Stereoselective Synthesis of Novel Adamantane Derivatives with High Activity Against Rimantadine-Resistant Influenza A Virus Strains

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Supporting Information

Table of Contents:

† NMR experiments; ‡X-Ray single crystal analysis study.

General. The manipulations with sensitive to air compounds were carried out under inert atmosphere of dry Ar. NMR spectra were recorded on Bruker Avance-300, 400 and 600 MHz instruments. Mass spectra were recorded on Finnigan Polaris Q Ion Trap spectrometer. Monoisotopic mass spectra (HRMS) were obtained from Bruker microTOF, Maxis. Optical rotation was measured on Perkin Elmer 341 instrument. Column chromatography was carried out using silica gel 60–230 mesh (Merck). Thin layer chromatography was run on Alugram Sil G/UV_{254} (Macherey-Nagel). Melting points were measured on a Suart SMP10 capillary melting point apparatus.

(*R*$_S$)-*N*-(Adamantan-1-yl)methylene)-2-methylpropane-2-sulfinamide ((*R*$_S$)-3).

A solution of adamantane-1-carbaldehyde **1** (2.00 g, 12.18 mmol), (*R*$_S$)-2-methyl-2-propanesulfinamide **(*R*$_S$)-2** (1.55 g, 12.79 mmol) in neat Ti(O*i*Pr)$_4$ (20.76 g, 21.60 mL, 73.03 mmol) was stirred with heating on a water bath at 70 °C for 18 h. The resulting mixture was diluted with THF (20 ml) and poured into water (200 mL) with stirred for 20 min, then filtered and the precipitate was washed twice with DCM. The aqueous layer was extracted with DCM (3x30 mL). The combined extracts were dried over Na_2SO_4, filtered through the pad of silica gel, and evaporated under reduced pressure. The residue was recrystallized from *n*-C_6H_{14} to afford **(*R*$_S$)-3** (2.38 g, 73%) as colorless crystals, m.p. 115-116 °C. $[\alpha]_D^{25}$ = –168.8° (C 1, $CHCl_3$). R_f= 0.1 (*n*-C_6H_{14}/EtOAc = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.76 (s, 1H, CH=); 2.20-1.98 (m, 3H, 3CH Ad); 1.82-1.65 (m, 12H, 6CH_2 Ad), 1.16 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 175.05; 56.33; 40.01; 39.09 3C; 36,51 3C; 27.75 3C; 22.24 3C. $C_{15}H_{25}NOS$ (267.43): calcd. C, 67.37; H, 9.42; N, 5.24; found C, 67.37; H, 9.61; N, 5.24.

(*S*$_S$)-*N*-(Adamantan-1-yl)methylene)-2-methylpropane-2-sulfinamide ((*S*$_S$)-3).

$[\alpha]_D^{25}$ = +168.2° (C 1, $CHCl_3$). $C_{15}H_{25}NOS$ (267.43): calcd. C, 67.37; H, 9.42; N, 5.24; found C, 67.22; H, 9.66; N, 5.26.

(*R*$_S$)-*N*-((*1S*)-1-(adamantan-1-yl)but-3-en-1-yl)-2-methylpropane-2-sulfinamide ((*S,R*$_S$)-4).

a) Zn-mediated allylation of (*S*$_S$)-3:

To Zn dust (0.073 g, 1.12 mmol) activated by stirring for 10 min with one drop of TMSCl in THF (3 mL) AllylBr (0.136 g, 0.097 mL, 1.12 mmol) was added at 5 °C. The mixture was then stirred at this temperature for five minutes followed by the dropwise addition of **(*S*$_S$)-3** (0.100 g, 0.37 mmol) in THF (1 mL) for 2 min. The reaction mixture was stirred additionally for 30 min at room temperature (TLC control) and quenched with a satd. NH_4Cl solution. The reaction mixture was diluted with diethylether, and the organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and evaporated

under reduced pressure to give pure **(S,R_S)-4** (0.110 g, 95%, *de* 99.7%) as white solid, m.p. 82-83 °C. $[\alpha]_D^{25}$ = –57.2 (C 1, $CHCl_3$). The isomers ratio was determined by chiral HPLC of *N*-Cbz-derivative **(*S*)-5** to be 99.85:0.15 (described below); major (*S*)-isomer peak — 6.5 min; minor (*R*)-isomer peak — 8.5 min. Column Chiralpak AD, eluent *n*-C_6H_{14}/*i*PrOH = 85:15, rate 1 mL/ min, UV 219 nm. R_f= 0.54 (*n*-C_6H_{14}/EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 5.96-5.83 (m, 1H, CH=); 5.12-5.05 (m, 2H, CH_2=); 3.09 (d, *J* = 6.1 Hz, 1H, NH); 2.85-2.80 (m, 1H, CHAd); 2.52 (dt, *J* = 5.2, 14.6 Hz, 1H, C$\underline{H}_A$H$_B$CHN); 2.11 (dt, *J* = 8.3, 14.4 Hz, 1H, CH$_A\underline{H}_B$CHN); 1.95 (s, 3H, 3CH Ad); 1.68-1.65 (m, 3H, Ad); 1.58-1.55 (m, 6H, Ad); 1.49-1.46 (m, 3H, Ad); 1.21 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 136.27; 117.91; 63.71; 56.38; 38.85 3C; 37.26; 37.00 3C; 34.56; 28.30 3C; 22.96 3C. $C_{18}H_{31}NOS$ (309.51): calcd. C, 69.85; H, 10,10; N, 4.53; found C, 69.77; H, 10.19; N, 4.41.

b) In-mediated allylation of (S_S)-3:

A mixture of In turnings (1.29 g, 11.22 mmol) and AllylBr (1.36 g, 0.97 mL, 11.22 mmol) was refluxed in THF (7 mL) for 30 min. It was cooled to room temperature and **30a** (1.00 g, 3.74 ммоль) dissolved in THF (1 mL) was added. The reaction mixture was stirred for 18 h at room temperature, quenched with satd. NH_4Cl (15 mL) and diluted with Et_2O. The organic layer was washed with brine and Na_2-EDTA solution, dried over Na_2SO_4 and evaporated under reduced pressure to dryness to give **(S,R_S)-4** (1.16 g, quant., *de* 97.1 %). The isomers ratio was determined by chiral HPLC of *N*-Cbz-derivative **(*S*)-5** to be 98.57:1.43 retention times: major (*S*)-isomer peak — 6.5 min; minor (*R*)-isomer peak — 8.5 min. Column Chiralpak AD, eluent *n*-C_6H_{14}/*i*PrOH = 85:15, rate 1 mL/ min, UV 219 nm.

(S_S)-*N*-((*1R*)-1-(adamantan-1-yl)but-3-en-1-yl)-2-methylpropane-2-sulfinamide ((R,S_S)-4).

The isomers ratio was determined by chiral HPLC of *N*-Cbz-derivative **(*R*)-5** to be 99.35:0.65 (described below); minor (*S*)-isomer peak — 6.5 min; major (*R*)-isomer peak — 9.0 min. $[\alpha]_D^{25}$ = +59.5° (C 1, $CHCl_3$). $C_{18}H_{31}NOS$ (309.51): calcd. C, 69.85; H, 10,10; N, 4.53; found C, 69.75; H, 10.24; N, 4.33. The isomers ratio was determined by chiral HPLC of *N*-Cbz-derivative **(*R*)-5** to be 99.35:0.65 (described below); minor (*S*)-isomer peak — 6.5 min; major (*R*)-isomer peak — 9.0 min.

Synthesis of adamantyl derivatives 6, 7, *rac*-5 for chiral HPLC.

***N*-[1-(Adamantan-1-yl)methylyden]-2-methyl-2-propanesulfonamide (6).**

Commercial m-CPBA 70% (1.0 g) was dissolved in DCM and dried with Na_2SO_4, then carefully decanted from drying agent and evaporated to dryness on the Rotavapor. The dry m-CPBA (0.13 g, 0.56 mmol) was added to a solution of the sulfinylimine (R_S)-**3** (0.15 g, 0.56 mmol) in DCM (4 mL) at room temperature. The reaction was completed in 1 min (TLC control). The mixture was diluted with DCM

(12 mL) and washed with a saturated solution of $NaHCO_3$ (3x6 mL). The organic phase was dried over Na_2SO_4, and the solvent was evaporated to give crude sulfonylimine **6** (0.103 g, 97%) which was used further without purification. Sulfonylimine **6** is partially hydrolysed during isolation and chromatography, however, for analythical purposes small amount of **6** was passed twice through the short silica gel column in (*n*-C_6H_{14}/EtOAc, 10:1) to furnish pure **6** as crystalline solid, m.p. 125-128 °C. R_f= 0.31 (EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) (δ, ppm): 8.29 (s, 1H, CH=N); 2.08 (br.s, 3H, 3CH, Ad); 1.81-1.68 (m, 12H, 6CH_2, Ad); 1.41 (s, 9H, *t*Bu). ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm): 186.29; 57.98; 38.23 3C; 36.53; 36.30 3C; 27.41 3C; 23.95 3C. HRMS Calcd for $C_{15}H_{25}NO_2S$: 284.1679 (M+H). Found: 284.1683 (MH^+).

***N*-[1-(Adamantan-1-yl)-3-butenyl]-2-methyl-2-propanesulfonamide (7).**

To Zn dust (0.051 g, 0.78 mmol) activated by stirring for 10 min with one drop of TMSCl in THF (3 mL) AllylBr (0.094 g, 0.067 mL, 0.78 mmol) was added at 5 °C. The mixture was then stirred at this temperature for 5 min. followed by the dropwise addition of sulfonamide **6** (0.147 g, 0.52 mmol) in THF (1 mL) for 2 min. The reaction mixture was stirred additionally for 40 min at room temperature (TLC control) and quenched with a satd. NH_4Cl solution. The reaction mixture was diluted with diethylether, and the organic layer was separated, washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was subjected to FC on silica gel in (*n*-C_6H_{14}/EtOAc, 10:1) to afford pure allylated product **7** (0.168 g, quant.) as a colorless solid, m.p. 122-123 °C (*n*-C_6H_{14}). R_f = 0.25 (*n*-C_6H_{14}/EtOAc, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 5.90 (ddt, *J* = 7.3, 10.2, 16.8 Hz, 1H, CH=); 5.15-5.07 (m, 2H, CH_2=); 3.64 (d, *J* = 10.2 Hz, 1H, NH); 3.14 (dt, *J* = 5.4, 10.2 Hz, 1H, CHAd); 2.57-2.50 (m, 1H, C$\underline{H}_A$H$_B$ allyl); 2.33-2.25 (m, 1H, CH$_A\underline{H}_B$ allyl); 2.01 (br.s, 3H, 3CH Ad); 1.71-1.60 (m, 9H, Ad); 1.55-1.52 (m, 3H, Ad); 1.41 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 136.12; 117.66; 63.07; 60.20; 39.28 3C; 37.37; 36.83 3C; 35.90; 28.33 3C; 24.53 3C. HRMS Calcd for $C_{18}H_{31}NO_2S$: 326.2148 (M+H). Found: 326.2142 (MH^+).

Benzyl ((*rac*)-1-(adamantan-1-yl)but-3-en-1-yl)carbamate (***rac*-5**).

To a flask charged with a solution of sulfonamide **7** (50 mg, 0.15 mmol) in DCM (0.3 ml) TfOH (0.11 g/0.066 ml, 0.75 mmol, 5 equiv.) was added and the mixture was heated on water bath at 50 °C for 10 min. The progress of the reaction was monitored by TLC (*n*-C_6H_{14}/EtOAc, 4:1). After the removal of sulfone group was completed the mixture was diluted with Et_2O (5 ml) followed by the addition of 20% NaOH (2 ml). To the vigorously stirred mixture CbzCl (76.7 mg/0.064 ml, 0.45 mmol, 3 equiv.) was added via pipette and stirring was continued for 30 min. The upper organic layer was separated, washed

with solution $NaHCO_3$ of and dried over K_2CO_3. Evaporation and column chromatography purification (*n*-C_6H_{14}/EtOAc, 6:1) gave rise to ***rac*-5** (45 mg, 89%) as crystalline solid, m.p. 83-84 °C (*n*-C_6H_{14}). R_f = 0.5 (*n*-C_6H_{14}/EtOAc, 4:1). In the proton spectra ***rac*-5** exists as a mixture of rotamers in ratio 5.6:1. ^{1}H NMR of major rotamer (400 MHz, $CDCl_3$) (δ, ppm): 7.38-7.28 (m, 5H, Ph); 5.77 (dddd, *J* = 5.7, 8.2, 10.2, 17.0 Hz, 1H, CH=); 5.12 (d, *J* = 12.3 Hz, 1H, C$\underline{H}_A$H$_B$Ph); 5.05 (d, *J* = 12.3 Hz, 1H, CH$_A\underline{H}_B$Ph); 5.05-4.96 (m, 2H, CH_2=); 4.48 (d, *J* = 10.5 Hz, 1H, NH); 3.36 (td, *J* = 3.1, 10.9 Hz, 1H, CHAd); 2.44 (dm, *J* = 14.2 Hz, 1H, C$\underline{H}_A$H$_B$ allyl); 1.98-1.97 (m, 3H, 3CH Ad); 1.86 (ddd, *J* = 8.2, 11.4, 14.2 Hz, CH$_A\underline{H}_B$ allyl); 1.71-1.68 (m, 3H, Ad); 1.62-1.49 (m, 9H, Ad). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 156.73; 136.77; 135.97; 128.46 2C; 128.00; 127.95 2C; 116.84; 66.56; 59.47; 38.54 3C; 36.99 3C; 36.36; 33.53; 28.30 3C. HRMS Calcd for $C_{22}H_{29}NO_2$: 362.2091 (M+Na). Found: 362.2092 (MNa^+).

***tert*-Butyl ((*1S*)-1-(adamantan-1-yl)but-3-en-1-yl)carbamate ((*S*)-8).**

To a solution of **(*S,R*$_S$)-4** (0.95 g, 3.07 mmol) in MeOH (5 mL) a solution of 4N HCl in dioxane (3.07 mL, 12.3 mmol) was added and the mixture was left for 2 h (TLC control). The solution was then evaporated under reduced pressure to dryness. To the solid residue were added THF (8 mL) and Et_3N (1.55 g, 2.14 mL, 15.35 mmol), after which the suspension was stirred at reflux for 10 min followed by Boc_2O (1.12 g, 5.13 mmol) addition, the heating was continued for 4 h. The suspension was concentrated on a rotary evaporator then diluted with n-hexane (15 mL) and water (10 mL). The organic layer was separated, dried over K_2CO_3, evaporated, and the residual solid was subjected to FC on silica gel in *n*-C_6H_{14}/EtOAc, 20:1 to afford the *N*-Boc-derivative **(*S*)-8** (0.75 g, 80%) as a colorless needles, m.p. 140-141 °C. $[\alpha]_D^{25}$= +23.4 (C 1, $CHCl_3$). R_f= 0.62 (*n*-C_6H_{14}/EtOAc, 20:1). Signals in NMR spectra are doubled due to presence of rotamers arising from hindered rotation around C-N amide bond. The NMR spectra are described for major rotamer (rotamer ratio 1:5.5). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 5.82-5.71 (m, 1H, CH=); 5.04-4.98 (m, 2H, CH_2=); 4.23 (d, *J* = 10.2 Hz, 1H, NH); 3.27 (td, *J* = 2.9, 11.1 Hz, 1H, CHAd); 2.40 (dm, *J* = 14.0 Hz, 1H, C$\underline{H}_A$H$_B$ allyl); 1.96 (m, 3H, 3CH); 1.82 (ddd, *J* = 8.3, 11.1, 14.0 Hz, 1H, CH$_A\underline{H}_B$ allyl); 1.70-1.67 (m, 3H, Ad); 1.62-1.59 (m, 3H, Ad); 1.55-1.48 (m, 6H, Ad); 1.41 (s, 9H, *t*Bu). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 156.24; 136.27; 116.41; 78.66; 58.74; 38.55 3C; 37.02 3C; 36.25; 28.40 3C; 28,33 3C. $C_{19}H_{31}NO_2$ (305.46): calcd. C, 74.71; H, 10.23; N, 4.59; found C, 74.67; H, 10.25; N, 4.48.

