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Facile asymmetric construction of a functionalized dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizine template

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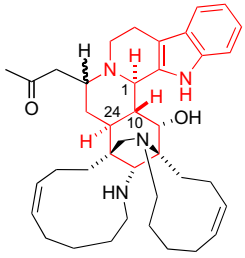
ABSTRACT

We report a highly diastereoselective approach for the synthesis of a functionalized dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizine ring system that is present as the heterocyclic core of the manadomanzamine alkaloids. We have achieved complete control over the relative and absolute stereochemistries at the three contiguous stereocentres at ring positions 1, 10 and 24 in only two linear synthetic steps. The introduction of useful functionality to the heterocyclic skeleton is significant as this may allow for future derivatization, and application of this route in an asymmetric synthesis of the manadomanzamine natural products.

1. Introduction

Manadomanzamines A and B (Fig. 1) were isolated by Hamann and co-workers from the Indonesian sponge *Acanthostrongylophora* sp.[1] These compounds were found to exhibit strong activity against *Mycobacterium tuberculosis* (Mtb) with MIC values of 1.9 and 1.5 μg/ml, respectively, and show activities against HIV-1 and AIDS opportunistic infections. The increasing occurrence and threat of tuberculosis has renewed interest in the development of anti-tuberculosis agents, since the W.H.O. estimates that currently one-third of the world's population is infected with TB, with 3.1 million deaths occurring per annum. Additionally, the value of a lead compound with activity against *both* HIV-1 and AIDS opportunistic infections is of significance. A plausible biosynthetic pathway to the manadomanzamines has been proposed from the more common manzamine alkaloids.[1]



Manadomanzamine A, 22 β-H
Manadomanzamine B, 22 α-H

Figure 1. The manadomanzamine alkaloids, highlighting the dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizine skeleton.

2. Results and discussion

2.1. Synthesis of functionalized *N*-acyliminium ion precursors

Although no total synthesis of the manadomanzamines has so far been reported, we recently achieved a stereoselective approach to a simple dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizine skeleton **1**.[2] This pentacyclic ring system, sometimes referred to as an 'inside yohimbane,' has been prepared in racemic fashion by Morrison and co-workers,[3] and has also been observed as a minor by-product in

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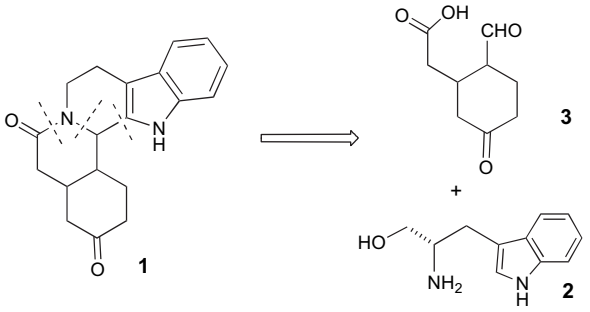
approaches to racemic yohimbine and reserpine by Martin.[4] For successful application in total synthesis an approach to the manadomanzamines through a dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizine intermediate would require the presence of a suitable synthetic 'handle' at a relevant position on a precursor template.

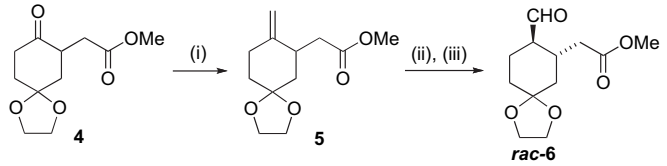
In this paper we report a highly diastereoselective construction of a dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizine, that delivers the three contiguous stereocentres at ring positions 1, 10 and 24 with the correct relative and absolute stereochemistry required by the natural products, and also introduces useful functionality to the heterocyclic template.[5] Our retrosynthetic analysis (Scheme 1) of a typical functionalized pentacyclic core, **1**, led back to the use of *S*-tryptophanol **2**, as both a source of the indole moiety and as the chiral auxiliary in an asymmetric *N*-acyliminium-induced cyclization.



Scheme 1. Retrosynthetic analysis of a functionalized dodecahydrobenz[*a*]indolo-[3,2-*h*]quinolizine core.

