Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

Synthesis of Novel and Potent Vorapaxar Analogues

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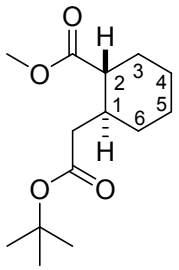
General Experimental

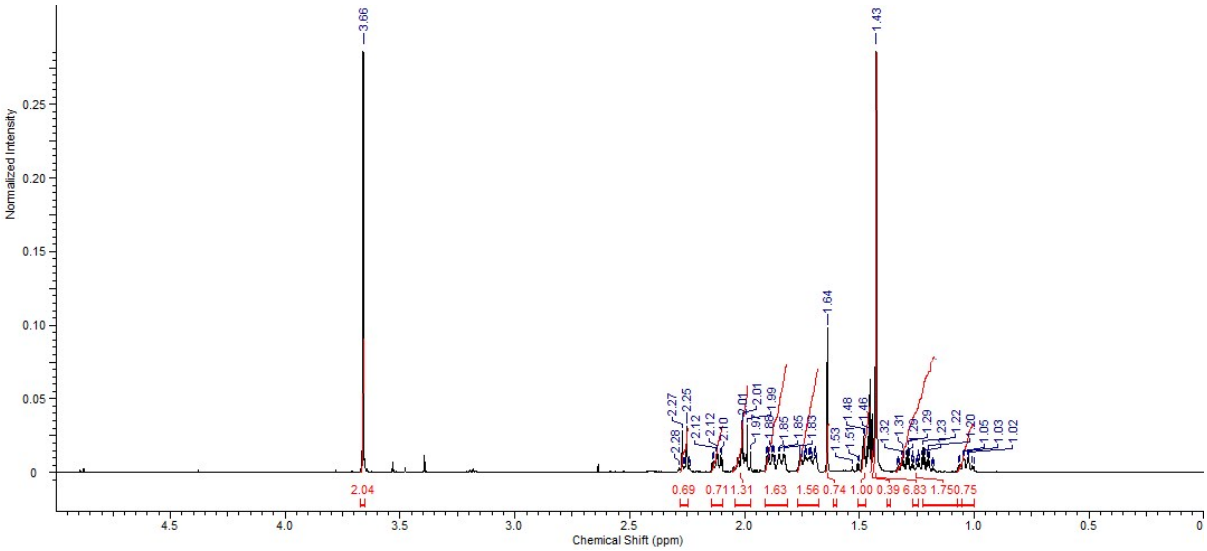
All solvents employed in this study were reagent grade. All reagents were purchased from Sigma-Aldrich, UK and Alfa Aesar, UK and used as received unless otherwise stated. All reactions were magnetically stirred and monitored by thin layer chromatography (TLC) on pre-coated silica gel plates (254 *μ*m) and/or by LCMS. Silica plates were initially examined under UV light and then developed using aqueous basic potassium permanganate stain. LCMS analysis was conducted on either System A, an Acquity UPLC BEH C18 column (2.1 mm × 50 mm ID, 1.7 μm packing diameter) eluting with 0.1% formic acid in H_2O (solvent A) and 0.1% formic acid in acetonitrile (MeCN) (solvent B), using the following elution gradient 0.0−1.5 min 3−100% B, 1.5−1.9 min 100% B, 1.9−2.0 min 3% B, at a flow rate of 1 mL min−1 at 40 °C. The UV detection was an averaged signal from wavelength of 210 to 350 nm, and mass spectra were recorded on a mass spectrometer using alternate-scan electrospray positive and negative mode ionization (ES +ve and ES −ve); or System B, an Acquity UPLC BEH C18 column (50 mm × 2.1 mm ID, 1.7 μm packing diameter) eluting with 10 mM ammonium bicarbonate ($(NH_4)HCO_3$) in H_2O adjusted to pH10 with ammonia solution (solvent A) and MeCN (solvent B) using the following elution gradient 0−1.5 min 1−97% B, 1.5−1.9 min 97% B, 1.9−2.0 min 100% B at a flow rate of 1 mL min−1 at 40 °C. Preperative TLC was carried out using 20 cm x 20 cm glass TLC plates with a silica gel 60 matrix, supplied by EMD/Merck KGaA. Flash chromatography was carried out with silica gel (33-70 *μ*m) supplied by Merck Co.. Automated column chromatography was performed using pre-packed silica gel columns on a Flashmaster II. The Flashmaster II is an automated multiuser flash chromatography system, available from Argonaut Technologies Ltd, which utilizes disposable, normal phase, SPE cartridges (2−100 g). Chiral column chromatography

was performed using various columns and conditions, see below for details. Quoted yields refer to chromatographically and spectroscopically pure compounds unless otherwise stated. ^{1}H NMR spectra were recorded at 600 MHz with a Bruker AMX600. ^{13}C NMR spectra were recorded at 150 MHz. Chemical shifts (δ values) are reported in parts per million (ppm) whilst coupling constants are reported in Hertz (Hz).

trans-Methyl 2-(2-(*tert*-butoxy)-2-oxoethyl)cyclohexanecarboxylate (1)



n-BuLi (1.6 M in hexanes) (70.0 mL, 112 mmol) was added to a stirred solution of DIPA (15.7 mL, 112 mmol) in anhydrous THF (30 mL) at -78 °C, under Ar. The solution was stirred at -78 °C for 20 mins. A solution of *tert*-butyl acetate (15.0 mL, 112 mmol) was added and stirring continued for 30 min at -78 °C. Next, a solution of (*E*)-methyl 7-iodohept-2-enoate (13.7 g, 51 mmol) in anhydrous THF (15 mL) was added. The reaction mixture was stirred for a further 30 min at -78 °C. Finally, solid KO*t*-Bu (12.6 g, 112 mmol) was added and stirring continued for a further 1 h at -78 °C. The reaction mixture was quenched with sat. aq. NH_4Cl (100 mL) and diluted with H_2O (50 mL). An extraction into EtOAc (2 x 100 mL) was completed and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude pale yellow liquid. Multiple purifications by flash column chromatography (0-2% Et_2O/CH_2Cl_2), (0-10% Et_2O/Pet. Ether) and (0-2% Et_2O/toluene) yielded *trans*-methyl 2-(2-(*tert*-butoxy)-2-oxoethyl)cyclohexanecarboxylate (**1**) (3.1 g, 12 mmol, 24%) as a colourless liquid; bp. 110-115 °C (at 2.1 mbar); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.66 (3H, s, COOCH_3), 2.26 (1H, d, *J* = 10.9, C*H*HCOO^{t}Bu), 2.12 (1H, dt, *J* = 11.2, 3.6, C^2*H*), 2.05-1.98 (2H, m, C^1*H* & C*H*HCOO^{t}Bu), 1.89 (1H, qd, *J* = 1.9, 13.2, C^3*H*H), 1.84 (1H, dd, *J* = 2.1, 13.0, C^6*H*H), 1.74 (1H, dtd, *J* = 12.8, 3.4, 1.1, C^4*H*H), 1.72-1.68 (1H, m, C^5*H*H), 1.47 (1H, td, *J* = 12.4, 2.6, C^{3}H*H*), 1.43 (9H, s, C(CH_3)$_3$), 1.30 (1H, tq, *J* = 12.8, 3.4, C^5 H*H*), 1.21 (1H, tq, *J* = 13.2, 3.8, C^{4}H*H*), 1.04 (1H, dq, *J* = 13.2, 3.4, C^{6}H*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.1 (*C*OCOMe), 171.8 (*C*OCO^{t}Bu), 80.4 (*C*(CH$_3$)$_3$), 51.7 (*C*H$_3$), 49.0 (*C*^{2}H), 40.9 (*C*H$_2$COO^{t}Bu), 36.3 (*C*^{1}H), 31.3 (*C*^{6}H), 30.0 (*C*^{3}H), 28.2 (C(*C*H$_3$)$_3$), 25.5 (*C*^{5}H), 25.4 (*C*^{4}H); IR (thin film) 2982 (C-H), 2930 (C-H), 2854 (C-H), 1713 (C=O), 1451 (C-H), 1366 (C-O), 1247 (C-O), 1151, 1108, 1025, 845 cm^{-1}; m/z (ES+) 257 (100%, $[M+H]^+$); HRMS (CI) calcd for $C_{13}H_{11}O_3$ $[M\text{-}OMe]^+$ 225.14907, observed 225.14872.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1.64
2.27
2.25
2.28
2.12
2.10
2.01
1.99
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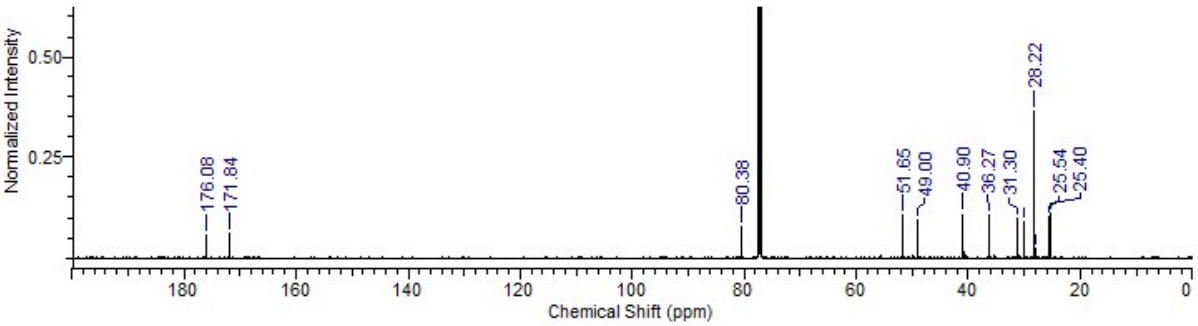
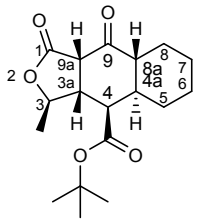
1.83
1.53
1.48
1.46
1.32
1.31
1.29
1.23
1.22
1.20
1.05
1.03
1.02
2.04
0.69
0.71
1.31
1.63
1.56
0.74
1.00
0.39
6.83
1.75
0.75
Chemical Shift (ppm)


Normalized Intensity
176.08
171.84
80.38
51.65
49.00
40.90
36.27
31.30
28.22
25.54
25.40
Chemical Shift (ppm)

tert-Butyl 3-methyl-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carboxylate

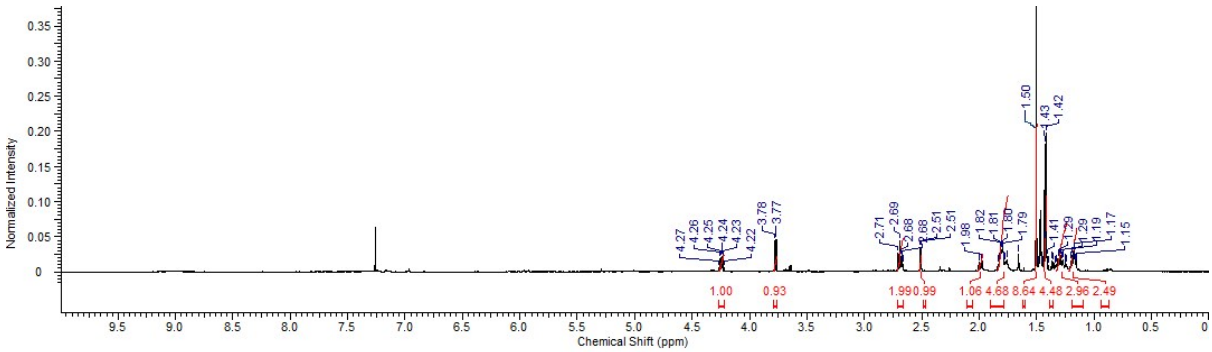
n-BuLi (2.5 M in hexane) (3.60 ml, 9.00 mmol) was added dropwise to a stirred solution of freshly distilled TMP (1.54 mL, 9.00 mmol) in anhydrous THF (10 mL) at -78 °C, under Ar. The solution was warmed to 0 °C and then re-cooled to -78 °C. A solution of *trans*-methyl 2-(2-(*tert*-butoxy)-2-oxoethyl)cyclohexanecarboxylate (**1**) (1.10 g, 4.30 mmol) in anhydrous THF (5 mL) was added, dropwise, and stirring continued for 45 min at -78 °C. Next, a solution of 5-methyl-2(5H)-furanone (**2**) (294 mg, 0.30 mmol) in anhydrous THF (5 mL) was added, dropwise, and stirring continued for 1 h at -78 °C. Finally, KO*t*-Bu (1.00 g, 9.00 mmol) was added. The reaction mixture was warmed to -40 °C, stirred for a further 3 h and then quenched with sat. aq. NH_4Cl (20 mL). An extraction into EtOAc (2 x 40 mL) was done and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude yellow oily solid. Multiple purifications by flash column chromatography yielded (3*R*,3a*S*,4*R*,4a*R*,8a*R*,9a*S*)-*tert*-butyl 3-methyl-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carboxylate (**3**) (117 mg, 0.36 mmol, 12%) and (3*R*,3a*S*,4*S*,4a*R*,8a*R*,9a*S*)-*tert*-butyl 3-methyl-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carboxylate (**4**) (47.5 mg, 0.15 mmol, 5%) as white solids.

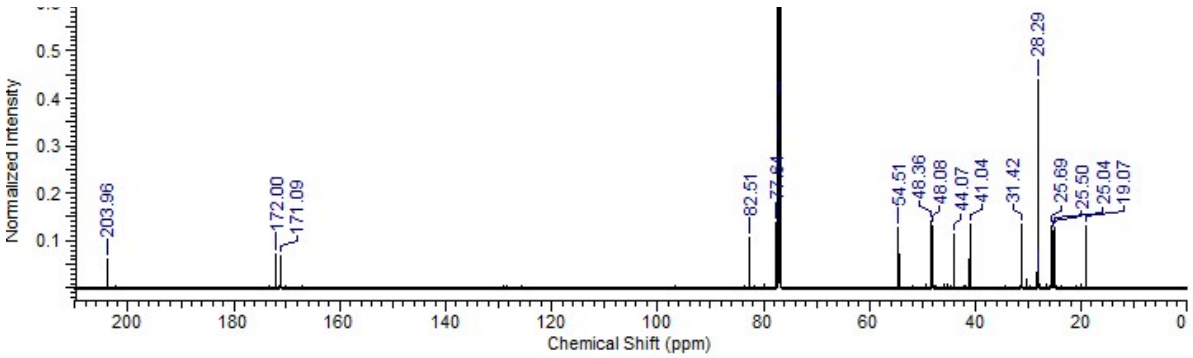
Data for (3*R*,3a*S*,4*R*,4a*R*,8a*R*,9a*S*)-*tert*-butyl 3-methyl-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carboxylate (**3**):



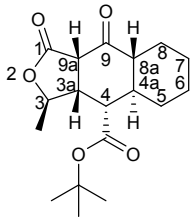
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.24 (1H, dd, *J* = 10.2, 6.0, C^3*H*Me), 3.77 (1H, d, *J* = 8.3, C^{9a}*H*), 2.71-2.66 (1H, m, C^{8a}*H*), 2.51 (1H, d, *J* = 4.9, C^4*H*), 2.01-1.96 (1H, m, C^8*H*H), 1.84-1.72 (4H, m, C^{4a}*H*, C^5*H*H, C^6*H*H & C^7*H*H), 1.50 (9H, s, C(C*H*$_3$)$_3$), 1.42 (3H, d, *J* = 6.0, C^{3}HC*H*$_3$), 1.33-1.23 (2H, m, C^{5}H*H* & C^{8}H*H*), 1.22-1.14 (2H, m, C^{6}H*H* & C^{7}H*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.0 (*C*^{9}O), 172.0 (*C*OO^{t}Bu), 171.1 (*C*^{1}O), 82.5 (*C*(CH$_3$)$_3$), 77.6 (*C*^{3}HMe), 54.5 (*C*^{9a}H), 48.4 (*C*^{3a}H), 48.1 (*C*^{8a}H), 44.1 (*C*^{4}H), 41.0 (*C*^{4a}H), 31.4 (*C*^{5}H$_2$), 28.3 (C(*C*H$_3$)$_3$), 25.7 (*C*^{8}H$_2$), 25.5 (*C*^{6}H$_2$), 25.0 (*C*^{7}H$_2$), 19.1

(C^3HCH_3); IR (thin film) 2988 (C-H), 2918 (C-H), 2855 (C-H), 1790 (C=O), 1727 (C=O), 1705 (C=O), 1198 (C-O), 1197, 1133, 1061, 913, 835 cm^{-1} ; m/z (CI) 267 (100%, $[M-C_4H_9]^+$); HRMS (CI) calcd for $C_{18}H_{27}O_5$ $[M+H]^+$ 323.1853, observed 323.1855.



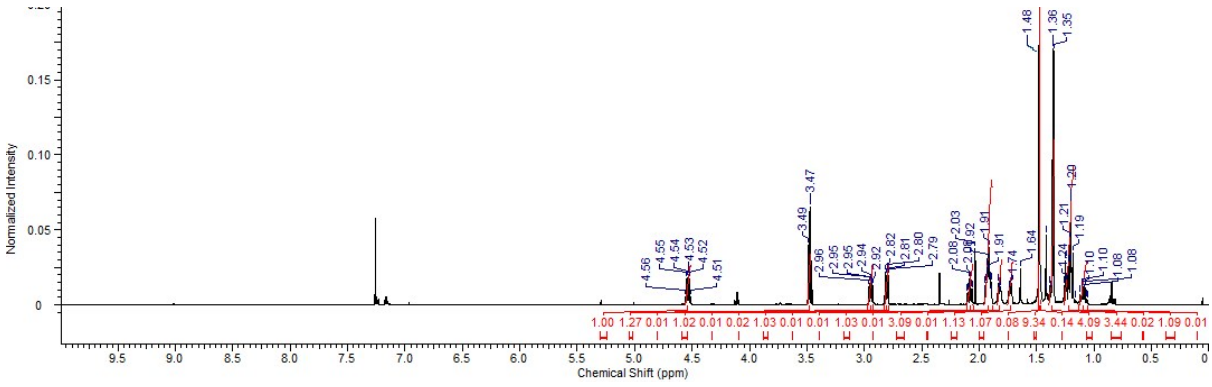


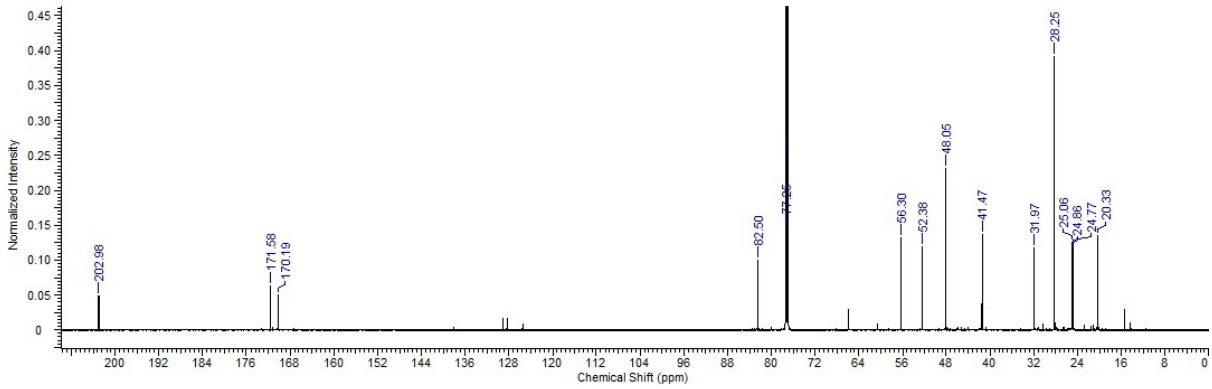
Data for (3*R*,3a*S*,4*S*,4a*R*,8a*R*,9a*S*)-*tert*-butyl 3-methyl-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carboxylate (**4**):



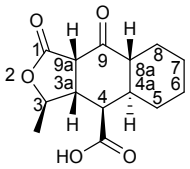
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.54 (1H, dq, *J* = 10.2, 6.0, C^3*H*Me), 3.48 (1H, d, *J* = 8.7, C^{9a}*H*), 2.94 (1H, ddd, *J* = 10.2, 8.7, 5.3, C^{3a}*H*), 2.81 (1H, dd, *J* = 11.5, 5.3, C^4*H*), 2.08 (1H, td, *J* = 11.8, 3.2, C^{8a}*H*), 1.96-1.88 (3H, m, C^{4a}*H*, C^5*H*H & C^8*H*H), 1.84-1.80 (1H, m, C^6*H*H), 1.75-1.71 (1H, m, C^7*H*H), 1.48 (9H, s, $C(CH_3)_3$), 1.36 (3H, d, *J* = 6.0, C^3HCH_3), 1.39-1.34 (1H, m, C^8H*H*), 1.26-1.17 (2H, m, C^6H*H* & C^7H*H*), 1.13-1.05 (1H, m, C^5H*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.0 (*C*^{9}O), 171.6 (*C*OO^tBu), 170.2 (*C*^{1}O), 82.5 (*C*$(CH_3)_3$), 77.3 (*C*^{3}HMe), 56.3 (*C*^{9a}H), 52.4 (*C*^{8a}H), 48.0 (*C*^{3a}H & *C*^{4}H),

41.5 (*C*^{4a}H), 32.0 (*C*^{5}H$_2$), 28.3 (C(*C*H$_3$)$_3$), 25.1 (*C*^{8}H$_2$), 24.9 (*C*^{6}H$_2$), 24.8 (*C*^{7}H$_2$), 20.3 (C^{3}H*C*H$_3$); IR (thin film) 2978 (C-H), 2933 (C-H), 2857 (C-H), 1784 (C=O), 1717 (C=O), 1367, 1194 (C-O), 1146, 1066, 985, 751 cm^{-1}; m/z (CI) 267 (100%, [M-C$_4$H$_9$]$^+$); HRMS (CI) calcd for C$_{18}$H$_{27}$O$_5$ [M+H]$^+$ 323.1853, observed 323.1856.

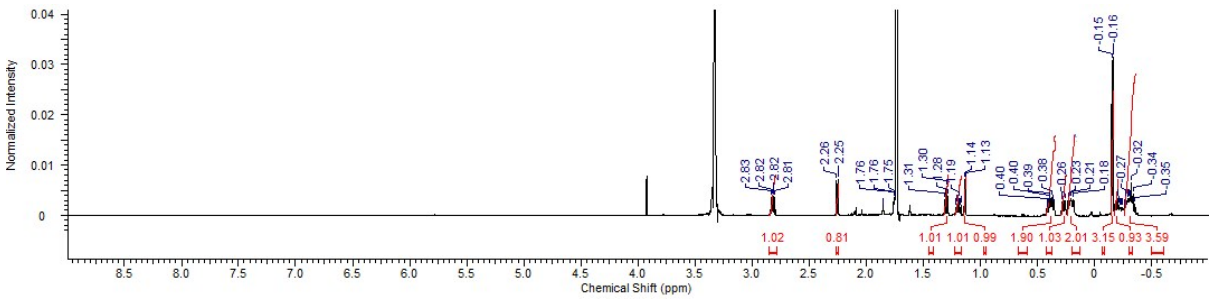




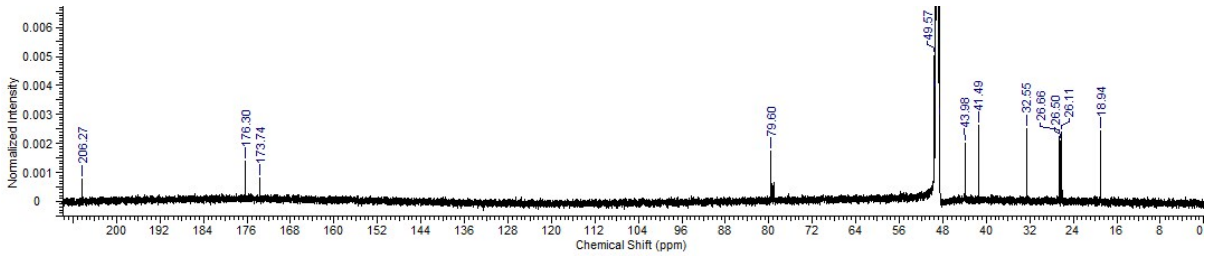
(3*R*,3a*S*,4*R*,4a*R*,8a*R*,9a*S*)-3-Methyl-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carboxylic acid



TFA (0.5 mL) was added dropwise to a stirred solution of (3*R*,3a*S*,4*R*,4a*R*,8a*R*,9a*S*)-*tert*-butyl 3-methyl-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carboxylate (**3**) (86.0 mg, 0.27 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C, under Ar. The reaction mixture was stirred at 20 °C for 16 h before being concentrated *in vacuo.* The residue was azeotroped with toluene to yield (3*R*,3a*S*,4*R*,4a*R*,8a*R*,9a*S*)-3-methyl-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carboxylic acid (69.8 mg, 0.26 mmol, 99%) as a white solid; ^{1}H NMR (600 MHz, MeOH-d_4) δ 4.39 (1H, td, *J* = 11.7, 6, C^3*H*Me), 3.82 (1H, d, *J* = 8.7, C^{9a}*H*), 2.87 (1H, dd, *J* = 10.4, 8.7, C^{3a}*H*), 2.76 (1H, td, *J* = 11.7, 3.4, C^{8a}*H*), 2.71 (1H, d, *J* = 4.9, C^4*H*), 1.97 (1H, dddd, *J* = 12.4, 11.7, 4.9, 3.8, C^{4a}*H*), 1.96-1.92 (1H, m, C^8*H*H), 1.87-1.82 (1H, m, C^5*H*H), 1.81-1.74 (2H, m, C^6*H*H & C^7*H*H), 1.42 (3H, d, *J* = 6.0, C^{3}HC*H*$_3$), 1.40-1.36 (1H, m, C^{5}H*H*), 1.31-1.21 (3H, m, C^{6}H*H*, C^{7}H*H* & C^{8}H*H*); ^{13}C NMR (150 MHz, MeOH-d_4) δ 206.3 (*C*^{9}O), 176.3 (*C*OOH), 173.7 (*C*^{1}O), 79.6 (*C*^{3}HMe), 49.6 (*C*^{3a}H), 49.2 (*C*^{8a}H), 49.0 (*C*^{9a}H), 44.0 (*C*^{4}H), 41.5 (*C*^{4a}H), 32.5 (*C*^{5}H$_2$), 26.7 (*C*^{8}H$_2$), 26.5 (*C*^{6}H$_2$), 26.1 (*C*^{7}H$_2$), 18.9 (C^{3}H*C*H$_3$); IR (thin film) 2928 (C-H), 2859 (C-H), 1775 (C=O), 1702 (C=O), 1581, 1416, 1201 (C-O), 1052 cm^{-1}; m/z (EI) 267 (100%, [M+H]$^+$); HRMS (EI) calcd for $C_{14}H_{18}O_5$ [M+H]$^+$ 266.1149, observed 266.1150.



Note: Peaks shifted right by about 1.5 ppm; MeOD peak used as reference.


