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Stereoselective synthesis of the indolizinoindole ring system

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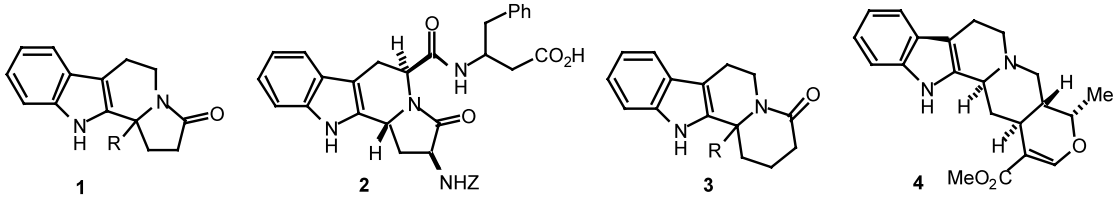
Abstract—We report a novel, facile and stereoselective approach to the indolizino[8,7-*b*]indole ring system from a readily available, non-racemic chiral template.

Indolizino[8,7-*b*]indoles of general structure **1** are of interest to the pharmaceutical industry having been used as intermediates in the preparation of diuretic compounds,[1] and are also known to exhibit analgesic and anti-inflammatory activity in their own right.[2] Other, more functionalised, templates such as **2** have been shown to act as β-turn mimics and display high binding affinity and selectivity for CCK_1 receptors.[3] The lactam homologue **3** is perhaps of greater significance in natural product chemistry, sharing the same heterocyclic skeleton with a plethora of highly bioactive indole alkaloids, including tacamine,[4] geissoschizine,[5] and ajmalicine **4**.[6]



Over recent years, we have reported a new approach to a range of non-racemic heterocycles involving stereoselective cyclisation onto *N*-acyliminium intermediates as the key ring-forming step. Based on our novel and stereoselective approach to both the isoindoloisoquinoline and pyrroloisoquinoline ring systems,[7] we recognised that a suitably substituted bicyclic lactam could act as a precursor for a stereoselective approach to the indolizino[8,7-*b*]indole ring system.

Our approach to the synthesis of the required bicyclic lactam substrate **5** followed the general method previously used in our group.[7] The β-amino alcohol derivative of (*S*)-tryptophan was reacted under Dean–Stark conditions with the appropriate keto-acid for 48 h (Scheme 1). Under these reaction conditions we were able to isolate the expected bicyclic lactam **5** in only 3% yield. The major product of the reaction, isolated in 55% yield, was found to be the target indolizino[8,7-*b*]indole derivative **6**.[8]

Examination of the crude reaction mixture by 250 MHz ^{1}H NMR spectroscopy revealed the formation of **6** as a single diastereoisomer.

The relative stereochemistry of product **6** was determined by single crystal X-ray analysis (Fig. 1), and was found to be as expected based on our experience of cyclisation reactions involving similar *N*-acyliminium precursors. Effectively, retention of configuration at the methyl-bearing chiral centre is observed if one considers bicyclic lactam **5** to be an intermediate.[7b,c]

Interestingly, compound **6** was observed to form two crystallographically unique hydrogen bonds: one intramolecular O(2)–H(2A)···O(1) {O(1)···O(2) = 2.597(2) Å, O(2)–H(2A)···O(1) = 154°} and one intermolecular N(2)–H(2)···O(2A) {N(2)···O(2A) = 2.788(3) Å, N(2)–H(2)···O(2A) = 168°} forming chains along the crystallographic *c*-direction.[9]

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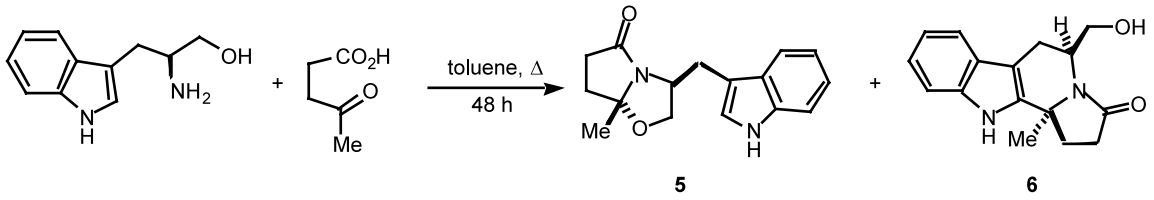

Scheme 1.

