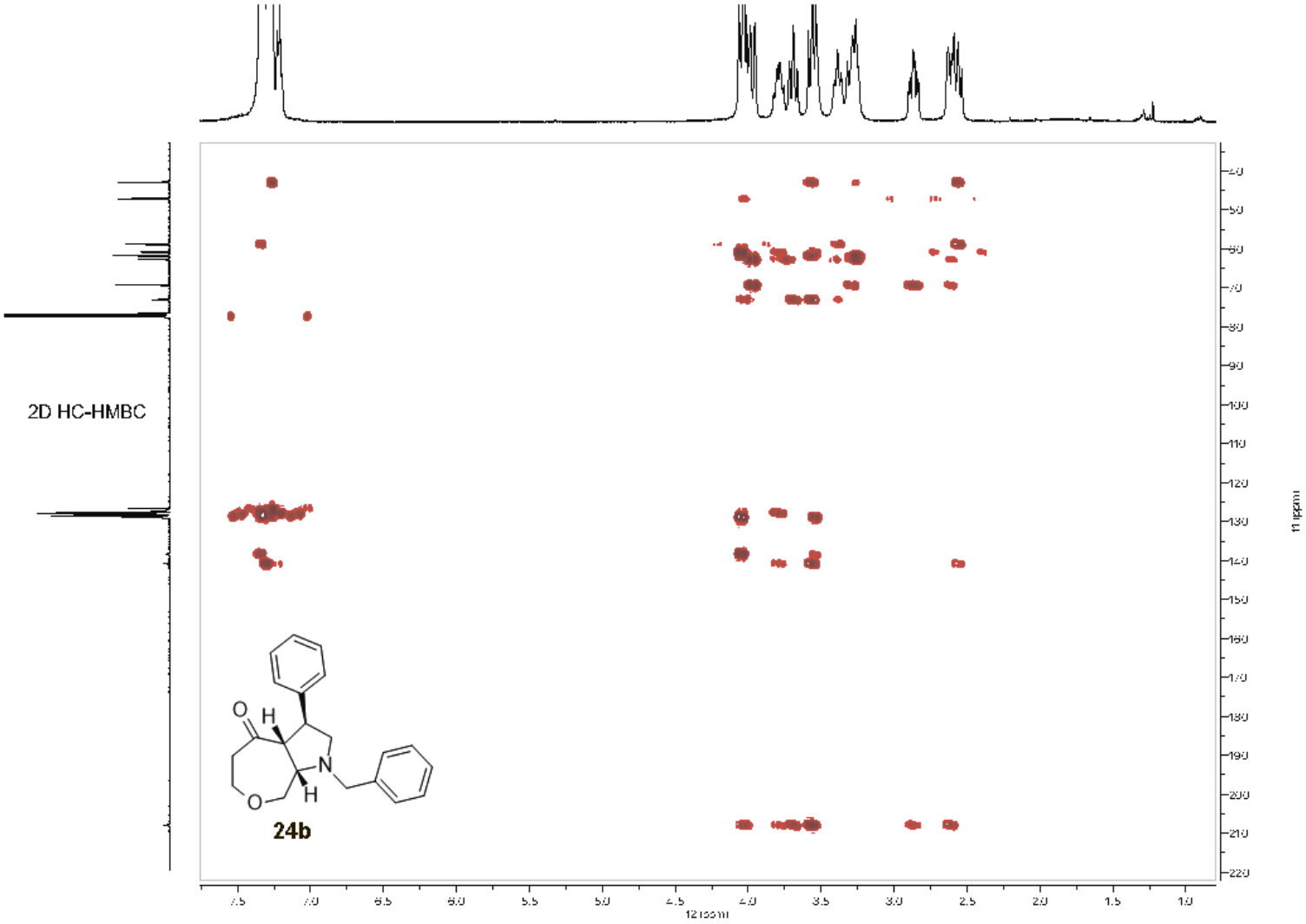
(3*SR*,3a*RS*,8a*SR*)-1-Benzyl-3-phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (24b). 2D ^{1}H-^{13}C-HSQC (qphase sensitive J1 (HC)=145Hz).



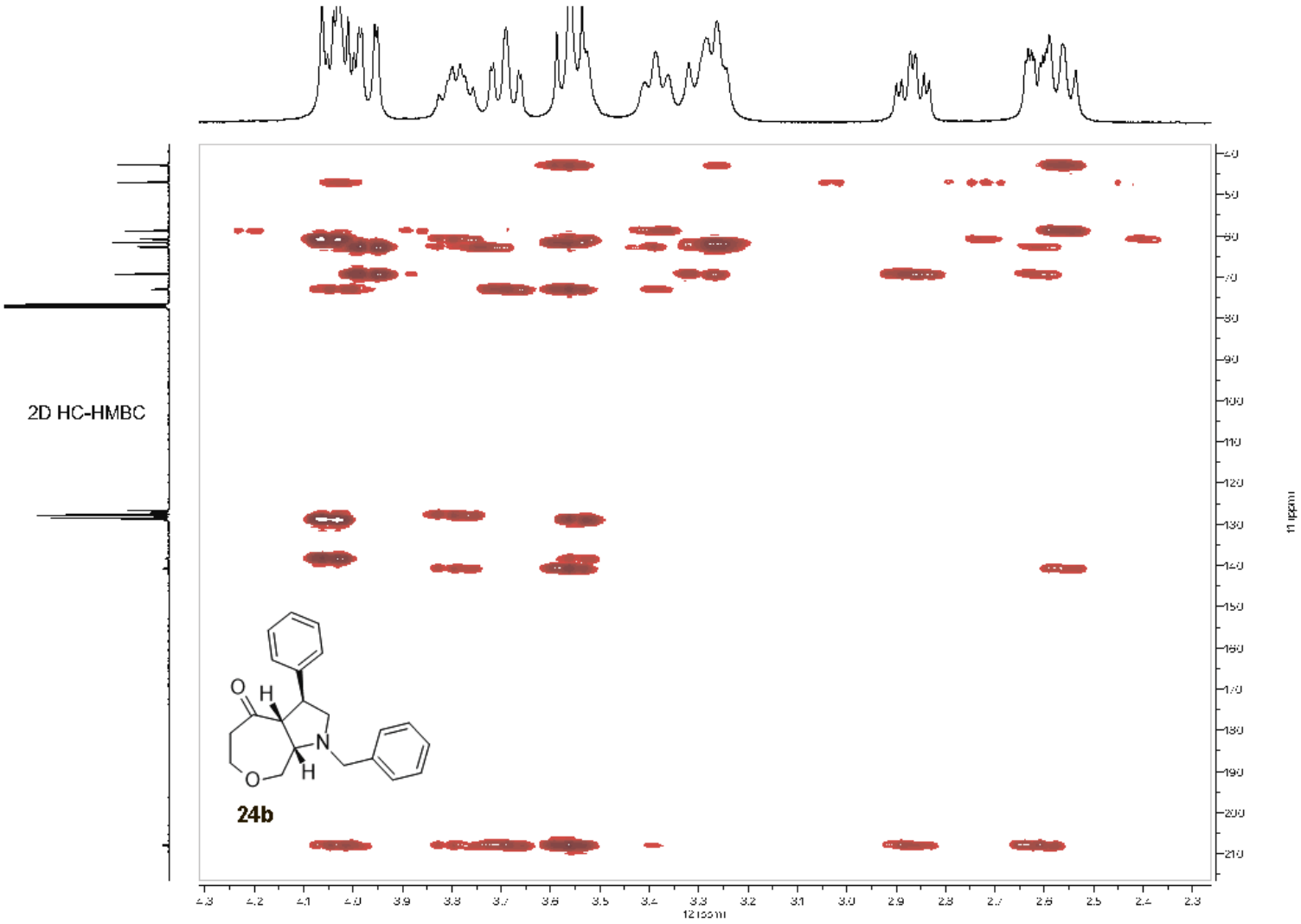
(3*SR*,3a*RS*,8a*SR*)-1-Benzyl-3-phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (24b). 2D ^{1}H-^{13}C-HSQC (qphase sensitive J1 (HC)=145Hz).



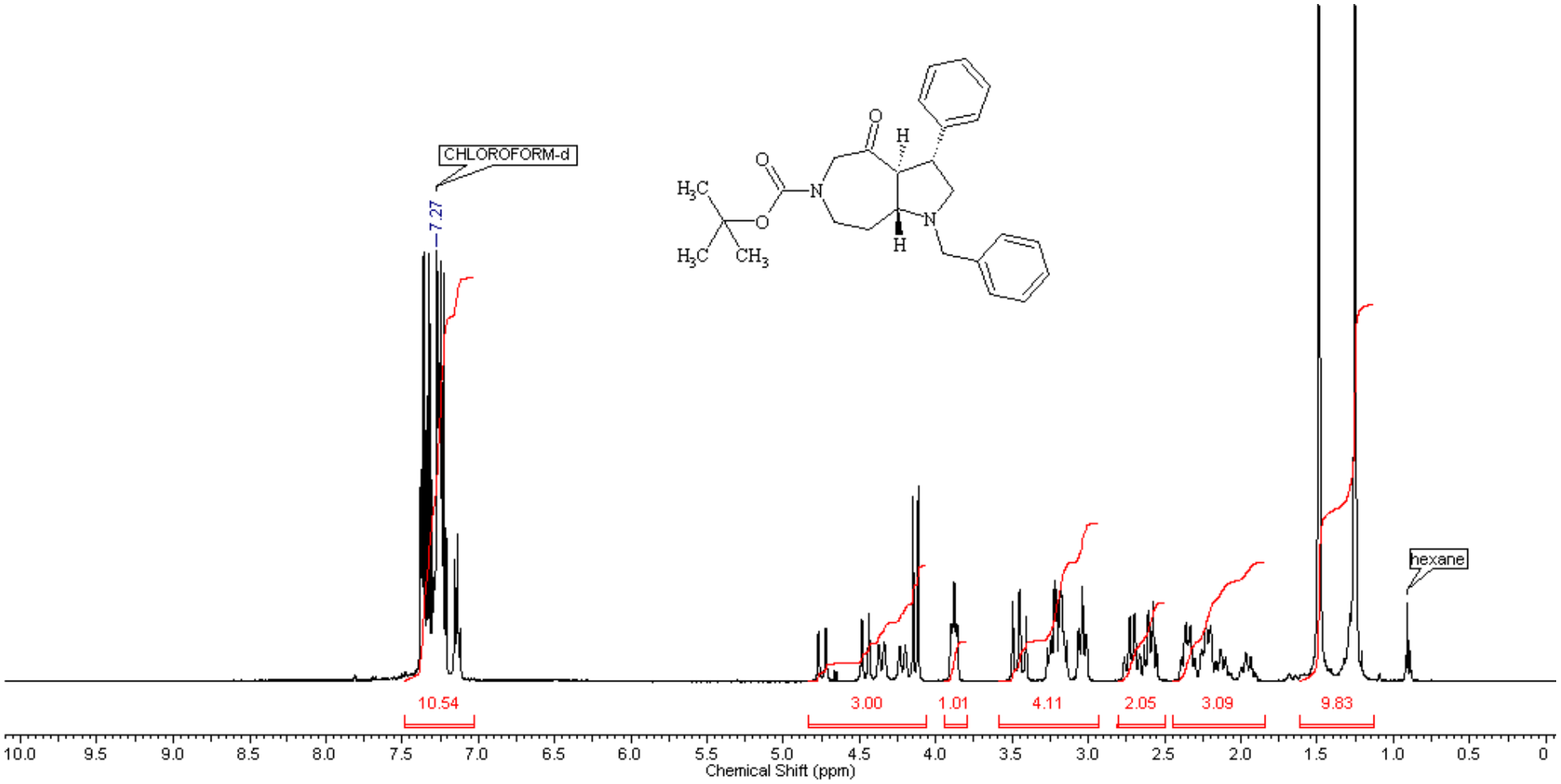
(3*SR*,3a*RS*,8a*SR*)-1-Benzyl-3-phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (24b). 2D ^{1}H-^{13}C-HMBC (longrange, J1(HC)=145Hz, J2(HC-long)=10Hz).



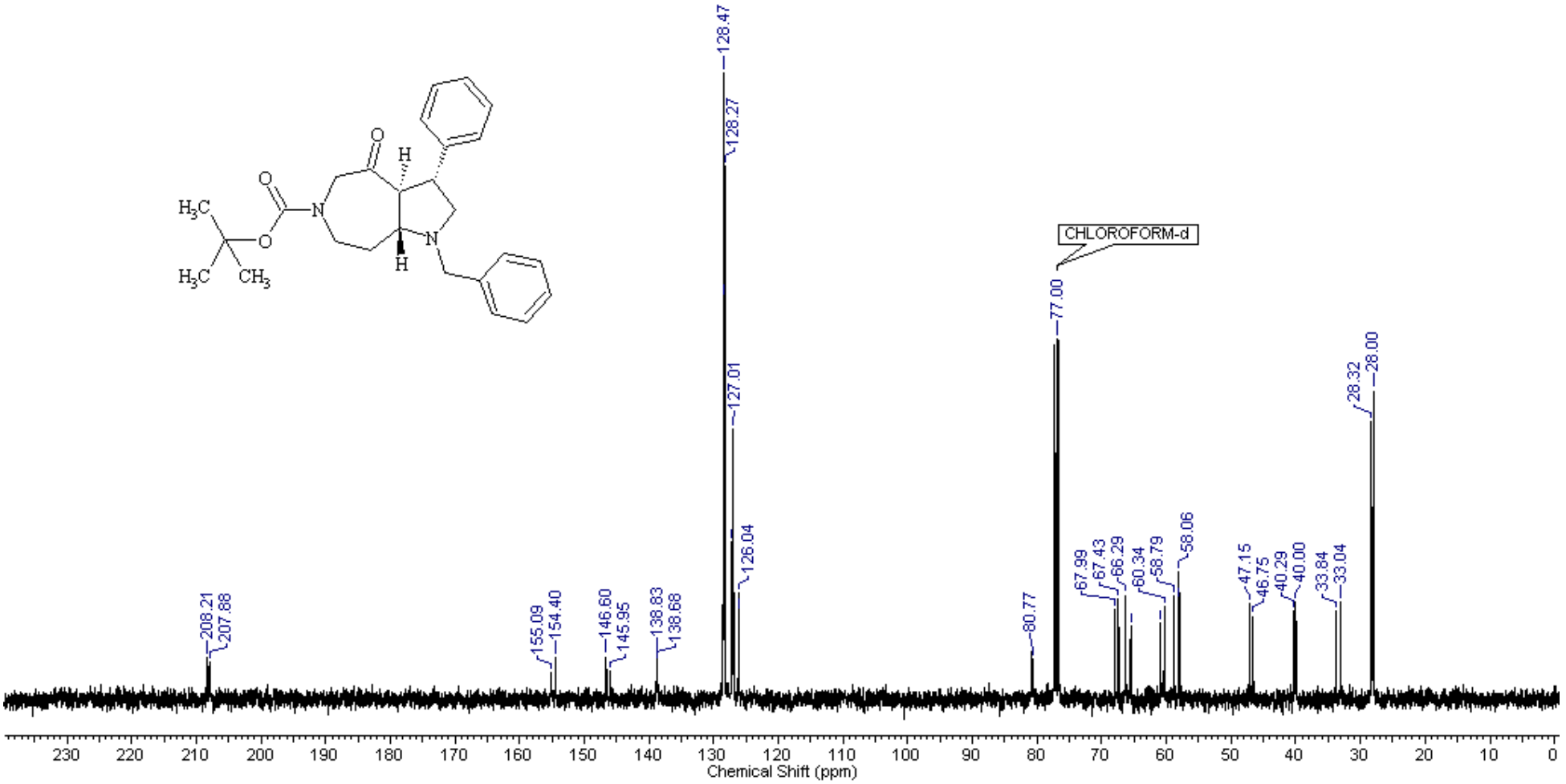
(3*SR*,3a*RS*,8a*SR*)-1-Benzyl-3-phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (24b). 2D ^{1}H-^{13}C-HMBC (longrange, J1(HC)=145Hz, J2(HC-long)=10Hz).



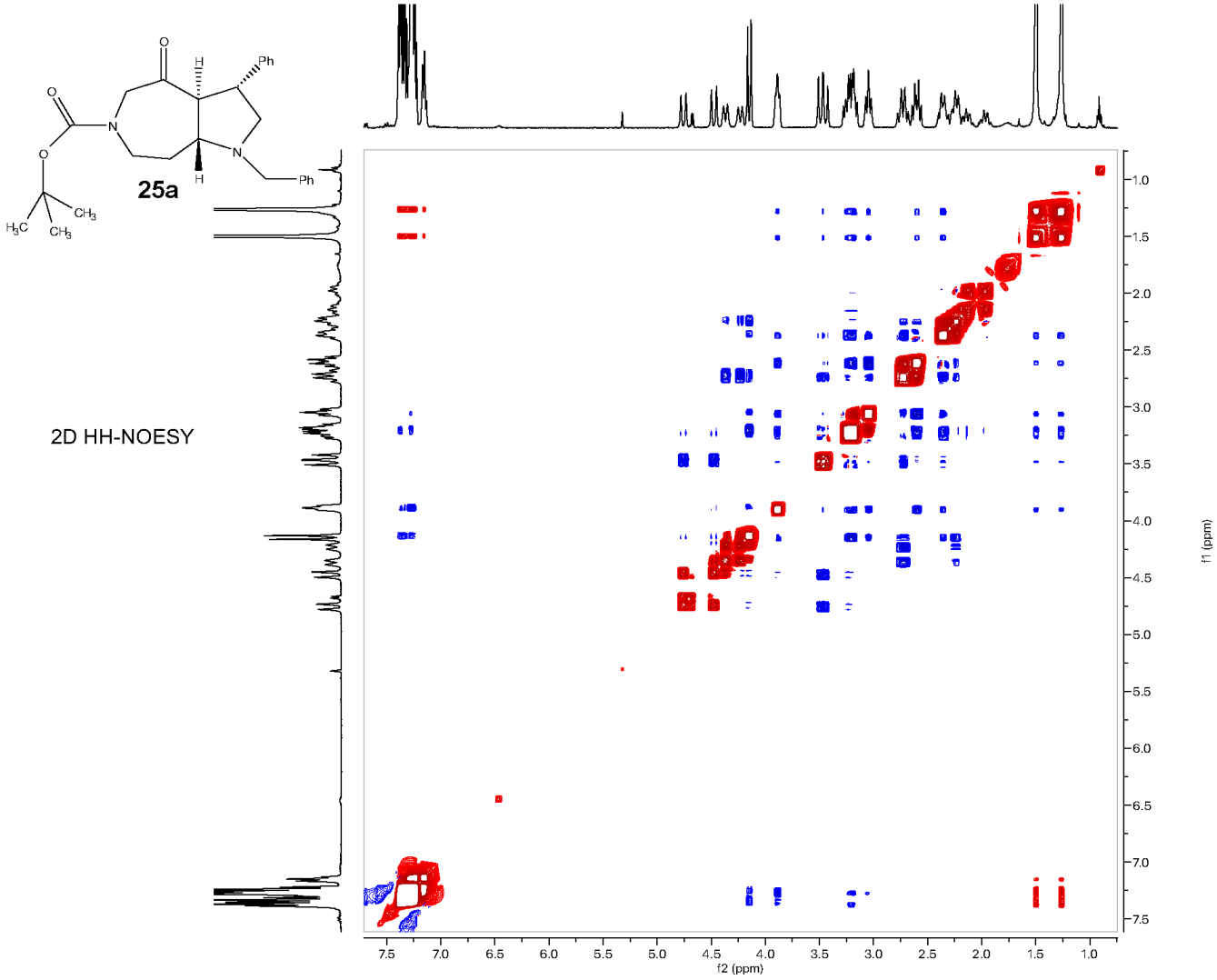
(3*RS*,3a*SR*,8a*RS*)-*Tert*-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate (25a). ^{1}H NMR ($CDCl_3$, 400 MHz)



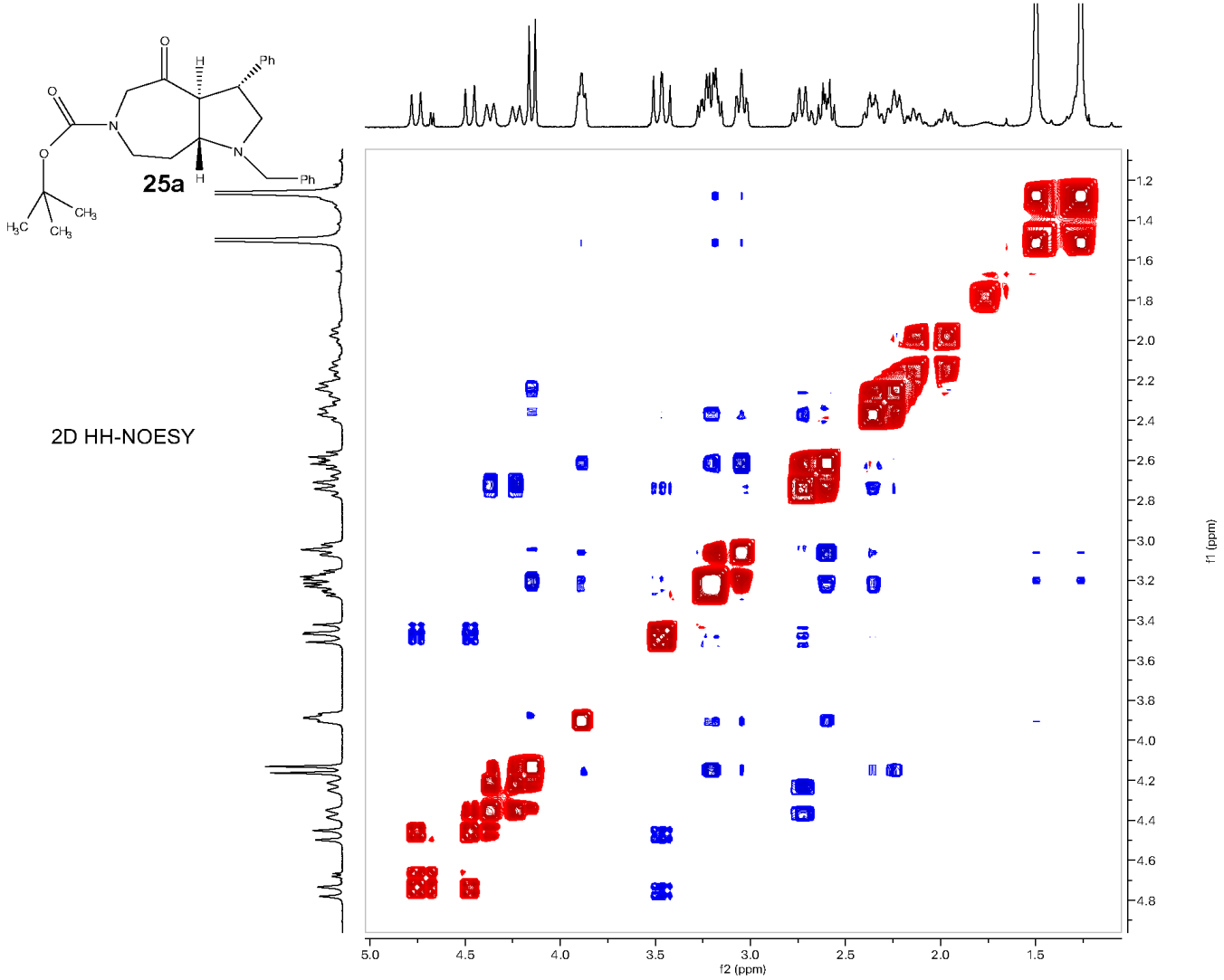
(3*RS*,3a*SR*,8a*RS*)-*Tert*-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate (25a). ^{13}C NMR ($CDCl_3$, 100 MHz)



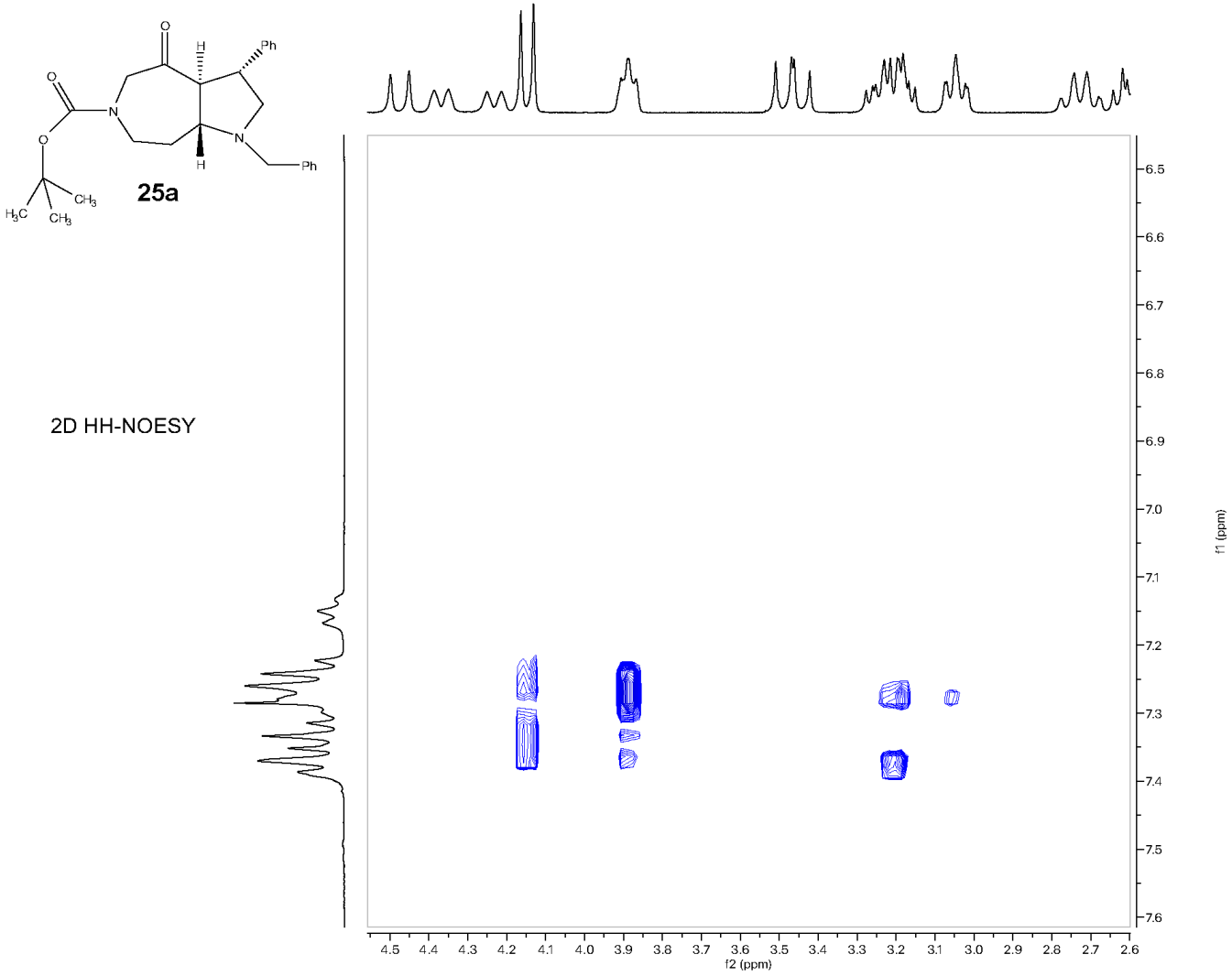
(3*RS*,3a*SR*,8a*RS*)-*Tert*-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate (25a). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms)



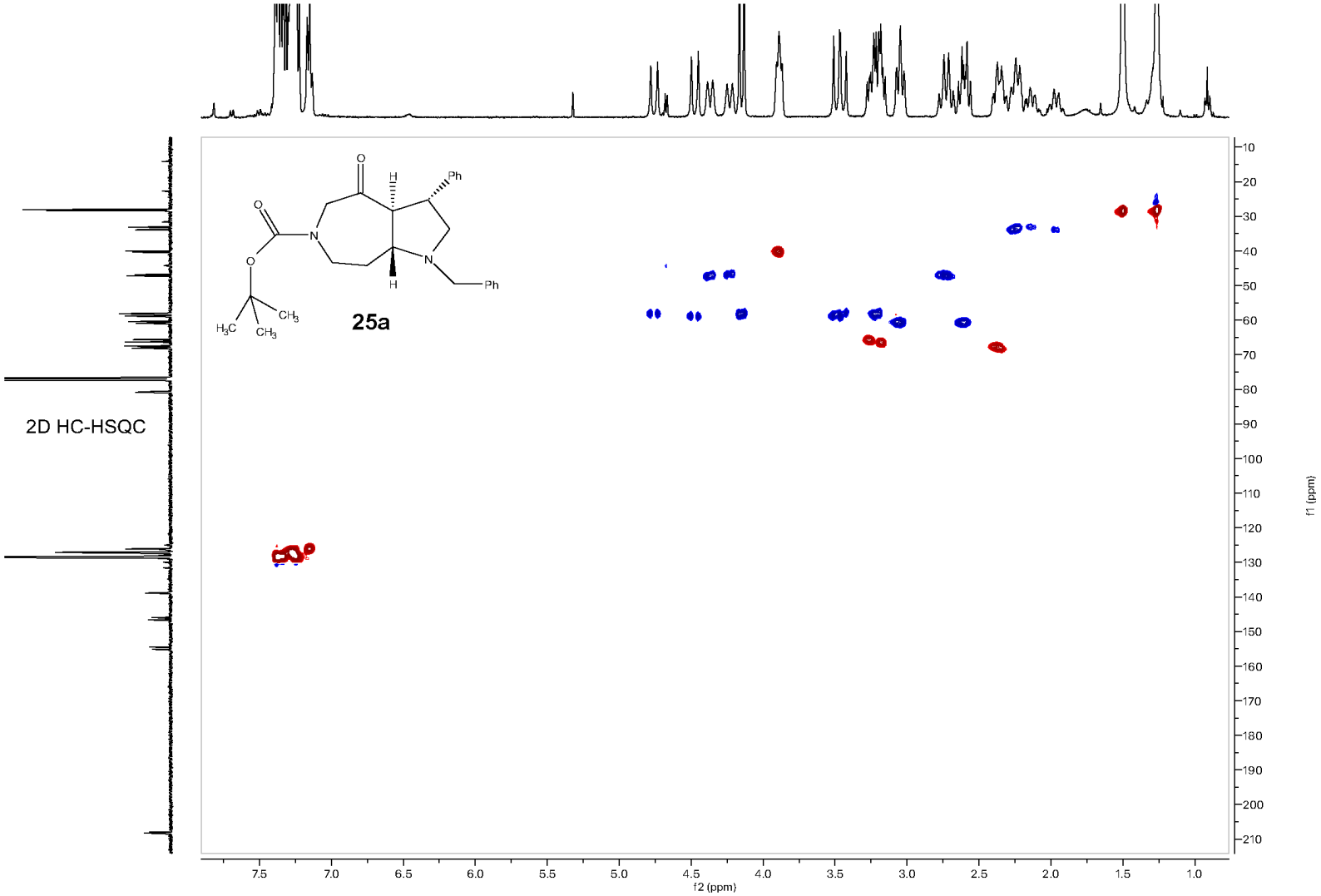
(3*RS*,3a*SR*,8a*RS*)-*Tert*-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate (25a). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms)



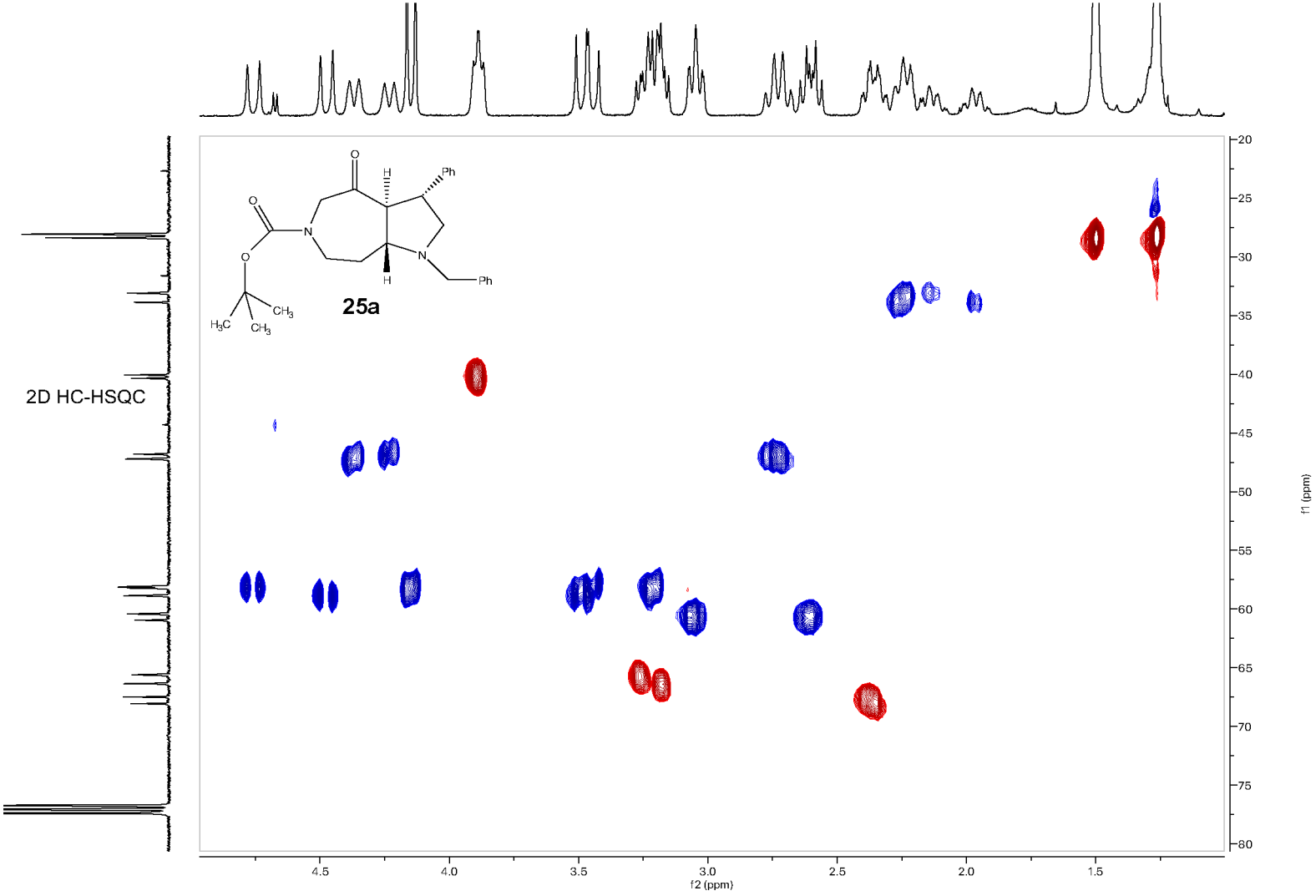
(3*RS*,3a*SR*,8a*RS*)-*Tert*-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate (25a). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms)



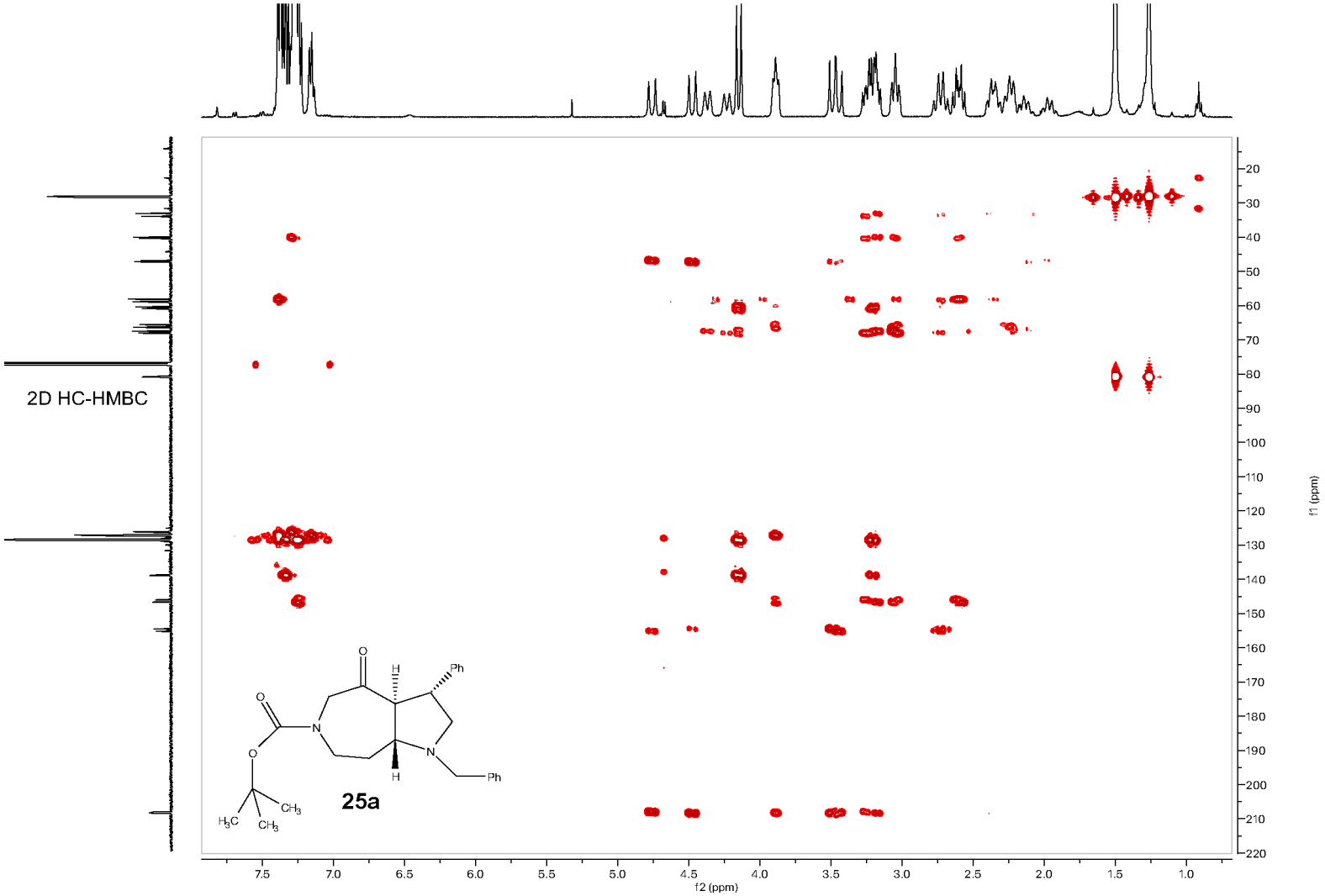
(3*RS*,3a*SR*,8a*RS*)-*Tert*-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate (25a). 2D ^{1}H-^{13}C-HSQC (qphase sensitive J1 (HC)=145Hz).



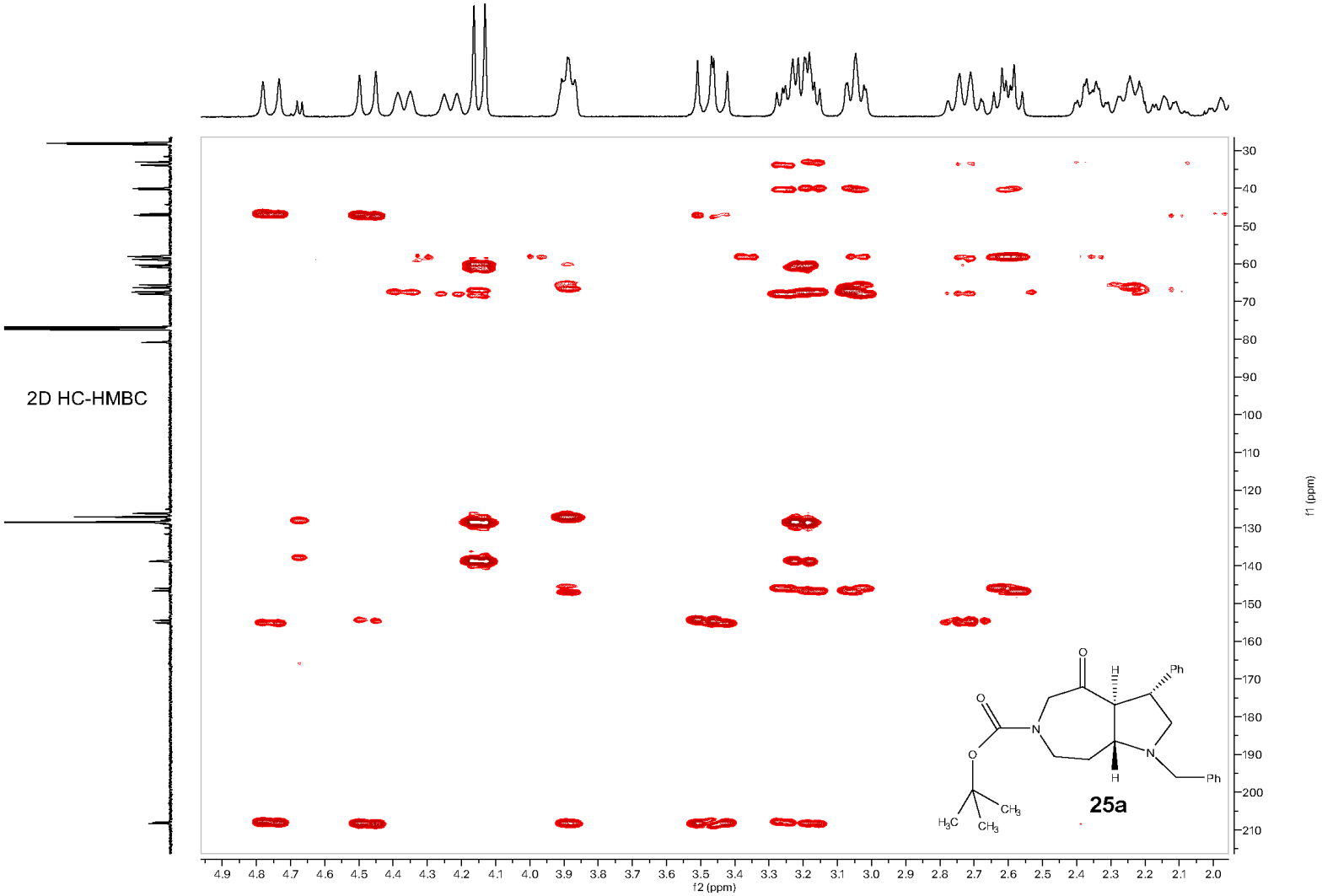
(3*RS*,3a*SR*,8a*RS*)-*Tert*-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate (25a). 2D ^{1}H-^{13}C-HSQC (qphase sensitive J1 (HC)=145Hz).



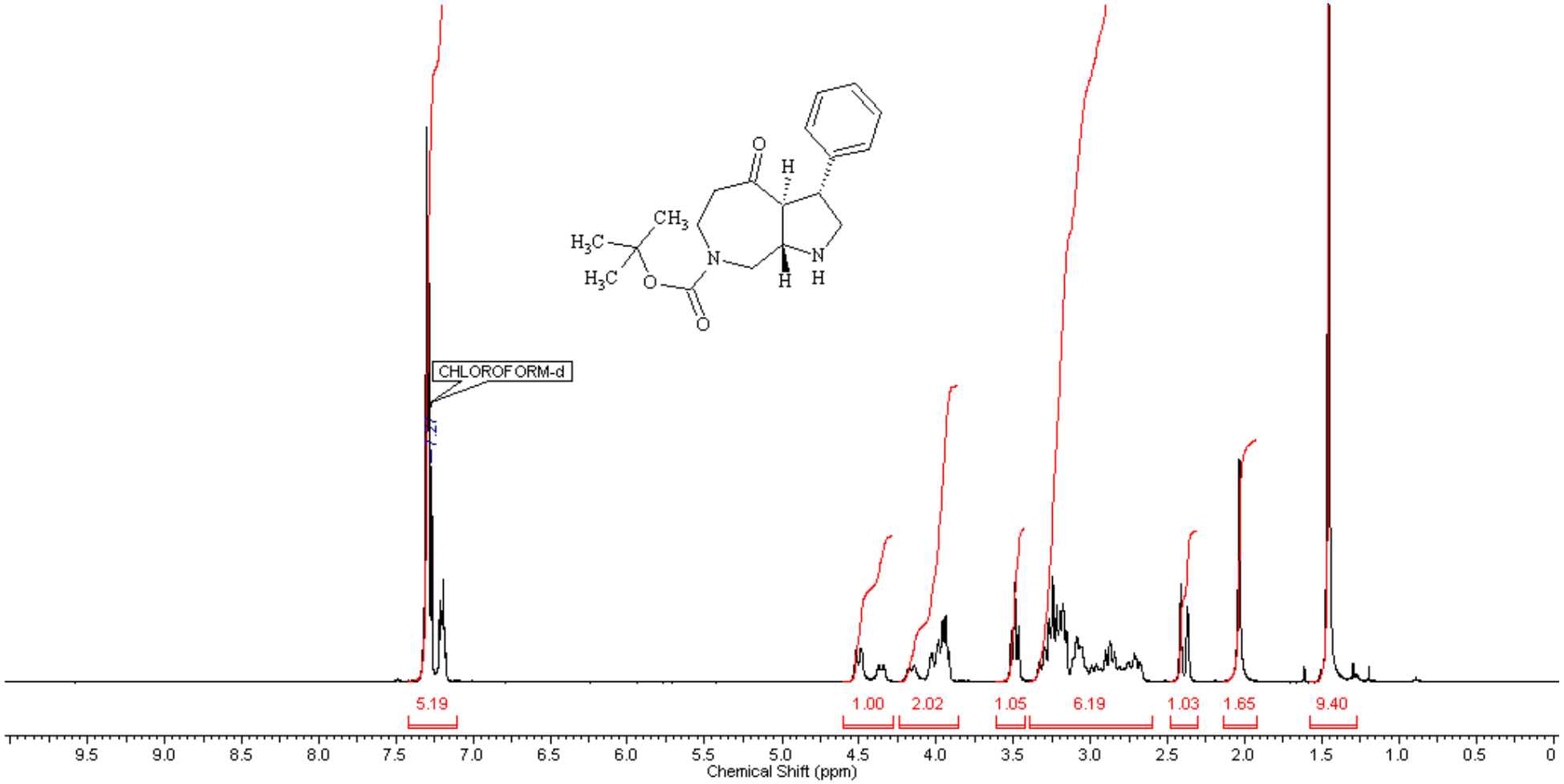
(3*RS*,3a*SR*,8a*RS*)-*Tert*-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate (25a). 2D ^{1}H-^{13}C-HMBC (longrange, J1(HC)=145Hz, J2(HC-long)=10Hz)



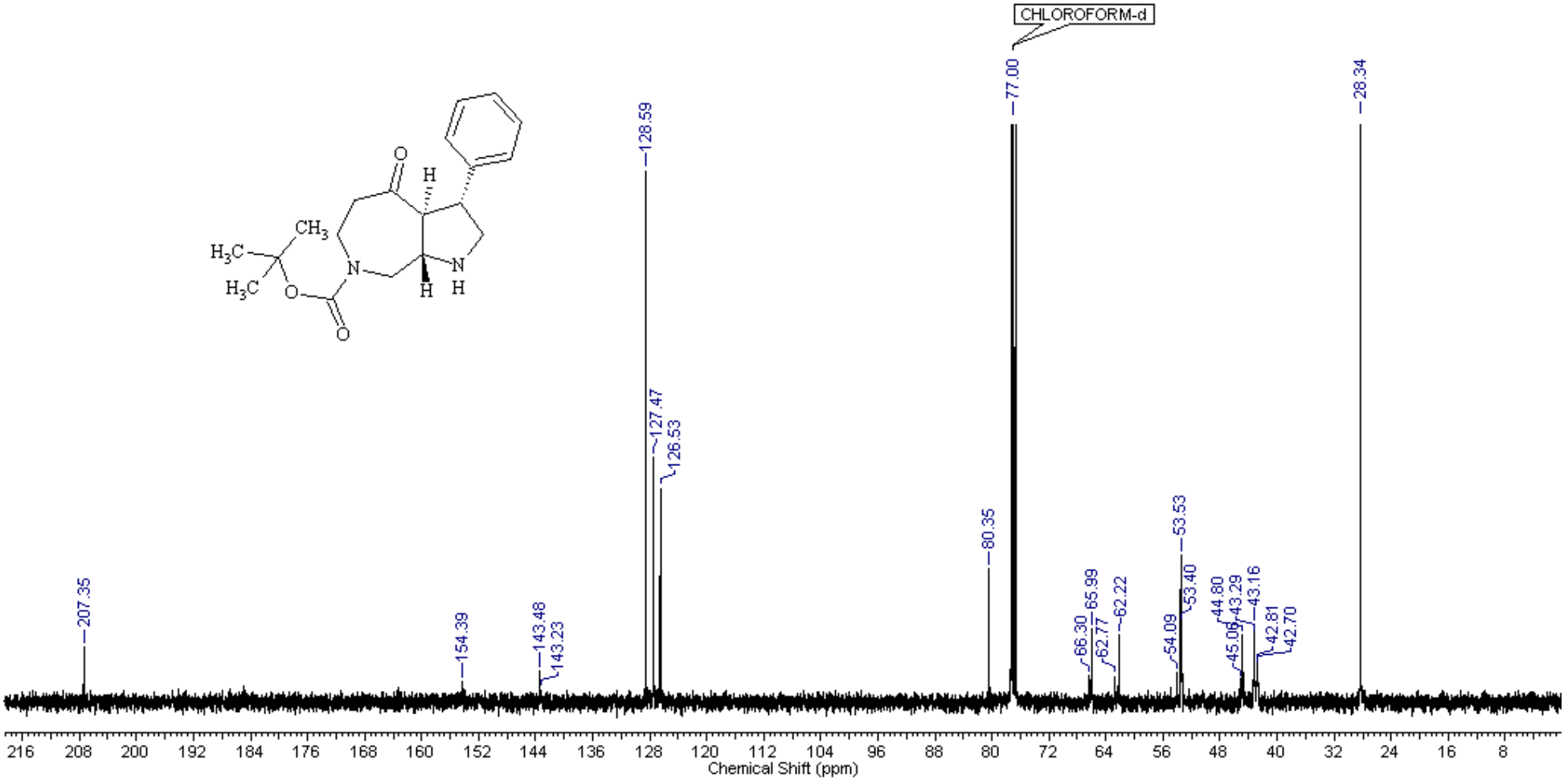
(3*RS*,3a*SR*,8a*RS*)-*Tert*-butyl 1-benzyl-4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate (25a). 2D ^{1}H-^{13}C-HMBC (longrange, J1(HC)=145Hz, J2(HC-long)=10Hz)



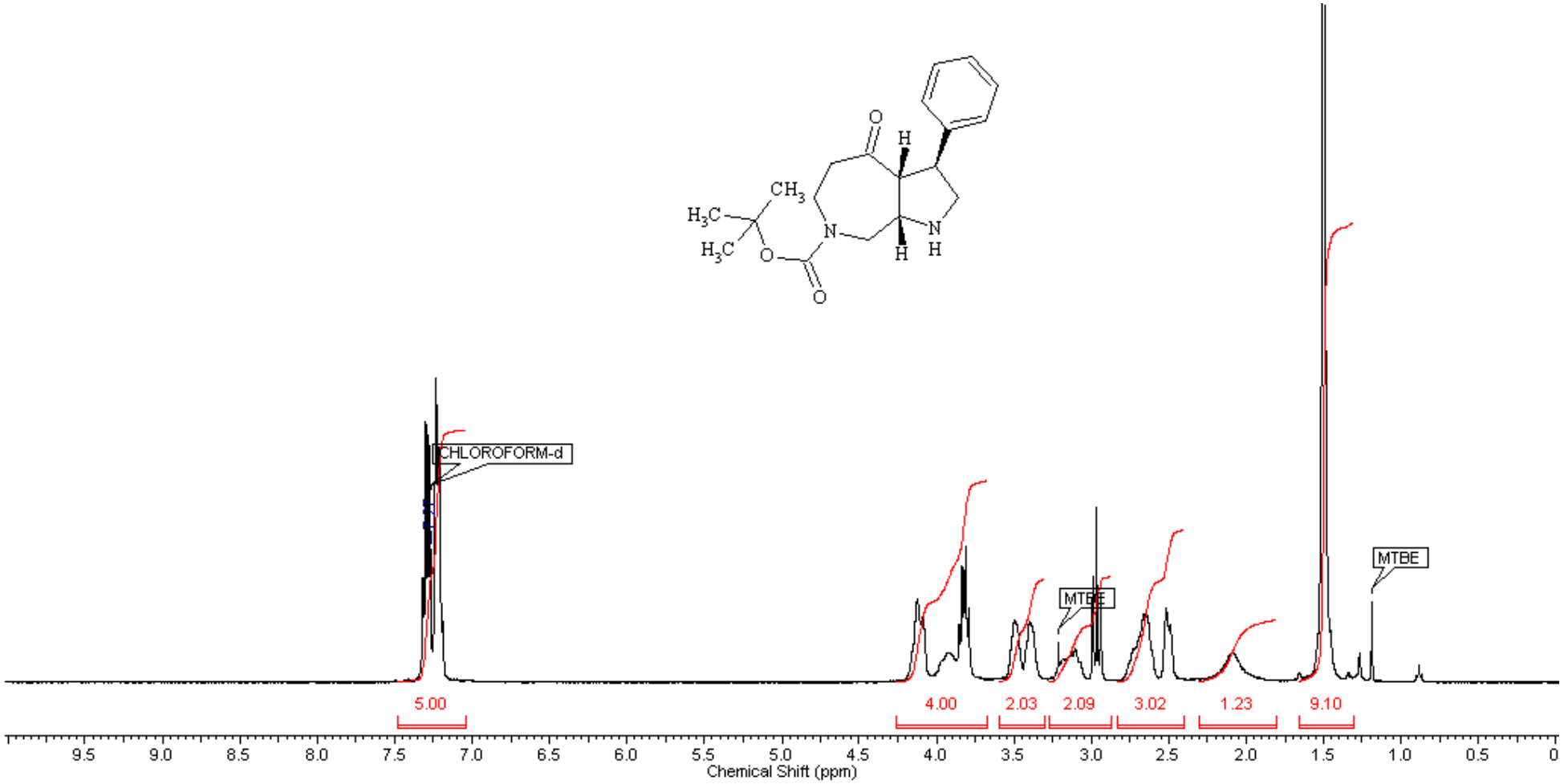
(3*RS*,3a*SR*,8a*SR*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate (26a). ^{1}H NMR ($CDCl_3$, 400 MHz)



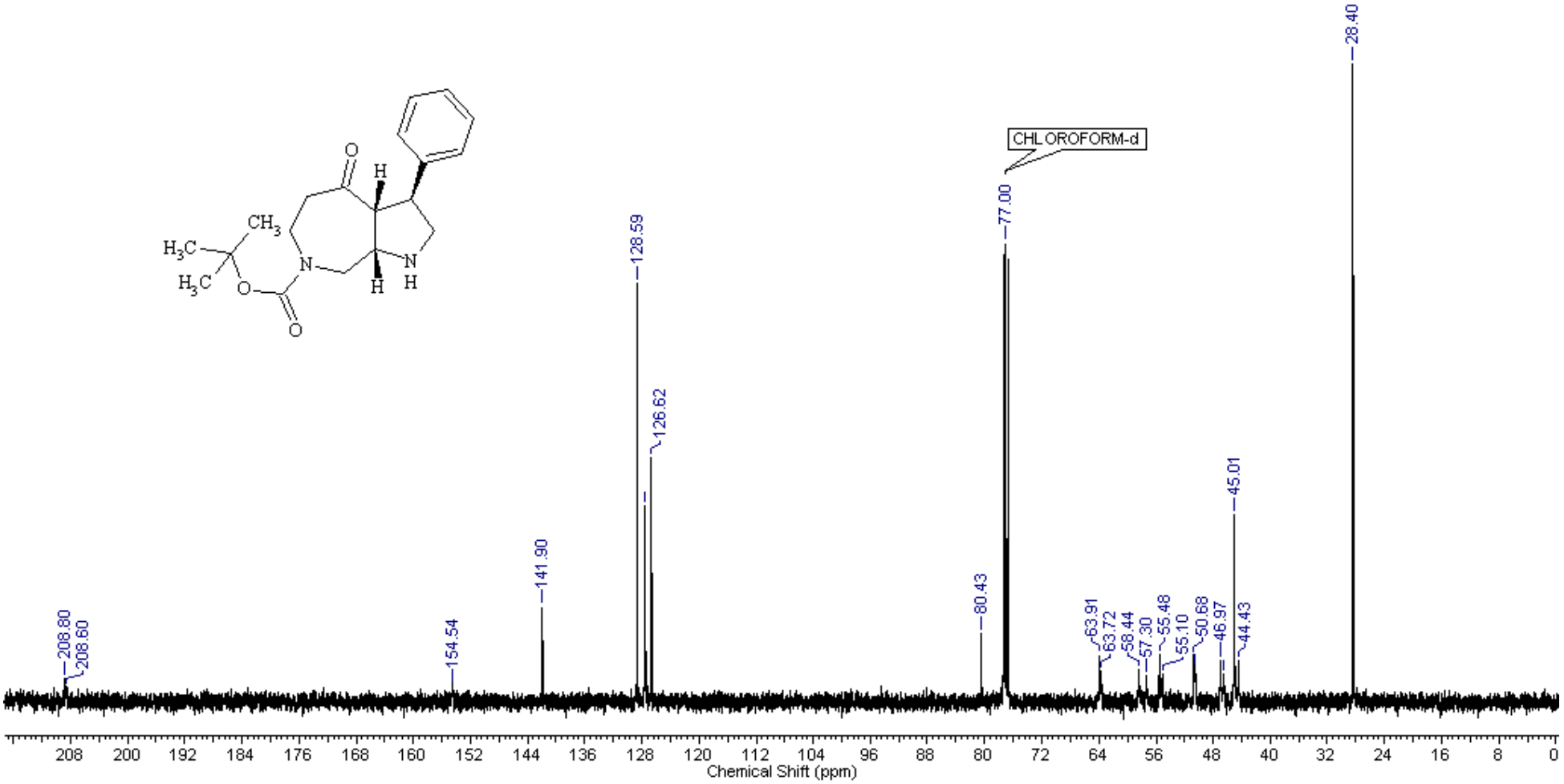
(3*RS*,3a*SR*,8a*SR*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate (26a). ^{13}C NMR ($CDCl_3$, 100 MHz)



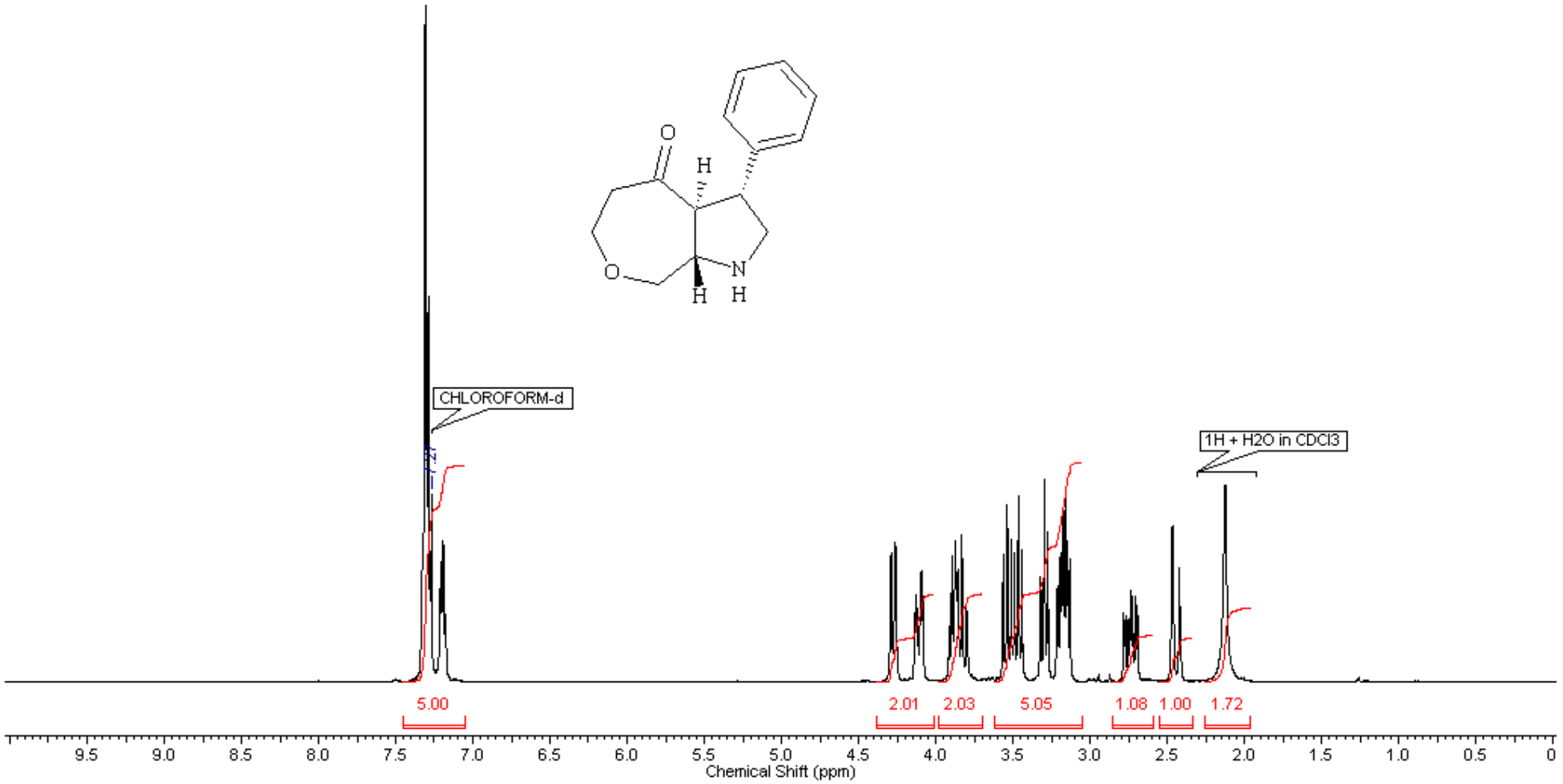
(3*SR*,3a*RS*,8a*SR*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate (26b). ^{1}H NMR ($CDCl_3$, 400 MHz)



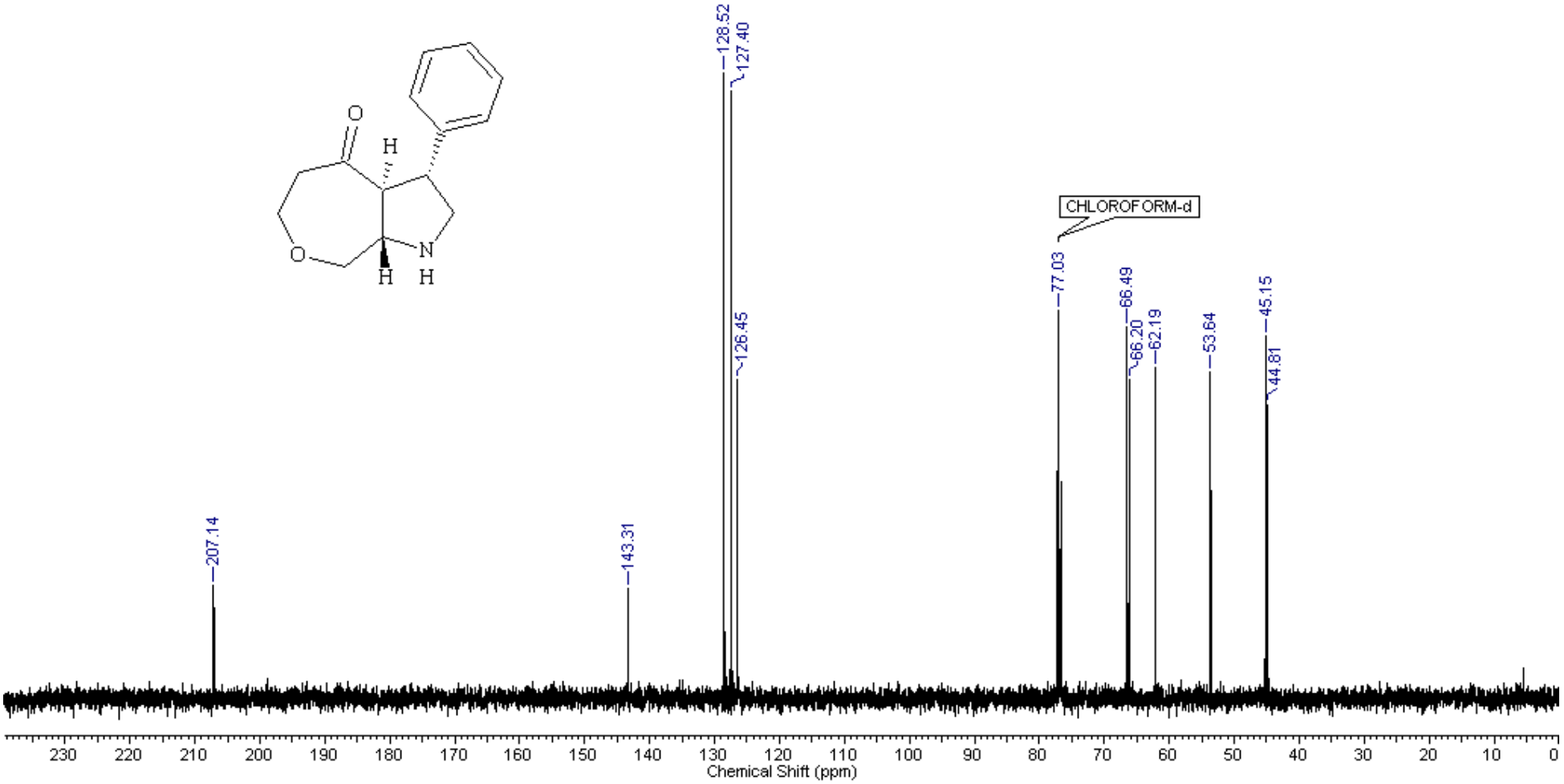
(3*SR*,3a*RS*,8a*SR*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate (26b). ^{13}C NMR ($CDCl_3$, 100 MHz)



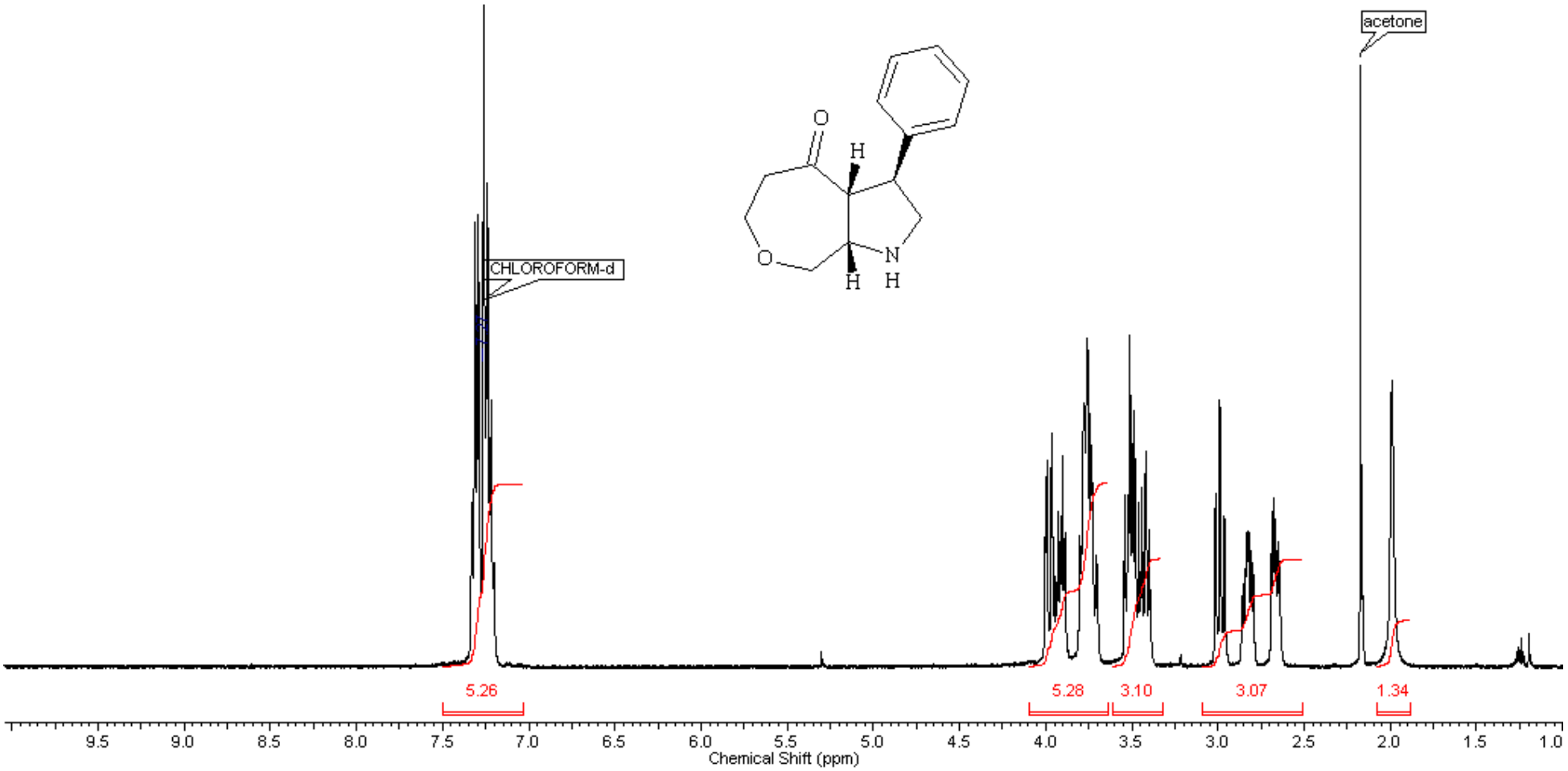
(3*RS*,3a*SR*,8a*SR*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (27a). ^{1}H NMR ($CDCl_3$, 400 MHz).



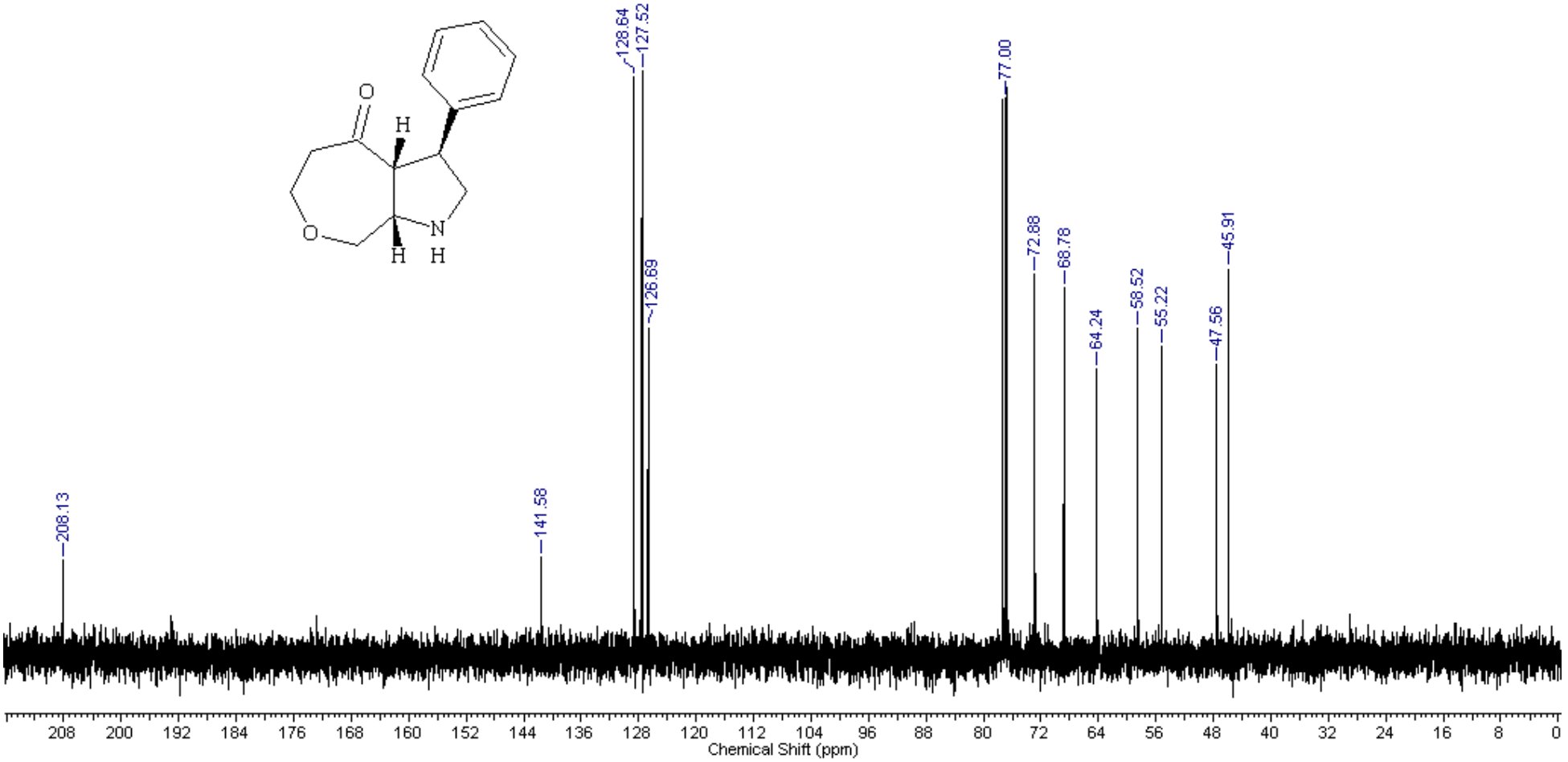
(3*RS*,3a*SR*,8a*SR*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (27a). ^{13}C NMR ($CDCl_3$, 100 MHz).



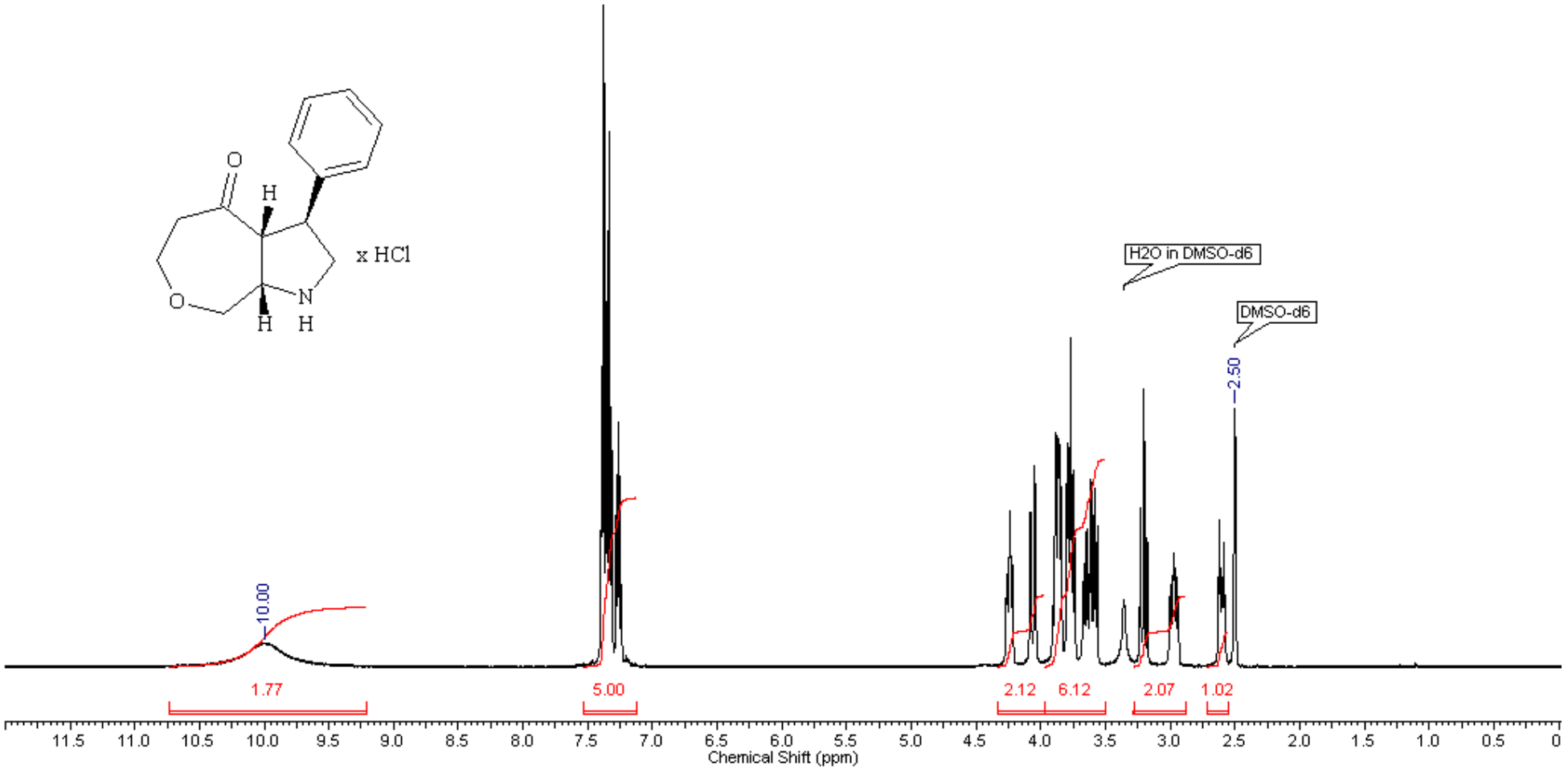
(3*SR*,3a*RS*,8a*SR*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (27b). ^{1}H NMR ($CDCl_3$, 400 MHz).



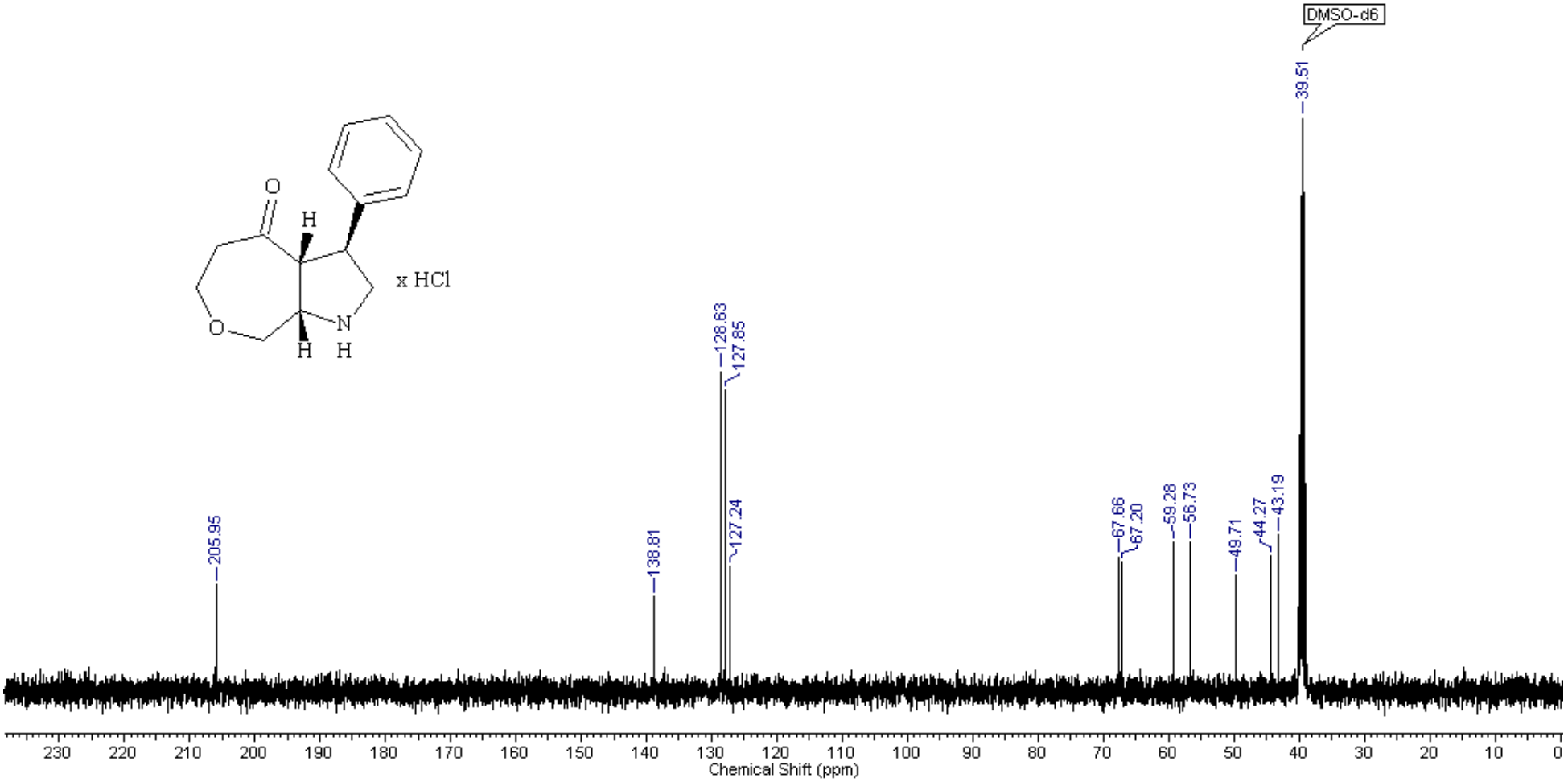
(3*SR*,3a*RS*,8a*SR*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (27b). ^{1}H NMR ($CDCl_3$, 400 MHz).



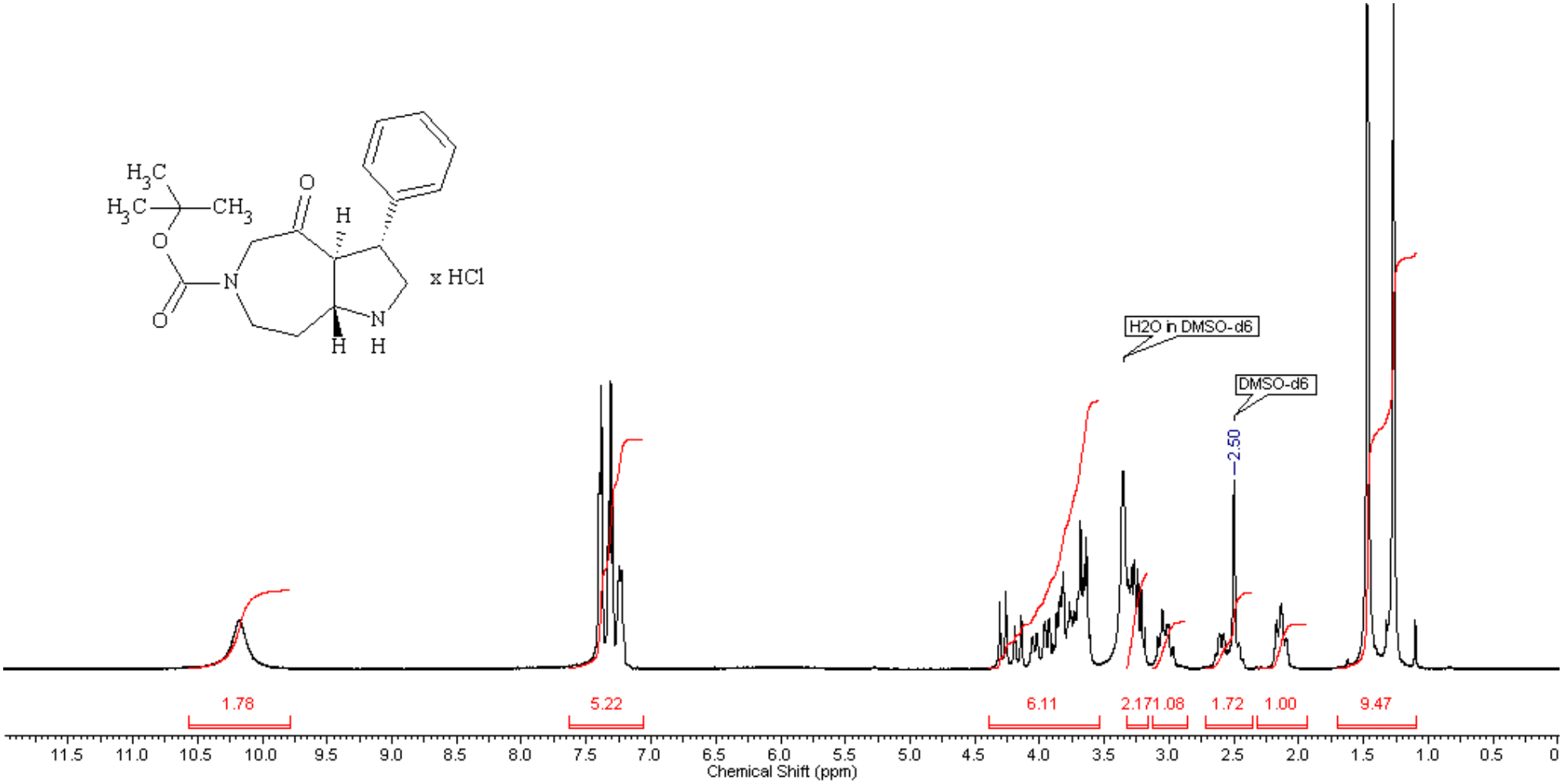
(3*SR*,3a*RS*,8a*SR*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one hydrochloride (27b). ^{1}H NMR (DMSO-d_6, 400 MHz)



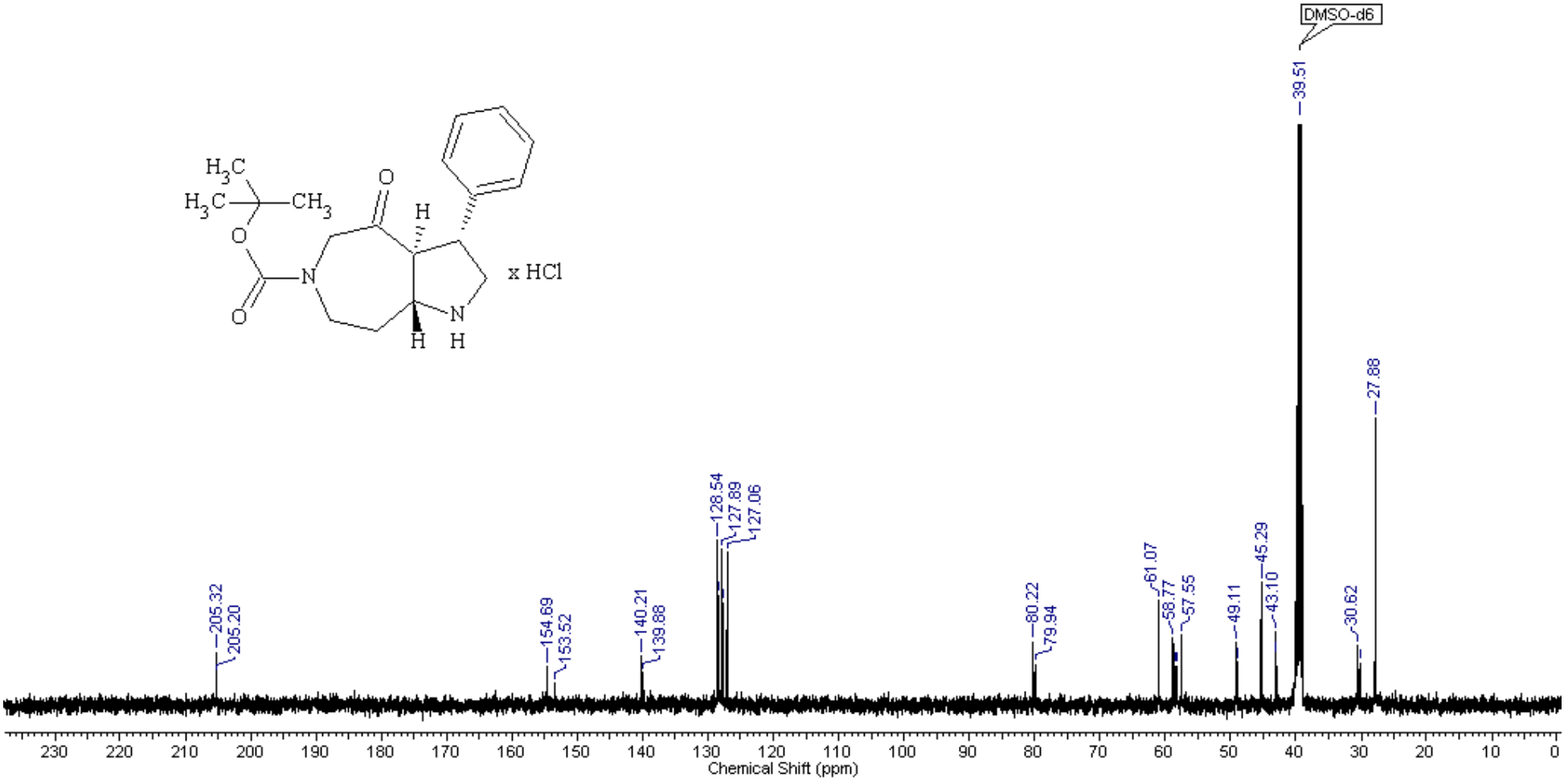
(3*SR*,3a*RS*,8a*SR*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one hydrochloride (27b). ^{13}C NMR (DMSO-d_6, 100 MHz)



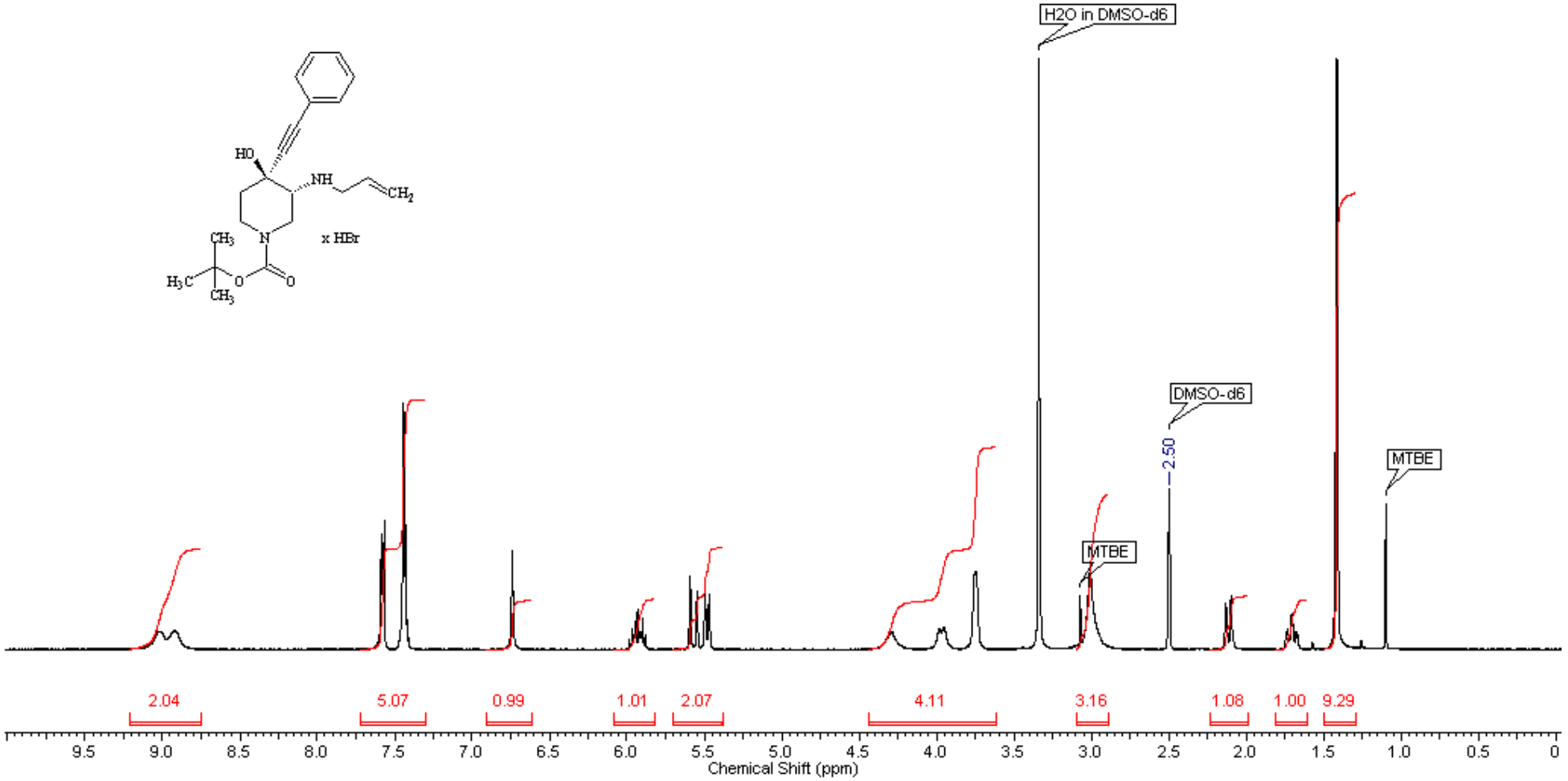
(3*RS*,3a*SR*,8a*RS*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate hydrochloride(28a). ^{1}H NMR (DMSO-d_6, 400 MHz).



