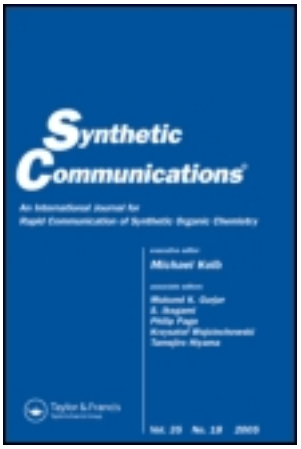

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N-ACYLIMINIUM CYCLIZATION AS AN APPROACH FOR AN ASYMMETRIC SYNTHESIS OF THE PYRROLO[2,1-*a*]BENZAZEPINE RING SYSTEM

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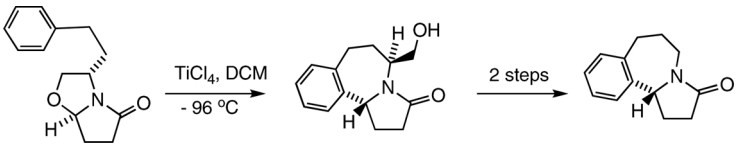
GRAPHICAL ABSTRACT



Abstract *In this article, we report a facile asymmetric synthesis of the pyrrolo[2,1-a]benzazepine ring system based around a stereoselective* N*-acyliminium cyclization of a novel chiral lactam template.*

Keywords Alkaloid; aminoalcohol; asymmetric; cyclization; *N*-acyliminium

INTRODUCTION

Our research group, and others, have had considerable success in recent years developing asymmetric routes to a wide range of important heterocyclic templates, based around the development of a highly diastereoselective *N*-acyliminium cyclization strategy.[1] Our own recent applications of this methodology in natural product synthesis have included targets from the *erythrina* group of alkaloids[1h,i] and several indole alkaloids.[1a,c,d,f] Given our success in the synthesis of the pyrroloisoquinoline ring system, found within the *erythrina* alkaloids,[1h,i] we decided to investigate the application of asymmetric *N*-acyliminium cyclization as an approach to the analogous

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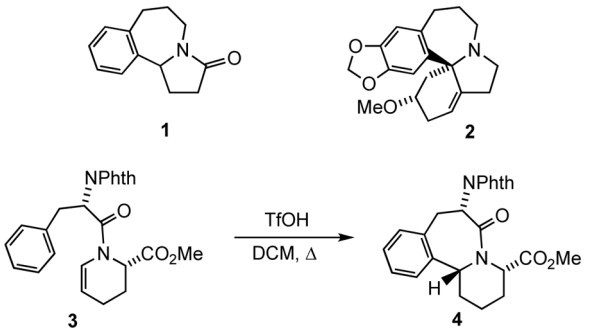
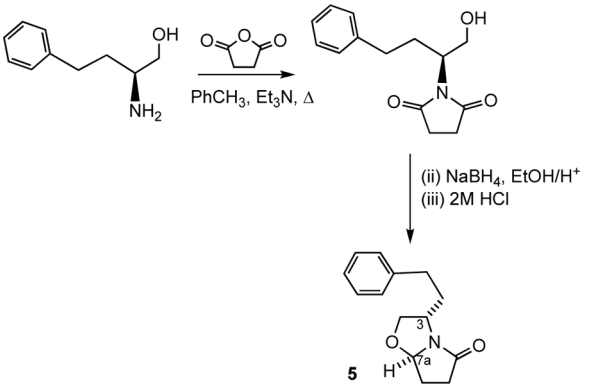
chiral pyrrolo[2,1-*a*]benzazepine ring system, **1**, the core of which is found as a subunit in the *homoerythrina* alkaloids. This natural product family includes dyshomoerythrine, **2**, which has been isolated from the New Zealand silver pine and shown to be active against several important agricultural pests.[2] Although several approaches for the synthesis of *homoerythrina* alkaloids (and structurally simpler pyrrolo[2,1-*a*]benzazepines) have been reported,[3] few involve the intermediacy of an *N*-acyliminium intermediate in an asymmetric cyclization reaction as an approach to construct the central seven-membered ring: Katritzky[4a] reported a titanium tetrachloride–induced cyclization of a benzotriazole derivative to yield the racemic 6,7,5-ring system, **1** (Scheme 1), and Padwa investigated the cyclization of furan onto an in situ–generated *N*-acyliminium species.[4b] Neither of these reports addressed the issue of asymmetric control in the cyclization step. Although not directly related to the 6,7,5-ring system under investigation herein, Flynn et al. were able to achieve diastereocontrol in the *N*-acyliminium cyclization of the chiral phenylalanine-derived enamide **3** to yield a 6,7,6-ring target, **4** (Scheme 1).[5]

