The Development of a Fully Regiocontrolled Synthesis of (±)-12a,12b-Monosecocolchicine using a Synthetic Equivalent for the 7-Methoxy-3-troponyl Anion

Martin G. Banwell,*[a] G. Lance Gravatt,[b] John S. Buckleton,[b] George R. Clark,[b] and C. E. F. Rickard[b]

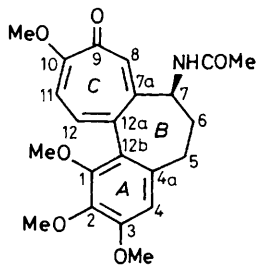
[a] *Department of Organic Chemistry, The University of Melbourne, Parkville, Victoria 3052, Australia*
[b] *Department of Chemistry, The University of Auckland, Private Bag, Auckland, New Zealand*

The lithio-species (**6**) acts as a synthetic equivalent for the 7-methoxy-3-troponyl anion (**3**) and has been employed in a fully regiocontrolled synthesis of the title compound (**2**).

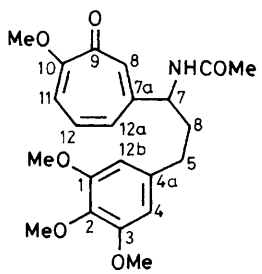
The unusual structural features and potent antimitotic properties associated with the alkaloid colchicine (**1**) have attracted considerable attention and eleven total or formal total syntheses of this compound have been reported to date.[1,2] Remarkably, none of the synthetic strategies developed so far has permitted the preparation of colchicine in a fully regiocontrolled manner. The introduction of the C-7-acetamido group and the creation of the proper arrangement of the carbonyl and methoxy moieties on the troponoid *C*-ring have been especially troublesome.[2] The latter difficulty arises because *O*-methylation of an unsymmetrical α-tropolone produces mixtures of the regioisomeric methyl ether derivatives.

As part of a programme aimed at providing efficient and flexible routes to colchicine and certain analogues[3] we have devised a potential solution to the above-mentioned problems which we now describe within the context of a convergent and fully regiocontrolled synthesis of the title compound (**2**).[4] Crucial to the success of this work has been the development of a synthetic equivalent for the troponyl anion (**3**).

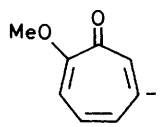
The route to compound (**2**) is outlined in Scheme 1. Thus, lithiation[5] [BuLi in hexane (1.0 equiv.), tetrahydrofuran (THF), −100 °C, 1 h] of the acetonide (**5**),† prepared in the usual manner from the known diol (**4**),[6] provided the anion (**6**) which reacted with (*E*)-3,4,5-trimethoxycinnamaldehyde (**7**)‡ (1.1 equiv., THF, −100 °C, 2 h) and gave, upon work-up, the condensation product (**8**) (77%) as a *ca.* 1:1 mixture of



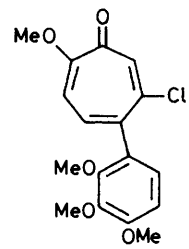
(**1**)



(**2**)



