Electronic Supplementary Information

Lithiated three-membered heterocycles as chiral nucleophiles in the enantioselective synthesis of 1-oxaspiro[2.3]hexanes

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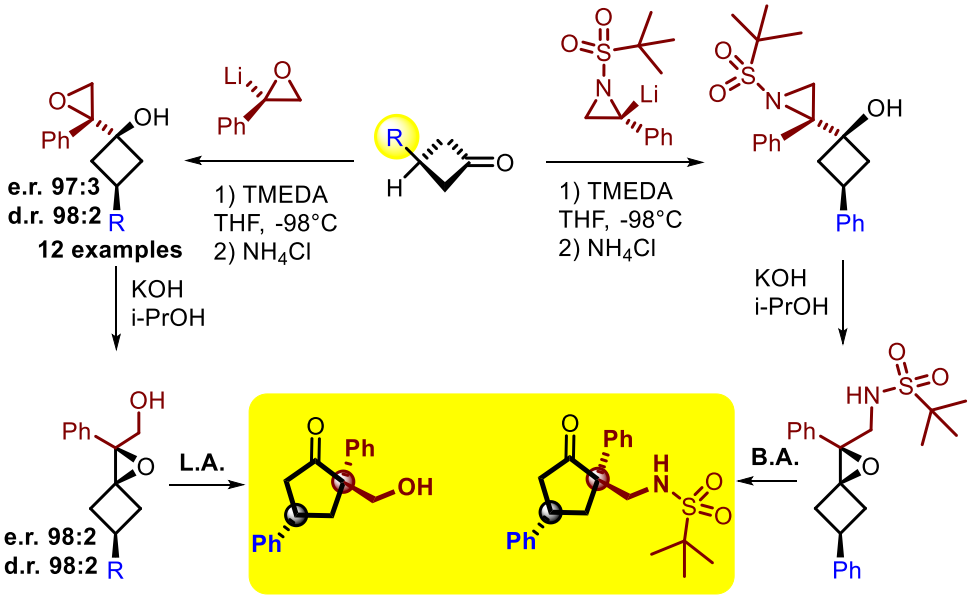

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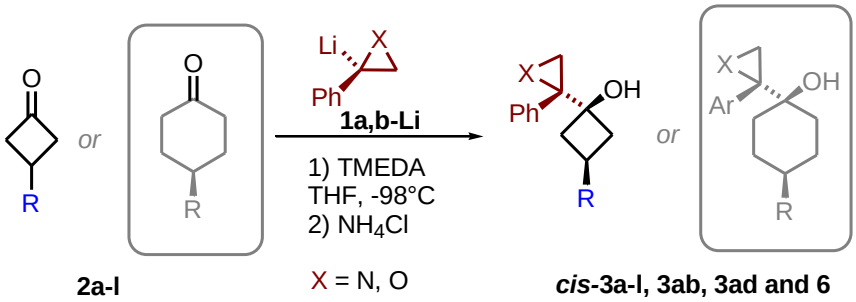
1. Materials and Methods

Unless stated otherwise, respectively the synthesis of compounds **3a-l** and **5a** were performed at the reported temperatures, in flame-dried round bottom flasks equipped with a stirring bar, under argon atmosphere as described below. Commercially available reagents were used as received unless otherwise noted. The cyclic ketones **2j-l** used in this work were purchased from Sigma Aldrich or TCI and used as received. Cyclobutanone derivatives **2a-i** were prepared following the corresponding literature or by modification of previously published procedures.[1] *s*-BuLi (1.4M in cyclohexane) was purchased from Sigma-Aldrich (titrated by using N-pivaloyl-o-toluidine prior use).[2] Bus-aziridine was prepared following previously published procedures.[3] *N*,*N*,*N*',*N*'-tetramethylethylenediamine (TMEDA) was distilled over finely powdered CaH_2. THF was distilled from sodium/ benzophenone ketyl. Ethyl acetate, was distilled using 3Å MS. Petroleum-ether (40-60) was dried on CaH_2. Flash chromatography was performed using Merck 70-200 mesh silica gel. Analytical thin layer chromatography was performed using 0.25 mm Aldrich silica gel 60-F plates. Yields refer to chromatography and spectroscopically pure materials. ^{1}H NMR spectra were recorded on a 500 MHz Varian spectrometers at 25°C using $CDCl_3$ (ref. 7.26 ppm). ^{13}C NMR were recorded at 126 MHz (ref. $CDCl_3$ 77.00 ppm) using $CDCl_3$, as solvent. Chemical shifts (δ) are given in ppm. Coupling constants (*J*) are reported in Hz. Infrared spectra were recorded on a FT-IR Bruker Equinox-55 spectrophotometer and are reported in wavenumbers (cm^{-1}). Low Mass Spectra Analysis were recorded on an Agilent-HP GC-MS (E.I. 70eV). High Resolution Mass Spectra (HRMS) of compounds **2-7** were obtained using an High Resolution Mass Spectrometer in fast atom bombardment (FAB+) ionization mode (ESI) acquired using a Bruker micrOTF-Q II or/and Agilent Q-TOF 6520. Melting points were determined with a Büchi M-560. Specific rotations $[\alpha]_D^T$ were measured using a polarimeter with a cell of path length 1.0 cm, at T °C and are given in 10^{-1} deg•cm^2•g^{-1}. Concentrations (cc) are given in g/100 mL. Chiral HPLC analysis were performed by using the following instruments: Perkin-Helmer Flexar coupled with a P-H Flexar UV/Vis LC detector, Hitachi laChrom with a DAD L-2450 detector, Agilent-Technologies DAD S1200 and chiral HPLC colums: Chiralpak AD-H, OD-H, AS-H and Phenomenex-Lux 1.

Enantiomerically enriched oxiranes **1b** and **1e** were prepared as described in the literature[4]

2. General procedure for the synthesis of chiral 1-(2-phenyloxiranyl)-3-substituted cyclobutanols and cyclohexanols 3a-l, 3ab, 3ad and (±)-1-(2-phenylaziridin-2-yl)-3-phenylcyclobutanol 6



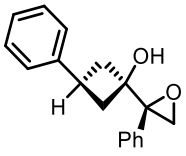
2a-l **cis-3a-l, 3ab, 3ad and 6**

Procedure A

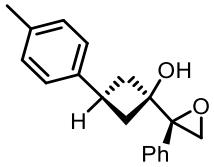
s-BuLi (1.4 M in cyclohexane, 950 µL, 1.3 mmol) was added dropwise to a stirred solution of (*R*)-styreneoxide (122 mg, 1.0 mmol) and TMEDA (460 µL, 3.0 mmol) in dry THF (9 mL) at -98 °C. After 10 minutes at -98 °C a precooled THF (4 mL) solution of cyclic ketones (1.0 mmol) was added. After 3 hours at -98 °C, saturated aqueous NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure. Purification by SiO_2 flash chromatography (hexanes-diethyl ether 10:1-1:1 as eluents) gave the enantiomerically enriched substituted cycloalkanols **3a-l** (and **3ab, 3ad**) as reported below.

Procedure B

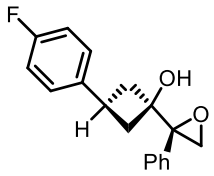
s-BuLi (1.4 M in cyclohexane, 950 µL, 1.3 mmol) was added dropwise to a stirred solution of (±)-1-(*tert*-butylsulfonyl)-2-phenylaziridine (239 mg, 1.0 mmol) and TMEDA (460 µL, 3.0 mmol) in dry THF (9 mL) at -98 °C. After 20 minutes at -98 °C a precooled THF (4 mL) solution of ketone **2a** (1.0 mmol) was added. After 3 hours at -98 °C, saturated aqueous NH_4Cl (10 mL) was added and the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated under reduced pressure. Purification by SiO_2 flash chromatography (hexanes-diethyl ether 1:1 as eluents) gave the racemic substituted cycloalkanols **6** as reported below.



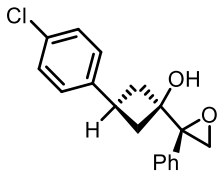
(1*s*,3*S*)-1-[(*R*)-(2-Phenyloxiran-2-yl]-3-phenylcyclobutanol (3a). Following the general procedure A described above, the reaction was performed in THF (9.0 mL) using cyclobutanone **2a** (146 mg, 1.0 mmol), **1a** (122 mg, 1.0 mmol), TMEDA (460µL, 3.0 mmol), *s*-BuLi (1.4M, 950µL, 1.3 mmol), -98° C. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Colourless oil (90%); IR ν_{max} (cm^{-1}): 3445, 3059, 3027, 3982, 2936, 1495, 1447, 1247, 1024, 934, 754, 699; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.58 (d, *J* = 6.8 Hz, 2H), 7.40-7.32 (m, 3H), 7.26 (dd, *J* = 13.8, 6.4 Hz, 2H), 7.17 (dd, *J* = 14.2, 7.2 Hz, 3H), 3.25 (d, *J* = 5.1 Hz, 1H), 2.86 (d, *J* = 5.1 Hz, 1H), 2.85-2.75 (m, 3H), 2.31-2.25 (m, 1H), 2.29 (s, 1H), 2.21-2.12 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 144.9, 136.9, 128.3, 128.1, 128.1, 127.8, 126.5, 125.9, 72.2, 62.4, 51.4, 40.7, 40.6, 29.8. HRMS (ESI-TOF) *m/z*: calculated for $C_{18}H_{18}NaO_2$ $[M+Na]^+$ 289.1199; found 289.1204; $[\alpha]^{20}_D$ = -28.2 (c 1.0, chloroform); Chiral HPLC: Phenomenex-Lux 1 column, 90:10 (Hexane:*i*-PrOH), 1.0 ml/min, (97:3 e.r.), major: 11.96 min, minor: 14.58 min.



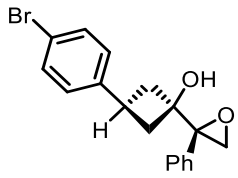
(1*s*,3*S*)-1-[(*R*)-(2-Phenyloxiran-2-yl]-3-(*p*-tolyl)cyclobutanol (3b). Following the general procedure A described above, the reaction was performed in THF (9.0 mL) using cyclobutanone **2b** (160 mg, 1.0 mmol), **1a** (122 mg, 1.0 mmol), TMEDA (460μL, 3.0 mmol), *s*-BuLi (1.4M, 950μL, 1.3 mmol), -98° C. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Colourless oil (90%); FT-IR ν_{max} (cm^{-1}): 3421, 2980, 2935, 1514, 1446, 1245, 1209, 1088, 1022, 931, 912, 807, 759, 699; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.50 (dd, *J* = 8.0, 1.3 Hz, 2H), 7.35-7.21 (m, 3H), 7.00 (s, 4H), 3.17 (d, *J* = 5.1 Hz, 1H), 2.78 (d, *J* = 5.1 Hz, 1H), 2.75-2.64 (m, 2H), 2.22 (s, 3H), 2.20-2.13 (m, 1H), 2.10-2.01 (m, 1H), 1.52 (br. s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 141.9, 136.9, 135.4, 128.9, 128.1, 128.0, 127.8, 126.4, 72.2, 62.4, 51.4, 40.8, 40.7, 29.5, 20.9; HRMS (ESI-TOF) *m/z*: calculated for $C_{18}H_{18}NaO_2$ $[M+Na]^+$ 303.1361; found 303.1359; $[\alpha]^{20}_D$ = -35.3 (c 2.3, chloroform); Chiral HPLC: Chiralpak AD-H column, 90:10 (Hexane:*i*-PrOH), 1.0 ml/min, (94:6 e.r.), major: 24.25 min, minor: 27.31 min.



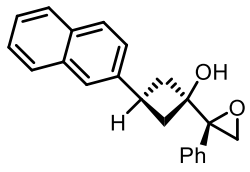
(1*s*,3*S*)-3-(4-fluorophenyl)-1-[(*R*)-2-phenyloxiran-2-yl]cyclobutanol (3c). Following the general procedure A described above, the reaction was performed in THF (9.0 mL) using cyclobutanone **2c** (167 mg, 1.0 mmol), **1a** (122 mg, 1.0 mmol), TMEDA (460μL, 3.0 mmol), *s*-BuLi (1.4M, 950μL, 1.3 mmol), -98° C. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Colorless oil (72%); FT-IR ν_{max} (cm^{-1}): 3435, 2980, 2934, 1509, 1246, 1221, 1157, 1079, 1022, 933, 830, 764, 699; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.53-7.45 (m, 1H), 7.27 (dt, *J* = 6.9, 4.4 Hz, 2H), 7.04 (dd, *J* = 8.5, 5.5 Hz, 1H), 6.86 (t, *J* = 8.7 Hz, 1H), 3.15 (d, *J* = 5.1 Hz, 1H), 2.77 (d, *J* = 5.1 Hz, 1H), 2.75-2.66 (m, 2H), 2.38 (s, 1H), 2.17-2.08 (m, 1H), 2.03 (td, *J* = 7.5, 3.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 161.2 (d, *J* = 244 Hz), 140.6 (d, *J* = 3.15 Hz), 136.7, 128.1, 128.0, 127.9, 127.8, 127.7, 114.9 (d, *J* = 21 Hz), 72.1, 62.3, 51.3, 40.7, 40.8, 29.2; HRMS (ESI-TOF) *m/z*: calculated for $C_{18}H_{17}FNaO_2$ $[M+Na]^+$ 307.1110; found 307.1142; $[\alpha]^{20}_D$ = -13.7 (c 1.5, chloroform); Chiral HPLC: Chiralpak AS-H column, 95:5 (Hexane:*i*-PrOH), 1.0 ml/min, (96:4 e.r.), major: 23.97 min, minor: 21.51 min.



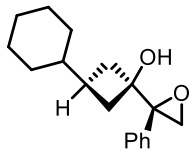
(1*s*,3*S*)-3-(4-chlorophenyl)-1-[(*R*)-2-phenyloxiran-2-yl]cyclobutanol (3d). Following the general procedure A described above, the reaction was performed in THF (9.0 mL) using cyclobutanone **2d** (180 mg, 1.0 mmol), **1a** (122 mg, 1.0 mmol), TMEDA (460μL, 3.0 mmol), *s*-BuLi (1.4M, 950μL, 1.3 mmol), -98° C. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Colourless oil (88%); IR ν_{max} (cm^{-1}): 3434, 2981, 2928, 2839, 1479, 1445, 1249, 1164, 1023, 937, 758, 693; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.63-7.53 (m, 2H), 7.42-7.32 (m, 3H), 7.24 (dd, *J* = 12.7, 4.4 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 1H), 3.24 (d, *J* = 5.1 Hz, 1H), 2.87 (d, *J* = 5.1 Hz, 1H), 2.80 (dq, *J* = 8.1, 4.0 Hz, 2H), 2.28-2.18 (m, 1H), 2.17-2.05 (m, 1H), 1.58 (s, 1H), 0.85 (ddd, *J* = 9.7, 4.6, 2.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 143.4, 136.7, 131.6, 128.3, 128.1, 128.1, 127.9, 127.7, 72.1, 62.4, 51.3, 40.6, 40.5, 29.3; HRMS (ESI-TOF) *m/z*: calculated for $C_{18}H_{17}ClNaO_2$ $[M+Na]^+$ 323.0815; found 323.0821; $[\alpha]^{20}_D$ = -18.1 (c 1.4, chloroform); Chiral HPLC: Chiralpak AS-H column, 90:10 (Hexane:*i*-PrOH), 1.0 ml/min, (97:3 e.r.), major: 20.02 min, minor: 18.89 min.



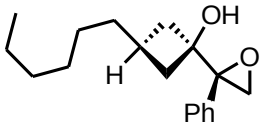
(1*s*,3*S*)-3-(4-bromophenyl)-1-[(*R*)-2-phenyloxiran-2-yl]cyclobutanol (3e). Following the general procedure A described above, the reaction was performed in THF (9.0 mL) using cyclobutanone **2e** (224 mg, 1.0 mmol), **1a** (122 mg, 1.0 mmol), TMEDA (460μL, 3.0 mmol), *s*-BuLi (1.4M, 950μL, 1.3 mmol), -98° C. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Colorless oil (80%); FT-IR(film) ν_{max} (cm^{-1}): 3434, 2984, 2924, 2856, 1494, 1461, 1250, 1189, 1024, 930, 755, 676; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.61-7.51 (m, 1H), 7.43-7.29 (m, 3H), 7.04 (d, *J* = 8.4 Hz, 1H), 3.23 (d, *J* = 5.1 Hz, 1H), 2.84 (t, *J* = 7.5 Hz, 1H), 2.82-2.69 (m, 2H), 2.27-2.16 (m, 1H), 2.16-2.03 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 143.9, 136.7, 131.2, 128.3, 128.1, 128.1, 127.7, 119.6, 72.1, 62.3, 51.3, 40.5, 40.5, 29.4; HRMS (ESI-TOF) *m/z*: calculated for $C_{18}H_{17}BrNaO_2$ $[M+Na]^+$ 367.0310; found 367.0313; $[\alpha]^{20}_D$ = -19.0 (c 2.0 chloroform); Chiral HPLC: Chiralpak AS-H column, 95:5 (Hexane:*i*-PrOH), 1.0 ml/min, (99:1 e.r.), major: 24.93 min, minor: 23.74 min.



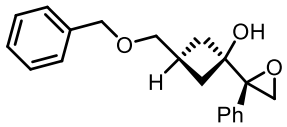
(1*s*,3*S*)-3-(naphthalen-2-yl)-1-[(*R*)-2-phenyloxiran-2-yl)cyclobutanol (3f). Following the general procedure A described above, the reaction was performed in THF (9.0 mL) using cyclobutanone **2f** (196 mg, 1.0 mmol), **1a** (122 mg, 1.0 mmol), TMEDA (460μL, 3.0 mmol), *s*-BuLi (1.4M, 950μL, 1.3 mmol), -98° C. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. White solid (72%); mp = 76-78 °C; FT-IR(film) ν_{max} (cm^{-1}): 3437, 3054, 2981, 2936, 1633, 1601, 1496, 1447, 1246, 1212, 1093, 1023, 933, 854, 820, 748, 702; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (t like, *J* = 9 Hz, 3H), 7.63 (d, *J* = 7 Hz,2H), 7.60 (s, 1H), 7.47-7.33 (m, 6H), 3.31-3.29 (m, 1H), 3.0 (p, *J* = 9 Hz, 1H), 2.93-2.84 (m, 3H), 2.40 (t, *J* = 11 Hz, 1H), 2.33 (s, br OH), 2.29 (t, *J* = 11 Hz, 1H); ^{13}C NMR (126 MHz $CDCl_3$) δ 142.5, 137.0, 133.5, 132.2, 128.3_4, 128.3_0, 128.2, 128.0, 127.7_1, 127.6_7, 126.2, 125.5, 125.4, 124.7, 72.4, 62.7, 51.6, 40.8, 40.7, 30.1; HRMS (ESI-TOF) *m/z*: calculated for $C_{22}H_{20}NaO_2$ $[M+Na]^+$ 339.1356; found 339.1364; $[\alpha]^{20}_D$ = -36.0 (c 1.0, chloroform); Chiral HPLC: Chiralpak AD-H column, 90:10 (Hexane:*i*-PrOH), 1.0 ml/min, (96:4 e.r.), major: 26.49 min, minor: 19.11 min.



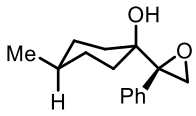
(1*s*,3*S*)-3-cyclohexyl-1-[(*R*)-2-phenyloxiran-2-yl]cyclobutanol (3g). Following the general procedure A described above, the reaction was performed in THF (9.0 mL) using cyclobutanone **2g** (152 mg, 1.0 mmol), **1a** (122 mg, 1.0 mmol), TMEDA (460μL, 3.0 mmol), *s*-BuLi (1.4M, 950μL, 1.3 mmol), -98° C. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Colorless oil (89 %); FT-IR ν_{max} (cm^{-1}): 3427, 2919, 2848, 1767, 1447, 1285, 1205, 1022, 933, 909, 755; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37-7.20 (m, 1H), 3.84 (dd, *J* = 3.9, 2.7 Hz, 1H), 3.12 (dd, *J* = 5.5, 4.1 Hz, 1H), 3.06-2.97 (m, 1H), 2.78 (dd, *J* = 5.5, 2.6 Hz, 1H), 2.75-2.68 (m, 1H), 1.79-1.71 (m, 1H), 1.68 (ddd, *J* = 10.7, 4.5, 2.7 Hz, 1H), 1.27-1.11 (m, 1H), 0.97-0.85 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 137.55, 128.3, 128.0, 125.4, 109.8, 52.2, 51.0, 50.6, 43.5, 30.7, 29.8, 26.1, 25.9; HRMS (ESI-TOF) *m/z*: calculated for $C_{18}H_{24}NaO_2$ $[M+Na]^+$ 295.1674; found 295.1687; $[\alpha]^{20}_D$ = -18.4 (c 1.0, chloroform); Chiral HPLC: Chiralpak AD-H column, 90:10 (Hexane:*i*-PrOH), 1.0 ml/min, (99:1 e.r.), major: 24.09 min, minor: 32.55 min.



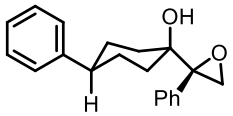
(1*r*,3*S*)-3-hexyl-1-[(*R*)-2-phenyloxiran-2-yl]cyclobutanol (3h). Following the general procedure A described above, the reaction was performed in THF (9.0 mL) using cyclobutanone **2h** (154 mg, 1.0 mmol), **1a** (122 mg, 1.0 mmol), TMEDA (460μL, 3.0 mmol), *s*-BuLi (1.4M, 950μL, 1.3 mmol), -98° C. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Inseparable mixture of diastereomers (80:20), analytical data refer to the major diastereomer. Colourless oil (94%); FT-IR ν_{max} (cm^{-1}): 3436, 2957, 2924, 2853, 1496, 1448, 1248, 1190, 1024, 933, 757, 701; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.52 (d, *J* = 7 Hz, 2H), 7.37-7.30 (m, 3H), 3.17 (d, *J* = 5 Hz, 1H), 2.80 (d, *J* = 5 Hz, 1H), 2.46 (dd, *J* = 13, 8 Hz, 2H), 1.72-1.67 (m, 1H), 1.64-1.59 (m, 1H), 1.58-1.52 (m, 1H), 1.38 (dd, *J* = 15, 7 Hz, 2H), 1.28-1.24 (m, 2H), 1.23-1.18 (m, 4H), 1.17-1.11 (m, 2H), 0.86 (t, *J* = 7 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 137.2, 128.1, 128.1, 128.0, 73.0, 62.7, 51.5, 39.2, 39.0, 37.6, 32.0, 29.3, 27.3, 25.6, 22.7, 14.2; HRMS (ESI-TOF) *m/z*: calculated for $C_{18}H_{26}NaO_2$ $[M+Na]^+$ 297.1825; found 297.1837.



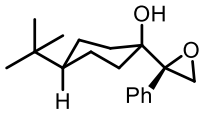
(1*s*,3*S*)-3-(benzyloxymethyl)-1-[(*R*)-2-phenyloxiran-2-yl]cyclobutanol (3i). Following the general procedure A described above, the reaction was performed in THF (9.0 mL) using cyclobutanone **2i** (190 mg, 1.0 mmol), **1a** (122 mg, 1.0 mmol), TMEDA (460μL, 3.0 mmol), *s*-BuLi (1.4M, 950μL, 1.3 mmol), -98° C. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Colourless oil (90%); FT-IR ν_{max} (cm^{-1}): 3421, 2932, 2853, 1495, 1452, 1246, 1207, 1087, 1026, 935, 755, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.52 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.39-7.19 (m, 4H), 4.52 (s, 1H), 3.54-3.38 (m, 2H), 3.06 (d, *J* = 5.2 Hz, 1H), 2.77 (d, *J* = 5.2 Hz, 1H), 2.55-2.45 (m, 1H), 2.17-2.03 (m, 1H), 1.93-1.81 (m, 1H), 1.80-1.68 (m, 1H), 1.34-1.19 (m, 1H), 0.94-0.82 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 137.9, 137.1, 127.8, 127.6, 127.6, 127.6, 74.3, 73.4, 73.1, 61.7, 51.3, 35.7, 34.6, 31.50, 25.9, 22.5, 14.0; HRMS (ESI-TOF) *m/z*: calculated for $C_{20}H_{22}NaO_3$ $[M+Na]^+$ 333.1467; found 333.1490; $[\alpha]^{20}_D$ = -22.3 (c 1.1, chloroform); Chiral HPLC: Phenomenex-Lux 1 column, 90:10 (Hexane:*i*-PrOH), 1.0 ml/min, (99:1 e.r.), major: 22.15 min, minor: 27.39 min.



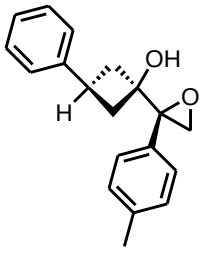
(1*s*,4*S*)-4-methyl-1-[(*R*)-2-phenyloxiran-2-yl]cyclohexanol (3j). Following the general procedure A described above, the reaction was performed in THF (9.0 mL) using cyclohexanone **2j** (112 mg, 1.0 mmol), **1a** (122 mg, 1.0 mmol), TMEDA (460μL, 3.0 mmol), *s*-BuLi (1.4M, 950μL, 1.3 mmol), -98° C. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Inseparable mixture of diastereomers (85:15), analytical data refer to the major diastereomer. Colourless oil (90%); FT-IR(film)ν_{max} (cm^{-1}): 3428, 2958, 2864, 1492, 1480, 1362, 1226, 1149, 1115, 1084, 930, 755, 696; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43-7.41 (m, 2H), 7.34-7.29 (m, 3H), 3.33 (d, *J* = 5.5 Hz, 1H), 2.71 (d, *J* = 5.5 Hz, 1H), 2.20 (br.s, 1H), 1.86-1.79 (m, 3H), 1.62-1.55 (m, 1H), 1.29-1.24 (m, 1H), 1.23-1.21 (m, 2H), 0.76 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 137.9, 137.1, 128.4, 127.7, 71.2, 66.5, 50.6, 50.5, 29.0, 28.5, 27.3, 26.9, 17.3; HRMS (ESI-TOF) *m/z*: calculated for $C_{15}H_{20}NaO_2$ $[M+Na]^+$ 255.1361; found 255.1362; $[\alpha]^{20}_D$ = -37.5 (c 0.6, chloroform); Chiral HPLC: Phenomenex-Lux 1 column, 95:5 (Hexane:*i*-PrOH), 1.0 ml/min, (97:3 e.r.), major: 22.02 min, minor: 27.13 min.



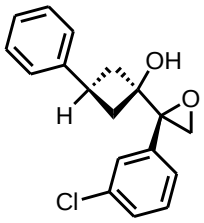
(1*s*,4*S*)-4-phenyl-1-[(*R*)-2-phenyloxiran-2-yl]cyclohexanol (3k). Following the general procedure A described above, the reaction was performed in THF (9.0 mL) using cyclohexanone **2k** (174 mg, 1.0 mmol), **1a** (122 mg, 1.0 mmol), TMEDA (460μL, 3.0 mmol), *s*-BuLi (1.4M, 950μL, 1.3 mmol), -98° C. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Colourless oil (88%); FT-IR (film)ν_{max} (cm^{-1}): 3460, 2927, 2860 1493, 1448, 1265, 1069, 1025, 962, 942, 752, 736, 698; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37 (dd, *J* = 7.5, 1.8 Hz, 1H), 7.26-7.18 (m, 2H), 7.15 (dd, *J* = 14.7, 7.3 Hz, 2H), 7.10-7.03 (m, 2H), 3.22 (d, *J* = 5.2 Hz, 1H), 2.68 (d, *J* = 5.2 Hz, 1H), 2.67-2.61 (m, 1H), 2.43-2.38 (m, 1H), 1.99 (s, 1H), 1.85 (ddd, *J* = 29.9, 11.6, 3.8 Hz, 2H), 1.79-1.65 (m, 2H), 1.63 (d, *J* = 12.3 Hz, 1H), 1.50-1.38 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 145.3, 137.9, 128.5, 128.3, 128.1, 127.7, 127.7, 126.9, 126.6, 126.5, 125.6, 71.8, 65.6, 51.1, 41.2, 39.8, 33.8, 33.1, 32.7, 28.4, 28.1; HRMS (ESI-TOF) *m/z*: calculated for $C_{20}H_{22}NaO_2$ $[M+Na]^+$ 317,1517; found 317,1538; $[\alpha]^{20}_D$ = -21.2 (c 2.2, chloroform); Chiral HPLC: phenomenex-Lux 1 column, 90:10 (Hexane:*i*-PrOH), 1.0 ml/min, (98:2 e.r.), major: 30.23 min, minor: 40.38 min.



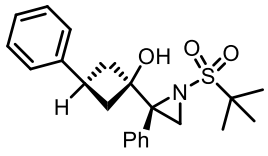
(1*s*,4*S*)-4-*tert*-butyl-1-[(*R*)-2-phenyloxiran-2-yl]cyclohexanol (3l). Following the general procedure A described above, the reaction was performed in THF (9.0 mL) using cyclohexanone **2l** (112 mg, 1.0 mmol), **1a** (122 mg, 1.0 mmol), TMEDA (460μL, 3.0 mmol), *s*-BuLi (1.4M, 950μL, 1.3 mmol), -98° C. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. White solid (93%), mp = 64-65° C; FT-IR(film)ν_{max} (cm^{-1}): 3426, 2954, 2865, 1492, 1444, 1364, 1230, 1188, 1117, 1076, 937, 905, 754, 697; ^{1}H NMR (500 MHz, CDC_3) δ: 7.43 (dd, *J* = 7.9, 1.3 Hz, 2H), 7.24 (tt, *J* = 8.5, 4.4 Hz, 3H), 3.21 (d, *J* = 5.1 Hz, 1H), 2.74 (d, *J* = 5.1 Hz, 1H), 1.98 (br.s, 1H), 1.82 (ddd, *J* = 13.3, 6.2, 3.3 Hz, 1H), 1.75 (ddd, *J* = 13.3, 6.2, 3.3 Hz, 1H), 1.59-1.50 (m, 1H), 1.50-1.44 (m, 1H), 1.31 (ddd, *J* = 17.0, 8.7, 2.1 Hz, 2H), 1.19-1.06 (m, 2H), 0.98 (tt, *J* = 11.6, 3.4 Hz, 1H), 0.74 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 138.5, 128.3, 127.7, 127.7, 64.9, 51.8, 46.5, 35.8, 35.6, 32.2, 27.5, 24.0, 23.9; HRMS (ESI-TOF) *m/z*: calculated for $C_{18}H_{26}NaO_2$ $[M+Na]^+$ 297,1830; found 297.1837; $[\alpha]^{20}_D$ = -33.7 (c 1.7, chloroform); Chiral HPLC: Phenomenex-Lux 1 column, 90:10 (Hexane:*i*-PrOH), 1.0 ml/min, (99:1 e.r.), major: 43.07 min, minor: 39.23 min.



(1*s*,3*S*)-1-[(*R*)-(3-Phenyl-1-(2-p-tolyl-oxiranyl)-cyclobutanol (3ab). Following the general procedure A described above, the reaction was performed in THF (9.0 mL) using cyclobutanone **2a** (146 mg, 1.0 mmol), **1b** (134 mg, 1.0 mmol), TMEDA (460μL, 3.0 mmol), *s*-BuLi (1.4M, 950μL, 1.3 mmol), -98° C. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Colorless oil (66%); ^{1}H NMR (600 MHz, $CDCl_3$) δ: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.39 (d, *J* = 8.1 Hz, 2H), 7.23-7.17 (m, 2H), 7.11 (dd, *J* = 13.0, 5.7 Hz, 5H), 3.17 (d, *J* = 5.1 Hz, 1H), 2.78 (d, *J* = 5.1 Hz, 1H), 2.76-2.72 (m, 2H), 2.29 (s, 3H), 2.28 (d, *J* = 2.6 Hz, 1H), 2.21 (t, *J* = 4.9 Hz, 1H), 2.12-2.07 (m, 1H); ^{13}C NMR (126 MHz $CDCl_3$) δ: 145.0, 137.8, 133.8, 128.8, 128.2, 127.7, 126.5, 125.9, 72.1, 62.4, 51.4, 40.6, 40.5, 29.8, 21.1; HRMS (ESI-TOF) *m/z*: calculated for $C_{19}H_{20}NaO_2$ $[M+Na]^+$ 303,1361; found 303,1369; $[\alpha]^{20}_D$ = -29.6 (c 1.1, chloroform); Chiral HPLC: Phenomenex-Lux 1 column, 90:10 (Hexane:*i*-PrOH), 1.0 ml/min, (94:6 e.r.), major: 20.45 min, minor: 23.02 min.



(1*s*,3*S*)-1-[(*R*)-(3-Chloro-phenyl)-oxiranyl]-3-phenyl-cyclobutanol (3ad). Following the general procedure A described above, the reaction was performed in THF (9.0 mL) using cyclobutanone **2a** (146 mg, 1.0 mmol), **1d** (154 mg, 1.0 mmol), TMEDA (460μL, 3.0 mmol), *s*-BuLi (1.4M, 950μL, 1.3 mmol), -98° C. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Colorless oil (62%); FT-IR(film) ν_{max} (cm^{-1}): 3435, 2985, 2918, 2850, 1599, 1422, 1265, 1151, 1095, 932, 741, 698; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.61-7.60 (m, 1H), 7.52-7.49 (m, 1H), 7.34-7.28 (m, 4H), 7.21-7.17 (m, 3H), 3.24 (d, *J* = 5.1 Hz, 1H), 2.97-2.90 (m, 1H), 2.85 (d, *J* = 5.0 Hz, 1H), 2.80-2.74 (m, 1H), 2.30-2.24 (m, 1H), 2.24 (br. s, 1H), 2.17-2.13 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 144.8, 139.2, 134.2, 129.5, 128.4, 128.4, 127.9, 126.6, 126.2, 126.0, 72.6, 61.7, 51.6, 41.0, 40.8, 29.9; HRMS (ESI-TOF) *m/z*: calculated for $C_{18}H_{16}ClO_2$ $[M-H]^-$ 299.0839; found 299.0835; $[\alpha]^{20}_D$ = -10.9 (c 1.0, chloroform); Chiral HPLC: Phenomenex-Lux 1 column, 90:10 (Hexane:*i*-PrOH), 1.0 ml/min, (91:9 e.r.), major: 14.48 min, minor: 13.80 min.



(1s*,3S*)-1-[(R*)-1-(tert-butylsulfonyl)-2-phenylaziridin-2-yl]-3-phenylcyclobutanol (6). Following the general procedure B described above, the reaction was performed in THF (9.0 mL) using cyclobutanone 2a (146 mg, 1.0 mmol), 1b (239 mg, 1.0 mmol), TMEDA (460μL, 3.0 mmol), s-BuLi (1.4M, 950μL, 1.3 mmol), -98° C. The crude product was purified by flash chromatography using hexanes-diethyl ether 1:1 as eluents. Deliquescent white solid (68%); ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.56-7.54 (m, 1H), 7.37-7.26 (m, 3H), 7.24-7.15 (m, 2H), 7.11 (dd, *J* = 16.3, 7.6 Hz, 2H), 3.14 (br. s, 1H), 2.98-2.90 (m, 1H), 2.89-2.80 (m, 2H), 2.71 (ddd, *J* = 13.4, 8.8, 4.8 Hz, 1H), 2.23 (dd, *J* = 12.4, 9.3 Hz, 1H), 2.16 (dd, *J* = 12.2, 9.2 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (126 MHz $CDCl_3$) δ: 144.6, 128.2, 127.8, 126.5, 126.0, 72.6, 61.4, 40.9, 40.5, 39.4, 30.1, 24.1; HRMS (ESI-TOF) *m/z*: calculated for $C_{22}H_{27}NNaO_3S$ $[M+Na]^+$ 408,1609; found 408,1612.

3. Optimization study of Payne rearrangement

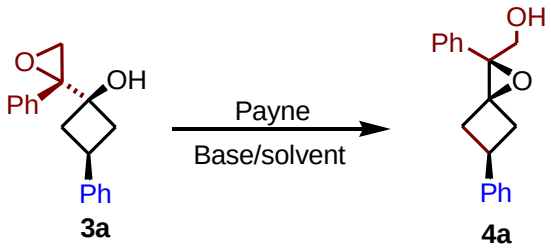
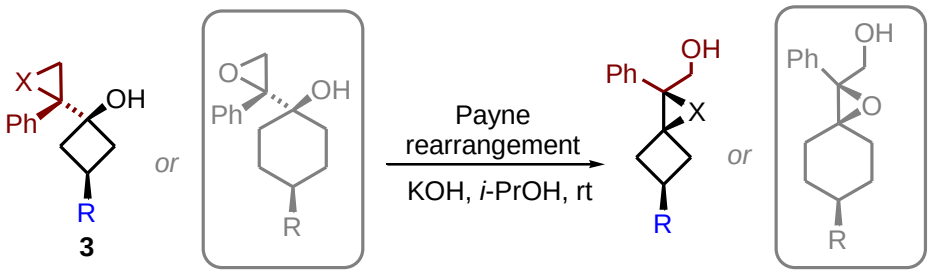


Table 1. Payne rearrangement base screening

Entry	Base	Solvent	Temp./°C	Conversion
1	KOH	*t*-BuOH	r.t.	93%
2	KOH	*i*-PrOH	r.t.	96%
3	KOH	EtOH	r.t.	42%
4	NaOH	*i*-PrOH	r.t.	92%
5	LiOH	*i*-PrOH	r.t.	75%
6	DBU	CH_2Cl_2	0°C	24%
7	DBU	CH_2Cl_2	r.t.	37%
8	DBU	THF	r.t.	41%
9	DABCO	CH_2Cl_2	r.t.	33%
10	KOH (1,5 eq.)	*i*-PrOH	r.t.	98%
11	KOH (2,0 eq.)	*i*-PrOH	r.t.	99%
12	KOH (3,0 eq.)	*i*-PrOH	r.t.	94%

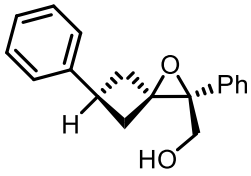
4. General procedure for the synthesis of oxaspiroalkanes 4a-k, 4ab, 4ad and (±)-azaspirooctane 7.



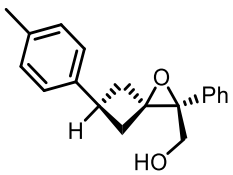
X = N, O

4a-k, 4ab, 4ad and 7

To a stirred solution of 2-phenyloxiranyl-cycloalkanol **3** (or azaspiro-cycloalkanol **6**) (0.37 mmol) in *i*-PrOH (5 mL), KOH (31 mg, 0.55 mmol) was added and the reaction mixture stirred for 4 h a r.t. The reaction mixture was diluted with a saturated solution of NH_4Cl (10 mL) and extracted with Et_2O (3 × 10 mL). The organic phase was dried on Na_2SO_4, filtered and concentrated under reduced pressure. Purification by SiO_2 flash chromatography (hexanes-diethyl ether 10:1-1:1 as eluents) gave the substituted oxaspiro-adducts **4a-k** and **7** as reported below.

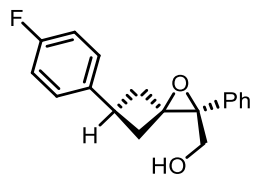


[(2*S*,3*s*,5*R*)-2,5-diphenyl-1-oxaspiro[2.3]hexan-2-yl]methanol (4a). Following the general procedure described above, the reaction was performed in *i*-PrOH (5.0 mL) KOH (31 mg, 0.55 mmol), **3a** (100 mg, 0.37 mmol), rt. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Colourless oil (98%); FT-IR (film)ν_{max} (cm^{-1}): 3456, 3060, 3027, 2930, 1736, 1603, 1496, 1448, 1030, 1010, 905, 753, 698; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.43-7.36 (m, 4H), 7.36-7.30 (m, 3H), 7.27 (d, *J* = 7 Hz, 2H), 7.22 (t, *J* = 8 Hz, 1H), 4.30-4.24 (m, 1H), 4.01 (dd, *J* = 12, 6 Hz, 1H), 3.28 (p, *J* = 9 Hz, 1H), 3.03-2.97 (m, 1H), 2.73 (dd, *J* = 13, 9 Hz, 1H), 2.50 (dd, *J* = 13, 9 Hz, 1H), 2.32-2.25 (m, 1H); ^{13}C NMR (151 MHz $CDCl_3$) δ: 144.6, 136.5, $128,6_0$, $128,5_8$, 128.0, 126.6, 126.4_5, 126.4_1, 66.9, 66.7, 64.0, 37.5, 37.1, 31.5; HRMS (ESI-TOF) *m/z*: calculated for $C_{18}H_{18}NaO_2$ $[M+Na]^+$ 289.1199; found 289.1208; $[\alpha]^{20}_D$ = -45.0 (c 1.0, chloroform); Chiral HPLC: Phenomenex-Lux 1 column, 90:10 (Hexane:*i*-PrOH), 1.0 ml/min, (99:1 e.r.), major: 11.91 min, minor: 16.56.

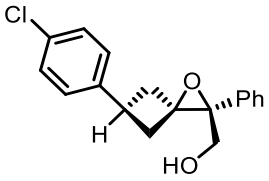


[(2*S*,3*s*,5*R*)-2-Phenyl-5-(*p*-tolyl)-1-oxaspiro[2.3]hexan-2-yl]methanol (4b). Following the general procedure described above, the reaction was performed in *i*-PrOH (5.0 mL) KOH (29 mg, 0.52 mmol), **3b** (100 mg, 0.35 mmol), rt. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Colourless oil (92%); FT-IR (film)ν_{max} (cm^{-1}): 3454, 3061, 3024, 2927, 1734, 1609, 1488, 1446, 1029, 1012, 905, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.477.27 (m, 5H), 7.21-7.05 (m, 4H), 4.25 (dd, *J* = 12.1, 4.6 Hz, 1H), 4.01 (dd, *J* = 12.2, 7.0 Hz, 1H), 3.23 (p, *J* = 8.7 Hz, 1H), 3.05-2.83 (m, 1H), 2.69 (dd, *J* = 12.9, 9.1 Hz, 1H), 2.46 (dd, *J* = 12.4, 9.6 Hz, 1H), 2.32 (s, 3H), 2.25 (ddd, *J* = 15.9, 8.6, 4.2 Hz, 1H), 1.93 (br.s, 3H), 1.79-1.58 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 141.4, 136.3, 135.8, 129.02, 128.4, 127.8, 126.3, 126.2, 66.7,

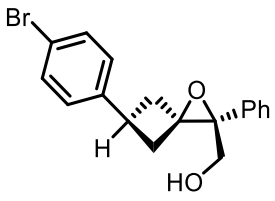
66.5, 63.9, 37.4, 37.0, 31.0, 20.9; HRMS (ESI-TOF) *m/z*: calculated for $C_{18}H_{17}BrNaO_2$ $[M+Na]^+$ 303,1361; found 303,1355; $[\alpha]^{20}_D$ = -20.0 (cc 1.0, chloroform); Chiral HPLC: Phenomenex-Lux 1 column, 90:10 (Hexane:*i*-PrOH), 1.0 ml/min, (97:3 e.r.), major: 37.25 min, minor: 32.88.



(2*S*,3*s*,5*R*)-[5-(4-Fluorophenyl)-2-phenyl-1-oxaspiro[2.3]hexan-2-yl]methanol (4c). Following the general procedure described above, the reaction was performed in *i*-PrOH (5.0 mL) KOH (29 mg, 0.51 mmol), **3c** (96 mg, 0.34 mmol), rt. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Colorless oil (90%); FT-IR (film)ν_{max} (cm^{-1}): 3455, 3029, 2944, 1732, 1612, 1469, 1450, 1028, 1001, 908, 699; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.35-7.20 (m, 5H), 7.15-7.08 (m, 2H), 6.90 (dd, *J* = 12.0, 5.4 Hz, 2H), 4.15 (d, *J* = 12.3 Hz, 1H), 3.92 (d, *J* = 12.3 Hz, 1H), 3.16 (dd, *J* = 10.8, 6.7 Hz, 1H), 2.90 (dddd, *J* = 12.9, 8.5, 4.1, 1.1 Hz, 1H), 2.64-2.53 (m, 1H), 2.40-2.30 (m, 1H), 2.19 (dddd, *J* = 12.9, 8.6, 4.1, 1.1 Hz, 1H), 1.81 (br.s, 1H);^{13}C NMR (126 MHz,$CDCl_3$) δ: 161.2 (d, *J* = 243.8 Hz), 141.2 (d, *J* = 3.2 Hz), 139.3, 128.2, 128.0 (d, *J* = 5.3 Hz), 127.9, 126.8, 114.95 (d, *J* = 21.2 Hz), 79.0, 75.1, 49.9, 40.3, 39.8, 29.2; HRMS (ESI-TOF) *m/z*: calculated for $C_{18}H_{17}FNaO_2$ $[M+Na]^+$ 307.1110; found 307.1142; $[\alpha]^{20}_D$ = -31.0 (c 0.9, chloroform); Chiral HPLC: Phenomenex-Lux 1 column, 95:5 (Hexane:*i*-PrOH), 1.0 ml/min, (98:2 e.r.), major: 51.21 min, minor: 46.97.

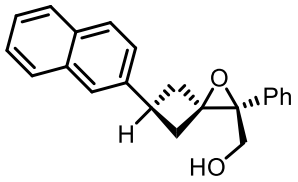


(2*S*,3*s*,5*R*)-[5-(4-Clorophenyl)-2-phenyl-1-oxaspiro[2.3]hexan-2-yl]methanol (4d). Following the general procedure described above, the reaction was performed in *i*-PrOH (5.0 mL) KOH (31 mg, 0.55 mmol), **3d** (112 mg, 0.37 mmol), rt. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Colorless oil (73%); FT-IR (film)ν_{max} (cm^{-1}): 3447, 3023, 2945, 1689, 1482, 1446, 1025, 1014, 907, 654; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42-7.37 (m, 3H), 7.34 (dd, *J* = 11.5, 4.5 Hz, 2H), 7.29-7.26 (m, 2H), 7.18 (d, *J* = 8.3 Hz, 2H), 4.23 (d, *J* = 12.1 Hz, 1H), 4.02 (d, *J* = 11.7 Hz, 1H), 3.23 (dd, *J* = 17.5, 8.8 Hz, 1H), 3.09-2.83 (m, 1H), 2.67 (dd, *J* = 13.1, 8.9 Hz, 1H), 2.43 (dd, *J* = 13.1, 8.9 Hz, 1H), 2.27 (ddd, *J* = 12.9, 8.6, 4.1 Hz, 1H), 1.53 (br.s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 142.9, 136.2, 131.9, 128.5, 128.4, 127.8, 127.8, 126.2, 66.5, 66.5, 63.8, 37.4, 37.0, 30.8; HRMS (ESI-TOF) *m/z*: calculated for $C_{18}H_{17}ClNaO_2$ $[M+Na]^+$ 323.0815; found 323.0822; $[\alpha]^{20}_D$ = -20.0 (c 1.2, chloroform); Chiral HPLC: Phenomenex-Lux 1 column, 95:5 (Hexane:*i*-PrOH), 1.0 ml/min, (98:2 e.r.), major: 36.29 min, minor: 31.13.

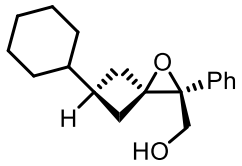


[(2*S*,3*s*,5*R*)-5-(4-Bromophenyl)-2-phenyl-1-oxaspiro[2.3]hexan-2-yl)methanol (4e). Following the general procedure described above, the reaction was performed in *i*-PrOH (4.0 mL) KOH (24 mg, 0.43 mmol), **3e** (100 mg, 0.29 mmol), rt. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Pale yellow oil (80%); FT-IR (film)ν_{max} (cm^{-1}): 3456, 3061, 3025, 2930, 1736, 1614, 1494, 1448, 1031, 1010, 905, 698; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.43 (d, *J* = 8.4 Hz, 2H), 7.40-7.35 (m, 2H), 7.35-7.30 (m, 3H), 7.13 (d, *J* = 8.3 Hz, 2H), 4.87 (d, *J* = 12.2 Hz, 1H), 4.18 (d, *J* = 12.2 Hz, 1H), 3.23 (dd, *J* = 17.4, 8.7 Hz, 1H), 2.92 (ddd, *J* = 12.6, 8.6, 4.0 Hz, 1H), 2.67 (dd, *J* = 12.9, 9.0 Hz, 1H), 2.43 (dd, *J* = 13.1, 9.0 Hz, 1H), 2.35-2.18 (m, 1H), 1.24 (dt, *J* = 9.9, 6.7 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 170.7, 143.2, 135.6, 128.3, 128.2, 127.9, 126.4, 120.1, 66.4, 65.9, 64.0, 37.0, 36.9, 30.8, 20.7; HRMS (ESI-TOF) *m/z*: calculated for $C_{18}H_{17}BrNaO_2$ $[M+Na]^+$ 367,0310; found 367,0308;

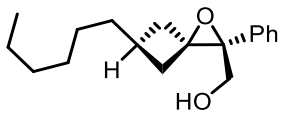
$[\alpha]^{20}_D$ = -33.0 (c 1.2, chloroform); Chiral HPLC: Phenomenex-Lux 1 column, 95:5 (Hexane:*i*-PrOH), 1.0 ml/min, (99:1 e.r.), major: 40.43 min, minor: 34.11.



