Chiral Bicyclic Lactams–An Asymmetric Synthesis of the Framework of the *Lycopodium* Alkaloid Magellanine Containing all Six Adjacent Stereogenic Centres

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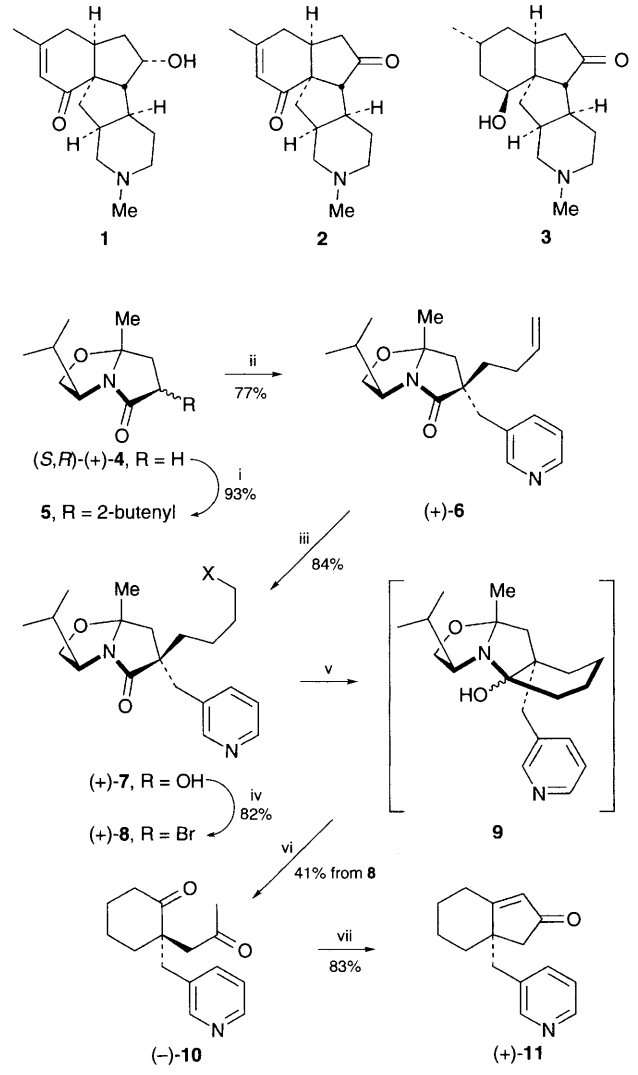
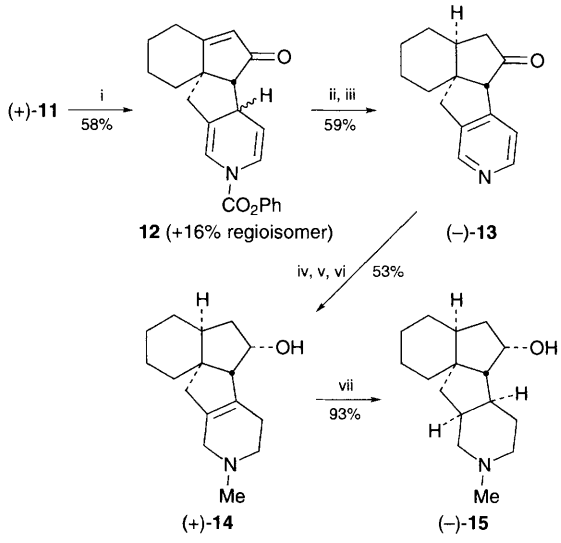
A concise bicyclic lactam-mediated asymmetric synthesis of the titled ring system is described.