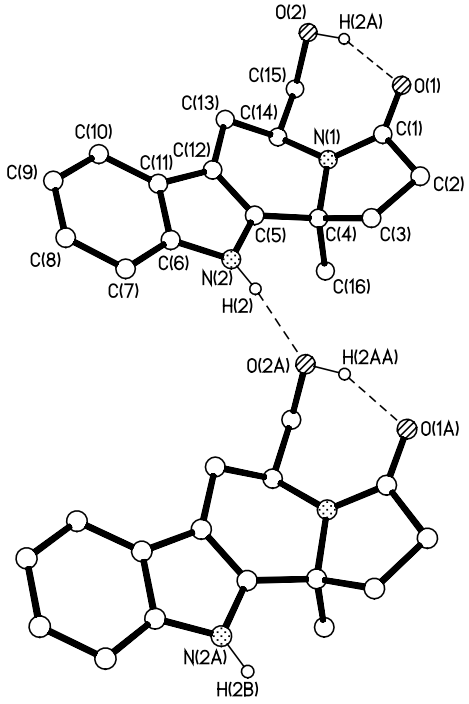

Figure 1. Crystal structure of **6**, omitting most H atoms and the solvent molecule of crystallisation. The intra- and intermolecular H-bonds are highlighted and the numbering scheme is defined.

Of course, one could envisage an alternative mechanism to explain the formation of **6** that avoids the intermediacy of bicyclic lactam **5**: a stereoselective Pictet–Spengler reaction in which condensation of the β-amino alcohol and keto-acid substrate results in formation of a tetrahydro-β-carboline derivative which then undergoes lactam formation to yield **6** in the final step.[10] To date, no intermediates have been observed by us that would support this hypothesis with our substrates.

An alternative approach to the indolizino[8,7-*b*]indole ring system was also investigated through formation and subsequent borohydride reduction of the imide intermediate **7**, accessed in 54% yield from the required β-amino alcohol and succinic anhydride.[7] In this approach, summarised in Scheme 2, the intermediate ethoxy-lactam derivative **8** was not isolated since, under the reaction conditions, direct cyclisation via an *N*-acyliminium intermediate was observed to yield the target heterocycle **9** in 45% yield and as a 9:1 mixture of diastereoisomers. The major diastereoisomer was isolated by crystallisation and the relative stereochemistry of this product was determined to be as shown in Scheme 2 by NOE studies.[11] Again, the relative stereochemistry observed on cyclisation of the attacking aromatic nucleus was as expected based on previous results from our group.[7c]

As noted above, access to the six-membered lactam homologue through application of this methodology would be highly attractive as it would allow access to a wide range of desirable indole targets. With this in mind we successfully prepared the bicyclic lactam substrate **10** as a 5:1 mixture of diastereoisomers in 58% overall yield. The relative stereochemistry of the major isomer, represented in Scheme 3, was determined by NOE studies.[12] Based on our previous work in a related area,[13] these substrate diastereoisomers were not separated, but were treated with $TiCl_4$ to promote the stereoselective cyclisation reaction (Scheme 3).

We were pleased to isolate the cyclised product, **11**, in 54% yield and ^{1}H NMR analysis of the crude reaction mixture revealed the formation of this product as a 5:2 mixture of diastereoisomers. A comparative NOE study was undertaken on the isolated diastereoisomers to confirm that the relative stereochemistry of the major diastereoisomer is as shown in Scheme 3.[14]

To demonstrate the potential synthetic utility of this new methodology we followed a method previously used by us to remove the hydroxymethyl auxiliary group (Scheme 4).[7b,c] Oxidation of **6** to the corresponding aldehyde was achieved in 90% yield using IBX (*o*-iodoxybenzoic acid) in DMSO;[15] subsequent decarbonylation gave a mixture of enamide **12** and target lactam **13**. This product mixture was subjected to catalytic hydrogenation to convert the unwanted enamide through to lactam **13**. Finally, lactam reduction generated the tertiary amine derivative **14** in 27% overall yield from the aldehyde.