Our approach began with the synthesis of the novel bicyclic lactam, **5**, which would serve as the *N*-acyliminium precursor in the key cyclization reaction. As highlighted in Scheme 2, condensation of *S*-2-amino-4-phenylbutan-1-ol with succinic anhydride under Dean–Stark conditions furnished the intermediate imide in good yield. The imide was then subjected to a reduction–cyclization cascade to deliver the desired bicyclic lactam, **5**, as a single diastereoisomer in good yield. The stereochemistry of compound **5** was established by nuclear Overhauser effect (NOE) studies and was found to be as expected from our previous studies on related templates.[1,6] (The protons at positions 3 and 7a do not show a positive NOE effect toward each other, suggesting a *trans* relationship between them. This result is as expected based on previous examples of a range of other bicyclic lactam templates prepared in an analogous fashion by our group.[1,6])

With compound **5** in hand, we turned our attention to the key *N*-acyliminium cyclization reaction. In our previous work, we have investigated the use of a range of activators and reaction conditions for this type of cyclization, including both Lewis and protic acids, and, depending on the structure of the bicyclic lactam, the reaction temperature required to achieve cyclization with a good level of diastereoselectivity. In the case of bicyclic lactam **5**, use of titanium tetrachloride (−78 °C, dichloromethane,



Scheme 1. Chiral pyrrolo[2,1-*a*]benzazepine targets.

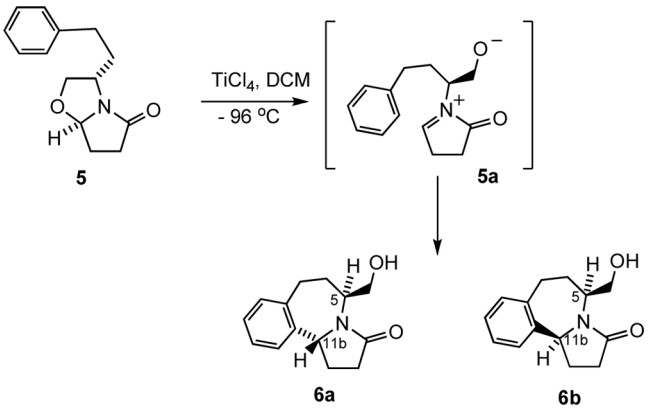


Scheme 2. Synthesis of the key *N*-acyliminium precursor.

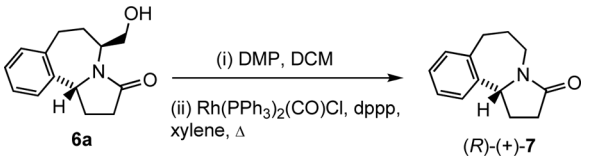
DCM), boron trifluoride–diethyl etherate (−78 °C, DCM), or 2 M HCl (rt, EtOH) as the activator for the cyclization reaction resulted in either re-isolation of the starting material or formation of complex, intractable mixtures of products.

The desired cyclization was finally achieved in almost quantitative yield (97%) by treating lactam **5** with 1.5 eq. of titanium tetrachloride in dry dichloromethane at −96 °C, followed by slow warming to room temperature (Scheme 3). Under these conditions, the desired pyrrolo[2,1-*a*]benzazepinone was formed as a 4:1 mixture of separable diastereoisomers, **6a** and **6b**. The relative stereochemistries of both **6a** and **6b** were established by NOE studies on the purified individual compounds. (For compound **6b**, the proton at position 11b shows a positive NOE with the proton at position 5, confirming the *cis* relationship between these protons. The protons at positions 5 and 11b do not show a positive NOE effect toward each other, suggesting a *trans* relationship between them in compound **6a**.)

