(16) Ring expansion of analogous ammonium ylids is also possible. For example, methylation of N-benzyl-α-vinylpiperidine with methyl iodide followed by treatment with lithium diisopropylamide (−20°) gives N-benzylazacyclonon-4-ene: E. Vedejs and M. Arco, to be submitted for publication.

E. Vedejs,* J. P. Hagen

Department of Chemistry, University of Wisconsin
Madison, Wisconsin 53706

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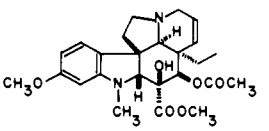
The Total Synthesis of (±)-Vindoline

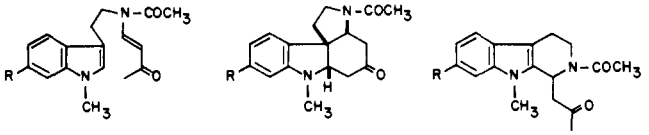
Sir:

Vindoline (**1**),[1] a highly functionalized pentacyclic indoline, is the major alkaloid of *Catharanthus roseus* G. Don. It lacks physiological activity but vinblastine and vincristine,[2] two "dimeric" *Vinca* alkaloids resulting from its combination with a tetracyclic indole, are clinically useful oncolytic agents. In this communication we outline a synthesis of vindoline (**1**) which proceeds with stereochemical control at all six chiral centers.



1

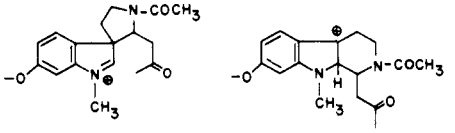
Previous experience[3] with the acid catalyzed cyclization of the vinylogous imide **2** to the tetracyclic isomer **5** suggested the 6-methoxy derivative **3** to be well suited for the synthesis of vindoline (**1**). To our surprise cyclization of **3** afforded only 9% of the tetracyclic ketone **6** and mostly its tricyclic isomer **8** that could not be cyclized further to **6**.[4] Thinking that the electron donating 6-methoxy group might facilitate the Wagner–Meerwein rearrangement of the initially formed spiroindolenium ion A to the benzylic ion B,[5] we examined the effect of electron withdrawing substituents. Acetate, mesylate, and tosylate **4** were prepared and their cyclizations examined. The acetate grouping proved to be unstable to boron trifluoride, but the highly acid stable mesylate[6] and particularly the tosylate **4** afforded the sought after cyclization products.



2 R = H
3 R = CH_3O
4 R = $C_7H_7SO_3$

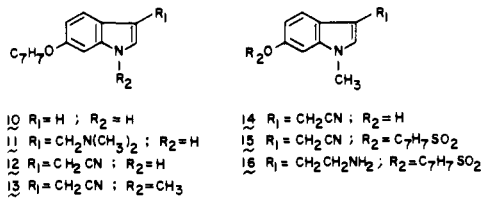
5 R = H
6 R = CH_3O
7 R = $C_7H_7SO_3$

8 R = CH_3O
9 R = $C_7H_7SO_3$



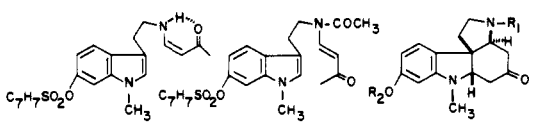
A **B**

Tosylate **4** was prepared as follows. Condensation of 6-benzyloxyindole (**10**)[7] with dimethylamine and formaldehyde in aqueous acetic acid gave the Mannich base **11**, mp 132–134°, which after quaternization with dimethyl sulfate was treated with aqueous sodium cyanide to give the nitrile **12**, mp 138°. Transformation to the tryptamine hydrochloride **16**, mp 196–199° dec (59% overall yield from **10**), was accomplished by methylation of **12** with methyl iodide–sodium hydride in dimethylformamide,[8] hydrogenation of the oily nitrile **13** over Pd/C in ethanol–ethyl acetate at 50 psi, treatment of the resulting phenol **14**, mp 149–152°, with tosyl chloride–sodium hydride in tetrahydrofuran, and, finally, hydrogenation of the tosylate **15**, mp 136°, over platinum in aqueous ethanol–ethyl acetate containing hydrochloric acid. Condensation of the hydrochloride **16** with 1-chloro-3-ketobutene-1 in ethanol–triethylamine provided the liquid *Z*-enamino ketone **17** (83%). Cyclization of **17** invariably led to the tricyclic secondary amine corresponding to **9** but the *E*-acetamide **18** (δ 5.64 (d, J = 14 Hz), 7.97 (d, J = 14 Hz)), prepared in 89% yield with acetyl chloride–sodium hydride in tetrahydrofuran, when heated at 90° in boron trifluoride etherate for 16 min gave the stereochemically homogeneous cis-cis[3] amine **7** in 89% yield and only 2% of the neutral isomer **9**. Clearly, Wagner–Meerwein rearrangement is slower in amide A than in the corresponding amine. The phenol **19**, mp 260–266° dec, available from the tosylate **7** in 79% yield by treatment with 20% potassium hydroxide in methanol–water at reflux afforded the methyl ether **20** mp 176–177° in quantitative yield when heated with dimethyl sulfate in acetone over suspended potassium carbonate. Removal of the acetyl group in **20** was accomplished with triethyloxonium fluoroborate in methylene chloride at room temperature over suspended sodium bicarbonate followed by aqueous work-up (82%).[9]



