A Fully Regiocontrolled Synthesis of Desacetamidoisocolchicine: Formal Total Synthesis of Colchicine

Martin G. Banwell,*[a] John N. Lambert,[a] Jacqueline M. Gulbis[b] and Maureen F. Mackay[b]

[a] *School of Chemistry, The University of Melbourne, Parkville, Victoria 3052, Australia*
[b] *Department of Chemistry, La Trobe University, Bundoora, Victoria 3083, Australia*

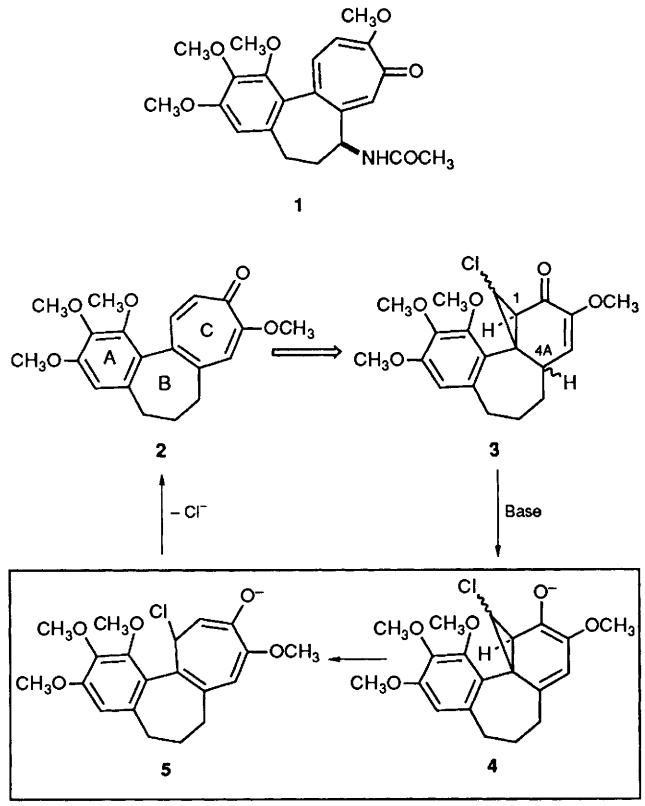
The tetracyclic compound **3a**, which has been synthesised in nine steps from the known cyclohexenone **6**, reacts with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give desacetamidoisocolchicine **2** in 84% yield; the acquisition of **2** constitutes a formal total synthesis of the alkaloid colchicine **1**.

The tropolone alkaloid colchicine **1**, isolated from various sources including the meadow saffron *Colchicum autumnale*, displays potent antimitotic properties and has been used in the treatment of gout,[1] Familial Mediterranean Fever,[1] glaucoma[2] and HIV-1 and -2.[3] In view of its unusual structural features and interesting pharmacological profile, much effort has been devoted to the synthesis of colchicine **1** and its congeners. Thirteen total or formal total syntheses of this compound have been reported to date[4,5] and nine of these rely on the acquisition of desacetamidoisocolchicine **2**, an advanced intermediate on Eschenmoser's original route[4] to the natural product. In connection with our own efforts to develop efficient and flexible routes to colchicine and related molecules,[6,7] we now report a strategy for the regiocontrolled preparation of **2**, which should be amenable to the synthesis of analogues. In contrast to previously reported[4,5] syntheses of desacetamidoisocolchicine, in the present work the troponoid C-ring has been generated directly in the final step by a process that delivers the seven-membered conjugated carbocycle with the appropriate substitution pattern and at the correct oxidation level.

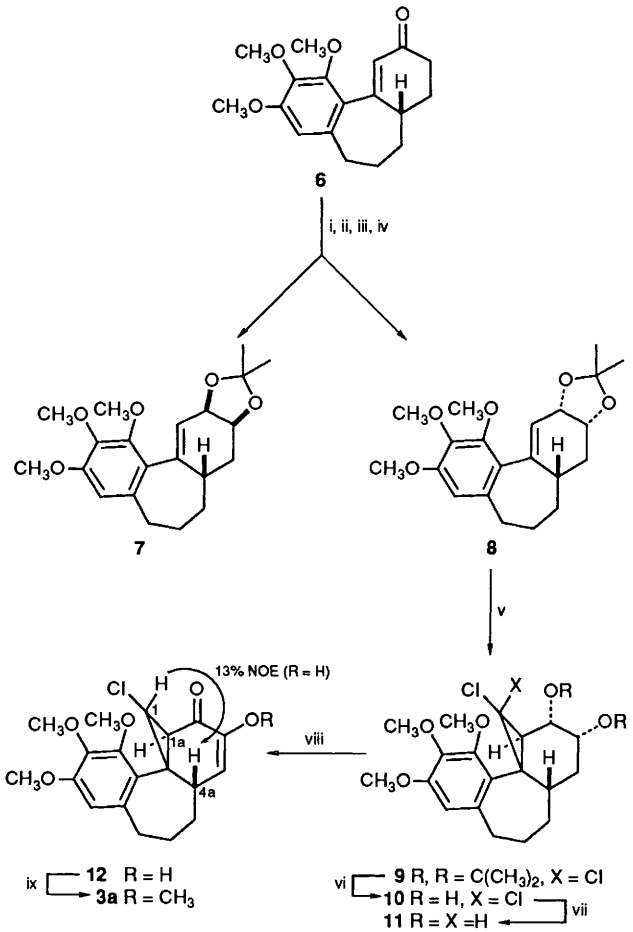
On the basis of earlier work associated with the synthesis of troponoid compounds,[7] we expected that the tetracyclic α-methoxyenones **3** would serve as precursors to desacetamidoisocolchicine **2** (Scheme 1). Specifically, it was anticipated that treatment of the former compounds with base would produce the extended enolates **4**, which should, in turn, undergo electrocyclic ring-opening to give cycloheptatriene **5**. Finally, elimination of chloride ion from intermediate **5** would produce the fully conjugated product **2**. These mechanistic proposals lead to the conclusion that any one of the four diastereoisomers represented by structure **3** should react to give cycloheptatriene **5** and, therefore, function as a precursor to the target troponoid **2**.