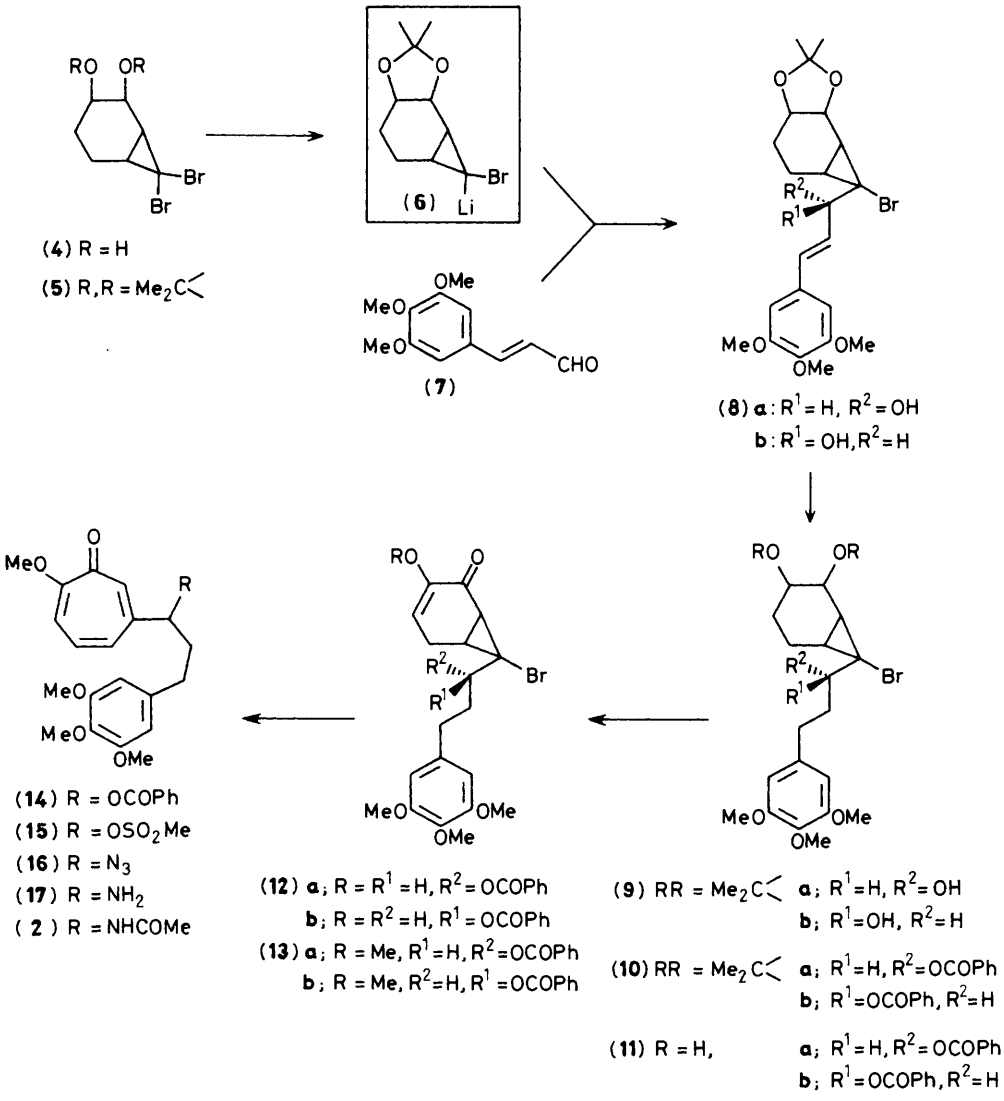
(**3**)



(**18**)

† All new compounds are racemic; only one enantiomer is depicted for clarity. All new substances had spectroscopic data (i.r., n.m.r., mass spectrum) consistent with the assigned structure and had satisfactory combustion or high resolution mass spectral analytical data. Yields refer to isolated compounds of analytical purity.

‡ Prepared from commercially available 3,4,5-trimethoxycinnamic acid by a methylation (diazomethane), reduction (di-isobutylaluminium hydride), oxidation (barium manganate) sequence.



