A direct asymmetric hetero-Claisen approach to 3-alkyl-3-aryloxindoles

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SUPPORTING INFORMATION

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General information

All reactions involving moisture sensitive reagents were performed under inert atmosphere (nitrogen or argon) *via* standard vacuum line techniques and with freshly dried solvents. All glassware was flame dried and allowed to cool under vacuum. Diethylether (Et_2O), tetrahydrofuran (THF), toluene, hexane and dichloromethane were obtained dry from a solvent purification system (MBraun, SPS-800). Petroleum ether is defined as petroleum ether 40-60 ˚C. All solvents and commercial reagents were used as supplied without further purification unless stated otherwise. Room temperature refers to 20-25 ˚C. Reduced pressure refers to the use of a Büchi Rotavapor R-2000 rotary evaporator with a Vacubrand CVC_2 vacuum controller or a Heidolph Laborota 4001 rotary evaporator with a vacuum controller. Analytical thin layer chromatography was performed on aluminium sheets coated with 60 F_{254} silica. TLC visualisation was carried out with ultraviolet light (254 nm), followed by staining 1% aqueous $KMnO_4$ solution. Flash column chromatography was performed on Kieselgel 60 silica in the solvent system stated. ^1H, ^{13}C and ^{19}F NMR spectra were acquired on either a Bruker Avance 300 (300 MHz ^1H, 75 MHz ^{13}C, 282 MHz ^{19}F) or a Bruker Avance II 400 (400 MHz ^1H, 100 MHz ^{13}C, 377 MHz ^{19}F) spectrometer at ambient temperature and in the deuterated solvent stated. Coupling constants (*J*) are reported in Hz. Data are expressed in chemical shifts in parts per million (ppm) relative to residual $CHCl_3$ solvent as the internal standard. Multiplicities are indicated by: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sextet, sept (septet) and m (multiplet). *app* stands for apparent and *br* for broad. Infrared spectra (ν_{max}) were recorded on a Perkin-Elmer Spectrum GX FT-IR Spectrometer using either NaCl plates (thin film) or KBr disc as stated. Only the characteristic peaks are quoted. Melting points were recorded on an Electrothermal apparatus and are uncorrected. HPLC analyses were performed on a GILSON apparatus using Daicel Chiralpak AD-H, Daicel Chiralcel OD-H column or Daicel Chiralcel OJ columns. Mass spectrometric (*m/z*) data was acquired either at the University of St Andrews Mass Spectrometry facility or at the EPSRC National Mass Spectrometry Service Centre in Swansea. HRMS carried out in St Andrews are quoted [M + H] and those carried out in Swansea are quoted $[M + H]^+$. Low and high resolution MS (ES) and MS (CI) were carried out on a Micromass LCT spectrometer and on a Micromass GCT spectrometer, respectively. Optical rotations were measured on a Perkin Elmer/Model-343 digital polarimeter operating at the sodium D line with a 100 mm path cell, and are reported as follows: $[\alpha]_D^T$ $deg.cm^3g^{-1}dm^{-1}$ (concentration $g/100cm^3$).

1. Preparation of alkylarylketenes

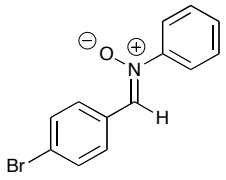
All alkylarylketenes were prepared from the corresponding acid chlorides according to literature procedures.[1]

Typical procedure for the preparation of alkylarylketenes. Triethylamine (1.0 equiv) was added dropwise over a 30-min period to a solution of acid chloride (1.0 equiv) in Et_2O (2 mL / mmol of starting material) at 0°C under nitrogen atmosphere and the reaction mixture was stirred overnight (16 hours) at 0°C. After warming to room temperature, Et_3N salts were removed by filtration under nitrogen and the filtrate was transferred *via* cannula to a Kugelrohr flask and concentrated. Distillation under reduced pressure afforded the corresponding alkylarylketenes.

2. Racemic version

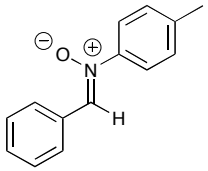
2.1. Preparation of nitrones 1-4

General procedure for the preparation of nitrones. The nitrones were prepared following the procedure reported by Fu[2]. Nitroarene (1.0 equiv), aldehyde (1.0 equiv) and NH_4Cl (1.3 equiv) were added to a mixture of EtOH (2 mL / mmol of starting material) and H_2O (2 mL / mmol of starting material) and the resulting mixture was cooled to 0°C. Zinc powder (2.0 equiv) was added at 0°C over a 4-hour period, then the reaction mixture was allowed to warm to room temperature and stirred for 16 hours. The reaction mixture was filtered through a pad of celite and washed with CH_2Cl_2. The filtrate was extracted with CH_2Cl_2 (4 * 50 mL) and the combined organic layers were dried ($MgSO_4$), filtered and concentrated to give the crude nitrone. The nitrones were purified by recrystallization. Yields were not optimized.

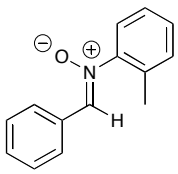


[1] a) Houdous, B. L.; Fu G. C. *J. Am. Chem. Soc.* **2002**, *124*, 1578-1579; b) Baigrie, L. M.; Seiklay, H. R.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 5391-5396; c) Sudo, A.; Uchino, S.; Endo, T. *J. Polym. Sci. Part A: Polym. Chem.* **2001**, *39*, 2093-2102.
[2] Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 4572-4573.

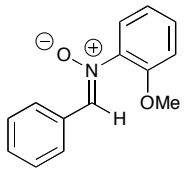
(*Z*)-*N*-(4-bromobenzylidene)aniline oxide 1 . The nitrone was obtained from 4-bromobenzaldehyde (9.25 g, 50 mmol, 1.0 equiv) and nitrobenzene (6.03 mL, 50 mmol, 1.0 equiv) following the above general procedure. The residue was purified by recrystallization from EtOH to give **1** (10.5 g, 90% yield) as a white solid (mp = 152-153°C). IR (KBr disc) ν 3056, 1559, 1545, 1485, 1459, 1397, 1300, 1285, 1191, 1173, 1072, 1011, 894, 840, 766, 687; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.50 (3H, m), 7.59-7.61 (2H, m), 7.75-7.77 (2H, m), 7.89 (1H, s), 8.27-8.29 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.8 (2 CH), 124.9 (C), 129.4 (2 CH), 129.7 (C), 130.3 (CH), 130.4 (2 CH), 132.0 (2 CH), 133.6 (CH), 149.1 (C); MS (ES^+) *m/z* 300 ([M(^{81}Br) + Na]$^+$, 98), 298 ([M(^{79}Br) + Na]$^+$, 100), 278 ([M(^{81}Br) + H]$^+$, 73), 276 ([M(^{79}Br) + H]$^+$, 74); HRMS (ES^+) [M(^{79}Br) + Na]$^+$ $C_{13}H_{10}{}^{79}BrNNaO$ requires 297.9838, found 297.9836 (–0.7 ppm).



(*Z*)-*N*-benzylidene-4-methylaniline oxide 2. The nitrone was obtained from benzaldehyde (5.08 mL, 50 mmol, 1.0 equiv) and 4-nitrotoluene (6.86 g, 50 mmol, 1.0 equiv) following the above general procedure. The residue was purified by recrystallization from CH_2Cl_2 / hexane to give **2** (5.88 g, 56% yield) as a yellowish solid (mp = 114-115°C). IR (KBr disc) ν 3108, 3073, 3050, 3022, 2919, 2857, 2360, 2342, 1597, 1574, 1550, 1503, 1445, 1420, 1394, 1295, 1191, 1175, 1082, 1068; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (3H, s), 7.25-7.28 (2H, m), 7.47 (3H, dt, *J* = 6.2, 1.4), 7.66-7.68 (2H, m), 7.90 (1H, s), 8.39 (2H, dt, *J* = 5.0, 2.4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3 (CH_3), 121.6 (2 CH), 128.8 (2 CH), 129.1 (2 CH), 129.8 (2 CH), 130.90 (C), 130.94 (CH), 134.3 (CH), 140.3 (C), 147.0 (C); MS (ES^+) *m/z* 234 ([M + Na]$^+$, 44), 212 ([M + H]$^+$, 100), 195 (M – O, 32); HRMS (ES^+) [M + H]$^+$ $C_{14}H_{14}NO$ requires 212.1075, found 212.1070 (–2.3 ppm).



(*Z*)-*N*-benzylidene-2-methylaniline oxide 3. The nitrone was obtained from benzaldehyde (2.54 mL, 25 mmol, 1.0 equiv) and 2-nitrotoluene (2.94 mL, 25 mmol, 1.0 equiv) following the above general procedure. The residue was purified by recrystallization from EtOH / petroleum ether to give **3** (4.62 g, 88% yield) as a yellowish solid (mp = 95-96°C). IR (KBr disc) ν 3052, 1605, 1573, 1559, 1554, 1489, 1463, 1444, 1404, 1320, 1304, 1236, 1207, 1188, 1125, 1084, 1068, 1039, 889, 825, 769, 757, 696; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (3H, s), 7.27-7.33 (2H, m), 7.37 (1H, dt, J = 7.3, 1.4), 7.41 (1H, dd, J = 7.6, 1.3), 7.49-7.51 (3H, m), 7.59 (1H, s), 8.38-8.40 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.1 (CH_3), 123.4 (CH), 126.7 (CH), 128.7 (2 CH), 128.8 (2 CH), 129.4 (CH), 130.5 (C), 130.9 (CH), 131.5 (CH), 131.8 (C), 137.6 (CH), 148.8 (C); MS (CI) *m/z* 212 ($[M + H]^+$, 100), 211 (M^+, 16), 196 ($[M – O + H]^+$, 33), 195 (M – O, 30), 194 ($[M – OH]^+$, 8), 118 ($[M – O – C_6H_5]^+$, 4), 107 ($[Me\text{-}C_6H_4\text{-}NH_2]^+$, 7); HRMS (CI) [M + H] $C_{14}H_{14}NO$ requires 212.1075, found 212.1078 (+1.2 ppm).



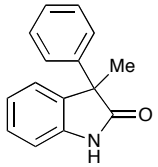
(*Z*)-*N*-benzylidene-2-methoxyaniline oxide 4. The nitrone was obtained from benzaldehyde (5.08 mL, 50 mmol, 1.0 equiv) and 2-nitroanisole (6.1 mL, 50 mmol, 1.0 equiv) following the above general procedure. The residue was purified by recrystallization from CH_2Cl_2 / hexane to give **4** (5.46 g, 48% yield) as a yellowish solid (mp = 143-144°C). IR (KBr disc) ν 3105, 3068, 3046, 3018, 2975, 2940, 2834, 2322, 1601, 1573, 1557, 1496, 1485, 1452, 1444, 1406, 1302, 1282, 1261, 1231, 1194, 1124, 1068; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.89 (3H, s), 7.02-7.07 (2H, m), 7.39 (1H, ddd, J = 8.4, 7.5, 1.7), 7.46-7.48 (3H, m), 7.62 (1H, dd, J = 8.2, 1.7), 7.65 (1H, s), 8.36-8.39 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.3 (CH_3), 112.6 (CH), 121.0 (CH), 125.4 (CH), 128.7 (2 CH), 129.2 (2 CH), 130.6 (CH), 130.7 (C), 130.9 (CH), 138.7 (C), 139.2 (CH), 151.5 (C); MS (ES^+) *m/z* 250 ($[M + Na]^+$, 100), 228 ($[M + H]^+$, 79), 211 (M – O, 20); HRMS (ES^+) $[M + Na]^+$ $C_{14}H_{13}NNaO_2$ requires 250.0838, found 250.0833 (–2.2 ppm).

2.2. General procedure

General procedure for alkylarylketene-*N*-arylnitrone rearrangement. A solution of ketene (0.4 mmol, 1.0 equiv) in THF (1.5 mL) was added dropwise to a solution of

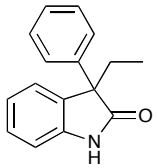
nitrone (0.4 mmol, 1.0 equiv) in THF (1.5 mL) at room temperature under nitrogen atmosphere and the reaction mixture was stirred for 30 minutes at room temperature. Aqueous 1M HCl (0.5 mL) was added, the mixture was stirred for 5 minutes and then extracted with Et_2O (3 * 10 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure.

2.3. Characterisation of racemic oxindoles 5-15



(±)

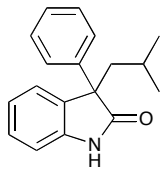
(±)-3-methyl-3-phenylindolin-2-one 5. The oxindole **(±)-5** was obtained from methylphenylketene (52.9 mg, 0.4 mmol, 1.0 equiv) and (*Z*)-*N*-(4-bromobenzylidene)aniline oxide **1** (92.7 mg, 0.4 mmol, 1.0 equiv) following the above general procedure. The residue was purified by column chromatography (EtOAc / Petroleum ether 10:90 to 30:70) to give the title product **(±)-5** (76.1 mg, 85% yield) as a white solid (mp = 139-140°C). IR (KBr disc) ν 3184 (NH), 3086, 3031, 2985, 2929, 2346, 1708 (C=O), 1618, 1597, 1473, 1453, 1442, 1374, 1325, 1301, 1221; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84 (3H, s), 6.99 (1H, d, J = 7.8), 7.07 (1H, td, J = 7.5, 0.9), 7.15 (1H, dd, J = 7.4, 0.6), 7.24 (1H, dd, J = 7.6, 1.2), 7.25-7.35 (5H, m), 8.88 (1H, *br* s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6 (CH_3), 52.8 (C), 110.3 (CH), 122.9 (CH), 124.5 (CH), 126.8 (2 CH), 127.5 (CH), 128.2 (CH), 128.8 (2 CH), 135.7 (C), 140.5 (C), 140.7 (C), 182.3 (C). MS (ES^+) *m/z* 246 ($[M + Na]^+$, 18), 241 ($[M + NH_4]^+$, 29), 224 ($[M + H]^+$, 100); HRMS (ES^+) $[M + H]^+$ $C_{15}H_{14}NO$ requires 224.1070, found 224.1070 (0.0 ppm).



(±)

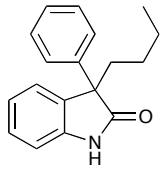
(±)-3-ethyl-3-phenylindolin-2-one 6. The oxindole **(±)-6** was obtained from ethylphenylketene (58.5 mg, 0.4 mmol, 1.0 equiv) and (*Z*)-*N*-(4-bromobenzylidene)aniline oxide **1** (92.7 mg, 0.4 mmol, 1.0 equiv) following the above

general procedure. The residue was purified by column chromatography (EtOAc / Petroleum ether 10:90 to 30:70) to give the title product **(±)-6** (78.3 mg, 83% yield) as a white solid (mp = 149-150°C). IR (KBr disc) ν 3200 (NH), 3085, 2980, 2965, 2934, 2869, 2364, 2345, 1705 (C=O), 1613, 1466; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (3H, t, J = 7.4), 2.26 (1H, dq, J = 14.7, 7.5), 2.47 (1H, dq, J = 14.7, 7.5), 6.97 (1H, ddd, J = 7.8, 0.9, 0.6), 7.10 (1H, dt, J = 7.5, 1.1), 7.19 (1H, dt, J = 7.5, 0.7), 7.23-7.35 (4H, m), 7.36-7.42 (2H, m), 8.61 (1H, *br* s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.4 (CH_3), 30.9 (CH_2), 58.2 (C), 110.4 (CH), 123.0 (CH), 125.4 (CH), 127.4 (2 CH), 127.7 (CH), 128.5 (CH), 129.0 (2 CH), 133.2 (C), 140.5 (C), 141.6 (C), 181.5 (C); MS (CI) *m/z* 238 ($[M + H]^+$, 100), 208 ($[M - C_2H_5]^+$, 7), 160 ($[M - C_6H_5]^+$, 10); HRMS (CI) [M + H] $C_{16}H_{16}NO$ requires 238.1232, found 238.1228 (–1.6 ppm).



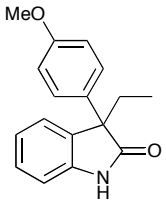
(±)

(±)-3-isobutyl-3-phenylindolin-2-one 7. The oxindole **(±)-7** was obtained from isobutylphenylketene (70.0 mg, 0.4 mmol, 1.0 equiv) and (*Z*)-*N*-(4-bromobenzylidene)aniline oxide **1** (92.7 mg, 0.4 mmol, 1.0 equiv) following the above general procedure. The residue was purified by column chromatography (EtOAc / Petroleum ether 10:90 to 30:70) to give the title product **(±)-7** (88.2 mg, 83% yield) as a yellowish solid (mp = 101-102°C). IR (KBr disc) ν 3214 (NH), 3090, 3060, 2958, 2931, 2870, 2361, 2343, 1710 (C=O), 1619, 1599, 1497, 1472, 1447, 1387, 1368, 1326, 1265, 1233, 1201; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.67 (3H, d, J = 6.7), 0.80 (3H, d, J = 6.6), 1.46 (1H, *app* dquint, J = 12.7, 6.4), 2.17 (1H, dd, J = 13.8, 5.2), 2.44 (1H, dd, J = 13.8, 7.4), 6.95 (1H, d, J = 7.7), 7.06 (1H, td, J = 7.5, 0.8), 7.17 (1H, d, J = 7.1), 7.20-7.28 (4H, m), 7.35-7.37 (2H, m), 9.27 (1H, *br* s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.2 (CH), 24.5 (CH_3), 25.8 (CH_3), 46.2 (CH_2), 57.0 (C), 110.5 (CH), 122.4 (CH), 125.6 (CH), 126.8 (2 CH), 127.3 (CH), 128.2 (CH), 128.6 (2 CH), 132.8 (C), 141.4 (C), 141.6 (C), 182.2 (C); MS (CI) *m/z* 266 ($[M + H]^+$, 100), 208 ($[M - C_4H_9]^+$, 4), 188 ($[M - C_6H_5]^+$, 2); HRMS (CI) [M + H] $C_{18}H_{20}NO$ requires 266.1545, found 266.1547 (+0.8 ppm).



(±)

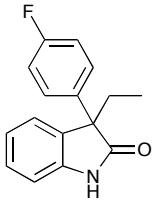
(±)-3-butyl-3-phenylindolin-2-one 8. The oxindole **(±)-8** was obtained from butylphenylketene (70.0 mg, 0.4 mmol, 1.0 equiv) and (*Z*)-*N*-(4-bromobenzylidene)aniline oxide **1** (92.7 mg, 0.4 mmol, 1.0 equiv) following the above general procedure. The residue was purified by column chromatography (EtOAc / Petroleum ether 10:90 to 30:70) to give the title product **(±)-8** (95.2 mg, 90% yield) as a yellowish solid (mp = 102-103°C). IR (KBr disc) ν 3192 (NH), 3089, 2954, 2926, 2858, 2364, 1723 (C=O), 1695, 1618, 1472; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (3H, t, J = 7.2), 0.88-0.97 (1H, m), 1.15-1.35 (3H, m), 2.19 (1H, td, J = 12.6, 3.9), 2.39 (1H, td, J = 12.7, 4.2), 6.94 (1H, d, J = 7.7), 7.09 (1H, td, J = 7.5, 0.9), 7.19 (1H, d, J = 7.1), 7.22-7.32 (4H, m), 7.37 (2H, dd, J = 8.4, 1.2), 7.92 (1H, *br* s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0 (CH_3), 23.0 (CH_2), 26.7 (CH_2), 37.4 (CH_2), 57.4 (C), 110.4 (CH), 122.6 (CH), 125.0 (CH), 127.0 (2 CH), 127.4 (CH), 128.1 (CH), 128.7 (2 CH), 133.3 (C), 140.4 (C), 141.4 (C), 181.9 (C); MS (CI) *m/z* 266 ($[M + H]^+$, 100), 208 ($[M - C_4H_9]^+$, 5), 188 ($[M - C_6H_5]^+$, 6); HRMS (CI) [M + H] $C_{18}H_{20}NO$ requires 266.1545, found 266.1541 (–1.5 ppm).



(±)

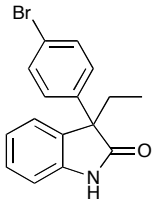
(±)-3-ethyl-3-(4-methoxyphenyl)indolin-2-one 9. The oxindole **(±)-9** was obtained from ethyl-(4-methoxyphenyl)ketene (70.5 mg, 0.4 mmol, 1.0 equiv) and (*Z*)-*N*-(4-bromobenzylidene)aniline oxide **1** (92.7 mg, 0.4 mmol, 1.0 equiv) following the above general procedure. The residue was purified by column chromatography (EtOAc / Petroleum ether 10:90 to 30:70) to give the title product **(±)-9** (90.5 mg, 85% yield) as a white solid (mp = 99-100°C). IR (KBr disc) ν 3184 (NH), 3081, 3028, 2965, 2932, 2839, 2365, 2346, 1708 (C=O), 1617, 1606, 1510, 1473, 1334, 1295, 1252, 1211, 1183, 1029; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.74 (3H, t, J = 7.3), 2.20 (1H, dq, J = 13.8, 7.0), 2.41 (1H, dq, J = 13.7, 7.0), 3.76 (3H, s), 6.83 (2H, d, J = 8.9), 6.94 (1H, d, J = 7.7), 7.06 (1H,

t, J = 7.5), 7.15 (1H, d, J = 7.1), 7.23 (1H, td, J = 7.6, 0.8), 7.27 (2H, d, J = 8.9), 8.73 (1H, *br* s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.1 (CH_3), 30.7 (CH_2), 55.4 (CH_3), 57.3 (C), 110.2 (CH), 114.0 (2 CH), 122.6 (CH), 125.0 (CH), 128.1 (CH), 128.2 (2 CH), 132.3 (C), 133.1 (C), 141.5 (C), 158.8 (C), 181.8 (C); MS (CI) *m/z* 268 ($[M + H]^+$, 100), 238 ($[M – C_2H_5]^+$, 17), 160 ($[M – C_6H_4\text{-}OMe]^+$, 69); HRMS (CI) [M + H] $C_{17}H_{18}NO_2$ requires 268.1338, found 268.1334 (–1.3 ppm).



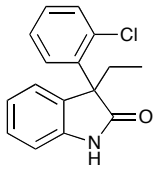
(±)

(±)-3-ethyl-3-(4-fluorophenyl)indolin-2-one 10. The oxindole **(±)-10** was obtained from ethyl-(4-fluorophenyl)ketene (65.7 mg, 0.4 mmol, 1.0 equiv) and (*Z*)-*N*-(4-bromobenzylidene)aniline oxide **1** (92.7 mg, 0.4 mmol, 1.0 equiv) following the above general procedure. The residue was purified by column chromatography (EtOAc / Petroleum ether 10:90 to 30:70) to give the title product **(±)-10** (85.9 mg, 84% yield) as a white solid (mp = 180°C). IR (KBr disc) ν 3199 (NH), 3087, 2979, 2967, 2936, 2879, 2346, 1706 (C=O), 1613, 1509, 1467, 1404, 1321, 1225, 1163; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.76 (3H, t, J = 7.3), 2.22 (1H, dq, J = 13.8, 7.1), 2.43 (1H, dq, J = 13.7, 7.0), 6.97-7.02 (3H, m), 7.11 (1H, td, J = 7.5, 0.9), 7.18 (1H, d, J = 7.2), 7.28 (1H, td, J = 7.6, 1.3), 7.32-7.38 (2H, m), 8.39 (1H, *br* s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.1 (CH_3), 31.0 (CH_2), 57.3 (C), 110.2 (CH), 115.4 and 115.6 (2 CH), 122.8 (CH), 125.2 (CH), 128.4 (CH), 128.8 and 128.9 (2 CH), 132.5 (C), 141.2 (C), 160.9 (C), 163.4 (C), 180.8 (C); ^{19}F NMR (377 MHz, $CDCl_3$) δ –116.0; MS (CI) *m/z* 256 ($[M + H]^+$, 100), 236 ($[M – F]^+$, 3), 226 ($[M – C_2H_5]^+$, 12), 160 ($[M – C_6H_4\text{-}F]^+$, 39); HRMS (CI) [M + H] $C_{16}H_{15}FNO$ requires 256.1138, found 256.1139 (+0.5 ppm).



(±)

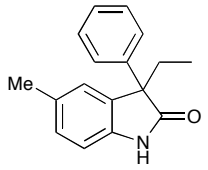
(±)-3-(4-bromophenyl)-3-ethylindolin-2-one 11. The oxindole **(±)-11** was obtained from (4-bromophenyl)ethylketene (90.0 mg, 0.4 mmol, 1.0 equiv) and (*Z*)-*N*-(4-bromobenzylidene)aniline oxide **1** (92.7 mg, 0.4 mmol, 1.0 equiv) following the above general procedure. The residue was purified by column chromatography (EtOAc / Petroleum ether 10:90 to 40:60) to give the title product **(±)-11** (108.9 mg, 86% yield) as a white solid (mp = 132-133°C). IR (KBr disc) ν 3204 (NH), 3083, 2969, 2927, 2878, 2367, 1703 (C=O), 1617, 1600, 1587, 1490, 1470, 1396, 1325, 1207, 1078, 1008; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.77 (3H, t, *J* = 7.3), 2.23 (1H, dq, *J* = 13.7, 7.0), 2.43 (1H, dq, *J* = 13.7, 7.0), 6.99 (1H, d, *J* = 7.7), 7.11 (1H, td, *J* = 7.3, 0.7), 7.16 (1H, d, *J* = 6.1), 7.22-7.34 (3H, m), 7.42-7.45 (2H, m), 9.41 (1H, *br* s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 9.0 (CH_3), 30.6 (CH_2), 57.6 (C), 110.5 (CH), 121.6 (C), 122.8 (CH), 124.9 (CH), 128.4 (CH), 128.9 (2 CH), 131.7 (2 CH), 132.2 (C), 139.2 (C), 141.5 (C), 181.3 (C); MS (ES^+) *m/z* 335 ([M(^{81}Br) + NH_4]$^+$, 53), 333 ([M(^{79}Br) + NH_4]$^+$, 53), 318 ([M(^{81}Br) + H]$^+$, 98), 316 ([M(^{79}Br) + H]$^+$, 100); HRMS (ES^+) [M(^{79}Br) + H]$^+$ $C_{16}H_{15}BrNO$ requires 316.0332, found 316.0336 (+1.4 ppm).



(±)

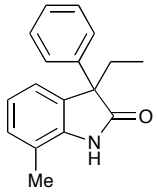
(±)-3-(2-chlorophenyl)-3-ethylindolin-2-one 12. The oxindole **(±)-12** was obtained from (2-chlorophenyl)ethylketene (72.3 mg, 0.4 mmol, 1.0 equiv) and (*Z*)-*N*-(4-bromobenzylidene)aniline oxide **1** (92.7 mg, 0.4 mmol, 1.0 equiv) following the above general procedure. The residue was purified by column chromatography (EtOAc / Petroleum ether 10:90 to 30:70) to give the title product **(±)-12** (91.0 mg, 84% yield) as a white solid (mp = 138-140°C). IR (KBr disc) ν 3180 (NH), 3085, 3035, 2989, 2974, 2939, 2923, 2882, 2856, 2360, 2336, 1707 (C=O), 1617, 1472, 1460, 1456, 1238, 1208, 1064; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (3H, t, *J* = 7.3), 2.31 (1H, dq, *J* = 13.2, 6.8), 2.44 (1H, dq, *J* = 13.2, 6.8), 6.78 (1H, d, *J* = 7.3), 6.92 (1H, d, *J* = 7.7), 6.98 (1H, t, *J* = 7.5), 7.19-7.25 (1H, m), 7.27 (1H, d, *J* = 6.8), 7.31 (1H, d, *J* = 6.5), 7.39 (1H, td, *J* = 7.6, 1.2), 7.77 (1H, d, *J* = 7.7), 9.29 (1H, *br* s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.0 (CH_3), 31.1 (CH_2), 57.0 (C), 109.7 (CH), 122.6 (CH), 123.0 (CH), 126.9 (CH), 128.0 (CH), 128.9 (CH), 129.4 (CH), 131.1 (CH), 132.8 (C), 134.6 (C), 137.9 (C), 142.3 (C), 181.1 (C); MS (ES^+) *m/z* 291 ([M(^{37}Cl) + NH_4]$^+$, 6), 289 ([M(^{35}Cl) + NH_4]$^+$, 17), 274 ([M(^{37}Cl)

+ H]$^+$, 33), 272 ([M(^{35}Cl) + H]$^+$, 100); HRMS (ES$^+$) [M(^{35}Cl) + H]$^+$ $C_{16}H_{15}ClNO$ requires 272.0837, found 272.0838 (+0.5 ppm).



(±)

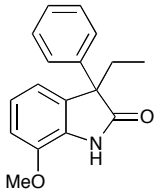
(±)-3-ethyl-5-methyl-3-phenylindolin-2-one 13. The oxindole **(±)-13** was obtained from ethylphenylketene (58.5 mg, 0.4 mmol, 1.0 equiv) and (*Z*)-*N*-benzylidene-4-methylaniline oxide **2** (84.5 mg, 0.4 mmol, 1.0 equiv) following the above general procedure. The residue was purified by column chromatography (EtOAc / Petroleum ether 10:90 to 30:70) to give the title product **(±)-13** (87.1 mg, 87% yield) as a white solid (mp = 160-161°C). IR (KBr disc) ν 3179 (NH), 3079, 3059, 3038, 2974, 2918, 2878, 2856, 2358, 1701 (C=O), 1623, 1601, 1491, 1457, 1448, 1337, 1215, 1131; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (3H, t, J = 7.3), 2.25 (1H, dq, J = 13.7, 7.0), 2.34 (3H, s), 2.47 (1H, dq, J = 13.7, 7.0), 6.87 (1H, d, J = 7.9), 6.98 (1H, s), 7.06 (1H, d, J = 7.8), 7.24-7.28 (1H, m), 7.33 (2H, t, J = 7.5), 7.39 (2H, t, J = 7.4), 8.93 (1H, *br* s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.1 (CH_3), 21.4 (CH_3), 30.4 (CH_2), 58.1 (C), 109.9 (CH), 125.6 (CH), 127.1 (2 CH), 127.3 (CH), 128.5 (CH), 128.7 (2 CH), 132.1 (C), 133.1 (C), 139.0 (C), 140.5 (C), 181.5 (C); MS (CI) *m/z* 252 ([M + H]$^+$, 100), 222 ([M – C_2H_5]$^+$, 7), 174 ([M – C_6H_5]$^+$, 9); HRMS (CI) [M + H] $C_{17}H_{18}NO$ requires 252.1388, found 252.1383 (–2.1 ppm).



