Supplementary Material (ESI) for Chemical Communications

Supplementary Information

Catalytic Asymmetric Synthesis of 1,1-Disubstituted Tetrahydro-β-carbolines by Phase-Transfer Catalyzed Alkylations

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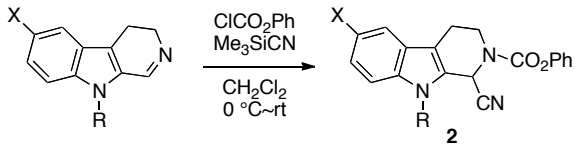
General Information:

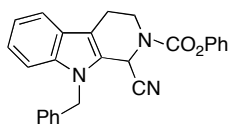
Infrared (IR) spectra were recorded on a Shimadzu IRPrestige-21 spectrometer. ^{1}H NMR spectra were measured on JEOL JNM-FX400 or JMTC-500 (400 MHz or 500 MHz) spectrometers. Data were reported as follows: chemical shifts in ppm from tetramethylsilane as an internal standard in $CDCl_3$, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (Hz). ^{13}C NMR spectra were measured on JEOL JNM-FX400 or JMTC-500 (100 MHz or 125 MHz) spectrometers with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments at 220 nm using 4.6 mm × 25 cm Daicel Chiralpak IA, IC and AD-H. High-resolution mass spectra (HRMS) were performed on Brucker microTOF. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm) were used. The products were purified by flash column chromatography on silica gel (silica gel 60; Merck 230-400 mesh or silica gel 60N; Kanto Chemical Co. Inc. spherical, neutral), or preparative thin layer chromatography on silica gel (PLC 60 F254. 0.5 mm). In experiments requiring dry solvent, CH_2Cl_2, toluene, and THF were purchased from Kanto Chemical Co. Inc. as "Dehydrated" and further purified by passing through neutral alumina under nitrogen atmosphere. Commercially obtained reagents were used as received.

Experimental Section:

General procedure for the synthesis of 1-cyanotetrahydro-β-carbolines 2.[1]

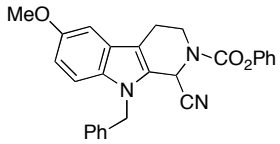


To a solution of cyclic imine (4.0 mmol) in dry CH_2Cl_2 (30 mL) was added phenyl chloroformate (4.4 mmol) at 0 °C under argon atmosphere. After stirring for 10 min, trimethylsilyl cyanide (4.0 mmol) was added to the reaction mixture at 0 °C. The reaction temperature was gradually warmed to room temperature, and the mixture was stirred overnight. Then, the reaction mixture was quenched by H_2O. The resulting mixture was stirred for additional 1 h, and extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4, and concentrated. The residue was purified by chromatography on silica gel (CH_2Cl_2/hexane = 1:1 as eluent) to afford the target product (62%~75% yields).

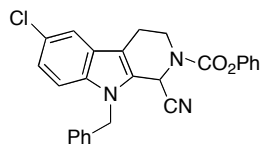


2a: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.71–7.58 (m, 14H), 6.03 (d, J = 30.2 Hz, 1H), 5.40–5.52 (m, 1H), 5.26 (d, J = 16.9 Hz, 1H), 4.55–4.76 (m, 1H), 3.35–3.61 (m, 1H), 2.88–3.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 153.5, 152.5, 150.7, 150.4, 137.7, 137.5, 136.2, 136.0, 129.4, 129.3, 129.0, 128.0, 126.3, 126.0, 125.8, 124.7, 124.2, 123.5, 123.4, 121.6, 121.4, 120.2, 120.1, 119.1, 118.9, 115.6, 115.2, 111.2, 110.6, 110.0, 109.8, 47.1, 43.0, 42.6, 40.9,

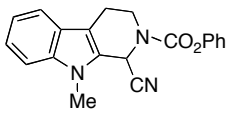
40.2, 21.1, 20.4; IR (neat) 2924, 1718, 1593, 1454, 1406, 1236, 1199, 1182; HRMS (ESI) exact mass calcd. for $C_{26}H_{21}N_3O_2$: Exact Mass: *m*/*z* 430.1526 ([M+Na]$^+$); found: *m*/*z* 430.1513 ([M+Na]$^+$).



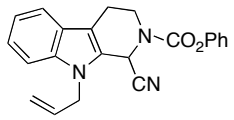
2b: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33–7.38 (m, 2H), 7.17–7.30 (m, 5H), 7.12–7.14 (m, 1H), 7.06–7.07 (m, 2H), 7.00–7.02 (m, 2H), 6.90–6.93 (m, 1H), 6.02 (d, *J* = 35.7 Hz, 1H), 5.46 (dd, *J* = 32.0, 17.0 Hz, 1H), 5.28 (d, *J* = 17.0 Hz, 1H), 4.64–4.72 (m, 1H), 3.86 (s, 3H), 3.40–3.61 (m, 1H), 2.87–3.09 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.5, 153.5, 152.4, 150.8, 150.4, 136.3, 136.1, 132.9, 132.7, 129.5, 129.4, 129.0, 128.0, 126.3, 126.2, 126.0, 125.2, 124.7, 121.4, 115.7, 115.6, 113.7, 113.5, 110.9, 110.7, 110.1, 100.7, 55.9, 47.4, 47.3, 43.1, 42.7, 41.1, 40.3, 21.2, 20.6; IR (neat) 2926, 1718, 1487, 1406, 1263, 1201; HRMS (ESI) exact mass calcd. for $C_{27}H_{23}N_3O_3$: Exact Mass: *m*/*z* 460.1632 ([M+Na]$^+$); found: *m*/*z* 460.1642 ([M+Na]$^+$).



2c: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.31–7.36 (m, 2H), 7.20–7.27 (m, 6H), 7.11–7.12 (m, 1H), 7.00–7.04 (m, 3H), 6.01 (d, = 39.1 Hz, 1H), 5.45 (dd, *J* = 35.7, 17.0 Hz, 1H), 5.26 (d, *J* = 17.0 Hz, 1H), 4.63–4.71 (m, 1H), 3.37–3.56 (m, 1H), 2.82–3.05 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7, 153.5, 152.4, 150.5, 150.2, 135.9, 135.7, 135.6, 135.4, 129.4, 129.0, 128.1, 126.7, 126.6, 126.2, 126.0, 125.8, 125.5, 123.7, 123.6, 121.3, 120.2, 118.6, 118.4, 115.3, 115.2, 111.1, 110.9, 110.2, 47.3, 42.8, 42.5, 40.8, 40.1, 20.9, 20.2, IR (neat) 2922, 1714, 1593, 1498, 1409, 1238, 1199; HRMS (ESI) exact mass calcd. for $C_{26}H_{20}ClN_3O_2$: Exact Mass: *m*/*z* 464.1136 ([M+Na]$^+$); found: *m*/*z* 464.1124 ([M+Na]$^+$).



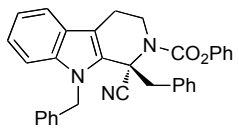
2d: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.56 (m, 1H), 7.15–7.42 (m, 8H), 6.27–6.30 (m, 1H), 4.69–4.75 (m, 1H), 3.76–3.80 (m, 3H), 3.37–3.59 (m, 1H), 2.89–3.08 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 152.7, 150.8, 150.6, 137.7, 137.6, 129.5, 126.2, 126.0, 125.7, 124.9, 124.2, 123.2, 123.1, 121.7, 121.5, 120.0, 119.9, 119.0, 118.8, 115.7, 115.2, 110.5, 109.8, 109.4, 43.0, 42.6, 41.1, 40.4, 29.8, 21.1, 20.6; IR (neat) 2928, 1718, 1593, 1492, 1406, 1236, 1192, 1083; HRMS (ESI) exact mass calcd. for $C_{20}H_{17}N_3O_2$: Exact Mass: *m*/*z* 354.1213 ([M+Na]$^+$); found: *m*/*z* 354.1218 ([M+Na]$^+$)



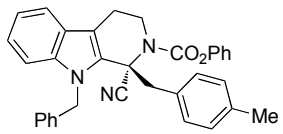
2e: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.9 Hz, 1H), 7.13–7.36 (m, 8H), 6.24–6.27 (m, 1H), 5.87–5.93 (m, 1H), 4.99–5.19 (m, 2H), 4.65–4.81 (m, 3H), 3.36–3.56 (m, 1H), 2.83–3.05 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 152.5, 150.7, 150.5, 137.1, 136.9, 132.3, 132.1, 129.3, 125.9, 125.8, 125.7, 124.6, 124.0, 123.2, 123.1, 121.5, 121.4, 120.0, 119.9, 118.9, 118.8, 117.6, 117.3, 115.7, 110.8, 110.1, 109.8, 45.8, 42.8, 42.5, 40.9, 40.2, 21.0, 20.4, IR (neat) 2924, 1718, 1492, 1406, 1236, 1201; HRMS (ESI) exact mass calcd. for $C_{22}H_{19}N_3O_2$: Exact Mass: *m*/*z* 380.1369 ([M+Na]$^+$); found: *m*/*z* 380.1359 ([M+Na]$^+$).

General procedure for the asymmetric alkylation of 1-cyanotetrahydro-β-carboline 2.

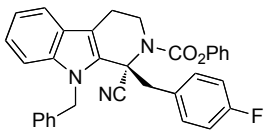
To a solution of 1-cyanotetrahydro-β-carboline **2** (0.050 mmol) and PTC (*S*,*S*)-**4b** (0.0010 mmol, 2 mol%) in 50% aqueous KOH (0.25 mL)-toluene (0.50 mL) was added alkyl halide (0.060 mmol) at 0 °C under argon atmosphere. The reaction mixture was vigorously stirred at 0 °C for 24 h and quenched with saturated aqueous NH_4Cl. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2. The combined extracts were washed with brine and dried over Na_2SO_4. After evaporation of solvents, the residue was purified by preparative thin layer chromatography (CH_2Cl_2/hexane as eluent) to afford the alkylation product. The enantiomeric excess of the product was determined by chiral HPLC analysis.



3a: $[\alpha]^{21}_{D}$ = –63.9 (*c* = 1.01, $CHCl_3$; 94% ee), HPLC analysis: Daicel Chiralpak AD-H, hexane/2-propanol = 20:1, flow rate = 1.0 mL/min, 220 nm; retention time: 38.3 min (major) and 50.0 min (minor). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.9 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 2H), 7.19–7.32 (m, 12H), 7.10 (t, *J* = 7.4 Hz, 2H), 6.65 (d, *J* = 6.2 Hz, 2H), 5.88 (d, *J* = 17.8 Hz, 1H), 5.74 (d, *J* = 17.8 Hz, 1H), 4.18–4.31 (br, 1H), 3.78–3.84 (br, 1H), 3.25–3.33 (m, 2H), 2.73–2.78 (m, 1H), 2.12–2.17 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 150.7, 138.9, 136.8, 132.8, 130.3, 129.5, 128.9, 128.1, 127.8, 127.7, 127.2, 126.3, 125.9, 125.0, 123.9, 121.8, 120.4, 119.0, 118.2, 114.0, 110.9, 55.7, 48.3, 42.5, 42.3, 20.2; IR (neat) 3032, 2924, 1720, 1593, 1494, 1454, 1367, 1193, 1168; HRMS (ESI) exact mass calcd. for $C_{33}H_{27}N_3O_2$: Exact Mass: *m*/*z* 520.1995 ([M+Na]$^+$); found: *m*/*z* 520.2011 ([M+Na]$^+$).

