Supplementary Material (ESI) for Chemical Communications

Doubly dearomatising intramolecular coupling of a nucleophilic and an electrophilic heterocycle

Heloise Brice and Jonathan Clayden

Supporting Information

General Information

NMR spectra were recorded on a Varian XL 300 or a Bruker Ultrashield 200, 300, 400 or 500 spectrometer. The chemical shifts (δ) are reported in ppm downfield of trimethylsilane and coupling constants (*J*) reported in Hertz and rounded to 0.5 Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), septet (sept), mulitiplet (m), broad (br) and apparent (ap) or a combination of these. Aromatic protons (Ar) are assigned where possible using the following abbreviations: pyridine (Py), indole (In) and quaternary (4^o). Where mixtures of diastereoisomers have been quoted or rotamers are observed they are described as major (maj) or minor (min) where possible. Solvents were used as internal standard when assigning NMR spectra (δ_H: $CDCl_3$ 7.27 ppm; δ_C: $CDCl_3$ 77.0 ppm; δ_H: DMSO-d_6 2.50 ppm; δ_C: DMSO-d_6 39.4 ppm; δ_H: CD_3OD 3.31 ppm; δ_C: CD_3OD 49.0 ppm). Coupling constants were calculated using MestReC 4.8.6 or ACDLabs 9.0 1D NMR processor software.

Low and high resolution mass spectra were recorded by staff at the University of Manchester. EI and CI spectra were recorded on a Fisons VG Trio 2000; and high resolution mass spectra (HRMS) were recorded on a Kratos Concept-IS mass spectrometer, and are accurate to ± 0.001. Infrared spectra were recorded on an Ati Matson Genesis Series FTIR spectrometer as a film on a sodium chloride plate. Only absorption maxima of interest are reported. Melting points (mpt) were determined on a GallenKamp apparatus and are uncorrected.

Thin layer chromatography (TLC) was performed using commercially available pre-coated plates (Macherey-Nagel alugram. Sil $G/_{UV254}$) and visualised with UV light at 254nm, potassium permanganate or anisaldehyde dip, or over iodine. Flash chromatography was carried out using Fluorochem Davisil 40-63u 60 Å.

All reactions were conducted under atmospheric conditions unless otherwise stated. Where a nitrogen atmosphere is employed, oven or flame dried glassware was used. Tetrahydrofuran (THF) and diethyl ether were distilled under nitrogen from sodium, using a benzophenone indicator. Dichloromethane and toluene were obtained by distillation from calcium hydride under nitrogen. Anhydrous dimethylsulfoxide and dimethylformamide were used as purchased. Petrol refers to the fraction of light petroleum ether boiling between 40-65 °C. All other solvents and commercially obtained reagents were used as received or purified using standard procedures.

General procedures

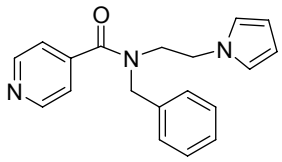
General procedure **I** for amide couplings.

A suspension of thionyl chloride (1.32 mL) and isonicotinic acid (0.369 g, 3.3 mmol) was stirred under an inert atmosphere at room temperature for 2 hours until a clear solution was obtained. The thionyl chloride was removed under reduced pressure and the resultant solid suspended in CH_2Cl_2 (10 mL). Pyridine (0.29 mL, 3.6 mmol) was added followed by the amine (3.0 mmol) and the solution was stirred for 1 hour at room temperature. Saturated sodium hydrogen carbonate solution was added (10 mL) and the solution extracted with CH_2Cl_2 (3 x 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2; EtOAc-petrol 1:3) to yield the amide.

General procedure **II** for dearomatising cyclisation.

Trifluoromethanesulfonic anhydride (0.08 mL, 0.5 mmol) was added dropwise to a stirred solution of the cyclisation precursor (0.5 mmol) and 2,6-lutidine (0.07 mL, 0.6 mmol) in CH_2Cl_2 (10 mL) under nitrogen at 0 ^oC. The solution was removed from the ice bath and stirred for 30 minutes at room temperature. Saturated sodium hydrogen carbonate solution (10 mL) was added and the solution extracted with CH_2Cl_2 (3 x 10 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2; EtOAc-petrol 1:3) to yield the dihydropyridine.

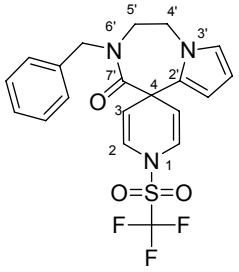
N-(2-(1H-Pyrrol-1-yl)ethyl)-N-benzyl isonicotinamide. **1**



From *N*-benzyl-2-(1*H*-pyrrol-1-yl)ethanamine (**S1**) using general procedure **I** gave the title compound (0.186 g, 76%) as an amorphous off white solid and a mixture of rotamers; R_f(EtOAc:hexane 3:1) 0.32; υ_{max}(film)/cm^{-1} 1660 (C=O); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.67 (2H$_{maj}$, d, *J* 5.5, py2-H and py6-H), 8.59 (2H$_{min}$, d, *J* 5.0, py2-H and py6-H), 7.29-7.40 (5H, m, Ar), 7.00 (2H$_{maj}$, d, *J* 6.5, py3-H and py5-H), 6.84 (2H$_{min}$, d, *J* 5.0, py3-H and py5-H), 6.71 (2H$_{maj}$, t, *J* 2.0, 2-H), 6.39 (2H$_{min}$, br s, 2-H), 6.25 (2H$_{maj}$, t, *J* 2.0, 3-H), 6.18 (2H$_{min}$, br s, 3-H), 4.76 (2H$_{min}$, s, PhCH$_2$), 4.23 (2H$_{maj}$, t, *J* 6.0, NCH$_2$), 3.89 (2H$_{min}$, t, *J* 5.5, NCH$_2$), 3.80 (2H$_{maj}$, s, PhCH$_2$), 3.67 (2H$_{maj}$, t, *J* 5.5, NCH$_2$), 3.40 (2H$_{min}$, t, *J* 5.5, NCH$_2$); δ_c ($CDCl_3$) 169.9 (C=O), 169.5 (C=O), 150.4 (py2-C and py6-C), 150.3 (py2-C and py6-C), 143.5 (4^o-C), 135.9 (4^o-C), 129.0 (Ph), 128.4 (Ph), 128.0 (Ph), 126.9 (Ph), 120.9 (py3-C and py5-C or 2-C), 120.8 (py3-C and py5-C or 2-C), 120.7

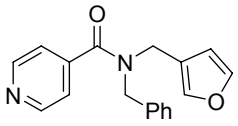
(py3-C and py5-C or 2-C), 109.4 (3-C), 109.2 (3-C), 53.4 (NCH_2Ph), 49.2 (NCH_2), 47.4 (NCH_2), 46.9 (NCH_2), 46.8 (NCH_2); m/z 306.2 (25%, MH^+) 328.2 (100% MNa^+); (Found: MH^+, 306.1603. $C_{19}H_{19}N_3O$ requires MH^+, 306.1601).

***6'-Benzyl-1-[(trifluoromethyl)sulfonyl]-1',4',5',6'-tetrahydro-1H,7'H-spiro[pyridine-4,8'-pyrrolo[2,3-d]azepin]-7'-one.* 2**



Triflic anhydride (0.04 mL, 0.25 mmol) was added dropwise to a stirred solution of **1** (0.076 g, 0.25 mmol) and 2,6-lutidine (0.035 mL, 0.325 mmol) in CH_2Cl_2 (5 mL) under nitrogen at 0 ^oC. The solution was removed from the ice bath and stirred for 30 minutes at room temperature. Saturated sodium hydrogen carbonate solution (5 mL) was added and the solution extracted with CH_2Cl_2 (3 x 5 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resultant red oil was purified by flash chromatography (SiO_2; EtOAc:petrol 1:4) to yield the title compound **2** (45 mg, 41%) as off white prisms m.pt. 132-134 ^oC (CH_2Cl_2) R_f (EtOAc:petrol 1:1) 0.65; υ_{max}(film)/cm^{-1} 1651 (C=O); δ_H(300MHz; $CDCl_3$) 7.28-7.38 (5H, m, Ph), 6.72 (2H, d, *J* 8.5, 2-H and 6-H), 6.56 (1H, t, *J* 2.5, NCH), 6.18 (1H, dd, 3.5, 3.0, pyrrole-H), 5.97 (1H, dd, *J* 3.5, 2.0, pyrrole-H), 5.58 (2H, d, *J* 8.5, 3-H and 5-H), 4.73 (2H, s, $PhCH_2$), 3.97-4.02 (2H, dt, *J* 5.0, 4.0, NCH_2), 3.86-3.91 (2H, dt, *J* 5.0, 4.0, NCH_2); δ_C 170.7 (C=O), 136.4 (Ph4^o-C), 131.5 (2'-C), 129.0 (Ph), 128.4 (Ph), 128.0 (Ph), 122.8 (pyrrole-C), 119.6 (q, *J* 325, CF_3), 119.2 (2-C), 112.0 (3-C), 112.0 (pyrrole-C), 108.8 (pyrrole-C), 52.9 ($PhCH_2$), 48.5 (4'-C), 46.9 (4-C), 45.9 (5'-C); m/z 438.3 (100%, MH^+), 460.0 (40% MNa^+). (Found: MH^+, 438.1098. $C_{20}H_{18}N_3O_3F_3S$ requires MH^+, 1094).

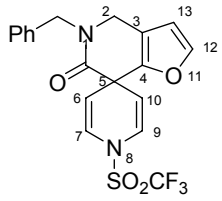
***N-Benzyl-N-((furan-3-yl)methyl)isonicotinamide.* 3**



From **S2** (0.850 g, 4. 5 mmol) using general procedure **I** gave the title compound (1.139 g, 87%) as a cream amorphous solid. R_f (EtOAc:petrol 1:1) 0.20; υ_{max}(film)/cm^{-1} 1638 (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) mixture of 2 rotamers δ 8.70 ($2H_{min}$, d, *J* 5.0, py2-H and py6-H), 8.65 ($2H_{maj}$, d, *J* 5.5, py2-H and py6-H), 7.43 ($1H_{maj}$, t, *J* 1.5, 2-H), 7.40 ($1H_{min}$, t, *J* 1.5, 2-H), 7.30-7.39 (6H, m, Ph and 5-H), 7.25 ($2H_{min}$, d, *J* 6.0, py3-H and py5-H), 7.15 ($2H_{maj}$, d, *J* 7.0, py3-H and py5-H), 6.44 ($1H_{maj}$, s, 4-H), 6.44 ($1H_{min}$, s, 4-H), 4.74

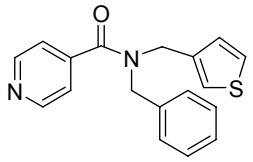
($2H_{min}$, s, NCH_2), 4.52 ($2H_{maj}$, s, NCH_2), 4.37 ($2H_{maj}$, s, NCH_2), 4.11 ($2H_{min}$, s, NCH_2); δ_c ($CDCl_3$) 169.6 (C=O), 169.4 (C=O), 150.3 (py2-C and py6-C), 144.1 (5-C), 143.7 (py4-C), 143.6 (5-C), 141.1 (2-C), 140.4 (2-C), 136.4 ($Ph4^o$), 135.7 ($Ph4^o$), 129.1 (Ph), 128.9 (Ph), 128.4 (Ph), 128.0 (Ph), 127.9 (Ph), 126.8 (Ph), 120.9 (py3-C and py5-C), 120.4 (3-C) 120.2 (3-C), 110.9 (4-C), 109.4 (4-C), 51.2 ($PhCH_2N$), 46.9 ($PhCH_2N$), 43.0 (NCH_2), 38.4 (NCH_2); m/z 293.3 (100%, MH^+); (Found: MH^+, 293.1292. $C_{18}H_{16}N_2O_2$ requires MH^+, 293.1285).

***2-Benzyl-9-trifluoromethanesulfonyl-2,9-di-aza-1H-furo[4,5-c]spiro[5.5]undeca-6,10-dien-1-one.* 4**



From **3** (0.146 g, 0.5 mmol) using modified general procedure **II** with triflic anhydride (0.17 mL, 1.0 mmol) and 2,6-lutidine (0.15 mL, 1.25 mmol) gave the title compound (0.169 g, 78%) as a colourless oil. R_f (EtOAc:petrol 1:1) 0.72; υ_{max}(film)/cm^{-1} 1645 (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.39 (1H, d, *J* 2.0, 12-H), 7.28-7.37 (5H, m, Ph), 6.80 (2H, d, *J* 8.0, 7-H and 9-H), 6.24 (1H, d, *J* 2.0, 13-H), 5.05 (2H, d, *J* 8.0, 6-H and 10-H), 4.76 (2H, s, NCH_2), 4.24 (2H, s, NCH_2); δ_c ($CDCl_3$) 169.0 (C=O), 149.7 (4-C), 144.3 (12-C), 136.3 ($Ph4^o$), 128.9 (Ph), 128.2 (Ph), 127.9 (Ph), 122.7 (7-C and 9-C), 119.5 (q, *J* 325.0, CF_3), 110.6 (3-C), 109.7 (6-C and 10-C), 107.7 (13-C), 51.4 (NCH_2Ph), 44.5 (NCH_2), 43.8 (5-C); m/z 447.1 (100%, MNa^+); (Found: MNH_4^+, 442.1035. $C_{19}H_{15}N_2O_4F_3S$ requires MNH_4^+, 442.1043).

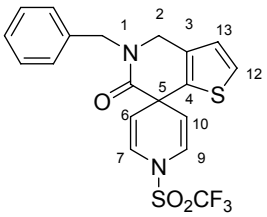
***N-Benzyl-N-((thiophen-3-yl)methyl)isonicotinamide.* 5**



From *N*-benzyl-(thiophen-3-yl)methanamine[1] using general procedure **I** gave the title compound (0.631 g, 83%) as a colourless oil. R_f(EtOAc:hexane 1:1) 0.11; υ_{max}(film)/cm^{-1} 1636 (C=O); ^{1}H-NMR ($CDCl_3$, 300 MHz) mixture of 2 rotamers δ 8.65 (2H, d, *J* 5.0, py2-H and py6-H), 7.28-7.40 (6H, m, Ar), 7.09-7.15 (2H, m, Ar), 7.03 ($1H_{maj}$, br s, 2-H), 6.84 ($1H_{maj}$, d, *J* 5.0, 4-H), 4.74 ($2H_{min}$, s, $PhCH_2$), 4.69 ($2H_{maj}$, s, $PhCH_2$), 4.35 ($2H_{maj}$, s, NCH_2), 4.31 ($2H_{min}$, s, NCH_2); δ_c ($CDCl_3$) 169.5 (C=O), 150.3 (py2-C and py6-C), 143.7 (4^o-C), 137.0 (4^o-C), 136.4 (4^o-C), 135.7 (4^o-C), 129.1 (Ar), 128.9 (Ar), 128.5 (Ar), 128.0 (Ar), 127.9 (Ar), 127.9 (Ar), 127.3 (Ar), 126.8 (Ar), 126.3 (Ar), 123.9 (Ar), 122.5 (Ar), 120.9 (Ar), 51.4 (NCH_2Ph), 47.2 (NCH_2),

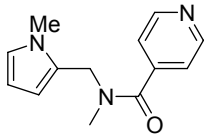
42.5 (NCH_2); m/z 309.2 (30%, MH^+) 333.1 (100% MNa^+); (Found: MNa^+, 309.1050. $C_{18}H_{17}NOS$ requires MNa^+, 309.1056).

***5'-Benzyl-1-[(trifluoromethyl)sulfonyl]-4',5'-dihydro-1H,6'H-spiro[pyridine-4,7'-thieno[3,2-c]pyridin]-6'-one.* 6**



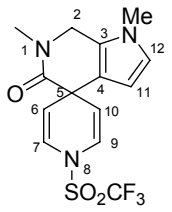
From *N*-benzyl-*N*-((thiophen-3-yl)methyl)isonicotinamide **5** using a modified general procedure **II** with trifluoromethanesulfonic anhydride (0.36 mL, 0.225 mmol, 0.9 equiv) gave the title compound (0.143 g, 65%) as colourless prisms m.pt. 148-150 ^oC (EtOAc); R_f (EtOAc:petrol 3:7) 0.43; υ_{max}(film)/cm^{-1} 1650 (C=O); δ_H(300MHz; $CDCl_3$) 7.28-7.39 (6H, m, Ph and 12-H), 6.74-6.77 (3H, m, 7-H, 9-H and 13-H), 5.23 (2H, d, *J* 8.5, 6-H and 10-H), 4.77 (2H, s, $PhCH_2$), 4.42 (2H, s, NCH_2); δ_C 168.7 (C=O), 140.9 (4^o-C), 136.5 ($Ph4^o$-C), 129.1 (Ar), 126.5 (Ar), 128.2 (Ar), 127.8 (Ar), 127.8 (Ar), 124.4 (12-C or 13-C), 119.8 (q, *J* 324, CF_3), 121.4 (7-C), 112.0 (6-C), 51.6 (CH_2Ph), 47.8 (NCH_2), 44.2 (5-C); m/z 441.2 (45%, MH^+), 463.2 (100%, MNa^+); (Found: MH^+, 441.0545. $C_{19}H_{15}N_2O_3F_3S_2$ requires MH^+, 441.0549).

***N-Methyl-N-((1-methyl-1H-pyrrol-2-yl)methyl)isonicotinamide.* 7**



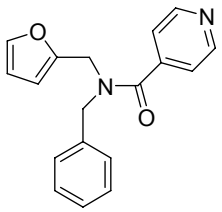
From *N*-methyl(1-methyl-1*H*-pyrrol-2-yl)methanamine[2] and isonicotinic acid using general procedure **I** gave the title compound (0.769 g, 99%) as a yellow oil. R_f (EtOAc:hexane 1:1) 0.05; υ_{max}(film)/cm^{-1} 1635 (C=O); ^{1}H-NMR (DMSO, 400 MHz) mixture of 2 rotamers δ 8.66 (2H, d, *J* 5.5, py2-H and py6-H), 7.40 (2H, dd, *J* 4.5, 1.5, py3-H and py5-H), 7.74 ($1H_{maj}$, s, 5-H), 6.60 ($1H_{min}$, s, 5-H), 6.08 ($1H_{maj}$, s, 3-H or 4-H), 5.94 ($1H_{maj}$ and 1H, ap t, *J* 3.5, 3-H and 4-H), 4.66 ($2H_{maj}$, br s, NCH_2), 4.38 ($2H_{maj}$, br s, NCH_2), 3.59 (2H, s, NCH_2), 3.34 (3H, s, NCH_3), 2.90 ($3H_{min}$, s, $CONCH_3$), 2.70 ($3H_{maj}$, s, $CONCH_3$); δ_c ($CDCl_3$) 168.2 (C=O), 167.5 (C=O), 149.9 (py2-C and py6-C), 143.8 (py4-C), 143.6 (py4-C), 126.7 (2-C), 126.4 (2-C), 123.1 (5-C), 122.0 (5-C), 120.9 (py3-C and py5-C), 109.7 (4-C), 107.6 (4-C), 106.5 (3-C), 106.3 (3-C), 46.5 (NCH_2), 41.0 (NCH_2), 35.3 (NCH_3), 33.4 (NCH_3), 33.1 (NCH_3), 32.1 (NCH_3); m/z 230.1 (100%, MH^+); (Found: MH^+, 230.1288 $C_{13}H_{15}N_3O$ requires MH^+, 230.1288).

***2,13-Dimethyl-9-trifluoromethanesulfonyl-2,9,13-aza-1H-pyrrolo[4,5-c]spiro[5.5]undeca-6,10-dien-1-one.* 8**



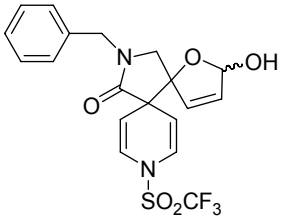
From **7** using general procedure **II** gave the title compound (0.088 g, 49%) as pink needles m.pt. 190-192 ^{o}C (EtOAc); R_f (EtOAc:petrol 1:1) 0.21; υ_{max}(film)/cm^{-1} 1641 (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.64 (2H, d, *J* 8.0, 7-H and 9-H), 6.61 (1H, d, *J* 3.0, 12-H), 5.85 (1H, d, *J* 2.0, 11-H), 5.06 (2H, d, *J* 8.0, 6-H and 10-H), 4.46 (2H, s, NCH_2), 3.54 (3H, s, NMe), 3.15 (3H, s, CONMe); δ_c ($CDCl_3$) 170.6 (C=O), 123.3 (12-C), 121.8 (3-C), 120.2 (7-C and 9-C), 119.6 (q, *J* 325.0, CF_3), 118.5 (4-C), 113.2 (6-C and 10-C), 105.8 (11-C), 47.4 (NCH_2), 42.7 (5-C), 36.3 (CON*C*H_3) 33.4 (NCH_3); m/z 362.0 (100%, MH^+); (Found: MH^+, 362.0786. $C_{14}H_{14}N_3O_3F_3S$ requires MH^+, 362.0781).

***N-Benzyl-N-((furan-2-yl)methyl)isonicotinamide.* 9**



From **S3** (13.9 mmol) and isonicotinic acid (15.3 mmol) using general procedure **I** gave the title compound (4.043 g, 99%) as a colourless oil. R_f (EtOAc:hexane 1:1) 0.14; υ_{max}(film)/cm^{-1} 1638 (C=O); ^{1} ^{1}H-NMR ($CDCl_3$, 400 MHz) mixture of 2 rotamers δ 8.72 (2H$_{maj}$ d, *J* 5.5, py2-H and py6-H), 8.65 (2H$_{min}$ d, *J* 5.0, py2-H and py6-H), 7.47 (2H$_{maj}$, d, *J* 5.5, py3-H and py5-H), 7.30-7.43 (6H, m, Ph, py3-H$_{min}$ and py5-H$_{min}$), 7.13 (1H, d, *J* 7.0, 5-H), 6.35 (1H, br s, 4-H), 6.29 (1H$_{min}$, d, *J* 2.0, 3-H), 6.15 (1H$_{maj}$, d, *J* 2.5, 3-H), 4.71 (2H$_{maj}$, s, NCH_2), 4.69 (2H$_{min}$, s, NCH_2), 4.43 (2H$_{min}$, s, NCH_2), 4.22 (2H$_{maj}$, s, NCH_2); δ_c ($CDCl_3$) 169.4 (C=O), 150.3 (py2-C and py6-C), 149.9 (2-C), 148.9 (2-C), 143.7 (py4-C or 5-C), 143.5 (py4-C or 5-C), 143.1 (py4-C or 5-C), 136.3 (Ph4^{o}), 135.7 (Ph4^{o}), 129.0 (Ph4^{o}), 128.8 (Ph), 128.5 (Ph), 128.0 (Ph), 127.8 (Ph), 126.8 (Ph), 121.3 (py3-C and py5-C), 121.0 (py3-C and py5-C), 110.4 (4-C), 109.4 (3-C), 51.8 (NCH_2), 47.0 (NCH_2), 44.6 (NCH_2), 40.3 (NCH_2); m/z 293 (100%, MH^+); (Found: MH^+, 293.1278. $C_{18}H_{17}N_2O_2$ requires MH^+, 293.1285).

