Electronic Supplementary Material (ESI) for Organic Chemistry Frontiers.

Enantioselective Isoquinuclidine Synthesis via Sequential Diels-Alder / Visible-Light Photoredox C–C Bond Cleavage: A Formal Synthesis of the Indole Alkaloid Catharanthine

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SUPPORTING INFORMATION

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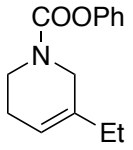
General Experimental Considerations

All commercial reagents, unless otherwise stated, were used as received (Aldrich, VWR or Fischer Scientific Ltd.). Dichloromethane and acetonitrile were distilled from CaH_2 under nitrogen. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone under nitrogen. FT-IR spectra were obtained on a Shimadzu FTIR-8400S, with samples loaded as a film onto NaCl plates. ^1H and ^{13}C NMR were obtained on Varian 300 or Varian 400 or Bruker 400 or Agilent 500 spectrometers as solutions in $CDCl_3$ with TMS and referenced to the TMS peak. For spectra taken in other NMR solvents, CD_3OD or CD_2Cl_2 or DMSO d-6, the ^1H spectra were referenced to the solvent residual protioisomers, and ^{13}C spectra (including $CDCl_3$ with TMS) referenced as to the NMR solvent.[1] Chemical shifts are expressed in parts per million values and coupling constants (*J*) are reported in Hertz (Hz) and rounded to the nearest 0.5 Hz. The following abbreviations are used to indicate multiplicities: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplets; q, quartets; m, multiplet. High Resolution Mass Spectra (HRMS) were recorded on a time-of-flight JMS-T1000LC spectrometer with a DART ion source. Melting points were obtained on a Fisher-Johns melting point apparatus and are uncorrected. Flash column chromatography on silica gel (60 Å, 230–400 mesh, low acidity, obtained from Silicycle Inc.) was performed using reagent grade solvents, as were filtrations through Alumina (neutral, Brockmann grade I). Analytical thin-layer chromatography (TLC) was performed on pre-coated aluminium-backed silica gel plates (Alugram SIL/G/UV254 purchased from Silicycle Inc.), visualized with a UV lamp (254 nm) or potassium molybdic acid solution in ethanol or aq. $KMnO_4$ or aq. *p*-anisaldehyde or aq. vanillin. Optical rotations were taken in a 25 °C chamber.

(1) Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Abraham Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics* **2010**, *29*, 2176–2179.

Preparation of phenyl 5-ethyl-3,6-dihydropyridine-1(2H)-carboxylate (13)

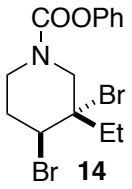


13

A solution of **11** (7.428 g, 26.7 mmol)[2] in EtOH (50 mL) was added to a solution of $NaBH_4$ (4.0 g, 110 mmol) in EtOH (60 mL) dropwise at 0 °C. The reaction mixture was allowed to warm to rt, and stirred for 22 h. The reaction mixture was diluted with CH_2Cl_2 (50 mL) and washed with water (50 mL). The aqueous phase was further extracted with CH_2Cl_2 (2 x 50 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was dissolved in toluene (25 mL). Phenylchloroformate (7.5 mL, 60 mmol) was added to the stirred reaction solution, dropwise, and the reaction mixture was then stirred for 16 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by flash chromatography (SiO_2, 0-20%, EtOAc:hex, gradient elution) yielding the title compound **13** (5.36 g, 87% over two steps) as an orange oil. $\mathbf{R_f}$ = 0.60 (20%, EtOAc:Hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$)[3] δ 7.33-7.24 (2H, m), 7.15-7.09 (1H, m), 7.07-7.00 (2H, m), 5.56-5.46 (1H, m), 3.96 (1H, s), 3.86 (1H, s), 3.61 (1H, app t, *J* = 5.5 Hz), 3.52 (1H, app t, *J* = 5.6 Hz), 2.14 (2H, br s), 1.95 (2H, q, *J* = 7.0 Hz), 0.99 (3H, q, *J* = 7.5 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$)[3] δ 154.1, 153.9, 151.6, 137.1, 136.4, 129.3, 125.3, 121.9, 118.3, 117.8, 46.5, 46.4, 41.5, 40.8, 27.5, 25.2, 24.7, 12.3; **IR** (neat, cm^{-1}) ν 2967, 1724, 1420, 1204, 845, 752; **HRMS** (m/z): $[M+H]^+$ for $C_{14}H_{17}NO_2$, calcd, 232.13375; found, 232.13414.

(2) Reding; M. T.; Fukuyama, T. *Org. Lett.* **1999**, *1*, 973-976.
(3) Compound **13** is a 1:1 mixture of rotamers, confirmed by a NOESY NMR spectrum, NMR spectra shown for **13** are from an analytical sample obtained by HPLC

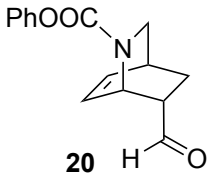
Preparation of (±)-phenyl (3*S,4*S**)-3,4-dibromo-3-ethylpiperidine-1-carboxylate (14)**



14

To a stirred solution of **13** (0.5456 g, 2.356 mmol) in CH_2Cl_2 (8 mL) was added Br_2 (0.130 mL, 2.56 mmol) dropwise, until a red color persisted. The reaction mixture was diluted with sat. aq. $Na_2S_2O_3$ (5 mL) and stirred for an additional 15 mins. The reaction mixture was diluted with brine (25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo* to yield the title compound **14** as a clear oil (0.903 g, 98%). **^{1}H NMR** (500 MHz, $CDCl_3$)[4] δ 7.29 (2H, t, *J* = 8.0 Hz), 7.13 (1H, t, *J* = 7.5 Hz), 7.06 (2H, d, *J* = 8.0 Hz), 4.60 (1H, s), 4.30-4.12 (2H, m), 3.54 (0.6H, d, *J* = 15.0 Hz), 3.48 (0.4H, t, *J* = 14.5 Hz), 3.38 (0.4H, d, *J* = 14.5 Hz), 3.32 (0.6H, t, *J* = 14.5 Hz), 2.94-2.66 (1H, m), 2.08-1.84 (3H, m), 1.11 (3H, t, *J* = 7.0 Hz); **^{13}C NMR** (125 MHz, CD_2Cl_2)[4] δ 153.9, 151.5, 129.4, 125.6, 125.5, 121.9, 121.8, 71.8, 71.4, 55.8, 51.4, 50.8, 40.2, 39.6, 34.2, 34.0, 31.6, 31.2, 29.9, 8.7; **IR** (neat, cm^{-1}) ν 3349, 2970, 1724, 1708, 1593, 1489, 1427, 1288, 1235, 1180, 1069, 1003, 845, 753, 691; **ESI-LRMS** (m/z): $[M+H]^+$ for $C_{14}H_{17}Br_2NO_2$, found, 391.0.

Preparation of (+)-phenyl (1*S*,4*S*,7*S*)-7-formyl-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (20)



20

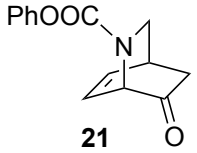
To a round bottom flask with **18** (11.098 g, 55.152 mmol) dissolved in MeCN:H_2O (114 mL:6 mL) was added acrolein (10.0 mL, 172 mmol). (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol·TFA (1.4493 g, 3.9236 mmol)[5] was added, and the vessel was then

(4) Compound **14** is a 0.6:0.4 ratio of rotamers, NMR spectra shown for **14** are from an analytical sample obtained by HPLC

(5) Nakano, H.; Osone, K.; Takeshita, M.; Kwon, E.; Seki, C.; Matsuyama, H.; Takano, N.; Kohari, Y. *Chem. Commun.* **2010**, *46*, 4827–4829.

submerged in a 1-2 °C bath (temperature varied by depth), and then stirred for 28 h. The reaction mixture was diluted with H_2O (500 mL) and extracted with EtOAc (3 x 500 mL). The organic phases were combined, washed with brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 0-100%, EtOAc:hex, gradient elution) yielding the title compound **20** (10.022 g, 71%) as a white solid. $\mathbf{R_f}$ = 0.50 (50%, EtOAc:Hexanes); **crude dr** ≥ 98:2 (^{1}H NMR); **product dr** (after chromatography) = 30:1 (1H NMR); **m.p.** = 93-94 °C; $\mathbf{[\alpha]_D^{25}}$ = +89.0° (*c* 1.2, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$)[6] δ 9.52 (0.6H, s), 9.49 (0.4H, s), 7.40-7.32 (2H, m), 7.23-7.16 (1H, m), 7.15-7.02 (2H, m), 6.52 (1H, dtd, *J* = 8.0, 7.0, 1.5 Hz), 6.39 (1H, dddd, *J* = 10.0, 8.0, 6.0, 1.5 Hz), 5.30 (1H, dddd, *J* = 6.0, 4.5, 3.0, 1.5 Hz), 3.54 (0.6H, dd, *J* = 10.5, 2.0 Hz), 3.40 (0.4H, dd, *J* = 10.5, 2.0 Hz), 3.24-3.15 (1.6H, m), 3.09 (0.4H, d, *J* = 10.5 Hz), 3.00-2.92 (1H, m), 1.98 (0.6H, ddt, *J* = 13.0, 4.5, 3.0 Hz), 1.93 (0.8H, ddd, *J* = 7.0, 3.0, 2.0 Hz), 1.86 (0.6, ddd, *J* = 13.0, 9.5, 2.5 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$)[6] δ 200.8, 200.3, 153.7, 153.0, 151.3 (2 peaks), 136.4, 136.2, 130.5, 130.3, 129.4, 129.4, 125.5, 125.4, 121.8, 52.4, 52.2, 48.0 (2 peaks), 46.6, 45.8, 30.9, 30.5, 23.6, 23.5; **IR** (neat, cm^{-1}) ν 2878, 1714, 1494, 1401, 1343, 1301, 1273, 1207, 1159, 1064, 731, 722, 692. **HRMS** (m/z): $[M+H]^+$ for $C_{15}H_{15}NO_3$, calcd, 258.11173; found, 258.11302.

Preparation of (+)-phenyl (1*S*,4*S*)-7-oxo-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (21).



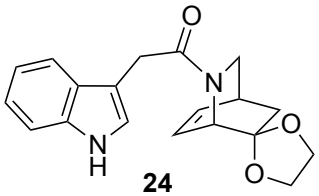
21

A 250 mL round bottomed flask was charged with **20** (1.785 g, 6.938 mmol), SiO_2 (21.164 g), $Ru(bpy)_3Cl_2{\cdot}(H_2O)_6$ (0.260 g), MeCN (90 mL), piperidine (0.69 mL, 21 mmol), and AcOH (0.59 mL, 10.4 mmol). The flask was affixed with a septum, and sparged with O_2 under sonication for 20 mins. The flask was then affixed with a strip of Blue LED lights (0.96 W, a Blue LED light strip containing 12 SMD LED 3528-type modules purchased from Walmart, 10 cm long strip), and the flask with lights was enclosed in aluminum foil. The reaction mixture was stirred for 14 h with the lights on. The reaction mixture was diluted with water (100 mL), and the biphasic solution was

(6) **20** is a 0.6:0.4 ratio of rotamers

extracted with EtOAc (3 x 100 mL). The organic phases were combined, washed with sat. aq. NaCl (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 0-100%, EtOAc:hex, gradient elution) yielding the title compound **21** (1.402 g, 83%) as a white solid. $\mathbf{R_f}$ = 0.33 (50%, EtOAc:Hexanes); **m.p.** = 135-136 °C (CH_2Cl_2); $\mathbf{[\alpha]_D^{25}}$ = +135.4° (*c* 0.99, $CHCl_3$, lit = +132.8 for 92% *ee*)[7]; **^{1}H NMR** (500 MHz, $CDCl_3$)[8] δ 7.40-7.27 (2H, m), 7.21-7.02 (3H, m), 6.70 (1H, dt, *J* = 15.0, 7.0 Hz), 6.48 (1H, ddd, *J* = 8.0, 6.5, 2.0 Hz), 5.06 (1H, dd, *J* = 12.5, 6.5 Hz), 3.68 (0.5H, dd, *J* = 10.0, 2.5 Hz), 3.56 (0.5H, dd, *J* = 10.5, 2.5 Hz), 3.39 (0.5H, d, *J* = 10.0 Hz), 3.26 (0.5H, d, *J* = 10.5 Hz), 3.23-3.12 (1H, m), 2.26 (2H, dd, *J* = 3.0, 1.5 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$)[8] δ 202.6, 153.5, 153.1, 151.1, 150.9, 140.0, 139.4, 129.3, 128.4, 127.8, 125.6, 121.7 (2 peaks), 58.5, 57.6, 46.8, 46.7, 36.7, 36.5, 32.4, 32.1; **IR** (neat, cm^{-1}) ν 2952, 1721, 1595, 1493, 1392, 1332, 1282, 1208, 1182, 1164, 1065, 840, 746, 693; **HRMS** (m/z): $[M+H]^+$ for $C_{14}H_{13}NO_3$, calcd, 244.09737; found, 244.09729.

Preparation of (+)-2-(1H-indol-3-yl)-1-((1*S*,4*S*)-6-azaspiro[bicyclo[2.2.2]octane-2,2'-[1,3]dioxolan]-7-en-6-yl)ethan-1-one (24)



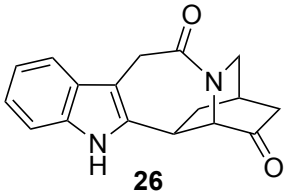
24

A solution of **21** (0.0550 g, 0.226 mmol) in toluene (2.5 mL) was added to *p*TsOH·H_2O (0.0010 g, 0.0053 mmol) and $MgSO_4$ (0.2 g). Ethylene glycol (0.2 mL) was added to the reaction mixture, and the solution heated at 140 °C for 20 h. $MgSO_4$ (0.2 g) and *p*TsOH·H_2O (0.0040 g, 0.021 mmol) were then added and the solution was stirred for 14 h. The reaction mixture was then diluted with sat. aq. $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic phases were dried ($MgSO_4$), and concentrated *in vacuo*. The residue was dissolved in DMSO/H_2O (1/1, 2 mL) and KOH (0.300 g, 5.35 mmol) was added. The reaction mixture was stirred for 36 h at 130 °C. The reaction solution was diluted with sat. aq. NH_4Cl (25mL) and then extracted with

(7) M. Hatano, M.; Goto, Y.; Izumiseki, A.; Akakura, M.; Ishihara, K. *J. Am. Chem. Soc.* **2015**, *137*, 13472-13475.
(8) Compound **21** is a 0.5:0.5 ratio of rotamers

CH_2Cl_2 (3 x 25 mL). The combined organic solutions were washed with sat. aq. NaCl (25 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue of **23** was dissolved in CH_2Cl_2 (4 mL). NEt_3 (0.070 mL, 0.50 mmol), EDCI (0.080 g, 0.42 mmol) were then added, followed by 3-indoleacetic acid (0.080 g, 0.46 mmol). The reaction mixture was then stirred for 39 h, and then was diluted with CH_2Cl_2 (25 mL) and washed with water (25 mL). The aqueous phase was further extracted with CH_2Cl_2 (2 x 25 mL). The combined organic phases were dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 0-10%, MeOH:CH_2Cl_2, gradient elution) yielding the known title compound **24** (0.0383 g, 52%) as a white solid.[9] $\mathbf{R_f}$ = 0.30 (5%, MeOH:CH_2Cl_2); m.p. = 73-74 °C; $\mathbf{[\alpha]_D^{25}}$ = 29.9° (*c* = 1.4, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$)[10] δ 8.43 (0.3H, s), 8.35 (0.7H, s), 7.64-7.49 (1H, m), 7.32 (1H, d, *J* = 8.0 Hz), 7.26 (0.3H, d, *J* = 2.0 Hz), 7.20-7.07 (2.4H, m), 7.01 (0.3H, s), 6.47 (0.9H, t, *J* = 7.0 Hz), 6.38 (0.8H, t, *J* = 7.0 Hz), 6.17 (0.3H, t, *J* = 7.0), 5.35-5.23 (1H, m), 4.28 (0.3H, d, *J* = 6.0 Hz), 4.12 (0.7H, dt, *J* = 9.1, 4.5 Hz), 4.01 (1H, m), 3.98-3.60 (4H, m), 3.57-3.40 (1H, m), 3.19-3.10 (1H, m), 2.88 (0.3H, s), 2.82 (0.7H, s), 1.96-1.72 (2H, m); **^{13}C NMR** (100 MHz, $CDCl_3$)[10] δ 170.9, 136.4, 136.3, 135.6, 130.9, 129.9, 127.6, 127.3, 122.8, 122.2, 122.1, 119.6, 119.5, 118.7, 118.5, 111.4, 111.3, 111.2, 111.1, 109.4, 108.9, 65.1, 65.0, 64.8, 64.4, 54.2, 47.8, 47.1, 46.4, 38.7, 37.8, 32.0, 31.8, 31.3, 31.1; **IR** (neat, cm^{-1}) ν 3280 (br), 2968, 2931, 1624, 1459, 1420, 1341, 1270, 1229, 1124, 1011, 949, 744; **HRMS** (m/z): $[M+H]^+$ for $C_{19}H_{20}N_2O_3$, calcd, 325.1547; found, 325.1551.