***tert*-Butyl ((*1R*)-1-(adamantan-1-yl)but-3-en-1-yl)carbamate ((*R*)-8).**

$[\alpha]_D^{25} = -23.2$ (C 1, $CHCl_3$). $C_{19}H_{31}NO_2$ (305.46): calcd. C, 74.71; H, 10.23; N, 4.59; found C, 74.61; H, 10.37; N, 4.54.

(*4S,6R*)-4-(Adamantan-1-yl)-6-(bromomethyl)-1,3-oxazinan-2-one ((*4S,6R*)-9a).

To a refluxed solution of NBS (0.5 g, 2.78 mmol) in DCM (8 mL) was added a solution of **(*S*)-8** (0.5 g, 1.64 mmol) in DCM (3 mL). The reaction mixture was refluxed for 2 h (TLC control), then evaporated under reduced pressure. To the residue Et_2O (10 mL) and 5% NaOH solution (8 mL) were added and the mixture was vigorously stirred for 10 min. The organic layer was separated, dried over K_2CO_3 and evaporated and the residue was subjected to flash chromatography on SiO_2 (*n*-C_6H_{14}/EtOAc, 1:1) to give **9a** (0.39 g, 72%) as a mixture of diastereoisomers in ratio *cis/trans* = 4:1. The major *cis*-isomer (***cis*-9a**) was obtained by recrystallization from EtOAc, m.p. 213-214 °C and its *cis*-configuration was supported by NOESY. $[\alpha]_D^{25} = +12.3$ (C 1, $CHCl_3$). R_f= 0.22 (*n*-C_6H_{14}/EtOAc, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 5.68 (s, 1H, NH); 4.37 (s, 1H, CHO); 3.56 (d, *J* = 9.9 Hz, 1H, $C\underline{H}_AH_BBr$); 3.43 (dd, *J* = 5.7, 9.9 Hz, 1H, $CH_A\underline{H}_BBr$); 3.07 (dd, *J* = 2.6, 10.8 Hz, 1H, CHAd); 2.11 (d, *J* = 12.4 Hz, 1H, $C\underline{H}_AH_B$ cycle); 2.03 (s, 3H, 3CH Ad); 1.74-1.71 (m, 3H, Ad); 1.64-1.58 (m, 4H, Ad and $CH_A\underline{H}_B$ cycle); 1.55-1.48 (m, 6H, Ad). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 154.13; 75.33; 59.63; 37.56 3C; 36.73 3C; 35.15; 32.93; 27.93 3C; 25.61. $C_{15}H_{22}BrNO_2$ (328.25): calcd. C, 54.89; H, 6.76; N, 4.27; found C, 54.99; H, 6.87; N, 4.29.

(*4R,6S*)-4-(Adamantan-1-yl)-6-(bromomethyl)-1,3-oxazinan-2-one ((*4R,6S*)-9a).

$[\alpha]_D^{25} = -12.2$ (C 1, $CHCl_3$). $C_{15}H_{22}BrNO_2$ (328.25): calcd. C, 54.89; H, 6.76; N, 4.27; found C, 55.19; H, 6.91; N, 4.26.

(*4S,6R*)-4-(1-Adamantyl)-6-(bromomethyl)-5,6-dihydro-4H-1,3-oxazin-2-yl *tert*-butyl ether (9b)

Ether **9b** was synthesized by following procedure for **9a** with exception of chromatography purification. Instead of purification of the residue after evaporation of the reaction mixture, its solution in EtOAc was rapidly passed through the 0.5 cm layer of silica gel on the filter funnel connected to a vacuum line and washed in EtOAc. EtOAc was evaporated, residual oil dissolved in *n*-C_6H_{14} and again evaporated to remove traces of EtOAc. The resulting transparent oil consisting of isomeric bromides **9b** (75%) was diluted with *n*-C_6H_{14} and placed in refrigerator at -25 °C for crystallization. The precipitated crystals were filtered and washed with chilled *n*-C_6H_{14}, that gave pure ***cis*-9b** (8%), m.p. 143-144 °C. ^{1}H NMR (500 MHz, C_6D_6) (δ, ppm): 3.76-3.71 (m, 1H, CHO); 2.94 (dd, *J* = 5.6, 10.7, 1H, $C\underline{H}_AH_BBr$); 2.88 (dd, *J* = 5.1, 10.7, 1H, $CH_A\underline{H}_BBr$); 2.72 (dd, *J* = 4.2, 11.6, 1H, CHN); 2.01 (m, 3H, 3CH, Ad); 1.75-1.73 (m, 3H, $3C\underline{H}_AH_B$, Ad); 1.70-1.67 (m, 6H, $3CH_A\underline{H}_B$, $3C\underline{H}_{A'}H_{B'}$, Ad); 1.51 (s, 9H, *t*Bu); 1.51-1.48 (m, 3H,

3$CH_{A'}\underline{H}_{B'}$, Ad); 1.36 (ddd, *J* = 2.6, 3.6, 12.9, 1H, C$\underline{H}_A$$H_B$CHN); 1.10 (dt, *J* = 11.6, 12.9, 1H, $CH_A\underline{H}_B$CHN). ^{13}C NMR (125.75 MHz, C_6D_6) (δ, ppm): 150.21 (C=N); 79.56 (O-C(Me)$_3$); 75.33 (CHO); 62.08 (CHN), 39.13 3C (3CH_2); 37.79 3C (3CH_2); 36.46 (C_{Ad}-CHN); 34.51 (CH_2Br); 29.09 3C (tBu); 28.30 3C (3CH); 25.82 (CH_2). $C_{19}H_{30}BrNO_2$ (384.35): calcd. C, 59.37; H, 7.87; N, 3.64; found C, 59.29; H, 7.99; N, 3.58.

(*S*)-4-(adamantan-1-yl)-6-methylene-1,3-oxazinan-2-one ((*S*)-10).

To a solution of crude mixture of the isomeric bromides **9b** (0.52 g, 1.35 mmol) in THF (15 mL) at 0 °C was added *t*BuOK (0.19 g, 1.70 mmol). The mixture was then stirred for 1 h at ambient temperature. The progress of the reaction was monitored by TLC (*n*-C_6H_{14}/EtOAc). After completion, the reaction mixture was cooled to -20 °C and quenched with AcOH (0.06 g, 0.057 mL, 1.0 mmol) in THF (2 mL). The mixture was filtered through a pad of Super Cel and washed with EtOAc. The filtrate was evaporated under reduced pressure at 40 °C and the residue was purified by FC on SiO_2 in *n*-C_6H_{14}/EtOAc, 2:1, that gave **(*S*)-10** (0.32 g, 96%) as a colorless crystals, m.p. 155-160 °C (dec). $[\alpha]_D^{25}$= +46.7 (C 1, $CHCl_3$). R_f= 0.31 (*n*-C_6H_{14}/EtOAc, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): δ 6.29 (br s, 1H, NH), 4.66 (s, 1H, =C$\underline{H}_a$$CH_b$), 4.27 (s, 1H, =$CH_aC\underline{H}_b$), 2.97 (dd, *J* = 9.2, 4.8 Hz, 1H, CHN), 2.47 (dd, *J* = 14.3, 4.9, 1H, C$\underline{H}_a$$CH_b$C=), 2.38 (dd, *J* = 14.3, 9.3, 1H, CH_aC$\underline{H}_b$C=), 2.10–1.95 (m, 3H), 1.77 – 1.45 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 152.89, 152.23, 93.65, 58.49, 37.65 (3C), 36.71 (3C), 35.29, 27.95 (3C), 25.34. $C_{15}H_{21}NO_2$ (247.34): calcd. C, 72.84; H, 8.56; N, 5.66; found C, 73.02; H, 8.85; N, 5.54.

(*R*)-4-(adamantan-1-yl)-6-methylene-1,3-oxazinan-2-one ((*R*)-10).

$[\alpha]_D^{25}$= –46.4° (C 1, $CHCl_3$). $C_{15}H_{21}NO_2$ (247.34): calcd. C, 72.84; H, 8.56; N, 5.66; found C, 72.94; H, 8.71; N, 5.59.

(*S*)-6-(Adamantan-1-yl)piperidine-2,4-dione ((*S*)-11).

To a suspension of a mixture of the isomeric bromides **9a** (0.20 g, 0.61 mmol) in THF (10 mL) at rt was added *t*BuOK (0.27 g, 2.44 mmol). The mixture was then stirred for 2 h at 45 °C. The progress of the reaction was monitored by TLC (EtOAc). After completion, the reaction mixture was cooled to -20 °C and quenched with AcOH (0.15 g, 0.14 mL, 2.44 mmol) in THF (2 mL) and H_2O (0.05 ml). The mixture was filtered through a pad of Super Cel and washed with EtOAc. The filtrate was evaporated under reduced pressure at 40 °C to afford **(*S*)-11** (0.14 g, 95%) as a colorless needles, m.p. 209-210 °C. $[\alpha]_D^{25}$= –32.6 (C 1, $CHCl_3$). R_f= 0.31 (EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) (δ, ppm): 7.15 (s, 1H, NH), 3.23 (s, 2H, $CH_2(CO)_2$); 3.22-3.19 (m, 1H, CHAd); 2.55 (d, *J* = 6.7 Hz, 2H, C$\underline{H}_2$CHAd); 2.05-1.98 (m, 3H, 3CH

Ad); 1.72-1.69 (m, 3H, Ad); 1.61-1.58 (m, 3H, Ad); 1.54-1.47 (m, 6H, Ad). ^{13}C NMR (75 MHz, $CDCl_3$) (δ, ppm): 204.47; 169.45; 57.95; 46.91; 38.56; 37.79 3C; 36.48 3C; 36.12; 27.86 3C. $C_{15}H_{21}NO_2$ (247.34): calcd. C, 72.84; H, 8.56; N, 5.66; found C, 72.69; H, 8.61; N, 5.59.

(*R*)-6-(Adamantan-1-yl)piperidine-2,4-dione ((*R*)-11).

$[\alpha]_D^{25}$= +33.0 (C 1, $CHCl_3$). $C_{15}H_{21}NO_2$ (247.34): calcd. C, 72.84; H, 8.56; N, 5.66; found C, 72.80; H, 8.56; N, 5.58.

(*4S,6S*)-6-((Adamantan-1-yl)-4-hydroxypiperidin-2-one ((*4S*,*6S*)-12)

To a suspension of **(*S*)-11** (0.25 g, 1.01 mmol) in THF (10 mL) at –90 °C was added $NaBH_4$ (0.38 g, 10.1 mmol). After stirring at this temperature for 4 hours NH_4Cl_{aq} (5 mL) and water (5 mL) were added and the phases were separated. Aqueous phase was extracted with EtOAc (2x20 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated. The residual solid was subjected to FC on silica gel in EtOAc/MeOH, 20:1 to afford **(*4S*,*6S*)-12** as a mixture of diastereomers in ratio *cis/trans* = 16.6:1 (0.22 g, 87%). R_f= 0.43 (EtOAc/MeOH = 20:1). Recrystallization from *n*-C_6H_{14}/EtOAc improved diastereomeric ratio to *cis/trans* = 19.7:1 (29%), m.p. 179-180 °C, $[\alpha]_D^{25}$= +37.0 (C 1, $CHCl_3$). *cis*-Configuration of major isomer was supported by NOESY. ^{1}H NMR (600 MHz, $CDCl_3$) (δ, ppm): δ 5.94 (s, 1H, NH), 4.03 – 3.93 (m, 1H, CHOH), 3.21 (s, 1H, OH), 2.93 (dd, *J* = 11.6, 4.1 Hz, 1H, CHAd), 2.69 (dd, *J* = 16.8, 3.5 Hz, 1H, $CH_{ax}\underline{H}_{eq}C$=O), 2.20 (dd, *J* = 16.8, 10.9 Hz, 1H, $C\underline{H}_{ax}H_{eq}C$=O), 2.07 (d, *J* = 11.1 Hz, 1H, $CH_{ax}\underline{H}_{eq}$CHAd), 2.00 (s, 3H, Ad), 1.71 (d, *J* = 12.2 Hz, 3H, Ad), 1.59 (d, *J* = 11.7 Hz, 3H, Ad), 1.53 – 1.45 (m, 6H, Ad), 1.43 (q, *J* = 11.9 Hz, 1H, $C\underline{H}_{ax}H_{eq}$CHAd). ^{13}C NMR (100 MHz, $CDCl_3$) (δ, ppm): 171.93, 65.09, 59.17, 40.85, 37.81 (3C), 36.79 (3C), 35.11, 31.42, 28.02 (3C). $C_{15}H_{23}NO_2$ (249.35): calcd. C, 72.25; H, 9.30; N, 5.62; found C, 72.16; H, 9.33; N, 5.52.

(4*R*,6*R*)-6-((Adamantan-1-yl)-4-hydroxypiperidin-2-one ((*4R*,*6R*)-12).

$[\alpha]_D^{25}$= –37.8 (C 1, $CHCl_3$). $C_{15}H_{23}NO_2$ (249.35): calcd. C, 72.25; H, 9.30; N, 5.62; found C, 72.21; H, 9.48; N, 5.57.

(*2R,4S*)-2-(Adamantan-1-yl)piperidin-4-ol hydrochloride ((*2R,4S*)-13).

To a solution of **(*4R*,*6R*)-12** (130 mg, 0.52 mmol) in THF (8 mL) was added at 0 °C dropwise a solution of BH_3*Me_2S (79 mg, 99 μL, 1.04 mmol) in THF (2 mL). After stirring at room temperature for 2 hours the reaction mixture was cooled to 0 °C and MeOH (2 mL) was added dropwise. The solvents were evaporated under reduced pressure to dryness. To the solid residue were added DCM (20 mL) and 10% NaOH solution (10 mL), after which the emulsion was stirred for 30 min. The aqueous phase was

extracted with DCM (2x10 mL). The organic phases were combined, dried over Na_2SO_4 and concentrated. After addition of HCl (3.4M in Et_2O) the precipitate was filtered to give **(*2R,4S*)-13** (120 mg, 85%). Recrystallization from EtOAc/MeOH gave **(*2R,4S*)-13** (42 mg, 35%) as a single diastereomer, m.p. >300 °C. $[\alpha]_D^{25}$= +11.9 (C 1, MeOH). R_f (free amine **13**) = 0.18 (EtOAc/MeOH/$NH_{3(aq)}$ = 100/25/1). ^{1}H NMR (400 MHz, DMSO-D_6) (δ, ppm): 8.63 (s, 1H, NH), 8.39 (s, 1H, NH), 5.10 (d, *J* = 4.5 Hz, 1H, OH), 3.68 – 3.52 (m, 1H, CHO), 3.21 (d, *J* = 12.6 Hz, 1H, CHN), 2.83 (dd, *J* = 23.2, 11.4 Hz, 1H, C$\underline{H}_a$CH_bN), 2.69 (t, *J* = 11.4 Hz, 1H, CH_aC$\underline{H}_b$N), 2.10 – 1.83 (m, 5H, Ad, C$\underline{H}_2$CH_2N), 1.76 – 1.47 (m, 13H, Ad, C$\underline{H}_a$CH_bCHN), 1.25 (dd, *J* = 24.0, 12.7 Hz, 1H, CH_aC$\underline{H}_b$CHN). $C_{15}H_{26}$ClNO (271.83): calcd. C, 66.28; H, 9.64; N, 5.15; found C, 66.43; H, 9.61; N, 5.08.