13-Benzyl -2-hydroxy-9-trifluoromethanesulfonyl-1-oxa-9,13-diaza-dispiro[4.0.5.3]tetradeca-3,7,10-trien-12-one. **10a**

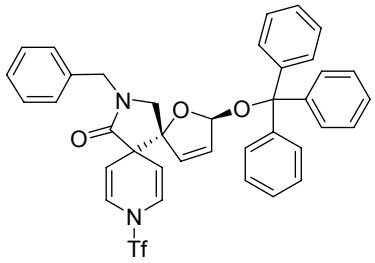


From **9** using general procedure **II** gave the title compound (0.007 g, 7%) as a yellow oil; 9:11 mix of 2 diastereoisomers.

or

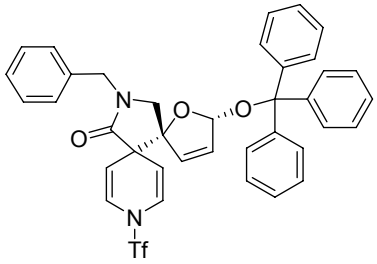
Trifluoromethanesulfonic anhydride (0.04 mL, 0.25 mmol) was added dropwise to a stirred solution of **9** (0.25 mmol) and 2,6-lutidine (0.035 mL, 0.3 mmol) in CH_2Cl_2 (5 mL, Laboratory Reagent Grade as brought from Fisher Scientific) under nitrogen at 0 ^oC and then warmed to room temperature for 30 minutes. Saturated ammonium chloride solution (0.5 mL) was added and the solution stirred for 20 mins at room temperature. Saturated sodium hydrogen carbonate solution (5 mL) was added and the solution extracted with CH_2Cl_2 (3 x 5 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2; EtOAc-petrol 7:20 to EtOAc) to yield the title compound **10a** (0.038 g, 34%) as a colourless oil and a 3:4 inseparable mixture of diastereoisomers. R_f (EtOAc:petrol 1:1) 0.33; υ_{max}(film)/cm^{-1} 3410 (OH), 1725 (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.24-7.38 (5H, m, Ph), 6.87 ($1H_{min}$, d, *J* 8.5, 7-H or 9-H), 6.77 ($1H_{maj}$, d, *J* 8.5, 7-H or 9-H), 6.73 ($1H_{min}$, d, *J* 8.5, 7-H or 9-H), 6.69 ($1H_{maj}$, d, *J* 8.5, 7-H or 9-H), 6.05 ($1H_{min}$, d, *J* 6.0, 12-H), 6.05 ($1H_{maj}$, d, *J* 6.0, 12-H), 5.98 ($1H_{min}$, d, *J* 5.0, 10-H), 5.98 ($1H_{maj}$, d, *J* 5.0, 10-H), 5.92 ($1H_{min}$, dd, *J* 6.5, 6.0, 11-H), 5.92 ($1H_{maj}$, dd, *J* 6.5, 6.0, 11-H), 5.31 ($1H_{min}$, dd, *J* 8.5, 2.5, 6-H or 10-H), 5.24 ($1H_{maj}$, dd, *J* 8.5, 2.5, 6-H or 10-H), 4.93 (1H, dd, *J* 8.5, 2.5, 6-H or 10-H), 4.91 (1H, dd, *J* 8.5, 2.5, 6-H or 10-H), 4.72 ($1H_{min}$, d, *J* 15.0, $PhCH_2$), 4.63 ($1H_{min}$, d, *J* 15.0, $PhCH_2$), 4.45 ($1H_{maj}$, d, *J* 14.5, $PhCH_2$), 4.35 ($1H_{maj}$, d, *J* 14.5, $PhCH_2$), 3.56 ($1H_{maj}$, d, *J* 11.0, 3-H), 3.47 ($1H_{min}$, d, *J* 11.0, 3-H), 3.30 ($1H_{maj}$, d, *J* 11.0, 3-H), 3.22 ($1H_{min}$, d, *J* 11.0, 3-H), 2.27 (1H, br s, OH), 2.22 (1H, br s, OH); δ_c ($CDCl_3$) 170.6 (C=O), 135.5 ($Ph4^o$), 135.5 ($Ph4^o$), 132.9 (10-C), 132.7 (10-C), 131.4 (11-C), 129.2 (Ph), 128.9 (Ph), 128.9 (Ph), 128.4 (Ph), 128.1 (Ph), 128.1 (Ph), 128.0 (Ph), 124.3 (7-C or 9-C), 124.2 (7-C or 9-C), 123.9 (7-C or 9-C), 123.8 (7-C or 9-C), 119.4 (q, *J* 325, CF_3), 107.6 (6-C or 10-C), 107.3 (6-C or 10-C), 106.4 (6-C or 10-C), 102.8 (12-C), 102.7 (12-C), 94.5 (4-C), 94.2 (4-C), 61.2 (5-C), 54.7 ($PhCH_2$), 53.6 ($PhCH_2$), 47.0 (3-C), 47.0 (3-C), m/z 443.2 (100%, MH^+), 465.2 (40%, MNa^+), 425.2 (35% M-OH); (Found: MH^+, 443.0876. $C_{19}H_{17}N_2O_5F_3S$ requires MH^+, 443.0883).

***13-Benzyl-2-triphenyloxy-9-trifluoromethanesulfonyl-1-oxa-9,13-diaza-dispiro[4.0.5.3]tetradeca-3,7,10-trien-12-one. anti*-10b**



Triflic anhydride (0.04 mL, 0.25 mmol) was added dropwise to a stirred solution of **9** (0.073 g, 0.25 mmol) and 2,6-lutidine (0.04 mL, 0.325 mmol) in CH_2Cl_2 (5 mL) under nitrogen at -20 ^oC. The resultant red solution was stirred for 1 minute and triphenylmethanol (0.325, 1.25 mmol) was added. The solution was stirred for a further hour and saturated sodium hydrogen carbonate solution (5 mL) was added. The solution was extracted with CH_2Cl_2 (3 x 5 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resultant oil was purified by flash chromatography (SiO_2; EtOAc:petrol 1:9 to 2:1) to yield the title compound **10b** (112 mg, 65%) as white plates mpt 102-104 ^oC (EtOAc); R_f (EtOAc:petrol 1:4) 0.31; υ_{max}(film)/cm^{-1} 1702 (C=O); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.22-7.46 (20H, m, Ph), 6.21 (2H, d, *J* 8.0, 8-H and 10-H), 5.73-5.76 (2H, m, 2-H and 3-H or 4-H), 5.26 (1H, d, *J* 3.0, 3-H or 4-H), 5.00 (1H, dd, *J* 8.5, 2.5, 7-H or 11-H), 4.90 (1H, dd, *J* 8.5, 2.5, 7-H or 11-H), 4.51 (2H, s, NCH_2Ph), 3.53 (1H, d, *J* 11.0, NCH_aH_b), 3.35 (1H, d, *J* 11.0, NCH_aH_b); δ_c ($CDCl_3$) 171.4 (C=O), 143.3 (4^o-Ph), 135.6 (4-C), 134.6 (3-C), 131.6 (Ph 4^o-C), 128.8 (Ph), 127.8 (Ph), 127.6 (Ph), 127.0 (Ph), 126.9 (Ph), 126.2 (Ph), 122.9 (8-C or 10-C), 122.4 (8-C or 10-C), 118.3 (q, *J* 324, CF_3), 106.7 (7-C or 11-C), 105.5 (7-C or 11-C), 103.5 (2-C), 93.1 (5-C or CPh_3), 86.8 (5-C or CPh_3), 53.2 ($PhCH_2N$), 51.7 (6-C), 45.8 (NCH_2); m/z 707.1 (100% MNa^+). (Found: MNH_4^+, 702.2230. $C_{38}H_{31}N_2O_5F_3S$ requires MNH_4^+, 702.2244).

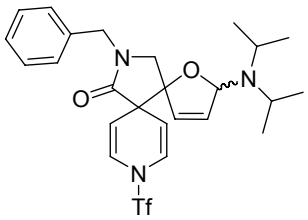
and its diastereoisomer ***syn*-10b**



(3 mg, 2%) as white prisms; R_f (EtOAc:petrol, 1:1) 0.71; υ_{max}(film)/cm^{-1} 1700 (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.44-7.46 (4H, m, Ph), 7.25-7.34 (14H, m, Ar), 7.15 (2H, ap. d, *J* 8.0, Ph), 6.82 (1H, d, *J* 8.5, 8-H or 10-H), 6.72 (1H, dd, *J* 8.0, 1.2, 8-H or 10-H), 5.97 (1H, s, 2-H), 5.77 (1H, d, *J* 6.0, 4-H), 5.47 (1H, dd, *J* 6.0,

1.0, 3-H), 5.33 (1H, dd, *J* 8.5, 2.0, 7-H or 11-H), 4.92 (1H, dd, *J* 8.5, 2.5, 7-H or 11-H), 4.62 (1H, d, *J* 15.0, NCH_aH_bPh), 4.35 (1H, d, *J* 15.0, NCH_aH_bPh), 3.37 (1H, d, *J* 11.5, NCH_aH_b), 2.96 (1H, d, *J* 11.5, NCH_aH_b); δ_c ($CDCl_3$) 144.4 (4^o-Ph), 135.6 (4-C), 132.4 (3-C), 128.9 (Ph), 128.8 (Ph), 128.7 (Ph), 128.7 (Ph), 128.1 (Ph), 127.9 (Ph), 127.8 (Ph), 123.8 (8-C or 10-C), 123.5 (8-C or 10-C), 104.7 (2-C), 94.1 (5-C or CPh_3), 87.9 (5-C or CPh_3), 53.6 ($PhCH_2N$ or 6-C), 53.0 ($PhCH_2N$ or 6-C), 46.7 (NCH_2); m/z 684.2 (10%, MH^+), 707.5 (100% MNa^+).

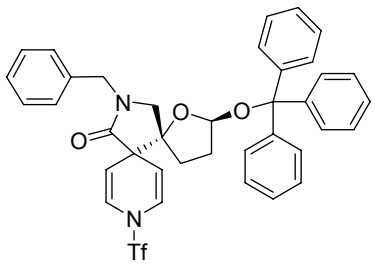
13-Benzyl-2-diisopropylamino-9-trifluoromethanesulfonyl-1-oxa-9,13-diaza-dispiro[4.0.5.3]tetradeca-3,7,10-trien-12-one. **10c**



Triflic anhydride (0.04 mL, 0.25 mmol) was added dropwise to a stirred solution of **9** (0.073 g, 0.25 mmol), diisopropylamine (0.18 mL, 1.25 mmol) and 2,6-lutidine (0.04 mL, 0.325 mmol) in CH_2Cl_2 (5 mL) under nitrogen at 0 ^{o}C. The solution was removed from the ice bath and stirred for 30 minutes at room temperature. Saturated sodium hydrogen carbonate solution (5 mL) was added and the solution extracted with CH_2Cl_2 (3 x 5 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The resultant oil was purified by flash chromatography (SiO_2; EtOAc:petrol 1:9 to 2:1) to yield the title compound **10d** (67 mg, 51%) as a yellow solid and as a 2:3 mixture of diastereoisomers; R_f (EtOAc:petrol 9:1) 0.40; υ_{max}(film)/cm^{-1} 1644 (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.44 ($1H_{min}$, d, *J* 12.0, 8-H or 10-H), 8.39 ($1H_{maj}$, d, *J* 12.0, 8-H or 10-H), 7.44 ($1H_{min}$, d, 1.0, 2-H), 7.13-7.38 (7H, m, Ph and $1H_{maj}$ 2-H), 6.35 ($1H_{min}$, dd, *J* 3.5, 1.5, 3-H or 4-H), 6.33 ($1H_{maj}$, dd, *J* 3.0, 2.0, 3-H or 4-H), 6.31 ($1H_{min}$, d, *J* 3.0, 3-H or 4-H), 6.23 ($1H_{maj}$, d, *J* 3.0, 3-H or 4-H), 6.11 ($1H_{min}$, d, *J* 12.0, 7-H or 11-H), 6.10 ($1H_{maj}$, d, *J* 11.5, 7-H or 11-H), 5.76 ($1H_{min}$, d, *J* 13.0, 7-H or 11-H), 5.75 ($1H_{maj}$, d, *J* 13.0, 7-H or 11-H), 4.94 ($1H_{min}$, d, *J* 15.0, NCH_aH_bPh), 4.79 ($1H_{maj}$, d, *J* 11.5, NCH_aH_bPh), 4.55 ($1H_{maj}$, d, *J* 11.0, NCH_aH_bPh), 4.46 ($1H_{min}$, d, *J* 15.5, NCH_aH_b), 4.41 ($1H_{min}$, d, *J* 15.0, NCH_aH_bPh), 4.37 ($1H_{maj}$, d, *J* 16.0, NCH_aH_b), 4.29 (1H, d, *J* 16.0, NCH_aH_b), 4.16-4.23 (1H, m, $CHMe_2$), 3.75 ($1H_{min}$, sept, *J* 7.0, $CHMe_2$), 3.68 ($1H_{maj}$, sept, *J* 7.0, $CHMe_2$), 1.28-1.32 (6H, m, $2CH_3$), 1.25 ($3H_{min}$, d, *J* 7.0, CH_3), 1.18 ($3H_{maj}$, d, *J* 7.0, CH_3), 1.13 ($3H_{min}$, d, *J* 7.0, CH_3), 0.95 ($3H_{maj}$, d, *J* 7.0, CH_3); δ_c ($CDCl_3$) 169.9 (C=O), 169.9 (C=O), 167.1 (8-C or 10-C), 167.1 (8-C or 10-C), 151.8 (8-C or 10-C), 151.6 (8-C or 10-C), 149.5 (4^o-C), 148.2 (4^o-C), 143.3 (2-C), 143.0 (2-C), 136.0 (Ph 4^o-C), 134.6 (Ph 4^o-C), 129.3 (Ph), 129.2 (Ph), 129.1 (Ph), 128.3 (Ph), 128.1 (Ph), 127.9 (Ph), 119.9 (q, *J* 324, CF_3), 111.8 (7-C or 11-C), 111.4 (7-C or 11-C), 110.6 (3-C or 4-C), 110.5 (3-C or 4-C), 110.3 (3-C or 4-C), 110.0 (3-C or 4-C), 100.7 (7-C or 11-C), 100.5 (7-C or 11-C), 51.7 ($CHMe_2$), 50.9 ($CHMe_2$), 50.9 ($CHMe_2$), 50.8 ($CHMe_2$), 49.9 ($PhCH_2N$), 46.7, ($PhCH_2N$), 44.2

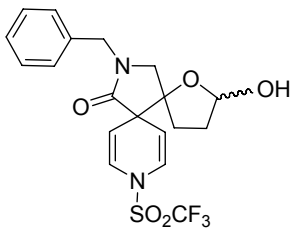
(CH_2N), 39.1, (NCH_2), 23.6 (CH_3), 23.4 (CH_3), 23.1 (CH_3), 19.9 (CH_3); m/z 548.2 (100%, MNa^+), (Found: MNa^+, 548.1803. $C_{25}H_{30}N_3O_4F_3S$ requires MNa^+, 548.1801).

13-Benzyl-2-triphenyloxy-9-trifluoromethanesulfonyl-1-oxa-9,13-diaza-dispiro[4.0.5.3]tetradeca-7,10-dien-12-one. **13**



A solution of trityl acetal **10b** (0.42 g, 0.61 mmol) in EtOAc (28 mL) and ethanol (28 mL) was passed twice through the H-cube using 10% Pd/C CatCart® 30, 20 °C, 1 bar H_2 and 0.8 $mLmin^{-1}$ The solution was evaporated under reduced pressure to yield the title compound **17** (0.397 g, 95%) as white plates m.pt. 162-165 °C (from $CDCl_3$). R_f (EtOAc-petrol, 3:17) 0.28; υ_{max}(film)/cm^{-1} 1688 (C=O); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.21-7.36 (20H, m, Ph), 6.67 (1H, d, *J* 8.5, 8-H or 10-H), 6.63 (1H, d, *J* 8.5, 8-H or 10-H), 5.34 (1H, dd, *J* 4.5, 2.0, 2-C), 4.98 (1H, dd, *J* 8.5, 2.5 7-H or 11-H), 4.75 (1H, dd, *J* 8.5, 2.5, 7-H or 11-H), 4.57 (1H, d, *J* 14.5, NCH_aH_bPh), 4.23 (1H, d, *J* 14.5, NCH_aH_bPh), 3.43 (1H, d, *J* 11.0, NCH_aH_b), 3.27 (1H, d, *J* 11.0, NCH_aH_b), 1.87 (2H, t, *J* 7.5, 4-H), 1.57-1.67 (2H, m, 3-H); δ_c ($CDCl_3$) 172.7 (C=O), 144.5 (4°-Ph), 135.8 (4°-Ph), 128.8 (Ph), 128.8 (Ph), 128.8 (Ph), 128.1 (Ph), 128.0 (Ph), 127.9 (Ph), 127.8 (Ph), 127.2 (Ph), 123.4 (8-C or 10-C), 123.4 (8-C or 10-C), 108.1 (7-C or 11-C), 107.4 (7-C or 11-C), 101.3 (2-C), 88.4 (5-C or CPh_3), 87.6 (5-C or CPh_3), 53.5 ($PhCH_2N$), 52.0 (6-C), 47.0 (NCH_2), 32.7 (3-C), 28.3 (4-C); m/z 709.1 (100%, MNa^+). (Found: MNa^+, 709.1936. $C_{38}H_{33}N_2O_5F_3S$ requires MNa^+, 709.1954).

13-Benzyl-2-hydroxy-9-trifluoromethanesulfonyl -1-oxa-9,13-diaza-dispiro[4.0.5.3]tetradeca-7,10-dien-12-one. **14a**



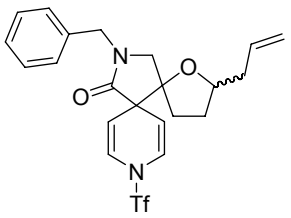
Triethylsilane (0.023 mL, 0.15 mmol) was added to a solution of trityl alcohol **13** (0.020 g, 0.03 mmol) in CH_2Cl_2 (1.5 mL) at room temperature under a nitrogen atmosphere and stirred for 1 minute. Trifluoroacetic acid (0.0025 mL) was added and the solution stirred for 3 hours. Saturated sodium hydrogen carbonate solution (5 mL) was added and the solution was extracted with CH_2Cl_2 (3 x 10 mL), dried ($MgSO_4$) and

evaporated under reduced pressure. The crude product was purified by flash chromatography (SiO_2; EtOAc-petrol 1:4 to EtOAc) to yield the title compound **14a** (13 mg, quant) as a colourless oil and a 2:1 inseparable mixture of diastereoisomers.

Or

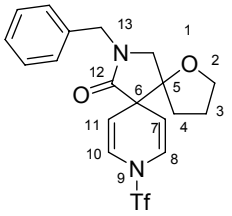
Diethylaluminium chloride (0.36 mL of a 1M solution in hexanes) was added to a solution of trityl alcohol **13** (0.025 g, 0.036 mmol) in CH_2Cl_2 (2.0 mL) at room temperature under a nitrogen atmosphere and stirred for 10 minutes. Saturated sodium hydrogen carbonate solution (2 mL) and a saturated aqueous solution of Rochelle's salt (10 mL) were added and the solution was extracted with CH_2Cl_2 (3 x 10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to yield the crude product which was purified by flash chromatography (SiO_2; EtOAc-petrol 1:4) to yield the title compound **14a** (14 mg, 87%) as a colourless oil and a 2:1 inseparable mixture of diastereoisomers. R_f (EtOAc:petrol 1:1) 0.23; υ_{max}(film)/cm^{-1} 3390 (OH), 1682 (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.28-7.38 (3H, m, Ph), 7.22-7.26 (2H, m, Ph), 6.85 (1H$_{min}$, d, *J* 9.0, 8-H or 10-H), 6.79 (1H$_{maj}$, d, *J* 9.0, 8-H or 10-H), 6.75 (1H, dd, *J* 9.0, 1.2, 8-H or 10-H), 5.55 (1H$_{maj}$, d, *J* 2.0, 2-H), 5.49 (1H$_{min}$, dd, *J* 7.0, 3.0, 2-H), 5.35 (1H$_{min}$, dd, *J* 8.5, 2.5, 7-H or 11-H), 5.28 (1H$_{maj}$, dd, *J* 8.5, 2.5, 7-H or 11-H), 4.85 (1H$_{min}$, dd, *J* 8.5, 2.5, 7-H or 11-H), 4.82 (1H$_{maj}$, dd, *J* 8.0, 2.5, 7-H or 11-H), 4.62 (1H$_{maj}$, d, *J* 15.0, NCH$_a$H$_b$Ph), 4.61 (1H$_{min}$, d, *J* 15.0, NCH$_a$H$_b$Ph), 4.41 (1H$_{min}$, d, *J* 15.0, NCH$_a$H$_b$Ph), 4.40 (1H$_{maj}$, d, *J* 15.0, NCH$_a$H$_b$Ph), 3.43 (1H$_{maj}$, d, *J* 11.0, NCH$_a$H$_b$), 3.37 (1H$_{maj}$, d, *J* 11.0, NCH$_a$H$_b$), 3.26 (1H$_{min}$, d, *J* 11.0, NCH$_a$H$_b$), 3.20 (1H$_{min}$, d, *J* 11.0, NCH$_a$H$_b$) 2.61 (1H$_{min}$, br d, *J* 2.4, OH), 2.58 (1H$_{maj}$, d, *J* 2.4, OH), 2.04-2.16 (1H, m, 4-H), 1.85-1.99 (2H + 1H$_{maj}$, m, 3-H and 4-H), 1.70 (1H$_{min}$, dt, *J* 13.0, 6.0, 4-H); δ_c ($CDCl_3$) 172.8 (C=O), 135.8 (Ph4^o-C), 135.7 (Ph4^o-C), 128.9 (Ph), 128.8 (Ph), 128.2 (Ph), 128.1 (Ph), 127.9 (Ph), 123.9 (8-C or 10-C), 123.9 (8-C or 10-C), 119.5 (q, *J* 325, CF_3), 108.0 (7-C or 11-C), 107.5 (7-C or 11-C), 107.4 (7-C or 11-C), 107.3 (7-C or 11-C), 99.2 (2-C), 98.6 (2-C), 89.3 (5-C), 89.2 (5-C), 56.1 (CH_2NPh), 52.3 (6-C), 52.1 (6-C), 47.0 (CH_2N), 32.9 (3-C), 32.8 (3-C), 28.2 (4-C), 27.8 (4-C); m/z 467 (100%, MNa$^+$), (Found: MH$^+$, 467.0859. $C_{19}H_{19}N_2O_5F_3S$ requires MH$^+$, 467.0859).

2-Allyl-13-benzyl-9-[(trifluoromethyl)sulfonyl]-1-oxa-9,13-diazadispiro[4.0.5.3] tetradeca-7,10-dien-12-one. **14b**



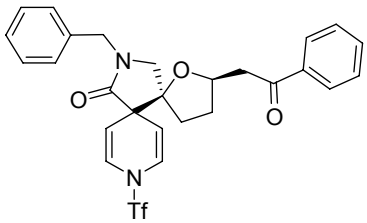
Bromotrimethylsilane (0.003 mL, 0.02 mmol) and allyl trimethylsilylane (0.08 mL, 0.5 mmol) were added to a solution of acetal **13** (0.034 g, 0.05 mmol) and indium(III)chloride (0.0022 g, 0.01 mmol) in acetonitrile (1.0 mL) under a nitrogen atmosphere at room temperature. The solution was stirred at room temperature for 4 hours and saturated sodium hydrogen carbonate solution (5 mL) was added. The solution was extracted with diethyl ether (3 x 5 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by flash chromatography (SiO_2; EtOAc-petrol 1:7 to 1:2) to yield the title compound **14b** (20 mg, 85%) as a colourless oil and as a 4:5 inseparable mixture of diastereoisomers. R_f (EtOAc:petrol 1:4) 0.23; υ_{max}(film)/cm^{-1} 1701 (C=O); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.29-7.38 (3H, m, Ph), 7.23-7.26 (2H, m, Ph), 6.82 (1H, d, *J* 8.5, 8-H or 10-H), 6.73 (1H, d, *J* 8.5, 8-H or 10-H), 5.62-5.83 (1H, m, C=CH_aH$_b$), 5.39 (1H$_{min}$, dd, *J* 8.5, 2.5, 7-H or 11-H), 5.35 (1H$_{maj}$, dd, *J* 8.5, 2.5, 7-H or 11-H), 5.01-5.11 (2H, m, CH=CH$_a$$H_b$), 4.83 (1H$_{maj}$, dd, *J* 8.5, 2.5, 7-C or11-C), 4.83 (1H$_{min}$, dd, *J* 8.5, 2.5, 7-H or 11-H), 4.62 (1H$_{min}$, d, *J* 15.0, NCH$_a$H$_b$-Ph), 4.52 (2H, s, NCH$_2$Ph), 4.41 (1H$_{min}$, d, *J* 15.0, NCH$_a$H$_b$Ph), 3.91-4.01 (1H, m, 2-H), 3.30 (1H$_{maj}$, d, *J* 10.5, NCH$_a$H$_b$), 3.23 (1H$_{min}$, d, *J* 11.0, NCH$_a$H$_b$), 3.22 (1H$_{maj}$, d, *J* 10.5, NCH$_a$H$_b$), 3.19 (1H$_{min}$, d, *J* 11.0, NCH$_a$H$_b$), 2.13-2.38 (2H, m, CH$_2$), 1.83-2.08 (2H, m, 3-H or 4-H), 1.47-1.79 (2H, m, 3-H or 4-H); δ$_c$ ($CDCl_3$) 173.1 (C=O$_{min}$), 173.0 (C=O$_{maj}$), 135.9 (Ph4^o-C$_{min}$), 135.8 (4^o-C$_{maj}$), 134.2 (CH$_2$*C*H=CH$_{2min}$), 134.1 (CH$_2$*C*H=CH$_{2maj}$), 128.8 (Ph$_{maj}$), 128.8 (Ph$_{min}$), 128.0 (Ph$_{maj\ and\ min}$), 127.7 (Ph$_{maj\ and\ min}$), 124.0 (8-C or 10-C$_{maj}$), 123.6 (8-C or 10-C$_{maj}$), 123.5 (8-C or 10-C$_{min}$), 123.4 (8-C or 10-C$_{min}$), 117.4 (*C*H$_2$CH=CH$_{2maj}$), 117.3 (*C*H$_2$CH=CH$_{2min}$), 108.3 (7-C or 11-C$_{min}$), 108.2 (7-C or 11-C$_{maj}$), 107.9 (7-C or 11-C$_{min}$), 107.5 (7-C or 11-C$_{maj}$), 88.1 (5-C$_{maj}$), 88.1 (5-C$_{min}$), 80.4 (2-C$_{maj}$), 78.8 (2-C$_{min}$), 56.1 (PhCH$_2$N$_{maj}$), 55.0 (PhCH$_2$N$_{min}$), 52.9 (6-C$_{maj}$), 52.2 (6-C$_{min}$), 46.8 (NCH$_{2maj}$), 46.8 (NCH$_{2min}$), 40.1 (CH$_{2maj}$), 39.4 (CH$_{2min}$), 30.7 (CH$_{2maj}$), 30.6 (CH$_{2maj}$), 30.2 (CH$_{2min}$), 30.0 (CH$_{2min}$); m/z 469.3 (100%, MH$^+$), 491.3 (25%, MNa$^+$). (Found: MH$^+$, 469.1400. $C_{22}H_{23}N_2O_4F_3S$ requires MH$^+$, 469.1403).

