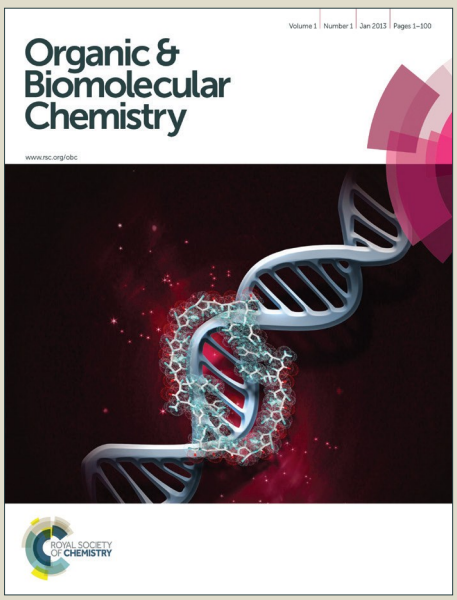
Organic & Biomolecular Chemistry

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Synthesis of Novel and Potent Vorapaxar Analogues

Emily Knight,[a] Eifion Robinson,[a] Natalia Smoktunowicz,[b] Rachel C. Chambers,[b] Abil E. Aliev,[a] Graham G. Inglis,[c] Vijay Chudasama*[a] and Stephen Caddick*[a]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

Vorapaxar is a first-in-class PAR-1 antagonistic drug based on the ent-himbacine scaffold. Detailed in this article are enantioselective and racemic routes to various novel vorapaxar analogues. Biological testing revealed these compounds to have moderate to excellent potencies against PAR-1 with the most potent analogue demonstrating an IC_{50} of 27 nM.

Introduction

The recent FDA approval of vorapaxar (Figure 1) for the "reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or peripheral arterial disease (PAD)" marked an exciting development in the blockade of thrombin induced cellular activities.[1] Vorapaxar is a first-in-class, highly potent protease activated receptor-1 (PAR-1) antagonist. PAR-1 is a seven transmembrane G-protein coupled receptor (7TM GPCR) expressed on many cell types throughout the body including platelets, endothelial cells and fibroblasts. It is agonised by an intramolecular mechanism following exposure to thrombin.[2] It is an important receptor in the pathway towards thrombus formation and is associated with cardiovascular disease, as well as cancer and various fibrotic diseases.[2] PAR-1 antagonists could thus be used to treat a number of serious conditions. With this in mind, disclosed herein is the synthesis of a series of novel vorapaxar analogues with particular focus on functionalisation at a position that has not been explored previously, *i.e.* the C-9 position.

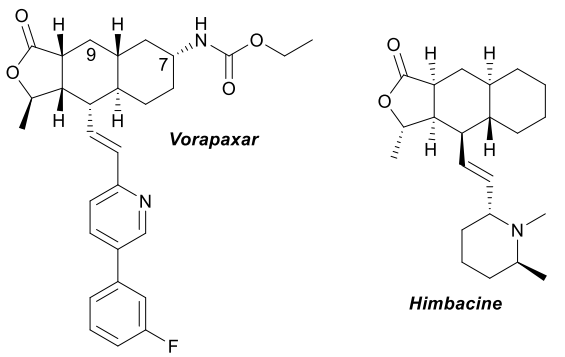
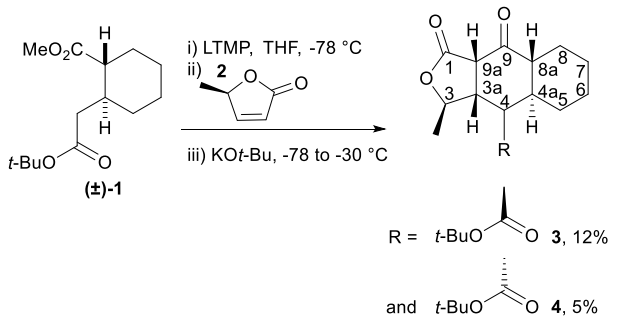