(±)

(±)-3-ethyl-7-methyl-3-phenylindolin-2-one 14. The oxindole **(±)-14** was obtained from ethylphenylketene (58.5 mg, 0.4 mmol, 1.0 equiv) and (*Z*)-*N*-benzylidene-2-methylaniline oxide **3** (84.5 mg, 0.4 mmol, 1.0 equiv) following the above general procedure. The residue was purified by column chromatography (EtOAc / Petroleum ether 10:90 to 20:80) to give the title product **(±)-14** (86.2 mg, 86% yield) as a white

solid (mp = 138-139°C). IR (KBr disc) ν 3215 (NH), 3074, 3025, 2959, 2923, 2875, 2364, 2345, 1703 (C=O), 1624, 1605, 1492, 1459, 1397, 1382, 1320, 1203; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (3H, t, J = 7.3), 2.25 (1H, dq, J = 13.8, 7.1), 2.31 (3H, s), 2.46 (1H, dq, J = 13.7, 7.0), 7.00-7.05 (2H, m), 7.08-7.09 (1H, m), 7.23-7.27 (1H, m), 7.29-7.33 (2H, m), 7.42 (2H, dd, J = 8.5, 1.2), 9.19 (1H, *br* s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.2 (CH_3), 16.7 (CH_3), 30.9 (CH_2), 58.3 (C), 119.5 (C), 122.53 (CH), 122.55 (CH), 127.1 (2 CH), 127.3 (CH), 128.6 (2 CH), 129.5 (CH), 132.3 (C), 140.2 (C), 140.4 (C), 181.7 (C); MS (CI) *m/z* 252 ($[M + H]^+$, 100), 222 ($[M - C_2H_5]^+$, 4), 174 ($[M - C_6H_5]^+$, 4); HRMS (CI) [M + H] $C_{17}H_{18}NO$ requires 252.1388, found 252.1385 (–1.3 ppm).

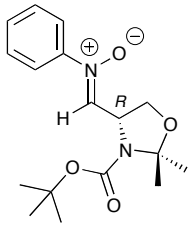


(±)

(±)-3-ethyl-7-methoxy-3-phenylindolin-2-one 15. The oxindole **(±)-15** was obtained from ethylphenylketene (58.5 mg, 0.4 mmol, 1.0 equiv) and (*Z*)-*N*-benzylidene-2-methoxyaniline oxide **4** (90.9 mg, 0.4 mmol, 1.0 equiv) following the above general procedure. The residue was purified by column chromatography (EtOAc / Petroleum ether 10:90 to 30:70) to give the title product **(±)-15** (99.6 mg, 93% yield) as a white solid (mp = 142-143°C). IR (KBr disc) ν 3201 (NH), 3076, 3031, 2963, 2929, 2875, 2835, 2364, 2345, 1710 (C=O), 1629, 1597, 1497, 1442, 1398, 1273, 1207, 1053; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (3H, t, J = 7.4), 2.24 (1H, dq, J = 13.8, 7.1), 2.24 (1H, dq, J = 13.7, 7.0), 3.91 (3H, s), 6.84 (1H, d, J = 7.6), 6.87 (1H, d, J = 8.0), 7.07 (1H, t, J = 7.9), 7.23-7.27 (1H, m), 7.29-7.33 (2H, m), 7.39-7.41 (2H, m), 7.65 (1H, *br* s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.2 (CH_3), 30.8 (CH_2), 55.7 (CH_3), 58.6 (C), 110.4 (CH), 117.4 (CH), 123.1 (CH), 127.0 (2 CH), 127.3 (CH), 128.6 (2 CH), 130.0 (C), 133.5 (C), 140.2 (C), 144.0 (C), 179.8 (C); MS (ES^+) *m/z* 285 ($[M + NH_4]^+$, 12), 268 ($[M + H]^+$, 100); HRMS (ES^+) $[M + H]^+$ $C_{17}H_{18}NO_2$ requires 268.1332, found 268.1333 (+0.4 ppm).

3. Asymmetric version

3.1. Preparation of chiral nitrone 16



(*R*,*Z*)-*N*-((3-(*tert*-butoxycarbonyl)-2,2-dimethyloxazolidin-4-yl)methylene)aniline oxide 16. $MgSO_4$ (1.32 g, 11 mmol, 1.1 equiv) was added to a solution of (*S*)-Garner's aldehyde[3] (2.29 g, 10 mmol, 1.0 equiv) in CH_2Cl_2 (70 mL) under nitrogen atmosphere and the reaction mixture was stirred for 5 minutes at room temperature. *N*-phenylhydroxylamine[4] (1.09 g, 10 mmol, 1.0 equiv) was added as a solid and the reaction mixture was stirred overnight (16 hours) at room temperature. $MgSO_4$ was removed by filtration under nitrogen and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc / petroleum ether 30:70 to 100:0) to give a yellowish solid (2.78 g, 87% yield). An analytical sample was obtained by recrystallization from dry Et_2O / dry hexane to give the title compound **(*R*,*Z*)-16** as a white solid (mp = 101°C). IR (KBr disc) ν 3072, 2979, 2935, 2369, 2346, 1696 (C=O), 1561, 1485, 1458, 1378, 1365, 1318, 1263, 1253, 1161, 1089; ^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 1.44-1.65 (15H, m), 4.20-4.30 (2H, m), 5.16 (1H, s), 7.29-7.36 (1H, m), 7.37-7.48 (3H, m), 7.67 (2H, s); ^{13}C NMR (100 MHz, $CDCl_3$, 293K, mixture of rotamers) δ 23.3 and 24.4 (CH_3), 26.6 and 27.4 (CH_3), 28.6 (3 CH_3), 55.5 and 56.3 (CH), 66.0 and 66.6 (CH_2), 80.6 and 81.1 (C), 94.2 and 94.7 (C), 121.5 and 121.7 (2 CH), 129.1 and 129.3 (CH), 130.3 and 130.5 (2 CH), 140.1 and 140.2 (CH), 146.8 (C), 151.7 and 152.4 (C); MS (CI) *m/z* 321 ($[M + H]^+$, 23), 265 (33), 207 (100); HRMS (CI) [M + H] $C_{17}H_{25}N_2O_4$ requires 321.1814, found 321.1808 (–2.0 ppm). The analysis of the product by ^{1}H NMR at 80°C revealed a diastereomerically pure compound (300 MHz, d_6-DMSO, 353K) δ 1.42 (9H, s), 1.51 (3H, s), 1.60 (3H, s), 4.01 (1H, dd, J = 9.1, 3.1), 4.25 (1H, dd, J = 9.1, 6.8), 5.06 (1H, td, J = 6.3, 2.7), 7.50-7.52 (3H, m), 7.72 (1H, d, J = 5.8), 7.77-7.81 (2H, m). $[\alpha]_D^{20}$ –94.4 (*c* 1.00, $CHCl_3$).

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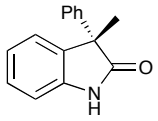
[3] (*S*)-Garner's aldehyde was prepared from *L*-serine according to a literature procedure: Foss, F. W. Jr.; Snyder, A. H.; Davis, M. D.; Rouse, M.; Okusa, M. D.; Lynch, K. R.; Macdonald, T. L. *Bioorg. Med. Chem*. **2007**, *15*, 663-677.

[4] *N*-phenylhydroxylamine was prepared from nitrobenzene according to a literature procedure: Tian, L.; Xu, G.-Y.; Ye, Y.; Liu, L.-Z. *Synthesis* **2003**, *9*, 1329-1334.

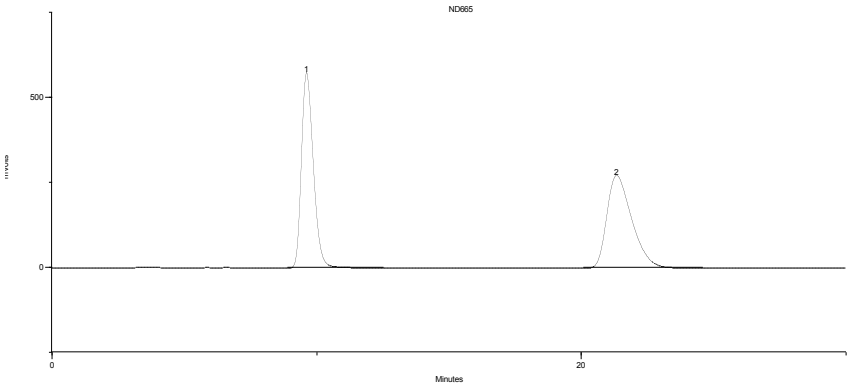
3.2. General procedure

General procedure for asymmetric alkylarylketene-*N*-arylnitrone rearrangement. A solution of alkylarylketene (0.4 mmol, 1.0 equiv) in THF (1.5 mL) was added dropwise to a solution of chiral nitrone **(*R*,*Z*)-16** (128.2 mg, 0.4 mmol, 1.0 equiv) in THF (1.5 mL) at –78°C under nitrogen atmosphere and the reaction mixture was stirred for 3 hours at –78°C. Saturated aqueous NH_4Cl (0.5 mL) was added at –78°C and the mixture was allowed to warm to room temperature, then, extracted with Et_2O (3 * 10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure.

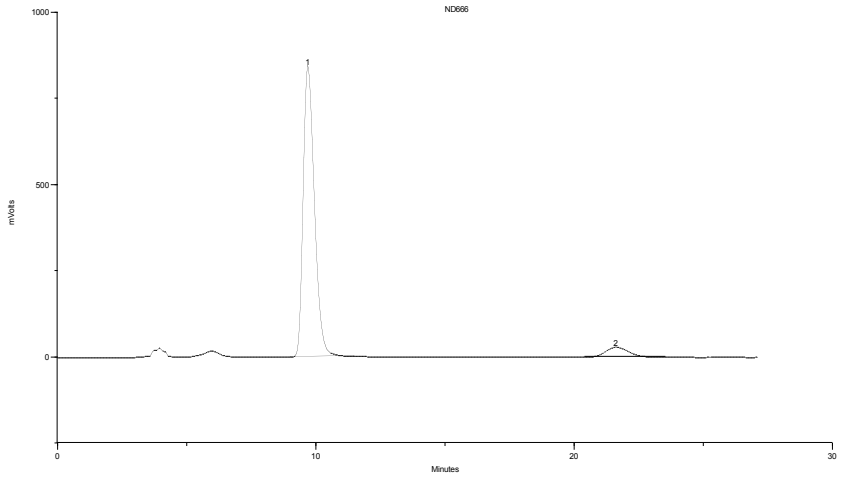
3.3. Characterisation of enantiomerically enriched oxindole 5 and determination of absolute configuration



(*S*)-3-methyl-3-phenylindolin-2-one 5. The oxindole **(*S*)-5** was obtained from methylphenylketene (52.9 mg, 0.4 mmol, 1.0 equiv) and chiral nitrone **16** (128.2 mg, 0.4 mmol, 1.0 equiv) following the above general procedure. The residue was purified by column chromatography (EtOAc / Petroleum ether 10:90 to 30:70) to give (*S*)-Garner's aldehyde (73.7 mg, 80% yield) as a yellowish oil and the desired product **(*S*)-5** (76.2 mg, 85% yield) as a white solid. HPLC analysis: 87% ee (Daicel Chiralcel OD-H column, eluent: hexane/^{i}PrOH 90:10, flow: 1 mL/min, wavelength: 254 nm, retention times: 9.7 min (major) and 21.6 min (minor)). $[\alpha]_D^{20}$ –86.9 (*c* 1.22, $CHCl_3$, 87% ee).



Peak Name	R. Time	Area	Area %
1	9.62	29973648	50.01
2	21.33	29958728	49.99



Peak Name	R. Time	Area	Area %
1	9.69	42835140	93.26
2	21.63	3095011	6.74

5 (unknown absolute configuration)

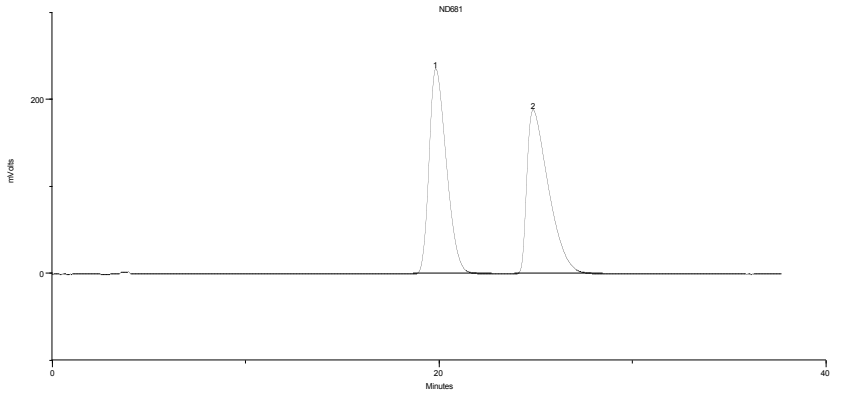
87% ee

(*S*)-**17**

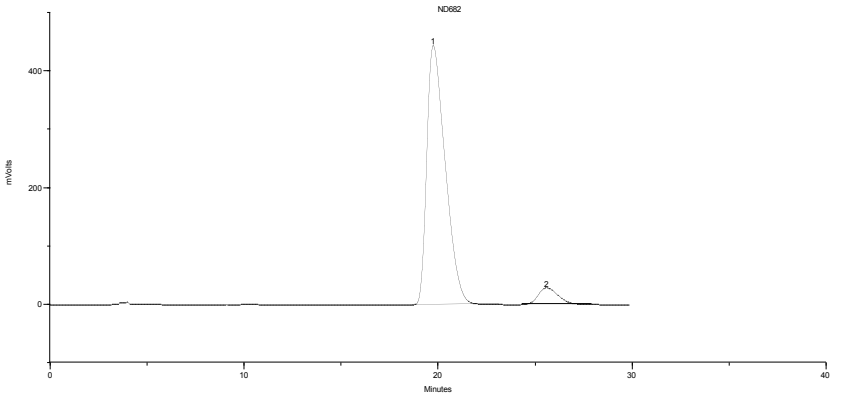
87% ee

(*S*)-1,3-dimethyl-3-phenylindolin-2-one 17. A solution of unknown absolute configuration 3-methyl-3-phenylindolin-2-one **5** (54.2 mg, 0.24 mmol, 1.0 equiv, 87% ee) in dry DMF (3 mL) was added to a suspension of NaH (60% dispersion in oil, 120.0 mg, 0.29 mmol, 1.2 equiv) in dry DMF (3 mL) at 0°C under nitrogen atmosphere and the reaction mixture was stirred for 30 minutes at 0°C. MeI (0.02 mL, 0.29 mmol, 1.2 equiv) was added at 0°C and the reaction mixture was allowed to warm to room temperature. Water was gradually added and the mixture was extracted with Et_2O (3 * 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc / Petroleum ether 10:90 to 15:85) to give the desired product **17** (52.0 mg, 90% yield) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.75 (3H, s), 3.20 (3H, s), 6.88 (1H, d, J = 7.8), 7.05 (1H, t, J = 7.5), 7.15 (1H, dt, J = 7.4, 0.6), 7.18-7.27 (5H, m), 7.29 (1H, dd, J = 7.7, 0.8). HPLC analysis: 87% ee (Daicel Chiralcel OD-H column, eluent: hexane/^{i}PrOH 99:1, flow: 1 mL/min, wavelength: 254 nm, retention

times: 19.8 min (major) and 25.6 min (minor)). $[\alpha]_D^{20}$ –81.2 (*c* 1.10, CH_2Cl_2, 87% ee). Lit.[5] $[\alpha]_D^{20}$ –86.0 (*c* 1.00, CH_2Cl_2, 94% ee) for *S*-enantiomer (absolute configuration determined by X-Ray).

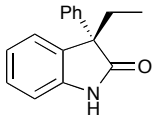


Peak Name	R. Time	Area	Area %
1	19.83	24451364	50.08
2	24.86	24370406	49.92



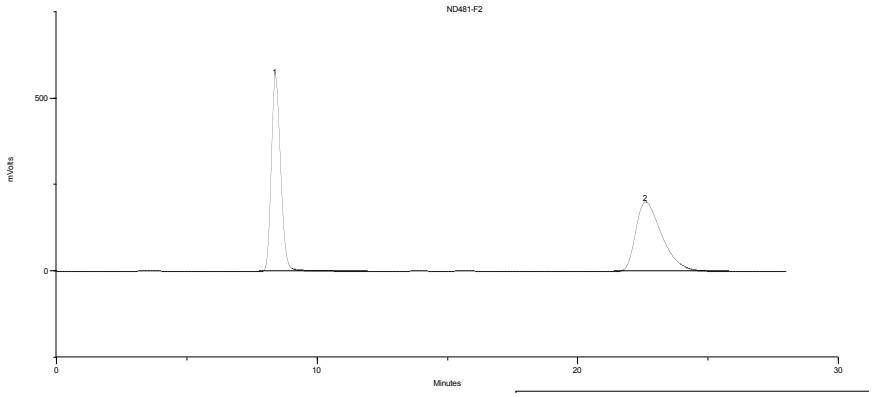
Peak Name	R. Time	Area	Area %
1	19.75	49087980	93.39
2	25.60	3475857	6.61

3.4. Characterisation of oxindoles 6, 8-10, 18-20

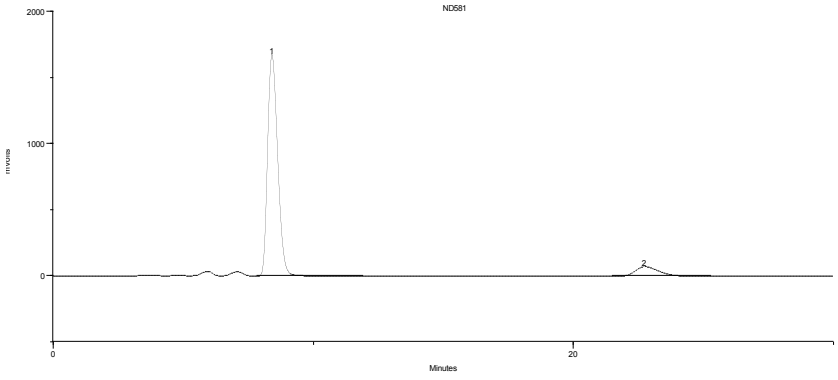


[5] Kündig, E. P.; Seidel, T. M.; Jia, Y.; Bernardinelli, G. *Angew. Chem. Int. Ed.* **2007**, *46*, 8484-8487.

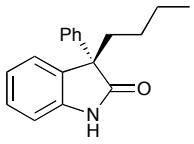
(*S*)-3-ethyl-3-phenylindolin-2-one 6. The oxindole **(*S*)-6** was obtained from ethylphenylketene (58.5 mg, 0.4 mmol, 1.0 equiv) and chiral nitrone **16** (128.2 mg, 0.4 mmol, 1.0 equiv) following the above general procedure. The residue was purified by column chromatography (EtOAc / Petroleum ether 10:90 to 30:70) to give (*S*)-Garner's aldehyde (71.9 mg, 78% yield) as a yellowish oil and the desired product **(*S*)-6** (76.1 mg, 80% yield) as a white solid. HPLC analysis: 81% ee (Daicel Chiralcel OD-H column, eluent: hexane/^{i}PrOH 90:10, flow: 1 mL/min, wavelength: 254 nm, retention times: 8.4 min (major) and 22.8 min (minor)). $[\alpha]_D^{20}$ –99.4 (*c* 0.89, $CHCl_3$, 81% ee).



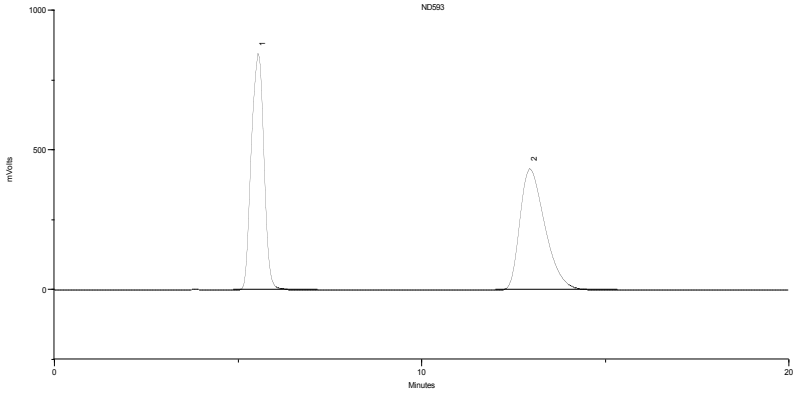
Peak Name	R. Time	Area	Area %
1	8.40	23734108	50.27
2	22.61	23476260	49.73



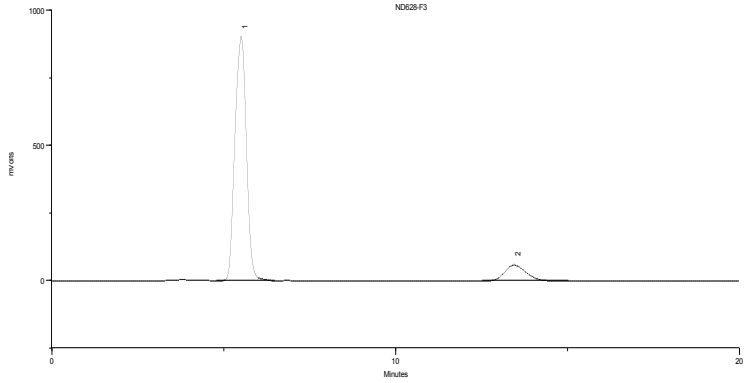
Peak Name	R. Time	Area	Area %
1	8.41	75975224	90.43
2	22.75	8044756	9.57



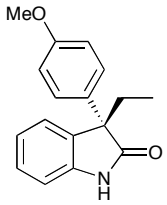
(*S*)-3-butyl-3-phenylindolin-2-one 8. The oxindole **(*S*)-8** was obtained from butylphenylketene (70.0 mg, 0.4 mmol, 1.0 equiv) and chiral nitrone **16** (128.2 mg, 0.4 mmol, 1.0 equiv) following the above general procedure. The residue was purified by column chromatography (EtOAc / Petroleum ether 10:90 to 30:70) to give (*S*)-Garner's aldehyde (75.0 mg, 82% yield) as a yellowish oil and the desired product **(*S*)-8** (86.7 mg, 82% yield) as a white solid. HPLC analysis: 78% ee (Daicel Chiralcel OD-H column, eluent: hexane/^{i}PrOH 90:10, flow: 1 mL/min, wavelength: 254 nm, retention times: 5.5 min (major) and 13.5 min (minor)). $[\alpha]_D^{20}$ –80.3 (*c* 0.96, $CHCl_3$, 78% ee).



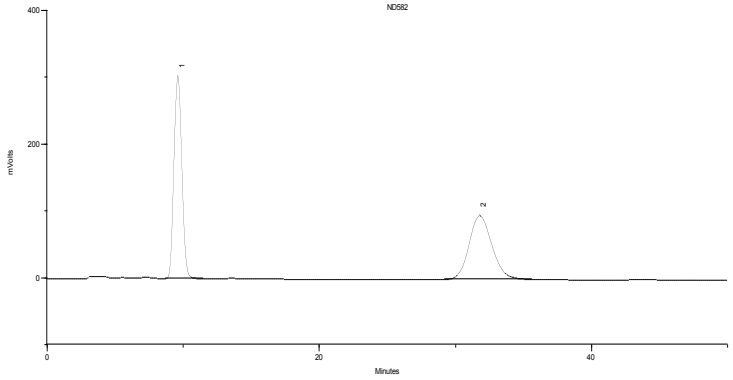
Peak Name	R. Time	Area	Area %
1	5.56	33730720	49.48
2	12.95	34443820	50.52



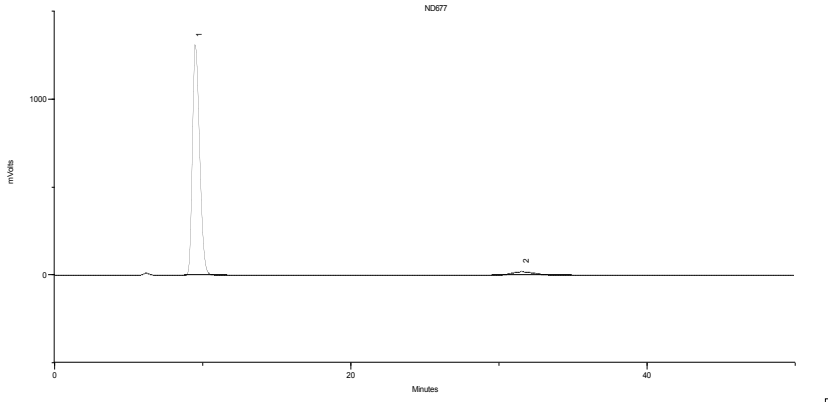
Peak Name	R. Time	Area	Area %
1	5.51	35117036	89.05
2	13.45	4319257	10.95



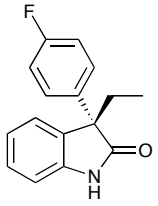
(*S*)-3-ethyl-3-(4-methoxyphenyl)indolin-2-one 9. The oxindole **(*S*)-9** was obtained from ethyl-(4-methoxyphenyl)ketene (70.5 mg, 0.4 mmol, 1.0 equiv) and chiral nitrone **16** (128.2 mg, 0.4 mmol, 1.0 equiv) following the above general procedure. The residue was purified by column chromatography (EtOAc / Petroleum ether 10:90 to 40:60) to give (*S*)-Garner's aldehyde (79.3 mg, 86% yield) as a yellowish oil and the desired product **(*S*)-9** (94.0 mg, 88% yield) as a white solid. HPLC analysis: 90% ee (Daicel Chiralcel OD-H column, eluent: hexane/^{i}PrOH 80:20, flow: 1 mL/min, wavelength: 254 nm, retention times: 9.5 min (major) and 31.6 min (minor)). $[\alpha]_{D}^{20}$ –137.3 (*c* 1.03, $CHCl_3$, 90% ee).



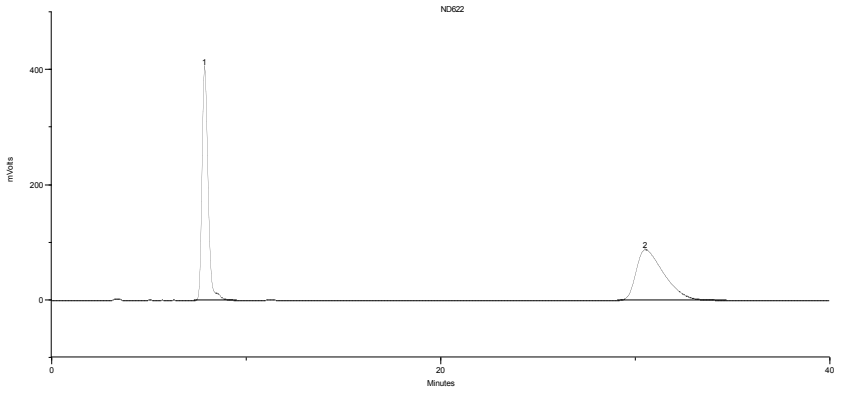
Peak Name	R. Time	Area	Area %
1	9.60	20425816	52.26
2	31.78	18661786	47.74



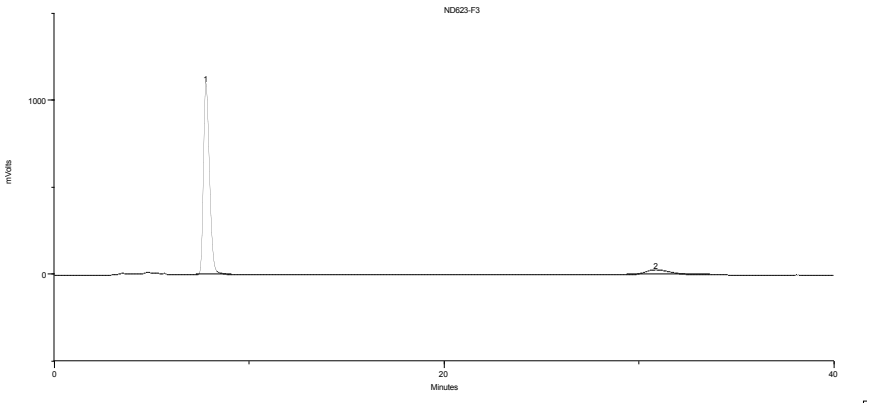
Peak Name	R. Time	Area	Area %
1	9.51	74145048	94.78
2	31.57	4084541	5.22



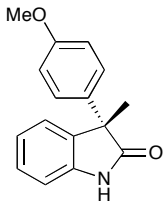
(*S*)-3-ethyl-3-(4-fluorophenyl)indolin-2-one 10. The oxindole **(*S*)-10** was obtained from ethyl-(4-fluorophenyl)ketene (65.7 mg, 0.4 mmol, 1.0 equiv) and chiral nitrone **16** (128.2 mg, 0.4 mmol, 1.0 equiv) following the above general procedure. The residue was purified by column chromatography (EtOAc / Petroleum ether 10:90 to 30:70) to give (*S*)-Garner's aldehyde (72.1 mg, 79% yield) as a yellowish oil and the desired product **(*S*)-10** (79.5 mg, 78% yield) as a white solid. HPLC analysis: 80% ee (Daicel Chiralcel OD-H column, eluent: hexane/^{i}PrOH 90:10, flow: 1 mL/min, wavelength: 254 nm, retention times: 7.8 min (major) and 30.9 min (minor)). $[\alpha]_{D}^{20}$ –107.6 (*c* 1.07, $CHCl_3$, 80% ee).



