

A Highly Stereoselective Synthesis of the Indolo[2,3-*a*]quinolizine Ring System and Application to Natural Product Synthesis

Steven M. Allin,^{*,[a]} Christopher I. Thomas,^[a] James E. Allard,^[a] Kevin Doyle,^[b] and Mark R. J. Elsegood^[a]

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We present a facile and highly stereoselective approach to the indolo[2,3-*a*]quinolizine ring system from a readily available, non-racemic chiral template. We demonstrate the potential for application of this methodology to natural product synthesis through conversion of the template to some repre-

sentative indole alkaloids with high enantiomeric purity in both enantiomeric series.

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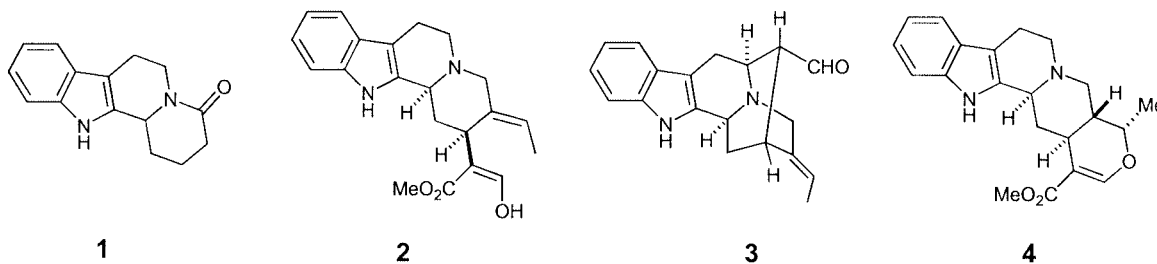
The indolo[2,3-*a*]quinolizine ring system **1** is of great interest and significance since this heterocyclic template is found within a plethora of highly bioactive indole alkaloids, including geissoschizine (**2**),^[1] vellosimine (**3**)^[2] and ajmalicine (**4**).^[3] The presence of the lactam carbonyl in templates such as **1** would allow for possible further functionalisation en route to the natural product targets. Recent approaches to the construction of this heterocyclic target system by other groups have included the diastereoselective vinylogous Mannich reaction,^[4] Bischler–Napieralski reaction,^[5] Fischer indole synthesis^[6] and the asymmetric Pictet–Spengler reaction.^[7]

We have recently developed a new and general approach for the stereoselective synthesis of a range of non-racemic heterocycles that involves the cyclisation of pendent aromatic substituents onto *N*-acyliminium intermediates as the key ring-forming step.^[8] Based on our novel approach to the indolizino[8,7-*b*]indole ring system,^[8a] we recognised that a suitably substituted bicyclic lactam could act as a

precursor in a stereoselective approach to the indolo[2,3-*a*]quinolizine ring system.

Our approach to the synthesis of the required bicyclic lactam substrate **5** followed the general method previously used in our group.^[8] The β -amino alcohol derivative of (*S*)-tryptophan was reacted under Dean–Stark conditions in toluene with an appropriate functionalised substrate for 48 h (Scheme 1). Under these reaction conditions we were able to isolate the expected bicyclic lactam in 69% yield as a 5:1 mixture of separable diastereoisomers, **5a** and **5b**.

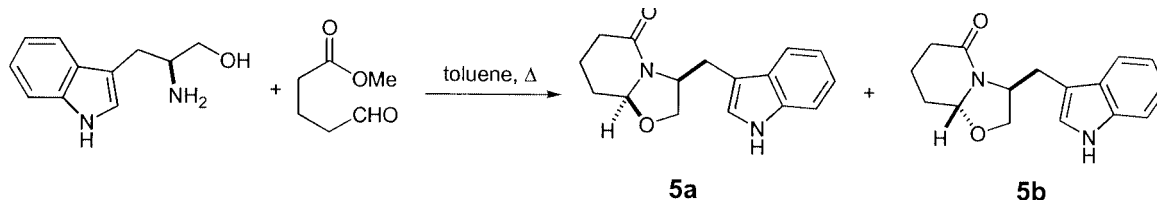
The relative stereochemistry of the major diastereoisomer **5a** was determined by single-crystal X-ray analysis.^[9] This indole-containing bicyclic lactam is a novel example of the fused 5,6-ring system favoured by Amat and Bosch,^[10] and the relative stereochemistry observed for the major isomer **5a** is consistent with results obtained both by these researchers and in our own previous work in other areas.^[8b]



In a previous communication we noted briefly that treatment of the initial mixture of diastereoisomers of substrate **5** with TiCl_4 gave the desired indolo[2,3-*a*]quinolizine target **6** in 54% yield, but with only a poor level of product diastereoselectivity (5:2).^[8a] We have since discovered that sim-

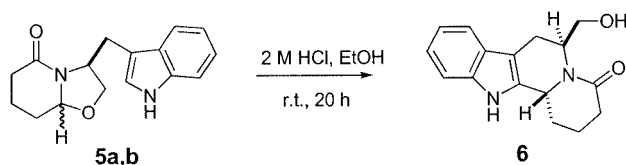
[a] Department of Chemistry, Loughborough University, Loughborough, Leicestershire, LE11 3TU, England
E-mail: s.m.allin@lboro.ac.uk

[b] OSI Pharmaceuticals, Watlington Road, Oxford, OX4 6LT, England



Scheme 1.

ply treating the mixture of bicyclic lactam substrate diastereoisomers, **5a** and **5b**, with 2 M HCl in ethanol at room temperature for 20 hours gives an excellent yield of 95% for the cyclisation reaction, and leads to the formation of the desired indolo[2,3-*a*]quinolizine product as a *single* diastereoisomer (Scheme 2).



Scheme 2.

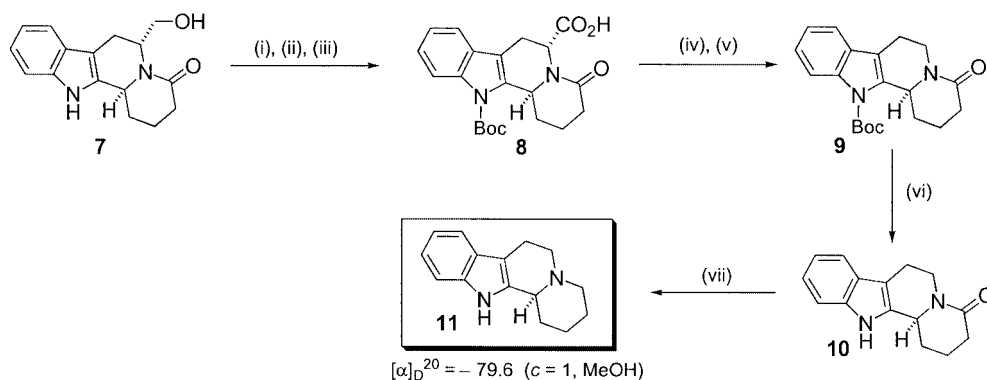
The relative stereochemistry of the single diastereoisomer **6** was determined by single-crystal X-ray analysis^[9] and was found to be as favoured in the TiCl_4 -mediated cyclisation reaction that had previously given only a 5:2 ratio of product diastereoisomers.

To highlight the synthetic utility of this methodology in the target synthesis of complex indole alkaloids and their synthetic analogues, we undertook the synthesis of a simple indole alkaloid, (*S*)-(-)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**11**), the main constituent of *Dracontomelum mangiferum* B1.^[11] In order to access the natural (*S*)-enantiomer of the target we were required to work with the enantiomer of the template. Hence compound **7** was prepared as a single diastereoisomer from (*R*)-tryptophan by analogous chemistry to that described above. Our synthetic route to the natural product **11** from **7** is highlighted in Scheme 3.