Fig. 1 Structures of vorapaxar and himbacine

Results and Discussion

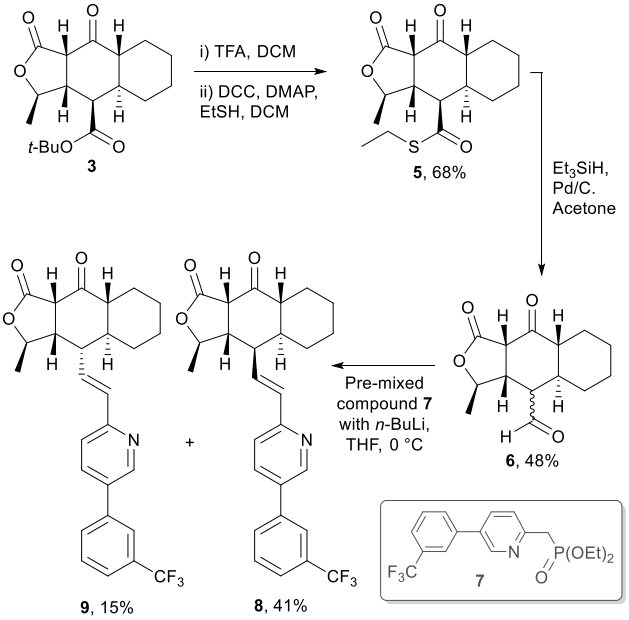
To begin, C-9-substituted vorapaxar analogues were to be synthesised on the basis of a published partial synthetic route towards natural product himbacine (Figure 1, and Schemes 1 & 2).[3-8] This route was designed to provide access to analogues that do not contain a carbamate group at C-7 and have a *m*-CF_3 on the aryl group rather a *m*-F substituent. These alterations will not affect the activity of the antagonist to any significant degree since they themselves were relatively late stage pharmacokinetic-based decisions made during the development of vorapaxar that were shown to have little impact on potency, *i.e.* the carbamate was introduced as a means to improve oral delivery and the use of *m*-F in place of *m*-CF_3 was to reduce lipophilicity.[9] Moreover, the synthesis of analogues without these late stage changes, when trialling a new synthetic route to vorapaxar analogues, is if anything a more sensible choice as it allows for direct comparison with the larger body of literature compounds made in the earlier stages of the development of vorapaxar.[9] Alteration(s) to the analogues described herein to aid pharmacokinetic properties without effecting potency can almost certainly be tuned into the core, if need be, at a later stage.

Initially, *trans*-methyl 2-(2-(*tert*-butoxy)-2-oxoethyl)cyclohexanecarboxylate (**(±)-1**)[4] and 5-methyl-2(5*H*)-furanone (**2**)[5] were synthesised using literature procedures. These were then reacted together using the conditions proposed by Casey *et al*. to give (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**) 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**) *via* kinetic resolution, albeit in low yields (12% and 5% respectively) (Scheme 1).



Scheme 1 Stereoselective tricycle synthesis

In order to furnish the desired C-9 functionalised vorapaxar analogues, the *tert*-butyl group of compounds **3/4** had to be replaced with the biaryl motif that is essential for the PAR-1 activity of vorapaxar.[6] To set about this, initially the *tert*-butyl group of the higher yielding tricycle (**3**) was removed using TFA/CH_2Cl_2 (Scheme 2). The resulting acid was then coupled to ethanethiol using DCC and DMAP. The formed thioester (**5**) was next reduced using mild reducing conditions of triethylsilane and catalytic palladium on carbon to give an aldehyde (**6**).[7] Finally, Horner-Emmons conditions were used for reaction with biaryl phosphonate ester **7**, which was prepared according to a literature procedure,[8] to form the desired C-9 functionalised vorapaxar analogues. Notably, prior to performing the Horner-Emmons reaction, the aldehyde underwent partial epimerisation at the C-4 position. This conveniently afforded both C-4 epimers of the final C-9-keto-analogues (**8** and **9**, Scheme 2), and meant that the lower yielding tricycle **4** did not need to be carried through the synthesis to obtain compound **9**.



Scheme 2 Development of tricycle to give novel enantiomerically pure vorapaxar analogues **8** and **9**

We noted from the outset that C-9-keto-analogues would have a useful carbonyl synthetic handle to allow the exploration of SAR in a direction as yet unexplored on vorapaxar. To the best of our knowledge, there are no vorapaxar analogues with substitution at the C-9 position. As an initial foray into the novel SAR possibilities, the ketone of compound **8** was reduced to an hydroxyl group using $NaBH_4$ to give compounds **10** and **11** (Figure 2) in 38% and 29% yield respectively. This was a significant transformation as it returned sp3 hybridisation at C-9, making the tricycle conformation more similar to that of vorapaxar. Additionally, compounds **8**-**11** would prove useful in exploring the effect on activity of sp2 *vs.* sp3 hybridisation at C-9. The stereochemical assignment of compounds **8**-**11** was made on the basis of ^1H NMR coupling constants and 2D NMR analysis; see ESI for further details.

