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An Asymmetric Synthesis of Both Enantiomers of the Indole Alkaloid Deplancheine

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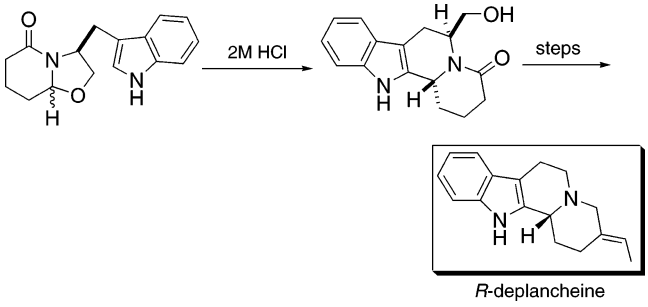


We report a novel, facile and asymmetric approach to both enantiomers of the indole alkaloid deplancheine from a readily available, nonracemic chiral template. The natural product and its antipode are isolated with >95% ee.

The indolo[2,3-*a*]quinolizine ring system is of great interest and significance because this heterocyclic template is found within a plethora of indole alkaloids (see Figure 1), including deplancheine **1**,[1] geissoschizine **2**,[2] and vellosimine **3**.[3] Recent approaches to the construction of this heterocyclic target system by other groups have included the diastereoselective vinylogous Mannich reaction,[4] the 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 wide range of nonracemic heterocycles. Our protocol involves the cyclization of pendent aromatic substituents onto *N*-acyliminium intermediates as a key ring-forming step.[8] On the basis of our novel approach to the indolizino[8,7-*b*]indole ring system,[8a] we recognized that a suitably substituted bicyclic lactam could act as a precursor in a stereoselective approach to the indolo[2,3-*a*]quinolizine ring system, and if successful this methodology might allow us novel and stereoselective access to a wide range of indole alkaloid targets and their synthetic derivatives.

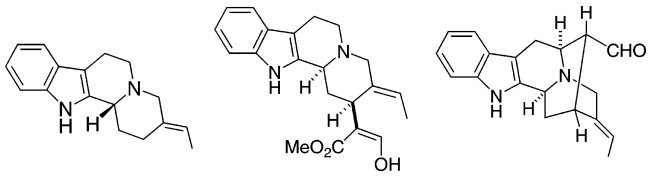
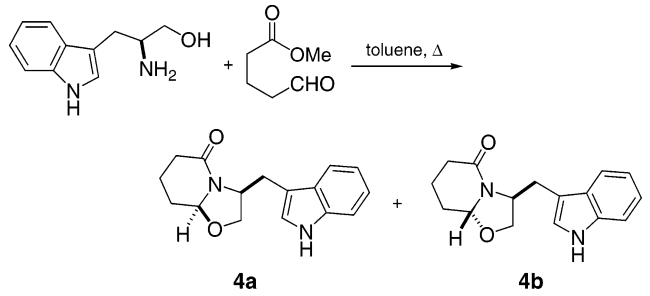
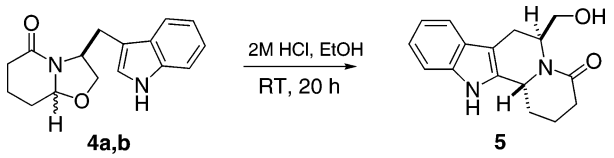


FIGURE 1. Some indole alkaloids containing the indolo[2,3-*a*]quinolizine template.

SCHEME 1. Preparation of Indolic Bicyclic Lactams



SCHEME 2. Stereoselective Cyclization of the Indole Nucleus



Deplancheine, **1**, an alkaloid isolated from the New Caledonian plant *Alstonia deplanchei*,[1] has been cited in several racemic approaches demonstrating the construction of the indolo[2,3-*a*]quinolizine ring system.[1b,c,d] As a consequence of the work of Meyers in 1986 that described an asymmetric approach to deplancheine, the absolute configuration of the natural product was determined to be *R*.[1a]

In this paper we describe a new and asymmetric synthesis of both enantiomers of deplancheine, which delivers the natural product and its enantiomer with >95% ee. Our route relies on a highly stereoselective