Scheme 1

diastereoisomers. Hydrogenation (1 atm H_2, 10% Pd on C, EtOH) of compounds (**8a,b**) produced the corresponding saturated alcohols (**9a,b**) (100%). The benzoates (**10a,b**) derived from (**9a,b**) [using PhCOCl (1.5 equiv.), 4-*N*,*N*-dimethylaminopyridine (12 equiv.), pyridine, 18 °C, 16 h] could be separated by fractional crystallisation from absolute methanol. The structure of the less soluble isomer (**10a**) (m.p. 156.5—158 °C) was established by *X*-ray crystallographic methods.§ Subjection of compound (**10a**) or its diastereoisomer (**10b**) (m.p. 109—111 °C) to acid hydrolysis [HCl (0.5 M) in 1 : 1 THF/H_2O, 18 °C, 30 h] provided the diols (**11a**) and (**11b**), respectively, in *ca.* 90% yield. Swern-type oxidation[7] [$(CF_3CO)_2O$ (2.0 equiv.), Me_2SO (2.6 equiv.), CH_2Cl_2, −60 °C, 1.5 h then NEt_3 (4.5 equiv.), −60 °C, 1.5 h] of either (**11a**) or (**11b**) afforded the corresponding α-hydroxyenones (**12a**) (75%, m.p. 123—125 °C) and (**12b**) (68%) which upon *O*-methylation [$(MeO)_2SO_2$ (44 equiv.), K_2CO_3 (30 equiv.), Me_2CO, 18 °C, 5 h] gave compounds (**13a**) (75%) and (**13b**) (71%, m.p. 125—131 °C) respectively. Base-induced ring-expansion[3,6] [1,8-diazabicyclo[5.4.0]undec-7-ene (10 equiv.), C_6H_6, 18 °C, 1 h] of either (**13a**) or (**13b**) then provided the tropolone methyl ether (**14**) [85% from (**13a**), 80% from (**13b**)].

The synthetic procedures outlined above produce a tropolone methyl ether, (**14**), which has a substitution pattern similar to that seen in colchicine. In addition, this compound possesses functionality on the side chain suitable for conversion into a C-7-acetamido group. In a formal sense, compound (**14**) could be envisaged as arising from condensation of the inaccessible troponyl anion (**3**) with (**7**) followed by benzoylation and hydrogenation. In effect, the anion (**6**) is acting as a synthetic equivalent for (**3**) in this reaction sequence.

While conversion of benzoate (**14**) into the corresponding mesylate (**15**) was readily achieved by standard methods [K_2CO_3 (1 equiv.), MeOH, 18 °C, 2 h then $MeSO_2Cl$ (1.1

§ *Crystal data:* $C_{30}H_{35}BrO_7$, M = 587.51, monoclinic, space group $P2_1/c$, a = 16.057(5), b = 11.369(2), c = 15.254(2) Å, β = 102.17(1)°, U = 2722.2 Å^3, Z = 4, D_c = 1.434 g cm^{-3}, $F(000)$ = 1224, λ(Mo-K_α) = 0.71069 Å, μ(Mo-K_α) = 16.50 cm^{-1}, θ_{max} = 22°, 1639 observed reflections [$I < 3\sigma(I)$] were collected on an Enraf-Nonius CAD4 diffractometer. The structure was solved by conventional Patterson and Fourier techniques, and refined by blocked full-matrix least-squares cycles with hydrogen atoms placed in geometrically derived positions. The final R factor was 0.046. The crystals contain one molecule per asymmetric unit. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

equiv.), NEt_3, CH_2Cl_2, 0—5 °C, 0.5 h; 79% yield], displacement of the mesyloxy group in the latter compound by a nitrogen-centred nucleophile proved difficult. However, it was discovered that treatment of (**15**) with sodium azide (2 equiv.) and 10 mole % 18-crown-6 (THF,18 °C, 16 h) would provide compound (**16**) (86%). Completion of the synthesis was then achieved by reduction (1 atm H_2, 10% Pd on C, MeOH) of (**16**) and subsequent acetylation (Ac_2O, pyridine) of the derived amine (**17**) to give the title compound (**2**)¶ [77% from (**16**)].