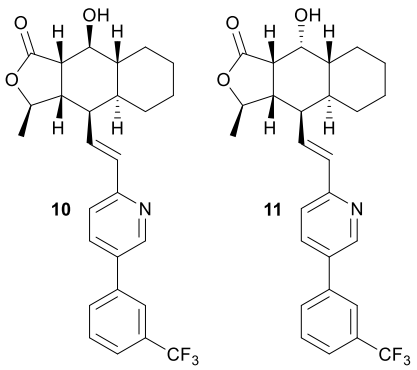
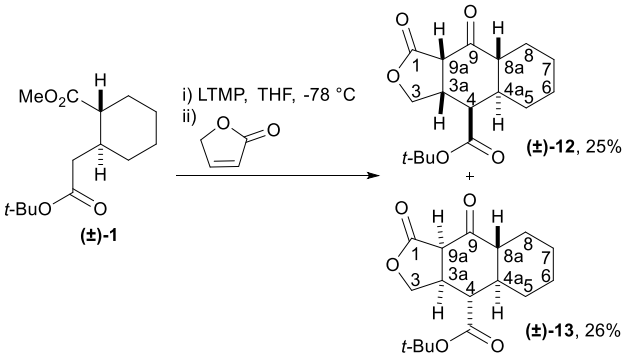


Fig. 2 Novel enantiomerically pure vorapaxar analogues **10** and **11**

Next we used commercially available 2-(5*H*)-furanone in place of methyl-furanone **2** for reaction with *trans*-methyl 2-(2-(tert-butoxy)-2-oxoethyl)cyclohexanecarboxylate **(±)-1** as a conduit to gain access to further distinct analogues of vorapaxar in terms of relative ring junction stereochemistry. The absence of the methyl group on 2-(5*H*)-furanone, and thus in subsequent vorapaxar analogues, would have no bearing as, in line with several examples in the literature, this methyl group is not thought to have an effect on PAR-1 antagonism.[10] The reaction of **(±)-1** and 2-(5*H*)-furanone led to the formation of racemic compounds **(±)-12** and **(±)-13**, which to our delight had distinct relative stereochemistries at C-9a/C-3a compared with C-8a/C-4a. For this reaction, the addition of KO*t*-Bu was not required for tricycle synthesis, which may have contributed to an increased overall yield of 51% for tricycle formation.



Scheme 3 Racemic tricycle synthesis

The synthetic route detailed in Scheme 2 was next repeated on **(±)-12** and **(±)-13**, which led to the formation of racemic PAR-1 analogues **(±)-14-16**. The racemic compounds were easier to synthesise and use of **(±)-12** and **(±)-13** allowed access to PAR-1 analogues with tricycle scaffolds with differing relative

stereochemical assignment at C-9a/C-3a compared with C-8a/C-4a, *i.e.* **(±)-14/15** and **(±)-16**, respectively. The enantiomeric pairs were then separated out into (+) and (–) enantiomers by chiral chromatography as the absolute stereochemistry of vorapaxar is believed to be important for PAR-1 potency.[11]

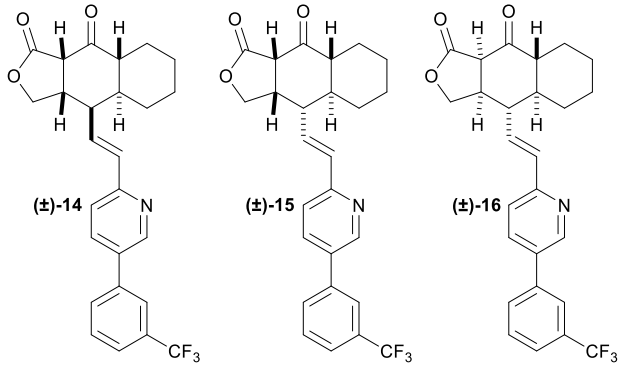


Fig. 3 Racemic novel vorapaxar analogues **(±)-14-16**

The results of the synthetic efforts gave 10 key compounds which were tested in a biological assay to determine their potency against PAR-1 (Figures 2-5, Table 1). The assay was based on monitoring PAR-1 induced calcium flux in response to thrombin using FLIPR.[12] The novel analogues showed concentration-dependent antagonism in human lung fibroblasts *vs.* 10 nM thrombin as the agonist. The academic tool, RWJ-58259,[13] was used as a positive control and for a potency comparator.

Enantiopure compounds **8-11** were tested initially (Figure 4). The most potent of these analogues, compound **9**, gave an IC_{50} of 0.5 µM. This meant that it had a similar potency to that of RWJ-58259 (IC_{50} = 0.17 µM). Unfortunately, the potencies of the compounds did not quite match that of vorapaxar (IC_{50} = 13 nM, in this assay). It was interesting to note that the hydroxyl-analogues (IC_{50}: **10** = 72 µM and **11** = 120 µM) were less potent than the keto-analogues (IC_{50}: **8** = 10.5 µM and **9** = 0.5 µM), indicating that the sp2 *vs.* sp3 hybridisation at C-9 was not critical to activity, and that (if anything) sp2 hybridisation may be moderately preferred.

