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Supporting Information

Concise Synthesis of the Antidepressive Drug Candidate GSK1360707 by a Highly Enantioselective Gold-Catalyzed Enyne Cycloisomerization Reaction

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General: All reactions were carried out in flame-dried glassware under Ar. All the solvents were purified by distillation over the drying agents indicated and were transferred under Ar. THF, Et_2O (Mg-anthracene), CH_2Cl_2 (CaH_2), MeCN, Et_3N (CaH_2), MeOH (Mg), hexane, toluene (Na/K). Flash chromatography: Merck silica gel 60 (230-400 mesh). IR: Nicolet FT-7199 spectrometer, wavenumbers in cm^{-1}. MS (EI): Finnigan MAT 8200 (70 eV), ESI MS: Finnigan MAT 95, accurate mass determinations: Bruker APEX III FT-MS (7 T magnet). NMR: Spectra were recorded on a Bruker DPX 300, AV 400 or AV 600 spectrometer in the solvents indicated; ^1H and ^{13}C chemical shifts (δ) are given in ppm relative to TMS, coupling constants (J) in Hz. The solvent signals were used as references and the chemical shifts converted to the TMS scale. All commercially available compounds (Acros, Fluka, Lancaster, Aldrich) were used as received unless stated otherwise.

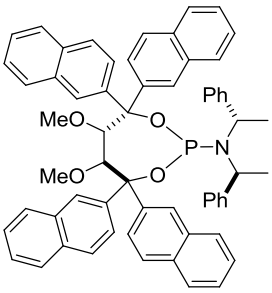
(2*S*,3*S*)-Diethyl 2,3-dimethoxysuccinate: Sodium hydride (960 mg, 40.0 mmol) was suspended in diethyl ether (200 mL) and the resulting suspension cooled to 0 °C (ice bath). Subsequently, (2*S*,3*S*)-diethyl tartrate (3.41 mL, 20.0 mmol) and dimethyl sulfate (3.89 mL, 41.0 mmol) were slowly added in parallel. The resulting mixture was stirred overnight at ambient temperature before the reaction was quenched with sat. aq. $NaHCO_3$ (100 mL). The aqueous phase was extracted with diethyl ether (3 x 50 mL), the combined organic layers were washed with aq. NH_4OH (50 mL, 10 % in H_2O), dried over $MgSO_4$ and evaporated to provide the title compound in quantitative yield as a colourless liquid. $[\alpha]_D^{20}$ = –72.4° (*c* =1.05, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 4.33-4.19 (m, 4H), 4.21 (s, 2H), 3.45 (s, 6H), 1.30 ppm (t, *J* = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 81.2, 61.3, 59.6, 14.2 ppm; IR (neat): $\tilde{\nu}$ = 2985, 2933, 2833, 1754, 1730, 1465, 1447, 1390, 1369, 1348, 1267, 1218, 1185, 1149, 1108, 1026, 926, 858, 810, 701 cm^{-1}; MS (70 eV): *m/z* (%): 234 [M^+] (8), 161 (18), 133 (55), 117 (73), 105 (19), 89 (35), 73 (23), 61 (55), 45 (89), 29 (100).[1]

(2*S*,3*S*)-2,3-Dimethoxy-1,1,4,4-tetra(naphthalen-2-yl)butane-1,4-diol: A solution of 2-bromonaphthalene (10.4 g, 50.0 mmol) in THF (100 mL) was cooled to −78 °C before *n*-BuLi (1.6 M in *n*-hexane, 31.3 mL, 50.0 mmol) was slowly added. The resulting yellow suspension was stirred for 1 h at that temperature before a cooled solution of (2*S*,3*S*)-diethyl 2,3-dimethoxysuccinate (2.34 g, 10.0 mmol) in THF (20 mL) was added dropwise. The resulting yellow suspension was stirred for 1 h at −78 °C before it was allowed to slowly reach ambient temperature over the course of 12 h. The reaction was quenched with aq. sat. NH_4Cl (50 mL). HCl (1 M, 5 mL) was added, the aqueous phase was extracted with methyl *tert*-butyl ether (3 x 50 mL), the combined organic layers were dried over $MgSO_4$, filtered and evaporated. The residue was purified by flash chromatography (Et_2O/pentane, 1/19 → 1/9 → 1/4) to give the title compound as a yellow foam (3.78 g, 58 %). $[\alpha]_D^{20}$ = +235.0° (*c* =1.02, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ = 8.29 (s, 2H), 8.22 (s, 2H), 8.02 (d, *J* = 8.5 Hz, 2H), 7.98-7.93 (m, 4H), 7.86 (dd, *J* = 8.5, 1.8 Hz, 2H), 7.80 (dd, *J* = 8.5, 1.8

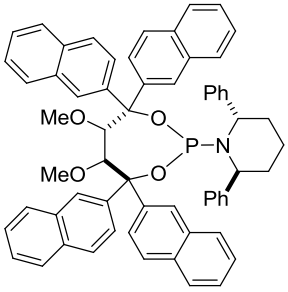
[1] K. Mori, *Tetrahedron* **1974**, 30, 4223-4227.

Hz, 2H), 7.73-7.67 (m, 6H), 7.61-7.54 (m, 4H), 7.44-7.37 (m, 4H), 5.24 (s, 2H), 4.86 (s, 2H), 2.71 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.8, 142.1, 133.3, 133.0, 132.5, 132.2, 128.4 (2C), 128.3, 127.6, 127.4, 127.2, 126.4, 126.3, 125.9, 125.9, 125.0, 124.9, 124.5, 124.2, 84.9, 80.6, 61.2 ppm; IR (neat): $\tilde{\nu}$ = 3426, 3055, 3017, 2962, 2931, 2830, 1666, 1630, 1598, 1505, 1444, 1354, 1271, 1241, 1198, 1160, 1124, 1074, 1018, 962, 900, 857, 819, 798, 772, 744, 686 cm^{-1}; MS (70 eV): *m/z* (%): 340 (18), 308 (85), 283 (100), 155 (93), 127 (33), 88 (5); HRMS (ESI): calcd for $C_{46}H_{38}O_4Na$ [M^+ + Na]: 677.2662, found: 677.2664.

(5*S*,6*S*)-5,6-Dimethoxy-4,4,7,7-tetra(naphthalen-2-yl)-*N*,*N*-bis((*S*)-1-phenylethyl)-1,3,2-dioxaphosphepan-2-amine (L6): Triethylamine (416 μL, 3.00 mmol) and PCl_3 (92 μL, 1.05 mmol) were successively added to a solution of (2*S*,3*S*)-2,3-dimethoxy-1,1,4,4-tetra(naphthalen-2-yl)butane-1,4-diol (655 mg, 1.00 mmol) and powdered 4Å molecular sieves (100 mg) in toluene (50 mL) at 0 °C. The cloudy mixture was heated to 60 °C for 1 h. After cooling to ambient temperature, the mixture was filtered under Ar, the filtrate was evaporated and the resulting yellowish foam dissolved in THF (5 mL).

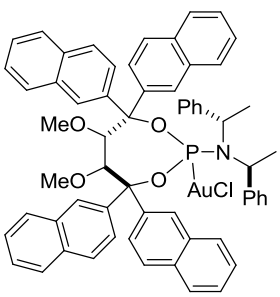


In parallel, *n*BuLi (1.6 M in *n*-hexane, 0.63 mL, 1.00 mmol) as added to a solution of (-)-bis-[(*S*)-1-phenylethyl]-amine (230 μL, 1.00 mmol) in THF (2 mL) at −10 °C and the resulting orange solution stirred at this temperature for 30 min before it was transferred via cannula to the chlorophosphite solution at −78 °C. The resulting orange mixture was stirred for 14 h at ambient temperature, the solvent was evaporated and crude material directly used in the next without further purification. ^{31}P NMR (162 MHz, C_6D_6): δ = 140.5 ppm.



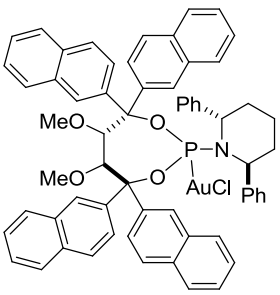
(2*S*,6*S*)-1-((5*S*,6*S*)-5,6-Dimethoxy-4,4,7,7-tetra(naphthalen-2-yl)-1,3,2-dioxaphosphepan-2-yl)-2,6-diphenylpiperidine (L7): Prepared according to the method described for **L6**. ^{31}P NMR (162 MHz, C_6D_6): δ = 135.0 ppm.

[(5*S*,6*S*)-5,6-Dimethoxy-4,4,7,7-tetra(naphthalen-2-yl)-*N*,*N*-bis((*S*)-1-phenylethyl)-1,3,2-dioxaphosphepan-2-amine] gold(I)chloride ([L6·AuCl]): Thiodiethanol (300 μL, 3.00 mmol) was slowly added to a solution of sodium tetrachloroaurate dihydrate (398 mg, 1.00 mmol) in water (50 mL) at 0 °C. A solution of the crude phosphoramidite **L6** in chloroform (10 mL) was introduced and the resulting heterogeneous mixture stirred for 1 h at 0 °C and for 3 h at ambient temperature. For work up, the phases were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with aq. sat. $NaHCO_3$, dried over $MgSO_4$, filtered and

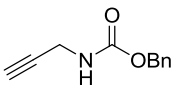


evaporated. The residue was purified by flash chromatography (CH_2Cl_2/*n*-hexane, 1/1) to give the title compound as a yellow solid (483 mg, 42 % based on the corresponding diol). $[\alpha]_D^{20}$ = +23.3° (*c* = 1.00, CH_2Cl_2); ^{1}H NMR (600 MHz, C_6D_6): δ = 9.08 (s, 1H), 8.60 (s, 1H), 8.25 (s, 1H), 8.11 (*br.* d, *J* = 8.7 Hz, 1H), 7.93-7.91 (m, 2H), 7.87-7.85 (m, 3H), 7.81 (d, *J* = 8.7 Hz, 1H), 7.69-7.62 (m, 7H), 7.55 (d, *J* = 8.1 Hz, 1H), 7.52 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.38-7.24 (m, 7H), 7.22-7.19 (m, 1H), 7.11-7.09 (m, 1H), 6.99-6.92 (m, 10H), 5.96 (br. s, 1H), 5.22 (*br.* s, 1H), 5.04 (br. s, 2H), 3.37 (br. s, 3H), 2.44 (s, 3H), 1.67 ppm (d, *J* = 7.1 Hz, 6H); ^{31}P NMR (162 MHz, C_6D_6): δ = 113.8 ppm; ^{13}C NMR (150 MHz, C_6D_6): δ = 142.3, 142.2, 141.4, 141.3, 140.4, 139.4, 139.4, 136.4, 133.7, 133.6, 133.5, 133.4, 133.3, 133.0, 132.9, 130.0, 129.0, 128.8, 128.7, 128.7, 128.5, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.3, 127.2, 127.1, 127.0, 126.9, 126.9, 126.8, 126.7, 126.7, 126.6, 125.4, 86.5, 81.3, 81.2, 60.3, 59.9, 53.3, 53.3, 21.1 ppm; IR (neat): $\tilde{\nu}$ = 3053, 2958, 2916, 2860, 2825, 1600, 1505, 1494, 1450, 1378, 1350, 1273, 1201, 1178, 1122, 1082, 1017, 1001, 962, 936, 904, 860, 812, 792, 766, 746, 698, 659 cm^{-1}; MS (ESI): *m/z* = 1162 [*M* + Na], 1178 [*M* + K]; HRMS (ESI): calcd for $C_{62}H_{54}NO_4PAuClNa$ [*M* + Na]: 1162.3037, found: 1162.3033.

[(2*S*,6*S*)-1-((5*S*,6*S*)-5,6-Dimethoxy-4,4,7,7-tetra(naphthalen-2-yl)-1,3,2-dioxaphosphe-pan-2-yl)-2,6-diphenylpiperidine] gold(I)chloride ([L7·AuCl]): Prepared analogously as a pale yellow foam (217 mg, 51 % based on the corresponding diol). $[\alpha]_D^{20}$ = +44.6° (*c* = 1.04, CH_2Cl_2); ^{1}H NMR (600 MHz, C_6D_6): δ = 9.27 (s, 1H), 8.53 (s, 1H), 8.31 (d, *J* = 7.9 Hz, 1H), 8.24 (d, *J* = 1.4 Hz, 1H), 7.95 (d, *J* = 1.4 Hz, 1H), 7.84-7.80 (m, 3H), 7.72 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.67-7.55 (m, 8H), 7.47 (d, *J* = 8.0 Hz, 1H), 7.38-7.35 (m, 3H), 7.32-7.24 (m, 9H), 7.22-7.19 (m, 1H), 7.14-7.12 (m, 1H), 7.10-7.07 (m, 2H), 7.03-7.00 (m, 4H), 5.93 (d, *J* = 6.8 Hz, 1H), 5.11 (d, *J* = 6.8 Hz, 1H), 4.89-4.85 (m, 2H), 3.21 (s, 3H), 2.42 (s, 3H), 2.22-2.06 (m, 2H), 2.02-1.97 (m, 2H), 1.54-1.50 ppm (m, 2H); ^{31}P NMR (162 MHz, C_6D_6): δ = 111.4 ppm; ^{13}C NMR (150 MHz, C_6D_6): δ = 141.8, 141.8, 140.4, 139.6, 139.5, 139.4, 139.3, 137.1, 137.1, 133.7, 133.6, 133.3, 133.3, 133.2, 133.1, 132.8, 130.0, 129.4, 129.2, 129.1, 128.9, 128.7, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.9, 127.9, 127.7, 127.7, 127.6, 127.2, 127.1, 127.0, 126.9, 126.8, 126.7, 126.7, 126.3, 126.0, 92.0, 91.9, 86.8, 82.0, 80.6, 80.6, 59.9, 59.6, 56.8, 56.8, 29.1, 20.9 ppm; IR (neat): $\tilde{\nu}$ = 3058, 3022, 2934, 2820, 1599, 1505, 1476, 1446, 1380, 1353, 1272, 1176, 1112, 1031, 1016, 1007, 959, 937, 890, 858, 819, 792, 743, 695, 677, 661 cm^{-1}; MS (ESI): *m/z* = 1174 [*M* + Na], 1190 [*M* + K]; HRMS (ESI): calcd for $C_{63}H_{54}NO_4PAuClNa$ [*M* + Na]: 1174.3037, found: 1174.3036.

