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A new asymmetric synthesis of (+)-12*b*-epidevinylantirhine

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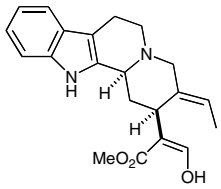
Abstract—We report a new asymmetric synthesis of the indole alkaloid derivative (+)-12*b*-epidevinylantirhine through stereoselective cyclization of a tethered indole nucleus onto an *N*-acyliminium ion intermediate, generated from a readily available non-racemic bicyclic lactam building block, and subsequent template modification through a highly diastereoselective conjugate addition protocol. In addition, we present the first X-ray crystal structure of this indole target.

The indole alkaloids and their synthetic analogues remain a major topic of synthetic endeavour due to their important structural and pharmacological properties. The indolo[2,3-*a*]quinolizine ring system is found within a plethora of alkaloids and related compounds including geissoschizine **1**,[1] geissoschizol **2**[2] and (+)-12*b*-epidevinylantirhine **3**.[2] Recent approaches to the construction of this heterocyclic target system by other groups have included the diastereoselective vinylogous Mannich reaction,[3] Bischler–Napieralski reaction,[4] Fischer indole synthesis,[5] an asymmetric Pictet–Spengler reaction,[6] and more recently our own contribution to the area: the stereoselective cyclization of a pendent indole substituent onto an *N*-acyliminium intermediate generated from bicyclic lactam templates such as **4**.[7] An alternative, but related, approach by Bosch, Amat and co-workers allows the construction of more highly functionalized substrates prior to a similar *N*-acyliminium-mediated cyclization.[8] In this letter we describe the application of our own methodology in target synthesis, and report a new asymmetric synthesis of (+)-12*b*-epidevinylantirhine, **3**. This target was originally isolated by Wenkert[2] during studies towards the synthesis of geissoschizine **1** and geissoschizol **2**, and has, to the best of our knowledge, only been prepared in an asymmetric fashion by Ihara and co-workers.[9]

Our new approach for the asymmetric synthesis of (+)-12*b*-epidevinylantirhine, **3**, began with the preparation of the enantiomerically pure key building block **11** from indolizino[2,3-*a*]quinolizidine derivative **5**, obtained as a single diastereoisomer on activation and cyclization of bicyclic lactam template **4** (Ar = 3′-indole), as previously reported (Scheme 1).[7]

On addition of 2 equiv of lithiated methyl 1,3-dithiolane-2-carboxylate to substrate **11**, we were pleased to observe the exclusive formation of the addition product



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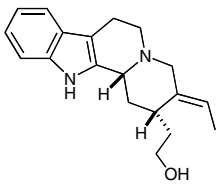

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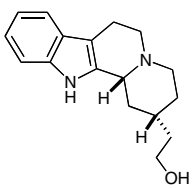

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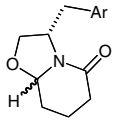

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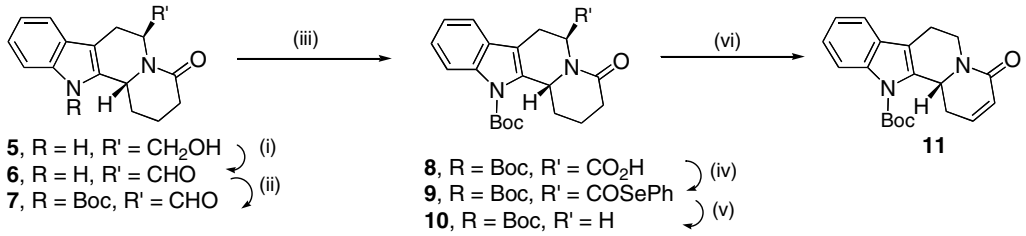
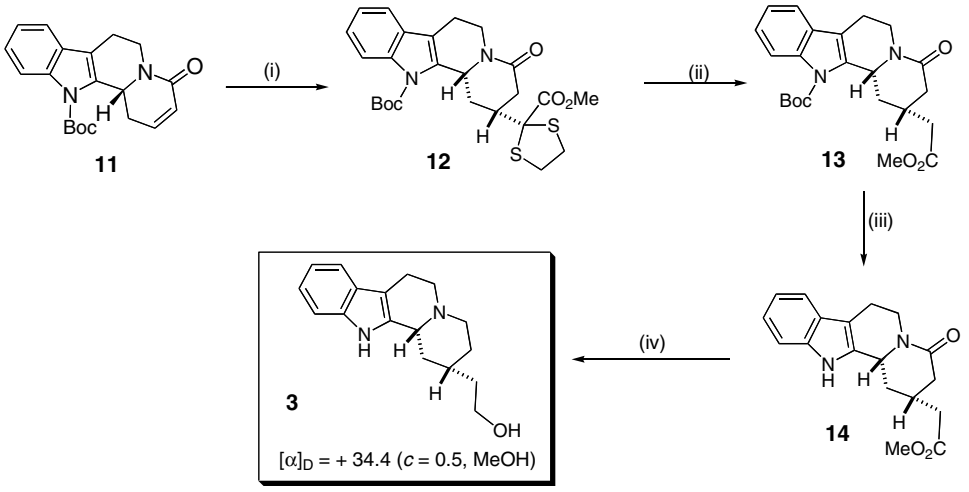