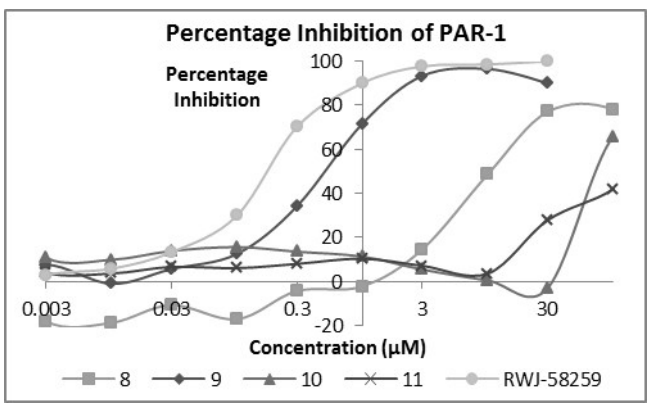


Fig. 4 The average (n = 6) percentage inhibition observed upon the addition of thrombin (10 nM) to human lung fibroblasts in buffer pre-incubated with Fluo-4 NW dye mix and 0.003 - 300 µM antagonist; Compounds **8**, **9**, **10**, **11** and RWJ-58259

Next, each of the enantiopure compounds obtained from **(±)-14-15**, were tested. In all cases, the compounds failed to reach 100% inhibition at a concentration of 30 µM. The concentration range was not extended to 300 µM, as seen with the compounds **8-11**, because solubility issues were starting to be observed at 30 µM. As seen in the vorapaxar literature, one enantiomer was shown to be more potent than its pair (IC_{50}: **(-)-14** = 2.4 µM, **(+)-14** = 15 µM, **(-)-15** = 0.1 µM and **(+)-15** = 7.5 µM).[11] In this series, the most potent compound (*i.e.* **(-)-15**) was slightly more potent than both compound **9** and RWJ-58259.‡

Finally, the analogues with distinct tricycle ring juncture stereochemistry, *i.e.* **(+)-16** and **(–)-16**, were tested (Figure 5). The enantiomeric pair derived from compound **16** had vastly distinct potencies (Figure 5). Compound **(-)-16** with an IC_{50} of 27 nM was the most potent of all of the compounds tested. It was more potent than RWJ-58259 (IC_{50} = 170 nM, in this assay) and approached the potency of vorapaxar (IC_{50} = 13 nM). Conversely, its enantiomeric partner (**(+)-16**) gave a *ca.* 100-fold increase in IC_{50}. This is one of the lowest potencies of the tested keto-analogues and 1000 times less potent than vorapaxar.‡

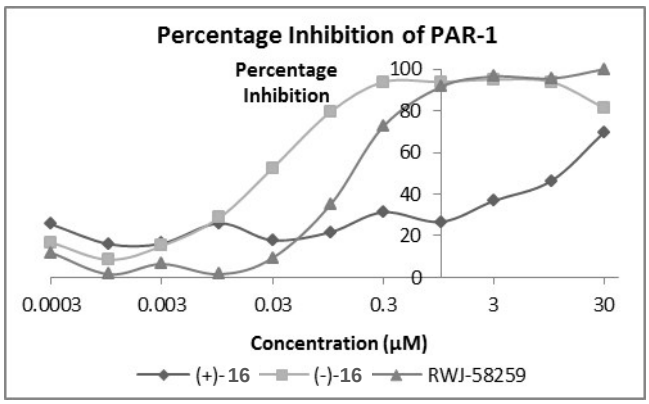


Fig. 5 The average (n = 6) percentage inhibition observed upon the addition of thrombin (10 nM) to human lung fibroblasts in buffer pre-incubated with Fluo-4 NW dye mix and 0.0003 - 30 µM antagonist; Compounds **(+)-16**, **(-)-16** and RWJ-58259

Table 1 IC_{50} values of vorapaxar, all vorapaxar analogues and RWJ-58259

Compound	IC_{50} (µM)[a]
Vorapaxar	0.013
8	10.5
9	0.5
10	72
11	120
(+)-14	15
(-)-14	2.4
(+)-15	7.5
(-)-15	0.1
(+)-16	13
(-)-16	0.027
RWJ-58259	0.17

[a] See ESI for details on biological assay used to determine these values.

