Concise Synthetic Route to Both Enantiomeric Forms of 2,3,4,4a-Tetrahydro[1,3]dioxolo[4,5-*j*]phenanthridin-6(5*H*)-one, the Tetracyclic Skeleton Associated with the Narcissus Alkaloids Lycoricidine and Narciclasine

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Both enantiomeric forms, (*S*)-**4** and (*R*)-**4**, of the tetracyclic skeleton associated with the title alkaloids **1** and **2** have been prepared; the key step involved silver isocyanate-promoted ring-opening of *gem*-dibromocyclopropane **5** and trapping of the resulting allylic isocyanate (±)-**6** with (−)-menthol.

The potent cytotoxic[1] and antiviral[2] properties associated with the narcissus alkaloids lycoricidine **1**, narciclasine **2** and pancratistatin **3** have prompted significant efforts directed towards the total synthesis of these structurally challenging compounds.[3] Although narciclasine **2** has so far defied synthesis, Danishefsky and Lee have reported[4] the preparation of (±)-**3** while Heathcock *et al.* have described[5] a simple route to the phenanthridinone nucleus associated with this latter compound. However, most effort[1,6,7] has focused on the preparation of the simplest member and recently Hudlicky and Olivo reported[7d] a short and enantiospecific synthesis of lycoricidine **1** starting from a readily available chiron. Subsequently Martin[7e] and Johnson[7f] described closely related routes to (±)-**1** and **1**, respectively. We now report a novel, convergent and 'low-tech' synthesis of both enantiomeric forms of the tetracyclic skeleton **4** associated with the title alkaloids. The strategy used has the potential for ready modification to the preparation of a wide range of analogues including natural products **1**–**3**.

The key intermediate, (±)-**6**, in the present synthesis (Scheme 1) was easily generated by reacting the dibromocarbene adduct **5**[8] of cyclopentene with 1.2 molar equivalents of freshly prepared silver isocyanate.[9] Compound **6** was not isolated but simply allowed to react with five molar equivalents of (−)-menthol {$[\alpha]_D$ = −50.5 (*c*. 9.85)†} which resulted in the formation of an inseparable 1 : 1 mixture of the diastereoisomeric carbamates **7a**‡ and **7b** (94%) (mp = 124–125.5 °C) {$[\alpha]_D$ = −45 (*c*. 1.35)}. Suzuki coupling[10] of this mixture with the boronic acid **8** (mp = 238–240 °C)§ afforded compounds **9a** (49%) (mp = 130–131 °C) {$[\alpha]_D$ = −178 (*c*. 1.10)} and **9b** (48%) (mp = 102–103 °C) {$[\alpha]_D$ = +108 (*c*. 0.82)} which could be separated from one another using a combination of fractional crystallisation and chromatographic techniques.¶ The absolute configuration at C-(4a) in carbamate **9a** was established by X-ray crystallography (see Fig. 1).‖ Subjection of compound **9a** to Bischler–Napieralski-type cyclisation[11] using phosphorous oxychloride[12] then gave lactam (*S*)-**4** (67%)** [mp *ca*. 350 °C (decomp.) (morphological changes at *ca*. 170 and 290 °C)] {$[\alpha]_D$ = +224 (*c*. 1.33)} while reaction of carbamate **9b** under exactly the same conditions afforded enantiomer (*R*)-**4** (74%)†† [mp *ca*. 350 °C (decomp.) (morphological changes at *ca*. 170 and 290 °C)] {$[\alpha]_D$ = −232 (*c*. 0.79)}.†† The enantiomeric purities of compounds (*S*)-**4** and (*R*)-**4** were established, by chiral HPLC techniques,§§ to be >98% enantiomeric excess (e.e.) in each case.

