Construction of the colchicine framework *via* two consecutive cyclopropane-mediated ring-expansion reactions

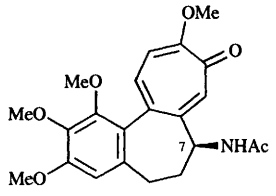
Martin G. Banwell,*[a] Mariana Berak[b] and David C. R. Hockless[a]

[a] *Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 0200, Australia*
[b] *School of Chemistry, The University of Melbourne, Parkville, Victoria 3052, Australia*

1 PERKIN COMMUNICATION

The seven-membered B- and C-rings of tropone 19, a molecule which embodies the framework of the alkaloid colchicine 1, have both been constructed *via* cyclopropane-mediated expansion of a six-membered ring precursor.

Colchicine **1**, an alkaloid isolated from various sources including the meadow saffron *Colchicum autumnale*,[1] is the prototypic anti-mitotic agent and has been investigated as a drug for the treatment of various human diseases including glaucoma,[2] multiple sclerosis,[3] hepatitis B[4] and HIV-1 and -2.[5] It is now used clinically to combat the effects of both gout and familial Mediterranean fever[1] and is also undergoing clinical development, at Abbott Laboratories and Merck Human Health Division, as an agent for treatment of the liver disease primary sclerosing cholangitis.[6]



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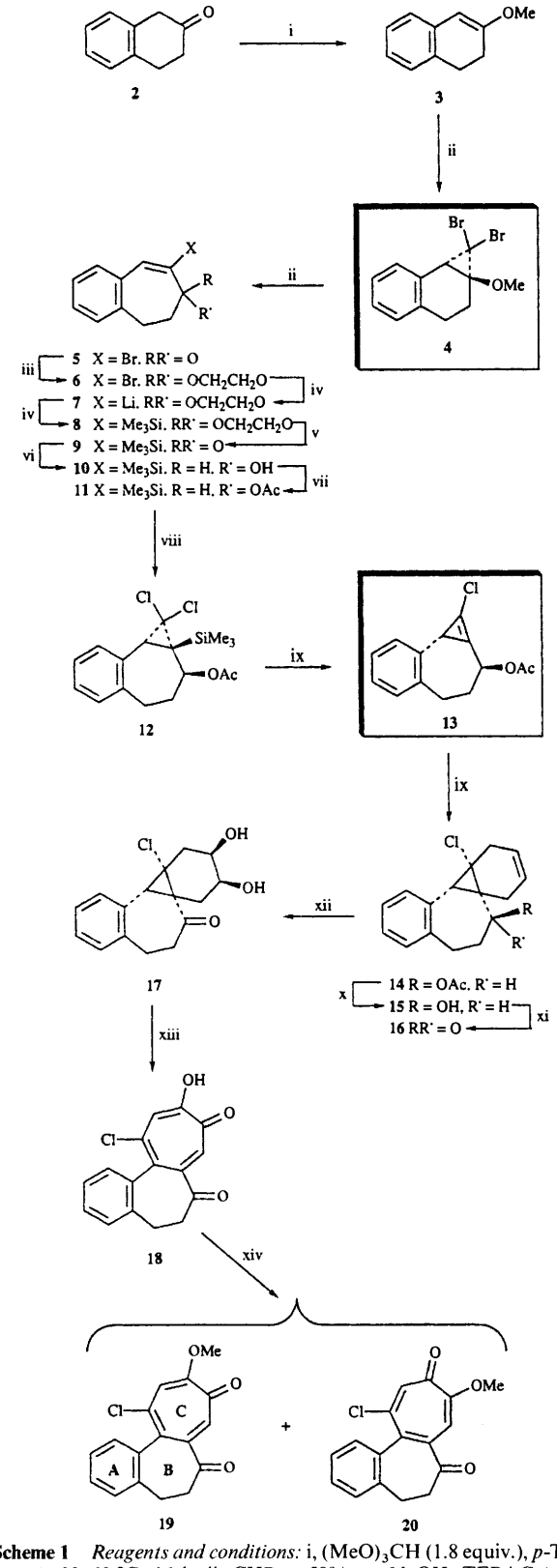
As a result of its intriguing biological activity and novel molecular architecture, colchicine has been the subject of numerous synthetic studies. To date more than a dozen syntheses of **1** have been reported.[7] However, a significant proportion of these are only formal total syntheses since they rely on the acquisition of an advanced intermediate associated with the original (1959) synthesis of **1**. Consequently, interest in developing flexible new methods for construction of the colchicine framework remains high[8] especially because of the need to prepare, in an economical manner, colchicinoids with substitution patterns other than those available through manipulation of the natural product itself. We now report a novel synthesis of the colchicine framework in which both seven-membered rings are constructed *via* cyclopropane-mediated ring-expansion of a six-membered ring. The reaction sequence used is relatively straightforward but potentially highly flexible and permits ready introduction of a C-7 substituent, as required for anti-mitotic activity in colchicinoids.[1]†