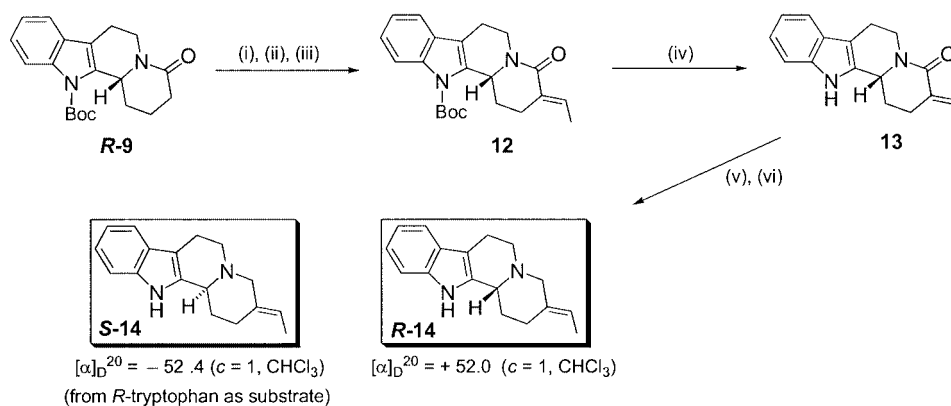
Our previous method to remove the hydroxymethyl group from templates such as **7** has involved a rhodium-induced decarbonylation sequence.^[8a] Due to the rather long reaction times generally needed for our substrates in this protocol we have now applied an easier approach that relies upon a decarboxylation strategy. Compound **7** was oxidised to the carboxylic acid derivative **8** through the corresponding aldehyde; from **8** we generated the acyl selenide derivative and subsequently performed a tin-mediated deacylation to yield the indolo[2,3-*a*]quinolizine ring system **9**. Deprotection of the indole nitrogen gave the known compound (*S*)-**10** in >95% *ee* by comparison of optical rotation data.^[12a] Reductive removal of the lactam carbonyl group completed the synthesis of the natural product. Target (*S*)-(-)-**11** was found to have an *ee* of 95% and the same absolute configuration as the natural product by comparison of optical rotation data.^[12b]

In order to further extend the application of our methodology we chose to pursue the synthesis of deplancheine, **14**, an alkaloid isolated from the New Caledonian plant *Alstonia deplanchei*.^[13] As a consequence of the work of Meyers in 1986 that described an asymmetric approach to deplancheine, the absolute configuration of the natural product was determined to be *R*.^[13a]

A successful synthesis of deplancheine would require us to further functionalise the lactam ring of the template. Construction of the requisite ethylidene moiety was achieved through a three-step procedure involving generation of the lithium enolate from (*R*)-**9**, prepared by analogous chemistry to that described in Scheme 3 but starting from (*S*)-tryptophan. Subsequent aldol reaction with acet-



Scheme 3. (i) 1-Hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide (IBX), DMSO, room temp., 24 h (60%); (ii) Et_3N , (Boc) $_2\text{O}$, DMAP, THF, room temp., 4 h (63%); (iii) NaClO_2 , NaH_2PO_4 , 1-methyl-1-cyclohexene, CH_3CN , *t*BuOH, H_2O , 0 °C to room temp., 18 h (70%); (iv) (PhSe) $_2$, PBu_3 , CH_2Cl_2 , 0 °C to room temp., 18 h (66%); (v) $n\text{Bu}_3\text{SnH}$, AIBN, toluene, 80 °C, 2 h (98%); (vi) TBAF, THF, Δ , 9 h (63%); (vii) LiAlH_4 , THF, Δ , 3 h then room temp., 12 h (96%).



Scheme 4. Asymmetric synthesis of deplancheine: (i) LDA, CH_3CHO , THF, -78°C to room temp., 24 h; (ii) Et_3N , MsCl , DCM, -40°C to room temp., 3 h; (iii) DBN, THF, room temp., 16 h (65% for 3 steps); (iv) TBAF, THF, Δ , 9 h (63%); (v) Me_3OBF_4 , 2,6-di-*t*-Bu-Py, DCM, room temp., 21 h; (vi) NaBH_4 , MeOH, 0°C , 0.5 h (77% for 2 steps).

aldehyde, activation of the hydroxy group by mesylation and finally DBN-induced elimination gave the initial target **12** (Scheme 4). We found that whereas a THF/DCM solvent mixture in the elimination step gave only a 4.7:1 ratio in favour of the desired *E*-isomer **12**, if the elimination procedure was carried out in THF alone as solvent the *E*-regioisomer of the ethylidene product **12** was obtained exclusively.^[14] TBAF-induced deprotection of the indole nitrogen atom liberated the lactam intermediate **13**.^[15]

The synthesis of (*R*)-deplancheine was completed through removal of the lactam carbonyl group as described in Scheme 4 through application of a route described by Martin and co-workers.^[16] The desired target, (*R*)-(+)-deplancheine (**14**), was obtained with an *ee* of >95% and the same absolute configuration as the natural product by comparison of optical rotation data.^[13a] An X-ray crystal struc-

ture of the product (*R*)-**14** was obtained and is presented Figure 1.

The crystals were obtained by slow evaporation of a dichloromethane solution of the compound. The asymmetric unit comprises two molecules of **14** and one molecule of water. The water molecule links together three molecules of **14** by strong H bonds, while the NH on N(27) forms a weak $\text{N}-\text{H}\cdots\pi$ interaction to the ring C(22B)–C(26) on a symmetry related molecule.

To demonstrate the potential synthetic utility of our methodology we have also undertaken an asymmetric synthesis of the enantiomer of deplancheine. Our route mirrors that described in Scheme 4, but uses the (*R*)-enantiomer of tryptophan as the starting material. The desired target, (*S*)-(–)-deplancheine (Scheme 4), was isolated with an *ee* of >95% by comparison of optical rotation data.^[13a]

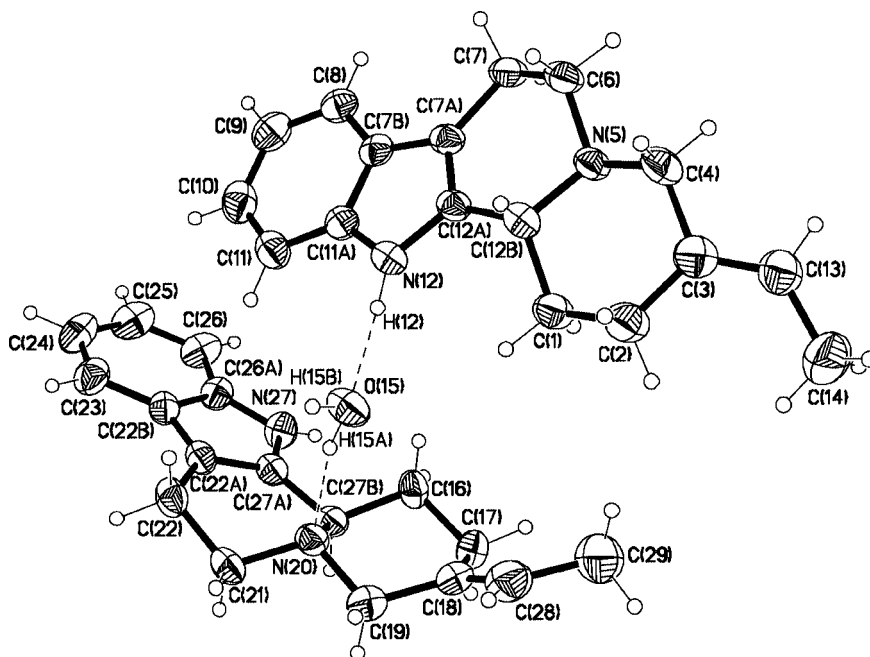


Figure 1. X-ray crystal structure of (*R*)-**14**.