Preparation of (-)-5,6,6*a*,9,10,13-hexahydro-12H-6,9-methanopyrido[1',2':1,2]azepino[4,5-b]indole-7,12(8H)-dione (26).



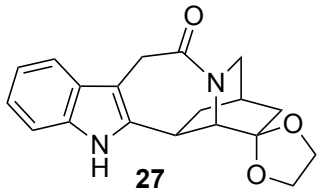
26

To a vial (10 mL) containing $PdCl_2(MeCN)_2$ (0.150, 0.578 mmol), $AgBF_4$ (0.160 g, 0.822 mmol), and **25** (0.1206 g, 0.430 mmol)[9] was added MeCN (5.0 mL). The reaction mixture was then stirred for 25 h at 85 °C. Then, the reaction mixture was cooled to 0 °C, diluted with MeOH (1 mL), followed by addition of $NaBH_4$ (0.046 g). The black

(9) Moisan, L.; Thuéry, P.; Nicolas, M.; Doris, E.; Rousseau, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 5334-5336.
(10) Known compound **24** is a 0.7:0.3 ratio of rotamers

reaction mixture was filtered over Celite, then concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 0-10%, MeOH:CH_2Cl_2, gradient elution) to yield known title compound **26** (0.0300 g, 25%) as a white solid.[9] Characterization data is shown below.

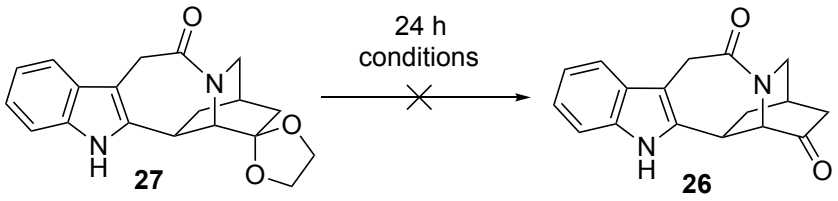
Preparation of (-)-5',6',6a',9',10',13'-hexahydro-8'H,12'H-spiro[[1,3]dioxolane-2,7'-[6,9]methanopyrido[1',2':1,2]azepino[4,5-b]indol]-12'-one (27).



27

To a stirred solution of $PdCl_2(MeCN)_2$ (0.348 g, 1.34 mmol), $AgBF_4$ (0.280 g, 1.44 mmol) in MeCN (20 mL) was added **24** (0.3484 g, 1.07 mmol) in MeCN (25 mL). The reaction mixture was then stirred for 18 h at 75 °C. Then, the reaction mixture was cooled to 0 °C, then diluted with MeOH (12 mL), followed by portionwise addition of $NaBH_4$ (0.15 g). The black reaction mixture was filtered over Celite, then concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 0-100%, EtOAc:hexanes, gradient elution) to yield the title compound **27** (0.2215 g, 64%) as a white solid (contaminated with 0.15 equivalents of CH_2Cl_2, and an unidentified inseparable impurity), which was used for the deprotection attempts, *vide supra*. $\mathbf{R_f}$ = 0.4 (5%, MeOH:CH_2Cl_2); **m.p.** = 300 °C (decomposition); $\mathbf{[\alpha]_D^{25}}$ = -35.9° (*c* 0.68, CH_2Cl_2); **^{1}H NMR** (500 MHz, DMSO-d6) δ 10.95 (s, 1H), 7.46 (1H, d, *J* = 7.5 Hz), 7.27 (1H, d, *J* = 8.0 Hz), 7.03 (1H, ddd, *J* = 8.0, 7.0, 1.5 Hz), 6.97 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz), 4.19-3.83 (m, 6H), 3.67 (1H, ddd, *J* = 11.5, 4.0, 2.5 Hz), 3.46 (1H, d, *J* = 15.5 Hz), 3.31-3.23 (1H, m), 2.96 (1H, d, *J* = 11.5 Hz), 2.21-2.11 (2H, m), 2.03-1.82 (2H, m), 1.13 (1H, ddd, *J* = 11.5, 6.5, 2.5 Hz); **^{13}C NMR** (125 MHz, DMSO-d6) δ 174.0, 139.1, 134.9, 127.4, 120.6, 118.6, 117.4, 110.7, 107.7, 100.87, 64.3, 63.9, 52.9, 47.7, 38.1, 32.2, 31.8, 31.1, 27.0; **IR** (neat, cm^{-1}) ν 2926, 2855, 1653, 1464, 1346, 1325, 1265, 1227, 1188, 1125, 1018, 980, 945; **HRMS (m/z)**: $[M+H]^+$ for $C_{19}H_{20}N_2O_3$, calcd, 325.15522; found, 325.15484.

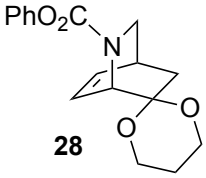
Attempted deprotection of compound 27.



Entry	Conditions	Result
1	*p*TsOH, acetone/water 10:1, rt	no conversion
2	*p*TsOH, acetone/water 10:1, reflux	no conversion
3	NaI (cat.), $CeCl_3 \cdot (H_2O)_7$, MeCN, 70 °C	no conversion
4	1N HCl/THF 1:1, rt	no conversion
5	1N HCl/THF 1:1, 75 °C	decomposition

Table A1: Ketal Deprotection Attempts

Preparation of (+)-phenyl (1*S*,4*S*)-6-azaspiro[bicyclo[2.2.2]octane-2,2'-[1,3]dioxan]-7-ene-6-carboxylate (28).

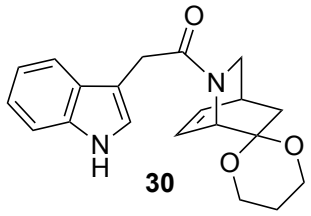


28

A round-bottomed flask charged with **21** (1.3023 g, 5.3535 mmol), benzene (80 mL), 1,3-propanediol (4.25 mL, 39.7 mmol) and *p*TsOH·H_2O (0.100 mg, 0.526 mmol) was affixed with a Dean Stark apparatus. The setup was purged with argon, and the solution was stirred under reflux for 42 h. K_2CO_3 (2 g) was added and the reaction mixture was stirred for 0.5 h. The solution was diluted with H_2O (30 mL) and extracted with EtOAc (3 x 75 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 0-

100%, EtOAc:hexanes, gradient elution) to yield the title compound **28** (1.5503 g, 96%) as a white solid. $\mathbf{R_f}$ = 0.50 (50%, EtOAc:hex); **m.p.** = 103-104 °C; $\mathbf{[\alpha]_D^{25}}$ = 33.5° (*c* 1.63, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$)[11] δ 7.41-7.29 (2H, m), 7.23-7.14 (1H, m), 7.16-7.10 (2H, m), 6.55-6.37 (2H, m), 5.55 (0.65H, dd, *J* = 6.5, 1.0 Hz), 5.38 (0.35H, d, *J* = 6.3 Hz), 4.34 (0.65H, td, *J* = 11.8, 3.1 Hz), 4.22 (0.35H, ddd, *J* = 12.0, 9.5, 3.5 Hz), 4.00 (0.65H, td, *J* = 11.5, 3.0 Hz), 3.99-3.88 (0.7H, m), 3.90-3.80 (1.65H, m), 3.54 (0.65H, dd, *J* = 10.1, 2.2 Hz), 3.41 (0.35H, dd, *J* = 10.5, 2.0 Hz), 3.22 (0.65H, dt, *J* = 10.0, 2.5 Hz), 3.09 (0.35H, dt, *J* = 10.5, 2.5 Hz), 2.91-2.81 (1H, m), 2.06-1.94 (0.65H, m), 1.89 (0.35H, ddq, *J* = 18.5, 9.5, 4.5 Hz), 1.81 (1H, ddd, *J* = 13.5, 9.0, 2.5 Hz), 1.74 (1H, tdd, *J* = 13.5, 3.5, 2.5 Hz), 1.60 (0.35H, dddd, *J* = 13.5, 4.5, 3.5, 1.0 Hz), 1.48 (0.65H, dp, *J* = 13.5, 3.0 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$)[11] δ 154.3, 153.6, 151.6, 135.4, 135.1, 130.2, 129.8, 129.4, 129.3, 125.4, 125.3, 122.0, 121.8, 102.6, 102.5, 61.3, 61.1 (2 peaks), 60.8, 49.2, 47.0, 46.9, 46.8, 40.7, 39.2, 31.5, 31.2, 25.0, 24.8; **IR** (neat, cm^{-1}) ν 2963, 2878, 1717, 1404, 1335, 1296, 1204, 1138, 1069, 988, 849, 748, 698; **HRMS (m/z)**: $[M+H]^+$ for $C_{17}H_{19}NO_4$, calcd, 302.13923; found, 302.13836.

Preparation of (+)-2-(1H-indol-3-yl)-1-((1*S*,4*S*)-6-azaspiro[bicyclo[2.2.2]octane-2,2'-[1,3]dioxan]-7-en-6-yl)ethan-1-one (30).



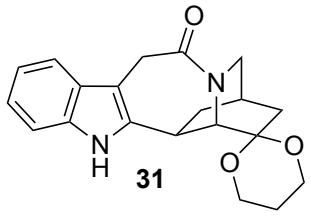
30

To a solution of **28** (1.5503 g, 5.1447 mmol), $NH_2NH_2{\cdot}H_2O$ (9.50 mL, 184 mmol) in MeOH:H_2O (30 mL:11 mL) was added KOH (9.13 g, 163 mmol). The mixture was sparged with argon under sonication for 0.5 h. The reaction mixture was then stirred under reflux for 61 h. The reaction mixture was diluted with H_2O (150 mL) and then extracted with CH_2Cl_2 (3 x 75 mL). The combined organic layers were washed with sat. aq. NaCl (75 mL), then dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue **29** was dissolved in CH_2Cl_2 (100 mL), and then NEt_3 (2.0 mL, 14 mmol), 3-indoleaceticacid (0.990 g, 5.65 mmol), EDC (1.083 g, 5.649 mmol) were added sequentially as the solution was stirred. The reaction mixture was stirred for 21 h, then

(11) Compound **28** is a 0.65:0.35 ratio of rotamers, confirmed by a NOESY NMR spectrum, NMR spectra shown for **28** are from an analytical sample obtained by HPLC

concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 0-100%, EtOAc:hexanes, gradient elution) to yield the title compound **30** (1.0895 g, 63%) as a clear oil which foams under vacuum. $\mathbf{R_f}$ = 0.40 (100%, EtOAc:hex); $\mathbf{[\alpha]_D^{25}}$ = 38.7° (*c* 0.99, $CHCl_3$); **^{1}H NMR** (600 MHz, $CDCl_3$)[12] δ 8.29 (1H, s), 7.63 (0.2H, d, *J* = 8.0 Hz), 7.57 (0.8H, d, *J* = 8.0 Hz), 7.33 (1H, dt, *J* = 8.0, 1.0 Hz), 7.21-7.15 (1H, m), 7.13-7.08 (1.8H, m), 7.03-7.00 (0.2H, m), 6.44 (1H, ddd, *J* = 7.5, 6.5, 1.0 Hz), 6.38 (1H, ddd, *J* = 8.0, 6.5, 1.5 Hz), 6.15 (0.8H, dd, *J* = 6.5, 1.0 Hz), 6.12 (0.2H, ddd, *J* = 8.0, 6.0, 1.5 Hz), 4.55 (0.2H, d, *J* = 5.5 Hz), 4.44 (0.8H, td, *J* = 12.0, 3.0 Hz), 4.05 (0.8H, td, *J* = 11.5, 3.0 Hz), 4.01 (0.2H, d, *J* = 16.0 Hz), 3.90 (0.2H, dddd, *J* = 11.5, 4.5, 3.0, 1.5 Hz), 3.87-3.78 (2H, m), 3.74 (0.9H, dd, *J* = 15.5, 1.0 Hz), 3.71 (0.9H, dd, *J* = 15.5, 1.0 Hz), 3.45 (0.8H, dd, *J* = 9.5, 2.0 Hz), 3.42 (0.2H, d, *J* = 11.5 Hz), 3.18 (0.8H, d, *J* = 9.5 Hz), 3.11 (0.2H, dt, *J* = 11.5, 2.5 Hz), 2.93-2.87 (0.2H, m), 2.80-2.74 (0.8H, m), 2.05-1.91 (1H, m), 1.85-1.78 (0.4H, m), 1.69 (1.6H, d, *J* = 3.0 Hz), 1.45 (1H, dq, *J* = 13.5, 2.5 Hz); **^{13}C NMR** (100 MHz, $CDCl_3$)[12] δ 171.2, 170.6, 136.4, 135.3, 134.9, 130.3, 129.8, 127.6, 122.8, 122.6, 122.2, 122.1, 119.5 (2 peaks), 119.0, 118.7, 111.3, 111.2, 109.8, 109.1, 102.6, 102.1, 61.5, 61.3, 61.1, 60.0, 55.9, 47.3, 46.2, 44.4, 41.1, 34.5, 32.0, 31.6, 31.3, 31.1, 25.5, 24.7; **IR** (neat, cm^{-1}) ν 3283 (br s), 2963, 2870, 1628, 1427, 1346, 1134, 1096, 1053, 980, 799, 741, 702; **HRMS (m/z)**: $[M+H]^+$ for $C_{20}H_{22}N_2O_3$, calcd, 339.17087; found, 339.17101.

Preparation of (+)-5',6',6a',9',10',13'-Hexahydro-8'H,12'H-spiro[[1,3]dioxane-2,7'-[6,9]methanopyrido[1',2':1,2]azepino[4,5-b]indol]-12'-one (31).



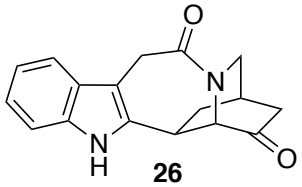
31

$PdCl_2(MeCN)_2$ (0.493, 1.90 mmol) was added to a solution of $AgBF_4$ (0.398 g, 2.05 mmol) in MeCN (20 mL). The solution was stirred for 1 h, then **30** (0.4948 g, 1.462 mmol) in MeCN (40 mL) was added. The reaction mixture was then stirred for 24.5 h at 75 °C. Then, the reaction mixture was cooled to 0 °C, then diluted with MeOH (20 mL), followed by portionwise addition of $NaBH_4$ (0.30 g). The black reaction mixture was

(12) Compound **30** is a 0.8:0.2 ratio of rotamers, confirmed by a NOESY NMR spectrum

filtered over Celite, then concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 0-100%, EtOAc:hexanes, gradient elution) to yield the known title compound **31** (0.2934 g, 59%) as a white which foams under vacuum. $\mathbf{R_f}$ = 0.40 (100%, EtOAc:hex), **m.p.** = 300 °C, $\mathbf{[\alpha]_D^{25}}$ = 42.3° (*c* 0.86, 1:1 MeOH:CH_2Cl_2); **^{1}H NMR** (400 MHz, CD_2Cl_2) δ 8.43 (1H, s), 7.48 (1H, d, *J* = 7.5 Hz), 7.27 (1H, d, *J* = 7.0 Hz), 7.09 (2H, pd, *J* = 7.0, 1.5 Hz), 4.53 (1H, s), 4.14-3.83 (5H, m), 3.77 (1H, dt, *J* = 11.5, 3.0 Hz), 3.69 (1H, d, *J* = 15.5 Hz), 3.42-3.30 (1H, m), 3.11 (1H, d, *J* = 11.4 Hz), 2.21-2.03 (3H, m), 1.83-1.72 (3H, m), 1.38-1.29 (1H, m); **^{13}C NMR** (100 MHz, CD_2Cl_2) δ 174.9, 139.2, 135.6, 128.1, 121.9, 119.9, 118.1, 110.9, 102.4, 99.1, 60.9, 60.3, 53.5, 48.4, 37.7, 33.1, 32.4, 31.3, 28.1, 25.7; **IR** (neat, cm^{-1}) ν 3256, 2932, 2870, 1636, 1458, 1427, 1350, 1246, 1142, 1111, 1096, 1053, 988, 972, 930, 737, 698; **HRMS (m/z)**: $[M+H]^+$ for $C_{20}H_{22}N_2O_3$, calcd, 339.17087; found, 339.17057.

Preparation of (-)-5,6,6a,9,10,13-hexahydro-12H-6,9-methanopyrido[1',2':1,2]azepino[4,5-b]indole-7,12(8H)-dione (26).