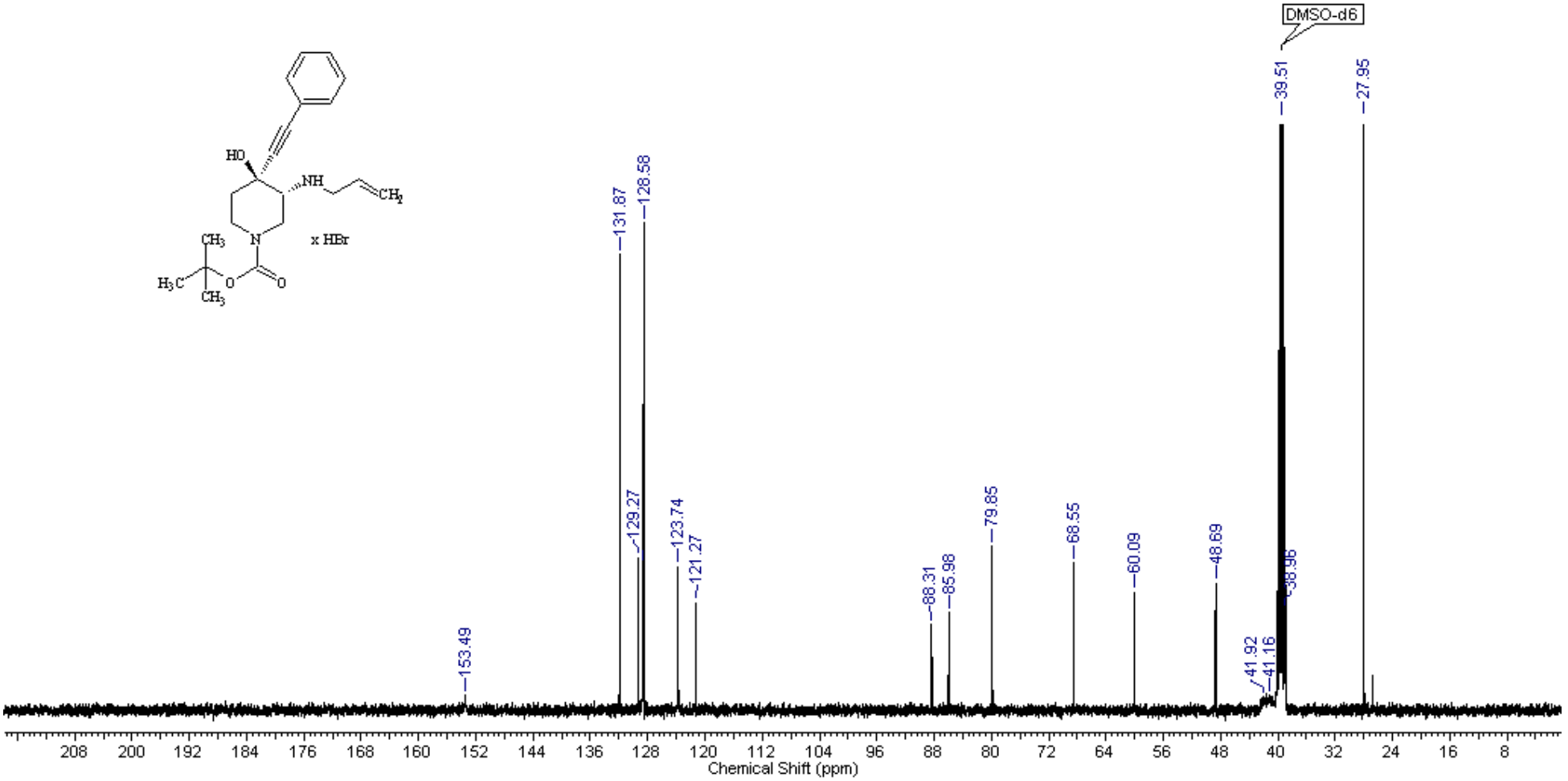
(3*RS*,3a*SR*,8a*RS*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate hydrochloride(28a). ^{13}C NMR (DMSO-d_6, 100 MHz).



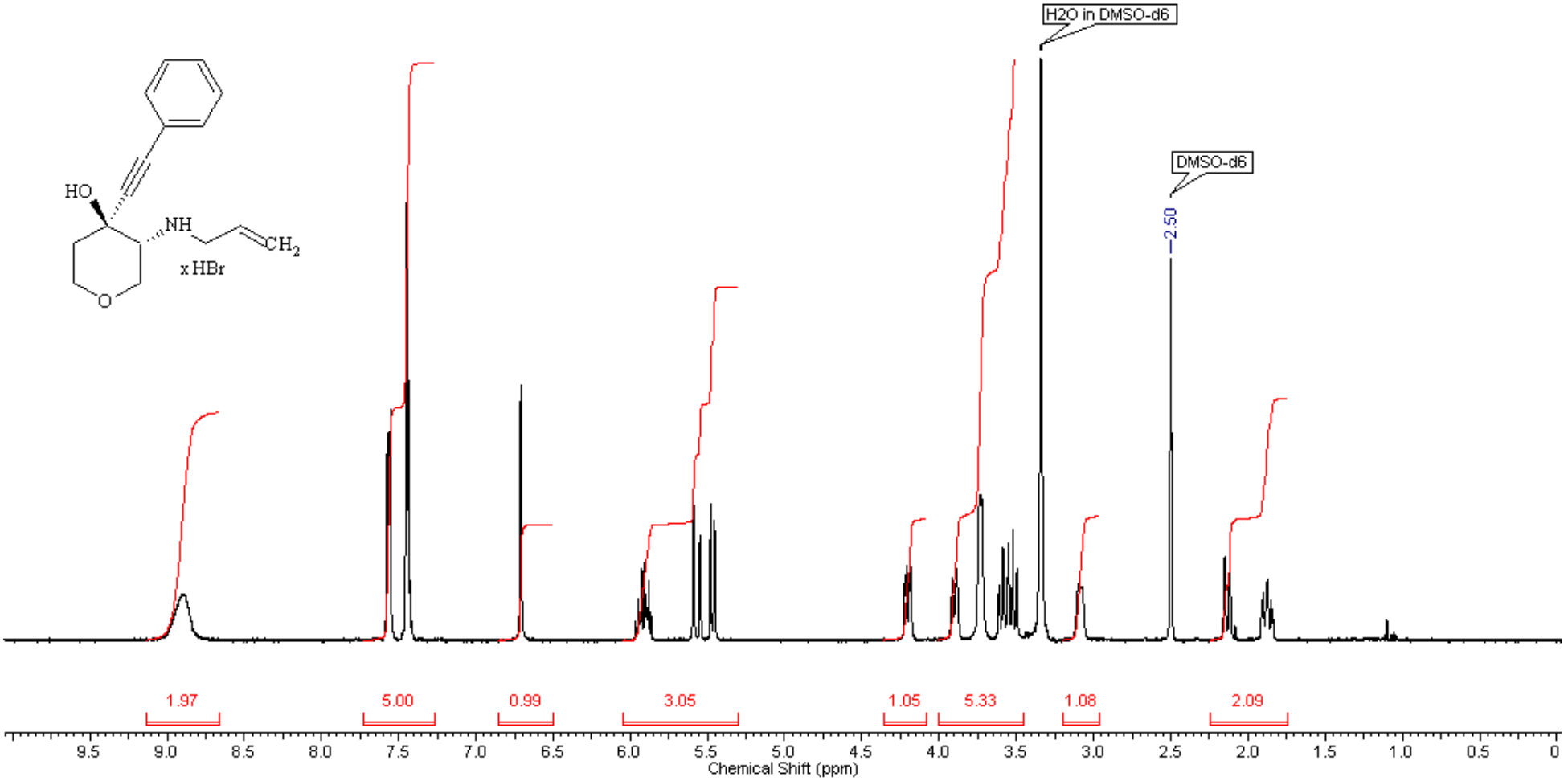
(3*RS*,4*SR*)-*Tert*-butyl 3-(allylamino)-4-hydroxy-4-(phenylethynyl)piperidine-1-carboxylate hydrobromide (31). ^{1}H NMR (400 MHz, DMSO-d_6).



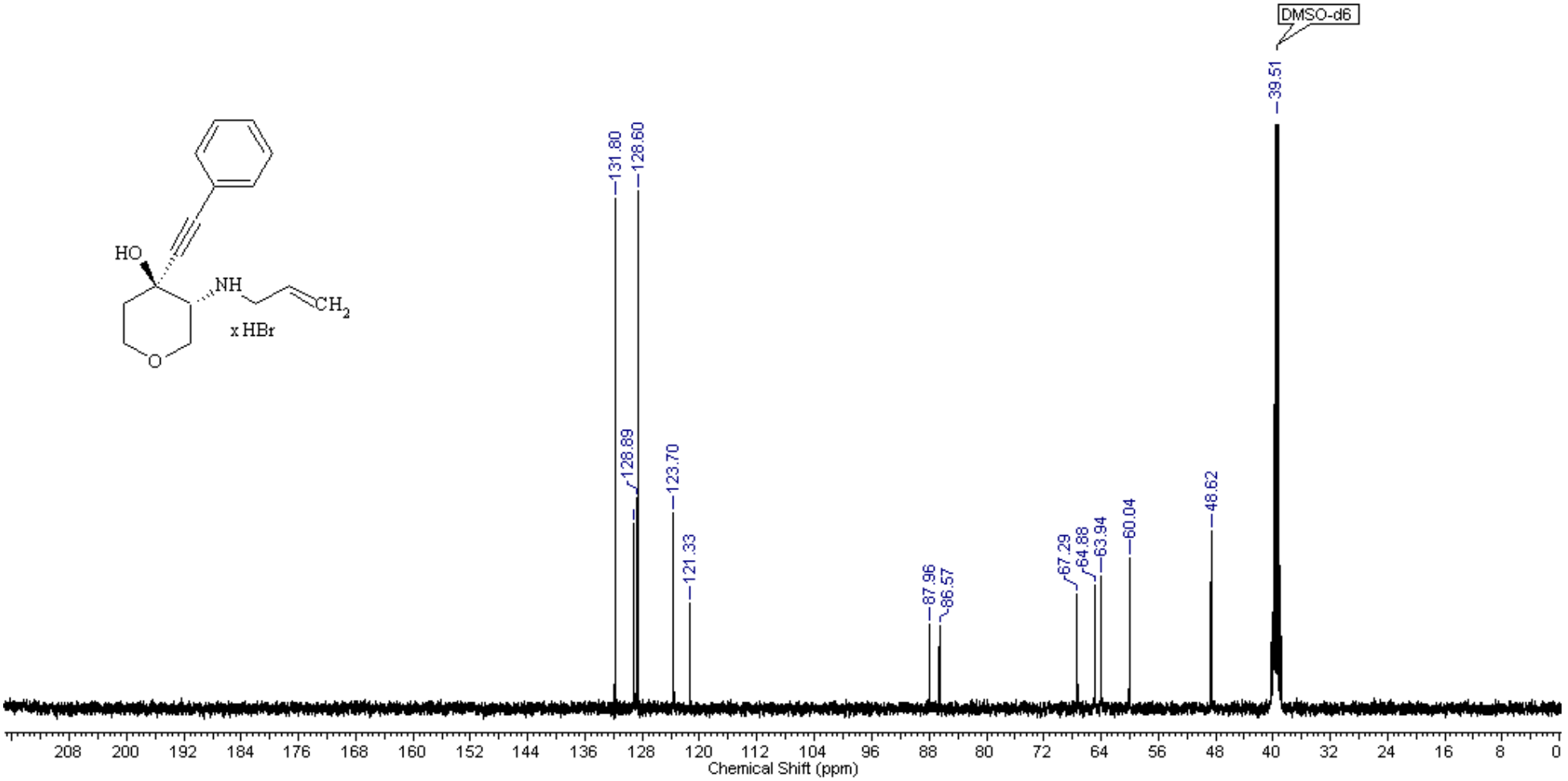
(3*RS*,4*SR*)-*Tert*-butyl 3-(allylamino)-4-hydroxy-4-(phenylethynyl)piperidine-1-carboxylate hydrobromide (31). ^{13}C NMR (DMSO-d_6, 100 MHz).



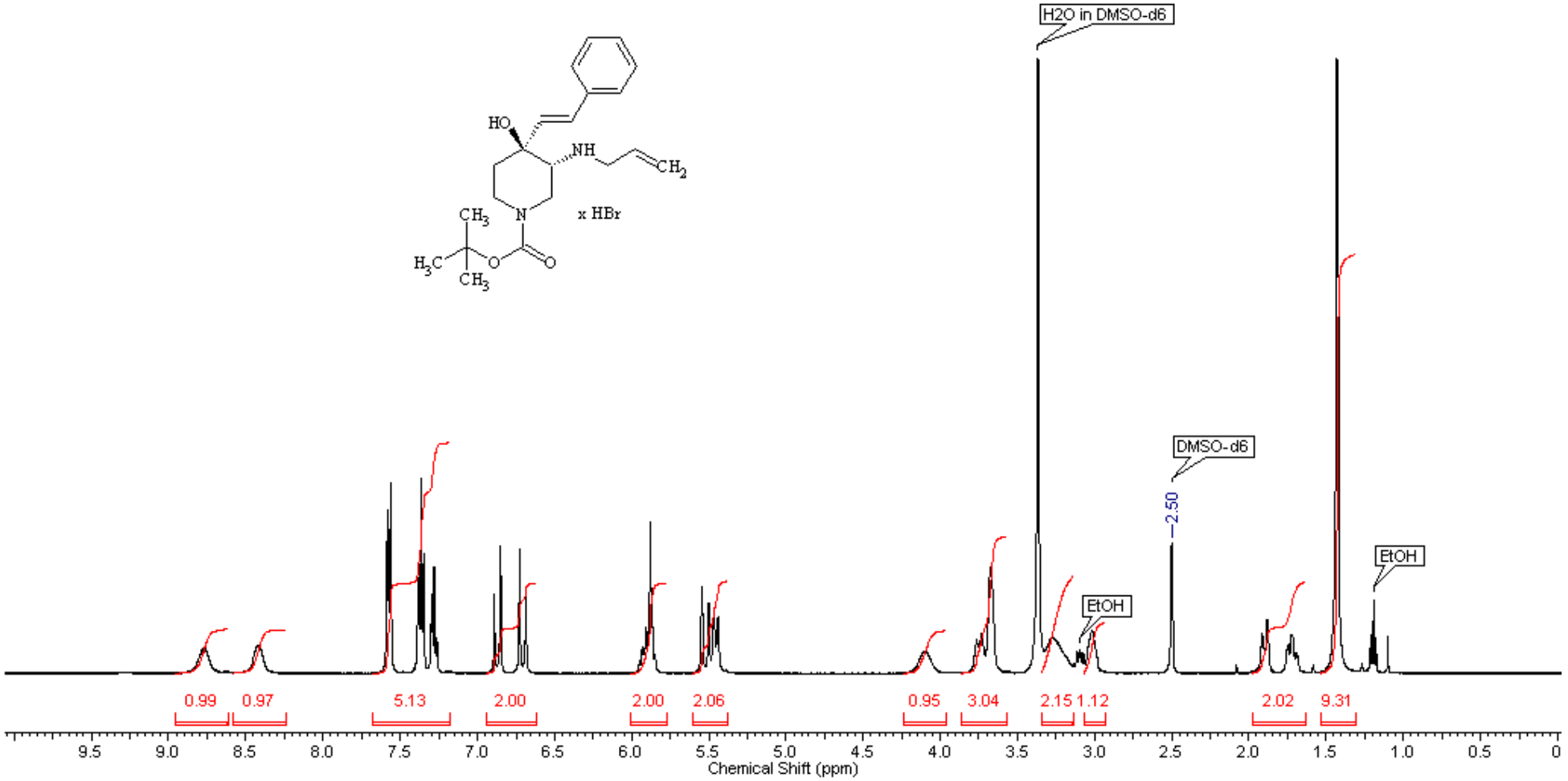
(3*RS*,4*SR*)-3-(Allylamino)-4-(phenylethynyl)tetrahydro-2*H*-pyran-4-ol hydrobromide (32). ^{1}H NMR (400 MHz, DMSO-d_6).



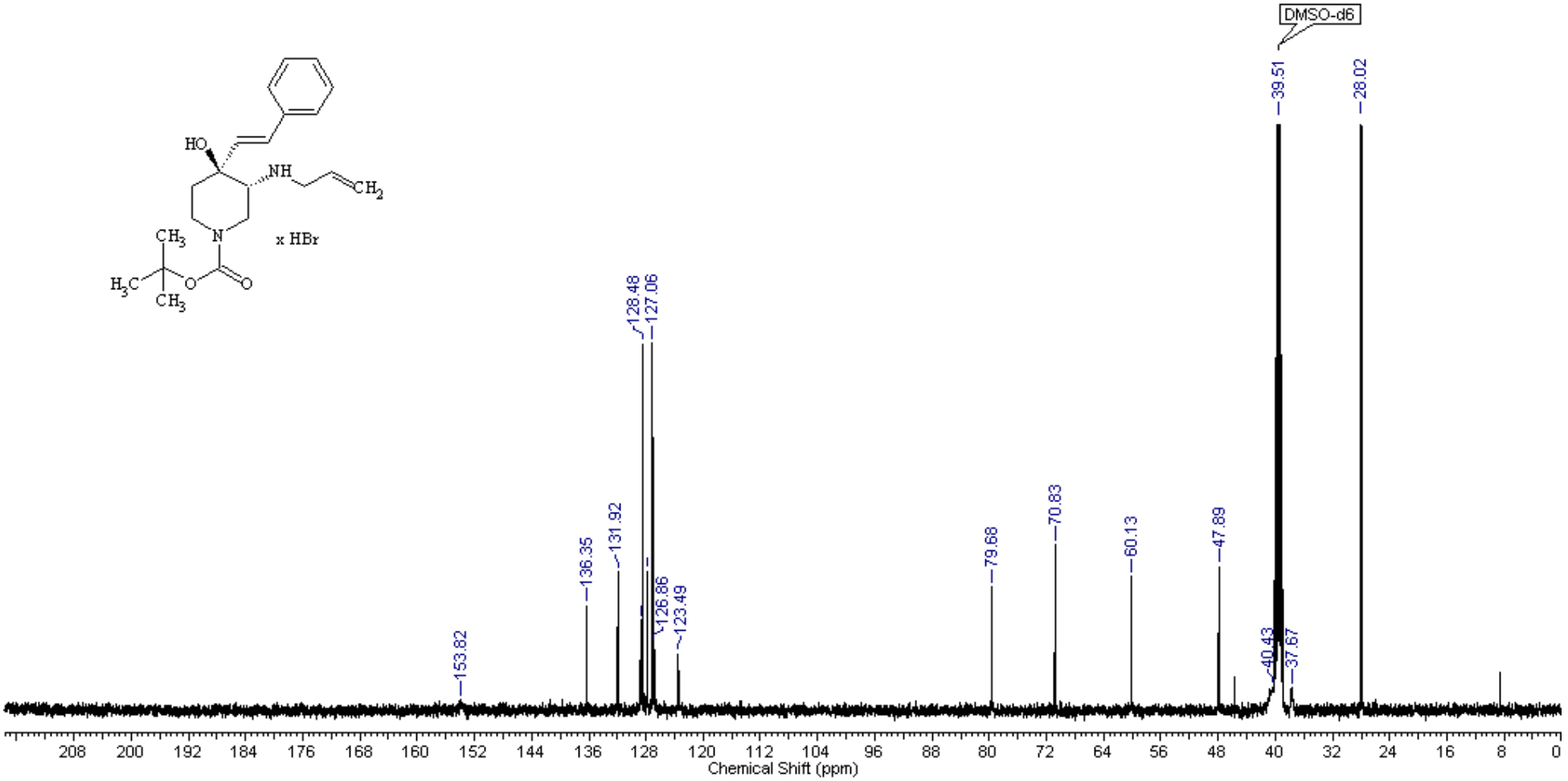
(3*RS*,4*SR*)-3-(Allylamino)-4-(phenylethynyl)tetrahydro-2*H*-pyran-4-ol hydrobromide (32). ^{13}C NMR (DMSO-d_6, 100 MHz).



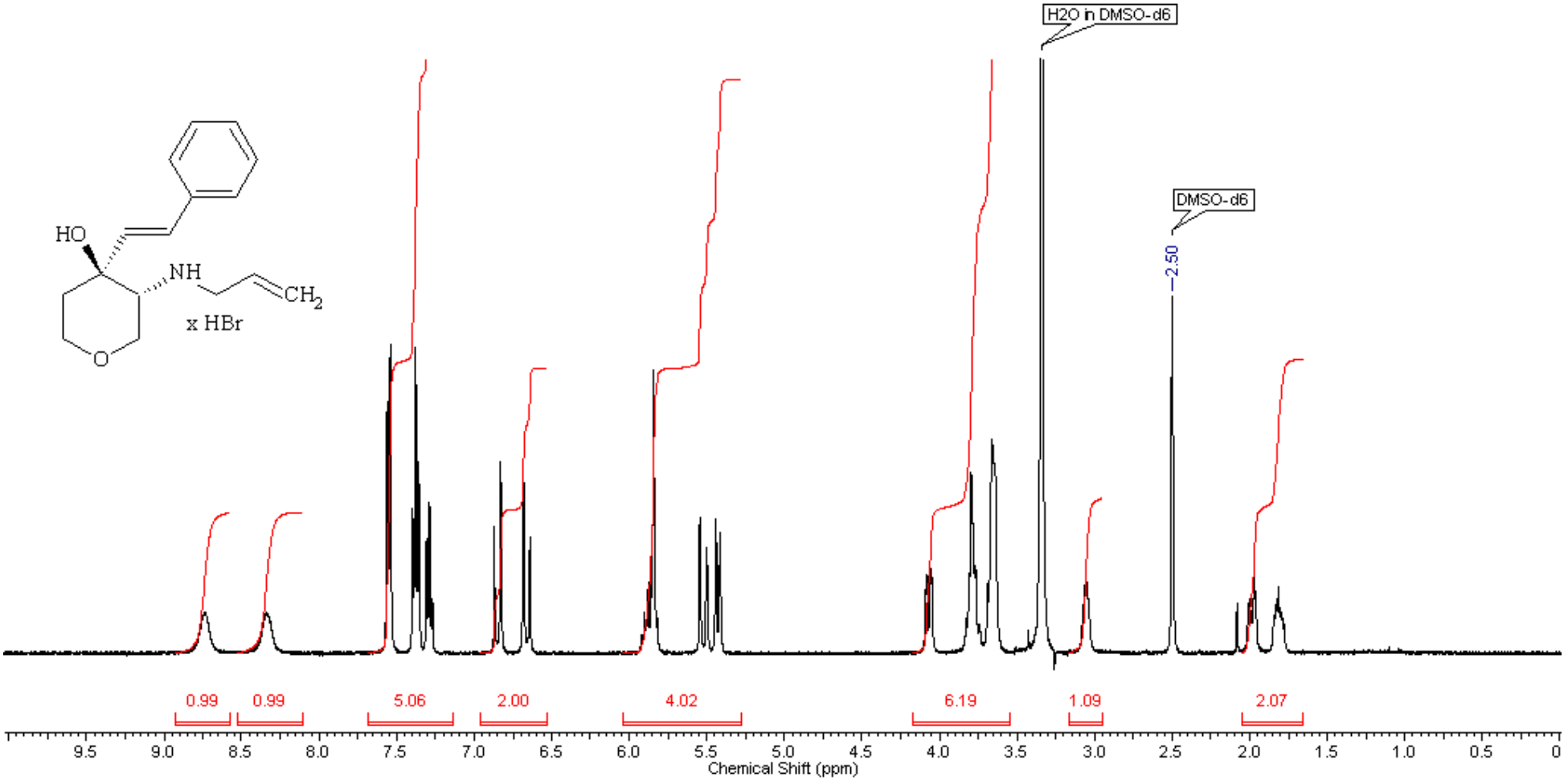
(3*RS*,4*SR*)-*Tert*-butyl 3-(allylamino)-4-hydroxy-4-((*E*)-styryl)piperidine-1-carboxylate hydrobromide (33). ^{1}H NMR (DMSO-d_6, 400 MHz).



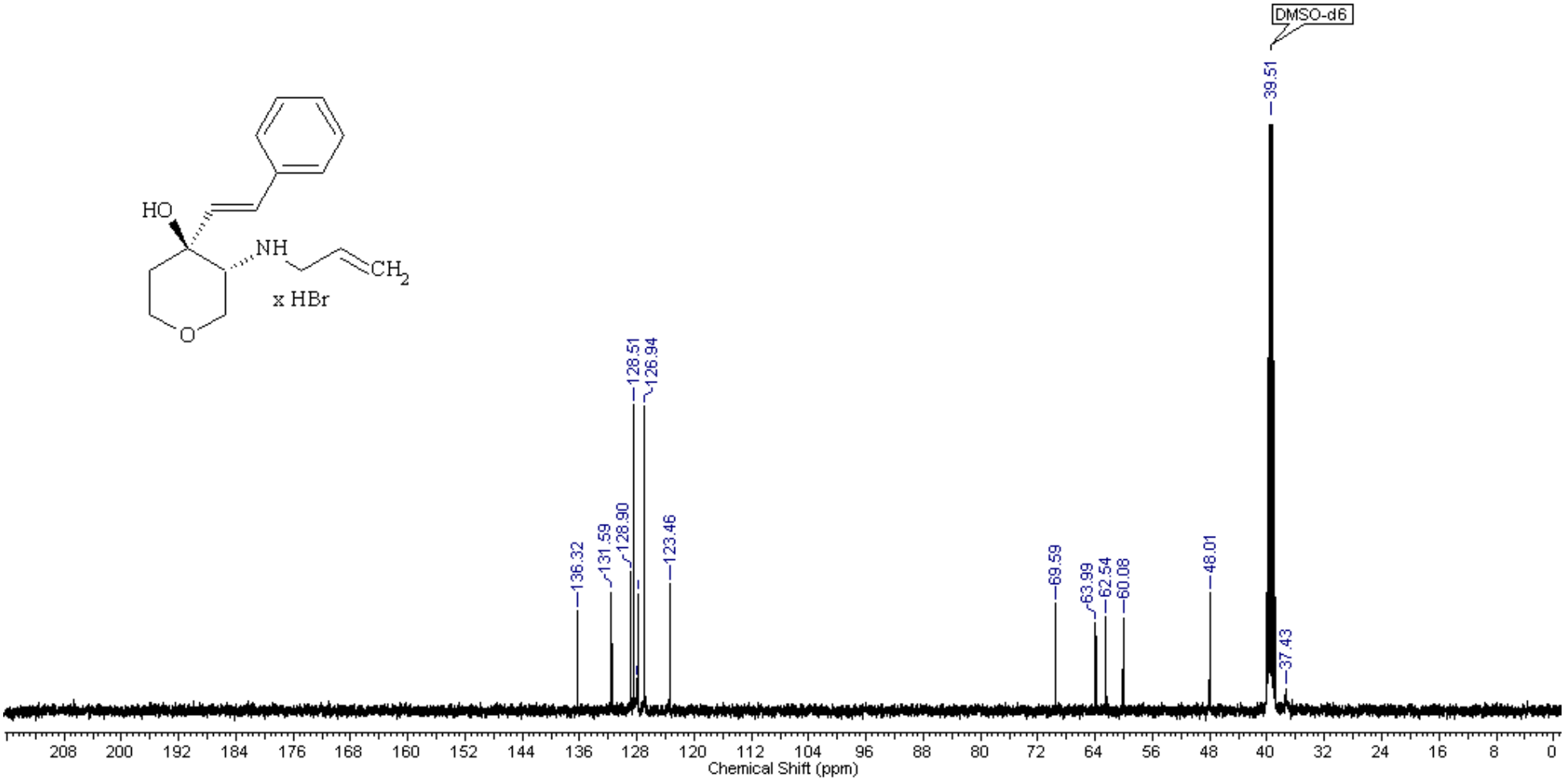
(3*RS*,4*SR*)-*Tert*-butyl 3-(allylamino)-4-hydroxy-4-((*E*)-styryl)piperidine-1-carboxylate hydrobromide (33). ^{13}C NMR (DMSO-d_6, 100 MHz).



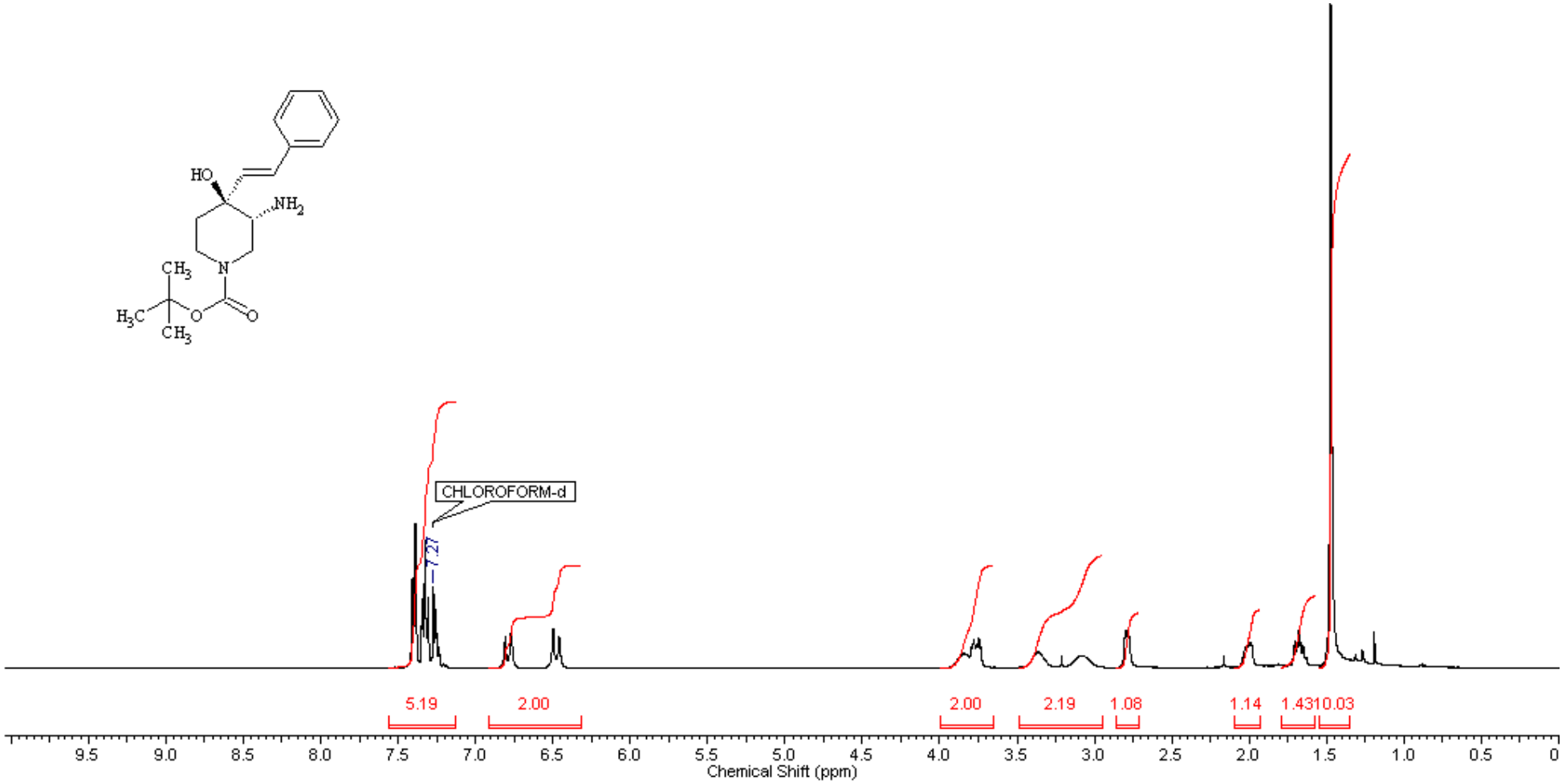
(3*RS*,4*SR*)-3-(Allylamino)-4-((*E*)-styryl)tetrahydro-2*H*-pyran-4-ol hydrobromide (34). ^{1}H NMR (400 MHz, DMSO-d$_6$).



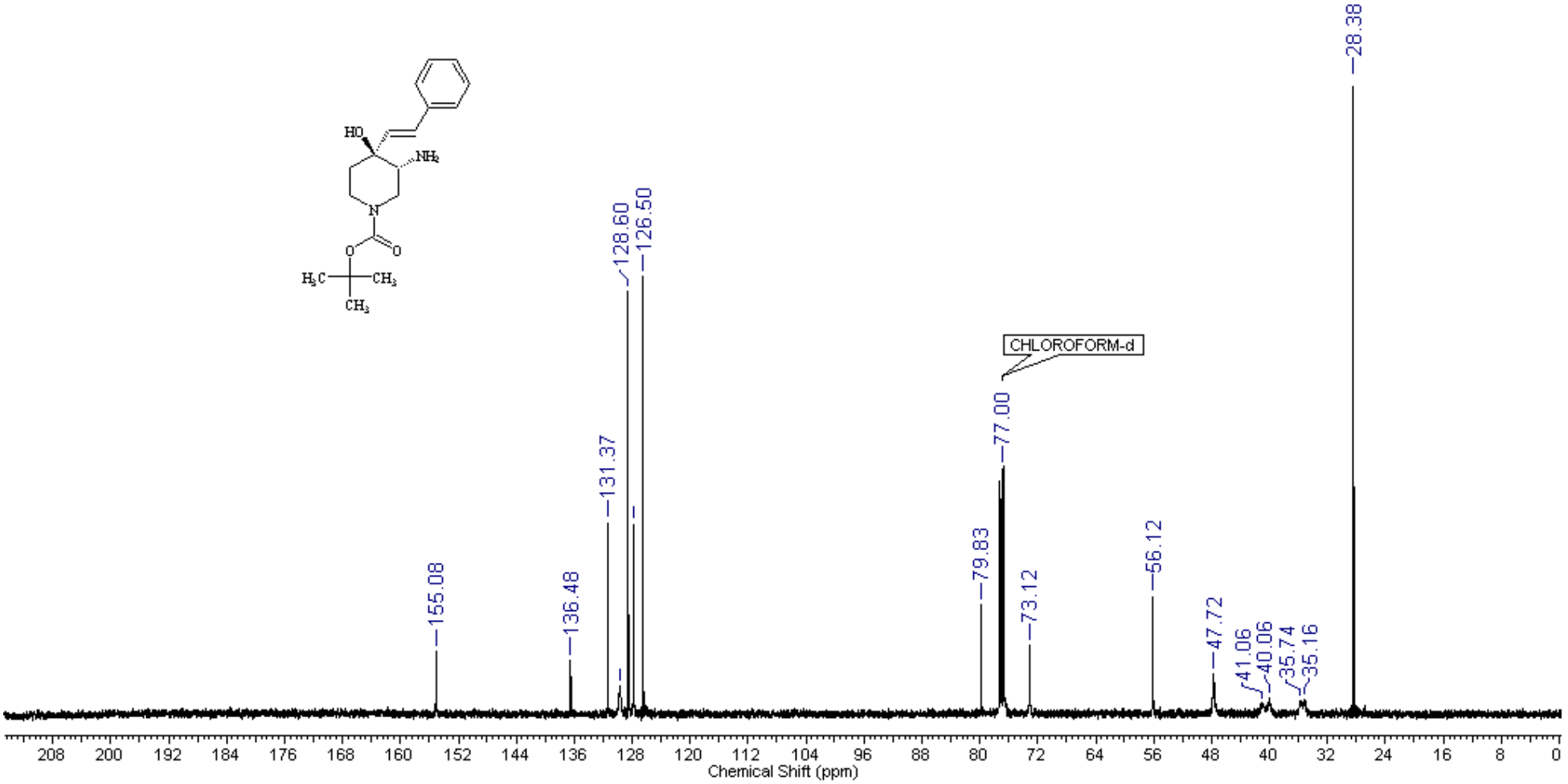
(3*RS*,4*SR*)-3-(Allylamino)-4-((*E*)-styryl)tetrahydro-2*H*-pyran-4-ol hydrobromide (34). ^{13}C NMR (100 MHz, DMSO-d$_6$).



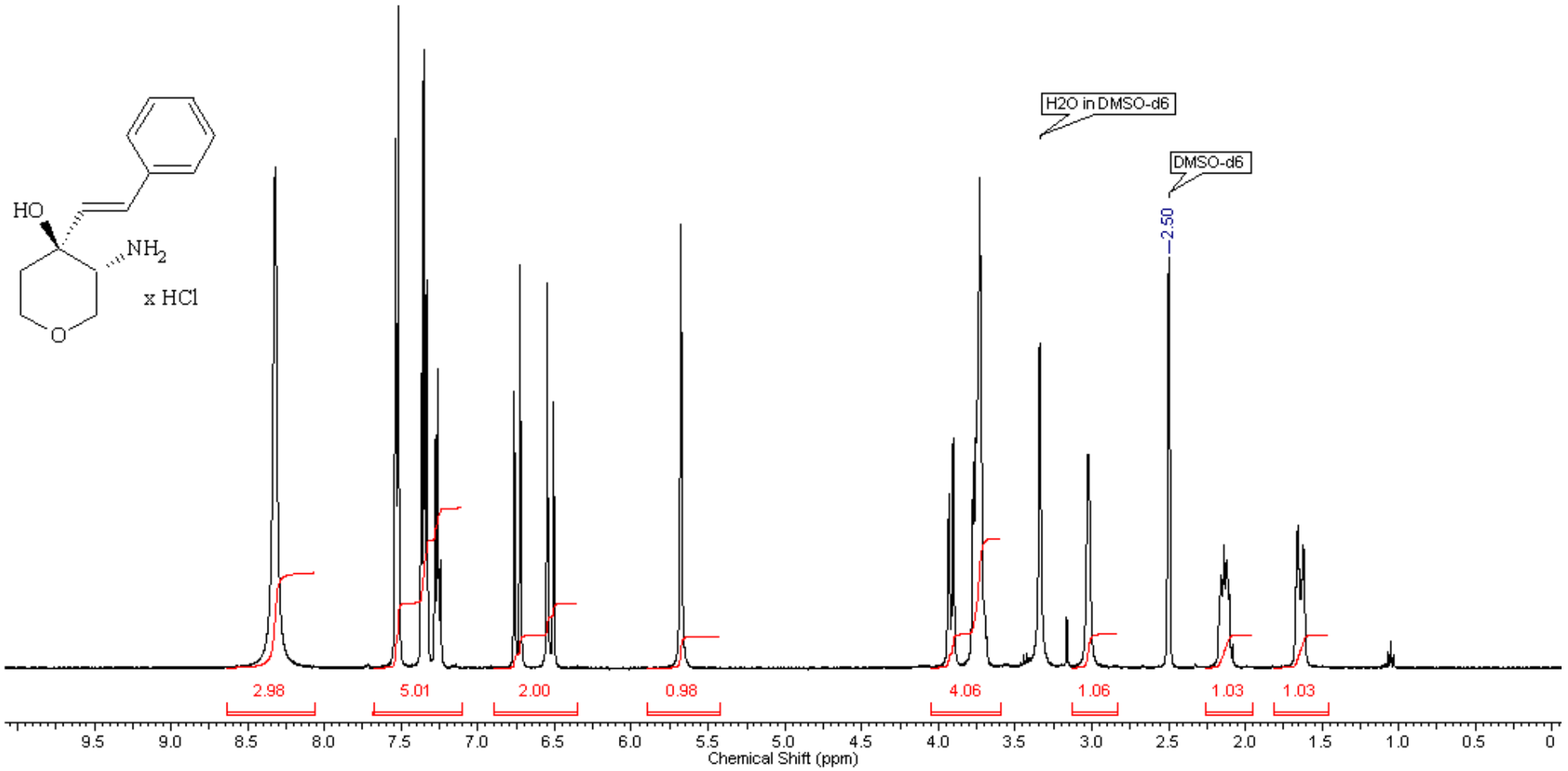
(3*RS*,4*SR*)-*Tert*-butyl 3-amino-4-hydroxy-4-((*E*)-styryl)piperidine-1-carboxylate (35). ^{1}H NMR ($CDCl_3$, 400 MHz).



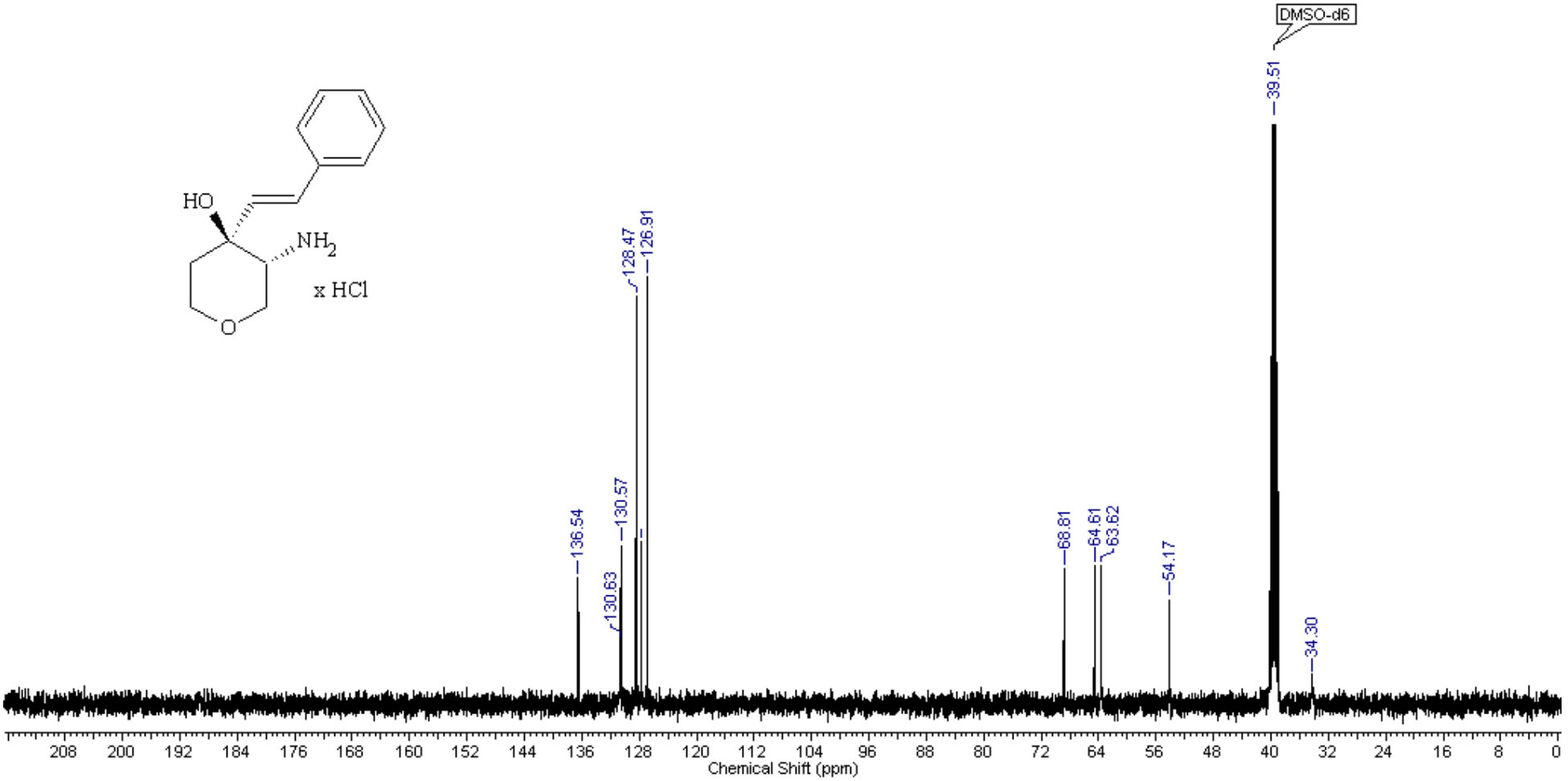
(3*RS*,4*SR*)-*Tert*-butyl 3-amino-4-hydroxy-4-((*E*)-styryl)piperidine-1-carboxylate (35). ^{13}C NMR ($CDCl_3$, 100 MHz).



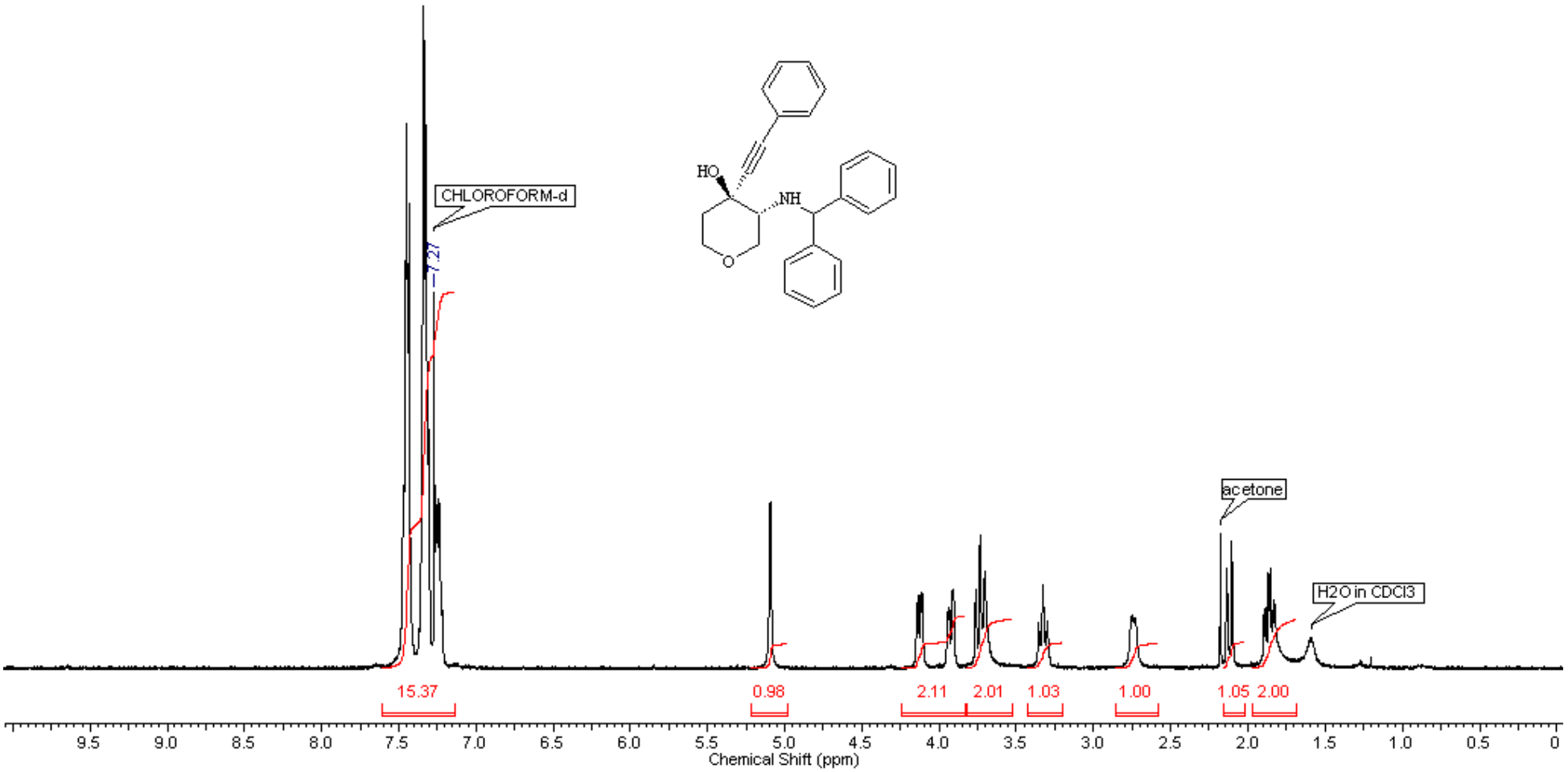
(3*RS*,4*SR*)-3-Amino-4-((*E*)-styryl)tetrahydro-2*H*-pyran-4-ol hydrochloride (36). ^{1}H NMR (400 MHz, DMSO-d$_6$).



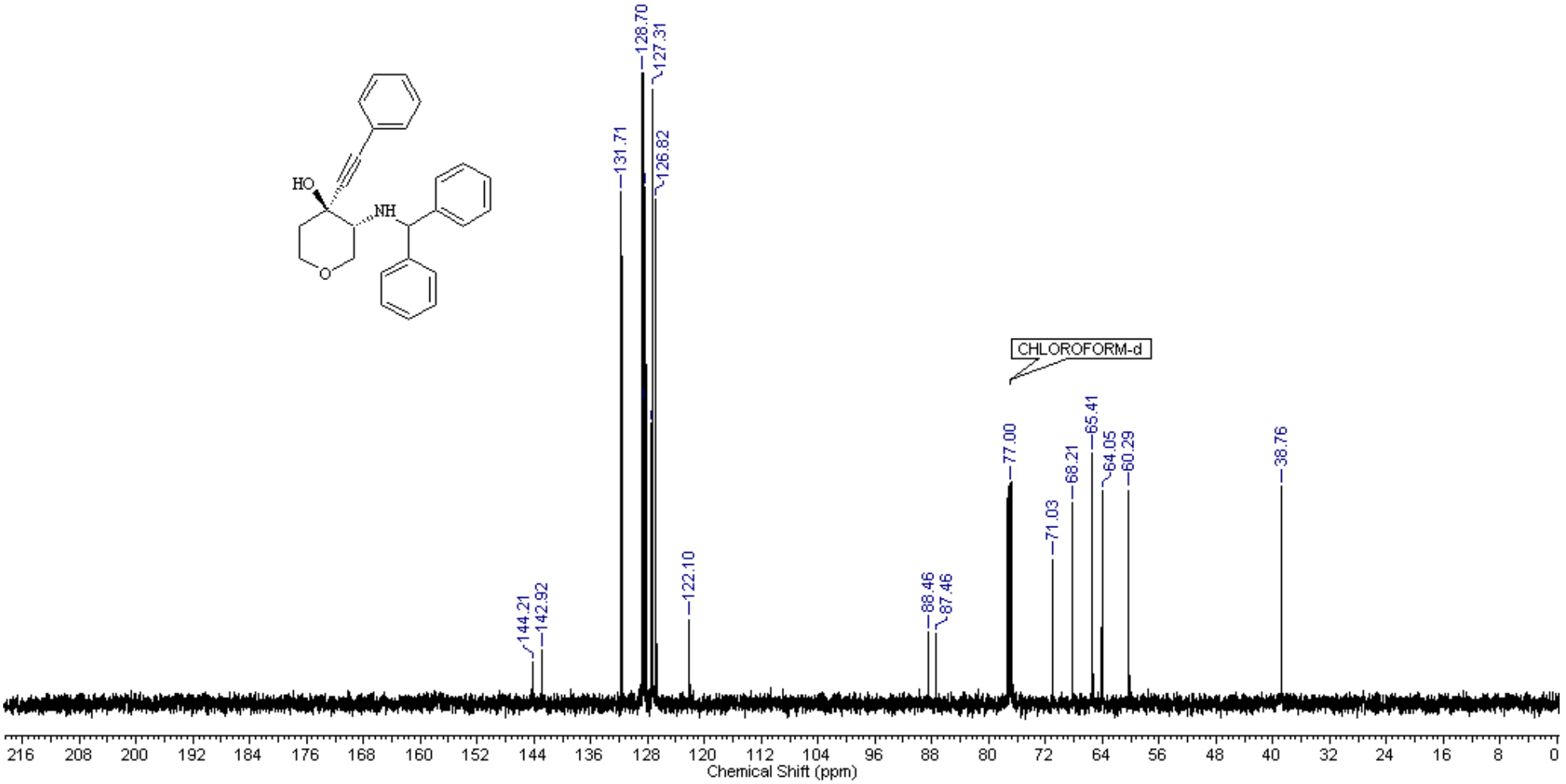
(3*RS*,4*SR*)-3-Amino-4-((*E*)-styryl)tetrahydro-2*H*-pyran-4-ol hydrochloride (36). ^{13}C NMR (100 MHz, DMSO-d_6).



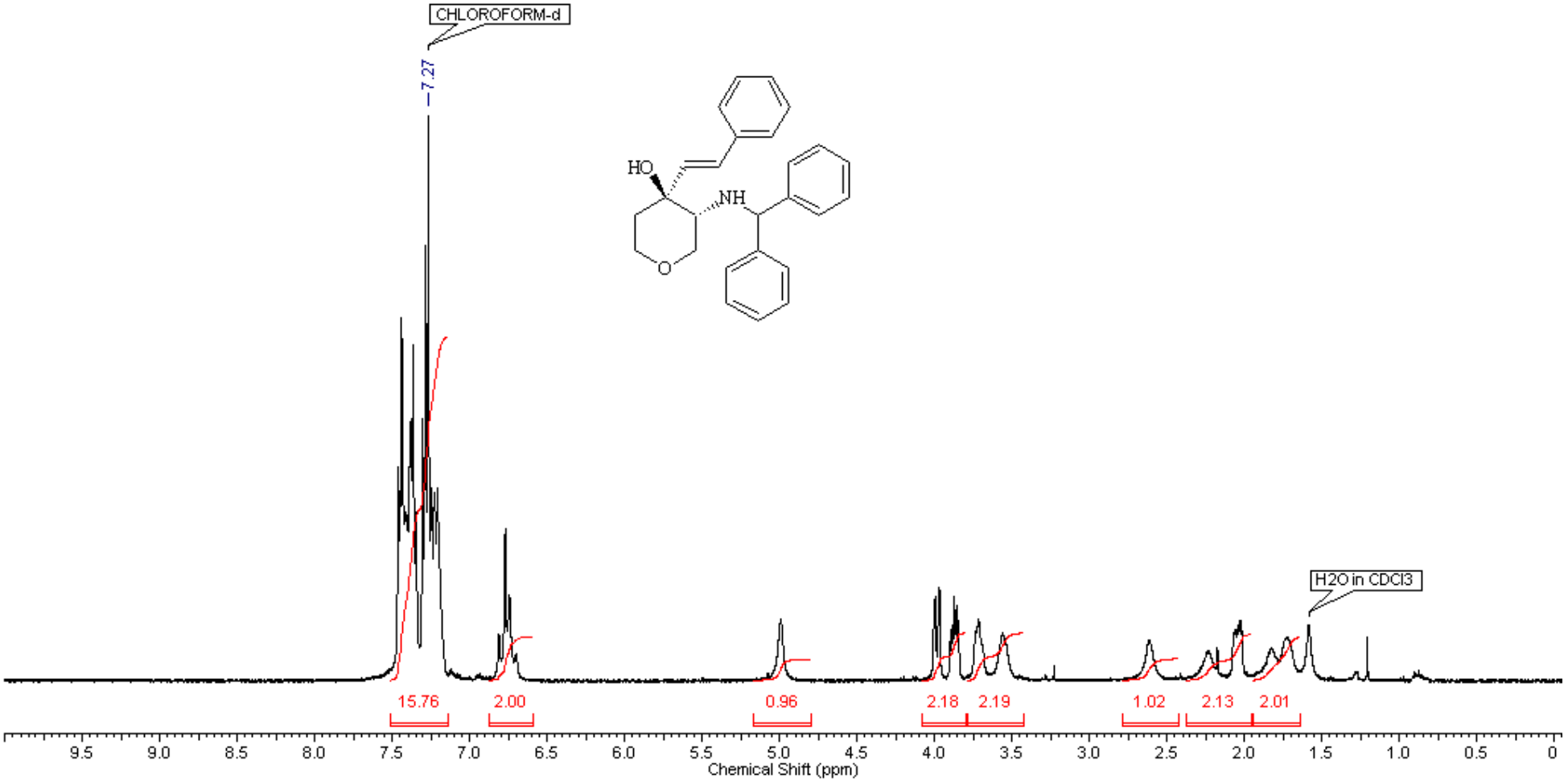
(3*RS*,4*SR*)-3-(Benzhydrylamino)-4-(phenylethynyl)tetrahydro-2*H*-pyran-4-ol (37). ^{1}H NMR ($CDCl_3$, 400 MHz).



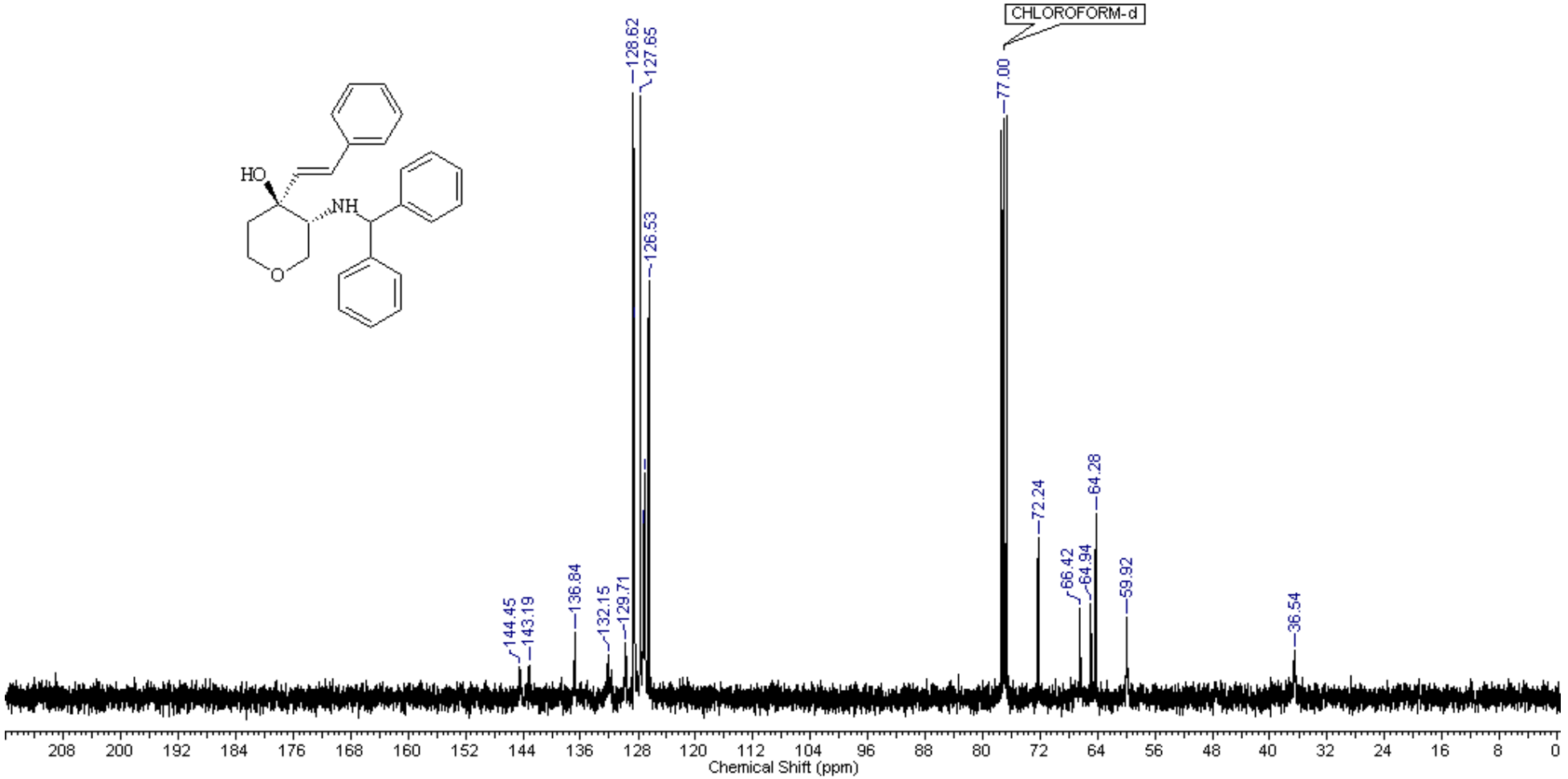
(3*RS*,4*SR*)-3-(Benzhydrylamino)-4-(phenylethynyl)tetrahydro-2*H*-pyran-4-ol (37). ^{13}C NMR ($CDCl_3$, 100 MHz).



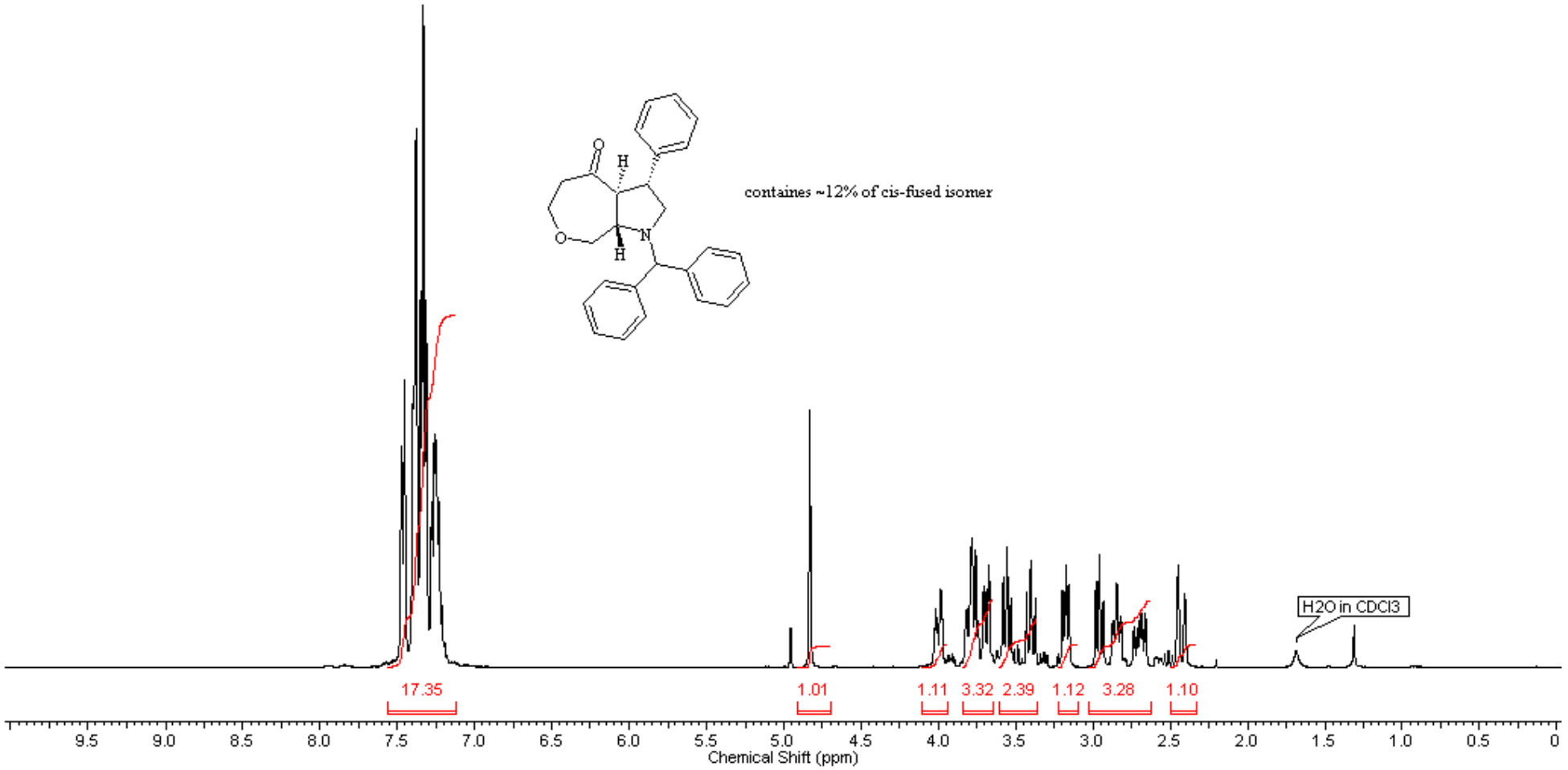
(3*RS*,4*SR*)-3-(Benzhydrylamino)-4-((*E*)-styryl)tetrahydro-2*H*-pyran-4-ol (38). ^{1}H NMR ($CDCl_3$, 400 MHz).



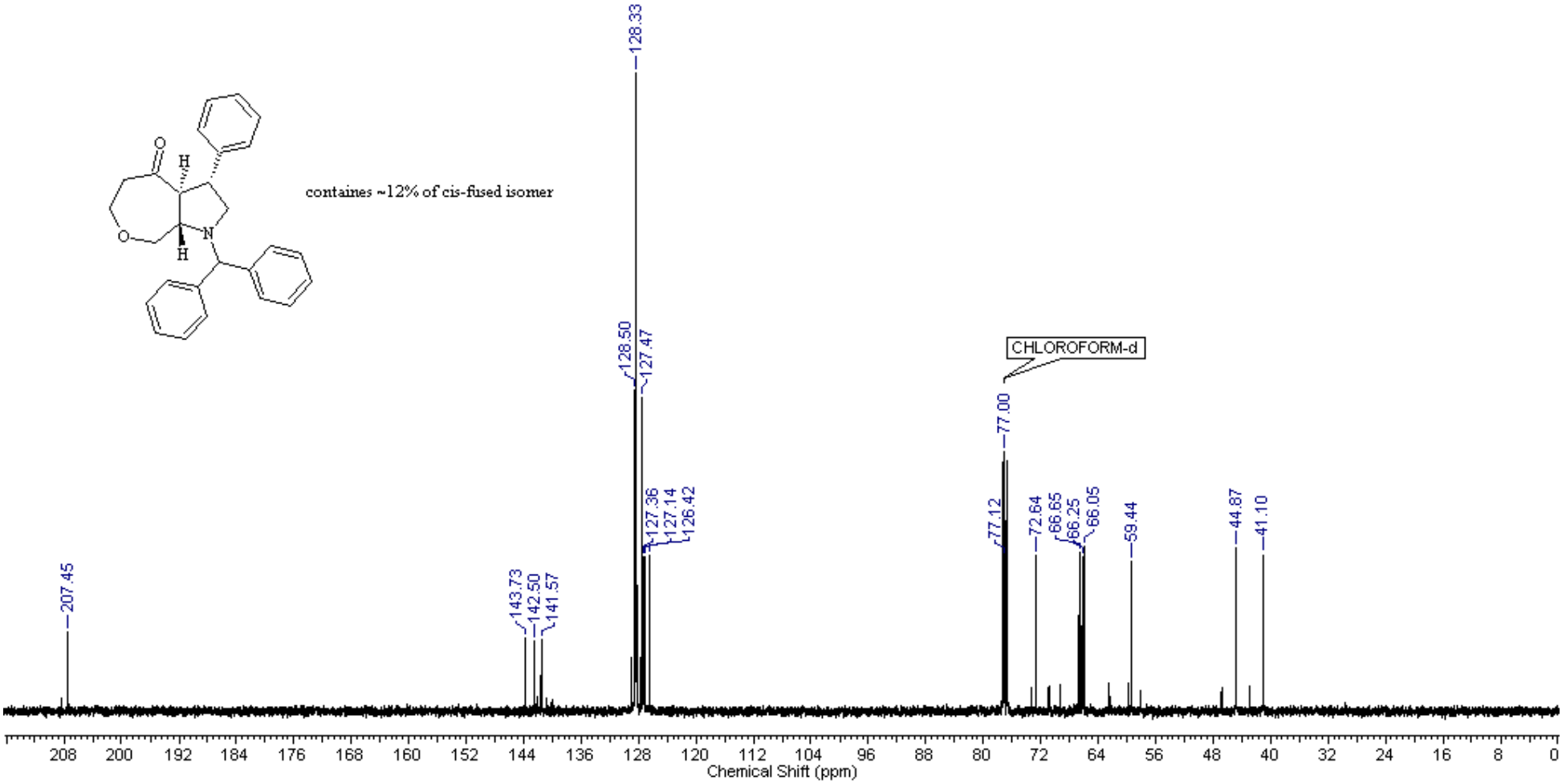
(3*RS*,4*SR*)-3-(Benzhydrylamino)-4-((*E*)-styryl)tetrahydro-2*H*-pyran-4-ol (38). ^{13}C NMR ($CDCl_3$, 100 MHz).



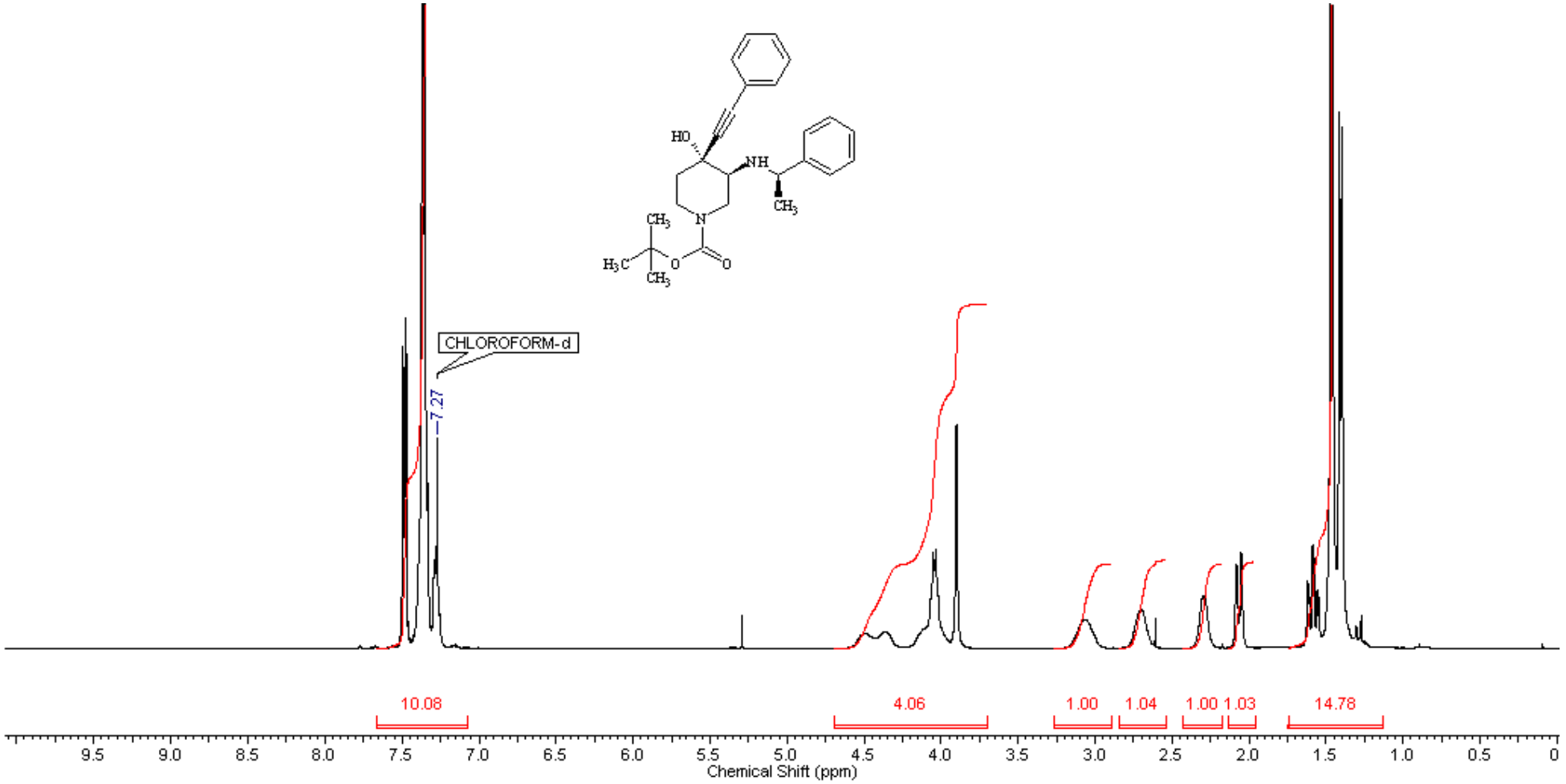
(3*RS*,3a*SR*,8a*SR*)-1-Benzhydryl-3-phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (39a). ^{1}H NMR ($CDCl_3$, 400 MHz).



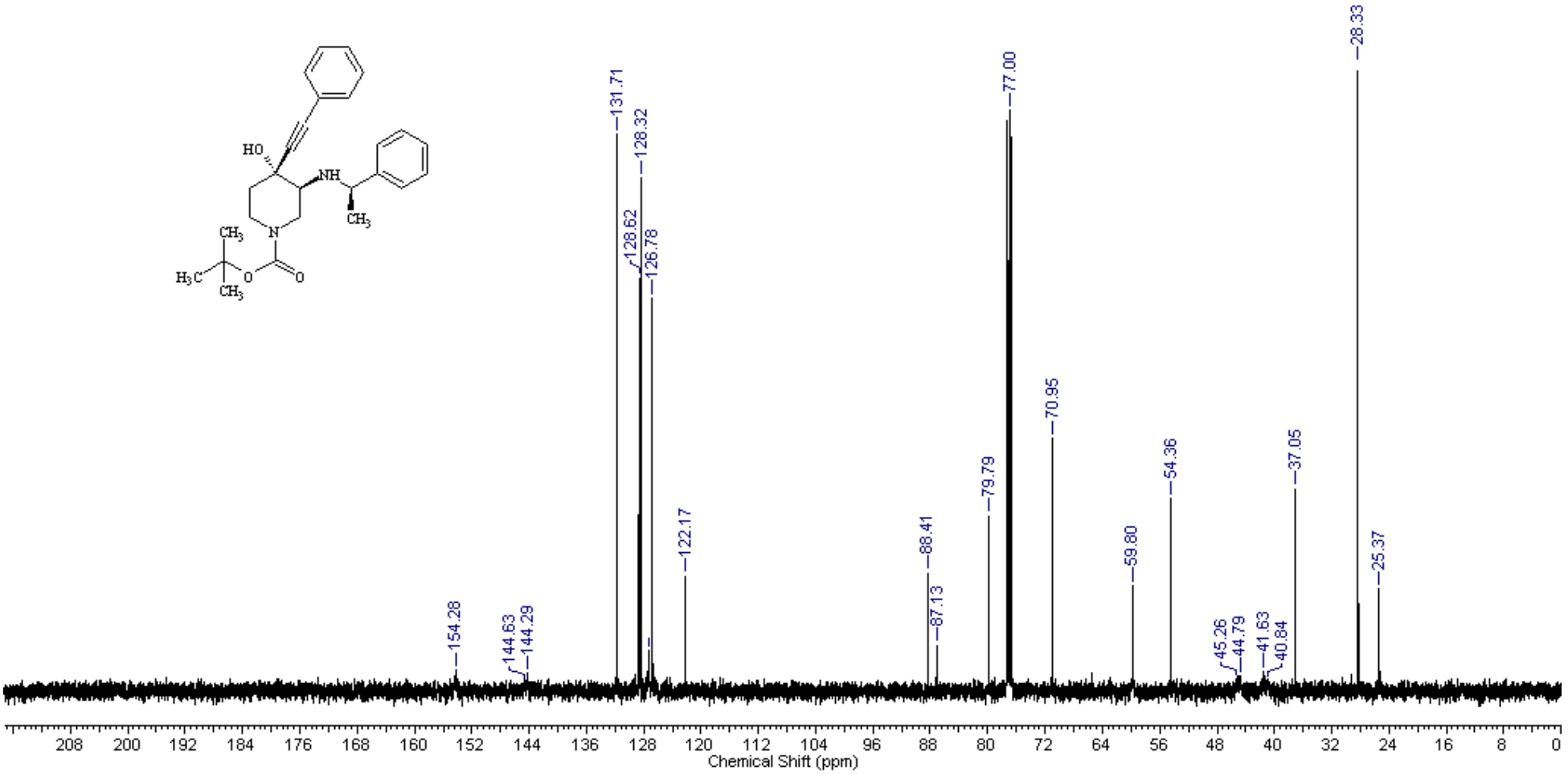
(3*RS*,3a*SR*,8a*SR*)-1-Benzhydryl-3-phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (39a). ^{13}C NMR ($CDCl_3$, 100 MHz.



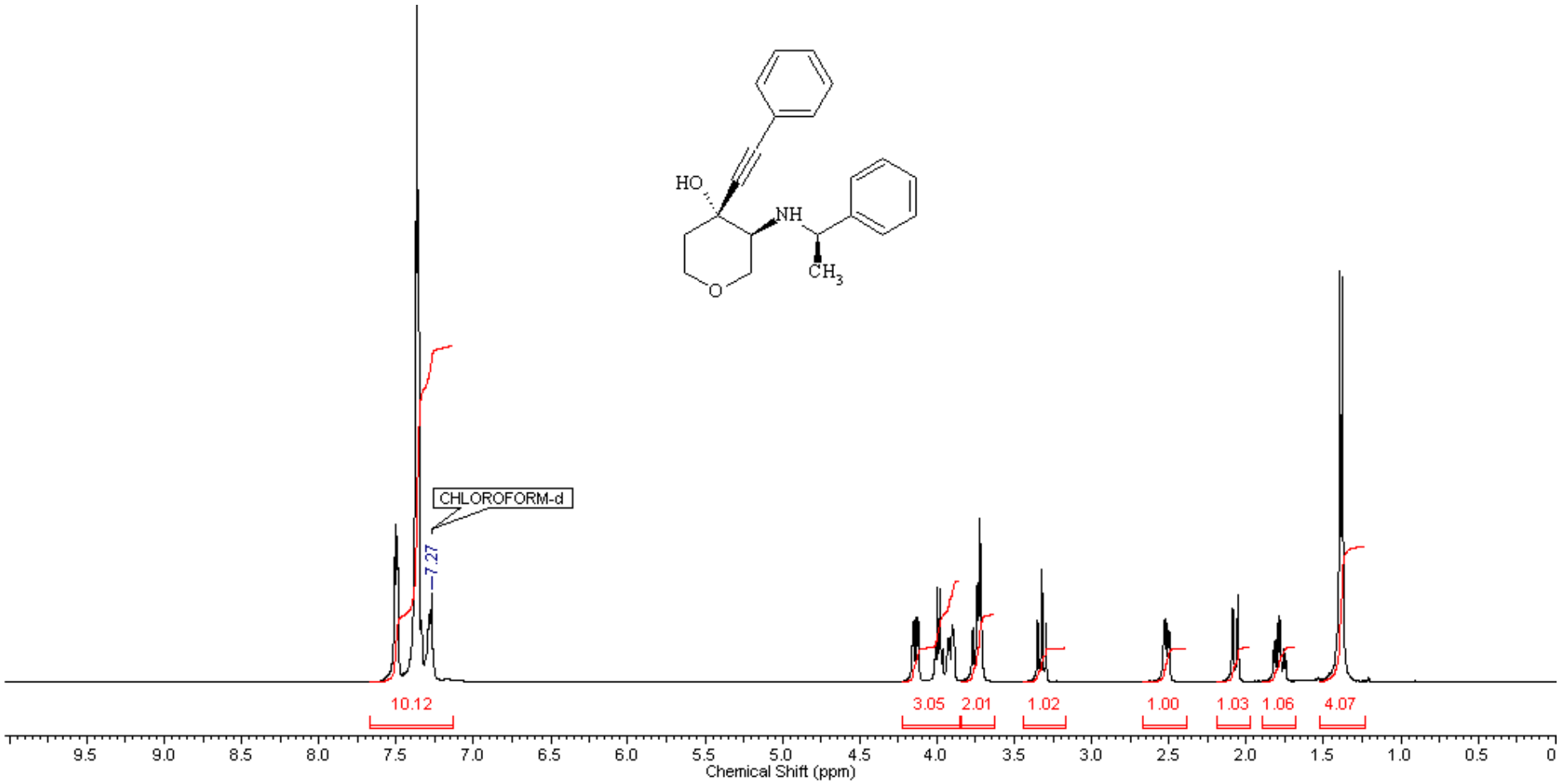
(3*S*,4*R*)-*Tert*-butyl 4-hydroxy-3-(((*R*)-1-phenylethyl)amino)-4-(phenylethynyl)piperidine-1-carboxylate (40). ^{1}H NMR ($CDCl_3$, 400 MHz)



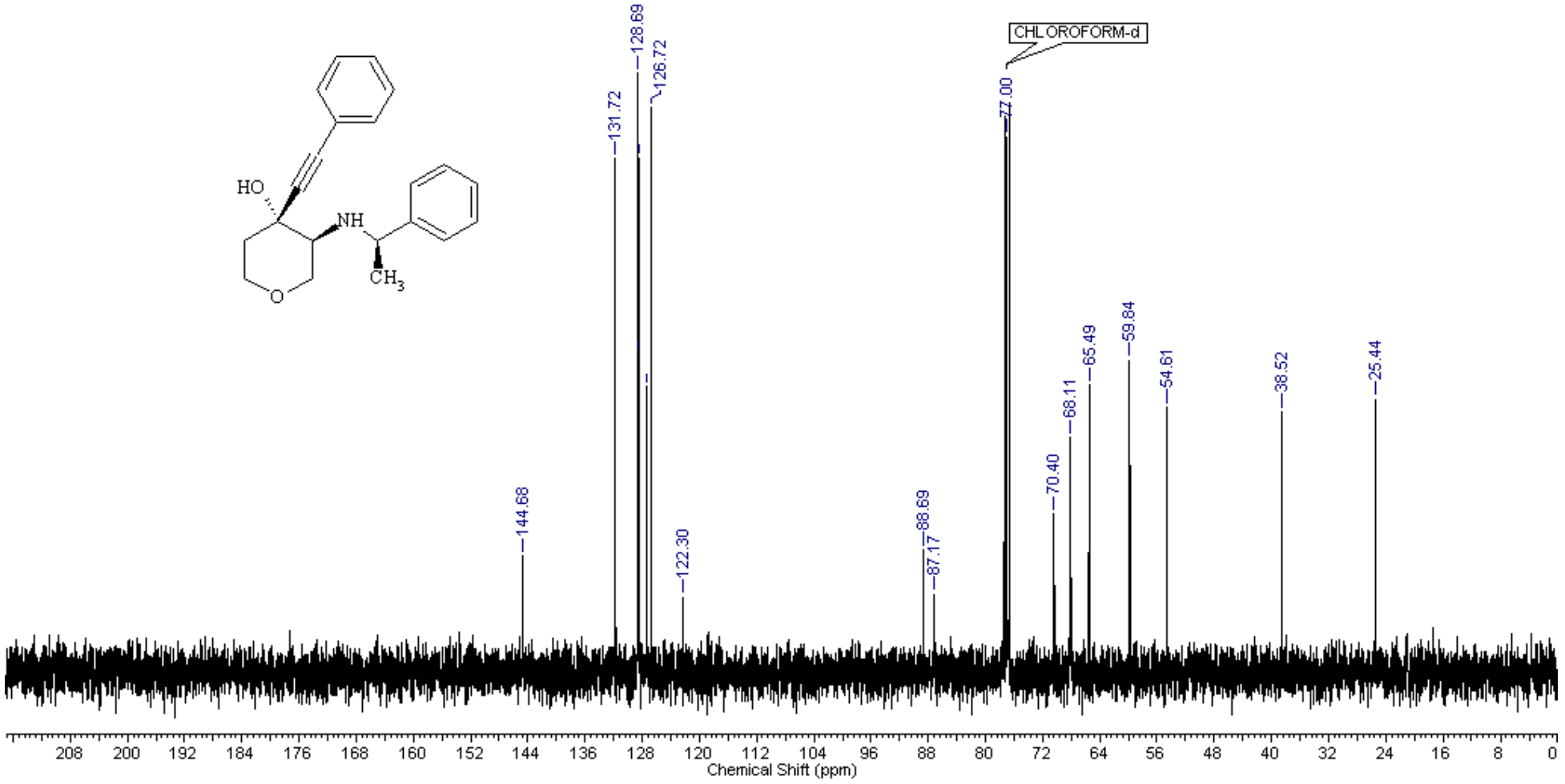
(3*S*,4*R*)-*Tert*-butyl 4-hydroxy-3-(((*R*)-1-phenylethyl)amino)-4-(phenylethynyl)piperidine-1-carboxylate (40). ^{13}C NMR ($CDCl_3$, 100 MHz)



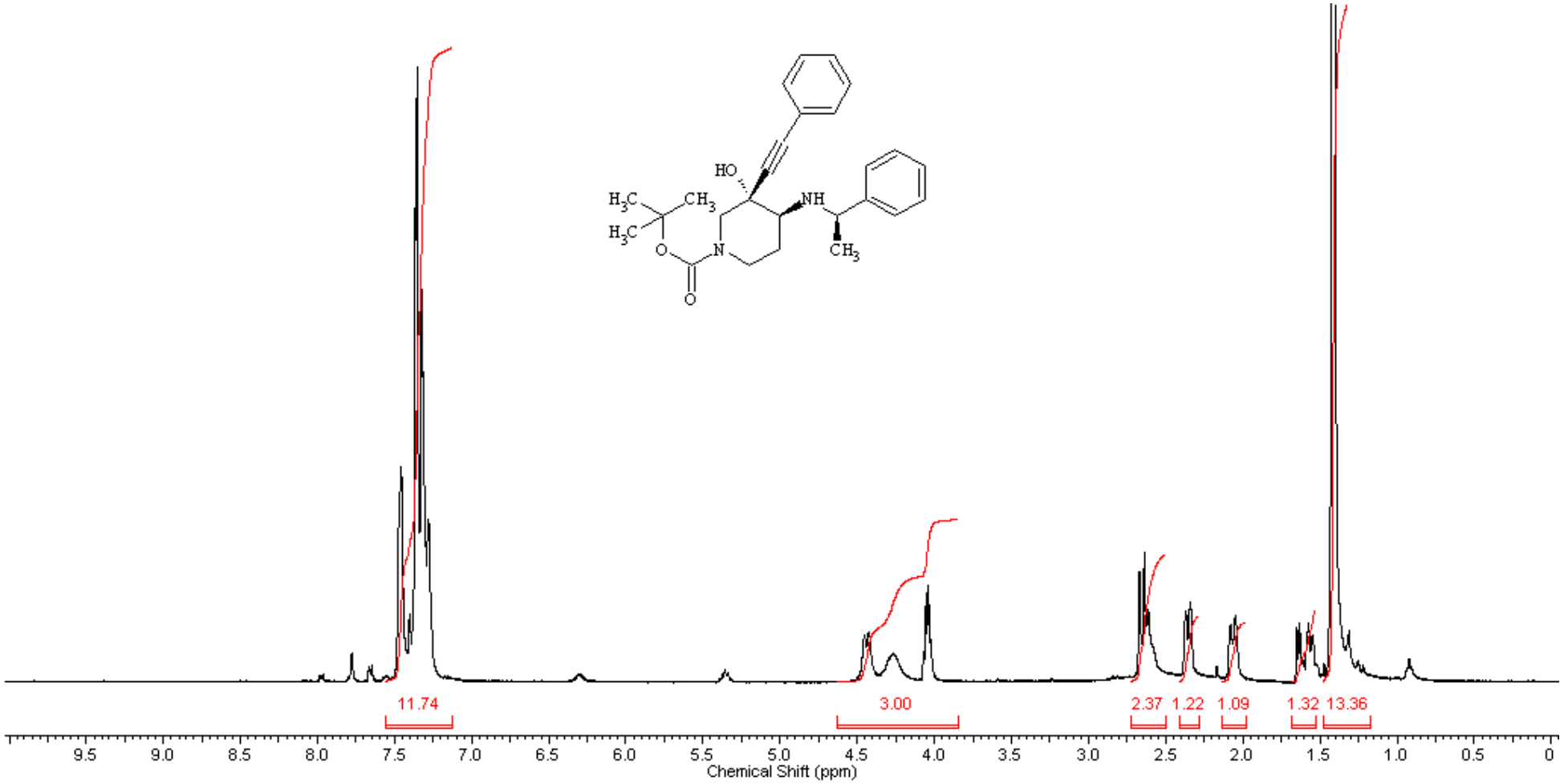
(3*S*,4*R*)-3-(((*R*)-1-Phenylethyl)amino)-4-(phenylethynyl)tetrahydro-2*H*-pyran-4-ol (41). ^{1}H NMR ($CDCl_3$, 400 MHz)



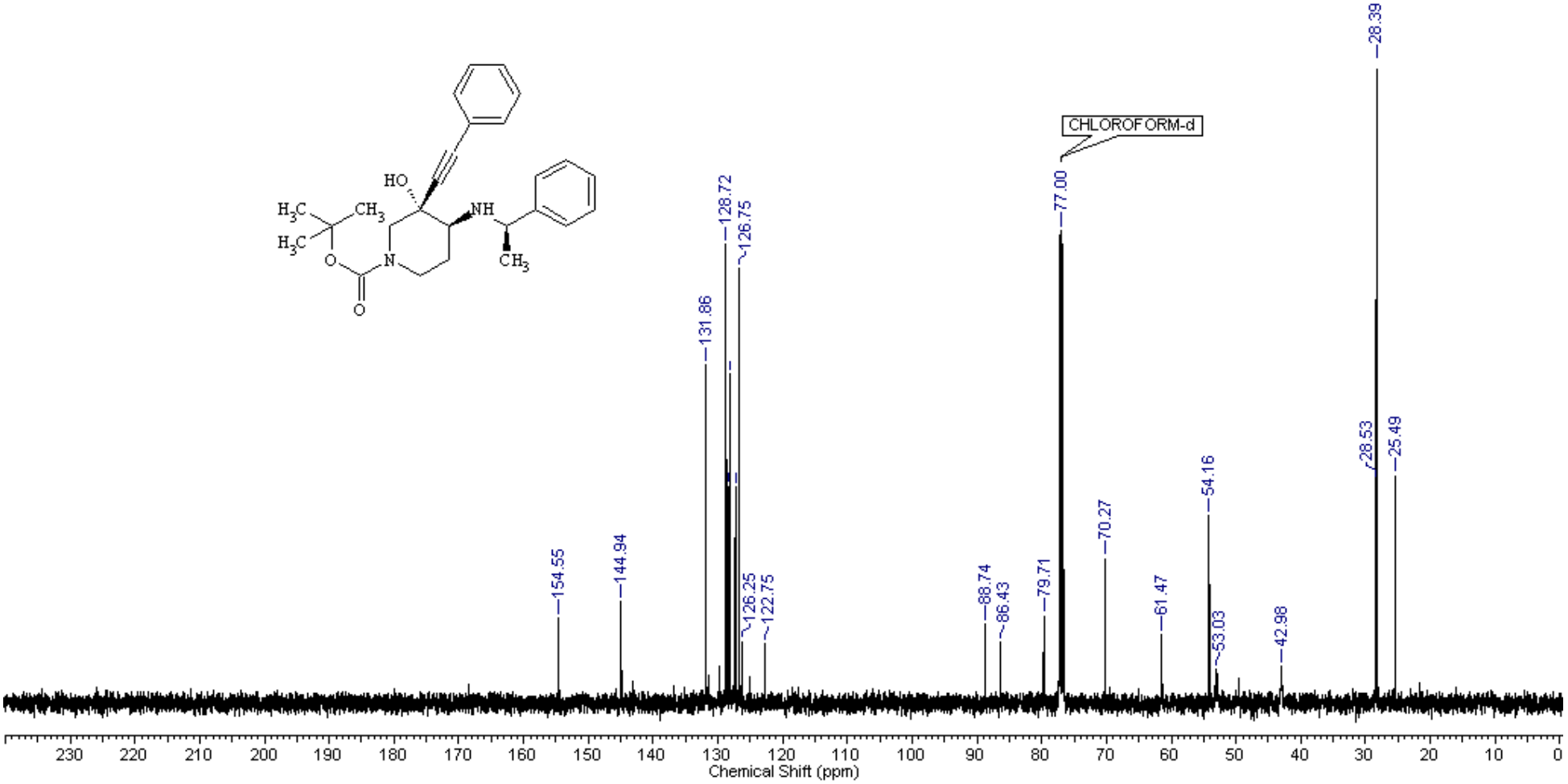
(3*S*,4*R*)-3-(((*R*)-1-Phenylethyl)amino)-4-(phenylethynyl)tetrahydro-2*H*-pyran-4-ol (41). ^{13}C NMR ($CDCl_3$, 100 MHz)



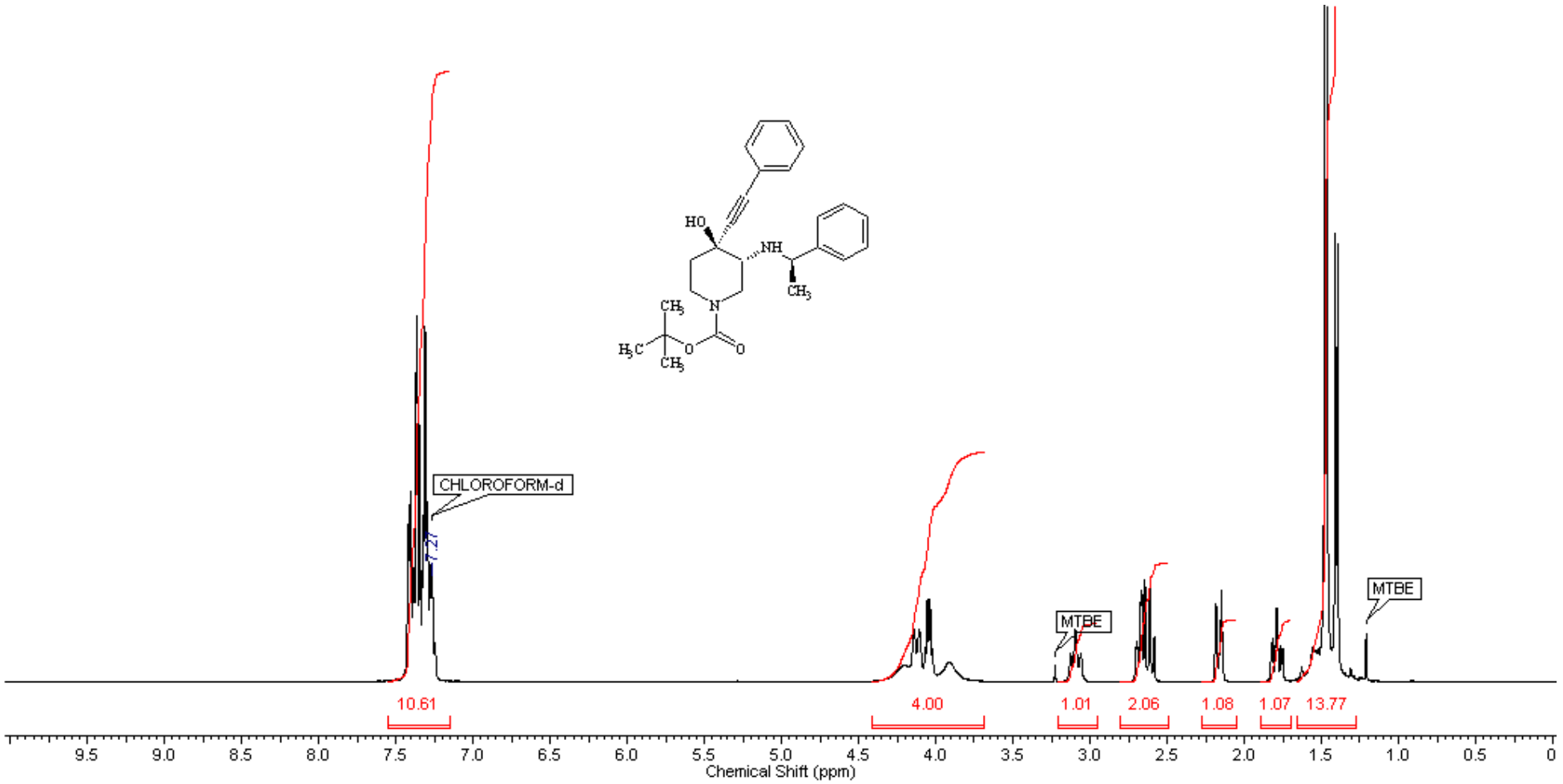
(3*S*,4*S*)-*Tert*-butyl 3-hydroxy-4-(((*R*)-1-phenylethyl)amino)-3-(phenylethynyl)piperidine-1-carboxylate (42). ^{1}H NMR ($CDCl_3$, 400 MHz, 55^{O}C).