The synthesis (Scheme 1) starts with commercially available β-tetralone **2** which is quantitatively converted into the enol ether **3** (100%) using conditions defined by Heesing and co-workers.[9] Reaction of this latter compound with phase-transfer generated dibromocarbene presumably gives adduct **4** as the primary reaction product, but this material undergoes *in situ* ring-expansion to afford, after aqueous acid work-up, the benzocycloheptenone **5**[10] (36%, mp 75–76 °C). Compound **5** was readily converted into the corresponding ethylene acetal, **6**‡ (85%, mp 91–92 °C) which was, in turn, subjected to treatment with Bu^{t}Li and trimethylsilyl chloride thereby affording, *via* the lithiated intermediate **7**, the alkenylsilane **8** (85%). Dichlorocarbene addition to the double bond associated with this last compound could not be effected under a variety of conditions and this outcome is attributed to the steric congestion within the molecule. As a consequence the acetal protecting group associated with compound **8** was removed, but the double bond within the resulting enone **9** (100%) was also unreactive towards dichlorocarbene, probably because of deactivation by the conjugated carbonyl group. Such problems were eventually overcome by selective 1,2-reduction of the enone **9** using the Luche reagent[11] and protecting the resultant allylic alcohol **10**§ (99%) as the corresponding acetate **11** (90%). This last compound then underwent smooth dichlorocarbene addition to give a single adduct **12** (89%, mp 126–127 °C). Treatment of cyclopropane **12** with tetrabutylammonium fluoride (TBAF) resulted in formation of the 1,3-ring-fused cyclopropene **13**, which was trapped in a Diels–Alder reaction with buta-1,3-diene to give the tetracyclic adduct **14** (61%, mp 108–109 °C) as the major reaction product.[12] In anticipation of potential problems associated with acyl group migration as a result of dihydroxylation of the norcarenyl double bond, the acetate group within compound **14** was removed hydrolytically and the resulting alcohol **15** (95%, mp 127–128 °C) oxidised to ketone **16** (95%, mp 124–125 °C) with pyridinium chlorochromate (PCC). This last compound then underwent smooth and diastereofacially selective *cis*-dihydroxylation on treatment with trimethylamine *N*-oxide (TMANO) and catalytic amounts of osmium tetroxide.[13] The diol **17** (77%, mp 202–203 °C) formed in this manner was subjected to single-crystal X-ray

† We have chosen to introduce a carbonyl group at C-7 because (i) colchicone (5,6-dihydro-1,2,3,10-tetramethoxybenzo[*a*]heptalene-7,9-dione) is itself a natural product (T. H. Al-Tel, M. H. Abu Zarga, S. S. Sabri, A. J. Freyer and M. Shamma, *J. Nat. Prod.*, 1990, **53**, 623) which is assuming increasing pharmacological significance (A. Brossi, personal communication to M. G. B.) and (ii) colchicone can be reduced to the corresponding C-7 alcohol [albeit non-enantioselectively (S. C. Peters and M. G. Banwell, unpublished observations; M. G. Banwell, S. C. Peters, R. J. Greenwood, M. F. Mackay, E. Hamel and C. M. Lin, *Aust. J. Chem.*, 1992, **45**, 1577)] which can, in turn, be converted into the C-7 acetamido group (see M. G. Banwell, *Pure Appl. Chem.*, 1996, **68**, 539) as required in colchicine **1**.

‡ All new compounds had spectroscopic data [IR, UV (where appropriate) and NMR and 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. The yields of new compounds are unoptimised.
§ All new compounds possessing one or more stereogenic centres are racemic but, for the sake of simplicity, only one enantiomer is shown.



