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Enolate amination and derivatization of a pyrroloisoquinoline template: towards novel peptidomimetics

Steven M. Allin [a,*], Joannah Towler [b], Sean N. Gaskell [b], Basu Saha [c], William P. Martin [d], Philip C. Bulman Page [e], Mark Edgar [b]

[a] School of Physical and Geographical Sciences, Keele University, Keele, ST5 5BG, UK
[b] Department of Chemistry, Loughborough University, Loughborough, LE11 3TU, UK
[c] Department of Chemical Engineering, Loughborough University, Loughborough, LE11 3TU, UK
[d] GSK Pharmaceuticals, Gunnels Wood Road, Stevenage, Herts., SG1 2NY, UK
[e] School of Chemistry and Pharmacy, University of East Anglia, Norwich, NR4 7TJ, UK

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ABSTRACT

Pyrroloisoquinoline-based peptidomimetics are of significant interest in bioorganic chemistry as these targets are known to exhibit type II′ β-turn activity. In this paper we present a novel approach to such pyrroloisoquinoline templates based on a stereoselective *N*-acyliminium-mediated cyclization reaction to construct the heterocyclic core, coupled with an enolate amination protocol. We have applied both symmetrical and unsymmetrical electrophilic aminating reagents based on azodicarboxylate functionality, and demonstrate the utility of our approach in the synthesis of a peptide target.

1. Introduction

Polycyclic lactam scaffolds have been developed as useful templates for the introduction of reverse-turn motifs, including β-turn activity, in the study of conformationally restricted peptide analogues.[1] The importance of this subject area to medicinal and biological chemistry is clear since reverse turns play a significant role in many biological recognition events. Fairlie and co-workers have recently suggested that more than 100 GPCR's are able to recognize, and bind, ligands containing a turn structure.[2] In terms of structural modification of peptide structures to produce pseudopeptides, the formation of hydrazinopeptides—in which an α-amino acid residue is replaced by an α-hydrazino acid—is of significant interest.[3] The hydrazino moiety offers additional opportunities for structural modification (e.g., at either hydrazino *N*-atom) and added potential for the formation of novel H-bonded organization in secondary protein structures. Several synthetic hydrazinopeptides have been shown to display turn-mimetic activity[4] and also possess wide–ranging biological activities (Fig. 1).[5]

Our research group has an interest in the synthesis of a wide range of non-racemic heterocyclic targets,[6] including the pyrroloisoquinoline ring system.[6a,b] Recently, Silvani and co-workers have prepared pyrroloisoquinoline-based peptide analogues, such as **1**, and have demonstrated that such compounds exhibit type II′ β-turn activity.[7] Routes to similar pyrroloisoquinoline-containing peptidomimetics have been reported by O'Donnell[8] and Meldal.[9] All of these approaches to the key pyrroloisoquinoline system have involved the application of Pictet–Spengler chemistry to construct the heterocycle with the required amino acid residues in place courtesy of the corresponding α-amino acid substrates employed in the Pictet–Spengler reaction. With this in mind, we envisaged a new approach to aminated pyrroloisoquinoline targets that involved the synthesis of the key non-racemic heterocyclic framework using our now well-established *N*-acyliminium cyclization methodology,[6] followed by electrophilic amination of the lactam ring to introduce the desired α-amino amide functionality.

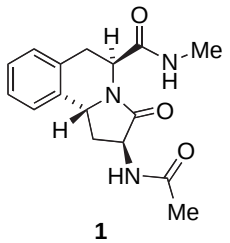

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Fig. 1. A pyrroloisoquinoline-derived β-turn mimetic.

* Corresponding author. E-mail address: s.m.allin@chem.keele.ac.uk (S.M. Allin).

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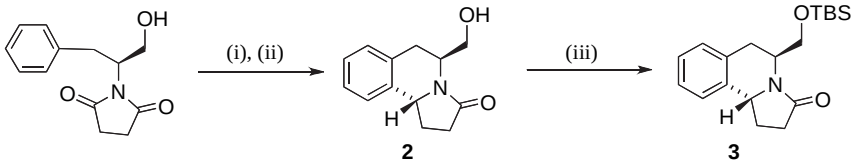
2. Results and discussion

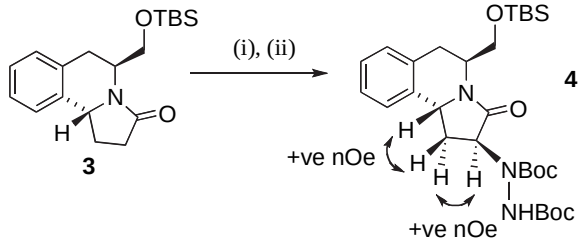
2.1. Synthesis and derivatization of the pyrroloisoquinoline template

Pyrroloisoquinoline template **2** was readily prepared as a single diastereoisomer,[6a,b] and converted to the corresponding silyl ether **3**, as shown in Scheme 1.

Enolate amination was achieved in a highly diastereoselective fashion through treatment of **3** with LDA in THF at low temperature and subsequently reacting the lithium enolate with the electrophilic aminating reagent di-*tert*-butyl azodicarboxylate (DBAD) to generate the desired α-hydrazino ketone product, **4**, in 85% yield as a ca. 15:1 mixture of product diastereoisomers by 400 MHz ^{1}H NMR spectroscopy (Scheme 2). Due to significant broadening of the NMR signals at ambient temperature, the NMR spectrum of **4** was best obtained in DMSO-d_6 at elevated temperature (100 °C). The major product diastereoisomer was isolated by column chromatography and the relative stereochemistry was confirmed by NOE studies indicating a cis relationship with respect to the newly added hydrazino substituent and the TBS-protected hydroxymethyl group, as shown in Scheme 2. Gratifyingly, compound **4** shares the same relative and absolute stereochemistry at the three chiral centres as Silvani's pyrroloisoquinoline β-turn lead, **1**.[7]



Scheme 1. Synthesis of pyrroloisoquinoline template: reagents and conditions: (i) $NaBH_4$ (10 equiv), EtOH, 0 °C, 3 h; (ii) 2 M HCl, EtOH, 20 h; then $TiCl_4$ (1.5 equiv), DCM, −78 °C, 3 h (52% over 2 steps); (iii) DMAP (0.1 equiv), imidazole (1.3 equiv), TBDMS-Cl, (1.25 equiv), DCM, rt, 20 h (98%).



