Stereoselective synthesis of the pyrroloisoquinoline ring system

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Received (in Cambridge, UK) 20th June 2001, Accepted 13th September 2001
First published as an Advance Article on the web 25th October 2001

In this paper we report a facile and stereoselective approach to the pyrroloisoquinoline ring system through the application of *N*-acyliminium chemistry from readily available non-racemic chiral templates. The stereochemical outcome of the cyclisation reactions has been determined by NOE and X-ray crystallography. We also demonstrate the synthetic potential of our new approach through removal of the pendant hydroxymethyl auxiliary from a product of cyclisation.

Introduction

The pyrroloisoquinoline ring system (**1**) is found as a major structural motif of the *Erythrina* alkaloid group of natural products. The genus *Erythrina* is common in tropical and sub-tropical regions and the alkaloids have been used in indigenous medicine.[1]

Members of the *Erythrina* family display curare-like and hypnotic activity, and a variety of pharmacological effects are associated with the erythrinane skeleton including sedative, hypotensive, neuromuscular blocking and CNS activity.[2]

There has been much interest in the synthesis of pyrroloisoquinolines over recent years, with many approaches involving *N*-acyliminium cyclisation as a key ring-forming step.[2,3] Lete *et al*. have identified suitable intermediates in the synthesis of this natural product group to include pyrroloisoquinolines **1** and the related unsaturated derivatives **2** (Fig. 1).[3d,e] In this paper we report a novel route to the pyrroloisoquinoline ring system that allows the introduction of asymmetry during the key ring-forming step.

Given the tetracyclic structure of the erythrinane skeleton, synthetic targets that contain an alkyl substituent at position 10b would be of potential interest in approaches to construct the A ring. Unsaturation in target systems such as **2** may provide a handle for additional derivatization through conjugate addition reactions.[4]

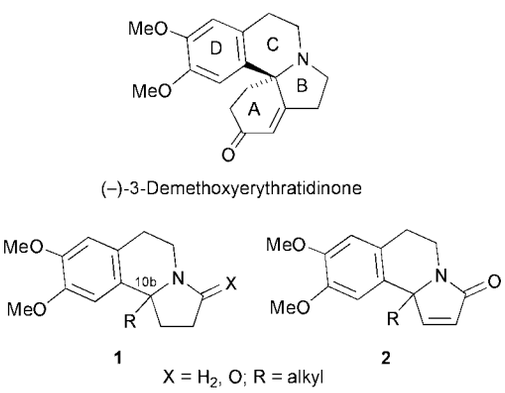
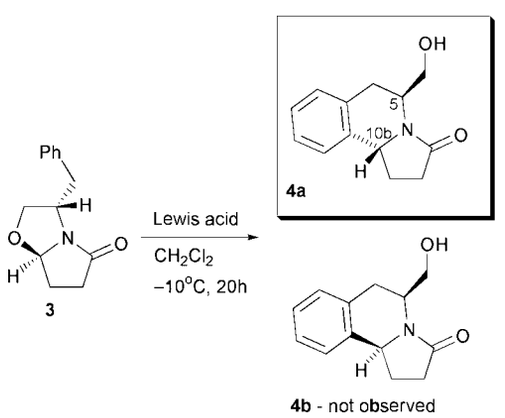


Fig. 1 Pyrroloisoquinoline targets.



Scheme 1 Lewis acid-induced cyclisation of **3**.

Results and discussion

Based on our novel stereoselective approach to the isoindoloisoquinoline ring system,[5] we reasoned that a suitably substituted bicyclic lactam could act as a precursor for a stereoselective approach to the core of the target erythrinane ring system. Although the bicyclic lactams of Meyers have been widely utilised in asymmetric synthesis,[6] to the best of our knowledge the present application, as a precursor in an intramolecular *N*-acyliminium mediated cyclisation reaction leading to pyrroloisoquinoline targets, represents a novel application of this popular chiral template.

Our synthesis of the required bicyclic lactam substrate **3** from commercially available (*S*)-phenylalaninol followed the general method previously described by Meyers *et al*.[7]

With **3** in hand, we turned to the proposed intramolecular *N*-acyliminium cyclisation study (Scheme 1, Table 1). On treating lactam **3** with $TiCl_4$ as Lewis acid activator at low temperature in dichloromethane, we were pleased to isolate the cyclised product in good yield. ^{1}H NMR analysis of the crude product mixture revealed the formation of only one product diastereoisomer. An NOE study was undertaken to confirm that, as expected,[5] the relative stereochemistry of the product diastereoisomer was as indicated in product **4a**, with inversion of stereochemistry at the newly created chiral centre.[8]

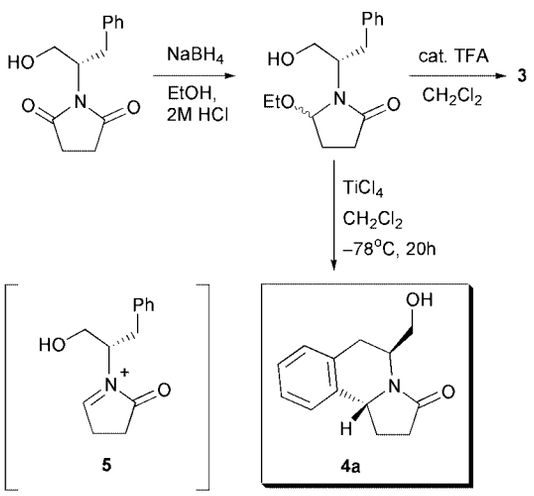
As can be appreciated from Table 1, other Lewis acids gave a similarly high level of diastereoselectivity in the cyclisation reaction; only boron trifluoride gave no cyclisation product, and in this case the starting material was re-isolated.

Table 1 Stereoselective cyclisation of **3**

Lewis acid	Yield, **4** (%)	Diastereoselectivity (**4a** : **4b**)[a]
$TiCl_4$	80	Exclusive[b]
$SnCl_4$	60	Exclusive
TMSOTf	78	Exclusive
$BF_3{\cdot}OEt_2$	No reaction[c]	

[a] Determined by 250 MHz ^{1}H NMR spectroscopy on crude product mixture. [b] Only compound **4a** observed by 250 MHz ^{1}H NMR spectroscopy. [c] Starting material re-isolated.

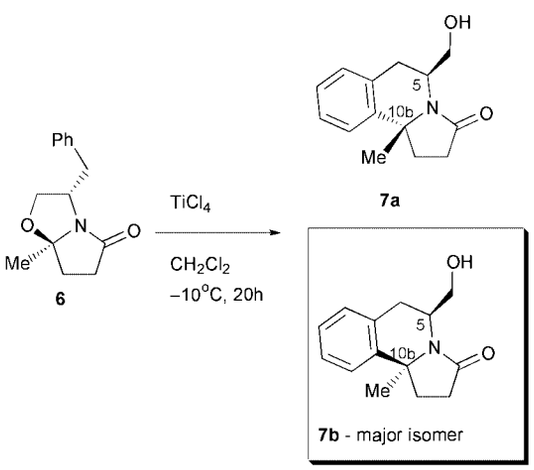
We were interested to find that access to cyclised product **4a** was available *via* a more direct route. The synthetic protocol followed by us to access the bicyclic lactam substrate **3** is highlighted in Scheme 2. Following reduction of the imide with



Scheme 2 Synthetic route to lactam **3** and reactivity of intermediates.

sodium borohydride in ethanol the corresponding ethoxylactam is cyclised under protic acid catalysis to generate the bicyclic lactam target. Under these conditions no sign of cyclisation to yield the pyrroloisoquinoline compound **4a** was observed. Interestingly, when the ethoxylactam intermediate was treated with $TiCl_4$, clean conversion to yield only **4a** was observed. Presumably, cyclisation to yield products **3** and **4a** proceeds *via* the same *N*-acyliminium ion intermediate, **5**.

A lower level of diastereoselectivity was observed on cyclisation of the corresponding methyl-substituted substrate **6**, obtained as a single diastereoisomer in one step by condensation of (*S*)-phenylalaninol with an equimolar amount of levulinic acid in toluene. In this case, treatment of **6** with $TiCl_4$ led to a mixture of product diastereoisomers in 87% yield with a diastereoselectivity of 2 : 1 (Scheme 3).



Scheme 3 Lewis acid-induced cyclisation of **6**.

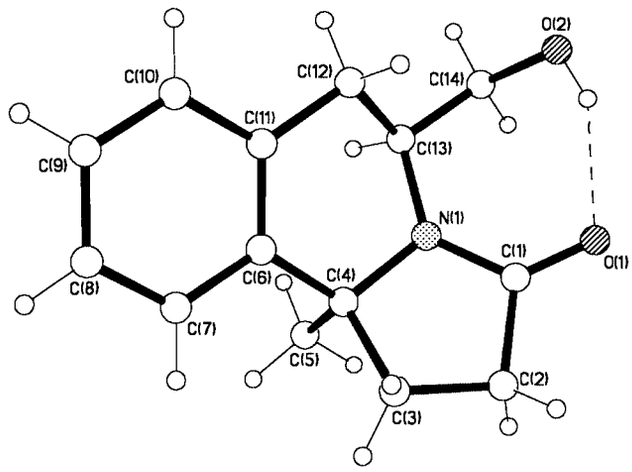


Fig. 2 X-Ray crystal structure of **7b**.

