Rapid Access to the Highly Oxygenated Aspidosperma Alkaloids Vindoline, Vindorosine, and Cathovaline

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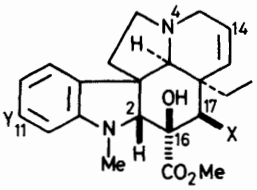
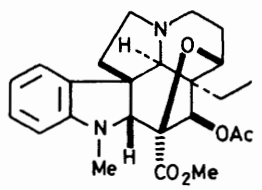
A highly expedient and efficient synthesis of vindoline (**1a**) and vindorosine (**1b**), *via* the hitherto unknown azadienes (**3a,b**), is reported.

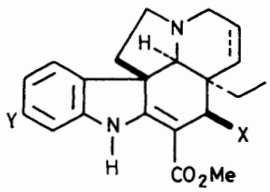
Vindoline (**1a**), vindorosine (**1b**), and cathovaline (**1c**) represent the ultimate step in the biological hydroxylation of the *Aspidosperma* skeleton leading to a unique 16,17-dioxygenated moiety. Despite wide interest in vindoline (**1a**) as the dihydroindole unit of the clinically useful antineoplastic agents vinblastine and analogues (*e.g.*, leurosine, leurosidine, and vindesine),[1] only three multi-step, low-yield synthetic approaches have been reported.[2] Consideration of the contiguous relationship between the three chiral centres (C-2, C-16, and C-17) in (**1a,b**) led to the development of a new and expeditious route to the above enantiomerically pure compounds starting from the naturally occurring β-anilinoacrylic



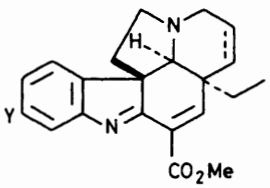
(1a) X = OAc, Y = OMe
(1b) X = OAc, Y = H
(1d) X = OH, Y = H



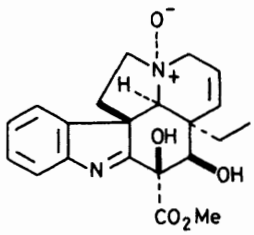
(1c)



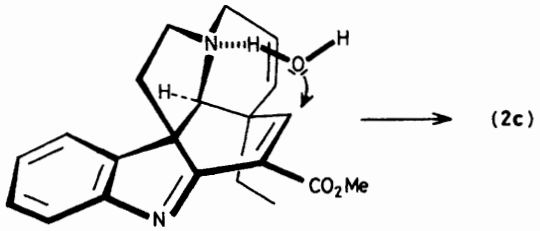
(2a) X = H, Y = OMe, Δ^{14}
(2b) X = Y = H, Δ^{14}
(2c) X = OH, Y = H, Δ^{14}
(2d) X = OH, Y = OMe, Δ^{14}
(2e) X = Y = H
(2f) X = OH, Y = H
(2g) X = OMe, Y = H
(2h) X = imidazol-1-yl, Y = H



(3a) Y = OMe, Δ^{14}
(3b) Y = H, Δ^{14}
(3c) Y = H,



(4)



(3b)

Scheme 1

alkaloids (−)-tabersonine (**2b**) and its (−)-11-methoxy derivative (**2a**). The key point of all the synthetic approaches is the introduction of the oxygenated function at position 17 with the 'right' stereochemistry. Our solution to this problem takes advantage of the reactivity of the azadienes (**3**), available by regioselective dehydrogenation of (**2a,b**), as predicted. In fact, the combination of imine moiety and methoxycarbonyl substituent in (**3**) could provide a synergism for attack at C-17 by a suitable oxygenated nucleophile. Furthermore, the likely N-4-neighbouring group participation and the concave–convex nature of the *Aspidosperma* skeleton in (**3**) bearing the bulky ethyl chain at C-20[3] might be expected to provide the geometrical bias required for stereochemical control at all the three pro-chiral centres [C-17(see Scheme 1), C-16, and finally, C-2].