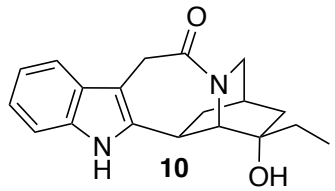


26

To a vial (20 mL) containing **31** (0.0968 g, 0.286 mmol), *p*TsOH·H_2O (0.030 g, 0.16 mmol), was added acetone:H_2O (7 mL:1.4 mL). The reaction mixture was then stirred for 171 h at 60 °C. Then, $NaHCO_3$ (0.1 g) was added to the solution. The reaction mixture was then concentrated *in vacuo.* Then, the residue was diluted with water (10 mL). The biphasic solution was extracted with CH_2Cl_2 (3 x 15 mL). The organic phases were combined, washed with sat. aq. NaCl (10 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 0-100%, EtOAc:hex, gradient elution) yielding the known title compound **26** (0.068 g, 85%) as a white solid.[9] $\mathbf{R_f}$ = 0.4 (100%, EtOAc:hex); **m.p.** = 286-287 °C; $\mathbf{[\alpha]_D^{25}}$ = -102.2° (*c* 0.59, 1:1 MeOH:CH_2Cl_2); **^{1}H NMR** (500 MHz, DMSO-d6) δ 11.08 (1H, s), 7.48 (1H, d, *J* = 8.0 Hz), 7.29 (1H, d, *J* = 8.0 Hz), 7.05 (1H, ddd, *J* = 8.0, 7.0, 1.5 Hz), 6.99 (1H, ddd, *J* = 8.0, 7.0, 1.0 Hz), 4.58 (1H, s), 4.14 (1H, dd, *J* = 15.5, 1.5 Hz), 3.82 (1H, dt, *J* = 12.0, 3.5 Hz), 3.51 (1H, d, *J* = 15.5 Hz), 3.41 (1H, dd, *J* = 10.5, 6.0 Hz), 3.12 (1H, d, *J* = 12.5 Hz), 2.71 (1H, dt, *J* = 19.0, 2.5 Hz), 2.54-2.47 (1H, m), 2.44 (1H, s), 2.35 (2H, tdd, *J* =

11.0, 3.5, 2.5 Hz), 1.39 (1H, ddt, *J* = 13.5, 6.0, 2.5 Hz); **^{13}C NMR** (125 MHz, DMSO-d6) δ 206.9, 174.4, 137.4, 135.1, 127.2, 120.9, 118.7, 117.6, 110.8, 100.7, 59.8, 49.8, 41.9, 32.6, 32.2, 31.0, 27.5; **IR** (neat, cm^{-1}) ν 2926, 2855, 1742, 1634, 1559, 1456, 1408, 1325, 1279, 1229, 1134, 1109, 978, 737, 702; **HRMS (m/z)**: $[M+H]^+$ for $C_{17}H_{16}N_2O_2$, calcd, 281.12900; found, 281.12842.

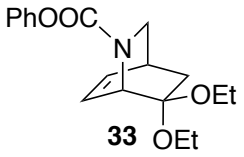
Preparation of (-)-7-ethyl-7-hydroxy-5,6,6a,7,8,9,10,13-octahydro-12H-6,9-methanopyrido[1',2':1,2]azepino[4,5-b]indol-12-one (10).



10

Ethynyl magnesium bromide (0.5 M, 1.0 mL, 0.50 mmol) was added to a stirred solution of **26** (0.0199 g, 0.0710 mmol) and THF (1 mL), at 0 °C. The reaction mixture was stirred for 3 h at 0 °C. The reaction was quenched with sat. aq. NH_4Cl (10 mL), then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with sat. aq. NaCl (10 mL), then dried ($MgSO_4$), and concentrated *in vacuo*. PtO_2 (0.5 mg, 0.002 mmol) was added to the residue, and the round-bottomed flask was purged with N_2, then MeOH (2.5 mL) was added. The flask was purged with a H_2, and then the solution was stirred for 16 h under a H_2 atmosphere. Then, the reaction solution was filtered over Celite, and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 0-10%, MeOH:CH_2Cl_2, gradient elution) yielding the title compound **10** (0.0176 mg, 80%) as a white solid. $\mathbf{R_f}$ = 0.25 (5%, MeOH:CH_2Cl_2); **m.p.** = decomposition at 250-255 °C, $\mathbf{[\alpha]_D^{25}}$ = -38° (*c* 0.70, EtOH); **^{1}H NMR** (500 MHz, DMSO-d6) δ 10.96 (1H, s), 7.45 (1H, d, *J* = 7.5), 7.27 (1H, dt, *J* = 8.0, 1.0 Hz), 7.10-6.89 (2H, m), 4.70 (1H, s), 3.96 (1H, dd, *J* = 15.0, 2.0 Hz), 3.89 (1H, s), 3.61 (1H, dd, *J* = 10.5, 6.5 Hz), 3.53 (1H, ddd, *J* = 11.5, 4.0, 2.5 Hz), 3.49 (1H, d, *J* = 15.5 Hz), 2.94 (1H, d, *J* = 12.0 Hz), 2.16 (1H, dddd, *J* = 13.0, 10.5, 4.0, 2.0 Hz), 1.98 (1H, s), 1.75 (1H, ddd, *J* = 13.5, 4.5, 2.5 Hz), 1.67-1.51 (3H, m), 1.16 (1H, ddt, *J* = 13.0, 6.5, 2.0 Hz), 0.95 (3H, t, *J* = 7.5 Hz); **^{13}C NMR** (125 MHz, DMSO-d6) δ 174.4, 140.3, 135.0, 127.4, 120.5, 118.5, 117.4, 110.6, 100.4, 71.1, 55.8, 48.1, 39.1, 34.0, 32.4, 32.3, 29.4, 27.1, 7.2; **IR** (neat, cm^{-1}) ν 3295, 2932, 1636, 1458, 1420, 1339, 1277, 1150, 1134, 976, 957, 741; **HRMS (m/z)**: $[M+H]^+$ for $C_{19}H_{22}N_2O_2$, calcd, 311.17595; found, 311.17539.

Preparation of (+)-phenyl (1*S*,4*S*)-7,7-diethoxy-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (33)

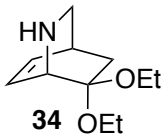


33

A vial was charged with **21** (0.1918 g, 0.7885 mmol), EtOH (1.5 mL), triethylorthoformate (3.0 mL), and *p*TsOH·H_2O (0.0300 mg, 0.158 mmol). The vial was purged with argon, and the solution was stirred at 70 °C for 20 h. K_2CO_3 (0.2 g) was added and the reaction mixture was stirred for 0.5 h. The solution was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (neutral alumina Brockmann grade 1, 0-100%, EtOAc:hexanes, gradient elution) to yield **33** (0.2263 g, 90%) as a clear oil. $\mathbf{R_f}$ = 0.37 (20%, EtOAc:hex); $\mathbf{[\alpha]_D^{25}}$ = + 51.5°(*c* 0.90, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$)[13] δ 7.38-7.30 (2H, m), 7.17 (1H, tdt, *J* = 7.5, 6.5, 1.0 Hz), 7.13-7.08 (2H, m), 6.51-6.37 (2H, m), 4.96-4.94 (0.4H, m), 4.92 (0.6H, dd, *J* = 6.0, 1.5 Hz), 3.75-3.61 (1H, m), 3.59-3.36 (4H, m), 3.22 (0.6H, dt, *J* = 10.0, 2.5 Hz), 3.09 (0.4H, dt, *J* = 10.5, 2.0 Hz), 2.85 (1H, qq, *J* = 5.5, 2.5 Hz), 1.82 (0.6H, dt, *J* = 13.0, 3.0 Hz), 1.77-1.69 (0.8H, m), 1.66 (0.6H, dd, *J* = 13.0, 2.5 Hz), 1.22 (1.2H, t, *J* = 7.0 Hz), 1.18 (1.8H, t, *J* = 7.0 Hz), 1.15 (3H, td, *J* = 7.0, 1.0 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 154.0, 153.5, 151.6, 134.6, 133.9, 131.6, 130.7, 129.3 (2 peaks), 125.2, 125.1, 121.8, 104.8, 104.5, 56.9, 56.7, 56.0, 55.8, 51.8, 50.6, 46.7, 46.4, 36.7, 36.5, 31.6, 31.2, 15.5 (2 peaks), 15.3 (2 peaks); **IR** (neat, cm^{-1}) ν 2974, 2734, 2884, 1721, 1495, 1402, 1335, 1296, 1269, 1207, 1163, 1126, 1055, 991, 966, 839, 750, 723; **HRMS** (m/z): $[M+H]^+$ for $C_{18}H_{23}NO_4$, calcd, 318.17053; found, 318.17138.

(13) Compound **33** is a 0.6:0.4 ratio of rotamers, confirmed by a NOESY NMR spectrum, NMR spectra shown for **33** are from an analytical sample obtained by HPLC

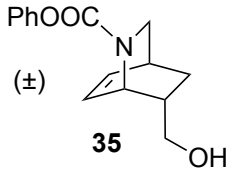
Preparation of (+)-(1S,4S)-7,7-diethoxy-2-azabicyclo[2.2.2]oct-5-ene (34)



34

To a solution of **33** (0.0278 g, 0.0876 mmol), $NH_2NH_2 \cdot H_2O$ (0.10 mL, 2.1 mmol) in MeOH:H_2O (0.75 mL:0.25 mL) was added KOH (0.1007 g, 1.795 mmol). The reaction vessel was purged with argon. The reaction mixture was then subjected to μwave irradiation to maintain a temperature of 140 °C for 1 h 10 mins. The reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (neutral alumina Brockmann grade 1, 0-20%, MeOH:CH_2Cl_2, gradient elution) to yield **34** (0.0070 g, 41%) as a clear oil. $\mathbf{R_f}$ = 0.075 (10%, MeOH:CH_2Cl_2), $\mathbf{[\alpha]_D^{25}}$ = -27.3° (*c* 0.70, MeOH); **^{1}H NMR** (500 MHz, CD_3OD) δ 6.70 (1H, t, *J* = 7.5 Hz), 6.32 (1H, ddd, *J* = 7.5, 6.0, 1.5 Hz), 4.29 (1H, dd, *J* = 6.0, 1.0 Hz), 3.70-3.39 (4H, m), 3.14 (1H, dd, *J* = 11.0, 2.0 Hz), 3.03 (1H, s), 2.74 (1H, dt, *J* = 11.0, 2.5 Hz), 1.96 (1H, dd, *J* = 13.5, 3.0 Hz), 1.60 (1H, dt, *J* = 13.4, 3.1 Hz), 1.25 (3H, t, *J* = 7.1 Hz), 1.13 (3H, t, *J* = 7.1 Hz); **^{13}C NMR** (150 MHz, CD_3OD) δ 139.2, 127.5, 102.6, 58.5, 57.7, 52.5, 49.0, 43.4, 36.3, 30.8, 15.4; **IR** (neat, cm^{-1}) 3200 (br), 3063, 2926, 1603, 1497, 1481, 1396, 1260, 1125, 1099, 1053, 964, 802, 752; **IR** (neat, cm^{-1}) ν 3200 (br), 3063, 2926, 1603, 1497, 1481, 1396, 1260, 1125, 1099, 1053, 964, 82, 802, 752; **HRMS (m/z)**: $[M+H]^+$ for $C_{11}H_{19}N_1O_2$, calcd, 198.14940; found, 198.15036.

Preparation of (±)-phenyl (1*S,4*S**,7*S**)-7-(hydroxymethyl)-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate ((±)-35).**



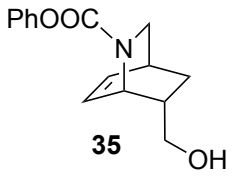
35

To a stirred solution of **18** (0.110 g, 0.547 mmol) in MeCN:H_2O (1.2 mL:0.05 mL) was added acrolein (0.10 mL, 1.6 mmol). Then, (±)-2-amino-3-methyl-1,1-diphenylbutan-1-ol·TFA (0.0202 g, 0.0547 mmol)[14] was added. The reaction mixture

(14) Synthesized by the method of Nakano, H.; Osone, K.; Takeshita, M.; Kwon, E.; Seki, C.; Matsuyama, H.; Takano, N.; Kohari, Y. *Chem. Commun.* **2010**, *46*, 4827–4829.

was stirred for 30 h at 0 °C, diluted with H_2O (10 mL), and then extracted with Et_2O (3 x 10 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The crude residue was diluted with EtOH (20 mL), and then cooled to 0 °C. $NaBH_4$ (100 mg, 2.6 mmol) was added, and the reaction mixture was stirred for 1 h. The reaction mixture was concentrated *in vacuo*. The crude residue was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 0-100%, EtOAc:hex, gradient elution) yielding the known title compound **35** (0.0372 g, 26%) as a viscous clear oil. Characterization data are shown below.

Preparation of (+)-phenyl (1*S*,4*S*,7*S*)-7-(hydroxymethyl)-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate ((+)-35).



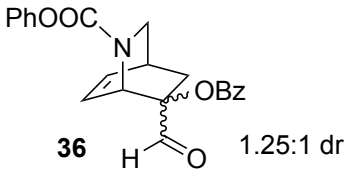
35

A portion of crude **20** (200 mg, from the above preparation) was diluted with EtOH (20 mL), and then cooled to 0 °C. $NaBH_4$ (50 mg, 1.3 mmol) was added to the solution. The reaction mixture was stirred for 1 h. The reaction mixture was concentrated *in vacuo*. The crude residue was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 0-100%, EtOAc:hex, gradient elution) yielding the known compound **(+)-35** (0.0863 g)[15] as a viscous clear oil. The enantiomeric excess (ee) was determined by HPLC (DAICEL Chiralcel AD-H), 0.5 mL/min, n-hexane:2-propanol 9:1 to 1:9 gradient over 60 min, 94% ee; $[\alpha]_D^{25}$ = +87.5° (*c* = 1.10, $CHCl_3$, lit = +95.0 for > 95% ee/21°C)[16]; **^{1}H NMR** (500 MHz, $CDCl_3$)[17] δ 7.34 (2H, ddd, *J* = 8.5, 7.5, 2.5 Hz), 7.17 (1H, td, *J* = 7.5, 1.0 Hz), 7.14-7.01 (2H, m), 6.46 (1H, dddd, *J* = 8.0, 6.0, 4.0, 1.5 Hz), 6.38 (1H, dddd, *J* = 8.0, 5.5, 4.0, 1.5 Hz), 5.02-4.96 (0.4H, m), 4.91 (0.6H, ddt, *J* = 6.0, 3.0, 1.5 Hz), 3.47 (0.6H, dd, *J* = 10.5, 2.0 Hz), 3.36-3.26 (1.5H, m), 3.18 (1.5H, ddd, *J* = 10.5, 6.5, 4.0 Hz), 3.07 (0.4H,

(15) Nakano, H.; Osone, K.; Takeshita, M.; Kwon, E.; Seki, C.; Matsuyama, H.; Takano, N.; Kohari, Y. *Chem. Commun.* **2010**, *46*, 4827–4829.
(16) M. Hatano, M.; Goto, Y.; Izumiseki, A.; Akakura, M.; Ishihara, K. *J. Am. Chem. Soc.* **2015**, *137*, 13472-13475.
(17) Compound **(+)-35** is a 0.6:0.4 ratio of rotamers

dt, *J* = 10.5, 2.5 Hz), 2.80 (1H, m), 2.49-2.34 (1H, m), 2.10 (1H, s), 1.82 (1H, ddt, *J* = 13.0, 9.5, 3.0 Hz), 0.86 (1H, dddt, *J* = 18.0, 13.0, 5.5, 3.0 Hz); **^{13}C NMR** (125 MHz, $CDCl_3$)[17] δ 153.8, 153.3, 151.5 (2 peaks), 135.3, 134.9, 130.6, 130.1, 129.30 (2 peaks), 125.2, 121.9, 121.9, 65.7, 65.6, 48.0, 47.6, 47.5, 47.2, 41.7, 41.6, 31.0, 30.7, 26.3, 26.2.

Preparation of phenyl (1*S*,4*S*,7*R*)-7-(benzoyloxy)-7-formyl-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate and phenyl (1*S*,4*S*,7*S*)-7-(benzoyloxy)-7-formyl-2-azabicyclo[2.2.2]oct-5-ene-2-carboxylate (36)).

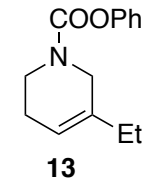


36 1.25:1 dr

O-benzoylhydroxylamine (1.050 g, 3.83 mmol)[18] was added to a stirred solution of **20** (0.984 g, 3.82 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 17.5 h and then diluted with water (50 mL). The biphasic solution was extracted with CH_2Cl_2 (3 x 50 mL). The organic phases were combined, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, 0-100%, EtOAc:hex, gradient elution) yielding **36** as an inseparable mixture of diastereomers (1.027 g, 71%) as an orange oil. **R_f** = 0.33 (33%, EtOAc:Hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$)[19] δ 10.33-9.06 (m, 1H), 8.20-6.97 (m, 11H), 6.81-5.16 (m, 2H), 4.67-3.95 (m, 1H), 3.91-2.82 (m, 2H), 2.72-1.03 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$)[19] δ 197.7, 197.2, 195.4, 195.3, 192.1, 170.6, 166.2, 166.1, 165.1, 154.8, 154.5, 153.3, 153.2, 151.3, 151.1, 150.9, 150.8, 139.4, 137.8 (2 peaks), 136.8, 135.7, 135.6, 133.9 (2 peaks), 133.7, 133.6, 133.4, 133.3, 130.2, 130.1, 130.0, 129.7 (2 peaks), 129.5 (2 peaks), 129.4 (2 peaks), 129.3 (3 peaks), 129.2 (2 peaks), 128.8, 128.7, 128.7, 128.6 (2 peaks), 128.5 (2 peaks), 128.4 (2 peaks), 127.9, 127.5, 125.8, 125.6, 125.5 (2 peaks), 125.4, 125.3, 124.3, 124.1, 121.7 (2 peaks), 121.5 (3 peaks), 121.4, 116.0, 86.6, 86.2, 68.5, 68.2, 67.2, 67.1, 53.5, 53.1, 50.2, 49.4, 47.0, 46.9, 46.8, 44.7, 35.0, 34.4, 33.8, 33.7, 32.5, 32.0, 30.9, 30.5; **IR** (neat, cm^{-1}) ν 2067, 2959, 2884, 1720, 1600, 1563, 1493, 1451, 1393, 1342, 1267, 1205, 1104, 1025, 750, 712; **HRMS (m/z)**: $[M+H]^+$ for $C_{22}H_{19}NO_5$, calcd, 378.13415; found, 378.13413.