A plethora of complex polycyclic alkaloids have been isolated from club mosses of the genus *Lycopodium*,[1] posing a diverse array of synthetic challenges for the organic chemist. Of particular interest are the compounds magellanine **1**,[2a] magellaninone **2**[2b] and paniculatine **3**[2c,d] isolated from *L. magellanicum* and *L. paniculatum* and possessing a highly condensed tetracyclic nucleus with five or six adjacent stereogenic centres. Recent synthetic efforts have culminated in the preparation of both **1** and **2** in enantiomerically pure[3] and racemic forms.[4,5]

We now describe a conceptually different approach to this class of compounds, which further underscores the versatility of our chiral bicyclic lactam methodology for the construction of asymmetric quaternary centres.[6] Our plan to access the stereochemically enriched framework hinged upon a recent disclosure from these laboratories[7] on the asymmetric synthesis of angularly-substituted hydrinden-2-ones (Scheme 1). Thus, a standard double metallation–alkylation sequence on the lactam **4** afforded a 5.9:1 ratio of diastereoisomers favouring **6**,† which could be isolated pure in good yield. The *endo* facial selectivity of the second alkylation is consistent with a multitude of related alkylations reported by us in recent years.[6,7]



Scheme 1 *Reagents and conditions*: i, LDA, DMPU–THF, −78 °C; 4-bromobutene, −78–0 °C; ii, LDA, DMPU–THF, −78 °C; 3-(bromomethyl)pyridine −78–0 °C; iii, 9-BBN, THF, 0 °C; NaOH, H_2O_2, 25 °C; iv, $(COBr)_2$, DMF, CH_2Cl_2, 0–25 °C; v, KH, Bu^{t}Li, THF, −78 °C; vi, $Bu_4NH_2PO_4$, THF–H_2O–CH_2Cl_2, reflux; vii, NaOEt, EtOH, 25 °C



Scheme 2 *Reagents and conditions*: i, PhOCOCl, $TiCl_4$, Pr^i_2NEt, CH_2Cl_2, −78 °C; ii, DDQ, benzene 25 °C; iii, H_2 (1 atm), Pd/C, EtOH, 25 °C; iv, L-Selectride, THF, −78—20 °C; v, MeI, MeCN, reflux; vi, $NaBH_4$, MeOH, 25 °C; vii, H_2 (1 atm), PtO_2, EtOH, 25 °C

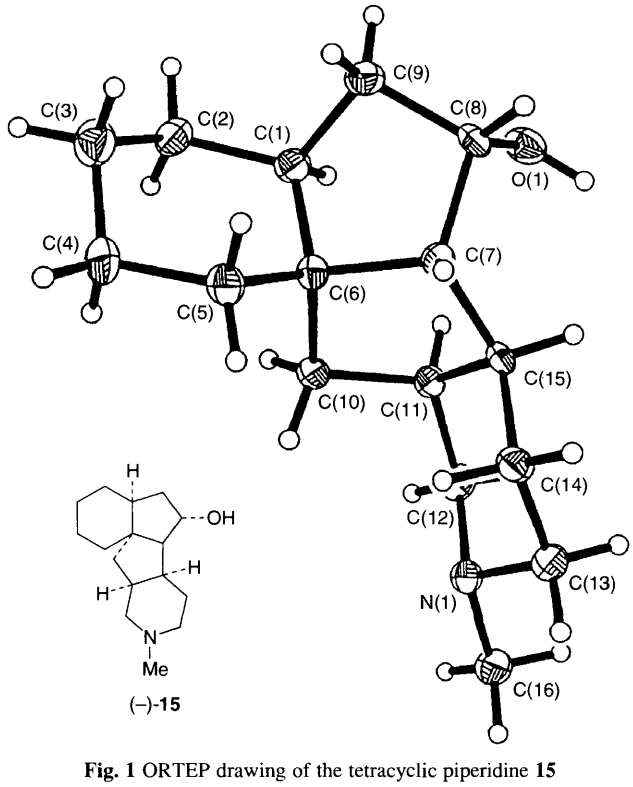


Fig. 1 ORTEP drawing of the tetracyclic piperidine **15**

Following hydroboration–oxidation, a novel bromination protocol featuring *in situ* formation of (bromomethylene)dimethyliminium bromide[8] afforded the unstable bromolactam **8**, which was immediately submitted to the halogen-metal exchange, followed by cyclization and hydrolysis of the resultant carbinolamine **9** to remove the chiral auxiliary.[7] Notably, the use of more standard bromination conditions (Ph_3P–NBS, *etc.*) resulted in formation of intractable mixtures of **8** and triphenylphosphine oxide. The resultant enantiomerically pure diketone **10** then underwent aldol condensation to furnish the pivotal hydrinden-2-one **11**.†