A variety of methods of converting (**2a,b**) into (**3a,b**) were investigated and it was found that oxidation of (**2b**) with benzeneseleninic anhydride[4] (1.1 equiv., benzene, 60 °C, 30 min), followed by the usual work-up, gave (**2c**)† as the single product‡ in 93% yield. ^1H and ^{13}C N.m.r. spectra established the site of oxidation as C-17 and the presence of the β-hydroxy group was suggested by four-bond 'W-type' coupling (*J* 2.1 Hz) between H-17 and H-21. The next step was selective oxygenation at C-16 which was readily accomplished [2.2 equiv. of *m*-chloroperoxybenzoic acid (MCPBA), 2.2 equiv. of potassium carbonate, dichloromethane–water (1:1), 0 °C, 20 min] to yield the 16-hydroxyindolenine-*N*-oxide (**4**)§ in 78% yield. However, due to the propensity of (**4**) to undergo decomposition, it was immediately converted into the stable (**1d**)-*N*-oxide¶ as a diastereoisomerically pure compound (83% yield) by reductive methylation [sodium cyanoborohydride, 40% aq. formaldehyde, acetate buffer (pH 4.2), room temp., 10 min] prior to removal of the *N*-oxide. This was achieved cleanly by treatment with W-2 Raney nickel in methanol (room temp., 10 min) to give (**1d**), identical in all respects with data reported for catharosine.[5] In order to avoid a highly strained *trans*-fused B–C ring junction, attack of a hydride on (**4**) must occur from the same side as the hydroxy groups. As evidence for the proposed stereochemical assignment, (**1d**) was converted (acetic anhydride, sodium acetate, room temp., 24 h) into the 17-acetoxy derivative (**1b**)† and this was identical with an authentic sample of vindorosine. The transformation of 11-methoxytabersonine (**2a**) by the sequence described above involving oxidation to the 17β-hydroxy compound (**2d**)† afforded vindoline (**1a**) in 55% overall yield. Surprisingly, treatment of the closely related (−)-vincadifformine (**2e**) with benzeneseleninic anhydride under comparable conditions led to a (4:1) thermodynamic mixture of (**2f**) and (**3c**),† respectively, in nearly quantitative yield. Since the same workup was used in all

† Selected spectroscopic data (^1H and ^{13}C n.m.r. in $CDCl_3$, coupling constants in Hz). Compound (**2c**): δ_H 9.17 (s, NH), 6.60 (br. s, OH), 4.68 (br. d, *J* 2.1, 17-H), 3.77 (s, CO_2Me), and 2.90 (d, *J* 2.1, 21-H); δ_C 97.2 (C-16), 70.0 (C-17), and 44.5 (C-20). Compound (**1b**): m.p. 141 °C (Et_2O); δ_H 9.20 (s, 16-OH), 4.10 (d, *J* 7.0, 17-H), 3.73 (s, CO_2Me), 3.70 (s, 2-H), 2.72 (s, NMe), and 2.53 (d, *J* 7.0, 17-OH). Compound (**2d**): δ_H 9.13 (s, NH), 6.45 (s, OH), 4.68 (d, *J* 2.0, 17-H), 3.78 (s, CO_2Me and ArOMe), and 2.87 (d, *J* 2.0, 21-H). Compound (**2f**): δ_H 9.11 (s, NH), 6.47 (s, OH), 4.80 (d, *J* 2.6, 17-H), 3.78 (s, CO_2Me), and 2.73 (d, *J* 2.6, 21-H). Compound (**3c**): $\lambda_{max.}$ (MeOH) 297 and 232 nm; δ_H 7.38 (d, *J* 2.7, 17-H), 3.89 (s, CO_2Me), and 2.66 (d, *J* 2.7, 21-H). Compound (**2g**): m.p. 148 °C (Et_2O); δ_H 9.42 (s, NH), 4.27 (d, *J* 1.3, 17-H), 3.80 (s, CO_2Me), 3.32 (s, OMe), and 2.93 (d, *J* 1.3, 21-H); δ_C 79.8 (C-17) and 55.7 (17-OMe). Compound (**2h**): m.p. 141 °C (Et_2O); δ_H 9.20 (s, NH), 7.67 (br. s, 2′-H), 7.10 (br. s, 5′-H), 6.90 (br. s, 4′-H), 5.70 (d, *J* 1.8,. 17-H), and 2.64 (d, *J* 1.8, 21-H).

‡ The diene (**3b**) cannot be isolated, even following the mildest possible work-up procedure.

§ This stereoselectivity could again be the result of the *syn*-directing effect of the 17β-hydroxy group during MCPBA oxidation.

¶ Since the *N*-oxide of (**1d**) has been transformed by Potier into (**1c**), our approach can also be considered as a synthesis of cathovaline (**1c**) (L. Diatta, Y. Langlois, N. Langlois, and P. Potier, *Bull. Soc. Chim. Fr.*, 1975, 671).

instances, we believe the differences in outcome are a result of subtle conformational changes. As expected, azadienes (**3**) undergo facile regio- and stereo-selective attack at C-17 by nucleophiles. In fact, (**3c**) on treatment with water or methanol under acid conditions or with imidazole in *N,N*-dimethylformamide at room temp., led to the corresponding derivatives (**2f**), (**2g**), and (**2h**),† respectively, in almost quantitative yield.

This method, because of its mildness and tolerance to functionality, should find wide application in the preparation of 17-substituted vindoline-like compounds from the more available β-anilinoacrylic precursors. Finally, our approach appears to follow the possible biogenetic conversion of β-anilinoacrylic alkaloids (**2a,b,e**) into vindoline and its derivatives.

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