Formation and reactions of azepino[4,5-*b*]indoles: an unprecedented ozone reaction in the formation of novel benzo[*c*]naphthyridinones†

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Herein we report the formation and interesting reactivity of several azepino[4,5-*b*]indole heterocycles. Initially, a key intramolecular Heck reaction is used to efficiently create the azepino[4,5-*b*]indole seven membered ring containing an exocyclic double bond. Treatment of the olefin with ozone results in an unprecedented secondary reaction of the Criegee intermediate, through intramolecular olefin trapping, to afford a benzo[*c*]naphthyridione containing a bridging cyclic peroxide.

Introduction

The azepino[4,5-*b*]indole ring system, containing a seven membered C ring, has recently been found in several new natural products such as arboflorine (**1**) and subincanadine F (**2**) (Fig. 1).[1,2] This ring system is widely represented in the iboga class of alkaloids (*e.g.*, ibogamine **3**), many exhibiting interesting biological activity. More recently, several reports have indicated that less functionalised versions of these [6,5,7] ring systems are potent agonists of the farnesoid X receptor (FXR).[3,4] Conventionally, these heterocyclic systems have been produced *via* key reactions such as Fischer indole synthesis,[5–7] Pictet–Spengler reaction (through the chloromethyl tetrahydro-β-carbolines),[8] radical oxidative aromatic substitution,[9] gold catalysed cyclisation,[10] electrocyclic ring closure[11] and Friedel–Crafts acylation.[12] Additionally, some of these key ring forming reactions have been used to target complex systems such as the naturally occurring iboga alkaloids.[13]

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Recently, we reported a novel domino Tsuji/Trost–Heck reaction for the formation of the seven membered ring systems including the azepino[4,5-*b*]indole **5** and 3-benzazepines (Fig. 1).[14] In these studies we have been able to create exclusively the seven membered C-ring with an exocyclic olefin from the corresponding halogenated precursor **4** (Fig. 1).

While the advantages of domino transformations, including the potential to save solvents, reagents, time and energy are clear,[15] the benefits of using an intramolecular Heck reaction in the synthesis of bioactive natural products such as **1** and **2** were left unexplored in our earlier report.[14] An approach through a more substituted or complex Heck precursor, has the potential to provide more advanced products through what would be considered a reasonably convergent synthesis. Alternatively, another pathway for further functionalisation and/or ring formation in a system like compound **5** is through a chemoselective transformation at the exocyclic olefin. Oxidation or oxidative cleavage at this point was envisaged as a possible starting point. However, in many instances the reaction of this olefin would compete with the reaction with a similar transformation at the reactive C2–C3 π-system of the indole ring. Such strongly oxidising rearrangements have been observed earlier by the groups of Cook and Le Quesne (Scheme 1),[16,17] where, upon treatment with OsO_4, an eventual pinacol rearrangement is proposed leading to oxindoles containing

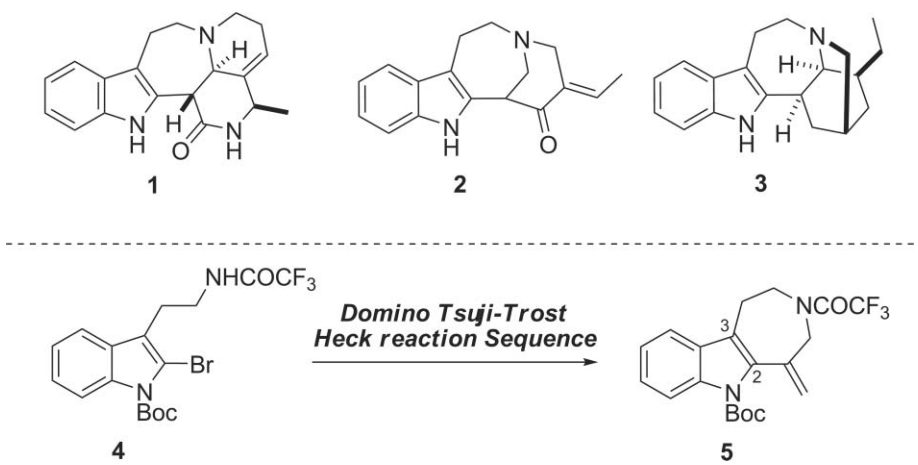
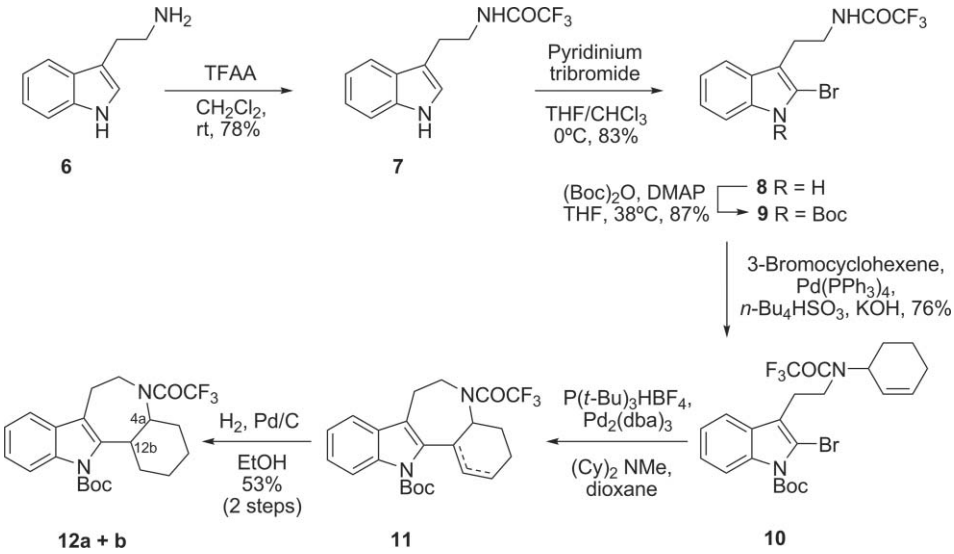


Fig. 1 Azepino[4,5-*b*]indole containing natural products (**1–3**) and a domino sequence for the synthesis of the azepino[4,5-*b*]indole ring system.



Scheme 1 Synthesis of the indolo[3,2-*d*][1]benzazepine ring system **11** and **12** through Tsuji–Trost Heck Approach.

