Lycoricidine and Pancratistatin Analogues from Cyclopentadiene

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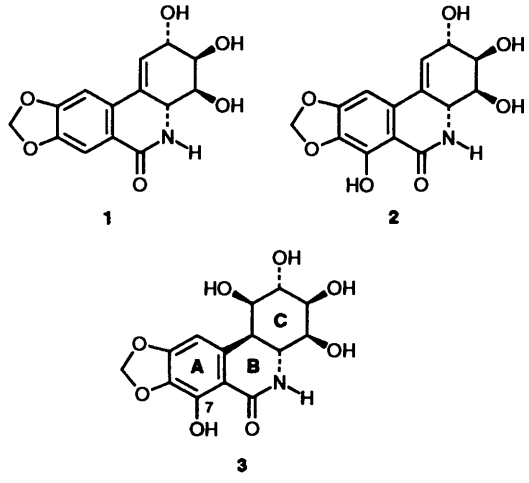
Concise synthetic routes from cyclopentadiene **4** to the lycoricidine and pancratistatin analogues **13**, **14** and **17** have been developed. The key step involved the silver isocyanate promoted ring opening of the *gem*-dibromocyclopropane **6** to give, after interception of the intermediate isocyanates by added methanol, the carbamates **7** and **8**. The X-ray crystal structures of compounds **13** and **16** have been determined.

The *Narcissus* alkaloids lycoricidine, narciclasine and pancratistatin, **1–3** respectively, have attracted considerable attention because of their intriguing range of biological properties.[1] For example, these compounds display significant cytotoxic activity and pancratistatin, the most potent but least abundant of the three, is now in demand for clinical trials by the National Cancer Institute. The origins of some of these cytotoxic effects are ascribed to the capacity of the compounds to inhibit protein synthesis in eukaryotic ribosomes.[2] In the case of narciclasine, this effect is exerted by the blocking of peptide bond formation on the 60-S ribosome unit.[3] In other studies[4] pancratistatin and its 7-deoxy-derivative were found to exhibit strong anti-RNA virus activity, while lycoricidine triacetate has been shown to display *in vitro* anti-viral activity. Compounds **1–3** also display potent growth regulating and/or insect antifeedant activities.[5]

As a result of their interesting properties and challenging molecular architectures there has been considerable effort expended to develop efficient syntheses of compounds **1–3**. To date, some six routes to lycoricidine[6] have been described together with several incomplete approaches.[7] In contrast, no total synthesis of narciclasine has been reported and a single, but somewhat lengthy, preparation of compound (±)-**3** has been developed.[8] Interest in the development of 'low-tech' syntheses of compounds **1–3** remains high.[9] Consequently, we now describe the rapid preparation of the lycoricidine and pancratistatin analogues **13**, **14** and **17** from cheap and abundant cyclopentadiene **4**.



Results and Discussion

In the initial stages (Scheme 1) cyclopentadiene **4** was readily converted, *via* $Pb(OAc)_4$-mediated oxidation,[10] into the corresponding diol, which was then transformed into the cyclohexanone acetal **5**‡ [70% from cyclopentadiene **4** based on $Pb(OAc)_4$ used] by standard methods. Dibromocarbene addition to the double bond was achieved under Makosza conditions[11] and this reaction proceeded stereoselectively to give the tricyclic adduct **6** (84%) (m.p. 53.5–54.5 °C). The illustrated *anti*-relationship between the cyclopropane and 1,3-dioxolane rings within compound **6** has not been rigorously proven, but examination of molecular models suggests that only the lower face (as drawn) of the double bond within precursor **5** is likely to be accessible to incoming electrophiles. Silver isocyanate[12] promoted electrocyclic ring-opening[13] of the *gem*-dibromocyclopropane **6** is presumed to give a regioisomeric mixture of ring-expanded allylic isocyanates. However, these were not isolated but, rather, intercepted by added methoxide ion to give the corresponding carbamates **7** (28%) (m.p. 153–154 °C) and **8** (40%) which could be separated from one another by MPLC. Suzuki cross-coupling[14] of the latter carbamate with the boronic acid **9**[9d] was readily achieved and the styrene **10** (82%) (m.p. 131–133 °C) thereby obtained. The acetal protecting group within compound **10** was then removed and the resulting diol **11** (m.p. 124–127 °C) converted into the corresponding diacetate **12** (89% from compound **10**). Bischler–Napieralski cyclisation[15] of carbamate **12** was effected using a combination of triflic anhydride (Tf_2O) and 4-(dimethylamino)-pyridine (DMAP). After acid-catalysed hydrolysis of the resulting imidates (and reacetylation due to partial acetate hydrolysis) the resulting diacetate **13**§ (85%) (m.p. 271–274 °C)