The sense of stereochemical induction observed in this cyclization—favoring the formation of the *anti* diastereoisomer **6a** (with respect to the *H*-atoms at the chiral centers)—was found to match that observed in our previous work on related



Scheme 3. Stereoselective cyclization to a pyrrolo[2,1-*a*]benzazepine target.



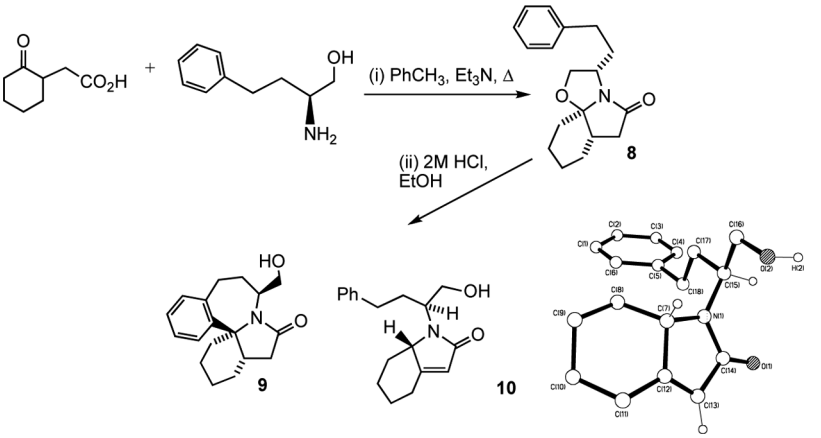
Scheme 4. Removal of the hydroxymethyl substituent.

ring systems.[7] This novel asymmetric cyclization, setting up a central seven-membered ring, can therefore be rationalized by application of the conformational models that we have developed previously.[7]

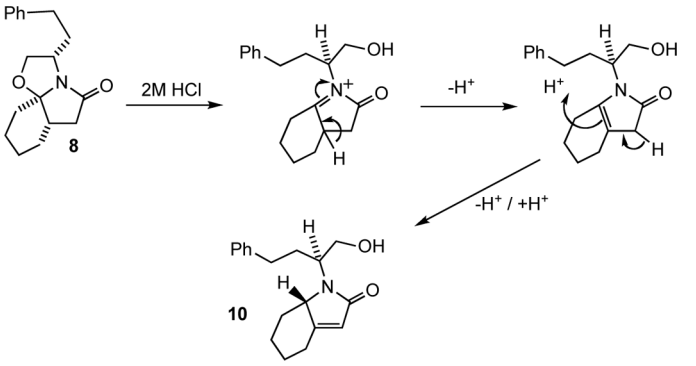
Cyclization of **5** to **6** was more difficult to achieve than the corresponding cyclizations undertaken previously in our laboratory, but this was not unexpected given that we were attempting to generate a seven-membered ring in the current study. The fact that the cyclization was found to proceed only at a *lower* temperature (i.e., −96 °C rather than −78 °C) with the *same* Lewis acid is intriguing, and we suggest that the lower temperature acts to promote the desired cyclization of the aromatic ring to yield the 6,7,5-product **6** (presumably the kinetic product) by slowing the reversible reformation of the 5,5-bicyclic lactam **5** (thermodynamic product). At higher temperatures, although *N*-acyliminium ion generation is to be expected, the preferred reaction is simply for the oxyanion, **5a**, to cyclize to regenerate the starting material, **5**.

To demonstrate the potential utility of this work, we applied a previously developed route for removal of the hydroxymethyl auxiliary tether from the major diasteroisomer, **6a**.[1e,h,i] Oxidation of the primary alcohol moiety in **6a** to yield an intermediate aldehyde was followed by a rhodium-induced decarbonylation to deliver the target amide, *R*-(+)-**7** (Scheme 4).

The structure of the *homoerythrina* alkaloids, exemplified by dyshomoerythrine **2**, is characterized by a tetracyclic ring skeleton. With a successful synthesis of a nonracemic pyrrolo[1,2-*a*]benzazepinone target having been achieved, we became more



Scheme 5. Unexpected formation and x-ray crystal structure of conjugated lactam **10**.



Scheme 6. Proposed mechanism for formation of the conjugated lactam **10**.

ambitious and attempted to access this tetracyclic ring system through an analogous procedure. To this end, novel tricyclic lactam **8** was prepared as highlighted in Scheme 5 and subjected to a range of typical reaction conditions to induce the cyclization (Scheme 5).

