

Total Synthesis of Colchicine. α -Methoxy-Substituted Oxyallyl [4 + 3] Cycloaddition Approach

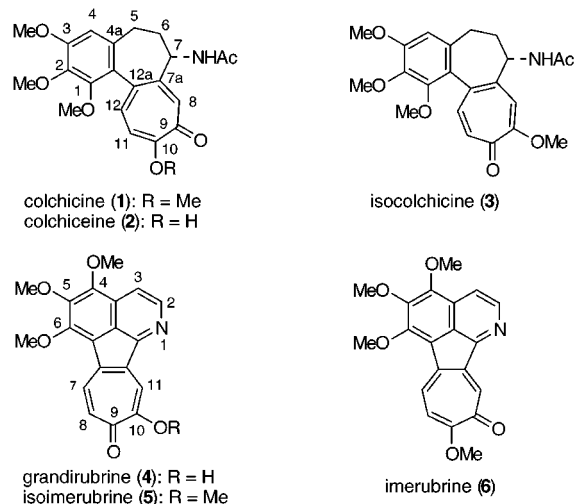
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Colchicine (**1**), the principal alkaloid constituent of *Colchicum autumnale*, possesses interesting biological features in arresting cell division during mitosis.¹ The antimitotic effects of colchicine result from its binding to tubulin and interference with microtubule-dependent cell functions. Although its high toxicity has precluded clinical utilization as a potential antitumor agent, it remains an important biochemical probe. Over the past three decades, colchicine has been the target of an unusually large number of synthetic studies, culminating in several elegant total syntheses.^{2,3} Despite a deceptively straightforward structure, **1** poses considerable synthetic challenges, which are in part due to the paucity of general synthetic methods for the tropolone ring. All of the previous syntheses, with a sole exception,^{3d} involve the penultimate intermediacy of colchicineine (**2**). Consequently, they suffer from lack of regiocontrol in the final methylation, resulting in equal amounts of **1** and **3**. Herein, we report a regioselective synthesis of (–)-

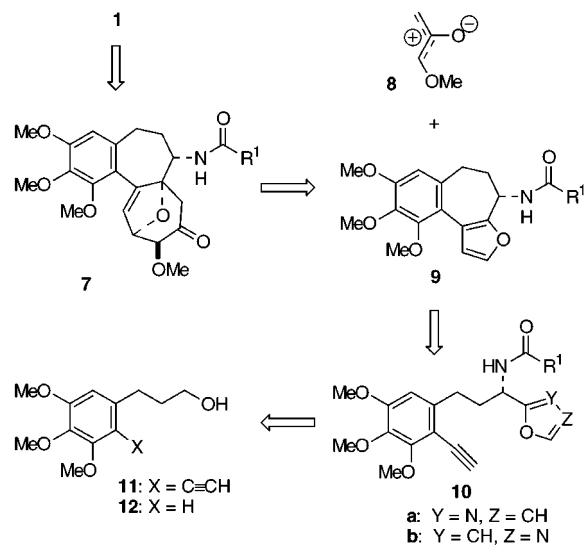
colchicine (**1**), which is also anticipated to provide a unified approach to structurally related tropolisoquinoline alkaloids, such as gradirubrine (**4**), isoimerubrine (**5**), and imerubrine (**6**).⁴



A general approach to these tropolone target structures was found in the [4 + 3] cycloaddition of the α -methoxy-substituted oxyallyl **8** to furan **9**, which was expected to afford stereo- and regioselectively the cycloadduct **7** (Scheme 1).^{5,6} Subsequent double elimination would then give colchicine (**1**), free from isocolchicine (**3**), by obviating the intermediacy of colchicineine (**2**). The requisite substrate **9** should be readily available by the intramolecular Diels–Alder reaction of the acetylenic oxazole **10**,⁷ which would in turn be prepared from the alcohol **11**. This synthetic plan stemmed from our ongoing interest in the applications of oxyallyl [4 + 3] cycloaddition reactions in natural product synthesis.⁸ In particular, we became interested in a key variant of utilizing α -heteroatom-substituted oxyallyls,⁶ while a few methods for their generation are known, to our knowledge, no synthetic application has been reported.

The acetylenic alcohol **11** was first prepared from the alcohol **12** by means of the Sonogashira coupling of the corresponding aryl iodide (Scheme 2).⁹ Swern oxidation, followed by addition of the anion prepared in situ from the

Scheme 1



(1) For general reviews, see: (a) Wildman, W. C.; Pursey, B. A. *Alkaloids* **1968**, *11*, 407. (b) Capraro, H.-G.; Brossi, A. *Alkaloids* **1984**, *23*, 1. (c) Boyé, O.; Brossi, A. *Alkaloids* **1992**, *41*, 125.