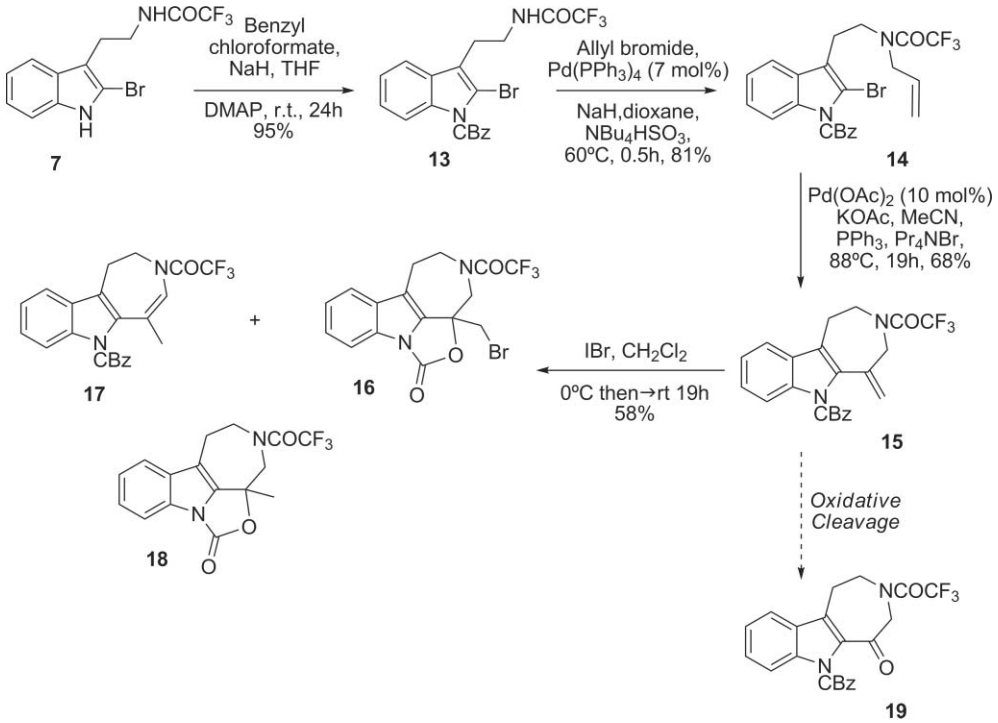
a spiro C3 attachment.[17] Nevertheless, in some instances the regioselectivity in indole derivatives upon treatment with OsO_4 has been observed for tethered olefins over C2–C3.[18] Similarly, ring expansion mediated by singlet oxygen, has been reported through indole based dioxetane intermediates[19] whilst reactions with Oxone™ have been used to produce the 3-hyrdroxyindoline.[20] Like the osmium tetroxide counterpart reaction[16] the indole ring system at C2–C3 is also prone to reaction with ozone. In uncomplicated systems the ring is simply cleaved to give a formylaminobenzaldehyde derivative.[21]

The synthesis of more advanced azepino[4,5-*b*]indoles systems, through our Tsuji–Trost allylation and Heck cross coupling approach, was investigated to include an additional cyclohexyl ring (Scheme 1). As previously, tryptamine (**6**) was treated with trifluoroacetic anhydride to afford the protected amide **7** in (78% yield). This compound was selectively brominated at C2 using pyridinium tribromide to furnish compound **8** in excellent yields (83%). Protection of the indole nitrogen using boc-anhydride gave the desired carbamate **9** (78%). Treatment of compound **9** under Tsuji–Trost allylation conditions ($Pd(PPh_3)_4$, NBu_4HSO_3, KOH) and 3-bromocyclohexene gave compound **10** containing the tethered unsaturated ring system (76%). The Heck reaction, P(*t*-Bu)$_3$HBF$_4$, $Pd_2(dba)_3{\cdot}CHCl_3$, $(Cy)_2NMe$ in dioxane, of compound **10** then afforded the tetracycle **11**.[22,23] Interestingly, such a ring system in this simple form has to date been reported in the literature only once.[24] Unfortunately, accompanying the standard Heck cross coupling pathway, resulting from initial β-hydride elimination, was additional double bond migration. Thus, the mixture of products **11** were isolated following standard chromatography conditions as an inseparable regioisomeric mixture. Subsequent hydrogenation of **11** afforded compound **12** as a 1 : 1 diastereomeric mixture at H4a–H12b, in 53%, over two steps. In this synthetic approach we have efficiently produced the protected indolo[3,2-*d*][1]benzazepine ring system **12** in 23% overall yield from tryptamine **6**. To these ends we consider this pathway, involving structural variation of the Heck precursor through allylation, to be viable option in the pursuit of complex indole based natural products.

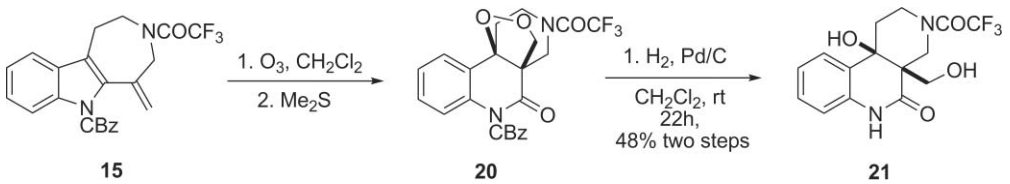
In the case of the simple azepino[4,5-*b*]indole ring system **5** the exocylic double bond was also investigated as a point for attachment of a D ring, possibly in a synthetic approach towards natural products **1** and **2**. In order to minimise the reactivity of the C2–C3 bond, electronically and possibly sterically, the CBz protecting group was chosen for the indole nitrogen. Thus, treatment of compound **7** with benzyl chloroformate, under standard conditions, afforded the *N*-CBz indole compound **13** (95%, Scheme 2). Subjection of this latter compound to allylation (allyl bromide, $Pd(PPh_3)_4$, NaH, 1,4-dioxane, NBu_4HSO_3) and a subsequent Heck reaction furnished the desired azepinoindole **15** scaffold in good yields (58%, over 2 steps). To further examine the reactivity of the terminal methylene moiety within compound **15** a solution of IBr was added. In this instance the isomer **17** and tetracycle **18**[25] were isolated in higher yields than expected, along with the expected compound **16**. The latter compound presumably a result of formation of the bromonium ion, sequential deprotection and ring closure.

Encouraged by the regioselectivity for the exocyclic double bond seen in the halogenation reaction we turned our attention to standard oxidative cleavage of compound **19**. Early attempts, treatment of **15** with oxidative cleavage reagent combinations like $NaIO_4/OsO_4$, $KMnO_4$/THF, $KMnO_4$/18-crown-6/benzene failed to cleave the exocyclic double bond and some cases only resulted in recovery of starting material. The $RuCl_3$ catalytic system,[26] however, proved too reactive and a complex mixture of compounds, presumably through several oxidation steps, was observed. Finally, we turned our attention to ozone mediated oxidative cleavage as seen in other indole systems with a remote olefin.[18] The rapid reaction that followed upon treatment with ozone, to our surprise, yielded the tetracyclic compound **20**, containing a benzo[*c*][2,7]naphthyridinone ring system (Scheme 3).

The overall *N*-heterocyclic skeletal structure of **20** was determined by a combination of NMR techniques including GCOSY, HSQC and HMBC. The presence of an 1,2-dioxolane was indicated from the chemical shifts of the ^{13}C nuclei directly attached to oxygen (82.2 and 82.1 ppm for C1, 75.2 and 74.5 ppm for C17)[23] and the ^{1}H NMR chemical shift of the OO–CH_2 protons



Scheme 2 Formation of CBz protected azepino[4,5-*b*]indole ring system **15** and subsequent halogenation reaction.



Scheme 3 Ozone mediated formation of benzo[*c*][2,7]naphthyridinone **21**.

(4.25–4.1 ppm),[23] which were typical of a 1,2-dioxolane.[27,28] Additionally, the IR spectra did not indicate any signals reserved for the presence of hydroxyl groups or a oxetane ring system (typically oxetanes show a strong absorbance at around 980–970 cm^{-1} due to ring breathing) which further indicated a 1,2-dioxolane.[29] Additionally, a positive peroxide test (starch, 10% KI soln) and a molecular ion $M^{+\cdot}$ of 476.1 provided further information.