13-Benzyl-9-[(trifluoromethyl)sulfonyl]-1-oxa-9,13-diazadispiro[4.0.5.3] tetradeca-7,10-dien-12-one. **14c**



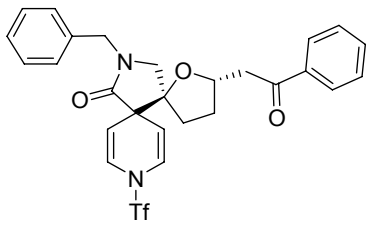
Bromotrimethylsilane (0.013 mL, 0.1 mmol) and triethylsilane (0.08 mL, 0.5 mmol) were added to a solution of acetal **13** (0.034 g, 0.05 mmol) and indium(III)chloride (0.011 g, 0.05 mmol) in acetonitrile (2.0 mL) under a nitrogen atmosphere at room temperature. The solution was stirred at room temperature for 20 minutes and saturated sodium hydrogen carbonate solution (5 mL) was added. The solution was extracted with diethyl ether (3 x 5 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by flash chromatography (SiO_2; EtOAc-petrol 1:7 to 1:2) to yield the title compound **14c** (21 mg, 98%) as a colourless oil R_f (EtOAc:petrol 1:4) 0.16; υ_{max}(film)/cm^{-1} 1699 (C=O); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.23-7.38 (5H, m, Ph), 6.80 (1H, d, *J* 8.5, 8-H or 10-H), 6.73 (1H, d, *J* 8.0, 8-H or 10-H), 5.34 (1H, dd, *J* 8.5, 2.5, 7-H or 11-H), 4.83 (1H, dd, *J* 8.5, 2.5, 7-H or 11-H), 4.65 (1H, d, *J* 14.5, NCH$_a$H$_b$Ph), 4.38 (1H, d, *J* 14.5, NCH$_a$H$_b$Ph), 3.83 (2H, t, *J* 6.5, 2-H), 3.26 (1H, d, *J* 11.0, NCH$_a$H$_b$), 3.21 (1H, d, *J* 11.0, NCH$_a$H$_b$), 2.03 (1H, dt, *J* 12.5, 7.0, 4-H), 1.80-1.91 (2H, m, 3-H and 4-H), 1.69 (1H, dt, *J* 12.5, 6.9, 3-H); δ_c ($CDCl_3$) 173.0 (C=O), 135.9 (Ph4^o-C), 128.8 (Ph), 128.0 (Ph), 127.8 (Ph), 123.8 (8-C or 10-C), 123.5 (8-C or 10-C), 108.3 (7-C or 11-C), 107.5 (7-C or 11-C), 87.9 (5-C), 68.8 (2-C), 55.1 (CH_2N), 52.6 (6-C), 47.0 (NCH_2), 30.6 (4-C), 25.6 (3-C); m/z 451.2 (100%, MNa$^+$). (Found: MNH$_4^+$, 446.1347. $C_{19}H_{19}N_2O_4F_3S$ requires MNH$_4^+$, 446.1356).

13-Benzyl-2-(2-oxo-2-phenylethyl)-9-[(trifluoromethyl)sulfonyl]-1-oxa-9,13-diazadispiro[4.0.5.3]tetradeca-7,10-dien-12-one. **14d**



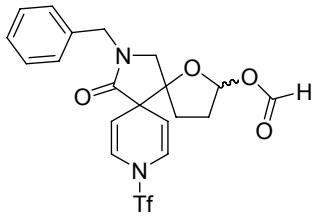
Bromotrimethylsilane (0.013 mL, 0.1 mmol) and (1-phenylvinyloxy)trimethylsilane (0.096 mL, 0.5 mmol) were added to a solution of acetal **13** (0.034 g, 0.05 mmol) and indium(III)chloride (0.011 g, 0.05 mmol) in acetonitrile (2.0 mL) under a nitrogen atmosphere at room temperature. The solution was stirred at room temperature for 40 minutes and saturated sodium hydrogen carbonate solution (5 mL) was added. The solution was extracted with ethyl acetate (3 x 5 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by flash chromatography (SiO_2; EtOAc-petrol 1:7 to 1:1) to yield the title compound *syn*-**14d** (6 mg, 22%) as a colourless oil. R_f (EtOAc:petrol 3:7) 0.32; υ_{max}(film)/cm^{-1} 1700 (C=O), 1684 (C=O); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.96 (2H, d, *J* 7.5, Ph), 7.61 (1H, t, *J* 7.0, Ph), 7.50 (2H, t, *J* 7.5, Ph), 7.30-7.35 (3H, m, Ph), 7.21 (2H, d, *J* 7.5, Ph), 6.79 (1H, d, *J* 8.0, 8-H or 10-H), 6.74 (1H, d, *J* 8.0, 8-H or 10-H), 5.29 (1H, dd, *J* 8.5, 2.5, 7-H or 11-H), 4.84 (1H, dd, *J* 8.5, 2.5, 7-H or 11-H), 4.63 (1H, d, *J* 15.0, NCH$_a$H$_b$Ph), 4.50 (1H, t, *J* 7.0, 2-H), 4.38 (1H, d, *J* 15.0, NCH$_a$H$_b$Ph), 3.42 (1H, dd, *J* 16.5, 6.5, COCH$_a$H$_b$), 3.27 (1H, d, *J* 11.0, NCH$_a$H$_b$), 3.21 (1H, d, *J* 10.5, NCH$_a$H$_b$), 3.00 (1H, dd, *J* 16.5, 7.0, COCH$_a$H$_b$), 2.07-2.17

(2H, m, 3-H or 4-H), 1.75 (1H, dt, *J* 13.5, 7.5, 3-H or 4-H), 1.53-1.56 (1H, m, 3-H or 4-H); δ_c ($CDCl_3$) 197.7 (PhC=O), 172.8 (C=O),136.8 (Ph4^o-C), 135.7 (Ph4^o-C), 133.5 (Ph), 128.8 (Ph), 128.8 (Ph), 128.1 (Ph), 127.9 (Ph), 127.8 (Ph), 123.6 (8-C or 10-C), 123.4 (8-C or 10-C), 108.3 (7-C or 11-C), 107.6 (7-C or 11-C), 88.0 (5-C), 75.8 (2-C), 54.9 (CH_2N), 52.1 (6-C), 46.9 (NCH_2), 43.5 (CH_2), 31.1 (4-C), 30.1 (3-C); m/z 547.6 (15%, MH^+), 564.1 (30%, MNH_4^+), 569.2 (100%, MNa^+). (Found: MH^+, 547.1518. $C_{27}H_{25}N_2O_5F_3S$ requires MH^+, 557.1509).



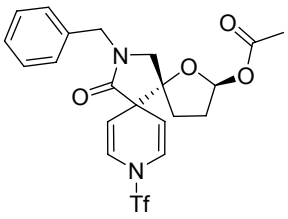
and its diastereoisomer *anti*-**14d** (8mg, 29%); R_f (EtOAc:petrol 3:7) 0.28; υ_{max}(film)/cm^{-1} 1699, (C=O),1687 (PhC=O); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.92 (2H, d, *J* 7.0, Ph), 7.60 (1H, t, *J* 7.5, Ph), 7.84 (2H, t, *J* 7.5, Ph), 7.26-7.31 (3H, m, Ph), 7.21 (2H, d, *J* 8.5, Ph), 6.83 (1H, d, *J* 8.5, 8-H or 10-H), 6.73 (1H, d, *J* 8.0, 8-H or 10-H), 5.36 (1H, dd, *J* 8.5, 2.5, 7-H or 11-H), 4.80 (1H, dd, *J* 8.5, 2.5, 7-H or 11-H), 4.57 (1H, d, *J* 15.0, NCH_aH_bPh), 4.47 (1H, dd, *J* 8.5, 6.5, 2-H), 4.36 (1H, d, *J* 14.5, NCH_aH_bPh), 3.30 (1H, ap.d, *J* 21.5, $COCH_aH_b$), 3.29 (1H, d, *J* 10.5, NCH_aH_b), 3.16 (1H, d, *J* 10.5, NCH_aH_b), 3.01 (1H, dd, *J* 16.5, 7.0, $COCH_aH_b$), 2.18-2.23 (1H, m, 3-H or 4-H), 2.07-2.11 (1H, m, 3-H or 4-H), 1.80 (1H, ddd, *J* 11.0, 7.5, 3.5, 3-H or 4-H), 1.60-1.65 (1H, m, 3-H or 4-H); δ_c ($CDCl_3$) 197.6 (PhC=O), 172.9 (C=O), 136.8 (Ph4^o-C), 135.8 (Ph4^o-C), 133.4 (Ph), 128.8 (Ph), 128.7 (Ph), 128.2 (Ph), 128.0 (Ph), 127.7 (Ph), 124.3 (8-C or 10-C), 123.7 (8-C or 10-C), 119.5 (q, *J* 324, CF_3), 107.9 (7-C or 11-C), 107.1 (7-C or 11-C), 88.1 (5-C), 56.1 (CH_2N), 52.9 (6-C), 46.8 (NCH_2), 44.6 (CH_2), 31.5 (4-C), 30.7 (3-C) (2-C missing; presumed under $CDCl_3$); m/z 547.5 (100%, MH^+), 564.3 (90%, MNH_4^+), 569.0 (80%, MNa^+). (Found: MNa^+, 569.1308. $C_{27}H_{25}N_2O_5F_3S$ requires MNa^+, 569.1328).

13-Benzyl -12-oxo-9-[(trifluoromethyl)sulfonyl]-oxa -9,13-diaza-dispiro[4.0.5.3]tetradeca-7,10-dien-2-yl formate. **14e**



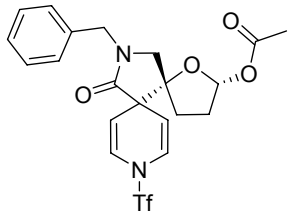
Formic acid (0.3 mL) was added to a solution of trityl alcohol **13** (0.034 g, 0.05 mmol) in diethyl ether (0.6 mL) and THF (0.5 mL) at room temperature and stirred for 10 minutes. The solution was diluted with brine, neutralized with saturated sodium hydrogen carbonate solution, extracted with EtOAc (3 x 15 mL) and dried ($MgSO_4$). The solution was evaporated under reduced pressure to yield the crude product which was purified by flash chromatography (SiO_2; EtOAc-pentane 1:4) to yield the title compound **14e** (13 mg, 55%) as a 2:1 inseparable mixture of diastereoisomers. R_f(EtOAc:petrol 1:1) 0.50; υ_{max}(film)/cm^{-1} 1732 (CHO), 1698 (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 8.01 (1H$_{min}$, s, CHO), 7.91 (1H$_{maj}$, s, CHO), 7.29-7.38 (3H, m, Ph), 7.20-7.23 (2H, m, Ph), 6.83 (1H$_{min}$, d, *J* 9.0, 8-H or 10-H), 6.82 (1H$_{maj}$, d, *J* 8.5, 8-H or 10-H), 6.79 (1H$_{maj}$, d, *J* 8.5, 8-H or 10-H), 6.77 (1H$_{min}$, d, *J* 8.0, 8-H or 10-H), 6.42 (1H$_{maj}$, d, *J* 4.0, 2-H), 6.34 (1H$_{min}$, d, *J* 3.0, 2-H), 5.32 (1H$_{maj}$, dd, *J* 8.5, 2.5, 7-H or 11-H), 5.21 (1H$_{min}$, dd, *J* 8.5, 2.5, 7-H or 11-H), 4.83 (1H, dd, *J* 8.5, 2.5, 7-H or 11-H), 4.67 (1H$_{min}$, d, *J* 15.0, NCH$_a$H$_b$Ph), 4.52 (2H$_{maj}$, s, NCH$_a$H$_b$Ph), 4.34 (1H$_{min}$, d, *J* 15.0, NCH$_a$H$_b$Ph), 3.38 (1H$_{maj}$, d, *J* 11.0, NCH$_a$H$_b$), 3.35 (1H$_{maj}$, d, *J* 11.5, NCH$_a$H$_b$), 3.28 (1H$_{min}$, d, *J* 11.0, NCH$_a$H$_b$), 3.25 (1H$_{min}$, d, *J* 11.0, NCH$_a$H$_b$), 2.21 (1H$_{maj}$, ddd, *J* 12.5, 7.5, 3.0, 3-H), 1.90-2.13 (3H, m, 3-H and 4-H), 1.79 (1H$_{min}$, m, 3-H or 4-H); δ_c ($CDCl_3$) 172.3 (C=O), 160.0 (C=O), 159.8 (C=O), 135.5 (Ph4^o-C), 135.4 (Ph4^o-C), 128.9 (Ph), 128.9 (Ph), 128.1 (Ph), 127.9 (Ph), 127.8 (Ph), 124.2 (8-C or 10-C), 124.1 (8-C or 10-C), 124.0 (8-C or 10-C), 107.8 (7-C or 11-C), 107.1 (7-C or 11-C), 106.9 (7-C or 11-C), 106.7 (7-C or 11-C), 98.5 (2-C), 97.7 (2-C), 91.1 (5-C), 55.8 (CH_2NPh), 54.9 (CH_2NPh), 52.1 (6-C), 51.9 (6-C), 47.0 (CH_2N), 46.7 (CH_2N), 31.8 (3-C), 31.7 (3-C), 28.0 (4-C), 27.0 (4-C); m/z 467 (60%, MH-CO), 495 (100%, MNa$^+$), (Found: MH$^+$, 473.0994. $C_{20}H_{19}N_2O_6F_3S$ requires MH$^+$, 473.0989).

13-Benzyl-12-oxo-9-[(trifluoromethyl)sulfonyl]-1-oxa-9,13-diazadispiro[4.0.5.3]tetradeca-7,10-dien-2-yl acetate. **14f**



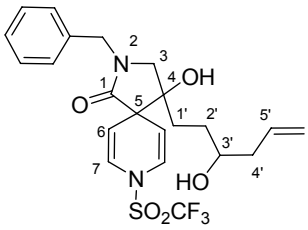
Acetic anhydride (0.01 mL, 0.067 mmol) was added to a solution of alcohol **14a** (0.025 g, 0.056 mmol) in pyridine (0.5 mL) under a nitrogen atmosphere at room temperature. The solution was stirred for 18 hours

then partitioned between brine (5 mL) and CH_2Cl_2 (3 x 5 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by flash chromatography (SiO_2; EtOAc-petrol 1:4) to yield the title compound *anti*-**14f** (0.013 g, 48%). R_f (EtOAc:petrol 3:7) 0.22; υ_{max}(film)/cm^{-1} 1747 (C=O), 1703 (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.28-7.37 (3H, m, Ph), 7.22 (2H, d, *J* 8.0, Ph), 6.81 (1H, d, *J* 8.5, 8-H or 10-H), 6.78 (1H, d, *J* 8.5, 8-H or 10-H), 6.33 (1H, d, *J* 4.5, 2-C), 5.34 (1H, dd, *J* 8.5, 3.0, 7-H or 11-H), 4.84 (1H, dd, *J* 8.5, 3.0, 7-H or 11-H), 4.59 (1H, d, *J* 14.5, NCH$_a$H$_b$Ph), 4.45 (1H, d, *J* 14.5, NCH$_a$H$_b$Ph), 3.37 (1H, d, *J* 11.0, NCH$_a$H$_b$), 3.30 (1H, d, *J* 11.0, NCH$_a$H$_b$), 2.14-2.22 (1H, m, 3-H), 1.88-2.04 (3H, m, 3-H and 4-H), 1.88 (3H, s, Me); δ_c ($CDCl_3$) 172.5 (C=O), 169.8 (C=O), 135.5 (4^o-Ph), 128.8 (Ph), 127.9 (Ph), 127.8 (Ph), 124.1 (8-C or 10-C), 123.9 (8-C or 10-C), 119.9 (q, *J* 324, CF_3), 107.9 (7-C or 11-C), 106.9 (7-C or 11-C), 98.4 (2-C), 90.6 (5-C), 55.1 ($PhCH_2N$), 52.2 (6-C), 46.7 (NCH_2), 31.7 (3-C), 27.1 (4-C), 21.2 (Me); m/z 487.2 (50%, MH$^+$), 509.3 (100%, MNa$^+$). (Found: MH$^+$, 487.1141. $C_{21}H_{21}N_2O_6F_3S$ requires MH$^+$, 487.1145).



and its diastereoisomer *syn*-**14f** (0.011 g, 40%); R_f (EtOAc:petrol 3:7) 0.26; υ_{max}(film)/cm^{-1} 1745 (C=O), 1698 (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.29-7.38 (3H, m, Ph), 7.22 (2H, d, *J* 8.0, Ph), 6.82 (1H, d, *J* 8.5, 8-H or 10-H), 6.76 (1H, d, *J* 8.5, 8-H or 10-H), 6.24 (1H, dd, *J* 3.5, 1.5, 2-C), 5.21 (1H, dd, *J* 8.5, 2.5, 7-H or 11-H), 4.83 (1H, dd, *J* 8.5, 2.5, 7-H or 11-H), 4.72 (1H, d, *J* 15.0, NCH$_a$H$_b$Ph), 4.29 (1H, d, *J* 15.0, NCH$_a$H$_b$-Ph), 3.27 (2H, s, NCH_2), 1.98-2.18 (3H, m, 3-H and 4-H), 2.02 (3H, s, Me), 1.78 (1H, ddd, *J* 12.5, 6.0, 2.5, 4-H); δ_c ($CDCl_3$) 172.3 (C=O), 170.0 (C=O), 135.6 (4^o-Ph), 128.8 (Ph), 128.1 (Ph), 127.9 (Ph), 123.9 (8-C or 10-C), 123.6 (8-C or 10-C), 120.0 (q, *J* 324, CF_3), 107.4 (7-C or 11-C), 107.3 (7-C or 11-C), 97.7 (2-C), 90.5 (5-C), 56.0 ($PhCH_2N$), 52.2 (6-C), 47.0 (NCH_2), 31.5 (3-C), 28.2 (4-C), 21.1 (Me); m/z 487.2 (15%, MH$^+$), 509.3 (100%, MNa$^+$). (Found: MH$^+$, 487.1142. $C_{21}H_{21}N_2O_6F_3S$ requires MH$^+$, 487.1145).

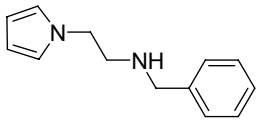
2-Benzyl-4-hydroxy-4-(3'-hydroxy-hex-5'- enyl)-8-trifluoromethanesulfonyl-2,8-diaza-spiro[4.5]deca-6,9-dien-1-one. **15**



Diethyl aluminium chloride (0.55 mL of a 1 M solution in hexane) was added to a colourless solution of trityl alcohol **13** (0.034 g, 0.05 mmol) in CH_2Cl_2 (2.5 mL) under a nitrogen atmosphere at room temperature. An

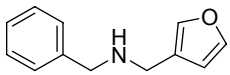
immediate bright yellow colour was observed and the solution was stirred for 2.5 minutes before addition of allyltributylstannane (0.77 mL, 2.5 mmol). The solution was stirred for 5 minutes and saturated sodium hydrogen carbonate solution (3 mL) was added followed by a solution of Rochelle's salt (10 mL). The solution was extracted with CH_2Cl_2 (3 x 10 mL), dried ($MgSO_4$) and evaporated under reduced pressure to yield the crude product which was purified by flash chromatography (SiO_2; EtOAc-petrol) to yield a 1:1 micture of the diastereoisomers of the title compound **15** (19 mg, 81%) as a colourless oil; R_f (EtOAc: CH_2Cl_2 1:1) 0.47; υ_{max}(film)/cm^{-1} 3387 (OH), 1682 (C=O); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.28-7.37 (3H, m, Ph), 7.24 (2H, d, *J* 6.5, Ph), 6.81 (1H, dd, *J* 8.5, 1.0, 7-H or 9-H), 6.70 (1H, d, *J* 8.5, 7-H or 9-H), 5.75 (1H, m, 5'-H), 5.41 (1H, dd, *J* 8.0, 2.5, 6-H or 10-H), 5.12-5.19 (2H, m, 6'-H), 4.81 (1H, dd, *J* 8.5, 2.5, 6-H or 10-H), 4.65 (1H, d, *J* 14.5, NCH$_a$H$_b$Ph), 4.53 (1H, br s, OH), 4.35 (1H, d, *J* 15.0, NCH$_a$H$_b$Ph), 3.60-3.66 (1H, m 3'-H), 3.24 (1H, d, *J* 11.0, NCH$_a$H$_b$), 3.16 (1H, d, *J* 11.0, NCH$_a$H$_b$), 2.41 (1H, br s, OH), 2.22-2.30 (1H, m, 4'-H), 2.11 (1H, dt, *J* 14.0, 8.5, 4'-H), 1.73-1.83 (1H, m, 1'-H), 1.50-1.70 (2H, m, 1'-H and 2'-H), 1.39-1.48 (1H, m, 2-H); δ_c ($CDCl_3$) 173.5 (C=O), 136.0 (Ph4^o-C), 128.8 (Ph), 128.0 (Ph), 127.8 (Ph), 123.9 (7-C or 9-C), 123.3 (7-C or 9-C), 119.5 (q, *J* 325, CF_3), 119.3 (6'-H), 108.3 (6-C or 10-C), 107.5 (6-C or 10-C), 70.7 (4-C or 3'-C), 70.5 (4-C or 3'C), 55.6 (NCH_2Ph), 53.9 (5-C), 47.1 (4'-C), 42.3 (3-C), 32.4 (1'-C), 29.8 (2'-C); m/z 487 (10%, MH$^+$), 509 (100%, MNa$^+$), (Found: MH$^+$, 487.1504. $C_{22}H_{25}N_2O_5F_3S$ requires MH$^+$, 487.1509).

N-Benzyl-2-(1H-pyrrol-1-yl)ethanamine. **S1**



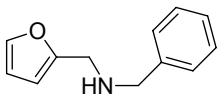
Finely ground sodium hydroxide (0.080 g, 2 mmol) and tetrabutylammonium bisulfate (0.034 g, 0.1 mmol) was added in one portion to a stirred solution of pyrrole (0.030 g, 0.45 mmol) and *N*-benzyl-2-chloroethylamine (0.085 g, 0.5 mmol) in acetonitrile (1.5 mL). The solution was heated to reflux for 1 hour, allowed to cool to room temperature and filtered. The filtrate was concentrated and the residue dissolved in EtOAc. The solution was washed with water, extracted with EtOAc (3 x 5 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2; EtOAc:petrol) to yield the title compound **S1** (0.049 g, 54%) as a brown oil; R_f (EtOAc:petrol 1:1) 0.36; υ_{max}(film)/cm^{-1} 2925 (NH); δ_H(300MHz; $CDCl_3$) 7.23-7.34 (5H, m, Ph), 6.69 (2H, t, *J* 2.0, 2-H), 6.16 (2H, t, *J* 2.0, 3-H), 4.03 (2H, t, *J* 6.0, $ArNCH_2$), 3.77 (2H, s, $PhCH_2$), 2.96 (2H, t, *J* 6.0, CH_2NH), 1.57 (1H, s, NH); δ_C140.2 (Ph4^o-C), 128.7 (Ph), 128.3 (Ph), 127.3 (Ph), 120.3 (2-C), 108.6 (3-C), 53.8 ($PhCH_2$), 50.1 (CH_2), 50.0 (CH_2); m/z 201.1 (100% MH$^+$), 223.1 (30%, MNa$^+$). (Found: MH$^+$, 201.1388. $C_{13}H_{16}N_2$ requires MH$^+$, 201.1386).