For the critical ring closure to assemble the tetracyclic alkaloid framework, we planned to adapt the known regioselective intermolecular 1,4-addition of enolates to activated acyloxypyridinium salts.[9a–d] Hence, treatment of **11** with phenyl chloroformate (Scheme 2) to activate the pyridine ring towards nucleophilic attack, followed by titanium enolate formation,[9c,10] resulted in isolation of the 1,4-dihydropyridine **12** as the major component of an inseparable 5:1 mixture of regioisomers. Intramolecular enolate addition to acylpyridinium salts are rather rare.[11] Oxidation[12] of the labile mixture **12**, followed by hydrogenation and separation of the pyridine isomers provided a single diastereoisomer of the tetracyclic ketopyridine **13**, the stereochemistry of which was confirmed by NOE experiments.

To set the stereochemistry of the AB ring junction, we envisaged that selective reduction of the carbonyl moiety of **13** would provide a hydroxy group amenably disposed for a directed hydrogenation[13] of the pyridine ring. Furthermore, examination of molecular models led to the expectation that an appropriately bulky reducing agent would deliver the requisite α-carbinol. Gratifyingly, treatment of **13** with L-Selectride provided a single carbinol diastereoisomer which was quantitatively converted to the pyridinium methiodide salt. Unfortunately, the pyridinium salt proved inert to moderate pressures (3 atm) of hydrogen and recourse was made to an alternative two-stage reduction protocol. Reduction of the methiodide salt with excess $NaBH_4$ provided a single regioisomer of the tetrahydropyridine **14** in excellent yield, a process hitherto rarely reported with polycyclic substrates.[14] Subsequent hydrogenation of **14** over Adams' catalyst (1 atm) smoothly produced a single diastereoisomer of the tetracyclic piperidine **15**,† whose structure was confirmed *via* a single crystal X-ray analysis (Fig. 1).‡

In summary, compound **15** has been prepared in 13 steps from the commercially available bicyclic lactam **4**, from which were derived all of the six stereogenic centres of magellanine.