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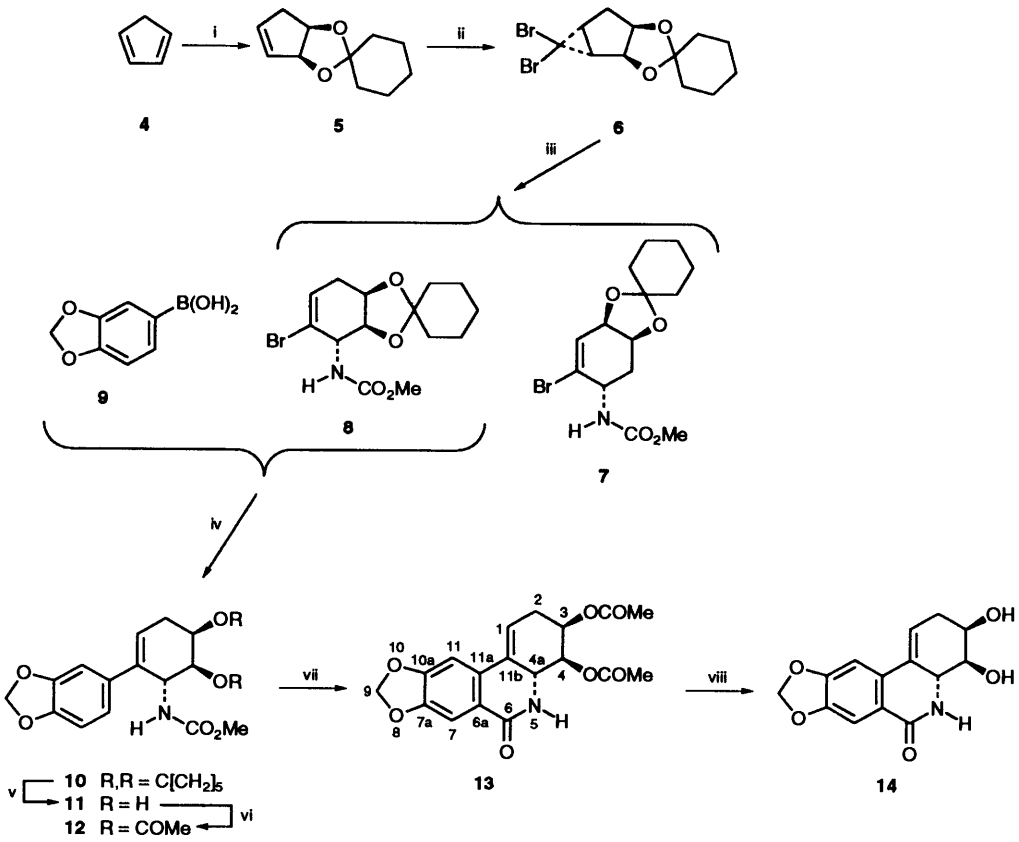
‡ All new compounds were racemic but only one enantiomer is depicted for clarity. All new substances had spectroscopic data (IR, UV, NMR, *m/z*) consistent with the assigned structure. Satisfactory combustion and/or high resolution, mass spectral analytical data were obtained for new compounds and/or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