Normalized Intensity
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0.001
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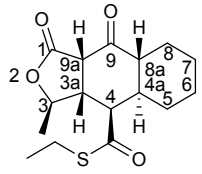
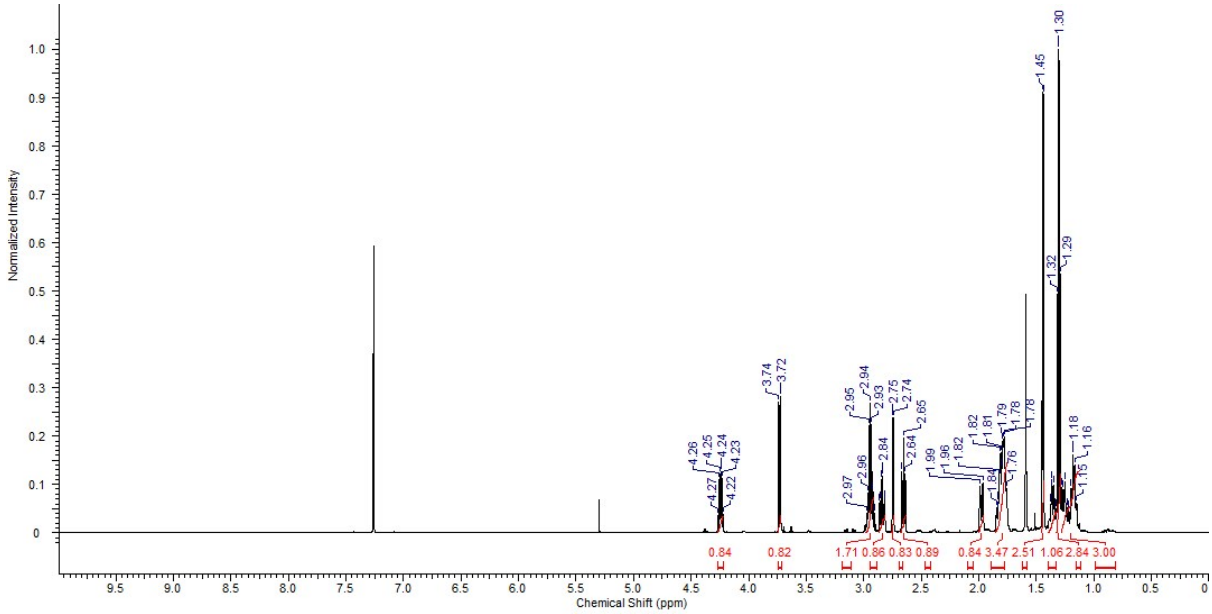
173.74
79.60
49.57
43.98
41.49
32.55
26.66
26.50
26.11
18.94
200
192
184
176
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

(3*R*,3a*R*,4*R*,4a*R*,8a*R*,9a*S*)-*S*-Ethyl 3-methyl-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carbothioate (5)



DCC (149 mg, 0.72 mmol) was added to a stirred solution of (3*R*,3a*S*,4*R*,4a*R*,8a*R*,9a*S*)-3-methyl-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carboxylic acid (160 mg, 0.60 mmol), ethanethiol (173 µL, 2.40 mmol) and DMAP (37.0 mg, 0.30 mmol) in CH_2Cl_2 (5 mL) at 0 °C, under Ar. The reaction mixture was stirred at 20 °C for 16 h before being filtered under vacuum to remove the precipitate. The filtrate was concentrated *in vacuo* to yield a crude colourless oil. Purification by flash column chromatography (0-2% Et_2O/CH_2Cl_2) yielded (3*R*,3a*R*,4*R*,4a*R*,8a*R*,9a*S*)-S-ethyl 3-methyl-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carbothioate (**5**) (128 mg, 0.41 mmol, 69%) as a white solid; Rf 0.64 (8% Et_2O/CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.24 (1H, dq, *J* = 10.5, 6.0, C^3*H*Me), 3.73 (1H, d, *J* = 8.7, C^{9a}*H*), 2.96 (1H, q, *J* = 6.5, SC*H*HCH$_3$), 2.92 (1H, q, *J* = 6.5, SCH*H*CH$_3$), 2.84 (1H, td, *J* = 11.9, 3.4, C^{8a}*H*), 2.75 (1H, d, *J* = 4.5, C^4*H*), 2.65 (1H, dd, *J* = 10.5, 8.7, C^{3a}*H*), 2.00-1.95 (1H, m, C^8*H*H), 1.86-1.74 (4H, m, C^{4a}*H*, C^5*H*H, C^6*H*H & C^7*H*H), 1.44 (3H, d, *J* = 6.0, C^{3}HC*H$_3$*), 1.40-1.32 (1H, m, C^{5}H*H*), 1.30 (3H, t, *J* = 7.3, SCH$_2$C*H$_3$*), 1.28-1.11 (3H, m, C^{6}H*H,* C^{7}H*H* & C^{8}H*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.8 (*C*^{9}O), 200.3 (*C*OSEt), 170.7 (*C*^{1}O), 77.3 (*C*^{3}HMe), 54.7 (*C*^{9a}H), 50.6 (*C*^{4}H), 48.8 (*C*^{8a}H), 48.3 (*C*^{3a}H), 41.8 (*C*^{4a}H), 31.4 (*C*^{5}H$_2$), 25.7 (*C*^{8}H$_2$), 25.3 (*C*^{6}H$_2$), 24.8 (*C*^{7}H$_2$), 24.1 (*C*H$_2$CH$_3$), 18.9 (C^{3}H*C*H$_3$), 14.6 (CH$_2$*C*H$_3$); IR (thin film) 2930 (C-H), 2854 (C-H), 1785 (C=O), 1708 (C=O), 1672, 1197 (C-O), 1059, 958 cm^{-1}; m/z (EI) 252 (100%, [M-SEt-Me+OH]$^+$); HRMS (EI) calcd for $C_{16}H_{22}O_4S$ [M+H]$^+$ 310.1233, observed 310.1233.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Chemical Shift (ppm)
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4.24
4.23
4.27
4.22
3.74
3.72
2.95
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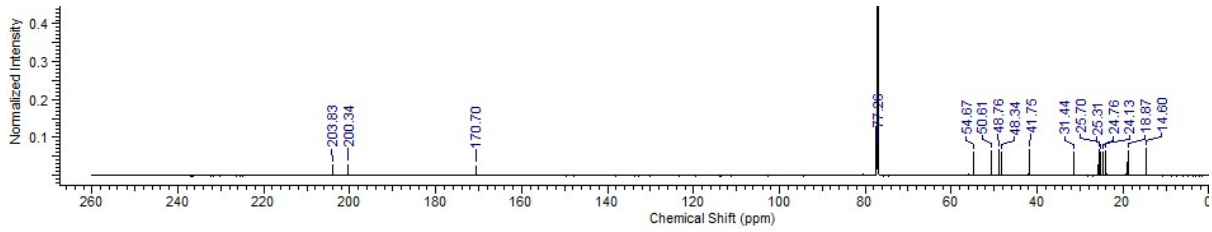
2.93
2.75
2.74
2.65
2.97
2.96
2.84
2.64
1.99
1.96
1.82
1.84
1.81
1.79
1.78
1.76
1.45
1.30
1.32
1.29
1.18
1.16
1.15
0.84
0.82
1.71
0.86
0.83
0.89
0.84
3.47
2.51
1.06
2.84
3.00


Normalized Intensity
Chemical Shift (ppm)
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170.70
77.26
54.67
50.61
48.76
48.34
41.75
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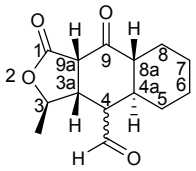
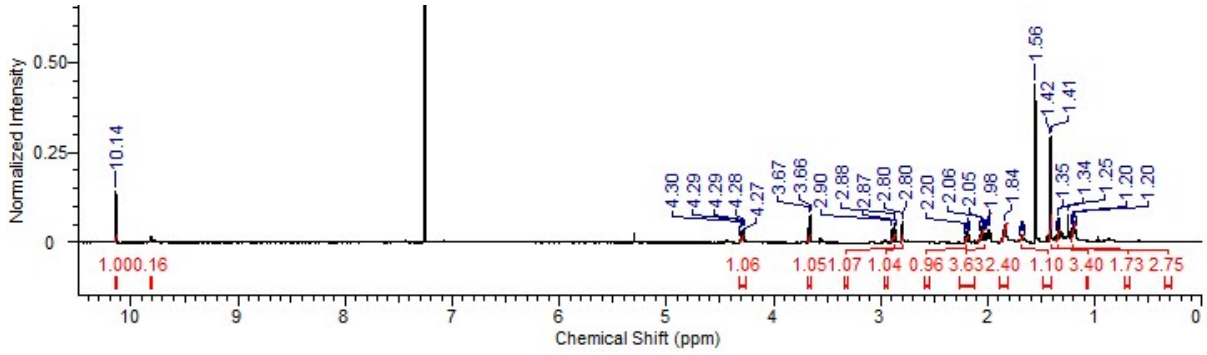
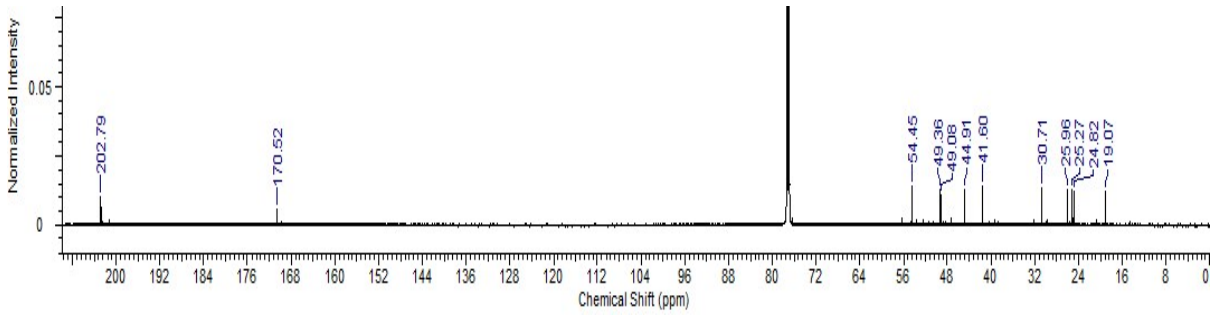
25.70
25.31
24.76
24.13
18.87
14.60

(3*R*,3a*S*,4a*S*,8a*R*,9a*S*)-3-Methyl-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carbaldehyde (6)



Triethylsilane (263 µL, 1.65 mmol) was added to a stirred suspension of (3*R*,3a*R*,4*R*,4a*R*,8a*R*,9a*S*)-S-ethyl 3-methyl-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carbothioate (**5**) (128 mg, 0.41 mmol), palladium on carbon (10%) (44.0 mg, 0.04 mmol) and $MgSO_4$ (to dry) in degassed acetone (5 mL) under Ar. The reaction mixture was stirred at 20 °C for 16 h before it was filtered over celite and concentrated *in vacuo*. Purification by flash column chromatography (0-2% Et_2O/CH_2Cl_2) gave partial racemisation at C^4 to yield (3*R*,3a*S*,4a*S*,8a*R*,9a*S*)-3-methyl-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carbaldehyde (**6**) (4*S*:4*R*; 1:0.16) (50 mg, 0.20 mmol, 48%) as a colourless film; Rf 0.44 (8% Et_2O/CH_2Cl_2); ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.14 (1H, s, 4*S*-C*H*O), 4.29 (1H, dq, *J* = 10.2, 6.0, 4*S*-C^3*H*Me), 3.67 (1H, d, *J* = 8.7, 4*S*-C^{9a}*H*), 2.88 (1H, dd, *J* = 10.2, 8.7, 4*S*-C^{3a}*H*), 2.80 (1H, d, *J* = 4.9, 4*S*-C^4*H*), 2.20 (1H, ddd, *J* = 12.4, 12.0, 3.4, 4*S*-C^{8a}*H*), 2.09-1.96 (3H, m, 4*S*-C^{4a}*H,* 4*S*-C^5*H*H & 4*S*-C^8*H*H), 1.88-1.81 (2H, m, 4*S*-C^6*H*H & 4*S*-C^7*H*H), 1.68 (1H, qd, *J* = 12.4, 3.4, 4*S*-C^{5}H*H*), 1.42 (3H, d, *J* = 6.0, C^{3}HC*H*$_3$), 1.36-1.32 (1H, m, 4*S*-C^{8}H*H*), 1.23-1.17 (2H, m, 4*S*-C^{6}H*H* & 4*S*-C^{7}H*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.8 (4*S*-*C*^{9}O), 202.7 (4*S*-*C*HO), 170.5 (4*S*-*C*^{1}O), 77.2 (4*S*-*C*^{3}HMe), 54.5 (4*S*-*C*^{9a}H), 49.4 (4*S*-*C*^{8a}H), 49.1 (4*S*-*C*^{4}H), 44.9 (4*S*-*C*^{3a}H), 41.6 (4*S*-*C*^{4a}H), 30.7 (4*S*-*C*^{5}H$_2$), 26.0 (4*S*-*C*^{8}H$_2$), 25.3 (4*S*-*C*^{6}H$_2$), 24.8 (4*S*-*C*^{7}H$_2$), 19.1 (4*S*-C^{3}H*C*H$_3$).




Normalized Intensity
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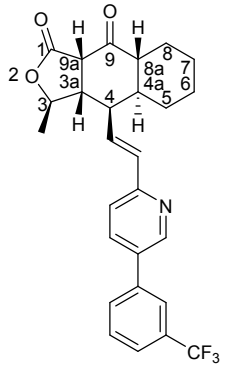
54.45
49.36
49.08
44.91
41.60
30.71
25.96
25.27
24.82
19.07
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

(3*R*,3a*S*,4a*S*,8a*R*,9a*S*)-3-Methyl-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)octahydronaphtho[2,3-c]furan-1,9(3H,9aH)-dione (8 and 9)

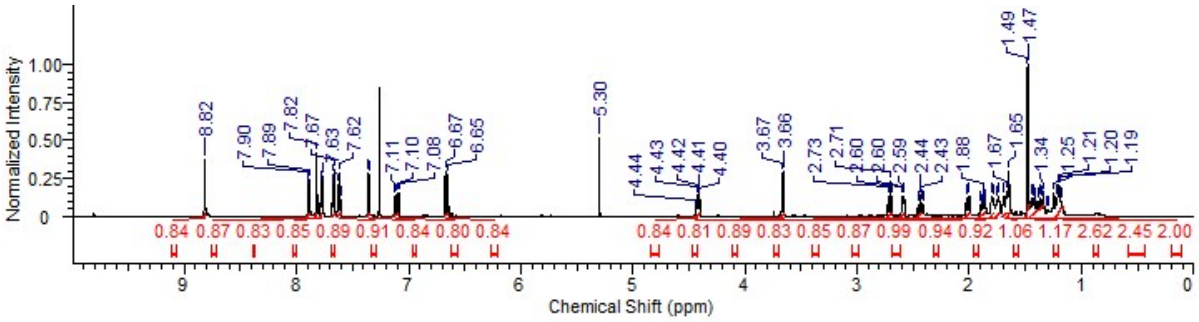
n-BuLi (1.6 M in hexanes) (150 µL, 0.24 mmol) was added dropwise to a stirred solution of diethyl (5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)methylphosphonate (**7**) (75 mg, 0.20 mmol) in anhydrous THF (1 mL) at 0 °C, under Ar. The solution was stirred at 0 °C for 10 min before (3*R*,3a*S*,4a*S*,8a*R*,9a*S*)-3-methyl-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carbaldehyde (**6**) (50 mg, 0.20 mmol) was added. The reaction mixture was stirred at 0 °C for 45 min and then quenched with sat. aq. NH_4Cl (5 mL). An extraction into EtOAc (10 mL) was done and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude yellow oil. Purification by flash column chromatography (0-15% Et_2O/CH_2Cl_2) and then (20-35% Et_2O/toluene) yielded (3*R*,3a*S*,4*R*,4a*S*,8a*R*,9a*S*)-3-methyl-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)octahydronaphtho[2,3-c]furan-1,9(3H,9aH)-dione (**8**) (39 mg, 0.083 mmol, 41%) and (3*R*,3a*S*,4*S*,4a*S*,8a*R*,9a*S*)-3-methyl-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)octahydronaphtho[2,3-c]furan-1,9(3H,9aH)-dione (**9**) (14 mg, 0.03 mmol, 15%) as white solids.

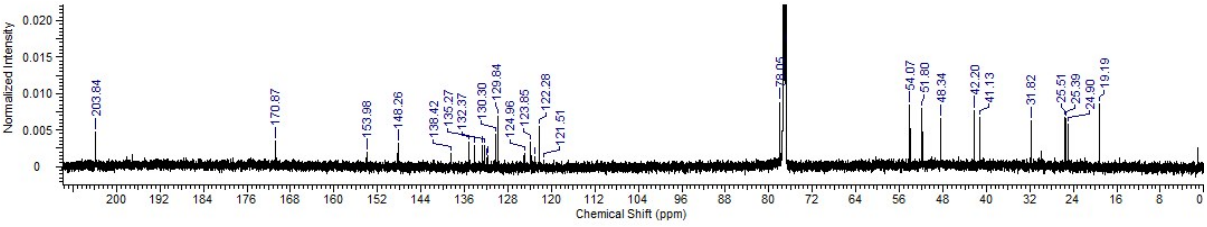
Data for (3*R*,3a*S*,4*R*,4a*S*,8a*R*,9a*S*)-3-methyl-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)octahydronaphtho[2,3-c]furan-1,9(3H,9aH)-dione (**8**):



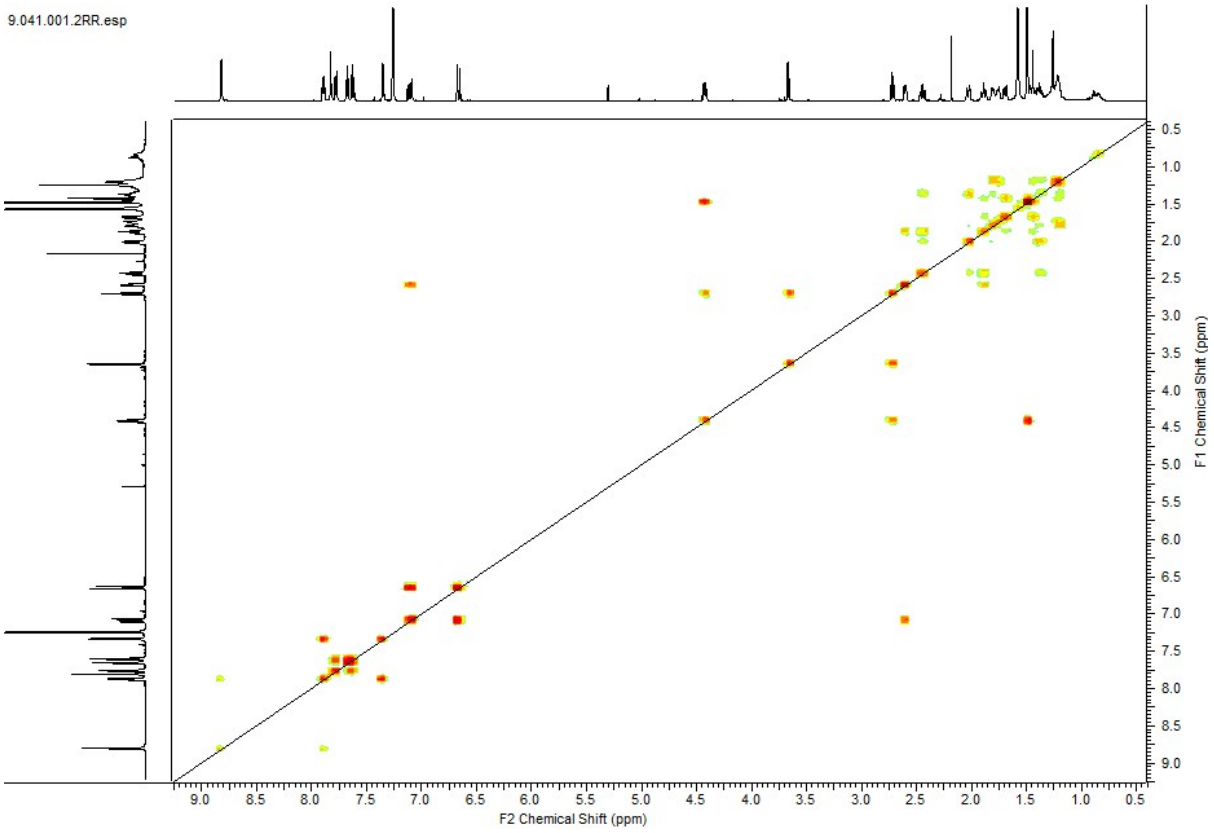
$[\alpha]_D^{20}$ = +14 (MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.82 (1H, d, *J* = 2.3, C*H*N), 7.89 (1H, dd, *J* = 8.3, 2.3, C*H*CCHN), 7.82 (1H, s, C*H*CCF_3), 7.78 (1H, d, *J* = 7.5, C*H*CCHCCF_3), 7.68 (1H, d, *J* = 7.5, CHC*H*CCF_3), 7.62 (1H, t, *J* = 7.9, C*H*CHCCF_3), 7.35 (1H, d, *J* = 7.9, C*H*CN), 7.10 (1H, dd, *J* = 15.4, 9.8, C^{4}HC*H*CHPyr), 6.66 (1H, d, *J* = 15.4, C^{4}HCHC*H*Pyr), 4.42 (1H, dq, *J* = 10.2, 6, C^3*H*Me), 3.66 (1H, d, *J* = 8.7,

C^{9a}*H*), 2.71 (1H, dd, *J* = 10.2, 8.7, C^{3a}*H*), 2.59 (1H, dd, *J* = 9.6, 4.0, C^{4}*H*), 2.44 (1H, td, *J* = 12.0, 3.6, C^{8a}*H*), 2.05-1.99 (1H, m, C^{8}*H*H), 1.88 (1H, tt, *J* = 12.3, 4, C^{4a}*H*), 1.82-1.77 (1H, m, C^{7}*H*H), 1.77-1.72 (1H, m, C^{6}*H*H), 1.71-1.66 (1H, m, C^{5}*H*H), 1.48 (3H, d, *J* = 6.0, C^{3}HC*H$_3$*), 1.46-1.40 (1H, m, C^{5}H*H*), 1.40-1.34 (1H, m, C^{8}H*H*), 1.23-1.17 (2H, m, C^{6}H*H* & C^{7}H*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.8 (*C*^{9}O), 170.9 (*C*^{1}O), 154.0 (*C*N), 148.3 (*C*HN), 138.4 (*C*CHCCF$_3$), 135.3 (*C*HCCHN), 134.2 (*C*CHN), 132.8 (C^{4}H*C*HCHPyr), 132.4 (C^{4}HCH*C*HPyr), 131.7 (q, *J* = 32.8, *C*CF$_3$), 130.3 (*C*HCCHCCF$_3$), 129.8 (*C*HCHCCF$_3$), 125.0 (q, *J* = 4.0, CH*C*HCCF$_3$), 123.8 (q, *J* = 4.0, C*C*HCCF$_3$), 122.3 (d, *J* = 247.6, *C*F$_3$), 122.3 (*C*HCN), 78.0 (*C*^{3}HMe), 54.1 (*C*^{9a}H), 51.8 (*C*^{3a}H), 48.3 (*C*^{8a}H), 42.2 (*C*^{4a}H), 41.1 (*C*^{4}H), 31.8 (*C*^{5}H$_2$), 25.5 (*C*^{6}H$_2$), 25.4 (*C*^{8}H$_2$), 24.9 (*C*^{7}H$_2$), 19.2 (C^{3}H*C*H$_3$); IR (thin film) 2921 (C-H), 2852 (C-H), 1783 (C=O), 1719 (C=O), 1447, 1335, 1265, 1167 (C-O), 1127, 804, 730 cm^{-1}; m/z (ES+) 470 (100%, [M+H]$^{+}$); HRMS (ES+) calcd for $C_{27}H_{27}NO_3F_3$ [M+H]$^{+}$ 470.1943, observed 470.1920.





COSY: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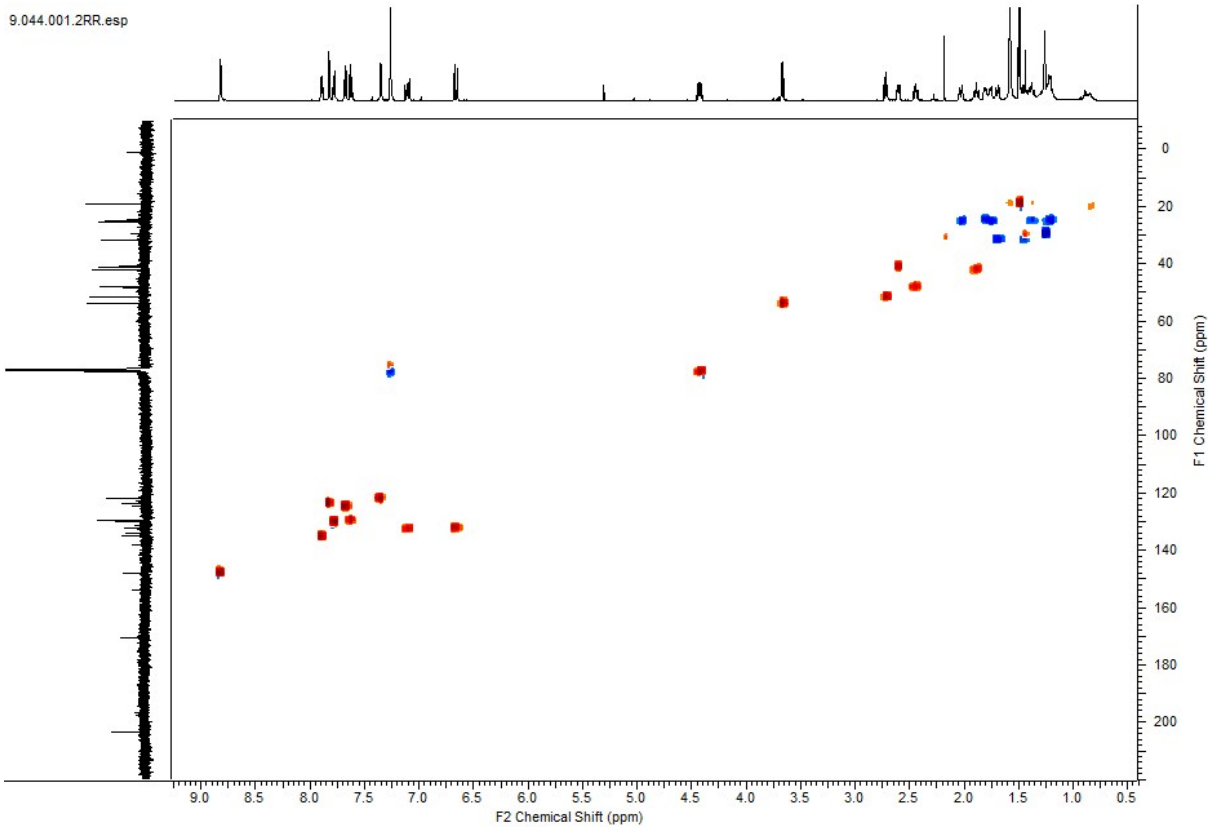
F1 Chemical Shift (ppm)

HSQC: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F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

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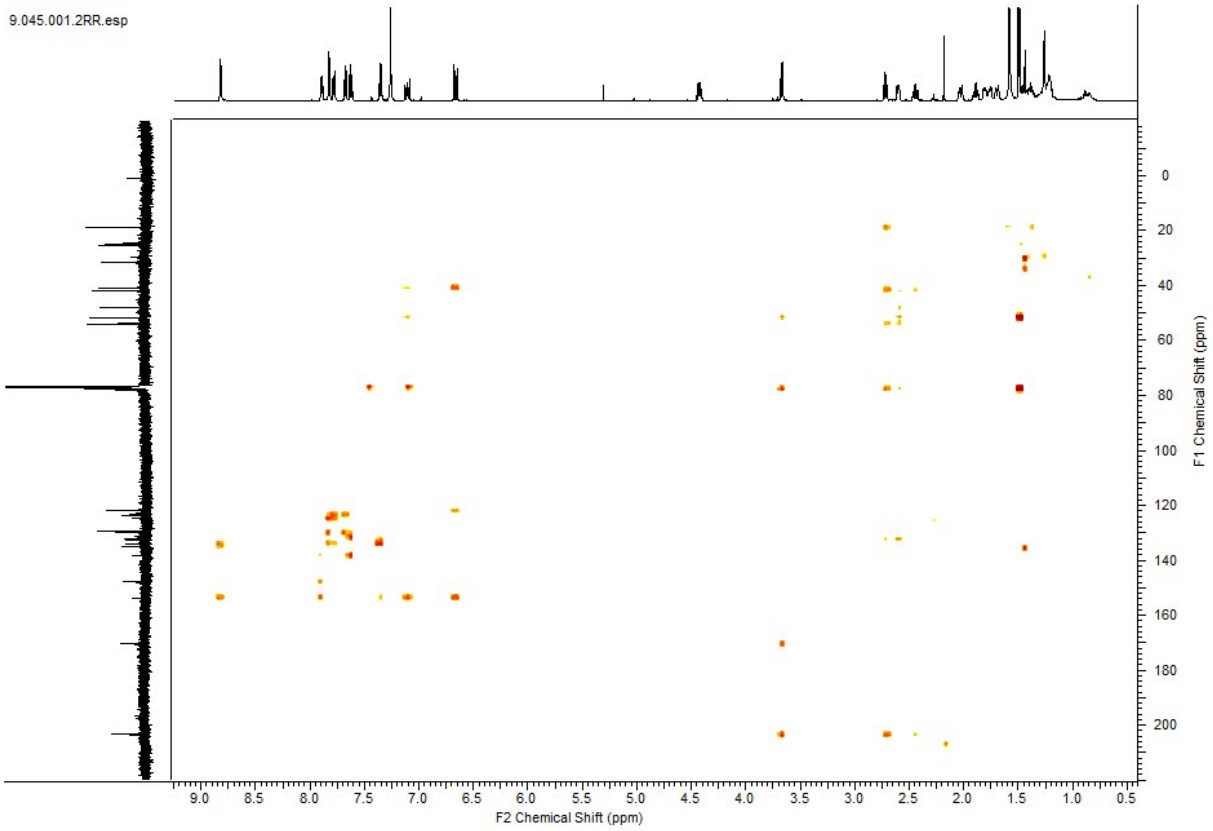
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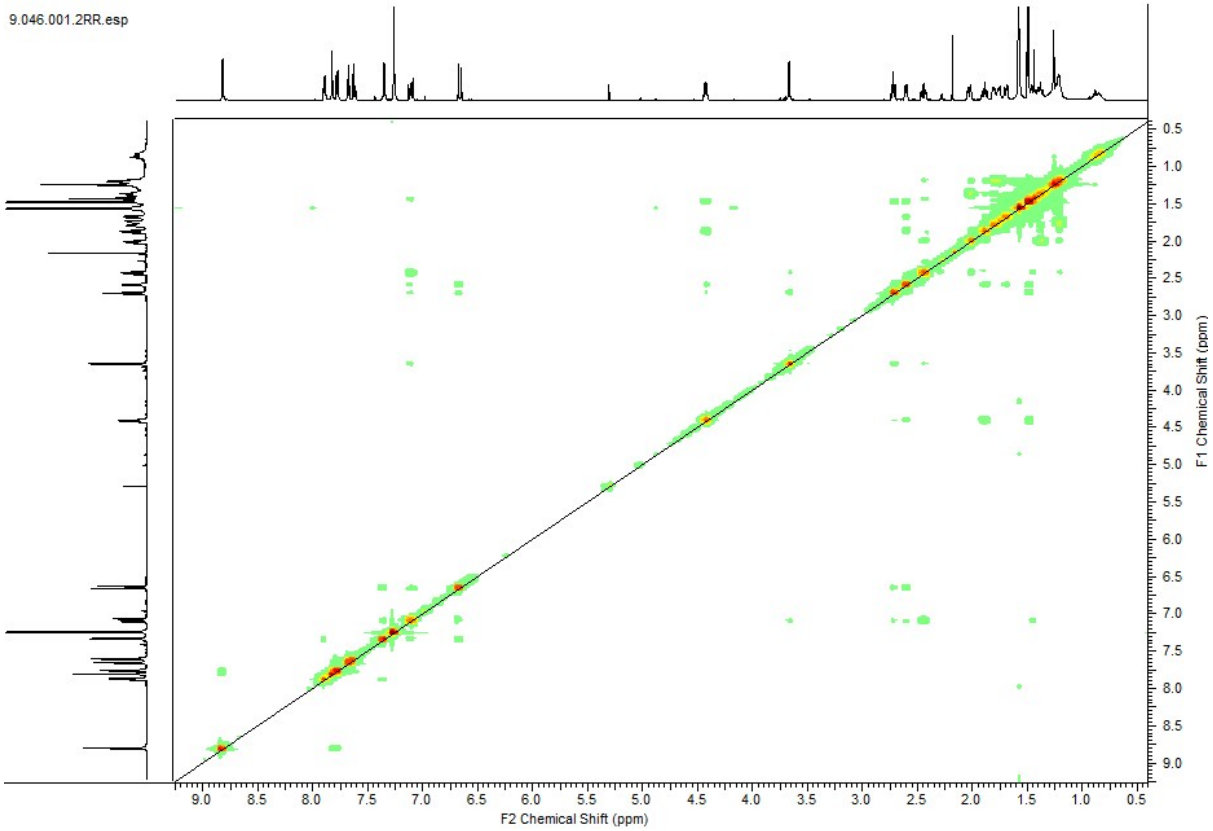
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