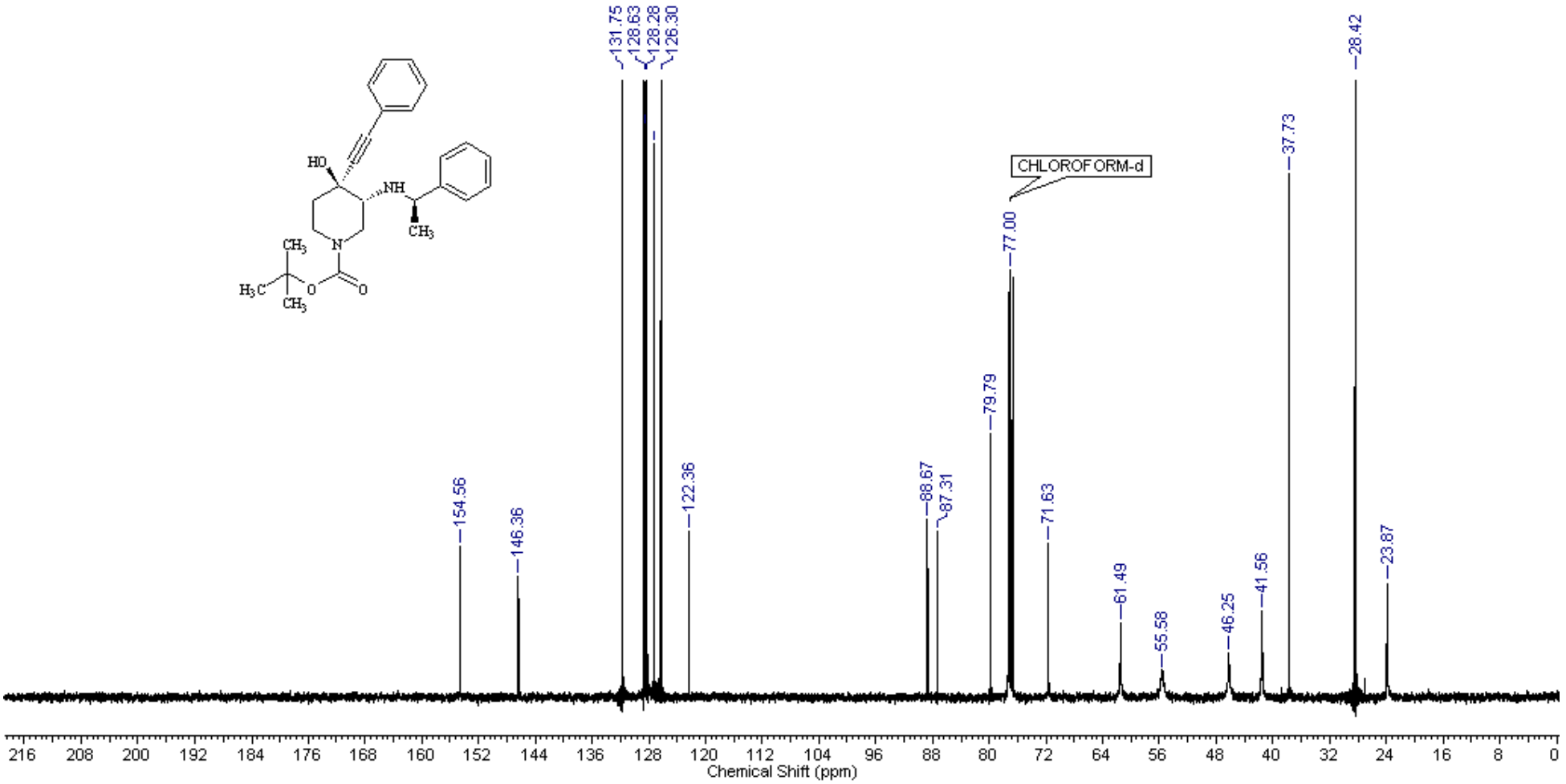
(3*S*,4*S*)-*Tert*-butyl 3-hydroxy-4-(((*R*)-1-phenylethyl)amino)-3-(phenylethynyl)piperidine-1-carboxylate (42). ^{13}C NMR ($CDCl_3$, 100 MHz, 55^{O}C).



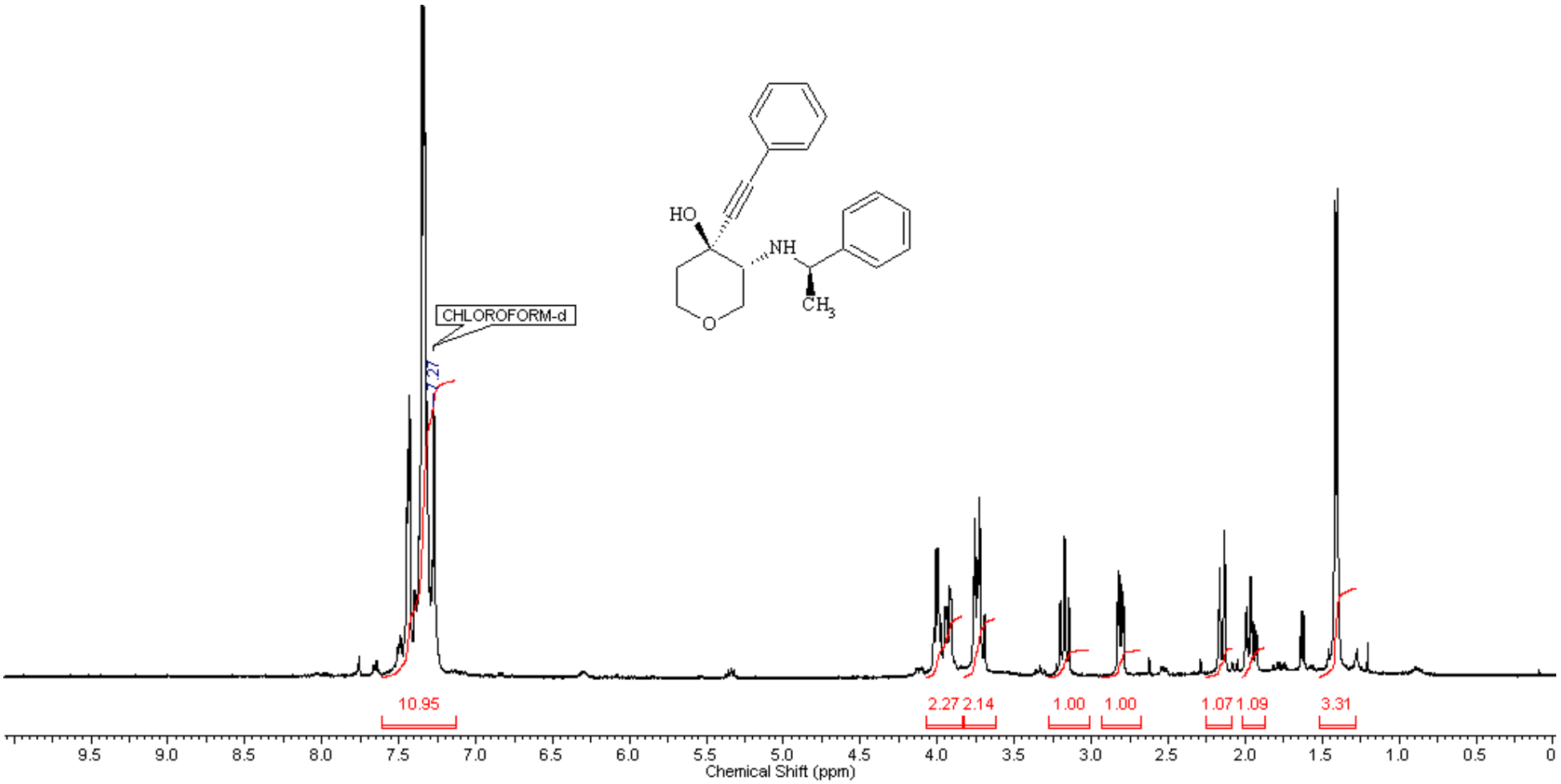
(3*R*,4*S*)-*tert*-butyl 4-hydroxy-3-(((*R*)-1-phenylethyl)amino)-4-(phenylethynyl)piperidine-1-carboxylate (43). ^{1}H NMR ($CDCl_3$, 400 MHz, 50^{O}C)



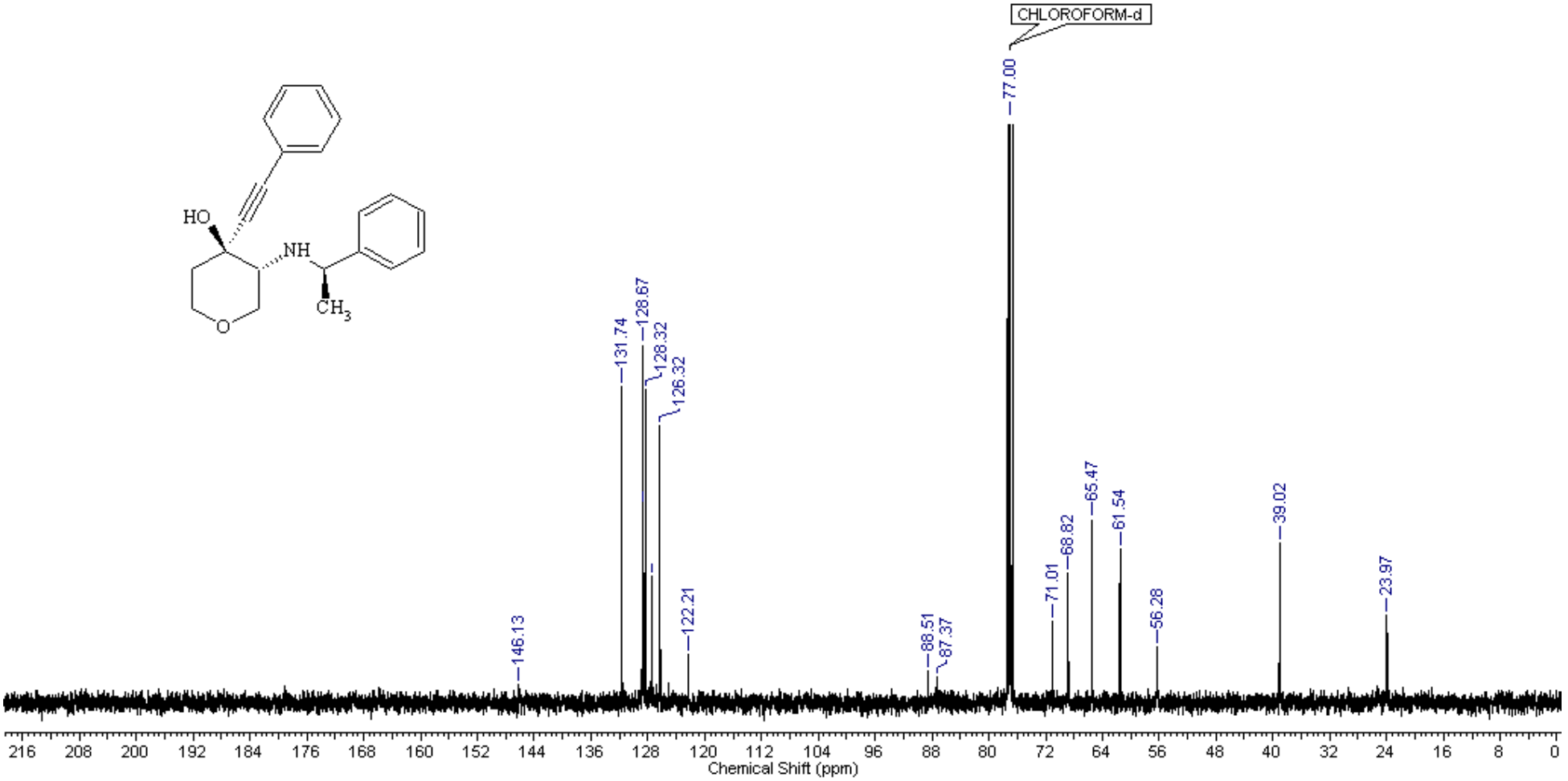
(3*R*,4*S*)-*tert*-butyl 4-hydroxy-3-(((*R*)-1-phenylethyl)amino)-4-(phenylethynyl)piperidine-1-carboxylate (43). ^{13}C NMR ($CDCl_3$, 100 MHz, 50^{O}C)



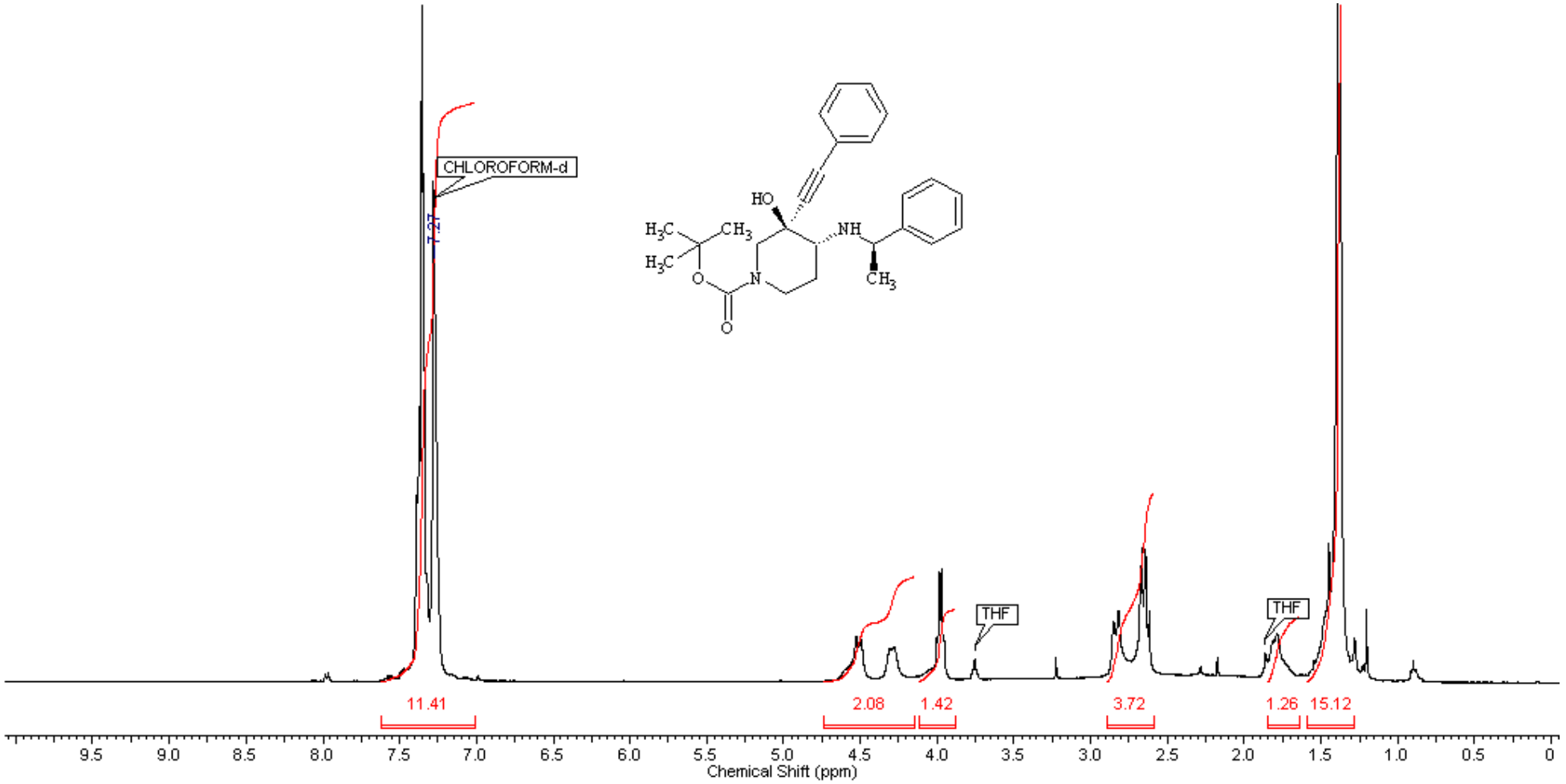
(3*R*,4*S*)-3-(((*R*)-1-Phenylethyl)amino)-4-(phenylethynyl)tetrahydro-2*H*-pyran-4-ol (44). ^{1}H NMR ($CDCl_3$, 400 MHz).



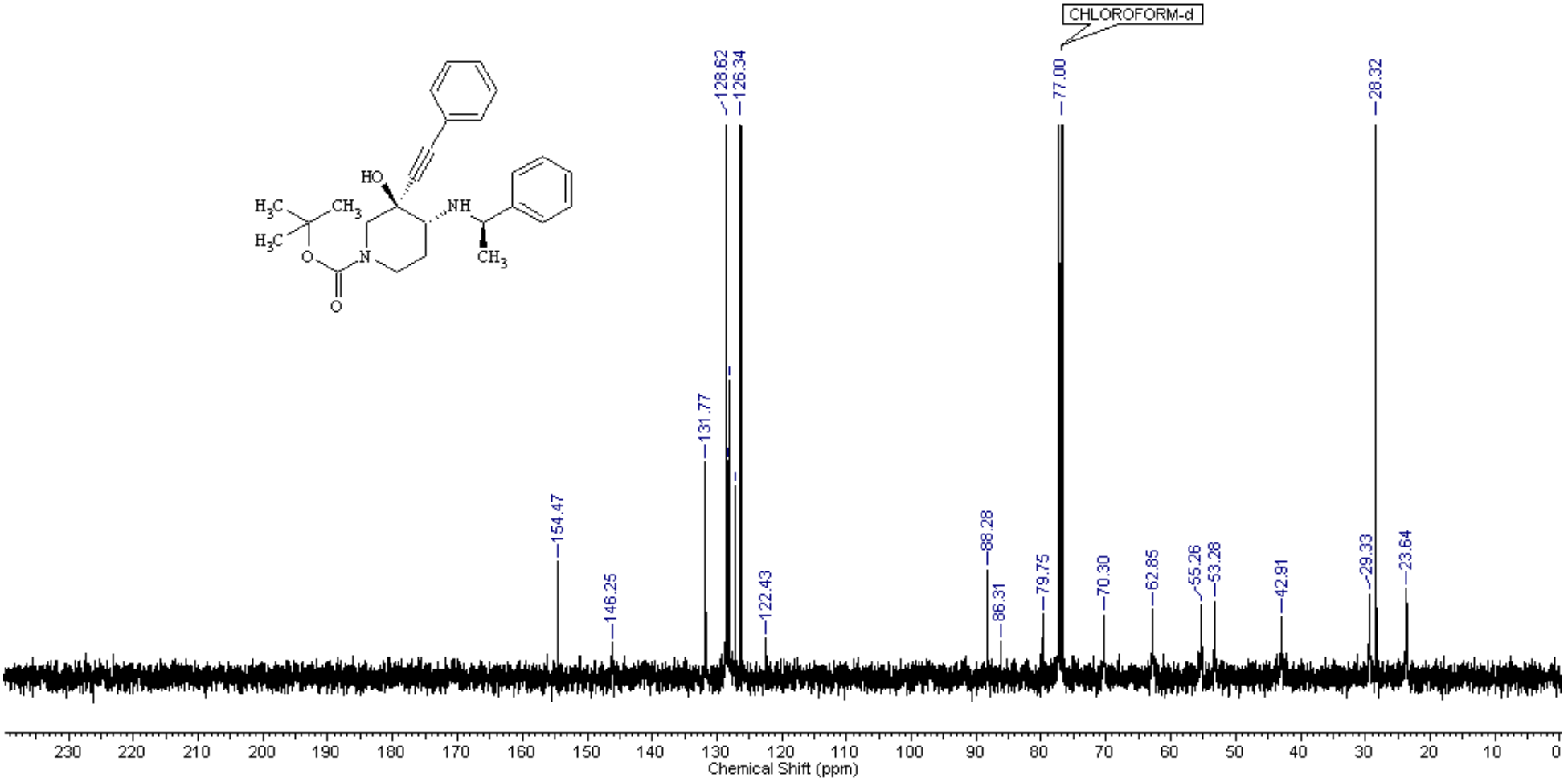
(3*R*,4*S*)-3-(((*R*)-1-Phenylethyl)amino)-4-(phenylethynyl)tetrahydro-2*H*-pyran-4-ol (44). ^{13}C NMR ($CDCl_3$, 100 MHz).



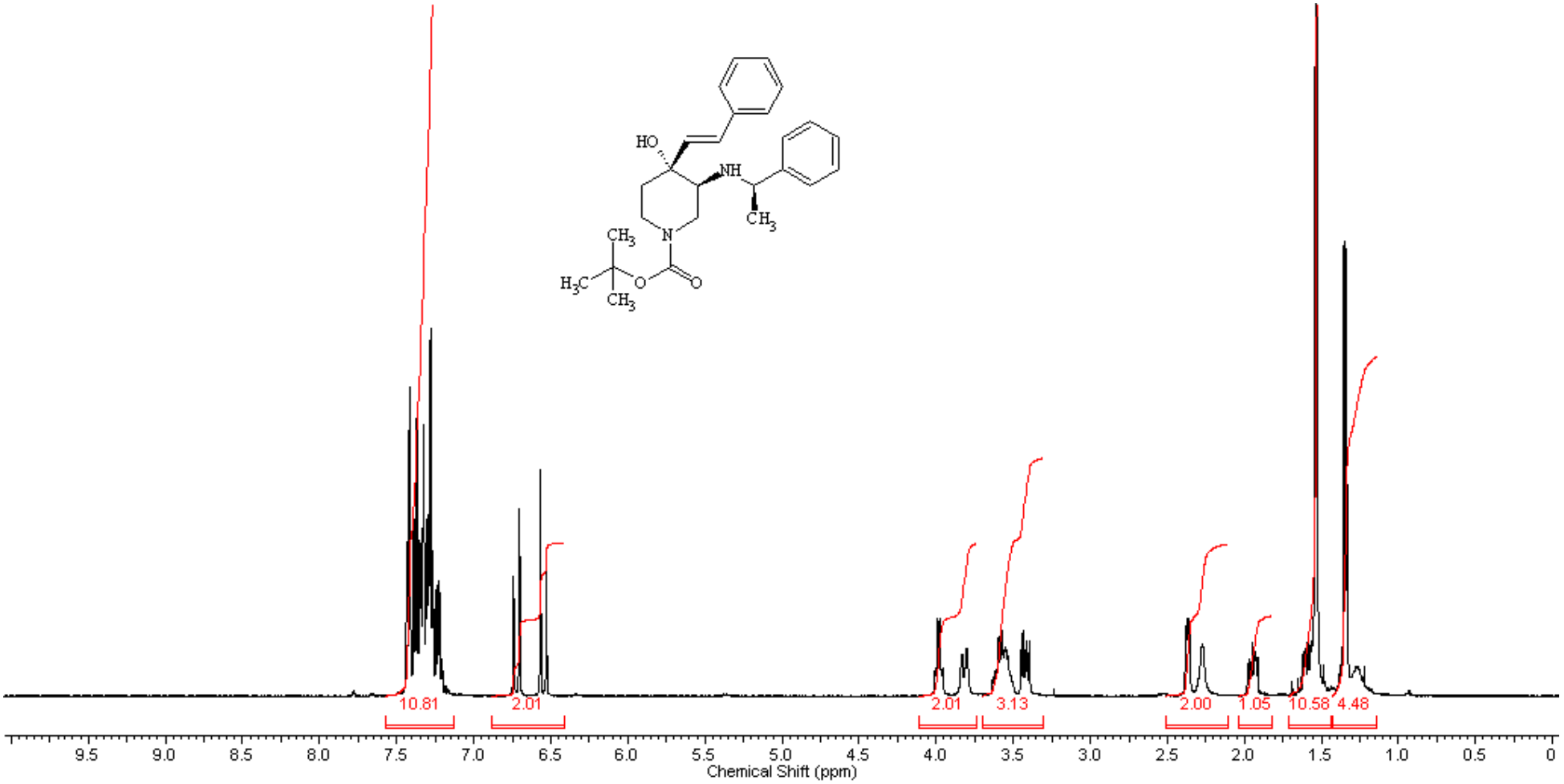
(3*R*,4*R*)-*Tert*-butyl 3-hydroxy-4-(((*R*)-1-phenylethyl)amino)-3-(phenylethynyl)piperidine-1-carboxylate (45). ^{1}H NMR ($CDCl_3$, 400 MHz).



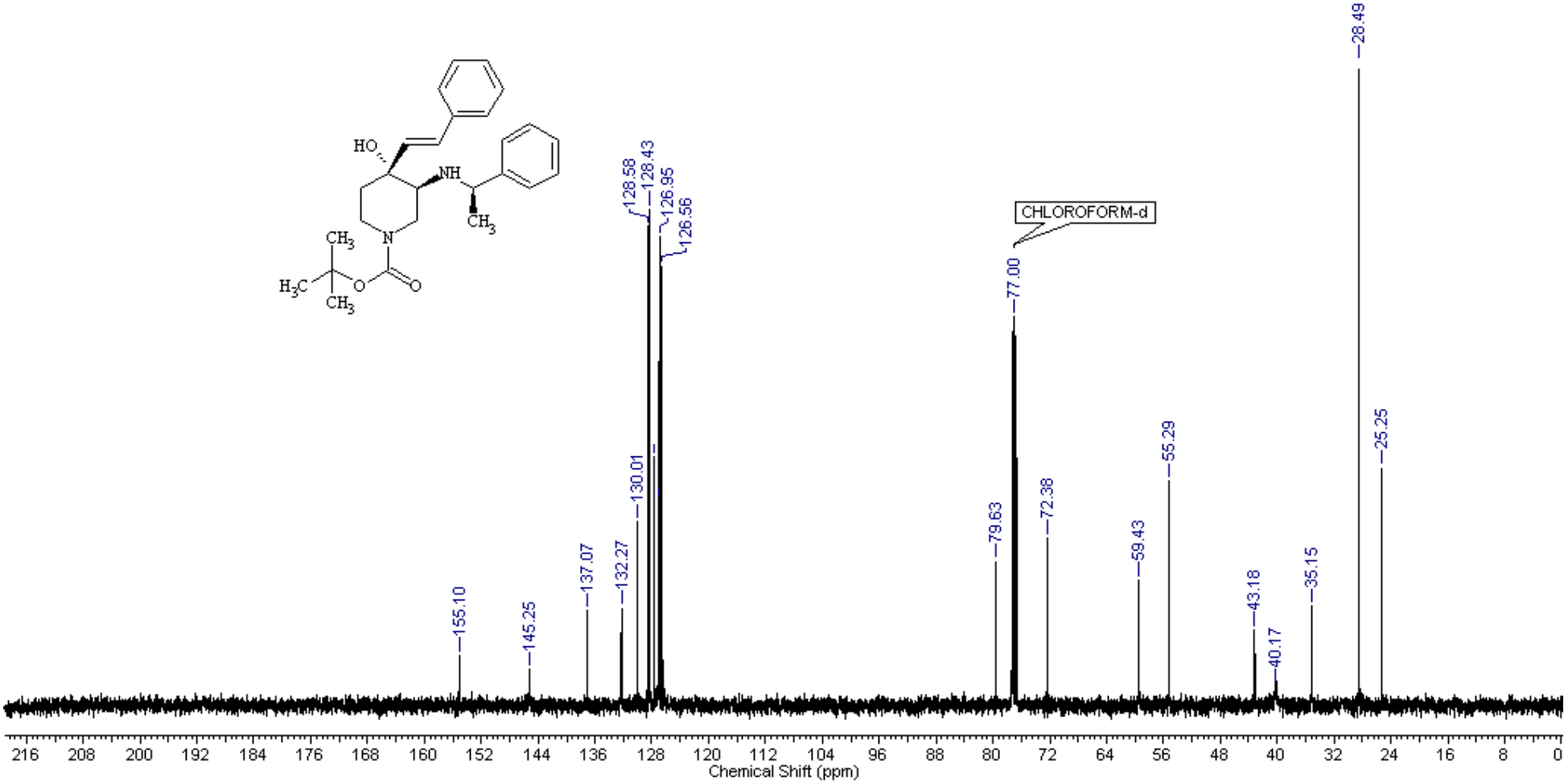
(3*R*,4*R*)-*Tert*-butyl 3-hydroxy-4-(((*R*)-1-phenylethyl)amino)-3-(phenylethynyl)piperidine-1-carboxylate (45). ^{13}C NMR ($CDCl_3$, 100 MHz).



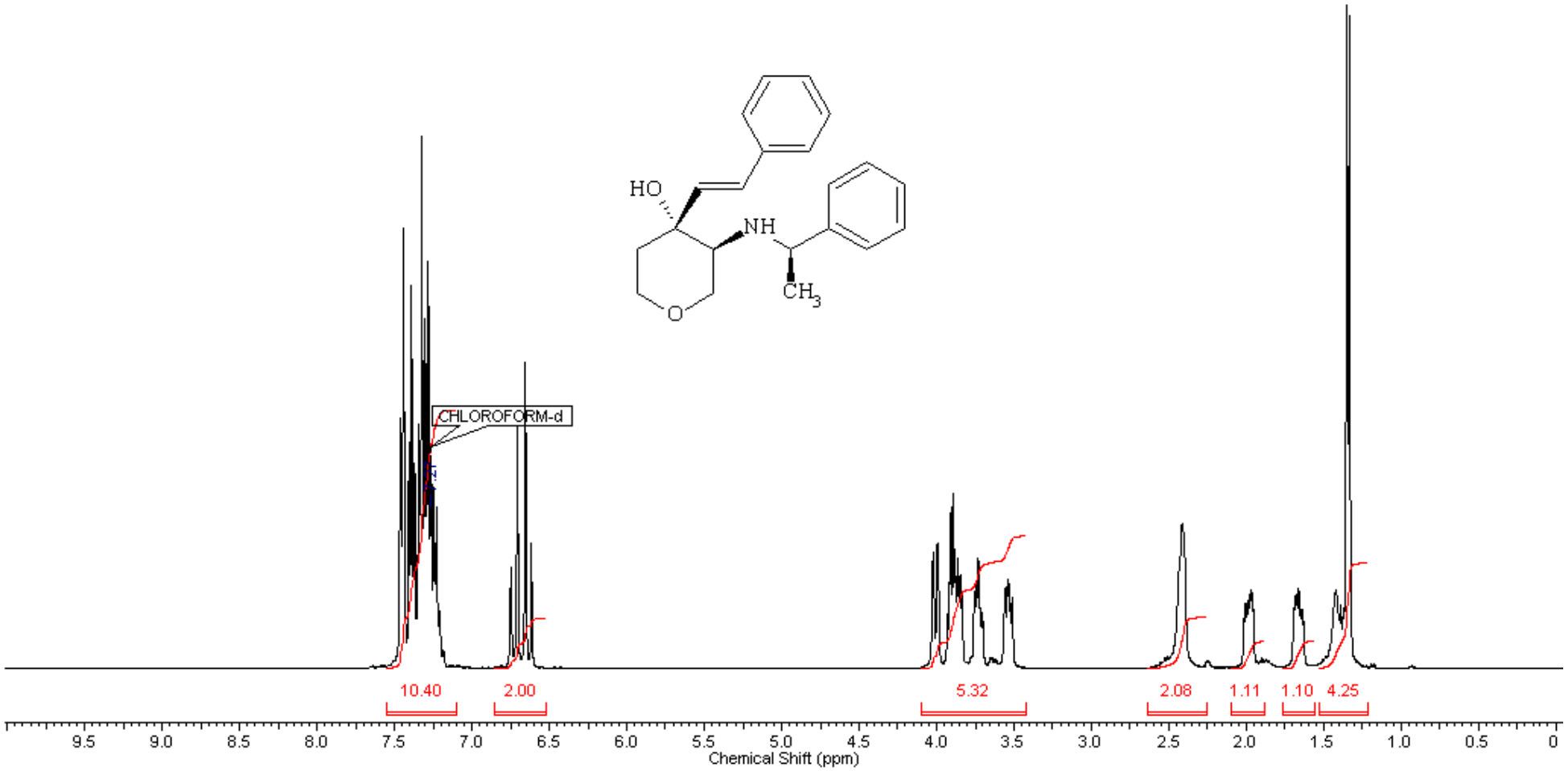
(3*S*,4*R*)-*Tert*-butyl 4-hydroxy-3-(((*R*)-1-phenylethyl)amino)-4-((*E*)-styryl)piperidine-1-carboxylate (46). ^{1}H NMR ($CDCl_3$, 400 MHz, 50^{O}C).



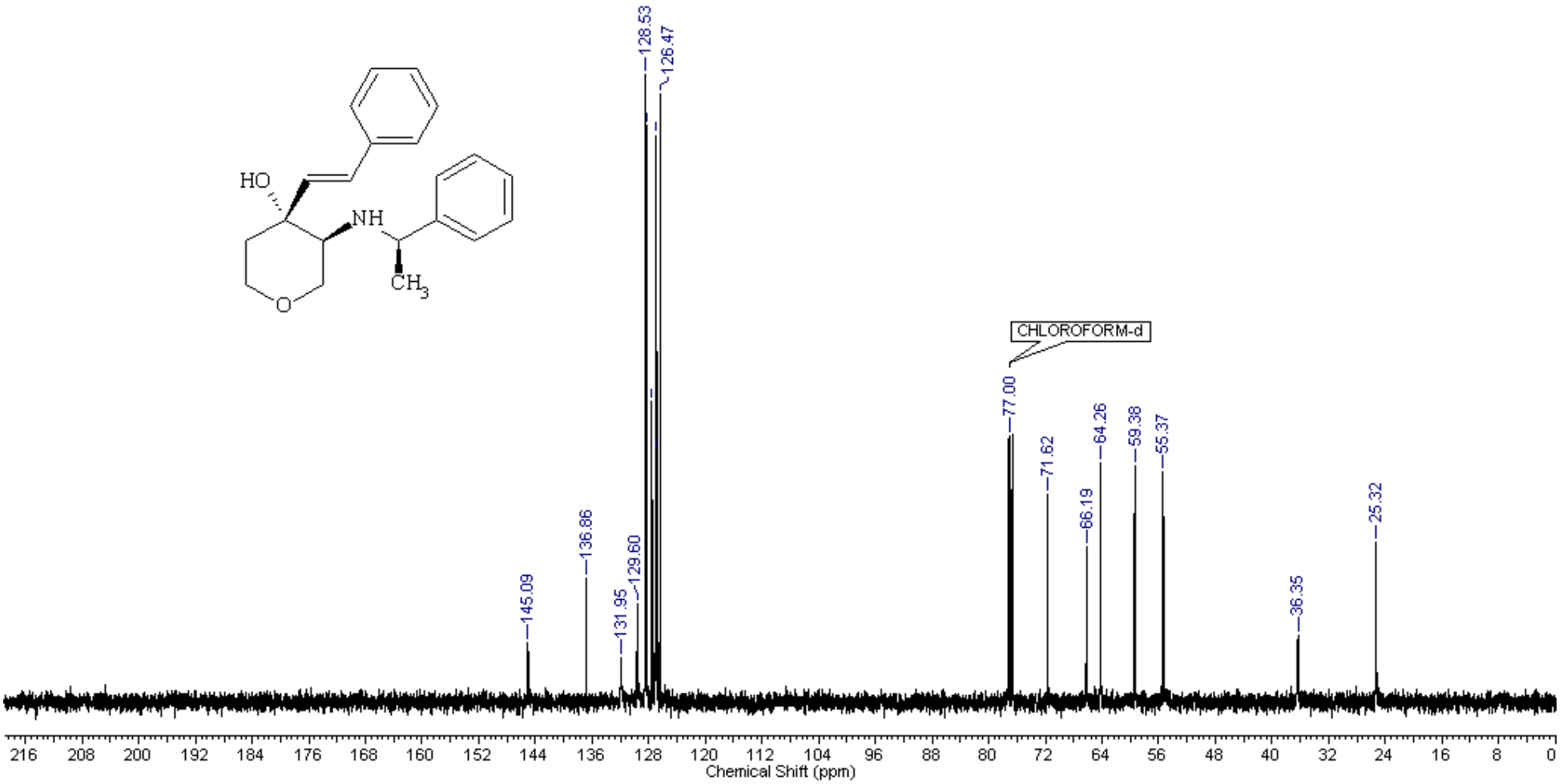
(3*S*,4*R*)-*Tert*-butyl 4-hydroxy-3-(((*R*)-1-phenylethyl)amino)-4-((*E*)-styryl)piperidine-1-carboxylate (46). ^{13}C NMR ($CDCl_3$, 100 MHz, 50^{O}C).



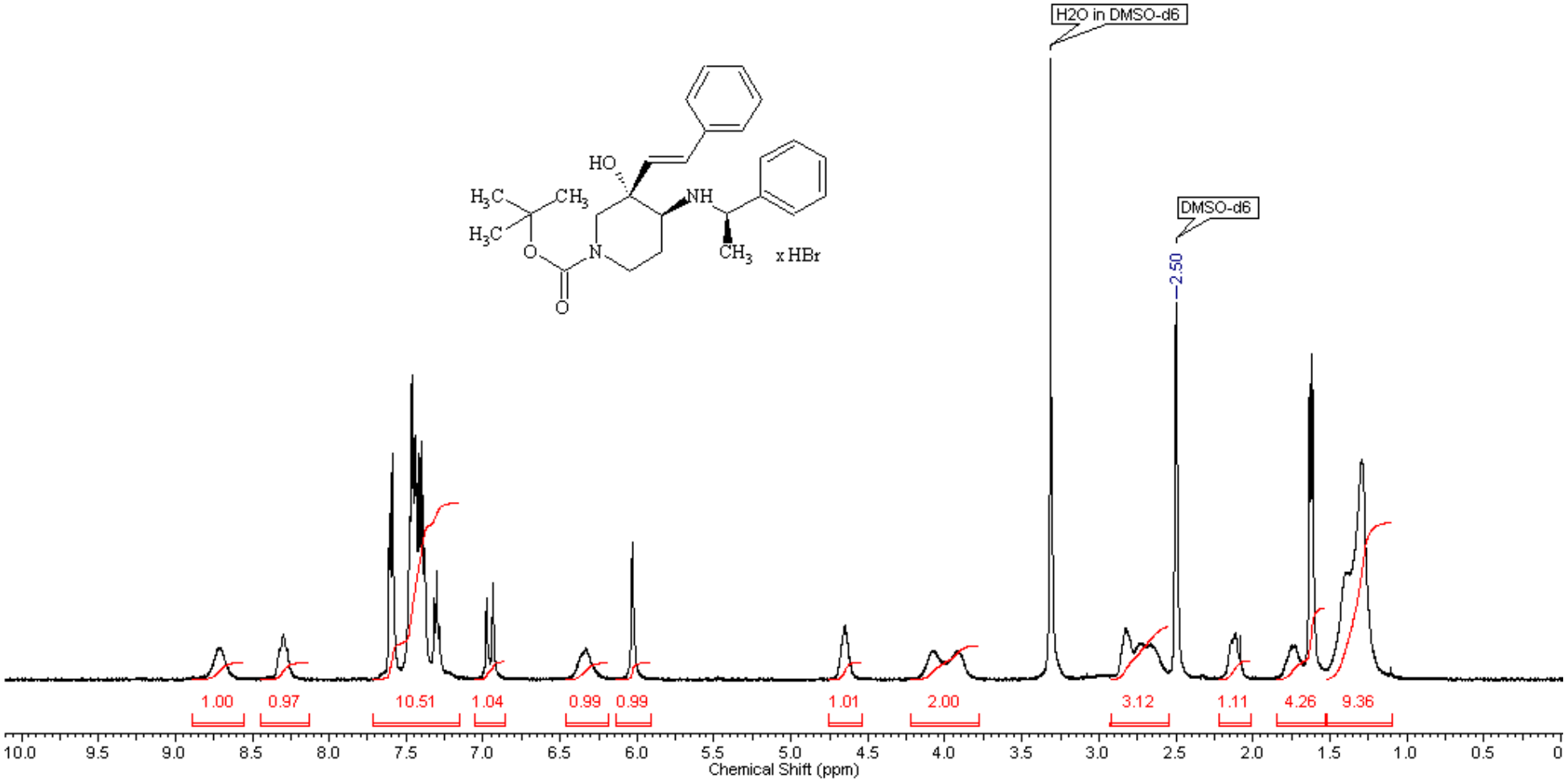
(3*S*,4*R*)-3-(((*R*)-1-Phenylethyl)amino)-4-((*E*)-styryl)tetrahydro-2*H*-pyran-4-ol (47). ^{1}H NMR ($CDCl_3$, 400 MHz).



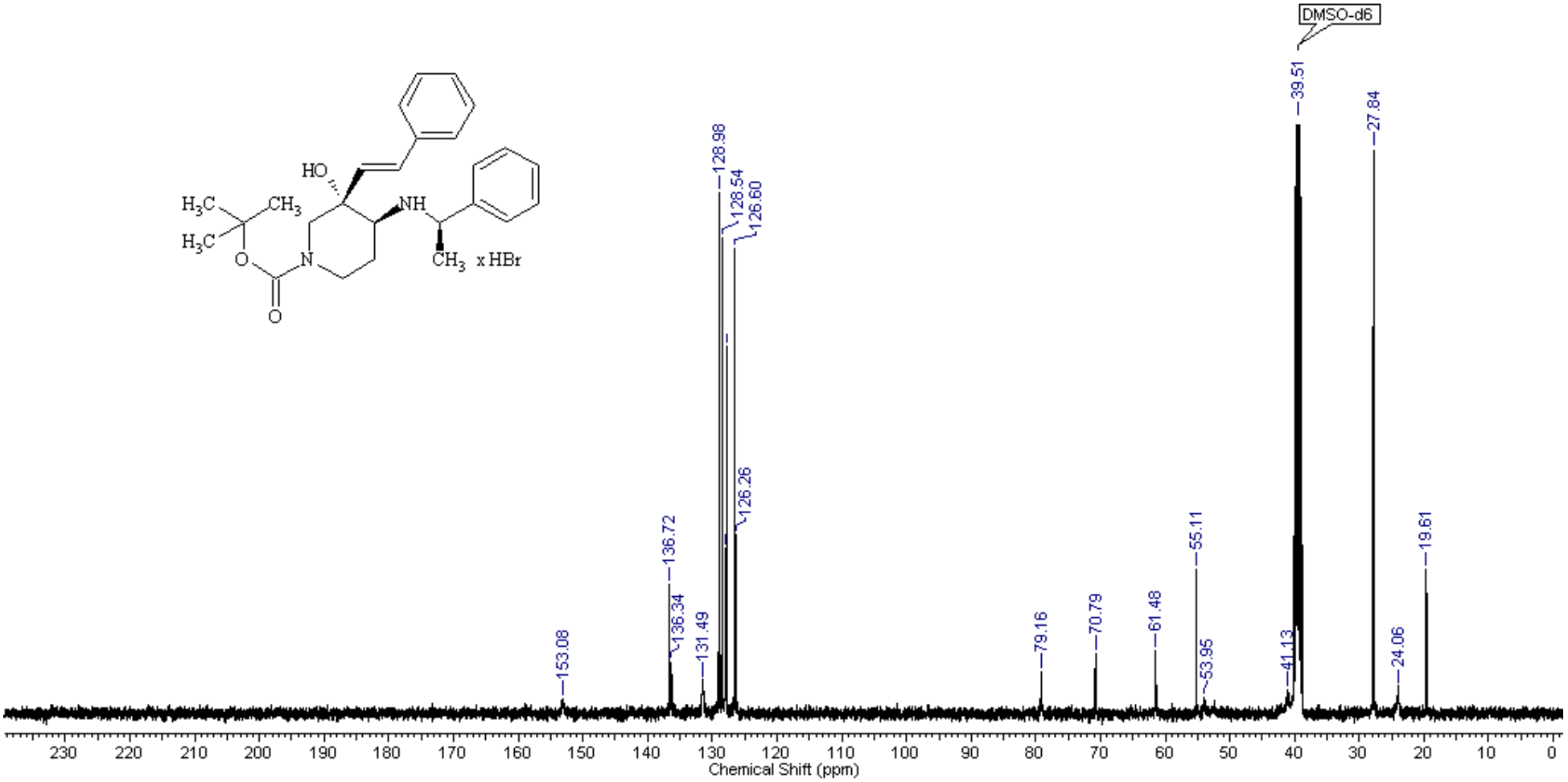
(3*S*,4*R*)-3-(((*R*)-1-Phenylethyl)amino)-4-((*E*)-styryl)tetrahydro-2*H*-pyran-4-ol (47). ^{13}C NMR ($CDCl_3$, 100 MHz).



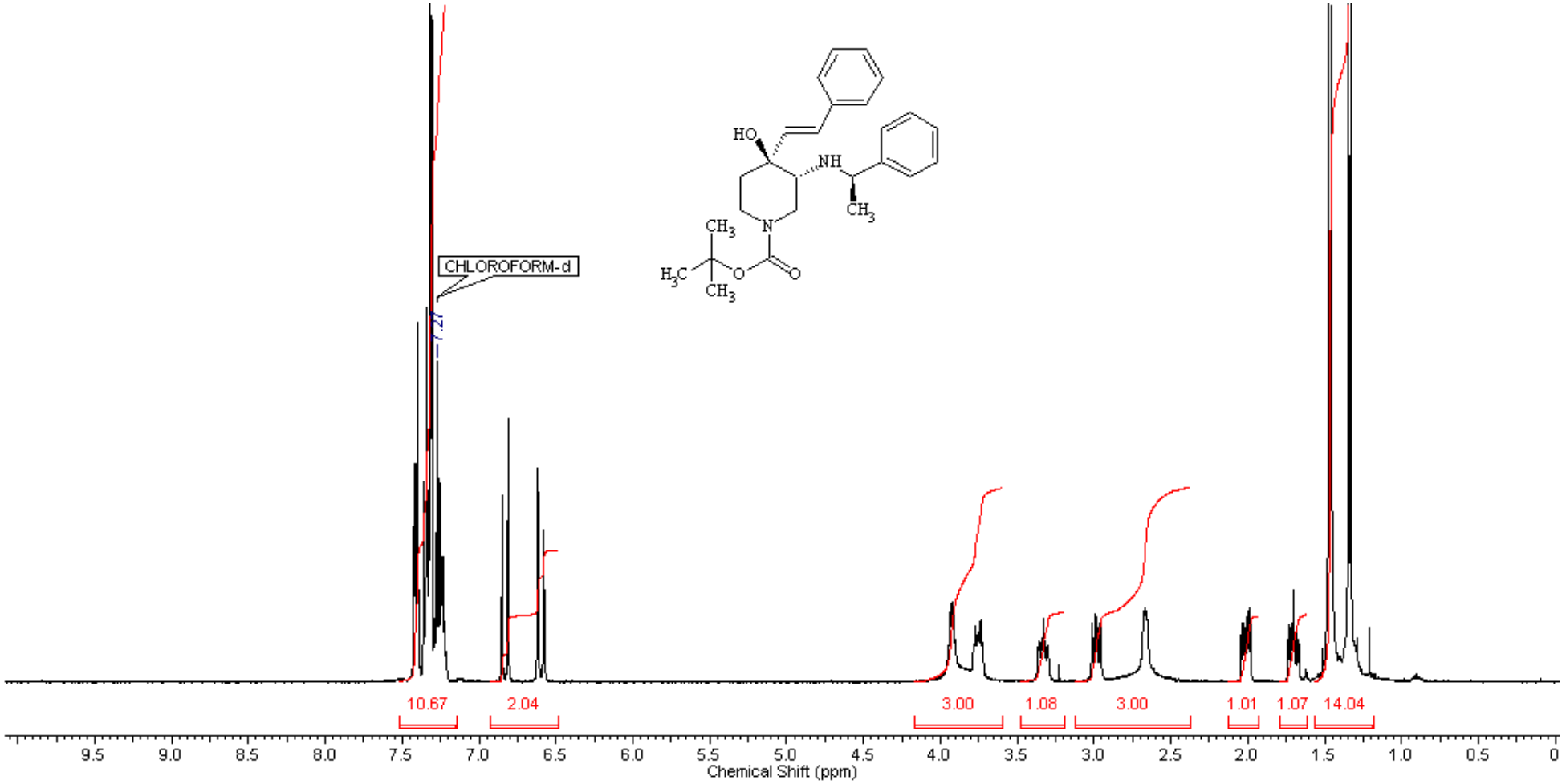
(3*S*,4*S*)-*Tert*-butyl 3-hydroxy-4-(((*R*)-1-phenylethyl)amino)-3-((*E*)-styryl)piperidine-1-carboxylate hydrobromide (48). ^{1}H NMR (DMSO-d_6, 400 MHz).



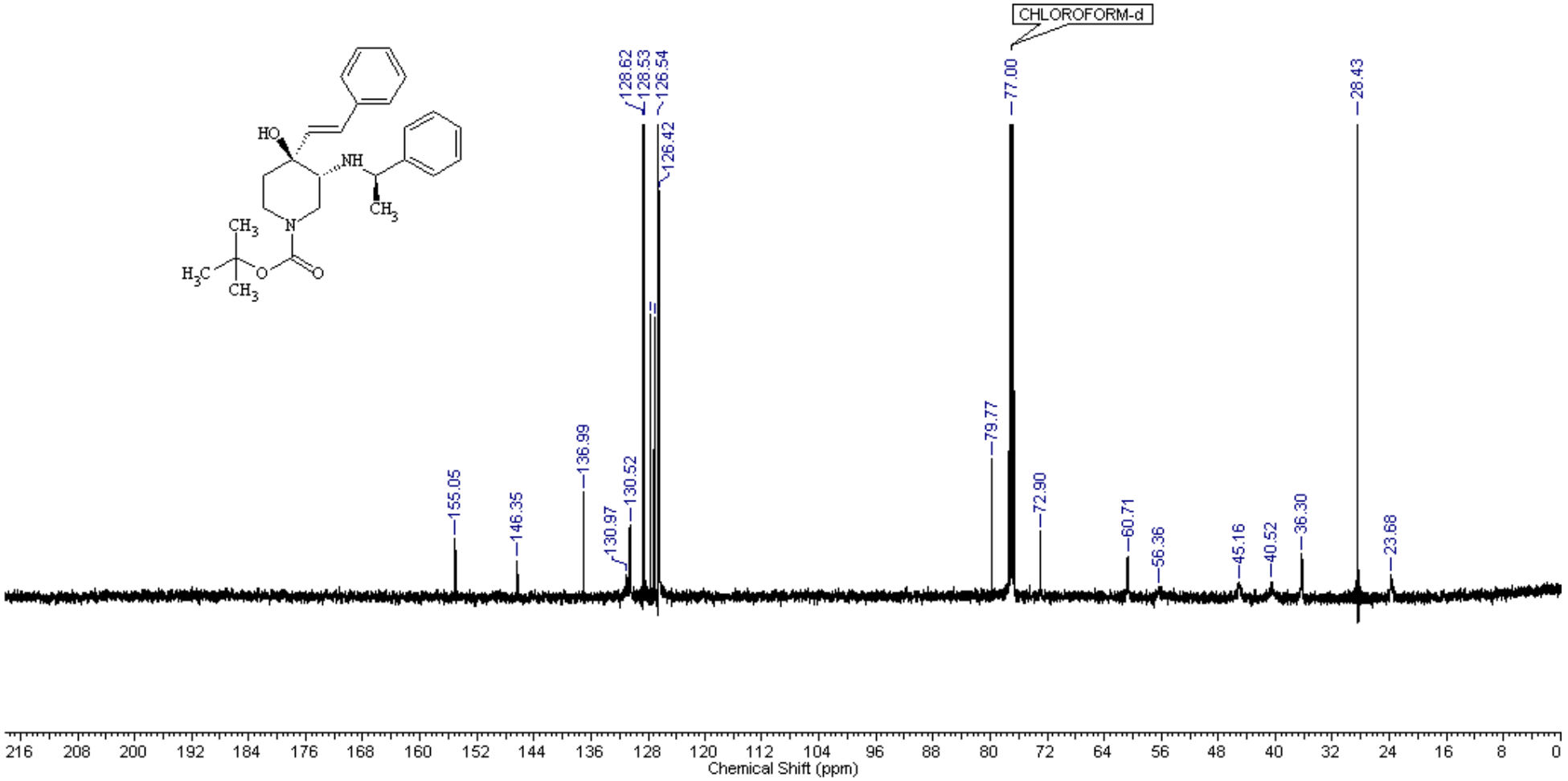
(3*S*,4*S*)-*Tert*-butyl 3-hydroxy-4-(((*R*)-1-phenylethyl)amino)-3-((*E*)-styryl)piperidine-1-carboxylate hydrobromide (48). ^{13}C NMR (DMSO-d_6, 100 MHz).



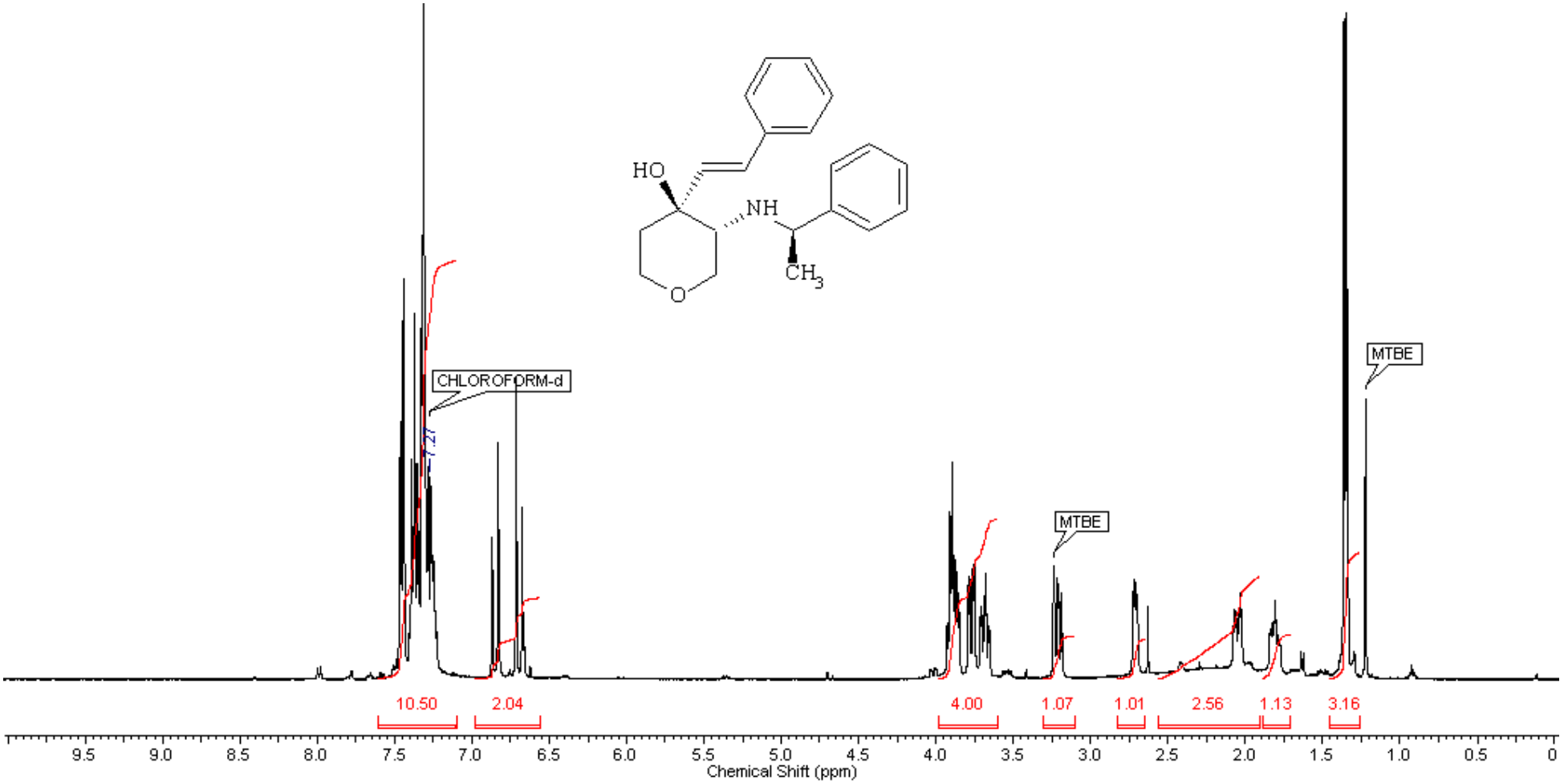
(3*R*,4*S*)-*Tert*-butyl 4-hydroxy-3-(((*R*)-1-phenylethyl)amino)-4-((*E*)-styryl)piperidine-1-carboxylate (49). ^{1}H NMR ($CDCl_3$, 400 MHz, 40^{O}C).



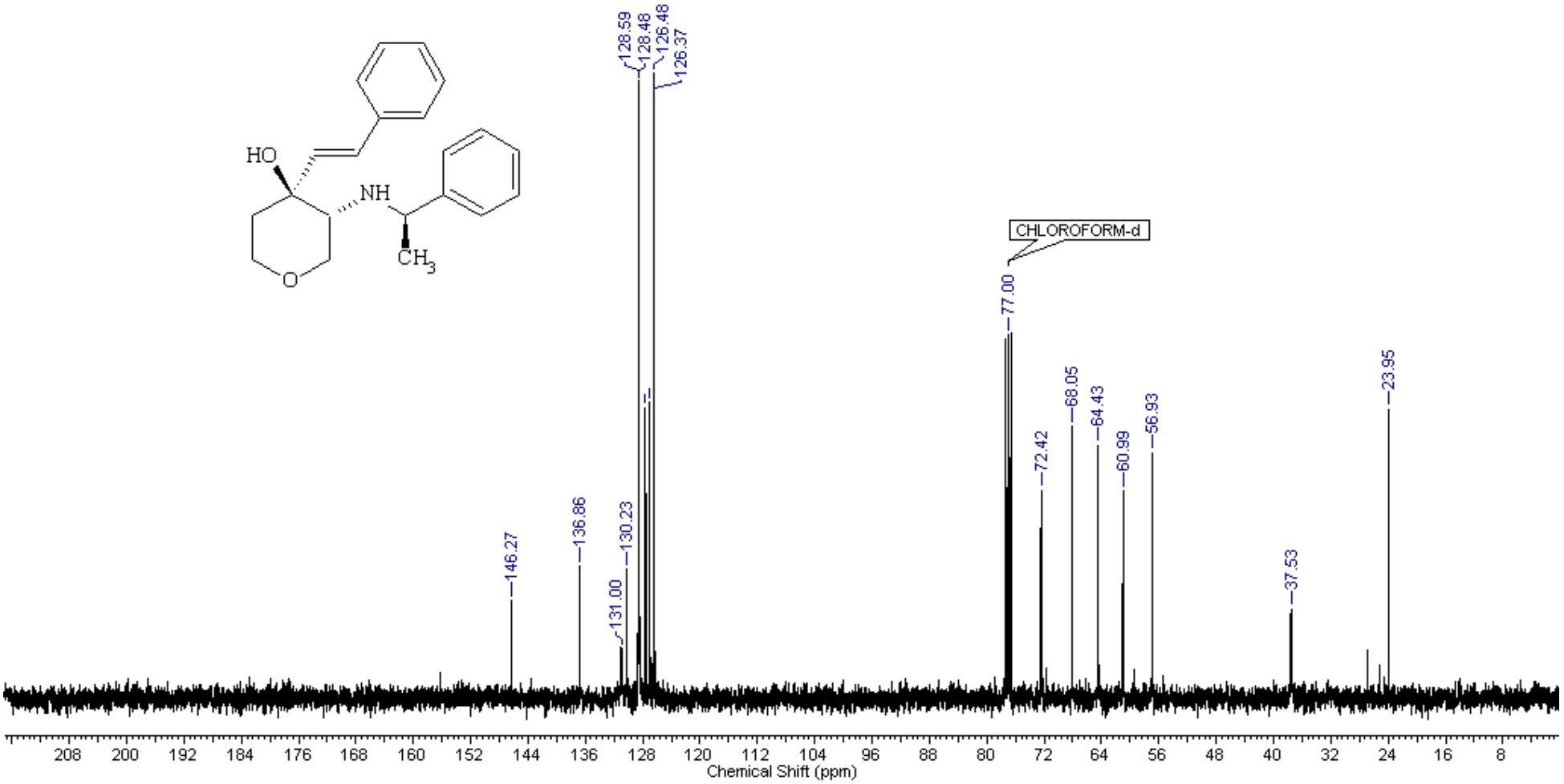
(3*R*,4*S*)-*Tert*-butyl 4-hydroxy-3-(((*R*)-1-phenylethyl)amino)-4-((*E*)-styryl)piperidine-1-carboxylate (49). ^{13}C NMR ($CDCl_3$, 100 MHz, 40^{O}C)



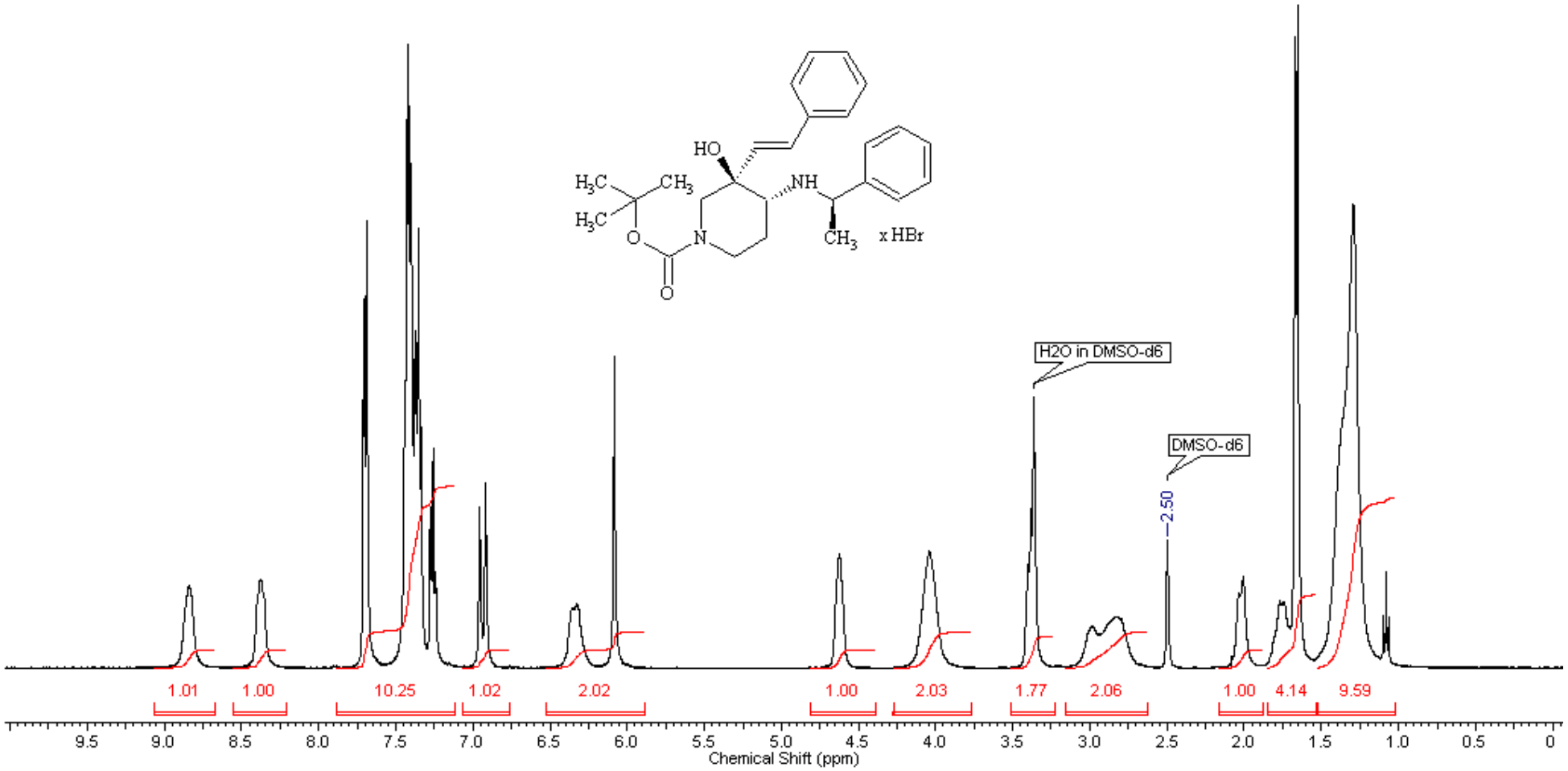
(3*R*,4*S*)-3-(((*R*)-1-Phenylethyl)amino)-4-((*E*)-styryl)tetrahydro-2*H*-pyran-4-ol (50). ^{1}H NMR ($CDCl_3$, 400 MHz).



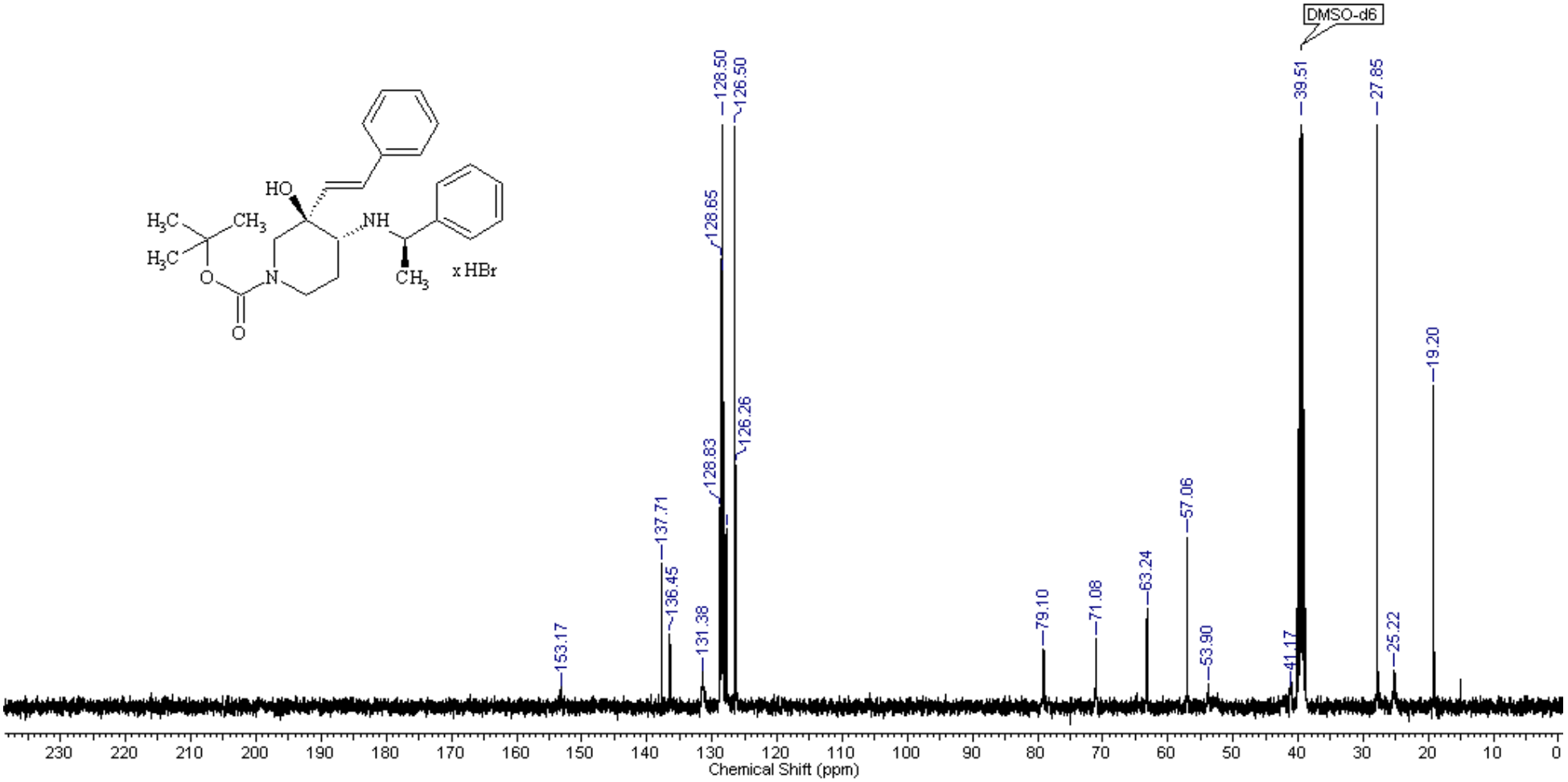
(3*R*,4*S*)-3-(((*R*)-1-Phenylethyl)amino)-4-((*E*)-styryl)tetrahydro-2*H*-pyran-4-ol (50). ^{13}C NMR ($CDCl_3$, 100 MHz).



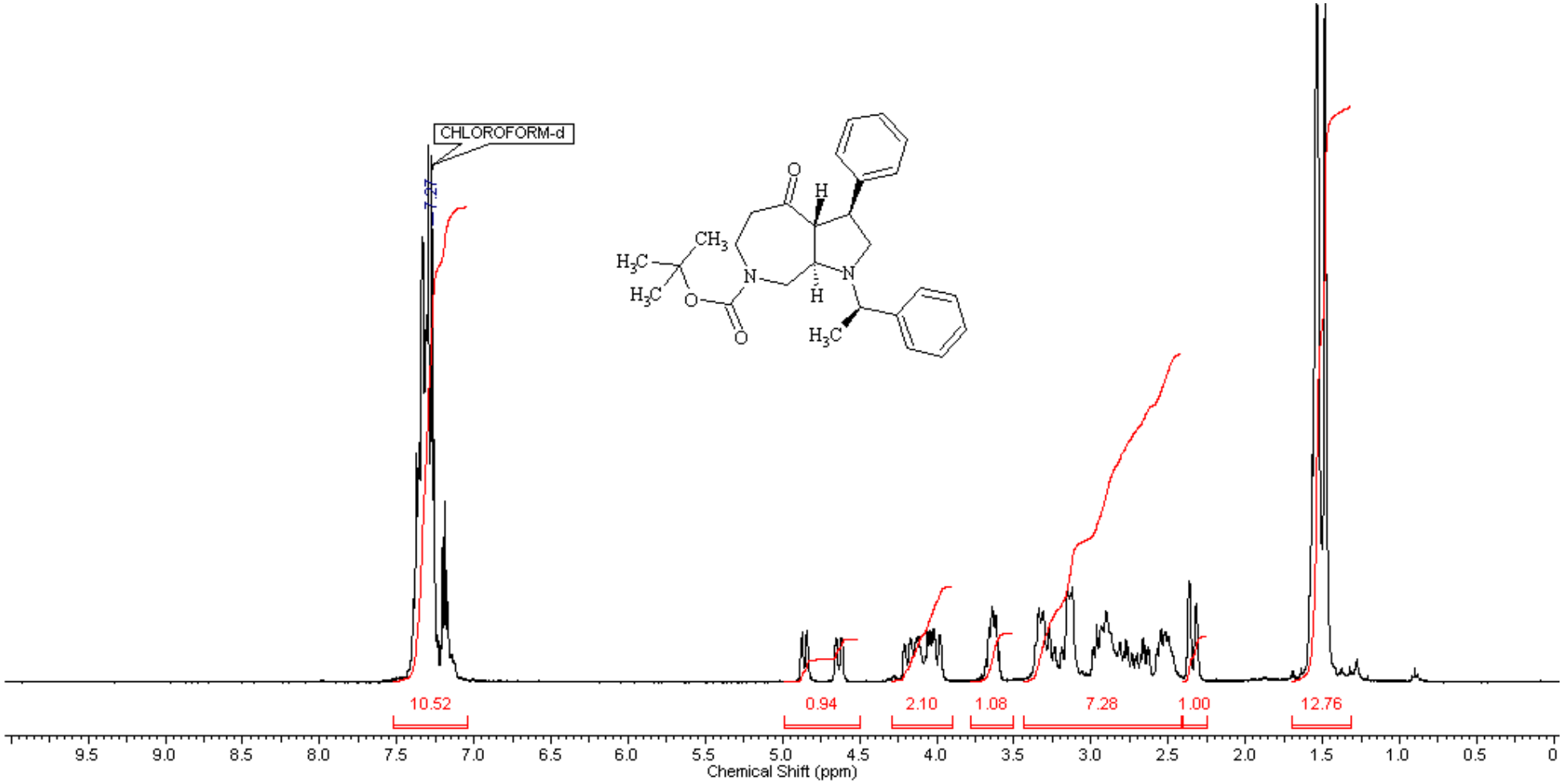
(3*R*,4*R*)-*Tert*-butyl 3-hydroxy-4-(((*R*)-1-phenylethyl)amino)-3-((*E*)-styryl)piperidine-1-carboxylate hydrobromide (51). ^{1}H NMR (DMSO-d_6, 400 MHz).



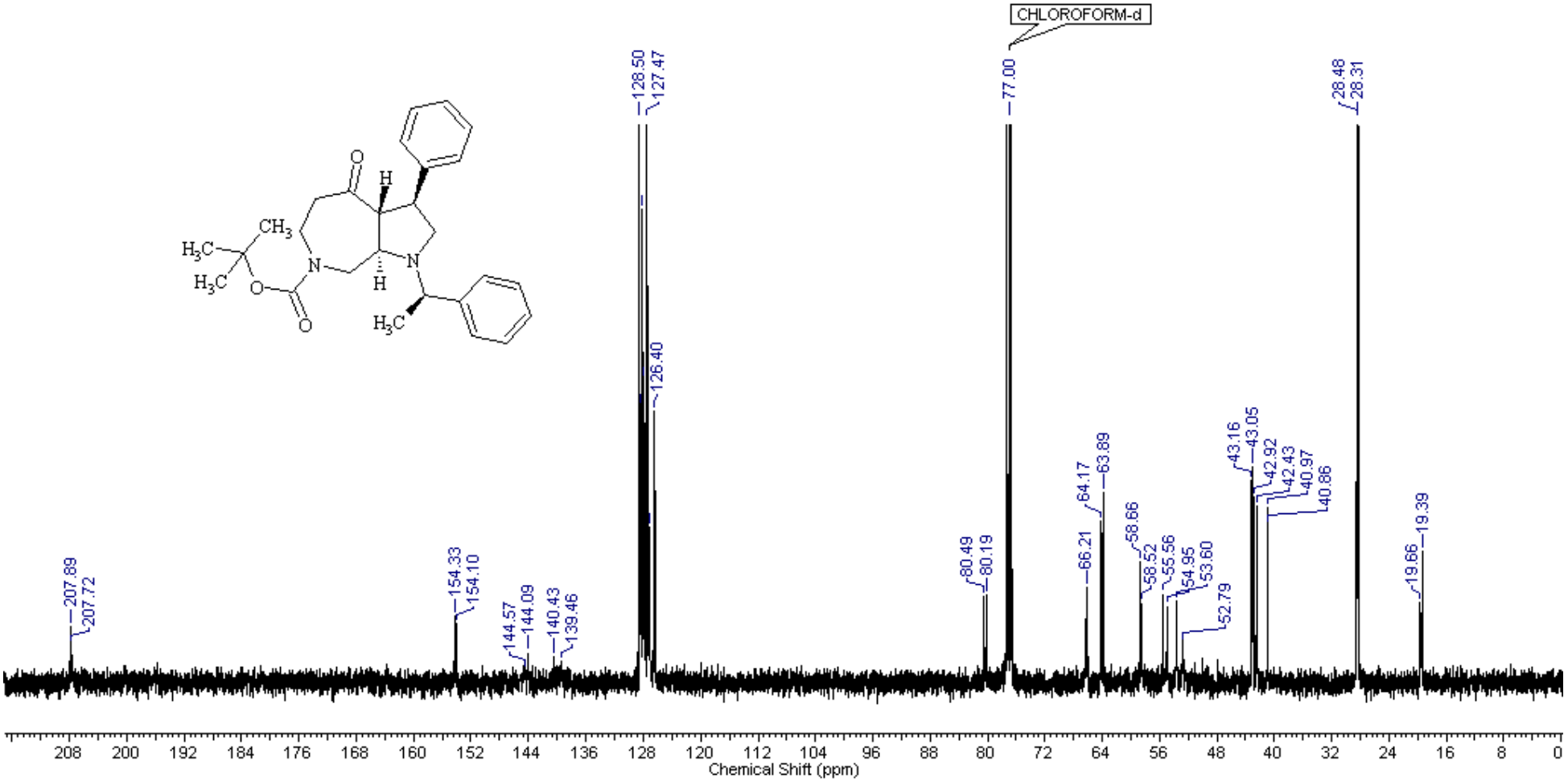
(3*R*,4*R*)-*Tert*-butyl 3-hydroxy-4-(((*R*)-1-phenylethyl)amino)-3-((*E*)-styryl)piperidine-1-carboxylate hydrobromide (51). ^{13}C NMR (DMSO-d_6, 100 MHz).



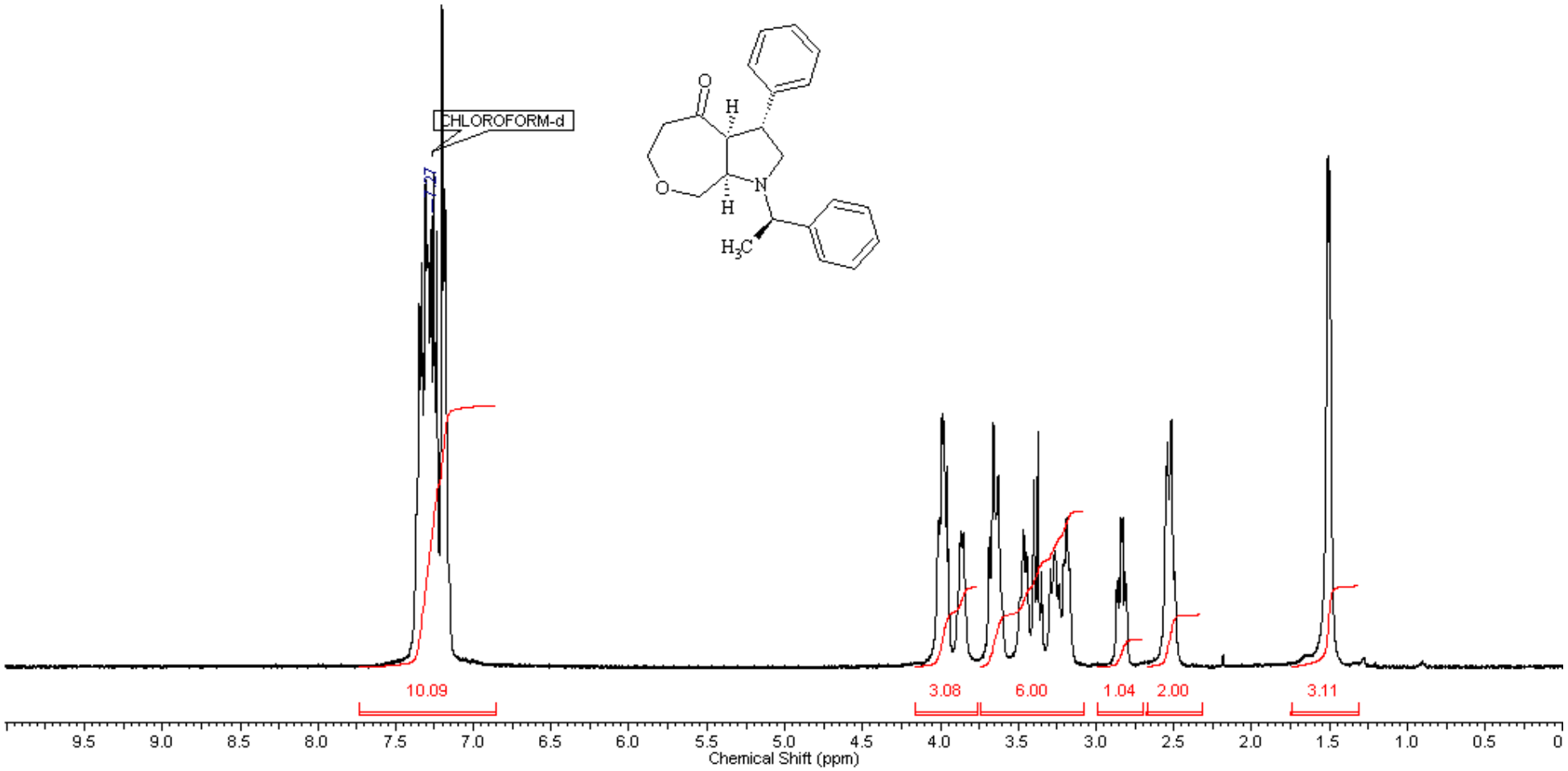
(3*S*,3a*R*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyl-1-((*R*)-1-phenylethyl)octahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate (52a). ^{1}H NMR ($CDCl_3$, 400 MHz).



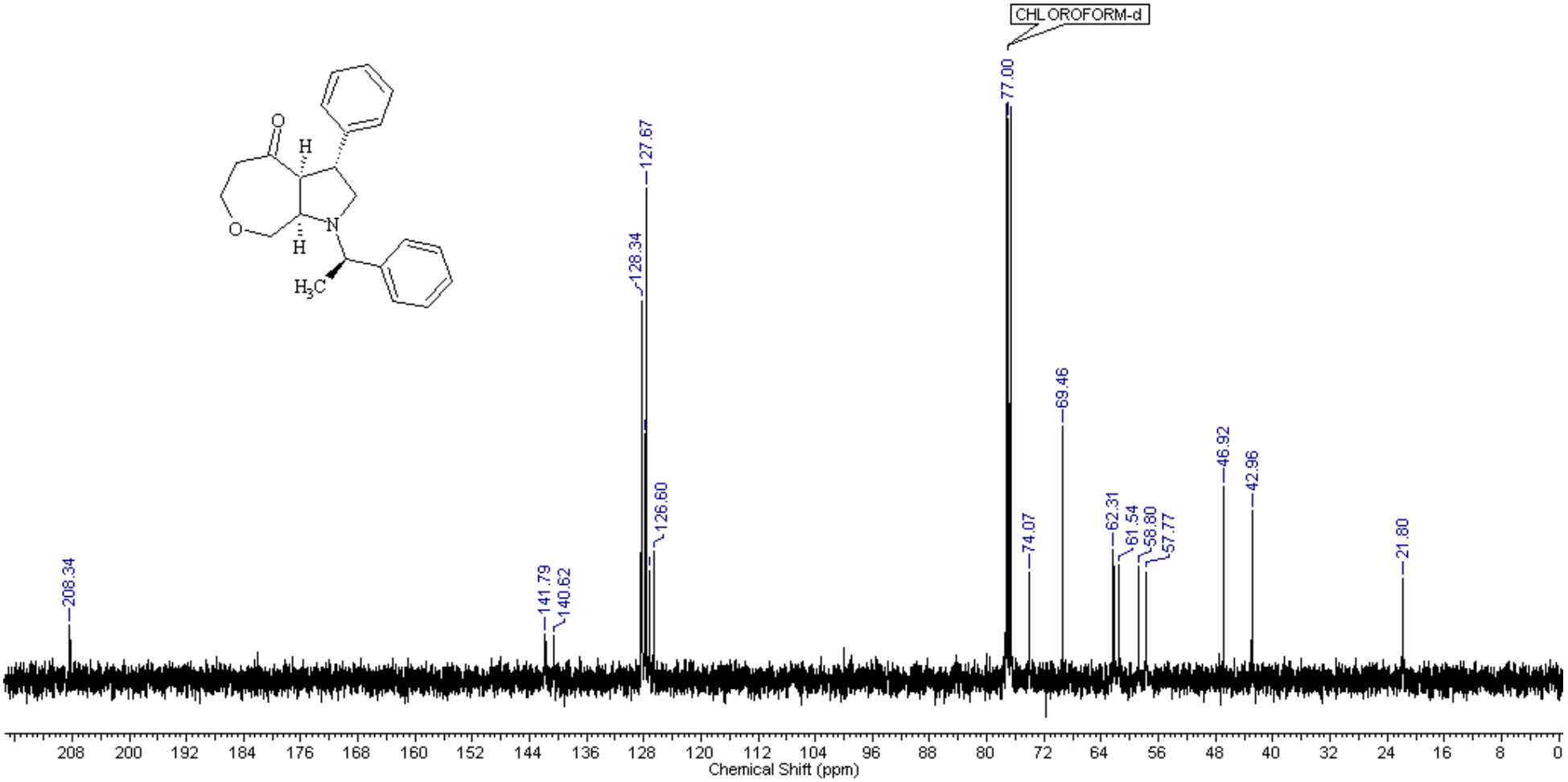
(3*S*,3a*R*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyl-1-((*R*)-1-phenylethyl)octahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate (52a). ^{13}C NMR ($CDCl_3$, 100 MHz)



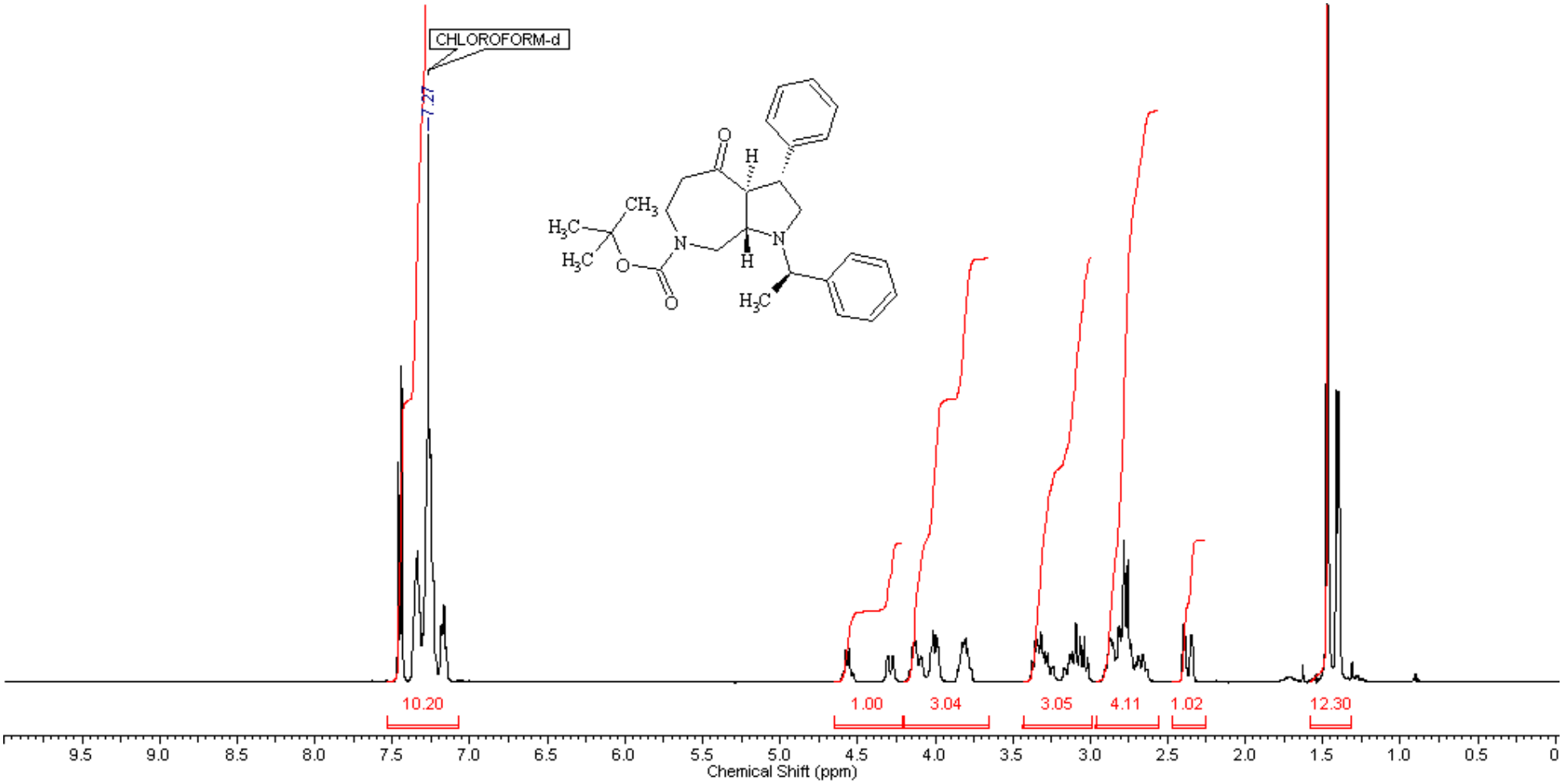
(3*R*,3a*S*,8a*R*)-3-Phenyl-1-((*R*)-1-phenylethyl)hexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (53b). ^{1}H NMR ($CDCl_3$, 400 MHz).



