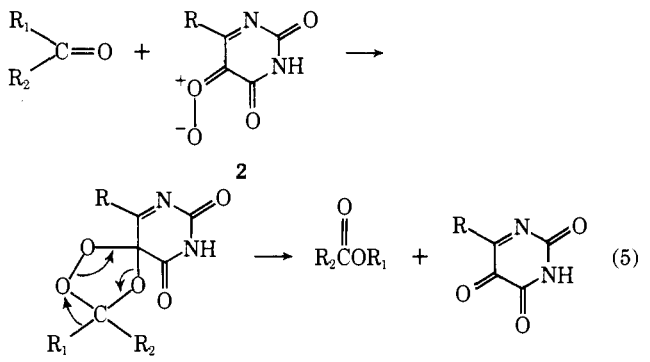
ations[4-6] seems reasonable.[18,19] Recently Ono and Bloch[20] reported evidence that squalene epoxidase is also a flavoenzyme. The present results thus indicate that the same intermediate is a reasonable possibility for the oxenoid reagent in biological epoxidations as well.

Two other types of flavin-containing monooxygenase reactions which can readily be rationalized if **2** is the oxidant are: (1) the conversion of a ketone to a lactone or ester (for example, camphor to camphor lactone[21]), and (2) the conversion of an aldehyde to an acid in a bioluminescent reaction.[22] It is suggested here that each of these proceeds through the intermediacy of an ozonide formed from the aldehyde or ketone reactant and the carbonyl oxide **2** (eq 5).



(5)

A rearrangement as shown would give the observed products; numerous chemical analogies[9,23] (including a very close analogy for the camphor conversion[24]) to these reactions can be found in the ozonide literature. In the bioluminescent reaction, one of the products, presumably the flavin fragment, would have to be formed in an electronically excited state. There is sufficient energy in the ozonide intermediate for this to occur, but the details of how the energy might be channeled into an excited state must await further study.