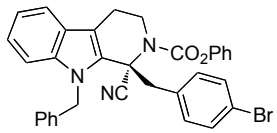


3b: $[\alpha]^{21}_{D}$ = –62.8 (*c* = 1.49, $CHCl_3$; 92% ee), HPLC analysis: Daicel Chiralpak IC, hexane/2-propanol = 5:1, flow rate = 1.0 mL/min, 220 nm; retention time: 19.2 min (minor) and 42.2 min (major). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 2H), 7.18-7.31 (m, 11H), 6.91 (d, *J* = 7.9 Hz, 2H), 6.53 (d, *J* = 6.2 Hz, 2H), 5.88 (d, *J* = 17.6 Hz, 1H), 5.73 (d, *J* = 17.6 Hz, 1H), 4.09–4.26 (br, 1H), 3.78–3.91 (br, 1H), 3.19–3.28 (m, 2H), 2.73–2.78 (m, 1H), 2.26 (s, 3H), 2.17–2.22 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 150.7, 138.9, 137.5, 136.8, 130.2, 129.7, 129.5, 128.9, 127.6, 127.3, 126.2, 125.9, 125.1, 123.8, 121.8, 120.3, 119.0, 118.2, 113.9, 110.9, 55.7, 48.3, 42.4, 41.9, 21.1, 20.2; IR (neat) 3032, 2922, 1722, 1593, 1494, 1452, 1369, 1195, 1165; HRMS (ESI) exact mass calcd. for $C_{34}H_{29}N_3O_2$: Exact Mass: *m*/*z* 534.2152 ([M+Na]$^+$); found: *m*/*z* 534.2150 ([M+Na]$^+$).

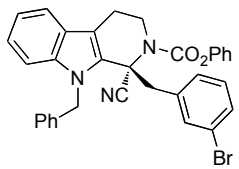


3c: $[\alpha]^{20}_{D}$ = –84.5 (*c* = 0.93, $CHCl_3$; 95% ee), HPLC analysis: Daicel Chiralpak IC, hexane/2-propanol = 3:1, flow rate = 1.0 mL/min, 220 nm; retention time: 11.2 min (minor) and 23.2 min (major). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.9 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.17–7.31 (m, 11H), 6.78 (t, *J* = 8.5 Hz, 2H), 6.53–6.59 (m, 2H), 5.86 (d, *J* = 18.1 Hz, 1H), 5.74 (d, *J* = 17.6 Hz, 1H), 4.19–4.31 (br, 1H), 3.73–3.81 (br, 1H), 3.39–3.53 (br, 1H), 3.23 (d, *J* =13.6 Hz, 1H), 2.74–2.79 (m, 1H), 2.10–2.16 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$)

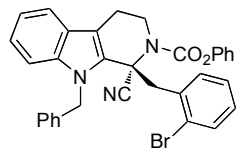
δ 163.4, 161.4, 153.7, 150.6, 138.8, 136.7, 131.8, 131.7, 129.5, 128.9, 128.5, 127.7, 126.8, 126.2, 126.0, 124.9, 124.0, 121.7, 120.5, 119.1, 117.9, 115.1, 114.9, 114.2, 110.9, 55.6, 48.3, 42.5, 41.7, 20.2; IR (neat) 3034, 2929, 1720, 1600, 1508, 1452, 1365, 1192, 1161; HRMS (ESI) exact mass calcd. for $C_{33}H_{26}FN_3O_2$: Exact Mass: *m/z* 538.1901 ([M+Na]$^+$); found: *m/z* 538.1913 ([M+Na]$^+$).



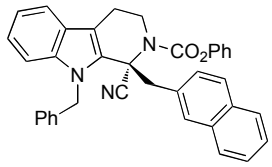
3d: $[\alpha]^{23}_D$ = –98.9 (*c* = 1.02, $CHCl_3$; 96% ee), HPLC analysis: Daicel Chiralpak IA, hexane/2-propanol = 3:1, flow rate = 1.0 mL/min, 220 nm; retention time: 9.5 min (major) and 13.0 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J*= 7.9, 0.8 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 2H), 7.17-7.33 (m, 13H), 6.46 (d, *J* = 8.0 Hz, 2H), 5.87 (d, *J* = 17.6 Hz, 1H), 5.74 (d, *J* = 17.6 Hz, 1H), 4.18–4.27 (br, 1H), 3.73–3.80 (br, 1H), 3.44–3.56 (br, 1H), 3.21(d, *J* =13.5 Hz, 1H), 2.74–2.81 (m, 1H), 2.13–2.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 150.6, 138.9, 136.7, 131.9, 131.8, 131.2, 129.5, 128.9, 127.8, 126.8, 126.2, 126.0, 124.9, 124.1, 122.0, 121.7, 120.6, 119.2, 117.9, 114.3, 110.9, 55.4, 48.3, 42.6, 42.0, 20.2; IR (neat) 3032, 2924, 1722, 1593, 1487, 1452, 1234, 1193, 1163; HRMS (ESI) exact mass calcd. for $C_{33}H_{26}BrN_3O_2$: Exact Mass: *m/z* 598.1101 ([M+Na]$^+$); found: *m/z* 598.1101 ([M+Na]$^+$).



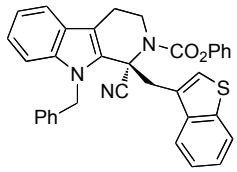
3e: $[\alpha]^{24}_D$ = –100.2 (*c* = 0.99, $CHCl_3$; 94% ee), HPLC analysis: Daicel Chiralpak IC, hexane/2-propanol = 3:1, flow rate = 1.0 mL/min, 220 nm; retention time: 11.4 min (minor) and 24.8 min (major). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.9 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 2H), 7.16–7.34 (m, 12H), 6.87–6.93 (m, 2H), 6.31–6.43 (br, 1H), 5.86 (d, *J* = 18.1 Hz, 1H), 5.75 (d, *J* = 17.6 Hz, 1H), 4.18–4.31 (br, 1H), 3.73–3.79 (br, 1H), 3.49–3.57 (br, 1H), 3.21 (d, *J* =13.0 Hz, 1H), 2.75–2.80 (m, 1H), 2.11–2.17 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 150.6, 138.9, 136.7, 135.1, 133.4, 130.8, 129.5, 129.4, 128.9, 128.6, 127.7, 126.6, 126.2, 126.0, 124.9, 124.1, 122.1, 121.9, 120.5, 119.2, 117.8, 114.4, 110.9, 55.5, 48.2, 42.6, 42.0, 20.3; IR (neat) 3061, 2927, 1722, 1593, 1452, 1367, 1234, 1194, 1163; HRMS (ESI) exact mass calcd. for $C_{33}H_{26}BrN_3O_2$: Exact Mass: *m/z* 598.1101 ([M+Na]$^+$); found: *m/z* 598.1092 ([M+Na]$^+$)



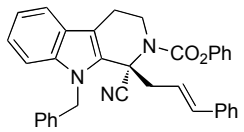
3f: $[\alpha]^{26}_D$ = –29.5 (*c* = 0.93, $CHCl_3$; 90% ee), HPLC analysis: Daicel Chiralpak IC, hexane/2-propanol = 3:1, flow rate = 1.0 mL/min, 220 nm; retention time: 18.6 min (minor) and 40.7 min (major). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.9 Hz, 1H), 7.45–7.48 (m, 1H), 7.34 (t, *J* =7.6 Hz, 2H), 7.06–7.29 (m, 13H), 6.93–6.96 (m, 1H), 5.77 (s, 2H), 4.21–4.32 (br, 1H), 4.11–4.15 (m, 1H), 3.62 (d, *J* =14.2 Hz, 1H), 3.44–3.51 (br, 1H), 2.89–2.95 (m, 1H), 2.47–2.51 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 150.6, 138.4, 136.7, 133.4, 133.1, 132.6, 129.4, 129.3, 128.8, 127.7, 127.5, 127.1, 126.2, 125.7, 125.6, 125.2, 123.8, 121.7, 120.3, 119.0, 117.3, 112.9, 111.0, 56.1, 48.4, 42.6, 42.3, 20.6; IR (neat) 3061, 2924, 1724, 1494, 1454, 1384, 1234, 1195, 1163; HRMS (ESI) exact mass calcd. for $C_{33}H_{26}BrN_3O_2$: Exact Mass: *m/z* 598.1101 ([M+Na]$^+$); found: *m/z* 598.1093 ([M+Na]$^+$).



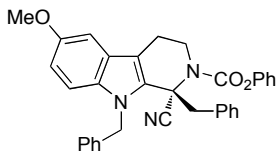
3g: $[\alpha]^{29}_{D}$ = –92.4 (*c* = 0.99, $CHCl_3$; 93% ee) HPLC analysis: Daicel Chiralpak IC, hexane/2-propanol = 3:1, flow rate = 1.0 mL/min, 220 nm; retention time: 12.9 min (minor) and 34.8 min (major)). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 1H), 7.50–7.55 (m, 3H), 7.39–7.43 (m, 4H), 7.15–7.33 (m, 12H), 6.59–6.70 (br, 1H), 5.92 (d, *J* = 18.1 Hz, 1H), 5.80 (d, *J* = 17.6 Hz, 1H), 4.36–4.50 (br, 1H), 3.70–3.82 (br, 1H), 3.47 (d, *J* =13.2 Hz, 1H), 3.21–3.33 (br, 1H), 2.67–2.72 (m, 1H), 2.03–2.08 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 150.7, 138.9, 136.8, 133.0, 132.6, 130.3, 129.7, 129.5, 128.9, 127.8, 127.7, 127.6, 127.5, 127.2, 126.3, 126.2, 126.1, 126.0, 125.1, 123.9, 121.8, 120.4, 119.1, 118.2, 114.2, 110.9, 55.7, 48.4, 42.7, 42.5, 20.3; IR (neat) 3057, 2929, 1720, 1593, 1494, 1452, 1371, 1193, 1163; HRMS (ESI) exact mass calcd. for $C_{37}H_{29}N_3O_2$: Exact Mass: *m*/*z* 570.2152 ([M+Na]$^+$); found: *m*/*z* 570.2155 ([M+Na]$^+$).



3h: $[\alpha]^{28}_{D}$ = –95.0 (c = 1.65, $CHCl_3$; 95% ee), HPLC analysis: Daicel Chiralpak IC, hexane/2-propanol = 3:1, flow rate = 1.0 mL/min, 220 nm; retention time: 14.6 min (minor) and 37.6 min (major). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.9 Hz, 1H), 7.53 (d, *J* = 7.9 Hz, 2H), 7.39 (t, *J* = 7.9 Hz, 2H), 7.18-7.32 (m, 11H), 7.07 (d, *J* = 7.9 Hz, 2H), 6.25–6.32 (br, 1H), 5.86 (d, *J* = 17.6 Hz, 1H), 5.77 (d, *J* = 17.6 Hz, 1H), 4.59 (d, *J* = 13.6 Hz, 1H), 3.76–3.78 (m, 1H), 3.47 (d, *J* =14.2 Hz, 1H), 3.17–3.24 (m, 1H), 2.75–2.81 (m, 1H), 2.21–2.26 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7, 150.6, 139.5, 139.4, 138.9, 136.8, 129.3, 128.9, 127.8, 127.7, 127.4, 126.3, 126.1, 126.0, 125.1, 124.3, 124.2, 124.0, 122.6, 121.8, 121.6, 120.5, 119.1, 117.8, 114.1, 110.9, 55.8, 48.4, 42.4, 35.3, 20.3; IR (neat) 3059, 2929, 1718, 1591, 1494, 1462, 1361, 1193, 1163; HRMS (ESI) exact mass calcd. for $C_{35}H_{27}N_3O_2S$: Exact Mass: *m*/*z* 576.1716 ([M+Na]$^+$); found: *m*/*z* 576.1700 ([M+Na]$^+$).