(*2S,4R*)-2-(adamantan-1-yl)piperidin-4-ol hydrochloride ((*2S,4R*)-13)

$[\alpha]_D^{25}$= –11.9° (C 1, MeOH). $C_{15}H_{26}$ClNO (271.83): calcd. C, 66.28; H, 9.64; N, 5.15; found C, 66.37; H, 9.57; N, 5.01.

Antiviral activity assay

We used influenza A viruses: etalon pandemic strain A/California/7/2009 (H1N1)pdm09 and modern pandemic strain A/IIV-Orenburg/29-L/2016 (H1N1)pdm09 that were resistant to rimantadine. The latter strain induced severe form of Influenza A infection with a lethal outcome.

Antiviral activity of the synthesized compounds was evaluated in 96-well plates with Madin Darby canine kidney (MDCK) cells monolayer. Adamantane derivatives (5 mg) were dissolved in distillated water (isomers **13** and rimantadine hydrochloride) or 96% ethanol (isomers **9a**-**12**) (1 ml) followed by addition of needle minimal essential medium (Needle MEM) (4 ml) with double set of aminoacids and L-glutamine which is used for cultivation MDCK cells. The final concentrations of substances stock were equal 1 mg/ml, which was diluted with Needle MEM before experiments to a set of concentrations 0,5; 1,0; 2,5; 5,0; 7,5 и 10,0 μg/ml.

Cell immuno-enzymatic analysis (IEA) MDCK cells monolayer in 96-well plates were treated with adamantane derivative at 6 different concentrations in 6 wells of repeat. After then dilutions of virus were added to the corresponding wells in working doses 100-1000 $TCID_{50}$/ml. After 24 h incubation at 37 °C under 5% CO_2 atmosphere the cells were fixed with 80% acetone in phosphate buffer. Cell immuno-enzyme analysis (IEA) was carried out according to the literature [1]. The percentage of virus activity inhibition by the test compounds was evaluated by the formula:

$$100-\frac{OD_{exp}-OD_{cc}}{OD_{vc}-OD_{cc}}\times 100\%,$$

where OD is optical density at 450 nm, OD_{cc} is OD_{450} of cell control, and OD_{vc} is OD_{450} of virus control.

[1] E. I. Burtseva, E. S. Shevchenko, and I. A. Leneva, *Vopr. Virusol.*, **2007**, *52*(2), 24 –29 (Russian).

Determination of the rate of decay of enol ester 10 in the MEM medium by ^{1}H NMR.

Compound **10** (10.8 mg) were dissolved in THF-D_8 (1.2 ml). This solution (0.3 ml) was mixed in a vial with MEM medium (0.3 ml) and additional volume of THF-D_8 (0.15 ml) was added to prevent the separation of **10** from the solution. After then it was transferred to NMR tube for registration of spectra.

The sample was heated on the water bath at 37 °C and the multiple proton spectra with water peak suppression were recorded in 1.5-2.0 h intervals until the conversion of **10** reaches 50%. Integration of the intensity of signal of olefin **10** was performed at 2.92 ppm (triplet) respectively to signals of a component of MEM medium at 2.81 ppm and additionally to residual THF peak at 1.77 ppm.

From the results was built a graph having trend line y = -0.0677x + 1.0035 (R^2 = 0.9989) from which calculated $T_{1/2}$ for **10** = 7.44 hours.

X-ray structures determination.

The X-ray crystal structure analyses were carried out on Bruker SMART APEX2 CCD (10-12; MoK_α radiation, graphite monochromator, φ and ω scan mode) and on Bruker SMART APEX2 DUO CCD (**(*S*)-8**; CuK_α radiation, φ and ω scan mode). The data sets were corrected for absorption with SADABS [1] and crystal structures were solved with the ShelXT [2] structure solution program using Direct Methods and refined with the ShelXL[3] refinement package using Least Squares minimization. Non-hydrogen atoms were refined anisotropically. The absolute structure for **(*S*)-8** were defined by the refinement of the Flack parameters. The hydrogen atoms of the amino groups were localized in the difference-Fourier maps and refined isotropically with displacement parameters [U_{iso}(H) = 1.2U_{eq}(N)]. The other hydrogen atoms were placed in calculated positions and refined within riding model with fixed isotropic displacement parameters [U_{iso}(H) = 1.2U_{eq}(C)].

In order to obtain electron density function we have used the Hansen-Coppens formalism [4] as implemented in the program package XD.[5] Input files were generated with the program InvariomTool. [6] Topological analysis of the invariom electron density distributions obtained from X-ray diffraction data in the harmonic approximation was carried out using the WINXPRO program package.[7] Potential

energy density v(**r**) was evaluated through the Kirzhnits's approximation [8] for kinetic energy density function g(**r**). Accordingly, the g(**r**) function is described as $(3/10)(3\pi^2)^{2/3}[\rho(\mathbf{r})]^{5/3}+(1/72)|\nabla\rho(\mathbf{r})|^2/\rho(\mathbf{r})+1/6\nabla^2\rho(\mathbf{r})$, giving in conjunction with the virial theorem $(2g(\mathbf{r})+v(\mathbf{r})=1/4\nabla^2\rho(\mathbf{r}))$ [9] the expression for v(**r**). Interaction energies were estimated by means of the Espinosa's correlation scheme – a semiquantitative relation between the energy of an interaction and the value of the potential energy density function v(**r**) in its bcp.[10] Having a very simple form as 0.5v(**r**), it was repeatedly shown to give accurate estimates in many cases (those are succinctly summarized in [11]).

Having a very simple form as 0.5v(**r**), it was repeatedly shown to give accurate estimates in many cases (those are succinctly summarized in [11]).

	(*S*)-8	**(*4S,6R*)-9b**	**(*S*)-10**	**(*R*)-11**	**(*4R,6R*)-12**
Empirical formula	$C_{19}H_{31}NO_2$	$C_{19}H_{30}BrNO_2$	$C_{15}H_{21}NO_2$	$C_{15}H_{21}NO_2$	$C_{15}H_{23}NO_2$
Formula weight	305.45	384.35	247.33	247.33	249.34
T, K	120	120	120	120	100
Crystal system	Monoclinic	Orthorhombic	Monoclinic	Orthorhombic	Orthorhombic
Space group	$P2_1$	$P2_12_12_1$	$P2_1$	$P2_12_12_1$	$C222_1$
Z	4	4	4	4	4
a, Å	10.3207(2)	10.6735(7)	10.433(2)	6.9530(14)	8.3872(17)
b, Å	17.1680(4)	11.9007(8)	11.252(2)	11.068(2)	10.676(2)
c, Å	10.4198(2)	14.2306(9)	11.150(2)	16.703(3)	28.705(6)
α, °	90	90	90	90	90
β, °	96.0380(10)	90	101.21(3)	90	90
γ, °	90	90	90	90	90
V, $Å^3$	1836.00(7)	1807.6(2)	1284.0(5)	1285.4(4)	2570.3(9)
d_{calc}, g/cm^3	1.105	1.412	1.279	1.278	1.289
μ, cm^{-1}	0.547	2.284	0.84	0.84	0.84
F(000)	672	808	536	536	1088
$2\theta_{max}$, °	135	58	50	61	50
Reflections collected	28420	37724	16376	16650	7778
Independent reflections	6252	4820	7210	3872	2948

Reflections with I>2σ(I)	6171	4269	6064	3230	2081
Parameters	411	212	334	163	164
R1	0.0323	0.0298	0.0514	0.0418	0.0784
wR2	0.0900	0.0651	0.1141	0.0992	0.1994
GOF	1.058	1.007	1.050	0.995	1.081

[1] G. M. Sheldrick, SADABS, v. 2.03, Bruker/Siemens Area Detector Absorption Correction Program; Bruker AXS Inc., Madison, WI, **2003**.
[2] G. M. Sheldrick, *Acta Cryst*. **2008**, A64, 112–122.
[3] G. M. Sheldrick, *Acta Crystallogr. Sect. C Struct. Chem.*, **2015**, *71*, 3–8.
[4] N. K. Hansen and P. Coppens, *Acta Crystallogr. A*, **1978**, *34*, 909-921.
[5] A. Volkov, P. Macchi, L. J. Farrugia, C. Gatti, P. Mallinson, T. Richter and T. Koritsanszky, XD, 2006.
[6] C. B. Hubschle and B. Dittrich, *J. Appl. Cryst.*, **2011**, *44*, 238-240.
[7] A. Stash and V. Tsirelson, *J. Appl. Crystallogr.*, **2002**, *35*, 371-373.
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[9] R. F. W. Bader, *Atoms In molecules. A Quantum Theory*, Clarendron Press, Oxford, 1990.
[10] E. Espinosa, I. Alkorta, I. Rozas, J. Elguero and E. Molins, *Chem. Phys. Letts.*, **2001**, *336*, 457-461.
[11] K. A. Lyssenko, *Mendeleev Commun.*, **2012**, *22*, 1-7.

The presence of all interactions shown in Fig. 1 in the main text was proved by the topological analysis of electron density function obtained by means of invariom model. The estimated values of N-H…O and C-H…O bonds energy was equal to 4.8-5.9 and 1.5-1.9 kcal/mol, respectively thus leading for the total dimerization energy equal to 14.1 kcal/mol in which the contribution of C-H..O interaction formed by adamantine moiety make the 25% contribution.

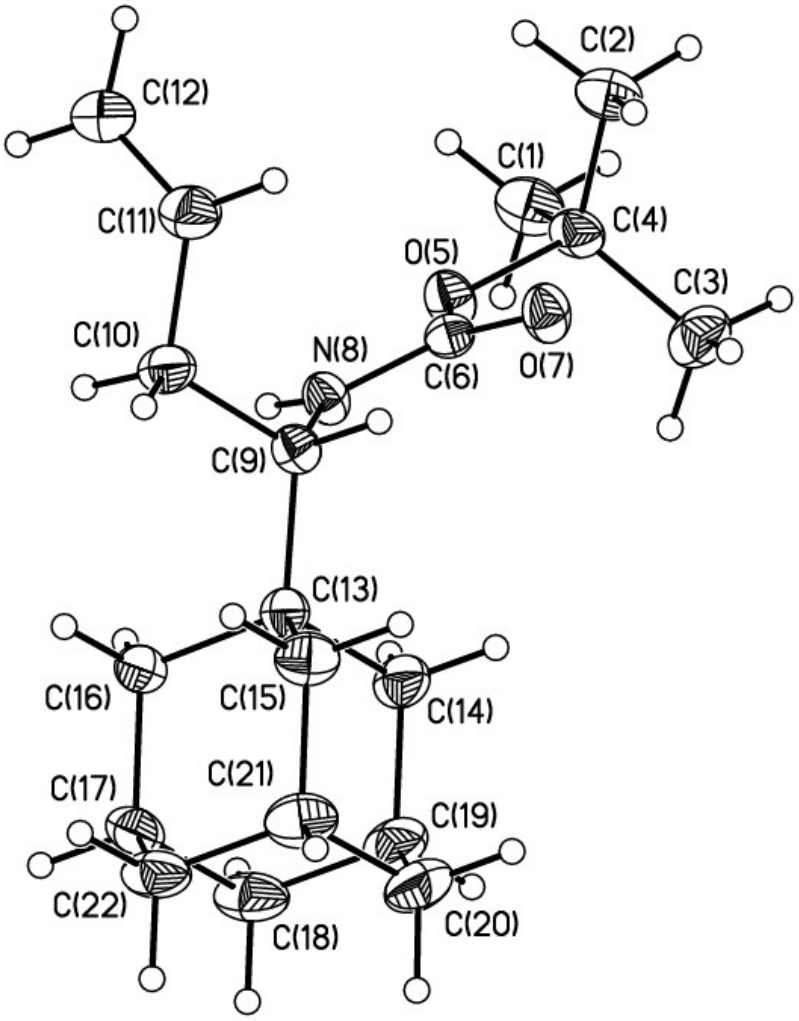


Fig. S1. The general view of (*S*)-**8** in representation of atoms by thermal ellipsoids (p=50%).

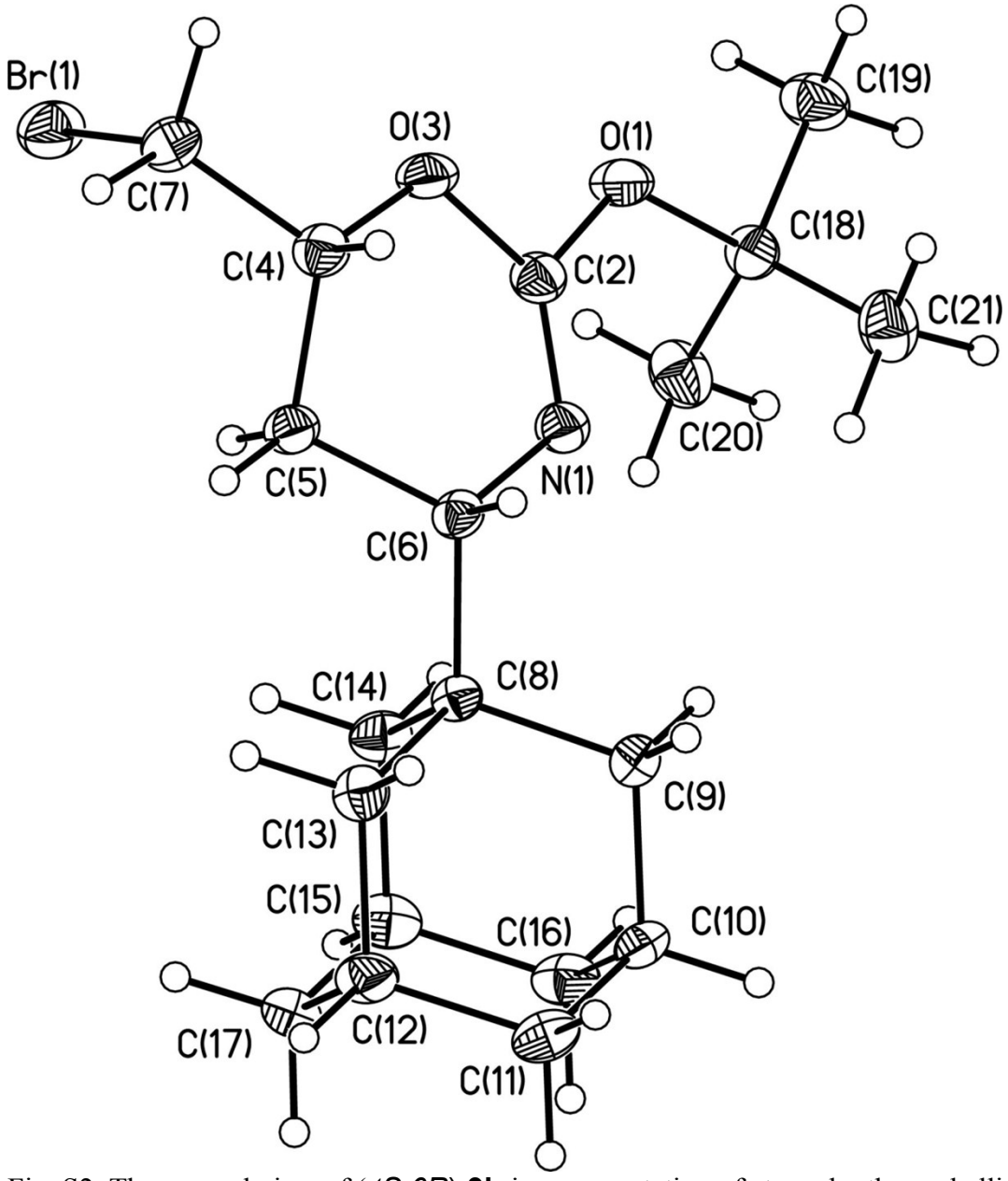


Fig. S2. The general view of (*4S,6R*)-**9b** in representation of atoms by thermal ellipsoids (p=50%).

