A Stereoselective Total Synthesis of (±)-γ-Lycorane

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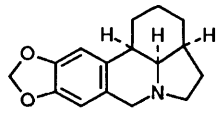
The allylic acetate **2** has been converted, over a number of steps, into the *gem*-dibromocyclopropane **8** which reacts with silver acetate to give the hexahydroindole **9**. This last compound is then readily elaborated to (±)-γ-lycorane **1**.

The lycorine-type natural products, which are characterised by the presence of the galanthan ring-system,[1] represent a significant sub-class within the *Amaryllidaceae* alkaloid family. Certain of these compounds display potentially useful biological properties including antiviral, insect antifeedant and antineoplastic activity, while others are known to inhibit plant growth and/or disrupt the formation of peptide bonds during protein synthesis.[1] As a consequence of such features, considerable effort has been directed towards the total synthesis of these alkaloids.[1] Unlike many of its congeners, the lycorine-derived degradation product γ-lycorane **1** does not appear to



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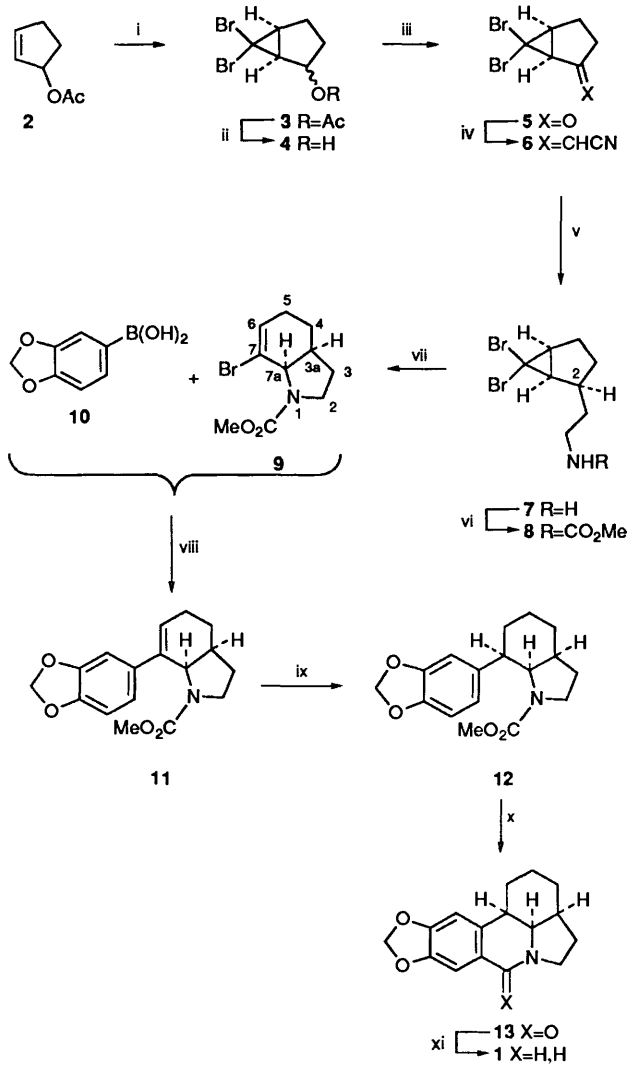
possess any useful pharmacological properties. Nevertheless, it has been a popular synthetic target[2] primarily because its pentacyclic structure provides a means to demonstrate the utility of new synthetic strategies. We now wish to report a novel and stereoselective total synthesis of compound **1**.

The synthetic sequence employed is shown in Scheme 1. Thus, dibromocarbene addition to the allylic acetate **2**[3] was achieved under Makosa conditions[4] using triethylbenzylammonium chloride (TEBAC) as phase transfer catalyst. The resulting 4:1 mixture of the diastereoisomeric bicyclo[3.1.0]hexanes **3** (70%)‡ was subjected to treatment with methanolic potassium hydroxide and the ensuing alcohols **4**[5] immediately oxidised to the corresponding ketone **5**[5] (86% from **3**) with pyridinium chlorochromate (PCC).[6] Treatment of compound **5** with diethyl cyanomethylphosphonate[7]/sodium hydride resulted in a Wadsworth–Emmons reaction and formation of the α,β-unsaturated nitrile **6** (97%) which was obtained as a 2:1 mixture of *E*- and *Z*-isomers [m.p. (major isomer) 72–73 °C]. Reduction of this mixture with molecular hydrogen in the presence of Adams' catalyst produced the saturated amine **7**§ which was immediately allowed to react with methyl chloroformate to give the corresponding carbamate **8** (54% from **6**). Compounds **7** and **8** are assumed to possess the illustrated stereochemistry at C-2 on the basis that there would be preferential delivery of hydrogen to the less hindered *exo*-face of the double bond in