The synthetic route employed in preparing compound **3** (and which ultimately provided isomer **3a**) is outlined in Scheme 2. Thus, treatment of the readily available tricyclic enone **6**† with manganese triacetate in refluxing benzene[9]

† Compound **6** has been prepared[8] by Robinson annulation of 6-hydroxymethylene-6,7,8,9-tetrahydro-2,3,4-trimethoxy-5*H*-benzocyclohepten-5-one (J. D. Hardstone and K. Schofield, *J. Chem. Soc.*, 1965, 5194) with 3-buten-2-one.



Scheme 1



Scheme 2 *Reagents and conditions*: (i), $Mn(OCOCH_3)_3$ (6.5 equiv.), benzene, reflux, 18 h; (ii), $NaBH_4$, $CeCl_3 \cdot 6H_2O$, CH_3OH, 0 °C, 0.5 h; (iii), KOH, CH_3OH, 0 °C, 0.5 h; (iv), $(CH_3)_2CO$, trace $HClO_4$, 0 °C, 1 h; (v), $Cl_3CCO_2CH_2CH_3$ (20 equiv.), $NaOCH_3$ (20 equiv.), pentane, 0–18 °C, 2–5 h; (vi), 4 : 1 CH_3OH/10 M aq. HCl, 0–18 °C, 1 h; (vii), Zn (120 equiv.), KOH (70 equiv.), CH_3CH_2OH, reflux, 5 h; (viii), $(CH_3)_2SO$ (9 equiv.), oxalyl chloride (3.5 equiv.), −60 °C, 15 min, then $(CH_3CH_2)_3N$ (14 equiv.); (ix), K_2CO_3 (16 equiv.), $(CH_3O)_2SO_2$ (23 equiv.), $(CH_3)_2CO$, 18 °C, 14 h.

resulted in the formation of a *ca.* 1 : 1 mixture of diastereoisomeric α′-acetoxylated products (79%), which could be separated chromatographically. Subjection of the more mobile isomer (m.p. = 172–174 °C)‡ to sequential treatment with sodium borohydride/cerium trichloride,[10] methanolic potassium hydroxide then acetone/perchloric acid resulted in the formation of the unsaturated acetonide **7** (m.p. = 95–97.5 °C) (73%). Application of an analogous reaction sequence to the chromatographically less mobile α′-acetoxyenone (m.p. = 121–123 °C) derived from **6** provided the isomeric acetonide **8** (m.p. = 60–62 °C) (82%). In both compounds **7** and **8** irradiation of the allylic hydrogen associated with the dioxolane moiety results in an NOE of *ca.* 5–6% for the adjacent hydrogen of the heterocyclic ring. This result suggests each isomer possesses the same relative stereochemistry between these pairs of hydrogens. Furthermore, the observation of a vicinal coupling constant of 6 Hz for these hydrogens suggests a *cis*-relationship between them[11] and, therefore, *cis*-ring-fusion in compounds **7** and **8**.

Reaction of compound **7** with ethyl trichloroacetate and sodium methoxide[12] failed to give any material derived from dichlorocarbene addition to the double bond. The product from this reaction (m.p. = 157–158 °C) (*ca.* 30%) had incorporated the elements of dichlorocarbene (presumably *via* an insertion process) but its structure has not been established unequivocally to date. In contrast, subjection of isomer **8** to the same conditions gave the dichlorocyclopropane **9** (m.p. = 102.5–103.5 °C) (71%), the structure of which has been confirmed by X-ray crystallographic methods (Fig. 1).§ This structure determination also establishes the relative stereochemistry between all the methine hydrogens in acetonide **8**

‡ All new compounds are racemic, however only one enantiomer is depicted for clarity. All new substances had spectroscopic data [IR, NMR, mass spectrum and UV (where appropriate)] consistent with the assigned structure. Satisfactory combustion and/or high resolution mass spectral analytical data were obtained for new compounds. Unless otherwise specified, yields refer to isolated compounds.