§ *Selected spectroscopic data for compound* **13**: ν_{max}(KBr)/cm^{-1} 3218, 1734, 1661, 1612, 1468, 1392, 1230, 1034 and 776; δ_H($CDCl_3$, 21 °C) 7.54 (1 H, s, H7), 6.95 (1 H, s, H10), 6.11 (1 H, br s), 6.05 (1 H, d, *J* 1, H9), 6.03 (1 H, d, *J* 1, H9), 6.02 (1 H, m, H1), 5.56 (1 H, m), 4.98 (1 H, dd, *J* 10 and 2), 4.68 (1 H, dm, *J* 10), 2.85 (1 H, dm, *J* 20), 2.51 (1 H, dm, *J* 20), 2.13 (3 H, s), 2.08 (3 H, s); δ_C($CDCl_3$, 21 °C) 170.6 (C), 170.3 (C), 164.7 (C), 151.6 (C), 148.2 (C), 131.6 (C), 128.3 (C), 121.3 (C), 119.6 (CH), 107.4 (CH), 102.9 (CH), 101.8 (CH_2), 74.0 (CH), 66.8 (CH), 50.2 (CH), 30.8 (CH_2), 21.0(4) (Me) and 21.0(1) (Me); *m/z* (EI, 70 eV) 359 (23%, M^+), 299 [12, $(M - MeCO_2H)^+$], 257 (47), 240 (59), 239 [100, $(M - 2 \times MeCO_2H)^+$], 228 (24) and 215 (26).

Selected spectroscopic data for compound **17**: ν_{max}(KBr)/cm^{-1} 3433, 2921, 1747, 1668, 1367, 1253, 1227 and 1039; δ_H[$(CD_3)_2SO$, 30 °C] 8.10 (1 H, s), 7.31 (1 H, s), 6.53 (1 H, d, *J* 1), 6.07 (2 H, s), 5.48 (1 H, dd, *J* 11 and 10, H1), 5.24 (1 H, m, H3), 5.10 (1 H, dd, *J* 10 and 5, H2), 3.58



Scheme 1 *Reagents and conditions:* i, $Pb(OCOMe)_4$ (0.66 mol equiv.), $MeCO_2H$, H_2O, 0–18 °C, 1 h then K_2CO_3, MeOH, 18 °C, 1.5 h then cyclohexanone (1 mol equiv.), *p*-$MeC_6H_4SO_3H$ (trace), C_6H_6, 80 °C, 1 h; ii, $CHBr_3$, 50% aq. NaOH, C_6H_6, TEBAC, 0–18 °C, 36 h; iii, AgOCN (4 mol equiv.), 1,4-dioxane, 100 °C, 120 h then NaOMe–MeOH, 18 °C, 12 h; iv, $Pd(PPh_3)_4$, C_6H_6, EtOH, 2 mol dm^{-3} aq. Na_2CO_3, 80 °C, 24 h; v, 4 mol dm^{-3} aq. HCl, THF, 18 °C, 14 h; vi, $(MeCO)_2O$ (2.8 mol equiv.), DMAP, C_5H_5N, CH_2Cl_2, 18 °C, 12 h; vii, Tf_2O (5 mol equiv.), DMAP (3 mol equiv.), CH_2Cl_2, 0–15 °C, 12 h then 2 mol dm^{-3} aq. HCl, THF, 18 °C, 14 h then $(MeCO)_2O$, DMAP, pyridine, 0–18 °C, 12 h; viii, NaOMe (6.00 mol equiv.), THF–MeOH, 18 °C, 12 h

was obtained and its structure confirmed by single crystal X-ray analysis (Fig. 1).* Sodium methoxide-mediated removal of the acetate units within compound **13** then afforded 2-deoxylycoricidine **14** (96%) (m.p. 285–287 °C).

A simple and effective protocol for construction of the pancratistatin analogue **17** (Scheme 2) has been developed using the carbamate **7** as starting material. Thus, Suzuki cross-coupling of compound **7** with the boronic acid **9** afforded the expected product **15** (87%) (m.p. 171–172 °C). This latter compound was then subjected to hydroboration[16] using BH_3–THF complex and the ensuing organoborane treated with alkaline hydrogen peroxide. Sequential treatment of the resulting alcohol with aqueous acid then acetic anhydride–pyridine finally afforded the triacetate **16** (42%) (m.p. 222–224 °C) the structure of which was established by single crystal X-ray analysis (Fig. 1).* The π-facial selectivity associated with the anti-Markovnikov hydration of the double-bond within compound **15** is presumably controlled by the bulky cyclohexanone acetal unit which directs BH_3 addition to the lower face (as drawn) of the molecule. As a consequence of this selectivity, formation of the critical[17] *trans*-BC-ring junction associated with the pancratistatin nucleus is assured in the next step of the reaction sequence. Indeed, subjection of compound **16** to Bischler–Napieralski cyclisation (using Tf_2O–DMAP) followed by acid hydrolysis cleanly afforded the pancratistatin analogue **17**§ (59%) [m.p. > 335 °C (sublimation from 300 °C onwards)].

