Tandem Cyclization–Cycloaddition Reaction of Rhodium Carbenoids as an Approach to the Aspidosperma Alkaloids

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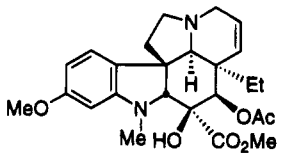
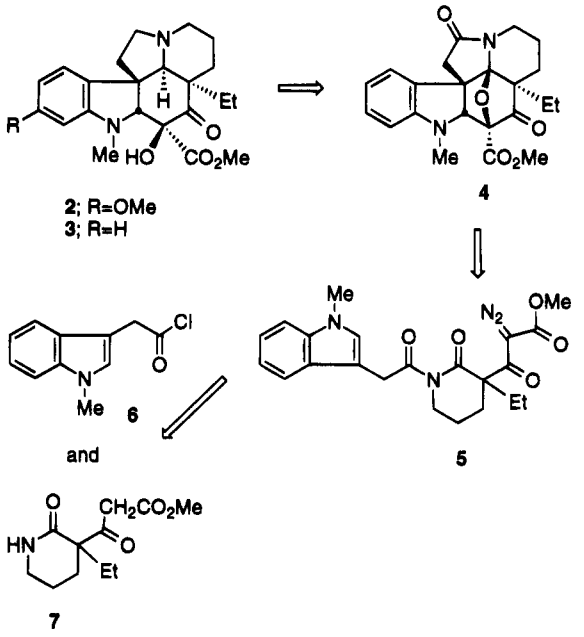
Synthesis of the pentacyclic skeleton common to the aspidosperma family of alkaloids has received considerable attention over the years.[1] Vindoline[2] (**1**) is one of the more heavily oxygenated and complex members of this family and has attracted a great deal of attention owing to its unusual structure and high pharmacological activity.[3] It is the main alkaloidal constituent of *Catharanthus roseus* (Vinca rosea) and corresponds to the dihydroindole component present in the potent bis-indole oncolytic agent, vinblastine.[4] Previous reports from our laboratories have described efficient syntheses of a wide variety of polycyclic nitrogen heterocycles that employ the *tandem cyclization–cycloaddition* reaction of rhodium carbenoids as the key strategic element.[5] In conjunction with our continuing interest in this area, we have developed a fundamentally new approach to the construction of the pentacyclic skeleton of the aspidosperma ring system.[6] This strategy has been successfully applied to the synthesis of desacetoxy-4-oxo-6,7-dihydrovindorosine (**3**). This target was selected since the closely related C_{16}-methoxy derivative (**2**) had previously been converted by Kutney and co-workers into vindoline in six steps.[7]



1; Vindoline

Our approach to the pentacyclic skeleton of the aspidosperma alkaloids is shown in antithetic format in Scheme 1 and is centered on the construction of the key oxabicyclic intermediate **4**. We reasoned that **3** should be accessible by reduction of **4**, which, by analogy with our previous work,[5] should be available by the tandem rhodium(II)-catalyzed cyclization–cycloaddition of diazo imide **5**. Cycloaddition of the initially formed dipole across the pendant indole π-system would be expected to result in the simultaneous generation of the CD-rings of the aspidosperma skeleton.[8] The stereospecific nature of the internal cycloaddition reaction should also lead to the correct relative stereochemistry of the four chiral centers about the C-ring. In this paper we describe our initial experiments that verify the underlying viability of this approach to the aspidosperma skeleton.

Scheme 1



The synthesis of diazo imide **5** commences with the easily available 3-carboxy-3-ethyl-2-piperidone (**8**).[9] Treatment of **8** with 1,1′-carbonyldiimidazole followed by reaction with the dianion of hydrogen methyl malonate[10] afforded β-ketoester **7** in 60% yield. N-Acylation of **7** with *N*-methylindole-3-acetyl chloride (**6**) using 4 Å molecular sieves as a neutral acid scavenger[11] gave the desired imide (65%) which was readily converted to the requisite diazo imide **5** (90%) using standard diazo transfer methodology.[12] When diazo imide **5** was treated with a catalytic quantity of $Rh_2(OAc)_4$ in benzene at 50 °C, cycloadduct **4** was isolated in 95% yield as a single diastereomer. The structure of **4** was firmly established by NMR analysis and by an X-ray crystallographic

(1) Cordell, G. A. In *The Alkaloids*; Manske, R. H. F., Rodrigo, R. G. A., Eds.; Academic Press: New York, 1979; Vol. 17, pp 199–384. Saxton, J. E. *Nat. Prod. Rep.* **1993**, *10*, 349–395.

(2) Gorman, M.; Neuss, N.; Biemann, K. *J. Am. Chem. Soc.* **1962**, *84*, 1058. Büchi, G.; Ando, M.; Ohnnuma, T. *J. Am. Chem. Soc.* **1975**, *97*, 6880.