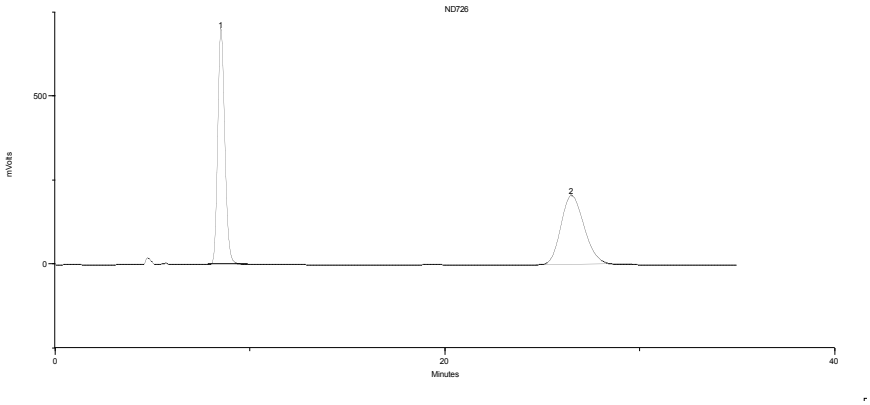
Peak Name	R. Time	Area	Area %
1	7.86	14667003	50.14
2	30.52	14585708	49.86



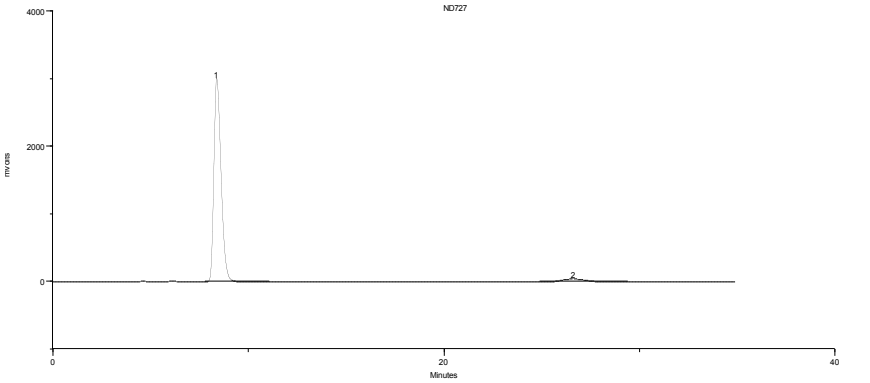
Peak Name	R. Time	Area	Area %
1	7.78	39830884	89.82
2	30.86	4514934	10.18



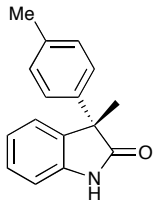
(*S*)-3-(4-methoxyphenyl)-3-methylindolin-2-one 18. The oxindole **(*S*)-18** was obtained from (4-methoxyphenyl)methylketene (64.9 mg, 0.4 mmol, 1.0 equiv) and chiral nitrone **16** (128.2 mg, 0.4 mmol, 1.0 equiv) following the above general procedure. The residue was purified by column chromatography (EtOAc / Petroleum ether 10:90 to 40:60) to give (*S*)-Garner's aldehyde (79.6 mg, 87% yield) as a yellowish oil and the desired product **(*S*)-18** (92.2 mg, 91% yield) as a white solid (mp = 97-98°C). IR (KBr disc) ν 3186 (NH), 3083, 2933, 2836, 2367, 2346, 1710 (C=O), 1618, 1514, 1473, 1442, 1375, 1328, 1294, 1256, 1218, 1179, 1026; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82 (3H, s), 3.79 (3H, s), 6.86 (1H, d, J = 8.9), 6.98 (1H, d, J = 7.6), 7.06 (1H, t, J = 7.5), 7.14 (1H, d, J = 7.4), 7.24-7.27 (3H, m), 9.36 (1H, *br* s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6 (CH_3), 52.2 (C), 55.4 (CH_3), 110.4 (CH), 114.1 (2 CH), 122.8 (CH), 124.3 (CH), 127.9 (2 CH), 128.1 (CH), 132.7 (C), 135.9 (C), 140.6 (C), 158.9 (C), 182.9 (C); MS (CI) *m/z* 254 ($[M + H]^+$, 100), 253 (M^+, 21), 238 ($[M – Me]^+$, 3), 146 ($[M – C_6H_4\text{-}OMe]^+$, 4); HRMS (CI) [M + H] $C_{16}H_{16}NO_2$ requires 254.1181, found 254.1188 (+2.7 ppm). HPLC analysis: 90% ee (Daicel Chiralcel OD-H column, eluent: hexane/^{i}PrOH 80:20, flow: 1 mL/min, wavelength: 254 nm, retention times: 8.4 min (major) and 26.6 min (minor)). $[\alpha]_D^{20}$ – 121.5 (*c* 1.00, $CHCl_3$, 90% ee).



Peak Name	R. Time	Area	Area %
1	8.51	29671078	50.73
2	26.49	28812298	49.27

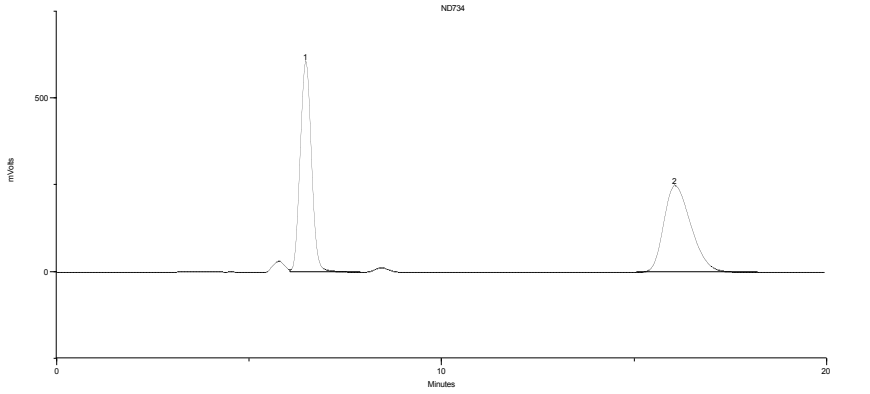


Peak Name	R. Time	Area	Area %
1	8.39	128354264	94.97
2	26.62	6798882	5.03

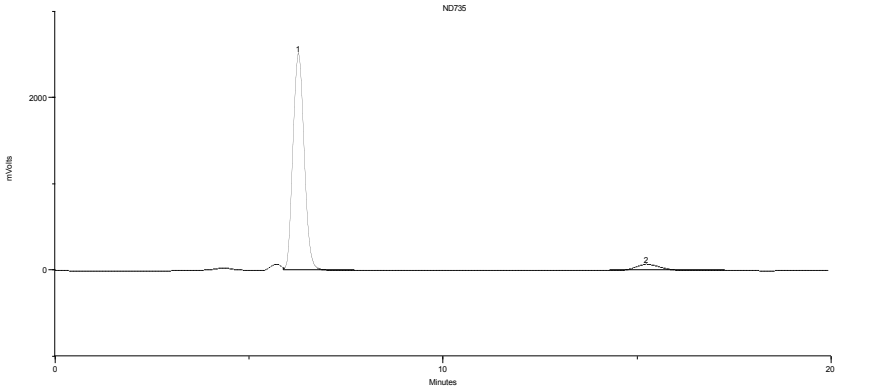


(*S*)-3-methyl-3-*p*-tolylindolin-2-one 19. The oxindole **(*S*)-19** was obtained from methyl-(*p*-tolyl)ketene (58.5 mg, 0.4 mmol, 1.0 equiv) and chiral nitrone **16** (128.2 mg, 0.4 mmol, 1.0 equiv) following the above general procedure. The residue was purified by column chromatography (EtOAc / Petroleum ether 10:90 to 30:70) to give the desired product **(*S*)-19** (79.3 mg, 84% yield) as a white solid (mp = 118-120°C). IR (KBr disc)

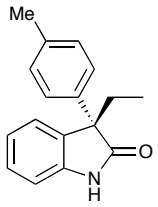
ν 3147 (NH), 3086, 3034, 2987, 2929, 2895, 2842, 2369, 2347, 1710 (C=O), 1620, 1509, 1475, 1457, 1373, 1328, 1299, 1216, 1018; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (3H, s), 2.32 (3H, s), 6.98 (1H, d, J = 7.8), 7.06 (1H, t, J = 7.5), 7.12-7.14 (3H, m), 7.20-7.27 (3H, m), 8.87 (1H, *br* s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1 (CH_3), 23.5 (CH_3), 52.6 (C), 110.4 (CH), 122.9 (CH), 124.4 (CH), 126.6 (2 CH), 128.1 (CH), 129.4 (2 CH), 135.9 (C), 137.1 (C), 137.7 (C), 140.6 (C), 182.7 (C); MS (CI) *m/z* 238 ($[M + H]^+$, 100), 165, 146 ($[M - C_6H_4\text{-}Me]^+$, 15), 119 ($[C_9H_{11}]^+$, 97); HRMS (CI) [M + H] $C_{16}H_{16}NO$ requires 238.1232, found 238.1235 (+1.3 ppm). HPLC analysis: 87% ee (Daicel Chiralcel OD-H column, eluent: hexane/^{i}PrOH 80:20, flow: 1 mL/min, wavelength: 254 nm, retention times: 6.3 min (major) and 15.2 min (minor)). $[\alpha]_D^{20}$ –83.1 (*c* 2.78, $CHCl_3$, 87% ee).



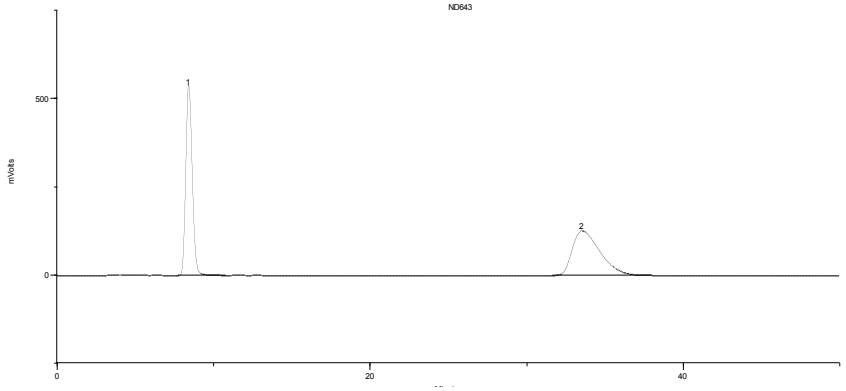
Peak Name	R. Time	Area	Area %
1	6.47	20815186	50.26
2	16.06	20600714	49.74



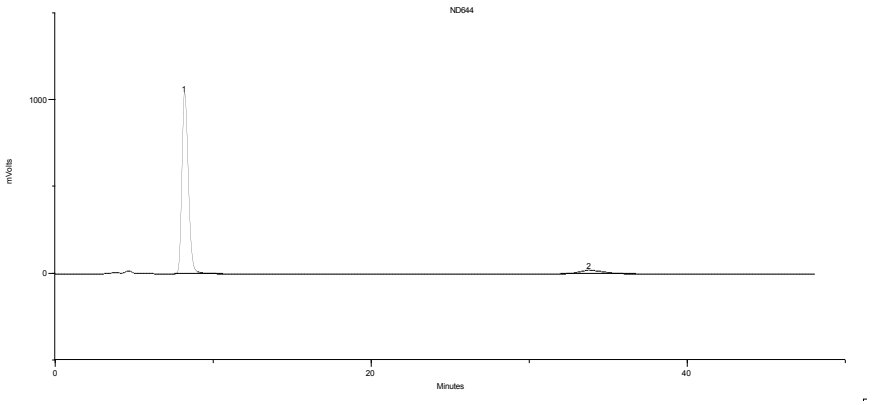
Peak Name	R. Time	Area	Area %
1	6.27	85315656	93.72
2	15.24	5720208	6.28



(*S*)-3-ethyl-3-*p*-tolylindolin-2-one 20. The oxindole **(*S*)-20** was obtained from ethyl-(*p*-tolyl)ketene (64.1 mg, 0.4 mmol, 1.0 equiv) and chiral nitrone **16** (128.2 mg, 0.4 mmol, 1.0 equiv) following the above general procedure. The residue was purified by column chromatography (EtOAc / Petroleum ether 10:90 to 30:70) to give (*S*)-Garner's aldehyde (80.0 mg, 87% yield) as a yellowish oil and the desired product **(*S*)-20** (91.6 mg, 91% yield) as a white solid (mp = 105-106°C). IR (KBr disc) ν 3200 (NH), 3085, 3031, 2972, 2964, 2934, 2919, 2879, 2852, 2363, 1701 (C=O), 1621, 1600, 1510, 1473, 1461, 1334, 1328, 1220, 1211, 1184, 1105, 1025; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.77 (3H, t, J = 7.4), 2.25 (1H, dq, J = 13.8, 7.1), 2.32 (3H, s), 2.46 (1H, dq, J = 13.7, 7.0), 6.98 (1H, d, J = 7.7), 7.09 (1H, td, J = 7.5, 1.0), 7.13 (2H, d, J = 8.0), 7.17 (1H, dd, J = 6.9, 0.3), 7.25 (1H, td, J = 8.0, 1.6), 7.27 (2H, d, J = 8.4), 9.06 (1H, *br* s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.1 (CH_3), 21.1 (CH_3), 30.5 (CH_2), 57.7 (C), 110.2 (CH), 122.6 (CH), 125.0 (CH), 127.0 (2 CH), 128.1 (CH), 129.4 (2 CH), 133.1 (C), 137.1 (C), 137.3 (C), 141.5 (C), 181.7 (C); MS (CI) *m/z* 252 ($[M + H]^+$, 100), 222 ($[M - C_2H_5]^+$, 14), 160 ($[M - C_6H_4$-$Me]^+$, 23); HRMS (CI) [M + H] $C_{17}H_{18}NO$ requires 252.1388, found 252.1383 (–2.1 ppm). HPLC analysis: 86% ee (Daicel Chiralcel OD-H column, eluent: hexane/^{i}PrOH 90:10, flow: 1 mL/min, wavelength: 254 nm, retention times: 8.2 min (major) and 33.8 min (minor)). $[\alpha]_D^{20}$ –101.4 (*c* 1.16, $CHCl_3$, 86% ee).



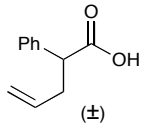
Peak Name	R. Time	Area	Area %
1	8.41	26032480	50.07
2	33.55	25960696	49.93



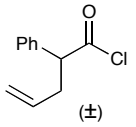
Peak Name	R. Time	Area	Area %
1	8.20	49338320	92.87
2	33.82	3789159	7.13

4. Application to a natural product analogue

4.1. Preparation of acid chloride 25

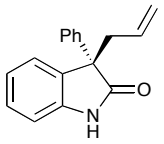


(±)-2-phenylpent-4-enoic acid. A solution of *n*-butyllithium (2.5 M in hexanes, 32.3 mL, 80.8 mmol, 2.2 equiv) was added dropwise to a solution of phenylacetic acid (5.00 g, 36.72 mmol, 1.0 equiv) in THF (150 mL) at –78°C under nitrogen atmosphere and the reaction mixture was allowed to warm to room temperature and stirred for 45 minutes. Neat allylbromide (12.7 mL, 146.9 mmol, 4.0 equiv) was added and the resulting solution was stirred at room temperature for 16 hours. The reaction mixture was quenched with aqueous 1M HCl solution and extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound (6.30 g, 97% yield) as a yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (1H, dddt, J = 14.4, 7.1, 6.8, 1.2), 2.77 (1H, dddt, J = 14.4, 8.4, 6.8, 1.2), 3.59 (1H, dd, J = 8.4, 7.1), 4.95 (1H, ddt, J = 10.2, 1.6, 0.9), 5.02 (1H, dq, J = 17.1, 1.6), 5.66 (1H, ddt, J = 17.1, 10.2, 6.8), 7.17-7.28 (5H, m).



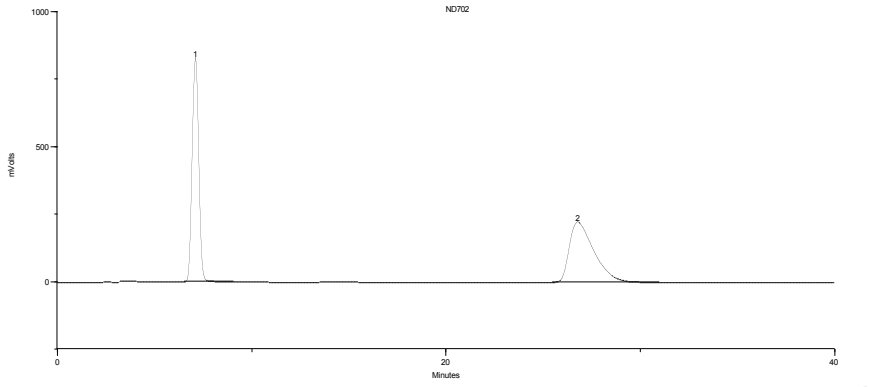
(±)-2-phenylpent-4-enoyl chloride 25. Thionyl chloride ($SOCl_2$, 13.0 mL, 178.8 mmol, 5.0 equiv) was added to a solution of (±)-2-phenylpent-4-enoic acid (6.30 g, 35.7 mmol, 1.0 equiv) in toluene (40 mL) at room temperature and the reaction mixture was heated overnight (16 hours) at 80°C. Toluene and excess $SOCl_2$ were removed under reduced pressure, then, traces of $SOCl_2$ were azeotropically removed with toluene (3 times). The residue was purified by Kugelrohr distillation (135°C / 2 mmHg) to give the title compound (5.78 g, 83% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52-2.64 (1H, m), 2.86-2.98 (1H, m), 4.07 (1H, t, J = 7.6), 5.08 (1H, *app* dt, J = 10.2, 1.3), 5.13 (1H, ddt, J = 17.1, 2.3, 1.1), 5.71 (1H, ddt, J = 17.1, 10.2, 6.7), 7.27-7.32 (2H, m), 7.32-7.43 (3H, m).

4.2. Preparation of oxindole 27 and determination of absolute configuration

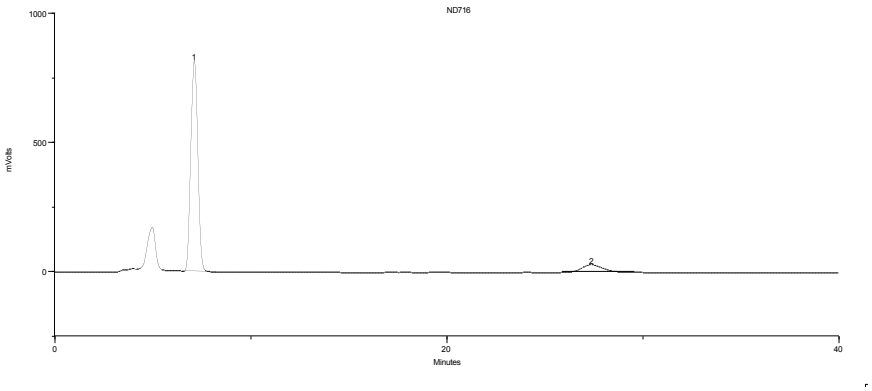


(*S*)-3-allyl-3-phenylindolin-2-one 27. Triethylamine (0.75 mL, 5.34 mmol, 2.0 equiv) was added dropwise over 2 hours to a solution of (±)-2-phenylpent-4-enoyl chloride **25** (1.04 g, 5.34 mmol, 2.0 equiv) in Et_2O (35 mL) at 0°C under nitrogen atmosphere and the reaction mixture was stirred for 2 hours at 0°C. After warming to room temperature, Et_3N salts were removed by filtration under nitrogen to yield a yellow solution of crude allylphenylketene **26** (^{1}H NMR analysis of the filtrate revealed about 50% purity). The etheral solution of the crude ketene was added dropwise to a solution of chiral nitrone **16** (0.86 g, 2.67 mmol, 1.0 equiv) in THF (35 mL) at –78°C under nitrogen atmosphere and the reaction mixture was stirred for 3 hours at –78°C. Saturated aqueous NH_4Cl (3 mL) was added at –78°C and the mixture was allowed to warm to room temperature, then, extracted with Et_2O (3 * 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc / Petroleum ether 5:95 to 30:70) to give the desired product **(*S*)-27** (0.62 g, 93% yield) as a white solid (mp = 110-111°C). IR (KBr disc) ν 3193 (NH), 3087, 3055, 3022, 2929, 2816, 2364, 2346, 1706 (C=O), 1613, 1498, 1467, 1445, 1434,

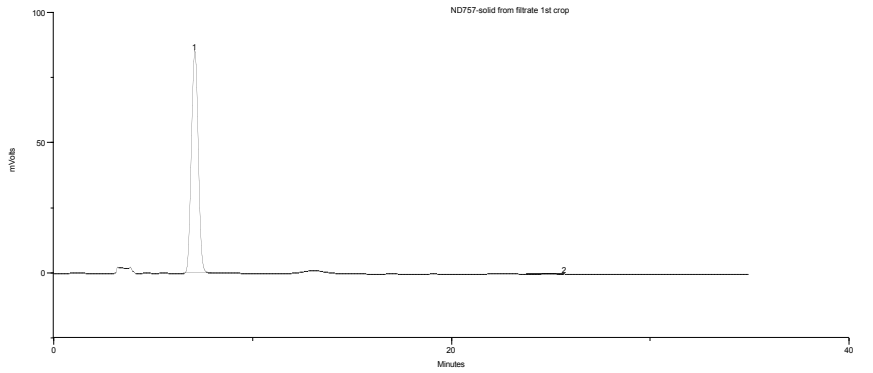
1407, 1322, 1223; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.93-3.02 (2H, m), 4.84 (1H, dd, J = 10.0, 1.2), 4.97 (1H, dd, J = 17.0, 1.4), 5.37 (1H, ddt, J = 17.1, 10.0, 7.1), 6.85 (1H, d, J = 7.7), 6.97 (1H, dt, J = 7.2, 0.8), 7.07-7.18 (3H, m), 7.22 (2H, t, J = 7.4), 7.29-7.31 (2H, m), 9.30 (1H, *br* s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.7 (CH_2), 57.2 (C), 110.4 (CH), 119.4 (CH_2), 122.5 (CH), 125.3 (CH), 127.1 (2 CH), 127.5 (CH), 128.3 (CH), 128.7 (2 CH), 132.3 (CH), 132.6 (C), 139.5 (C), 141.3 (C), 181.1 (C); MS (CI) *m/z* 250 ($[M + H]^+$, 100), 208 ($[M – allyl]^+$, 40); HRMS (CI) [M + H] $C_{17}H_{16}NO$ requires 250.1232, found 250.1230 (–0.8 ppm). HPLC analysis: 80% ee (Daicel Chiralcel OD-H column, eluent: hexane/^{i}PrOH 90:10, flow: 1 mL/min, wavelength: 254 nm, retention times: 7.1 min (major) and 27.4 min (minor)). The product was recrystallized from Et_2O / hexane to give a white solid of 99.2% ee (Same conditions as above, retention times: 7.1 min (major) and 24.9 min (minor)). $[\alpha]_D^{20}$ –148.4 (*c* 0.28, $CHCl_3$, >99% ee).



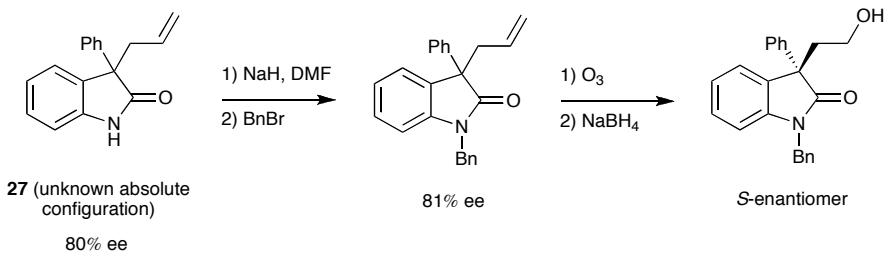
Peak Name	R. Time	Area	Area %
1	7.11	32977542	50.11
2	26.77	32833458	49.89



Peak Name	R. Time	Area	Area %
1	7.12	34261136	90.01
2	27.36	3801382	9.99



Peak Name	R. Time	Area	Area %
1	7.10	3434986	99.58
2	24.93	14335	0.42



27 (unknown absolute configuration)

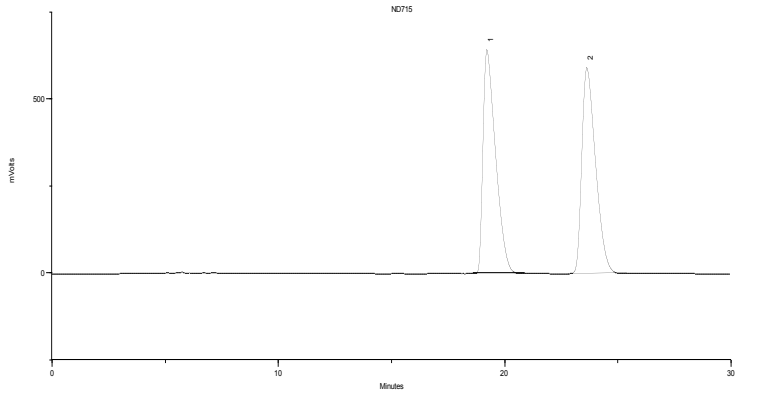
80% ee

81% ee

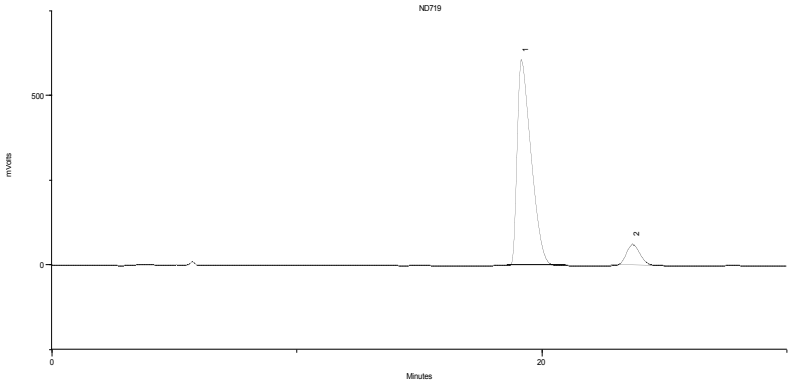
S-enantiomer

(*S*)-1-benzyl-3-(2-hydroxyethyl)-3-phenylindolin-2-one. A solution of unknown absolute configuration 3-allyl-3-phenylindolin-2-one **27** (84.2 mg, 0.34 mmol, 1.0 equiv, 80% ee) in dry DMF (5 mL) was added to a suspension of NaH (60% dispersion in oil, 16.2 mg, 0.41 mmol, 1.2 equiv) in dry DMF (5 mL) at 0°C under nitrogen atmosphere and the reaction mixture was stirred for 30 minutes at 0°C. Benzyl bromide (0.05 mL, 0.41 mmol, 1.2 equiv) was added at 0°C and the reaction mixture was allowed to warm to room temperature. Water was gradually added and the mixture was extracted with Et_2O (3 * 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc / Petroleum ether 5:95 to 10:90) to give 3-allyl-1-benzyl-3-phenylindolin-2-one (104.3 mg, 91% yield) as a white solid (mp = 81-82°C). IR (KBr disc) ν 3085, 3068, 3035, 3007, 2934, 2909, 2851, 2366, 2346, 1703 (C=O), 1608, 1490, 1471, 1433, 1369, 1350, 1192, 1172, 1109, 1082, 991, 925; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.10 (2H, dq, J = 13.5, 7.2), 4.83 (1H, d, J = 15.7), 4.91-4.96 (1H, m), 4.96 (1H, d, J = 15.6), 5.08 (1H, d, J = 17.0), 5.36-5.47 (1H, m), 6.75 (1H, dd, J = 7.8, 0.4), 7.04-7.08 (1H, m), 7.17-7.21 (1H, m), 7.22-7.33 (9H, m), 7.37-7.40 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.1 (CH_2), 44.1 (CH_2), 56.5 (C), 109.4 (CH), 119.5 (CH_2), 122.6 (CH), 125.3

(CH), 127.1 (2 CH), 127.4 (2 CH), 127.5 (CH), 127.7 (CH), 128.2 (CH), 128.7 (2 CH), 128.8 (2 CH), 131.9 (C), 132.6 (CH), 136.0 (C), 139.8 (C), 143.1 (C), 178.2 (C); MS (CI) *m/z* 340 ($[M + H]^+$, 100), 298 ($[M – allyl]^+$, 12); HRMS (CI) [M + H] $C_{24}H_{22}NO$ requires 340.1701, found 340.1699 (–0.7 ppm); HPLC analysis: 81% ee (Daicel Chiralpak AD-H column, eluent: hexane/^{i}PrOH 90:10, flow: 1 mL/min, wavelength: 254 nm, retention times: 19.2 min (major) and 23.7 min (minor)). $[\alpha]_D^{20}$ –78.4 (*c* 2.00, $CHCl_3$, 81% ee).



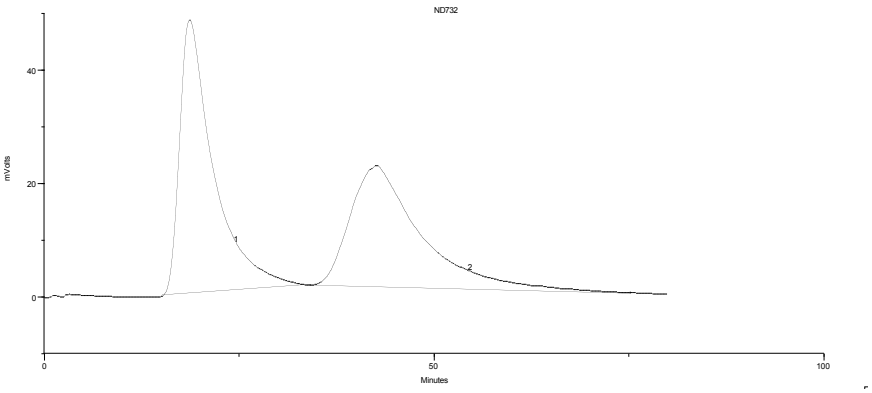
Peak Name	R. Time	Area	Area %
1	19.22	41524632	49.83
2	23.63	41806356	50.17



Peak Name	R. Time	Area	Area %
1	19.17	39930088	90.61
2	23.70	4135598	9.39

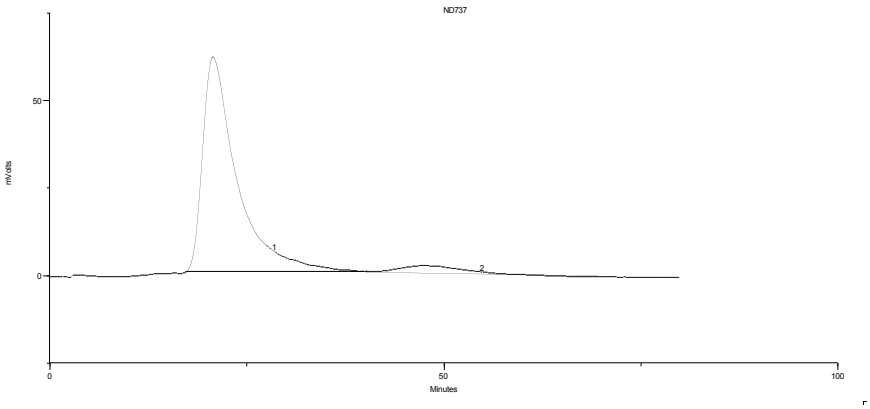
A solution of unknown absolute configuration 3-allyl-1-benzyl-3-phenylindolin-2-one (98.3 mg, 0.29 mmol, 1.0 equiv, 81% ee) in CH_2Cl_2 (30 mL) at –78°C was purged with oxygen for about 3 minutes, then ozone was bubbled in the solution until the solution turns blue. The reaction mixture was purged with oxygen until complete discoloration (about 5-6 minutes) then Me_2S (0.04 mL, 0.58 mmol, 2.0 equiv) was added at –78°C. The

reaction mixture was allowed to warm to room temperature before concentration under reduced pressure. The crude aldehyde was dissolved in EtOH (6 mL) and $NaBH_4$ (109.6 mg, 2.90 mmol, 10 equiv) was added at room temperature. After stirring for 1 hour at room temperature, the reaction was quenched with 0.5M aqueous NaOH (30 mL) and extracted with EtOAc (3 * 20 mL). The organic layers were combined, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc / Petroleum ether 40:60 to 50:50) to give (*S*)-1-benzyl-3-(2-hydroxyethyl)-3-phenylindolin-2-one (60.4 mg, 61% yield over 2 steps) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (1H, dt, J = 13.9, 6.0), 2.86 (1H, dt, J = 13.9, 6.9), 3.51-3.63 (2H, m), 4.95 (2H, s), 6.80 (1H, d, J = 7.7), 7.09 (1H, t, J = 7.5), 7.22 (1H, dt, J = 7.7, 1.1), 7.25-7.35 (9H, m), 7.38-7.41 (2H, m). $[\alpha]_D^{20}$ –44.9 (*c* 2.48, $CHCl_3$), lit.[6] $[\alpha]_D^{23}$ –40.58 (*c* 0.36, $CHCl_3$, 84% ee). HPLC analysis: Daicel Chiralcel OJ column, eluent: hexane/^{i}PrOH 90:10, flow: 1 mL/min, wavelength: 254 nm, retention times: 20.7 min (major) and 47.5 min (minor). The absolute (*S*)-configuration was assigned by comparison of the HPLC retention times with that of the literature reported by Overman and co-workers:[7] Daicel Chiracel OJ column, eluent: hexane/^{i}PrOH 70:30, flow: 1 mL/min, wavelength: 254 nm, retention times: 12.2 min (*S*-enantiomer, major) and 24.2 min (*R*-enantiomer, minor). Overman *et al.* assigned the absolute (*S*)-configuration by chemical derivatization to (*S*)-5,7-dibromo-3-(2-hydroxyethyl)-3-phenylindolin-2-one and subsequent X-ray crystallographic analysis.