In summary, we report a facile and highly stereoselective approach to the important indolo[2,3-*a*]quinolizine template from readily available non-racemic substrates, and have demonstrated the structural modification of the template to deliver indole alkaloids with high enantiomeric purity in both enantiomeric series. Current work is focused on extending the methodology described in this paper to other, more complex indole alkaloid targets. Our progress will be reported in due course.

Experimental Section

General Information: Solvents and Reagents: All solvents where necessary were dried, distilled and stored over 4-Å molecular sieves prior to use. IBX = 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide. Chromatographic Procedures: Analytical thin-layer chromatography (TLC) was carried out using aluminium-backed plates coated with silica (0.2 mm). Plates were visualised under UV light ($\lambda = 254$ nm) or by staining with either potassium permanganate solution or PMA (phosphomolybdic acid). Flash column chromatography was carried out using Merck Kieselgel (70–230 Mesh ASTM). Samples were applied as saturated solutions in an appropriate solvent or pre-adsorbed onto the minimum quantity of silica. Hand bellows were used to apply pressure when required at the column. Spectra: IR spectra were recorded in the range from 4000 to 600 cm^{-1} . Solid samples were run as nujol mull, and liquids as thin films. Nuclear Magnetic Resonance (NMR) spectra: Multiplicities were recorded as broad peaks (br.), singlets (s), doublets (d), triplets (t), double doublets (dd) and multiplets (m). All NMR samples were made up in deuterated chloroform with all values quoted in ppm relative to tetramethylsilane as internal reference. Coupling constants (*J* values) are reported in Hertz (Hz). Diastereoisomer ratios were calculated from the integration of suitable peaks in the proton NMR spectroscopy.

3-([1*H*-Indol-3-yl]methyl)hexahydrooxazolo[3,2-*a*][1,3]pyridin-5-one (5): (2*S*)-2-Amino-3-(1*H*-indol-3-yl)propan-1-ol (3.0 g, 15.8 mmol) and methyl 5-oxopentanoate (2.1 g, 15.8 mmol) were added to toluene (150 mL) and refluxed under Dean–Stark conditions for 48 hours. The mixture was cooled to room temperature and the solvent removed under reduced pressure to yield the target compound. 250 MHz ^1H NMR spectroscopy on the crude product mixture revealed the formation of **5** as a 5:1 mixture of diastereoisomers. These diastereoisomers were purified and separated by flash column chromatography over silica using ethyl acetate as eluent (2.90 g, 69%).

Major Isomer (3*S*,8*aS*)-5a: Isolated as a yellow solid which was recrystallized from dichloromethane to yield colourless needles; M.p. 152–156 °C. $[\alpha]_{\text{D}} = -39.1$ ($c = 1.7$, CH_2Cl_2). $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_2$: calcd. C 71.09, H 6.71, N 10.36; found C 71.04, H 6.69, N 10.27. IR (thin film, DCM, cm^{-1}): $\tilde{\nu}_{\text{max}} = 3274$ (NH), 1628 (NC=O). ^1H NMR (400 MHz, CDCl_3): $\delta = 1.43$ – 1.57 (m, 1 H), 1.67 – 1.77 (m, 1 H), 1.96 – 2.01 (m, 1 H), 2.24 – 2.28 (m, 1 H), 2.41 – 2.45 (m, 2 H), 2.68 (dd, $J = 16, 8$ Hz, 1 H), 3.67 – 3.76 (m, 2 H), 4.03 (d, $J = 8$ Hz, 1 H), 4.28 – 4.33 (m, 1 H), 4.68 (dd, $J = 12, 4$ Hz, 1 H), 7.03 (d, $J = 4$ Hz, 1 H), 7.05 – 7.22 (m, 2 H), 7.36 (d, $J = 8$ Hz, 1 H), 7.82 (d, $J = 8$ Hz, 1 H), 8.24 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 17.6$ (CH_2), 27.0 (CH_2), 28.4 (CH_2), 31.1 (CH_2), 56.1 (CH), 70.0 (CH_2), 89.0 (CH), 111.1 (CH), 112.6 (C), 119.4 (CH), 119.6 (CH), 122.2 (CH), 122.4 (CH), 127.7 (C), 136.2 (C), 168.1 (NC=O) ppm. MS (EI): m/z (%) = 270 (100) [M^+] (found: M^+ , 270.13690. $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_2$ requires 270.13683).

Minor Isomer (3*S*,8*aR*)-5b: Isolated as a pale yellow oil. $[\alpha]_{\text{D}} = +14.3$ ($c = 2.0$, CH_2Cl_2) $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_2$: calcd. C 71.09, H 6.71, N 10.36; found C 70.97, H 6.69, N 10.35. IR (thin film, DCM, cm^{-1}): $\tilde{\nu}_{\text{max}} = 3279$ (NH), 1628 (NC=O). ^1H NMR (400 MHz, CDCl_3): $\delta = 1.33$ – 1.42 [m, 1 H, $\text{CH}(\text{H})\text{CH}_2\text{CH}_2\text{C}=\text{O}$], 1.51 – 1.59 [m, 1 H, $\text{CH}_2\text{CH}(\text{H})\text{CH}_2\text{C}=\text{O}$], 1.80 – 1.88 [m, 1 H, $\text{CH}_2\text{CH}(\text{H})\text{CH}_2\text{C}=\text{O}$], 2.14 – 2.18 [m, 1 H, $\text{CH}(\text{H})\text{CH}_2\text{CH}_2\text{C}=\text{O}$], 2.27 – 2.37 [m, 1 H, $\text{CH}(\text{H})\text{C}=\text{O}$], 2.53 [dd, $J = 16, 8$ Hz, $\text{CH}(\text{H})\text{C}=\text{O}$, 1 H], 3.05 [dd, $J = 16, 8$ Hz, $\text{CH}(\text{H})\text{C}=\text{C}$, 1 H], 3.32 [dd, $J = 16, 4$ Hz, 1 H, $\text{CH}(\text{H})\text{C}=\text{C}$], 3.69 [dd, $J = 8.8, 7.2$ Hz, 1 H, $\text{CH}(\text{H})\text{O}$], 4.04 – 4.09 [m, 1 H, $\text{CH}(\text{H})\text{O}$], 4.46 (dd, $J = 8, 4$ Hz, 1 H, $\text{NCH}(\text{OCH}_2)$), 4.60 – 4.67 (m, 1 H, NCHCH_2O), 7.01 (d, $J = 4$ Hz, 1 H, $\text{C}=\text{CHNH}$), 7.10 – 7.14 (m, 1 H, *ArH*), 7.17 – 7.21 (m, 1 H, *ArH*), 7.36 (d, $J = 8$ Hz, 1 H, *ArH*), 7.69 (d, $J = 8$ Hz, 1 H, *ArH*), 8.34 (br. s, 1 H, *NH*) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 14.2$ (CH_2), 27.6 (CH_2), 28.2 (CH_2), 31.4 (CH_2), 54.5 (CH), 69.7 (CH_2), 87.3 (CH), 111.1 (CH), 111.2 (C), 119.2 (CH), 119.5 (CH), 122.2 (CH), 122.6 (CH), 127.8 (C), 136.3 (C), 168.8 (NC=O) ppm. MS (EI): m/z (%) = 270 (23.3) [M^+] (found: M^+ , 270.13690. $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_2$ requires 270.13683).