Our research group, and others, have had considerable success in recent years in the development of asymmetric routes to several important heterocyclic templates, based around the development of highly diastereoselective *N*-acyliminium cyclization strategies.[6] Our own recent applications of this methodology in natural product synthesis have included targets from the *Erythrina* group of alkaloids and several indole alkaloids.

Access to a useful equivalent of the trifunctional substrate **3** was not trivial. Application of standard Wittig conditions to keto-ester **4**, itself formed through enolate alkylation of the commercially available mono-protected diketone, delivered alkene substrate **5** in essentially quantitative yield. Hydroboration of **5** employing pyridinium chlorochromate as oxidant in a process mirroring an in situ procedure applied to 1,4-cyclohexanedione monoethylene acetal and reported by Bonjoch[7] afforded key aldehyde **6** in 70% yield over two steps (Scheme 2). Compound **6** was isolated as a mixture of the inseparable cis and trans isomers (ca. 1:4), with the trans isomer predominating.



Scheme 2. Preparation of key multi-functional substrate **6**. Reagents and conditions: (i) CH_3PPh_3Br (2.0 equiv), NaH (3.0 equiv), THF, rt, 99%; (ii) $H_3B{-}SMe_2$ (0.6 equiv, 2 M THF) then (iii) PCC (2.5 equiv), DCM, 70% over two steps.

Cyclocondensation of racemic *cis*/*trans*-**6** with *S*-tryptophanol under Dean–Stark conditions in toluene for 24 h gave a 1:1 mixture of two separable, highly functionalized diastereoisomers **7a**, **b** in 45% isolated overall yield (Fig. 2). Although the isolated yield is only moderate, the ^{1}H NMR spectrum of the crude reaction mixture shows **7a** and **7b** to be the major products of this reaction, with no sign of any unreacted aldehyde substrate **6**. The use of racemic multifunctional aldehyde substrates such as **6** in stereoselective

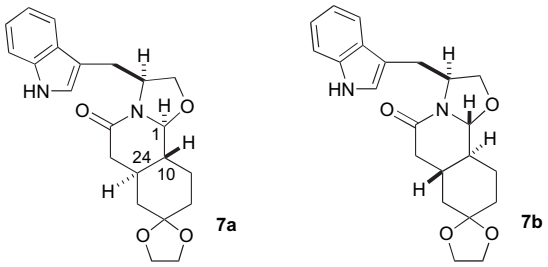


Figure 2. Functionalized *N*-acyliminium precursors.

condensation reactions has been much explored by Bosch and Amat.[8] Presumably the dynamic kinetic resolution that is well known for this class of substrate under cyclocondensation conditions occurs here to give the preferred trans orientation in **6** during the formation of **7**.

The relative and absolute stereochemistry of the desired precursor **7a**, matching that of the natural products at centres 10 and 24 was determined by NOE studies and also confirmed by X-ray crystallography on the isolated compound (Fig. 3), and that of isomer **7b**, the 'unnatural' isomer, by NOE studies. In summary: when irradiating either *H*-1 or *H*-24 of **7b**, a signal enhancement of the other proton is observed, but unlike in **7a** no positive NOE exists between the proton at *H*-1 and proton at the tryptophanol stereocentre in **7b**. Furthermore, no signal augmentation of the proton at the 10-position occurred when irradiating neighbouring protons *H*-1 and *H*-24 in **7b**. In synthetic terms, the stereochemistry at the noted C-1 position of the *N*-acyliminium ion precursors **7a** or **7b** is of no significance since this corresponding aminal centre will form a planar iminium carbon atom in subsequent reaction steps.