(2) In the previous syntheses, deacetamidocolchicine was employed as the key intermediate, which was subsequently converted to **1** by the introduction of an amino group at C-7: (a) Schreiber, J.; Leimgruber, W.; Pesaro, M.; Schudel, P.; Threlfall, T.; Eschenmoser, A. *Helv. Chim. Acta* **1961**, *44*, 540. (b) van Tاملen, E. E.; Spencer, T. A.; Allen, D. S.; Orvis, R. L. *Tetrahedron* **1961**, *14*, 8. (c) Scott, A. I.; McCapra, F.; Buchanan, R. L.; Day, A. C.; Young, D. W. *Tetrahedron* **1965**, *21*, 3605. (d) Martel, J.; Toromanoff, E.; Huynh, C. *J. Org. Chem.* **1965**, *30*, 1752. (e) Kato, M.; Kido, F.; Wu, M. D.; Yoshikoshi, A. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1516. (f) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6713 and references therein.

(3) (a) Nakamura, T. Murase, Y.; Hayashi, R.; Endo, Y. *Chem. Pharm. Bull.* **1962**, *10*, 281. (b) Woodward, R. B. *The Harvey Lectures Series 59*; Academic Press: New York, 1965; p 31. (As cited in: Fleming, I. *Selected Organic Syntheses*; Wiley: New York, 1973; pp 202–207.) (c) Evans, D. A.; Tanis, S. P.; Hart, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 5813. (d) Banwell, M. G. *Pure Appl. Chem.* **1996**, *68*, 539.

(4) For a general review, see: (a) Buck, K. T. *Alkaloids* **1984**, *23*, 301. For successful total syntheses, see: (b) Banwell, M. G.; Hamel, E.; Ireland, N. K.; Mackay, M. F. *Heterocycles* **1994**, *39*, 205. (c) Banwell, M. G.; Ireland, N. K. *J. Chem. Soc., Chem. Commun.* **1994**, 591. (d) Boger, D. L.; Takahashi, K. *J. Am. Chem. Soc.* **1995**, *117*, 12452.

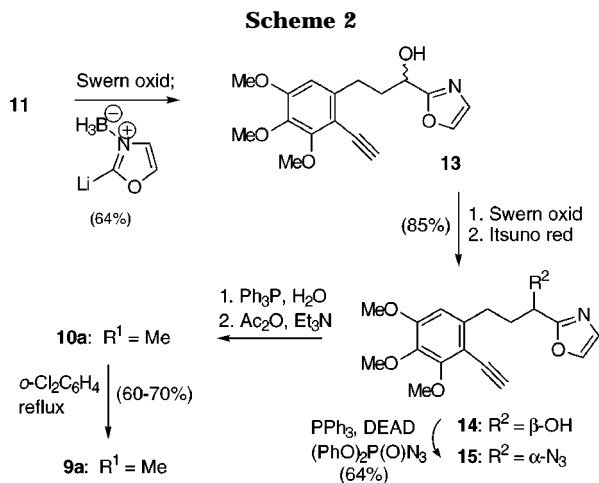
(5) For general reviews of oxyallyl cations, see: (a) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163. (b) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 1. (c) Mann, J. *Tetrahedron* **1986**, *42*, 4611. (d) Hosomi, A.; Tominaga, Y. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, Chapter 5.1.

(6) Only a handful of reports appeared for the preparation α -alkoxy-substituted oxyallyl cations: (a) Föhlisch, B.; Krimmer, D.; Gehrlach, E.; Käshammer, D. *Chem. Ber.* **1988**, *121*, 1585. (b) Murray, D. H.; Alibizati, K. F. *Tetrahedron Lett.* **1990**, *31*, 4109. (c) More recently, the first report on α -nitrogen-substituted oxyallyl cations appeared: Walters, M. A.; Arcand, H. R.; Lawrie, D. J. *Tetrahedron Lett.* **1995**, *36*, 23.

(7) An intramolecular Diels–Alder reaction of acetylenic oxazoles for the preparation of fused-ring furans has been popularized and termed as bis-heteroannulation by Jacobi and co-workers: Jacobi, P. A.; Blum, C. A.; DeSimone, R. W.; Udodong, U. E. S. *J. Am. Chem. Soc.* **1991**, *113*, 5384 and references therein.

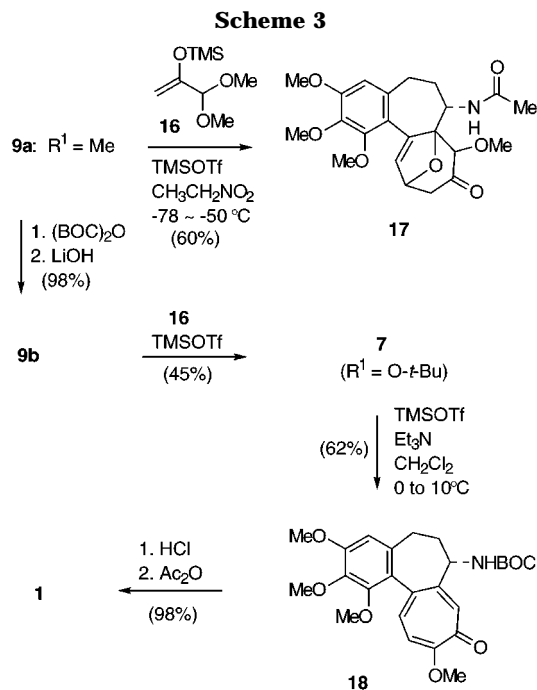
(8) By embedding the oxyallyl function in a ring, we recently developed the useful variant of employing cyclic oxyallyls, which broaden the scope and synthetic utility of the [4 + 3] oxyallyl cycloadditions: (a) Jin, S.-j.; Choi, J.-R.; Oh, J.; Lee, D.; Cha, J. K. *J. Am. Chem. Soc.* **1995**, *117*, 10914. (b) Lee, J.; Oh, J.; Jin, S.-j.; Choi, J.-R.; Atwood, J. L.; Cha, J. K. *J. Org. Chem.* **1994**, *59*, 6955 and references therein.