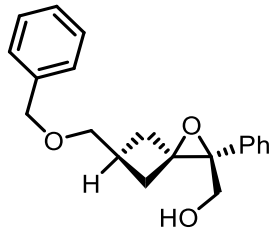
[(2*S*,3*s*,5*R*)-5-(Naphthalen-2-yl)-2-phenyl-1-oxaspiro[2.3]hexan-2-yl)methanol (4f). Following the general procedure described above, the reaction was performed in *i*-PrOH (4.0 mL) KOH (24 mg, 0.42 mmol), **3f** (90 mg, 0.28 mmol), rt. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Pale yellow oil (72%); FT-IR (film)ν_{max} (cm^{-1}): 3455, 3052, 3027, 2932, 1734, 1612, 1489, 1445, 1028, 1012, 917, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (t, *J* = 8.2 Hz, 3H), 7.51–7.29 (m, 4H), 4.28 (d, *J* = 12.2 Hz, 1H), 4.05 (d, *J* = 12.2 Hz, 1H), 3.51–3.35 (m, 1H), 3.07 (ddd, *J* = 12.6, 11.6, 7.9 Hz, 1H), 2.90–2.73 (m, 1H), 2.59 (dd, *J* = 12.4, 8.9 Hz, 1H), 2.40–2.26 (m, 1H), 1.87 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 141.7, 136.3, 133.4, 132.1, 128.4, 128.2, 127.8, 127.6, 126.3, 126.1, 125.4, 125.1, 124.5, 66.8, 66.6, 63.8, 37.3, 36.9, 31.9, 31.5, 29.7; HRMS (ESI-TOF) m/z: calculated for $C_{22}H_{20}NaO_2$ $[M+Na]^+$ 339,1361; found 339,1355; $[\alpha]^{20}_D$ = -53.0 (c 1.0, chloroform); Chiral HPLC: Phenomenex-Lux 1 column, 95:5 (Hexane:*i*-PrOH), 1.0 ml/min, (97:3 e.r.), major: 29.12 min, minor: 39.43 min.



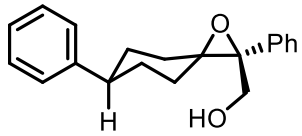
[(2*S*,3*s*,5*R*)-5-Cyclohexyl-2-phenyl-1-oxa-spiro[2.3]hexan-2-yl]methanol (4g). Following the general procedure described above, the reaction was performed in *i*-PrOH (5.0 mL) KOH (33 mg, 0.58 mmol), **3g** (106 mg, 0.39 mmol), rt. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. White solid (92%) mp: 55°C; FT-IR (film)ν_{max} (cm^{-1}): 3432, 2959, 2934, 2850, 1461, 1422, 1029, 910, 771, 735, 697; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33-7.26 (m, 2H), 7.25-7.17 (m, 3H), 4.13 (dd, *J* = 12.1, 4.0 Hz, 1H), 3.85 (dd, *J* = 12.1, 6.6 Hz, 1H), 2.48 (ddd, *J* = 12.8, 8.7, 3.7 Hz, 1H), 2.12 (dd, *J* = 12.6, 9.0 Hz, 1H), 1.88 (dd, *J* = 12.9, 8.5 Hz, 1H), 1.83-1.72 (m, 1H), 1.69-1.52 (m, 6H), 1.50 (br.s, 1H), 1.20-0.98 (m, 4H), 0.70 (dt, *J* = 33.3, 12.0 Hz, 2H); ^{13}C NMR (126 MHz $CDCl_3$) δ: 136.6, 128.2, 127.6, 126.2, 67.0, 66.4, 63.9, 44.6, 34.0, 33.6, 32.7, 30.3, 30.1, 26.4, 25.9, 25.9; HRMS (ESI-TOF) *m/z*: calculated for $C_{18}H_{24}NaO_2$ $[M+Na]^+$ 295,1674; found 295,1681; $[\alpha]^{20}_D$ = -17.8 (c 0.8, chloroform); Chiral HPLC: Phenomenex-Lux 1 column, 95:5 (Hexane:*i*-PrOH), 1.0 ml/min, (99:1 e.r.), major: 59.01 min, minor: 74.47 min.



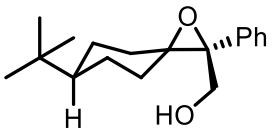
[(2*S*,3*s*,5*R*)-(5-Hexyl-2-phenyl-1-oxaspiro[2.3]hexan-2-yl]methanol (4h). Following the general procedure described above, the reaction was performed in *i*-PrOH (5.0 mL) KOH (24 mg, 0.42 mmol), **3h** (78 mg, 0.28 mmol), rt. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Colorless oil (80%); FT-IR (film)ν_{max} (cm^{-1}): 3436, 2957, 2924, 2853, 1459, 1419, 1041, 1028, 909, 761, 734, 700; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.34 (m, 2H), 7.32-7.28 (m, 3H), 4.20 (dd, , *J* = 12, 5 Hz, 1H), 3.91 (dd, , *J* =12, 7 Hz, 1H), 2.65-2.59 (m, 1H), 2.13 (dd , *J* =13, 7 Hz, 1H), 2.00-1.85 (m, 3H), 1.54-1.42 (m, 2H), 1.31-1.15 (m, 8H), 0.87 (t, *J* = 7 Hz, 3H); ^{13}C NMR (126 MHz $CDCl_3$) δ 136.7, 128.4, 127.8, 126.44, 64.1, 37.3, 35.9, 35.5, 32.0, 29.3, 27.6, 27.1; HRMS (ESI-TOF) *m/z*: calculated for $C_{18}H_{26}NaO_2$ $[M+Na]^+$ 297.1825; found 297.1830; $[\alpha]^{20}_D$ = +16 (c 1.0, chloroform); Chiral HPLC: Phenomenex-Lux 1 column, 99:1(Hexane:*i*-PrOH), 1.0 ml/min, (99:1 e.r.), major: 15.41 min, minor: 16.63 min.



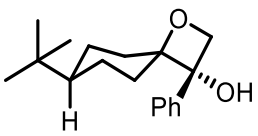
[(2*S*,3*s*,5*R*)-5-(benzyloxy)methyl)-2-phenyl-1-oxaspiro[2.3]hexan-2-yl]methanol (4i). Following the general procedure described above, the reaction was performed in *i*-PrOH (4.0 mL) KOH (23 mg, 0.40 mmol), **3i** (85 mg, 0.27 mmol), rt. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Colorless oil (80%); FT-IR (film)ν_{max} (cm^{-1}): 3415, 2891, 2878, 1456, 1419, 1028, 908, 761, 699; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.55-7.48 (m, 1H), 7.36-7.21 (m, 4H), 4.49 (s, 2H), 4.15 (d, *J* = 12.3 Hz, 1H), 3.86 (d, *J* = 12.3 Hz, 1H), 3.49 (dd, *J* = 6.1, 2.9 Hz, 1H), 2.67-2.57 (m, 1H), 2.31 (dt, *J* = 12.9, 7.8 Hz, 2H), 2.04 (dd, *J* = 12.1, 5.2 Hz, 1H), 1.99-1.94 (m, 1H); ^{13}C NMR (126 MHz $CDCl_3$) δ: 137.9, 137.1, 128.3, 127.8, 127.7, 127.6, 127.6, 127.5, 74.3, 73.4, 73.1, 61.7, 51.3, 35.7, 34.6, 31.5, 25.9, 22.5, 14.0; HRMS (ESI-TOF) *m/z*: calculated for $C_{20}H_{22}NaO_3$ $[M+Na]^+$ 333,1467; found 333,1498; $[\alpha]^{20}_D$ = -32.0 (c 1.0, chloroform); Chiral HPLC: Chiralpak AS-H column, 92:8 (Hexane:*i*-PrOH), 1.0 ml/min, (99:1 e.r.), major: 33.19 min, minor: 38.31 min.



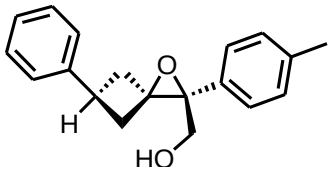
[(2*S*,3*s*,6*R*)-2,6-Diphenyl-1-oxaspiro[2.5]octan-2-yl)methanol (4k). Following the general procedure described above, the reaction was performed in *i*-PrOH (6.0 mL) KOH (27 mg, 0.48 mmol), **3k** (95 mg, 0.32 mmol), rt. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Colorless oil (92%); FT-IR (film)ν_{max} (cm^{-1}): 3457, 3026, 2982, 2878, 1445, 1352, 1248, 1229, 1064, 1012, 925, 768, 696;^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43 (d, *J* = 7.4 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.30 (dd, *J* = 14.2, 6.9 Hz, 3H), 7.21 (dd, *J* = 12.9, 5.9 Hz, 3H), 4.17 (d, *J* = 11.9 Hz, 1H), 3.99 (d, *J* = 11.9 Hz, 1H), 2.70-2.48 (m, 1H), 2.20-2.06 (m, 1H), 2.02 (dd, *J* = 9.1, 2.7 Hz, 2H), 1.74 (dd, *J* = 9.4, 5.2 Hz, 3H), 1.53-1.35 (m, 1H), 1.25 (br.s, 1H), 1.14 (d, *J* = 11.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 145.8, 137.7, 128.3, 128.2, 127.5, 126.6, 126.2, 70.0, 68.6, 64.8, 43.1, 33.4, 32.3, 31.5, 30.5; HRMS (ESI-TOF) *m/z*: calculated for $C_{20}H_{22}NaO_2$ $[M+Na]^+$ 317,1517; found 317,1538; $[\alpha]^{20}_D$ = -29.4 (cc 1.3, chloroform); Chiral HPLC: Chiralpak AD-H column, 95:5 (Hexane:*i*-PrOH), 1.0 ml/min, (94:6 e.r.), major: 30.50 min, minor: 24.94 min.



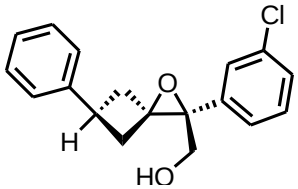
[(2*S*,3*s*,6*R*)-6-(*tert*-butyl)-2-phenyl-1-oxaspiro[2.5]octan-2-yl]methanol (4l). Following the general procedure described above, the reaction was performed in *i*-PrOH (6.0 mL) KOH (36 mg, 0.64 mmol), **3l** (120 mg, 0.43 mmol), rt. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. White solid (78%); mp = 69-71° C; FT-IR (film)ν_{max} (cm^{-1}): 3471, 2960, 2942, 2857, 1446, 1363, 1261, 1212, 1066, 1008, 900, 869, 779, 703, 695; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37 (m, 4H), 7.33-7.28 (m, 1H), 4.14 (dd, *J* = 11.8, 5.1 Hz, 1H), 3.96 (dd, *J* = 11.9, 5.4 Hz, 1H), 2.04-1.89 (m, 2H), 1.83 (td, *J* = 13.1, 3.4 Hz, 1H), 1.57 (dd, *J* = 9.2, 3.9 Hz, 1H), 1.54 (br.s, 1H), 1.23 (dt, *J* = 12.1, 9.5 Hz, 1H), 1.15-1.07 (m, 1H), 1.07-1.02 (m, 1H), 0.97 (td, *J* = 12.4, 2.8 Hz, 1H), 0.86 (s, 9H); ^{13}C NMR (126 MHz $CDCl_3$) δ: 137.9, 128.2, 127.4, 126.7, 69.9, 69.3, 64.8, 47.2, 32.3, 31.5, 30.6, 27.6, 27.0, 25.5; HRMS (ESI-TOF) *m/z*: calculated for $C_{18}H_{26}NaO_2$ $[M+Na]^+$ 297,1830; found 297.1827; $[\alpha]^{20}_D$ = -21,23 (c 0.5, chloroform); Chiral HPLC: Chiralpak AD-H column, 92:8 (Hexane:*i*-PrOH), 1.0 ml/min, (99:1 e.r.), major: 29.25 min, minor: 34.78 min.



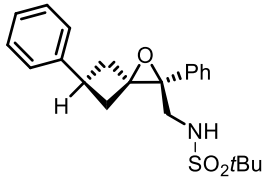
(3*S*,4*s*,7*R*)-7-(*tert*-butyl)-3-phenyl-1-oxaspiro[3.5]nonan-3-ol (5). Colorless oil (15%); FT-IR ν_{max} (cm^{-1}): 3445, 3032, 3007, 2944, 1601, 1485, 1444, 1029, 1008, 956, 739; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.29-7.22 (m, 3H), 1.96 (br.s, 1H), 1.86-1.77 (m, 1H), 1.78-1.71 (m, 1H), 1.60-1.52 (m, 1H), 1.49-1.43 (m, 1H), 1.32 (tdd, *J* = 13.3, 4.0, 1.9 Hz, 1H), 1.15-1.07 (m, 1H), 1.02-0.94 (m, 1H), 0.74 (s, 9H); ^{13}C NMR (126 MHz $CDCl_3$) δ; 138.4, 128.3, 127.8, 127.7, 72.6, 64.9, 52.1, 46.5, 35.8, 35.6, 27.5, 24.1, 23.9; HRMS (ESI-TOF) *m/z*: calculated for $C_{18}H_{26}NaO_2$ $[M+Na]^+$ 297,1830; found 297.1838.



[(2*S*,3*s*,5*R*)-(5-Phenyl-2-p-tolyl-1-oxa-spiro[2.3]hex-2-yl)-methanol (4ab). Following the general procedure described above, the reaction was performed in *i*-PrOH (5.0 mL) KOH (31 mg, 0.55 mmol), **3a** (100 mg, 0.37 mmol), rt. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Colourless oil (96%); FT-IR (film)ν_{max} (cm^{-1}): 3450, 3048, 3025, 2938, 1604, 1483, 1448, 1032, 1012, 908; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 7.25 (t, *J* = 7.6 Hz, 2H), 7.18 (dd, *J* = 7.4, 5.9 Hz, 4H), 7.14 (t, *J* = 8.3 Hz, 2H), 4.18 (dd, *J* = 18.6, 9.1 Hz, 1H), 3.92 (d, *J* = 12.2 Hz, 1H), 3.24-3.14 (m, 1H), 2.96-2.86 (m, 1H), 2.69-2.61 (m, 1H), 2.41 (ddd, *J* = 13.0, 9.0, 0.9 Hz, 1H), 2.29 (s, 3H), 2.26-2.18 (m, 1H); ^{13}C NMR (151 MHz $CDCl_3$) δ: 144.5, 137.5, 133.2, 129.1, 128.4, 126.4, 126.2, 66.6, 66.5, 63.9, 37.3, 36.9, 31.3, 21.1; HRMS (ESI-TOF) *m/z*: calculated for $C_{19}H_{20}NaO_2$ $[M+Na]^+$ 303,1361; found 303,1370; $[\alpha]^{20}_D$ = -30.0 (c 1.0, chloroform); Chiral HPLC: Phenomenex-Lux 1 column, 91:10 (Hexane:*i*-PrOH), 1.0 ml/min, (91:9 e.r.), major: 19.52 min, minor: 28.76.



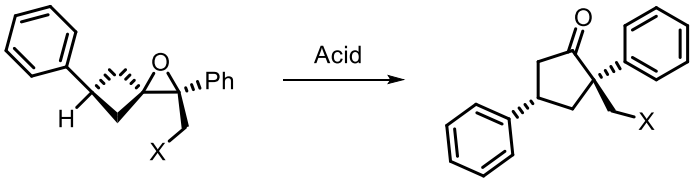
[(2*S*,3*s*,5*R*)-[2-(3-Chloro-phenyl)-5-phenyl-1-oxa-spiro[2.3]hex-2-yl]-methanol (4ad). Following the general procedure described above, the reaction was performed in *i*-PrOH (4.0 mL) KOH (24 mg, 0.43 mmol), **3ad** (80 mg, 0.20 mmol), rt. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Colourless oil (94%); FT-IR (film)ν_{max} (cm^{-1}): 3433, 2932, 1638, 1495, 1448, 1422, 1030, 1011, 925, 787, 752, 696; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.20 (m, 9H), 4.23 (d, *J* = 12.3 Hz, 1H), 3.98 (d, *J* = 12.3 Hz, 1H), 3.31-3.23 (m, 1H), 2.99-2.94 (m, 1H), 2.75-2.70 (m, 1H), 2.52-2.48 (m, 1H), 2.29-2.24 (m, 1H), 1.84 (br. s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.3, 138.7, 134.6, 129.8, 128.6, 128.2, 126.7, 126.5, 126.4, 124.6, 67.1, 66.2, 63.9, 37.4, 36.9, 31.43; HRMS (ESI-TOF) *m/z*: calculated for $C_{18}H_{17}ClNaO_2$ $[M+Na]^+$ 323.0815; found 323.0810; $[\alpha]^{20}_D$ = -30.0 (c 1.0, chloroform); Chiral HPLC: Phenomenex-Lux 1 column, 90:10 (Hexane:*i*-PrOH), 1.0 ml/min, (88:12 e.r.), major: 12.02 min, minor: 22.15 min.



(±)-*N*-{[(2*S*,3*s*,5*R*)-2,5-diphenyl-1-oxaspiro[2.3]hexan-2-yl]methyl}-2-methylpropane-2-sulfonamide (7). Following the general procedure described above, the reaction was performed in *i*-PrOH (4.0 mL) KOH (15 mg, 0.27 mmol), **6** (70 mg, 0.18 mmol), rt. The crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Waxy solid (72%); ^{1}H NMR (500 MHz, CD_3OD) δ: 7.46-7.41 (m, 1H), 7.38-7.32 (m, 2H), 7.31-7.27 (m, 2H), 7.26-7.23 (m, 2H9, 7.21-7.14 (m, 1H),

4.01 (d, *J* = 14.1 Hz, 1H), 3.37 (d, *J* = 14.1 Hz, 1H), 3.32-3.29 (m, 1H), 3.01 (dddd, *J* = 12.8, 8.5, 4.1, 1.2 Hz, 1H), 2.59 (ddd, *J* = 12.8, 8.9, 1.2 Hz, 1H), 2.30 (ddd, *J* = 12.9, 8.9, 1.1 Hz, 1H), 2.19 (dddd, *J* = 13.0, 8.8, 4.1, 1.3 Hz, 1H), 1.25 (s, 5H); ^{13}C NMR (126 MHz CD_3OD) δ: 148.4, 140.3, 131.9, 131.7, 131.2, 130.7, 129.9, 129.7, 70.5, 69.6, 63.5, 40.6, 40.4, 34.8, 34.8, 27.1, 27.1; IR ν_{max} (cm^{-1}): 3479, 2983, 2935, 1777, 1732, 1602, 1495, 1455, 1303, 1124, 951, 754,699; HRMS (ESI-TOF) *m/z*: calculated for $C_{22}H_{27}NNaO_3S$ $[M+Na]^+$ 408,1609; found 408,1615.

5. Acid catalyzed C4-C5 ring expansion of spirocycle-adducts 4a and 7. Synthesis of cyclopentanones 8 and 9.



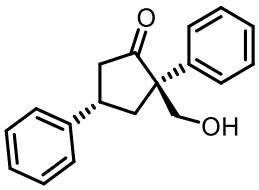
4a X = OH
7 X = NH-Bus

8 X = OH
9 X = NH-Bus

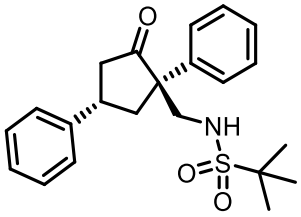
Table 1. Acid screening

Entry	Acid (mol%)	Solvent	Temp. °C	Yield%	d.r.
1	LiI	CH_2Cl_2	rt	-	-
2	LiBr	CH_2Cl_2	rt	-	-
3	$AlMe_3$	CH_2Cl_2	-78	23	73:27
4	$AlMe_3$	CH_2Cl_2	0	37	60:40
5	$TiCl_4$ (20)	EtOAc	-78	34	80:20
6	Me_2AlCl (20)	CH_2Cl_2	-78	94	80:20
7	Me_2AlCl (20)	toluene	-40	58	73:27
8	$FeCl_3$ (20)	CH_2Cl_2	r.t.	-	-
9	BF_3-OEt_2 (20)	CH_2Cl_2	-78	60	70:30
10	$SnCl_4$ (20)	CH_2Cl_2	-78	20	70:30
11	TBDMSOTf	CH_2Cl_2	CH_2Cl_2	-	-
12	MSA (20)	CH_2Cl_2	-78	84	45:55
13	PTSA (20)	CH_2Cl_2	-78	>98	50:50
14	AcOH (20)[a]	$CHCl_3$	rt	>98	90:10[a]

a) reactions were performed using the azaspiro-derivative **6**



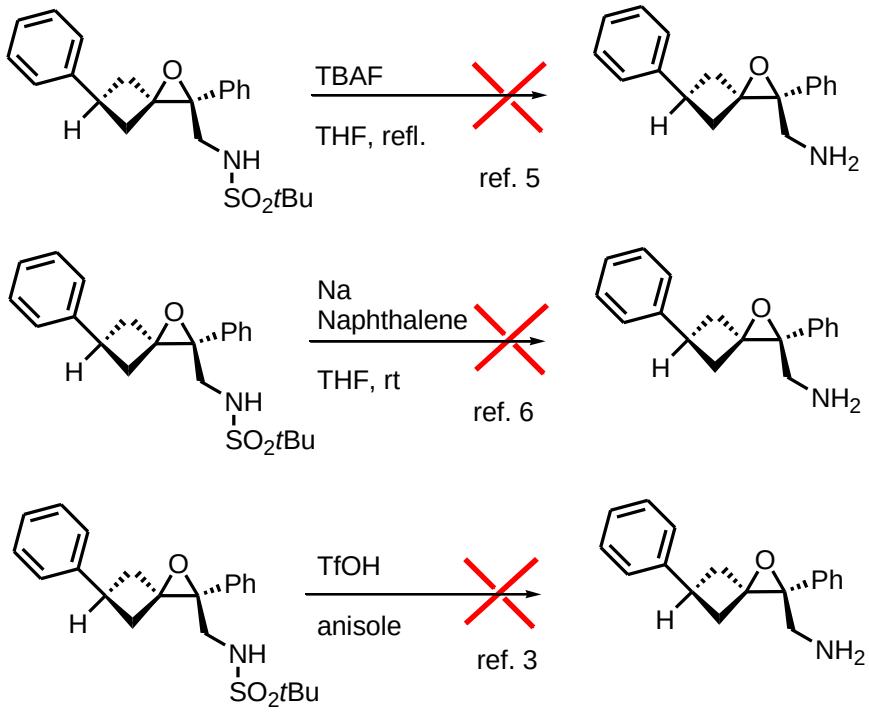
(2*R,4*R**)-2-Hydroxymethyl-2,4-diphenylcyclopentanone (8).** To a stirred solution of (1-oxaspiro[2.3]hex-2-yl]methanol adduct **4a** (50 mg, 0.18 mmol) in dry CH_2Cl_2 (3 mL), Me_2AlCl (1.0 M sol in hexane, 0.037 mmol, 37μL) was added dropwise at -78° C. After 1h the reaction mixture was concentrated under reduced pressure and the crude product was purified by flash chromatography using hexanes-diethyl ether 10:1-1:1 as eluents. Yellow oil (94%). Mixture of diastereomers (80:20) analytical data refer to the major diastereomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42-7.39 (m, 3H), 7.35-7.31 (m, 3H), 7.25 (t, *J* = 7.1 Hz, 4H), 4.03 (d, *J* = 11.3 Hz, 1H), 3.72 (d, *J* = 11.2 Hz, 1H), 3.32 (ddd, *J* = 18.4, 10.4, 6.6 Hz, 1H), 2.88-2.79 (m, 2H), 2.57 (t, *J* = 12.9 Hz, 1H), 2.41 (dd, *J* = 19.6, 11.4 Hz, 1H), 2.02 (br.s, 1H); ^{13}C NMR (126 MHz $CDCl_3$) δ: 218.6, 142.7, 136.9, 129.0, 128.6, 127.6, 126.8, 126.7, 126.7, 67.6, 61.9, 45.9, 38.8, 37.5; HRMS (ESI-TOF) *m/z*: calculated for $C_{18}H_{18}NaO_2$ $[M+Na]^+$ 289,1204; found 289,1211.



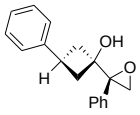
2-methyl-*N*-{[(1*R,4*R**)-2-oxo-1,4-diphenylcyclopentyl]methyl)} propane-2-sulfonamide (9).** To a stirred solution of (1-oxaspiro[2.3]hexan-2-yl)methyl]-2-methylpropane-2-sulfonamide adduct **7** (70 mg, 0.18 mmol), acetic acid (2.0 μL 0.036 mmol) was added dropwise in chloroform (3 mL) at room temperature. The reaction mixture was stirred for 1,5 hours, then was concentrated under reduced pressure and the crude product was purified by flash chromatography using hexanes-diethyl ether 5:1-1:1 as eluents. Waxy solid (>98%); IR ν_{max} (cm^{-1}): 3397, 2974, 1728, 1406, 1320, 1128, 1073, 831, 757, 701, 659;^{1}H NMR (500 MHz, CD_3Cl) δ: 7.44–7.39 (m, 3H), 7.38–7.28 (m, 4H), 7.27–7.22 (m, 3H), 4.36 (t, *J* = 6 Hz, NH), 3.65–3.48 (m, 2H), 3.33–3.23 (m, 1H), 2.95 (ddd, *J* = 13, 5., 3 Hz, 1H), 2.84 (ddd, *J* = 20, 8, 3 Hz, 1H), 2.52 (t, *J* = 13 Hz, 1H), 2.39 (dd, *J* = 20, 11 Hz, 1H), 1.29 (s, 9 H); ^{13}C NMR (126 MHz CD_3Cl) δ: 218.1, 142.4, 136.6, 129.4, 128.84, 128.2, 126.9, 126.9, 126.9, 126.8, 126.7, 61.4, 59.7, 51.4, 45.5, 39.4, 37.5, 24.4; HRMS (ESI-TOF) *m/z*: calculated for $C_{22}H_{27}NNaO_3S$ $[M+Na]^+$ 408.1604; found 408.1608.

6. Deprotection of sulfonamide 7

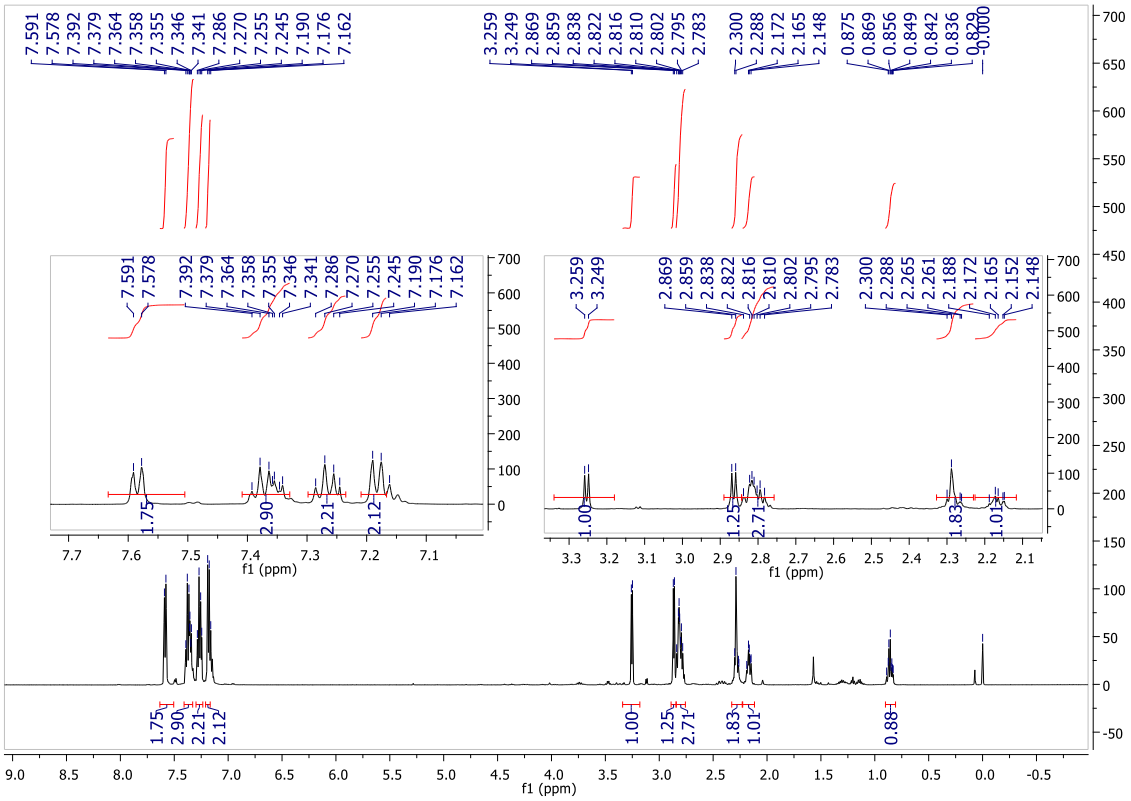
Different methodologies suitable for deprotecting the sulfonamide function were screened. However these attempts did not lead to obtaining the cleavage of the *N*-Bus bond. Below we report our attempts and the literature notes from which the individual procedures have been extrapolated.

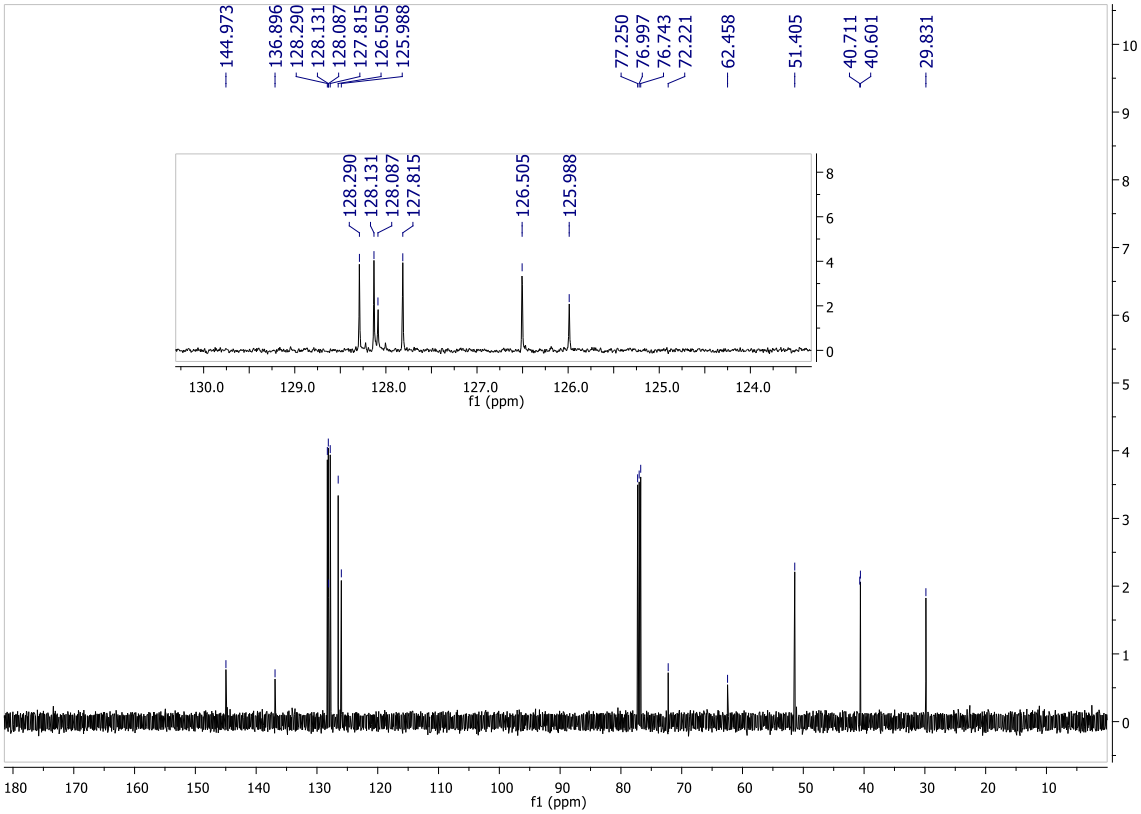


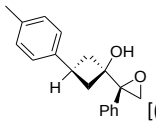
7. ^{1}H and ^{13}C NMR spectra of compounds 3a-l, 3ab, 3ad and 6



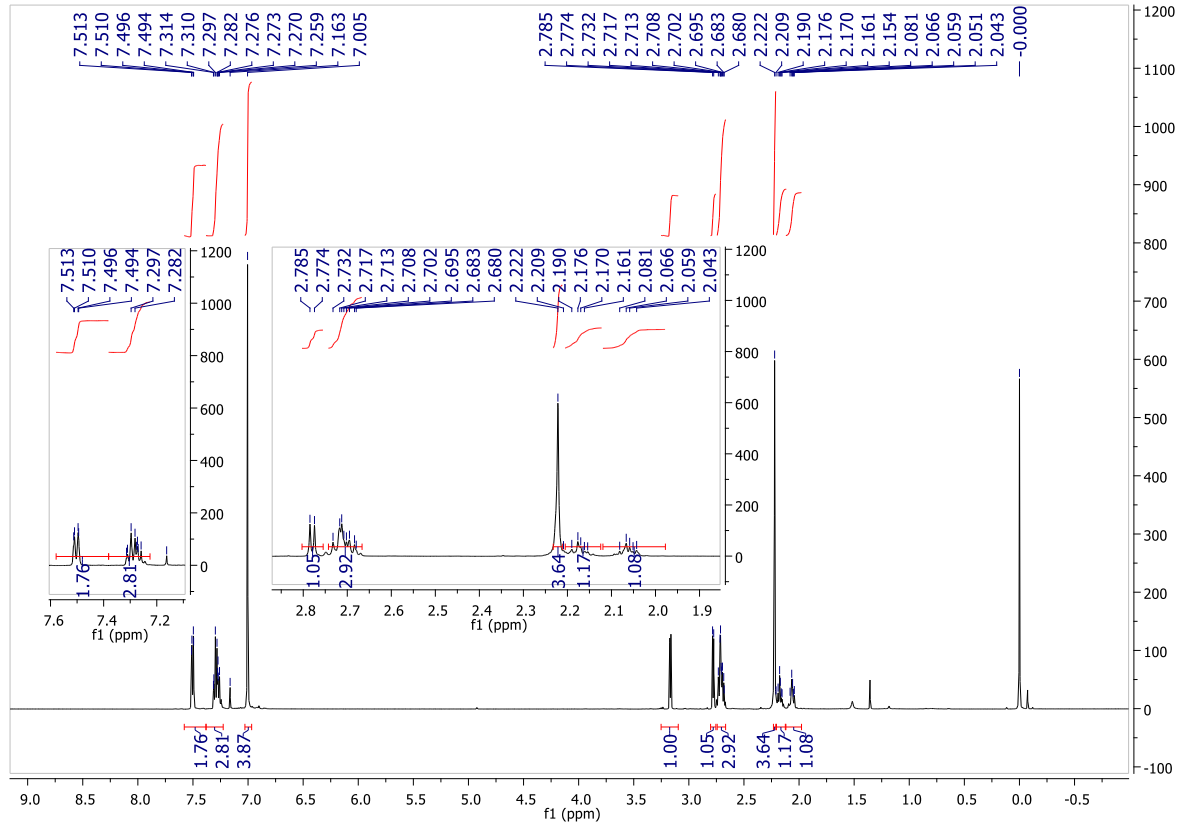
(1*s*,3*S*)-1-[(*R*)-(2-Phenyloxiran-2-yl]-3-phenylcyclobutanol **(3a)**

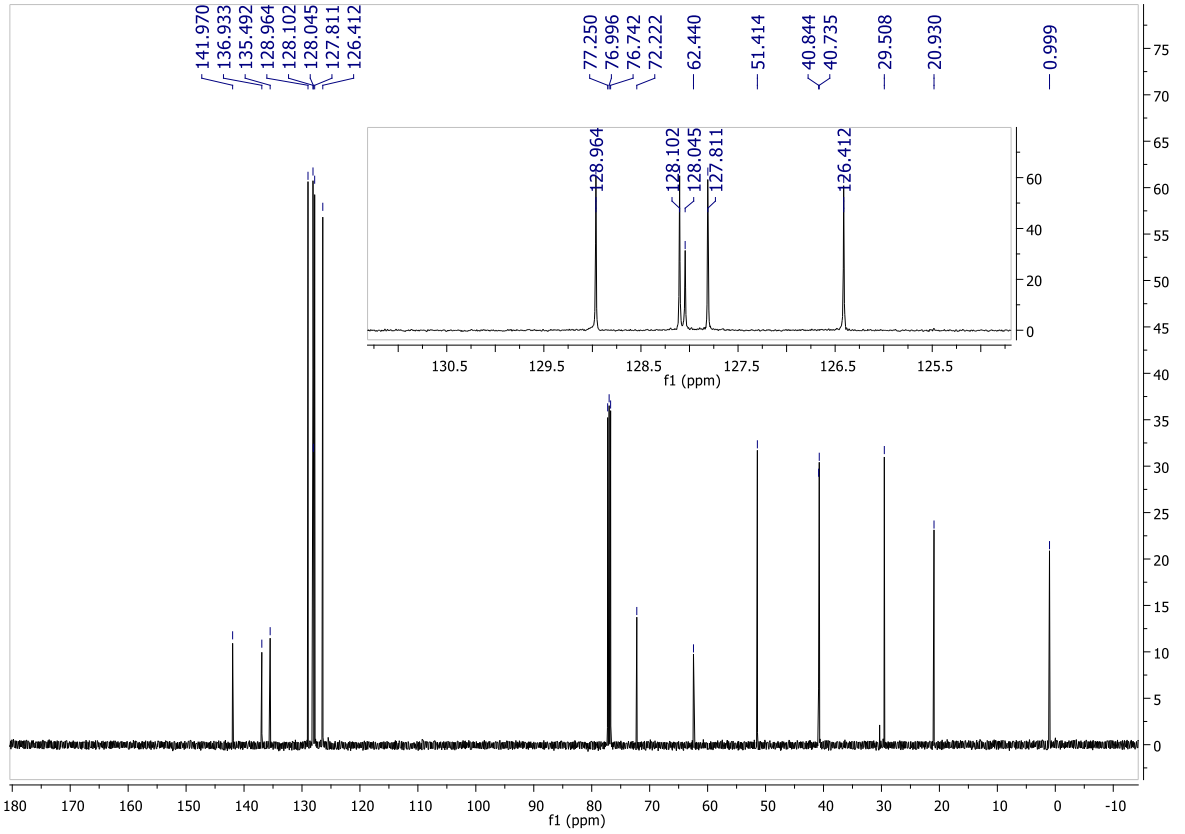


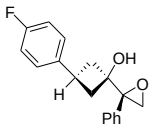




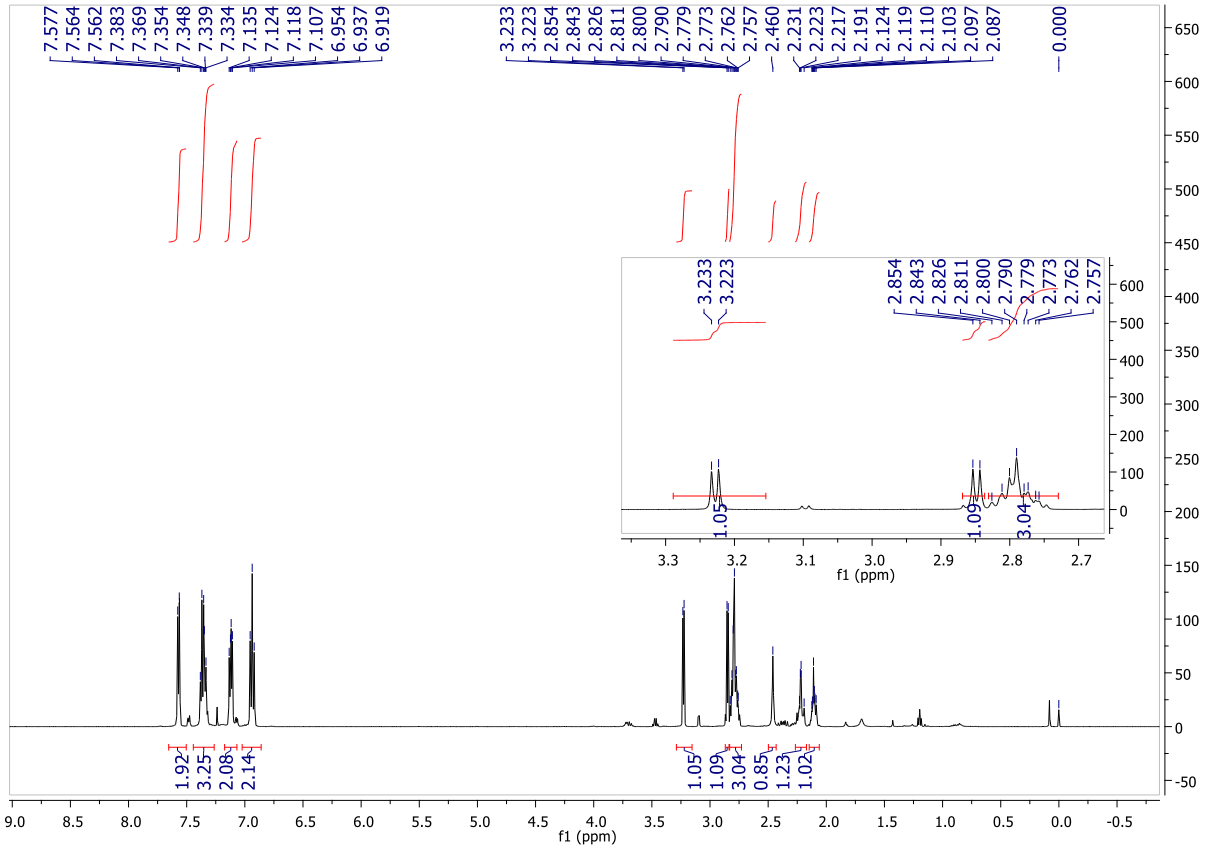
[(2*S*,3*s*,5*R*)-2-Phenyl-5-(p-tolyl)-1-oxaspiro[2.3]hexan-2-yl]methanol **(3b)**

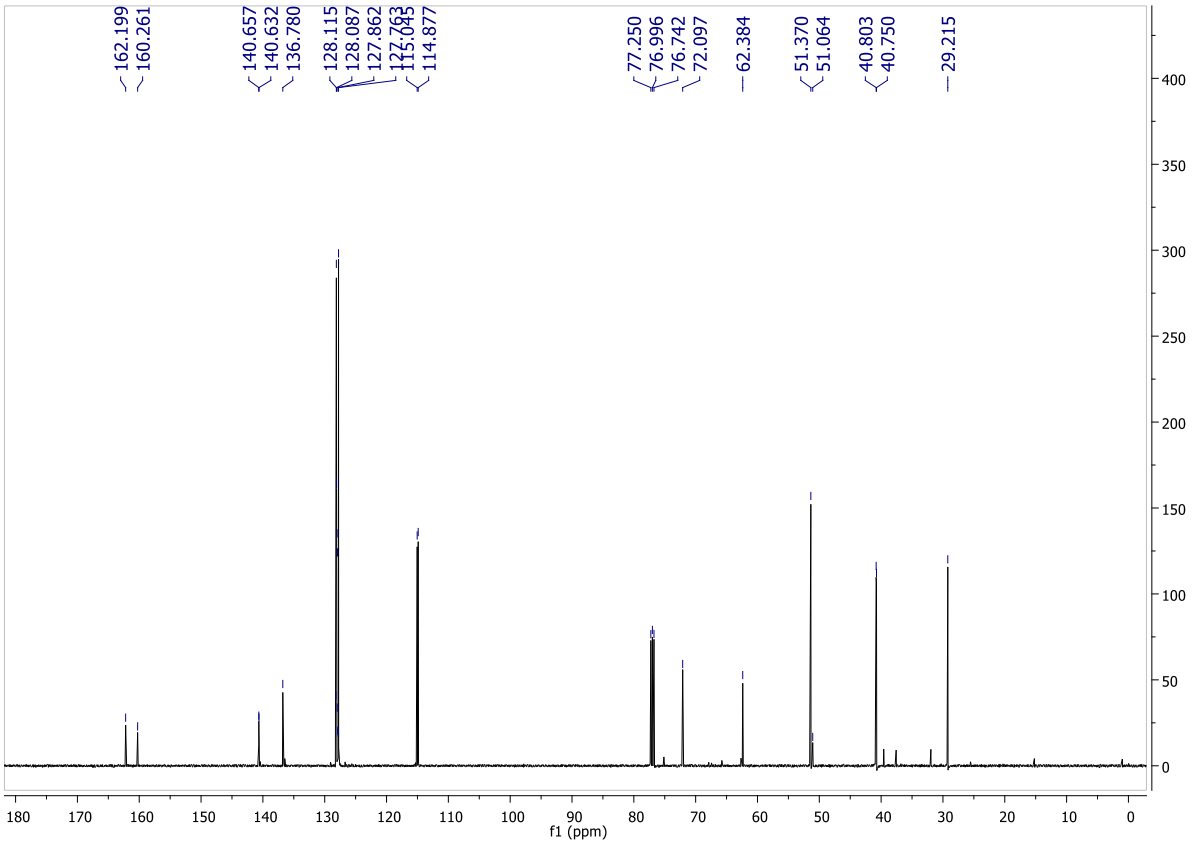


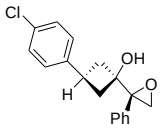




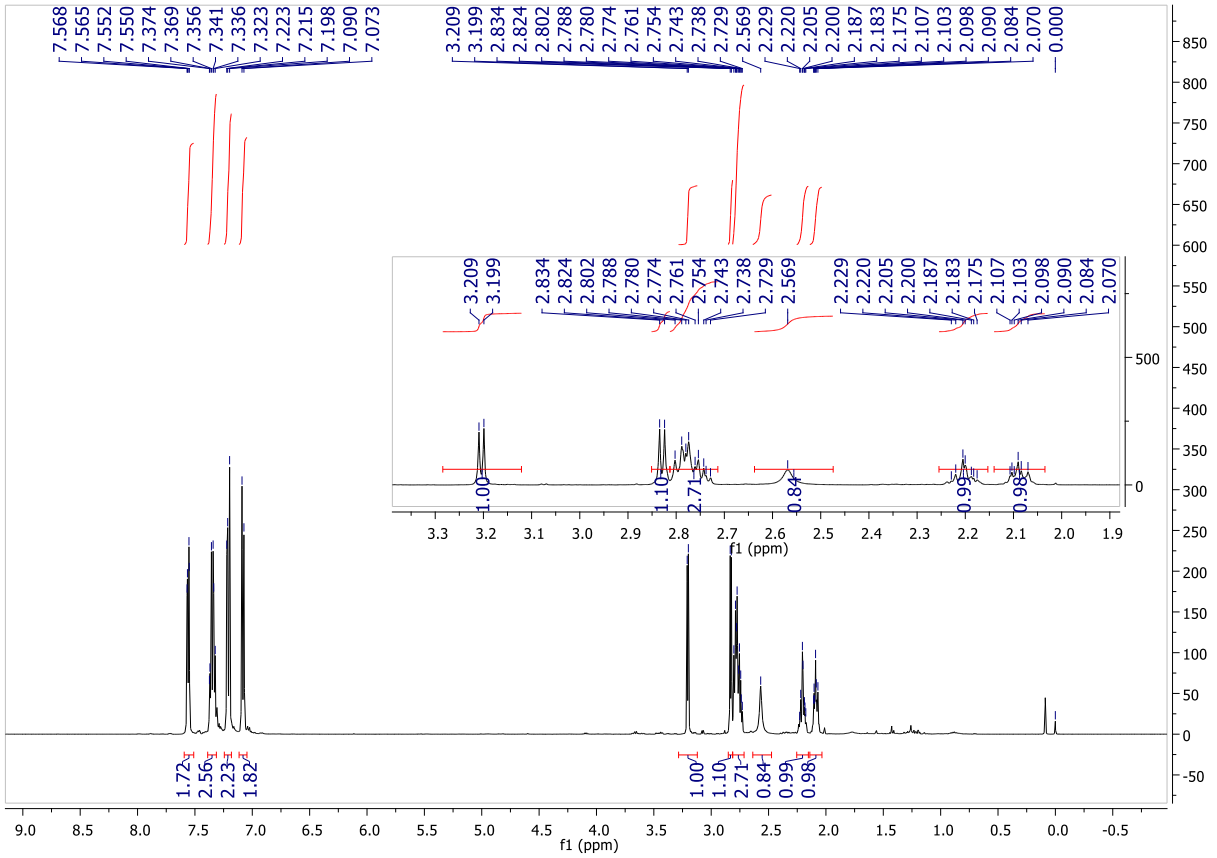
(1*s*,3*S*)-3-(4-Fluorophenyl)-1-[(*R*)-2-phenyloxiran-2-yl]cyclobutanol **(3c)**

