A Biomimetic and Fully Regiocontrolled Total Synthesis of (±)-Colchicine

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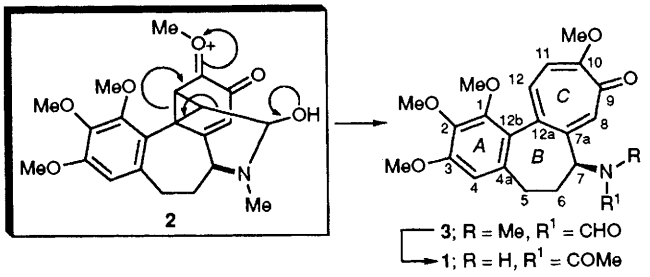
The first fully regiocontrolled total synthesis of the alkaloid colchicine **1** is described; the key step of the reaction sequence is the efficient biomimetic conversion of the σ-homo-*o*-benzoquinone monoacetal **11** into the α-tropolone-*O*-methyl ether **13**.

Despite extensive efforts over the last three and a half decades, a fully regiocontrolled total synthesis[1] of the potent antimitotic agent[2] colchicine **1** has remained elusive. The first synthesis of the alkaloid, described[1a] by Eschenmoser and Schreiber in 1959, highlighted two key problems that, hitherto, have not been resolved simultaneously within the one reaction sequence. Site-selective introduction of the C-7 acetamido group in **1** has been somewhat problematical, although solutions have been advanced by Nakamura,[1c] Woodward[1d] and Evans.[1e] The second difficulty stems from the rapid equilibrium between the two major tautomeric forms of colchiceine (10-demethylcolchicine), the free tropolone which is the final intermediate in all previous total syntheses of **1**. As a result of this equilibrium, *O*-methylation of colchiceine affords a *ca.* 1:1 mixture of colchicine and isocolchicine, the latter product differing from **1** in that the positions of the methoxy and carbonyl moieties (as well as the associated double-bonds) in ring-*C* are reversed.

We now describe a total synthesis of (±)-colchicine in which these longstanding problems of regiochemical control have been overcome. A key feature of the present work has involved mimicking the final stages of the proposed biosynthesis of **1** (Scheme 1).[3] Specifically, it was anticipated that treatment of the acetal **11** (Scheme 2) with acid would generate the *O*-methylated σ-homo-*o*-benzoquinone **12** which should undergo a biomimetic fragmentation[4] (*cf.* **2**→**3**, Scheme 1) to give, after proton loss, the colchicinoid **13**.

The synthesis of the key acetal **11** is shown in Scheme 2. Thus, the *tert*-butyldimethyl silyl ether **4**‡ of 5-bromo-2-methoxyphenol[5] was subjected to a halogen–metal exchange reaction with n-butyllithium and the resulting organometallic **5** quenched with 3-(3′,4′,5′-trimethoxyphenyl)propanal.[6] Attempts to convert the ensuing alcohol **6** into the tricyclic system **9**, *via* intramolecular oxidative coupling,[6] were unsuccessful due to a competing cyclialkylation reaction. However, treatment of **6** with tetra-n-butylammonium fluoride afforded the free phenol **7** (m.p. 142–144 °C) (61% yield from **4**) which, following procedures developed by Umezawa and coworkers,[7] was oxidised with lead tetraacetate to give an inseparable



Scheme 1 Final stages in the biosynthesis of colchicine

ca. 1:1 mixture of **8** (100%). Reaction of these latter compounds with trifluoroacetic acid then afforded the desired **9** (m.p. 220–225 °C) (42%). Treatment of **9** with thallium(III) nitrate in methanol at −20 °C[8] then provided the expected cyclohexadienone **10** (m.p. 160–162 °C) (97%) the structure of which was confirmed by single-crystal X-ray analysis (Fig. 1).§ Nucleophilic cyclopropanation of compound **10** with dimethylsulfoxonium methylide[9] proceeded both regio- and stereo-selectively to give a single tetracyclic compound **11** (m.p. 164–168 °C) (75% at 82% conversion)¶ but the stereochemical relationship between the hydroxy and cyclopropyl moieties has not been established unequivocally to date. Treatment of **11** with 16 equiv. of trifluoroacetic acid in dichloromethane at room temperature resulted in the smooth generation of 7-hydroxydesacetamidocolchicine **13**[10] (m.p. 227–230 °C) (89% at 53% conversion) which was identical in all respects with an authentic sample.‖ Presumably the high yields associated with this conversion derive, at least in part, from the capacity of the trimethoxyphenyl moiety to stabilise the carbocation resulting from cyclopropane ring-cleavage in **12**. Conversion of **13** into (±)-colchicine was accomplished