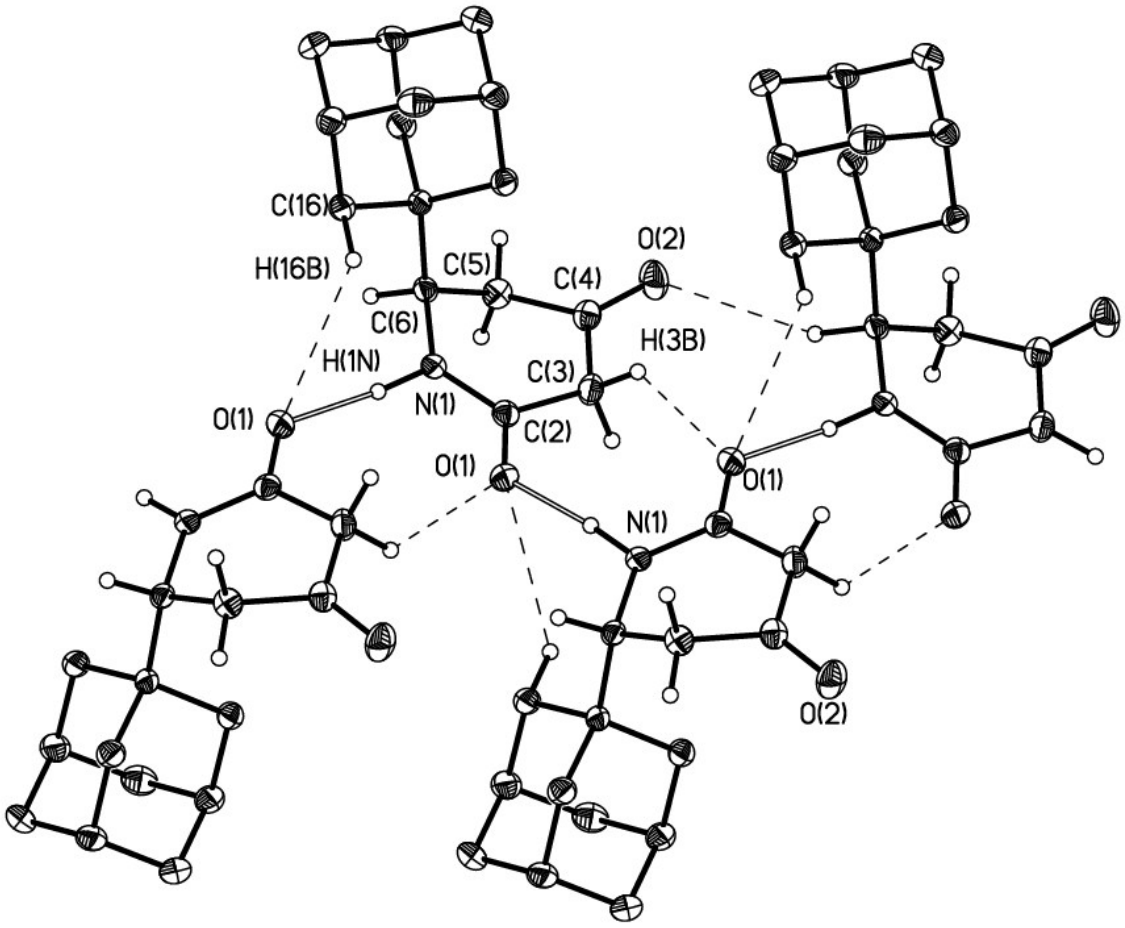


Fig. S3. The general view of N-H…O and C-H…O bonded chains in the crystal of (*R*)-**11** in representation of atoms by thermal ellipsoids (p=50%). The presence of all interactions shown was proved by the topological analysis of electron density obtained by means of invariom model.

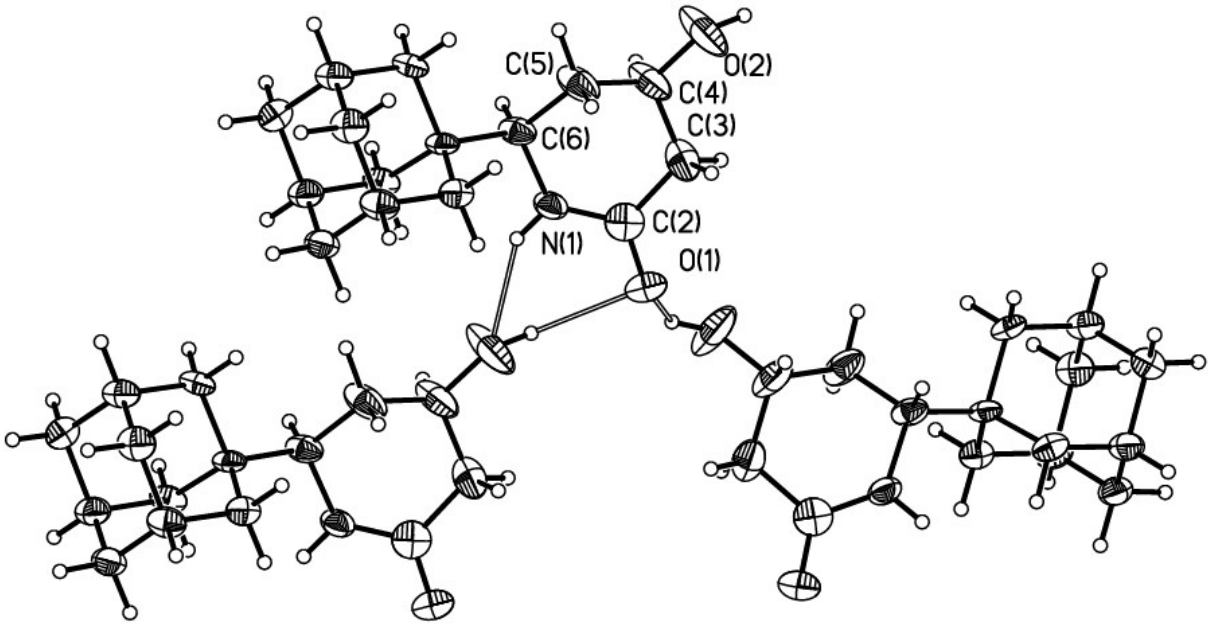
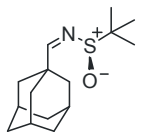
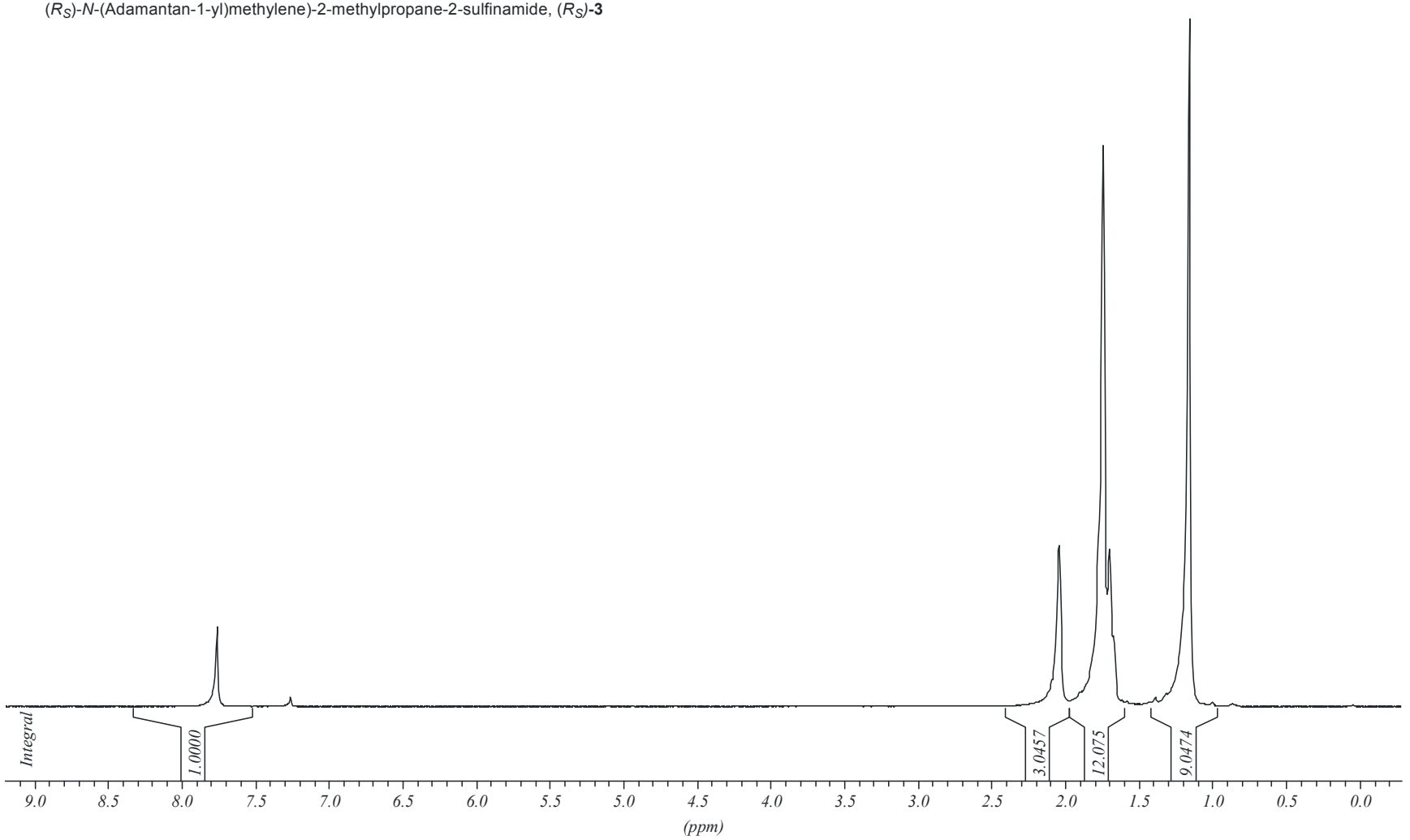
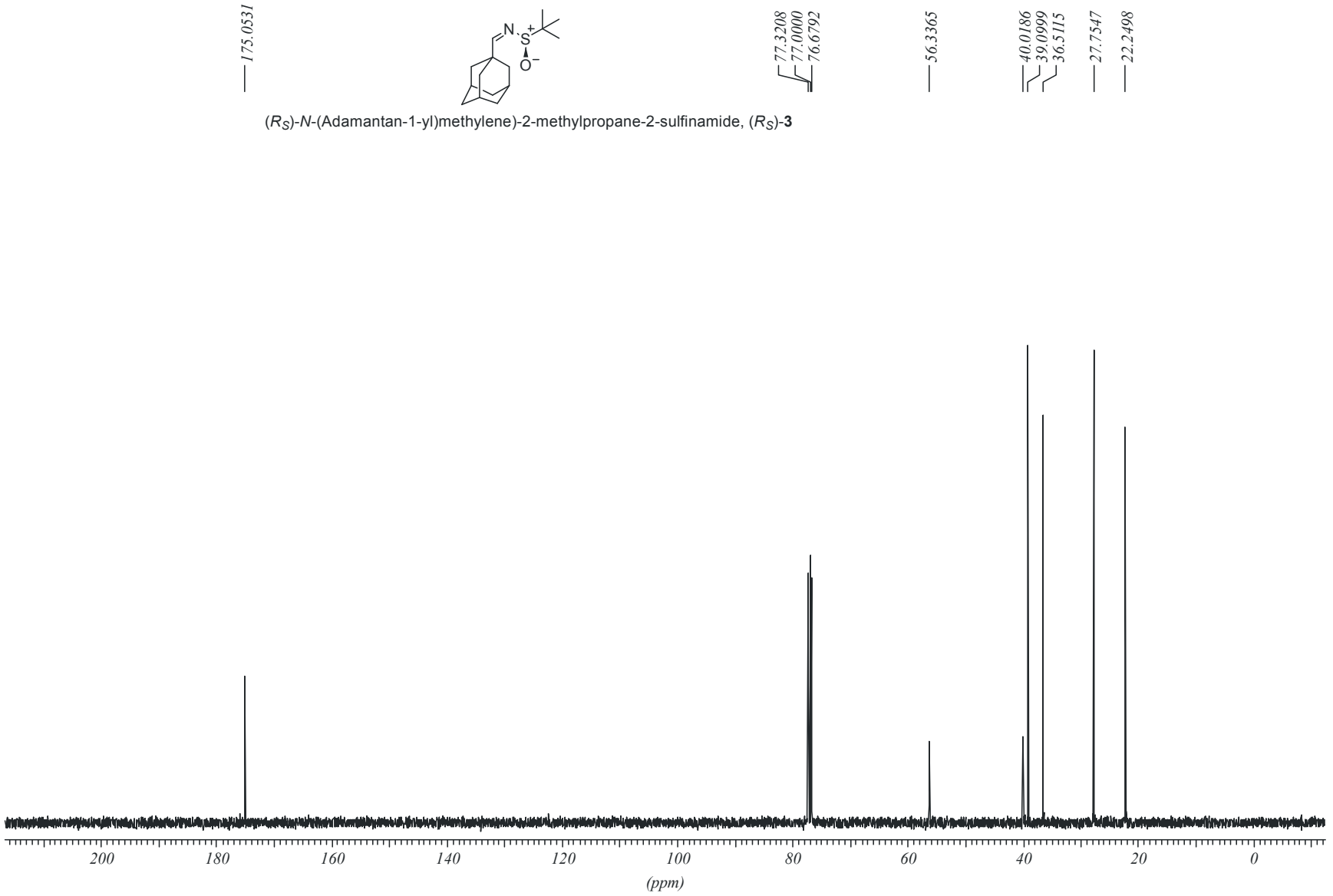


Fig. S4. The general view of N-H…O bonded chains in the crystal of (*4R*,*6R*)-**12** in representation of atoms by thermal ellipsoids (p=50%). The anisotropy of atomic displacement parameters of OH group excludes the possibility to analyze the interatomic interactions by means of invariom model.

