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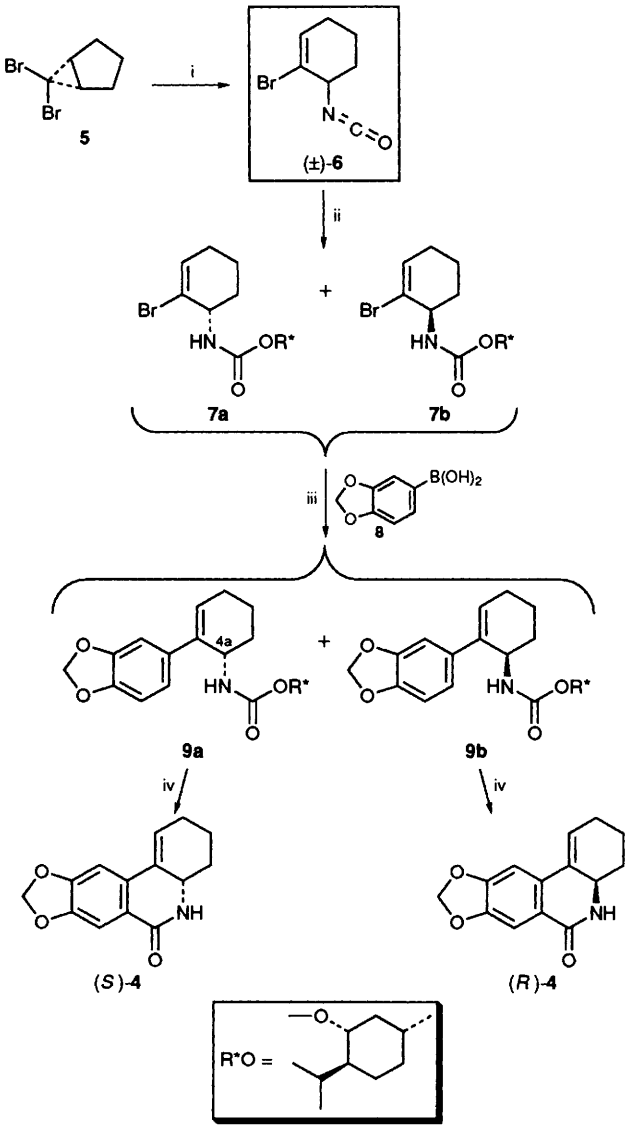
Both enantiomeric forms, (*S*)-**4** and (*R*)-**4**, of the tetracyclic skeleton associated with the title alkaloids **1** and **2** have been prepared; the key step involved silver isocyanate-promoted ring-opening of *gem*-dibromocyclopropane **5** and trapping of the resulting allylic isocyanate (±)-**6**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

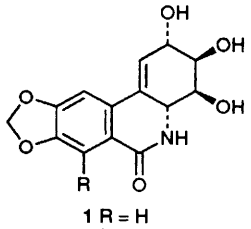
The key intermediate, (±)-**6**, in the present synthesis (Scheme 1) was easily generated by reacting the dibromocarbene adduct **5**[8] of cyclopentene with 1.2 molar equivalents of freshly prepared silver isocyanate.[9] Compound **6** was not isolated but simply allowed to react with five molar equivalents 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.

We thank Dr J. M. Lawlor for valuable discussions and the Australian Research Council for financial support. C. J. C. is the grateful recipient of an Australian Post-Graduate Research Award.

Received, 11th August 1993; Com. 3/04875F



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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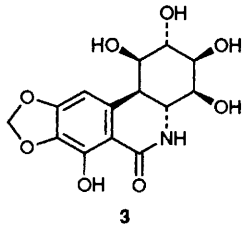
2 R = OH



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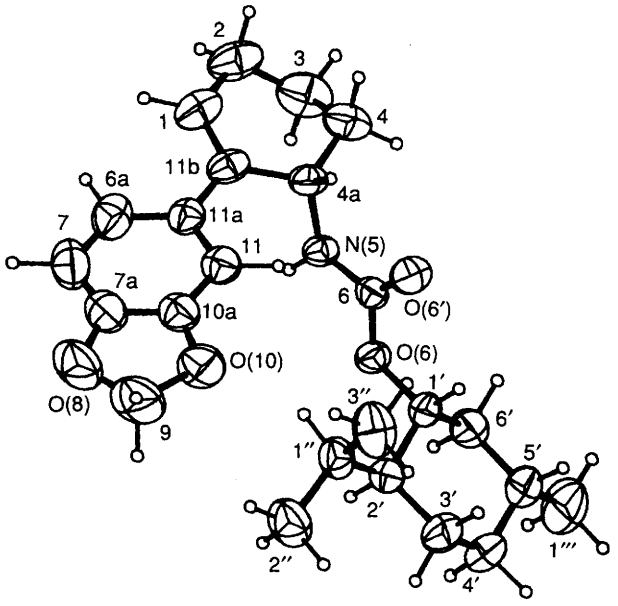

Fig. 1 ORTEP[15] Drawing of carbamate **9a** (the C symbol for carbon has been omitted)

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.)].