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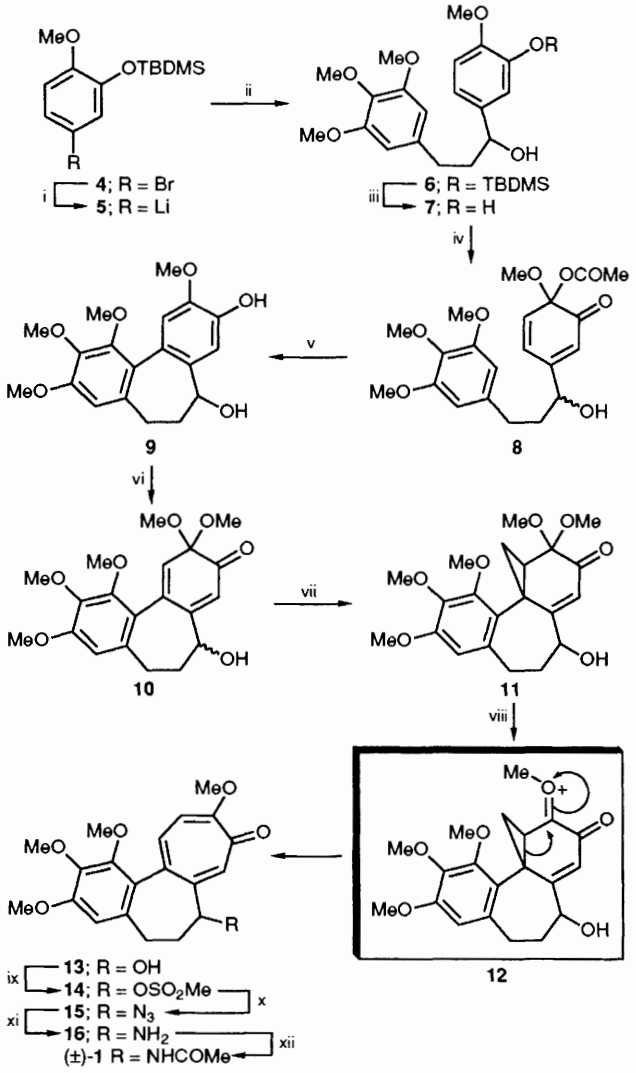
‡ All new compounds, except **4**, were racemic but only one enantiomer is depicted for clarity. All new substances had spectroscopic data (IR, NMR and mass spectrum) consistent with the assigned structure. Satisfactory combustion and/or high resolution mass spectral analytical data were obtained for new compounds.

§ *Crystal data* for **10**: $C_{20}H_{24}O_7$, M = 376.4, monoclinic, space group $P2_1/c$, a = 9.412(3), b = 9.438(2), c = 21.866(5) Å, β = 92.32(2)°, U = 1941(1) Å^3, $F(000)$ = 800, Z = 4, D_m 1.29(1), D_c 1.288(1) g cm^{-3}, μ 7.73 cm^{-1} (Cu-Kα). Intensities were recorded for 3374 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 292(1) K. Intensity data were corrected for Lorentz and polarisation effects, but no correction was made for absorption. The structure was solved by direct methods using XTAL3.0[13] and full-matrix least-squares refinements carried out with SHELX76[14] converged at R = 0.037, R_w = 0.045 for 1433 terms with $I \geq 2\sigma I$. The non-H atoms were given anisotropic temperature factors. The H atoms at C(5), C(1′) and C(4′) were included at idealised positions with those at C(1′) and C(4′) given a common isotropic temperature factor [U = 0.136(8) Å^2]. The remaining H atoms were given individual isotropic temperature factors and their parameters varied. The function minimised was $\Sigma w(|F_o| - |F_c|)^2$, with $w = [\sigma^2|F_o| + 0.00041\,|F_c|^2]^{-1}$. At convergence (Δρ) max, (Δρ) min, +0.12, −0.15 e Å^{-3}. An isotropic extinction correction of the form $F_c = F\{1 - 1.082 \times 10^{-6}|F|^2/\sin\theta\}$ 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.