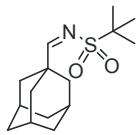


(R_S)-*N*-(Adamantan-1-yl)methylene)-2-methylpropane-2-sulfinamide, (R_S)-**3**

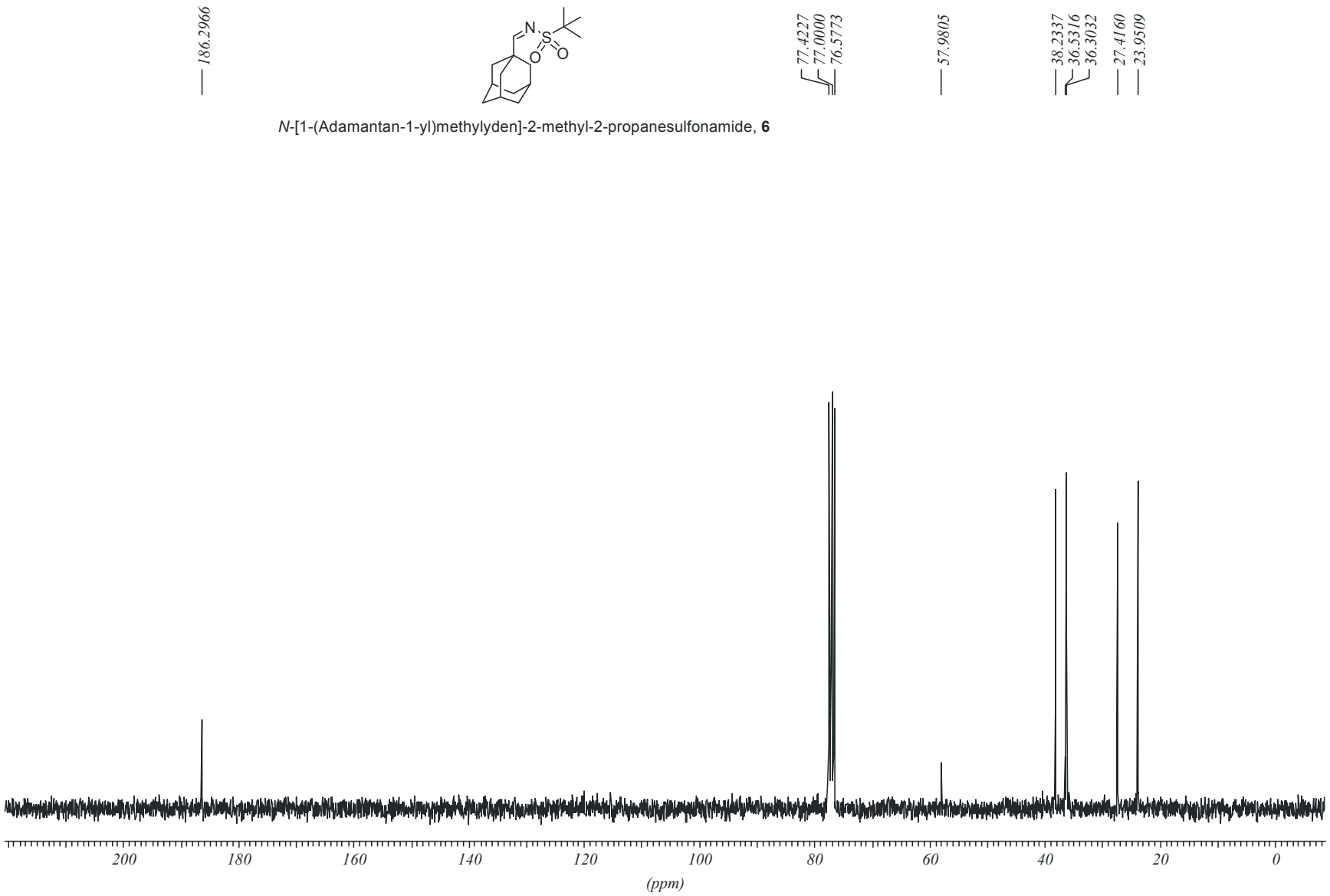




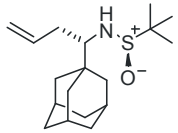
(R_S)-*N*-(Adamantan-1-yl)methylene)-2-methylpropane-2-sulfinamide, (R_S)-**3**



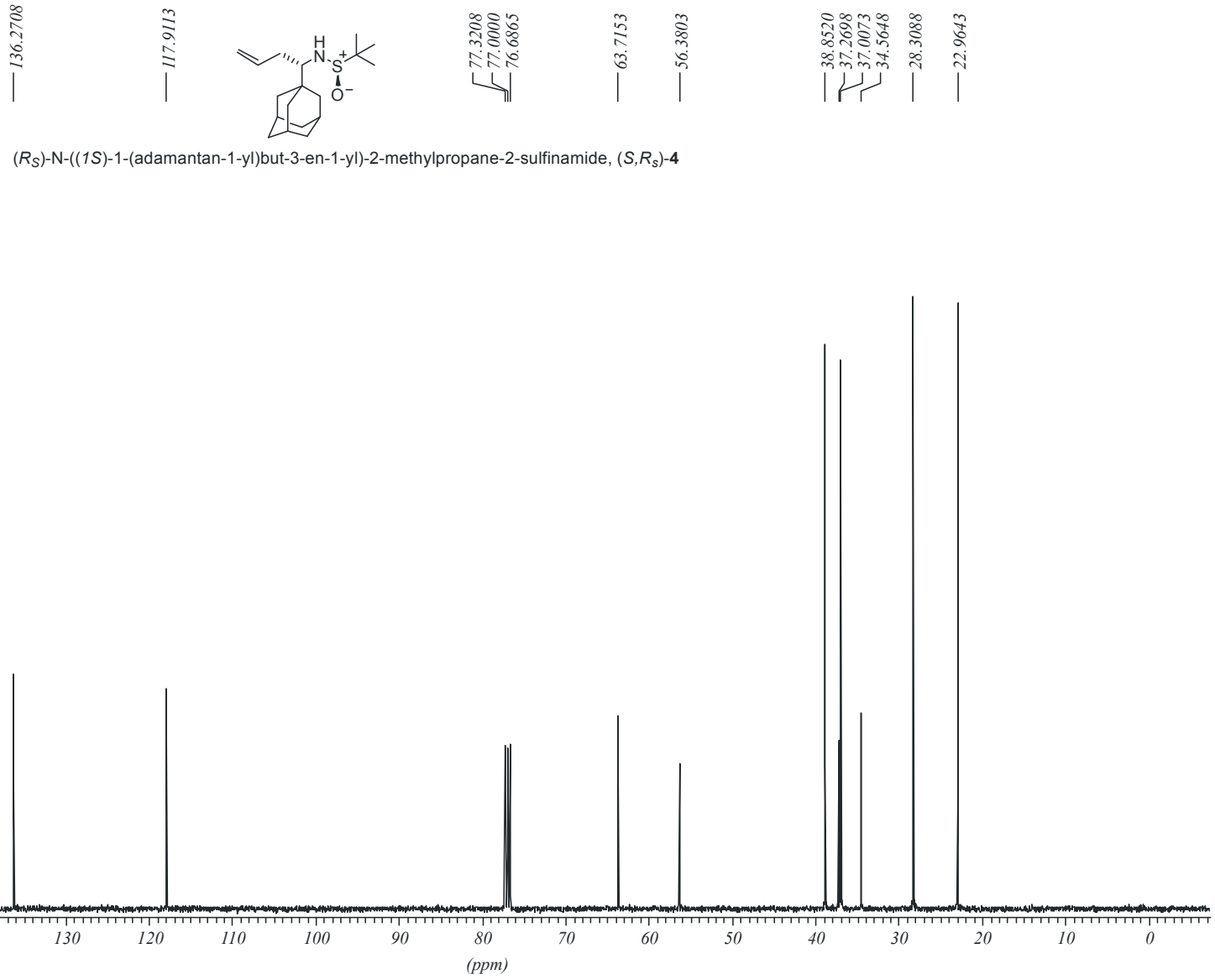
N-[1-(Adamantan-1-yl)methylyden]-2-methyl-2-propanesulfonamide, **6**



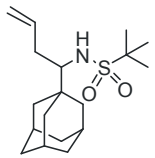
N-[1-(Adamantan-1-yl)methylyden]-2-methyl-2-propanesulfonamide, **6**



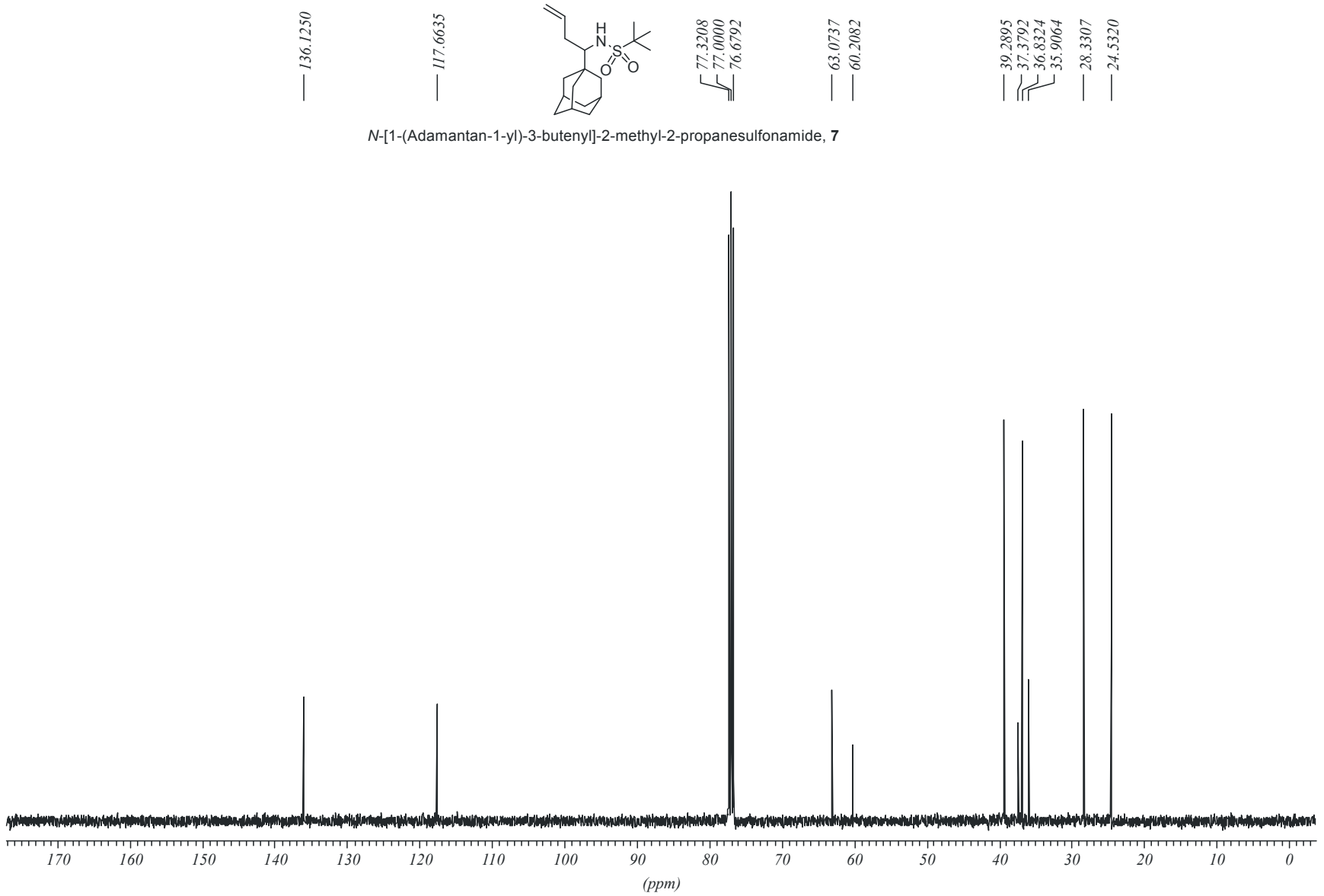
(R_S)-N-((*1S*)-1-(adamantan-1-yl)but-3-en-1-yl)-2-methylpropane-2-sulfinamide, (S,R_s)-**4**



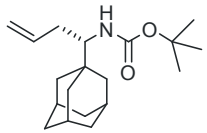
(R_S)-N-((*1S*)-1-(adamantan-1-yl)but-3-en-1-yl)-2-methylpropane-2-sulfinamide, (S,R_s)-**4**



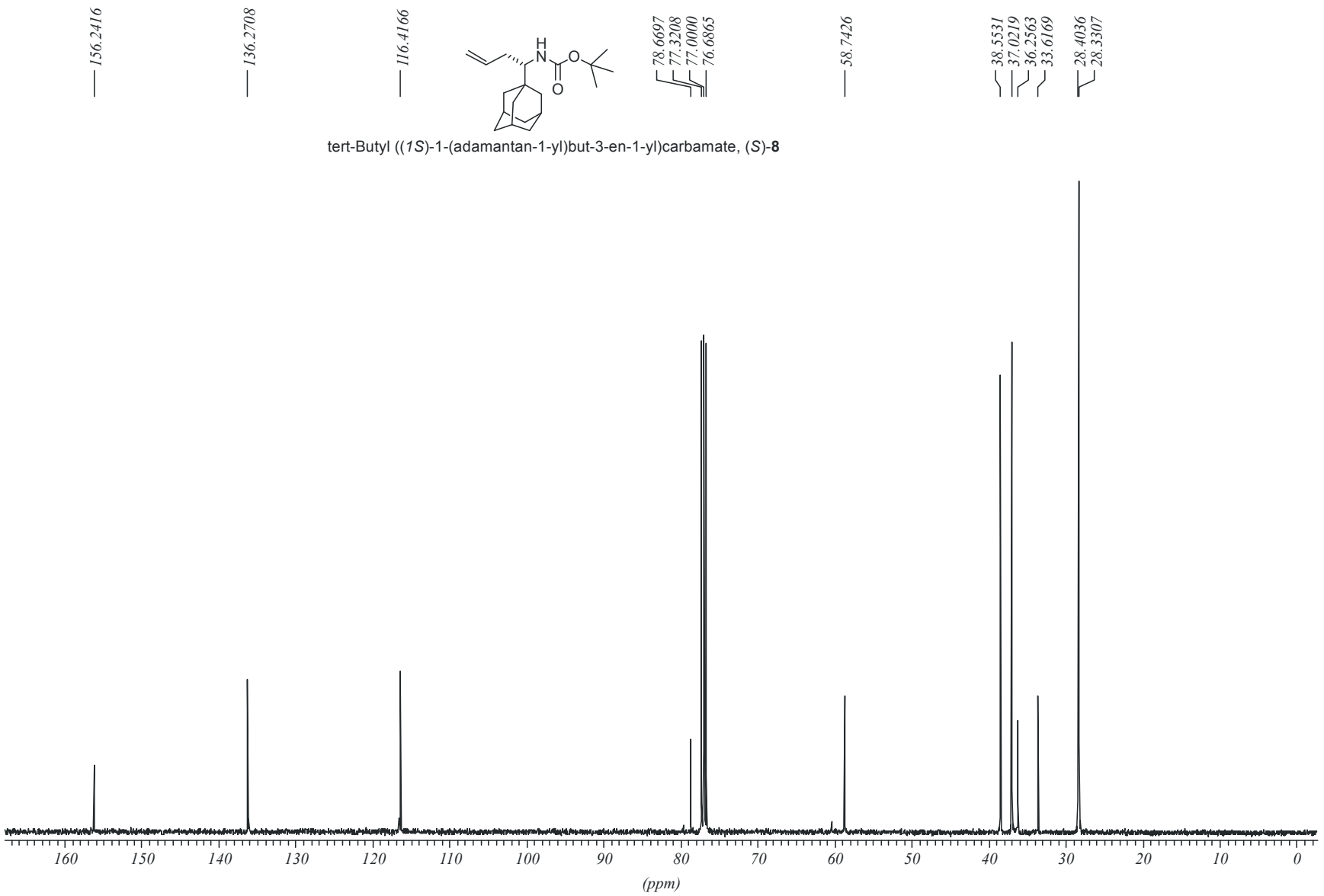
N-[1-(Adamantan-1-yl)-3-butenyl]-2-methyl-2-propanesulfonamide, **7**