NOESY: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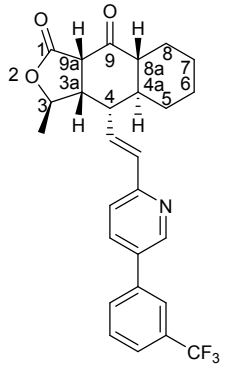
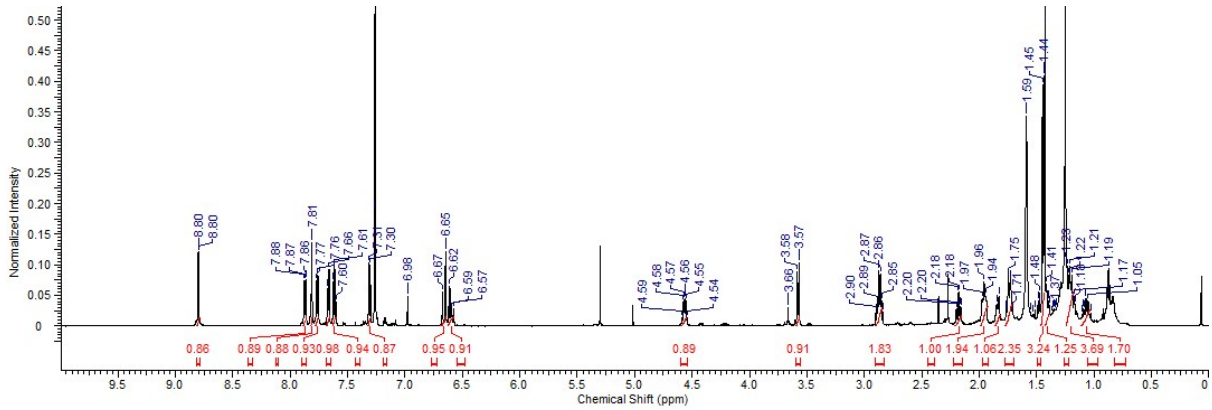
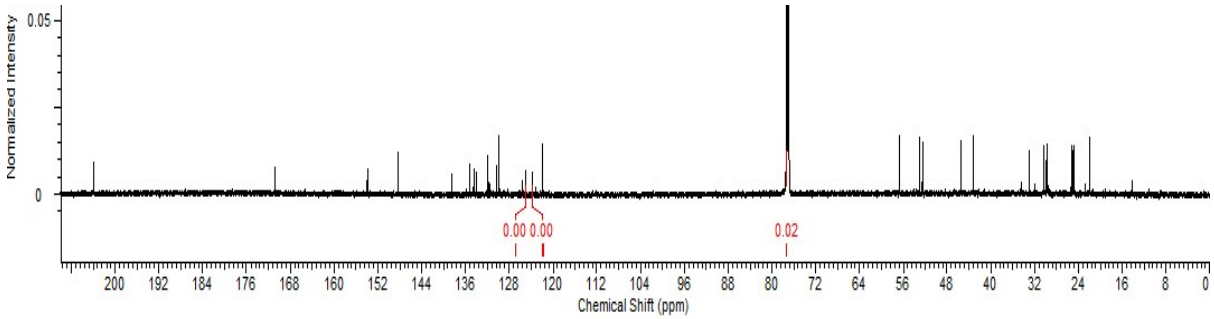
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

Data for (3*R*,3a*S*,4*S*,4a*S*,8a*R*,9a*S*)-3-methyl-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)octahydronaphtho[2,3-c]furan-1,9(3H,9aH)-dione (**9**):

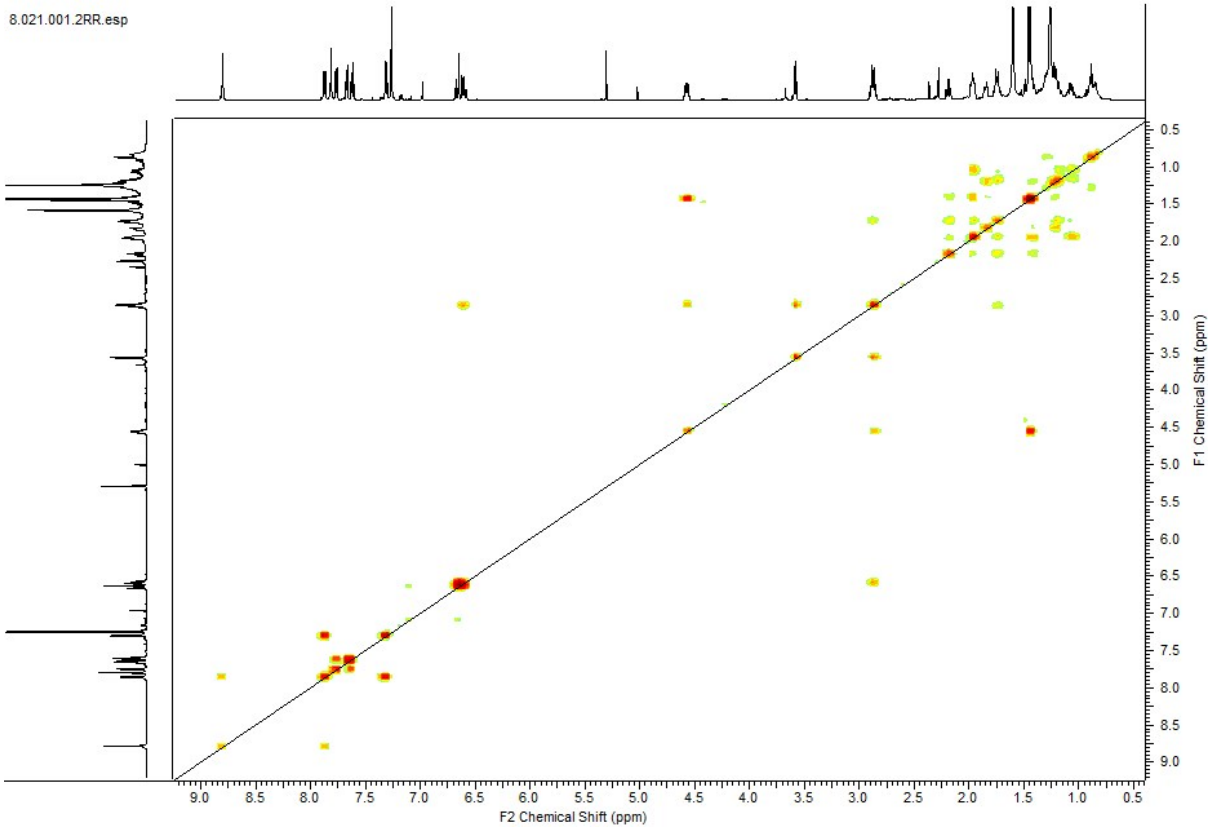


^{1}H NMR (600 MHz, $CDCl_3$) δ 8.80 (1H, d, *J* = 2.4, C*H*N), 7.87 (1H, dd, *J* = 8.1, 2.4, C*H*CCHN), 7.81 (1H, s, C*H*CCF_3), 7.76 (1H, d, *J* = 7.9, C*H*CCHCCF_3), 7.67 (1H, d, *J* = 7.9, CHC*H*CCF_3), 7.61 (1H, t, *J* = 7.9, C*H*CHCCF_3), 7.31 (1H, d, *J* = 8.1, C*H*CN), 6.66 (1H, d, *J* = 15.4, C^{4}HCHC*H*Pyr), 6.60 (1H, dd, *J* = 15.4, 9.4, C^{4}HC*H*CHPyr), 4.57 (1H, dq, *J* = 9.4, 6.0, C^{3}*H*Me), 3.58 (1H, d, *J* = 7.9, C^{9a}*H*), 2.90-2.83 (2H, m, C^{3a}*H* & C^{4}*H*), 2.18 (1H, td, *J* = 11.6, 3.2, C^{8a}*H*), 1.99-1.92 (2H, m, C^{5}*H*H & C^{8}*H*H), 1.86-1.81 (1H, m, C^{6}*H*H), 1.78-1.69 (2H, m, C^{4a}*H* & C^{7}*H*H), 1.44 (3H, d, *J* = 6.0, C^{3}HC*H*$_3$), 1.42-1.38 (1H, m, C^{8}H*H*), 1.24-1.16 (2H, m, C^{6}H*H* & C^{7}H*H*), 1.11-1.01 (1H, m, C^{5}H*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.9 (*C*^{9}O), 170.8 (*C*^{1}O), 153.9 (*C*N), 148.4 (*C*HN), 138.5 (*C*CHCCF_3), 135.2 (*C*HCCHN), 134.5 (C^{4}HCH*C*HPyr), 134.1 (*C*CHN), 131.9 (C^{4}H*C*HCHPyr), 131.7 (q, *J* = 32.1, *C*CF_3), 130.3 (*C*HCCHCCF_3), 129.8 (*C*HCHCCF_3), 124.9 (q, *J* = 3.8, CH*C*HCCF_3), 124.1 (d, *J* = 271.7, *C*F_3), 123.8 (q, *J* = 3.8, C*C*HCCF_3), 122.0 (*C*HCN), 77.3 (*C*^{3}HMe), 56.7 (*C*^{9a}H), 53.1 (*C*^{8a}H), 52.5 (*C*^{3a}H), 45.5 (*C*^{4}H), 43.3 (*C*^{4a}H), 33.1 (*C*^{5}H_2), 25.3 (*C*^{6}H_2), 25.0 (*C*^{8}H_2), 24.8 (*C*^{7}H_2), 21.9 (C^{3}H*C*H_3); IR (thin film) 2922 (C-H), 2855 (C-H), 1781 (C=O), 1714 (C=O), 1440, 1335, 1268, 1123 (C-O), 1074, 810, 703 cm^{-1}; m/z (EI) 469 (100%, $[M]^+$); HRMS (EI) calcd for $C_{27}H_{26}NO_3F_3$ $[M]^+$ 469.1859, observed 469.1859.


Normalized Intensity
Chemical Shift (ppm)


Normalized Intensity
Chemical Shift (ppm)

COSY: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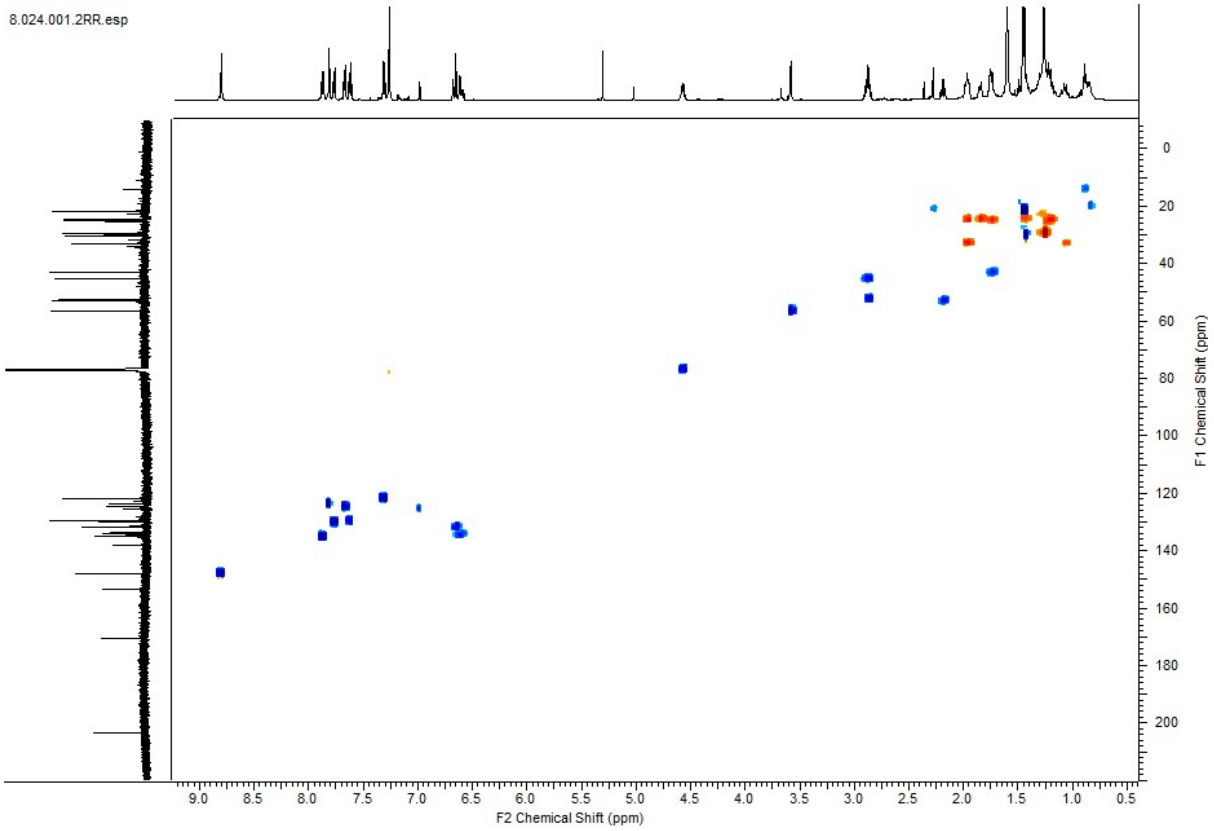
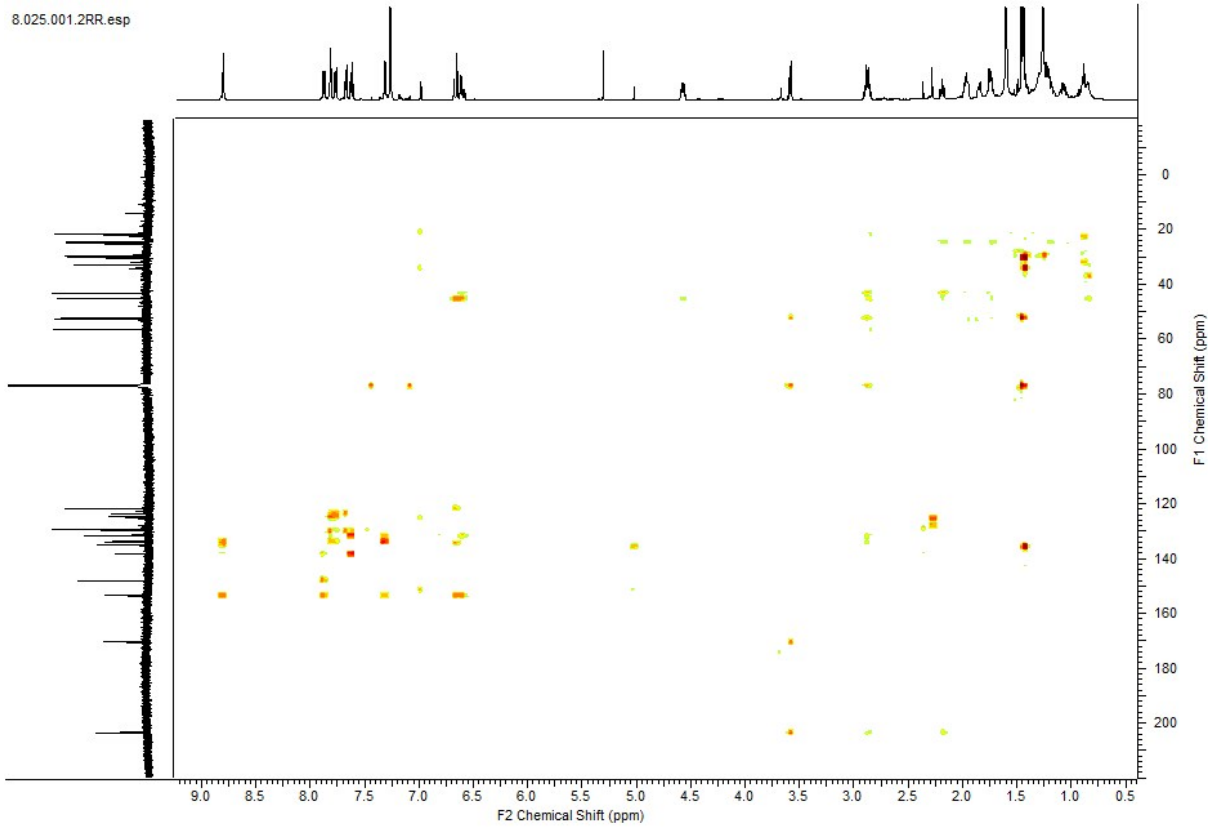
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

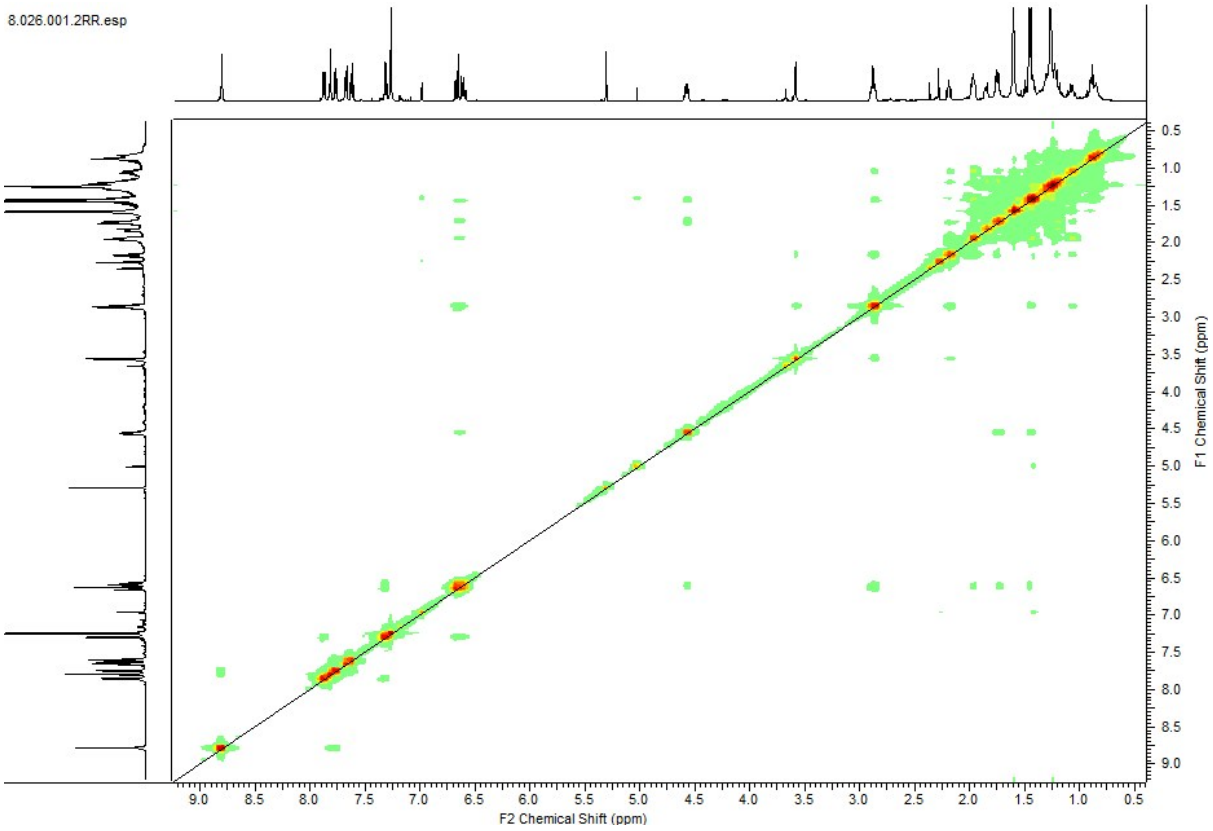
HSQC:


8.024.001.2RR.esp
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

HMBC:


8.025.001.2RR.esp
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

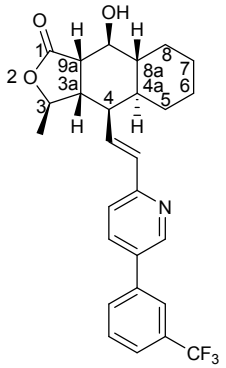
NOESY:



(3*R*,3a*S*,4*R*,4a*S*,8a*R*,9a*S*)-9-Hydroxy-3-methyl-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)decahydronaphtho[2,3-c]furan-1(3H)-one (10 and 11)

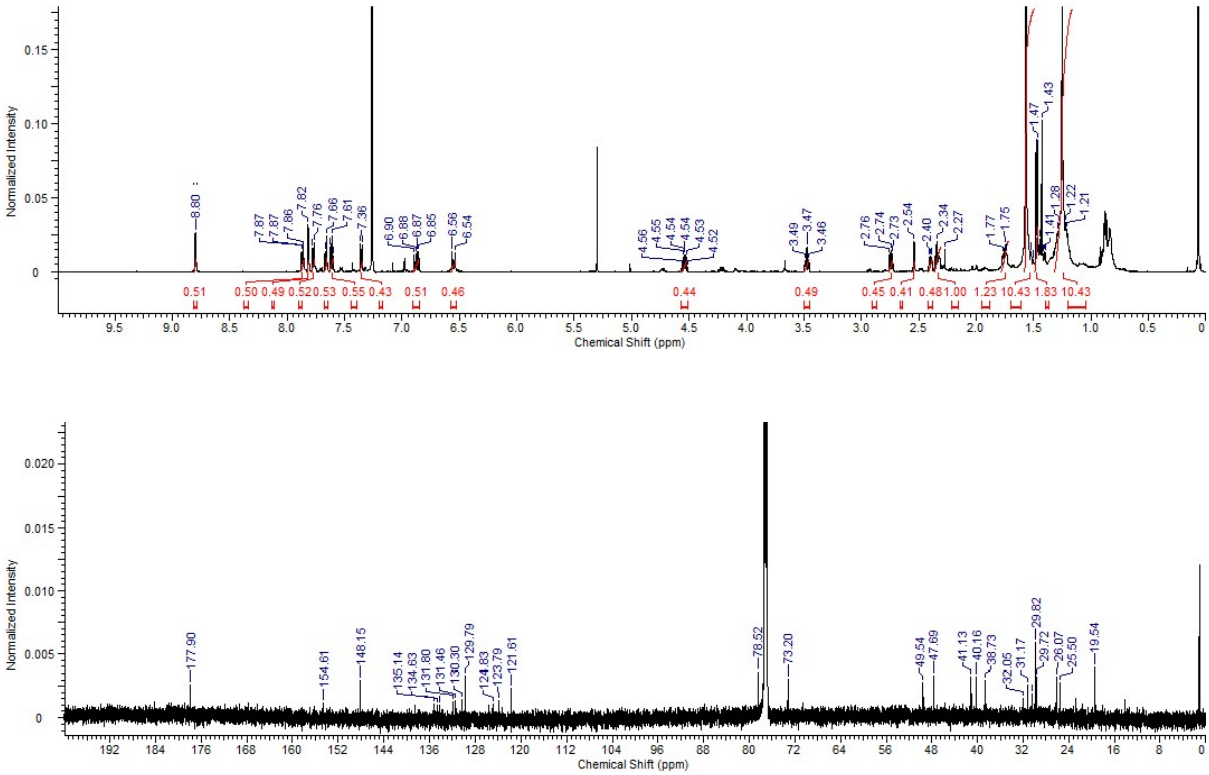
$NaBH_4$ (2.13 mg, 0.06 mmol) was added to a stirred solution of (3*R*,3a*S*,4*R*,4a*S*,8a*R*,9a*S*)-3-methyl-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)octahydronaphtho[2,3-c]furan-1,9(3H,9aH)-dione (**8**) (24.0 mg, 0.05 mmol) in anhydrous THF (2 mL) and MeOH (2 mL) at 0 °C, under Ar. The reaction mixture was stirred at 0 °C for 15 min and then quenched with sat. aq. NH_4Cl (0.5 mL). An extraction into Et_2O (5 mL) was done and the organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude yellow gum. Purification by flash column chromatography (0-2% Et_2O/CH_2Cl_2) yielded (3*R*,3a*S*,4*R*,4a*S*,8a*R*,9*R*,9a*S*)-9-hydroxy-3-methyl-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)decahydronaphtho[2,3-c]furan-1(3H)-one as a mixture of isomers. Purification by preparative thin layer chomatography (0-2% Et_2O/CH_2Cl_2) yielded (3*R*,3a*S*,4*R*,4a*S*,8a*R*,9*R*,9a*S*)-9-hydroxy-3-methyl-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)decahydronaphtho[2,3-c]furan-1(3H)-one (**10**) (9 mg, 0.02 mmol, 38%) and (3*R*,3a*S*,4*R*,4a*S*,8a*R*,9*S*,9a*S*)-9-hydroxy-3-methyl-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)decahydronaphtho[2,3-c]furan-1(3H)-one (**11**) (7 mg, 0.02 mmol, 29%) as white solids.

Data for (3*R*,3a*S*,4*R*,4a*S*,8a*R*,9*R*,9a*S*)-9-hydroxy-3-methyl-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)decahydronaphtho[2,3-c]furan-1(3H)-one (**10**):

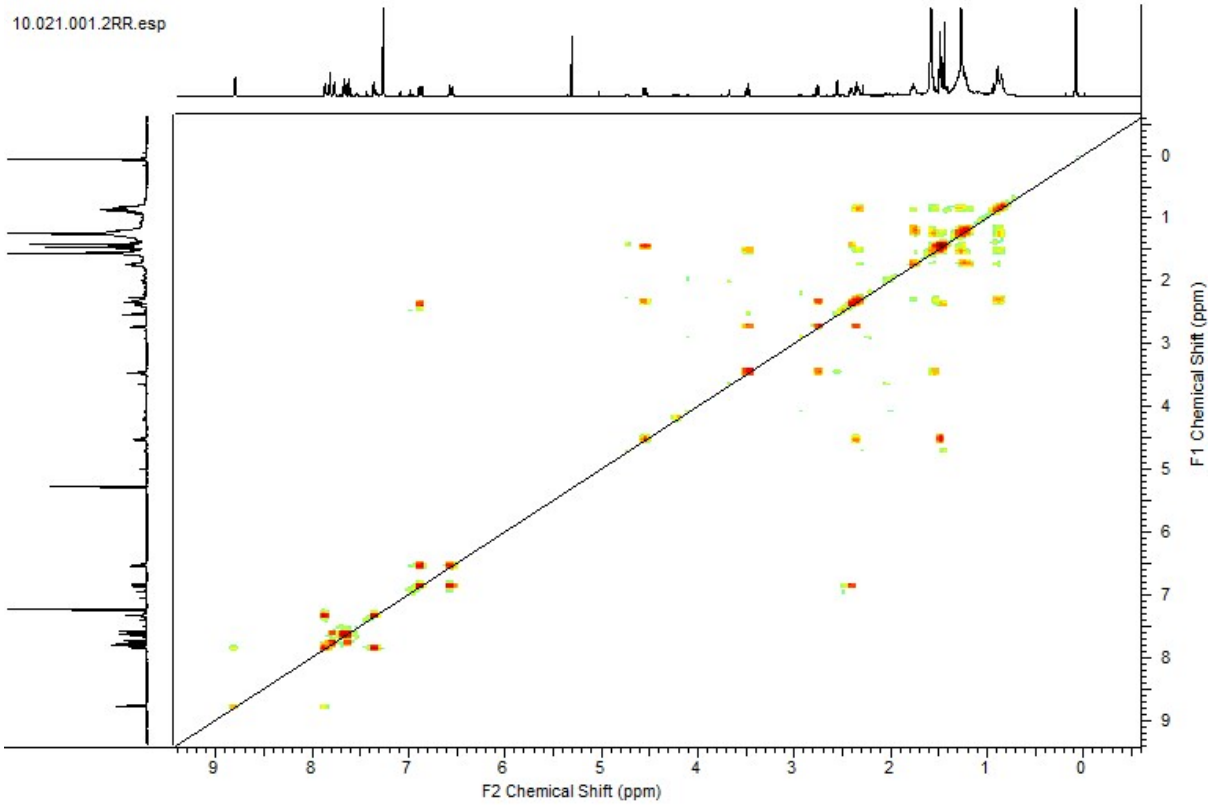


^{1}H NMR (600 MHz, $CDCl_3$) δ 8.80 (1H, d, *J* = 1.9, C*H*N), 7.86 (1H, dd, *J* = 8.1, 1.9, C*H*CCHN), 7.82 (s1H,, C*H*CCF_3), 7.77 (1H, d, *J* = 7.5, C*H*CCHCCF_3), 7.66 (1H, d, *J* = 7.5, CHC*H*CCF_3), 7.61 (1H, t, *J* = 7.9, C*H*CHCCF_3), 7.35 (1H, d, *J* = 8.1, C*H*CN),

6.88 (1H, dd, *J* = 15.4, 9.8, C^{4}HC*H*CHPyr), 6.55 (1H, d, *J* = 15.4, C^{4}HCHC*H*Pyr), 4.54 (1H, dq, *J* = 10.4, 6.0, C^{3}*H*Me), 3.47 (1H, ddd, J = 10.9, 9.8, 1.1, C^{9}*H*OH), 2.74 (1H, dd, *J* = 9.8, 7.9, C^{9a}*H*), 2.54 (1H, d, *J* = 1.9, O*H*), 2.40 (1H, dd, *J* = 9.6, 4.0, C^{4}*H*), 2.36-2.30 (2H, m, C^{3a}*H* & C^{8}*H*H), 1.78-1.72 (2H, m, C^{6}*H*H & C^{7}*H*H), 1.58-1.49 (3H, m, C^{4a}*H*, C^{5}*H*H & C^{8a}*H*), 1.47 (1H, d, *J* = 6.0, C^{3}HC*H*$_3$),1.32-1.16 (4H, m, C^{5}H*H*, C^{6}H*H,* C^{7}H*H &* C^{8}H*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.9 (*C*^{1}O), 154.6 (*C*N), 148.1 (*C*HN), 131.8 (*C*CHCCF$_3$), 131.5 (*C*HCCHN), 131.3 (C^{4}H*C*HCHPyr), 130.9 (q, *J* = 32.1, *C*CF$_3$), 130.3 (C^{4}HCH*C*HPyr & *C*HCCHCCF$_3$), 129.9 (*C*CHN), 129.8 (*C*HCHCCF$_3$), 124.9 (q, *J* = 3.6, CH*C*HCCF$_3$), 123.8 (q, *J* = 3.6, C*C*HCCF$_3$), 124.1 (d, *J* = 272.1, *C*F$_3$), 121.6 (*C*HCN), 78.5 (*C*^{3}HMe), 73.2 (*C*^{9}HOH), 49.5 (*C*^{3a}H), 47.7 (*C*^{9a}H), 41.1 (*C*^{4}H), 40.2 (*C*^{4a}H), 38.7 (*C*^{8a}H), 32.1 (*C*^{5}H$_2$), 31.2 (*C*^{8}H$_2$), 26.1 (*C*^{6}H$_2$) 25.5 (*C*^{7}H$_2$), 19.5 (C^{3}HC*H*$_3$); IR (thin film) 2921 (C-H), 2851 (C-H), 1764 (C=O), 1440, 1334, 1267, 1166 (C-O), 1124, 1075, 1051, 804, 755 cm^{-1}; m/z (ES+) 472 (100%, [M]$^{+}$); HRMS (EI) calcd for $C_{27}H_{28}NO_3F_3$ [M-H]$^{+}$ 471.2016, observed 471.2016.