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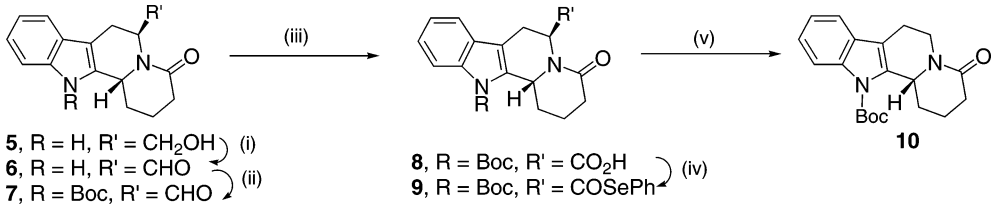
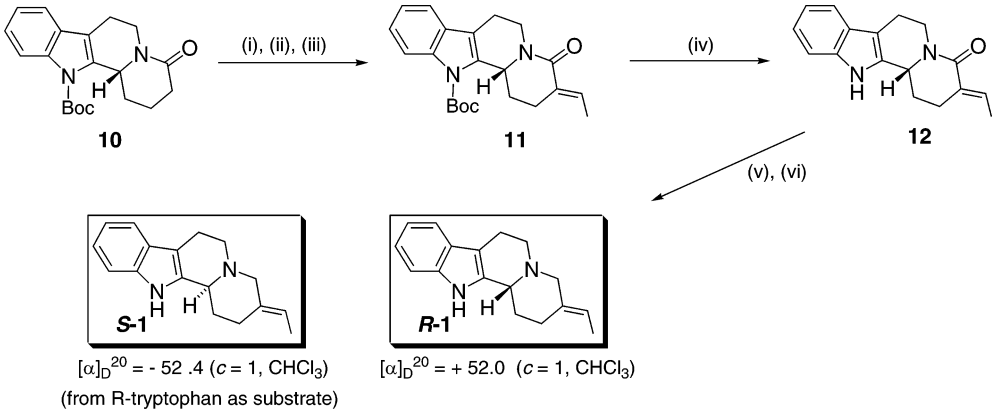
SCHEME 3. Template Manipulation to Access the Key Ring System[a]



[a] Reagents and conditions: (i) IBX, DMSO, rt, 24 h (70%); (ii) Et_3N, $(Boc)_2O$, DMAP, THF, rt, 4 h (98%); (iii) $NaClO_2$, NaH_2PO_4, 1-methyl-1-cyclohexene, CH_3CN, *t*-BuOH, H_2O, 0 °C to rt, 18 h (83%); (iv) $(PhSe)_2$, PBu_3, CH_2Cl_2, 0 °C to rt, 18 h (83%); (v) *n*-Bu_3SnH, AIBN, toluene, 80 °C, 2 h (73%).

SCHEME 4. Asymmetric Synthesis of Deplancheine[a]



[a] Reagents and conditions: (i) LDA, CH_3CHO, THF, −78 °C to rt, 24 h; (ii) Et_3N, MsCl, DCM, −40 °C to rt, 3 h; (iii) DBN, THF, rt, 16 h (65% for 3 steps); (iv) TBAF, THF, Δ, 9 h (63%); (v) Me_3OBF_4, 2,6-di-*t*-Bu-Py, DCM, rt, 21 h; (vi) $NaBH_4$, MeOH, 0 °C, 0.5 h (77% for 2 steps).

cyclization reaction to access the indolo[2,3-*a*]quinolizine template from a readily available nonracemic chiral template.

Our approach to the synthesis of the required bicyclic lactam substrate **4** 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 functionalized substrate[9] 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, **4a** and **4b**.

The relative stereochemistry of the major diastereoisomer **4a** has been determined by single-crystal X-ray analysis.[10] This indole-containing bicyclic lactam is a novel example of the fused 5,6-ring system favored by Amat and Bosch,[11] and the relative stereochemistry observed for the major isomer **4a** is consistent with results obtained both by these researchers and our own previous work in other areas.[8b]

Treatment of the mixture of bicyclic lactam diastereoisomers, **4a** and **4b**, with 2 M HCl in ethanol at room temperature for 20 h gave an excellent yield of 95% for the cyclization reaction and led 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 **5** has been determined by single-crystal X-ray analysis.[10]

The stereochemical outcome of this reaction was as expected on the basis of our previous work with related aromatic systems and follows the previously proposed model used to rationalize product stereochemistry.[8c−e]

To highlight the potential synthetic utility of our new methodology in the target synthesis of complex indole alkaloids and their synthetic analogues, we then undertook the synthesis of the indole alkaloid (*R*)-(+)-deplancheine, **1**.

