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Highly stereoselective synthesis of the indolo[2,3-*a*]quinolizine ring system and application to indole natural product synthesis

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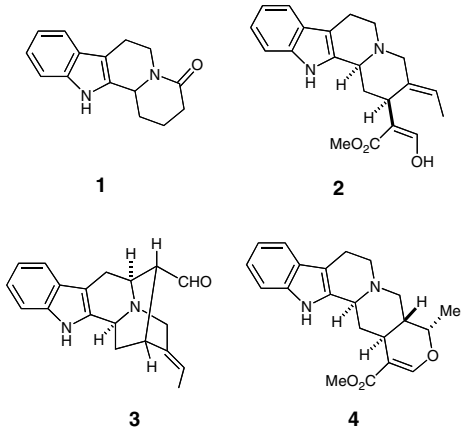
Abstract—We report a novel, facile and highly stereoselective approach to the indolo[2,3-*a*]quinolizine ring system from a readily available, non-racemic chiral template. We demonstrate the potential for application of this methodology to natural product synthesis through conversion of the template to a simple indole alkaloid with high enantiomeric purity.

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



We have recently developed a new and general approach for the stereoselective synthesis of a range of non-racemic heterocycles that involves the cyclisation of pendent aromatic substituents onto *N*-acyliminium intermediates as the key ring-forming step.[8] Based on our novel approach to the indolizino[8,7-*b*]indole ring system,[8a] we recognised that a suitably substituted bicyclic lactam could act as a precursor in a stereoselective approach to the indolo[2,3-*a*]quinolizine ring system.

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

The relative stereochemistry of the major diastereoisomer **5a** was determined by single crystal X-ray analysis (Fig. 1).[9] This indole-containing bicyclic lactam is a novel example of the fused 5,6-ring system favoured by Amat et al.,[10] and the relative stereochemistry observed for the major isomer **5a** is consistent with results obtained both by these researchers and in our own previous work in other areas.[8b]

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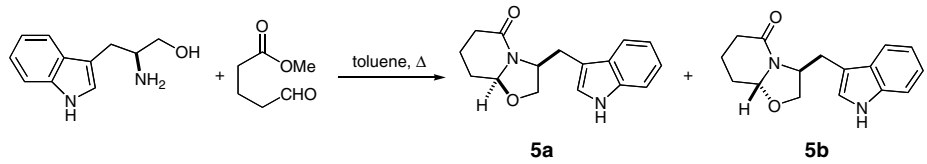


Scheme 1.

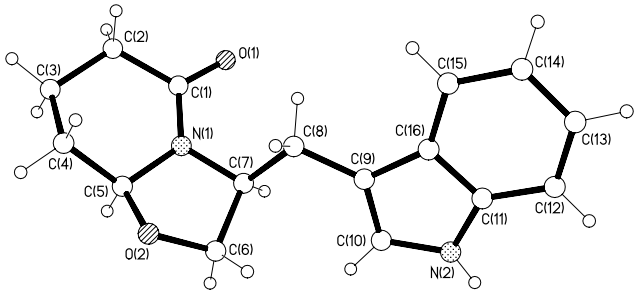
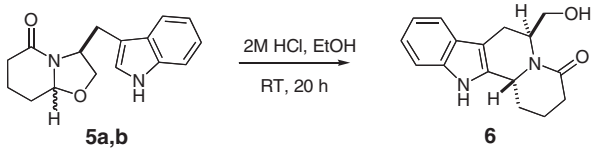


Figure 1. Crystal structure of **5a**.

In a previous communication, we noted briefly that treatment of the initial mixture of diastereoisomers of substrate **5** with $TiCl_4$ gave the desired indolo[2,3-*a*]quinolizine target **6** in 54% yield, but with only a poor level of product diastereoselectivity (5:2).[8a] We have now discovered that simply treating the mixture of bicyclic lactam substrate diastereoisomers, **5a** and **5b**, with 2 M HCl in ethanol at room temperature for 20 h gives an excellent yield of 95% for the cyclisation reaction, and leads to the formation of the desired indolo[2,3-*a*]quinolizine product as a *single* diastereoisomer (Scheme 2).