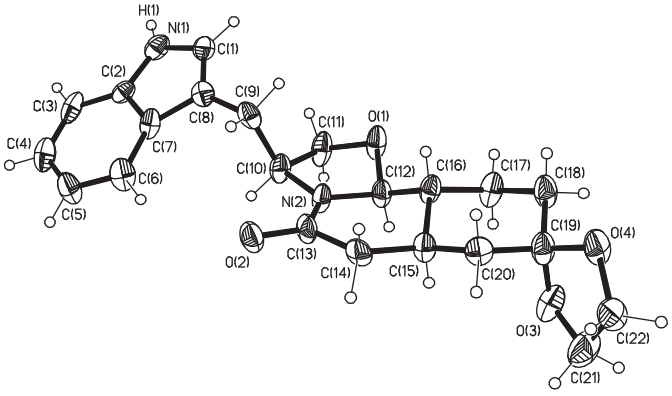
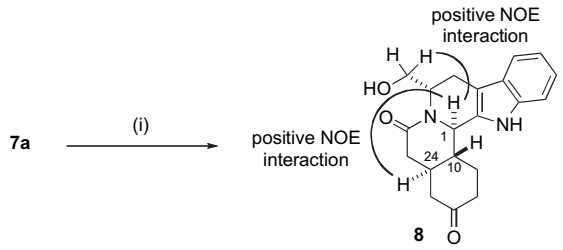


Figure 3. Ellipsoid plot of compound **7a**.

2.2. Stereoselective cyclization reactions

With the required asymmetric building blocks in hand we turned our attention to the stereoselective cyclization step and subjected the functionalized chiral templates to an acid-induced cyclization. Reaction of **7a**, promoted by 2 M HCl in EtOH at 50 °C for 3 h, gave clean cyclization in 56% yield to a single diastereoisomer of product **8** with concomitant (and complete) deprotection of the acetal protecting group (Scheme 3). These reaction conditions are slightly harsher than in our preliminary publication on the unfunctionalized template,[2] in which the analogous cyclization was carried out at room temperature. In this current study, cyclization of **7a** at room temperature led to mixtures of the desired cyclized product **8** and uncyclized, but acetal-deprotected substrate **7a**.

Structural elucidation of product **8** was again achieved by NOE studies to confirm that the relative and absolute stereochemistry of



Scheme 3. Stereoselective cyclization of **7a**. Reagents and conditions: (i) 2 M HCl in EtOH, 70 °C, 72 h, 77%.

the three contiguous chiral centres in **8** matched that of the manadomanzamine natural products. In summary: irradiation of the proton at ring position 1 gave a positive NOE between the proton at position 24 and to one of the hydroxymethyl CH_2 protons. These protons must therefore be on the same 'face' of the template and, with the stereochemistry of positions *C*-10 and *C*-24 known from the X-ray crystal structure of **7a**, we can assign the stereochemistry of **8** as shown. No signal enhancement was observed for *H*-10 whilst irradiating *H*-1.

Cyclization of the 'unnatural' template **7b** was achieved under similar reaction conditions (2 M HCl in EtOH, 50 °C, 18 h) to deliver **9** in 58% yield as a single diastereoisomer, with structural elucidation confirmed by NOE (Fig. 4). Irradiation of *H*-1 resulted in a signal enhancement of both *H*-10 and of the hydroxymethyl group (i.e., a positive NOE). Furthermore, when irradiating *H*-10 a signal enrichment of *H*-1 is observed, but no such relationship is observed between *H*-10 and *H*-24.

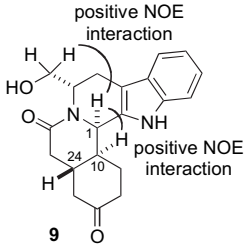
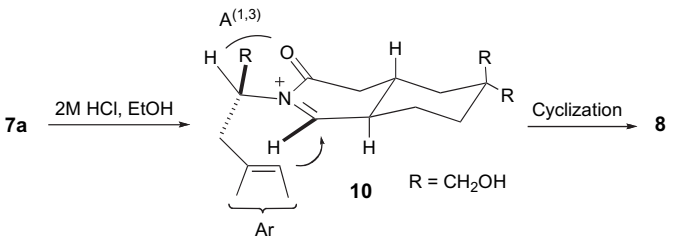


Figure 4. Structural elucidation of the 'unnatural' product isomer.