References and Notes

(1) (a) This research was supported by research grants (AM 13448 and CA 17717) from the National Institutes of Health. (b) Taken in part from the PhD Thesis of R.E.K.
(2) G. A. Hamilton, *J. Am. Chem. Soc.*, **88**, 3391 (1964).
(3) G. A. Hamilton, *Adv. Enzymol. Relat. Areas Mol. Biol.*, **32**, 55 (1969).
(4) G. A. Hamilton, *Prog. Bioorg. Chem.*, **1**, 83 (1971).
(5) G. A. Hamilton, J. R. Giacin, T. M. Hellman, M. E. Snook, and J. W. Weller, *Ann. N.Y. Acad. Sci.*, **212**, 4 (1973).
(6) G. A. Hamilton in "Molecular Mechanisms of Oxygen Activation", O. Hayaishi Ed., Academic Press, New York, N.Y., 1974, p 405.
(7) V. Ulirich, *Angew. Chem., Int. Ed. Engl.*, **11**, 701 (1972).
(8) D. M. Jerina and J. W. Daly, *Science*, **185**, 573 (1974) and references therein.
(9) P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958).
(10) W. B. DeMore and C. L. Lin, *J. Org. Chem.*, **38**, 985 (1973).
(11) Further details will be given in the full paper (R. E. Keay and G. A. Hamilton, in preparation) or can be found in the PhD Thesis of R.E.K., The Pennsylvania State University, 1975.
(12) D. Swern in "Organic Peroxides", Vol. II, D. Swern, ed., Wiley-Interscience, New York, N.Y., 1971, p 335.
(13) The catechol product was analyzed by gas chromatography after conversion to the dimethyl ether as previously described.[14]
(14) G. A. Hamilton, J. W. Hanifin, Jr., and J. P. Friedman, *J. Am. Chem. Soc.*, **88**, 5269 (1966).
(15) The *direct* reaction of ozone with phenol gives some catechol but in the usual protocol this is not occurring because all the *free* ozone is removed by the N_2 flush (step 2).
(16) S. W. Benson and R. Shaw, ref 12, Vol. I, 1970, p 105.
(17) The difference in the reactivities of the cis and trans alkenes is presumably because **5** must approach in a plane approximately parallel to the alkene plane but above or below it. With cis alkenes the transition state can thus be reached with no steric interaction between the alkene substituents and **5**, whereas this is not possible with the trans alkenes.
(18) An elaboration[5] of the original suggestion[4] for the enzymic reactions, involving an intermediate α-hydroperoxy ether which undergoes a Cope-type rearrangement to ultimately give the catechol, has recently been shown to be unlikely (R. E. Keay and G. A. Hamilton, *J. Org. Chem.*, **39**, 3604 (1974)).
(19) The recent suggestion (H. W. Orf and D. Dolphin, *Proc. Nat. Acad. Sci., U.S.A.*, **71**, 2646 (1974)), that the oxenoid reagent in flavin-containing monooxygenases is an oxaziridine, is unlikely for the following reasons among others: (1) H_2O_2 is a product of the enzymic reactions when a poor substrate is used, and there is no reasonable mechanism for the formation of H_2O_2 from the proposed oxaziridine reagent, and (2) oxaziridines are well-defined chemical compounds; there is no indication that they will transfer oxygen atoms to alkenes or phenols. The conclusions, derived from molecular orbital calculations by Orf and Dolphin, on the reactivity of the suggested carbonyl oxide intermediate **2** are negated by the present results, but in any event the calculations are irrelevant to the reactivity of the species because they are ground state calculations whereas reactivity depends on differences between ground and transition states.
(20) T. Ono and K. Bloch, *J. Biol. Chem.*, **250**, 1571 (1975).
(21) C. A. Yu and I. C. Gunsalus, *J. Biol. Chem.*, **244**, 6149 (1969).
(22) J. W. Hastings, C. Balny, C. LePeuch, and P. Douzou, *Proc. Nat. Acad. Sci. U.S.A.*, **70**, 3468 (1973); K. Yoshida and T. Nakamura, *J. Biochem.*, **78**, 985 (1974) and references therein.
(23) E. G. E. Hawkins, "Organic Peroxides", Van Nostrand, Princeton, N.J. 1961; A. G. Davies, "Organic Peroxides", Butterworth, London, 1961.
(24) P. S. Bailey, *Chem. Ber.*, **88**, 795 (1955).
(25) G. A. Hamilton and J. R. Giacin, *J. Am. Chem. Soc.*, **88**, 1584 (1966); D. M. Jerina, D. R. Boyd, and J. W. Daly, *Tetrahedron Lett.*, 457 (1970).
(26) Very recent theoretical calculations (W. R. Wadt and W. A. Goddard III, *J. Am. Chem. Soc.*, **97**, 3004 (1975)) indicate that a simple carbonyl oxide may exist primarily in a three-membered ring cyclized form or as a diradical. Whether this is also true for α-carbonyl carbonyl oxides is not clear but in any event mechanisms very similar to those of eq 3 and 4 would still apply.
(27) NIH Special Research Fellow (GM 57203), 1975, in the laboratory of O. Hayaishi, Department of Medical Chemistry, Kyoto University, Kyoto, Japan.

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Macrocycle Synthesis by Repeatable 2,3-Sigmatropic Shifts. Ring-Growing Reactions

Sir:

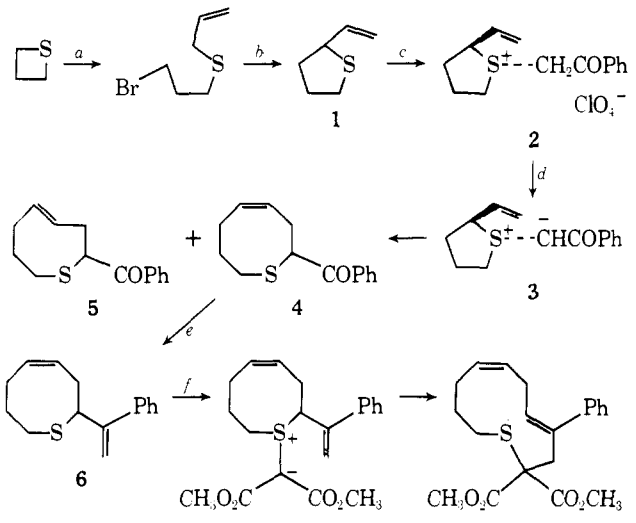
Multicarbon ring expansion can be achieved by fragmentation of a bicyclic intermediate derived from a monocyclic precursor[1,2] or by central bond cleavage in a bicyclic transition state for thermal,[1,3] photochemical,[4] or solvolytic rearrangement.[5] These reactions could be used to prepare macrocycles from readily available five- or six-membered rings if two or more ring expansions could be performed in succession. However, none of the methods reported previously can be repeated easily because the necessary functionality is lost during the fragmentation or rearrangement step.

