An Expeditious Route to both Enantiomers of all Carbon Quaternary Stereocenters at C-3 Carbon of Lactams via [3,3]-Sigmatropic Rearrangement: Total Synthesis of (-)-Physostigmine.

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I) Experimental Section.
II) ^{1}H NMR and ^{13}C NMR spectra of compounds.
III) HPLC-data.

I) Experimental Section.

All moisture-sensitive reactions were performed under an atmosphere of argon and glasswares were dried in an oven at 125 °C prior to use. Dry tetrahydrofuran (THF) and diethyl ether (Et_2O) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns and dried by distillation over sodium/benzophenone. Toluene and dimethylformamide (DMF) were distilled over calcium hydride and stored over 4Å molecular sieves. Pyridine and triethylamine (TEA) were distilled over potassium hydroxide. Solvents used for chromatography were distilled at respective boiling points using known procedures.

All commercial reagents were obtained from Sigma-Aldrich Chemical Co. and S. D. Fine Chemical Co. India. Reactions were monitored by thin layer chromatography (TLC, 0.25 mm E.Merck silica gel plates, 60F254) and visualized by using UV light, ethanolic solution of phosphomolybdic acid, iodine and KMnO4 solution. Column chromatography was performed on silica gel 60-120/100-200/ 230-400 mesh obtained from S. D. Fine Chemical Co. India or SRL India. Typical syringe and cannula techniques were used to transfer air and moisture sensitive reagents.

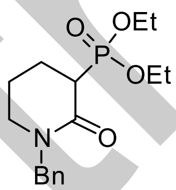
All melting points were uncorrected in degree Celsius and were recorded on a BUCHI Melting point M-560 apparatus. IR spectra were recorded on a Perkin-Elmer FT-IR Spectrometer. 1H NMR spectra were recorded on BRUKER AC-200, BRUKER 400 UltraShield and BRUKER 800 ULTRASHIELD PLUS instruments using deuteriated solvent. Chemical shifts are reported in ppm. Proton coupling constants (*J*) are reported as absolute values in Hz and multiplicity (br, broadened; s, singlet; d, doublet; t, triplet; dd, doublet of doublet; dt, doublet of triplet; td, triplet of doublet; m, multiplet). 13C NMR spectra were recorded on BRUKER AC-200, BRUKER 400 UltraShield and BRUKER 800

ULTRASHIELD PLUS instruments operating at 50MHz, 100MHz and 200MHz respectively. 13C NMR chemical shifts are reported in ppm relative to the central line of CDCl3 (δ 77.0). Electro spray ionization (ESI) mass spectrometry (MS) experiments were performed on Agilent Technologies 6530 Accurate-Mass Q-TOF LC/MS. Optical rotations were measured on a Digipol 781 M6U Automatic Polarimeter. HPLC were performed on Agilent Technologies 1260 Infinity.

General procedure for the preparation of lactam Phosphonates: Illustrated by the synthesis of diethyl(3-benzyl-2-oxocyclohexyl)phosphonate (9, 65% yield) from 1-benzylpiperidin-2-one[1] (8)

To a stirring solution of 1-benzylpiperidin-2-one (**8**) (20 g, 0.105 mol) in dry THF (300 mL) at -78 ^{o}C was added 1.0 M LiHMDS (158.6 mL, 0.158 mol). After 30 min stirring, diethylchlorophosphate (19.8 mL, 0.137 mol) was introduced to the reaction mixture and stirred overnight. Reaction mixture was quenched by adding saturated aqueous solution of ammonium chloride, extracted with EtOAc (3×150 mL), washed with water and brine, dried over anhydrous Na_2SO_4. Combined organic layers concentrated and purified by silica gel flash column chromatography using ethyl acetate: hexane (6:4→8:2) to afford diethyl(3-benzyl-2-oxocyclohexyl)phosphonate (**9**) (22.6 g, 0.069 mol, 65%) as a brown oil. R_f = 0.3 (SiO_2, ethyl acetate: hexane, 9: 1);

diethyl(3-benzyl-2-oxocyclohexyl)phosphonate (9)



9

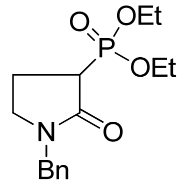
IR (neat) 3443, 2982, 2934, 1633, 1493, 1451, 1392, 1356, 1284, 1247, 1166, 1097, 1026, 970 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) = 1.30 - 1.40 (m, 6H, CH_3), 1.63 - 1.76 (m, 1 H, CH_2CH_2N), 2.00 - 2.28 (m, 3 H, CH_2CH_2N and $CHCH_2$), 3.01 - 3.31 (m, 3 H, CHP, CH_2N), 4.12 - 4.32 (m, 4 H, $2OCH_2$), 4.51 (d, *J*=14.81 Hz, 1 H, NCH_2Ph), 4.73 (d, *J*=14.81 Hz, 1 H, CH_2Ph), 7.18 - 7.38 (m, 5 H, 5Ar-C*H*);

^{13}C NMR (100 MHz, $CDCl_3$) = 16.2 (CH_3), 16.4 (CH_3), 21.3 (CH_2), 23.1 (CH_2), 41.0 (CH), 42.3 (CH), 47.1 (CH_2), 50.4 (CH_2), 62.0 (CH_2), 62.9 (CH_2), 127.2 (Ar-CH), 127.8 (2 × Ar-CH), 128.5 (2 × Ar-CH), 136.7 (Ar-C), 165.0 (NCO);

HR-MS (ESI) = calcd for $C_{16}H_{24}NO_4P$: 348.1341, found: 348.1326 (+Na);

diethyl(3-benzyl-2-oxocyclopentyl)phosphonate (19a, 64% yield**) from 1-benzylpyrrolidin-2-one**[1]



19a

Brown oil; R_f = 0.4 (SiO_2, ethyl acetate-hexane, 9:1);

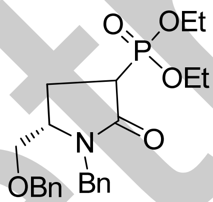
IR (neat) 3463, 2983, 2929, 1686, 1437, 1253, 1023, 968, 736, 702 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) =1.22 - 1.43 (m, 6 H, CH_3), 2.22 - 2.44 (m, 2 H, NCH_2CH_2), 2.93 - 3.10 (m, 1 H, NCH_2), 3.13 - 3.28 (m, 1 H, NCH_2), 3.41 (q, *J*=8.23 Hz, 1 H, CHP), 4.06 - 4.31 (m, 4 H, OCH_2), 4.43 (d, *J*=14.86 Hz, 1 H, NCH_2Ph), 4.54 (d, *J*=14.86 Hz, 1 H, NCH_2Ph), 7.12 - 7.42 (m, 5 H, 5Ar-CH);

^{13}C NMR (100 MHz, $CDCl_3$) = 16.3 (CH_3), 16.3 (CH_3), 20.1 (CH_2), 40.2 (CH), 41.6 (CH), 45.2 (CH_2), 46.8 (CH_2), 62.2 (CH_2), 62.9 (CH_2), 127.5 (s, 1 C), 128.0 (Ar-CH), 128.6 (2X Ar-CH), 135.9 (2X Ar-CH), 169.2 (NCO);

HR-MS (ESI) = calcd for $C_{15}H_{22}NO_4P$: 334.1184, found: 334.1189 (+Na);

diethyl((5S)-1-benzyl-5-((benzyloxy)methyl)-2-oxopyrrolidin-3-yl)phosphonate (19b, 68% yield**) from (S)-1-benzyl-5-((benzyloxy)methyl)pyrrolidin-2-one**[2]



19b

Brown oil; R_f = 0.3 (SiO_2, ethyl acetate-hexane, 9:1);

IR (neat) 3471, 3087, 3062, 3031, 2983, 2930, 2908, 2867, 1693, 1682, 1452, 1426, 1250, 1027, 968, 800, 736, 701, 581cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) =1.29 - 1.42 (m, 6 H, CH_3), 2.15 - 2.32 (m, 2 H, CH_2), 2.32 - 2.52 (m, 1 H, CH), 2.97 - 3.24 (m, 1 H, CHP), 3.34 (dd, J_1=10.07, J_2=3.53 Hz, 1 H, OCH_2), 3.43 - 3.56 (m, 1 H, OCH_2), 3.66 - 3.74 (m, 1 H, CH), 4.00 (d, *J*=15.11 Hz, 1 H, OCH_2Ar), 4.13 - 4.32 (m, 4 H, OCH_2), 4.33 - 4.47 (m, 2 H, NCH_2Ar), 4.96 (d, *J*=15.11 Hz, 1 H, OCH_2Ar), 7.15 - 7.42 (m, 10 H, 10Ar-CH);

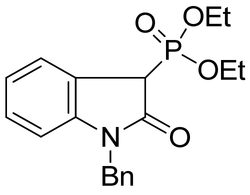
^{13}C NMR (100 MHz, $CDCl_3$) = 16.2 (CH_3), 16.3 (CH_3), 23.1 (CH_2), 23.8 (CH_2), 39.3 (CH), 39.7 (CH), 40.8 (CH), 41.1 (CH), 44.6 (CH_2), 45.4 (CH_2), 55.4 (CH), 55.6 (CH), 62.1 (CH_2), 62.2 (CH_2), 62.8 (CH_2), 63.1 (CH_2), 69.3 (CH_2), 72.1 (CH_2), 73.0 (CH_3), 73.1 (CH_3), 127.2

(Ar-CH), 127.6 (Ar-CH), 127.6 (Ar-CH), 127.7 (Ar-CH), 127.7 (Ar-CH), 127.9 (Ar-CH), 128.2 (Ar-CH), 128.3 (Ar-CH), 128.3 (Ar-CH), 136.1 (Ar-C), 136.5 (Ar-C), 137.4 (Ar-C), 137.4 (Ar-C), 169.5 (NCO), 169.7 (NCO);

HR-MS (ESI) = calcd for $C_{15}H_{22}NO_4P$: 454.1759, found: 454.1738 (+Na);

$[\alpha]_D^{23.3}$= +31.293 (c = 0.72, MeOH); containing mixture of diastereomer;

diethyl(1-benzyl-2-oxoindolin-3-yl)phosphonate (26a, 91% yield**) from 1-benzylindolin-2-one**[3a]



26a

Light yellow oil; R_f = 0.45 (SiO_2, ethyl acetate-hexane, 2:8);

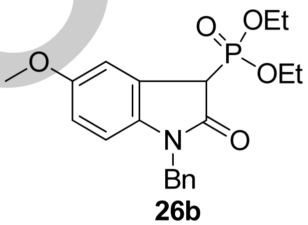
IR (neat) 3491, 3058, 3031, 2984, 2933, 2911, 1713, 1554, 1452, 1421, 1286, 1028, 1009, 953, 822, 731 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) = 1.32 (t, J=7.05 Hz, 6 H, CH_3), 4.04 - 4.29 (m, 4 H, O-CH_2), 5.30 (s, 2 H, N-CH_2), 6.23 (s, 1 H, CHP), 7.08 - 7.21 (m, 5 H, Ar-CH), 7.21 - 7.36 (m, 3 H, Ar-CH), 7.48 - 7.61 (m, 1 H, Ar-CH);

^{13}C NMR (100 MHz, $CDCl_3$) = 15.9 (CH_3), 45.3 (CH_2), 65.1 (CH_2), 65.2 (CH_2), 84.8 (CH), 109.3 (Ar-CH),120.2 (Ar-CH), 120.3 (Ar-CH), 121.1 (Ar-CH), 126.2 (Ar-C) 126.5 (2X Ar-CH) 127.4 (Ar-CH) 128.6 (2X Ar-CH) 131.9 (Ar-C) 137.1 (Ar-C),142.5 (N-CO);

HR-MS (ESI) = calcd for $C_{19}H_{22}NO_4P$: 382.1184, found: 382.1172 (+Na);

diethyl(1-benzyl-5-methoxy-2-oxoindolin-3-yl)phosphonate (26b, 83% yield**) from 1-benzyl-5-methoxyindolin-2-one**[3b]



26b

Light yellow oil; R_f = 0.4 (SiO_2, ethyl acetate-hexane, 3:7);

IR (neat) 3494, 3063, 3031, 2968, 2937, 2911, 2833, 1701, 1623, 1581, 1549, 1483, 1451, 1393, 1370, 1340, 1164, 1131, 1110, 898, 799, 755, 733, 697 cm^{-1};

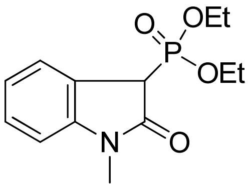
^{1}H NMR (400 MHz, $CDCl_3$) = 1.33 (t, J=7.05 Hz, 6 H, CH_3), 3.84 (s, 3 H, O-Me), 4.11 - 4.31 (m, 4 H, CH_2), 5.26 (s, 2 H, Ar-CH_2), 6.20 (s, 1 H, CHP), 6.79 (dd, J=8.81, 2.27 Hz, 1

H, Ar-H), 7.01 - 7.09 (m, 2 H, Ar-H), 7.14 (d, J=7.05 Hz, 2 H, Ar-H), 7.20 - 7.35 (m, 3 H, Ar-H);

^{13}C NMR (100 MHz, $CDCl_3$) = 15.8 (CH_3), 15.9 (CH_3), 45.3 (CH_2), 55.6 (O-Me), 65.0 (CH_2), 84.7 (CH), 102.7 (Ar-CH), 110.1 (Ar-CH), 110.5 (Ar-CH), 126.3 (Ar-CH), 126.5 (Ar-C), 126.9 (Ar-C), 127.2 (Ar-CH), 128.5 (Ar-CH), 137.1 (Ar-C), 142.7 (Ar-C), 154.4 (CO);

HR-MS (ESI) = calcd for $C_{20}H_{24}NO_5P$: 412.1290, found: 412.1277 (+Na);

diethyl(1-methyl-2-oxoindolin-3-yl)phosphonate (26c, 86% yield**) from 1-methylindolin-2-one**[3b]



26c

Light yellow oil; R_f = 0.4 (SiO_2, ethyl acetate-hexane, 3:7);

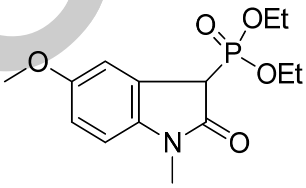
IR (neat) 3404, 2984, 2933, 1706, 1615, 1471, 1495, 1371, 1039, 911, 733, 649 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) = 1.40 (td, J=7.11, 0.88 Hz, 6 H, CH_3), 1.64(bs, from H_2O), 3.66 (s, 3 H, N-Me), 4.14 - 4.39 (m, 4 H, $2CH_2$), 6.13 (s, 1 H, CHP), 7.08 - 7.14 (m, 1 H, Ar-CH), 7.16 - 7.26 (m, 2 H, Ar-CH), 7.52 (d, J=7.81 Hz, 1 H, Ar-CH);

^{13}C NMR (100 MHz, $CDCl_3$) = 16.0 (CH_3), 16.1 (CH_3), 28.0 (N-Me), 65.2 (CH_2), 84.6 (CH_2), 108.8 (Ar-CH), 120.0 (Ar-CH), 120.1 (Ar-CH), 120.9 (Ar-CH), 126.0 (Ar-C), 132.4 (Ar-C), 142.6 (CO);

HR-MS (ESI) = calcd for $C_{13}H_{18}NO_4P$: 306.0871, found: 306.0867 (+Na);

diethyl(5-methoxy-1-methyl-2-oxoindolin-3-yl)phosphonate (26d, 87% yield**) from 5-methoxy-1-methylindolin-2-one**[3c]



26d

Light green oil; yield-87%; R_f = 0.4 (SiO_2, ethyl acetate-hexane, 4:6);

IR (neat) 3484, 2988, 2940, 2837, 1709, 1603, 1497, 1292, 1239, 1149, 1030, 980, 945, 806, 761, 692 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) = 1.39 (td, *J*=7.11, 1.13 Hz, 6 H, CH_3), 3.61 (s, 3 H, N-Me), 3.84 (s, 3 H, O-Me), 4.19 - 4.37 (m, 4 H, -O-CH_2), 6.07 (s, 1 H, CHP), 6.83 (dd, *J*=8.81, 2.27 Hz, 1 H, Ar-CH), 7.01 (d, *J*=2.27 Hz, 1 H, Ar-CH), 7.12 (d, *J*=8.81 Hz, 1 H, Ar-CH);

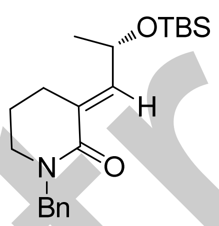
^{13}C NMR (100 MHz, $CDCl_3$) = 15.9 (CH_3), 28.1 (N-Me), 55.7 (O-Me), 65.1 (O-CH_2), 84.5 (CH), 102.6 (Ar-CH), 109.5 (Ar-CH), 110.3 (Ar-CH), 126.2 (Ar-C), 127.4 (Ar-C), 142.7 (Ar-C), 154.3 (N-CO);

HR-MS (ESI) = calcd for $C_{14}H_{20}NO_5P$: 336.0977, found: 336.0978 (+Na);

General Procedure for the *Horner-Wadsworth-Emmons* olefination reaction: Illustrated by the synthesis of 1-benzyl-3-(2-hydroxypropylidene)piperidin-2-one

NaH (1.825 g, 76.06 mmol) was added to a stirring solution of diethyl(3-benzyl-2-oxocyclohexyl)phosphonate **9 (**25.5 g, 72.44 mmol) in 300 mL THF at 0 ºC. After 5 min. (*S*)-2-((*t*-butyldimethylsilyl)oxy)propanal (**10**) (20.43 g ,108.67 mmol) in 50 mL anhydrous THF was transferred through cannula into the flask and stirred for 30 min. Reaction was quenched by adding saturated NH_4Cl solution and the aqueous layer was extracted with ethyl acetate (3×200 mL), washed with water and brine, dried over anh.Na_2SO_4, concentrated and purified through column chromatography to give **11** and **12** (*trans:cis* = 1:1.5) in combined yield of 99%.

(*S,E*)-1-benzyl-3-(2-hydroxypropylidene)piperidin-2-one (11) (combined yield-99%)



11

Colourless liquid; R_f = 0.24 (SiO_2, ethyl acetate-hexane, 2:8);

IR (neat) 2954, 2929, 2889, 2856, 1666, 1621, 1488, 1453, 1358, 1343, 1310, 1255, 1082, 1139, 890, 833, 777, 737, 701, 667, 646 cm^{-1}

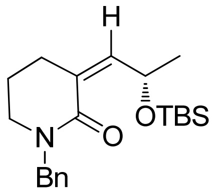
^{1}H NMR (400 MHz, $CDCl_3$) = 0.06 (d, *J*=3.78 Hz, 6 H, Si-Me), 0.89 (s, 9 H, *t*-Bu), 1.25 (d, *J*=6.29 Hz, 3 H, CH_3), 1.76 - 1.87 (m, 2 H, CH_2), 2.35 - 2.46 (m, 1 H, CH_2), 2.53 - 2.64 (m, 1 H, CH_2), 3.19 - 3.32 (m, 2 H, CH_2), 4.55 - 4.66 (m, 2 H, Ar-CH_2), 4.69 - 4.80 (m, 1 H, CH), 6.80 - 6.92 (m, 1 H, olefin-CH), 7.19 - 7.37 (m, 5 H, Ar-CH);

^{13}C NMR (100 MHz, $CDCl_3$) = -4.7 (CH_3), -4.5 (CH_3), 18.1 (C), 22.6 (CH_2), 23.5 (CH_3), 24.9 (CH_2), 25.8 (CH_3), 47.0 (CH_2), 50.9 (CH_2), 65.6 (CH), 126.8 (Ar-C), 127.3 (Ar-CH), 128.0 (Ar-CH), 128.5 (Ar-CH), 137.3 (C), 142.2 (CH), 164.7 (CO);

HR-MS (ESI) = calcd for $C_{21}H_{33}NO_2Si$: 382.2178, found: 382.2176 (+Na);

[α]$_D^{25.9}$= -4.549 (c = 3.35, MeOH);

(*S*,*Z*)-1-benzyl-3-(2-hydroxypropylidene)piperidin-2-one (12)



12

Colourless liquid; R_f = 0.42 (SiO_2, ethyl acetate-hexane, 1:9);

IR (neat) 2953, 2928, 2855, 1661, 1623, 1488, 1453, 1859, 1250, 1070, 832, 776, 700 cm^{-1};

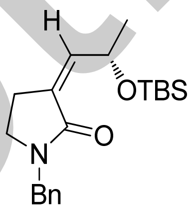
^{1}H NMR (400 MHz, $CDCl_3$) = 0.06 (d, *J*=3.02 Hz, 6 H, Si-Me), 0.87 - 0.91 (m, 9 H, *t*-Bu), 1.31 (d, *J*=6.29 Hz, 3 H, Me), 1.73 - 1.94 (m, 2 H, CH_2) ,2.40 - 2.51 (m, 2 H, CH_2), 3.23 (dd, *J*=7.30, 5.04 Hz, 2 H, CH_2), 4.42 (d, *J*=14.60 Hz, 1 H, Ar-CH_2), 4.83 (d, *J*=14.86 Hz, 1 H, Ar-CH_2), 5.46 - 5.61 (quin, *J*=6.55 Hz, 1 H, CH), 5.73 - 5.82 (m, 1 H, d, *J*=7.55 Hz, olefin CH), 7.16 - 7.36 (m, 5 H, Ar-H);

^{13}C NMR (100 MHz, $CDCl_3$) = -4.6 (CH_3), 18.2 (C), 23.5 (CH_2), 23.7 (CH_3), 25.9 (CH_3), 31.9 (CH_2), 47.2 (CH_2), 49.9 (CH_2), 66.4 (CH), 126.2 (Ar-C), 127.1 (Ar-CH), 127.8 (Ar-CH), 128.4 (Ar-CH), 137.3 (C), 146.1 (CH), 164.5 (CO);

HR-MS (ESI) = calcd for $C_{21}H_{33}NO_2Si$: 382.2178 found: 382.2177 (+Na);

[α]$_D^{26.9}$=-40.753 (c = 3.345, MeOH);

(*S*,*Z*)-1-benzyl-3-(2-((tert-butyldimethylsilyl)oxy)propylidene)pyrrolidin-2-one (20a) (combined 99% yield)



20a

Colourless liquid; R_f = 0.58 (SiO_2, ethyl acetate-hexane, 2:8);

IR (neat) 2955, 2929, 2856, 2887, 1688, 1666, 1446, 1425, 1360, 1306, 1257, 1126, 1065, 999, 901, 834, 776, 700 643, 535 cm^{-1} ;

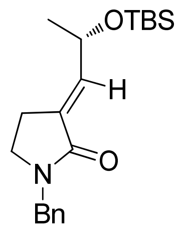
^{1}H NMR (400 MHz, $CDCl_3$) = 0.10 (s, 3 H, Si-Me), 0.07 (s, 3 H, Si-Me), 0.90 (s, 9 H, *t*-Bu), 1.26 (d, *J*=6.04 Hz, 3 H, Me), 2.58 - 2.68 (m, 2 H, CH_2), 3.25 (td, *J*=6.80, 4.03 Hz, 2 H, CH_2), 4.46 - 4.55 (m, 2 H, Ar-CH_2), 5.81 - 5.86 (m, 1 H, olefin CH), 5.86 - 5.96 (m, 1 H, CH), 7.19 - 7.27 (m, 2 H, Ar-CH), 7.28 - 7.37 (m, 3 H, Ar-CH);

^{13}C NMR (100 MHz, $CDCl_3$) = -4.7 (CH_3), -4.6 (CH_3), 18.1 (C), 24.3 (CH_3), 24.9 (CH_2), 25.9 (CH_3), 43.6 (CH_2), 46.8 (CH_2), 63.4 (CH), 127.3 (Ar-C), 127.5 (Ar-CH), 128.1 (Ar-CH), 128.6 (Ar-CH), 136.4 (C), 141.1 (CH), 167.6 (CO);

HR-MS (ESI) = calcd for $C_{20}H_{31}NO_2Si$: 368.2022, found: 368.2015 (+Na);

$[\alpha]_D^{26.3}$=+19.733 (c = 7.65, MeOH);

(*S,E*)-1-benzyl-3-(2-((tert-butyldimethylsilyl)oxy)propylidene)pyrrolidin-2-one (21a)



21a

Colourless liquid; R_f = 0.41 (SiO_2, ethyl acetate-hexane, 2:8);

IR (neat) 2954, 2929, 2856, 2888, 1695, 1675, 1494, 1444, 1425, 1305, 1254, 1087, 892, 834, 777, 700, 673 cm^{-1} ;

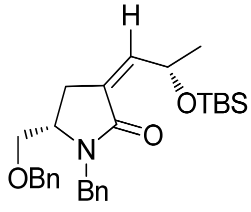
^{1}H NMR (400 MHz, $CDCl_3$) = 0.04 (d, J=6.55 Hz, 6 H, Si-Me), 0.88 (s,9 H, *t*-Bu), 1.25 (d, J=6.29 Hz, 3 H, CH_3), 2.60 - 2.77 (m, 2 H, CH_2), 3.28 (t, J=6.80 Hz, 2 H, CH_2), 4.45 - 4.56 (m, 2 H, Ar-CH_2), 4.56 - 4.67 (m, 1 H, CH), 6.49 (dt, J=7.24, 2.80 Hz, 1 H, olefin-CH), 7.21 - 7.41 (m, 5 H, Ar-CH);

^{13}C NMR (100 MHz, $CDCl_3$) = -4.8 (CH_3), -4.6 (CH_3), 18.1 (C), 21.7 (CH_2), 23.4 (CH_3), 25.7 (CH_3), 43.8 (CH_2), 47.1 (CH_2), 66.8 (CH), 127.5 (Ar-CH), 128.2 (Ar-CH), 128.6 (Ar-CH), 129.1 (Ar-C), 136.3 (C), 136.7 (CH), 168.4 (CO);

HR-MS (ESI) = calcd for $C_{20}H_{31}NO_2Si$: 368.2022, found: 368.2014 (+Na);

$[\alpha]_D^{26.8}$=+6.162 (c = 1.85, MeOH);

(*S,Z*)-1-benzyl-5-((benzyloxy)methyl)-3-((*S*)-2-hydroxypropylidene)pyrrolidin-2-one (20b) (combined 99% yield)



20b

Colourless liquid; R_f = 0.38 (SiO_2, ethyl acetate-hexane, 1:9);

IR (neat) 3064, 3031, 2954, 2928, 2856, 1667, 1441, 1360, 1253, 1077, 834, 776, 700 cm^{-1} ;

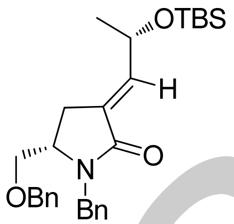
^{1}H NMR (400 MHz, $CDCl_3$) = 0.10 (s, 3 H, Si-CH_3), 0.07 (s, 3 H, Si-CH_3), 0.91 (s, 9 H, *t*-Bu), 1.28 (d, *J*=5.54 Hz, 3 H, CH_3), 2.49 (d, *J*=16.62 Hz, 1 H, CH_2), 2.73 (ddd, *J*=16.37, 8.56, 1.76 Hz, 1 H, CH_2), 3.40 (d, *J*=4.53 Hz, 2 H, CH_2), 3.62 (dd, *J*=8.31, 3.53 Hz, 1 H, CH), 4.16 (d, *J*=14.86 Hz, 1 H, Ar-CH_2), 4.42 (s, 2 H, Ar-CH_2), 4.97 (d, *J*=14.86 Hz, 1 H, Ar-CH_2), 5.77 - 5.99 (m, 2 H, CH and Olefin-CH), 7.09 - 7.52 (m, 10 H, Ar-CH);

^{13}C NMR (100 MHz, $CDCl_3$) = -4.8 (CH_3), -4.6 (CH_3), 18.1 (C), 24.3 (CH_3), 25.9 (CH_3), 29.4 (CH_2), 45.0, (CH_2), 54.0 (CH), 63.6 (CH), 71.0 (CH_2), 73.1 (CH_2), 126.9 (Ar-C), 127.3 (Ar-CH), 127.6 (Ar-CH), 127.7 (Ar-CH), 128.1 (Ar-CH), 128.4 (Ar-CH), 128.5 (Ar-CH), 136.9 (Ar-C), 137.6 (C), 141.1 (CH), 168.0 (CO).

HR-MS (ESI) = calcd for $C_{28}H_{39}NO_3Si$: 488.2597, found: 488.2586 (+Na);

$[\alpha]_D^{23.6}$= +66.042 (*c* = 1.40, MeOH);

(*S,E*)-1-benzyl-5-((benzyloxy)methyl)-3-((*S*)-2-hydroxypropylidene)pyrrolidin-2-one (21b)



21b

Colourless liquid; R_f = 0.18 (SiO_2, ethyl acetate-hexane, 1:9);

IR (neat) 3064, 3031, 2954, 2929, 2888, 2857, 1695, 1675, 1437, 1421, 1361, 1302, 1252, 1124, 1089, 1003, 896, 834, 777, 699 cm^{-1} ;

^{1}H NMR (400 MHz, $CDCl_3$) = 0.07 (d, *J*=5.54 Hz, 6 H, Si-CH_3), 0.90 (s, 9 H, *t*-Bu), 1.27 (d, *J*=6.29 Hz, 3 H, CH_3), 2.52 - 2.62 (m, 1 H, CH_2), 2.79 (ddd, *J*=17.12, 8.31, 2.77 Hz, 1 H, CH_2), 3.37 - 3.46 (m, 2 H, CH_2), 3.64 - 3.74 (m, 1 H, CH), 4.27 (d, *J*=14.86 Hz, 1 H, Ar-CH_2), 4.34 - 4.44 (m, 2 H, Ar-CH_2), 4.48 - 4.57 (m, 1 H, CH), 4.98 (d, *J*=15.11 Hz, 1 H, Ar-CH_2), 6.49 - 6.57 (m, 1 H, olefin-CH), 7.16 - 7.39 (m, 10 H, Ar-CH);

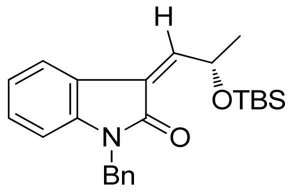
^{13}C NMR (100 MHz, $CDCl_3$) = -4.9 (CH_3), -4.6 (CH_3), 18.0 (C), 23.3 (CH_3), 25.7 (CH_3), 26.1 (CH_2), 45.2 (CH_2), 54.3 (CH), 66.8 (CH), 70.9 (CH_2), 73.0 (CH_2), 127.2 (Ar-CH), 127.5 (Ar-CH), 127.6 (Ar-CH), 128.0 (Ar-CH), 128.2 (Ar-CH), 128.4 (Ar-CH), 128.6 (Ar-C), 136.5 (CH), 136.8 (Ar-C), 137.5 (CH), 168.9 (CO);

HR-MS (ESI) = calcd for $C_{28}H_{39}NO_3Si$: 488.2597, found: 488.2587 (+Na);

$[\alpha]_D^{23.8}$= +69.598 (*c* = 2.1, MeOH);

Horner-Wadsworth-Emmons olefination of **26** was carried out in dry toluene instead of THF by following same experimental procedure as described above and **10** was used in 3 equiv. to get best result.

(*S,Z*)-1-benzyl-3-(2-((tert-butyldimethylsilyl)oxy)propylidene)indolin-2-one (27a) (89% combined yield**)**



27a

Yellow liquid; R_f = 0.62 (SiO_2, ethyl acetate-hexane, 1:9);

IR (neat) 2955, 2930, 2890, 1857, 1712, 1610, 1467, 1353, 1255, 1187, 1087, 1032, 1003, 836, 778, 747, 697 cm^{-1};

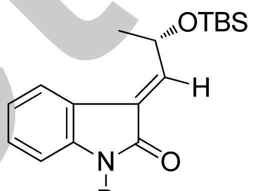
^{1}H NMR (400 MHz, CDCl$_3$) = 0.12 (s, 3 H, CH_3), 0.09 (s, 3 H, CH_3), 0.92 (s, 9 H, *t*-Bu), 1.40 (d, *J*=6.29 Hz, 3 H, CH_3), 4.94 (d, *J*=3.27 Hz, 2 H, Ar-CH_2), 5.92 - 6.06 (m, 1 H, CH), 6.70 (d, *J*=7.81 Hz, 1 H, Ar-CH), 6.82 (d, *J*=8.06 Hz, 1 H, CH), 7.01 (t, *J*=7.30 Hz, 1 H, Ar-CH), 7.12 - 7.21 (m, 1 H, Ar-CH), 7.26 - 7.34 (m, 5 H, Ar-CH), 7.44 (d, *J*=7.55 Hz, 1 H, Ar-CH);

^{13}C NMR (100 MHz, CDCl$_3$) = -4.7 (CH_3), -4.6 (CH_3), 18.2 (C), 23.6 (CH_3), 25.9 (CH_3), 43.3 (Ar-CH_2), 64.3 (CH), 108.9 (Ar-CH), 119.5 (Ar-CH), 122.0 (Ar-CH), 122.6 (Ar-C), 124.3 (Ar-C), 127.2 (Ar-CH), 127.5 (Ar-CH), 128.7 (Ar-CH), 128.9 (Ar-CH), 136.0 (Ar-C), 141.9 (C), 145.6 (CH), 166.6 (CO);

HR-MS (ESI) = calcd for $C_{24}H_{31}NO_2Si$: 416.2022, found: 416.2018 (+Na);

$[\alpha]_D^{21.4}$ =+24.320 (*c* = 0.5, MeOH);

(*S,E*)-1-benzyl-3-(2-((tert-butyldimethylsilyl)oxy)propylidene)indolin-2-one (28a)



28a

Yellow liquid; R_f = 0.54 (SiO_2, ethyl acetate-hexane, 1:9);

IR (neat) 2955, 2931, 2857, 1709, 1657, 1594, 1485, 1437, 1371, 1249, 1181, 1087, 834, 778 cm^{-1};

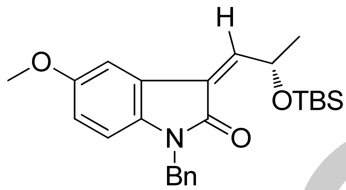
^{1}H NMR (400 MHz, CDCl$_3$) = 0.09 (d, *J*=9.32 Hz, 6 H, Si-Me), 0.89 - 0.95 (m, 9 H, *t*-Bu), 1.45 (d, *J*=6.55 Hz, 3 H, Me), 4.89 - 5.07 (m, 2 H, Ar-CH_2), 5.16 - 5.28 (m, 1 H, CH), 6.74 (d, *J*=7.81 Hz, 1 H, Ar-CH), 7.03 (t, *J*=7.55 Hz, 1 H, Ar-CH), 7.11 (d, *J*=7.81 Hz, 1 H, olefin-CH), 7.16 - 7.22 (m, 1 H, Ar-CH), 7.22 - 7.37 (m, 5 H, Ar-CH), 7.44 (d, *J*=7.55 Hz, 1 H, Ar-CH);

^{13}C NMR (100 MHz, $CDCl_3$) = -4.7 (CH_3), -4.5 (CH_3), 18.1 (C), 22.7 (CH_3), 25.7 (CH_3), 43.6 (CH_2), 66.0 (CH), 109.2 (Ar-CH), 121.3 (Ar-C), 122.1 (Ar-CH), 124.1 (Ar-CH), 124.7 (Ar-C), 127.2 (Ar-CH), 127.5 (Ar-CH), 128.7 (Ar-CH), 129.1 (Ar-CH), 135.9 (C), 143.0 (Ar-C), 145.8 (CH), 167.9 (CO);

HR-MS (ESI) = calcd for $C_{24}H_{31}NO_2Si$: 416.2022, found: 416.2018 (+Na);

$[\alpha]_D^{21.6}$ =-36.923 (*c* = 1.62, MeOH);

(*S*,*Z*)-1-benzyl-3-(2-((tert-butyldimethylsilyl)oxy)propylidene)-5-methoxyindolin-2-one (27b) (89% combined yield with *cis*:*trans* = 1:4)



27b

Yellow liquid; R_f = 0.56 (SiO_2, ethyl acetate-hexane, 1:9);

IR (neat) 3032, 2955, 2931, 2891, 2887, 1703, 1599, 1470, 1490, 1437, 1862, 1254, 1173, 1079, 779, 834, 697 cm^{-1};

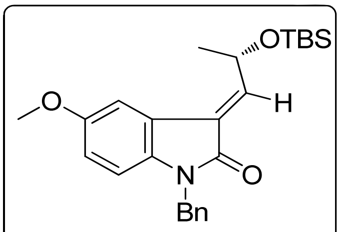
^{1}H NMR (400 MHz, $CDCl_3$) = 0.14 (s, 3 H, Si-Me), 0.10 (s, 3 H, Si-Me), 0.93 (s, 9 H, *t*-Bu), 1.41 (d, *J*=6.29 Hz, 3 H, CH_3), 3.80 (s, 3 H, O-CH_3), 4.84 - 5.00 (m, 2 H, Ar-CH_2), 6.01 (quin, *J*=6.36 Hz, 1 H, CH), 6.58 (d, *J*=8.31 Hz, 1 H, Ar-CH), 6.72 (d, *J*=8.31 Hz, 1 H, CH), 6.80 (d, *J*=8.06 Hz, 1 H, Ar-CH), 7.04 (s, 1 H, Ar-CH), 7.20 - 7.42 (m, 5 H, Ar-CH);

^{13}C NMR (100 MHz, $CDCl_3$) = -4.7 (CH_3), -4.6 (CH_3), 18.1 (C), 23.6 (CH_3), 25.8 (CH_3) 43.3 (CH) 55.8 (CH_3) 64.2 (CH) 106.2 (Ar-CH) 109.4 (Ar-CH) 114.0 (Ar-CH) 123.5 (Ar-C) 124.6 (Ar-C) 127.2 (Ar-CH) 127.4 (Ar-CH) 128.7 (Ar-CH) 135.7 (Ar-C) 136.0 (C) 145.6 (CH) 155.6 (Ar-C) 166.5 (CO);

HR-MS (ESI) = calcd for $C_{25}H_{33}NO_3Si$: 446.2127, found: 446.2118 (+Na);

$[\alpha]_D^{23.6}$=+9.459 (*c* = 0.37, MeOH);

(*S*,*E*)-1-benzyl-3-(2-((tert-butyldimethylsilyl)oxy)propylidene)-5-methoxyindolin-2-one (28b)



28b

Yellow liquid; R_f = 0.41 (SiO_2, ethyl acetate-hexane, 1:9);

IR 3032, 2955, 2930, 2891, 2887, 1709, 1599, 1470, 1490, 1437, 1862, 1254, 1173, 1079, 779, 834, 697 cm^{-1};

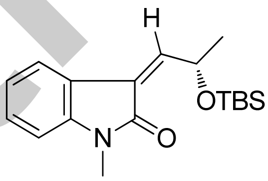
^{1}H NMR (400 MHz, $CDCl_3$) = 0.09 (d, J=9.32 Hz, 6 H, Si-Me), 0.92 (s, 9 H, *t*-Bu), 1.44 (d, J=6.55 Hz, 3 H, CH_3), 3.79 (s, 3 H, O-CH_3), 4.84 - 5.02 (m, 2 H, Ar-CH_2), 5.12 - 5.26 (m, 1 H, CH), 6.61 (d, J=8.56 Hz, 1 H, Ar-CH), 6.72 (dd, J=8.56, 2.27 Hz, 1 H, Ar-CH), 7.00 - 7.14 (m, 2 H, Ar-CH & 1H olefin-CH), 7.23 - 7.38 (m, 5 H, Ar-CH);

^{13}C NMR (100 MHz, $CDCl_3$) = -4.7 (CH_3), -4.5 (CH_3), 18.1 (C), 22.7 (CH_3), 25.8 (CH_3), 43.7 (CH_2), 55.8 (CH_3), 65.9 (CH), 109.3 (Ar-CH), 112.2 (Ar-CH), 112.8 (Ar-CH), 122.3 (Ar-C), 125.1 (Ar-C), 127.2 (Ar-CH), 127.5 (Ar-CH), 128.7 (Ar-CH), 136.0 (Ar-C), 136.8 (C), 146.1 (CH), 155.4 (Ar-C), 167.8 (CO);

HR-MS (ESI) = calcd for $C_{25}H_{33}NO_3Si$: 6.2127, found: 446.2123 (+Na);

$[\alpha]_D^{23.7}$=-15.186 (c = 0.41, MeOH)

(*S*,*Z*)-3-(2-((tert-butyldimethylsilyl)oxy)propylidene)-1-methylindolin-2-one (27c) (86% combined yield with *cis*:*trans* = 1:4)



27c

Yellow liquid; R_f = 0.58 (SiO_2, ethyl acetate-hexane, 1:9);

IR (neat) 3058, 2955, 2930, 2888, 2857, 1707, 1656, 1612, 1471, 1380, 1255, 1080, 1045, 895, 833, 878, 746 cm^{-1};

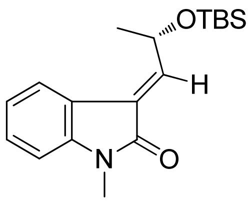
^{1}H NMR (400 MHz, $CDCl_3$) = 0.09 (s, 3 H, Si-Me), 0.05 (s, 3 H, Si-Me), 0.89 (s, 9 H, *t*-Bu), 1.35 (d, J=6.31 Hz, 3 H, CH_3), 3.22 (s, 3 H, N-CH_3), 5.87 - 6.01 (m, 1 H, CH), 6.78 (d, J=7.81 Hz, 1 H, Ar-CH), 6.81 (d, J=7.81 Hz, 1 H, CH), 7.05 (td, J=7.55, 0.76 Hz, 1 H, CH), 7.27 - 7.32 (m, 1 H, Ar-CH), 7.43 (d, J=7.30 Hz, 1 H, Ar-CH);

^{13}C NMR (100 MHz, $CDCl_3$) = ppm -4.7 (CH_3), -4.6 (CH_3), 18.1 (C), 23.6 (CH_3), 25.7 (CH_3), 25.8 (CH_3), 64.3 (CH), 107.9 (Ar-CH), 119.4 (Ar-CH), 121.9 (Ar-CH), 122.4 (Ar-C), 124.3 (Ar-C), 128.9 (Ar-CH), 142.7 (C), 145.3 (CH), 166.6 (CO);

HR-MS (ESI) = calcd for $C_{18}H_{27}NO_2Si$: 340.1709, found: 340.1703 (+Na);

$[\alpha]_D^{25}$= +28.712 (*c* = 1.46, MeOH);

(*S,E*)-3-(2-((tert-butyldimethylsilyl)oxy)propylidene)-1-methylindolin-2-one (28c)



28c

Yellow liquid; R_f = 0.38 (SiO_2, ethyl acetate-hexane, 1:9);

IR (neat) 3057, 2954, 2930, 2888, 2857, 1714, 1659, 1610, 1469, 1337, 1252, 1143, 1085, 1002, 778, 747, 687 cm^{-1};

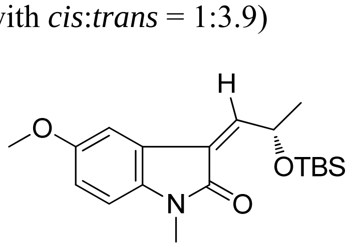
^1H NMR (400 MHz, $CDCl_3$) = 0.07 (s, 3 H, Si-Me), 0.05 (s, 3 H, Si-Me), 0.90 (s, 9 H, *t*-Bu), 1.41 (d, *J*=6.55 Hz, 3 H, CH_3), 3.24 (s, 3 H, N-CH_3), 5.06 - 5.27 (m, 1 H, CH), 6.83 (d, *J*=7.81 Hz, 1 H, Ar-CH), 6.90 - 7.12 (m, 2 H, Olefin-CH and Ar-CH), 7.25 - 7.36 (m, 1 H, Ar-CH), 7.42 (d, *J*=7.55 Hz, 1 H, Ar-CH);

^{13}C NMR (100 MHz, $CDCl_3$) = -4.8 (CH_3), -4.6 (CH_3), 18.1 (C), 22.7 (CH_3), 25.6 (CH_3), 25.7 (CH_3), 26.0 (CH_3), 65.9 (CH), 108.1 (Ar-CH), 121.1 (Ar-C), 122.0 (Ar-CH), 123.9 (Ar-CH), 124.9 (Ar-C), 129.1 (Ar-CH), 143.8 (C), 145.3 (CH), 167.8 (CO);

HR-MS (ESI) = calcd for $C_{18}H_{27}NO_2Si$: 340.1709, found: 340.1703 (+Na);

$[\alpha]_D^{25.2}$=-40.941 (*c*= 1.95, MeOH);

(*S,Z*)-3-(2-((tert-butyldimethylsilyl)oxy)propylidene)-5-methoxy-1-methylindolin-2-one (27d) (90% combined yield with *cis*:*trans* = 1:3.9)



27d

Yellow liquid; R_f = 0.52 (SiO_2, ethyl acetate-hexane, 1:9);

IR (neat) 2955, 2931, 2858, 2888, 1703, 1493, 1472, 1372, 1255, 1147, 1085, 1049, 881, 835, 811 cm^{-1};

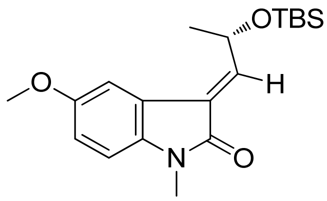
^{1}H NMR (400 MHz, CDCl$_3$) = 0.02 - 0.13 (m, 6 H, Si-Me), 0.91 (s, 9 H, *t*-Bu), 1.36 (d, *J*=6.29 Hz, 3 H, CH$_3$), 3.20 (s, 3 H, N-CH$_3$), 3.82 (s, 3 H, O-CH$_3$), 5.94 (m, 1 H, CH), 6.73 (d, *J*=7.81 Hz, 1 H, CH), 6.70 (d, *J*=8.56 Hz, 1 H, Ar-CH), 6.83 (dd, *J*=8.31, 2.52 Hz, 1 H, Ar-CH), 7.02 (d, *J*=2.52 Hz, 1 H, Ar-CH).

^{13}C NMR (100 MHz, CDCl$_3$) = -4.7 (CH$_3$), -4.6 (CH$_3$), 18.1 (C), 23.6 (CH$_3$), 25.7 (CH$_3$), 25.8 (CH$_3$), 55.9 (CH$_3$), 64.3 (CH), 106.3 (Ar-CH), 108.3 (Ar-CH), 114.1 (Ar-CH), 123.5 (Ar-C), 124.7 (Ar-C), 136.7 (C), 145.4 (CH), 155.6 (Ar-C), 166.5 (CO).

HR-MS (ESI) = calcd for $C_{19}H_{29}NO_3Si$: 370.1814, found: 370.1811 (+Na);

[α]$_D^{27.0}$ =+9.454 (*c* = 1.27, MeOH);

(*S,E*)-3-(2-((tert-butyldimethylsilyl)oxy)propylidene)-5-methoxy-1-methylindolin-2-one (28d)



28d

Yellow liquid; R$_f$= 0.34 (SiO$_2$, ethyl acetate-hexane, 1:9);

IR (neat) 2930, 2857, 1711, 1659, 1489, 1470, 1256, 1142, 1123, 1087, 1033, 834, 721, 675 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$) = 0.01 - 0.09 (m, 6 H, Si-Me), 0.90 (s, 10 H, *t*-Bu), 1.41 (d, *J*=6.29 Hz, 3 H, CH$_3$), 3.22 (s, 3 H, N-CH$_3$), 3.83 (s, 3 H, O-CH$_3$), 5.16 (quin, *J*=6.80 Hz, 1 H, CH), 6.73 (d, *J*=8.31 Hz, 1 H, CH), 6.84 (dd, *J*=8.44, 2.39 Hz, 1 H, Ar-CH), 6.97 - 7.10 (m, 2 H, Ar-CH);

^{13}C NMR (100 MHz, CDCl$_3$) = -4.7 (CH$_3$), -4.5 (CH$_3$), 18.1 (C), 22.7 (CH$_3$), 25.7 (CH$_3$), 26.1 (CH$_3$), 55.9 (CH$_3$), 65.9 (CH), 108.1 (Ar-CH), 112.2 (Ar-CH), 112.8 (Ar-CH), 122.2 (Ar-C), 125.3 (Ar-C), 137.9 (C), 145.6 (CH), 155.4 (Ar-C), 167.7 (CO);

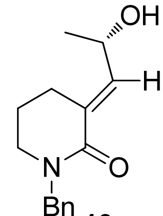
HR-MS (ESI) = calcd for $C_{19}H_{29}NO_3Si$: 370.1814, found: 370.1805 (+Na);

[α]$_D^{27.1}$ =-22.568 (*c* = 1.76, MeOH);

General procedure for O-TBS group deprotection: illustrated by 13.

In a 250 mL round bottom flask, **11** (12.670 g, 0.035 mol) dissolved in methanol (120 mL) was cooled at 0^{0}C and *p*-toluenesulfonic acid monohydrate (0.67 g, 3.5 mmol) was added while stirring. After stirring at room temp for 2 h, methanol was removed and saturated NaHCO$_3$ solution was added. Aqueous layer was extracted with ethyl acetate (3×100 mL), washed with water and brine and dried over Na$_2$SO$_4$, concentrated *in vacuo* to give crude product which on purification by silica gel flash column chromatography produced corresponding allylic alcohol **13** in quantitative yield.

(*S,E*)-1-benzyl-3-(2-hydroxypropylidene)piperidin-2-one (13, quantitative yield**)**



13

Light brown solid; mp-64.1-65.1 ºC; R_f = 0.11 (SiO_2, ethyl acetate-hexane, 1:1);

IR (neat) 3391, 3062, 3030, 2968, 2928, 2866, 1660, 1602, 1491, 1453, 1346, 1258, 1204, 1062, 740, 700 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$) = 1.24 (d, *J*=6.44 Hz, 3 H, <u>CH_3</u>), 1.63 - 1.81 (m, 2 H, <u>CH_2</u>), 2.25 - 2.63 (m, 2 H, <u>CH_2</u>), 2.96 (br.s, 1 H, <u>OH</u>), 3.13 - 3.26 (m, 2 H, <u>CH_2</u>), 4.43 - 4.64 (m, 3 H, <u>Ar-CH_2</u> & <u>CH</u>), 6.81 (dt, *J*=8.46, 1.77 Hz, 1 H, <u>olefin-CH</u>), 7.09 - 7.35 (m, 5 H, <u>Ar-CH</u>);

^{13}C NMR (50 MHz, $CDCl_3$) = 22.4 (CH_2), 22.6 (CH_3), 24.6 (CH_2), 47.0 (CH_2), 50.9 (CH_2), 64.1 (CH), 127.2 (Ar-CH), 127.9 (Ar-CH), 128.4 (Ar-CH), 137.0 (C), 141.4 (CH), 164.7 (CO);

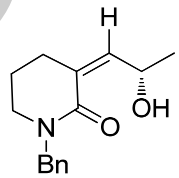
HR-MS (ESI) = calcd for $C_{15}H_{19}NO_2$: 268.1313, found: 268.1307 (+Na);

$[\alpha]_D^{27.5}$ =+11.112 (*c* = 3.29, MeOH)

ee>99%;

HPLC [DICEL CHIRALCEL OD-H COLUMN; 1 mL/min; solvent system: ^{i}PrOH: Hexane =6: 94; retention time 65.4 min.]

(*S,Z*)-1-benzyl-3-(2-hydroxypropylidene)piperidin-2-one (14, quantitative yield**)**



14

Light brown liquid; R_f = 0.4 (SiO_2, ethyl acetate-hexane, 1:1);

IR (neat) 3415, 3029, 2929, 2859, 1749, 1717, 1757, 1604, 1491, 1453, 1360, 1250, 1198, 1064, 736, 702 cm^{-1};

^{1}H NMR (200 MHz, $CDCl_3$) = 1.27 (d, *J*=6.57 Hz, 3 H, <u>CH_3</u>), 1.67 - 1.89 (m, 2 H, <u>CH_2</u>), 2.35 - 2.49 (m, 2 H, <u>CH_2</u>), 3.14 - 3.28 (m, 2 H, <u>CH_2</u>), 4.36 (br. s., 1 H, <u>OH</u>), 4.58 (s, 2 H, <u>Ar-</u>

CH2), 4.71 (quin, *J*=6.44 Hz, 1 H, CH), 5.86 (dt, *J*=5.94, 1.52 Hz, 1 H, CH), 7.10 - 7.39 (m, 5 H, Ar-CH);

^{13}C NMR (50 MHz, $CDCl_3$) = 22.6 (CH_3), 23.0 (CH_2), 32.0 (CH_2), 47.5 (CH_2), 50.3 (CH_2), 63.6 (CH), 127.4 (Ar-CH), 127.8 (Ar-CH), 128.6 (Ar-CH), 130.4 (Ar-C), 136.7 (C), 145.1 (CH), 165.4 (CO);

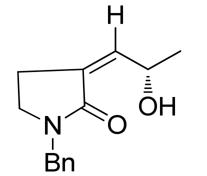
HR-MS (ESI) = calcd for $C_{15}H_{19}NO_2$: 268.1313, found: 268.1305 (+Na);

$[\alpha]_D^{27.5}$ =-16.845 (*c* = 3.6, MeOH)

ee>99%;

HPLC [KROMASIL 5-AmyCoat COLUMN; 1 mL/min; solvent system: ^{i}PrOH: Hexane =5: 95; retention time 45.5 min.]

(*S,Z*)-1-benzyl-3-(2-hydroxypropylidene)pyrrolidin-2-one (22a, quantitative yield**)**



22a

Colourless solid, mp-92.1-94.1 °C; R_f = 0.32 (SiO_2, ethyl acetate-hexane, 1:1);

IR (neat) 3407, 3066, 2968, 2925, 1677, 1650, 1434, 1359, 1294, 1169, 1119, 1067, 886, 752, 697, 646 cm^{-1};

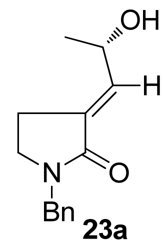
^{1}H NMR (400 MHz, $CDCl_3$) = 1.37 (d, *J*=6.60 Hz, 3 H, CH_3), 1.59(H_2O), 2.71 (ddt, J_1=6.67, 4.42, 2.25, 2.25 Hz, 2 H, CH_2), 3.33 (t, *J*=6.79 Hz, 2 H, CH_2), 4.53 (s, 2 H, Ar-CH_2), 4.89 (br. s., 1 H, OH), 5.91 (br. s., 1 H, CH), 6.01 - 6.11 (m, 1 H, olefin-CH), 7.26 (m, 2 H, Ar-CH), 7.28 - 7.39 (m, 3 H, Ar-CH);

^{13}C NMR (100 MHz, $CDCl_3$) = 23.2 (CH_3), 25.3 (CH_2), 44.3 (CH_2), 47.3 (CH_2), 64.3 (CH), 127.8 (Ar-CH), 128.2 (Ar-CH), 128.7 (Ar-CH), 131.4 (Ar-C), 135.7 (C), 141.1 (CH), 168.6 (CO);

HR-MS (ESI) = calcd for $C_{14}H_{17}NO_2$: 254.1157, found: 254.1154 (+Na);

$[\alpha]_D^{27.5}$ =+8.216 (*c* = 3.15, MeOH)

(*S,E*)-1-benzyl-3-(2-hydroxypropylidene)pyrrolidin-2-one (23a, quantitative yield**)**



23a

Light brown liquid; R_f = 0.1 (SiO_2, ethyl acetate-hexane, 6:4);

IR (neat) 3393, 2969, 2924, 1959, 1493, 1448, 1363, 1312, 1254, 1158, 1118, 1063, 723 cm^{-1};

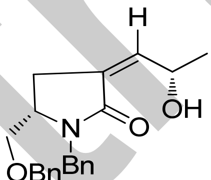
^{1}H NMR (400 MHz, CDCl$_3$) = 1.34 (d, *J*=6.55 Hz, 3 H, CH_3) 2.17 (br. s., 1 H, OH) 2.60 - 2.72 (m, 1 H, CH_2) 2.73 - 2.82 (m, 1 H, CH_2) 3.29 (t, *J*=6.80 Hz, 2 H, CH_2) 4.49 - 4.59 (m, 3 H, N-CH_2-Ar, & CH) 6.49 (dt, *J*=7.81, 2.77 Hz, 1 H, olefin-CH) 7.23 - 7.26 (m, 2 H, Ar-CH) 7.28 - 7.37 (m, 3 H, Ar-CH)

^{13}C NMR (100 MHz, CDCl$_3$) = 21.5 (CH_2), 22.6 (CH_3), 43.8 (CH_2), 47.2 (CH_2), 65.8 (CH), 127.6 (Ar-CH), 128.2 (Ar-CH), 128.6 (Ar-CH), 131.2 (Ar-C), 135.5 (CH), 136.1 (C), 168.37 (CO);

HR-MS (ESI) = calcd for $C_{14}H_{17}NO_2$: 254.1157, found: 254.1150 (+Na);

$[\alpha]_D^{27.2}$ =+6.111 (*c* = 4.23, MeOH)

(*S*,*Z*)-1-benzyl-5-((benzyloxy)methyl)-3-((*S*)-2-hydroxypropylidene)pyrrolidin-2-one (22b, quantitative yield**)**



22b

Colourless liquid; R_f = 0.5 (SiO_2, ethyl acetate-hexane, 6:4);

IR (neat) 3411, 3064, 3031, 2971, 2926, 2964, 1668, 1647, 1495, 1445, 1359, 1253, 115, 1077, 911, 733, 700 cm^{-1}

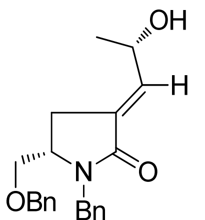
^{1}H NMR (400 MHz, CDCl$_3$) = 1.37 (d, *J*=6.55 Hz, 3 H, CH_3), 2.52 - 2.60 (m, 1 H, CH_2), 2.71 - 2.82 (m, 1 H, CH_2), 3.41 - 3.49 (m, 2 H, CH_2), 3.66 - 3.76 (m, 1 H, CH), 4.21 (d, *J*=14.86 Hz, 1 H, Ar-CH_2), 4.38 - 4.47 (m, 2 H, Ar-CH_2), 4.86 - 5.04 (m, 2 H, Ar-CH_2 & CH), 5.93 (br. s., 1 H, OH), 6.01 - 6.08 (m, 1 H, olefin-CH), 7.20 (d, *J*=6.55 Hz, 2 H, Ar-CH), 7.24 - 7.52 (m, 8 H, Ar-CH);

^{13}C NMR (100 MHz, CDCl$_3$) = 23.1 (CH_3), 29.5 (CH_2), 45.3 (CH_2), 54.7 (CH), 64.4 (CH), 70.6 (CH_2), 73.2 (CH_2), 127.5 (Ar-CH), 127.6 (Ar-CH), 127.8 (Ar-CH), 128.0 (Ar-CH), 128.4 (Ar-CH), 128.5 (Ar-CH), 130.5 (Ar-C), 136.2 (Ar-C), 137.4 (C) 141.0 (CH), 169.0 (CO);

HR-MS (ESI) = calcd for $C_{22}H_{25}NO_3$: 374.1732, found: 374.1722 (+Na);

[α]$_D$$^{24.3}$ =+93.074 (*c* = 1.54, MeOH);

(*S,E*)-1-benzyl-5-((benzyloxy)methyl)-3-((*S*)-2-hydroxypropylidene)pyrrolidin-2-one (23b, quantitative yield**)**



23b

Colourless solid; mp-94.1-95.8 ºC; R_f = 0.25 (SiO_2, ethyl acetate-hexane, 6:4);

IR (neat) 3391, 3063, 3031, 2970, 2863, 1664, 1495, 1441, 1361, 1307, 1246, 1117, 1067, 910, 732, 700 cm^{-1}

^{1}H NMR (400 MHz, $CDCl_3$) = 1.40 (d, *J*=6.46 Hz, 3 H, CH_3), 2.58 (dt, *J*=17.24, 2.97 Hz, 1 H, CH_2), 2.86 (ddd, *J*=17.24, 8.51, 2.71 Hz, 1 H, CH_2), 3.42 - 3.56 (m, 2 H, CH_2), 3.72 (dq, *J*=8.47, 4.17 Hz, 1 H, CH), 4.28 (d, *J*=14.97 Hz, 1 H, Ar-CH_2), 4.40 - 4.53 (m, 2 H, Ar-CH_2), 4.53 - 4.66 (m, 1 H, CH), 5.06 (d, *J*=14.97 Hz, 1 H, Ar-CH_2), 6.58 (dt, *J*=7.85, 2.68 Hz, 1 H, olefin-CH) ,7.19 - 7.48 (m, 10 H, Ar-CH);

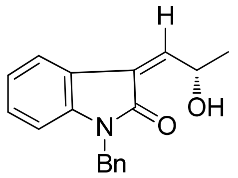
^{13}C NMR (100 MHz, $CDCl_3$) = 22.6 (CH_3), 25.9 (CH_3), 45.3 (CH_2), 54.3 (CH), 65.7 (CH), 70.8 (CH_2), 73.1 (CH_2), 127.3 (Ar-CH), 127.6 (Ar-CH), 127.8 (Ar-CH), 128.1 (Ar-CH), 128.3 (Ar-CH), 128.4 (Ar-CH), 130.4 (Ar-C), 135.7 (CH), 136.6 (C), 137.5 (Ar-C), 168.9 (CO);

HR-MS (ESI) = calcd for $C_{22}H_{25}NO_3$: 374.1732, found: 374.1723 (+Na);

[α]$_D$$^{24.9}$ =+110.569 (*c* = 2.60, MeOH);

E and *Z* isomer in oxindole ring system were found isomerizing at room temperature in the presence of light. Some isomerisation during TBS group deprotection was also observed. ***E*** and *Z* isomers were purified by silica gel flash column chromatography (using ethyl acetate and n-hexane) and proceed for the next step immediately.