Conclusions

In conclusion, an enantioselective route to himbacine-like tricycles has been adapted and developed to give a number of novel vorapaxar analogues which were tested biologically. The nanomolar potency found with compound **(–)-16** is very significant because the novel scaffold has the potential for further growth to investigate the SAR of vorapaxar, a first-in-class

PAR-1 antagonist drug. Whilst there is excellent recent work on C-7-spirocyclic analogues of vorapaxar,[14] and examples of functionalisation at other positions on the core, to the best of our knowledge these are the first PAR-1 active vorapaxar analogues with substitution at the C-9 position or with the differing relative stereochemistry on the tricycle. Consequently, especially with readily functionalisable groups at the C-9 position, there is the prospect of developing further novel and potent PAR-1 inhibitors which could be used for the treatment of cancer and various fibrotic diseases.

Experimental section

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 μm) 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 μm) 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 (MgSO4), 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.

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

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, $C^{8}HH$), 1.84-1.72 (4H, m, $C^{4a}H$, $C^{5}HH$, $C^{6}HH$ & $C^{7}HH$), 1.50 (9H, s, $C(CH_3)_3$), 1.42 (3H, d, J = 6.0, $C^{3}HCH_3$), 1.33-1.23 (2H, m, $C^{5}HH$ & $C^{8}HH$), 1.22-1.14 (2H, m, $C^{6}HH$ & $C^{7}HH$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 204.0 ($C^{9}O$), 172.0 ($COO^{t}Bu$), 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 ($C(CH_3)_3$), 25.7 ($C^{8}H_2$), 25.5 ($C^{6}H_2$), 25.0 ($C^{7}H_2$), 19.1 ($C^{3}HCH_3$); 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, $C^{3}HMe$), 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, $C^{4a}H$, $C^{5}HH$ & $C^{8}HH$), 1.84-1.80 (1H, m, $C^{6}HH$), 1.75-1.71 (1H, m, $C^{7}HH$), 1.48 (9H, s, $C(CH_3)_3$), 1.36 (3H, d, J = 6.0, $C^{3}HCH_3$), 1.39-1.34 (1H, m, $C^{8}HH$), 1.26-1.17 (2H, m, $C^{6}HH$ & $C^{7}HH$), 1.13-1.05 (1H, m, $C^{5}HH$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.0 ($C^{9}O$), 171.6 ($COO^{t}Bu$), 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 ($C(CH_3)_3$), 25.1 ($C^{8}H_2$), 24.9 ($C^{6}H_2$), 24.8 ($C^{7}H_2$), 20.3 ($C^{3}HCH_3$); 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%, $[M-C_4H_9]^+$); 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 (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, $C^{3}HMe$), 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, $C^{8}HH$), 1.87-1.82 (1H, m, $C^{5}HH$), 1.81-1.74 (2H, m, $C^{6}HH$ & $C^{7}HH$), 1.42 (3H, d, J = 6.0, $C^{3}HCH_3$), 1.40-1.36 (1H, m, $C^{5}HH$), 1.31-1.21 (3H, m, $C^{6}HH$, $C^{7}HH$ & $C^{8}HH$); ^{13}C NMR (150 MHz, MeOH-d_4) δ 206.3 ($C^{9}O$), 176.3 ($COOH$), 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 ($C^{3}HCH_3$); 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.

(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, $C^{3}HMe$), 3.73 (1H, d, J = 8.7, $C^{9a}H$), 2.96 (1H, q, J = 6.5, $SCHHCH_3$), 2.92 (1H, q, J = 6.5, $SCHHCH_3$), 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, $C^{8}HH$), 1.86-1.74 (4H, m, $C^{4a}H$, $C^{5}HH$, $C^{6}HH$ & $C^{7}HH$), 1.44 (3H, d, J = 6.0, $C^{3}HCH_3$), 1.40-1.32 (1H, m, $C^{5}HH$), 1.30 (3H, t, J = 7.3, SCH_2CH_3), 1.28-1.11 (3H, m, $C^{6}HH$, $C^{7}HH$ & $C^{8}HH$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.8 ($C^{9}O$), 200.3 ($COSEt$), 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 (CH_2CH_3), 18.9 ($C^{3}HCH_3$), 14.6 (CH_2CH_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.

(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*-CHO), 4.29 (1H, dq, J = 10.2, 6.0, 4*S*-$C^{3}HMe$), 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*-$C^{5}HH$ & 4*S*-$C^{8}HH$), 1.88-1.81 (2H, m, 4*S*-$C^{6}HH$ & 4*S*-$C^{7}HH$), 1.68 (1H, qd, J = 12.4, 3.4, 4*S*-$C^{5}HH$), 1.42 (3H, d, J = 6.0, $C^{3}HCH_3$), 1.36-1.32 (1H, m, 4*S*-$C^{8}HH$), 1.23-1.17 (2H, m, 4*S*-$C^{6}HH$ & 4*S*-$C^{7}HH$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.8 (4*S*-$C^{9}O$), 202.7 (4*S*-CHO), 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*-$C^{3}HCH_3$).