(1 H, td, *J* 11 and 5, H4a), 3.25 (1 H, t, *J* 11, H11b), 2.10 (1 H, dm, *J* 16), 2.09 (3 H, s), 2.00 (3 H, s), 1.96 (1 H, dm, *J* 16), 1.95 (3 H, s); δ_C[$(CD_3)_2SO$, 30 °C] 170.3 (C), 169.6(5) (C), 169.6(2) (C), 163.9 (C), 150.3 (C), 146.3 (C), 134.1 (C), 124.1 (C), 107.4 (CH), 103.7 (CH), 101.8 (CH_2), 73.8 (CH), 70.2 (CH), 67.8 (CH), 48.3 (CH), 43.3 (CH), 31.2 (CH_2), 20.9 (Me), 20.6 (Me) and 20.4 (Me); *m/z* (EI, 70 eV) 419 (1%, M^+), 359 [1, $(M - MeCO_2H)^+$], 299 [4, $(M - 2 \times MeCO_2H)^+$], 257 (17), 240 (26) and 239 [100, $(M - 3 \times MeCO_2H)^+$].

* *Crystallographic data for compound* **13**: $C_{18}H_{17}NO_7$, M = 359.33, T = 293(1)K; Monoclinic, space group $P2_1/n$ with a = 10.037(2), b = 12.9438(11), c = 13.4600(8) Å, β = 107.171(10)°, U = 1670.7(3) $Å^3$, D_c (Z = 4) = 1.429 g cm^{-3}, $F(000)$ = 752, μ(Cu-Kα) = 9.41 cm^{-1}; 3440 unique data ($2\theta_{max}$ = 150°), 1768 with $I > 2\sigma(I)$; conventional $R1[I > 2\sigma(I)]$ = 0.0830, $wR2$ [all data] = 0.2389, GOF [all data] = 1.065.

Crystallographic data for compound **16**: $C_{21}H_{25}NO_{10}$, M = 451.42, T = 293(1); Monoclinic, space group $P2_1/c$ with a = 19.246(3), b = 7.0952(13), c = 16.623(3) Å, β = 101.88(2)°, U = 2221.3(7) $Å^3$, D_c (Z = 4) = 1.350 g cm^{-3}, $F(000)$ = 952, μ(Cu-Kα) = 9.21 cm^{-1}; 3681 unique data ($2\theta_{max}$ = 130°), 2358 with $I > 2\sigma(I)$; conventional $R1[I > 2\sigma(I)]$ =0.0457, $wR2$ [all data] = 0.0979, GOF [all data] = 1.010.

Data were measured on an Enraf–Nonius CAD4MachS diffractometer (graphite crystal monochromator, λ = 1.5418 Å) using the ω:2θ scan method; absorption corrections were applied. Refinement, with anisotropic displacement parameters applied to each of the non-hydrogen atoms, was by full-matrix least squares on F^2 (SHELXL-93)[19] using all data, $wR2 = [(\Sigma w(F_o^2 - F_c^2)^2/\Sigma w(F_o^2)^2]^{\frac{1}{2}}$. All hydrogens were located and refined. Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre. See 'Notes to Authors', Issue No. 1.

§ See footnote § on p. 3515.