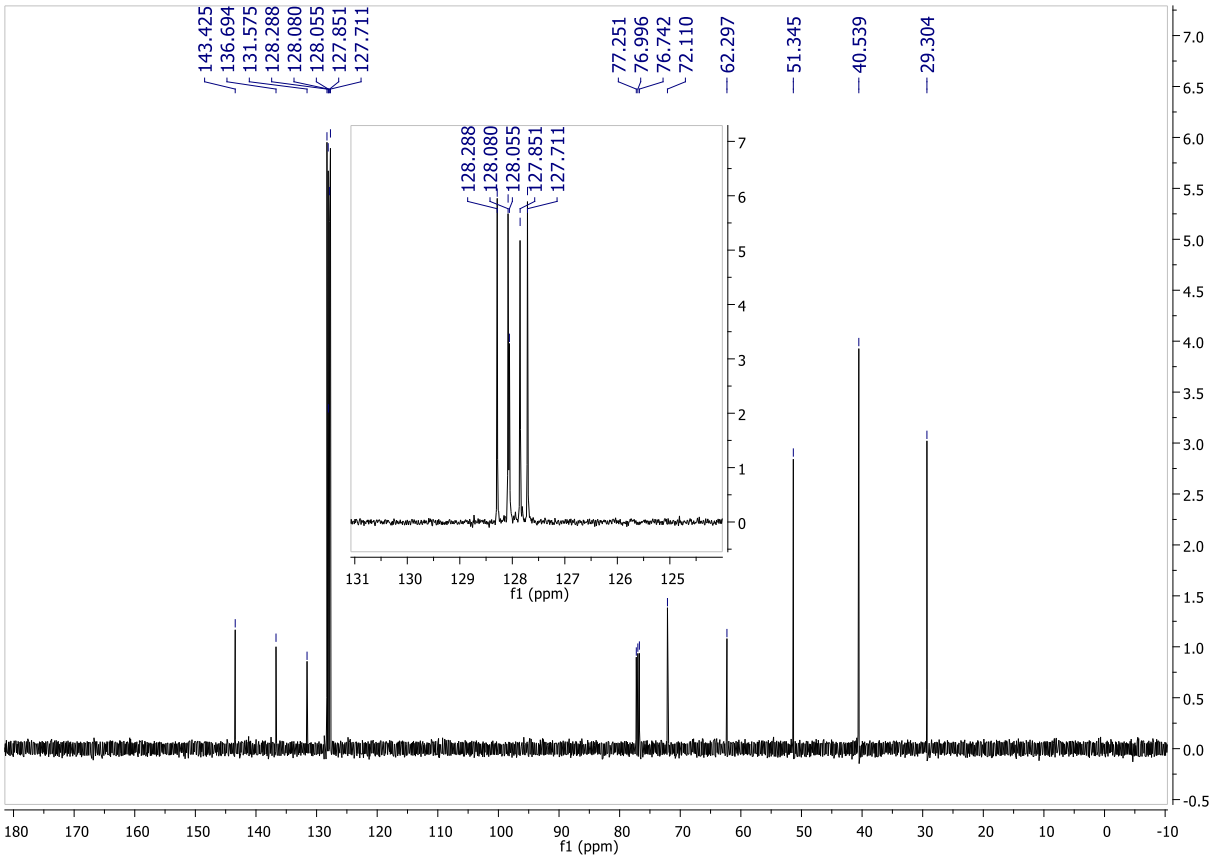


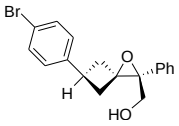




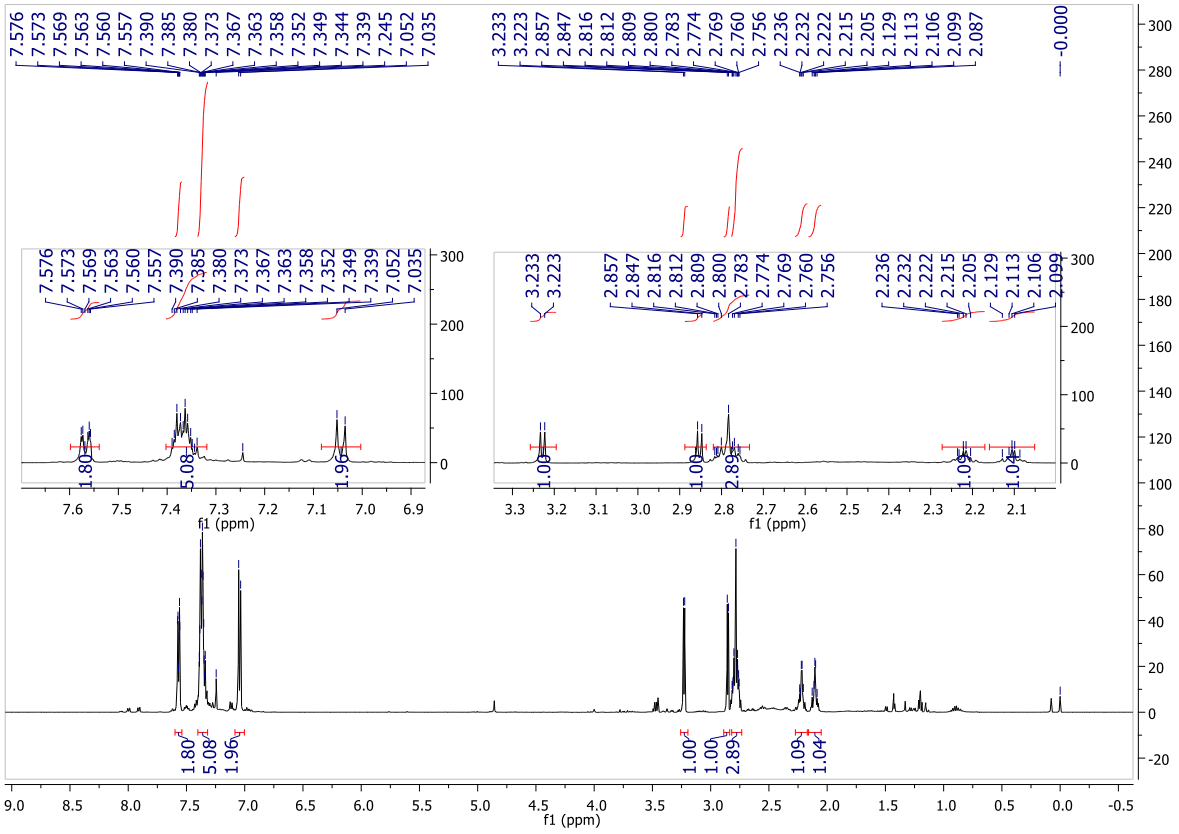
(1*s*,3*S*)-3-(4-Chlorophenyl)-1-[(*R*)-2-phenyloxiran-2-yl]cyclobutanol **(3d)**

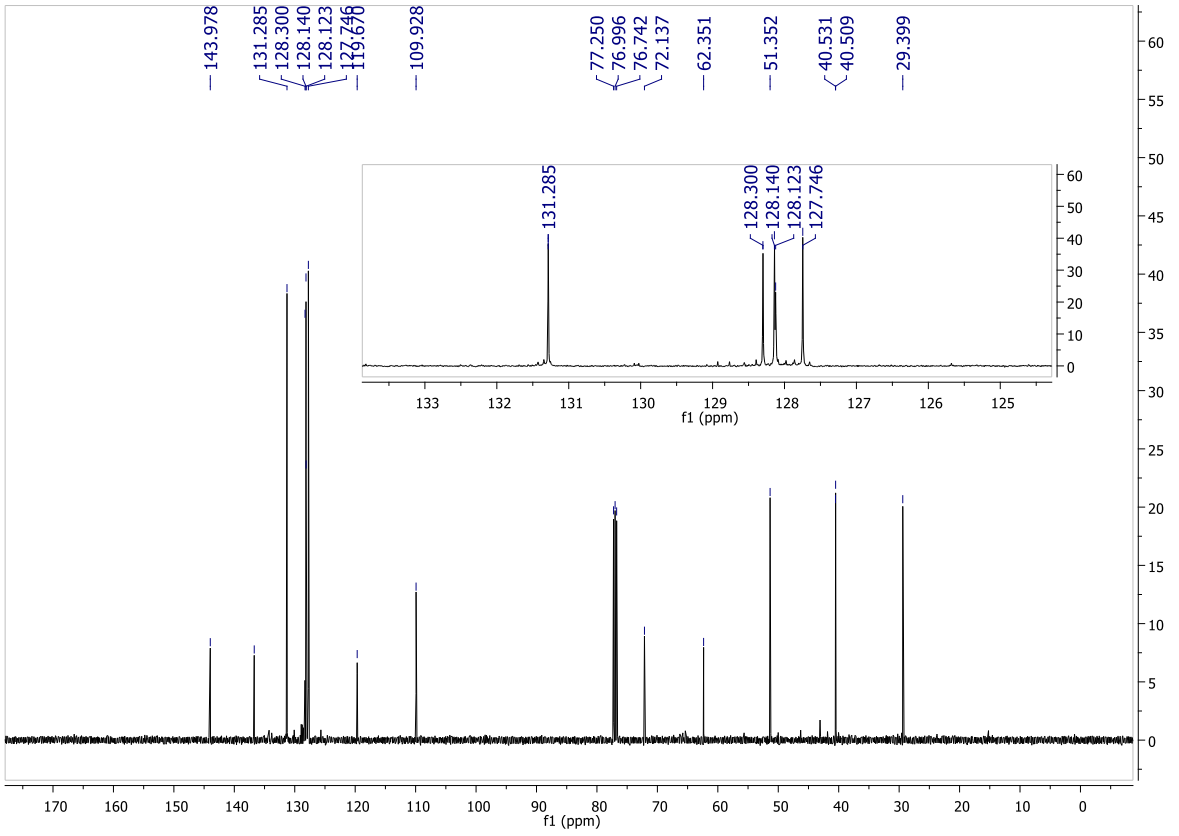


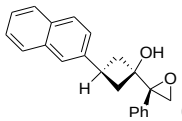




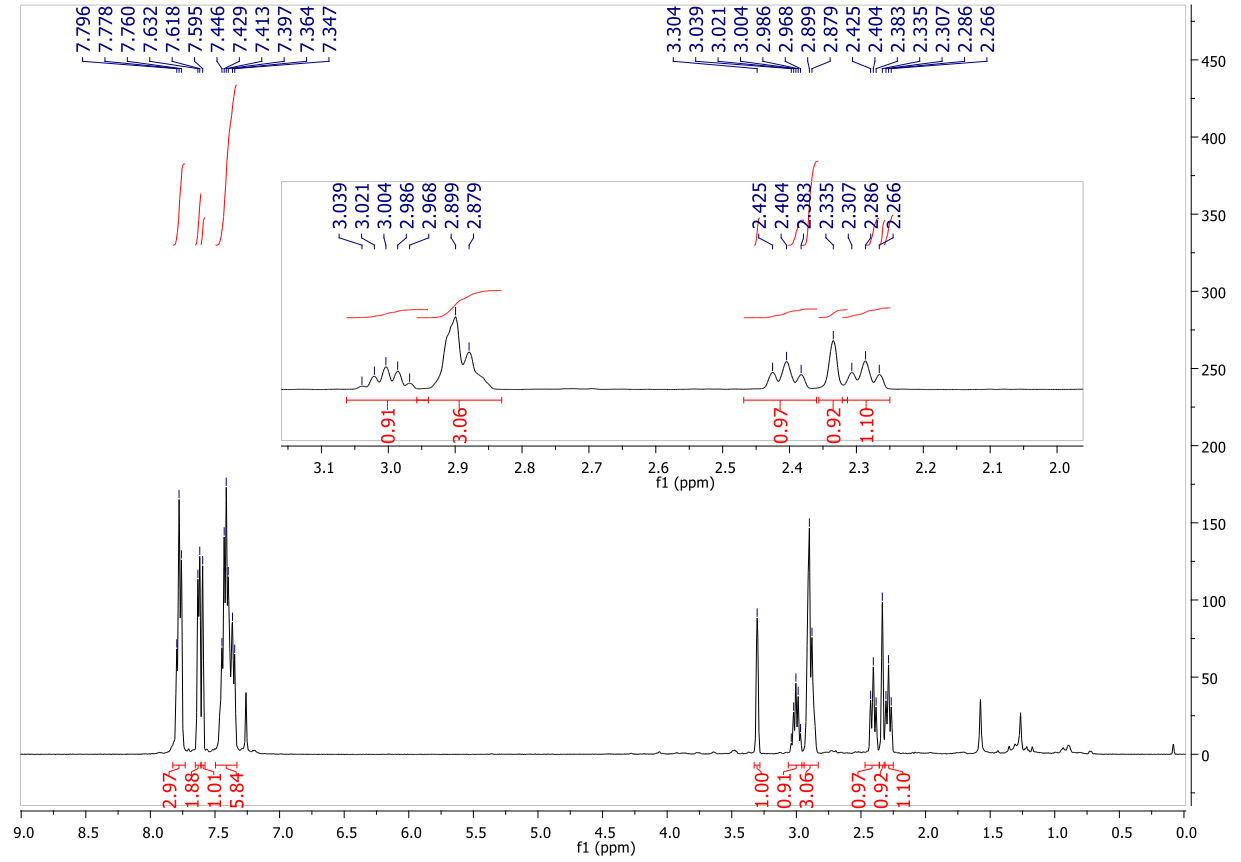
(2*S*,3*s*,5*R*)-[5-(4-Bromophenyl)-2-phenyl-1-oxaspiro[2.3]hexan-2-yl]methanol **(3e)**

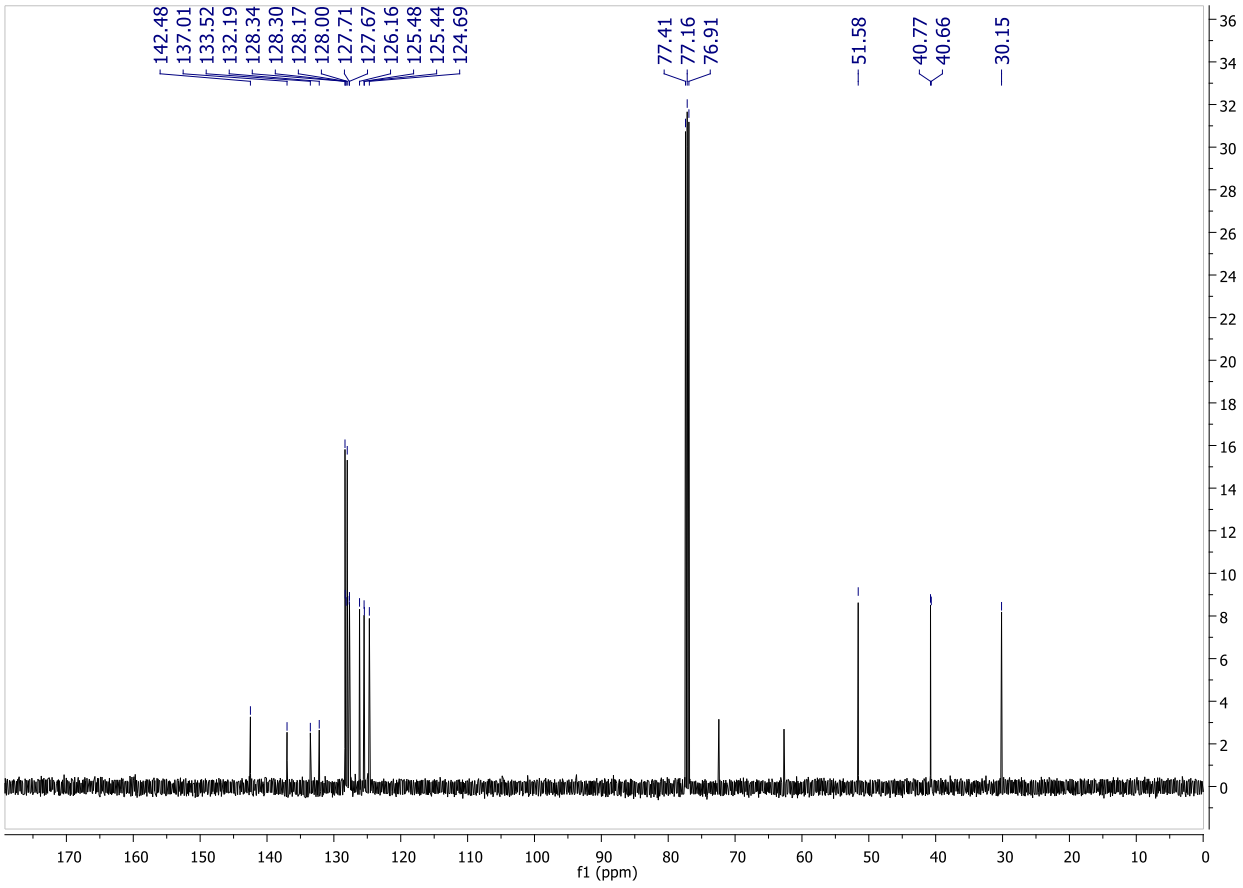


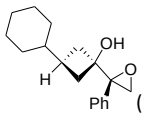




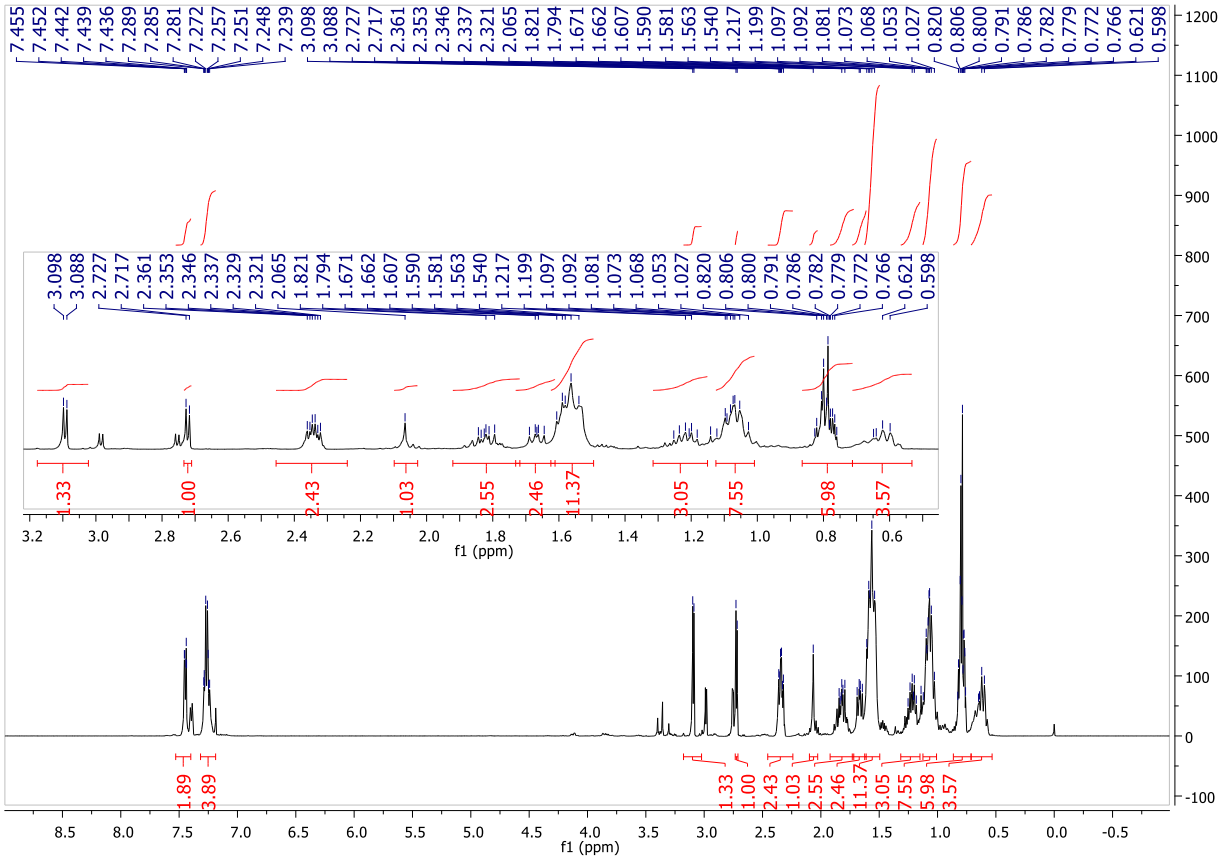
(1*s*,3*S*)-3-(naphthalen-2-yl)-1-[(*R*)-2-phenyloxiran-2-yl)cyclobutanol **(3f)**

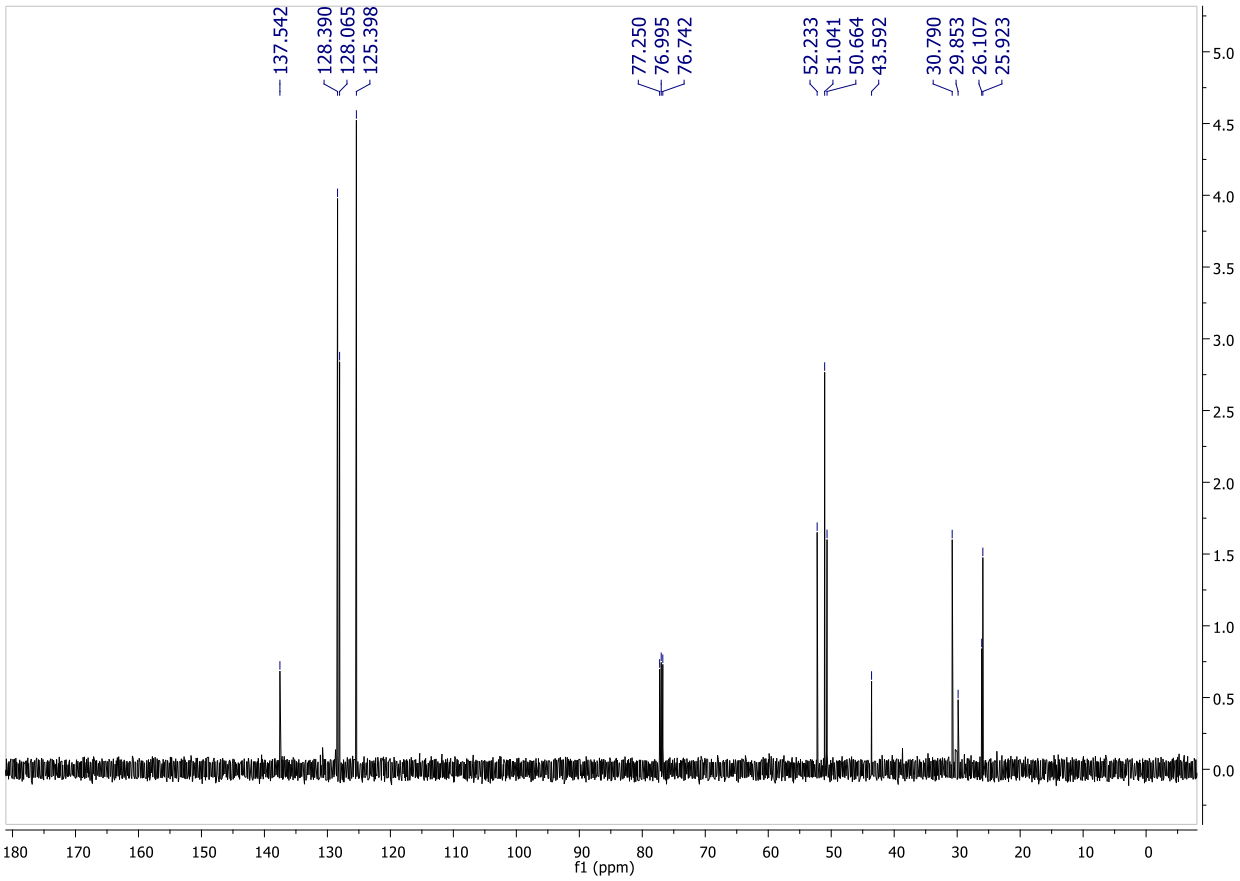


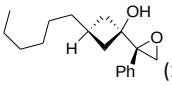




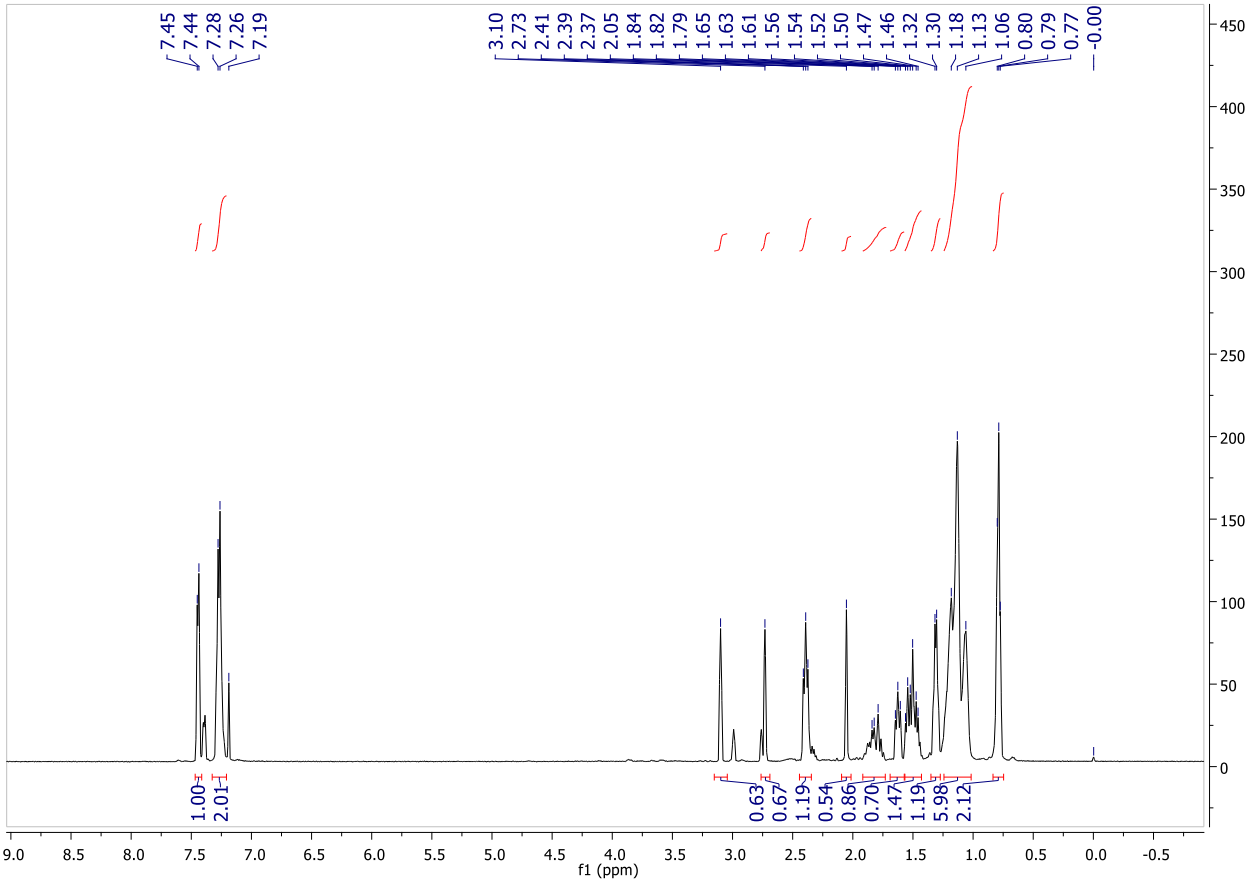
(1*s*,3*S*)-3-cyclohexyl-1-[(*R*)-2-phenyloxiran-2-yl]cyclobutanol **(3g)**

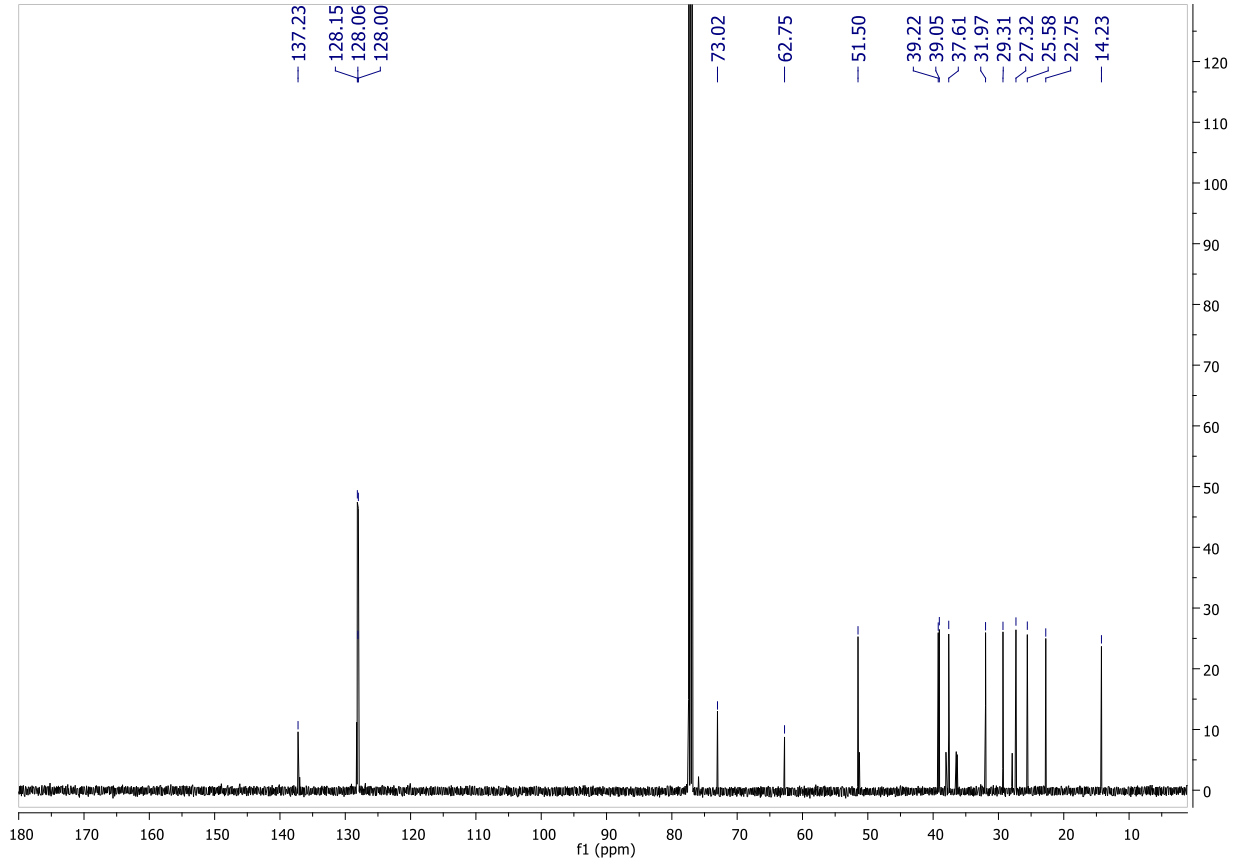


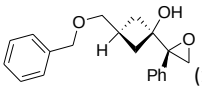




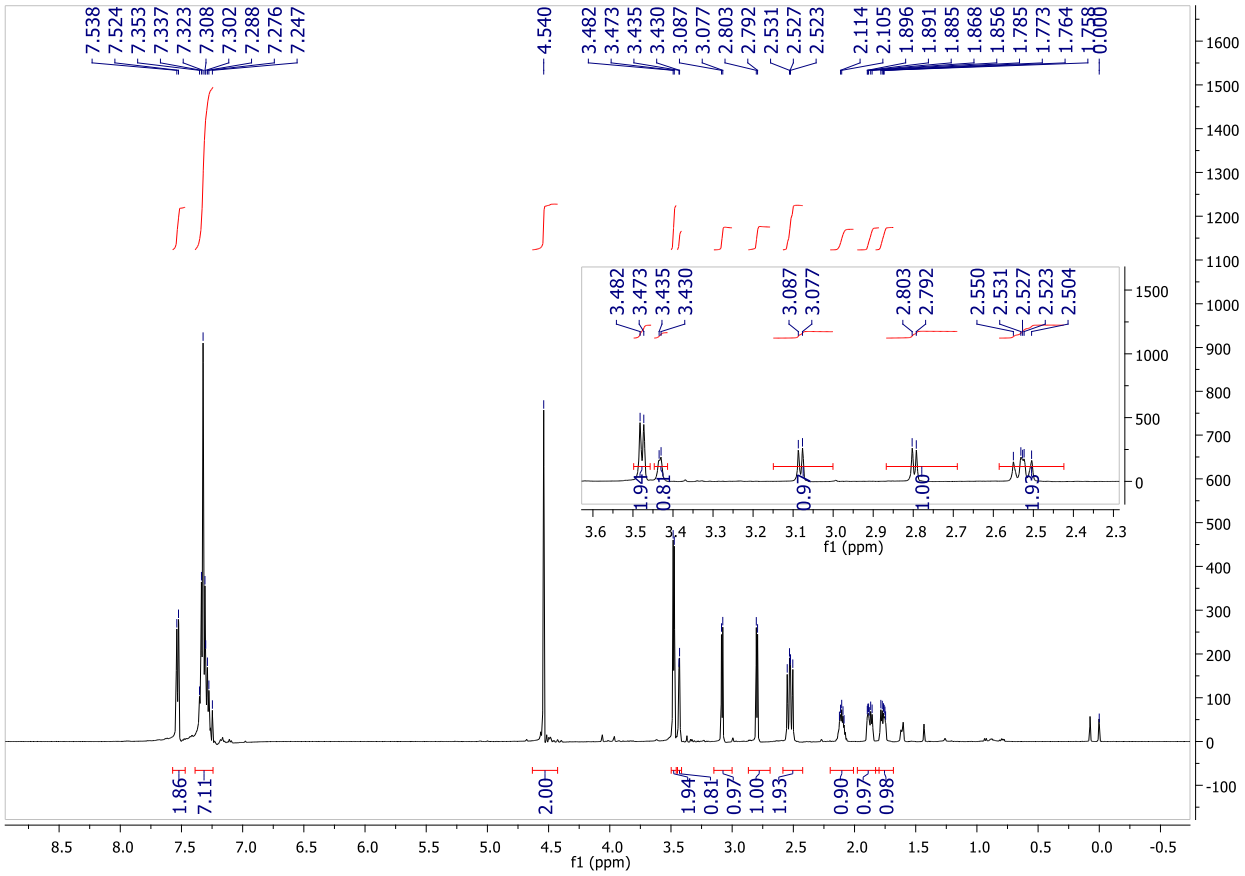
(1*s*,3*S*)-3-Hexyl-1-[(*R*)-2-phenyloxiran-2-yl]cyclobutanol **(3h)**

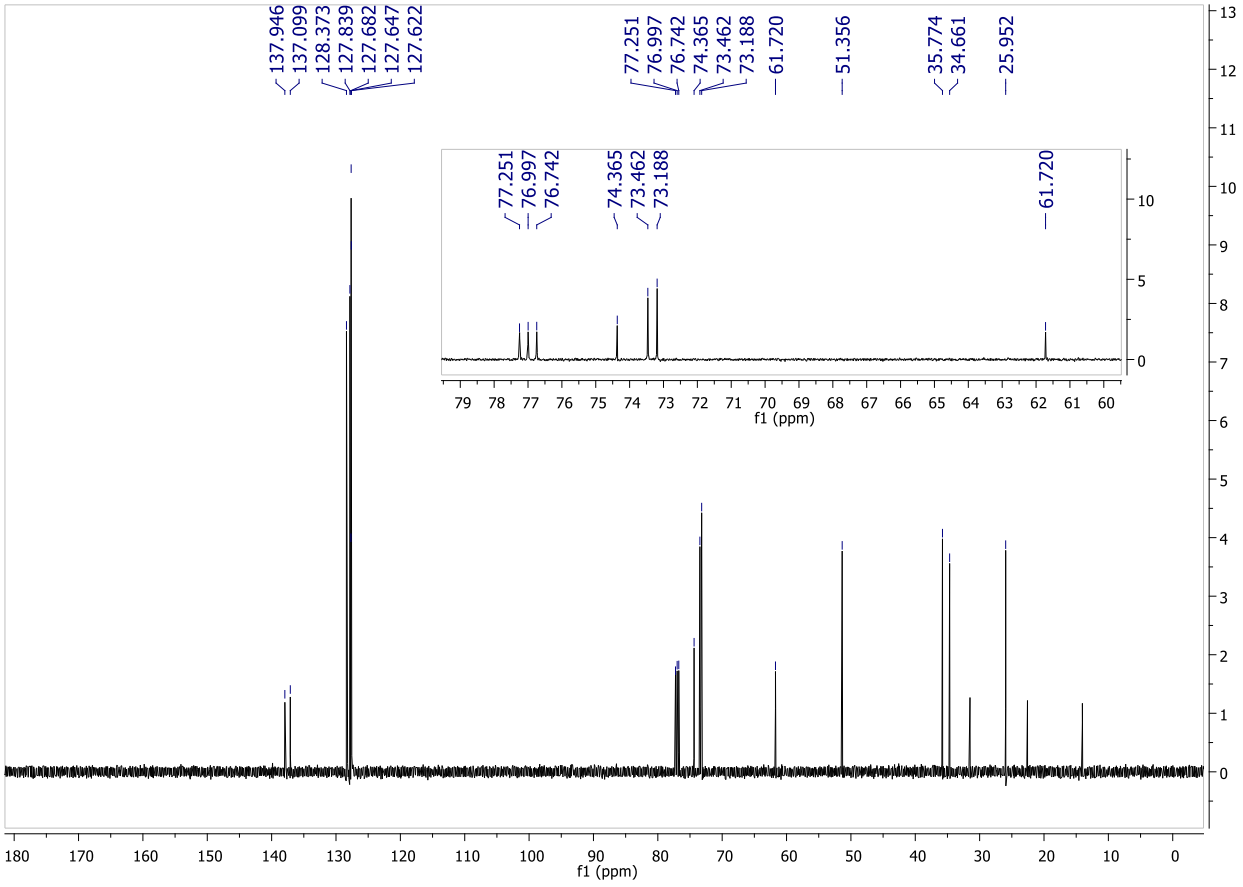


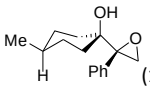




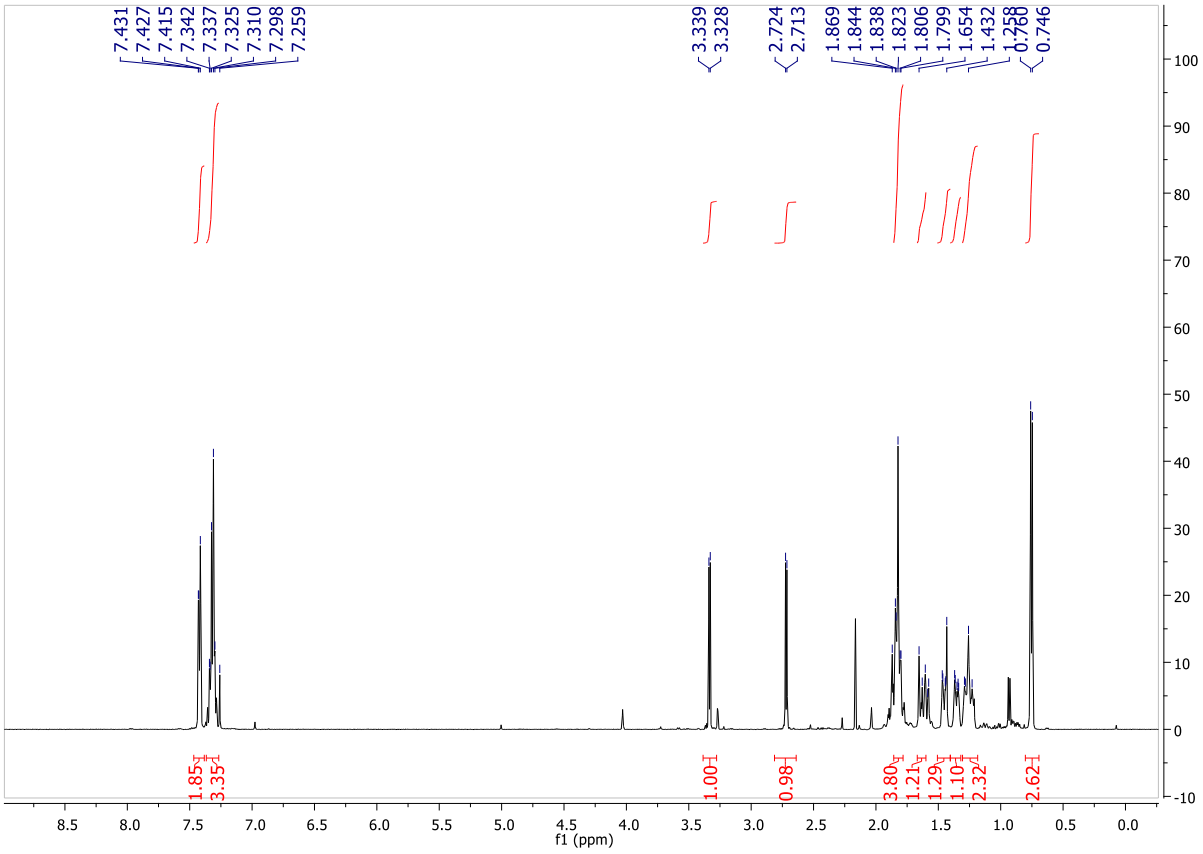
(1*s*,3*S*)-3-(benzyloxymethyl)-1-[(*R*)-2-phenyloxiran-2-yl]cyclobutanol **(3i)**

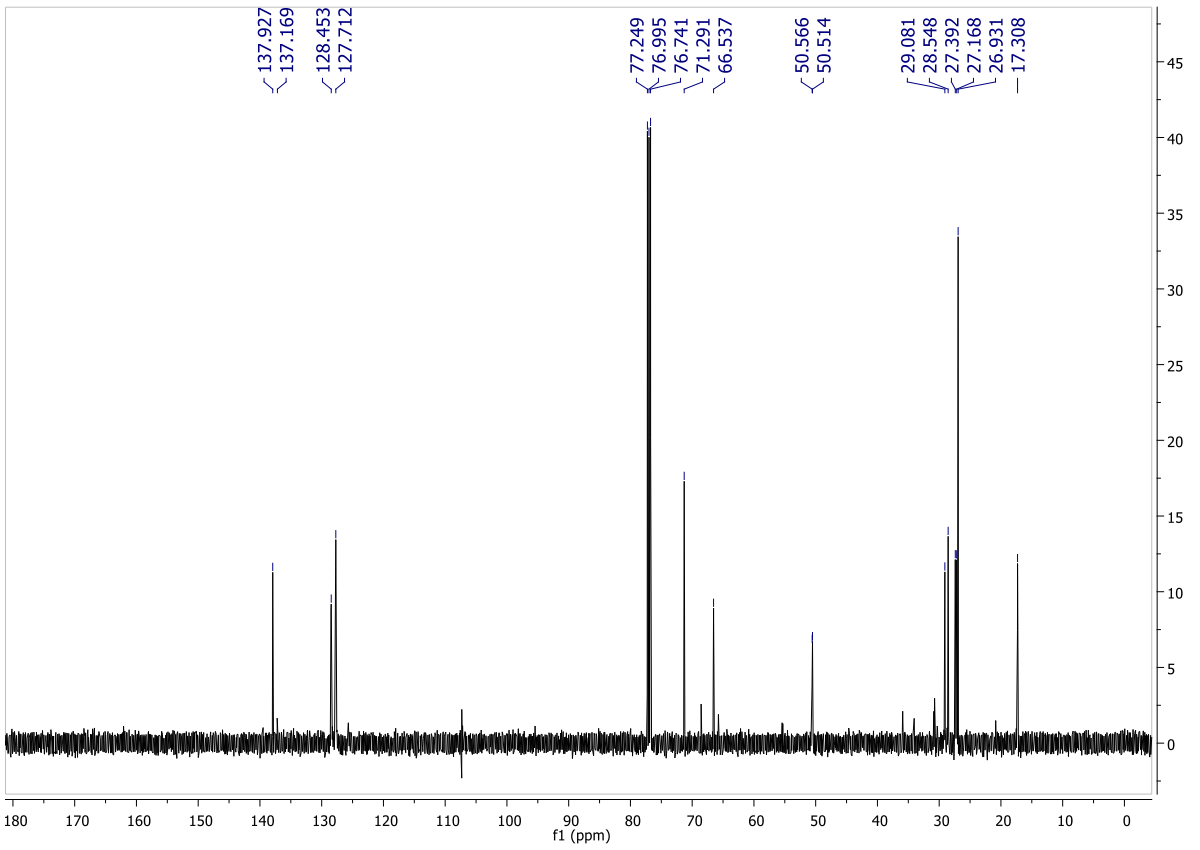


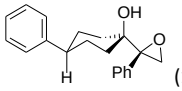




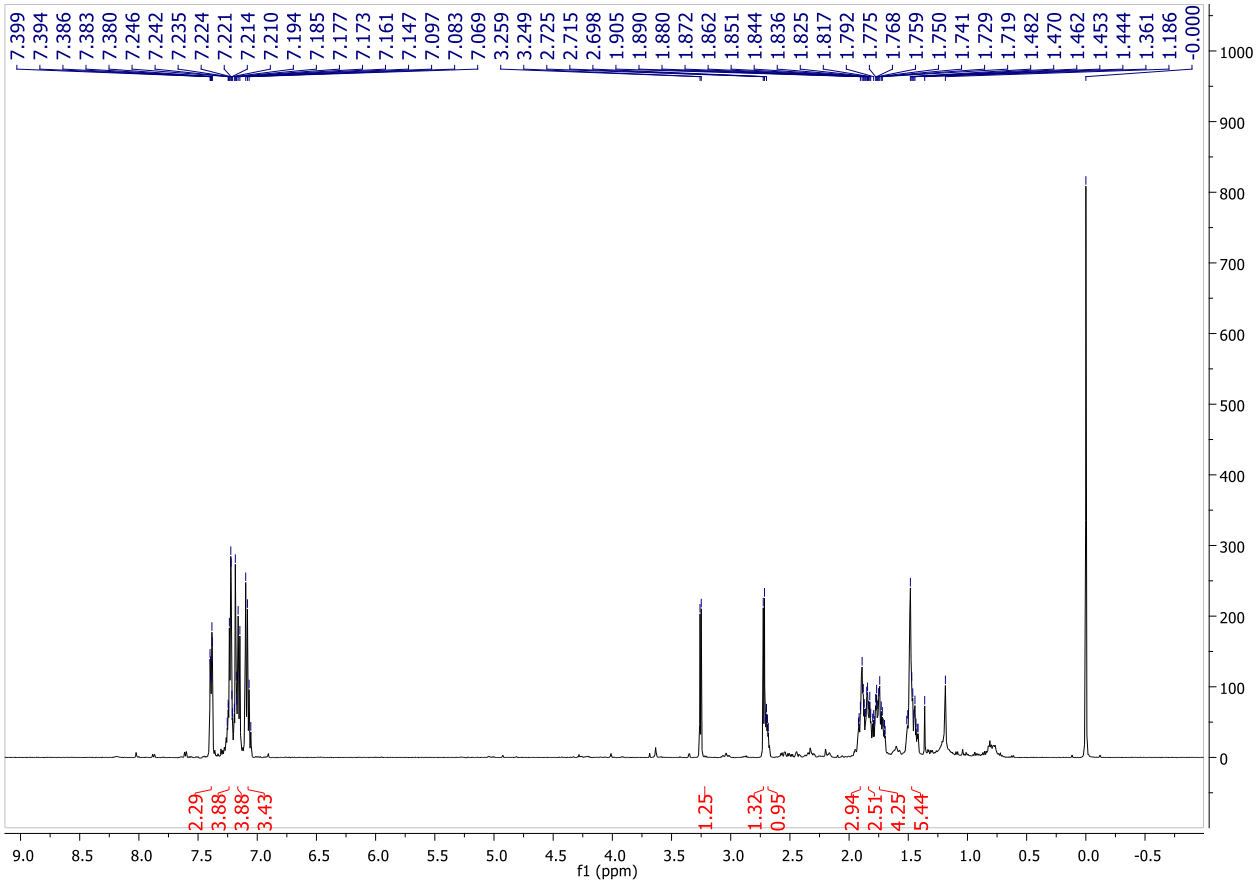
(1*s*,4*S*)-4-methyl-1-[(*R*)-2-phenyloxiran-2-yl]cyclohexanol **(3j)**