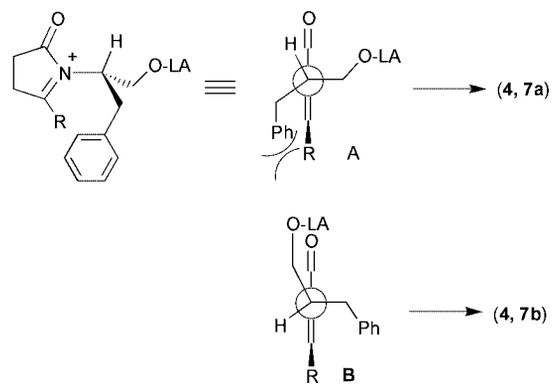


Fig. 3 Proposed conformational rationale for stereoselective cyclisations.

In line with our previous studies on the related isoindoloisoquinoline system,[5] we attempted the same cyclisation reaction replacing $TiCl_4$ by TMSOTf, expecting perhaps a similar increase in diastereoselectivity as noted[5] for the isoindoloisoquinolines. Unfortunately, in this case, TMSOTf gave no cyclisation.

Lowering the reaction temperature to −78 °C did not lead to an increase in product diastereoselectivity. Separation of the diastereoisomers was achieved by column chromatography, using ethyl acetate as eluent, and the relative stereochemistry of the major isomer was investigated by NOE techniques and found to be as indicated in product **7b**[9]—this product having been formed with "retention" of stereochemistry, in contrast to the reaction of substrate **3**. The structure was also confirmed by single crystal X-ray analysis (Fig. 2). Interestingly, **7b** forms an intramolecular hydrogen bond ($OH\cdots O'$ = 1.95(2)Å, ∠O–H–O′ = 149(2)°).

In order to rationalise the stereochemical outcome of the cyclisation reactions described in this paper, we have invoked the conformational models[10] highlighted in Fig. 3 in which activation of the bicyclic lactam substrate by a Lewis acid leads to a formal *N*-acyliminium species as an intermediate.

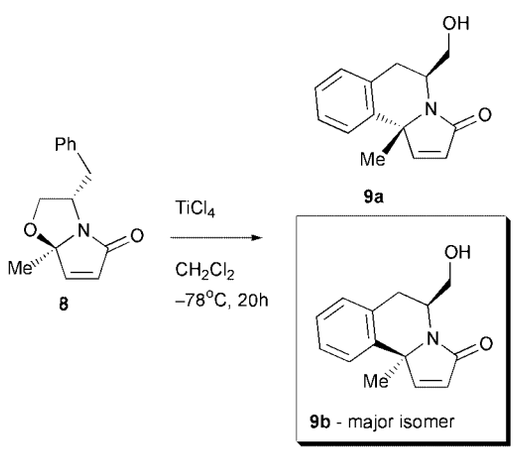
In conformation **A** (R = H), leading to the favoured product **4a**, the carbonyl moiety is "eclipsed" in a 1,3-fashion by the hydrogen atom at the β-amino alcohol chiral centre. The angular H-atom (R = H) at the iminium carbon atom provides no significant steric bulk to interfere with the steric positioning of the benzyl or Lewis acid-complexed oxymethyl groups. In this model, the Lewis acid-complexed oxymethyl group is viewed as the larger substituent.[10]

The alternative conformation, **B**, which would lead to the minor (unobserved) diastereoisomer **4b**, has the benzyl group positioned as the larger substituent. In this scenario an unfavourable 1,3-interaction appears to exist between the

carbonyl group and the more bulky Lewis acid-complexed oxymethyl group.

With substrate **6**, the steric influence exercised by the angular methyl substituent (R = Me) at the iminium carbon atom overrides the conformational effect noted above and this leads to a major diastereoisomer of opposite relative stereochemistry. One can envisage interactions between this angular methyl group and the benzyl substituent (**A**, R = Me). Bond rotation about the extra-annular C–N bond leads to an alternative conformation **B** (R = Me) with minimised steric interference from the iminium carbon substituent, which furnishes the observed major product diastereoisomer **7b** with retention of stereochemistry. We have not ruled out the possible influence of chelation control with a Lewis acid such as $TiCl_4$ in conformations such as **A** and **B**. Such an effect, that of changing the sense and level of diastereoselectivity by increasing the relative size of this angular iminium substituent, has been reported by Meyers and Burgess, and was also rationalised using similar conformational models.[11]

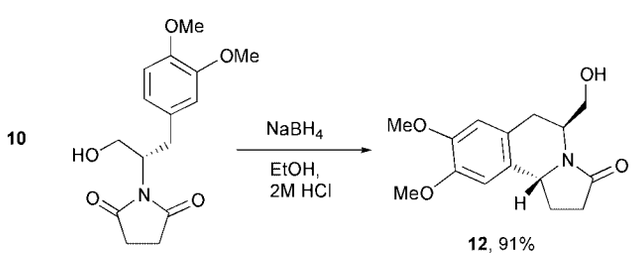
Interestingly, a slight increase in the level of diastereoselectivity was observed on cyclisation of the corresponding unsaturated alkyl-substituted lactam **8** when compared to the saturated analogue **6** (Scheme 4). Whereas **6** produced the



Scheme 4 Lewis acid-induced cyclisation of **8**.

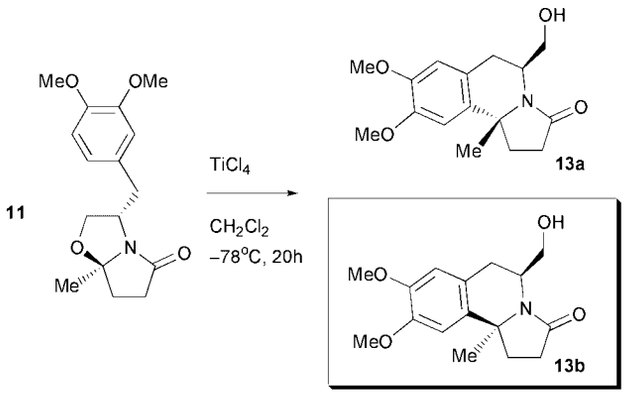
cyclised product **7** as a 2 : 1 mixture of diastereoisomers, cyclisation of the unsaturated substrate **8** proceeded in 91% yield with a modest increase in diastereoselectivity to 3 : 1, also in favour of the product of retention of stereochemistry, **9b**.

In order to further apply this new methodology to the stereoselective synthesis of more highly functionalised pyrroloisoquinolines, imide **10** and bicyclic lactam **11** were prepared as described above from the appropriate β-amino alcohol and subjected to the conditions shown in Schemes 5 and 6 respectively.



Scheme 5 Reductive cyclisation of imide **10**.

A more direct route for the synthesis of the functionalised pyrroloisoquinoline **12** was available from imide **10**. Subjecting imide **10** to a typical sodium borohydride reduction as described in Scheme 2, *en route* to the expected ethoxylactam precursor of the corresponding bicyclic lactam, resulted in direct and highly stereoselective cyclisation to **12** in excellent



Scheme 6 Lewis acid-induced cyclisation of **11**.

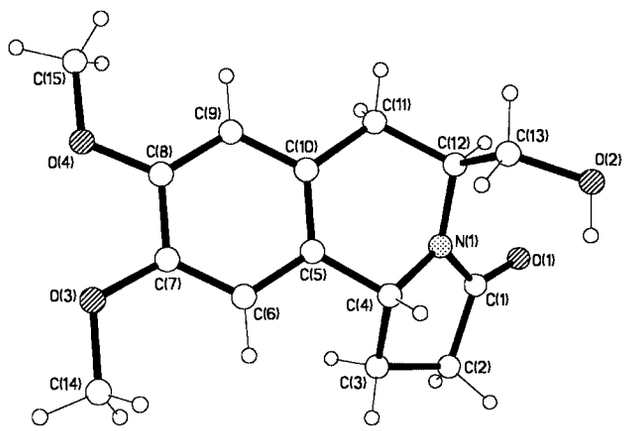


Fig. 4 X-Ray crystal structure of **12**.