In an effort to gauge the efficiency of this initial reaction the crude workup material following ozonolysis was treated with hydrogen and Pd/C resulting in the cleavage of the *O–O* bond and hydrogenolysis of the CBz group to afford diol **21** (48% over two steps). A single crystal X-ray structure determination further confirmed the structure of compound **21** (Fig. 2) along with other key spectroscopic techniques confirming the existence of two new hydroxyl groups and the tricyclic ring system.

A mechanism for the ozone mediated ring rearrangement is proposed in Scheme 4. Mechanisms involving a direct formation of ozonide **22** or the equivalent trioxolane (Pathway A) were initially considered; however, even after the formation of an oxindole C3 spiro compound, a pathway to the bridged peroxide was difficult to envisage.[16,17] Having eliminated Pathway A and suggesting ozone does not initially react with the exocylcic olefin, a second pathway through reaction at C2–C3 was considered. In

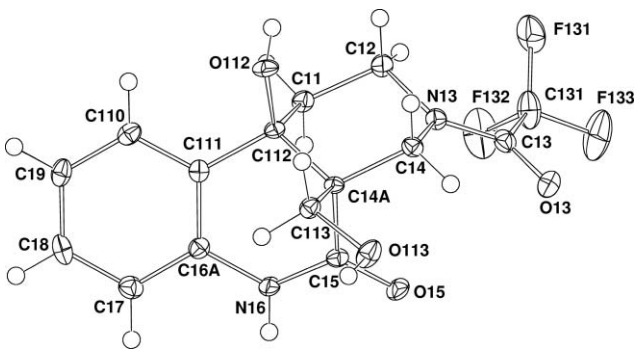
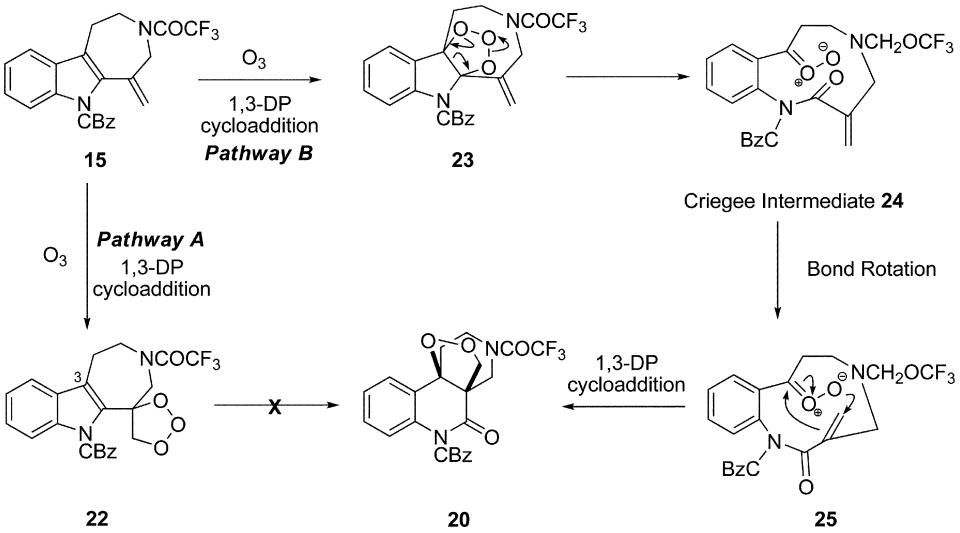


Fig. 2 Molecular structure of compound **21**. The non-hydrogen atoms are drawn as 50% ellipsoids.

this pathway (Pathway B), an initial formation of ozonide **23** is proposed.[30] The Criegee intermediate **24** formed from the ozonide exposes a carbonyl oxide moiety as well as a carbonyl group as part of an acrylamide. Surprisingly, the standard ozonolysis mechanism of a 1,3-dipolar cycloaddition of the carbonyl and the carbonyl oxide is in this case disfavoured, probably due to the less reactive and restricted nature of the carbonyl moiety. In our proposed mechanism, bond rotation (to conformer **25**) places the acrylate olefin in a more fortuitous position for a 1,3-dipolar



Scheme 4 Proposed mechanism for the formation of the benzo[*c*][2,7]naphthyridinone **20** containing a cyclic peroxide.

cycloaddition, to form the observed cyclic peroxide **20**. To our knowledge, the intramolecular or internal trap of this Criegee intermediate with an alternative 1,3-dipolar cycloaddition is new, where most systems with two olefinic moieties each undergo a reaction with an equivalent of ozone.[31] The group of Kuczkowski, however, has reported the intermolecular reaction of carbonyl oxides generated from enol ethers, with unreacted enol ether to give 1,2-dioxolanes.[32]

Interestingly, the hexahydro benzo[*c*][2,7]naphthyridinone ring system found in **20** and **21** is rarely reported in the literature.[33, 34] Furthermore, the cyclic peroxide moiety within **20** adds to the structural complexity of this molecule. Such stable 1,2-dioxolane cyclic peroxides of this nature are being sought for their possible activity against *Plasmodium falciparum* in the search for new antimalaria compounds.[35]

Conclusion

In this work we have investigated the formation and reaction of new azepino[4,5-*b*]indoles scaffolds through a Tsuji–Trost and Heck cross coupling approach. In one of these ring systems, bearing an exocyclic methylene, we have observed an unprecedented ozone promoted formation of the hexahydro benzo[*c*][2,7]naphthyridinone ring system. In this heterocyclic ring forming process, we propose a unique mechanism involving an unprecedented 1,3-dipolar cycloaddition of the Criegee intermediate.

Experimental

General

All reactions were performed in flame dried glassware under an argon atmosphere unless stated otherwise. Solvents were dried and purified according to the method defined by Armarego and Chai, unless stated otherwise.[36] All reactions involving heating were immediately placed in an oil bath preheated to the specified temperature. All palladium mediated cross coupling reactions were carried out using degassed solvents or degassed using the freeze, pump, thaw method. Ozone was generated using a Welsbach laboratory ozonator model T-408 fed with pure oxygen operating at 1 L min^{-1} flow rate, 4.4 psi internal pressure and with the input voltage to the high voltage transformer set to 75 V. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F_{254}, pre-coated aluminium sheets. Visualisation of developed plates was achieved through the use of a 254 nm or 365 nm UV lamp or staining with phosphomolybdic acid. Column chromatography was performed using silica gel 60 (0.063–0.200 mm), as supplied by Merck, with the eluents indicated. HPLC was performed with a Grace-Apollo 250 × 10 mm, 5 micron, C18 semi-preparative column coupled to a UV detector. Proton (^{1}H) and carbon (^{13}C) NMR spectra were acquired on either a Bruker Advance (AV) 500 Spectrometer (500.13 MHz, 125.8 MHz, for ^{1}H and ^{13}C, respectively) at 25 °C or a Bruker Advance (AV) 600 Spectrometer (600.1 MHz and 150.9 MHz for ^{1}H and ^{13}C, respectively) at 25 °C. For ^{1}H and ^{13}C, $CDCl_3$ and [D_6]acetone were used as solvents. Chemical shift are reported on a δ scale in ppm. Signals are quoted as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). ^{13}C assignments were aided with the use of DEPT135 analysis.[23] Mass spectra were acquired on a VG AutoSpec instrument through electron impact ionisation (EI). HRMS was performed with a resolution of approximately 10 000. Infrared (IR) spectra were recorded with a PerkinElmer Spectrum One Spectrometer FT-IR spectrometer. Samples were analysed as thin films on NaCl discs, $CHCl_3$ solution between NaCl plates or pressed KBr plates.