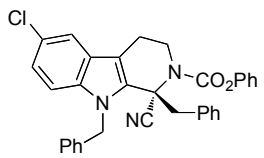


3i: $[\alpha]^{28}_{D}$ = –51.3 (*c* = 1.0, $CHCl_3$; 60% ee), HPLC analysis: Daicel Chiralpak AD-H, hexane/2-propanol = 20:1, flow rate = 1.0 mL/min, 220 nm; retention time: 21.4 min (major) and 45.2 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.5 Hz, 1H), 7.06–7.42 (m, 18H), 6.23 (d, *J* = 15.7 Hz, 1H), 5.86 (d, *J* = 17.9 Hz, 1H), 5.65–5.75 (m, 2H), 4.12–4.16 (m, 1H), 4.01–4.03 (m, 1H), 3.80–3.86 (m, 1H), 2.89–3.01 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 150.7, 138.7, 136.7, 136.5, 135.6, 129.6, 129.5, 128.9, 128.6, 127.9, 127.6, 127.4, 126.2, 125.9, 125.8, 125.1, 123.9, 121.7, 120.7, 120.6, 120.5, 119.1, 118.1, 115.3, 113.1, 110.8, 55.2, 48.0, 43.2, 41.2, 20.9; IR (neat) 3030, 2927, 1724, 1593, 1494, 1462, 1363, 1194, 1163; HRMS (ESI) exact mass calcd. for $C_{35}H_{29}N_3O_2$: Exact Mass: *m*/*z* 562.1891 ([M+K]$^+$); found: *m*/*z* 562.1876 ([M+K]$^+$).

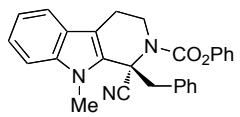


6a: $[\alpha]^{28}_{D}$= –74.2 (*c* = 1.0, $CHCl_3$; 92% ee), HPLC analysis: Daicel Chiralpak AD-H, hexane/2-propanol = 20:1, flow rate = 1.0 mL/min, 220 nm; retention time: 43.7min (major) and 44.8 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (t, *J* =7.7 Hz, 2H), 7.10–7.32 (12H, m), 6.90–6.95 (m, 2H), 6.66 (d, *J* = 7.0 Hz, 2H), 5.83 (d, *J* = 17.6

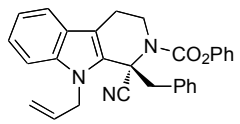
Hz, 1H), 5.70 (d, J = 17.6 Hz, 1H), 4.14–4.30 (br, 1H), 3.87 (s, 3H), 3.70–3.86 (br, 1H), 3.24–3.33 (m, 2H), 2.68–2.74 (m, 1H), 2.08–2.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 153.7, 150.7, 136.9, 133.9, 132.8, 130.4, 129.5, 128.9, 128.1, 127.7, 127.6, 126.2, 125.9, 125.4, 118.1, 115.3, 113.9, 113.5, 111.8, 100.6, 55.8, 55.7, 48.4, 42.5, 42.1, 20.2; IR (neat) 3030, 2929, 1722, 1593, 1367, 1232, 1193, 1161; HRMS (ESI) exact mass calcd. for $C_{34}H_{29}N_3O_3$: Exact Mass: m/z 550.2101 ([M+Na]$^+$); found: m/z 550.2102 ([M+Na]$^+$).



6b: $[\alpha]^{28}_D$ = –93.4 (c = 1.0, $CHCl_3$; 96% ee), HPLC analysis: Daicel Chiralpak AD-H, hexane/2-propanol = 20:1, flow rate = 1.0 mL/min, 220 nm; retention time: 41.6min (major) and 45.8 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.51 (m, 3H), 7.10–7.33 (m, 13H), 6.62 (d, J = 7.3 Hz, 2H), 5.83 (d, J = 17.6 Hz, 1H), 5.73 (d, J = 17.4 Hz, 1H), 4.19–4.31 (br, 1H), 3.72–3.81 (br, 1H), 3.27–3.36 (m, 2H), 2.66–2.73 (m, 1H), 2.02–2.09 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 150.7, 138.7, 131.9, 131.7, 131.3, 129.6, 126.5, 126.1, 124.6, 123.6, 122.0, 121.7, 120.3, 119.1, 117.9, 113.5, 109.7, 55.4, 42.8, 41.9, 31.9, 20.1; IR (neat) 3030, 2920, 1720, 1593, 1365, 1234, 1193, 1163; HRMS (ESI) exact mass calcd. for $C_{33}H_{26}ClN_3O_2$: Exact Mass: m/z 554.1606 ([M+Na]$^+$); found: m/z 554.1594 ([M+Na]$^+$).



6c: $[\alpha]^{24}_D$ = +7.2 (c = 1.0, $CHCl_3$; 92% ee), HPLC analysis: Daicel Chiralpak AD-H, hexane/2-propanol = 20:1, flow rate = 1.0 mL/min, 220 nm; retention time: 27.8 min (major) and 43.1 min (minor). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17-7.48 (m, 12H), 6.58–6.65 (br, 2H), 4.37–4.45 (br, 1H), 4.09 (s, 3H), 3.74–3.81 (br, 1H), 3.51–3.55 (m, 1H), 3.20–3.33 (br, 1H), 2.67–2.70 (m, 1H), 2.07–2.10 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 150.7, 138.6, 132.7, 130.3, 129.6, 129.5, 128.2, 127.8, 125.9, 124.8, 123.4, 121.8, 120.0, 119.0, 118.1, 113.2, 109.6, 55.7, 42.6, 42.2, 31.8, 20.0; IR (neat) 3061, 2924, 1720, 1593, 1494, 1462, 1371, 1195, 1163; HRMS (ESI) exact mass calcd. for $C_{27}H_{23}N_3O_2$: Exact Mass: m/z 444.1682 ([M+Na]$^+$); found: m/z 444.1672 ([M+Na]$^+$).

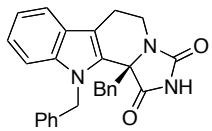


6d: $[\alpha]^{24}_D$ = –31.8 (c = 1.0, $CHCl_3$; 94% ee), HPLC analysis: Daicel Chiralpak AD-H, hexane/2-propanol = 20:1, flow rate = 1.0 mL/min, 220 nm; retention time: 28.9min (major) and 48.2 min (minor). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11–7.49 (m, 12H), 6.63–6.75 (br, 2H), 6.08–6.16 (1H, m), 5.05–5.33 (m, 4H), 4.32–4.47 (br, 1H), 3.72–3.84 (br, 1H), 3.49–3.55 (m, 1), 3.22–3.32 (br, 1H), 2.67-2.72 (m, 1H), 2.07–2.13 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 150.7, 138.3, 132.8, 130.3, 129.5, 128.1, 127.8, 126.7, 125.9, 125.0, 123.6, 121.8, 120.2, 119.0, 118.2, 117.9, 113.6, 100.9, 55.5, 47.3, 42.5, 42.4, 20.0; IR (neat) 3062, 2929 1718, 1593, 1363, 1317, 1232, 1194, 1163; HRMS (ESI) exact mass calcd. for $C_{29}H_{25}N_3O_2$: Exact Mass: m/z 470.1839 ([M+Na]$^+$); found: m/z 470.1828 ([M+Na]$^+$).

Transformation of the alkylation product.

To a solution of the alkylation product **3a** (0.020 mmol, 94% ee) in MeOH (0.30 mL) was

added a mixture of $LiOH{\cdot}H_2O$ (0.20 mmol) and 30% aqueous H_2O_2 (23 μL) in H_2O (0.15 mL) at 0 °C. The reaction mixture was stirred at room temperature overnight, and then quenched with saturated aqueous Na_2SO_3. The organic materials were extracted with CH_2Cl_2, and the extracts were dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by preparative thin layer chromatography (CH_2Cl_2 as eluent) to afford the product **7** in 98% yield (94% ee).



7: $[\alpha]^{28}_{D}$ = +20.6 (*c* = 1.0, $CHCl_3$; 94% ee), HPLC analysis: Daicel Chiralpak AD-H, hexane/2-propanol = 3:1, flow rate = 1.0 mL/min, 220 nm; retention time: 13.2 min (major) and 19.0 min (minor). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.69 (br, 1H), 7.53–7.56 (m, 1H), 7.11–7.27 (m, 9H), 7.05 (dd, *J*= 7.4, 2.1 Hz, 2H), 6.97 (d, *J* = 7.3 Hz, 2H), 6.53 (d, *J* = 17.9 Hz, 1H), 5.73 (d, *J* = 17.9 Hz, 1H), 4.47 (dd, *J* = 13.3, 5.8 Hz, 1H), 3.43 (d, *J* = 14.3 Hz, 1H), 3.18–3.26 (m, 1H), 3.01–3.10 (m, 2H), 2.88–2.93 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 154.8, 138.2, 137.9, 133.2, 130.1, 129.8, 128.7, 128.4, 127.5, 127.1, 126.0, 125.6, 123.3, 120.0, 118.7, 110.8, 110.5, 68.3, 48.6, 42.0, 35.7, 21.3; IR (neat) 3061, 3030, 2924, 1768, 1712, 1409, 1350, 1267, 1195, 1114; HRMS (ESI) exact mass calcd. for $C_{27}H_{23}N_3O_2$: Exact Mass: *m/z* 444.1682 ($[M+Na]^+$); found: *m/z* 444.1696 ($[M+Na]^+$).

Determination of Absolute Configuration

The alkykation product **3d** was recrystallized from hexane/AcOEt. The single crystal was mounted on a MicroMeshTM (MiTeGen). Data of X-ray diffraction were collected by a Rigaku RAXIS-RAPID Imaging Plate two-dimensional area detector using graphite-monochromated CuKa (l = 1.54187 Å) to a maximam 2*θ* value of 136.5°. The crystal structure was solved by the direct methods and refined by the full-matrix least squares using the program SHELXL-97.[2] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined by using the riding model. The absolute configuration was determined by reference to the Flack parameter[3] –0.01(3).

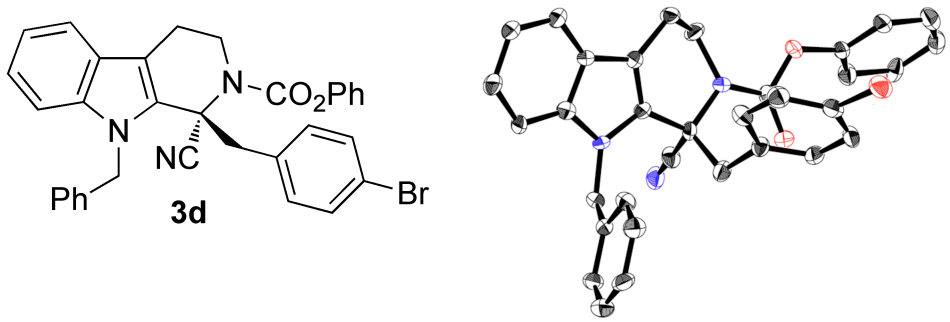
The crystallographic data were summarized in the following table.

empirical formula	$C_{33}H_{26}BrN_3O_2$
formula weight	576.49
crystal system	monoclinic
space group	$P2_1$ (#4)
a, Å	10.73100(19)
b, Å	21.0995(4)
c, Å	11.9876(3)
β	91.2195(11)°
V , Å^3	2713.60(9)
Z	4
*D*calc, g/cm^3	1.411
T, °C	–150
μ (CuKα), cm^{-1}	23.472

no. of reflns meased	27742
no. of reflns obsd	9568
no. of reflns variable	704
R_1 (I >2σ(I))	0.0686
R (All reflections)	0.1212
Rw (All reflections)	0.2107
Goodness of Fit	1.111
Flack Parameter (Friedel pairs = 4467)	–0.01(3)

The crystal structure has been deposited at the Cambridge Crystallographic Data Centre (CCDC 787177). The data can be obtained free of charge via the Internet at www.ccdc.cam.ac.uk/data_request/cif.