Scheme 2. Stereoselective amination using DBAD: reagents and conditions: (i) LDA (1.4 equiv), −78 °C, THF, 15 min; (ii) DBAD (1.3 equiv), −78 °C to rt, 20 h (85%).

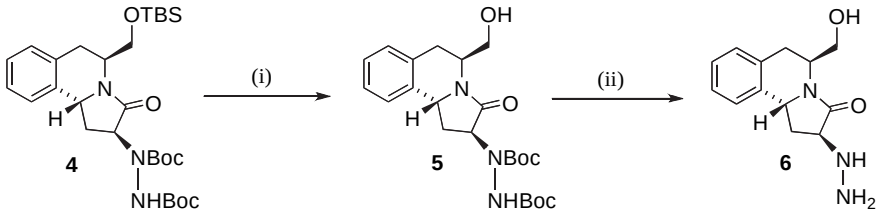
2.2. Peptide coupling

From compound **4** we were able to remove the TBS-protection to generate primary alcohol **5**, and subsequently remove both Boc-protecting groups using standard methodologies to yield the novel hydrazino alcohol **6** (Scheme 3).

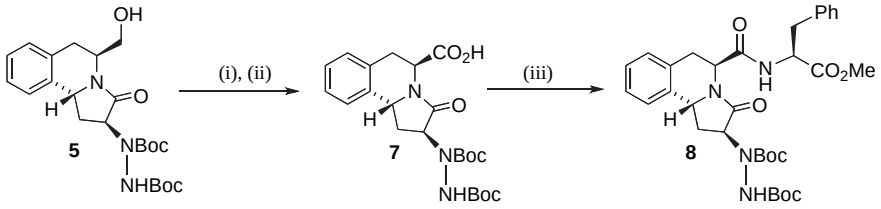
Having successfully developed a highly stereoselective route for introduction of an amine-based substituent into the α-position of the lactam ring of the pyrroloisoquinoline template, and with a view to the potential application of such a system in biological chemistry, we have also investigated the further manipulation of the pyrroloisoquinoline template to prepare a typical peptide derivative. Primary alcohol **5** was oxidised to the corresponding carboxylic acid, **7**, through a two-step procedure (Scheme 4), and **7** was subsequently utilized in an EDCI-induced coupling with (*S*)-phenylalanine methyl ester to form the hydrazino peptoid, **8**. Due to significant broadening of the NMR signals at ambient temperature, the NMR spectrum of **8** was best obtained in DMSO-d_6 at elevated temperature (100 °C).

2.3. Application of an unsymmetrical aminating reagent

Although the use of DBAD as the electrophilic aminating reagent was successful in our work, in some respects this reagent suffers from the drawback of having the same protecting group (i.e., a Boc group) on each of the hydrazine nitrogen atoms in the product. It would be of significant advantage, providing added flexibility, if a suitable reagent containing orthogonal protection could be applied. This would potentially allow an operator to deprotect each



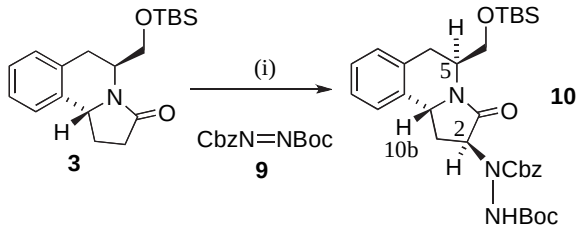
Scheme 3. Deprotection of aminated product: reagents and conditions: (i) TBAF (1 equiv), THF, rt, 5 min (45%); (ii) TFA (50 equiv), rt, 24 h (70%).



Scheme 4. Derivatization to a peptidic product: reagents and conditions: (i) IBX (1.5 equiv), DMSO, rt, 24 h (61%); (ii) $NaClO_2$ (8 equiv), NaH_2PO_4 (7 equiv), 1-methyl-1-cyclohexene, MeCN, *t*-BuOH, H_2O, 0 °C, 17 h (80%); (iii) (*S*)-phenylalanine methyl ester hydrochloride (1.1 equiv), EDCI (1.1 equiv), HOABt (1.1 equiv), NMM (1.1 equiv), DCM, −15 °C, 3 h (57%).

nitrogen atom of the α-hydrazine substituent in turn, so opening the possibility of building up a more complex target structure through derivatization at either *N*-centre of the α-hydrazino group.

A suitably differentiated azodicarboxylate reagent, **9**, has previously been used by Jùrgensen in the synthesis of aminated 2-naphthols,[10] and we were interested to see how this reagent would perform in our own work. Thus, reagent **9** was prepared accordingly to the method of MacKay[11] and applied to the enolate amination of pyrroloisoquinoline **3** (Scheme 5).



Scheme 5. Application of an unsymmetrical aminating reagent: reagents and conditions: (i) LDA (1.4 equiv), **9** (1 equiv), THF, −78 °C to rt, 20 h (41%).

We were pleased to find that the desired hydrazino product **10** was formed as the major product of the reaction and could be obtained in 41% isolated yield following column chromatography. Other by-products were formed in this reaction (as observed by TLC analysis and by NMR spectroscopy on the crude reaction mixture), although we were unable to isolate and characterize these. As a result we are unable to comment confidently at this stage on the diastereoselectivity of the amination step, or on the overall regioselectivity when using reagent **9** in this enolate amination reaction.

Compound **10** was isolated as a single diastereoisomer (by 400 MHz ^{1}H NMR spectroscopy) with the regiochemistry shown in Scheme 5 (with regards to the amination using reagent **9**). An NOE study was performed on compound **10** to support the assignment of relative stereochemistry at the newly created α-aminated centre (position 2), and the result was consistent with that observed for compound **4**. Neither of the protons at positions 5 and 10b, nor the protons at positions 2 and 10b, shows a positive NOE effect towards each other. This would suggest a trans relationship between the protons at positions 5 and 10b, and between those at positions 2 and 10b, respectively. The stereochemistry at position 5 is unambiguous, relating to the original enantiomerically pure amino-alcohol substrate applied to the synthesis of the heterocyclic template. Due to significant broadening of the NMR signals at ambient temperature, the NMR spectrum of **10** was obtained in DMSO-d_6 at elevated temperature (100 °C).