§ *Crystal data* for **9**: $C_{22}H_{28}Cl_2O_5$, M = 439.3, monoclinic, space group $C2/c$, a = 28.885(3), b = 7.561(1), c = 22.815(3) Å, β = 119.57(1)°, U = 4333.8(8) Å^3, $F(000)$ = 1872, Z = 8, D_m = 1.339(5), D_c = 1.346 g cm^{-3}, μ = 28.3 cm^{-1} (Cu-Kα). Intensities were recorded for 4129 unique reflections by a θ/2θ scan to a $2\theta_{max}$ 130° on a Siemens AED-3-circle diffractometer with Ni-filtered Cu-Kα radiation (λ = 1.5418 Å) at 296(1) K. The intensities were corrected for Lorentz and polarisation factors and for absorption. The structure was solved by direct methods (SHELXS-86)[15] and full-matrix refinement (SHELX76)[16] converged at R = 0.051, R_w = 0.074, S = 1.65 (316 parameters varied) for 3140 data ($I \geq 2\sigma I$). The non-H atoms were given anisotropic temperature factors, the methyl H-atoms were included at idealised positions (U = 0.112(4) Å^2), and the remaining H-atoms given individual isotropic temperature factors and their parameters varied. The function minimised was $w(|F_o| - |F_c|)^2$ with $w = (\sigma|F_o|^2 + 0.0013|F_o|^2)^{-1}$. At convergence $(\Delta\rho)_{max}$ = +0.31 and $(\Delta\rho)_{min}$ = −0.34 e Å^{-3}. An isotropic extinction parameter of the form $F_c = F[1 - 1.3 \times 10^{-7}|F|^2/\sin\theta]$ was applied to the calculated structure amplitudes. 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.

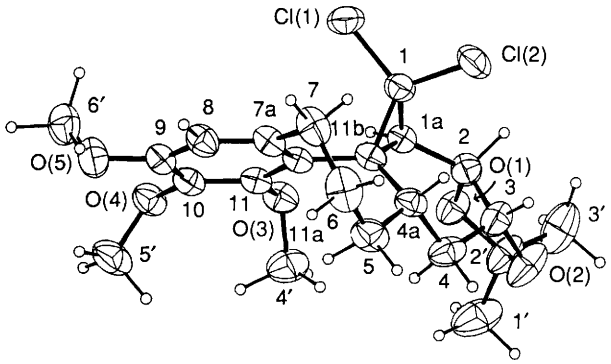


Fig. 1 ORTEP drawing of dichlorocyclopropane **9**

and, by implication, isomer **7**. Removal of the acetonide protecting group in **9** was readily achieved with aqueous acid and the resulting dichlorodiol **10** (95%) was subjected to reductive dechlorination[13] (using zinc in ethanolic potassium hydroxide) thereby providing the monochlorocyclopropane **11** (m.p. = 147.5–148.5 °C) (74%). Swern oxidation of diol **11**[14] gave the hydroxyenone **12** (m.p. = 129.5–131 °C) in an unoptimised yield of 25%. The observation of a 13% NOE at H-4a in **12** upon irradiation of H-1 indicated that the chlorine resides on the face of the cyclopropane ring closer to the aromatic methoxy groups in both this compound and the precursor diol **11**. *O*-Methylation (dimethyl sulphate/potassium carbonate) of hydroxyenone **12** then afforded the target compound **3a** (m.p. = 102–104 °C) (69%).‡ The observation of a vicinal coupling constant of 4.5-Hz between H-1 and H-1a in compounds **12** and **3a**, which suggests a *trans*-relationship between these cyclopropyl hydrogens,[15] lends further support to the stereochemical assignment at C-1.

As expected,[7] reaction of a benzene solution of **3a** with ten molar equivalents of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature resulted in its smooth conversion (48 h) into **2** (84%) (m.p. = 148.5–149 °C; lit.[4b] m.p. = 147–148 °C). The material obtained in this manner displayed spectroscopic properties consistent with the assigned structure and in good agreement¶ with those reported[4b] earlier by Evans and co-workers for deacetamidoisocolchicine **2**.

¶ There are two minor errors in the ^{13}C NMR data reported[4b] for **2**: the resonances at δ 133.1 and 141.2 should appear as doublets (and not singlets). The ^{13}C NMR data obtained at 100 MHz on our own sample of **2** are as follows: δ ($CDCl_3$) 30.8(t), 33.1(t), 37.5(t), 56.0(q), 56.1(q), 60.8(q), 61.2(q), 107.3(d), 116.9(d), 127.0(s), 133.3(d), 135.4(s), 135.8(s), 140.9(s), 141.3(d), 144.1(s), 150.5(s), 153.3(s), 163.3(s), 179.4(s).

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