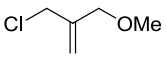


Benzyl prop-2-ynylcarbamate (8): Benzyl chloroformate (46 mL, 0.28 mol) was added over a period of 1 h to a stirred solution of prop-2-yn-1-amine **7** (16 mL, 0.25 mol) and $NaHCO_3$ (42 g, 0.50 mol) in ethanol/water (500 mL, 1:1, v/v) at 0 °C. After stirring for 1 h at 0 °C and 12 h at room temperature, the mixture was diluted with water (200 mL) and methyl *tert*-butylether (250 mL). The aqueous phase was extracted with methyl *tert*-butyl ether (2 x 250 mL), the combined organic layers were dried over $MgSO_4$, filtered and evaporated. The

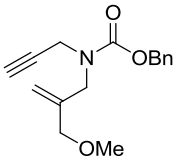


remaining brown liquid was dried for 3h at 120 °C and $7 \cdot 10^{-3}$ mbar before it was taken up in dichloromethane (50 mL) and filtered through a short plug of silica eluting with methyl *tert*-butyl ether/hexanes (1:4 → 1:1). The solvent was evaporated to give the title compound as a colourless crystalline solid in quantitative yield (47.2 g) ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C): δ = 7.36-7.29 (m, 5H), 5.14 (s, 2H), 4.85 (s, 1H), 3.99 (dd, *J* = 5.7, 2.6 Hz, 2H), 2.23 ppm (t, *J* = 2.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C): δ = 155.8, 136.5, 128.5, 128.2, 128.1, 79.7, 71.6, 67.2, 31.1 ppm; IR (neat): $\tilde{\nu}$ = 3294, 3065, 3033, 2953, 1697, 1586, 1513, 1454, 1424, 1350, 1325, 1239, 1138, 1080, 1044, 979, 915, 824, 776, 736, 695 cm^{-1}; MS (70 eV): *m/z* (%): 189 [M^+] (8), 128 (14), 108 (88), 91 (100), 79 (30), 65 (20), 51 (10), 39 (21); HRMS (ESI): calcd for $C_{11}H_{11}NO_2$ [M^+]: 189.0790, found: 189.0792. The physical and spectroscopic properties matched those described in the literature.[2]

3-Chloro-2-(methoxymethyl)prop-1-ene (5): Sodium methoxide (21.6 g, 400 mmol) was added in one portion to a solution of methallyl dichloride (11.6 mL, 100 mmol) in methanol (100 mL) at 70 °C and the resulting suspension vigourusly stirred for 1h at the same temperature. The reaction was quenched with water (100 mL) and the biphasic mixture allowed to cool to ambient temperature. The product was extracted with pentane (3 x 100 mL), the combined organic layers were dried ($MgSO_4$), filtered and evaporated. Flash chromatography of the residue (pentane/diethyl ether, 100:0 → 98:2) gave compound **5** as a colourless liquid (5.1 g, 41 %, 53 % brsm). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.30 (d, *J* = 1.1 Hz, 1H), 5.23 (q, *J* = 1.1 Hz, 1H), 4.09 (d, *J* = 1.1 Hz, 2H), 4.02 (s, 2H), 3.35 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 141.9, 116.7, 72.6, 58.2, 45.1 ppm. The physical and spectroscopic properties matched those described in the literature.[3]



Benzyl 2-(methoxymethyl)allyl(prop-2-ynyl)carbamate (9). At 0 °C sodium hydride (264 mg, 11.0 mmol) was added to a solution of benzyl carbamate **8** (1.89 g, 10.0 mmol) and 3-chloro-2-(methoxymethyl)prop-1-ene **5** (1.45 g, 12.0 mmol) in THF/DMF (1/1, 50 mL). The resulting white suspension was stirred at ambient temperature until TLC indicated consumption of the substrate. Thereafter, water (25 mL) was added and the product extracted with ethyl acetate (3 x 25 mL), the combined organic layers were washed with brine (25 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue (pentane/diethyl ether, 9:1 → 4:1) gave the desired product as a colourless liquid (2.48 g, 91 %). ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C): δ = 7.38-7.28 (m, 5H), 5.18 (s, 3H), 5.06 (s, 1H), 4.10 (s, 2H), 4.06 (s, 2H), 3.85 (s, 2H), 3.29 (s, 3H), 2.20 ppm (t, *J* = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C): δ = 155.8, 141.2, 136.7, 128.4, 128.0, 127.9, 114.1, 79.1, 73.7, 71.8, 67.6, 58.0, 48.7, 36.0 ppm; IR (neat): $\tilde{\nu}$ = 3291, 3067, 3033, 2983, 2931, 2893, 2820, 1698, 1587, 1534, 1498, 1453, 1411, 1367, 1353, 1290, 1229, 1193, 1107, 994, 946, 909, 877, 824, 768, 735, 696, 675 cm^{-1}; MS (70 eV): *m/z* (%): 273 [M^+] (1), 198 (2), 138 (24), 128 (1), 106 (7), 91 (100), 77 (6), 65 (8), 55 (5), 39 (5); HRMS (ESI): calcd for $C_{16}H_{19}NO_3Na$ [M^+ + Na]: 296.1257, found: 296.1256.



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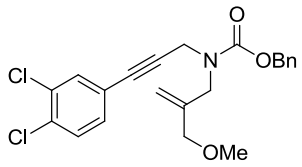
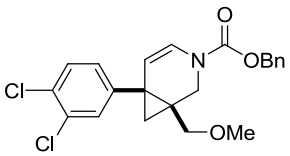
2 T. Masquelin, D. Obrecht, *Synthesis* **1995**, 276-284.

3 R. M. Wilson, R. K. Thalji, R. G. Bergman, J. A. Ellman, *Org. Lett*. **2006**, *8*, 1745-1747.

Benzyl 3-(3,4-dichlorophenyl)prop-2-ynyl(2-(methoxymethyl)allyl)carbamate (10). 

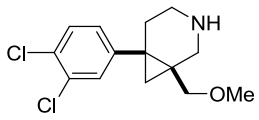
Triethylamine (1.72 mL, 13.4 mmol), $PdCl_2(PPh_3)_2$ (157 mg, 220 μmol) and copper iodide (85.4 mg, 450 μmol) were added to a solution of alkyne **9** (2.45 g, 8.96 mmol) and 1,2-dichloro-4-iodobenzene **4** (2.69 g, 9.86 mmol) in DMF (10 mL) and the resulting dark orange solution was stirred at ambient temperature until TLC indicated consumption of the substrate (5 h). At this point, aq. sat. NH_4Cl (25 mL) was added and the product extracted with ethyl acetate (3 x 25 mL), the combined organic layers were washed with 2-dimethylaminoethanethiol hydrochloride (25 mL, 10 % in water) and brine (25 mL), dried ($MgSO_4$), filtered and evaporated. Flash chromatography of the residue (hexanes/ethyl acetate, 19:1 → 9:1) gave the desired product as a pale yellow liquid (3.56 g, 95 %). ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C): δ = 7.47 (d, J = 1.4 Hz, 1H), 7.39-7.30 (m, 6H), 7.20 (dd, J = 8.3, 1.4 Hz), 5.20 (s, 3H), 5.09 (s, 1H), 4.31 (s, 2H), 4.10 (s, 2H), 3.88 (s, 2H), 3.30 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C): δ = 155.8, 141.3, 136.7, 133.4, 132.9, 132.6, 130.8, 130.3, 128.5, 128.1, 127.9, 122.9, 114.1, 86.9, 81.6, 73.7, 67.6, 58.0, 49.1, 36.9 ppm; IR (neat): $\tilde{\nu}$ = 3066, 3033, 2982, 2926, 2891, 2819, 1700, 1586, 1546, 1498, 1457, 1408, 1367, 1351, 1227, 1193, 1106, 1031, 993, 910, 879, 819, 767, 752, 734, 696, 683 cm^{-1}; MS (70 eV): *m/z* (%): 418 [M^+] (1), 326 (21), 282 (28), 253 (7), 223 (5), 183 (16), 91 (100), 64 (4); HRMS (ESI): calcd for $C_{22}H_{21}O_3Cl_2N$+Na [M^+ + Na]: 440.0791, found: 440.0793.

(+)-(1*S*,6*R*)-Benzyl 6-(3,4-dichlorophenyl)-1-(methoxymethyl)-3-azabicyclo[4.1.0]-hept-4-ene-3-carboxylate ((+)-14). 

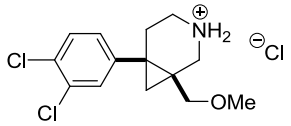
A mixture containing [**L6**·AuCl] (31.4 mg, 27.5 μmol) and $AgBF_4$ (4.87 mg, 25.0 μmol) in toluene (2 mL) was stirred for 10 min at ambient temperature and for 5 min at 0 °C in a capped vial before it was transferred to a cold (0 °C) solution of enyne **10** (418 mg, 1.00 mmol) in toluene (3 mL) via cannula equipped with a PTFE filter (Perfect-Flow®, 0.45 μm pore size, ∅ 13 mm) to retain the precipitates. The resulting yellow solution was stirred until TLC showed complete conversion of the substrate. At this point, the solution was loaded on top of a silica gel column and the product eluted with methyl *tert*-butyl ether/hexanes (1:19 → 1:9) to give the title compound as a colourless oil (367 mg, 88 %). $[\alpha]_D^{20}$ = +179.0° (*c* 1.00, MeOH, 95 % *ee*); ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C): δ = 7.41 (d, J = 2.1 Hz, 1H), 7.39-7.31 (m, 6H), 7.14 (dd, J = 8.3, 2.1 Hz, 1H), 6.62 (*br.* s, 1H), 5.23 (s, 2H), 5.16 (d, J = 8.4 Hz, 1H), 4.28 (d, J = 12.2 Hz, 1H), 3.43 (d, J = 12.2 Hz, 1H), 3.11 (s, 3H), 3.09 (d, J = 14.6 Hz, 2H), 2.97 (d, J = 10.2 Hz, 1H), 1.44 (d, J = 5.1 Hz, 1H), 1.29 ppm (d, J = 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 60 °C): δ = 154.0, 141.6, 136.3, 132.3, 131.5, 130.9, 130.1, 128.8, 128.6, 128.3, 128.1, 122.4, 114.1, 75.2, 67.8, 58.7, 42.1, 29.7, 27.8, 22.8 ppm; IR (neat): $\tilde{\nu}$ = 3067, 3034, 2982, 2926, 2891, 2830, 1705, 1647, 1592, 1554, 1497, 1470, 1448, 1411, 1389, 1339, 1304, 1233, 1193, 1171, 1100, 1056, 1029, 1002, 951, 908, 884, 850, 823, 804, 783, 762, 729, 696, 676 cm^{-1}; MS (70 eV): *m/z* (%): 418 [M^+] (1), 328 (8), 282 (13), 250 (4), 91 (100), 65 (5), 45 (13); HRMS (ESI): calcd for $C_{22}H_{21}O_3Cl_2N_1Na_1$ [M^+ + Na]: 440.0791, found: 440.0791; HPLC: 250 mm Chiralpak IA, 5 μm, No.:

IA00CE-LH028, *n*-heptane/*i*-propanol = 70/30, flow rate = 1.0 mL/min; major enantiomer t_R = 5.76 min; minor enantiomer t_R = 11.31 min.