tert-Butyl 2-bromo-3-{2-[cyclohex-2-en-1-yl(trifluoroacetyl) amino]ethyl}-1*H*-indole-1-carboxylate (10)

Toluene (7 mL) was added to a Schlenk flask followed by powdered KOH (156 mg, 2.78 mmol), *n*-Bu_4NHSO_4 (45.0 mg, 0.13 mmol), bromide (**9**) (300 mg, 0.69 mmol) and the mixture was stirred for 10 min. 3-bromocyclohexene (201 μL, 0.28 g, 1.75 mmol) was then added followed by $Pd(PPh_3)_4$ (90 mg, 0.08 mmol, 11 mol%) and the mixture was heated to 60 °C for 2.7 h. The reaction mixture was cooled to 0 °C, water (5 mL) was added slowly and the ensuing solution stirred rapidly for 5 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2

(3 × 5 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was subjected to flash chromatography (1 : 1 toluene/hexanes → 65 : 35 toluene/hexanes) to afford compound **10** (263 mg, 76% yield) as a colourless oil (R_f 0.7, in acetone/toluene 5 : 95). ^{1}H NMR (500.13 MHz, [D_6]acetone): δ = 8.11-8.05 (m, 1 H, ArH), 7.73-7.67 (m, 0.85 H, ArH), 7.55-7.50 (m, 0.15 H, ArH), 7.35-7.25 (m, 2H, ArH), 6.05-5.96 (m, 1H, C*H*=CH), 5.75-5.70 (m, 0.15H, CH=C*H*), 5.55 (d, J = 10.7 Hz, 0.85H, CH=C*H*), 5.0-4.9 (m, 0.15 H, CH=CH–C*H*), 4.55 (brs, 0.85H, CH=CH–C*H*), 3.65-3.55 (m, 0.3H, CH_2), 3.50-3.35 (m, 1.70H, CH_2), 3.15-3.00 (m, 2H, CH_2), 2.2-1.6 (m, 15H, 3×CH_2 + 3×CH_3); ^{13}C NMR (125.8 MHz, [D_6]acetone): δ = 157.3 (q, J = 35.1 Hz, *C*OCF$_3$), 149.6, 149.5 (C=O), 137.4 (C-Ar), 134.2, 132.7 (*C*H=CH), 129.5, 129.1 (C-Ar), 127.8, 127.2 (CH-Ar), 125.53, 125.49 (CH-Ar), 124.0, 123.9 (CH=*C*H), 121.0, 119.9 (C-Ar), 119.3, 118.8 (CH-Ar), 117.7 (q, J = 287.3, CF_3), 116.1, 116.0 (CH-Ar), 110.5, 110.2 (C-Ar), 85.9, 85.7 (O–C), 55.8 (q, J = 3.5 Hz), 55.6 (CH), 44.5 (q, J = 3.1 Hz), 43.7 (CH_2), 28.3 (3×CH_3), 29.2, 27.5, 27.4, 25.2, 24.9, 24.5 (3×CH_2), 22.3, 22.0 (CH_2); HR-EIMS: calcd. for $C_{23}H_{26}BrF_3N_2O_3$ 516.1058 and 514.1078; found 516.1062 and 514.1084; IR (neat): ν_{max} = 2938, 1738, 1683, 1448, 1351, 1315, 1209, 1152, 1044, 759 cm^{-1}.

tert-Butyl *rel*-(4a*R*, 12b*S*)-5-(trifluoroacetyl)-2,3,4,4a,5,6,7,12b-octahydroindolo[3,2-*d*][1]benzaepine-12(1*H*)-carboxylate (12a) and *tert*-butyl *rel*-(4a*R*,12b*R*)-5-(trifluoroacetyl)-2,3,4,4a,5,6,7,12b-octahydroindolo[3,2-*d*][1]benzazepine-12(1*H*)-carboxylate (12b)

$Pd_2(dba)_3$·$CHCl_3$ (14.0 mg, 0.013 mmol, 10 mol%) was added to a flask under argon containing (**10**) (70.0 mg, 0.13 mmol) followed by P(*t*-Bu)$_3$HBF$_4$ (8.0 mg, 0.027 mmol). 1,4-Dioxane (2 mL) was then added *via* syringe followed by *N*,*N*-dicyclohexylmethylamine (72.0 µL, 65.6 mg, 0.33 mmol). The mixture was heated to 100 °C for 6 h with continuous stirring. The mixture was allowed to cool to ambient temperature and concentrated *in vacuo*. The resulting material was subjected to flash chromatography (1 : 1 toluene/hexanes → 65 : 35 toluene/hexanes). Fractions from R_f ≈ 0.6 to 0.3 (acetone/toluene, 2 : 98) were combined to afford a crude mixture of double bond regioisomers (45 mg). This mixture was immediately dissolved in EtOH (4 mL) and Pd/C 10% (7 mg) was added with continuous stirring under H_2 at rt for 18 h. The mixture was concentrated under reduced pressure and filtered through a plug of silica (hexanes → 5 : 95 EtOAc/hexanes) to afford an otherwise pure mixture of **12a** and **12b**. This mixture was separated by using semi-preparative HPLC (MeCN–H_2O, 85 : 15, 4 mL min^{-1}).

12b

A colourless oil (15 mg, 25% yield). R_t = 14 min. ^{1}H NMR (600.13 MHz, [D_6]acetone): δ = 8.05 (d, J = 8.3 Hz, 1H, HAr), 7.55 (d, J = 8.0 Hz, 1H, HAr), 7.25-7.17 (m, 2H, ArH), 4.50 (t, J = 11.1 Hz, 1H, CH), 4.02-3.92 (m, 3H, CH + CH_2), 3.45-3.35 (m, 1H, CH_2), 3.30-3.25 (m, 1H, CH_2), 2.65 (q, J = 11.1 Hz, 1H, CH_2), 2.23 (d, J = 12.9 Hz, 1H, CH_2), 1.95-1.85 (m, 2H, CH_2), 1.80-1.75 (m, 1H, CH_2), 1.71-1.65 (m, 9H, 3×CH_3), 1.55-1.45 (m, 2H, CH_2), 1.42-1.35 (m, 1H, CH_2); ^{13}C NMR (150.9 MHz, [D_6]acetone): δ = 157.2 (q, J = 34.2 Hz, *C*OCF$_3$), 151.0 (C=O), 139.4 (C-Ar), 137.0 (C-Ar), 130.4 (C-Ar), 124.6 (CH-Ar), 123.3 (CH-Ar), 118.5 (CH-Ar), 117.3 (q, J = 289.1 Hz, CF_3), 116.3 (CH-Ar), 113.7 (C-Ar), 84.8 (O–C), 61.2 (CH), 48.5 (CH), 42.0 (CH_2), 34.1 (CH_2), 29.7 (CH_2), 28.3 (3×CH_3), 27.0 (CH_2), 26.5 (CH_2), 20.9 (CH_2); HR-EIMS: calcd. for $C_{23}H_{27}F_3N_2O_3$ 436.1974; found 436.1976; IR ($CHCl_3$): ν_{max} = 2934, 1732, 1689, 1457, 1371, 1319, 1200, 1140, 1050, 753 cm^{-1}.