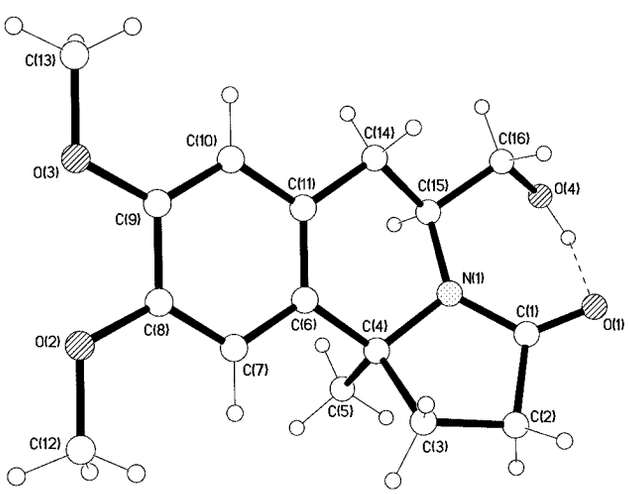


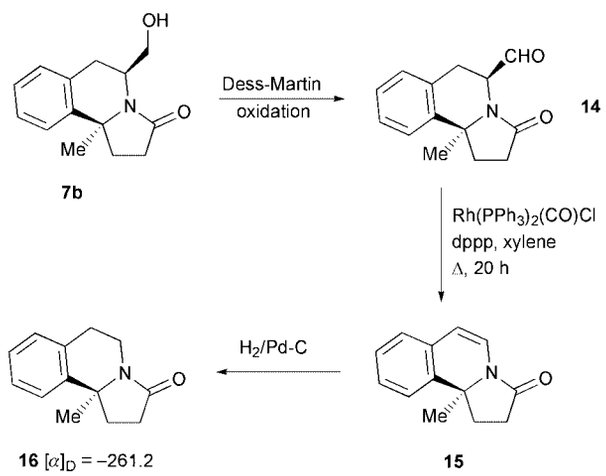
Fig. 5 X-Ray crystal structure of **13b**.

yield (91%). Presumably, under the acidic reaction conditions, the more nucleophilic methoxy-substituted aryl ring is able to cyclise onto the *N*-acyliminium intermediate that may be generated *in situ*. In this case, we were able to confirm the relative stereochemistry of this product by single crystal X-ray analysis (Fig. 4). Interestingly, these studies revealed that **12** forms H-bonded chains *via* the hydroxy O*H* and carbonyl groups on neighbouring molecules [$OH\cdots O'$ = 1.87(2) Å, ∠O–H–O′ = 164(2)°].

The alkyl-substituted lactam **11** gave a diastereoisomer ratio of 2 : 1 (Scheme 6) on Lewis acid-induced cyclisation. The major isomer **13b**, the product of retention of stereochemistry, was isolated by column chromatography and the relative stereochemistry confirmed by single crystal X-ray analysis (Fig. 5). Compound **13b** forms an intramolecular hydrogen bond, similar to that in **7b** ($OH\cdots O'$ = 1.81(2) Å, ∠O–H–O′ = 154(2)°).

As can be seen, pyrroloisoquinolines **12** and **13b** have opposite relative stereochemistries at the aromatic substituent at the new chiral centre, in agreement with the corresponding NOE studies on the related, simpler pyrroloisoquinoline compounds **4a** and **7b**.

In order to demonstrate the synthetic potential of the stereoselective cyclisation methodology we were required to establish conditions for removal of the pendant hydroxymethyl substituent (auxiliary) from a product of cyclisation. Our initial attempt involved oxidation of the primary alcohol group of pyrroloisoquinoline **7b**, which had been isolated as a single diastereoisomer by column chromatography. The Dess–Martin periodinane oxidation proceeded in 89% yield to provide aldehyde **14** as a single diastereoisomer. Following a method previously applied in our laboratory we attempted a Rh-catalyzed decarbonylation but found that the reaction proceeded to give only enamide **15**, with no sign of the desired compound **16** (Scheme 7).



Scheme 7 Removal of the hydroxymethyl auxiliary group.

Attempts were made to vary the reaction conditions in order to access **15** directly using the Rh-decarbonylation, but without success. In addition, the one step removal of hydroxymethyl groups using Raney-Ni (W2), as described by Martin and Bur, was also unsuccessful on this substrate.[12] Nevertheless, we were subsequently able to convert enamide **15** into the desired compound **16** in 89% yield by catalytic hydrogenation.

In summary, we report a facile and highly stereoselective approach to the pyrroloisoquinoline ring system from readily available non-racemic substrates. We have also demonstrated that efficient removal of the pendant hydroxymethyl auxiliary is possible from a product of cyclisation.

Experimental

Where necessary, solvents were dried, distilled and stored over 4 Å molecular sieves prior to use. Reagent chemicals were purchased from Lancaster Synthesis Ltd. and Aldrich Chemical Co. Ltd, and were purified, where necessary, before use.

Flash-column chromatography was carried out using Merck silica gel (70–230 mesh ASTM). Analytical thin layer chromatography (TLC) was carried out using aluminium-backed plates coated with 0.2 mm silica. Plates were visualised under UV light (at 254 nm) or by staining with either potassium permanganate solution or iodine. Yields quoted are for isolated, purified products.

Infrared spectra were recorded in the range 4000–600 cm^{-1}, using a Perkin Elmer Paragon 100 FT-IR spectrometer as Nujol mulls or as liquid films. ^1H and ^{13}C NMR spectra were recorded using either a Bruker Avance 400 MHz Spectrometer or a Bruker AC 250 MHz Spectrometer. NMR samples were made up in deuterated solvents with all values quoted in ppm relative to TMS as reference. Coupling constants (*J* values) are reported in hertz (Hz). Diastereoisomer ratios were calculated from the integration of suitable peaks in the ^1H NMR spectra. Mass spectra were recorded using a Fisons VG Quattro II SQ instrument and Accurate-Mass mass spectra were recorded using a Kratos MS80 instrument. Melting points were determined on a Gallenkamp melting point apparatus. Elemental analyses were carried out on a Perkin Elmer 2400 CHN Elemental Analyser. Optical rotations were measured at 25 °C using an Optical Activity AA-10 Automatic Polarimeter and are reported in units of 10^{-1} deg cm^2 g^{-1}.

1-[(2*S*)-3-Hydroxy-2-(phenylmethyl)ethyl]tetrahydro-1*H*-pyrrole-2,5-dione

Succinic anhydride (0.33 g, 3.31 mmol) and (*S*)-(−)-2-amino-3-phenylpropan-1-ol (0.50 g, 3.31 mmol) were dissolved in toluene (45 ml) under a nitrogen atmosphere. Triethylamine (1 ml) was added to the stirring mixture and the solution was heated at reflux for 18 hours. The solvent was removed by rotary evaporation and the resulting yellow oil was purified by flash column chromatography using 25% hexanes in ethyl acetate as eluent to yield a white solid (0.67 g, 87%), a portion of which was recrystallised from dichloromethane and hexanes. Mp 130–131 °C; $[\alpha]_D = -89.8$ ($c = 0.48$, CH_2Cl_2) (Found: C, 66.48; H, 6.38; N, 5.84; $C_{13}H_{15}NO_3$ requires C, 66.94; H, 6.48; N, 6.00%); ν_{max}(Nujol mull)/cm^{-1} 3411 (OH), 1764 and 1685 (imide); δ_H(250 MHz, $CDCl_3$) 2.45–2.70 (4H, m, 2 × CH_2CO), 2.80–2.91 (1H, br s, O*H*), 3.12 (2H, d, *J* 7.4, CH_2Ar), 3.84 (1H, dd, *J* 12.0, 3.3, C*H*(H)OH), 4.00 (1H, dd, *J* 11.9, 6.8, C*H*(H)OH), 4.45–4.58 (1H, m, NC*H*), 7.16–7.30 (5H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 28.0 (2 × CH_2CO), 33.8 (CH_2Ar), 55.8 (N*C*H), 62.4 (CH_2OH), 126.8 (Ar*C*H), 128.5 (2 × Ar*C*H), 129.1 (2 × Ar*C*H), 137.2 (Ar*C*), 178.0 (*C*O), 183.8 (*C*O); MS (EI) *m*/*z* 233 [M^+, 7.6%] (Found: M^+, 233.10541. $C_{13}H_{15}NO_3$ requires 233.10519).

(3*S*,7a*R*)-3-(Phenylmethyl)perhydropyrrolo[2,1-*b*][1,3]oxazol-5-one, 3

1-[(2*S*)-3-Hydroxy-2-(phenylmethyl)ethyl]tetrahydro-1*H*-pyrrole-2,5-dione (2.00 g, 8.58 mmol) was dissolved in absolute ethanol (100 ml) and cooled to 0 °C. Sodium borohydride (3.25 g, 85.8 mmol) was then added with stirring. 2 M HCl in absolute ethanol (4.36 ml, 8.58 mmol) was added slowly *via* syringe over a 3 hour period. The solution was acidified to pH 1–3 by addition of 2 M HCl in absolute ethanol over a 15 minute period, affording a white suspension which was stirred for an additional 20 hours at room temperature. The mixture was quenched by addition to a saturated aqueous sodium bicarbonate solution (100 ml) and extracted with dichloromethane (3 × 50 ml). The organic extracts were dried over anhydrous magnesium sulfate and the solvent removed by rotary evaporation to yield a colourless oil (1.43 g, 63%). The resulting oil, which was not purified, was then either refluxed in toluene for 24 hours, or stirred with a catalytic amount of TFA (5 mol%) in dichloromethane for 20 hours at room temperature. After the appropriate time the solvent was evaporated under reduced pressure to yield a colourless oil. This was purified further by flash column chromatography using a 1 : 1 mixture of hexanes and ethyl acetate as eluent yielding white crystals (0.17 g, 46%), a portion of which was recrystallised from dichloromethane and hexanes. Mp 57–58 °C; $[\alpha]_D = +43.9$ ($c = 0.26$, $CHCl_3$) (Found: C, 71.83; H, 6.98; N, 6.39; $C_{13}H_{15}NO_2$ requires C, 71.89; H, 6.91; N, 6.45%); ν_{max}(Nujol mull)/cm^{-1} 1684 (lactam); δ_H(400 MHz, $CDCl_3$) 1.97–2.06 (1H, m, C*H*(H)CH_2CO), 2.29–2.38 (1H, m, C*H*(H)CH_2CO), 2.44–2.53 (1H, m, C*H*(H)CO), 2.59–2.68 (1H, m, C*H*(H)CO), 2.78 (1H, dd, *J* 13.8, 8.2, C*H*(H)Ar), 3.03 (1H, dd, *J* 14.0, 6.0, C*H*(H)Ar), 3.65 (1H, dd, *J* 8.8, 6.4, C*H*(H)O), 4.07 (1H, dd, *J* 8.8, 7.2,