(6*S*,12*bR*)-1,2,3,6,7,12*b*-Hexahydro-6-(hydroxymethyl)indolo[2,3-*a*]quinolizin-4(12*H*)-one (6): Compound **5a** (3.1 g, 11.5 mmol) was dissolved in absolute ethanol (100 mL) under nitrogen. The resulting solution was acidified to pH 1 by the addition of 2 M HCl in ethanol, and the mixture was stirred for a further 20 hours at room temperature. After this time the reaction was quenched by addition of saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate (3×150 mL). The organic fraction was dried with anhydrous magnesium sulfate and the solvent removed by rotary evaporation to yield a light brown solid (2.9 g, 95%). 250 MHz ^1H NMR spectroscopy on the crude product mixture revealed formation of **6** as a single diastereoisomer, which was recrystallised from absolute ethanol to yield the target compound as colourless block-like crystals, m.p. 288–290 °C. $[\alpha]_{\text{D}} = +128.8$ ($c = 0.50$, EtOH). $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_2$: calcd. C 71.09, H 6.71, N 10.36; found C 70.75, H 6.67, N 10.28. IR (thin film, DCM, cm^{-1}): $\tilde{\nu}_{\text{max}} = 3277$ (NH), 1618 (NC=O). ^1H NMR (400 MHz, DMSO): $\delta = 1.52$ – 1.62 (m, 1 H), 1.73 – 1.86 (m, 2 H), 2.26 – 2.43 (m, 2 H), 2.59 – 2.63 (m, 1 H), 2.66 (dd, $J = 16, 8$ Hz, 1 H), 2.80 (d, $J = 16$ Hz, 1 H), 3.35 – 3.37 (m, 2 H), 4.65 (d, $J = 8$ Hz, 1 H), 4.81 (t, $J = 4$ Hz, 1 H), 5.22 (q, $J = 7.5$ Hz, 1 H), 6.95 – 6.99 (m, 1 H), 7.04 – 7.08 (m, 1 H), 7.32 (d, $J = 8$ Hz, 1 H), 7.40 (d, $J = 8$ Hz, 1 H), 10.09 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz; DMSO): $\delta = 19.4$ (CH_2), 21.0 (CH_2), 29.0 (CH_2), 32.7 (CH_2), 48.2 (CH), 50.6 (CH), 60.2 (CH_2), 105.1 (C), 111.4 (CH), 118.1 (CH), 118.8 (CH), 121.3 (CH), 127.1 (C), 133.7 (C), 136.7 (C), 168.8 (NC=O) ppm. MS (EI): m/z (%) = 270 (100) [M^+] (found: M^+ , 270.13626. $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_2$ requires 270.13683).

Three-Step Route to Access 8

(6*R*,12*bS*)-1,2,3,4,6,7,12,12*b*-Octahydro-4-oxoindolo[2,3-*a*]quinolizine-6-carbaldehyde: To a solution of **7** (5.0 g, 18.5 mmol) in dimethyl sulfoxide (40 mL) was added IBX (15.4 g, 55.5 mmol) with stirring under nitrogen. After 24 hours stirring at room temperature the solvent was removed and the resulting solid was re-suspended in ethyl acetate (250 mL), before filtering through a small pad of celite. The filtrate was washed with water (3×250 mL), the organic phase was then dried with anhydrous magnesium sulfate, filtered and the solvents evaporated to dryness to yield the target compound which was purified by flash column chromatography over silica using ethyl acetate as eluent. The purified aldehyde was afforded as a pale yellow foam (3.0 g, 60%), m.p. 97.5–99 °C. $[\alpha]_{\text{D}} = -201.3$ ($c = 1.2$, CH_2Cl_2). IR (thin film, DCM, cm^{-1}): $\tilde{\nu}_{\text{max}} = 3271$ (NH), 1727 (CHO), 1617 (NBoc[C=O]). ^1H NMR (400 MHz, CDCl_3): $\delta = 1.66$ – 1.77 [m, 1 H, $\text{CH}(\text{H})\text{CH}_2\text{CH}_2\text{C}=\text{O}$], 1.99 – 2.05

(m, 2 H, $\text{CH}_2\text{CH}_2\text{C}=\text{O}$), 2.40–2.48 [m, 1 H, $\text{CH}(\text{H})\text{CH}_2\text{CH}_2\text{C}=\text{O}$], 2.49–2.54 [m, 1 H, $\text{CH}(\text{H})\text{C}=\text{O}$], 2.69–2.76 [m, 1 H, $\text{CH}(\text{H})\text{C}=\text{O}$], 3.10 [ddd, $J = 16, 8, 4$ Hz, 1 H, $\text{CH}(\text{H})\text{CHCHO}$], 3.41–3.47 [m, 1 H, $\text{CH}(\text{H})\text{CHCHO}$], 4.89–4.93 (m, 1 H, $\text{C}=\text{CCH}$), 5.97–5.99 (m, 1 H, CHCHO), 7.11–7.24 (m, 2 H, ArH), 7.30–7.32 (m, 1 H, ArH), 7.53–7.55 (m, 1 H, ArH), 8.15 (br. s, 1 H, NH), 9.49 (s, 1 H, CHO) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 19.5$ (CH_2), 20.0 (CH_2), 29.6 (CH_2), 32.0 (CH_2), 52.2 (CH), 56.8 (CH), 106.4 (C), 111.1 (CH), 118.3 (CH), 120.0 (CH), 122.6 (CH), 126.5 (C), 132.7 (C), 136.5 (C), 170.4 ($\text{NC}=\text{O}$), 199.3 (CHO) ppm. MS (EI): m/z (%) = 268 (75.9) [M^+], (found: M^+ , 268.12130. $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_2$ requires 268.12118).

(6*R*,12*bS*)-tert-Butyl-6-formyl-1,2,3,4,6,7-hexahydro-4-oxoindolo[2,3-*a*]quinolizine-12(12*bH*)-carboxylate: (6*R*,12*bS*)-1,2,3,4,6,7,12,12*b*-octahydro-4-oxoindolo[2,3-*a*]quinolizine-6-carbaldehyde (3.5 g, 13.1 mmol) was dissolved in anhydrous tetrahydrofuran (40.0 mL) under nitrogen. Triethylamine (3.7 mL, 26.2 mmol), 4-(Dimethylamino)pyridine (0.35 g, 2.7 mmol) and di-*tert*-butyl dicarbonate (3.8 g, 17.1 mmol) were added successively, and the resulting solution was stirred at room temperature under nitrogen for 4 hours. After this time the volatiles were removed by rotary evaporation and the resulting residue was re-dissolved in ethyl acetate (200 mL) and washed successively with saturated aqueous ammonium chloride (2×200 mL), saturated aqueous sodium hydrogencarbonate (2×200 mL) and brine (200 mL). The organic layer was dried with anhydrous magnesium sulfate, the solvent removed under rotary evaporation and the crude product was adsorbed onto silica and purified by flash column chromatography over silica using ethyl acetate/hexane (3:2) as eluent. The product was isolated as a yellow oil (2.6 g, 63%). $[\alpha]_{\text{D}} = -925.3$ ($c = 3.0$, CH_2Cl_2). IR (thin film, DCM, cm^{-1}): $\tilde{\nu}_{\text{max}} = 1729$ (CHO), 1653 ($\text{NBoc}[\text{C}=\text{O}]$). ^1H NMR (400 MHz, CDCl_3): $\delta = 1.41$ – 1.50 [m, 1 H, $\text{C}=\text{CCHCH}(\text{H})$], 1.67 [s, 9 H, $\text{OC}(\text{CH}_3)_3$], 1.96–2.04 (m, 2 H, $\text{CH}_2\text{CH}_2\text{C}=\text{O}$), 2.50–2.59 [m, 1 H, $\text{CH}(\text{H})\text{C}=\text{O}$], 2.61–2.65 [m, 1 H, $\text{C}=\text{CCHCH}(\text{H})$], 2.71–2.78 [m, 1 H, $\text{CH}(\text{H})\text{C}=\text{O}$], 2.96 [ddd, $J = 16, 8, 4$ Hz, 1 H, $\text{C}=\text{CCH}(\text{H})$], 3.35–3.40 [m, 1 H, $\text{C}=\text{CCH}(\text{H})$], 5.26–5.29 (m, 1 H, $\text{C}=\text{CCH}$), 5.92–5.94 (m, 1 H, NCHCHO), 7.24–7.34 (m, 2 H, ArH), 7.47–7.49 (m, 1 H, ArH), 8.04–8.06 (m, 1 H, ArH), 9.52 (s, 1 H, CHO) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 19.3$ (CH_2), 20.5 (CH_2), 28.4 ($3 \times \text{CH}_3$), 30.6 (CH_2), 31.7 (CH_2), 54.0 (CH), 56.1 (CH), 84.6 (C), 114.7 (C), 115.7 (CH), 118.2 (CH), 123.1 (CH), 125.0 (CH), 128.1 (C), 134.5 (C), 136.9 (C), 149.8 [$\text{NC}(\text{O})\text{OtBu}$], 170.9 ($\text{NC}=\text{O}$), 199.1 (CHO) ppm. MS (EI): m/z (%) = 368 (54.1) [M^+] (found: M^+ , 368.17367. $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_4$ requires 368.17361).