With the unsymmetrical amination product **10** in hand we found that we were readily able to remove the protecting groups in an orthogonal fashion (Scheme 6). Following the method reported by Jùrgensen,[10] the Cbz-group was selectively removed from the secondary amine moiety by catalytic hydrogenation to yield the mono Boc-protected pyrroloisoquinoline, **11**, in 88% yield. This reaction also provided information on the regiochemistry of the amination itself. The 400 MHz ^{1}H NMR of compound **11** shows the appearance of a new broad singlet peak at 4.35 ppm, integrating accurately for 1H, and also a 1H signal (N*H*) for the existing *tert*-butyl carbamate functionality at 6.40 ppm. This is evidence that the Cbz protection in **10** is situated on the α-*N*-atom and not the alternative β-position. If the Cbz group were at the β-position the new amine peak would be expected to integrate to 2, and importantly there would be an absence of the additional N*H* signal at 6.4 ppm. It was notable that removal of the Cbz-group resulted in simplification of NMR analysis, with the NMR spectrum for compound **11** obtained in $CDCl_3$ at ambient temperatures.

Following desilylation of the primary alcohol group with TBAF, the Boc-protecting group on the primary amine functionality was then removed on treatment with TFA to yield the α-hydrazino pyrroloisoquinoline target, **6**, that had also been prepared from the amination protocol using DBAD (Scheme 3).

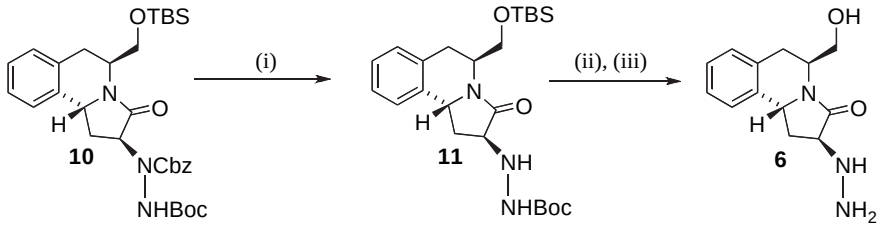
3. Conclusion

In summary, we have developed a novel approach to aminated pyrroloisoquinoline systems based on a stereoselective *N*-acyliminium-mediated cyclization reaction to construct the heterocyclic template, and an enolate amination protocol to functionalize the lactam ring. We have applied both symmetrical and unsymmetrical electrophilic aminating reagents based on azodicarboxylate functionality, and have applied our methodology in the synthesis of a peptide target. The use of an unsymmetrical electrophilic aminating reagent allows us to apply orthogonal deprotection of our intermediates, adding additional flexibility to our approach. Future work will aim to investigate the effects of incorporation of the aminated templates into novel peptide structures.

4. Experimental section

4.1. General

All infrared spectra were obtained using an FT-IR spectrophotometer; thin film spectra were acquired using sodium chloride plates. All ^{1}H and ^{13}C NMR spectra were obtained at 400 and 100 MHz, respectively, in deuteriochloroform solution unless otherwise stated, using TMS (tetramethylsilane) as the internal reference. Mass spectra were recorded utilizing either electron-impact (EI), fast atom bombardment (FAB), or electrospray (ES). Analysis by GC–MS utilized a 15 m×0.25 mm DB-5 column and an electron-impact low-resolution mass spectrometer. Melting points are uncorrected. Optical rotation values were measured operating at λ=589 nm, corresponding to the sodium D line, at the temperatures indicated. All chromatographic manipulations used silica gel as the adsorbent. Reactions were monitored using thin layer chromatography (TLC) on aluminium-backed plates coated with F_{254} silica gel. TLC plates were visualized by UV radiation at a wavelength of 254 nm, or stained by exposure to an ethanolic solution of phosphomolybdic acid (acidified with concentrated sulfuric acid), followed by charring where appropriate. Reactions requiring



Scheme 6. Orthogonal deprotection of **10**: reagents and conditions: (i) $NH_4^+HCO_2^-$, Pd/C, MeOH, 2 h (88%); (ii) TBAF, THF, rt, 5 min (48%); (iii) TFA (20 equiv, 24 h (55%).

anhydrous conditions were carried out using flame-dried glassware under a nitrogen atmosphere unless otherwise stated. Reaction solvents were used as obtained commercially unless otherwise stated. Light petroleum (bp 40–60 °C) was distilled from calcium chloride prior to use. Ethyl acetate was distilled over calcium sulfate or chloride. Dichloromethane was distilled over calcium hydride.

4.1.1. (S)-1-(1-Hydroxy-3-phenylpropan-2-yl)pyrrolidine-2,5-dione[6b]. Succinic anhydride (1.20 g, 12.0 mmol) and (*S*)-2-amino-3-phenyl-1-propanol (1.80 g, 12.0 mmol) were stirred in toluene (100 ml) under a nitrogen atmosphere. Triethylamine (3 ml) was added to the resultant solution and the mixture heated under reflux for 18 h. After 18 h, the reaction was cooled to room temperature and the solvent removed by rotary evaporation. The crude product was adsorbed onto silica gel and chromatographed using silica gel as absorbent and ethyl acetate as eluent to produce a colourless solid (1.70 g, 62%). Mp 130–131 °C. R_f (EtOAc) 0.6. ^{1}H NMR (400 MHz; $CDCl_3$) 2.50–2.63 (4H, m), 3.07–3.17 (2H, m), 3.84 (1H, dd, *J*=3.5, 11.9 Hz), 4.00 (1H, dd, *J*=7.6, 11.9 Hz), 4.48–4.55 (1H, m), 7.18–7.29 (5H, m). ^{13}C NMR (100 MHz; $CDCl_3$) 27.8 (2C), 33.7, 55.7, 62.1, 126.8, 128.5 (2C), 129.1 (2C), 137.2, 178.2 (2C). IR (thin film, CH_2Cl_2, cm^{-1}) 3419, 1763, 1682. MS (EI) *m*/*z* 233 [M^+, 3%] (calcd for $C_{13}H_{15}NO_3$: 233.1052 (M^+). Found 233.1055).