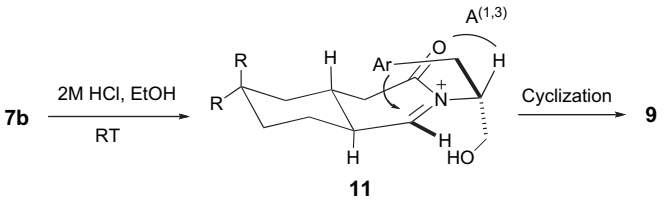
2.3. Rationalization of the stereochemical control

Highly diastereoselective cyclization reactions of the indolyl nucleus onto *N*-acyliminium intermediates of this type are well established.[6b,e,f,h,9] The stereocontrol is understood to arise from a preferred conformation, such as **10**, having minimal $A^{(1,3)}$ strain between the H-atom at the stereogenic centre of the tryptophanol moiety and the lactam carbonyl group in the transition state.[10] Cyclization of the indolyl nucleus thus takes place from a pro-equatorial orientation in **10**, leading to axial orientation of all three H-substituents at positions C-1, 10 and 24 in **8**, matching the natural product's stereochemistry at these three contiguous asymmetric centres (Scheme 4).



Scheme 4. Rationalization of the stereochemical outcome of cyclization of **7a**.

In the case of lactam substrate **7b**, as outlined in Scheme 5, the stereocontrol arises through the preferred conformation **11**, minimizing the $A^{(1,3)}$ strain between the H-atom at the stereogenic centre of the tryptophanol moiety and the lactam carbonyl group, despite the fact that the transition state must lead to a pro-axial attack onto the iminium species by the indolyl nucleus.



Scheme 5. Rationalization of the stereochemical outcome of cyclization of **7b**.

3. Conclusion

In summary we report an asymmetric synthesis of a functionalized dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizine, a heterocyclic core found within the structure of the manadomanzamine alkaloids, in only two linear synthetic steps from readily available precursors (from **6** and tryptophanol, **2**). Our route allows the controlled formation of the correct relative and absolute stereochemistries at the three contiguous chiral centres at positions C-1, C-10 and C-24 of the heterocyclic skeleton, and also the introduction of a useful synthetic handle to the dodecahydrobenz[*a*]indolo[3,2-*h*]quinolizine skeleton. Although not described in this paper, we have established several routes for removal of the hydroxymethyl auxiliary group from similar heterocyclic templates.[6a,b] Our current work is centred on the development of this synthetic route to allow access to more highly functionalized intermediates and to pursuing a total synthesis of the manadomanzamine alkaloids and synthetic analogues.

4. Experimental section

All infrared spectra were obtained using an FTIR spectrophotometer; thin film spectra were acquired using sodium chloride plates. All ^{1}H and ^{13}C NMR spectra were obtained at 400 and 100 MHz, respectively, in deuteriochloroform solution unless otherwise stated, using TMS (tetramethylsilane) as the internal reference. Mass spectra were recorded utilizing electron-impact (EI), fast atom bombardment (FAB), or electrospray (ES). Analysis by GC–MS utilized a 15 m×0.25 mm DB-5 column and an electron-impact low-resolution mass spectrometer. Melting points are uncorrected. Optical rotation values were measured operating at λ=589 nm, corresponding to the sodium D line, at the temperatures indicated. All chromatographic manipulations used silica gel as the adsorbent. Reactions were monitored using thin layer chromatography (TLC) on aluminium-backed plates coated with F254 silica gel. TLC plates were visualized by UV radiation at a wavelength of 254 nm, or stained by exposure to an ethanolic solution of phosphomolybdic acid (acidified with concentrated sulfuric acid), followed by charring where appropriate. Reactions requiring anhydrous conditions were carried out using flame-dried glassware under a nitrogen atmosphere unless otherwise stated. Reaction solvents were used as obtained commercially unless otherwise stated. Light petroleum (bp 40–60 °C) was distilled from calcium chloride prior to use. Ethyl acetate was distilled over calcium sulfate or chloride. Dichloromethane was distilled over calcium hydride.