COSY: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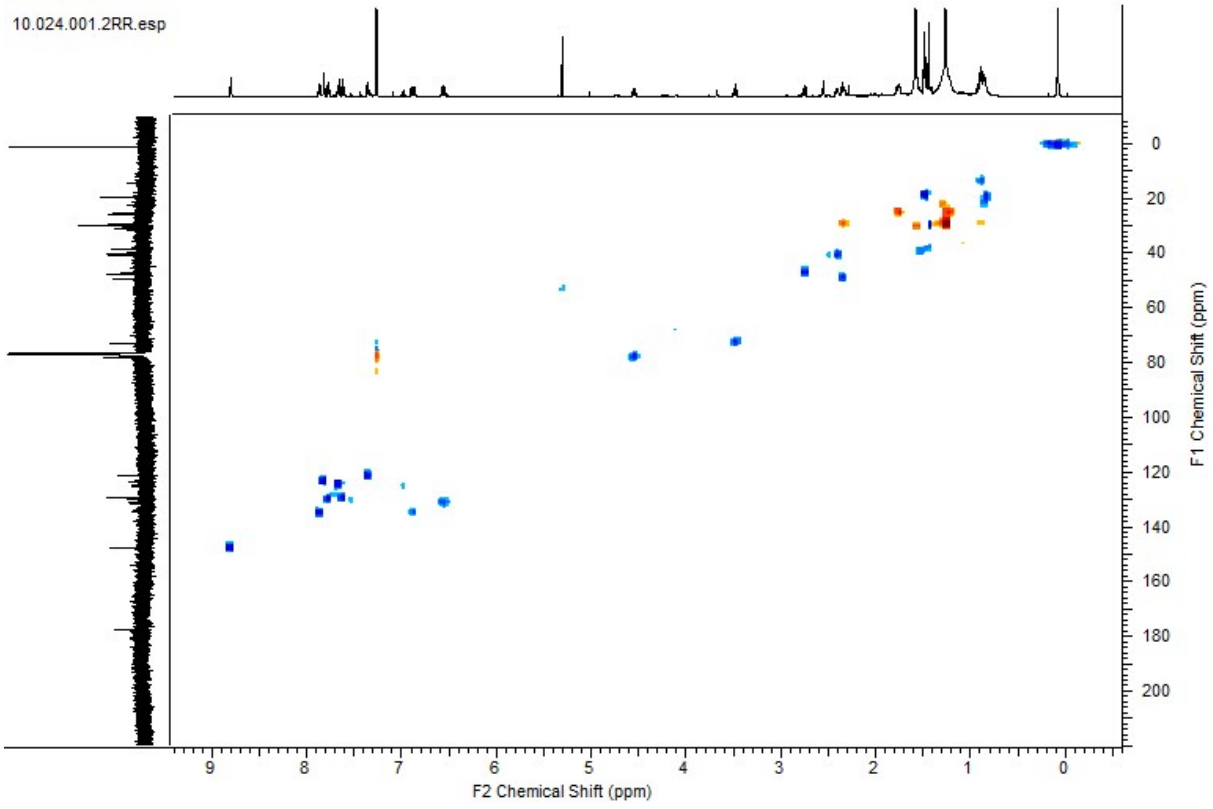
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

HSQC: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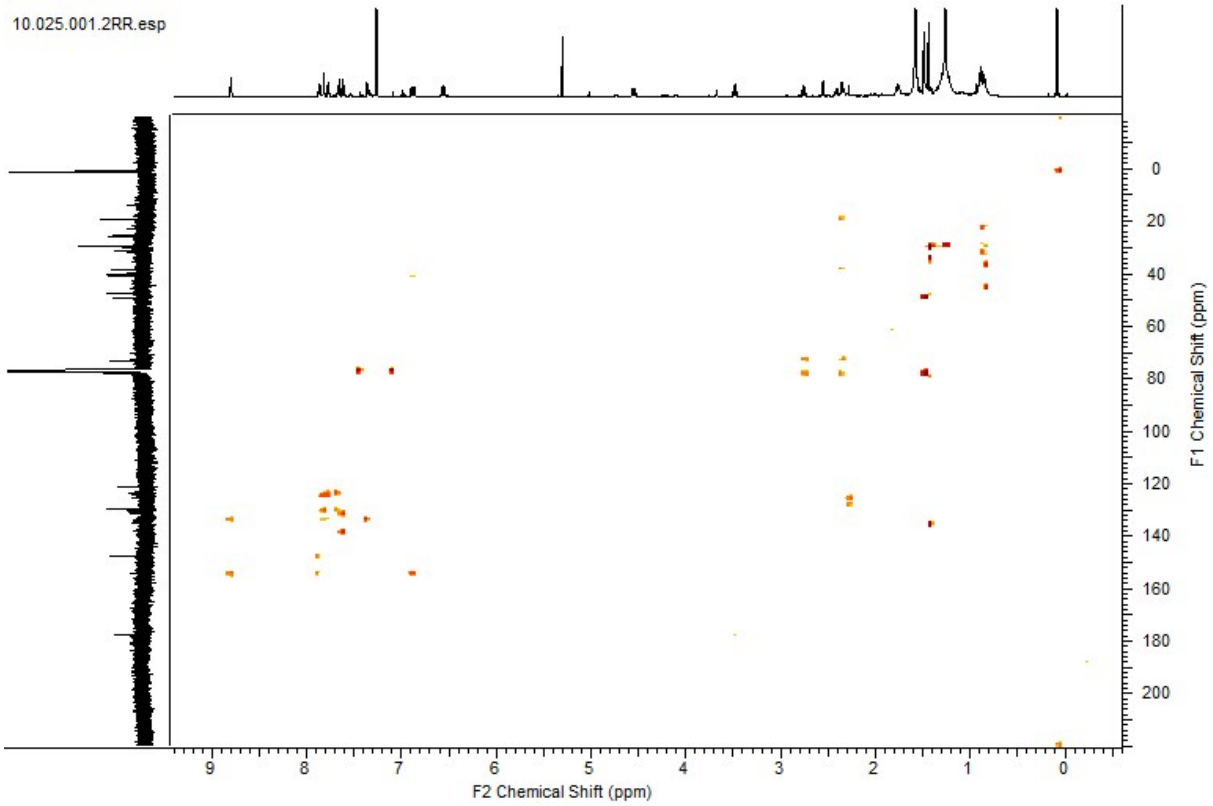
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

HMBC: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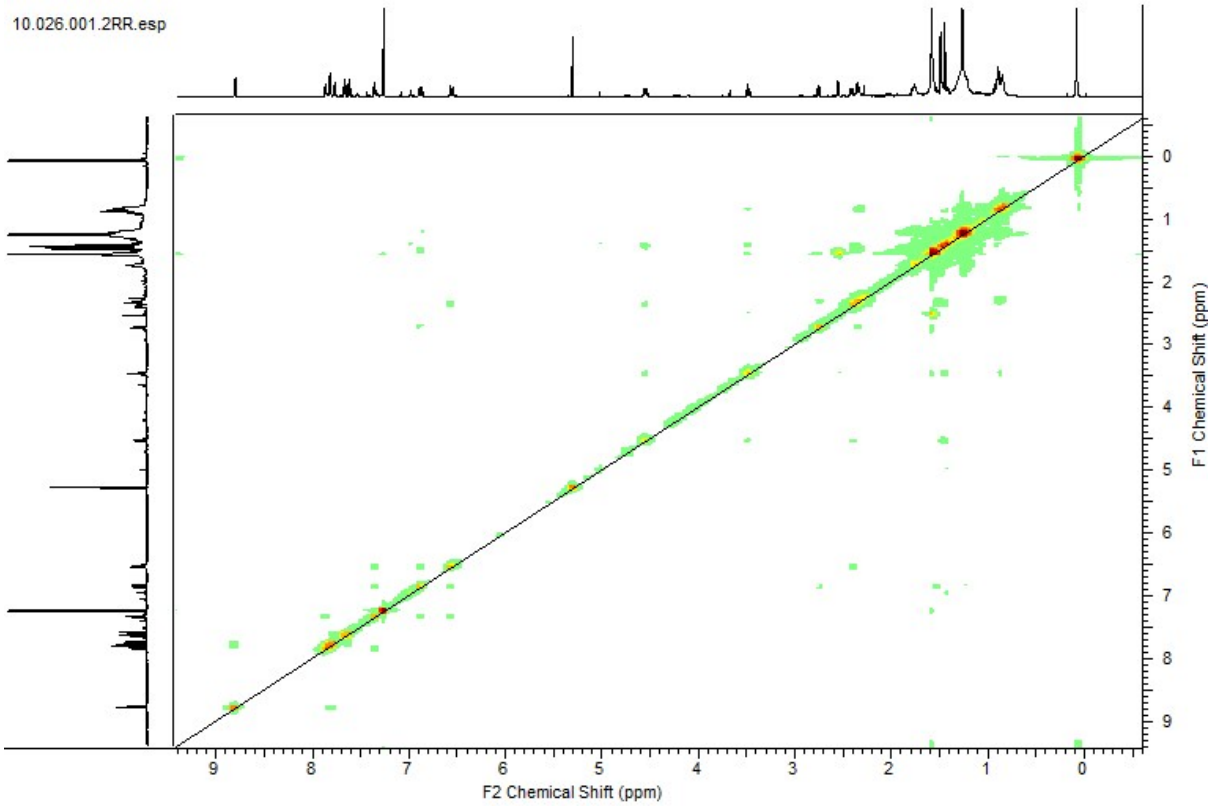
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

NOESY: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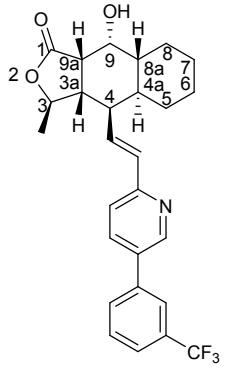
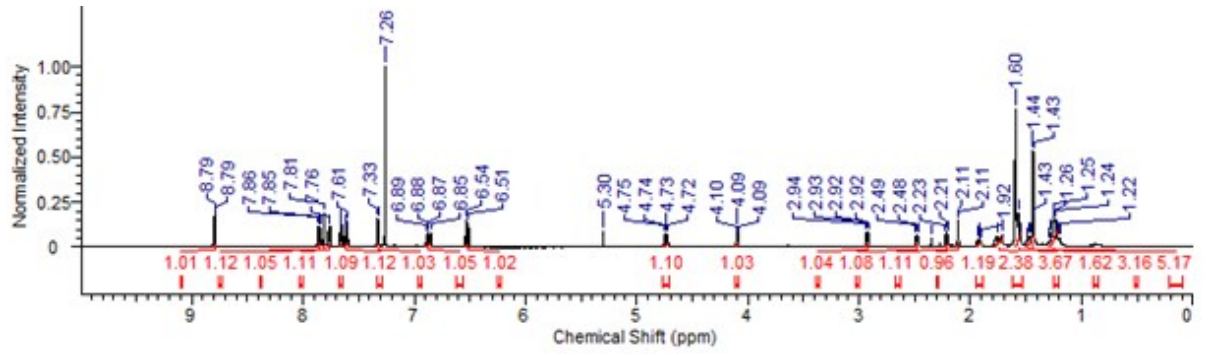
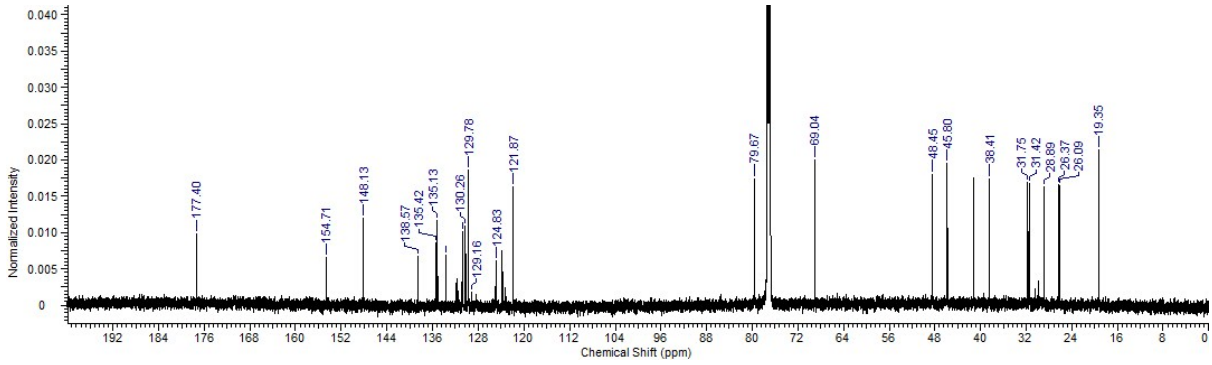
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

Data for (3*R*,3a*S*,4*R*,4a*S*,8a*R*,9*S*,9a*S*)-9-hydroxy-3-methyl-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)decahydronaphtho[2,3-c]furan-1(3H)-one (**11**):

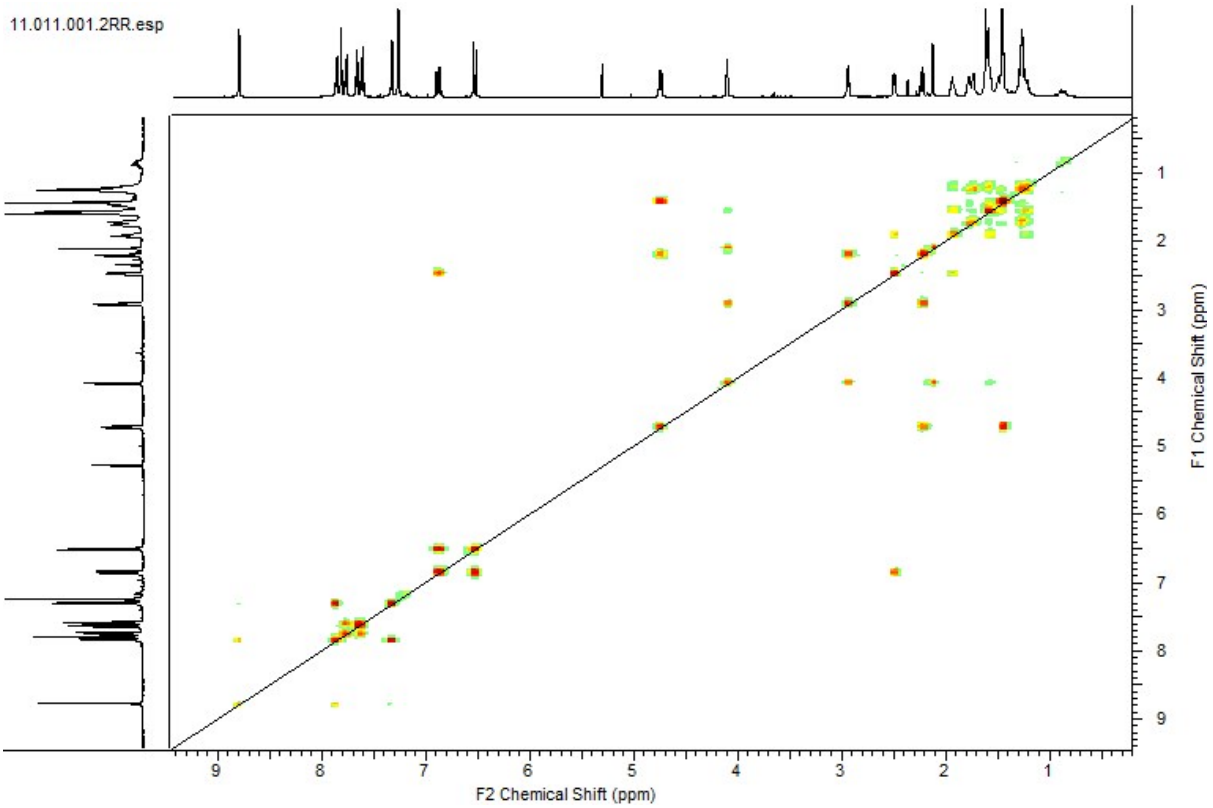


^{1}H NMR (600 MHz, $CDCl_3$) δ 8.79 (1H, d, *J* = 1.9, C*H*N), 7.85 (1H, dd, *J* = 8.1, 1.9, C*H*CCHN), 7.81 (1H, s, C*H*CCF_3), 7.76 (1H, d, *J* = 7.5, CHC*H*CCF_3), 7.66 (1H, d, *J* = 7.5, C*H*CCHCCF_3), 7.61 (1H, t, *J* = 7.9, C*H*CHCCF_3), 7.32 (1H, d, *J* = 8.3, C*H*CN), 6.87 (1H, dd, *J* = 15.4, 10.2, C^{4}HC*H*CHPyr), 6.52 (1H, d, *J* = 15.4, C^{4}HCHC*H*Pyr), 4.74 (1H, dq, *J* = 10.5, 6.0, C^3*H*Me), 4.09 (1H, td, *J* = 4.9, 2.3, C^9*H*), 2.93 (1H, dd, *J* = 8.3, 4.9, C^{9a}*H*), 2.48 (1H, dd, *J* = 10.2, 4.2, C^4*H*), 2.21 (1H, dd, *J* = 10.5, 8.3, C^{3a}*H*), 2.11 (1H, d, *J* = 4.9, O*H*), 1.92 (1H, tt, *J* = 11.7, 4.5, C^{4a}*H*), 1.78-1.70 (2H, m, C^6*H*H & C^7*H*H), 1.59-1.54 (3H, m, C^5*H*H, C^8*H*H & C^{8a}*H*), 1.51-1.44 (1H, m, C^{8}H*H*), 1.44 (3H, d, *J* = 6.0, C^{3}HC*H*$_3$), 1.31-1.19 (3H, m, C^{5}H*H,* C^{6}H*H* & C^{7}H*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.4 (*C*^{1}O), 154.7 (*C*N), 148.1 (*C*HN), 138.6 (*C*CHCCF_3), 135.4 (C^{4}H*C*HCHPyr), 135.1 (*C*HCCHN), 133.7 (*C*CHN), 131.7 (q, *J* = 32.1, *C*CF_3), 130.8 (C^{4}HCH*C*HPyr), 130.3 (*C*HCCHCCF_3), 129.8 (*C*HCHCCF_3), 124.8 (q, *J* = 4.0, CH*C*HCCF_3), 123.8 (q, *J* = 4.0, C*C*HCCF_3), 124.1 (d, *J* = 271.7, *C*F_3), 121.9 (*C*HCN), 79.7 (*C*^{3}HMe), 69.0 (*C*^{9}HOH), 48.4 (*C*^{3a}H), 45.8 (*C*^{9a}H), 41.3 (*C*^{4}H), 38.4 (*C*^{8a}H$_2$), 31.7 (*C*^{4a}H), 31.4 (*C*^{5}H$_2$), 28.9 (*C*^{8}H$_2$), 26.4 (*C*^{6}H$_2$), 26.1 (*C*^{7}H$_2$), 19.3 (C^{3}H*C*H$_3$); IR (thin film) 2924 (C-H), 2853 (C-H), 1761 (C=O), 1440, 1334, 1267, 1165 (C-O), 1124, 1075, 1050, 803, 700 cm^{-1}; m/z (ES+) 472 (100%, $[M]^+$); HRMS (ES+) calcd for $C_{27}H_{29}NO_3F_3$ $[M]^+$ 472.2100, observed 472.2089.


Normalized Intensity
Chemical Shift (ppm)


Normalized Intensity
Chemical Shift (ppm)

COSY: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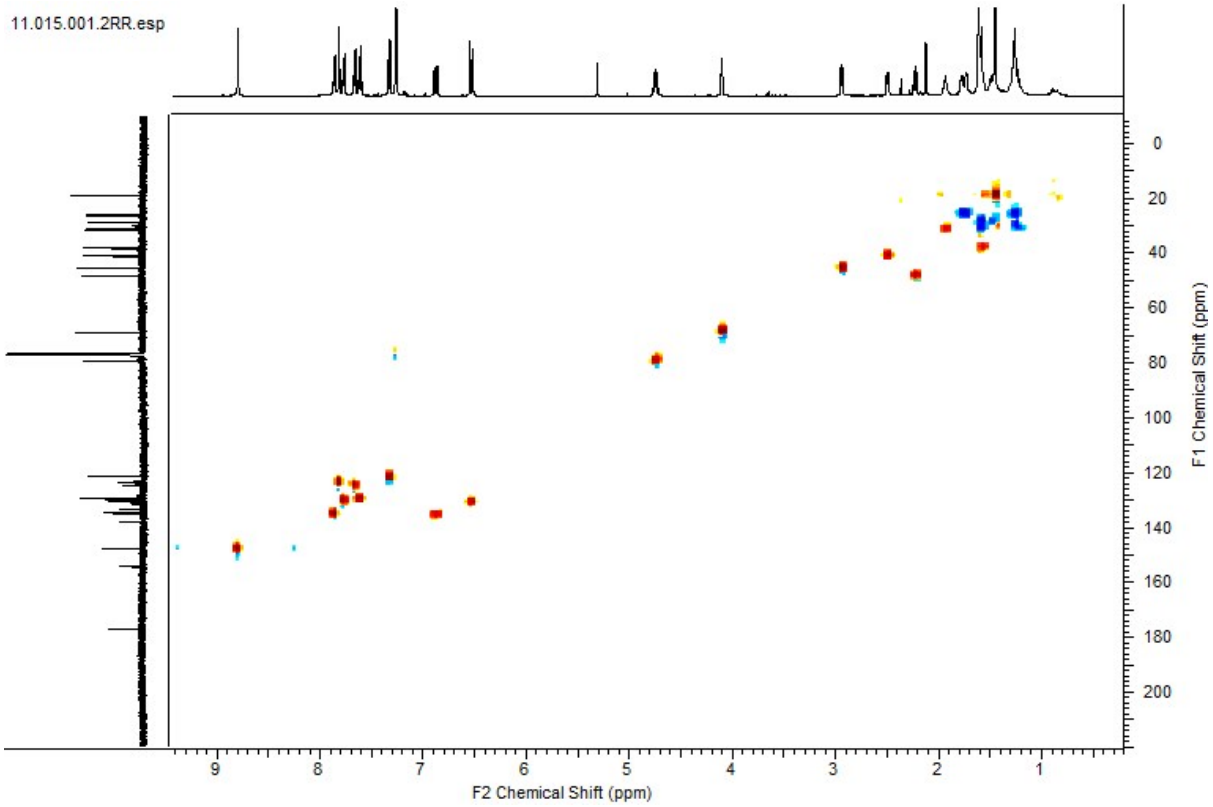
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

HSQC: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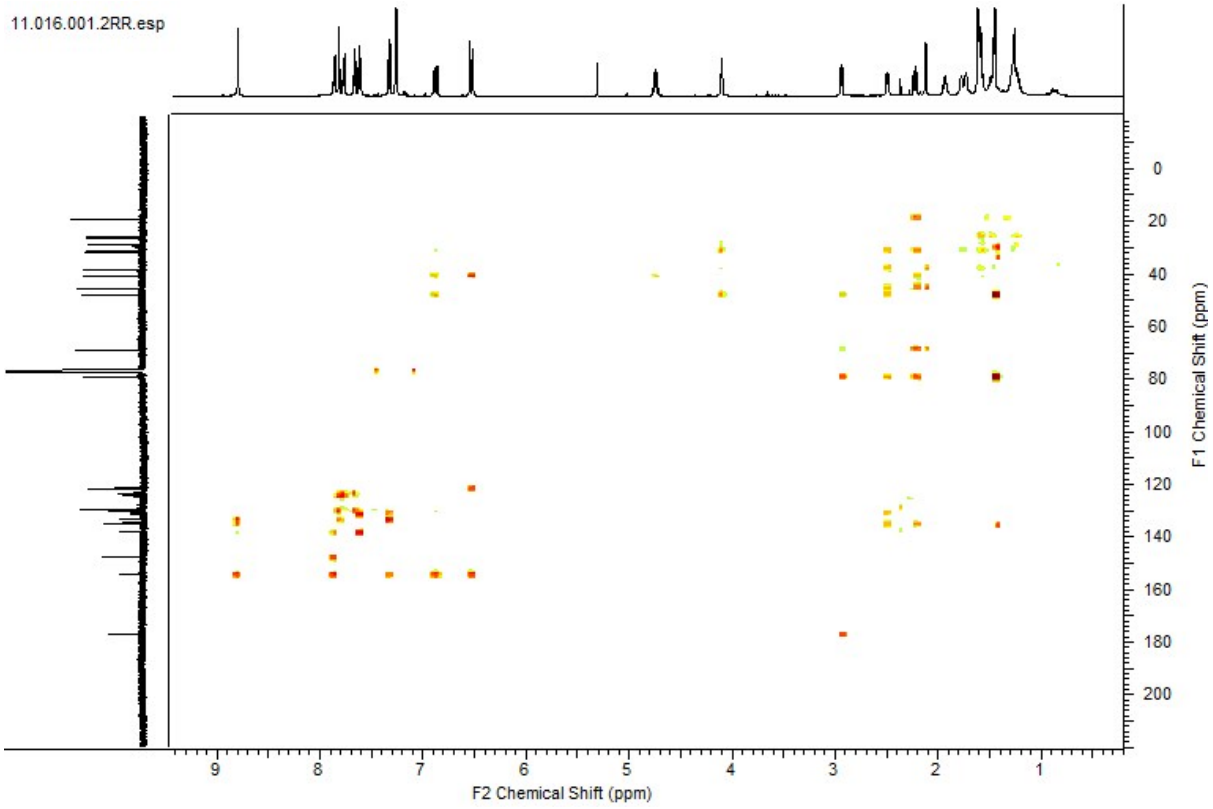
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

HMBC: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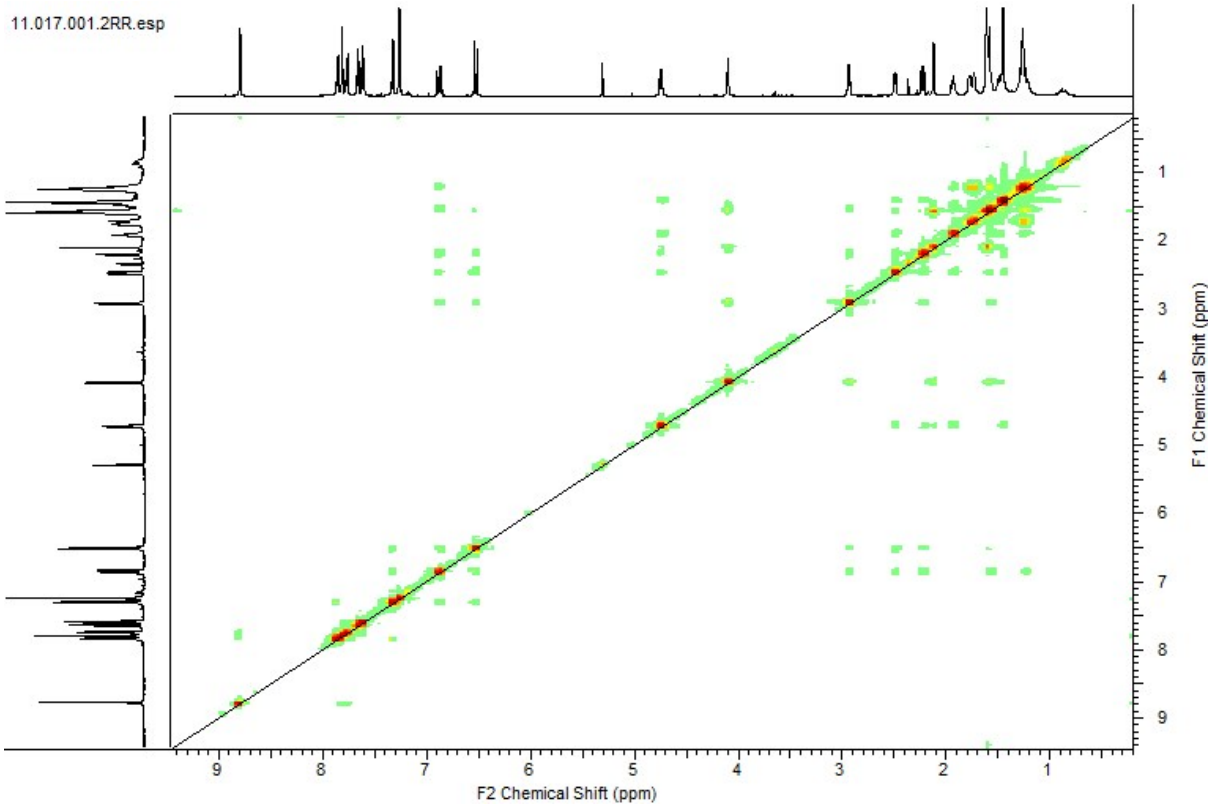
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