*4.1.2. (5S,10bR)-5-(Hydroxymethyl)-1,2,5,6-tetrahydropyrrolo[2,1-a]-isoquinolin-3(10bH)-one, (**2**)[6b].* (*S*)-1-(1-Hydroxy-3-phenylpropan-2-yl)pyrrolidine-2,5-dione (5.00 g, 21.4 mmol) was dissolved in absolute ethanol (100 ml) and cooled to 0 °C. Sodium borohydride (8.11 g, 214.4 mmol) was then added with stirring. A 2 M solution of HCl in absolute ethanol (10.7 ml, 21.4 mmol) was then added slowly via syringe over a 3 h period. The resulting solution was acidified to pH 1–3 by the 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 a saturated aqueous solution of sodium hydrogen carbonate and extracted with dichloromethane (3×50 ml). The dichloromethane layers were then combined and dried over anhydrous magnesium sulfate, filtered and the solvent removed by rotary evaporation to yield an ethoxy lactam intermediate as a colourless oil (4.60 g). Without purification the intermediate ethoxy lactam (4.60 g, 17.6 mmol) was dissolved in anhydrous dichloromethane (100 ml) under a nitrogen atmosphere and cooled to −78 °C. Titanium tetrachloride (2.89 ml, 26.4 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 (3×50 ml). The dichloromethane layers were then combined and dried over anhydrous magnesium sulfate, filtered and the solvent removed by rotary evaporation to yield the target compound as a single diastereoisomer, by 400 MHz ^{1}H NMR spectroscopy, which was purified by column chromatography using silica gel as absorbent and 10% methanol in dichloromethane as eluent to yield a pale green solid (2.00 g, 52%). Mp 110–111 °C. R_f (10% MeOH/DCM) 078. ^{1}H NMR (400 MHz; $CDCl_3$) 1.97–2.07 (1H, m), 2.41–2.51 (1H, m), 2.59–2.74 (3H, m), 3.04 (1H, dd, *J*=6.4, 16.4 Hz), 3.59–3.73 (2H, m), 4.14 (1H, br s), 4.43–4.49 (1H, m), 4.83 (1H, t, *J*=7.6 Hz), 7.09–7.31 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) 26.6, 29.6, 31.7, 49.5, 54.5, 62.8, 124.3, 126.9, 127.2, 128.7, 132.3, 136.7, 175.2. IR (thin film, CH_2Cl_2, cm^{-1}) 3374, 1643. MS (EI) *m*/*z* 217 [M^+, 8%] (calcd for $C_{13}H_{15}NO_2$: 217.1103 (M^+). Found: 217.1105.).

*4.1.3. (5S,10bR)-5-((tert-Butyldimethylsilyloxy)methyl)-1,2,5,6-tetrahydropyrrolo[2,1-a]isoquinolin-3(10bH)-one, (**3**).* Imidazole (0.39 g, 5.82 mmol) and 4-dimethylaminopyridine (0.05 g, 0.45 mmol) followed by (5*S*,10b*R*)-5-(hydroxymethyl)-1,2,5,6-tetrahydropyrrolo [2,1-*a*]isoquinolin-3(10b*H*)-one, **2**, (0.97 g, 4.47 mmol) were dissolved in anhydrous dichloromethane (20 ml) under a nitrogen atmosphere. To this solution, *tert*-butyldimethylsilylchloride (0.84 ml, 5.59 mmol) was added and the reaction was stirred at room temperature for 20 h. After 20 h, the resulting mixture was filtered to remove the solid phase and concentrated under reduced pressure. The crude product was adsorbed onto silica gel and chromatographed using silica gel as absorbent and 10% methanol in dichloromethane as eluent to isolate the target compound as an oil (1.45 g, 98%). R_f (10% MeOH/DCM) 0.38. $[\alpha]_D^{20}$ +33 [*c* 1.12 in CH_2Cl_2]. ^{1}H NMR (400 MHz, $CDCl_3$) 0.01 (3H, s), 0.02 (3H, s), 0.84 (9H, s), 1.90–2.00 (1H, m), 2.41–2.49 (1H, m), 2.50–2.68 (3H, m), 2.89 (1H, dd, *J*=3.2, 16.4 Hz), 3.02 (1H, dd, *J*=6.8, 16.4 Hz), 3.66 (1H, dd, *J*=6.0, 10.4 Hz), 3.76 (1H, dd, *J*=6.0, 10.4 Hz), 4.46–4.51 (1H, m), 4.81 (1H, t, *J*=8.0 Hz), 7.14–7.25 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) −5.5, −5.6, 18.0, 25.7 (3C), 26.9, 29.3, 31.7, 48.0, 54.9, 62.7, 124.2, 126.5, 127.0, 129.2, 132.8, 137.1, 173.7. IR (thin film, CH_2Cl_2, cm^{-1}) 1702. MS (EI) *m*/*z* 331 [M^+, 22%] (Calcd for $C_{19}H_{29}NO_2Si$: 331.1968 (M^+). Found: 331.1963).