(3) Antitumor Bisindole Alkaloids from *Catharanthus roseus*. In *The Alkaloids*; Brossi, A., Suffness, M., Eds.; Academic Press: San Diego, 1990; Vol. 37.

(4) Noble, R. L.; Beer, C. T.; Cutts, J. H. *Ann. N. Y. Acad. Sci.* **1958**, *76*, 882. Svoboda, G. H.; Neuss, N.; Gorman, M. J. *J. Am. Pharm. Assoc. Sci. Ed.* **1959**, *48*, 659.

(5) Padwa, A.; Hertzog, D. L.; Chinn, R. L. *Tetrahedron Lett.* **1989**, *30*, 4077. Padwa, A.; Hertzog, D. L. *Tetrahedron* **1993**, *49*, 2589. Hertzog, D. L.; Austin, D. J.; Nadler, W. R.; Padwa, A. *Tetrahedron Lett.* **1992**, *33*, 4731. Padwa, A.; Hertzog, D. L.; Nadler, W. R.; Osterhout, M. H.; Price, A. T. *J. Org. Chem.* **1994**, *59*, 1418. Osterhout, M. H.; Nadler, W. R.; Padwa, A. *Synthesis* **1994**, 123. Marino, J. P., Jr.; Osterhout, M. H.; Price, A. T.; Semones, M. A.; Padwa, A. *J. Org. Chem.* **1994**, *59*, 5518.

(6) For some earlier syntheses see: Stork, G.; Dolfini, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 2872. Ban, Y.; Sato, Y.; Inoue, I.; Nagai, M.; Oishi, T.; Terashima, M.; Yonemitsu, O.; Kanaoka, Y. *Tetrahedron Lett.* **1965**, 2261. Overman, L. E.; Sworin, M.; Burk, R. M. *J. Org. Chem.* **1983**, *48*, 2685. Magnus, P.; Gallagher, T.; Brown, P.; Pappalardo, P. *Acc. Chem. Res.* **1984**, *17*, 35. Wenkert, E. *Pure Appl. Chem.* **1981**, *53*, 1271. Feldman, P. L.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 1603. Kuehne, M. E.; Earley, W. G. *Tetrahedron* **1983**, *39*, 3707. For other leading references, see: Desmaële, D.; d'Angelo, J. *J. Org. Chem.* **1994**, *59*, 2292.

(7) Kutney, J.; Bunzli-Trepp, U.; Chan, K. K.; de Souza, J. P.; Fujise, Y.; Honda, T.; Katsube, J.; Klein, F. K.; Leutwiler, A.; Morehead, S.; Rohr, M.; Worth, B. R. *J. Am. Chem. Soc.* **1978**, *100*, 4220.

(8) Padwa, A.; Hertzog, D. L.; Nadler, W. R. *J. Org. Chem.* **1994**, *59*, 7072.

(9) Liebman, A. A.; Malarek, D. H.; Dorsky, A. M.; Kaegi, H. H. *J. Heterocycl. Chem.* **1974**, *11*, 1105.

(10) Rapoport, H.; Feldman, P. L.; Mayer, M. P. *J. Org. Chem.* **1985**, *50*, 5223.

(11) Weinstock, L. M.; Karady, S.; Roberts, F. E.; Hoinowski, A. M.; Brenner, G. S.; Lee, T. B. K.; Lumma, W. C.; Sletzinger, M. *Tetrahedron Lett.* **1975**, *11*, 3979.

(12) Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 733. Taber, D. F.; Ruckle, R. E., Jr.; Hennessy, M. J. *J. Org. Chem.* **1986**, *51*, 1663.

