Cyclopropyl compounds as chemical building blocks: Total syntheses of the alkaloids (–)-colchicine, imerubrine and grandirubrine

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Abstract: Fully regio-controlled total syntheses of the title alkaloids (**1**), (**13**) and (**14**) have been developed. In each case, the key step involved acid- or thermally-promoted ring-expansion of the appropriate σ-homo-*o*-benzoquinone or σ-homo-*o*-benzoquinone monoacetal to generate the troponoid ring associated with the target compounds.

The high strain energy but generally excellent kinetic stability and predictable behaviour of cyclopropyl compounds makes them attractive building blocks for chemical synthesis.[1,2] A major focus of efforts in our laboratories has been to exploit such qualities of three-membered carbocycles in the synthesis of various natural products and related compounds. Some aspects of this work are presented here.

(-)-Colchicine (**1**) has been isolated from, *inter alia*, the meadow saffron *Colchicum autumnale* and might well be described as the prototypic anti-mitotic drug although clinical applications of this alkaloid are restricted because of its toxicity.[3] The useful biological properties and novel structure of this compound has resulted in considerable effort being directed towards its synthesis.[4] It has been suggested[3,5] that the troponoid C-ring of colchicine is formed late in the biosynthetic process, possibly by the route illustrated in Scheme 1. This suggestion prompted us to examine whether elements of such a pathway could be mimicked in the laboratory thus permitting development of what would be the first regio- and enantio-controlled total synthesis of (**1**). Such an approach has been very fruitful.
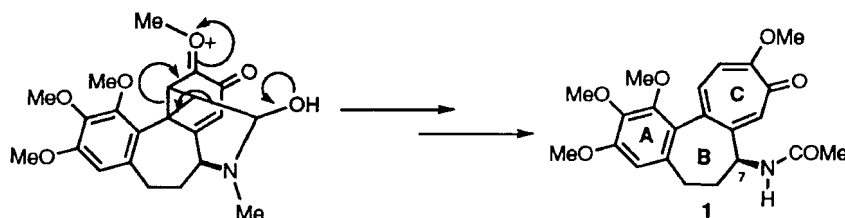
Scheme 1: Late Stages in the Biosynthesis of Colchicine (**1**)

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Our synthesis (Scheme 2)[b] begins with benzaldehyde (2) and acetophenone (3) which are readily elaborated, *via* an initial Claisen-Schmidt condensation reaction, to the 1,3-diarylpropanol (4). Subjection of this last compound to an oxidative coupling protocol developed by Umezawa[7] ultimately afforded the dibenzocycloheptenone (5). In anticipation of the enantioselective introduction of the C-7 acetamido group associated with (1) it was necessary, for various reasons, to form alcohol (6) with the *R*-configuration at C-7 (colchicine numbering). To these ends, the ketone (5) was subjected to enantioselective reduction with stoichiometric quantities of the CBS-reagent[8] and, after debenzylation, the target compound (6) was obtained in 94% ee. Taylor-McKillop oxidation[9] of this phenol followed by nucleophilic cyclopropanation of the derived cyclohexadienone (7) with dimethylsulfoxonium methylide then provided the key σ-homo-*o*-benzoquinone mono-acetal (8) (98% ee after one recrystallisation), the structure (including absolute configuration) of which was established by single-crystal X-ray analysis.[10]
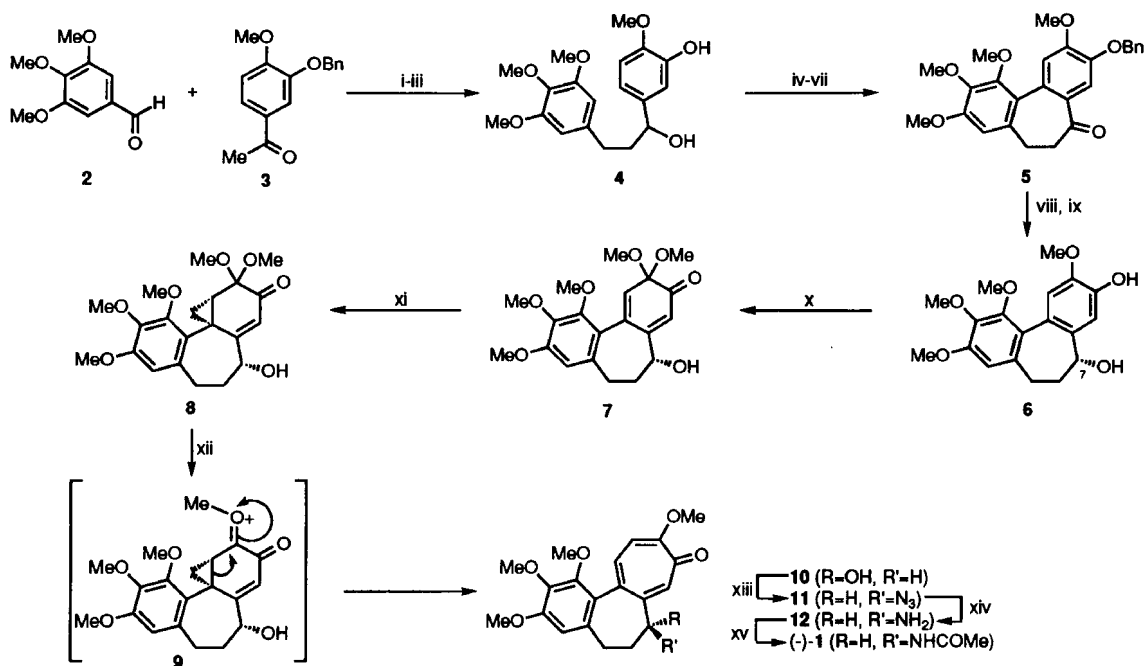