Unfortunately, the desired target **9** could not be obtained under any reaction conditions tried by us, including both Lewis and protic acid activation. Instead the only identifiable product to be observed was formation of a single diastereoisomer of the conjugated lactam **10**, in up to 80% yield. The structure of **10** was confirmed by x-ray crystallography using synchrotron radiation (Scheme 5).[8] Formation of **10** can be explained by initial formation of the expected *N*-acyliminium intermediate, followed by a series of proton losses and corresponding double bond migrations from the *N*-acyliminium species, through the enamide, to the more favored conjugated lactam, **10** (Scheme 6). Interestingly, the formation of an analogous conjugated amide as a by-product in a related *N*-acyliminium cyclization reaction was recently observed by Tietze, albeit in the racemic series.[9]

In conclusion, we have developed a new and facile asymmetric synthesis of the pyrrolo[2,1-*a*] benzazepine ring system based around a stereoselective *N*-acyliminium cyclization reaction of a novel template.

EXPERIMENTAL

All solvents were dried, distilled, and stored over 4-Å molecular sieves prior to use. Analytical thin-layer chromatography (TLC) was carried out using aluminium-backed plates coated with 0.2 mm silica. Plates were visualised under ultraviolet (UV) light (at 254 nm) or by staining with either potassium permanganate solution or 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 preadsorbed onto the minimum quantity of silica. Hand bellows were used to apply pressure when required at the column. Infrared (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 (^{1}H and ^{13}C) were recorded using either Bruker AC-250 or DPX-400 instruments.

Multiplicities were recorded as broad peaks (br), singlets (s), doublets (d), triplets (t), and multiplets (m). All NMR samples were made up in deuterated chloroform with all values quoted in parts per million (ppm) relative to tetramethylsilane (TMS) as internal reference, unless otherwise stated. Coupling constants (J values) are reported in hertz (Hz). Diastereoisomer ratios were calculated from the integration of suitable peaks in the proton NMR.

(S)-2-Amino-4-phenylbutan-1-ol

(*S*)-Homophenylalanine hydrochloride salt (2.44 g, 11.34 mmol) was dissolved in the minimum amount of methanol. Sodium carbonate (1.20 g, 11.34 mmol) was added in one portion, and the mixture was allowed to stir for 5 min. The resulting solution was filtered and evaporated under reduced pressure to yield (*S*)-homophenylalanine as a white solid, (1.90 g, 98%). Trimethylsilylchloride (5.39 mL, 42.46 mmol) was added to lithium borohydride (10.61 mL, 21.23 mmol) in tetrahydrofuran (THF; 30 ml) over 5 min under an atmosphere of nitrogen. (*S*)-Homophenylalanine (1.90 g, 10.61 mmol) was cautiously added to the resulting mixture, and the reaction mixture was stirred at room temperature for 24 h. After 24 h, methanol (30 mL) was cautiously added dropwise, and the volatiles were removed using a rotary evaporator. The residue was treated with 20% potassium hydroxide solution (75 mL) and extracted into dichloromethane (3×50 mL). The organic extracts were combined, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed under reduced pressure to yield the target compound as a colorless oil (1.31 g, 75%):

$[\alpha]_D{}^{20} = -4.7$ (c 0.5, MeOH);[10] IR (thin film, CH_2Cl_2) 3343 cm^{-1}; ^1H NMR (MeOD, 400 MHz) 1.48–1.55 (1 H, m), 1.62–1.69 (1 H, m), 2.52–2.73 (3 H, m), 3.19–3.30 (1 H, m), 3.45–3.49 (1 H, m), 7.03–7.17 (5 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) 32.5, 36.1, 52.4, 66.5, 126.0, 128.3, 128.3, 128.5, 128.5, 141.7; HRMS (EI) 165 (M^+, 5%), 166 (MH^+, 100%). Calcd. for $C_{10}H_{15}NO$: 165.11536; found: 165.11516.

