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A new asymmetric synthesis of the natural enantiomer of the indolizidino[8,7-*b*]indole alkaloid (+)-harmicine

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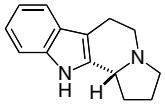
Abstract—We report a novel, facile and asymmetric approach for the synthesis of the indole alkaloid (+)-harmicine via a highly diastereoselective *N*-acyliminium cyclization reaction as a key synthetic step, and verify the relative stereochemistry of the key synthetic intermediate in this approach through X-ray crystallography.

Leishmaniasis, a disease spread by the bite of the sand fly, is found in tropical and sub-tropical regions, affecting some 12 million people in 88 countries. Symptoms of this disease vary from skin sores to fever, anaemia and damage to the spleen and liver. Common therapies have included the use of antimony-containing drugs, although less toxic treatments are currently in development.[1] Screening of the leaf extract of the Malaysian plant *Kopsia griffithii* by Kam and Sim showed strong *anti*-leishmania activity that was traced back to the fraction containing the indolizidino[8,7-*b*]indole alkaloid, (+)-harmicine, **1**.[2]



(+)-Harmicine, **1**

(+)-Harmicine has previously been prepared in racemic form by Knolker and Agarwal,[3] and asymmetric routes to (*S*)-*ent*-harmicine have been achieved by Ohsawa and co-workers, who were also able to establish that the absolute configuration of the naturally occurring compound was *R*.[4] Our research group has had considerable success in the development of asymmetric routes to several important heterocyclic templates over recent years, based around the development of a highly diastereoselective *N*-acyliminium cyclization strategy.[5] Our recent applications of this methodology in natural product synthesis has included targets from the *erythrina* group of alkaloids,[5f,i] and several indole alkaloids, including deplancheine.[5a,d,e,g] In this Letter we report the successful application of our *N*-acyliminium strategy in a new asymmetric synthesis of (*R*)-(+)-harmicine, **1**, the naturally occurring enantiomer.

Our approach to (+)-harmicine began with the synthesis of imide **2**, prepared from the β-amino alcohol derivative of (*S*)-tryptophan. Subjecting imide **2** to sodium borohydride reduction, as described in Scheme 1, resulted in a direct and highly diastereoselective cyclization to give the indolizidino[8,7-*b*]indole derivative **3** as a 9:1 mixture of diastereoisomers in 43% yield (Scheme 1). The major isomer was isolated by recrystallization from ethanol and its relative stereochemistry was confirmed by X-ray crystallographic analysis[6] (Scheme 1). Presumably, under the acidic reaction conditions, the electron-rich indole moiety is able to cyclize onto the *N*-acyliminium intermediate that is generated in situ.

The stereochemical outcome of the reaction can be rationalized based on models previously proposed by our group for similar types of substrates.[5k] The high degree of stereocontrol arises from a preferred conformation, shown in Scheme 1, having minimal $A^{(1,3)}$ strain between the H-atom at the stereogenic centre of the tryptophanol moiety and the lactam carbonyl group in the transition state.

To complete the synthesis of (+)-harmicine we were required to remove the hydroxymethyl auxiliary group

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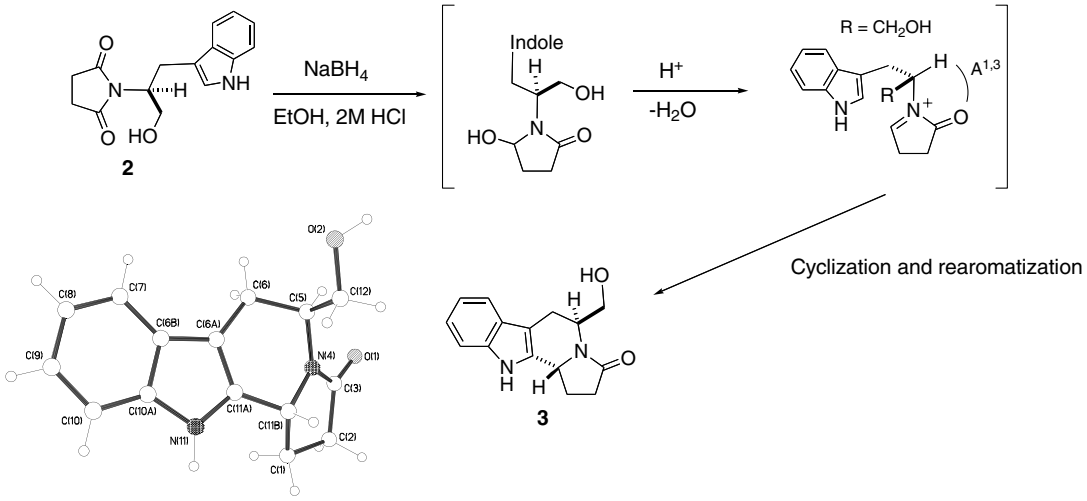
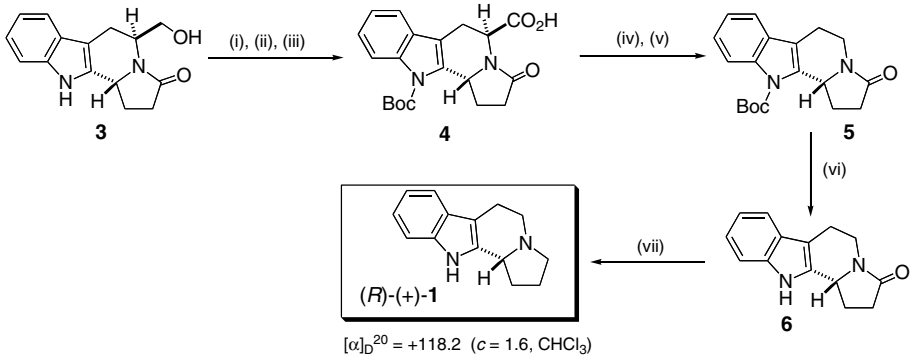


Scheme 1.