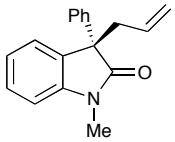
Peak Name	R. Time	Area	Area %
1	18.61	24445704	51.64
2	42.63	22892964	48.36

[6] He, R.; Ding, C.; Maruoka, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 4559-4561.
[7] Dounay, A. B.; Hatanaka, K.; Kodanko, J.; Oestreich, M.; Overman, L.; Pfeifer, L. A.; Weiss, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 6261-6271.



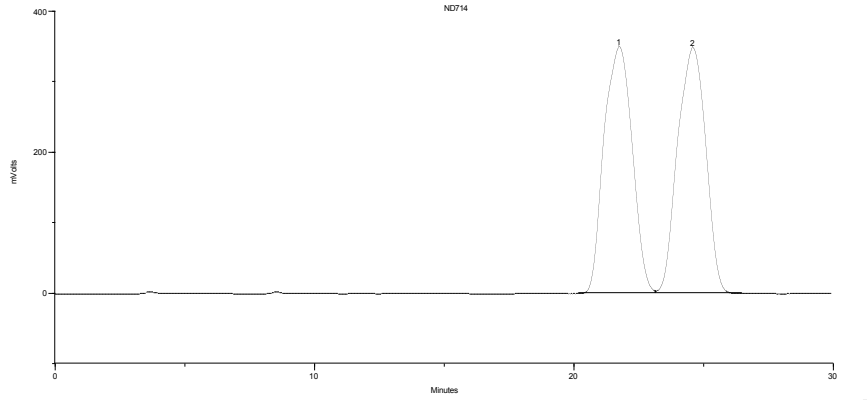
Peak Name	R. Time	Area	Area %
1	20.69	31233726	92.49
2	47.45	2534396	7.51

4.3. Synthesis of hexahydropyrroloindole 29

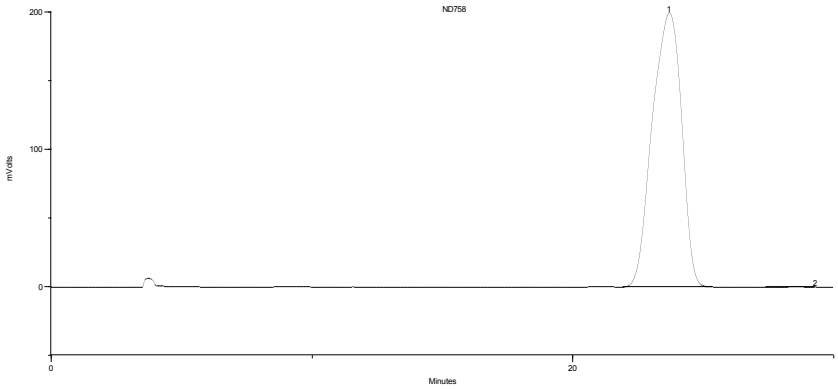


(*S*)-3-allyl-1-methyl-3-phenylindolin-2-one 28. A solution of (*S*)-3-allyl-3-phenylindolin-2-one **(*S*)-27** (61.2 mg, 0.246 mmol, 1.0 equiv, >99% ee) in dry DMF (4 mL) was added to a suspension of NaH (60% dispersion in oil, 11.8 mg, 0.295 mmol, 1.2 equiv) in dry DMF (4 mL) at 0°C under nitrogen atmosphere and the reaction mixture was stirred for 30 minutes at 0°C. MeI (0.02 mL, 0.295 mmol, 1.2 equiv) was added at 0°C and the reaction mixture was allowed to warm to room temperature. Water was gradually added and the mixture was extracted with Et_2O (3 * 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc / Petroleum ether 10:90 to 20:80) to give the title product **(*S*)-28** (59.8 mg, 93% yield) as a colorless cloudy oil. IR (NaCl) ν 3057, 3035, 2979, 2936, 1715 (C=O), 1641, 1612, 1494, 1471, 1447, 1373, 1348, 1254, 1080, 922; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.96 (2H, d, J = 7.1), 3.13 (3H, s), 4.84 (1H, d, J = 10.2), 4.95 (1H, d, J = 17.0), 5.32 (1H, ddt, J = 17.1, 10.0, 7.2), 6.82 (1H, d, J = 7.8), 7.04 (1H, t, J = 7.5), 7.16-7.26 (5H, m), 7.31 (2H, d, J = 8.1); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5 (CH_3), 42.1 (CH_2), 56.5 (C), 108.3 (CH), 119.3 (CH_2), 122.6 (CH), 125.3 (CH), 127.2 (2 CH), 127.5 (CH), 128.3 (CH), 128.7 (2 CH), 131.8 (C), 132.5 (CH), 139.6 (C), 144.0 (C), 178.1 (C); MS (CI) *m/z* 264 ($[M + H]^+$,

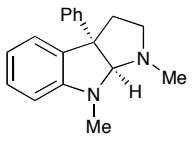
100), 222 ([M – allyl]$^+$, 35), 186 ([M – C_6H_5]$^+$, 3); HRMS (CI) [M + H] $C_{18}H_{18}NO$ requires 264.1388, found 264.1391 (+1.0 ppm). HPLC analysis: >99% ee (Daicel Chiralpak AD-H column, eluent: hexane/^{i}PrOH 99:1, flow: 1 mL/min, wavelength: 254 nm, retention times: 23.7 min (major) and 28.6 min (minor)). $[\alpha]_D^{20}$ –160.7 (*c* 0.30, $CHCl_3$, >99% ee).



Peak Name	R. Time	Area	Area %
1	21.75	44409216	50.19
2	24.59	44074456	49.81



Peak Name	R. Time	Area	Area %
1	23.70	25985810	99.92
2	28.62	21064	0.08

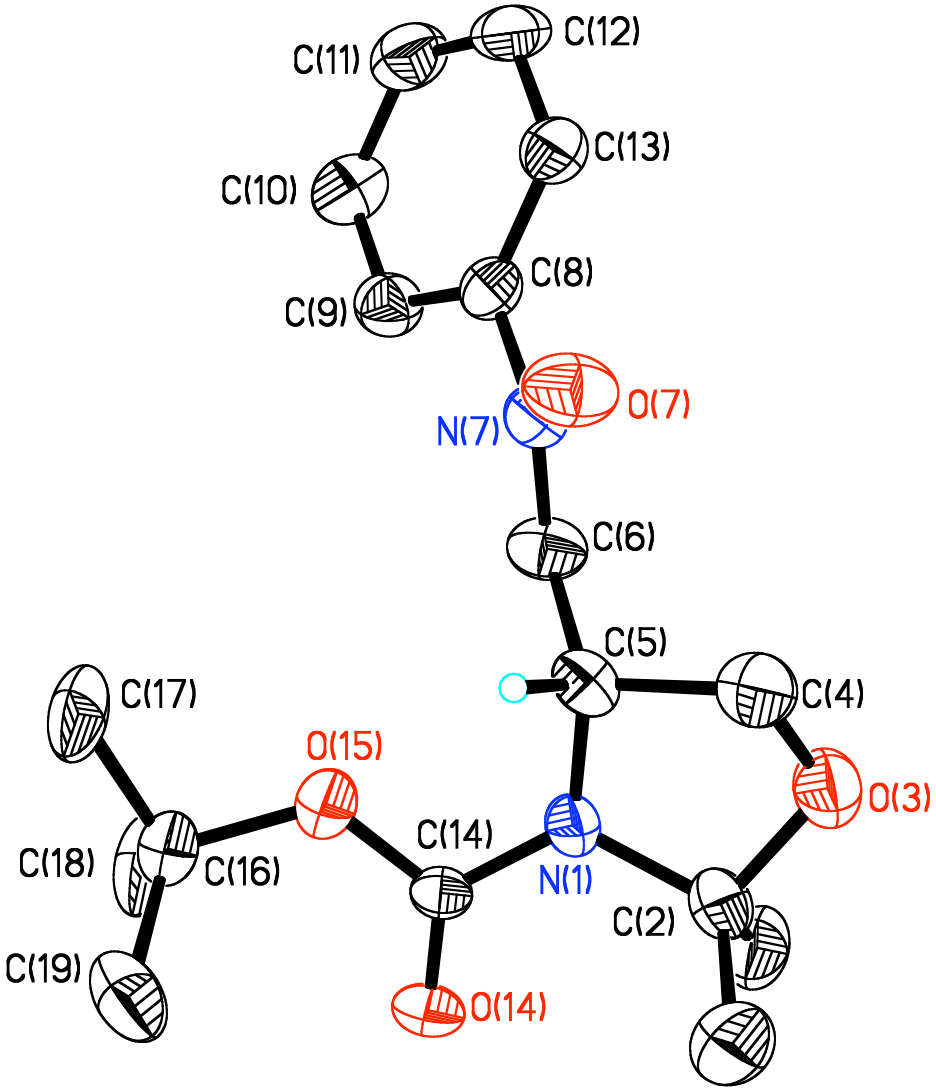


(3a*S*,8a*S*)-1,8-dimethyl-3a-phenyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indole 29.[6] A solution of (*S*)-3-allyl-1-methyl-3-phenylindolin-2-one **(*S*)-28** (55.0 mg, 0.209 mmol,

1.0 equiv, >99% ee) in CH_2Cl_2 (21 mL) at –78°C was purged with oxygen for about 5 minutes, then ozone was bubbled in the solution until the solution turns blue. The reaction mixture was purged with oxygen until complete discoloration (about 10 minutes) then Me_2S (0.03 mL, 0.418 mmol, 2.0 equiv) was added at –78°C. The reaction mixture was allowed to warm to room temperature before concentration under reduced pressure. The crude aldehyde was dissolved in THF (10 mL) and $MgSO_4$ (50.3 mg, 0.418 mmol) was added. After stirring for 5 minutes at room temperature, a solution of methylamine (2M in THF, 1.04 mL, 2.09 mmol, 10 equiv) was added dropwise and the reaction mixture was stirred overnight (16 hours) at room temperature. $MgSO_4$ was removed by filtration under nitrogen and the excess of methylamine was removed under reduced pressure. A solution of $LiAlH_4$ (2M in THF, 0.21 mL, 0.418 mmol, 2.0 equiv) was added dropwise to the resulting solution of imine under nitrogen atmosphere at room temperature and the reaction mixture was heated at reflux for 2 hours. After cooling to room temperature, excess $LiAlH_4$ was decomposed by careful addition of EtOAc (12 mL). Saturated aqueous $NaHCO_3$ (15 mL) was added and the phases were separated. The aqueous layer was extracted with EtOAc (2 * 15 mL) and the combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc / Petroleum ether / Et_3N 50:50:1) to give the title compound **(3a*S*,8a*S*)-29** (34.7 mg, 63% yield over 3 steps) as a colorless oil. IR (NaCl) ν 3447, 3055, 3025, 2962, 2793, 1684, 1603, 1493, 1445, 1427, 1381, 1345, 1300, 1255, 1153, 1122, 1039, 1022, 960, 919, 740, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (1H, dt, J = 10.2, 3.4), 2.55 (3H, s), 2.74 (2H, dt, J = 7.1, 4.5), 2.90 (1H, dq, J = 8.3, 2.6), 3.00 (3H, s), 4.52 (1H, s), 6.49 (1H, d, J = 7.9), 6.67 (1H, tt, J = 7.4, 1.7), 6.92 (1H, dd, J = 7.3, 0.8), 7.12 (1H, dt, J = 7.7, 1.2), 7.17-7.22 (1H, m), 7.29-7.30 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.0 (CH_3), 38.6 (CH_3), 39.9 (CH_2), 53.5 (CH_2), 61.5 (C), 98.3 (CH), 106.7 (CH), 117.8 (CH), 124.6 (CH), 126.3 (CH), 126.6 (2 CH), 128.1 (CH), 128.5 (2 CH), 135.2 (C), 146.9 (C), 152.3 (C); MS (CI) *m/z* 265 ([M + H]$^+$, 100), 264 (M$^+$, 79); HRMS (CI) [M + H] $C_{18}H_{21}N_2$ requires 265.1705, found 265.1707 (+0.9 ppm). $[\alpha]_D^{20}$ +114.2 (*c* 1.06, $CHCl_3$, >99% ee[8]). Lit.[6] $[\alpha]_D^{23}$ +111.63 (*c* 0.62, $CHCl_3$, 90% ee) for (3a*S*,8a*S*)-enantiomer.

[8] The enantiopurity of **29** could not be assigned unambiguously by HPLC analysis, but was assigned as >99% ee on the assumption that no racemization had taken place in the conversion from **28**.

5. X-Ray crystal structure of chiral nitrone 16



X-Ray crystal structure of (*R*,*Z*)-**16**
(thermal ellipsoids drawn at the 50% probability level)

6. ^{1}H and ^{13}C NMR Spectra of new compounds


8.294
8.290
8.289
8.276
8.272
8.267
7.894
7.773
7.765
7.761
7.753
7.752
7.748
7.613
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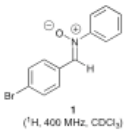
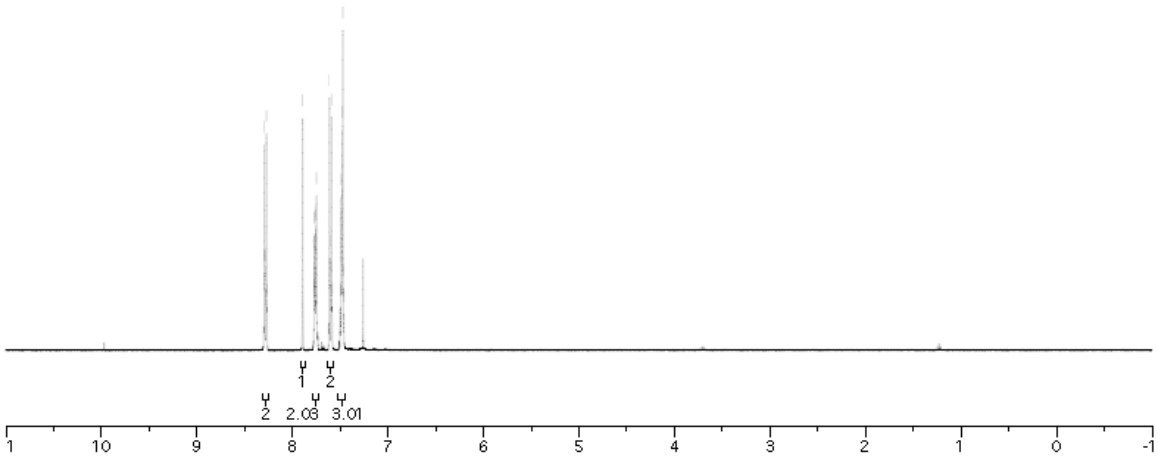
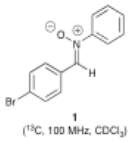
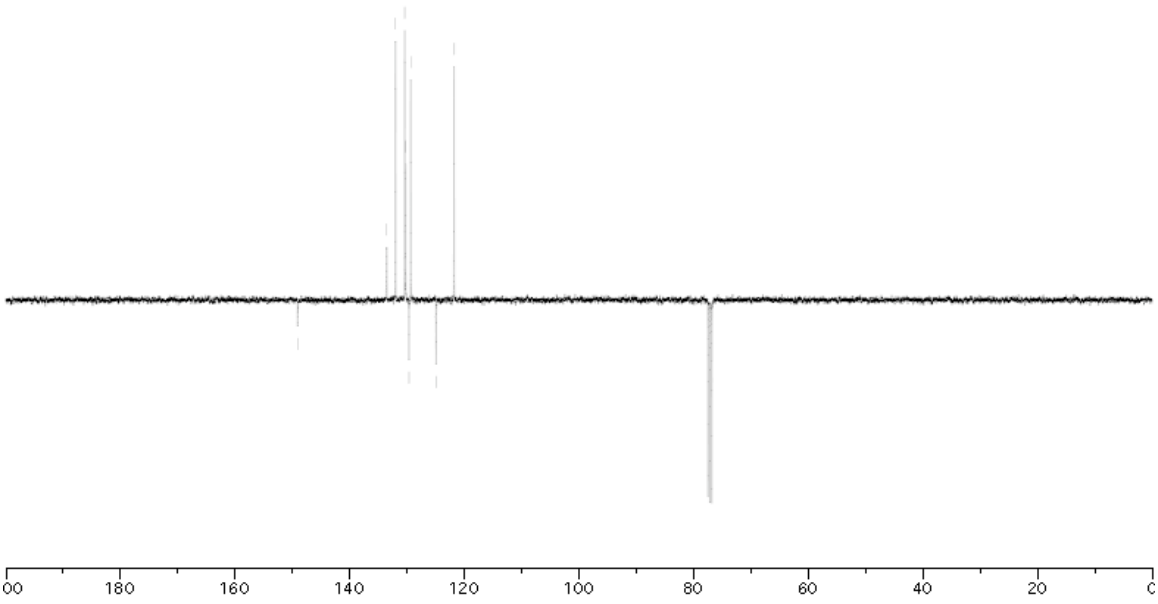
7.485
7.478
7.473
7.468
7.462

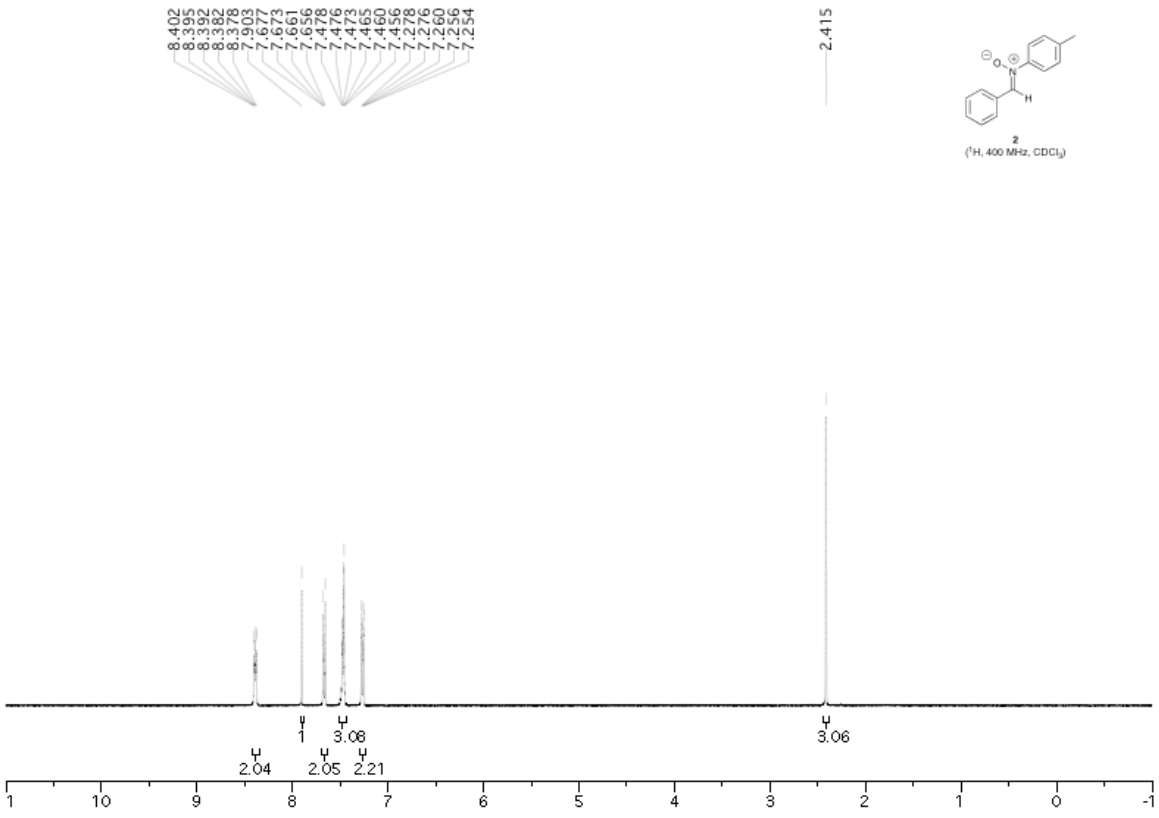

Br
H
1
(1H, 400 MHz, CDCl3)

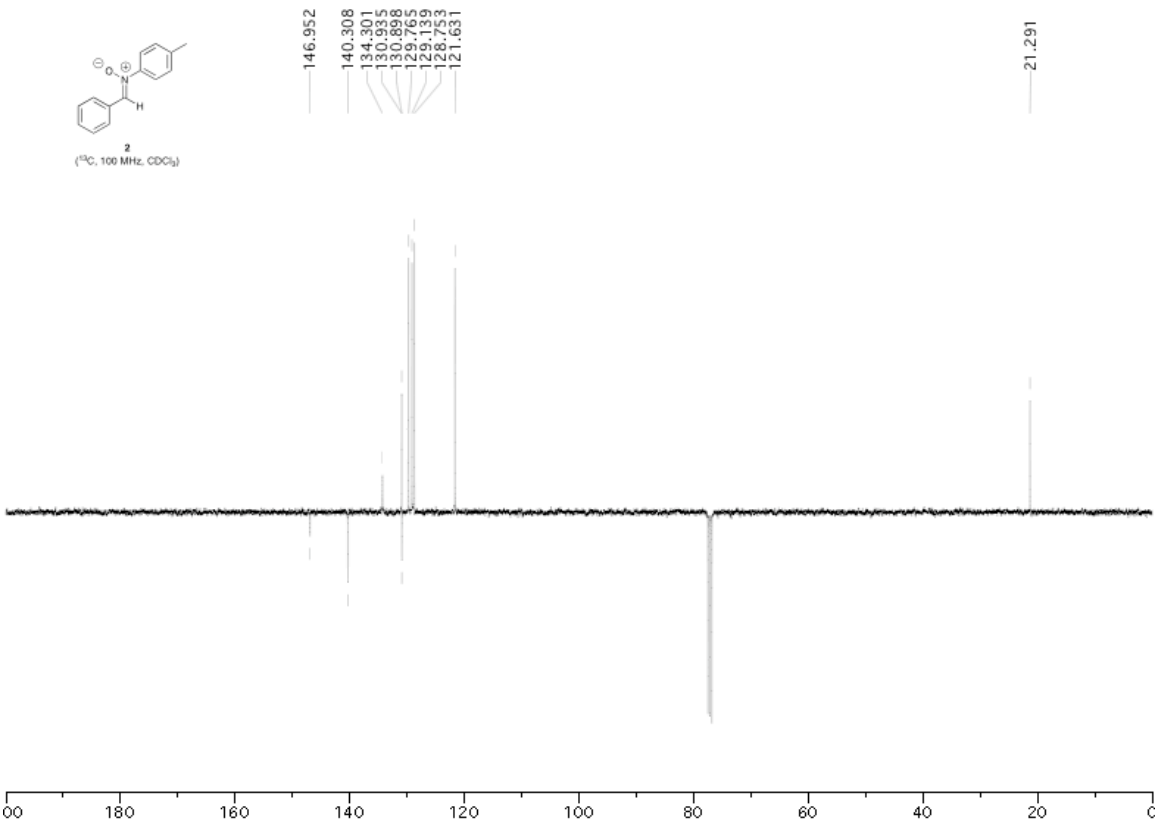

1
2
2.08
3.01
1
2
10
9
8
7
6
5
4
3
2
1
0
-1

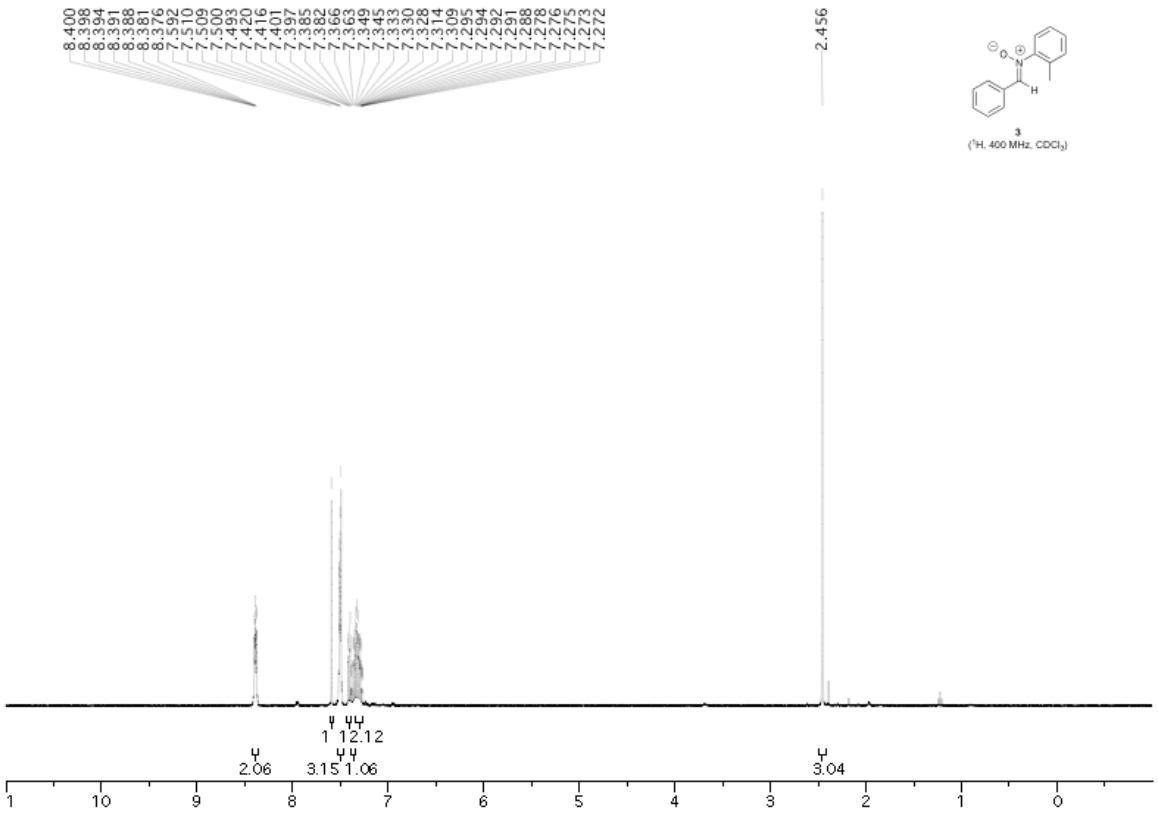

Br
H
1
(13C, 100 MHz, CDCl3)

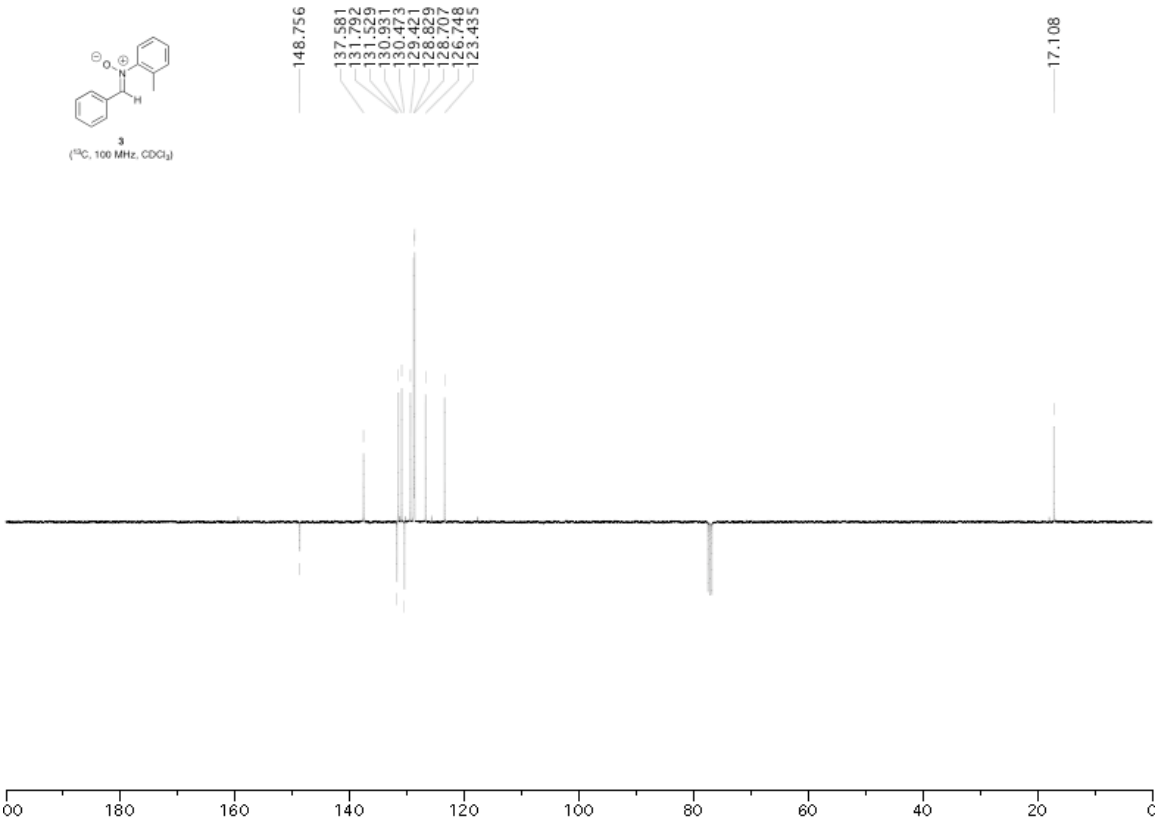
149.088
133.570
132.031
130.404
130.263
129.664
129.358
124.925
121.805