*4.1.4. (2S,5S,10bR)-2-N,N′-Bis-(3,3-tert-butyl ester)-hydrazino-5-(tert-butyl-dimethyl-silanyloxymethyl-1-5,6,10b-tetrahydro-2H-pyrrolo[2,1-a]isoquinolin-3-one, (**4**).* *n*-Butyl lithium (1.9 ml, 4.98 mmol) was cautiously added to a stirred solution of diisopropylamine (0.71 ml, 4.98 mmol) in anhydrous tetrahydrofuran (20 ml) at 0 °C under a nitrogen atmosphere. The reaction was stirred at 0 °C for further 15 min, then cooled to −78 °C. (5*S*,10b*R*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-1,2,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(10b*H*)-one, **3**, (1.20 g, 3.61 mmol) in anhydrous tetrahydrofuran (20 ml) was added and the reaction was allowed to stir for 15 min at −78 °C. Di-*tert*-butyl azodicarboxylate (1.08 g, 4.69 mmol) in anhydrous tetrahydrofuran (15 ml) was then added dropwise via syringe at −78 °C and the reaction was then allowed to warm to room temperature overnight. The reaction was quenched by addition of saturated ammonium chloride and the product extracted into ethyl acetate (3×60 ml). The combined organic phases were then dried over anhydrous magnesium sulfate and the solvent removed on the rotary evaporator to yield the target compound as a 15:1 mixture of diastereoisomers by ^{1}H NMR spectroscopy on the crude reaction product. The crude product was adsorbed onto silica and purified by column chromatography using silica gel as absorbent and using a 2:1 mixture of light petroleum and ethyl acetate as eluent to yield a yellow solid (1.83 g, 85%). Mp 70–72 °C. R_f (2:1, petroleum ether/EtOAc) 0.6. $[\alpha]_D^{20}$ −16.3 [*c* 1.08 in CH_2Cl_2]. ^{1}H NMR (400 MHz, DMSO, 100 °C) 0.01 (3H, s), 0.02 (3H, s), 0.85 (9H, s), 1.42 (9H, s), 1.45 (9H, s), 2.33–2.34 (1H, m), 2.69–2.73 (1H, m), 2.86–2.99 (2H, m), 3.69 (1H, dd, *J*=6.8, 10.0 Hz,), 3.77 (1H, dd, *J*=4.4, 10.0 Hz), 4.16–4.18 (1H, m), 4.55 (1H, dd, *J*=6.0, 8.4 Hz), 4.75 (1H, t, *J*=7.2 Hz), 7.19–7.24 (4H, m), 8.45 (1H, s). ^{13}C NMR (100 MHz, DMSO, 100 °C) −6.1 (2C), 17.2, 25.2 (3C), 27.4 (3C), 27.5 (3C), 28.4, 28.9, 48.2, 52.0, 62.9, 78.4, 79.2, 80.1, 123.3, 125.8, 126.3, 128.2, 132.8, 136.8, 153.6, 155.1, 168.2. IR (thin film, CH_2Cl_2, cm^{-1}) 3271, 1715, 1682. MS (FAB) *m*/*z* 562 [M+H^+, 22%] (Calcd for $C_{29}H_{48}N_3O_6Si$: 562.3312 (M+H^+). Found: 562.3304).

*4.1.5. Di-tert-butyl-1-((2S,5S,10bR)-5-(hydroxymethyl)-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-2-yl)hydrazine-1,2-dicarboxylate, (**5**).* To a solution of (2*S*,5*S*,10b*R*)-2-*N*,*N*′-bis-(3,3-*tert*-butyl ester)-hydrazino-5-(*tert*-butyl-dimethyl-silanyloxymethyl-1-5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-α]isoquinolin-3-one, **4**, (0.33 g, 0.59 mmol) in tetrahydrofuran (20 ml) was added a 1 M solution of tetra-butyl ammonium fluoride in tetrahydrofuran (0.58 ml, 0.58 mmol) and the reaction was stirred for 5 min at room temperature under a nitrogen atmosphere. The resultant solution was concentrated and chromatographed through a pad of silica gel using 2:1 light petroleum/ethyl acetate as eluent to yield the target compound as a yellow solid (0.12 g, 45%). Mp 92–95 °C. R_f (2:1, petroleum ether/EtOAc) 0.45. $[\alpha]_D^{20}$ +16.8 [*c* 1.00 in CH_2Cl_2]. ^{1}H NMR

(400 MHz, DMSO, 100 °C) 1.45 (9H, s), 1.46 (9H, s), 2.31–2.35 (1H, m), 2.72–2.78 (1H, m), 2.85–3.02 (2H, m), 3.50–3.59 (2H, m), 4.15–4.18 (1H, m), 4.41 (1H, t, *J*=6.0 Hz), 4.53 (1H, dd, *J*=4.4, 8.4 Hz), 4.79 (1H, t, *J*=6.8 Hz), 7.18–7.26 (4H, m), 8.40 (1H, br s). ^{13}C NMR (100 MHz, DMSO, 100 °C) 28.4 (3C), 28.5 (3C), 29.4, 30.3, 49.9, 52.7, 60.4, 61.7, 80.3, 81.2, 124.3, 126.8, 127.3, 129.4, 133.8, 137.8, 154.6, 156.0, 164.9. IR (thin film, CH_2Cl_2, cm^{-1}) 3409, 3273, 1697. MS (EI) *m*/*z* 448 [M+H$^+$, 4%] (Calcd for $C_{23}H_{34}N_3O_6$: 448.2449 (M+H$^+$). Found: 448.2441.).

*4.1.6. 2-((2S,5S,10bR)-5-(Hydroxymethyl)-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-2-yl)hydrazine, (**6**).* Di-*tert*-butyl-1-((2*S*,5*S*,10b*R*)-5-(hydroxymethyl)-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-2-yl)hydrazinocarboxylate, **5**, (90 mg, 0.20 mmol) and trifluoroacetic acid (0.78 ml, 10.1 mmol) were allowed to stir at room temperature under a nitrogen atmosphere for 24 h. After this time the mixture was concentrated under reduced pressure, and the residue treated with an aqueous 3 M solution of HCl (15 ml) and the solution allowed to stir for further 1 h. After this time the solution was concentrated under reduced pressure and the residue dissolved in water (20 ml) and washed with ethyl acetate (3×20 ml). The aqueous phase was then evaporated to dryness using a rotary evaporator to yield a yellow oil (30 mg, 70%). R_f (10% MeOH/DCM) 0.11. $[\alpha]_D^{20}$ +14.5 [*c* 0.58 in MeOH]. ^{1}H NMR (400 MHz, D_2O) 2.38–2.46 (1H, m), 2.51–2.58 (1H, m), 2.67 (1H, dd, *J*=3.2, 16.4 Hz), 2.96 (1H, dd, *J*=6.8, 16.4 Hz), 3.51–3.59 (1H, dd, *J*=8.8, 12 Hz), 3.62–3.67 (1H, dd, *J*=5.2, 12 Hz), 3.83–3.86 (1H, dd, *J*=4.4, 8.8 Hz), 4.22–4.28 (1H, m), 4.92 (1 t, *J*=7.2 Hz), 7.10–7.37 (4H, m). ^{13}C NMR (100 MHz, D_2O) 28.5, 29.5, 49.7, 52.7, 59.2, 60.7, 124.3, 126.9, 127.6, 129.2, 132.3, 135.4, 172.0. IR (thin film, CH_2Cl_2, cm^{-1}) 3386, 1680. MS (EI) *m*/*z* 248 [M+H$^+$, 100%] (Calcd for $C_{13}H_{18}N_3O_2$: 248.1394 (M+H$^+$). Found: 248.1395).

