J. CHEM. SOC., CHEM. COMMUN., 1992

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

Martin G. Banwell,* ^a John N. Lambert, ^a Maureen F. Mackayt^b and Richard J. Greenwood^b

School of Chemistry, The University of Melbourne, Parkville, Victoria 3052, Australia
Department of Chemistry, La Trobe University, Bundoora, Victoria 3083, Australia

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 synthesis¹ of the potent antimitotic agent² 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 (\pm) -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 fragmentation⁴ (cf. 2 \rightarrow 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 $4\ddagger$ of 5-bromo-2methoxyphenol⁵ 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

[‡] 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.

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 °C⁸ 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 methylide9 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 13¹⁰ (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 (\pm) -colchicine was accomplished

§ 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, $\beta = 92.32(2)^\circ$, $U = 1941(1) \text{ Å}^3$, F(000) = 800, Z = 4, $D_m 1.29(1)$, $D_c 1.288(1) \text{ g cm}^{-3}$, μ 7.73 cm^{-1} (Cu-K\alpha). Intensities were recorded for 3374 unique reflections by an ω -2 θ scan, $2\theta_{max}$ 130° on a Rigaku-AFC four circle diffractometer with Cu-Ka radiation (graphite crystal monochromator, $\lambda = 1.5418$ 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 XTAL3.013 and full-matrix least-squares refinements carried out with SHELX76¹⁴ converged at R = 0.037, $R_w = 0.045$ for 1433 terms with $I \ge 2\sigma$ 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 $[U = 0.136(8) \text{ Å}^2]$. The remaining H atoms were given individual isotropic temperature factors and their parameters varied. The function minimised was $\Sigma w(|F_0| - |F_c|)^2$, with $w = [\sigma^2 |F_o| + 0.00041 |F_c|^2]^{-1}$. At convergence $(\Delta \rho) \max, (\Delta \rho) \min,$ +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: ¹³C NMR (100 MHz, CDCl₃, 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; ¹H NMR (400 MHz, CDCl₃, 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⁺], 347 (41), 101 (94), 75 (75); IR (KBr) γ_{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

[†] Author to whom correspondence should be addressed regarding the X-ray crystallographic results.



Scheme 2 Reagents and conditions: i, BunLi (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.), CH₂Cl₂, 0°C, 0.5 h, 100%; v, CF₃CO₂H (50 equiv.), 1:1 C₆H₆-THF, 0°C, 0.75 h, 42%; vi, Tl(NO₃)₃ (1.4 equiv.), MeOH, -20 °C, 0.5 h, 97%; vii, H₂CSOMe₂ (1.1 equiv.), DMSO, 18 °C, 6 h, 75% at 82% conversion; viii, CF₃CO₂H (16 equiv.), CH₂Cl₂, 18 °C, 7 h, 89% at 53% conversion; ix, MeSO₂Cl (1.6 equiv.), Et₃N(2.2 equiv.), CH₂Cl₂, 0°C, 0.5 h, 100%; x, NaN₃ (5 equiv.), DMSO, 50 °C, 24 h, 85%; xi, H₂ (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; $TBDMS = Bu'Me_2Si$

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. 26012a 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.

We thank the Australian Research Council and the Anti-Cancer Council of Victoria (ACCV) for generous financial support. J. N. L. gratefully acknowledges the provision of an ACCV Post-Graduate Research Scholarship. One of us (M. G. B.) would like to acknowledge the interest and encouragement provided by Professor Sir Alan Battersby and Professor Albert Eschenmoser. Dr Steve Peters is thanked for providing a generous sample of 7-oxodesacetamidocolchicine.