Scheme 1. Reagents and conditions: (i) IBX, DMSO, rt, 24 h (70%); (ii) Et_3N, $(Boc)_2O$, DMAP, THF, rt, 4 h (98%); (iii) $NaClO_2$, NaH_2PO_4, 1-methyl-1-cyclohexene, CH_3CN, *t*-BuOH, H_2O, 0 °C to rt, 18 h (83%); (iv) $(PhSe)_2$, PBu_3, CH_2Cl_2, 0 °C to rt, 18 h (83%); (v) *n*-Bu_3SnH, AIBN, toluene, 80 °C, 2 h (73%); (vi) LDA, PhSeBr, THF, −78 °C to rt, 24 h; then $NaIO_4$, $NaHCO_3$, MeOH, H_2O, rt, 18 h (85% for two steps).



Scheme 2. Reagents and conditions: (i) methyl 1,3-dithiolane-2-carboxylate (2 equiv), *n*-BuLi (2 equiv), THF, −78 °C to rt, 24 h (47%); (ii) $NiCl_2{\cdot}6H_2O$ (10 equiv), $NaBH_4$ (30 equiv), THF–MeOH (1:3), 0 °C to rt, 4 h (73%); (iii) HCOOH (neat), rt, 28 h (71%); (iv) $LiAlH_4$ (8 equiv), THF, Δ 3 h, then rt 12 h (50%).

12 as a single diastereoisomer in 47% yield (Scheme 2). Analysis of compound **12** by X-ray crystallography[10] confirmed that the protons at positions 2 and 12b had cis relative stereochemistry, as required for the current target, (+)-12*b*-epidevinylantirhine **3**,[2,9] and also found in the natural products geissoschizine **1**[1] and geissoschizol **2**.[2]

The stereocontrol observed in the addition reaction is presumably under thermodynamic control, with the addition of the stabilized nucleophile being ultimately reversible in nature. However, other studies by our group have shown that one cannot discount the possibility of a conformational change in the template caused by appropriate choice of *N*-protection on the indole ring.[11] The conjugate addition of carbon nucleophiles to α,β-unsaturated lactams is known to be challenging, and although in our case the addition of the lithiated methyl 1,3-dithiolane-2-carboxylate to compound **11** proceeded well, previous work on similar templates, including Overman's derivatization of racemic and enantiomerically pure indolo[2,3-*a*]quinolizine derivatives, has required the presence of an activating group on the substrate.[12]

Our transformation of **12** to target **3** involved the desulfurization[13] of the dithioacetal moiety with nickel boride, furnishing **13** in 73% yield, as detailed in Scheme 2. With **13** in hand we then achieved the deprotection of the indole nitrogen through removal of the *N*-Boc protecting group on treatment of **13** with neat formic acid to generate **14** in 71% yield. Completion of the synthesis involved reduction of both the lactam carbonyl and the methyl ester moieties, and this global reduction was achieved with excess lithium aluminium hydride to furnish the desired target **3** in 50% yield.

Whilst the spectroscopic data of our compound **3** matched that reported in the literature,[9] the optical rotation, found to be +34.4 (*c* 0.5, CH_3OH), did not correspond to the value of +12.3 (*c* 0.5, CH_3OH) that was previously reported.[9]

We were able to obtain an X-ray crystal structure[14] of target **3**, both to confirm the final structure and also to determine that the protons at the chiral centres were present with cis relative stereochemistry as required (Fig. 1).