ORTEP view of the alkykation product **3d** with thermal ellipsoids drawn at the 30% probability level (hydrogen atoms are omitted for clarity).



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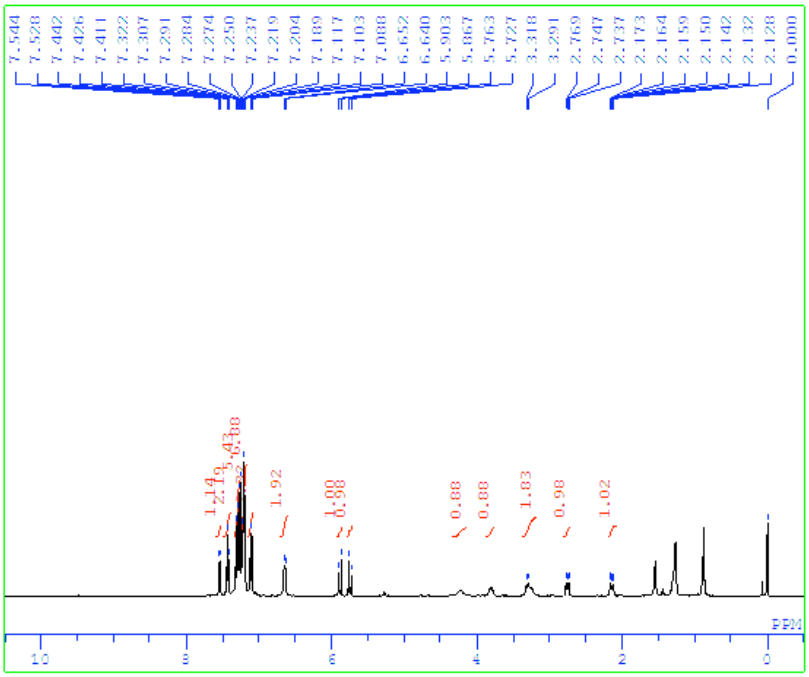
1 (a) Y. Liu, S. Luo, X. Fu, F. Fang, Z. Zhuang, W. Xiong, X. Jia and H. Zhai, *Org. Lett.*, 2006, **8**, 115; (b) H. W. Gibson, M. A. G. Berg, J. Clifton Dickson, P. R. Lecavalier, H. Wang and J. S. Merola, *J. Org. Chem.*, 2007, **72**, 5759; (c) Z. Chen, G. Hu, D. Li, J. Chen, Y. Li, H. Zhou and Y. Xie, *Bioorg. Med. Chem.*, 2009, **17**, 2351.