(–)-GSK1360707 ((–)-1). Azabicyclo[4.1.0]hept-4-ene (+)-**14** (325 mg, 0.780 mmol) was dissolved in



ethyl acetate/methanol (1/1, 10 mL). Na_2CO_3 (83 mg, 0.78 mmol) and palladium black (2.1 mg, 20 μmol) were added and the resulting suspension was stirred for 30 h under 1 atm of hydrogen at ambient temperature. The solvent was evaporated, aq. sat. $NaHCO_3$ (25 mL) was added and the product extracted with diethyl ether (4 x 25 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated, giving (–)-GSK1360707 as a colourless oil (202 mg, 91 %). $[\alpha]_D^{20}$ = –7.5° (*c* = 0.58, CCl_4); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 2.1 Hz, 1H), 7.35 (d, *J* = 8.4 Hz, 1H), 7.17 (dd, *J* = 8.4, 2.1 Hz, 1H), 3.32 (d, *J* = 12.9 Hz, 1H), 3.12 (s, 3H), 3.08 (d, *J* = 12.9 Hz, 1H), 2.94 (d, *J* = 9.9 Hz, 1H), 2.83 (d, *J* = 9.9 Hz, 1H), 2.79-2.72 (m, 1H), 2.69-2.62 (m, 1H), 2.03-1.91 (m, 1H), 1.87-1.78 (m, 1H), 1.72 (*br.* s, 1H), 1.03-0.99 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.5, 132.0, 131.3, 130.1, 130.0, 128.8, 77.1, 58.6, 47.5, 42.8, 33.5, 28.9, 25.9, 19.7 ppm; IR (neat): $\tilde{\nu}$ = 2922, 2891, 2852, 2824, 1675, 1638, 1594, 1552, 1469, 1393, 1376, 1321, 1259, 1192, 1132, 1098, 1029, 954, 872, 820, 800, 770, 733, 707, 674 cm^{-1}; MS (70 eV): *m/z* (%): 286 [M^+] (17), 254 (53), 240 (13), 221 (37), 213 (97), 189 (40), 176 (19), 154 (19), 115 (15), 100 (67), 68 (44), 43 (45); HRMS (ESI): calcd for $C_{14}H_{18}OCl_2$ [M^+ + H]: 286.0759, found: 286.0757. The physical and spectroscopic properties matched those described in the literature.[4]



(-)-GSK1360707·HCl ((–)-1·HCl): A solution of hydrochloric acid (1 M in diethyl ether, 1.6 mL, 1.6 mmol) was added dropwise to a stirred solution of (–)-GSK1360707 (202 mg, 0.710 mmol) in diethyl ether (20 mL) at 0 °C. The resulting suspension was stirred for 10 min at 0 °C and for 30 min at ambient temperature. The solvent was decanted and the white solid dried in vacuo to provide the title compound in quantitative yield (229 mg). $[\alpha]_D^{20}$ = –27.8° (*c* = 1.05, $CHCl_3$); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.18 (s, 1H), 8.98 (s, 1H), 7.76 (d, *J* = 2.0 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 1H), 7.44 (dd, *J* = 8.3, 2.0 Hz, 1H), 3.45 (d, *J* = 13.1 Hz, 1H), 3.16-3.09 (m, 2H), 3.05 (s, 3H), 2.99 (d, *J* = 9.8 Hz, 1H), 2.83-2.74 (m, 1H), 2.61 (d, *J* = 9.8 Hz, 1H), 2.21-2.07 (m, 1H), 2.06 (dt, *J* = 14.5, 4.1 Hz, 1H), 1.30 (d, *J* = 6.0 Hz, 1H), 1.26 ppm (d, *J* = 6.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 143.5, 131.4, 130.7, 130.3, 129.6, 129.3, 76.4, 57.9, 43.7, 38.3, 28.7, 26.9, 22.1, 19.0 ppm; IR (neat): $\tilde{\nu}$ = 2928, 2807, 2769, 2749, 2653, 2627, 2541, 2440, 1592, 1552, 1472, 1395, 1380, 1197, 1134, 1100, 1029, 950, 886, 818, 772, 710, 677 cm^{-1}; MS (ESI): *m/z* = 286 [*M* - Cl], 607 [2*M* - Cl]; HRMS (ESI): *calcd.* for $C_{14}H_{18}NOCl_4$ [*M* + Cl]: 356.0148, *found*: 356.0151. The physical and spectroscopic properties matched those described in the literature.[5]

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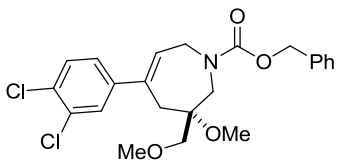
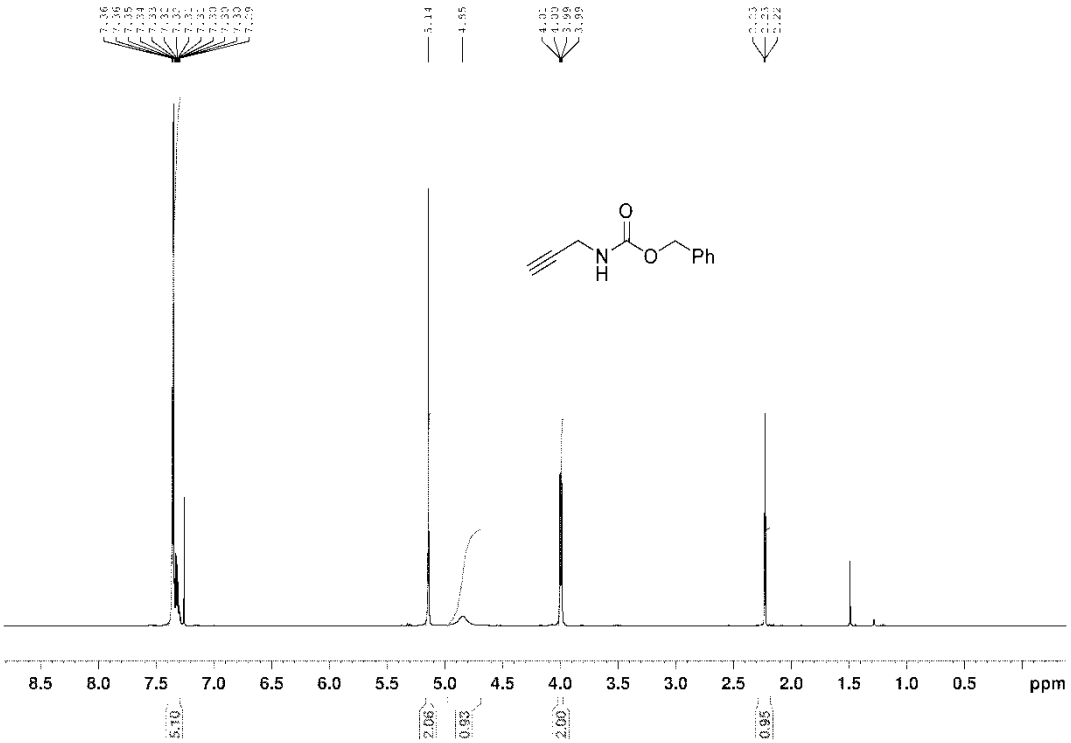
4 V. I. Elitzin, K. A. Harvey, H. Kim, M. Salmons, M. J. Sharp, E. A. Tabet, M. A. Toszko, *Org. Process Res. Dev.* **2010**, *14*, 912-917.

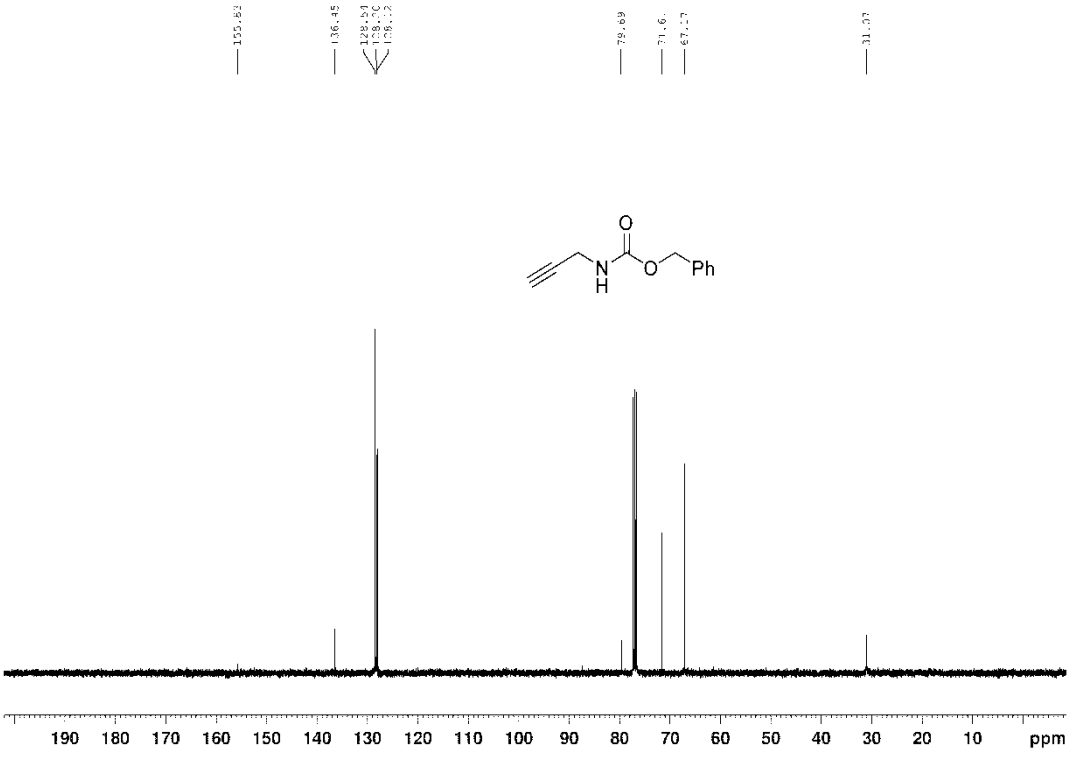
5 B. Bertani, R. DiFabio, F. Micheli, G. Tedesco, S. Terreni, PCT Int. Appl. WO/2008/031772, **2008**.

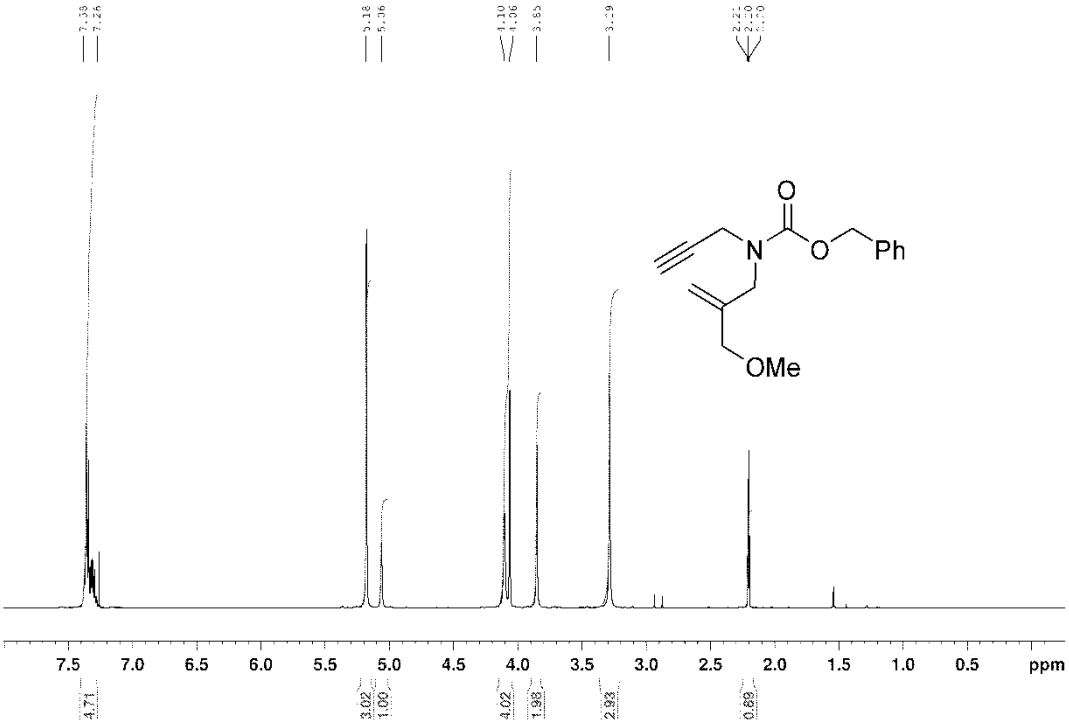
Benzyl 5-(3,4-dichlorophenyl)-3-methoxy-3-(methoxymethyl)-2,3,4,7-tetrahydro-1*H*-azepin-1-carboxylate (15): A mixture containing $[(PhO)_3PAuCl]$ (3.0 mg, 5.5 μmol) and $AgBF_4$ (1.0 mg, 5.0 μmol) in dichloromethane/methanol (1/1, 1 mL) was stirred for 10 min at ambient temperature in a capped vial before it was transferred to a solution of enyne **10** (42 mg, 0.10 mmol) in dichloromethane/methanol (1/1, 1 mL) via cannula equipped with a PTFE filter (Perfect-Flow®, 0.45 μm pore size, ∅ 13 mm) to retain the precipitates. The colourless solution was stirred for 24 h before it was directly loaded on top of a silica gel column and the product eluted with methyl *tert*-butyl ether/hexanes (1:19 → 1:9) to give the title compound as a colourless oil (22 mg, 49 %, 95 % brsm). ^{1}H NMR (400 MHz, $CDCl_3$, 60 °C): δ = 7.50 (*br.* s, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.38-7.29 (m, 5H), 7.23 (*br.* d, *J* = 8.1 Hz, 1H), 5.31 (*br.* s, 1H), 5.20-5.14 (m, 1H), 5.17 (s, 2H), 5.05 (s, 1H), 4.13 (d, *J* = 7.0 Hz, 2H), 3.96 (s, 2H), 3.87 (s, 2H), 3.49 (s, 3H), 3.29 ppm (s, 3H); IR (neat): $\tilde{\nu}$ = 3063, 3033, 2930, 2844, 2820, 1697, 1654, 1587, 1553, 1497, 1464, 1412, 1380, 1366, 1297, 1221, 1183, 1115, 1089, 1027, 977, 933, 910, 825, 767, 752, 734, 696, 676 cm^{-1}; MS (70 eV): *m/z* (%): 449 [M^+] (<1), 364 (12), 358 (21), 314 (98), 282 (7), 215 (19), 180 (8), 145 (12), 112 (3), 91 (100), 65 (7), 55 (29), 45 (17); HRMS (ESI): calcd for $C_{23}H_{25}O_4Cl_2N$+Na [M^+ + Na]: 472.1053, found: 472.1052. Due to the instability of the compound, ^{13}C NMR data could not be recorded.