12a

A colourless oil (17 mg, 28% yield). R_t = 18 min. ^{1}H NMR (600.13 MHz, [D_6]acetone): δ = 8.1-8.0 (m, 1H, HAr), 7.44 (d, J = 7.7 Hz, 1H, HAr), 7.30-7.18 (m, 2H, HAr), 4.66 (br. s, 0.8H, CH), 4.57-3.67 (m, 2.2H, CH + CH_2), 4.3-4.2 (m, 1H, CH_2), 3.45-3.37 (m, 0.2H, CH_2), 3.22-3.14 (m, 0.8H, CH_2), 3.11-3.05 (m, 0.8H, CH_2), 2.94-2.89 (m, 0.2H, CH_2), 2.25-2.20 (m, 0.8H, CH_2), 2.29-1.88 (m, 3.2H, CH_2), 1.71-1.5 (m, 13H, 2×CH_2 + 3×CH_3); ^{13}C NMR (150.9 MHz, [D_6]acetone): δ = 156.1 (q, J = 34.8 Hz, *C*OCF$_3$), 150.5, 150.4 (C=O), 137.8, 137.0 (C-Ar), 136.1, 135.9 (C-Ar), 130.1, 129.9 (C-Ar), 124.2, 124.1 (CH-Ar), 122.6 (C-Ar), 117.9 (CH-Ar), 117.0 (q, J = 288.1, CF_3), 115.9, 115.5 (C-Ar), 115.4, 115.2 (CH-Ar), 84.1, 84.09 (O–C), 56.0, 54.2 (q, J = 2.7 Hz) (CH), 43.0 (q, J = 2.9 Hz), 42.4 (CH_2), 35.8, 35.75 (CH), 32.9, 31.1, 30.9, 307 (2×CH_2), 27.5, 27.45 (3×CH_3), 26.7, 25.2, 24.4, 22.2 (2×CH_2), 20.4, 20.0 (CH_2); HR-EIMS: calcd. for $C_{23}H_{27}F_3N_2O_3$ 436.1974; found 436.1966; IR ($CHCl_3$): ν_{max} = 2934, 1727, 1682, 1457, 1371, 1318, 1200, 1140, 1050, 755 cm^{-1}.

Benzyl 2-bromo-3-{2-[(trifluoroacetyl)amino]ethyl}-1*H*-indole-1-carboxylate (13)

NaH (60% in oil, 0.95 g, 23.8 mmol) was added to a solution of indole (**7**) (7.22 g, 21.5 mmol) in THF (90 mL) at 0 °C. The suspension was stirred for 0.5 h at rt before DMAP (40 mg, 0.3 mmol) was added followed by benzyl chloroformate (4.0 mL, 4.8 g, 28 mmol) was added slowly and the mixture was stirred at rt for 24 h. The mixture was concentrated under reduced pressure and subjected to flash chromatography (5 : 95 EtOAc/hexanes→ 10 : 90 EtOAc/hexanes). Residual benzyl alcohol was removed from the resulting solid at 0.05 mm Hg and 50 °C. Compound **13** (9.65 g, 95% yield) was obtained as a white solid (R_f 0.5, in acetone/toluene 5 : 95); m.p. 114-117 °C; ^{1}H NMR (500.13 MHz, [D_6]acetone): δ = 8.65 (brs, 1 H, NH), 8.07 (d, J = 6.8 Hz, 1H, HAr), 7.61 (d, J = 8.2 Hz, 3H, HAr), 7.46-7.38 (m, 3H, HAr), 7.3-7.24 (m, 3H, HAr), 5.55 (s, 2H, O–CH_2), 3.62 (q, J = 6.7 Hz, 2H, CH_2), 3.05 (t, J = 7.0 Hz, 2H, CH_2); ^{13}C NMR (125.8 MHz, [D_6]acetone): δ = 157.8 (q, J = 36.2 Hz, *C*OCF$_3$), 151.0 (C=O), 137.3 (C-Ar), 136.1 (C-Ar), 129.8 (C-Ar), 129.7 (CH-Ar), 129.51 (CH-Ar), 129.49 (CH-Ar), 125.6 (CH-Ar), 124.1 (CH-Ar), 121.5 (C-Ar), 119.1 (CH-Ar), 117.0 (q, J = 287.5, CF_3), 116.2 (CH-Ar), 110.3 (C-Ar), 69.9 (O–CH_2), 39.4 (CH_2), 25.3 (CH_2); HR-EIMS: calcd. for $C_{20}H_{16}BrF_3N_2O_3$ 468.0296 and 470.0275; found 468.0304 and 470.0276; IR ($CHCl_3$): ν_{max} = 1726, 1546, 1449, 1388, 1348, 1308, 1172, 1104 cm^{-1}.

Benzyl 3-{2-[allyl(trifluoroacetyl)amino]ethyl}-2-bromo-1*H*-indole-1-carboxylate (14)

1,4-Dioxane (20 mL) was added *via* syringe to a Schlenk tube followed by Bu_4NHSO_4 (154 mg, 0.45 mmol). Aryl bromide (**13**)

(1.0 g, 2.0 mmol) was then added followed by NaH (60% in oil, 120 mg, 3.0 mmol) and the mixture was stirred from 10 min. Allyl bromide (0.48 mL, 0.67 g, 5.54 mmol) was added followed rapidly by $Pd(PPh_3)_4$ (254 mg, 0.22 mmol, 7 mol%) and the reaction flask was placed into a oil bath at 60 °C for 0.5 h. The reaction was cooled to 0 °C, water (15 mL), CH_2Cl_2 (10 mL) were added and the solution stirred rapidly for 5 min. The phases were separated and the aqueous phase was extracted with (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude material was subjected to flash chromatography (hexanes → 5 : 95 EtOAc/hexanes) to afford compound **14** (842 mg, 81% yield) as a colourless oil (R_f 0.6, in acetone/toluene 5 : 95). ^{1}H NMR (500.13 MHz, [D_6]acetone): δ = 8.12-8.06 (m, 1 H, HAr), 7.69-7.64 (m, 0.7H, HAr), 7.63-7.55 (m, 2.3H, HAr), 7.46-7.36 (m, 3H, HAr), 7.34-7.25 (m, 2H, HAr), 5.9-5.75 (m, 1H, C*H*=CH$_2$), 5.57-5.54 (m, 2H, O–CH$_2$), 5.34-5.2 (m, 2H, CH=C*H*$_2$), 4.2 (d, J = 6.0 Hz, 0.7H, CH$_2$), 4.04 (d, J = 5.8 Hz, 1.3H, CH$_2$), 3.66-3.58 (m, 2H, CH$_2$), 3.16-3.05 (m, 2H, CH$_2$); ^{13}C NMR (125.8 MHz, [D_6]acetone): δ = 157.1 (q, J = 35.5 Hz, *C*OCF$_3$), 151.06, 151.01 (C=O), 137.34, 137.33 (C-Ar), 136.1, 136.08 (C-Ar), 133.3, 132.6 (*C*H=CH$_2$), 129.73, 129.69, 129.52, 129.51, 129.5 (3×CH-Ar), 129.68, 129.4 (C-Ar), 125.8, 125.7 (CH-Ar), 124.3, 124.2 (CH-Ar), 121.3, 120.4 (C-Ar), 119.3, 118.9 (CH=*C*H$_2$), 119.16, 118.78 (CH-Ar), 117.6, 117.5 (q, J = 288.0 Hz, CF$_3$), 110.6, 110.3 (C-Ar), 70.0, 69.9 (O–CH$_2$), 51.4 (q, J = 3.3 Hz), 50.0 (CH$_2$), 46.5, 46.3 (q, J = 3.1 Hz) (CH$_2$), 25.3, 23.3(CH$_2$); HR-EIMS: calcd. for $C_{23}H_{20}BrF_3N_2O_3$ 508.0609 and 510.0589; found 508.0610 and 510.0587; IR ($CHCl_3$): ν_{max} = 2978, 1744, 1688, 1449, 1388, 1346, 1308, 1172, 1150, 1104 cm^{-1}.