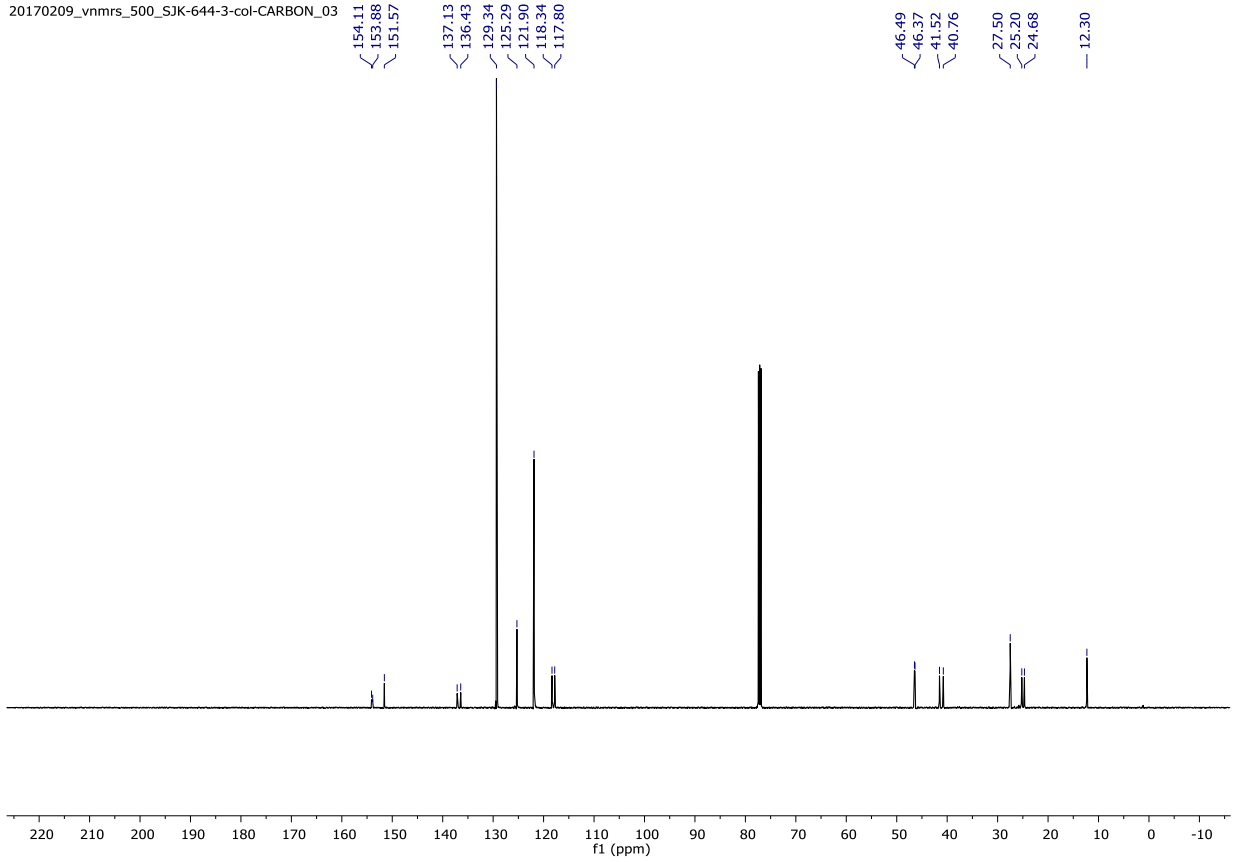
(18) Beshara, C. S.; Hall, A.; Jenkins, R. L.; Jones, K. L.; Jones, T. C.; Killeen, N. M.; Taylor, P. H.; Thomas, S. P.; Tomkinson, N. C. O. *Org. Lett.* **2005**, *7*, 5729–5732.
(19) The 5:4 mixture of diastereomers of **36** are both rotameric, 3 and 2 rotamers respectively

20170209_vnmrs_500_SJK-644-3-col-PROTON_01

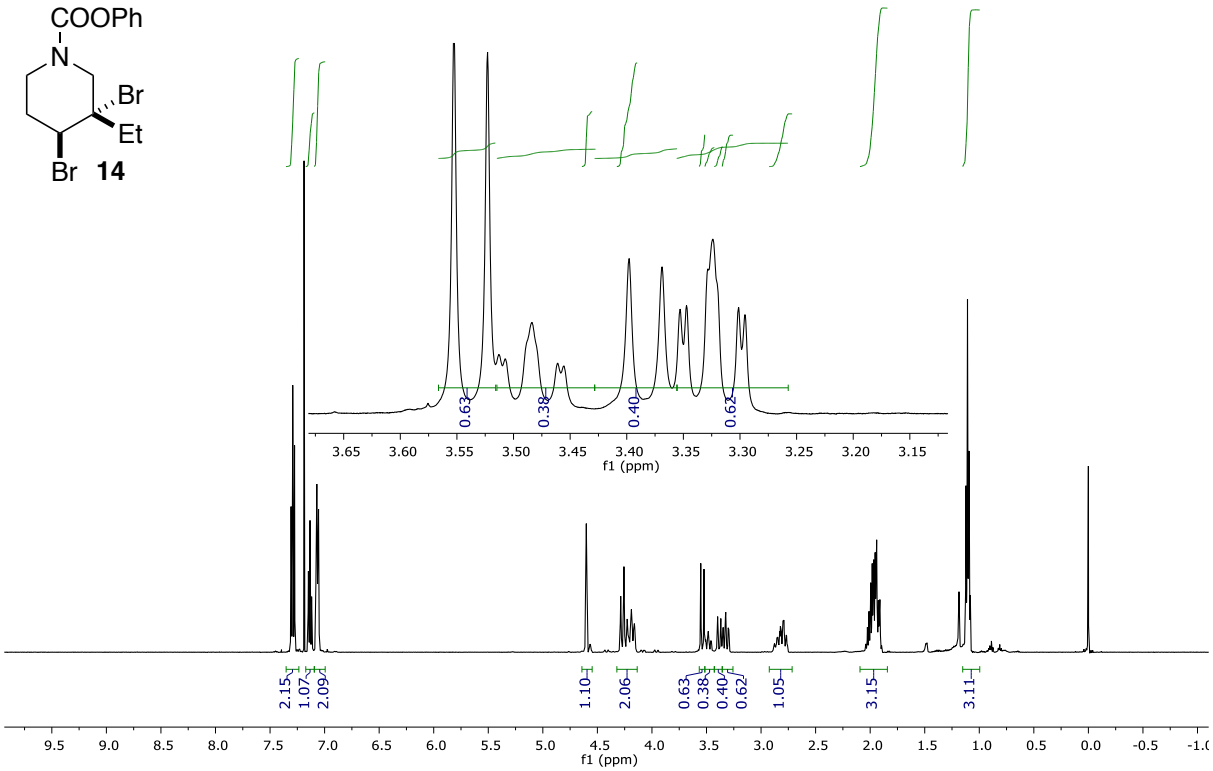


13

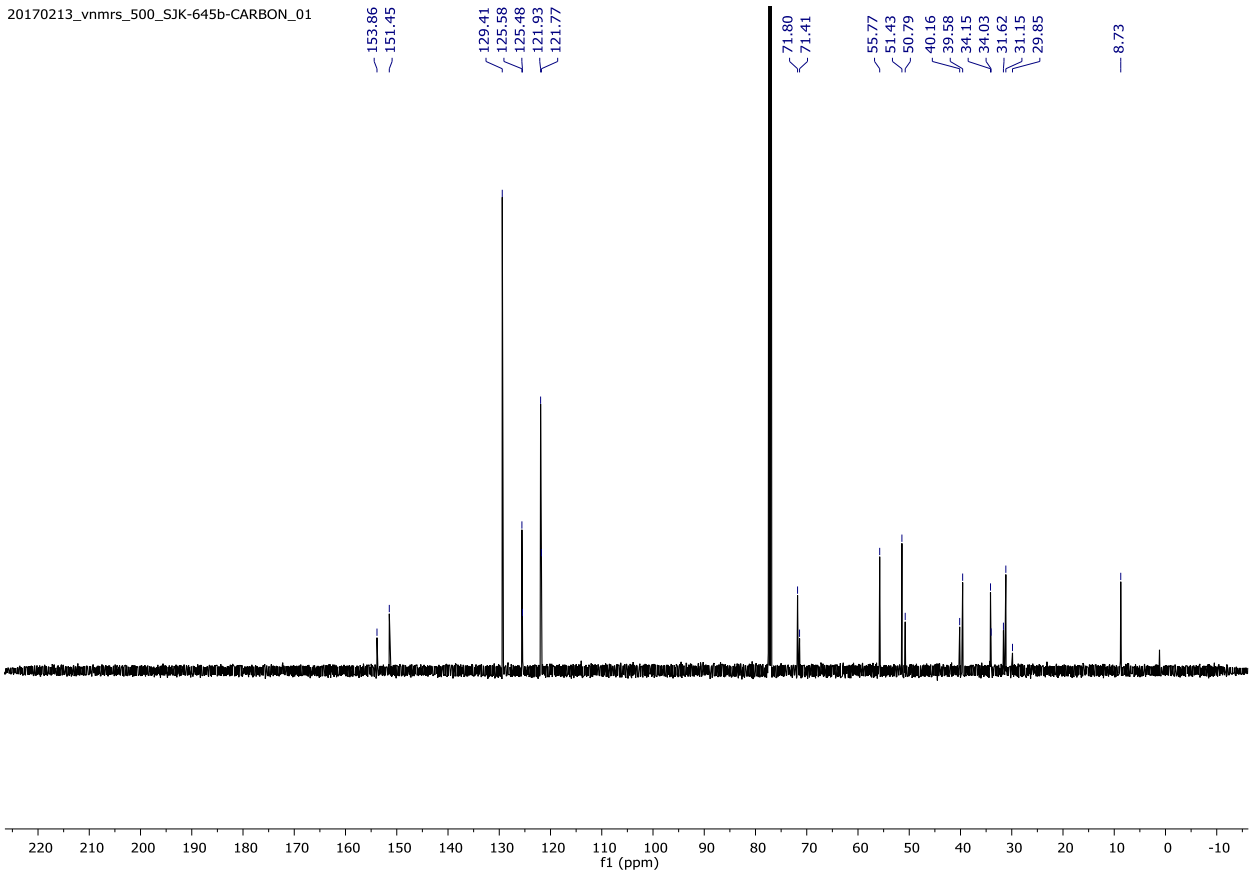
20170209_vnmrs_500_SJK-644-3-col-CARBON_03