2 G. M. Sheldrick, SHELX-97: Program for Crystal Structure Refinement, University of Gottingen, Germany, 1997.

3 H. D. Flack, *Acta Cryst.*, 1983, **A39**, 876.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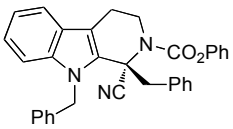
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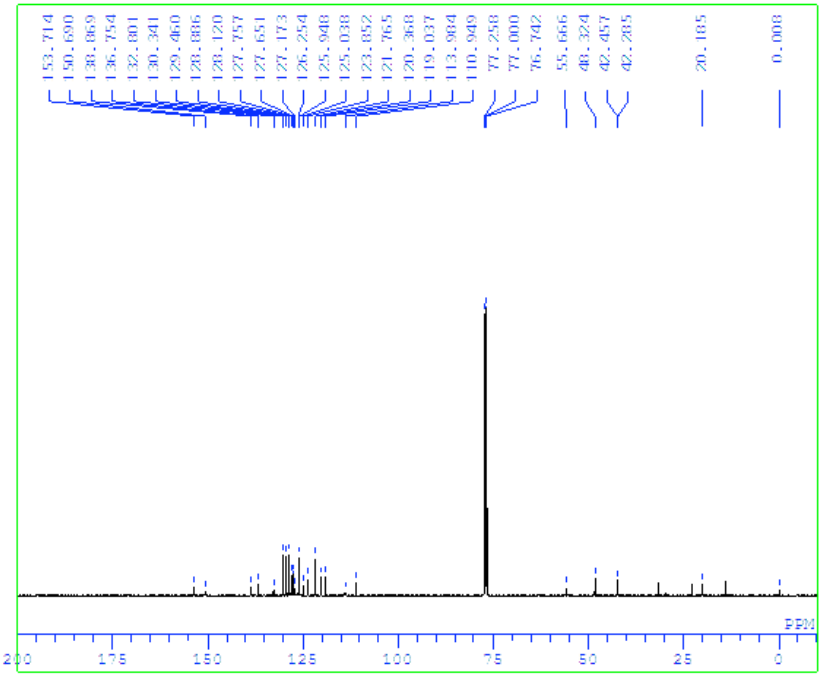
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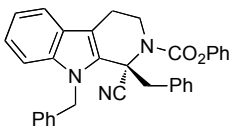
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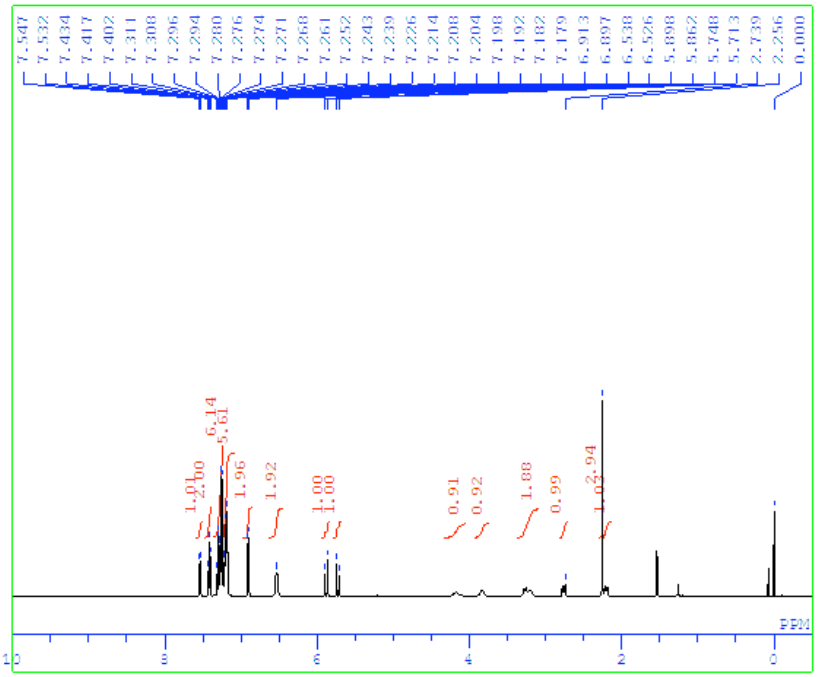
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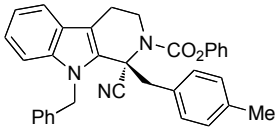
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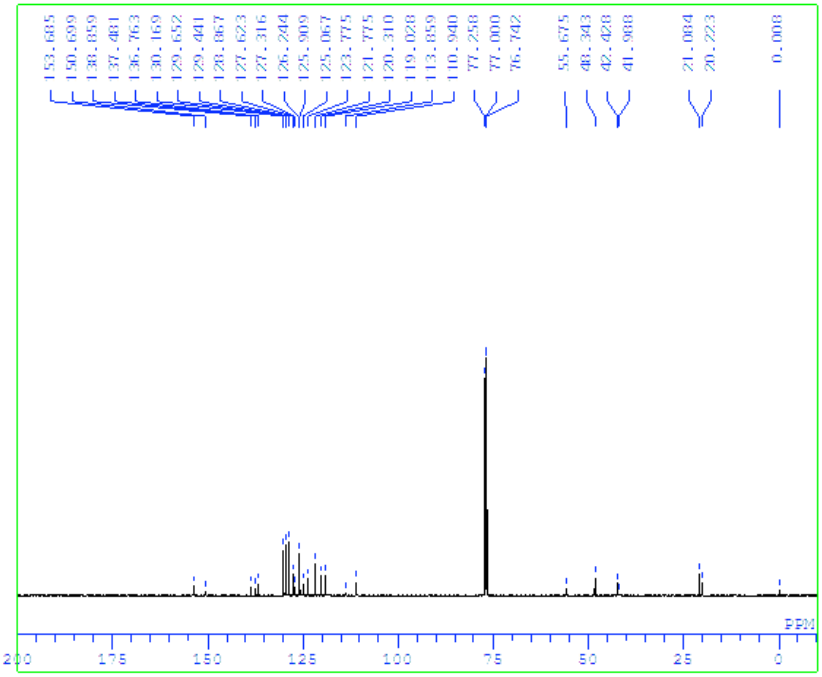
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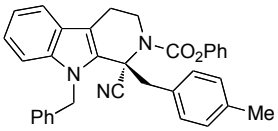
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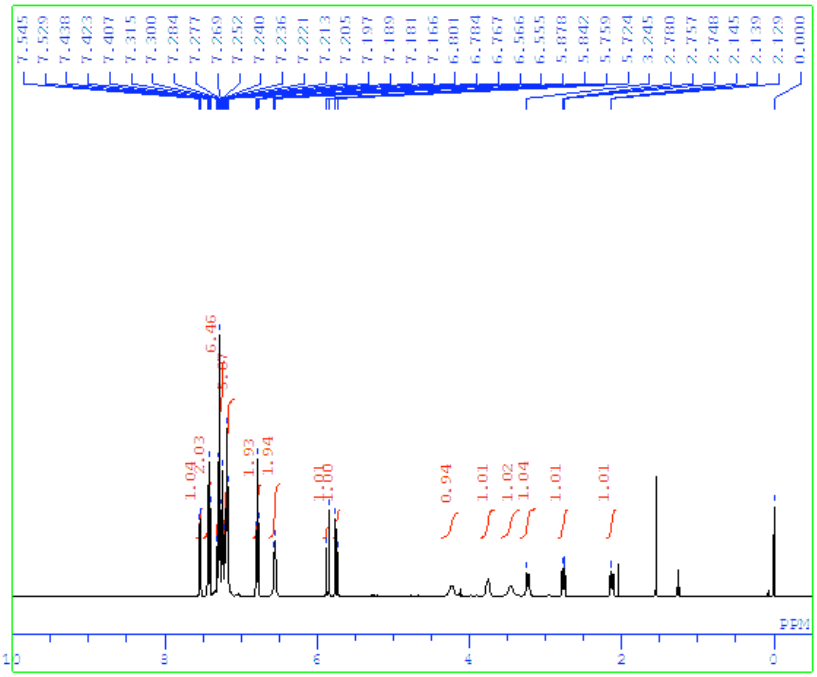
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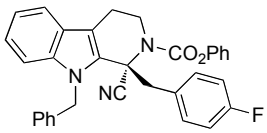
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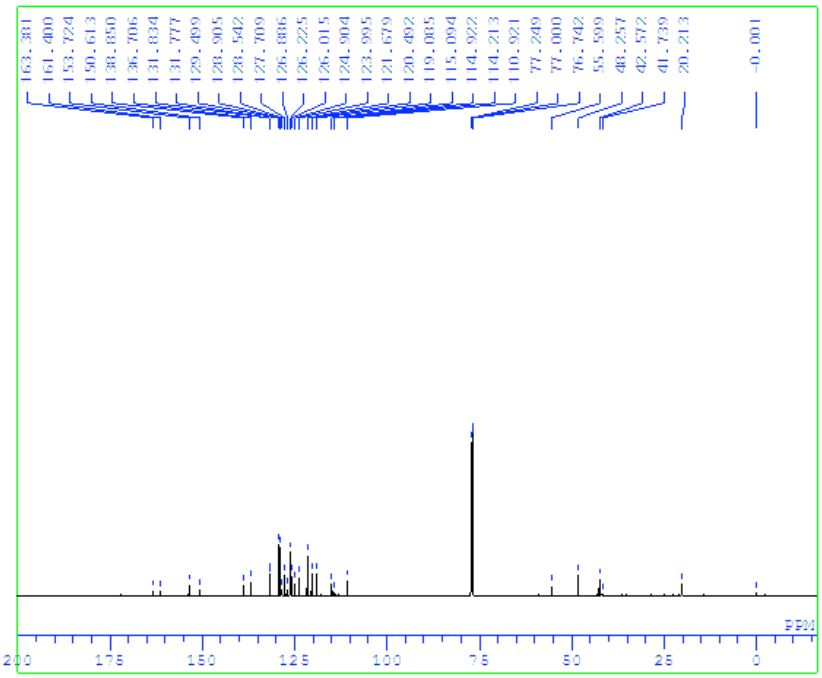
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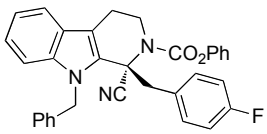
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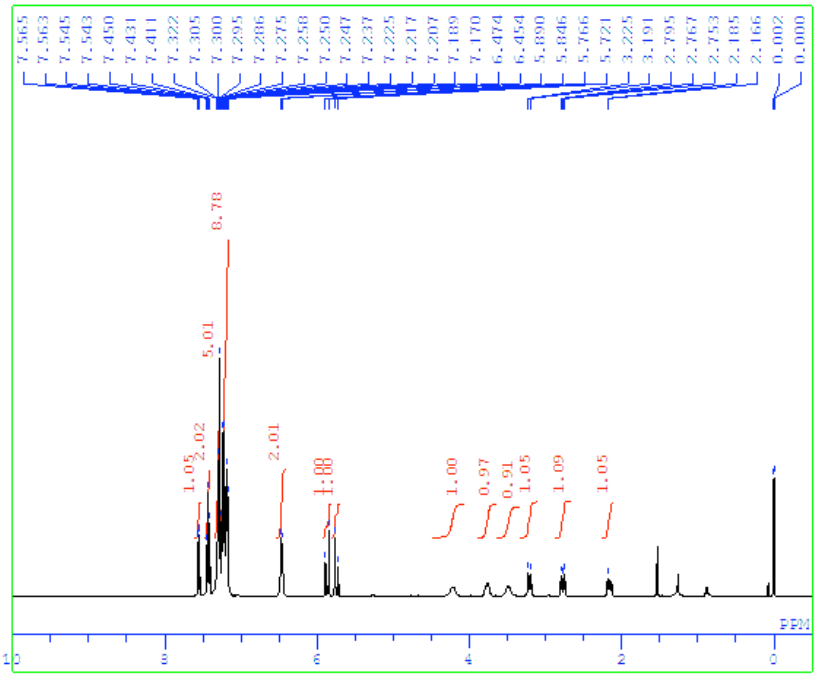
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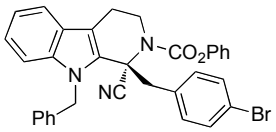
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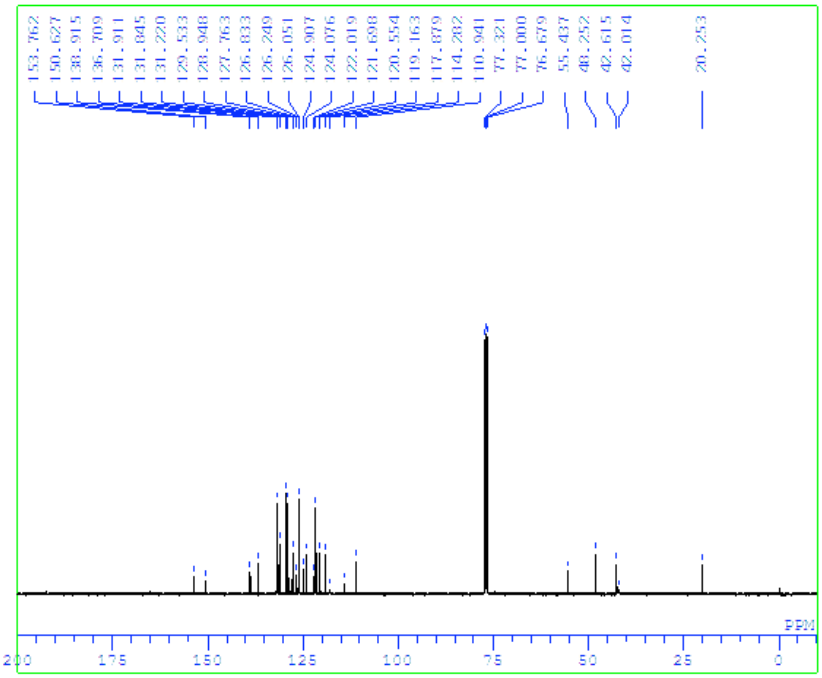
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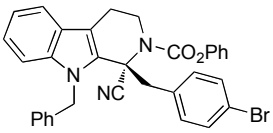
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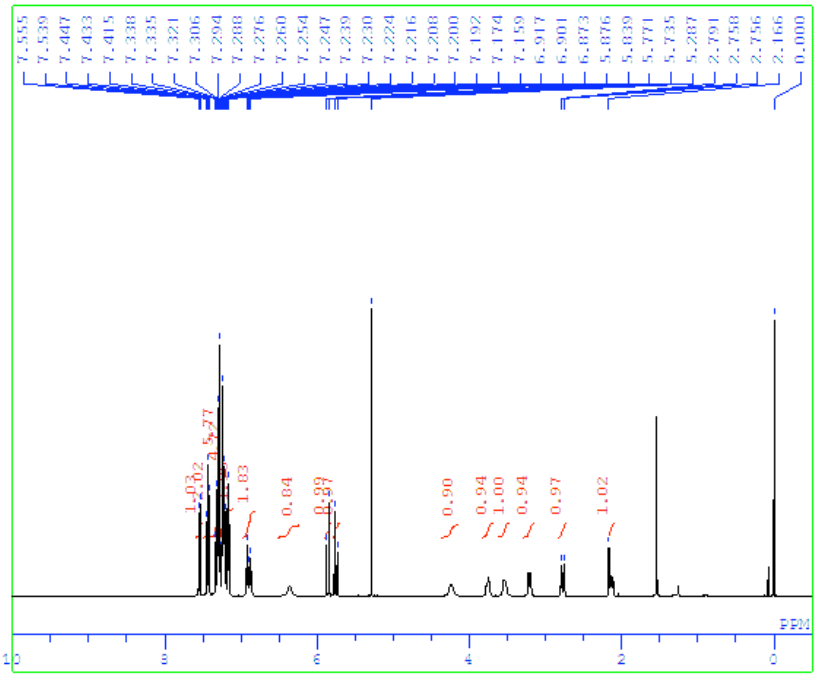
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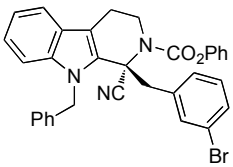
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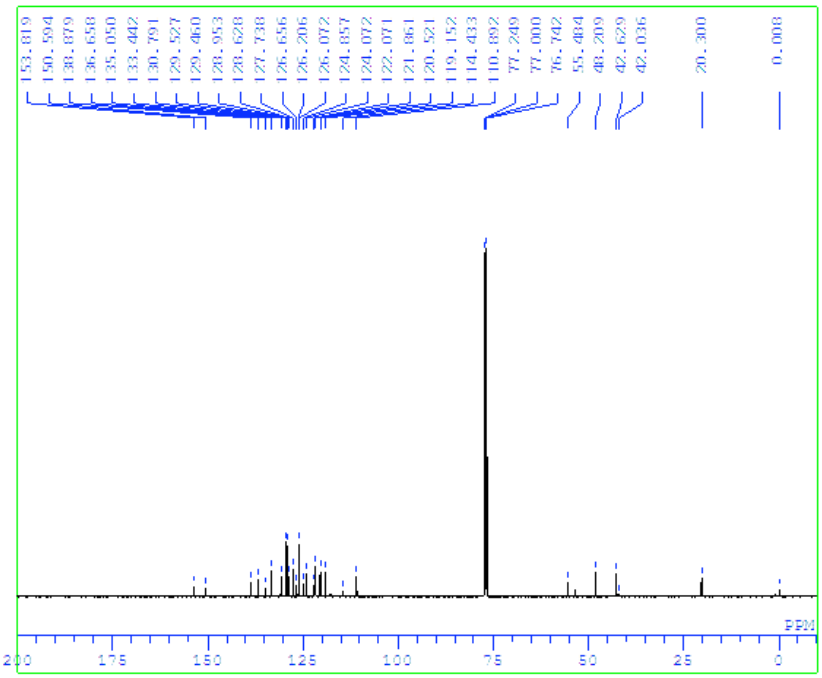