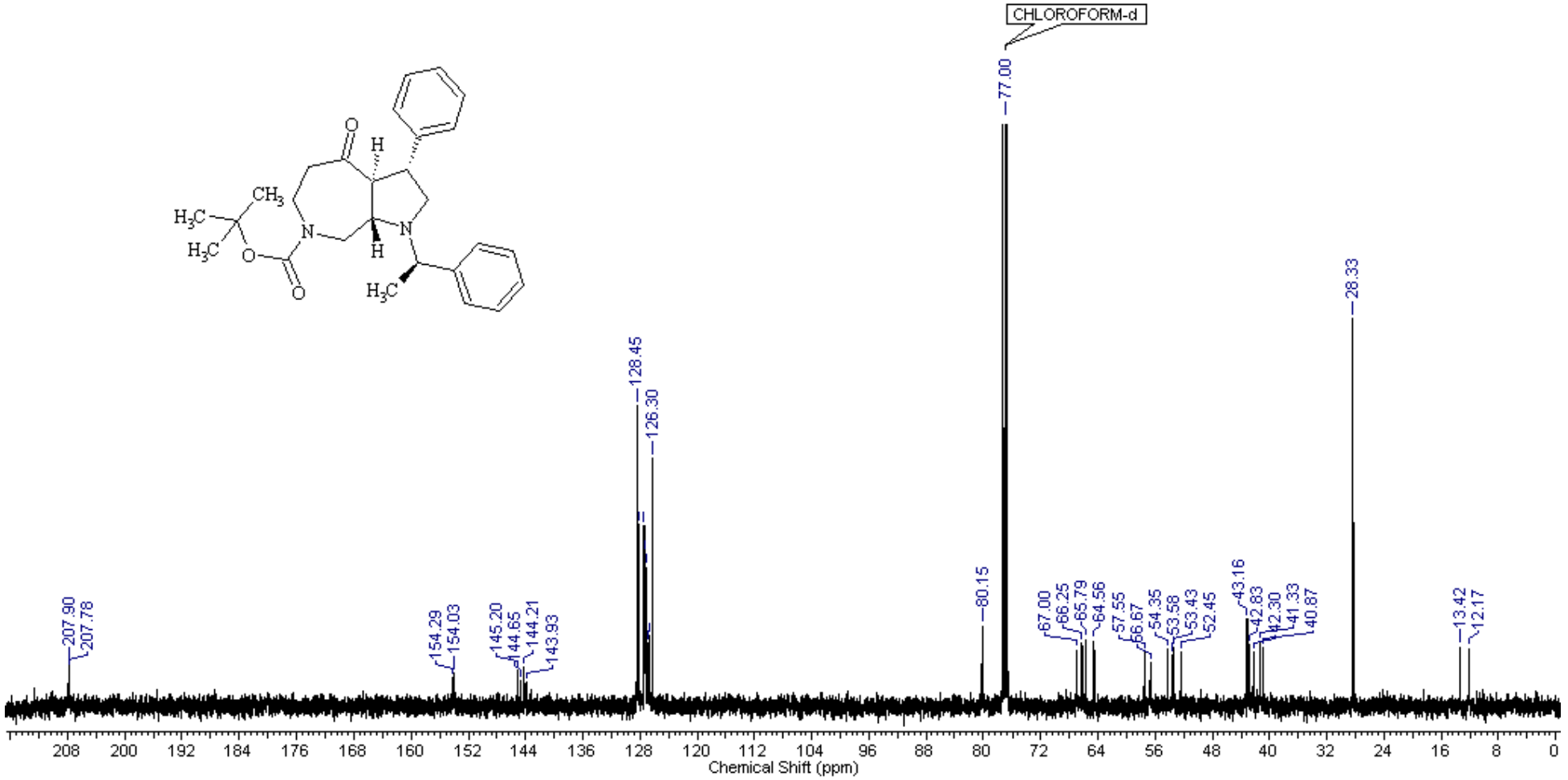
(3*R*,3a*S*,8a*R*)-3-Phenyl-1-((*R*)-1-phenylethyl)hexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (53b). ^{13}C NMR ($CDCl_3$, 100 MHz)



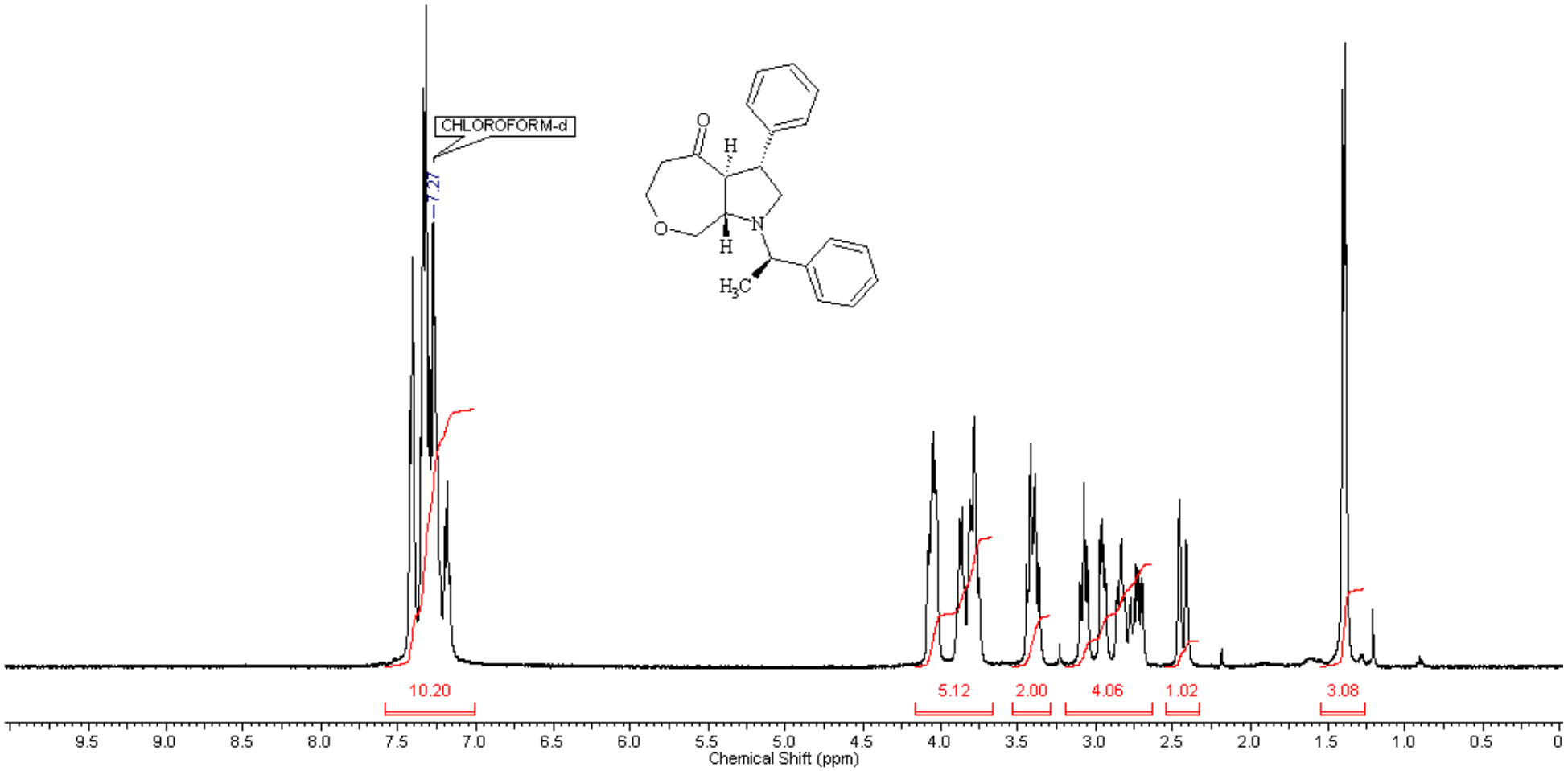
(3*R*,3a*S*,8a*S*)-Tert-butyl 4-oxo-3-phenyl-1-((*R*)-1-phenylethyl)octahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate (55a). ^{1}H NMR ($CDCl_3$, 400 MHz).



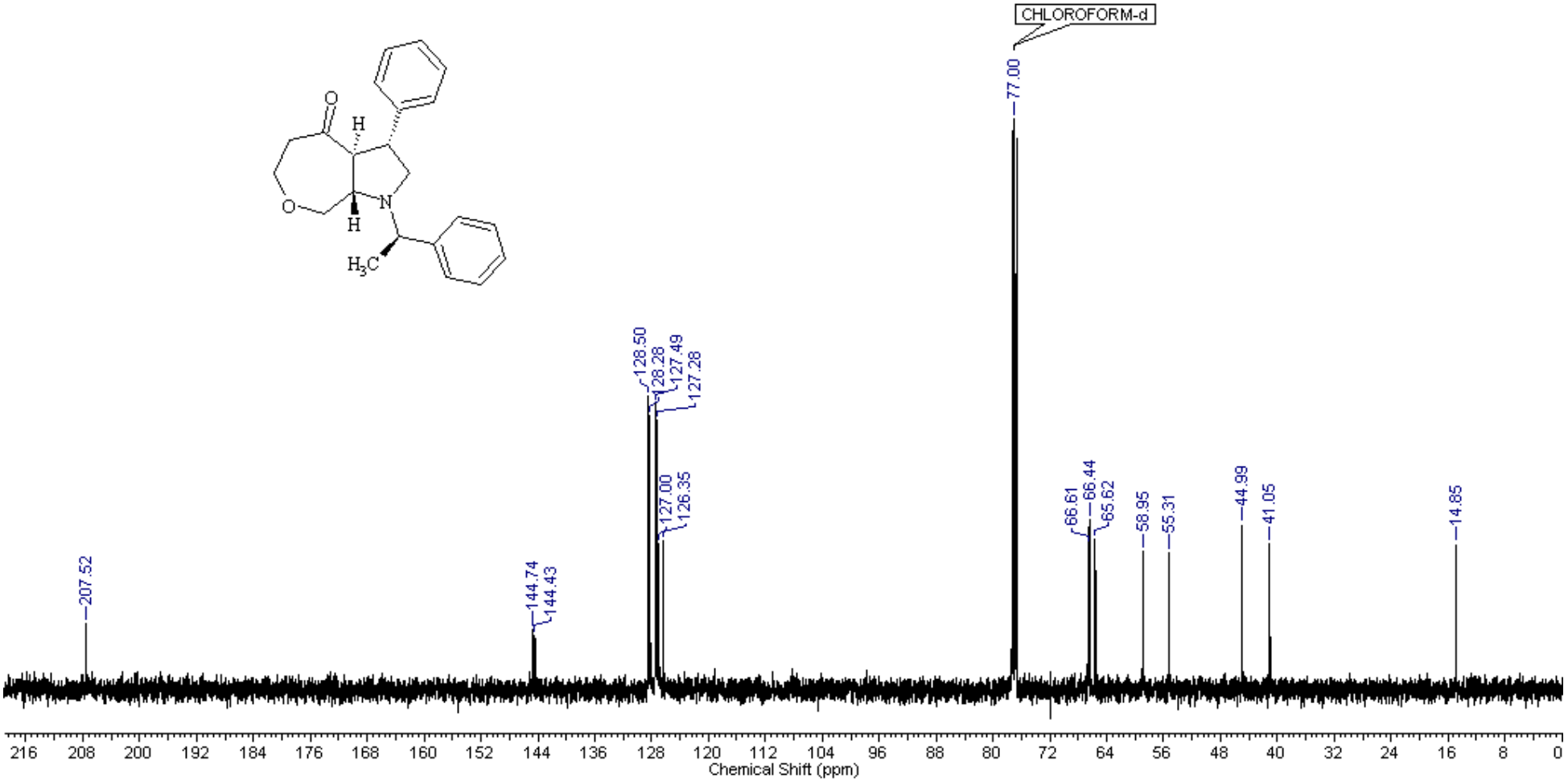
(3*R*,3a*S*,8a*S*)-Tert-butyl 4-oxo-3-phenyl-1-((*R*)-1-phenylethyl)octahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate (55a). ^{13}C NMR ($CDCl_3$, 100 MHz).



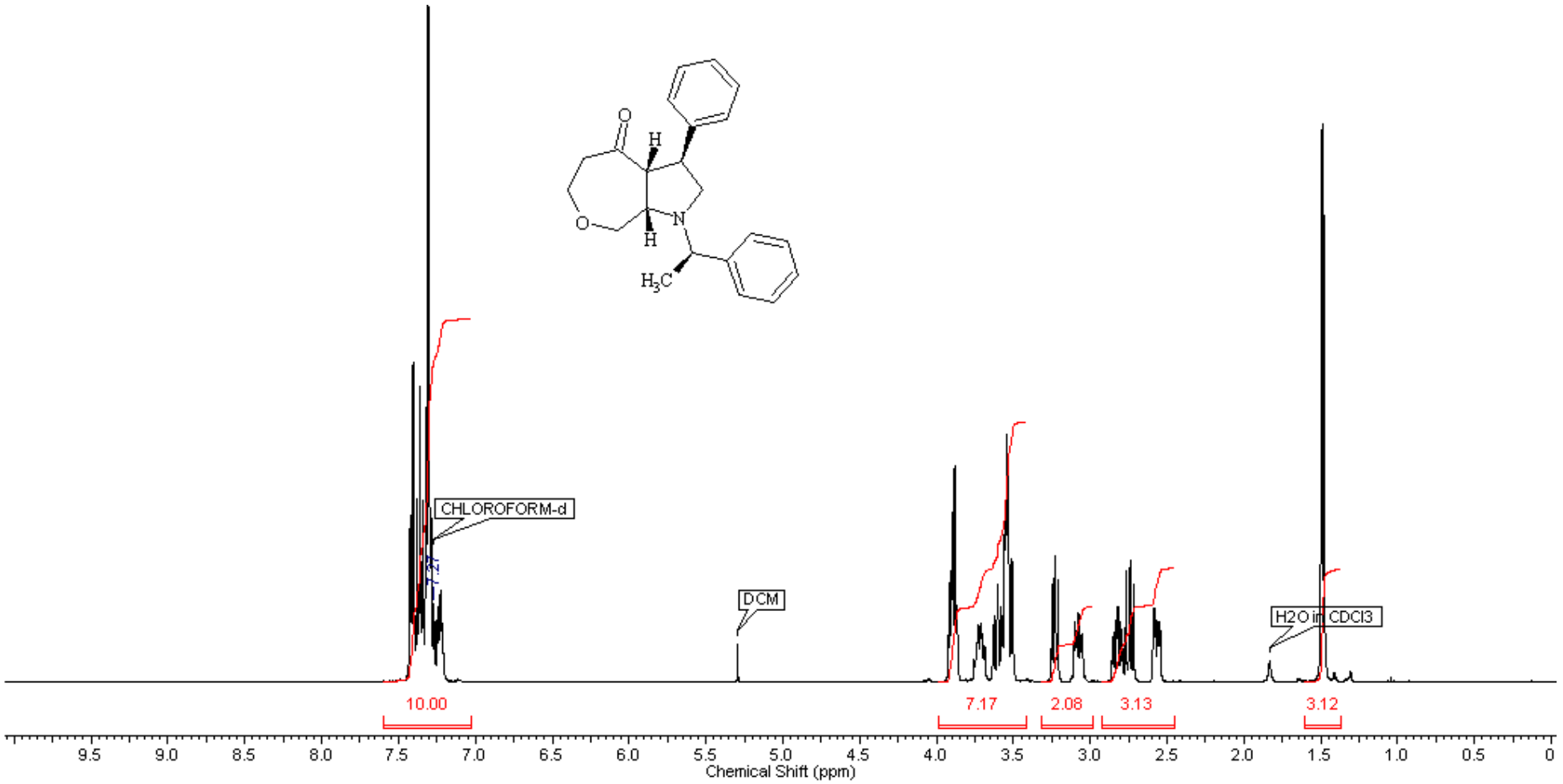
(3*R*,3a*S*,8a*S*)-3-Phenyl-1-((*R*)-1-phenylethyl)hexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (56a). ^{1}H NMR ($CDCl_3$, 400 MHz).



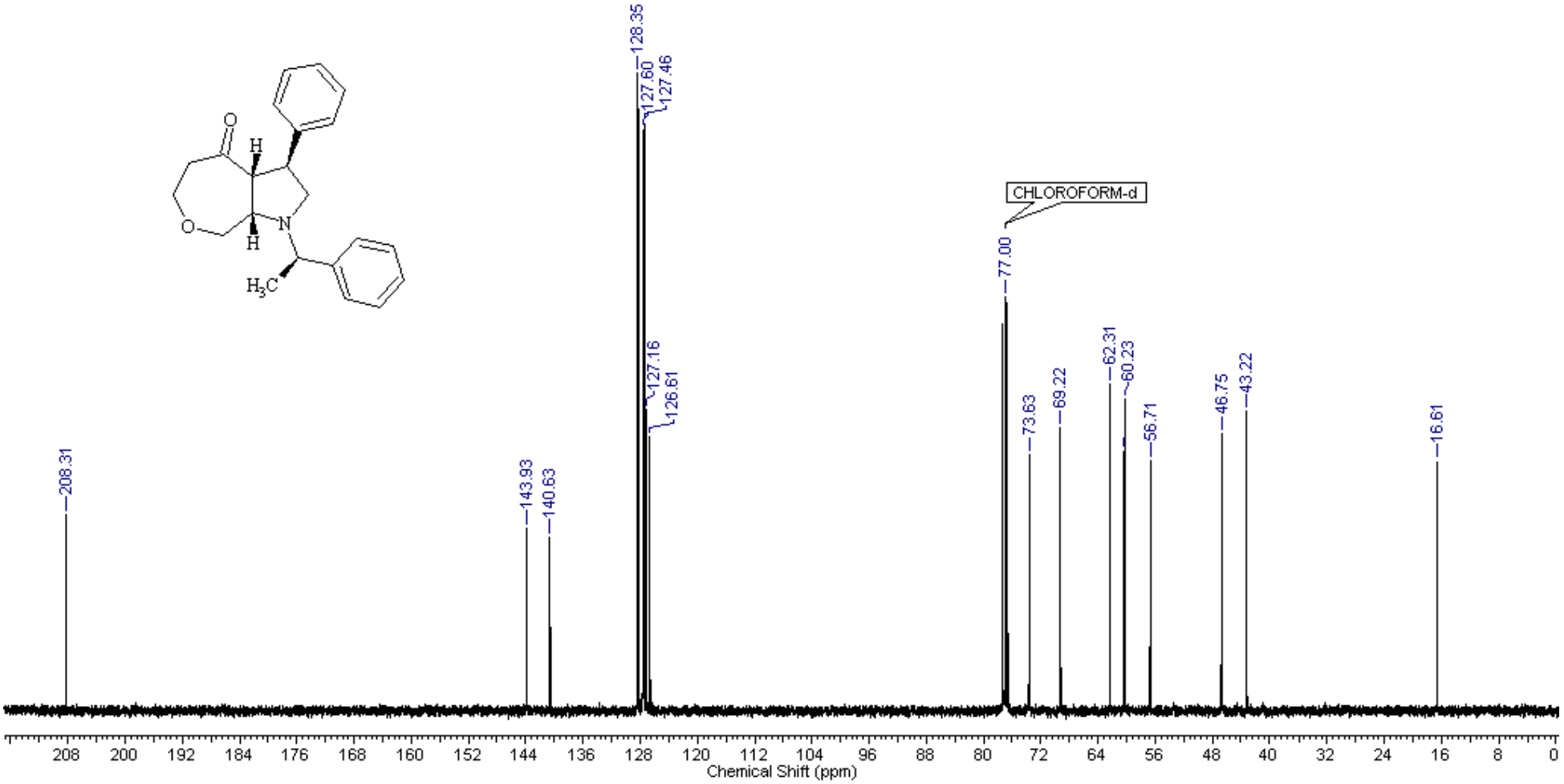
(3*R*,3a*S*,8a*S*)-3-Phenyl-1-((*R*)-1-phenylethyl)hexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (56a). ^{13}C NMR ($CDCl_3$, 100 MHz).



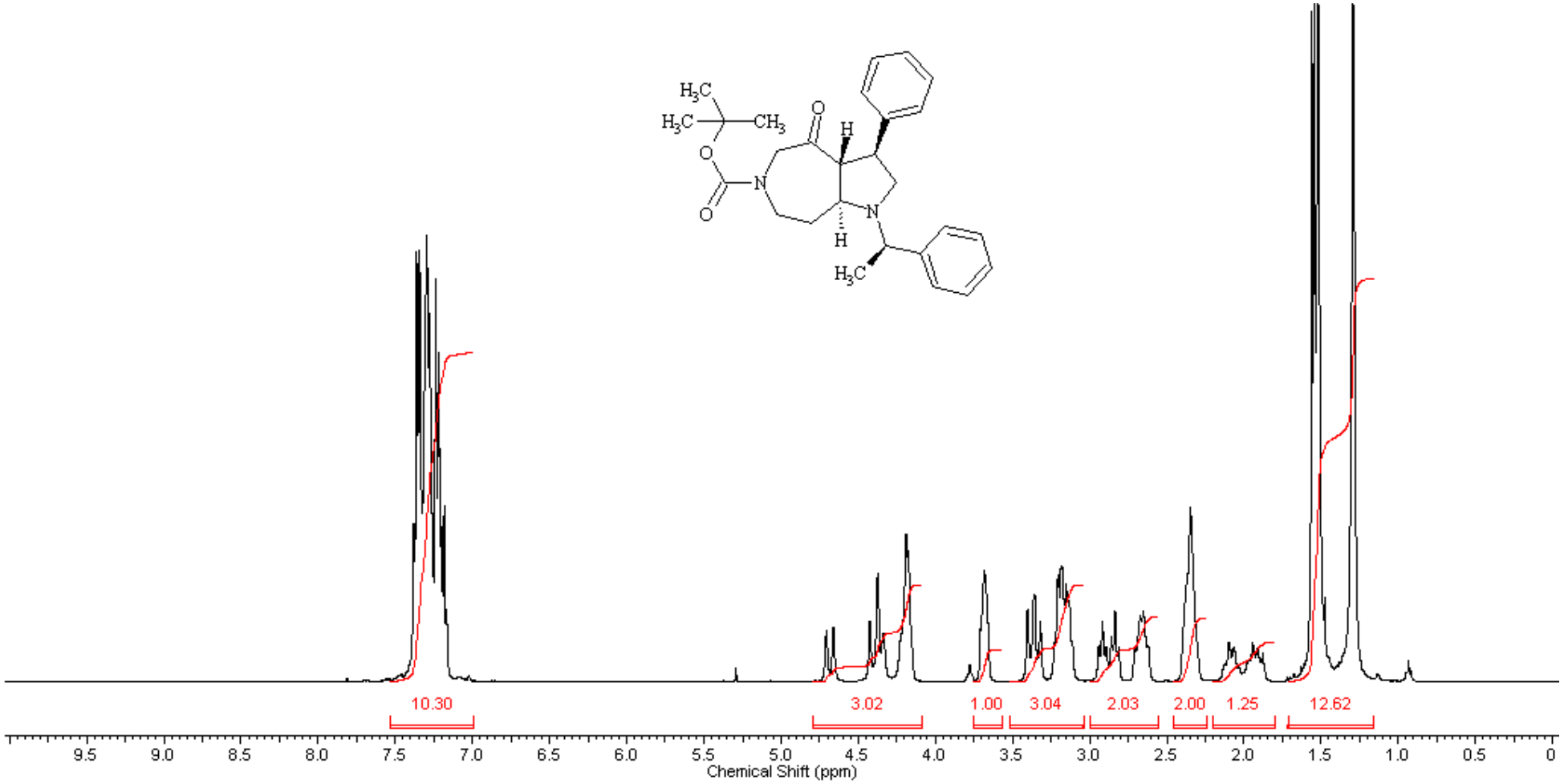
(3*S*,3a*R*,8a*S*)-3-Phenyl-1-((*R*)-1-phenylethyl)hexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (56b). ^{1}H NMR ($CDCl_3$, 400 MHz).



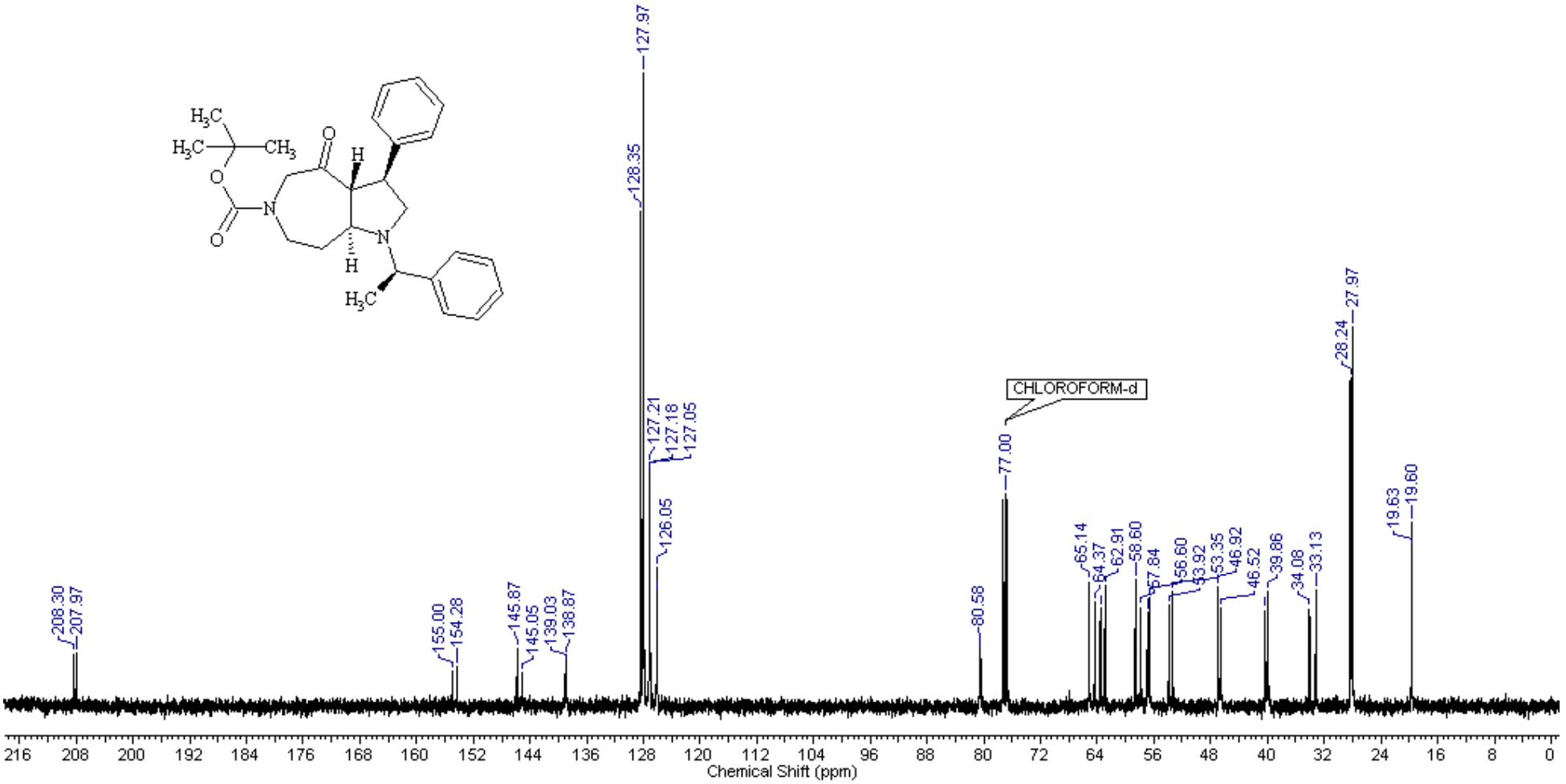
(3*S*,3a*R*,8a*S*)-3-Phenyl-1-((*R*)-1-phenylethyl)hexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one (56b). ^{13}C NMR ($CDCl_3$, 100 MHz).



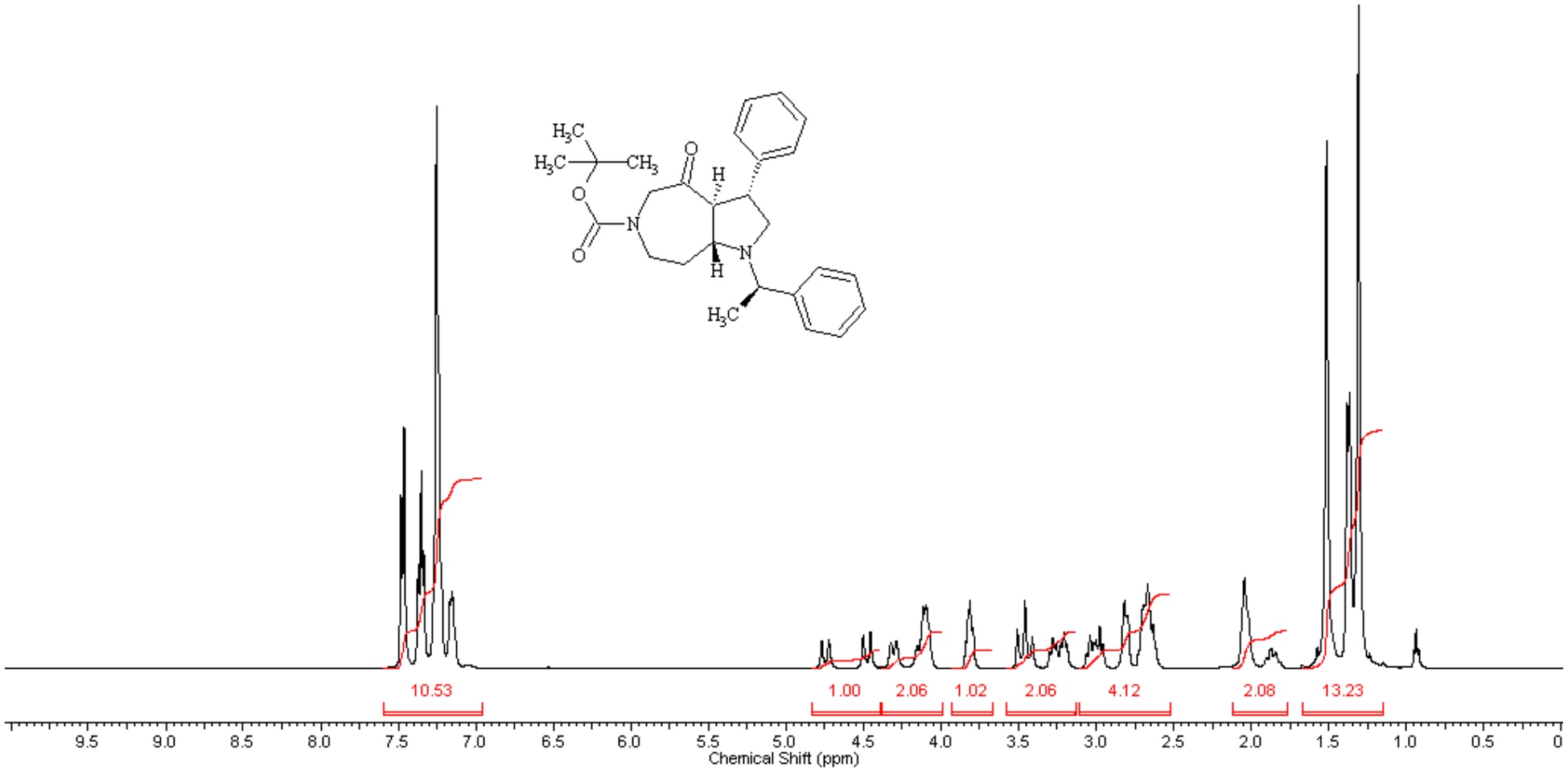
(3*S*,3a*R*,8a*S*)-*Tert*-butyl 4-oxo-3-phenyl-1-((*R*)-1-phenylethyl)octahydropyrrolo[2,3-d]azepine-6(2*H*)-carboxylate (54a). ^{1}H NMR ($CDCl_3$, 400 MHz).



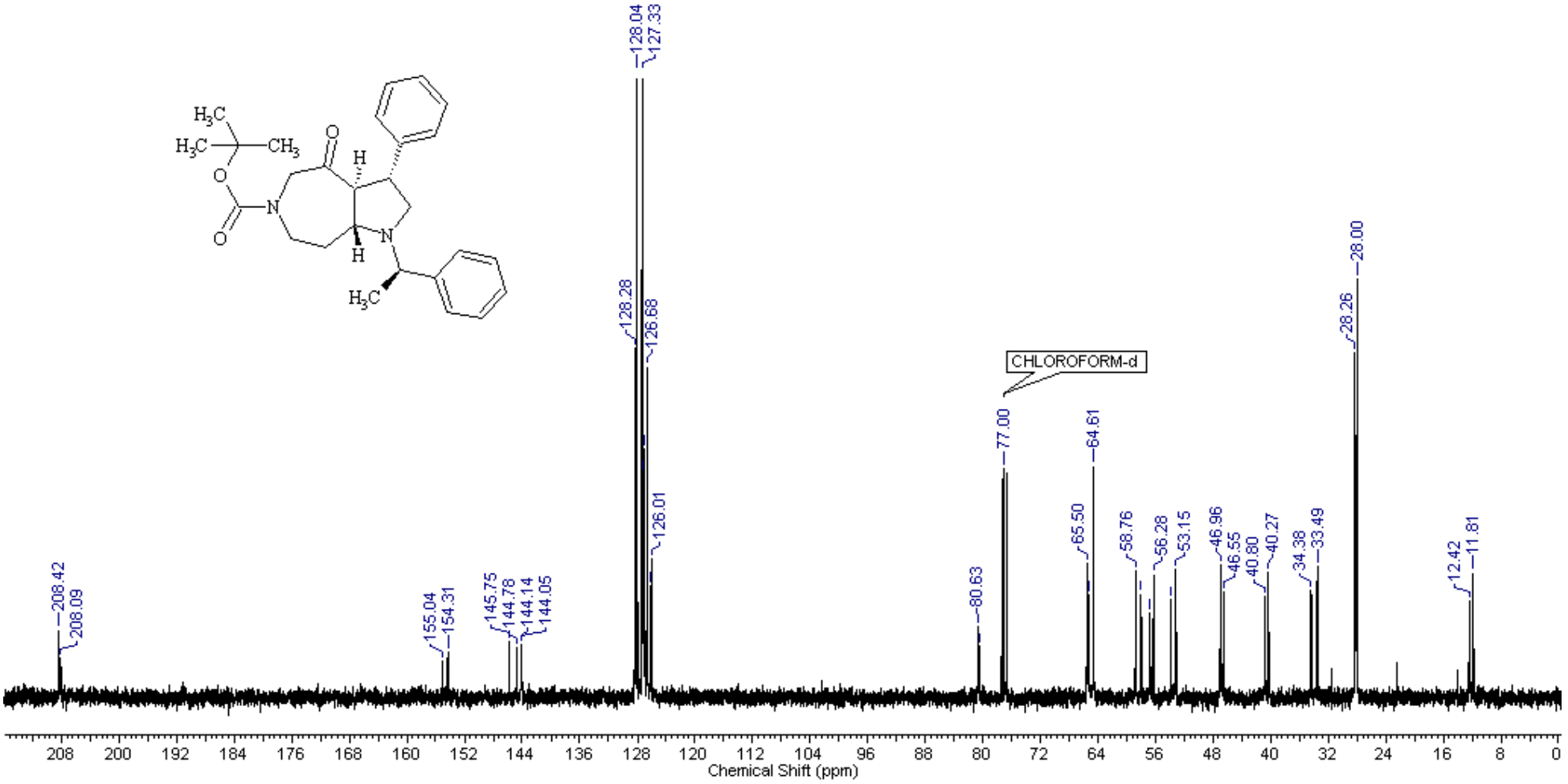
(3*S*,3a*R*,8a*S*)-*Tert*-butyl 4-oxo-3-phenyl-1-((*R*)-1-phenylethyl)octahydropyrrolo[2,3-d]azepine-6(2*H*)-carboxylate (54a). ^{13}C NMR ($CDCl_3$, 100 MHz).



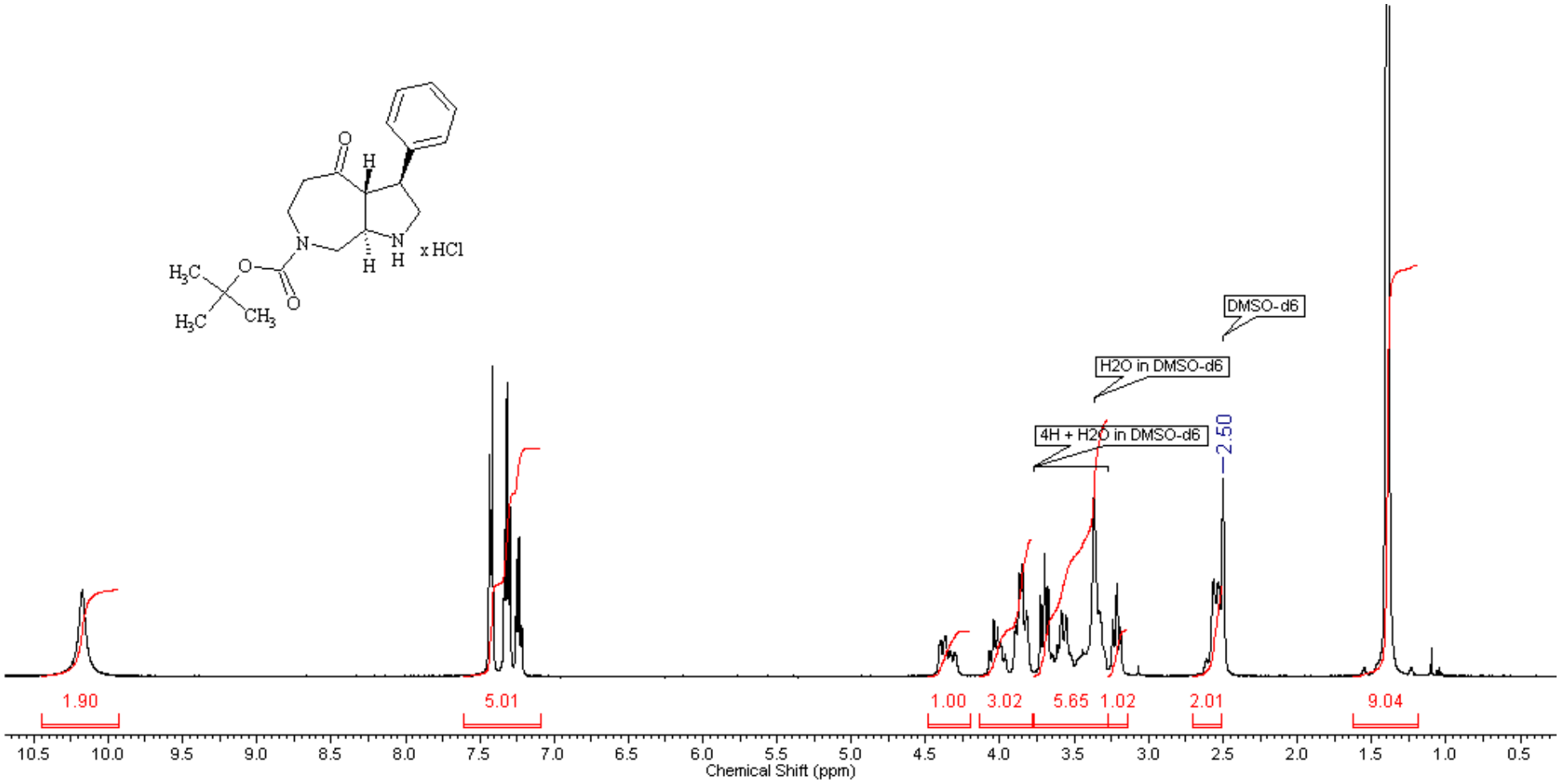
(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyl-1-((*R*)-1-phenylethyl)octahydropyrrolo[2,3-d]azepine-6(2*H*)-carboxylate (57a). ^{1}H NMR ($CDCl_3$, 400 MHz).



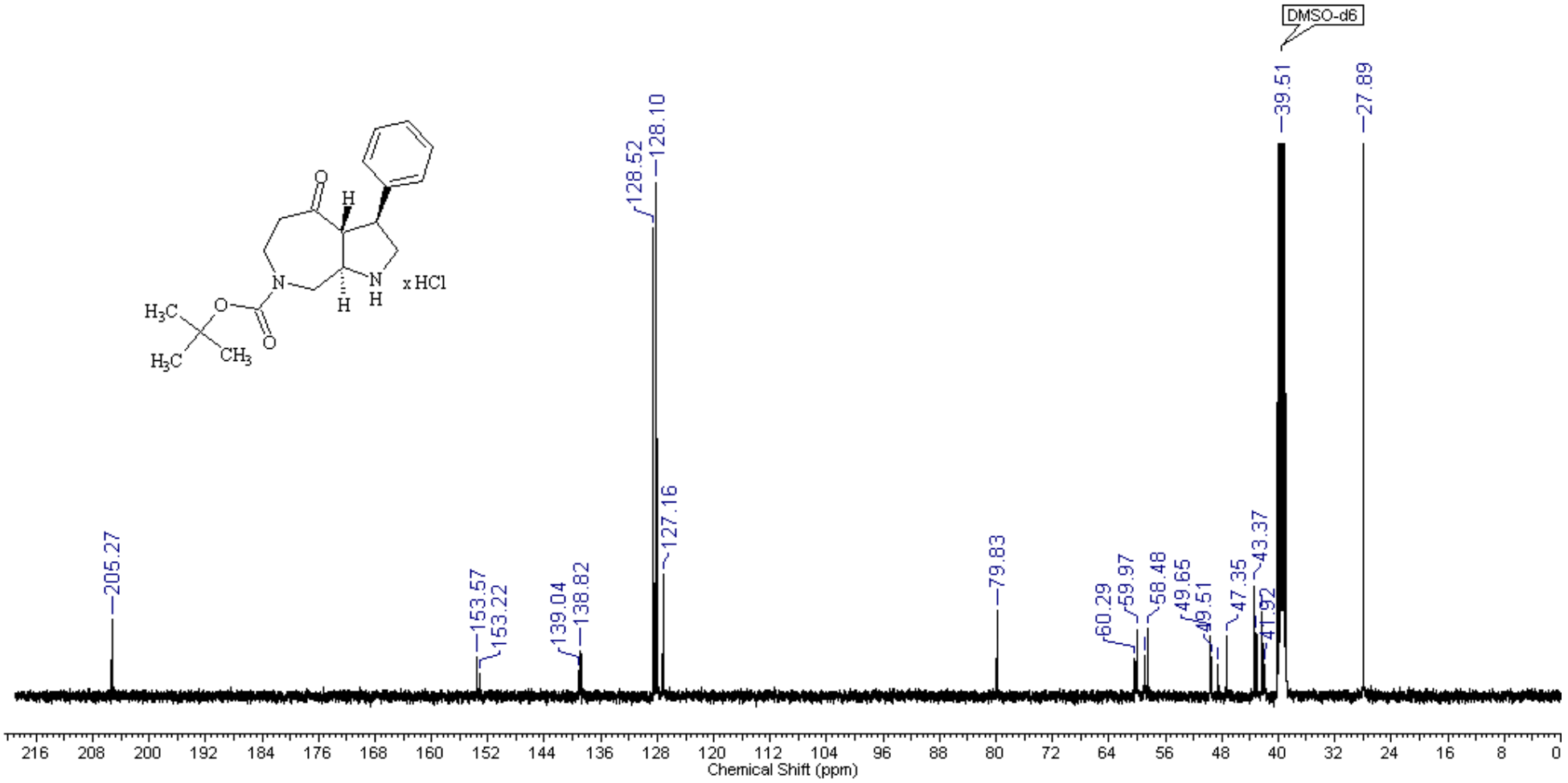
(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyl-1-((*R*)-1-phenylethyl)octahydropyrrolo[2,3-d]azepine-6(2*H*)-carboxylate (57a). ^{13}C NMR ($CDCl_3$, 100 MHz).



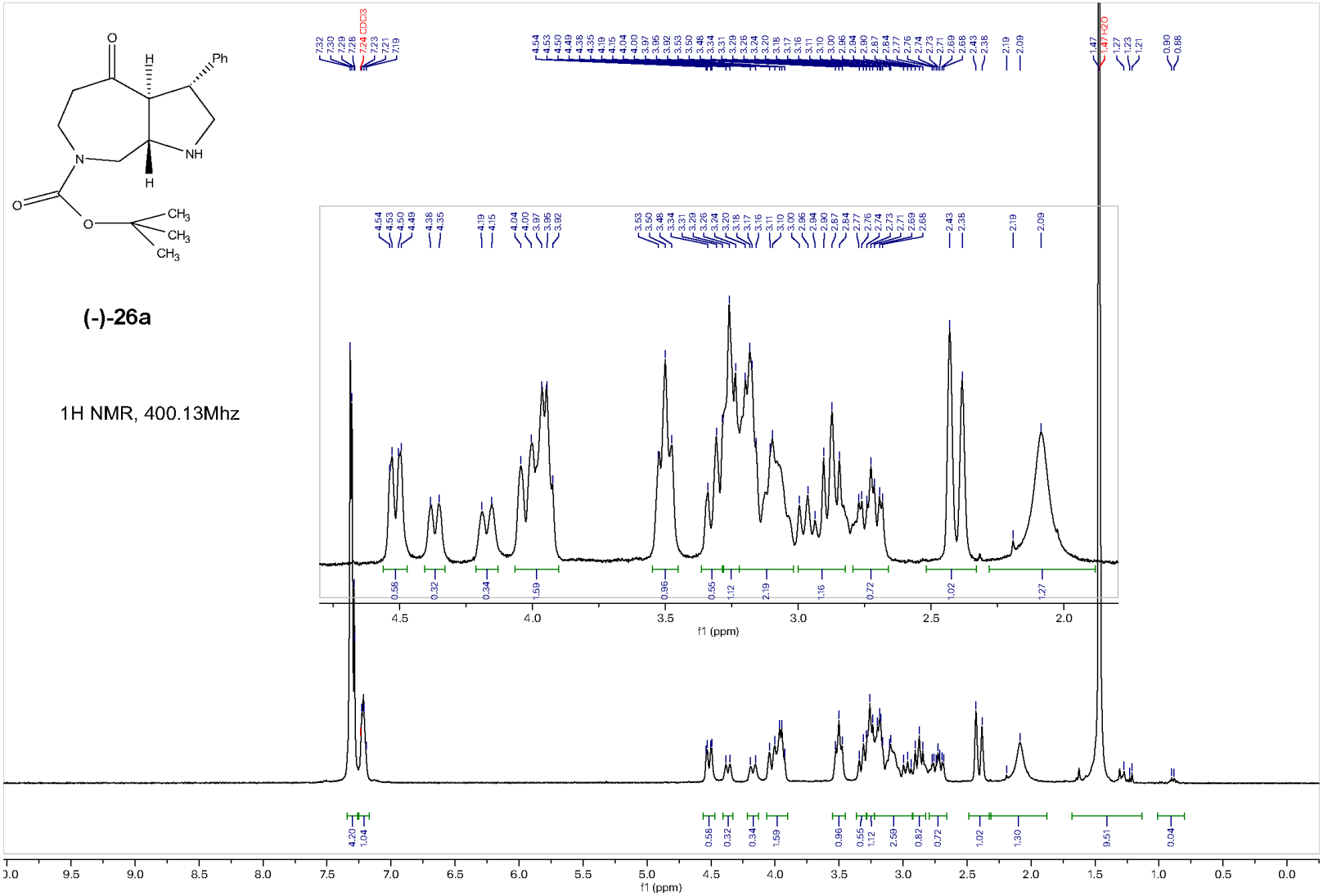
(3*S*,3a*R*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate hydrochloride ((+)-26a). ^{1}H NMR (DMSO-d_6, 400 MHz)



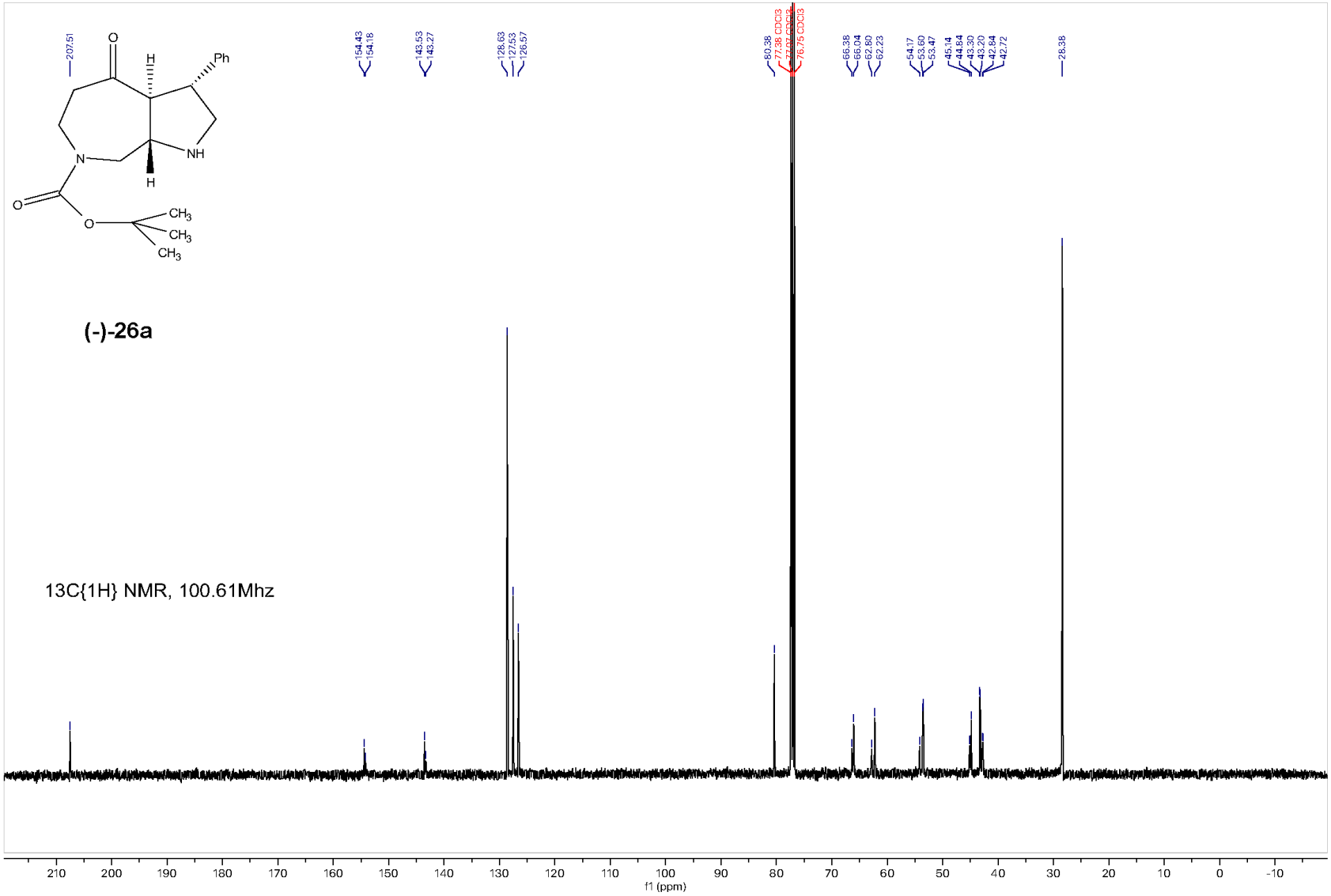
(3*S*,3a*R*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate hydrochloride ((+)-26a). ^{13}C NMR (DMSO-d_6, 100 MHz)



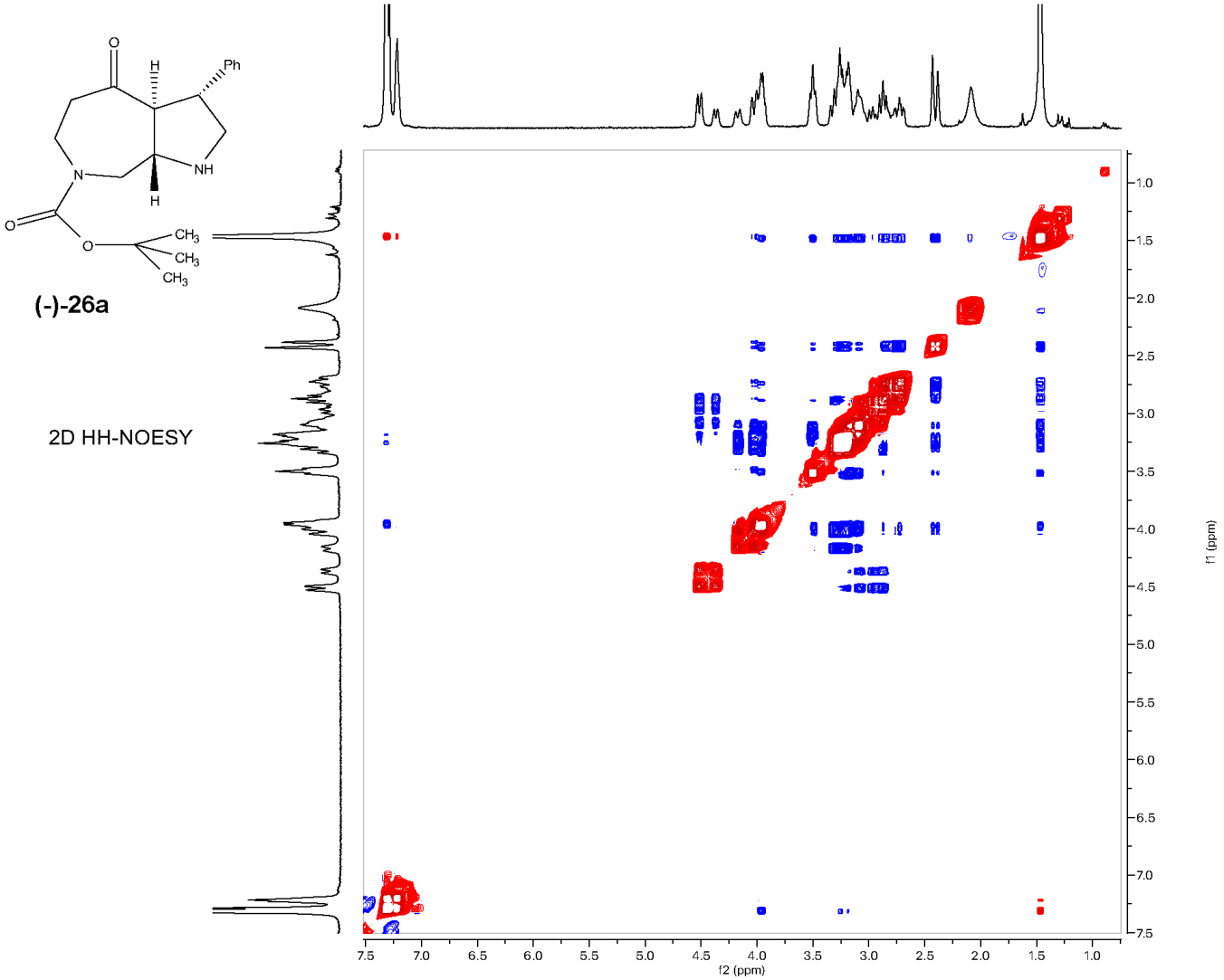
(3*R*,3a*S*,8a*S*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((-)-26a). ^{1}H NMR ($CDCl_3$, 400 MHz)



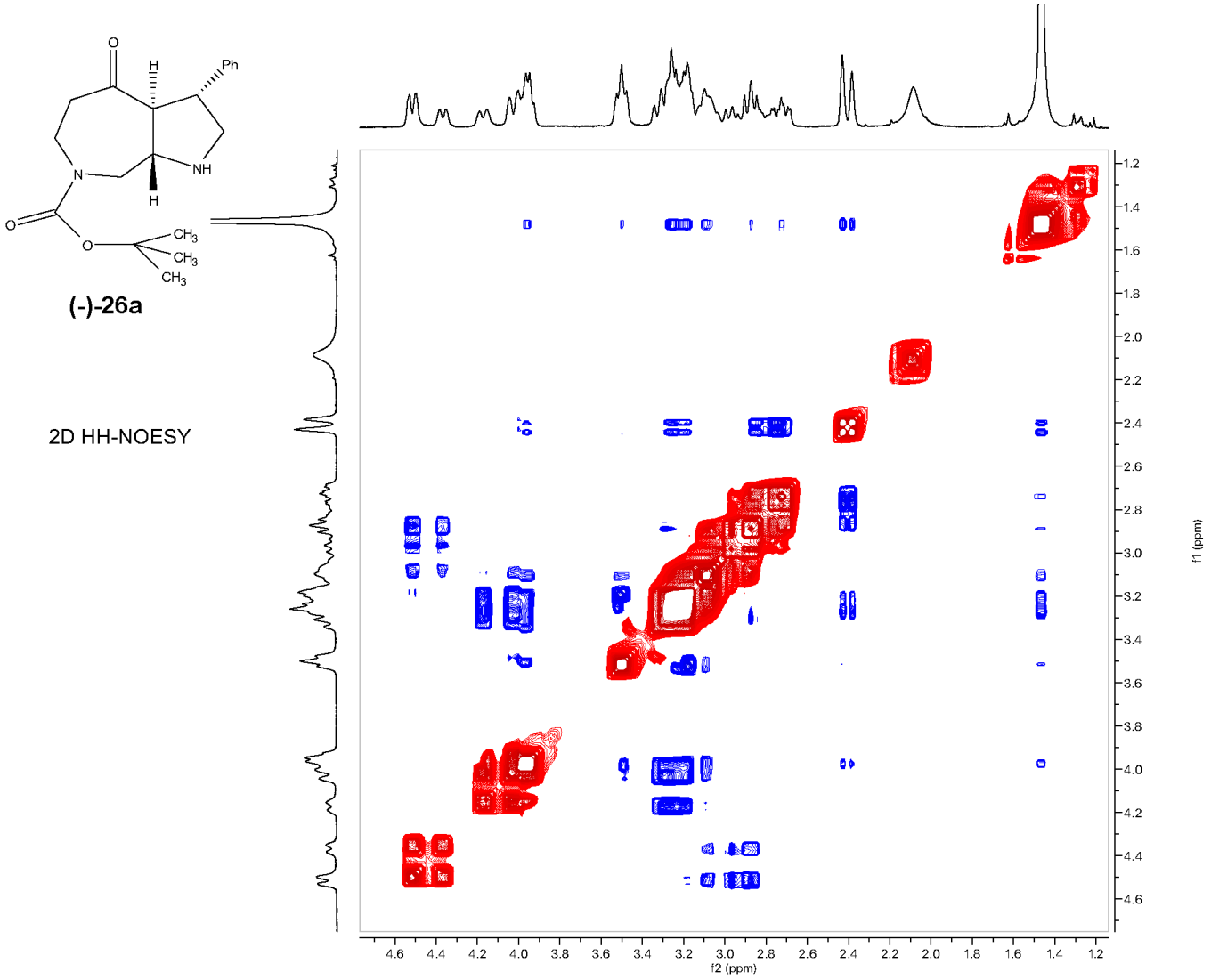
(3*R*,3a*S*,8a*S*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((-)-26a). ^{13}C NMR ($CDCl_3$, 100 MHz)



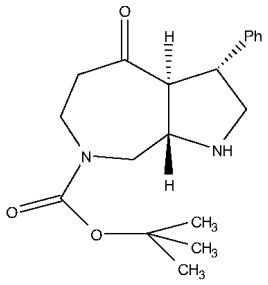
(3*R*,3a*S*,8a*S*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((-)-26a). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms).



(3*R*,3a*S*,8a*S*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((-)-26a). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms).

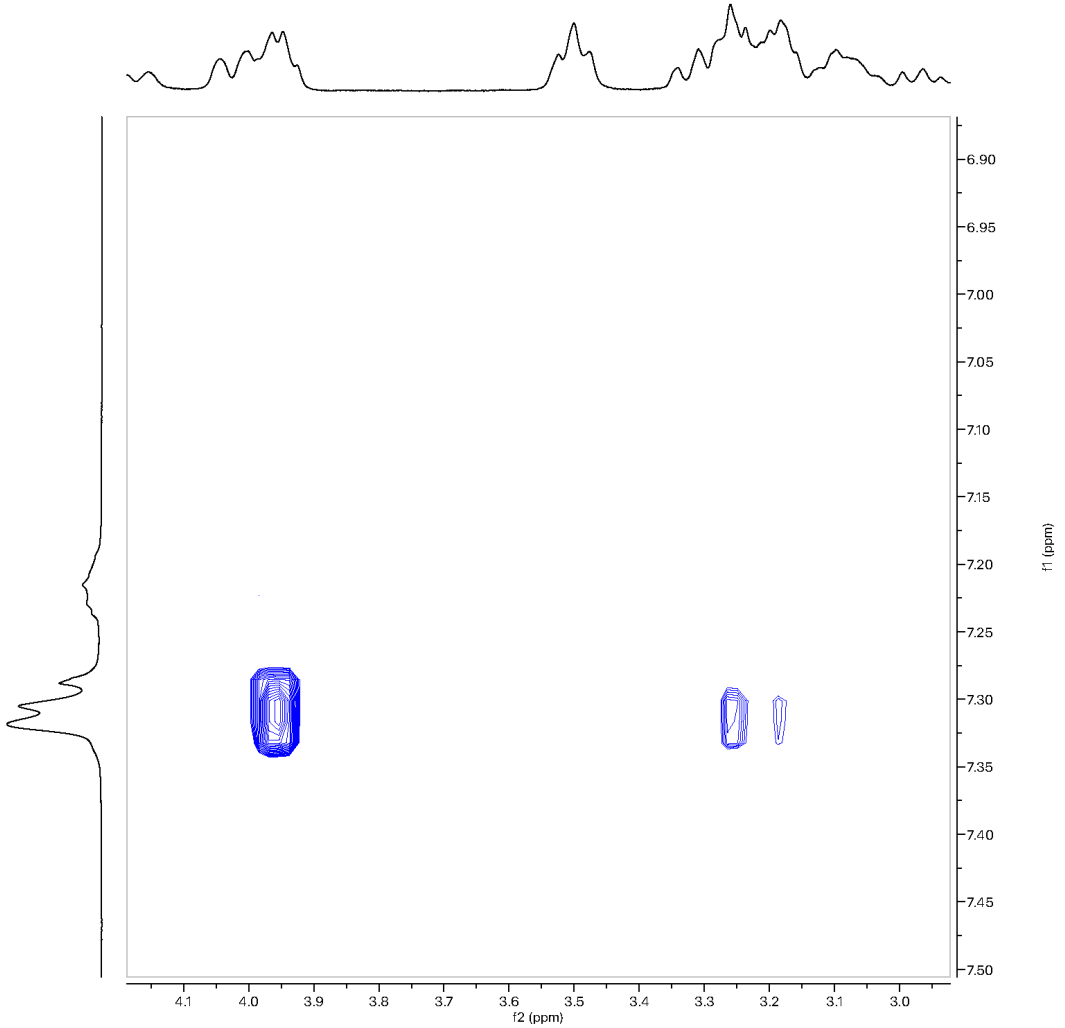


(3*R*,3a*S*,8a*S*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((-)-26a). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms)

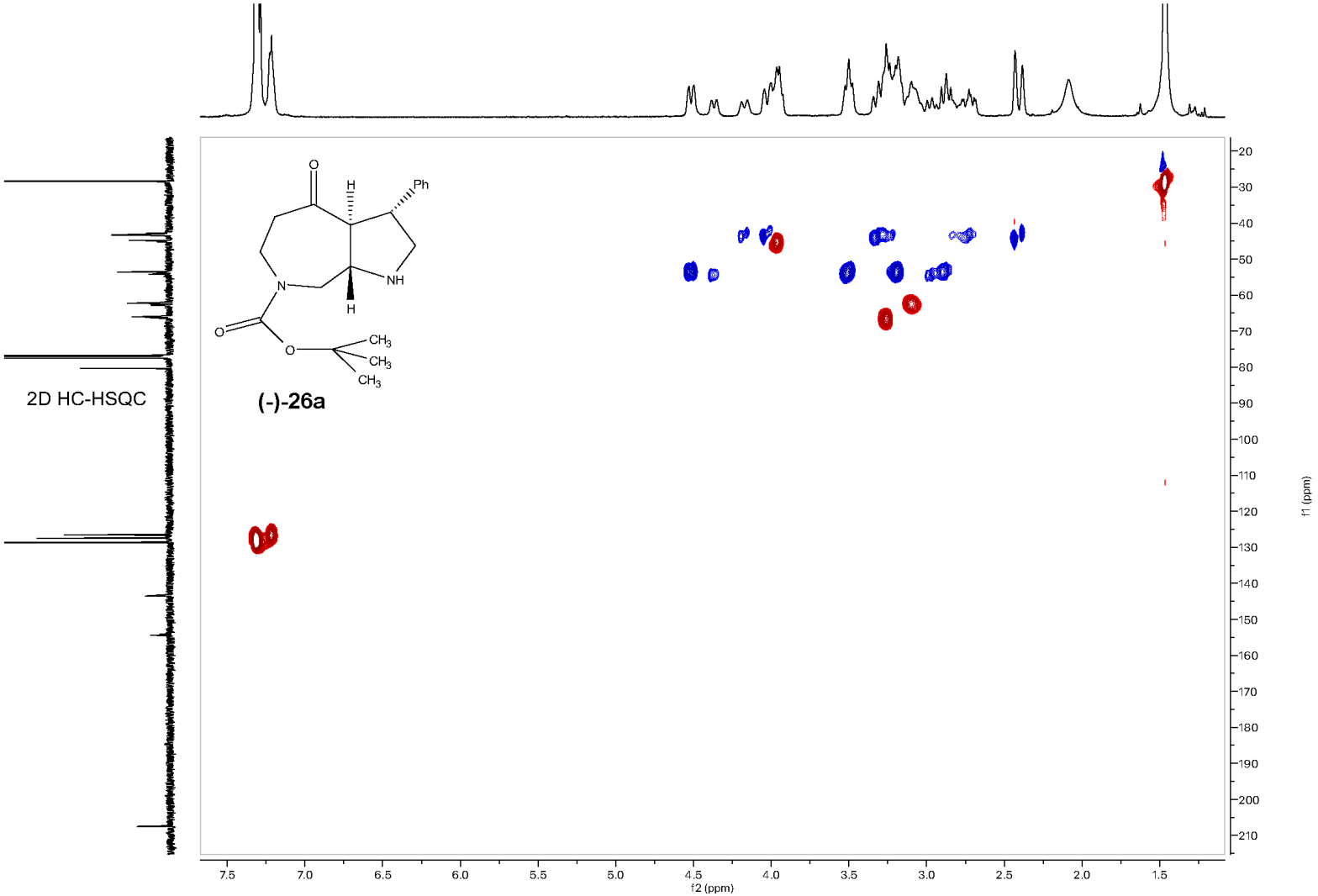


(-)-26a

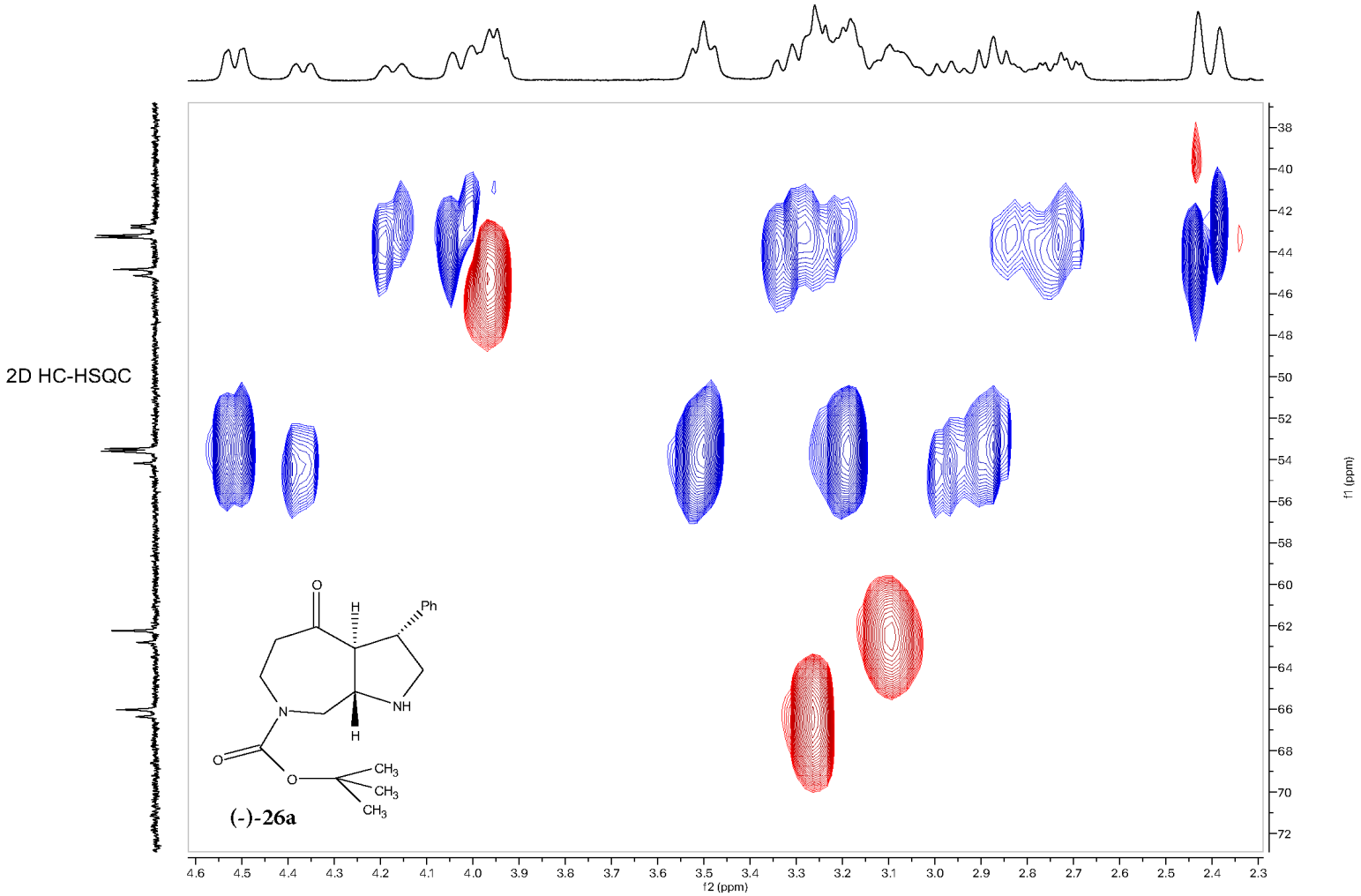
2D HH-NOESY



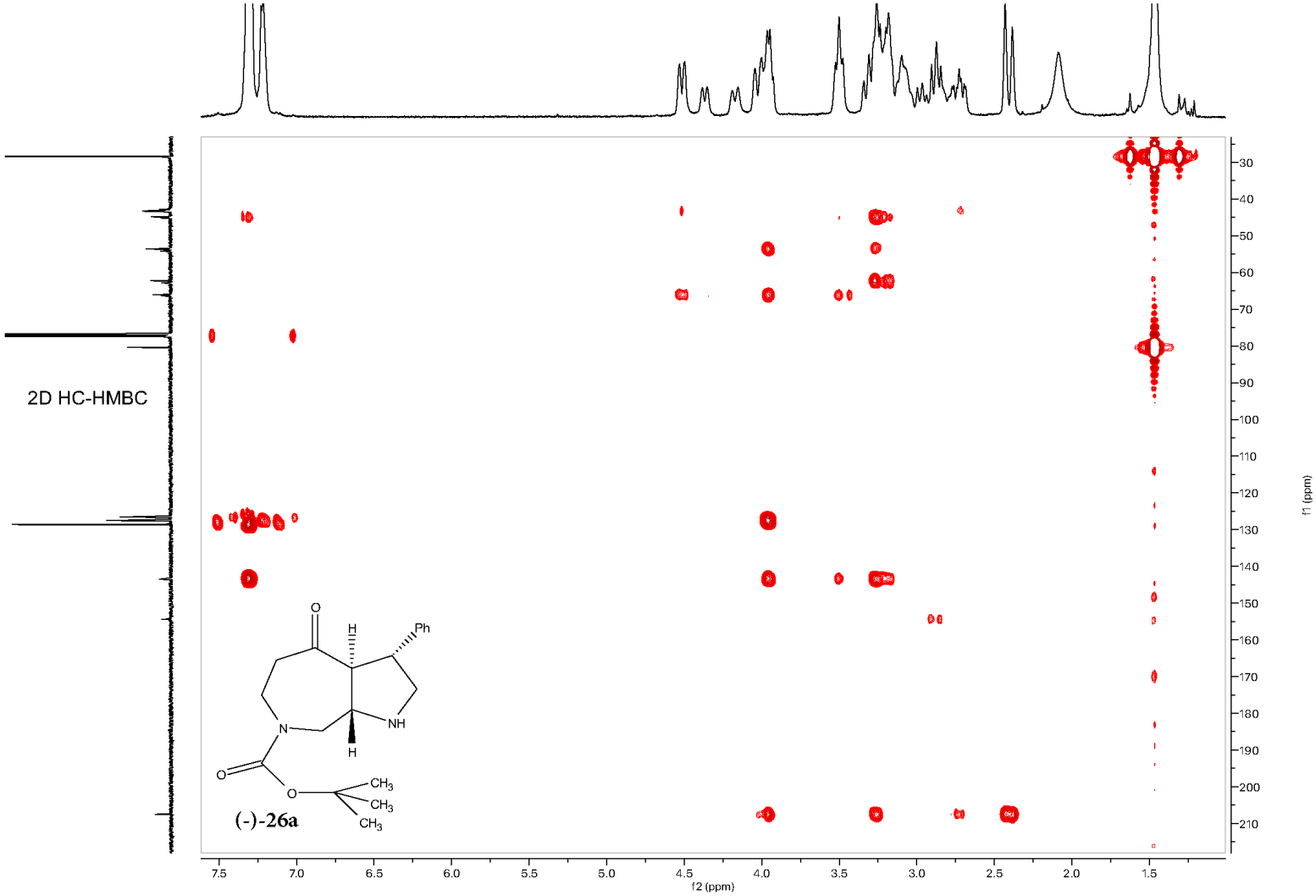
(3*R*,3a*S*,8a*S*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((-)-26a). 2D ^{1}H-^{13}C-HSQC (qphase sensitive J1 (HC)=145Hz).



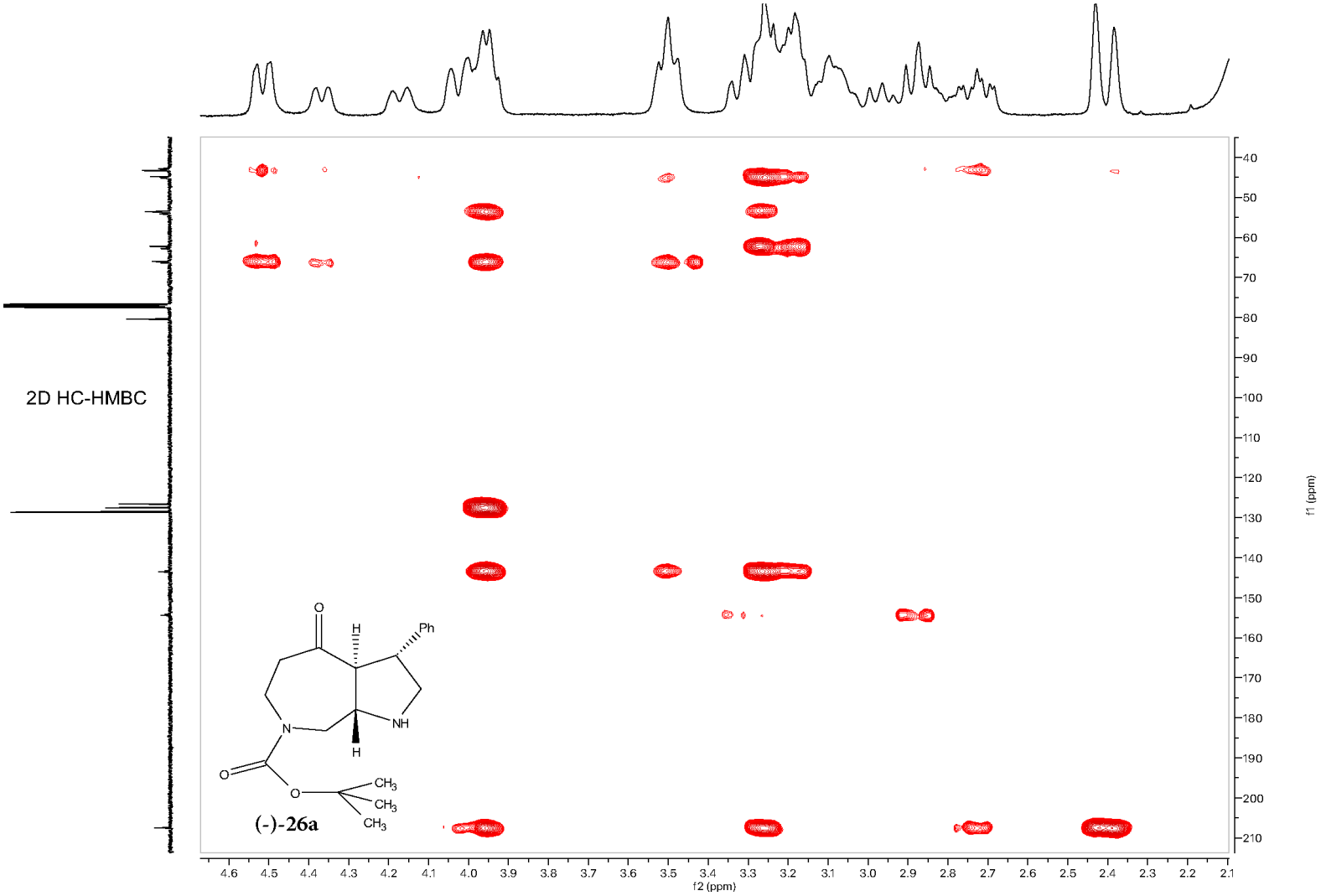
(3*R*,3a*S*,8a*S*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((-)-26a). 2D ^{1}H-^{13}C-HSQC (qphase sensitive J1 (HC)=145Hz).



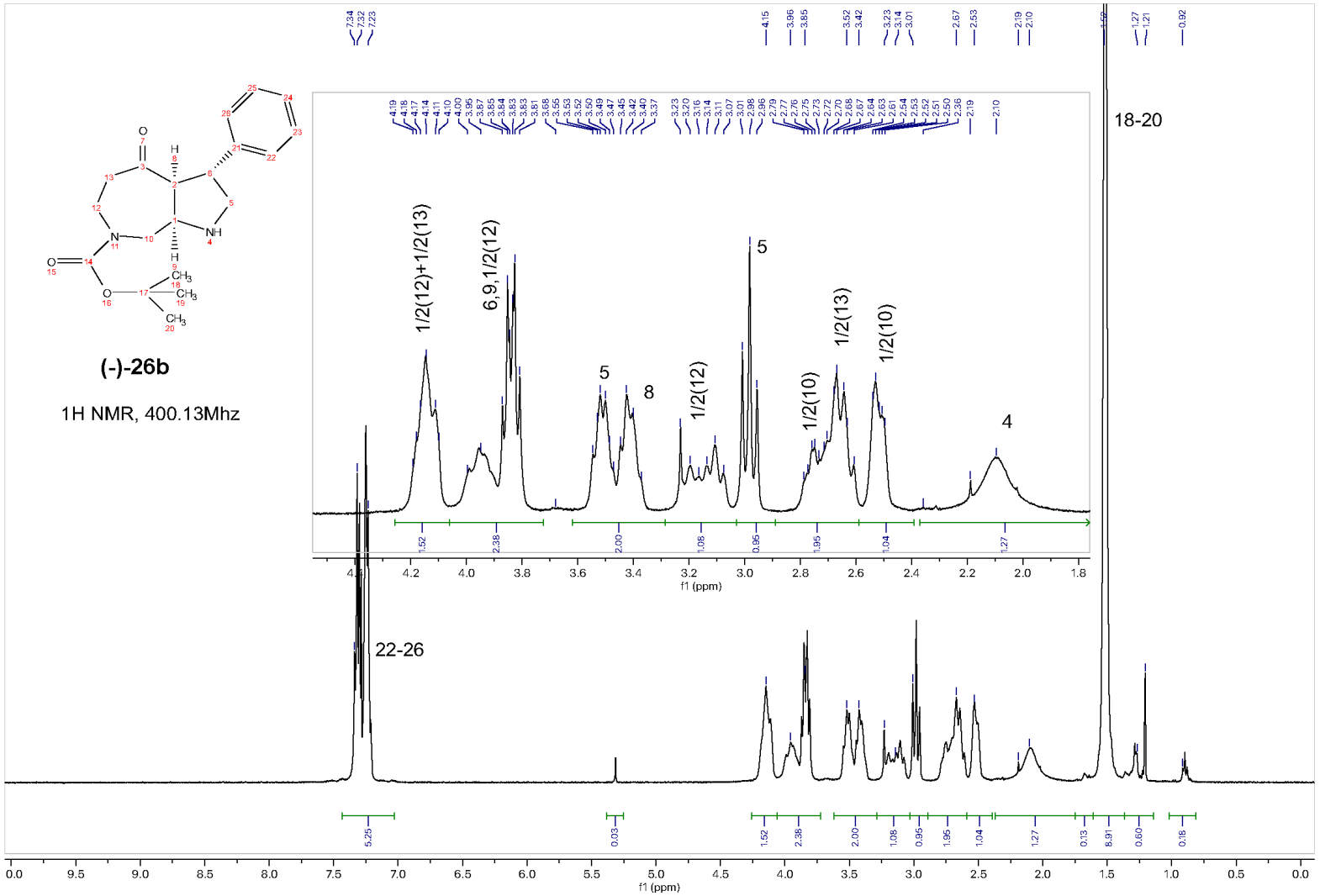
(3*R*,3a*S*,8a*S*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((-)-26a).). 2D ^{1}H-^{13}C-HMBC (longrange, J1(HC)=145Hz, J2(HC-long)=10Hz).



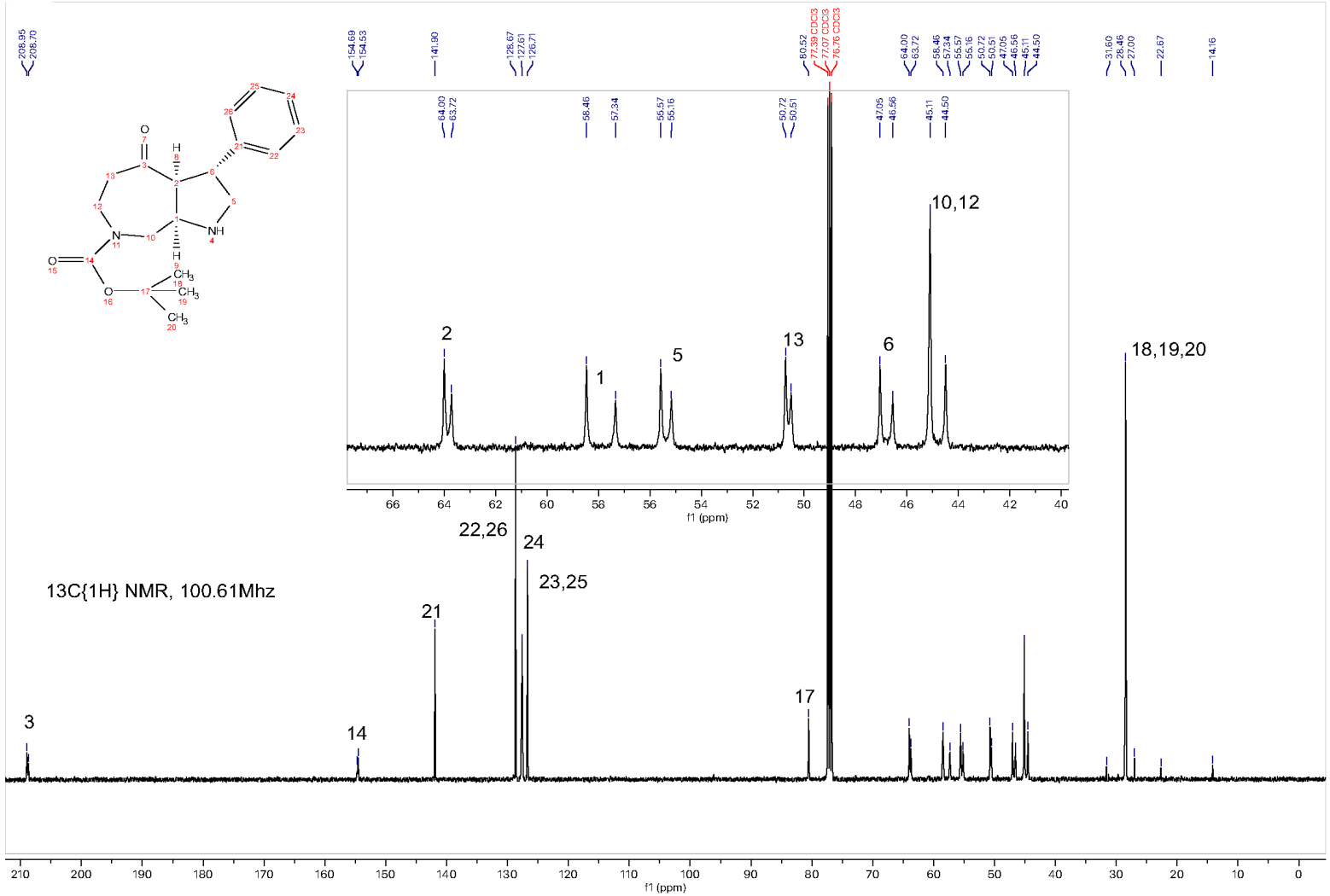
(3*R*,3a*S*,8a*S*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((-)-26a).). 2D ^{1}H-^{13}C-HMBC (longrange, J1(HC)=145Hz, J2(HC-long)=10Hz).