In summary, we report a new, facile and highly stereoselective approach for the synthesis of the indole alkaloid derivative (+)-12*b*-epidevinylantirhine.[15] Our method combines two highly diastereoselective protocols: rapid construction of the core indolo[2,3-*a*]quinolizine ring system, with efficient template manipulation through stereoselective conjugate addition to an α,β-unsaturated

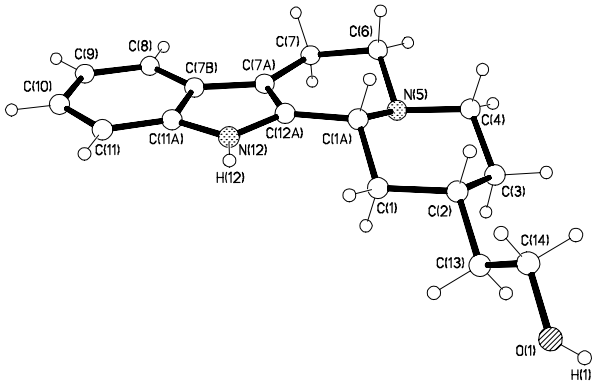


Figure 1. Crystal structure of (+)-12*b*-epidevinylantirhine.

lactam. Current work is focused on extending the methodology described in this letter to other, more complex indole alkaloid targets. Our progress will be reported in due course.

Acknowledgements

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10. Crystallography for **12**: $C_{25}H_{30}N_2O_5S_2$, $M = 502.63$, monoclinic, $P2_1$, $a = 10.5505(7)$, $b = 9.3807(6)$, $c = 12.4921(8)$ Å, $\beta = 100.281(2)°$, $V = 1216.51(14)$ Å^3, $Z = 2$, 10,789 data measured, $R_{int} = 0.0192$, $wR2 = 0.0905$ for all 5594 unique data, $R1 = 0.0379$ for 5007 data with $F^2 \geqslant 2\sigma(F^2)$. Absolute structure parameter $= -0.03(6)$—thus reliably determined. CCDC 286786 contains supplementary crystallographic data in cif format. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK. Fax: +44 1223 336033, e-mail: deposit@ccdc.cam.ac.uk).
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14. Crystallography for **3**: $C_{17}H_{22}N_2O$, $M = 270.37$, orthorhombic, $P2_12_12_1$, $a = 6.6981(9)$, $b = 10.1667(14)$, $c = 22.163(3)$ Å, $V = 1509.2(4)$ Å^3, $Z = 4$, 8832 data measured, $R_{int} = 0.0543$, $wR2 = 0.1472$ for all 1958 unique data, $R1 = 0.0622$ for 1351 data with $F^2 \geqslant 2\sigma(F^2)$. Absolute structure parameter $= 0(5)$—thus not reliably determined. Two unique H-bonds: N(12)–H(12)···O(1′) and O(1)–H(1)···N(5″) {Symmetry operations for equivalent atoms: $' = -x+1,\ y+1/2,\ -z+1/2$; $'' = -x,\ y-1/2,\ -z+1/2$}, with each molecule making four H-bonds to its neighbours in a thick-sheet structure. CCDC 296935.
15. Selected data for compound **3**; colourless needles, mp 239–240 °C; $[\alpha]_D$ 34.4 (*c* 0.5, MeOH); δ_H (400 MHz; MeOH) 1.16–1.24 (1H, m), 1.38–1.48 (1H, m), 1.50–1.63 (2H, m), 1.69–1.82 (1H, m), 1.69–1.82 (1H, m), 2.36–2.42 (1H, m), 2.44–2.48 (1H, m), 2.57–2.64 (1H, m), 2.69–2.74 (1H, m), 2.94–3.04 (1H, m), 2.94–3.04 (1H, m), 3.07–3.13 (1H, m), 3.29–3.34 (1H, m) 3.67–3.70 (2H, m), 6.94–6.98 (1H, m), 7.01–7.05 (1H, m), 7.27–7.29 (1H, m), 7.36–7.38 (1H, m), [OH, NH not visible]; δ_C (100 MHz; $CDCl_3$) 22.4, 32.9, 33.8, 36.7, 40.5, 54.4, 56.5, 60.4, 61.7, 107.7, 111.9, 118.6, 119.8, 121.9, 128.4, 135.9, 138.1; MS (EI) *m*/*z* 270 [M^+, 14.1%] (Found: M^+, 270.17290. $C_{17}H_{22}N_2O$ requires 270.17321).