## References and Notes


(1) Tylosin tartrate is sold commercially under the registered trademark Tylan by Elanco Products company, a division of Eli Lilly. For pertinent biological information see: J. M. McGuire, W. S. Bonieces, C. E. Higgins, M. M. Hoehn, W. M. Stark, J. Westhead, and R. N. Wolfe, *Antibiot. Chemother.*, **11**, 320 (1961).

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(7) The basic mycaminose sugar is stable to the hydrolysis conditions used to remove the neutral mycarose and mycinose sugars. More vigorous acid hydrolysis leads to aglycone degradation. Conditions have been previously reported which allow efficient scission of mycaminose from the aglycone. All of the methods involve conversion of the *N,N*-dimethylamine to the corresponding *N*-oxide. Glycosidic cleavage then proceeds using modified Polonovski conditions (A. Nakagawa, K. Suzuki, K. Iwasaki, K. Kaji, S. Ōmura, A. Jakubowski, and M. Tishler, *Chem. Pharm. Bull.*, **24**, 1749 (1976); N. N. Girotra and N. L. Wendler, *Tetrahedron Lett.*, 227 (1975), or trifluoroacylation followed by mild acid hydrolysis.[3] In the 14-membered ring macrolide series, a Cope elimination of the *N*-oxide of desosamine followed by elimination of the resulting neutral sugar has been reported: R. A. LeMahieu, M. Carson, R. W. Kierstead, L. M. Fern, and E. Grunberg, *J. Med. Chem.*, **17**, 953 (1974). This concept was first demonstrated by Celmer in his elegant studies defining the absolute configuration of the 14-membered ring macrolides: W. D. Celmer, *J. Am. Chem. Soc.*, **87**, 1797 (1965).

(8) It was felt that cleavage of the mycinose linkage via the $C_4'''$ ketone could possibly be carried out using a Reformatsky type reaction analogous to the reported elimination of bromine from $\alpha$-bromo ketones. See: T. A. Spencer, R. W. Britton, and D. S. Watt, *J. Am. Chem. Soc.*, **89**, 5727 (1967). However, due to the ease of glycosidic scission using the conditions reported in this communication, the above approach was not investigated.

(9) W. D. Celmer, "Antibiotics Annual 1958–1959", Medical Encyclopedia, Inc., New York, 1959, pp. 277.

(10) All compounds have IR, UV, NMR, and $^{13}C$ NMR spectra consistent with their structures. High-resolution mass spectral data were obtained for all compounds, the results of which supported their structures.

(11) S. Rakhit and K. Singh, *J. Antibiot.*, **27**, 221 (1974).

(12) Compound **14A:** mp 113–114 °C (from ether); NMR ($CDCl_3$) $\delta$ 9.4–10 (br s, 1 H, NH), 6.88 (dd, 1 H, $C_2H$), 5.88 (dd, 1 H, $C_3H$), 3.90 (s, 3 H, $OCH_3$), 2.40 (s, 3 H, acetate methyl). Upon irradiation of the NH ($\delta$ 9.7) both the $C_2$ ($\delta$ 6.88) and $C_3$ ($\delta$ 5.88) protons collapse to doublets with $J$ = 3 Hz. The high-resolution mass spectrum gives a parent *m/e* 139.0631 indicating $C_7H_9O_2N$ (±0.3 ppm).

(13) Compound **14B:** NMR ($CDCl_3$) $\delta$ 7.26 (m, 5 H, aromatics), 6.78 (d, $J$ = 3 Hz, 1 H, $C_2H$), 5.90 (d, $J$ = 3 Hz, 1 H, $C_3H$), 5.56 (s, 2 H, benzyl $CH_2$), 3.90 (s, 3 H, $OCH_3$), 2.43 (s, 3 H, acetate methyl). The high resolution mass spectrum gives a parent *m/e* 229.1091 indicating $C_{14}H_{15}O_2N$ (±1.2 ppm).