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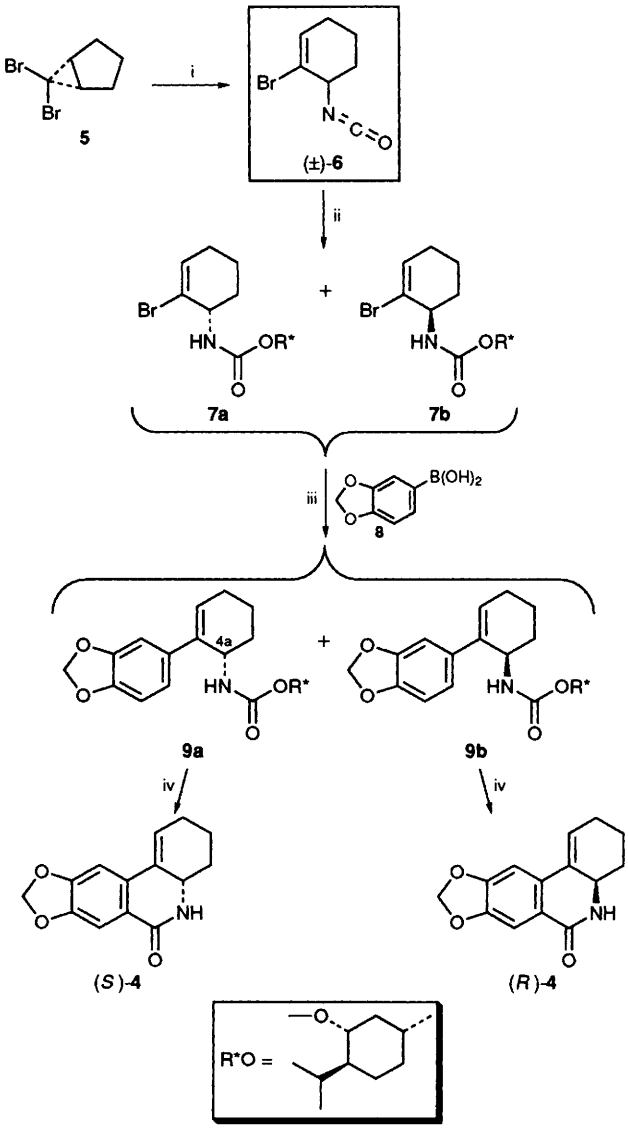
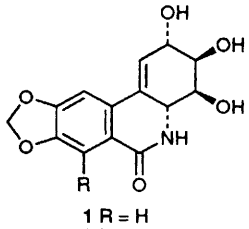


Scheme 1 *Reagents and conditions*: (i) AgNCO (1.2 mol equiv.), 1,4-dioxane, 100 °C, 4 h; (ii) (−)-menthol (5 mol. equiv.), 1,4-dioxane, 100 °C, 24 h; (iii) $Pd(PPh_3)_4$ (3 mol.%), 2 mol dm^{-3} aq. Na_2CO_3, 1 : 10 C_2H_5OH–C_6H_6, 80 °C, 12 h; (iv) $POCl_3$, 80 °C (sealed tube), 7 h then *ca*. 0.2 mol dm^{-3} HCl in 10 : 1 THF–H_2O, 18 °C, 0.5 h



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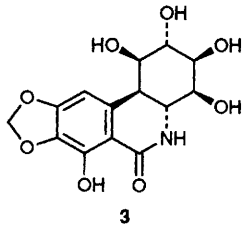
2 R = OH



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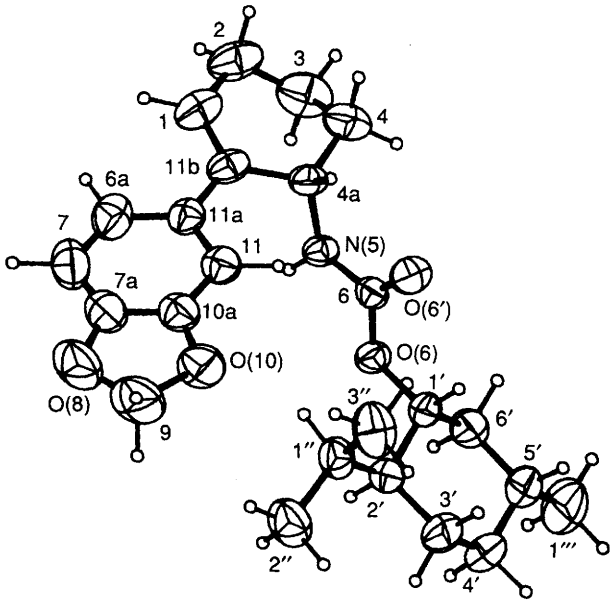

Fig. 1 ORTEP[15] Drawing of carbamate **9a** (the C symbol for carbon has been omitted)

Footnotes

† This optical rotation was determined in ethanol solution at 19 °C. All other rotations were determined in chloroform solution at 18–19 °C.