(*S,Z*)-1-benzyl-3-(2-hydroxypropylidene)indolin-2-one (29a, yield 91%**)**



29a

Yellow liquid; R_f = 0.65 (SiO_2, ethyl acetate-hexane, 1:1);

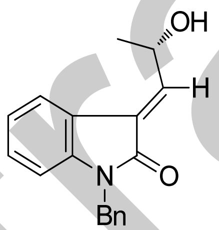
^{1}H NMR (400 MHz, $CDCl_3$) = 1.52 (d, *J*=6.80 Hz, 3 H, CH_3), 4.97 (s, 2 H, Ar-CH_2), 5.12 - 5.38 (m, 2 H, CH & OH), 6.74 (d, *J*=7.81 Hz, 1 H, Ar-CH), 6.99 - 7.07 (m, 2 H, Ar-CH & olefin-CH), 7.19 (t, *J*=8.18 Hz, 2 H, 2Ar-CH), 7.27 - 7.36 (m, 5 H, Ar-CH), 7.42 (d, *J*=7.55 Hz, 1 H, Ar-CH);

^{13}C NMR (100 MHz, $CDCl_3$) = 22.75 (CH_3), 43.69 (CH_2), 64.85 (CH), 109.30 (Ar-CH), 119.65 (Ar-CH), 122.52 (Ar-CH), 122.68 (Ar-C), 127.28 (Ar-CH), 127.70 (Ar-CH),127.80(Ar-C), 128.81 (Ar-CH), 129.23 (Ar-CH), 135.58 (Ar-C), 141.75 (C), 145.30 (CH), 167.63 (CO);

HR-MS (ESI) = calcd for $C_{18}H_{17}NO_2$: 302.1157, found: 302.1151 (+Na);

$[\alpha]_D^{25.4}$ =+4.533 (*c* 0.75, MeOH);

(*S*,*E*)-1-benzyl-3-(2-hydroxypropylidene)indolin-2-one (30a, yield 93%**)**



30a

Yellow solid, mp-105.5-107 °C; R_f = 0.48 (SiO_2, ethyl acetate-hexane, 1:1);

IR (neat) 3414, 3062, 3032, 2975, 2928, 1697, 1650, 1610, 1486, 1356, 1189, 1109, 1067, 910, 778, 730, 697 cm^{-1};

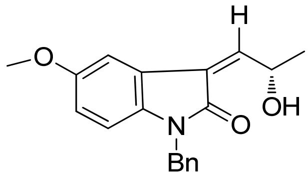
^{1}H NMR (400 MHz, $CDCl_3$) = 1.53 (d, *J*=6.55 Hz, 3 H, CH_3), 3.23 (br. s., 1 H, OH), 4.75 (d, *J*=15.86 Hz, 1 H, Ar-CH_2), 4.95 (d, *J*=15.86 Hz, 1 H, Ar-CH_2), 5.24 (t, *J*=6.80 Hz, 1 H, CH), 6.67 (d, *J*=7.81 Hz, 1 H, Ar-CH), 7.00 - 7.06 (m, 1 H, Ar-CH), 7.09 (d, *J*=8.06 Hz, 1 H, olefin-CH), 7.14 - 7.21 (m, 1 H, Ar-CH), 7.22 - 7.33 (m, 5 H, Ar-CH), 7.50 (d, *J*=7.55 Hz, 1 H, Ar-CH);

^{13}C NMR (100 MHz, $CDCl_3$) = 21.9 (CH_3), 43.6 (CH_2), 64.8 (CH), 109.2 (Ar-CH), 121.0 (Ar-C), 122.3 (Ar-CH), 124.3 (Ar-CH), 126.3 (Ar-C), 127.2 (Ar-CH), 127.5 (Ar-CH), 128.7 (Ar-CH), 129.3 (Ar-CH), 135.6 (Ar-C), 142.8 (C), 144.2 (CH), 168.0 (CO);

HR-MS (ESI) = calcd for $C_{18}H_{17}NO_2$: 302.1157, found: 302.1150 (+Na);

[α]$_D^{25.4}$ =-32.131 (*c* = 1.52, MeOH);

(*S,Z*)-1-benzyl-3-(2-hydroxypropylidene)-5-methoxyindolin-2-one (29b, yield 89%**):**



29b

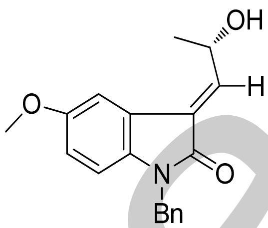
Yellow liquid; R_f = 0.55 (SiO_2, ethyl acetate-hexane, 1:1);

IR (neat) 3430, 2926, 1696, 1600, 1490, 1371, 1284, 1179, 1049, 910, 731, 698 cm^{-1};

HR-MS (ESI) = calcd for $C_{19}H_{19}NO_3$: 332.1263, found: 332.1280 (+Na);

[α]$_D^{23}$ = 8.000 (*c* = 0.90, MeOH);

(*S,E*)-1-benzyl-3-(2-hydroxypropylidene)-5-methoxyindolin-2-one (30b, yield 94%**):**

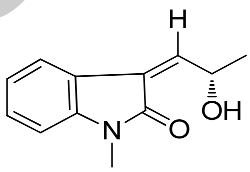


30b

Yellow liquid, R_f = 0.43 (SiO_2, ethyl acetate-hexane, 1:1);

HR-MS (ESI) = calcd for $C_{19}H_{19}NO_3$: 332.1263, found: 332.1272 (+Na);

(*S, Z*)-3-(2-hydroxypropylidene)-1-methylindolin-2-one (29c, yield 93%)



29c

Yellow liquid; R_f = 0.46 (SiO_2, ethyl acetate-hexane, 1:1);

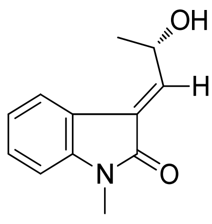
^{1}H NMR (400 MHz, $CDCl_3$) = 1.26 (grease),1.49 (d, *J*=6.80 Hz, 3 H, CH_3), 1.67(H_2O), 3.27 (s, 3 H, -CH_3), 5.16 (s, 1 H , OH), 5.41 - 5.57 (m, 1 H, CH), 6.83 (d, *J*=7.81 Hz, 1 H, Ar-CH), 6.97 (d, *J*=5.54 Hz, 1 H, Ar-CH), 7.07 (t, *J*=7.55 Hz, 1 H, CH), 7.30 (t, *J*=7.68 Hz, 1 H, Ar-CH), 7.41 (d, *J*=7.30 Hz, 1 H, Ar-CH);

^{13}C NMR (100 MHz, $CDCl_3$) = 22.69 (CH_3), 26.03 (CH_3), 64.83 (CH), 108.32 (Ar-CH), 119.54 (Ar-CH), 122.49 (Ar-CH), 122.54 (Ar-C), 127.87 (Ar-C), 129.26 (Ar-CH), 142.48 (C), 144.97 (CH), 167.59 (CO);

HR-MS (ESI) = calcd for $C_{12}H_{13}NO_2$: 226.0844, found: 226.0838 (+Na);

$[\alpha]_D^{24.9}$ =-11.157 (*c* 1.52, MeOH);

(*S, Z*)-3-(2-hydroxypropylidene)-1-methylindolin-2-one (30c, yield 89%**)**



30c

Canary yellow solid, mp- 163.7-165.5 °C; R_f = 0.36 (SiO_2, ethyl acetate-hexane, 1:1);

IR (neat) 3441, 2971, 2928, 1686, 1645, 1607, 1467, 1380, 1066, 1048, 779, 747 cm^{-1};

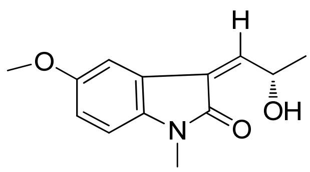
^{1}H NMR (400 MHz, $CDCl_3$) = 1.47 (d, *J*=6.55 Hz, 3 H, CH_3), 2.94 - 3.10 (m, 3 H, N-CH_3), 3.31 (br. s., 1 H, OH), 5.07 - 5.23 (m, 1 H, CH), 6.66 (d, *J*=7.05 Hz, 1 H, Ar-CH), 6.93 (d, *J*=8.06 Hz, 1 H, olefin-CH), 7.02 (t, *J*=7.55 Hz, 1 H, Ar-CH), 7.13 - 7.26 (m, 1 H, Ar-CH), 7.46 (d, *J*=7.55 Hz, 1 H, Ar-CH);

^{13}C NMR (100 MHz, $CDCl_3$) = 21.8 (CH_3), 25.9 (CH_3), 64.5 (CH), 108.1 (Ar-CH), 120.8 (Ar-C), 122.2 (Ar-CH), 124.1 (Ar-CH), 126.3 (Ar-C), 129.3 (Ar-CH), 143.5 (C), 144.2 (CH), 168.0 (CO);

HR-MS (ESI) = calcd for $C_{12}H_{13}NO_2$: 226.0844, found: 226.0836 (+Na);

$[\alpha]_D^{20.9}$ =-61.867 (*c* = 1.42, MeOH);

(*S, Z*)-3-(2-hydroxypropylidene)-5-methoxy-1-methylindolin-2-one (29d, yield 91%**)**



29d

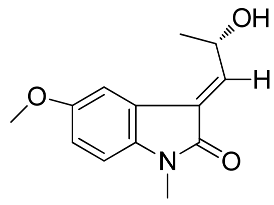
Yellow liquid; R_f = 0.37 (SiO_2, ethyl acetate-hexane, 1:1);

^{1}H NMR (400 MHz, $CDCl_3$) = 1.45 (d, *J*=6.80 Hz, 3 H, CH_3), 3.18 (s, 3 H, N-CH_3), 3.79 (s, 3 H, O-CH_3), 5.16 (br. s., 1 H, OH), 5.57 (m, 1 H, CH), 6.67 (d, *J*=8.56 Hz, 1 H, Ar-CH), 6.80 (dd, *J*=8.56, 2.52 Hz, 1 H, Ar-CH), 6.88 (d, *J*=5.54 Hz, 1 H, olefin-CH), 6.95 (d, *J*=2.27 Hz, 1 H, Ar-CH).

^{13}C NMR (100 MHz, CDCl$_3$) = 22.61 (CH$_3$), 25.98 (CH$_3$), 55.80 (CH$_3$), 64.66 (CH), 106.24 (Ar-CH), 108.67 (Ar-CH), 114.21 (Ar-CH), 123.45 (Ar-C), 127.98 (Ar-C), 136.30 (C), 145.05 (CH), 155.90 (Ar-C), 167.30 (CO).

HR-MS (ESI) = calcd for $C_{13}H_{15}NO_3$: 256.0950, found: 256.0945 (+Na);

(*S, E*)-3-(2-hydroxypropylidene)-5-methoxy-1-methylindolin-2-one (30d, yield 96%**)**



30d

Yellow solid; mp-124.5-126 °C; R_f = 0.27 (SiO$_2$, ethyl acetate-hexane, 1:1);

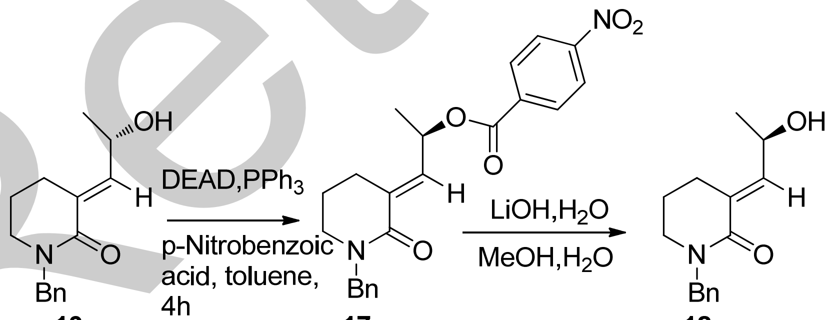
IR (neat) 3437, 2925, 1716, 1470, 1494, 1470, 1373, 1349, 1186, 1037, 754 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$) = 1.45 (d, *J*=6.55 Hz, 3 H, CH$_3$), 3.04 (s, 3 H, N-CH$_3$), 3.40 (br. s., 1 H, OH), 3.80 (s, 3 H, O-CH$_3$), 5.06 - 5.16 (m, 1 H, CH), 6.55 (d, *J*=8.56 Hz, 1 H, Ar-CH), 6.76 (dd, *J*=8.56, 2.52 Hz, 1 H, Ar-CH), 6.92 (d, *J*=8.06 Hz, 1 H, olefin-CH), 7.07 (d, *J*=2.27 Hz, 1 H, Ar-CH);

^{13}C NMR (100 MHz, CDCl$_3$) = 21.8 (CH$_3$), 25.9 (CH$_3$), 55.9 (CH$_3$), 64.4 (CH), 108.2 (Ar-CH), 111.8 (Ar-CH), 113.4 (Ar-CH), 121.7 (Ar-C), 126.6 (Ar-C), 137.4 (C), 144.5 (CH), 155.5 (Ar-C), 167.8 (CO);

HR-MS (ESI) = calcd for $C_{13}H_{15}NO_3$: 256.0950, found: 256.0944 (+Na);

Inversion of stereocenter of 13 by Mitsonubu Recation: Preparation of 18



13 **17** **18**

A two neck round bottom flask, equipped with gas inlet and magnetic stirrer, containing 15 mL toluene, **13** (.680 g, 2.77 mmol) was with PPh$_3$ (2.18 g, 8.83 mmol), DEAD (1.52 mL, 9.71 mmol) and p-Nitrobenzoic acid (1.483 g, 8.88 mmol) and stirred for 3-4 h. Reaction mixture was quenched by adding saturated NaHCO$_3$ solution. Aqueous layer was extracted with ethyl acetate, washed successively with water and brine, dried (Na$_2$SO$_4$) and concentrated *in vacuo* to give crude product which was purified through silica gel flash column chromatography to give **17** (1.046 g, 2.58 mmol, 93%). Saponification of **17** (1.046 g, 2.58 mmol) by stirring (4 h) at r.t. with LiOH-H_2O (0.543 g, 12.94 mmol) in MeOH: H_2O (2:1) followed by usual work up and purification provided **18** (0.604 g, 2.46 mmol, 95%) as a colourless liquid.

***(R,E)*-1-benzyl-3-(2-hydroxypropylidene)piperidin-2-one (18)**

Light brown solid; mp-64.1-65.5 °C; R_f = 0.2 (SiO_2, ethyl acetate-hexane, 3:7);

IR (neat) 3391, 3029, 2967, 2926, 1659, 1601, 1491, 1452, 1345, 1257, 1204, 1264, 1164, 1062, 738, 700 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) = 1.25 (d, *J*=6.29 Hz, 3 H, CH_3), 1.70 - 1.76 (m, 2 H, CH_2), 2.35 - 2.42 (m, 1 H, CH_2), 2.50 - 2.58 (m, 1 H, CH_2), 3.15 - 3.23 (m, 2 H, CH_2), 4.52 - 4.61 (m, 3 H, Ar-CH_2 & CH), 6.81 (d, *J*=8.31 Hz, 1 H, olefin-CH), 7.13 - 7.30 (m, 5 H, Ar-CH);

^{13}C NMR (100 MHz, $CDCl_3$) = 22.4 (CH_2), 22.7 (CH_3), 24.7 (CH_2), 47.0 (CH_2), 51.0 (CH_2), 64.2 (CH), 127.3 (Ar-CH), 127.9 (Ar-CH), 128.5 (Ar-CH), 128.7 (Ar-C), 137.0 (C), 141.2 (CH), 164.7 (CO);

HR-MS (ESI) = calcd for $C_{15}H_{19}NO_2$: 268.1313, found: 268.1306 (+Na);

$[\alpha]_D^{27.2}$ =-8.667 (*c* = 0.9, MeOH);

General Procedure for Jhonson-Claisen rearrangement;

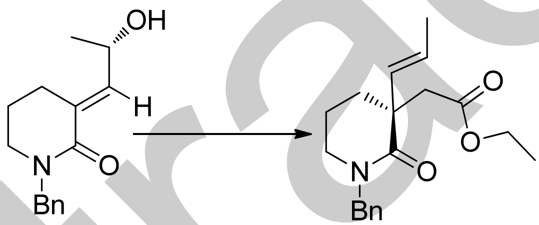
(S,E)-1-benzyl-3-(2-hydroxypropylidene)piperidin-2-one (**13**) was subjected for [3,3]-sigmatropic rearrangement under several reaction condition (see Table 1), however, best result was observed when **13** ((10.562 g, 43.08 mmol) was refluxed with 130 mL triethylorthoacetate and propionic acid (0.32 mL, 4.308 mmol) for 2-8 h.

Table-1: Optimization of Jhonson-Claisen rearrangement

Sl.no	Condition	Conversion to product
1.	$Hg(OAc)_2$, ethyl vinyl ether, 48 h, 45 ^{0}C	SM recovered
2.	$Pd(OAc)_2$, ethyl vinyl ether, 48 h, 45 ^{0}C	SM recovered
3.	$Pd(OAc)_2$1,10-phenanthroline, ethyl vinyl ether, 48h, 45^{0}C	SM recovered
4	$Pd(OAc)_2$, 1,10-phenanthroline, tri(ethylene glycol) divinyl ether, 48 h, 80^{0}C	SM recovered
5	$Pd(OAc)_2$, 1,10-phenanthroline, tri(ethylene glycol) divinyl ether, 48 h, 120^{0}C	Complex reaction mixture
6	2 equiv. Triethylorthoacetate, 0.1 equiv. Propionic acid, 80^{0}C, 6 h, Toluene	SM recovered
7	2 equiv. Triethylorthoacetate, 0.1 equiv. Propionic acid, 95^{0}C, 6 h, Toluene	10% conversion
8	2 equiv. Triethylorthoacetate, 0.1 equiv. Propionic acid, 100 ^{0}C, 10 h, Toluene	15% conversion
9	2 equiv. Triethylorthoacetate, 0.1 equiv. Propionic	23% conversion

	acid,reflux, 6 h, Toluene	
10	5 equiv. Triethylorthoacetate, 0.1 equiv. Propionic acid, reflux, 12 h, Toluene	69% conversion
11	5 equiv. Triethylorthoacetate, 0.2 equiv. Propionic acid, reflux, 12 h, Toluene	65% conversion
12	10 equiv. Triethylorthoacetate, 0.2 equiv. Propionic acid, reflux, 12 h, Toluene	76% conversion
13	10 equiv. Triethylorthoacetate, 0.1 equiv. Propionic acid, reflux, 12 h, Toluene	78% conversion
14	5 equiv. Triethylorthoacetate, 0.1 equiv. Propionic acid, reflux, 21 h, Toluene	71% conversion
15	10 eqviv Triethylorthoacetate, 0.1 equiv. Propionic acid, reflux, 21 h, Toluene	82% conversion
16	5 equiv. Triethylorthoacetate, 0.1 equiv. Propionic acid, 140^0C, 3 h, xylene	60% conversion
17	Triethylorthoacetate (neat), 0.1 equiv. Propionic acid, 80^0C, 3 h	10% conversion
18	Triethylorthoacetate (neat), 0.1 equiv. Propionic acid, 110^0C, 6 h	50% conversion
19	Triethylorthoacetate (neat), 0.1 equiv. Propionic acid, reflux, 2-8 h	100% conversion

(*R, E*)-ethyl-2-(1-benzyl-2-oxo-3-(prop-1-en-1-yl)piperidin-3-yl)acetate (15, 97% yield**)**



13 **15**

Colourless liquid; R_f = 0.55 (SiO_2, ethyl acetate-hexane, 2:8);

IR (neat) 3029, 2936, 2869, 1733, 1639, 1491, 1451, 1355, 1180, 1031, 963, 736, 701 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) = 1.24 (t, *J*=7.18 Hz, 3H, <u>CH_3</u>), 1.71 (d, *J*=6.29 Hz, 3H, <u>CH_3</u>), 1.78 (d, *J*=13.09 Hz, 1 H, <u>CH_2</u>), 1.91 (d, *J*=12.09 Hz, 1 H, <u>CH_2</u>), 2.17 (td, *J*=13.16, 3.15 Hz, 1 H, <u>CH_2</u>), 2.38 (d, *J*=16.62 Hz, 1 H, <u>CH_2</u>), 3.14 - 3.25 (m, 2 H, <u>CO-CH_2</u> & <u>N-CH_2</u>), 3.26 - 3.36 (m, 1 H, <u>CH_2</u>), 4.09 - 4.15 (m, 2 H, <u>CH_2</u>), 4.50 (d, *J*=14.60 Hz, 1 H, <u>Ar-CH_2</u>), 4.76 (d, *J*=14.86 Hz, 1 H, <u>Ar-CH_2</u>), 5.40 - 5.49 (m, 1 H, <u>olefin-CH</u>), 5.59 (dq, *J*=15.71, 6.35 Hz, 1 H, <u>olefin-CH</u>), 7.22 - 7.38 (m, 5 H, <u>Ar-CH</u>);

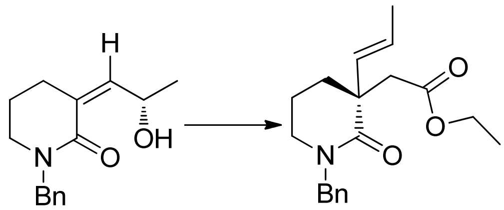
^{13}C NMR (100 MHz, $CDCl_3$) = 14.1 (CH_3), 18.0 (CH_3), 19.3 (CH_2), 31.0 (CH_2), 43.3 (CH_2), 46.4 (C), 47.5 (CH_2), 50.5 (CH_2), 60.1 (CH_2), 125.7 (CH), 127.1 (Ar-CH), 128.0 (Ar-CH), 128.4 (Ar-CH), 134.2 (CH), 137.4 (Ar-C), 171.5 (NCO), 172.1 (OCO);

HR-MS (ESI) = calcd for $C_{19}H_{25}NO_3$: 338.1732, found: 338.1732 (+Na);

$[\alpha]_D^{20.8}$ =+26.222 (*c* = 3.15, MeOH); *ee* > 99%;

HPLC [DICEL CHIRALCEL OD-H COLUMN; 1 mL/min; solvent system: ⁱPrOH: Hexane =10: 90; retention time 6.7 min.];

(*S, E*)-ethyl-2-(1-benzyl-2-oxo-3-(prop-1-en-1-yl)piperidin-3-yl)acetate (16, yield-97%**)**

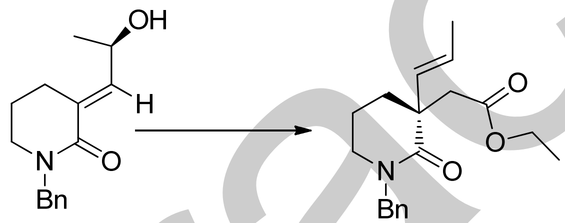


14 16

$[\alpha]_D^{24.8}$ =-23.324 (*c* = 1.36, MeOH); *ee* > 99%;

HPLC [DICEL CHIRALCEL OD-H COLUMN; 1 mL/min; solvent system: ⁱPrOH: Hexane =10: 90; retention time 9.5 min.];

(*S,E*)-ethyl-2-(1-benzyl-2-oxo-3-(prop-1-en-1-yl)piperidin-3-yl)acetate(16) from 18 (yield-93% **)**

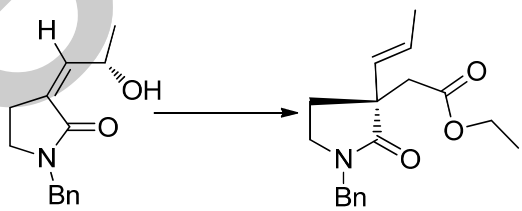


18 16

$[\alpha]_D^{24.8}$ =-22.608 (*c* = 2.5, MeOH); *ee* = 97%;

HPLC [DICEL CHIRALCEL OD-H COLUMN; 1 mL/min; solvent system: ⁱPrOH: Hexane =10: 90; retention time 6.7 min. (minor isomer) and 9.6 min. (major isomer).

(*S,E*)-ethyl-2-(1-benzyl-2-oxo-3-(prop-1-en-1-yl)pyrrolidin-3-yl)acetate (24a, yield-95%**)**



22a 24a

colourless liquid; R_f = 0.41 (SiO_2, ethyl acetate-hexane, 2:8);

IR (neat) 3030, 1692, 1743, 1494, 1435, 1370, 1270, 1181, 1113, 1030, 972, 738, 701 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) =1.24 (t, *J*=7.18 Hz, 3 H, OCH_2CH_3), 1.69 (dd, *J*=6.04, 1.01 Hz, 3 H, CH_3), 2.11 - 2.27 (m, 2 H, CH_2), 2.66 - 2.76 (m, 2 H, OCH_2), 3.12 - 3.23 (m, 2 H, N-CH_2), 4.12 (q, *J*=7.05 Hz, 2 H, OCH_2), 4.48 (s, 2 H, Ar-CH_2), 5.44 - 5.54 (m, 1 H, olefin-

CH), 5.60 (dq, *J*=15.71, 6.01 Hz, 1 H, olefin-CH), 7.22 - 7.26 (m, 2 H, 2Ar-CH), 7.27 - 7.37 (m, 3 H, Ar-CH);

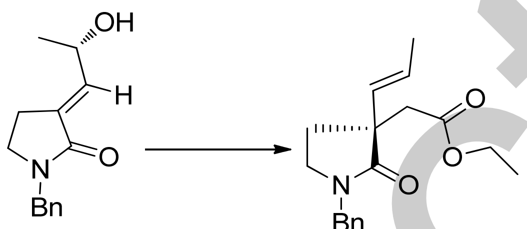
^{13}C NMR (100 MHz, CDCl$_3$) = 14.1 (CH$_3$), 17.9 (CH$_2$), 29.6 (CH$_2$), 40.8 (CH$_2$), 43.4 (CH$_2$), 46.8 (CH$_2$), 48.3 (C), 60.2 (CH$_2$), 125.6 (olefin-CH), 127.4 (Ar-CH), 127.9 (Ar-CH), 128.5 (Ar-CH), 130.9 (olefin-CH), 136.3 (Ar-C), 171.0 (NCO), 175.4 (OCO);

HR-MS (ESI) = calcd for $C_{18}H_{23}NO_3$: 324.1576, found: 324.1572 (+Na);

$[\alpha]_D^{23.5}$ =-23.162 (*c* = 1.91, MeOH); *ee* > 99%;

HPLC [DICEL CHIRALCEL OD-H COLUMN; 1 mL/min; solvent system: ^{i}PrOH: Hexane =10: 90; retention time 11.2 min.];

(*R,E*)-ethyl-2-(1-benzyl-2-oxo-3-(prop-1-en-1-yl)pyrrolidin-3-yl)acetate (25a, yield-95%)

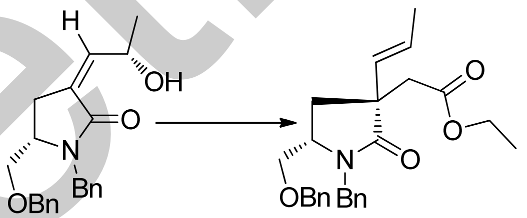


23a **25a**

$[\alpha]_D^{24.7}$ =+22.057 (*c* = 0.70, MeOH); *ee* > 99%;

HPLC [DICEL CHIRALCEL OD-H COLUMN; 1 mL/min; solvent system: ^{i}PrOH: Hexane =10: 90; retention time 8.5 min.];

Ethyl-2-((*3S,5S*)-1-benzyl-5-((benzyloxy)methyl)-2-oxo-3-((*E*)-prop-1-en-1-yl)pyrrolidin-3-yl)acetate (24b, yield 94%)



22b **24b**

Colourless liquid; R_f = 0.48 (SiO_2, ethyl acetate-hexane, 2:8);

IR (neat) 3063, 3031, 2979, 2916, 2861, 1733, 1691, 1451, 1370, 1258, 1181, 1104, 1029, 734, 700 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$) = 1.16 (t, *J*=7.12 Hz, 3 H, OCH$_2$CH$_3$), 1.58 (d, *J*=6.02 Hz, 3 H, CH$_3$), 1.92 (dd, *J*=12.69, 9.32 Hz, 1 H, CH$_2$CO), 2.19 (dd, *J*=12.91, 6.75 Hz, 1 H, CH$_2$CO), 2.60 - 2.76 (m, 2 H, CH$_2$), 3.32 - 3.44 (m, 2 H, Ar-CH$_2$), 3.47 - 3.61 (m, 1 H, CH), 3.98 - 4.13 (m, 3 H, N-CH$_2$-Ar & O-CH$_2$-Ar), 4.23 - 4.38 (m, 2 H, OCH$_2$CH$_3$), 4.81 (d, *J*=14.97 Hz, 1

H, O-CH_2-Ar), 5.34 - 5.44 (d, J=16 Hz, 1 H, olefin-CH), 5.44 - 5.57 (m, 1 H, olefin-CH), 7.06 (d, *J*=5.87 Hz, 2 H, Ar-CH), 7.15 - 7.21 (m, 5 H, Ar-CH), 7.21 - 7.32 (m, 3 H, Ar-CH);

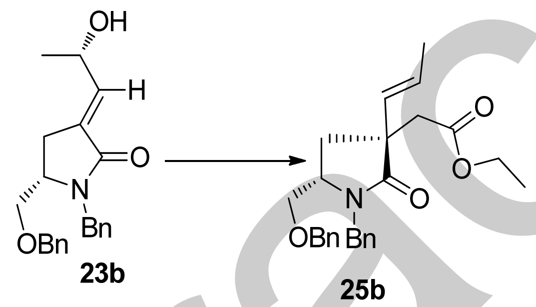
^{13}C NMR (100 MHz, $CDCl_3$) = 14.1 (CH_3), 17.9 (CH_3), 33.2 (CH_2), 41.1 (CH_2), 44.9 (CH_3), 47.9 (C), 54.0 (CH), 60.3 (CH_2), 71.2 (CH_2), 73.2 (CH_2), 125.8 (olefin-CH), 127.1 (Ar-CH), 127.7 (Ar-CH), 127.9 (Ar-CH), 128.3 (Ar-CH), 128.3 (Ar-CH), 130.9 (olefin-CH), 136.9 (Ar-C), 137.6 (Ar-C), 171.1 (NCO), 176.0 (OCO);

HR-MS (ESI) = calcd for $C_{26}H_{31}NO_4$: 444.2151, found: 444.2147 (+Na);

$[\alpha]_D^{24.6}$ =+19.720 (*c* = 1.54, MeOH); *ee* > 99 %;

HPLC [DICEL CHIRALCEL OD-H COLUMN; 1 mL/min; solvent system: ^{i}PrOH: Hexane =10: 90; retention time 11.5 min.];

Ethyl-2-((*3R,5S*)-1-benzyl-5-((benzyloxy)methyl)-2-oxo-3-((*E*)-prop-1-en-1-yl)pyrrolidin-3-yl)acetate (25b, yield 95%)



Colourless liquid; R_f = 0.48 (SiO_2, ethyl acetate-hexane, 2:8);

IR (neat) 3063, 3031, 2979, 2918, 2860, 1732, 1692, 1496, 1451, 1370, 1255, 1109, 1030, 973, 740, 700 cm^{-1};

^{1}H NMR (800 MHz, $CDCl_3$) = 1.23 (t, *J*=7.04 Hz, 3 H, OCH_2CH_3), 1.65 (d, *J*=4.99 Hz, 3 H, CH_3), 2.05 (dd, *J*=13.50, 4.11 Hz, 1 H, CH_2CO), 2.37 (dd, *J*=13.50, 9.10 Hz, 1 H, CH_2CO), 2.65 - 2.67 (m, 1 H, CH_2), 2.69 - 2.71 (m, 1 H, CH_2), 3.44 (dd, *J*=9.68, 4.70 Hz, 1 H, Ar-CH_2), 3.48 (dd, *J*=9.68, 5.58 Hz, 1 H, Ar-CH_2), 3.66 (dq, *J*=9.46, 4.67 Hz, 1 H, CH), 4.10 (q, *J*=7.14 Hz, 2 H, OCH_2CH_3), 4.22 (d, *J*=14.67 Hz, 1 H, O-CH_2-Ar), 4.39 (d, *J*=11.74 Hz, 1 H, N-CH_2-Ar), 4.44 (d, *J*=11.74 Hz, 1 H, N-CH_2-Ar), 4.92 (d, *J*=14.97 Hz, 1 H, O-CH_2-Ar), 5.44 - 5.76 (m, 2 H, olefin-CH), 7.15 - 7.34 (m, 8 H, Ar-CH), 7.34 - 7.45 (m, 2 H, Ar-CH);

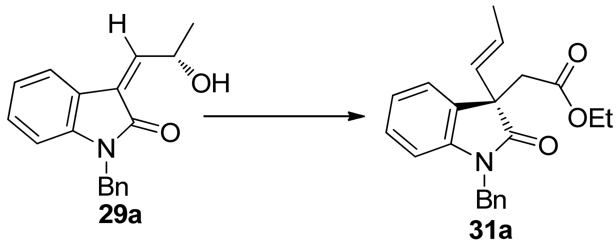
^{13}C NMR (201 MHz, $CHCl_3$) = 14.1 (CH_3), 18.0 (CH_3), 32.5 (CH_2), 41.4 (CH_2), 45.6 (CH_3), 47.6 (C), 54.3 (CH), 60.3 (CH_2), 71.5 (CH_2), 73.1 (CH_2), 125.4 (olefin-CH), 127.2 (Ar-CH), 127.6 (Ar-CH), 127.7 (Ar-CH), 128.2 (Ar-CH), 128.3 (Ar-CH), 128.4 (olefin-CH), 133.0 (Ar-CH), 136.8 (Ar-C), 137.7 (Ar-C), 170.9 (NCO), 176.1 (OCO);

HR-MS (ESI) = calcd for $C_{26}H_{31}NO_4$: 444.2151, found: 444.2150 (+Na);

$[\alpha]_D^{24.5}$ =+66.641 (*c* = 3.29, MeOH); *ee* > 99 %;

HPLC [DICEL CHIRALCEL OD-H COLUMN; 1 mL/min; solvent system: ^{i}PrOH: Hexane =10: 90; retention time 8.6 min.];

(*S,E*)-ethyl-2-(1-benzyl-2-oxo-3-(prop-1-en-1-yl)indolin-3-yl)acetate (31a, yield 89%**)**



Colourless liquid;

IR (neat) 3030, 2980, 2919, 1714, 1612, 1489, 1466, 1360, 1184, 1030, 971, 753, 698 cm^{-1};

^{1}H NMR (800 MHz, CDCl$_3$) = 0.94 - 0.97 (m, 3 H, OCH$_2$<u>CH$_3$</u>), 1.68 (dd, *J*=6.53, 1.51 Hz, 3 H, <u>CH$_3$</u>), 2.99 (d, *J*=16.56 Hz, 1 H, <u>CH$_2$CO</u>), 3.26 (d, *J*=16.56 Hz, 1 H, <u>CH$_2$CO</u>), 3.84 (dq, J_1=10.67, J_2=7.32 Hz, 1 H, <u>-OCH$_2$</u>), 3.95 (dq, J_1=11.04, J_2=7.03 Hz, 1 H, <u>-OCH$_2$</u>), 4.87 (d, *J*=16.06 Hz, 1 H, <u>-NCH$_2$-Ar</u>), 5.06 (d, *J*=16.06 Hz, 1 H, <u>-NCH$_2$-Ar</u>), 5.48 (dq, *J*=15.56, 6.53 Hz, 1 H, <u>olefin-CH</u>), 5.64 (dd, *J*=15.56, 1.51 Hz, 1 H, <u>olefin-CH</u>), 6.74 (d, *J*=7.53 Hz, 1 H, <u>Ar-CH</u>), 7.05 (t, *J*=7.53 Hz, 1 H, <u>Ar-CH</u>), 7.17 - 7.20 (m, 1 H, <u>Ar-CH</u>), 7.21 (d, *J*=7.03 Hz, 1 H, <u>Ar-CH</u>), 7.26 - 7.29 (m, 1 H, <u>Ar-CH</u>), 7.32 - 7.34 (m, 2 H, <u>Ar-CH</u>), 7.35 - 7.37 (m, 2 H, <u>Ar-CH</u>);

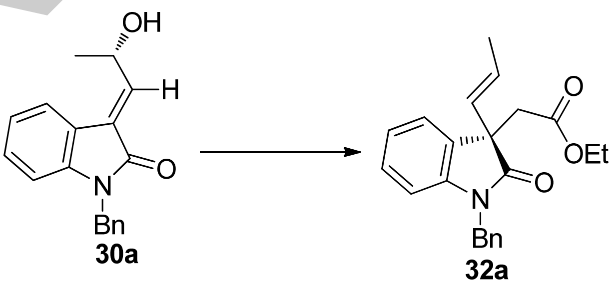
^{13}C NMR (200 MHz, CDCl$_3$) = 13.7 (CH$_3$), 17.8 (CH$_3$), 40.6 (CH$_2$), 43.9 (CH$_2$), 52.0 (C), 60.4 (CH$_2$), 109.2 (Ar-CH), 122.2 (Ar-CH), 123.7 (Ar-CH), 127.1 (olefin-CH), 127.2 (Ar-CH), 127.4 (Ar-CH), 128.1 (Ar-CH), 128.6 (Ar-CH), 129.9 (olefin-CH), 130.4 (Ar-C), 136.0 (Ar-C), 143.0 (Ar-C), 169.5 (NCO), 177.9 (OCO);

HR-MS (ESI) = calcd for $C_{22}H_{23}NO_3$: 372.1576, found: 372.1582 (+Na);

$[\alpha]_D^{19.8}$ =+9.622(*c* = 0.37, MeOH); *ee* =77%;

HPLC [DICEL CHIRALCEL OD-H COLUMN; 1 mL/min; solvent system: ^{i}PrOH: Hexane =10: 90; retention time 7.6 min. (minor isomer) 10.7 min. (major isomer)];

(*R,E*)-ethyl-2-(1-benzyl-2-oxo-3-(prop-1-en-1-yl)indolin-3-yl)acetate (32a, yield 91%**)**

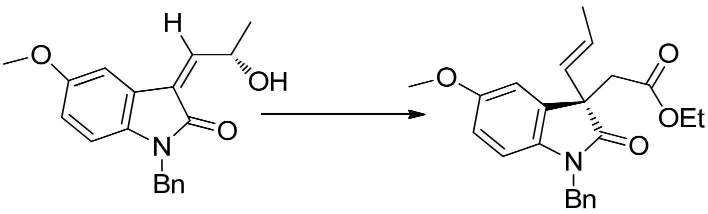


Colourless liquid;

$[\alpha]_D^{19.7}$ = -16.392 (*c* =0.51, MeOH); *ee* =79%

HPLC [DICEL CHIRALCEL OD-H COLUMN; 1 mL/min; solvent system: ^{i}PrOH: Hexane =10: 90; retention time 7.5 min. (major isomer) 10.7 min. (minor isomer)];

(*S,E*)-ethyl-2-(1-benzyl-5-methoxy-2-oxo-3-(prop-1-en-1-yl)indolin-3-yl)acetate(31b yield 88%**)**



29b **31b**

Colourless liquid; R_f = 0.4 (SiO_2, ethyl acetate-hexane, 2:8);

IR (neat) 3031, 2979, 2937, 1727, 1711, 1601, 1488, 1347, 1195, 1028, 970, 871, 807, 739, 698, 608 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) = 0.98 (t, *J*=7.05 Hz, 3 H, OCH_2CH_3), 1.67 (d, *J*=6.29 Hz, 3 H, CH_3), 2.94 (d, *J*=16.37 Hz, 1 H, CH_2CO), 3.23 (d, *J*=16.37 Hz, 1 H, CH_2CO), 3.76 (s, 3 H, O-CH_3), 3.83 - 4.01 (m, 2 H, O -CH_2), 4.83 (d, *J*=15.61 Hz, 1 H, Ar-CH_2), 5.01 (d, *J*=15.86 Hz, 1 H, Ar-CH_2), 5.47 (dd, *J*=15.36, 6.29 Hz, 1 H, olefin-CH), 5.61 (d, *J*=15.36 Hz, 1 H, olefin-CH), 6.60 (d, *J*=8.56 Hz, 1 H, Ar-CH), 6.66 - 6.70 (m, 1 H, Ar-CH), 6.79 - 6.85 (m, 1 H, Ar-CH), 7.24 - 7.38 (m, 5 H, Ar-CH).

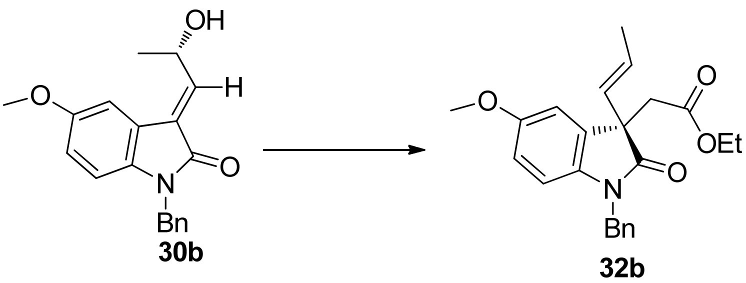
^{13}C NMR (100 MHz, $CDCl_3$) = 13.8 (CH_3), 17.8 (CH_3), 40.6 (CH_2), 44.0 (CH_2), 52.4 (C), 55.7 (CH_3), 60.4 (CH_2), 109.5 (Ar-CH), 111.4 (Ar-CH), 112.1 (Ar-CH), 127.2 (Ar-CH), 127.2 (Ar-CH), 127.4 (olefin-CH), 128.6 (Ar-CH), 130.0 (olefin-CH), 131.9 (Ar-C), 136.1 (Ar-C), 136.6 (Ar-C), 155.7 (Ar-C), 169.5 (NCO), 177.6 (OCO).

HR-MS (ESI) = calcd for $C_{23}H_{25}NO_4$: 402.1681, found: 402.1654 (+Na);

$[\alpha]_D^{23.5}$ = +6.560 (*c* =1.75, MeOH); *ee* =64%;

HPLC [DICEL CHIRALCEL OD-H COLUMN; 1 mL/min; solvent system: ^{i}PrOH: Hexane =10: 90; retention time 8.9 min. (minor isomer) 11.5 min. (major isomer)];

(*R,E*)-ethyl-2-(1-benzyl-5-methoxy-2-oxo-3-(prop-1-en-1-yl)indolin-3-yl)acetate (32b,yield-92%**)**

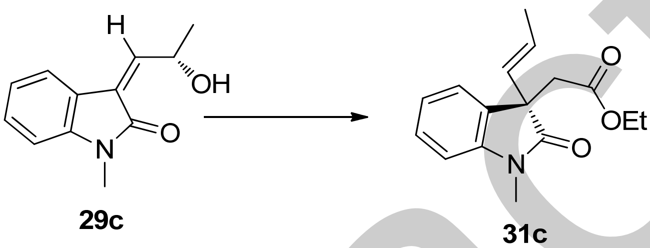


Colourless liquid;

$[\alpha]_D^{23.3}$ = -10.800 (*c* =0.65, MeOH); *ee* =61%;

HPLC [DICEL CHIRALCEL OD-H COLUMN; 1 mL/min; solvent system: ^{i}PrOH: Hexane =10: 90; retention time 8.6 min. (major isomer) 11.6 min. (minor isomer)];

(*S,E*)-ethyl-2-(1-benzyl-2-oxo-3-(prop-1-en-1-yl)indolin-3-yl)acetate (31c, yield 88%**)**



Colourless liquid; R_f = 0.38 (SiO_2, ethyl acetate-hexane, 2:8);

IR (neat) 2925, 2855, 1716, 1613, 1470, 1373, 1349, 1186, 1034, 754 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) = 0.98 (t, *J*=7.05 Hz, 3 H, $OCH_2\underline{CH_3}$), 1.63 (dd, *J*=6.29, 1.01 Hz, 3 H, $\underline{CH_3}$), 2.91 (d, *J*=16.11 Hz, 1 H, $\underline{CH_2}$), 3.17 (d, *J*=16.11 Hz, 1 H, $\underline{CH_2}$), 3.24 (s, 3 H, $\underline{N\text{-}CH_3}$), 3.81 - 3.92 (m, 2 H, $-O\underline{CH_2}CH_3$), 5.39 - 5.49 (m, 1 H, Olefin CH), 5.51 - 5.59 (m, 1 H, Olefin CH), 6.86 (d, *J*=7.81 Hz, 1 H, Ar-CH), 7.06 (t, *J*=7.55 Hz, 1 H, Ar-CH), 7.19 (d, *J*=7.30 Hz, 1 H, Ar-CH), 7.27 - 7.32 (m, 1 H, Ar-CH);

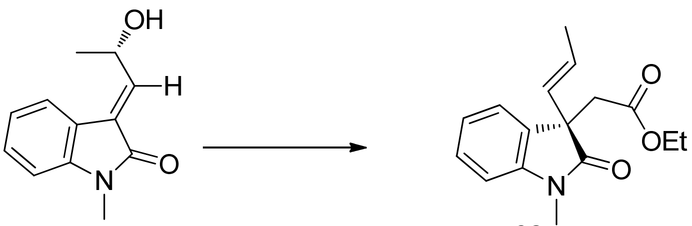
^{13}C NMR (100 MHz, $CDCl_3$) = 13.8 (CH_3), 17.8 (CH_3), 26.4 (CH_3), 40.8 (CH_2), 51.9 (C), 60.3 (CH_2), 108.1 (Ar-CH), 122.2 (AR-CH), 123.7 (AR-CH), 127.0 (olefin-CH), 128.2 (AR-CH), 129.7 (olefin-CH), 130.4 (Ar-C), 144.0 (Ar-C), 169.5 (NCO) 177.9 (OCO);

HR-MS (ESI) = calcd for $C_{16}H_{19}NO_3$: 296.1263, found: 296.1255 (+Na);

$[\alpha]_D^{23.4}$ = +20.987 (*c* =1.5, MeOH); *ee* =75%;

HPLC [DICEL CHIRALCEL OD-H COLUMN; 1 mL/min; solvent system: ^{i}PrOH: Hexane =12: 88; retention time 7.3 min. (minor isomer) 9.0 min. (major isomer)];

(*R,E*)-ethyl-2-(1-methyl-2-oxo-3-(prop-1-en-1-yl)indolin-3-yl)acetate (32c, yield 90% **)**



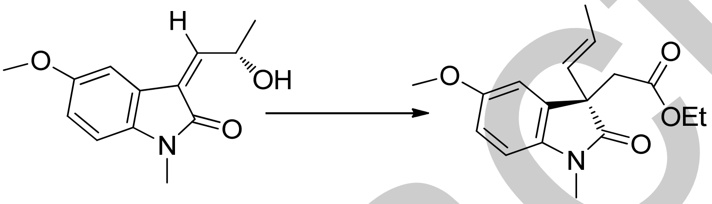
30c **32c**

Colourless liquid;

$[\alpha]_D^{23.2}$ = -18.892 (*c* =0.65, MeOH), *ee* = 96%;

HPLC [DICEL CHIRALCEL OD-H COLUMN; 1 mL/min; solvent system: ^{i}PrOH: Hexane =12: 88; retention time 7.2 min. (major isomer) 9.1 min. (minor isomer)];

(*S,E*)-ethyl-2-(1-benzyl-5-methoxy-2-oxo-3-(prop-1-en-1-yl)indolin-3-yl)acetate (31d,yield-89%**)**



29d **31d**

Colourless liquid; R_f = 0.25 (SiO_2, ethyl acetate-hexane, 2:8);

IR (neat) 2938, 2836, 1727, 1712, 1602, 1497, 1369, 1287, 1235, 1119, 1037, 970, 883, 809, 741, 560 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) = 1.01 (t, *J*=7.05 Hz, 3 H, $OCH_2\underline{CH_3}$), 1.63 (d, *J*=6.29 Hz, 3 H, $\underline{CH_3}$), 2.88 (d, *J*=16.11 Hz, 1 H, $\underline{CH_2CO}$), 3.17 (d, *J*=16.11 Hz, 1 H, $\underline{CH_2CO}$), 3.21 (s, 3 H, $\underline{N\text{-}CH_3}$), 3.80 (s, 3 H, $\underline{O\text{-}CH_3}$), 3.83 - 3.95 (m, 2 H, $\underline{O\text{-}CH_2}$), 5.41 - 5.49 (m, 1 H, olefin-CH), 5.50 - 5.60 (d, *J*=16Hz, 1 H, olefin-CH), 6.74 - 6.77 (m, 1 H, Ar-CH), 6.78 - 6.86 (m, 2 H, Ar-CH);

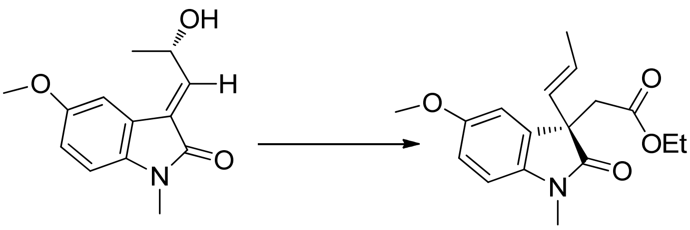
^{13}C NMR (100 MHz, $CDCl_3$) = 13.8 (CH_3), 17.8 (CH_3), 26.4 (CH_3), 40.7 (CH_2), 52.3 (C), 55.7 (CH_3), 60.4 (CH_2), 108.3 (Ar-CH), 111.5 (Ar-CH), 112.1 (Ar-CH), 127.0 (olefin-CH), 129.7 (olefin-CH), 131.8 (Ar-C), 137.6 (Ar-C), 155.7 (Ar-C), 169.5 (NCO), 177.5 (OCO);

HR-MS (ESI) = calcd for $C_{17}H_{21}NO_4$: 326.1368, found: 326.1362 (+Na); *ee* = 91.08%;

$[\alpha]_D^{22.8}$ = +19.333 (*c* =1.2, MeOH), *ee* = 91%;

HPLC [DICEL CHIRALCEL OD-H COLUMN; 1 mL/min; solvent system: ^{i}PrOH: Hexane =15: 85; retention time 7.5 min. (minor isomer) 10.4 min. (major isomer)];

(*R,E*)-ethyl-2-(5-methoxy-1-methyl-2-oxo-3-(prop-1-en-1-yl)indolin-3-yl)acetate (32d, yield 92%**)**



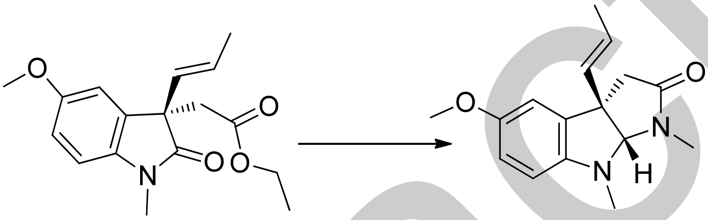
30d 32d

Colourless liquid;

[α]$_D^{23.8}$ =-35.949 (*c* = 2.65, $CHCl_3$); *ee* = 95%;

HPLC [DICEL CHIRALCEL OD-H COLUMN; 1 mL/min; solvent system: ^{i}PrOH: Hexane =15: 85; retention time 8.2 min. (major isomer) 10.5 min. (minor isomer)];

Synthesis of (3a*R*, 8a*S*)-5-methoxy-1,8-dimethyl-3a-((*E*)-prop-1-en-1-yl)-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indol-2(1H)-one (33, yield 66%**)**



32d 33

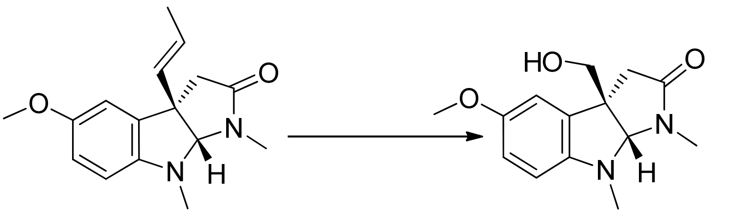
To a 50 mL round bottom flask, equipped with reflux condenser, **32d** (0.254 g, 0.837 mmol) dissolved in $MeNH_2$ (15 mL, 32% in ethanol) was introduced and heated to 70 ºC while stirring for 24 h. It was cooled to room temperature and concentrated, diluted with water (20 mL) and extracted with ethyl acetate (3×20 mL), washed with water and brine, dried over Na_2SO_4 and concentrated under reduced pressure to produce corresponding amide (0.170 g, 0.589 mmol, 70%) which was carried forward without purification.
To a solution of amide (0.170 g, 0.589 mmol) in THF (20 mL) was added LAH (0.089 g, 2.361 mmol) at 0 °C under an Ar-atmosphere. The mixture was stirred at 0 °C for 1 h. EtOAc (5 mL) followed by NaCl (aq) (10 mL) was added. The organic layer was separated, washed with water and dried over Na2SO4, concentrated and crude product was purified by silica gel flash column chromatography (EtOAc:n-Hexane; 3:7) which produced **33** (0.151 g, 0.554 mmol, 94%).
^{1}H NMR (400 MHz, $CDCl_3$) = 1.68 (d, *J*=6.55 Hz, 3 H, CH_3), 2.77 (br. s., 2 H, CH_2CO), 2.92 (s, 3 H, N-CH_3), 3.02 (s, 3 H, N-CH_3), 3.76 (s, 3 H, O-CH_3), 4.67 (s, 1 H, CH), 5.40 (dd, *J*=15.36, 6.29 Hz, 1 H, olefin-CH), 5.64 (d, *J*=15.36 Hz, 1 H, olefin-CH), 6.46 (d, *J*=8.56 Hz, 1 H, Ar-CH), 6.63 (d, *J*=2.52 Hz, 1 H, Ar-CH), 6.73 (dd, *J*=8.31, 2.52 Hz, 1 H, Ar-CH),

^{13}C NMR (100 MHz, $CDCl_3$) = 17.7 (CH_3), 28.3 (CH_3), 37.2 (CH_3), 42.5 (CH_2), 52.0 (C), 56.0 (CH_3), 92.1 (CH), 109.2 (Ar-CH), 111.3 (Ar-CH), 113.6 (Ar-CH), 125.9 (olefin-CH), 133.8 (olefin-CH), 134.9 (Ar-C), 144.1 (Ar-C), 153.8 (Ar-C), 172.7 (CO).

HR-MS (ESI) = calcd for $C_{16}H_{20}N_2O_2$: 295.1422 found: 295.1420 (+Na);

[α]$_D^{22.4}$=+13.305 (*c* = 1.58, MeOH); *de* = >99%

Synthesis of (3a*R*, 8a*S*)-3a-(hydroxymethyl)-5-methoxy-1,8-dimethyl-3,3a,8,8a-tetrahydropyrrolo[2,3-b]indol-2(1H)-one (34, yield-44% over two steps**)**

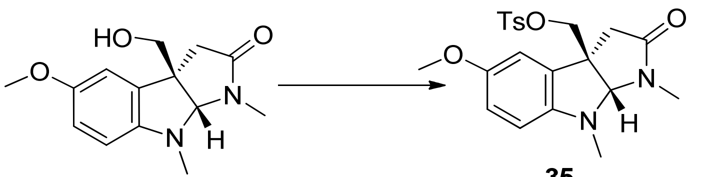


33 **34**

To a solution of **33** (0.126 g, 0.463 mmol) in dioxane-water (3:1, 8 mL) was added 2,6-lutidine (0.22 mL, 1.852 mmol), OsO4 (2.14 % in 2-methyl-2-propanol, 0.00235 g, 0.0092 mmol) and NaIO4 (0.580 g, 1.852 mmol).The reaction mixture was stirred at 25 °C for 4 h and diluted with water (20 mL), extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were washed with brine and dried over Na_2SO_4, concentrated to obtain corresponding crude aldehyde (0.075 g, 0.288 mmol, 62%) which was used for next reaction without purification.
To a solution of aldehyde (0.075 g, 0.288) in methanol (4 mL) was added $NaBH_4$ (0.044 g, 1.153mmol) at 0 ^oC under Ar-atmosphere. The reaction was allowed to stir at that temp. for 30 min. Reaction mixture was quenched with aq. saturated NH_4Cl solution and extracted with ethyl acetate (3×20 mL), washed with brine and dried over Na_2SO_4, concentrated and crude product was purified by silica gel flash column chromatography (EtOAc: n-Hexane; 8:2) to produce corresponding alcohol **34** (0.054 g, 0.206 mmol, 71%) as a colourless oil.
IR (neat) 3381, 2925, 1669, 1454, 1278, 1127, 1031, 872, 811, 600 cm^{-1};
^{1}H NMR (400 MHz, $CDCl_3$) = 2.03 (br. s., 1 H, OH), 2.65 (q, *J*=17.12 Hz, 2 H, $COCH_2$), 2.94 (s, 3 H, N-CH_3), 3.02 (s, 3 H, N-CH_3), 3.66 (br. s., 1 H, O-CH_2), 3.76 (m, 4 H, O-CH_3 & O-CH_2), 4.86 (s, 1 H, CH), 6.48 (d, *J*=8.31 Hz, 1 H, Ar-CH), 6.66 (s, 1 H, 1H from Ar-CH), 6.75 (d, *J*=8.56 Hz, 1 H, Ar-CH);
^{13}C NMR (100 MHz, $CDCl_3$) = 28.0 (CH_3), 37.6 (CH_3), 39.0 (CH_2), 52.0 (C), 56.0 (CH_3), 66.6 (CH_2), 88.9 (CH), 109.6 (Ar-CH), 110.2 (Ar-CH), 114.2 (Ar-CH), 132.5 (Ar-C), 145.3 (Ar-C), 153.8 (Ar-C), 172.5 (CO);

HR-MS (ESI) = calcd for $C_{14}H_{18}N_2O_3$: 285.1215, found: 185.1205 (+Na);

[α]$_D^{24.6}$ =+53.777 (*c* = 0.08, MeOH);
Synthesis of ((3a*R*,8a*S*)-5-methoxy-1,8-dimethyl-2-oxo-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-3a-yl)methyl 4-methylbenzenesulfonate (35, 79% yield**)**



34 35

P-Toluenesulfonylchloride (0.067 g, 0.354 mmol) was added to a stirred and ice-cooled solution of **36** (0.062 g, 0.236 mmol) in anhydrous pyridine (4 mL) under an Ar-atmosphere. The reaction mixture was stirred for 48h at ambient temperature and poured onto ice water (10 mL). The aqueous layer was extracted with dichloromethane (3×10 mL), washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, concentrated and purified by silica gel flash column chromatography (EtOAc: n-Hexane; 4:6) to afford **35** (0.083g , 0.199 mmol, 79%) as a colourless oil.
IR (neat) 2923, 1692, 1500, 360, 1277, 1222, 1176, 1029, 969, 813, 731, 664, 553 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) = 2.46 (s, 3 H, Ar-CH_3), 2.58 (d, *J*=16.87 Hz, 1 H, CH_2CO), 2.69 (d, *J*=17.12 Hz, 1 H, CH_2CO), 2.89 (s, 3 H, N-CH_3), 3.00 (s, 3 H, N-CH_3), 3.69 (s, 3 H, O-CH_3), 3.97 - 4.12 (m, 2 H, CH_2-OTs), 4.80 (s, 1 H, CH), 6.40 - 6.50 (m, 2 H, Ar-CH), 6.74 (dd, *J*=8.56, 2.27 Hz, 1 H, Ar-CH), 7.33 (m, *J*=7.81 Hz, 2 H, Ar-CH), 7.68 (m, *J*=8.06 Hz, 2 H, Ar-CH);

^{13}C NMR (100 MHz, $CDCl_3$) = 21.6 (CH_3), 27.9 (CH_3), 37.1 (CH_3), 38.2 (CH_2), 49.9 (C), 55.9 (CH_3), 71.1 (CH_2), 87.7 (CH), 109.8 (Ar-CH), 110.2 (Ar-CH), 114.8 (Ar-CH), 127.8 (Ar-CH), 129.9 (Ar-CH), 130.7 (Ar-C), 132.1 (Ar-C), 144.4 (Ar-C), 145.2 (Ar-C), 153.8 (Ar-C), 171.2 (CO);

HR-MS (ESI) = calcd for $C_{21}H_{24}N_2O_5S$: 439.1304, found: 439.1326 (+Na);

$[\alpha]_D^{23.1}$ =+37.463 (*c* = 0.18, MeOH);

Synthesis of (-)-Esermethole (36, yield-66%)

35 36

To a 25 mL two neck round bottom flask, equipped with reflux condenser, **35** (0.026 g, 0.062 mmol) dissolved in THF (2 mL) followed by LAH (0.0095 g, 0.251 mmol) were added at 0 °C and the mixture was refluxed for 3 h under an Ar-atomosphere. The reaction mixture was cooled to 0 °C, EtOAc (10 mL) was added, organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The resultant crude was purified by silica gel flash column chromatography (10% methanol in CH_2Cl_2) to afford esermethole **36** (0.0095 g, 0.0409 mmol, 66%) as a light yellow oil which transformed to physostigmine using known protocol.[4]
IR (neat) 2926, 2862, 1596, 1499, 1279, 1221, 1032 cm^{-1};

^{1}H NMR (400 MHz, CDCl$_3$) = 1.46 (s, 3 H, CH$_3$), 1.97 - 2.06 (m, 2 H, CH$_2$), 2.53 - 2.59 (m, 3 H, CH$_3$), 2.62 - 2.67 (m, 1 H, CH$_2$), 2.79 - 2.84 (m, 1 H, CH$_2$), 2.90 - 2.94 (m, 3 H, CH$_3$), 3.76 (s, 3 H, CH$_3$), 4.16 (s, 1 H, CH), 6.39 (d, *J*=8.36 Hz, 1 H, Ar-CH), 6.61 - 6.72 (m, 2 H, Ar-CH);
^{13}C NMR (100 MHz, CHCl$_3$) = 27.7 (CH$_3$), 55.9 (CH$_3$), 97.9 (CH), 107.7 (Ar-CH), 109.7 (Ar-CH), 112.3 (Ar-CH), 137.8 (Ar-C), 146.2 (Ar-C), 153.1 (Ar-C);

HR-MS (ESI) = calcd for $C_{14}H_{20}N_2O$: 233.1654, found: 233.1638 (+H);

$[\alpha]_D^{33.2}$ =-133 (*c* = 0.4, benzene); *ee* = >99%;

HPLC [DICEL CHIRALPAK OD-H COLUMN; 0.5 mL/min; solvent system: ^{i}PrOH: Hexane =1: 99; retention time 18.1 min.] which match with previously reported HPLC data.[5]

Physostigmine (3)

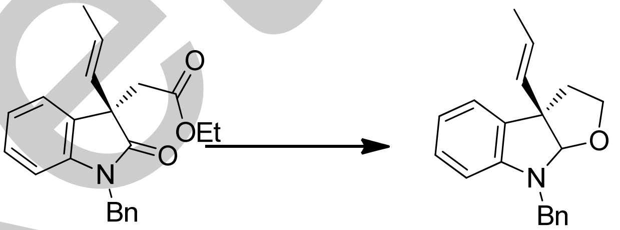
^{1}H NMR (400MHz, CDCl$_3$) = 1.43 (s, 3 H, CH$_3$), 2.01 - 1.94 (m, 3 H CH$_3$), 2.58 - 2.52 (s, 3 H, CH$_3$), 2.68 - 2.61 (m, 1H, CH$_2$), 2.76 (m, 1 H, CH$_3$), 2.98 - 2.82 (m, 6 H, CH$_3$), 4.18 (s, 1 H, CH), 4.95 (br. s., 1 H, NH), 6.35 (d, *J* = 8.3 Hz, 1 H, Ar-CH), 6.94 - 6.70 (m, 2 H, Ar-CH);

^{13}C NMR (100MHz, CDCl$_3$) = 27.1 (CH$_3$), 27.7 (CH$_3$), 37.1 (CH$_3$), 38.0 (CH$_3$), 40.5 (CH$_2$), 52.7 (CH), 53.1(CH$_2$), 97.8 (Ar-CH), 106.7 (CH), 116.2 (Ar-CH), 120.5 (Ar-CH), 137.3 (Ar-C), 143.2 (Ar-C), 149.4 (Ar-C), 156.1 (NHCO);

HR-MS (ESI) = calcd for $C_{15}H_{21}N_3O_2$: 276.1712, found: 276.1709 (+H);

$[\alpha]_D^{33.2}$ = -114.8 (*c* = 0.4, benzene);

Synthesis of (3a*R*)-8-benzyl-5-methoxy-3a-((*E*)-prop-1-en-1-yl)-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indole (37, 96% yield**)**



32a **37**

To a solution of **32a** (0.106 g, 0.303 mmol) in THF (10 mL) taken in a 50 mL two neck round bottom flask, placed at 0 °C under an Ar-atmosphere, LAH (0.046 g, 1.21 mmol) was added and the reaction mixture was stirred at 0 °C for 5-10 min. following which EtOAc (20 mL) and NaCl (aq) (10 mL) were added. The organic layers were washed with water and brine solution, dried over Na_2SO_4 and concentrated. The resultant crude product was purified by silica gel flash column chromatography (EtOAc: n-Hexane; 5: 95) produced **37** (0.084 g, 0.288 mmol, 96%) as a colourless liquid.