C*H*(H)O), 4.32–4.41 (1H, m, NC*H*CH_2O), 5.02 (1H, dd, *J* 6.0, 2.4, NC*H*O), 7.17–7.35 (5H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 24.5 (*C*$H_2$$CH_2$CO), 31.6 (*C*$H_2$CO), 39.3 (*C*$H_2$Ar), 55.3 (NC*H*-$CH_2$O), 71.8 (*C*$H_2$O), 91.8 (N*C*HO), 126.8 (Ar*C*H), 128.5 (2 × Ar*C*H), 129.1 (2 × Ar*C*H), 136.8 (Ar*C*), 179.4 (*C*O); MS (EI) *m*/*z* 217 [M^+, 26.4%] (Found: M^+, 217.11065. $C_{13}H_{15}NO_2$ requires 217.11028).

(5*S*,10b*R*)-5-(Hydroxymethyl)-1,2,3,5,6,10b-hexahydropyrrolo-[2,1-*a*]isoquinolin-3-one, 4a

(3*S*,7a*R*)-3-(Phenylmethyl)perhydropyrrolo[2,1-*b*][1,3]oxazol-5-one **3** (0.15 g, 0.69 mmol) was dissolved in dry dichloromethane (10 ml) under a nitrogen atmosphere. The mixture was cooled to −10 °C and 1.5 equivalents of $TiCl_4$ (0.11 ml, 1.04 mmol) were added dropwise by syringe. After stirring at this temperature for 10 minutes, the mixture was allowed to reach room temperature and left to stir for 20 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 ml), extracted with dichloromethane (3 × 10 ml) and dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation and the diastereoselectivity of the reaction determined by ^{1}H NMR spectroscopy. The resulting yellow oil (0.12 g, 80%) was then further purified by column chromatography using 10% MeOH in dichloromethane as eluent. The solvent was removed by rotary evaporation to yield a pale green powder (0.08 g, 53%), a portion of which was recrystallised from dichloromethane and hexanes to give colourless, needle-like crystals. Mp 110–111 °C; $[a]_D$ = +13.3 (*c* = 0.08, CH_2Cl_2) (Found: C, 71.82; H, 7.00; N, 6.31; $C_{13}H_{15}NO_2$ requires C, 71.89; H, 6.91; N, 6.45%); ν_{max}(Nujol mull)/cm^{-1} 3262 (OH), 1648 (lactam); δ_H(250 MHz, $CDCl_3$) 1.93–2.12 (1H, m, C*H*(H)CH_2CO), 2.40–2.56 (1H, m, CH_2-C*H*(H)CO), 2.57–2.71 (3H, m, C*H*(H)CH_2CO, CH_2C*H*(H)-CO and ArC*H*(H)CHN), 3.05 (1H, dd, *J* 16.3, 6.5, ArC*H*-(H)CHN), 3.65 (1H, dd, *J* 11.5, 8.4, C*H*(H)OH), 3.74 (1H, dd, *J* 11.5, 5.0, C*H*(H)OH), 4.35–4.48 (1H, m, NC*H*CH_2OH), 4.82 (1H, t, *J* 7.5, NC*H*Ar), 7.09–7.30 (4H, m, Ar*H*); O*H* not visible; δ_C(100 MHz, $CDCl_3$) 26.5 (*C*$H_2$$CH_2$CO), 29.7 (Ar*C*$H_2$CHN), 31.6 (*C*$H_2$CO), 49.8 (N*C*HAr), 54.6 (N*C*HCH$_2$OH), 63.3 (*C*H_2OH), 124.2 (Ar*C*H), 126.8 (Ar*C*H), 127.3 (Ar*C*H), 129.1 (Ar*C*H), 132.5 (Ar*C*), 136.8 (Ar*C*), 175.3 (*C*O); MS (EI) *m*/*z* 217 [M^+, 8.2%] (Found: M^+, 217.11065. $C_{13}H_{15}NO_2$ requires 217.11028).

(5*S*,10b*R*)-5-(Hydroxymethyl)-1,2,3,5,6,10b-hexahydropyrrolo-[2,1-*a*]isoquinolin-3-one, 4a, from direct cyclisation of ethoxy-lactam intermediate

1-[(2*S*)-3-Hydroxy-2-(phenylmethyl)ethyl]tetrahydro-1*H*-pyrrole-2,5-dione (2.00 g, 8.58 mmol) was dissolved in absolute ethanol (100 ml) and cooled to 0 °C. Sodium borohydride (3.25 g, 85.8 mmol) was then added with stirring. 2 M HCl in absolute ethanol (4.36 ml, 8.58 mmol) was added slowly *via* syringe over a 3 hour period. The solution was then acidified to pH 1–3 by addition of 2 M HCl in absolute ethanol over a 15 minute period, affording a white suspension which was stirred for an additional 20 hours at room temperature. The mixture was quenched by addition to saturated aqueous sodium bicarbonate solution (100 ml) and extracted with dichloromethane (3 × 50 ml). The organic extracts were dried over anhydrous magnesium sulfate and the solvent removed by rotary evaporation to yield the ethoxy lactam intermediate as a colourless oil (1.38 g). This was not further purified, and was used directly in the Lewis acid mediated cyclisation to yield **4a** as described below.

The intermediate ethoxy lactam (1.38 g, 5.25 mmol) was dissolved in dry dichloromethane (100 ml) under a nitrogen atmosphere. The mixture was cooled to −78 °C and 1.5 equivalents of $TiCl_4$ (0.86 ml, 7.88 mmol) were added dropwise by syringe. After stirring at this temperature for 10 minutes, the mixture was then allowed to reach room temperature and left stirring for 20 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (50 ml), extracted with dichloromethane (3 × 50 ml) and dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation and the diastereoselectivity of the reaction determined by ^{1}H NMR spectroscopy on the crude reaction mixture. The green oil (1.11 g, 97%) was purified by column chromatography using 10% MeOH in dichloromethane as eluent. The solvent was removed by rotary evaporation to yield a pale green powder (0.95 g, 83%) which had identical spectral properties to the compound prepared by the alternative route.

(3*S*,7a*R*)-7a-Methyl-3-(phenylmethyl)perhydropyrrolo[2,1-*b*]-[1,3]oxazol-5-one, 6

(*S*)-2-Amino-3-phenylpropan-1-ol (1.00 g, 6.61 mmol) and levulinic acid (0.68 ml, 6.61 mmol) were dissolved in toluene (150 ml) and refluxed under Dean–Stark conditions for 48 hours. The solution was then allowed to cool before the solvent was removed by rotary evaporation. The resulting purple oil was adsorbed onto silica and purified by column chromatography using a 1 : 1 mixture of diethyl ether and hexanes as eluent. Evaporation of the desired fraction afforded the target compound as pale yellow crystals (1.48 g, 97%), a portion of which was recrystallised from dichloromethane and hexanes to yield colourless needles. Mp 73–74 °C; $[a]_D$ = +59.4 (*c* = 0.33, $CHCl_3$) (Found: C, 72.32; H, 7.32; N, 5.92; $C_{14}H_{17}NO_2$ requires C, 71.72; H, 7.36; N, 6.06%); ν_{max}(DCM)/cm^{-1} 1696 (lactam); δ_H(250 MHz, $CDCl_3$) 1.43 (3H, s, C*H*$_3$), 2.07–2.20 (2H, m, C*H*$_2$$CH_2$CO), 2.39–2.52 (1H, m, C*H*(H)CO), 2.67–2.83 (2H, m, C*H*(H)CO, C*H*(H)Ar), 3.13 (1H, dd, *J* 13.6, 5.5, CH(H)Ar), 3.88 (1H, dd, *J* 8.9, 6.4, C*H*(H)O), 4.05 (1H, dd, *J* 8.9, 7.2, C*H*(H)O), 4.23–4.37 (1H, m, NC*H*O), 7.19–7.35 (5H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 25.0 (*C*H_3), 33.3 (*C*H_2CO), 34.7 (*C*H_2-CH_2CO), 40.3 (*C*H_2Ar), 55.8 (N*C*HO), 71.4 (*C*H_2O), 100.0 (*C*-CH_3), 126.7 (Ar*C*H), 128.6 (2 × Ar*C*H), 129.3 (2 × Ar*C*H), 137.1 (Ar*C*), 178.2 (*C*O); MS (EI) *m*/*z* 231 [M^+, 25.6%] (Found: M^+, 231.12589. $C_{14}H_{17}NO_2$ requires 231.12593).