4.1.7. (2S,5S,10bR)-2-N,N′-Bis-(3,3-tert-butyl ester)-hydrazino-3-oxo-1,2,3,5,6,10b-hexa hydro-pyrrolo[2,1-a]isoquinoline-5-carbaldehyde. o-Iodoxybenzoic acid (221 mg, 0.794 mmol) was added to a solution of (2*S*,5*S*,10b*R*)-2-*N*,*N*′-bis-(3,3-*tert*-butyl ester)-hydrazino-5-hydroxymethyl-1,5,6,10b-tetrahydro-2*H*-pyrrolo[2,1-*a*]isoquinolin-3-one, **5**, (237 mg, 0.530 mmol) in dimethyl sulfoxide (20 ml) and the reaction stirred for 24 h at room temperature. The reaction mixture was added to a solution of ethyl acetate/water and the organic product extracted with ethyl acetate (3×30 ml). The organic layer was washed with water (3×30 ml), dried over anhydrous magnesium sulfate, filtered and evaporated to a crude yellow solid. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 1:1 ethyl acetate/light petroleum as eluent to isolate the target compound as a colourless solid (144 mg, 61%). Mp 84–87 °C. R_f (2:1, petroleum ether/EtOAc) 0.6. $[\alpha]_D^{20}$ −8.80 [*c* 1.00 in CH_2Cl_2]. ^{1}H NMR (400 MHz, DMSO, 100 °C) 1.46 (18H, s), 2.31–2.38 (1H, m), 2.83–3.20 (3H, m) 4.65 (1H, dd, *J*=3.2, 9.2 Hz), 4.72 (1H, dd, *J*=5.2, 7.6 Hz), 4.89 (1H, t, *J*=7.2 Hz), 7.17–7.36 (4H, m), 8.57 (1H, br s), 9.64 (1H, s). ^{13}C NMR (100 MHz, DMSO, 100 °C) 26.9, 28.4 (3C), 28.5 (3C), 31.2, 53.3, 56.7, 60.0, 80.4, 81.3, 124.7, 127.4, 127.5, 129.1, 132.3, 137.4, 154.5, 156.0, 170.0, 200.0. IR (thin film, CH_2Cl_2, cm^{-1}) 3281, 1730, 1700. MS (ES) *m*/*z* 446 [M+H$^+$, 100%] (Calcd for $C_{23}H_{32}N_3O_6$: 446.2291 (M+H$^+$). Found: 446.2364).

*4.1.8. (2S,5S,10bR)-2-N,N′-Bis-(3,3-tert-butyl ester)-hydrazino-3-oxo-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-a]isoquinoline-5-carboxylic acid, (**7**).* A solution of (2*S*,5*S*,10b*R*)-2-*N*,*N*′-bis-(3,3-*tert*-butyl ester)-hydrazino-3-oxo-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinoline-5-carbaldehyde (862 mg, 1.94 mmol) in acetonitrile (28 ml), *tert*-butanol (80 ml) and 1-methyl-1-cyclohexene (28 ml) was stirred rapidly as it cooled to 0 °C. A solution of sodium chlorite (1.68 g, 14.9 mmol) and sodium dihydrogen phosphate (1.63 g, 13.5 mmol) in water (55 ml) was added dropwise over a 10 min period and the reaction stirred at room temperature for 17 h. The reaction mixture was added to a solution of saturated brine/ethyl acetate (1:1) (50 ml) and product extracted with ethyl acetate (3×50 ml). The organic extracts were combined and washed with a 1 M solution of sodium hydrosulfite, dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to a crude brown residue. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 2:1 light petroleum/ethyl acetate as eluent to produce a yellow solid (713 mg, 80%). The product still contained some impurities that we were unable to remove by chromatography. For this reason, the intermediate carboxylic acid was reacted on in its crude state.

*4.1.9. (2S,5S,10bR,3′S)-2-N,N′-Bis-(3,3-tert-butyl ester)-hydrazino-2-[(3-oxo-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-a]isoquinoline-5-carbonyl)-amino]-3-phenyl-propionic acid methyl ester, (**8**).* (2*S*,5*S*,10b*R*)-2-*N*,*N*′-Bis-(3,3-*tert*-butyl ester)-hydrazino-3-oxo-1,2,3,5,6,10b-hexa hydro-pyrrolo[2,1-*a*]isoquinoline-5-carboxylic acid, **7**, (713 mg, 1.55 mmol) was dissolved in anhydrous dichloromethane (30 ml) and cooled to −15 °C under nitrogen. 1-Hydroxyazabenzotriazole (231 mg, 1.70 mmol) and 1-ethyl-3-[(dimethylamino) propyl]carbodiimide hydrochloride (326 mg, 1.70 mmol) were added and reaction stirred for 20 min at −15 °C. *N*-Methyl morpholine (172 mg, 0.19 ml, 1.70 mmol) and (*S*)-phenylalanine methyl ester hydrochloride (366 mg, 1.70 mmol) were added and the reaction stirred for a further 3 h at −15 °C. An ice-cold solution of 1 M HCl (6 ml) was added and reaction extracted with dichloromethane (3×30 ml). The organic phase was washed with saturated sodium bicarbonate, dried over anhydrous magnesium sulfate, filtered and the solvent removed by rotary evaporation to yield a crude orange residue. The crude product was adsorbed onto silica and chromatographed using silica gel as absorbent and 1:1 ethyl acetate/light petroleum as eluent to isolate the target compound as a colourless solid (549 mg, 57%). Mp 89–92 °C. R_f (EtOAc) 0.75. $[\alpha]_D^{20}$ −28.0 [*c* 1.10 in CH_2Cl_2]. ^{1}H NMR (400 MHz, DMSO, 100 °C) 1.48 (18H, s), 2.34 (1H, ddd, *J*=6.0, 10.0, 13.6 Hz), 2.76–2.82 (1H, m), 2.91–3.05 (2H, m), 3.07–3.23 (2H, m), 3.60 (3H, s), 4.48 (1H, dd, *J*=4.4, 9.6 Hz), 4.59–4.64 (1H, m), 4.67–4.72 (1H, m), 4.76 (1H, dd, *J*=3.6, 7.2 Hz), 7.05–7.26 (9H, m), 7.75 (1H, d, *J*=8.0 Hz), 8.62 (1H, br s). ^{13}C NMR (100 MHz, DMSO, 100 °C) 28.4 (3C), 28.6 (3C), 29.8, 30.5, 37.4, 50.8, 52.1, 52.9, 54.1, 60.9, 80.4, 81.5, 124.7, 126.8, 126.9, 127.2, 128.5 (2C), 129.0, 129.3 (2C), 132.7, 137.4, 137.6, 154.8, 155.9, 169.6, 169.8, 171.9. IR (thin film, CH_2Cl_2, cm^{-1}) 3342, 1738, 1699. MS (ES) *m*/*z* 623 [M+H$^+$, 100%] (Calcd for $C_{33}H_{43}N_4O_8$: 623.3081 (M+H$^+$). Found 623.3077).