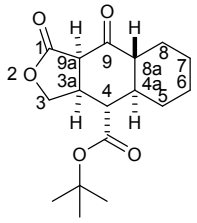
NOESY:


11.017.001.2RR.esp
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

rac-tert-Butyl 1,9-dioxododecahydronaphtho[2,3-c]furan-4-carboxylate (12 and 13)

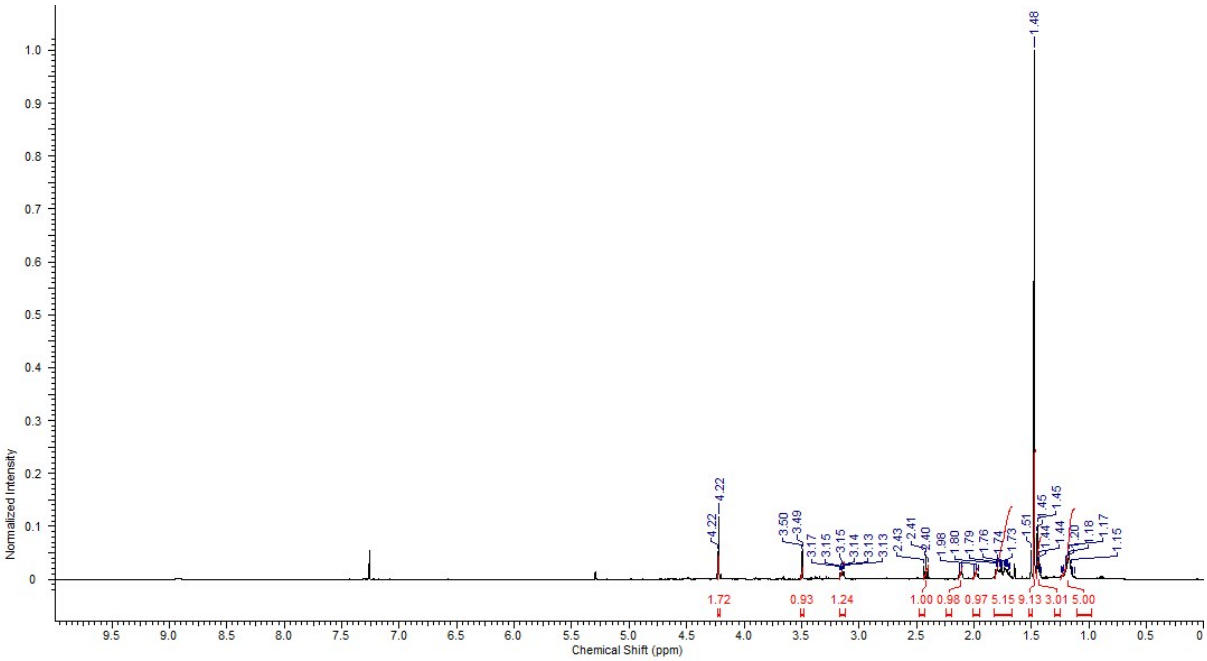
n-BuLi (2.7 M in heptanes) (12.8 mL, 34.5 mmol) was added dropwise to a stirred solution of freshly distilled TMP (5.87 mL, 34.5 mmol) in anhydrous 2-MeTHF (40 mL) at -78 °C, under N_2. The solution was warmed to 0 °C and then re-cooled to -78 °C. A solution of *trans*-methyl 2-(2-(*tert*-butoxy)-2-oxoethyl)cyclohexanecarboxylate (**1**) (4.21 g, 16.4 mmol) in anhydrous 2-MeTHF (40 mL) was added dropwise and stirring continued for 30 min at -78 °C. Next, furan-2(5H)-one (0.58 mL, 8.21 mmol) was added dropwise. The reaction mixture was stirred for a further 3 h, quenched with sat. aq. NH_4Cl (50 mL) and diluted with H_2O (25 mL). An extraction into EtOAc (2 x 50 mL) was done and the combined organic layers were washed with brine (30 mL), dried (hydrophobic frit) and concentrated *in vacuo* to yield a crude yellow oil with white precipitate. Purification by automated column chromatography (0-100% EtOAc/cyclohexane) yielded (3a*S**,4*R**,4a*S**,8a*S**,9a*S**)-*tert*-butyl 1,9-dioxododecahydronaphtho[2,3-c]furan-4-carboxylate (**13**) (663 mg, 2.15 mmol, 26%) and (3a*S**,4*R**,4a*R**,8a*R**,9a*S**)-*tert*-butyl 1,9-dioxododecahydronaphtho[2,3-c]furan-4-carboxylate (**12**) (644 mg, 2.09 mmol, 25%) as white solids.

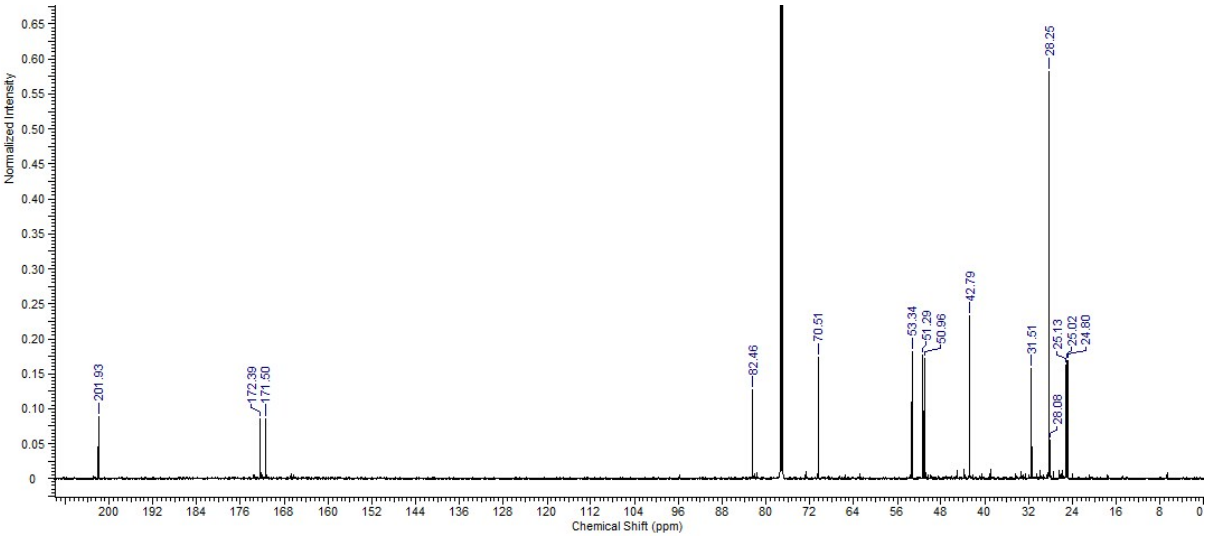
Data for (3a*S**,4*R**,4a*S**,8a*S**,9a*S**)-*tert*-butyl 1,9-dioxododecahydronaphtho[2,3-c]furan-4-carboxylate (**13**):



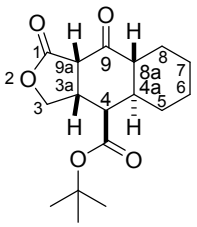
^{1}H NMR (600 MHz, $CDCl_3$) δ 4.22 (1H, d, *J* = 3.8, C^{3}H*H*), 4.21 (1H, s, C^3*H*H), 3.49 (1H, d, *J* = 7.5, C^{9a}*H*), 3.15 (1H, ddd, *J* = 11.5, 7.5, 3.8, C^{3a}*H*), 2.41 (1H, t, *J* = 11.5, C^4*H*), 2.14-2.10 (1H, m, C^8*H*H), 1.99 (1H, ddd, *J* = 12.0, 10.7, 3.6, C^{8a}*H*), 1.82-1.66 (4H, m, C^{4a}*H*, C^5*H*H, C^6*H*H & C^7*H*H), 1.48 (9H, s, C(C*H*$_3$)$_3$), 1.46-1.41 (1H, m, C^{8}H*H*), 1.25-1.12 (3H, m, C^{5}H*H*, C^{6}H*H* & C^{7}H*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.9 (*C*^{9}O), 172.4 (*C*O^{t}Bu), 171.5 (*C*^{1}O), 82.5 (*C*(CH$_3$)$_3$), 70.5 (*C*^{3}H$_2$), 53.3 (*C*^{9a}H), 51.3 (*C*^{8a}H), 51.0 (*C*^{4}H), 42.8 (*C*^{4a}H), 42.8 (*C*^{3a}H), 31.5 (*C*^{8}H$_2$), 28.2 (C(*C*H$_3$)$_3$), 25.1 (*C*^{5}H$_2$), 25.0 (*C*^{6}H$_2$), 24.8 (*C*^{7}H$_2$); IR (thin film) 2974 (C-H), 2929 (C-H), 2856 (C-H), 1795 (C=O), 1715 (C=O), 1367 (C-H), 1244 (C-O), 1157, 1021, 845 cm^{-1}; m/z (ES+)

326 (100%, $M[NH_4^+]^+$); HRMS (EI) calcd for $C_{17}H_{24}O_5$ $[M+H]^+$ 308.1618, observed 308.1613.

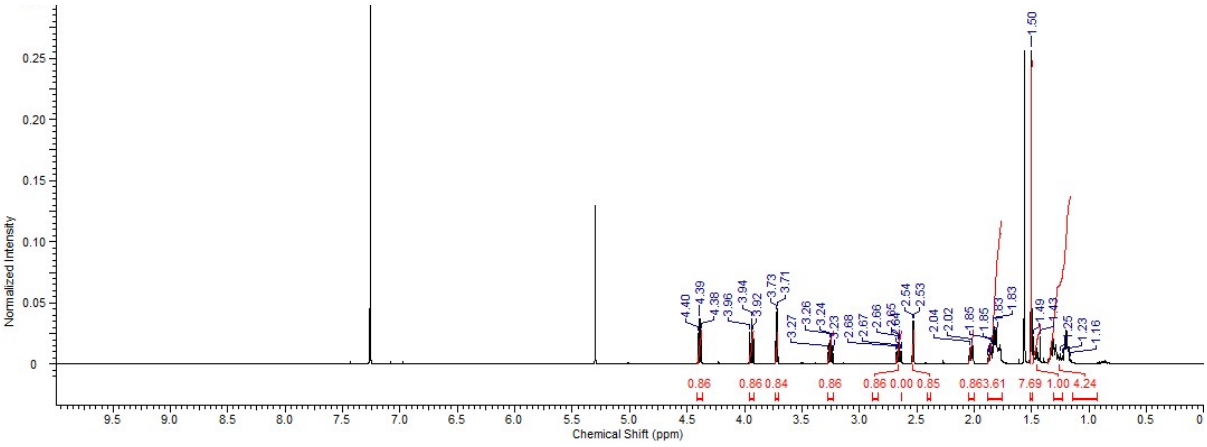


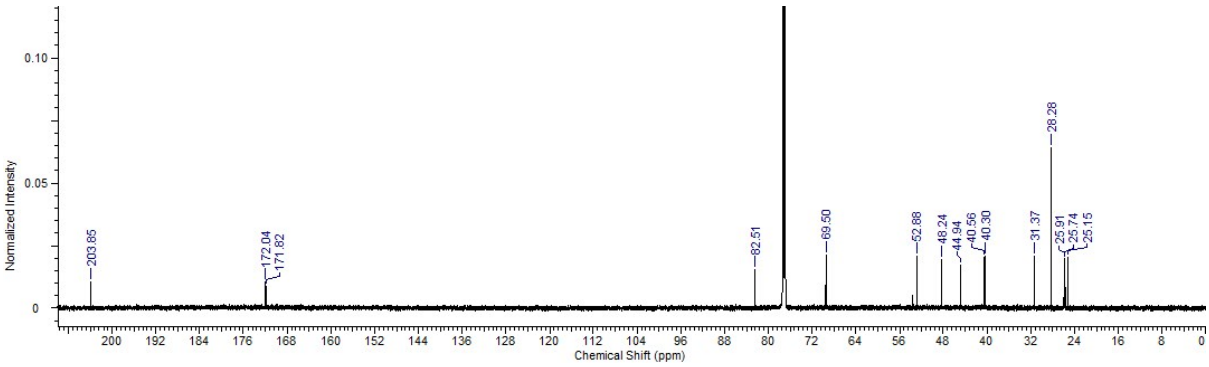


Data for (3a*S**,4*R**,4a*R**,8a*R**,9a*S**)-*tert*-butyl 1,9-dioxododecahydronaphtho[2,3-c]furan-4-carboxylate (**12**):



^{1}H NMR (600 MHz, $CDCl_3$) δ 4.39 (1H, t, *J* = 8.3, C^{3}*H*H), 3.94 (1H, t, *J* = 9.8, C^{3}H*H*), 3.72 (1H, d, *J* = 8.7, C^{9a}*H*), 3.25 (1H, ddd, *J* = 9.8, 8.7, 8.3, C^{3a}*H*), 2.66 (1H, td, *J* = 12.0, 3.6, C^{8a}*H*), 2.53 (1H, d, *J* = 4.5, C^{4}*H*), 2.03 (1H, d, *J* = 14.7, C^{8}*H*H), 1.85 (1H, tdd, *J* = 12.0, 4.5, 3.4, C^{4a}*H*), 1.84-1.76 (3H, m, C^{5}*H*H, C^{6}*H*H & C^{7}*H*H), 1.50 (9H, s, C(C*H*$_3$)$_3$), 1.49-1.42 (1H, m, C^{8}H*H*), 1.36-1.15 (3H, m, C^{5}H*H*, C^{6}H*H* & C^{7}H*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.8 (*C*^{9}O), 172.0 (*C*OO^{t}Bu), 171.8 (*C*^{1}O), 82.5 (*C*(CH$_3$)$_3$), 69.5 (*C*^{3}H$_2$), 52.9 (*C*^{9a}H), 48.2 (*C*^{8a}H), 44.9 (*C*^{4}H), 40.6 (*C*^{4a}H), 40.3 (*C*^{3a}H), 31.4 (*C*^{8}H$_2$), 28.3 (C(*C*H$_3$)$_3$), 25.9 (*C*^{5}H$_2$), 25.7 (*C*^{6}H$_2$), 25.1 (*C*^{7}H$_2$); IR (thin film) 2926 (C-H), 2850 (C-H), 1778 (C=O), 1715 (C=O), 1698 (C=O), 1365 (C-H), 1204 (C-O), 1138, 1002, 845 cm^{-1}; m/z (ES+) 326 (100%, [M+NH$_4$]$^{+}$); HRMS (ES-) calcd for $C_{17}H_{23}O_5$ [M-H]$^{+}$ 307.1545, observed 307.1546.

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160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
8
0
Chemical Shift (ppm)

Structures of 12 and 13.

The structures of **12** and **13** were established using dihedral angle dependence of vicinal $^3J_{HH}$ coupling constants. Three-dimensional structures satisfying approximately the values of the observed $^3J_{HH}$ couplings were first built, which were then optimised using molecular mechanics calculations (force field MMX, software used PCMODEL, version 8.5).[1,2] Optimised geometries are shown in Figure S1.

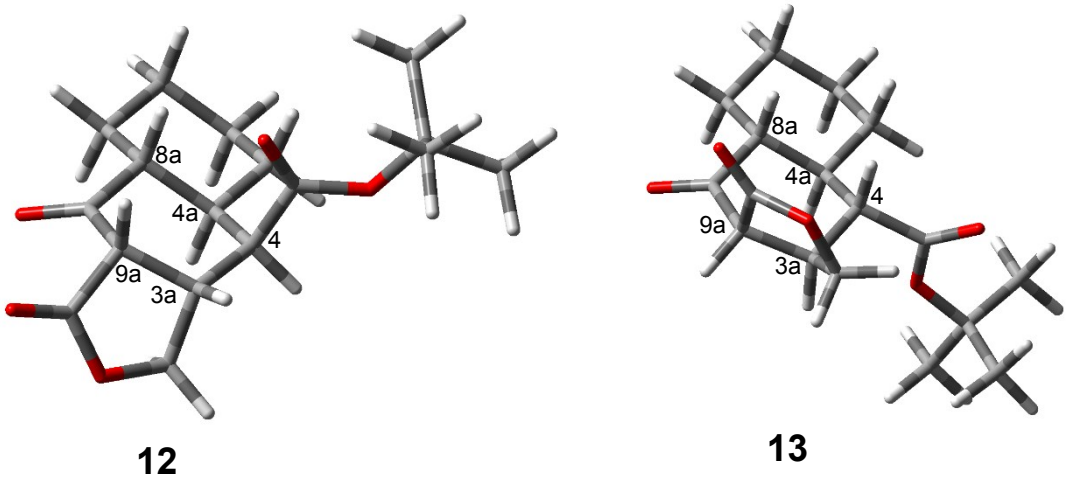


Figure S1. Optimised molecular geometries of **12** and **13** from molecular mechanics calculations.

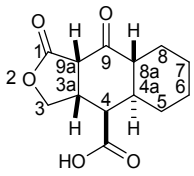
We then used the Karplus-type relationship derived by Haasnoot et al.[3] in order to predict the values of vicinal $^3J_{HH}$ coupling constants using the dihedral angle between protons in structures shown in Figure S1. The advantage of the equation by Haasnoot et al. over the original Karplus equation is that the electronegativity of the nearby substituents and their orientation are also taken into account in predicting $^3J_{HH}$ coupling constants. As can be seen from Table S1, the experimentally observed values of $^3J_{HH}$ coupling constants are reproduced well by the predicted values. In particular, no splitting was observed due to the $^3J_{HH}$ coupling for the proton pair (3a,4) in **12**. The dihedral angle H_{3a}-C-C-H_4 is 78° and the predicted value is 0.61 Hz in **12**. Since this value is of the same order of magnitude as the half-height linewidth (~1 Hz) of each peak in the ^{1}H spectrum, no splitting due to the $^3J_{3a4}$ coupling is observed in the experimental spectrum.

Table S1. Experimental ($^3J^{exp}$, in Hz) and predicted ($^3J^{calc}$, in Hz) values of $^3J_{HH}$ coupling constants in **12** and **13**. The corresponding dihedral angles ϕ (in degrees) are also shown.

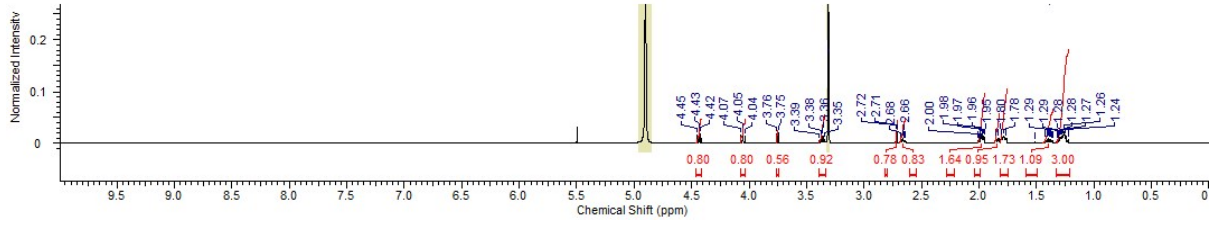
Proton pair	**12**			**13**		
	ϕ / °	$^3J^{calc}$ / Hz	$^3J^{exp}$ / Hz	ϕ / °	$^3J^{calc}$ / Hz	$^3J^{exp}$ / Hz
4a,8a	179	12.34	12.0	178	12.32	a
4,4a	52	4.22	4.5	178	12.78	11.5
3a,4	78	0.61	~0	168	12.56	11.5
3a,9a	34	7.86	8.7	39	7.02	7.5

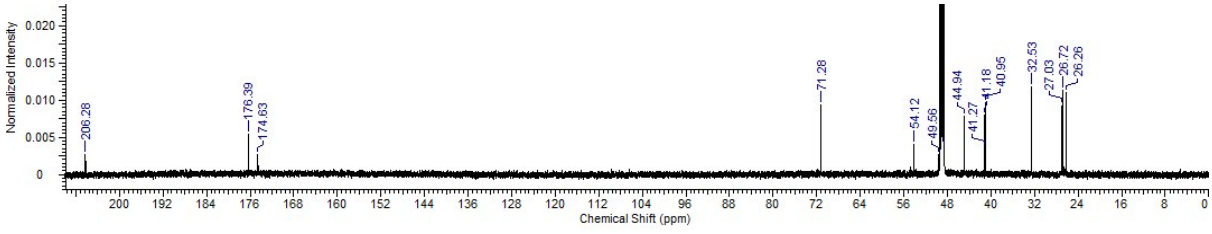
[a]From resolution enhancements of the ^{1}H NMR spectrum of **13**, three doublet splittings were measured for H_{8a}: 12.0, 10.7 and 3.6 Hz. The smallest splitting of 3.6 Hz can be attributed to the *J* coupling with the equatorial proton at C_8. The remaining two axial-axial couplings cannot be distinguished due to severe overlap of signals of protons at C_{4a} and C_5-C_8. Thus, the experimental value of $^3J_{4a8a}$ is either 12.0 or 10.7 Hz, confirming the axial orientation of protons C_{4a} and C_{8a}.

(3a*S,4*R**,4a*R**,8a*R**,9a*S**)-1,9-Dioxododecahydronaphtho[2,3-c]furan-4-carboxylic acid**

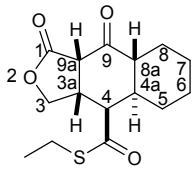


TFA (0.3 mL) was added dropwise to a stirred solution of (3a*S**,4*R**,4a*R**,8a*R**,9a*S**)-*tert*-butyl 1,9-dioxododecahydronaphtho[2,3-c]furan-4-carboxylate (**13**) (50.0 mg, 0.16 mmol) in anhydrous CH_2Cl_2 (0.3 mL) at 0 °C, under Ar. The reaction mixture was stirred at 20 °C for 16 h before being concentrated *in vacuo.* The residue was azeotroped with toluene to yield (3a*S**,4*R**,4a*R**,8a*R**,9a*S**)-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carboxylic acid (40.0 mg, 0.16 mmol, 99%) as a white solid; ^{1}H NMR (600 MHz, MeOH-d_4) δ 4.43 (1H, dd, *J* = 9.2, 8.3, C^3*H*H), 4.05 (1H, dd, *J* = 9.8, 9.2, C^{3}H*H*), 3.75 (1H, d, *J* = 9.0, C^{9a}*H*), 3.37 (1H, ddd, *J* = 9.8, 9.0, 8.3, C^{3a}*H*), 2.72 (1H, d, *J* = 4.9, C^4*H*), 2.69-2.64 (1H, m, C^{8a}*H*), 1.98-1.95 (1H, m, C^8*H*H), 1.98 (1H, dddd, J = 13.2, 12.0, 4.9, 3.0, C^{4a}*H*), 1.87-1.82 (1H, m, C^5*H*H), 1.82-1.75 (2H, m, C^6*H*H & C^7*H*H), 1.44-1.35 (1H, m, C^{5}H*H*), 1.32-1.21 (3H, m, C^{6}H*H*, C^{7}H*H* & C^{8}H*H*); ^{13}C NMR (150 MHz, MeOH-d_4) δ 206.3 (*C*^{9}O), 176.4 (*C*OOH), 174.6 (*C*^{1}O), 71.3 (*C*^{3}H$_2$), 54.1 (*C*^{9a}H), 49.4 (*C*^{8a}H), 44.9 (*C*^{4}H), 41.2 (*C*^{3a}H), 41.0 (*C*^{4a}H), 32.5 (*C*^{5}H$_2$), 27.0 (*C*^{8}H$_2$), 26.7 (*C*^{6}H$_2$), 26.3 (*C*^{7}H$_2$); IR (thin film) 2936 (C-H), 2857 (C-H), 1759 (C=O), 1701 (C=O), 1170, 1000, 839, 800, 719, 645, 549 cm^{-1}; m/z (ES+) 253 (100%, [M+H]$^+$); HRMS (ES-) calcd for $C_{13}H_{15}O_5$ [M-H]$^+$ 251.0920, observed 251.0919.

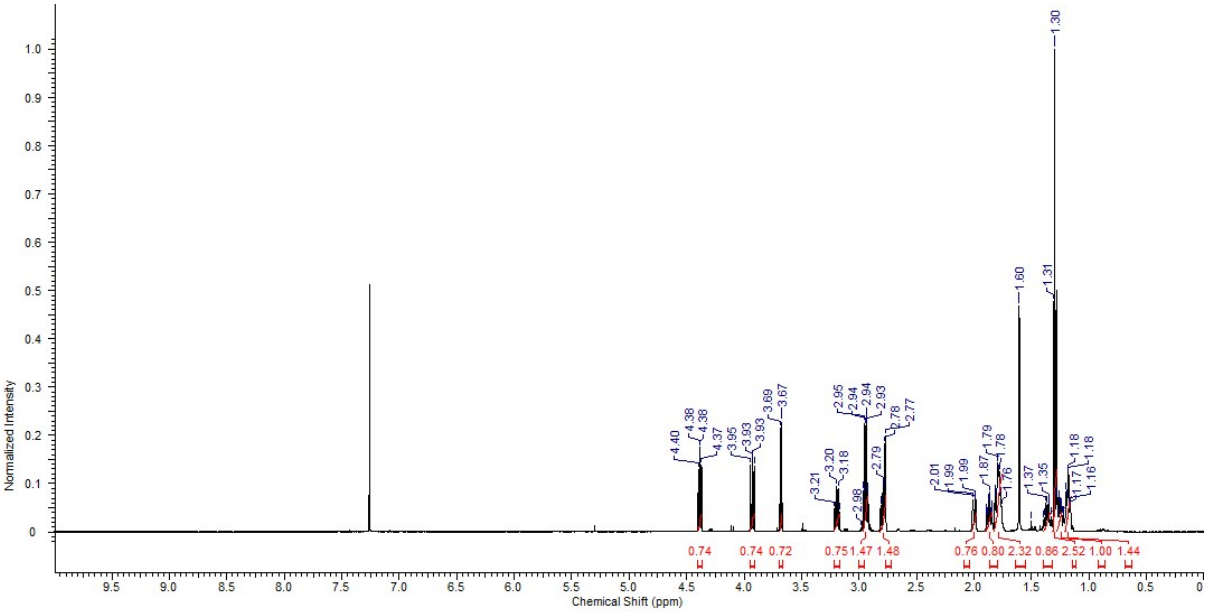




(3a*R,4*R**,4a*R**,8a*R**,9a*S**)-*S*-ethyl 1,9-Dioxododecahydronaphtho[2,3-c]furan-4-carbothioate**