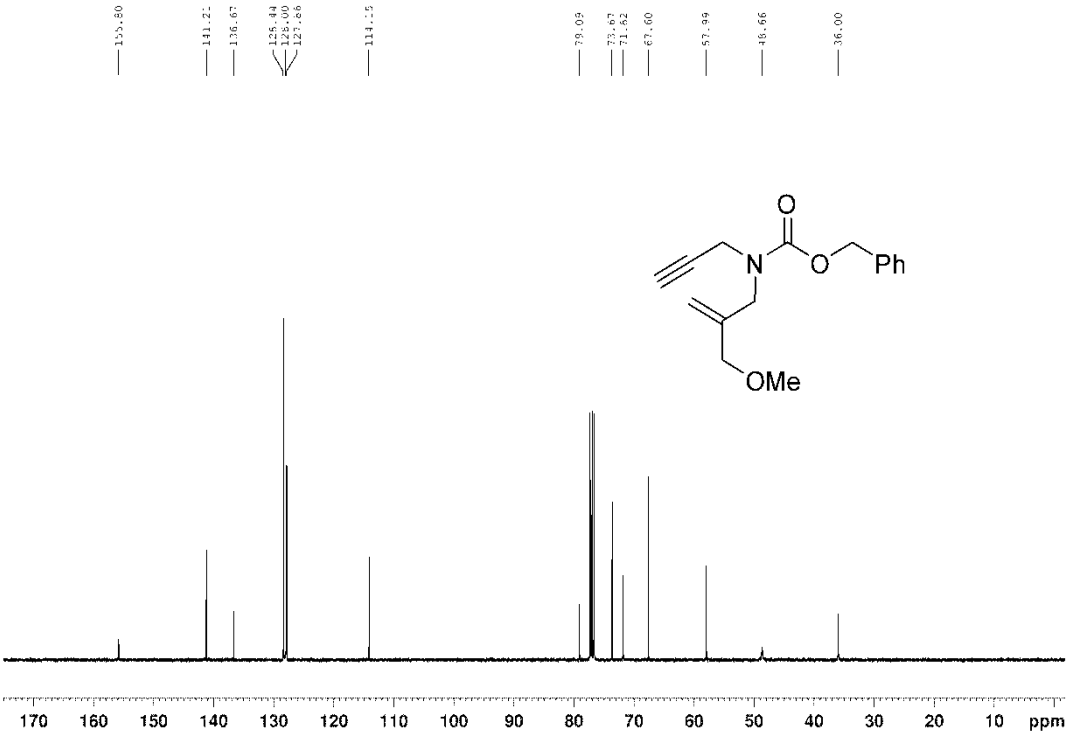


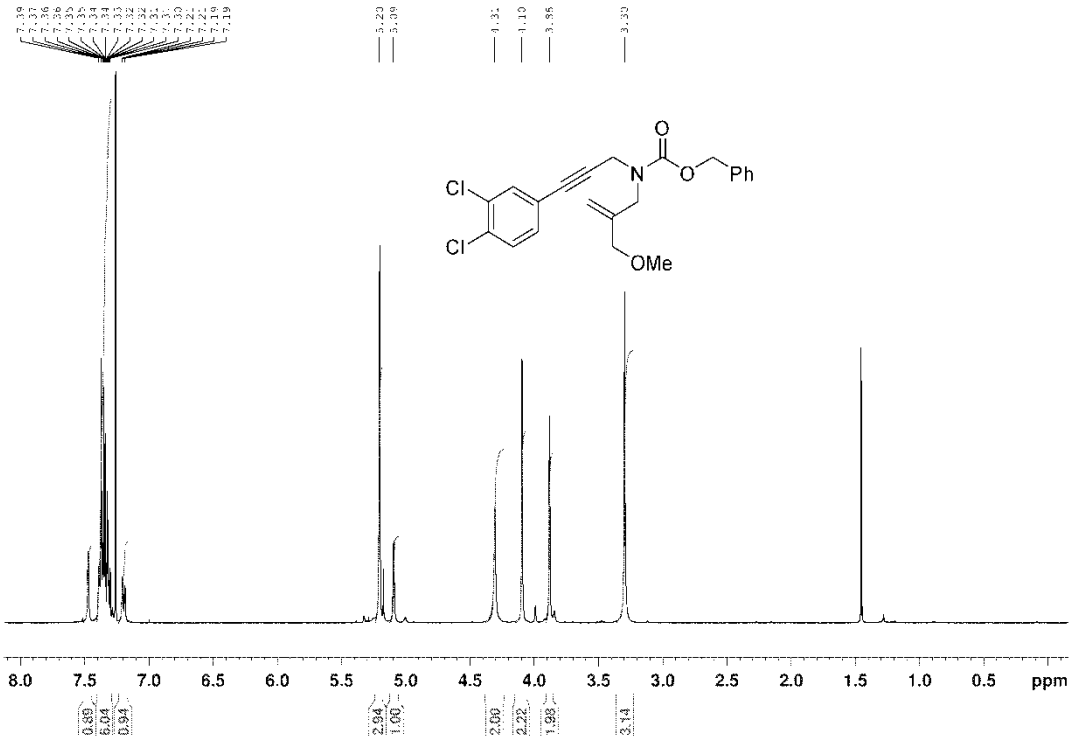
NMR Spectra (note that all spectra of Cbz-derivatives were recorded at +60 °C to minimize line broadening, cf. the Experimental Section)


O
N
H
O
Ph
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
5.18
2.06
0.83
2.00
0.95


O
N
H
O
Ph
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.33
7.26
5.18
5.06
4.10
4.06
3.85
3.29
2.22
2.20
O
N
O
Ph
OMe
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
4.71
3.02
1.00
4.02
1.98
2.93
0.89


155.80
141.25
136.67
128.44
128.00
127.68
114.15
79.09
73.67
71.62
67.60
57.99
48.66
36.00
O
N
O
Ph
OMe
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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Cl
O
N
O
Ph
OMe
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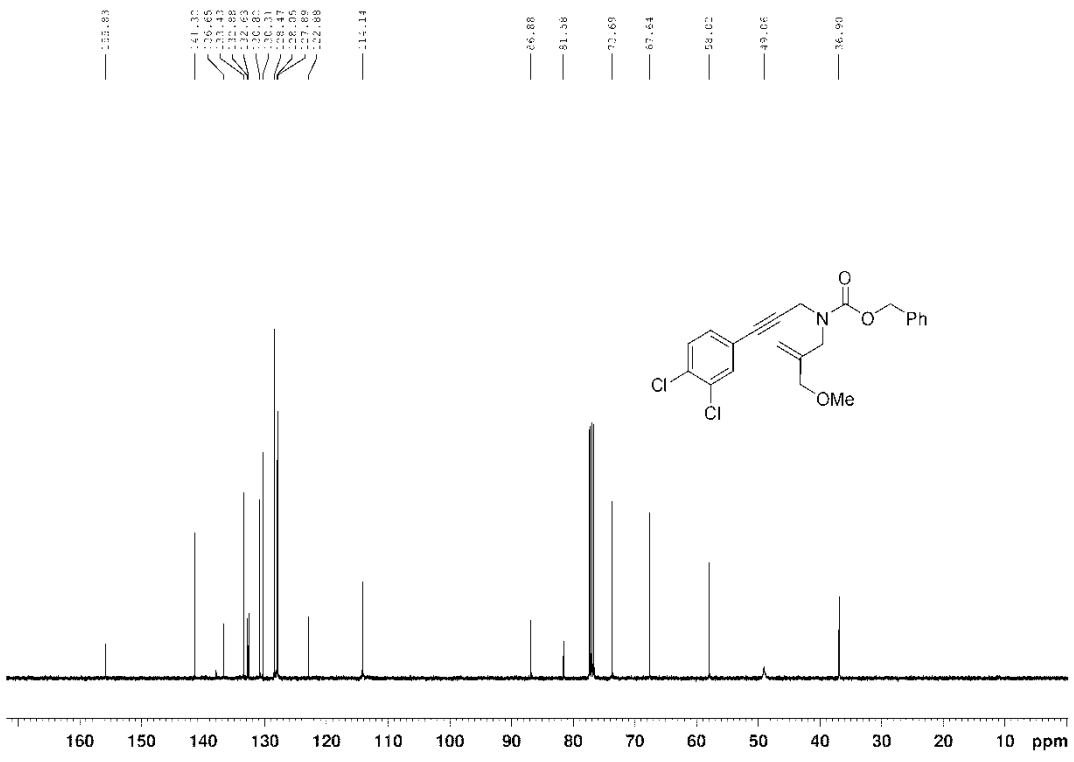
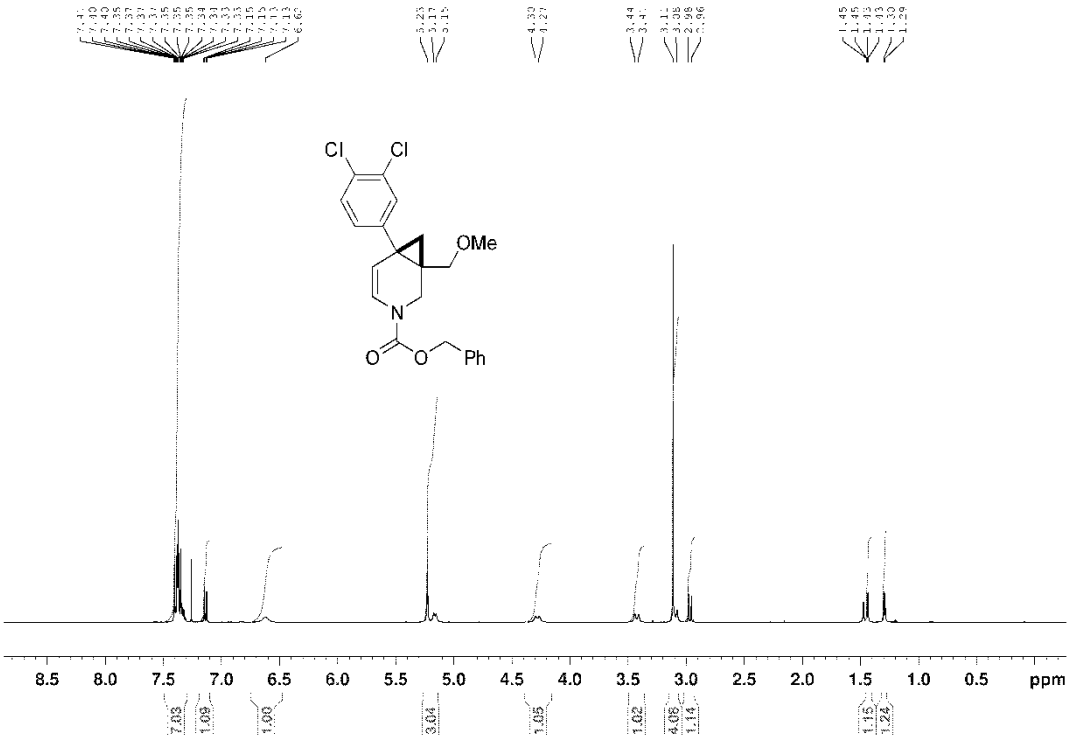
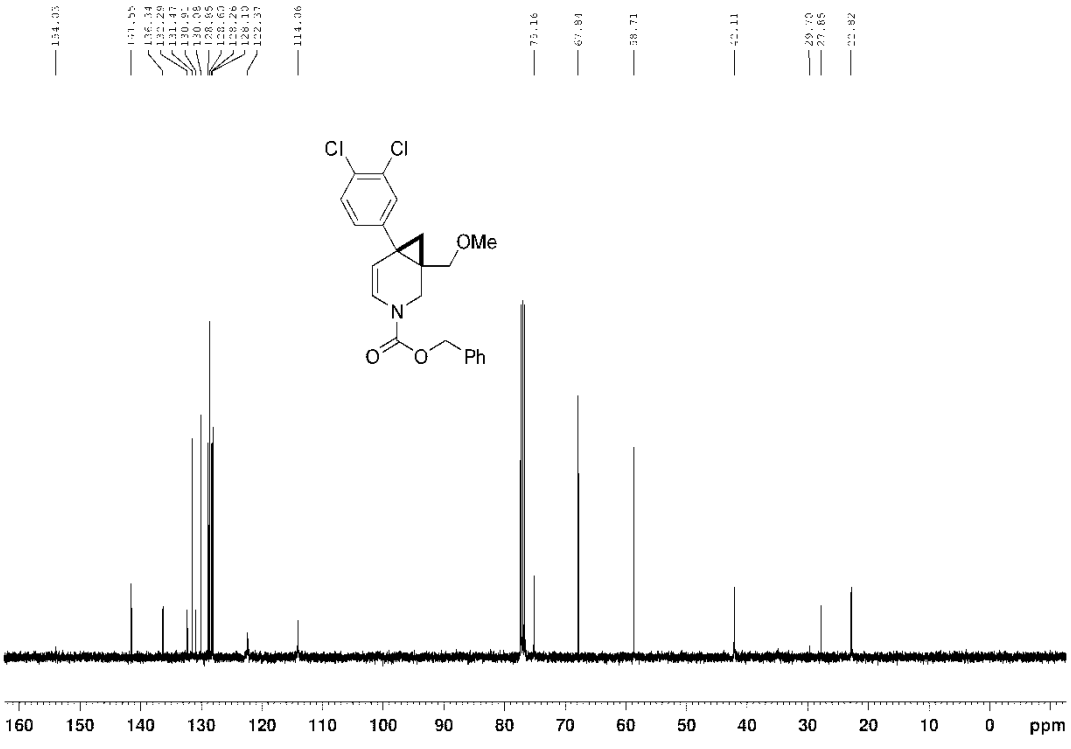
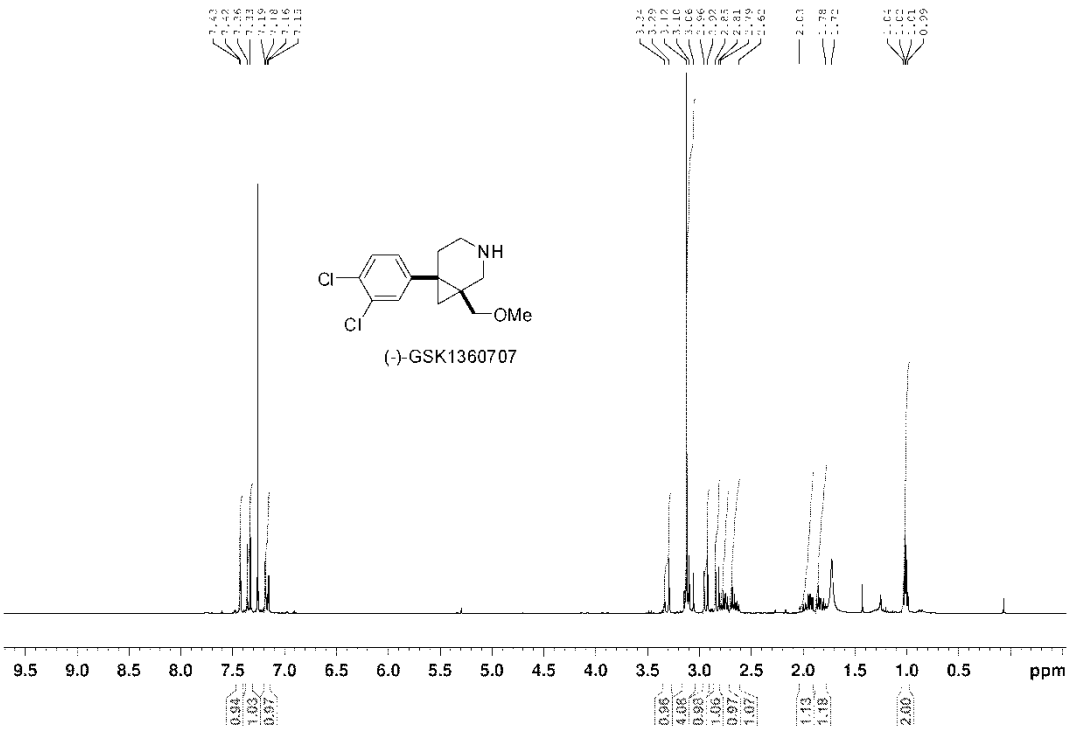
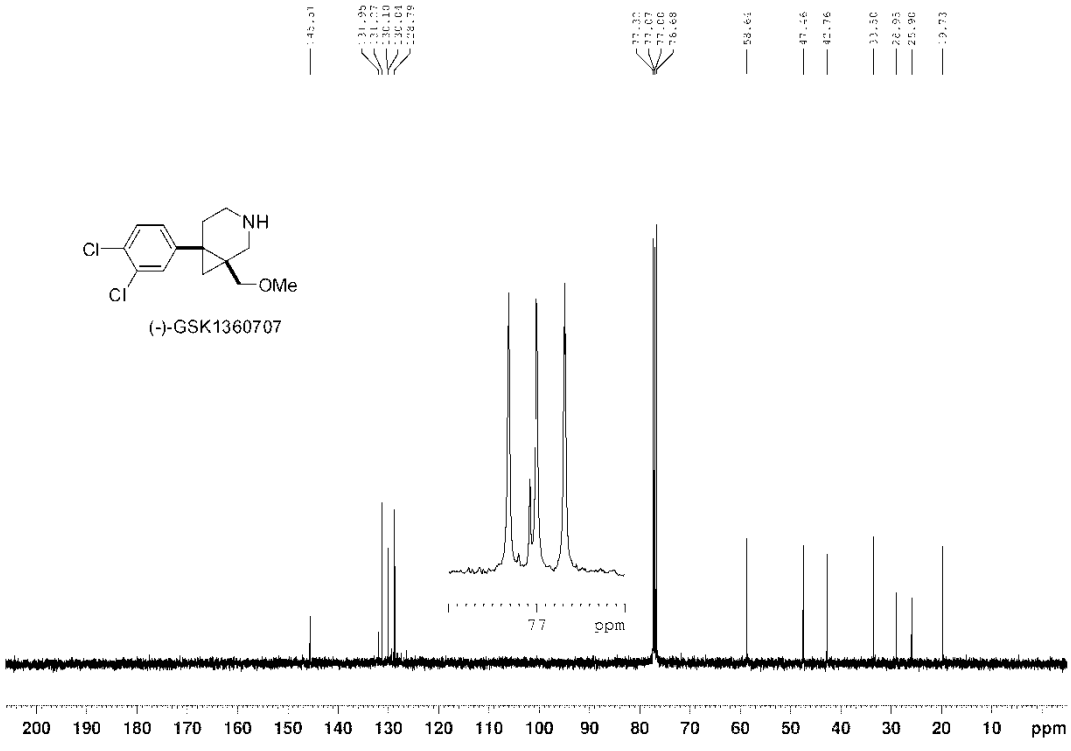
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