4.1.10. 1-Benzyl 2-tert-butyl hydrazine-1,2-dicarboxylate[10,11]. A solution of Boc-hydrazine (3.20 g, 24.21 mmol) in dichloromethane (100 ml) was cooled to −78 °C under a nitrogen atmosphere. Benzyl chloroformate (4.09 ml, 29.06 mmol) was cautiously added with stirring, followed by sodium carbonate (2.50 g, 24.21 mmol). The reaction was then stirred for 24 h. After this time the reaction mixture was evaporated to dryness and redissolved in hot ethyl acetate (100 ml, refluxed for 1 h). The hot solution was then filtered and the solvent removed by evaporation under reduced pressure to yield a white solid that was used without further purification (6.31 g, 98%). Mp 252–253 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 1.53 (9H, s), 5.17 (2H, s), 6.33 (1H, s), 6.53 (1H, s), 7.31–7.37 (5H, m). ^{13}C NMR (400 MHz, $CDCl_3$) 28.1 (3C), 67.8, 81.9, 127.0, 128.3, 128.4 (2C), 128.6, 135.6, 155.7, 156.7. IR (thin film, CH_2Cl_2, cm^{-1}) 3302, 1715. MS (EI) *m*/*z* 266 [M+H$^+$, 100%] (Calcd for $C_{13}H_{19}N_2O_4$: 267.1339 (M+H$^+$). Found: 267.13418).

*4.1.11. (E)-1-Benzyl 2-tert-butyl diazene-1,2-dicarboxylate, (**9**)*[10,11]. 1-Benzyl 2-*tert*-butyl hydrazine-1,2-dicarboxylate (3.29 g, 12.48 mmol) was added in one portion to a solution of *N*-bromosuccinimide (1.34 g,

11.32 mmol) and pyridine (0.91 ml, 11.32 mmol) in dichloromethane (150 ml) in a separating funnel. After 30 min, during which time the funnel was occasionally shaken to ensure dissolution of all the hydrazine, the reaction mixture was washed with water (3×75 ml), and the organic phase was then dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to yield an orange oil (0.66 g, 20%). R_f (3:1, petroleum ether/EtOAc) 0.83. ^{1}H NMR (400 MHz, $CDCl_3$) 1.53 (9H, s), 5.36 (2H, s), 7.32–7.38 (5H, m). ^{13}C NMR (400 MHz, $CDCl_3$) 27.3 (3C), 70.7, 87.2, 128.6, 128.8 (2C), 128.9, 129.2, 133.7, 158.9, 160.4. IR (thin film, CH_2Cl_2, cm^{-1}) 1774.

*4.1.12. 1-Benzyl 2-tert-butyl 1-((2S,5S,10bR)-5-((tert-butyldimethylsilyloxy)methyl)-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-2-yl)hydrazine-1,2-dicarboxylate, (**10**).* *n*-Butyl lithium (0.85 ml, 2.14 mmol) was cautiously added to a stirring solution of diisopropylamine (0.30 ml, 2.14 mmol) in anhydrous tetrahydrofuran (20 ml) at 0 °C and under a nitrogen atmosphere. The reaction was stirred at 0 °C for a further 15 min then cooled to −78 °C. (5*S*,10b*R*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-1,2,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolin-3(10b*H*)-one, **3**, (0.52 g, 1.55 mmol) in anhydrous tetrahydrofuran (20 ml) was added and the reaction was allowed to stir for 15 min at −78 °C. (*E*)-1-benzyl 2-*tert*-butyl diazene-1,2-dicarboxylate, **9**, (0.41 g, 1.55 mmol) in anhydrous tetrahydrofuran (15 ml) was then added dropwise at −78 °C and the reaction allowed to warm to room temperature overnight. The reaction was quenched by addition of saturated ammonium chloride and the product extracted into ethyl acetate (3×50 ml). The combined organic phases were then dried over anhydrous magnesium sulfate and the solvent removed by rotary evaporation. The crude product was adsorbed onto silica and purified by column chromatography using silica gel as absorbent and using a 2:1 mixture of light petroleum and ethyl acetate as eluent to yield a yellow solid (0.34 g, 41%). Mp 68–70 °C. R_f (2:1, petroleum ether/EtOAc) 0.55. $[\alpha]_D^{20}$ +9.5 [*c* 0.38 in MeOH]. ^{1}H NMR (400 MHz, DMSO, 100 °C) 0.03 (6H, s), 0.84 (9H, s), 1.43 (9H, s), 2.33–2.45 (1H, m), 2.70–2.85 (1H, m), 2.85–3.0 (2H, m), 3.66–3.70 (1H, m), 3.78 (1H, dq, *J*=4.8, 10.4 Hz), 4.17–4.20 (1H, m), 4.60–4.70 (1H, m), 4.78 (1H, t, *J*=6.8 Hz), 5.09–5.16 (2H, m), 7.18–7.23 (4H, m), 7.34–7.40 (5H), 8.80 (1H, br s). ^{13}C NMR (100 MHz, DMSO, 100 °C) −5.1 (2C), 18.2, 26.1 (3C), 28.5 (3C), 29.4, 29.5, 49.2, 53.0, 60.5, 63.8, 67.7, 80.5, 124.2, 126.8, 127.3, 127.9 (2C), 128.2, 128.6, 129.2 (2C), 133.7, 136.7 (2C), 155.6 (2C), 168.8. IR (thin film, CH_2Cl_2, cm^{-1}) 2921, 1756, 1715. MS (FAB) *m*/*z* 595 [M+H$^+$, 21%] (Calcd for $C_{32}H_{46}N_3O_6Si$: 596.31559 (M+H$^+$). Found: 596.31533).