4.1. Methyl 2-(8-oxo-1,4-dioxaspiro[4.5]decan-7-yl)acetate (4)

1,4-Cyclohexanedione monoethylene acetal (2.0 g, 12.80 mmol) was dissolved in anhydrous tetrahydrofuran (30 ml) under an inert

atmosphere and the solution cooled to −78 °C. Potassium hexamethyldisilazide (KHMDS) (28.2 ml, 14.80 mmol) was added at such a rate that the temperature did not rise above −70 °C and the reaction was stirred at this temperature for 1 h. Methyl bromoacetate (1.32 ml, 14.80 mmol) was added drop-wise to the mixture and after 30 min the reaction was allowed to warm to room temperature over 4 h. The reaction was quenched with addition of water (50 ml) and extracted into ethyl acetate (3×75 ml). The organic fractions were combined, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The crude product was adsorbed onto silica and purified by flash column chromatography over silica eluting with 1:1 light petroleum–ethyl acetate to give the target compound as a pale yellow oil (2.10 g, 72%). ^{1}H NMR (400 MHz; $CDCl_3$) 1.82 (1H, t, *J*=13.2 Hz), 2.00 (1H, dd, *J*=4.8, 13.6 Hz), 2.03–2.14 (2H, m), 2.20 (1H, dd, *J*=6.0, 16.8 Hz), 2.40 (1H, ddd, *J*=2.4, 4.8, 14.4 Hz), 2.68–2.77 (2H, m), 3.19–3.24 (1H, m), 3.68 (3H, s), 4.00–4.09 (4H, m). ^{13}C NMR (100 MHz; $CDCl_3$) 33.9, 34.6, 37.8, 40.2, 43.1, 51.7, 64.7, 64.8, 107.1, 172.5, 209.6. IR (thin film, cm^{-1}) 1715, 1174. MS (FAB) *m*/*z* 228 $[M+H]^+$ (Calcd for $C_{11}H_{16}O_5$: 228.1076. Found: 228.1074).

4.2. Methyl 2-(8-methylene-1,4-dioxaspiro[4.5]decan-7-yl)-acetate (5)

To a mixture of methyltriphenylphosphonium bromide (3.52 g, 9.86 mmol) and sodium hydride (395 mg, 9.86 mmol) under nitrogen was added anhydrous tetrahydrofuran (50 ml) around the sides of the flask. The reaction mixture was stirred vigorously for 45 min to give a bright yellow suspension at which time methyl 2-(8-oxo-1,4-dioxaspiro[4.5]decan-7-yl)acetate **4** (1.50 g, 6.58 mmol) was added drop-wise as a solution in anhydrous tetrahydrofuran (15 ml). Upon complete addition a deep red colouration was observed and the reaction left to stir vigorously for a further 3 h. The reaction mixture was cooled to 0 °C and quenched by a careful addition of water (100 ml), followed by extraction into ethyl acetate (3×75 ml). The combined organics were dried over anhydrous magnesium sulfate, filtered and concentrated under reduced pressure to yield a pale yellow oil. The crude oil was suspended in diethyl ether to precipitate triphenylphosphine oxide and the resulting filtrate evaporated to dryness on the rotary evaporator to furnish the target compound as a colourless oil (1.46 g, 99%). ^{1}H NMR (400 MHz; $CDCl_3$) 1.40–1.46 (1H, m), 1.60–1.66 (1H, m), 1.76–1.82 (1H, m), 1.88 (1H, ddd, *J*=2.4, 4.4, 12.8 Hz), 2.31–2.38 (3H, m), 2.65 (1H, dd, *J*=7.2, 15.2 Hz), 2.81–2.89 (1H, m), 3.68 (3H, s), 3.93–4.00 (4H, m), 4.62 (1H, s), 4.77 (1H, s). ^{13}C NMR (100 MHz; $CDCl_3$) 32.3, 36.2, 36.8, 37.5, 41.4, 51.6, 64.3, 64.4, 106.8, 108.4, 149.1, 173.1. IR (thin film, cm^{-1}) 1738, 1647, 1167. MS (FAB) *m*/*z* 226 $[M+H]^+$ (Calcd for $C_{12}H_{18}O_4$: 226.1283. Found: 226.1288).