(*S*)-1-(1-Hydroxy-4-phenylbutan-2-yl)pyrrolidine-2,5-dione

Succinic anhydride (0.48 g, 4.84 mmol) and (*S*)-2-amino-4-phenylbutan-1-ol (0.80 g, 4.84 mmol) were stirred in toluene (100 mL) under an atmosphere of nitrogen. Triethylamine (1 mL) was added to the solution, and the mixture was heated at reflux for 18 h. After this time, the reaction was cooled to room temperature, and solvent was removed by rotary evaporation to yield a brown oil. The crude product was adsorbed onto silica gel and chromatographed using silica gel as absorbent and ethyl acetate as eluent to produce a colorless solid (0.71 g, 60%): mp 74–76 °C; $[\alpha]_D{}^{20} - 96$ (c 0.05, CH_2Cl_2); IR (thin film, CH_2Cl_2) 3387, 1766, 1692 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 2.00–2.08 (1 H, m), 2.30–2.58 (6 H, m), 2.76–2.83 (2 H, m), 3.76 (1 H, dd, J 4.0, 12.0), 3.94–3.98 (1 H, m), 4.26–4.32 (1 H, m), 7.16–7.29 (5 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) 27.9, 28.0, 32.8, 54.5, 63.2, 63.7, 126.1, 128.3 (2C), 128.4 (2C), 140.8, 178.3 (2C); HRMS (EI) 248 (MH^+, 100%). Calcd. for $C_{14}H_{18}NO_3$: 248.1287 (MH^+); found: 248.1282.

(3*S*,7a*R*)-3-Phenethyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one, 5

(*S*)-1-(1-Hydroxy-4-phenylbutan-2-yl)pyrrolidine-2,5-dione (1.68 g, 6.82 mmol) was dissolved in absolute ethanol (30 mL) and cooled to 0 °C. Sodium borohydride (2.58 g, 68.20 mmol) was then added with stirring. A 2 M solution of HCl in absolute ethanol (3.40 mL, 6.82 mmol) was then slowly added via syringe over a 3-h period. The resulting solution was acidified to pH 1–3 by addition of a 2 M solution of HCl in absolute ethanol over a 15-min period. This afforded a white suspension, which was stirred for a further 20 h. The reaction was quenched with sodium hydrogen carbonate and extracted with dichloromethane (3 × 30 mL). The dichloromethane layers were then combined and dried over anhydrous magnesium sulfate, and solvent was removed by rotary evaporation to yield the target cyclized compound as a single diastereoisomer, which was purified by column chromatography using silica gel as absorbent and ethyl acetate as eluent to yield a colorless oil (0.89 g, 57%): $[\alpha]_D^{20} + 16$ (*c* 0.12, MeOH), IR (thin film, CH_2Cl_2) 1682, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 1.74–1.89 (3 H, m), 2.07–2.10 (1 H, m), 2.36–2.40 (1 H, m), 2.52–2.57 (1 H, m), 2.63–2.78 (2 H, m), 3.50–3.54 (1 H, m), 4.08–4.11 (1 H, dd, *J* 2.4, 6.0), 4.19–4.23 (1 H, m), 5.12 (1 H, dd, *J* 2.0, 6.0), 7.18–7.31 (5 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) 24.2, 31.6, 32.8, 36.0, 54.9, 72.6, 91.6, 126.0, 128.3, 128.4, 128.5 (2C), 141.4, 179.8; HRMS (EI) 232 (MH^+, 100%). Calcd. for $C_{14}H_{18}NO_2$: 232.1338 (MH^+); found: 232.1333.

5-(Hydroxymethyl)-5,6,7,11b-tetrahydro-1*H*-benzo[*c*]pyrrolo[1,2-*a*] azepin-3(2*H*)-one, 6

(3*S*,7a*R*)-3-Phenethyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-one, **5** (0.37 g, 1.60 mmol), was dissolved in anhydrous dichloromethane (25 mL) under a nitrogen atmosphere and cooled to −96 °C. Titanium tetrachloride (0.26 mL, 2.40 mmol) was then slowly added via syringe over a 30-min period. The reaction was allowed to reach room temperature and stirred for a further 20 h. The reaction was quenched with aqueous ammonium chloride and extracted with dichloromethane (3 × 30 ml). The dichloromethane extracts were then combined and dried over anhydrous magnesium sulfate, and the solvent was removed by rotary evaporation to yield the target cyclized compound as a 4:1 mixture of diastereoisomers, which were separated by column chromatography using silica gel as absorbent and 10% methanol in dichloromethane as eluent to yield a white solid, **6a**, and opaque oil, **6b**, in a combined yield of 0.36 g (97%).