(14) Coupling constants for 2,4-disubstituted pyrroles, $J$ = 1.1 Hz: L. M. Jackman, and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, New York, p 306.



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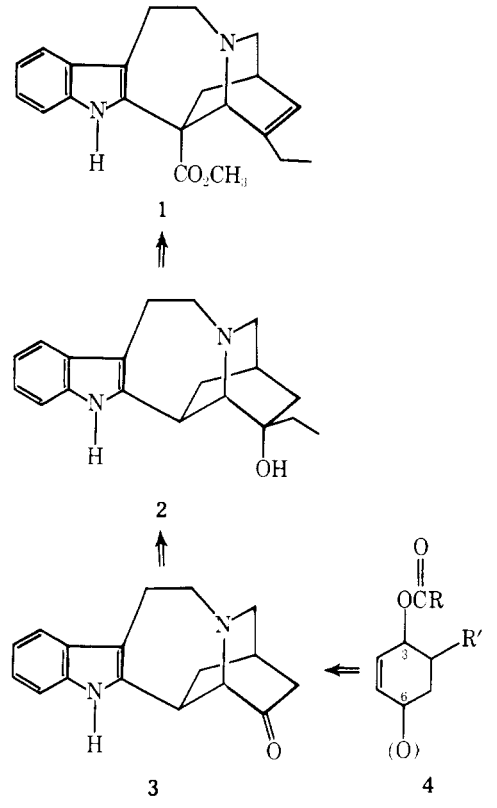
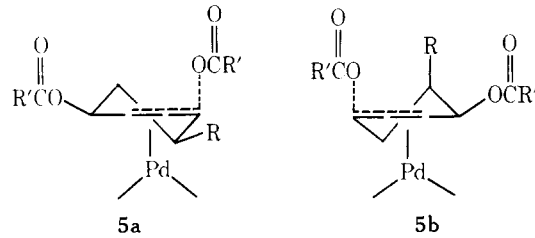
## Synthesis of (±)-Catharanthine via Organopalladium Chemistry

*Summary:* A synthesis of 16-decarbomethoxy-20($S^*$)-hydroxydihydrocatharanthine, an intermediate that has been converted to catharanthine in two stages, is available in seven steps from acrolein and (*E,E*)-1,4-dipivaloxy-1,3-butadiene.

*Sir:* The partial synthesis of vinblastine and vincristine, clinically important antitumor agents, from catharanthine and vindoline makes the synthesis of these latter alkaloids of prime importance.[1,2] The development of a convenient route into the iboga alkaloids immediately led us to focus on the most important member of this family, catharanthine (1).[3] We chose as our target the alcohol **2** since Büchi, in an elegant




procedure, was able in two stages to introduce the carbomethoxy group[4] and effect dehydration.[3a] A synthesis of the alcohol **2** is most easily envisioned from the ketone **3**. For our approach based upon palladium-catalyzed reactions,[5,6] the synthesis requires a cyclohexene **4** that bears oxygen substituents at the 3 and 6 positions. In the simplest approach, these substituents would both be acyloxy groups (i.e., **5**) in which selective ionization of the 3 substituent induced by palladium(0) would be required. Because of lower steric re-




pulsions, the transition state resembling **5a** might be thought to be of lower energy than that resembling **5b** and thus produce the correct product. Scheme I outlines our synthesis.