Benzyl 5-methylene-3-(trifluoroacetyl)-2,3,4,5-tetrahydroazepino[4,5-*b*]indole-6(1*H*)-carboxylate (15)

KOAc (1.10 g, 11.2 mmol) was added to a flask under argon containing aryl bromide **14** (1.876 g, 3.68 mmol) followed by *n*-Pr$_4$NBr (1.06 g, 3.98 mmol), PPh_3 (97.0 mg, 0.36 mmol) and finally $Pd(OAc)_2$ (82.0 mg, 0.36 mmol). MeCN (85 mL) was added and the mixture was heated to 88 °C for 19 h. The mixture was concentrated *in vacuo* and subjected to flash chromatography (1 : 1 toluene/hexanes → 80 : 20 toluene/hexanes) to afford compound **15** (1.07 g, 68% yield) as a colourless oil (R_f 0.5, in acetone/toluene 5 : 95). ^{1}H NMR (600.13 MHz, [D_6]acetone): δ = 8.07-8.02 (m, 1H, HAr), 7.53-7.47 (m, 3H, HAr), 7.44-7.35 (m, 3H, HAr), 7.34-7.30 (m, 1H, HAr), 7.27-7.23 (m, 1H, HAr), 5.56 (d, J = 0.7 Hz, 0.5H, C=C*H*$_2$), 5.53 (s, 0.5H, C=C*H*$_2$), 5.41 (s, 1H, O–CH$_2$), 5.39 (s, 1H, O–CH$_2$), 5.26 (s, 0.5H, C=C*H*$_2$), 5.24 (s, 0.5H, C=C*H*$_2$), 4.50 (s, 1H, CH$_2$), 4.45, (s, 1H, CH$_2$), 4.04-4.00 (m, 1H, CH$_2$), 3.96 (t, J = 5.8 Hz, 1H, CH$_2$), 3.09-3.05 (m, 2H, CH$_2$); ^{13}C NMR (150.9 MHz, [D_6]acetone): δ = 156.74, 156.72 (q, J = 35.5 Hz, *C*OCF$_3$), 152.2, 151.1 (C=O), 138.0, 137.9 (C), 136.15, 136.1, 136.0, 135.4, 135.0, 133.2 (3×C), 130.2, 130.16 (C), 129.7, 129.67 (CH-Ar), 129.5, 129.42 (CH-Ar), 129.41, 129.40 (CH-Ar), 125.12, 125.06 (CH-Ar), 123.0, 122.99 (CH-Ar), 122.8, 121.1 (C=*C*H$_2$), 120.4, 119.8 (C), 119.75, 119.65 (CH-Ar), 117.6, 117.4 (q, J = 287.8 Hz, CF$_3$), 115.4, 115.3 (CH-Ar), 69.75, 69.7 (O–CH$_2$), 55.3 (q, J = 3.7 Hz), 55.2 (CH$_2$), 45.5 (q, J = 3.0 Hz), 44.5 (CH$_2$), 27.0, 24.1 (CH$_2$) ppm; HR-EIMS: calcd. for $C_{23}H_{19}F_3N_2O_3$ 428.1348; found 428.1361; IR ($CHCl_3$): ν_{max} = 2958, 1735, 1688, 1456, 1388, 1320, 1149, 1107 cm^{-1}.

2a-(Bromomethyl)-4-(trifluoroacetyl)-3,4,5,6-tetrahydro-2a*H*-2-oxa-4,10b-diazabenzo[*a*]cycopenta[*cd*]azulen-1-one (16), benzyl-5-methyl-3-(trifluoroacetyl)-2,3-dihydroazepino[4,5-*b*]indole-6(1*H*)-carboxylate (17), 2a-methyl-4-(trifluoroacetyl)-3,4,5,6-tetrahydro-2a*H*-3-oxa-4,10b-diazabenzo[*a*]cyclopenta[*cd*]azulen-1-one (18)

Alkene **15** (368 mg, 0.86 mmol) was dissolved in CH_2Cl_2 (21 mL) and cooled to 0 °C. IBr (177 mg, 0.86 mmol) was added and the mixture was stirred at 0 °C for 0.75 h then allowed to warm to rt and stirred for 19 h. Aqueous $Na_2S_2O_3$ (0.5 M, 20 mL) was added and the resulting mixture was stirred rapidly and the phases separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting material was subjected to flash chromatography (1 : 1 toluene/hexanes → 90 : 10 toluene/hexanes). First to elute was the alkene **17** which after recrystallization from hexanes was obtained as white needles (122 mg, 33% yield, R_f 0.5, in acetone/toluene 5 : 95). Next to elute was tetracycle **18** which after trituration from hexanes was obtained as a white solid (23 mg, 8% yield, R_f 0.44, in acetone/toluene 5 : 95). Last to elute was the bromide **16** which was obtained as a white solid (61 mg, 17% yield, R_f 0.40, in acetone/toluene 5 : 95).

Benzyl-5-methyl-3-(trifluoroacetyl)-2,3-dihydroazepino[4,5-*b*]indole-6(1*H*)-carboxylate (17)