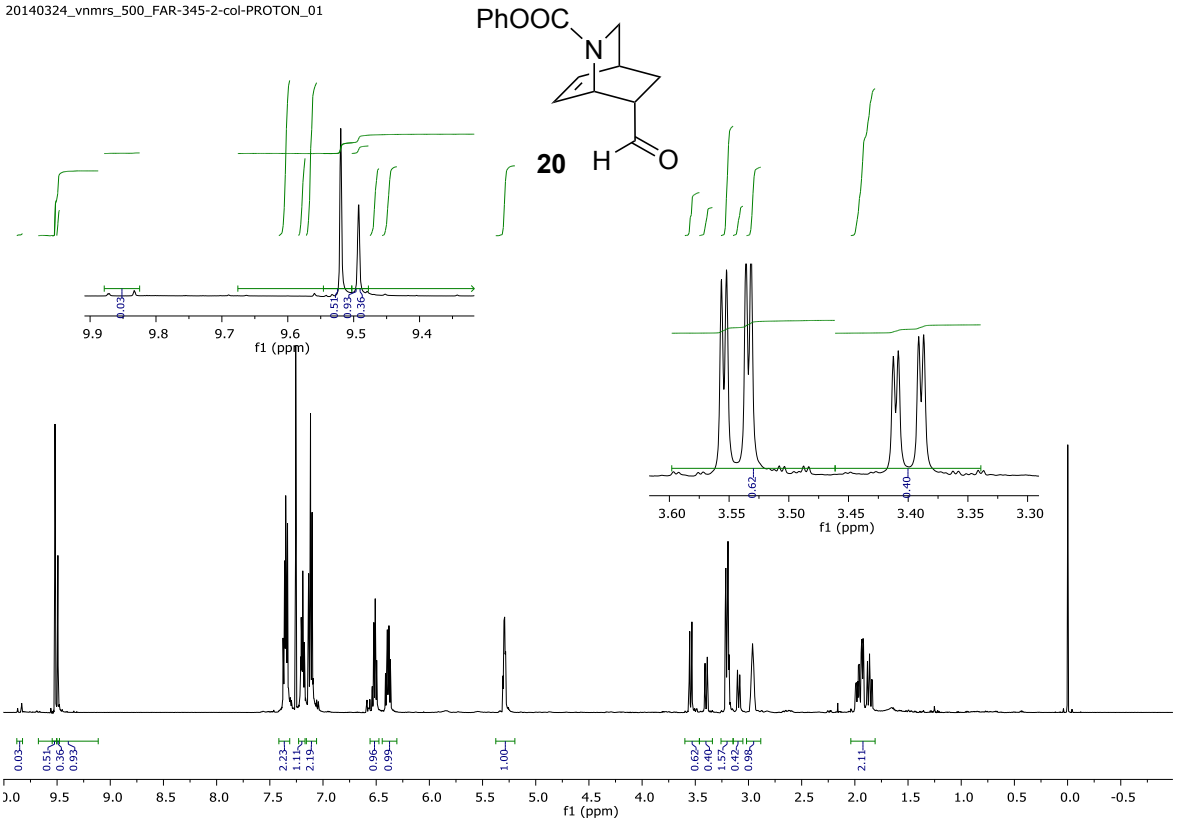
20170213_vnmrs_500_SJK-645b-PROTON_01



20170213_vnmrs_500_SJK-645b-CARBON_01



20140324_vnmrs_500_FAR-345-2-col-PROTON_01



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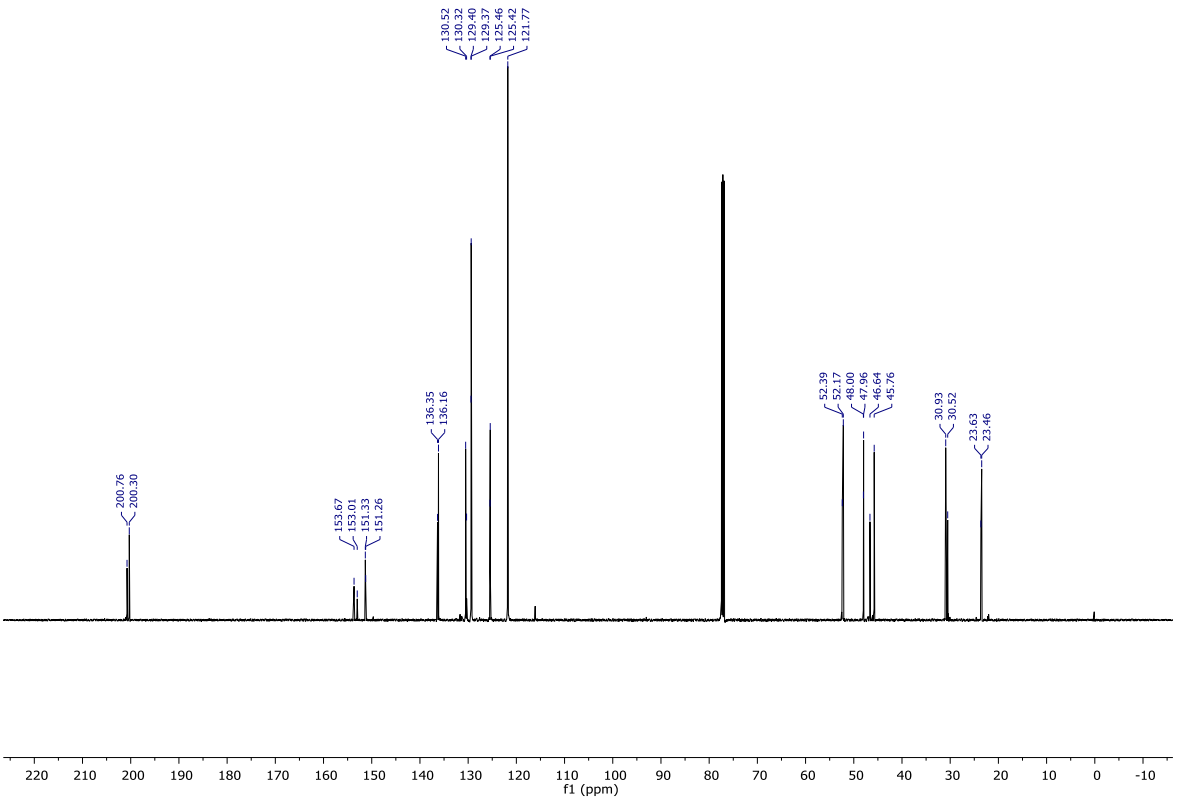
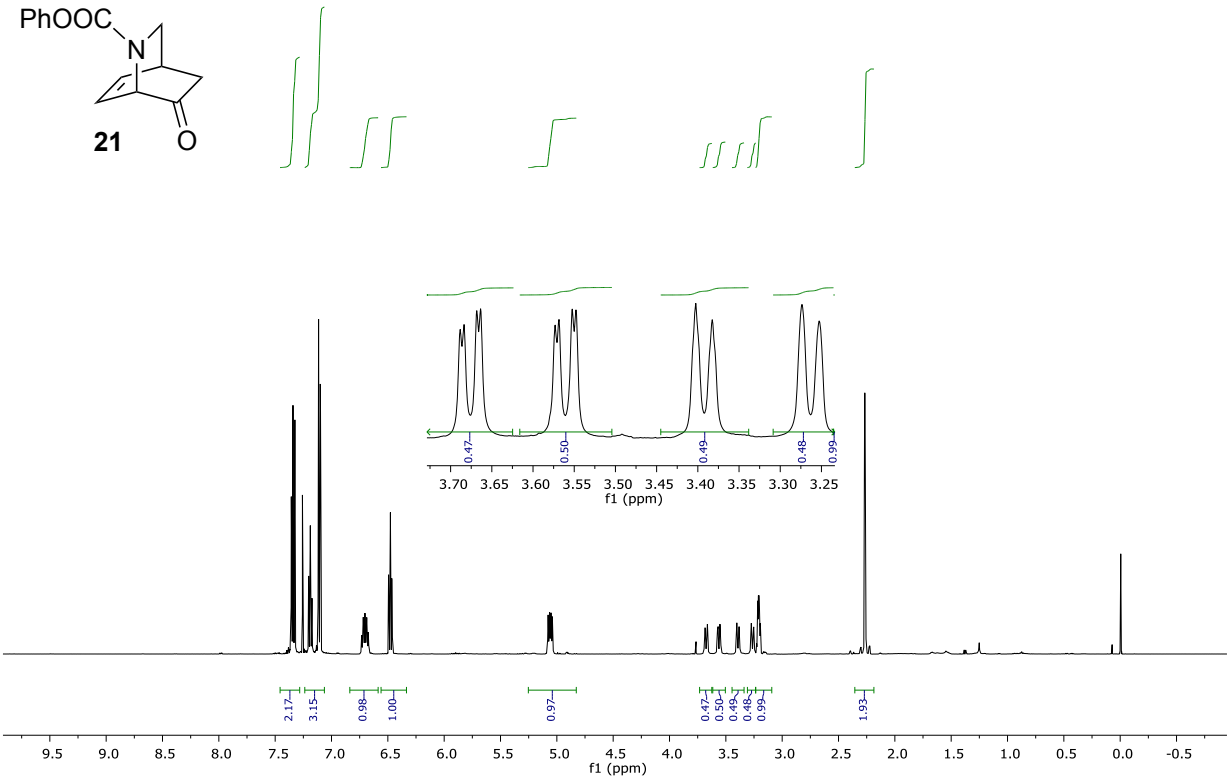
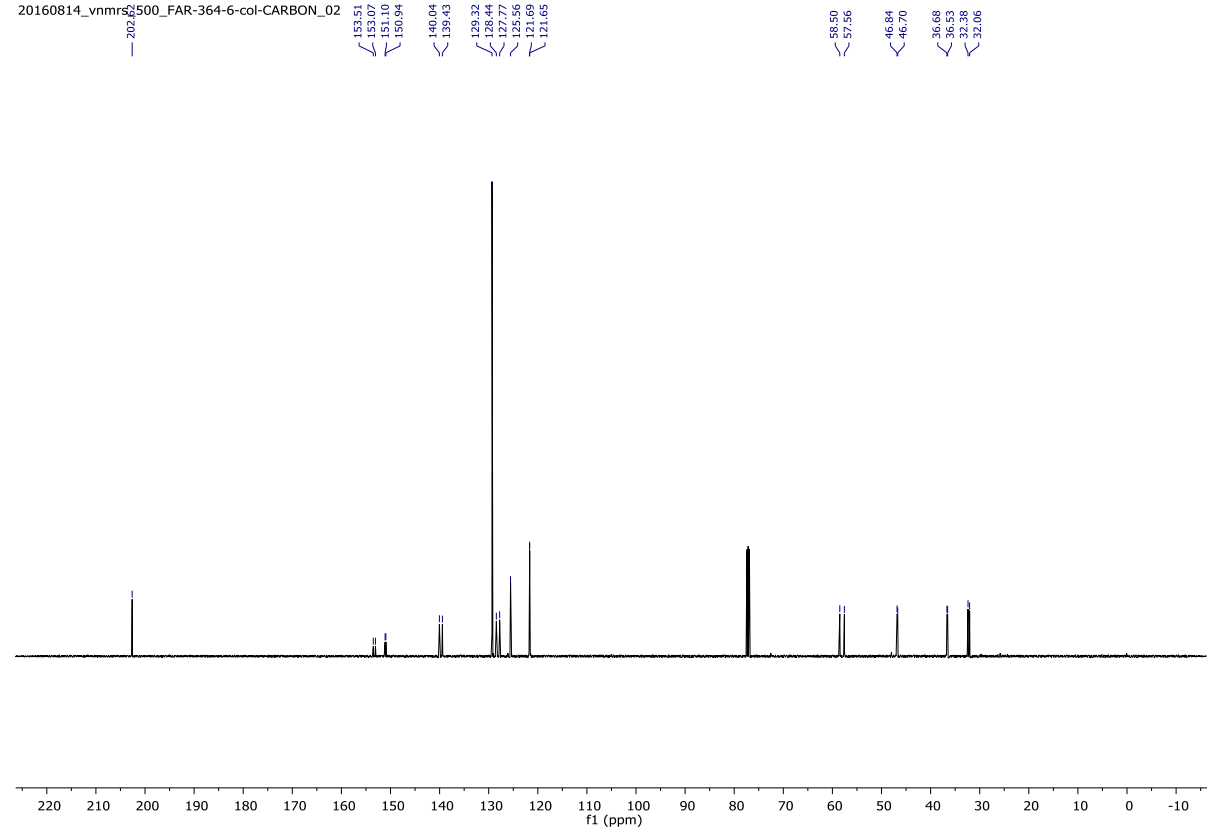
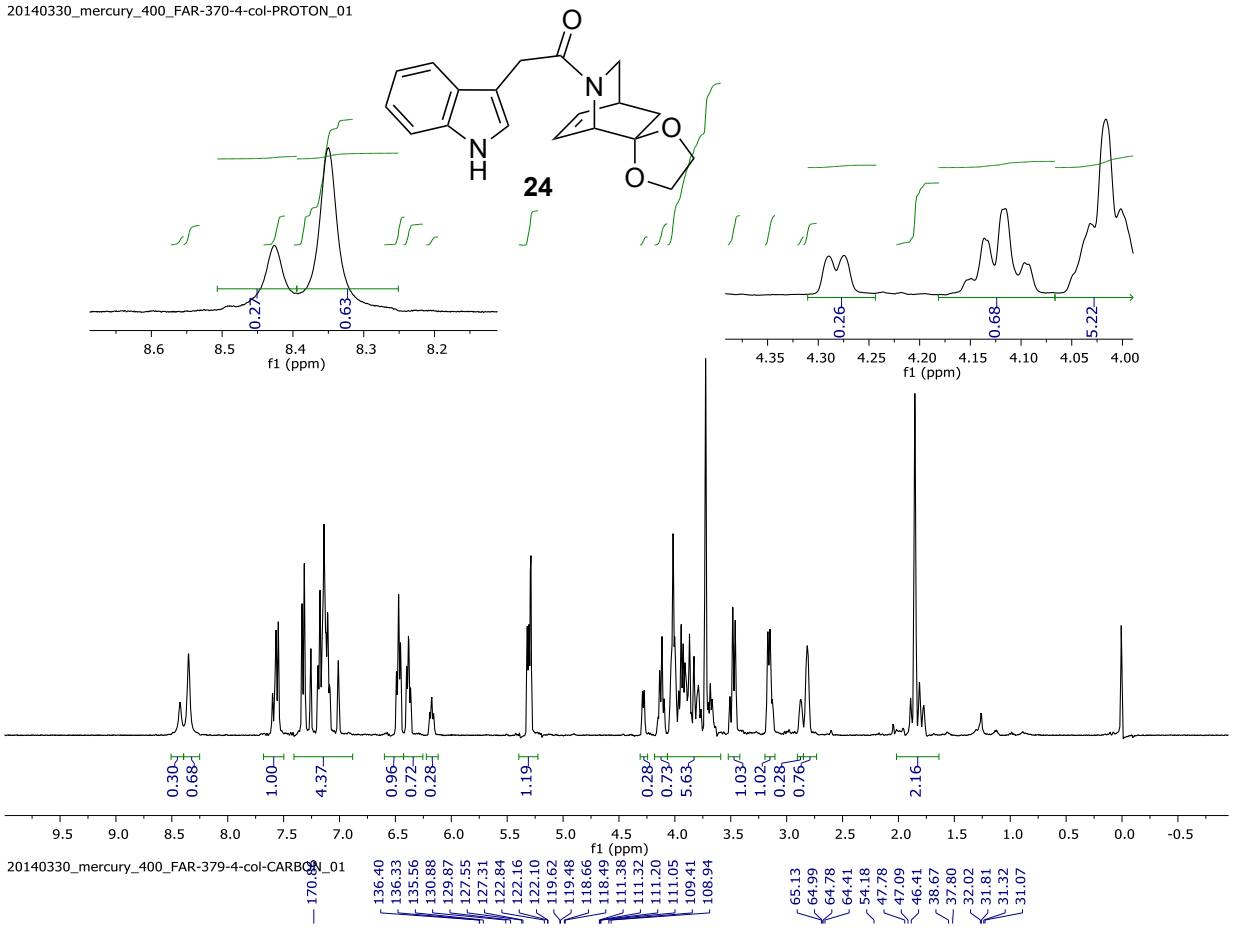


20160814_vnmrs_500_FAR-364-5-col-PROTON_01



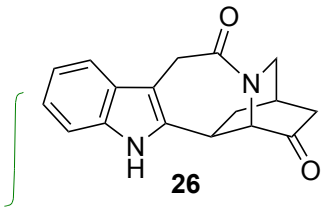
20160814_vnmrs_500_FAR-364-6-col-CARBON_02



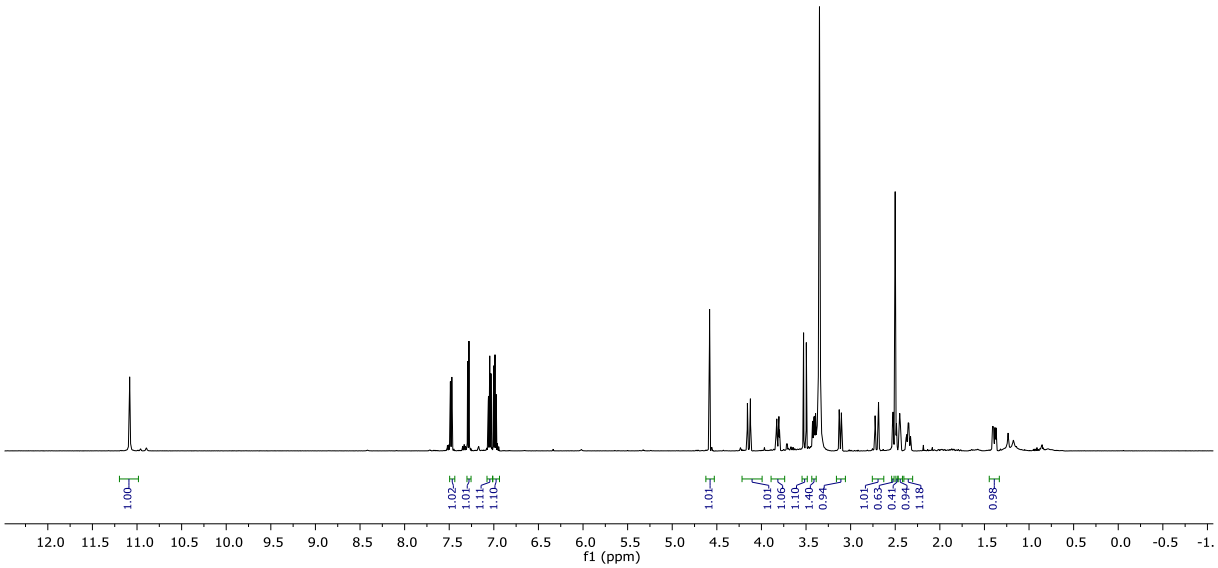

20140330_mercury_400_FAR-370-4-col-PROTON_01
24
f1 (ppm)

20140330_mercury_400_FAR-379-4-col-CARBON_01
f1 (ppm)