R_f = 0.56 (SiO_2, ethyl acetate-hexane, 5:95);

IR (neat) 3027, 2933, 2895, 1604, 1491, 1452, 1357, 1020, 740, 697 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) = 1.70 (dd, *J*=6.42, 1.13 Hz, 3 H, CH_3), 2.19 - 2.24 (m, 1 H, CH_2), 2.28 - 2.35 (m, 1 H, CH_2), 3.54 - 3.60 (m, 1 H, CH_2), 4.04 (t, *J*=7.81 Hz, 1 H, CH_2). 4.53 (d, *J*=3.53 Hz, 2 H, N-CH_2), 5.27 (s, 1 H, CH), 5.45 - 5.56 (m, 1 H, Olefin-CH), 5.67 - 5.74 (m, 1 H, Olefin-CH), 6.30 - 6.36 (m, 1 H, Ar-H), 6.72 (t, *J*=7.43 Hz, 1 H, Ar-H), 7.06 (dt, *J*=7.24, 3.56 Hz, 2 H, Ar-H), 7.20 - 7.39 (m, 5 H, Ar-H);

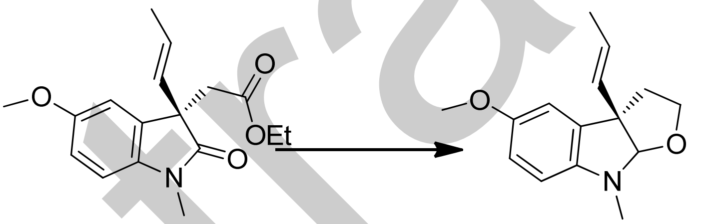
^{13}C NMR (100 MHz, $CDCl_3$) = 17.9 (CH_3), 40.4 (CH_2), 48.5 (CH_2), 58.6 (C), 67.5 (CH_2), 102.6 (Ar-CH), 105.5 (Ar-CH), 117.5 (Ar-CH), 124.4 (Ar-CH), 125.1 (Olefin-CH), 126.9 (Ar-CH), 127.2 (Ar-CH), 128.2 (Ar-CH), 128.4 (Ar-CH), 131.5 (C), 133.5 (Olefin-CH), 138.3 (C), 150.4 (C);

HR-MS (ESI) = calcd for $C_{20}H_{21}NO$: 314.1521, found: 314.1514 (+Na);

$[\alpha]_D^{23.5}$ =+46.300 (*c* = 0.8, MeOH);

HPLC [KROMASIL 100-5C8 COLUMN; 1 mL/min; solvent system: ACN: H_2O =60: 40; retention time 4.84 min. (major diastereomer) and 9.45 min. (minor diastereomer)];

Synthesis of (3a*R*)-5-methoxy-8-methyl-3a-((*E*)-prop-1-en-1-yl)-3,3a,8,8a-tetrahydro-2H-furo[2,3-b]indole (38, yield-94%)



32d **38**

To a solution of **32d** (0.114 g, 0.376 mmol) in THF (10 mL) taken in 50 mL two neck round bottom flask and placed at 0 °C under an Ar-atmosphere, LAH (0.057 g, 1.504 mmol) was added. The reaction mixture was stirred at 0 °C for 5-10 mins following EtOAc (20 mL) and NaCl (aq) (10 mL) were added. The organic layers were washed with water and brine solution, dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel flash column chromatography (EtOAc:n-Hexane; 05: 95) produced **38** (0.087 g, 0.355 mmol, 94%) as a colourless liquid.

IR(neat) 3469,3027, 2937, 2874, 2828, 1596, 1497, 1450, 1277, 1217, 1115, 1033, 1016, 970, 948, 906, 799, 693, 533 cm^{-1};

^{1}H NMR (400 MHz, $CDCl_3$) =1.68 (dd, *J*=6.29, 1.51 Hz, 3 H, CH_3), 2.14 - 2.18 (m, 1 H, CH_2), 2.24 - 2.32 (m, 1 H, CH_2), 2.88 (s, 3 H, N-CH_3), 3.46 (ddd, *J*=11.20, 8.44, 4.78 Hz, 1 H, O-CH_2), 3.76 (s, 3 H, O-CH_3), 4.00 (td, *J*=7.81, 1.26 Hz, 1 H, O-CH_2), 5.13 (s, 1 H, CH), 5.50 (dq, J=15.39, 6.45 Hz, 1 H, olefin-CH), 5.64 - 5.72 (d, J=16 Hz, 1 H, olefin-CH), 6.34 (d, J=8.06 Hz, 1 H, Ar-CH), 6.64 - 6.73 (m, 2 H, Ar-CH);

^{13}C NMR (100 MHz, $CDCl_3$) = 17.8 (CH_3), 31.5 (CH_3), 40.0 (CH_2), 55.9 (CH_3), 58.8 (C), 67.8 (CH_2), 104.3 (CH), 105.7 (Ar-CH), 111.8 (Ar-CH), 112.4 (Ar-CH), 125.3 (olefin-CH), 133.0 (olefin-CH), 133.1 (Ar-C), 145.5 (Ar-C), 152.6 (Ar-C);

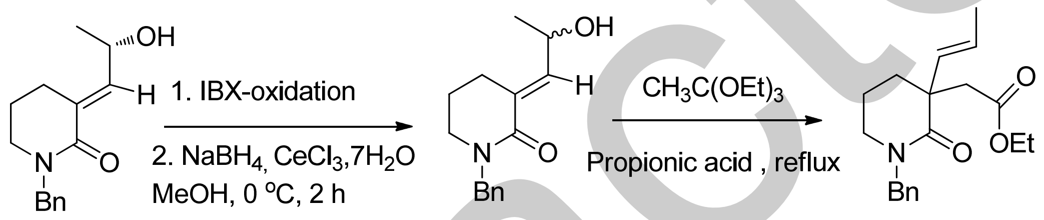
HR-MS (ESI) = calcd for $C_{15}H_{19}NO_2$: 268.1313, found: 268.1305 (+Na);

$[\alpha]_D^{25.4}$ =+4.014 (c = 2.83, MeOH);

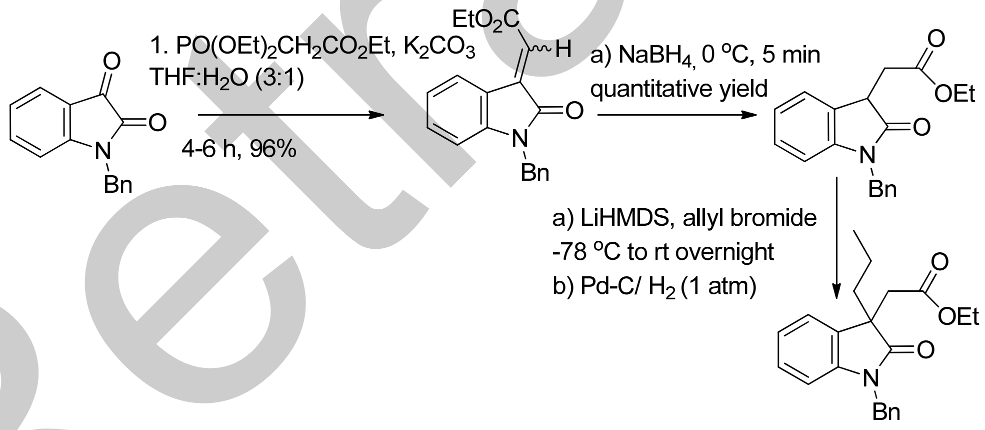
HPLC [KROMASIL 100-5C8 COLUMN; 1 mL/min; solvent system: ACN: H_2O = 60: 40; retention time 6.82 min. single diastereomer];

Racemic standards are prepared by following the reaction pathways as shown below.

(a) For pyrrolidinone and piperidinone ring system:

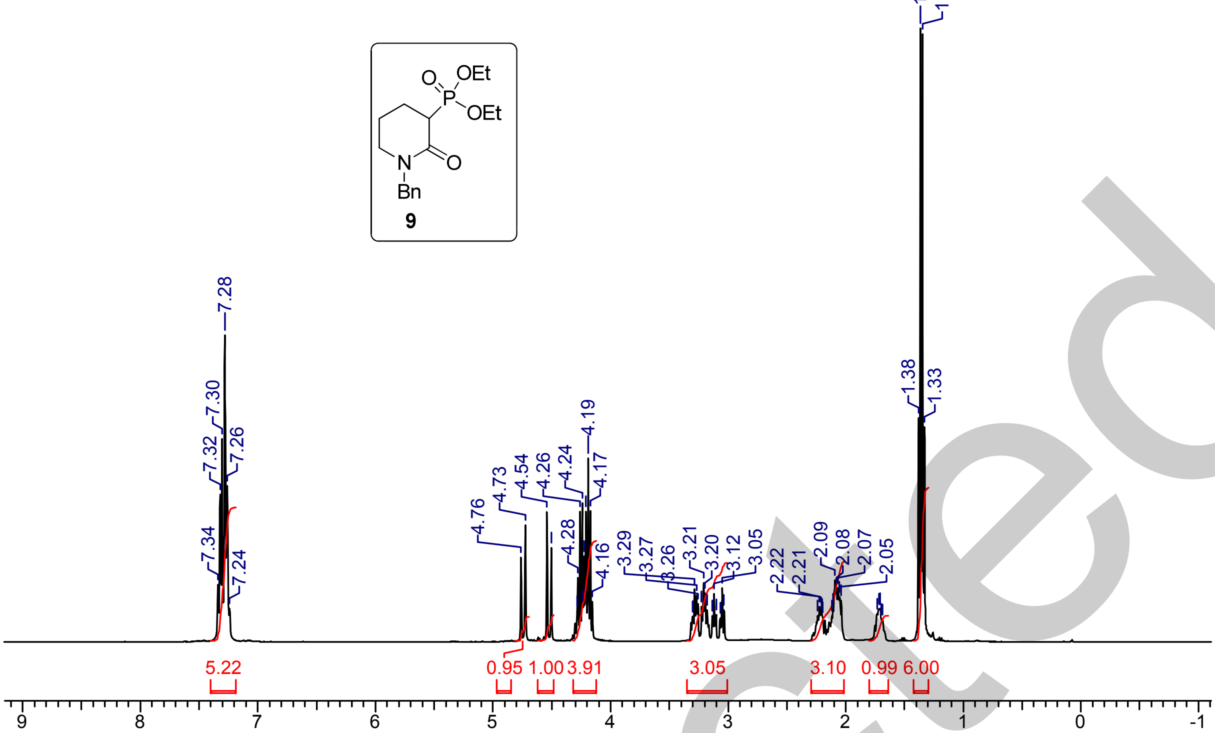


(b) For oxindole ring system:

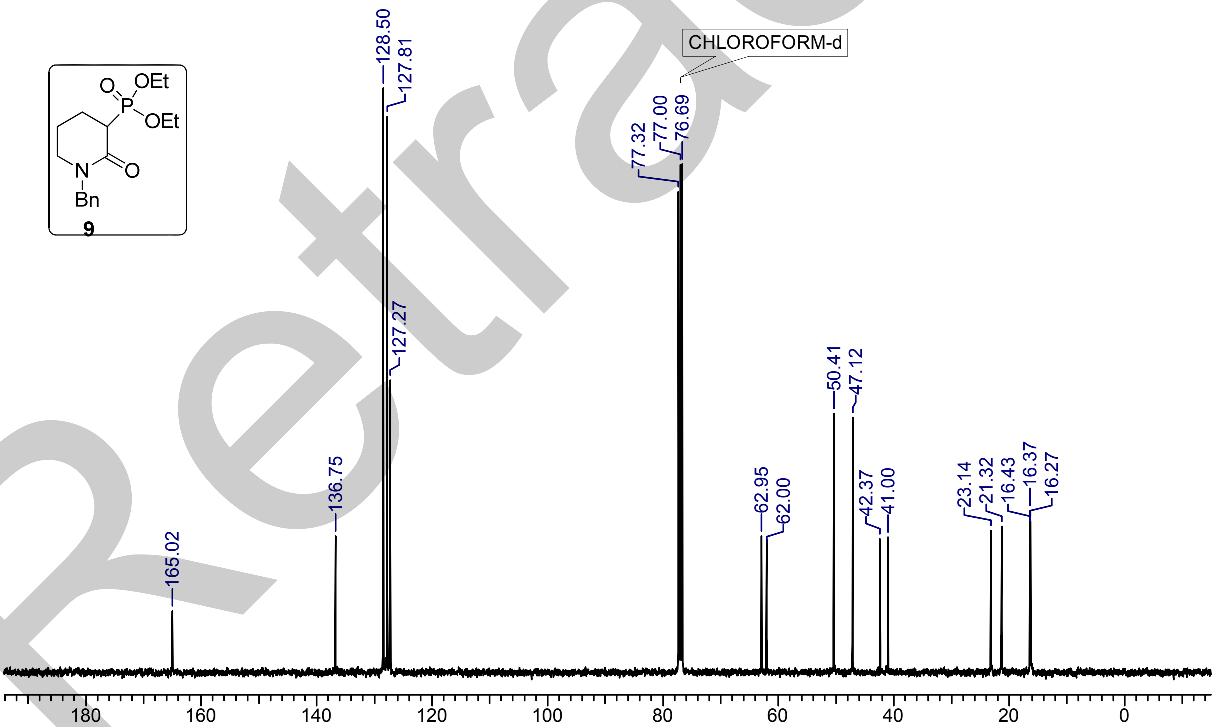


II) ^{1}H NMR and ^{13}C NMR spectra of compounds:

Tue5av400#014 JK-099.001.001.1r.esp



Tue5av400#014 JK-099.003.001.1r.esp



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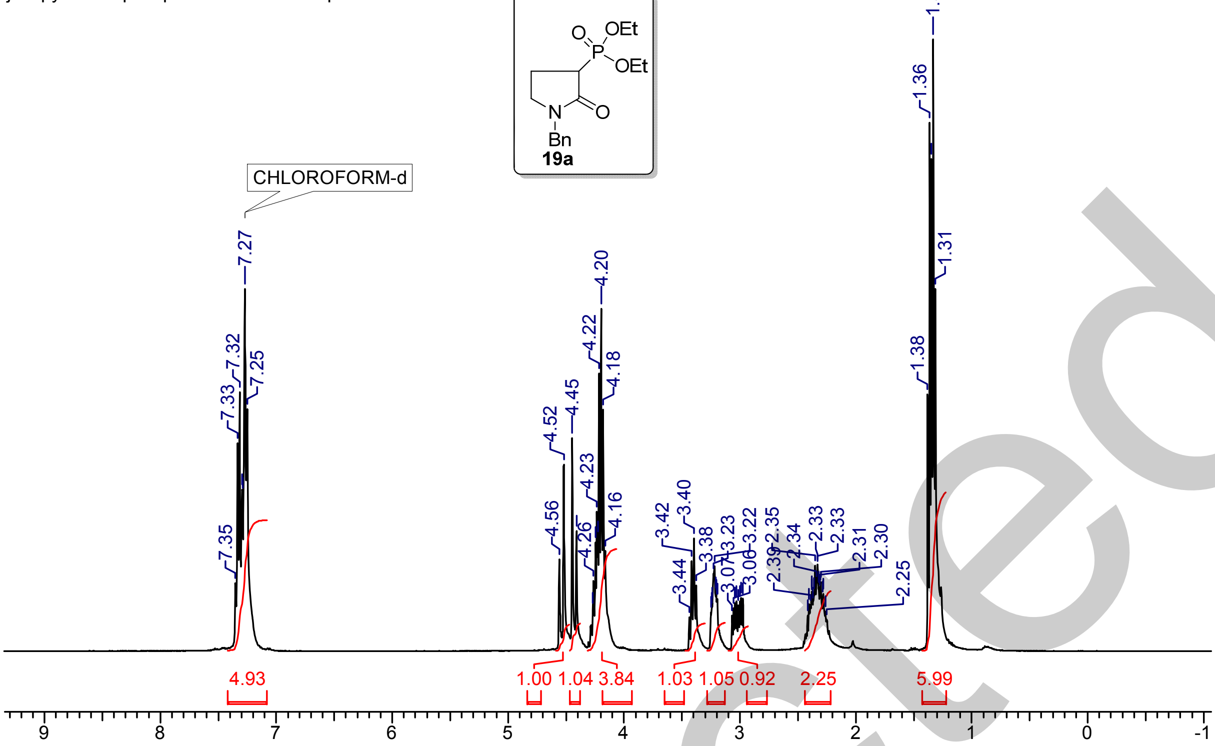

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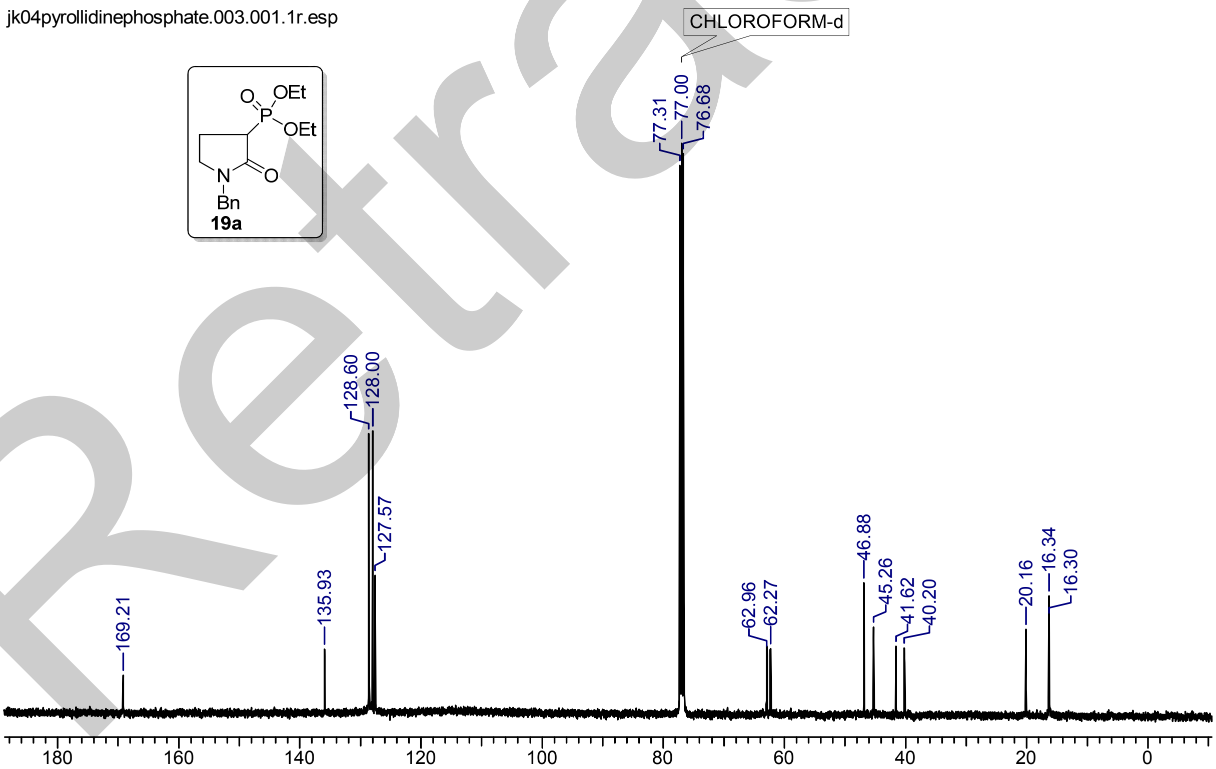

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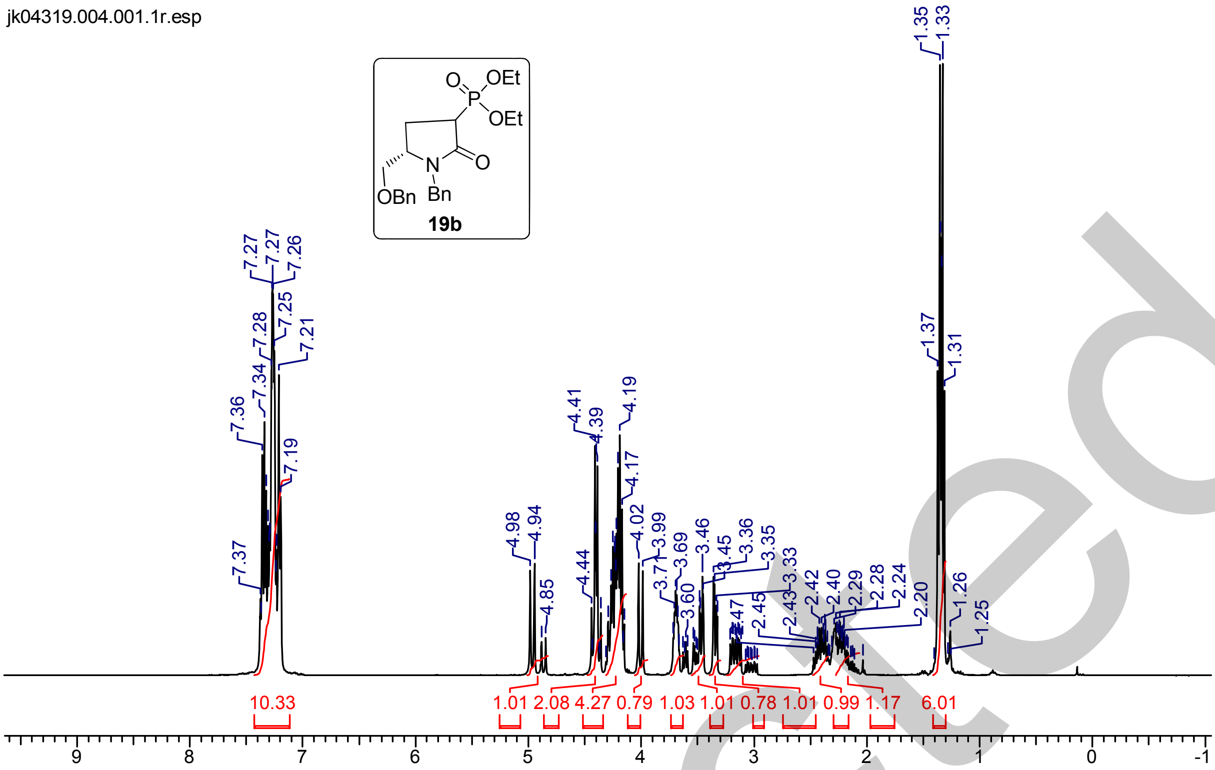

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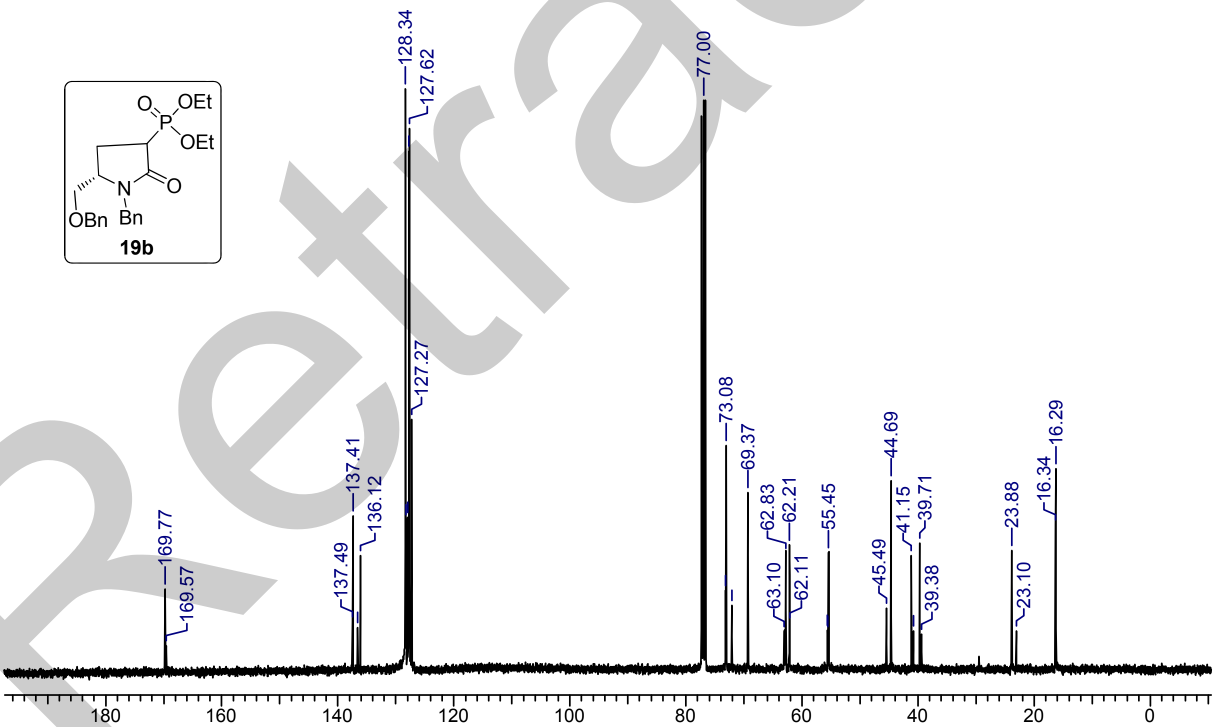

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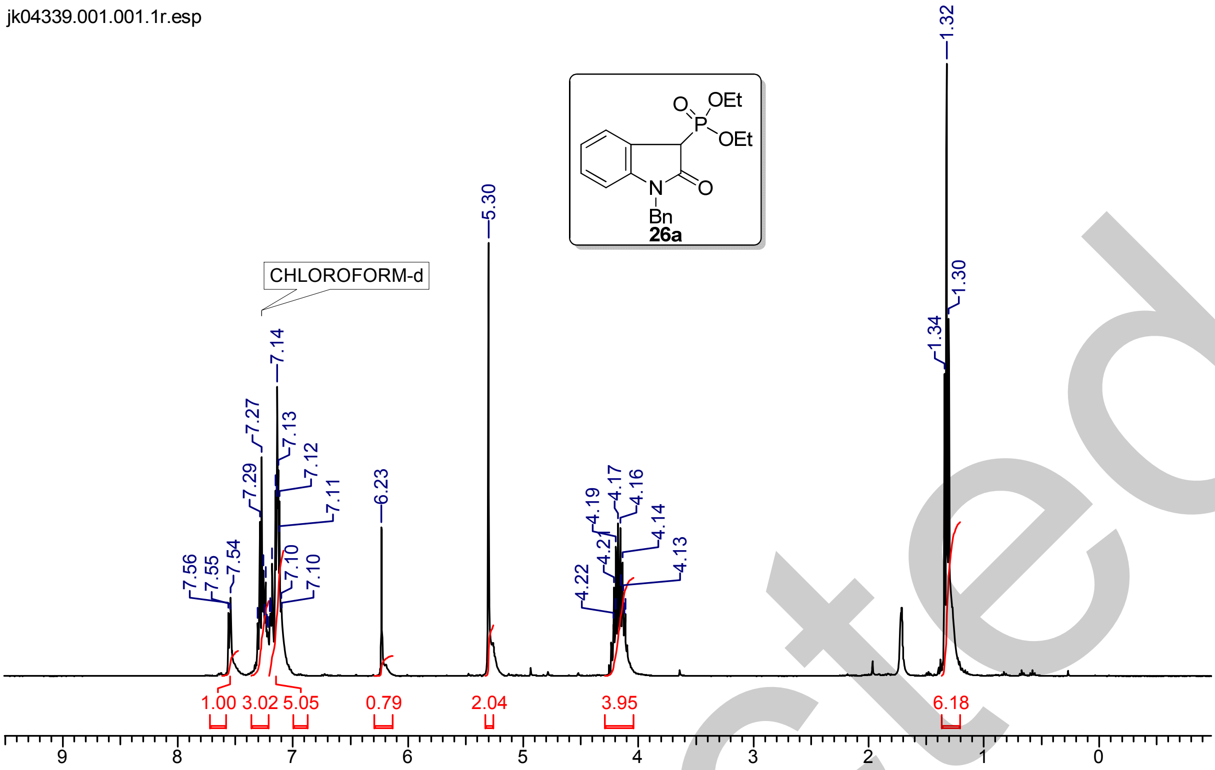

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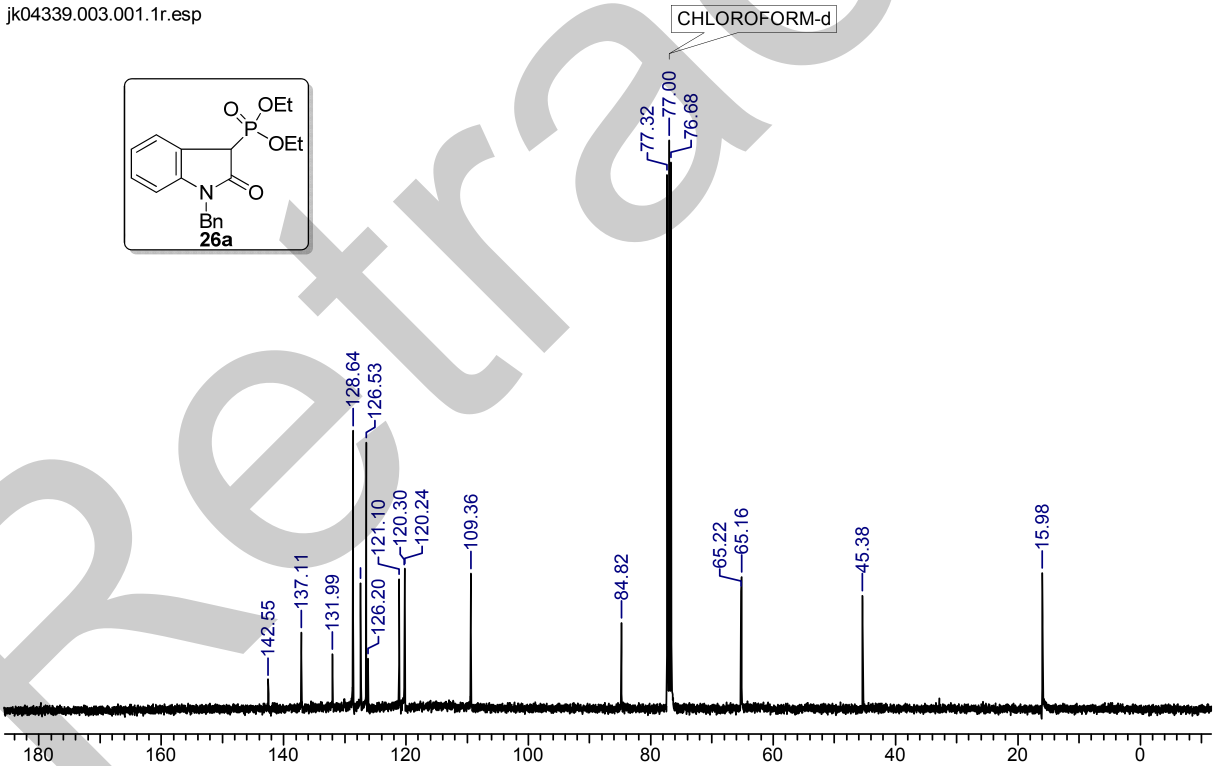

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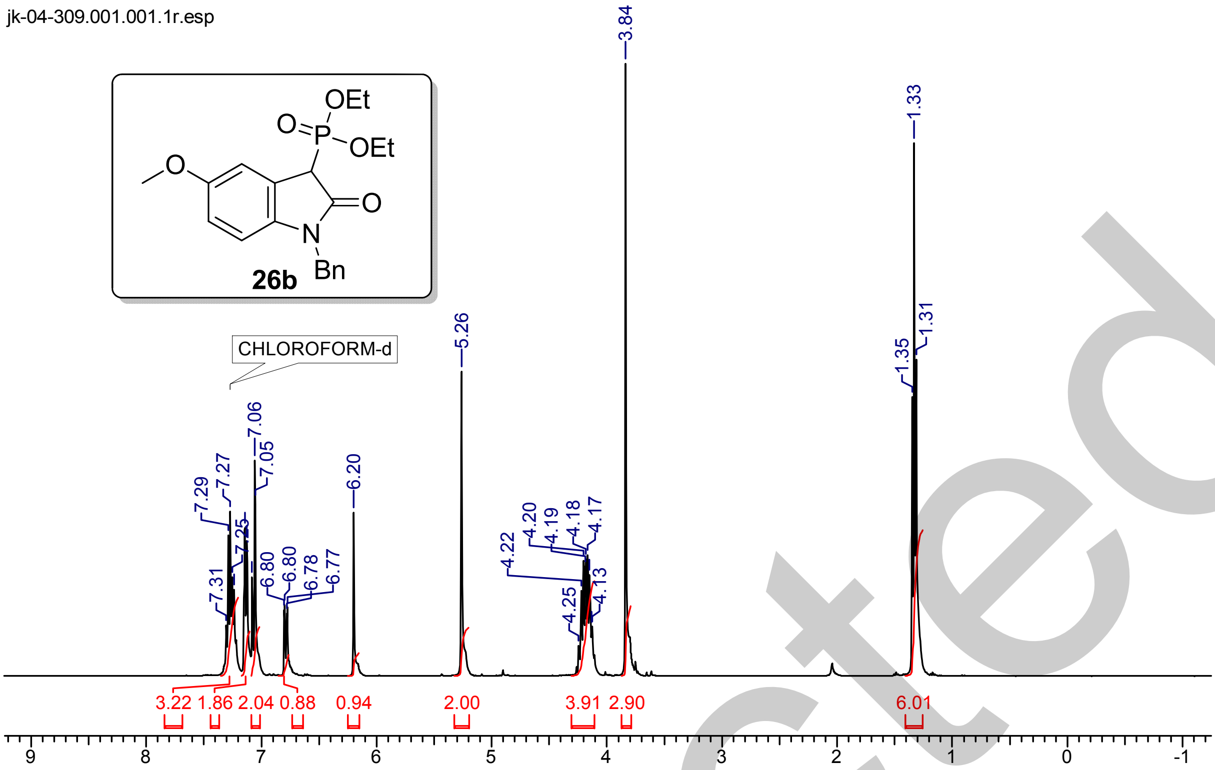

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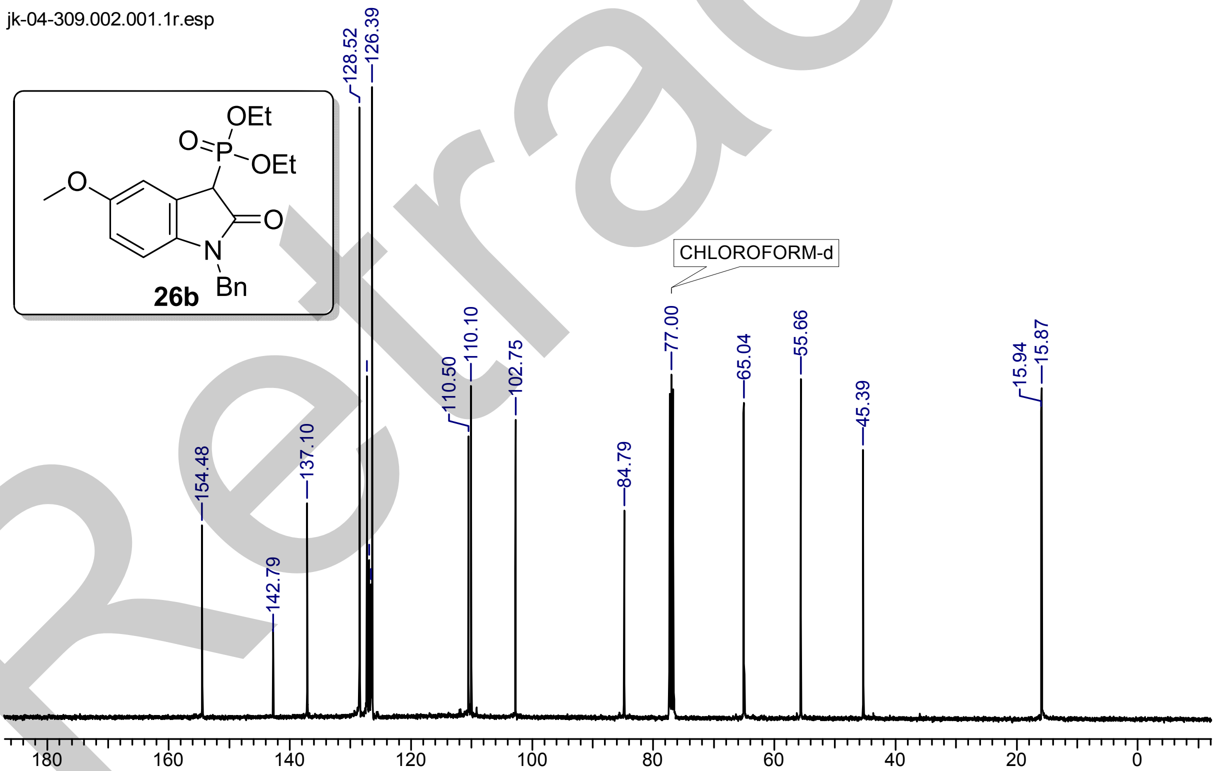

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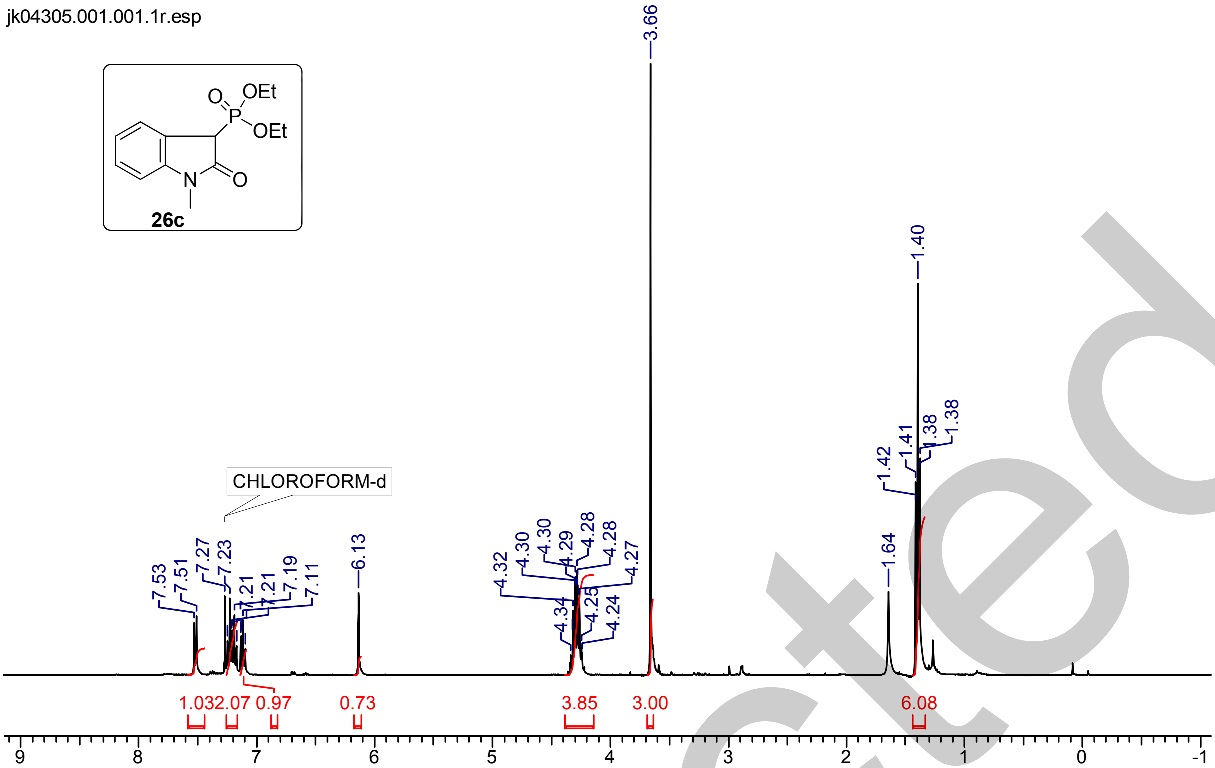

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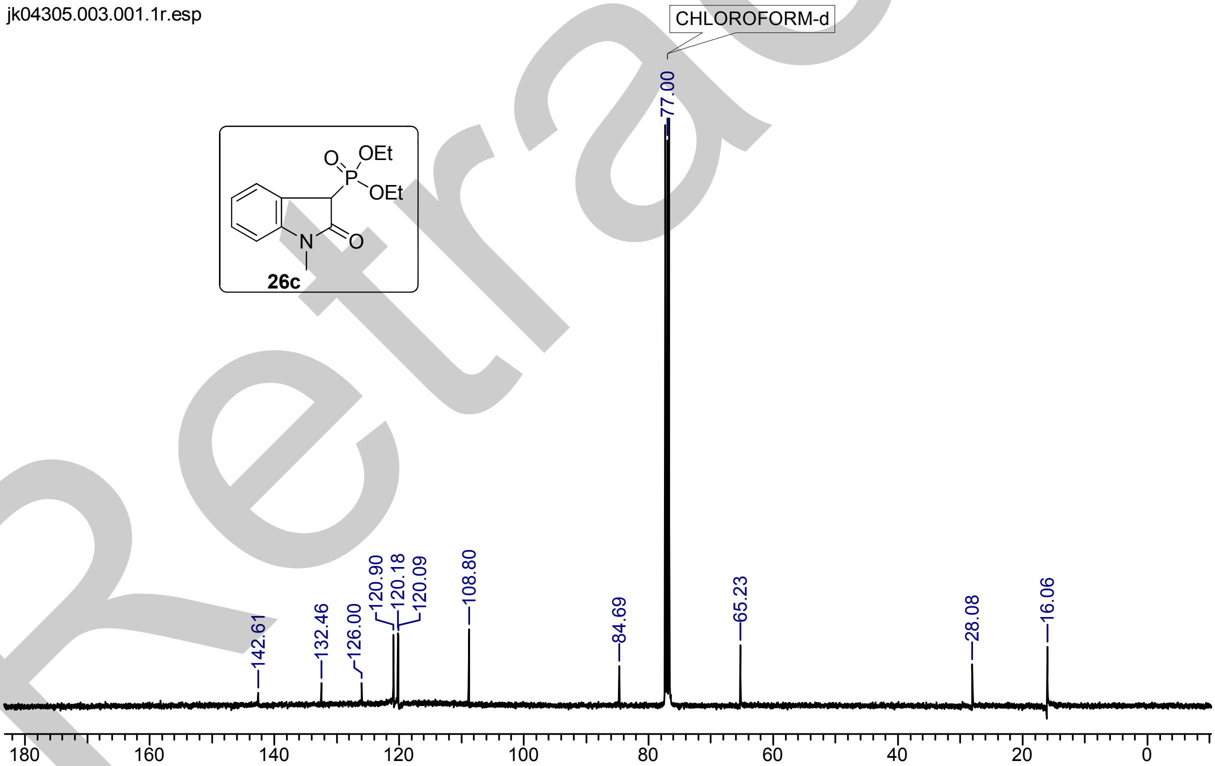

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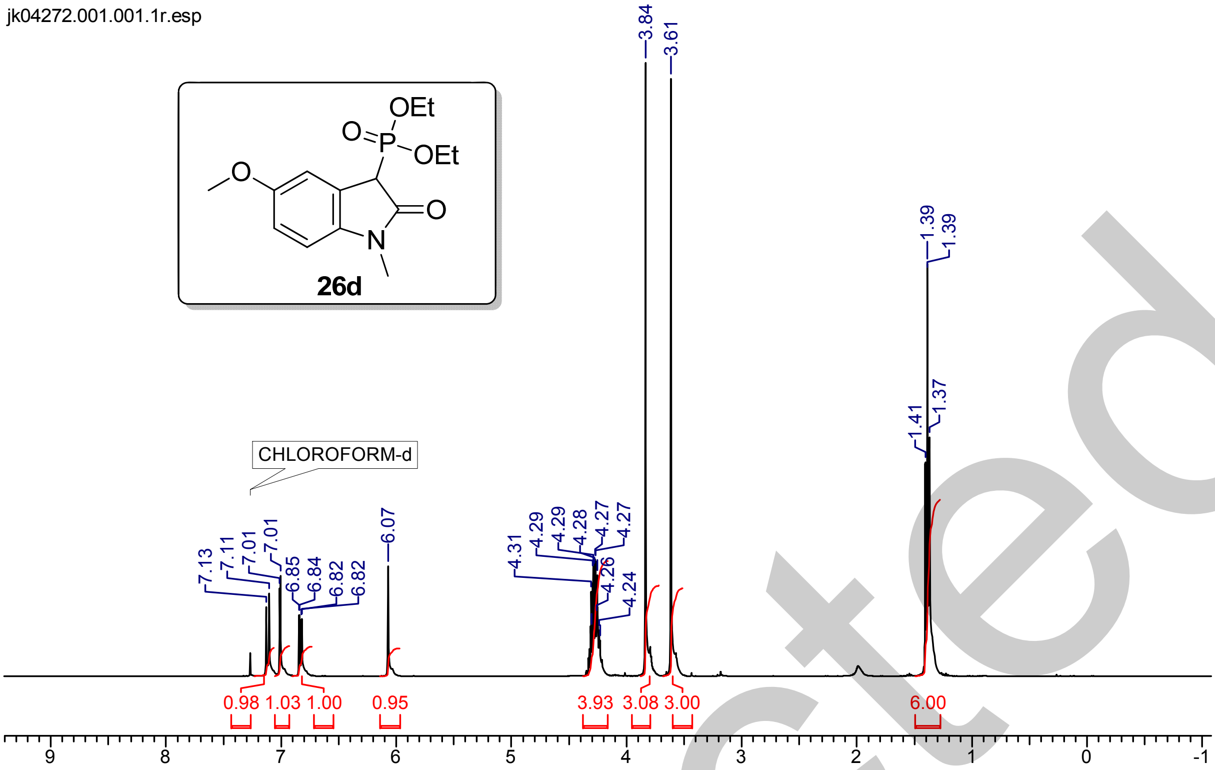

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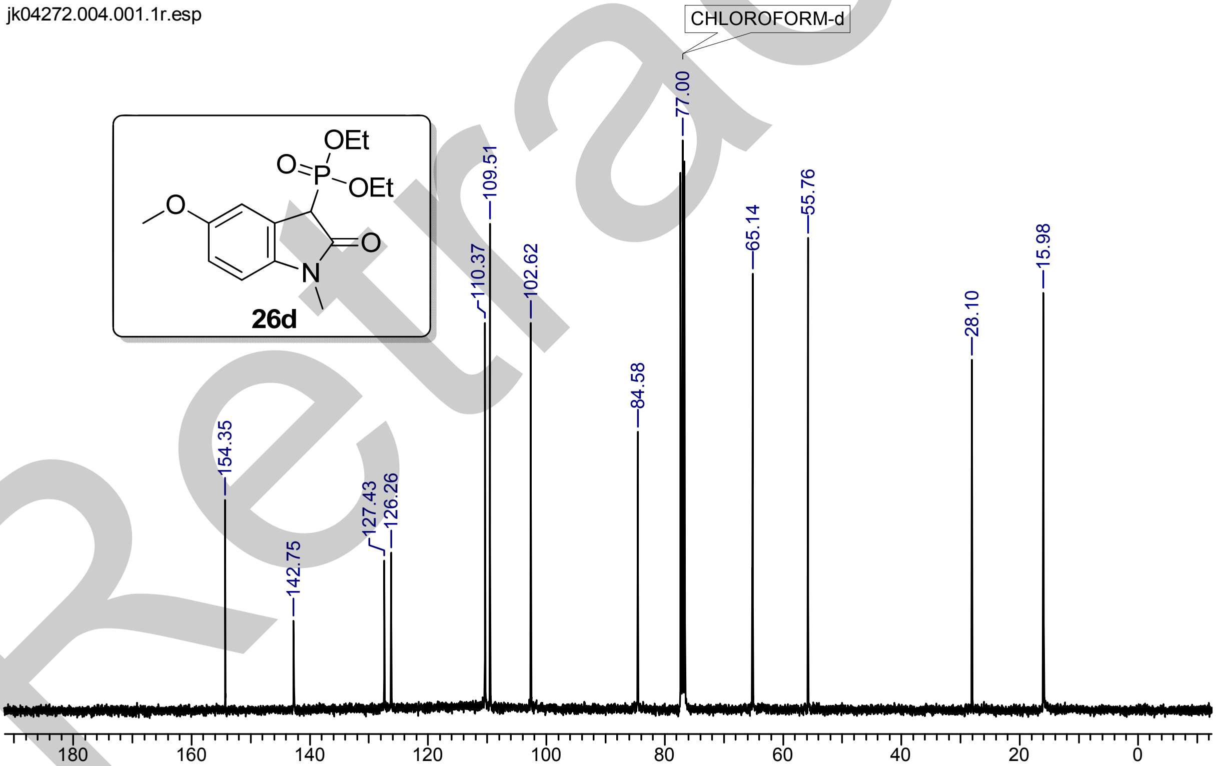

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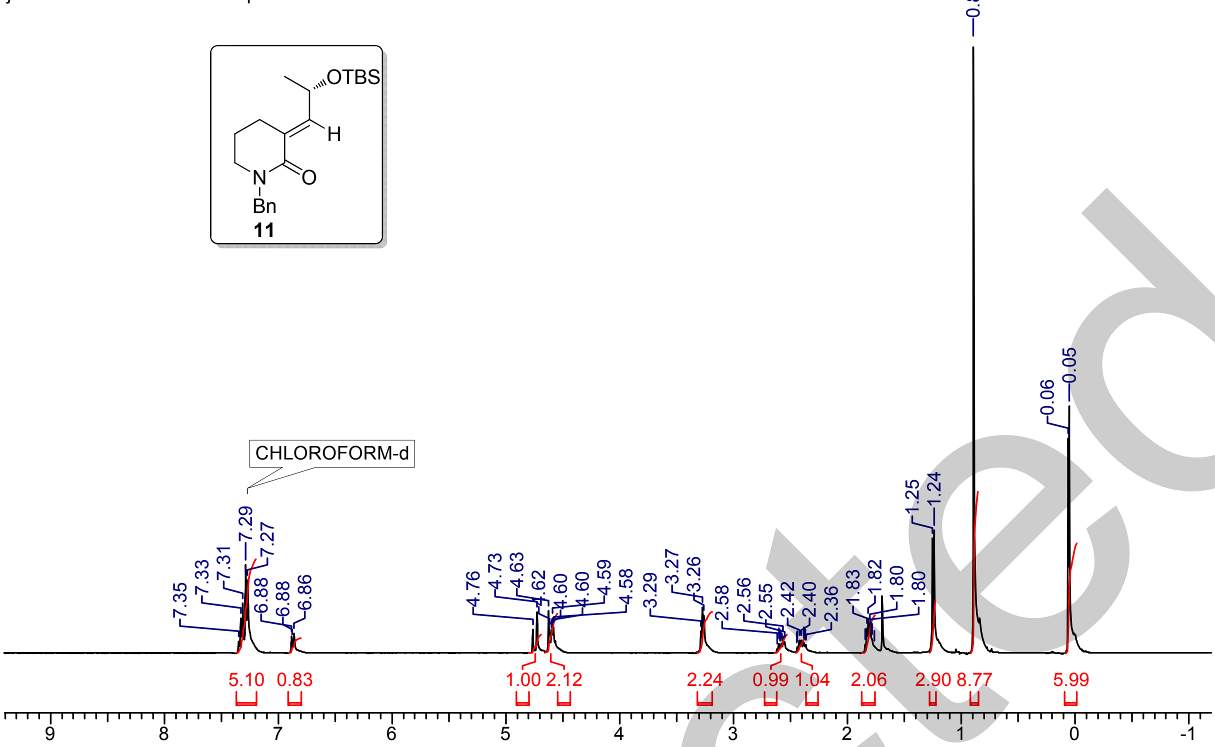

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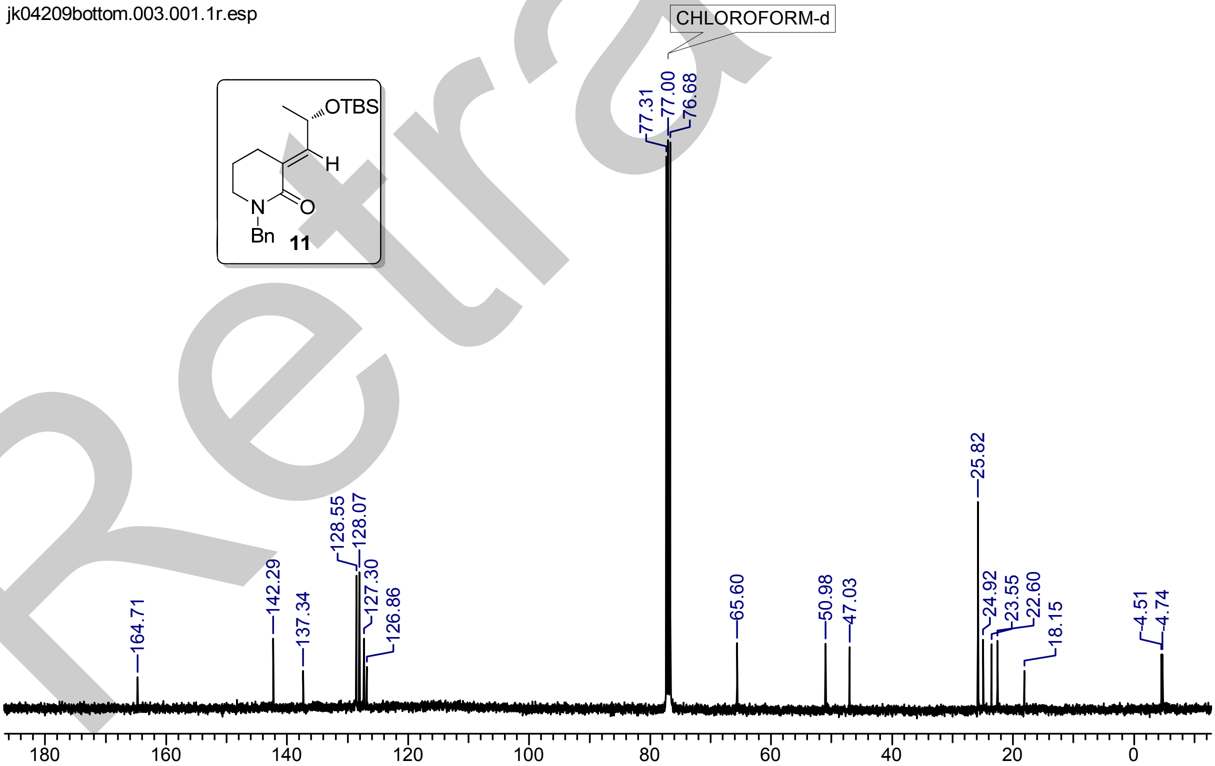

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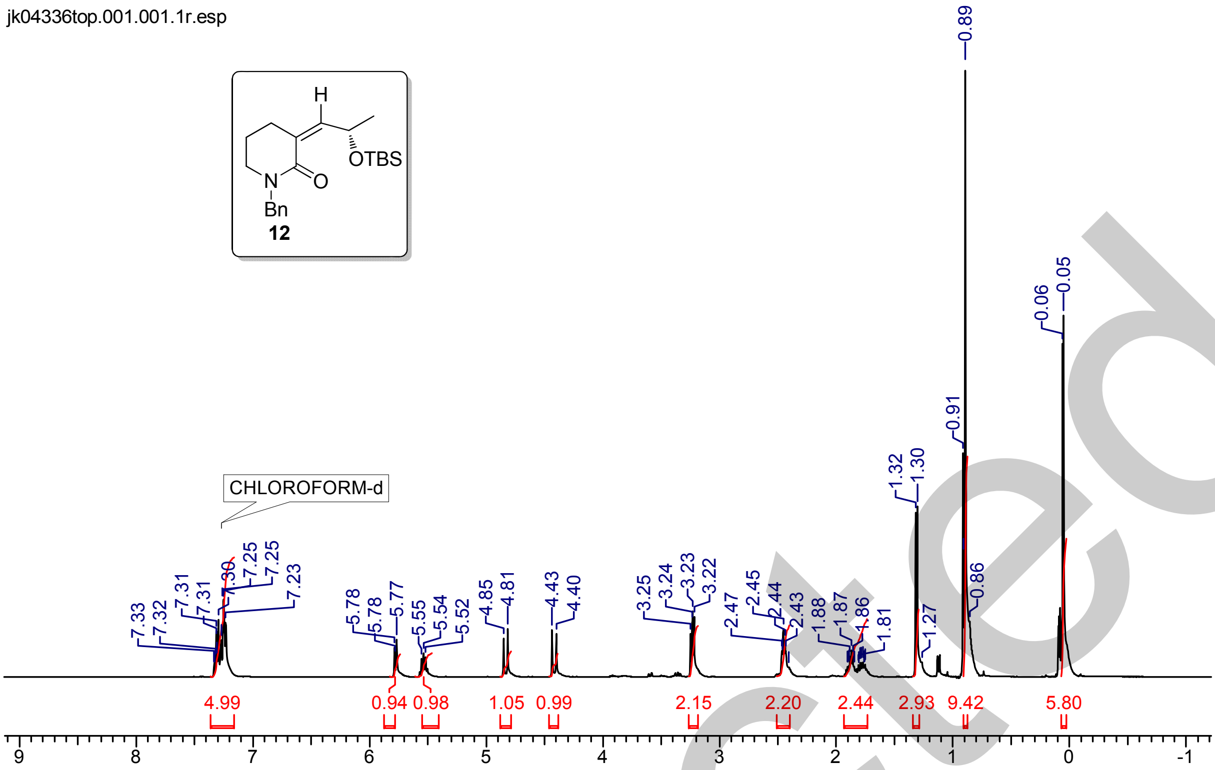

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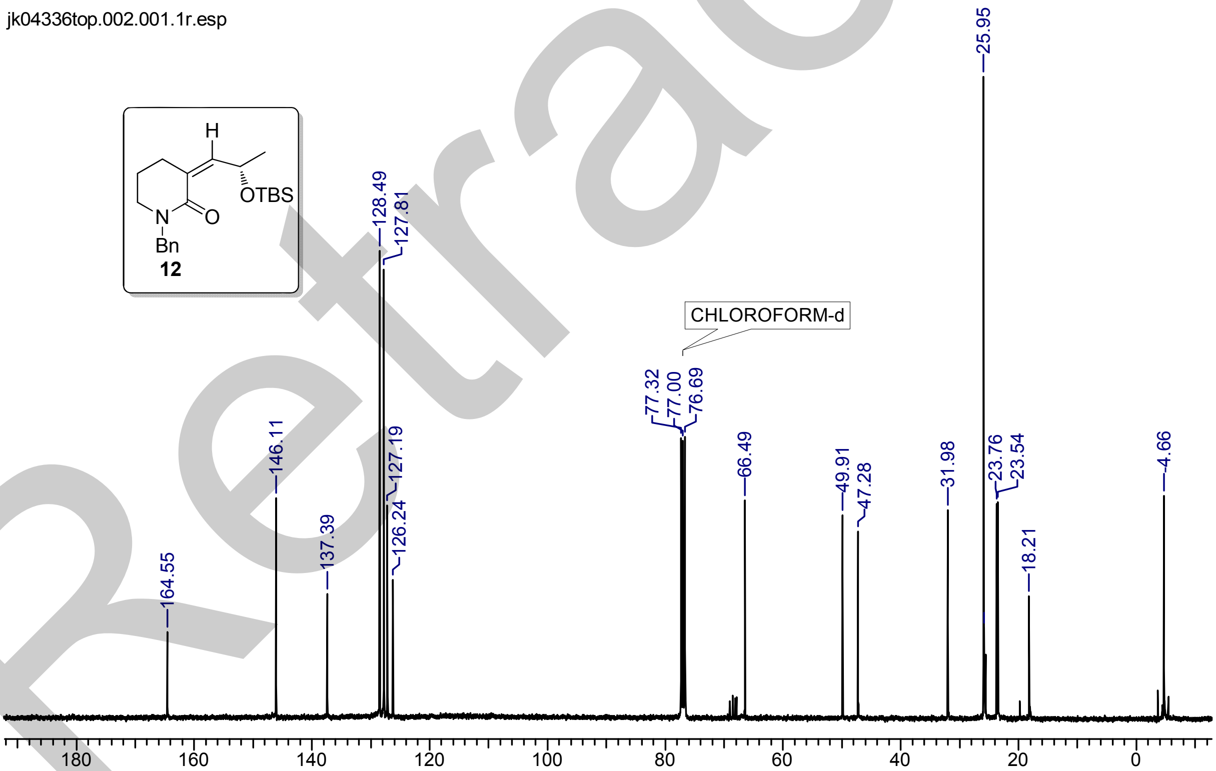

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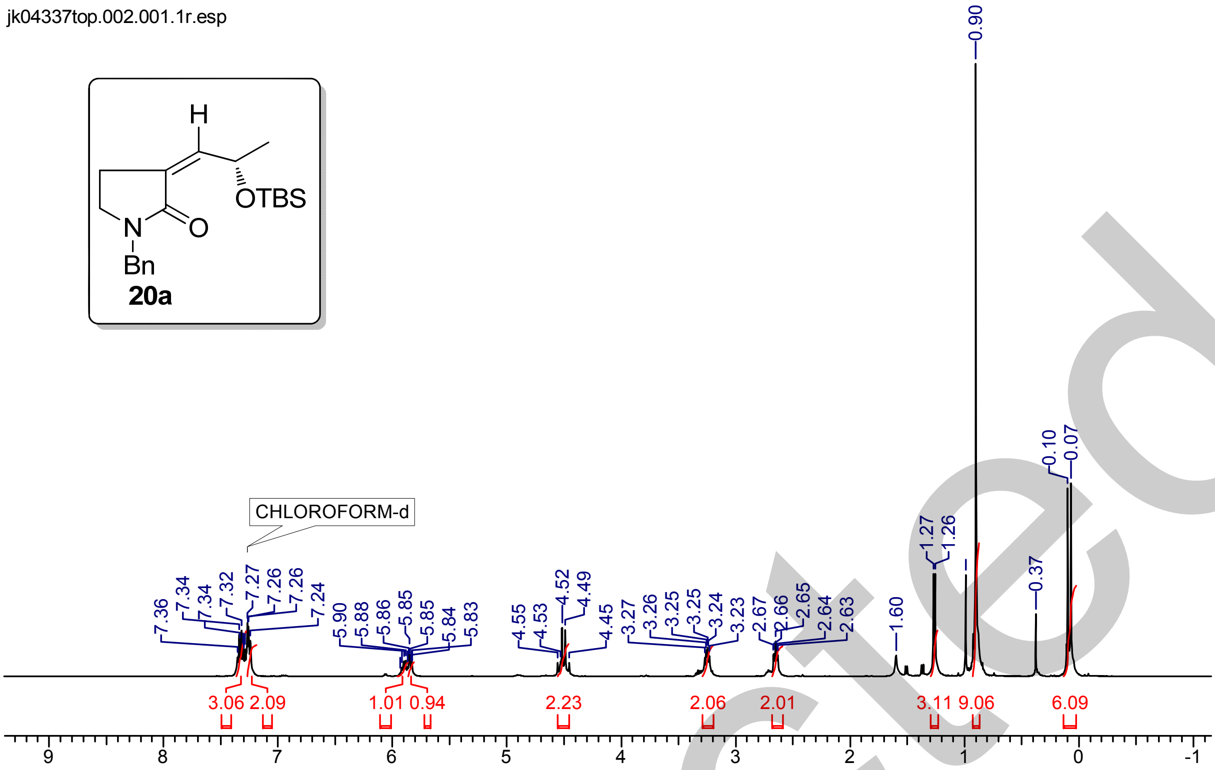