(5*S*,10b*S*)-5-(Hydroxymethyl)-10b-methyl-1,2,3,5,6,10b-hexa-hydropyrrolo[2,1-*a*]isoquinolin-3-one, 7b

(3*S*,7a*R*)-7a-Methyl-3-(phenylmethyl)perhydropyrrolo[2,1-*b*]-[1,3]oxazol-5-one **6** (0.15 g, 0.65 mmol) was dissolved in dry dichloromethane (10 ml) under a nitrogen atmosphere. The mixture was cooled to −10 °C and 1.5 equivalents of $TiCl_4$ (0.11 ml, 0.98 mmol) were added dropwise by syringe. After stirring at this temperature for 10 minutes, the mixture was allowed to reach room temperature and left stirring for a further 20 hours. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 ml), extracted with dichloromethane (3 × 10 ml) and dried over anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and the diastereoselectivity of the reaction determined by ^{1}H NMR spectroscopy on the crude reaction mixture. The yellow solid (0.13 g, 87%) was purified to yield the individual diastereoisomers by flash column chromatography using 100% ethyl acetate as eluent. The solvent was removed by rotary evaporation to yield the target pyrroloisoquinoline diastereoisomers as colourless crystals.

Major isomer (7b, 53%). Mp 103–105 °C (DCM–hexanes); $[a]_D$ = −226.9 (*c* = 0.25, $CHCl_3$) (Found: C, 72.71; H, 7.32; N, 5.88; $C_{14}H_{17}NO_2$ requires C, 72.73; H, 7.36; N, 6.06%); ν_{max}(Nujol mull)/cm^{-1} 3386 (OH), 1654 (lactam); δ_H(250 MHz, $CDCl_3$) 1.59 (3H, s, C*H*$_3$), 2.17 (1H, dd, *J* 21.7, 11.4, C*H*(H)CH_2CO), 2.34–2.50 (2H, m, C*H*(H)CH_2CO and C*H*(H)CO), 2.61–2.73 (1H, m, C*H*(H)CO), 2.72 (1H, dd, *J* 16.3, 3.8, ArC*H*(H)CHN), 3.12 (1H, dd, *J* 16.3, 11.4, ArC*H*(H)CHN), 3.63–3.75 (1H, m, NC*H*CH_2OH), 3.94–4.12 (2H, m, C*H*$_2$OH), 4.75–5.00 (1H, br

s, O*H*), 7.07–7.29 (4H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 27.9 (*C*H_3), 31.7 (*C*H_2CO), 31.9 (Ar*C*H_2CHN), 35.3 (*C*$H_2$$CH_2$CO), 54.2 (N*C*HC$H_2$OH), 62.9 (*C*$H_2$OH), 65.0 (*C*-$CH_3$), 125.0 (Ar*C*H), 127.2 (Ar*C*H), 127.3 (Ar*C*H), 129.5 (Ar*C*H), 132.7 (Ar*C*), 142.6 (Ar*C*), 174.5 (*C*O); MS (EI) *m*/*z* 231 [M^+, 6.9%] (Found: M^+, 231.12556. $C_{14}H_{17}NO_2$ requires 231.12593).

Minor isomer (7a, 9%). Mp 107–109 °C (DCM–hexanes); $[\alpha]_D$ = +30.8 (*c* = 0.25, $CHCl_3$); ν_{max}(Nujol mull)/cm^{-1} 3422 (OH), 1655 (lactam); δ_H(250 MHz, $CDCl_3$) 1.55 (3H, s, C*H*$_3$), 2.32–2.51 (3H, m, C*H*$_2$$CH_2$O and C*H*(H)CO), 2.65–2.77 (1H, m, C*H*(H)CO), 2.84 (1H, dd, *J* 16.1, 9.2, ArC*H*(H)CHN), 3.04 (1H, dd, *J* 16.3, 6.8, ArC*H*(H)CHN), 3.69–3.88 (2H, m, C*H*$_2$OH), 4.18–4.32 (1H, m, NC*H*CH_2OH), 4.38–4.53 (1H, br s, O*H*), 7.08–7.34 (4H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 29.1 (*C*H_3), 29.7 (*C*H_2CO), 30.3 (Ar*C*H_2CHN), 35.0 (*C*$H_2$$CH_2$CO), 52.6 (N*C*HC$H_2$OH), 63.0 (*C*-$CH_3$), 67.8 (*C*$H_2$OH), 123.4 (Ar*C*H), 126.9 (Ar*C*H), 127.3 (Ar*C*H), 128.4 (Ar*C*H), 131.9 (Ar*C*), 142.6 (Ar*C*), 176.2 (*C*O).

(3*S*,7a*R*)-7a-Methyl-3-(phenylmethyl)-2,3,5,7a-tetrahydropyrrolo[2,1-*b*][1,3]oxazol-5-one, 8

A solution of LDA (4.30 ml, 2 M solution in heptane, 8.66 mmol) in anhydrous THF (20 ml) was cooled to −78 °C and (3*S*,7a*R*)-7a-methyl-3-(phenylmethyl)perhydropyrrolo[2,1-*b*]-[1,3]oxazol-5-one, **6** (1.00 g, 4.34 mmol), in anhydrous THF (10 ml) was slowly added dropwise and stirred for 3 hours. Benzeneselenenyl chloride (1.24 g, 6.50 mmol) in THF (5 ml) was added dropwise and the solution warmed to 0 °C and stirred for an additional 1 hour. Water (3.0 ml), acetic acid (0.6 ml) and H_2O_2 (2.34 g of a 35% solution) was added and the reaction mixture was maintained below 25 °C for approximately 30 minutes and then stirred for an additional 12 hours at room temperature. The solution was poured into saturated aqueous sodium bicarbonate solution (100 ml) and a 1 : 1 ether–hexane mixture (100 ml), and the organic layer was washed successively with water, HCl (0.1 M), water and saturated aqueous sodium chloride solution. Flash column chromatography using ethyl acetate and hexanes (1 : 3) as eluent gave reclaimed starting material (0.39 g) and the target compound as colourless crystals (0.50 g, 51%), a portion of which was recrystallised from dichloromethane and hexanes. Mp 72–73 °C; $[\alpha]_D$ = −7.0 (*c* = 0.14, $CHCl_3$) (Found: C, 73.14; H, 6.46; N, 6.11; $C_{14}H_{15}NO_2$ requires C, 73.34; H, 6.59; N, 6.11%); ν_{max}(DCM)/cm^{-1} 1712 (lactam), 1670 and 1654 (C=C); δ_H(400 MHz, $CDCl_3$) 1.51 (3H, s, C*H*$_3$), 2.91 (1H, dd, *J* 13.8, 9.0, C*H*(H)Ar), 3.14 (1H, dd, *J* 13.6, 5.6, C*H*(H)Ar), 4.00–4.11 (2H, m, C*H*$_2$O), 4.21–4.28 (1H, m, NC*H*CH_2O), 6.00 (1H, d, *J* 5.2, CHC*H*CO), 7.00 (1H, d, *J* 5.6, C*H*CHCO), 7.22–7.33 (5H, m, Ar*H*); δ_C(100 MHz, $CDCl_3$) 22.8 (*C*H_3), 40.1 (*C*H_2Ar), 57.1 (N*C*HCH_2O), 73.5 (*C*H_2O), 100.8 (*C*-CH_3), 126.7 (Ar*C*H), 127.8 (CH*C*HCO), 128.5 (2 × Ar*C*H), 129.3 (2 × Ar*C*H), 137.3 (Ar*C*), 151.3 (*C*HCHCO), 178.1 (*C*O); MS (EI) *m*/*z* 229 [M^+, 29.4%] (Found: M^+, 229.11067. $C_{14}H_{15}NO_2$ requires 229.11028).

(5*S*,10b*S*)-5-(Hydroxymethyl)-10b-methyl-3,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one, 9b

(3*S*,7a*R*)-7a-Methyl-3-(phenylmethyl)-2,3,5,7a-tetrahydropyrrolo[2,1-*b*][1,3]oxazol-5-one **8** (0.18 g, 0.79 mmol) was dissolved in dry dichloromethane (10 ml) under a nitrogen atmosphere. The mixture was cooled to −78 °C and 1.5 equivalents of $TiCl_4$ (0.13 ml, 1.19 mmol) were added dropwise by syringe. After stirring at this temperature for 10 minutes, the mixture was allowed to reach room temperature and left stirring for a further 20 hours. The reaction mixture was quenched with saturated ammonium chloride solution (20 ml), extracted with dichloromethane (3 × 20 ml) and dried over anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and the diastereoselectivity of the reaction determined by ^{1}H NMR spectroscopy on the crude reaction mixture. The yellow oil (0.17 g, 91%) was purified by flash column chromatography using 100% ethyl acetate as eluent. The solvent was removed by rotary evaporation to yield the target pyrroloisoquinoline diastereoisomers as colourless crystals.