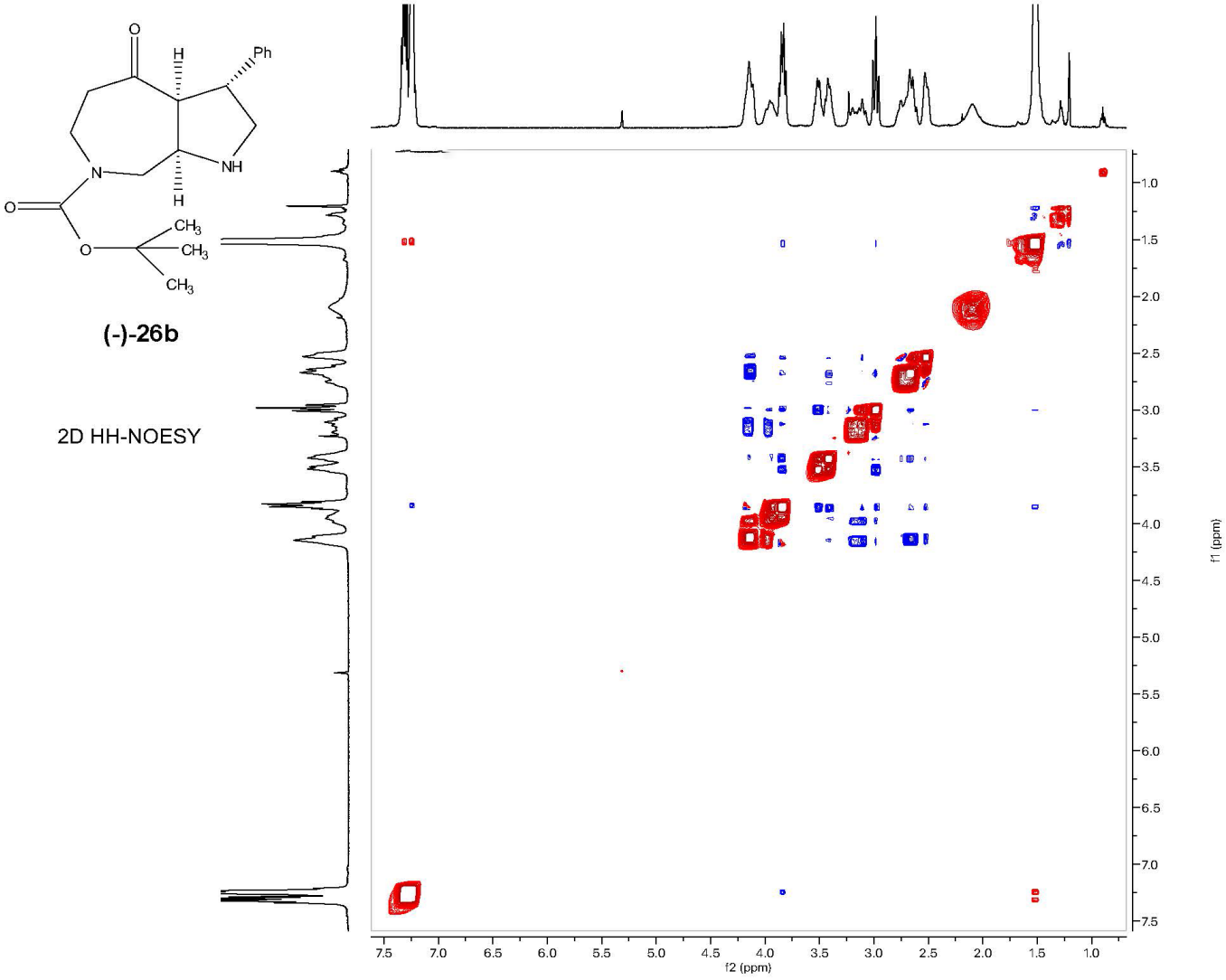
(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((-)-26b). ^{1}H NMR ($CDCl_3$, 400 MHz)



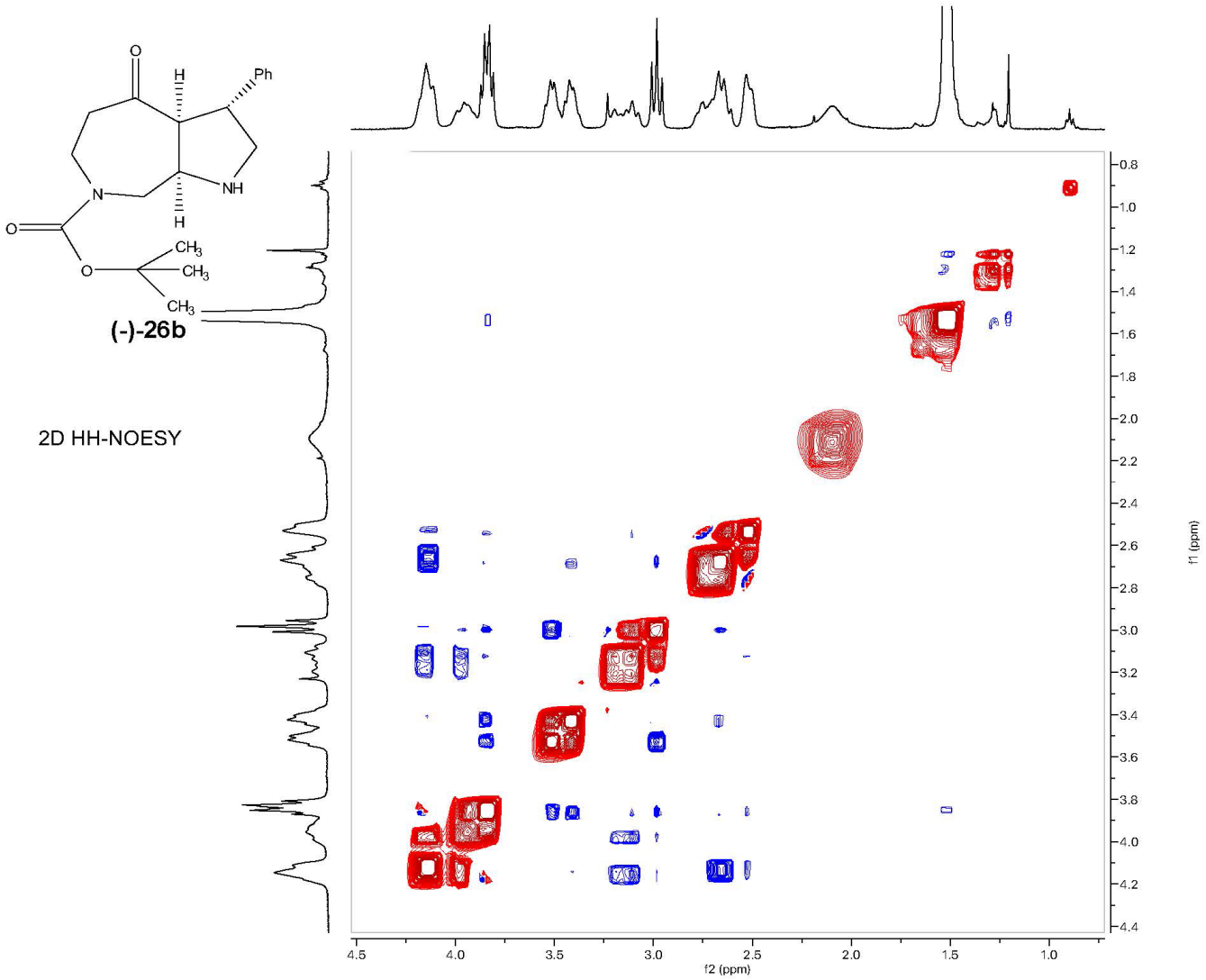
(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((-)-26b). ^{13}C NMR ($CDCl_3$, 100 MHz)



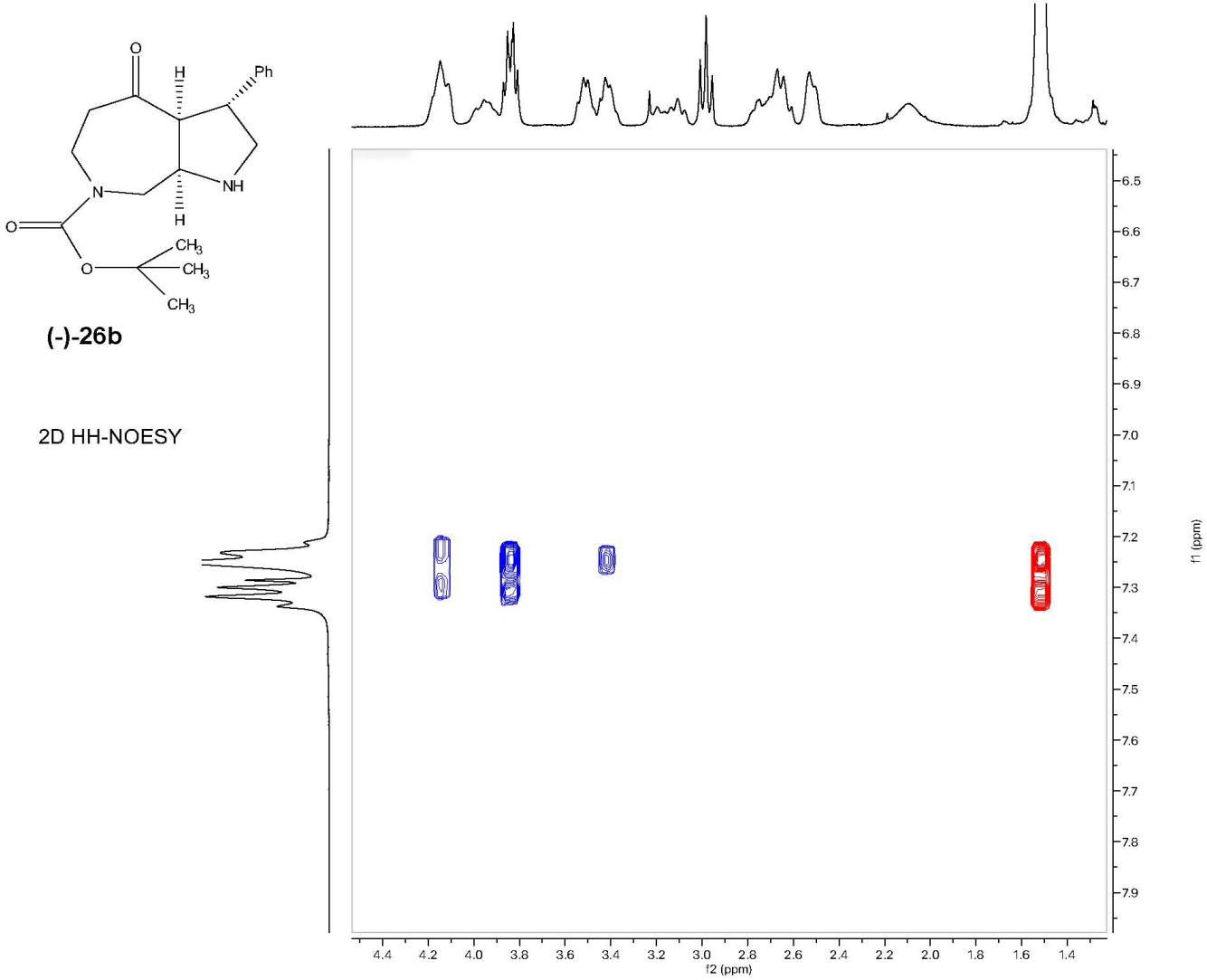
(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((-)-26b). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms).



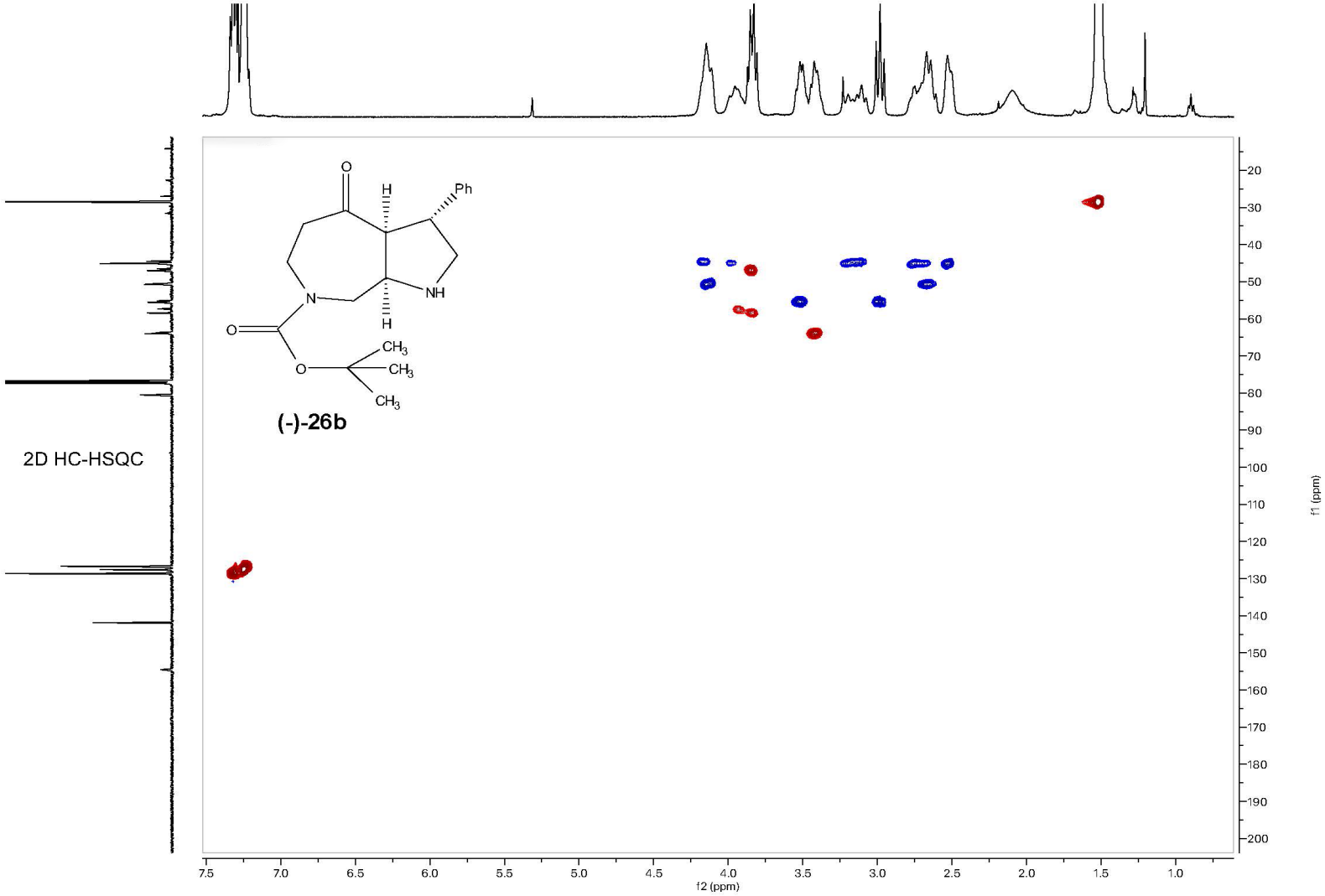
(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((-)-26b). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms).



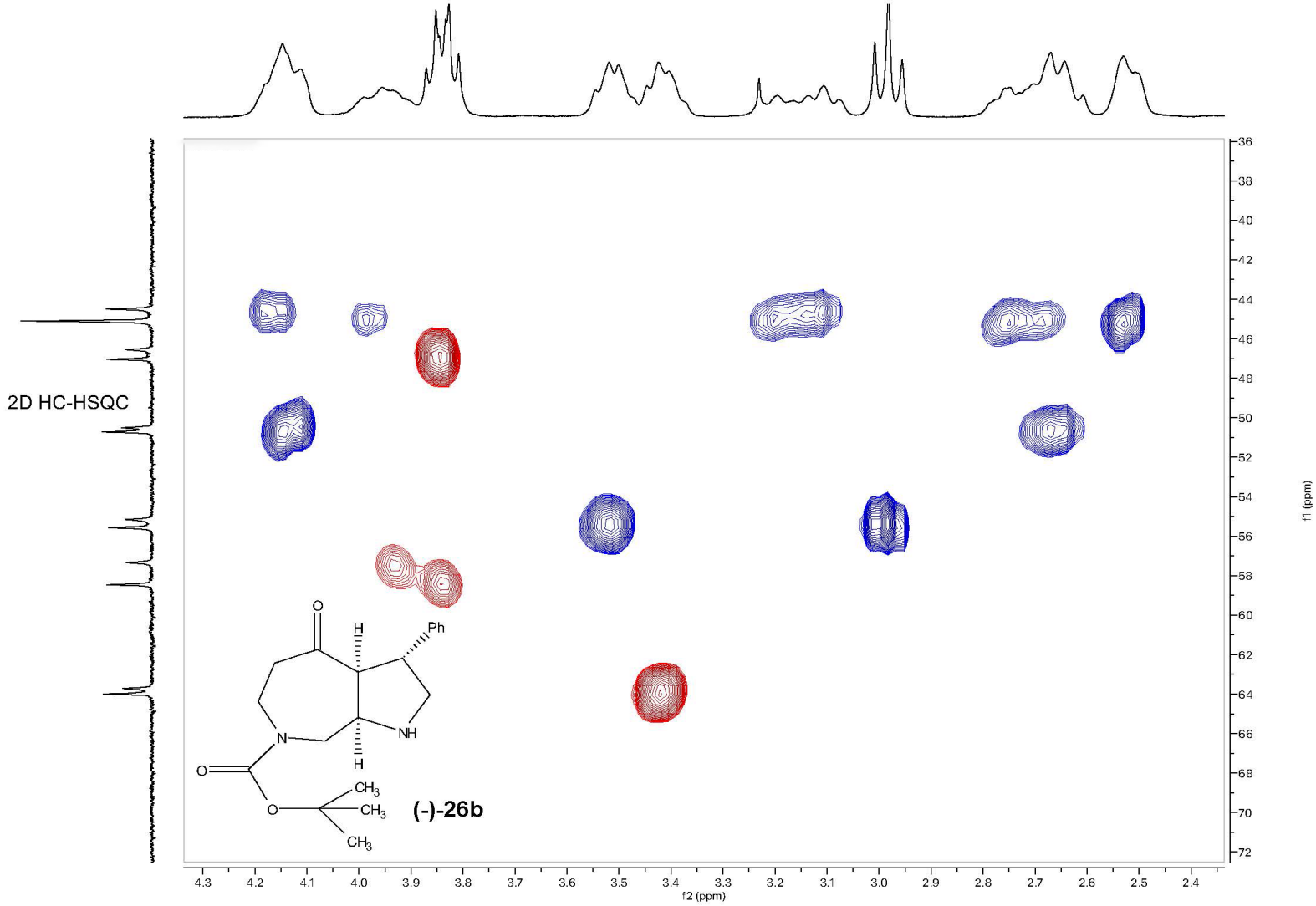
(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((-)-26b). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms).



(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((-)-26b). 2D ^{1}H-^{13}C-HSQC (qphase sensitive J1 (HC)=145Hz).



(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((-)-26b). 2D ^{1}H-^{13}C-HSQC (qphase sensitive J1 (HC)=145Hz).



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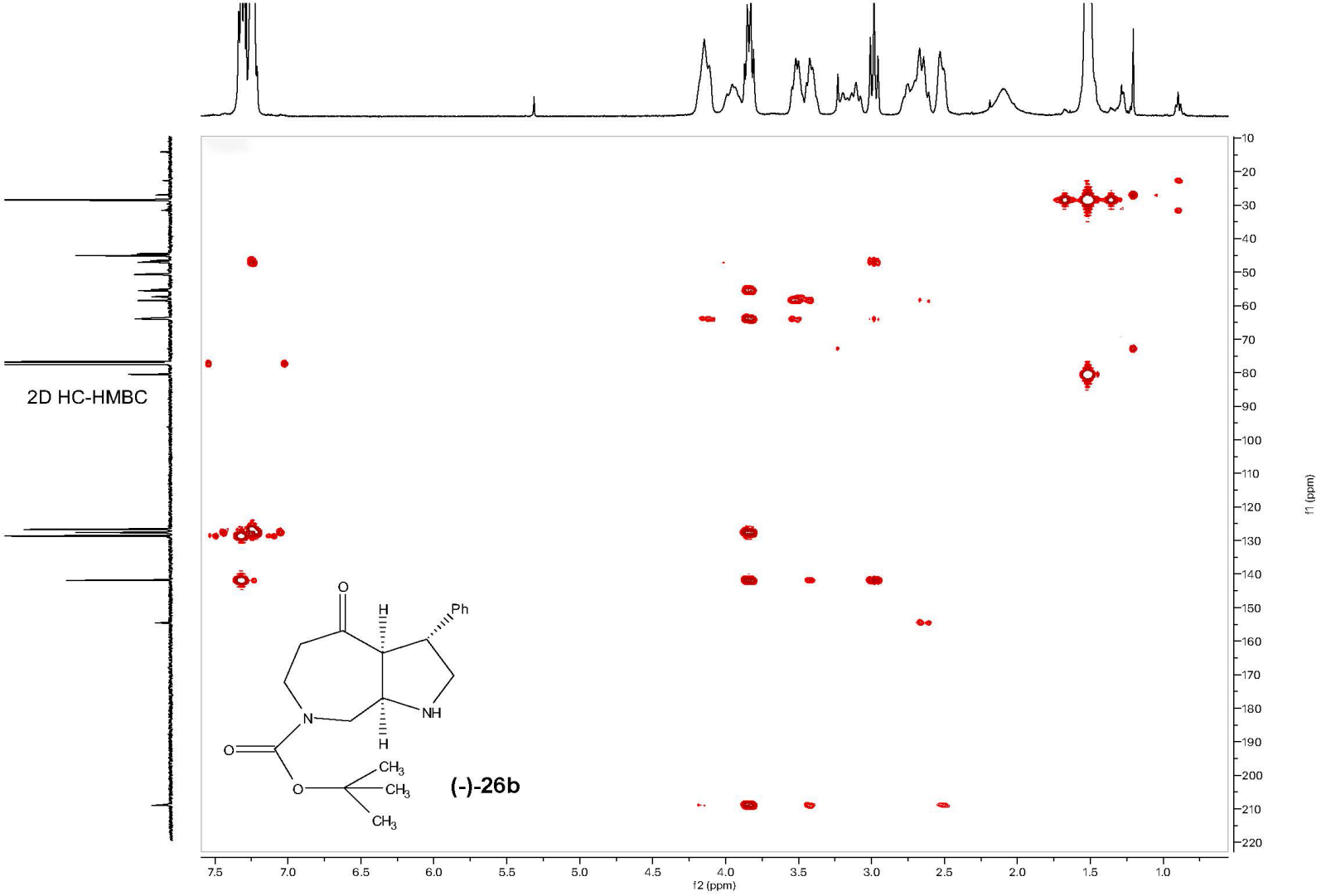

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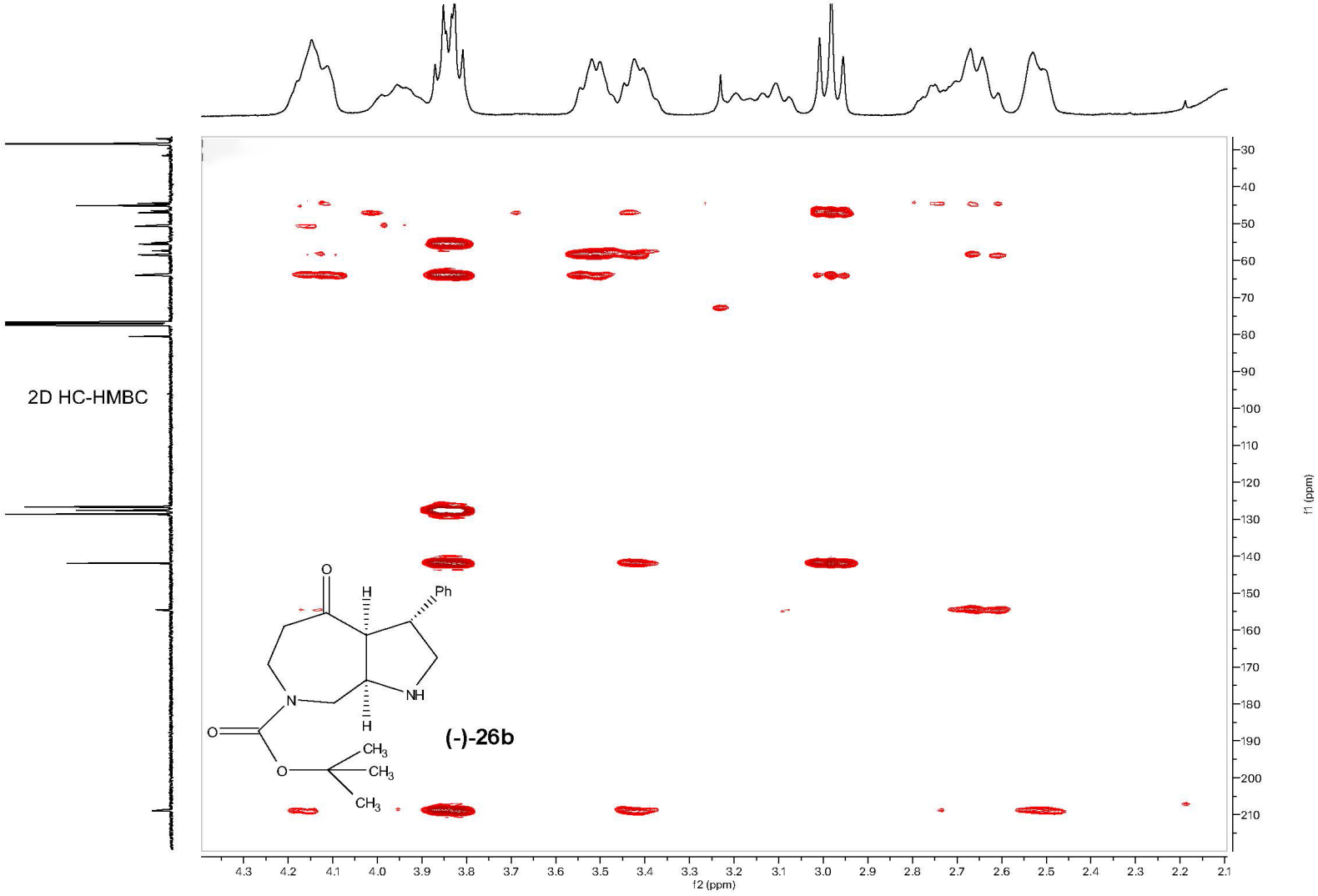
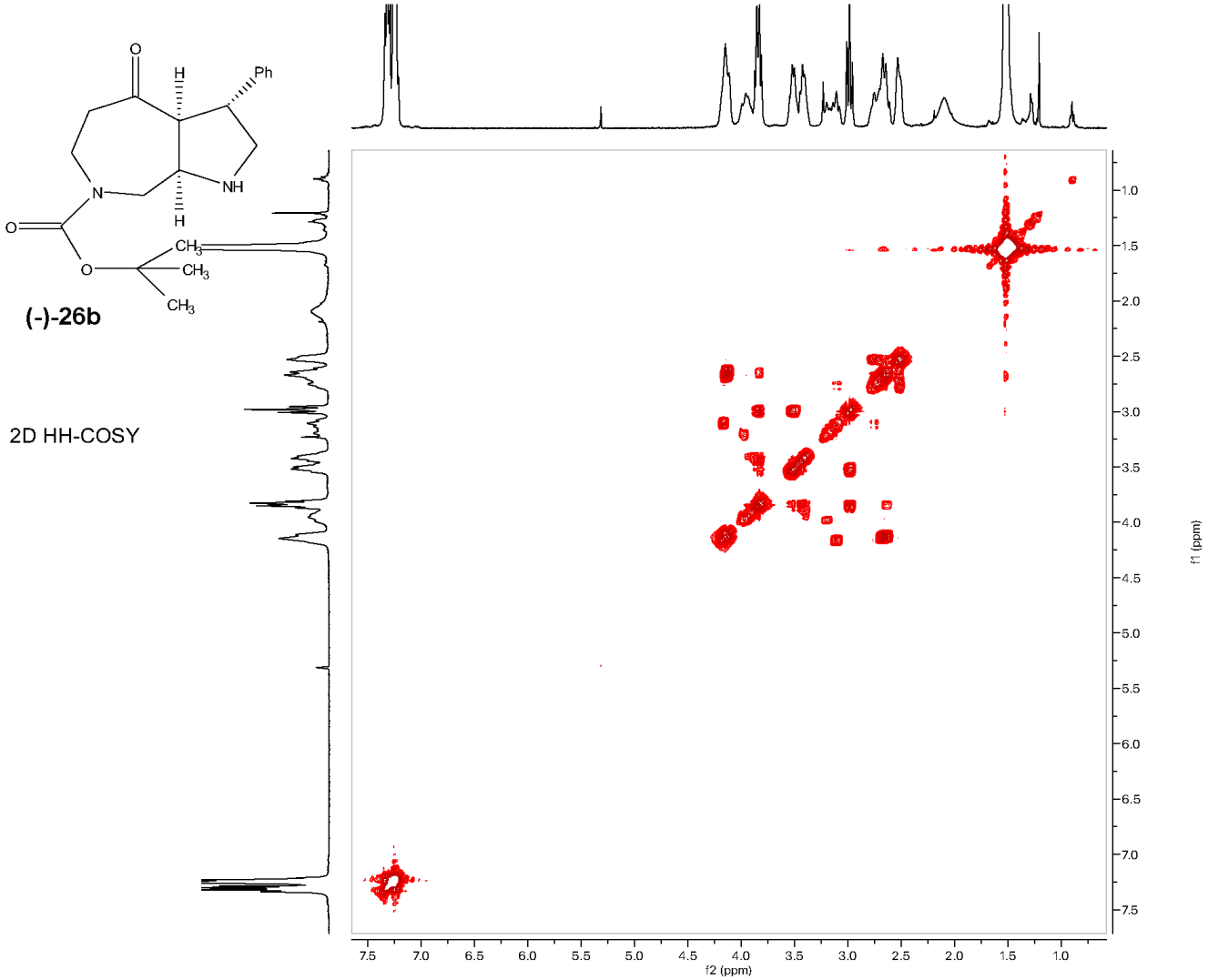
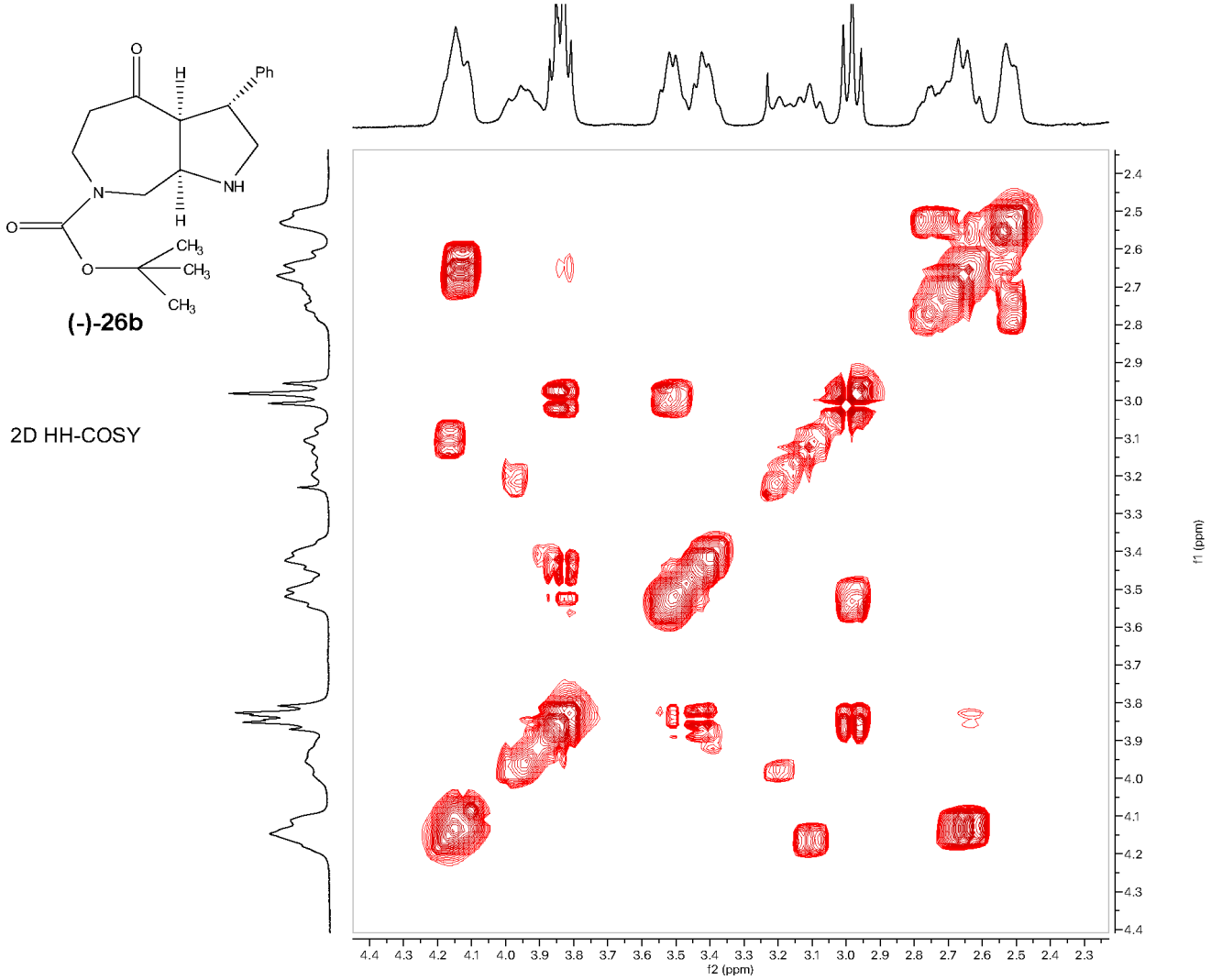


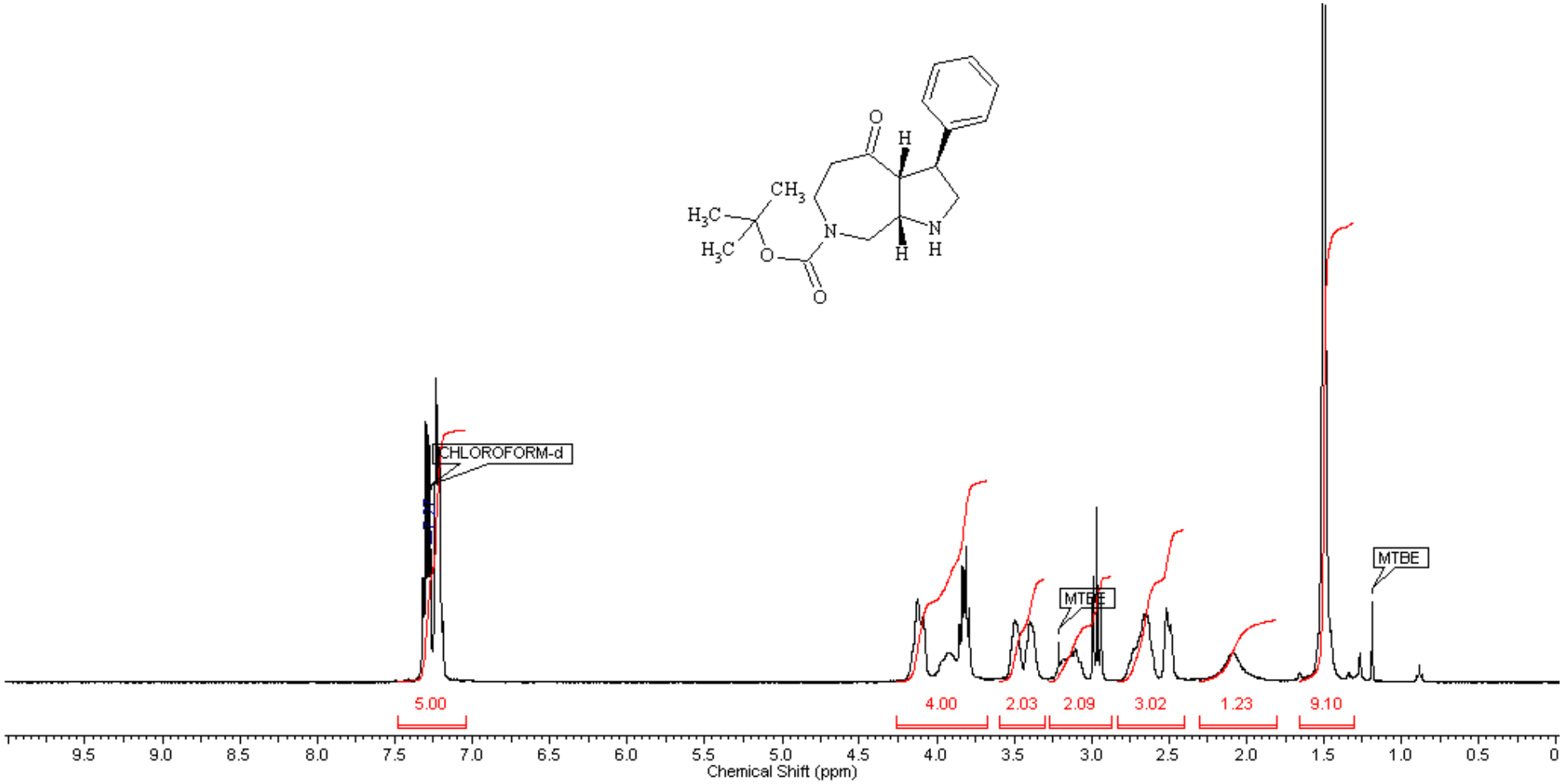
(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((-)-26b). 2D 1H-1H-COSY.



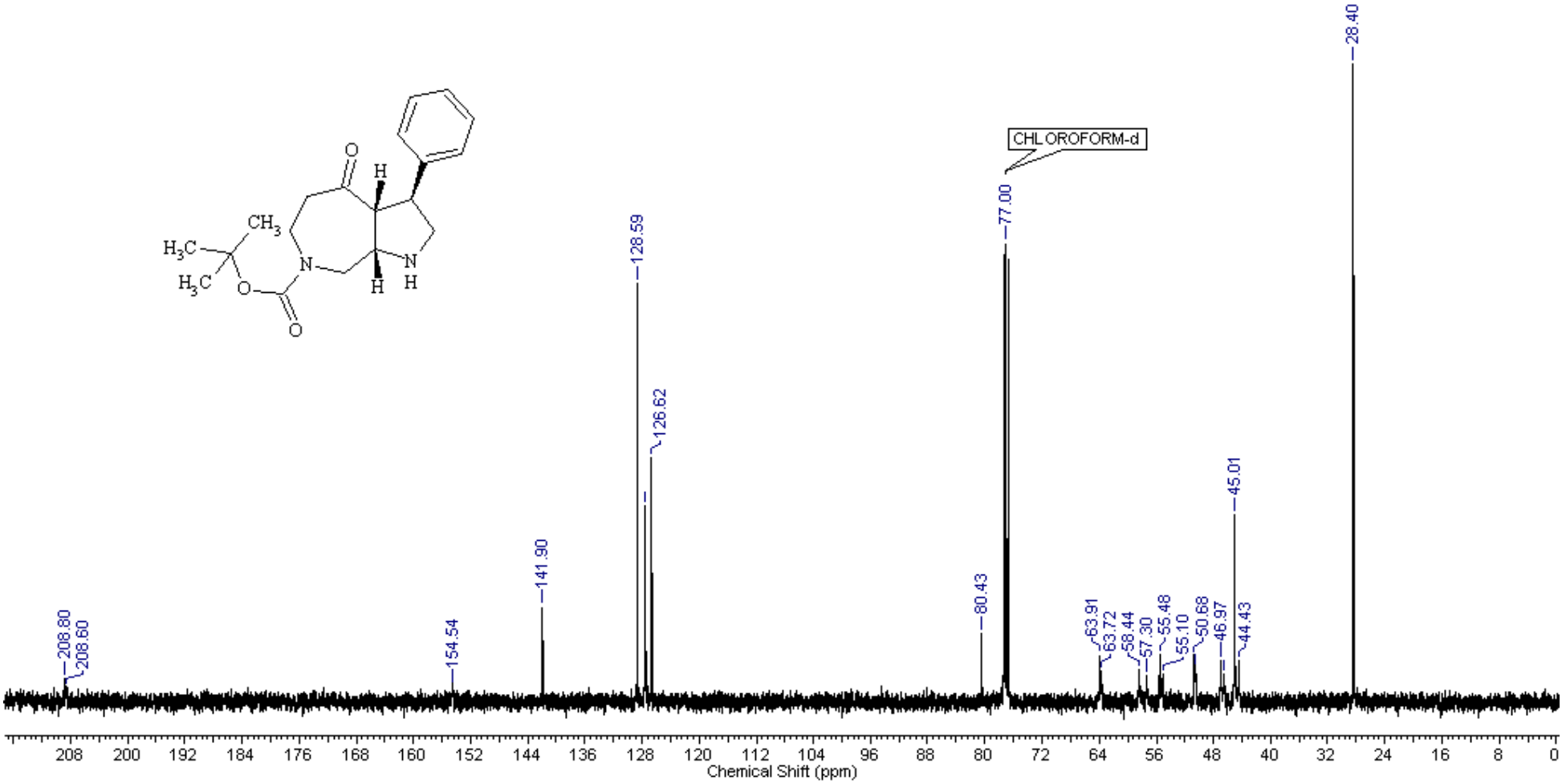
(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((-)-26b). 2D 1H-1H-COSY.



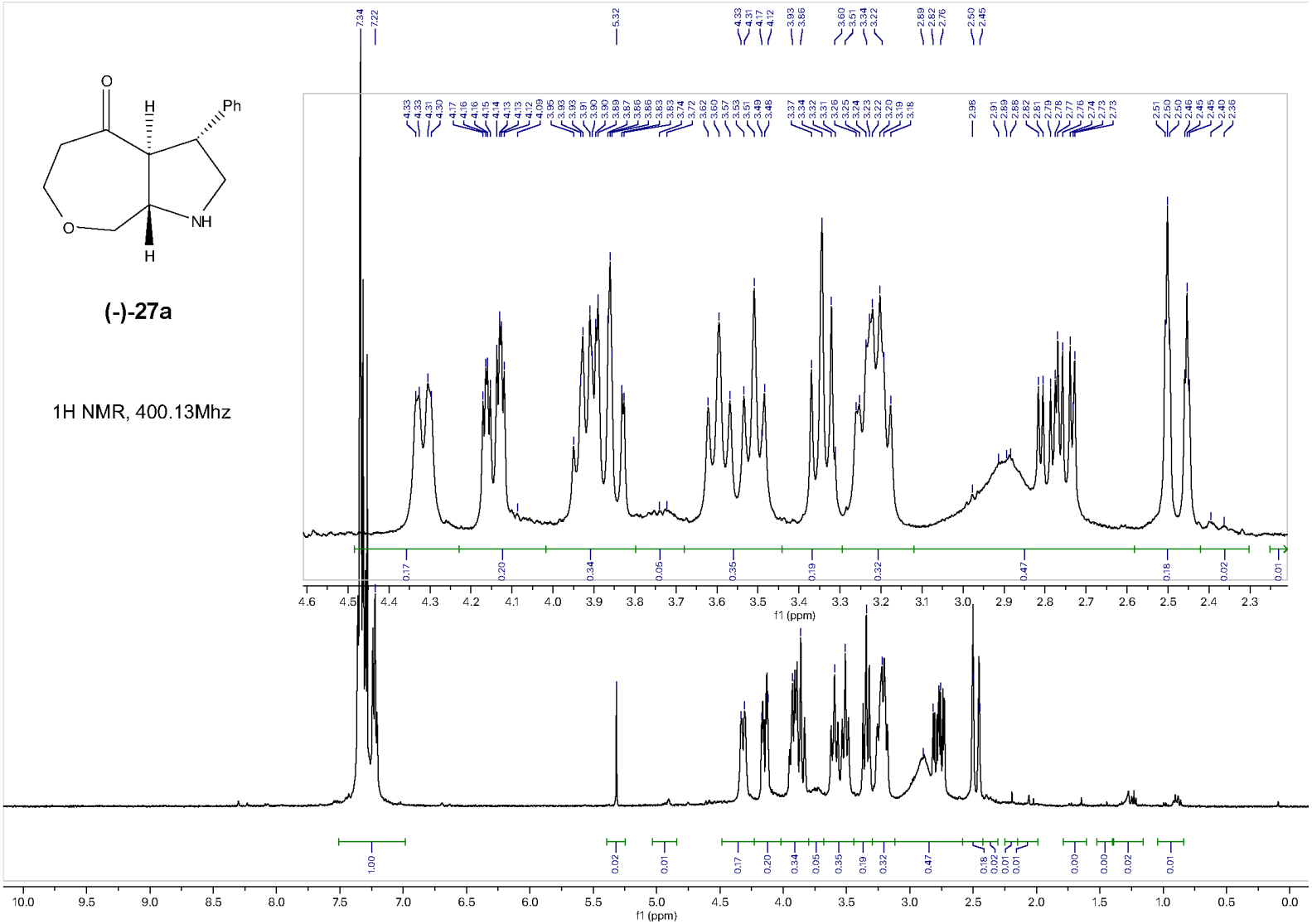
(3*S*,3a*R*,8a*S*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((+)-26b). ^{1}H NMR ($CDCl_3$, 400 MHz)



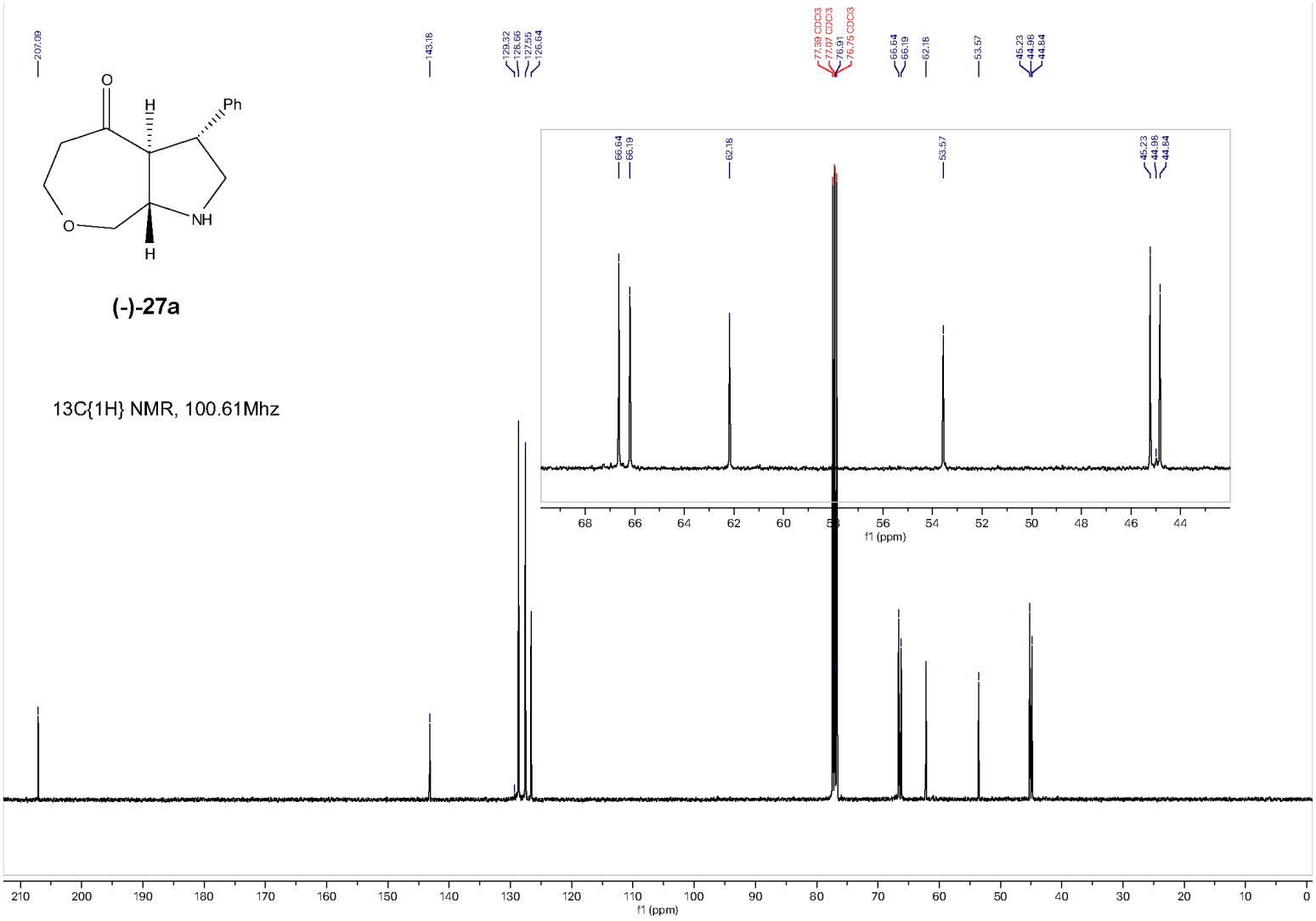
(3*S*,3a*R*,8a*S*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*c*]azepine-7(1*H*)-carboxylate ((+)-26b). ^{13}C NMR ($CDCl_3$, 100 MHz)



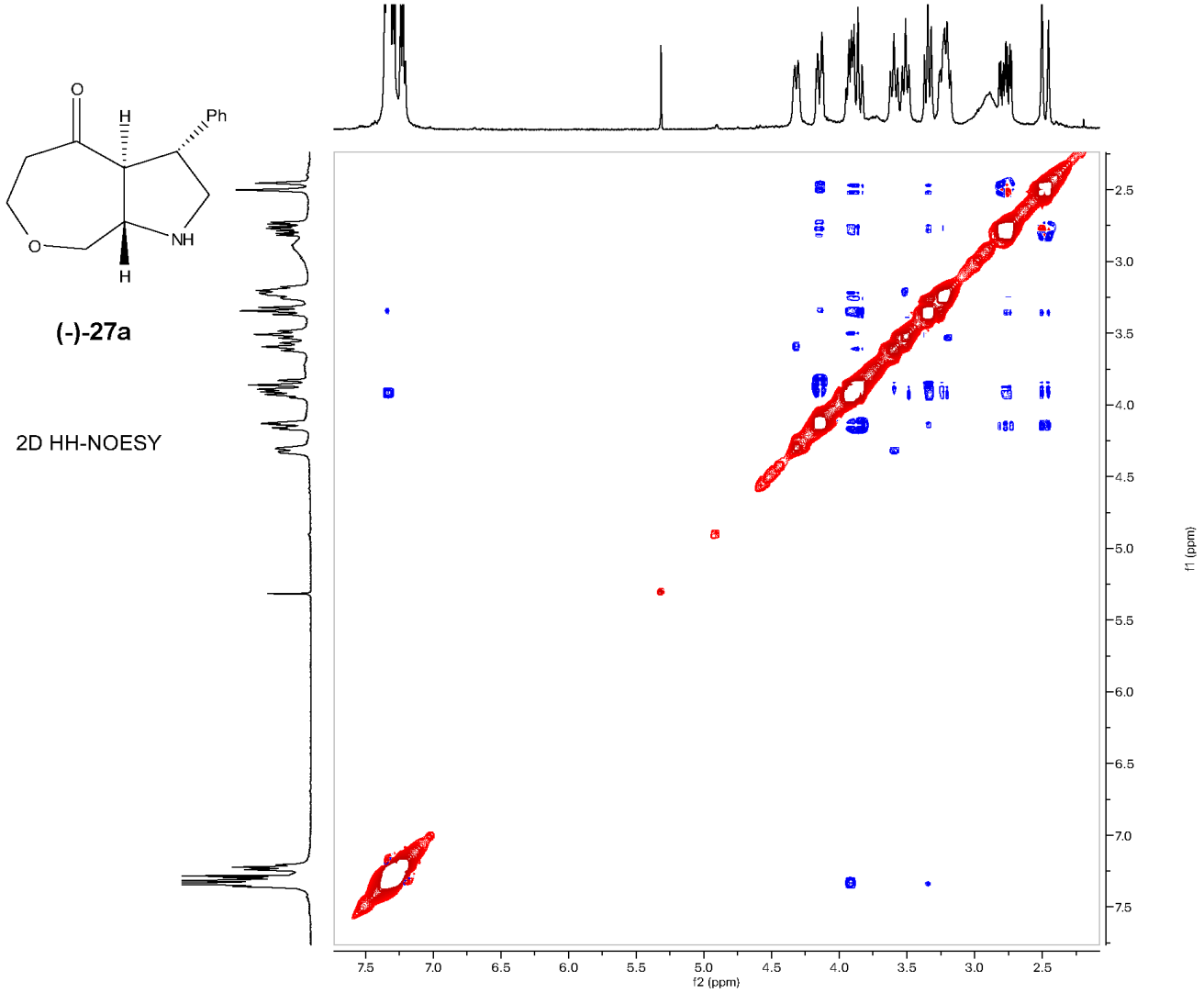
(3*R*,3a*S*,8a*S*)-3-phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one ((-)-27a). ^{1}H NMR ($CDCl_3$, 400 MHz).



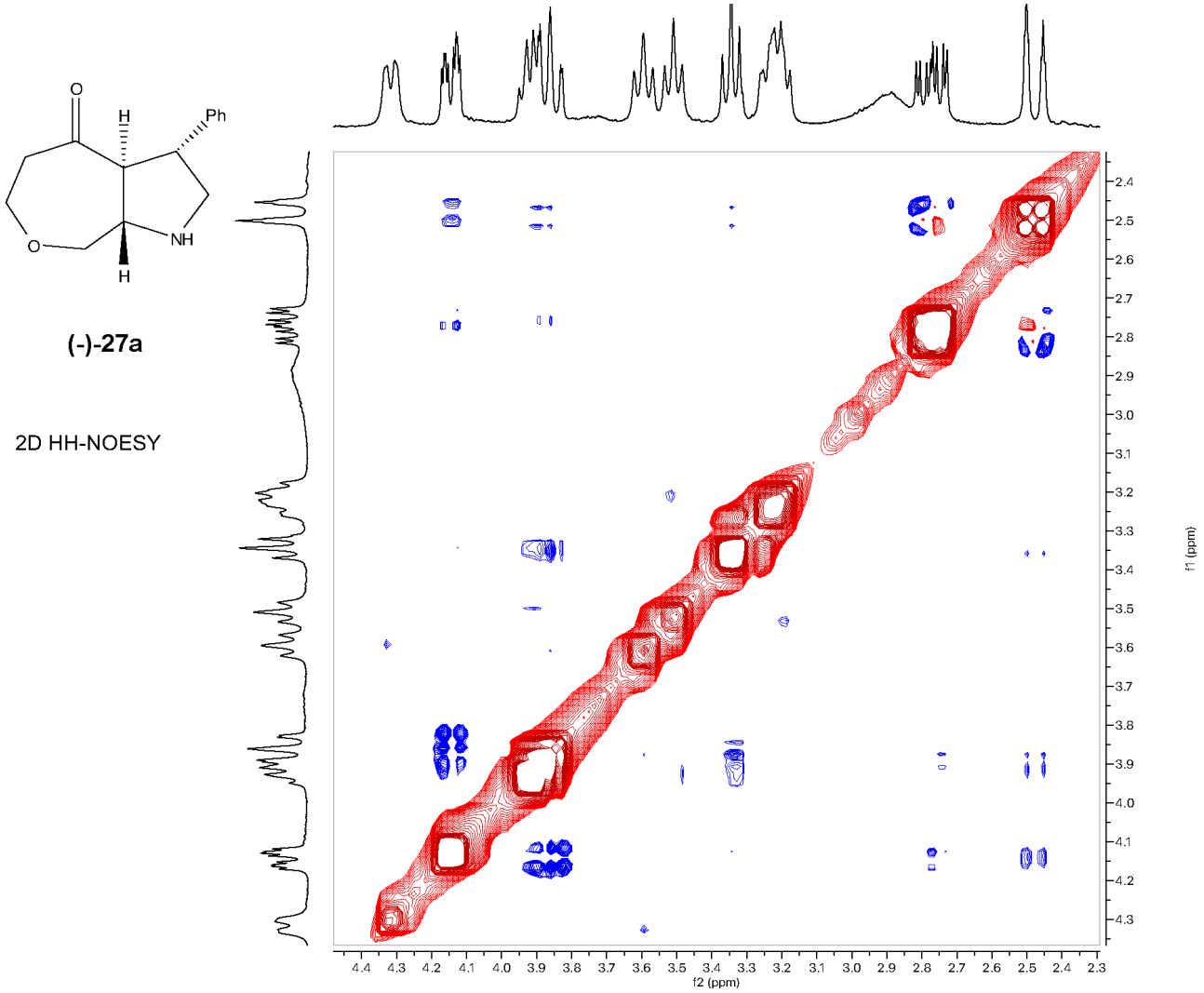
(3*R*,3a*S*,8a*S*)-3-phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one ((-)-27a). ^{13}C NMR ($CDCl_3$, 100 MHz).



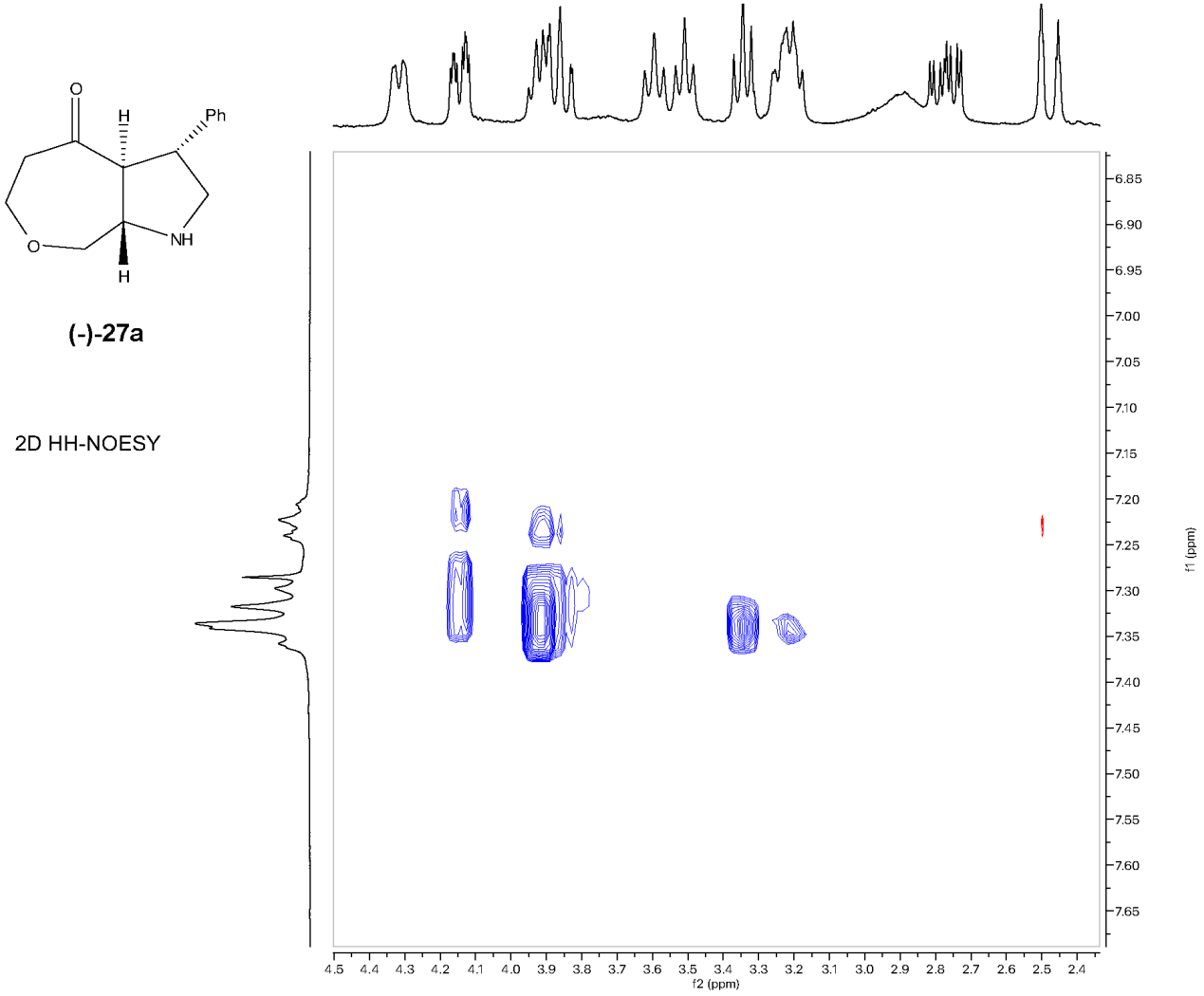
(3*R*,3a*S*,8a*S*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one ((-)-27a). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms)



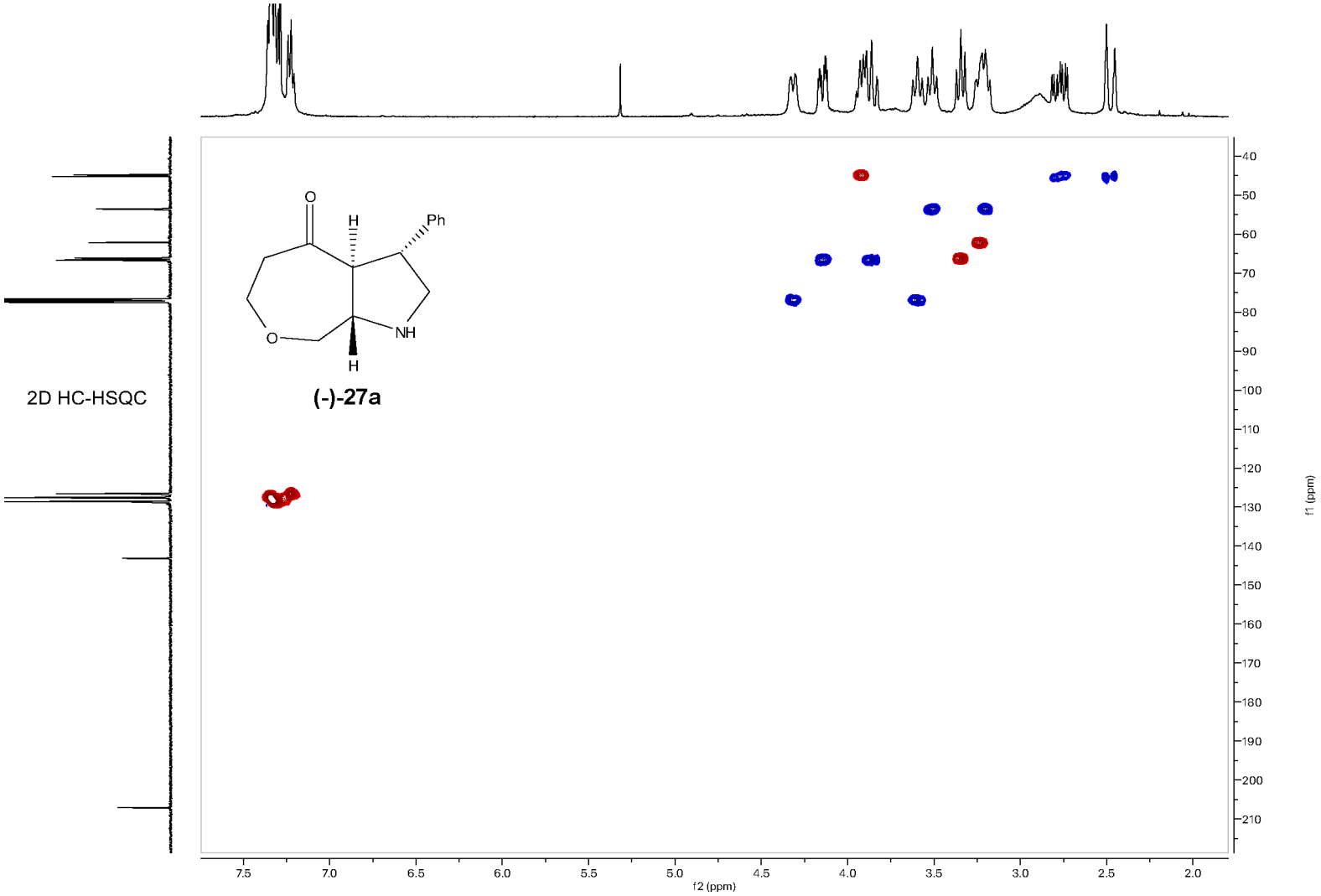
(3*R*,3a*S*,8a*S*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one ((-)-27a). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms)



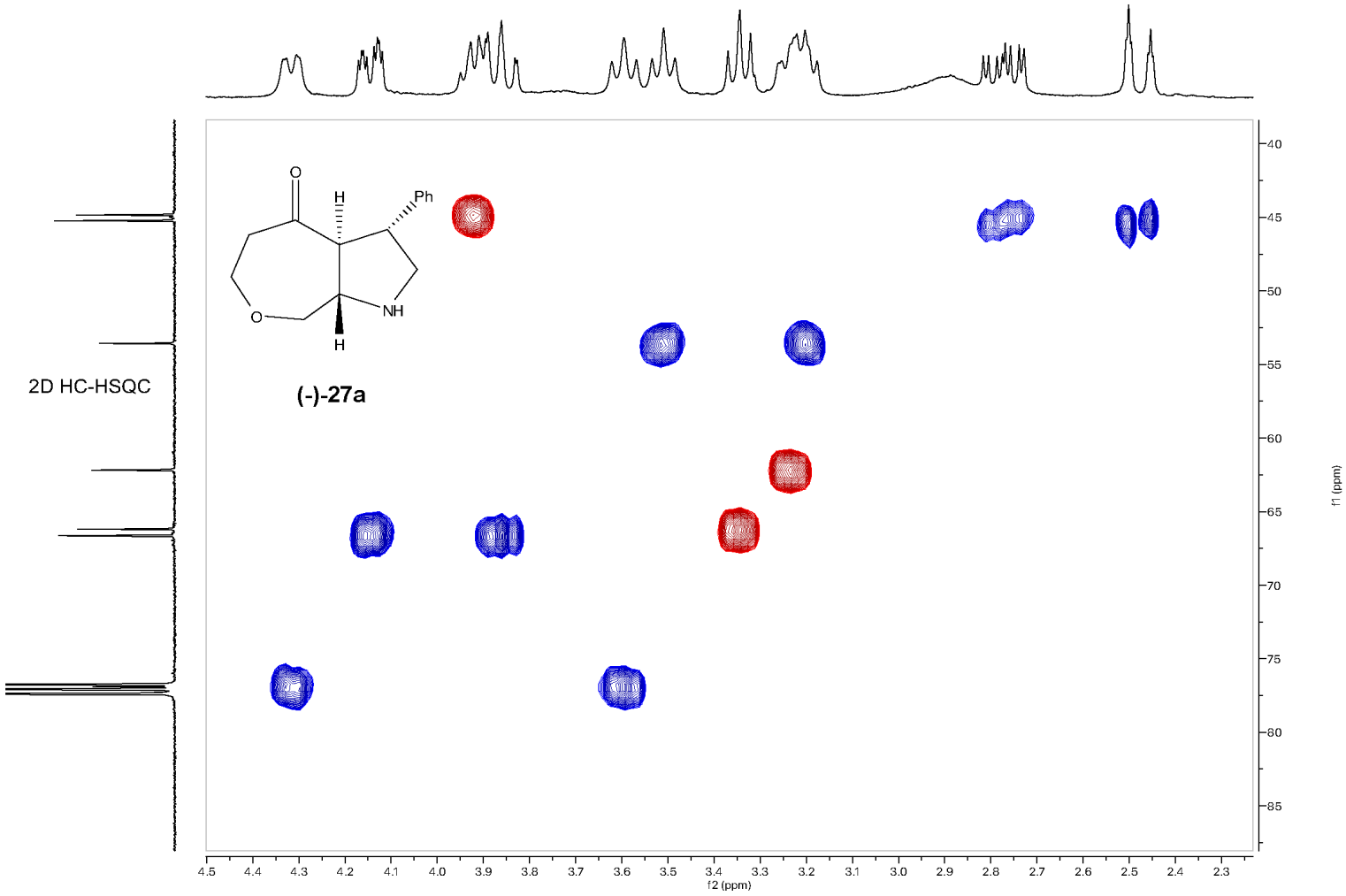
(3*R*,3a*S*,8a*S*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one ((-)-27a). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms)



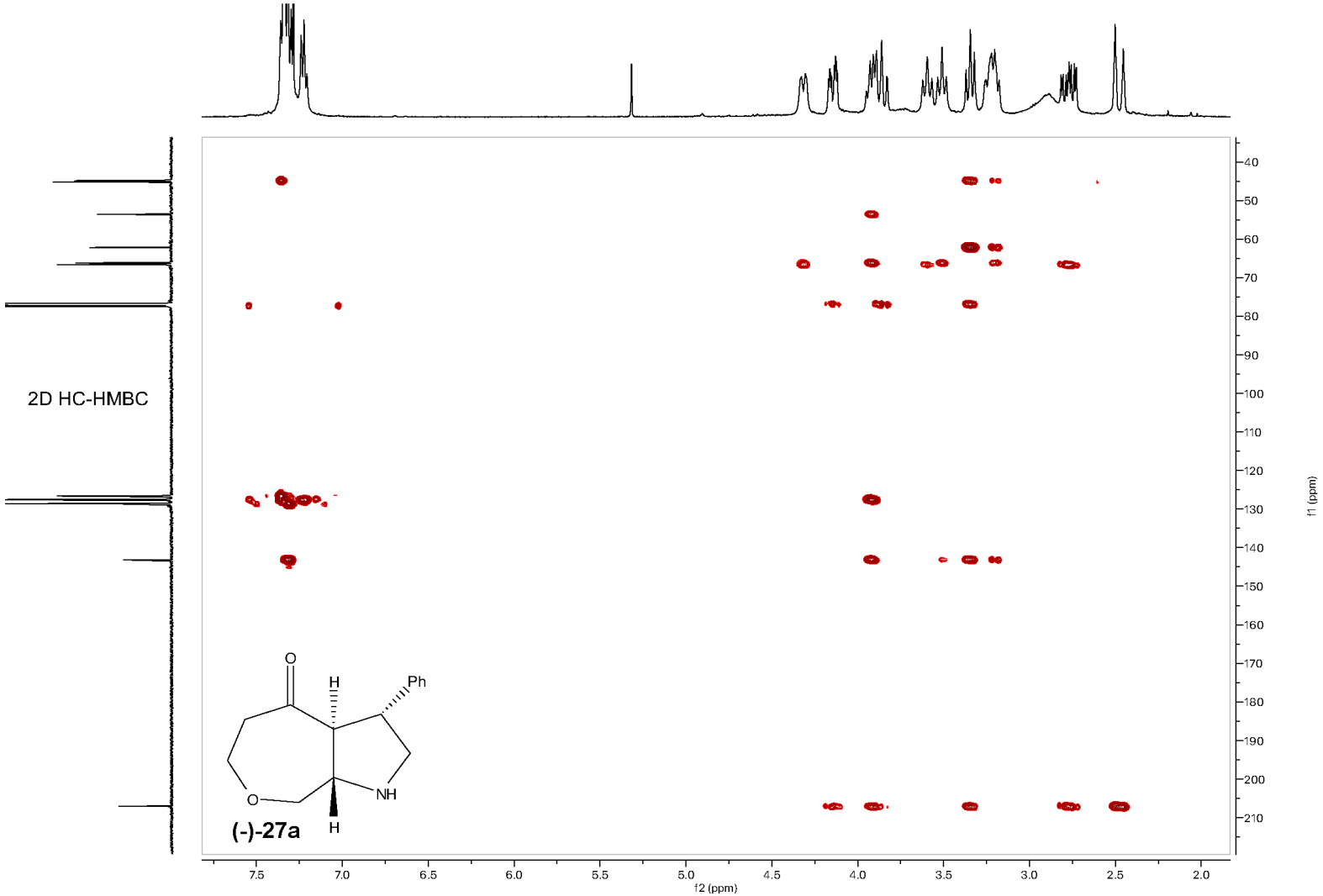
(3*R*,3a*S*,8a*S*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one ((-)-27a). 2D ^{1}H-^{13}C-HSQC (qphase sensitive J1 (HC)=145Hz)



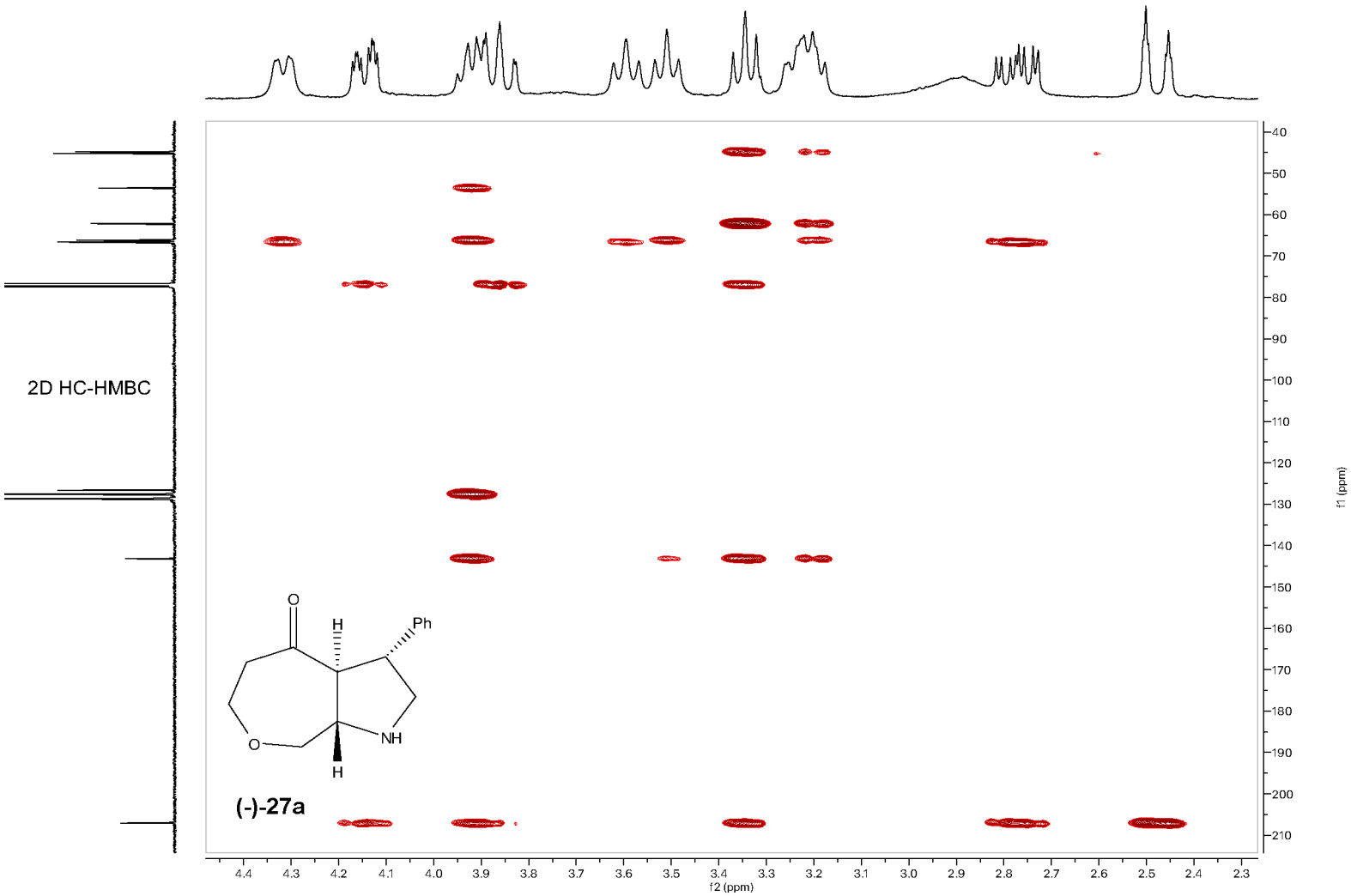
(3*R*,3a*S*,8a*S*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one ((-)-27a). 2D ^{1}H-^{13}C-HSQC (qphase sensitive J1 (HC)=145Hz)



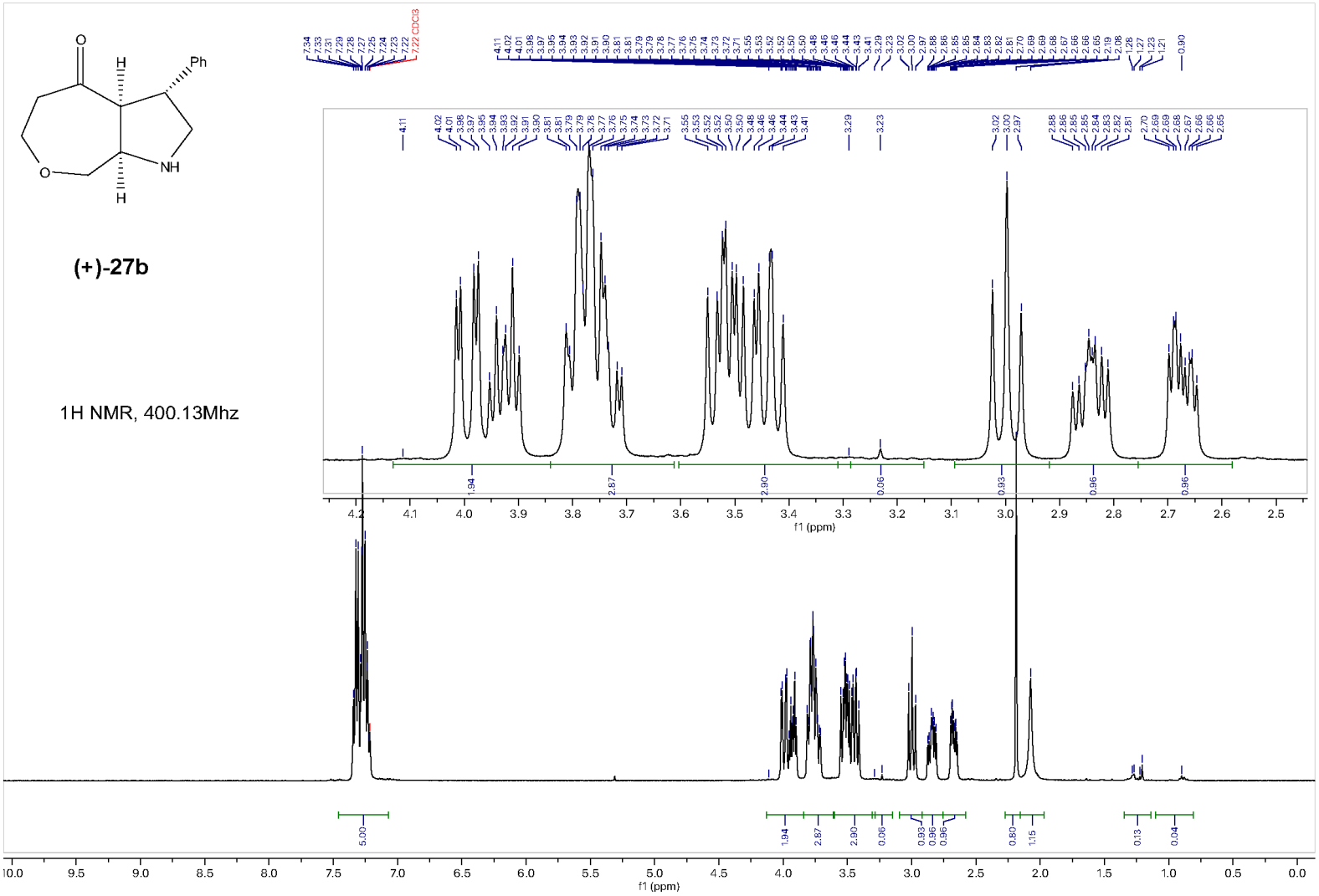
(3*R*,3a*S*,8a*S*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one ((-)-27a). 2D ^{1}H-^{13}C-HMBC (longrange, J1(HC)=145Hz, J2(HC-long)=10Hz)



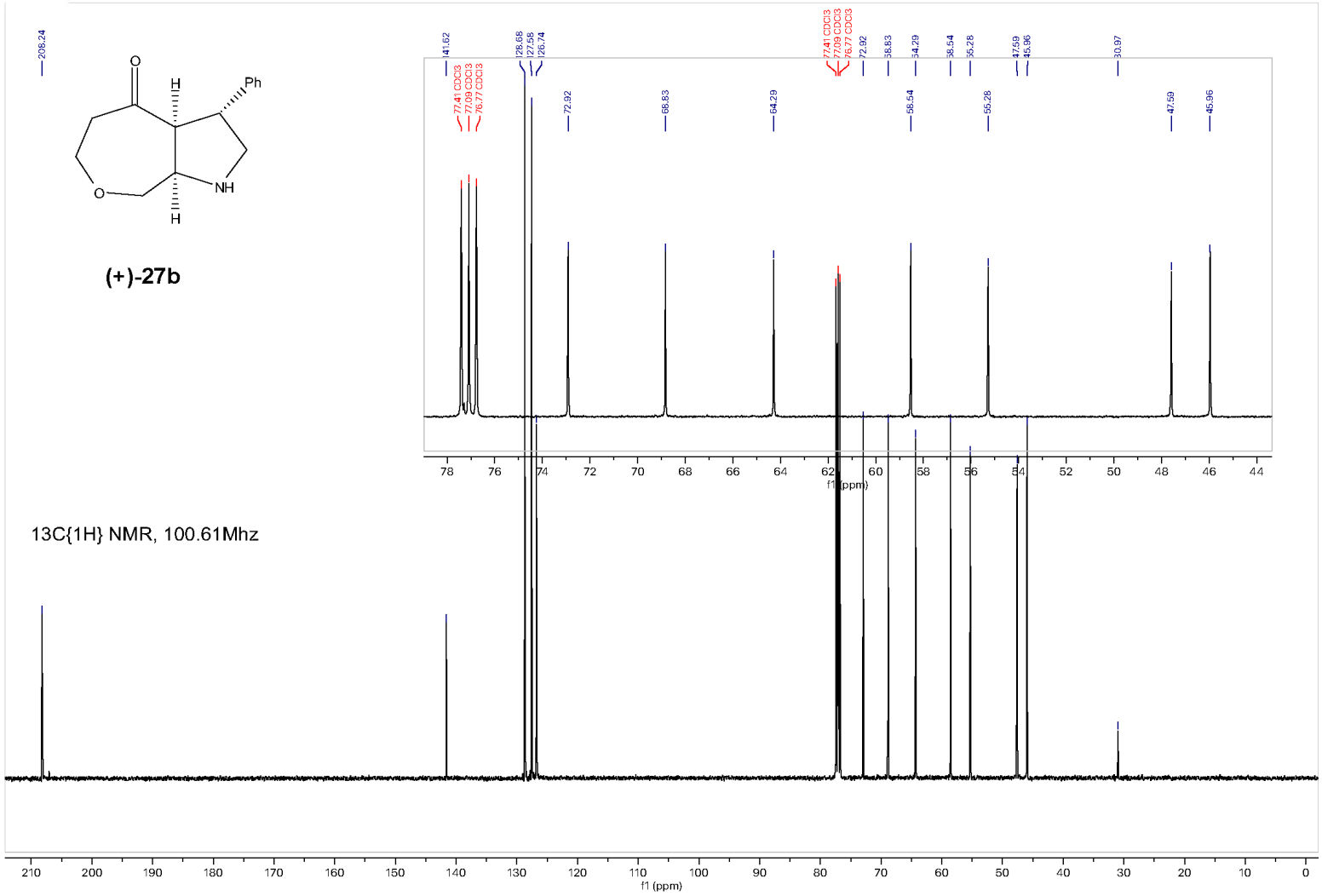
(3*R*,3a*S*,8a*S*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one ((-)-27a). 2D ^{1}H-^{13}C-HMBC (longrange, J1(HC)=145Hz, J2(HC-long)=10Hz)



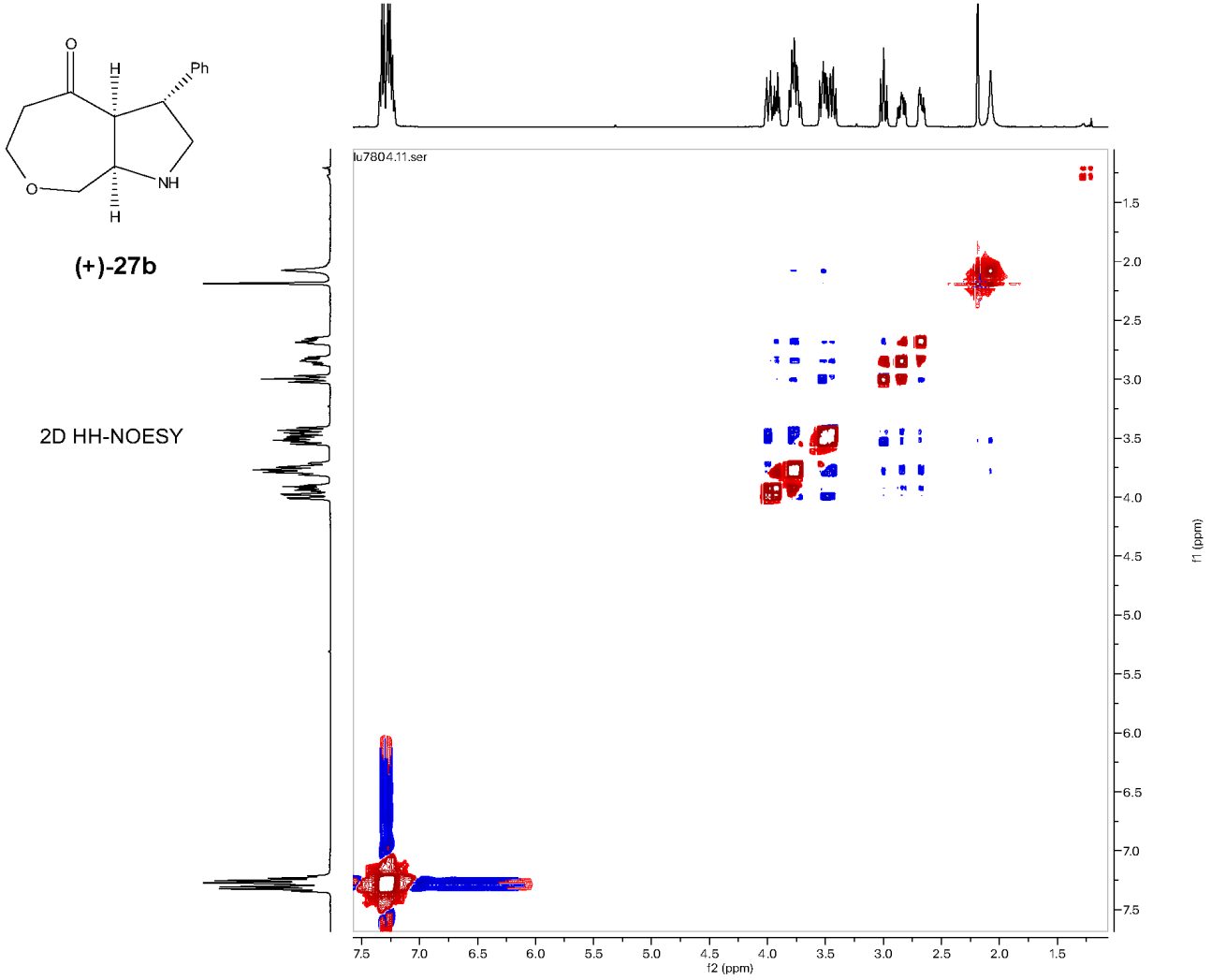
(3*R*,3a*S*,8a*R*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one ((+)-27b). ^{1}H NMR ($CDCl_3$, 400 MHz)



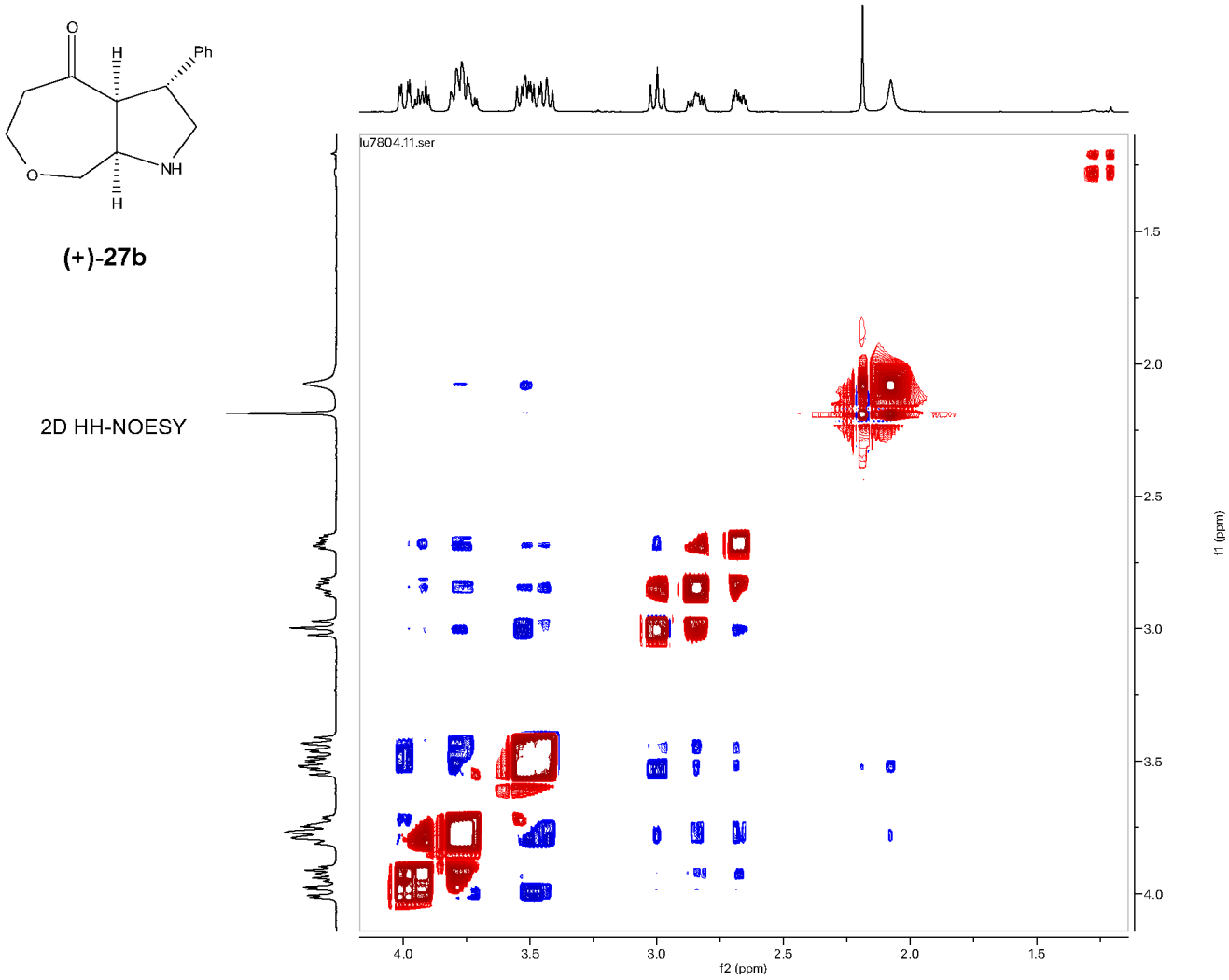
(3*R*,3a*S*,8a*R*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one ((+)-27b). ^{1}H NMR ($CDCl_3$, 400 MHz).



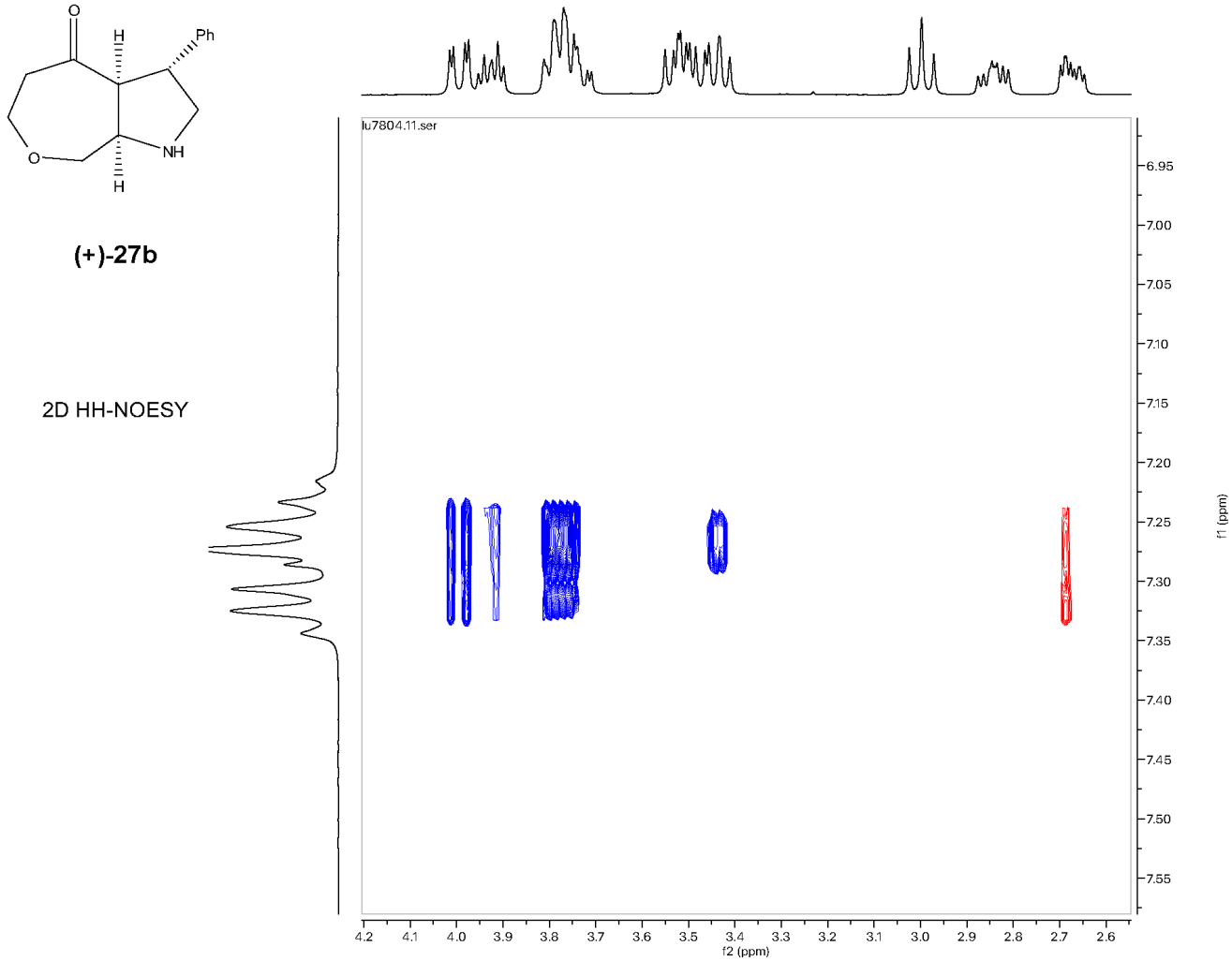
(3*R*,3a*S*,8a*R*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one ((+)-27b). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms).



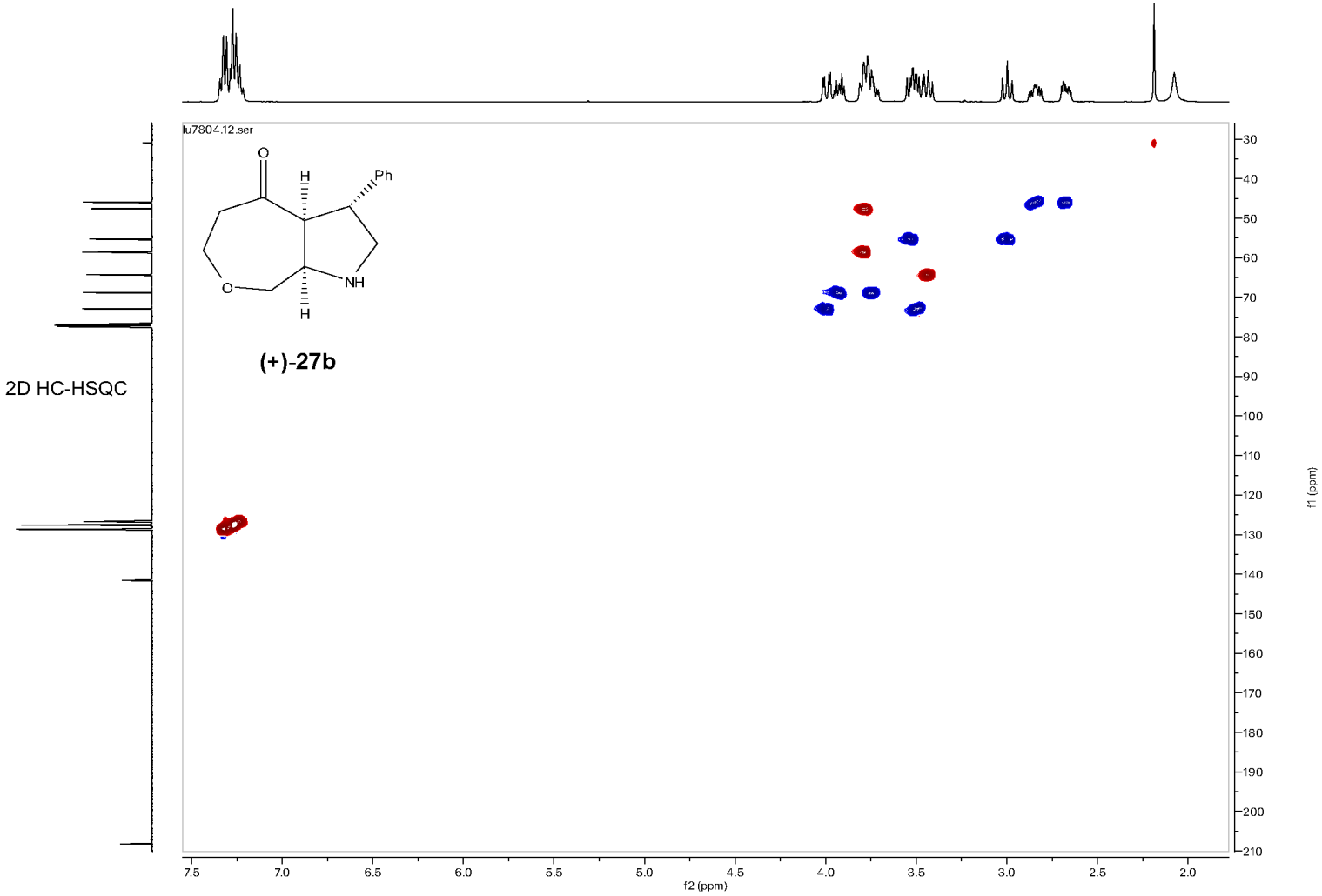
(3*R*,3a*S*,8a*R*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one ((+)-27b). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms).