*4.1.13. tert-Butyl-2-((2S,5S,10bR)-5-((tert-butyldimethylsilyloxy)methyl)-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-2-yl)hydrazinecarboxylate, (**11**).* 1-Benzyl 2-*tert*-butyl 1-((2*S*,5*S*,10b*R*)-5-((*tert*-butyldimethylsilyloxy)methyl)-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-2-yl)hydrazine-1,2-dicarboxylate, **10** (0.35 g, 0.58 mmol) was dissolved in methanol (10 ml) and added to a suspension of palladium on carbon (0.18 g, loading 10% Pd) under a nitrogen atmosphere. Ammonium formate (3.50 g, 55 mmol) in methanol (10 ml) was added dropwise and allowed to stir at room temperature for 2 h. After this time, the solution was filtered through Celite and the resulting solution was extracted with ethyl acetate (3×30 ml) and the combined organic phases were dried over anhydrous sodium sulfate and the solvent removed by rotary evaporation to yield the crude product, which was purified by column chromatography using silica gel as adsorbent and ethyl acetate as eluent to produce a yellow solid (0.23 g, 88%). Mp 118–120 °C. R_f (EtOAc) 0.47. $[\alpha]_D^{20}$ +4.3 [*c* 0.28 in MeOH]. ^{1}H NMR (400 MHz, $CDCl_3$) −0.045 (6H, s), 0.81 (9H, s), 1.44 (9H, s), 2.35–2.36 (1H, m), 2.49–2.52 (1H, m) 2.96 (2H, dq, *J*=5.4, 16.4 Hz), 3.69 (2H, dd, *J*=5.4, 10 Hz), 3.78 (1H, dd, *J*=5.4, 10 Hz), 4.28–4.30 (1H, m), 4.35 (1H, br s), 4.79 (1H, t, *J*=8.0), 6.40 (1H, br s), 7.12–7.24 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) −5.5, −5.44, 18.1, 25.8 (3C), 28.4 (3C), 29.3, 30.1, 49.1, 53.1, 61.0, 63.1, 80.7, 123.7, 126.5, 127.3, 129.1, 133.6, 136.9, 156.7, 171.9. IR (thin film, CH_2Cl_2, cm^{-1}) 3286, 1688. MS (EI) *m*/*z* 462 [M+H$^+$, 100%] (Calcd for $C_{24}H_{40}N_3O_4Si$: 462.2783 (M+H$^+$). Found: 462.2780).

4.1.14. tert-Butyl-1-((2S,5S,10bR)-5-(hydroxymethyl)-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-2-yl)hydrazinocarboxylate. To a solution of *tert*-butyl 2-((2*S*,5*S*,10b*R*)-5-((*tert*-butyldimethylsilyloxy)methyl)-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-2-yl)hydrazinocarboxylate, **11**, (0.15 g, 0.35 mmol) in tetrahydrofuran (20 ml) was added a 1 M solution of tetra-butyl ammonium fluoride in tetrahydrofuran (0.35 ml, 0.35 mmol) and the reaction stirred for 5 min at room temperature under a nitrogen atmosphere. The resultant solution was concentrated under reduced pressure and chromatographed through a pad of silica using ethyl acetate as eluent to yield the target compound as a yellow oil (59 mg, 48%). R_f (EtOAc) 0.2. $[\alpha]_D^{20}$ +18.9 [*c* 0.17 in MeOH]. ^{1}H NMR (400 MHz, $CDCl_3$) 1.45 (9H, s), 2.24–2.27 (1H, m), 2.69–2.74 (2H, m), 2.99–3.05 (1H, m), 3.40–3.43 (1H, m), 3.61–3.81 (4H, m), 4.37–4.38 (1H, m), 4.95 (1H, t, *J*=7.2 Hz), 7.11–7.23 (4H, m). ^{13}C NMR (100 MHz, $CDCl_3$) 28.4 (3C), 29.5, 50.2, 52.7, 61.5, 62.4, 73.4, 80.8, 124.2, 126.8, 127.3, 129.0, 132.6, 136.4, 156.7, 173.0. IR (thin film, CH_2Cl_2, cm^{-1}) 3400, 3284, 1692. MS (EI) *m*/*z* 348 [M+H$^+$, 100%] (Calcd for $C_{18}H_{26}N_3O_4$: 348.1918 (M+H$^+$). Found: 348.1920).

*4.1.15. 2-((2S,5S,10bR)-5-(hydroxymethyl)-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolin-2-yl)hydrazinium, (**6**).* *tert*-Butyl-2-((2*S*,5*S*,10b*R*)-5-(hydroxymethyl)-3-oxo-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-2-yl)hydrazinecarboxylate (0.11 g, 0.33 mmol, from Section 4.1.14) and trifluoroacetic acid (0.51 ml, 6.56 mmol) were allowed to stir at room temperature under a nitrogen atmosphere for 24 h. After 24 h, the mixture was concentrated under reduced pressure, and the residue treated with aqueous 3 M solution of HCl (15 ml) and the solution allowed to stir for further 1 h. After 1 h, the solution was concentrated under reduced pressure and the residue dissolved in water (20 ml) and washed with ethyl acetate (3×20 ml). The aqueous phase was then evaporated to dryness using a rotary evaporator to yield a yellow oil (51 mg, 55%). Spectral analysis was identical to that reported above (See Section 4.1.6).

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Supplementary data

Supplementary data associated with this article can be found in online version at 10.1016/j.tet.2010.10.012.

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