1,4-Dipivaloxy-1,3-butadiene,[7,8] mp 113–115 °C, gave a single Diels–Alder adduct **6**[8] with acrolein in the presence of boron trifluoride etherate. The NMR spectrum ($H_A$, $\delta$ 5.60, t, $J$ = 4 Hz; $H_C$, 5.24, dd, $J$ = 10, 6 Hz; $H_B$, 3.76, ddd, $J$ = 11, 4, 3 Hz) confirms the stereochemistry as shown. Reductive amination by first forming the imine and then quenching with sodium borohydride gave the first cyclization substrate **7**,[8] mp 119–121 °C, in addition to the alcohol corresponding to **6** which results from incomplete imine formation. The aminobis(pivalate) **7** was added to a preheated solution of the palladium catalyst in acetonitrile containing triethylamine with TLC monitoring to determine when reaction was complete (~20 min) to give isoquinuclidine **8**.[8] Comparison of the spectral data to related isoquinuclidines as well as the successful completion of the project confirms the assignment. A single isomeric byproduct, tentatively assigned structure **11**[8] on the basis of spectral comparison to **12** and interpretation of the 270-MHz proton [$H_A$, $\delta$ 5.00, s; $H_B$, 3.5, d, $J$ = 6 Hz; $H_C$, 3.29, ddd, $J$ = 10, 6.5, 2 Hz; $H_D$, 2.59, d, $J$ = 10 Hz; $H_E$, 2.43,

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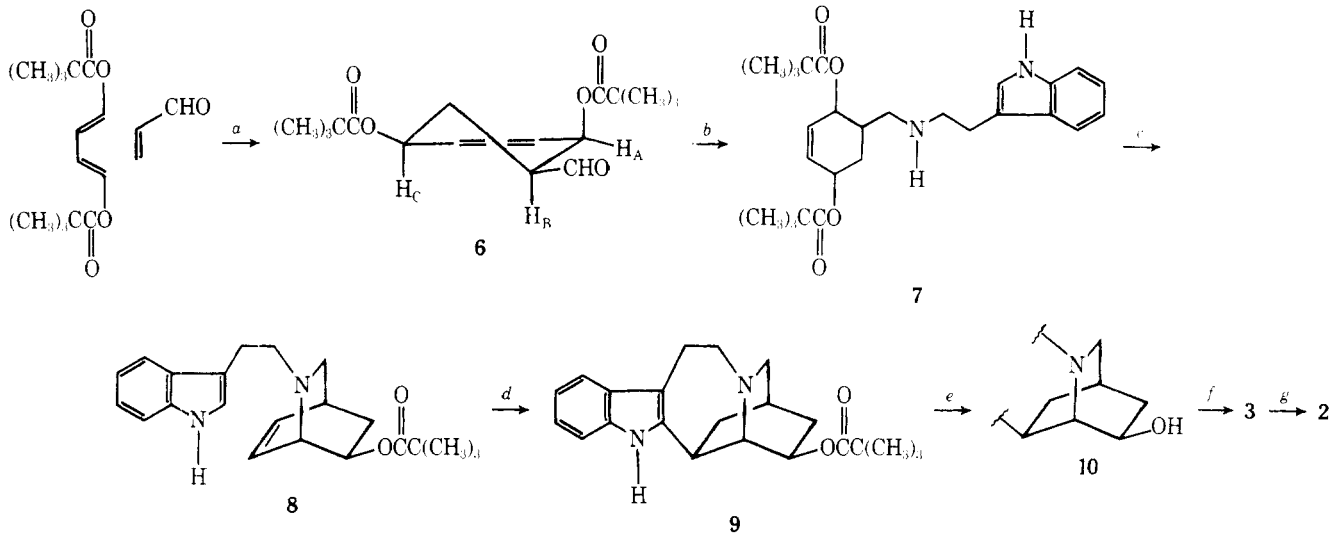
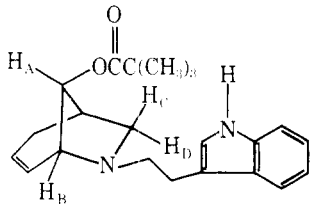
**Scheme I. A Synthesis of the Büchi Catharanthine Intermediate 2**



[a] $PhCH_3$, 5 mol % $BF_3 \cdot Et_2O$, −30 to −10 °C, 80–90%. [b] Tryptamine, $PhCH_3$, $MgSO_4$, −5 °C then $CH_3OH$, $NaBH_4$, −5 °C, 64%. [c] 5 mol % $(Ph_3P)_4Pd$, $(C_2H_5)_3N$, $CH_3CN$, 75 °C, 32%. [d] $(CH_3CN)_2PdCl_2$, $AgBF_4$, $(C_2H_5)_3N$, $CH_3CN$, 25 → 67 °C, then $NaBH_4$, $CH_3OH$, 0 °C, 22%. [e] $CH_3Li$, ether, room temperature. [f] $C_5H_5NSO_3$, $Me_2SO$, $(C_2H_5)_3N$, room temperature, 88% overall from **9**. [g] $C_2H_5MgBr$, THF–ether, −78 to −10 °C, 85%.