¶ *Selected spectral data* for **11**: ^{13}C NMR (100 MHz, $CDCl_3$, 22 °C) δ 188.9, 169.9, 152.9, 152.8, 141.2, 137.1, 122.4, 115.1, 108.2, 95.8, 71.2, 62.1, 61.1, 56.0, 50.8, 49.1, 34.5, 33.6, 28.9, 28.2, 24.8; ^{1}H NMR (400 MHz, $CDCl_3$, 22 °C) δ 6.57 (s, 1H), 6.06 (d, J 1.4 Hz, 1H), 4.03 (m, 1H), 3.87 (s, 3H, OMe), 3.86 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.53 (s, 3H, OMe), 3.31 (s, 3H, OMe), 3.28 (m, 1H), 3.22 (dd, J 9.0 and 7.3 Hz, 1H), 2.67 (dd, J 13.9 and 8.3 Hz, 1H), 2.31 (m, 1H), 1.79 (dd, J 20.0 and 10.7 Hz, 1H), 1.63 (d, J 5.1 Hz, 1H, OH), 1.31 (dd, J 9.0 and 3.9 Hz, 1H), 1.21 (dd, J 7.3 and 3.9 Hz, 1H); MS m/z (EI, 70 eV) 390 (100%) [$M^{+\cdot}$], 347 (41), 101 (94), 75 (75); IR (KBr) ν_{max} cm^{-1} 1670; UV (EtOH) λ_{max}/nm 207 (49, 600), 231 (16, 000), 264 (10, 500).

‖ An authentic sample of **13** was prepared by degrading natural (−)-colchicine (Aldrich) to 7-oxodesacetamidocolchicine [using variations (M. G. Banwell and S. C. Peters, unpublished work) of established procedures (M. A. Iorio, A. Brossi and J. V. Silverton, *Helv. Chim. Acta*, 1978, **61**, 1213)] then reducing the latter compound with sodium borohydride.[10]



Scheme 2 *Reagents and conditions*: i, Bu^{n}Li (1 equiv.), THF, −100 °C, 10 min; ii, 3-(3′,4′,5′-trimethoxyphenyl)propanal (1.5 equiv.), THF, −100 to 18 °C, 16 h; iii, tetra-*n*-butylammonium fluoride (1.1 equiv.), CH_2Cl_2, 3 Å molecular sieves, 0 °C, 0.5 h, 61% from **4**; iv, $Pb(OCOMe)_4$ (1.1 equiv.), CH_2Cl_2, 0 °C, 0.5 h, 100%; v, CF_3CO_2H (50 equiv.), 1:1 C_6H_6–THF, 0 °C, 0.75 h, 42%; vi, $Tl(NO_3)_3$ (1.4 equiv.), MeOH, −20 °C, 0.5 h, 97%; vii, H_2CSOMe_2 (1.1 equiv.), DMSO, 18 °C, 6 h, 75% at 82% conversion; viii, CF_3CO_2H (16 equiv.), CH_2Cl_2, 18 °C, 7 h, 89% at 53% conversion; ix, $MeSO_2Cl$ (1.6 equiv.), Et_3N(2.2 equiv.), CH_2Cl_2, 0 °C, 0.5 h, 100%; x, NaN_3 (5 equiv.), DMSO, 50 °C, 24 h, 85%; xi, H_2 (1 atm), Pd on C, EtOH, 18 °C, 2.5 h; xii, $(MeCO)_2O$ (40 equiv.), pyridine, 18 °C, 5 min, 73% from **15**; THF = tetrahydrofuran; DMSO = dimethyl sulfoxide; TBDMS = Bu^{t}Me$_2$Si

using established methodology.[1b,11] Thus, the mesylate, **14**, derived from **13** was treated with sodium azide and the resulting azido compound **15** (83% yield from **13**) reduced to the corresponding amine **16** which was acetylated to give (±)-colchicine (m.p. 260–264 °C, lit. m.p. 260[12a] and 280 °C[12b]) (73% yield from **15**) identical in all respects with a sample of racemic material (mixed m.p. 260–264 °C) kindly provided by Professor A. Brossi.

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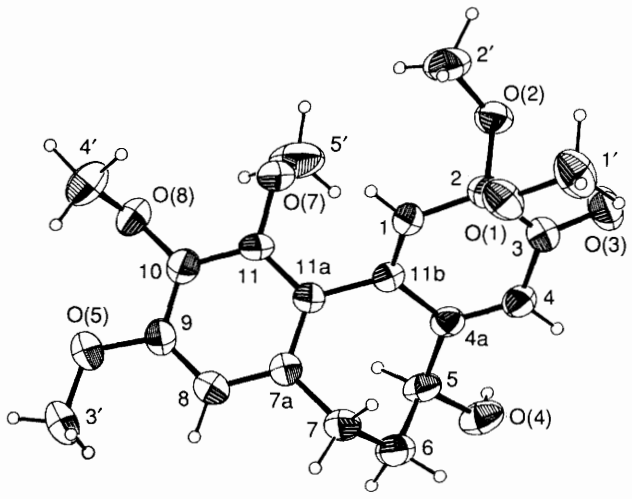

Fig. 1 ORTEP[15] drawing of cyclohexadienone **10** (the C symbol for carbons has been omitted)

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