Major isomer (9b, 50%). Mp 101–103 °C (DCM–hexanes); $[\alpha]_D$ = −292.0 (*c* = 0.27, $CHCl_3$); ν_{max}(DCM)/cm^{-1} 3315 (OH), 1662 (lactam); δ_H(400 MHz, $CDCl_3$) 1.64 (3H, s, C*H*$_3$), 2.74 (1H, dd, *J* 16.8, 3.6, ArC*H*(H)CHN), 3.32 (1H, dd, *J* 16.6, 12.2, ArC*H*(H)CHN), 3.73–3.82 (1H, m, NC*H*CH_2OH), 4.02–4.09 (1H, m, C*H*(H)OH), 4.28 (1H, dd, *J* 12.4, 2.4, C*H*(H)OH), 5.30 (1H, dd, *J* 10.0, 4.4, O*H*), 6.08 (1H, d, *J* 5.6, CHC*H*CO), 7.16–7.25 (4H, m, Ar*H*), 7.40 (1H, d, *J* 5.6, C*H*CHCO); δ_C(100 MHz, $CDCl_3$) 26.9 (*C*H_3), 32.3 (*C*H_2CHN), 53.4 (N*C*HCHCH_2-OH), 61.7 (*C*H_2OH), 68.8 (*C*-CH_3), 125.8 (CH*C*HCO), 126.0 (Ar*C*H), 126.4 (Ar*C*H), 127.3 (Ar*C*H), 130.0 (Ar*C*H), 133.5 (Ar*C*), 136.8 (Ar*C*), 153.6 (*C*HCHCO), 170.5 (*C*O); MS (EI) *m*/*z* 229 [M^+, 4.5%] (Found: M^+, 229.11023. $C_{14}H_{15}NO_2$ requires 229.11028).

Minor isomer (9a, 25%). Mp 118–120 °C (DCM–hexanes); $[\alpha]_D$ = +26.0 (*c* = 0.10, $CHCl_3$); ν_{max}(DCM)/cm^{-1} 3388 (OH), 1669 (lactam); δ_H(400 MHz, $CDCl_3$) 1.60 (3H, s, C*H*$_3$), 2.99 (1H, dd, *J* 15.8, 11.0, ArC*H*(H)CHN), 3.08 (1H, dd, *J* 15.8, 6.8, ArC*H*(H)CHN), 3.74 (1H, dd, *J* 10.9, 3.3, C*H*(H)OH), 3.84 (1H, dd, *J* 10.9, 7.7, C*H*(H)OH), 3.90 (1H, br s, O*H*), 4.11–4.18 (1H, m, NC*H*CH_2OH), 6.20 (1H, d, *J* 6.0, CHC*H*CO), 7.15–7.27 (4H, m, Ar*H*), 7.57 (1H, d, *J* 6.0, C*H*CHCO); δ_C(100 MHz, $CDCl_3$) 26.7 (*C*H_3), 29.8 (*C*H_2CHN), 53.5 (N*C*HCH_2OH), 67.6 (*C*-CH_3), 68.2 (C*H*$_2$OH), 124.1 (Ar*C*H), 125.3 (CH-*C*HCO), 127.0 (Ar*C*H), 127.9 (Ar*C*H), 129.0 (Ar*C*H), 133.0 (Ar*C*), 138.3 (Ar*C*), 153.0 (*C*HCHCO), 173.2 (*C*O).

1-[(1*R*)-2-(3,4-Dimethoxyphenyl)-1-(hydroxymethyl)ethyl]tetrahydro-1*H*-pyrrole-2,5-dione, 10

Succinic anhydride (0.45 g, 4.45 mmol) and (2*S*)-2-amino-3-(3,4-dimethoxyphenyl)propan-1-ol (0.94 g, 4.45 mmol) were dissolved in toluene (50 ml), and triethylamine (1.2 ml) was added to the stirring mixture. The solution was heated at reflux for 24 hours before the solvent was removed by rotary evaporation to give a white solid (0.90 g, 69%), a portion of which was recrystallised from ethyl acetate and hexanes to give colourless crystals. Mp 124–125 °C; $[\alpha]_D$ = −72.9 (*c* = 0.21, CH_2Cl_2) (Found: C, 61.18; H, 6.45; N, 4.61; $C_{15}H_{19}NO_5$ requires C, 61.42; H, 6.53; N, 4.78%); ν_{max}(DCM)/cm^{-1} 3449 (OH), 1771 and 1696 (imide); δ_H(250 MHz, $CDCl_3$) 2.53–2.60 (4H, m, 2 × C*H*$_2$CO), 2.98–3.14 (2H, m, C*H*$_2$Ar), 3.79–3.90 (1H, m, C*H*(H)OH), 3.84 (3H, s, C*H*$_3$O), 3.85 (3H, s, C*H*$_3$O), 4.01 (1H, dd, *J* 11.9, 7.3, C*H*(H)OH), 4.45–4.57 (1H, m, NC*H*CH_2OH), 6.65–6.79 (3H, m, Ar*H*), O*H* not visible; δ_C(100 MHz, $CDCl_3$) 27.9 (2 × *C*H_2CO), 33.3 (*C*H_2Ar), 55.6 (N*C*HCH_2OH), 55.87 (*C*H_3O), 55.9 (*C*H_3O), 62.2 (*C*H_2OH), 111.2 (Ar*C*H), 112.1 (Ar*C*H), 121.1 (Ar*C*H), 129.6 (Ar*C*), 147.8 (Ar*C*OCH$_3$), 148.9 (Ar*C*OCH$_3$), 178.1 (2 × *C*O); MS (EI) *m*/*z* 293 [M^+, 19.6%] (Found: M^+, 293.12610. $C_{15}H_{19}NO_5$ requires 293.12632).

(3*S*,7a*R*)-3-(3,4-Dimethoxyphenylmethyl)-7a-methylperhydropyrrolo[2,1-*b*][1,3]oxazol-5-one, 11

(2*S*)-2-Amino-3-(3,4-dimethoxyphenyl)propan-1-ol (0.78 g, 3.70 mmol) and levulinic acid (0.43 ml, 3.70 mmol) were dissolved in toluene (75 ml) and refluxed under Dean–Stark conditions for 48 hours. The solution was allowed to cool before the solvent was removed by rotary evaporation giving a red–brown oil. Purification by flash column chromatography using ethyl acetate and hexanes (2 : 1) as eluent yielded a pale yellow oil as the target compound (0.87 g, 81%). $[\alpha]_D$ = +36.5 (*c* = 0.37,

$CHCl_3$); ν_{max}(thin film)/cm^{-1} 1706 (lactam); δ_H(250 MHz, $CDCl_3$) 1.45 (3H, s, CH_3), 2.11–2.22 (2H, m, CH_2CH$_2$CO), 2.41–2.53 (1H, m, CH(H)CO), 2.68–2.83 (1H, m, CH(H)CO), 2.73 (1H, dd, *J* 13.9, 9.4, ArCH(H)CH), 3.09 (1H, dd, *J* 13.9, 5.6, ArCH(H)CH), 3.83–3.93 (1H, m, CH(H)OH), 3.83 (3H, s, CH_3O), 3.89 (3H, s, CH_3O), 4.05 (1H, dd, *J* 9.0, 7.2, CH(H)O), 4.23–4.34 (1H, m, NCHCH$_2$O), 6.72–6.83 (3H, m, ArH); δ_C(100 MHz, $CDCl_3$) 25.0 (*C*H$_3$), 33.3 (*C*H$_2$CO), 34.7 (*C*H$_2$-CH$_2$CO), 39.8 (*C*H$_2$Ar), 55.7 (*C*H$_3$O), 55.9 (*C*H$_3$O), 56.0 (N*C*HCH$_2$O), 71.4 (*C*H$_2$O), 100.1 (*C*-CH$_3$), 111.3 (Ar*C*H), 112.4 (Ar*C*H), 121.3 (Ar*C*H), 129.7 (Ar*C*), 147.9 (Ar*C*-OCH$_3$), 149.0 (Ar*C*-OCH$_3$), 178.3 (*C*O); MS (EI) *m*/*z* 291 [M$^+$, 87.5%] (Found: M$^+$, 291.14700. $C_{16}H_{21}NO_4$ requires 291.14706).