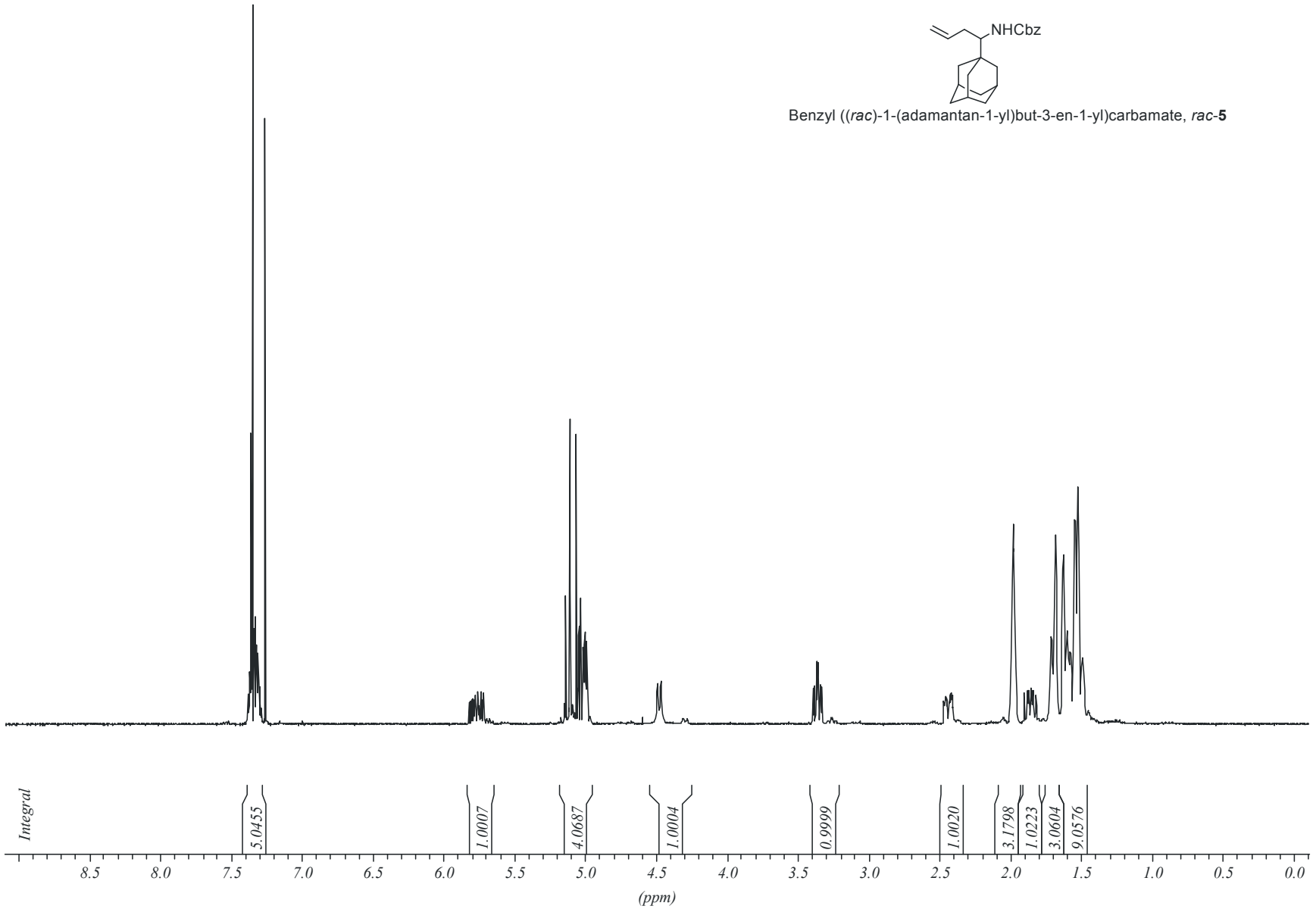
N-[1-(Adamantan-1-yl)-3-butenyl]-2-methyl-2-propanesulfonamide, **7**



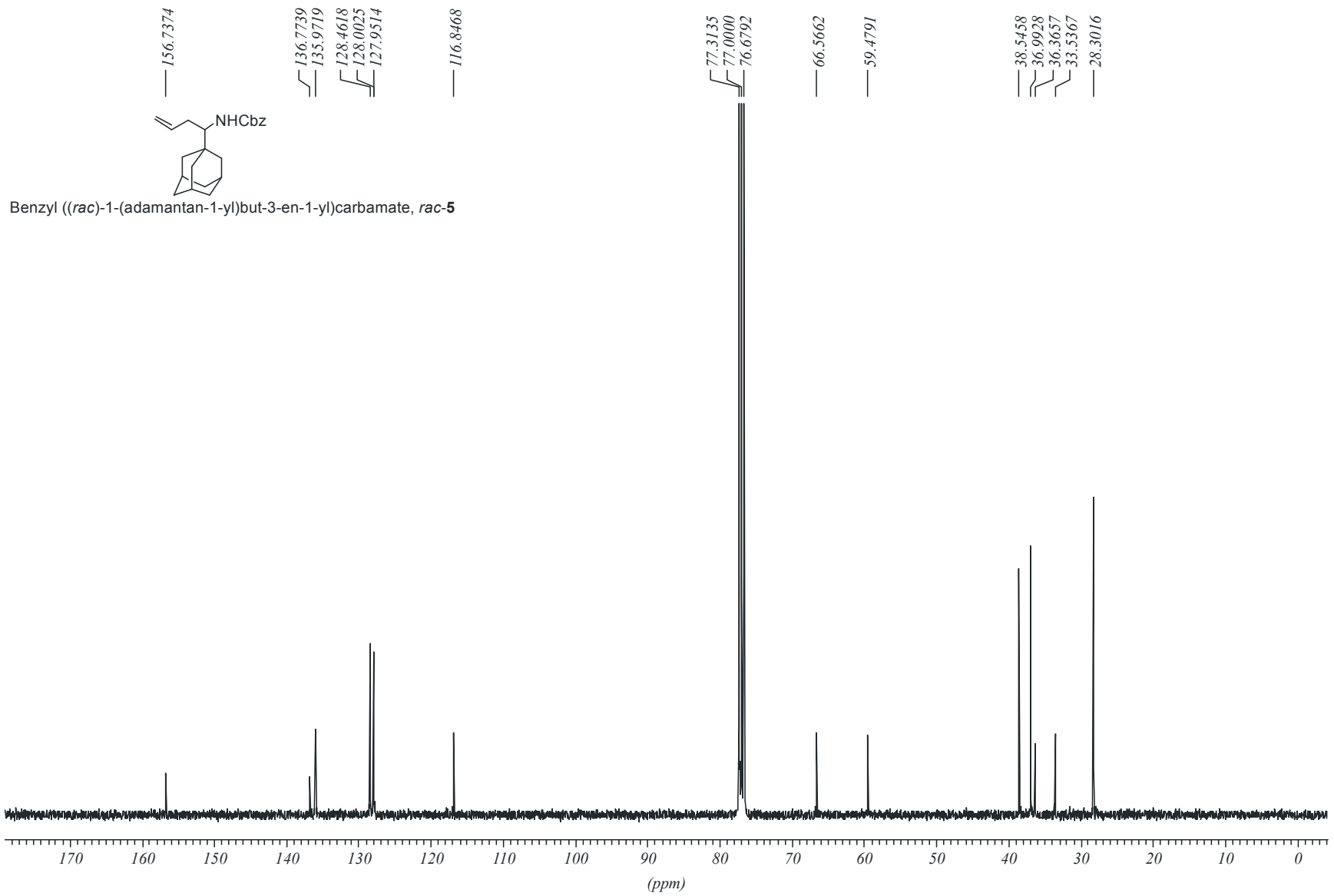
tert-Butyl ((*1S*)-1-(adamantan-1-yl)but-3-en-1-yl)carbamate, (*S*)-**8**



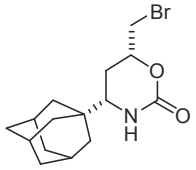
tert-Butyl ((*1S*)-1-(adamantan-1-yl)but-3-en-1-yl)carbamate, (*S*)-**8**



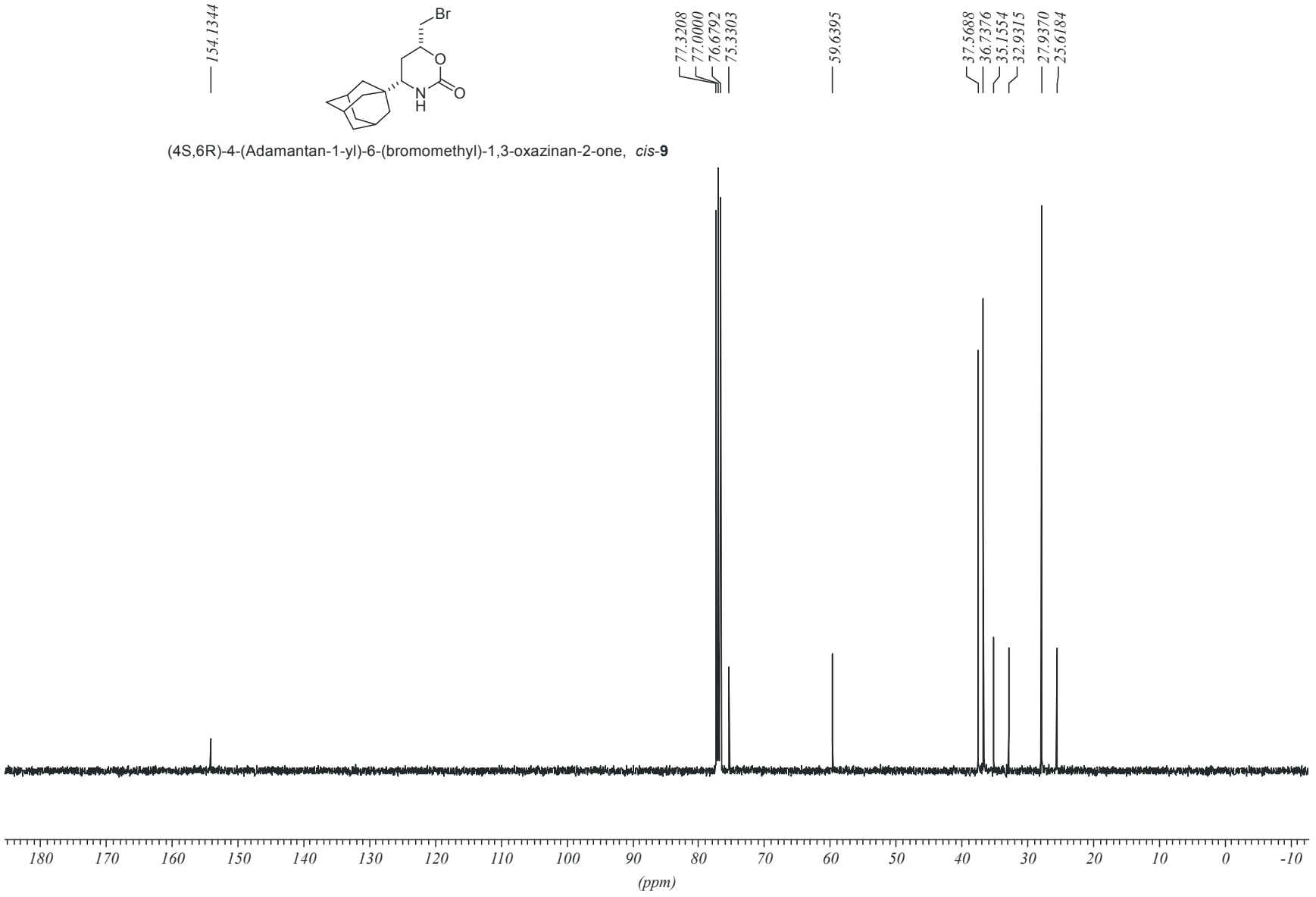
Benzyl ((*rac*)-1-(adamantan-1-yl)but-3-en-1-yl)carbamate, *rac*-**5**



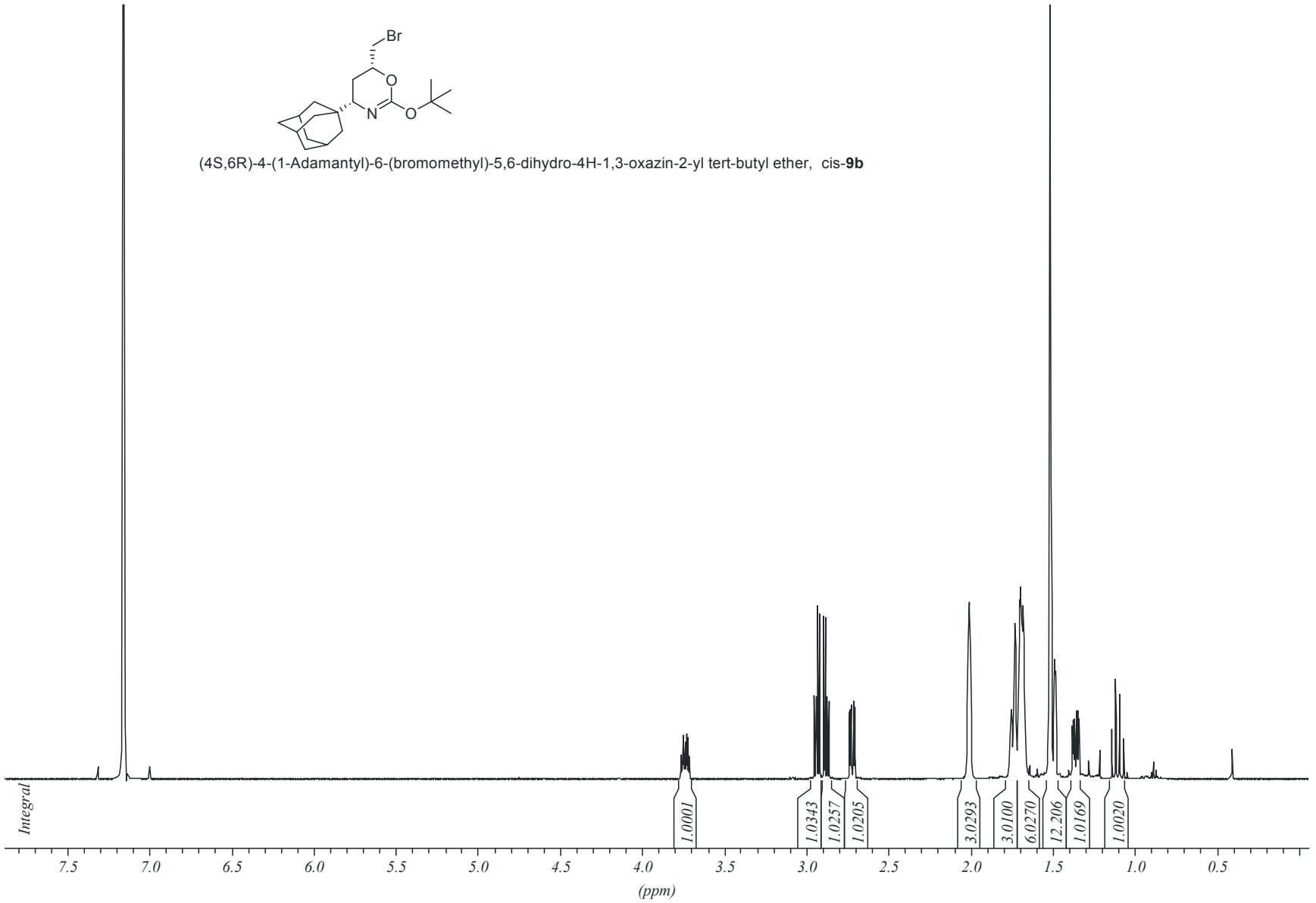
Benzyl ((*rac*)-1-(adamantan-1-yl)but-3-en-1-yl)carbamate, *rac*-**5**