***N-((Furan-3-yl)methyl)(phenyl)methanamine* S2**



Methanesulfonyl chloride (0.17 mL, 2.2 mmol) was added dropwise to a colourless solution of 3-furan methanol (0.17 mL, 2.0 mmol) and triethylamine (0.31 mL) in dry CH_2Cl_2 (10 mL) under a nitrogen atmosphere at 0 ^oC. The solution was stirred for 35 minutes at 0 ^oC then benzylamine (0.24 mL, 2.2 mmol) was added and the solution allowed to warm to room temperature and stirred for 20 hours. Saturated sodium hydrogen carbonate solution (10 mL) was added and the solution was extracted with CH_2Cl_2 (2 x 10 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2; EtOAc:hexane:methanol) to yield the title compound **S2** (0.108 g, 33%) as a yellow oil. R_f (EtOAc:petrol 1:1) 0.20; υ_{max}(film)/cm^{-1} 3062 (NH) 2823 (CH); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.39 (1H, t, *J* 1.5, 2-H), 7.36 (1H, dd, *J* 1.5, 1.0, 5-H), 7.33 (4H, d, *J* 4.5, Ph), 7.24-7.29 (1H, m, Ph), 6.40 (1H, d, *J* 1.0, 4-H), 3.81 (2H, s, NCH_2), 3.67 (2H, s, NCH_2), 1.67 (1H, br s, NH); δ_c ($CDCl_3$) 143.1 (5-C), 140.1 (Ph4^o-C), 139.9 (2-C), 128.4 (Ph), 128.2 (Ph), 127.0 (Ph), 123.9 (2-C), 110.4 (4-C), 53.1 ($PhNCH_2$), 43.5 (NCH_2); m/z 188.2 (100%, MH^+); (Found: MH^+, 188.1072. $C_{12}H_{13}NO$ requires MH^+, 188.1070).

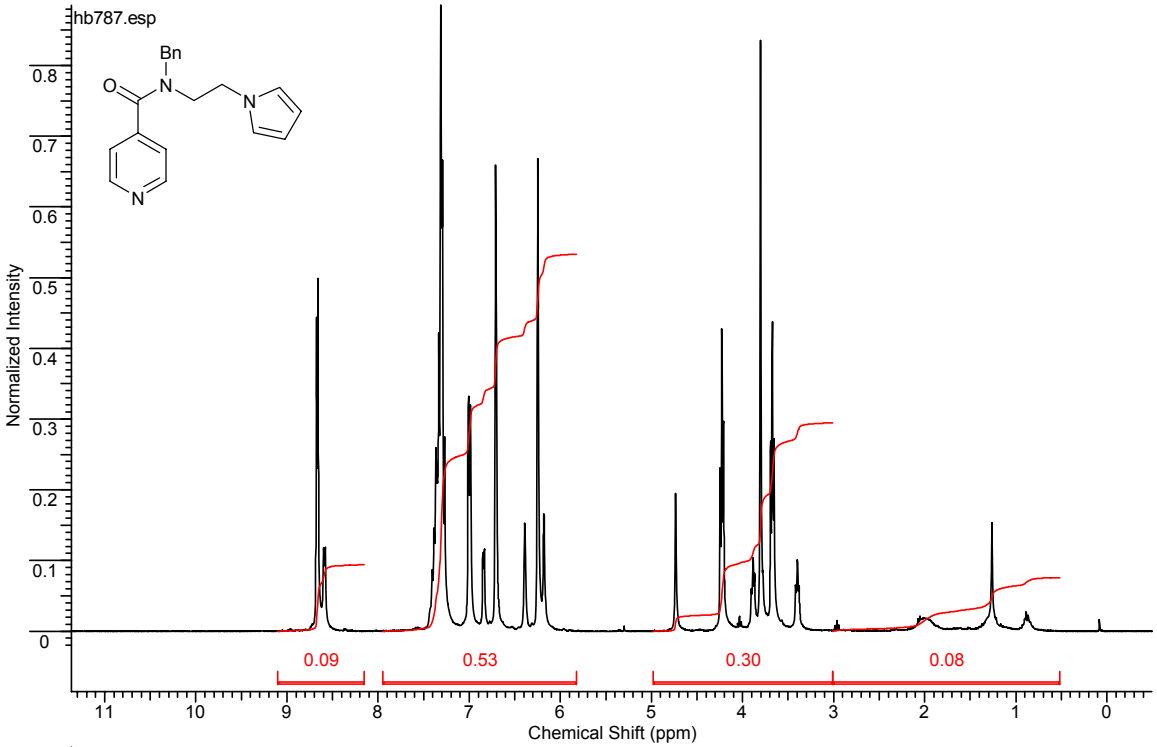
***N-((Furan-2-yl)methyl)(phenyl)methanamine.* S3**

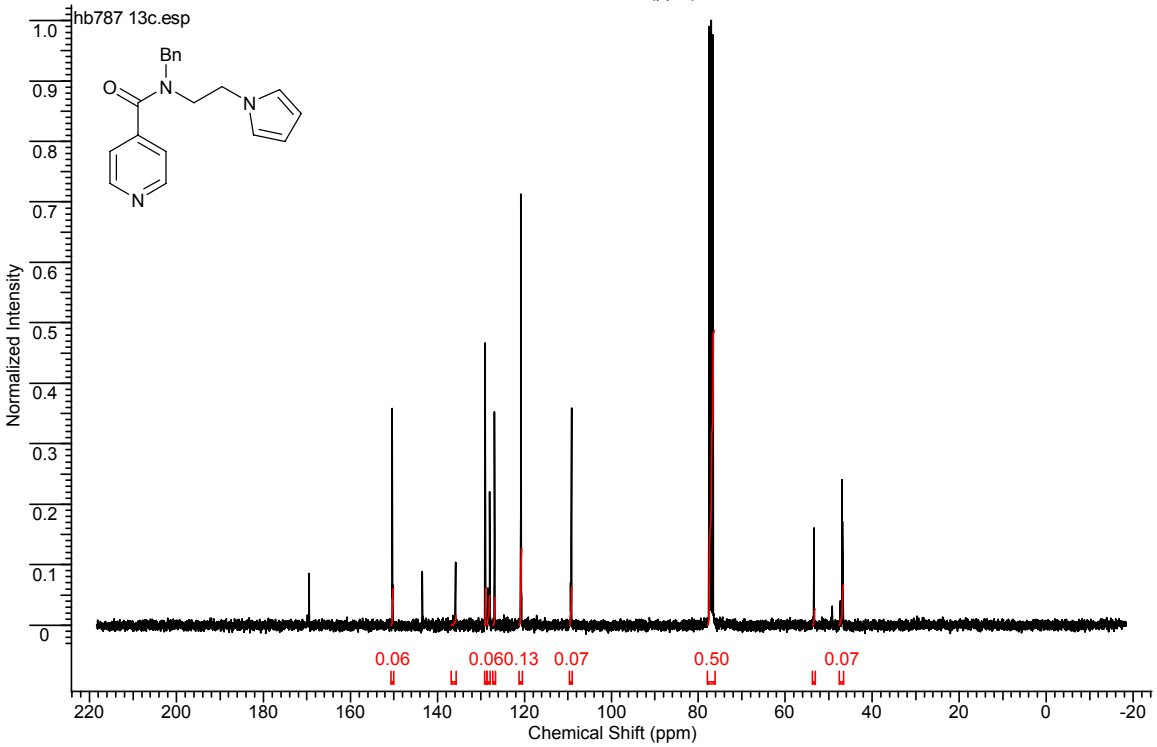


Sodium triacetoxyborohydride (1.59 g, 7.5 mmol) was added to a solution of the benzaldehyde (0.56 mL, 5.5 mmol), the furfurylamine (0.44 mL, 5.0 mmol) and acetic acid (0.31 mL, 5.5 mmol) in CH_2Cl_2 (10 mL) under nitrogen at room temperature and stirred for 16 hours. Sodium hydroxide (1 M, 15 mL) was added and the solution extracted with CH_2Cl_2 (3 x 15 mL), dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by flash chromatography (SiO_2; EtOAc-petrol) to yield the title compound (0.514 g, 55%) as a colourless oil. R_f (EtOAc:petrol 1:3) 0.15; υ_{max}(film)/cm^{-1} 3027 (NH); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.37 (1H, dd, *J* 2.0, 1.0, 5-H), 7.33 (4H, d, *J* 4.5, Ph), 7.23-7.28 (1H, m, Ph), 6.32 (1H, dd, *J* 3.0, 2.0, 4-H), 6.18 (1H, dd, *J* 3.0, 0.5, 3-H), 3.79 (4H, s, 2 x NCH_2), 1.70 (1H, s, NH); δ_c ($CDCl_3$) 153.8 (2-C), 141.8 (5-C), 139.9 (Ph 4^o), 128.4 (Ph), 128.3 (Ph), 127.0 (Ph), 110.1 (4-C), 107.0 (3-C), 52.8 (NCH_2 Ph), 45.4 (NCH_2); m/z 188 (100%, MH^+); (Found: MH^+,188.1066. $C_{12}H_{13}NO$ requires MH^+, 188.1070).

NMR spectra

1





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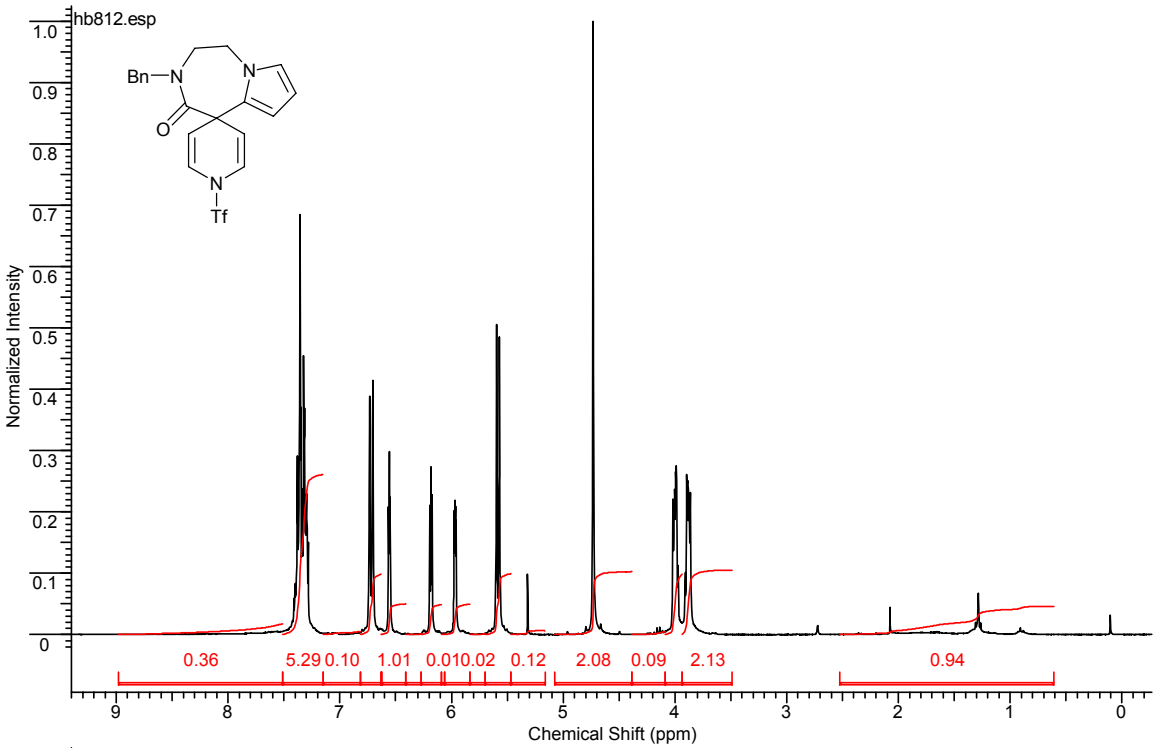
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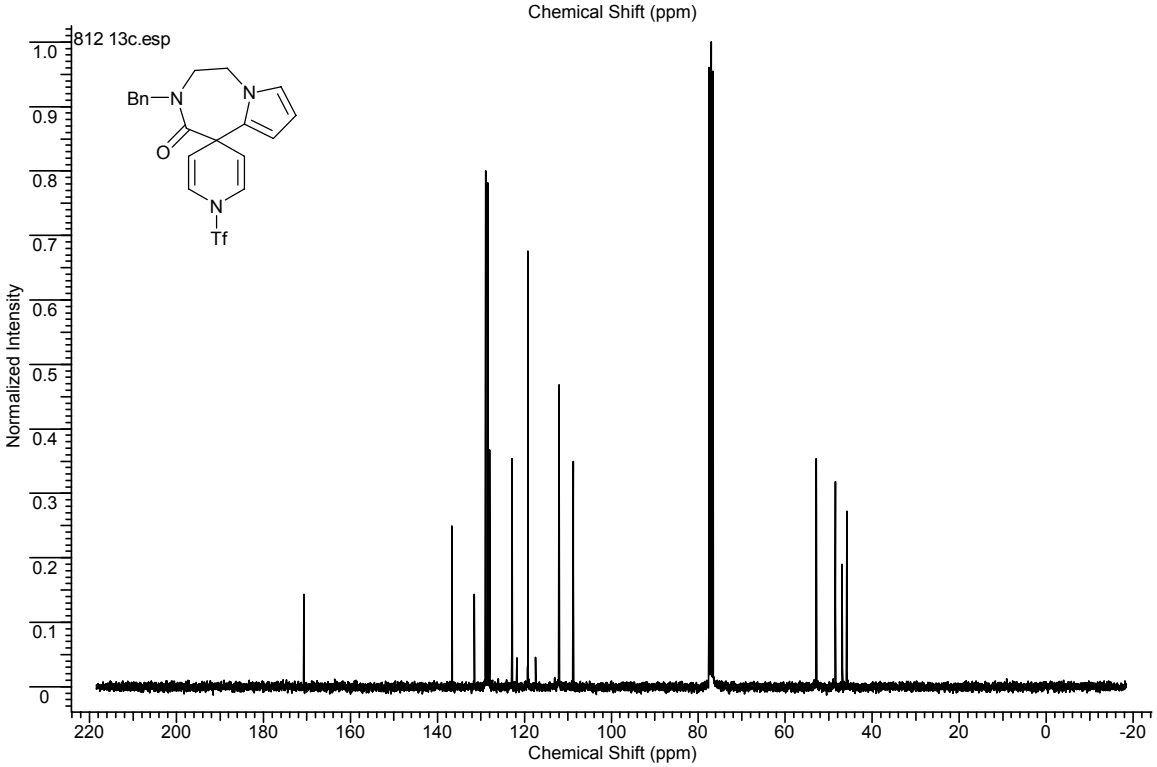
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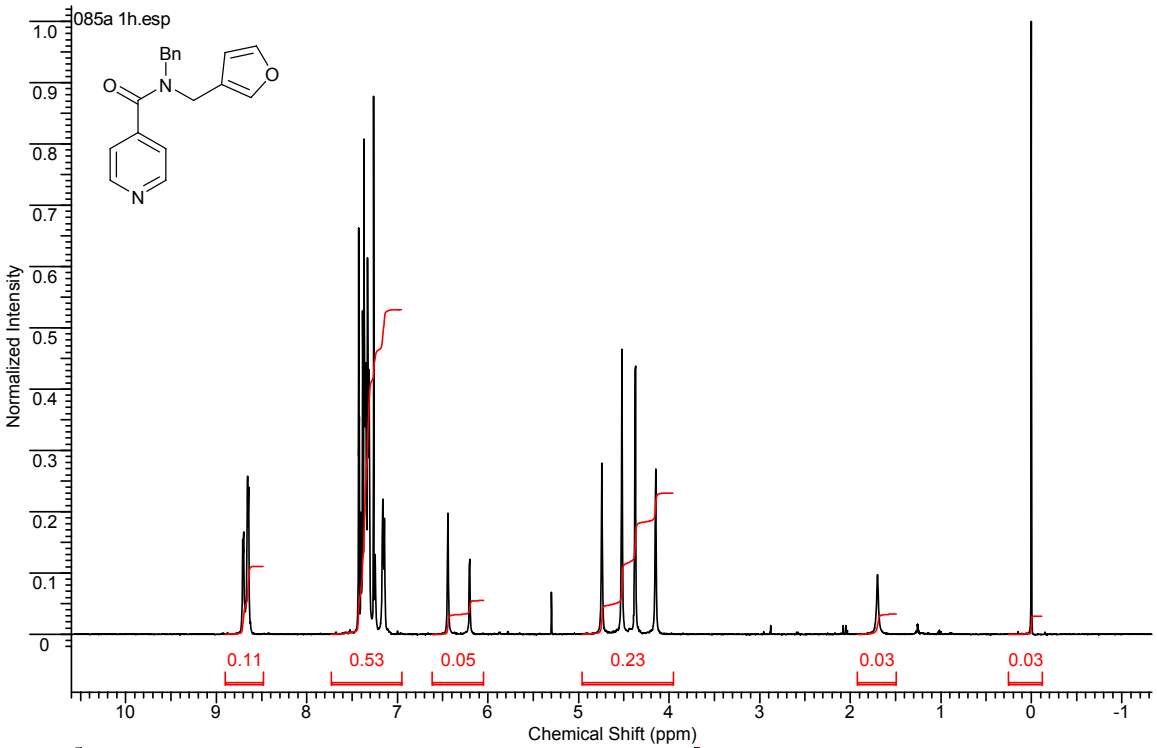
Chemical Shift (ppm)

3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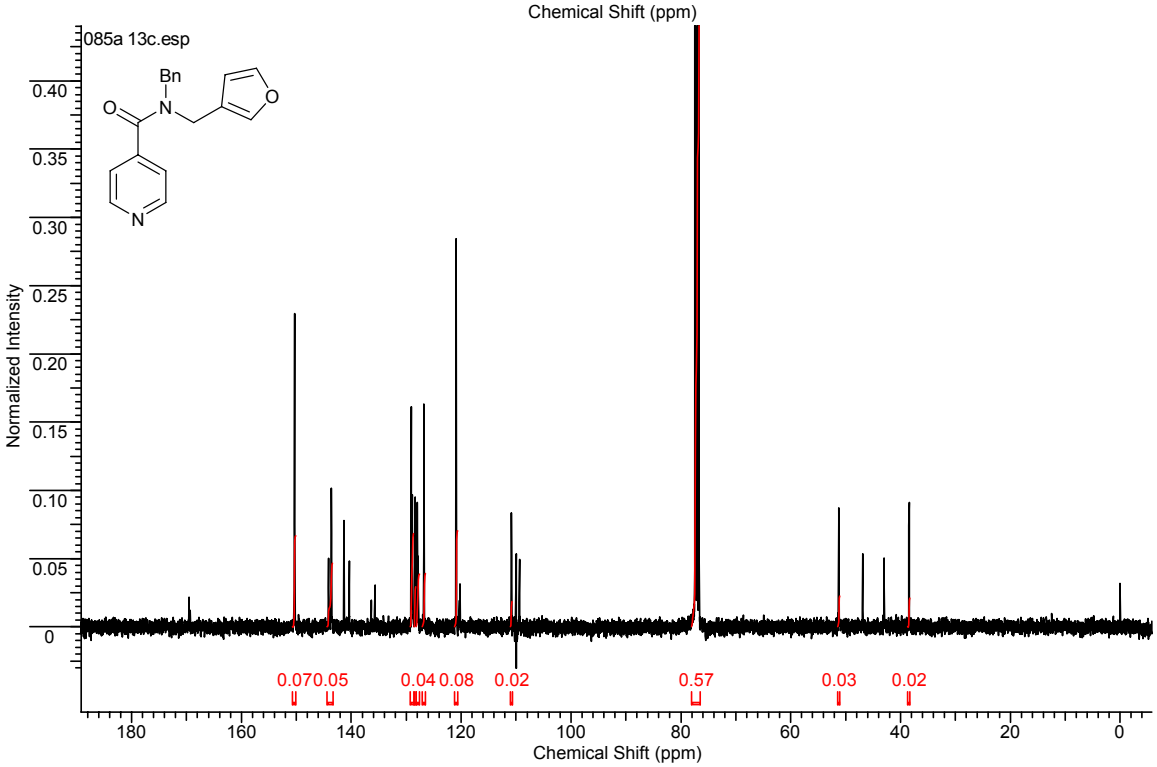
Chemical Shift (ppm)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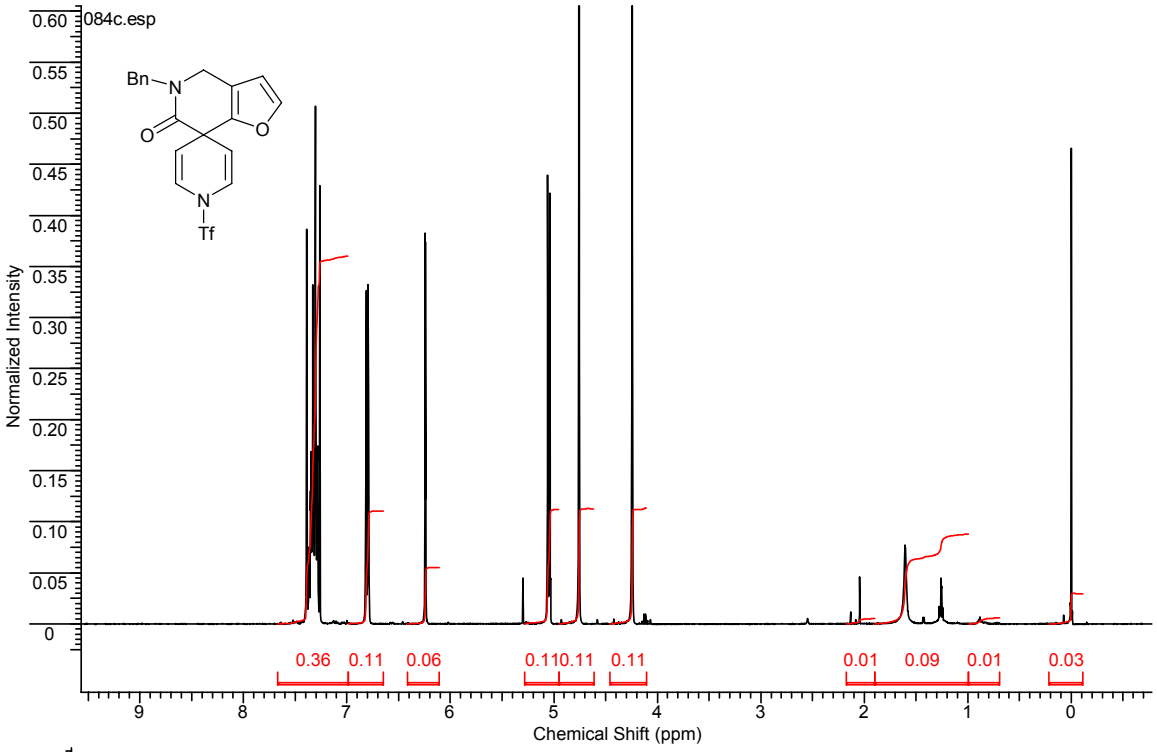
Chemical Shift (ppm)