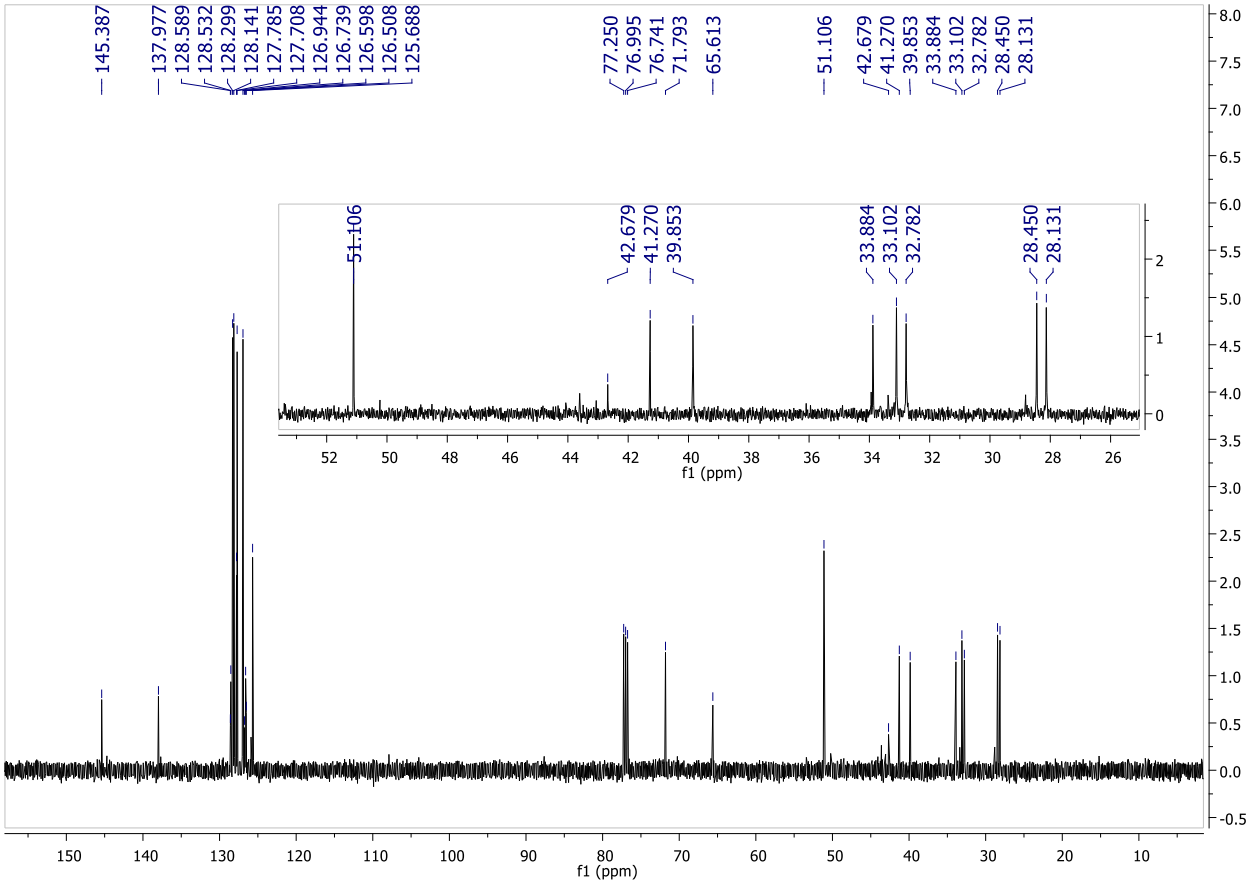


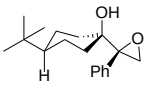




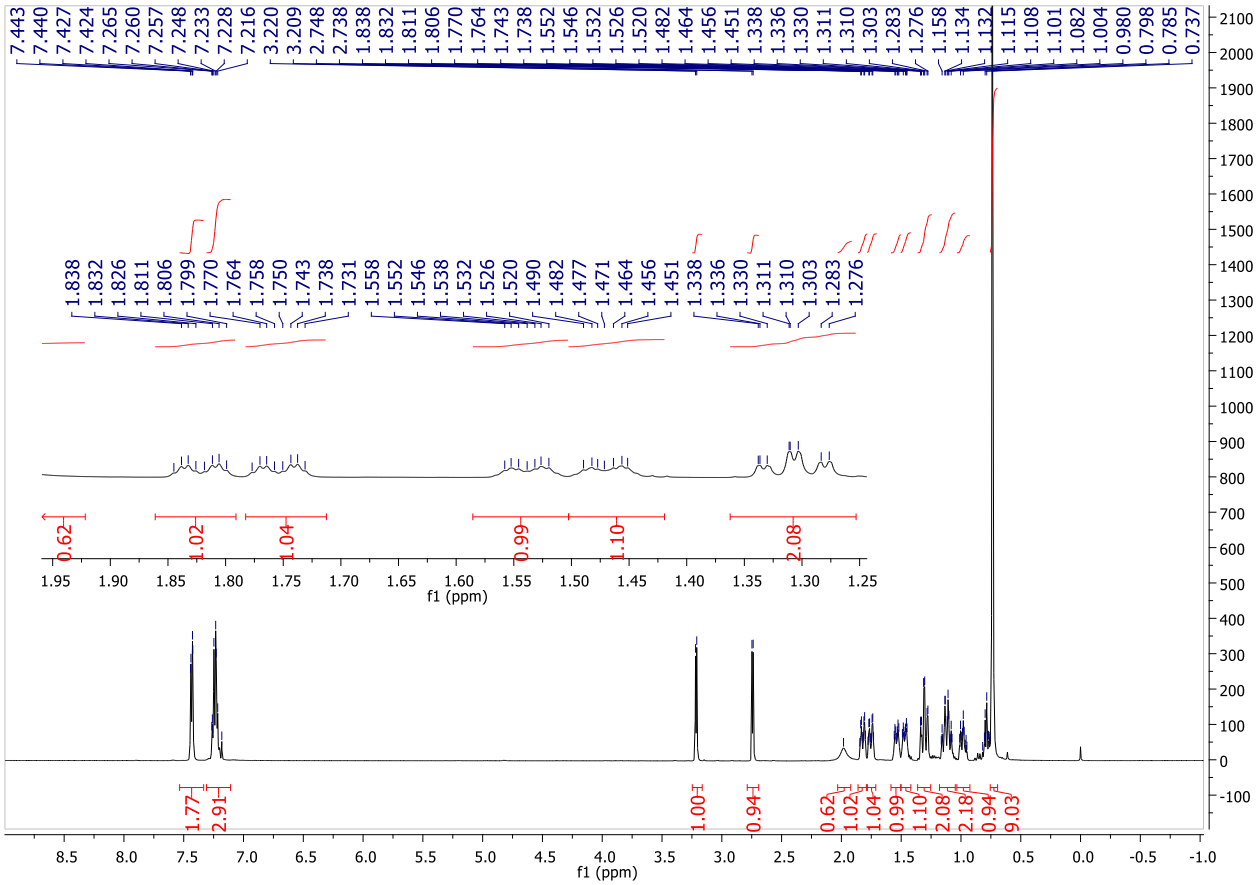
(1*s*,4*S*)-4-phenyl-1-[(*R*)-2-phenyloxiran-2-yl]cyclohexanol **(3k)**

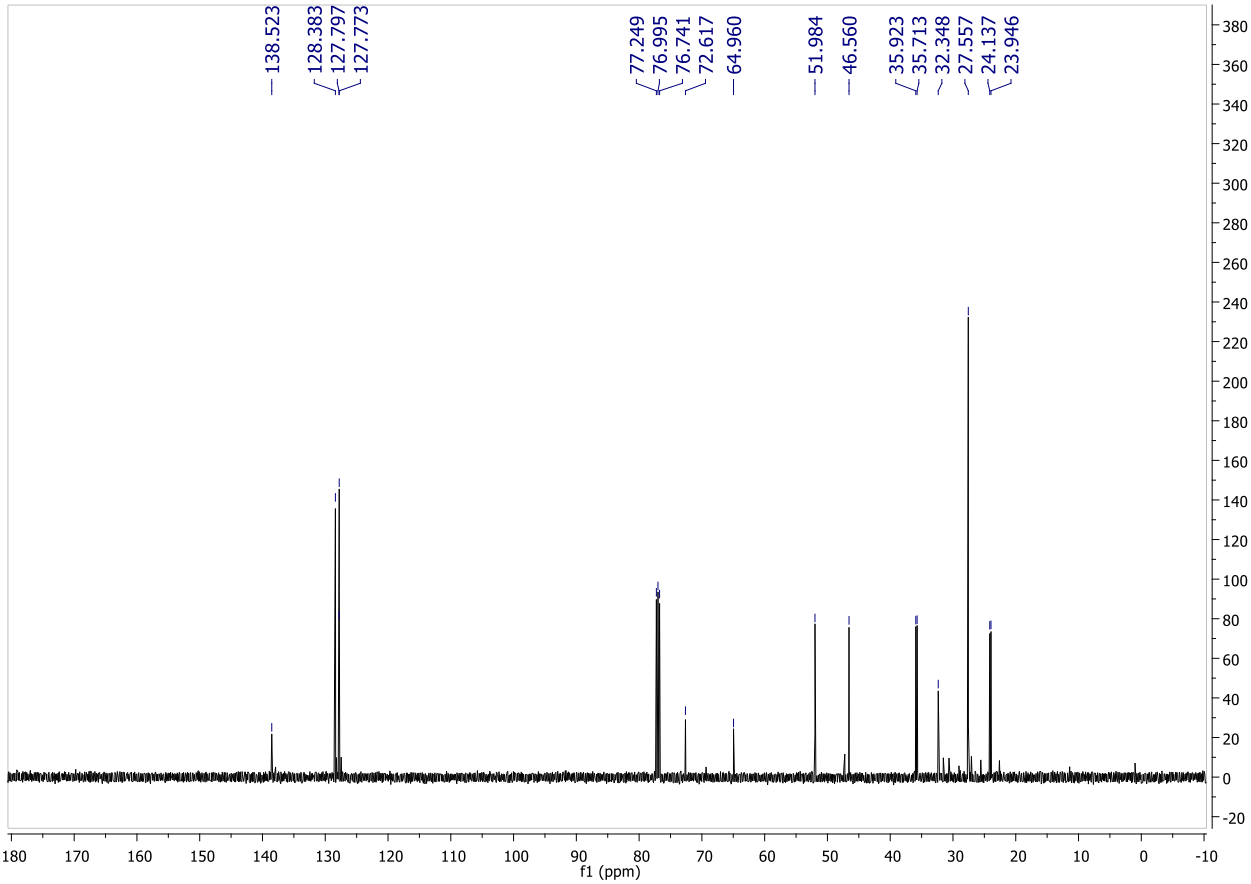


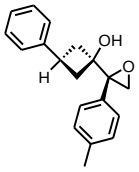




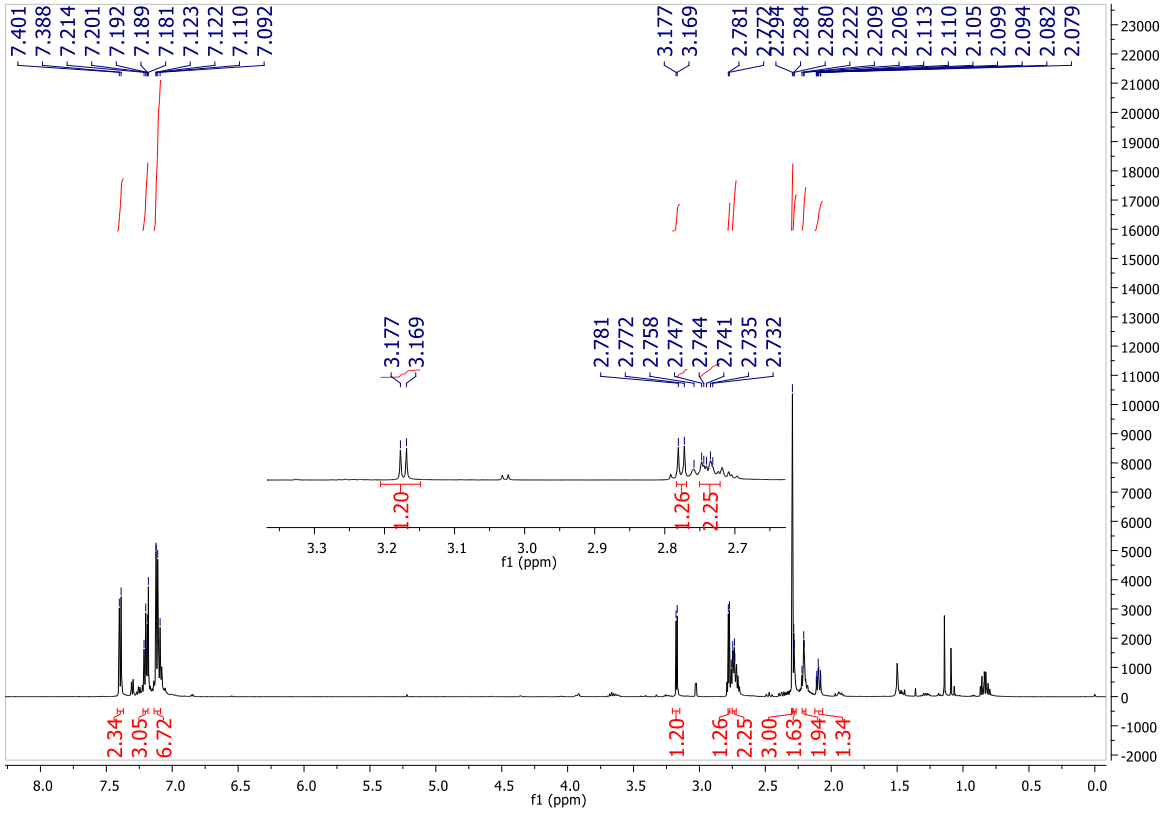
(1*s*,4*S*)-4-tert-butyl-1-[(*R*)-2-phenyloxiran-2-yl]cyclohexanol **(3l)**

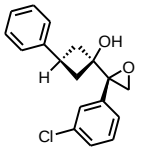


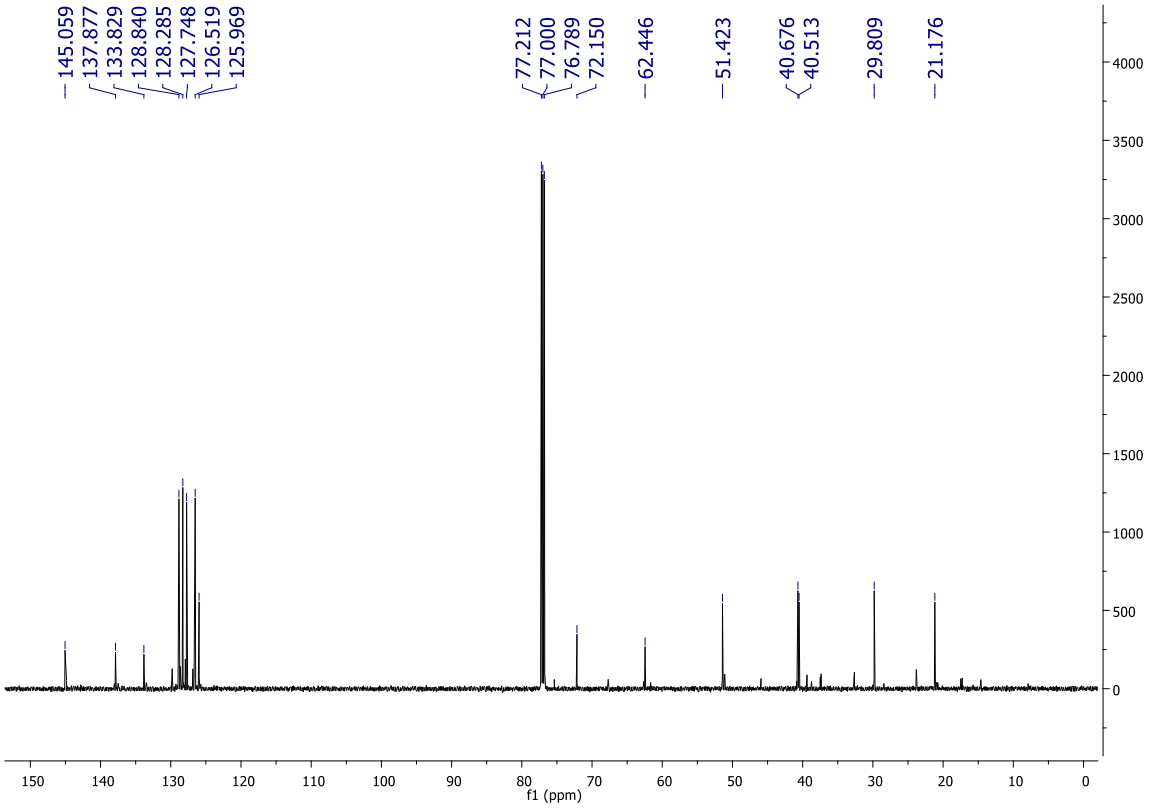




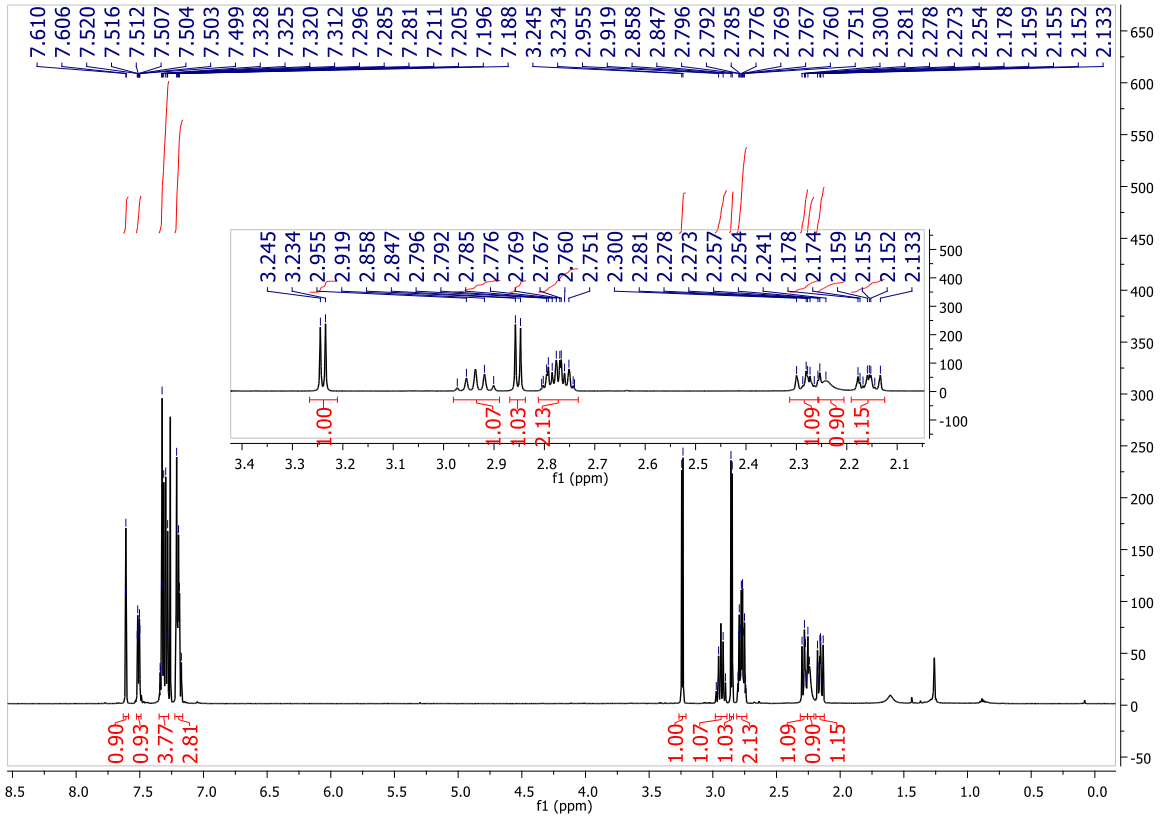
(1*s*,3*S*)-1-[(*R*)-(3-Phenyl-1-(2-p-tolyl-oxiranyl)-cyclobutanol **(3ab)**

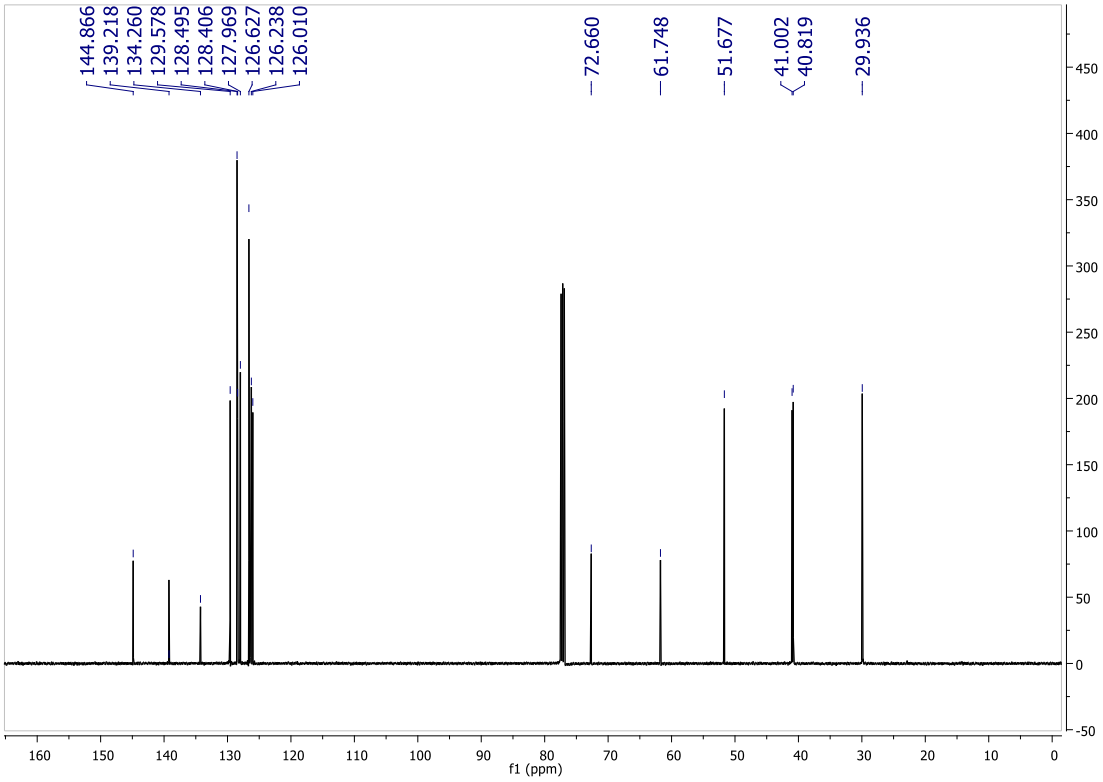


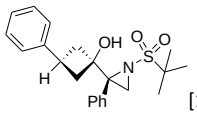




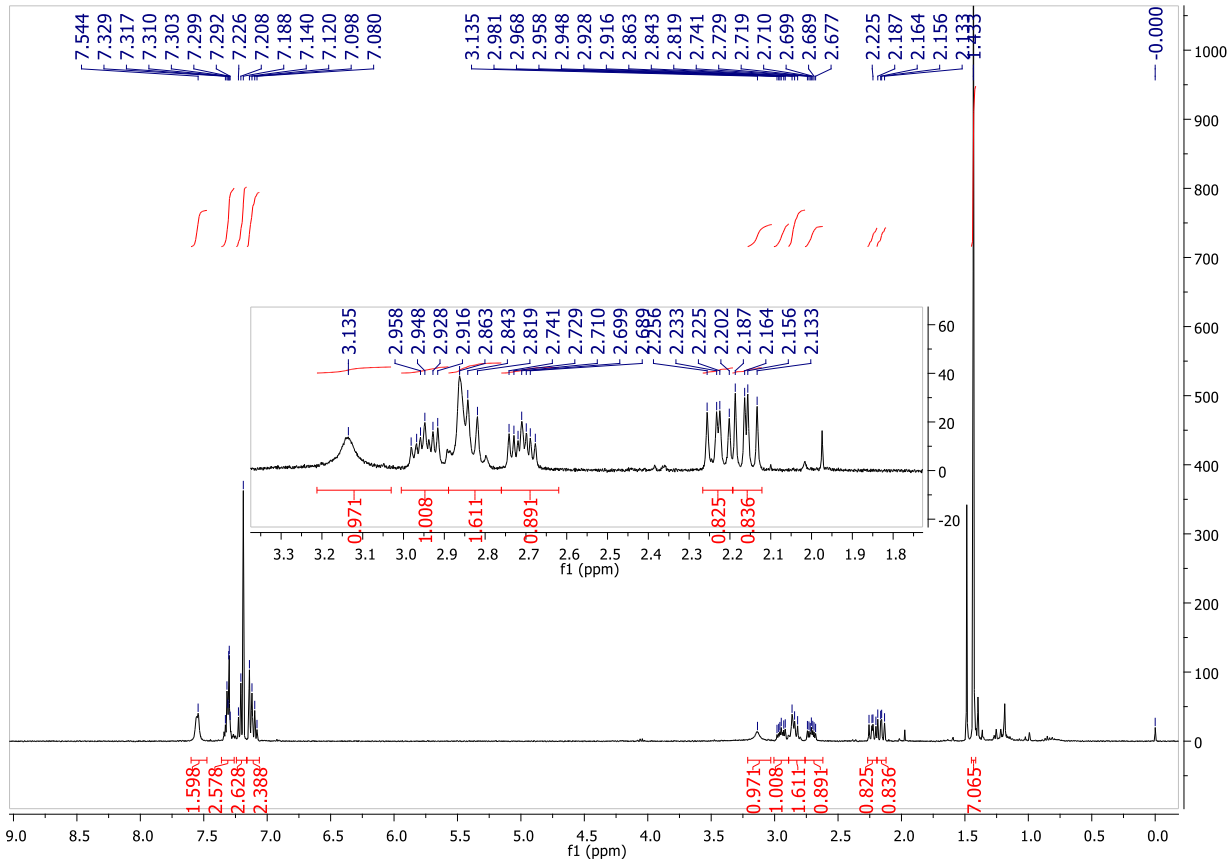
(1*s*,3*S*)-1-[(3-Chloro-phenyl)-oxiranyl]-3-phenyl-cyclobutanol **(3ad)**

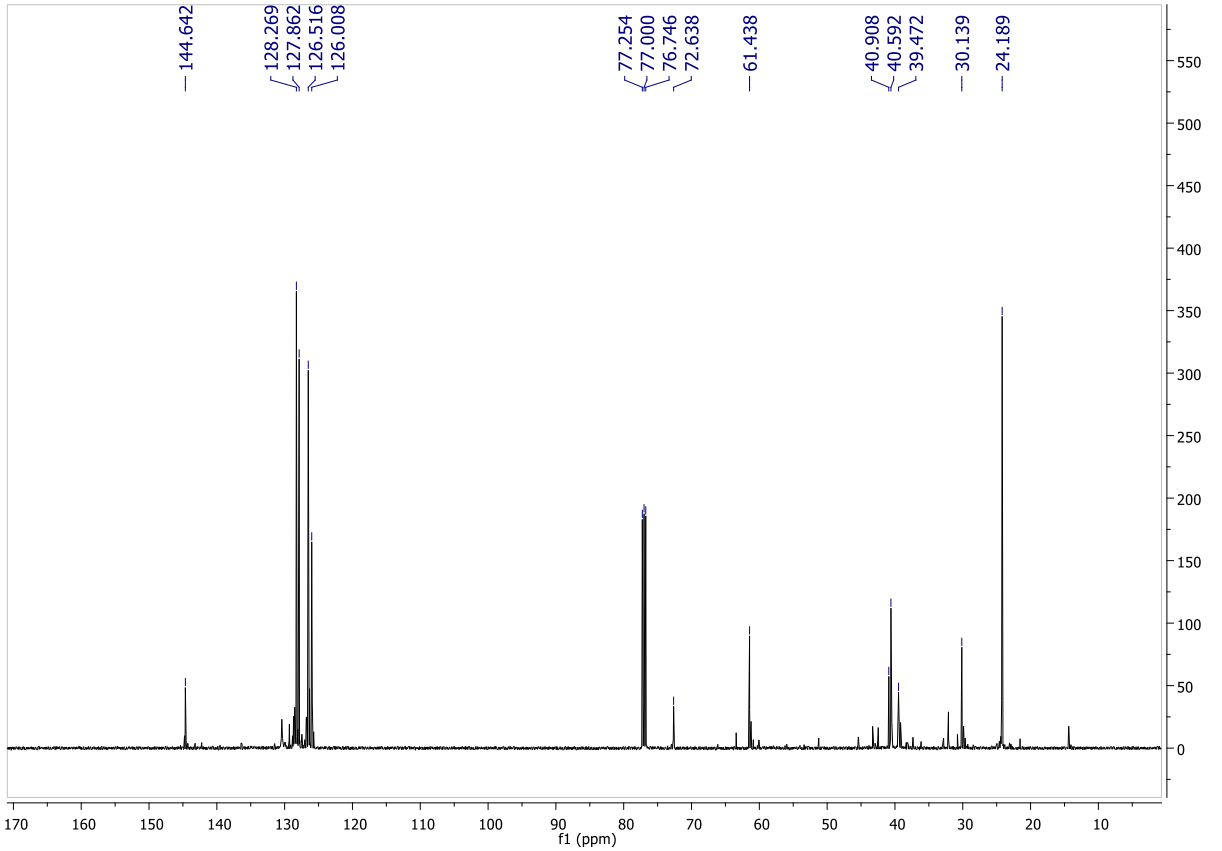




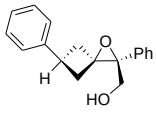


[1-(*tert*-butylsulfonyl)-2-phenylaziridin-2-yl]-3-phenylcyclobutanol **(6)**

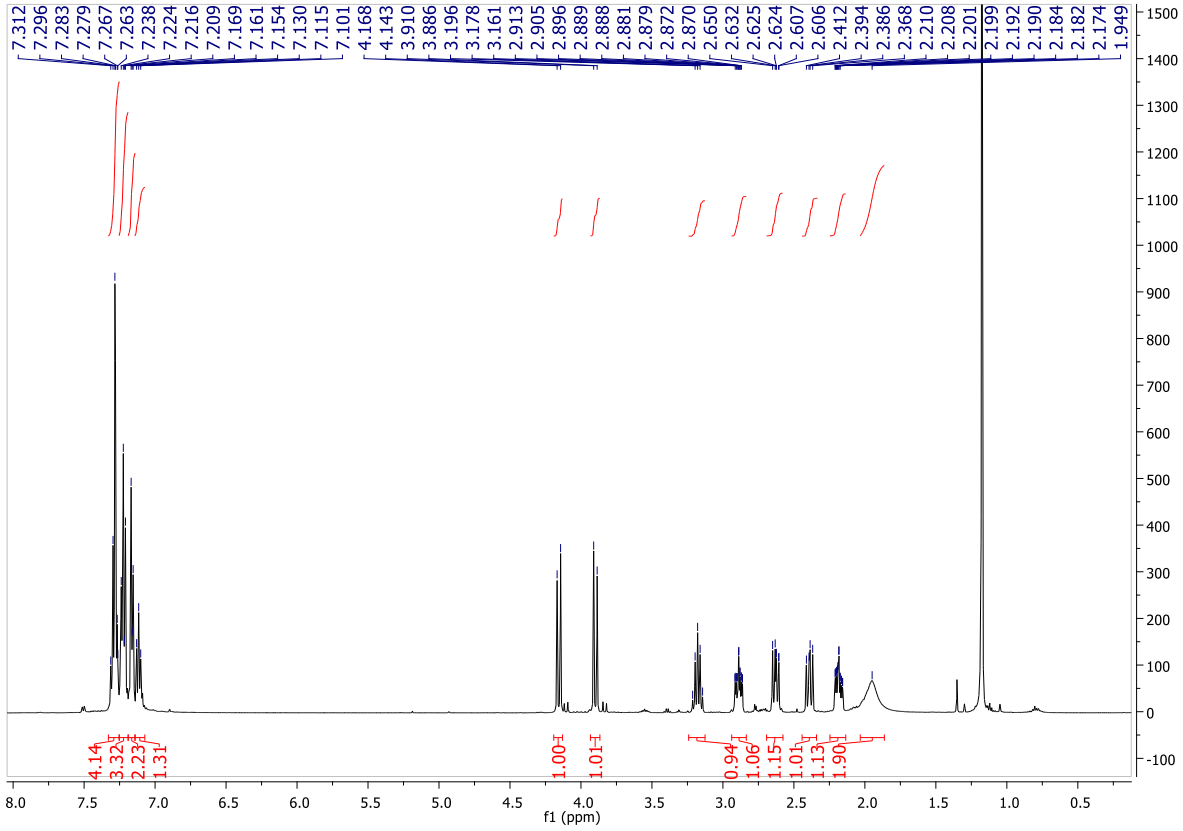


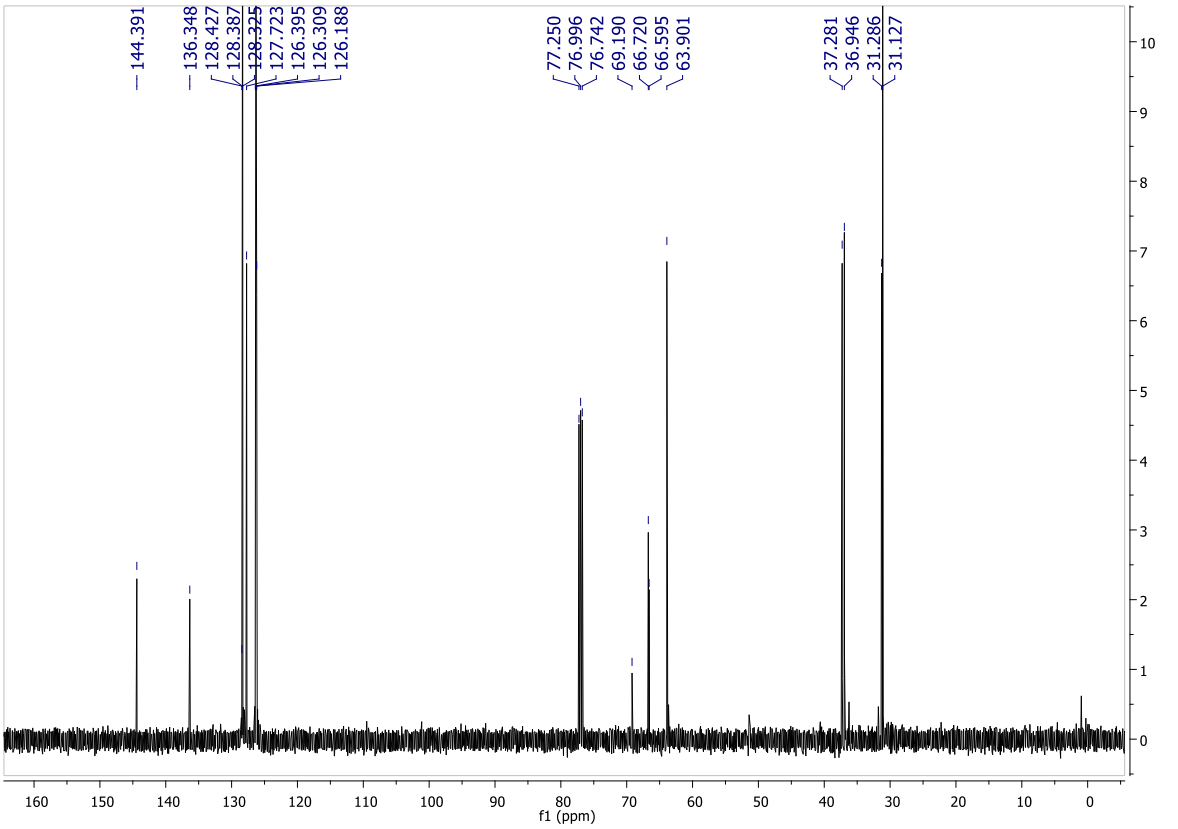


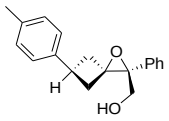
8. ^{1}H and ^{13}C NMR spectra of compounds 4a-k, 4ab, 4ad, 5, and 7



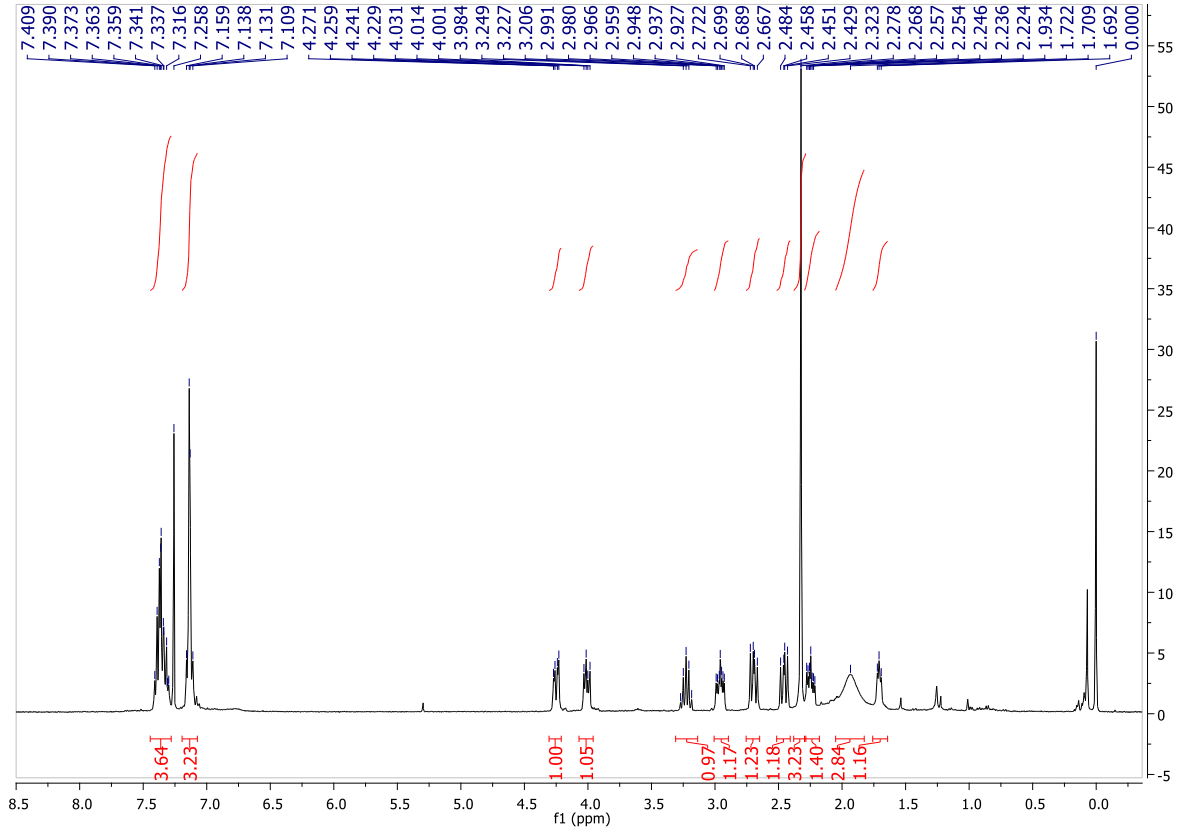
[(2*S*,3*s*,5*R*)-2,5-diphenyl-1-oxaspiro[2.3]hexan-2-yl]methanol **(4a)**

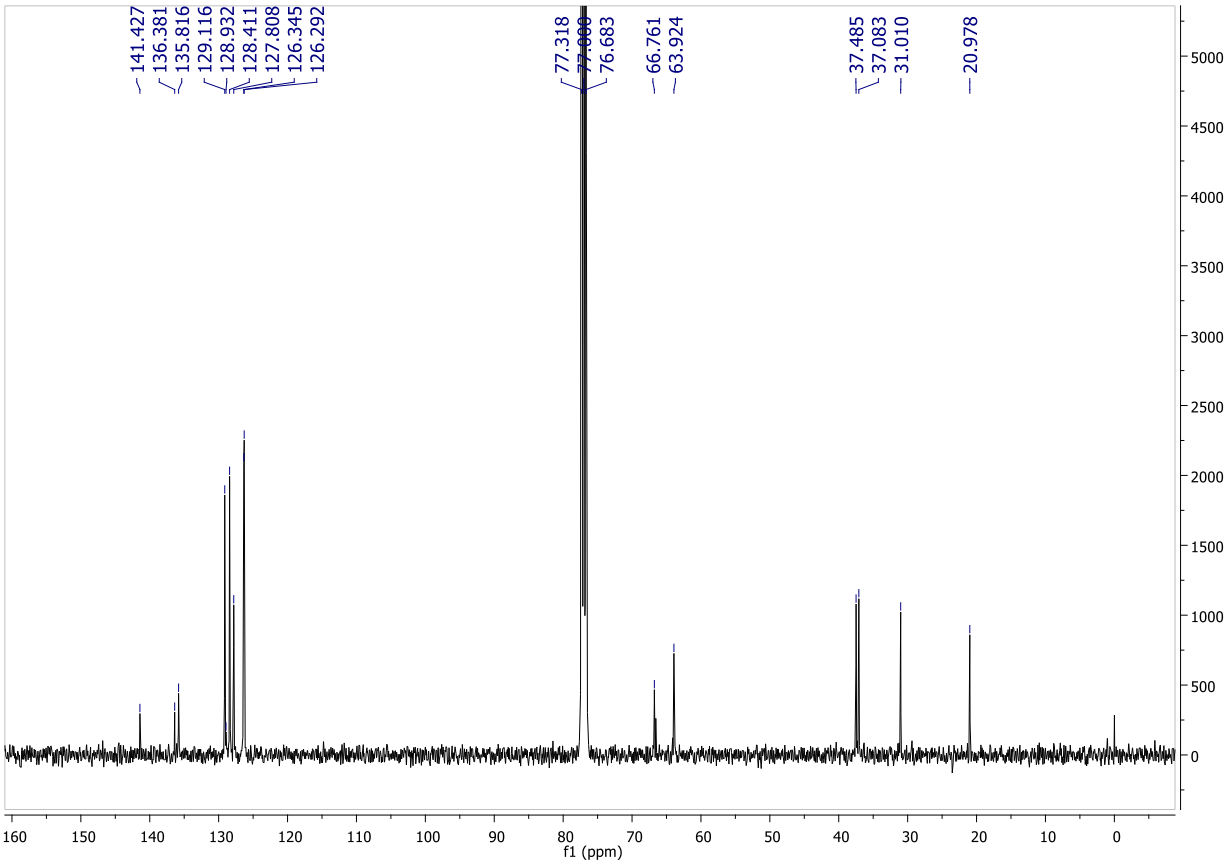


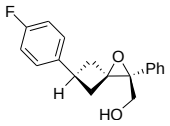




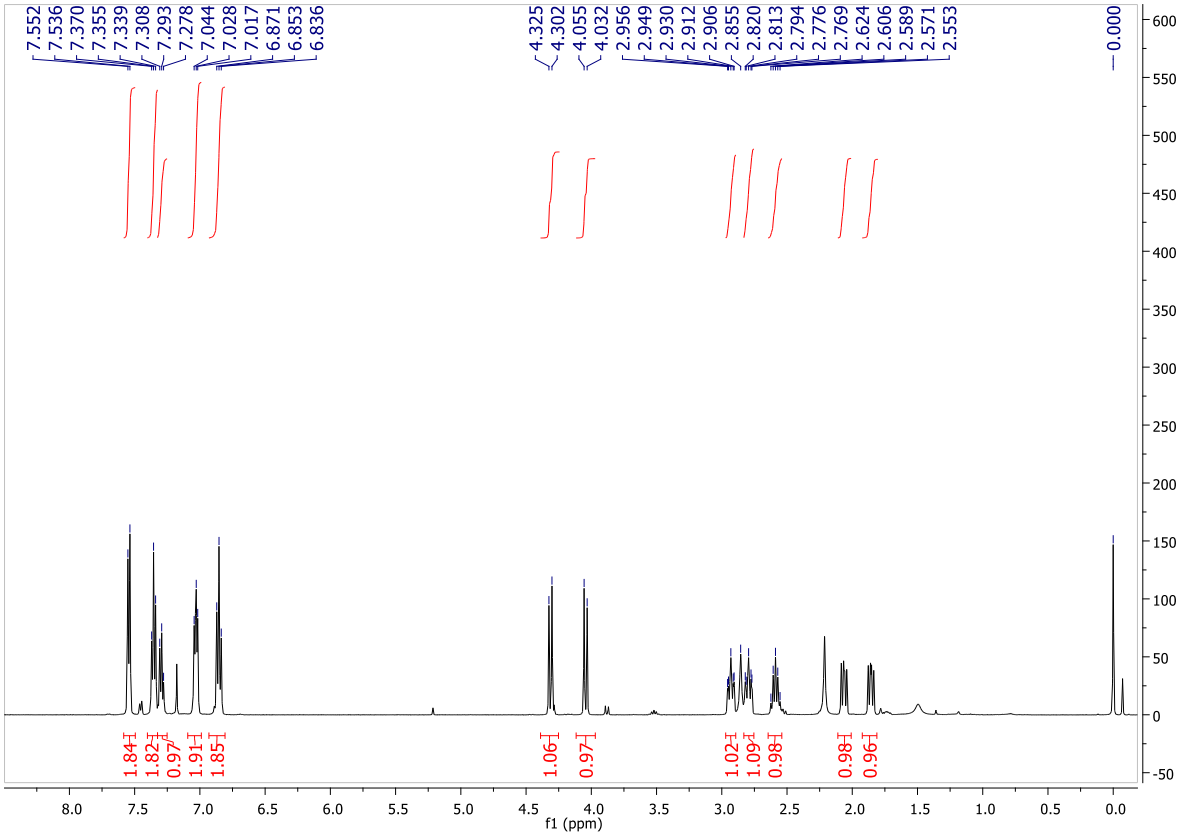
[(2*S*,3*s*,5*R*)-2-Phenyl-5-(p-tolyl)-1-oxaspiro[2.3]hexan-2-yl]methanol **(4b)**