4.3. Methyl 2-((7*S*,8*R*)-8-formyl-1,4-dioxaspiro[4.5]decan-7-yl)-acetate (*rac*-6)

Methyl 2-(8-methylene-1,4-dioxaspiro[4.5]decan-7-yl)acetate **5** (2.00 g, 8.33 mmol) in anhydrous tetrahydrofuran (30 ml) under nitrogen was treated with borane–dimethylsulfide complex (2 M in tetrahydrofuran, 2.50 ml, 5.00 mmol). The mixture was stirred vigorously for 1 h and then all volatiles were removed under reduced pressure to give a colourless oil. The crude oil was taken up in a minimum amount of dichloromethane and added drop-wise to a solution of pyridinium chlorochromate (4.31 g, 19.99 mmol) in dichloromethane (40 ml). The reaction mixture was then heated at reflux for 2 h before being allowed to cool to room temperature and diluted with diethyl ether (50 ml). The organic phases were decanted and filtered through a silica pad and the remaining black solids washed exhaustively with further portions of diethyl ether (5×30 ml). All volatiles were removed under reduced pressure to yield a crude oil that was purified by flash column chromatography over silica using 4:1 hexane–ethyl acetate as eluent to yield the target compound, a colourless oil, as a mixture of inseparable diastereoisomers in a 4:1 ratio in favour of the trans isomer (1.49 g, 70%). Data for the major isomer: ^{1}H NMR (400 MHz; $CDCl_3$) 1.51–1.59 (1H, m), 1.63–1.80 (3H, m), 1.84–1.93 (1H, m), 2.03–2.09 (1H, m), 2.45–2.60 (3H, m), 2.64 (1H, q, *J*=4.0 Hz), 3.67 (3H, s), 3.91–3.98 (4H, m), 9.76 (1H, s). ^{13}C NMR (100 MHz; $CDCl_3$) 22.1, 31.9, 32.4, 36.4, 37.7, 49.2, 51.6, 64.2, 64.4, 108.2, 173.0, 203.6. IR (thin film, cm^{-1}) 1732, 1176. MS (FAB) *m*/*z* 242 $[M+H]^+$ (Calcd for $C_{12}H_{18}O_5$: 242.1233. Found: 242.1232). A characteristic peak for the minor isomer was observed at 9.57 (d) in the ^{1}H NMR spectrum, corresponding to the aldehyde proton.

4.4. (3′*S*,6a′*S*,10a′*R*,10b′*S*)-3′-((1*H*-Indol-3-yl)methyl)-octahydrospiro[[1,3]dioxolane-2,8′-oxazolo[2,3-*a*]isoquinolin]-5′(6′*H*)-one (7)

(*S*)-2-Amino-3-(1*H*-indol-3-yl)propan-1-ol (1.12 g, 5.47 mmol) and methyl 2-((7*S*,8*R*)-8-formyl-1,4-dioxaspiro[4.5]decan-7-yl)-acetate, *rac*-**6** (1.40 g, 5.47 mmol) were added to toluene (50 ml) and heated at reflux under Dean–Stark conditions for 24 h. The mixture was allowed to cool to room temperature and the solvent removed under reduced pressure to yield the crude target compound. 400 MHz ^{1}H NMR analysis of the crude reaction mixture revealed the formation of **7** as a 1:1 mixture of diastereoisomers. These isomers were purified and separated by flash column chromatography over silica using 4:1/light petroleum–ethyl acetate as eluent (940 mg, 45%).

Compound **7a** (464 mg), isolated as a white solid: mp 205–207 °C. $[\alpha]_D^{20}=-27.9$ [*c* 1.0 in CH_2Cl_2]. ^{1}H NMR (400 MHz; $CDCl_3$) 1.29–1.47 (3H, m), 1.51–1.61 (1H, m), 1.77–1.92 (3H, m), 2.00–2.21 (2H, m), 2.54 (1H, dd, *J*=6.0, 18.0 Hz), 2.63 (1H, dd, *J*=10.4, 13.6 Hz), 3.67–3.69 (1H, m), 3.72–3.77 (1H, m), 3.92–3.98 (4H, m), 4.03 (1H, d, *J*=9.2 Hz), 4.27–4.33 (1H, m), 4.34 (1H, d, *J*=8.8 Hz), 7.02 (1H, d, *J*=1.6 Hz), 7.10–7.21 (2H, m), 7.35 (1H, d, *J*=8.0 Hz), 7.80 (1H, d, *J*=7.6 Hz), 8.2 (1H, s). ^{13}C NMR (100 MHz; $CDCl_3$) 24.8, 26.8, 32.4, 33.5, 38.8, 40.7, 42.4, 56.3, 64.4, 64.5, 70.2, 92.3, 108.0, 111.0, 112.7, 119.4, 119.6, 122.2, 122.3, 127.7, 136.2, 167.1. IR (thin film, CH_2Cl_2, cm^{-1}) 1631, 1229. MS (FAB) *m*/*z* 382 $[M+H]^+$ (Calcd for $C_{22}H_{26}N_2O_4$: 382.1971. Found: 382.1967).