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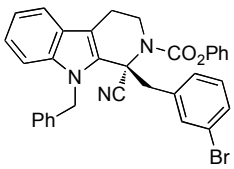
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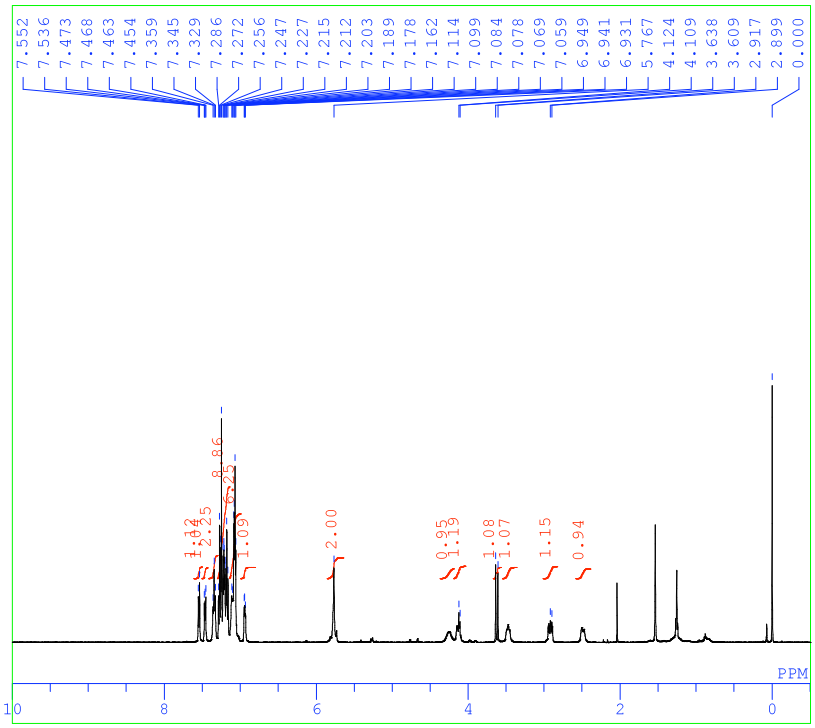
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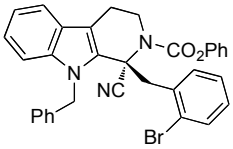
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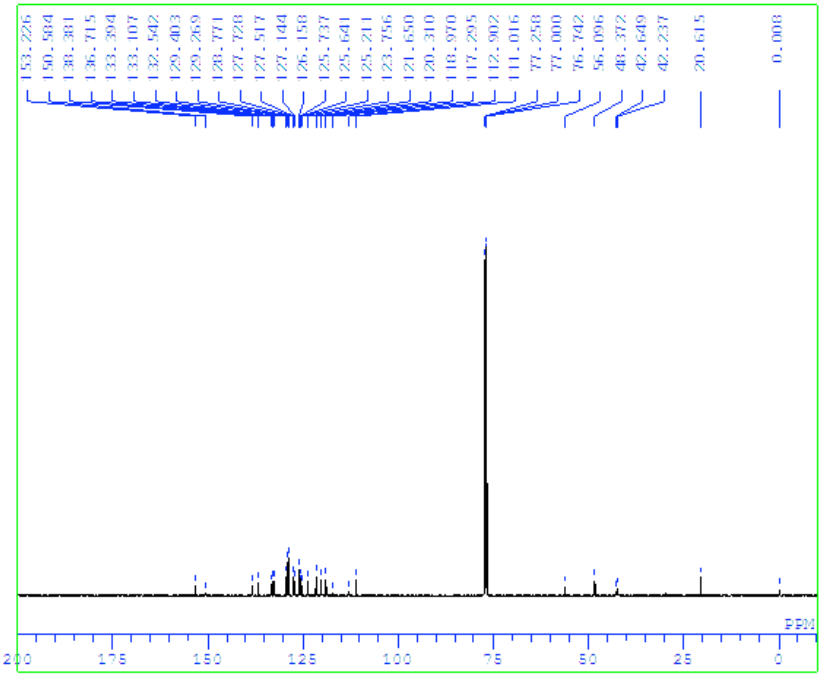
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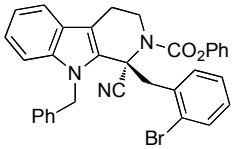
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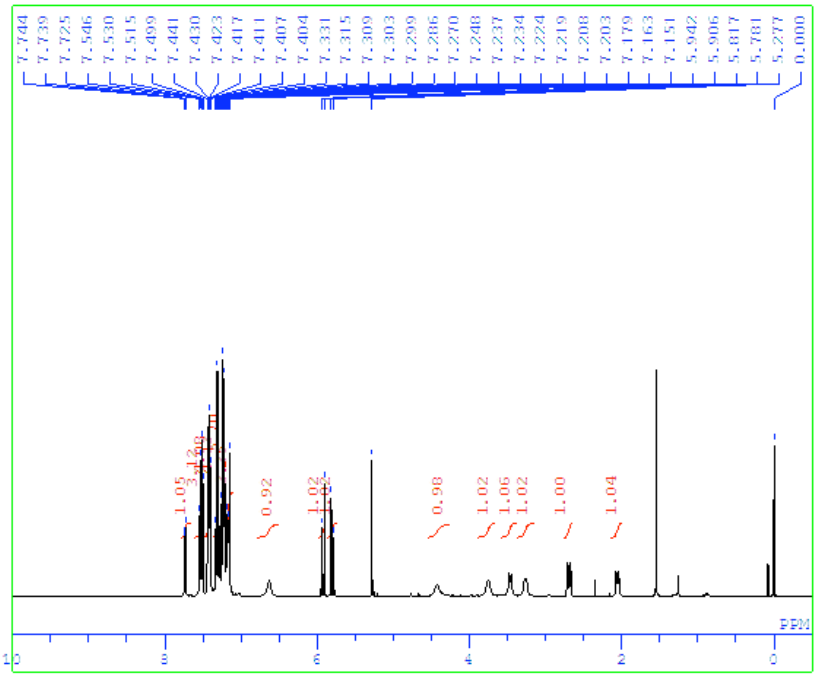
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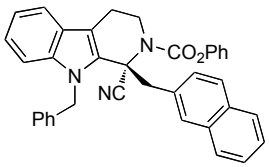
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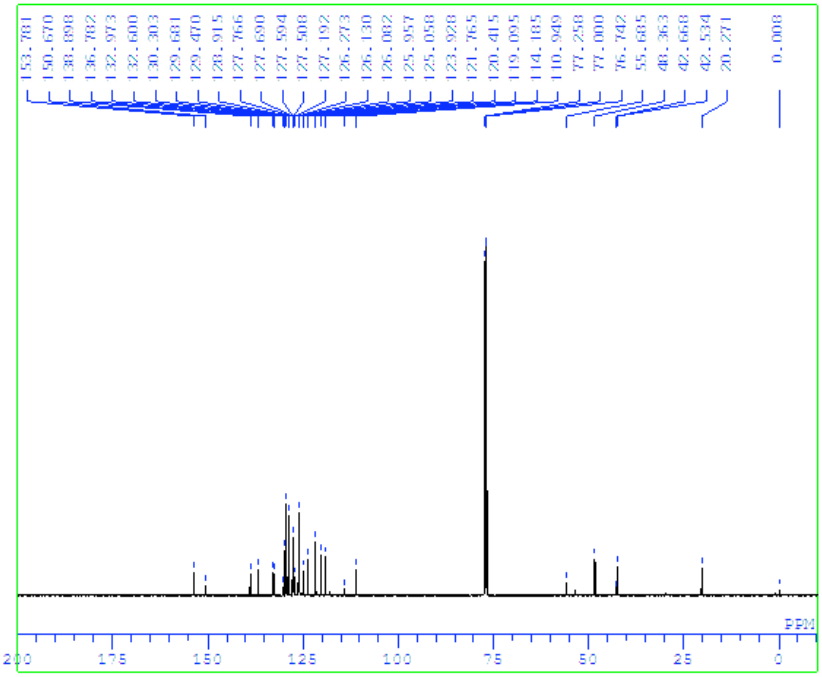
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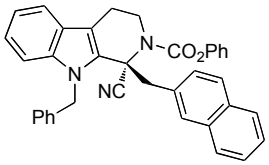
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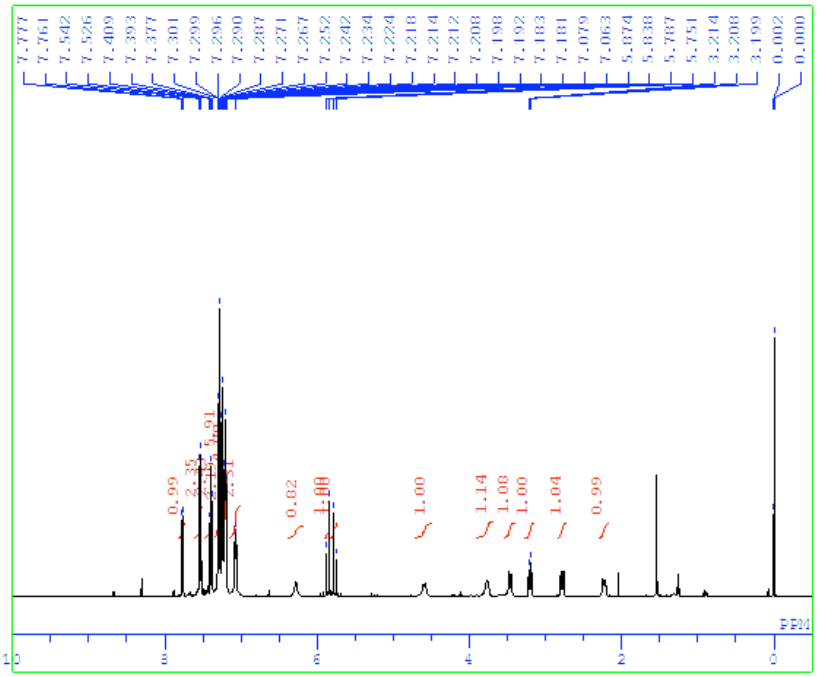
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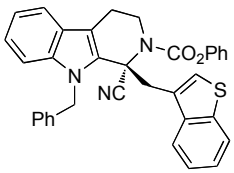
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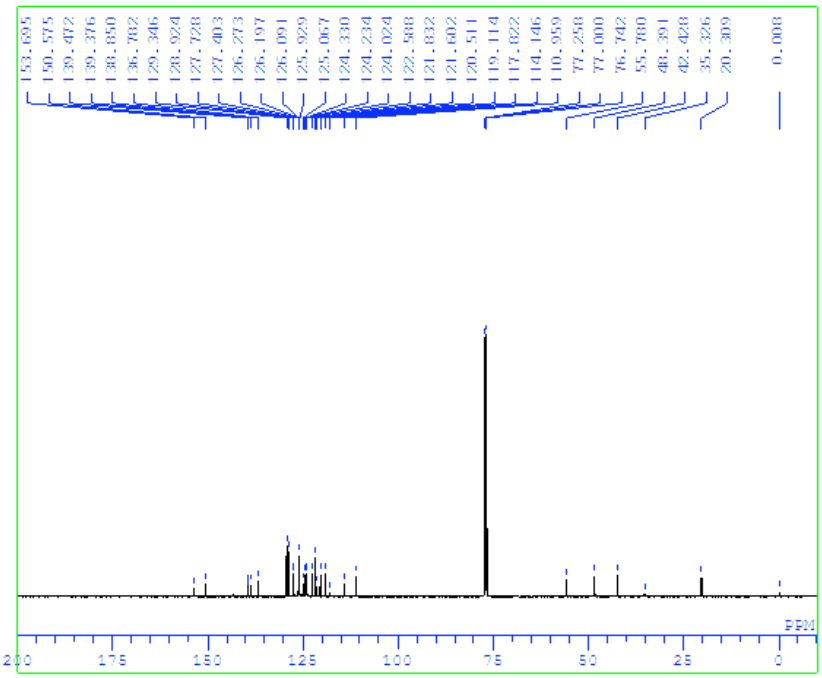
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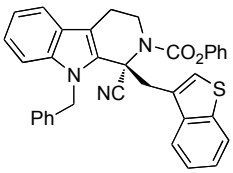
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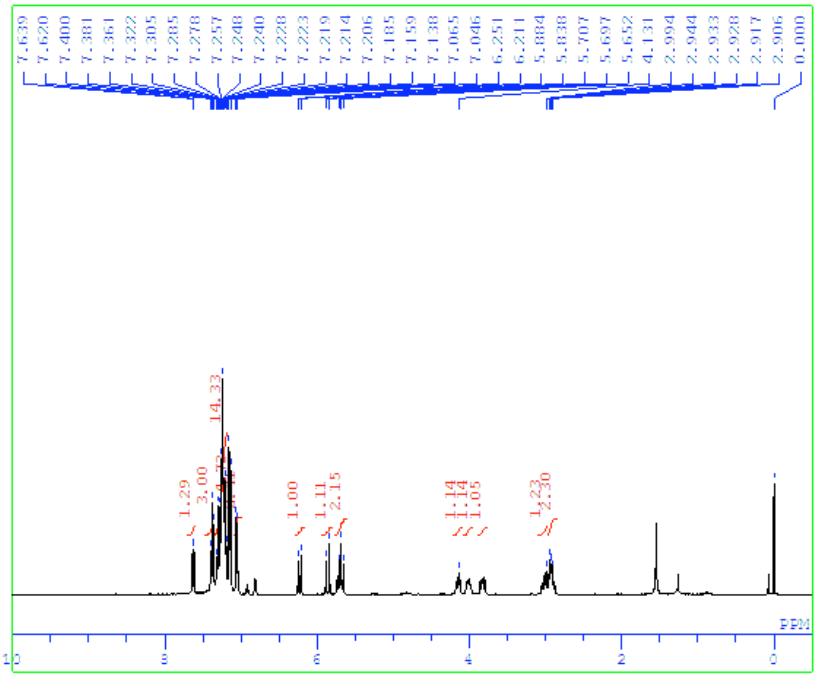
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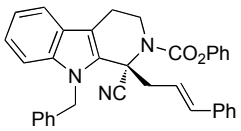
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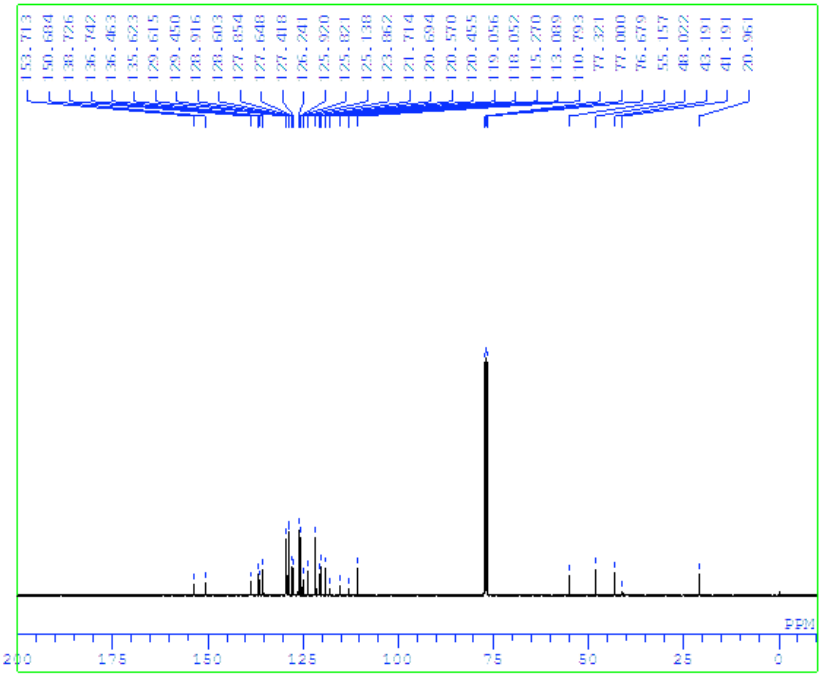
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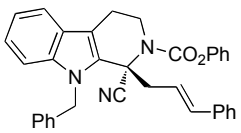
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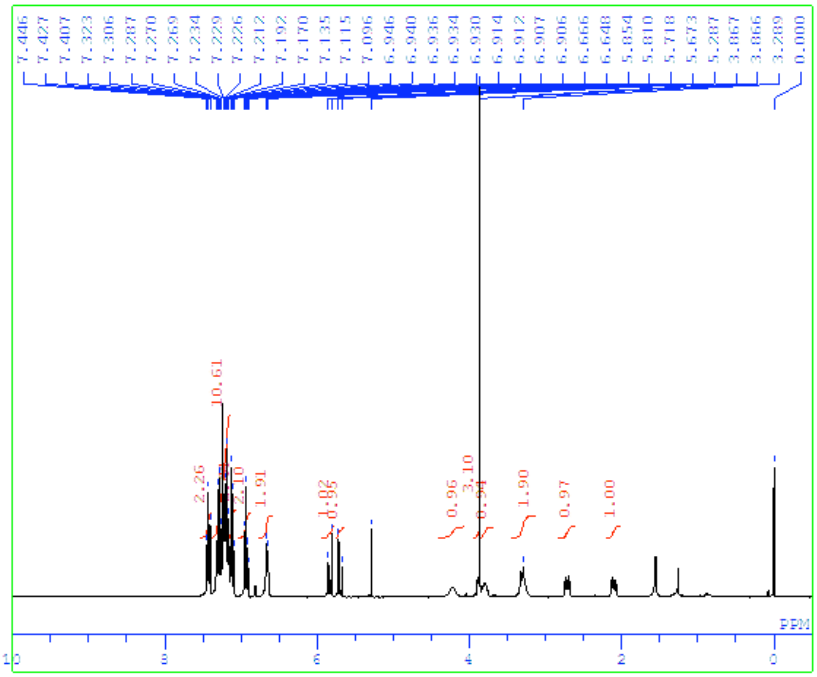
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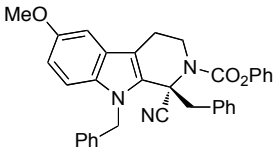
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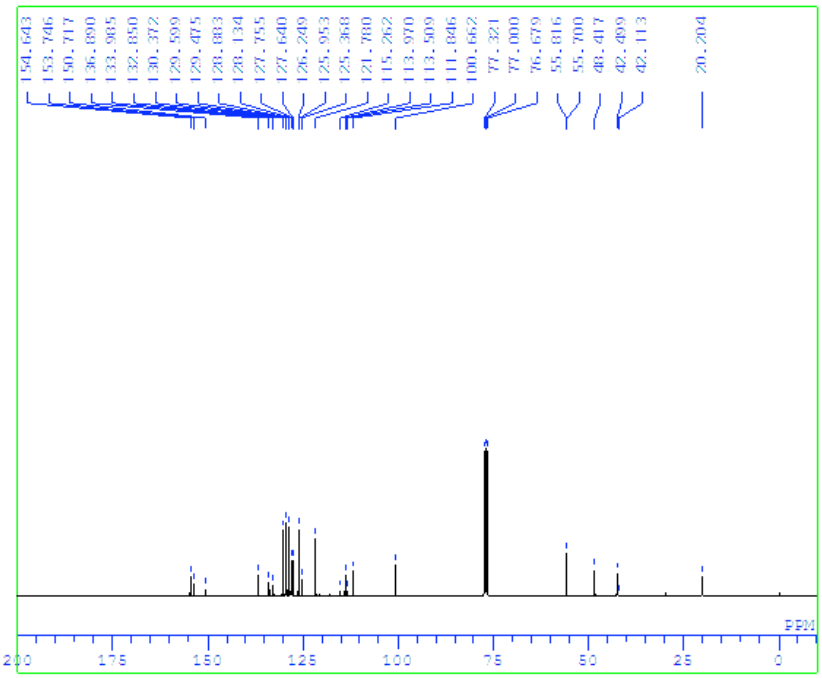
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125.953