Cl
Cl
O
N
O
Ph
OMe
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


Cl
Cl
OMe
N
O
O
Ph
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
7.03
1.09
1.00
3.04
1.05
1.02
4.06
1.14
1.15
1.24


Cl
Cl
OMe
N
O
O
Ph
160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


NH
Cl
Cl
OMe
(-)-GSK1360707
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm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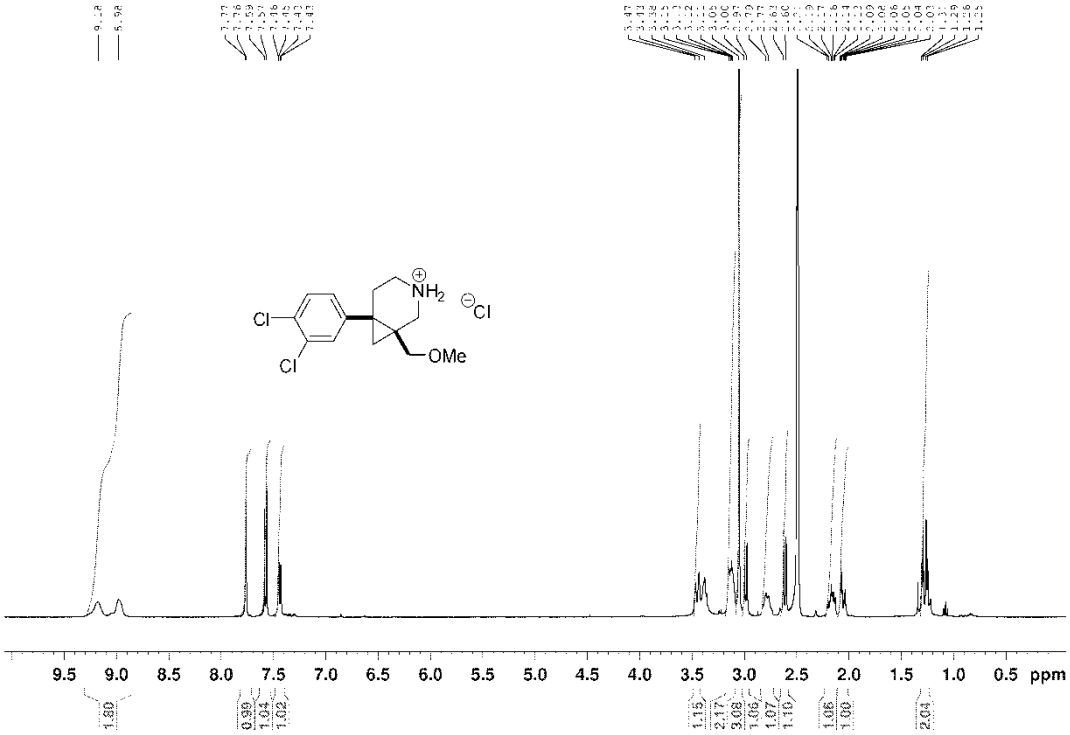
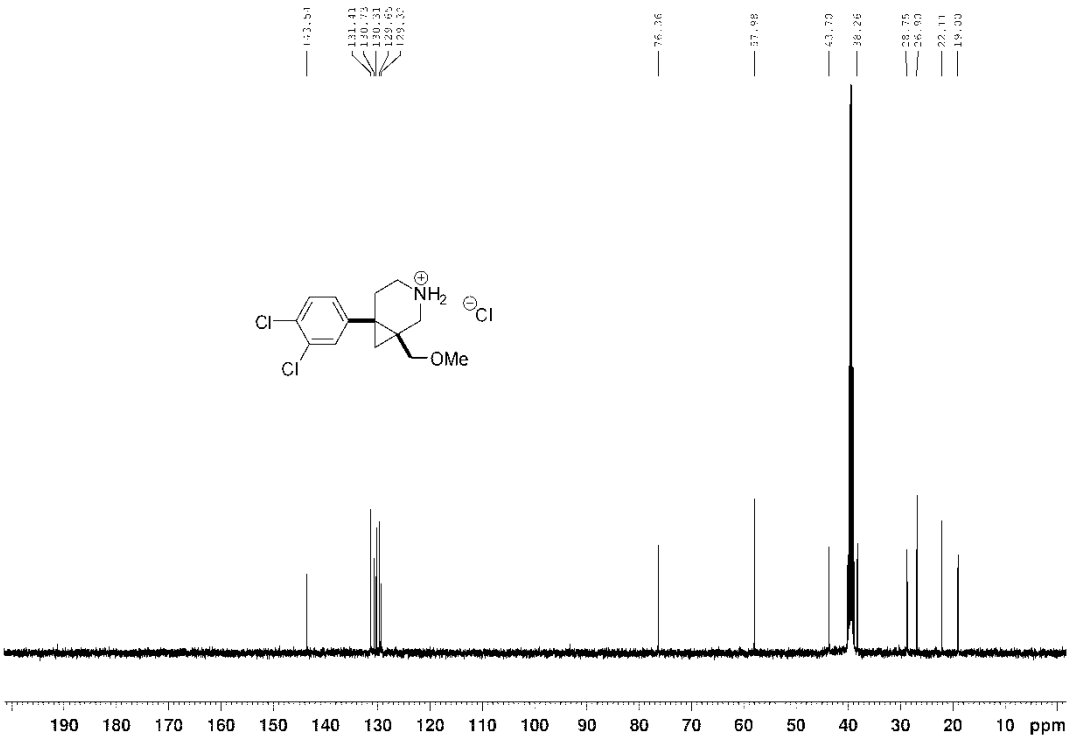
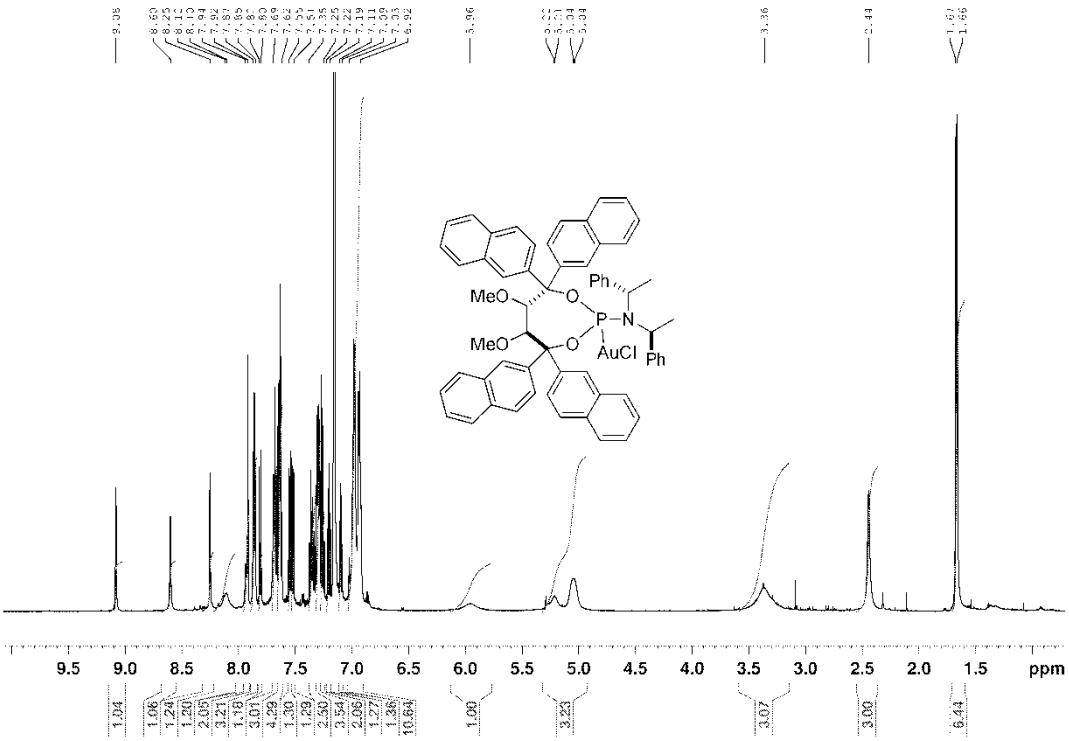
Cl
Cl
OMe
(-)-GSK1360707
77 ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