(5*S*,11b*R*)-5-(Hydroxymethyl)-5,6,7,11b-tetrahydro-1*H*-benzo[*c*]pyrrolo [1,2-*a*]azepin-3(2*H*)-one, 6a. Mp 90–92 °C; $[\alpha]_D + 296$ (*c* 0.05, $CHCl_3$); IR (thin film, CH_2Cl_2) 3386, 2926, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 1.48–1.57 (1 H, m), 2.08–2.24 (2 H, m), 2.40–2.44 (2 H, m), 2.48–2.56 (1 H), 2.63–2.68 (1 H, m), 2.91 (1 H, t, *J* 12.0), 3.53–3.65 (2 H, m), 3.91 (1 H, br.s), 4.58–4.66 (1 H, m), 5.06–5.28 (1 H, m), 7.11–7.20 (4 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) 27.9, 28.6, 30.4, 30.6, 52.2, 59.1, 63.0, 126.5 (2C), 127.2, 130.5, 139.5, 140.2, 176.7; HRMS (EI) 232 (MH^+, 100%). Calcd. for $C_{14}H_{18}NO_2$: 232.1338 (MH^+); found: 232.1333.

(5*S*, 11b*S*)-5-(Hydroxymethyl)-5,6,7,11b-tetrahydro-1*H*-benzo[*c*]pyrrolo [1,2-*a*]azepin-3(2*H*)-one, 6b. $[\alpha]_D^{20} - 306.7$ (*c* 0.03, $CHCl_3$); IR (thin film, CH_2Cl_2)

3379, 2925, 1659 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 1.59–1.66 (1 H, m), 2.06–2.12 (1 H, m), 2.46–2.53 (2 H, m), 2.60–2.69 (3 H, m), 2.87–2.92 (1 H, m), 3.32–3.35 (1 H, m), 3.72–3.74 (1 H, m), 4.01–4.04 (1 H, d, *J* 12.8), 4.94 (1 H, dd, *J* 7.2, 9.2), 5.54 (1 H, d, *J* 10.8), 7.08–7.27 (4 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) 26.3, 30.0, 30.3, 31.8, 56.9, 62.8, 67.5, 127.1, 127.3, 128.2, 131.1, 137.3, 138.5, 176.2; HRMS (EI) 232 (MH^+, 100%). Calcd. for $C_{14}H_{18}NO_2$: 232.1338 (MH^+); found: 232.1332.

(5*S*, 11b*R*)-3-Oxo-2,3,5,6,7,11*b*-hexahydro-1*H*-benzo[*c*]pyrrolo[1,2-*a*] azepine-5-carbaldehyde

Dess Martin periodinane (0.31 g, 0.74 mmol) was added to a solution of (5*S*,11b*R*)-5-(hydroxymethyl)-5,6,7,11b-tetrahydro-1*H*-benzo[*c*]pyrrolo[1,2-*a*]azepin-3(2*H*)-one, **6a** (0.25 g, 0.74 mmol), in dichloromethane (40 ml) under an atmosphere of nitrogen. The resulting mixture was allowed to stir at room temperature for 2 h. After 2 h, the solvent was removed under reduced pressure, and the residue was suspended in diethyl ether (20 mL) and washed with aqueous sodium hydrogen carbonate (100 mL), containing sodium thiosulfate (25 g), followed by saturated brine (20 mL). The diethyl ether layer was dried over anhydrous magnesium sulfate, and solvent was removed by rotary evaporation to yield a brown oil, which was adsorbed onto silica and purified by column chromatography using silica gel as absorbent and ethyl acetate as eluent to yield a light brown oil (96 mg, 60%). Oxidation to the aldehyde was accompanied by some epimerization of the α-amino aldehyde stereocentre, as previously observed on following this route in other related studies.[1i] The data of the major diastereoisomer are taken from the crude mixture of aldehyde diastereoisomers (2:1 ratio): $[\alpha]_D^{20}$ + 182.8 (*c* 0.07, $CHCl_3$);