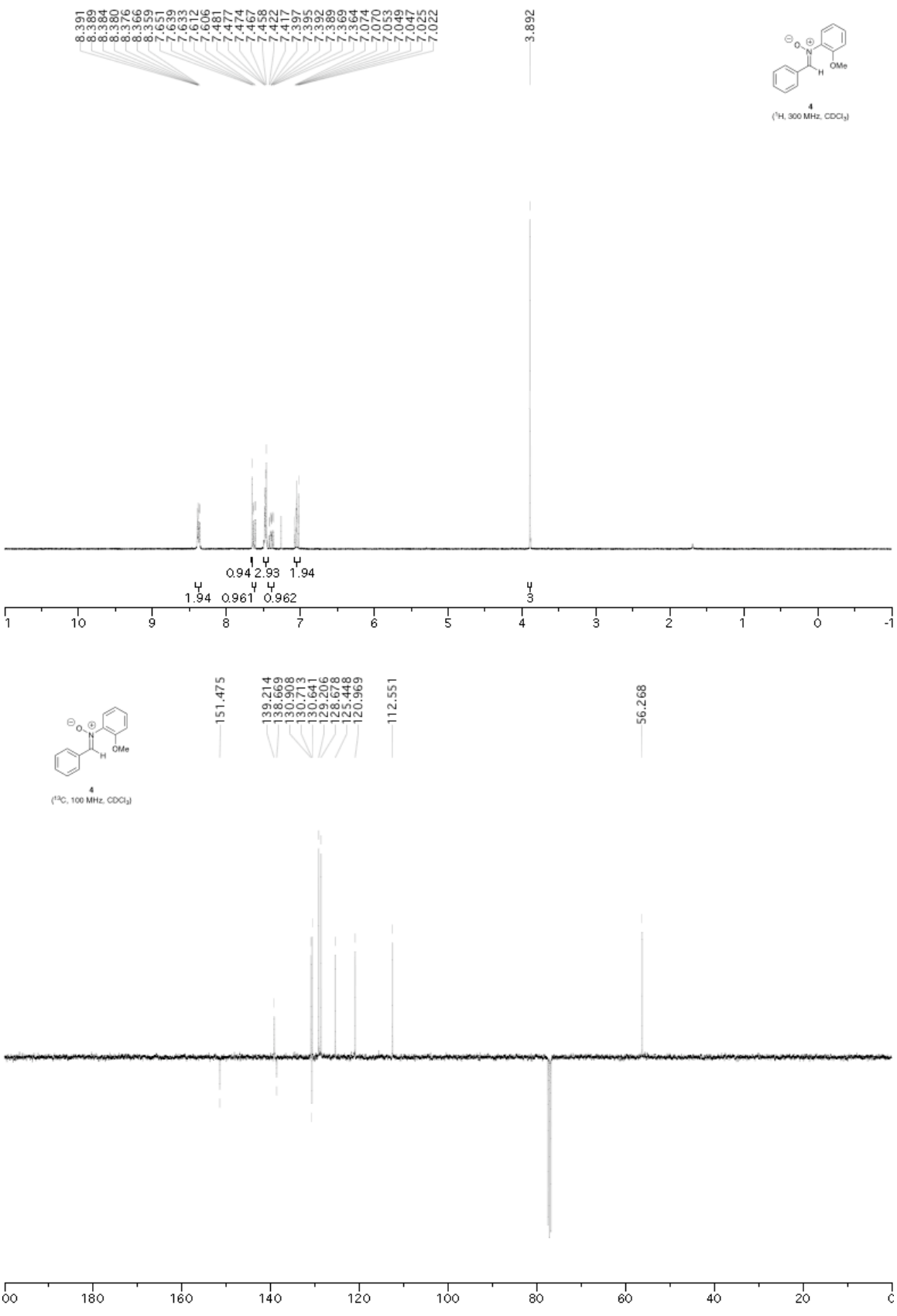

00
180
160
140
120
100
80
60
40
20
0

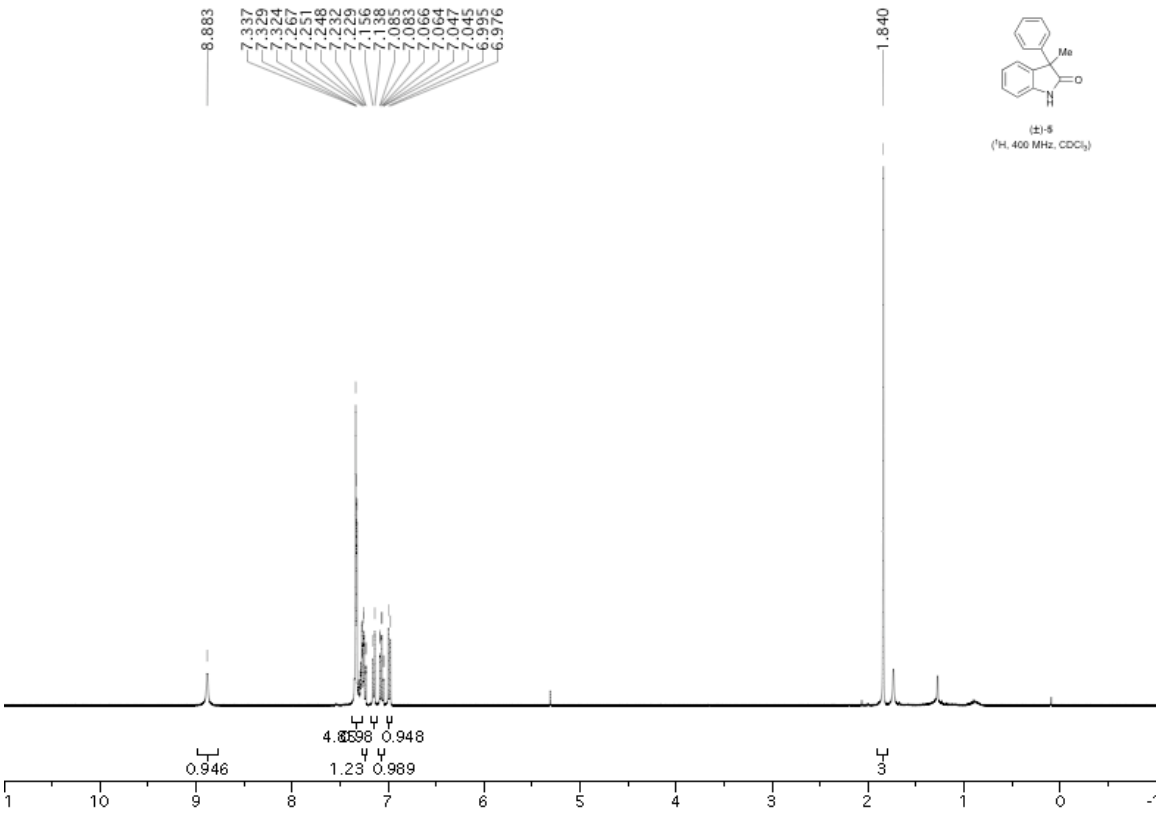

8.402
8.395
8.392
8.382
8.378
7.903
7.677
7.673
7.661
7.656
7.478
7.476
7.473
7.465
7.460
7.456
7.278
7.276
7.260
7.256
7.254
2.415
2
(1H, 400 MHz, CDCl3)
1
3.08
3.06
2.04
2.05
2.21

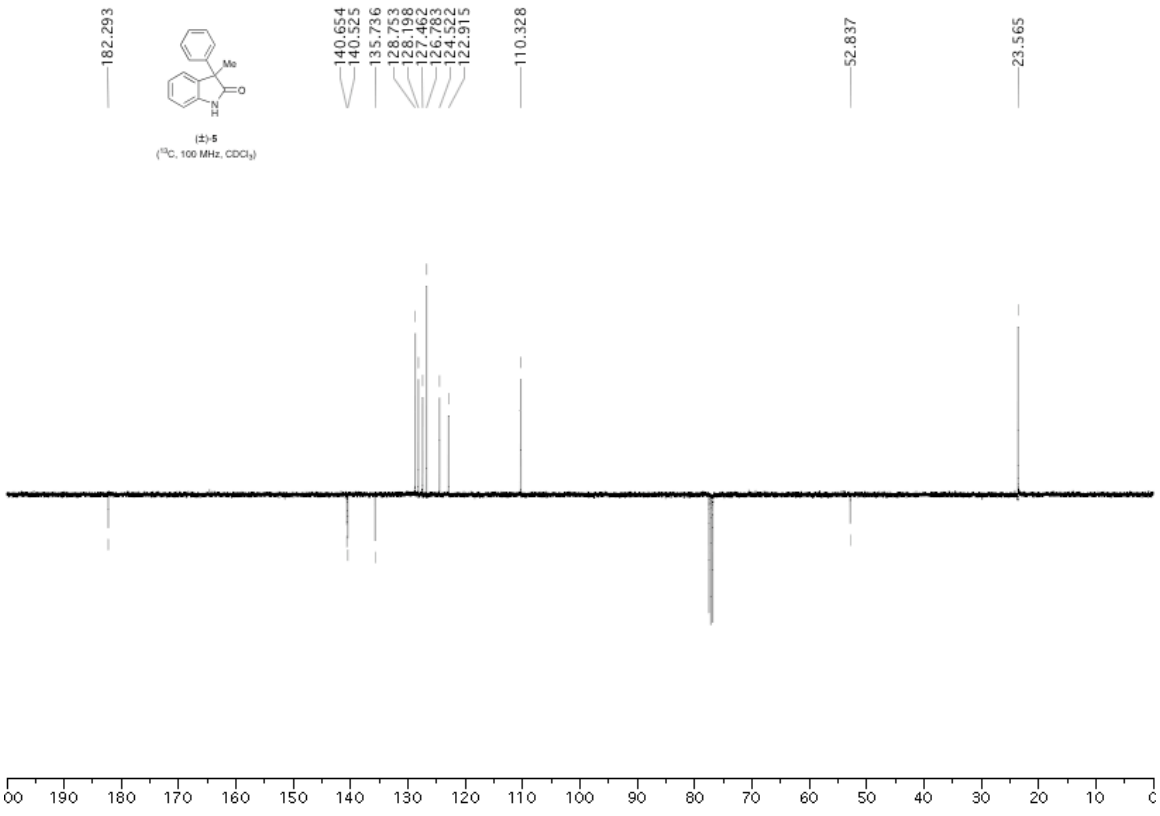

146.952
140.308
134.301
130.935
130.898
129.765
129.139
128.753
121.631
21.291
2
(13C, 100 MHz, CDCl3)

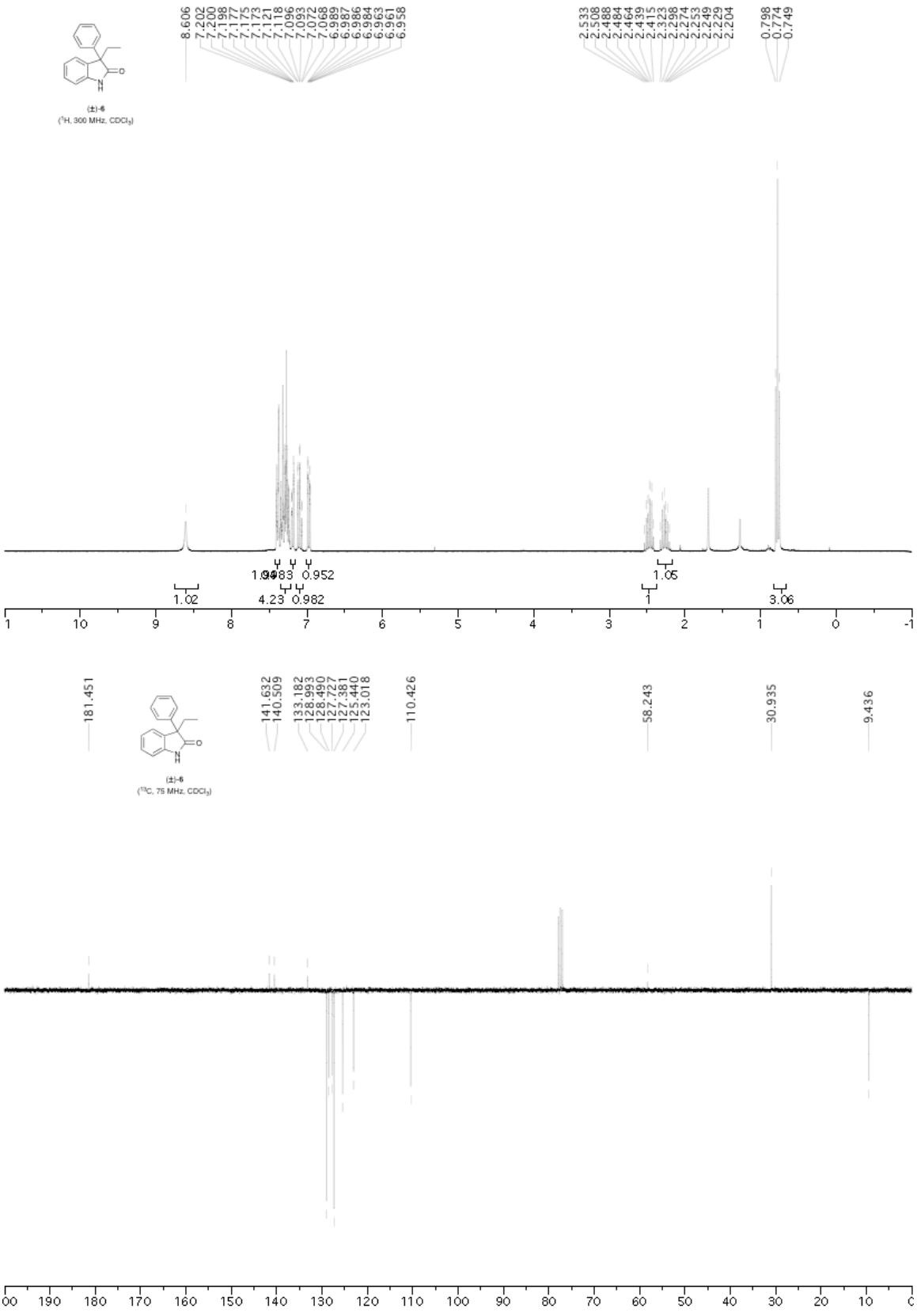

8.400
8.398
8.394
8.391
8.388
8.381
8.376
7.592
7.510
7.509
7.500
7.493
7.420
7.416
7.401
7.397
7.385
7.382
7.366
7.363
7.349
7.345
7.333
7.330
7.328
7.314
7.309
7.295
7.294
7.292
7.291
7.288
7.278
7.276
7.275
7.273
7.272
2.456
3
(1H, 400 MHz, CDCl3)
2.06
1
12.12
3.15
1.06
3.04

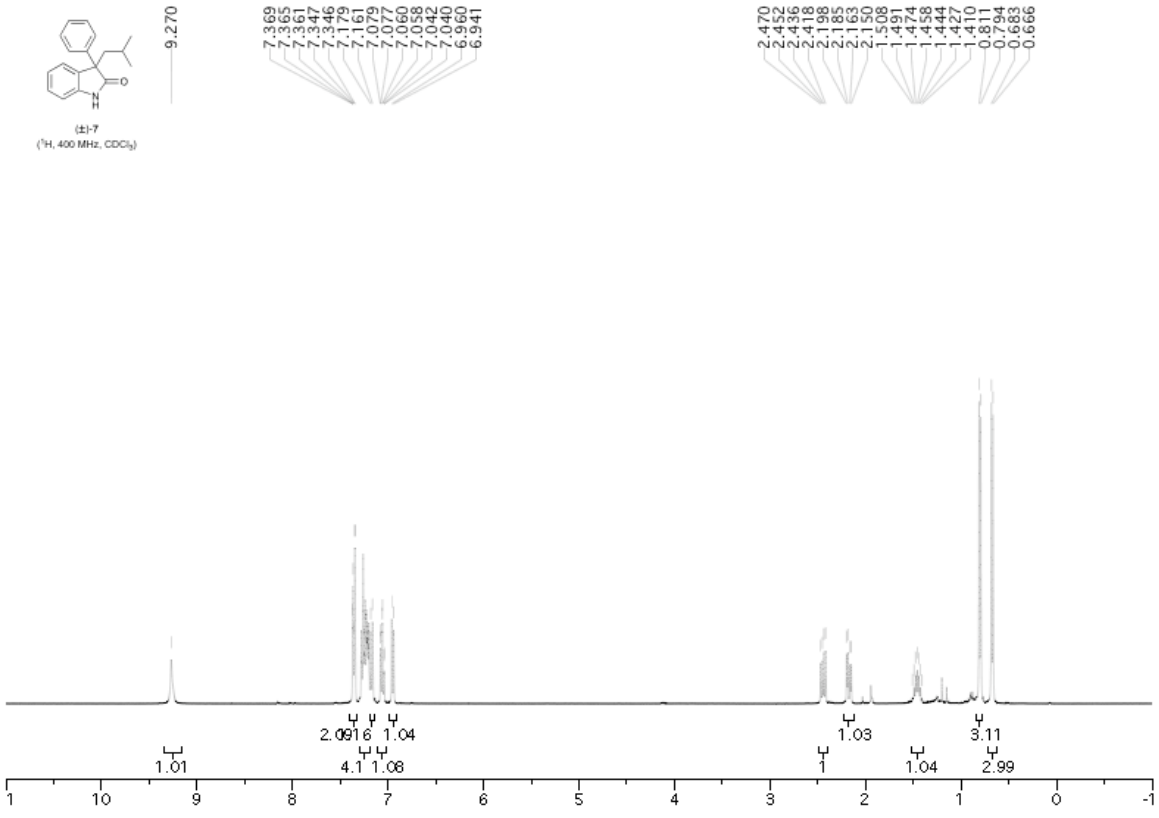

148.756
137.581
131.792
131.529
130.931
130.473
129.421
128.829
128.707
126.748
123.435
17.108
3
(13C, 100 MHz, CDCl3)

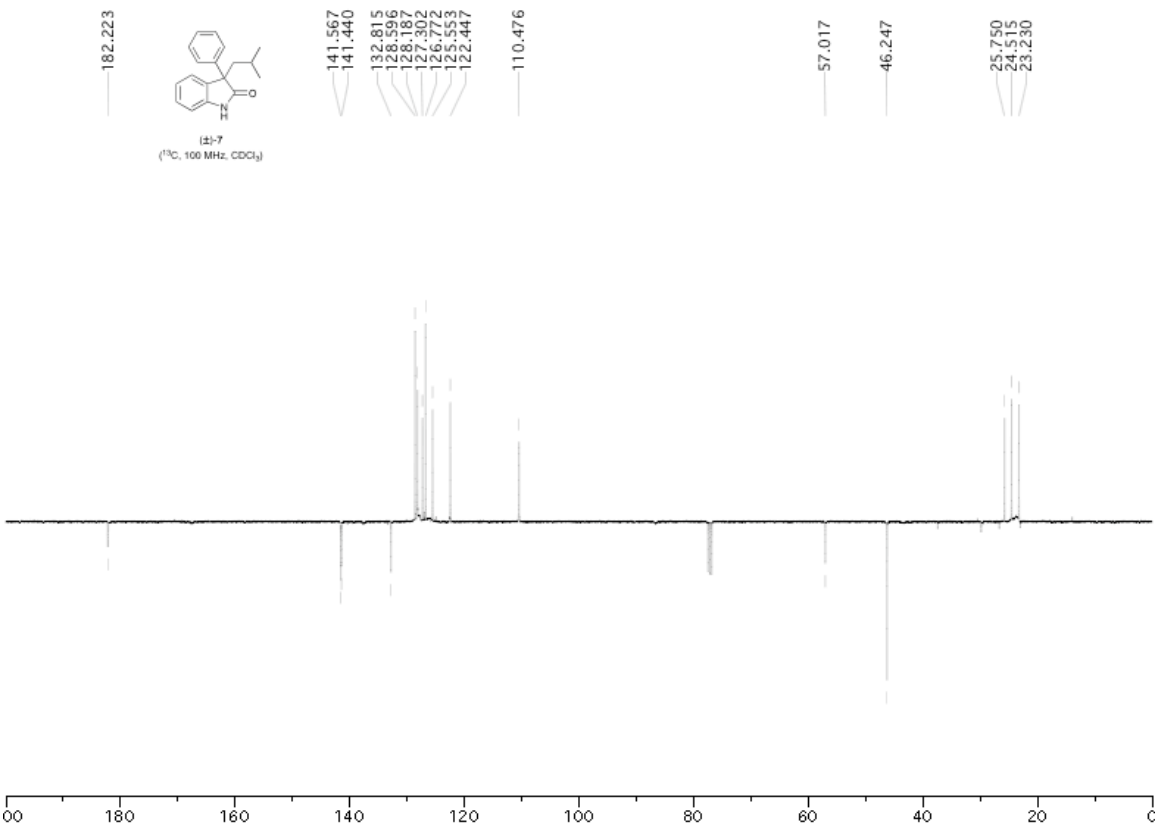

8.391
8.389
8.384
8.380
8.376
8.366
8.359
7.651
7.639
7.633
7.612
7.606
7.481
7.477
7.474
7.467
7.458
7.422
7.417
7.397
7.395
7.392
7.389
7.369
7.364
7.074
7.070
7.053
7.049
7.047
7.025
7.022
3.892
OMe
4
(1H, 300 MHz, CDCl3)
0.94 2.93 1.94
1.94 0.961 0.962
3
151.475
139.214
138.669
130.908
130.713
130.641
129.206
128.678
125.448
120.969
112.551
56.268
4
(13C, 100 MHz, CDCl3)

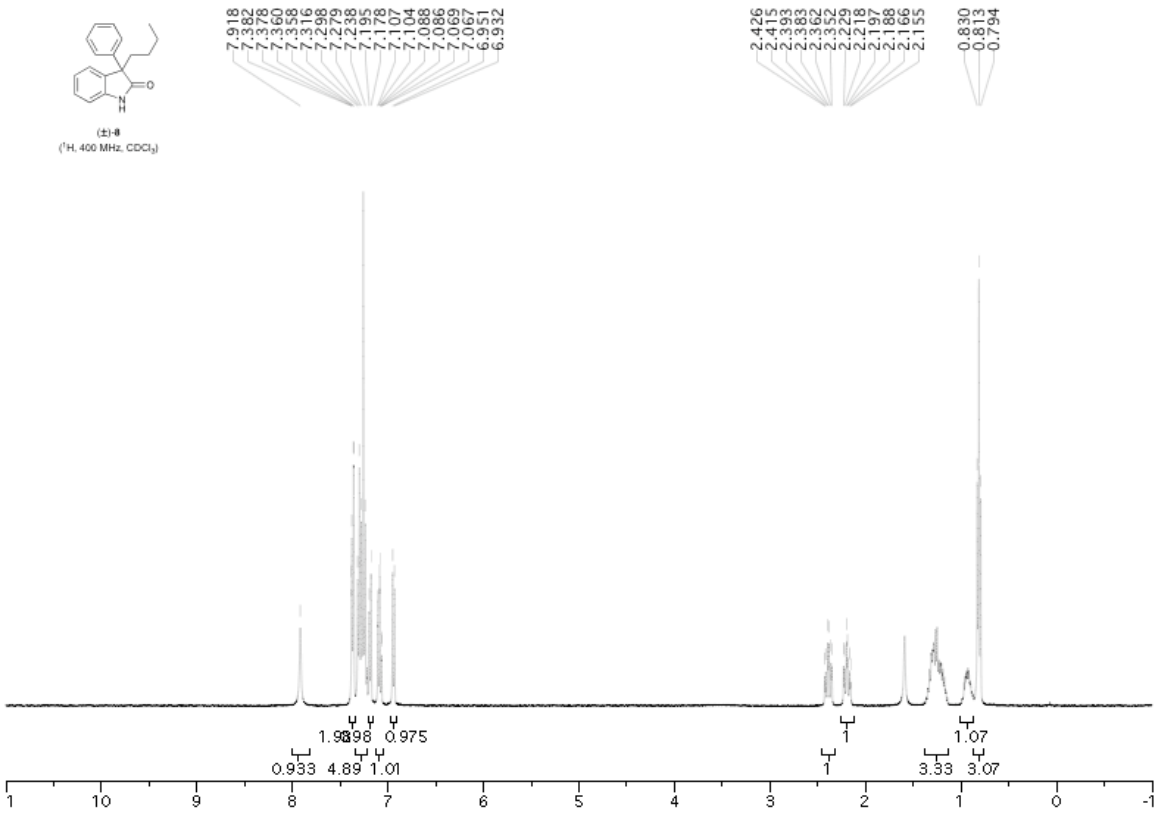

8.883
7.337
7.329
7.324
7.267
7.251
7.248
7.232
7.229
7.156
7.138
7.085
7.083
7.066
7.064
7.047
7.045
6.995
6.976
1.840
Me
O
N
H
(±)-5
(1H, 400 MHz, CDCl3)
0.946
1.23
0.989
3

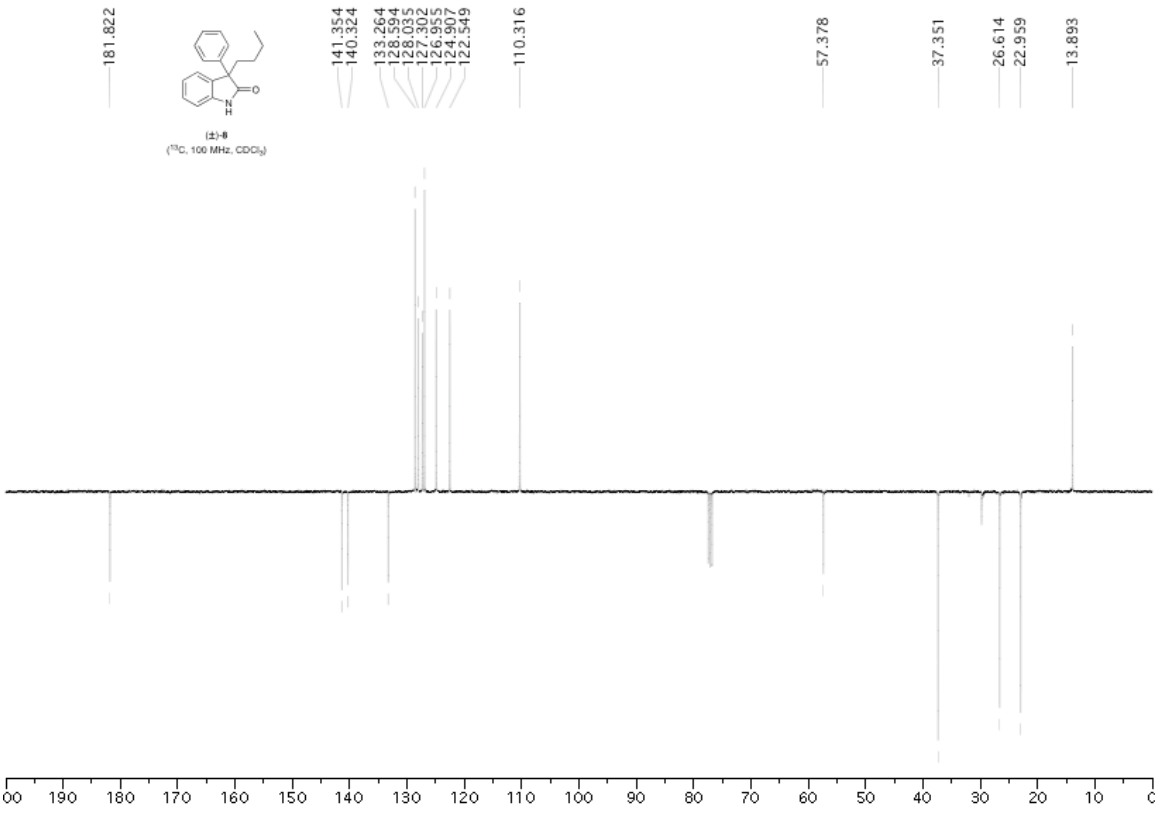

182.293
140.654
140.525
135.736
128.753
128.198
127.462
126.783
124.522
122.915
110.328
52.837
23.565
Me
O
N
H
(±)-5
(13C, 100 MHz, CDCl3)

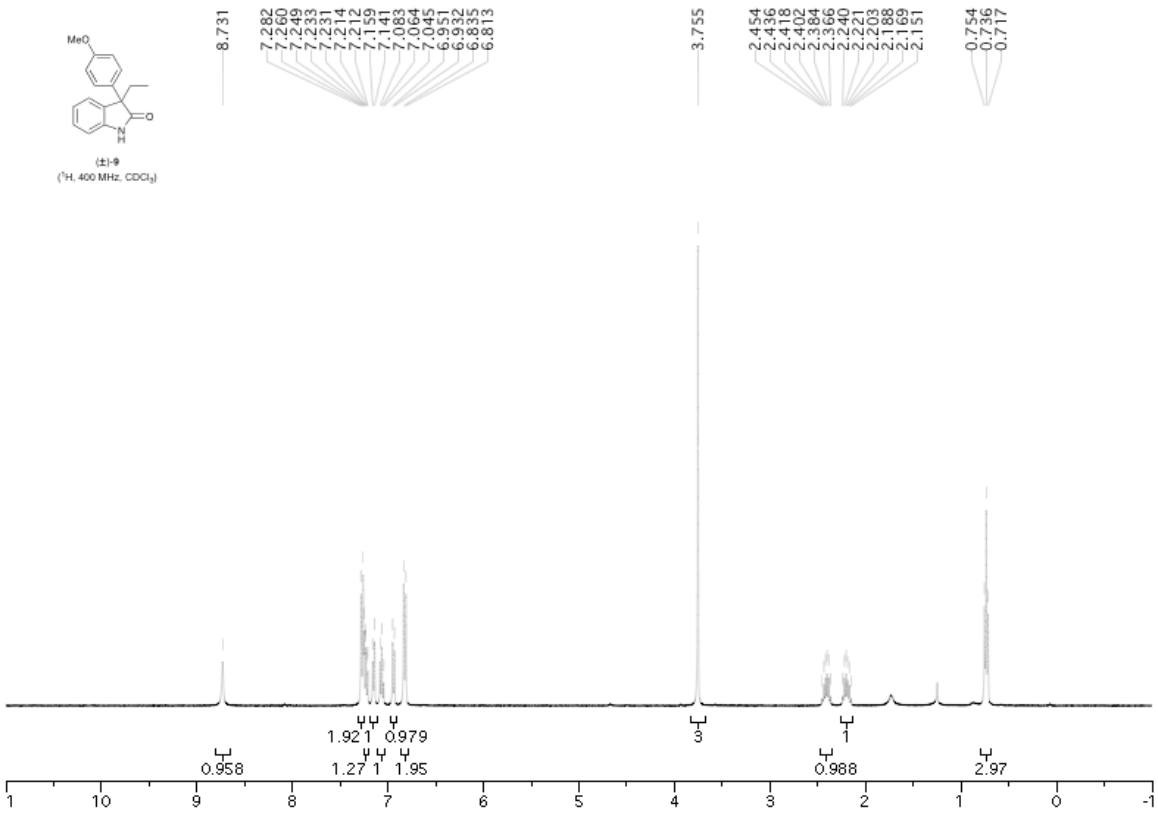

(±)-6
(¹H, 300 MHz, CDCl₃)
8.606
7.202
7.200
7.198
7.177
7.175
7.173
7.121
7.118
7.096
7.093
7.072
7.068
6.989
6.987
6.986
6.984
6.963
6.961
6.958
2.533
2.508
2.488
2.484
2.464
2.439
2.415
2.323
2.298
2.274
2.253
2.249
2.229
2.204
0.798
0.774
0.749
1.02
4.23
0.982
1
1.05
3.06
(±)-6
(¹³C, 75 MHz, CDCl₃)
181.451
141.632
140.509
133.182
128.993
128.490
127.727
127.381
125.440
123.018
110.426
58.243
30.935
9.436