NH2
Cl
Cl
Cl
OMe
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm


NH2
Cl
Cl
Cl
OMe
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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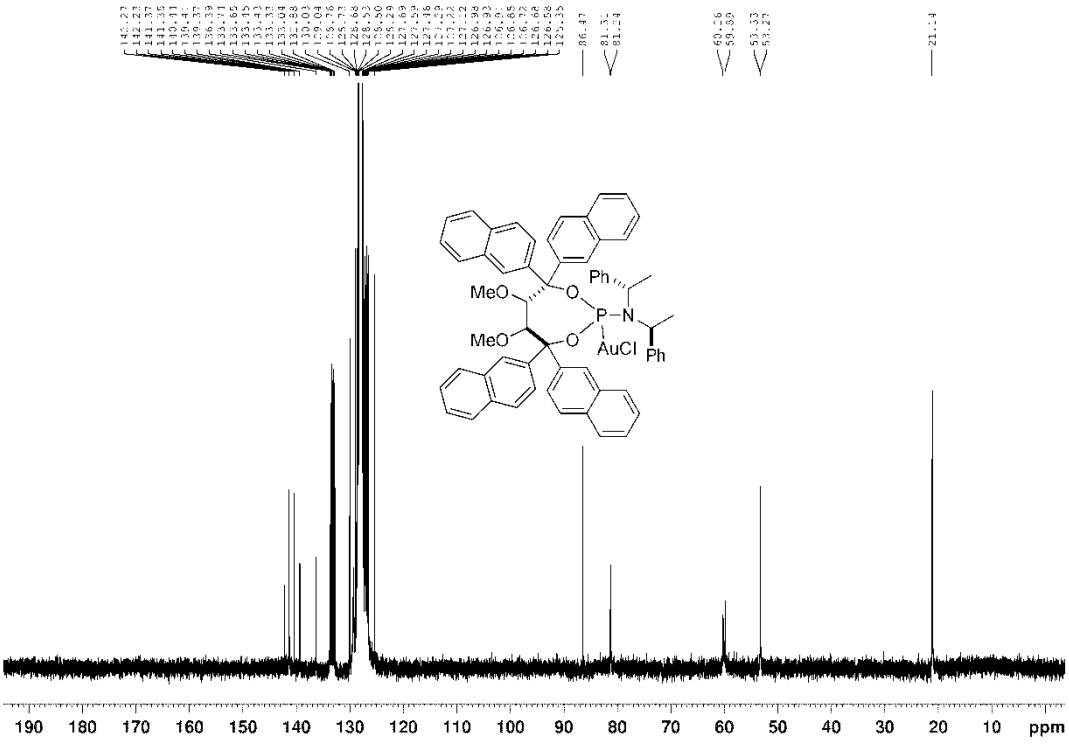
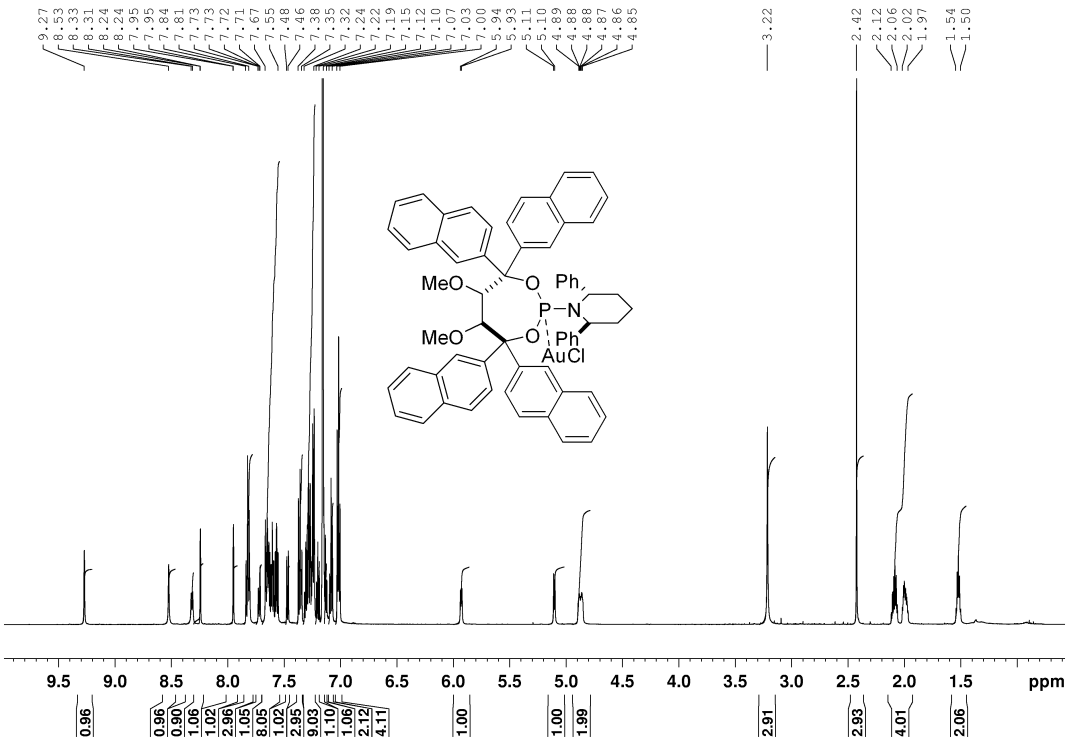
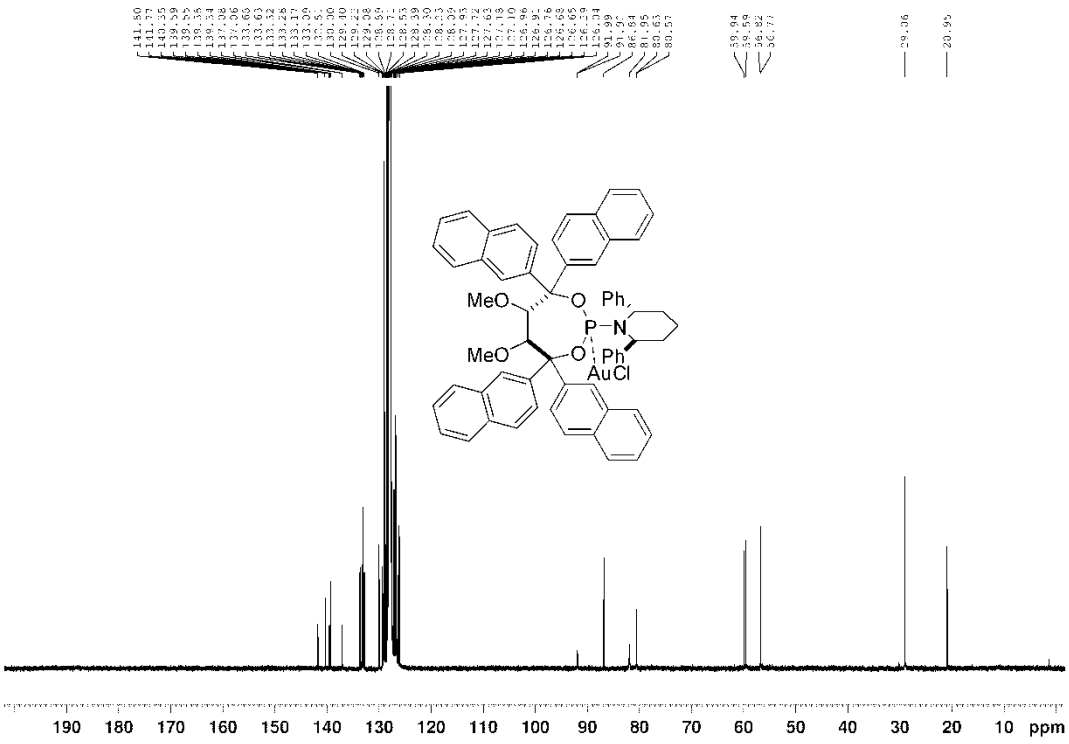
MeO
O
O
P–N
AuCl
Ph
Ph
ppm


MeO
MeO
O
O
P–N
AuCl
Ph
Ph
ppm


MeO
O
Ph
P
N
MeO
O
Ph
AuCl


MeO
O
Ph
P
N
MeO
O
Ph
AuCl

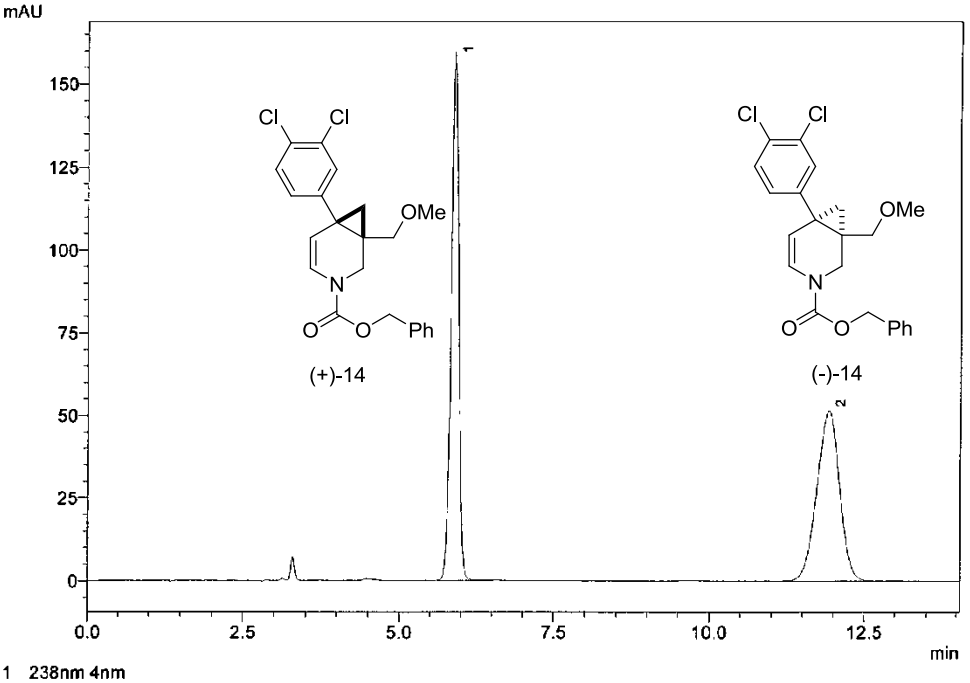
HPLC-Traces

(±)-**14** obtained with $[(PhO)_3PAuCl]/AgBF_4$ dichloromethane at RT.

Gerät : Instrument1

Operator :
Sample Name : TLL-TB-448-01
Vial # : 21
Injection Volume : 2 uL
Data File Name : TLL-TB-448-01-7.lcd
Method File Name : Teller-chiral.lcm

TLL-TB-448-01 (solution in n-Heptan/2-Prop.=3:1)
250 mm Chiralpak IA, 4.6 mm i.D., 5 µm, No.: IA00CE-LH028
n-Heptan / 2-Propanol = 70:30
1.0 mL/min, 298 K, 6.2 MPa
DAD, 238 nm



1 238nm 4nm

PDA Ch1 238nm 4nm

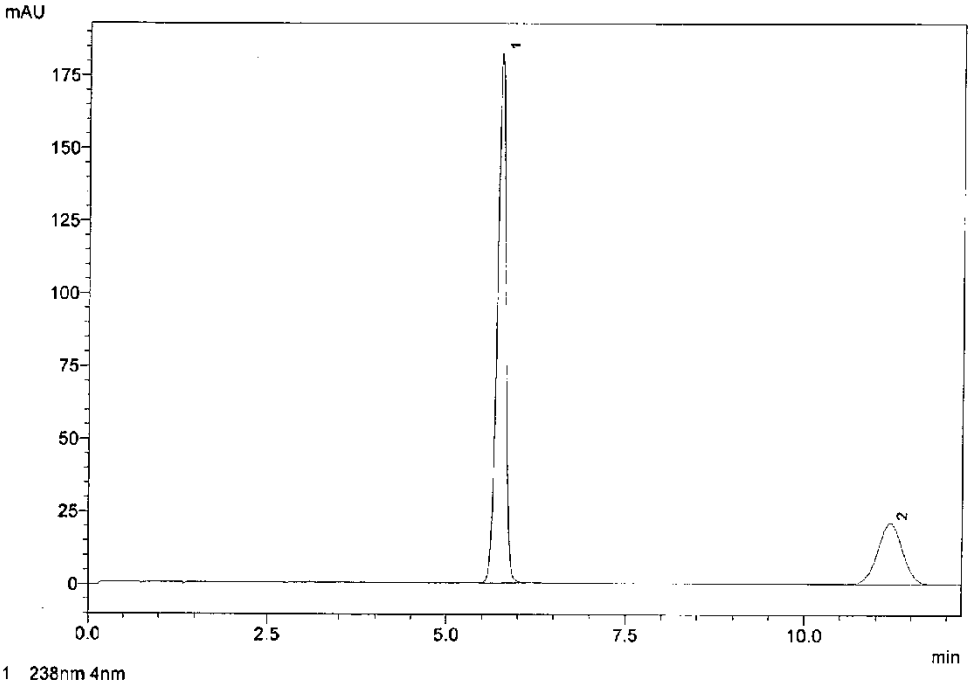
Peak #	Ret. Time	Area %	Name
1	5.89	50.00	
2	11.92	50.00	
Total		100.00	

HPLC trace obtained with [**L1**·AuCl]/$AgBF_4$ in dichloromethane at RT (Table 1, entry 1).