Scheme 1 *Reagents and conditions:* i, $CHBr_3$, 50% aq. NaOH, C_6H_6, TEBAC, 0 °C→18 °C, 24 h; ii, KOH, MeOH, 18 °C, 16 h; iii, PCC (2 mol. equiv.), CH_2Cl_2, 0 °C→18 °C, 10 h; iv, $(EtO)_2P(O)CH_2CN$ (1.5 mol equiv.), NaH (1.5 mol equiv.), DME, 0 °C→18 °C, 3 h; v, H_2 (3 atm), PtO_2, EtOH, $CHCl_3$, 18 °C, 3 h; vi, $ClCO_2Me$ (6 mol equiv.), THF, K_2CO_3, H_2O, 0 °C→18 °C, 16 h; vii, AgOAc (1.1 mol equiv.), TFE, 18 °C, 5 h; viii, $Pd(PPh_3)_4$, C_6H_6, EtOH, 2 mol dm^{-3} aq. Na_2CO_3, 80 °C, 6 h; ix, H_2 (1 atm), 10% Pd-on-C, EtOAc, 18 °C, 16 h; x, $POCl_3$(neat), 80 °C, 24 h; xi, $LiAlH_4$, THF, 65 °C, 3 h.

precursor **6**. In the crucial step of the reaction sequence, a 2,2,2-trifluoroethanol (TFE) solution of compound **8** was treated with silver acetate and, as a result, compound **9** was produced in 87% yield. The formation of this hexahydroindole derivative can be rationalised in terms of silver-ion promoted electrocyclic

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‡ All new compounds were racemic but only one enantiomer is depicted for clarity. All new substances had spectroscopic data (IR, UV, NMR, mass spectra) consistent with the assigned structure. Satisfactory combustion and/or high resolution mass spectral analytical data were obtained for new compounds and/or suitable derivatives.

§ Only trace amounts (< 3% as determined by HPLC analysis) of the alternate diastereoisomer are formed in this reaction.

ring-opening of the *gem*-dibromocyclopropane **8** and intramolecular nucleophilic capture of the incipient cationic species[8] so-formed by the pendant carbamate nitrogen.[9] The excellent regio- and stereo-selectivities observed in the 'cation-π-cyclisation'[8] reaction leading to product **9** arise because the short linkage between the reacting centres effectively precludes other modes of cyclisation. Suzuki cross-coupling[10] of compound **9** with the readily available boronic acid **10**[11] resulted in formation of styrene **11** (87%) which was then subjected to catalytic hydrogenation. In this way the corresponding saturated product **12** (95%) was obtained. The illustrated stereochemistry in this carbamate was established by converting the compound, *via* a Bischler–Napieralski cyclisation,[12] into the previously reported[2b] lactam **13** (79%). The ^{1}H and ^{13}C NMR spectra of compound **13** matched perfectly with those derived from an authentic sample.[2b] Finally, conversion of lactam **13** into the target compound (±)-**1** was achieved by reduction of the former compound under conditions defined by Bäckvall *et al.*[2c] The ^{1}H NMR, ^{13}C NMR, IR and mass spectra of compound (±)-**1** (84%) obtained in this manner were in excellent agreement with published[2c] data.

Experimental

Compound **9**.—A solution of compound **8** (100 mg, 0.29 mmol) in TFE (4 cm^3) was treated in one portion with silver acetate (56 mg, 0.34 mmol) and the resulting mixture stirred in the dark at 18 °C under an atmosphere of nitrogen for 5 h. The reaction mixture was then filtered through a pad of Celite to remove the precipitated silver salts. The pad was washed with quantities of ethyl acetate and the combined filtrates concentrated under reduced pressure to give a pale yellow oil. This material was then subjected to flash chromatography[13] (silica gel, 3:7 ethyl acetate–hexane elution). Concentration of the appropriate fractions (R_F 0.4) then afforded compound **9** (66 mg, 87%) as a clear, colourless oil [Found: $(M - CH_3\cdot)^+$, 243.9969. $C_{10}H_{14}BrNO_2$ requires $(M - CH_3\cdot)^+$, 243.9973]; ν_{max}(NaCl)/cm^{-1} 1703, 1448 and 1382; δ_H(300 MHz, $CDCl_3$) 6.12 (1 H, m, 6-H), 4.61 (1 H, br s, 7a-H), 3.73 (3 H, s, OCH_3), 3.53 (1 H, br s, 2-H), 3.38 (1 H, m, 2-H), 2.51 (1 H, br s), 2.21–2.00 (2 H, complex m) and 1.94–1.73 (4 H, complex m); δ_C(75 MHz, $CDCl_3$) 156.3, 131.2, 124.1, 60.2, 52.3, 44.9, 38.5, 25.2, 22.8 and 21.5; *m/z* (EI, 70 eV) (%) 246 (0.3) 244 [0.4, $(M - CH_3\cdot)^+$], 230 (1.6) 228 [1.4, $(M - CH_3O\cdot)^+$], 202 (2.4) 200 [2.6, $(7 - CH_3OCO\cdot)^+$] and 180 [100, $(M - Br\cdot)^+$].

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