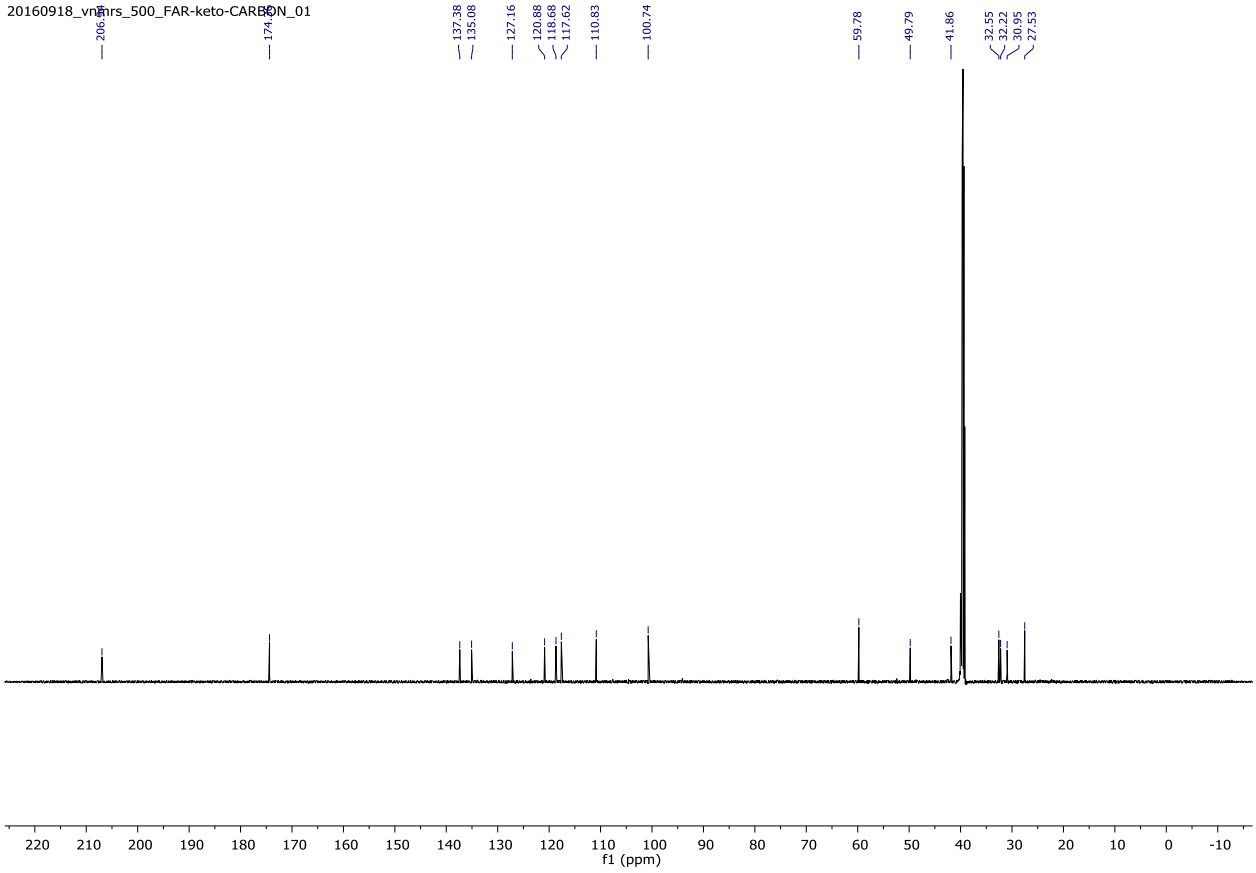
20160918_vnmrs_500_FAR-keto-PROTON_01

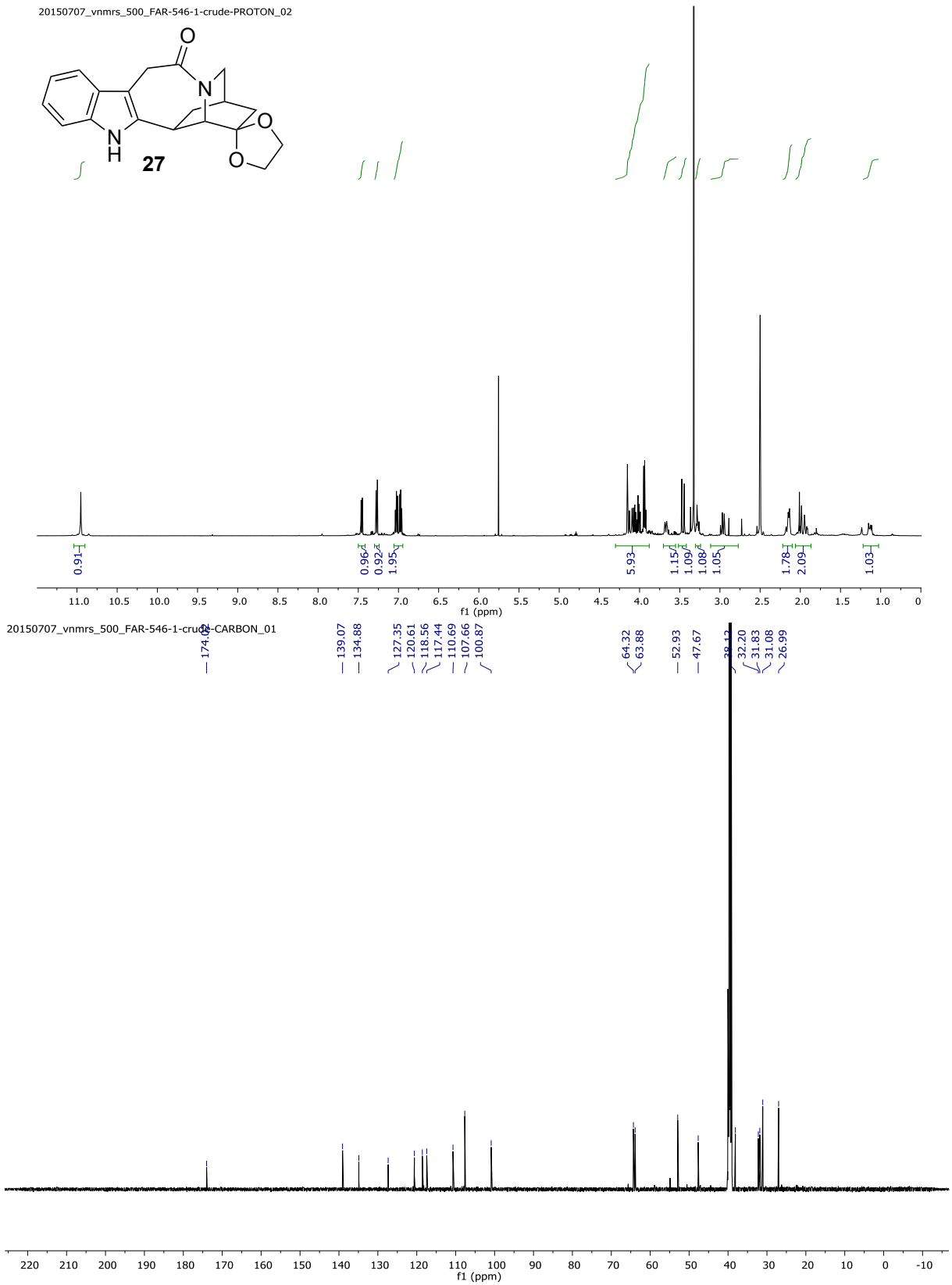


26



20160918_vnmrs_500_FAR-keto-CARBON_01

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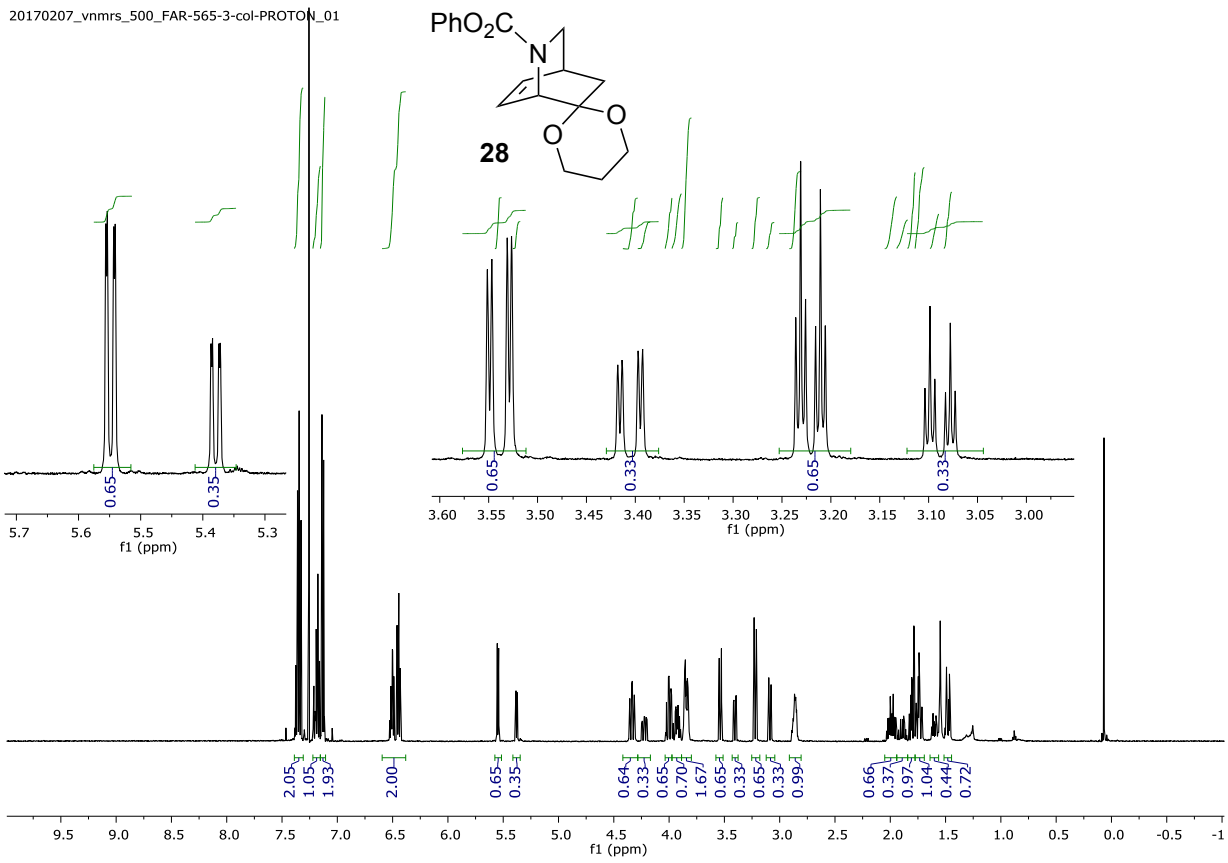
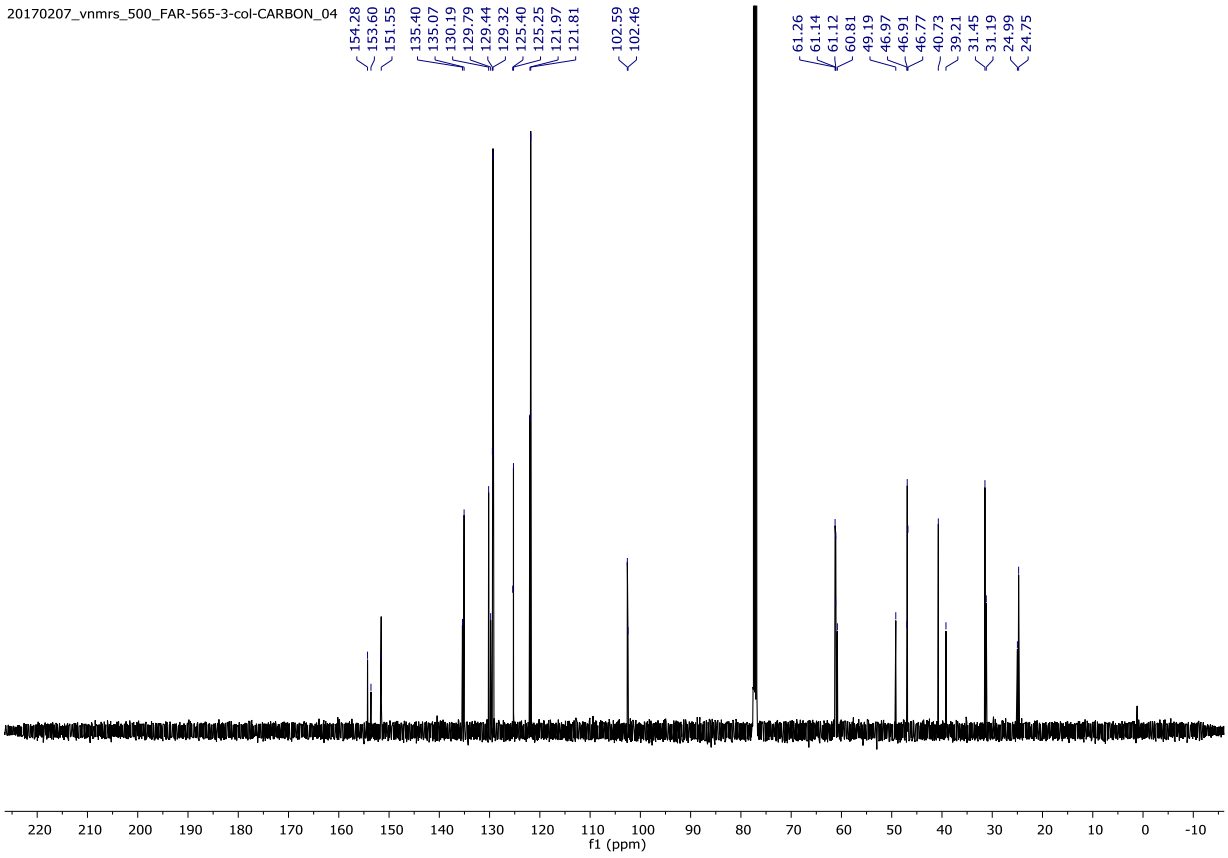
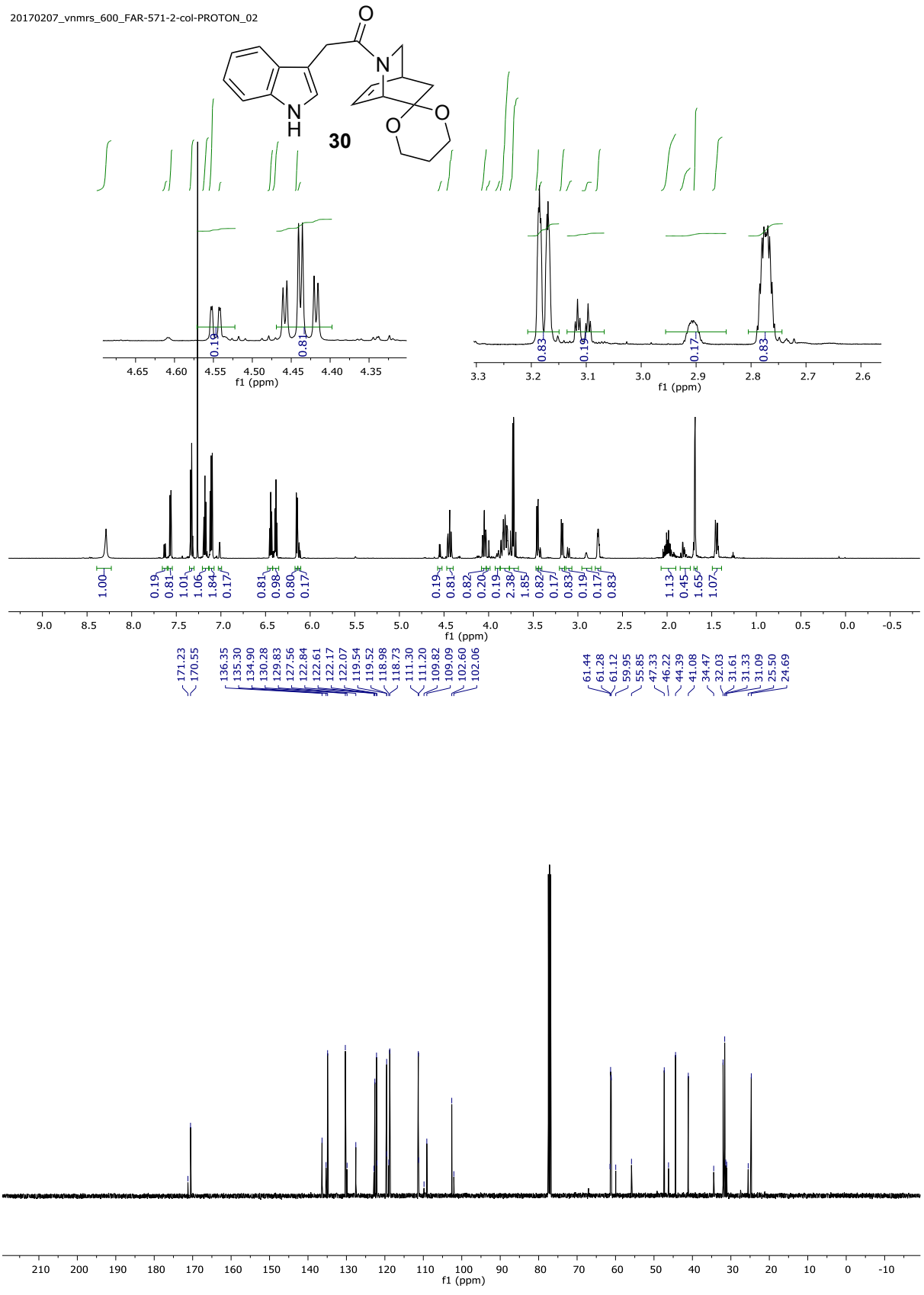
O
N
N
H
O
O
27
0.91
0.96
0.92
1.95
5.93
1.15
1.09
1.08
1.05
1.78
2.09
1.03
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0
f1 (ppm)
20150707_vnmrs_500_FAR-546-1-crude-CARBON_01
174.02
139.07
134.88
127.35
120.61
118.56
117.44
110.69
107.66
100.87
64.32
63.88
52.93
47.67
32.20
31.83
31.08
26.99
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


20170207_vnmrs_500_FAR-565-3-col-PROTON_01
PhO2C
N
O
O
28
f1 (ppm)


20170207_vnmrs_500_FAR-565-3-col-CARBON_04
f1 (ppm)


20170207_vnmrs_600_FAR-571-2-col-PROTON_02
30
f1 (ppm)

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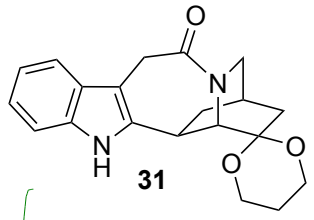
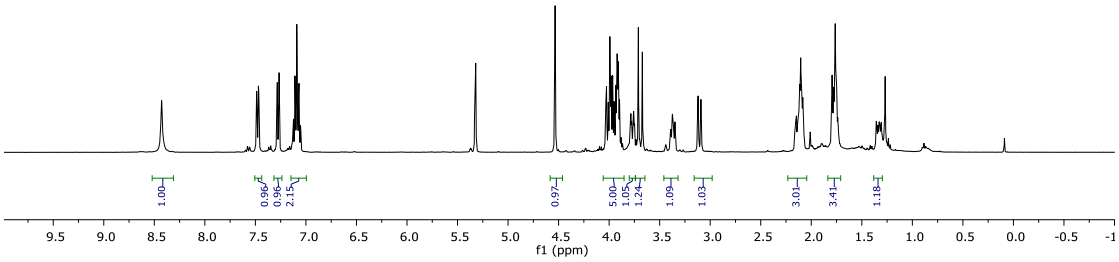