4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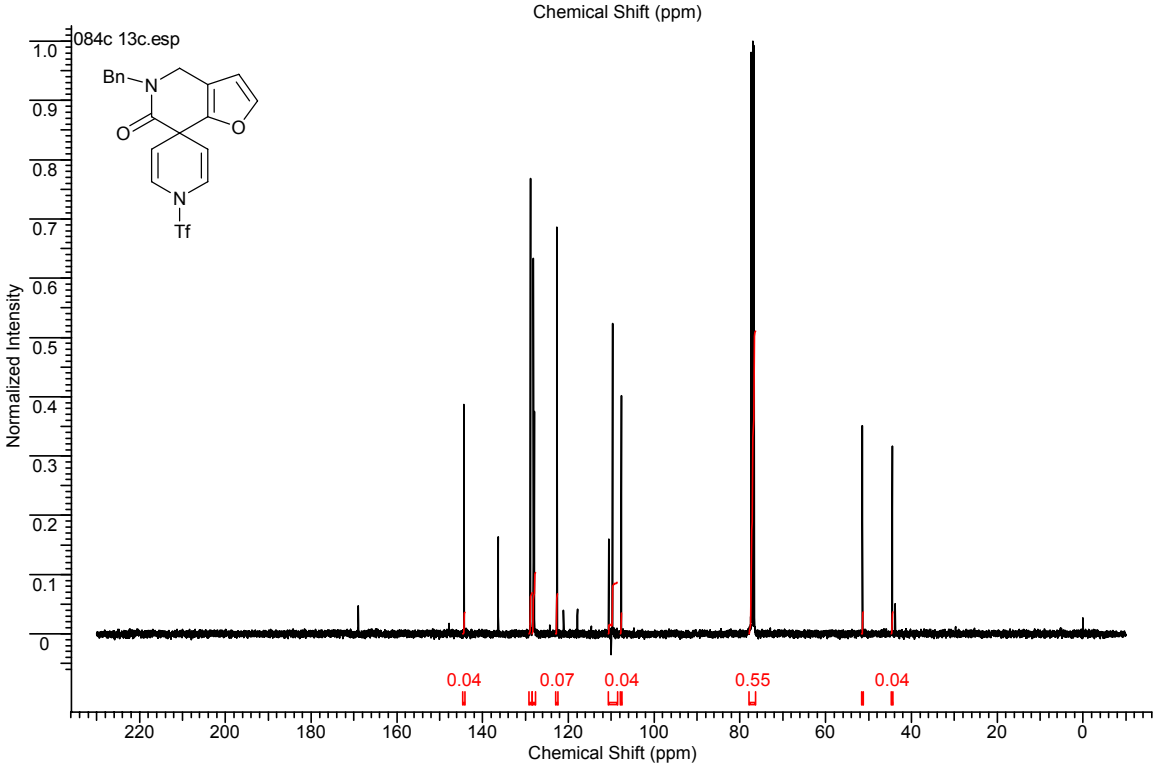
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0.04
0.55
0.04
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20
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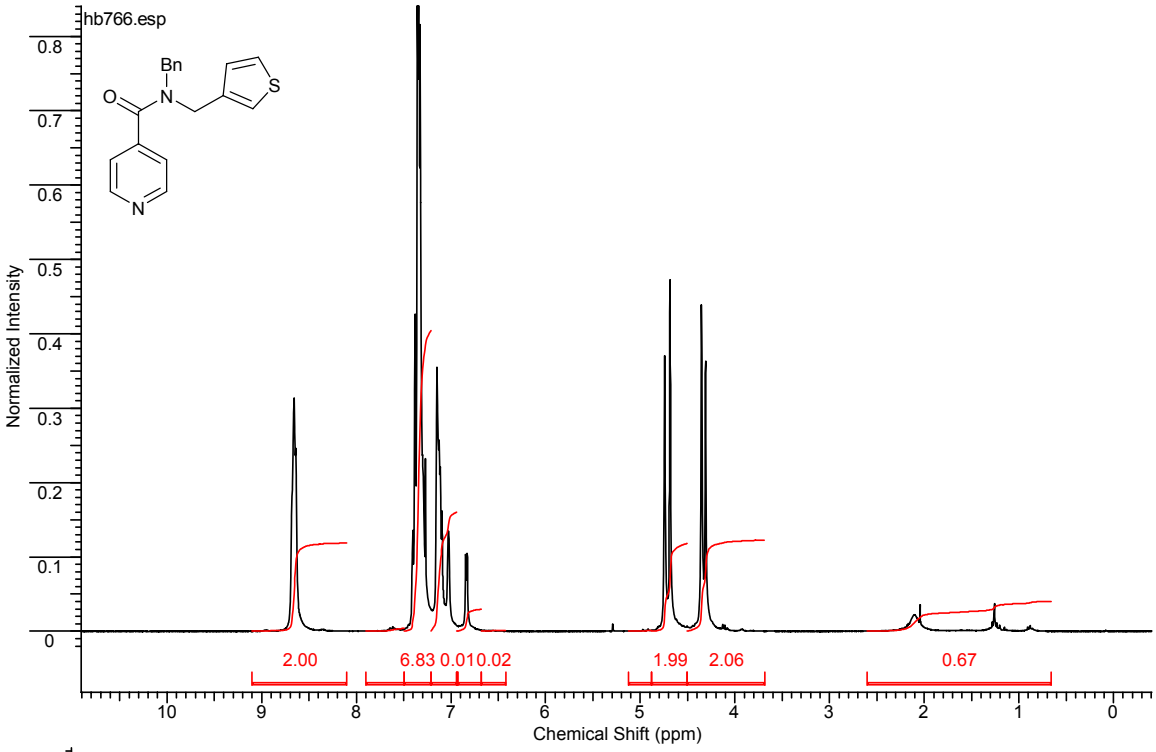
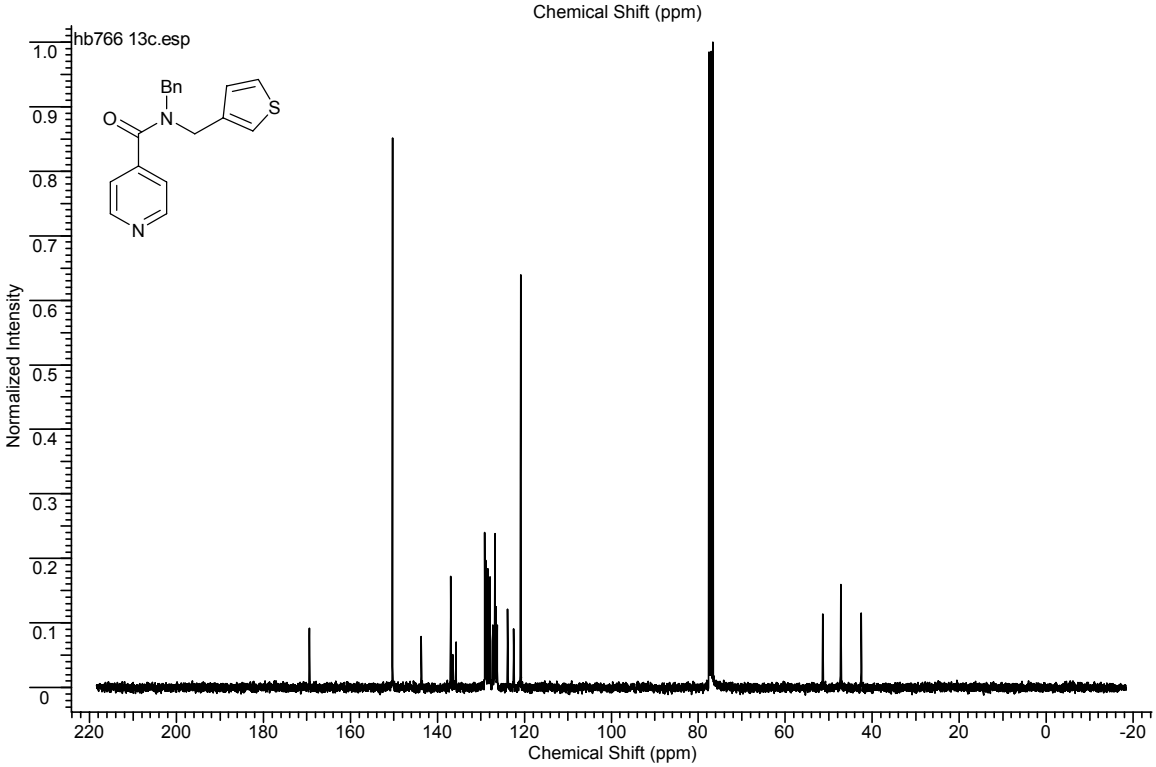
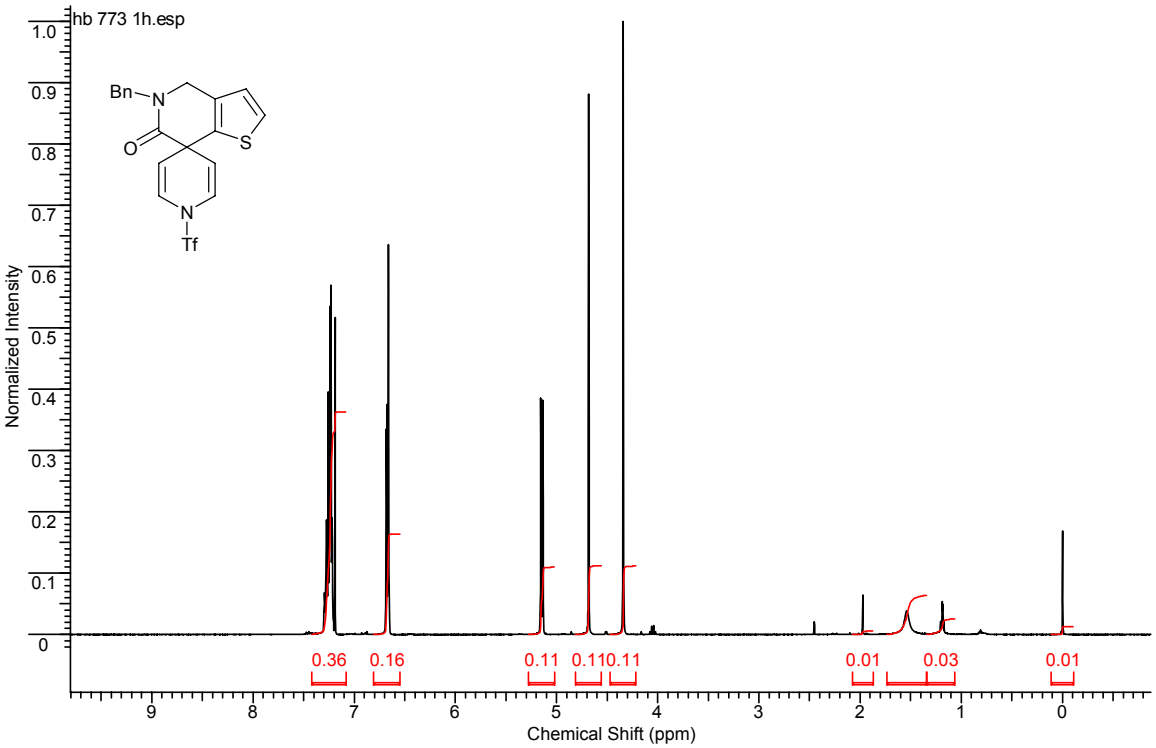
Chemical Shift (ppm)

5

Supporting information for Brice, Clayden: Doubly dearomatising intramolecular coupling



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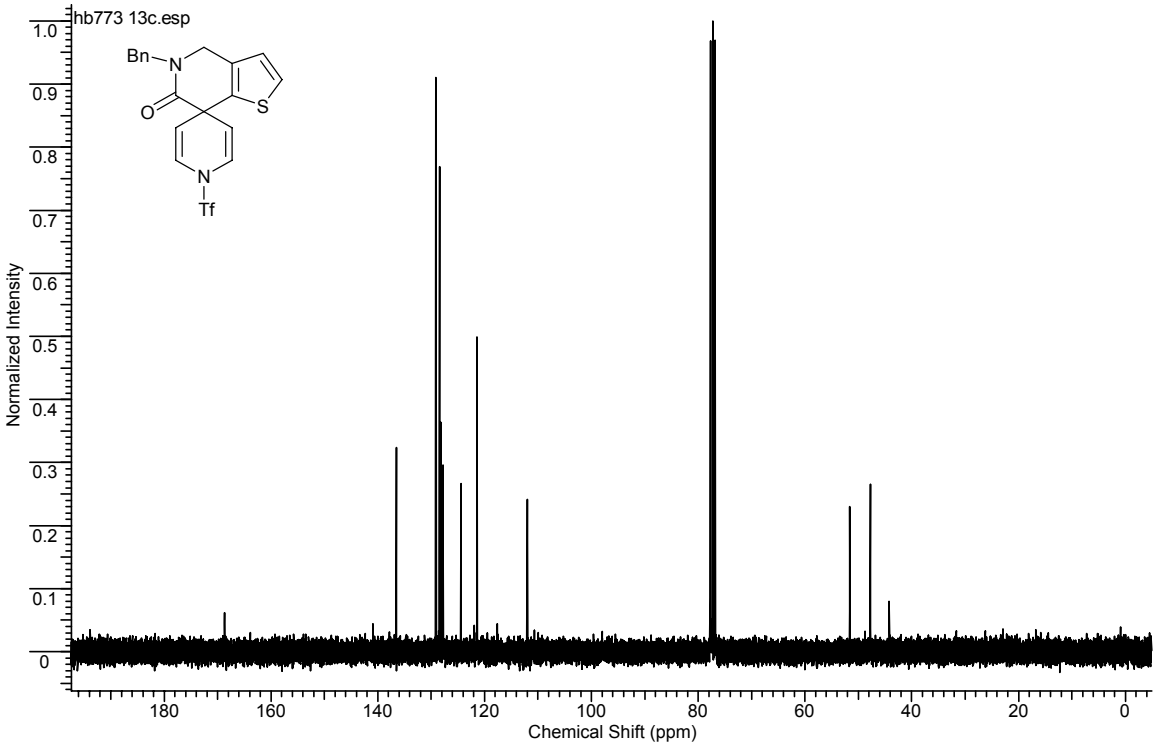
0.01
Chemical Shift (ppm)

6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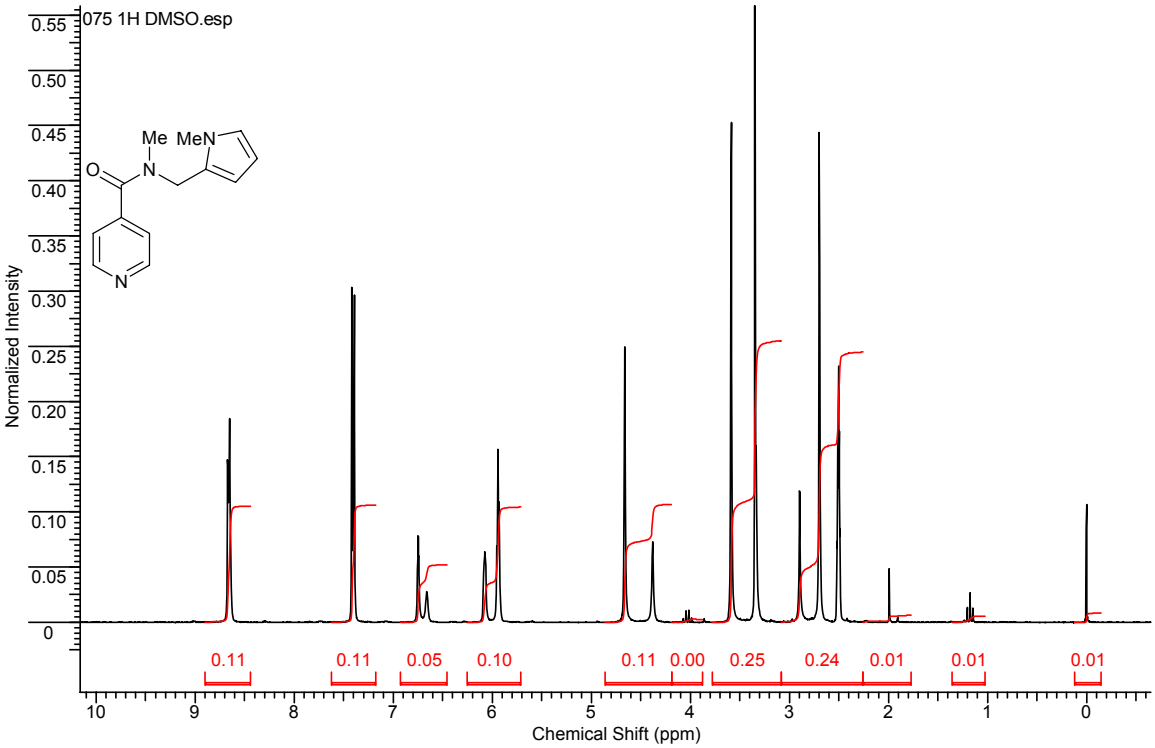
Chemical Shift (ppm)