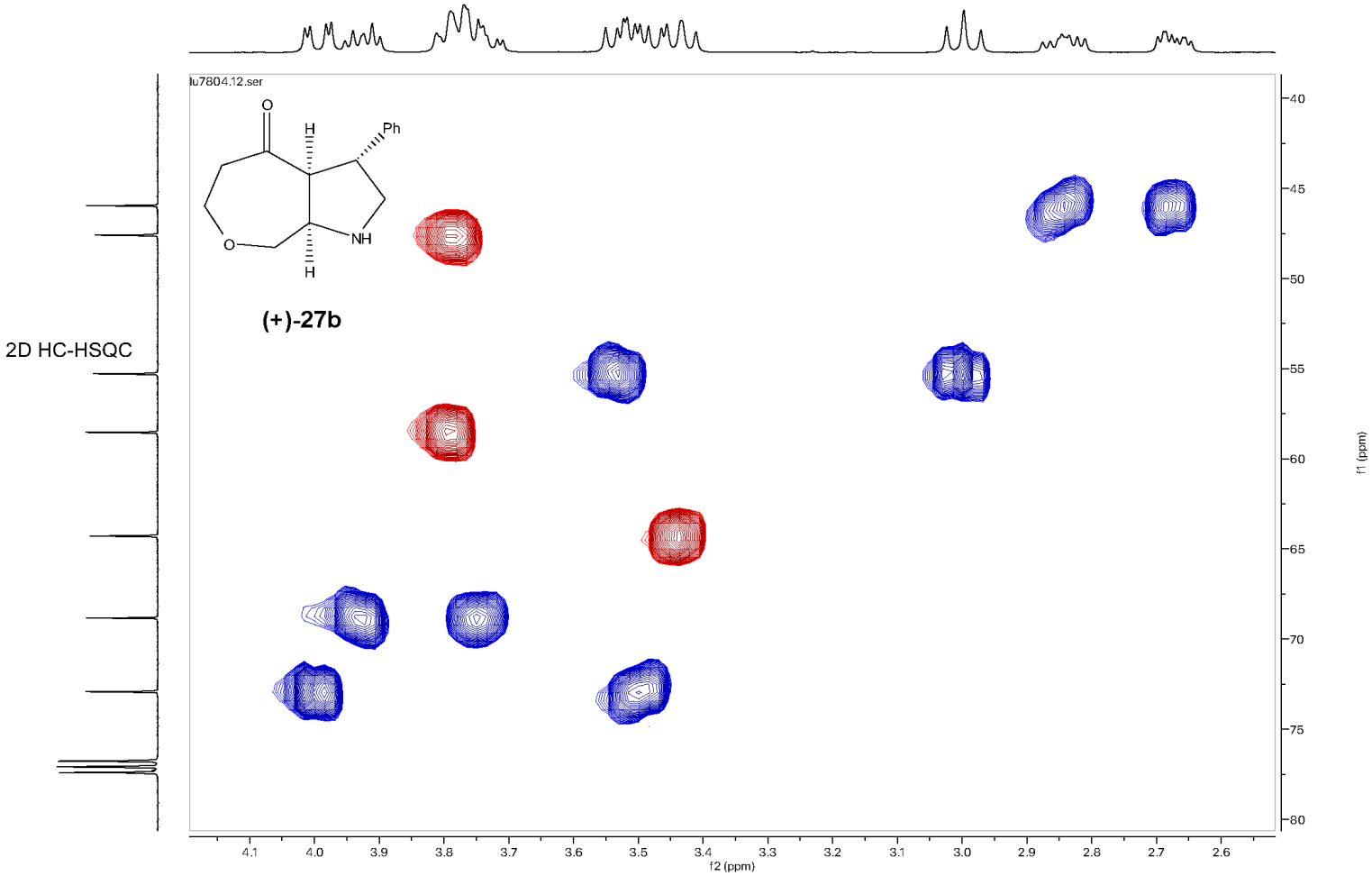
(3*R*,3a*S*,8a*R*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one ((+)-27b). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms)



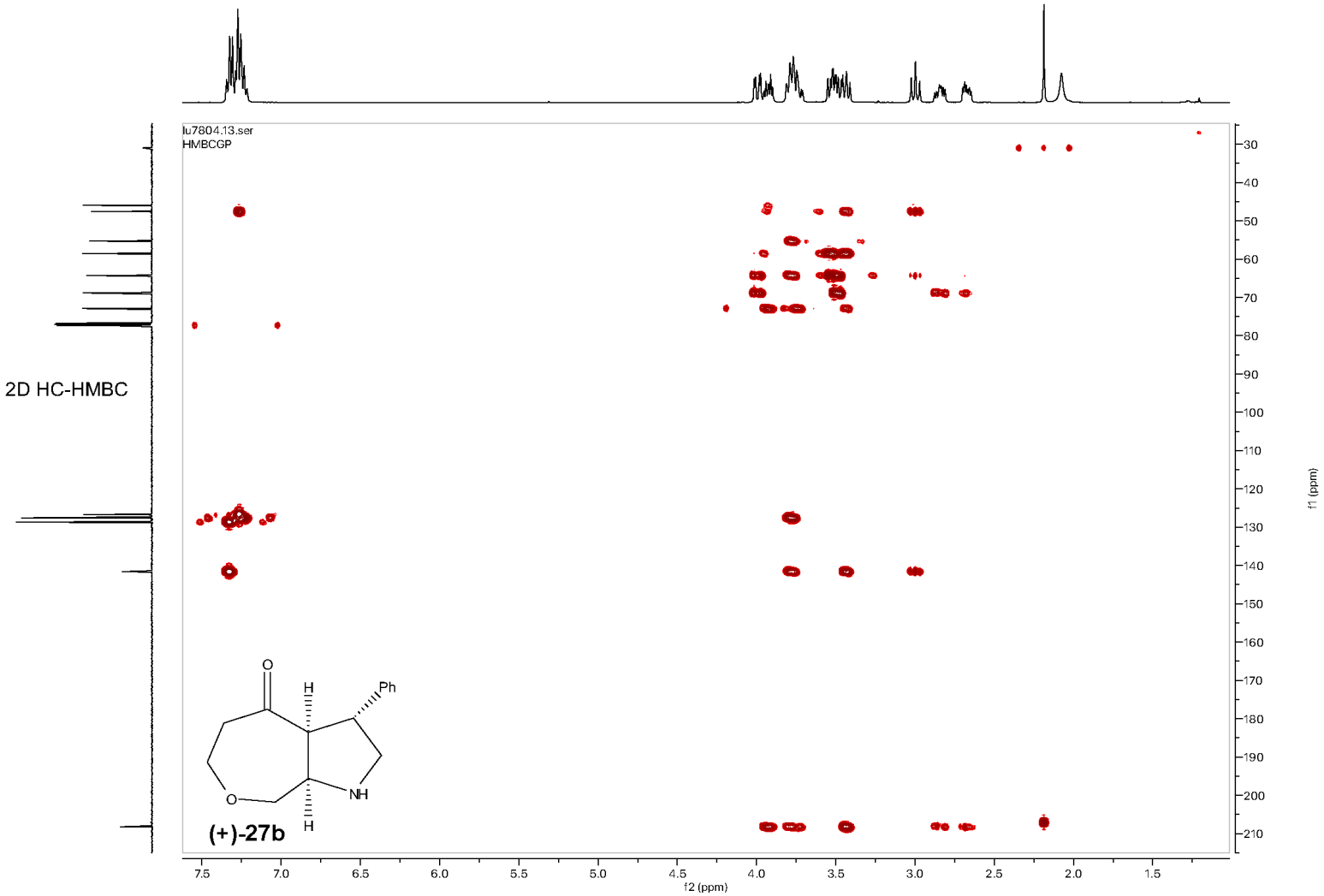
(3*R*,3a*S*,8a*R*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one ((+)-27b). 2D ^{1}H-^{13}C-HMBC (longrange, J1(HC)=145Hz, J2(HC-long)=10Hz)



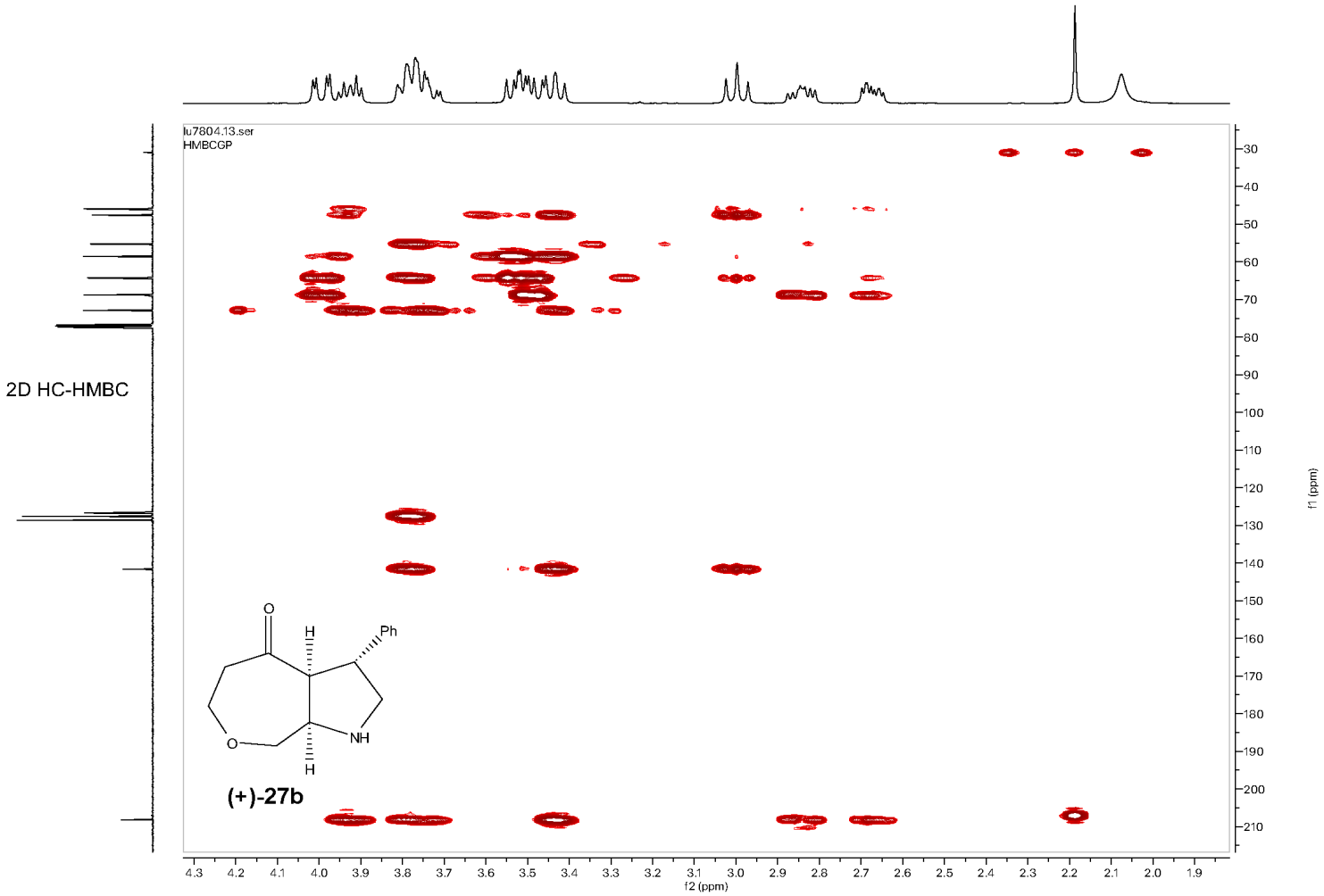
(3*R*,3a*S*,8a*R*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one ((+)-27b). 2D ^{1}H-^{13}C-HMBC (longrange, J1(HC)=145Hz, J2(HC-long)=10Hz)



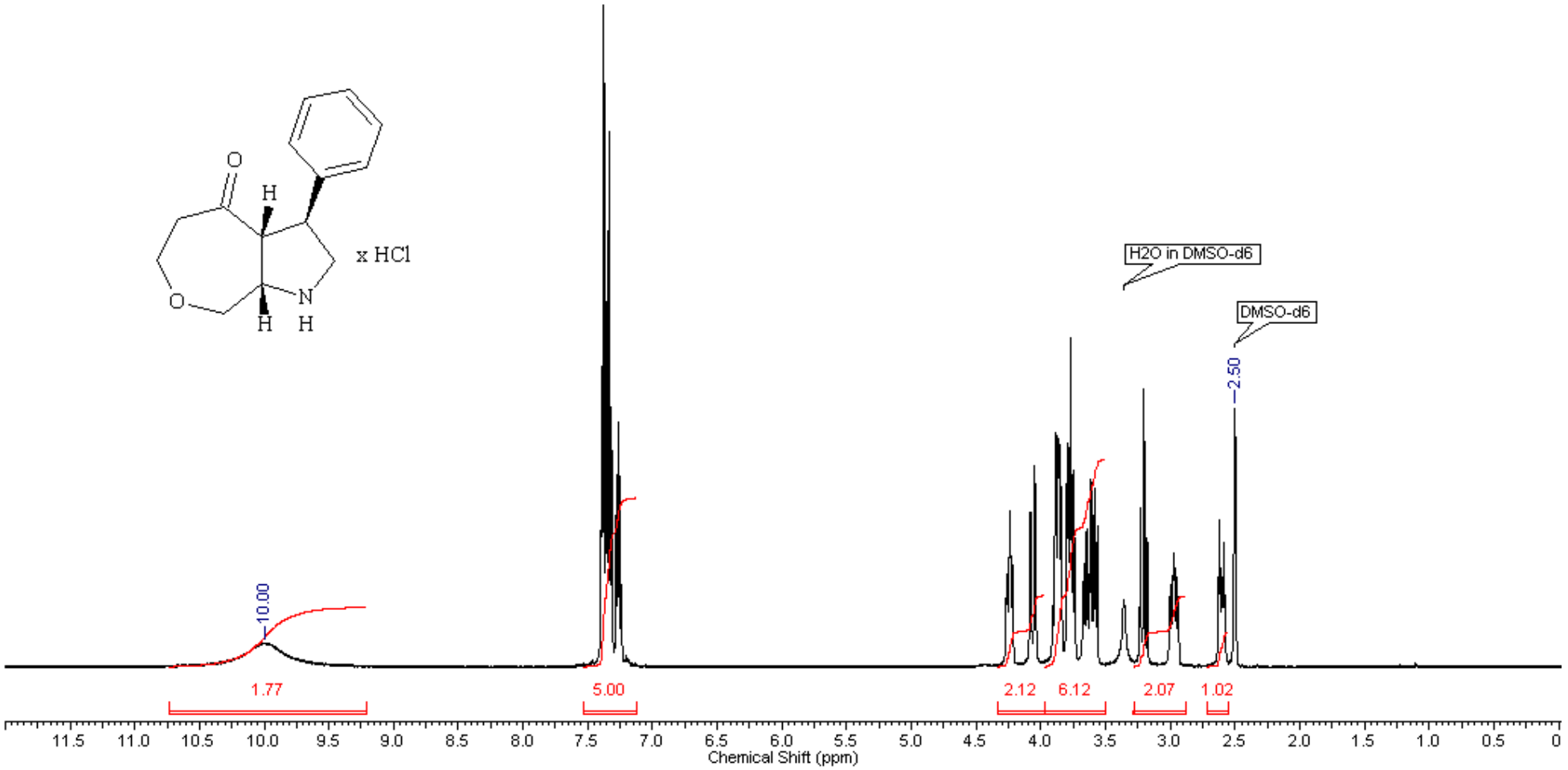
(3*R*,3a*S*,8a*R*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one ((+)-27b). 2D ^{1}H-^{13}C-HMBC (2D13C{1H} – 13C with CPD decoupling for sensitivity increase)



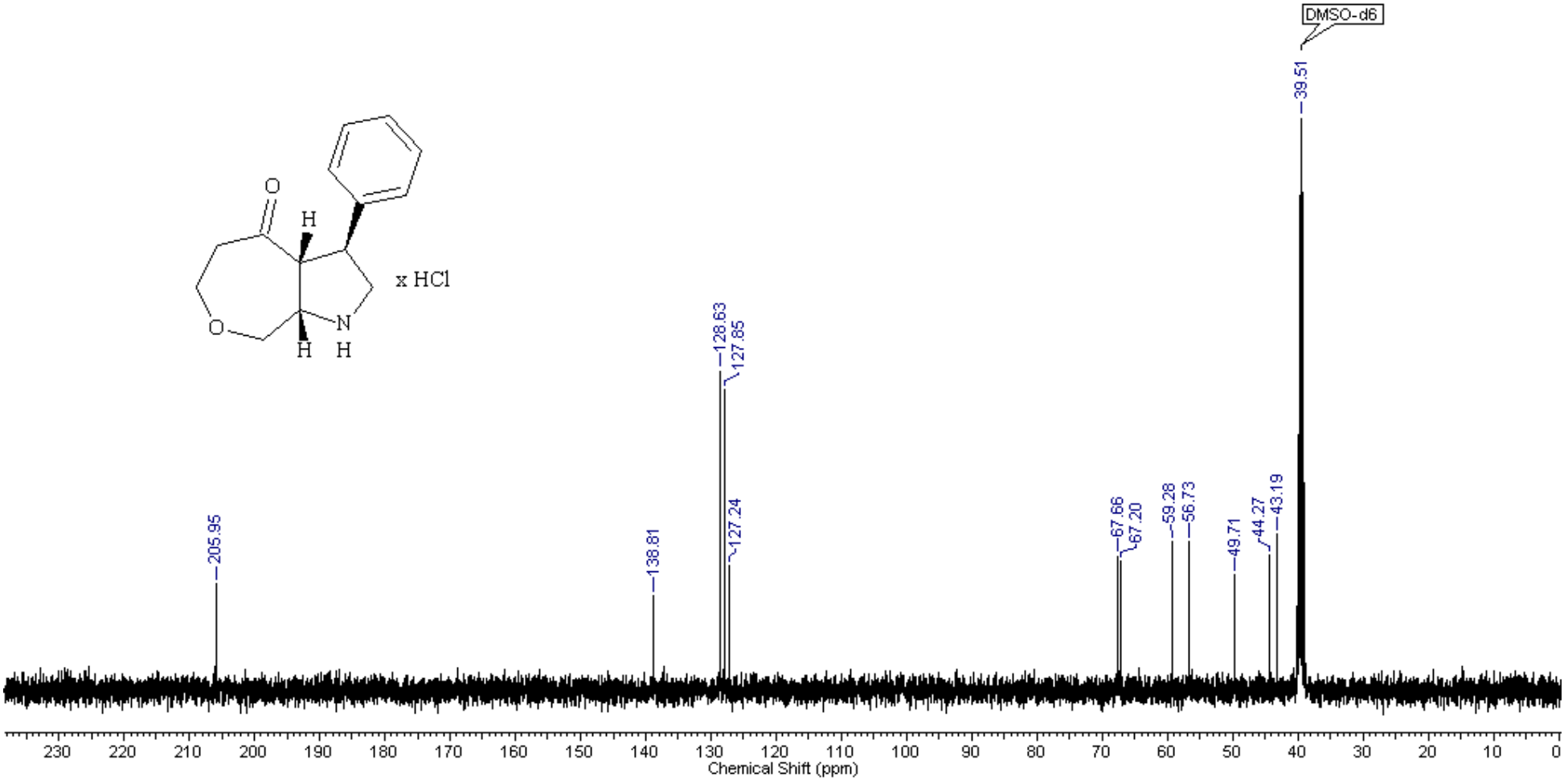
(3*R*,3a*S*,8a*R*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one ((+)-27b). 2D ^{1}H-^{13}C-HMBC (2D13C{1H} – 13C with CPD decoupling for sensitivity increase)



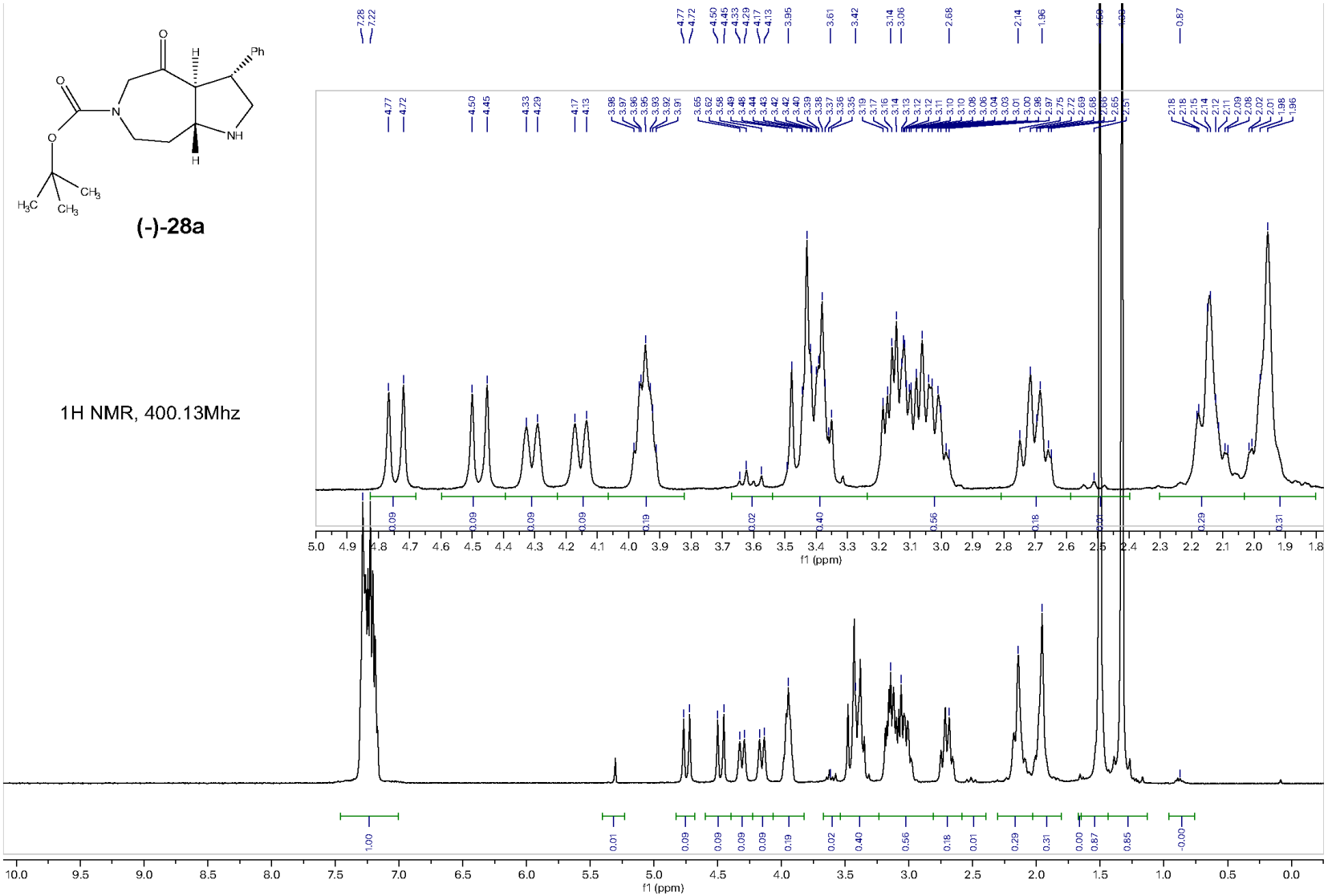
(3*S*,3a*R*,8a*S*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one hydrochloride ((-)-27b). ^{1}H NMR (DMSO-d_6, 400 MHz)



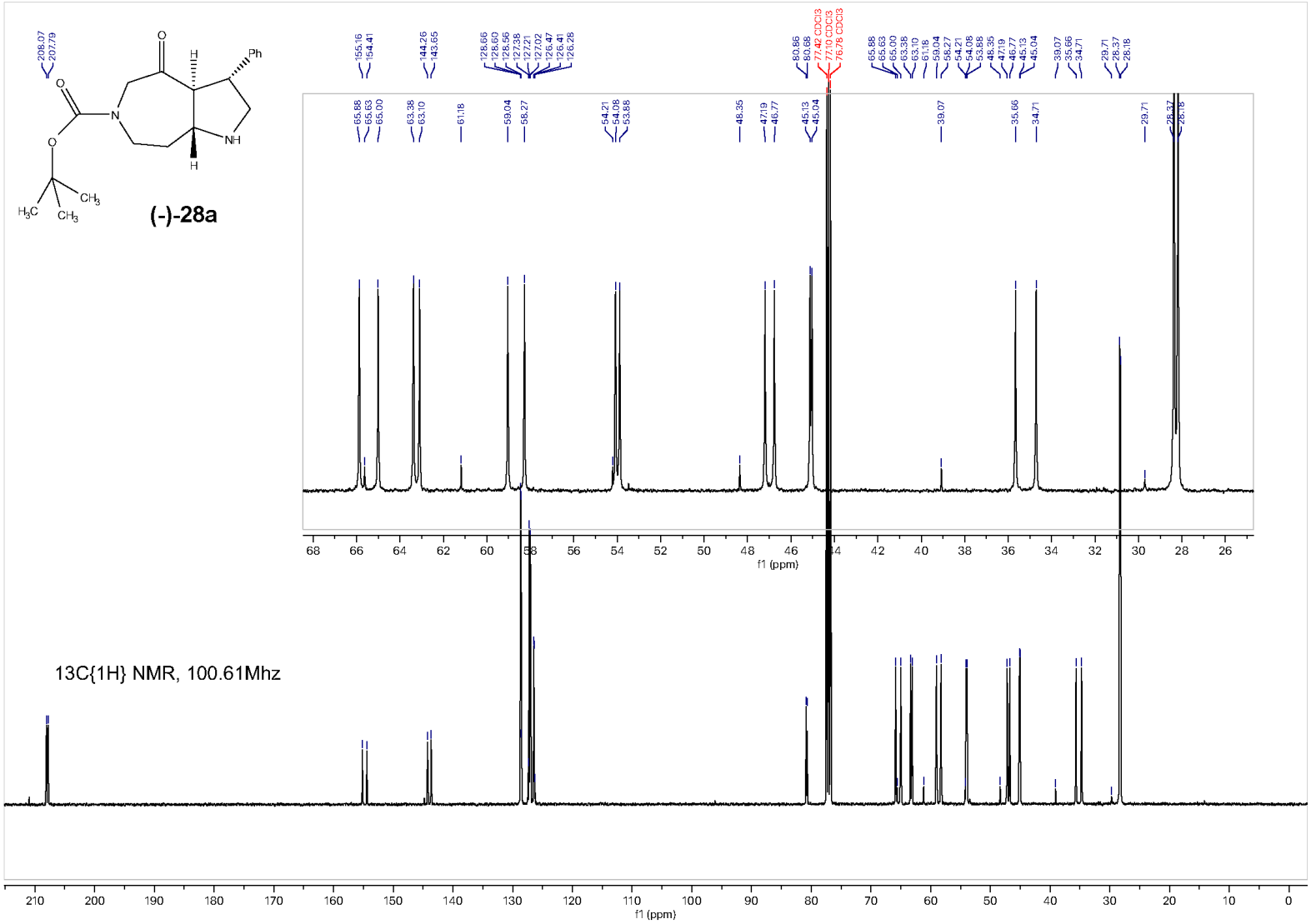
(3*S*,3a*R*,8a*S*)-3-Phenylhexahydro-1*H*-oxepino[3,4-*b*]pyrrol-4(2*H*)-one hydrochloride ((-)-27b). ^{13}C NMR (DMSO-d_6, 100 MHz)



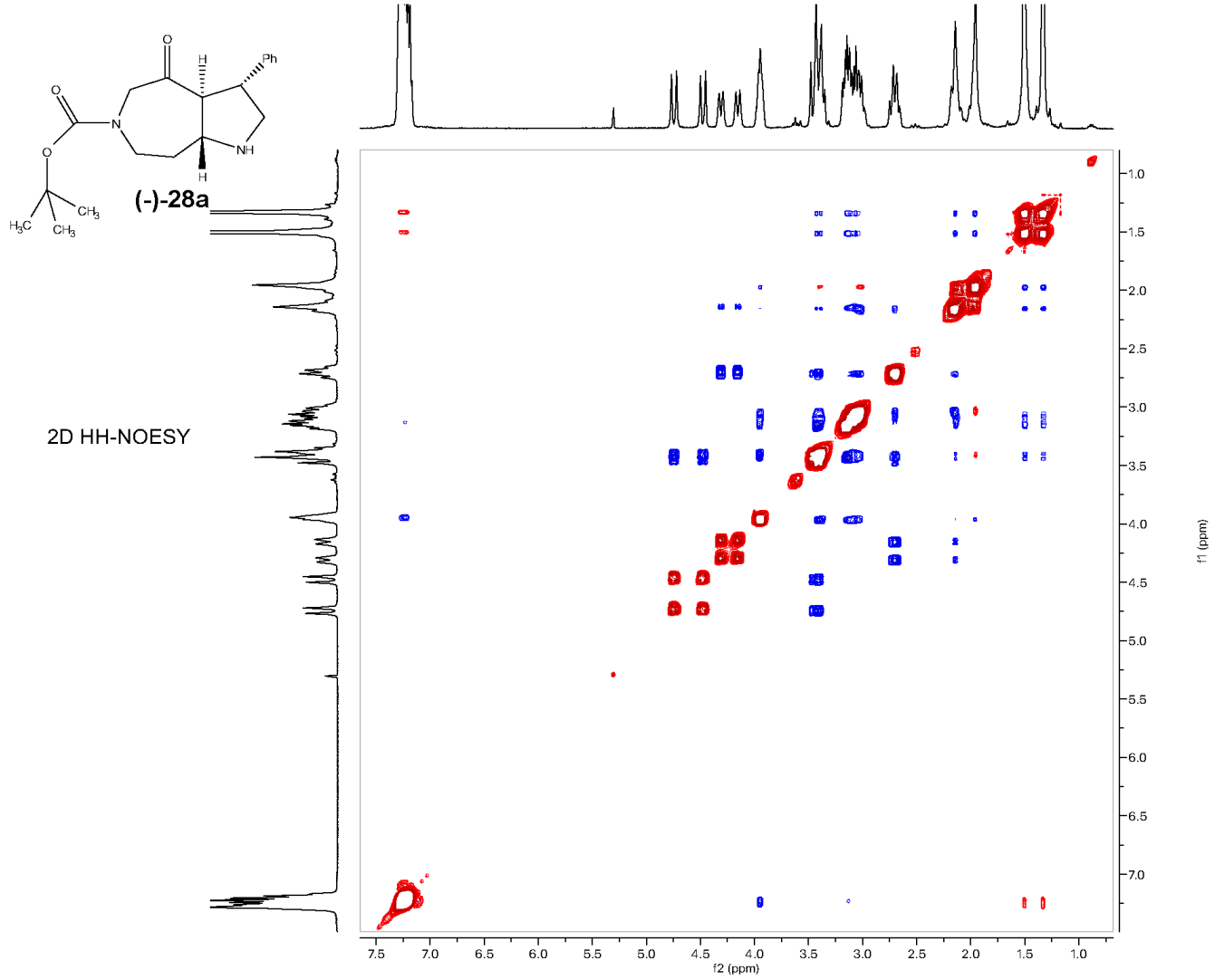
(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate ((-)-28a). ^{1}H NMR ($CDCl_3$, 400 MHz).



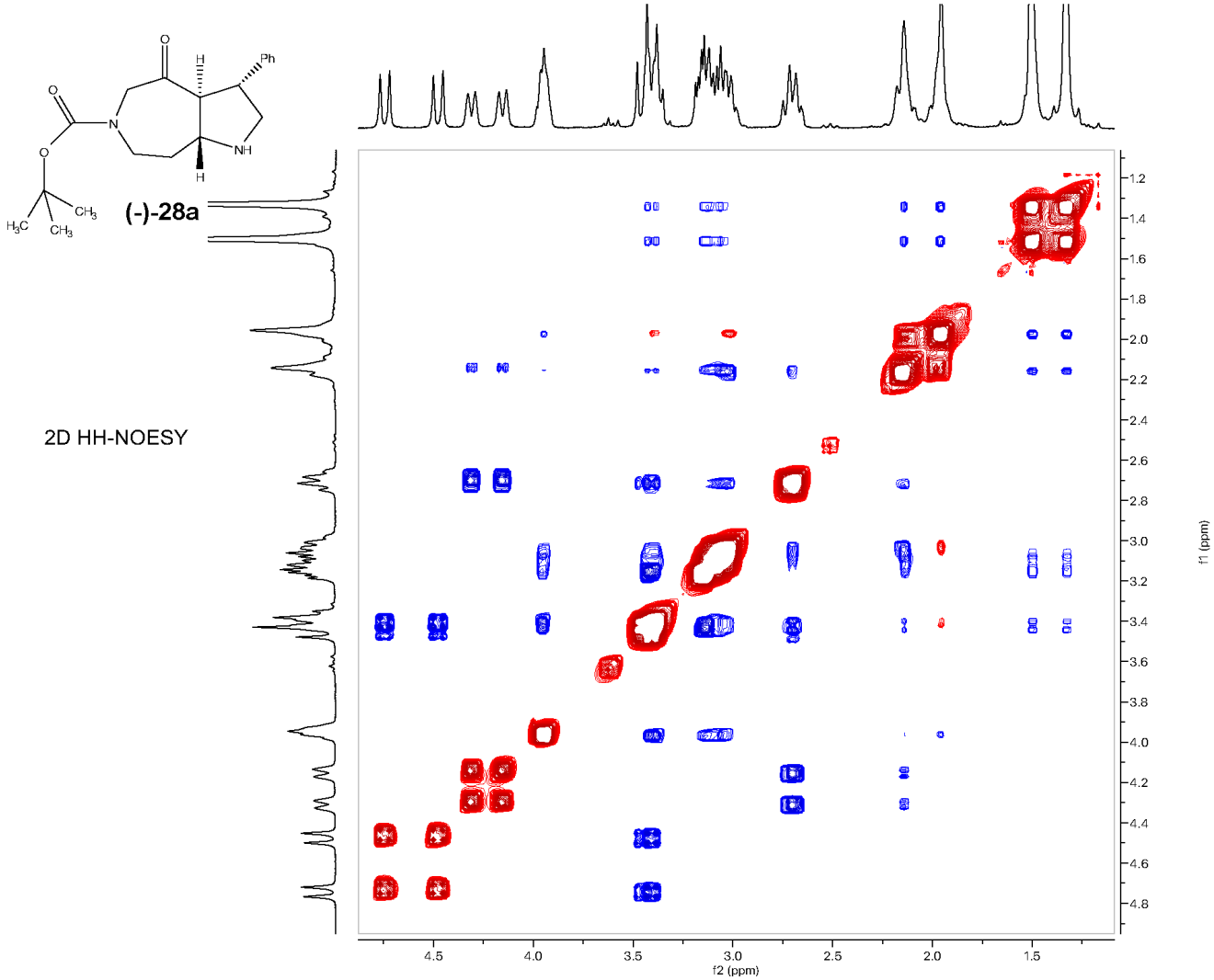
(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate ((-)-28a). ^{13}C NMR ($CDCl_3$, 100 MHz).



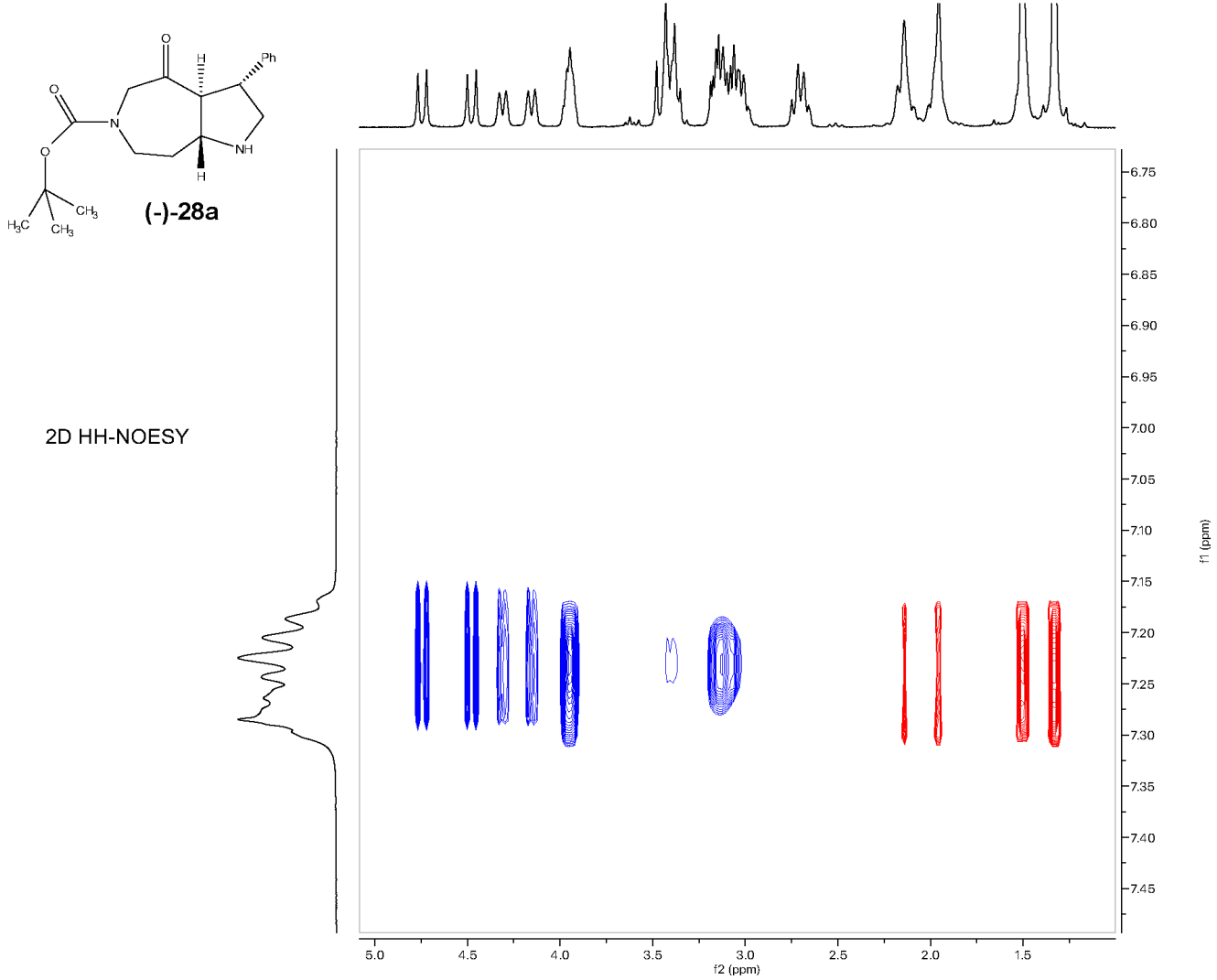
(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate ((-)-28a). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms)



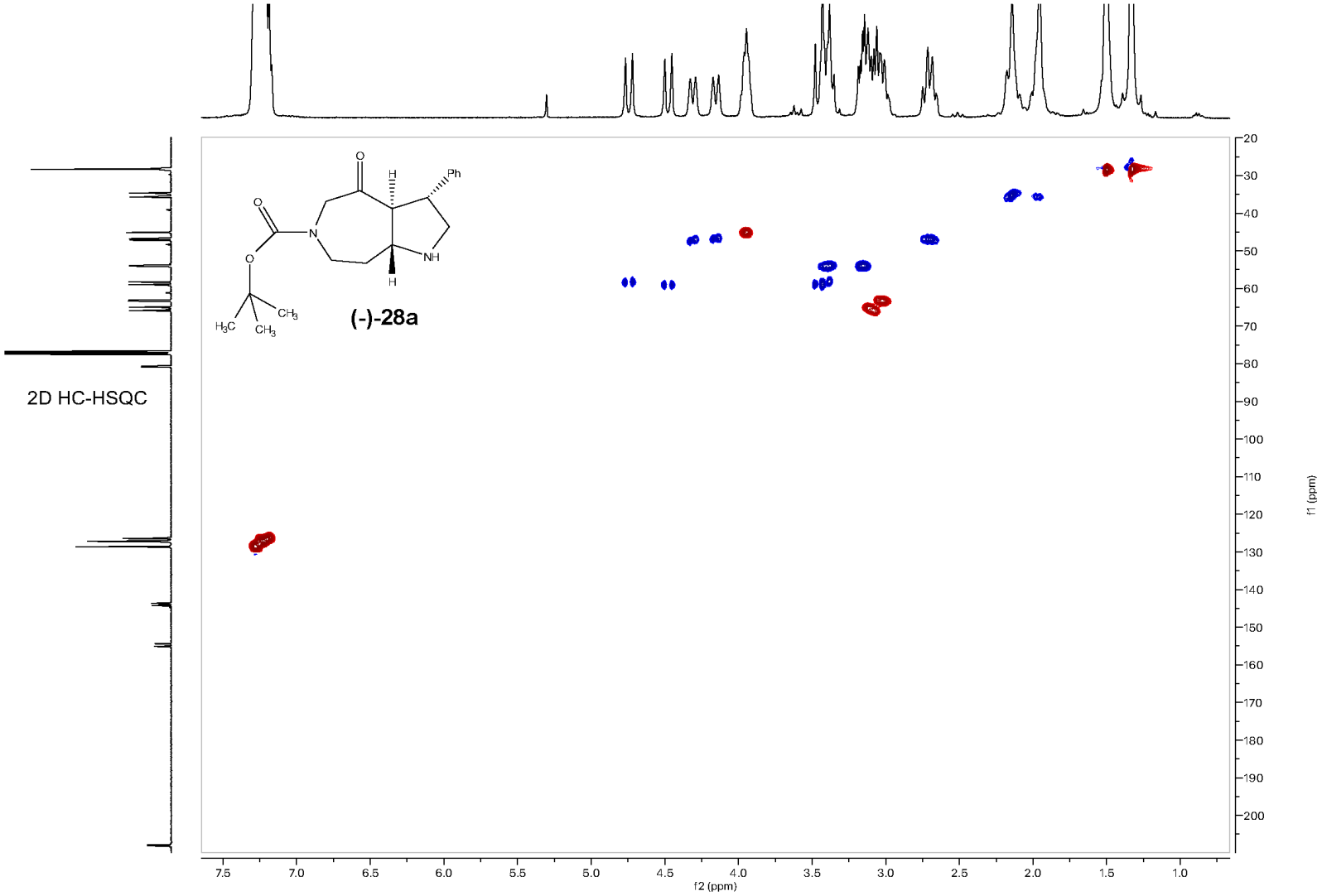
(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate ((-)-28a). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms)



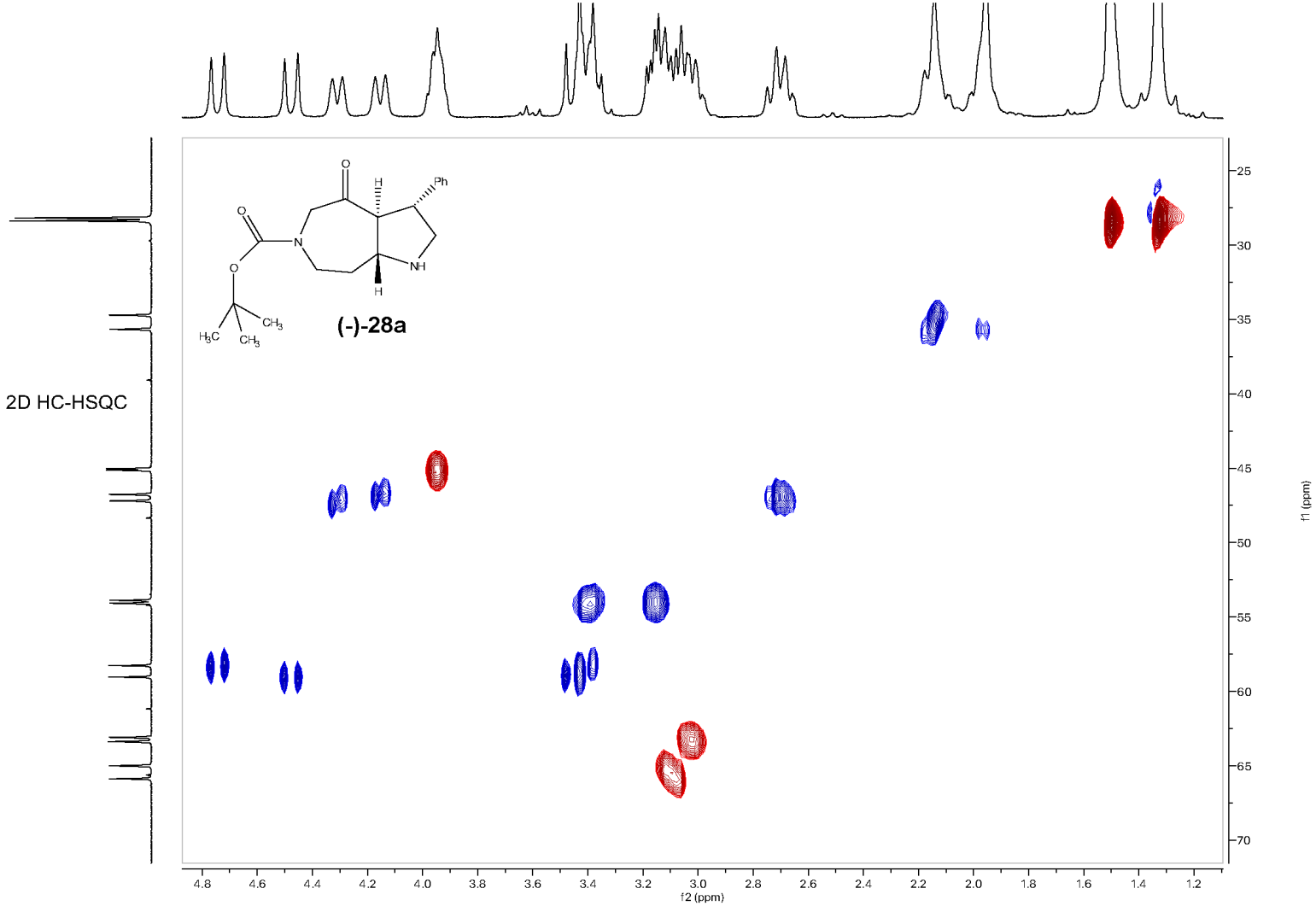
(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate ((-)-28a). 2D ^{1}H-^{1}H-NOESY (phase sensitive, mixing time = 500ms)



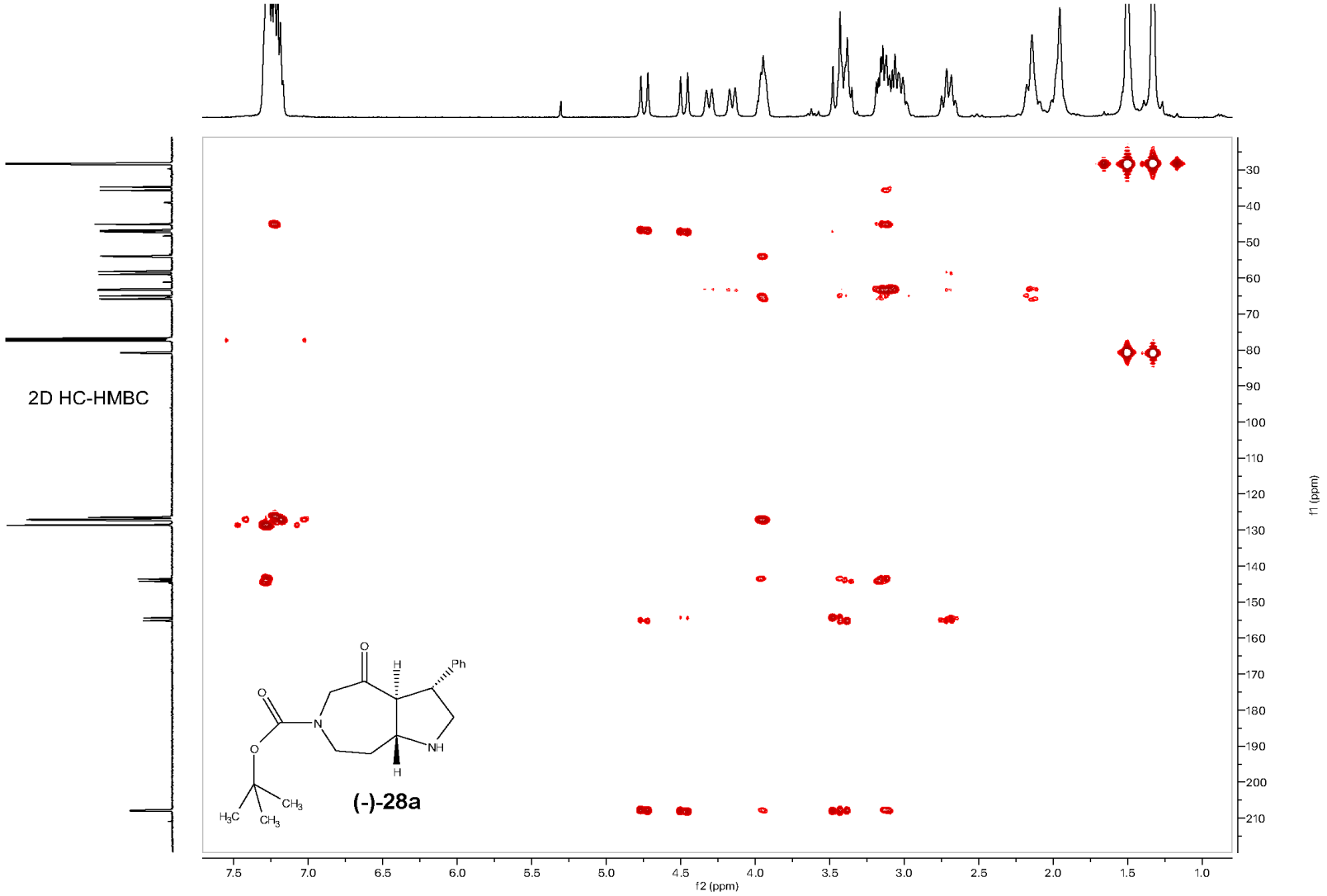
(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate ((-)-28a). 2D ^{1}H-^{13}C-HSQC (qphase sensitive J1 (HC)=145Hz).



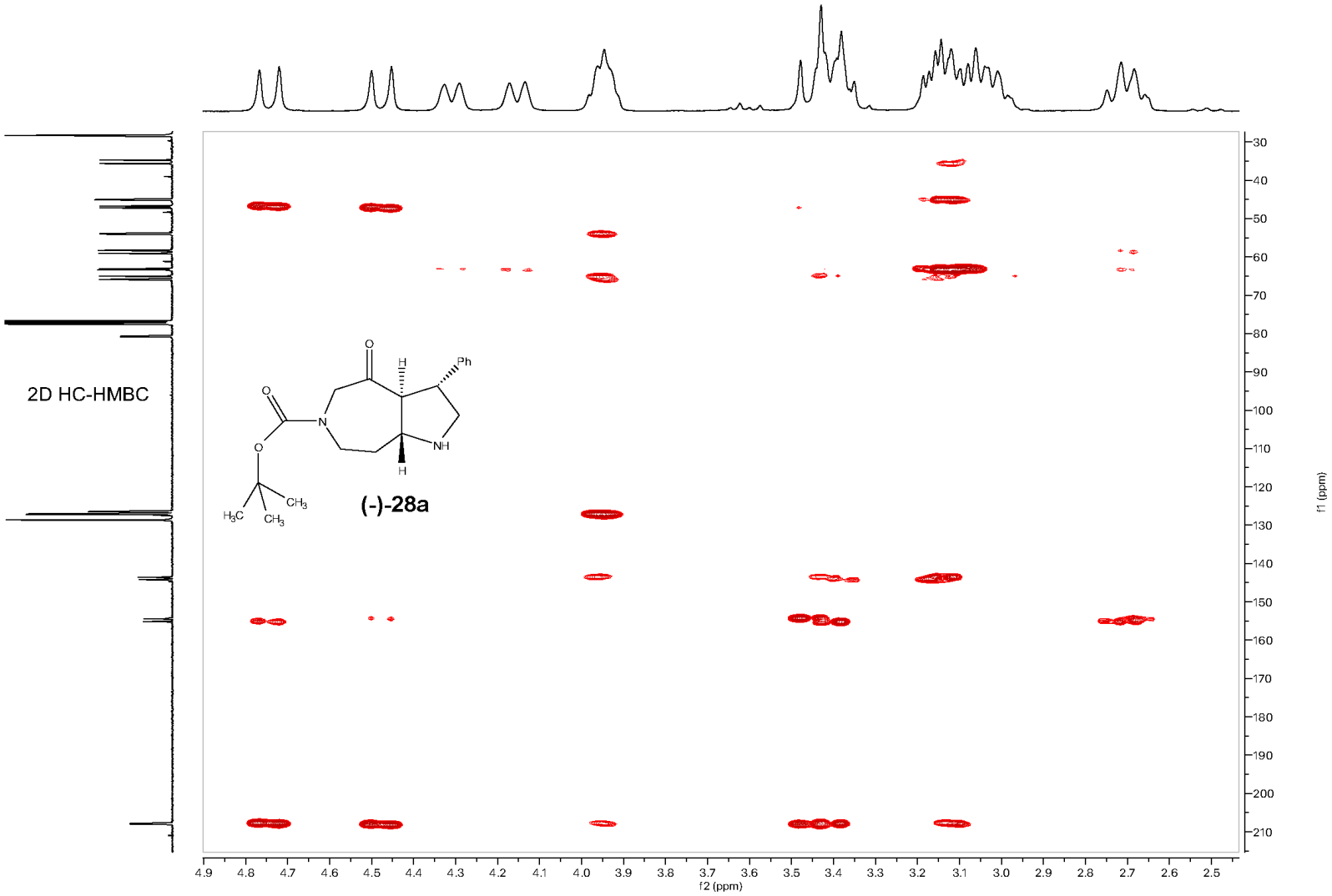
(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate ((-)-28a). 2D ^{1}H-^{13}C-HSQC (qphase sensitive J1 (HC)=145Hz).



(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate ((-)-28a). 2D ^{1}H-^{13}C-HMBC – longrange, J1(HC)=145Hz, J2(HC-long)=10Hz.



(3*R*,3a*S*,8a*R*)-*Tert*-butyl 4-oxo-3-phenyloctahydropyrrolo[2,3-*d*]azepine-6(2*H*)-carboxylate ((-)-28a). 2D ^{1}H-^{13}C-HMBC – longrange, J1(HC)=145Hz, J2(HC-long)=10Hz.



Single Crystal X-ray Diffraction Data

Checkcif for compound 24b

checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: I

```
Bond precision:  C-C = 0.0025 A          Wavelength=1.54180

Cell:          a=5.7640(5)       b=11.1643(7)     c=14.7076(10)
               alpha=70.895(5)   beta=81.858(6)   gamma=85.321(6)
Temperature:   295 K
```

	Calculated	Reported
Volume	884.68(12)	884.68(12)
Space group	P -1	P -1
Hall group	-P 1	-P 1
Moiety formula	C21 H23 N O2	C21 H23 N O2
Sum formula	C21 H23 N O2	C21 H23 N O2
Mr	321.40	321.40
Dx,g cm-3	1.207	1.207
Z	2	2
Mu (mm-1)	0.607	0.607
F000	344.0	344.0
F000’	344.97	
h,k,lmax	7,13,18	7,13,17
Nref	3421	3150
Tmin,Tmax	0.930,0.953	
Tmin’	0.913	

```
Correction method= Not given

Data completeness= 0.921          Theta(max)= 71.110

R(reflections)= 0.0500( 1071)     wR2(reflections)= 0.1014( 3150)

S = 0.600                 Npar= 181
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level A

PLAT029_ALERT_3_A _diffrn_measured_fraction_theta_full value Low . 0.921 Why?

Alert level B

PLAT026_ALERT_3_B Ratio Observed / Unique Reflections (too) Low .. 34% Check
PLAT230_ALERT_2_B Hirshfeld Test Diff for C14 --C15 . 9.3 s.u.
PLAT230_ALERT_2_B Hirshfeld Test Diff for C32 --C37 . 9.7 s.u.

Alert level C

GOODF01_ALERT_2_C The least squares goodness of fit parameter lies
outside the range 0.80 <> 2.00
Goodness of fit given = 0.600
PLAT165_ALERT_3_C Nr. of Status R Flagged Non-Hydrogen Atoms ..... 12 Note
PLAT242_ALERT_2_C Low 'MainMol' Ueq as Compared to Neighbors of C32 Check

---

Alert level G

PLAT005_ALERT_5_G No Embedded Refinement Details Found in the CIF Please Do !
PLAT793_ALERT_4_G Model has Chirality at C1 (Centro SPGR) S Verify
PLAT793_ALERT_4_G Model has Chirality at C4 (Centro SPGR) S Verify
PLAT793_ALERT_4_G Model has Chirality at C10 (Centro SPGR) R Verify
PLAT899_ALERT_4_G SHELXL97 is Deprecated and Succeeded by SHELXL/ 2018 Note

---

1 **ALERT level A** = Most likely a serious problem - resolve or explain
3 **ALERT level B** = A potentially serious problem, consider carefully
3 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
5 **ALERT level G** = General information/check it is not something unexpected

0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
4 ALERT type 2 Indicator that the structure model may be wrong or deficient
3 ALERT type 3 Indicator that the structure quality may be low
4 ALERT type 4 Improvement, methodology, query or suggestion
1 ALERT type 5 Informative message, check

---

checkCIF publication errors

Alert level A

PUBL006_ALERT_1_A _publ_requested_journal is missing
e.g. 'Acta Crystallographica Section C'
PUBL008_ALERT_1_A _publ_section_title is missing. Title of paper.
PUBL010_ALERT_1_A _publ_author_address is missing. Author(s) address(es).
PUBL012_ALERT_1_A _publ_section_abstract is missing.
Abstract of paper in English.

Alert level G

PUBL017_ALERT_1_G The _publ_section_references section is missing or
empty.

---

4 **ALERT level A** = Data missing that is essential or data in wrong format
1 **ALERT level G** = General alerts. Data that may be required is missing

---

Publication of your CIF

You should attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the nature of your study may justify the reported deviations from journal submission requirements and the more serious of these should be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. *checkCIF* was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

If level A alerts remain, which you believe to be justified deviations, and you intend to submit this CIF for publication in a journal, you should additionally insert an explanation in your CIF using the Validation Reply Form (VRF) below. This will allow your explanation to be considered as part of the review process.

Validation response form

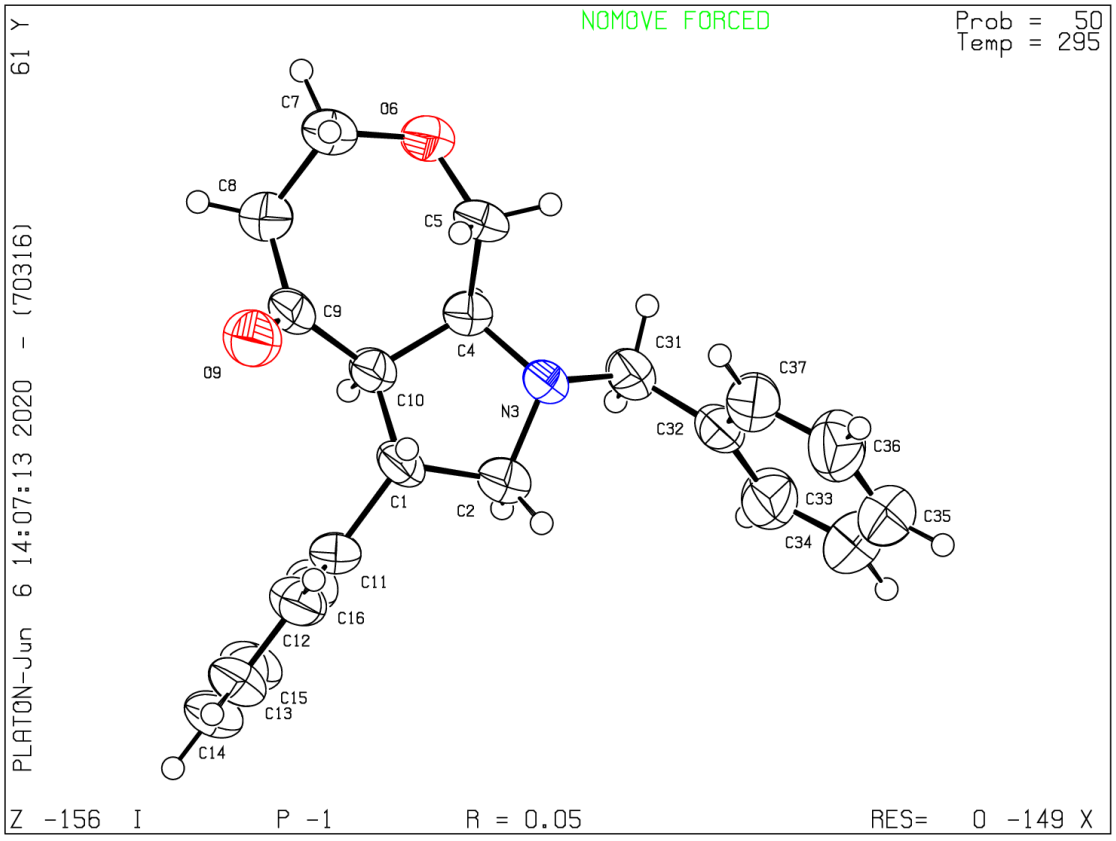
Please find below a validation response form (VRF) that can be filled in and pasted into your CIF.

```
# start Validation Reply Form
_vrf_PUBL006_GLOBAL
;
PROBLEM: _publ_requested_journal is missing
RESPONSE: ...
;
_vrf_PUBL008_GLOBAL
;
PROBLEM: _publ_section_title is missing. Title of paper.
RESPONSE: ...
;
_vrf_PUBL010_GLOBAL
;
PROBLEM: _publ_author_address is missing. Author(s) address(es).
RESPONSE: ...
;
_vrf_PUBL012_GLOBAL
;
PROBLEM: _publ_section_abstract is missing.
RESPONSE: ...
;
_vrf_PLAT029_I
;
PROBLEM: _diffrn_measured_fraction_theta_full value Low .      0.921 Why?
RESPONSE: ...
;
# end Validation Reply Form
```

If you wish to submit your CIF for publication in Acta Crystallographica Section C or E, you should upload your CIF via the web. If you wish to submit your CIF for publication in IUCrData you should upload your CIF via the web. If your CIF is to form part of a submission to another IUCr journal, you will be asked, either during electronic submission or by the Co-editor handling your paper, to upload your CIF via our web site.

PLATON version of 04/06/2020; check.def file version of 02/06/2020

Datablock I - ellipsoid plot



Checkcif for compound 25a

checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: I

```
Bond precision:  C-C = 0.0022 A          Wavelength=1.54184

Cell:              a=11.490(2)      b=17.453(3)      c=23.207(4)
                   alpha=90         beta=90          gamma=90
Temperature:       295 K

                 Calculated                Reported
Volume           4653.8(14)                4653.8(14)
Space group      P b c a                   P b c a
Hall group       -P 2ac 2ab                -P 2ac 2ab
Moiety formula   C26 H32 N2 O3             C26 H32 N2 O3
Sum formula      C26 H32 N2 O3             C26 H32 N2 O3
Mr               420.54                    420.54
Dx,g cm-3        1.200                     1.200
Z                8                         8
Mu (mm-1)        0.622                     0.622
F000             1808.0                    1808.0
F000'            1813.17
h,k,lmax         14,21,29                  14,21,29
Nref             4786                      4488
Tmin,Tmax        0.883,0.883               0.709,0.957
Tmin'            0.883

Correction method= # Reported T Limits: Tmin=0.709 Tmax=0.957
AbsCorr = REFDELF

Data completeness= 0.938          Theta(max)= 74.910

R(reflections)= 0.0391( 3469)     wR2(reflections)= 0.1056( 4488)

S = 1.028                 Npar= 280
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level B

PLAT029_ALERT_3_B _diffrn_measured_fraction_theta_full value Low . 0.952 Why?
PLAT230_ALERT_2_B Hirshfeld Test Diff for C14 --C15 . 12.0 s.u.

Alert level C

PLAT230_ALERT_2_C Hirshfeld Test Diff for C13 --C14 . 5.7 s.u.
PLAT230_ALERT_2_C Hirshfeld Test Diff for C15 --C16 . 6.5 s.u.
PLAT230_ALERT_2_C Hirshfeld Test Diff for C34 --C35 . 6.8 s.u.
PLAT242_ALERT_2_C Low 'MainMol' Ueq as Compared to Neighbors of C73 Check

Alert level G

PLAT793_ALERT_4_G Model has Chirality at C3 (Centro SPGR) S Verify
PLAT793_ALERT_4_G Model has Chirality at C4 (Centro SPGR) R Verify
PLAT793_ALERT_4_G Model has Chirality at C10 (Centro SPGR) S Verify
PLAT941_ALERT_3_G Average HKL Measurement Multiplicity ..... 1.0 Low

0 **ALERT level A** = Most likely a serious problem - resolve or explain
2 **ALERT level B** = A potentially serious problem, consider carefully
4 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
4 **ALERT level G** = General information/check it is not something unexpected

0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
5 ALERT type 2 Indicator that the structure model may be wrong or deficient
2 ALERT type 3 Indicator that the structure quality may be low
3 ALERT type 4 Improvement, methodology, query or suggestion
0 ALERT type 5 Informative message, check

checkCIF publication errors

Alert level A

PUBL006_ALERT_1_A _publ_requested_journal is missing
e.g. 'Acta Crystallographica Section C'
PUBL008_ALERT_1_A _publ_section_title is missing. Title of paper.
PUBL010_ALERT_1_A _publ_author_address is missing. Author(s) address(es).
PUBL012_ALERT_1_A _publ_section_abstract is missing.
Abstract of paper in English.

Alert level G

PUBL017_ALERT_1_G The _publ_section_references section is missing or
empty.

4 **ALERT level A** = Data missing that is essential or data in wrong format
1 **ALERT level G** = General alerts. Data that may be required is missing

Publication of your CIF

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If level A alerts remain, which you believe to be justified deviations, and you intend to submit this CIF for publication in a journal, you should additionally insert an explanation in your CIF using the Validation Reply Form (VRF) below. This will allow your explanation to be considered as part of the review process.

Validation response form

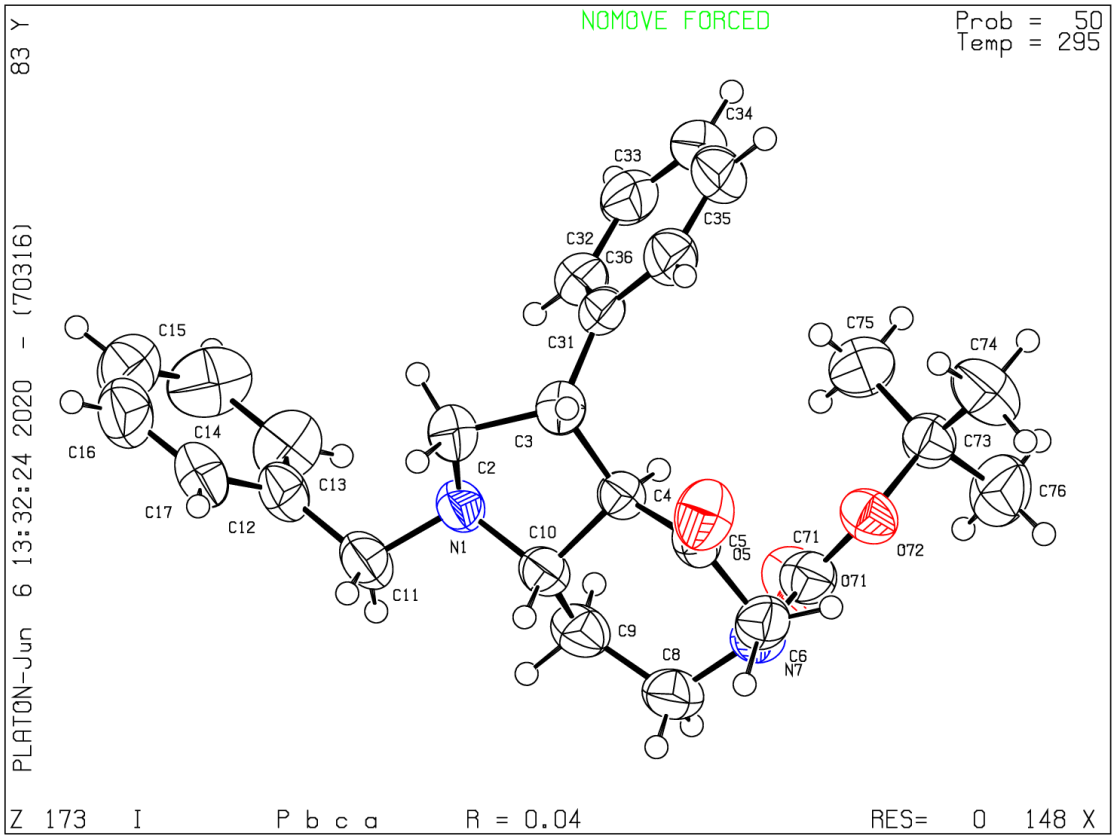
Please find below a validation response form (VRF) that can be filled in and pasted into your CIF.

```
# start Validation Reply Form
_vrf_PUBL006_GLOBAL
;
PROBLEM: _publ_requested_journal is missing
RESPONSE: ...
;
_vrf_PUBL008_GLOBAL
;
PROBLEM: _publ_section_title is missing. Title of paper.
RESPONSE: ...
;
_vrf_PUBL010_GLOBAL
;
PROBLEM: _publ_author_address is missing. Author(s) address(es).
RESPONSE: ...
;
_vrf_PUBL012_GLOBAL
;
PROBLEM: _publ_section_abstract is missing.
RESPONSE: ...
;
# end Validation Reply Form
```

If you wish to submit your CIF for publication in Acta Crystallographica Section C or E, you should upload your CIF via the web. If you wish to submit your CIF for publication in IUCrData you should upload your CIF via the web. If your CIF is to form part of a submission to another IUCr journal, you will be asked, either during electronic submission or by the Co-editor handling your paper, to upload your CIF via our web site.

PLATON version of 04/06/2020; check.def file version of 02/06/2020

Datablock I - ellipsoid plot



Checkcif for compound 46

checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: I

```
Bond precision:  C-C = 0.0103 A          Wavelength=1.54180

Cell:            a=5.7669(2)     b=13.5407(5)     c=31.6039(11)
                 alpha=90        beta=90          gamma=90
Temperature:     295 K
```

	Calculated	Reported
Volume	2467.88(15)	2467.88(15)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	P 2ac 2ab
Moiety formula	C26 H34 N2 O3	C26 H34 N2 O3
Sum formula	C26 H34 N2 O3	C26 H34 N2 O3
Mr	422.55	422.55
Dx,g cm-3	1.137	1.137
Z	4	4
Mu (mm-1)	0.586	0.586
F000	912.0	912.0
F000’	914.58	
h,k,lmax	7,16,38	7,16,38
Nref	4681[2726]	4579
Tmin,Tmax	0.889,0.889	0.928,0.943
Tmin’	0.889	

```
Correction method= # Reported T Limits: Tmin=0.928 Tmax=0.943
AbsCorr = REFDELF

Data completeness= 1.68/0.98      Theta(max)= 70.348

R(reflections)= 0.0735( 2491)     wR2(reflections)= 0.1904( 4579)

S = 0.848                 Npar= 280
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level B

```
PLAT241_ALERT_2_B High   'MainMol' Ueq as Compared to Neighbors of        C38 Check
PLAT340_ALERT_3_B Low Bond Precision on  C-C Bonds ..............    0.01025 Ang.
```

Alert level C

```
STRVA01_ALERT_2_C           Chirality of atom sites is inverted?
          From the CIF: _refine_ls_abs_structure_Flack    0.800
          From the CIF: _refine_ls_abs_structure_Flack_su    0.600
PLAT220_ALERT_2_C NonSolvent Resd 1  C   Ueq(max) / Ueq(min) Range        3.8 Ratio
PLAT241_ALERT_2_C High   'MainMol' Ueq as Compared to Neighbors of        C36 Check
PLAT242_ALERT_2_C Low    'MainMol' Ueq as Compared to Neighbors of        C13 Check
PLAT242_ALERT_2_C Low    'MainMol' Ueq as Compared to Neighbors of        C34 Check
PLAT242_ALERT_2_C Low    'MainMol' Ueq as Compared to Neighbors of        C35 Check
PLAT250_ALERT_2_C Large U3/U1 Ratio for Average U(i,j) Tensor ....        2.3 Note
PLAT260_ALERT_2_C Large Average Ueq of Residue Including       O11      0.113 Check
PLAT420_ALERT_2_C D-H Without Acceptor       N31      --H31      .     Please Check
PLAT907_ALERT_2_C Flack x > 0.5, Structure Needs to be Inverted? .       0.80 Check
```

Alert level G

```
PLAT007_ALERT_5_G Number of Unrefined Donor-H Atoms ..............          2 Report
PLAT032_ALERT_4_G Std. Uncertainty on Flack Parameter Value High .      0.600 Report
PLAT791_ALERT_4_G Model has Chirality at C3          (Sohnke SpGr)          S Verify
PLAT791_ALERT_4_G Model has Chirality at C4          (Sohnke SpGr)          R Verify
PLAT791_ALERT_4_G Model has Chirality at C32         (Sohnke SpGr)          R Verify
PLAT941_ALERT_3_G Average HKL Measurement Multiplicity ...........        1.7 Low
```

```
   0 ALERT level A = Most likely a serious problem - resolve or explain
   2 ALERT level B = A potentially serious problem, consider carefully
  10 ALERT level C = Check. Ensure it is not caused by an omission or oversight
   6 ALERT level G = General information/check it is not something unexpected

   0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
  11 ALERT type 2 Indicator that the structure model may be wrong or deficient
   2 ALERT type 3 Indicator that the structure quality may be low
   4 ALERT type 4 Improvement, methodology, query or suggestion
   1 ALERT type 5 Informative message, check
```

checkCIF publication errors

Alert level A

```
PUBL006_ALERT_1_A  _publ_requested_journal is missing
           e.g. 'Acta Crystallographica Section C'
PUBL008_ALERT_1_A  _publ_section_title is missing. Title of paper.
PUBL010_ALERT_1_A  _publ_author_address is missing. Author(s) address(es).
PUBL012_ALERT_1_A  _publ_section_abstract is missing.
           Abstract of paper in English.
```

Alert level G

```
PUBL017_ALERT_1_G The _publ_section_references section is missing or
           empty.
```

```
  4 ALERT level A = Data missing that is essential or data in wrong format
  1 ALERT level G = General alerts. Data that may be required is missing
```

Publication of your CIF

You should attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the nature of your study may justify the reported deviations from journal submission requirements and the more serious of these should be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. *checkCIF* was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

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Validation response form

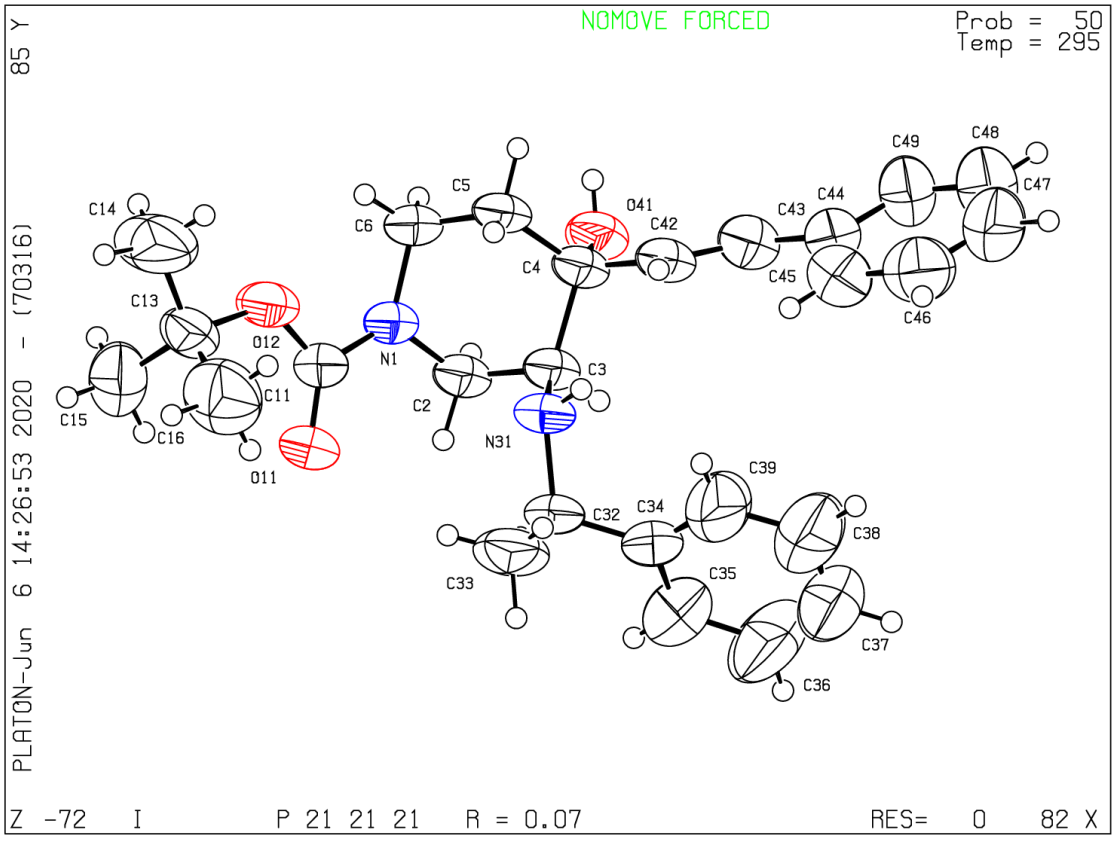
Please find below a validation response form (VRF) that can be filled in and pasted into your CIF.

```
# start Validation Reply Form
_vrf_PUBL006_GLOBAL
;
PROBLEM: _publ_requested_journal is missing
RESPONSE: ...
;
_vrf_PUBL008_GLOBAL
;
PROBLEM: _publ_section_title is missing. Title of paper.
RESPONSE: ...
;
_vrf_PUBL010_GLOBAL
;
PROBLEM: _publ_author_address is missing. Author(s) address(es).
RESPONSE: ...
;
_vrf_PUBL012_GLOBAL
;
PROBLEM: _publ_section_abstract is missing.
RESPONSE: ...
;
# end Validation Reply Form
```

If you wish to submit your CIF for publication in Acta Crystallographica Section C or E, you should upload your CIF via the web. If you wish to submit your CIF for publication in IUCrData you should upload your CIF via the web. If your CIF is to form part of a submission to another IUCr journal, you will be asked, either during electronic submission or by the Co-editor handling your paper, to upload your CIF via our web site.

PLATON version of 04/06/2020; check.def file version of 02/06/2020

Datablock I - ellipsoid plot



Checkcif for compound 47

checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: I

```
Bond precision:  C-C = 0.0143 A          Wavelength=0.71073

Cell:            a=10.2800(4)     b=10.8668(5)     c=17.8313(8)
                 alpha=90         beta=90          gamma=90
Temperature:     295 K
```

	Calculated	Reported
Volume	1991.95(15)	1991.95(15)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	P 2ac 2ab
Moiety formula	C21 H26 N O2, Br	C21 H26 N O2, Br
Sum formula	C21 H26 Br N O2	C21 H26 Br N O2
Mr	404.33	404.33
Dx,g cm-3	1.348	1.348
Z	4	4
Mu (mm-1)	2.077	2.077
F000	840.0	840.0
F000’	839.16	
h,k,lmax	14,15,25	14,15,25
Nref	6352[3562]	6277
Tmin,Tmax	0.667,0.660	0.795,0.813
Tmin’	0.654	

```
Correction method= # Reported T Limits: Tmin=0.795 Tmax=0.813
AbsCorr = REFDELF

Data completeness= 1.76/0.99      Theta(max)= 31.012

R(reflections)= 0.0505( 1856)     wR2(reflections)= 0.1329( 6277)

S = 0.659                 Npar= 229
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level B

PLAT026_ALERT_3_B Ratio Observed / Unique Reflections (too) Low .. 30% Check

Alert level C

GOODF01_ALERT_2_C The least squares goodness of fit parameter lies outside the range 0.80 <> 2.00
Goodness of fit given = 0.659
PLAT234_ALERT_4_C Large Hirshfeld Difference N31 --C3 . 0.16 Ang.
PLAT341_ALERT_3_C Low Bond Precision on C-C Bonds ..... 0.01429 Ang.
PLAT790_ALERT_4_C Centre of Gravity not Within Unit Cell: Resd. # 1 Note
C21 H26 N O2

Alert level G

PLAT007_ALERT_5_G Number of Unrefined Donor-H Atoms ..... 2 Report
PLAT791_ALERT_4_G Model has Chirality at C3 (Sohnke SpGr) S Verify
PLAT791_ALERT_4_G Model has Chirality at C4 (Sohnke SpGr) R Verify
PLAT791_ALERT_4_G Model has Chirality at C32 (Sohnke SpGr) R Verify
PLAT941_ALERT_3_G Average HKL Measurement Multiplicity ..... 1.8 Low

0 **ALERT level A** = Most likely a serious problem - resolve or explain
1 **ALERT level B** = A potentially serious problem, consider carefully
4 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
5 **ALERT level G** = General information/check it is not something unexpected

0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
1 ALERT type 2 Indicator that the structure model may be wrong or deficient
3 ALERT type 3 Indicator that the structure quality may be low
5 ALERT type 4 Improvement, methodology, query or suggestion
1 ALERT type 5 Informative message, check

checkCIF publication errors

Alert level A

PUBL006_ALERT_1_A _publ_requested_journal is missing
e.g. 'Acta Crystallographica Section C'
PUBL008_ALERT_1_A _publ_section_title is missing. Title of paper.
PUBL010_ALERT_1_A _publ_author_address is missing. Author(s) address(es).
PUBL012_ALERT_1_A _publ_section_abstract is missing.
Abstract of paper in English.

Alert level G

PUBL017_ALERT_1_G The _publ_section_references section is missing or empty.

4 **ALERT level A** = Data missing that is essential or data in wrong format
1 **ALERT level G** = General alerts. Data that may be required is missing

Publication of your CIF

You should attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the nature of your study may justify the reported deviations from journal submission requirements and the more serious of these should be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. *checkCIF* was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

If level A alerts remain, which you believe to be justified deviations, and you intend to submit this CIF for publication in a journal, you should additionally insert an explanation in your CIF using the Validation Reply Form (VRF) below. This will allow your explanation to be considered as part of the review process.

Validation response form

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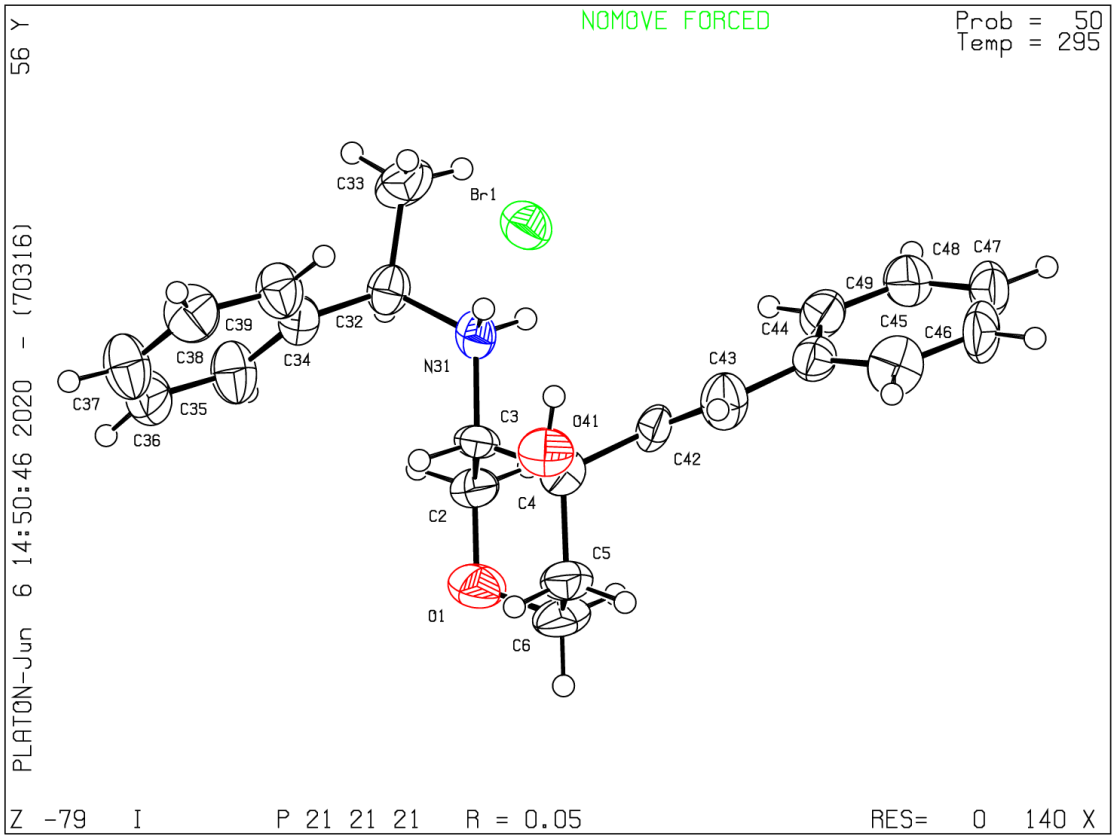
```
# start Validation Reply Form
_vrf_PUBL006_GLOBAL
;
PROBLEM: _publ_requested_journal is missing
RESPONSE: ...
;
_vrf_PUBL008_GLOBAL
;
PROBLEM: _publ_section_title is missing. Title of paper.
RESPONSE: ...
;
_vrf_PUBL010_GLOBAL
;
PROBLEM: _publ_author_address is missing. Author(s) address(es).
RESPONSE: ...
;
_vrf_PUBL012_GLOBAL
;
PROBLEM: _publ_section_abstract is missing.
RESPONSE: ...
;
# end Validation Reply Form
```

If you wish to submit your CIF for publication in Acta Crystallographica Section C or E, you should upload your CIF via the web. If you wish to submit your CIF for publication in IUCrData you should upload your CIF via the web. If your CIF is to form part of a submission to another IUCr journal, you will be asked, either during electronic submission or by the Co-editor handling your paper, to upload your CIF via our web site.