(6*R*,12*bS*)-12-(tert-Butoxycarbonyl)-1,2,3,4,6,7,12,12*b*-octahydro-4-oxoindolo[2,3-*a*]quinolizine-6-carboxylic Acid (8): A solution of (6*R*,12*bS*)-*tert*-butyl-6-formyl-1,2,3,4,6,7-hexahydro-4-oxoindolo[2,3-*a*]quinolizine-12(12*bH*)-carboxylate (2.6 g, 7.1 mmol) in acetonitrile (35.0 mL), *tert*-butyl alcohol (130.0 mL) and 1-methyl-1-cyclohexene (63.0 mL) was stirred rapidly as it was cooled to 0 °C. A solution of sodium chlorite (80% grade) (6.3 g, 54.7 mmol) and sodium dihydrogen phosphate (6.3 g, 49.7 mmol) in water (130.0 mL) was added dropwise over a period of 10 minutes at 0 °C. The solution was then stirred at room temperature for a further 18 hours. After this time the reaction was partitioned between ethyl acetate (300 mL) and brine (200 mL). The ethyl acetate layer was then washed with 1 M aqueous sodium dithionite solution (100 mL). The organic layer was dried with anhydrous magnesium sulfate and the solvents evaporated to dryness to give the target compound which was purified by flash column chromatography over silica eluting with ethyl acetate yielding a yellow oil (1.9 g, 70%). $[\alpha]_{\text{D}} = -530$ ($c = 1.0$, CH_2Cl_2). IR (thin film, DCM, cm^{-1}):

$\tilde{\nu}_{\text{max}} = 3379$ (OH), 1640 ($\text{NC}=\text{O}$). ^1H NMR (400 MHz, CDCl_3): $\delta = 1.34$ – 1.40 [m, 1 H, $\text{C}=\text{CCHCH}(\text{H})$], 1.64 [s, 9 H, $\text{OC}(\text{CH}_3)_3$], 1.82–1.91 (m, 2 H, $\text{CH}_2\text{CH}_2\text{C}=\text{O}$), 2.45–2.62 [m, 1 H, $\text{CH}(\text{H})\text{C}=\text{O}$], 2.45–2.62 [m, 1 H, $\text{C}=\text{CCHCH}(\text{H})$], 2.45–2.62 [m, 1 H, $\text{CH}(\text{H})\text{C}=\text{O}$], 2.83–2.89 [m, 1 H, $\text{C}=\text{CCH}(\text{H})$], 3.35–3.41 [m, 1 H, $\text{C}=\text{CCH}(\text{H})$], 5.33–5.36 (m, 1 H, $\text{C}=\text{CCH}$), 5.98–6.0 (m, 1 H, NCHCO_2H), 7.18–7.28 (m, 2 H, ArH), 7.39–7.41 (m, 1 H, ArH), 8.03 (d, $J = 8$ Hz, 1 H, ArH), 8.80 (br. s, 1 H, CO_2H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 19.0$ (CH_2), 23.2 (CH_2), 28.2 ($3 \times \text{CH}_3$), 30.4 (CH_2), 31.3 (CH_2), 49.8 (CH), 54.1 (CH), 84.4 (C), 115.0 (C), 115.7 (CH), 118.4 (CH), 123.0 (CH), 124.8 (CH), 128.4 (C), 133.9 (C), 136.8 (C), 149.9 [$\text{NC}(\text{O})\text{OtBu}$], 172.1 ($\text{NC}=\text{O}$), 173.0 [$\text{C}(\text{O})\text{OH}$] ppm. MS (EI): m/z (%) = 384 (2) [M^+] (found: M^+ , 384.16768. $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_5$ requires 384.16852).

Radical-Induced Decarboxylation Strategy

(6*R*,12*bS*)-tert-Butyl-1,2,3,4,6,7-hexahydro-4-oxo-6-[(phenylselenanyl)carbonyl]indolo[2,3-*a*]quinolizine-12(12*bH*)-carboxylate: To a flask containing compound **8** (1.9 g, 4.95 mmol) under nitrogen was added anhydrous dichloromethane (30.0 mL) followed by diphenyl diselenide (2.4 g, 7.5 mmol). The resulting mixture was cooled to 0 °C and tributylphosphane (90% grade) (3.1 mL, 10.1 mmol) was added dropwise. The solution was warmed to room temperature and stirring continued for a further 18 hours at room temperature. Dichloromethane (100 mL) and water (100 mL) were added and the aqueous layer was extracted with a further (100 mL) of dichloromethane. The combined organic fractions were washed with brine (100 mL), dried with anhydrous magnesium sulfate and the solvents evaporated to dryness to give the crude product which was purified by flash column chromatography over silica eluting with hexane/ethyl acetate (8:2), then ethyl acetate/hexane (3:2) giving the title compound as a pale yellow foam (1.72 g, 66%), m.p. 75–77 °C. $[\alpha]_{\text{D}} = -84$ ($c = 1.0$, CH_2Cl_2). IR (thin film, DCM, cm^{-1}): $\tilde{\nu}_{\text{max}} = 1729$ (COSePh), 1654 ($\text{NC}=\text{O}$). ^1H NMR (400 MHz, CDCl_3): $\delta = 1.44$ – 1.54 [m, 1 H, $\text{C}=\text{CCHCH}(\text{H})$], 1.70 [s, 9 H, $\text{OC}(\text{CH}_3)_3$], 1.95–2.11 (m, 2 H, $\text{CH}_2\text{CH}_2\text{C}=\text{O}$), 2.60–2.68 [m, 1 H, $\text{C}=\text{CCHCH}(\text{H})$], 2.60–2.68 [m, 1 H, $\text{CH}(\text{H})\text{C}=\text{O}$], 2.78–2.85 [m, 1 H, $\text{CH}(\text{H})\text{C}=\text{O}$], 2.87–2.93 [m, 1 H, $\text{C}=\text{CCH}(\text{H})$], 3.47–3.52 [m, 1 H, $\text{C}=\text{CCH}(\text{H})$], 5.56–5.59 (m, 1 H, NCHCOSePh), 6.15–6.17 (m, 1 H, ArH), 7.24–7.32 (m, 5 H, ArH), 7.39–7.40 (m, 2 H, ArH), 7.43–7.46 (m, 1 H, ArH), 8.03–8.06 (m, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 19.0$ (CH_2), 22.4 (CH_2), 28.3 ($3 \times \text{CH}_3$), 31.1 (CH_2), 31.8 (CH_2), 54.1 (CH), 59.6 (CH), 84.5 (C), 114.8 (C), 115.7 (CH), 118.4 (CH), 123.1 (CH), 124.9 (CH), 125.4 (C), 128.3 (C), 128.9 (CH), 129.2 ($2 \times \text{CH}$), 133.5 (C), 136.0 ($2 \times \text{CH}$), 136.8 (C), 149.9 [$\text{NC}(\text{O})\text{OtBu}$], 171.6 ($\text{NC}=\text{O}$), 200.3 (COSePh) ppm. MS (CI): m/z (%) = 525 (6.7) [MH^+] (found: MH^+ , 525.13013. $\text{C}_{27}\text{H}_{29}\text{N}_2\text{O}_4\text{Se}$ requires 525.12925).