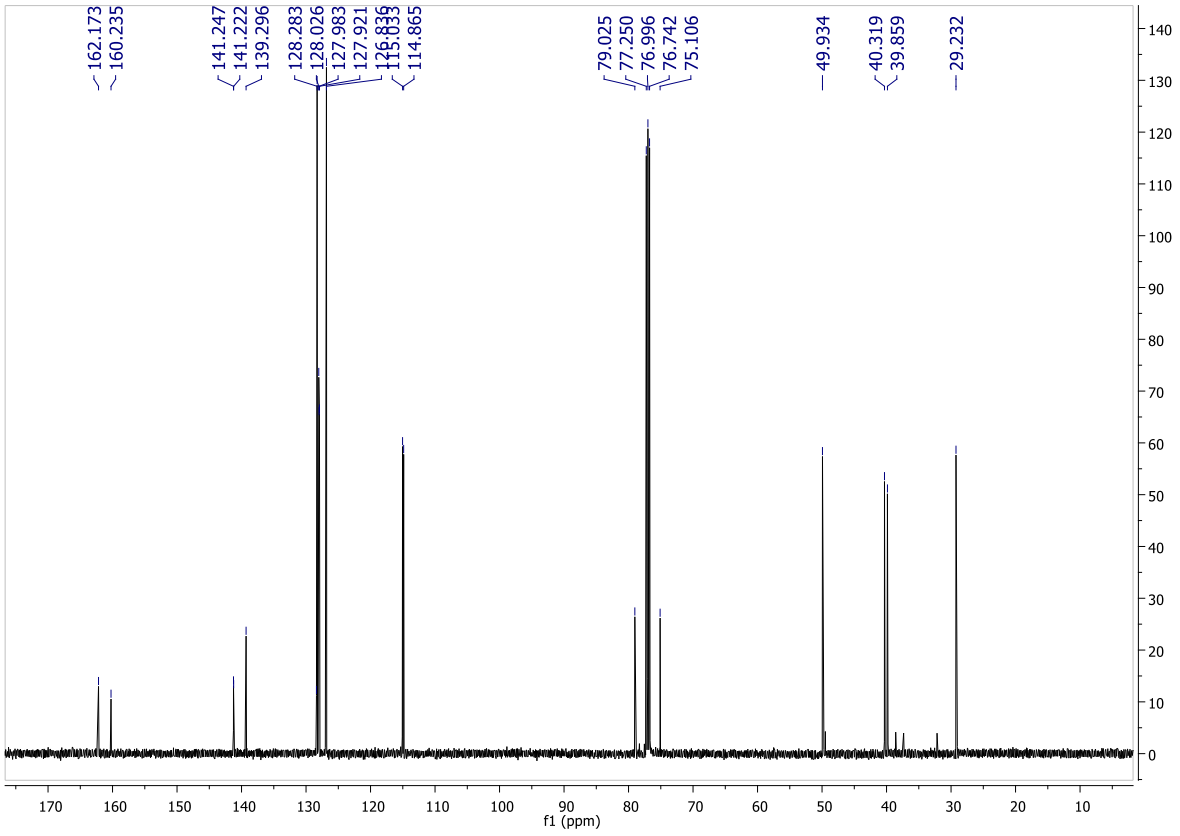


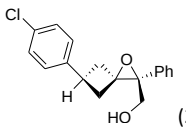




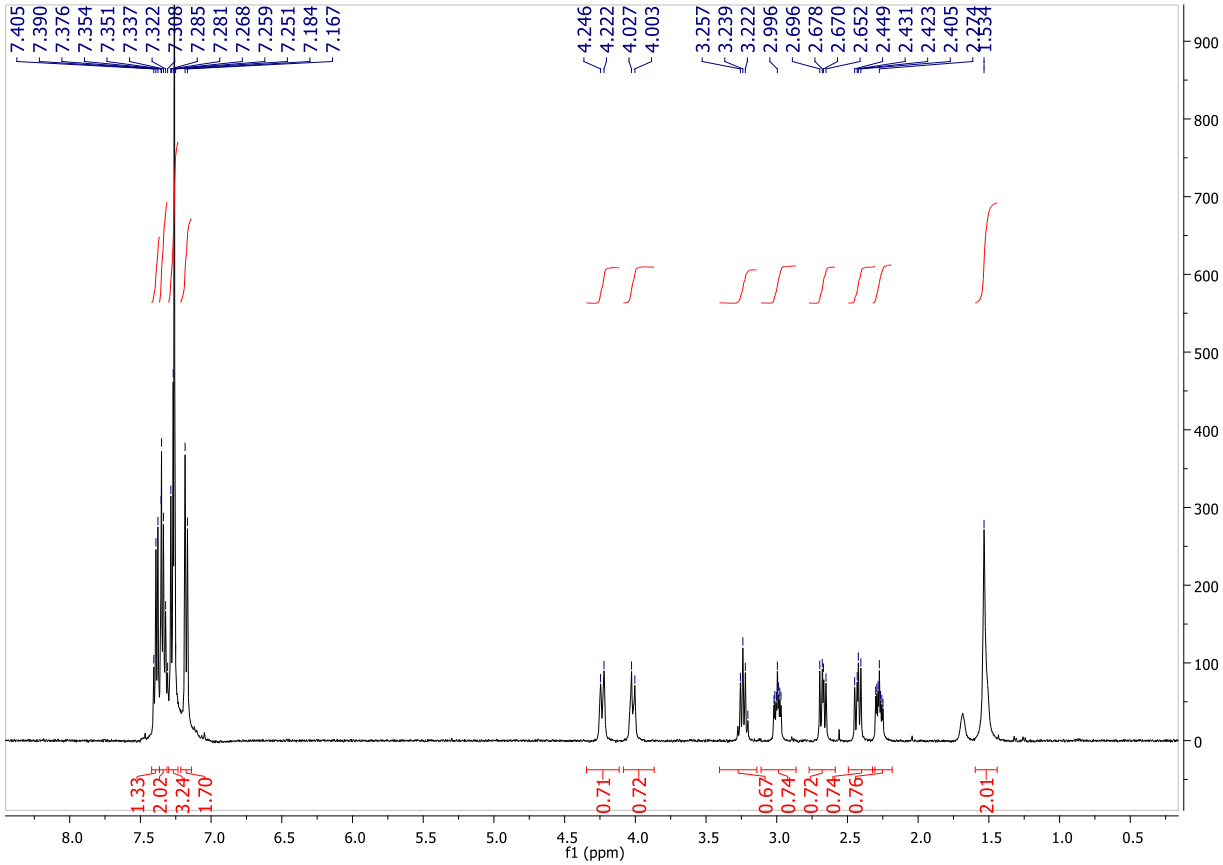
(2*S*,3*s*,5*R*)-[5-(4-Fluorophenyl)-2-phenyl-1-oxaspiro[2.3]hexan-2-yl]methanol **(4c)**

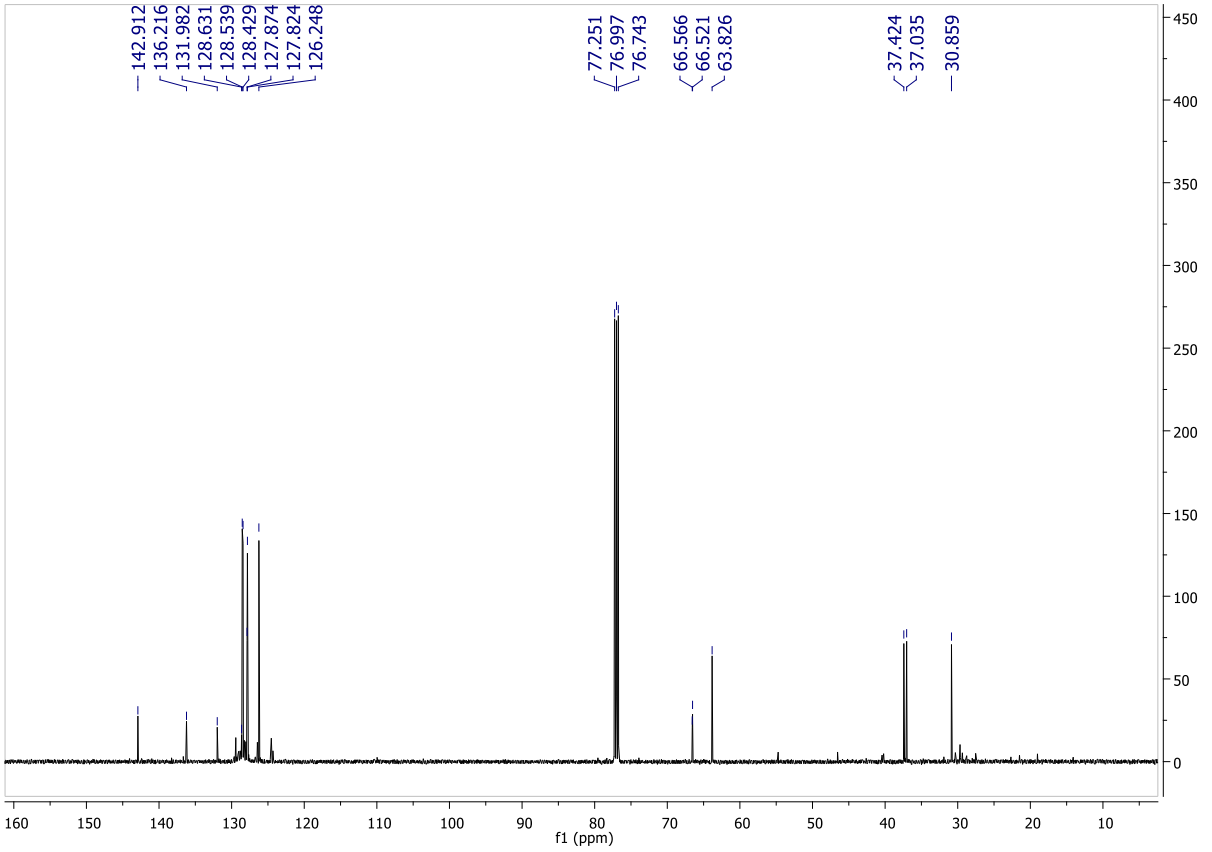


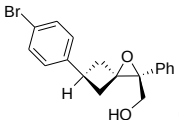




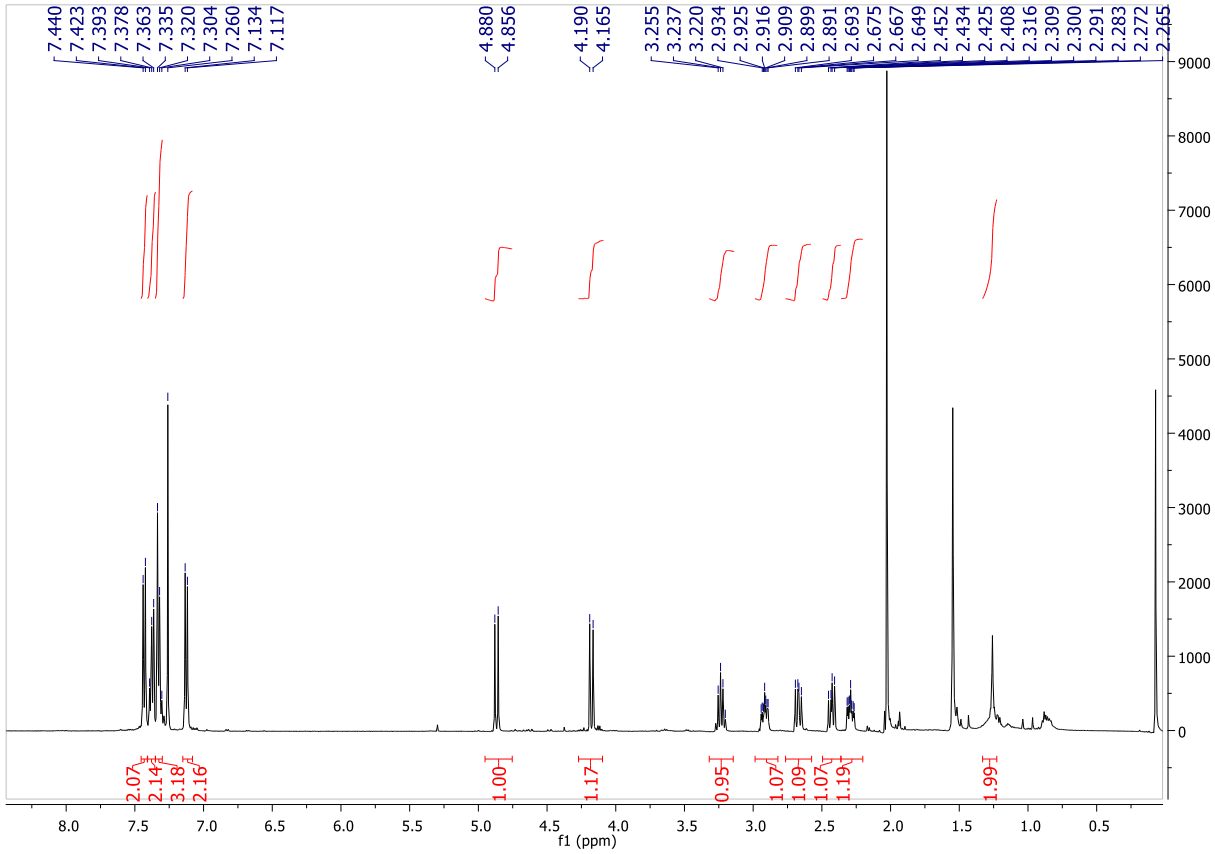
(2*S*,3*s*,5*R*)-[5-(4-Chlorophenyl)-2-phenyl-1-oxaspiro[2.3]hexan-2-yl]methanol **(4d)**

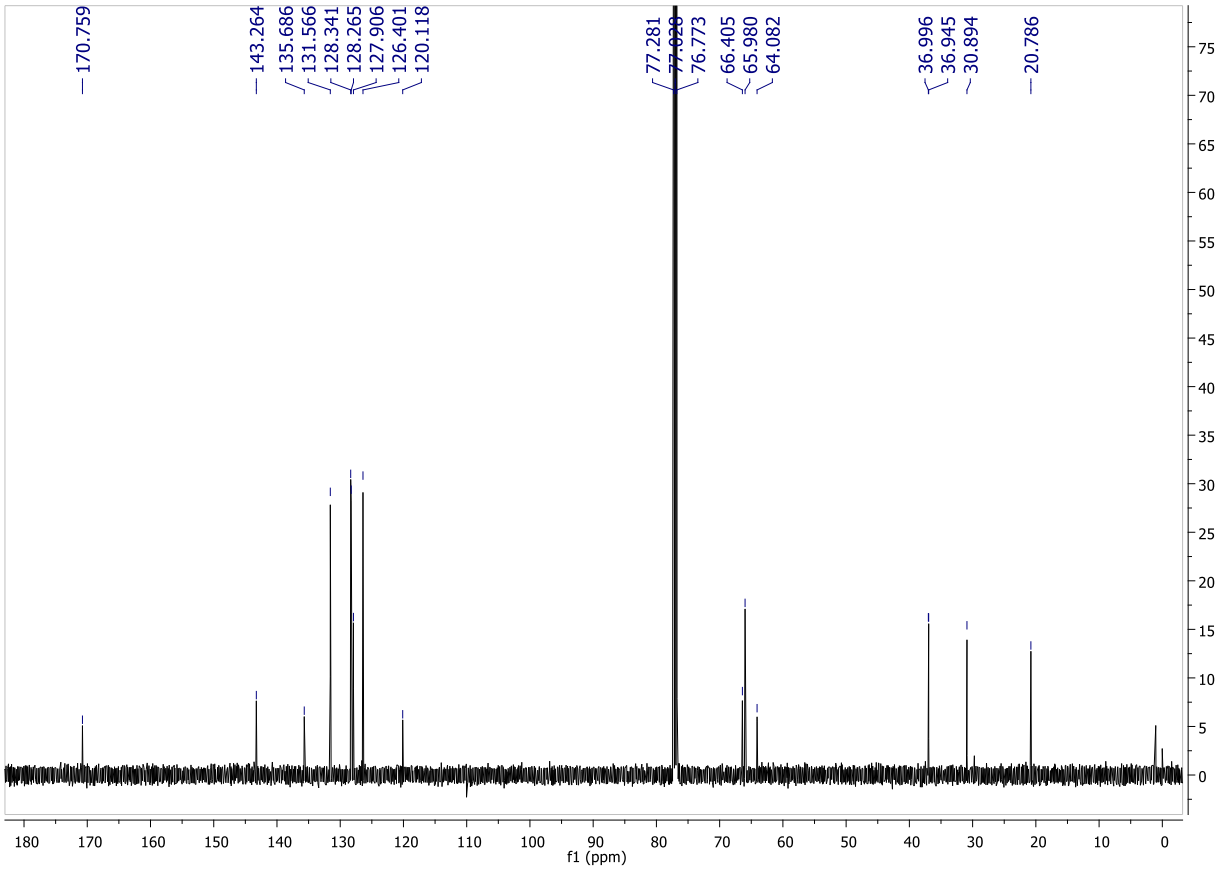


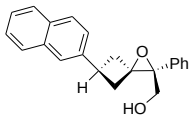




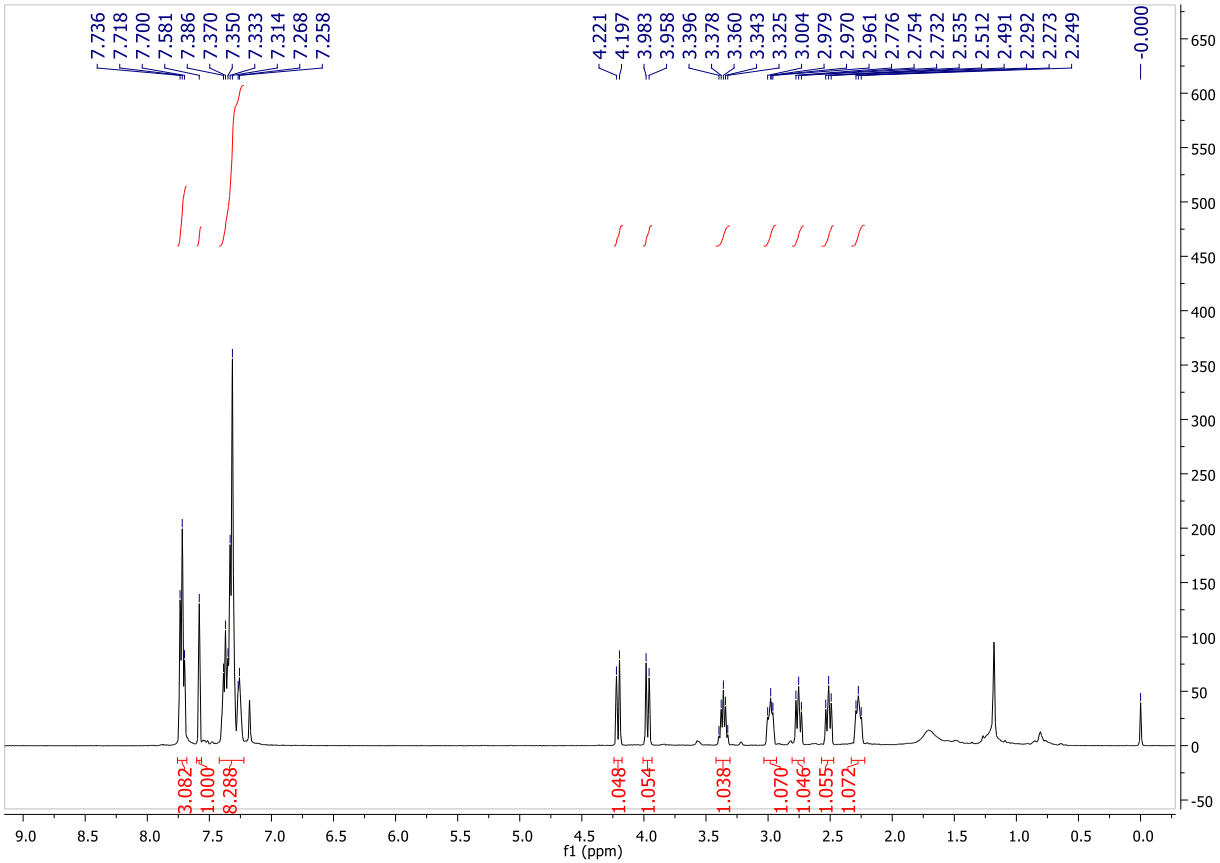
(2*S*,3*s*,5*R*)-[5-(4-Bromophenyl)-2-phenyl-1-oxaspiro[2.3]hexan-2-yl]methanol **(4e)**

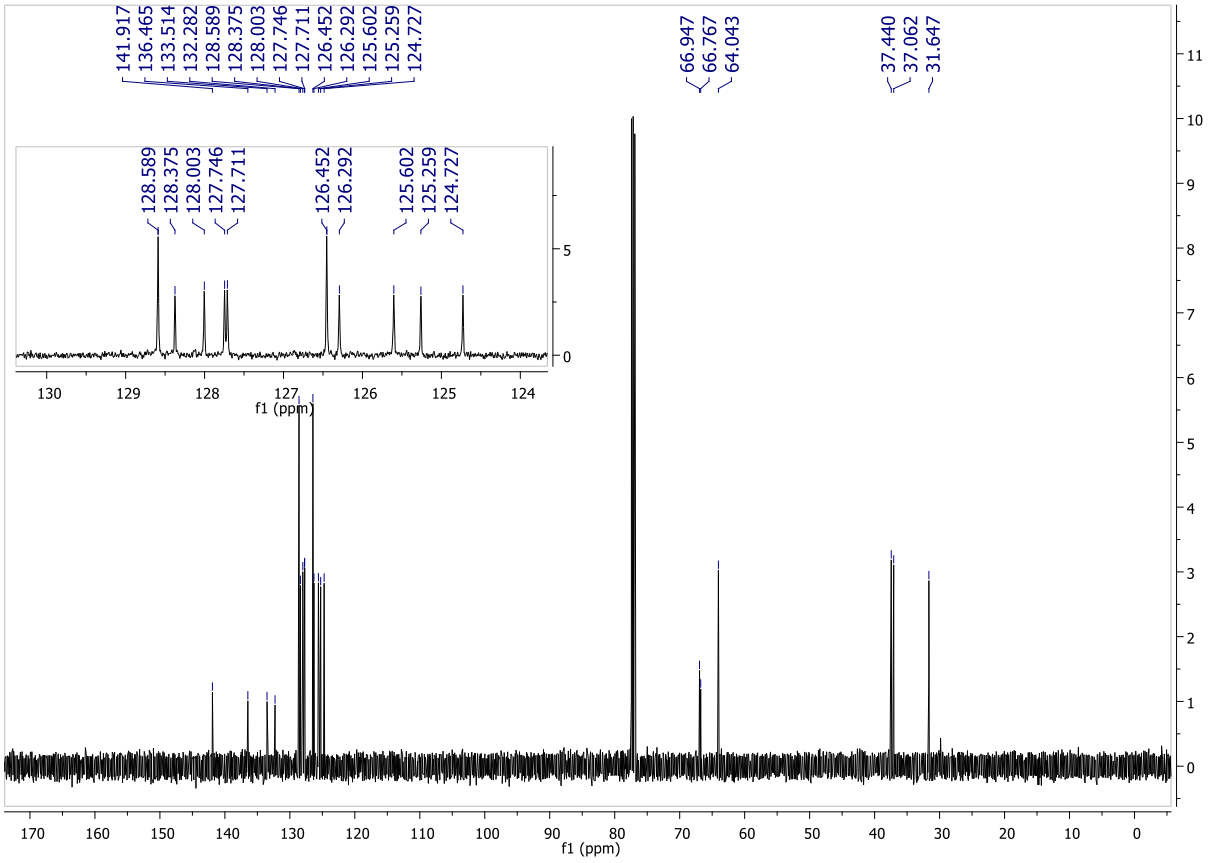


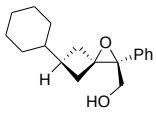




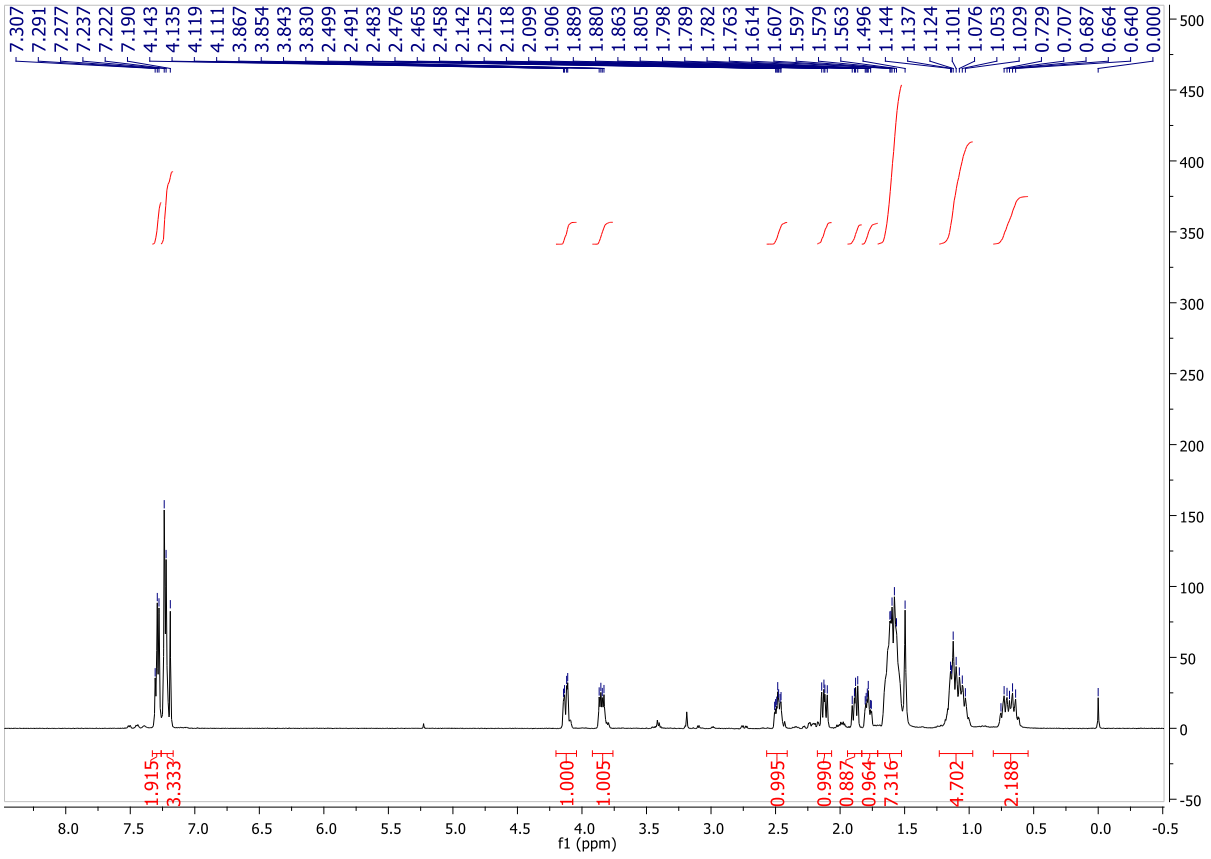
[(2*S*,3*s*,5*R*)-5-(Naphthalen-2-yl)-2-phenyl-1-oxaspiro[2.3]hexan -2-yl)methanol **(4f)**

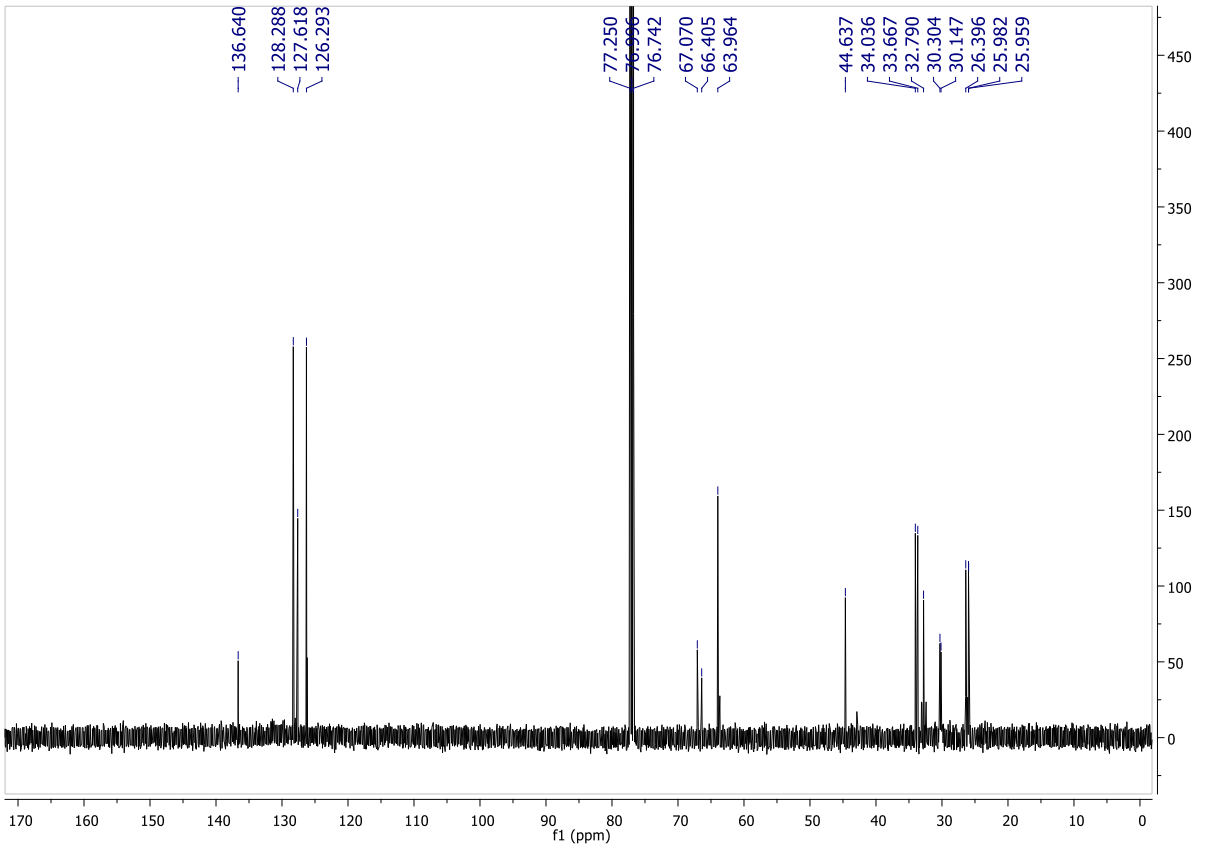


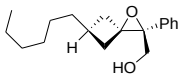




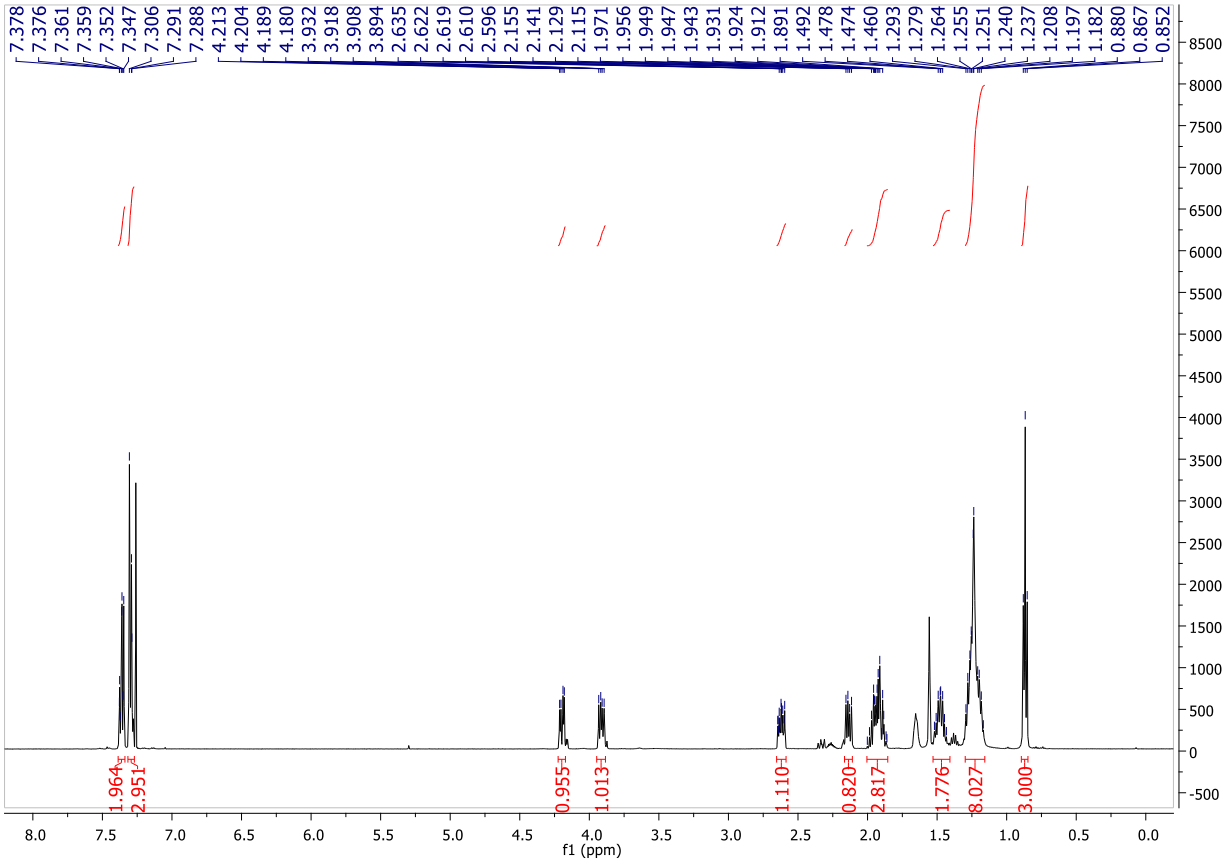
[(2*S*,3*s*,5*R*)-5-Cyclohexyl-2-phenyl-1-oxa-spiro[2.3]hexan-2-yl]methanol **(4g)**

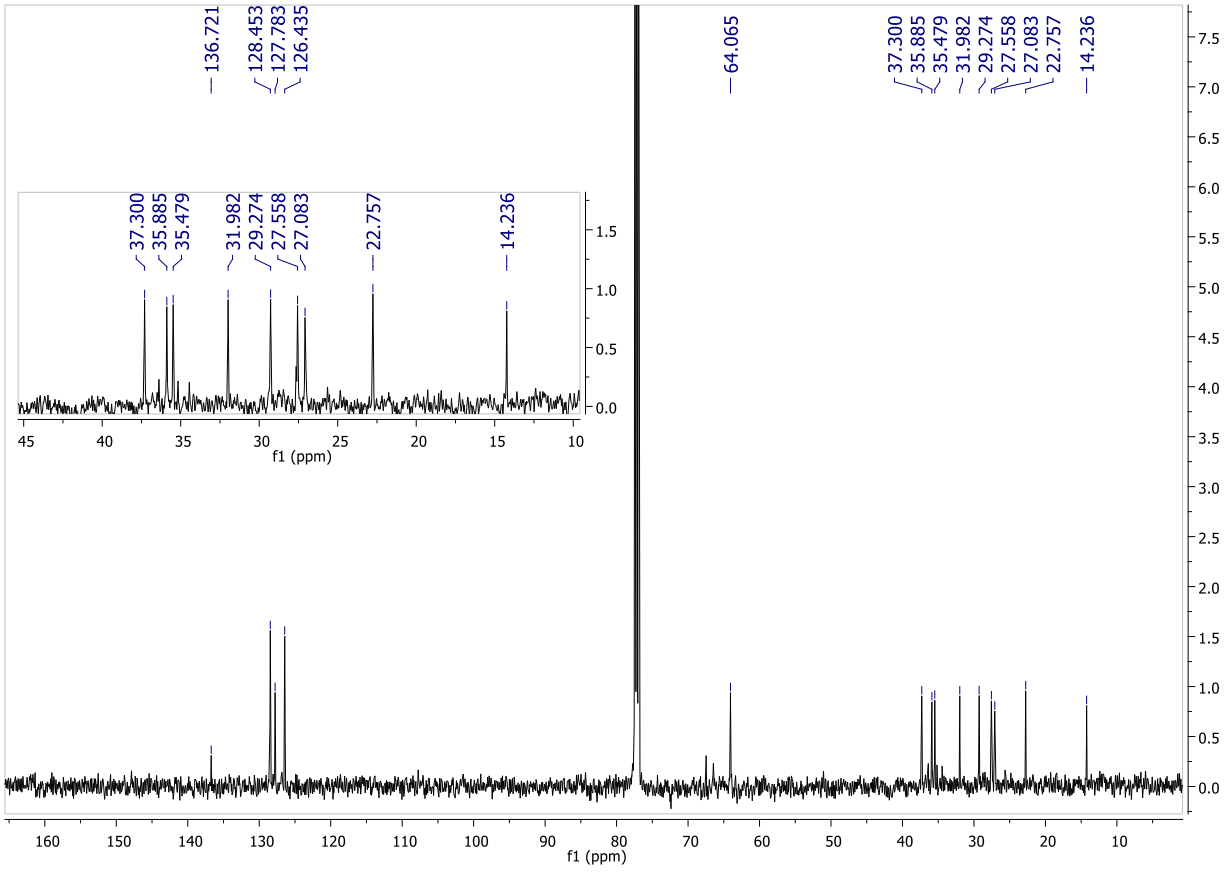


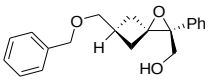




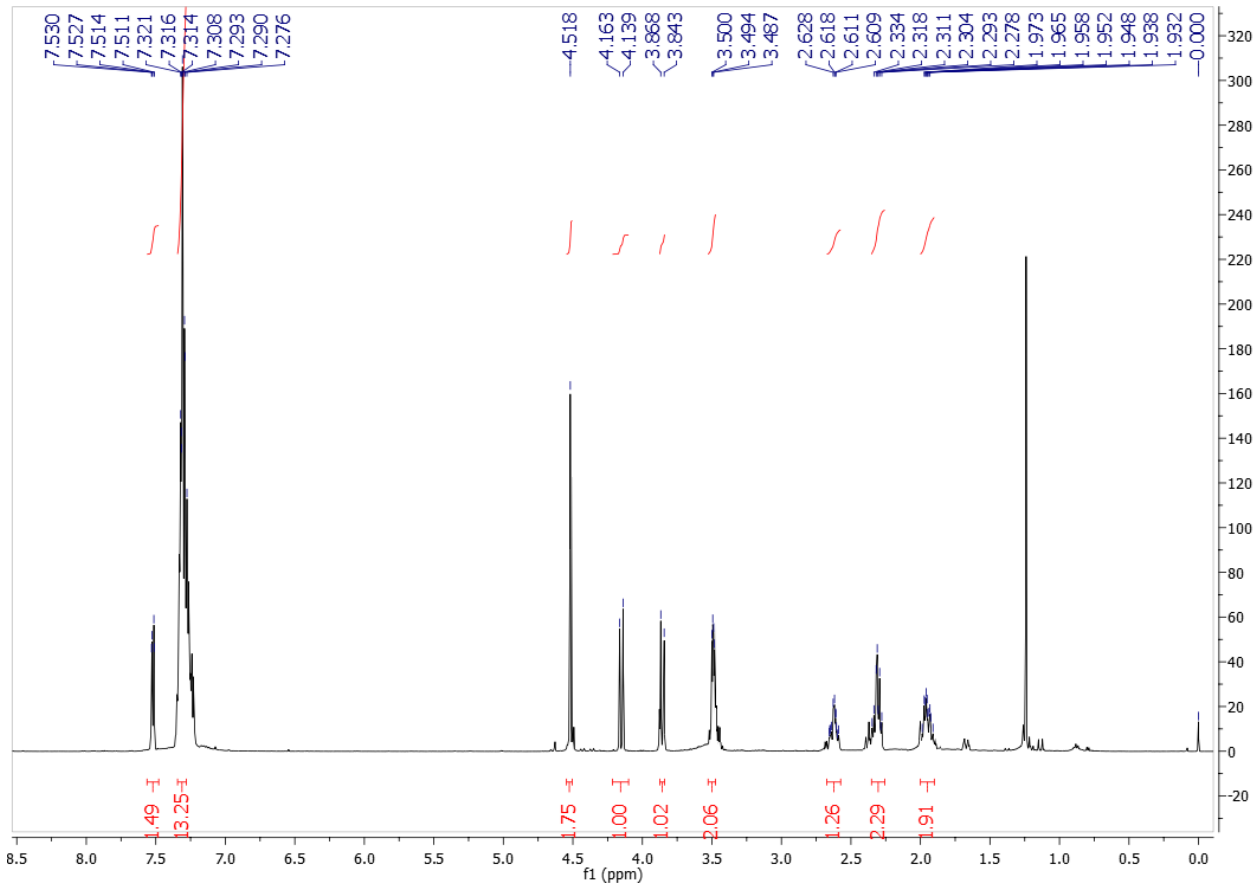
[(2*S*,3*s*,5*R*)-5-Hexyl-2-phenyl-1-oxa-spiro[2.3]hexan-2-yl]methanol **(4h)**

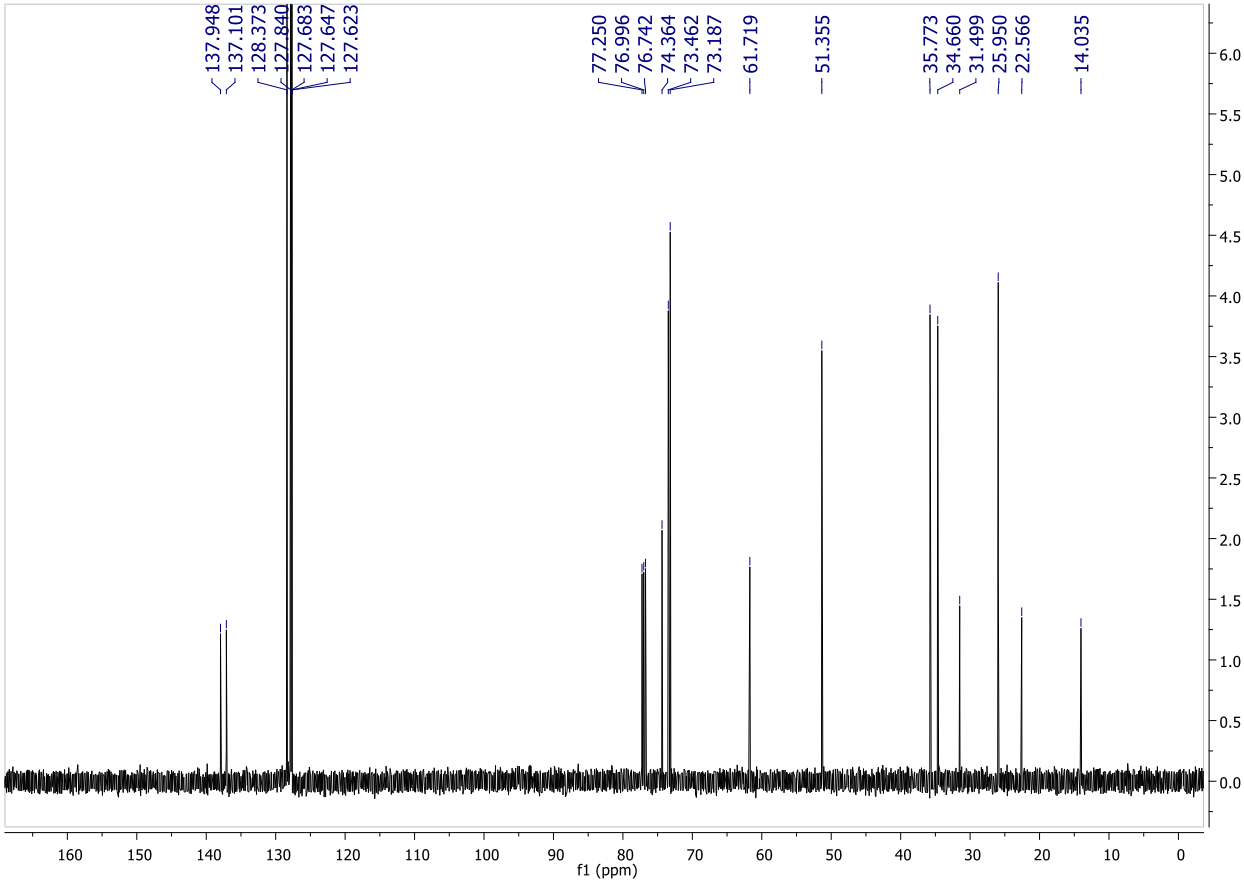


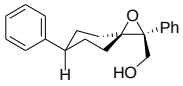




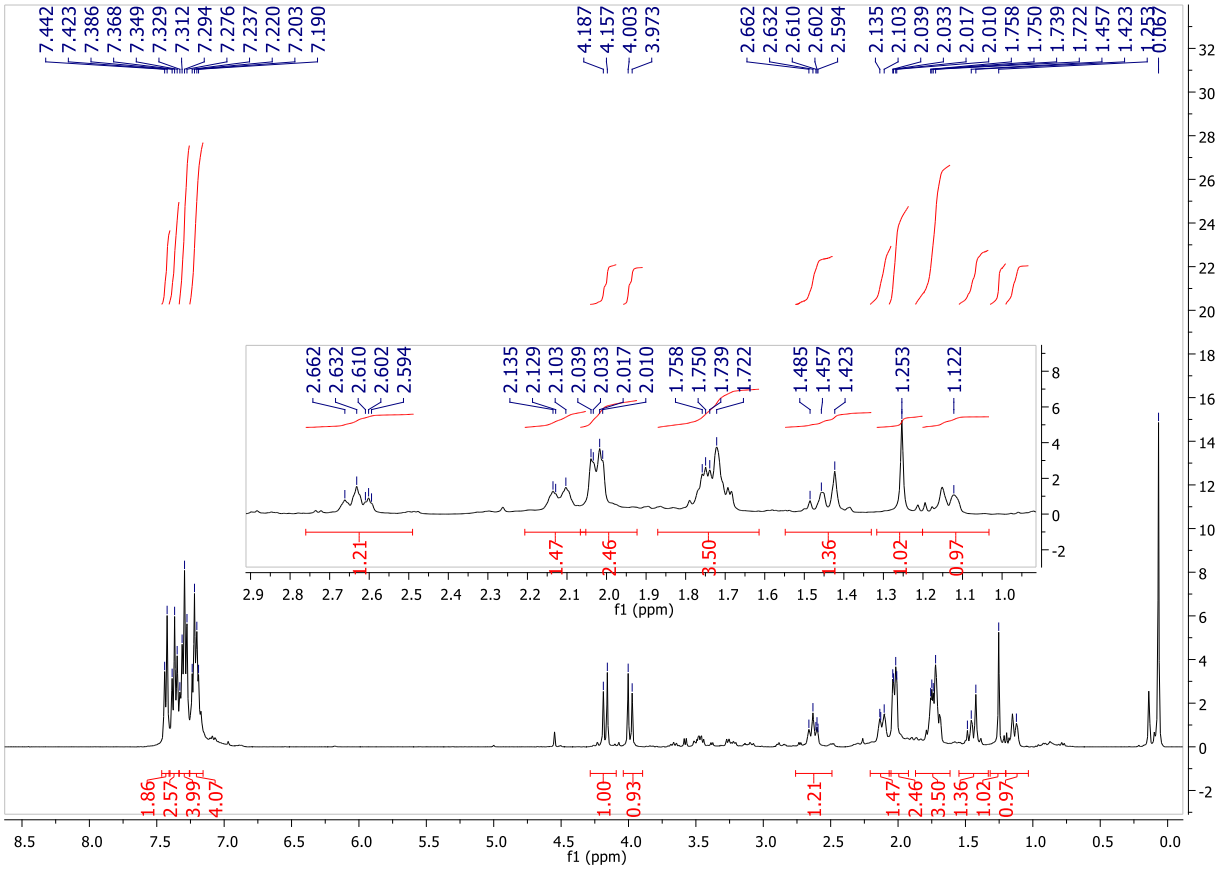
[(2*S*,3*s*,5*R*)-5-(benzyloxy)methyl)-2-phenyl-1-oxaspiro[2.3]hexan-2-yl]methanol **(4i)**