31

in CD_2Cl_2



FAR-577-2-col.2.fid
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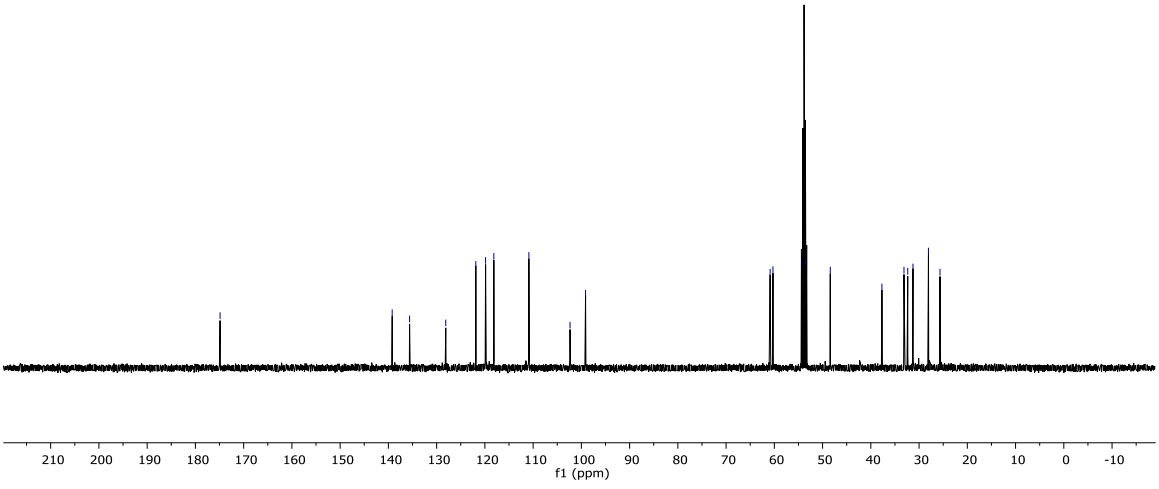
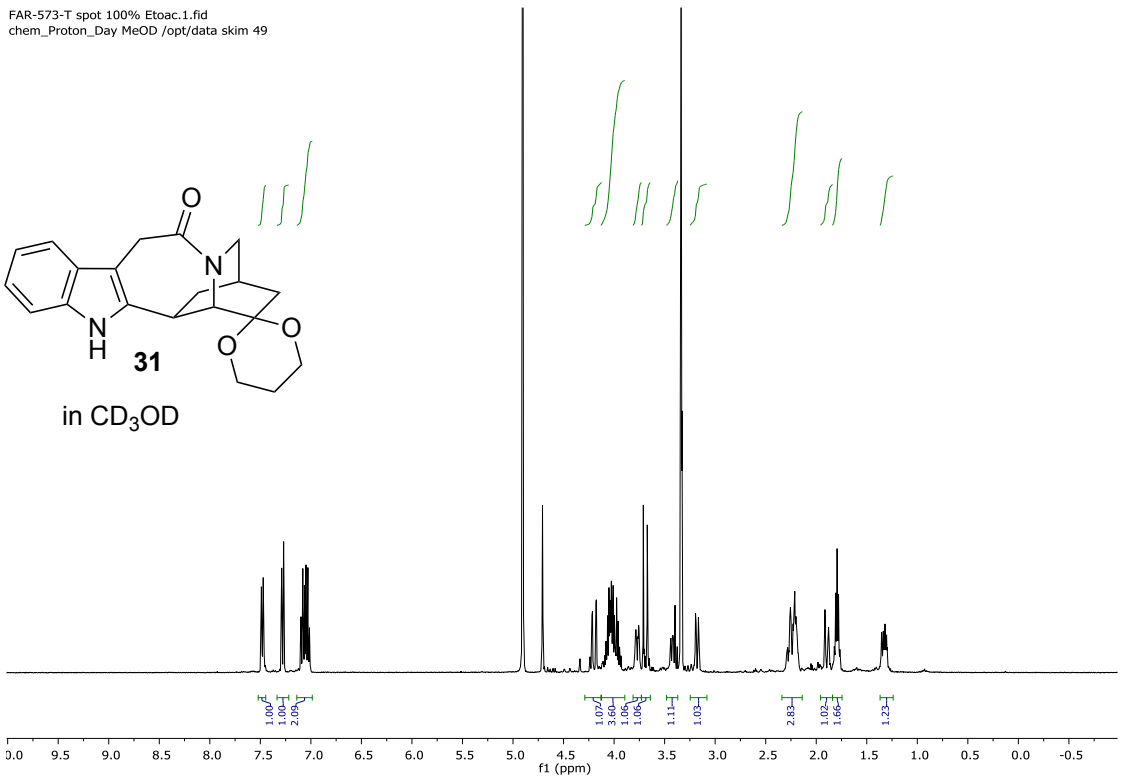
175.89
139.21
135.61
128.11
121.88
119.85
118.14
110.88
102.35
99.13
60.87
60.29
53.51
48.41
37.70
33.13
32.35
31.26
28.05
25.66

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O
N
N
H
O
O
31
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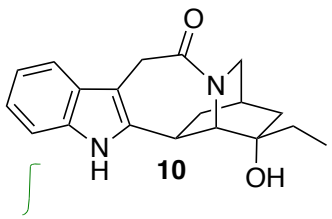
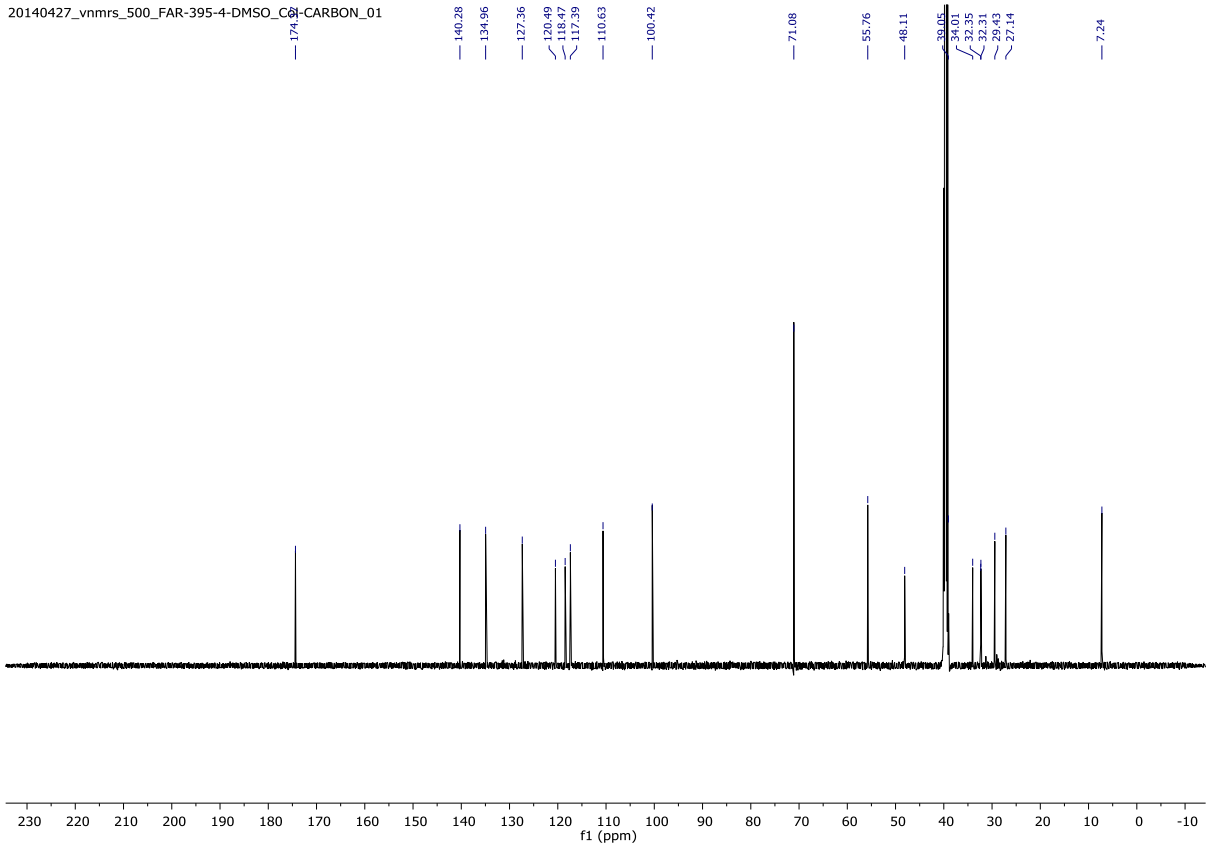
2.09
1.07
3.61
1.06
1.06
1.11
1.03
2.83
1.02
1.66
1.23
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

20140427_vnmrs_500_FAR-395-4-DMSO_Col-PROTON_01

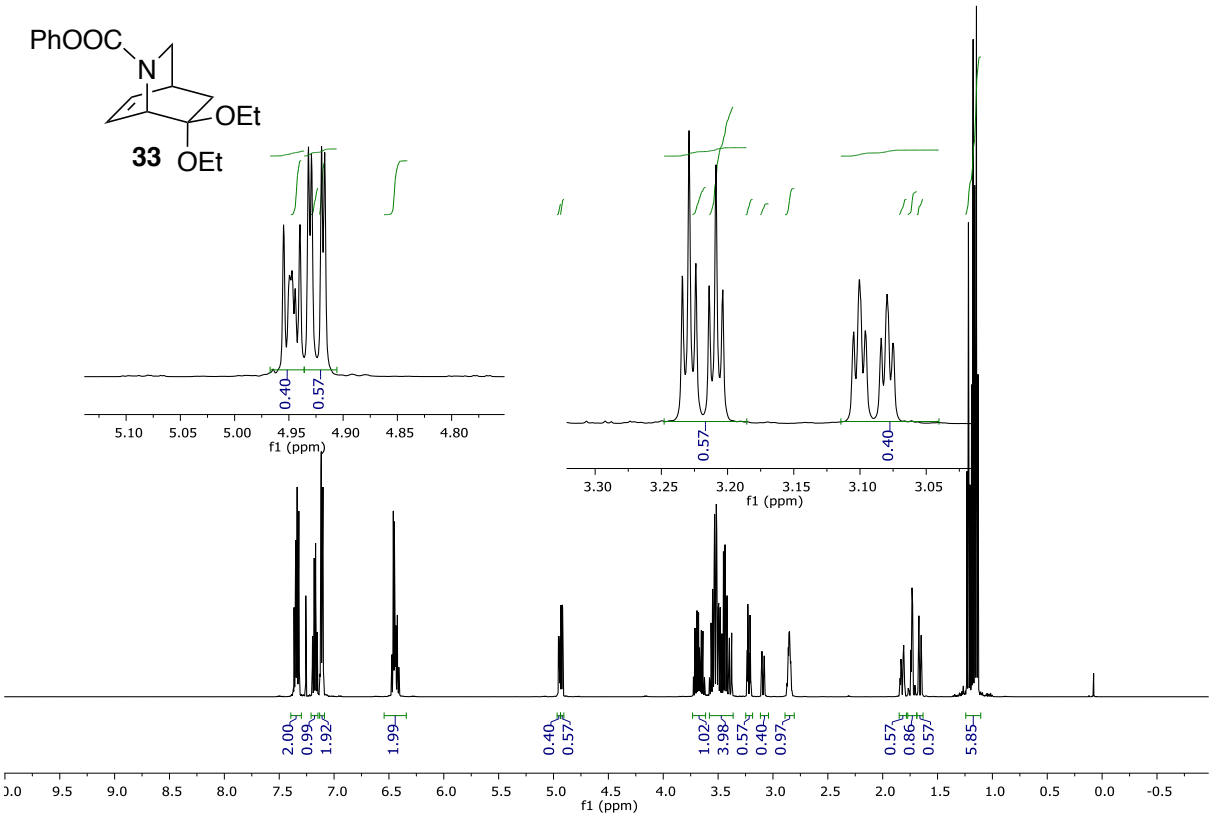


10

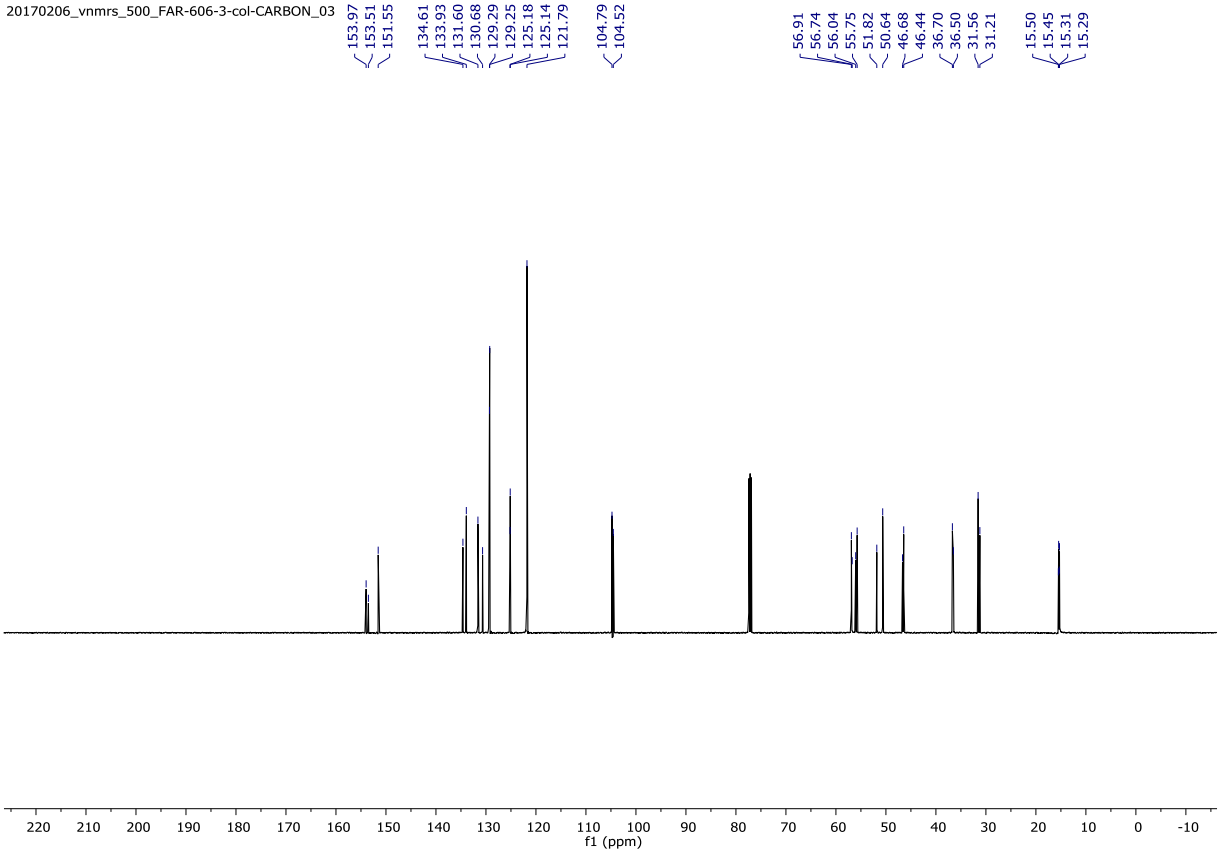
20140427_vnmrs_500_FAR-395-4-DMSO_Col-CARBON_01



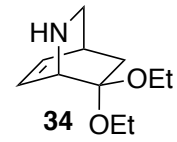
20170206_vnmrs_500_FAR-606-3-col-PROTON_01