(12*bS*)-tert-Butyl-1,2,3,4,6,7-hexahydro-4-oxoindolo[2,3-*a*]quinolizine-12(12*bH*)-carboxylate (9): A three-necked flask fitted with a condenser, glass stopper and a suba seal was flushed with nitrogen. A solution of (6*R*,12*bS*)-*tert*-butyl-1,2,3,4,6,7-hexahydro-4-oxo-6-[(phenylselenanyl)carbonyl]indolo[2,3-*a*]quinolizine-12(12*bH*)-carboxylate (1.7 g, 3.2 mmol) in anhydrous toluene (20.0 mL) was added through a cannula. The solution was then degassed with nitrogen for 15 minutes before adding tri-*n*-butyltin hydride (3.5 mL, 13.2 mmol) via syringe. The resulting mixture was heated to 80 °C in an oil bath whereupon azobisisobutyronitrile (0.1 g, 0.6 mmol) was added portionwise over a 2 hour period at 80 °C. After 2 hours stirring at 80 °C the mixture was cooled to room temperature and the solvent removed on the rotary evaporator. The resulting crude oil was adsorbed onto silica and purified by flash column chromatography over silica eluting with hexane followed

by ethyl acetate/hexane (3:1). The target compound was isolated as a colourless oil (1.1 g, 98%). $[\alpha]_{\text{D}} = -77.3$ ($c = 1.8$, CH_2Cl_2). IR (thin film, DCM, cm^{-1}): $\tilde{\nu}_{\text{max}} = 1732$ $[\text{NC}=\text{O}(\text{O}i\text{Bu})]$, 1644 ($\text{NC}=\text{O}$). ^1H NMR (400 MHz, CDCl_3): $\delta = 1.32$ – 1.42 [m, 1 H, $\text{C}=\text{CCHCH}(\text{H})$], 1.67 [s, 9 H, $\text{OC}(\text{CH}_3)_3$], 1.79– 1.86 (m, 2 H, $\text{CH}_2\text{CH}_2\text{C}=\text{O}$), 2.34– 2.43 [m, 1 H, $\text{CH}(\text{H})\text{C}=\text{O}$], 2.54– 2.77 [m, 1 H, $\text{C}=\text{CCHCH}(\text{H})$], 2.54– 2.77 [m, 1 H, $\text{CH}(\text{H})\text{C}=\text{O}$], 2.54– 2.77 (m, 2 H, $\text{CH}_2\text{CH}_2\text{N}$), 2.54– 2.77 [m, 1 H, $\text{CH}(\text{H})\text{N}$], 5.05– 5.15 [m, 1 H, $\text{CH}(\text{H})\text{N}$], 5.05– 5.15 (m, 1 H, $\text{C}=\text{CCH}$), 7.18– 7.30 (m, 2 H, ArH), 7.37 (d, $J = 8$ Hz, 1 H, ArH), 8.06 (d, $J = 8$ Hz, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 19.5$ (CH_2), 21.6 (CH_2), 28.1 ($3\times\text{CH}_3$), 30.2 (CH_2), 32.1 (CH_2), 38.8 (CH_2), 56.0 (CH), 84.1 (C), 115.5 (CH), 118.2 (CH), 118.2 (C), 122.9 (CH), 124.5 (CH), 128.6 (C), 135.2 (C), 136.8 (C), 150.1 $[\text{NC}(\text{O})\text{O}i\text{Bu}]$, 169.4 ($\text{NC}=\text{O}$) ppm. MS (EI): m/z (%) = 340 (13.8) $[\text{M}^+]$ (found: M^+ , 340.17884. $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}_3$ requires 340.17862).

(12bS)-1,2,3,6,7,12b-Hexahydroindolo[2,3-a]quinolizine-4(12H)-one (10): Compound **9** (0.23 g, 0.68 mmol) was dissolved in anhydrous tetrahydrofuran (10.0 mL) under nitrogen. A 1.0 M solution of tetrabutylammonium fluoride in tetrahydrofuran (6.8 mL, 6.8 mmol) was then added, and the mixture was heated under reflux for 9 hours. After this time the mixture was cooled to room temperature and water (40.0 mL) was added. The mixture was extracted with ethyl acetate (2×70.0 mL), and the organic fractions were dried with anhydrous magnesium sulfate and the solvent removed on the rotary evaporator. The crude product was adsorbed onto silica and purified by flash column chromatography over silica using ethyl acetate as eluent to give the target compound as an off-white solid (0.1 g, 63%), m.p. 238–240 °C. $[\alpha]_{\text{D}} = -286$ ($c = 1.0$, CHCl_3). IR (thin film, DCM, cm^{-1}): $\tilde{\nu}_{\text{max}} = 1651$ ($\text{NC}=\text{O}$). ^1H NMR (400 MHz, CDCl_3): $\delta = 1.76$ – 1.89 [m, 1 H, $\text{CH}(\text{H})\text{CH}_2\text{CH}_2\text{C}=\text{O}$], 1.76– 1.89 [m, 1 H, $\text{CH}(\text{H})\text{CH}_2\text{C}=\text{O}$], 2.36– 2.47 [m, 1 H, $\text{CH}(\text{H})\text{CH}_2\text{CH}_2\text{C}=\text{O}$], 2.36– 2.47 [m, 1 H, $\text{CH}(\text{H})\text{C}=\text{O}$], 2.57– 2.62 [m, 1 H, $\text{CH}(\text{H})\text{C}=\text{O}$], 2.72– 2.82 [m, 1 H, $\text{CH}(\text{H})\text{CH}_2\text{N}$], 2.84– 2.89 [m, 1 H, $\text{CH}(\text{H})\text{CH}_2\text{N}$], 2.84– 2.89 [m, 1 H, $\text{CH}(\text{H})\text{N}$], 4.76– 4.80 (m, 1 H, $\text{C}=\text{CCH}$), 5.14– 5.22 [m, 1 H, $\text{CH}(\text{H})\text{N}$], 7.11– 7.21 (m, 2 H, ArH), 7.33– 7.36 (m, 1 H, ArH), 7.51 (d, $J = 8$ Hz, 1 H, ArH), 7.85 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 19.4$ (CH_2), 21.0 (CH_2), 29.1 (CH_2), 32.5 (CH_2), 40.1 (CH_2), 54.4 (CH), 109.8 (C), 110.9 (CH), 118.5 (CH), 119.9 (CH), 122.2 (CH), 127.0 (C), 133.3 (C), 136.2 (C), 169.1 ($\text{NC}=\text{O}$) ppm. MS (EI): m/z (%) = 240 (100.0) $[\text{M}^+]$ (found: M^+ , 240.12632. $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}$ requires 240.12626).