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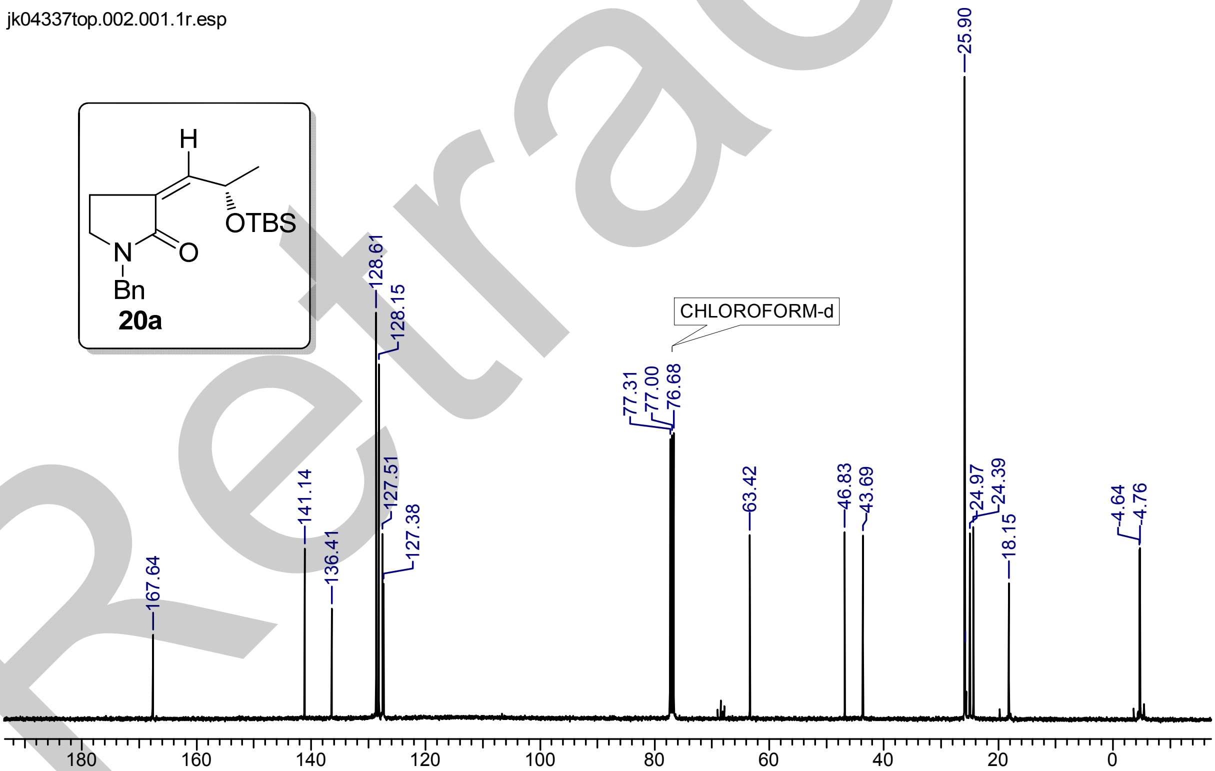

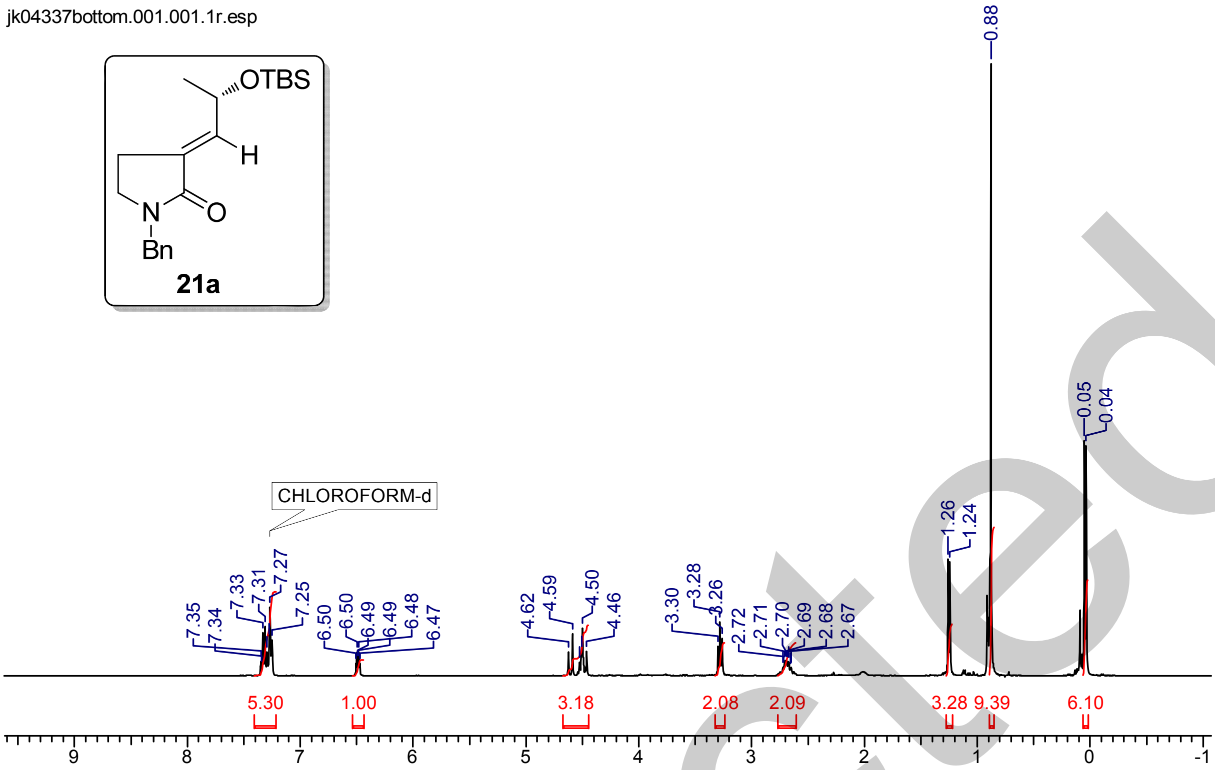
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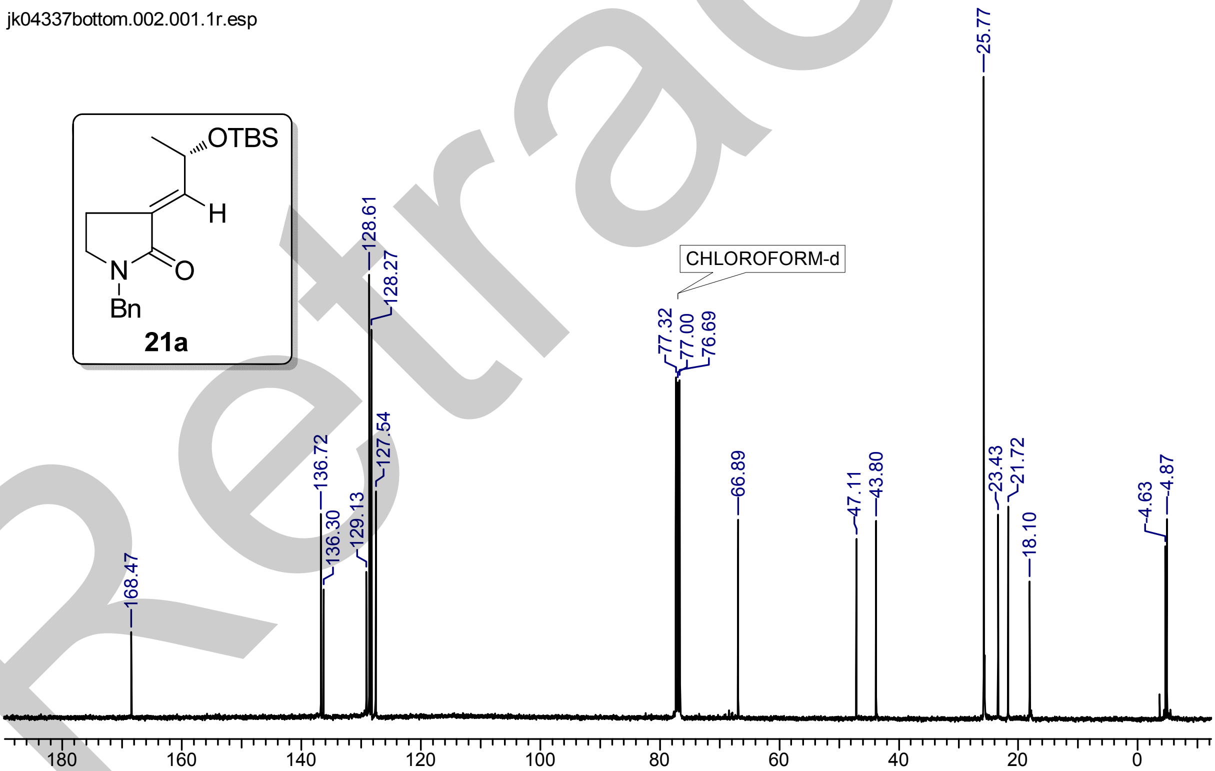
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77.00
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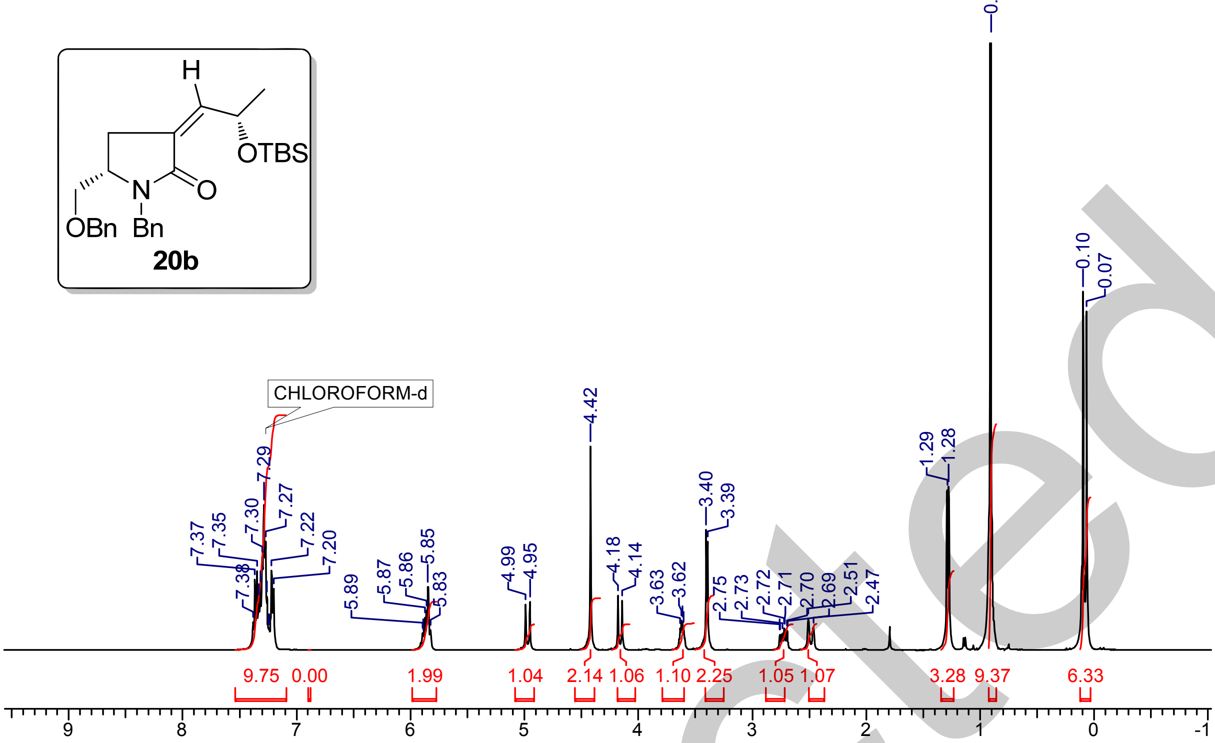

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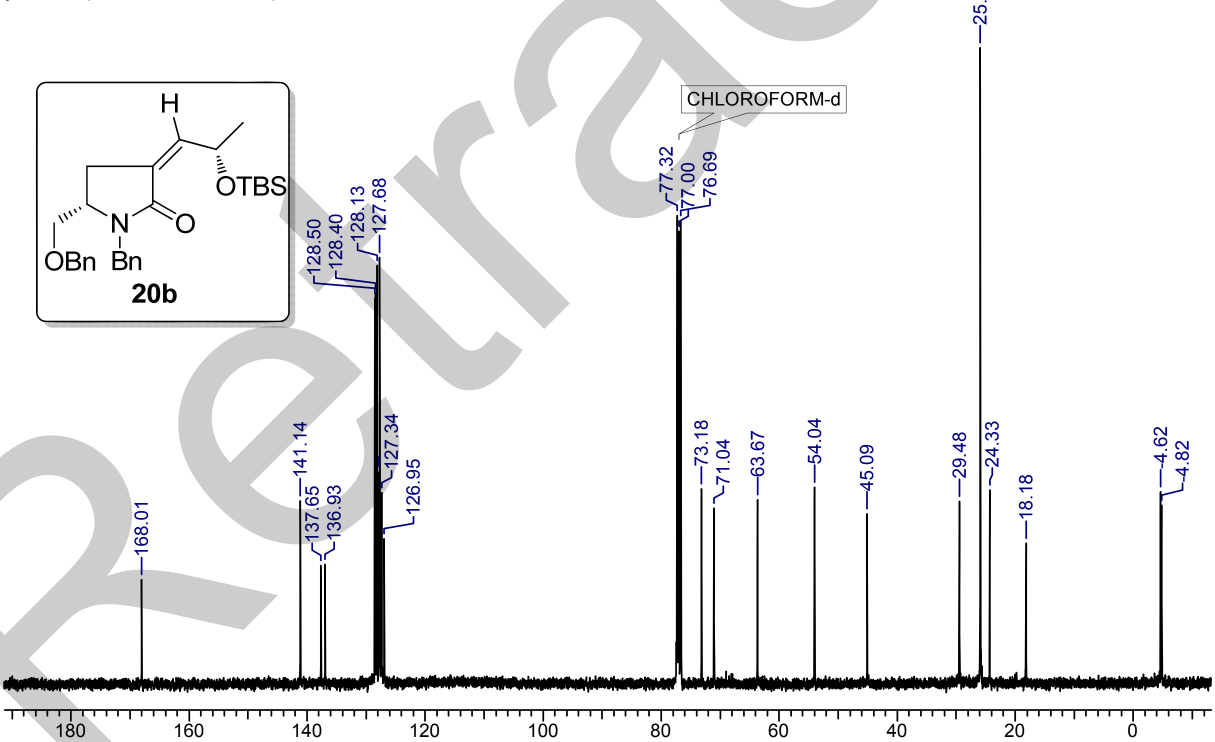

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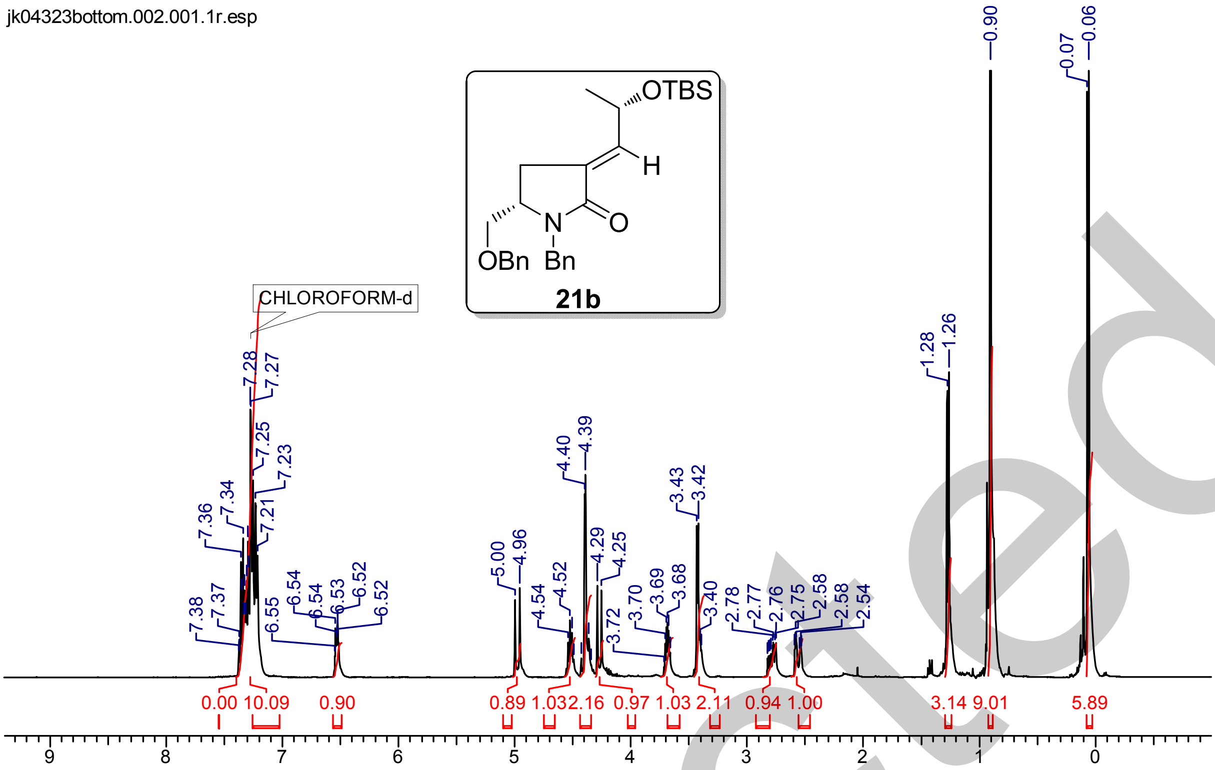

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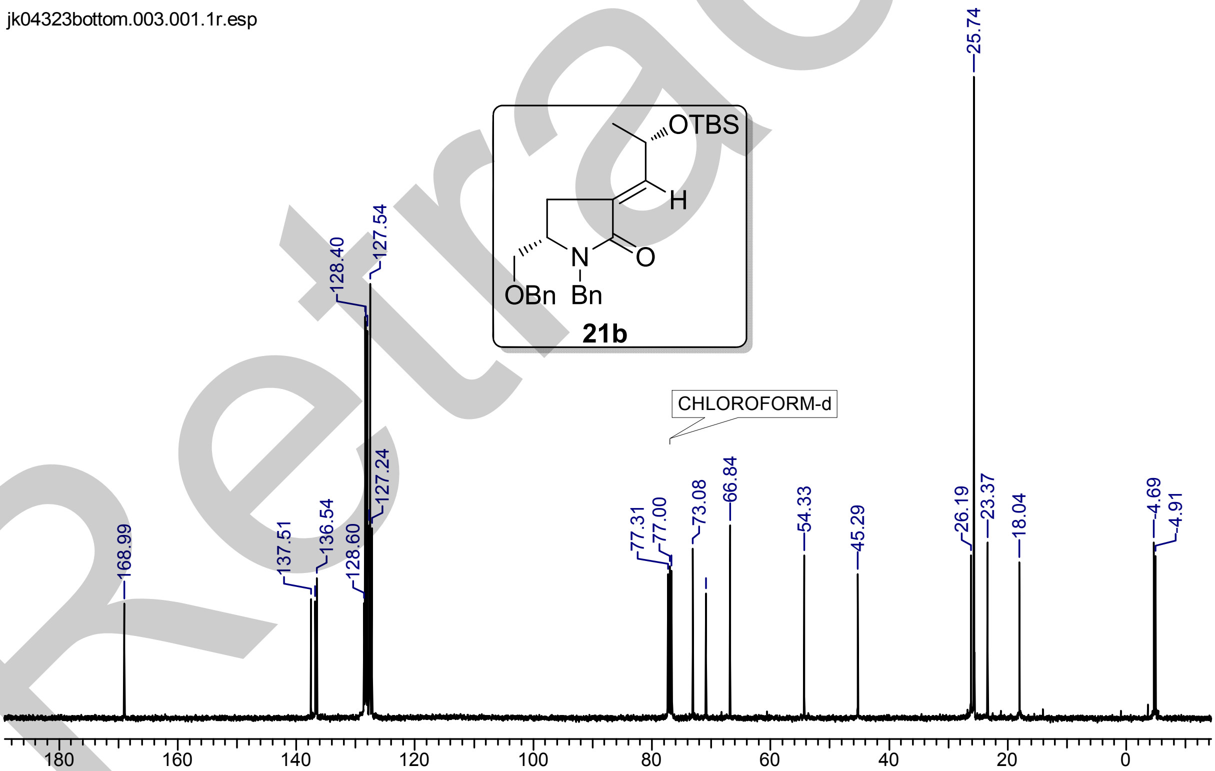

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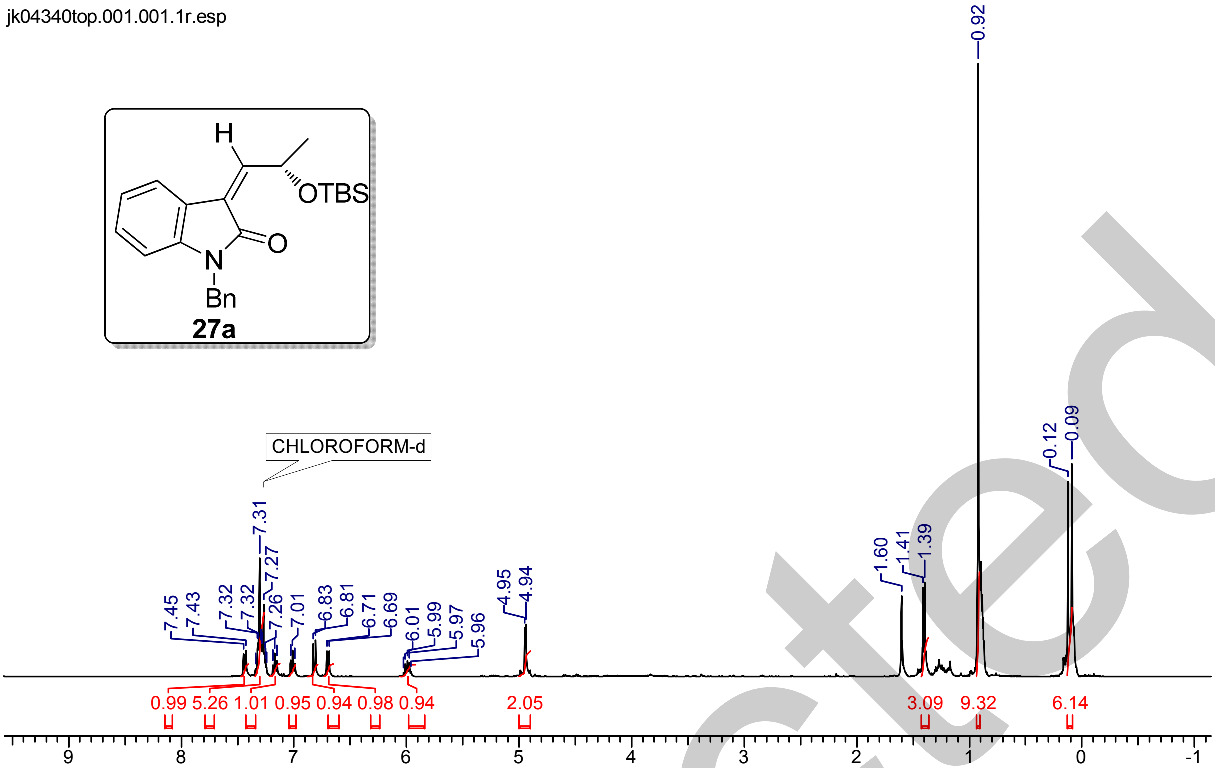

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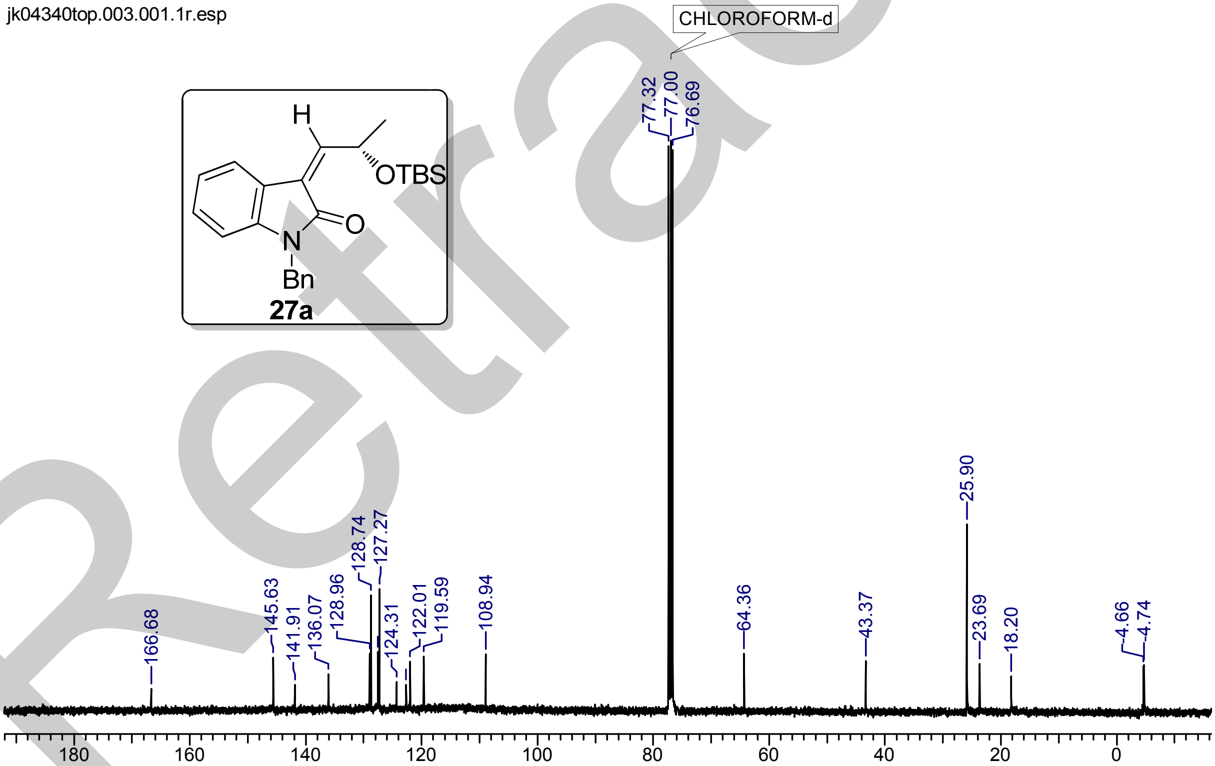

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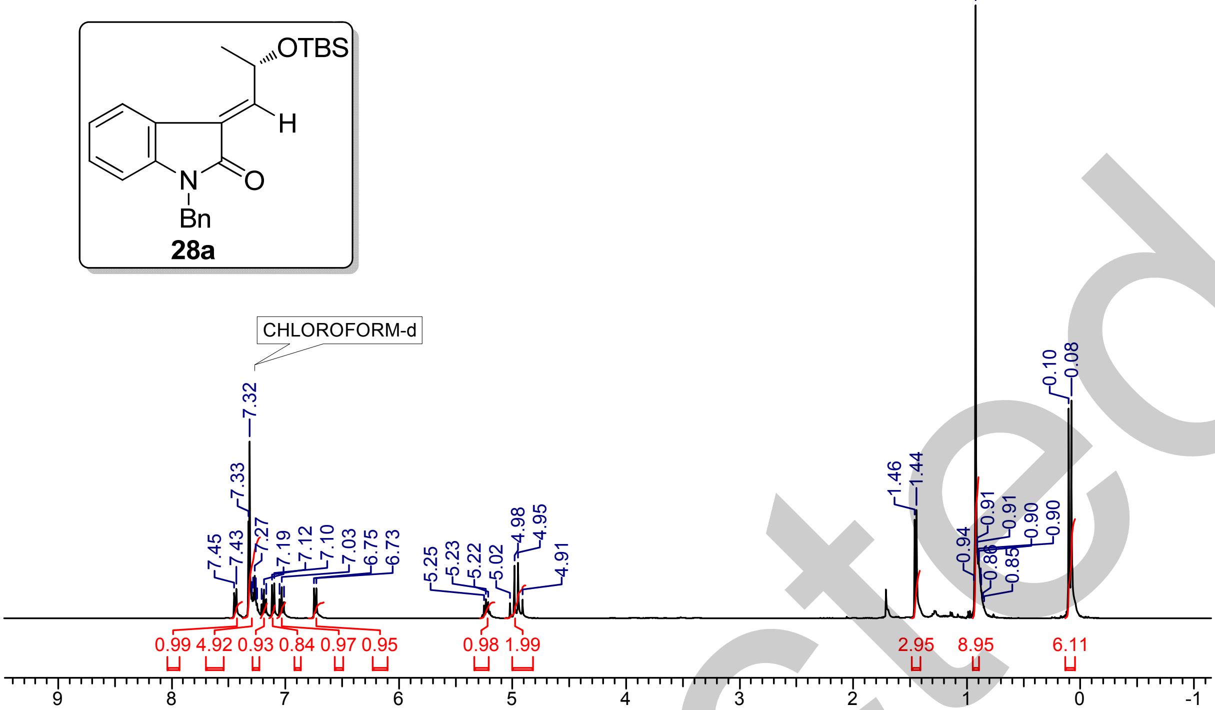

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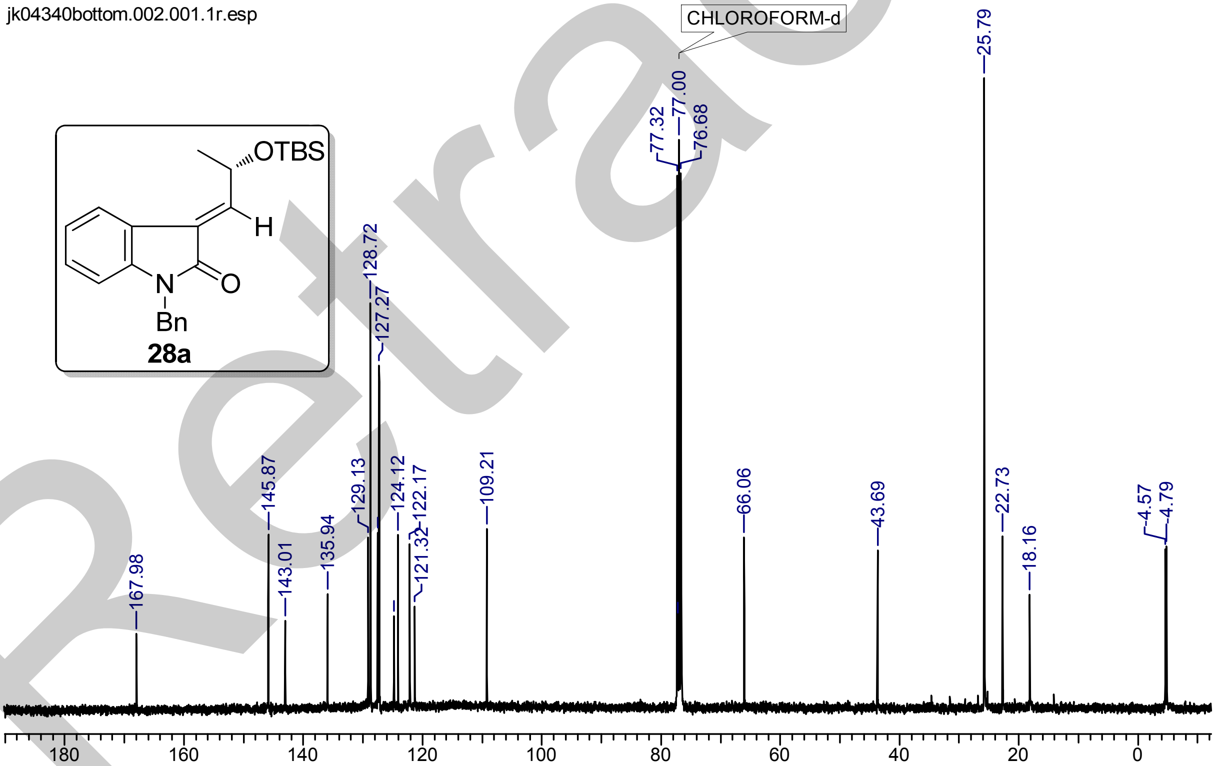

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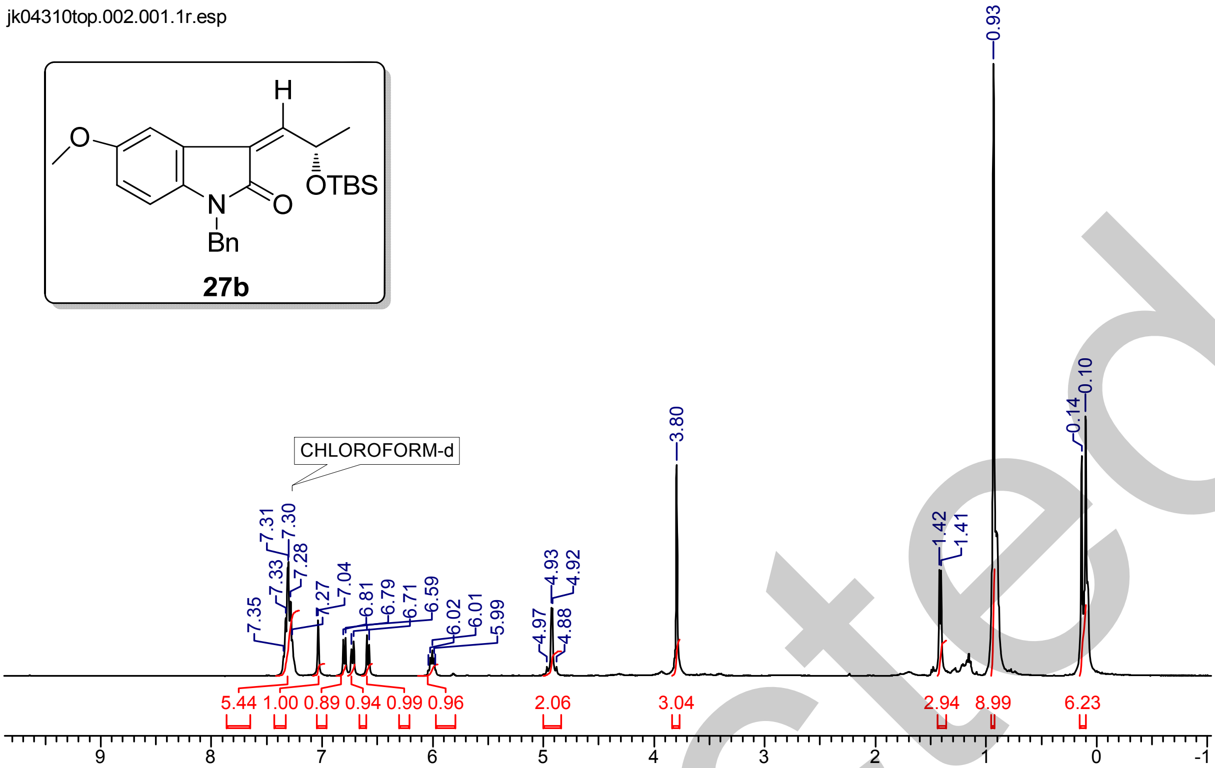

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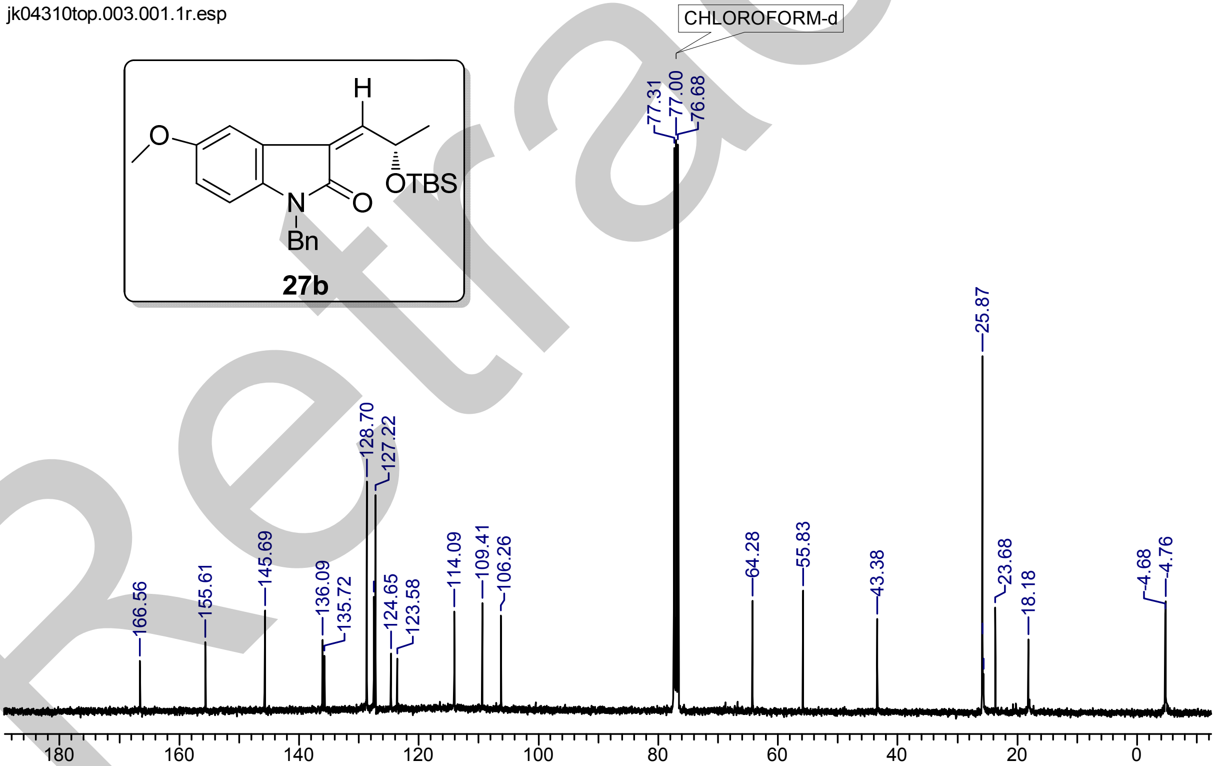

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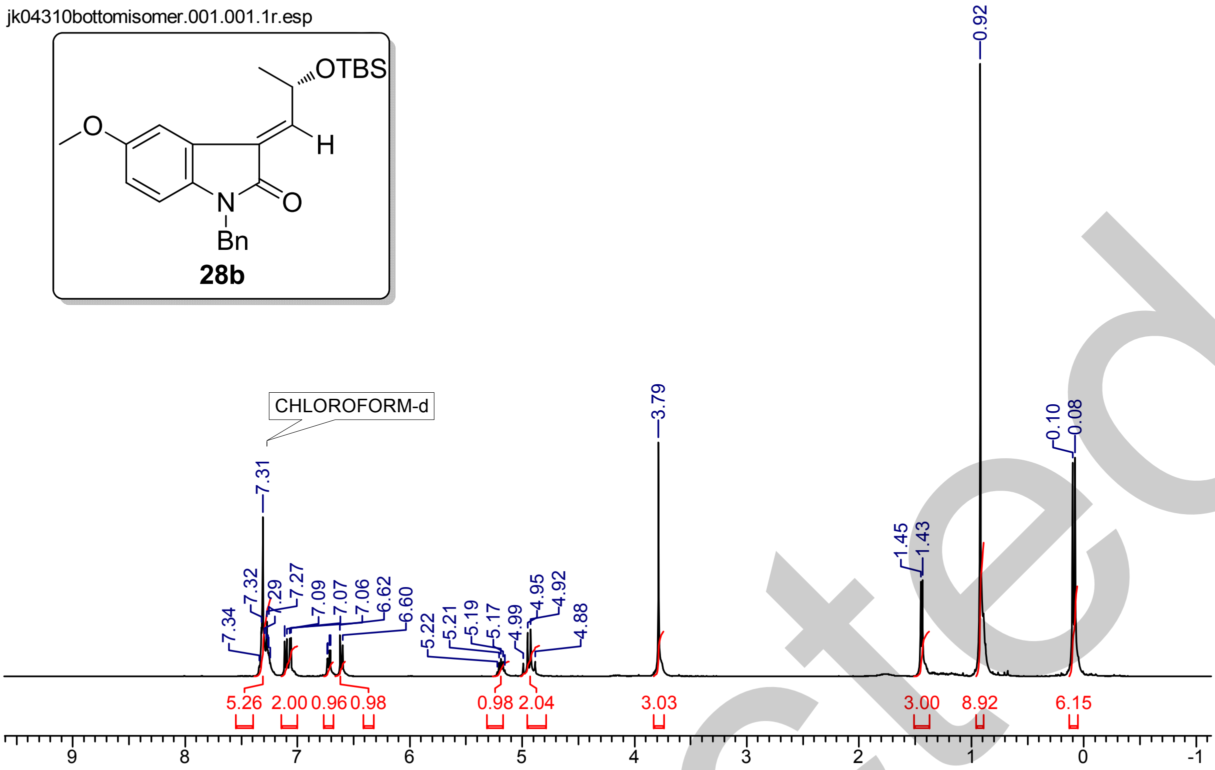

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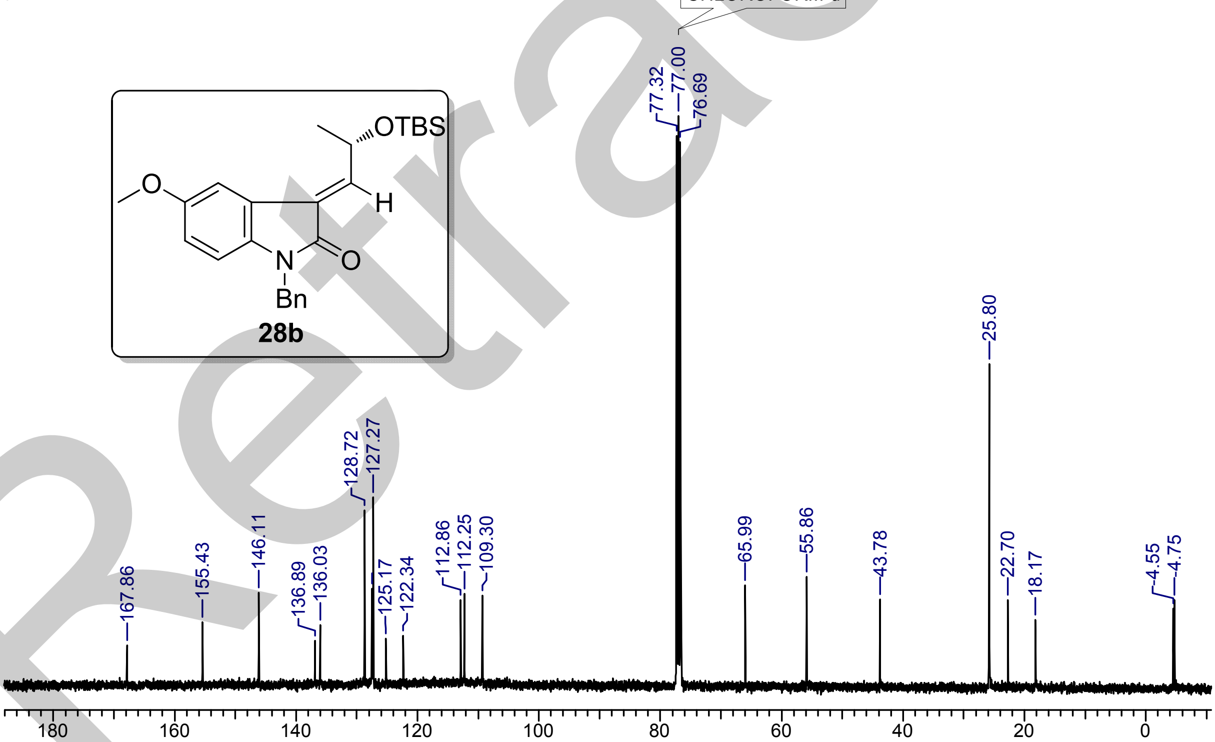

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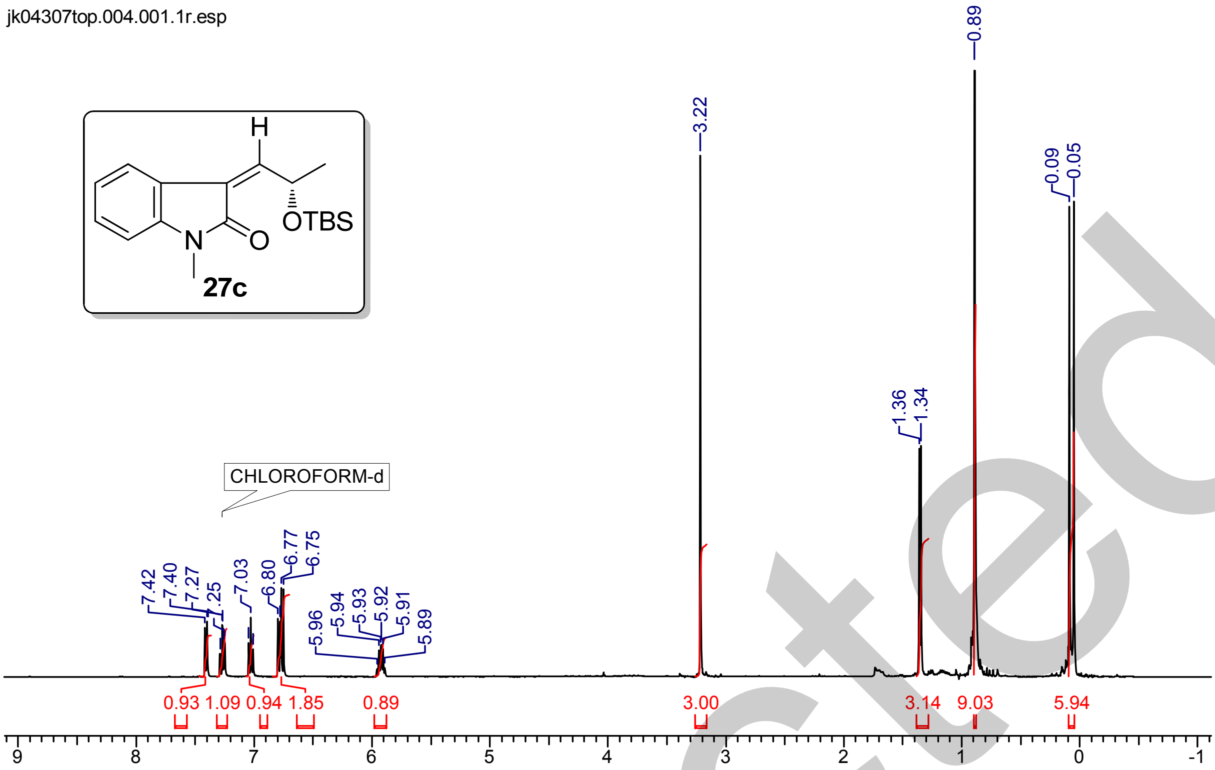

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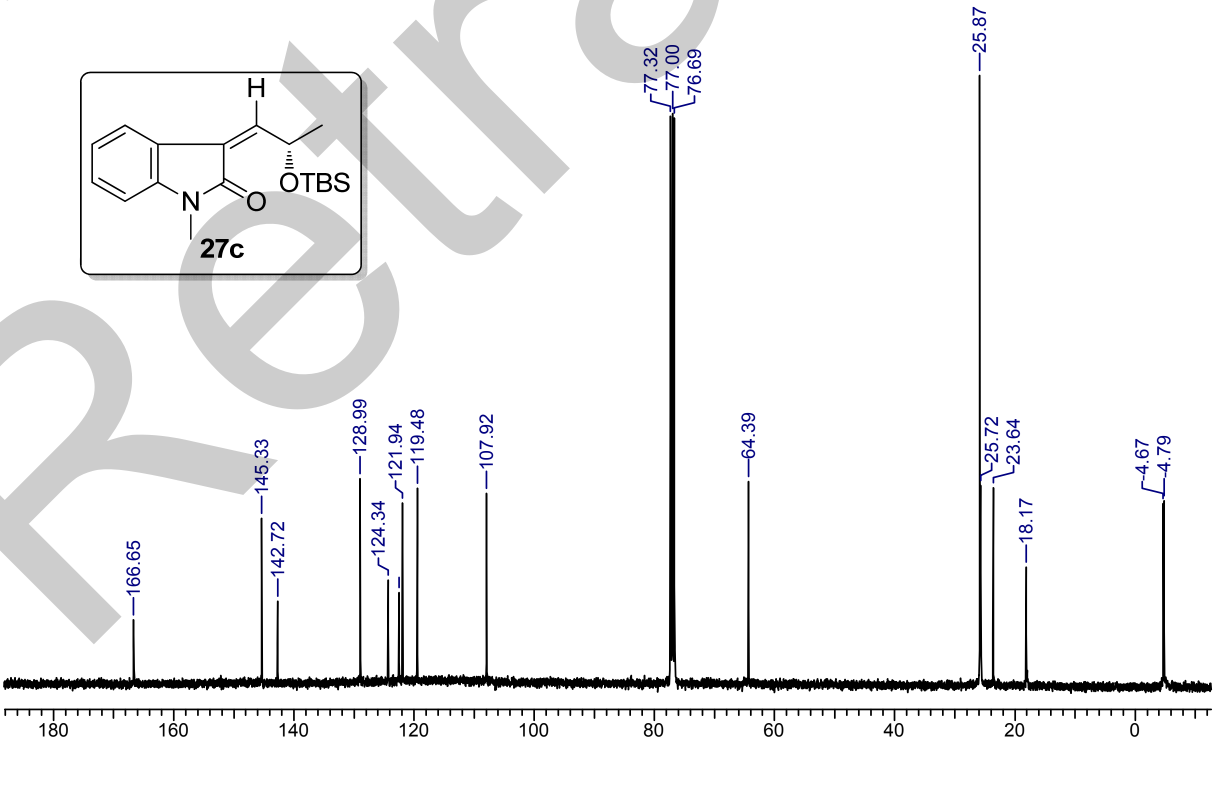

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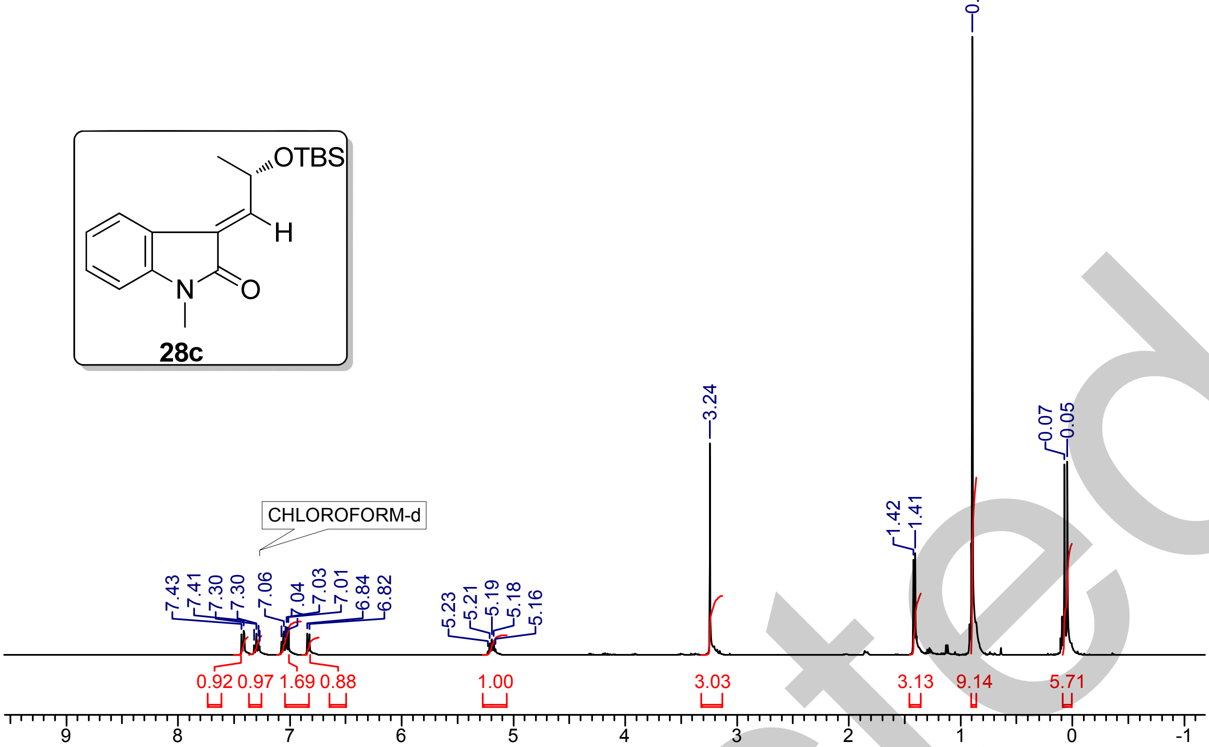

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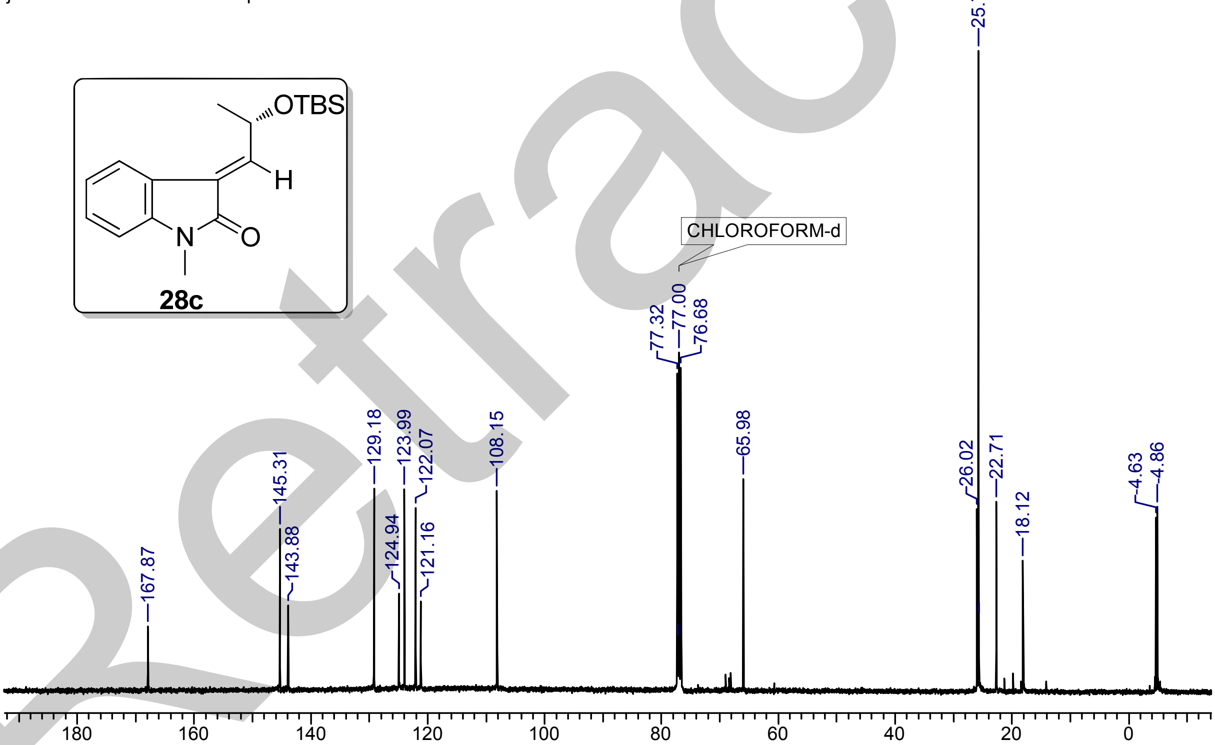

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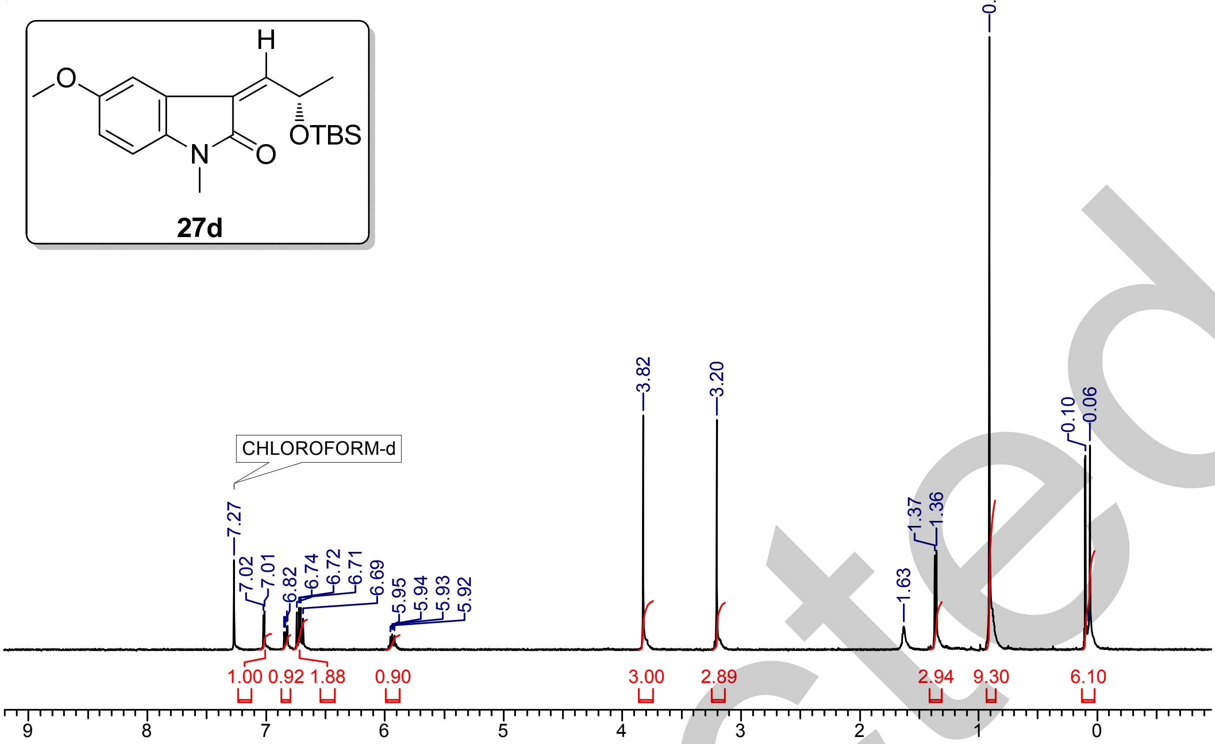

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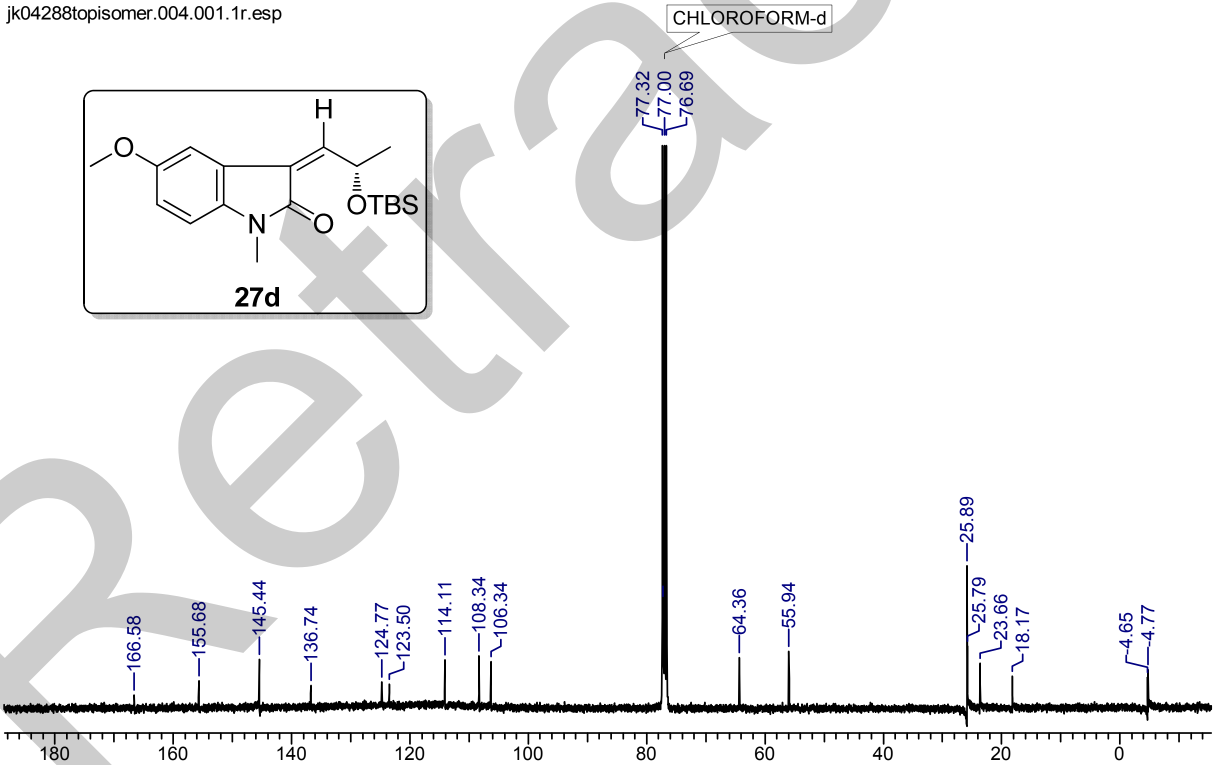

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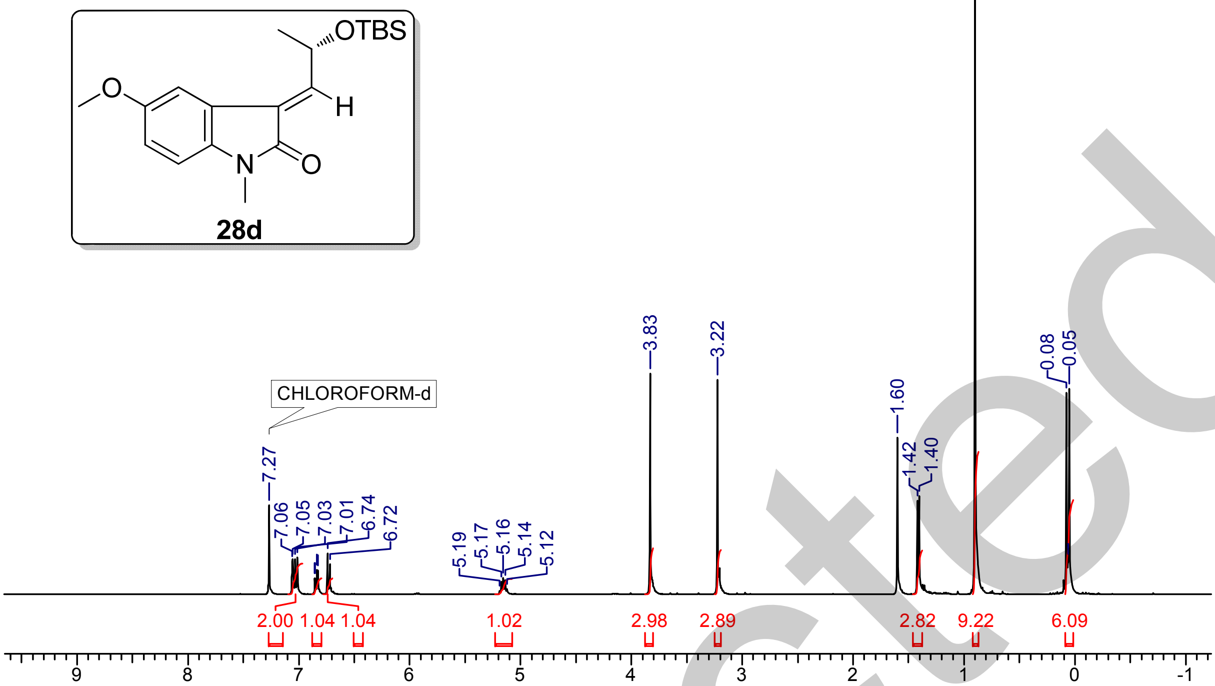