IR (thin film, CH_2Cl_2) 2926, 1750, 1683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 2.05–2.88 (8 H, m), 5.04–5.12 (2 H, m), 7.12–7.27 (4 H, m), 9.59 (1 H, dd, *J* 12.8); ^{13}C NMR (100 MHz, $CDCl_3$) 25.4, 26.6, 30.0, 30.5, 59.6, 63.7, 127.0, 127.4, 128.1, 130.4, 137.7, 140.2, 175.3, 199.3; HRMS (EI) 230 (MH^+, 100%). Calcd. for $C_{14}H_{16}NO_2$: 230.1181 (MH^+); found: 230.1177.

(*R*)-5,6,7,11*b*-Tetrahydro-1*H*-benzo[*c*]pyrrolo[1,2-*a*]azepin-3(2*H*)-one, 7

[Bis(triphenylphosphine)]rhodium (I) carbonyl chloride (14 mg, 0.02 mmol) was added to anhydrous xylene (10 mL) under a nitrogen atmosphere. The mixture was then stirred at 80 °C for 15 min. 1,3-Bis(diphenylphosphino)propane (19 mg, 0.1 mmol) was added, and the mixture was heated at 80 °C for 30 min. To the stirring mixture was added (5*S*,11*bR*)-3-oxo-2,3,5,6,7,11b-hexahydro-1*H*-benzo[*c*] pyrrolo[1,2-*a*]azepine-5-carbaldehyde (90 mg, 0.39 mmol), and the mixture was heated under reflux for 240 h. After 240 h, the solvent was removed under reduced pressure, and the crude product was adsorbed onto silica gel and chromatographed using silica gel as absorbent and ethyl acetate as eluent to yield a brown oil (45 mg, 57%): $[\alpha]_D^{20}$ + 12 (*c* 0.70, $CHCl_3$); IR (thin film, CH_2Cl_2) 2926, 1679 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 1.73–1.79 (1 H, m), 2.00–2.05 (1 H, m), 2.17–2.23 (1 H, m), 2.36–2.51 (3 H, m), 2.64–2.70 (1 H, m), 2.92–2.99 (2 H, m), 4.10–4.16 (1 H, m), 4.83–4.86 (1 H, t, *J* 8.4), 7.12–7.27 (4 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) 25.7, 28.0, 31.0, 31.2, 39.6, 64.1, 126.5, 126.8, 128.4, 132.1, 138.6, 139.1, 174.3; HRMS (EI) 202 (MH^+, 100%). Calcd. for $C_{13}H_{16}NO$: 202.1233 (MH^+); found: 202.1226.

2-(2-Oxocyclohexyl)ethanoic Acid[1i]

Ethyl-2-cyclohexanoate (2.00 g, 10.86 mmol) was dissolved in a mixture of THF (20 mL) and water (10 mL). Lithium hydroxide (0.70 g, 16.28 mmol) was added, and the mixture was stirred at room temperature for 20 h. The reaction mixture was concentrated, resuspended in water (30 mL), and acidified to pH 3 by careful addition of aqueous 1 M HCl. The aqueous layer was then extracted into ethyl acetate (3×40 mL) and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to afford a colorless oil (1.66 g, 98%): IR (thin film, CH_2Cl_2) 3365, 1616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 1.38–2.87 (11 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) 25.2, 27.8, 33.8, 34.3, 41.8, 46.9, 179.5, 211.2; HRMS (EI) 157 (MH^+, 100%). Calcd. for $C_8H_{13}O_3$: 157.0865 (MH^+); found: 157.0857.

(3*S*,6*aS*,10*R*)-3-Phenethylhexahydro-2*H*-oxazolo[3,2-*i*]indol-5(3*H*)-one, 8