Scheme 1 *Reagents and conditions:* i, $(MeO)_3CH$ (1.8 equiv.), *p*-TsOH (trace), 20–60 °C, 16 h; ii, $CHBr_3$, 50% aq. NaOH, TEBAC (trace), 60 °C, 11 h, then H_3O^+ work-up; iii, $HOCH_2CH_2OH$ (4.0 equiv.), *p*-TsOH (trace), C_6H_6, reflux, 3 h; iv, TMSCl (4.0 equiv.), TMEDA (10.5 equiv.), THF, −100 °C then 1.7 M Bu^{t}Li in pentane (2.0 equiv.), −100 to 0 °C, 3 h; v, $(CO_2H)_2$ (3.2 equiv.), H_2O–CH_2Cl_2 with trace EtOH, 50 °C, 8 h; vi, $NaBH_4$ (1.7 equiv.), $CeCl_3{\cdot}7H_2O$ (1.1 equiv.), CH_3OH, 0–18 °C, 0.75 h; vii, Ac_2O (3.5 equiv.), DMAP (0.03 equiv.), pyridine, 5 °C, 40 h; viii, $CHCl_3$, 50% aq. NaOH, TEBAC (trace), 0–18 °C, 48 h; ix, buta-1,3-diene (*ca.* 30 equiv.), TBAF (1.3 equiv.), THF, 18 °C, 0.5 h; x, KOH (30 equiv.), MeOH, 0–18 °C, 1 h; xi, PCC (2.6 equiv.), CH_2Cl_2, 0–18 °C, 3 h; xii, OsO_4 (1 mol%), TMANO (1.05 equiv.), Bu^{t}OH, H_2O, pyridine, 83 °C, 8 h; xiii, $(F_3CCO)_2O$ (2.9 equiv.), DMSO, CH_2Cl_2, −60 °C, 1.5 h, then NEt_3 (7 equiv.), −60 °C, 1.5 h; xiv, $(MeO)_2SO_2$ (54 equiv.), K_2CO_3 (18 equiv.), Me_2CO, 18 °C, 14 h

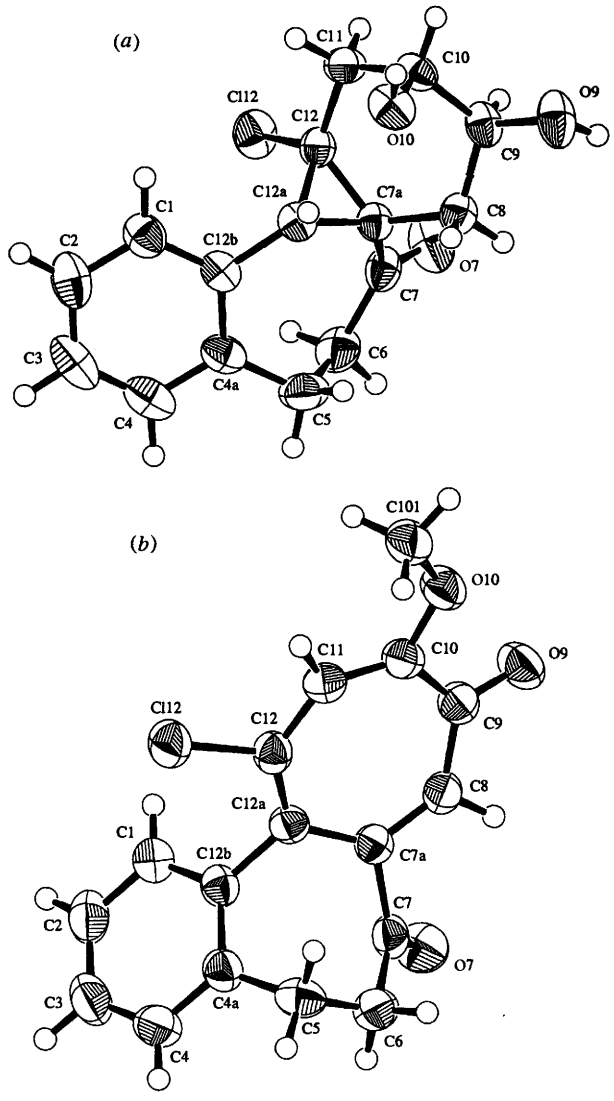


Fig. 1 ORTEP drawings of (*a*) compound **17** and (*b*) compound **19**, derived from X-ray crystallographic data

analysis [Fig. 1(*a*)],¶ thereby establishing the illustrated stereochemistries within all of compounds **12** to **17**. Treatment of the diol with the Swern reagent derived from trifluoroacetic anhydride and DMSO[14] resulted in formation of the tropolone **18**,[15] which was immediately subjected to *O*-methylation using dimethyl sulfate (DMS) and potassium carbonate. In this

¶ *Crystal data* for compound **17**: $C_{16}H_{17}ClO_3$, M = 292.76, T = 213(1) K, triclinic, space group $P\bar{1}$, a = 7.1122(7), b = 9.6596(9), c = 11.244(1) Å, α = 104.067(8), β = 102.759(9), γ = 103.555(8)°, U = 696.1(1) Å^3, D_c (Z = 2) = 1.397 g cm^{-3}, F(000) = 308, μ(Cu-Kα) = 24.89 cm^{-1}, semi-empirical absorption correction; 2063 unique data ($2\theta_{max}$ = 120.1°), 1535 with $I > 3\sigma(I)$; R = 0.035, wR = 0.035, GOF = 1.68.