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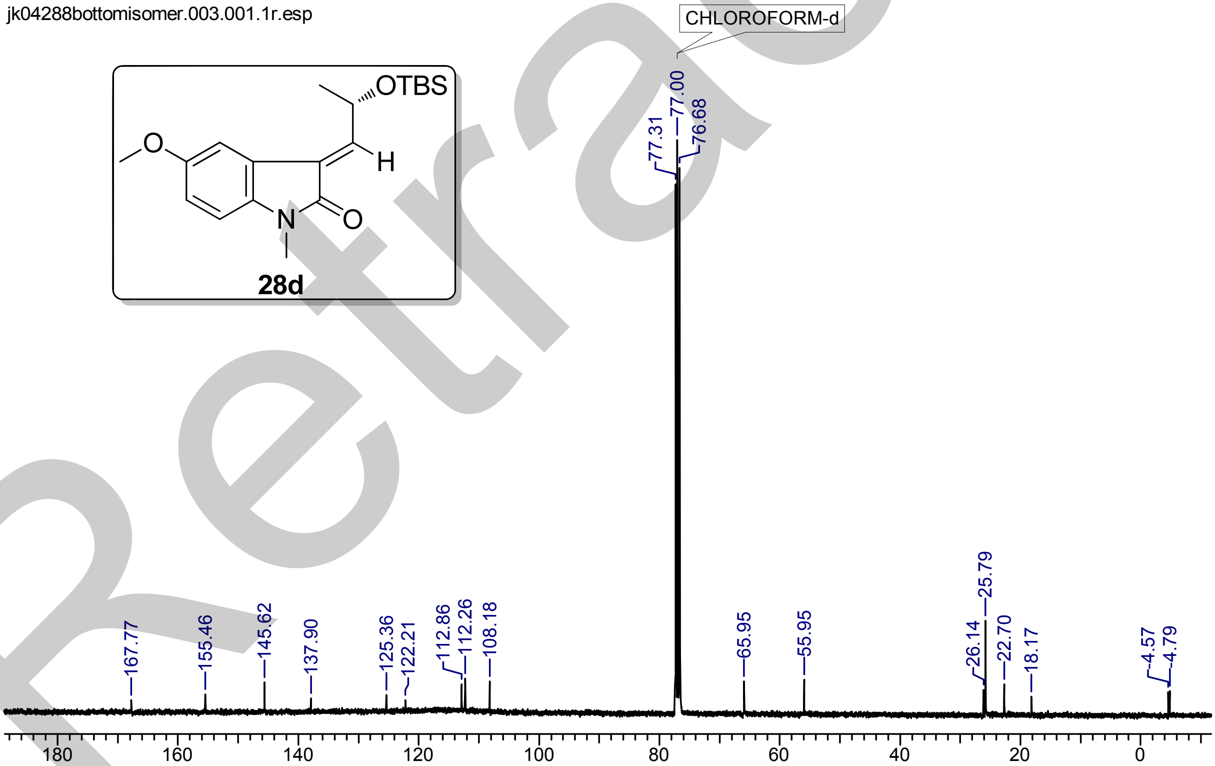

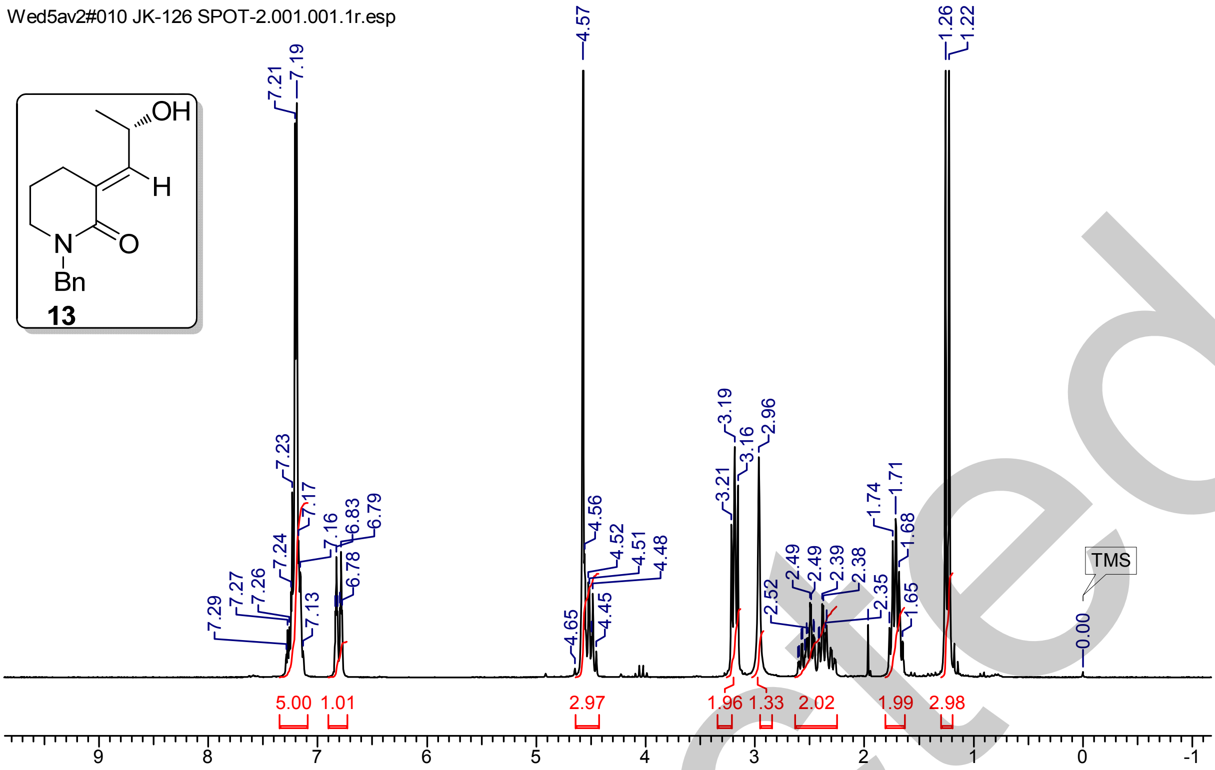
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TMS
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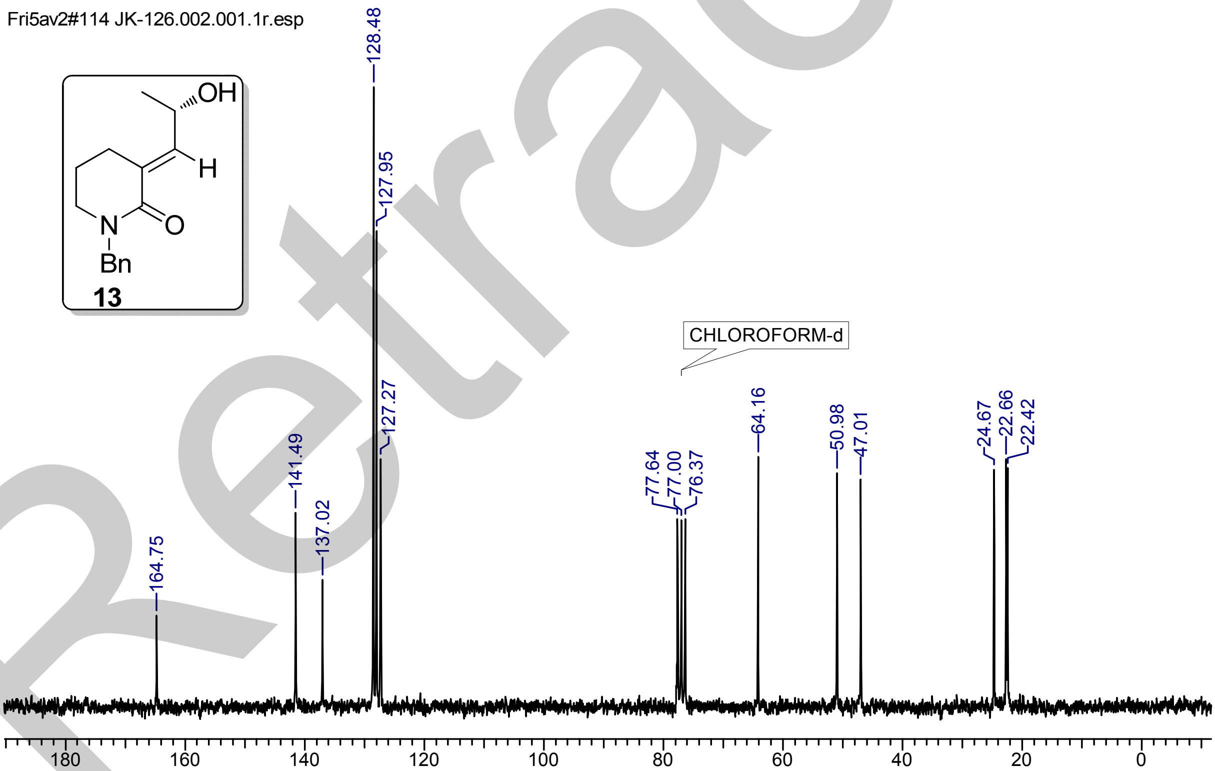
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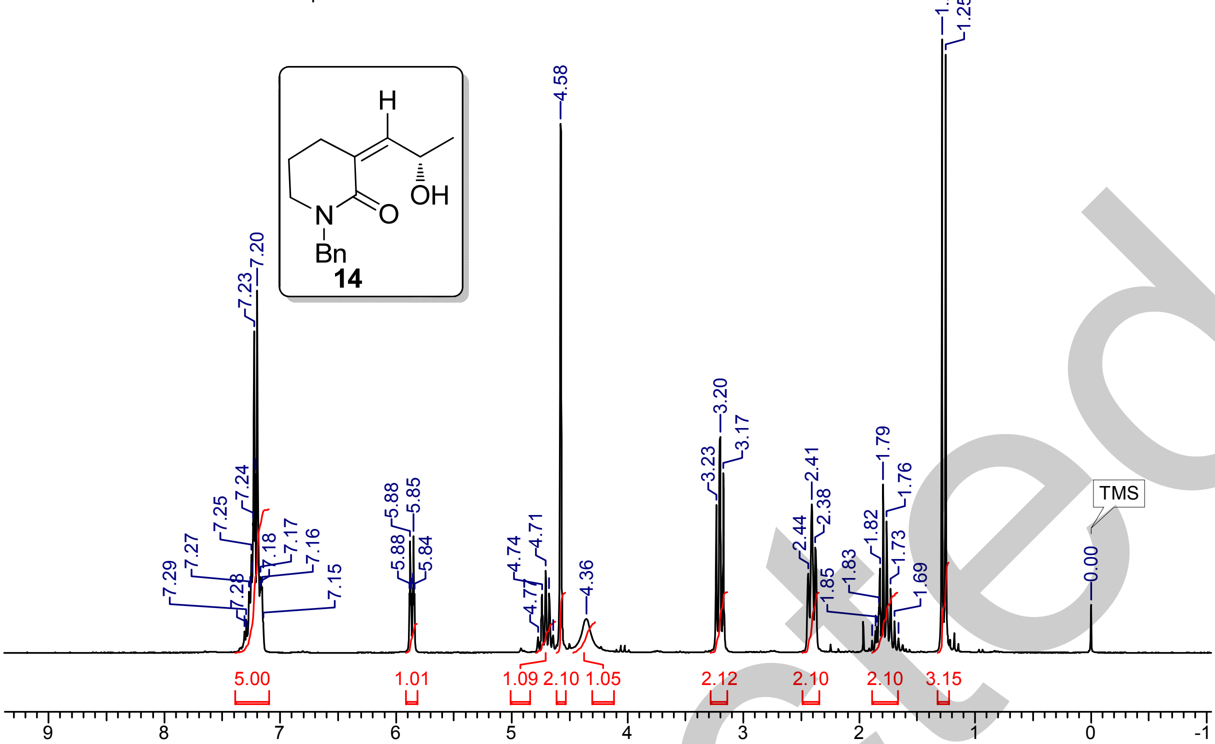

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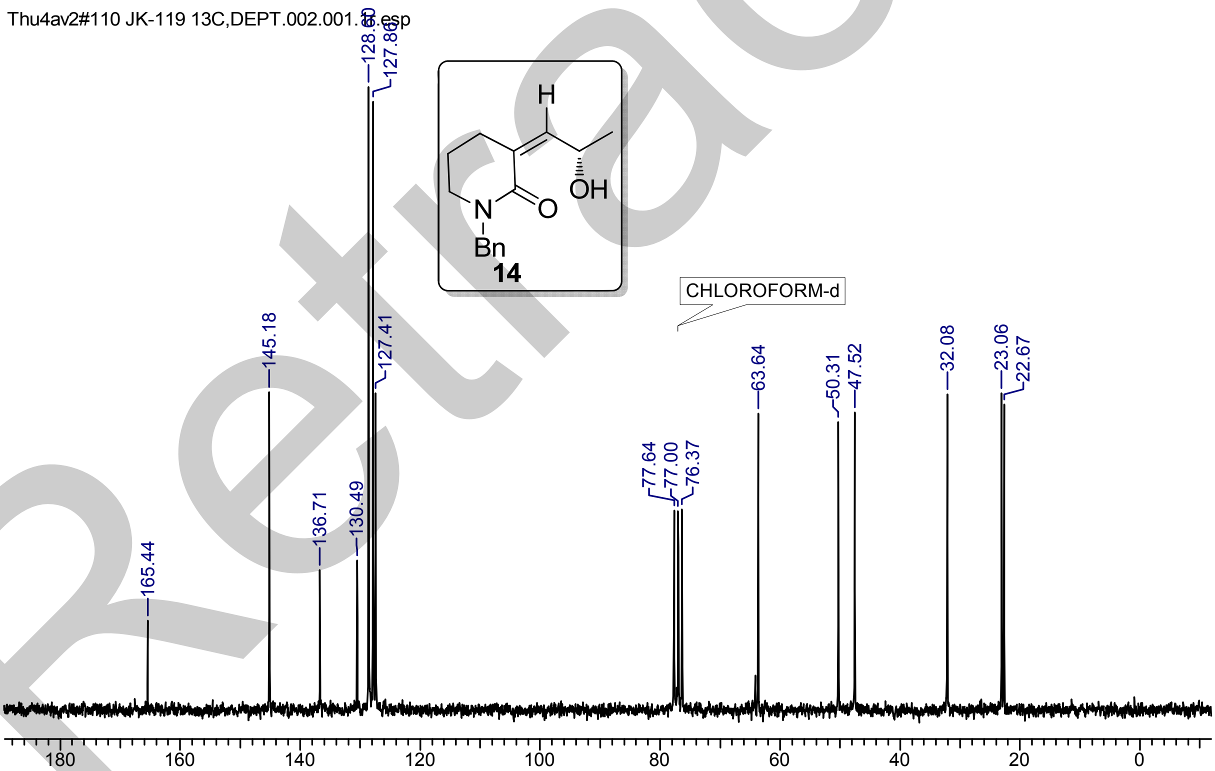

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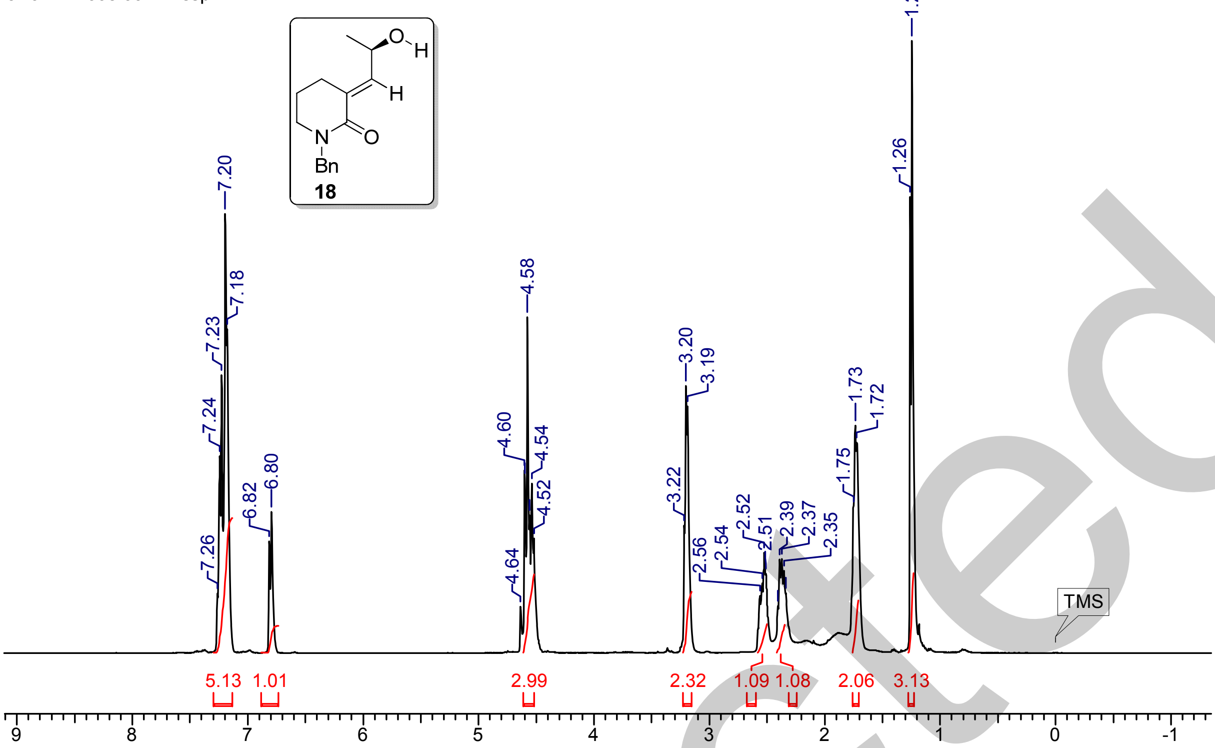

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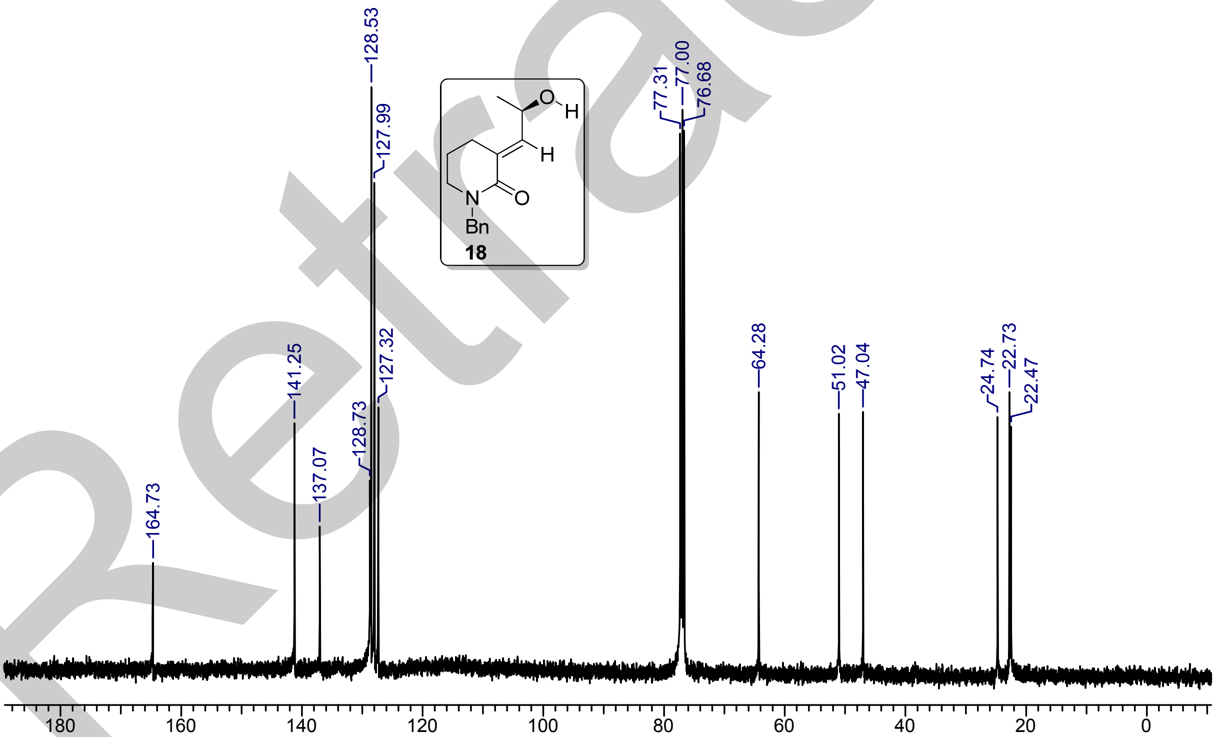

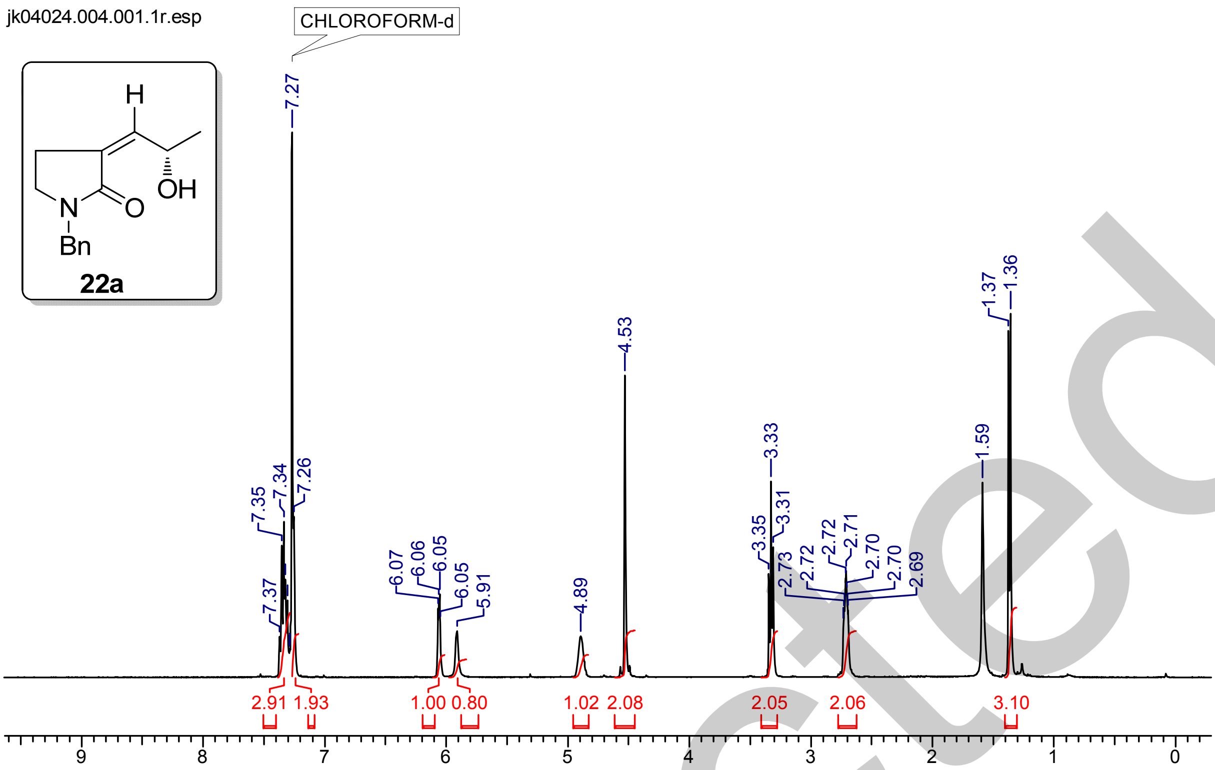
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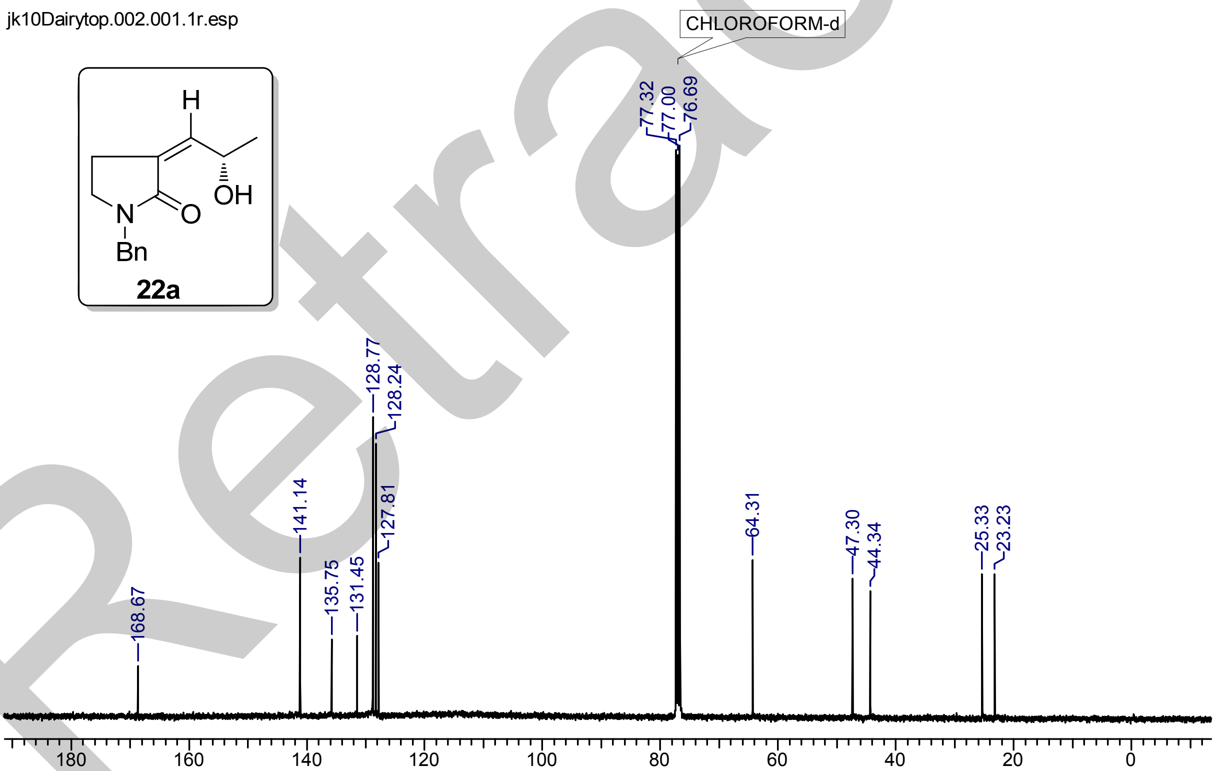
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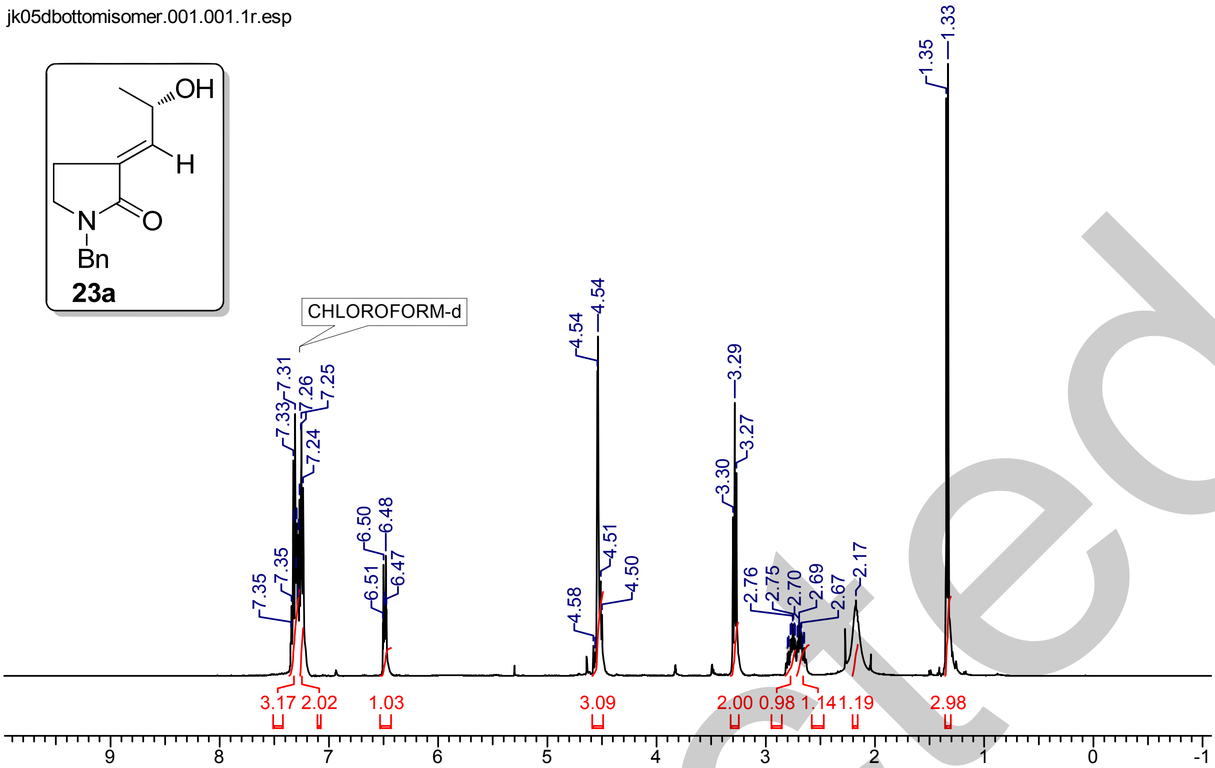

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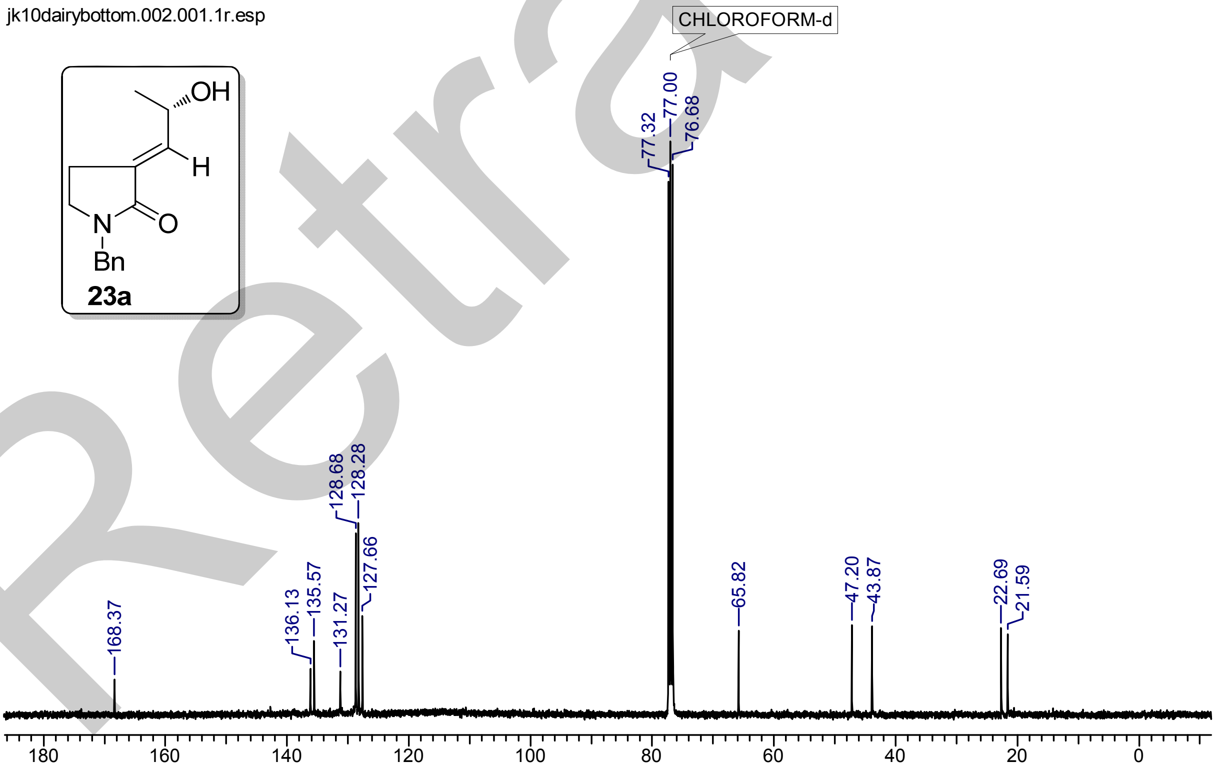

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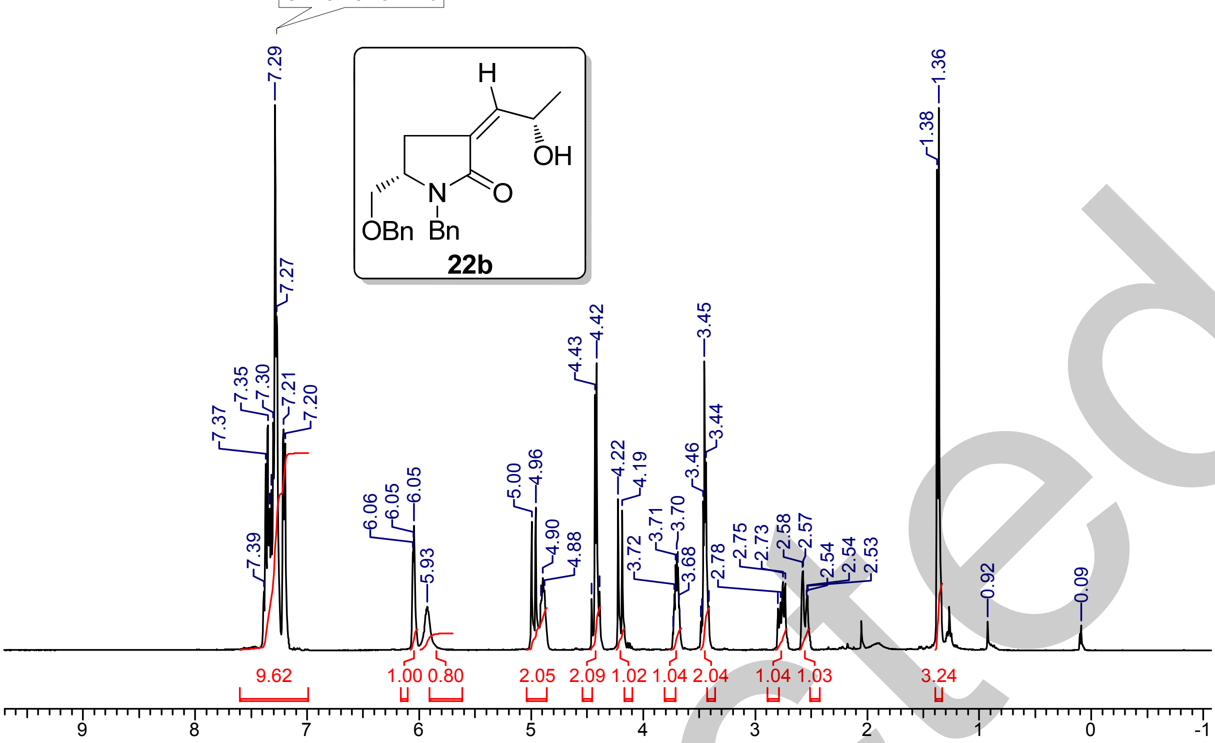

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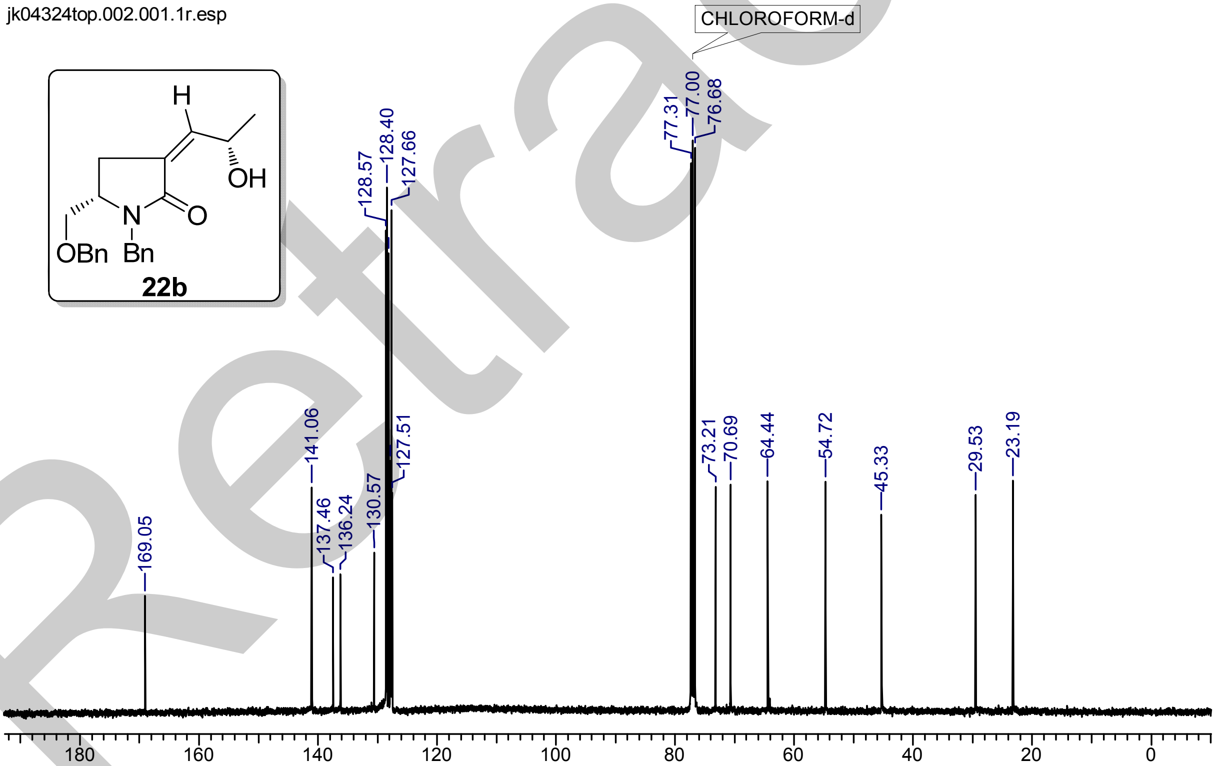

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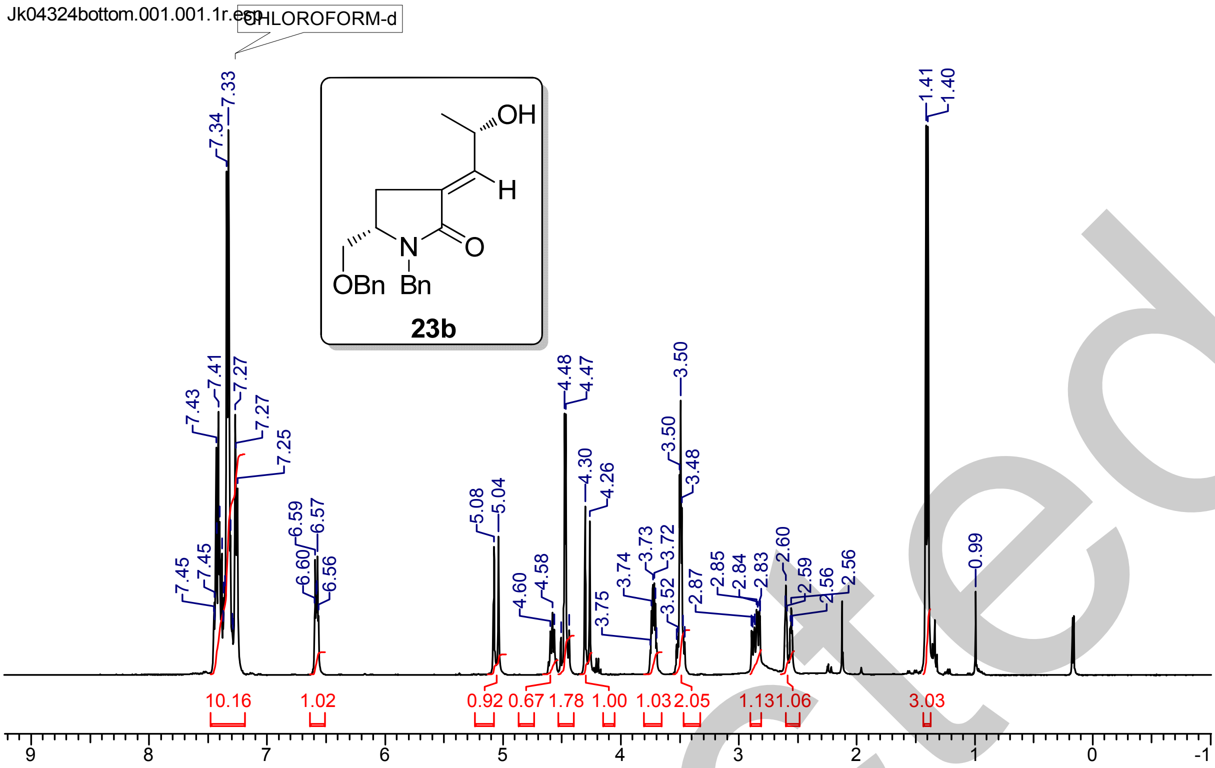

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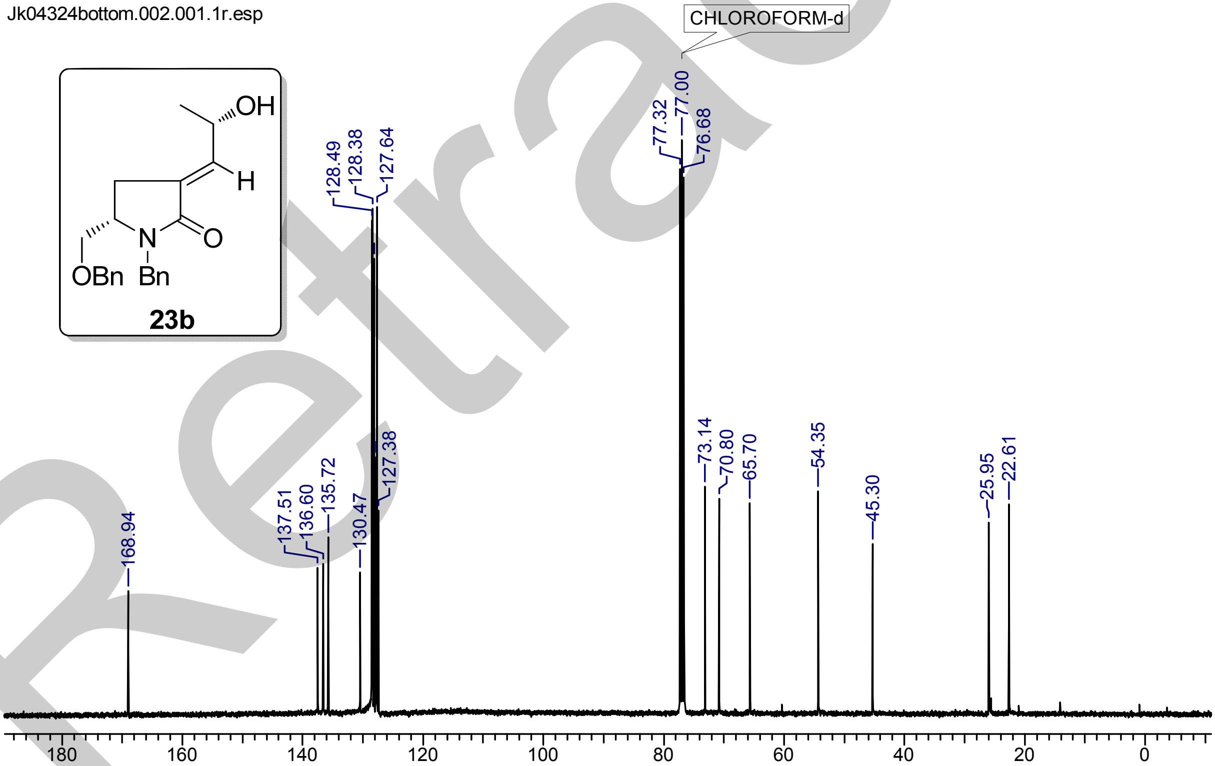

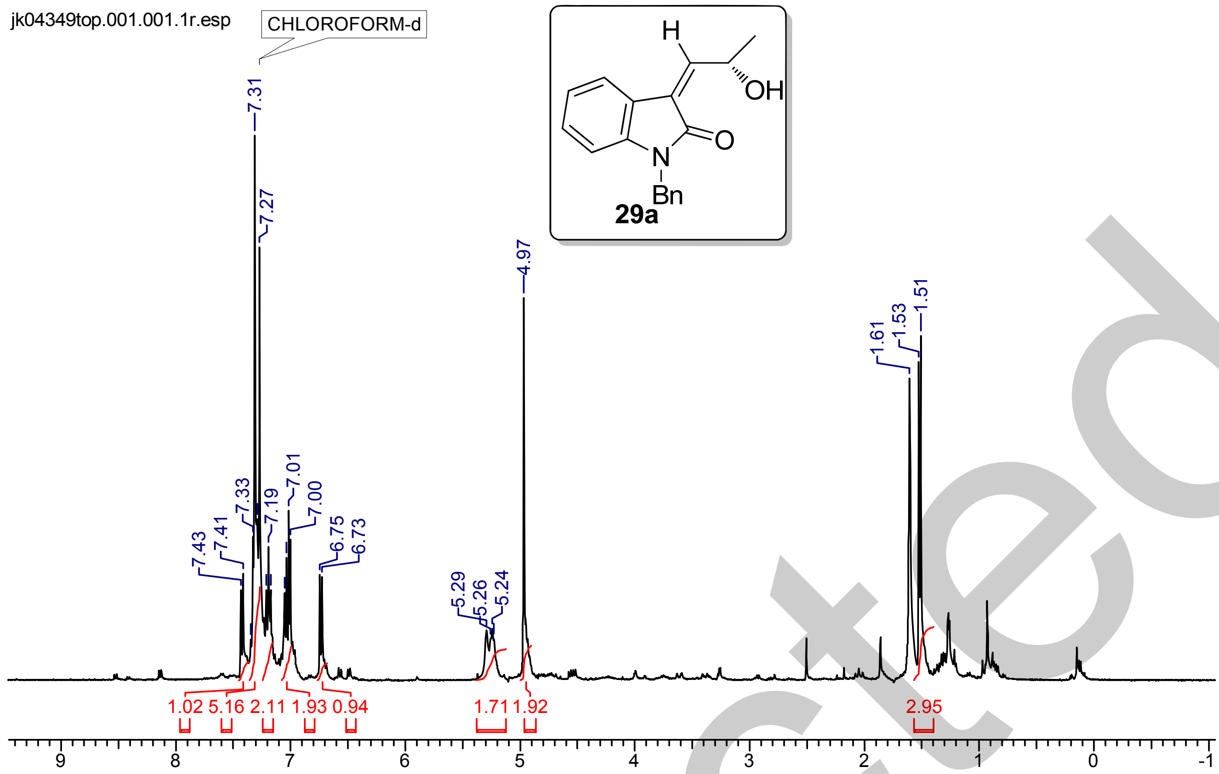
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1.02
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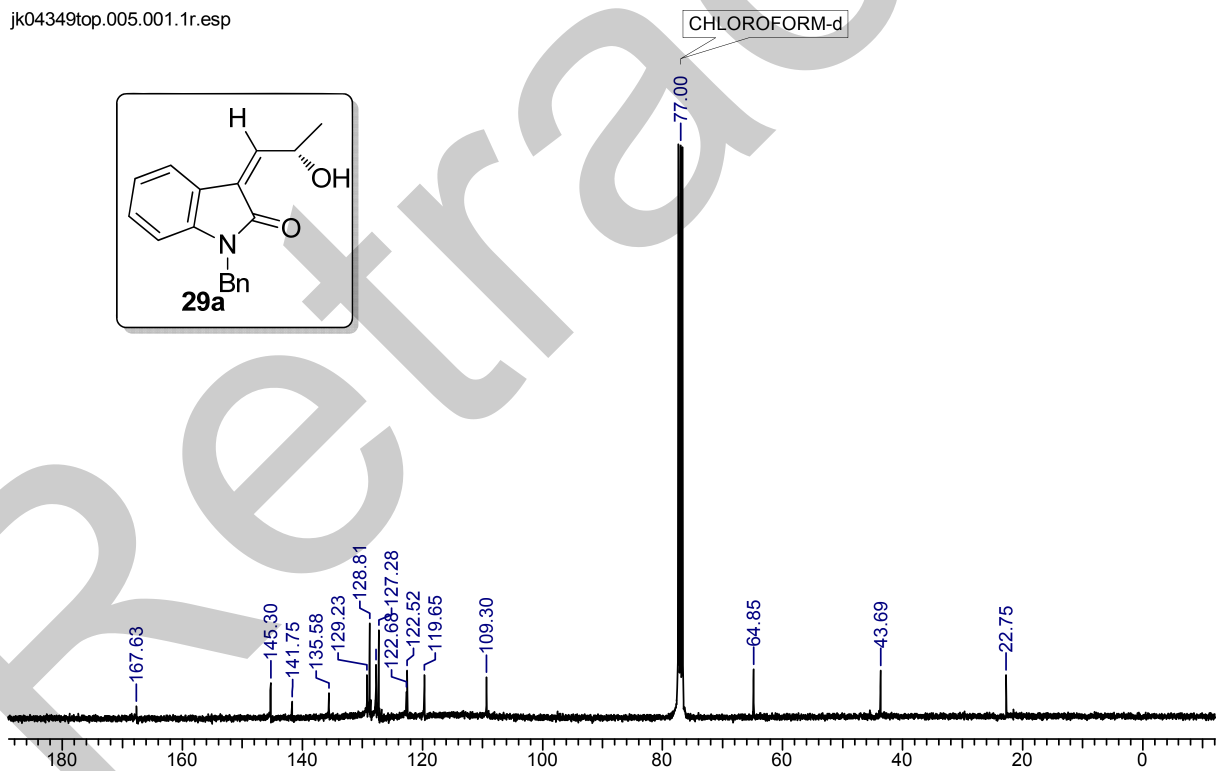
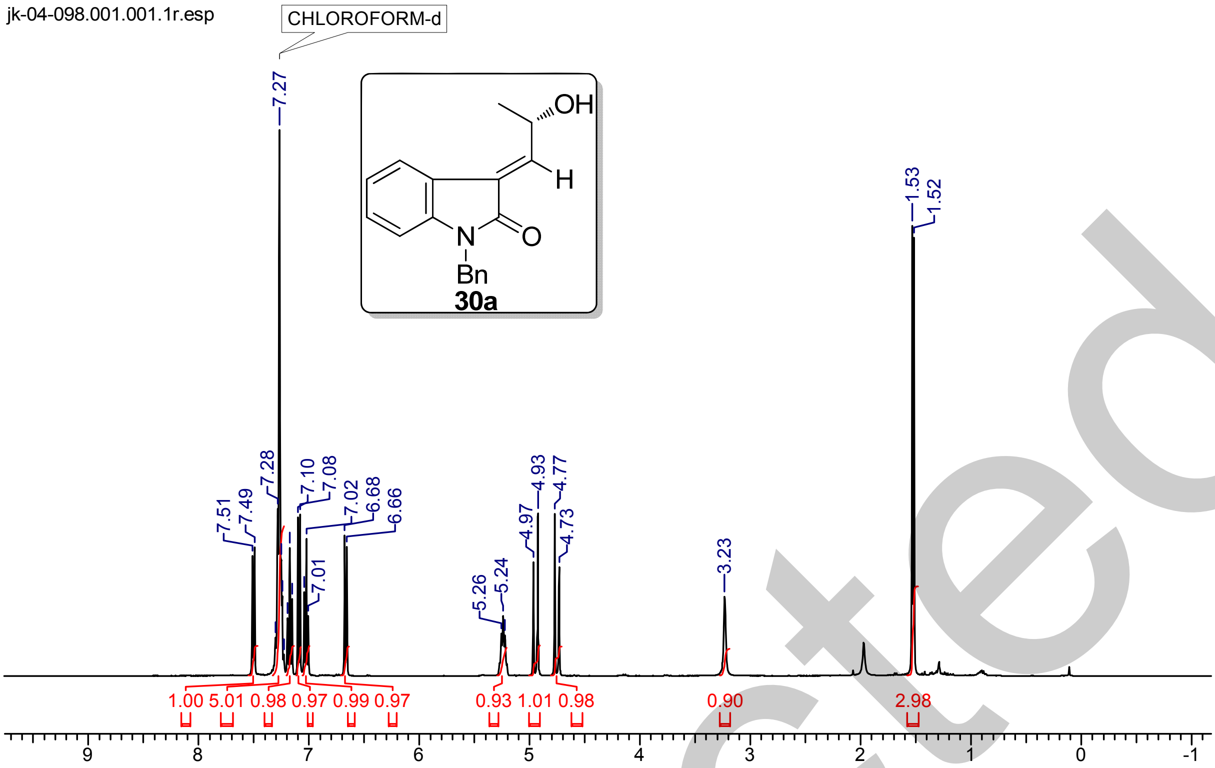
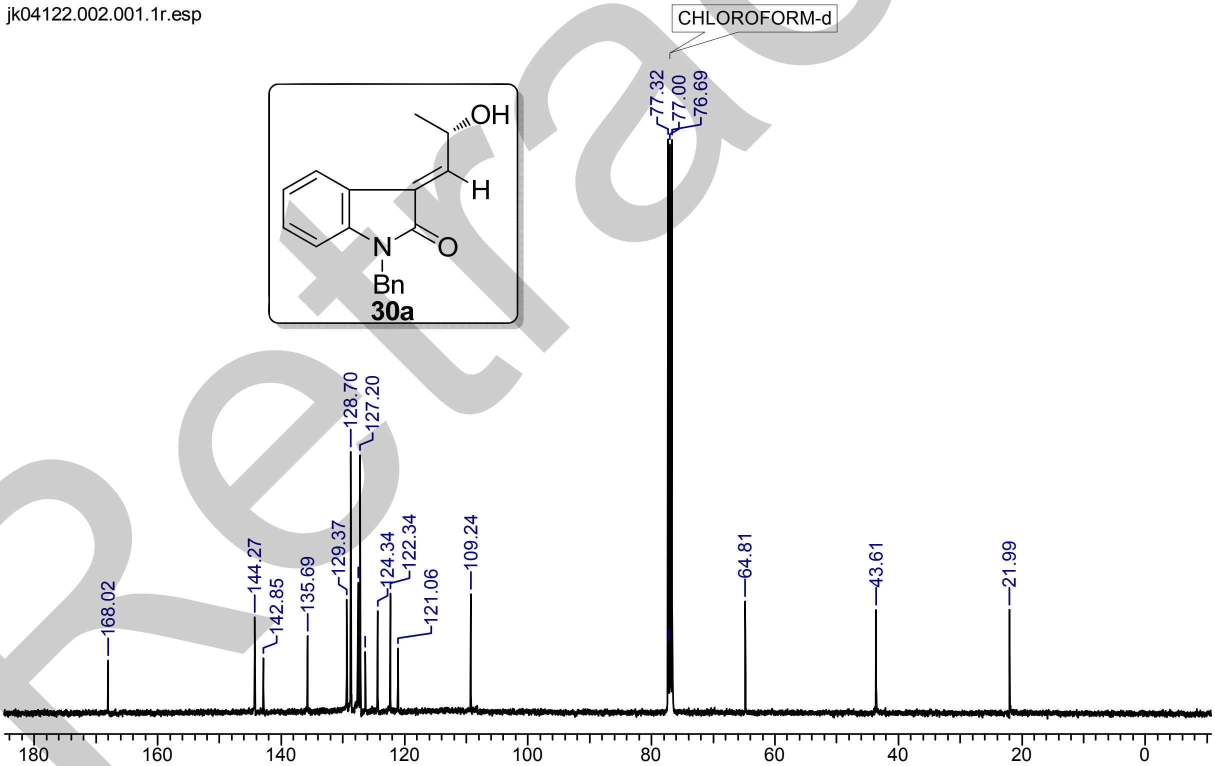
O
N
Bn
29a


jk04349top.005.001.1r.esp
CHLOROFORM-d
77.00
167.63
145.30
141.75
135.58
129.23
128.81
127.28
122.68
122.52
119.65
109.30
64.85
43.69
22.75
180
160
140
120
100
80
60
40
20
0
H
OH
O
N
Bn
29a