Scheme 2: Total Synthesis of (-)-Colchicine (1)

Reagents and conditions: (i) NaOH, MeOH, RT, 48h, 96%; (ii) H$_2$, Pd on C, MeCO$_2$Et, 15°C, 10h, 96%; (iii) NaBH$_4$, THF/MeOH, 15°C, 1.5h, 96%; (iv) Pb(OCOMe)$_4$, 3Å sieves, CH$_2$Cl$_2$, 15°C, 1h, 100%; (v) CF$_3$CO$_2$H, 3Å sieves, THF/C$_6$H$_6$, 0°C, 1h, 42%; (vi) BnBr, K$_2$CO$_3$, MeCN, 82°C, 4h, 88%; (vii) NMO, TPAP, 4Å sieves, CH$_2$Cl$_2$, 15°C, 43h, 98%; (viii) CBS-reagent, THF, 15°C, 6h, 88%; (ix) H$_2$, Pd on C, MeCO$_2$Et, 15°C, 9h, 99%; (x) Tl(NO$_3$)$_3$, MeOH, -20°C, 0.5h, 83%; (xi) Me$_3$S(O)I, NaH, DMSO, 15°C, 7h, 54% @ 82% conversion; (xii) CF$_3$CO$_2$H, CH$_2$Cl$_2$, 15°C, 3h, 48%; (xiii) *i*-PrO$_2$CN=NCO$_2$Pr-*i*, PPh$_3$, Zn(N$_3$)$_2$·2(C$_5$H$_5$N), THF, 15°C, 38h, 30%; (xiv) PPh$_3$, H$_2$O, THF, 15°C, 63h; (xv) (MeCO)$_2$O, C$_5$H$_5$N, 15°C, 0.25h, 60% from 11.

Reaction of compound (8) with trifluoroacetic acid in dichloromethane resulted in the desired (biomimetic) ring-expansion and formation of troponoid (10) (98% ee). Most likely, this key conversion proceeds *via* the oxonium ion (9). Mitsunobu chemistry[11] was used to effect S$_N$2 displacement of the hydroxy group in compound (10) by azide ion. The resulting azido-compound (11) (> 95% ee) was subjected to reduction under Staudinger conditions and the amine (12) so-formed was immediately acetylated thereby affording (-)-colchicine (1) (> 81%ee).

The partial racemisation observed in the final stages of this synthesis is attributed to the substantial acidity of the C-7 proton associated with the intermediate phosphoimine involved in the azide reduction step. Presumably this and other steps in the sequence can be optimised so as to provide a truly enantioselective total synthesis of this most fascinating of alkaloids.
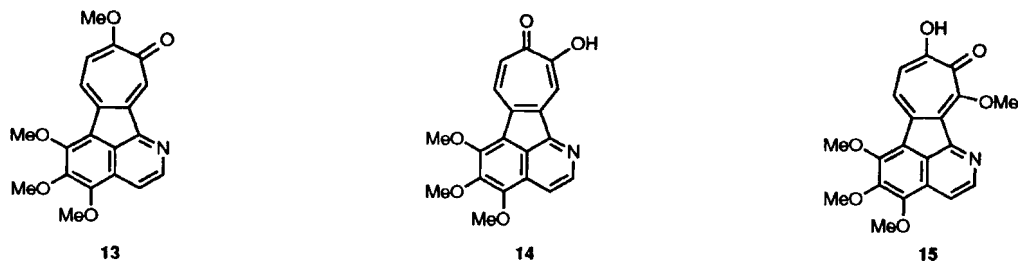
The tropoloisoquinoline alkaloids imerubrine (13),[12] grandirubrine (14)[13] and pareirubrine (15),[14] which have been isolated from various South American plants, are structurally (and probably biogenetically) related to colchicine (1). Compound (15) shows antileukaemic activity[14] but, to the best of our knowledge, no biological properties have yet been ascribed to congeners (13) and (14). However, crude extracts of the plants from which compounds (13) and (14) are obtained have been patented as wound healing agents and are used in the treatment of uterine haemorrhages.[15] Alkaloids (13) and (14) have been the subject of a number of synthetic studies[16] but prior to the work described here no total synthesis of any of the tropoloisoquinoline alkaloids has been reported.