‡ All new compounds had spectroscopic data [IR, UV (where appropriate), NMR, mass spectrum] consistent with the assigned structure. Satisfactory combustion and/or high resolution mass spectral analytical data were obtained for new compounds and/or suitable derivatives. Reported yields refer to isolated materials.

§ Boronic acid **8** was prepared as follows: the Grignard reagent derived from 4-bromo-1,2-(methylenedioxy)benzene (ALDRICH) was reacted with 1.2 molar equivalents of tri-n-butylborate in tetrahydrofuran (THF) at −78 °C and the resulting arylboronic ester then hydrolysed at 18 °C with 2 mol dm^{-3} aqueous HCl to give the required compound in 88% overall yield.

¶ To effect separation the following procedure can be used: the mixture of carbamates **9a** and **9b** is dissolved in warm hexane–dichloromethane and on cooling the former compound crystallises from the solution. Subjection of the mother liquors to MPLC (1:4 diethyl ether–hexane elution, silica) then allows for the ready separation of carbamate **9b** (R_f 0.3) from residual **9a** (R_f 0.4).

‖ *Crystal data* for **9a**: $C_{24}H_{33}NO_4$, M = 399.5, monoclinic space group $P2_1$, a = 10.984(1), b = 5.217(1), c = 19.252(2) Å, β = 93.54(1), U = 1101.1(4) Å^3, $F(000)$ = 432, Z = 2, D_m 1.203(5), D_c 1.205 g cm^{-3}, μ 6.14 cm^{-1} (Cu-Kα). Intensities were recorded for 1743 unique reflections by an ω–2Θ scan, $2\Theta_{max}$ 130° on a Rigaku-AFC four circle diffractometer with Cu-Kα radiation (graphite crystal monochromator, λ = 1.5418 Å) at 290(1) K. Intensity data were corrected for Lorentz and polarisation effects and for absorption. The structure was solved by direct methods with SHELXS-86[13] and full-matrix least-squares refinement with SHELX-76[14] converged at R = 0.048, R_w = 0.068 for 1574 terms with $I \geq 2\sigma I$. The non-H atoms were given anisotropic temperature factors and the H-atoms given the same isotropic temperature factor as the atom to which they were bonded. The function minimised was $\Sigma w (|F_o| - |F_c|)^2$ with $w = [\sigma^2|F_o| + 0.0025 |F_o|)^2]^{-1}$. At convergence $(\Delta\rho)_{max}$, $(\Delta\rho)_{min}$ +0.13, −0.18 e Å^{-3}. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

** Yields for this step remain unoptimised.

‡‡ *Selected spectra data* for **4**; ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.8, 151.4, 147.6, 133.4, 130.9, 124.8, 121.5, 107.4, 102.7, 101.6, 50.7, 29.9, 25.8 and 20.1; ^1H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 6.89 (s, 1H), 6.11 (m, 1H), 6.06 (broad m, 1H, NH), 6.01 (d, J 1.2 Hz, 1H), 5.99 (d, J 1.2 Hz, 1H), 4.34 (m, 1H), 2.42–2.18 (complex m, 2H), 2.12 (m, 1H), 1.90 (m, 1H), 1.74–1.56 (complex m, 2H); MS m/z (EI, 70 eV) 243 (100%) [$M^{+\cdot}$], 215 (89) [$M^{+\cdot}$ − CO]; ν_{max} cm^{-1} 1675 and 1616.

§§ Chiral HPLC analysis was conducted using a Chiralcel OD analytical column (4.6 mm × 25 cm) with 2:8 ethanol–hexane for elution. At a flow rate of 1 cm^3 min^{-1} (*R*)-**4** and (*S*)-**4** eluted at 12.0 and 21.0 min, respectively. Subjection of an authentic sample of (±)-**4** to the same analysis revealed two peaks of equal area and with the same retention times as the individual enantiomers. A sample of (±)-**4** was prepared in the following manner: isocyanate **6** was trapped with methanol and the carbamate (96%) (mp = 123.5–124 °C) so-formed was subjected to Suzuki coupling with boronic acid **8**. The resulting aryl substituted carbamate (90%) (mp = 136–137 °C) was then treated with $POCl_3$ to give (±)-**4** (52%) [mp *ca.* 350 °C (decomp.)].

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