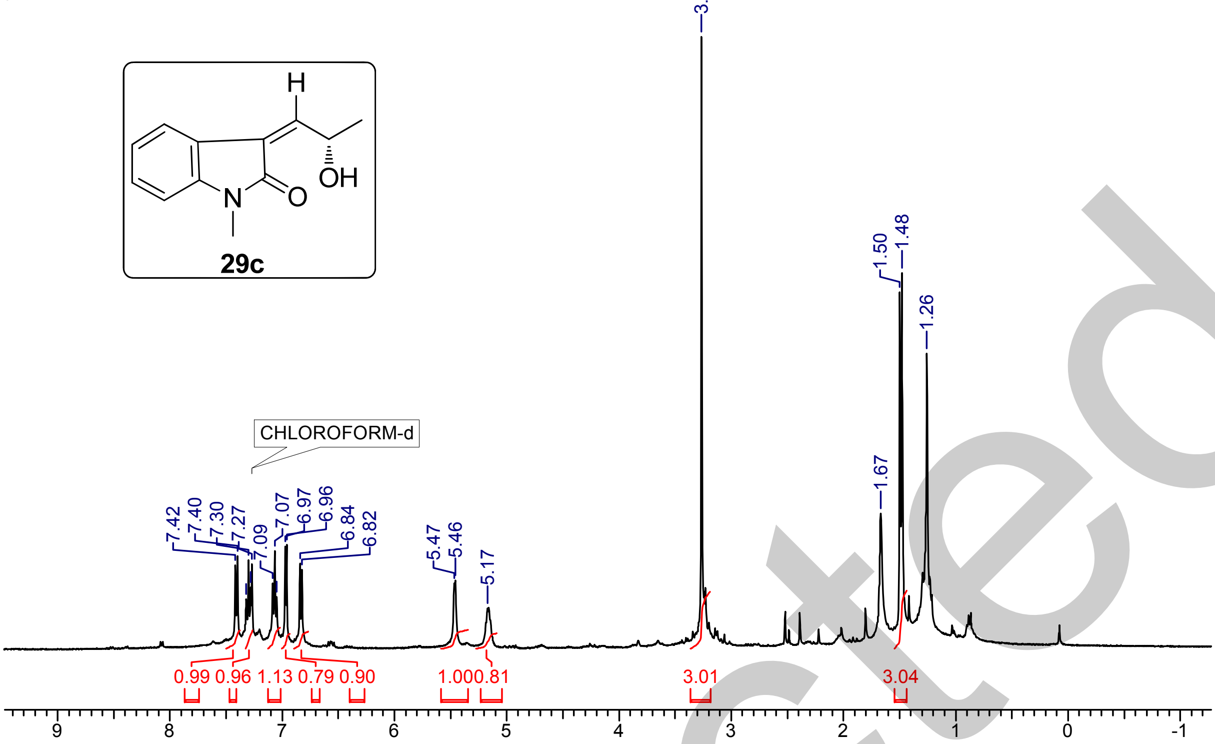
jk-04-098.001.001.1r.esp



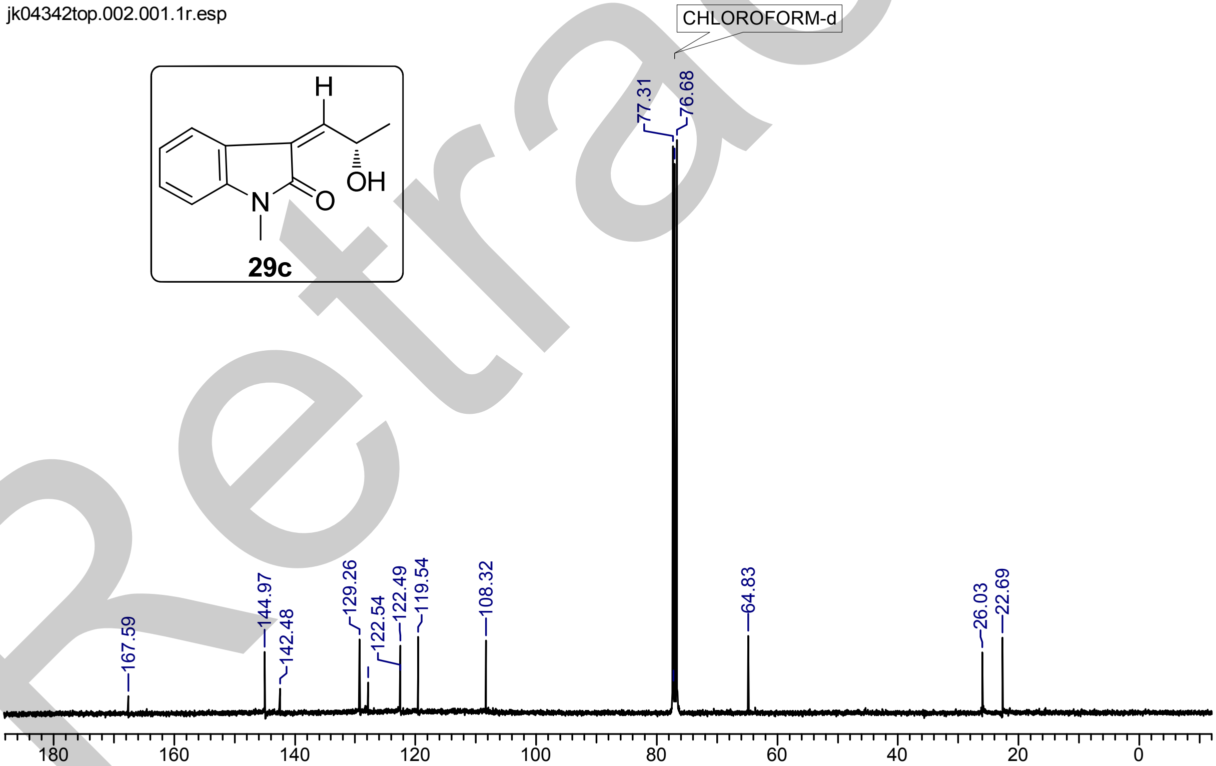
jk04122.002.001.1r.esp



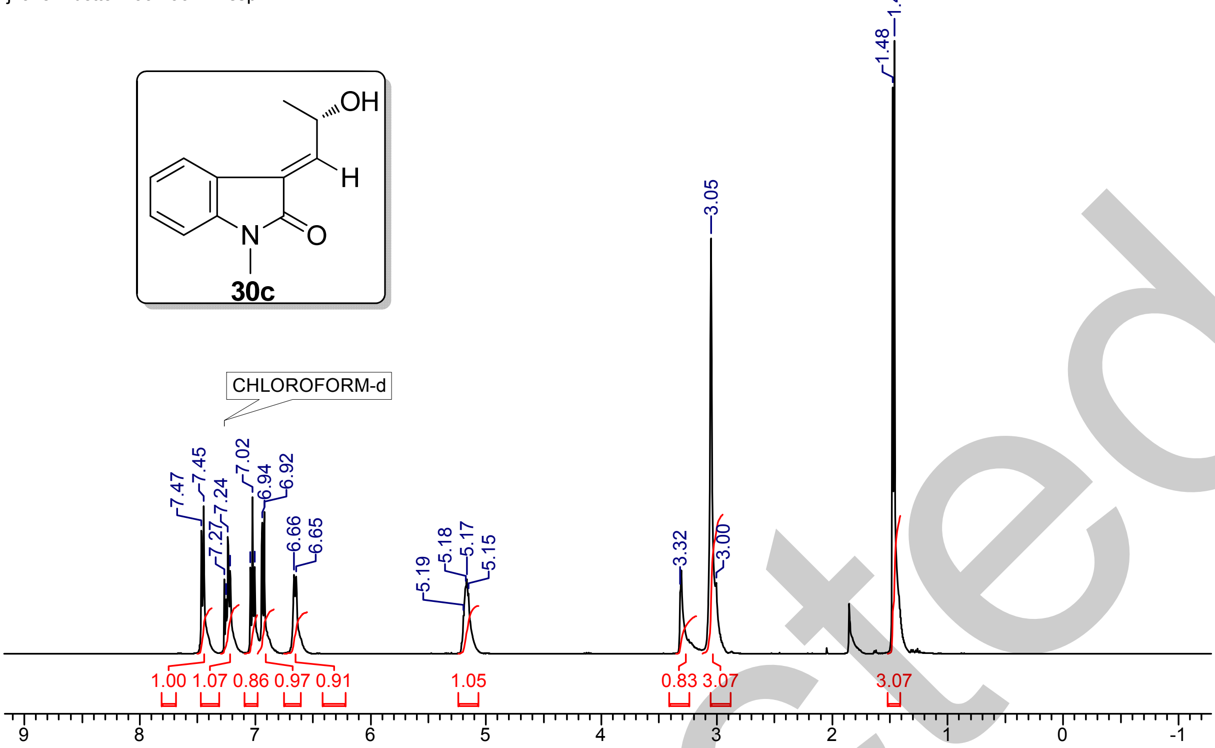
jk04342top.004.001.1r.esp



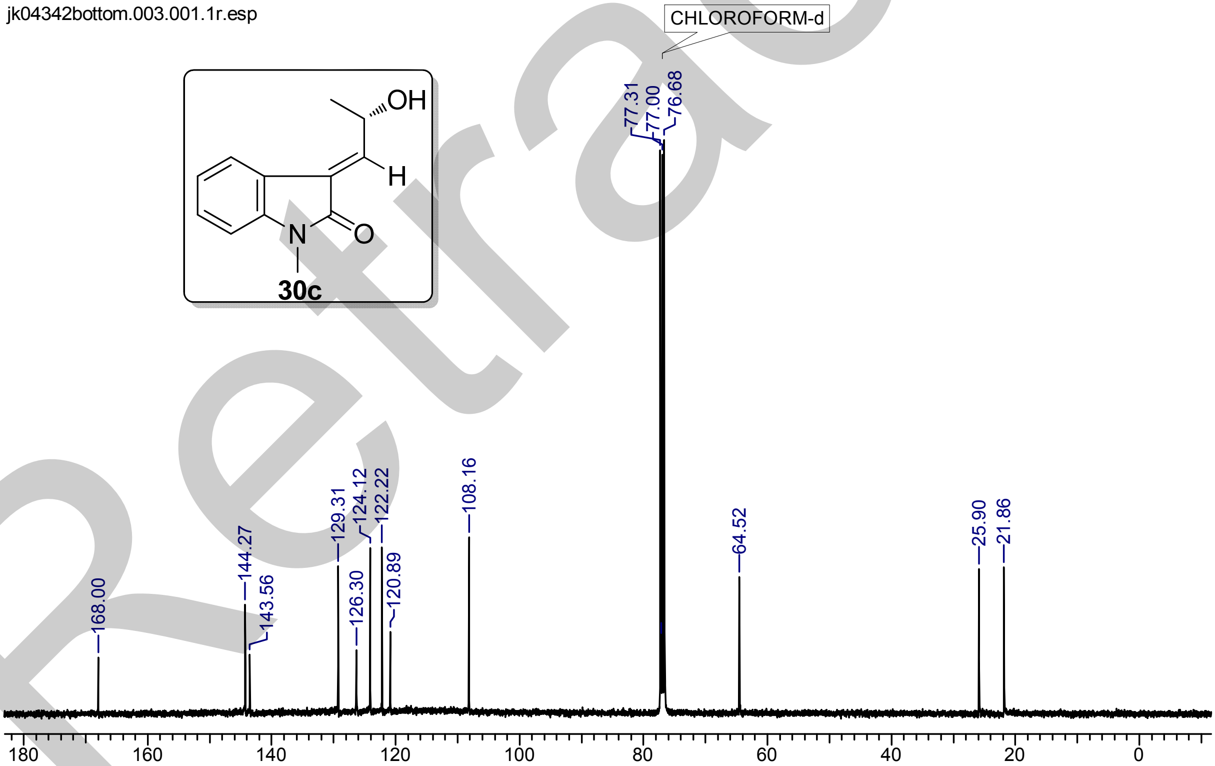
jk04342top.002.001.1r.esp

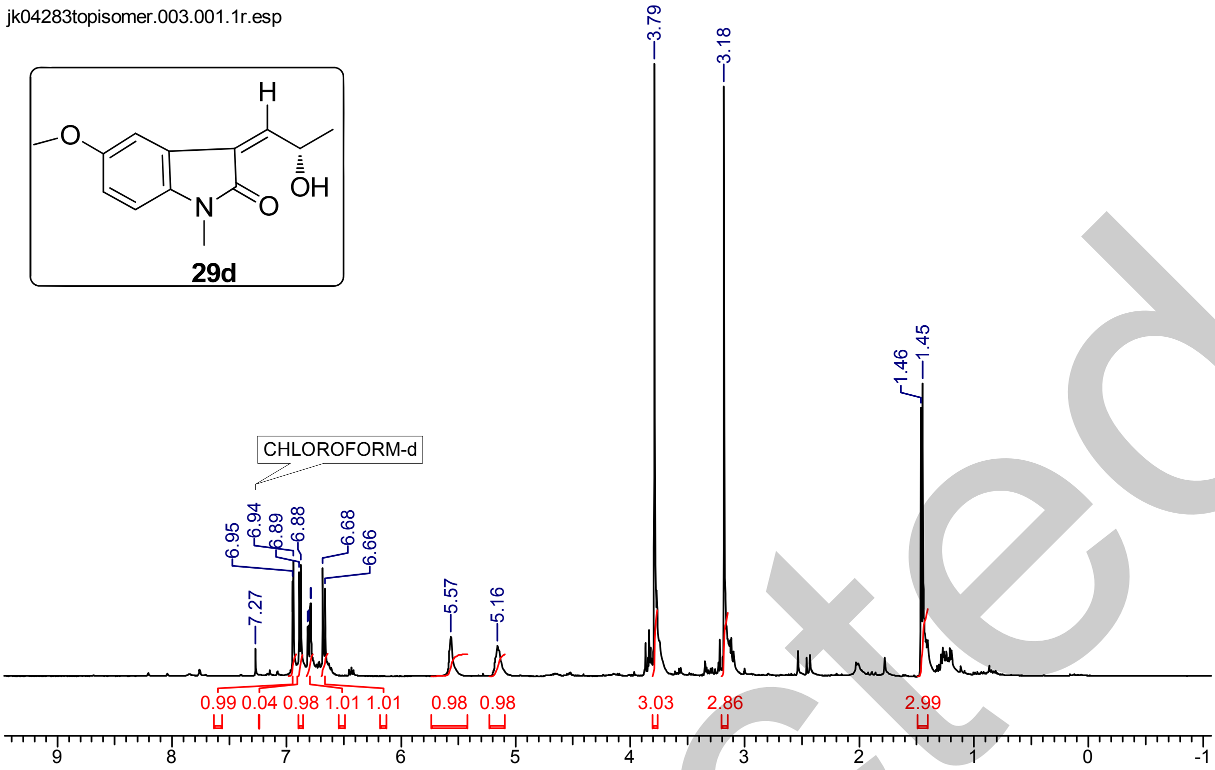


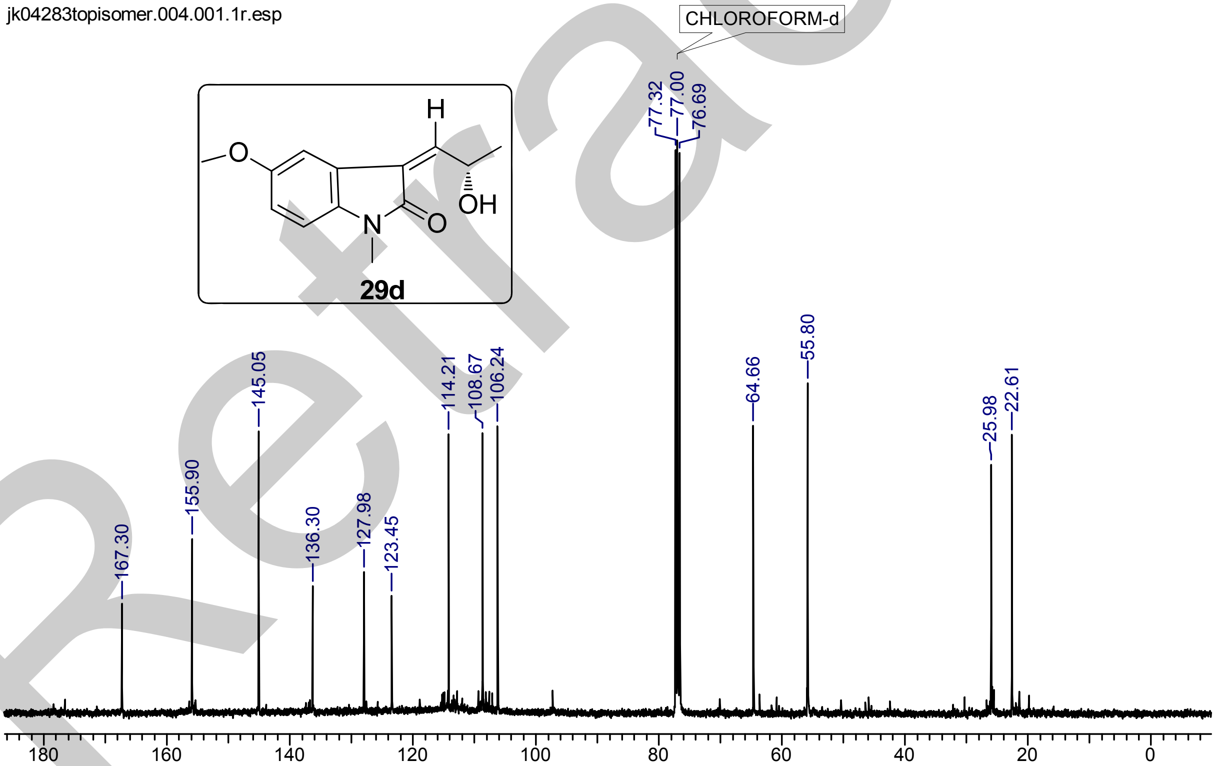
jk04342bottom.002.001.1r.esp



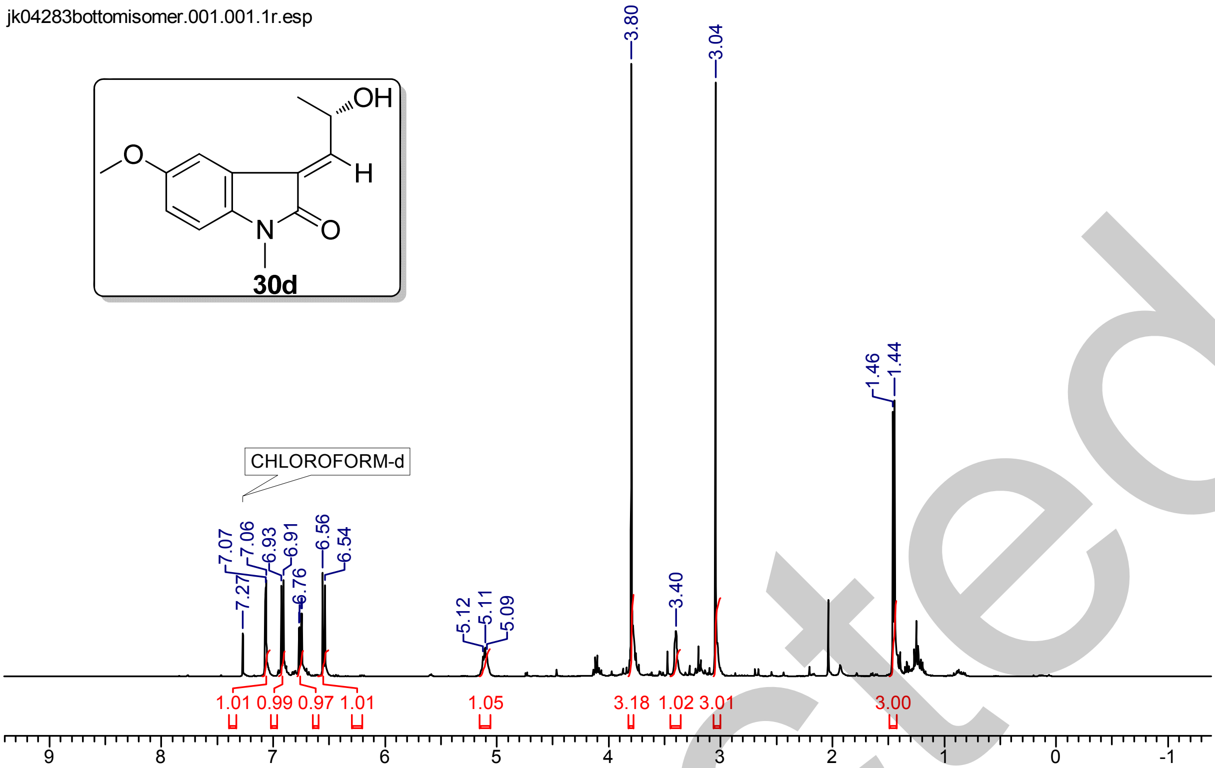
jk04342bottom.003.001.1r.esp



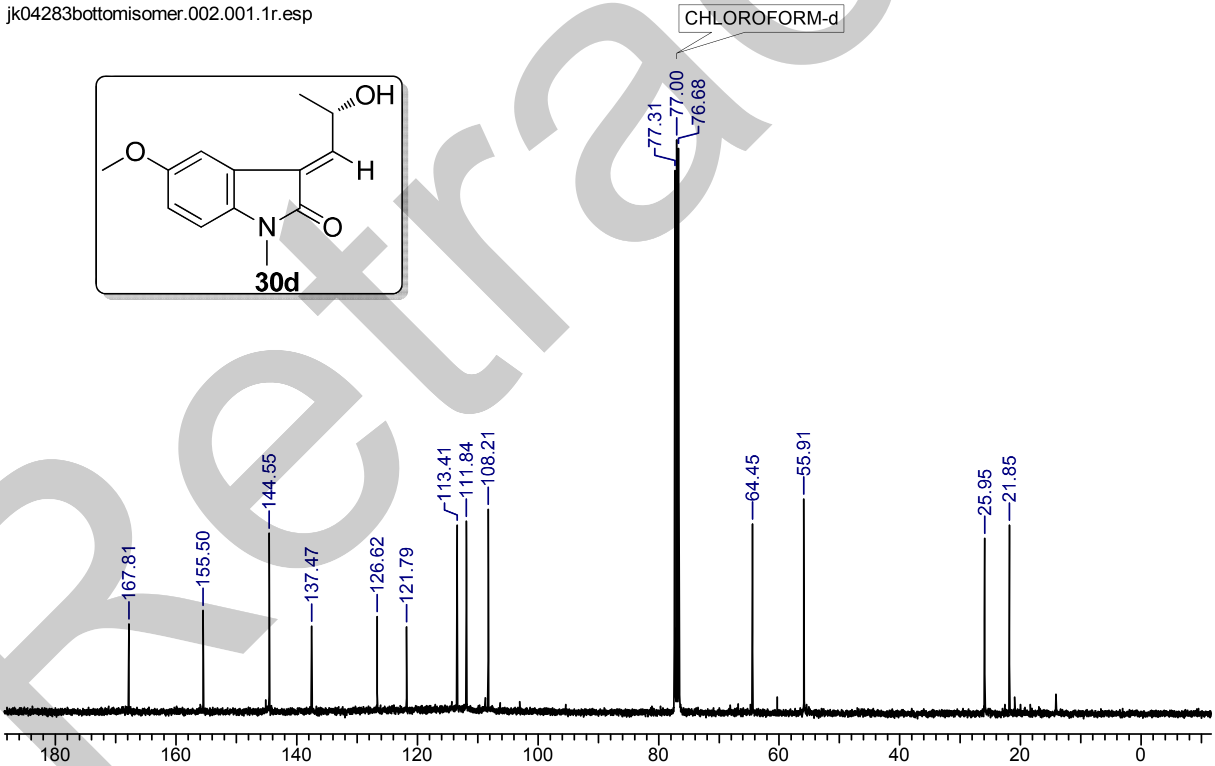

jk04283topisomer.003.001.1r.esp
29d
CHLOROFORM-d
3.79
3.18
1.46
1.45
7.27
6.95
6.94
6.89
6.88
6.68
6.66
5.57
5.16
0.99 0.04 0.98 1.01 1.01
0.98
0.98
3.03
2.86
2.99


jk04283topisomer.004.001.1r.esp
29d
CHLOROFORM-d
77.32
77.00
76.69
167.30
155.90
145.05
136.30
127.98
123.45
114.21
108.67
106.24
64.66
55.80
25.98
22.61

jk04283bottomisomer.001.001.1r.esp

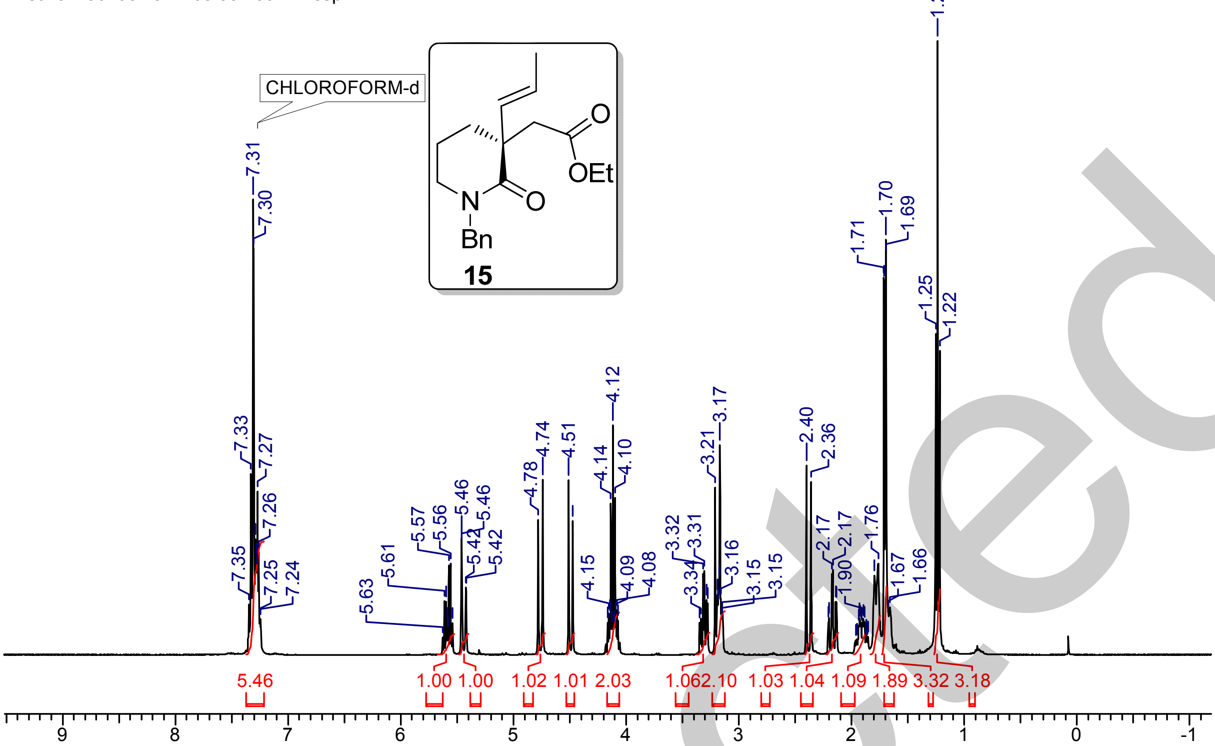


jk04283bottomisomer.002.001.1r.esp

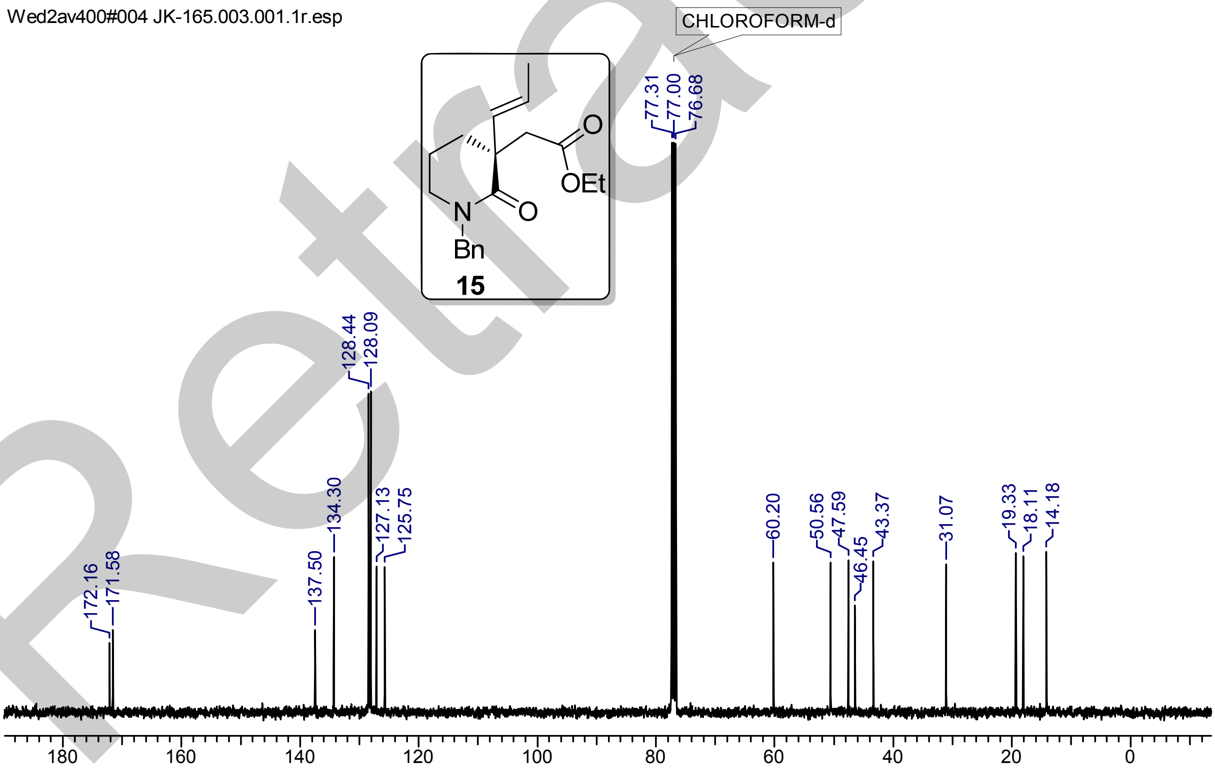


NMR of **15** and **16** are similar.

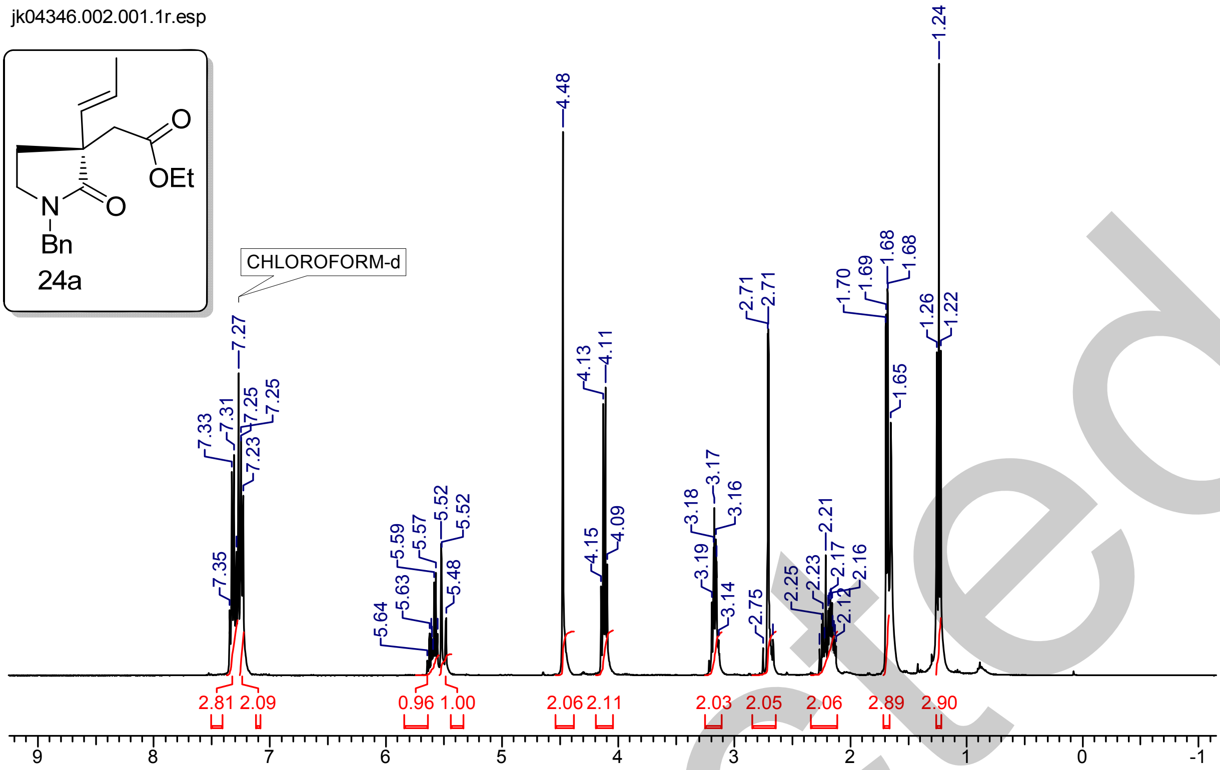
Wed2av400#004 JK-165.001.001.1r.esp

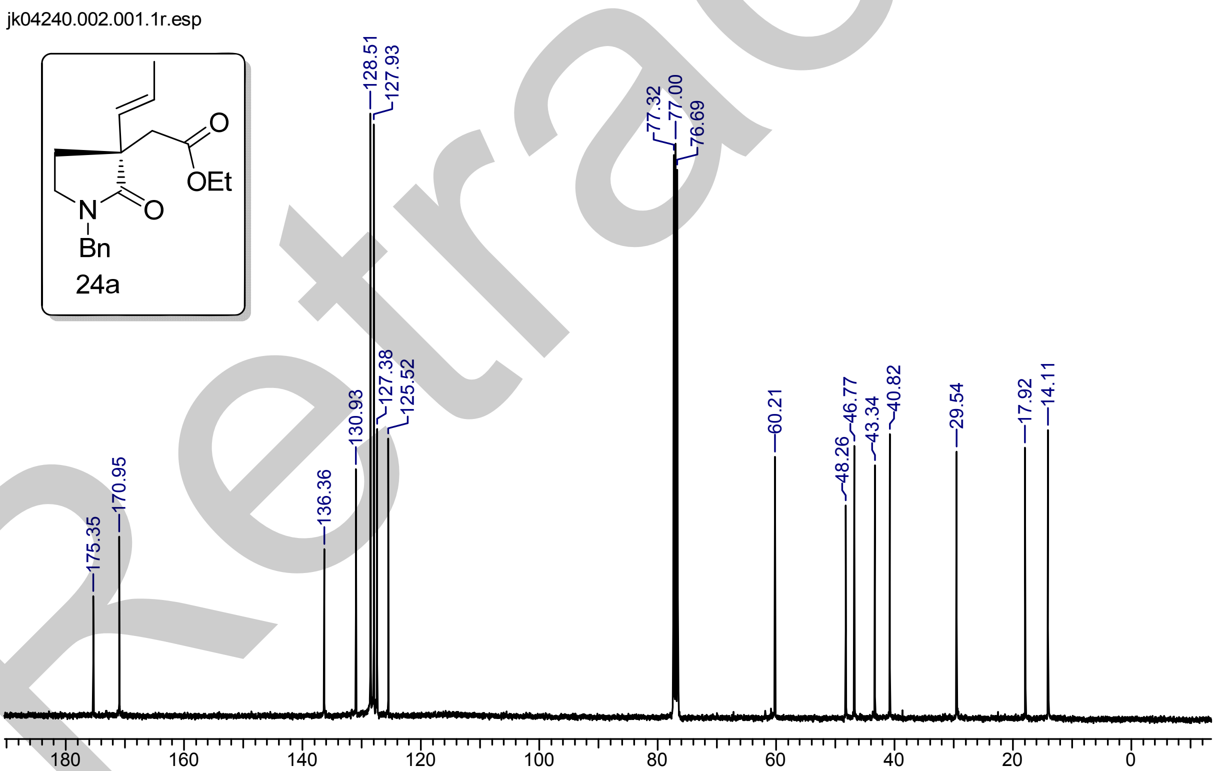


Wed2av400#004 JK-165.003.001.1r.esp

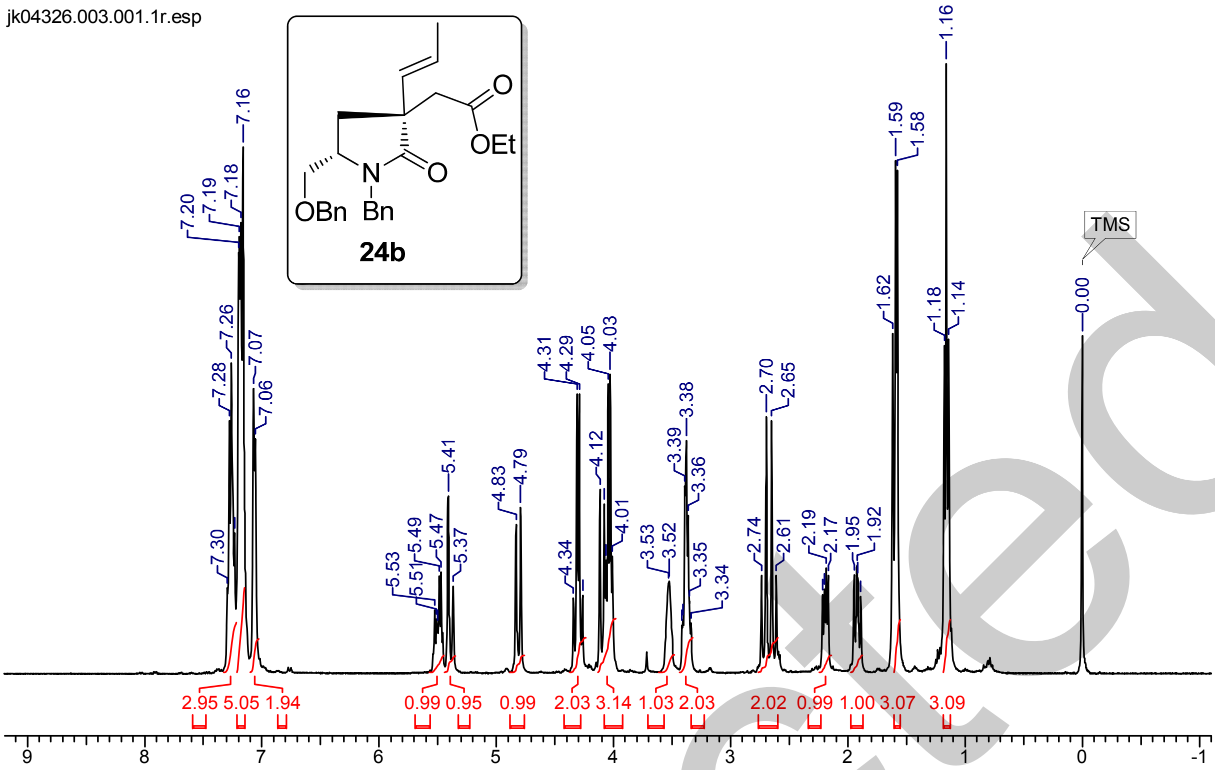


NMR of 24a and 25a are similar

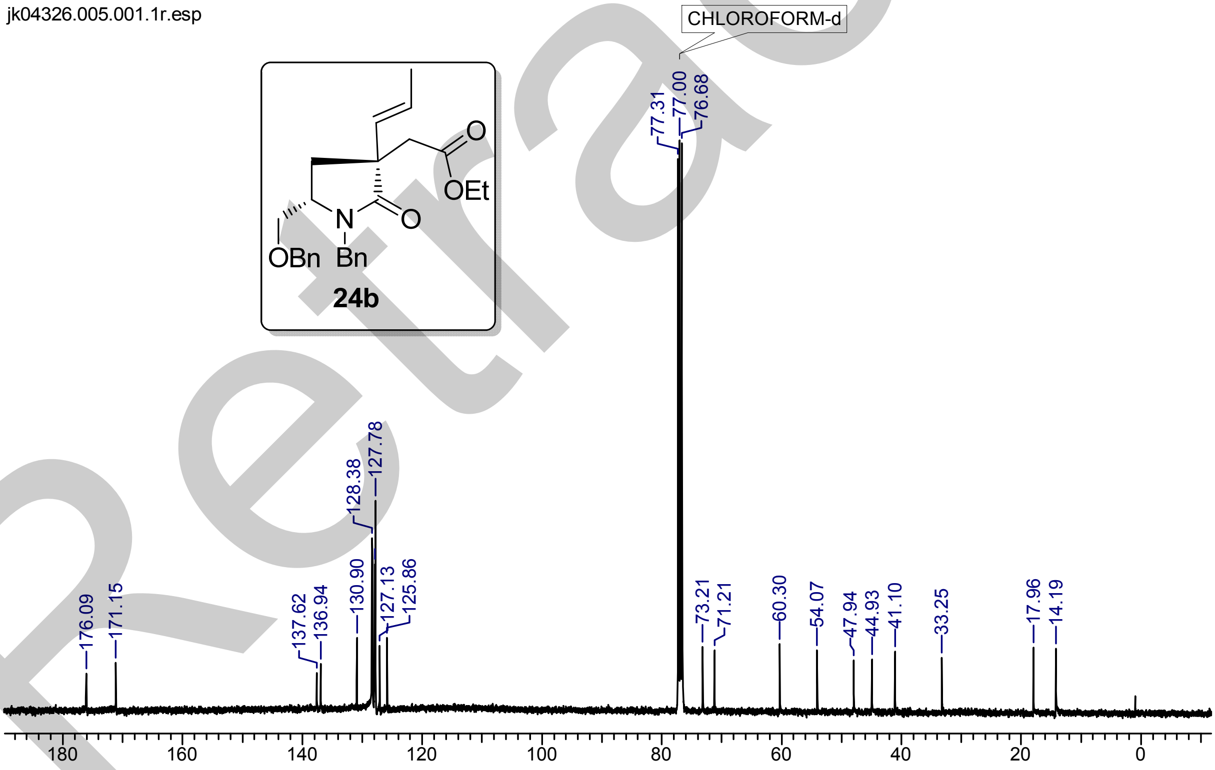

jk04346.002.001.1r.esp
OEt
O
N
Bn
24a
CHLOROFORM-d
7.35
7.33
7.31
7.27
7.25
7.25
7.23
5.64
5.63
5.59
5.57
5.52
5.52
5.48
4.48
4.15
4.13
4.11
4.09
3.19
3.18
3.17
3.16
3.14
2.75
2.71
2.71
2.25
2.23
2.21
2.17
2.16
2.12
1.70
1.69
1.68
1.68
1.65
1.26
1.24
1.22
2.81 2.09 0.96 1.00 2.06 2.11 2.03 2.05 2.06 2.89 2.90
9 8 7 6 5 4 3 2 1 0 -1


jk04240.002.001.1r.esp
OEt
O
N
Bn
24a
175.35
170.95
136.36
130.93
128.51
127.93
127.38
125.52
77.32
77.00
76.69
60.21
48.26
46.77
43.34
40.82
29.54
17.92
14.11
180 160 140 120 100 80 60 40 20 0

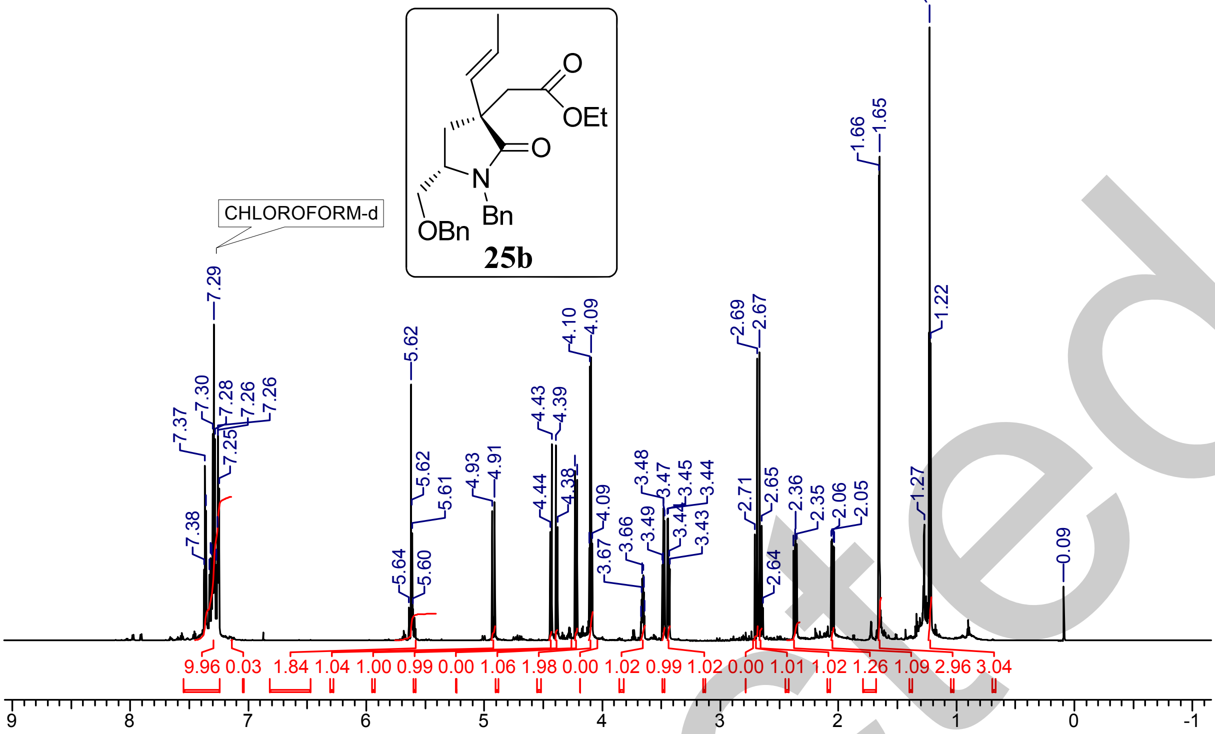
jk04326.003.001.1r.esp



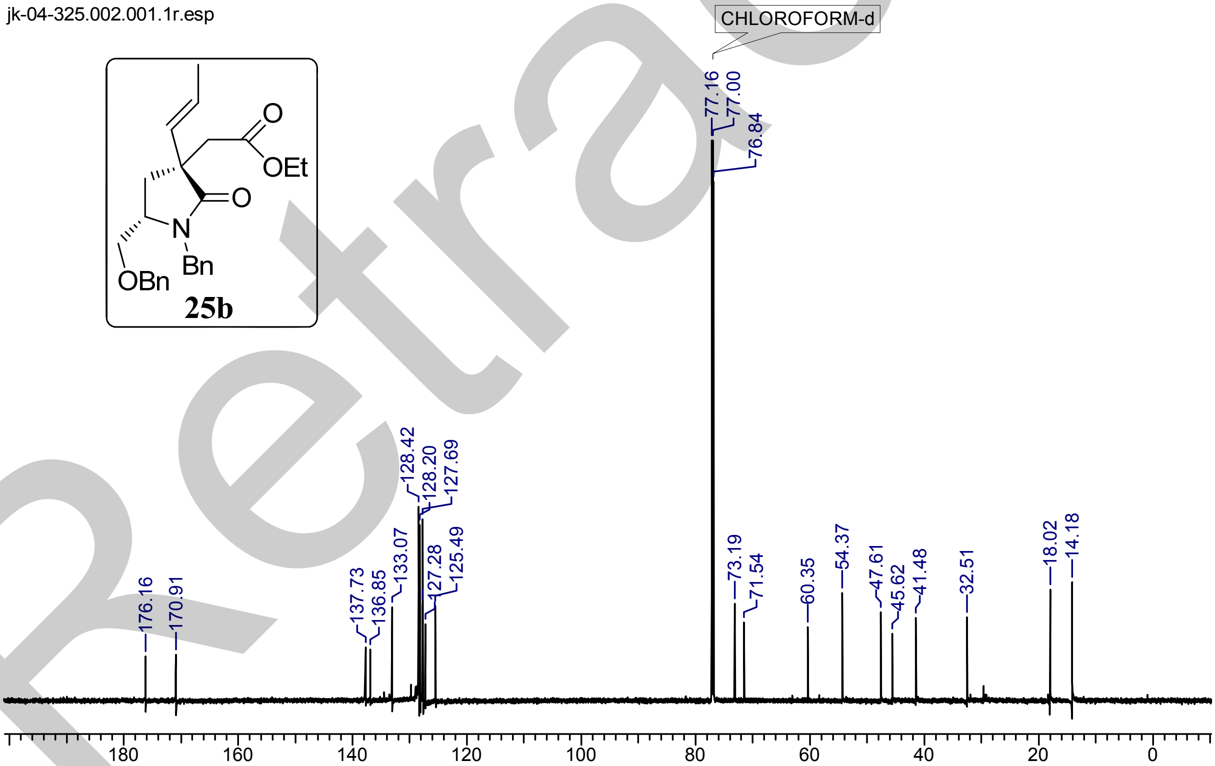
jk04326.005.001.1r.esp



jk-04-325.001.001.1r.esp

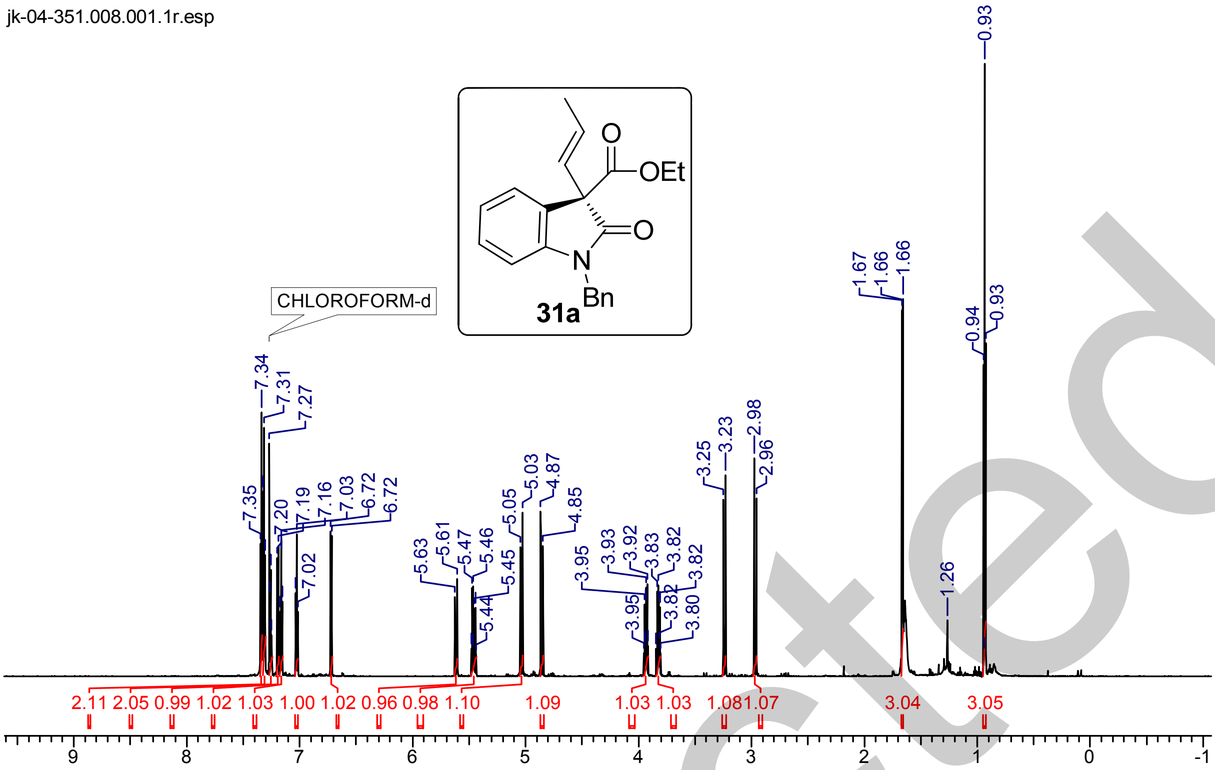


jk-04-325.002.001.1r.esp

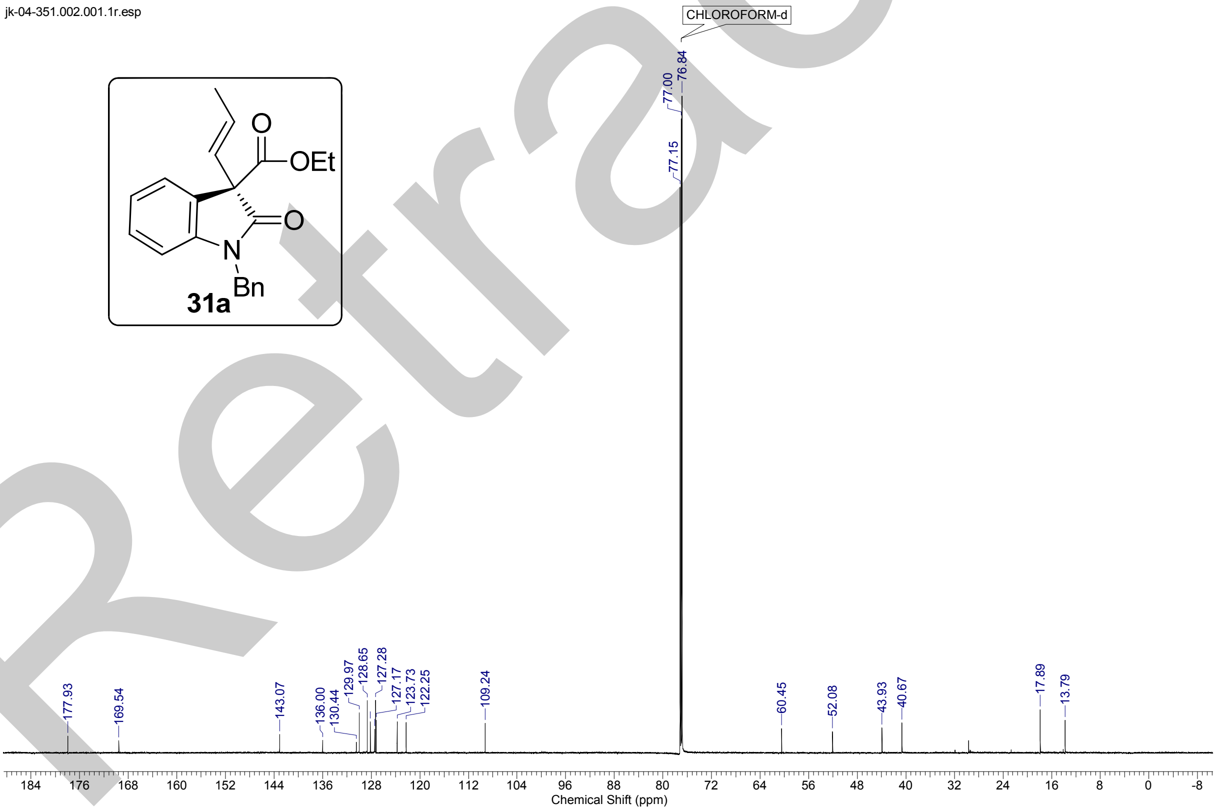


NMR of **31a** and **32a** are similar.