For compound **19**: $C_{17}H_{13}ClO_3$, M = 300.74, T = 295(1) K, orthorhombic, space group *Pbca*, a = 11.752(2), b = 9.001(1), c = 26.863(2) Å, U = 2841(1) Å^3, D_c (Z = 8) = 1.406 g cm^{-3}, F(000) = 1248, μ(Cu-Kα) = 24.62 cm^{-1}, semi-empirical absorption correction; 2451 unique data ($2\theta_{max}$ = 120.1°), 1381 with $I > 3\sigma(I)$; R = 0.037, wR = 0.029, GOF = 1.77.

Data were measured on a Rigaku AFC6R rotating anode diffractometer (graphite crystal monochromator, λ = 1.541 80 Å). Refinement was by full-matrix least-squares analysis on F using the TEXSAN structure analysis software of Molecular Structure Corporation.[16] Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/48.

manner a 6:1 mixture of compound **19** (mp 229–230 °C) and **20** (mp 198–199 °C) (42% combined yield from **17**) was obtained. These two compounds were readily separated from one another by chromatography on silica gel and the structure of compound **19** was confirmed by X-ray crystallography [Fig. 1(*b*)].¶ Troponoid **19** embodies the complete carbocyclic framework associated with colchicine **1**.

Experimental

5-Acetoxy-11c-chloro-1,4,6,7,11b,11c-hexahydro-5*H*-benzo[*c*]-benzo[2,3]cyclopropa[1,2-*a*]cycloheptene 14

A solution of cyclopropane **12** (354 mg, 0.99 mmol) in THF (5 cm^3) was placed in an Ace™ pressure tube. The tube and its contents were cooled to −30 °C and butadiene (3 cm^3) was then condensed into it. TBAF (1.3 cm^3 of a 1.0 M solution in THF, 1.28 mmol) was added and the tube sealed whilst the contents were still frozen. The reaction mixture was then warmed to room temperature and subjected to magnetic stirring for 0.5 h before being re-cooled to −30 °C. The tube was then opened (fumehood), the thawed contents poured onto water (20 cm^3) and the resulting mixture extracted with CH_2Cl_2 (3 × 20 cm^3). The combined extracts were dried, filtered and concentrated under reduced pressure to afford a brown oil which was subjected to flash chromatography (silica, 9:1 hexane–EtOAc elution). Concentration of the appropriate fractions (R_f 0.4) gave a light brown oil which was subjected to preparative TLC (silica, 9:1 hexane–EtOAc elution). Extraction of the major band then gave compound **14** (184 mg, 61%) as a white solid which could be subjected to the next step of the reaction sequence. A portion of this material was further purified by semi-preparative HPLC (Waters μ-porasil column, 9:1 hexane–EtOAc elution, flow rate 2.0 cm^3 min^{-1}) which provided, after concentration of the appropriate fractions (R_t 13.5 min), a spectroscopically pure sample of compound **14** as white crystalline masses, mp 108–109 °C (Found, $M^{+\cdot}$, 302.1067. $C_{18}H_{19}{}^{35}ClO_2$ requires $M^{+\cdot}$, 302.1074); ν_{max}(KBr)/cm^{-1} 2910, 1733, 1240 and 1026; δ_H(300 MHz) 7.25–7.10 (4 H, complex m, aromatic Hs), 5.67 (1 H, m, H2 or H3), 5.59 (1 H, m, H3 or H2), 4.76 (1 H, dd, *J* 11 and 7,‖ H5), 3.10 (1 H, m), 2.96–2.79 (3 H, complex m), 2.61 (1 H, dd, *J* 13 and 7), 2.49 (1 H, complex m), 2.40 (1 H, s, H11b), 2.21 (1 H, apparent septet, *J ca.* 7), 2.01 (3 H, s, $OCOCH_3$) and 1.77 (1 H, complex m); δ_C(75 MHz) 169.5 ($OCOCH_3$), 139.4, 134.3, 131.0, 128.9, 127.3, 126.5, 123.7, 123.5, 73.1, 52.1, 36.3, 30.2, 28.1, 27.6, 26.9, 24.1 and 21.2; *m/z* (EI, 70 eV) 302 (0.3%), 267 [0.8, $(M - Cl^{\cdot})^+$], 242 [11, $(M - AcOH)^{+\cdot}$], 207 [16, $(M - AcOH - Cl^{\cdot})^+$], 141 (89) and 130 (100).

‖ *J* Values in Hz.

Acknowledgements

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