Gerät : Instrument1

Operator :
Sample Name : TLL-TB-463-01
Vial # : 52
Injection Volume : 1 uL
Data File Name : TLL-TB-463-01-1.lcd
Method File Name : Teller-chiral.lcm

IA
n-Heptane / 2-Propanol = 70:30
1.0 mL/min, 298 K, 2.3 MPa
DAD, 220 nm



1 238nm 4nm

PDA Ch1 238nm 4nm

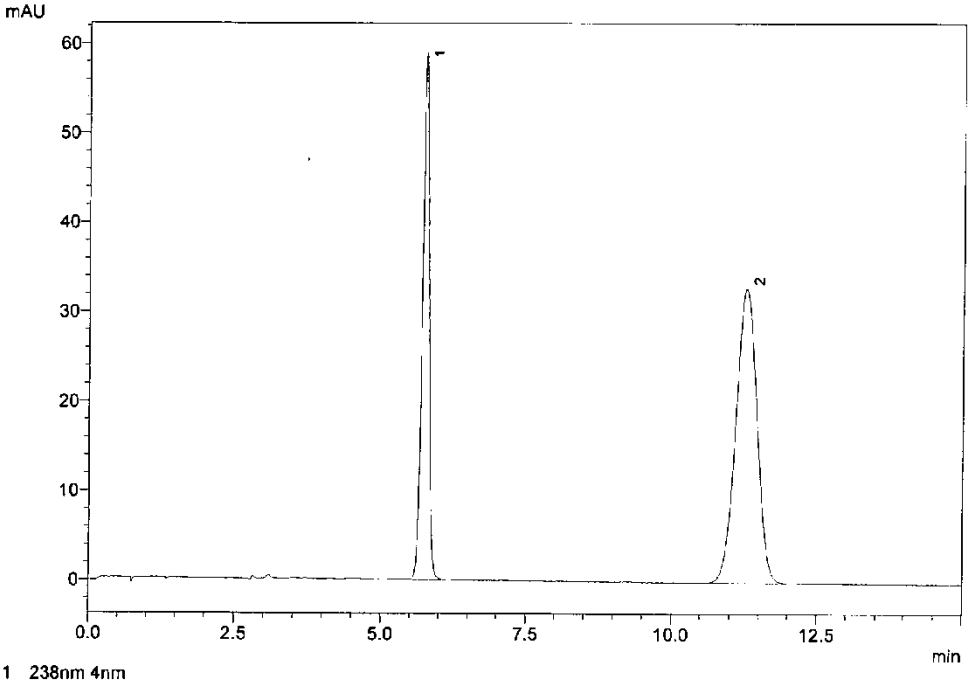
Peak #	Ret. Time	Area %	Name
1	5.75	74.11	
2	11.20	25.89	
Total		100.00	

HPLC trace obtained with [**L1**·AuCl]/$AgBF_4$ in toluene at RT (Table 1, entry 1).

Gerät : Instrument1

Operator :
Sample Name : TLL-TB-466-01
Vial # : 62
Injection Volume : 2 uL
Data File Name : TLL-TB-466-01-1.lcd
Method File Name : Teller-chiral.lcm

IA
n-Heptane / 2-Propanol = 70:30
1.0 mL/min, 298 K, 2.3 MPa
DAD, 220 nm



1 238nm 4nm

PDA Ch1 238nm 4nm

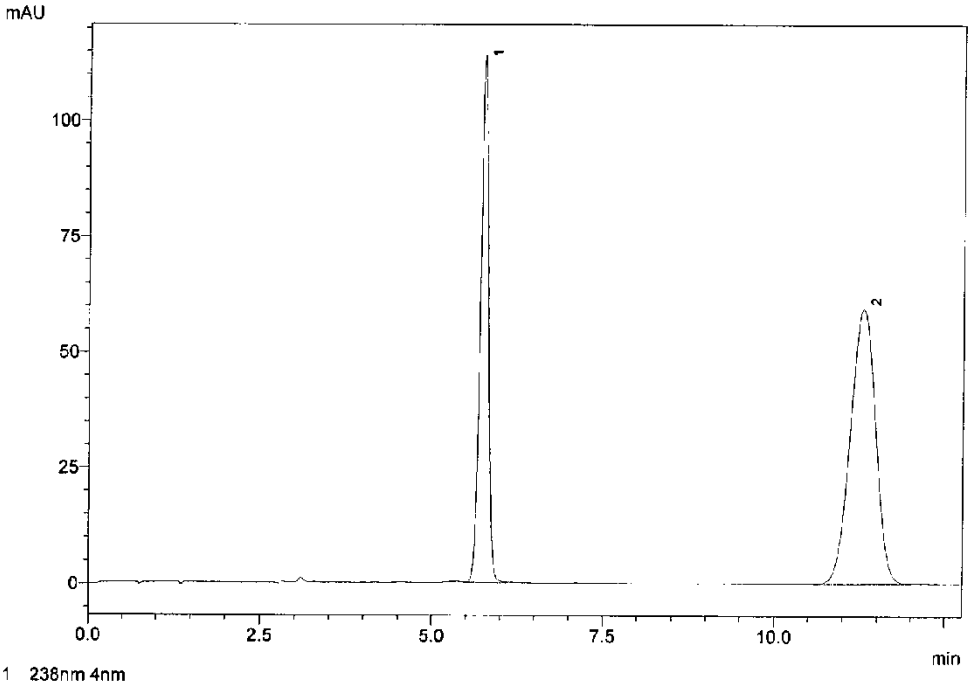
Peak #	Ret. Time	Area %	Name
1	5.75	37.06	
2	11.28	62.94	
Total		100.00	

HPLC trace obtained with [**L2**·AuCl]/$AgBF_4$ in dichloromethane at RT (Table 1, entry 2).

Gerät : Instrument1

Operator :
Sample Name : TLL-TB-460-01
Vial # : 32
Injection Volume : 2 uL
Data File Name : TLL-TB-460-01-1.lcd
Method File Name : Teller-chiral.lcm

IA
n-Heptane / 2-Propanol = 70:30
1.0 mL/min, 298 K, 2.3 MPa
DAD, 220 nm



1 238nm 4nm

PDA Ch1 238nm 4nm

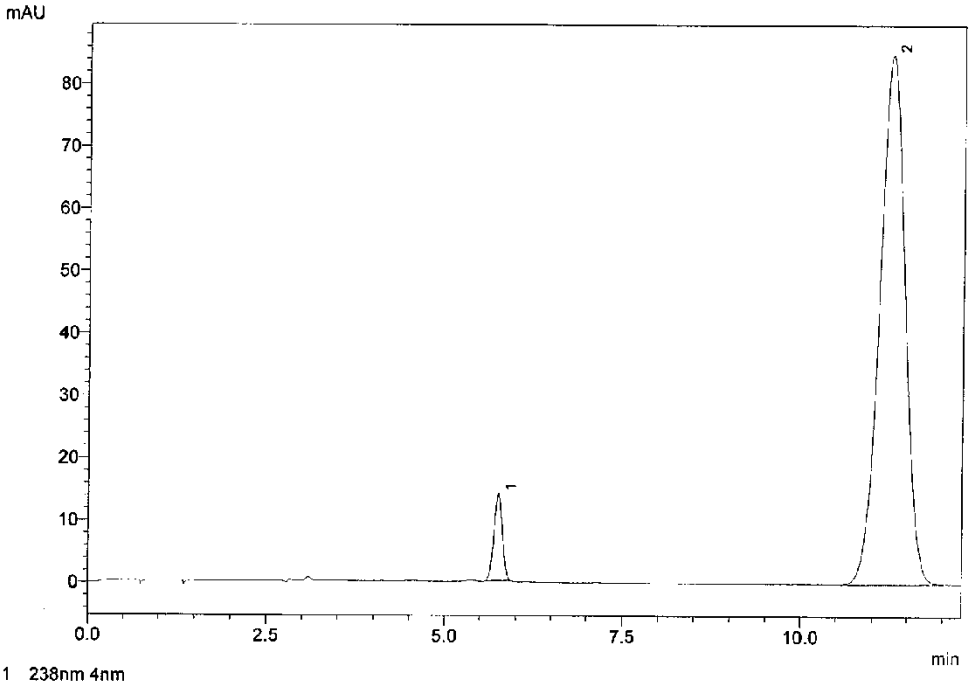
Peak #	Ret. Time	Area %	Name
1	5.75	38.54	
2	11.29	61.46	
Total		100.00	

HPLC trace obtained with [**L3**·AuCl]/$AgBF_4$ in toluene at RT (Table 1, entry 3).

Gerät : Instrument1

Operator :
Sample Name : TLL-TB-467-01
Vial # : 63
Injection Volume : 2 uL
Data File Name : TLL-TB-467-01-1.lcd
Method File Name : Teller-chiral.lcm

IA
n-Heptane / 2-Propanol = 70:30
1.0 mL/min, 298 K, 2.3 MPa
DAD, 220 nm



1 238nm 4nm

PDA Ch1 238nm 4nm

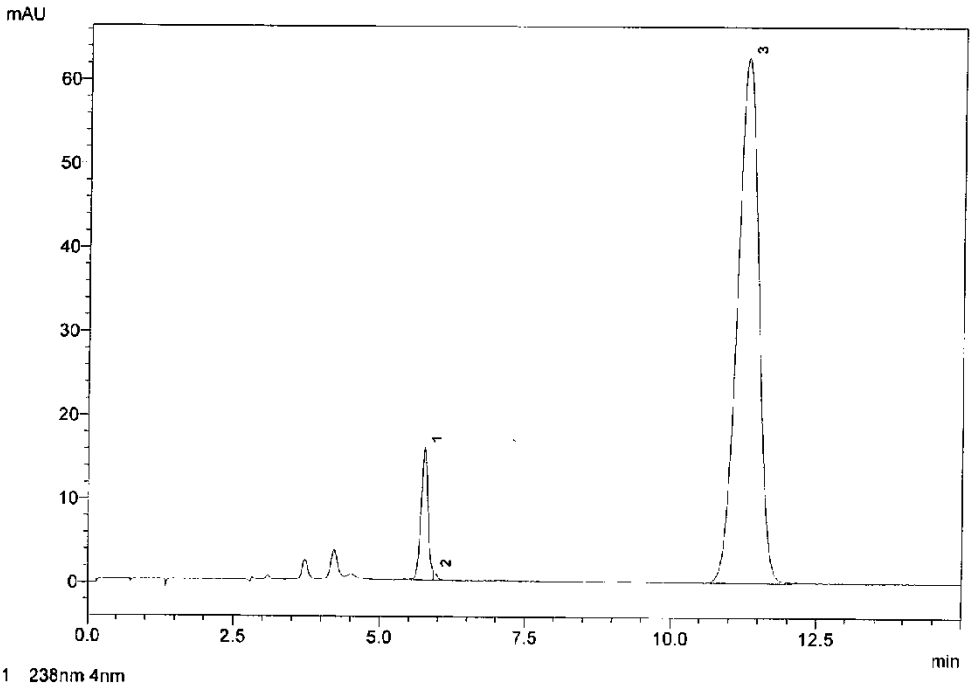
Peak #	Ret. Time	Area %	Name
1	5.75	5.02	
2	11.27	94.98	
Total		100.00	

HPLC trace obtained with [**L4**·AuCl]/$AgBF_4$ in toluene at RT (Table 1, entry 4).

Gerät : Instrument1

Operator :
Sample Name : TLL-TB-461-01
Vial # : 50
Injection Volume : 2 uL
Data File Name : TLL-TB-461-01-1.lcd
Method File Name : Teller-chiral.lcm

IA
n-Heptane / 2-Propanol = 70:30
1.0 mL/min, 298 K, 2.3 MPa
DAD, 220 nm



1 238nm 4nm

PDA Ch1 238nm 4nm

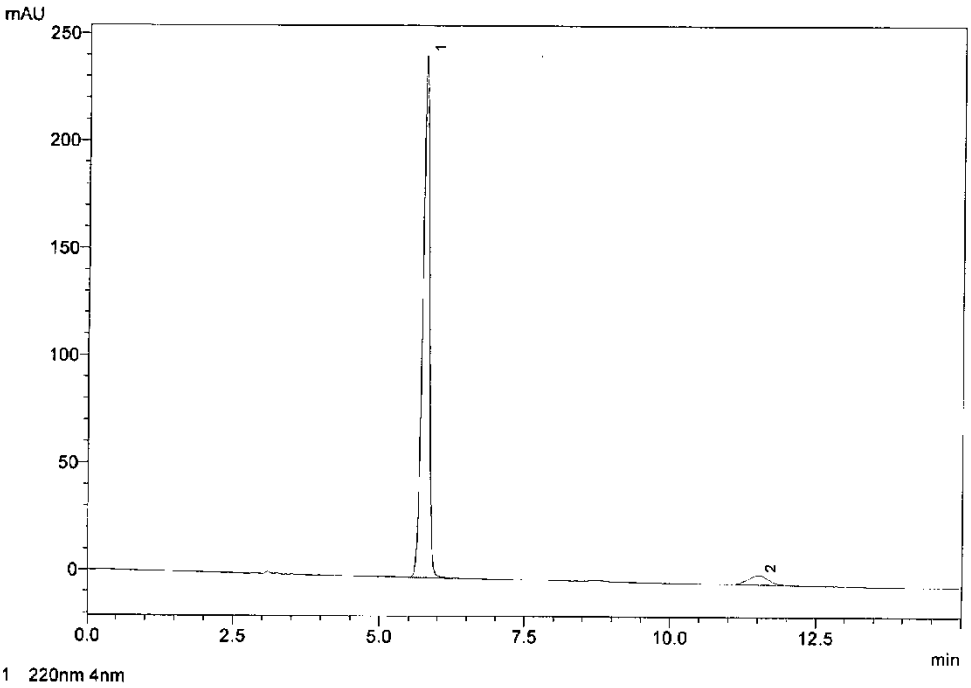
Peak #	Ret. Time	Area %	Name
1	5.76	7.81	
2	5.93	0.26	
3	11.29	91.93	
Total		100.00	

HPLC trace obtained with [**L5**·AuCl]/$AgBF_4$ in toluene at RT (Table 1, entry 5).