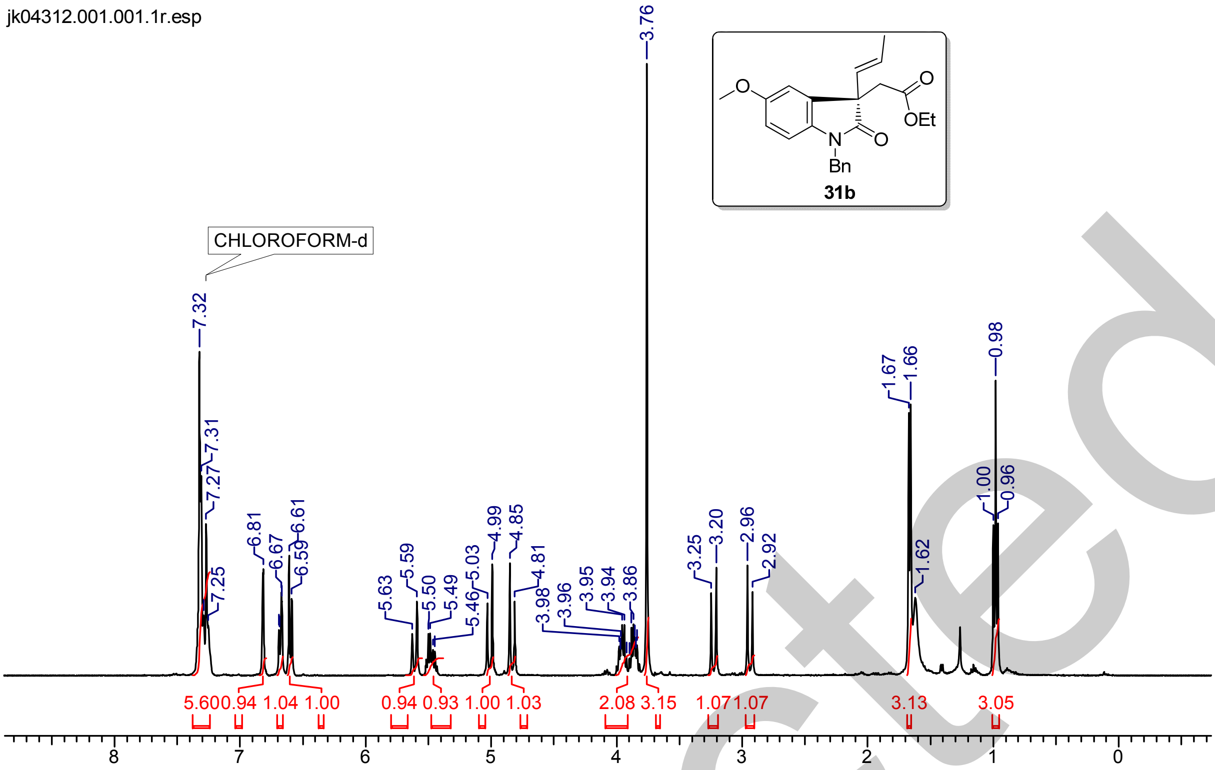
jk-04-351.008.001.1r.esp

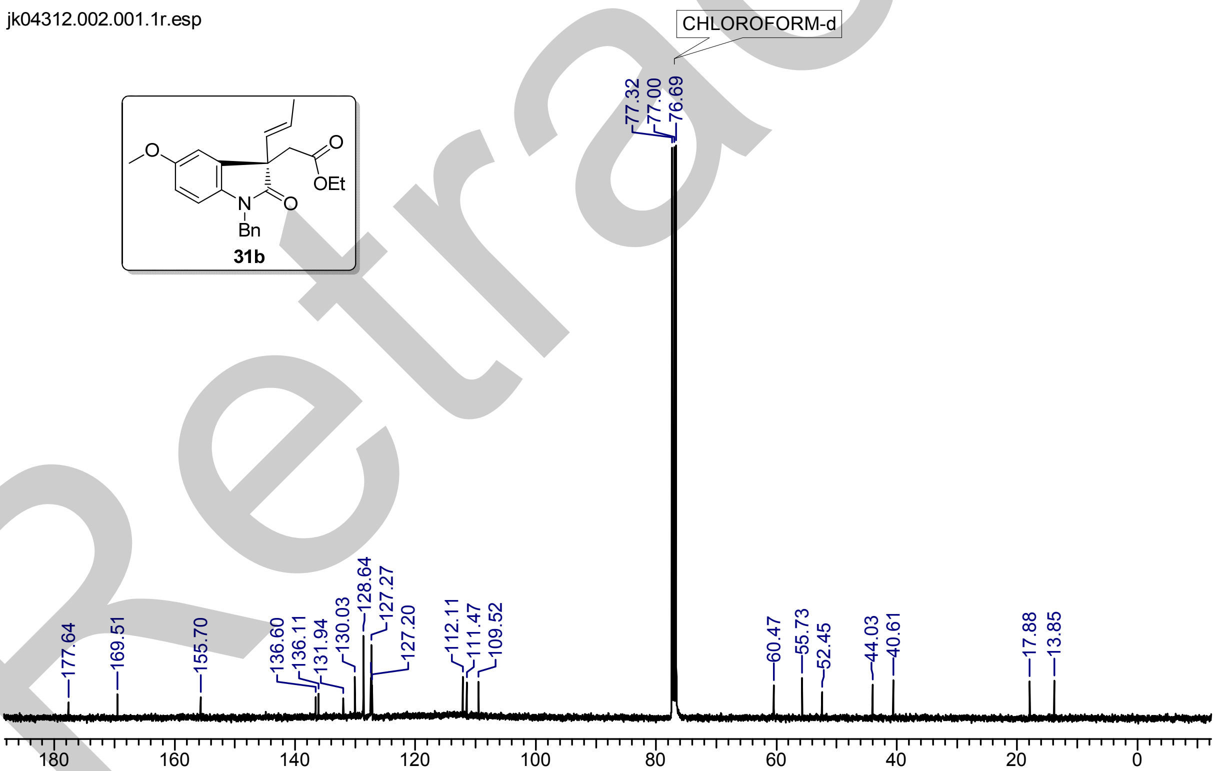


jk-04-351.002.001.1r.esp

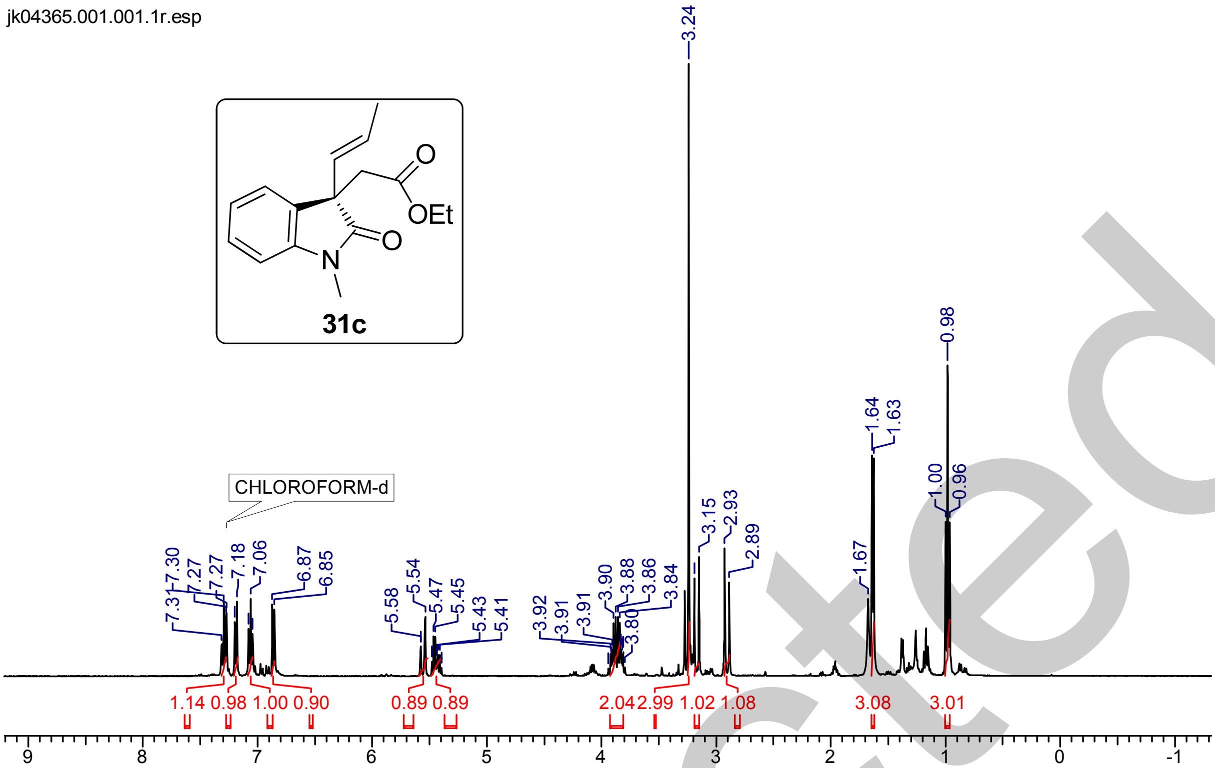


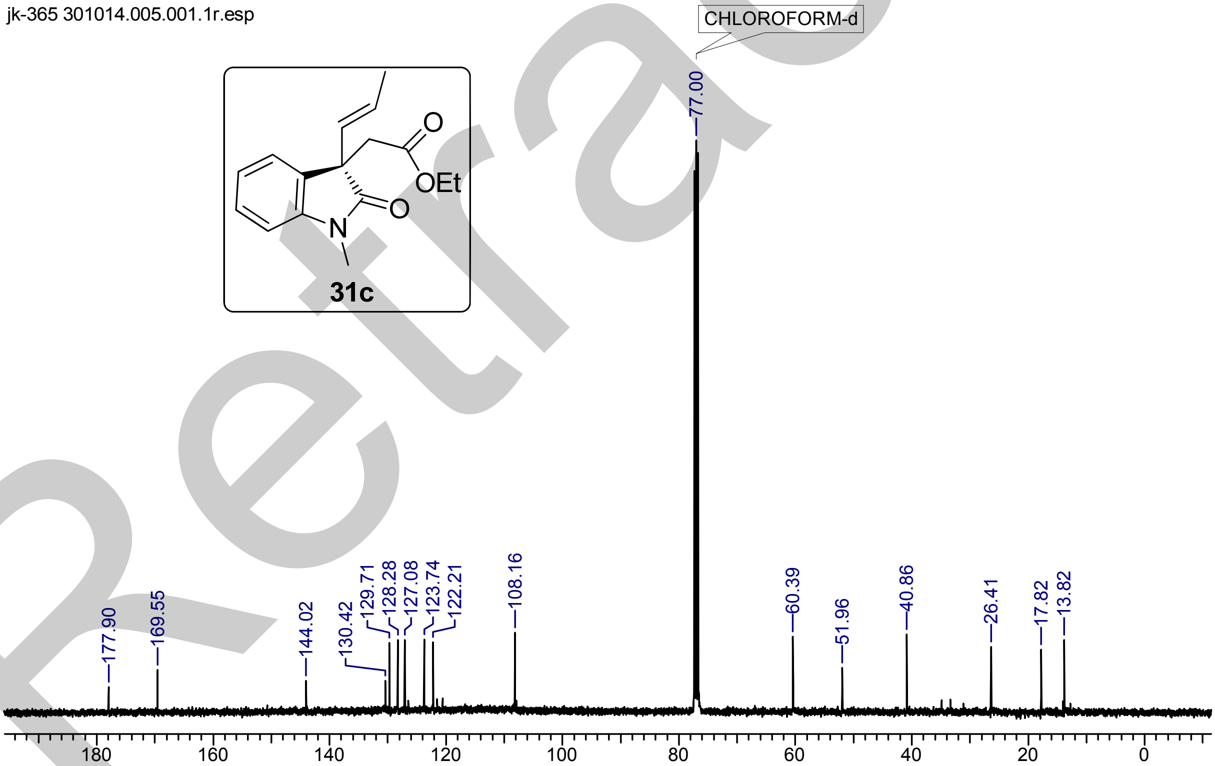
NMR of **31b** and **32b** are similar





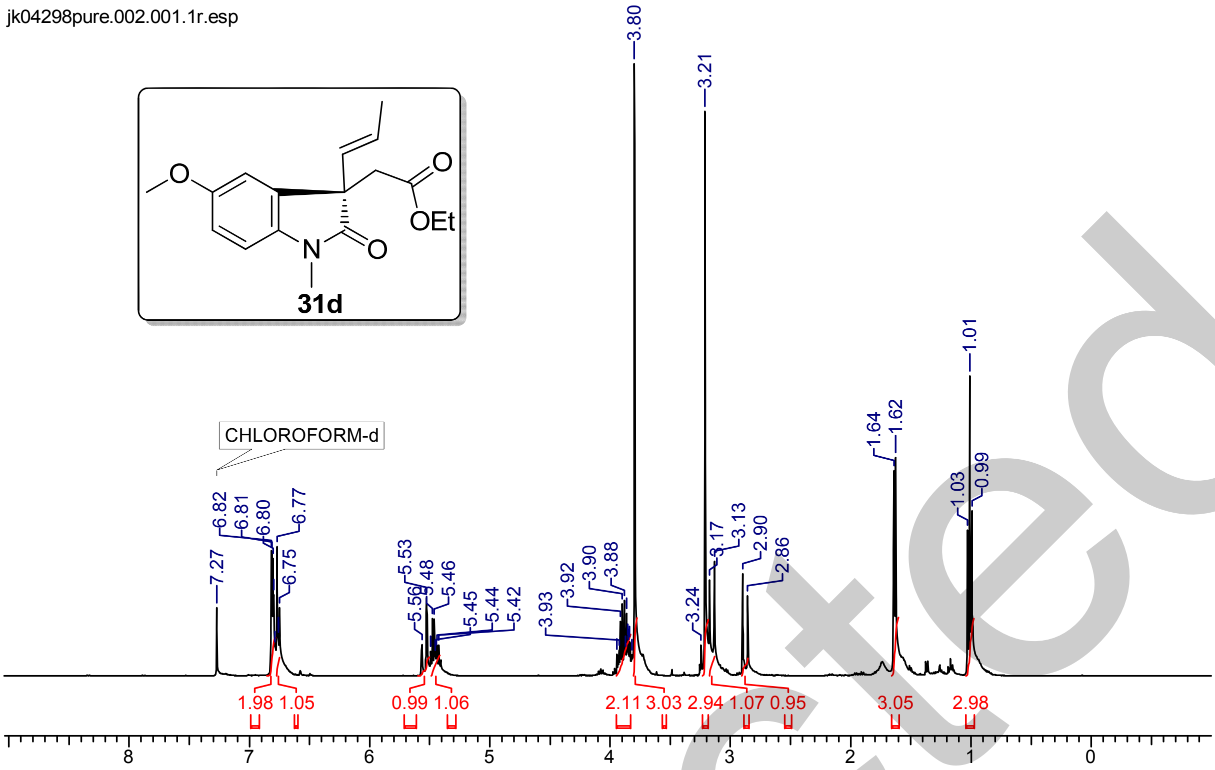
NMR of **31c** and **32c** are similar



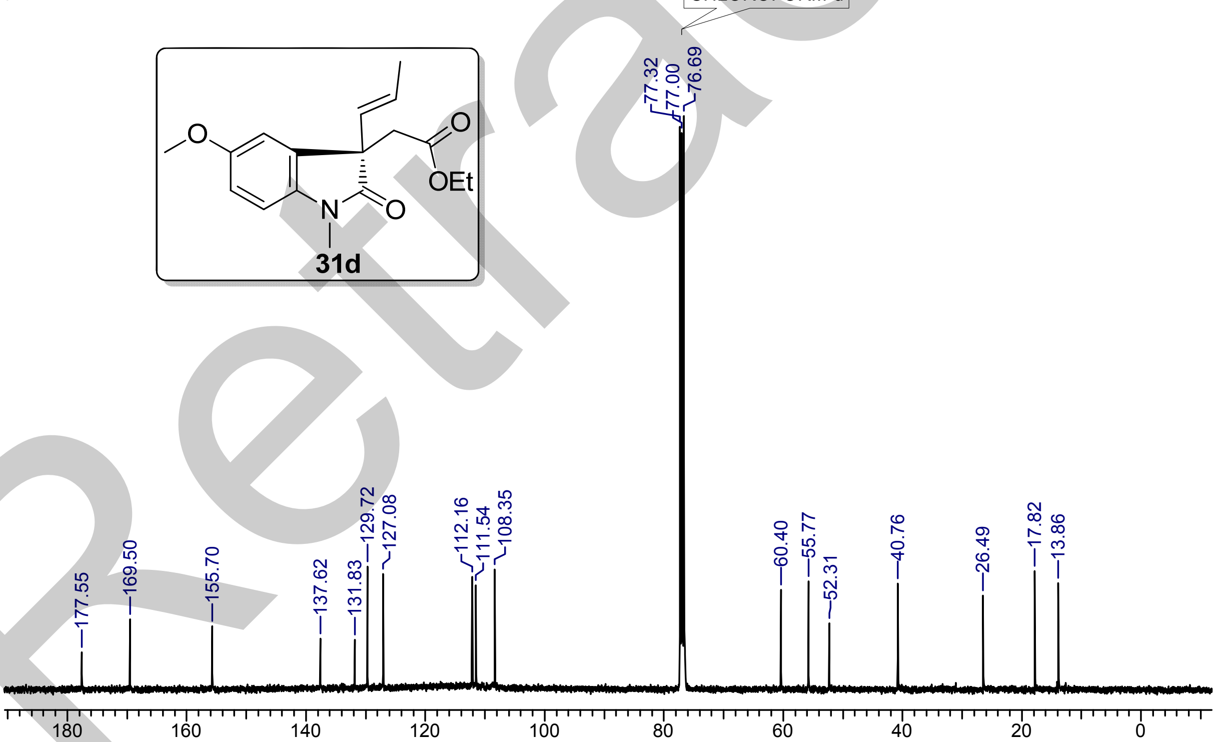


NMR of **31d** and **32d** are similar

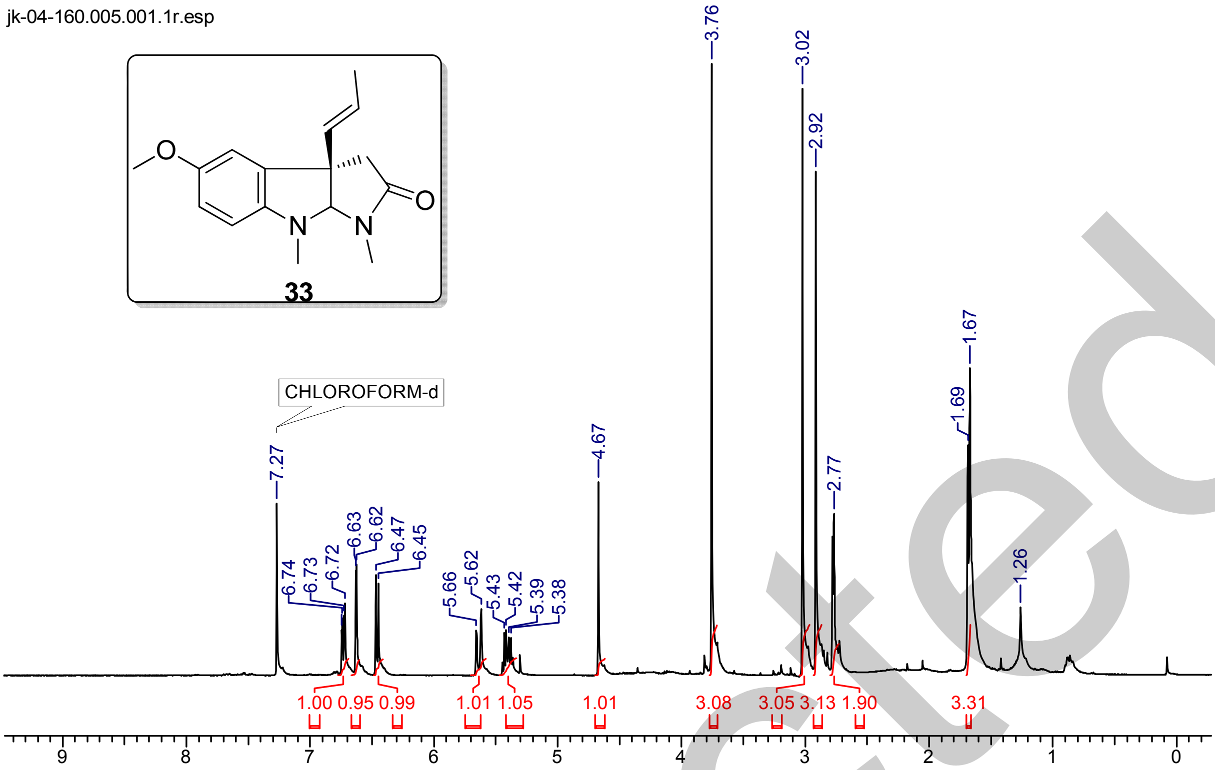
jk04298pure.002.001.1r.esp



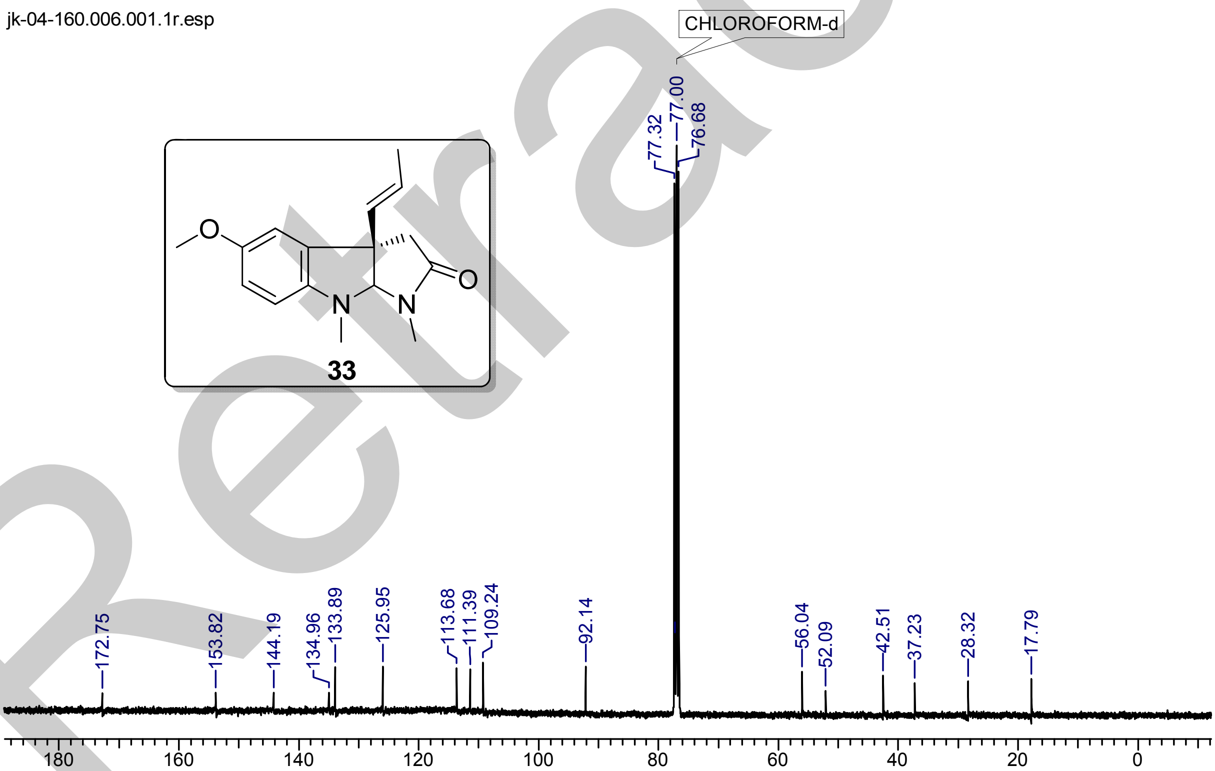
jk04298pure.003.001.1r.esp



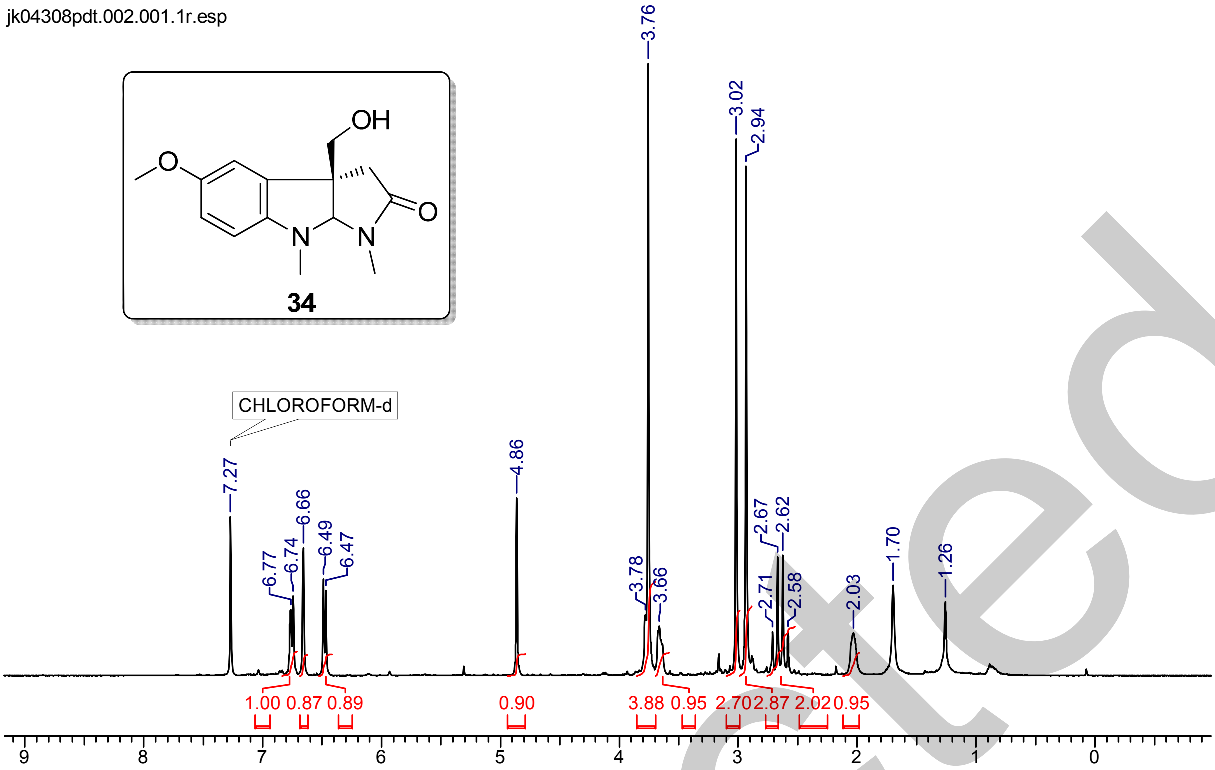
jk-04-160.005.001.1r.esp



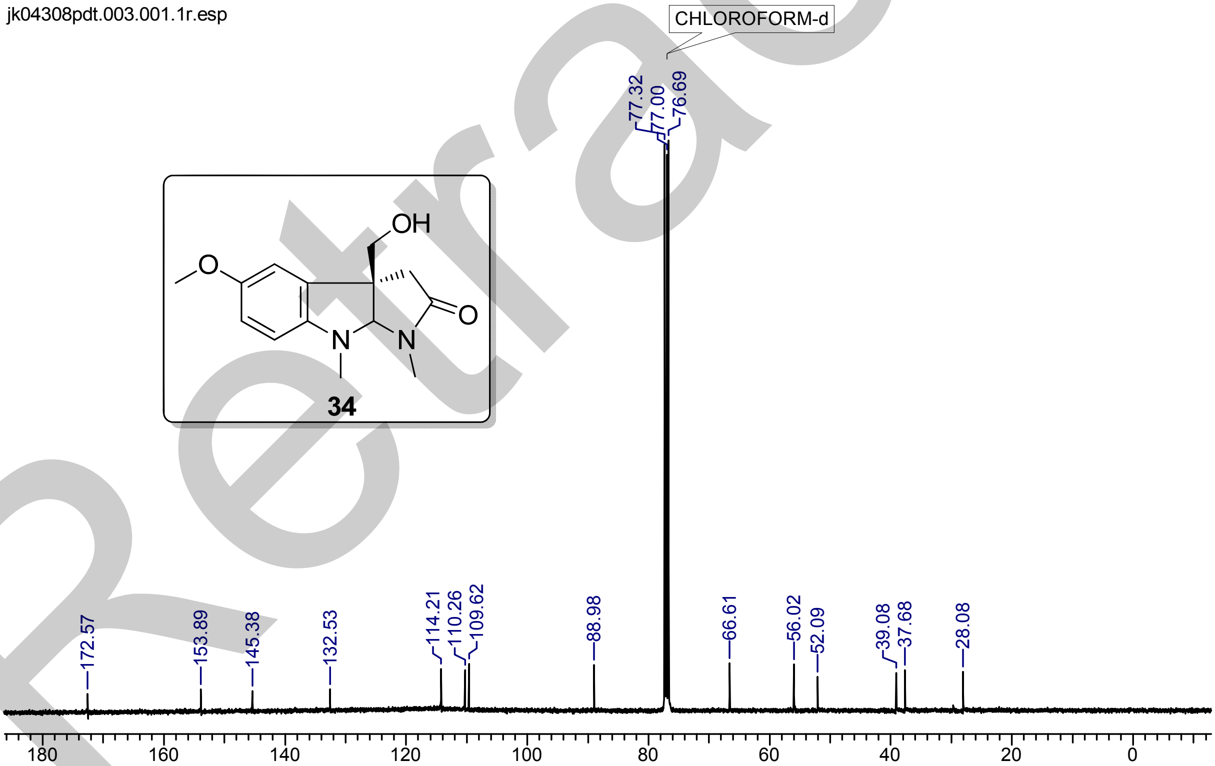
jk-04-160.006.001.1r.esp



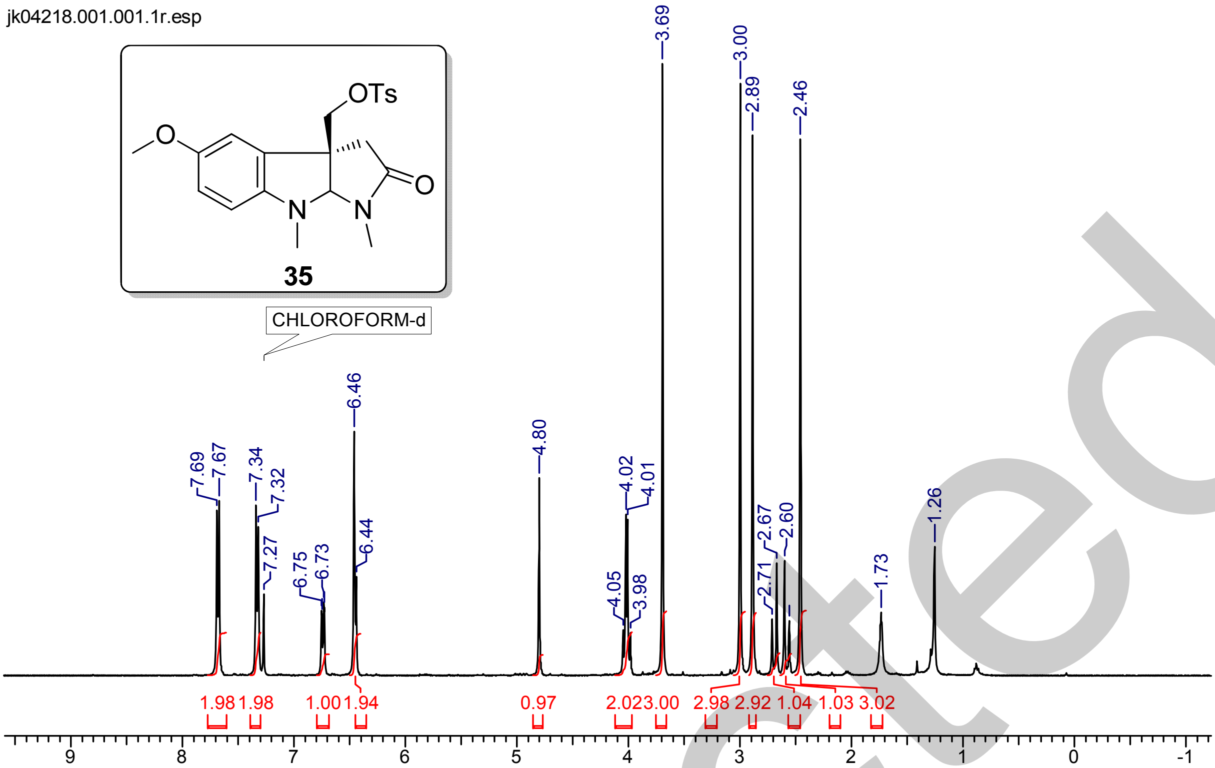
jk04308pdt.002.001.1r.esp



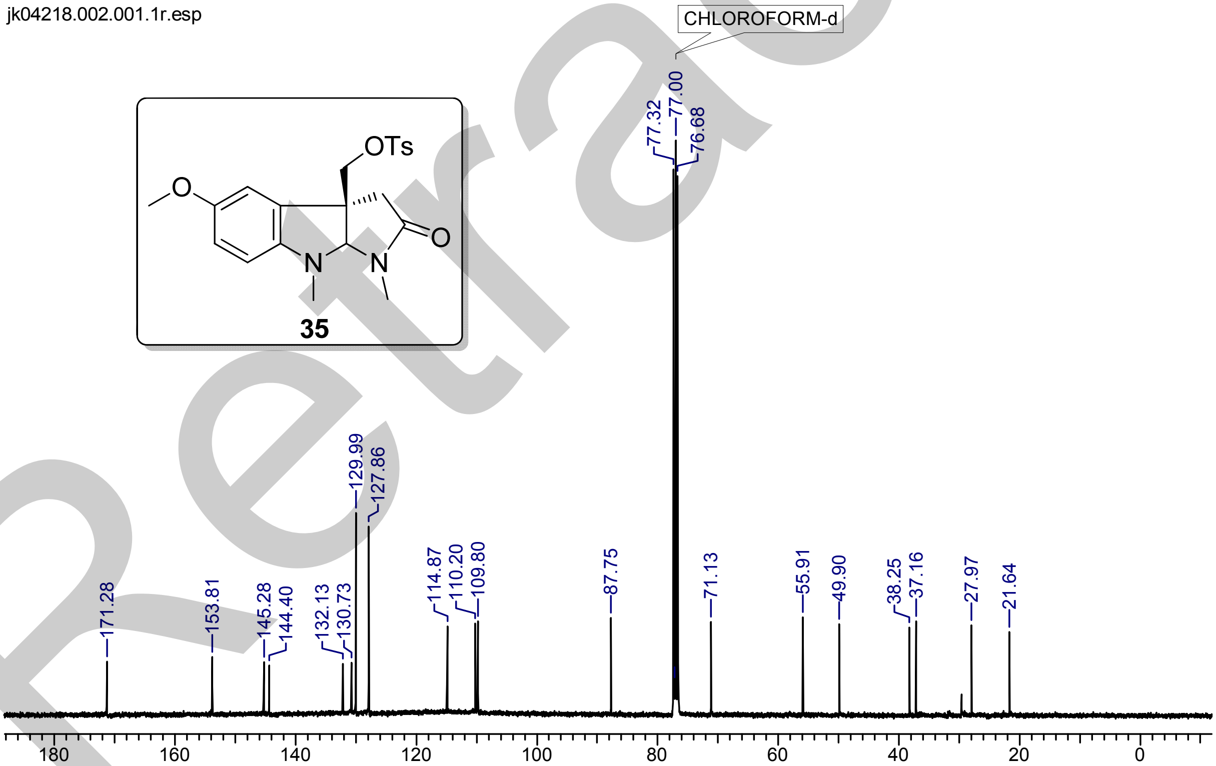
jk04308pdt.003.001.1r.esp

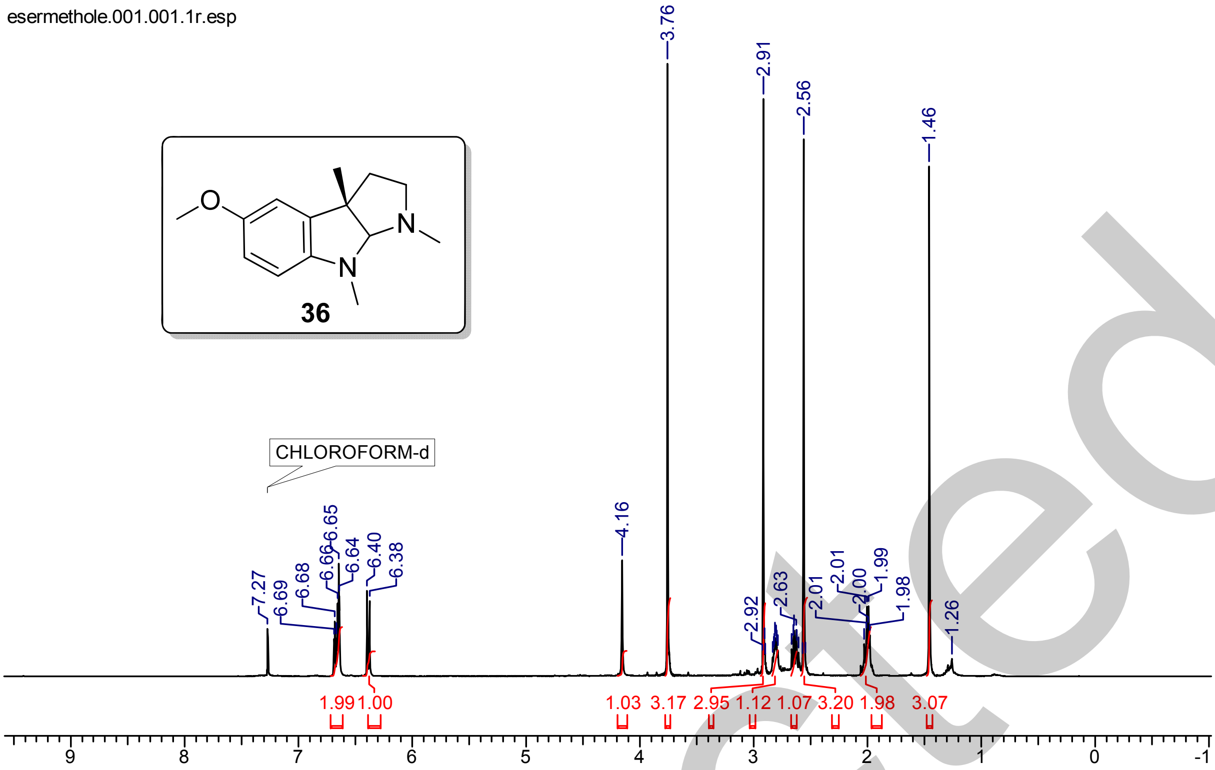


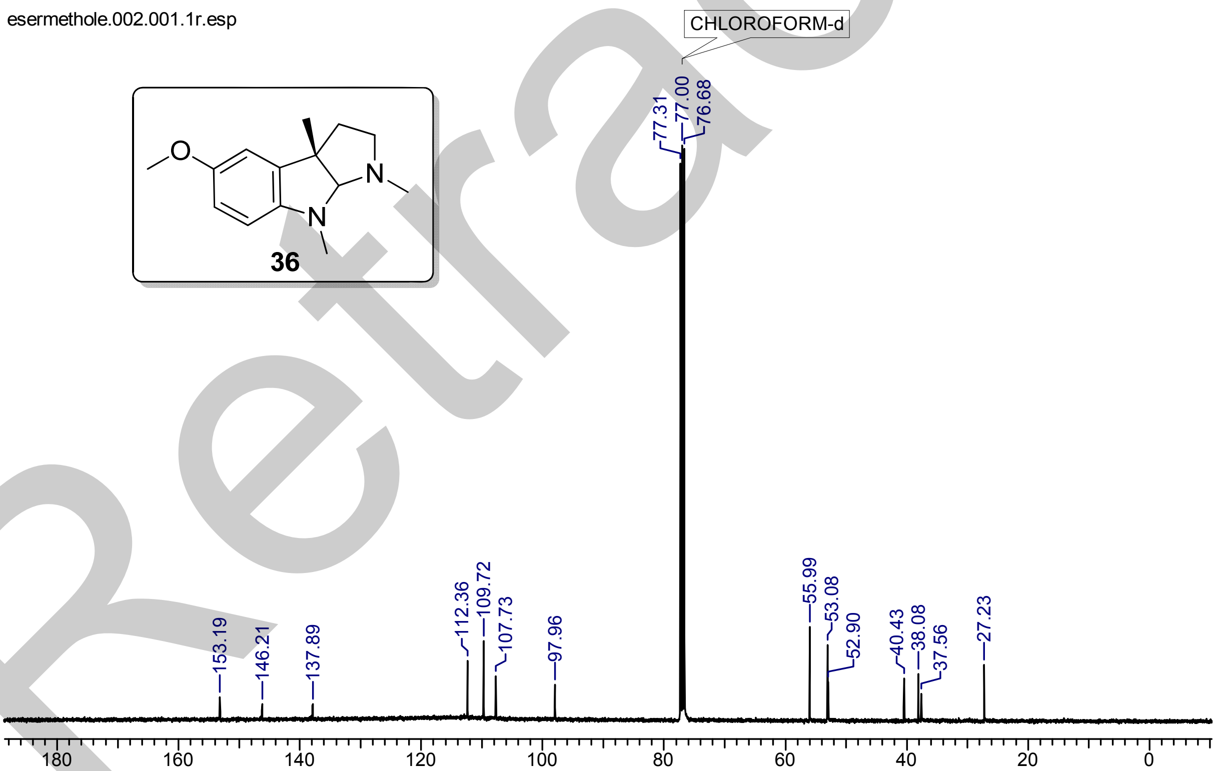
jk04218.001.001.1r.esp

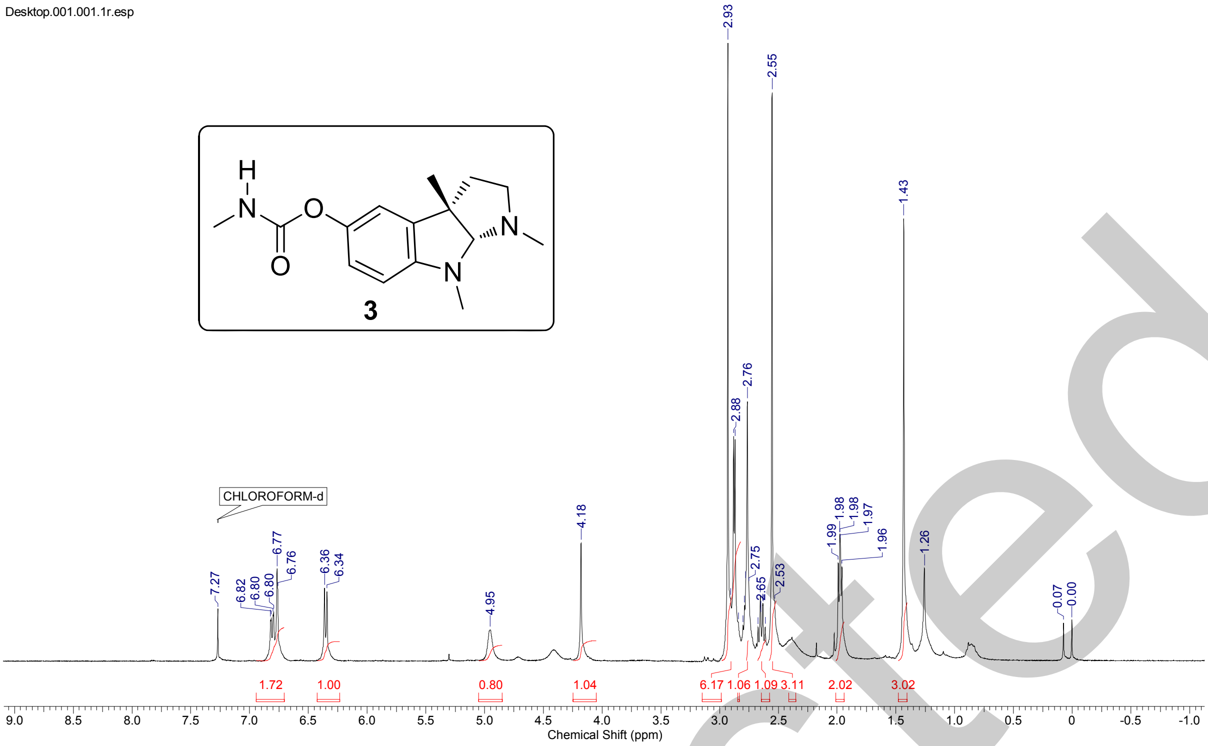


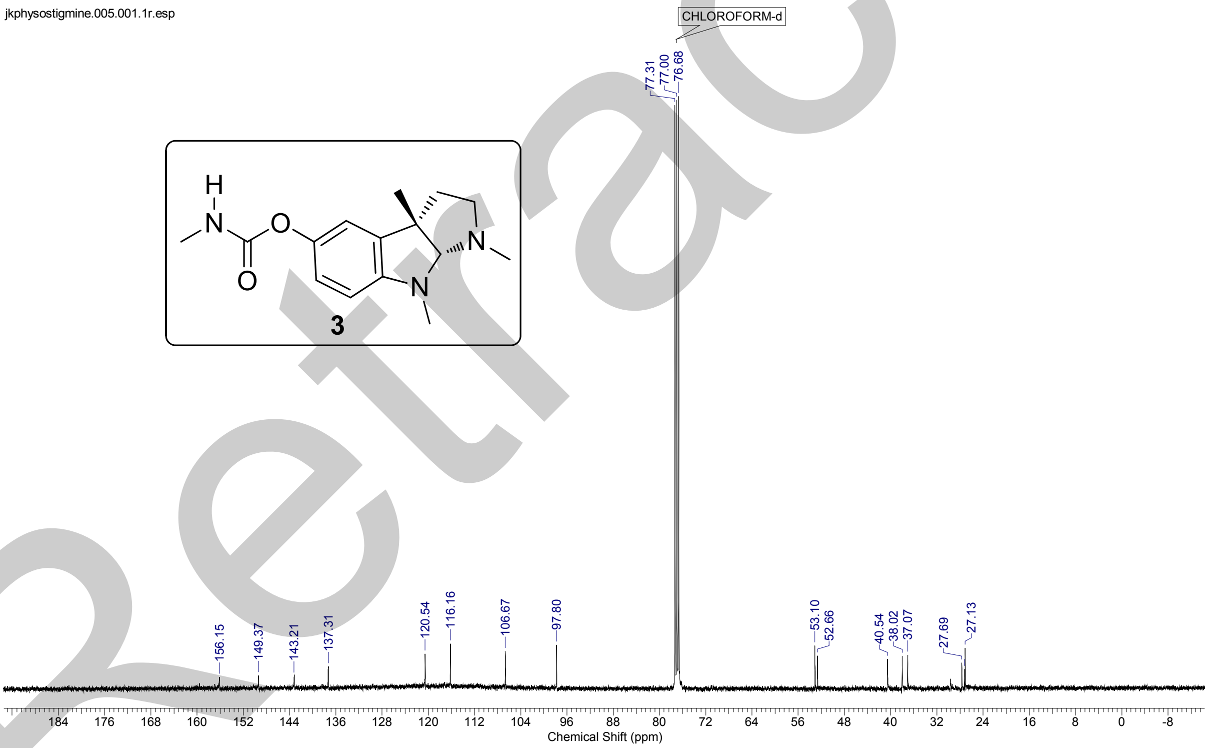
jk04218.002.001.1r.esp

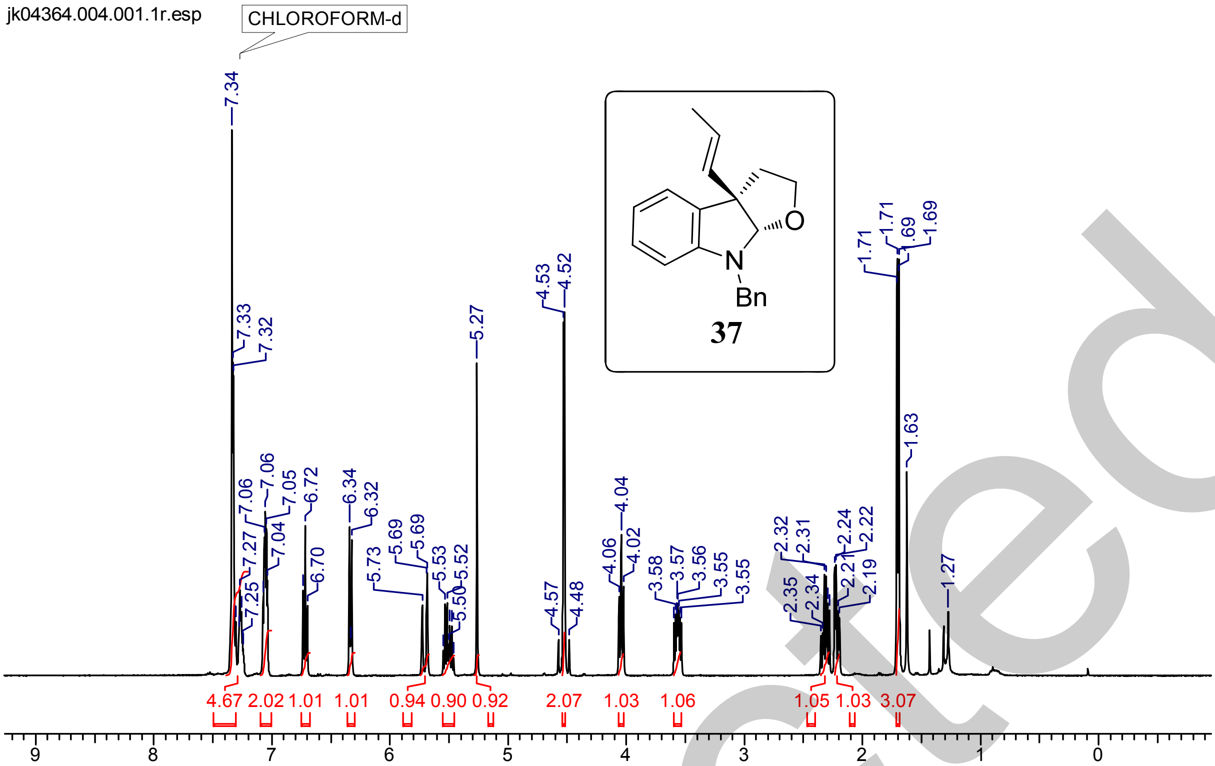


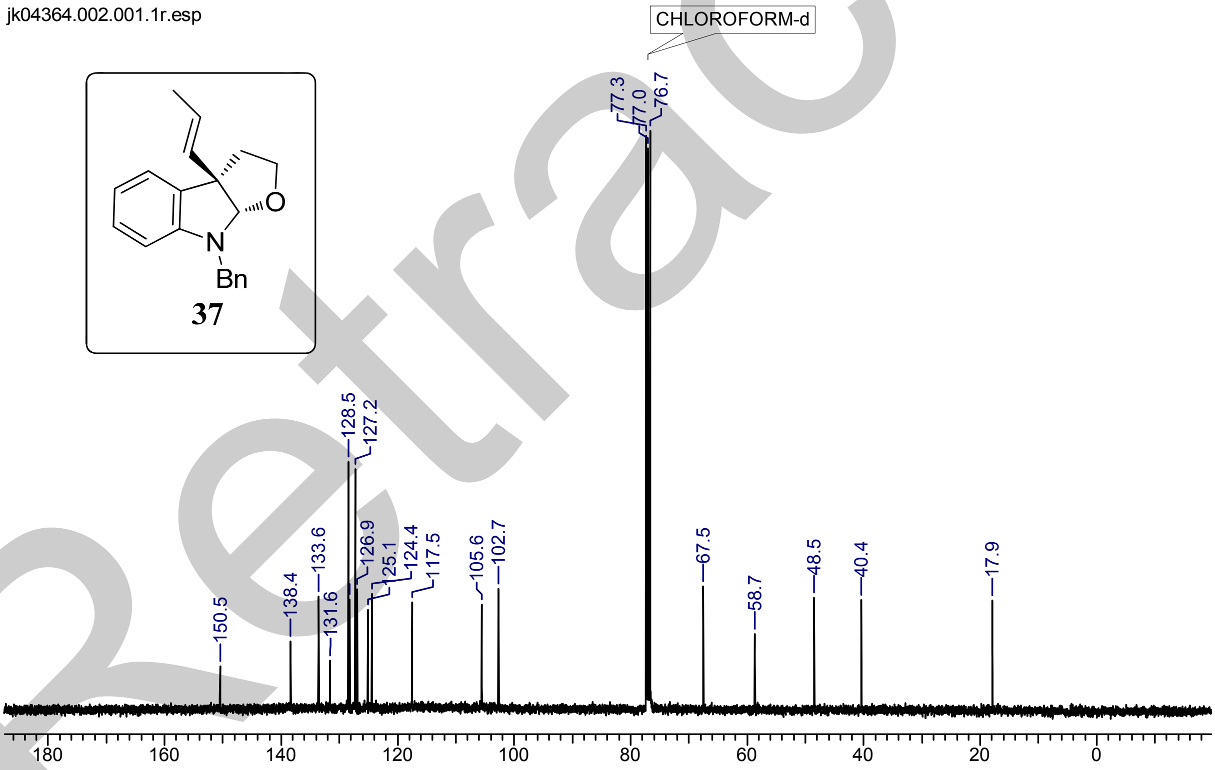

esermethole.001.001.1r.esp
36
CHLOROFORM-d
7.27
6.69
6.68
6.66
6.65
6.64
6.40
6.38
4.16
3.76
2.92
2.91
2.63
2.56
2.01
2.01
2.00
1.99
1.98
1.46
1.26
1.99
1.00
1.03
3.17
2.95
1.12
1.07
3.20
1.98
3.07
9
8
7
6
5
4
3
2
1
0
-1


esermethole.002.001.1r.esp
36
CHLOROFORM-d
77.31
77.00
76.68
153.19
146.21
137.89
112.36
109.72
107.73
97.96
55.99
53.08
52.90
40.43
38.08
37.56
27.23
180
160
140
120
100
80
60
40
20
0

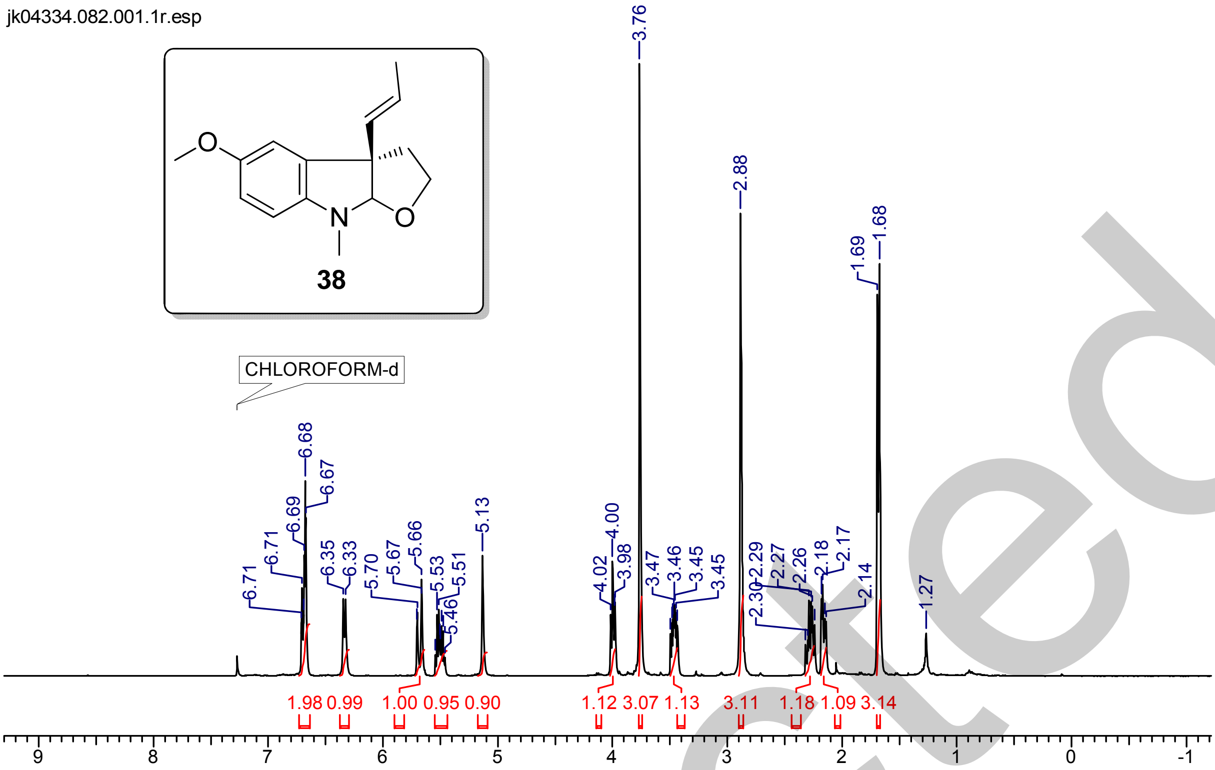

Desktop.001.001.1r.esp
CHLOROFORM-d
7.27
6.82 6.80 6.80 6.77 6.76
6.36 6.34
4.95
4.18
2.93 2.88 2.76 2.75 2.65 2.55 2.53
1.99 1.98 1.98 1.97 1.96
1.43
1.26
0.07 0.00
1.72 1.00 0.80 1.04 6.17 1.06 1.09 3.11 2.02 3.02
H
N
O
O
N
N
3
Chemical Shift (ppm)


jkphysostigmine.005.001.1r.esp
CHLOROFORM-d
77.31 77.00 76.68
156.15 149.37 143.21 137.31 120.54 116.16 106.67 97.80
53.10 52.66 40.54 38.02 37.07 27.69 27.13
H
N
O
O
N
N
3
Chemical Shift (ppm)

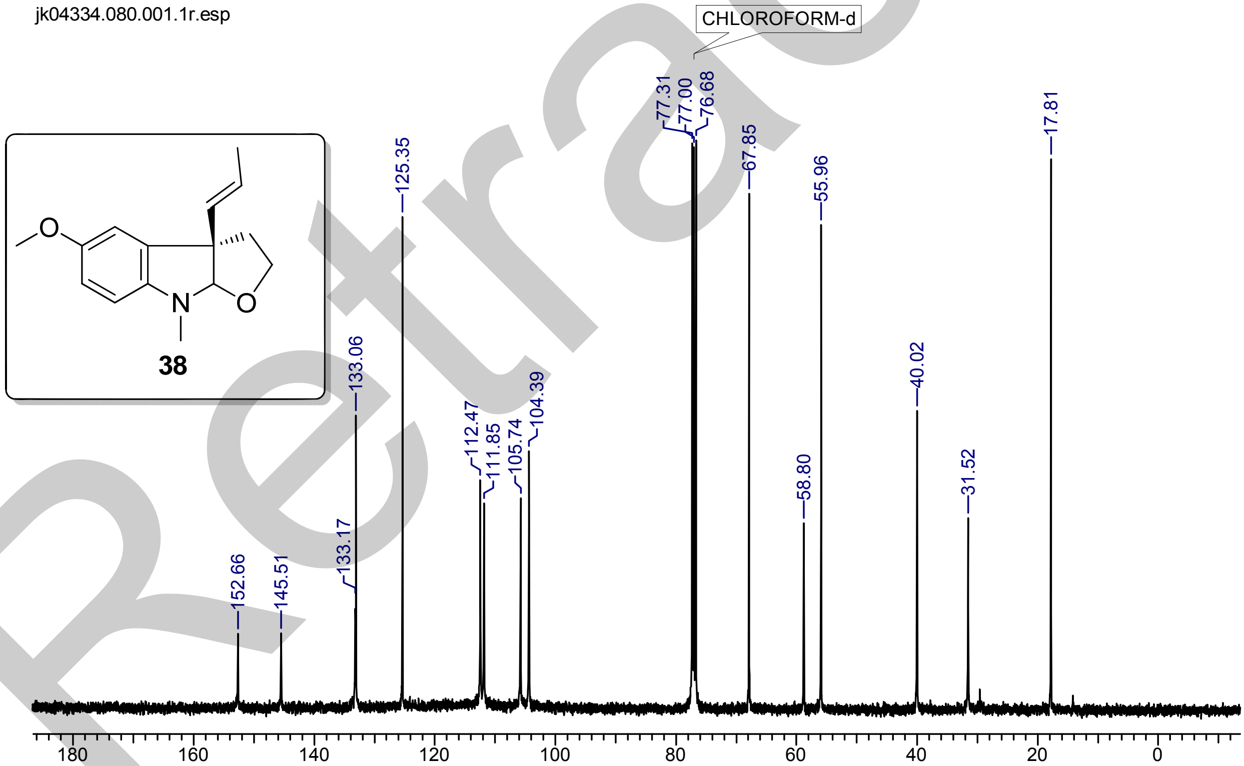

jk04364.004.001.1r.esp
CHLOROFORM-d
7.34
7.33
7.32
7.27
7.25
7.06
7.06
7.05
7.04
6.72
6.70
6.34
6.32
5.73
5.69
5.69
5.53
5.52
5.50
5.27
4.57
4.53
4.52
4.48
4.06
4.04
4.02
3.58
3.57
3.56
3.55
3.55
2.35
2.34
2.32
2.31
2.24
2.22
2.21
2.19
1.71
1.71
1.69
1.69
1.63
1.27
4.67
2.02
1.01
1.01
0.94
0.90
0.92
2.07
1.03
1.06
1.05
1.03
3.07
O
N
Bn
37


jk04364.002.001.1r.esp
CHLOROFORM-d
77.3
77.0
76.7
128.5
127.2
150.5
138.4
133.6
131.6
126.9
125.1
124.4
117.5
105.6
102.7
67.5
58.7
48.5
40.4
17.9
O
N
Bn
37

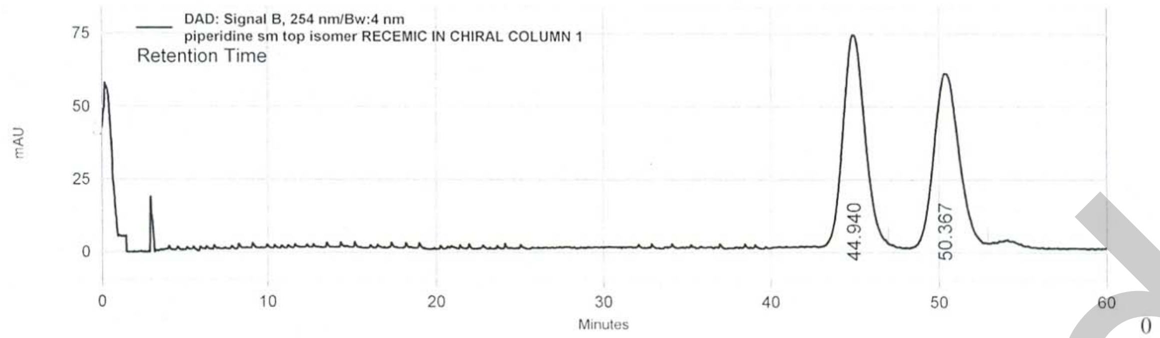
jk04334.082.001.1r.esp



jk04334.080.001.1r.esp

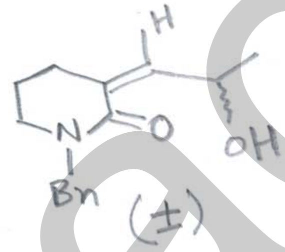


III) HPLC Data.



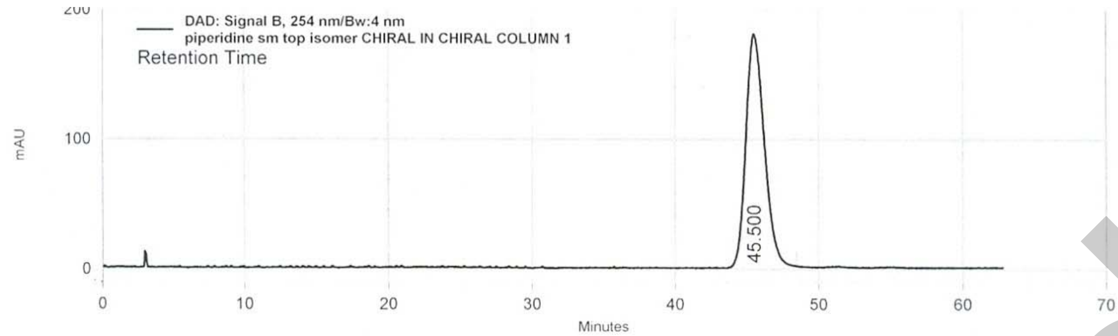
DAD: Signal B,
254 nm/Bw:4 nm
Results

S.No.	Retention Time	Area	Area %	Height	Height %
1	44.94	13393829	51.41	150972	54.86
2	50.37	12658947	48.59	124248	45.14
Totals		26052776	100.00	275220	100.00



Column- Kromasil 5-amycoat (250×4.5)

IPA: n-Hexane (5:95), flow rate- 1mL/min, wavelength-254 nm.

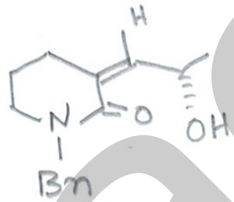


0

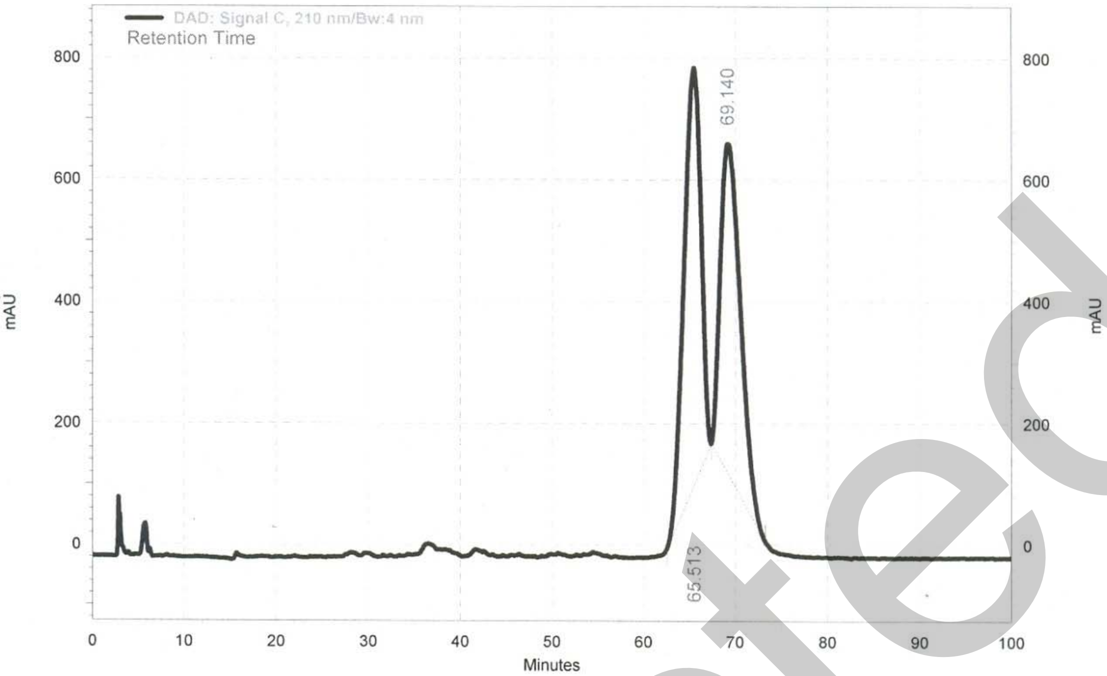
DAD: Signal B,
254 nm/Bw:4 nm
Results

S.No.	Retention Time	Area	Area %	Height	Height %
1	45.50	33491581	100.00	376593	100.00

Totals		33491581	100.00	376593	100.00



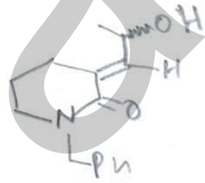
Top isomer



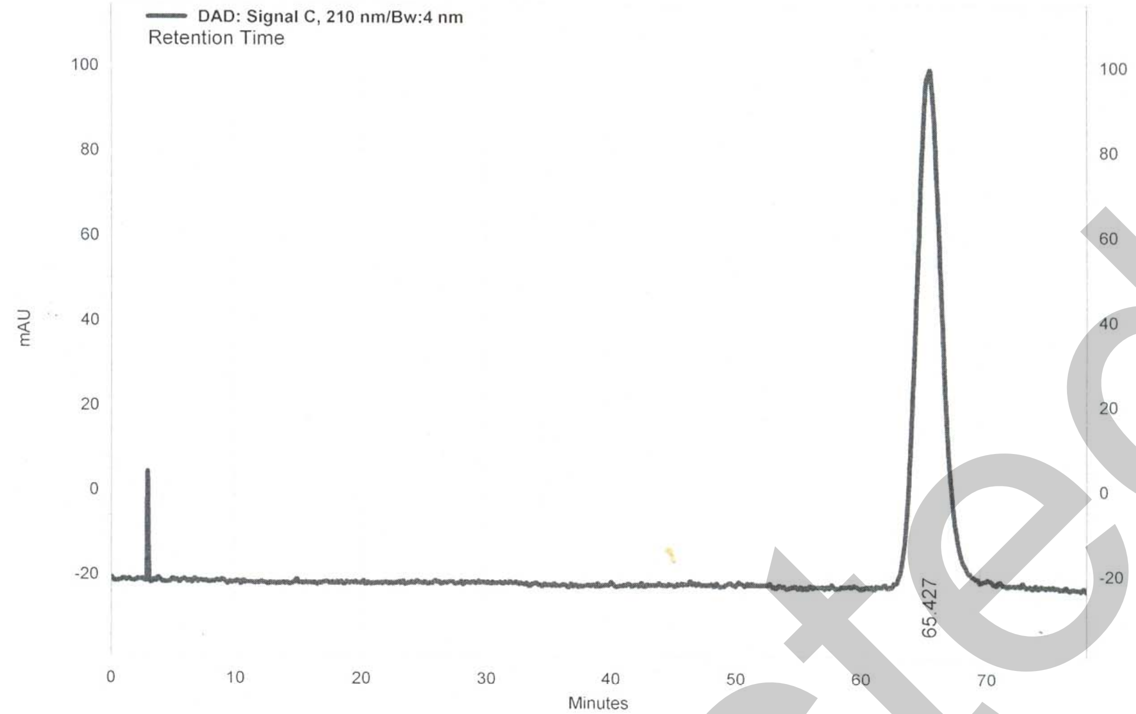
DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %

Column: CHIRALCEL OD-H(150*4.6)
Solvent: IPA:n-HEXANE = 6:94
WAVELENGTH-210 NM
Flow Rate : 1 mL/min
Pressure:34.5 bar
Operator : JAGADISH
Date : 17/1/2014



(±)

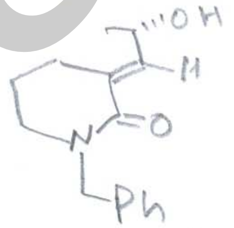


DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
65.427	35733659	100.00	255410	100.00

Totals	35733659	100.00	255410	100.00

Column: CHIRALCEL OD-H(150*4.6)
Solvent: IPA:n-HEXANE = 6:94
WAVELENGTH-210 NM
Flow Rate : 1 mL/min
Pressure:34.5 bar
Operator : JAGADISH
Date : 17/1/2014

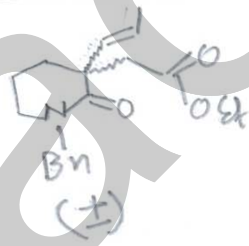


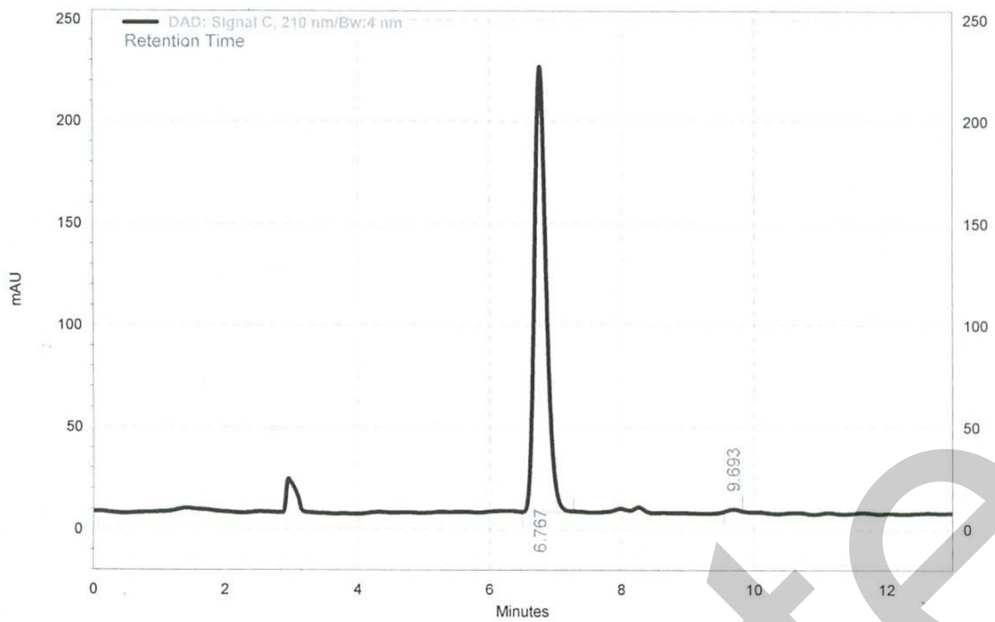
Bottom isomer.

DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %

Column: CHIRALCEL OD-H
n-HEXANE:IPA(90:10)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
PRESSURE- 46 bar
Operator :JAGADISH

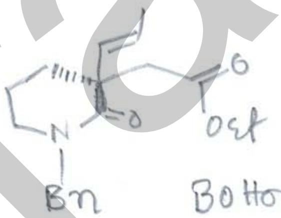




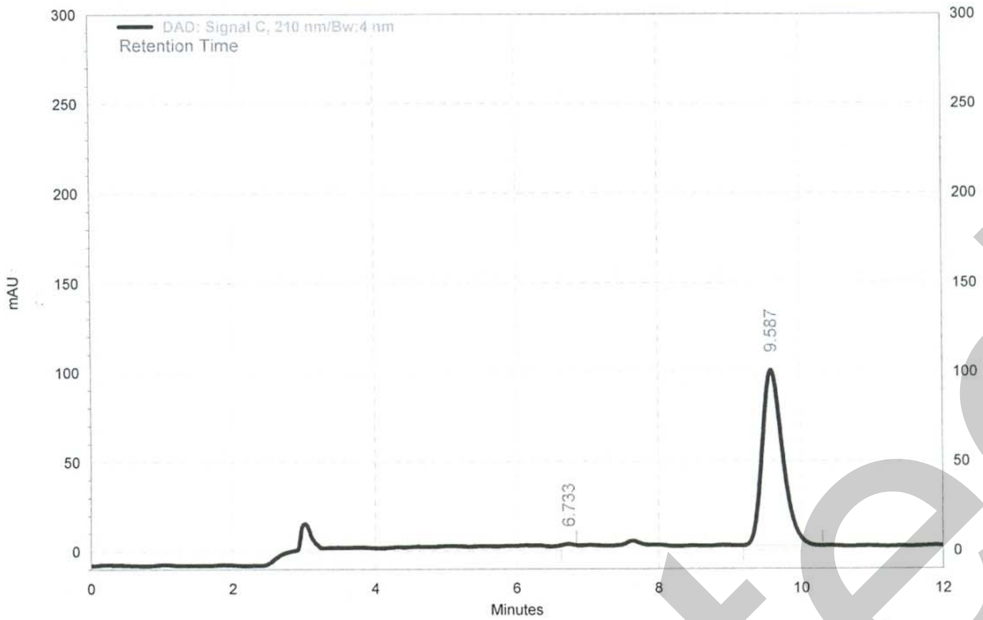
DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
6.767	5621690	99.64	457840	99.56
9.693	20490	0.36	2033	0.44
Totals	5642180	100.00	459873	100.00

Column: CHIRALCEL OD-H
n-HEXANE:IPA(90:10)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
PRESSURE- 46 bar
Operator :JAGADISH



Bottom isomer to Product.