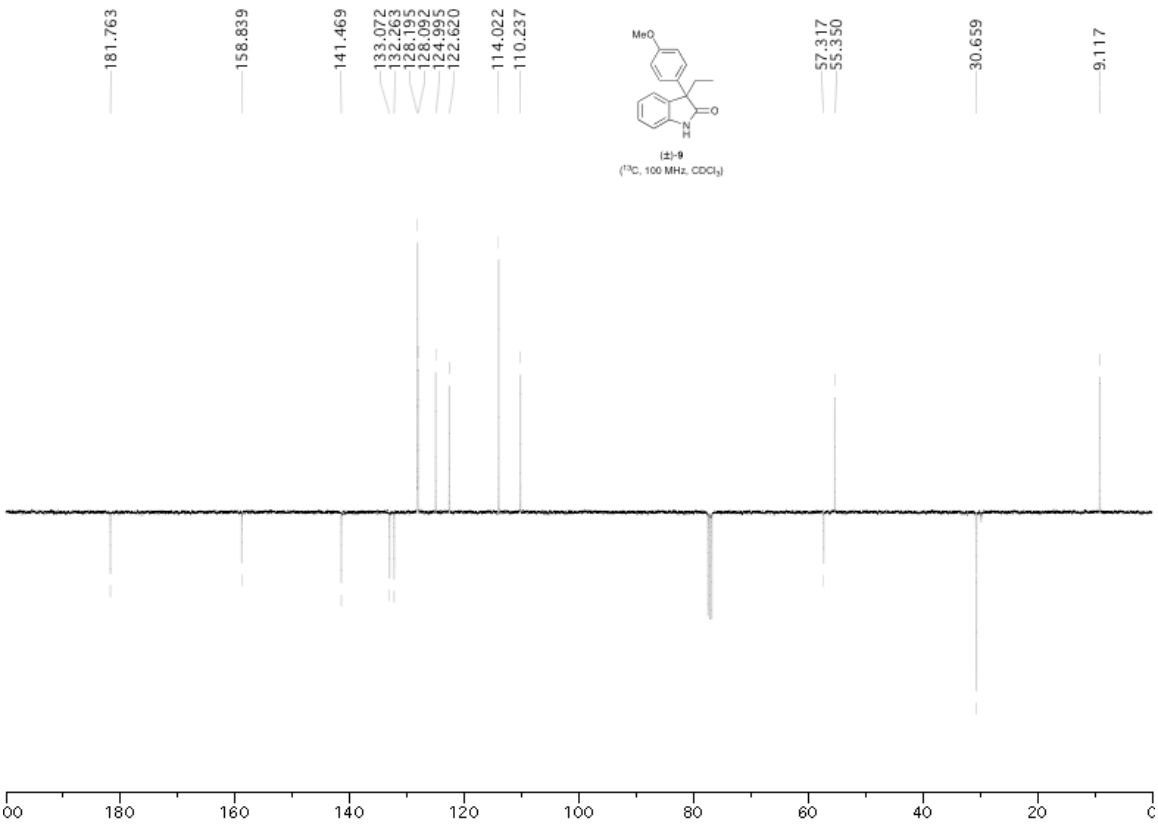

(±)-7
(1H, 400 MHz, CDCl3)
9.270
7.369
7.365
7.361
7.347
7.346
7.179
7.161
7.079
7.077
7.060
7.058
7.042
7.040
6.960
6.941
2.470
2.452
2.436
2.418
2.198
2.185
2.163
2.150
2.508
1.491
1.474
1.458
1.444
1.427
1.410
0.811
0.794
0.683
0.666
2.09
1.6
1.04
1.01
4.1
1.08
1.03
3.11
1
1.04
2.99

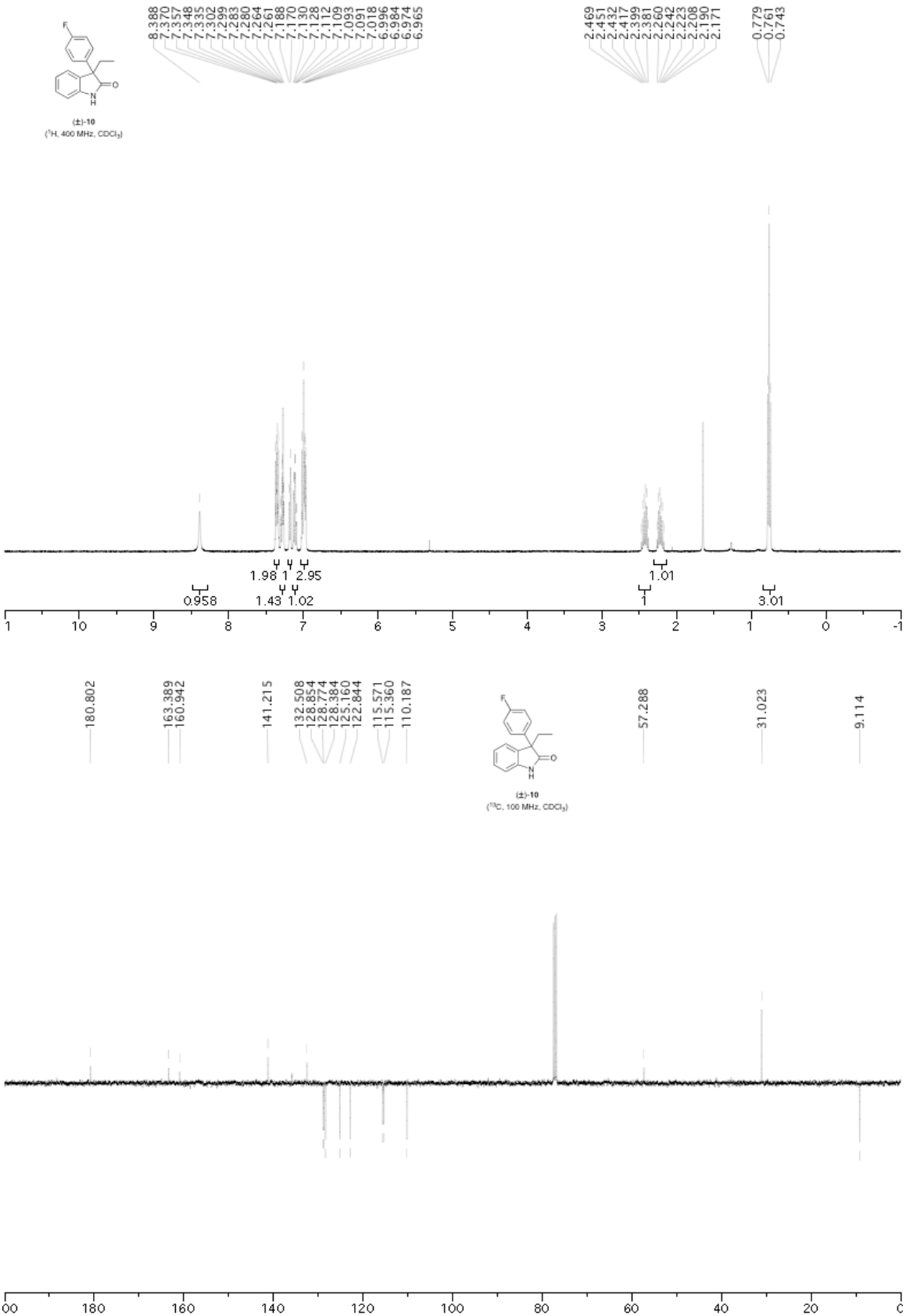

182.223
141.567
141.440
132.815
128.596
128.187
127.302
126.772
125.553
122.447
110.476
57.017
46.247
25.750
24.515
23.230
(±)-7
(13C, 100 MHz, CDCl3)

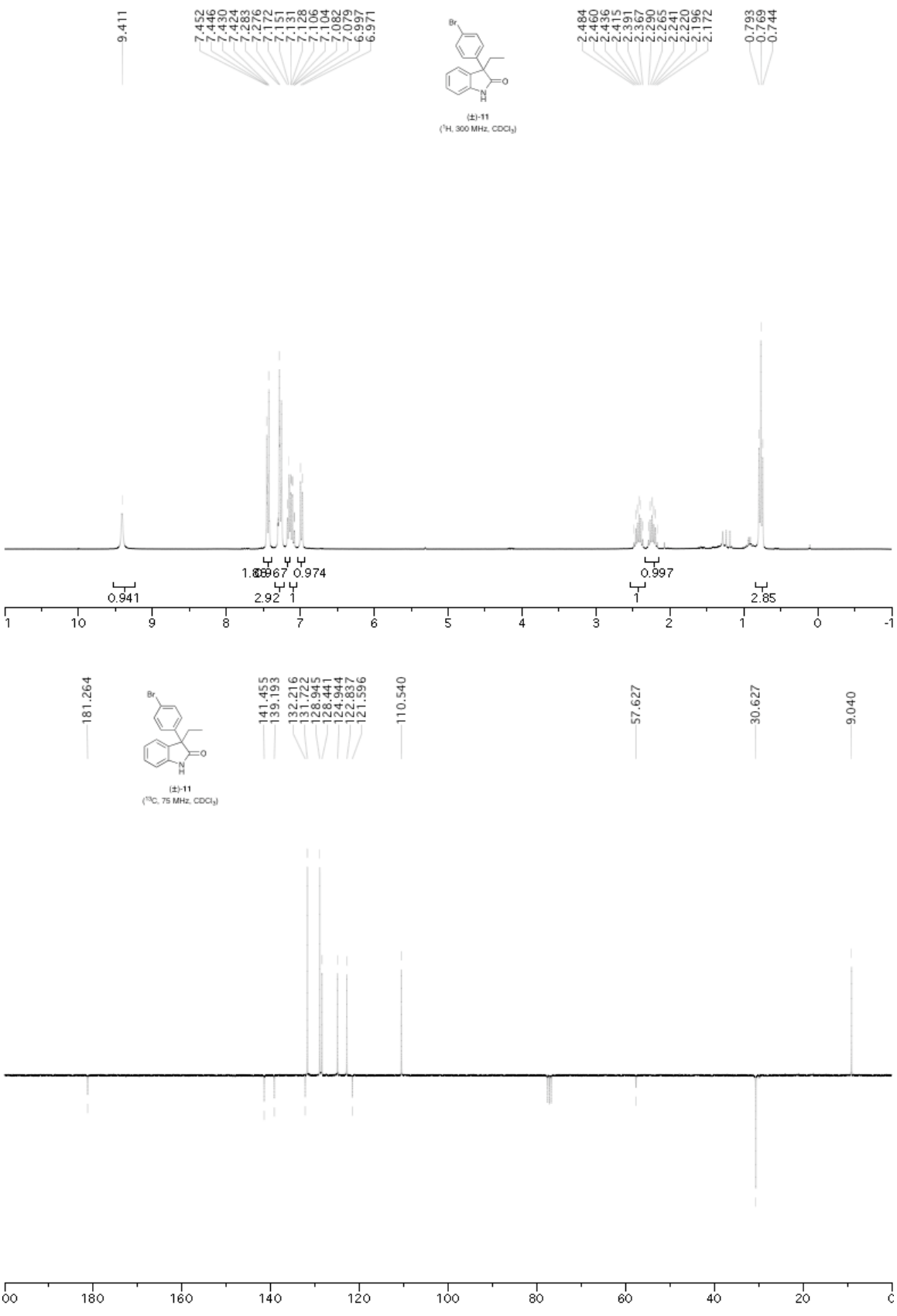

7.918
7.382
7.378
7.360
7.358
7.316
7.298
7.279
7.238
7.195
7.178
7.107
7.104
7.088
7.086
7.069
7.067
6.951
6.932
2.426
2.415
2.393
2.383
2.362
2.352
2.229
2.218
2.197
2.188
2.166
2.155
0.830
0.813
0.794
(±)-8
(1H, 400 MHz, CDCl3)
0.933
4.89
1.01
0.975
1
3.33
3.07
1.07

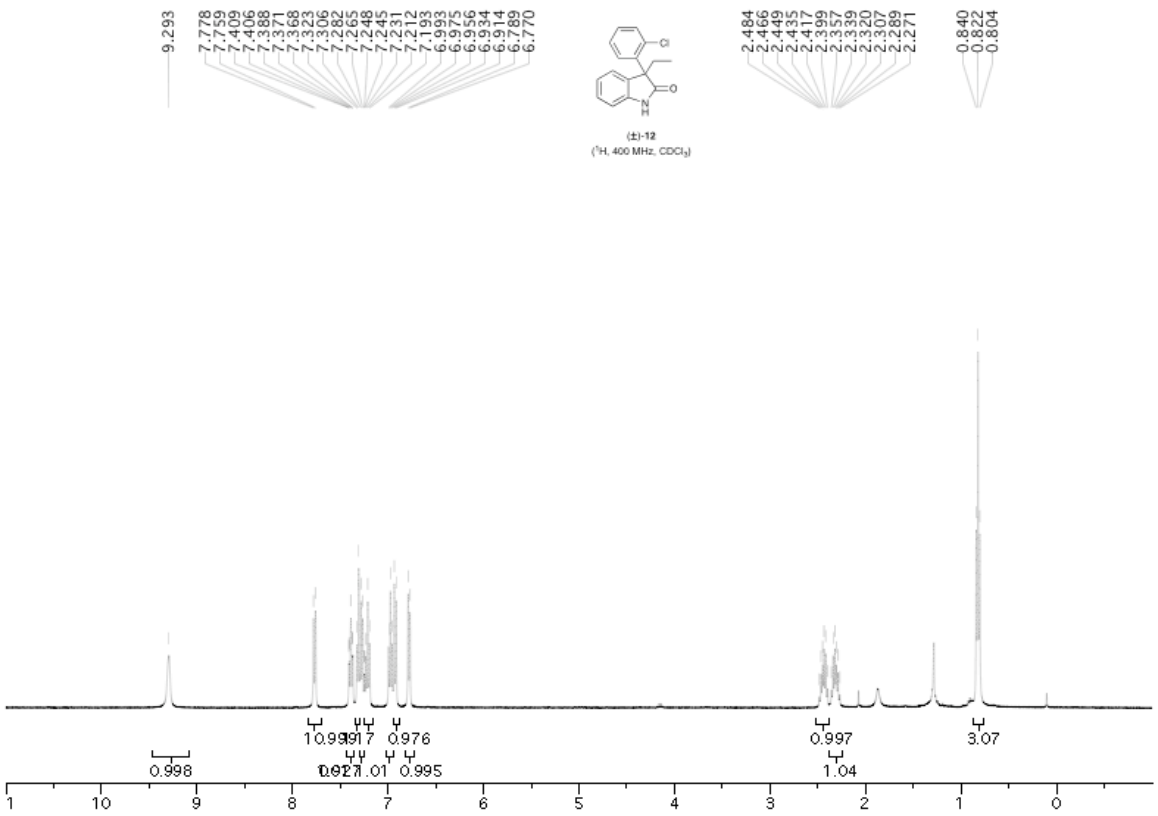

181.822
141.354
140.324
133.264
128.594
128.035
127.302
126.955
124.907
122.549
110.316
57.378
37.351
26.614
22.959
13.893
(±)-8
(13C, 100 MHz, CDCl3)

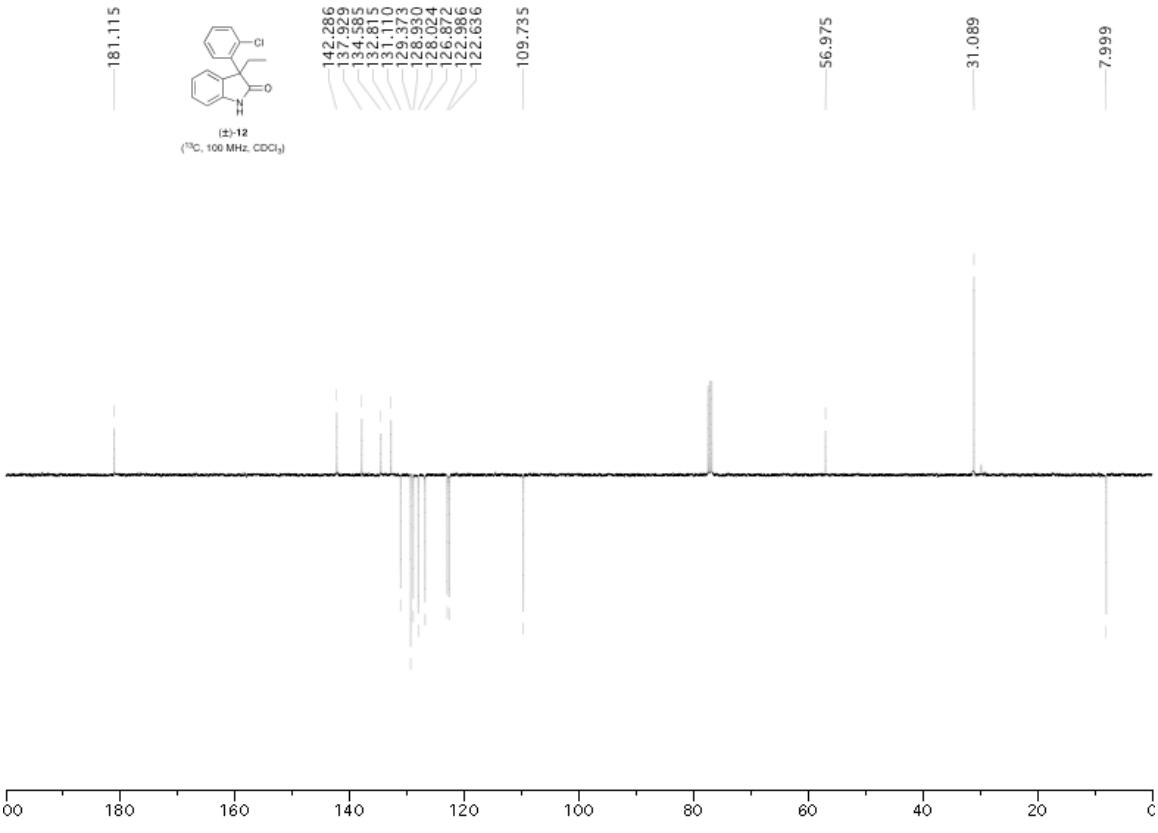

MeO
(±)-9
(1H, 400 MHz, CDCl3)
8.731
7.282
7.260
7.249
7.233
7.231
7.214
7.212
7.159
7.141
7.083
7.064
7.045
6.951
6.932
6.835
6.813
3.755
2.454
2.436
2.418
2.402
2.384
2.366
2.240
2.221
2.203
2.188
2.169
2.151
0.754
0.736
0.717
0.958
1.92
1
1.27
1
0.979
1.95
3
1
0.988
2.97

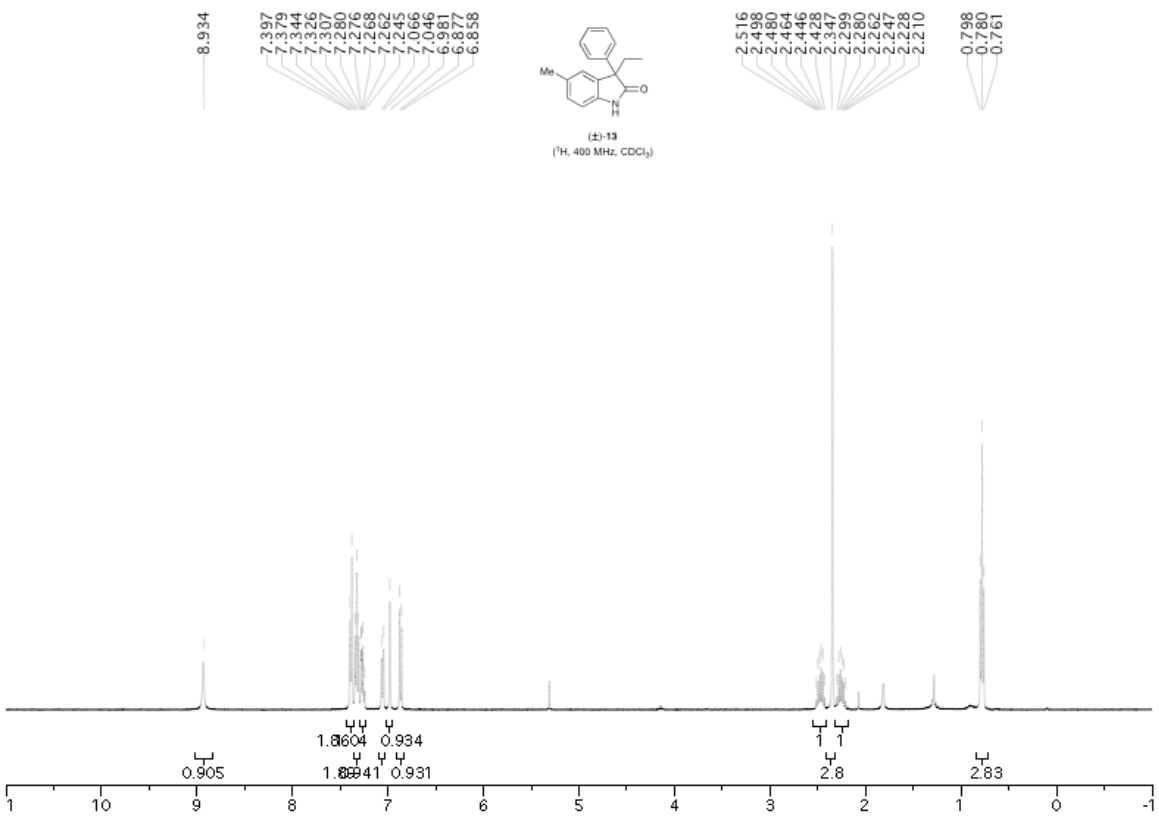

181.763
158.839
141.469
133.072
132.263
128.195
128.092
124.995
122.620
114.022
110.237
57.317
55.350
30.659
9.117
MeO
(±)-9
(13C, 100 MHz, CDCl3)

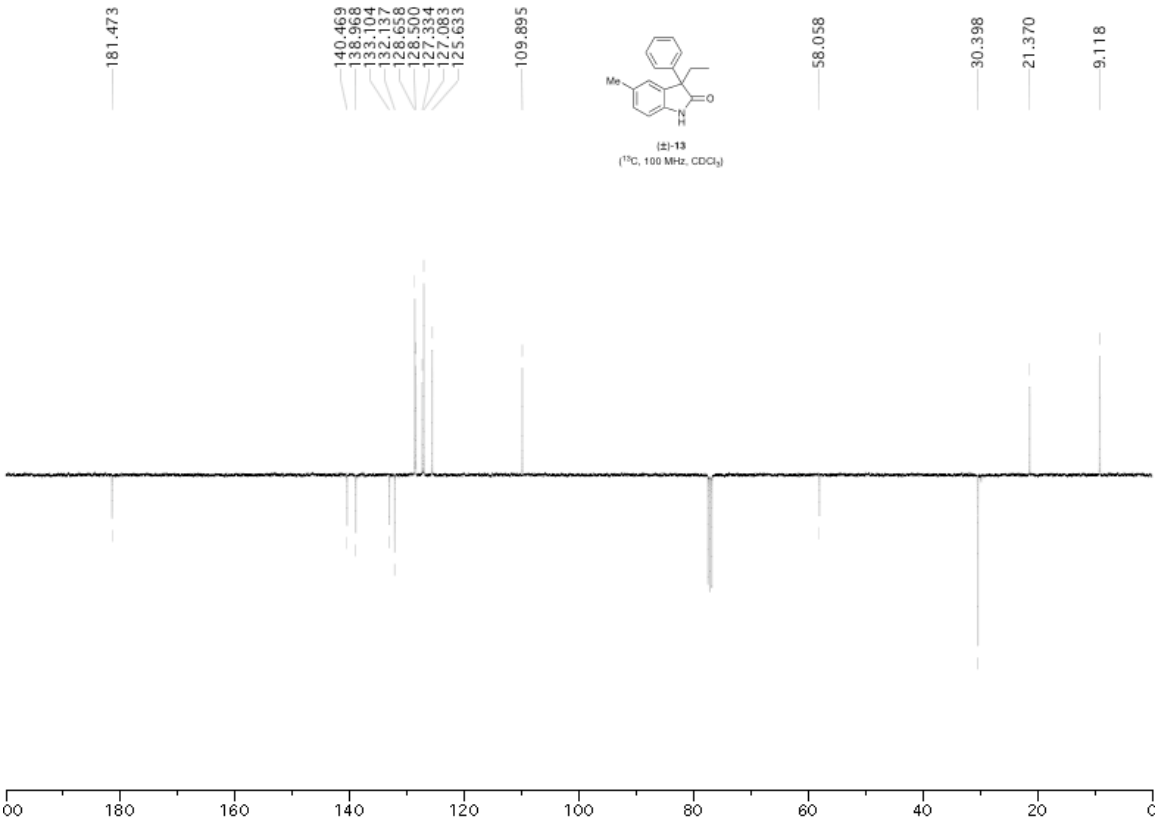

(±)-10
(1H, 400 MHz, CDCl3)
8.388
7.370
7.357
7.348
7.335
7.302
7.299
7.283
7.280
7.264
7.261
7.188
7.170
7.130
7.128
7.112
7.109
7.093
7.091
7.018
6.996
6.884
6.874
6.965
2.469
2.451
2.432
2.417
2.399
2.381
2.260
2.242
2.223
2.208
2.190
2.171
0.779
0.761
0.743
0.958
1.98
1
2.95
1.43
1.02
1.01
1
3.01
180.802
163.389
160.942
141.215
132.508
128.854
128.774
128.384
125.160
122.844
115.571
115.360
110.187
57.288
31.023
9.114
(±)-10
(13C, 100 MHz, CDCl3)

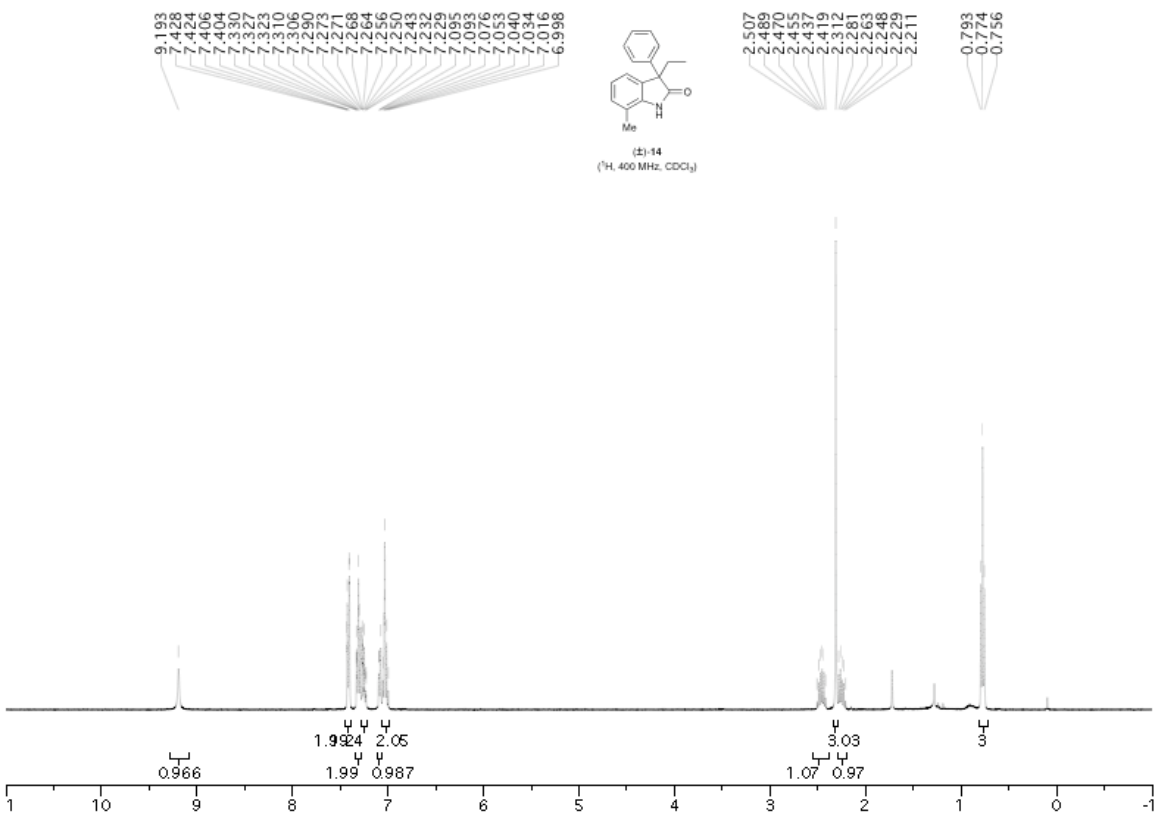

9.411
7.452
7.446
7.430
7.424
7.283
7.276
7.172
7.151
7.131
7.128
7.106
7.104
7.082
7.079
6.977
6.971
2.484
2.460
2.436
2.415
2.391
2.367
2.290
2.265
2.241
2.220
2.196
2.172
0.793
0.769
0.744
(±)-11
(1H, 300 MHz, CDCl3)
0.941
2.92
1
0.997
2.85
181.264
141.455
139.193
132.216
131.722
128.945
128.441
124.944
122.837
121.596
110.540
57.627
30.627
9.040
(±)-11
(13C, 75 MHz, CDCl3)