125.368
121.760
115.262
113.970
113.509
111.846
100.662
77.321
77.000
76.679
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42.113
20.204
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150
125
100
75
50
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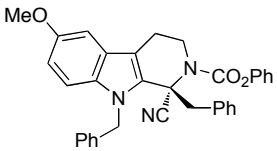
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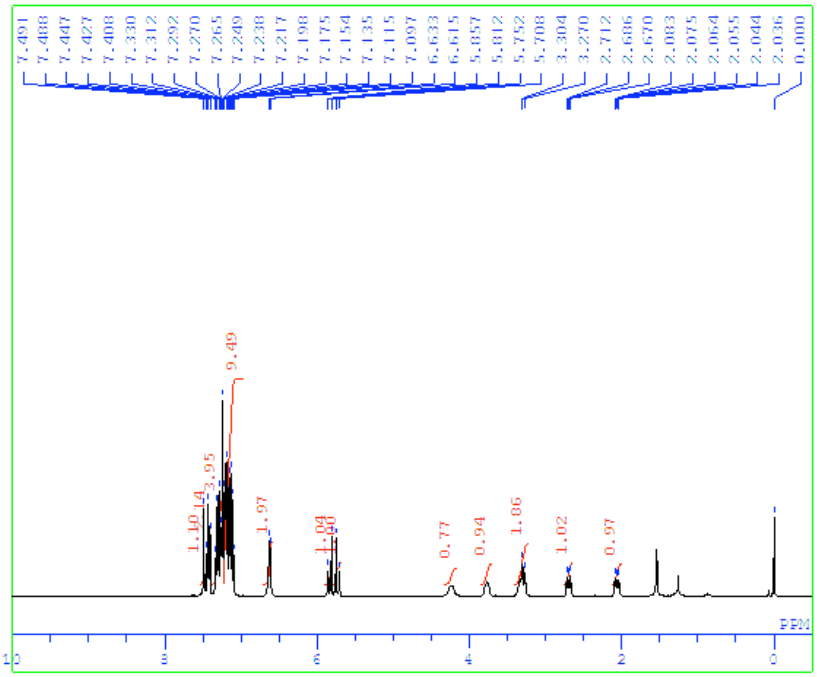
NC
Ph
Ph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7.115
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5.812
5.752
5.708
3.304
3.270
2.712
2.686
2.670
2.083
2.075
2.064
2.055
2.044
2.036
0.000
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3.95
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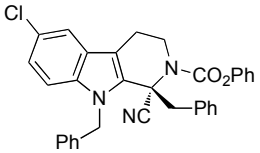
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Ph
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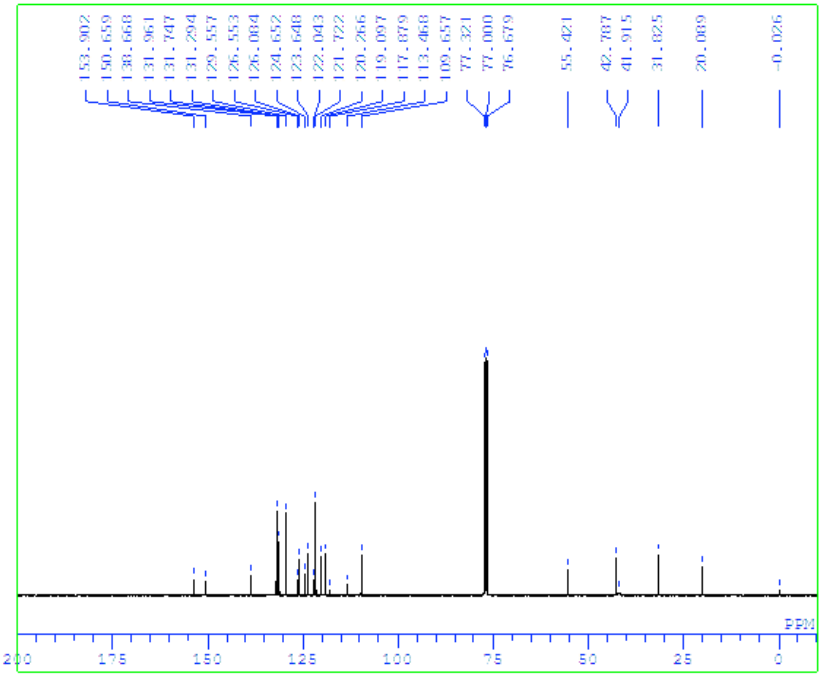
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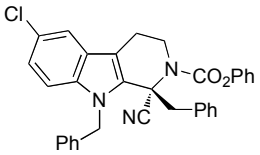
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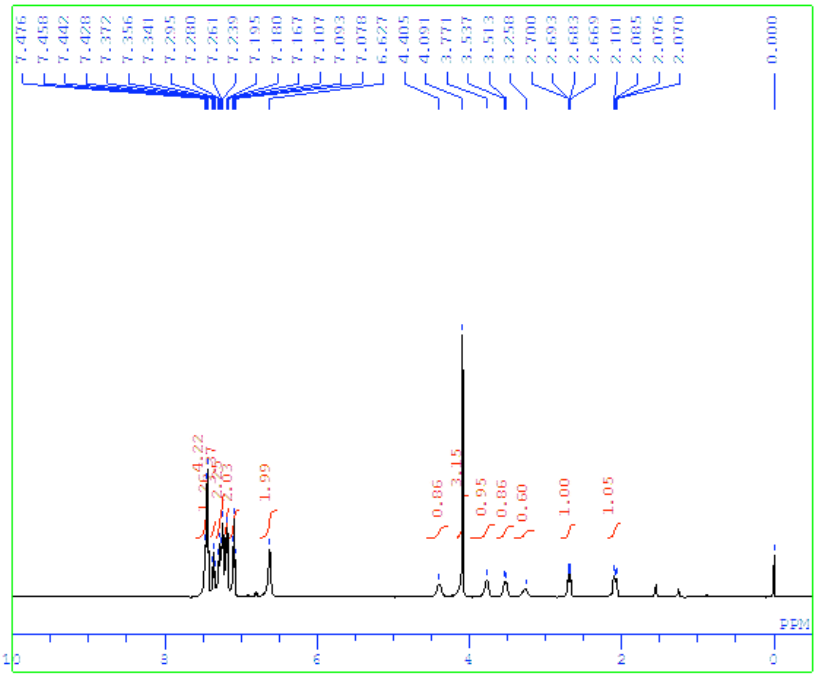
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6.627
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3.537
3.513
3.258
2.700
2.693
2.683
2.669
2.101
2.085
2.076
2.070
0.000
4.22
2.57
2.03
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0.95
0.86
0.60
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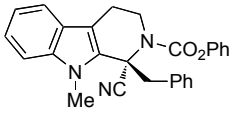
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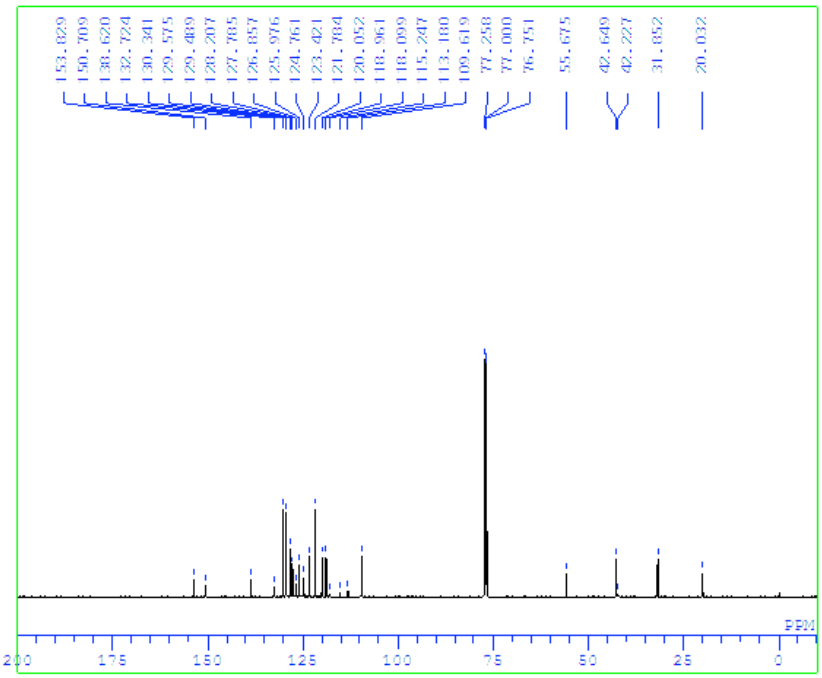
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115.247
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77.258
77.000
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75
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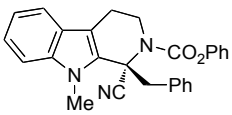