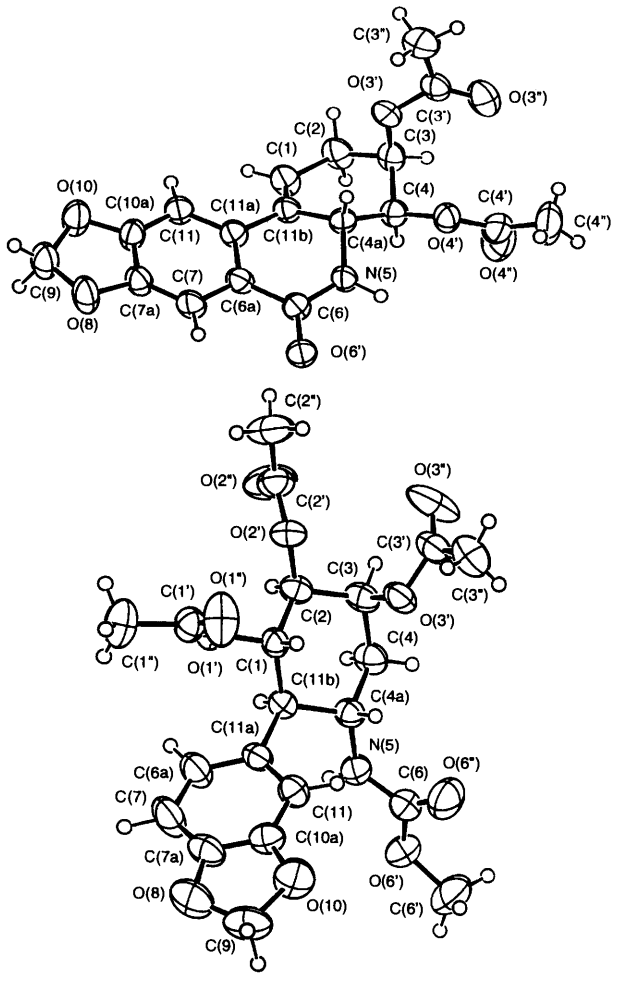
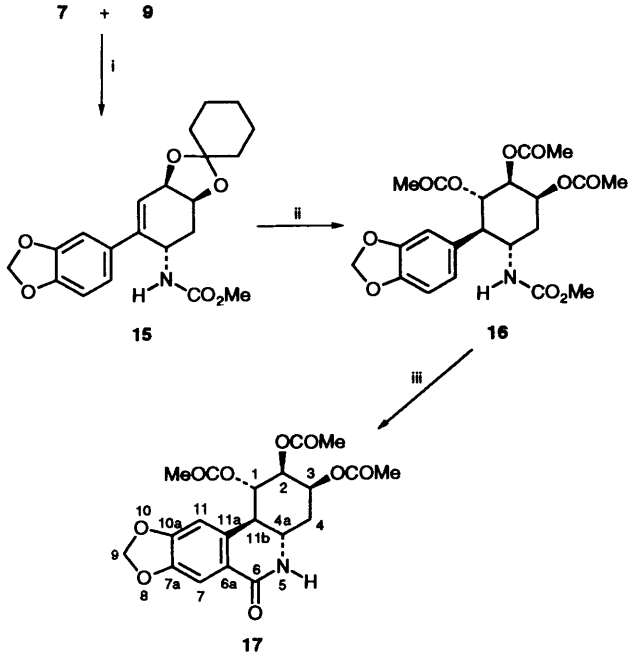


Fig. 1 ORTEP[18] drawings of compounds **13** and **16** (below) derived from X-ray crystallographic data



Scheme 2 *Reagents and conditions:* i, $Pd(PPh_3)_4$, C_6H_6, EtOH, 2 mol dm^{-3} aq. Na_2CO_3, 80 °C, 24 h; ii, BH_3 (1.2 mol equiv.), THF, 0–18 °C, 6 h then NaOH–H_2O_2, 0–18 °C, 3.5 h then 6 mol dm^{-3} aq. HCl, THF, 18 °C, 12 h then $(MeCO)_2O$, DMAP, C_5H_5N, CH_2Cl_2, 35–18 °C, 10 h; iii, Tf_2O (5 mol equiv.), DMAP (3 mol equiv.), CH_2Cl_2, 0–15 °C, 12 h then 2 mol dm^{-3} aq. HCl, THF, 18 °C, 20 h