We wish to describe an approach to macrocyclic compounds by a series of 2,3-sigmatropic shifts.[6] We refer to this process as a ring-growing sequence to denote an easily repeatable reaction scheme which allows systematic ring enlargement. In the first step, an α-vinyl heterocycle such as **1** is converted into a carbonyl-stabilized ylid **3** (Scheme I). Rearrangement of **3** under the conditions of ylid generation (toluene solution, 90°)[7] gives a mixture of ring expansion products **4** (67%)[8] and **5** (7%).[9,10] On the basis of extensive NMR decoupling studies in the presence of $Eu(fod)_3$, **4** is conclusively shown to be the desired eight-membered ring having a cis double bond ($J_{4,5}$ = 11 Hz) while **5** can only be the corresponding trans isomer ($J_{4,5}$ = 16 Hz).

Wittig reaction of **4** and methylidenetriphenylphosphorane affords a new α-vinyl heterocycle **6** which is ready for further ring expansion. Copper bronze catalyzed decomposition of dimethyl diazomalonate in the presence of **6** at 100° results in a single major product **8**. Spectral and analytical evidence supports the 11-membered ring structure.[11] In particular, the methyl ester and C_3 methylene hydrogens are observed as singlets at room temperature, indicating a large, conformationally flexible ring having no centers of asymmetry.

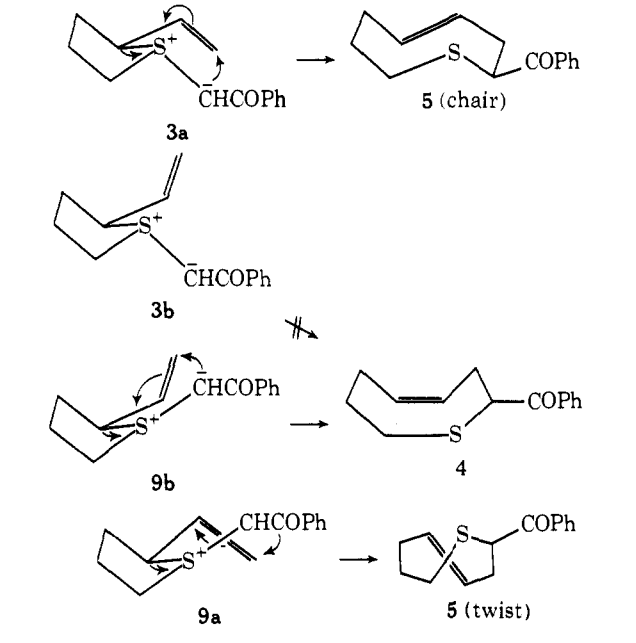
Interesting conformational questions arise in connection

Scheme I



[a] $CH_2=CHCH_2Br$; 85%. [b] $LiN(i\text{-}Pr)_2$, −70°; 85%. [c] $C_6H_5COCHN_2$, 60% $HClO_4$, CH_3CN;[13] 75%. [d] 1,8-Diazabicyclo[5.4.0] undec-7-ene (DBU), toluene 90°. [e] $(C_6H_5)_3P=CH_2$. [f] $(CH_3O_2C)_2CN_2$, copper bronze, 100°.

Scheme II



with the conversion of **2** into **4** and **5**. The highly stereoselective alkylation of **1** to **2** is consistent only with formation of the sulfonium salt having trans stereochemistry as shown. Consequently, the ylid **3** obtained intially from **2** upon DBU treatment must also be the trans isomer. A five-center transition state[12] for 2,3-sigmatropic shift derived from conformation **3a** appears feasible, but this reaction pathway should give only the minor product **5**. It is not possible to force the cissoid conformer **3b** into a reasonable five-center transition state which might lead to **4** (Scheme II).

In order to explain formation of **4**, it is necessary to equilibrate trans ylid **3** with the cis isomer **9**. This can be accomplished by pyramidal inversion[14] at sulfur in the ylid **3** or the sulfonium salt **2**. Two new transition state geometries are then possible, transoid **9a** or cissoid **9b**, which would rearrange to **5** and **4**, respectively.