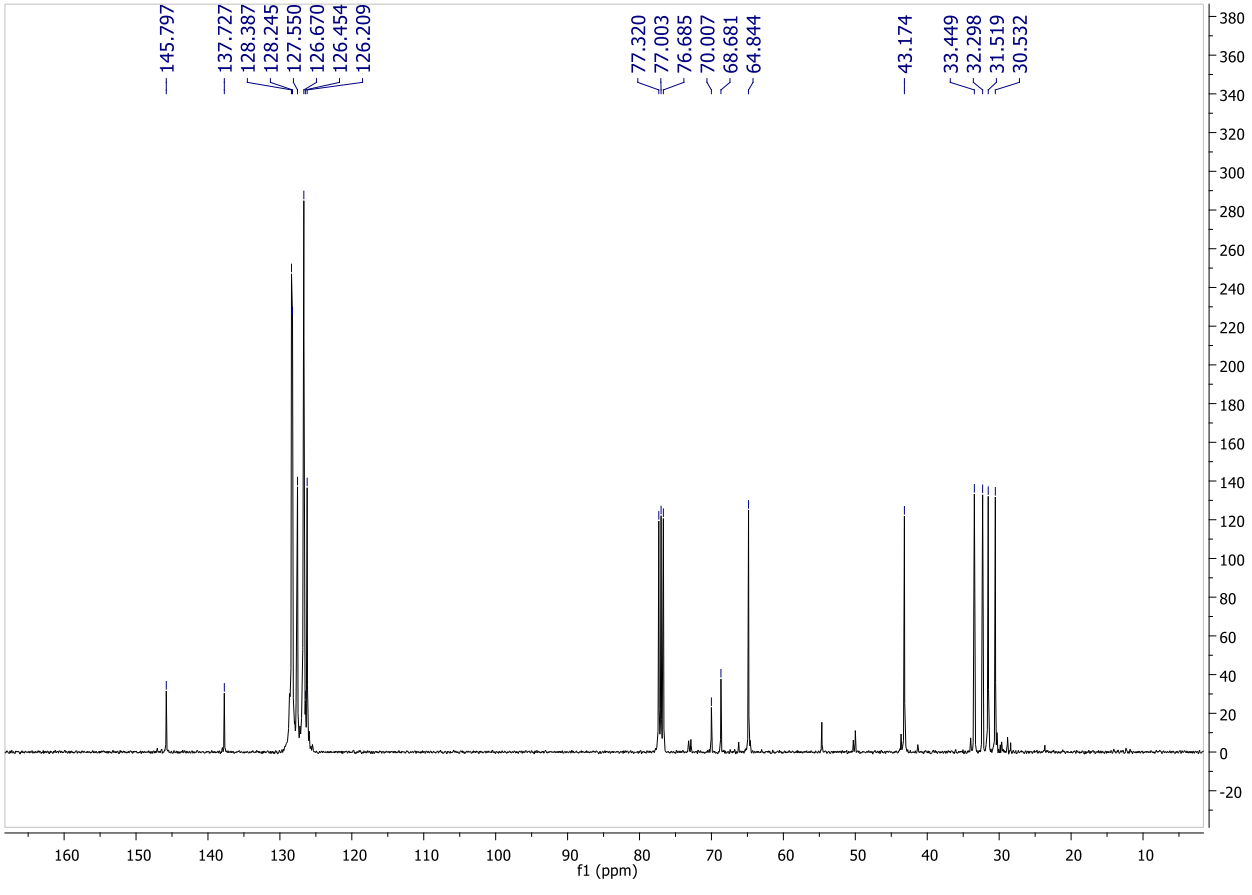


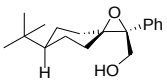




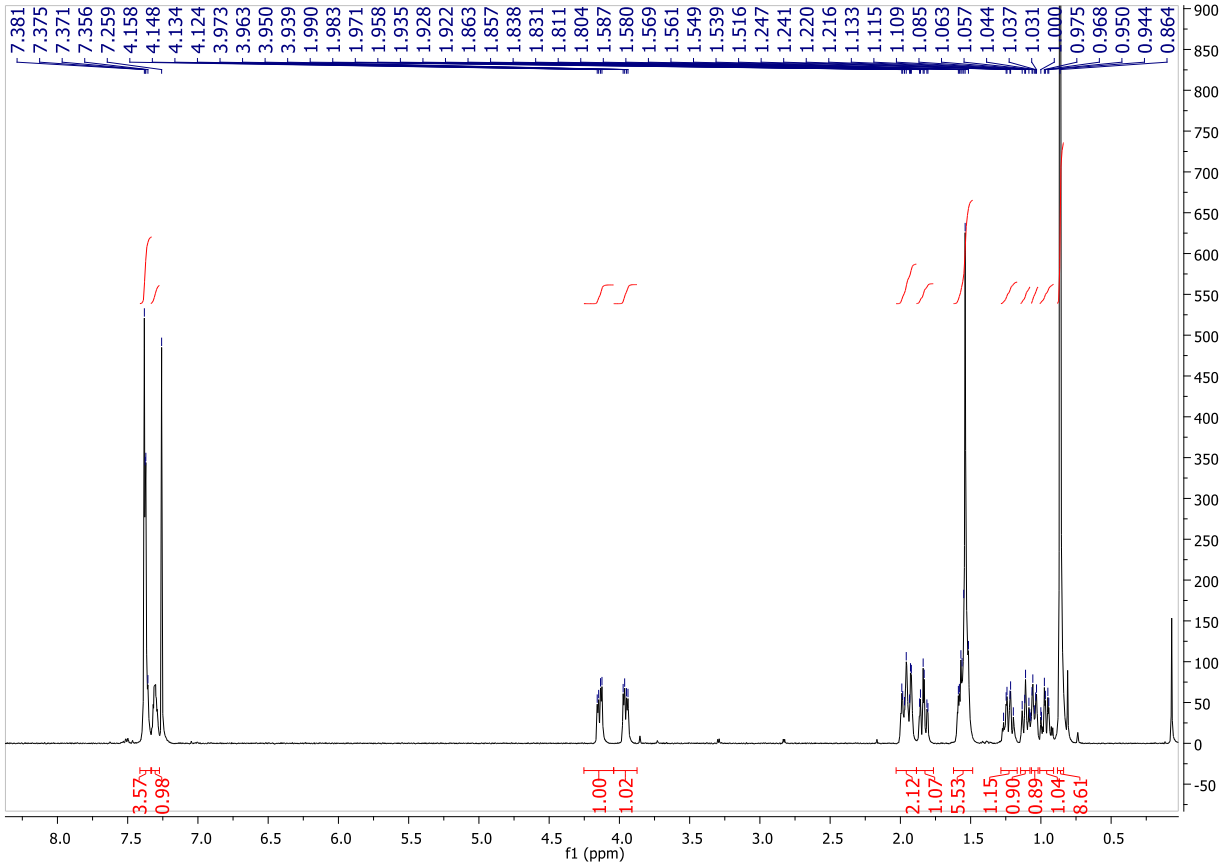
[(2*S*,3*s*,6*R*)-2,6-Diphenyl-1-oxaspiro[2.5]octan-2-yl)methanol **(4k)**

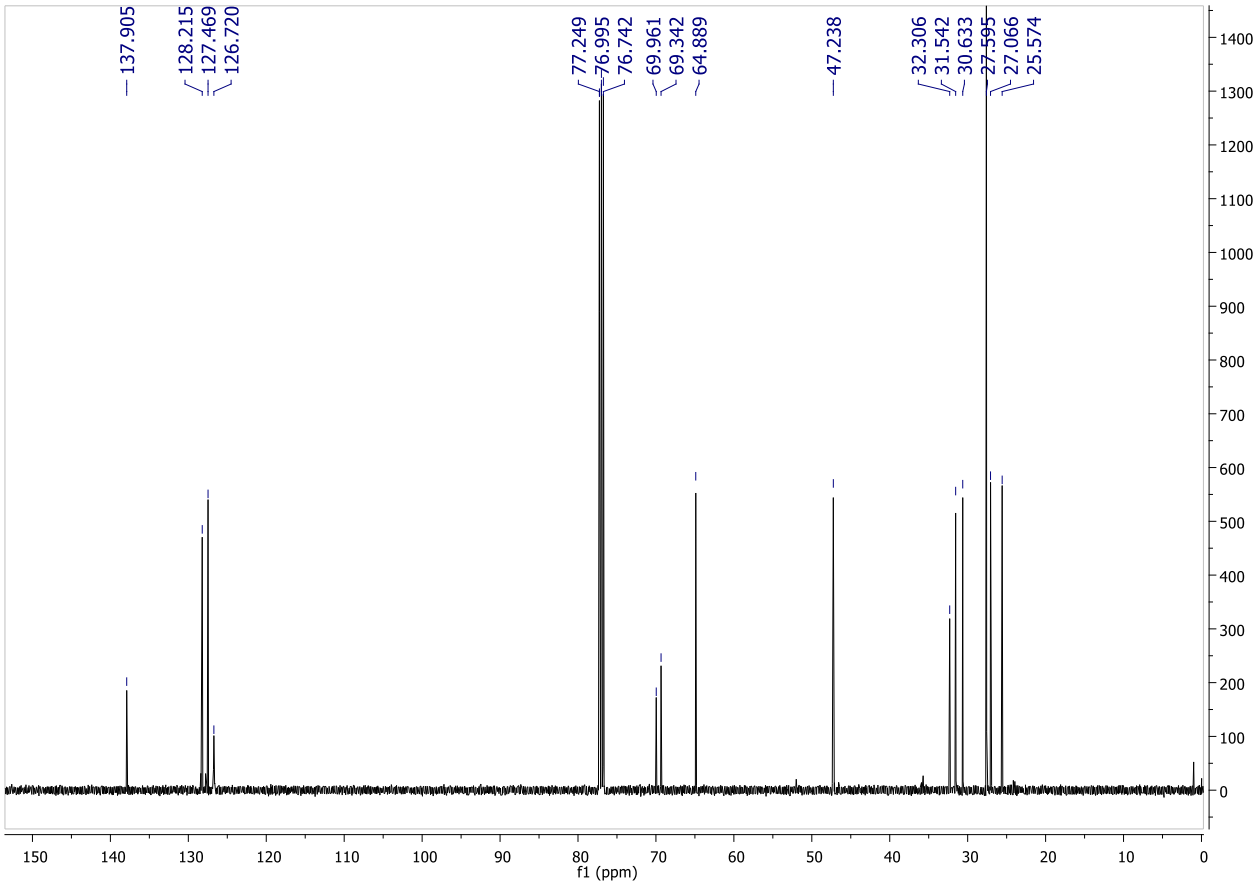


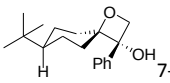




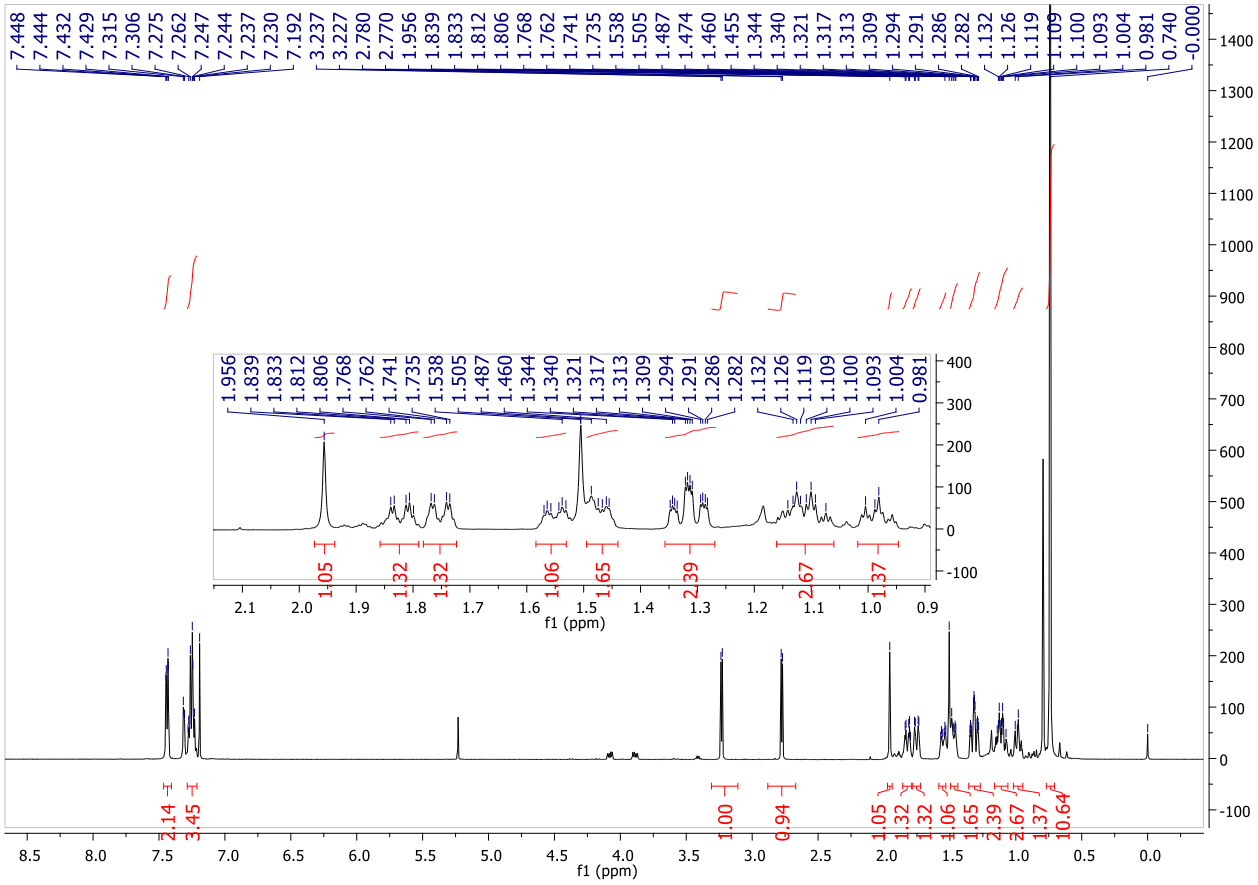
[(2*S*,3*s*,6*R*)-6-(tert-Butyl)-2-phenyl-1-oxaspiro[2.5]octan-2-yl]methanol **(4l)**

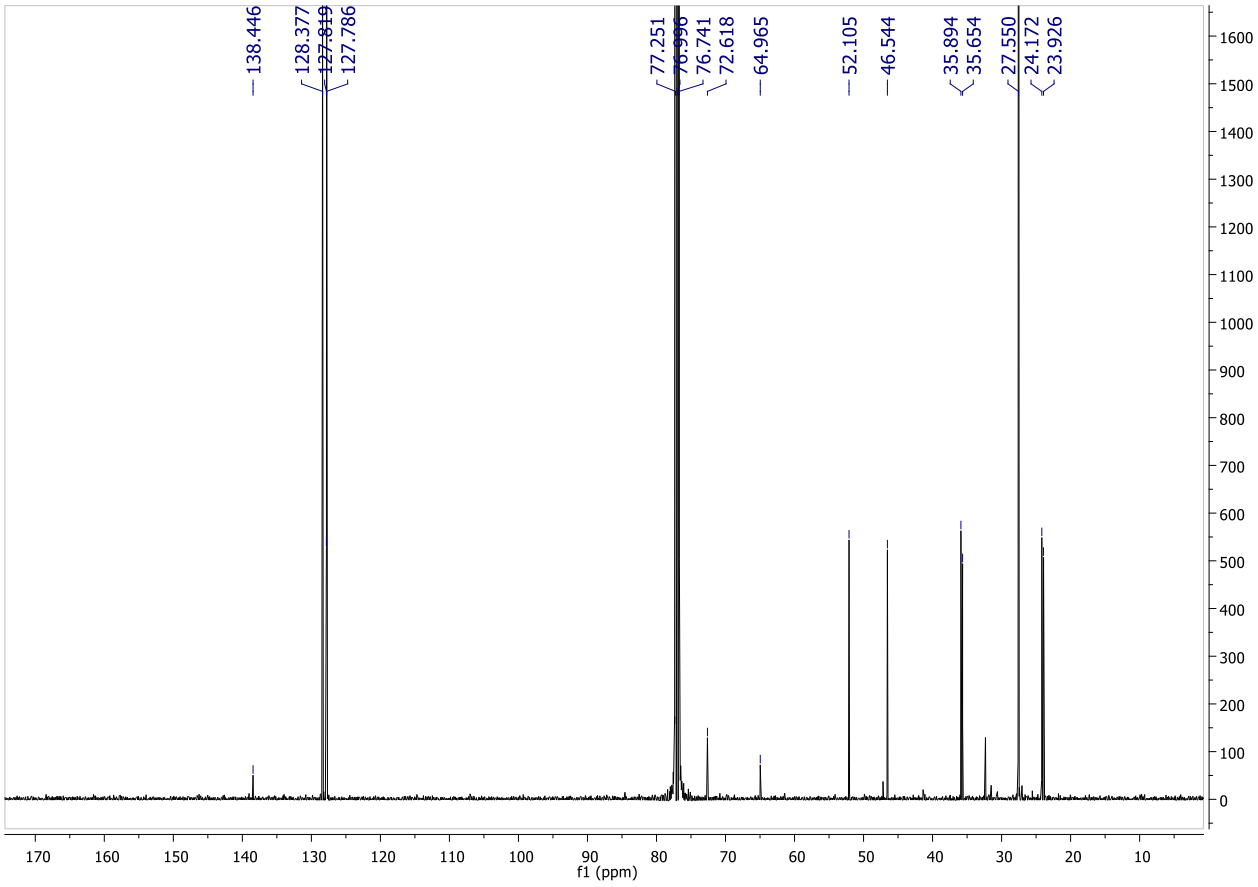


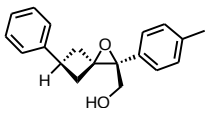




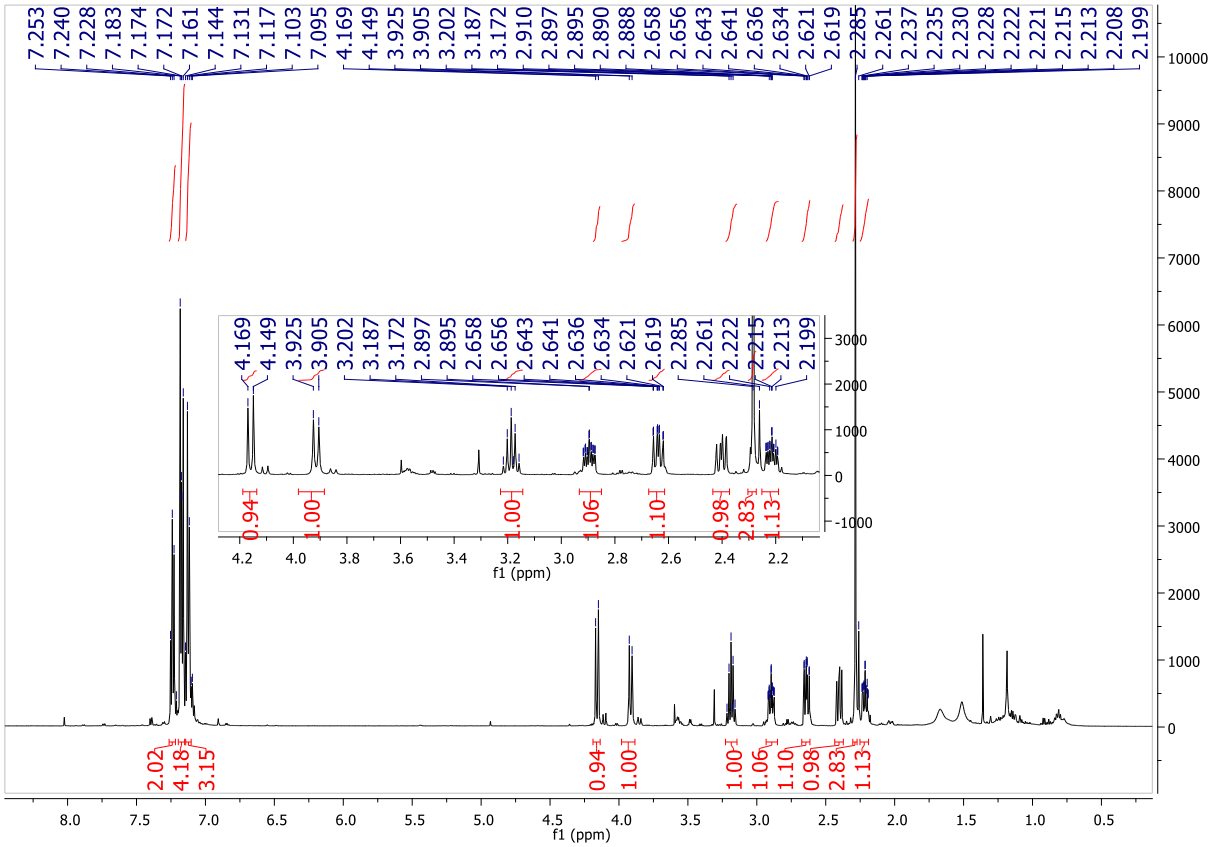
7-tert-Butyl-3-phenyl-1-oxaspiro[3.5]nonan-3-ol **(5)**

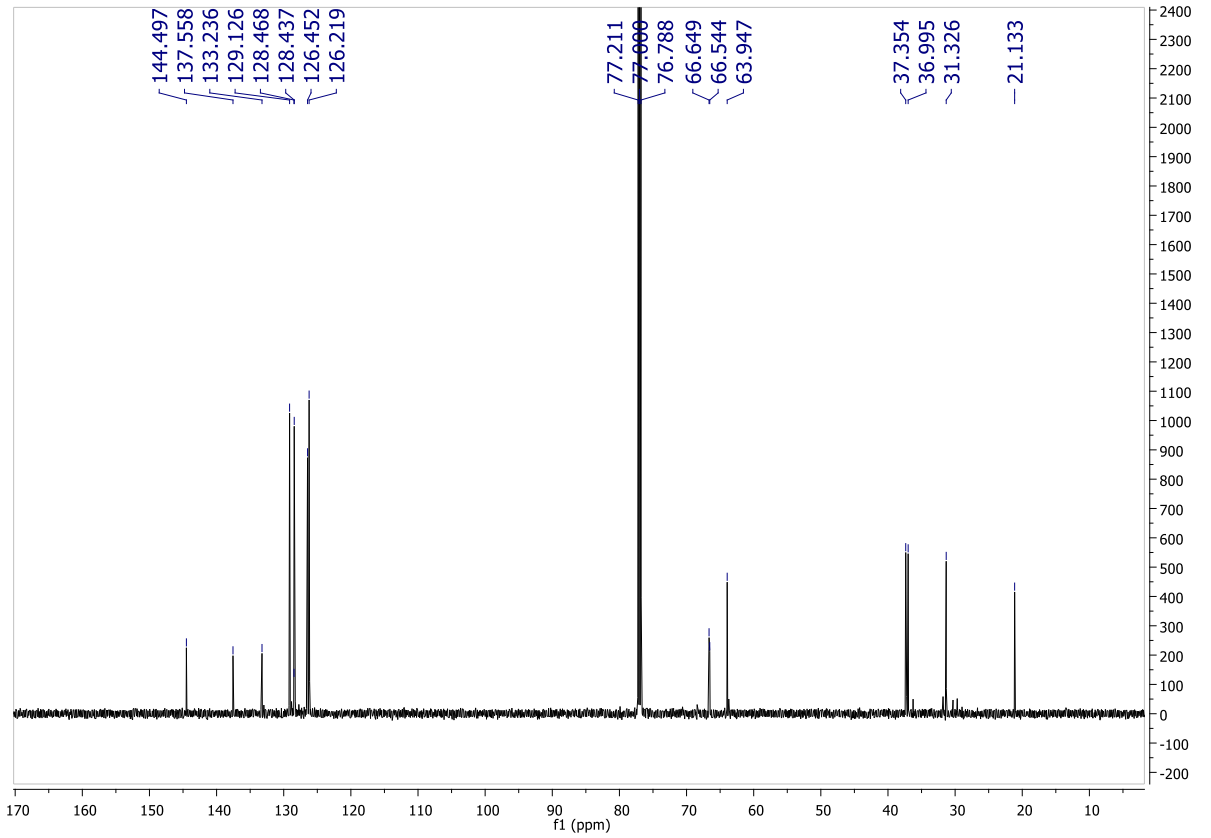


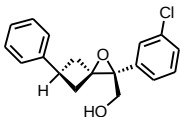




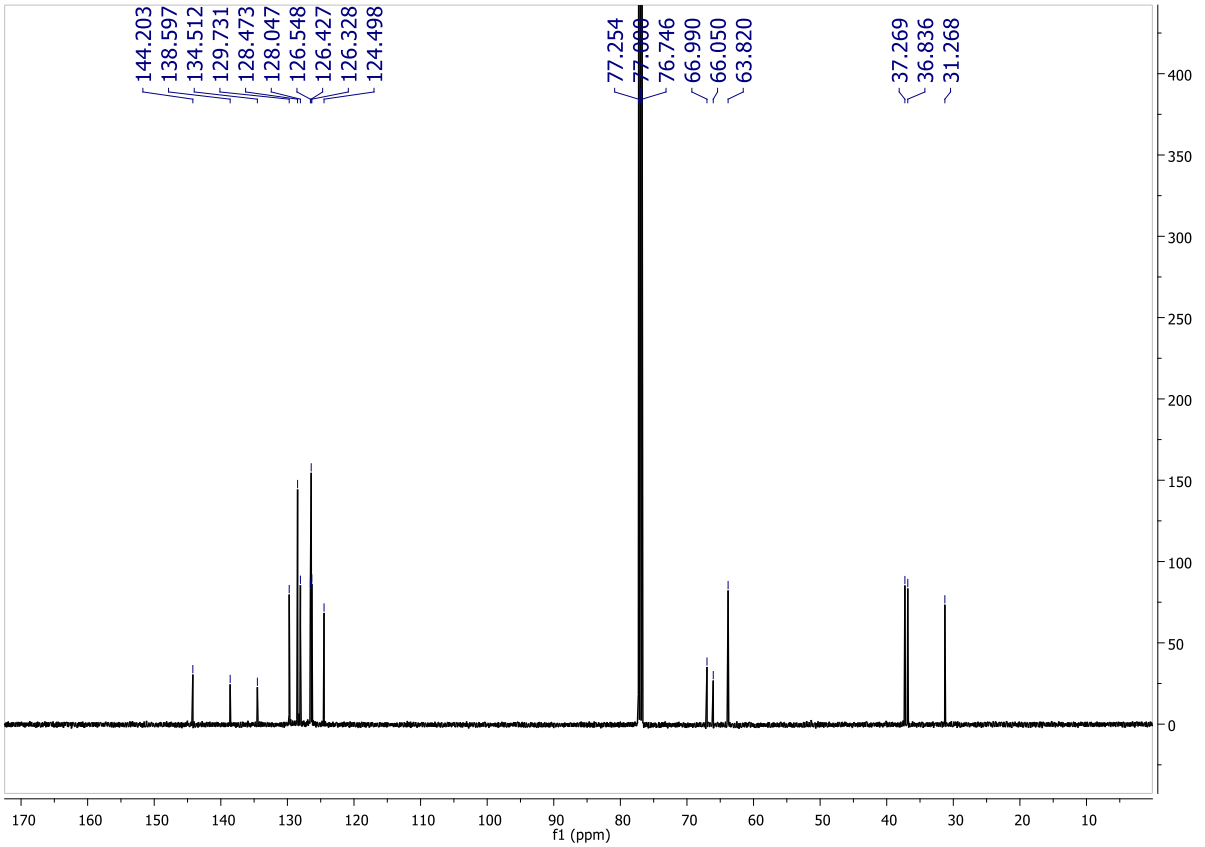
[(2S,3s,5R)-(5-Phenyl-2-p-tolyl-1-oxa-spiro[2.3]hex-2-yl)-methanol **(4ab)**

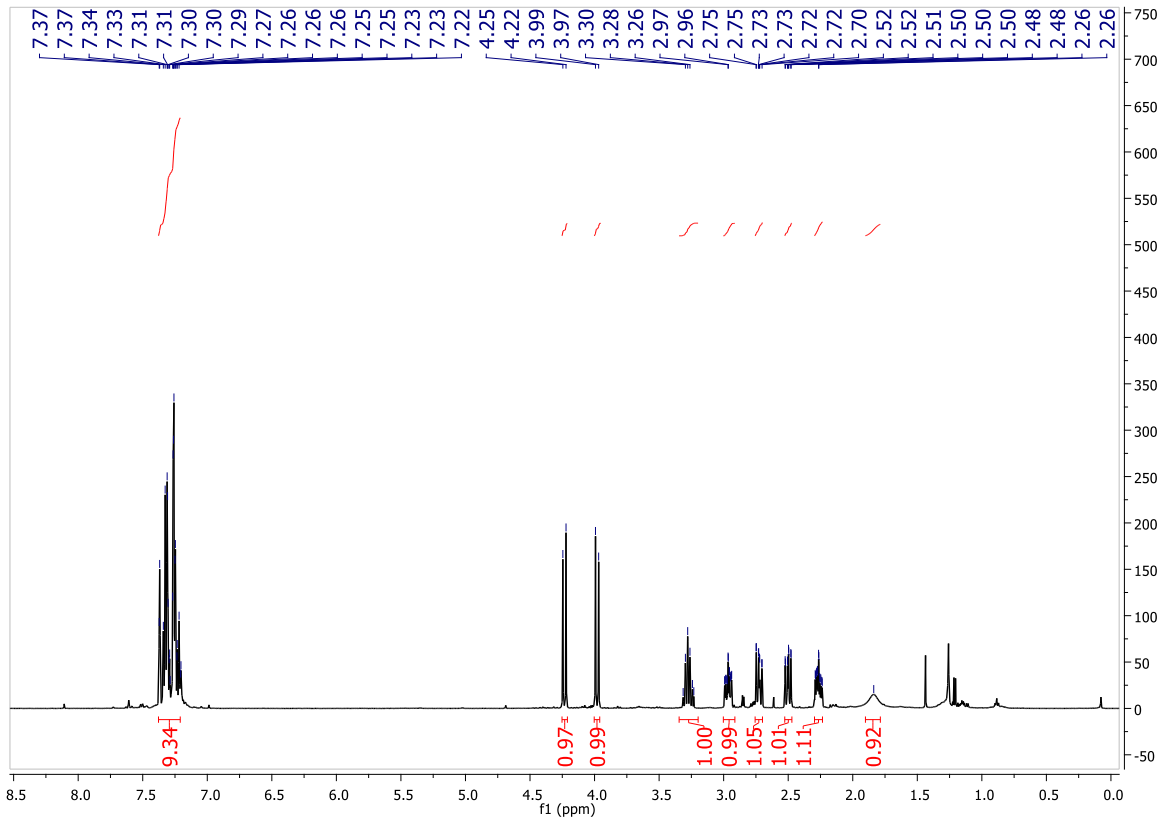


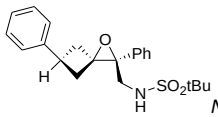




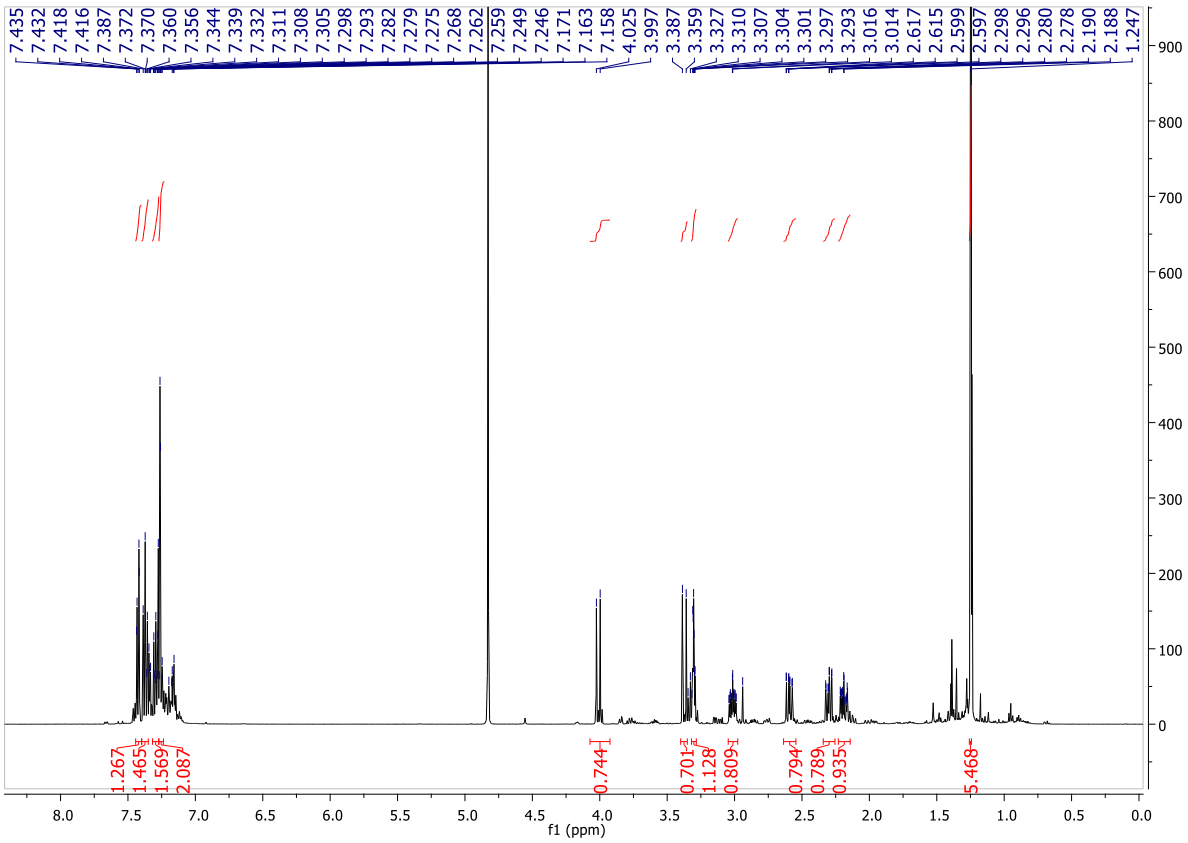
[(2*S*,3*s*,5*R*)-[2-(3-Chloro-phenyl)-5-phenyl-1-oxa-spiro[2.3]hex-2-yl]-methanol **(4ad)**

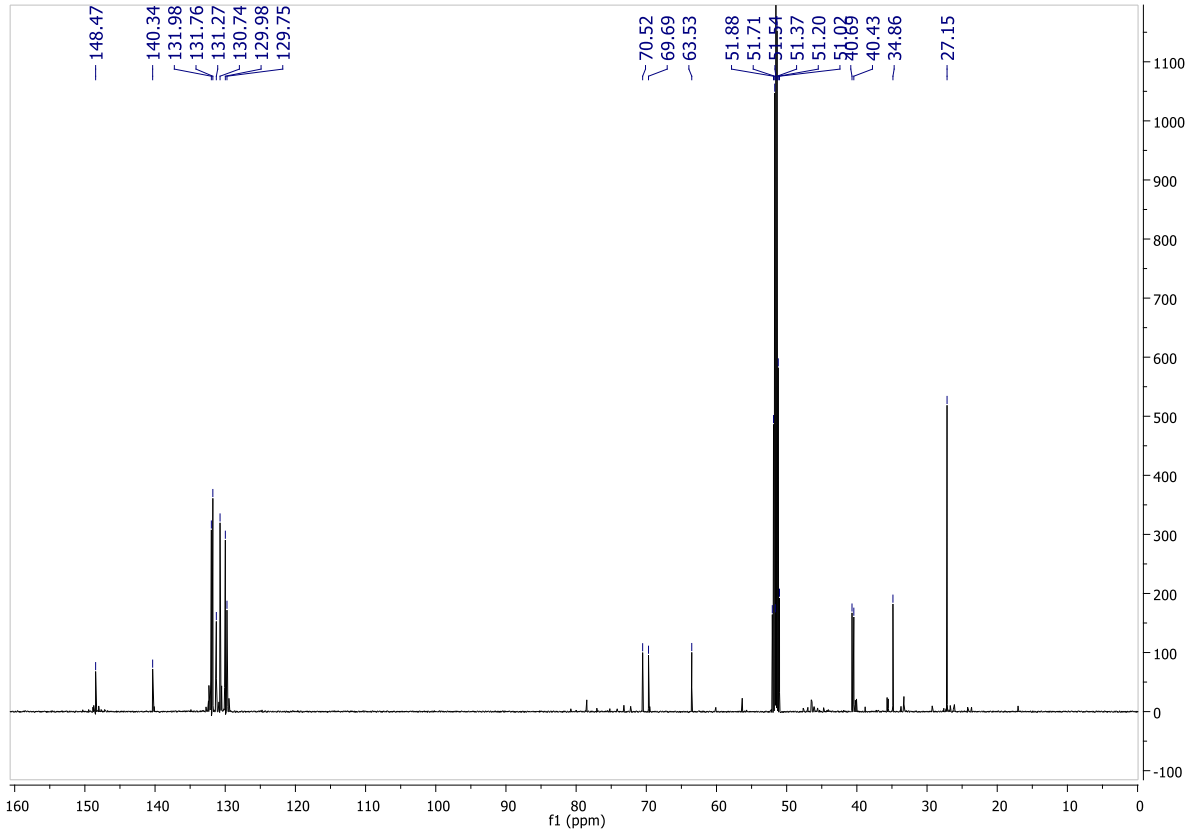




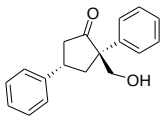


N-{[(2S,3s,5R)-2,5-diphenyl-1-oxaspiro[2.3]hexan-2-yl]methyl}-2-methylpropane-2-sulfonamide **(7)**

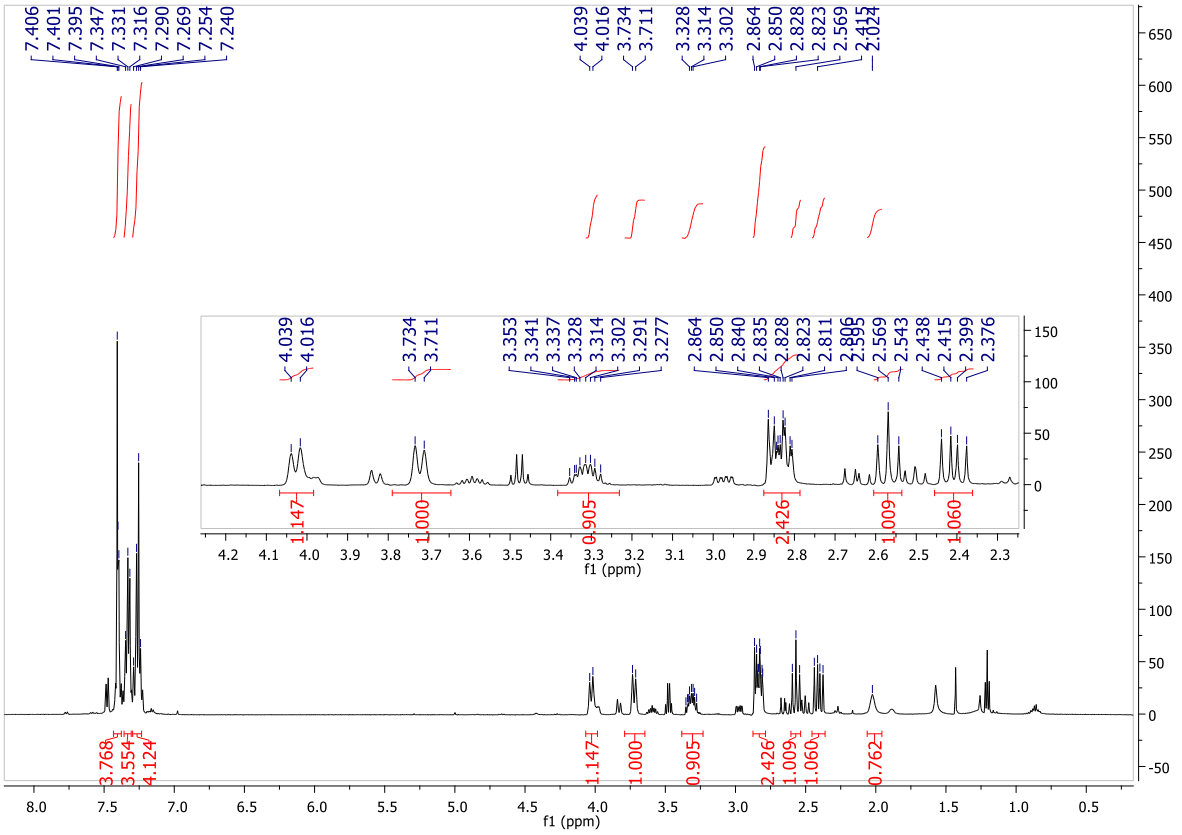


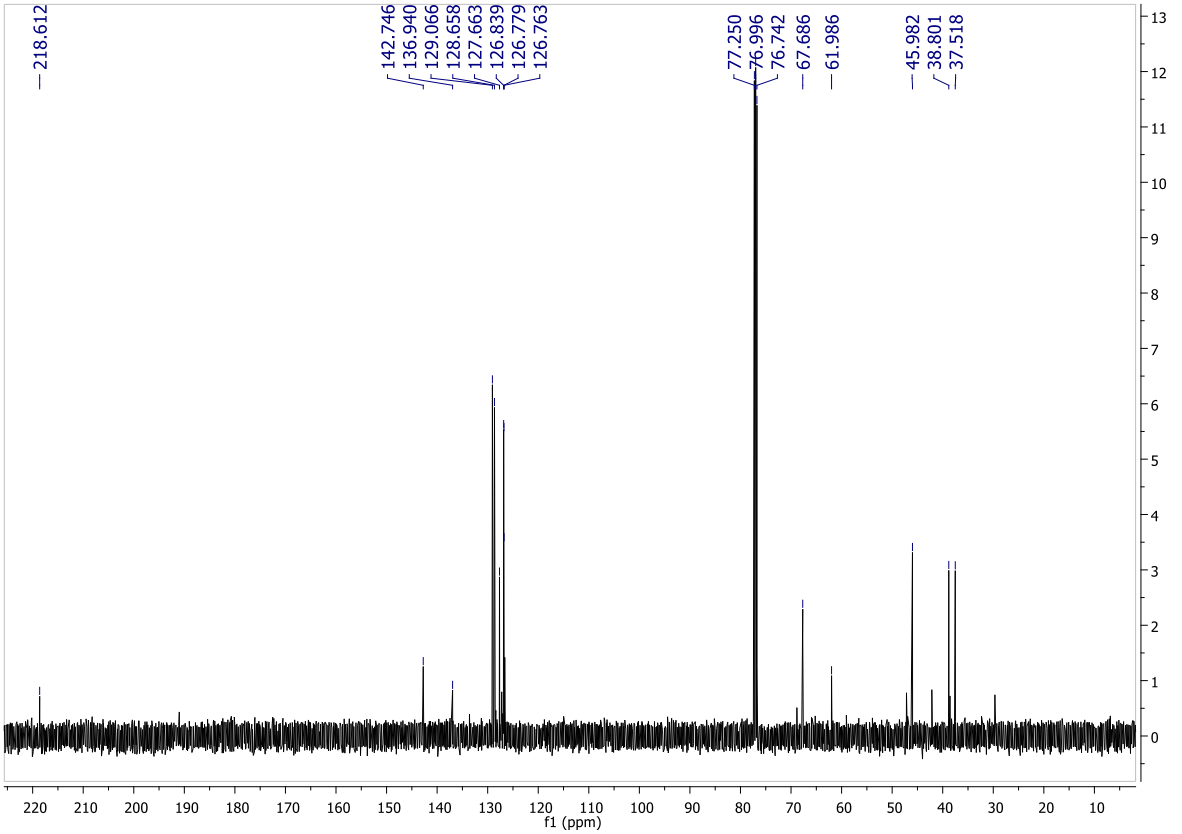


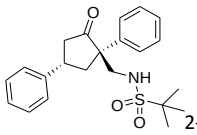
9. ^{1}H and ^{13}C NMR spectra of compounds 8 and 9



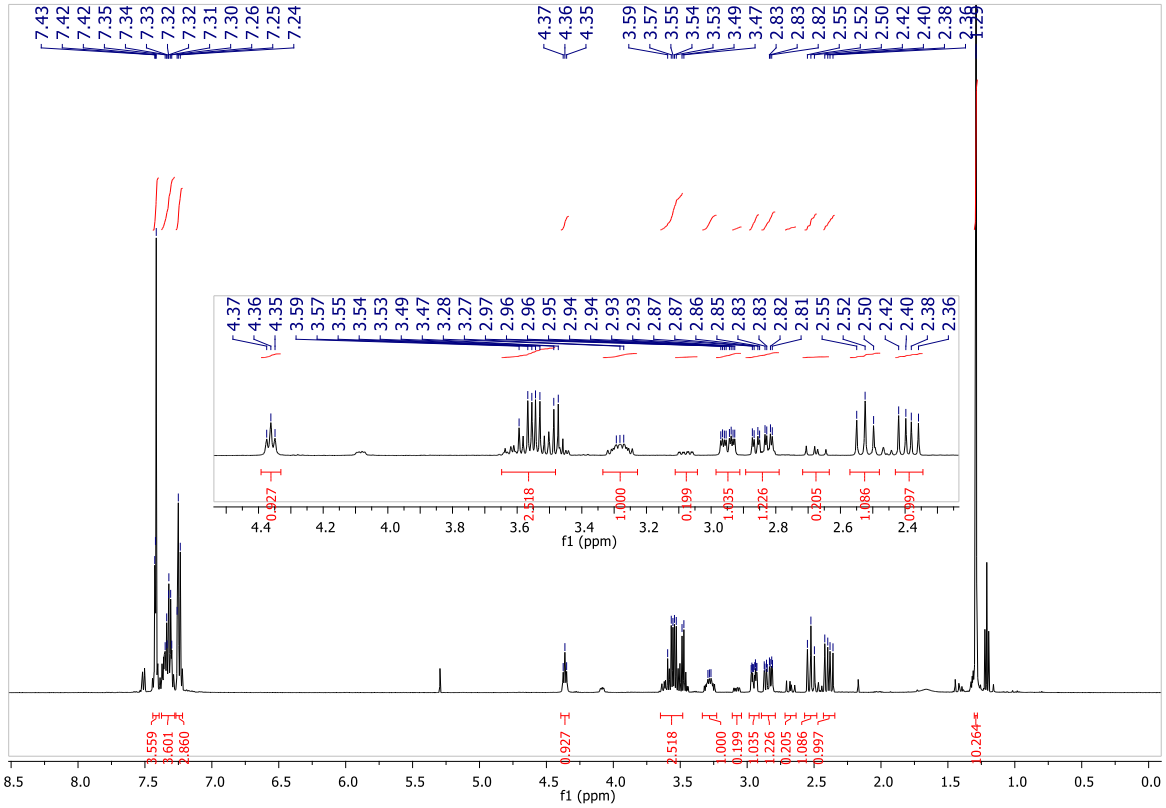
2-Hydroxymethyl-2,4-diphenyl-cyclopentanone **(8)**