7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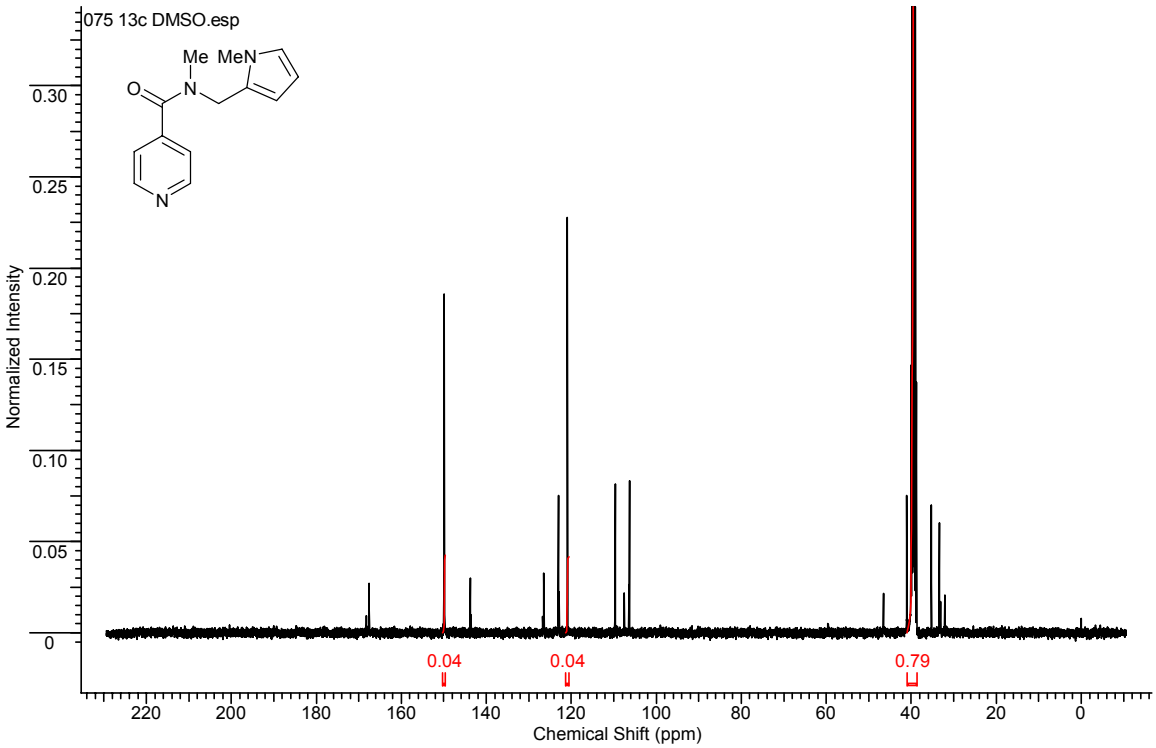
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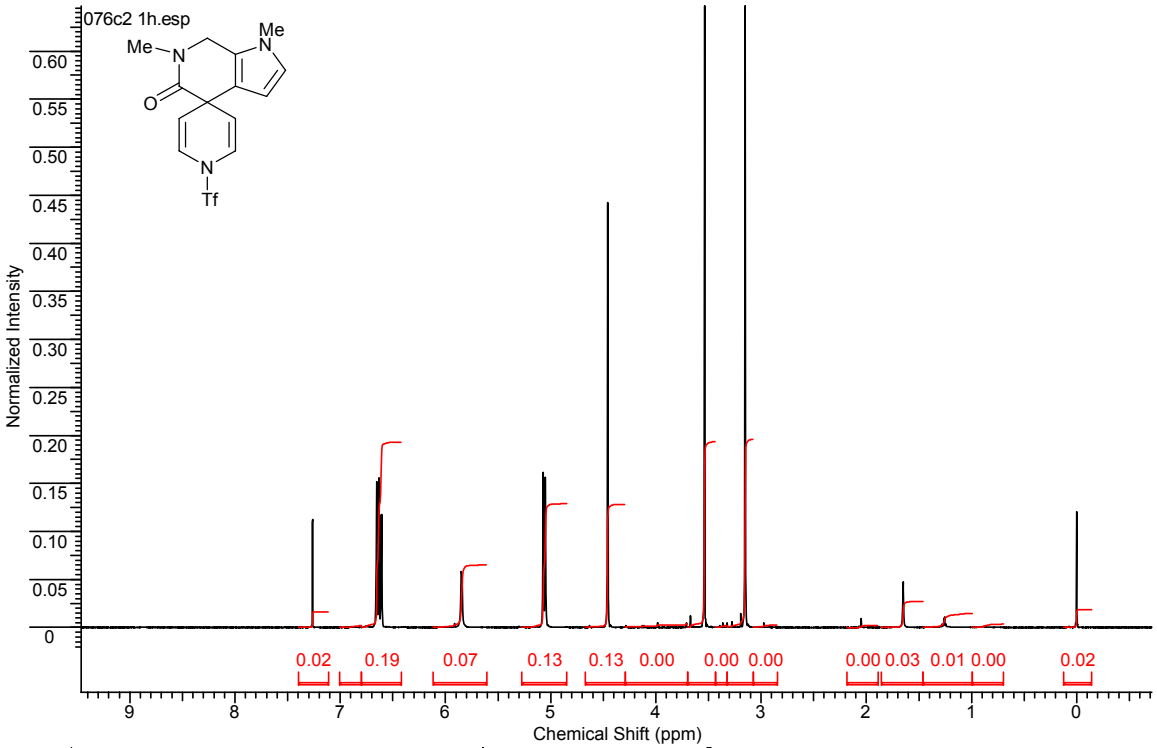
8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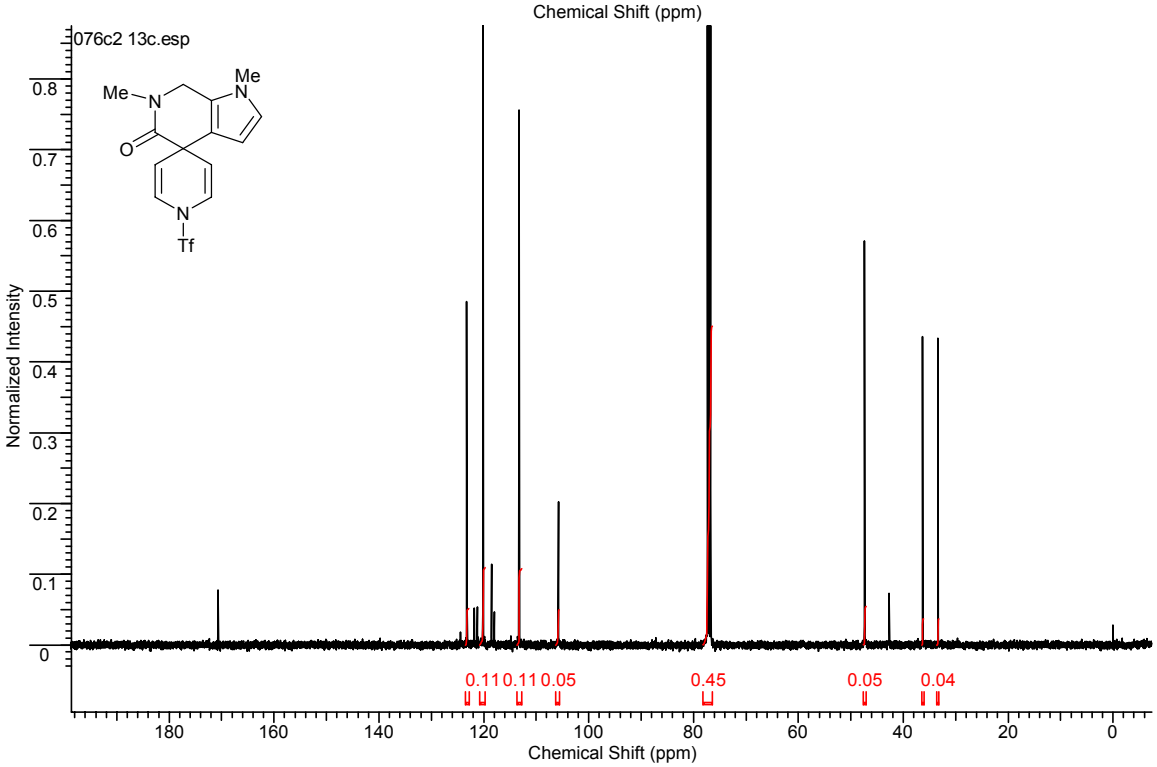
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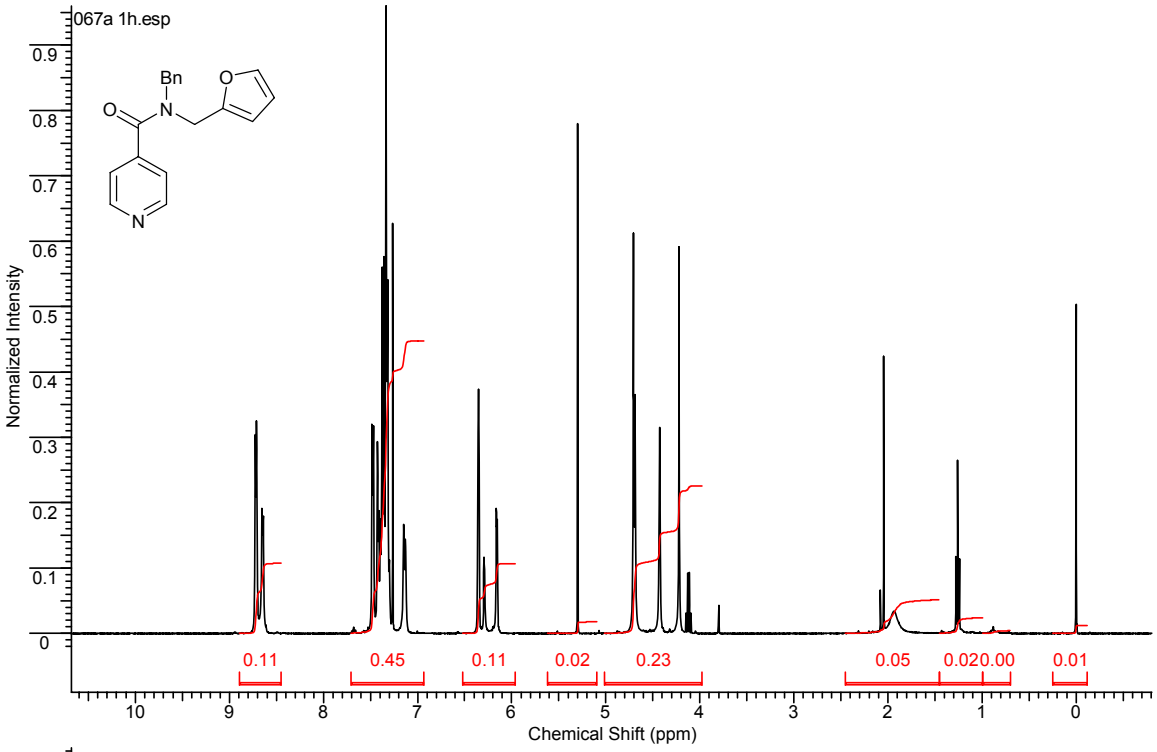
9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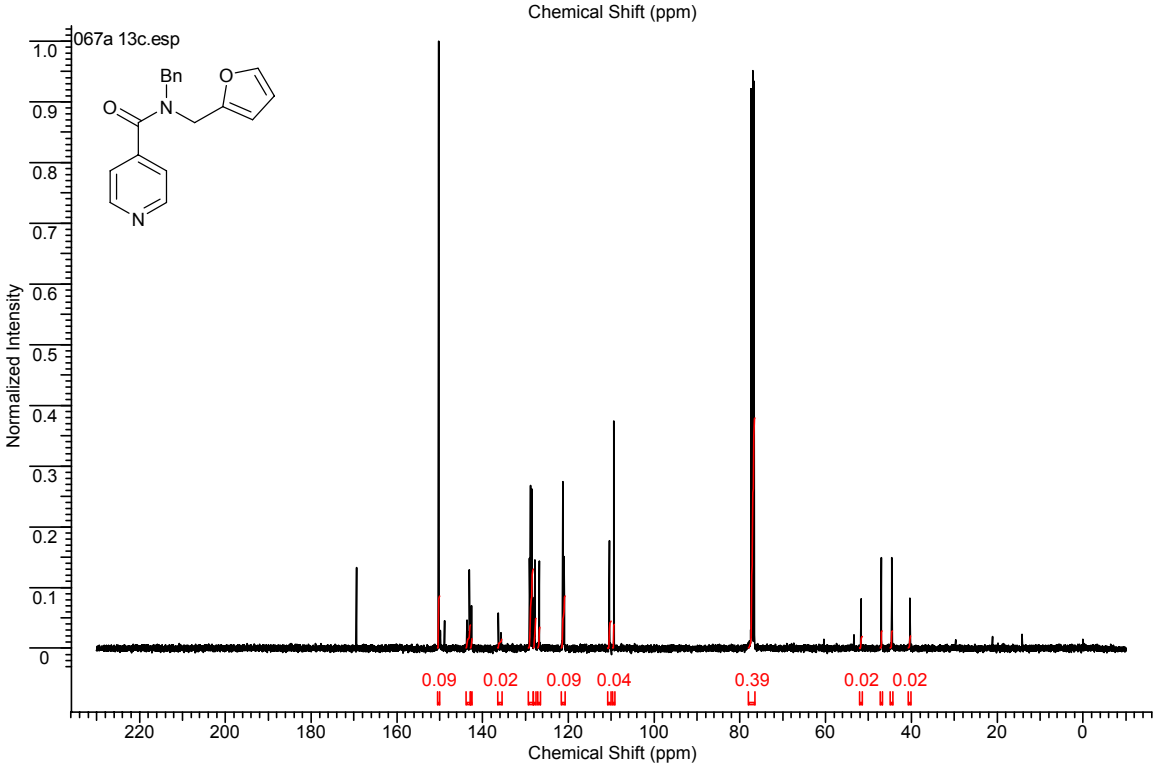
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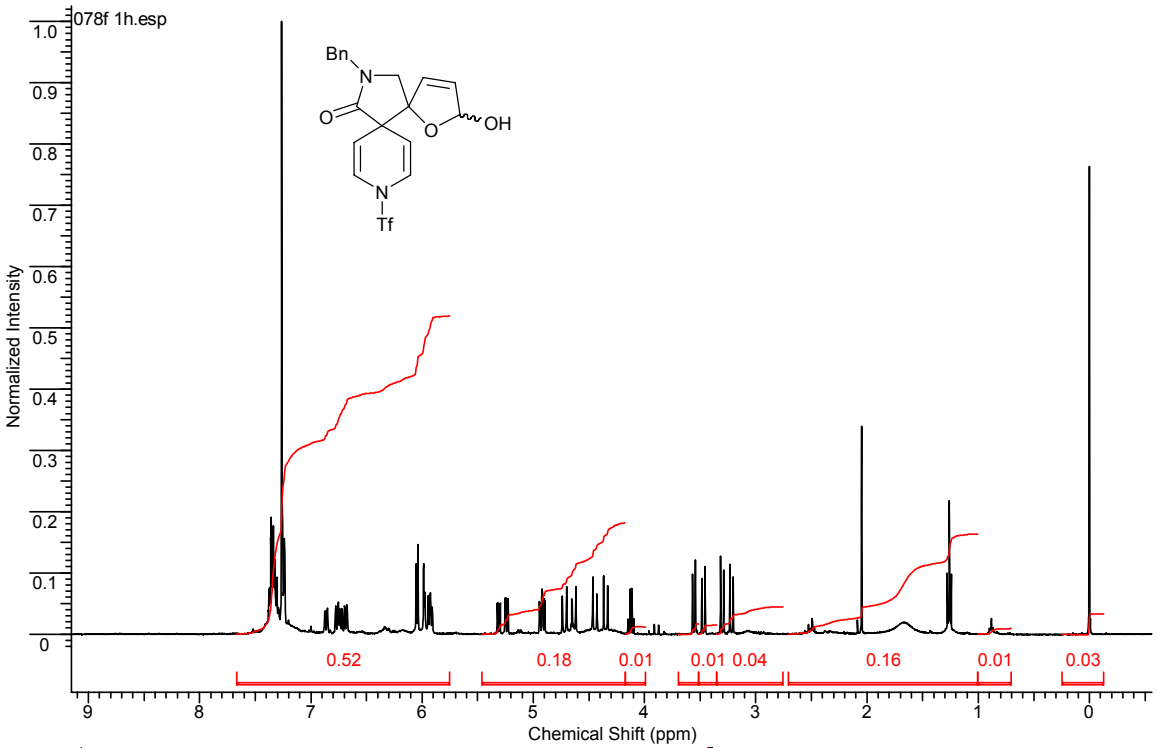
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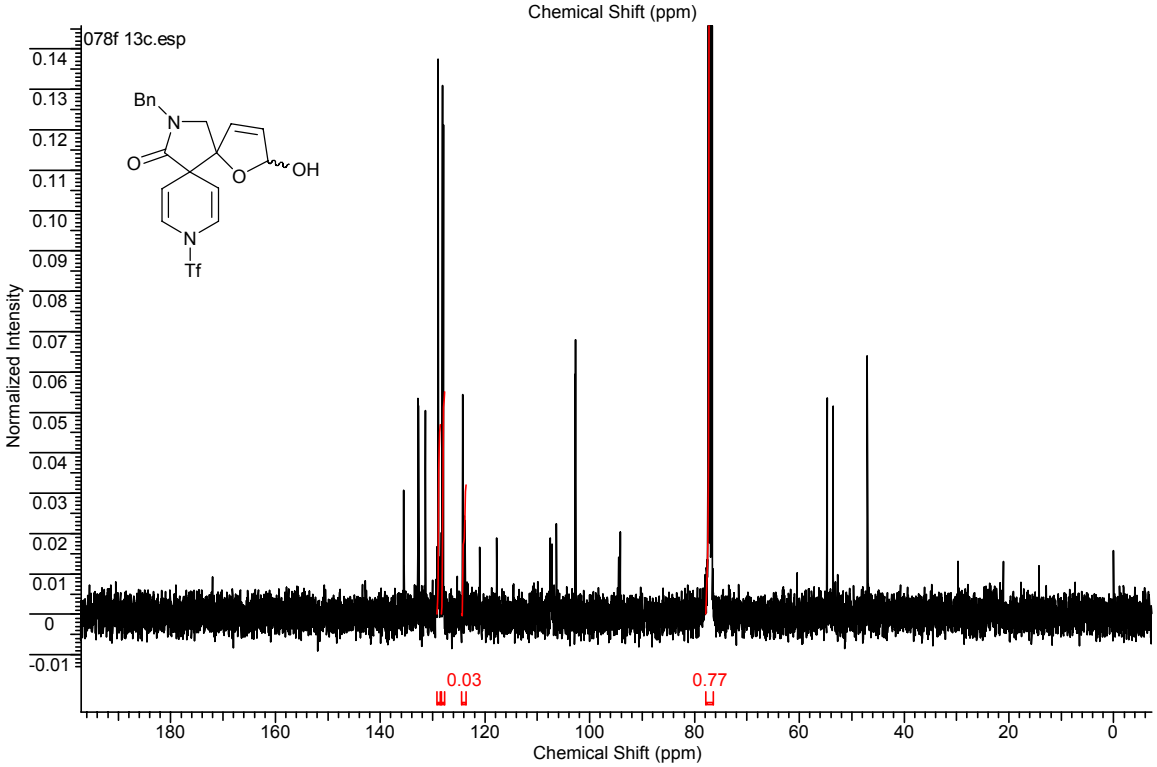
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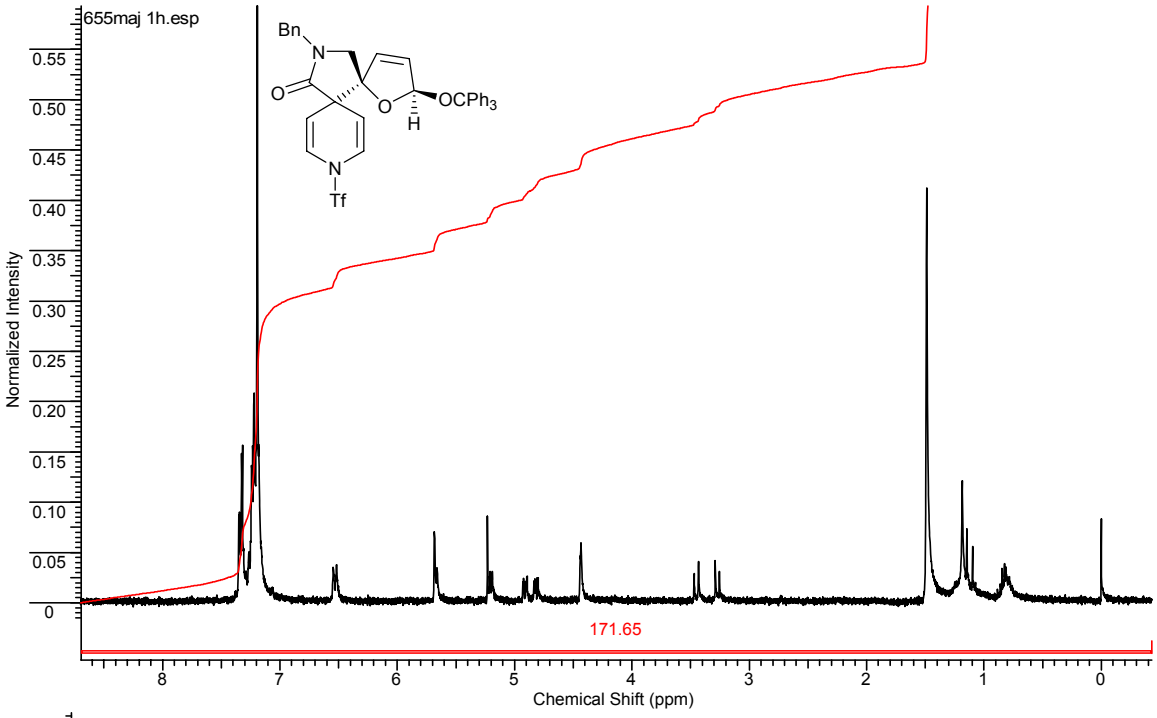
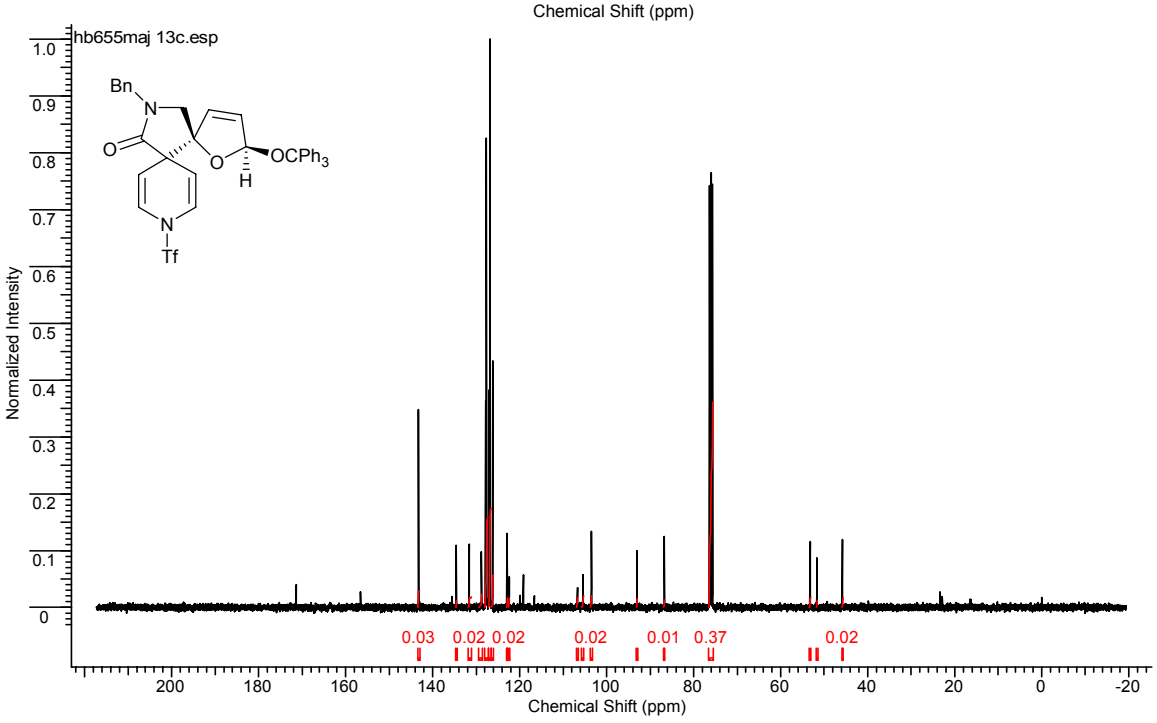
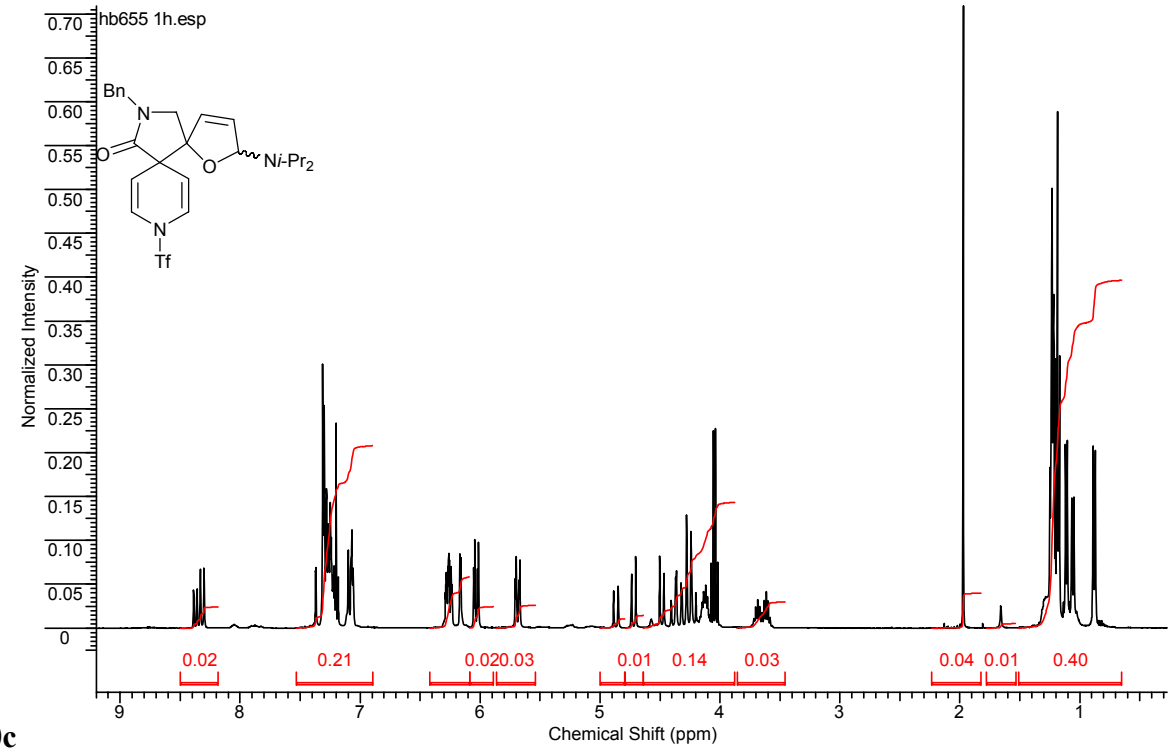
Chemical Shift (ppm)

Anti-10b

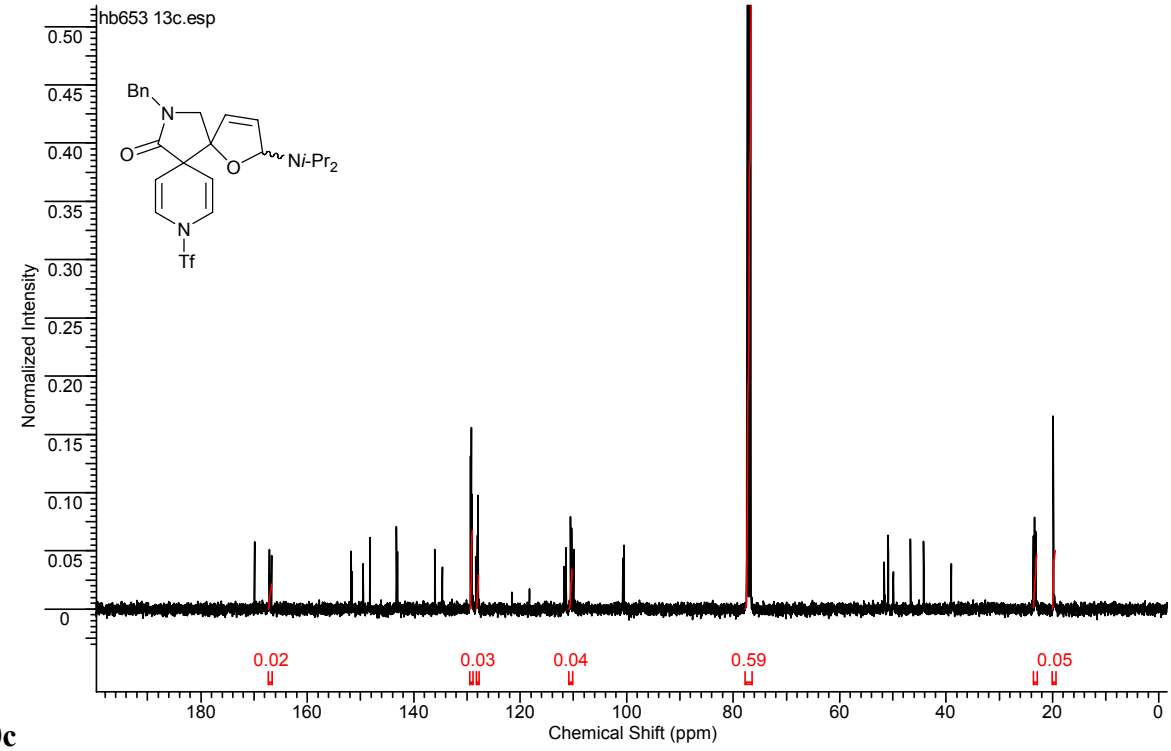
Supporting information for Brice, Clayden: Doubly dearomatising intramolecular coupling






hb655 1h.esp
Bn
N
O
O
Ni-Pr2
N
Tf
Normalized Intensity
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0.02
0.21
0.02
0.03
0.01
0.14
0.03
0.04
0.01
0.40
9
8
7
6
5
4
3
2
1
Chemical Shift (ppm)

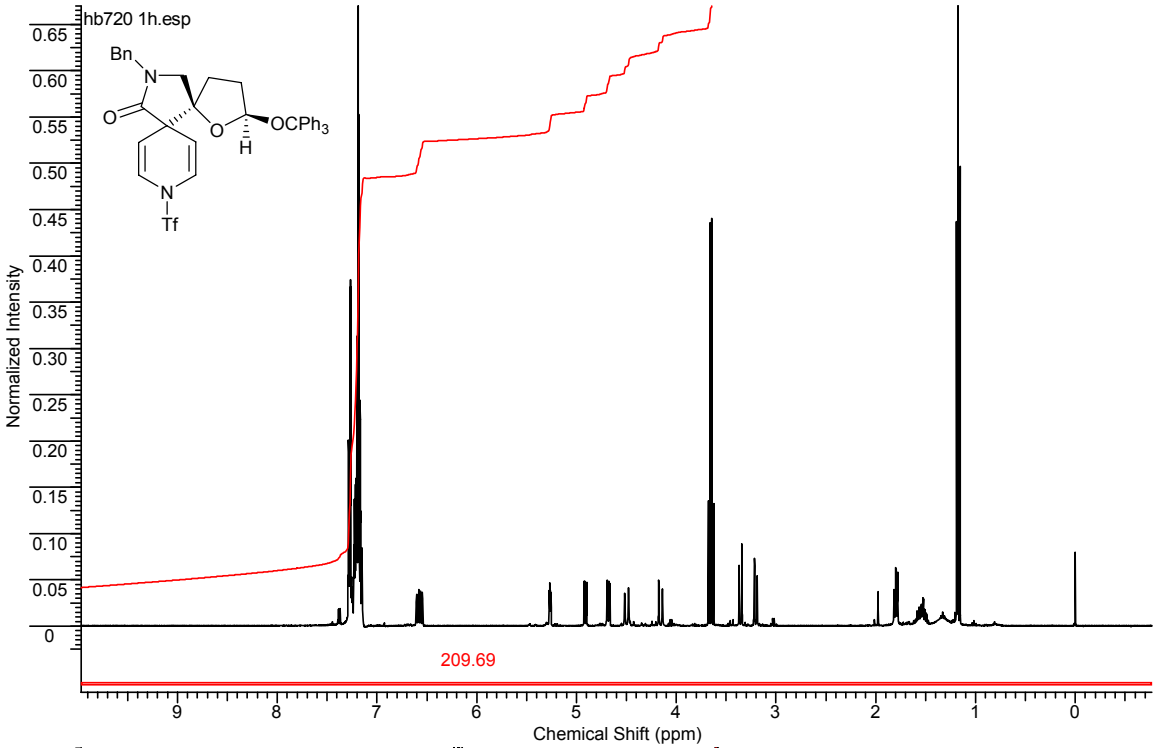
10c

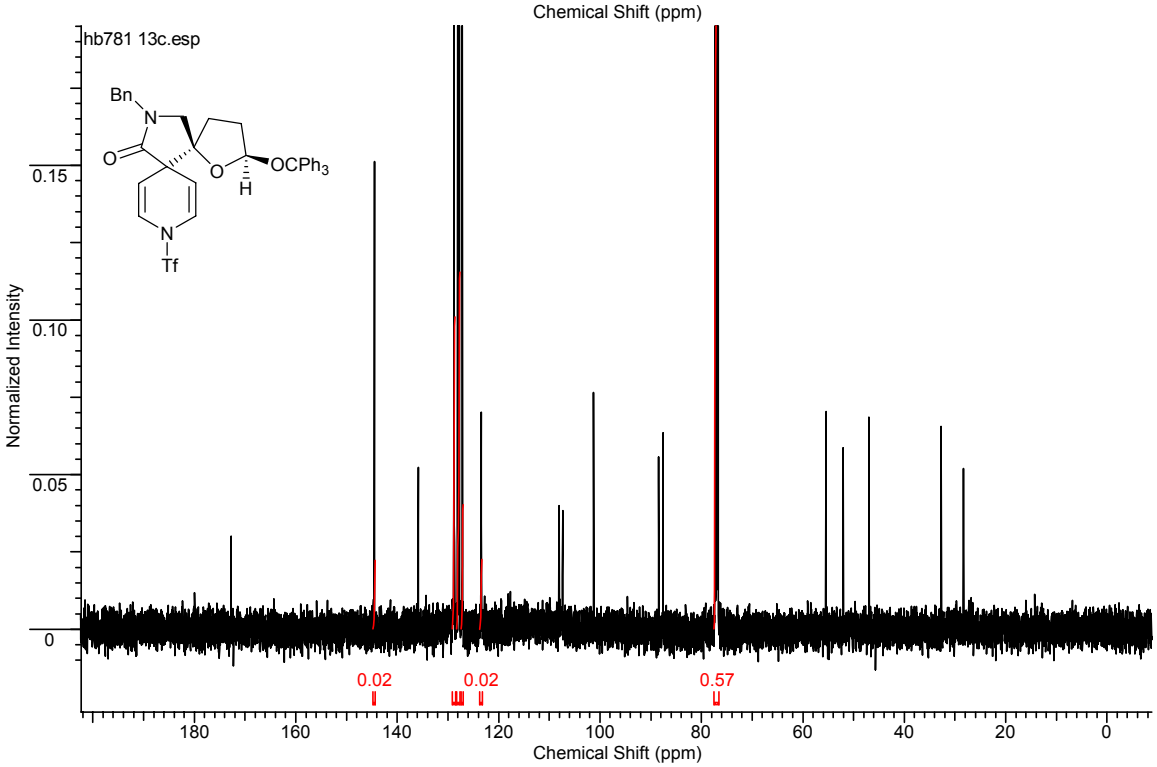

hb653 13c.esp
Bn
N
O
O
Ni-Pr2
N
Tf
Normalized Intensity
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0.02
0.03
0.04
0.59
0.05
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