10 R_1 = H ; R_2 = H
11 R_1 = $CH_2N(CH_3)_2$; R_2 = H
12 R_1 = CH_2CN ; R_2 = H
13 R_1 = CH_2CN ; R_2 = CH_3

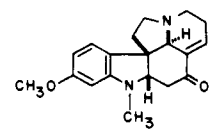
14 R_1 = CH_2CN ; R_2 = H
15 R_1 = CH_2CN ; R_2 = $C_7H_7SO_2$
16 R_1 = $CH_2CH_2NH_2$; R_2 = $C_7H_7SO_2$



17 **18**

19 R_1 = $COCH_3$; R_2 = H
20 R_1 = $COCH_3$; R_2 = CH_3
21 R_1 = H ; R_2 = CH_3

Condensation of the air-sensitive amine **21** with acrolein in methanol containing sodium methoxide followed by dehydration of the crude aldols with methanesulfonyl chloride in pyridine gave the unsaturated ketone **22** (oil): ir ($CHCl_3$) 1685, 1610 cm^{-1}, δ 6.96 (d of d, J = 5 Hz and 2 Hz) in 60% yield. Ethylation with ethyl iodide in *tert*-butyl alcohol–dimethylformamide containing potassium *tert*-butoxide yielded a single β,γ-unsaturated ketone **23**, mp 168–172° (53%), with α-oriented ethyl group (three proton triplet at δ 0.4!). Condensation of the sodium hydride generated enolate of ketone **23** with dimethylcarbonate gave the ketoester **24** (mixture of keto and enol forms) in 72% yield. Hydroxylation of **24** with 98% hydrogen peroxide in *tert*-butyl alcohol–dimethoxyethane containing potassium *tert*-butoxide afforded the internally hydrogen bonded (ir($CHCl_3$) 3200–2400 cm^{-1}) β-hydroxy ketone **25**, mp 160–161° (76%). Reduction of this ketone **25** with various hydrides was found to give mixtures of epimeric alcohols but prior addition of aluminum chloride (−25°, tetrahydrofuran) followed by reduction with sodium bis(2-methoxyethoxy)aluminum hydride (−20°) gave a single epimer in 56% yield. Apparently the space consuming atoms in the aluminum complex C prevent hydride attack from the β-side of the molecule. Acetylation of this alcohol with acetic anhydride–sodium acetate afforded racemic vindoline (**1**), mp 203–



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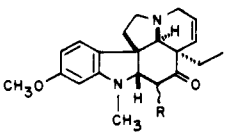
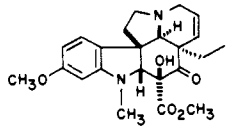


23 R=H
24 R=CO_2CH_3



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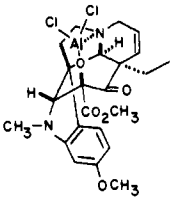

C

205°, identical with natural material, mp 172–174°, according to chromatographic and spectral comparisons.

Acknowledgments. This work was supported generously by the National Institutes of Health (GM 09868) and the Hoffmann-La Roche Foundation. We are indebted to Drs. J. Belletire and G. Trammel for exploratory research on vindoline.

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(2) J. W. Moncrief and W. N. Lipscomb, *Acta Crystallogr.*, **21**, 322 (1966); N. Neuss, M. Gorman, W. Hargrove, N. J. Cone, K. Biemann, G. Büchi, and R. E. Manning, *J. Am. Chem. Soc.*, **86**, 1440 (1964).
(3) G. Büchi, K. E. Matsumoto, and H. Nishimura, *J. Am. Chem. Soc.*, **93**, 3299 (1971).
(4) Experiments by Dr. M. T. Cox.
(5) See R. Iyer, A. H. Jackson, and P. V. R. Shannon, *J. Chem. Soc., Chem. Commun.* 461 (1972).
(6) J. H. Looker, *J. Org. Chem.*, **24**, 1039 (1959).
(7) We are indebted to Drs. W. Leimgruber and P. Wehrli, Hoffmann-LaRoche Inc., Nutley, N.J., for this material.
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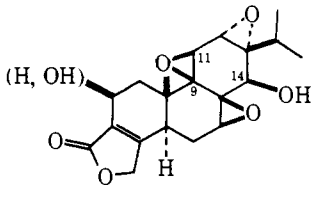
(9) S. Hanessian, *Tetrahedron Lett.*, 1549 (1967).