In the initial stages[17] of our regio-controlled total synthesis of imerubrine (Scheme 3)[18] carboxylic acid chloride (16) and β-phenylethylamine (17) were condensed and the resulting amide then elaborated, using a protocol developed by Cava *et al.*,[19] to the 2,3-dihydroazafluoranthene (18). Dehydrogenation of the derived *tert*-butyldimethylsilylether (19) was readily accomplished using palladium on carbon and the fully aromatised product (20) subjected to desilylation thereby affording azafluoranthene (21). Taylor-McKillop oxidation of compound (21) provided the expected dienone (22) which was immediately subjected to nucleophilic cyclopropanation thereby providing σ-homo-*o*-benzoquinone mono-acetal (23) the structure of which was confirmed by single-crystal X-ray analysis.[20] Trifluoroacetic acid promoted ring-expansion of this last compound then proceeded smoothly to give imerubrine (13), the
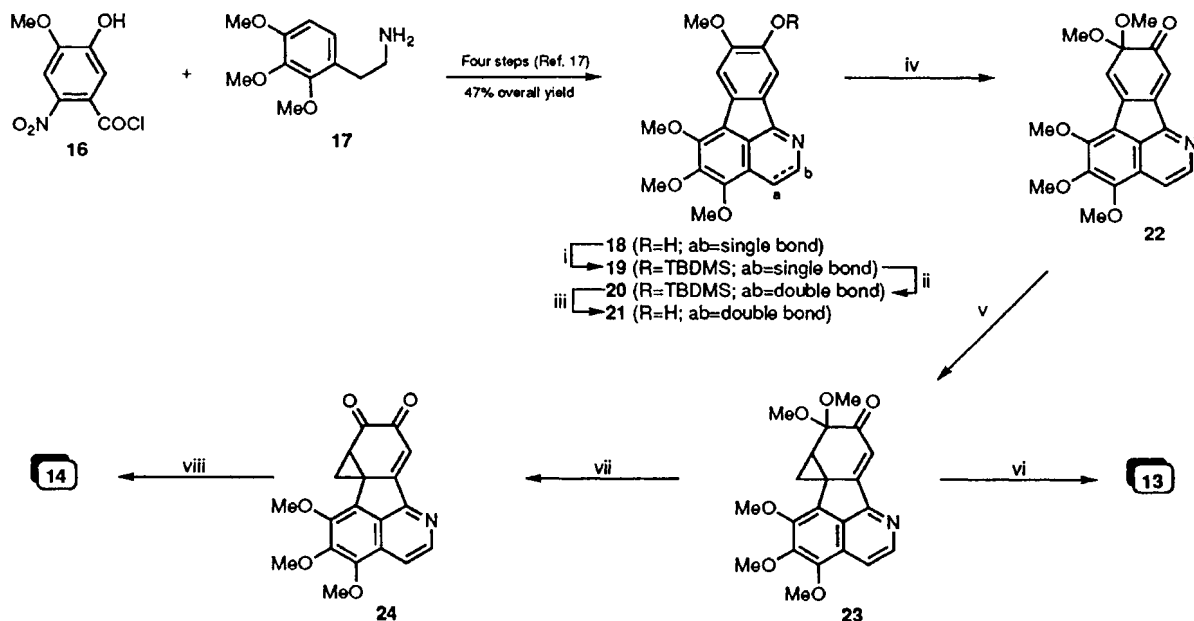
Scheme 3: Total Syntheses of Imerubrine (13) and Grandirubrine (14)

Reagents and conditions: (i) TBDMSCl, DMF, Hünig's base, 18°C, 5min., 100%; (ii) 5% Pd on C, *p*-cymene, 177°C, 4h; (iii) TBAF, THF, 0°C, 10min., 85% from 19; (iv) Tl(NO3)3, MeOH, -20°C, 0.5h, 98%; (v) Me3S(O)I, NaH, DMSO, 15°C, 24h, 38%; (vi) CF3CO2H, CH2Cl2, 15°C, 2h, 70%; (vii) 10% aq. HCl/THF, 15°C, 4h; (viii) THF, 66°C, 30h, 87% from 23.

physical and spectroscopic data for which matched those reported for the natural product. Grandirubrine was readily prepared by hydrolysis of acetal (23) to the corresponding σ-homo-*o*-benzoquinone (24) which isomerised to the natural product (14) on gentle heating. Efforts to adapt this chemistry to the preparation of pareirubrine (15) are currently underway.

Samples of synthetically-derived tropoloisoquinolines (13) and (14) have been tested for tubulin binding activity (such tests have frequently been used as a relatively simple prescreen to identify colchicinoids more likely to possess useful *in vivo* anti tumour activity).[20] Both compounds were examined at several concentrations in a highly sensitive polymerisation system. Compound (14) proved to be inactive ($IC_{50} > 100\mu M$) but imerubrine (13) had weak activity yielding an IC_{50} value of 46 μM. For comparison, under the same conditions IC_{50} values of 0.80 μM and 0.46 μM have been obtained for colchicine and podophyllotoxin, respectively.

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