10c

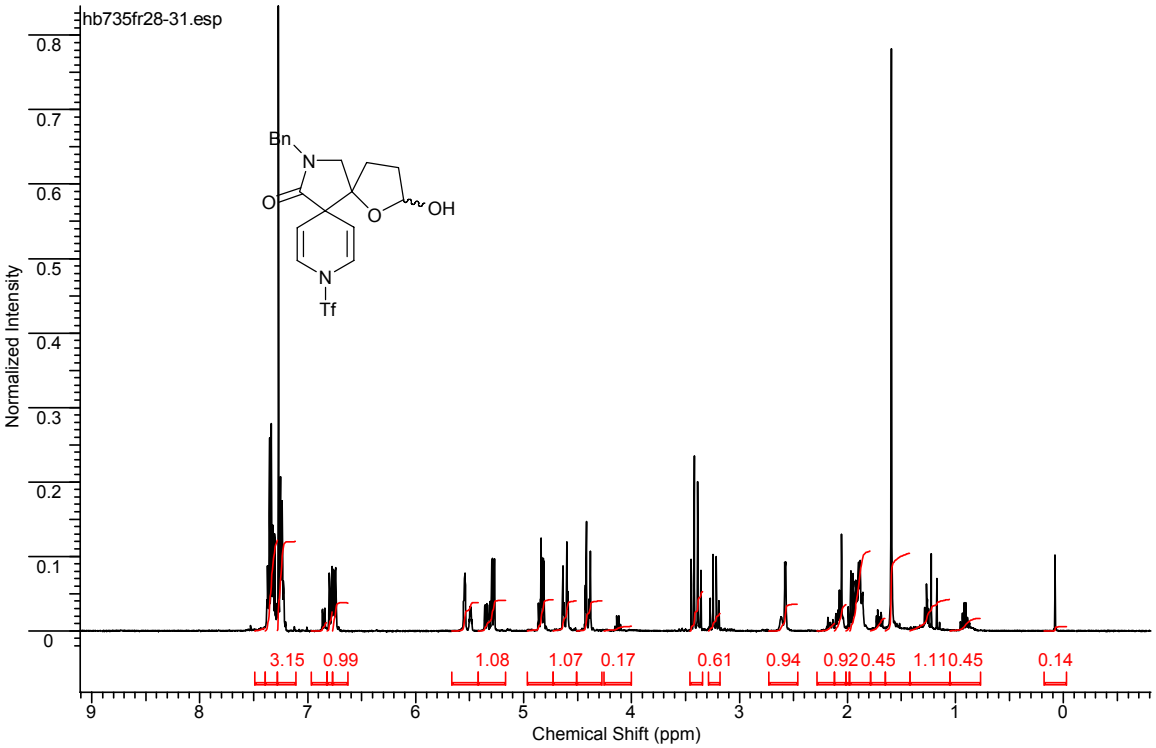
13

Supporting information for Brice, Clayden: Doubly dearomatising intramolecular coupling

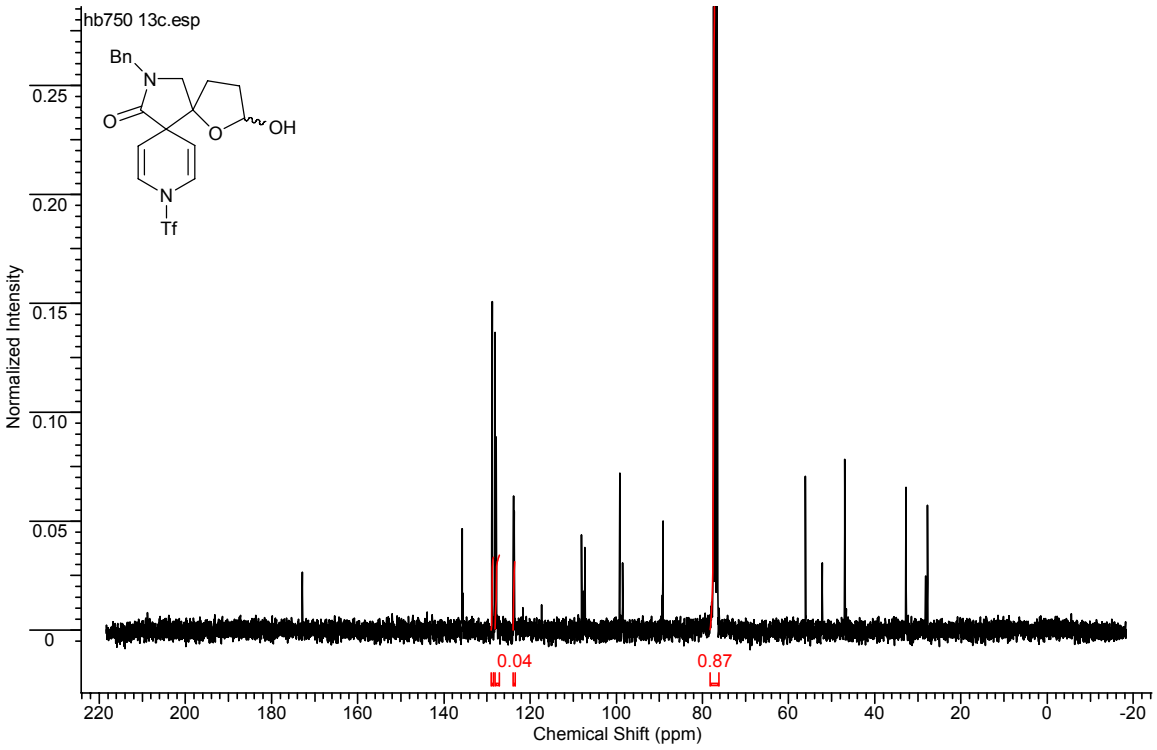


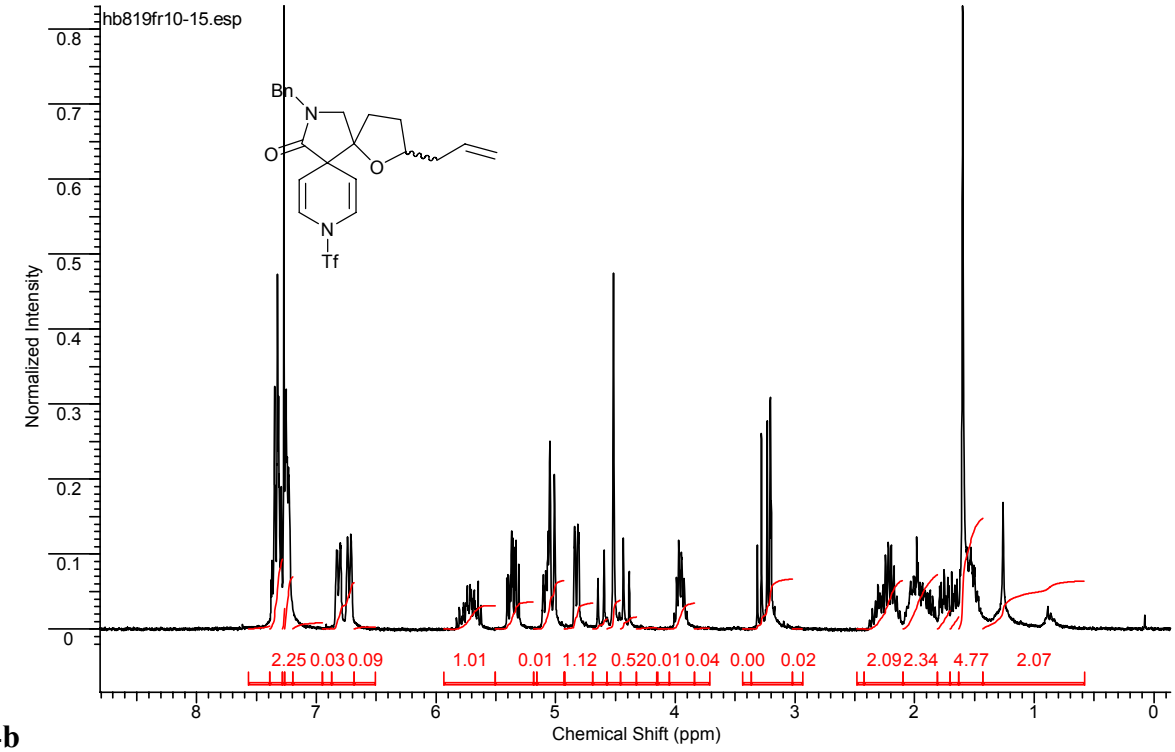


Supporting information for Brice, Clayden: Doubly dearomatising intramolecular coupling

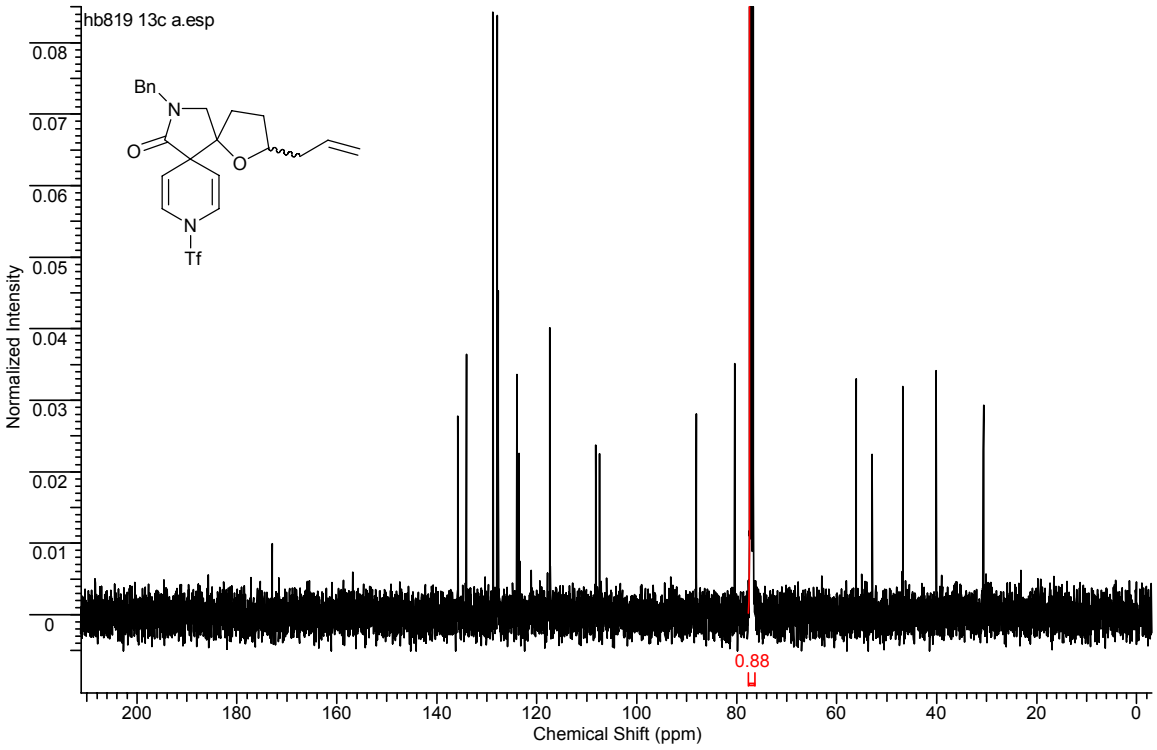


14a

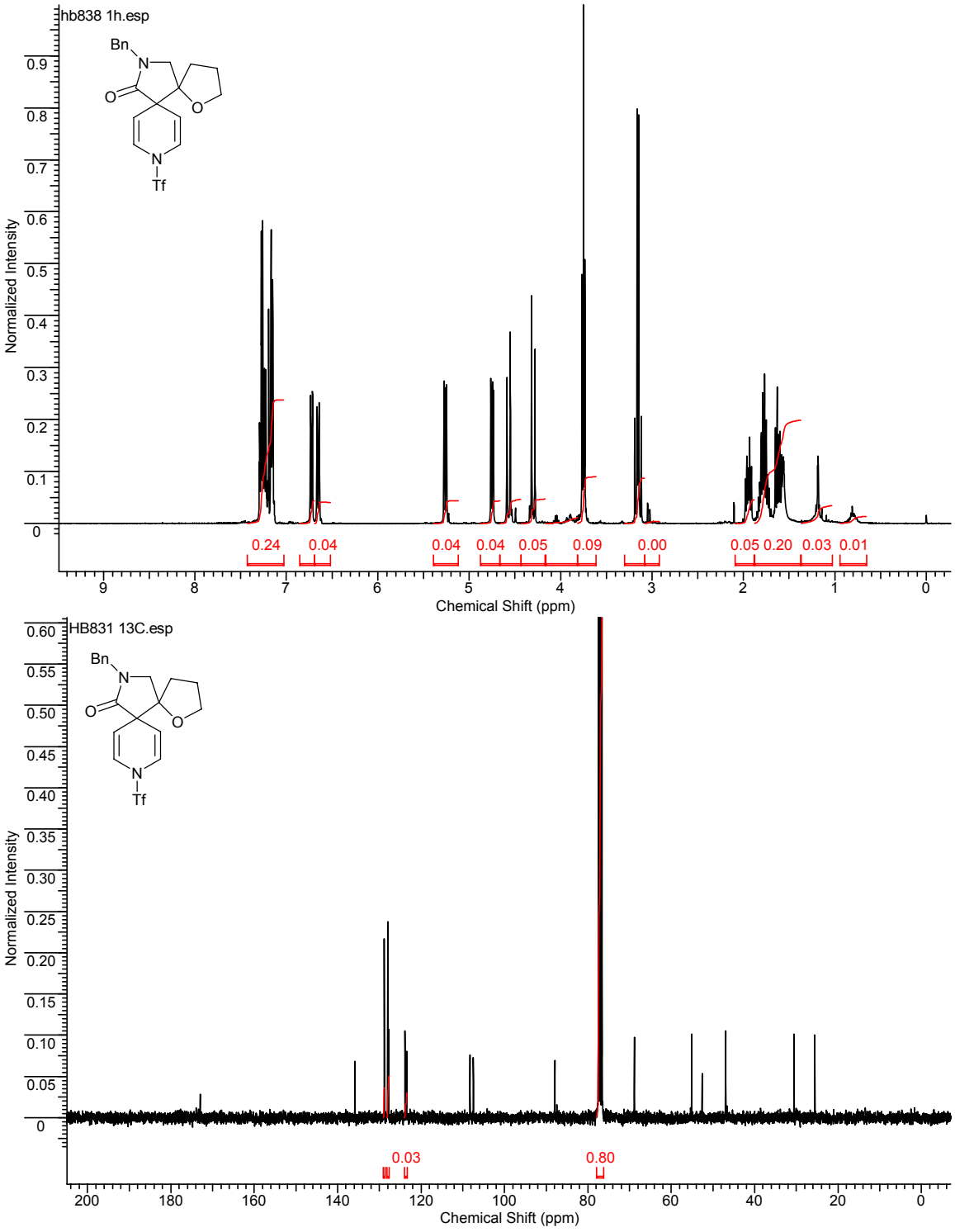



hb819fr10-15.esp
Bn
N
O
O
N
Tf
Normalized Intensity
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
2.25 0.03 0.09
1.01
0.01 1.12
0.52 0.01 0.04
0.00
0.02
2.09 2.34
4.77
2.07
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

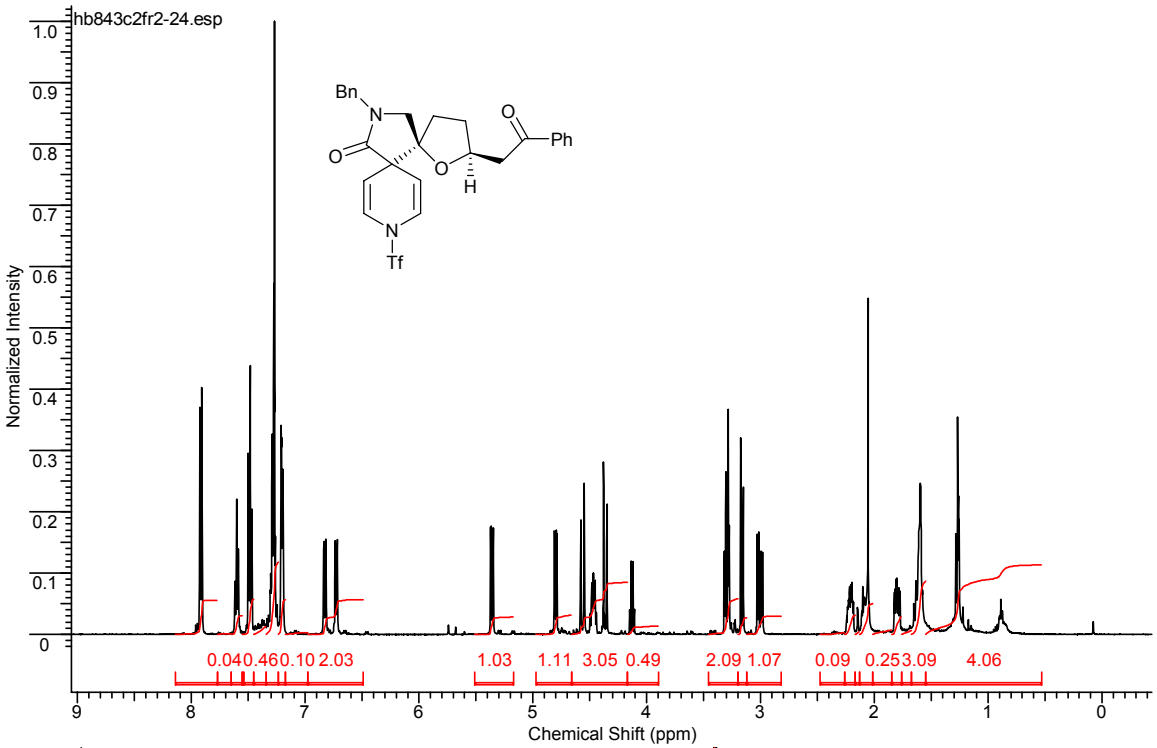
14b

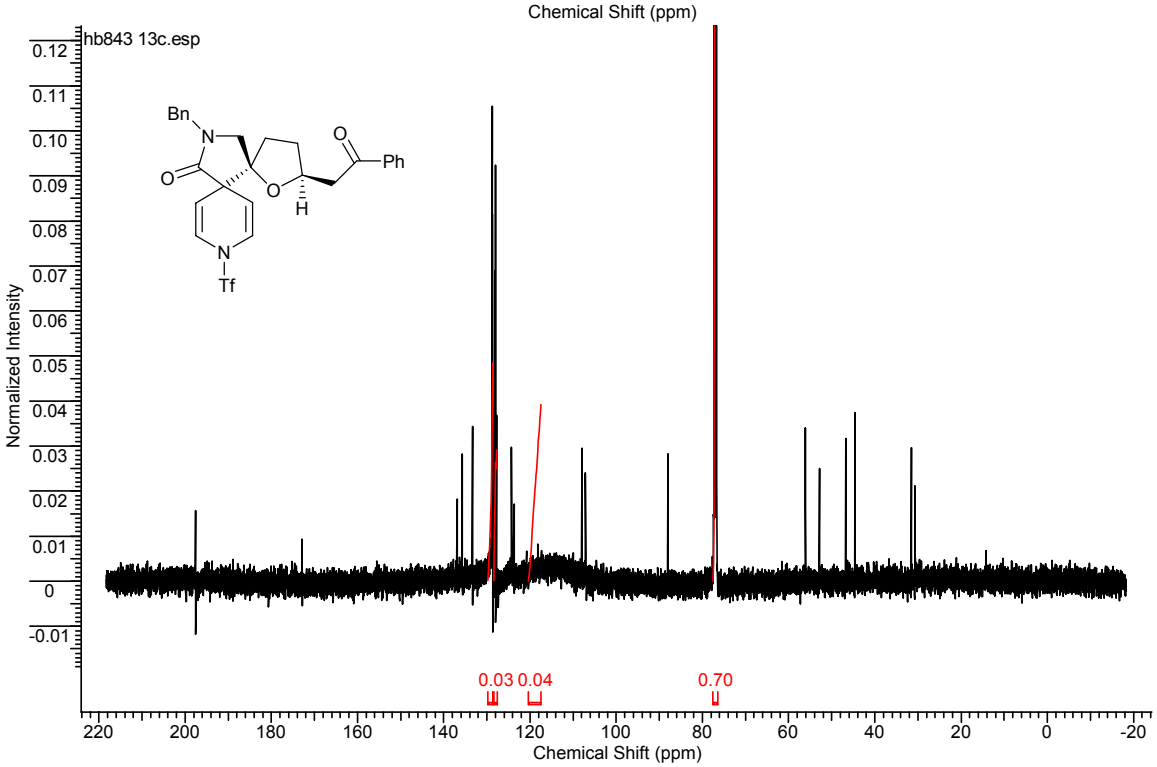

hb819 13c a.esp
Bn
N
O
O
N
Tf
Normalized Intensity
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
0.88
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