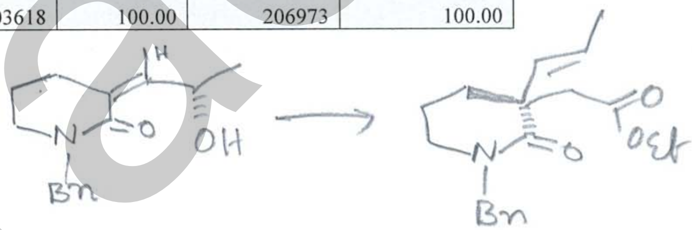


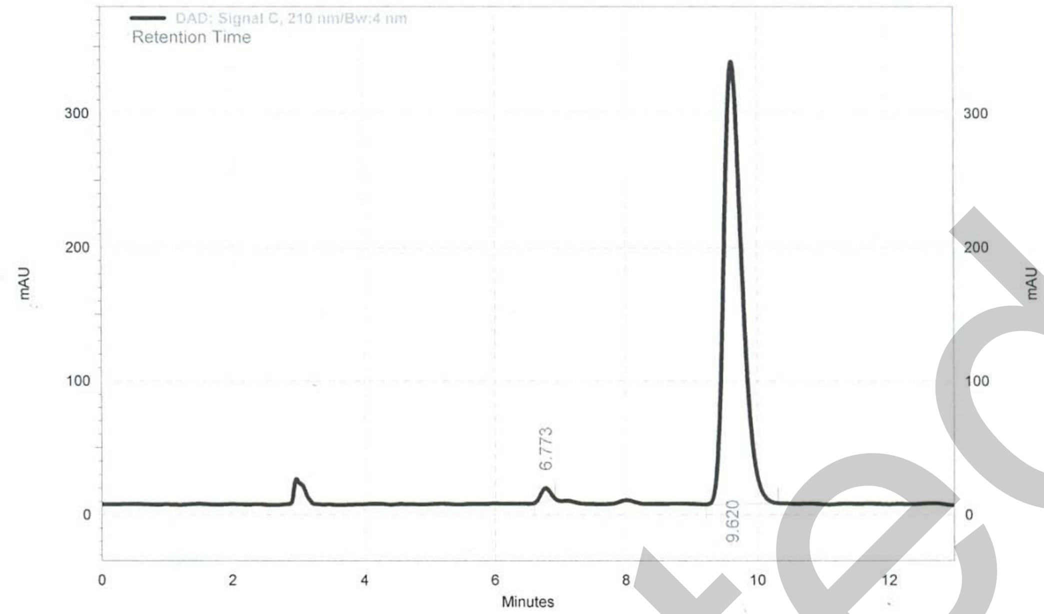
DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
6.733	11226	0.27	1443	0.70
9.587	4092392	99.73	205530	99.30

Totals				
	4103618	100.00	206973	100.00

Column: CHIRALCEL OD-H
n-HEXANE:IPA(90:10)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
PRESSURE- 46 bar
Operator :JAGADISH



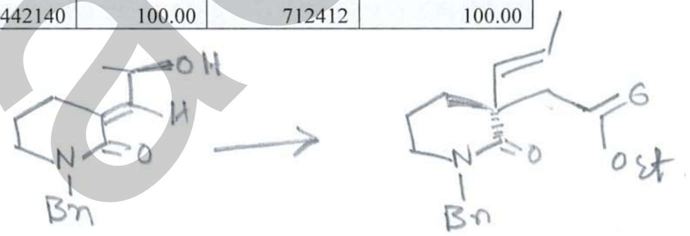


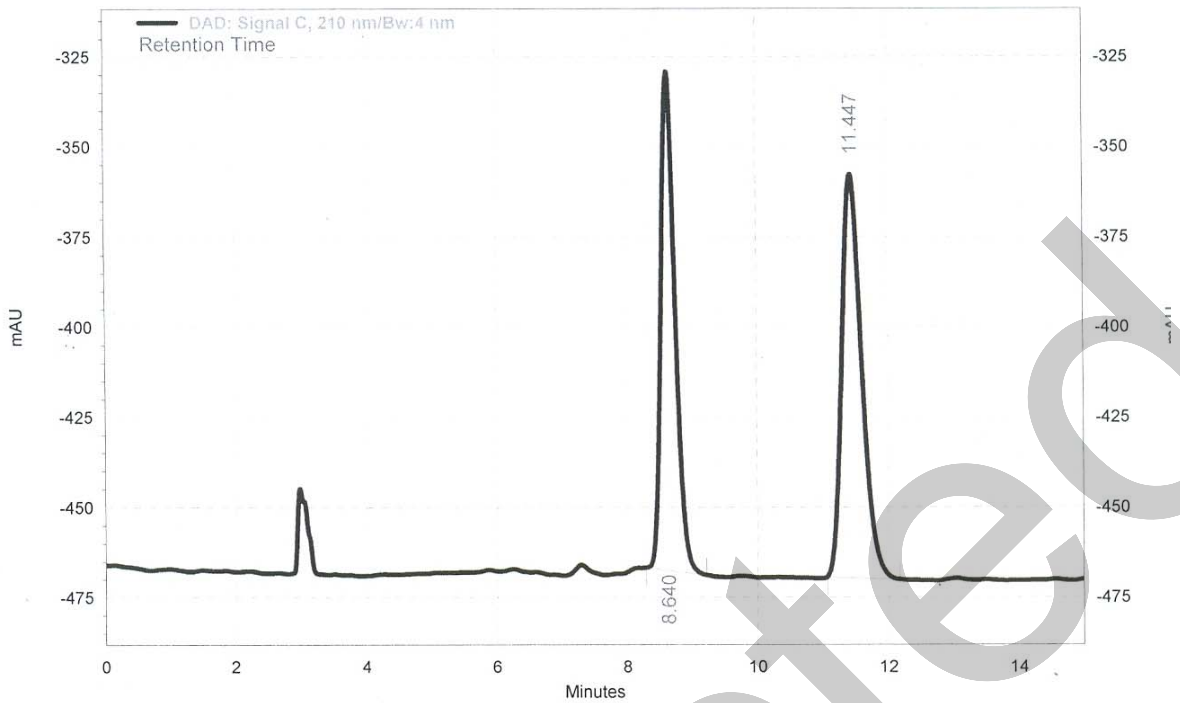
DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
6.773	184199	1.37	19155	2.69
9.620	13257941	98.63	693257	97.31

Totals	13442140	100.00	712412	100.00

Column: CHIRALCEL OD-H
n-HEXANE:IPA(90:10)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
PRESSURE- 46 bar
Operator :JAGADISH

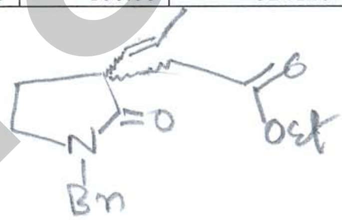


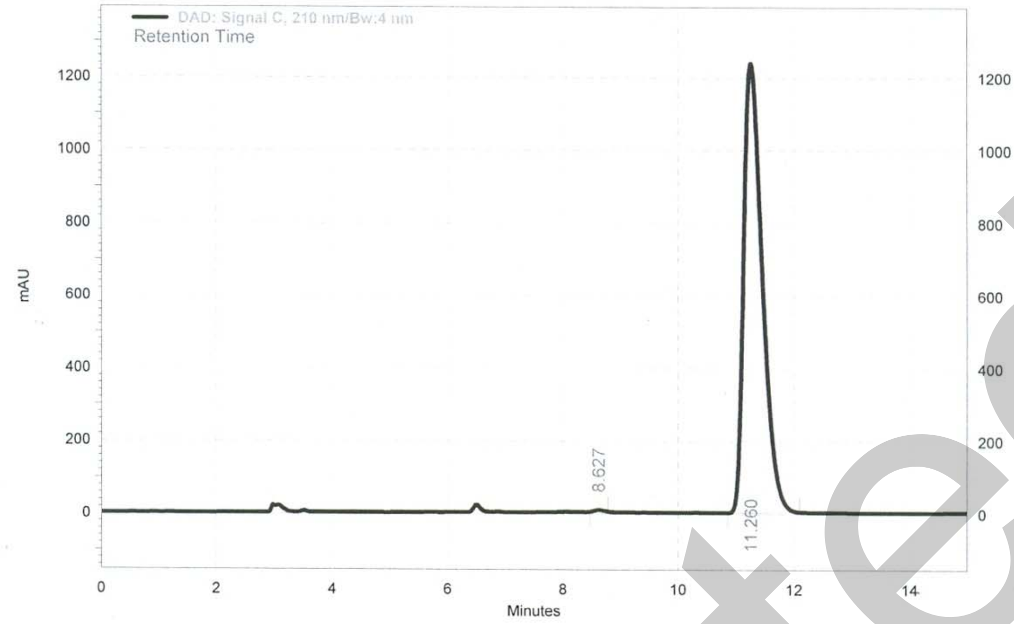


DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
8.640	4362883	47.01	289779	55.29
11.447	4917970	52.99	234347	44.71
Totals	9280853	100.00	524126	100.00

Column: CHIRALCEL OD-H
n-HEXANE:IPA(90:10)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
PRESSURE- 42 bar
Operator :JAGADISH



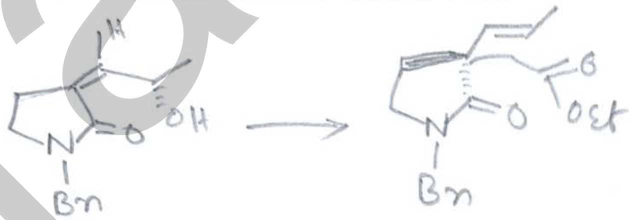


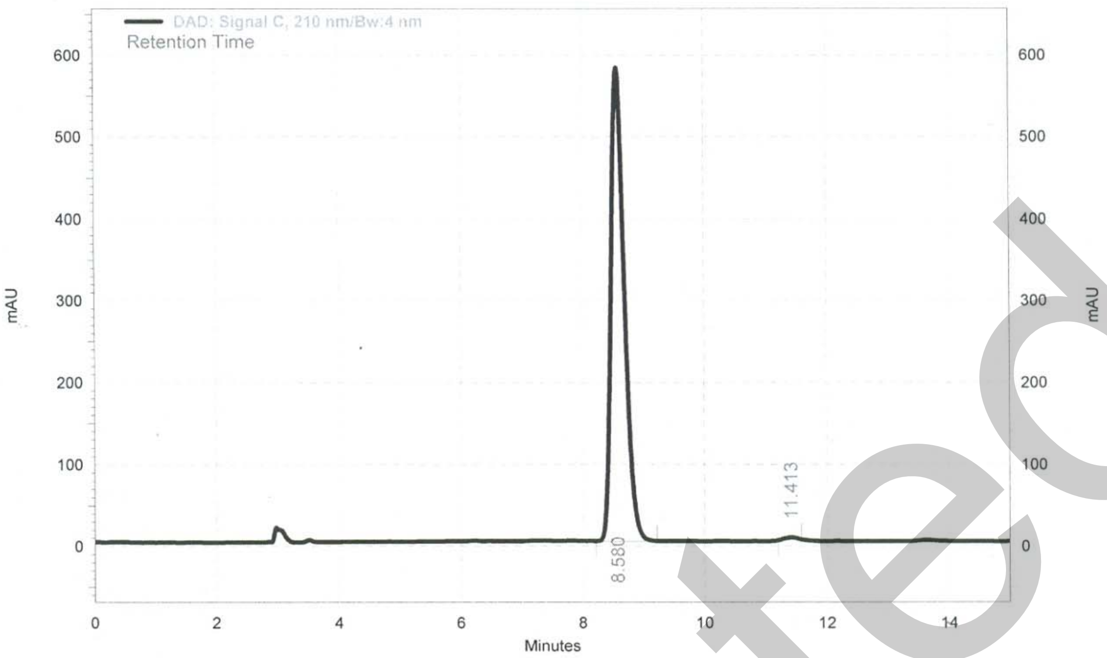
DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
8.627	105709	0.18	10033	0.39
11.260	57520882	99.82	2591143	99.61

Totals	57626591	100.00	2601176	100.00

Column: CHIRALCEL OD-H
n-HEXANE:IPA(90:10)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
PRESSURE- 42 bar
Operator :JAGADISH



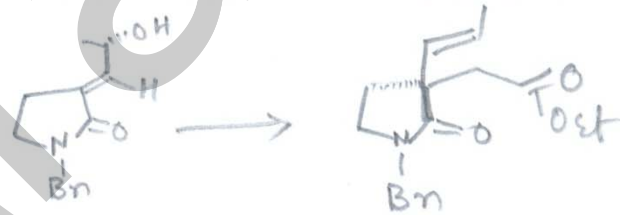


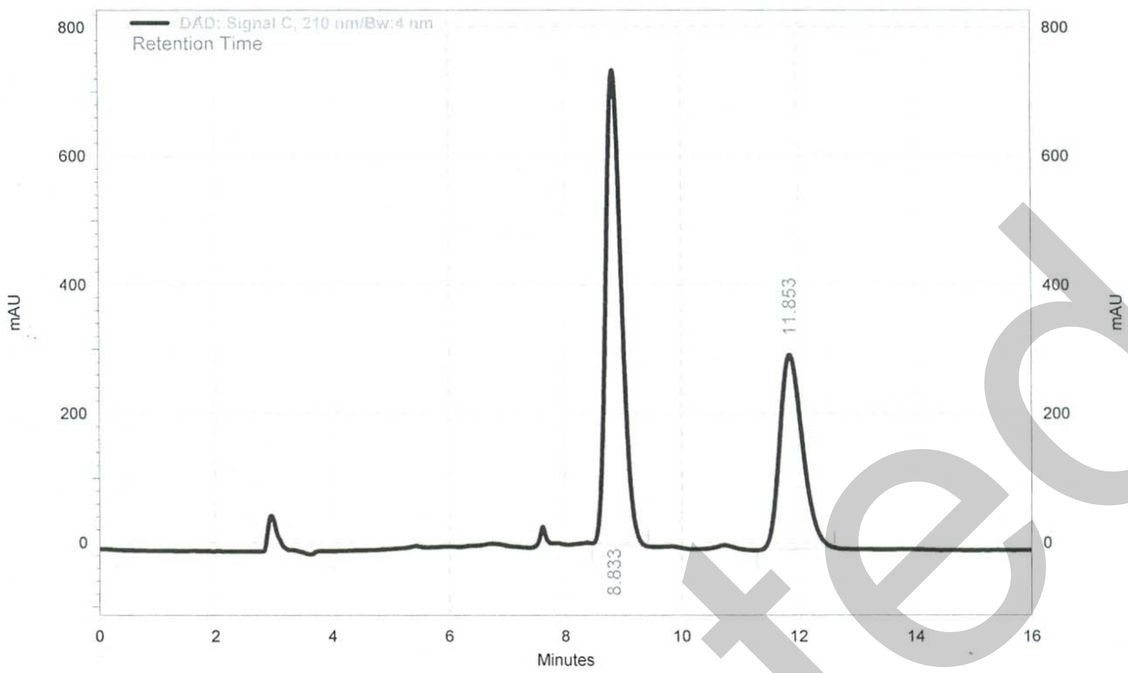
DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
8.580	18439286	99.56	1212620	99.51
11.413	81209	0.44	6004	0.49

Totals				
	18520495	100.00	1218624	100.00

Column: CHIRALCEL OD-H
n-HEXANE:IPA(90:10)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
PRESSURE- 42 bar
Operator :JAGADISH

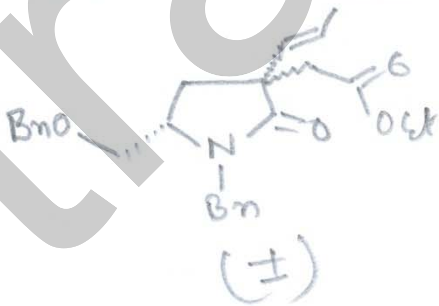


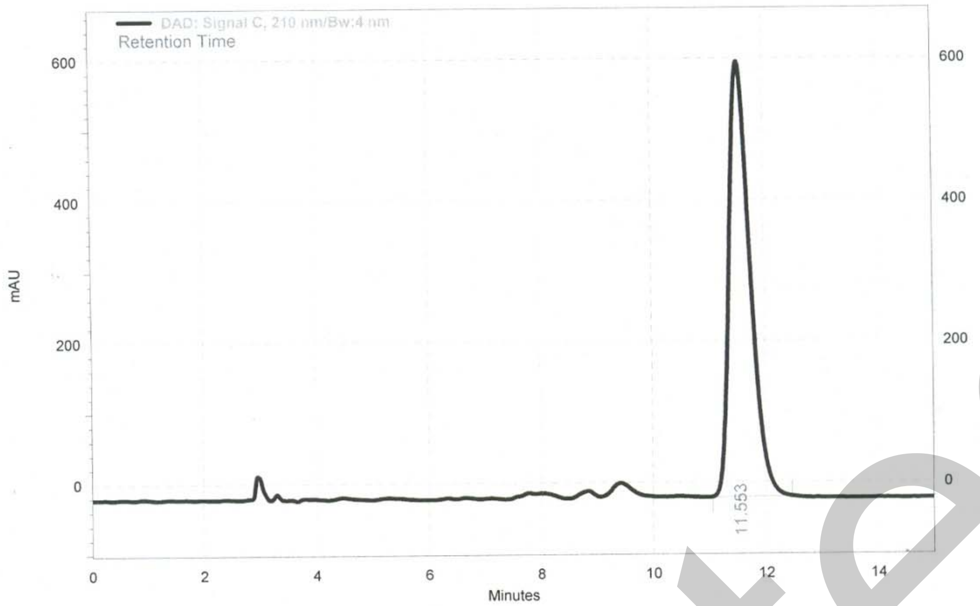


DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
8.833	28824699	62.81	1544363	70.96
11.853	17064525	37.19	632126	29.04
Totals	45889224	100.00	2176489	100.00

Column:Chiralcel OD-H
IPA:n-Hexane (90:10)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
Operator :JAGADISH



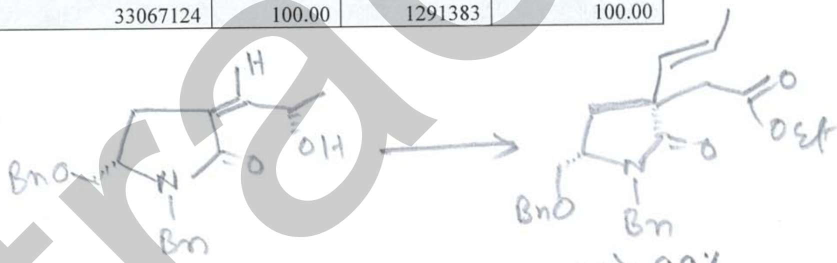


DAD: Signal C,
210 nm/Bw:4 nm
Results

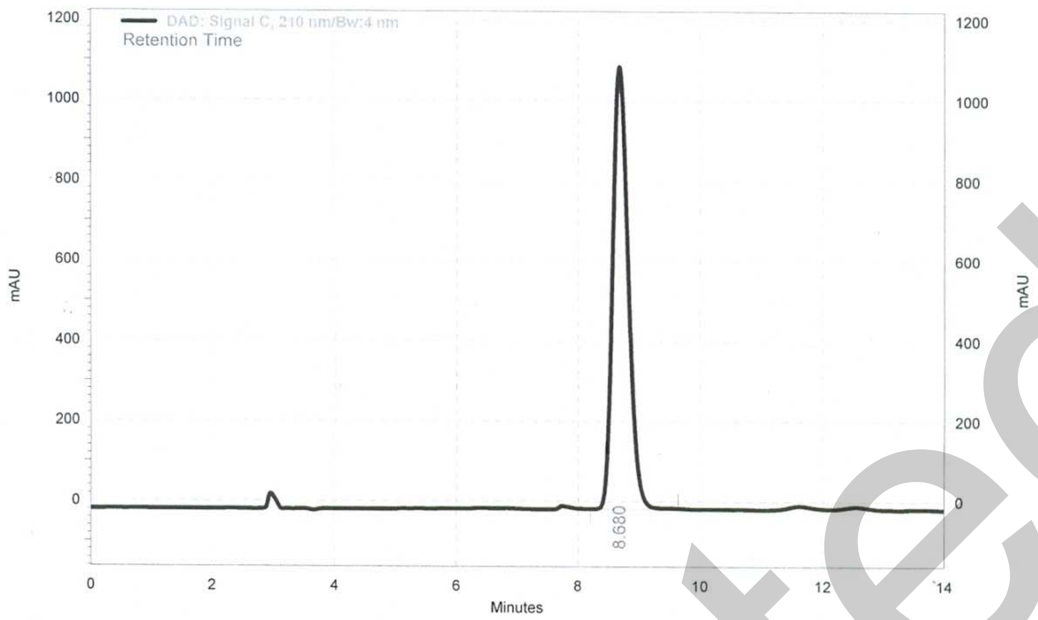
Retention Time	Area	Area %	Height	Height %
11.553	33067124	100.00	1291383	100.00

Totals				
	33067124	100.00	1291383	100.00

Column:Chiralcel OD-H
IPA:n-Hexane(90:10)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
Operator :JAGADISH



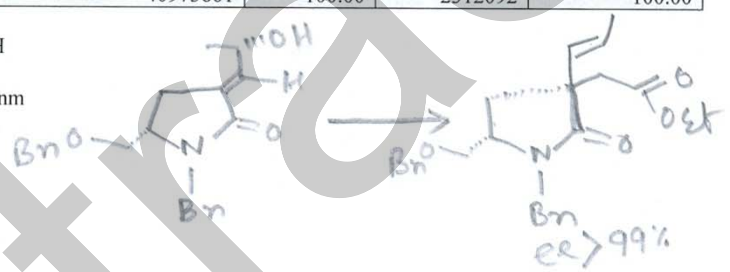
ee> 99%

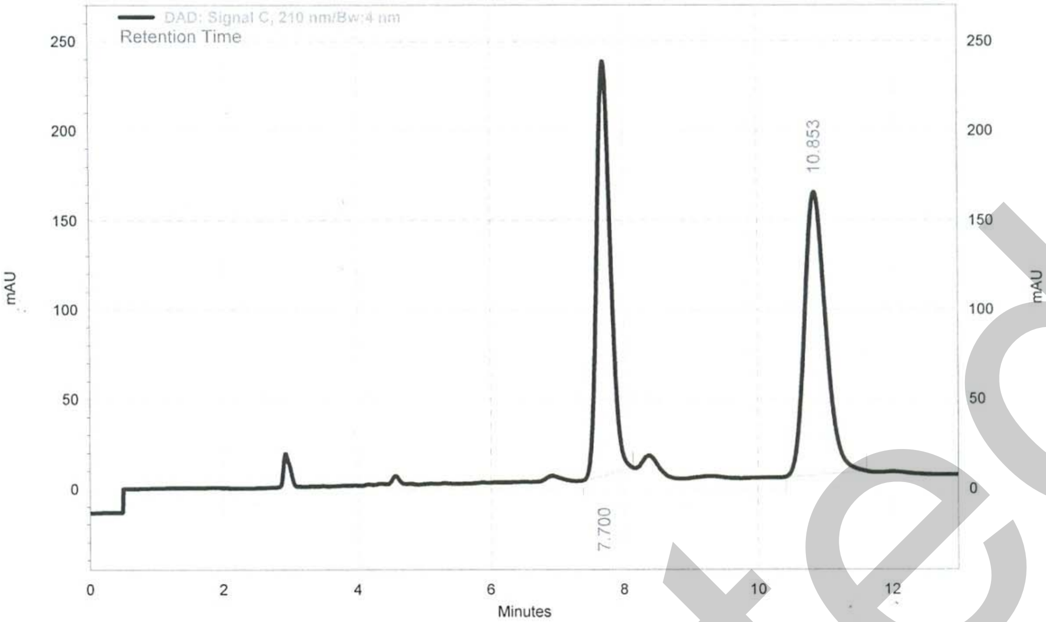


DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
8.680	40973861	100.00	2312092	100.00
Totals	40973861	100.00	2312092	100.00

Column:Chiralcel OD-H
IPA:n-Hexane
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
Operator :JAGADISH



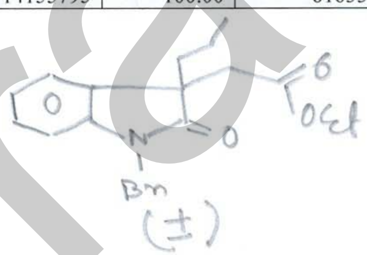


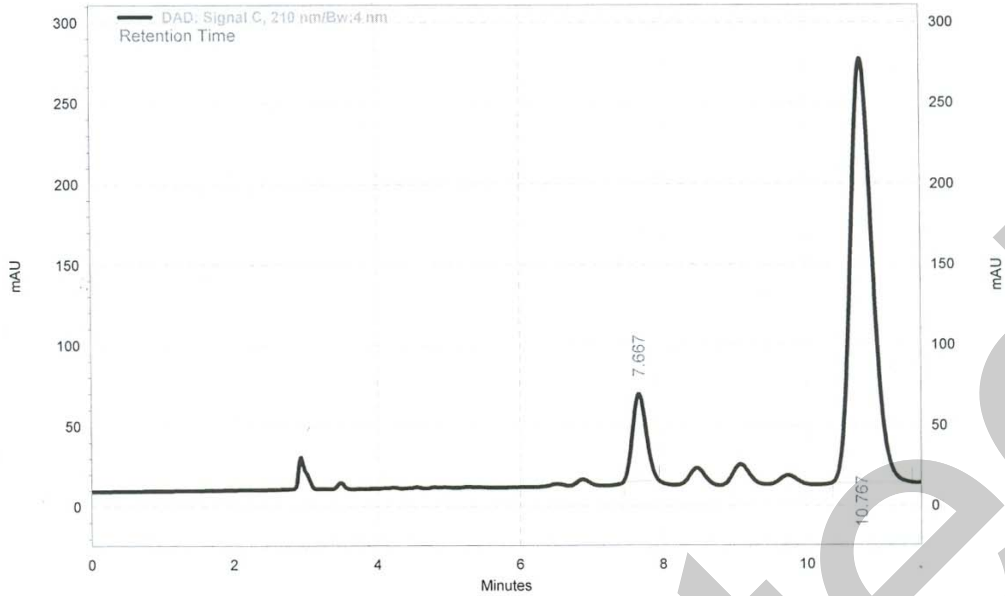
DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
7.700	6918542	48.87	484756	59.38
10.853	7237253	51.13	331575	40.62

Totals	14155795	100.00	816331	100.00

Column: CHIRALCEL OD-H
n-HEXANE:IPA(90:10)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
PRESSURE- 44 bar
Operator :JAGADISH



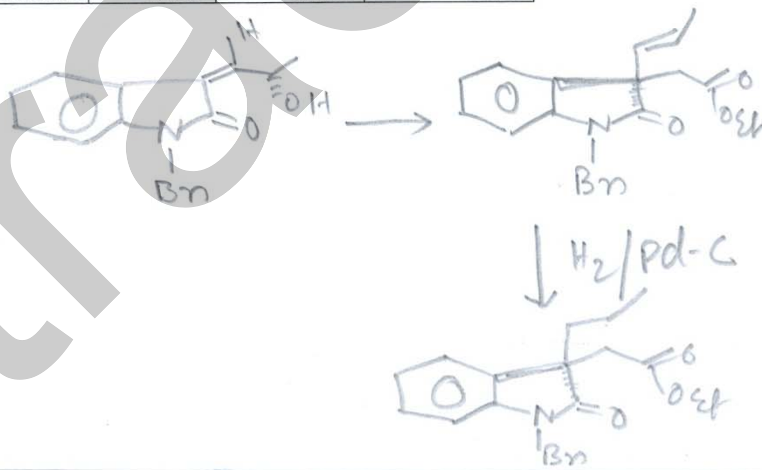


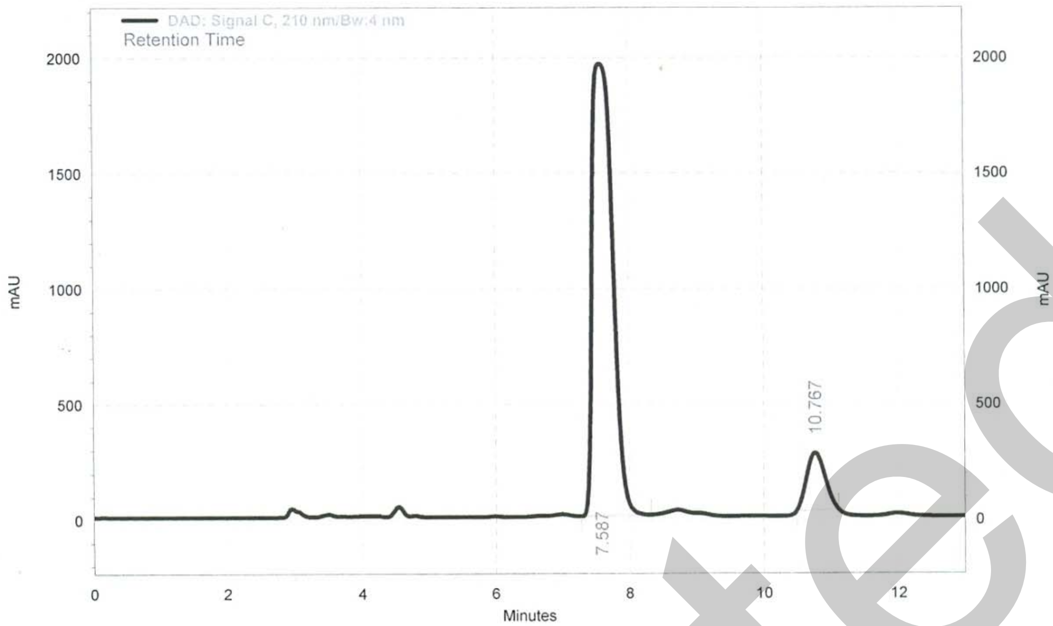
DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
7.667	1506919	11.48	112943	17.00
10.767	11624705	88.52	551399	83.00

Totals	13131624	100.00	664342	100.00

Column: CHIRALCEL OD-H
n-HEXANE:IPA(90:10)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
PRESSURE- 44 bar
Operator :JAGADISH

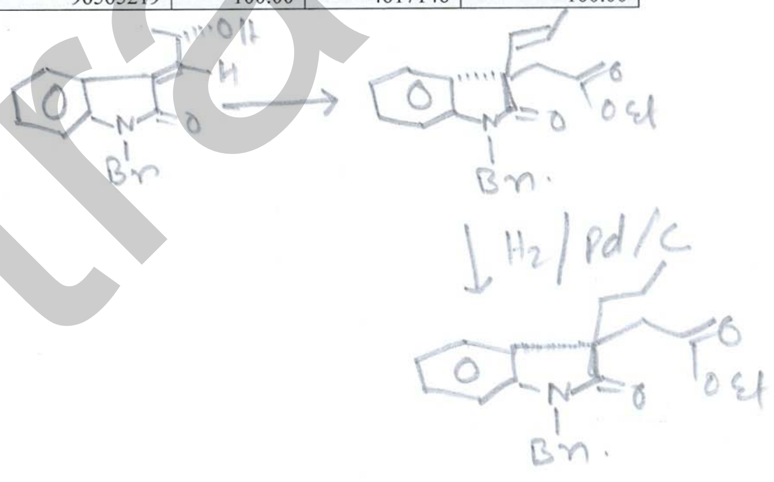


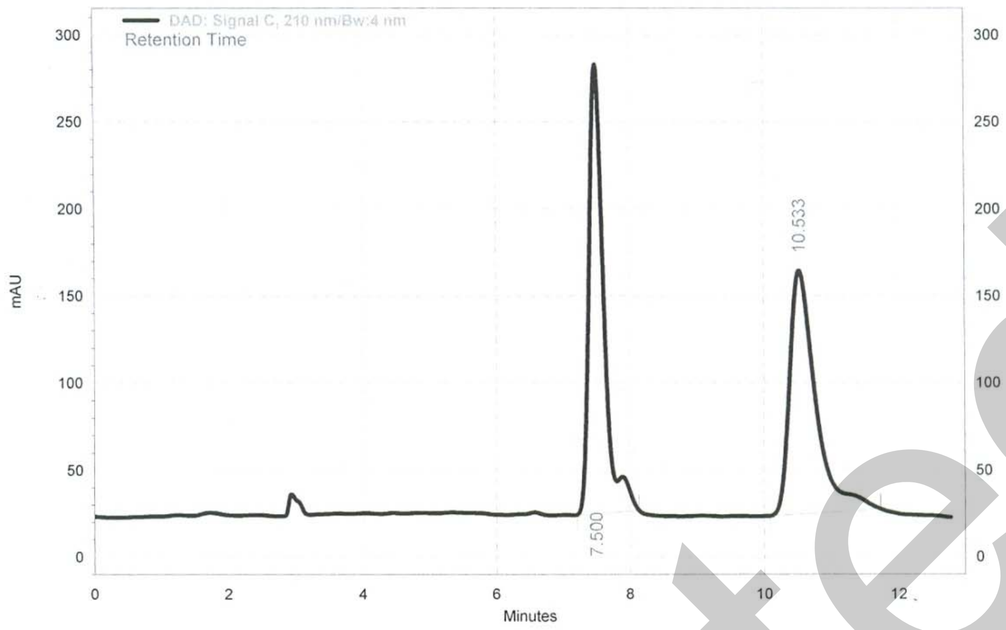


DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
7.587	86849418	89.94	4103010	88.86
10.767	9715801	10.06	514136	11.14
Totals	96565219	100.00	4617146	100.00

Column: CHIRALCEL OD-H
n-HEXANE:IPA(90:10)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
PRESSURE- 44 bar
Operator :JAGADISH



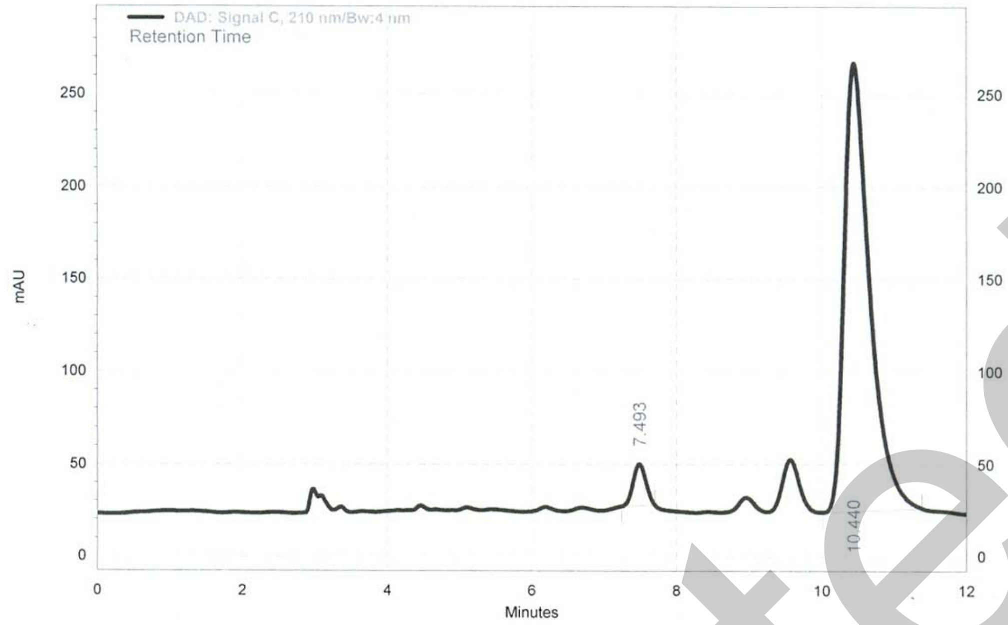


DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
7.500	8235947	51.13	540716	64.85
10.533	7872862	48.87	293068	35.15

Totals	16108809	100.00	833784	100.00

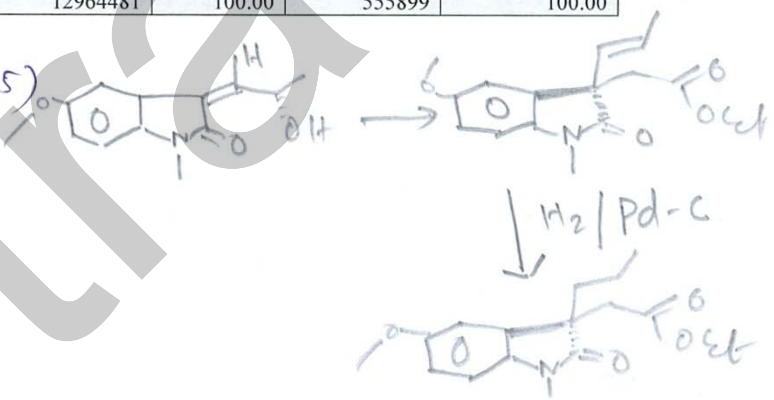
Column: CHIRALCEL OD-H
n-HEXANE:IPA(~~90:10~~)(85: 15)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
PRESSURE- 44 bar
Operator :JAGADISH

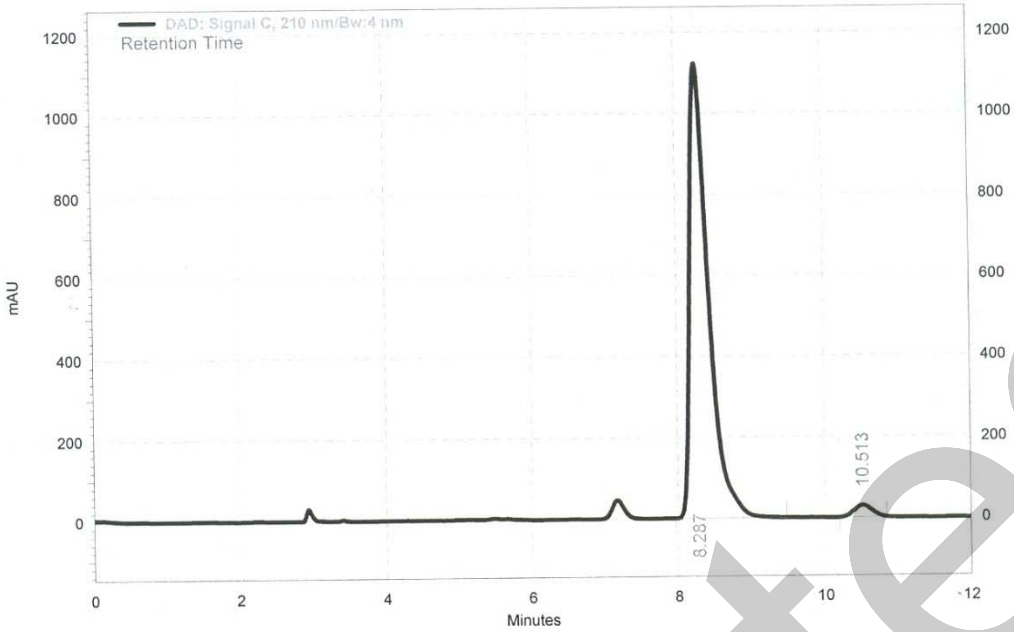


DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
7.493	578075	4.46	47210	8.49
10.440	12386406	95.54	508689	91.51
Totals	12964481	100.00	555899	100.00

Column: CHIRALCEL OD-H
n-HEXANE:IPA(~~90:10~~) (8.5:1.5)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
PRESSURE- 44 bar
Operator :JAGADISH



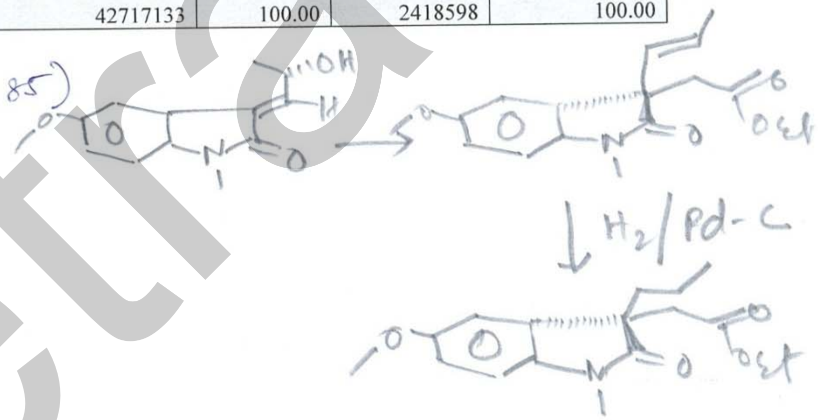


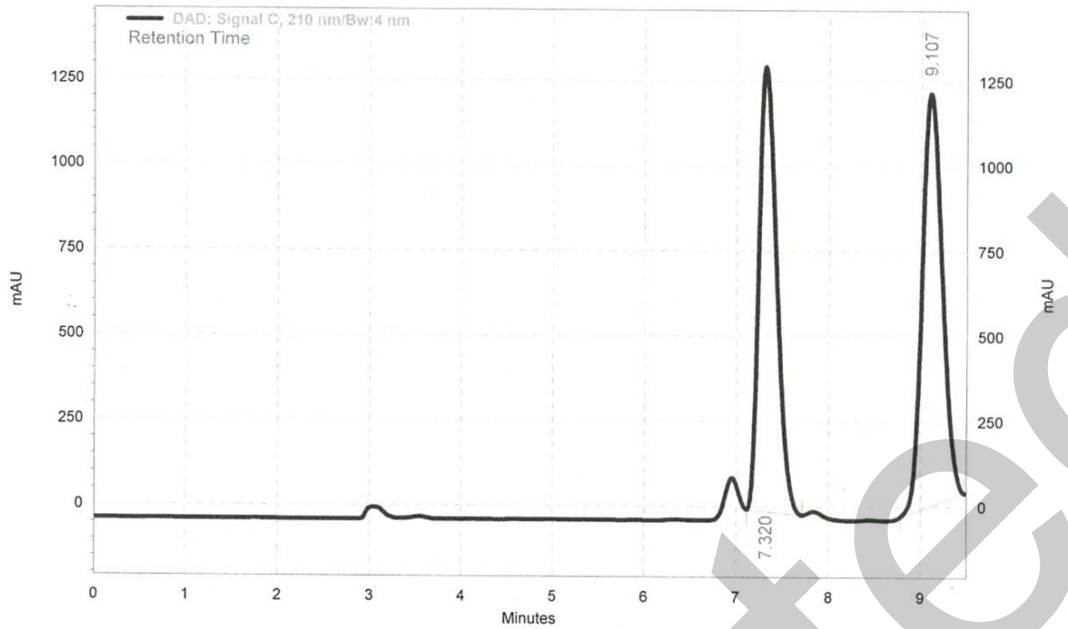
DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
8.287	41647079	97.50	2356817	97.45
10.513	1070054	2.50	61781	2.55

Totals				
	42717133	100.00	2418598	100.00

Column:Chiralcel OD-H
IPA:n-Hexane(~~10:90~~) (15:85)
WAVWLWNGTH-210 nm
FLOWRATE-1ML/min
Operator :JAGADISH



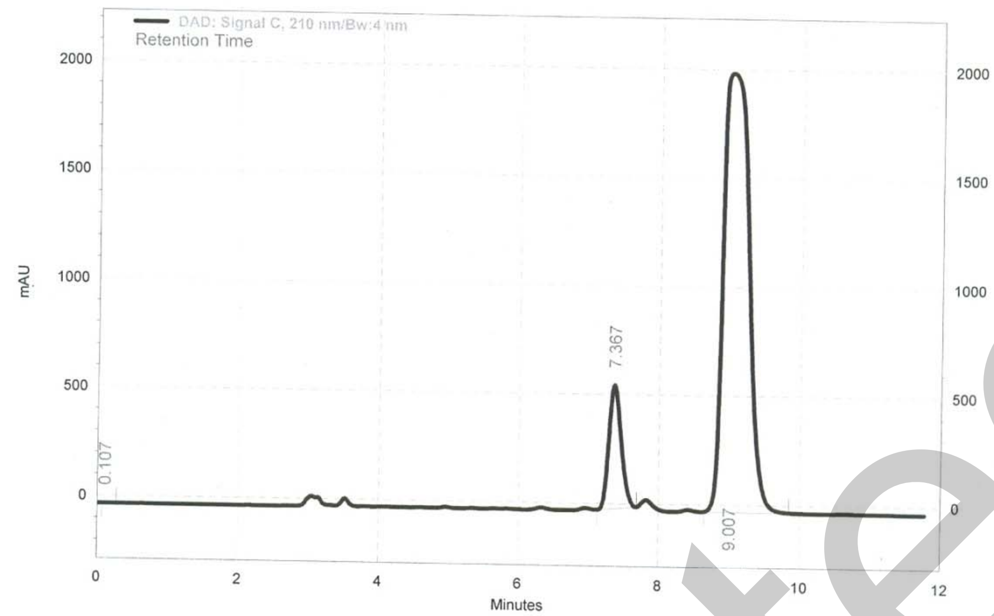


DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
7.320	36260955	48.50	2738802	51.87
9.107	38497620	51.50	2541491	48.13

Totals				
	74758575	100.00	5280293	100.00

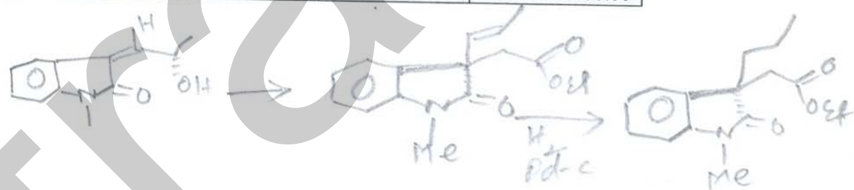
Column:CHIRALCEL OD-H
IPA:n-HEXANE(12:88)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
PRESSURE-45 BAR
Operator :JAGADISH

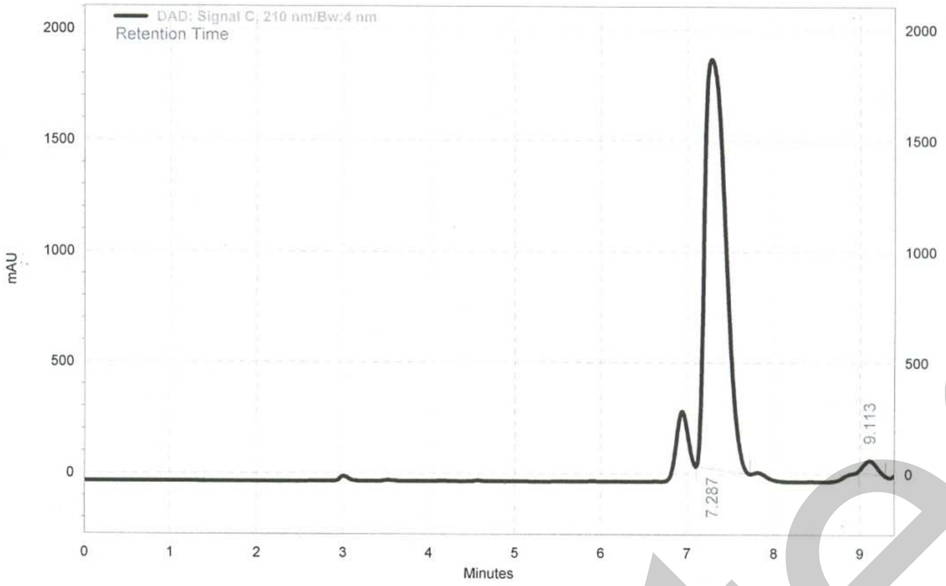


DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
0.107	1186	0.00	149	0.00
7.367	14473300	12.09	1184396	21.91
9.007	105269480	87.91	4220569	78.08
Totals	119743966	100.00	5405114	100.00

Column:CHIRALCEL OD-H
IPA:n-HEXANE(12:88)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
PRESSURE-45 BAR
Operator :JAGADISH

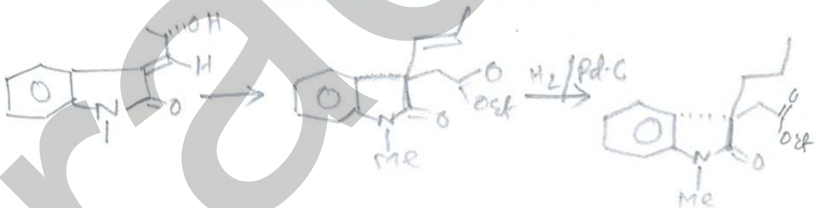


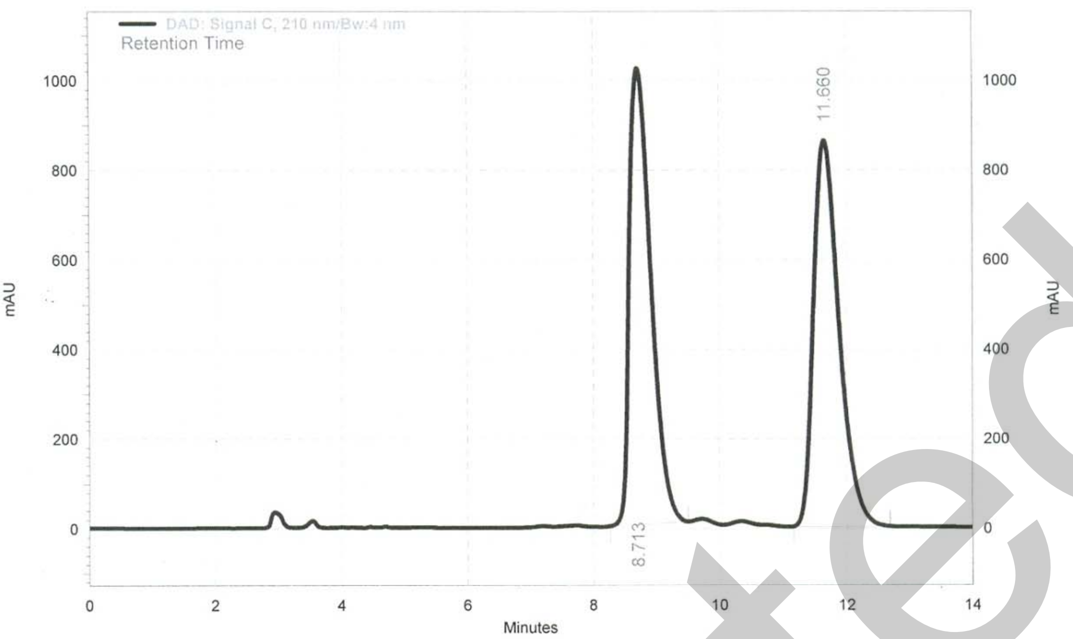


DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
7.287	63806881	98.12	3867025	97.06
9.113	1220465	1.88	117335	2.94
Totals	65027346	100.00	3984360	100.00

Column:CHIRALCEL OD-H
IPA:n-HEXANE(12:88)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
PRESSURE-45 BAR
Operator :JAGADISH

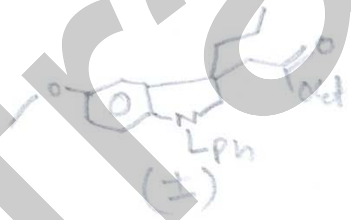


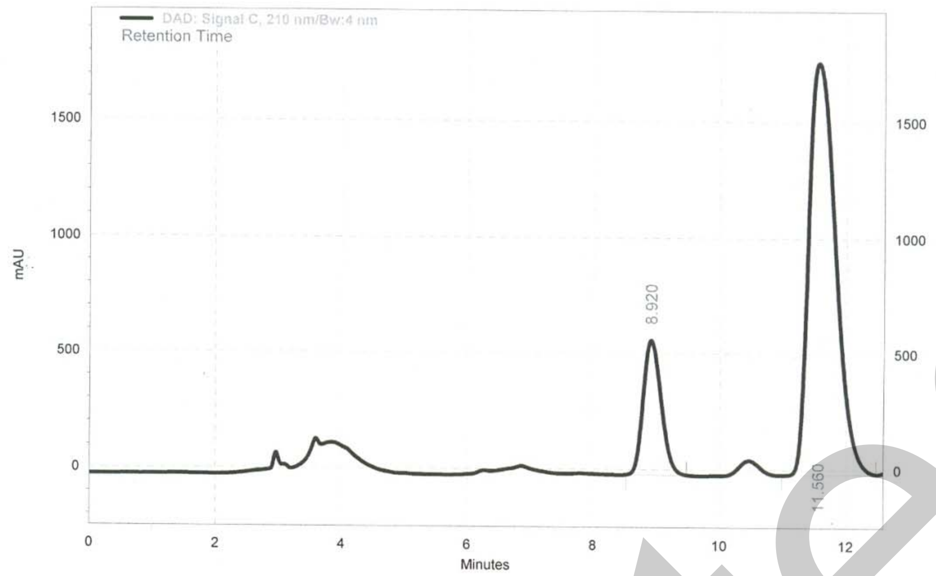


DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
8.713	50691185	50.11	2135159	54.16
11.660	50462657	49.89	1807279	45.84
Totals	101153842	100.00	3942438	100.00

Column:CHIRALCEL OD-H
IPA:n-HEXANE(10:90)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
PRESSURE-45 BAR
Operator :JAGADISH

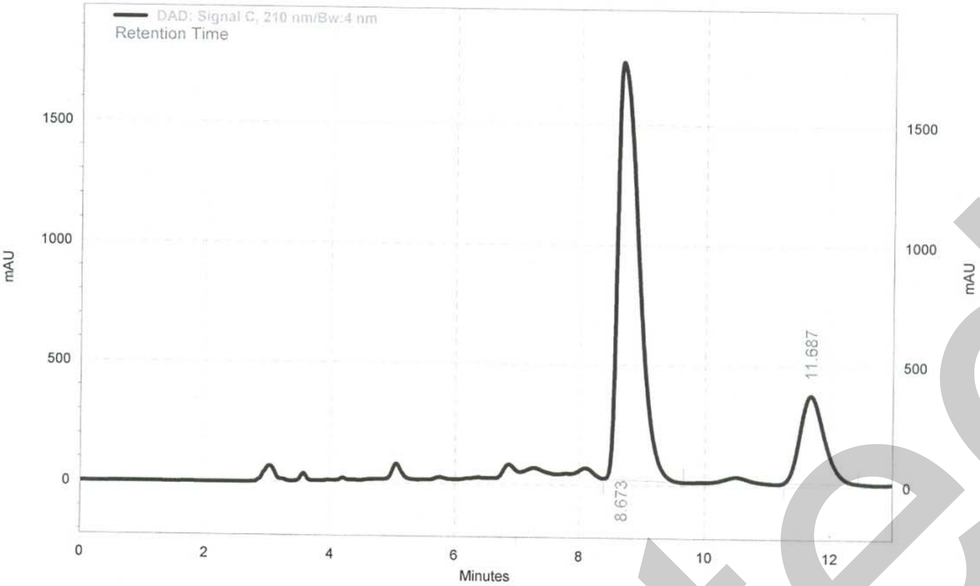




DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
8.920	23953478	17.87	1214743	24.57
11.560	110064515	82.13	3728579	75.43
Totals	134017993	100.00	4943322	100.00

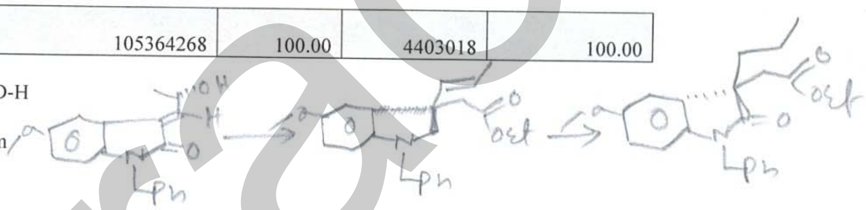
Column:CHIRALCEL OD-H
IPA:n-HEXANE(10:90)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
PRESSURE-45 BAR
Operator :JAGADISH



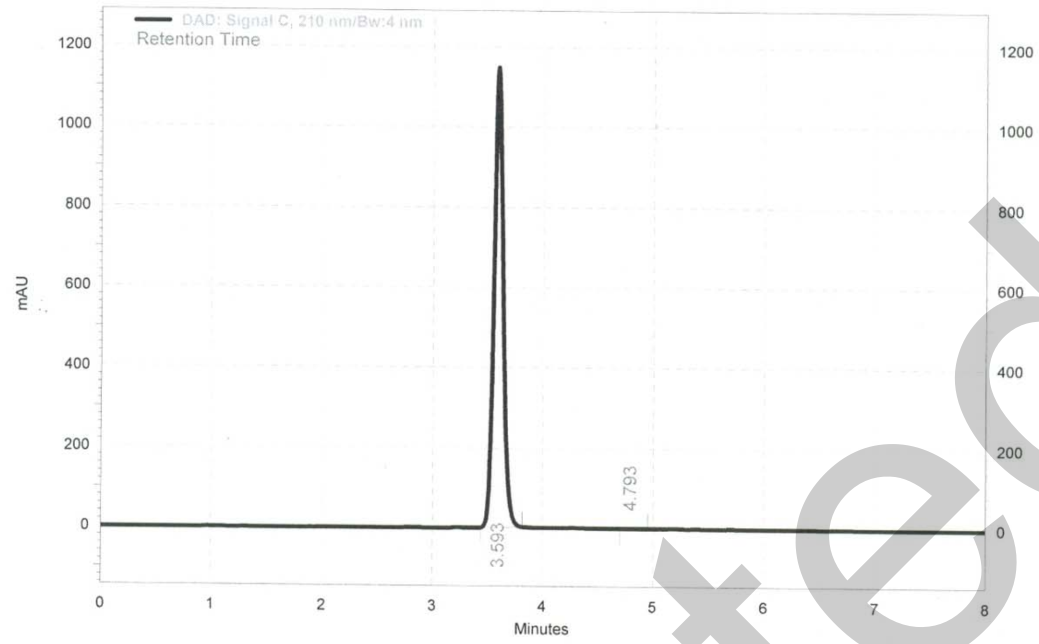
DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
8.673	85099562	80.77	3642668	82.73
11.687	20264706	19.23	760350	17.27
Totals	105364268	100.00	4403018	100.00

Column:CHIRALCEL OD-H
IPA:n-HEXANE(10:90)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
PRESSURE-45 BAR
Operator :JAGADISH



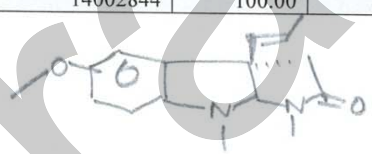
HPLC of compound **33:**



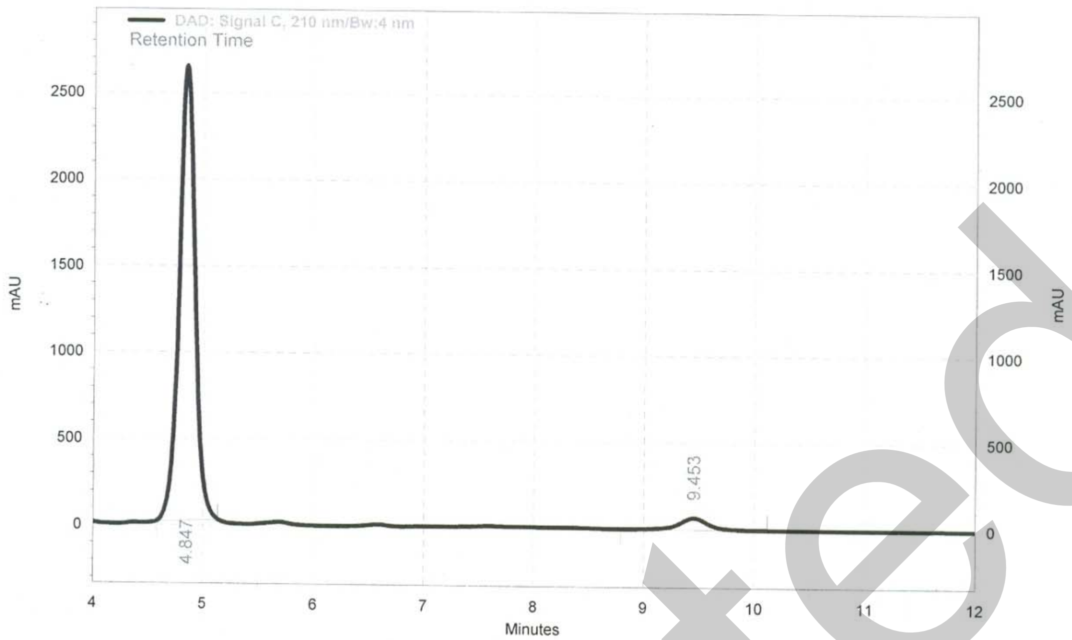
DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
3.593	13998845	99.97	2405846	99.98
4.793	3999	0.03	416	0.02
Totals	14002844	100.00	2406262	100.00

Column:Kromasil 100 5C-8
ACN:H20(58:42)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
PRESSURE-99 BAR
Operator :JAGADISH



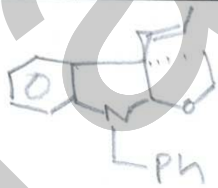
HPLC of compound- **37**:



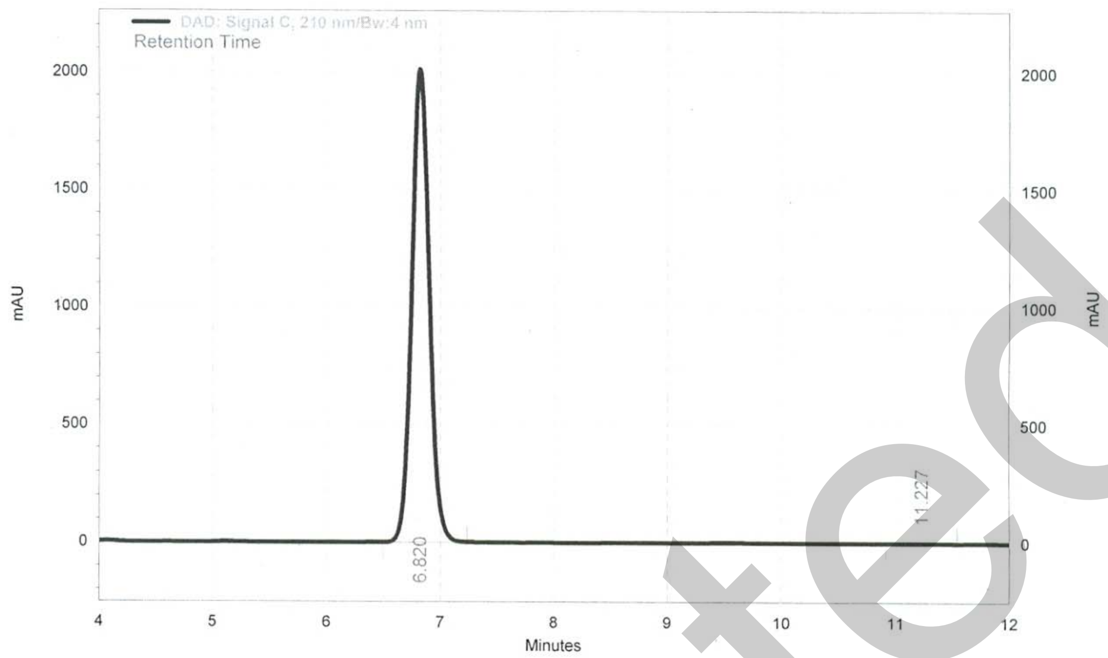
DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
4.847	55106601	95.29	5507461	97.47
9.453	2723532	4.71	143235	2.53
Totals	57830133	100.00	5650696	100.00

Column:Kromasil 100 5C-8
ACN:H20(60:40)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
PRESSURE-99 BAR
Operator :JAGADISH



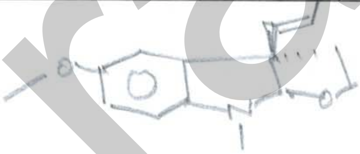
HPLC of compound- **38**:



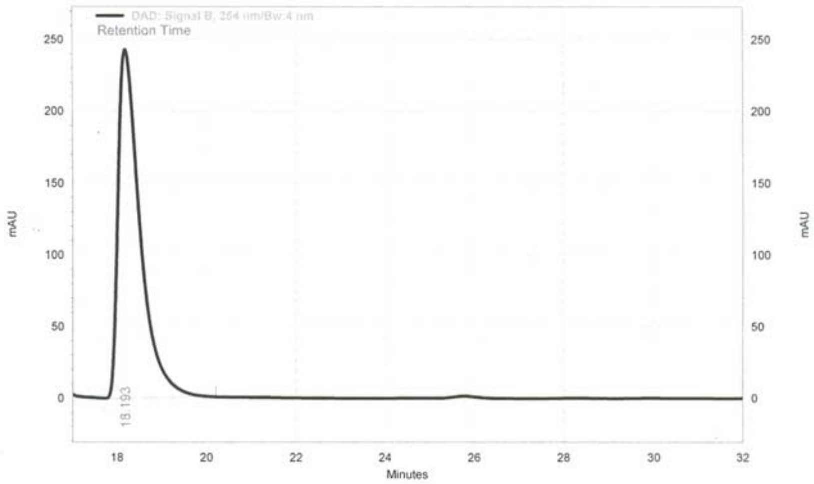
DAD: Signal C,
210 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
6.820	45255447	99.90	4219510	99.93
11.227	43395	0.10	2794	0.07
Totals	45298842	100.00	4222304	100.00

Column:Kromasil 100 5C-8
ACN:H20(60:40)
WAVWLWNGTH-210nm
FLOWRATE-1ML/min
PRESSURE-99 BAR
Operator :JAGADISH



HPLC of (-)-Esermethole



DAD: Signal B,
254 nm/Bw:4 nm
Results

Retention Time	Area	Area %	Height	Height %
18.193	17456300	100.00	508797	100.00
Totals	17456300	100.00	508797	100.00

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