DCC (29.7 mg, 0.14 mmol) was added to a stirred solution of (3a*S**,4*R**,4a*R**,8a*R**,9a*S**)-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carboxylic acid (30.0 mg, 0.12 mmol), ethanethiol (26.0 µL, 0.36 mmol) and DMAP (7.00 mg, 0.06 mmol) in DMF (1 mL) at 0 °C, under Ar. The reaction mixture was stirred at 20 °C for 2 h before being diluted with CH_2Cl_2 (10 mL) and washed with H_2O (2 x 5 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude pink solid. Purification by column chromatography (0-50% Et_2O/Pet. Ether) yielded (3a*R**,4*R**,4a*R**,8a*R**,9a*S**)-*S*-ethyl 1,9-dioxododecahydronaphtho[2,3-c]furan-4-carbothioate (10.5 mg, 0.035 mmol, 29%) as a white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.38 (1H, dd, *J* = 9.0, 8.1, C^3*H*H), 3.93 (1H, dd, *J* = 10.8, 9.0, C^{3}H*H*), 3.68 (1H, d, *J* = 8.7, C^{9a}*H*), 3.19 (1H, ddd, *J* = 10.9, 8.7, 8.1, C^{3a}*H*), 2.94 (2H, qd, *J* = 7.5, 2.6, C*H*$_2$CH$_3$), 2.79 (1H, td, *J* = 12.2, 12.0, 3.8, C^{8a}*H*), 2.78 (1H, d, *J* = 4.5, C^4*H*), 2.02-1.97 (1H, m, C^8*H*H), 1.87 (1H, dddd, *J* = 12.2, 12.0, 4.5, 3.8, C^{4a}*H*), 1.83-1.75 (3H, m, C^5*H*H, C^6*H*H & C^7*H*H), 1.40-1.32 (1H, m, C^{8}H*H*), 1.30 (3H, t, *J* = 7.5, CH$_2$C*H*$_3$), 1.28-1.21 (1H, m, C^{5}H*H*), 1.21-1.15 (2H, m, C^{6}H*H* & C^{7}H*H*)**;** ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.7 (*C*^{9}O), 200.4 (*C*OSEt), 171.5 (*C*^{1}O), 69.1 (*C*^{3}H$_2$), 53.1 (*C*^{9a}H), 51.4 (*C*^{4}H), 48.4 (*C*^{8a}H), 41.2 (*C*^{4a}H), 40.7 (*C*^{3a}H), 31.5 (*C*^{5}H$_2$), 25.7 (*C*^{8}H$_2$), 25.6 (*C*^{6}H$_2$), 24.8 (*C*^{7}H$_2$), 24.1 (*C*H$_2$CH$_3$), 14.6 (CH$_2$*C*H$_3$); IR (thin film) 2931 (C-H), 2887 (C-H), 1793 (C=O), 1708 (C=O), 1672 (C=O), 1203, 1137, 982, 897 cm^{-1}; m/z (ES+) 297 (100%, $[M+H]^+$); HRMS (ES$^-$) calcd for $C_{15}H_{19}O_4S$ $[M-H]^+$ 295.1003, observed 295.1004.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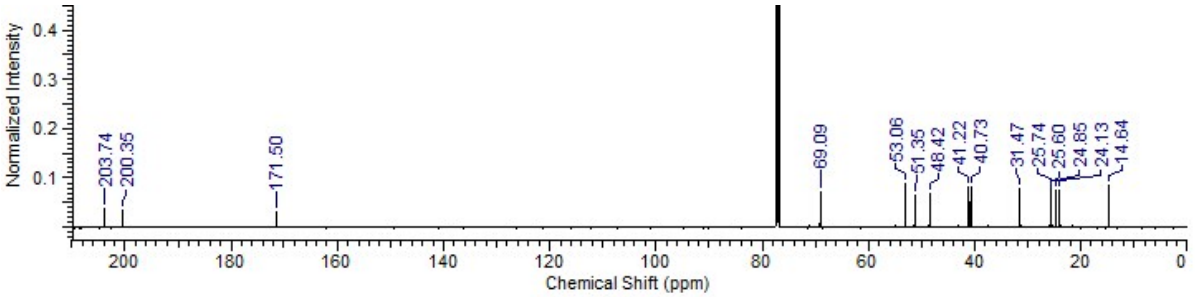
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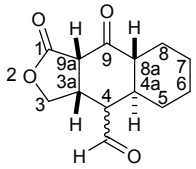
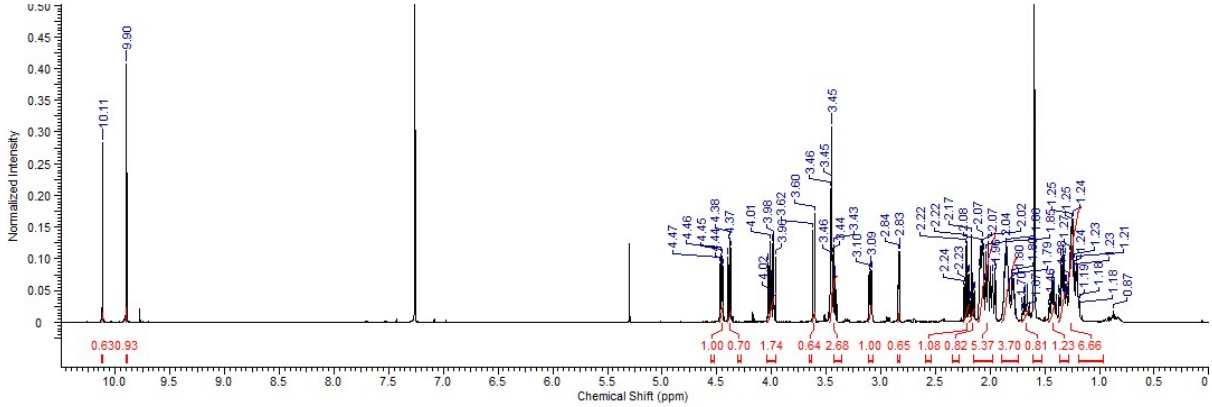
24.85
24.13
14.64

rac-(3a*S*,4a*S*,8a*R*,9a*S*)-1,9-Dioxododecahydronaphtho[2,3-c]furan-4-carbaldehyde



Triethylsilane (15 µL, 0.09 mmol) was added to a stirred suspension of *rac*-(3a*R*,4*R*,4a*R*,8a*R*,9a*S*)-*S*-ethyl 1,9-dioxododecahydronaphtho[2,3-c]furan-4-carbothioate (10.0 mg, 0.03 mmol), palladium on carbon (10%) (4.00 mg, 0.003 mmol) in degassed acetone (0.2 mL). The reaction mixture was stirred at 20 °C for 16 h before being filtered through celite and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (0-2% Et_2O/CH_2Cl_2) gave partial racemisation at C^4 to yield *rac*-(3a*S*,4a*S*,8a*R*,9a*S*)-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carbaldehyde (4*S*:4*R*; 0.7:1) (7.00 mg, 0.03 mmol, 99%) as a white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 10.11 (1H, s, 4*S*-C*H*O), 9.90 (1H, d, *J* = 1.5, 4*R*-C*H*O), 4.47-4.44 (1H, m, 4*R*-C^3*H*H), 4.38 (1H, dd, *J* = 9.0, 7.9, 4*S*-C^3*H*H), 4.04-3.96 (2H, m, 4*R*-C^{3}H*H* & 4*S*-C^{3}H*H*), 3.61 (1H, d, *J* = 9.0, 4*S*-C^{9a}*H*), 3.47-3.40 (3H, m, 4*R*-C^{9a}*H,* 4*R*-C^{3a}*H* & 4*S*-C^{3a}*H*), 3.09 (1H, dd, *J* = 11.7, 3.0, 4*R*-C^4*H*), 2.83 (1H, d, *J* = 4.5, 4*S*-C^4*H*), 2.22 (1H, td, *J* = 11.7, 3.4, 4*R*-C^{8a}*H*), 2.17 (1H, td, *J* = 11.7, 3.8, 4*S*-C^{8a}*H*), 2.11-1.94 (6H, m, 4*R*-C^{4a}*H,* 4*S*-C^{4a}*H,* 4*R*-C^7*H*H, 4*S*-C^7*H*H, 4*R*-C^8*H*H & 4*S*-C^8*H*H), 1.90-1.74 (3H, m, 4*R*-C^5*H*H, 4*R*-C^7*H*H & 4*S*-C^7*H*H), 1.71-1.63 (1H, m, 4*S*-C^5*H*H), 1.47-1.39 (1H, m, 4*R*-C^{8}H*H*), 1.37-1.15 (7H, m, 4*R*-C^{5}H*H,* 4*S*-C^{5}H*H,* 4*R*-C^{6}H*H,* 4*S*-C^{6}H*H,* 4*R*-C^{7}H*H,* 4*S*-C^{7}H*H* & 4*S*-C^{8}H*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.8 (4*S*-*C*^{9}O), 202.8 (4*R*-*C*^{9}O), 202.6 (4*R*-*C*HO), 201.3 (4*S*-*C*HO), 171.4 (4*R*-*C*^{1}O), 171.0 (4*S*-*C*^{1}O), 69.4 (4*R*-*C*^{3}H$_2$), 68.0 (4*S*-*C*^{3}H$_2$), 54.0 (4*S*-*C*^{9a}H), 52.9 (4*S*-*C*^{4}H), 52.9 (4*R*-*C*^{9a}H), 52.6 (4*S*-*C*^{8a}H), 50.0 (4*R*-*C*^{4}H), 49.4 (4*R*-*C*^{8a}H), 41.0 (4*R*-*C*^{4a}H), 40.2 (4*S*-*C*^{4a}H), 39.0 (4*S*-*C*^{3a}H), 36.8 (4*R*-*C*^{3a}H), 32.0 (4*S*-*C*^{5}H$_2$), 30.6 (4*R*-*C*^{5}H$_2$), 26.0 (4*R*-*C*^{8}H$_2$), 25.7 (4*S*-*C*^{8}H$_2$), 24.9 (4*S*-*C*^{6}H$_2$ & 4*R*-*C*^{6}H$_2$), 24.8 (4*R*-*C*^{7}H$_2$), 24.6 (4*S*-*C*^{7}H$_2$); IR (thin film) 2928 (C-H), 2858 (C-H), 1779 (C=O), 1705 (C=O), 1208, 1165, 1120, 1016, 750 cm^{-1}; m/z (ES+) 237 (100%, $[M+H]^+$); HRMS (EI) calcd for $C_{13}H_{16}O_4$ $[M-H]^+$ 236.1043, observed 236.1044.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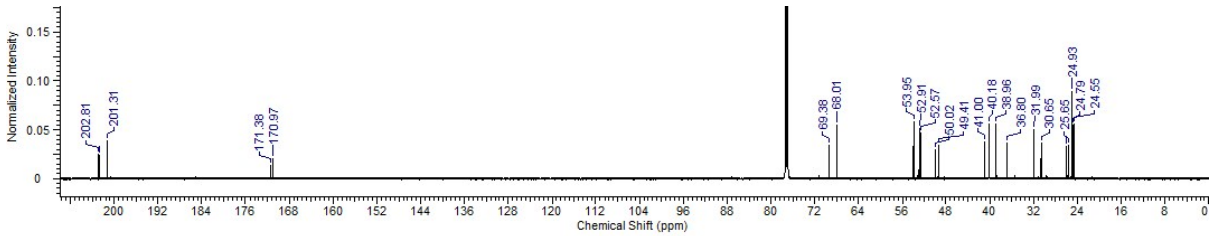
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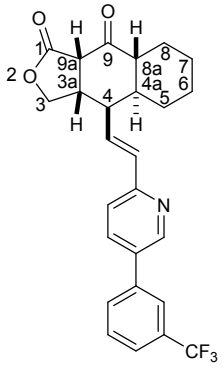
38.96
36.80
31.99
30.65
25.65
24.79
24.93
24.55

rac-(3a*S*,4a*S*,8a*R*,9a*S*)-4-((*E*)-2-(5-(3-(Trifluoromethyl)phenyl)pyridin-2-yl)vinyl)octahydronaphtho[2,3-c]furan-1,9(3H,9aH)-dione (14 and 15)

n-BuLi (1.6 M in hexanes) (144 µL, 0.23 mmol) was added dropwise to a stirred solution of diethyl ((5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)methyl)phosphonate (**7**) (79.0 mg, 0.21 mmol) in anhydrous THF (1 mL) at 0 °C, under Ar. The solution was stirred at 0 °C for 10 min before a solution of *rac*-(3a*S*,4a*S*,8a*R*,9a*S*)-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carbaldehyde (50 mg, 0.21 mmol) in anhydrous THF (1 mL) was added. The reaction mixture was stirred at 0 °C for 45 min and then quenched with sat. aq. NH_4Cl (10 mL). An extraction into EtOAc (2 x 5 mL) was done and the combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a crude yellow gum. Purification by flash column chromatography (0-2% Et_2O/CH_2Cl_2) yielded *rac*-(3a*S*,4a*S*,8a*R*,9a*S*)-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)octahydronaphtho[2,3-c]furan-1,9(3H,9aH)-dione as a mixture of isomers. Purification by preparative TLC (0-2% Et_2O/CH_2Cl_2) yielded (3a*S**,4*R**,4a*S**,8a*R**,9a*S**)-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)octahydronaphtho[2,3-c]furan-1,9(3H,9aH)-dione (**14**) (47.3 mg, 0.10 mmol, 49%) and (3a*S**,4*S**,4a*S**,8a*R**,9a*S**)-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)octahydronaphtho[2,3-c]furan-1,9(3H,9aH)-dione (**15**) (24.5 mg, 0.05 mmol, 26%) as white solids.

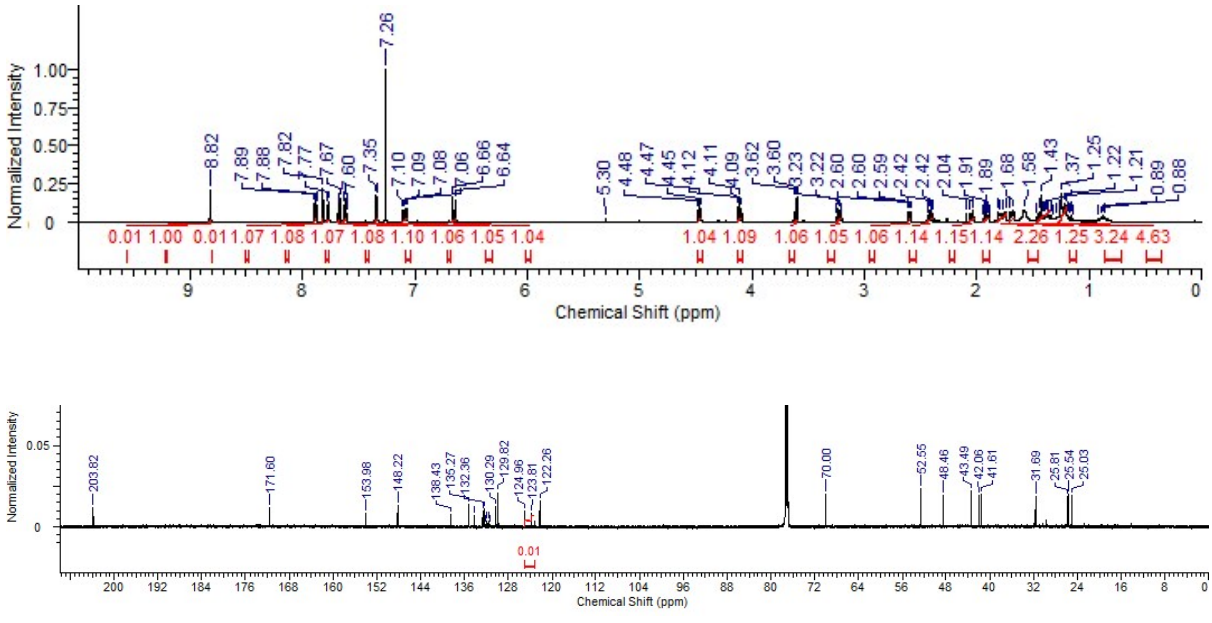
Data for (3a*S**,4*R**,4a*S**,8a*R**,9a*S**)-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)octahydronaphtho[2,3-c]furan-1,9(3H,9aH)-dione (**14**):



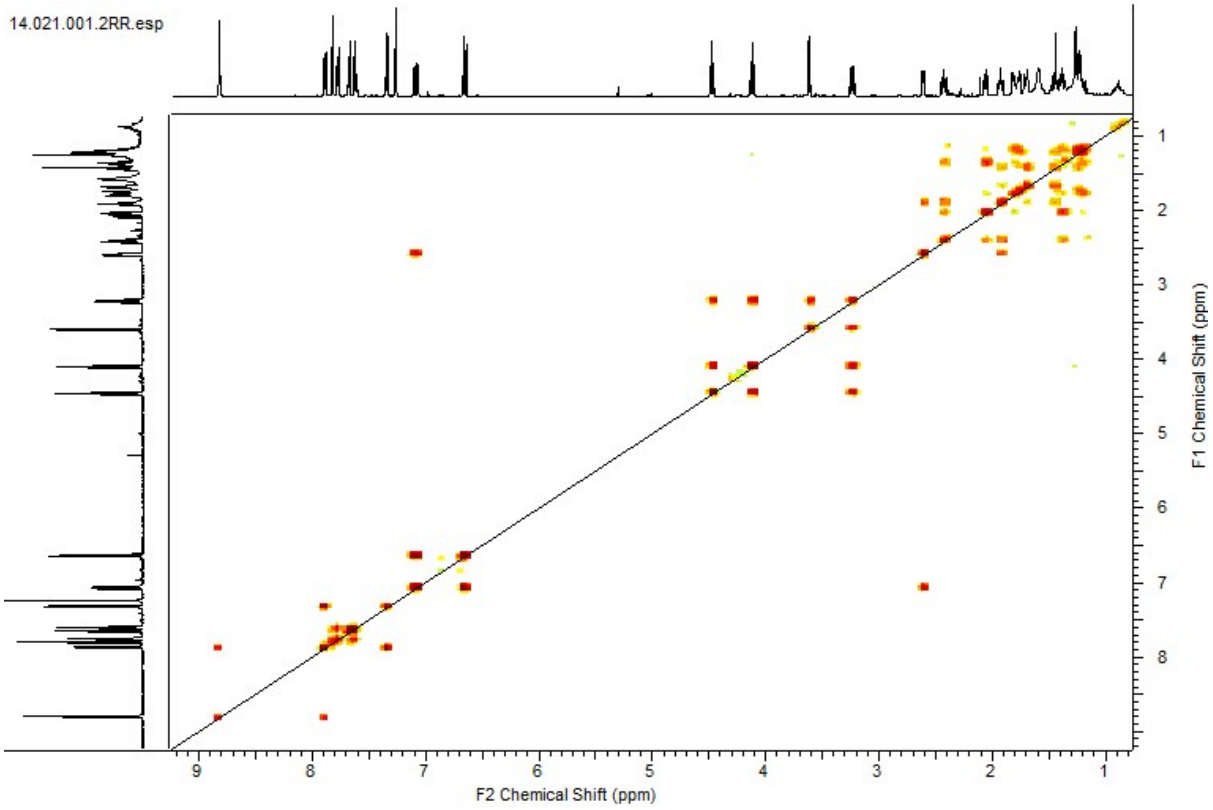
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.82 (1H, s, C*H*N), 7.88 (1H, dd, *J* = 7.9, 2.3, C*H*CCHN), 7.82 (1H, s, C*H*CCF_3), 7.77 (1H, d, *J* = 7.9, C*H*CCHCCF_3), 7.67 (1H, d, *J* = 7.5, CHC*H*CCF_3), 7.62 (1H, t, *J* = 7.5, C*H*CHCCF_3), 7.34 (1H, d, *J* = 8.3, C*H*CN), 7.08 (1H, dd, *J* = 15.4, 9.8, C^{4}HC*H*CHPyr), 6.65 (1H, d, *J* = 15.1, C^{4}HCHC*H*Pyr),

4.47 (1H, t, *J* = 8.5, C^{3}*H*H), 4.11 (1H, t, *J* = 9.8, C^{3}H*H*), 3.61 (1H, d, *J* = 9.0, C^{9a}*H*), 3.23 (1H, ddd, *J* = 9.8, 9.0, 8.5, C^{3a}*H*), 2.60 (1H, dd, *J* = 9.8, 3.6, C^{4}*H*), 2.42 (1H, td, *J* = 12.2, 3.6, C^{8a}*H*), 2.07-2.02 (1H, m, C^{8}*H*H), 1.91 (1H, tt, *J* = 12.2, 3.6, C^{4a}*H*), 1.83-1.78 (1H, m, C^{7}*H*H), 1.78-1.73 (1H, m, C^{6}*H*H), 1.72-1.67 (1H, m, C^{5}*H*H), 1.48-1.40 (2H, m, C^{8}H*H*), 1.40-1.34 (1H, m, C^{5}H*H*), 1.23-1.15 (2H, m, C^{6}H*H* & C^{7}H*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.8 (*C*^{9}O), 171.6 (*C*^{1}O), 154.0 (*C*N), 148.2 (*C*HN), 138.4 (*C*CHCCF$_3$), 135.3 (*C*HCCHN), 134.2 (*C*CHN), 132.7 (C^{4}H*C*HCHPyr), 132.4 (C^{4}HCH*C*HPyr), 131.8 (q, *J* = 32.1, *C*CF$_3$), 130.3 (*C*HCCHCCF$_3$), 129.8 (*C*HCHCCF$_3$), 125.0 (q, *J* = 3.6, C*C*HCCF$_3$), 123.8 (q, *J* = 3.6, CH*C*HCCF$_3$), 124.1 (d, *J* = 271.7, *C*F$_3$), 122.3 (*C*HCN), 70.0 (*C*^{3}H$_2$), 52.5 (*C*^{9a}H), 48.5 (*C*^{8a}H), 43.5 (*C*^{3a}H), 42.1 (*C*^{4}H), 41.6 (*C*^{4a}H), 31.7 (*C*^{5}H$_2$), 25.8 (*C*^{8}H$_2$), 25.5 (*C*^{6}H$_2$), 25.0 (*C*^{7}H$_2$); IR (thin film) 2930 (C-H), 2855 (C-H), 1784 (C=O), 1708 (C=O), 1478, 1440, 1335, 1164, 1124, 1018, 755 cm^{-1}; m/z (ES+) 456 (100%, [M+H]$^{+}$); HRMS (ES^{-}) calcd for $C_{26}H_{23}NO_3F_3$ [M-H]$^{+}$ 454.1631, observed 454.1630.

Chiral column purification (40%EtOH/Heptane, f=30ml/min, Column 30mm x 25cm Chiralcel OJ-H) gave (+)-(3a*S*,4*R*,4a*S*,8a*R*,9a*S*)-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)octahydronaphtho[2,3-c]furan-1,9(3H,9aH)-dione ((+)-**14**) with an $[\alpha]_D^{25}$ = +13.2 (MeOH) and (-)-(3a*S*,4*R*,4a*S*,8a*R*,9a*S*)-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)octahydronaphtho[2,3-c]furan-1,9(3H,9aH)-dione ((-)-**14**) with an $[\alpha]_D^{25}$ = -13.4 (MeOH).



COSY: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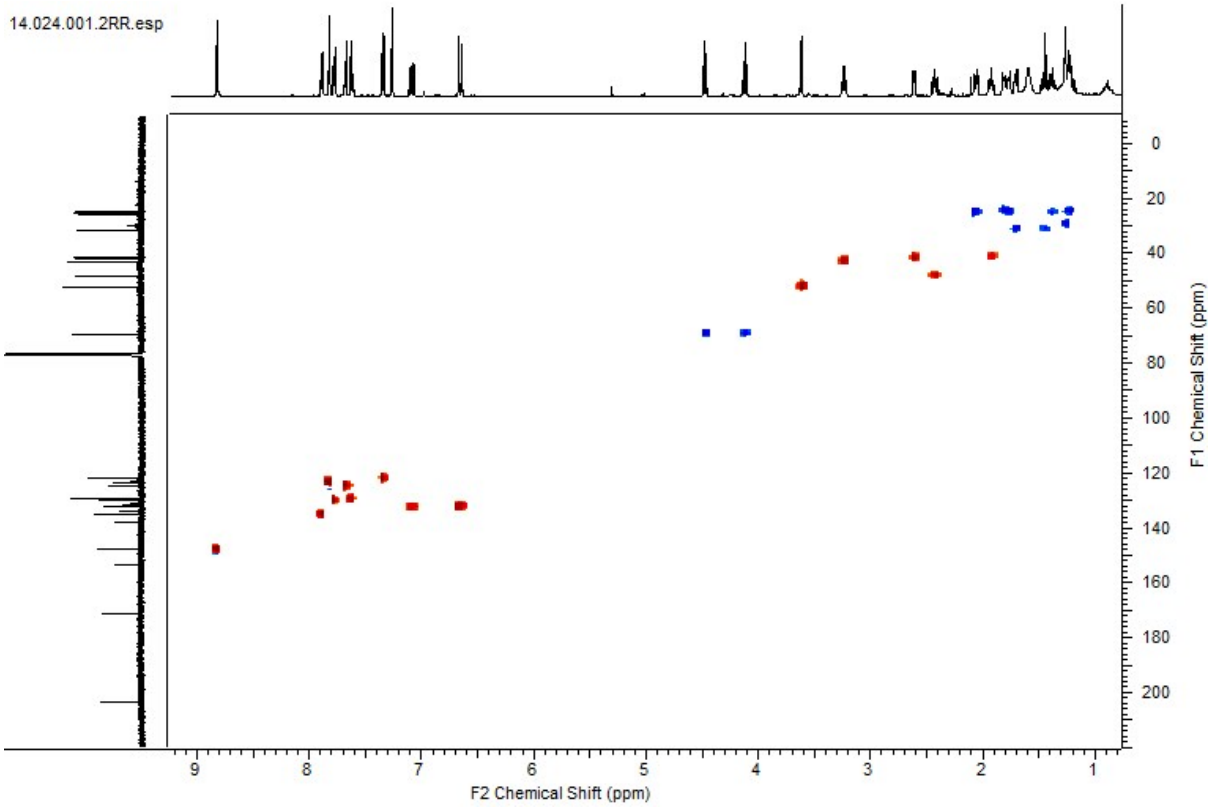
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

HSQC: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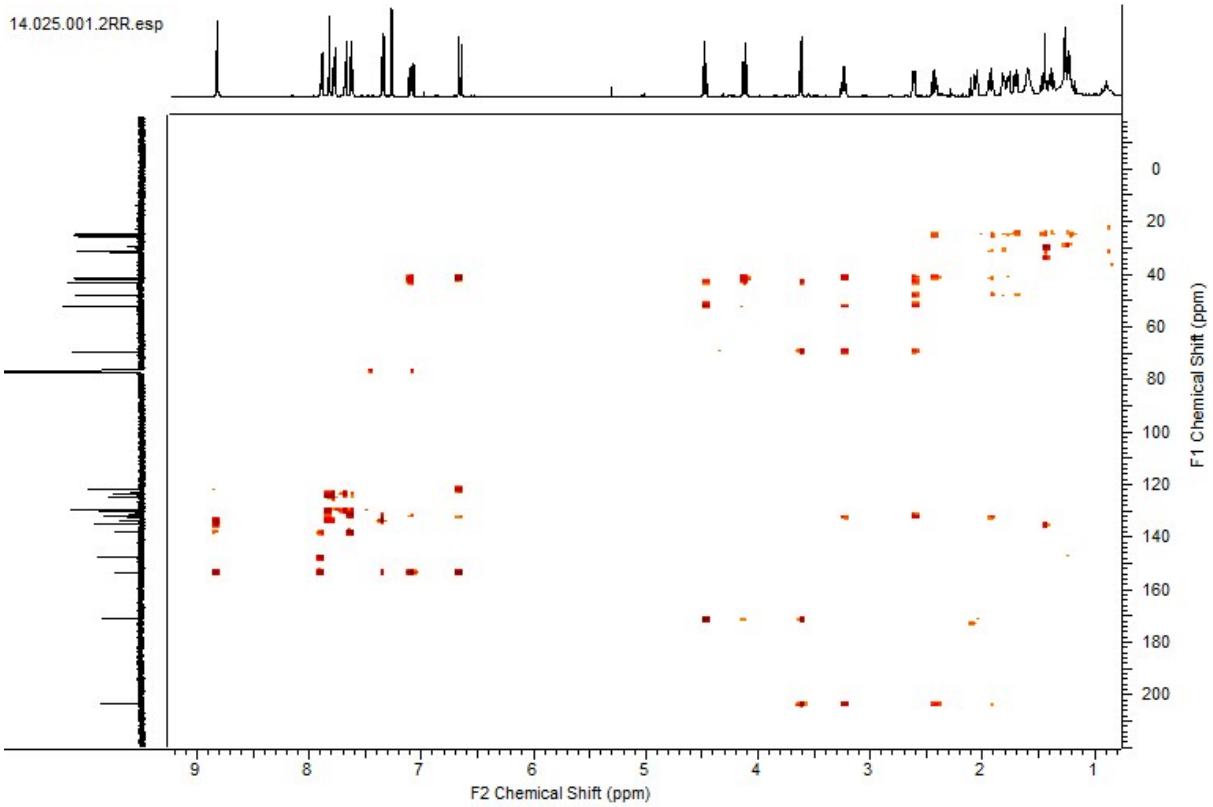
F1 Chemical Shift (ppm)

HMBC: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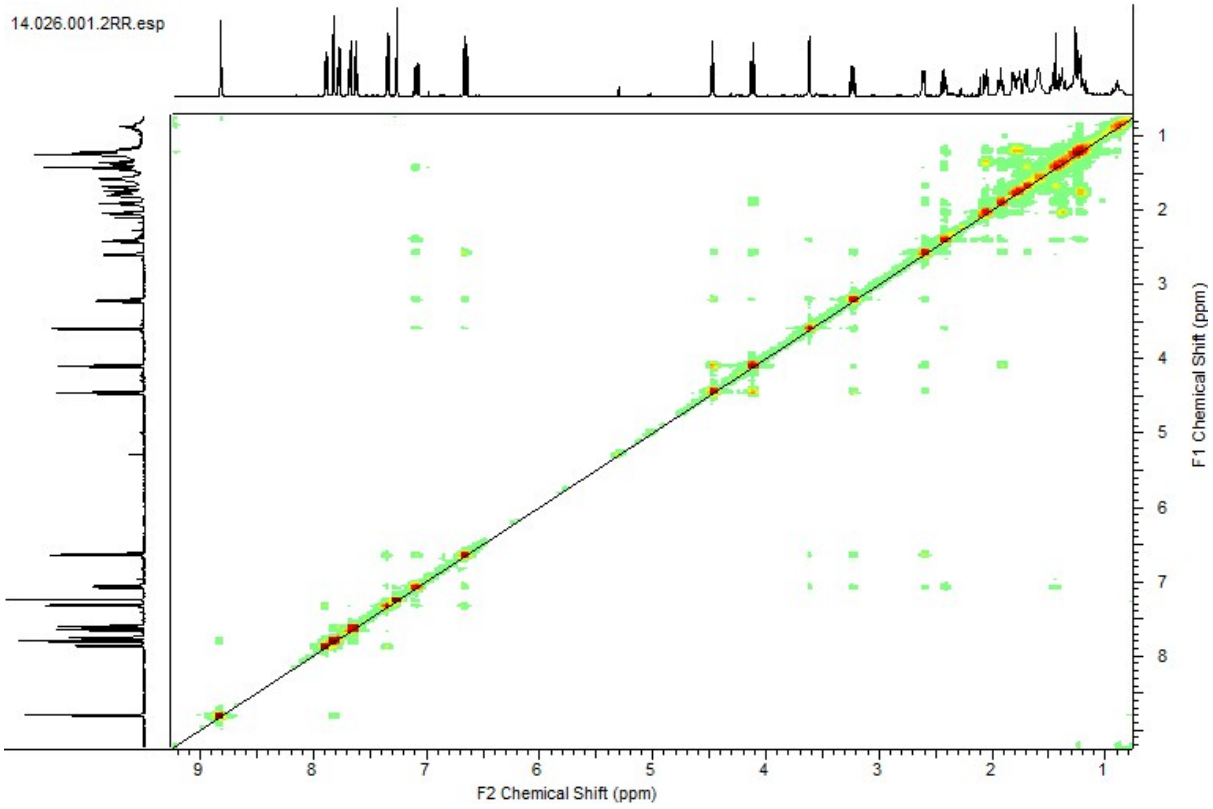
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