PLATON version of 04/06/2020; check.def file version of 02/06/2020

Datablock I - ellipsoid plot



Checkcif for compound 48

checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: I

```
Bond precision:  C-C = 0.0197 A          Wavelength=1.54186

Cell:            a=9.1272(13)     b=11.6147(14)     c=25.235(4)
                 alpha=90         beta=90           gamma=90
Temperature:     295 K

                Calculated                Reported
Volume          2675.2(7)                 2675.2(7)
Space group     P 21 21 21                P 21 21 21
Hall group      P 2ac 2ab                 P 2ac 2ab
Moiety formula  C26 H35 N2 O3, Br         C26 H35 N2 O3, Br
Sum formula     C26 H35 Br N2 O3          C26 H35 Br N2 O3
Mr              503.46                    503.46
Dx,g cm-3       1.250                     1.250
Z               4                         4
Mu (mm-1)       2.305                     2.305
F000            1056.0                    1056.0
F000'           1055.87
h,k,lmax        11,14,30                  11,14,30
Nref            5079[ 2893]               5003
Tmin,Tmax       0.794,0.794               0.726,0.812
Tmin'           0.794

Correction method= # Reported T Limits: Tmin=0.726 Tmax=0.812
AbsCorr = REFDELF

Data completeness= 1.73/0.99      Theta(max)= 70.120

R(reflections)= 0.0949( 1293)     wR2(reflections)= 0.1764( 5003)

S = 0.849                 Npar= 181
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level A

PLAT026_ALERT_3_A Ratio Observed / Unique Reflections (too) Low .. 26% Check

Author Response: The crystals were of very-very poor quality

Alert level B

PLAT230_ALERT_2_B Hirshfeld Test Diff for O3 --C3 . 7.7 s.u.
PLAT230_ALERT_2_B Hirshfeld Test Diff for C3 --C31 . 8.0 s.u.
PLAT230_ALERT_2_B Hirshfeld Test Diff for C32 --C33 . 9.4 s.u.
PLAT234_ALERT_4_B Large Hirshfeld Difference O12 --C11 . 0.30 Ang.
PLAT341_ALERT_3_B Low Bond Precision on C-C Bonds ..... 0.01975 Ang.

Alert level C

PLAT220_ALERT_2_C NonSolvent Resd 1 C Ueq(max) / Ueq(min) Range 5.3 Ratio
PLAT230_ALERT_2_C Hirshfeld Test Diff for C2 --C3 . 6.4 s.u.
PLAT230_ALERT_2_C Hirshfeld Test Diff for C3 --C4 . 6.4 s.u.
PLAT234_ALERT_4_C Large Hirshfeld Difference N1 --C6 . 0.18 Ang.
PLAT234_ALERT_4_C Large Hirshfeld Difference N1 --C11 . 0.22 Ang.
PLAT234_ALERT_4_C Large Hirshfeld Difference C13 --C14 . 0.24 Ang.
PLAT234_ALERT_4_C Large Hirshfeld Difference C13 --C15 . 0.22 Ang.
PLAT241_ALERT_2_C High 'MainMol' Ueq as Compared to Neighbors of C2 Check
PLAT241_ALERT_2_C High 'MainMol' Ueq as Compared to Neighbors of C11 Check
PLAT241_ALERT_2_C High 'MainMol' Ueq as Compared to Neighbors of C31 Check
PLAT241_ALERT_2_C High 'MainMol' Ueq as Compared to Neighbors of C33 Check
PLAT242_ALERT_2_C Low 'MainMol' Ueq as Compared to Neighbors of O12 Check
PLAT242_ALERT_2_C Low 'MainMol' Ueq as Compared to Neighbors of N1 Check
PLAT242_ALERT_2_C Low 'MainMol' Ueq as Compared to Neighbors of C3 Check
PLAT242_ALERT_2_C Low 'MainMol' Ueq as Compared to Neighbors of C32 Check

---

Alert level G

PLAT002_ALERT_2_G Number of Distance or Angle Restraints on AtSite 7 Note
PLAT003_ALERT_2_G Number of Uiso or Uij Restrained non-H Atoms ... 15 Report
PLAT007_ALERT_5_G Number of Unrefined Donor-H Atoms ..... 3 Report
PLAT171_ALERT_4_G The CIF-Embedded .res File Contains EADP Records 4 Report
PLAT176_ALERT_4_G The CIF-Embedded .res File Contains SADI Records 3 Report
PLAT186_ALERT_4_G The CIF-Embedded .res File Contains ISOR Records 1 Report
PLAT791_ALERT_4_G Model has Chirality at C3 (Sohnke SpGr) S Verify
PLAT791_ALERT_4_G Model has Chirality at C4 (Sohnke SpGr) S Verify
PLAT791_ALERT_4_G Model has Chirality at C41 (Sohnke SpGr) R Verify
PLAT860_ALERT_3_G Number of Least-Squares Restraints ..... 97 Note
PLAT941_ALERT_3_G Average HKL Measurement Multiplicity ..... 1.7 Low

---

1 **ALERT level A** = Most likely a serious problem - resolve or explain
5 **ALERT level B** = A potentially serious problem, consider carefully
15 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
11 **ALERT level G** = General information/check it is not something unexpected

0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data

```
  16 ALERT type 2 Indicator that the structure model may be wrong or deficient
   4 ALERT type 3 Indicator that the structure quality may be low
  11 ALERT type 4 Improvement, methodology, query or suggestion
   1 ALERT type 5 Informative message, check
```

checkCIF publication errors

Alert level A

```
PUBL006_ALERT_1_A  _publ_requested_journal is missing
            e.g. 'Acta Crystallographica Section C'
PUBL008_ALERT_1_A  _publ_section_title is missing. Title of paper.
PUBL010_ALERT_1_A  _publ_author_address is missing. Author(s) address(es).
PUBL012_ALERT_1_A  _publ_section_abstract is missing.
            Abstract of paper in English.
```

Alert level G

```
PUBL017_ALERT_1_G The _publ_section_references section is missing or
            empty.
```

```
   4 ALERT level A = Data missing that is essential or data in wrong format
   1 ALERT level G = General alerts. Data that may be required is missing
```

Publication of your CIF

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```
# start Validation Reply Form
_vrf_PUBL006_GLOBAL
;
PROBLEM: _publ_requested_journal is missing
```

```
RESPONSE: ...
;
_vrf_PUBL008_GLOBAL
;
PROBLEM: _publ_section_title is missing. Title of paper.
RESPONSE: ...
;
_vrf_PUBL010_GLOBAL
;
PROBLEM: _publ_author_address is missing. Author(s) address(es).
RESPONSE: ...
;
_vrf_PUBL012_GLOBAL
;
PROBLEM: _publ_section_abstract is missing.
RESPONSE: ...
;
# end Validation Reply Form
```

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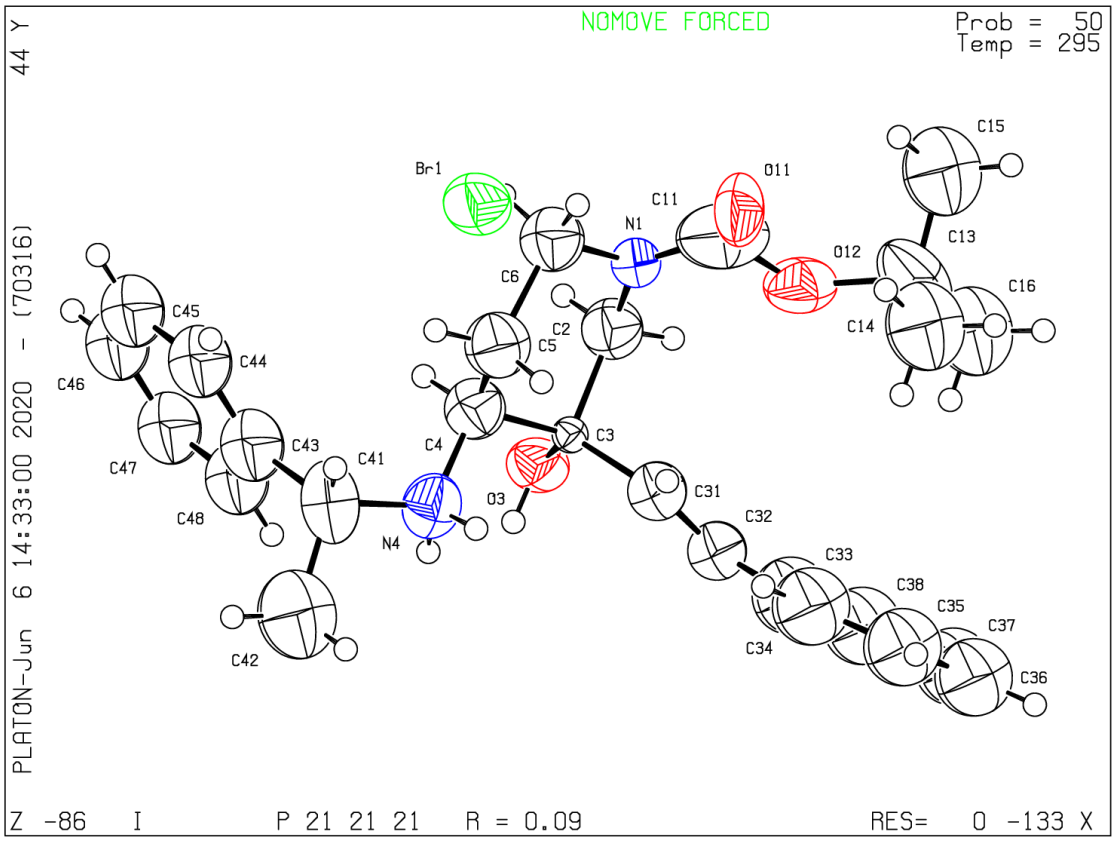
PLATON version of 04/06/2020; check.def file version of 02/06/2020

Datablock I - ellipsoid plot



Checkcif for compound 53b

checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

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No syntax errors found. CIF dictionary Interpreting this report

Datablock: I

```
Bond precision:  C-C = 0.0026 A          Wavelength=1.54180

Cell:            a=5.6234(2)     b=15.5257(5)     c=21.3791(5)
                 alpha=90        beta=90          gamma=90
Temperature:     295 K
```

	Calculated	Reported
Volume	1866.55(10)	1866.55(10)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	P 2ac 2ab
Moiety formula	C22 H25 N O2	C22 H25 N O2
Sum formula	C22 H25 N O2	C22 H25 N O2
Mr	335.43	335.43
Dx,g cm-3	1.194	1.194
Z	4	4
Mu (mm-1)	0.595	0.595
F000	720.0	720.0
F000’	722.01	
h,k,lmax	6,19,26	6,19,26
Nref	3621[2116]	2114
Tmin,Tmax	0.931,0.971	
Tmin’	0.915	

```
Correction method= Not given

Data completeness= 1.00/0.58      Theta(max)= 71.230

R(reflections)= 0.0407( 1112)     wR2(reflections)= 0.0980( 2114)

S = 0.549                 Npar= 191
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level B

```
GOODF01_ALERT_2_B  The least squares goodness of fit parameter lies
           outside the range 0.60 <> 4.00
           Goodness of fit given =      0.549
```

Alert level C

```
PLAT086_ALERT_2_C Unsatisfactory S Value (Too Low or Not Given) ..       0.55 Check
PLAT165_ALERT_3_C Nr. of Status R Flagged Non-Hydrogen Atoms .....         12 Note
PLAT230_ALERT_2_C Hirshfeld Test Diff for    C7       --C8       .        5.7 s.u.
PLAT230_ALERT_2_C Hirshfeld Test Diff for    C13      --C14      .        6.7 s.u.
PLAT230_ALERT_2_C Hirshfeld Test Diff for    C35      --C36      .        5.5 s.u.
PLAT241_ALERT_2_C High   'MainMol' Ueq as Compared to Neighbors of         C7 Check
```

Alert level G

```
PLAT005_ALERT_5_G No Embedded Refinement Details Found  in the CIF     Please Do !
PLAT791_ALERT_4_G Model has Chirality at C1          (Sohnke SpGr)          R Verify
PLAT791_ALERT_4_G Model has Chirality at C4          (Sohnke SpGr)          R Verify
PLAT791_ALERT_4_G Model has Chirality at C10         (Sohnke SpGr)          S Verify
PLAT791_ALERT_4_G Model has Chirality at C31         (Sohnke SpGr)          R Verify
PLAT981_ALERT_1_G No non-zero f" Anomalous Scattering Values Found     Please Check
```

---

0 **ALERT level A** = Most likely a serious problem - resolve or explain
1 **ALERT level B** = A potentially serious problem, consider carefully
6 **ALERT level C** = Check. Ensure it is not caused by an omission or oversight
6 **ALERT level G** = General information/check it is not something unexpected

1 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
6 ALERT type 2 Indicator that the structure model may be wrong or deficient
1 ALERT type 3 Indicator that the structure quality may be low
4 ALERT type 4 Improvement, methodology, query or suggestion
1 ALERT type 5 Informative message, check

---

checkCIF publication errors

Alert level A

```
PUBL006_ALERT_1_A  _publ_requested_journal is missing
           e.g. 'Acta Crystallographica Section C'
PUBL008_ALERT_1_A  _publ_section_title is missing. Title of paper.
PUBL010_ALERT_1_A  _publ_author_address is missing. Author(s) address(es).
PUBL012_ALERT_1_A  _publ_section_abstract is missing.
           Abstract of paper in English.
```

Alert level G

```
PUBL017_ALERT_1_G The _publ_section_references section is missing or
           empty.
```

---

4 **ALERT level A** = Data missing that is essential or data in wrong format
1 **ALERT level G** = General alerts. Data that may be required is missing

---

Publication of your CIF

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Validation response form

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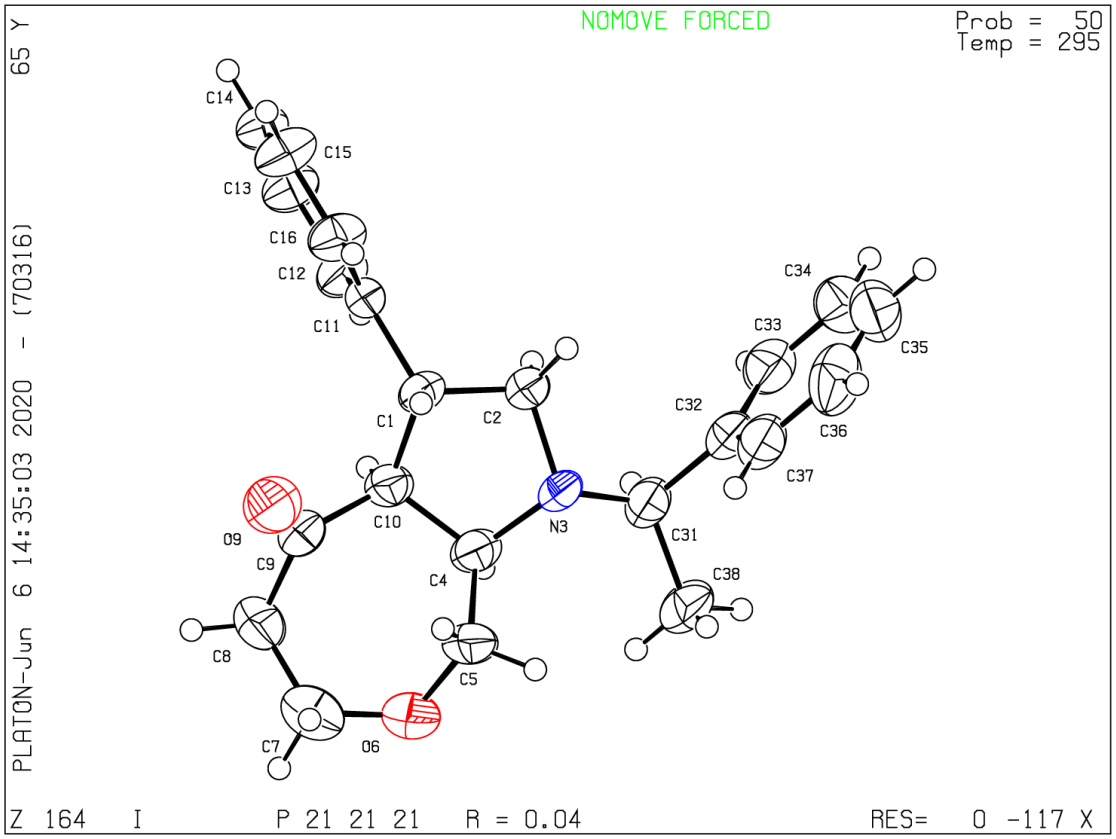
```
# start Validation Reply Form
_vrf_PUBL006_GLOBAL
;
PROBLEM: _publ_requested_journal is missing
RESPONSE: ...
;
_vrf_PUBL008_GLOBAL
;
PROBLEM: _publ_section_title is missing. Title of paper.
RESPONSE: ...
;
_vrf_PUBL010_GLOBAL
;
PROBLEM: _publ_author_address is missing. Author(s) address(es).
RESPONSE: ...
;
_vrf_PUBL012_GLOBAL
;
PROBLEM: _publ_section_abstract is missing.
RESPONSE: ...
;
# end Validation Reply Form
```

If you wish to submit your CIF for publication in Acta Crystallographica Section C or E, you should upload your CIF via the web. If you wish to submit your CIF for publication in IUCrData you should upload your CIF via the web. If your CIF is to form part of a submission to another IUCr journal, you will be asked, either during electronic submission or by the Co-editor handling your paper, to upload your CIF via our web site.

PLATON version of 04/06/2020; check.def file version of 02/06/2020

Datablock I - ellipsoid plot



Checkcif for compound 55a

checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: I

```
Bond precision:  C-C = 0.0088 A          Wavelength=1.54180

Cell:            a=5.8222(2)     b=18.1399(5)     c=23.3280(8)
                 alpha=90        beta=90          gamma=90
Temperature:     295 K
```

	Calculated	Reported
Volume	2463.77(14)	2463.77(14)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	P 2ac 2ab
Moiety formula	C27 H34 N2 O3	C27 H34 N2 O3
Sum formula	C27 H34 N2 O3	C27 H34 N2 O3
Mr	434.56	434.56
Dx,g cm-3	1.172	1.172
Z	4	4
Mu (mm-1)	0.602	0.602
F000	936.0	936.0
F000’	938.65	
h,k,lmax	7,22,28	7,22,28
Nref	4690[2720]	4629
Tmin,Tmax	0.887,0.887	0.940,0.944
Tmin’	0.887	

```
Correction method= # Reported T Limits: Tmin=0.940 Tmax=0.944
AbsCorr = REFDELF

Data completeness= 1.70/0.99      Theta(max)= 70.147

R(reflections)= 0.0531( 1574)     wR2(reflections)= 0.1377( 4629)

S = 0.527                 Npar= 289
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level B

```
GOODF01_ALERT_2_B  The least squares goodness of fit parameter lies
           outside the range 0.60 <> 4.00
           Goodness of fit given =      0.527
PLAT026_ALERT_3_B Ratio Observed / Unique Reflections (too) Low ..        34% Check
```

Alert level C

```
STRVA01_ALERT_4_C           Flack parameter is too small
          From the CIF: _refine_ls_abs_structure_Flack   -0.900
          From the CIF: _refine_ls_abs_structure_Flack_su    0.600
PLAT086_ALERT_2_C Unsatisfactory S Value (Too Low or Not Given) ..       0.53 Check
PLAT234_ALERT_4_C Large Hirshfeld Difference C83      --C86      .       0.17 Ang.
PLAT242_ALERT_2_C Low    'MainMol' Ueq as Compared to Neighbors of        C83 Check
PLAT340_ALERT_3_C Low Bond Precision on  C-C Bonds ..............     0.0088 Ang.
```

Alert level G

```
PLAT032_ALERT_4_G Std. Uncertainty on Flack Parameter Value High .      0.600 Report
PLAT791_ALERT_4_G Model has Chirality at C3          (Sohnke SpGr)          R Verify
PLAT791_ALERT_4_G Model has Chirality at C4          (Sohnke SpGr)          S Verify
PLAT791_ALERT_4_G Model has Chirality at C10         (Sohnke SpGr)          S Verify
PLAT791_ALERT_4_G Model has Chirality at C11         (Sohnke SpGr)          R Verify
PLAT941_ALERT_3_G Average HKL Measurement Multiplicity ...........        1.7 Low
```

```
   0 ALERT level A = Most likely a serious problem - resolve or explain
   2 ALERT level B = A potentially serious problem, consider carefully
   5 ALERT level C = Check. Ensure it is not caused by an omission or oversight
   6 ALERT level G = General information/check it is not something unexpected

   0 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
   3 ALERT type 2 Indicator that the structure model may be wrong or deficient
   3 ALERT type 3 Indicator that the structure quality may be low
   7 ALERT type 4 Improvement, methodology, query or suggestion
   0 ALERT type 5 Informative message, check
```

checkCIF publication errors

Alert level A

```
PUBL006_ALERT_1_A  _publ_requested_journal is missing
           e.g. 'Acta Crystallographica Section C'
PUBL008_ALERT_1_A  _publ_section_title is missing. Title of paper.
PUBL010_ALERT_1_A  _publ_author_address is missing. Author(s) address(es).
PUBL012_ALERT_1_A  _publ_section_abstract is missing.
           Abstract of paper in English.
```

Alert level G

```
PUBL017_ALERT_1_G The _publ_section_references section is missing or
           empty.
```

```
   4 ALERT level A = Data missing that is essential or data in wrong format
   1 ALERT level G = General alerts. Data that may be required is missing
```

Publication of your CIF

You should attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the nature of your study may justify the reported deviations from journal submission requirements and the more serious of these should be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. *checkCIF* was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

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Validation response form

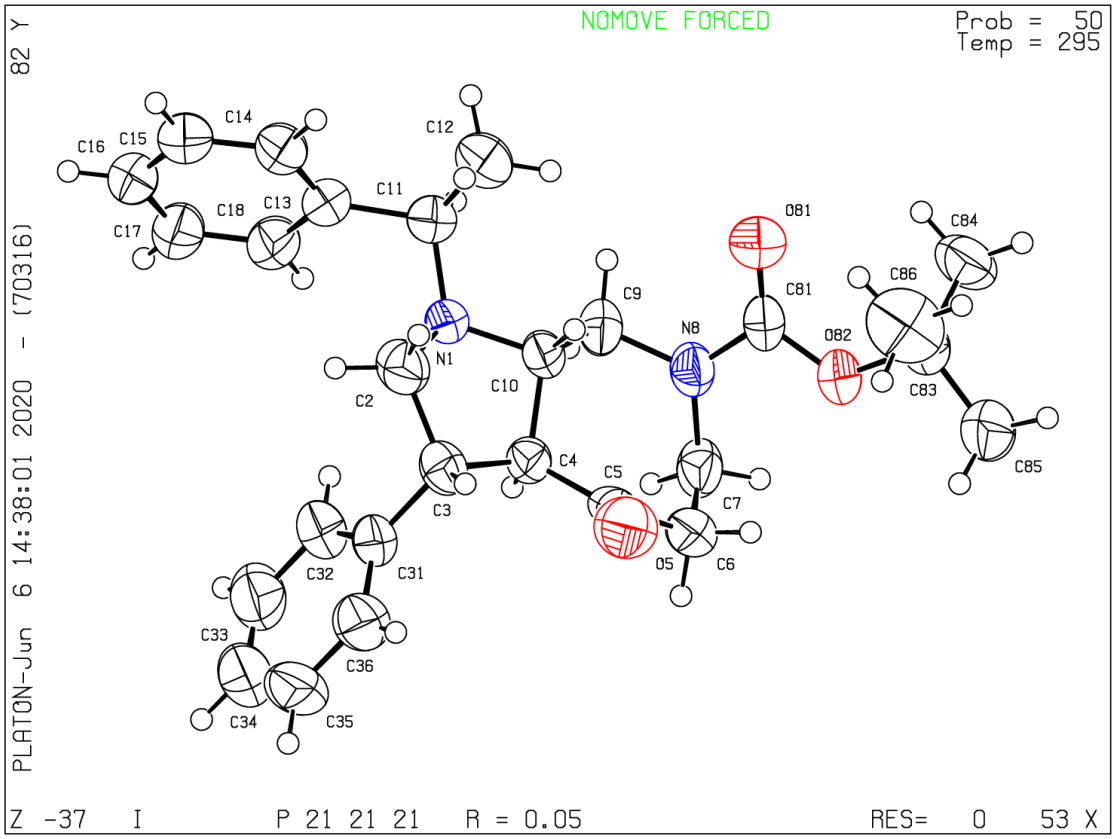
Please find below a validation response form (VRF) that can be filled in and pasted into your CIF.

```
# start Validation Reply Form
_vrf_PUBL006_GLOBAL
;
PROBLEM: _publ_requested_journal is missing
RESPONSE: ...
;
_vrf_PUBL008_GLOBAL
;
PROBLEM: _publ_section_title is missing. Title of paper.
RESPONSE: ...
;
_vrf_PUBL010_GLOBAL
;
PROBLEM: _publ_author_address is missing. Author(s) address(es).
RESPONSE: ...
;
_vrf_PUBL012_GLOBAL
;
PROBLEM: _publ_section_abstract is missing.
RESPONSE: ...
;
# end Validation Reply Form
```

If you wish to submit your CIF for publication in Acta Crystallographica Section C or E, you should upload your CIF via the web. If you wish to submit your CIF for publication in IUCrData you should upload your CIF via the web. If your CIF is to form part of a submission to another IUCr journal, you will be asked, either during electronic submission or by the Co-editor handling your paper, to upload your CIF via our web site.

PLATON version of 04/06/2020; check.def file version of 02/06/2020

Datablock I - ellipsoid plot



Checkcif for compound 56a

checkCIF/PLATON report

You have not supplied any structure factors. As a result the full set of tests cannot be run.

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found. CIF dictionary Interpreting this report

Datablock: I

```
Bond precision:  C-C = 0.0019 A          Wavelength=1.54180

Cell:            a=5.7280(1)     b=16.4639(3)     c=19.5056(5)
                 alpha=90        beta=90          gamma=90
Temperature:     295 K
```

	Calculated	Reported
Volume	1839.48(7)	1839.48(7)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	P 2ac 2ab
Moiety formula	C22 H25 N O2	C22 H25 N O2
Sum formula	C22 H25 N O2	C22 H25 N O2
Mr	335.43	335.43
Dx,g cm-3	1.211	1.211
Z	4	4
Mu (mm-1)	0.603	0.603
F000	720.0	720.0
F000’	722.01	
h,k,lmax	7,20,24	7,20,23
Nref	3598[2101]	2085
Tmin,Tmax	0.897,0.941	
Tmin’	0.860	

```
Correction method= Not given

Data completeness= 0.99/0.58      Theta(max)= 71.880

R(reflections)= 0.0507( 1849)     wR2(reflections)= 0.1316( 2085)

S = 1.053                 Npar= 191
```

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level B

```
PLAT230_ALERT_2_B Hirshfeld Test Diff for    C32      --C37      .        8.9 s.u.
```

Alert level C

```
PLAT165_ALERT_3_C Nr. of Status R Flagged Non-Hydrogen Atoms .....         12 Note
PLAT230_ALERT_2_C Hirshfeld Test Diff for    C11      --C12      .        6.7 s.u.
PLAT230_ALERT_2_C Hirshfeld Test Diff for    C14      --C15      .        6.0 s.u.
```

Alert level G

```
PLAT005_ALERT_5_G No Embedded Refinement Details Found  in the CIF     Please Do !
PLAT791_ALERT_4_G Model has Chirality at C1          (Sohnke SpGr)          R Verify
PLAT791_ALERT_4_G Model has Chirality at C4          (Sohnke SpGr)          S Verify
PLAT791_ALERT_4_G Model has Chirality at C10         (Sohnke SpGr)          S Verify
PLAT791_ALERT_4_G Model has Chirality at C31         (Sohnke SpGr)          R Verify
PLAT981_ALERT_1_G No non-zero f" Anomalous Scattering Values Found     Please Check
```

```
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   6 ALERT level G = General information/check it is not something unexpected

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   4 ALERT type 4 Improvement, methodology, query or suggestion
   1 ALERT type 5 Informative message, check
```

---

checkCIF publication errors

Alert level A

```
PUBL006_ALERT_1_A  _publ_requested_journal is missing
            e.g. 'Acta Crystallographica Section C'
PUBL008_ALERT_1_A  _publ_section_title is missing. Title of paper.
PUBL010_ALERT_1_A  _publ_author_address is missing. Author(s) address(es).
PUBL012_ALERT_1_A  _publ_section_abstract is missing.
            Abstract of paper in English.
```

Alert level G

```
PUBL017_ALERT_1_G The _publ_section_references section is missing or
            empty.
```

```
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   1 ALERT level G = General alerts. Data that may be required is missing
```