M.p. 106-108 °C; ^{1}H NMR (600.13 MHz, $CDCl_3$): δ = 8.16 (d, J = 8.3 Hz, 0.95H, HAr), 8.12 (d, J = 8.3 Hz, 0.05H, HAr), 7.55-7.46 (m, 3H, HAr), 7.44-7.39 (m, 3H, HAr), 7.38-7.34 (m, 1H, HAr), 7.32-7.27 (m, 1H, HAr), 6.79-6.77 (m, 0.05H, C=C*H*), 6.56-6.53 (m, 0.95H, C=C*H*), 5.46 (s, 0.1H, O–CH$_2$), 5.43 (s, 1.9H, O–CH$_2$), 4.2 (t, J = 5.6 Hz, 0.1H, CH$_2$), 4.14 (t, J = 6.5 Hz, 1.9H, CH$_2$), 3.0 (t, J = 6.0 Hz, 0.1H, CH$_2$), 2.98 (t, J = 6.5 Hz, 1.9H, CH$_2$), 2.04 (d, J = 1.2 Hz, 0.15H, CH$_3$), 2.00 (d, J = 1.3 Hz, 2.75H, CH$_3$);^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 156.5 (q, J = 35.8 Hz, *C*OCF$_3$), 151.2 (C=O), 137.2 (C-Ar), 134.5 (C-Ar), 134.4 (C-Ar), 131.5 (q, J = 0.9 Hz, *C*=CH), 129.0 (CH-Ar), 128.98 (CH-Ar), 128.8 (CH-Ar), 128.5 (C-Ar), 125.8 (CH-Ar), 123.5 (CH-Ar), 122.2 (C-Ar), 122.21 (q, J = 2.3 Hz, C=*C*H), 118.5 (CH-Ar), 116.3 (q, J = 288.4 Hz, CF$_3$), 115.7 (CH-Ar), 69.4 (O–CH$_2$), 56.1 (CH$_2$), 21.3 (CH$_2$), 19.3 (CH$_3$); HR-EIMS: calcd. for $C_{23}H_{19}F_3N_2O_3$ 428.1348; found 428.1353. IR ($CHCl_3$): ν_{max} = 2958, 1736, 1698, 1630, 1456, 1420, 1388, 1317, 1154, 1089 cm^{-1}.

2a-Methyl-4-(trifluoroacetyl)-3,4,5,6-tetrahydro-2a*H*-3-oxa-4,10b-diazabenzo[*a*]cyclopenta[*cd*]azulen-1-one (18)

M.p. 162-164 °C; ^{1}H NMR (600.13 MHz, $CDCl_3$): δ = 7.93-7.86 (m, 1H, HAr), 7.53-7.45 (m, 1H, HAr), 7.41-7.34 (m, 2H, HAr), 5.0 (d, J = 12.6 Hz, 0.9H, CH$_2$), 4.4 (brd, J = 15.3 Hz, 0.9H, CH$_2$), 4.3 (brd, J = 13.61 Hz, 0.1H, CH$_2$), 3.31-3.24 (m, 1H, CH$_2$), 3.1-2.96 (m, 3H, CH$_2$), 1.8 (s, 0.3H, CH$_3$), 1.76 (s, 2.7H, CH$_3$); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 158.0 (q, J = 36.4 Hz, *C*OCF$_3$), 149.3 (C=O), 142.8 (C-Ar), 133.9 (C-Ar), 131.5 (C-Ar), 124.9 (CH-Ar), 124.5 (CH-Ar), 119.6 (CH-Ar), 116.7 (q, J = 287.6 Hz, CF$_3$), 113.9 (C-Ar), 111.5 (CH-Ar), 82.4 (O–C), 55.2 (CH$_2$), 52.0 (q, J = 3.6 Hz, CH$_2$), 25.3 (CH$_2$), 23.4 (CH$_3$); HR-EIMS: calcd. for

$C_{23}H_{19}F_3N_2O_3$ 338.0878; found 338.0881; IR (KBr): ν_{max} = 2923, 1778, 1694, 1453, 1362, 1307, 1194, 1164, 1133, 763 cm^{-1}.

2a-(Bromomethyl)-4-(trifluoroacetyl)-3,4,5,6-tetrahydro-2a*H*-2-oxa-4,10b-diazabenzo[*a*]cycopenta[*cd*]azulen-1-one (16)

M.p. 168-170 °C; ^{1}H NMR (600.13 MHz, $CDCl_3$): δ = 7.9 (d, J = 7.6 Hz, 1 H, HAr), (d, J = 7.3 Hz, 1H, HAr), 7.45-7.35 (m, 2H, HAr), 5.0 (d, J = 13.1 Hz, 1H, CH_2), 4.45 (brd, J = 15.3 Hz, 1H, CH_2), 3.9 (d, J = 12.0 Hz, 1H, CH_2), 3.75 (d, J = 12.0 Hz, 1H, CH_2), 3.35-3.27 (m, 1H, CH_2), 3.24 (d, J = 13.1 Hz, 1H, CH_2), 3.15-3.0 (m, 2H, CH_2); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 158.4 (q, J = 36.8 Hz, $COCF_3$), 148.7 (C=O), 139.1 (C-Ar), 133.7 (C-Ar), 131.6 (C-Ar), 125.4 (CH-Ar), 124.7 (CH-Ar), 119.9 (CH-Ar), 116.5 (q, J = 287.8 Hz, CF_3), 113.9 (CH-Ar), 113.6 (C-Ar), 82.3 (O–C), 53.6 (CH_2), 52.1 (q, J = 2.7 Hz, CH_2), 34.5 (CH_2), 25.4 (CH_2); HR-EIMS: calcd. for $C_{16}H_{12}BrF_3N_2O_3$ 415.9983 and 417.9963; found 415.9980 and 417.9932; IR ($CHCl_3$): ν_{max} = 2971, 1782, 1693, 1454, 1365, 1149 cm^{-1}.

rel-(4a*R*,10b*R*)-10b-Hydroxy-4a-(hydroxymethyl)-3-(trifluoroacetyl)-2,3,4,4,6,10b-hexahydrobenzo[*c*]-2,7-naphthyridin-5(1*H*)-one (21)

Alkene **15** (877 mg, 2.04 mmol) was dissolved in CH_2Cl_2 (132 mL) and cooled to 0 °C. The solution was purged by bubbling pure O_2 through it for 10 min with stirring. A mixture of O_3 in O_2 (2% O_3 by weight approx) was then bubbled through the solution for 10 min at 1 L min^{-1}. The solution was then purged again with O_2 for 10 min and then N_2 for 5 min. Me_2S (1.49 mL, 1.26 g, 20.3 mmol) was then added at 0 °C and the solution stirred for 20 min under N_2. The resulting mixture was concentrated *in vacuo*. The crude residue was purified by rapidly filtering though a plug of silica (100% CH_2Cl_2). The resulting semi-pure peroxide was dissolved in CH_2Cl_2 (130 mL), Pd/C 10% (100 mg) was added and the mixture was stirred under H_2 at atmospheric pressure at r.t for 22 h. The Pd/C was filtered off, the solution was concentrated *in vacuo* and the resulting material subjected to flash chromatography (CH_2Cl_2→ 5 : 95 MeOH–CH_2Cl_2) to afford the diol **21** (338 mg, 48% yield) at as a white solid (R_f 0.4, in MeOH–CH_2Cl_2 10 : 90). M.p. 208-211 °C; ^{1}H NMR (600.13 MHz, [D_6]acetone): δ = 9.55-9.4 (m, 1H, NH), 7.63-7.58 (m, 1H, HAr), 7.28-7.23 (m, 1H, HAr), 7.14-7.08 (m, 1H, HAr), 6.95 (d, J = 7.8 Hz, 1H, HAr), 5.35 (br. s, 0.65H, OH), 5.29 (br. s, 0.35H, OH), 5.10 (d, J = 13.0 Hz, 0.65H, O–CH_2), 4.78 (br. s, 0.65H, OH), (m, 0.7H, O–CH_2 + OH), 4.37-4.31 (m, 0.35H, CH_2), 3.88-3.80 (m, 1.65H, CH_2), 3.76 (d, J = 13.1 Hz, 0.35H, O–CH_2), 3.74-3.64 (m, 1.65H, CH_2), 3.4 (d, J = 13.0 Hz, 0.65H, O–CH_2), 3.35-3.29 (m, 0.35H, CH_2), 1.92-1.81 (m, 1H, CH_2), 1.69-1.63 (m, 1H, CH_2);^{13}C NMR (150.9 MHz, [D_6]acetone): δ = 169.0, 168.8 (C=O), 156.2, 155.5 (q, J = 36.2 Hz, $COCF_3$), 134.3, 134.2 (C-Ar), 130.1, 129.9 (C-Ar), 128.47, 128.46 (CH-Ar), 124.7, 124.6 (CH-Ar), 123.23 123.22 (CH-Ar), 116.74, 116.69 (q, J = 288.2 Hz, CF_3), 114.7 (CH-Ar), 72.2, 71.8 (C), 63.1, 62.9 (CH_2), 51.7, 51.1 (C), 42.7 (q, J = 3.9 Hz), 40.9 (q, J = 3.6 Hz), 40.7, 38.5 (2×CH_2), 36.5, 35.3 (CH_2); HR-EIMS: calcd. for $C_{15}H_{15}F_3N_2O_4$ 344.0984; found 344.0985; IR (KBr): ν_{max} = 2965, 1693, 1680, 1597, 1497, 1486, 1371, 1200, 1176, 1149, 1006, 756 cm^{-1}.