(12bS)-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-a]quinolizine (11): Lithium aluminium hydride (0.07 g, 1.68 mmol) was weighed into a pre-dried three-necked flask fitted with a condenser under nitrogen. Anhydrous tetrahydrofuran (13.0 mL) was added and the suspension was cooled to 0 °C with an ice bath. Compound **10** (0.07 g, 1.68 mmol) in anhydrous tetrahydrofuran (4.0 mL) was added dropwise to the hydride solution at 0 °C. The resulting mixture was heated under reflux for 3 hours and then stirred at room temperature for a further 12 hours. Ether (5.0 mL) was added, and the reaction was quenched by the careful addition of saturated aqueous sodium potassium tartrate solution. The mixture was stirred for another 1 hour before the addition of anhydrous magnesium sulfate prior to filtration through a celite pad. The reaction vessel was washed out with ethyl acetate and filtered through the celite pad. The filtrate was evaporated under reduced pressure to yield the crude product which was adsorbed onto silica and purified by flash column chromatography over silica using ethyl acetate as eluent to give the target compound as a yellow solid (0.09 g, 96%), a small portion of which was recrystallised from dichloromethane to yield yellow plate-like crystals; m.p. 146–148 °C (ref.^[13a] M.p. 149–

150 °C). $[\alpha]_{\text{D}} = -79.6$ ($c = 1.0$, MeOH) [ref.^[13a] $[\alpha]_{\text{D}} = -86.5\pm 2$ ($c = 1.0$, MeOH)]. IR (thin film, DCM, cm^{-1}): $\tilde{\nu}_{\text{max}} = 3441$ (NH). ^1H NMR (400 MHz, CDCl_3): $\delta = 1.40$ – 1.52 [m, 1 H, $\text{C}=\text{CCHCH}_2\text{CH}(\text{H})$], 1.57 [ddd, $J = 24$, 16, 4 Hz, 1 H, $\text{HC}=\text{CCHCH}(\text{H})$], 1.69– 1.77 [m, 2 H, $\text{C}=\text{CCH}(\text{CH}_2)_2\text{CH}_2$], 1.85– 1.89 [m, 1 H, $\text{C}=\text{CCHCH}_2\text{CH}(\text{H})$], 2.02– 2.05 [m, 1 H, $\text{C}=\text{CCHCH}(\text{H})$], 2.37 [dt, $J = 8$, 4 Hz, 1 H, $\text{HC}=\text{CCH}(\text{CH}_2)_3\text{CH}(\text{H})\text{N}$], 2.58– 2.73 [m, 1 H, $\text{C}=\text{CCH}_2\text{CH}(\text{H})\text{N}$], 2.58– 2.73 [m, 1 H, $\text{C}=\text{CCH}(\text{H})\text{CH}_2\text{N}$], 2.96– 3.02 [m, 1 H, $\text{C}=\text{CCH}_2\text{CH}(\text{H})\text{N}$], 2.96– 3.02 [m, 1 H, $\text{C}=\text{CCH}(\text{H})\text{CH}_2\text{N}$], 3.02– 3.08 [m, 1 H, $\text{C}=\text{CCH}(\text{CH}_2)_3\text{CH}(\text{H})\text{N}$], 3.21 (d, $J = 8$ Hz, 1 H, $\text{HC}=\text{CCH}$), 7.06– 7.15 (m, 2 H, ArH), 7.28 (d, $J = 8$ Hz, 1 H, ArH), 7.46 (d, $J = 8$ Hz, 1 H, ArH), 7.73 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 21.6$ (CH_2), 24.3 (CH_2), 25.7 (CH_2), 30.0 (CH_2), 53.6 (CH_2), 55.7 (CH_2), 60.2 (CH), 108.2 (C), 110.7 (CH), 118.1 (CH), 119.4 (CH), 121.3 (CH), 127.5 (C), 135.1 (C), 136.0 (C) ppm. MS (EI): m/z (%) = 226 (72.3) $[\text{M}^+]$ (found: M^+ , 226.14700. $\text{C}_{15}\text{H}_{18}\text{N}_2$ requires 226.14700).

(12bR)-(E)-tert-Butyl-3-ethylidene-1,2,3,4,6,7-hexahydro-4-oxoindolo[2,3-a]quinolizine-12(12b)-carboxylate (12): To a stirred solution of diisopropylamine (1.3 mL, 8.8 mmol) in anhydrous tetrahydrofuran (10.0 mL) was added *n*-butyllithium (2.5 M solution in hexanes) (3.5 mL, 8.8 mmol) dropwise at 0 °C under nitrogen. The reaction mixture was stirred for 15 min at 0 °C and then cooled to –78 °C whereupon a solution of (12bR)-tert-butyl-1,2,3,4,6,7-hexahydro-4-oxoindolo[2,3-a]quinolizine-12(12b)-carboxylate (**R**)-**9** (1.0 g, 2.9 mmol) in anhydrous tetrahydrofuran (15.0 mL) was added through a cannula. The resulting mixture was stirred for a further 30 min at –78 °C after which time acetaldehyde (1.6 mL, 29.0 mmol) was added dropwise via syringe. The reaction was warmed to room temperature overnight and then quenched by the addition of saturated aqueous ammonium chloride solution (30.0 mL) and extracted with ethyl acetate (2×50 mL). The combined organic extracts were dried with anhydrous magnesium sulfate and the solvent was removed under reduced pressure to yield a yellow oil. The crude oil was dissolved in anhydrous dichloromethane (15.0 mL) under nitrogen. Triethylamine (1.2 mL, 8.7 mmol) was added and the mixture cooled to –40 °C before adding methanesulfonyl chloride (0.34 mL, 4.4 mmol). After 20 minutes stirring at –40 °C the reaction was warmed to room temperature and stirred for an additional 3 hours. After this time the solvent was removed and the mesylate dissolved in anhydrous tetrahydrofuran (35.0 mL) to which 1,5-diazabicyclo[4.3.0]non-5-ene (1.1 mL, 8.7 mmol) was added and stirred at room temperature for 16 hours. The solvent was removed and the residue re-dissolved in dichloromethane (80 mL) which was washed with saturated aqueous ammonium chloride solution (60 mL). The organic fraction was dried with anhydrous magnesium sulfate and the solvents evaporated to dryness to give the crude product. 250 MHz ^1H NMR spectroscopy of the crude product revealed formation of the product as a single *trans* geometrical isomer which was purified by flash column chromatography over silica using hexane/ethyl acetate (5:1) as eluent (0.70 g, 65%).

trans Isomer 12: Isolated as a pale yellow oil. $[\alpha]_{\text{D}} = +140.4$ ($c = 2.0$, CH_2Cl_2). IR (thin film, DCM, cm^{-1}): $\tilde{\nu}_{\text{max}} = 1734$ $[\text{NC}=\text{O}(\text{O}i\text{Bu})]$ 1591 ($\text{C}=\text{C}$). ^1H NMR (400 MHz, CDCl_3): $\delta = 1.47$ – 1.52 (m, 1 H), 1.70 (s, 9 H), 1.77 (d, $J = 8$ Hz, 3 H), 2.40– 2.49 (m, 1 H), 2.58– 2.64 (m, 1 H), 2.71– 2.72 (m, 1 H), 2.73– 2.76 (m, 2 H), 2.84– 2.90 (m, 1 H), 5.13– 5.23 (m, 2 H), 7.00– 7.05 (m, 1 H), 7.23– 7.32 (m, 2 H), 7.43– 7.46 (m, 1 H), 8.06– 8.08 (m, 1 H) ppm. ^{13}C NMR (100 MHz, CDCl_3): $\delta = 13.7$ (CH_3), 21.5 (CH_2), 23.4 (CH_2), 28.2 ($3\times\text{CH}_3$), 30.3 (CH_2), 39.1 (CH_2), 55.1 (CH), 84.2 (C), 115.6 (CH), 118.2 (C), 118.3 (CH), 123.0 (CH), 124.5 (CH), 128.6 (C), 129.3 (C), 134.2 (CH), 135.0 (C), 136.7 (C), 150.2 $[\text{NC}(\text{O})\text{O}i\text{Bu}]$, 164.9

(NC=O) ppm. MS (EI): m/z (%) = 366 (8.9) [M^+] (found: M^+ , 366.19484. $C_{22}H_{26}N_2O_3$ requires 366.19434). When the DBN elimination was carried out in a 1:1 mixture of tetrahydrofuran and dichloromethane, a 4.7:1 mixture of *trans:cis* geometrical isomers was obtained; these were separated by column chromatography over silica using hexane/ethyl acetate (5:1) as eluent.