Masayoshi Ando, George Büchi,* Takeshi Ohnuma
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts 02139
Received August 11, 1975

Synthesis of (±)-7β,8α-Dihydroxy-9β,10β-epoxy-7,8,-9,10-tetrahydrobenzo[*a*]pyrene, a Potential Metabolite of the Carcinogen Benzo[*a*]pyrene with Stereochemistry Related to the Antileukemic Triptolides

Sir:

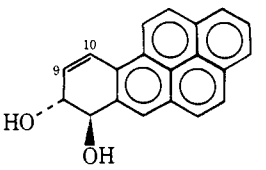
The antileukemic diterpenoid triepoxides, triptolide and tripdiolide (**1**), have been suggested[1] to effect their high biological activity through alkylation of biologically important macromolecular thiols at C-9 of the 9,11-epoxide. An-



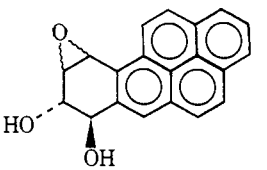
1

chimeric assistance by the proximate 14β-hydroxyl group markedly enhances the rate of adduct formation between **1** and simple thiols. A steroid in which a neighboring hydroxyl group enhances the rate of epoxide ring opening is also known.[2] The same stereochemical situation present in triptolide, an epoxide ring and a hydroxyl group two positions removed on the same face of a six-membered ring, may also be invoked to explain the metabolism induced binding[3] of carcinogenic polycyclic aromatic hydrocarbons to cellular macromolecules. We herein describe the synthesis and reactions of the title compound, a potential metabolite from the environmental carcinogen benzo[*a*]pyrene (BP).

Our interest in this synthesis was stimulated by the key observation of Borgen et al.[4] who demonstrated that *trans*-7,8-dihydroxy-7,8-dihydro-BP (**2a**) was much more extensively bound to DNA on further metabolism by liver microsomes than were either of two other metabolic dihydrodiols or BP itself. The above observation was confirmed by Sims et al.[5] who suggested diol epoxide **3** as the active binding agent and claimed its synthesis[6] by the action of *m*-chloroperoxybenzoic acid on diol **2a.** Although the question of rel-



2a

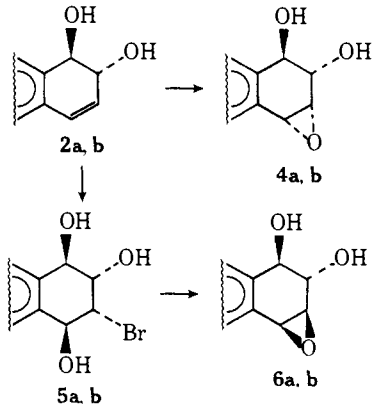


3

ative stereochemistry between the hydroxyl groups and the 9,10-oxirane was not considered in this study,[5] there is ample precedent to expect that epoxidation should occur on the face of the molecule which bears the 8-OH[7] to produce the isomer of diol epoxide **3** in which anchimeric assistance of nucleophilic attack on the oxirane by the 7-OH is impossible as the oxirane and 7-OH are trans. The corresponding epimer of triptolide has low biological activity and is 20-fold slower on reaction with propanethiol.[1] The isomeric sterol epoxides display an 18-fold difference in rates of reaction with azide.[2]

trans-1,2-Dihydroxy-1,2-dihydronaphthalene[8] (**2b**) was chosen as a simple model compound to test possible synthetic routes to the isomers of the BP diol epoxide **3.** In solution, the dihydrodiol prefers the conformation in which the hydroxyl groups occupy pseudo-equatorial positions,[9] the conformation in which both hydroxyl groups should act in concert[7] to direct epoxidation such that the 1-OH and the oxirane are trans (Scheme I). Reaction of **2b** with *m*-chloroperoxybenzoic acid (CH_2Cl_2, 0°, 2 hr) cleanly produced 1β,2α-dihydroxy-3α,4α-epoxy-1,2,3,4-tetrahydronaphthalene[10] (**4b**) in 60% yield (mp 153–155°). As anticipated, the reaction was highly stereoselective, and only the stereoisomer **4b** was isolated.

Scheme I



a = BP series
b = naphthalene series