(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}HCH_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}HC*H*CHPyr), 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*$^5H_2$), 25.5 (*C*$^6H_2$), 25.4 (*C*$^8H_2$), 24.9 (*C*$^7H_2$), 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. 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}HCH_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}HC*H*CHPyr), 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), 123.8 (q, *J* = 3.8, C*C*HCCF_3), 124.1 (d, *J* = 271.7, *C*F_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*$^5H_2$), 25.3 (*C*$^6H_2$), 25.0 (*C*$^8H_2$), 24.8 (*C*$^7H_2$), 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.

(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, $C^{4a}H$, $C^{5}HH$ & $C^{8a}H$), 1.47 (1H, d, J = 6.0, $C^{3}HCH_3$),1.32-1.16 (4H, m, $C^{5}HH$, $C^{6}HH$, $C^{7}HH$ & $C^{8}HH$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.9 ($C^{1}O$), 154.6 (CN), 148.1 (CHN), 131.8 ($CCHCCF_3$), 131.5 ($CHCCHN$), 131.3 ($C^{4}HCHCHPyr$), 130.9 (q, J = 32.1, CCF_3), 130.3 ($C^{4}HCHCHPyr$ & $CHCCHCCF_3$), 129.9 ($CCHN$), 129.8 ($CHCHCCF_3$), 124.9 (q, J = 3.6, $CHCHCCF_3$), 123.8 (q, J = 3.6, $CCHCCF_3$), 124.1 (d, J = 272.1, CF_3), 121.6 ($CHCN$), 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 ($C^{3}HCH_3$); 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. 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, CHN), 7.85 (1H, dd, J = 8.1, 1.9, $CHCCHN$), 7.81 (1H, s, $CHCCF_3$), 7.76 (1H, d, J = 7.5, $CHCHCCF_3$), 7.66 (1H, d, J = 7.5, $CHCCHCCF_3$), 7.61 (1H, t, J = 7.9, $CHCHCCF_3$), 7.32 (1H, d, J = 8.3, $CHCN$), 6.87 (1H, dd, J = 15.4, 10.2, $C^{4}HCHCHPyr$), 6.52 (1H, d, J = 15.4, $C^{4}HCHCHPyr$), 4.74 (1H, dq, J = 10.5, 6.0, $C^{3}HMe$), 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, OH), 1.92 (1H, tt, J = 11.7, 4.5, $C^{4a}H$), 1.78-1.70 (2H, m, $C^{6}HH$ & $C^{7}HH$), 1.59-1.54 (3H, m, $C^{5}HH$, $C^{8}HH$ & $C^{8a}H$), 1.51-1.44 (1H, m, $C^{8}HH$), 1.44 (3H, d, J = 6.0, $C^{3}HCH_3$), 1.31-1.19 (3H, m, $C^{5}HH$, $C^{6}HH$ & $C^{7}HH$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 177.4 ($C^{1}O$), 154.7 (CN), 148.1 (CHN), 138.6 ($CCHCCF_3$), 135.4 ($C^{4}HCHCHPyr$), 135.1 ($CHCCHN$), 133.7 ($CCHN$), 131.7 (q, J = 32.1, CCF_3), 130.8 ($C^{4}HCHCHPyr$), 130.3 ($CHCCHCCF_3$), 129.8 ($CHCHCCF_3$), 124.8 (q, J = 4.0, $CHCHCCF_3$), 123.8 (q, J = 4.0, $CCHCCF_3$), 124.1 (d, J = 271.7, CF_3), 121.9 ($CHCN$), 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 ($C^{3}HCH_3$); 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.