Publication of your CIF

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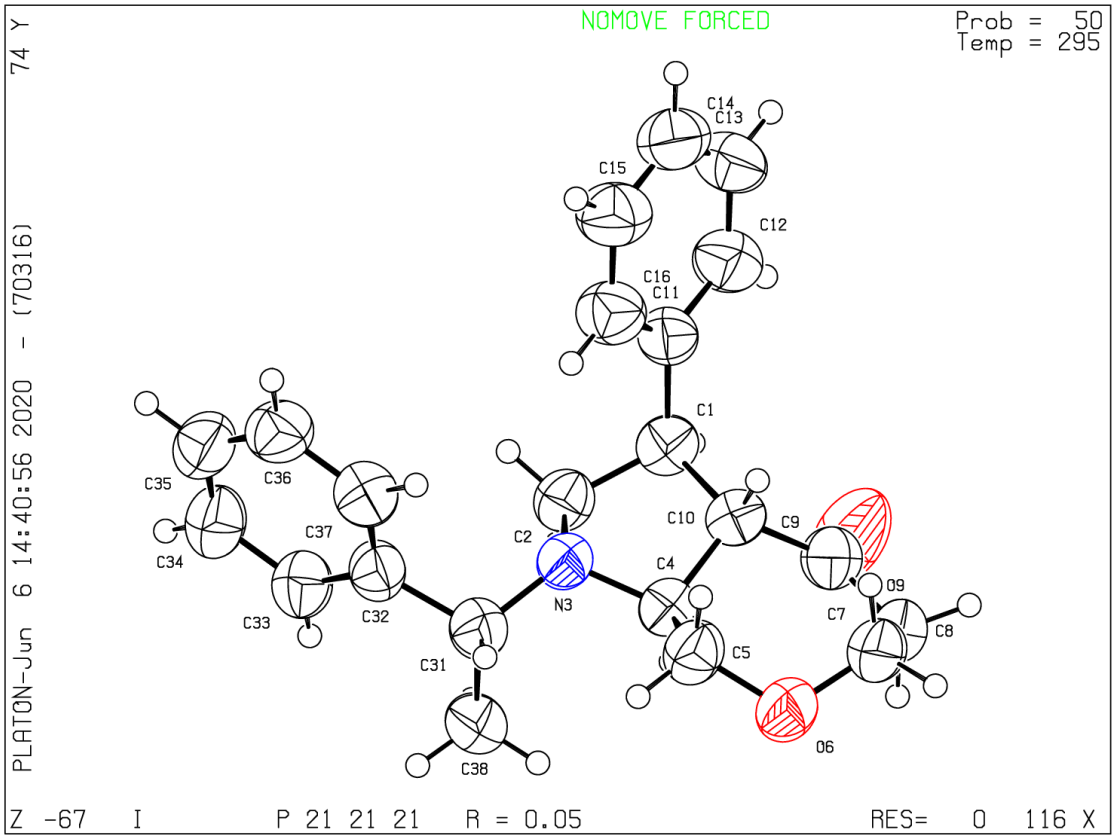
_vrf_PUBL006_GLOBAL
;
PROBLEM: _publ_requested_journal is missing
RESPONSE: ...
;
_vrf_PUBL008_GLOBAL
;
PROBLEM: _publ_section_title is missing. Title of paper.
RESPONSE: ...
;
_vrf_PUBL010_GLOBAL
;
PROBLEM: _publ_author_address is missing. Author(s) address(es).
RESPONSE: ...
;
_vrf_PUBL012_GLOBAL
;
PROBLEM: _publ_section_abstract is missing.
RESPONSE: ...
;
# end Validation Reply Form
```

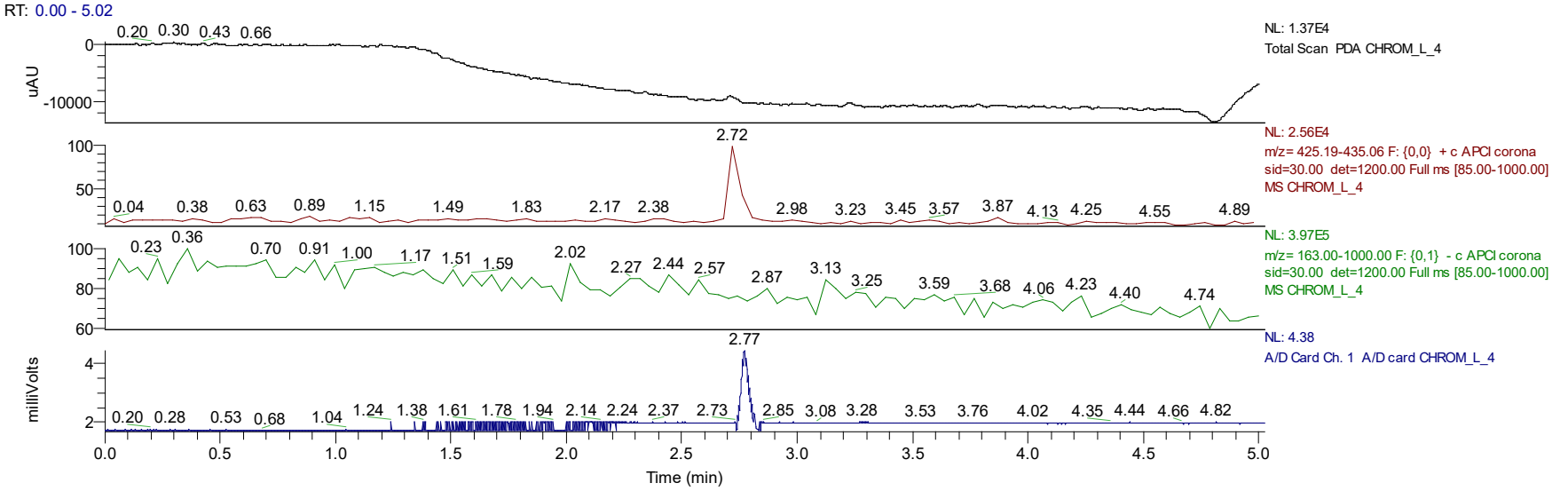
If you wish to submit your CIF for publication in Acta Crystallographica Section C or E, you should upload your CIF via the web. If you wish to submit your CIF for publication in IUCrData you should upload your CIF via the web. If your CIF is to form part of a submission to another IUCr journal, you will be asked, either during electronic submission or by the Co-editor handling your paper, to upload your CIF via our web site.

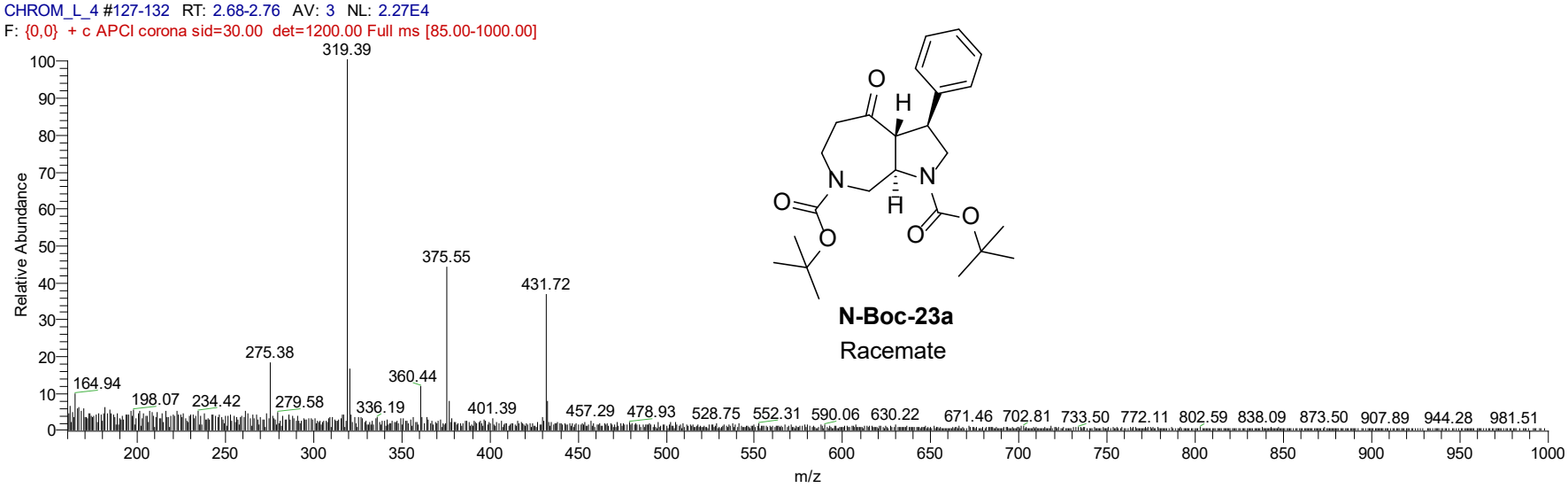
PLATON version of 04/06/2020; check.def file version of 02/06/2020

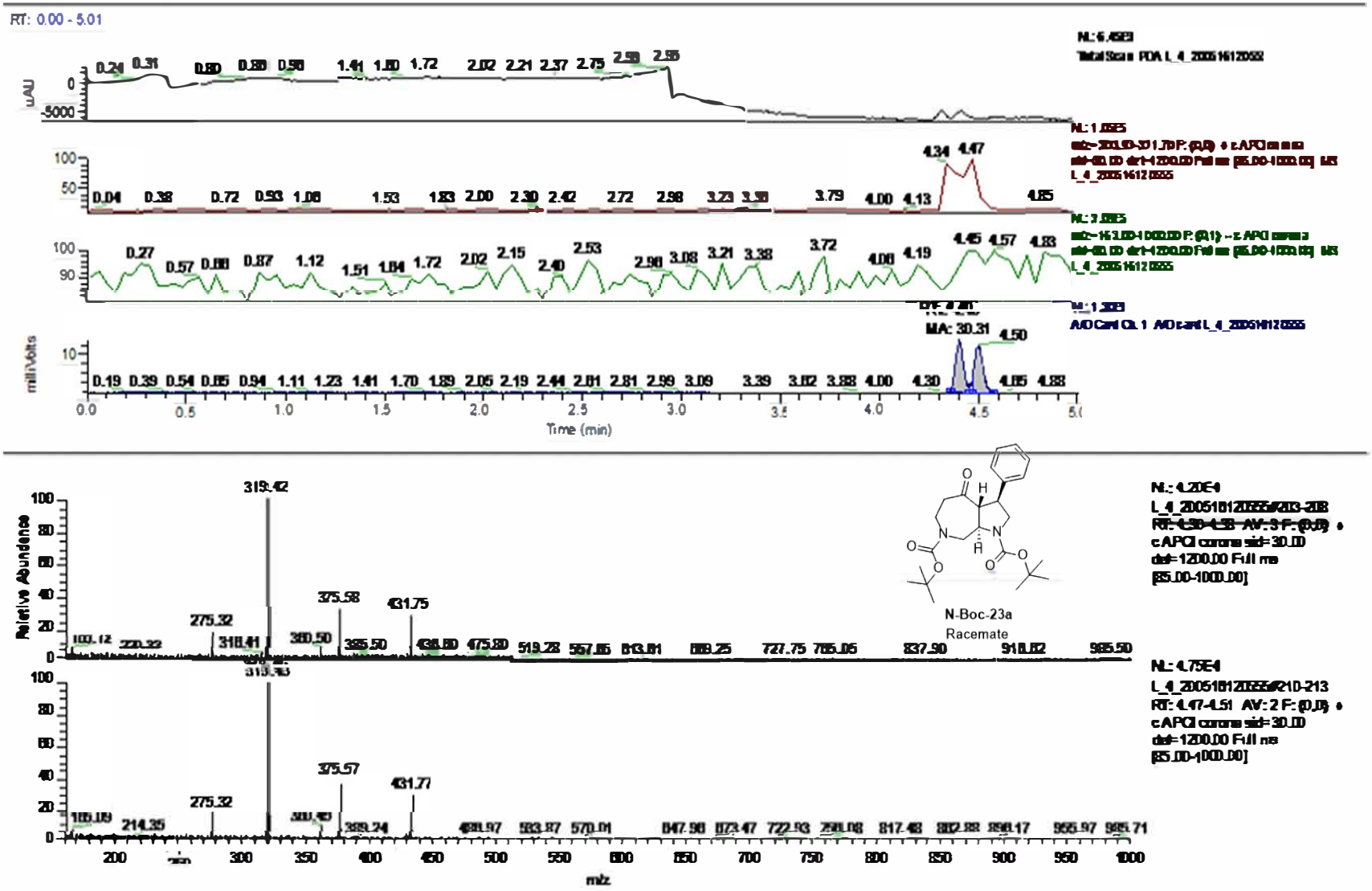
Datablock I - ellipsoid plot

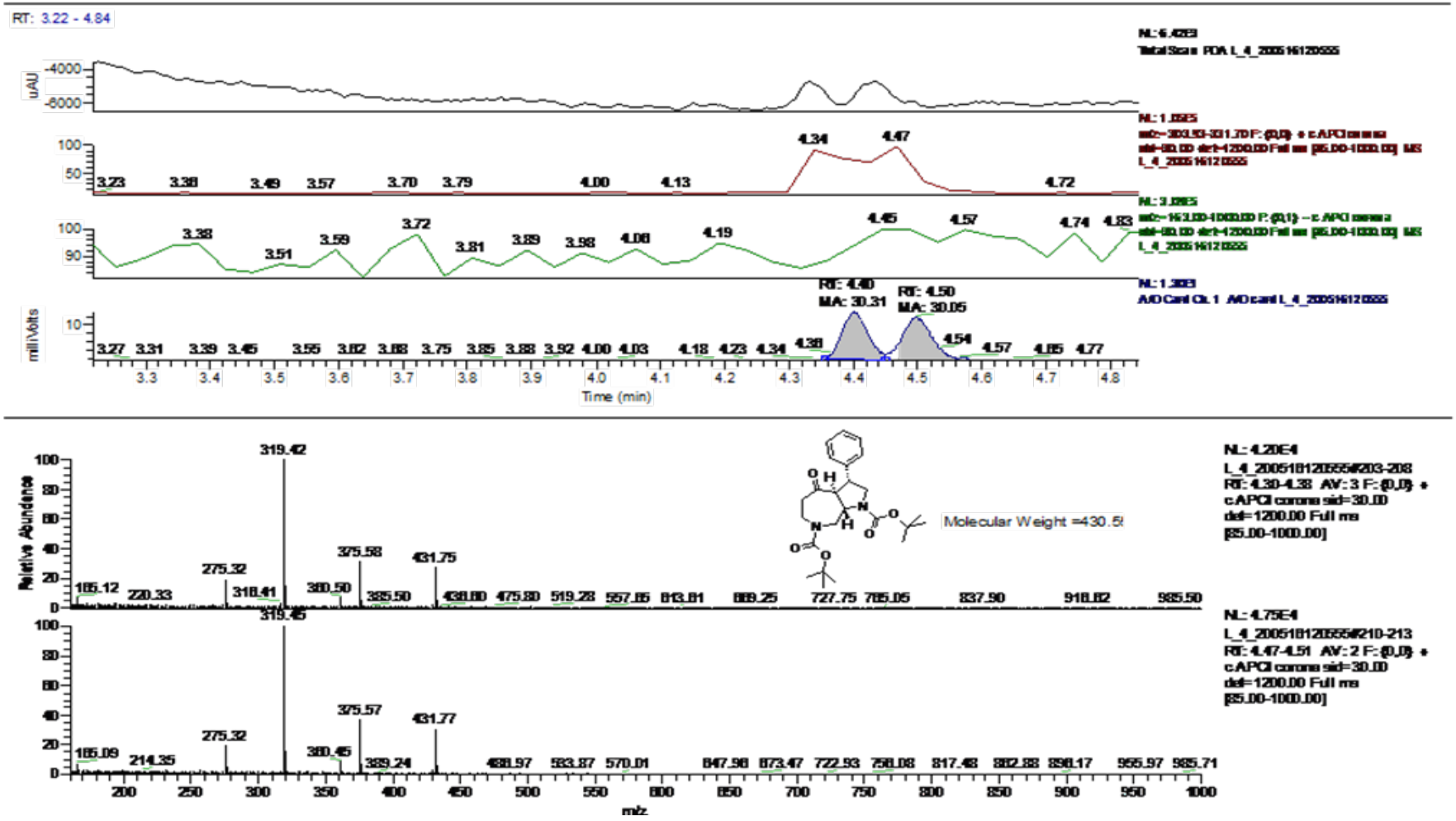


GC/MS-Traces compounds

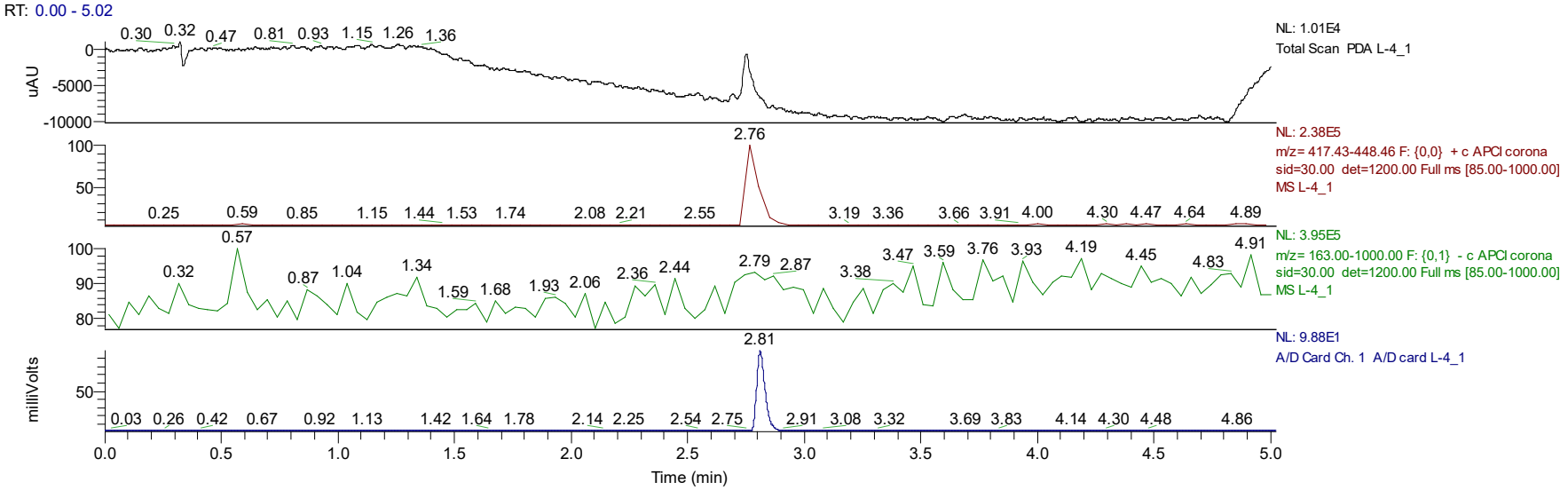


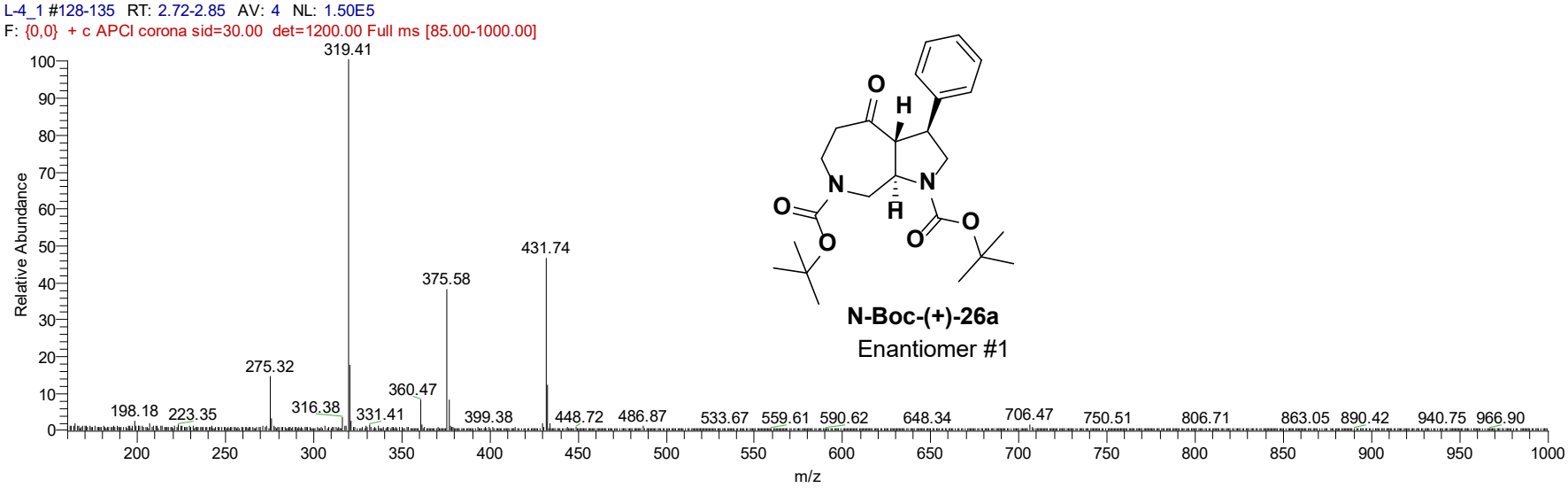


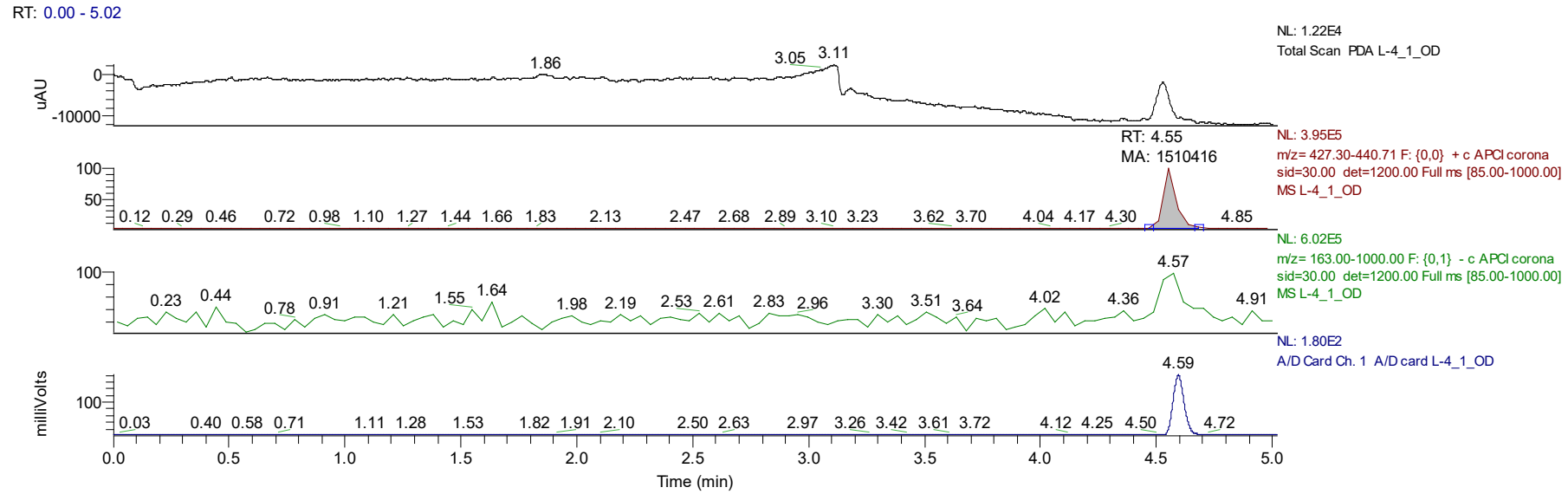

RT: 0.00 - 5.01
mAU
milliVolts
Time (min)
MA: 30.31
N-Boc-23a
Racemate
Relative Abundance
m/z

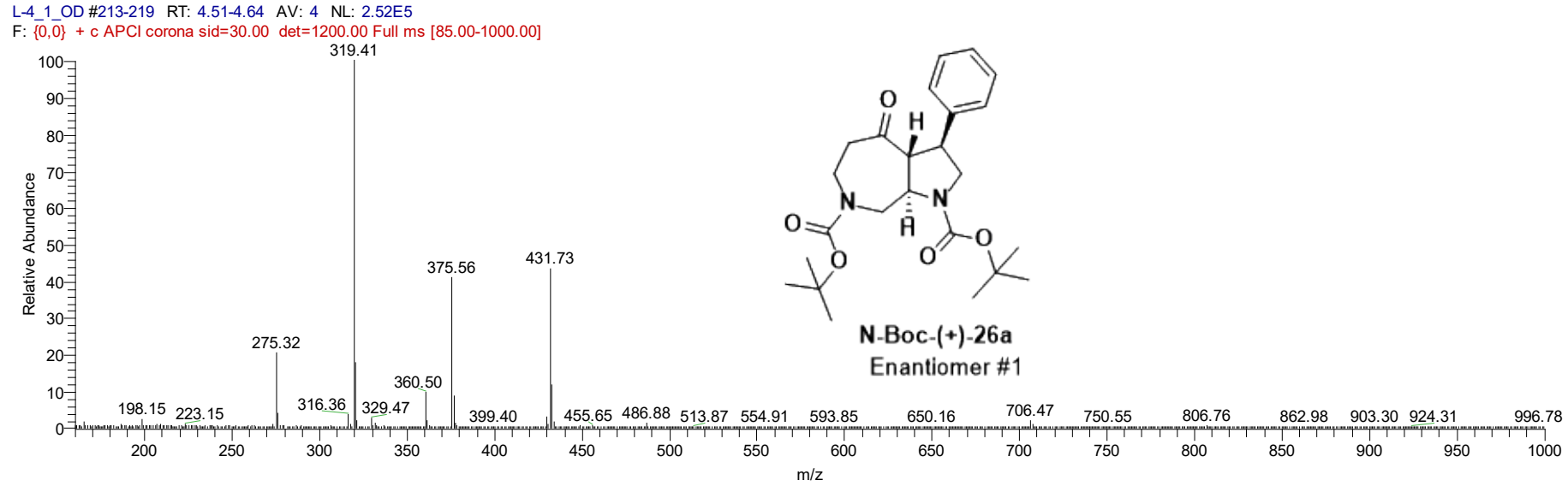


Area %	Peak Area	RT
50.2	30.31	4.40
49.8	30.05	4.50

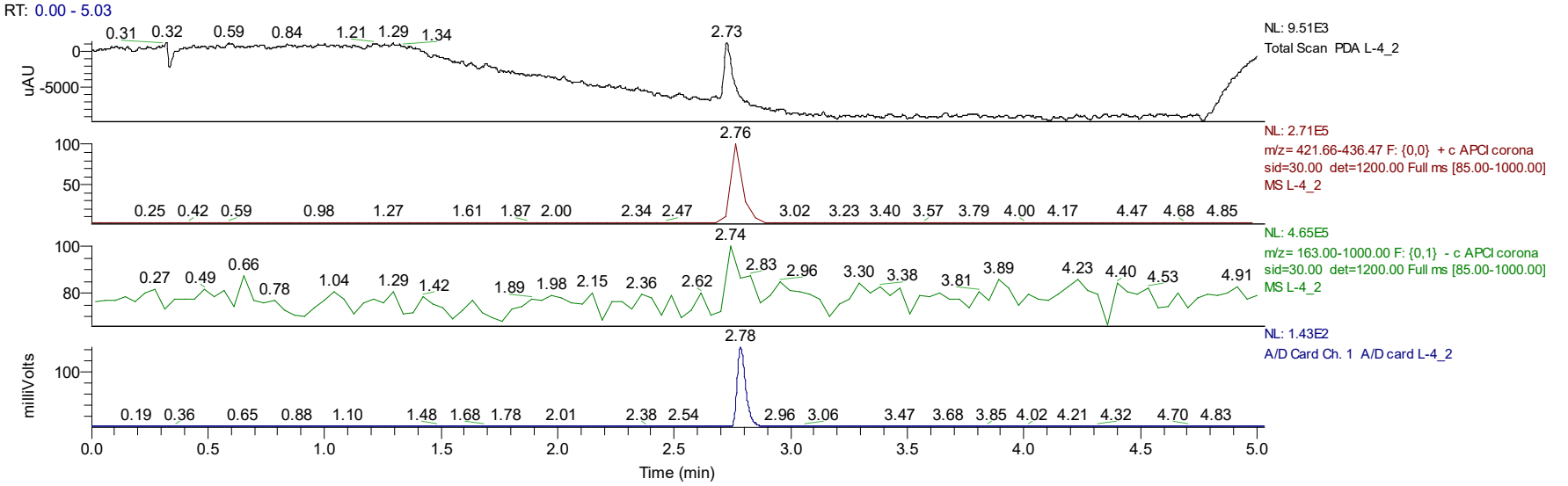

RT: 0.00 - 5.02
NL: 1.01E4
Total Scan PDA L-4_1
uAU
NL: 2.38E5
m/z= 417.43-448.46 F: {0,0} + c APCI corona
sid=30.00 det=1200.00 Full ms [85.00-1000.00]
MS L-4_1
NL: 3.95E5
m/z= 163.00-1000.00 F: {0,1} - c APCI corona
sid=30.00 det=1200.00 Full ms [85.00-1000.00]
MS L-4_1
NL: 9.88E1
A/D Card Ch. 1 A/D card L-4_1
milliVolts
Time (min)

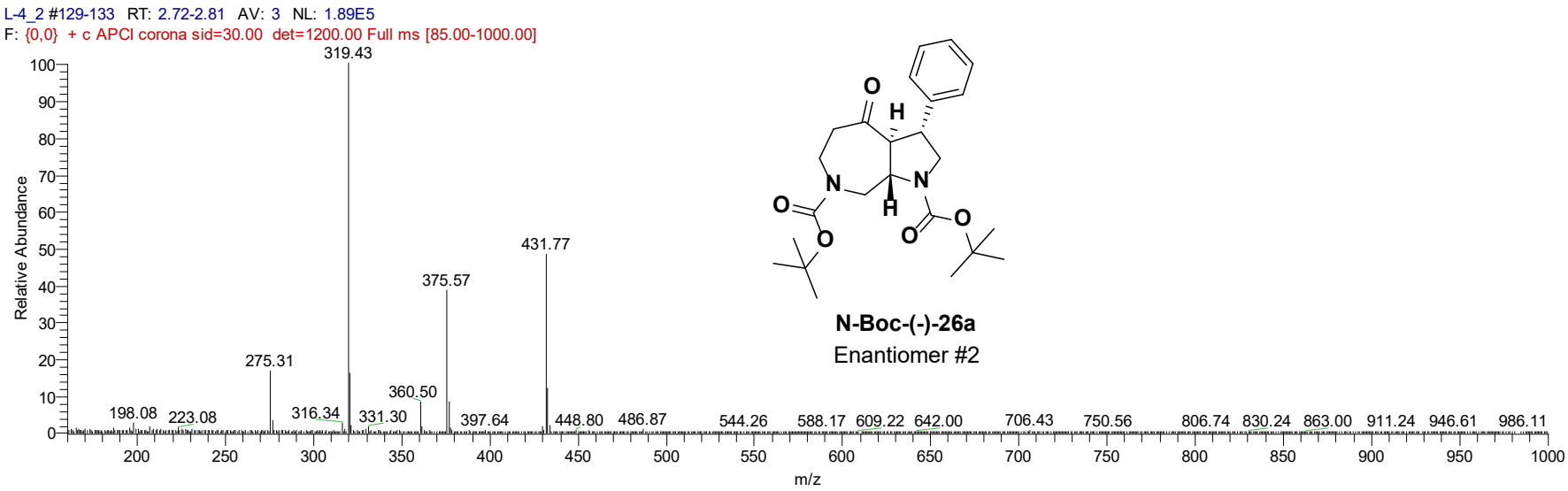

L-4_1 #128-135 RT: 2.72-2.85 AV: 4 NL: 1.50E5
F: {0,0} + c APCI corona sid=30.00 det=1200.00 Full ms [85.00-1000.00]
Relative Abundance
m/z
N-Boc-(+)-26a
Enantiomer #1



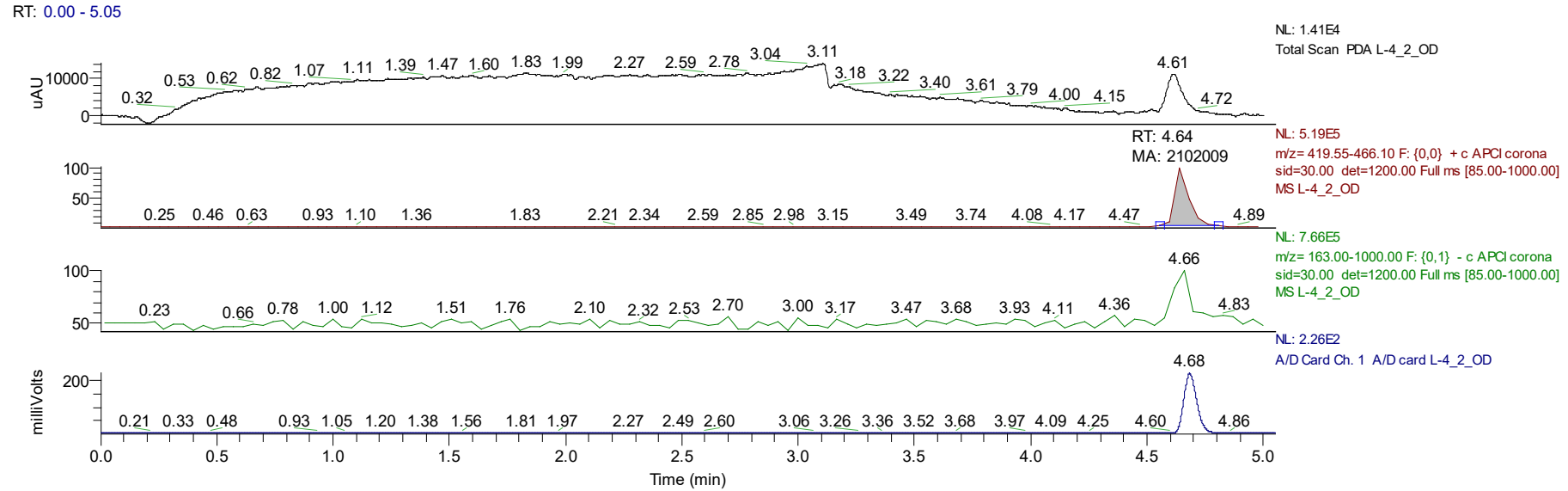


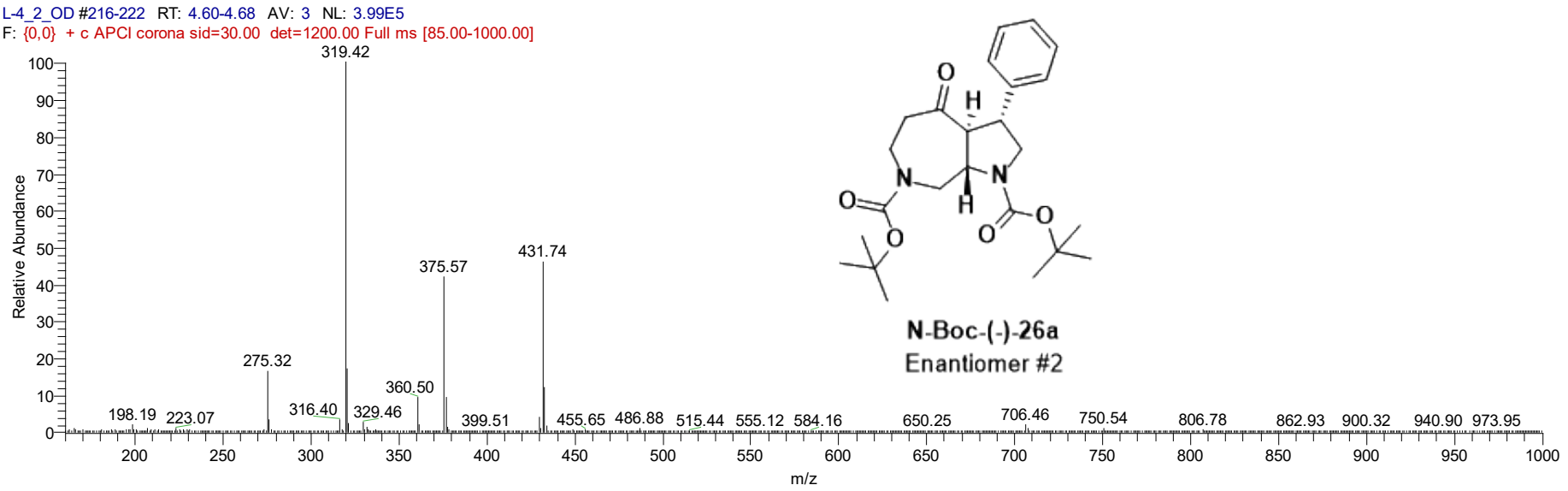
Area %	Peak Area	RT
100	1510416	4.55



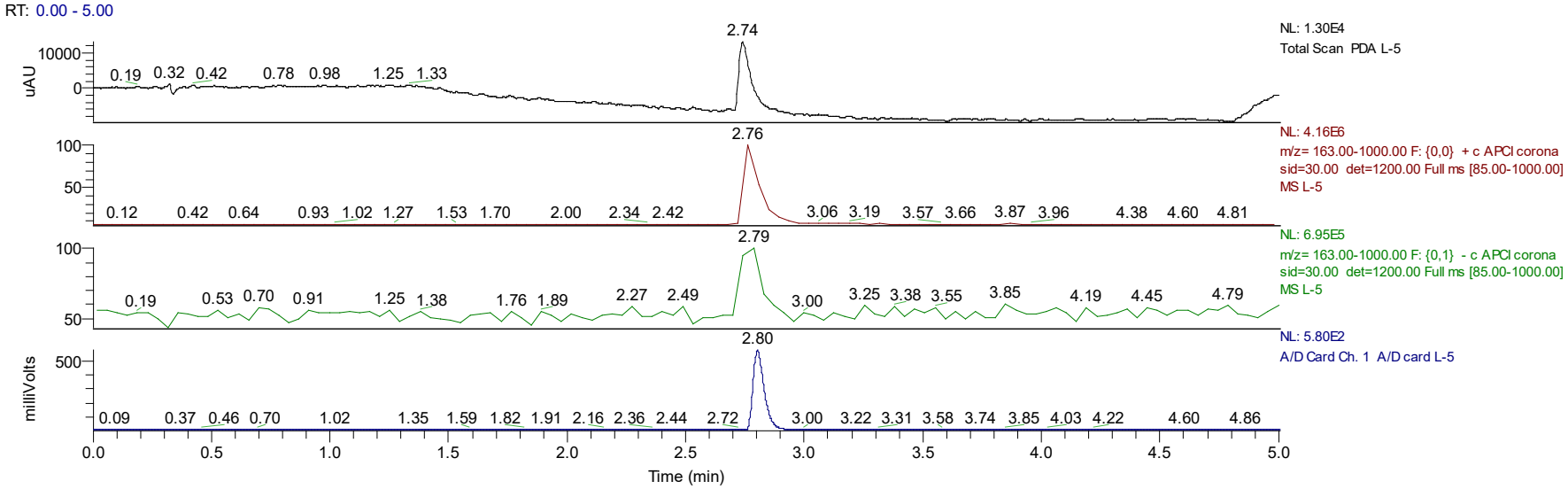


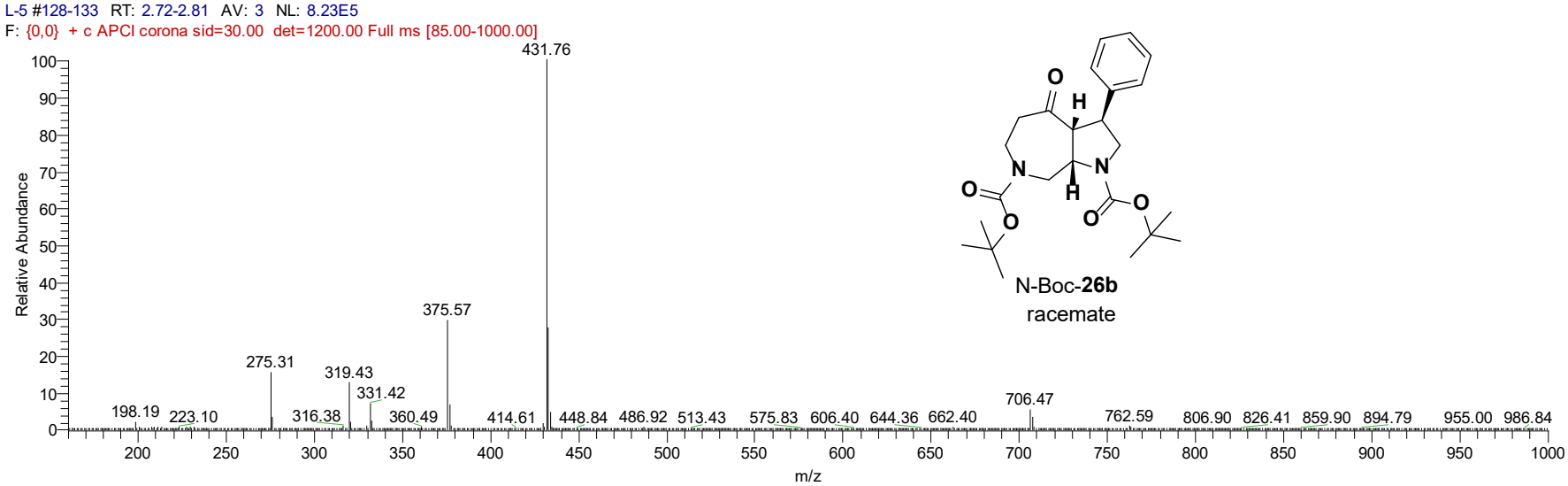
N-Boc-(-)-26a
Enantiomer #2



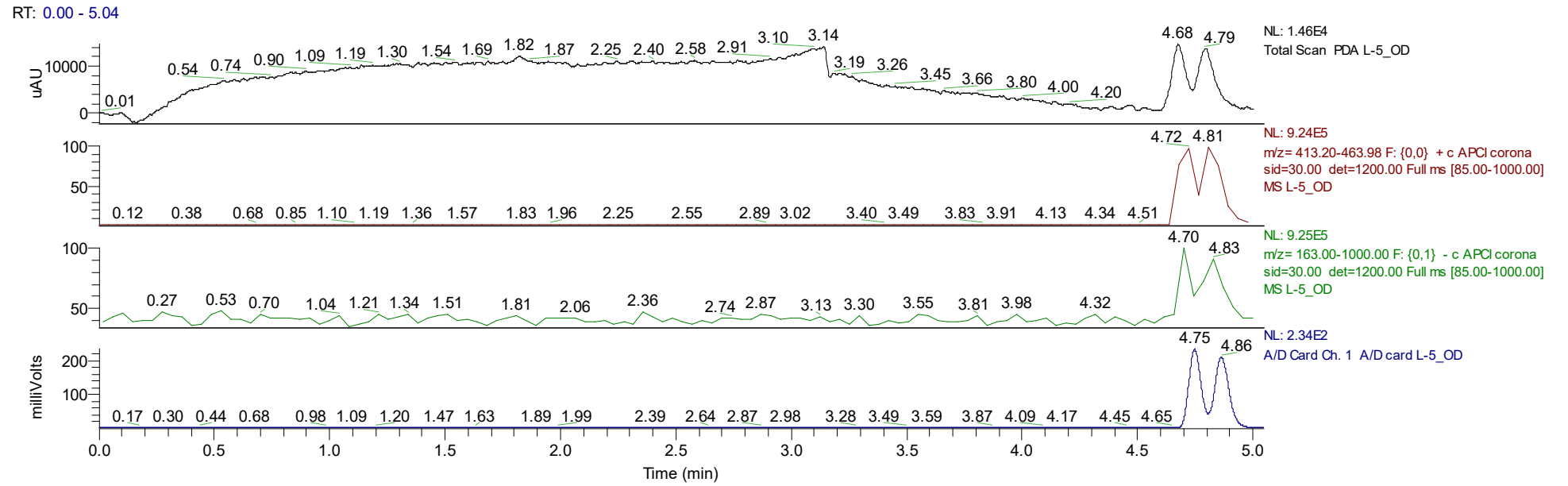


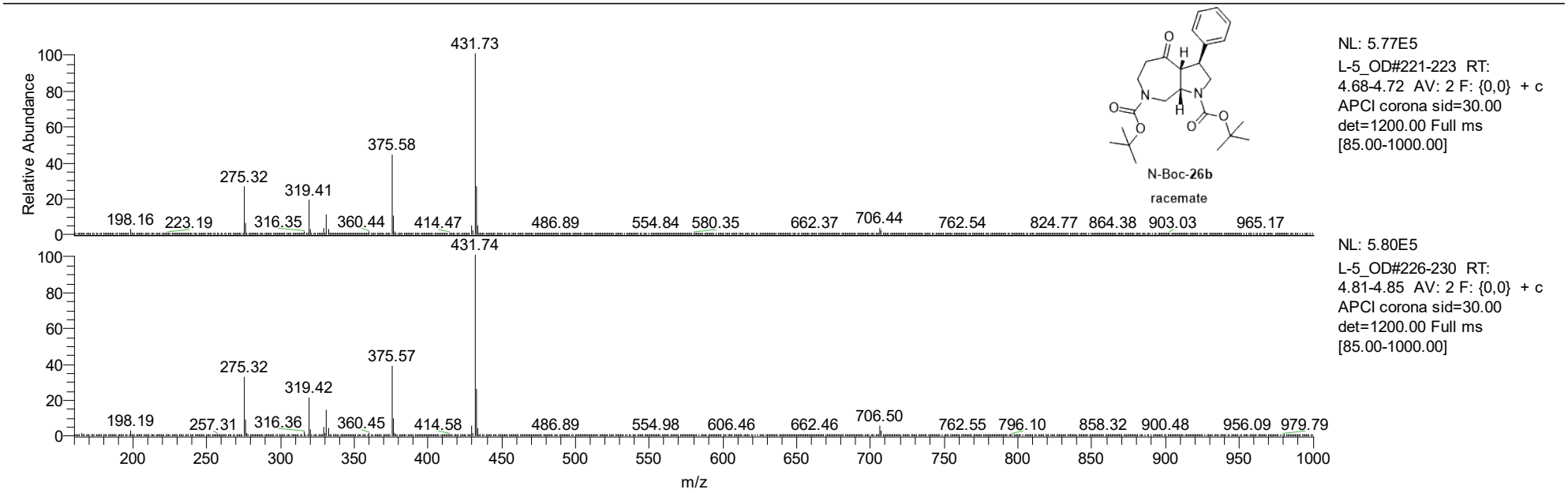
Area %	Peak Area	RT
100	2102009	4.64

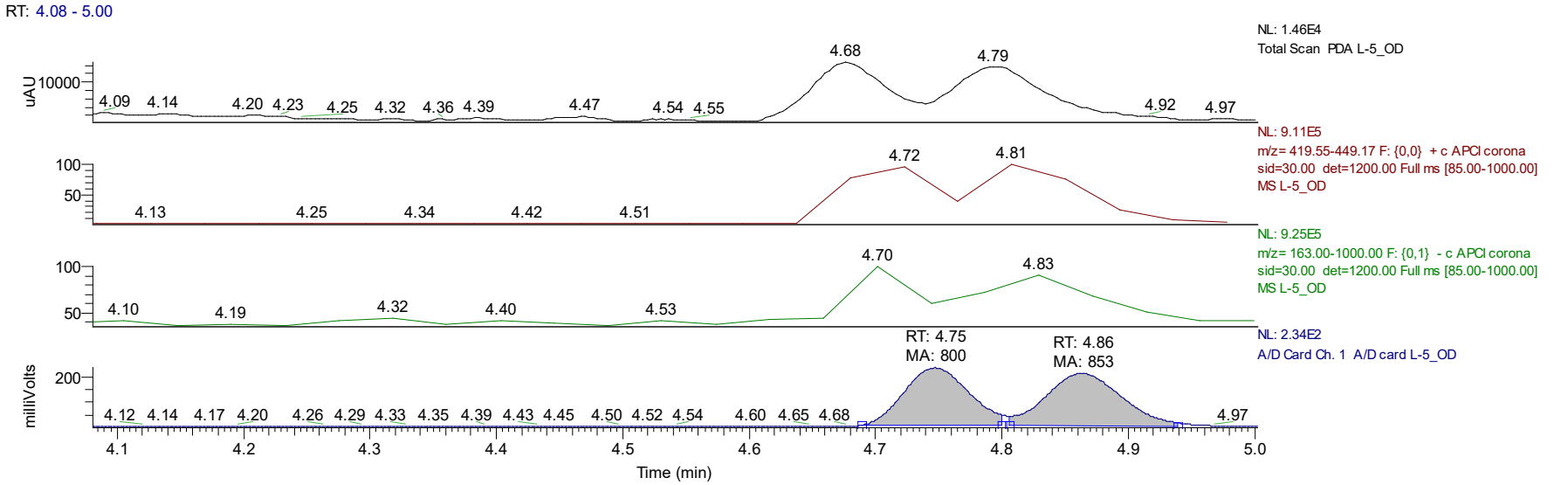


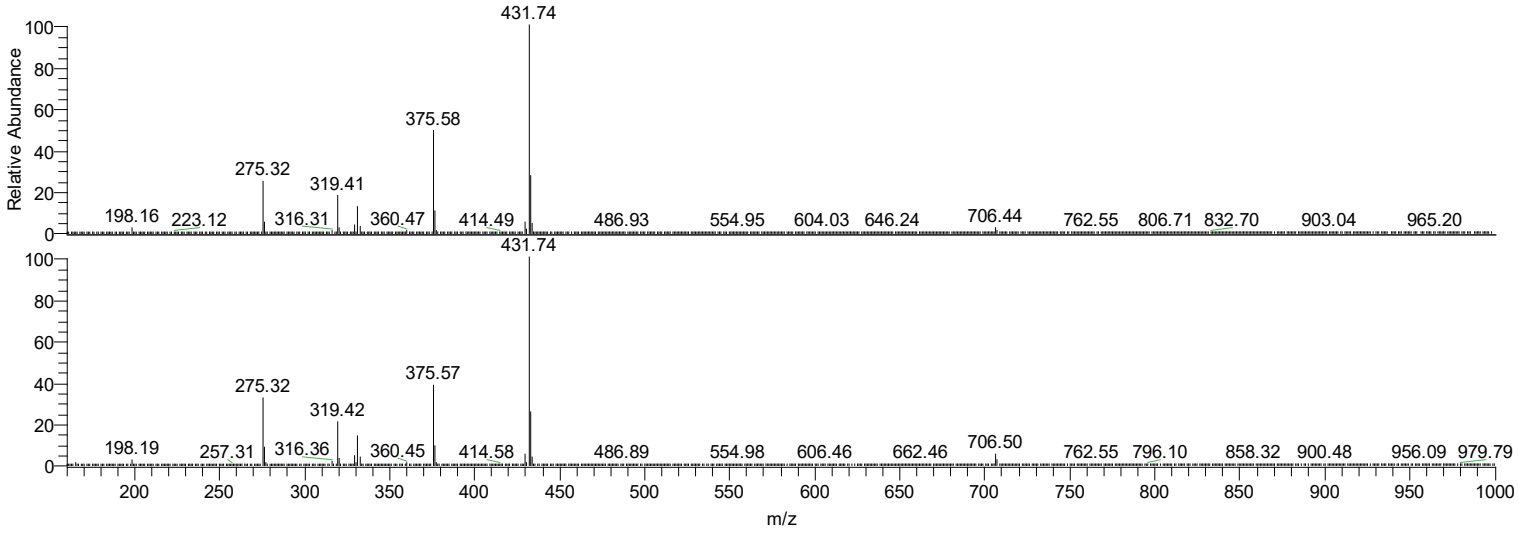


N-Boc-**26b**
racemate

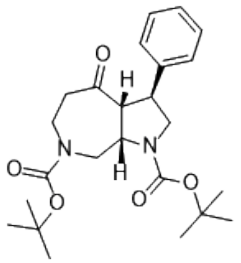

RT: 0.00 - 5.04
uAU
10000
0
0.01 0.54 0.74 0.90 1.09 1.19 1.30 1.54 1.69 1.82 1.87 2.25 2.40 2.58 2.91 3.10 3.14 3.19 3.26 3.45 3.66 3.80 4.00 4.20 4.68 4.79
NL: 1.46E4
Total Scan PDA L-5_OD
100
50
0.12 0.38 0.68 0.85 1.10 1.19 1.36 1.57 1.83 1.96 2.25 2.55 2.89 3.02 3.40 3.49 3.83 3.91 4.13 4.34 4.51 4.72 4.81
NL: 9.24E5
m/z= 413.20-463.98 F: {0,0} + c APCI corona sid=30.00 det=1200.00 Full ms [85.00-1000.00] MS L-5_OD
100
50
0.27 0.53 0.70 1.04 1.21 1.34 1.51 1.81 2.06 2.36 2.74 2.87 3.13 3.30 3.55 3.81 3.98 4.32 4.70 4.83
NL: 9.25E5
m/z= 163.00-1000.00 F: {0,1} - c APCI corona sid=30.00 det=1200.00 Full ms [85.00-1000.00] MS L-5_OD
milliVolts
200
100
0.17 0.30 0.44 0.68 0.98 1.09 1.20 1.47 1.63 1.89 1.99 2.39 2.64 2.87 2.98 3.28 3.49 3.59 3.87 4.09 4.17 4.45 4.65 4.75 4.86
NL: 2.34E2
A/D Card Ch. 1 A/D card L-5_OD
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0
Time (min)


Relative Abundance
100
80
60
40
20
0
198.16 223.19 275.32 316.35 319.41 360.44 375.58 414.47 431.73 486.89 554.84 580.35 662.37 706.44 762.54 824.77 864.38 903.03 965.17
N-Boc-26b
racemate
NL: 5.77E5
L-5_OD#221-223 RT: 4.68-4.72 AV: 2 F: {0,0} + c APCI corona sid=30.00 det=1200.00 Full ms [85.00-1000.00]
198.19 257.31 275.32 316.36 319.42 360.45 375.57 414.58 431.74 486.89 554.98 606.46 662.46 706.50 762.55 796.10 858.32 900.48 956.09 979.79
NL: 5.80E5
L-5_OD#226-230 RT: 4.81-4.85 AV: 2 F: {0,0} + c APCI corona sid=30.00 det=1200.00 Full ms [85.00-1000.00]
200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950 1000
m/z



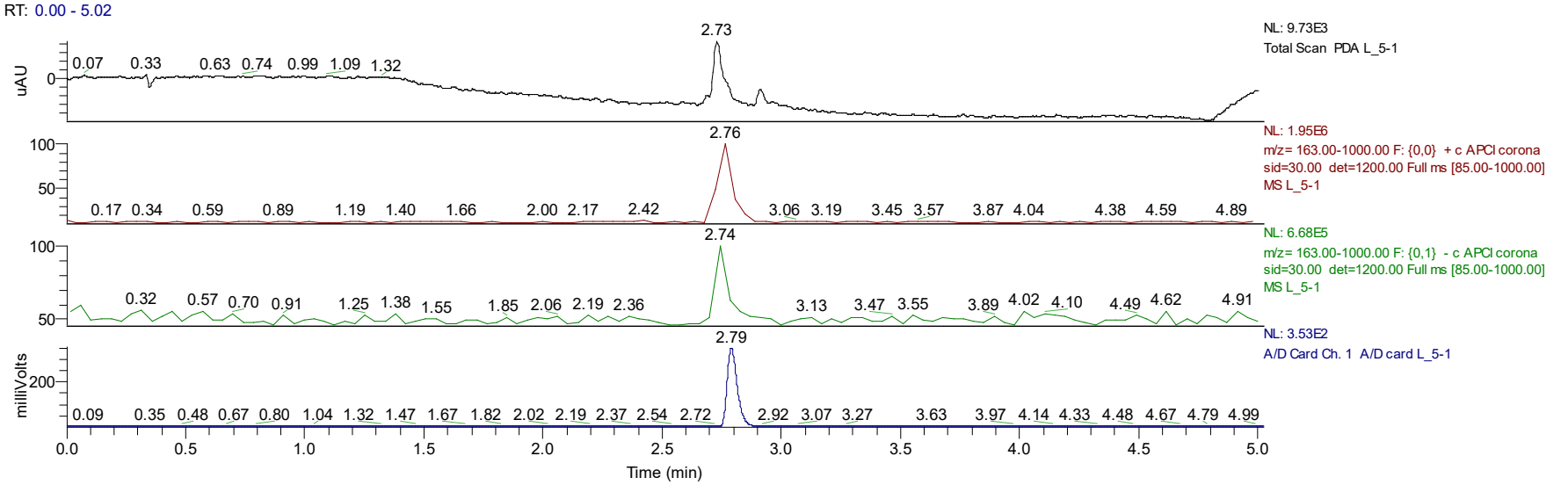


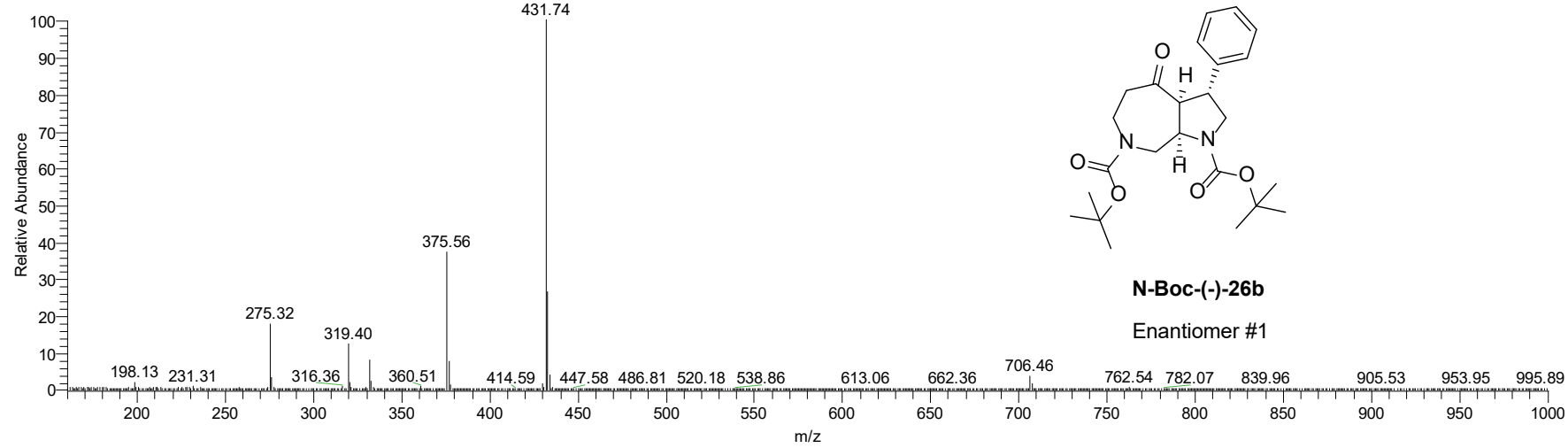
Area %	Peak Area	RT
48.4	800	4.75
51.6	853	4.86



N-Boc-**26b**

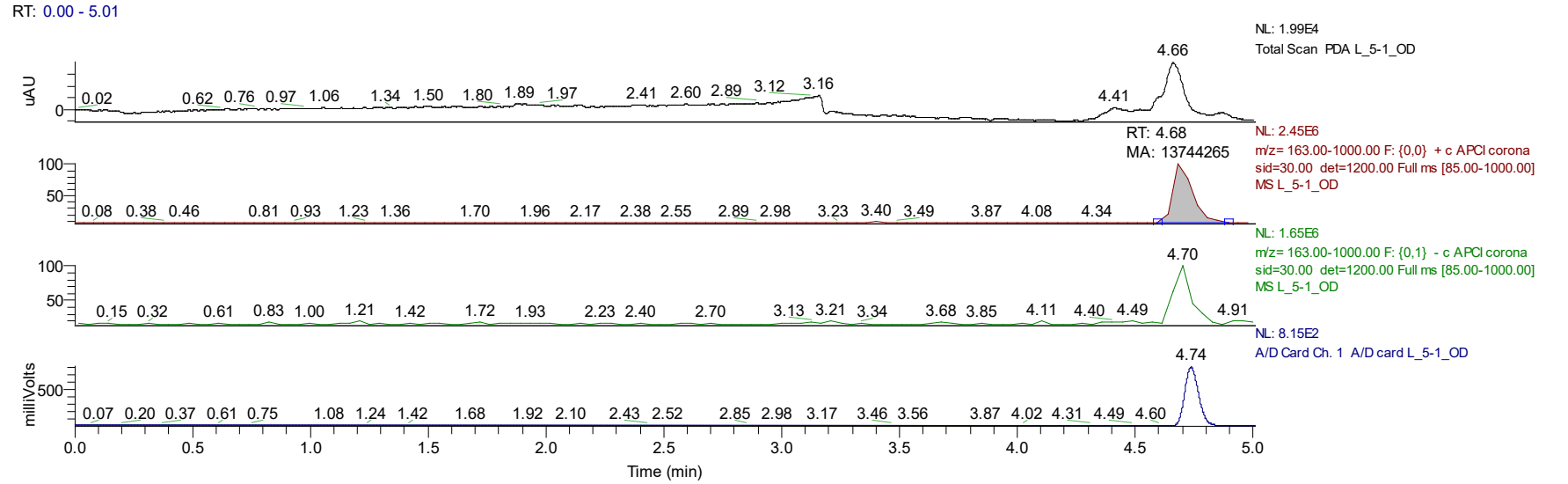
racemate

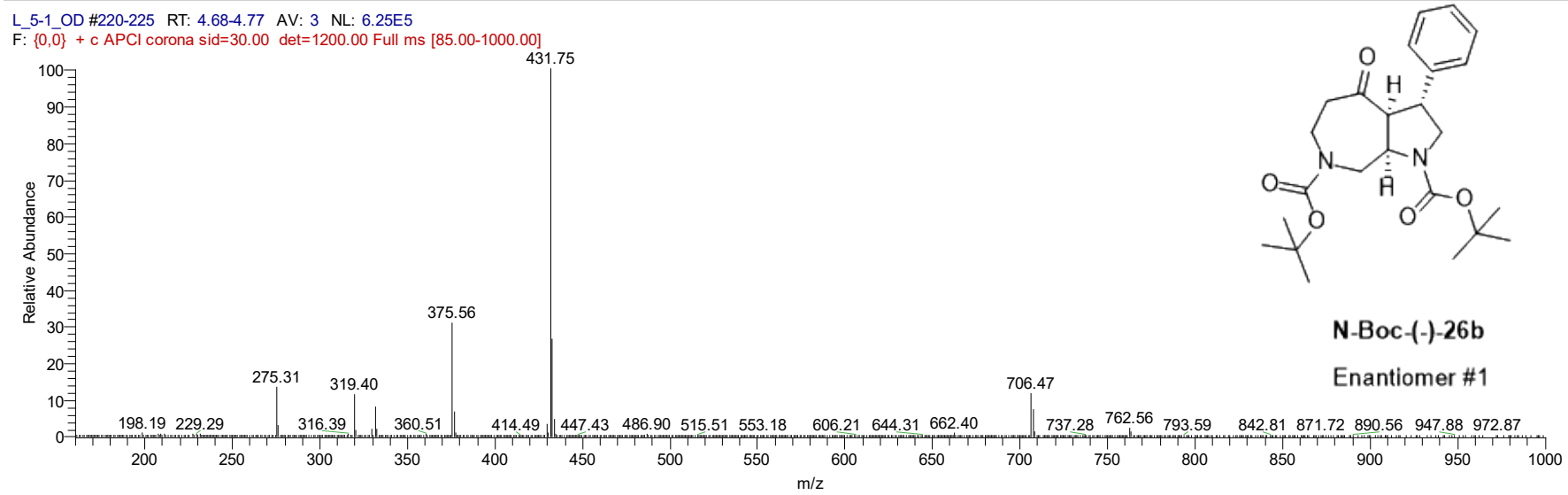




N-Boc-(-)-26b

Enantiomer #1

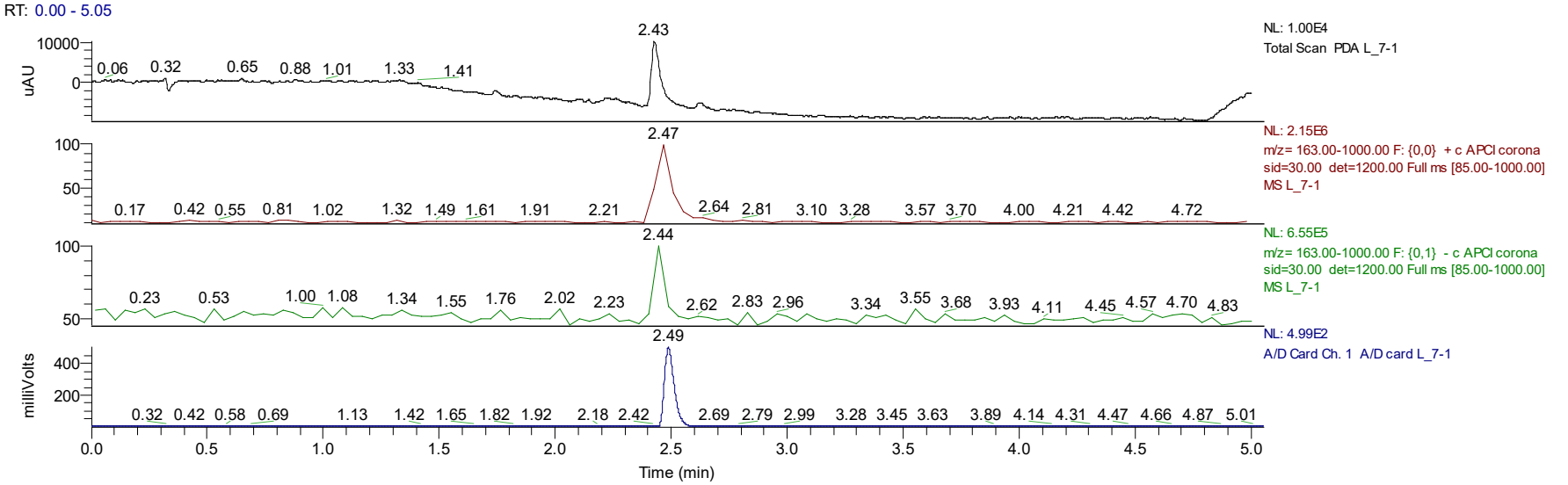


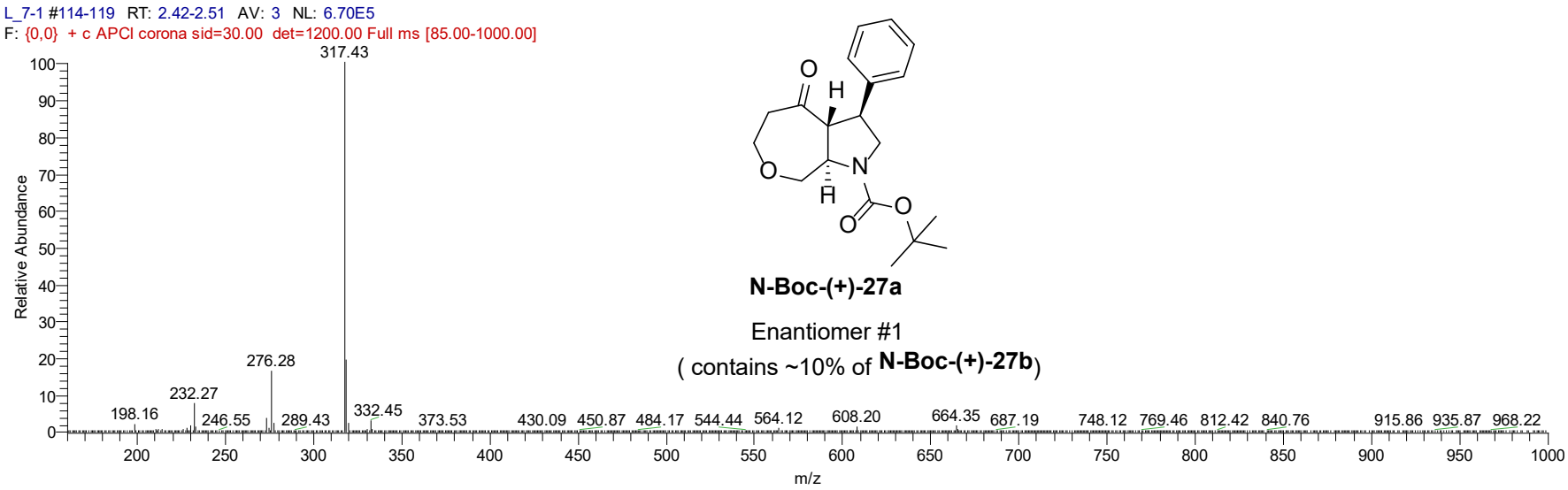


N-Boc-(-)-26b

Enantiomer #1

Area %	Peak Area	RT
100	13744265	4.68

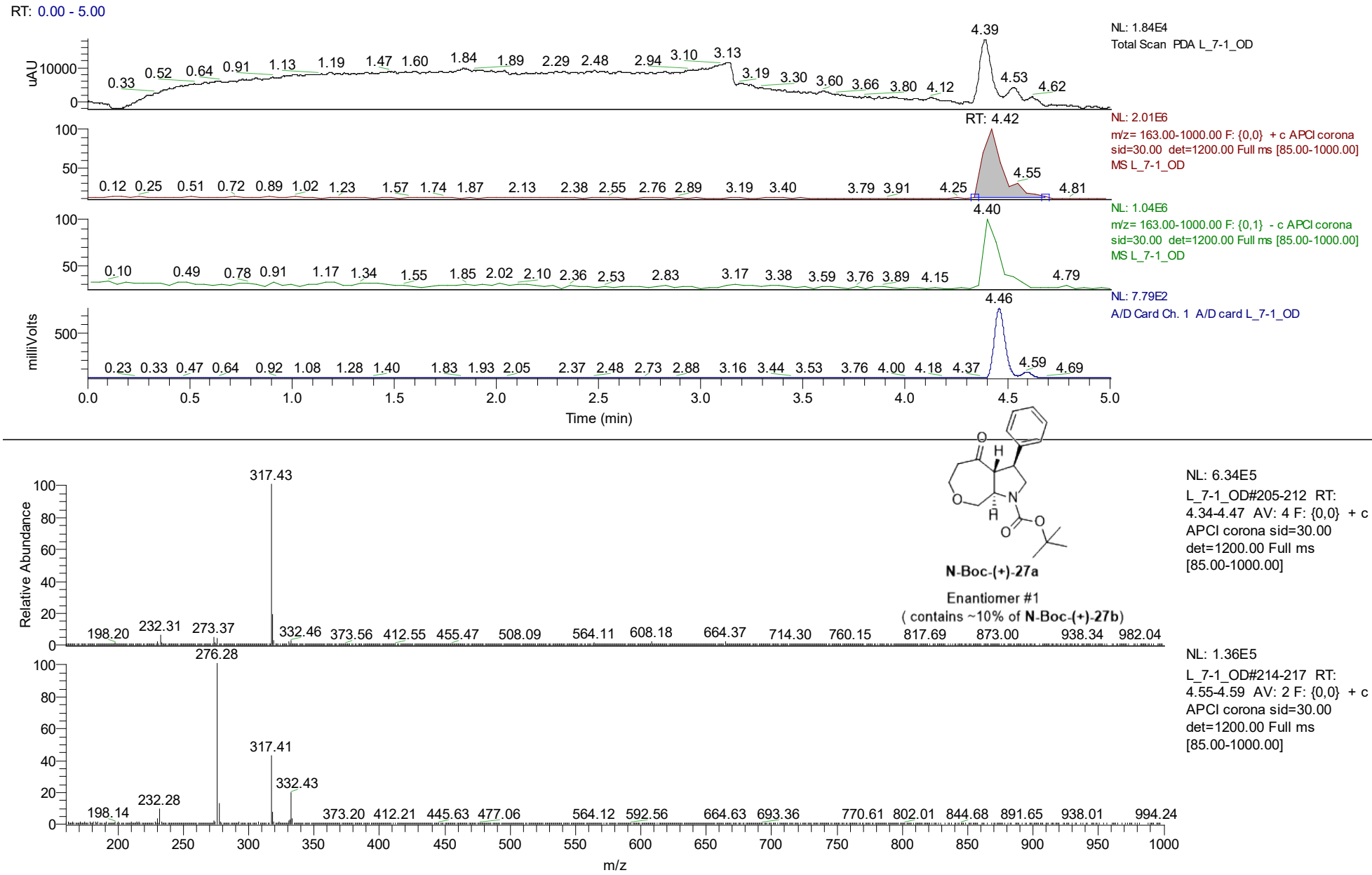


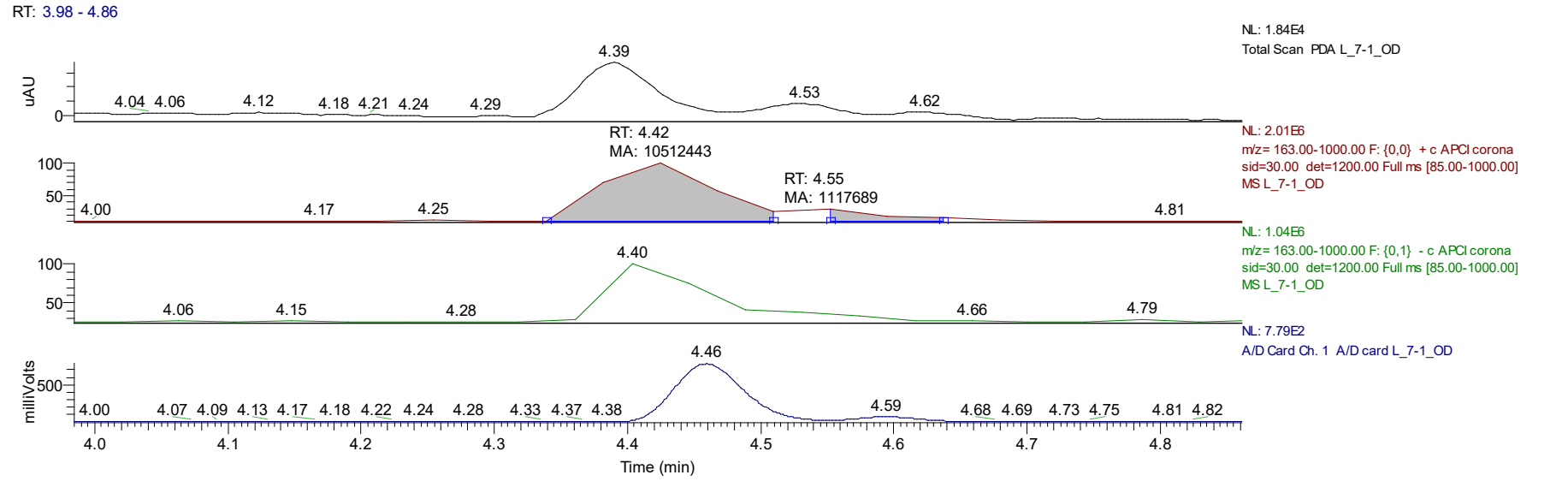


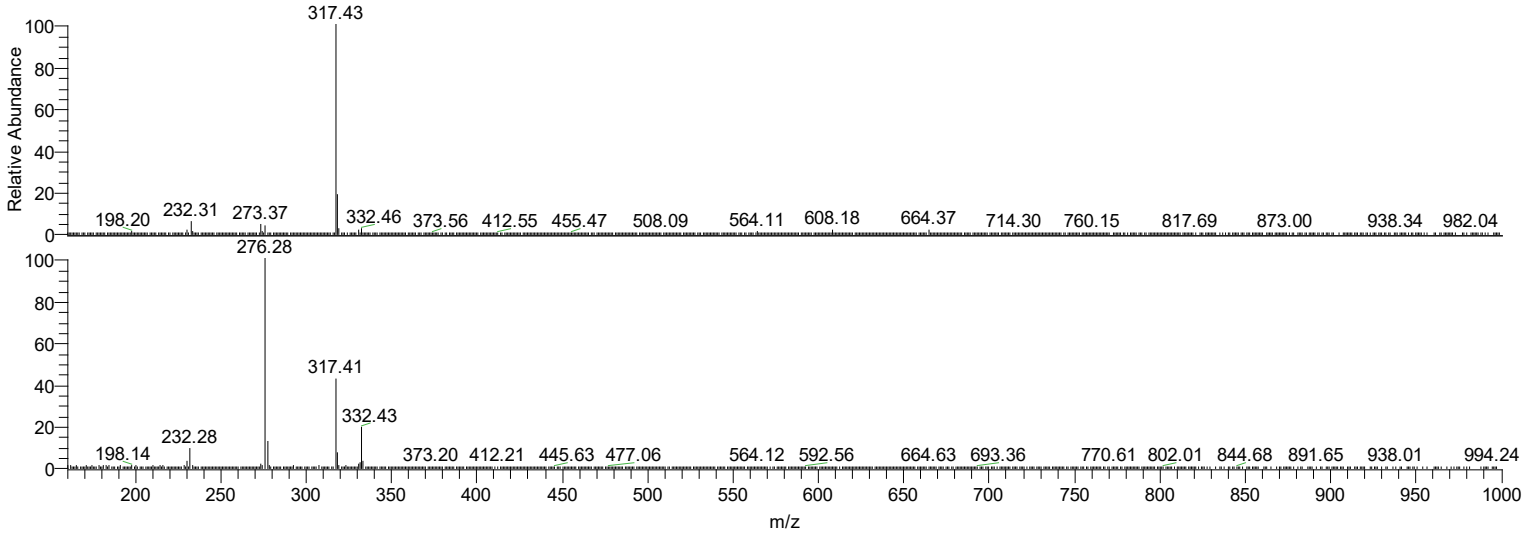
N-Boc-(+)-27a

Enantiomer #1

(contains ~10% of **N-Boc-(+)-27b**)

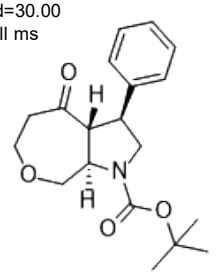

RT: 0.00 - 5.00
uAU
NL: 1.84E4
Total Scan PDA L_7-1_OD
RT: 4.42
NL: 2.01E6
m/z= 163.00-1000.00 F: {0,0} + c APCI corona
sid=30.00 det=1200.00 Full ms [85.00-1000.00]
MS L_7-1_OD
NL: 1.04E6
m/z= 163.00-1000.00 F: {0,1} - c APCI corona
sid=30.00 det=1200.00 Full ms [85.00-1000.00]
MS L_7-1_OD
milliVolts
NL: 7.79E2
A/D Card Ch. 1 A/D card L_7-1_OD
Time (min)
Relative Abundance
317.43
276.28
317.41
332.43
m/z
N-Boc-(+)-27a
Enantiomer #1
(contains ~10% of N-Boc-(+)-27b)
NL: 6.34E5
L_7-1_OD#205-212 RT: 4.34-4.47 AV: 4 F: {0,0} + c APCI corona sid=30.00 det=1200.00 Full ms [85.00-1000.00]
NL: 1.36E5
L_7-1_OD#214-217 RT: 4.55-4.59 AV: 2 F: {0,0} + c APCI corona sid=30.00 det=1200.00 Full ms [85.00-1000.00]





NL: 6.34E5
L_7-1_OD#205-212 RT: 4.34-4.47 AV: 4 F: {0,0} + c APCI corona sid=30.00 det=1200.00 Full ms [85.00-1000.00]

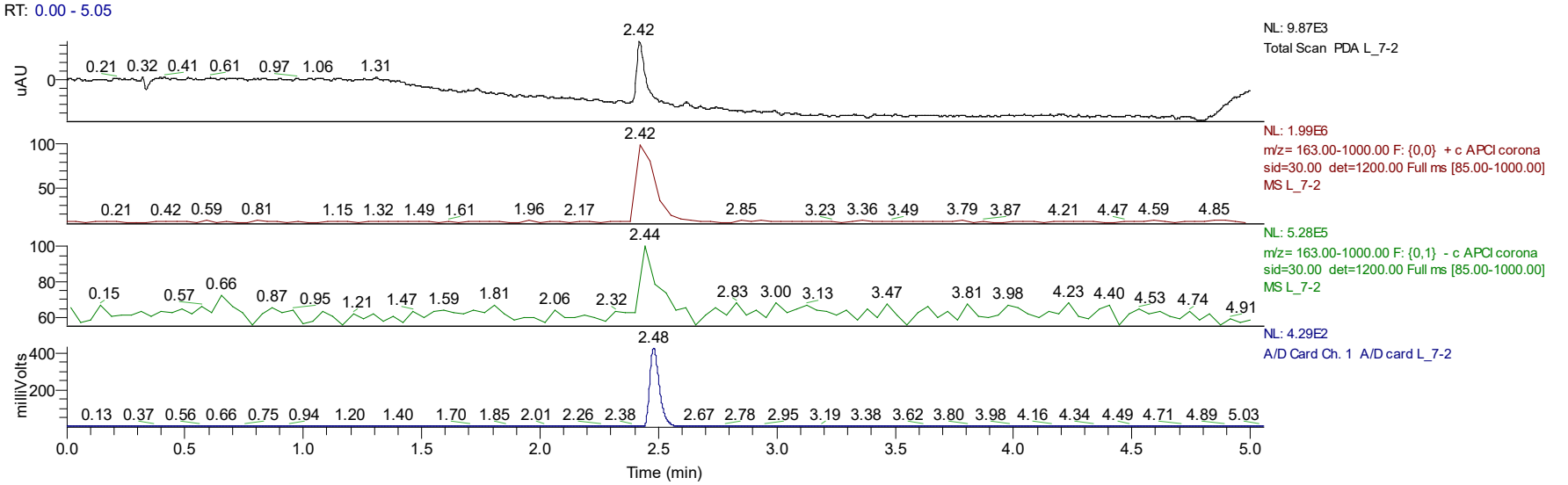
NL: 1.36E5
L_7-1_OD#214-217 RT: 4.55-4.59 AV: 2 F: {0,0} + c APCI corona sid=30.00 det=1200.00 Full ms [85.00-1000.00]

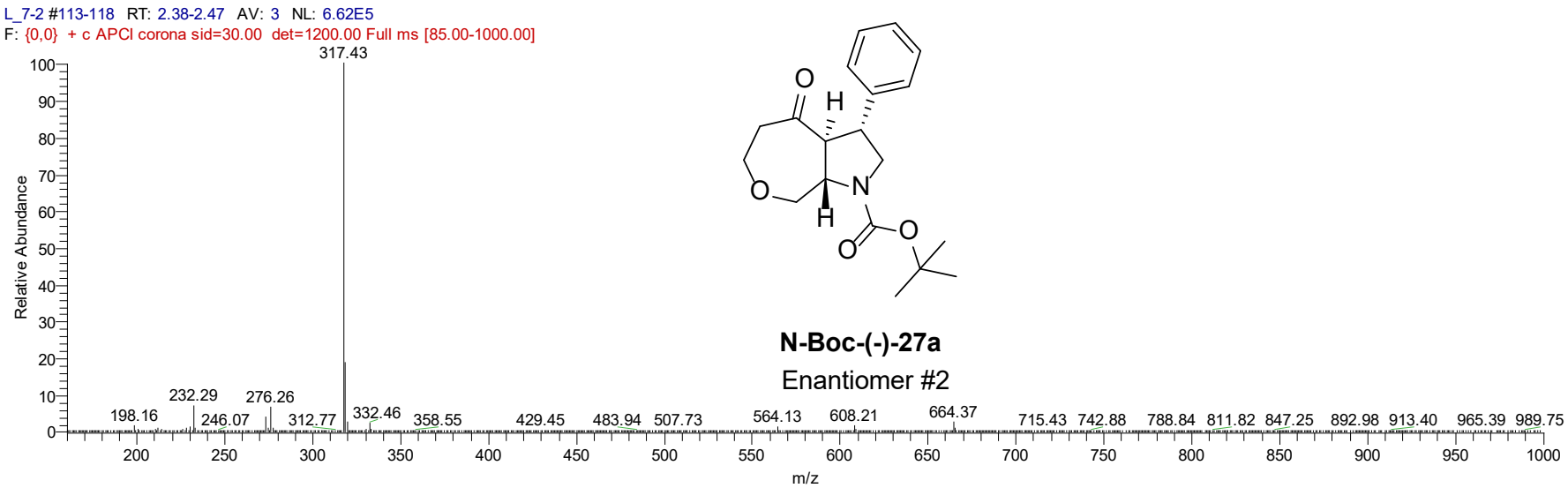


N-Boc-(+)-27a

Enantiomer #1
(contains ~10% of **N-Boc-(+)-27b**)

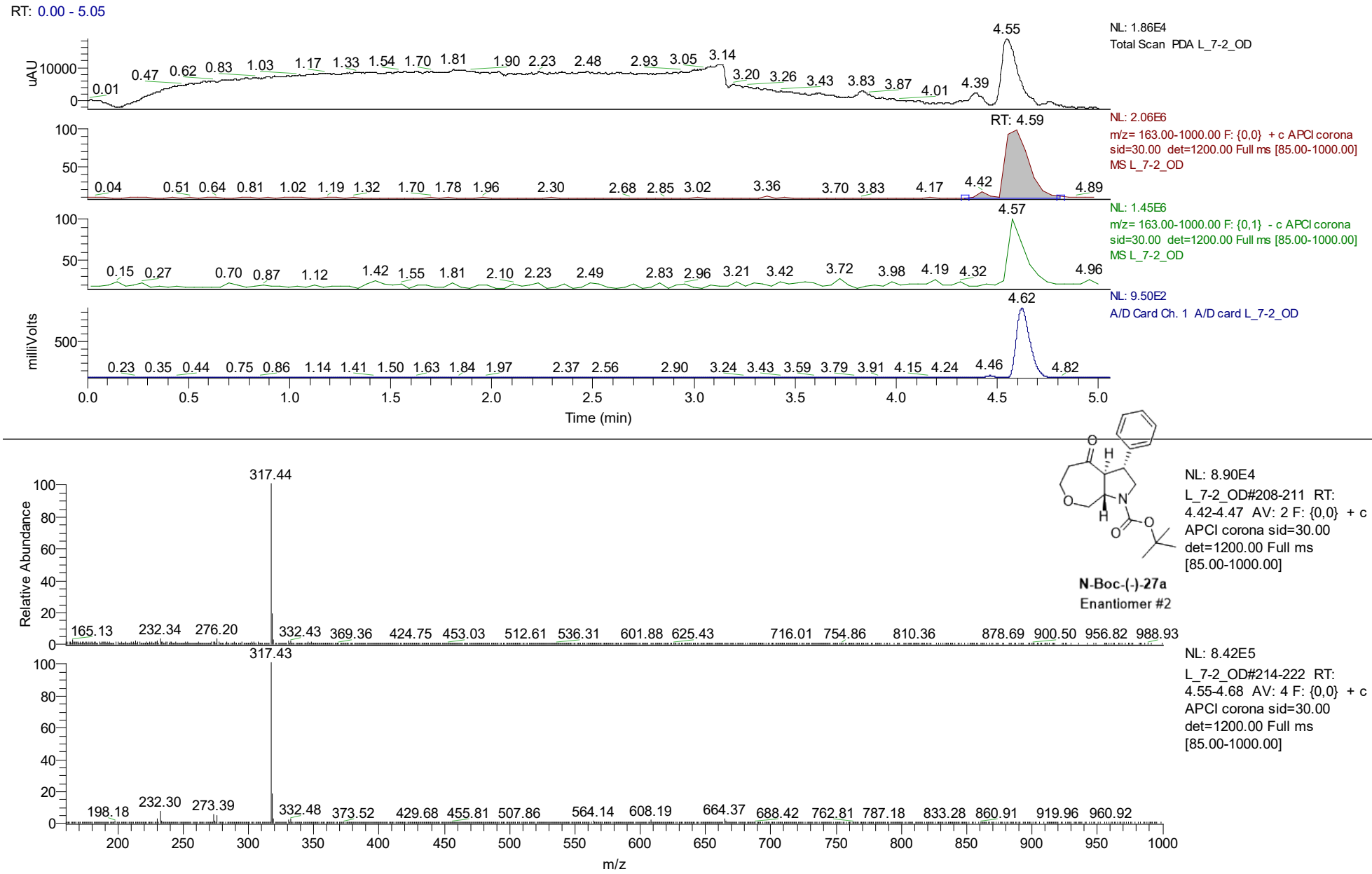
Area %	Peak Area	RT
90.4	10512443	4.42
9.6	1117689	4.55

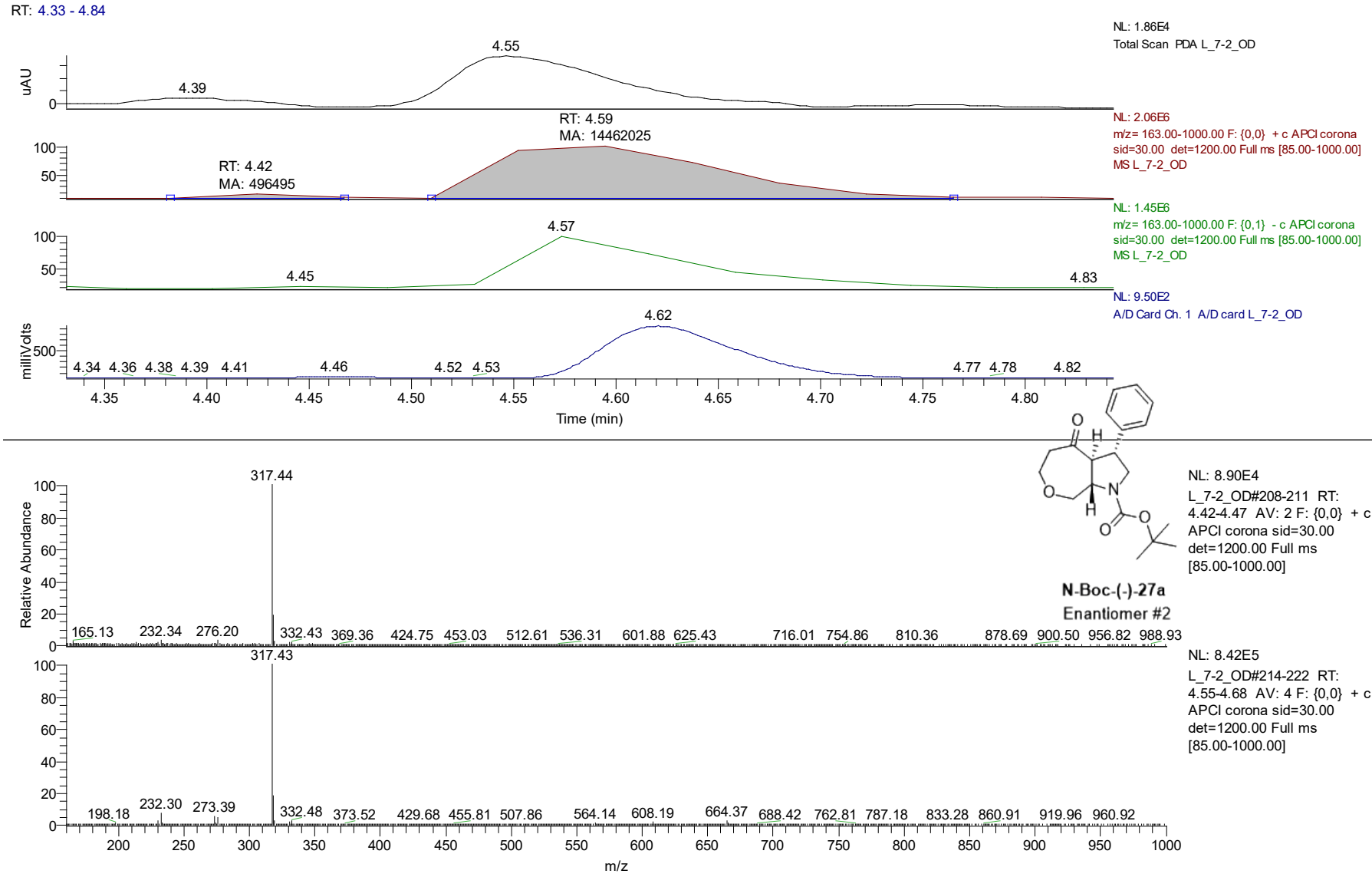




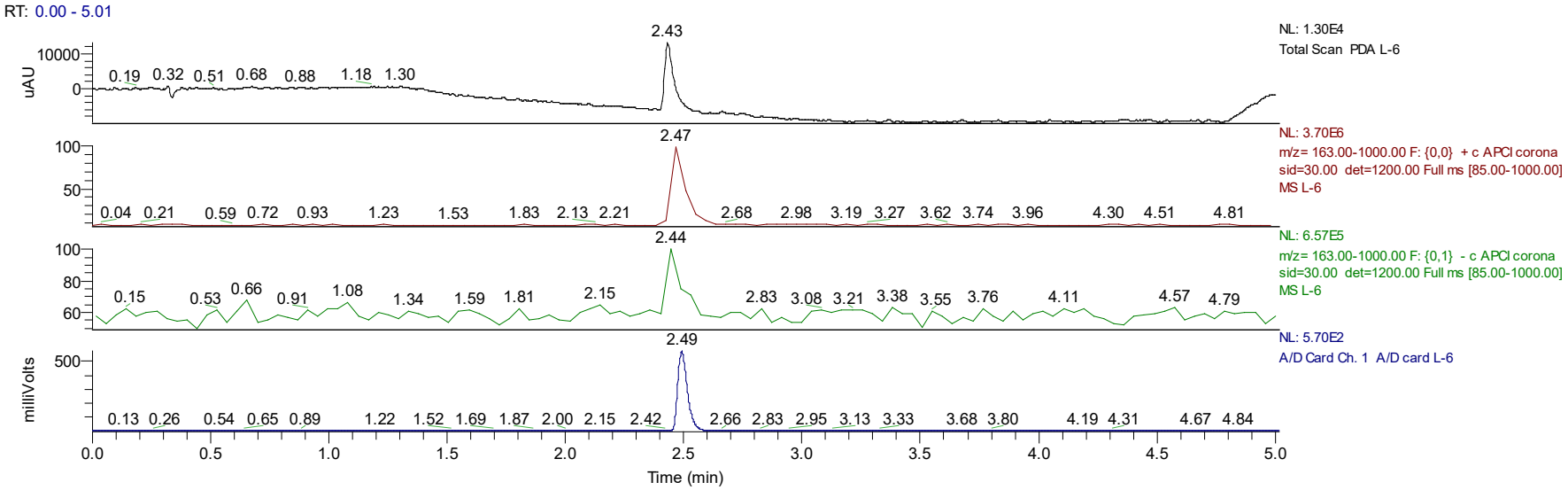
N-Boc-(-)-27a

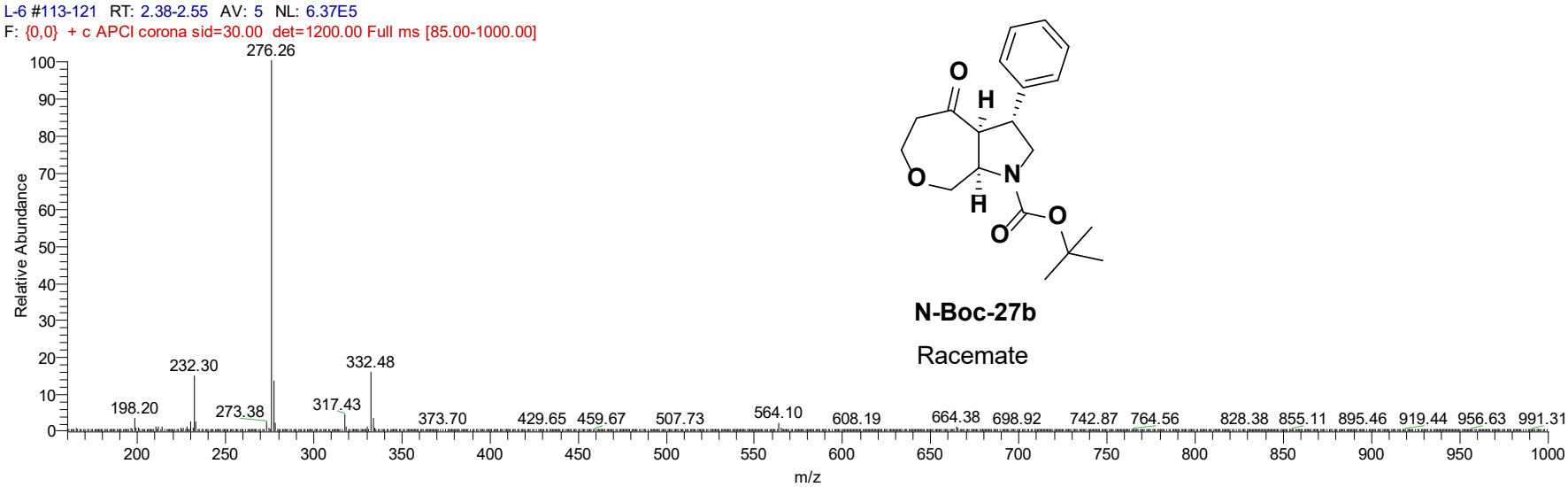
Enantiomer #2


RT: 0.00 - 5.05
uAU
NL: 1.86E4
Total Scan PDA L_7-2_OD
NL: 2.06E6
m/z= 163.00-1000.00 F: {0,0} + c APCI corona sid=30.00 det=1200.00 Full ms [85.00-1000.00] MS L_7-2_OD
RT: 4.59
NL: 1.45E6
m/z= 163.00-1000.00 F: {0,1} - c APCI corona sid=30.00 det=1200.00 Full ms [85.00-1000.00] MS L_7-2_OD
NL: 9.50E2
A/D Card Ch. 1 A/D card L_7-2_OD
milliVolts
Time (min)
Relative Abundance
317.44
317.43
m/z
N-Boc-(-)-27a
Enantiomer #2
NL: 8.90E4
L_7-2_OD#208-211 RT: 4.42-4.47 AV: 2 F: {0,0} + c APCI corona sid=30.00 det=1200.00 Full ms [85.00-1000.00]
NL: 8.42E5
L_7-2_OD#214-222 RT: 4.55-4.68 AV: 4 F: {0,0} + c APCI corona sid=30.00 det=1200.00 Full ms [85.00-1000.00]



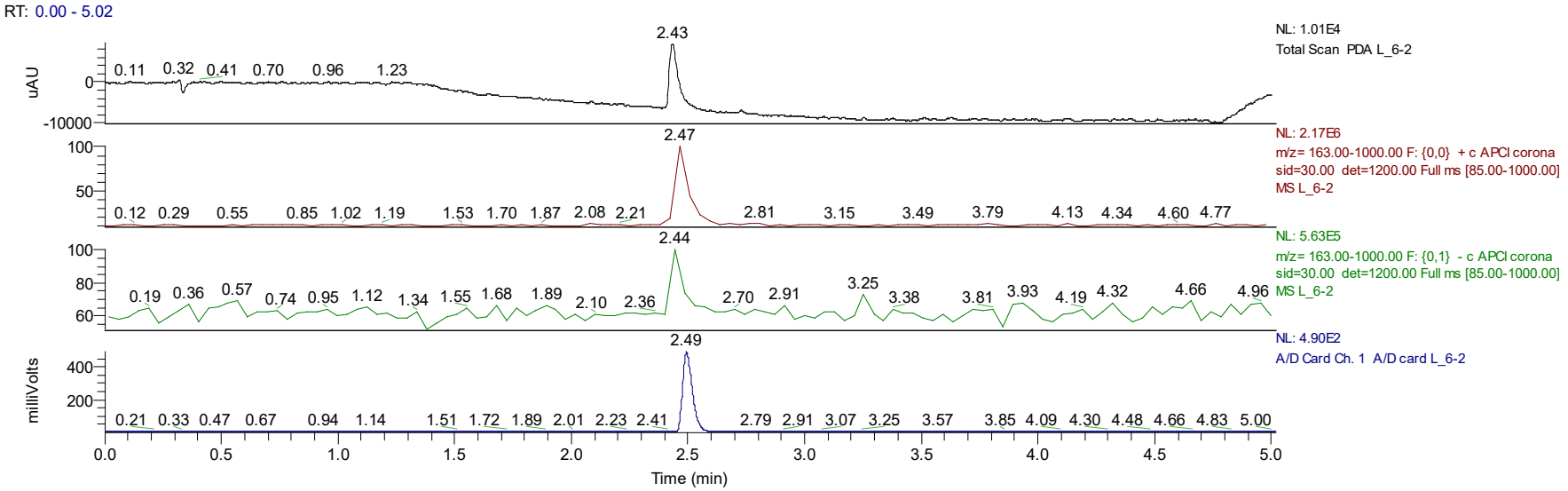
Area %	Peak Area	RT
3.4	496495	4.42
96.6	14462025	4.59

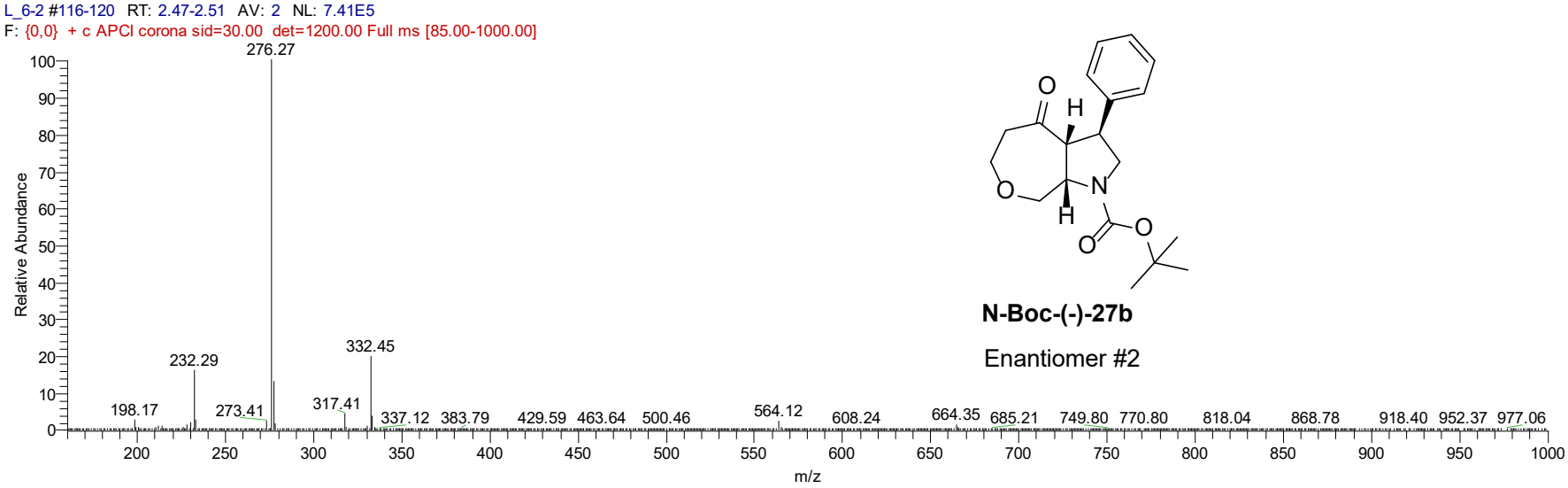




N-Boc-27b

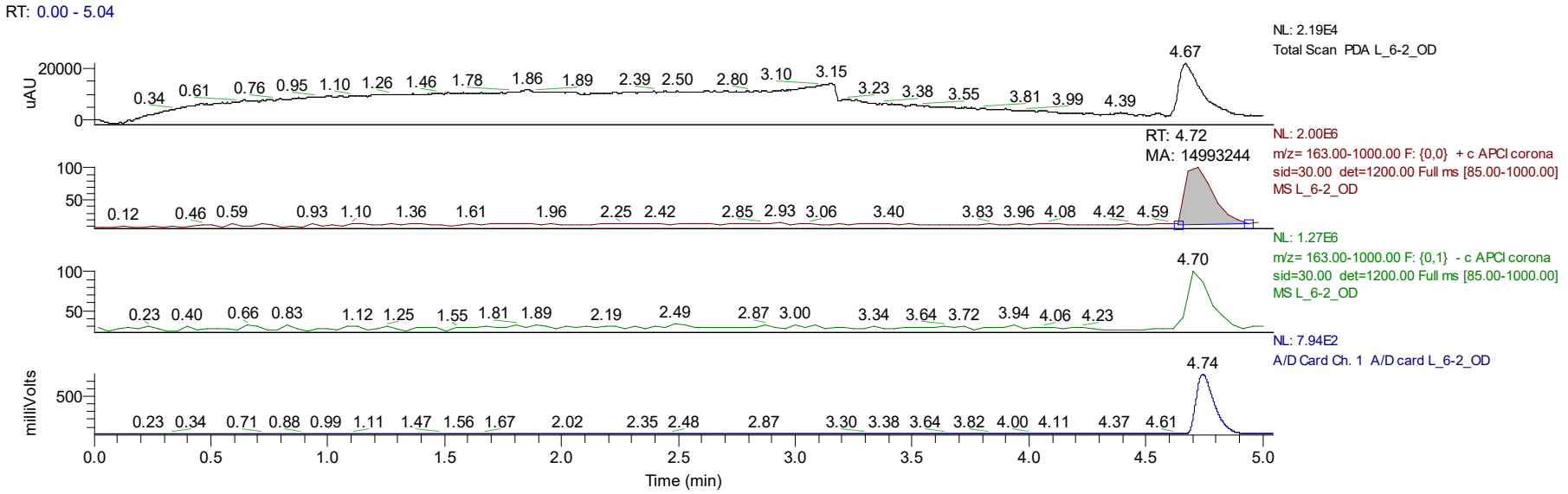
Racemate

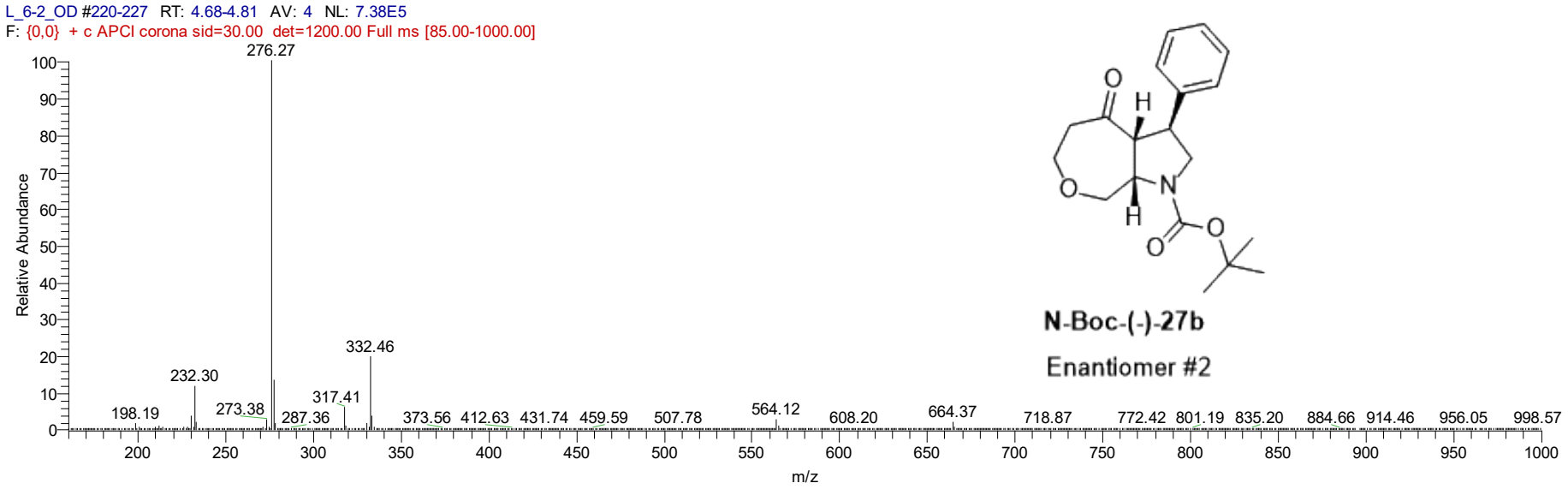




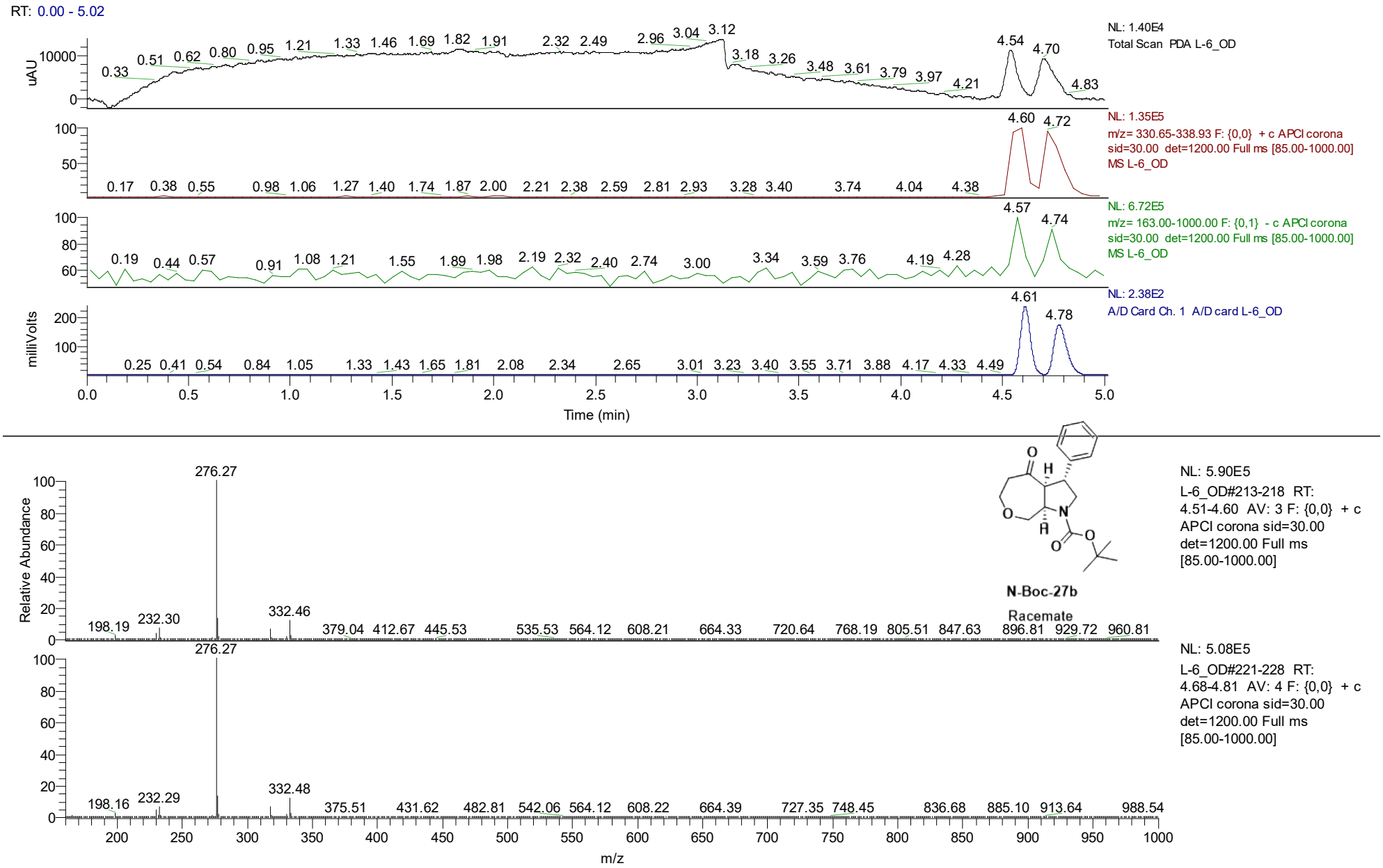
N-Boc-(-)-27b

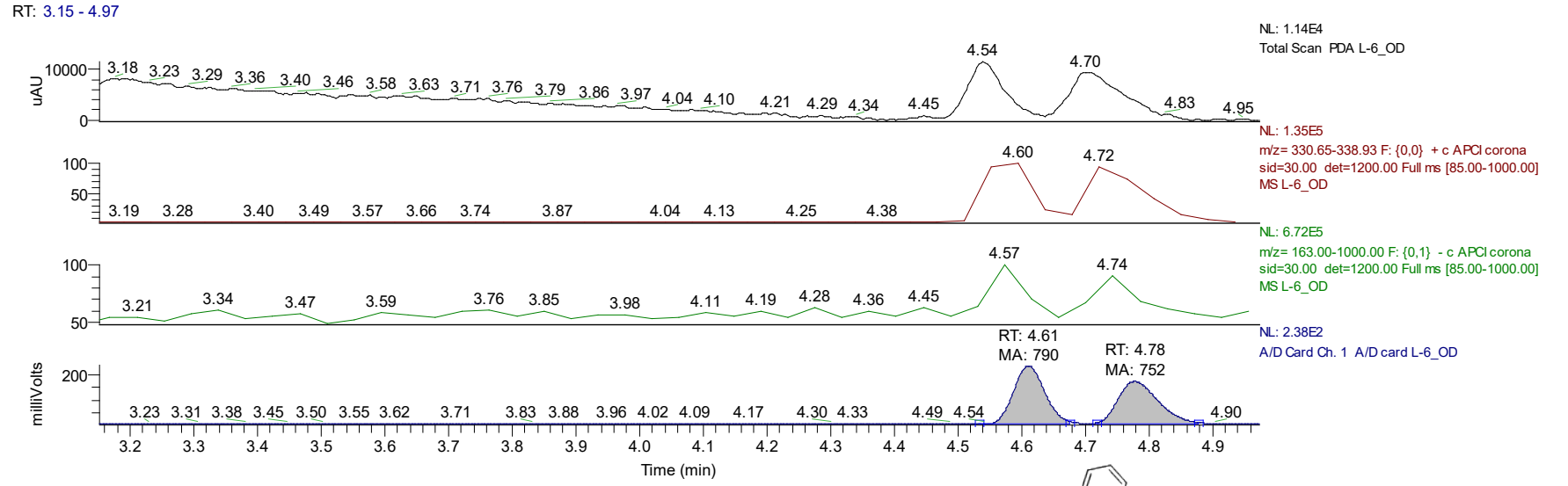
Enantiomer #2

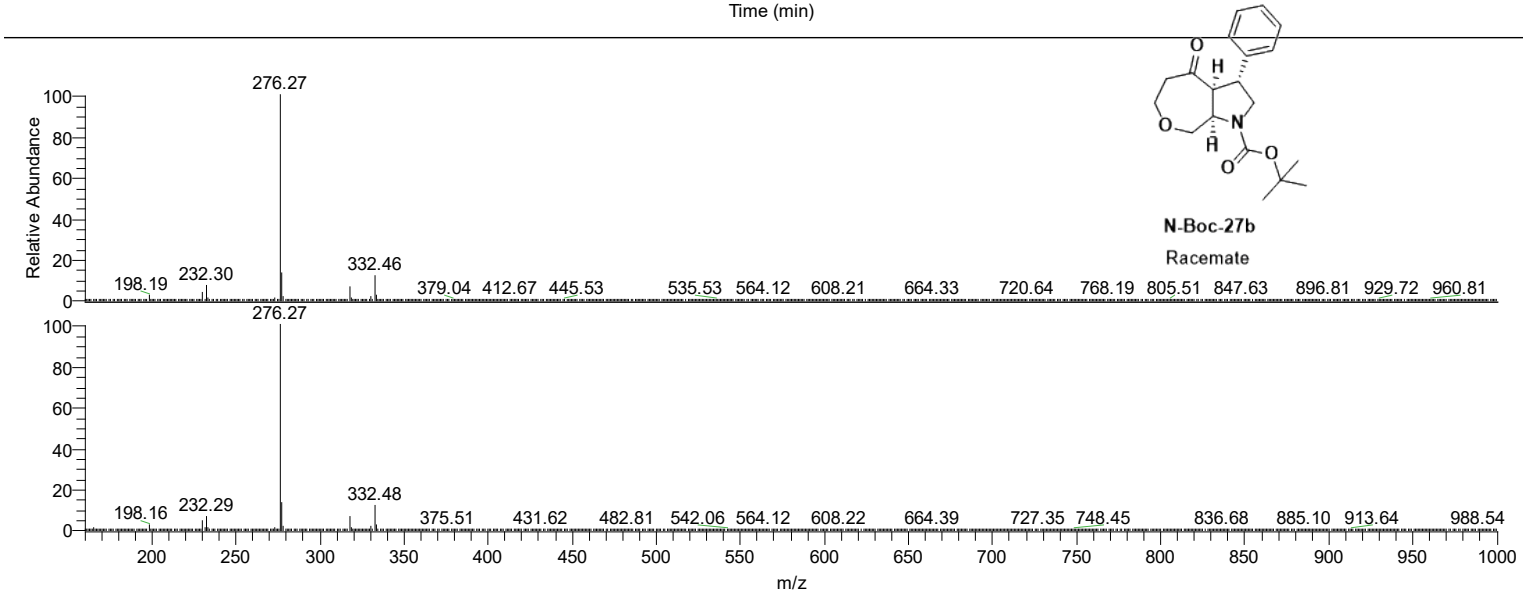




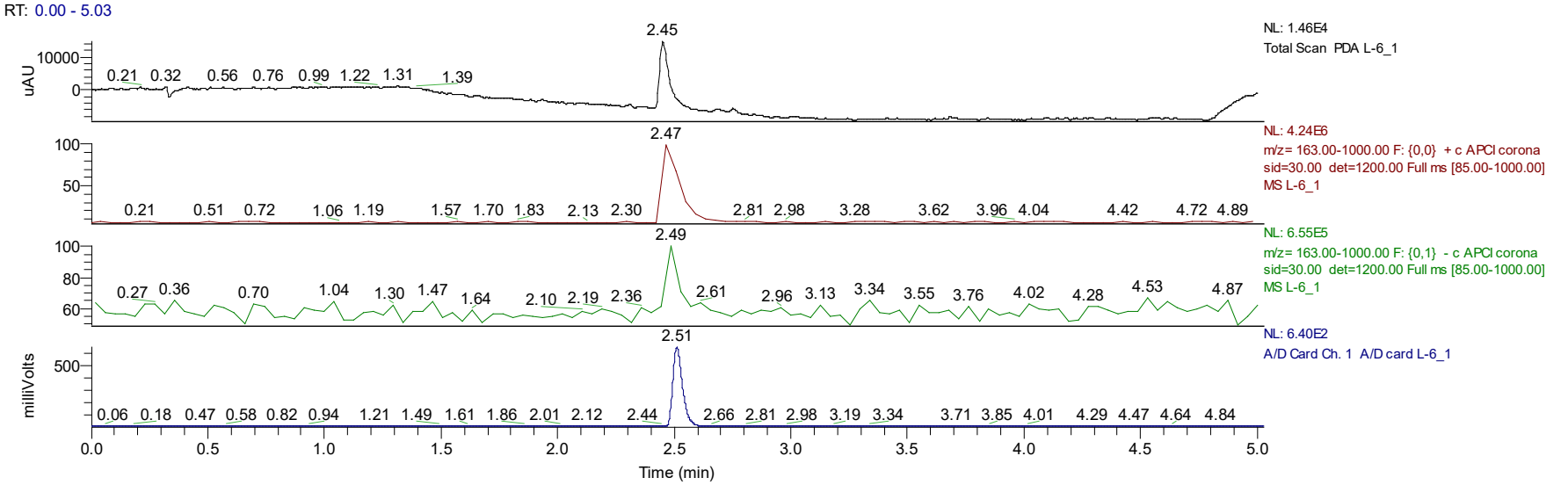
Area %	Peak Area	RT
100	14993244	4.72

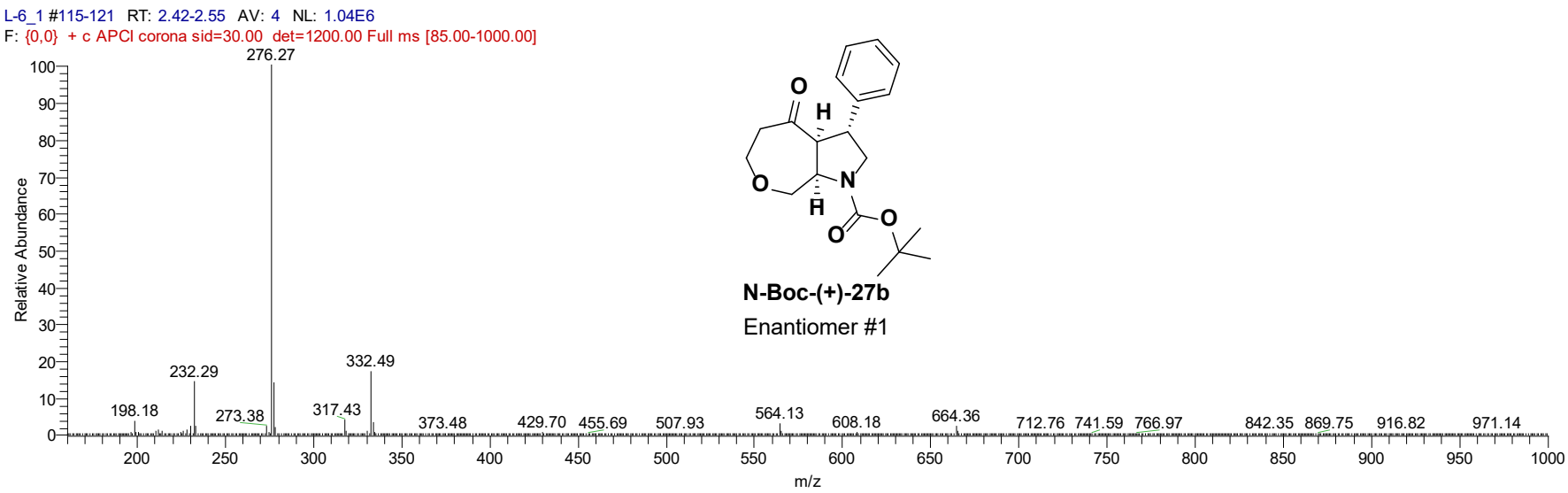

RT: 0.00 - 5.02
uAU
NL: 1.40E4
Total Scan PDA L-6_OD
NL: 1.35E5
m/z= 330.65-338.93 F: {0,0} + c APCI corona sid=30.00 det=1200.00 Full ms [85.00-1000.00] MS L-6_OD
NL: 6.72E5
m/z= 163.00-1000.00 F: {0,1} - c APCI corona sid=30.00 det=1200.00 Full ms [85.00-1000.00] MS L-6_OD
milliVolts
NL: 2.38E2
A/D Card Ch. 1 A/D card L-6_OD
Time (min)
N-Boc-27b
Racemate
Relative Abundance
NL: 5.90E5
L-6_OD#213-218 RT: 4.51-4.60 AV: 3 F: {0,0} + c APCI corona sid=30.00 det=1200.00 Full ms [85.00-1000.00]
NL: 5.08E5
L-6_OD#221-228 RT: 4.68-4.81 AV: 4 F: {0,0} + c APCI corona sid=30.00 det=1200.00 Full ms [85.00-1000.00]
m/z

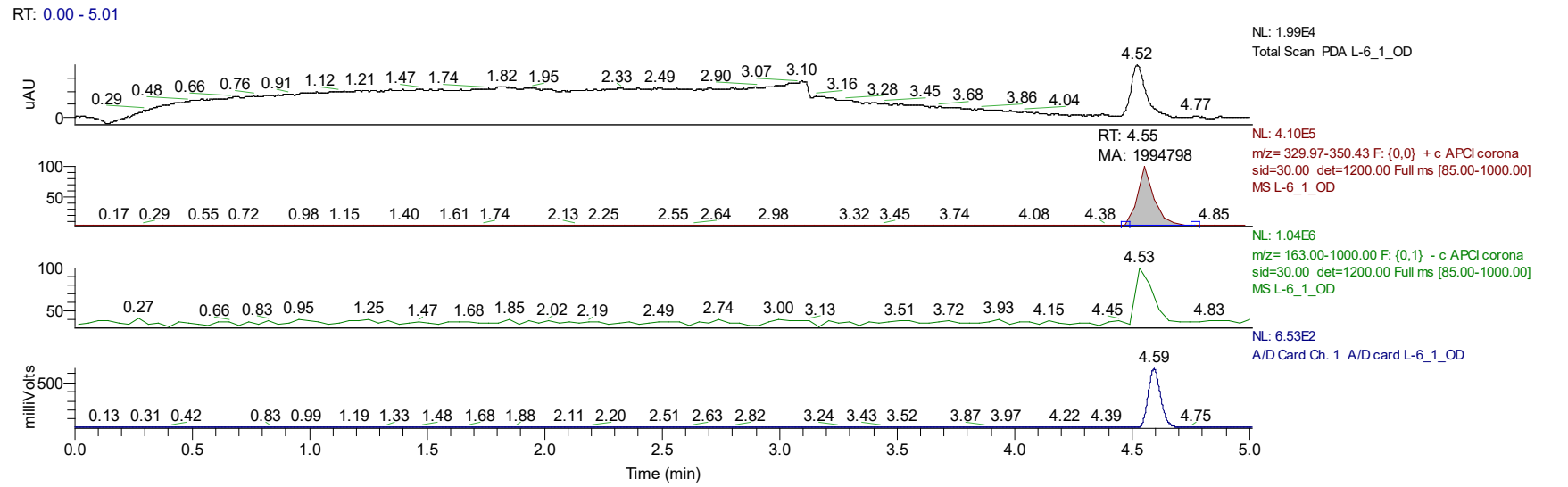


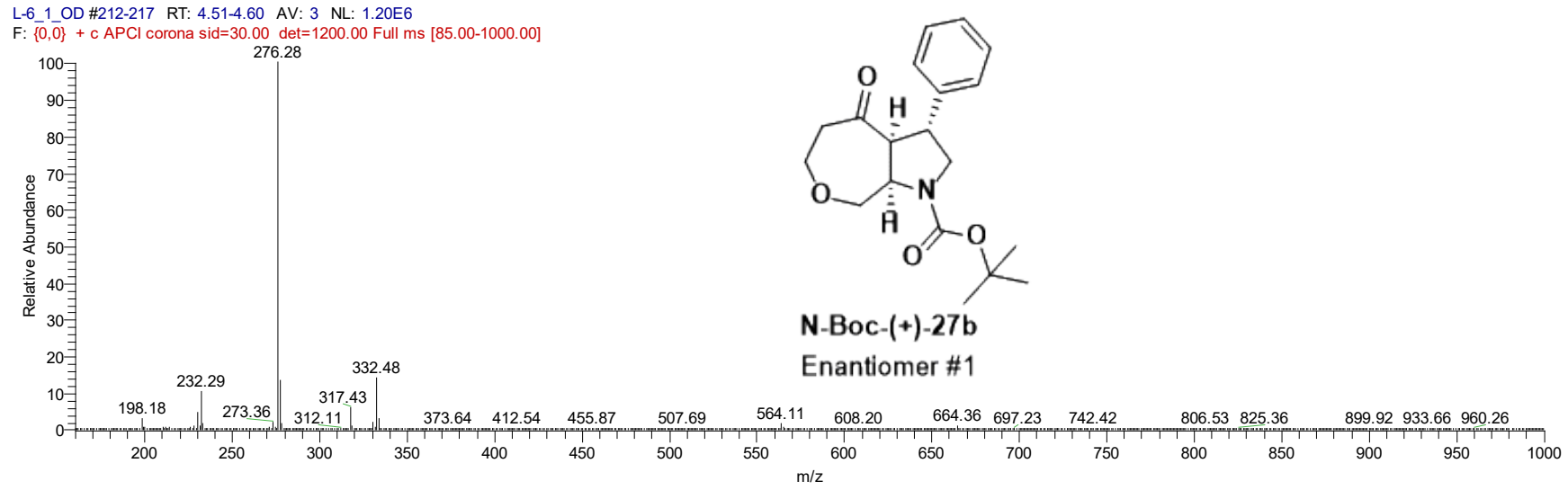


Area %	Peak Area	RT
51.2	790	4.61
48.8	752	4.78

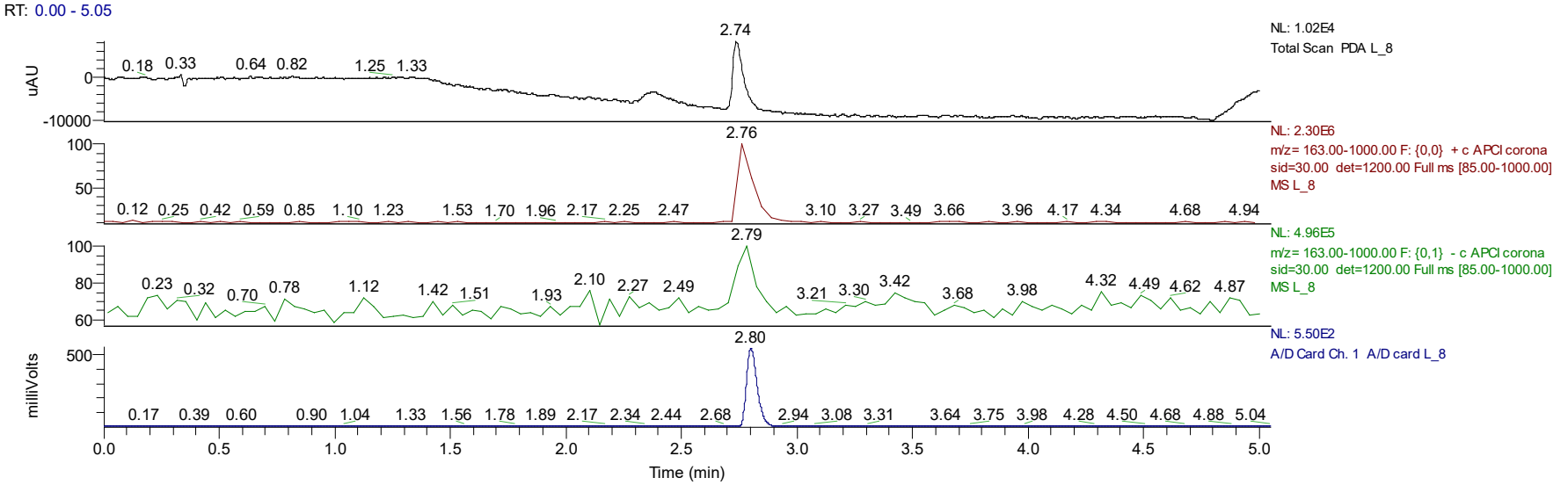

RT: 0.00 - 5.03
2.45
NL: 1.46E4
Total Scan PDA L-6_1
uAU
10000
0
0.21 0.32 0.56 0.76 0.99 1.22 1.31 1.39
2.47
NL: 4.24E6
m/z= 163.00-1000.00 F: {0,0} + c APCI corona
sid=30.00 det=1200.00 Full ms [85.00-1000.00]
MS L-6_1
100
50
0.21 0.51 0.72 1.06 1.19 1.57 1.70 1.83 2.13 2.30 2.81 2.98 3.28 3.62 3.96 4.04 4.42 4.72 4.89
2.49
NL: 6.55E5
m/z= 163.00-1000.00 F: {0,1} - c APCI corona
sid=30.00 det=1200.00 Full ms [85.00-1000.00]
MS L-6_1
100
80
60
0.27 0.36 0.70 1.04 1.30 1.47 1.64 2.10 2.19 2.36 2.61 2.96 3.13 3.34 3.55 3.76 4.02 4.28 4.53 4.87
2.51
NL: 6.40E2
A/D Card Ch. 1 A/D card L-6_1
milliVolts
500
0.06 0.18 0.47 0.58 0.82 0.94 1.21 1.49 1.61 1.86 2.01 2.12 2.44 2.66 2.81 2.98 3.19 3.34 3.71 3.85 4.01 4.29 4.47 4.64 4.84
0.0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0 4.5 5.0
Time (min)

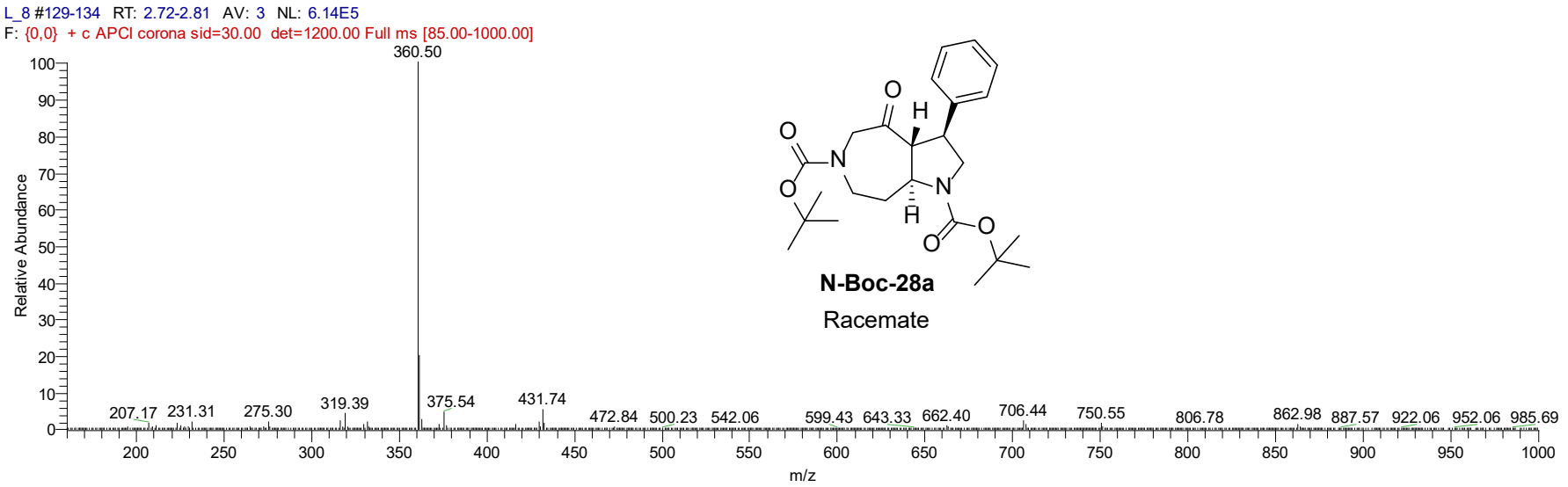

L-6_1 #115-121 RT: 2.42-2.55 AV: 4 NL: 1.04E6
F: {0,0} + c APCI corona sid=30.00 det=1200.00 Full ms [85.00-1000.00]
276.27
Relative Abundance
100
90
80
70
60
50
40
30
20
10
0
232.29
332.49
198.18
273.38
317.43
373.48
429.70
455.69
507.93
564.13
608.18
664.36
712.76
741.59
766.97
842.35
869.75
916.82
971.14
200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950 1000
m/z
O
H
O
N
H
O
O
N-Boc-(+)-27b
Enantiomer #1





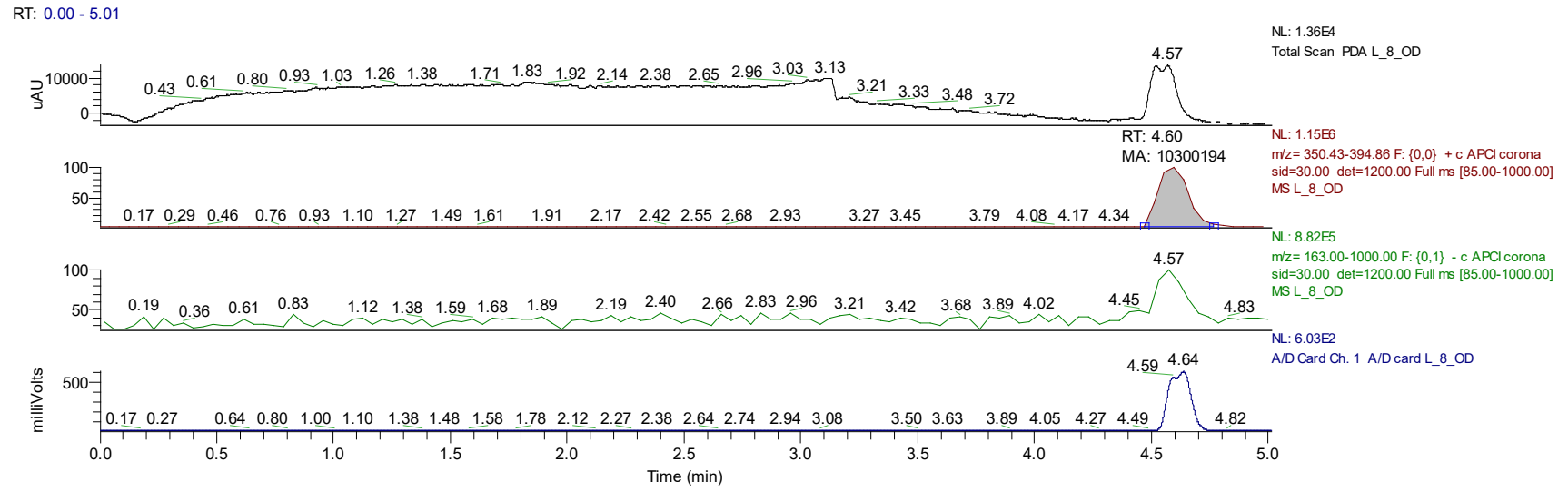
Area %	Peak Area	RT
100	1994798	4.55

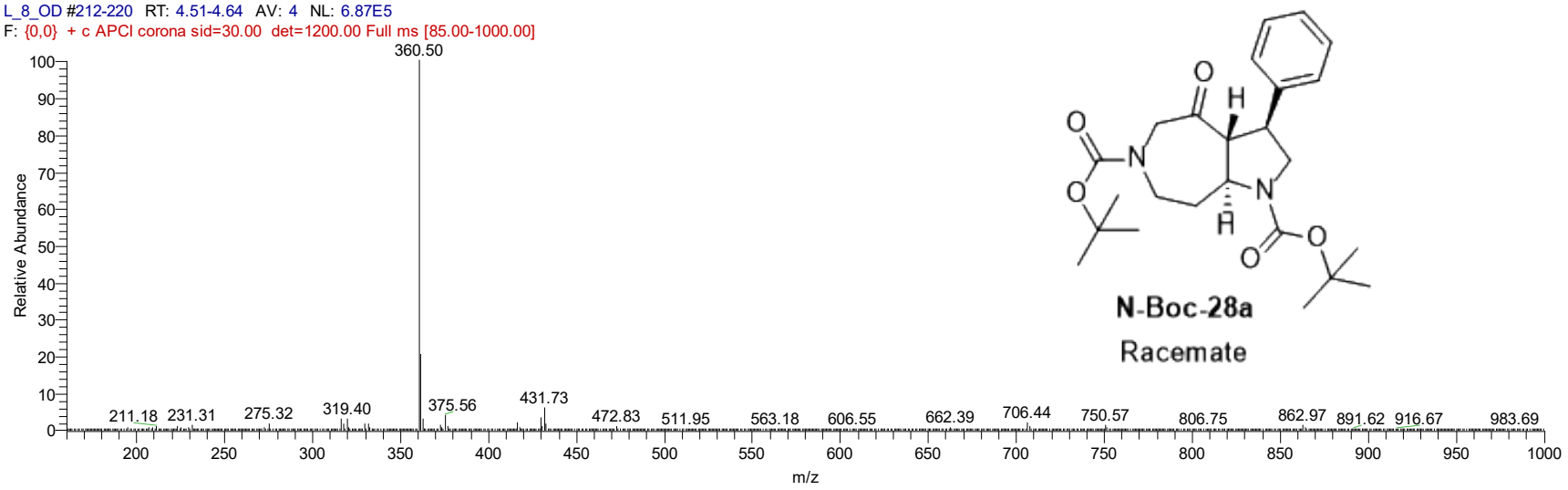




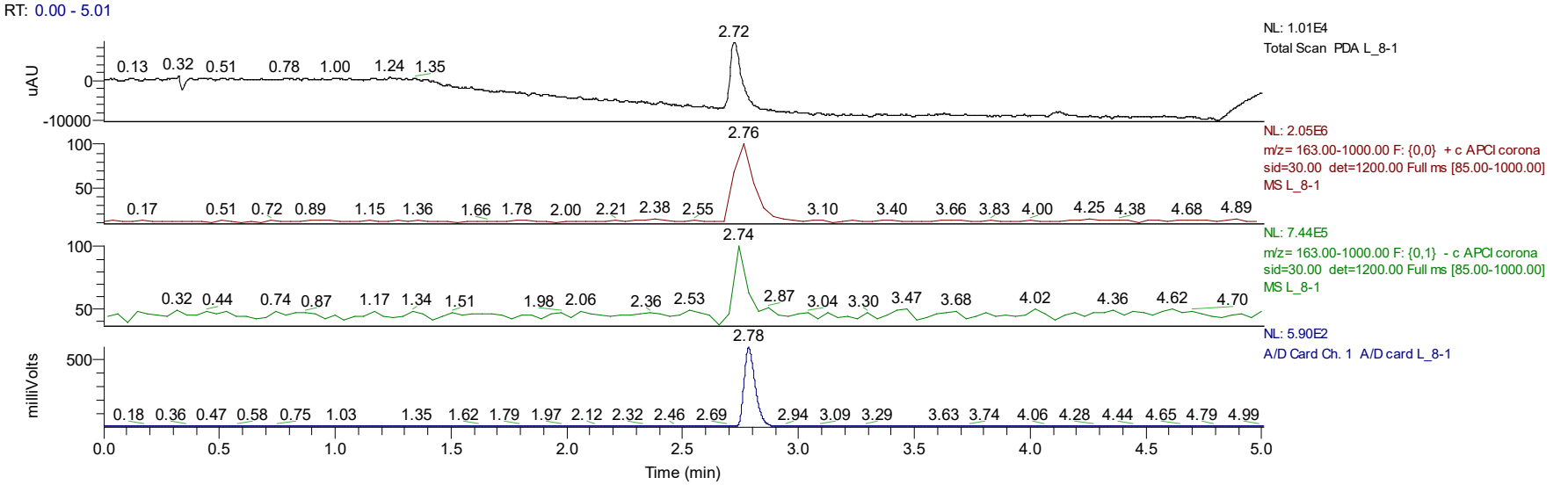
N-Boc-28a

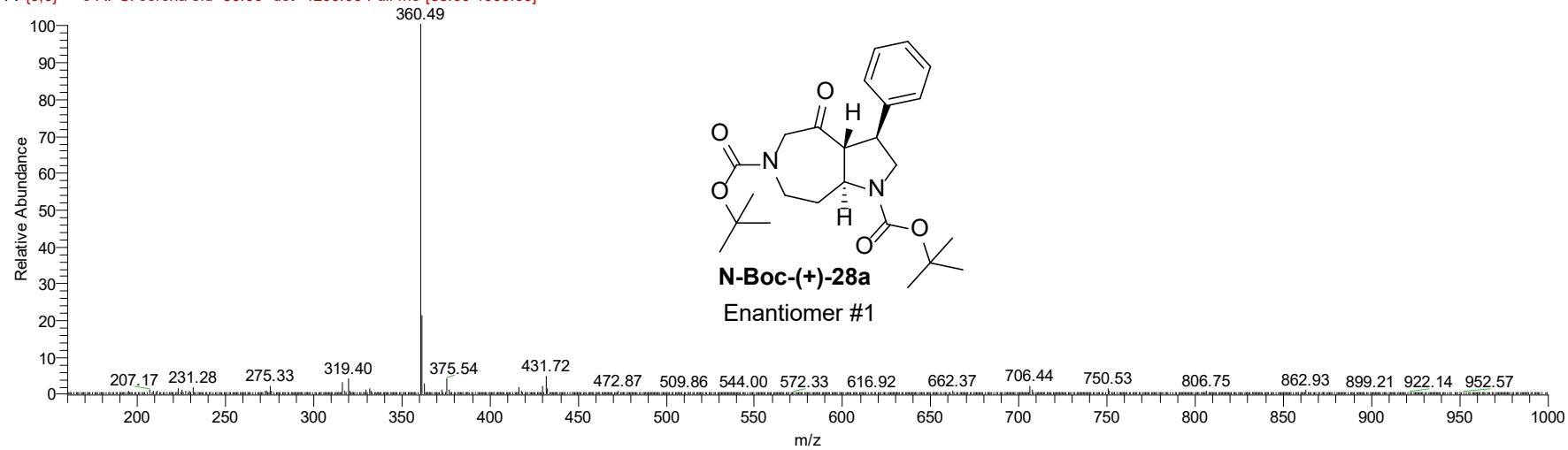
Racemate

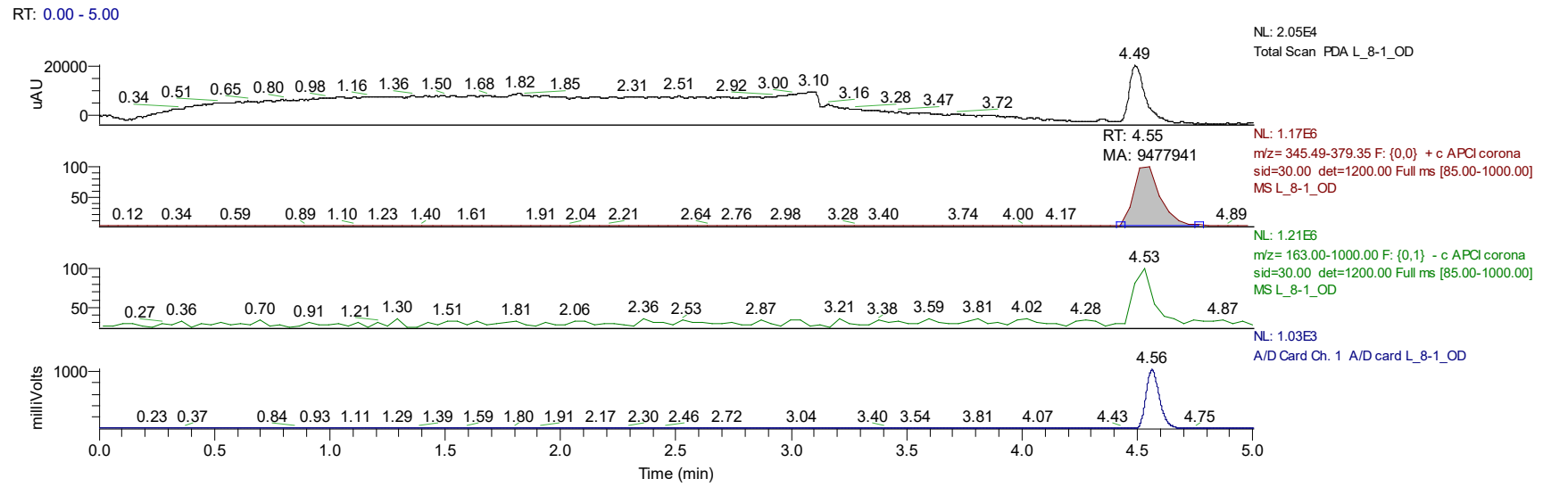


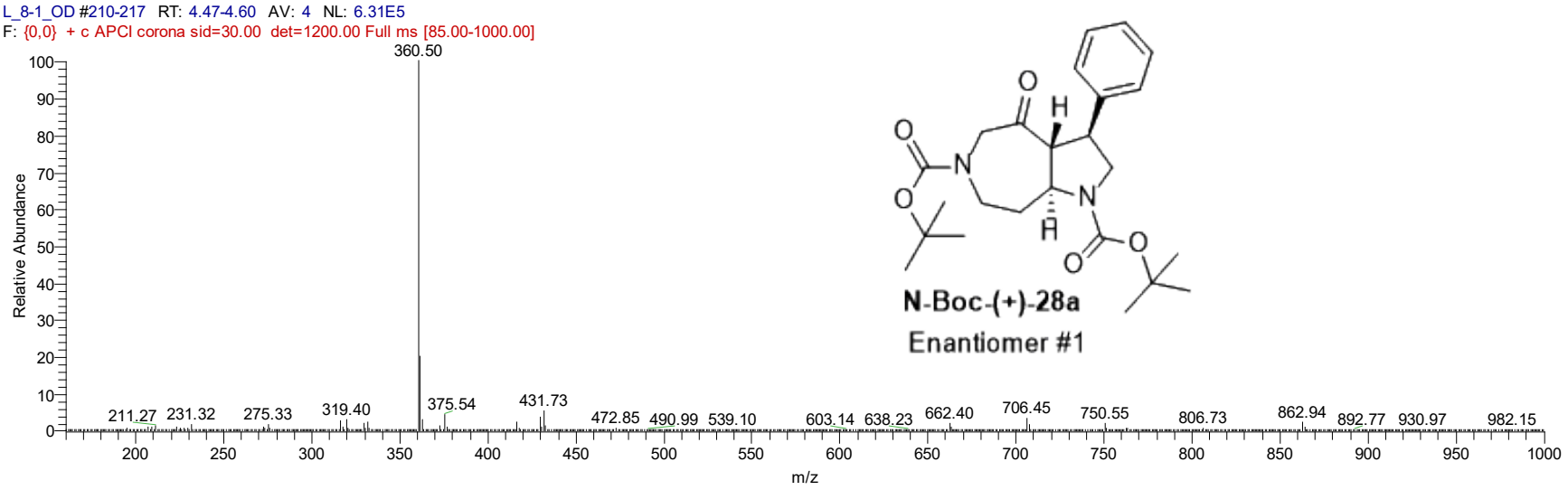


Area %	Peak Area	RT
48	4944093	4.59
52	5356101	4.64

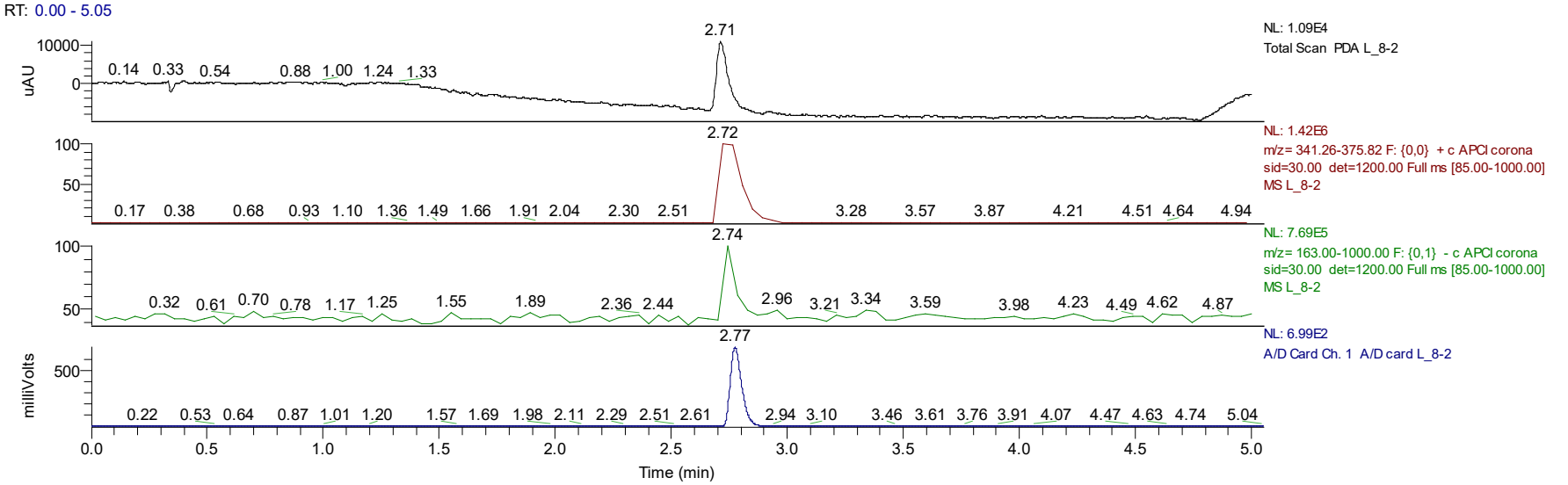

RT: 0.00 - 5.01
NL: 1.01E4
Total Scan PDA L_8-1
NL: 2.05E6
m/z= 163.00-1000.00 F: {0,0} + c APCI corona
sid=30.00 det=1200.00 Full ms [85.00-1000.00]
MS L_8-1
NL: 7.44E5
m/z= 163.00-1000.00 F: {0,1} - c APCI corona
sid=30.00 det=1200.00 Full ms [85.00-1000.00]
MS L_8-1
NL: 5.90E2
A/D Card Ch. 1 A/D card L_8-1
uAU
milliVolts
Time (min)

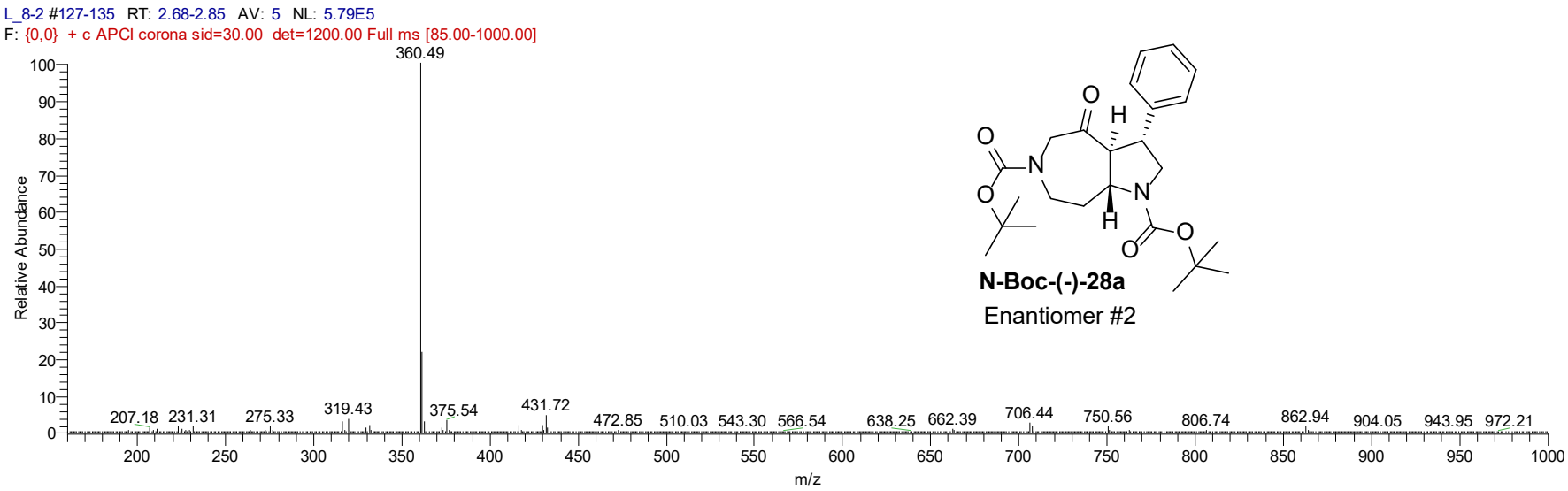

L_8-1 #127-134 RT: 2.68-2.81 AV: 4 NL: 5.75E5
F: {0,0} + c APCI corona sid=30.00 det=1200.00 Full ms [85.00-1000.00]
Relative Abundance
m/z
N-Boc-(+)-28a
Enantiomer #1





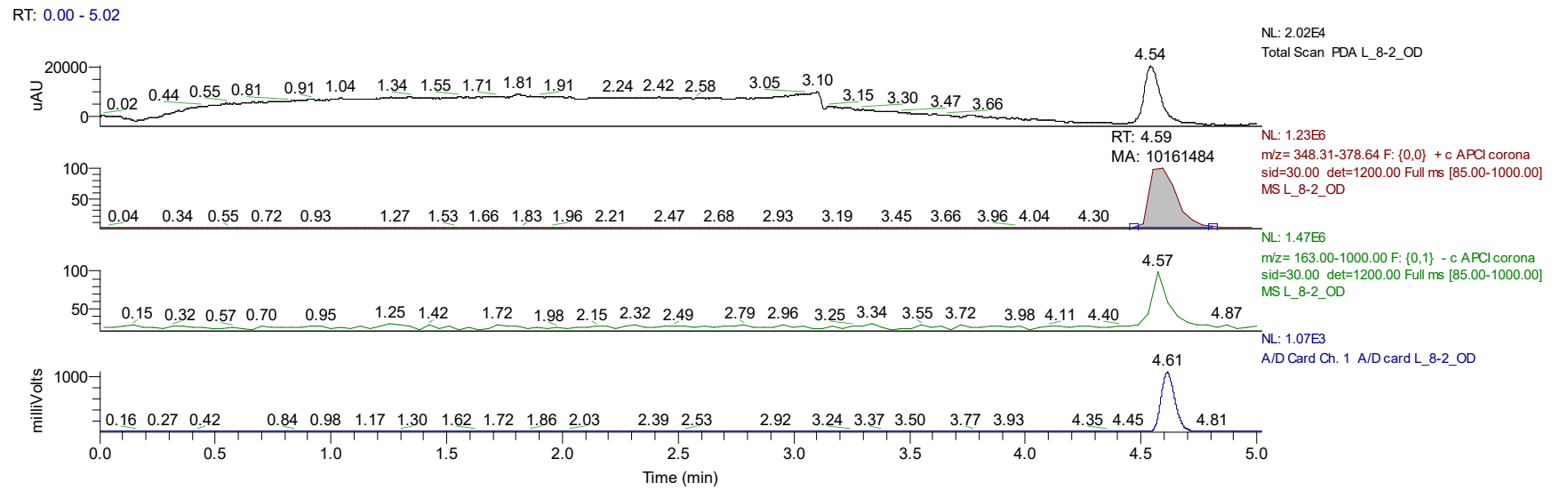
Area %	Peak Area	RT
100	9477941	4.55

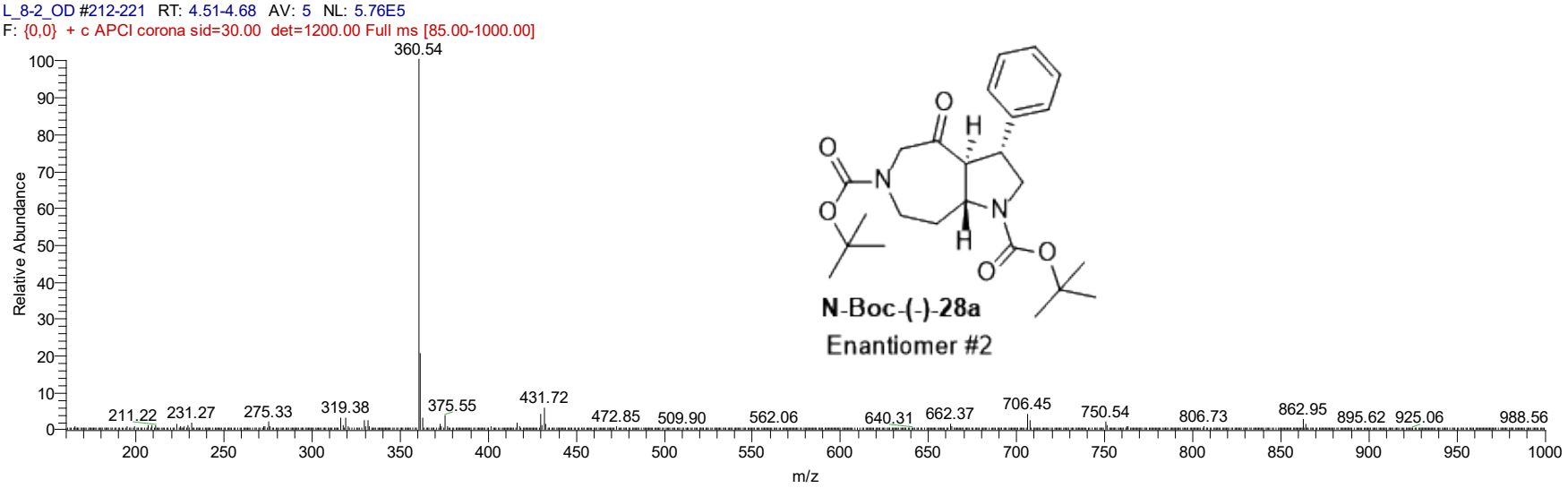




N-Boc-(-)-28a

Enantiomer #2





Area %	Peak Area	RT
100	10161484	4.59