In summary, we report a facile and highly stereoselective approach to a range of indole-containing heterocycles from readily available non-racemic substrates. Current work is focused on extending this methodology to specific indole alkaloid targets, and our progress will be reported in due course.

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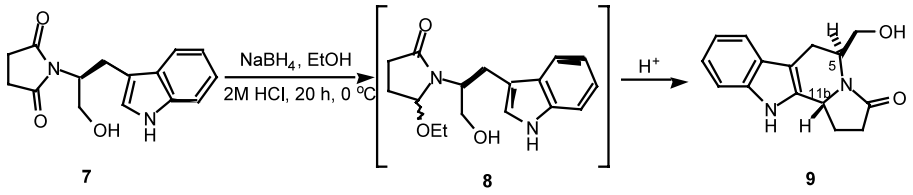
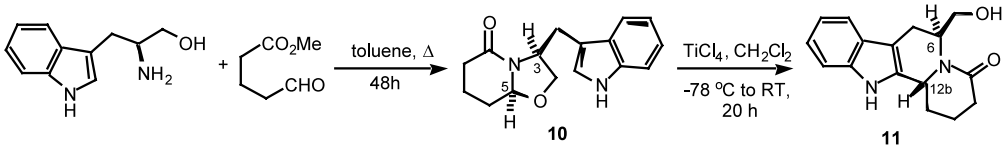
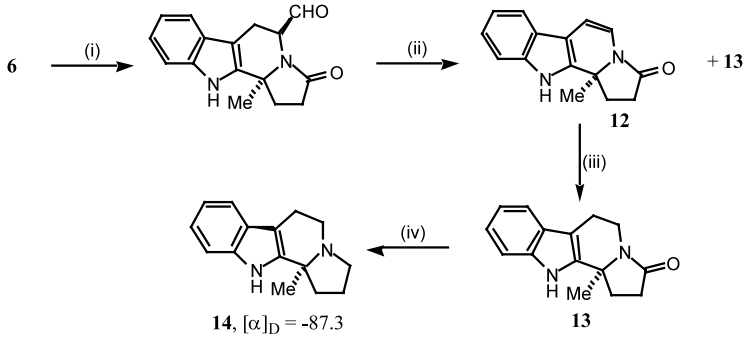


Scheme 2.



Scheme 3.



Scheme 4. *Reagents and conditions*: (i) IBX, DMSO, 24 h; (ii) $Rh(PPh_3)_2(CO)Cl$, xylene, Δ, 5 days; (iii) H_2/10% Pd–C, EtOH, 48 h; (iv) Red-Al, toluene, 20 h, rt.

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8. Compound **5** was observed to begin to convert to **6** on standing in an NMR tube in $CDCl_3$ solvent.
9. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC 198533).
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11. The absence of an NOE between the protons situated at positions 5 and 11b of product **9** is consistent with the proposed structure. As we were unable to isolate the minor diastereoisomer we were unable to carry out a comparative NOE study. This result is in agreement with related work from our group (Ref. 7b).
12. We were able to perform a set of comparative NOE studies on the separable diastereoisomers of product **10**. In the case of the major diastereoisomer, **10**, an NOE was observed between protons at positions 3 and 5. In the case of the minor diastereoisomer, no NOE was observed. Both results are in accord with previous results from our group detailing the preparation of 5,6-fused bicyclic lactams (Ref. 11).
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14. We were able to perform a set of comparative NOE studies on the separable diastereoisomers of product **11**. In the case of the minor diastereoisomer an NOE was observed between protons at positions 6 and 12b. In the case of the major diastereoisomer, **11**, no NOE was observed.
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