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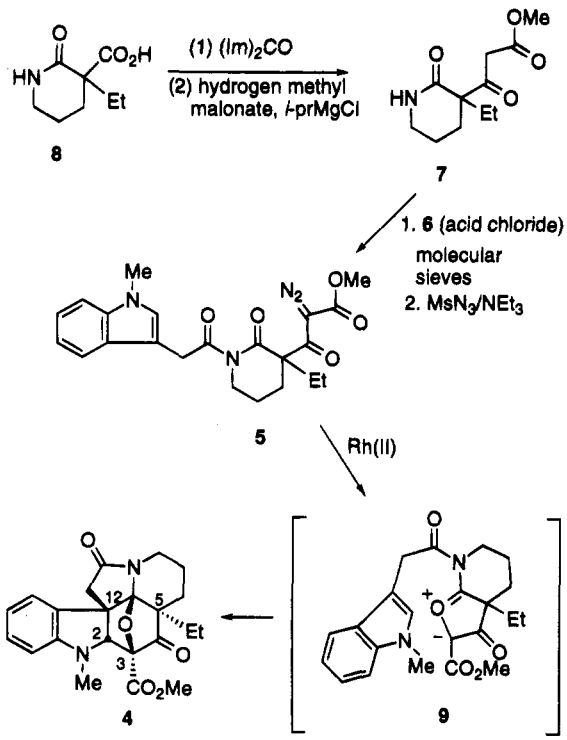
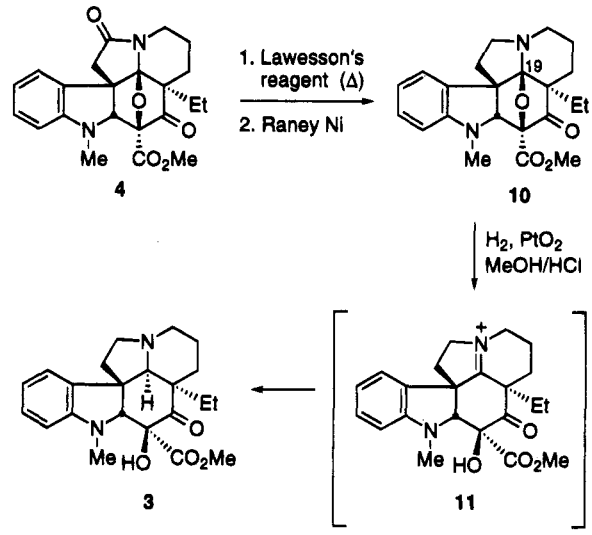


analysis[13] (*N*-benzyl derivative) which revealed that the cycloadduct contains the same relative stereochemical centers (C_2, C_3, C_5, and C_{12}) found in vindoline.[14] The formation of **4** arises by cyclization of the initially formed rhodium carbenoid derived from **5** onto the neighboring piperidone carbonyl oxygen to give dipole **9** which subsequently cycloadds across the indole π-bond.[15] The isolation of **4** is the consequence of *endo* cycloaddition with regard to the dipole, and this is in full accord with the lowest energy transition state.[16] The cycloaddition can also be considered doubly diastereoselective in that the indole moiety approaches the dipole exclusively from the side of the ethyl group and away from the more sterically encumbered piperidone ring.

Having established a viable route to cycloadduct **4**, efforts were next focused on the reduction of the C_{10} lactam carbonyl group and reductive opening of the C_3–C_{19} oxido bridge. Treatment of **4** with Lawesson's reagent furnished the expected thiolactam (85%) which was cleanly reduced (96%) to amine **10** when exposed to Ra/Ni in refluxing THF.[17] To our delight, reduction of the oxido bridge was achieved by catalytic hydrogenation over PtO_2 using *acidic* methanol as the solvent to give **3** in 94% yield as a single diastereomer.[18] The C_{19}-stereochemistry was unequivocally established by a single X-ray crystal analysis.[13] The overall reduction presumably proceeds by an acid-catalyzed ring opening of the *N,O*-acetal group to generate a transient iminium ion (*i.e.*, **11**) which reacts further with hydrogen from the least congested face.



In conclusion, the successful preparation of desacetoxy-4-oxo-6,7-dihydrovindorosine **3** in seven steps was accomplished in 27.2% overall yield and establishes the merit of our method as outlined in Scheme 1. The *tandem cyclization–cycloaddition sequence* is particularly attractive as four of the stereocenters are formed in one step with a high degree of stereocontrol. Work to extend these discoveries to the total synthesis of vindoline are in progress, and the results of these investigations will be reported in due course.

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Supporting Information Available: Experimental details for the preparation of, as well as spectroscopic data for, all new compounds (7 pages).

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(13) The authors have deposited coordinates for structures **4** (*N*-benzyl) and **3** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(14) Moza, B. K.; Troja'nek, J. *Collect. Czech. Chem. Commun.* **1963**, *28*, 1427. Büchi, G.; Matsumoto, K. E.; Nishimura, H. *J. Am. Chem. Soc.* **1971**, *93*, 3299.

(15) Padwa, A.; Hornbuckle, S. F. *Chem. Rev.* **1991**, *91*, 263.

(16) Molecular mechanics calculations were used to model energy differences between the *endo* and *exo* diastereomers.

(17) Yde, B.; Yousif, N. M.; Pedersen, U.; Lawesson, S. O. *Tetrahedron* **1984**, *40*, 2047. Laronze, J. Y.; Laronze-Fontaine, J.; Lévy, J.; Le Men, J. *Tetrahedron Lett.* **1974**, *10*, 491.

(18) Benchekroun-Mounir, N.; Dugat, D.; Gramain, J. C. *Tetrahedron Lett.* **1992**, *28*, 4001.