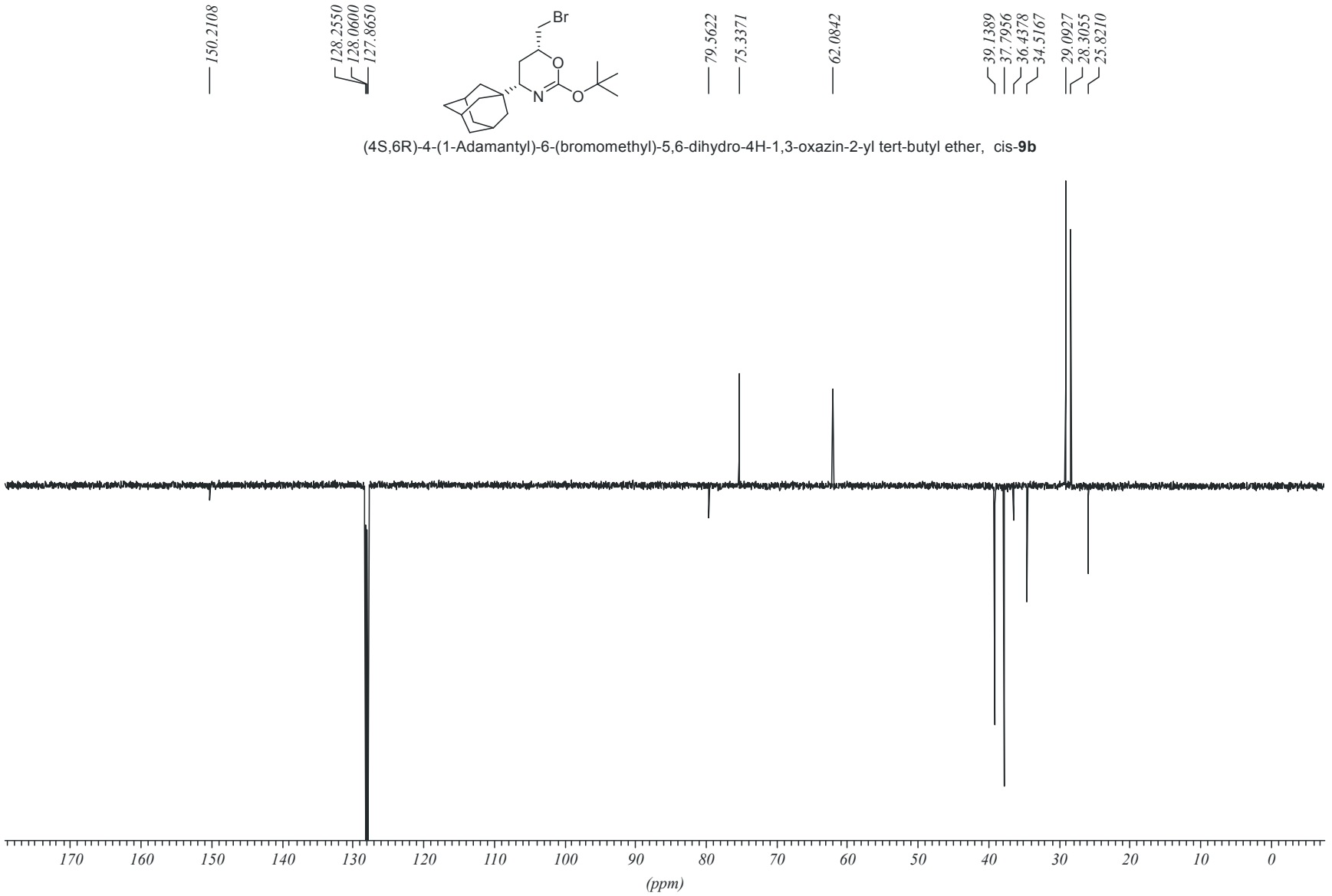


(4S,6R)-4-(Adamantan-1-yl)-6-(bromomethyl)-1,3-oxazinan-2-one, *cis*-**9**

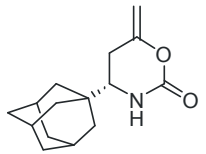


(4S,6R)-4-(Adamantan-1-yl)-6-(bromomethyl)-1,3-oxazinan-2-one, *cis*-**9**

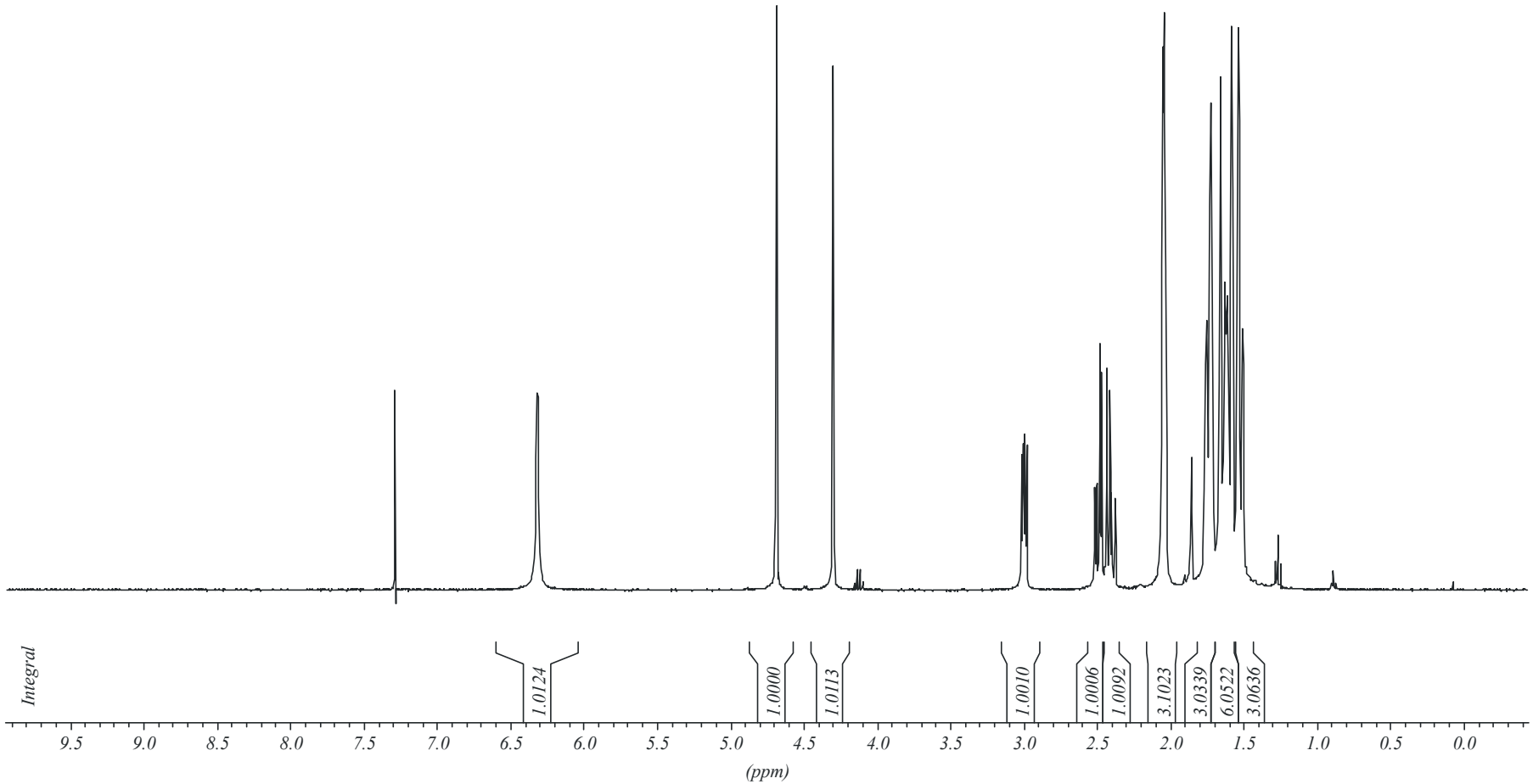

Br
O
N
O
(4S,6R)-4-(1-Adamantyl)-6-(bromomethyl)-5,6-dihydro-4H-1,3-oxazin-2-yl tert-butyl ether, cis-9b
Integral
1.0001
1.0343
1.0257
1.0205
3.0293
3.0100
6.0270
12.206
1.0169
1.0020
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

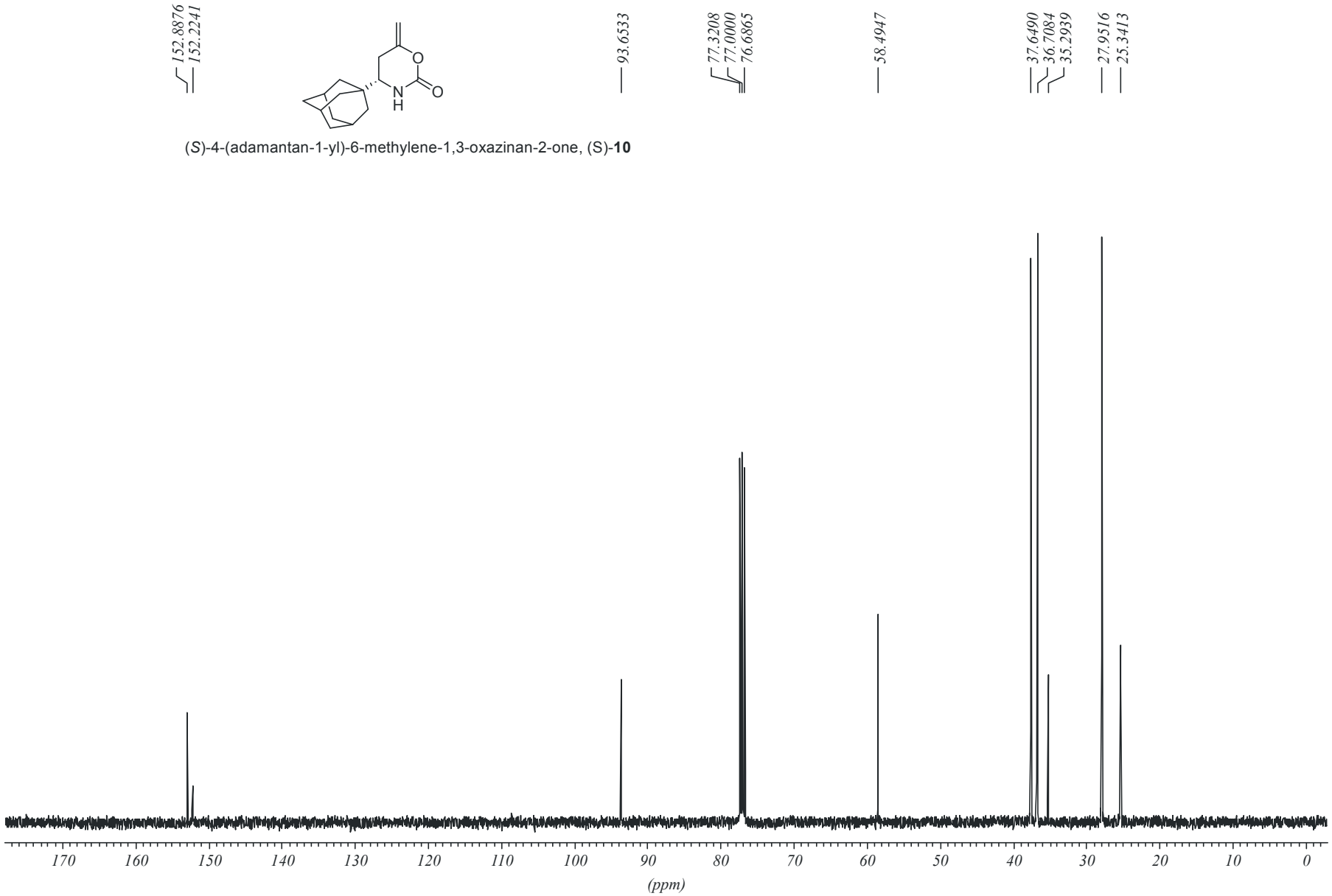


(4S,6R)-4-(1-Adamantyl)-6-(bromomethyl)-5,6-dihydro-4H-1,3-oxazin-2-yl tert-butyl ether, cis-**9b**

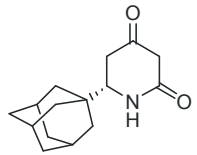


(*S*)-4-(adamantan-1-yl)-6-methylene-1,3-oxazinan-2-one, (S)-**10**

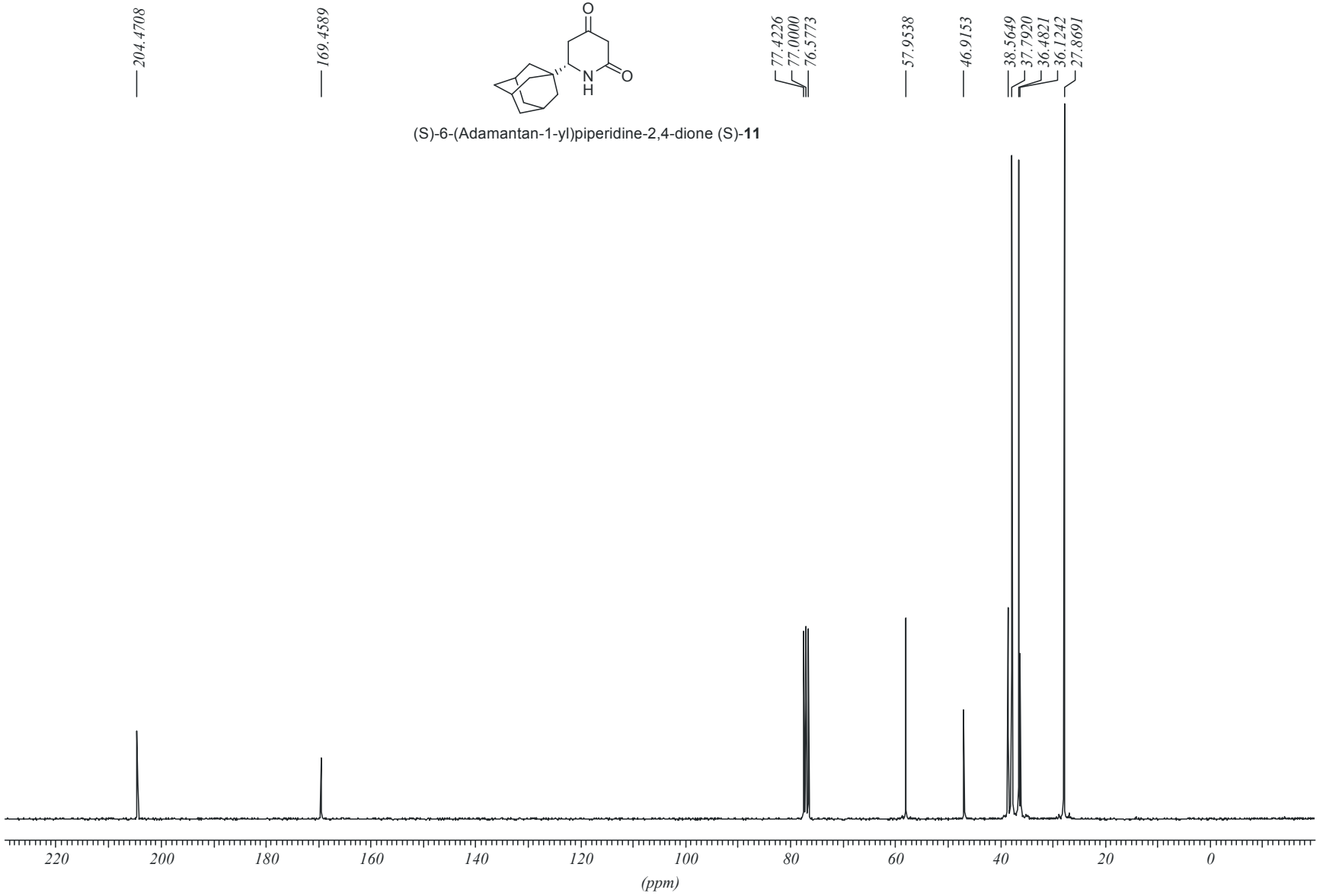




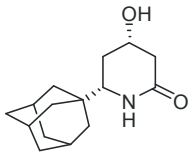
(*S*)-4-(adamantan-1-yl)-6-methylene-1,3-oxazinan-2-one, (S)-**10**