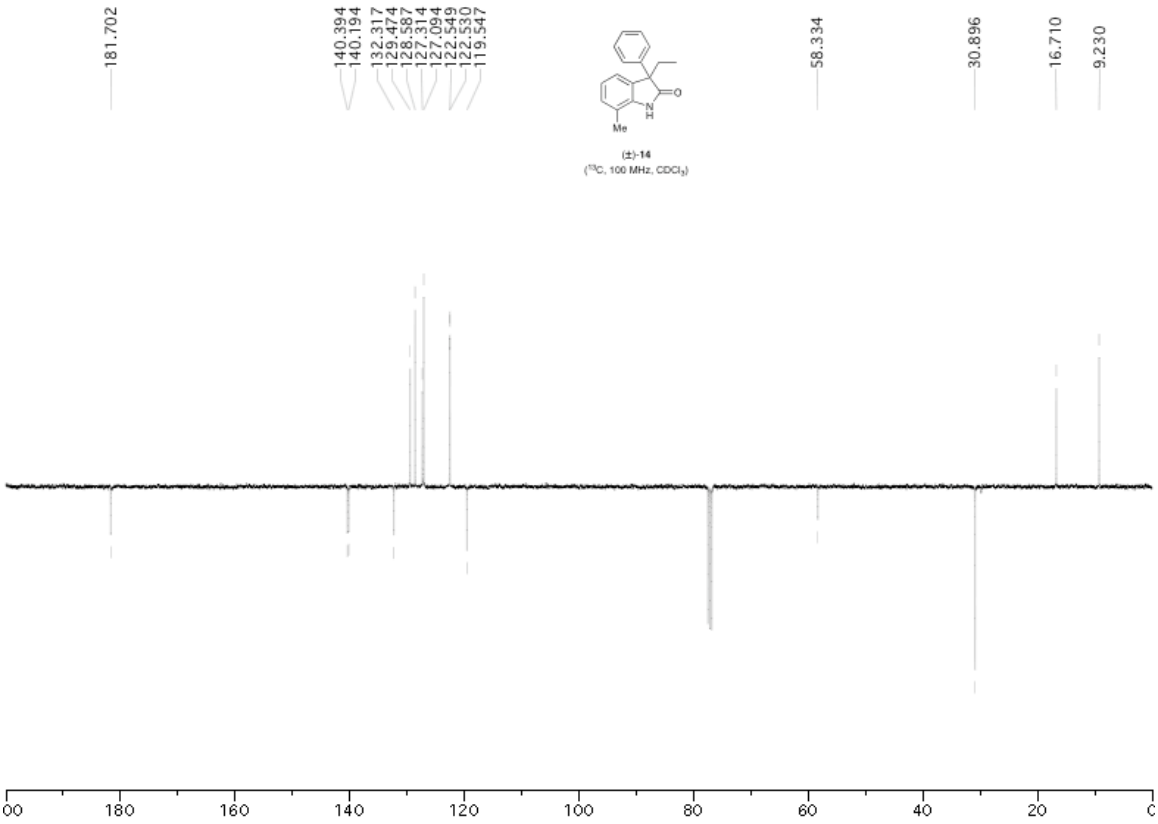

9.293
7.778
7.759
7.409
7.406
7.388
7.371
7.368
7.323
7.306
7.282
7.265
7.248
7.245
7.231
7.212
7.193
6.993
6.975
6.956
6.934
6.914
6.789
6.770
2.484
2.466
2.449
2.435
2.417
2.399
2.357
2.339
2.320
2.307
2.289
2.271
0.840
0.822
0.804
(±)-12
(1H, 400 MHz, CDCl3)
0.998
10.99
1.17
0.976
0.92
1.01
0.995
0.997
1.04
3.07

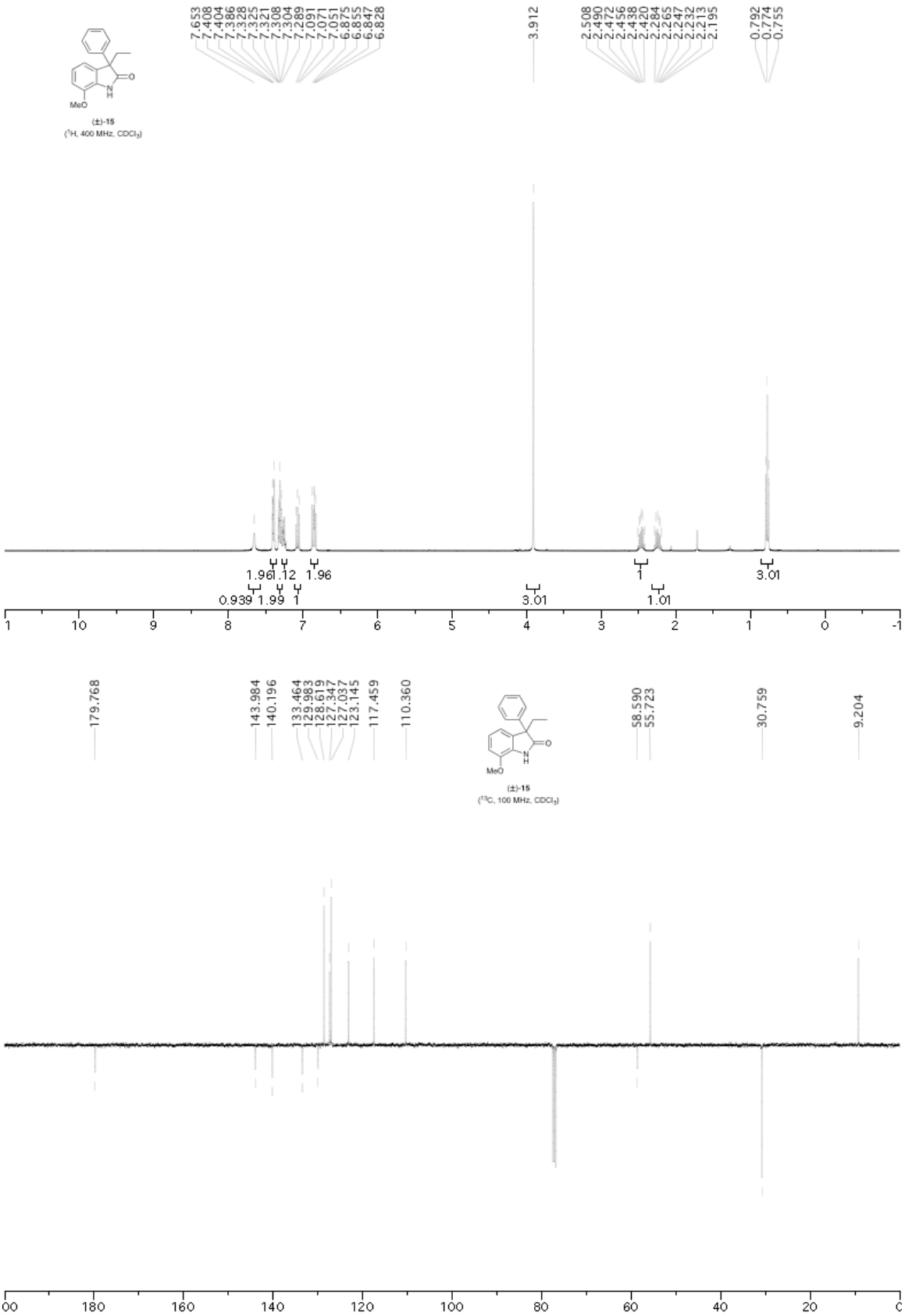

181.115
142.286
137.929
134.585
132.815
131.110
129.373
128.930
128.024
126.872
122.986
122.636
109.735
56.975
31.089
7.999
(±)-12
(13C, 100 MHz, CDCl3)

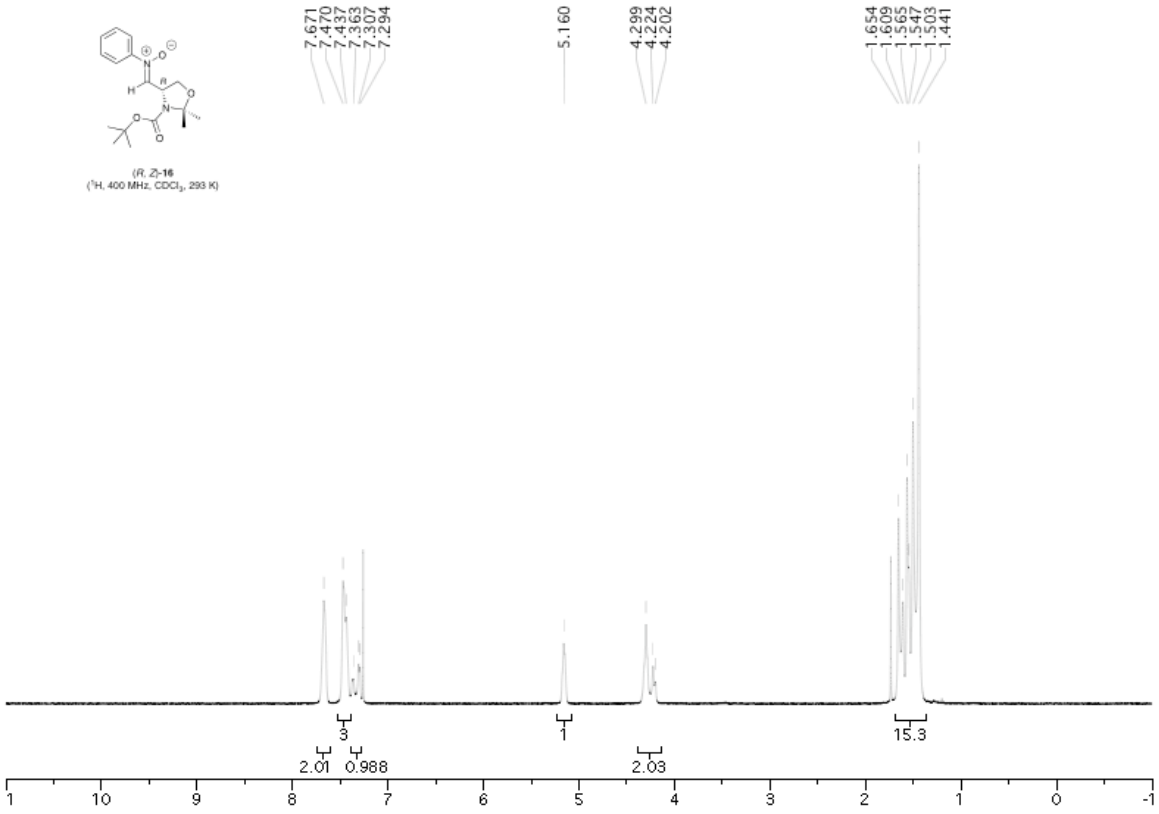

8.934
7.397
7.379
7.344
7.326
7.307
7.280
7.276
7.268
7.262
7.245
7.066
7.046
6.981
6.877
6.858
2.516
2.498
2.480
2.464
2.446
2.428
2.347
2.299
2.280
2.262
2.247
2.228
2.210
0.798
0.780
0.761
Me
O
N
H
(±)-13
(1H, 400 MHz, CDCl3)
0.905
1.8604
0.934
1.8941
0.931
1
1
2.8
2.83

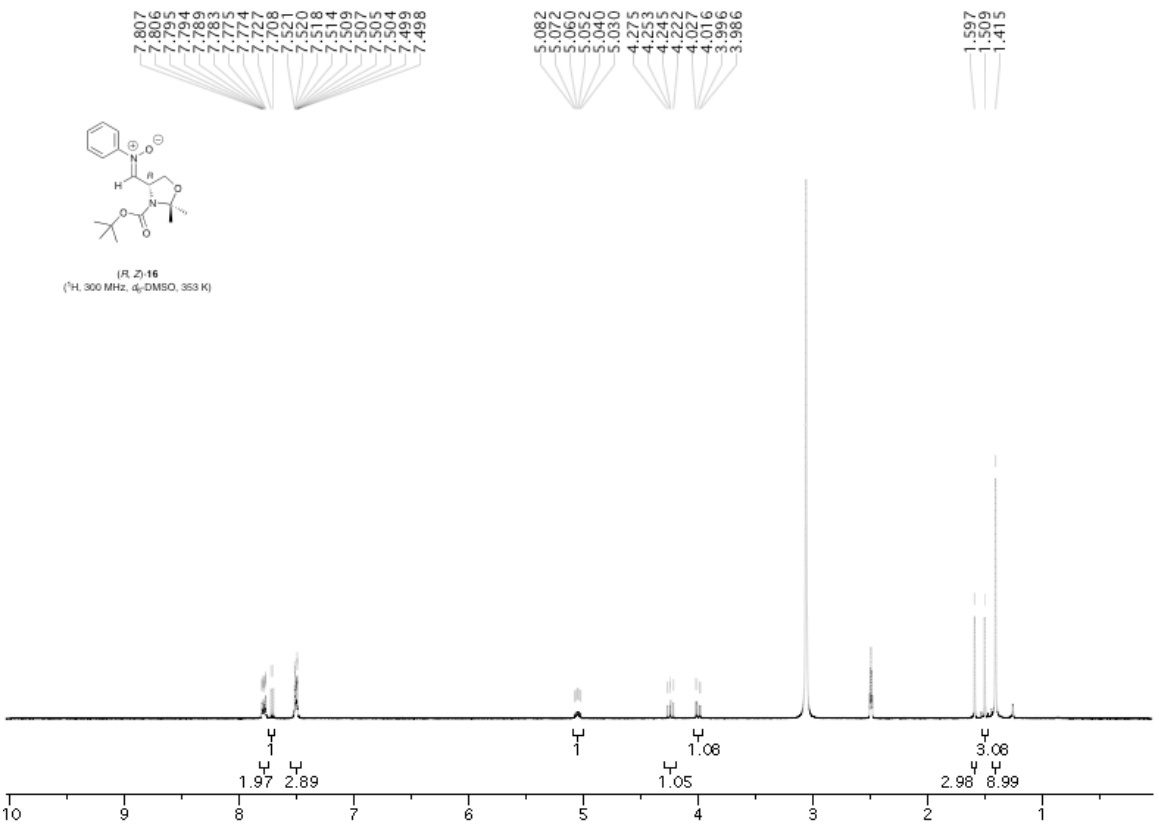

181.473
140.469
138.968
133.104
132.137
128.658
128.500
127.334
127.083
125.633
109.895
58.058
30.398
21.370
9.118
Me
O
N
H
(±)-13
(13C, 100 MHz, CDCl3)

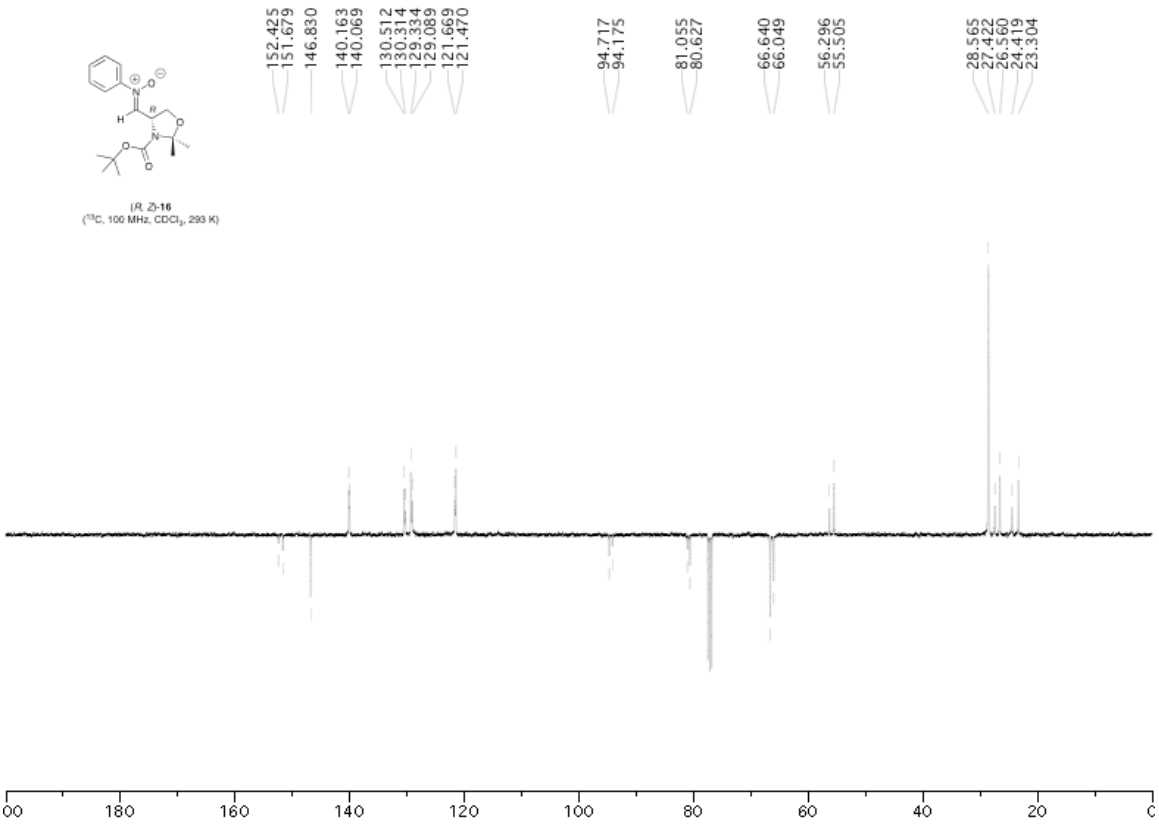

9.193
7.428
7.424
7.406
7.404
7.330
7.327
7.323
7.310
7.306
7.290
7.273
7.271
7.268
7.264
7.256
7.250
7.243
7.232
7.229
7.095
7.093
7.076
7.053
7.040
7.034
7.016
6.998
2.507
2.489
2.470
2.455
2.437
2.419
2.312
2.281
2.263
2.248
2.229
2.211
0.793
0.774
0.756
Me
(±)-14
(1H, 400 MHz, CDCl3)
0.966
1.99
1.99
2.24
2.05
0.987
1.07
0.97
3.03
3
1
10
9
8
7
6
5
4
3
2
1
0
-1

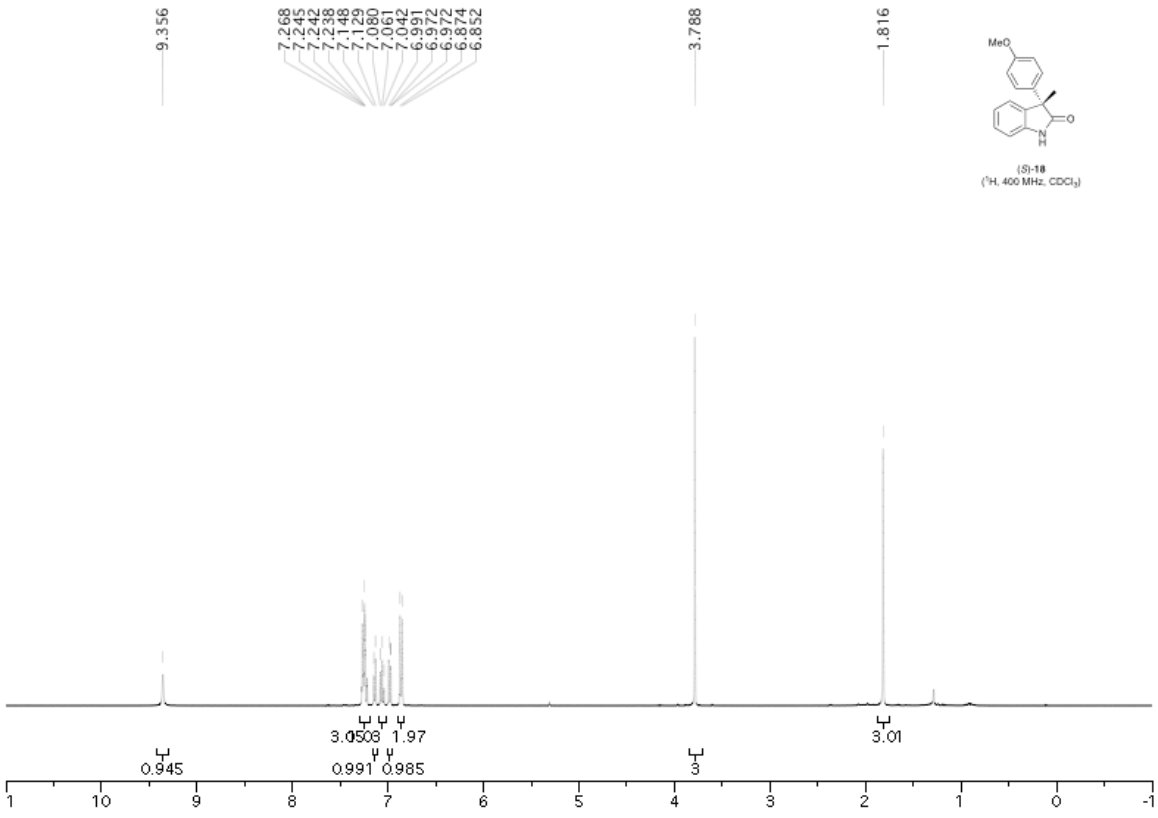

181.702
140.394
140.194
132.317
129.474
128.587
127.314
127.094
122.549
122.530
119.547
58.334
30.896
16.710
9.230
Me
(±)-14
(13C, 100 MHz, CDCl3)
00
180
160
140
120
100
80
60
40
20
0

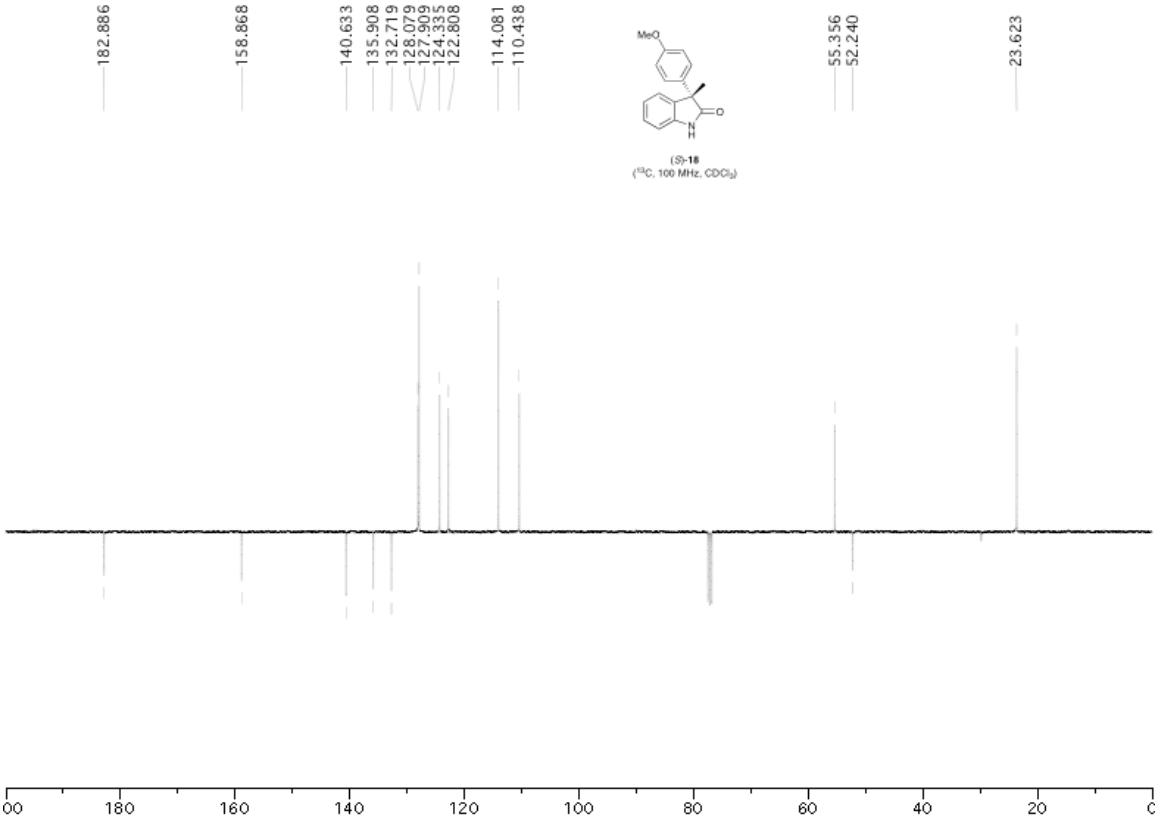

7.653
7.408
7.404
7.386
7.328
7.325
7.321
7.308
7.304
7.289
7.091
7.071
7.051
6.875
6.855
6.847
6.828
3.912
2.508
2.490
2.472
2.456
2.438
2.420
2.284
2.265
2.247
2.232
2.213
2.195
0.792
0.774
0.755
MeO
(±)-15
(1H, 400 MHz, CDCl3)
1.96
1.12
1.96
0.939
1.99
1
3.01
1
1.01
3.01
179.768
143.984
140.196
133.464
129.983
128.619
127.347
127.037
123.145
117.459
110.360
58.590
55.723
30.759
9.204
MeO
(±)-15
(13C, 100 MHz, CDCl3)

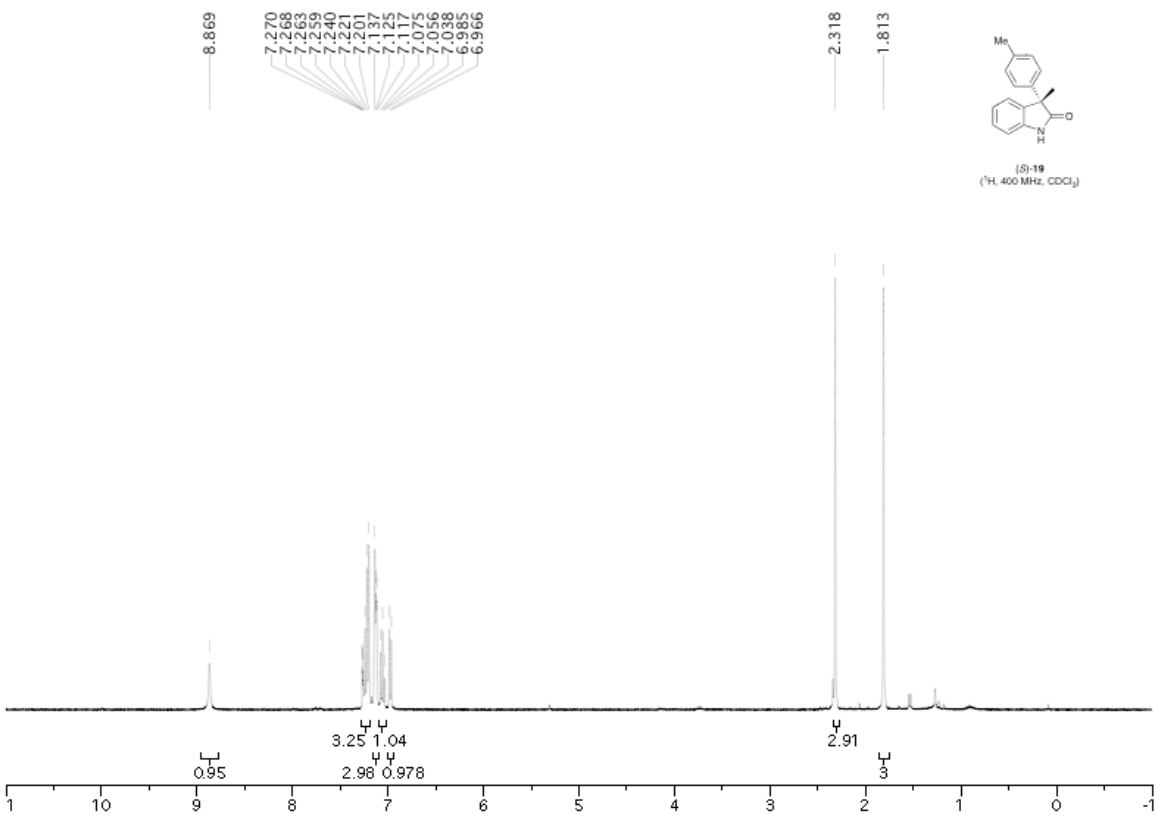

7.671
7.470
7.437
7.363
7.307
7.294
5.160
4.299
4.224
4.202
1.654
1.609
1.565
1.547
1.503
1.441
(R, Z)-16
(1H, 400 MHz, CDCl3, 293 K)
3
1
15.3
2.01
0.988
2.03
1
10
9
8
7
6
5
4
3
2
1
0
-1

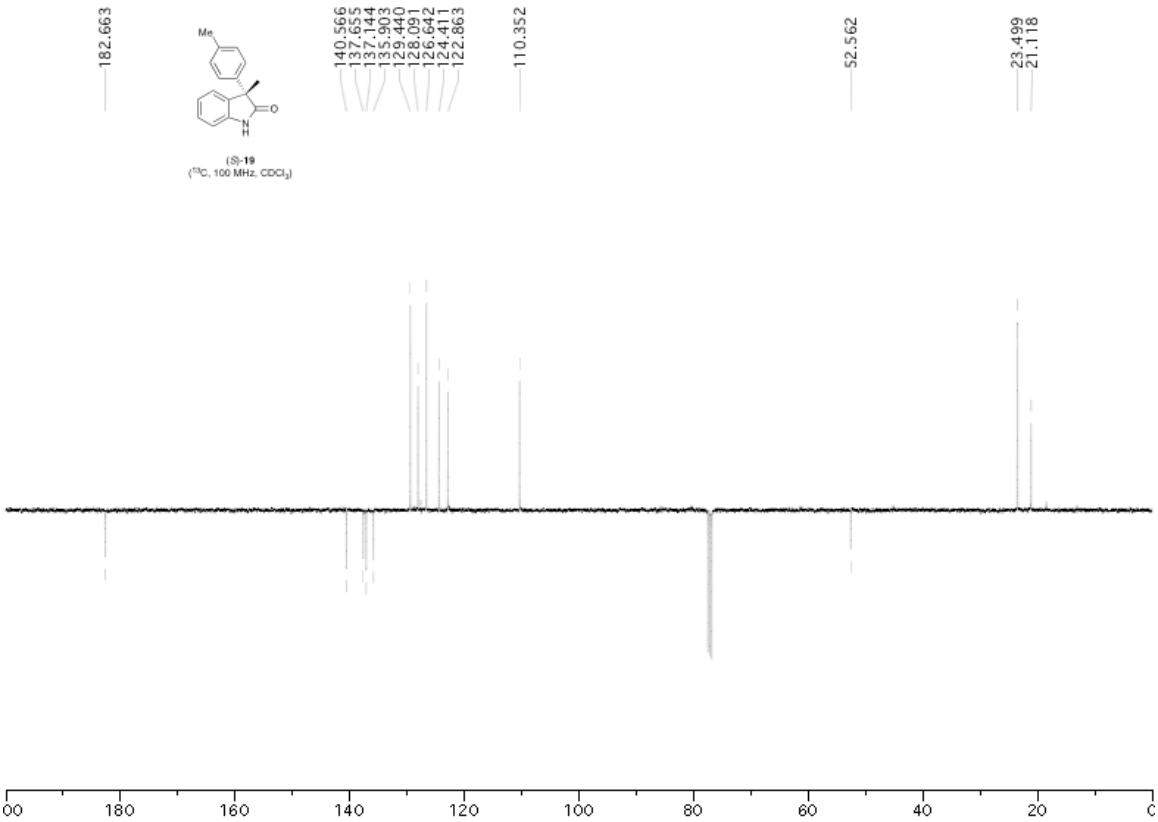

7.807
7.806
7.795
7.794
7.789
7.783
7.775
7.774
7.727
7.708
7.521
7.520
7.518
7.514
7.509
7.507
7.505
7.504
7.499
7.498
5.082
5.072
5.060
5.052
5.040
5.030
4.275
4.253
4.245
4.222
4.027
4.016
3.996
3.986
1.597
1.509
1.415
(R, Z)-16
(1H, 300 MHz, d6-DMSO, 353 K)
1
1
1.08
3.08
1.97
2.89
1.05
2.98
8.99
10
9
8
7
6
5
4
3
2
1