Received, 8th April 1992; Com. 2/01876D



Fig. 1 ORTEP15 drawing of cyclohexadienone 10 (the C symbol for carbons has been omitted)

References

- 1 Some of the reported total or formal total syntheses of colchicine are: (a) J. Schreiber, W. Leimgruber, M. Pesaro, P. Schudel, T. Threlfall and A. Eschenmoser, *Helv. Chim. Acta*, 1961, **44**, 540 (total synthesis); (b) E. E. van Tamelen, T. A. Spencer Jr, D. S. Allen and R. L. Orvis, Tetrahedron, 1961, 14, 8 (total synthesis); (c) T. Nakamura, Chem. Pharm. Bull., 1962, 10, 299 (deacetylcolchiceine); (d) R. B. Woodward, The Harvey Lecture Ser., 1963, 59, 31 (total synthesis); (e) D. A. Evans, S. P. Tanis and D. J. Hart, J. Am. Chem. Soc., 1981, 103, 5813 (two syntheses-one total synthesis and one synthesis of desacetamidoisocolchicine); (f) E. Wenkert and H-S. Kim, in Studies in Natural Products Chemistry, Stereoselective Synthesis (Part B), ed. Atta-ur-Rahman, Elsevier, Amsterdam, 1989, vol. 3, p. 5 (advanced intermediate in Nakamura synthesis—see 1c above); (g) M. G. Banwell, J. N. Lambert, J. M. Gulbis and M. F. Mackay, J. Chem. Soc., Chem. Commun., 1990, 1450 (desacetamidoisocolchicine). For excellent summaries of much of the synthetic work on colchicine see (h)SYNFORM, 1990, 8, 207; (i) I. Fleming, Selected Organic Syntheses, John Wiley and Sons, London, 1972, pp. 183-207.
- 2 For comprehensive discussions of the biological properties of colchicine see (a) H-G. Capraro and A. Brossi, in The Alkaloids, ed. A. Brossi, Academic Press, New York 1984, vol. 23, pp. 1-70; (b) A. Brossi, H. J. C. Yeh, M. Chrzanowska, J. Wolff, E. Hamel, C. M. Lin, F. Quin, M. Suffness and J. V. Silverton, Med. Res. Rev., 1988, 8, 77; (c) A. Brossi, J. Med. Chem., 1990, 33, 2311.
- 3 A. R. Battersby, E. MacDonald and A. V. Stachulski, J. Chem. Soc., Perkin Trans. 1, 1983, 3053 and references cited therein.
- 4 M. G. Banwell and M. P. Collis, J. Chem. Soc., Chem. Commun., 1991, 1343
- 5 E. M. Hindmarsh, I. Knight and R. Robinson, J. Chem. Soc., 1917, 940.
- 6 J. S. Sawyer and T. L. Macdonald, Tetrahedron Lett., 1988, 38, 4839
- 7 H. Hara, H. Shinoki, O. Hoshino and B. Umezawa, Heterocycles, 1983, 20, 2155.
- A. McKillop, D. H. Perry, M. Edwards, S. Antus, L. Farkas, M. Nogradi and E. C. Taylor, J. Org. Chem., 1976, 41, 282. Yu. G. Gololobov, A. N. Nevmeyanov, V. P. Lysenko and I. E.
- Boldeskul, Tetrahedron, 1987, 43, 2609.
- 10 T. H. Al-Tel, M. H. Abu Zarga, S. S. Sabri, A. J. Freyer and M. Shamma, J. Nat. Prod., 1990, 53, 623.
- 11 M. G. Banwell, G. L. Gravatt, J. S. Buckleton, G. R. Clark and C. E. F. Rickard, J. Chem. Soc., Chem. Commun., 1989, 865.
- 12 (a) H. Corrodi and E. Hardegger, Helv. Chim. Acta, 1957, 40, 193; (b) A. Bladé-Font, Tetrahedron Lett., 1977, 2977.
- 13 The XTAL User's Manual-Version 3.0, ed. S. R. Hall and J. M. Stewart, Universities of Western Australia and Maryland, 1990.
- 14 G. M. Sheldrick, SHELX76, program for crystal structure determination, University of Cambridge, England, 1976.
- 15 C. K. Johnson, ORTEPII, Report ORNL-5138 Oak Ridge National Laboratory, Tennessee, USA, 1976.