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 ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.22 (1H, d, J = 3.8, $C^{3}HH$), 4.21 (1H, s, $C^{3}HH$), 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, $C^{8}HH$), 1.99 (1H, ddd, J = 12.0, 10.7, 3.6, $C^{8a}H$), 1.82-1.66 (4H, m, $C^{4a}H$, $C^{5}HH$, $C^{6}HH$ & $C^{7}HH$), 1.48 (9H, s, $C(CH_3)_3$), 1.46-1.41 (1H, m, $C^{8}HH$), 1.25-1.12 (3H, m, $C^{5}HH$, $C^{6}HH$ & $C^{7}HH$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.9 ($C^{9}O$), 172.4 ($COO^{t}Bu$), 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 ($C(CH_3)_3$), 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, $C^{3}HH$), 3.94 (1H, t, J = 9.8, $C^{3}HH$), 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, $C^{8}HH$), 1.85 (1H, tdd, J = 12.0, 4.5, 3.4, $C^{4a}H$), 1.84-1.76 (3H, m, $C^{5}HH$, $C^{6}HH$ & $C^{7}HH$), 1.50 (9H, s, $C(CH_3)_3$), 1.49-1.42 (1H, m, $C^{8}HH$), 1.36-1.15 (3H, m, $C^{5}HH$, $C^{6}HH$ & $C^{7}HH$); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.8 ($C^{9}O$), 172.0 ($COO^{t}Bu$), 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 ($C(CH_3)_3$), 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.

(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, $C^{3}HH$), 4.05 (1H, dd, J = 9.8, 9.2, $C^{3}HH$), 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, $C^{8}HH$), 1.98 (1H, dddd, J = 13.2, 12.0, 4.9, 3.0, $C^{4a}H$), 1.87-1.82 (1H, m, $C^{5}HH$), 1.82-1.75 (2H, m, $C^{6}HH$ & $C^{7}HH$), 1.44-1.35 (1H, m, $C^{5}HH$), 1.32-1.21 (3H, m, $C^{6}HH$, $C^{7}HH$ & $C^{8}HH$); ^{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.

***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.

***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^5HH), 1.23-1.15 (2H, m, C^6HH & C^7HH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.8 (C^9O), 171.6 (C^1O), 154.0 (*C*N), 148.2 (*C*HN), 138.4 (*C*CHCCF$_3$), 135.3 (*C*HCCHN), 134.2 (*C*CHN), 132.7 (C^4HCHCHPyr), 132.4 (C^4HCHCHPyr), 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^3H_2), 52.5 ($C^{9a}H$), 48.5 ($C^{8a}H$), 43.5 ($C^{3a}H$), 42.1 (C^4H), 41.6 ($C^{4a}H$), 31.7 (C^5H_2), 25.8 (C^8H_2), 25.5 (C^6H_2), 25.0 (C^7H_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). 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**): ^1H 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^4HCHCHPyr), 6.49 (1H, dd, *J* = 15.4, 9.8, C^4HCHCHPyr), 4.43 (1H, dd, *J* = 9.0, 8.3, C^3HH), 4.15 (1H, dd, *J* = 11.7, 9.0, C^3HH), 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^4H), 2.21 (1H, td, *J* = 11.7, 3.0, $C^{8a}H$), 2.00-1.93 (2H, m, C^5HH & C^8HH), 1.87-1.82 (1H, m, C^7HH), 1.75 (2H, qd, *J* = 11.3, 3.4, $C^{4a}H$ & C^6HH), 1.49-1.40 (1H, m, C^8HH), 1.28-1.15 (2H, m, C^6HH & C^7HH), 1.13-1.05 (1H, m, C^5HH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.8 (C^9O), 171.7 (C^1O), 153.9 (*C*N), 148.2 (*C*HN), 138.4 (*C*CHCCF$_3$), 135.2 (*C*HCCHN), 134.2 (*C*CHN), 133.2 (C^4HCHCHPyr), 132.4 (C^4HCHCHPyr), 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^3H_2), 54.7 ($C^{9a}H$), 52.9 ($C^{8a}H$), 45.3 (C^4H), 44.6 ($C^{3a}H$), 42.9 ($C^{4a}H$), 33.0 (C^5H_2), 25.2 (C^8H_2), 24.9 (C^6H_2), 24.8 (C^7H_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).

(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^3HH), 4.27 (1H, dd, *J* = 9.8, 4.5, C^3HH), 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^4H), 2.19-2.12 (1H, m, C^8HH), 2.06- 2.01 (1H, m, $C^{8a}H$), 1.89-1.82 (2H, m, C^6HH & C^7HH), 1.81-1.73 (2H, m, C^5HH & $C^{4a}H$), 1.26-1.18 (4H, m, C^5HH, C^6HH, C^7HH & C^8HH); ^{13}C NMR (150 MHz, $CDCl_3$) δ 201.5 (C^9O), 177.5 (*C*OOH), 171.2 (C^1O), 70.6 (C^3H_2), 53.2 ($C^{9a}H$), 51.1 (C^4H), 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.