Gerät : Instrument1

Operator :
Sample Name : TLL-TC-006-01
Vial # : 80
Injection Volume : 1 uL
Data File Name : TLL-TC-006-01-1.lcd
Method File Name : Teller-chiral.lcm

IA
n-Heptane / 2-Propanol = 70:30
1.0 mL/min, 298 K, 2.3 MPa
DAD, 220 nm



1 220nm 4nm

PDA Ch1 220nm 4nm

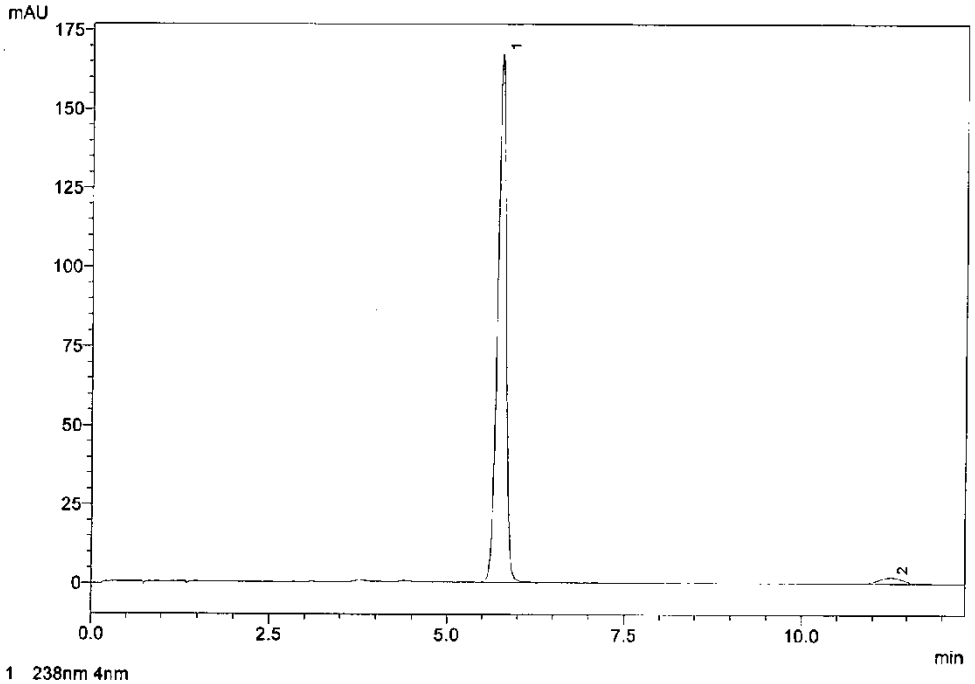
Peak #	Ret. Time	Area %	Name
1	5.77	95.10	
2	11.52	4.90	
Total		100.00	

HPLC trace obtained with [**L6**·AuCl]/$AgBF_4$ in toluene at RT (Table 1, entry 6).

Gerät : Instrument1

Operator :
Sample Name : TLL-TB-462-01
Vial # : 51
Injection Volume : 1 uL
Data File Name : TLL-TB-462-01-1.lcd
Method File Name : Teller-chiral.lcm

IA
n-Heptane / 2-Propanol = 70:30
1.0 mL/min, 298 K, 2.3 MPa
DAD, 220 nm



1 238nm 4nm

PDA Ch1 238nm 4nm

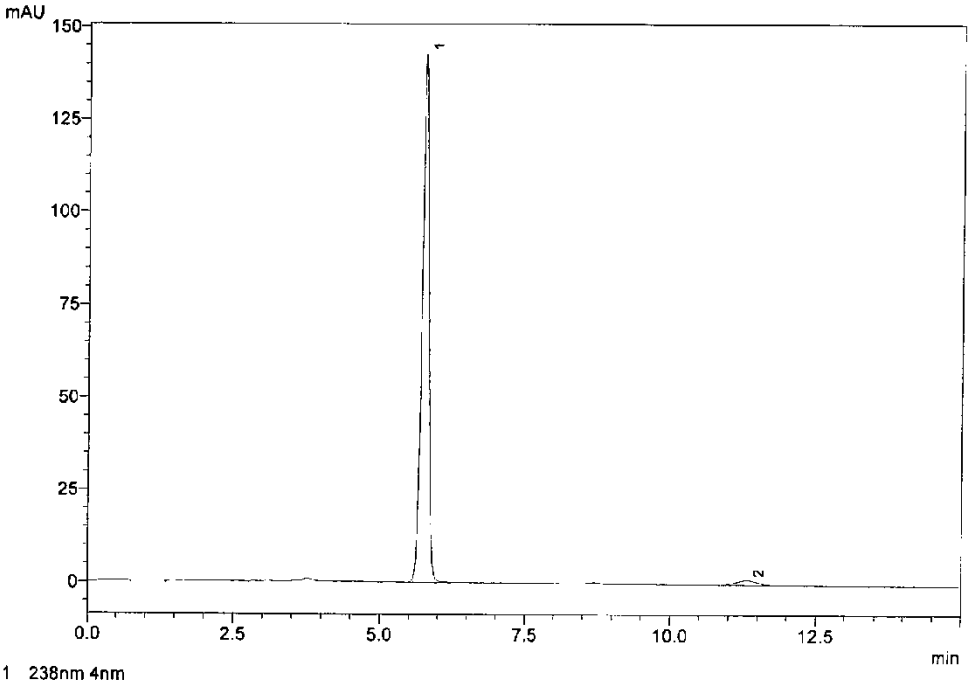
Peak #	Ret. Time	Area %	Name
1	5.76	96.55	
2	11.26	3.45	
Total		100.00	

HPLC trace obtained with [**L6**·AuCl]/$AgBF_4$ in toluene at 0°C (Table 1, entry 7).

Gerät : Instrument1

Operator :
Sample Name : TLL-TB-465-01
Vial # : 61
Injection Volume : 2 uL
Data File Name : TLL-TB-465-01-1.lcd
Method File Name : Teller-chiral.lcm

IA
n-Heptane / 2-Propanol = 70:30
1.0 mL/min, 298 K, 2.3 MPa
DAD, 220 nm



1 238nm 4nm

PDA Ch1 238nm 4nm

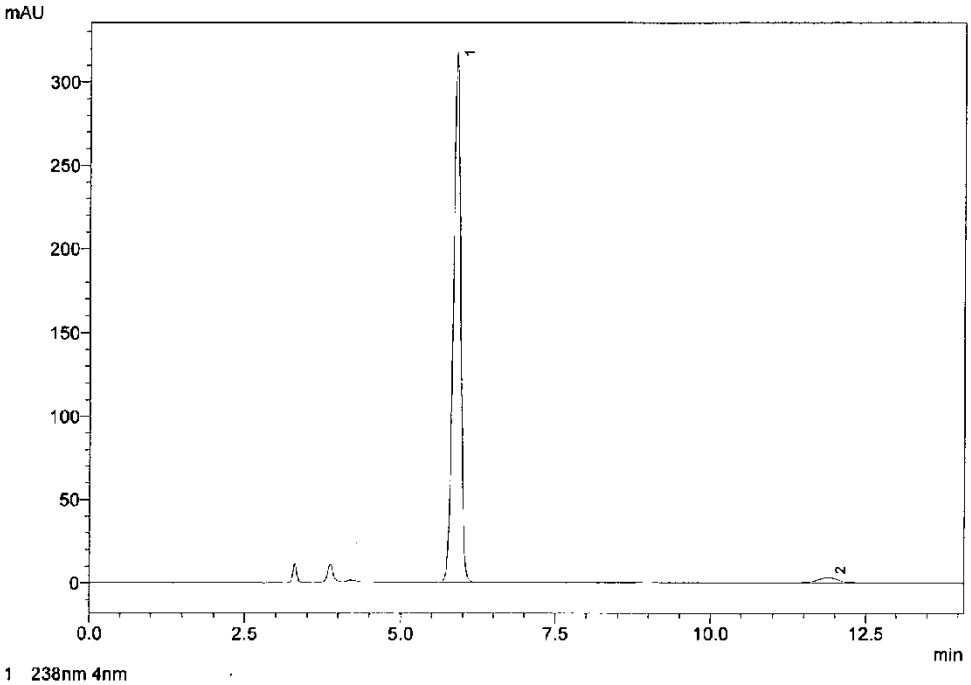
Peak #	Ret. Time	Area %	Name
1	5.76	97.41	
2	11.31	2.59	
Total		100.00	

HPLC trace obtained with [**L7**·AuCl]/$AgBF_4$ in Toluene at RT (Table 1, entry 8).

Gerät : Instrument1

Operator :
Sample Name : TLL-TB-452-01
Vial # : 20
Injection Volume : 2 uL
Data File Name : TLL-TB-452-01-9.lcd
Method File Name : Teller-chiral.lcm

TLL-TB-452-01 (solution in n-Heptan/2-Prop.=3:1)
250 mm Chiralpak IA, 4.6 mm i.D., 5 µm, No.: IA00CE-LH028
n-Heptan / 2-Propanol = 70:30
1.0 mL/min, 298 K, 6.2 MPa
DAD, 238 nm



1 238nm 4nm

PDA Ch1 238nm 4nm

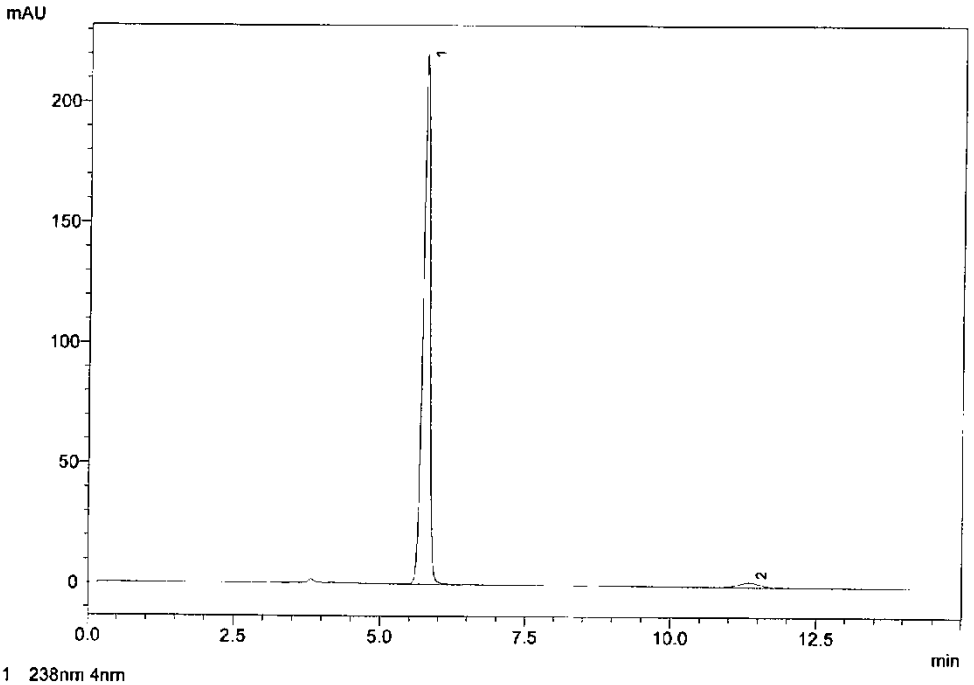
Peak #	Ret. Time	Area %	Name
1	5.89	97.01	
2	11.90	2.99	
Total		100.00	

HPLC trace obtained with [**L7**·AuCl]/$AgBF_4$ in toluene at 0°C (Table 1, entry 9).

Gerät : Instrument1

Operator :
Sample Name : TLL-TB-464-01
Vial # : 60
Injection Volume : 2 uL
Data File Name : TLL-TB-464-01-1.lcd
Method File Name : Teller-chiral.lcm

IA
n-Heptane / 2-Propanol = 70:30
1.0 mL/min, 298 K, 2.3 MPa
DAD, 220 nm



1 238nm 4nm

PDA Ch1 238nm 4nm

Peak #	Ret. Time	Area %	Name
1	5.76	97.40	
2	11.35	2.60	
Total		100.00	