¶ ^{1}H n.m.r. (400 MHz, $CDCl_3$) δ 7.27 (br. s, 1H, H-8), 7.07 (dd, $J_{12,12a}$ 10.7, $J_{11,12}$ 10.0 Hz, 1H, H-12), 6.83 (dd, $J_{12,12a}$ 10.7, $J_{8,12a}$ 1.4 Hz, 1H, H-12a), 6.75 (br. d, $J_{NH,7}$ 8.0 Hz, 1H, N*H*COCH$_3$), 6.70 (d, $J_{11,12}$ 10.0 Hz, 1H, H-11), 6.37 (s, 2H, H-4 and -12b),4.80 (m, 1H, H-7), 3.93 (s, 3H), 3.83 (s, 6H), 3.82 (s, 3H), 2.64 (m, 2H), 2.02 (m, 2H), 1.99 (s, 3H); ^{13}C n.m.r. (100 MHz, CD_3OD) δ 181.3, 172.7, 166.2, 155.4, 154.3, 138.1, 137.3, 134.8, 134.4, 129.9, 114.9, 106.7, 61.0, 57.5, 56.8, 56.5, 38.3, 33.9, 22.6; *m/z* (electron impact, 70 eV) 401 ($M^{+\bullet}$, 21%) 342 ($M^{+\bullet} - CH_3CONH_2$, 38) 43 ($CH_3CO^+$, 100); *m/z* for $M^{+\bullet}$ calc. 401.1838, obs. 401.1833; ν_{max}(NaCl, neat) 3300, 2950, 2855, 1650, 1625, 1595, and 1560 cm^{-1}. These data are in good agreement with data reported by Yamamoto *et al.*[4] for compound (**2**). However, unlike the Japanese workers, we could not obtain this compound in a crystalline state.

In order to gain some indication of its potential as an antimitotic agent, racemic (**2**) has been subjected to a tubulin binding assay (P. Kerekes, P. N. Sharma, A. Brossi, C. F. Chignell, and F. R. Quinn, *J. Med. Chem.*, 1985, **28**, 1204) and shown to be inactive [racemic colchicine, while less active than the natural enantiomer, displays significant tubulin binding properties (A. Brossi, H. J. C. Yeh, M. Chrzanowska, J. Wolff, E. Hamel, C. M. Lin, F. Quin, M. Suffness, and J. Silverton, *Med. Res. Rev.*, 1988, **8**, 77)]. This outcome is consistent with the notion that an *AC*-ring axis is an essential requirement for tubulin binding activity in colchicine analogues.

We have recently described[3] the regiocontrolled synthesis of the bicyclic colchicine analogue (**18**), a molecule which contains the aryl-tropolonoid bond lacking in compound (**2**). In principle, an amalgamation of the synthetic strategies employed in the preparation of each of these compounds should permit the development of an efficient and fully regiocontrolled total synthesis of colchicine.

We thank Professor A. Brossi (NIH) for carrying out tubulin binding studies on compound (**2**). One of us (M.G.B.) thanks the Australian Research Grants Committee for supporting aspects of this work.

Received, 20th January 1989; Com. 9/00326F

References

1 D. L. Boger and C. E. Brotherton, *J. Am. Chem. Soc.*, 1986, **108**, 6713 and references cited therein.
2 I. Fleming, 'Selected Organic Synthesis,' Wiley, New York, 1973.
3 M. G. Banwell, K. A. Herbert, J. S. Buckleton, G. R. Clark, C. E. F. Rickard, C. M. Lin, and E. Hamel, *J. Org. Chem.*, 1988, **53**, 4945.
4 H. Yamamoto, A. Hara, S. Inokawa, and T. Nozoe, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 3106, have reported a non-regioselective synthesis of (**2**) which starts with the naturally occurring tropolone β-thujaplicin.
5 H. Siegel, *Top. Curr. Chem.*, 1982, **106**, 55.
6 M. G. Banwell and R. Onrust, *Tetrahedron Lett.*, 1985, **26**, 4543.
7 C. M. Amon, M. G. Banwell, and G. L. Gravatt, *J. Org. Chem.*, 1987, **52**, 4851.