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

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



Scheme 2.

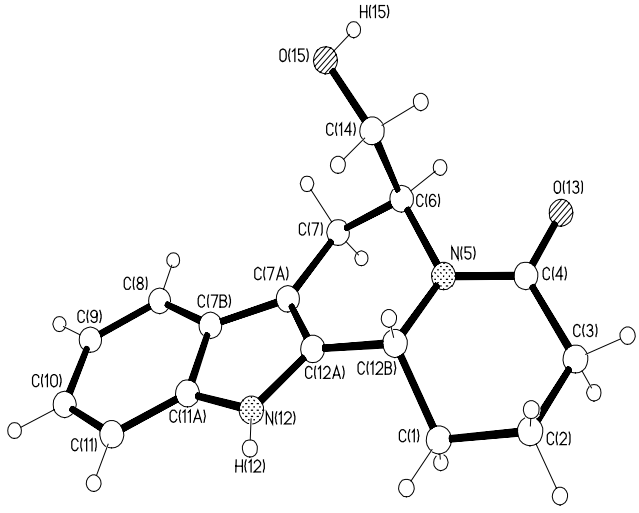
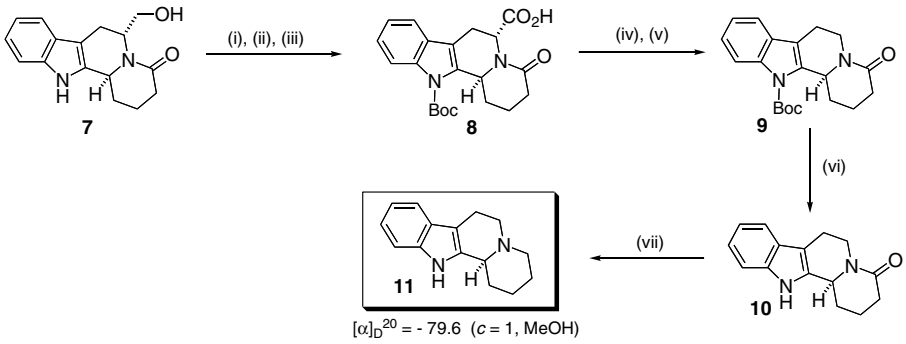


Figure 2. Crystal structure of **6**.

an X-ray crystal structure of **7** was also obtained. Our synthetic route to the natural product **11** from **7** is highlighted in Scheme 3.

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

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



Scheme 3. Reagents and conditions: (i) IBX, DMSO, rt, 24 h (65%); (ii) Et_3N, $(Boc)_2O$, DMAP, THF, rt, 4 h (54%); (iii) $NaClO_2$, NaH_2PO_4, 1-methyl-1-cyclohexane, CH_3CN, *t*-BuOH, H_2O, 0 °C to rt, 18 h (70%); (iv) $(PhSe)_2$, PBu_3, CH_2Cl_2, 0 °C to rt, 18 h (66%); (v) *n*-Bu_3SnH, AIBN, toluene, 80 °C, 2 h (98%); (vi) TBAF, THF, Δ, 3 h then rt, 9 h (63%); (vii) $LiAlH_4$, THF, Δ, 9 h (96%).

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12. (a) Compound **10** gave $[\alpha]_D^{20}$ −286 (*c* 1, $CHCl_3$). The same compound is quoted as having $[\alpha]_D^{20}$ −232 (*c* 1.02, $CHCl_3$) at an ee of 96%[13]; (b) Compound **11**: $[\alpha]_D^{20}$ −79.6 (*c* 1, MeOH); lit.[13]: $[\alpha]_D^{20}$ −84 (*c* 1, MeOH).
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