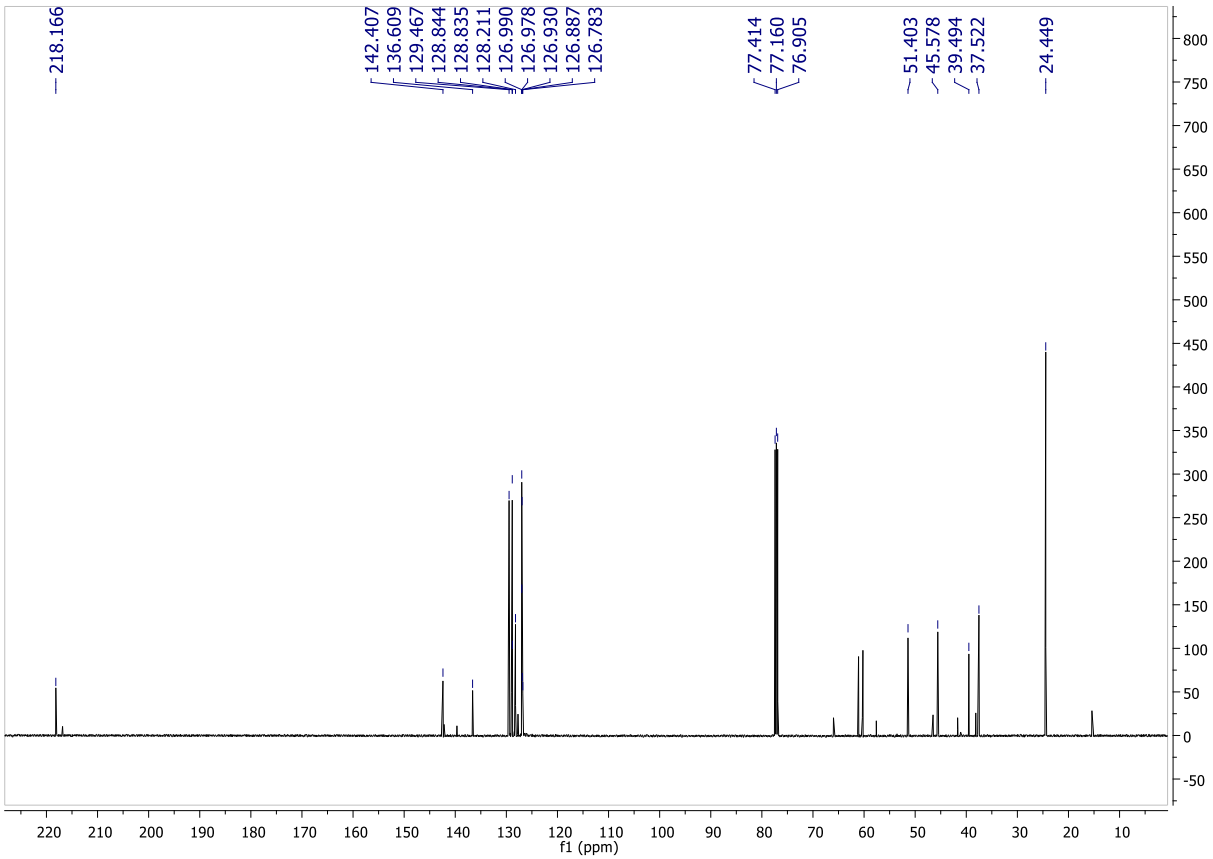




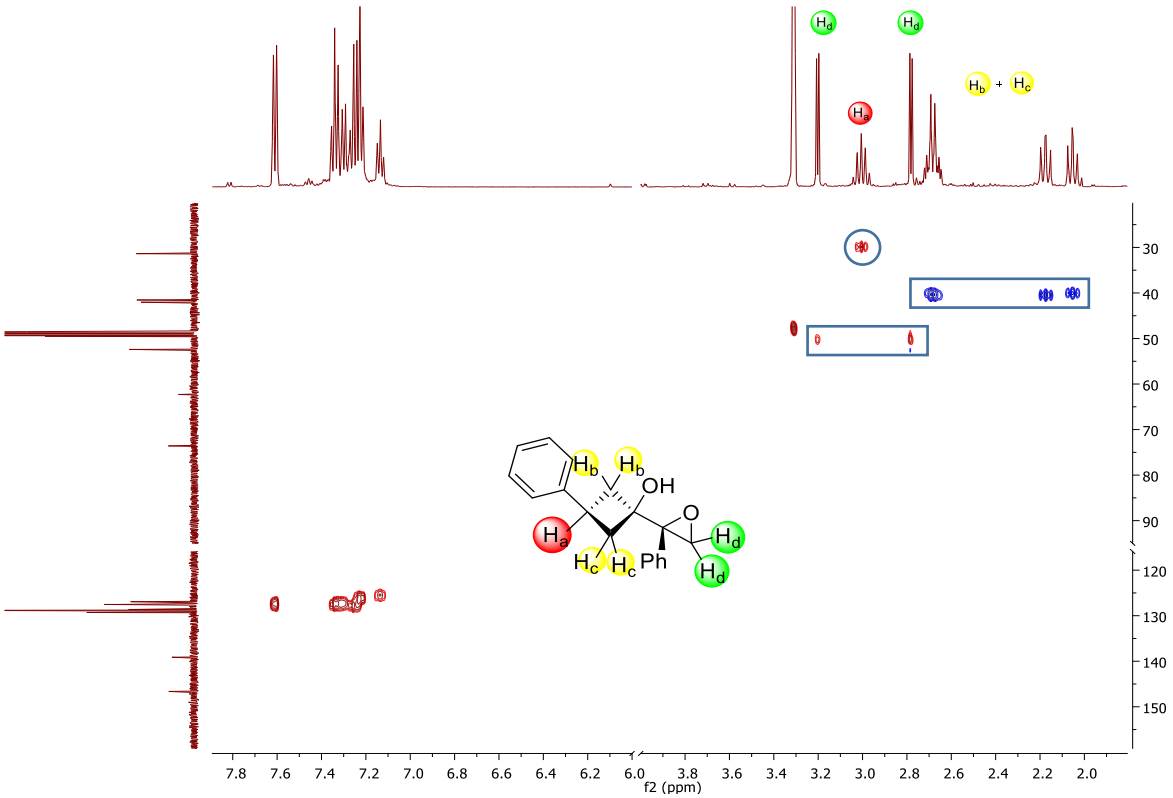


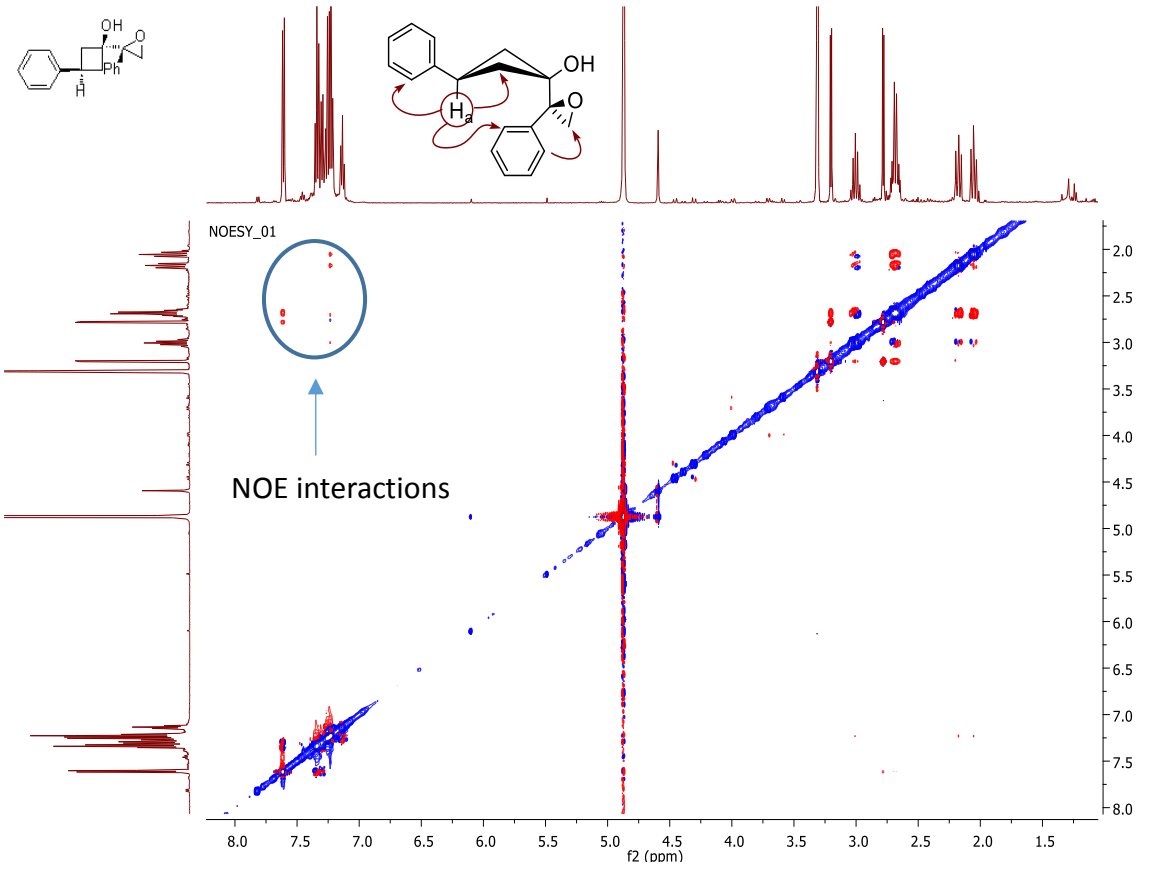
2-methyl-*N*-{(2-oxo-1,4-diphenylcyclopentyl)methyl]propane-2-sulfonamide **(9)**

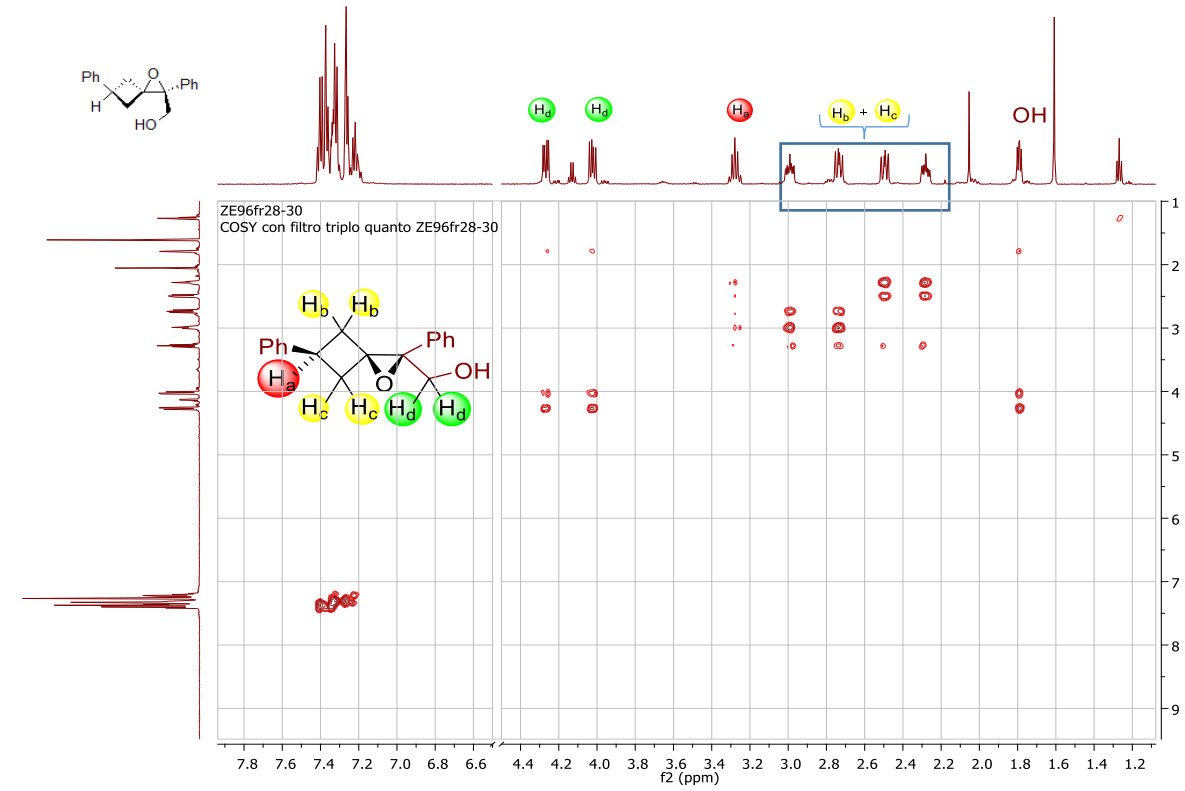


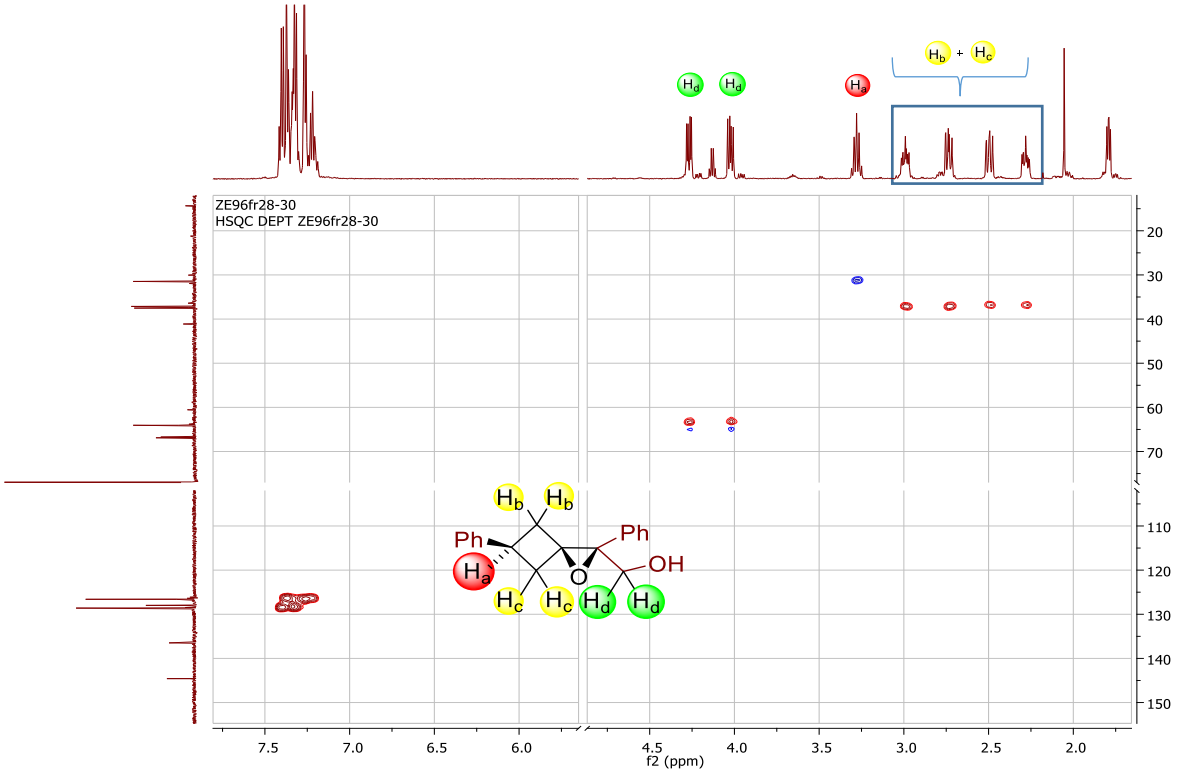


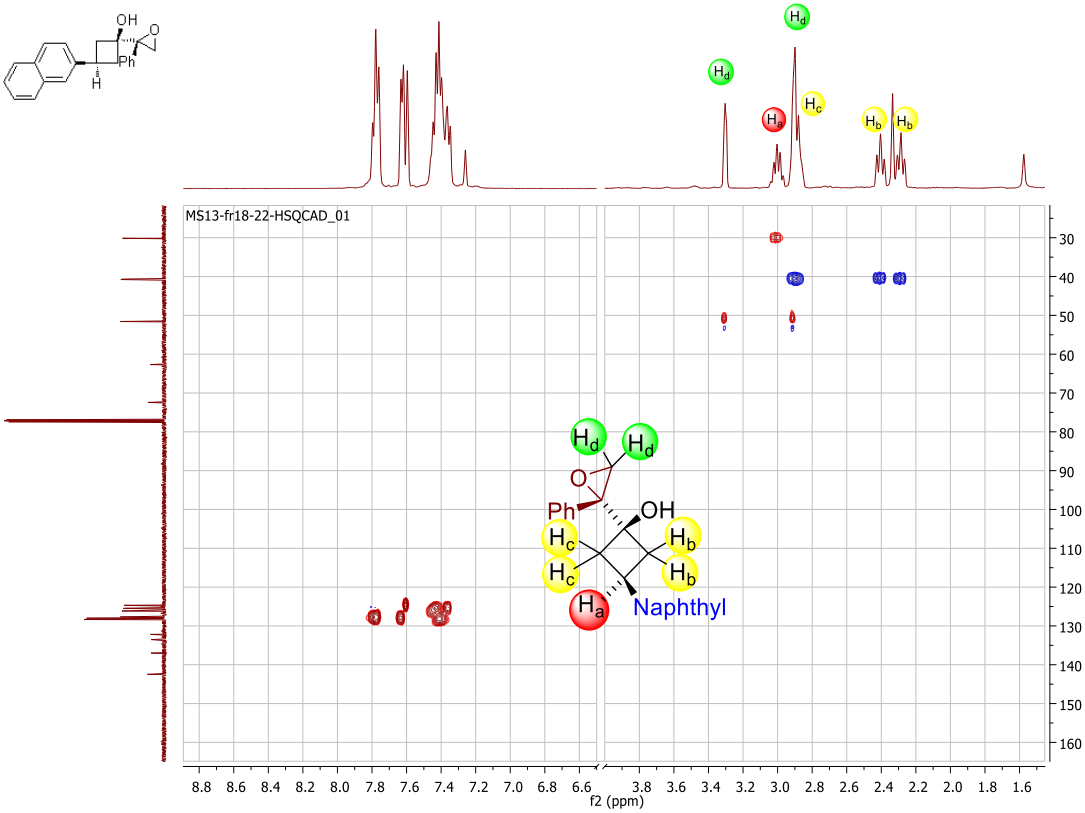
10. Representative D2-NMR experiments (COSY, NOESY, HSQC) of compounds 3a,3f,3h,4a,4f,4h,*cis*-6,7,9

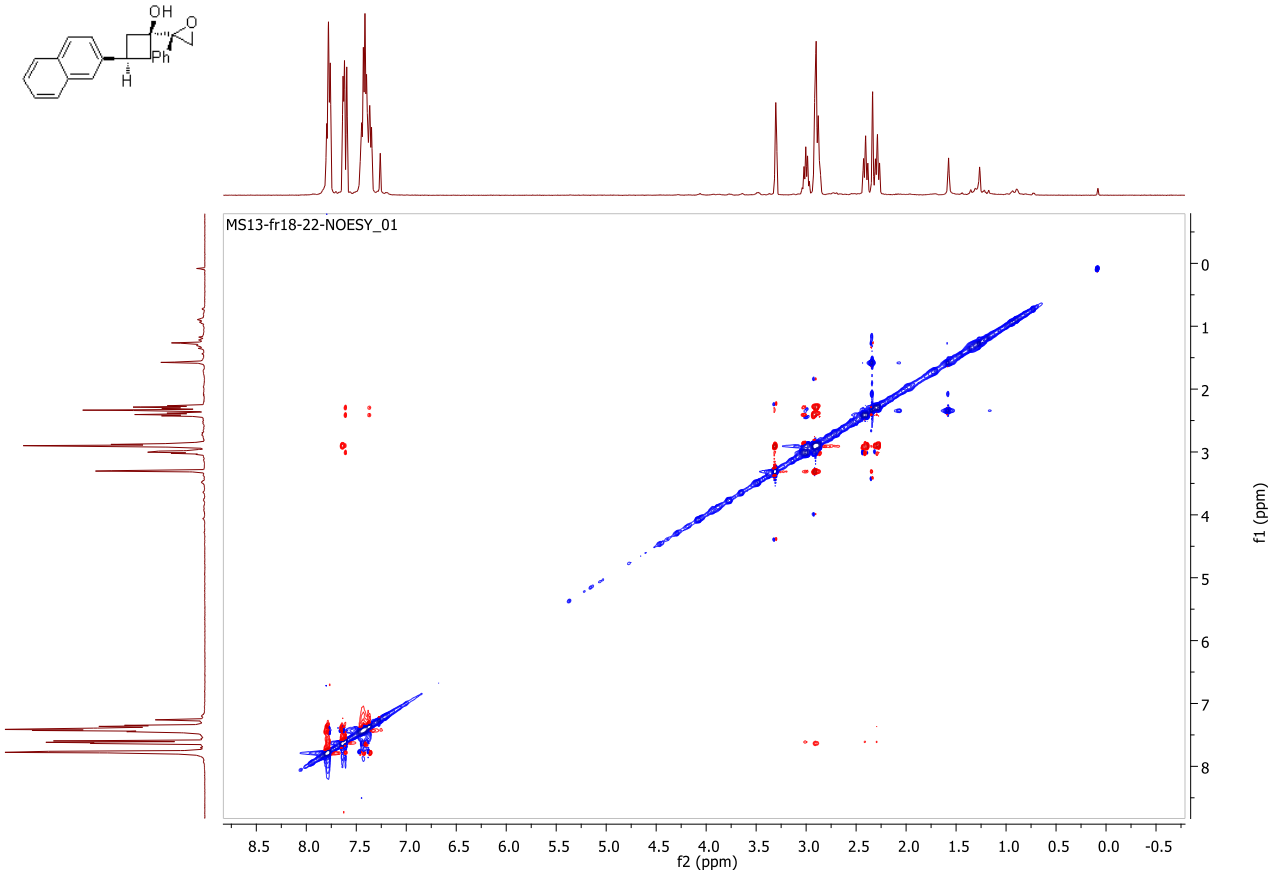


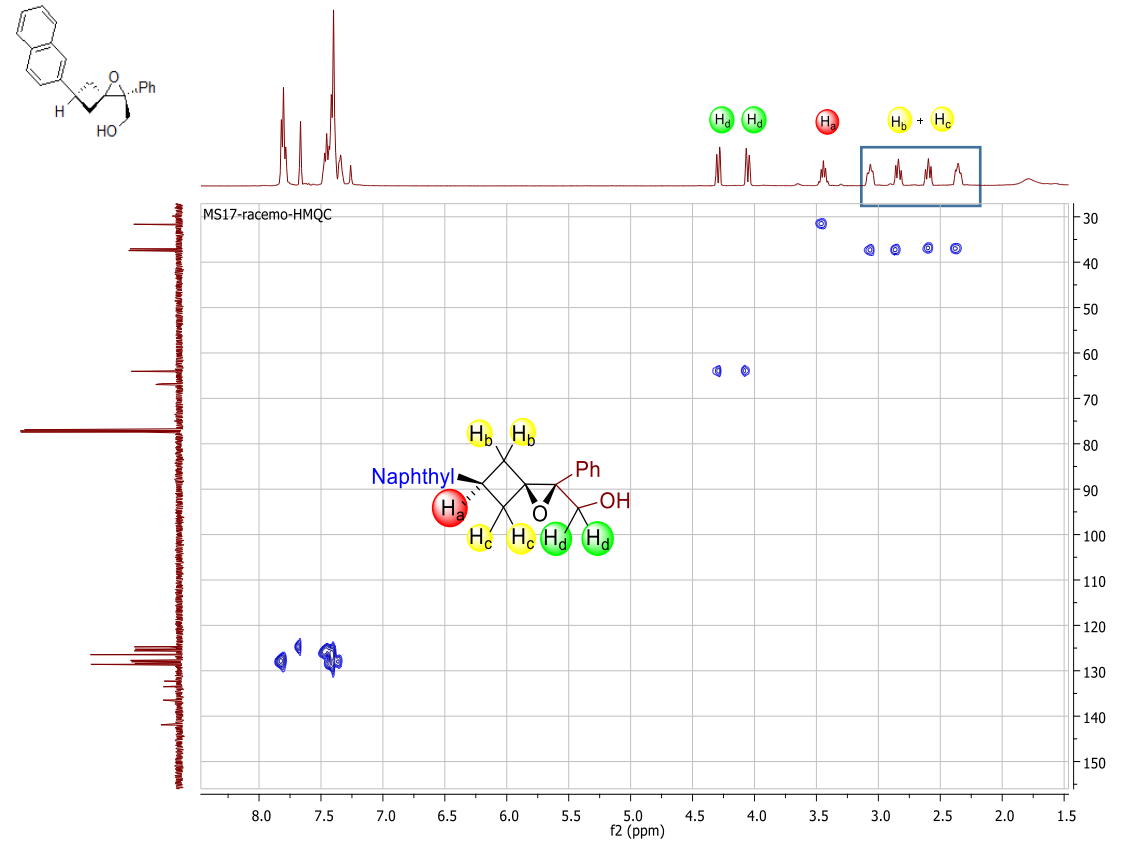


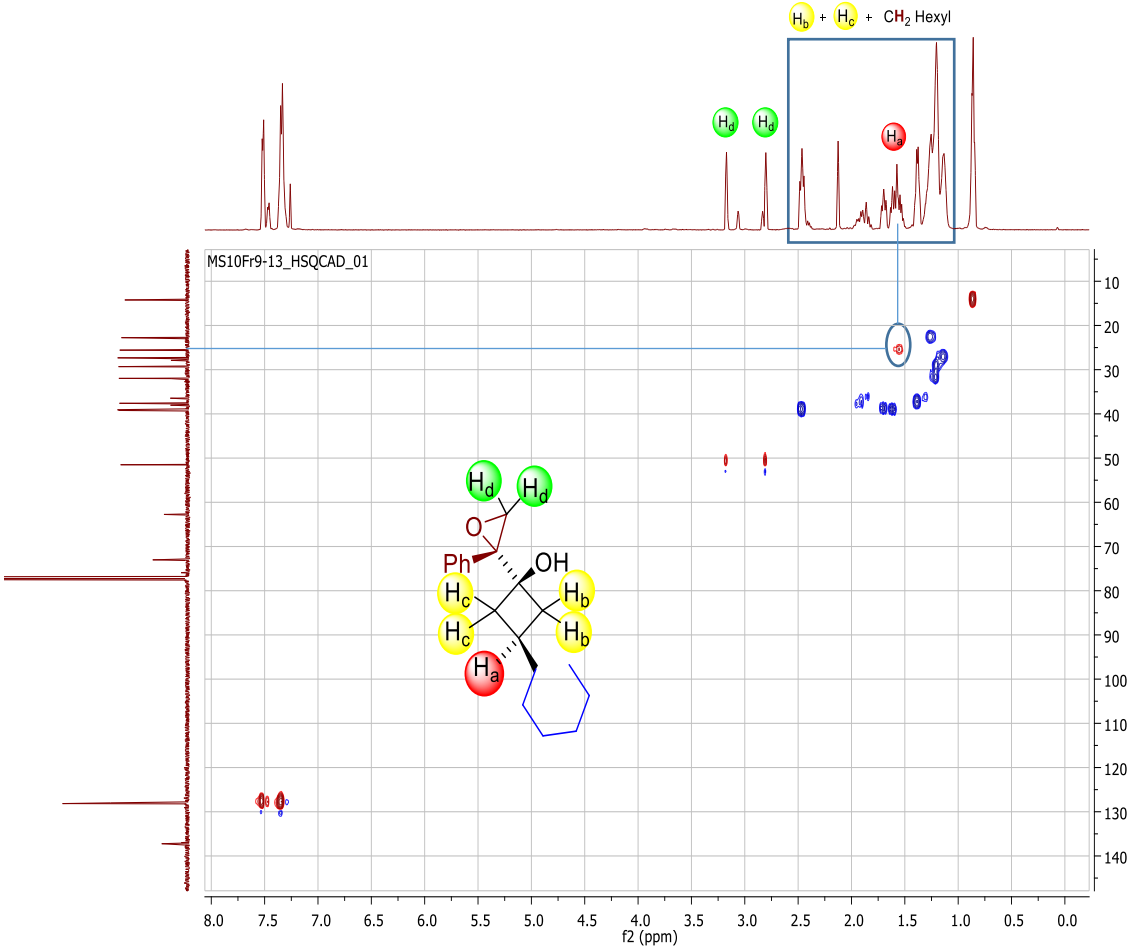

Ph
O
Ph
H
HO
Hd
Hd
Ha
Hb + Hc
OH
ZE96fr28-30
COSY con filtro triplo quanto ZE96fr28-30
Hb
Hb
Ph
Ph
Ha
O
OH
Hc
Hc
Hd
Hd
7.8 7.6 7.4 7.2 7.0 6.8 6.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2
f2 (ppm)
1 2 3 4 5 6 7 8 9

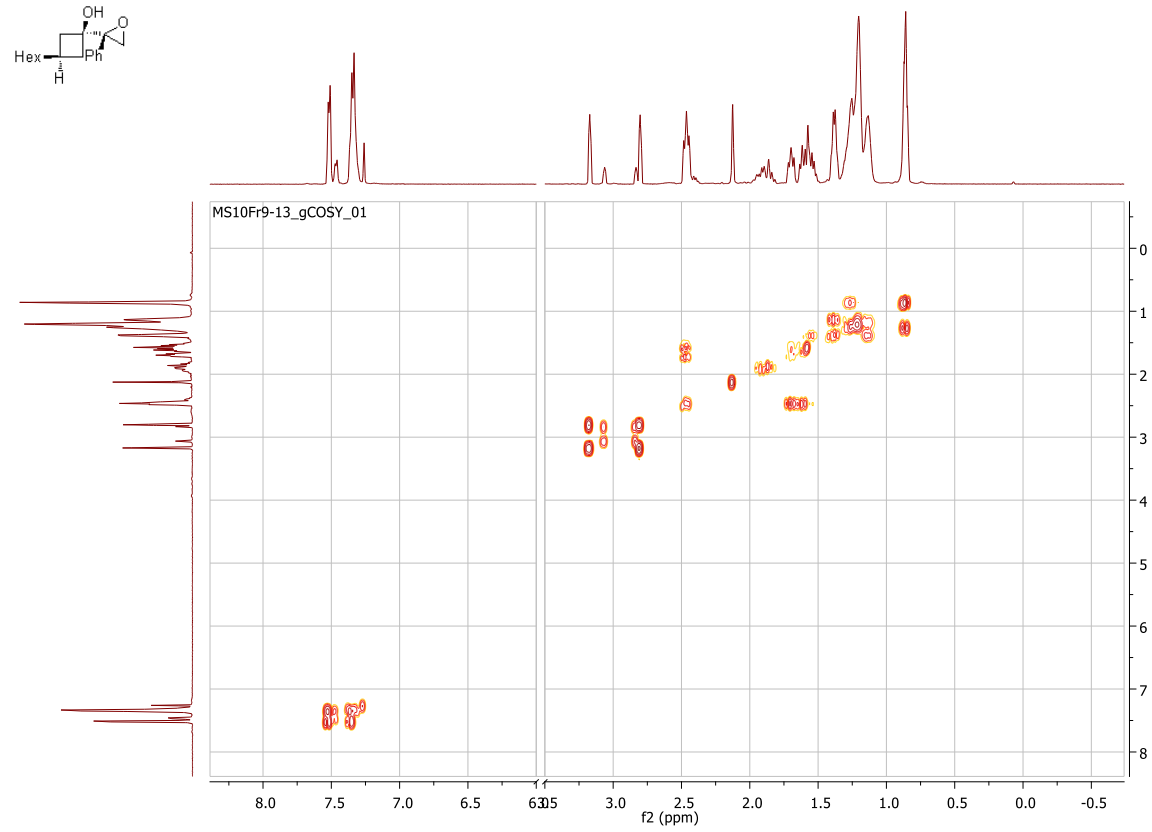

Hd
Hd
Ha
Hb + Hc
ZE96fr28-30
HSQC DEPT ZE96fr28-30
Hb
Hb
Ph
Ph
Ha
O
OH
Hc
Hc
Hd
Hd
7.5 7.0 6.5 6.0 4.5 4.0 3.5 3.0 2.5 2.0
f2 (ppm)
20 30 40 50 60 70 110 120 130 140 150

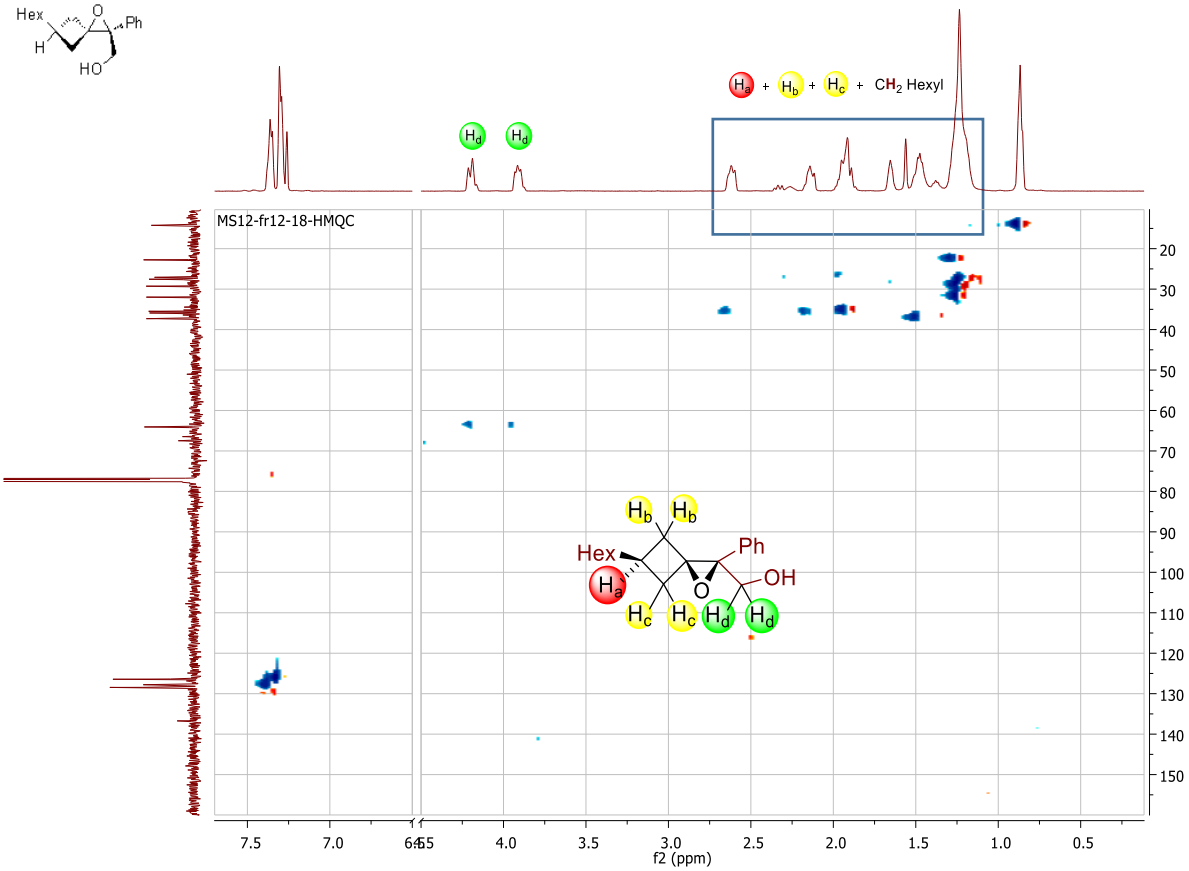

MS13-fr18-22-HSQCAD_01
Hd
Ha
Hc
Hb
Ph
OH
O
Naphthyl
f2 (ppm)

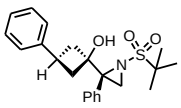

MS13-fr18-22-NOESY_01
f2 (ppm)
f1 (ppm)

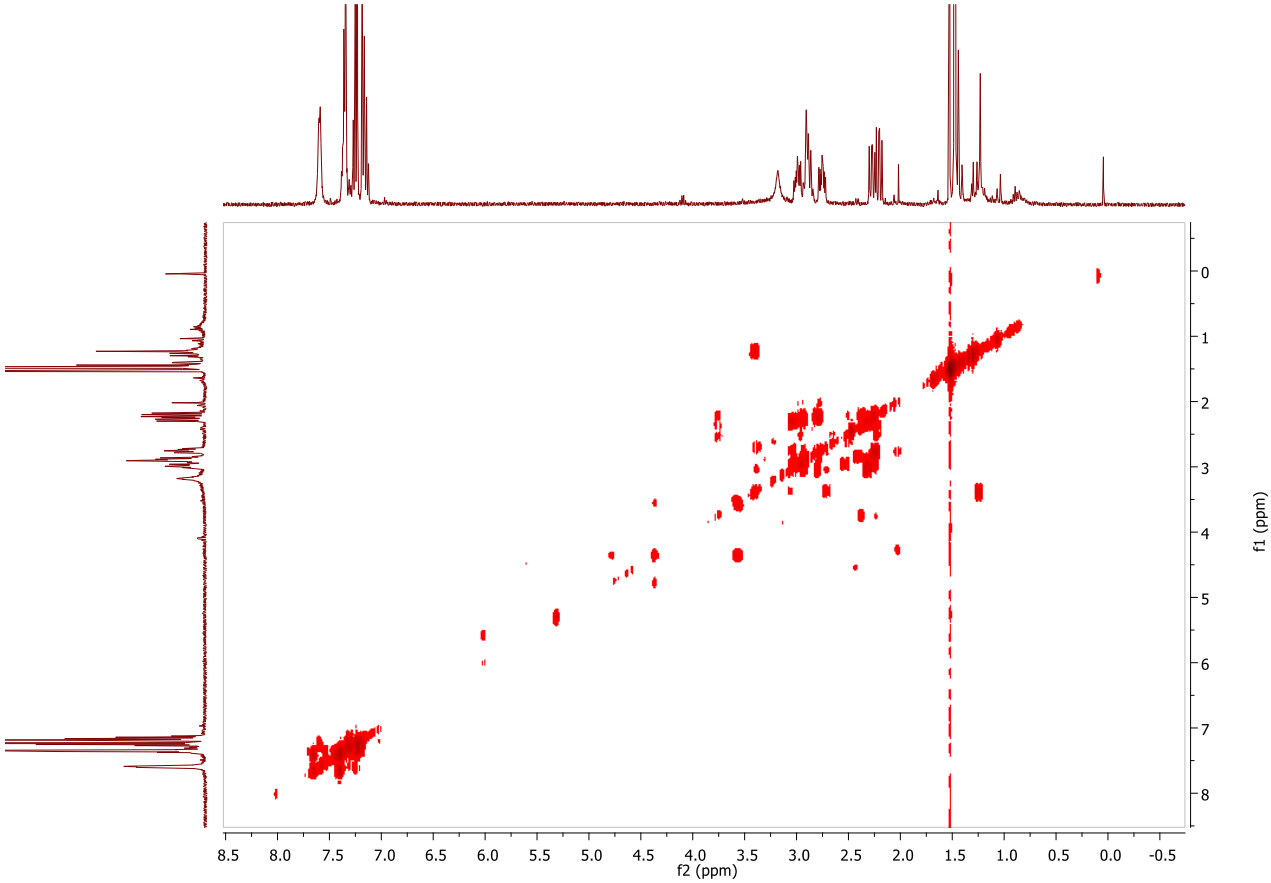

MS17-racemo-HMQC
Naphthyl
Ph
OH
f2 (ppm)

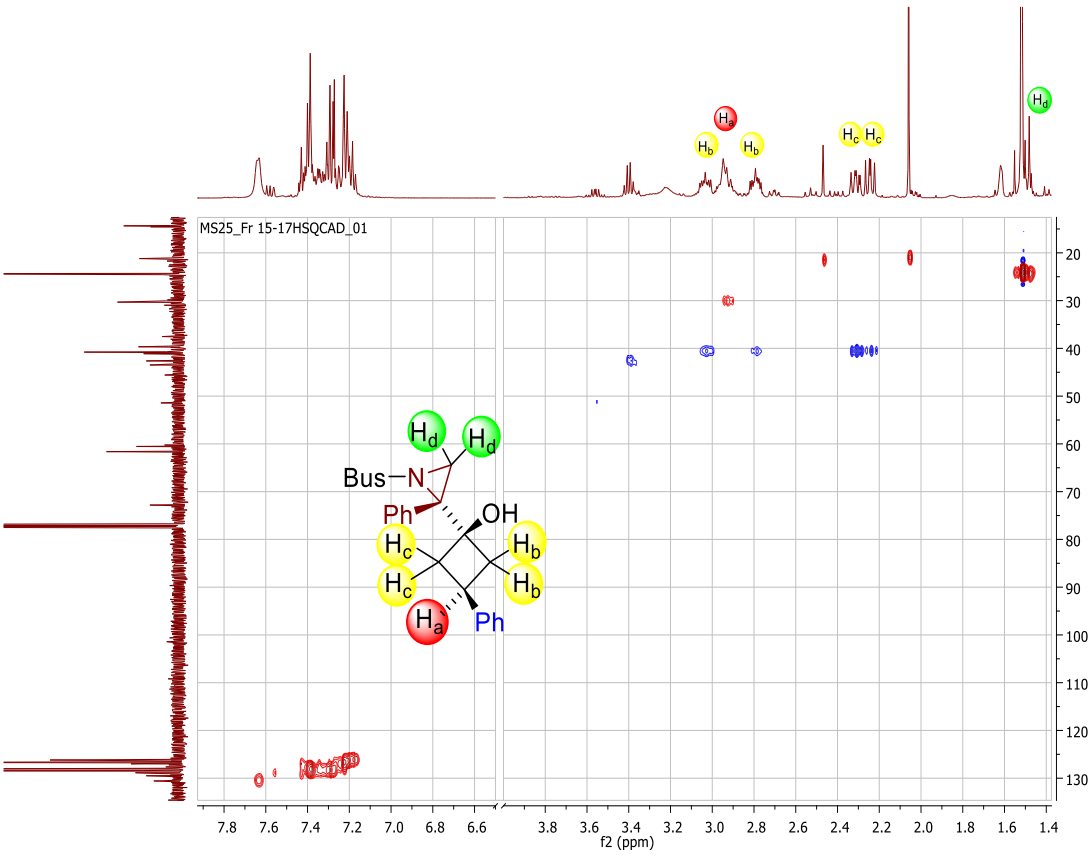

MS10Fr9-13_HSQCAD_01
Ph
OH
f2 (ppm)

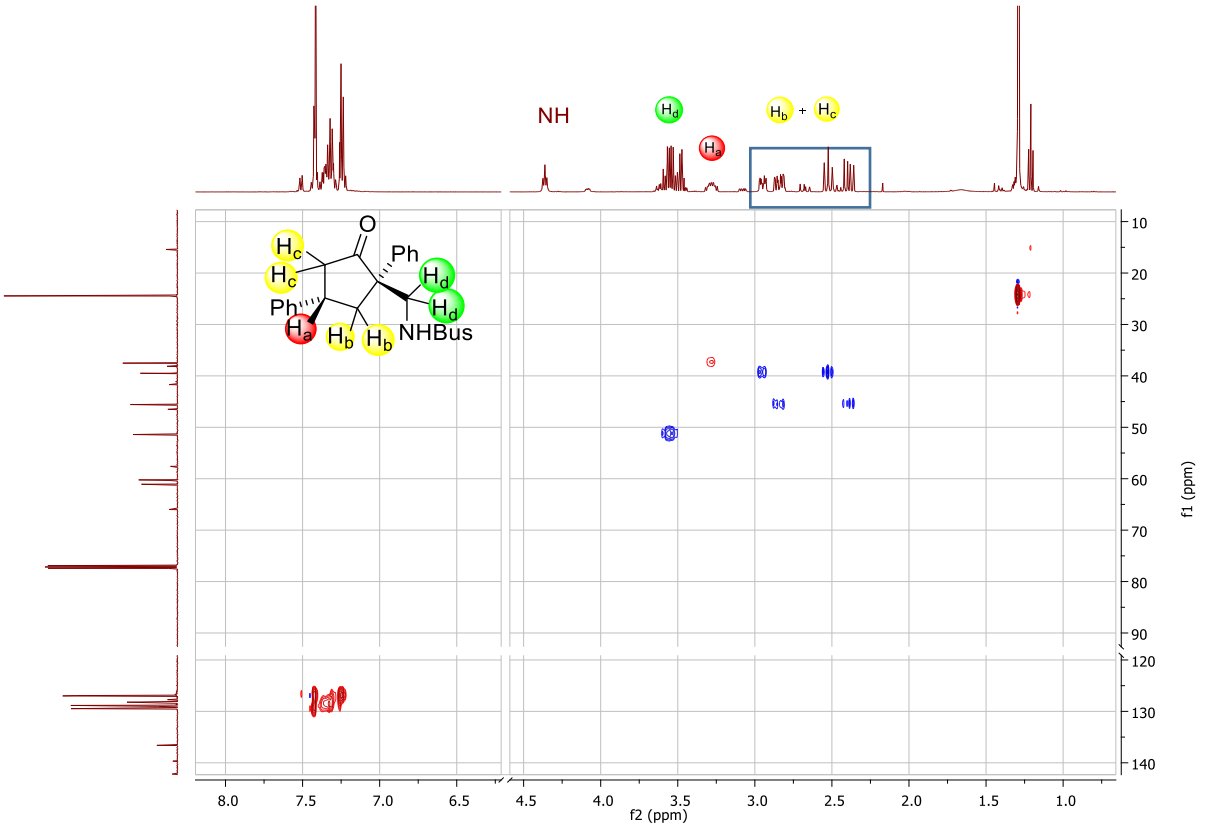

OH
O
Hex
Ph
H
MS10Fr9-13_gCOSY_01
f2 (ppm)

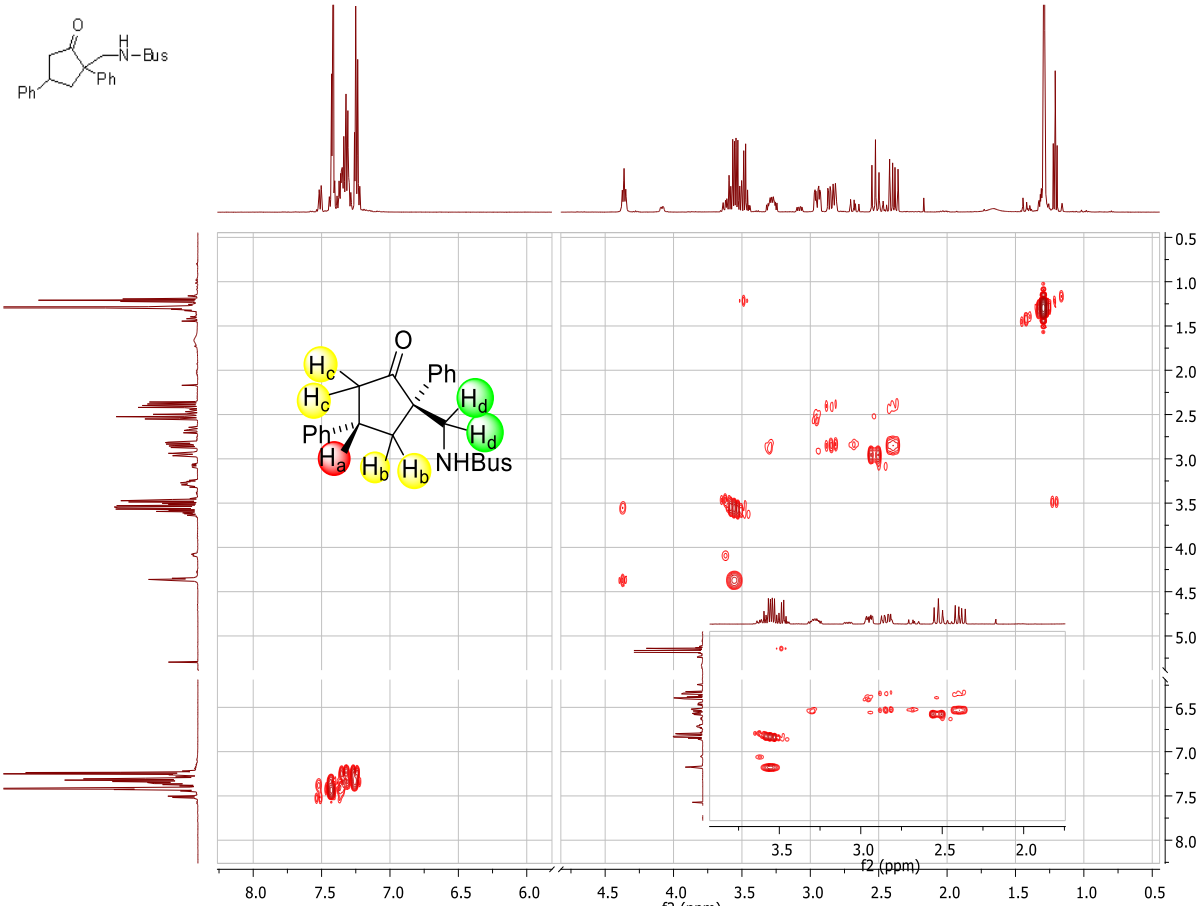

Hex
O
Ph
H
HO
Hd
Hd
Ha + Hb + Hc + CH2 Hexyl
MS12-fr12-18-HMQC
Hb
Hb
Hex
Ph
OH
Ha
O
Hc
Hc
Hd
Hd
f2 (ppm)


OH
O
O
S
N
H
Ph

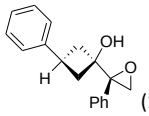

f2 (ppm)
f1 (ppm)


MS25_Fr 15-17HSQCAD_01
Bus—N
Ph
OH
Ph
f2 (ppm)

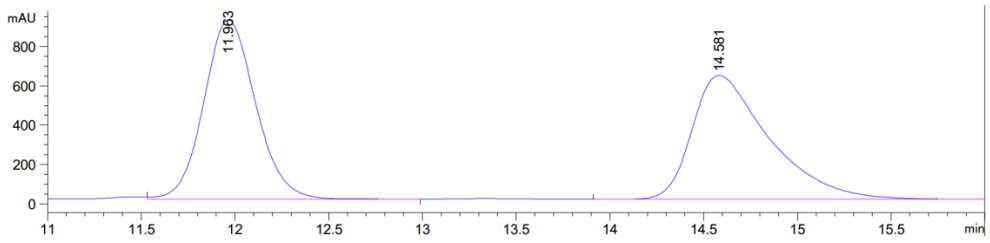

NH
Hd
Ha
Hb + Hc
O
Ph
Hc
Hc
Hd
Hd
Ph
Ha
Hb
Hb
NHBus
f2 (ppm)
f1 (ppm)

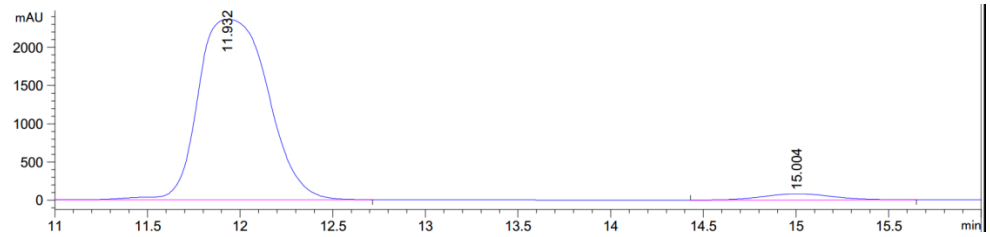

O
H
N
Bus
Ph
Ph
Hc
Hc
Ph
Hd
Hd
Ha
Hb
Hb
NHBus
f2 (ppm)