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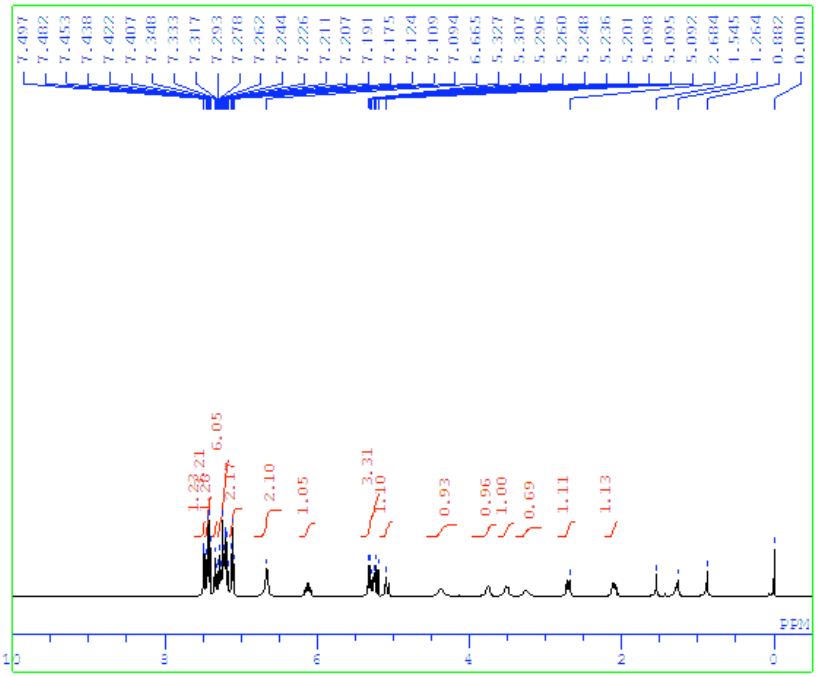
CO2Ph
N
Me
NC
Ph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7.226
7.211
7.207
7.191
7.175
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7.109
7.094
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5.327
5.307
5.296
5.260
5.248
5.236
5.201
5.098
5.095
5.092
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1.264
0.882
0.000
1.23
1.21
6.05
2.17
2.10
1.05
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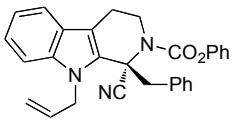
0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N
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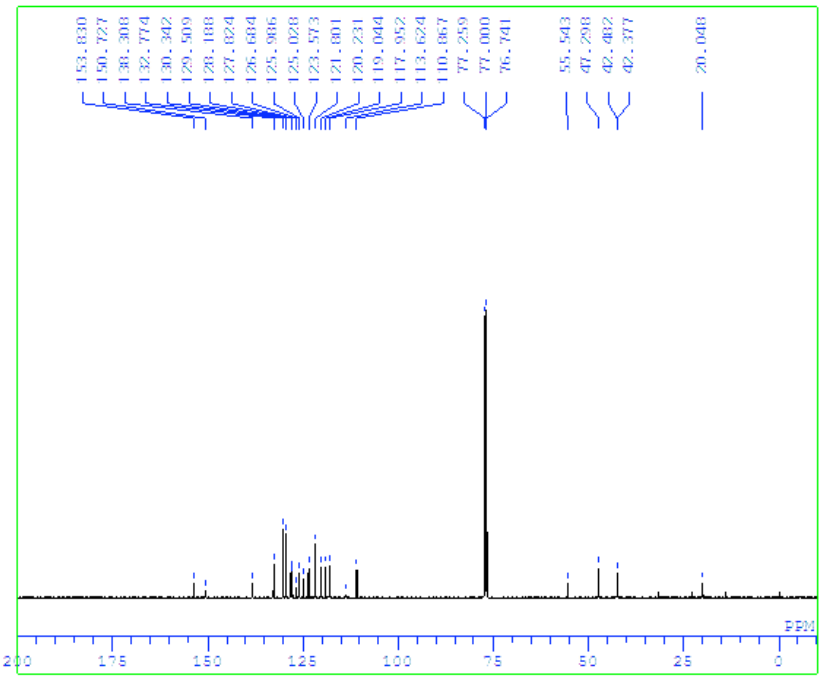
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120.231
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117.952
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77.000
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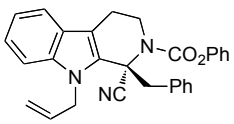
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N
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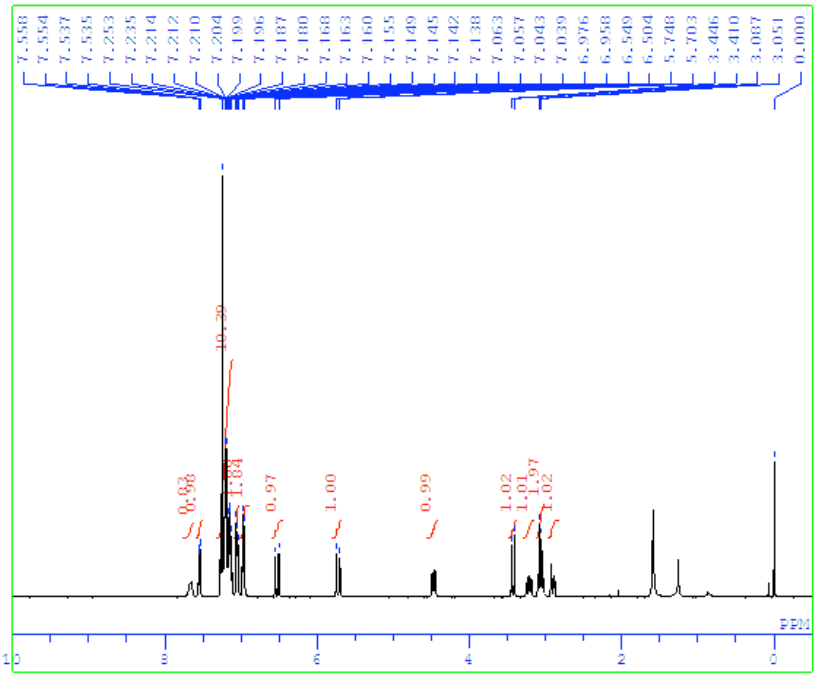
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7.039
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0.98
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1.01
1.97
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PPM
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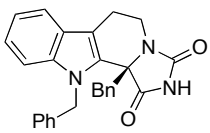
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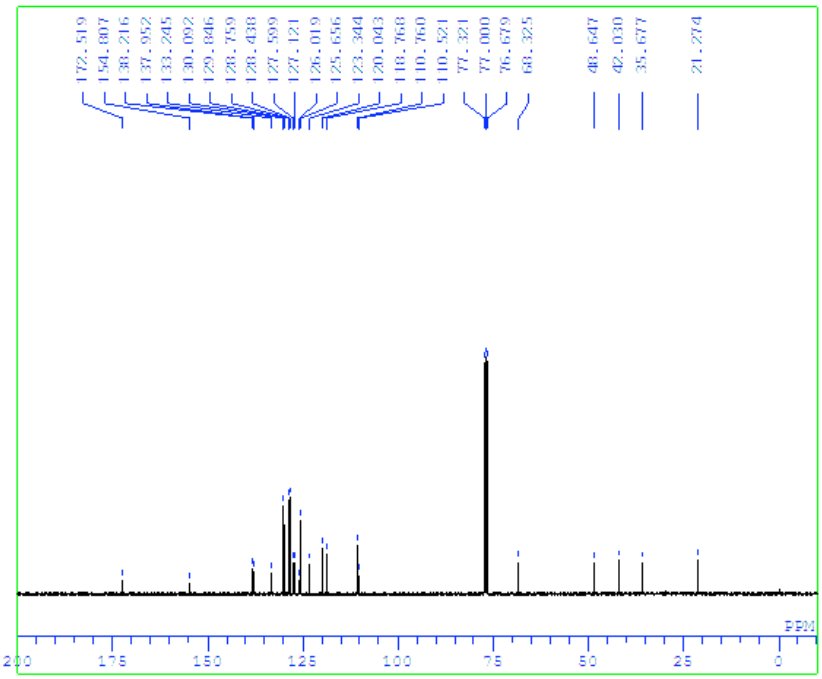
Bn
NH
Ph
O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77.000
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21.274
PPM
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150
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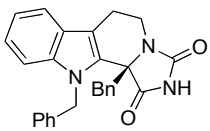
N
O
N
Bn
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O