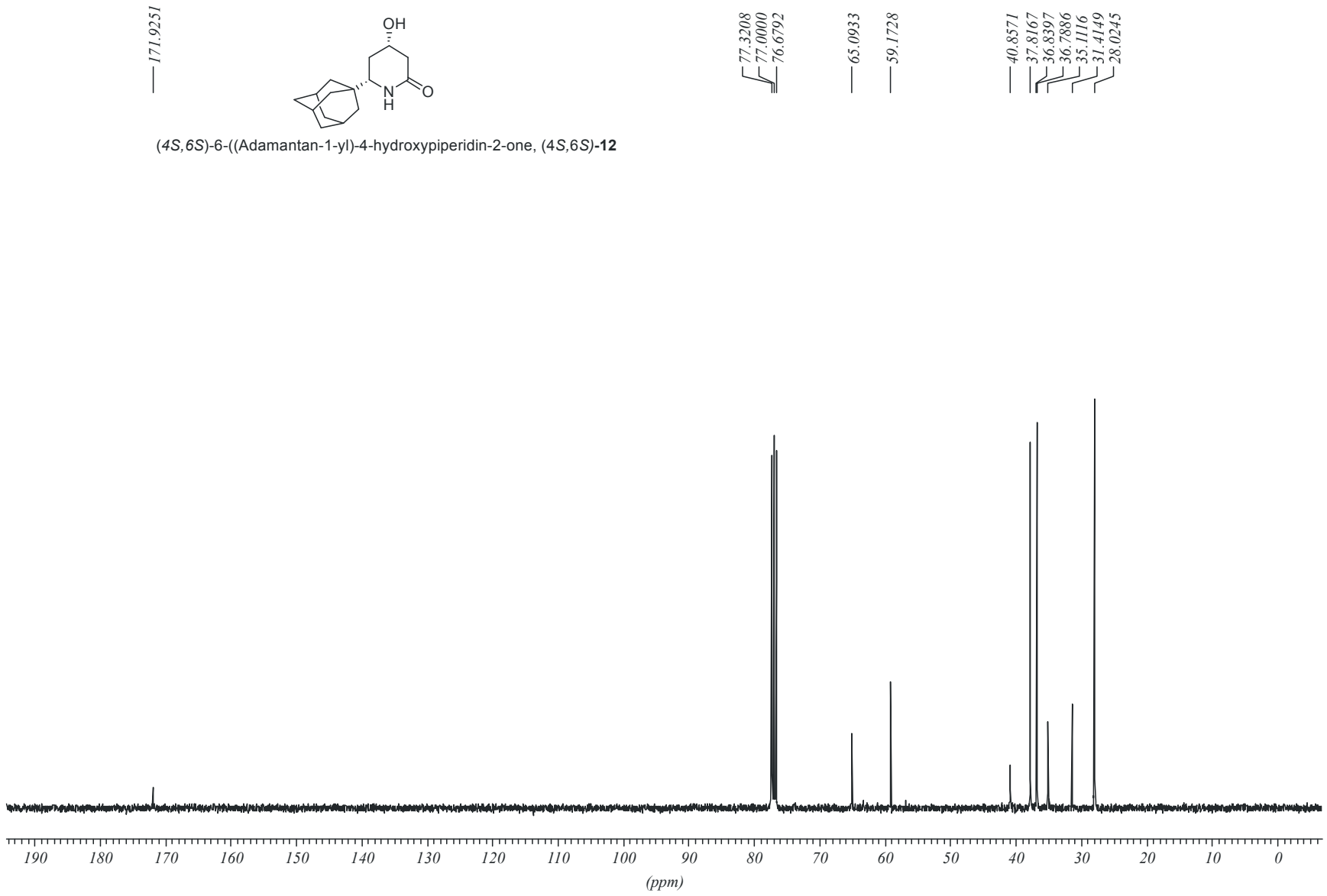
(S)-6-(Adamantan-1-yl)piperidine-2,4-dione (S)-**11**



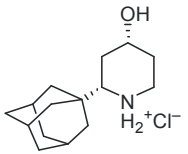
(S)-6-(Adamantan-1-yl)piperidine-2,4-dione (S)-**11**



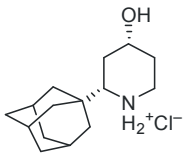
(*4S,6S*)-6-((Adamantan-1-yl)-4-hydroxypiperidin-2-one, (4*S*,6*S*)-**12**



(*4S,6S*)-6-((Adamantan-1-yl)-4-hydroxypiperidin-2-one, (4*S,6S)*-**12**

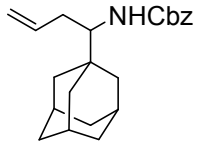


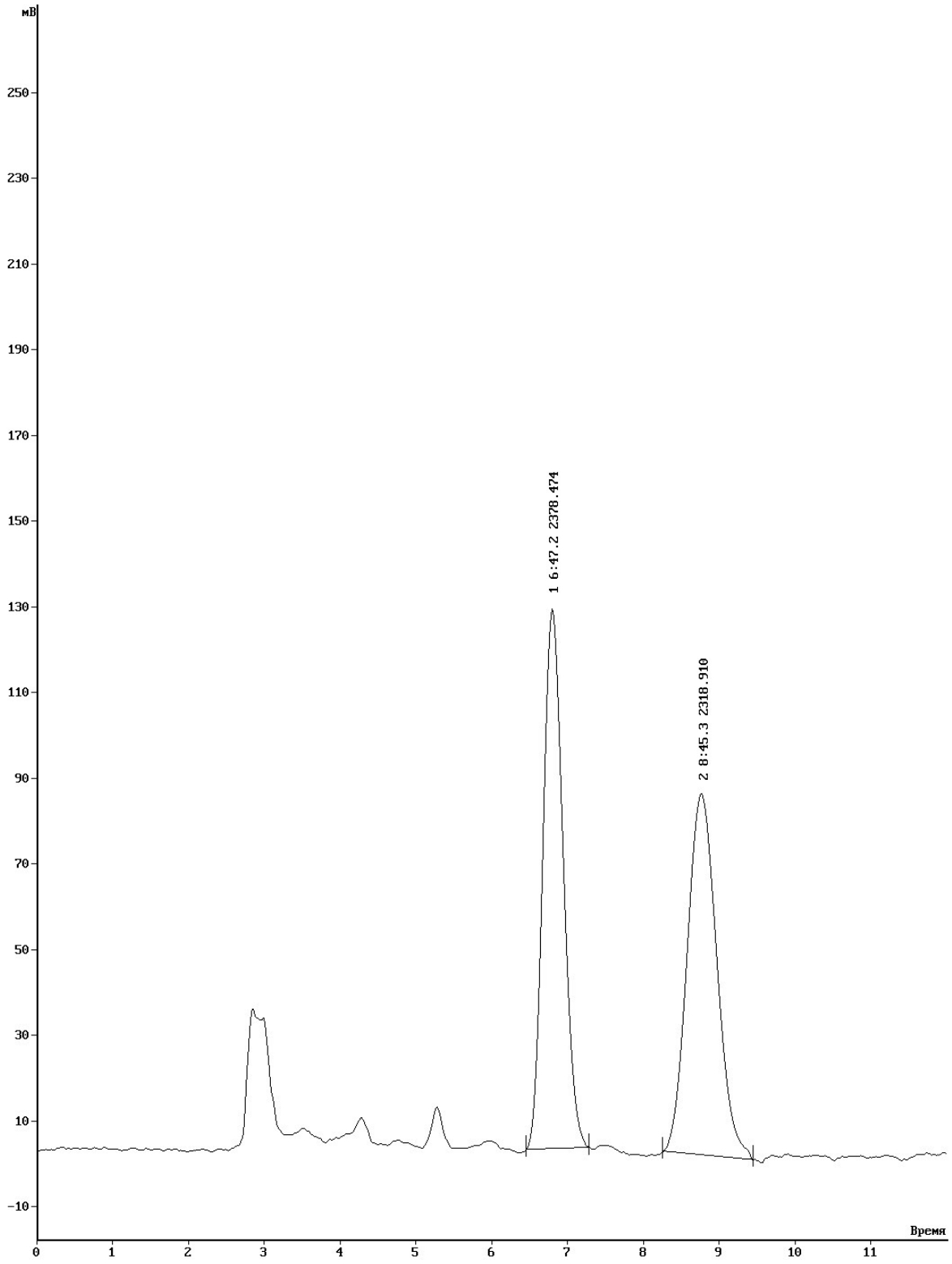
(2S,4R)-2-(adamantan-1-yl)piperidin-4-ol hydrochloride, (2*S*,4*R)*-**13**



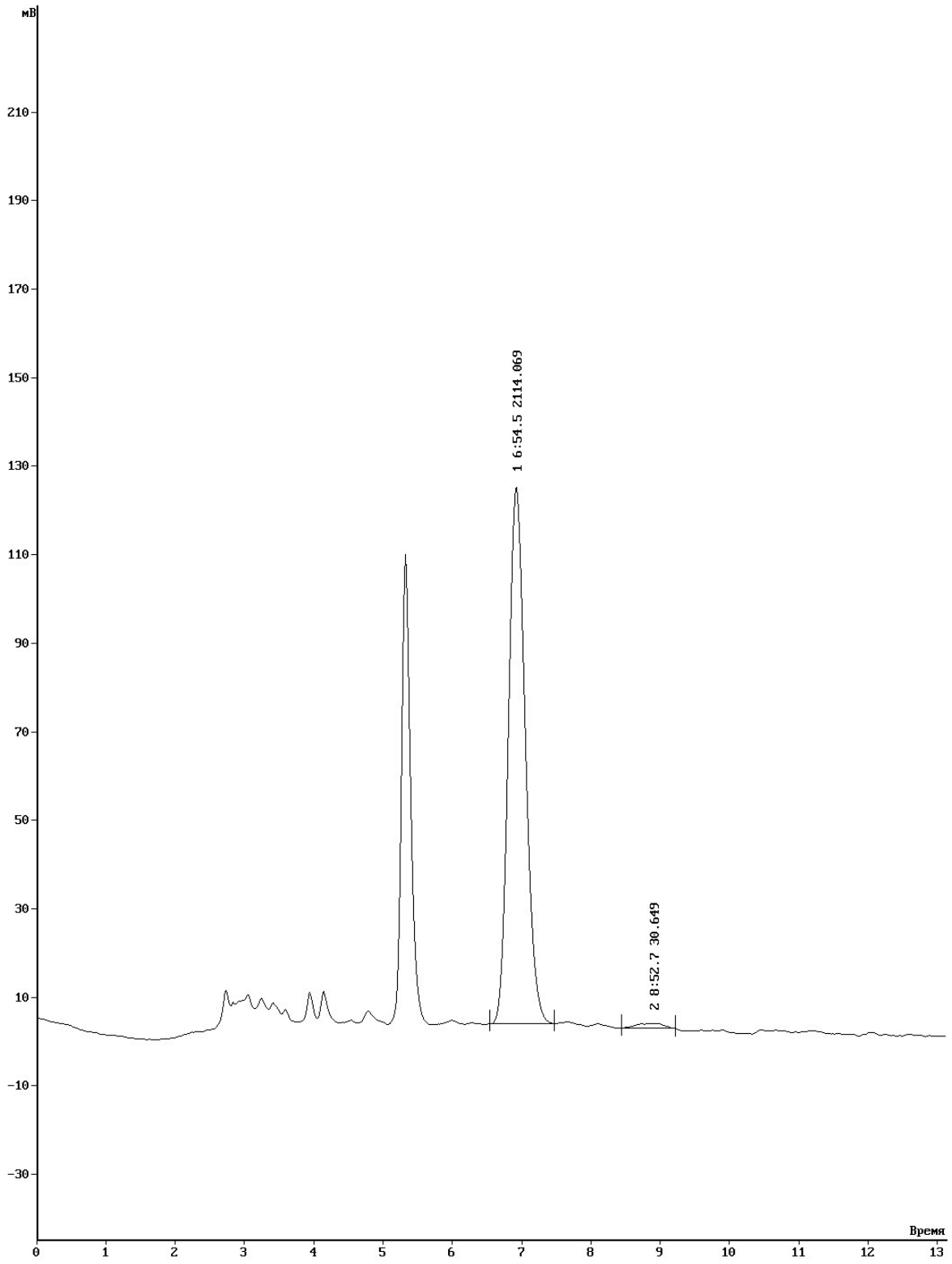
(2S,4R)-2-(adamantan-1-yl)piperidin-4-ol hydrochloride, (2*S,4R)*-**13**

Enantiomeric analysis of Benzyl (1-(adamantan-1-yl)but-3-en-1-yl)carbamate (***rac*-5**).
Column Chiralpak AD, eluent *n*-C_6H_{14}/*iso*-PrOH =85/15, flow rate 1.0 ml/min, UV 219 nm.

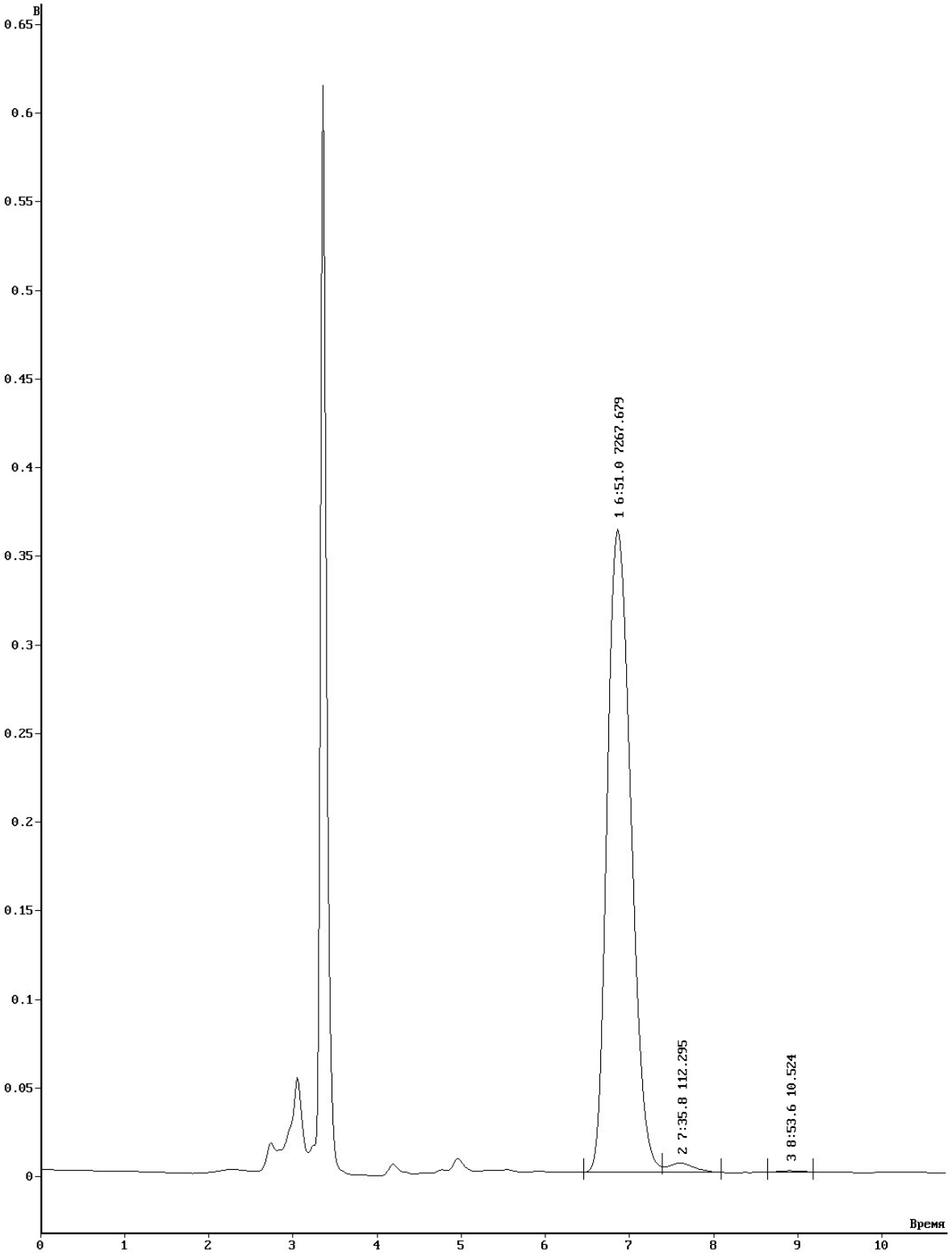




In-mediated allylation, **(*S*)-5**, *ee* 97.1%



Zn-mediated allylation, **(*S*)-5**, *ee* 99.7%



Zn-mediated allylation, **(*R*)-5**, *ee* 98.7%