11. HPLC traces of compounds 3 and 4

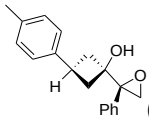


(1*s*,3*S*)-1-[(*R*)-(2-Phenyloxiran-2-yl]-3-phenylcyclobutanol **(3a)**

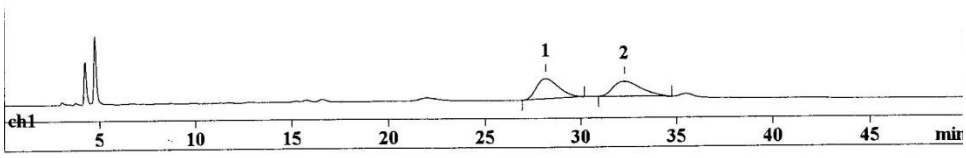


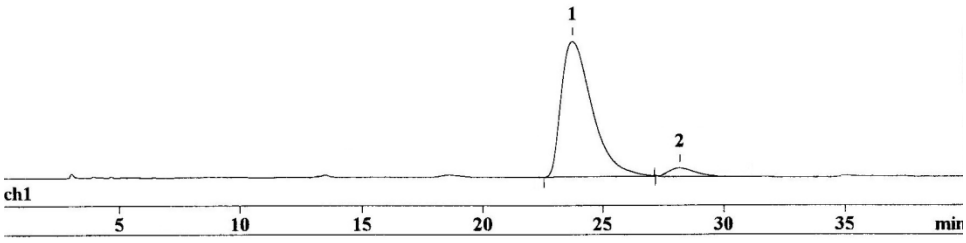


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.932	BB	0.4178	6.14731e4	2360.42358	96.6742
2	15.004	BB	0.3993	2086.60693	81.33622	3.2815



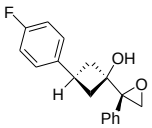
(1*s*,3*S*)-1-[(*R*)-(2-Phenyloxiran-2-yl]-3-(p-tolyl)cyclobutanol **(3b)**



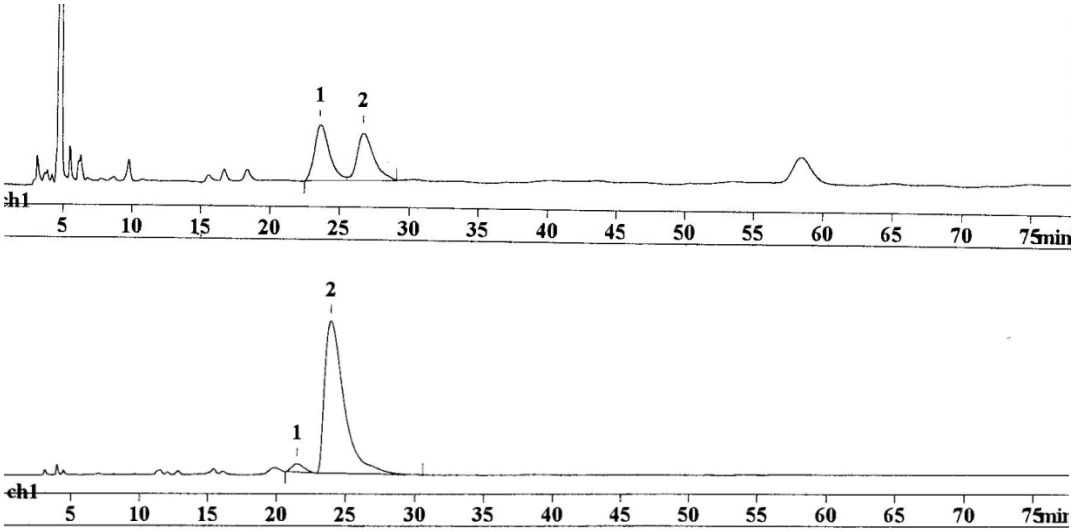


Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

No	Retention min	Area mV*sec	Area %	Name
1	24.15	6173.113	93.46	
2	27.01	431.729	6.54	
2	40.00	6604.842	100.00	

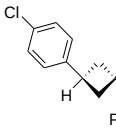


(1*s*,3*S*)-3-(4-fluorophenyl)-1-[(*R*)-2-phenyloxiran-2-yl]cyclobutanol **(3c)**

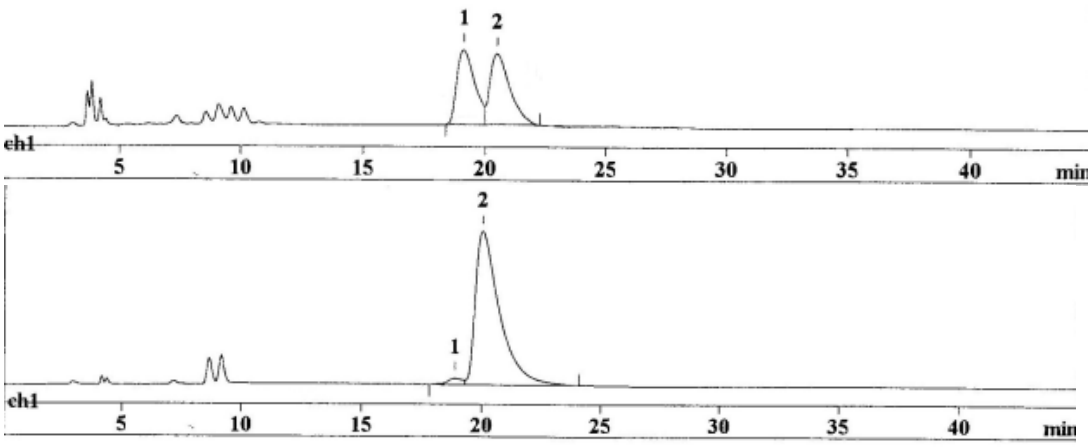


Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

No	Retention min	Area mV*sec	Area %	Name
1	21.51	519.985	3.51	
2	23.97	14294.281	96.49	
2	78.00	14814.266	100.00	

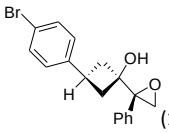


(1*s*,3*S*)-3-(4-Chlorophenyl)-1-[(*R*)-2-phenyloxiran-2-yl]cyclobutanol **(3d)**

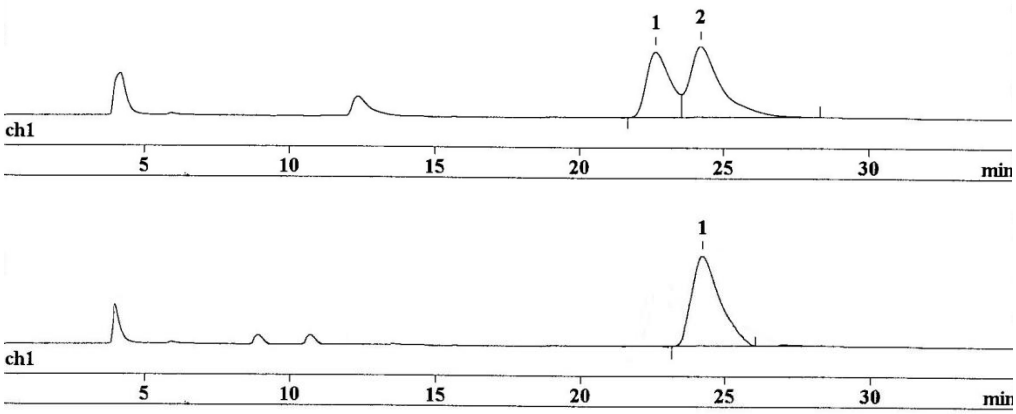


Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

No	Retention min	Area mV*sec	Area %	Name
1	18.89	155.131	2.69	
2	20.02	5622.045	97.31	
2	45.00	5777.175	100.00	

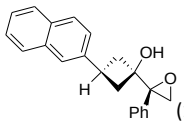


(1*s*,3*S*)-3-(4-Bromophenyl)-1-[(*R*)-2-phenyloxiran-2-yl]cyclobutanol **(3e)**

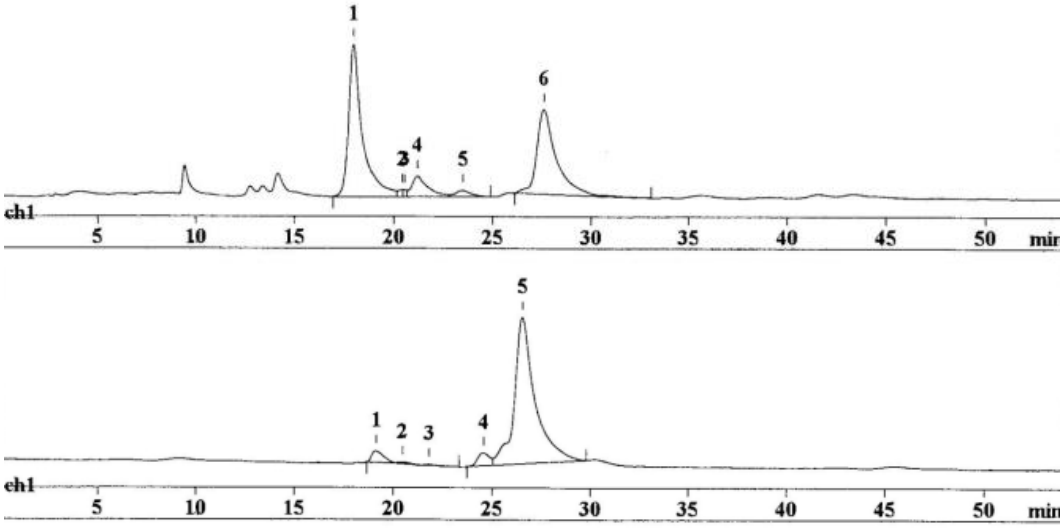


Quantitation method: Absolute concentration

No	Retention min	Area mV*sec	Area %	Name
1	24.93	43857.011	100.00	

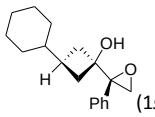


(1*s*,3*S*)-3-(Naphthalen-2-yl)-1-[(*R*)-2-phenyloxiran-2-yl)cyclobutanol **(3f)**

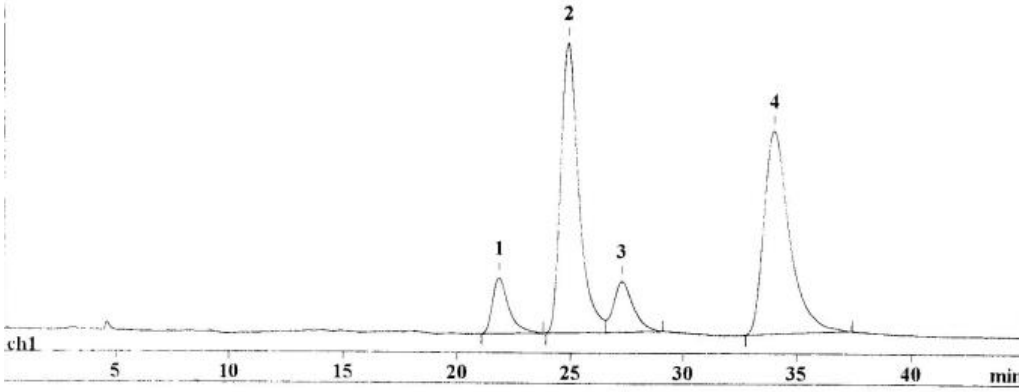


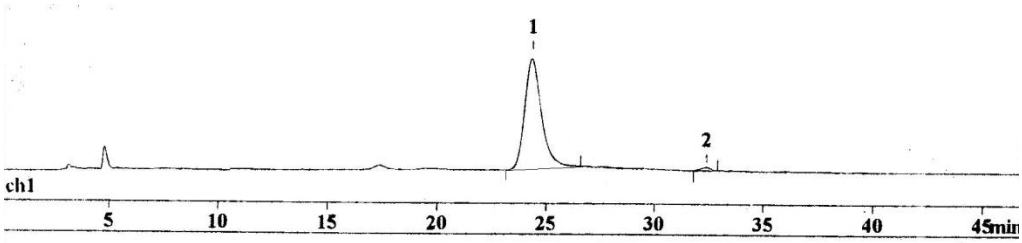
Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

No	Retention min	Area mV*sec	Area %	Name
1	19.11	192.358	4.17	
2	20.42	37.105	0.80	
3	21.80	14.761	0.32	
4	24.54	208.803	4.53	
5	26.49	4157.913	90.17	
5	54.00	4610.941	100.00	



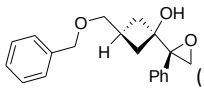
(1*s*,3*S*)-3-cyclohexyl-1-[(*R*)-2-phenyloxiran-2-yl]cyclobutanol **(3g)**



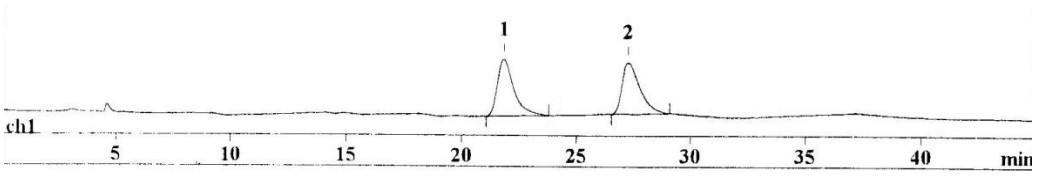


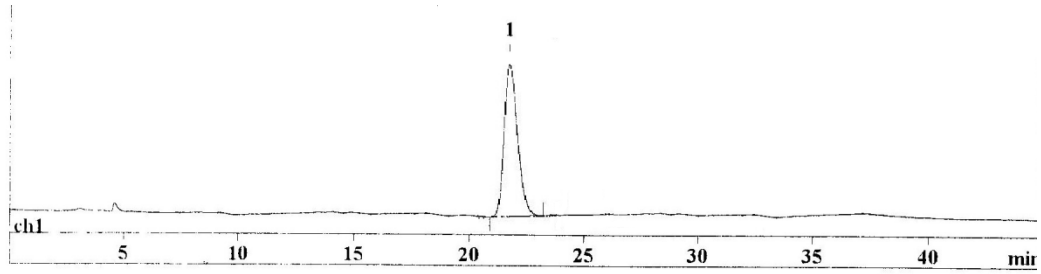
Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

No	Retention min	Area mV*sec	Area %	Name
1	24.09	11103.149	99.38	
2	32.55	69.593	0.62	
2	46.86	11172.742	100.00	



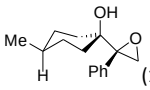
(1*s*,3*S*)-3-(benzyloxymethyl)-1-[(*R*)-2-phenyloxiran-2-yl]cyclobutanol **(3i)**



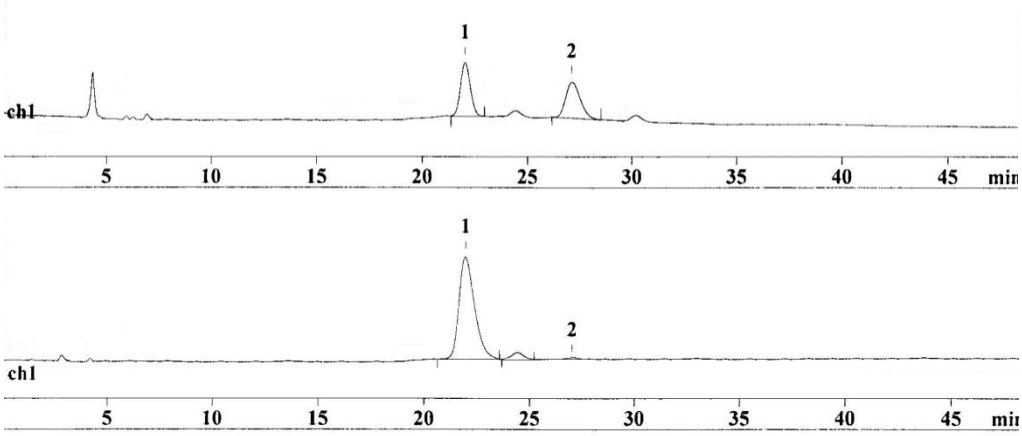


Quantitation method: Absolute concentration

No	Retention min	Area mV*sec	Area %	Name
1	22.15	6395.389	100.00	

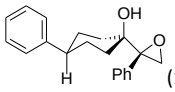


(1*s*,4*S*)-4-methyl-1-[(*R*)-2-phenyloxiran-2-yl]cyclohexanol **(3j)**

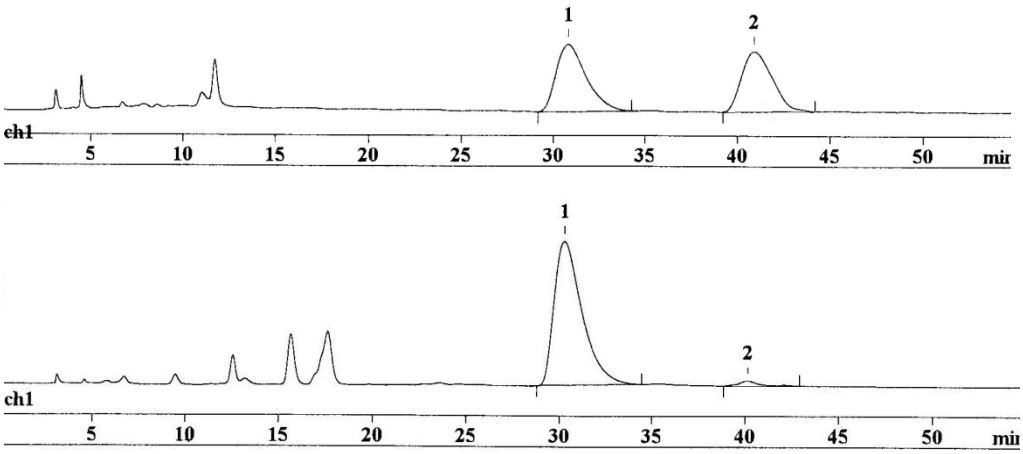


Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

No	Retention min	Area mV*sec	Area %	Name
1	22.02	1175.062	97.13	
2	27.13	37.720	2.87	
2	48.51	1209.782	100.00	

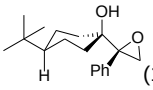


(1*s*,4*S*)-4-phenyl-1-[(*R*)-2-phenyloxiran-2-yl]cyclohexanol **(3k)**

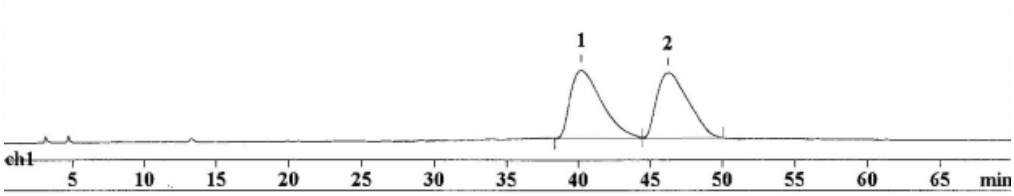


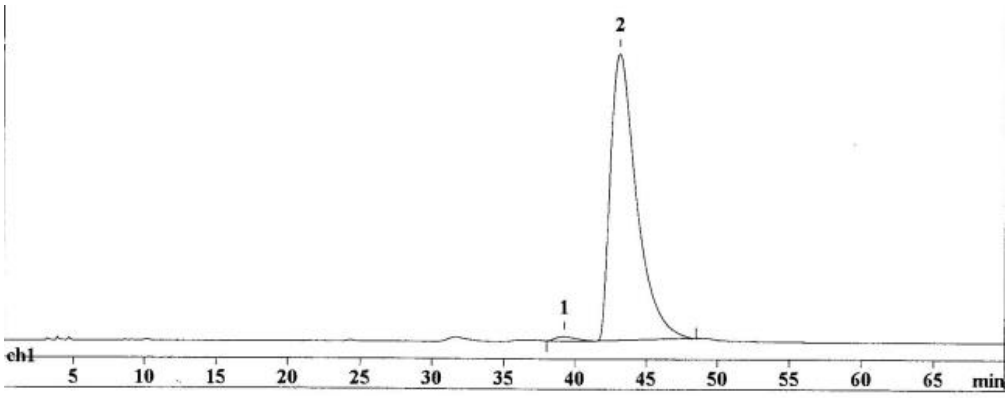
Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

No	Retention min	Area mV*sec	Area %	Name
1	30.23	10595.896	98.05	
2	40.38	539.633	1.95	
2	55.00	11135.529	100.00	



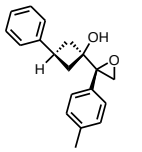
(1*s*,4*S*)-4-tert-butyl-1-[(*R*)-2-phenyloxiran-2-yl]cyclohexanol **(3l)**



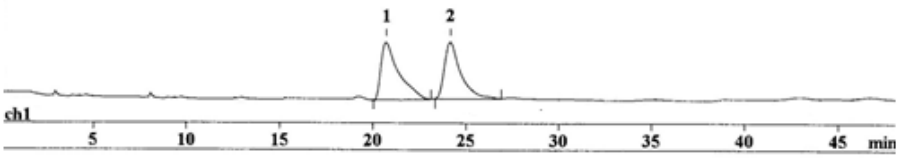


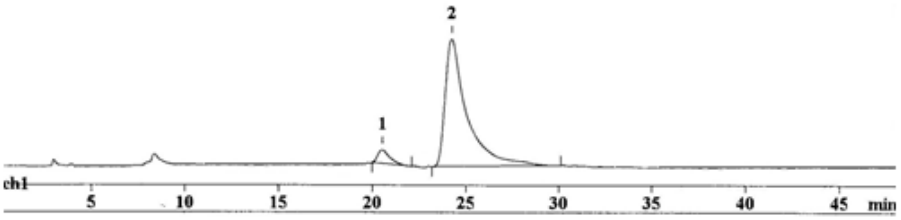
Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

No	Retention min	Area mV*sec	Area %	Name
1	39.23	710.719	1.20	
2	43.07	58373.934	98.80	
2	70.00	59084.653	100.00	



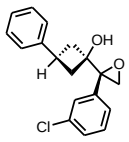
(1*s*,3*S*)-1-[(*R*)-(3-Phenyl-1-(2-p-tolyl-oxiranyl)-cyclobutanol **(3ab)**



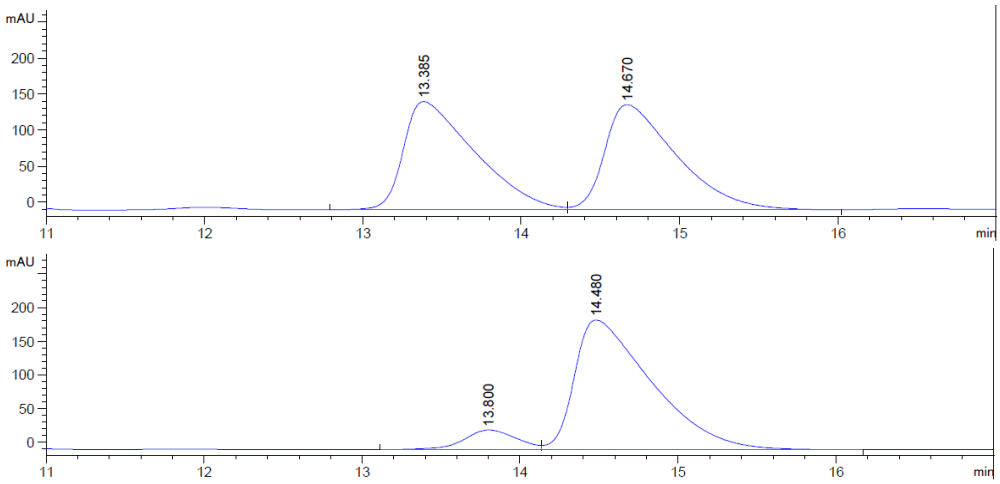


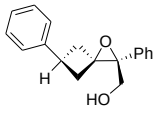
Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

No	Retention min	Area mV*sec	Area %	Name
1	20.45	165.894	5.94	
2	23.02	2626.948	94.06	
2	45.00	2792.842	100.00	

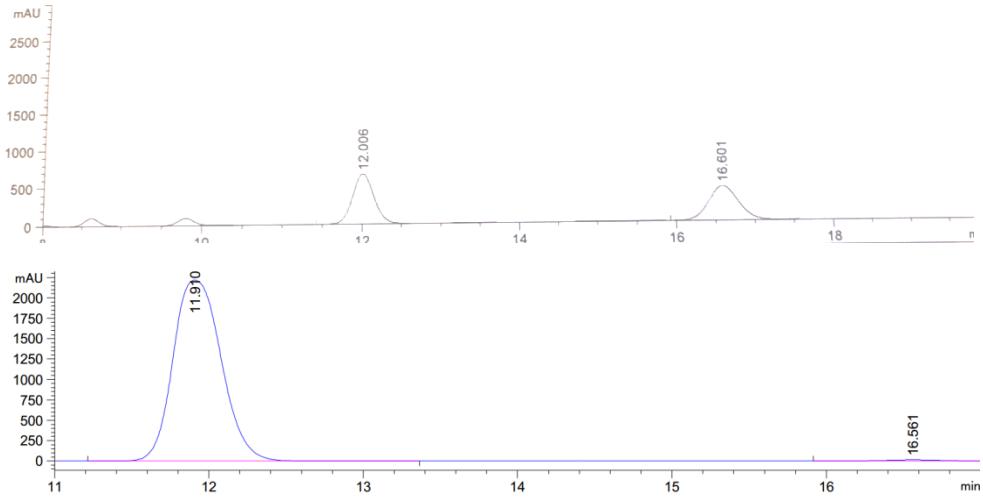


(1*s*,3*S*)-1-[(*R*)-(3-Chloro-phenyl)-oxiranyl]-3-phenyl-cyclobutanol **(3ad)**

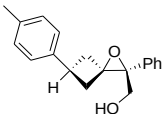




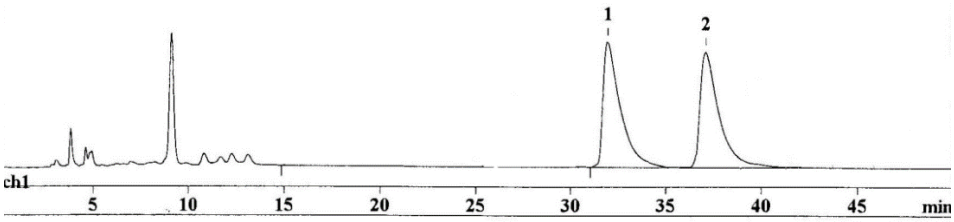
[(2*S*,3*s*,5*R*)-2,5-diphenyl-1-oxaspiro[2.3]hexan-2-yl]methanol **(4a)**

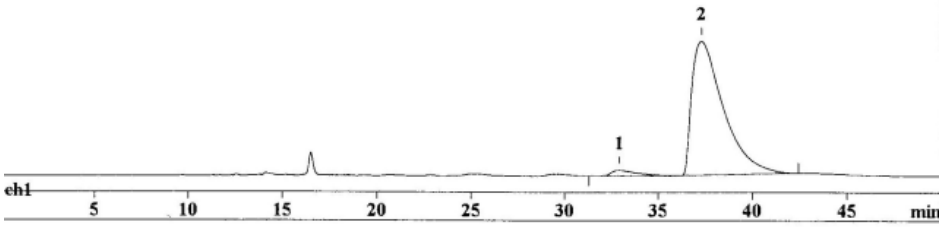


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.910	BB	0.3421	4.79466e4	2219.06689	99.2376
2	16.561	BB	0.3944	368.37634	14.30523	0.7624



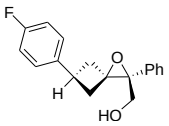
[(2*S*,3*s*,5*R*)-2-Phenyl-5-(p-tolyl)-1-oxaspiro[2.3]hexan-2-yl]methanol **(4b)**



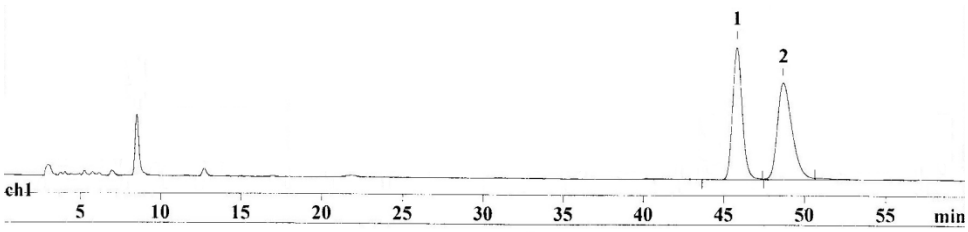


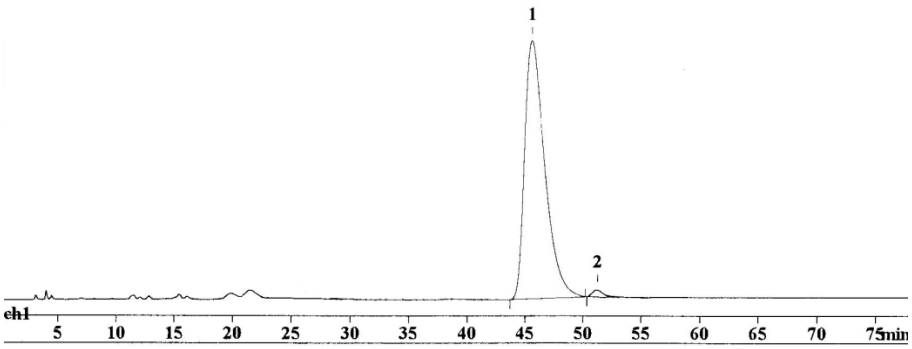
Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

No	Retention min	Area mV*sec	Area %	Name
1	32.88	1513.702	3.20	
2	37.25	45764.280	96.80	
2	50.00	47277.982	100.00	



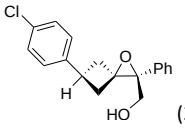
(2*S*,3*s*,5*R*)-[5-(4-Fluorophenyl)-2-phenyl-1-oxaspiro[2.3]hexan-2-yl]methanol **(4c)**



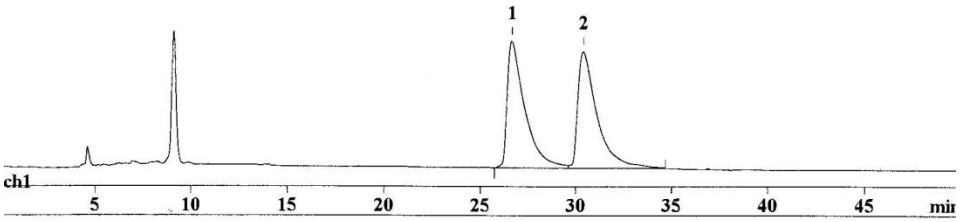


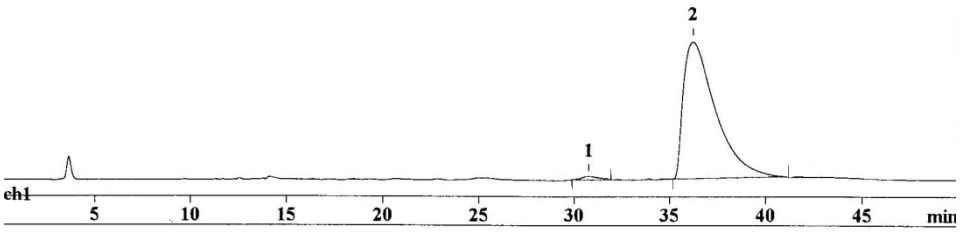
Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

No	Retention min	Area mV*sec	Area %	Name
1	46.97	270.912	1.86	
2	51.21	14294.281	98.14	
2	78.00	14565.193	100.00	



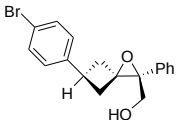
(2*S*,3*s*,5*R*)-[5-(4-Chlorophenyl)-2-phenyl-1-oxaspiro[2.3]hexan-2-yl]methanol **(4d)**



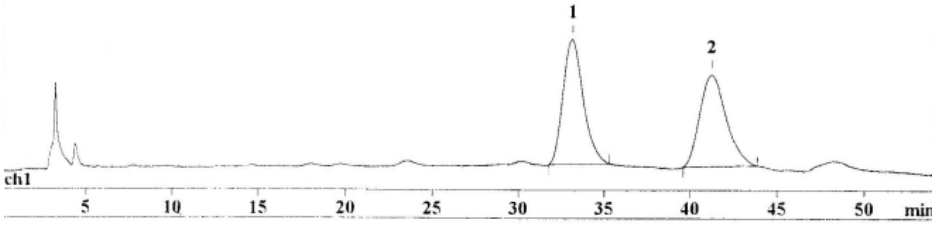


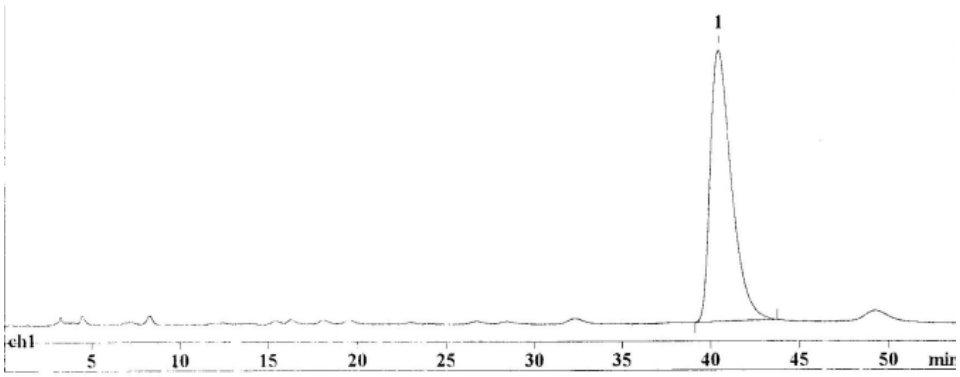
Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

No	Retention min	Area mV*sec	Area %	Name
1	31.13	1043.822	2.23	
2	36.29	45764.180	97.77	
2	50.00	46808.002	100.00	



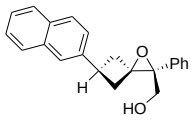
(2*S*,3*s*,5*R*)-[5-(4-Bromophenyl)-2-phenyl-1-oxaspiro[2.3]hexan-2-yl]methanol **(4e)**



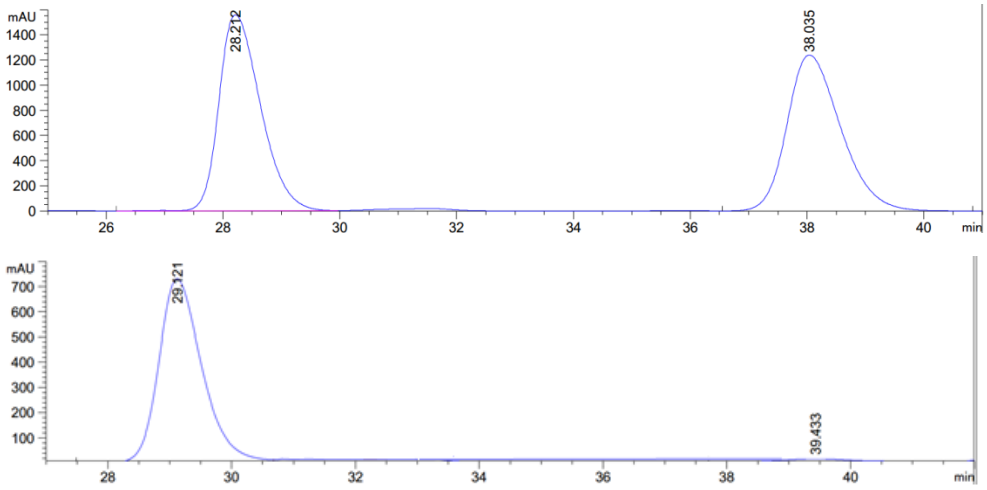


Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

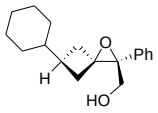
No	Retention min	Area mV*sec	Area %	Name
1	40.43	3558.049	100.00	



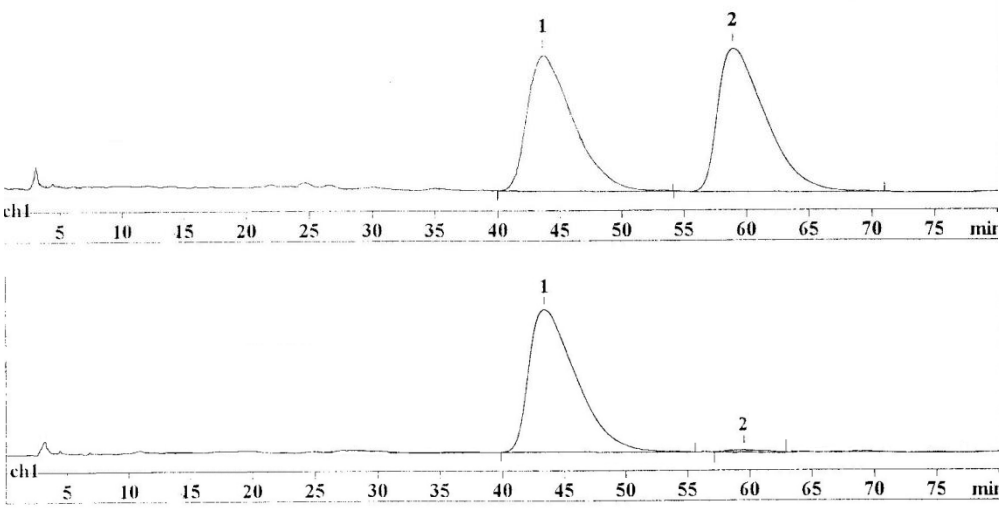
[(2*S*,3*s*,5*R*)-5-(Naphthalen-2-yl)-2-phenyl-1-oxaspiro[2.3]hexan -2-yl)methanol **(4f)**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.121	BV	0.7358	3.51984e4	728.35657	96.8471
2	39.433	BB	1.1740	1145.89722	12.83028	3.1529
Totals :				3.63443e4	741.18685	

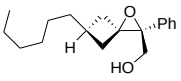


[(2*S*,3*s*,5*R*)-5-Cyclohexyl-2-phenyl-1-oxa-spiro[2.3]hexan-2-yl]methanol **(4g)**

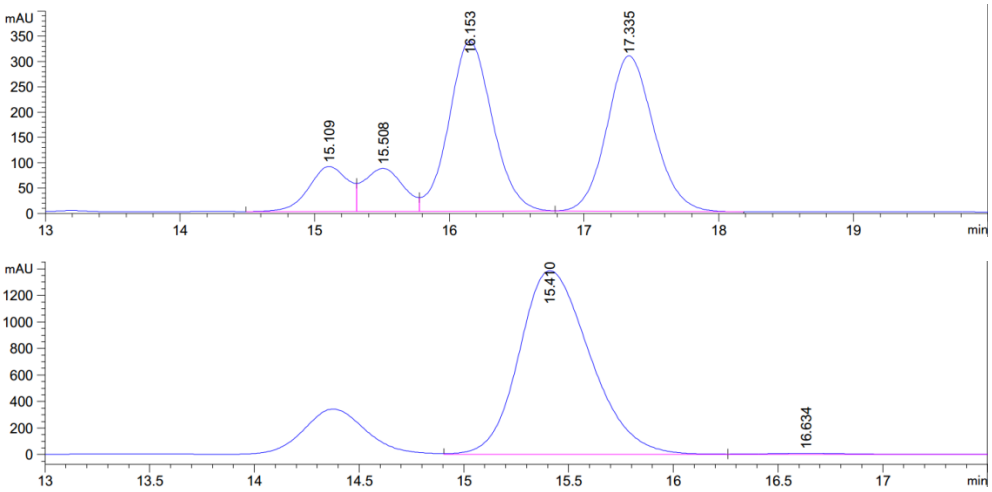


Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

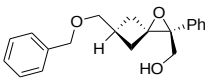
No	Retention min	Area mV*sec	Area %	Name
1	43.77	2397.168	99.65	
2	59.72	8.179	0.34	
2	80.00	2405.347	100.00	



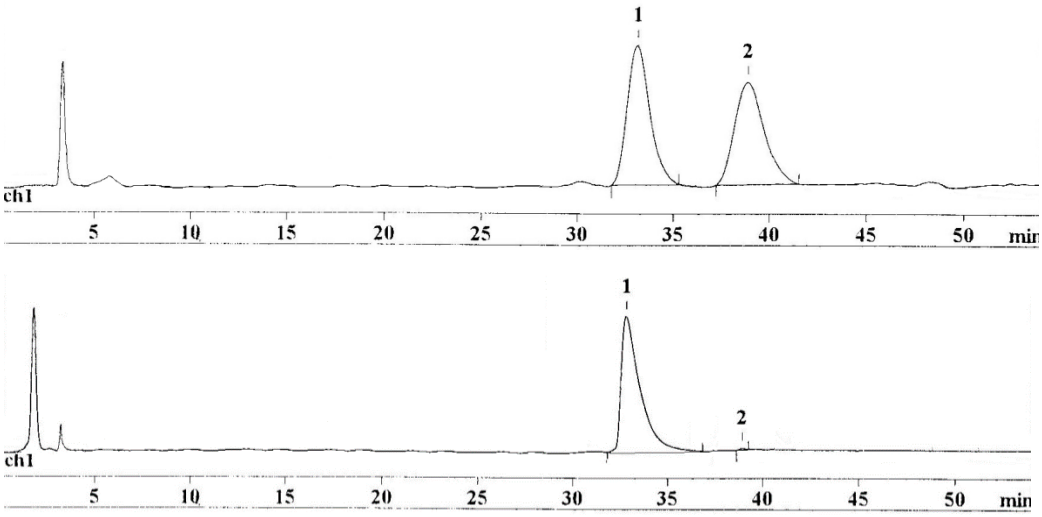
[(2*S*,3*s*,5*R*)-5-Hexyl-2-phenyl-1-oxa-spiro[2.3]hexan-2-yl]methanol **(4h)**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.410	VV	0.3647	3.26053e4	1384.76416	99.3012
2	16.634	VB	0.3800	229.45914	9.10516	0.6988
Totals :				3.28348e4	1393.86932	

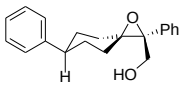


[(2*S*,3*s*,5*R*)-5-(benzyloxy)methyl)-2-phenyl-1-oxaspiro[2.3]hexan-2-yl]methanol **(4i)**

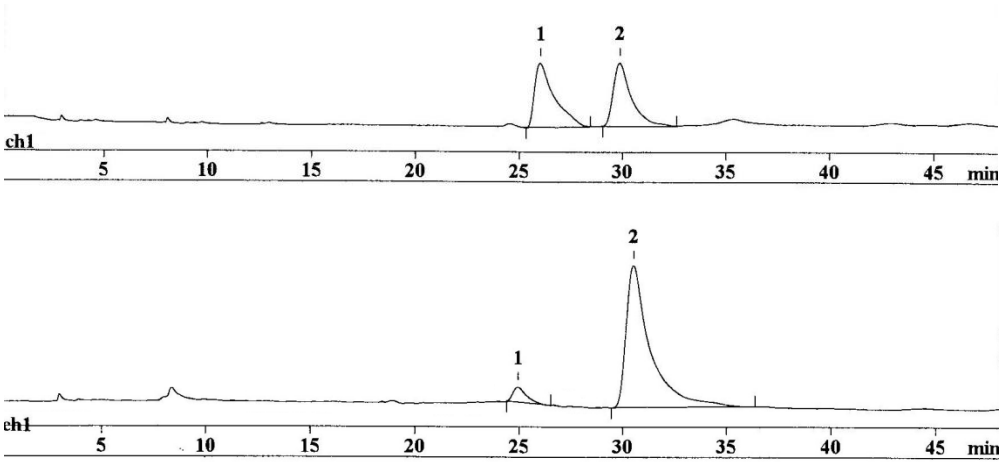


Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

No	Retention min	Area mV*sec	Area %	Name
1	33.19	1206.187	99.12	
2	38.31	10.708	0.88	
2	60.00	1216.895	100.00	

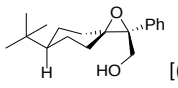


[(2*S*,3*s*,6*R*)-2,6-Diphenyl-1-oxaspiro[2.5]octan-2-yl)methanol **(4k)**

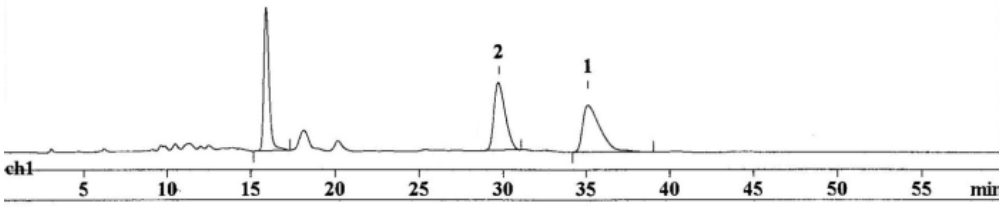


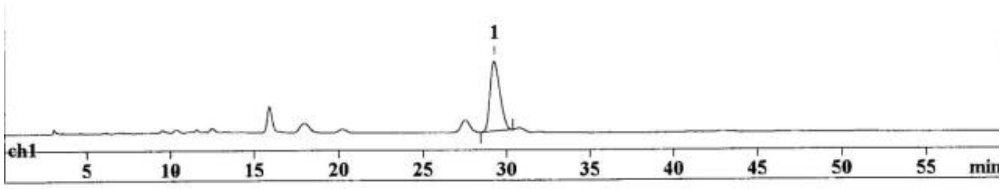
Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

No	Retention min	Area mV*sec	Area %	Name
1	24.94	155.365	5.55	
2	30.50	2643.870	94.45	
2	48.11	2799.234	100.00	



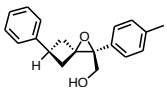
[(2*S*,3*s*,6*R*)-6-(tert-Butyl)-2-phenyl-1-oxaspiro[2.5]octan-2-yl]methanol **(4l)**



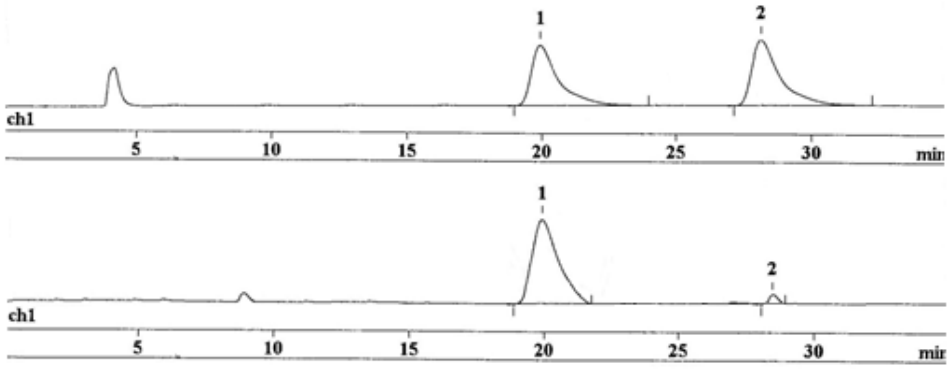


Quantitation method: Absolute concentration
Standard component: No
Normalization: 100.00

No	Retention min	Area mV*sec	Area %	Name
1	29.25	1508.713	100.00	

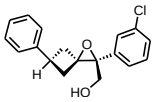


[(2S,3s,5R)-(5-Phenyl-2-p-tolyl-1-oxa-spiro[2.3]hex-2-yl)-methanol **(4ab)**

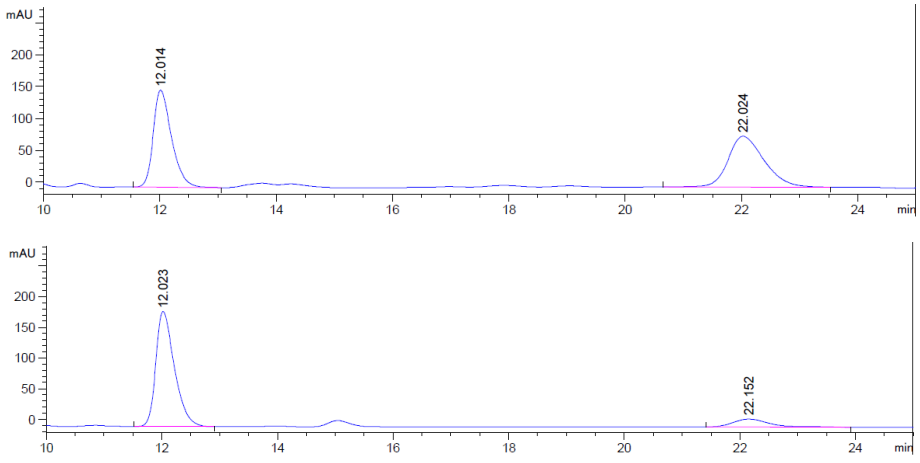


Quantitation method: Absolute concentration

No	Retention min	Area mV*sec	Area %	Name
1	19.52	4157.685	90.17	
2	28.76	453.255	9.83	
2	54.00	4610.941	100.00	



[(2*S*,3*s*,5*R*)-[2-(3-Chloro-phenyl)-5-phenyl-1-oxa-spiro[2.3]hex-2-yl]-methanol **(4ad)**



12. References and notes

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