References

1 G. Cerriotti, *Nature* (London), 1967, **213**, 595; T. Okamoto, Y. Torii and Y. Isogai, *Chem. Pharm. Bull.*, 1968, **16**, 1860; A. Mondon and K. Krohn, *Chem. Ber.*, 1975, **108**, 445; L. Carrasco, M. Fresno and D. Vazques, *FEBS Lett.*, 1975, **52**, 236; A. Jimenez, L. Sanchez and D. Vazquez, *FEBS Lett.*, 1975, **55**, 33; G. R. Pettit, V. Gaddamidi, D. L. Herald, S. B. Singh, G. M. Cragg, J. M. Schmidt, F. E. Boettner, M. Williams and Y. Sagawa, *J. Nat. Prod.*, 1986, **49**, 995; B. G. Ugarkar, J. DaRe and E. M. Schubert, *Synthesis*, 1987, 715.

2 B. Gabrielsen, T. P. Monath, J. W. Huggins, D. F. Kefauver, G. R. Pettit, G. Groszek, M. Hollingshead, J. J. Kirsi, W. M. Shannon, E. M. Schubert, J. DaRe, B. Ugarkar, M. A. Ussery and M. J. Phelan, *J. Nat. Prod.*, 1992, **55**, 1569 and references therein.

3 For a comprehensive review concerning the isolation, structure elucidation, biological properties and synthetic approaches to compounds **1–3** as well as related systems see S. F. Martin, in *The Alkaloids*, ed. A. Brossi, Academic Press, New York, 1987, vol. 30, pp. 251–376.

4 S. Danishefsky and J. Y. Lee, *J. Am. Chem. Soc.*, 1989, **111**, 4829.

5 R. S. C. Lopes, C. C. Lopes and C. H. Heathcock, *Tetrahedron Lett.*, 1992, **33**, 6775. For other pancratistatin model studies see R. D. Clark and M. Souchet, *Tetrahedron Lett.*, 1990, **31**, 193.

6 Synthetic approaches to lycoricidine: G. E. Keck and S. A. Fleming, *Tetrahedron Lett.*, 1978, 4763; G. E. Keck, E. Boden and U. Sonnewald, *Tetrahedron Lett.*, 1981, **22**, 2615; T. Weller and D. Seebach, *Tetrahedron Lett.*, 1982, **23**, 935; R. C. Thompson and J. Kallmerten, *J. Org. Chem.*, 1990, **55**, 6076; M. C. McIntosh and S. M. Weinreb, *J. Org. Chem.*, 1993, **58**, 4823.

7 Total syntheses of lycoricidine: (*a*) S. Ohta and S. Kimoto, *Chem. Pharm. Bull.*, 1976, **24**, 2977; (*b*) H. Paulsen and M. Stubbe, *Liebigs Ann. Chem.*, 1983, 535; (*c*) N. Chida, M. Ohtsuka and S. Ogawa, *Tetrahedron Lett.*, 1991, **32**, 4525; (*d*) T. Hudlicky and H. F. Olivo, *J. Am. Chem. Soc.*, 1992, **114**, 9694; (*e*) S. F. Martin and H.-H. Tso, *Heterocycles*, 1993, **35**, 85; (*f*) L. Su and C. R. Johnson, Abstract A-119, Program Booklet, 33rd National Organic Chemistry Symposium, Montana State University, Bozeman, Montana, June 13–17, 1993.

8 J. Sonnenberg and S. Winstein, *J. Org. Chem.*, 1962, **27**, 748.

9 C. H. Heathcock and A. Hassner, *Org. Synth.*, 1971, **51**, 112.

10 N. Miyaura, T. Yanagi and A. Suzuki, *Synth. Commun.*, 1981, **11**, 513.

11 G. Fodor and S. Nagubandi, *Tetrahedron*, 1980, **36**, 1279.

12 For related cyclisations see Ref. 3 and W. H. Pearson and J. M. Schkeryantz, *J. Org. Chem.*, 1992, **57**, 6783.

13 G. M. Sheldrick, SHELX-86, in *Crystallographic Computing*, ed. G. M. Sheldrick, C. Krüger and R. Goddard, Oxford University Press, 1985, pp. 175–189.

14 G. M. Sheldrick, SHELX-76 *Program for Crystal Structure Determination*, University of Cambridge, Cambridge, UK, 1976.

15 C. K. Johnson, ORTEPII, Report ORNL-5138 Oak Ridge National Laboratory, Tennessee, USA, 1976.