Compound **7b** (476 mg), isolated as a white solid: mp 182–183 °C. $[\alpha]_D^{20}=19.6$ [*c* 1.0 in CH_2Cl_2]. ^{1}H NMR (400 MHz; $CDCl_3$) 1.17–1.42 (3H, m), 1.49–1.58 (1H, m), 1.76–1.90 (3H, m), 1.97–2.00 (2H, m), 2.60 (1H, dd, *J* 5.2, 18.0), 2.99 (1H, dd, *J* 8.8, 14.0), 3.36 (1H, dd, *J* 3.6, 14.4), 3.66 (1H, dd, *J* 1.6, 7.2), 3.89–3.97 (4H, m), 4.05 (1H, dd, *J* 7.6, 8.8), 4.22 (1H, d, *J* 8.0), 4.56–4.63 (1H, m), 6.99 (1H, d, *J* 2.0), 7.10–7.21 (2H, m), 7.35 (1H, d, *J* 8.0), 7.69 (1H, d, *J* 8.0), 8.10 (1H, s). ^{13}C NMR (100 MHz; $CDCl_3$) 25.6, 27.4, 31.2, 33.4, 38.6, 40.6, 41.9, 54.9, 64.4, 64.5, 70.0, 91.1, 107.9, 111.1, 111.3, 119.1, 119.7, 122.3, 122.4, 127.8, 136.2, 167.7. IR (thin film, CH_2Cl_2, cm^{-1}) 1631, 1230. MS (FAB) *m*/*z* 382 $[M+H]^+$ (Calcd for $C_{22}H_{26}N_2O_4$: 382.1971. Found: 382.1965).

4.5. 7-Hydroxymethyl-1,4a′*S*,5,7′*S*,8,13,13b′*R*,13c′*R*-octahydro-2*H*,4*H*-6a,13-diaza-indeno[1,2-*c*]phenanthrene-3,6-dione (8)

(3′*S*,6a′*S*,10a′*R*,10b′*S*)-3′-((1*H*-Indol-3-yl)methyl)octahydrospiro-[[1,3]dioxolane-2,8′-oxazolo[2,3-*a*]isoquinolin]-5′(6′*H*)-one **7a** (0.33 g, 0.86 mmol) was dissolved in a 2 M solution of hydrochloric acid in absolute ethanol (15 ml), and the mixture stirred for 72 h at 70 °C. After this time, the reaction was quenched by addition of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3×30 ml). The combined organic fractions were dried over anhydrous magnesium sulfate and the solvent removed by rotary evaporation to yield a crude yellow solid. 400 MHz ^{1}H NMR analysis

of the crude product mixture revealed the formation of **8** as a single diastereoisomer. Purification by flash column chromatography over silica with 95:5/ethyl acetate–methanol as eluent gave the target compound as an off-white solid (220 mg, 77%): mp 202–204 °C. $[\alpha]_D^{20}$=52.0 [*c* 0.5 in CH_3OH]. ^1H NMR (400 MHz; DMSO) 1.64–1.73 (1H, m), 1.90–2.06 (3H, m), 2.10–2.31 (4H, m), 2.45–2.67 (3H, m), 3.19–3.33 (2H, m), 4.34 (1H, d, *J*=8.4 Hz), 4.66 (1H, t, *J*=5.6 Hz), 5.04–5.09 (1H, m), 6.84–6.88 (1H, m), 6.94–6.98 (1H, m), 7.26–7.29 (2H, m), 10.47 (1H, s). ^{13}C NMR (100 MHz; DMSO) 20.9, 30.8, 35.5, 39.3, 39.9, 40.9, 45.9, 48.6, 54.2, 59.6, 106.7, 111.5, 117.6, 118.7, 121.2, 126.5, 132.9, 136.5, 168.0, 209.0. IR (thin film, CH_2Cl_2, cm^{-1}) 3317, 1621. MS (FAB) *m*/*z* 338 $[M+H]^+$ (Calcd for $C_{20}H_{22}N_2O_3$: 338.1709. Found: 338.1715).