For characterisation purposes; benzyl *rel*-(1*R*,10*R*)-9-oxo-12-(trifluoroacetyl)-15,16-dioxa-8,12-diazatetracyclo [8.4.3.0^{1,10}.0^{2,7}]heptadeca-2,4,6-triene-8-carboxylate (20)

A pure sample of the peroxide may be obtained by subjecting the crude residue mentioned above to flash chromatography (hexanes → 15 : 85 EtOAc/hexanes) to afford the peroxide as a colorless oil (R_f 0.3, in acetone/toluene 5 : 95); ^{1}H NMR (500.13 MHz, $CDCl_3$): δ = 7.6 (d, J = 7.4 Hz, 1H, HAr), 7.47-7.35 (m, 5H, HAr), 7.47-7.35 (m, 5H, HAr), 7.33-7.24 (m, 2H, HAr), 6.85-6.76 (m, 1H, HAr), 5.45 (m, 2H, O–CH_2), 5.26 (d, J = 13.4 Hz, 0.65H, CH_2), 4.76 (d, J = 13.8 Hz, 0.35H, CH_2), 4.23 (d, J = 7.2 Hz, 0.35H, OO–CH_2), 4.16 (d, J = 6.7 Hz, 0.65H, OO–CH_2), 4.13-4.07 (m, 1H, OO–CH_2), 4.07-4.01 (m, 0.35H, CH_2), 4.01 (m, 0.35H, CH_2), 3.85-3.77 (m, 0.65H, CH_2), 3.70 (d, J = 13.8 Hz, 0.35H, CH_2), 3.56-3.48 (m, 0.65H, CH_2), 3.42-3.31 (m, 1H, CH_2), 2.35-2.05 (m, 2H, CH_2); ^{13}C NMR (125.8 MHz,$CDCl_3$): δ = 164.6, 164.1 (C=O), 156.8, 155.6 (q, J = 36.2 Hz, $COCF_3$), 152.4, 152.2 (C=O), 133.8, 133.7 (C-Ar), 132.7, 132.6 (C-Ar), 130.4, 130.3 (CH-Ar), 129.2, 129.15 (CH-Ar), 128.96, 128.9, 128.8 (2×CH-Ar), 126.8, 126.5, 125.9 (2×CH-Ar), 125.2, 124.4 (C-Ar), 116.4, 116.1 (CH-Ar), 116.3, 116.2 (q, J = 288.2 Hz, CF_3), 82.2, 82.1 (C), 75.2, 74.5 (OO–CH_2), 71.2, 71.17 (O–CH_2), 60.96, 60.90 (C), 44.6 (q, J = 3.6 Hz), 42.5 (CH_2), 50.0 (q, J = 3.7 Hz), 39.0 (CH_2), 30.7, 29.8 (CH_2); HR-EIMS: calcd. for $C_{23}H_{19}F_3N_2O_6$ 476.1195; found 476.1185; IR ($CHCl_3$): ν_{max} = 2956, 1775, 1705, 1605, 1497, 1458, 1363, 1179, 1150 cm^{-1}.

X-Ray crystallography for compounds 18 and 21

Crystallographic data for the structures were collected at 100(2) K on an Oxford Diffraction Gemini diffractometer fitted with graphite-monochromated Mo-Kα radiation. Following multi-scan absorption corrections and solution by direct methods, the structures were refined against F^2 with full-matrix least-squares using the program SHELXL-97.[37] Hydroxyl hydrogen atoms for **21** were located and refined with restrained geometries. All remaining hydrogen atoms were added at calculated positions and refined by use of a riding model with isotropic displacement parameters based on those of the parent atom. Anisotropic displacement parameters were employed throughout for the non-hydrogen atoms.

Compound 18

Triclinic, space group $P\bar{1}$, a = 7.7998(5), b = 8.4873(5), c = 11.8596(6) Å, α = 72.423(5), β = 80.473(5), γ = 72.510(6)°, V = 711.42(7) Å^3, Z = 2. Measured reflections = 10 493, unique reflections = 5697, R_1 = 0.045 for 3855 reflections with $I > 2\sigma(I)$, wR_2 = 0.120 (all data). CCDC number 767164.

Compound 21

Orthorhombic, space group $P2_12_12_1$, a = 10.0807(2), b = 19.0872(4), c = 22.9900(5) Å, V = 4423.56(16) Å^3, Z = 12. Measured reflections = 59 406, unique reflections = 8485, R_1 = 0.037 for 6891 reflections with $I > 2\sigma(I)$, wR_2 = 0.079 (all data). CCDC number 767165. The structure consists of three crystallographically independent molecules in the asymmetric unit

with two molecules having the same, and one molecule the opposite, chirality. The hydrogen atoms of the amine groups and hydroxyl groups of the three molecules are all involved in hydrogen bonding. Hydrogen bonding details are in the cif and the supplementary material. Full crystallographic details for both **18** and **21** are available in the ESI.†

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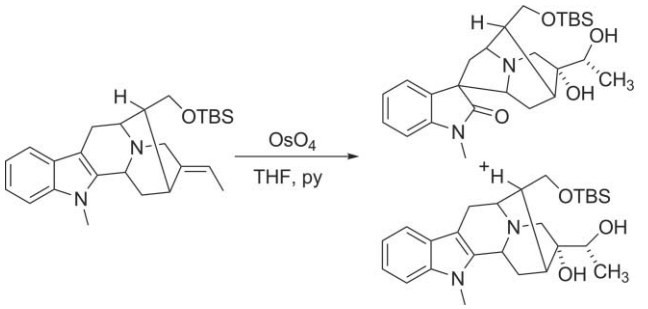

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23 Compounds **11**, **12a**, **12b**, **15**, **16**, **17**, **18**, **20** and **21** have hindered rotation about C–N due to the partial double bond character within the amide protecting group. Due to slow site exchange at room temperature a doubling of signals in both the 1H and ^{13}C-NMR spectra were observed.
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