(*S*)-2-Amino-4-phenylbutan-1-ol (0.30 g, 1.90 mmol) and 2-(2-oxocyclohexyl) ethanoic acid (0.31 g, 1.90 mmol) were dissolved in toluene (100 mL) and refluxed under Dean–Stark conditions for 48 h. After 48 h, the solution was allowed to cool to room temperature, and the solvent was removed under reduced pressure. The crude product was adsorbed onto silica gel and chromatographed using silica gel as absorbent and a 3:1 mixture of ethyl acetate and light petroleum as eluent to yield a yellow oil (0.29 g, 55%): $[\alpha]_D^{20} + 89.4$ (*c* 0.47, $CHCl_3$); IR (thin film, CH_2Cl_2) 1707 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 1.39–1.83 (8 H, m), 1.89–1.99 (2 H, m), 2.31–2.45 (2 H, m), 2.60–2.79 (3 H, m), 3.82–3.86 (1 H, m), 4.02–4.08 (1 H, m), 4.15–4.18 (1 H, m), 7.17–7.30 (5 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) 19.8, 20.8, 25.3, 32.8, 33.0, 37.0, 39.2, 41.8, 54.6, 72.6, 99.7, 126.0, 128.4 (4C), 141.5, 176.6; HRMS (FAB) 286 (MH^+, 100%). Calcd. for $C_{18}H_{24}NO_2$: 286.18070 (MH^+); found: 286.18097.

(*S*)-1-((*R*)-1-Hydroxy-4-phenylbutan-2-yl)-5,6,7,7*a*-tetrahydro-1*H*-indol-2(4*H*)-one, 10

(3*S*,6*aS*,10*R*)-3-Phenethylhexahydro-2*H*-oxazolo[3,2-*i*]indol-5(3*H*)-one, **8** (0.50 g, 1.75 mmol), was dissolved in a solution of 2 M HCl in absolute ethanol (15 mL), and the mixture was stirred at room temperature for 20 h. After 20 h, the reaction was quenched by addition of saturated sodium hydrogen carbonate and extracted into ethyl acetate (3×40 mL). The combined organic fractions were dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The crude product was adsorbed onto silica gel and chromatographed using silica gel as absorbent using a 2:1 mixture of ethyl acetate and light petroleum as eluent to yield a colorless solid (0.40 g, 80%), a portion of which was recrystallized from dichloromethane and hexanes to yield colorless crystals: mp 90–92 °C (DCM/hexanes); $[\alpha]_D^{20} + 52.0$ (*c* 0.1, MeOH); IR (thin film, CH_2Cl_2) 3407, 2920, 1659 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 1.02–1.12 (1 H, m), 1.23–1.38 (2 H, m), 1.83–1.86 (1 H, m), 1.98–2.04 (1 H, m), 2.05–2.34 (4 H, m), 2.56–2.63 (1 H, m), 2.71–2.78 (2 H, m), 3.45–3.48 (1 H, m), 3.67 (1 H, dd, *J* 5.6, 11.2), 3.81–3.93 (2 H, m), 3.81 (1 H, d, *J* 7.7), 5.73 (1 H, s), 7.18–7.30 (5 H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) 23.1, 27.1, 28.4,

30.2, 32.6, 33.5, 56.1, 63.8, 64.6, 118.7, 126.0, 128.3 (2C), 128.5 (2C), 141.4, 162.7, 173.1; HRMS (FAB) 286 (MH^+, 100%). Calcd. for $C_{18}H_{24}NO_2$: 286.1807 (MH^+); found: 286.18097.

X-Ray Data for 10

$C_{18}H_{23}NO_2$, $M = 285.37$, orthorhombic, space group $P2_12_12_1$, $a = 8.4089(7)$, $b = 11.0955(9)$, $c = 16.2864(13)$ Å, $V = 1519.5(2)$ Å^3, $T = 150$ K, $Z = 4$, crystal dimensions $0.37 \times 0.05 \times 0.03\,mm^3$, silicon 111 monchromated synchrotron radiation ($\lambda = 0.6710$ Å), $\mu = 0.163\,mm^{-1}$; 12279 data measured using a Bruker APEX 2 CCD diffractometer, 2709 data were unique, $R_{int} = 0.088$. All unique data were used in refinement against F^2 values to give final $wR = 0.1478$ (on F^2 for all data), $R = 0.0544$ [for 2463 data with $F^2 > 4\sigma(F^2)$]; absolute structure could not be determined. Friedel pairs were merged. Programs used were Bruker APEX 2, SAINT, SHELXTL,[8] and local programs. Crystallographic data (excluding structure factors) for the structure in this article has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 773806. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [Fax: +44(0)-1223–336033 or e-mail: deposit@ccdc.ac.uk].

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