***cis* Isomer:** Isolated as a yellow oil. $[a]_D = +218.4$ ($c = 4.0$, CH_2Cl_2). IR (thin film, DCM, cm^{-1}): $\tilde{\nu}_{max} = 1731$ [NC=O(O)*t*Bu] 1660 (C=C). 1H NMR (400 MHz, $CDCl_3$): $\delta = 1.22$ – 1.533 (m, 2 H), 1.69 (s, 9 H), 2.17 (d, $J = 8$ Hz, 3 H), 2.47–2.52 (m, 1 H), 2.57–2.62 (m, 1 H), 2.73–2.78 (m, 2 H), 2.80–2.88 (m, 1 H), 5.06–5.18 (m, 2 H), 5.92–5.97 (m, 1 H), 7.23–7.32 (m, 2 H), 7.44–7.47 (m, 1 H), 8.04–8.06 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 15.8$ (CH_3), 21.6 (CH_2), 28.2 ($3 \times CH_3$), 30.3 (CH_2), 30.6 (CH_2), 38.8 (CH_2), 55.7 (CH), 84.2 (C), 115.5 (CH), 118.3 (CH), 118.4 (C), 123.0 (CH), 124.5 (CH), 128.7 (C), 128.7 (C), 135.4 (CH), 136.8 (C), 136.8 (CH), 150.2 [NC(O)*Ot*Bu], 165.4 (NC=O) ppm. MS (EI): m/z (%) = 366 (13.1) [M^+] (found: M^+ , 366.19395. $C_{22}H_{26}N_2O_3$ requires 366.19434).

(12b*R*)-(E)-3-Ethylidene-1,2,3,6,7,12b-hexahydroindolo[2,3-*a*]quinolizin-4(12*H*)-one (13): Compound **12** (0.7 g, 1.91 mmol) was dissolved in anhydrous tetrahydrofuran (8.0 mL) under nitrogen. A 1.0 M solution of tetrabutyl ammonium fluoride in tetrahydrofuran (19.1 mL, 19.1 mmol) was then added, and the mixture was heated under reflux for 9 hours. After this time the mixture was cooled to room temperature and water (30.0 mL) was added. The mixture was extracted with ethyl acetate (2×50.0 mL), and the organic fractions were dried with anhydrous magnesium sulfate and the solvent removed on the rotary evaporator. The crude product was adsorbed onto silica and purified by flash column chromatography over silica using hexane/ethyl acetate (3:1) as eluent to give the target compound as a yellow solid (0.32 g, 63%), a portion of which was recrystallised from diethyl ether to give a yellow crystalline solid, m.p. 198–202 °C. $[a]_D = +77.2$ ($c = 1.0$, CH_2Cl_2). IR (thin film, DCM, cm^{-1}): $\tilde{\nu}_{max} = 3238$ (NH), 1746 (NC=O). 1H NMR (400 MHz, $CDCl_3$): $\delta = 1.72$ – 1.82 (m, 1 H), 1.77 (dd, $J = 8$, 4 Hz, 3 H), 2.31–2.41 (m, 1 H), 2.50–2.58 (m, 1 H), 2.77–2.97 (m, 4 H), 4.81–4.84 (m, 1 H), 5.18–5.25 (m, 1 H), 7.00–7.06 (m, 1 H), 7.09–7.19 (m, 2 H), 7.31–7.34 (m, 1 H), 7.49–7.51 (m, 1 H, *ArH*) 8.57 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.7$ (CH_3), 21.1 (CH_2), 22.7 (CH_2), 28.9 (CH_2), 40.6 (CH_2), 54.0 (CH), 109.4 (C), 111.0 (CH), 118.3 (C), 119.6 (CH), 122.0 (CH), 126.8 (C), 129.2 (C), 133.4 (C), 134.1 (CH), 136.4 (C), 164.7 (NC=O) ppm. MS (EI): m/z (%) = 266 (100) [M^+] (found: M^+ , 266.14191. $C_{17}H_{18}N_2O$ requires 266.14191).

(12b*R*)-(E)-3-Ethylidene-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (14): A slurry of compound **13** (0.32 g, 1.2 mmol) and trimethyloxonium tetrafluoroborate (0.48 g, 3.3 mmol) in anhydrous dichloromethane (40.0 mL) containing 2,6-di-*tert*-butylpyridine (0.80 mL, 3.5 mmol) was stirred at room temperature under nitrogen for 21 hours. After this time the reaction was cooled to 0 °C and anhydrous methanol (16.0 mL) was added. After 15 min sodium borohydride (0.48 g, 12.0 mmol) was added carefully and the mixture stirred at 0 °C for a further 30 minutes. The reaction was warmed to room temperature, and saturated aqueous sodium hydrogencarbonate solution (40.0 mL) and ethyl acetate (40.0 mL) were added. The layers were separated and the aqueous layer extracted with ethyl acetate (2×30.0 mL). The combined organic fractions were dried with anhydrous magnesium sulfate and the solvent removed under reduced pressure to give the crude product which was adsorbed onto silica and purified by flash column chromatography over silica eluting with 98:2 ethyl acetate/triethyl-

amine. The target compound was isolated as a yellow solid (0.23 g, 77%), a portion of which was recrystallised from dichloromethane to yield yellow needles; m.p. 139.5–140.5 °C (ref.^[13a] m.p. 140 °C). $[a]_D = +52.0$ ($c = 1.0$, $CHCl_3$) [ref.^[13a] $[a]_D = +56 \pm 2$ ($c = 1.0$, $CHCl_3$)]. IR (thin film, DCM, cm^{-1}): $\tilde{\nu}_{max} = 3455$ (NH). 1H NMR (400 MHz, $CDCl_3$): $\delta = 1.52$ – 1.60 (m, 1 H), 1.63 (d, $J = 8$ Hz, 3 H), 1.95–2.02 (m, 1 H), 2.15–2.20 (m, 1 H), 2.61–2.75 (m, 2 H), 2.80–2.84 (m, 1 H), 2.98–3.11 (m, 3 H), 3.32–3.35 (m, 1 H), 3.38–3.41 (m, 1 H), 5.43 (q, $J = 8$ Hz, 1 H), 7.06–7.15 (m, 2 H), 7.30–7.33 (m, 1 H), 7.46–7.48 (m, 1 H), 7.76 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): 12.7 (CH_3), 21.6 (CH_2), 25.9 (CH_2), 30.3 (CH_2), 52.9 (CH_2), 60.2 (CH), 63.5 (CH_2), 108.4 (C), 110.7 (CH), 118.2 (CH), 119.4 (CH), 119.4 (CH), 121.3 (CH), 127.4 (C), 134.0 (C), 134.6 (C), 136.0 (C) ppm. MS (EI): m/z (%) = 252 [M^+ , 98.6%] (found: M^+ , 252.16261. $C_{17}H_{20}N_2$ requires 252.16265).

X-ray Crystal Structure of (R)-14: Crystal data for **14**·1/2H₂O: $C_{17}H_{21}N_2O_{0.5}$, $M = 261.36$, monoclinic, $P2_1$, $a = 12.7620(16)$, $b = 6.8946(9)$, $c = 17.222(2)$ Å, $\beta = 98.533(2)^\circ$, $V = 1498.5(3)$ Å³, $Z = 4$, $D_c = 1.158$ g cm⁻³, $\mu(Mo-K\alpha) = 0.070$ mm⁻¹, $T = 150(2)$ K, yellow blocks; 8486 reflections measured with a Bruker SMART 1000 CCD diffractometer, of which 4933 were independent, data corrected for absorption on the basis of symmetry equivalent and repeated data (min and max transmission factors: 0.960, 0.987) and L_p effects, $R_{int} = 0.032$, structure solved by direct methods, F^2 refinement, $R_1 = 0.043$ for 3705 data with $F^2 > 2s(F^2)$, $wR_2 = 0.105$ for all data, 367 parameters. CCDC-261811 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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