14c

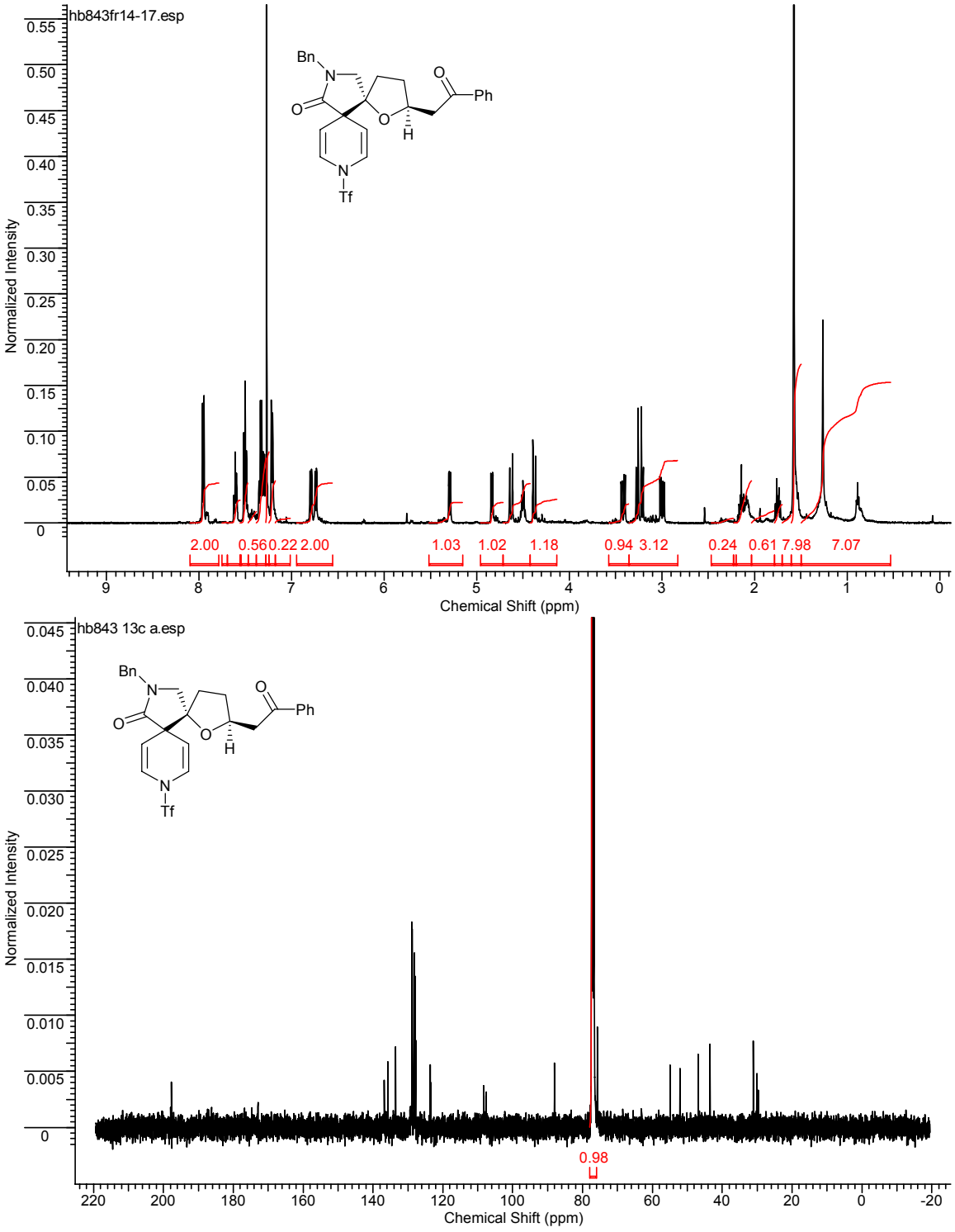

hb838 1h.esp
Bn
N
O
O
N
Tf
Normalized Intensity
0.24
0.04
0.04
0.04
0.05
0.09
0.00
0.05
0.20
0.03
0.01
Chemical Shift (ppm)
HB831 13C.esp
Bn
N
O
O
N
Tf
Normalized Intensity
0.03
0.80
Chemical Shift (ppm)

Anti-14d

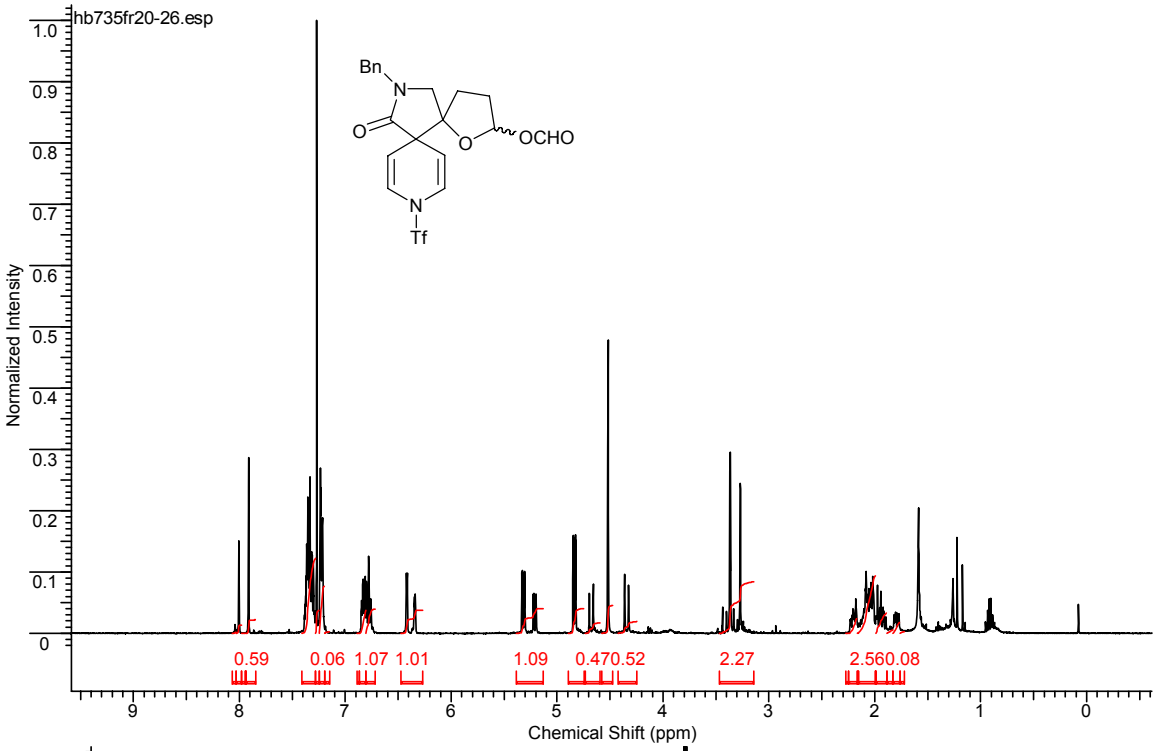

hb843c2fr2-24.esp
Bn
N
O
O
Ph
O
H
N
Tf
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.04 0.46 0.10 2.03
1.03
1.11 3.05 0.49
2.09 1.07
0.09 0.25 3.09
4.06
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

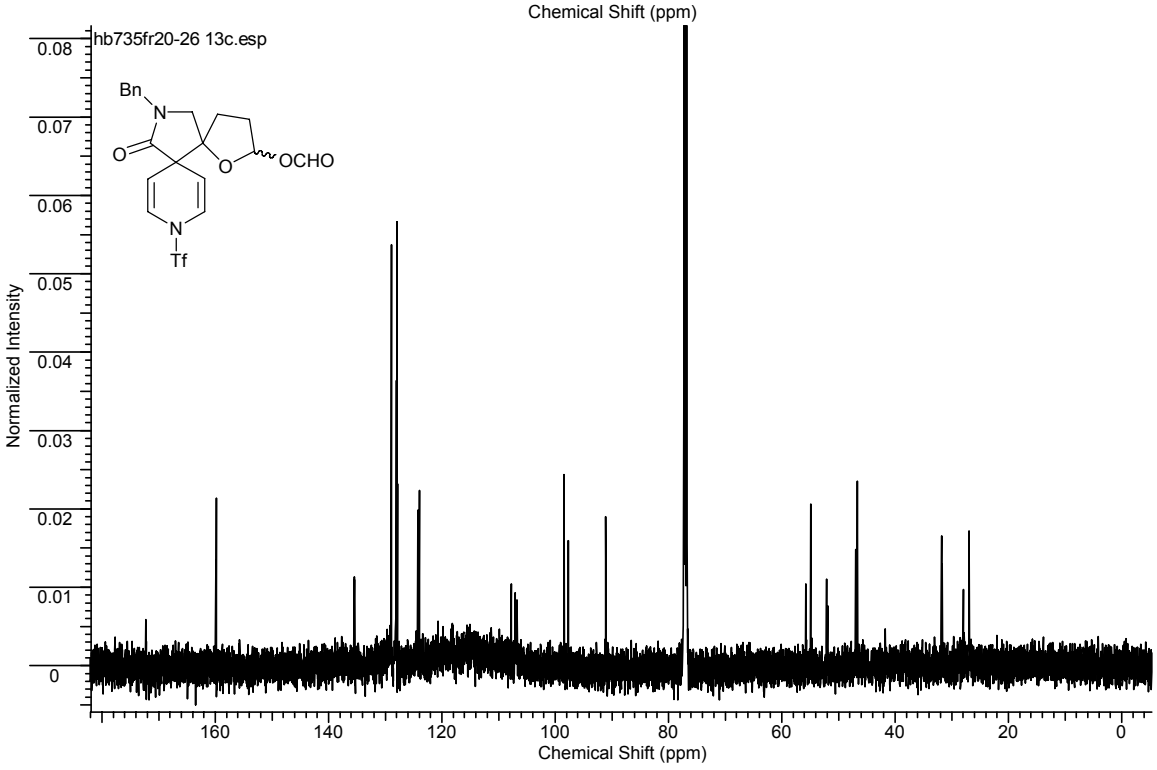

hb843 13c.esp
Bn
N
O
O
Ph
O
H
N
Tf
Normalized Intensity
0.12
0.11
0.10
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
-0.01
0.03 0.04
0.70
220
200
180
160
140
120
100
80
60
40
20
0
-20
Chemical Shift (ppm)

Syn-14d

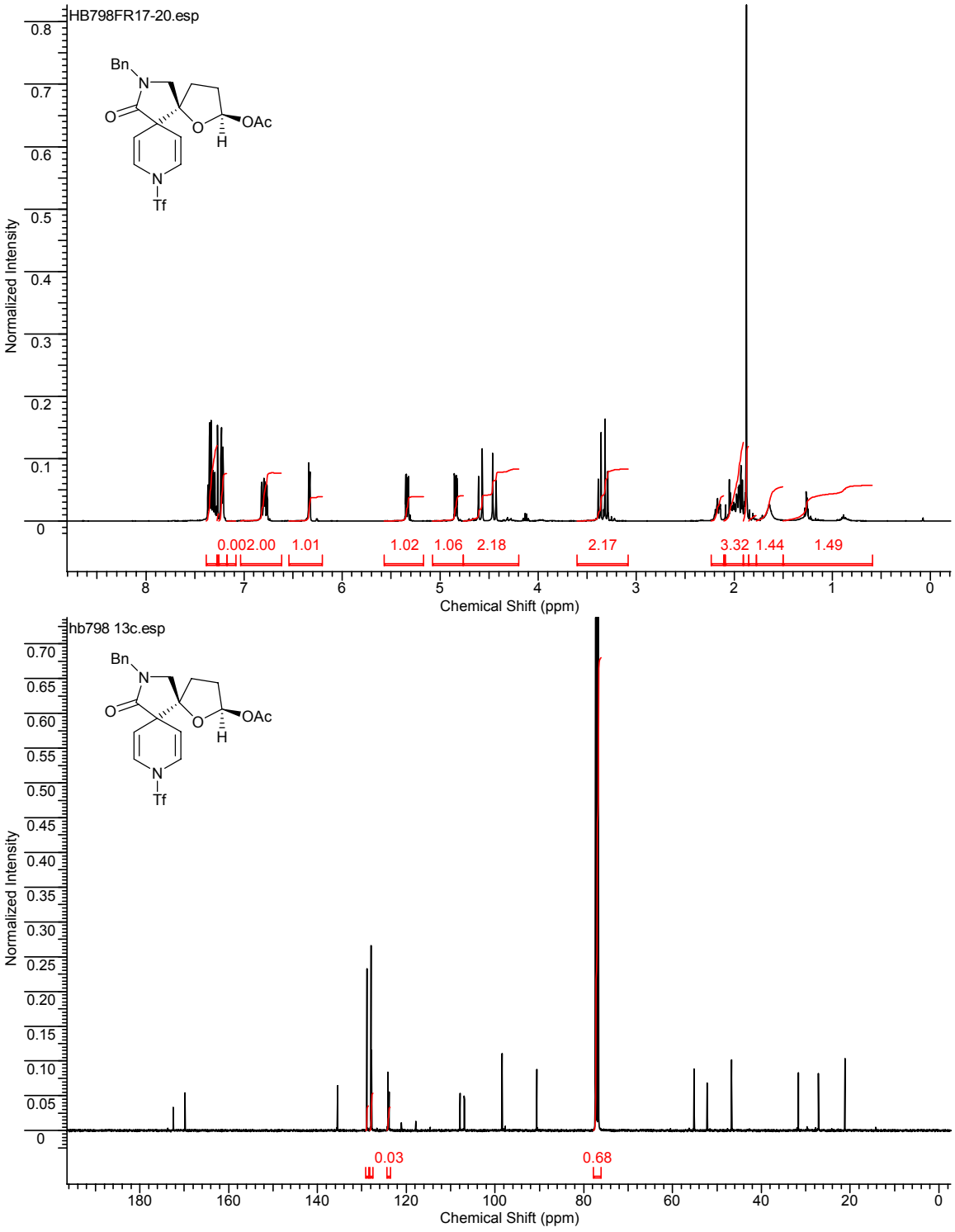

hb843fr14-17.esp
Normalized Intensity
Chemical Shift (ppm)
2.00 0.56 0.22 2.00 1.03 1.02 1.18 0.94 3.12 0.24 0.61 7.98 7.07
Bn
N
O
O
Ph
O
H
N
Tf
hb843 13c a.esp
Normalized Intensity
Chemical Shift (ppm)
0.98

14e


hb735fr20-26.esp
Bn
N
O
O
OCHO
N
Tf
Normalized Intensity
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.59
0.06
1.07
1.01
1.09
0.47
0.52
2.27
2.56
0.08
9
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)

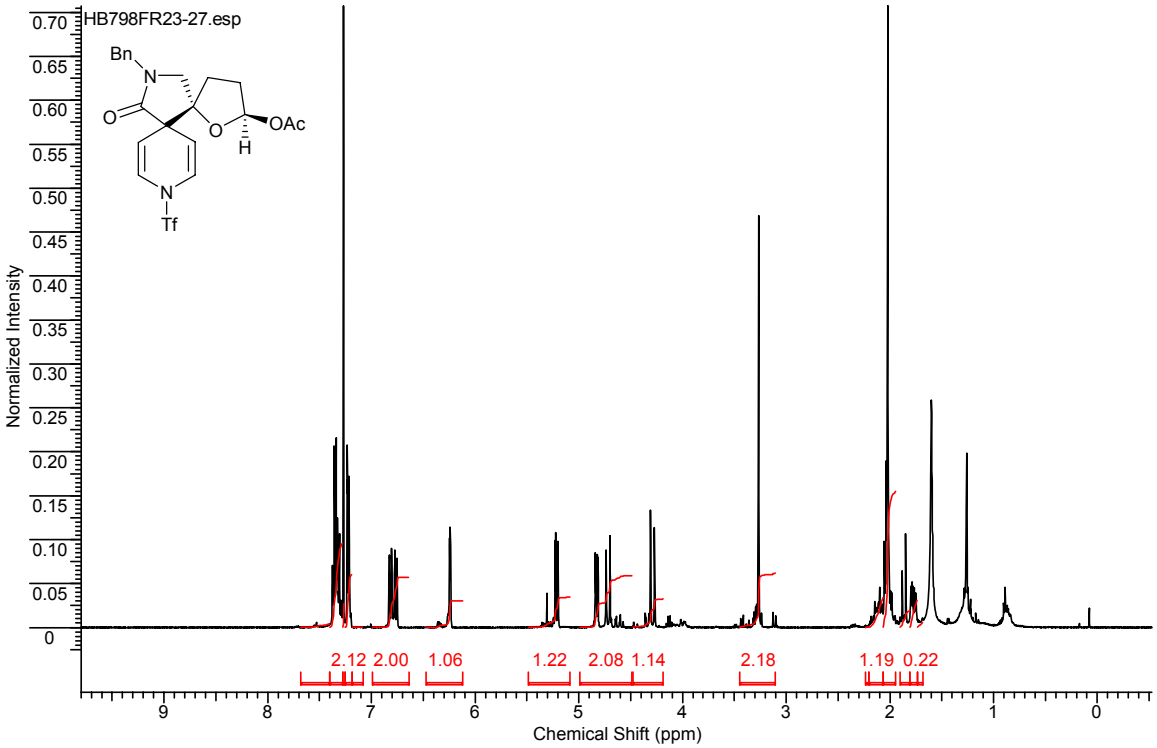

hb735fr20-26 13c.esp
Bn
N
O
O
OCHO
N
Tf
Normalized Intensity
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

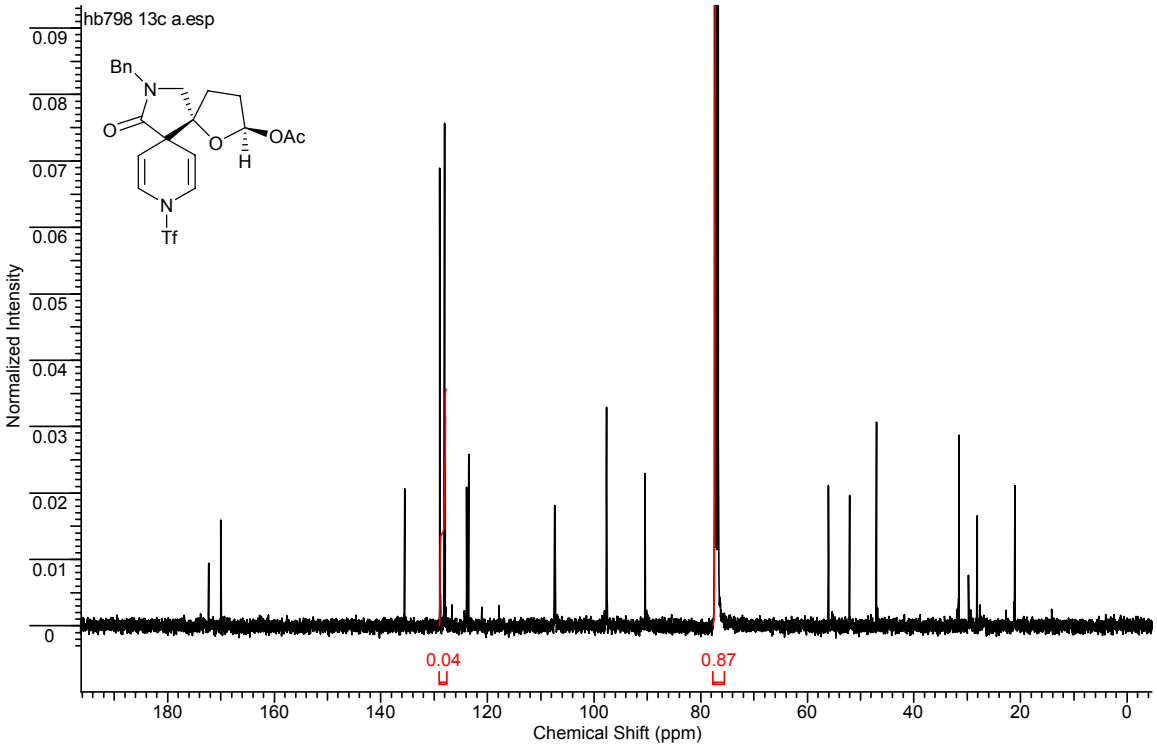
Anti-14f


HB798FR17-20.esp
Bn
N
O
O
OAc
H
N
Tf
Normalized Intensity
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
0.00
2.00
1.01
1.02
1.06
2.18
2.17
3.32
1.44
1.49
8
7
6
5
4
3
2
1
0
Chemical Shift (ppm)
hb798 13c.esp
Bn
N
O
O
OAc
H
N
Tf
Normalized Intensity
0.70
0.65
0.60
0.55
0.50
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0
0.03
0.68
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

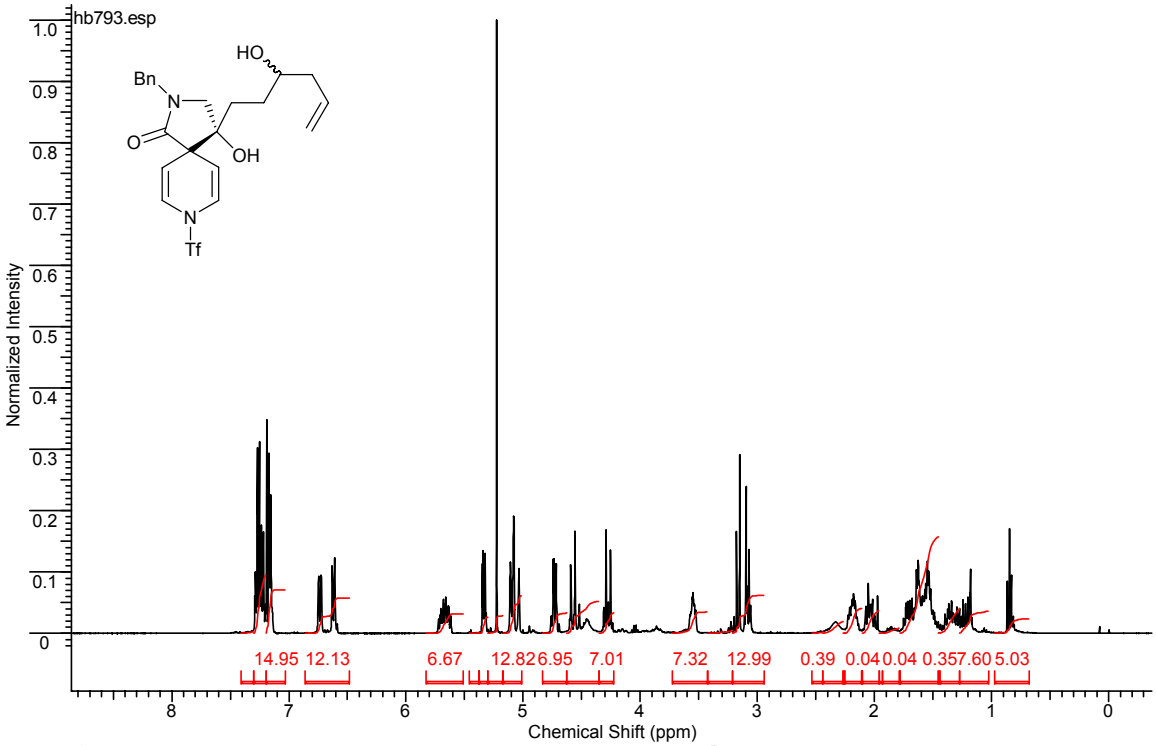
Syn-14f

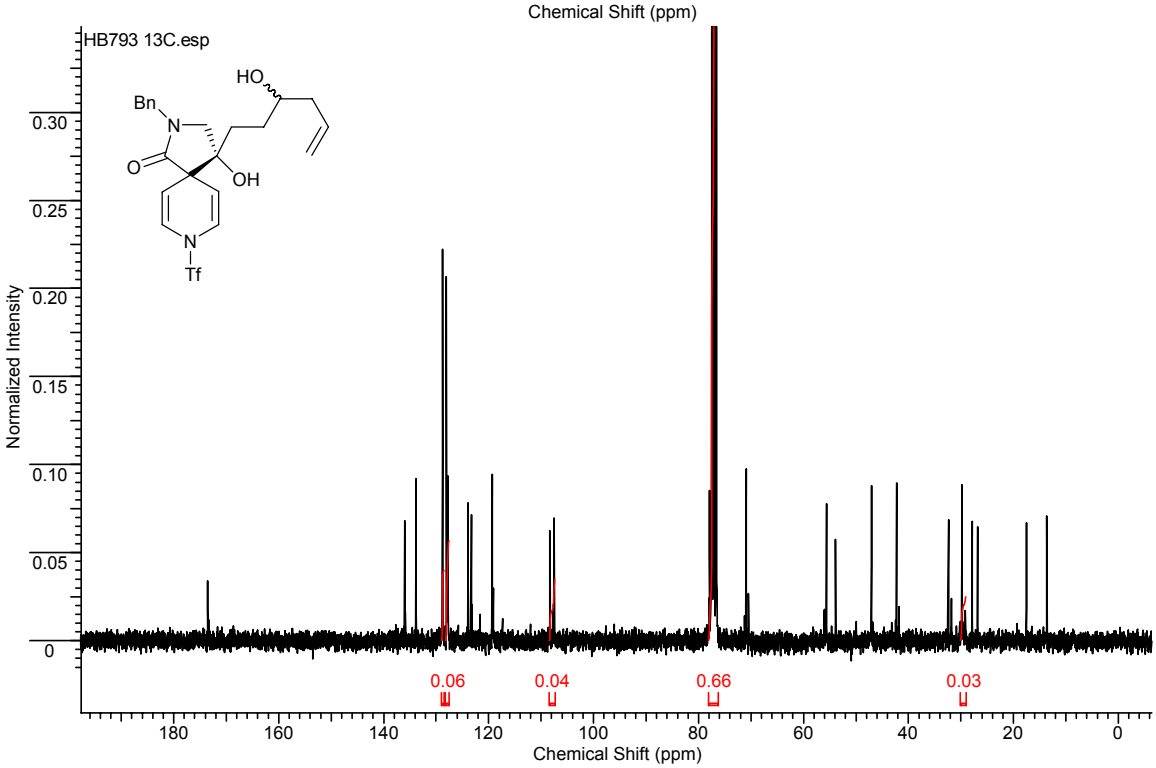
Supporting information for Brice, Clayden: Doubly dearomatising intramolecular coupling





15





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[2] M. K. Scott, E. W. Baxter, D. J. Bennett, R. E. Boyd, P. S. Blum, E. E. Codd, M. J. Kukla, E. Malloy, B. E. Maryanoff, M. E. Ortegon, C. R. Rasmussen, A. B. Reitz, M. J. Renzi, C. F. Schwender, R. P. Shank, R. G. Sherrill, J. L. Vaught, F. J. Villani, N. Yim, *J. Med. Chem.* **1995**, *38*, 4198.
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