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

EDCl (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; ^1H NMR (600 MHz, $CDCl_3$) δ 4.38 (1H, d, *J* = 9.6, C^3HH), 4.18 (1H, dd, *J* = 9.6, 4.7, C^3HH), 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, CH_2CH_3), 2.70 (1H, t, *J* = 11.1, C^4H), 2.15-2.10 (1H, m, C^8HH), 2.02 (1H, td, *J* = 11.2, 3.2, $C^{8a}H$), 1.85-1.69 (4H, m, $C^{4a}H$, C^5HH, C^6HH & C^7HH), 1.30-1.27 (3H, m, CH_2CH_3), 1.27-1.09 (4H, m, C^5HH, C^6HH, C^7HH & C^8HH); 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.

***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.

(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 (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).

Notes and references

[a] *Department of Chemistry, University College London, 20 Gordon Street, London, WC1H 0AJ, UK. E-mails: v.chudasama@ucl.ac.uk and s.caddick@ucl.ac.uk.*
[b] *Centre for Inflammation and Tissue Repair, 5 University Street, London WC1E 6JJ.*
[c] *GSK, Gunnels Wood Road, Stevenage, Herts SG1 2NY.*

† Electronic Supplementary Information (ESI) available: [^{1}H and ^{13}C NMR spectra of all novel compounds]. See DOI: 10.1039/b000000x/

‡ Without any information on the absolute stereochemistry of either enantiomer of any one of **14**-**16** it is not appropriate to postulate as to what is the precise structure of each enantiomer.

1 M. J. Krantz and S. Kaul, *JAMA Internal Medicine*, 2015, **175**, 9-10.
2 P. F. Mercer and R. C. Chambers, *Biochim Biophys Acta.*, 2013, **1832**, 1018-1027.
3 M. Casey and R. McCarthy, *Synlett*, 2011, **06**, 801-804.
4 M. Yamaguchi, M. Tsukamoto and I. Hirao, *Tetrahedron Lett.*, 1985, **26**, 1723-1726.
5 C. Harcken, R. Brückner and E. Rank, *Chem. Eur. J.*, 1998, **4**, 2342-2352.
6 Y. Xia, S. Chackalamannil, M. Clasby, D. Doller, K. Eagen, W. J. Greenlee, H. G. Tsai, J. Agans-Fantuzzi, H. S. Ahn, G. C. Boykow, Y. S. Hsieh, C. A. Lunn and M. Chintala, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4509-4513.
7 T. Fukuyama, S. C. Lin and L. Li, *J. Am. Chem. Soc.*, 1990, **112**, 7050-7051.
8 M. C. Clasby, S. Chackalamannil, M. Czarniecki, D. Doller, K. Eagen, W. Greenlee, G. Kao, Y. Lin, H. Tsai, Y. Xia, H. S. Ahn, J. Agans-Fantuzzi, G. Boykow, M. Chintala, C. Foster, A. Smith-Torhan, K. Alton, M. Bryant, Y. Hsieh, J. Lau and J. Palamanda, *J. Med. Chem.*, 2007, **50**, 129-138.
9 S. Chackalamannil, Y. Wang, W. J. Greenlee, Z. Hu, Y. Xia, H. S. Ahn, G. Boykow, Y. Hsieh, J. Palamanda, J. Agans-Fantuzzi, S. Kurowski, M. Graziano, M. Chintala, *J. Med. Chem.*, 2008, **51**, 3061-3064.
10 Y. Xia, S. Chackalamannil, T. M. Chan, M. Czarniecki, D. Doller, K. Eagen, W. Greenlee, H. Tsai, Y. Wang, H. S. Ahn, G. Boykow, A. T. McPhail, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 4969-4972
11 S. Chackalamannil, Y. Xia, W. J. Greenlee, M. Clasby, D. Doller, H. Tsai, T. Asberom, M. Czarniecki, H. S. Ahn, G. Boykow, C. Foster, J. Agans-Fantuzzi, M. Bryant, J. Lau and M. Chintala, *J. Med. Chem.*, 2005, **48**, 5884-5887.
12 (a) K. S. Schroeder and B. D. Neagle, *J. Biomol. Screen.*, 1996, **1**, 75-80; (b) A. Ortiz-Stern, X. Deng, N. Smoktunowicz, P. F. Mercer and R. C. Chambers, *J. Cell. Physiol.*, 2012, **227**, 3575-3584.

13 B. P. Damiano, C. K. Derian, B. E. Maryanoff, H. C. Zhang and P. A. Gordon, *Cardiovasc. Drug Rev.*, 2003, **21**, 313-326.
14 M. V. Chelliah, K. Eagen, Z. Guo, S. Chackalamannil, Y. Xia, H. Tsai, W. J. Greenlee, H.-S. Ahn, S. Kurowski, G. Boykow, Y. Hsieh and M. Chintala, *ACS Med. Chem. Lett.*, 2014, **5**, 561-565 and references therein.