(5*S*,10b*R*)-5-(Hydroxymethyl)-8,9-dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one, 12

1-[(1*S*)-2-(3,4-Dimethoxyphenyl)-1-(hydroxymethyl)ethyl]-tetrahydro-1*H*-pyrrole-2,5-dione (0.13 g, 0.43 mmol), **10**, was dissolved in absolute ethanol (10ml) and cooled to 0 °C and sodium borohydride (0.16 g, 4.30 mmol) was then added with stirring. 2 M HCl in absolute ethanol (8.46 ml, 4.30 mmol) was added slowly *via* syringe over a period of an hour affording a white suspension which was stirred for an additional 20 hours at room temperature. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 ml), extracted with dichloromethane (3 × 10 ml) and dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation and the diastereoselectivity of the reaction determined by ^{1}H NMR spectroscopy on the crude reaction mixture. Solvent removal at this stage yielded a white solid (0.11 g, 91%), a portion of which was recrystallised using dichloromethane and hexanes to give the target compound as colourless crystals. Mp 177–179 °C; $[\alpha]_D$ = +110.8 (*c* = 0.25, $CHCl_3$) (Found: C, 64.64; H, 6.83; N, 4.96; $C_{15}H_{19}NO_4$ requires C, 64.97; H, 6.91; N, 5.05%); ν_{max}(DCM)/cm^{-1} 3263 (OH), 1664 (lactam); δ_H(400 MHz, $CDCl_3$) 1.86–1.98 (1H, m, CH(H)CH$_2$CO), 2.41–2.51 (1H, m, CH(H)CO), 2.56–2.69 (3H, m, CH(H)CH$_2$CO; CH(H)CO and ArCH(H)CHN), 2.99 (1H, dd, *J* 16.2, 6.6, ArCH(H)CHN), 3.56–3.70 (3H, m, CH_2OH and OH), 3.86 (3H, s, CH_3O), 3.87 (3H, s, CH_3O), 4.44–4.52 (1H, m, NCH-CH$_2$OH), 4.77 (1H, t, *J* 7.7, NCHAr), 6.58 (1H, s, ArH), 6.62 (1H, s, ArH); δ_C(100 MHz, $CDCl_3$) 27.2 (*C*H$_2$CH$_2$CO), 29.1 (Ar*C*H$_2$CHN), 31.8 (*C*H$_2$CO), 49.3 (N*C*H), 54.2 (N*C*H-CH$_2$OH), 56.0 (*C*H$_3$O), 56.1 (*C*H$_3$O), 62.7 (*C*H$_2$OH), 107.5 (Ar*C*H), 111.9 (Ar*C*H), 124.2 (Ar*C*), 128.5 (Ar*C*), 148.1 (Ar*C*-OCH$_3$), 148.2 (Ar*C*-OCH$_3$), 175.0 (*C*O); MS (EI) *m*/*z* 277 [M$^+$, 29.4%] (Found: M$^+$, 277.13141. $C_{15}H_{19}NO_4$ requires 277.13141).

(5*S*,10b*S*)-5-(Hydroxymethyl)-10b-methyl-8,9-dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one, 13b[3j]

(3*S*,7a*R*)-3-(3,4-Dimethoxyphenylmethyl)-7a-methylperhydro-pyrrolo[2,1-*b*][1,3]oxazol-5-one **11** (0.50 g, 1.72 mmol) was dissolved in dry dichloromethane (30 ml) under a nitrogen atmosphere. The mixture was cooled to −78 °C and 1.5 equivalents of $TiCl_4$ (0.28 ml, 2.58 mmol) were added dropwise by syringe. After stirring at this temperature for 10 minutes, the mixture was allowed to reach room temperature and left stirring for a further 20 hours. The reaction mixture was quenched with saturated ammonium chloride solution (30 ml), extracted with dichloromethane (3 × 30 ml) and dried using anhydrous magnesium sulfate. The solvent was removed by rotary evaporation and the diastereoselectivity of the reaction determined by ^{1}H NMR spectroscopy on the crude reaction mixture. The yellow solid (0.46 g, 91%) was purified by flash column chromatography using 100% ethyl acetate as eluent, and recrystallised from ethyl acetate and hexanes to yield the target pyrroloisoquinoline diastereoisomers as colourless crystals.

Major isomer (13b, 69%)[3j]. Mp 138–139 °C (DCM–hexanes); $[\alpha]_D$ = −222.5 (*c* = 0.28, $CHCl_3$) (Found: C, 65.76; H, 7.21; N, 4.74; $C_{16}H_{21}NO_4$ requires C, 65.96; H, 7.27; N, 4.81%); ν_{max}(DCM)/cm^{-1} 3384 (OH), 1655 (lactam); δ_H(250 MHz, $CDCl_3$) 1.57 (3H, s, CH_3), 2.08–2.21 (1H, m, CH(H)CH$_2$CO), 2.34–2.49 (2H, m, CH(H)CH$_2$CO and CH(H)CO), 2.58–2.75 (1H, m, CH(H)CO), 2.62 (1H, dd, *J* 16.1, 4.1, ArCH(H)CHN), 3.05 (1H, dd, *J* 15.9, 11.3, ArCH(H)CHN), 3.61–3.70 (1H, m, NCHCH$_2$OH), 3.86 (3H, s, CH_3O), 3.87 (3H, s, CH_3O), 3.97–4.04 (2H, m, CH_2OH), 4.93 (1H, t, *J* 7.4 OH), 6.55 (1H, s, ArH), 6.59 (1H, s, ArH); δ_C(100 MHz, $CDCl_3$) 27.3 (*C*H$_3$), 31.1 (*C*H$_2$CO), 31.3 (*C*H$_2$CHN), 34.9 (*C*H$_2$CH$_2$CO), 54.0 (N*C*HCH$_2$OH), 55.9 (*C*H$_3$O), 56.2 (*C*H$_3$O), 62.5 (*C*H$_2$OH), 64.3 (*C*-CH$_3$), 107.6 (Ar*C*H), 111.4 (Ar*C*H), 124.5 (Ar*C*), 134.1 (Ar*C*), 148.0 (Ar*C*-OCH$_3$), 148.2 (Ar*C*-OCH$_3$), 174.1 (*C*O); MS (EI) *m*/*z* 291 [M$^+$, 14.1%] (Found: M$^+$, 291.14742. $C_{16}H_{21}NO_4$ requires 291.14706).

Minor isomer (13a, 5%). Mp 152–154 °C (DCM–hexanes); $[\alpha]_D$ = +70.4 (*c* = 0.41, $CHCl_3$); ν_{max}(DCM)/cm^{-1} 3390 (OH), 1660 (lactam); δ_H(250 MHz, $CDCl_3$) 1.53 (3H, s, CH_3), 2.23–2.48 (3H, m, CH_2CH$_2$CO and CH(H)CO), 2.69–2.81 (1H, m, CH(H)CO), 2.79 (1H, dd, *J* 16.2, 8.3, ArCH(H)CHN), 2.97 (1H, dd, *J* 16.2, 7.1, ArCH(H)CHN), 3.71–3.81 (2H, m, CH_2OH), 3.87 (3H, s, CH_3O), 3.88 (3H, s, CH_3O), 4.24–4.35 (1H, m, NCHCH$_2$OH), 6.65 (1H, s, ArH), 6.66 (1H, s, ArH), OH not visible; δ_C(100 MHz, $CDCl_3$) 29.0 (*C*H$_3$), 29.2 (*C*H$_2$-CO), 30.5 (Ar*C*H$_2$CHN), 35.6 (*C*H$_2$CH$_2$CO), 51.4 (N*C*H-CH$_2$OH), 56.0 (*C*H$_3$O), 56.2 (*C*H$_3$O), 62.5 (*C*-CH$_3$), 66.1 (*C*H$_2$OH), 107.2 (Ar*C*H), 111.7 (Ar*C*H), 123.7 (Ar*C*), 134.3 (Ar*C*), 148.1 (Ar*C*-OCH$_3$), 148.13 (Ar*C*-OCH$_3$), 175.5 (*C*O).

(5*S*,10b*S*)-10b-Methyl-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo-[2,1-*a*]isoquinoline-5-carbaldehyde, 14

A solution of (5*S*,10b*S*)-5-(hydroxymethyl)-10b-methyl-1,2,3,-5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one **7b** (0.15 g, 0.65 mmol) in dichloromethane (5 ml) was added to a solution of Dess–Martin periodinane (0.30 g, 0.71 mmol) in dichloromethane (10 ml) with stirring. After 20 hours, the mixture was diluted with ether (30 ml) and poured into saturated aqueous sodium bicarbonate solution (30 ml) containing a seven-fold excess of sodium thiosulfate (1.23 g, 4.97 mmol). The mixture was washed with saturated aqueous sodium bicarbonate solution and then with water. The ether was evaporated off to give a colourless oil (0.13 g, 89%) which required no further purification. $[\alpha]_D$ = −93.09 (*c* 0.28, $CHCl_3$); ν_{max}(thin film)/cm^{-1} 1727 (CHO), 1683 (lactam); δ_H(250 MHz, $CDCl_3$) 1.57 (3H, s, CH_3), 2.37–2.52 (3H, m, CH_2CH$_2$CO and CH(H)CO), 2.61–2.80 (1H, m, CH(H)CO), 3.21 (2H, d, *J* 6.0, ArCH_2CHN), 4.32 (1H, t, *J* 6.1, NCHCHO), 7.10–7.31 (4H, m, ArCH), 9.63 (1H, s, CHO); δ_C(100 MHz, $CDCl_3$) 28.0 (*C*H$_2$CO), 28.6 (*C*H$_3$), 29.8 (Ar*C*H$_2$CHN), 34.8 (*C*H$_2$CH$_2$CO), 57.5 (NC*H*CHO), 62.4 (*C*-CH$_3$), 123.8 (Ar*C*H), 127.4 (Ar*C*H), 127.4 (Ar*C*H), 128.9 (Ar*C*H), 130.9 (Ar*C*), 142.8 (Ar*C*), 175.1 (*C*O), 198.4 (*C*HO); MS (EI) *m*/*z* 229 [M$^+$, 2.7%] (Found: M$^+$, 229.11061. $C_{14}H_{15}$-NO_2 requires 229.11028).