NOESY: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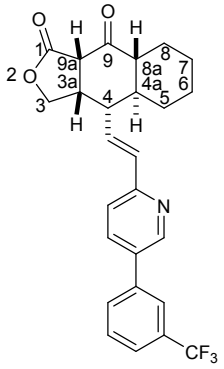
F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

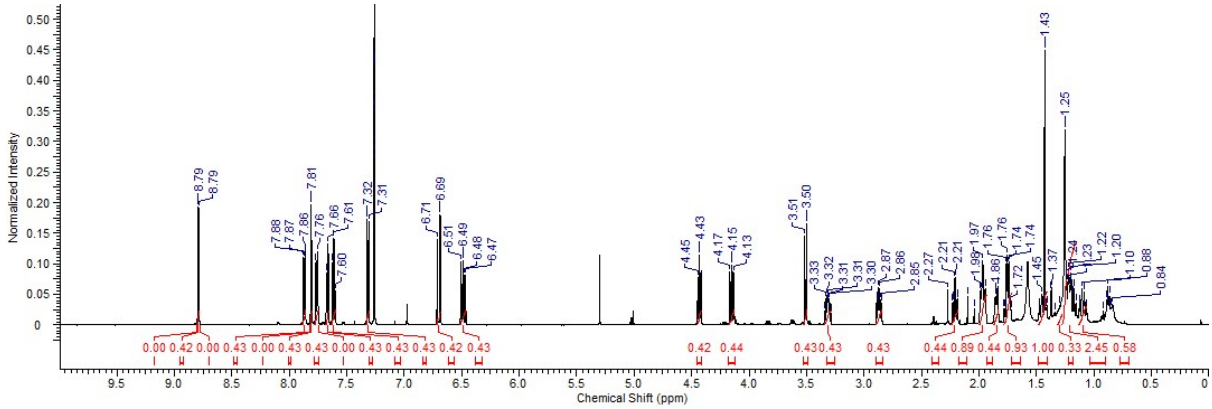
Data for (3a*S**,4*S**,4a*S**,8a*R**,9a*S**)-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)octahydronaphtho[2,3-c]furan-1,9(3H,9aH)-dione (**15**):

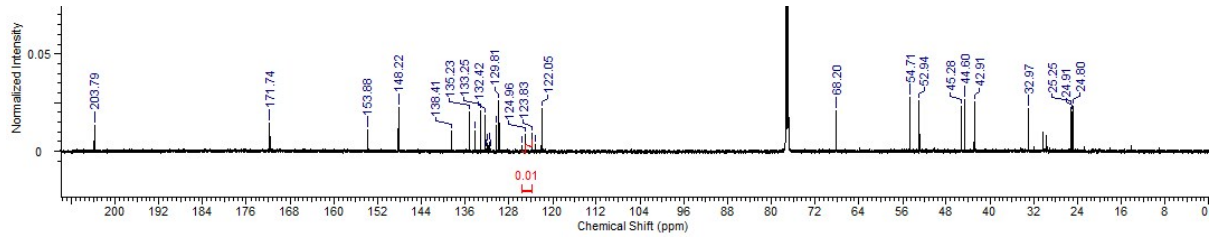


^{1}H NMR (600 MHz, $CDCl_3$) δ 8.79 (1H, d, *J* = 2.3, C*H*N), 7.87 (1H, dd, *J* = 8.1, 2.3, C*H*CCHN), 7.81 (1H, s, C*H*CCF_3), 7.76 (1H, d, *J* = 7.5, C*H*CCHCCF_3), 7.67 (1H, d, *J* = 7.5, CHC*H*CCF_3), 7.61 (1H, t, *J* = 7.5, C*H*CHCCF_3), 7.32 (1H, d, *J* = 8.3, C*H*CN), 6.70 (1H, d, *J* = 15.4, C^{4}HCHC*H*Pyr), 6.49 (1H, dd, *J* = 15.4, 9.8, C^{4}HC*H*CHPyr), 4.43 (1H, dd, *J* = 9.0, 8.3, C^{3}*H*H), 4.15 (1H, dd, *J* = 11.7, 9.0, C^{3}H*H*), 3.51 (1H, d, *J* = 8.7, C^{9a}*H*), 3.32 (1H, dddd, *J* = 11.7, 8.7, 8.3, 5.6, C^{3a}*H*), 2.87 (1H, ddd, *J* = 11.3, 9.8, 5.6, C^{4}*H*), 2.21 (1H, td, *J* = 11.7, 3.0, C^{8a}*H*), 2.00-1.93 (2H, m, C^{5}*H*H & C^{8}*H*H), 1.87-1.82 (1H, m, C^{7}*H*H), 1.75 (2H, qd, *J* = 11.3, 3.4, C^{4a}*H* & C^{6}*H*H), 1.49-1.40 (1H, m, C^{8}H*H*), 1.28-1.15 (2H, m, C^{6}H*H* & C^{7}H*H*), 1.13-1.05 (1H, m, C^{5}H*H*)**;** ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.8 (*C*^{9}O), 171.7 (*C*^{1}O), 153.9 (*C*N), 148.2 (*C*HN), 138.4 (*C*CHCCF_3), 135.2 (*C*HCCHN), 134.2 (*C*CHN), 133.2 (C^{4}HCH*C*HPyr), 132.4 (C^{4}H*C*HCHPyr), 131.8 (q, *J* = 32.1, *C*CF_3), 130.3 (*C*HCCHCCF_3), 129.8 (*C*HCHCCF_3), 125.0 (q, *J* = 3.6, CH*C*HCCF_3), 123.8 (q, *J* = 3.6, C*C*HCCF_3), 124.7 (d, *J* = 272.0, *C*F_3), 122.0 (*C*HCN), 68.2 (*C*^{3}H_2), 54.7 (*C*^{9a}H), 52.9 (*C*^{8a}H), 45.3 (*C*^{4}H), 44.6 (*C*^{3a}H), 42.9 (*C*^{4a}H), 33.0 (*C*^{5}H_2), 25.2 (*C*^{8}H_2), 24.9 (*C*^{6}H_2), 24.8 (*C*^{7}H_2); IR (thin film) 2923 (C-H), 2853 (C-H), 1782 (C=O), 1703 (C=O), 1333, 1160, 1119, 1074, 1010, 801, 699 cm^{-1}; m/z (ES+) 456 (100%, $[M+H]^+$); HRMS (ES$^-$) calcd for $C_{26}H_{23}NO_3F_3$ $[M-H]^+$ 454.1616, observed 454.1630.

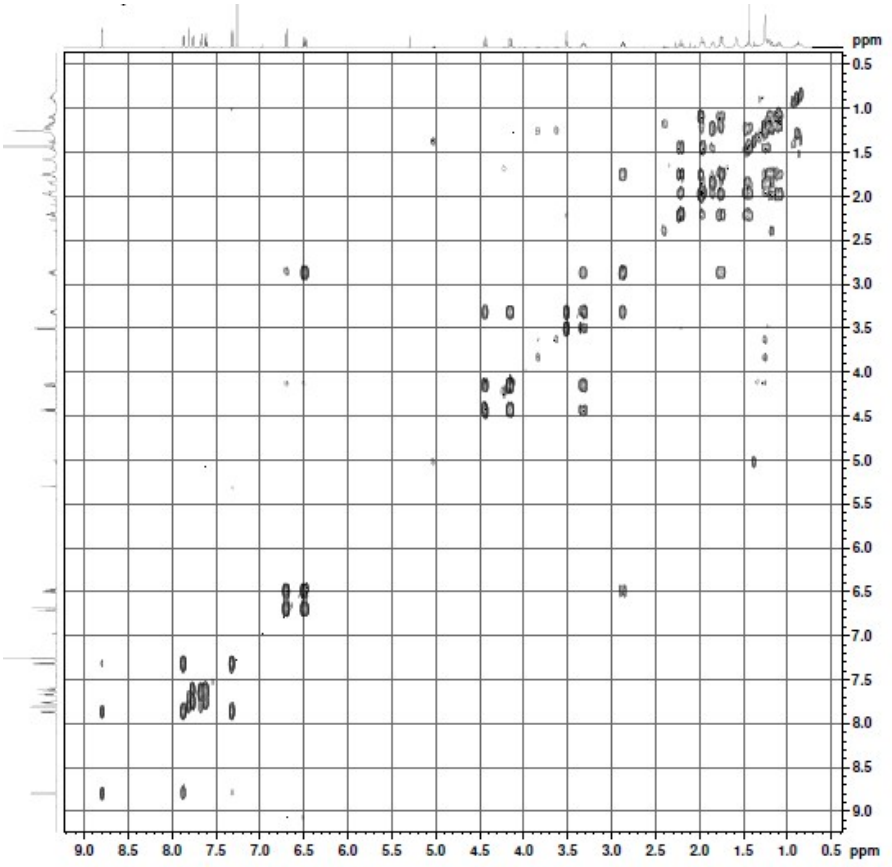
Chiral column purification (50%EtOH/Heptane, f=25ml/min,Column 22.1mm x 25cm (R;R) Whelk O-1) gave (+)-(3a*S*,4*S*,4a*S*,8a*R*,9a*S*)-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)octahydronaphtho[2,3-c]furan-1,9(3H,9aH)-dione ((+)-**15**) with an $[\alpha]_D^{25}$ = +30.4 (MeOH) and (-)-(3a*S*,4*S*,4a*S*,8a*R*,9a*S*)-4-((*E*)-2-

(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)octahydronaphtho[2,3-c]furan-1,9(3H,9aH)-dione ((-)-**15**) with an $[\alpha]_D^{25}$ = -31.6 (MeOH).

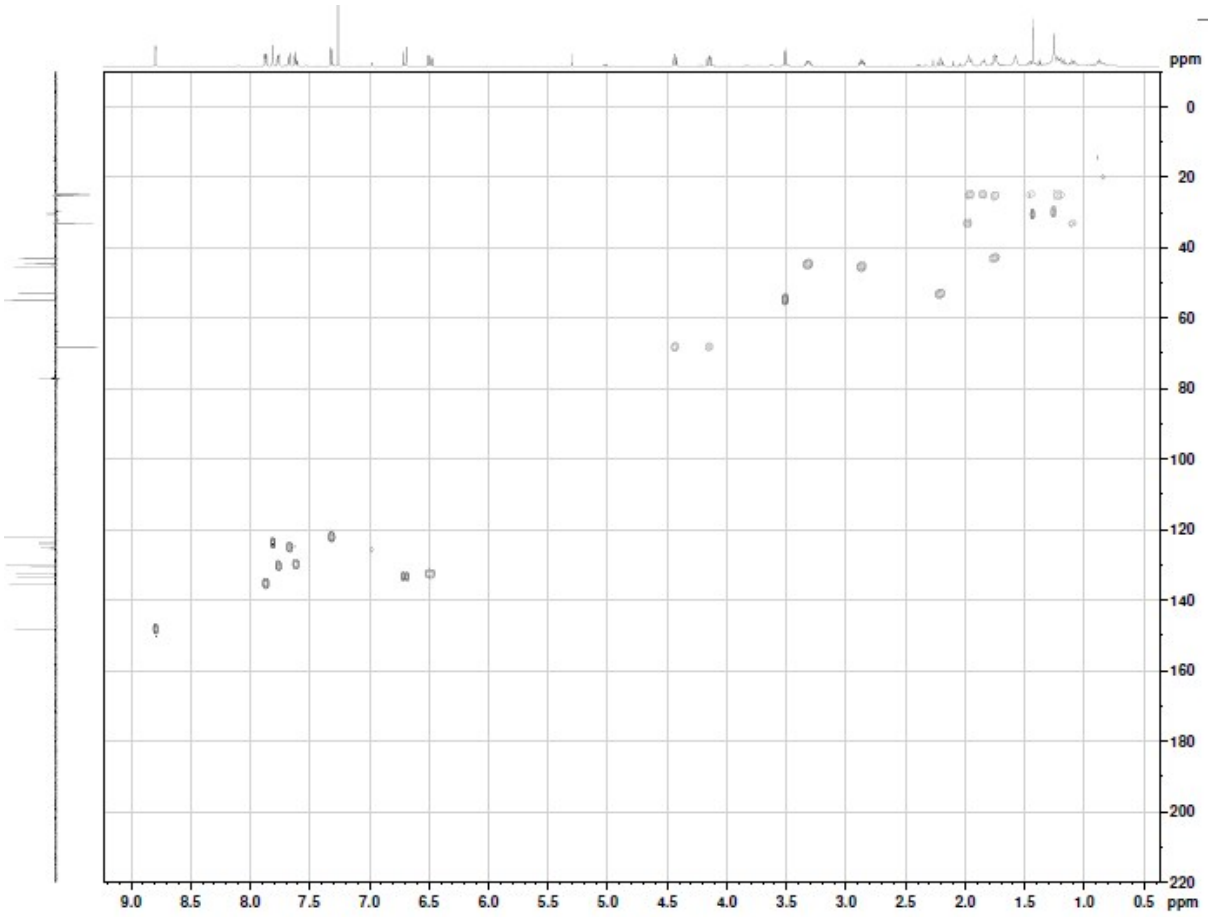




COSY:



HSQC: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220
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8.5
8.0
7.5
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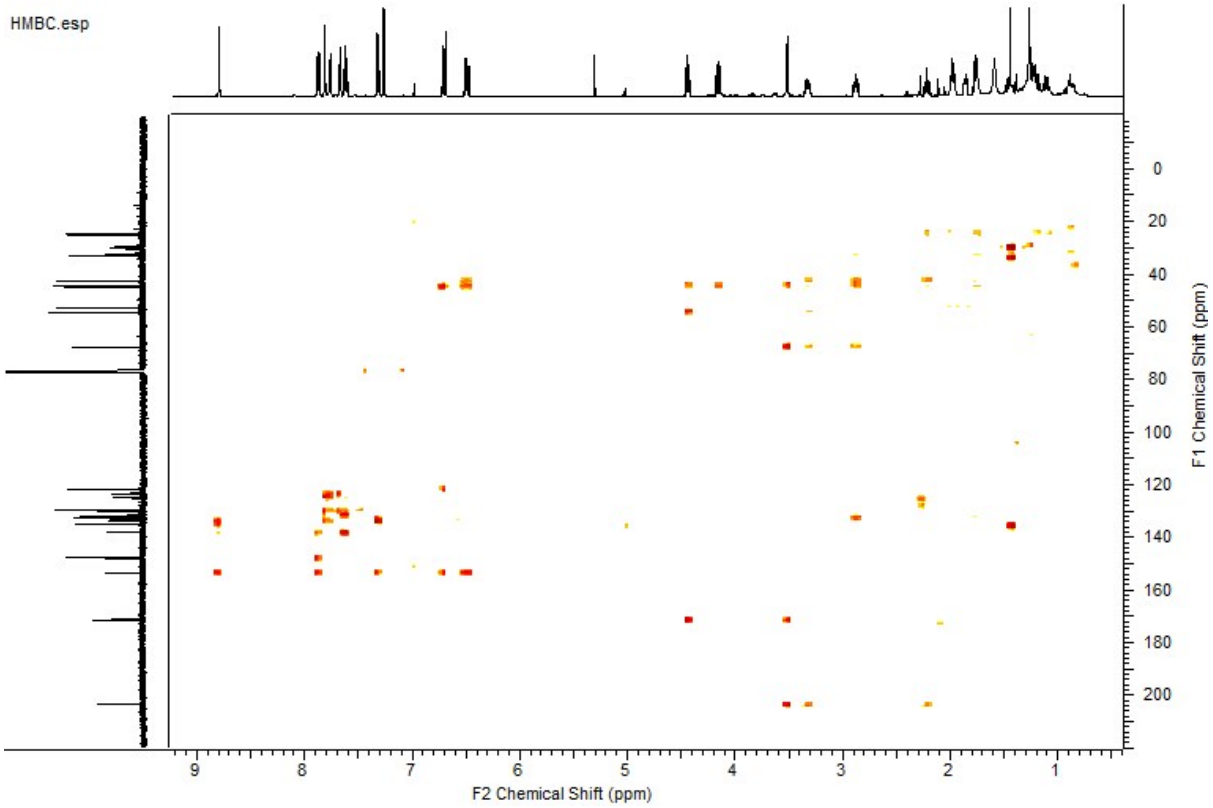
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

HMBC:


HMBC.esp
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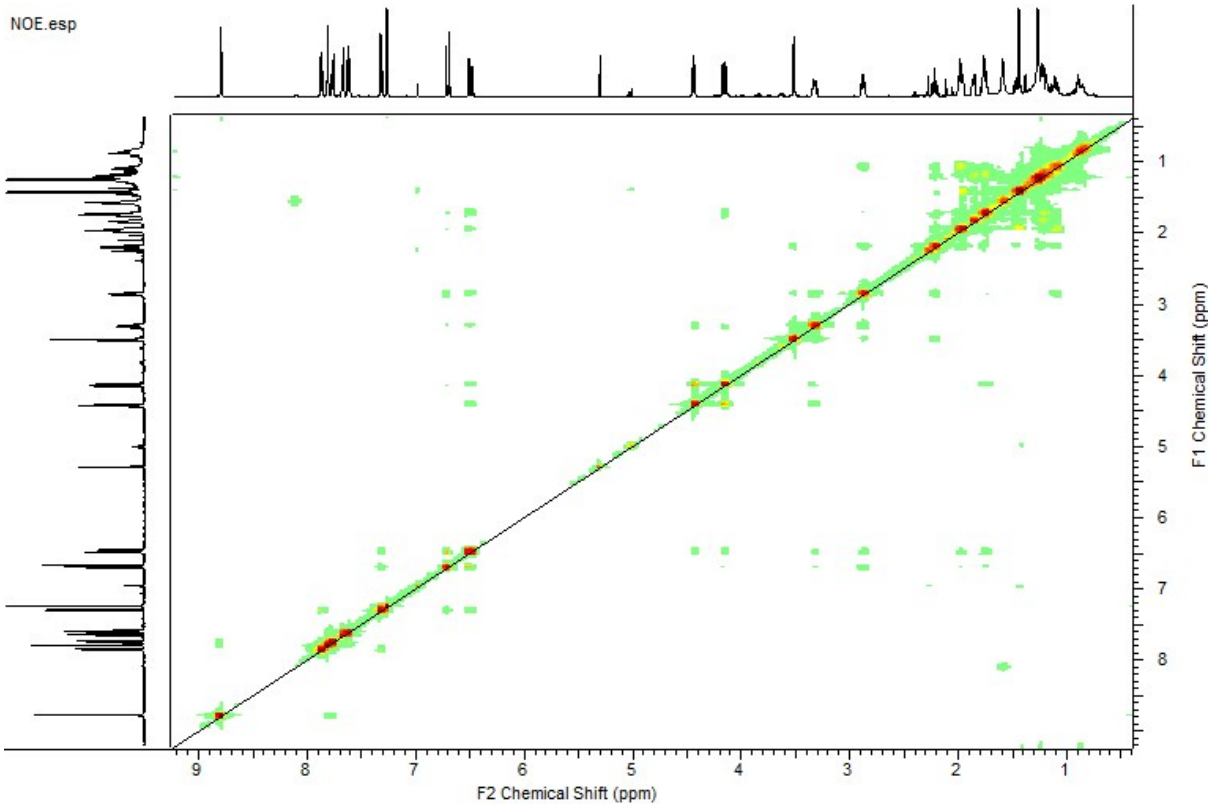
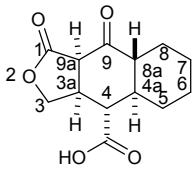
20
40
60
80
100
120
140
160
180
200
F1 Chemical Shift (ppm)
9
8
7
6
5
4
3
2
1
F2 Chemical Shift (ppm)

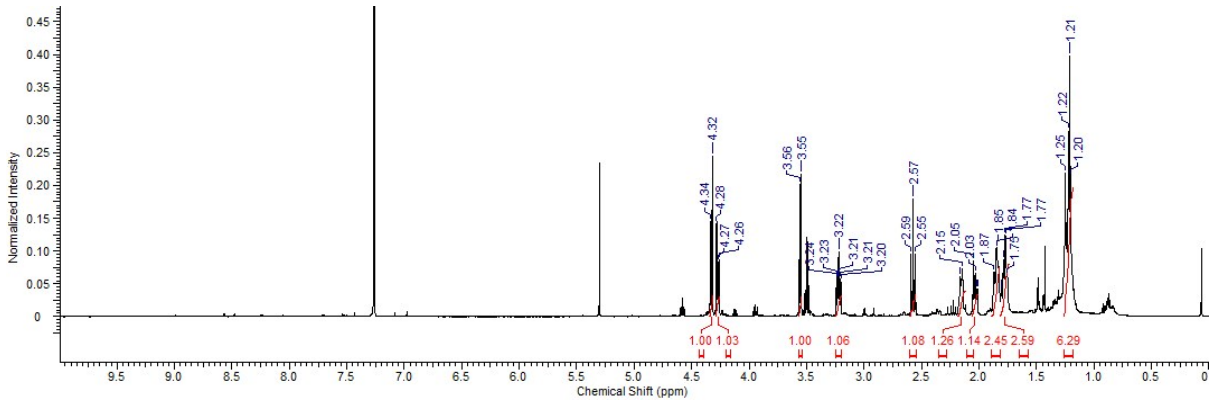
NOESY:

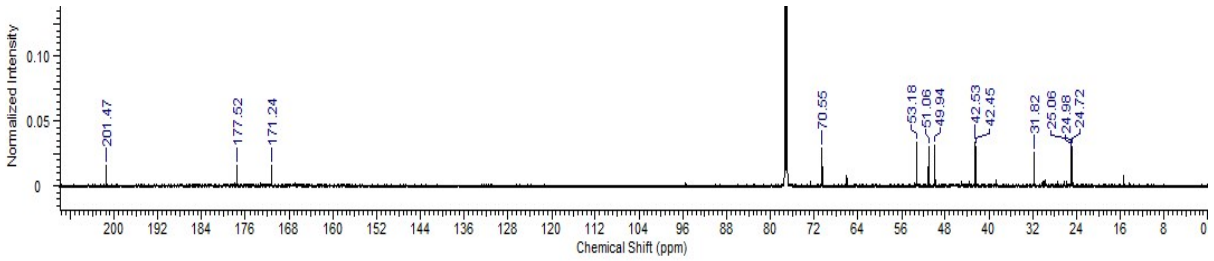


(3a*S,4*R**,4a*S**,8a*S**,9a*S**)-1,9-Dioxododecahydronaphtho[2,3-c]furan-4-carboxylic acid**



TFA (3.00 mL, 38.9 mmol) was added to a stirred solution of (3a*S**,4*R**,4a*S**,8a*S**,9a*S**)-*tert*-butyl 1,9-dioxododecahydronaphtho[2,3-c]furan-4-carboxylate (**12**) (1.09 g, 3.53 mmol) in CH_2Cl_2 (6 mL) at 0 °C, under N_2. The reaction mixture was stirred at 20 °C for 16 h before being concentrated *in vacuo*. The residue was azeotroped with toluene (25 mL) to yield a crude pink solid. Purification by trituration (CH_2Cl_2) yielded (3a*S**,4*R**,4a*S**,8a*S**,9a*S**)-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carboxylic acid (441 mg, 1.75 mmol, 49%) as a white solid; 1H NMR (600 MHz, $CDCl_3$) δ 4.33 (1H, d, *J* = 9.8, C^3*H*H), 4.27 (1H, dd, *J* = 9.8, 4.5, C^3H*H*), 3.55 (1H, d, *J* = 7.6, C^{9a}*H*), 3.22 (1H, ddd, *J* = 11.5, 7.6, 4.5, C^{3a}*H*), 2.57 (1H, t, *J* = 11.5, C^4*H*), 2.19-2.12 (1H, m, C^8*H*H), 2.06- 2.01 (1H, m, C^{8a}*H*), 1.89-1.82 (2H, m, C^6*H*H & C^7*H*H), 1.81-1.73 (2H, m, C^5*H*H & C^{4a}*H*), 1.26-1.18 (4H, m, C^5H*H*, C^6H*H*, C^7H*H* & C^8H*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.5 (*C*^{9}O), 177.5 (*C*OOH), 171.2 (*C*^{1}O), 70.6 (*C*$^3H_2$), 53.2 (*C*^{9a}H), 51.1 (*C*^{4}H), 49.9 (*C*^{8a}H), 42.5 (*C*^{3a}H), 42.4 (*C*^{4a}H), 31.8 (*C*$^5H_2$), 25.1 (*C*$^8H_2$), 25.0 (*C*$^6H_2$), 24.7 (*C*$^7H_2$); IR (thin film) 2930 (C-H), 2869 (C-H), 1779 (C=O), 1705 (C=O), 1171, 1166, 1018 cm^{-1}; m/z (ES+) 253 (100%, $[M+H]^+$); HRMS (EI) calcd for $C_{13}H_{16}O_5$ $[M]^+$ 252.0992, observed 252.0982.

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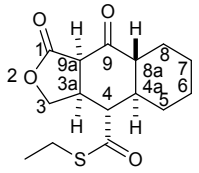
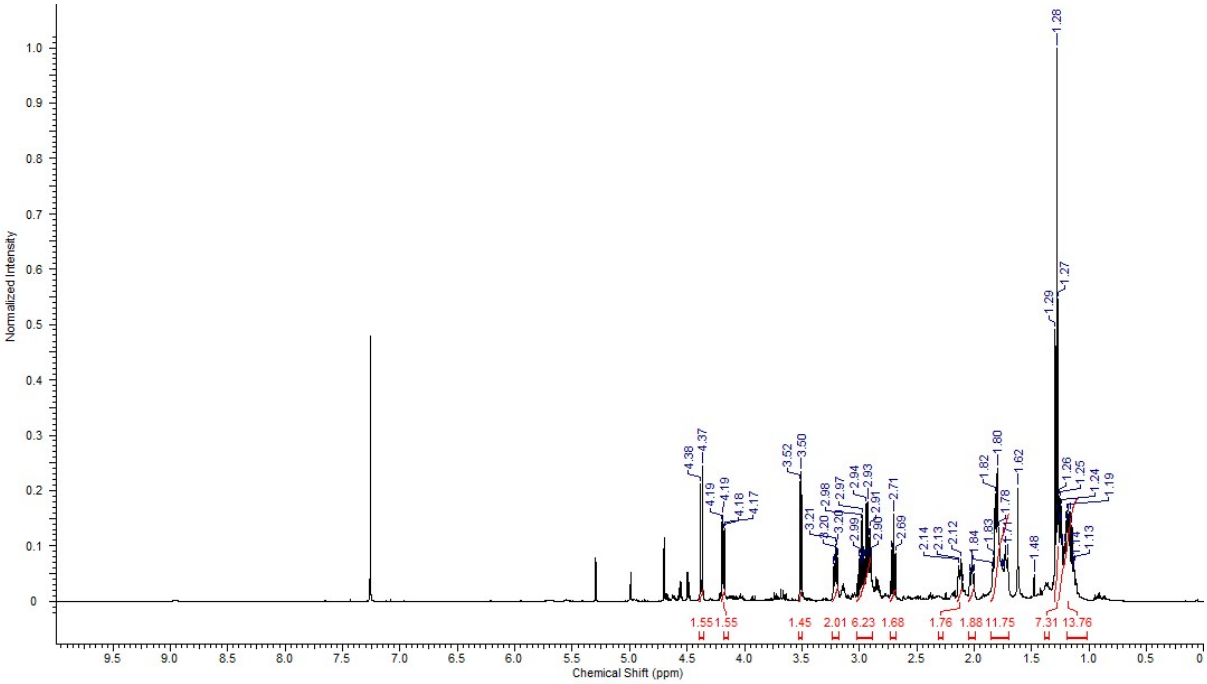
177.52
171.24
70.55
53.18
51.06
49.94
42.53
42.45
31.82
25.06
24.98
24.72
200 192 184 176 168 160 152 144 136 128 120 112 104 96 88 80 72 64 56 48 40 32 24 16 8 0
Chemical Shift (ppm)

(3a*R,4*R**,4a*S**,8a*S**,9a*S**)-*S*-ethyl 1,9-Dioxododecahydronaphtho[2,3-c]furan-4-carbothioate**