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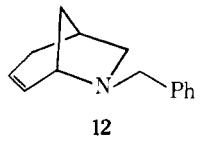

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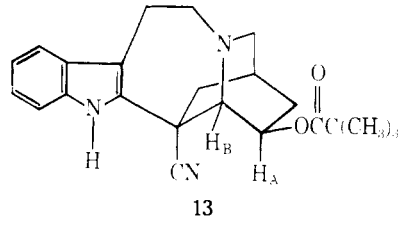

13

m] and $^{13}C$ NMR spectra was also isolated in variable yields. The lower selectivity is somewhat surprising and may result from a steric acceleration for ionization via **5b** similar to that invoked to rationalize enhanced rates of chromic acid oxidations of sterically hindered alcohols.[9]

Cyclization of the isoquinuclidine to alkaloid ring skeleton **9**, mp 172–175 °C, was best achieved under our previously described conditions.[5b] An alternative that also appears promising is treatment with palladium trifluoroacetate[10] in acetonitrile at room temperature for 36 h followed by sodium borohydride.

The pivalate was cleaved with methyllithium in ether at room temperature and the crude alcohol **10**, contaminated with 1,1,2,2-tetramethyl-1-propanol, and subjected to the Doering modification of the Moffatt oxidation[11] to produce the ketone **3**.[8] The ketone is a versatile intermediate for the synthesis of catharanthine analogues. The catharanthine synthesis is formally completed by exclusive exo addition of ethylmagnesium bromide to give only **2**. Confirmation of the structure was achieved by comparison with an authentic sample by IR, NMR, TLC, and mixture melting point (mp 200.5–203 °C, mmp 201–204 °C).

Since deethyl derivatives of catharanthine are potentially interesting as intermediates toward modified vinblastines and vincristines, we explored introduction of the carbomethoxy group at the stage of the pivalate **9**. Treatment of this pivalate with *tert*-butyl hypochlorite in methylene chloride–carbon tetrachloride in the presence of triethylamine at −20 °C to room temperature for 1 h followed by KCN in DMA at 70 °C for 24 h[4] gave the desired cyano compound **13**,[8] mp 210–211 °C, in 49% yield. In addition to the analogy to the Büchi chemistry, the structure is confirmed by 270-MHz NMR spectroscopy, where $H_B$ appears as a doublet, $J$ = 2.9 Hz, at $\delta$ 3.71 which collapses to a singlet by irradiation of $H_A$ (dt, $J$ = 9.0, 2.9 Hz) at $\delta$ 5.38. The much higher yield of the cyanation at this stage compared to cyanation of **2**[3a] also suggests that proceeding to catharanthine from **13** would be advantageous.

The palladium-based route to iboga alkaloids now appears to be a general approach to this important family. The route can tolerate reasonable functionality and allows considerable improvement in the number of synthetic steps. Its success makes the extension to other alkaloid classes an exciting challenge for the future and illustrates the valuable role transition metals can play in complex synthesis.

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**Supplementary Material Available:** Spectral characterization data (IR, NMR, and mass spectroscopy and elemental analyses) for all new compounds (3 pages). Ordering information is given on any current masthead page.

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(6) For a review see B. M. Trost, *Tetrahedron*, **33**, 2615 (1977).
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(8) All new compounds have been fully characterized by IR, NMR, and mass spectroscopy; elemental compositions by high-resolution mass spectroscopy and/or combustion analysis have been obtained. For details, see Appendix which is submitted as supplementary material.
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