20170206_vnmrs_500_FAR-606-3-col-CARBON_03

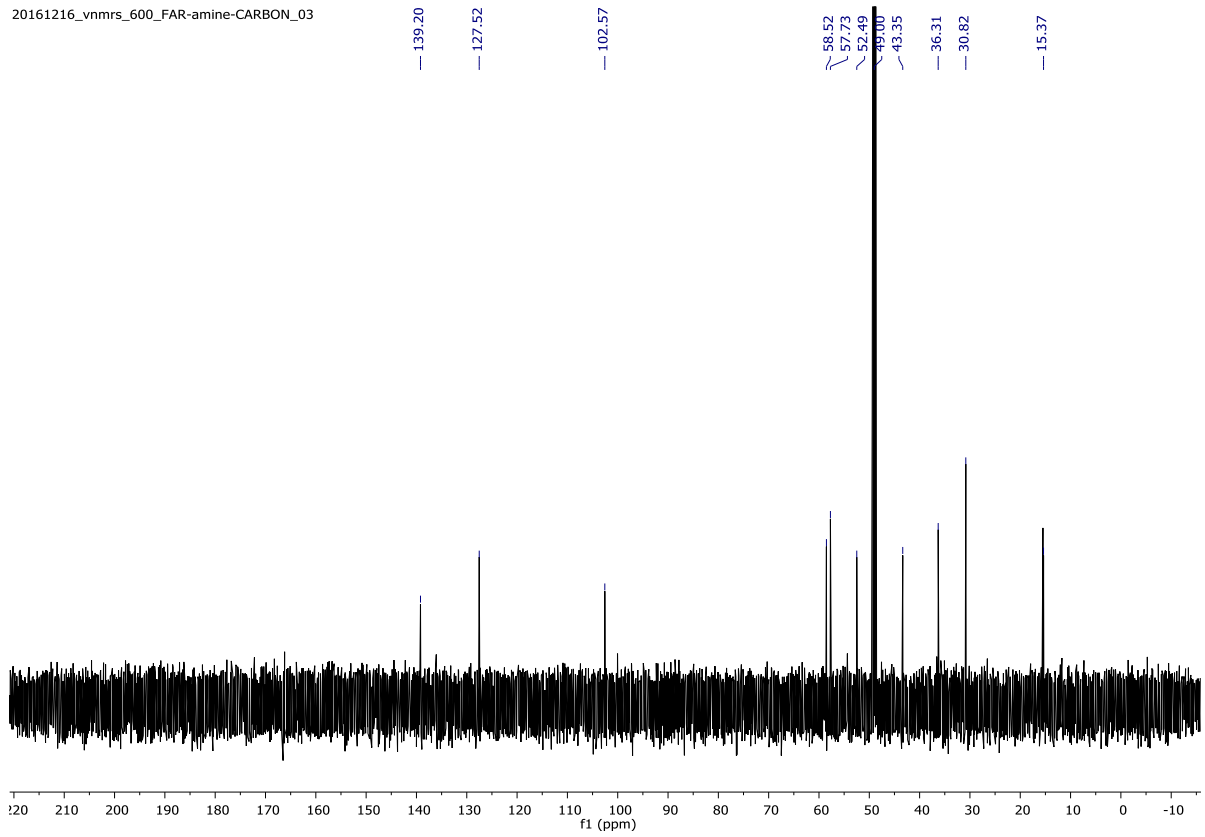


20161213_vnmrs_500_FAR-606-3-aq-PROTON_01

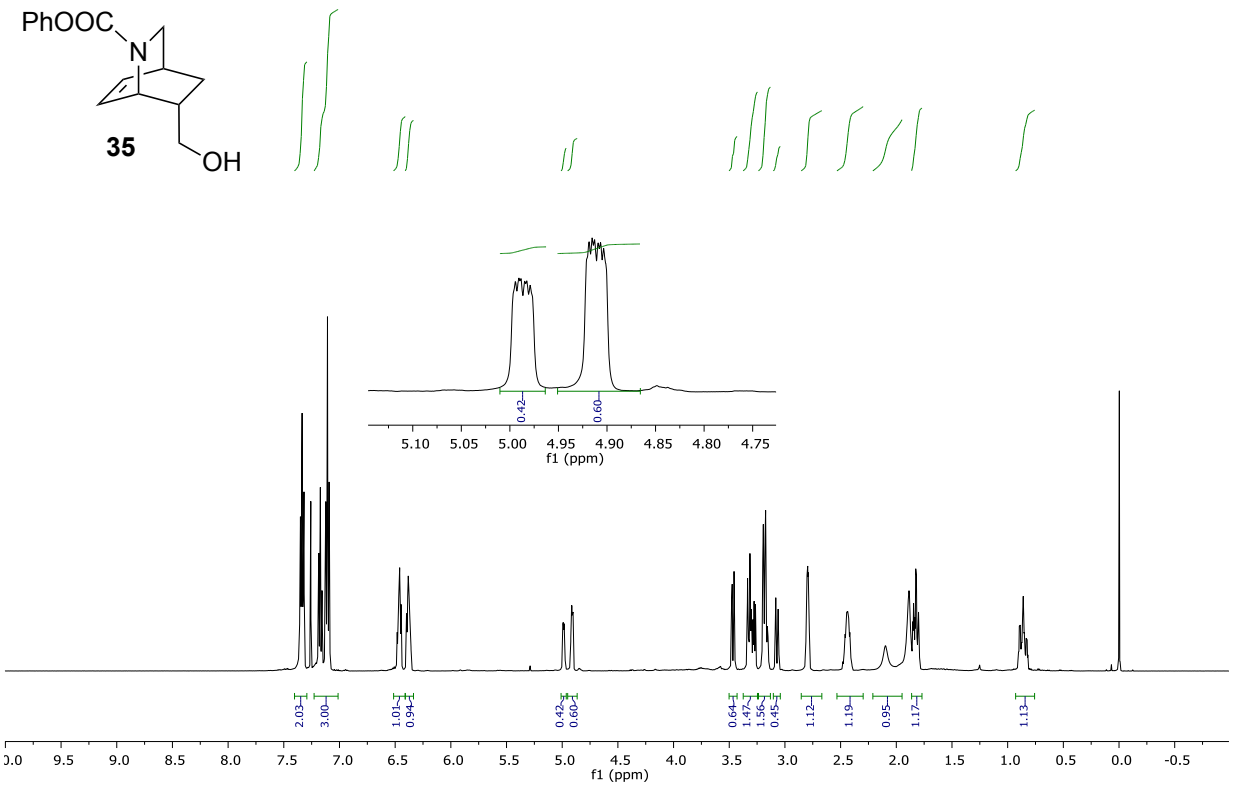


34

20161216_vnmrs_600_FAR-amine-CARBON_03



20160919_vnmrs_500_FAR-ent-ol-PROTON_01
FAR-ent-ol



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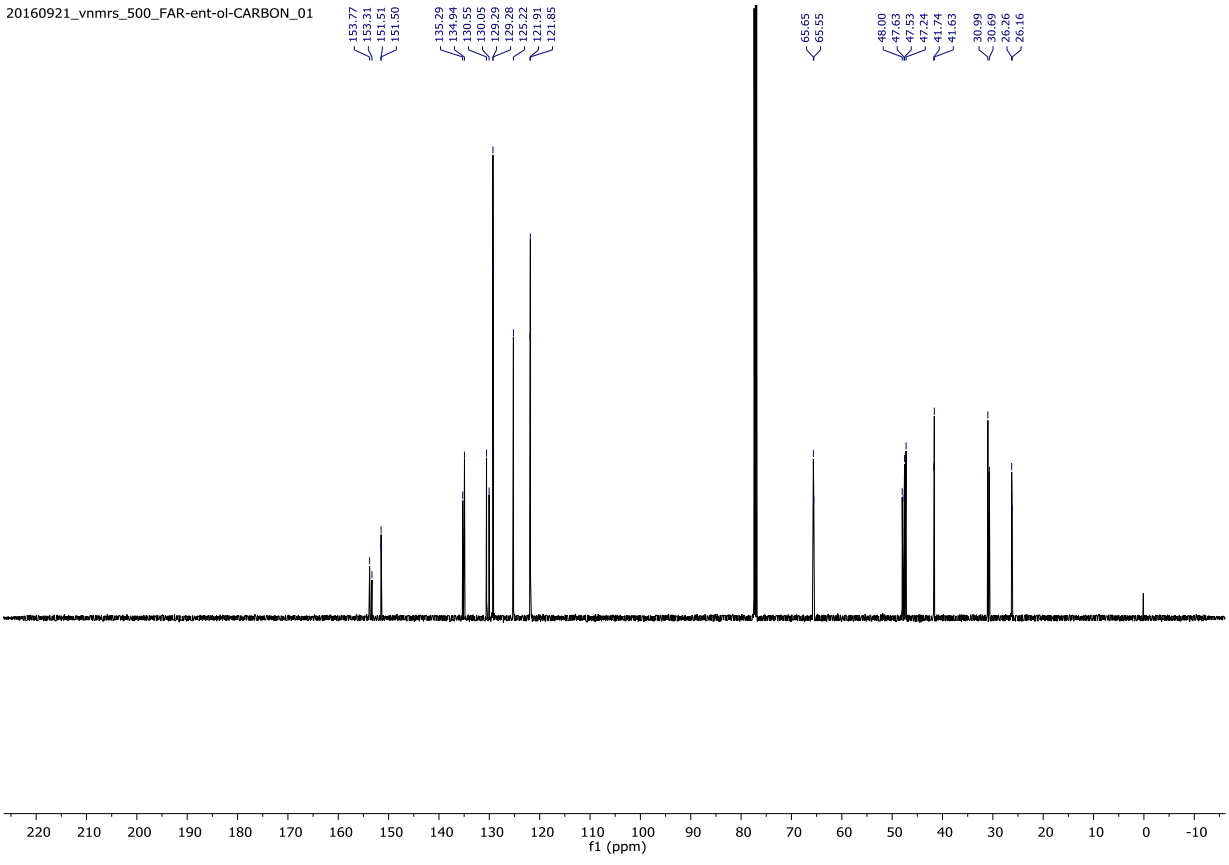
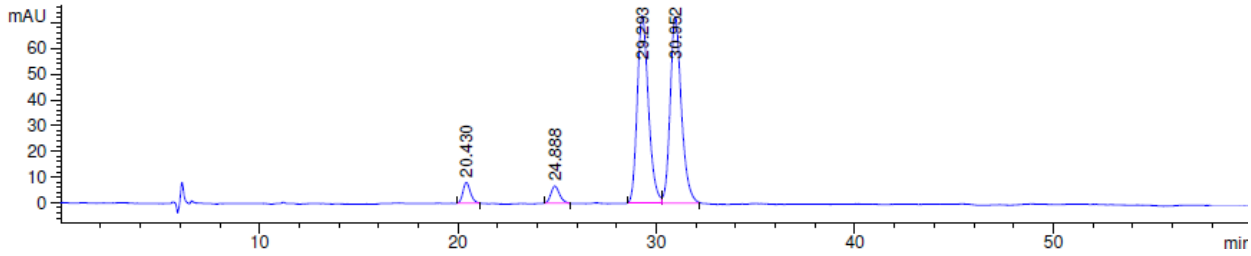


Racemic 35



Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.430	BB	0.3847	211.54041	7.99489	3.4569
2	24.888	BB	0.3870	201.93298	6.67378	3.2999
3	29.293	BV	0.5982	2851.90845	72.93575	46.6049
4	30.952	VB	0.5930	2853.94507	72.53896	46.6382
Totals :				6119.32690	160.14337	

ADH Column

Retention time endo enantiomer A: 29.3

Retention time endo enantiomer B: 31.0

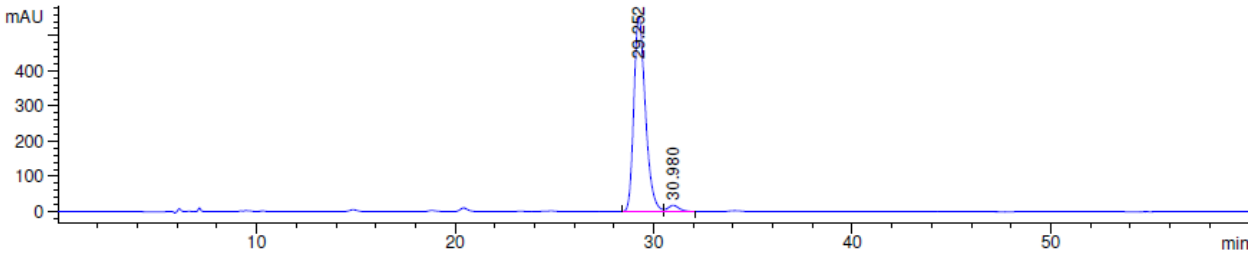
Ratio (enantiomer A):(enantiomer B) = 1.0:1.0

Retention time exo enantiomer A: 20.4

Retention time exo enantiomer B: 24.9

Ratio (enantiomer A):(enantiomer B) = 1.05:1.0

Enantioenriched 35



Signal 1: DAD1 A, Sig=210,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.252	BV	0.6190	2.23561e4	553.75763	96.9145
2	30.980	VB	0.5744	711.76532	17.80308	3.0855
Totals :				2.30679e4	571.56071	

ADH Column

Retention time major enantiomer: 29.3

Retention time minor enantiomer: 31.0

Ratio (major enantiomer):(minor enantiomer) = 97:3

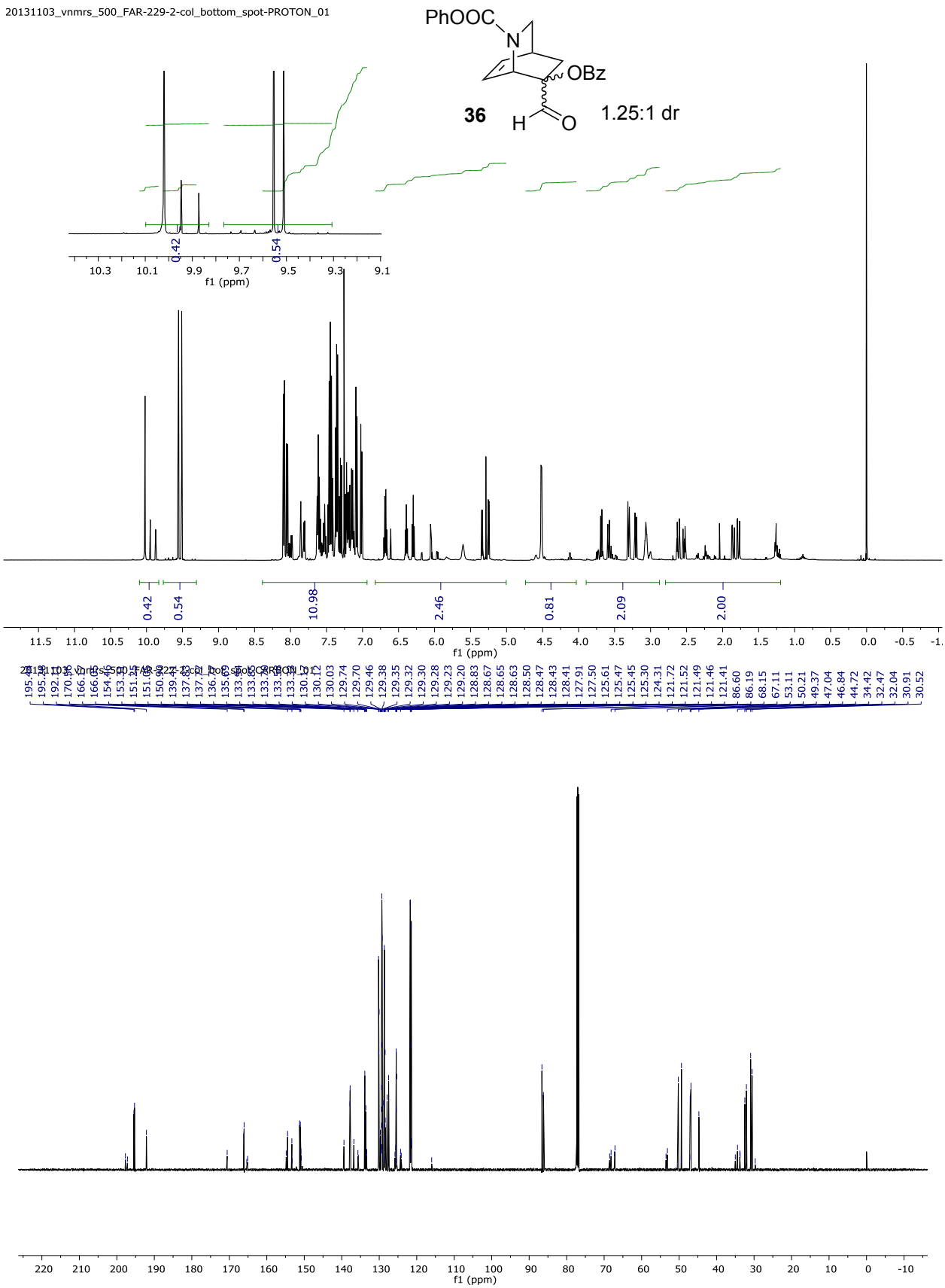
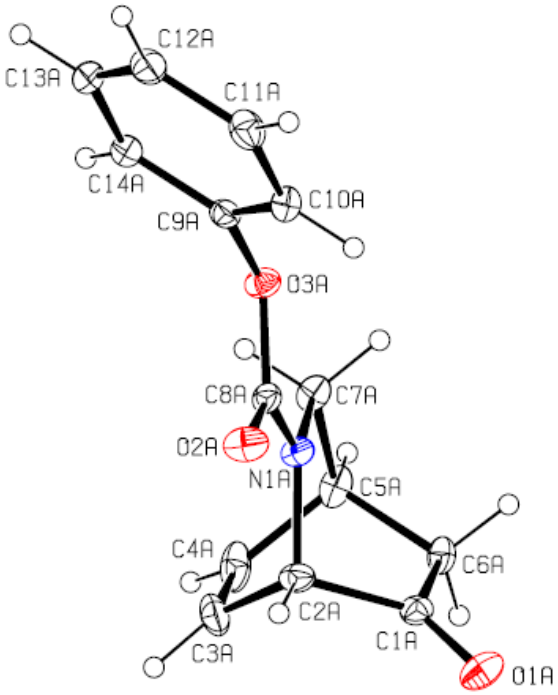

20131103_vnmrs_500_FAR-229-2-col_bottom_spot-PROTON_01
PhOOC
N
OBz
H
O
36
1.25:1 dr
0.42
0.54
10.98
2.46
0.81
2.09
2.00
f1 (ppm)

Table A2. Crystal data and structure refinement for **21**



Identification code	d16137_a
Empirical formula	C14 H13 N O3
Formula weight	243.25
Temperature	150(2) K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 10.0137(6) Å
	b = 10.3706(6) Å
	c = 11.9870(7) Å
Volume	1171.23(12) $Å^3$
Z	4
Density (calculated)	1.380 Mg/m^3
Absorption coefficient	0.803 mm^{-1}
F(000)	512
Crystal size	0.260 x 0.240 x 0.090 mm^3
Theta range for data collection	3.919 to 67.218°.
Index ranges	-11<=h<=10, -12<=k<=12, -14<=l<=14
Reflections collected	17855
Independent reflections	4105 [R(int) = 0.0404]
Completeness to theta = 67.219°	98.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7529 and 0.6786
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4105 / 1 / 325
Goodness-of-fit on F^2	1.090
Final R indices [I>2sigma(I)]	R1 = 0.0276, wR2 = 0.0695
R indices (all data)	R1 = 0.0278, wR2 = 0.0697
Absolute structure parameter	0.08(4)
Extinction coefficient	n/a
Largest diff. peak and hole	0.161 and -0.253 $e.Å^{-3}$