EDCI (502 mg, 2.62 mmol) was added to a stirred solution of (3a*S**,4*R**,4a*S**,8a*S**,9a*S**)-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carboxylic acid (440 mg, 1.74 mmol), ethanethiol (0.52 mL, 6.98 mmol) and DMAP (21.3 mg, 0.17 mmol) in CH_2Cl_2 (20 mL) under N_2. The reaction mixture was stirred at 20 °C for 2 h and then quenched with sat. aq. NH_4Cl (10 mL). An extraction into CH_2Cl_2 (10 mL) was done and the organic layer was dried (hydrophobic frit) and concentrated *in vacuo* to yield *(*3a*R**,4*R**,4a*S**,8a*S**,9a*S**)-*S*-ethyl 1,9-dioxododecahydronaphtho[2,3-c]furan-4-carbothioate (482 mg, 1.62 mmol, 93%) as an off-white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.38 (1H, d, *J* = 9.6, C^3*H*H), 4.18 (1H, dd, *J* = 9.6, 4.7, C^{3}H*H*), 3.51 (1H, d, *J* = 7.5, C^{9a}*H*), 3.21 (1H, ddd, *J* = 11.6, 7.4, 4.7, C^{3a}*H*), 3.02-2.89 (2H, m, C*H*$_2$CH$_3$), 2.70 (1H, t, *J* = 11.1, C^4*H*), 2.15-2.10 (1H, m, C^8*H*H), 2.02 (1H, td, *J* = 11.2, 3.2, C^{8a}*H*), 1.85-1.69 (4H, m, C^{4a}*H*, C^5*H*H, C^6*H*H & C^7*H*H), 1.30-1.27 (3H, m, CH$_2$C*H*$_3$), 1.27-1.09 (4H, m, C^{5}H*H*, C^{6}H*H*, C^{7}H*H* & C^{8}H*H*); IR (thin film) 2930 (C-H), 2876 (C-H), 1783 (C=O), 1706 (C=O), 1671 (C=O), 1448, 1362, 1203, 1137, 1012, 981, 896 cm^{-1}; m/z (ES+) 297 (100%, [M+H]$^+$); HRMS (EI) calcd for $C_{15}H_{20}O_4S$ [M]$^+$ 296.1077, observed 296.1076.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4.19
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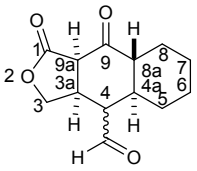
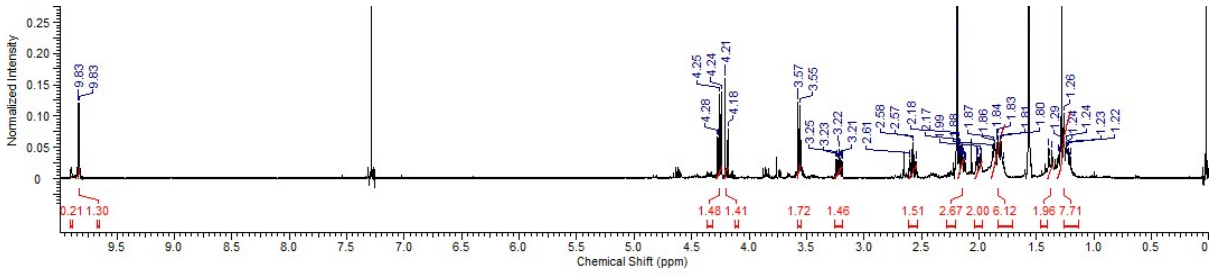
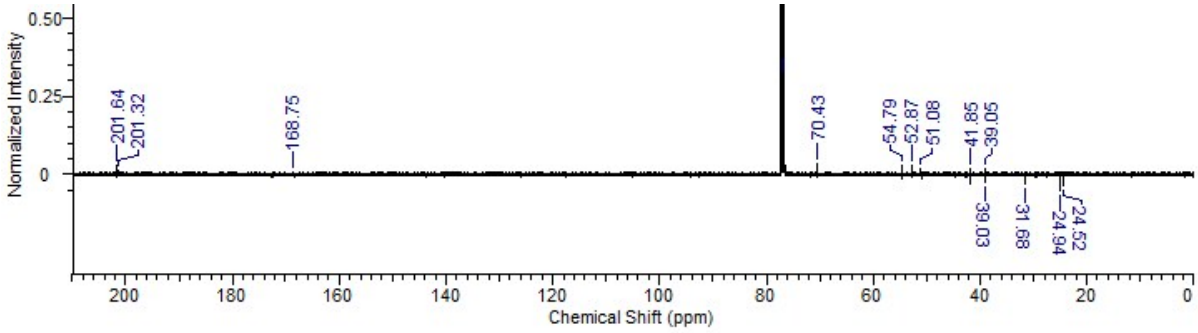
2.13
2.12
1.84
1.82
1.80
1.78
1.62
1.48
1.26
1.25
1.24
1.19
1.13
1.55 1.55 1.45 2.01 6.23 1.68 1.76 1.88 11.75 7.31 13.76

rac-(3a*S*,4a*R*,8a*S*,9a*S*)-1,9-Dioxododecahydronaphtho[2,3-c]furan-4-carbaldehyde



Triethylsilane (1.02 mL, 6.41 mmol) was added to a stirred solution of (3a*R**,4*R**,4a*S**,8a*S**,9a*S**)-*S*-ethyl 1,9-dioxododecahydronaphtho[2,3-c]furan-4-carbothioate (475 mg, 1.60 mmol), palladium on carbon (10%) (171 mg, 1.60 mmol) and $MgSO_4$ (to dry) in anhydrous, degassed acetone (25 mL) under N_2. The reaction mixture was stirred at 20 °C for 16 h before being filtered through celite and the filtrate concentrated *in vacuo*. Purification by flash column chromatography (0-100% EtOAc/cyclohexane) gave partial racemisation at C^4 to yield *rac*-(3a*S*,4a*R*,8a*S*,9a*S*)-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carbaldehyde (4*S*:4*R*; 1:6) (130 mg, 0.55 mmol, 34%) as a colourless oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.90-9.89 (1H, m, 4*S*-C*H*O), 9.83 (1H, d, *J* = 2.8, 4*R*-C*H*O), 4.26 (1H, dd, *J* = 9.8, 4.7, 4*R*-C^3*H*H), 4.20 (1H, d, *J* = 9.6, 4*R*-C^{3}H*H*), 3.56 (1H, d, *J* = 7.8, 4*R*-C^{9a}*H*), 3.22 (1H, ddd, *J* = 11.6, 7.5, 4.5, 4*R*-C^{3a}*H*), 2.57 (1H, td, *J* = 11.4, 2.9, 4*R*-C^4*H*), 2.18-2.11 (2H, m, 4*R*-C^8*H*H & 4*R*-C^{8a}*H*), 2.04-1.97 (2H, m, 4*R*-C^6*H*H & 4*R*-C^7*H*H), 1.89-1.77 (2H, m, 4*R*-C^5*H*H & 4*R*-C^{4a}*H*), 1.40-1.35 (1H, m, 4*R*-C^{8}H*H*), 1.32-1.19 (3H, m, 4*R*-C^{5}H*H*, 4*R*-C^{6}H*H* & 4*R*-C^{7}H*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.6 (4*R*-*C*^{9}O), 201.3 (4*R*-*C*HO), 168.7 (4*R*-*C*^{1}O), 70.4 (4*R*-*C*^{3}H$_2$), 54.8 (4*R*-*C*^{4}H), 52.9 (4*R*-*C*^{9a}H), 51.1 (4*R*-*C*^{8a}H), 41.8 (4*R*-*C*^{4a}H), 39.1 (4*R*-*C*^{3a}H), 31.7 (4*R*-*C*^{5}H$_2$), 24.9 (4*R*-*C*^{8}H$_2$ & 4R-*C*^{6}H$_2$), 24.5 (4*R*-*C*^{7}H$_2$), 19.1 (4*S*-C^{3}H*C*H$_3$); IR (thin film) 2927 (C-H), 2855 (C-H), 1770 (C=O), 1713 (C=O), 1125, 730 cm^{-1}; m/z (ES+) 237 (100%, $[M+H]^+$); HRMS (EI) calcd for $C_{13}H_{16}O_4$ $[M]^+$ 236.1043, observed 236.1049.

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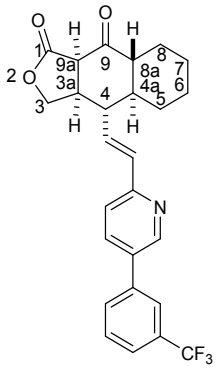
39.03
31.68
24.64
24.52
200
180
160
140
120
100
80
60
40
20
0
Chemical Shift (ppm)

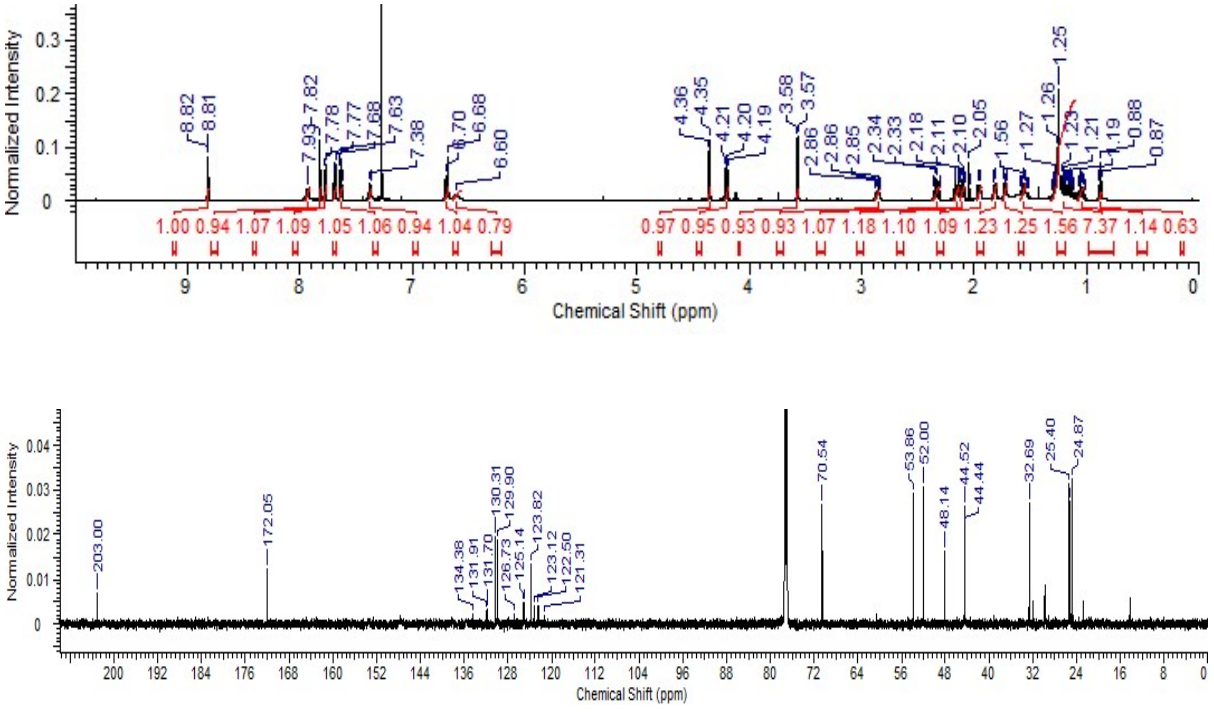
(3a*S,4*R**,4a*R**,8a*S**,9a*S**)-4-((*E*)-2-(5-(3-(Trifluoromethyl)phenyl)pyridin-2-yl)vinyl)octahydronaphtho[2,3-c]furan-1,9(3H,9aH)-dione (16)**



n-BuLi (2.7 M in heptanes) (0.25 mL, 0.66 mmol) was added dropwise to a stirred solution of diethyl (5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)methylphosphonate (**7**) (226 mg, 0.60 mmol) in anhydrous 2-MeTHF (10 mL) at 0 °C, under N_2. The solution was stirred at 0 °C for 10 min before a solution of *rac*-(3a*S*,4a*R*,8a*S*,9a*S*)-1,9-dioxododecahydronaphtho[2,3-c]furan-4-carbaldehyde (130 mg, 0.55 mmol) in anhydrous 2-MeTHF (10 mL) was added. The reaction mixture was stirred at 0 °C for a further 1 h and then quenched with sat. aq. NH_4Cl (5 mL). An extraction into EtOAc (10 mL) was done and the organic phase was washed with brine (5 mL), dried (hydrophobic frit) and concentrated *in vacuo* to yield a crude yellow gum. Purification by automated column chromatography (0-100% EtOAc/cyclohexane) yielded (3a*S**,4*R**,4a*R**,8a*S**,9a*S**)-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)octahydronaphtho[2,3-c]furan-1,9(3H,9aH)-dione (**16**) (76.0 mg, 0.17 mmol, 25 %) as a yellow glassy solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.82 (1H, d, *J* = 2.0, C*H*N), 7.90 (1H, dd, *J* = 8.1, 2.4, C*H*CCHN), 7.83 (1H, s, C*H*CCF_3), 7.78 (1H, d, *J* = 7.6, C*H*CCHCCF_3), 7.69 (1H, d, *J* = 7.8, CHC*H*CCF_3), 7.63 (1H, t, *J* = 7.6, C*H*CHCCF_3), 7.36 (1H, dd, *J* = 8.2, 0.6, C*H*CN), 6.70 (1H, d, *J* = 15.4, C^{4}HCHC*H*Pyr), 6.56 (1H, dd, *J* = 15.4, 9.4, C^{4}HC*H*CHPyr), 4.37 (1H, d, *J* = 9.4, C^3*H*H), 4.20 (1H, dd, *J* = 9.4, 4.8, C^{3}H*H*), 3.58 (1H, d, *J* = 7.4, C^{9a}*H*), 2.85 (1H, ddd, *J* = 11.1, 7.4, 4.8, C^{3a}*H*), 2.34 (1H, td, *J* = 11.1, 9.4, C^4*H*), 2.20-2.08 (1H, m, C^{8a}*H* & C^8*H*H), 2.02-1.94 (1H, m, C^5*H*H), 1.86-1.66 (2H, m, C^6*H*H & C^7*H*H), 1.56 (1H, qd, *J* = 11.2, 3.4, C^{4a}*H*), 1.34-1.00 (4H, m, C^{5}H*H*, C^{6}H*H*, C^{7}H*H* & C^{8}H*H*); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.0 (*C*^{9}O), 172.1 (*C*^{1}O), 152.6 (*C*N), 147.8 (*C*HN), 138.2 (*C*CHCCF_3), 134.7 (*C*HCCHN), 134.4 (*C*CHN), 134.3 (C^{4}HCH*C*HPyr), 131.9 (C^{4}H*C*HCHPyr), 131.8 (q, *J* = 32.1, *C*CF_3), 130.3 (*C*HCCHCCF_3), 129.9

(*C*HCHCCF$_3$), 125.1 (q, *J* = 3.6, CH*C*HCCF$_3$), 123.9 (q, *J* = 3.6, C*C*HCCF$_3$), 124.0 (d, *J* = 272.0, *C*F$_3$), 122.5 (*C*HCN), 70.5 (*C*^{3}H$_2$), 53.9 (*C*^{9a}H), 52.0 (*C*^{8a}H), 48.2 (*C*^{4}H), 44.5 (*C*^{3a}H), 44.4 (*C*^{4a}H), 32.7 (*C*^{5}H$_2$), 25.4 (*C*^{8}H$_2$), 25.3 (*C*^{6}H$_2$), 24.9 (*C*^{7}H$_2$); IR (thin film) 2930 (C-H), 2858 (C-H), 1772 (C=O), 1706 (C=O), 1335, 1167, 1119, 1072, 998, 971, 810 cm^{-1}; m/z (ES+) 455 (100%, [M+H]$^+$); HRMS (EI) calcd for $C_{26}H_{24}O_3F_3N$ [M+H]$^+$ 455.17028, observed 455.17029.

Chiral column purification (70%EtOH/Heptane, f=20ml/min,Column 30mm x 25cm Chiralpak AD-H) gave (+)-(3a*S*,4*R*,4a*R*,8a*S*,9a*S*)-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)octahydronaphtho[2,3-c]furan-1,9(3H,9aH)-dione ((+)-**16**) with an $[\alpha]_D^{25}$ = +31.4 (MeOH) and (-)-(3a*S*,4*R*,4a*R*,8a*S*,9a*S*)-4-((*E*)-2-(5-(3-(trifluoromethyl)phenyl)pyridin-2-yl)vinyl)octahydronaphtho[2,3-c]furan-1,9(3H,9aH)-dione ((-)-**16**) with an $[\alpha]_D^{25}$ = -31.3 (MeOH).



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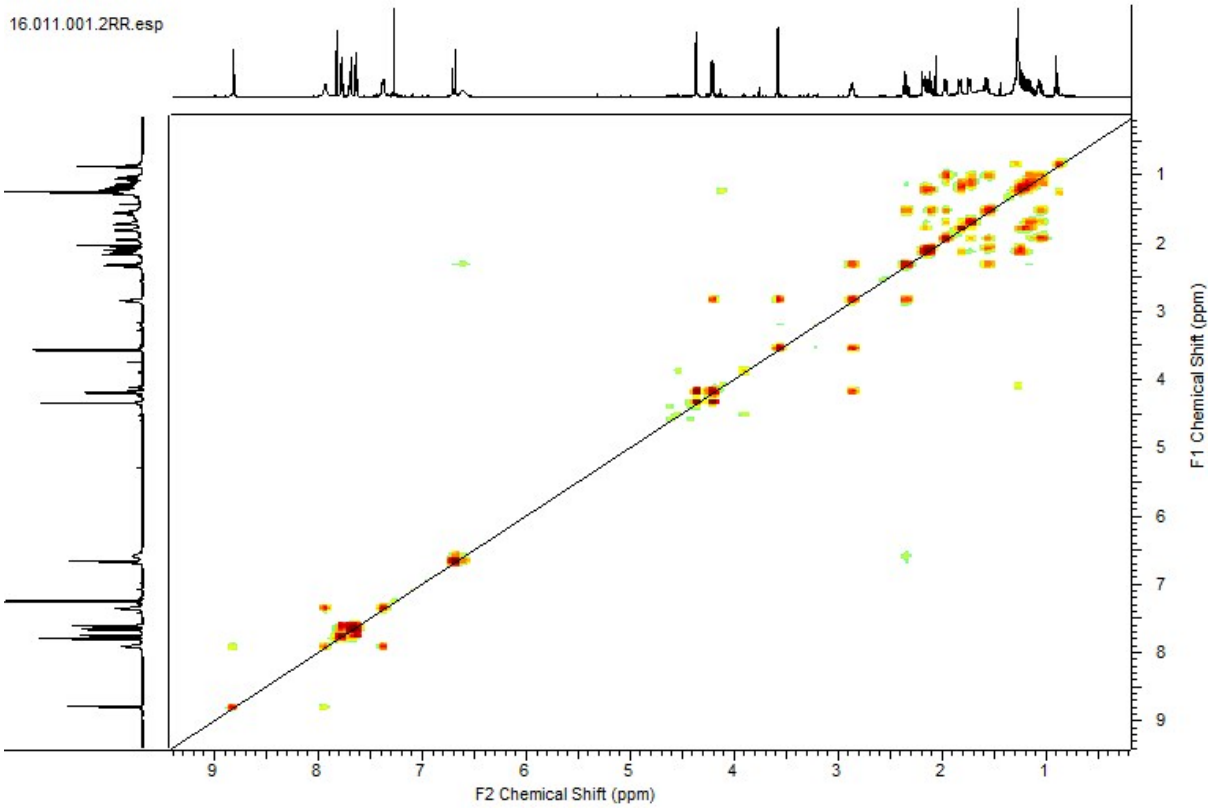
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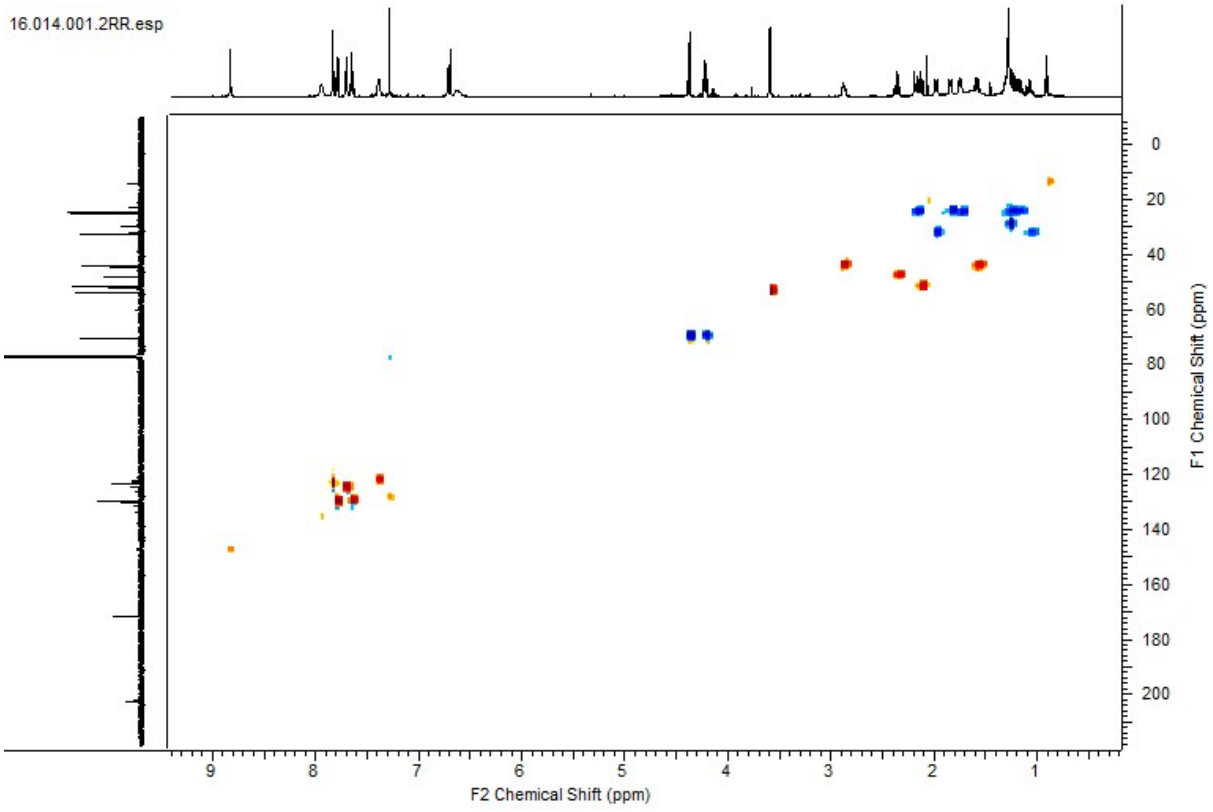
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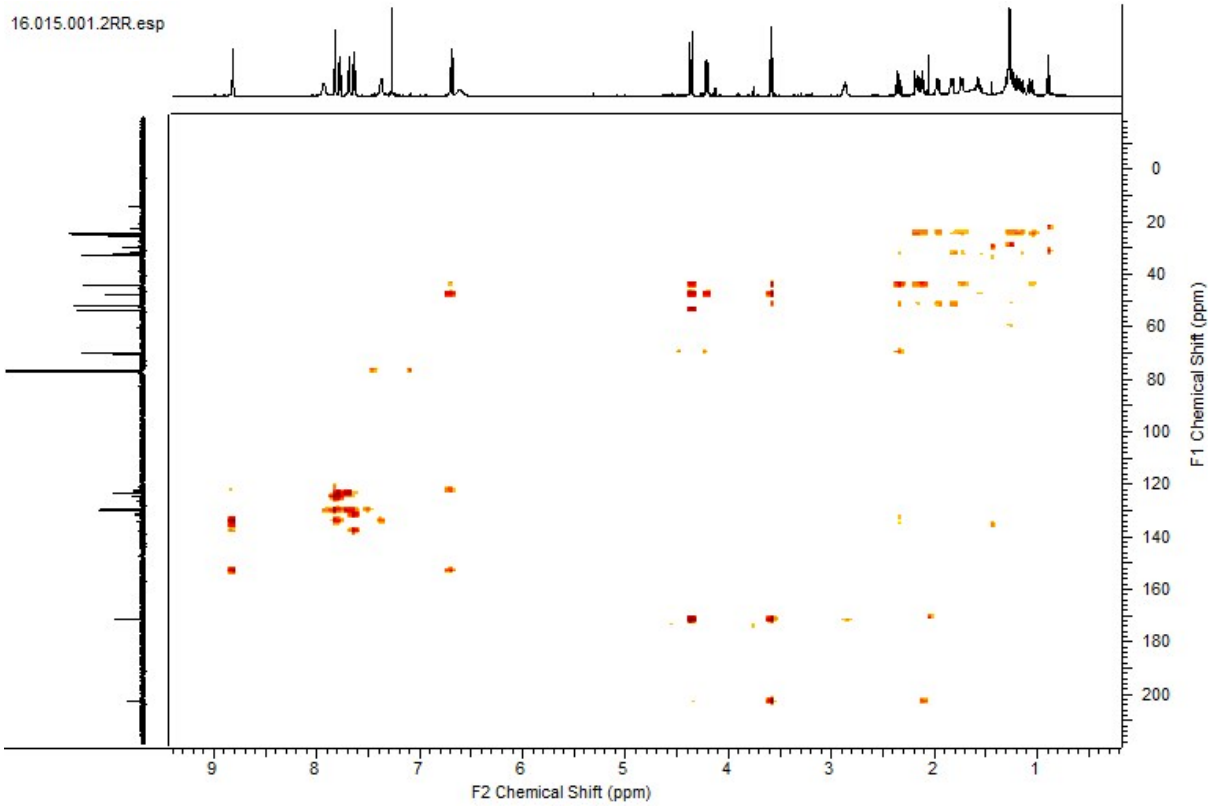
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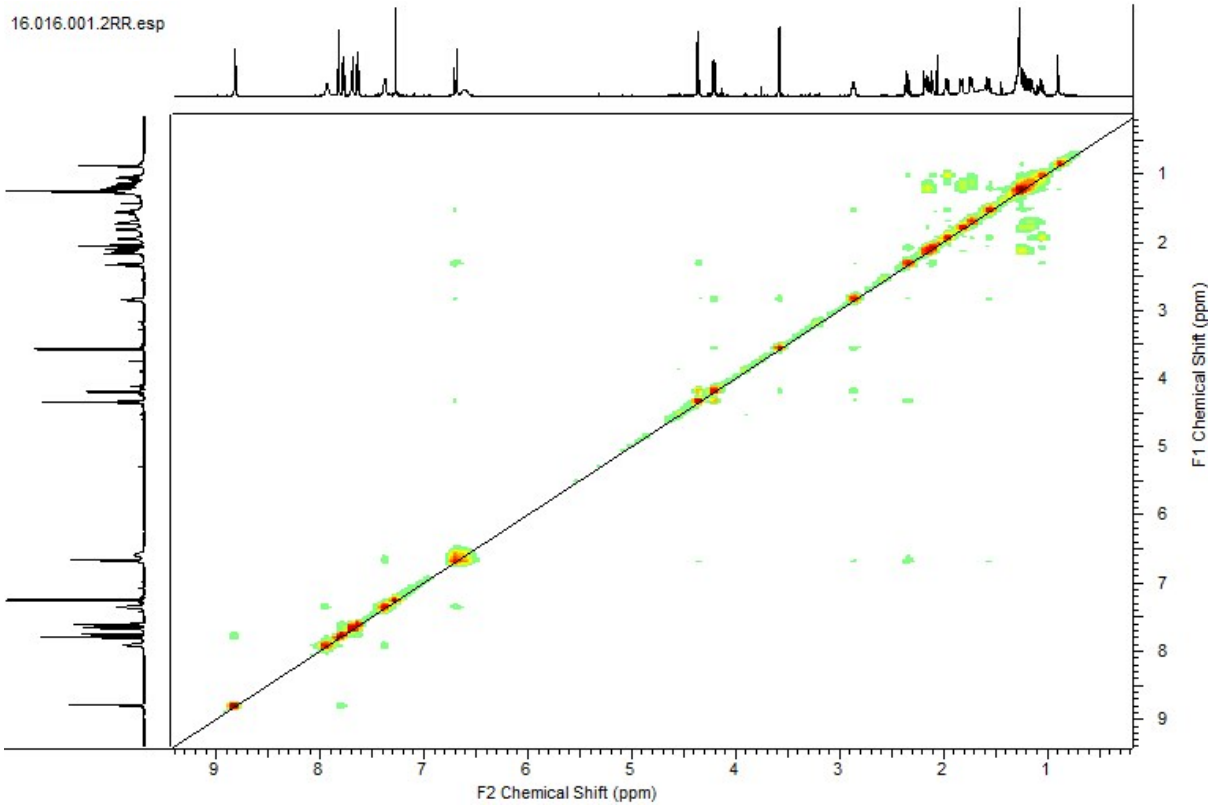
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F2 Chemical Shift (ppm)
F1 Chemical Shift (ppm)

Biology

Biological testing of compounds was done in collaboration with Prof Rachel Chambers' research group at the Centre for Inflammation and Tissue Repair (UCL, Division of Medicine). Calcium ion mobilisation assay work was assisted by Dr Natalia Smoktunowicz and Dr Manuela Plate.

Materials and methods

Reagents:

Thrombin, extracted from human plasma, was purchased from Calbiochem (Merck Biosciences, UK). PAR-1 agonist peptide and reverse peptide were supplied by Bachem. The RWJ-58259 sample used as standard was synthesised by Dr Eifion Robinson (UCL).

Cell culture:

Primary human lung fibroblasts (pHLFs), grown from explant cultures of normal adult lung tissue, were a gift from Dr Robin J McAnulty (University College London). Cells were maintained in DMEM at 37 °C (10% CO_2) supplemented with glutamine (4 mM), penicillin, streptomycin, and 10% (v/v) FBS (all from Invitrogen) and were below passage 10 when used for experiments.

Measurement of intracellular Ca^{2+} levels:

pHLFs were seeded in clear-bottom, black, 96-well microplates at a density of 10,000 cells/well, incubated for 48 h and then quiesced for 24 h. Intracellular Ca^{2+} levels were assessed using the Fluo-4 AM kit (Invitrogen, UK) according to the manufacturer's instructions. The dye was dissolved in assay buffer (20 mM HEPES in HBSS) supplemented with 2.5 mM probenecid. Wells were aspirated and solutions of test compounds (3 mM in DMSO) were added to the relevant wells. Serial dilution using dye buffer solution was done to give the desired final concentrations (100 µL per well). For positive controls, the equivalent volume of DMSO only was diluted in the dye buffer solution and added to the relevant wells. The cells were then incubated again at 37 °C (10% CO_2) for 30 min and at ambient conditions, in the dark, for 30 min. Cells were then stimulated by addition of a solution of thrombin in assay buffer (50 µL, 10 nM final concentration) and changes in intracellular Ca^{2+} concentration were monitored in real-time using a fluorescent imaging plate reader (FLIPR® Tetra System, Molecular Devices, Inc). Measurements were taken every 1

sec for 1 min, then every 6 sec for a further 2 min. Experiments were performed in three replicates, on the same plate, at least twice. The data was plotted as percentage inhibition.[4]

References

(1) PCMODEL, version 8.5, Serena Software, Gilbert, K.E., Bloomington.

(2) Schlecht, M. F. Molecular Modeling on the PC. Wiley-VCH, New York, **1998**.

(3) Haasnoot, C.A.G.; DeLeeuw, F.A.A.M.; Altona, C. *Tetrahedron* **1980**, *36*, 2783.

4. Ortiz-Stern A, Deng X, Smoktunowicz N, Mercer PF, Chambers RC. PAR-1-dependent and PAR-independent pro-inflammatory signaling in human lung fibroblasts exposed to thrombin. *Journal of Cellular Physiology.* 2012;227(11):3575-3584.