(9) This conversion was achieved by standard methods in 84% overall yield: (1) TIPSOTf, 2,6-lutidine; (2) I₂, CF₃CO₂Ag, CHCl₃; (3) HC≡CTMS, Et₂NH, (Ph₃P)₂PdCl₂, CuI, DMSO; (4) TBAF, THF.



oxazole–borane complex using the method of Vedejs, afforded the oxazole **13**.¹⁰ For the enantioselective installation of the C-7 acetamido group, the (*R*)-alcohol **14** was first prepared by Itsuno reduction in 64% yield and 85–90% ee (estimated by the NMR studies with a chiral shift reagent).^{11,12} Subsequent conversion to the azide **15** was achieved with inversion of configuration by means of Mitsunobu chemistry.¹³ Reduction of the azide functionality and acetylation then afforded the acetylenic oxazole **10a** (where R¹ = Me) in nearly quantitative yield. Thermolysis (*o*-dichlorobenzene, reflux) provided the furan **9a** (where R¹ = Me) in 60~70% yield and with little racemization. Interestingly, “bis-heteroannulation” of **10a** was found to proceed more slowly than that of the isomeric oxazole **10b**.¹⁴

The key [4 + 3] cycloaddition of the furan **9a** was carried out by adaptation of Albizati's procedure involving in situ generation (with TMSOTf) of α -methoxy(trimethylsilyloxy)-allyl cation (e.g., **8**) from the trimethylsilyl enol ether **16** of pyruvic aldehyde dimethyl acetal (Scheme 3).^{6b} Surprisingly, the undesired regioisomer **17** was isolated as the sole product (60% yield based on 50% conversion of the starting material). On the other hand, the cycloaddition of the carbamate **9b** (R¹ = *O*-*t*-Bu), which was readily prepared from **9a** by standard methods,¹⁵ furnished the desired cycloadduct **7** (R¹ = *O*-*t*-Bu) as a single diastereomer in 45% yield (based on 50% conversion of the starting material). Its structure rests on ¹H NMR analysis; regiochemistry was unequivocally established by the splitting pattern of meth-



ylene protons at C-8 (colchicine numbering). While inconsequential, the stereochemical assignment was tentatively made based on the expected approach of the W-shaped oxyallyl cation from the less hindered, β -face of the furan in a “compact” (endo-like) mode.⁵ It is presently unclear what factors are responsible for the remarkable divergence in the regioselectivity of the [4 + 3] cycloadditions of **9a** and **9b**. Subsequent double elimination of the oxa bridge proved to be challenging. Ultimately, the 2-methoxytropone **18**, a fully assembled colchicine derivative, was prepared (62%) in one step by a slightly modified procedure of Föhlich and Mann employing an excess of TMSOTf and Et₃N in CH₂Cl₂.¹⁶ Finally, the BOC amino protecting group was replaced by the *N*-acetyl group to complete a total synthesis of (–)-**1** in ~90% ee.¹⁷

In summary, the [4 + 3] cycloaddition of an α -alkoxy-substituted oxyallyl cation to a suitable furan provides an efficient, regioselective entry to colchicine (**1**). This [4 + 3] cycloaddition methodology is anticipated to also offer a unified approach to structurally related tropoloisoquinoline alkaloids **4–6**. Mechanistic studies to elucidate the origin of the regioselective cycloadditions of **9a,b** are currently underway and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization/spectral data (27 pages).

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(17) The synthetic substance was found to be identical with an authentic sample of natural colchicine: mp 153–154 °C; [α]_D = –143.5° (*c* = 0.4, CHCl₃) [α]_D = –161.4° (*c* = 0.43, CHCl₃) for natural colchicine.

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(12) Cf. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, 109, 5551. (b) Follet, M. *Acros Org. Acta* **1996**, 2, 12. (c) Mathre, D. J.; Thompson, A. S.; Douglas, A. W.; Hoogsteen, K.; Carroll, J. D.; Corley, E. G.; Grabowski, E. J. *J. Org. Chem.* **1993**, 58, 2880.

(13) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, 23, 1977.

(14) The acetamido oxazole moiety of **10b** was prepared by the introduction of the (trichloromethyl)carbinol, followed by its conversion to the α -azido ester by the method of Corey (Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, 114, 1906) and subsequent treatment with TosMIC (van Leusen, A. M.; Hoogenboom, B. E.; Siderius, H. *Tetrahedron Lett.* **1972**, 23, 2369). Complete details will be reported in a full paper.

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