(10b*S*)-10b-Methyl-1,2,3,10b-tetrahydropyrrolo[2,1-*a*]-isoquinolin-3-one, 15

[Bis(triphenylphosphine)]rhodium(I) carbonyl chloride (0.02 g, 0.03 mmol) was added to anhydrous xylene (10 ml) under a nitrogen atmosphere. The mixture was stirred at 80 °C for 15 minutes. 1,3-Bis(diphenylphosphino)propane (0.03 g, 0.06 mmol) was added, and the mixture was heated at 80 °C for 30 minutes. (5*S*,10b*S*)-10b-Methyl-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-5-carbaldehyde **14** (0.13 g, 0.57 mmol) in anhydrous xylene (10 ml) was added and the mixture was heated at reflux for 20 hours. The solvent was removed by rotary evaporation giving a thick green oil.

Purification by flash column chromatography using ethyl acetate and hexanes (1 : 1) as mobile phase gave the product as colourless crystals (0.07 g, 64%), a portion of which was recrystallised from dichloromethane and hexanes. Mp 134–136 °C; $[a]_D = -667.9$ ($c = 0.29$, CH_2Cl_2); ν_{max}(DCM)/cm^{-1} 1700 (lactam); δ_H(250 MHz, $CDCl_3$) 1.33 (3H, s, CH_3), 2.36–2.57 (3H, m, CH_2CH$_2$CO and CH(H)CO), 2.61–2.78 (1H, m, CH(H)CO), 6.03 (1H, d, J 7.6, ArCHCHN), 6.90 (1H, d, J 7.4, ArCHCHN), 7.05–7.12 (2H, m, ArH), 7.17–7.28 (2H, m, ArH); δ_C(100 MHz, $CDCl_3$) 26.1 (CH_3), 30.0 (CH_2CO), 33.0 (CH_2-CH$_2$CO), 61.9 (C-CH$_3$), 111.3 (CH=CH), 120.8 (CH=CH), 123.0 (ArCH), 125.3 (ArCH), 127.6 (ArCH), 127.8 (ArCH), 129.9 (ArC), 138.6 (ArC), 171.9 (CO); MS (EI) m/z 199 [M$^+$, 12.7%] (Found: M$^+$, 199.09935. $C_{13}H_{13}NO$ requires 199.09971).

(10b*S*)-10b-Methyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]-isoquinolin-3-one, 16

(10b*S*)-10b-Methyl-1,2,3,10-tetrahydropyrrolo[2,1-*a*]isoquinolin-3-one **15** (0.09 g, 0.45 mmol) was dissolved in absolute ethanol (10 ml) in a Schlenk tube. The reaction mixture was purged with nitrogen. A catalytic amount of 10% palladium–charcoal was added to the mixture, a balloon filled with hydrogen was fitted and the system purged with hydrogen, the mixture was then stirred for a further 20 hours. The mixture was filtered through Celite, the reaction vessel was washed with dichloromethane (3 × 10 ml) and poured onto the Celite. The organic extracts were collected, dried using anhydrous magnesium sulfate and evaporated off to give colourless needle-like crystals (0.08 g, 89%), a portion of which was recrystallised from dichloromethane and hexanes. Mp 125–127 °C; $[a]_D = -261.2$ ($c = 0.30$, $CHCl_3$) (Found: C, 77.52; H, 7.32; N, 6.83; $C_{13}H_{15}NO$ requires C, 77.58; H, 7.51; N, 6.91%); ν_{max}(DCM)/cm^{-1} 1671 (lactam); δ_H(250 MHz, $CDCl_3$) 1.52 (3H, s, CH_3), 2.09 (1H, dd, J 21.5, 11.4, CH(H)CH$_2$CO), 2.35–2.47 (2H, m, CH(H)CH$_2$CO and CH(H)CO), 2.55–2.68 (1H, m, CH(H)CO), 2.71–2.80 (1H, m, ArCH(H)CH$_2$N), 2.86–3.01 (1H, m, ArCH-(H)CH$_2$N), 3.03–3.16 (1H, m, CH$_2$CH(H)N), 4.25–4.35 (1H, m, CH$_2$CH(H)N), 7.07–7.26 (4H, m, ArH); δ_C(100 MHz, $CDCl_3$) 27.5 (CH_3), 28.5 (CH_2CH$_2$N), 30.7 (CH_2CH$_2$CO), 34.0 (CH$_2$CH_2N), 34.7 (CH$_2$CH_2CO), 61.1 (C-CH$_3$), 125.0 (ArCH), 126.8 (ArCH), 126.9 (ArCH), 129.2 (ArCH), 132.3 (ArC), 142.7 (ArC), 172.3 (CO); MS (EI) m/z 201 [M$^+$, 3.3%] (Found: M$^+$, 201.11492. $C_{13}H_{15}NO$ requires 201.11536).

X-Ray crystallography for 7b, 12 and 13b†

General. Intensity data were collected using Bruker SMART 1000 CCD diffractometer with graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). Data were measured using ω-scans and narrow frames. Programs used were Bruker SMART,[13] SAINT,[13] SHELXTL[14] and local programs.

Crystal data for 7b. $C_{14}H_{17}NO_2$, $M = 231.29$, monoclinic, space group $P2_1$, $a = 7.7150(6)$, $b = 8.0282(6)$, $c = 10.0287(8)$ Å, $\beta = 109.876(2)°$, $V = 584.15(8)$ Å^3, $T = 150$ K, $Z = 2$, μ(Mo-Kα) = 0.088 mm^{-1}, 5096 data measured of which 2514 were unique, $R_{int} = 0.012$, all unique data used in refinement against F^2 values to give final $wR = 0.0807$ (on F^2 for all data), $R = 0.0298$ {for 2421 data with $F^2 > 4\sigma(F^2)$}, absolute structure parameter $x = -0.0(10)$ {therefore not determined}.

Crystal data for 12. $C_{15}H_{19}NO_4$, $M = 277.31$, orthorhombic, space group $P2_12_12_1$, $a = 5.3164(3)$, $b = 11.9673(7)$, $c = 20.8468(12)$ Å, $V = 1326.34(13)$ Å^3, $T = 150$ K, $Z = 4$, μ(Mo-Kα) = 0.101 mm^{-1}, 11448 data measured of which 3150 were unique, $R_{int} = 0.021$, all unique data used in refinement against F^2 values to give final $wR = 0.0835$ (on F^2 for all data), $R = 0.0333$ {for 2853 data with $F^2 > 4\sigma(F^2)$}, absolute structure parameter $x = -0.2(9)$ (therefore not determined).

Crystal data for 13b. $C_{16}H_{21}NO_4$, $M = 291.34$, monoclinic, space group $P2_1$, $a = 10.5447(10)$, $b = 9.5411(9)$, $c = 14.7057(13)$ Å, $V = 1475.9(2)$ Å^3, $T = 150$ K, $Z = 4$, μ(Mo-Kα) = 0.094 mm^{-1}, 12656 data measured of which 6544 were unique, $R_{int} = 0.019$, all unique data used in refinement against F^2 values to give final $wR = 0.0786$ (on F^2 for all data), $R = 0.0349$ {for 5287 data with $F^2 > 4\sigma(F^2)$}, absolute structure parameter $x = -0.1(6)$ {therefore not determined}. There are two, similar molecules in the asymmetric unit.

† CCDC reference numbers 166688, 166689 and 172096. See http://www.rsc.org/suppdata/p1/b1/b105402n/ for crystallographic files in .cif or other electronic format.

Acknowledgements

The authors wish to thank Loughborough University and GlaxoSmithKline Pharmaceuticals (joint studentship to SLJ) for facilities and financial support of this research. We also thank Professors H. Heaney, W. R. Bowman and P. C. B. Page for helpful comments during the course of this work and in the preparation of this manuscript.

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9 We were able to perform a set of comparative NOE studies on the separable diastereoisomeric products **7a** and **7b**. In the case of **7b**, an NOE was observed between the methyl group at position 10b and the proton at position 5. In the case of the minor diastereoisomer **7a**, no NOE was observed. Both results are in accord with the predicted structures for the isolated diastereoisomers, and with the recent publications by Katritzky *et al*. (ref. 3*i*) and by Lete and co-workers (ref. 3*j*).

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