Our previously applied method to remove the hydroxymethyl "auxiliary" group from templates such as **5** has involved a rhodium-induced decarbonylation sequence.[8a] As a result of the rather long reaction times generally needed for our substrates in this protocol we have now applied a more facile approach that relies upon a decarboxylation strategy. Compound **5** was oxidized to the carboxylic acid derivative **8** through the corresponding aldehyde; from **8** we then generated the corresponding acyl selenide derivative **9** and subsequently performed a tin-mediated deacylation to yield the desired indolo[2,3-*a*]quinolizine template **10** (Scheme 3).

Construction of the ethylidene moiety was achieved through a three-step procedure involving generation of the lithium enolate from **10** and subsequent aldol reaction with acetaldehyde, activation of the hydroxyl group by mesylation, and finally DBN-induced elimination to

(9) Methyl 5-oxopentanoate: Huckstep, M.; Taylor, R. J. K.; Caton, H. P. L. *Synthesis* **1982**, 881.

(10) Crystallographic data (excluding structure factors) for structures **4a** (R = 0.072) and **5** (R = 0.031) in this paper have been deposited with the Cambridge Crystallographic Data Centre (CCDC 227217−227218).

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give the initial target **11** (Scheme 4). We found that whereas a THF/DCM solvent mixture in the elimination step gave only a 4.7:1 ratio in favor of the desired *E*-isomer **11**, if the elimination procedure was carried out in THF alone as solvent the *E*-regioisomer of the ethylidene product **11** was obtained exclusively.[12] TBAF-induced deprotection of the indole nitrogen atom liberated the lactam intermediate **12**.

The synthesis of (*R*)-deplancheine was completed through removal of the lactam carbonyl group as described in Scheme 4 through application of a route described by Martin and co-workers.[2] The desired target, (*R*)-(+)-deplancheine, **1**, was obtained with an ee of >95% and the same absolute configuration as the natural product by comparison of optical rotation data.[1a] An X-ray crystal structure of the product *R*-**1** was obtained and is presented in Supporting Information.[13]

To demonstrate the potential synthetic utility of our methodology we have also undertaken an asymmetric synthesis of the enantiomer of the natural product. Our route mirrors that described in Schemes 1−4 but uses the *R*-enantiomer of tryptophan as the starting material. The desired target, (*S*)-(−)-deplancheine (Scheme 4), was isolated with an ee of >95% by comparison of optical rotation data.[1a]

In summary, we report a facile and highly stereoselective approach to the important indolo[2,3-*a*]quinolizine template from readily available nonracemic substrates and have demonstrated the structural modification of the template to deliver a simple indole alkaloid with high enantiomeric purity and in both enantiomeric series. 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.

Acknowledgment. We acknowledge Loughborough University and OSI Pharmaceuticals for a joint studentship to C.I.T. We thank Professor Stephen F. Martin for helpful discussions, and Professor Larry Overman for the supply of a racemic sample of deplancheine and copies of corresponding NMR spectra.

Supporting Information Available: Experimental procedures for the synthesis of compounds **1** and **4**−**12**; ^{1}H NMR and ^{13}C NMR spectra for compounds **1**, **4**, **5**, **8**, and **10**−**12**; crystallographic data for compound *R*-**1** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) The *E*-regioisomer was found to display a chemical shift of δ 7.0−7.05 ppm for the olefinic proton, whereas the *Z*-regioisomer displayed the olefinic proton in a more upfield position of δ 5.92−5.97 ppm. This pattern is in line with reports of NMR data of geometrical isomers of similar indolo[2,3-*a*]quinolizidines.[14] Compound **11** was ultimately converted to target **1**, for which structural confirmation was obtained by X-ray crystallography, thus confirming the *E* stereochemistry of both the final product and its precursors.

(13) Crystal data for **1**·1/2H_2O: $C_{17}H_{21}N_2O_{0.5}$, M = 261.36, monoclinic, $P2_1$, a = 12.7620(16), b = 6.8946(9), c = 17.222(2) Å, β = 98.533(2)°, V = 1498.5(3) Å^3, Z = 4, D_c = 1.158 g cm^{-3}, μ(Mo K_a) = 0.070 mm^{-1}, T = 150(2) K, yellow blocks; 8486 reflections measured on a Bruker SMART 1000 CCD diffractometer, of which 4933 were independent, data corrected for absorption on the basis of symmetry equivalent and repeated data (min and max transmission factors 0.960, 0.987) and Lp effects, R_{int} = 0.032, structure solved by direct methods, F^2 refinement, R_1= 0.043 for 3705 data with $F^2 > 2s(F^2)$, wR_2 = 0.105 for all data, 367 parameters.

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