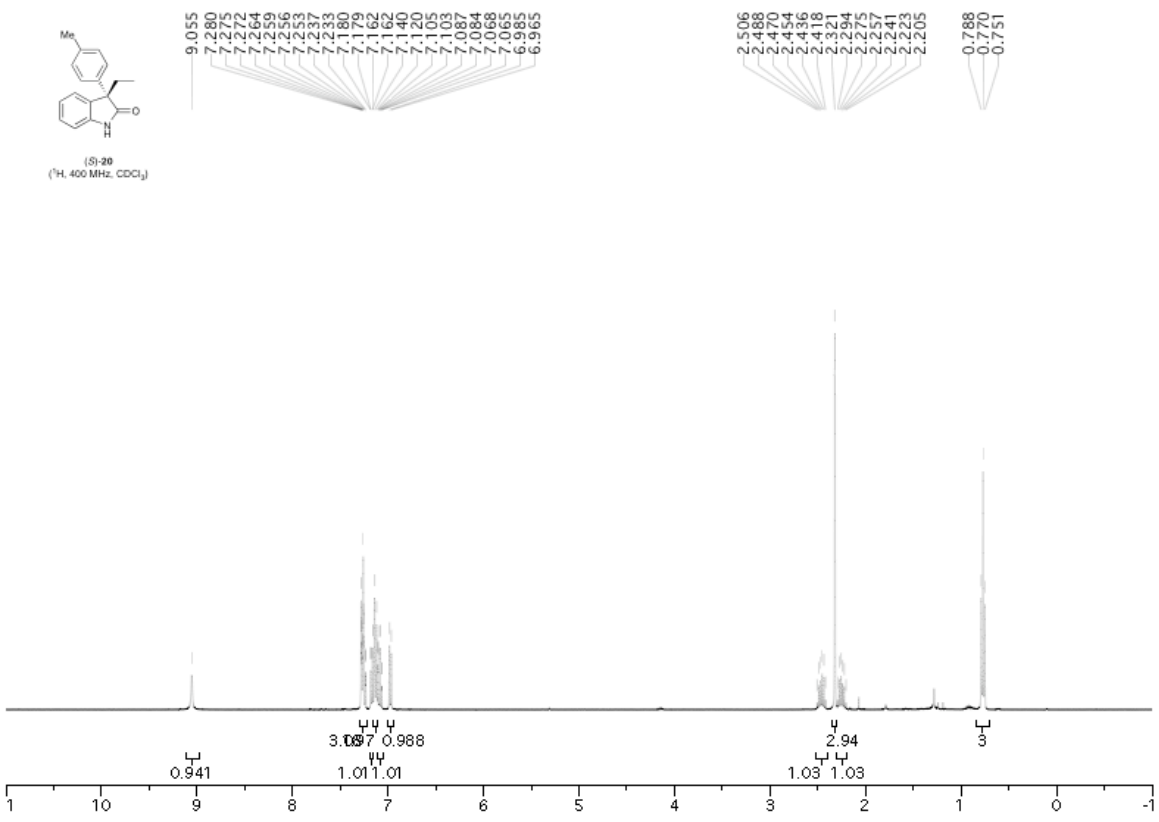

152.425
151.679
146.830
140.163
140.069
130.512
130.314
129.334
129.089
121.669
121.470
94.717
94.175
81.055
80.627
66.640
66.049
56.296
55.505
28.565
27.422
26.560
24.419
23.304
(R, Z)-16
(13C, 100 MHz, CDCl3, 293 K)
00
180
160
140
120
100
80
60
40
20
0

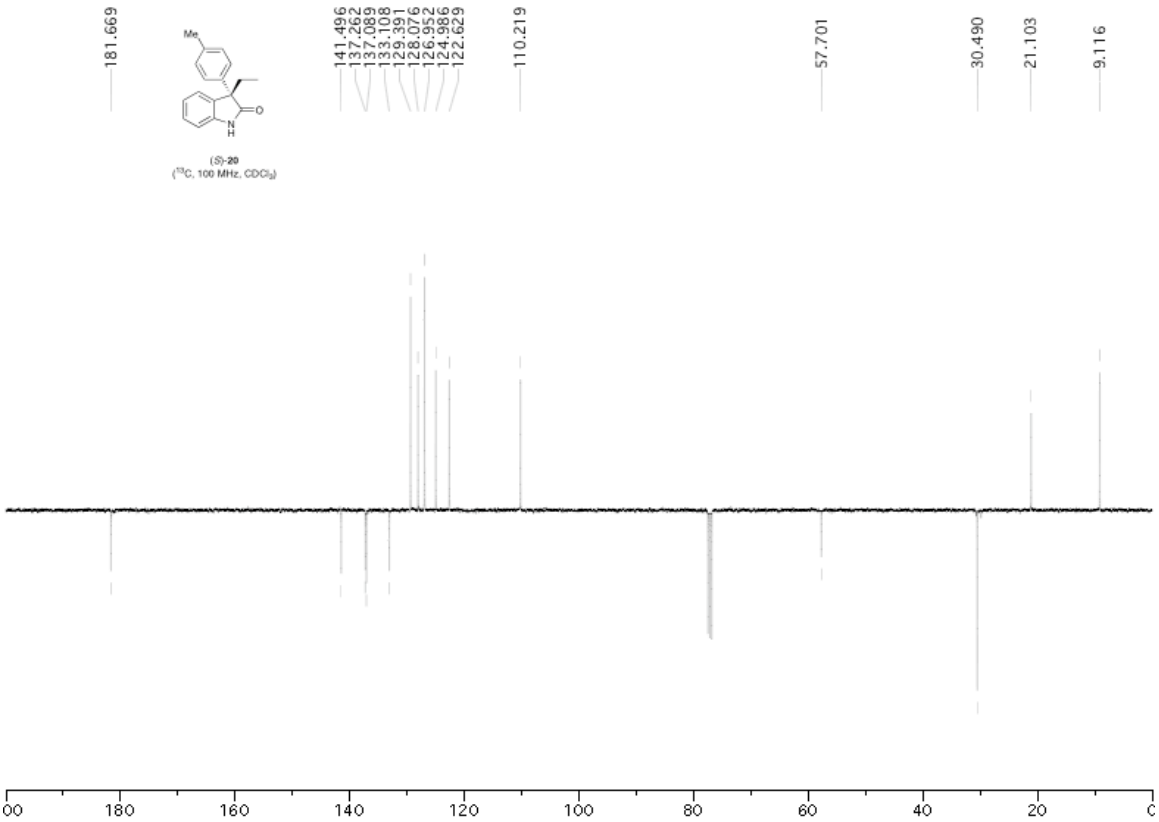

9.356
7.268
7.245
7.242
7.238
7.148
7.129
7.080
7.061
7.042
6.991
6.972
6.972
6.874
6.852
3.788
1.816
MeO
O
N
H
(S)-18
(1H, 400 MHz, CDCl3)
3.0508
1.97
0.945
0.991
0.985
3
3.01

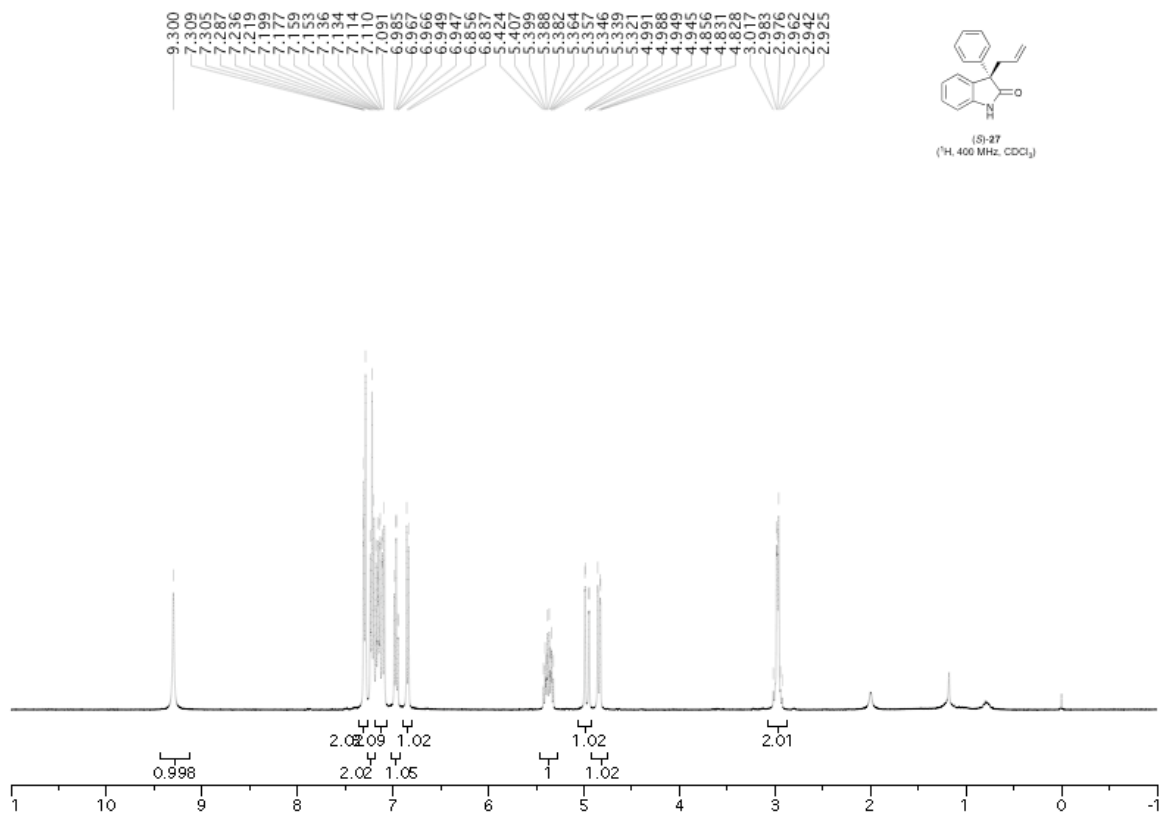

182.886
158.868
140.633
135.908
132.719
128.079
127.909
124.335
122.808
114.081
110.438
55.356
52.240
23.623
MeO
O
N
H
(S)-18
(13C, 100 MHz, CDCl3)

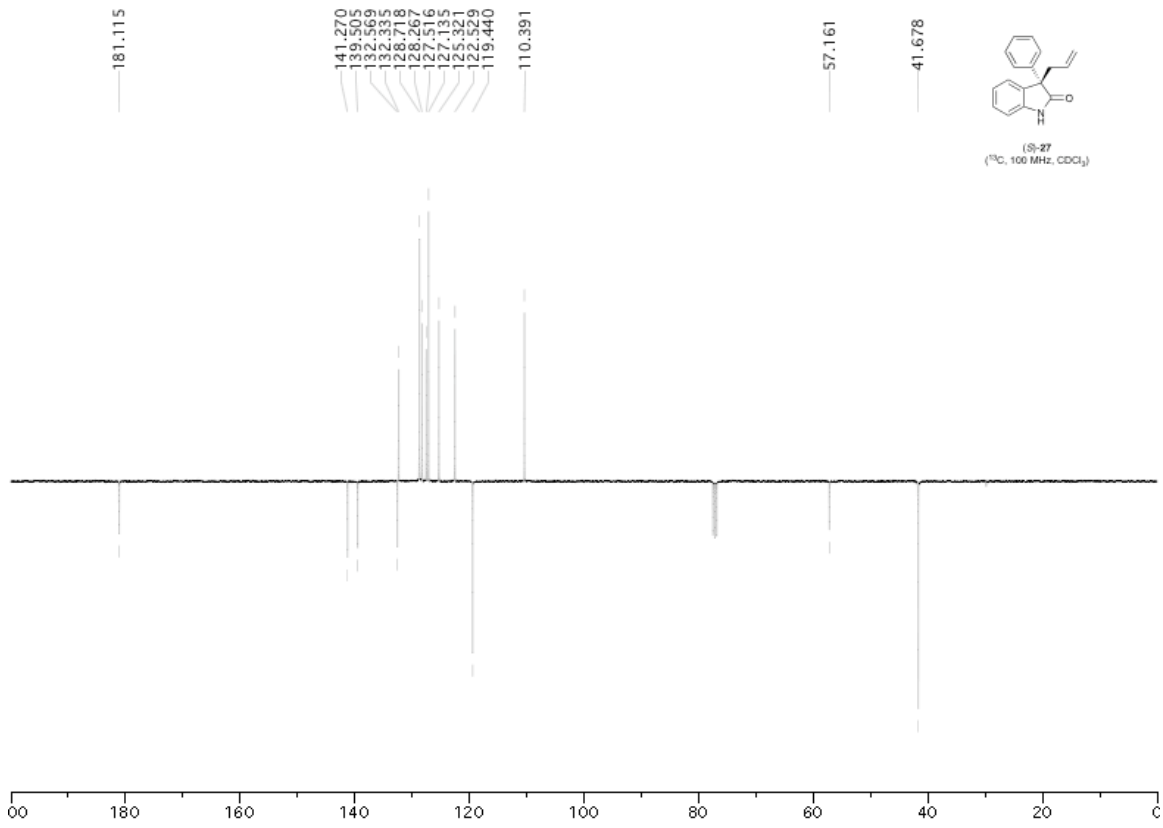

8.869
7.270
7.268
7.263
7.259
7.240
7.221
7.201
7.137
7.125
7.117
7.075
7.056
7.038
6.885
6.966
2.318
1.813
(S)-19
(1H, 400 MHz, CDCl3)
3.25
1.04
2.91
0.95
2.98
0.978
3

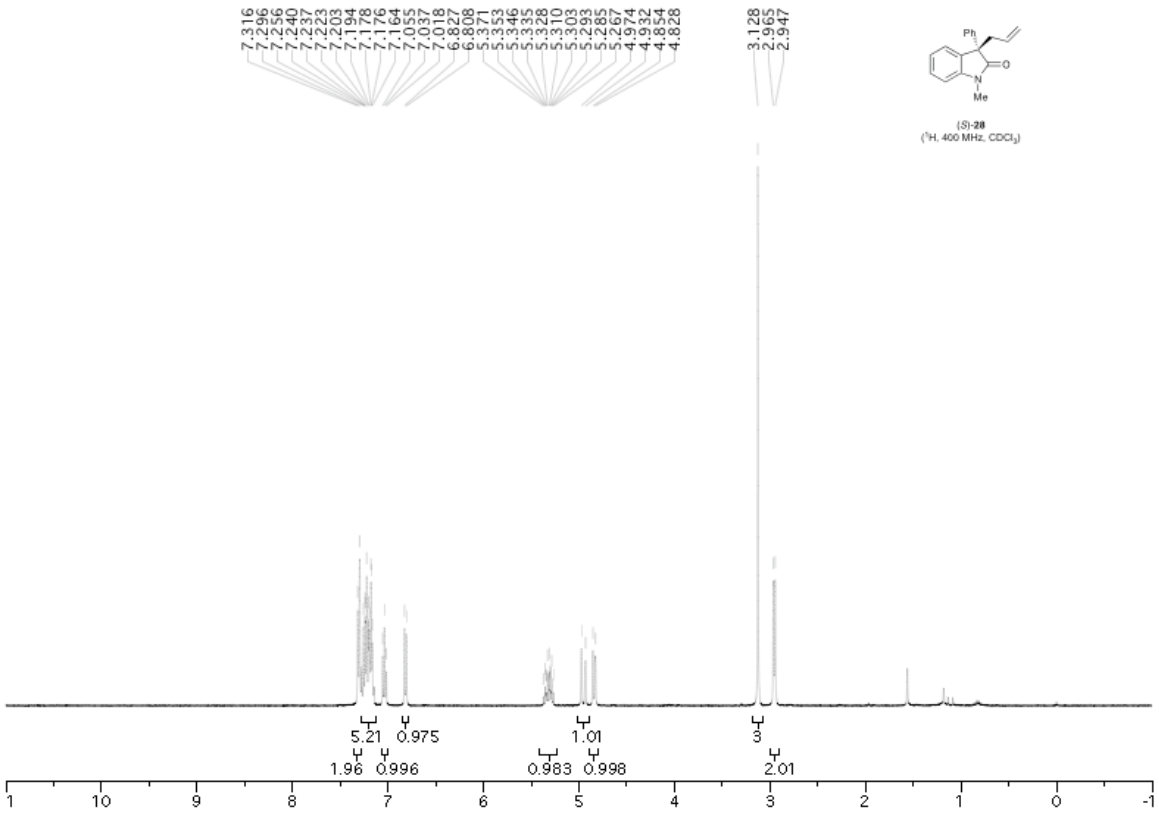

182.663
140.566
137.655
137.144
135.903
129.440
128.091
126.642
124.411
122.863
110.352
52.562
23.499
21.118
(S)-19
(13C, 100 MHz, CDCl3)

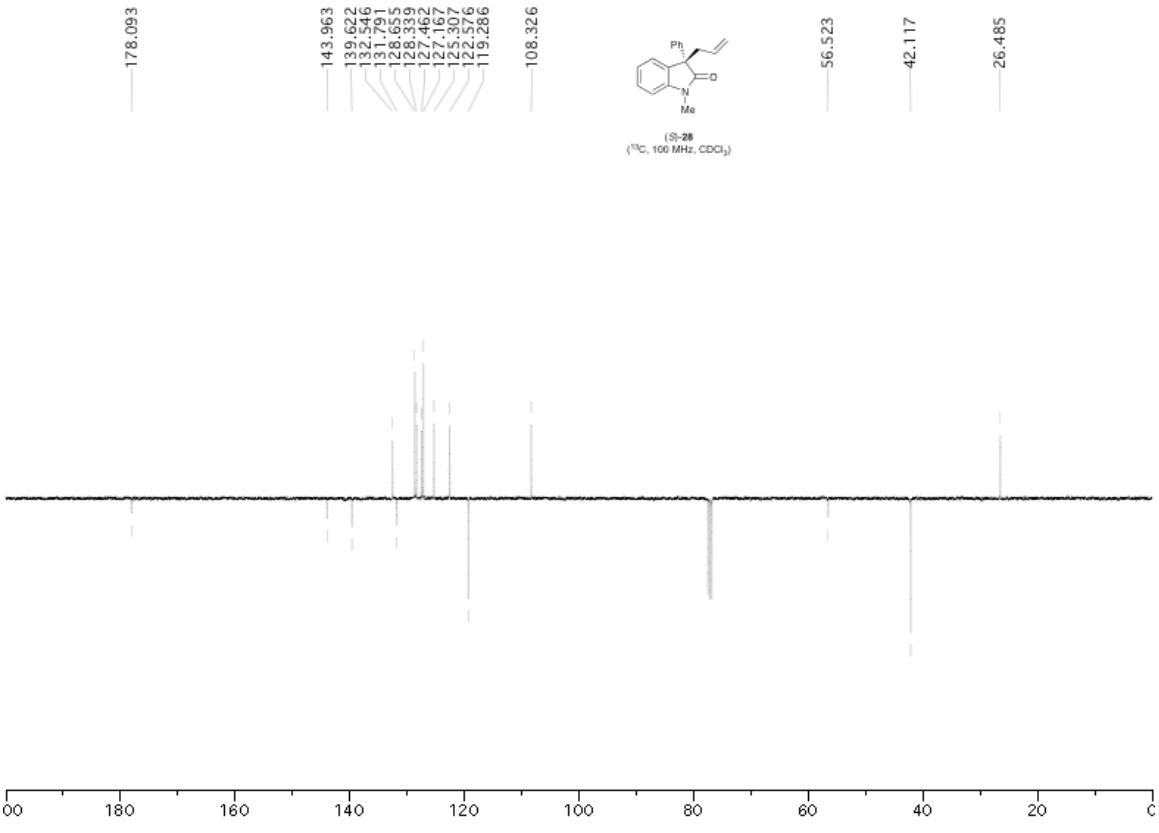

(S)-20
(1H, 400 MHz, CDCl3)
9.055
7.280
7.275
7.272
7.264
7.259
7.256
7.253
7.237
7.233
7.180
7.179
7.162
7.162
7.140
7.120
7.105
7.103
7.087
7.084
7.068
7.065
6.985
6.965
2.506
2.488
2.470
2.454
2.436
2.418
2.321
2.294
2.275
2.257
2.241
2.223
2.205
0.788
0.770
0.751
0.941
3.08
3.97
0.988
1.01
1.01
2.94
3
1.03
1.03

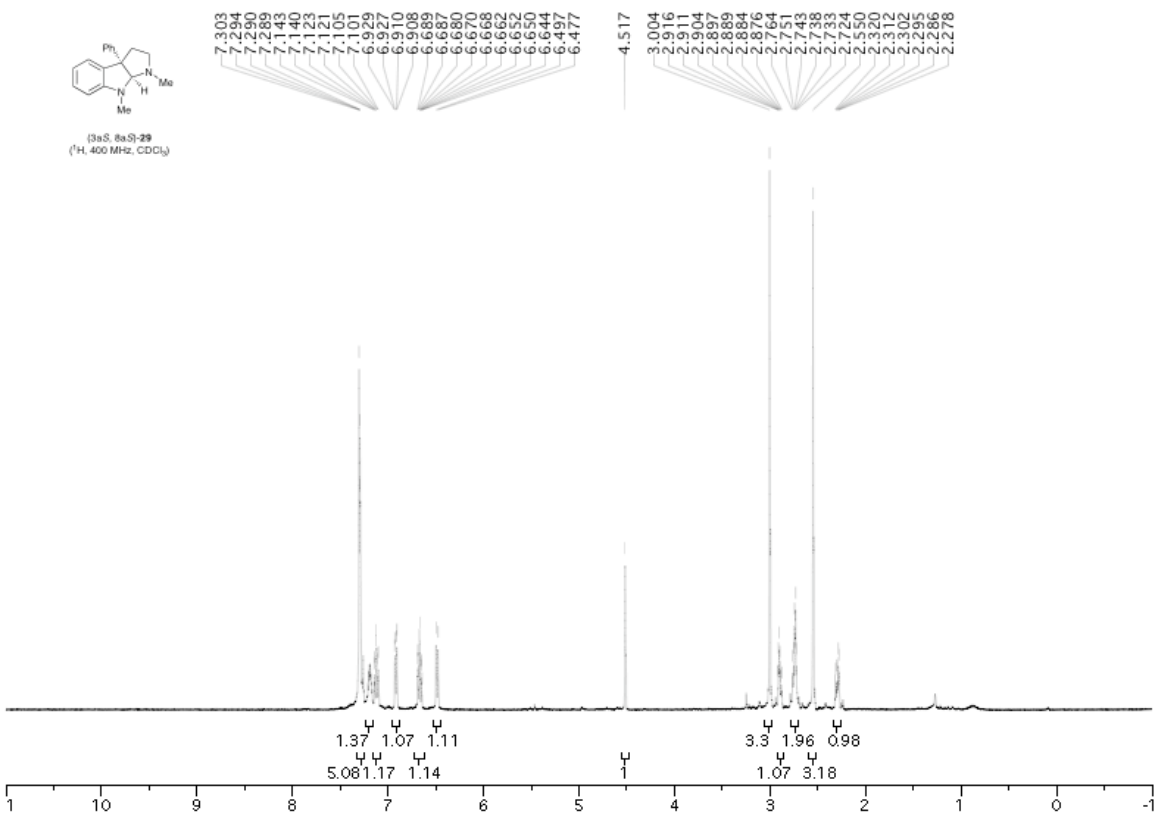

(S)-20
(13C, 100 MHz, CDCl3)
181.669
141.496
137.262
137.089
133.108
129.391
128.076
126.952
124.986
122.629
110.219
57.701
30.490
21.103
9.116

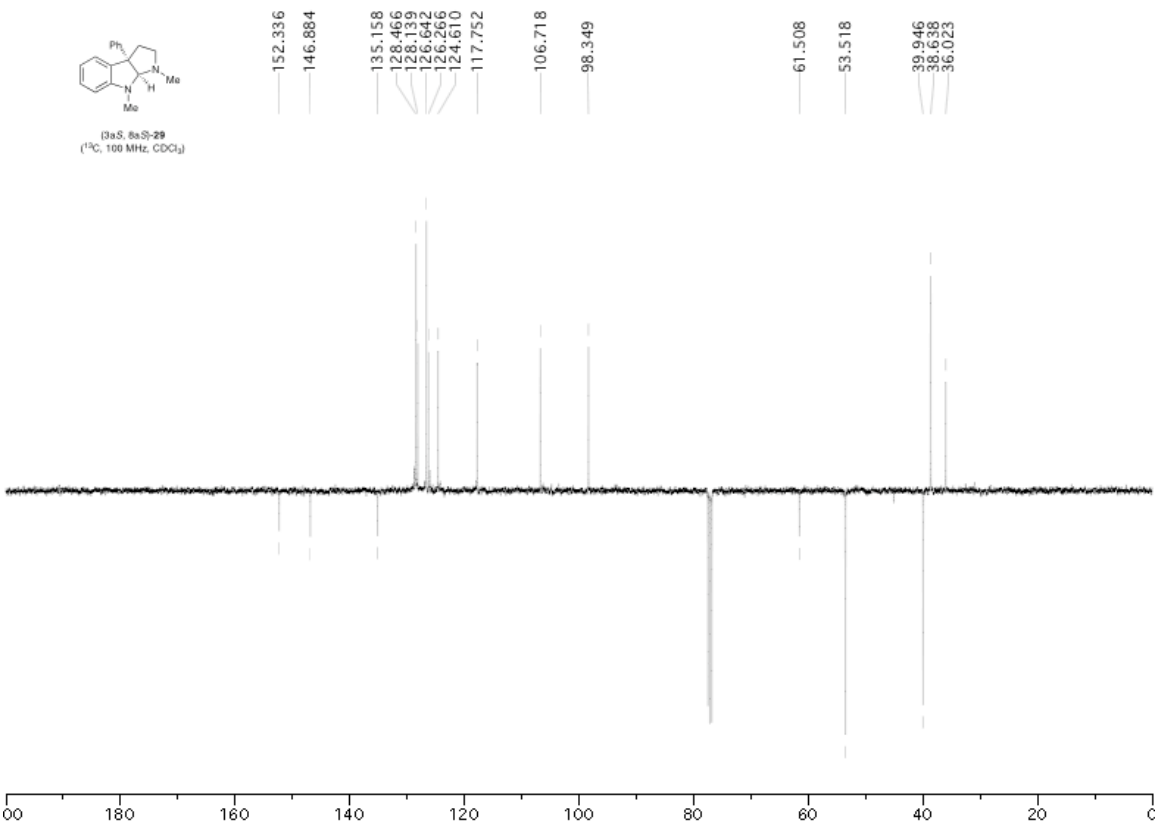

9.300
7.309
7.305
7.287
7.236
7.219
7.199
7.177
7.159
7.153
7.136
7.134
7.114
7.110
7.091
6.885
6.867
6.866
6.849
6.847
6.556
6.837
5.424
5.407
5.399
5.388
5.382
5.364
5.357
5.346
5.339
5.321
4.991
4.988
4.949
4.945
4.856
4.831
4.828
3.017
2.983
2.976
2.962
2.942
2.925
(S)-27
(1H, 400 MHz, CDCl3)
0.998
2.02
2.09
1.02
2.02
1.05
1
1.02
1.02
2.01
1
10
9
8
7
6
5
4
3
2
1
0
-1


181.115
141.270
139.505
132.589
132.315
128.718
128.267
127.516
127.135
125.321
122.529
119.440
110.391
57.161
41.678
(S)-27
(13C, 100 MHz, CDCl3)
200
180
160
140
120
100
80
60
40
20
0


7.316
7.296
7.256
7.240
7.237
7.223
7.203
7.194
7.178
7.176
7.164
7.055
7.037
7.018
6.827
6.808
5.371
5.353
5.346
5.335
5.328
5.310
5.303
5.293
5.285
5.267
4.974
4.932
4.854
4.828
3.128
2.965
2.947
(S)-28
(1H, 400 MHz, CDCl3)
5.21
0.975
1.01
3
1.96
0.996
0.983
0.998
2.01


178.093
143.963
139.622
132.546
131.791
128.655
128.339
127.462
127.167
125.307
122.576
119.286
108.326
56.523
42.117
26.485
(S)-28
(13C, 100 MHz, CDCl3)


7.303
7.294
7.290
7.289
7.143
7.140
7.123
7.121
7.105
7.101
6.929
6.927
6.910
6.908
6.689
6.687
6.680
6.670
6.668
6.662
6.652
6.650
6.644
6.497
6.477
4.517
3.004
2.916
2.911
2.904
2.897
2.889
2.884
2.876
2.764
2.751
2.743
2.738
2.733
2.724
2.550
2.320
2.312
2.302
2.295
2.286
2.278
(3aS, 8aS)-29
(1H, 400 MHz, CDCl3)
1.37
1.07
1.11
5.08
1.17
1.14
1
3.3
1.96
0.98
1.07
3.18


152.336
146.884
135.158
128.466
128.139
126.642
126.266
124.610
117.752
106.718
98.349
61.508
53.518
39.946
38.638
36.023
(3aS, 8aS)-29
(13C, 100 MHz, CDCl3)