4.6. 7-Hydroxymethyl-1,4a′*R*,5,7′*S*,8,13,13b′*R*,13c′*S*-octahydro-2*H*,4*H*-6a,13-diaza-indeno[1,2-*c*]phenanthrene-3,6-dione (9)

(3′*S*,6a′*R*,10a′*S*,10b′*R*)-3′-((1*H*-Indol-3-yl)methyl)octahydrospiro-[[1,3]dioxolane-2,8′-oxazolo[2,3-*a*]isoquinolin]-5′(6′*H*)-one **7b** (0.27 g, 0.71 mmol) was dissolved in a 2 M solution of hydrochloric acid in absolute ethanol (15 ml), and the mixture stirred for 72 h at 70 °C. After this time, the reaction was quenched by addition of saturated aqueous sodium bicarbonate and extracted with ethyl acetate (3×30 ml). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and the solvent removed by rotary evaporation to yield a crude yellow solid. 400 MHz ^1H NMR analysis of the crude product mixture revealed the formation of **9** as a single diastereoisomer. Purification by flash column chromatography over silica using 95:5/ethyl acetate–methanol as eluent gave the target compound as an off-white solid (160 mg, 70%): mp 212–213 °C. $[\alpha]_D^{20}$=9.9 [*c* 0.5 in CH_3OH]. ^1H NMR (400 MHz; $CDCl_3$) 2.00–2.25 (2H, m), 2.30–2.34 (2H, m), 2.39–2.80 (8H, m), 3.11 (1H, ddd, *J*=2.0, 6.4, 16.0 Hz), 3.62–3.72 (2H, m), 5.02 (1H, d, *J*=5.2 Hz), 5.25–5.28 (1H, m), 7.08–7.20 (2H, m), 7.30 (1H, d, *J*=8.0 Hz), 7.45 (1H, d, *J*=7.6 Hz), 8.38 (1H, s). ^{13}C NMR (100 MHz; $CDCl_3$) 21.5, 28.2, 34.0, 40.3, 41.0, 41.6, 46.7, 51.1, 52.3, 61.6, 111.1, 111.2, 118.1, 120.0, 122.7, 126.8, 130.0, 136.2, 172.0, 208.6. IR (thin film, CH_2Cl_2, cm^{-1}) 3311, 1633. MS (FAB) *m*/*z* 338 $[M+H]^+$ (Calcd for $C_{20}H_{22}N_2O_3$: 338.1709. Found: 338.1713).

4.7. Crystal data for 7a

$C_{22}H_{26}N_2O_4$, *M*=382.45, orthorhombic, $P2_12_12_1$, *a*=15.0528(18), *b*=15.7363(19), *c*=16.173(2) Å, *V*=3831.0(8) $Å^3$, *Z*=8, D_c=1.326 g cm^{-3}, μ(Mo Kα)=0.092 mm^{-1}, *T*=150(2) K, colourless block, 0.42×0.29×0.23 mm^3; 31,767 reflections measured on a Bruker APEX II CCD diffractometer, of which 4188 were independent, data corrected for absorption on the basis of symmetry equivalent and repeated data (min and max transmission factors: 0.963, 0.979) and Lp effects, R_{int}=0.0509, structure solved by direct methods, F^2 refinement, R_1=0.092 for 4188 data with $F^2>2\sigma(F^2)$, wR_2=0.218 for all data; 511 parameters. Two molecules of **7a** in the asymmetric unit with different conformations. Absolute structure could not be determined from the diffraction data but was set from the known chiral centres. Friedel pairs were merged.

The crystal structure of **7a** has two molecules in the asymmetric unit, shown in Figures SI1 and SI2 below. They have different conformations at the O(3)/O(4) hinge and different torsion angles around the C(10)/C(9)/C(8)/C(1) linkage.

The crystal structure has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 734488.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.09.097.

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