Scheme 2. Reagents and conditions: (i) IBX, DMSO, rt, 24 h (72%); (ii) Et_3N, $(Boc)_2O$, DMAP, THF, rt, 4 h (73%); (iii) $NaClO_2$, NaH_2PO_4, CH_3CN, *t*-BuOH, cyclohexene, 0 °C to rt, 18 h (79%); (iv) $(PhSe)_2$, PBu_3, CH_2Cl_2, 0 °C to rt, 18 h (66%); (v) *n*-Bu_3SnH, AIBN, toluene, Δ, 2 h (90%); (vi) TBAF, THF, Δ, 2 h then at rt, 9 h (69%); (vii) $LiAlH_4$, THF, Δ, 3 h (80%).

from compound **3**. Previous methods applied within our group to remove the hydroxymethyl 'auxiliary' substituent from other heterocyclic templates have involved a rhodium-induced decarbonylation sequence.[5f] Due to the rather long reaction times generally needed for substrates in this decarbonylation protocol we have now applied a more facile approach that relies upon a decarboxylation strategy (Scheme 2), used successfully by our group in recent natural product syntheses.[5a,d,e] Compound **3** was oxidized to the carboxylic acid derivative **4** through the corresponding aldehyde; from **4** we generated the acyl selenide derivative and subsequently performed a tin-mediated deacylation to yield the core indolizidino[8,7-*b*]indole ring system **5**. Deprotection of the indole nitrogen gave **6**, from which reductive removal of the lactam carbonyl group completed the synthesis of the natural product, **1**, (*R*)-(+)-harmicine, in 80% yield by LAH reduction in THF (Scheme 2). The optical rotation of our target compound, (*R*)-(+)-**1**, was determined to be +118.2 (*c* 1.6, $CHCl_3$) and was comparable to that reported by Kam and Sim for the isolated natural product [+119; (*c* 0.086, $CHCl_3$)].[2]

In summary we have reported a new and highly stereoselective synthesis of the indolizidino[8,7-*b*]indole alkaloid (*R*)-(+)-harmicine from a readily available, enantiomerically pure imide substrate.[7] Following acceptance of this Letter, our attention was brought to a recent asymmetric synthesis of (+)-harmicine by Czarnocki and Drabowicz that gave the natural product in 79% ee.[8]

Acknowledgements

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6. Crystallographic data (excluding structure factors) for structure **3** ($R = 0.0464$) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 641155. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
7. Data for selected compounds. Compound **3**: colourless needles, mp 266–267 °C; $[\alpha]_D$ 144.8 (*c* 0.48, EtOH); δ_H (400 MHz, DMSO) 1.77–1.85 (1H, m), 2.25–2.31 (1H, m), 2.50–2.58 (2H, m), 2.73 (1H, dd, *J* 2.1, 6.6), 2.82 (1H, d, *J* 15.8), 3.38 (2H, t, *J* 7.96), 4.47–4.52 (1H, m), 4.84–4.88 (2H, m), 6.95–6.99 (1H, m), 7.04–7.07 (1H, m), 7.31–7.34 (1H, m), 7.38–7.40 (1H) and 11.02 (1H, s); δ_C (100 MHz, DMSO) 21.1, 25.5, 31.1, 48.0, 50.7, 60.1, 104.1, 111.1, 117.7, 118.4, 120.9, 126.9, 133.4, 136.1, 172.6; MS (EI) *m/z* 256 [M^+, 87%] (M^+, 256.1215. $C_{15}H_{16}N_2O_2$ requires 256.1212). Compound *R*-(+)-**1**: yellow crystalline solid, mp 161–164 °C; $[\alpha]_D$ 118.2 (*c* 1.6, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.77–2.05 (3H, m), 2.35–2.44 (1H, m), 2.74–2.77 (1H, m), 2.88–2.96 (2H, m), 3.07–3.19 (2H, m), 3.31 (1H, ddd, *J* 2.0, 5.2, 12.8), 4.46–4.49 (1H, m), 7.06 (1H, dt, *J* 1.2, 7.6 Hz), 7.12 (1H, dt, *J* 1.2, 7.6 Hz), 7.36 (1H, d, *J* 7.2 Hz), 7.43 (1H, d, *J* 7.2 Hz) and 9.35 (1H, br s); δ_C (100 MHz, $CDCl_3$) 17.4, 23.1, 29.7, 45.9, 49.5, 57.6, 106.6, 111.3, 118.0, 119.3, 121.6, 126.7, 133.1, 136.4; MS (EI) *m/z* 212 [M^+, 75%] (M^+, 212.1184. $C_{14}H_{16}N_2$ requires 212.1181).
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