Experimental

Methyl (3a'SR,5'SR,7a'RS)-6'-*Bromospiro*[*cyclohexane*-1,2'-3a',4',5',7a'-*tetrahydro*-1',3'-*benzodioxole*]-5'-*carbamate* **7** *and Methyl* (3a'SR,4'SR,7a'RS)-5'-*Bromospiro*[*cyclohexane*-1,2'-3a',4',7',7a'-*tetrahydro*-1',3'-*benzodioxole*]-4'-*carbamate* **8**.—A mixture of the cyclopropane **6** (11.0 g, 31.3 mmol), freshly prepared AgOCN (18.8 g, 125 mmol) and anhydrous 1,4-dioxane (200 cm^3) was heated at reflux under a nitrogen atmosphere for 5 days. During this time, every effort was made to ensure that the reaction mixture was not exposed to any source of light. NaOMe (20 cm^3 of a 0.1 mol dm^{-3} solution in methanol) was then added to the cooled reaction mixture and stirring at *ca.* 18 °C was continued for 12 h. The reaction mixture was then filtered through a 1 cm deep plug of TLC grade silica gel which was eluted with Et_2O (200 cm^3). The combined filtrates were concentrated under reduced pressure to give a light brown oil. This material was then subjected to MPLC (silica, CH_2Cl_2–Et_2O–hexane, 1:3:6 elution).

Concentration of the fractions (R_f 0.2) containing the less mobile component afforded a white solid, which was recrystallised (Et_2O–hexane) to give the *carbamate* **7** (2.92 g, 28%) as white rods, m.p. 153–154.5 °C (Found: C, 48.6; H, 5.9; Br, 23.3; N, 4.3%; M^+, 345.0584. $C_{14}H_{20}{}^{79}BrNO_4$ requires C, 48.6; H, 5.8; Br, 23.1; N, 4.1%; *M*, 345.0576); ν_{max}(KBr)/cm^{-1} 3294, 2937, 1699, 1545, 1301, 1111 and 1063; $\delta_H[(CD_3)_2CO$, 50 °C] 6.35 (1 H, br s), 6.09 (1 H, m), 4.52–4.44 (3 H, complex m), 3.62 (3 H, s), 2.41 (1 H, dt, *J* 14 and 5), 2.04 (1 H, m), 1.57 (8 H, m) and 1.38 (2 H, br s); $\delta_C[(CD_3)_2CO$, 50 °C] 157.3, 131.5, 129.5, 110.2, 73.7, 72.7, 52.1, 49.4, 38.6, 36.6, 34.0, 25.8, 24.7 and 24.6; *m/z* (70 eV) 347 (15%), 345 (15, M^+), 266 [28, $(M - Br)^+$], 232 (31), 230 (33), 208 (62), 206 (63), 76 (100) and 54 (93).

Concentration of the fractions (R_f 0.3) containing the more mobile component afforded the *carbamate* **8** (4.33 g, 40%) as a colourless oil (Found: M^+, 345.0584. $C_{14}H_{20}{}^{79}BrNO_4$ requires *M*, 345.0576); ν_{max}(NaCl)/cm^{-1} 2932, 1709, 1527, 1447, 1363, 1249, 1092 and 1037; $\delta_H[(CD_3)_2CO]$ 6.65 (1 H, br s), 6.19 (1 H, m), 4.49 (1 H, m), 4.35–4.27 (2 H, complex m), 3.60 (3 H, br s), 2.59 (1 H, dm, *J* 18), 2.34 (1 H, dddd, *J* 18, 7, 3 and 1), 1.62–1.45 (8 H, br s) and 1.35 (2 H, br s); $\delta_C[(CD_3)_2CO]$ 157.4, 130.2, 121.4, 109.3, 79.2, 71.6, 57.2, 52.1, 37.7, 35.0, 30.6, 25.8, 24.6 and 24.4; *m/z* (70 eV) 347 (7%), 345 (7, M^+), 304 (37), 302 [38, $(M - HNCO)^+$], 266 [42, $(M - Br)^+$], 232 (21), 230 (21), 200 (18), 198 (18), 168 (52), 140 (67), 76 (54) and 53 (100).

Acknowledgements

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