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Footnotes

† *Selected physical and spectroscopic data* for **6** (all coupling constants measured in Hz): $[\alpha]^{25}_D$ + 72.6 (*c* 1.0, $CHCl_3$); δ_H (300 MHz, $CDCl_3$): 0.80 (d, *J* 6.6, 3 H), 1.01 (d, *J* 6.6, 3 H), 1.37 (s, 3 H), 1.58 (m, 2 H), 1.76 (m, 1 H), 1.89 (d, *J* 14.3, 1 H), 2.26 (d, *J* 14.3, 1 H), 2.08 (m, 2 H), 2.58 (d, *J* 13.5, 1 H), 3.00 (d, *J* 13.5, 1 H), 3.48 (m, 2 H), 3.68 (m, 1 H), 4.95 (d, *J* 10.0, 1 H), 5.03 (d, *J* 17.2, 1 H), 5.77 (ddt, *J* 17.2, 10.0, 6.5, 1 H), 7.14 (dd, *J* 7.7, 4.8, 1 H), 7.45 (dt, *J* 7.7, 2.0, 1 H), 8.40 (m, 2 H); δ_C (75 MHz, $CDCl_3$): 18.88 (q), 20.85 (q), 25.20 (q), 29.09 (t), 34.05 (d), 38.08 (t), 40.24 (t), 41.22 (t), 52.34 (s), 62.45 (s), 69.86 (t), 95.53 (s), 115.19 (t), 122.94 (d), 133.17 (s), 137.51 (d), 137.8 (d), 147.97 (d), 151.49 (d), 182.90 (s); ν_{max}/cm^{-1} 1704, 1641; MS (EI, 70 eV): 328 (M^+), 313, 285, 274, 243. For **11**: mp 58.5–59.5 °C; $[\alpha]^{25}_D$ + 18.2 (*c* 0.72, CH_2Cl_2); δ_H (300 MHz, $CDCl_3$): 1.37–1.55 (m, 2 H), 1.70–1.89 (m, 2 H), 1.95 (d, *J* 18.6, 1 H), 2.03–2.17 (m, 2 H), 2.42 (d, *J* 18.6, 1 H), 2.57 (dt, *J* 5.4, 13.2, 1 H), 2.78 (br d, *J* 13.0, 1 H), 2.90 (ABq, *J* 14.0, $\Delta\delta_{AB}$ 9.0, 2 H), 5.81 (d, *J* 1.2, 1 H), 7.18 (dd, *J* 7.8, 4;8, 1 H), 7.39 (d, *J* 8.1, 1 H), 8.35 (d, *J* 1.5, 1 H), 8.45 (dd, *J* 4.8, 1.5, 1 H); δ_C (75 MHz, $CDCl_3$): 21.75 (t), 27.98 (t), 28.41 (t), 38,11 (t), 39.23 (t), 47.44 (s), 48.21 (t), 123.20 (d), 128.60 (d), 132.85 (s), 137.26 (d), 148.27 (d), 151.03 (d), 185.39 (s), 206.65 (s); ν_{max}/cm^{-1} 1693, 1621, 1589; MS (EI, 70 eV): 227 (M^+), 199, 184, 156, 135. For **15**: mp 177–178 °C (blocks from CH_2Cl_2–hexanes); $[\alpha]^{26}_D$ − 10.0 (*c* 0.21, $CHCl_3$) δ_H (300 MHz, C_6D_6): 0.70 (br s, disappears on D_2O wash, 1 H), 1.12–1.64 (series of m, 13 H), 1.69 (dd, *J* 6.6, 4.5, 1 H), 1.78–1.96 (m, 4 H), 2.07–2.09 (m, 2 H), 2.13 (s, 3 H), 2.55–2.64 (m, 2 H), 3.99 (app t, *J* 5.6, 1 H); δ_H (75 MHz, C_6D_6): 22.38 (t), 25.11 (t), 25.97 (t), 30.31 (t), 36.65 (d), 39.21 (t), 39.88 (t), 40.93 (t), 41.29 (d), 41.57 (d), 47.50 (q), 51.97 (s), 56.45 (t), 58.04 (t), 64.15 (d), 73.14 (d); ν_{max}/cm^{-1} 3167; MS (FAB): 250 (MH^+), 180, 179, 111.

‡ *Crystal data* for **15**: $C_{16}H_{27}NO$, *M* = 249.4, monoclinic, *a* = 10.891(2), *b* = 12.437(2), *c* = 11.029(2) Å, β = 106.22(3)°, *V* = 1434.4(4) Å^3, space group $P2_1$, *Z* = 4, D_c = 1.155 Mg m^{-3}, *F*(000) = 552, μ(Mo-Kα) = 0.071 mm^{-1}. A clear colourless irregular shaped block of dimensions 0.60 × 0.38 × 0.26 mm was used. Data were measured on a Siemens P4/Unix diffractometer with graphite monochromated MoKα radiation (λ = 0.71073 Å) at 173 K within 3° ≤2θ ≤ 55°. The structure was solved by direct methods [Siemens SHELXTL PLUS (UNIX)] an the non-hydrogen atoms refined anisotropically using full-matrix least-squares giving final *R* = 5.99% and w*R* = 7.92% for 2584 observed reflections and 324 parameters. Atomic coordinates, bond lengths and angles and thermal parameters Have been deposited at the Cambridge Crystallographic Data Centre. See Information for Authors, Issue No. 1.

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