The observed > ninefold preference for rearrangement via **9b** over **3a** + **9a** contrasts markedly with 2,3-sigmatropic shifts of acyclic analogues which invariably favor the trans olefin.[12,15] This difference is undoubtedly due to the strain energy of a trans double bond in the incipient eight-membered ring resulting from **3a** or **9a**. In ring expansion of **7** to **8**, the normal preference for rearrangement to a trans olefin should be restored because bond angle strain is no longer a major factor.

In principle, a ring-growing sequence can be continued indefinitely by feeding a diet of RCOCH: fragment and Wittig reagent to an α-vinyl heterocycle.[16] Only two isolated intermediates are required for every three carbons incorporated into the ring, and heterocycles of any desired size could be grown by selecting five-, six-, or seven-membered starting materials. We are exploring extensions of this concept to carbocycle synthesis by sulfur extrusion. Related studies directed toward macrocyclic lactone and lactam natural products are also in progress.

Acknowledgment. This work was supported by the National Science Foundation.

References and Notes

(1) Reviews: J. A. Marshall, *Rec. Chem. Prog.*, **30**, 3 (1969); C. D. Gutsche and D. Redmore, *Adv. Alicyclic Chem.*, (1968).

(2) J. B. Hendrickson and R. K. Boeckman, Jr., *J. Am. Chem. Soc.*, **93**, 1307 (1971); P. S. Wharton and M. D. Baird, *J. Org. Chem.*, **38**, 2932 (1971); J. Becker and G. Ohloff, *Helv. Chim. Acta*, **54**, 2889 (1971); J. Borowitz, V. Bandurco, M. Heyman, R. D. G. Rigby, and S.-N. Heng, *J. Org. Chem.*, **38**, 1234 (1973); J. R. Mahajan, G. A. L. Ferreira, C. H. Araujo, and B. J. Nunes, *Synthesis*, 313 (1973); D. Felix, J. Schreiber, G. Ohloff, and A. Eschenmoser, *Helv. Chim. Acta*, **54**, 2896 (1971).

(3) R. W. Thies, M. T. Wilis, A. W. Chin, L. E. Schick, and E. S. Walton, *J. Am. Chem. Soc.*, **95**, 5281 (1973); E. N. Marveil and W. Whailey, *Tetrahedron Lett.*, 509 (1970); R. W. Thies and M. T. Wilis, *Ibid.*, 513 (1970); R. W. Thies and Y. B. Choi, *J. Org. Chem.*, **38**, 4067 (1973); K. Takeda, H. Minato, and M. Ishikawa, *J. Chem. Soc.*, 4578 (1964); N. H. Fischer and T. J. Mabry, *Chem. Commun.*, 1235 (1967); J. K. Crandall and R. J. Watkins, *J. Org. Chem.*, **38**, 913 (1971).

(4) E. J. Corey and A. G. Hortman, *J. Am. Chem. Soc.*, **87**, 5736 (1965); R. C. Cookson and P. Singh, *J. Chem. Soc. C*, 1477 (1971); R. G. Carlson, J. Harman-Ashley Huber, and D. E. Henton, *J. Chem. Soc., Chem. Commun.*, 223 (1973); R. G. Carlson and A. V. Prabhn, *J. Org. Chem.*, **39**, 1753 (1974).

(5) R. W. Thies and J. E. Billigmaier, *J. Org. Chem.*, **38**, 1758 (1973).

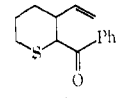
(8) Nonrepeatable ring expansion by 2,3-sigmatropic shift has been reported for certain nitrogen-containing heterocycles: D. Lednicer and C. R. Hauser, *J. Am. Chem. Soc.*, **79**, 4449 (1957); G. C. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 3572 (1962); H. Daniel and F. Weygand, *Justus Liebigs Ann. Chem.*, **671**, 111 (1964); A. G. Anderson, Jr., and M. T. Wilis, *J. Org. Chem.*, **33**, 536 (1968); T. Durst, R. Van Den Elzer, and M. J. LeBelle, *J. Am. Chem. Soc.*, **94**, 9261 (1972); Y. Tamura, J. Minamikawa, Y. Kita, J. H. Kim, and M. Ikeda, *Tetrahedron*, **29**, 1063 (1973).

(7) Generation of ylid at 25° (DBU in THF) affords **4** (23%) and **5** (2%) after 1.25 hr, together with unreacted **2** (ca. 30%).

(8) Characterization of **4**: NMR ($CDCl_3$, δ) 7.96 (2 H, dd, J = 8, 2 Hz), 7.3–7.5 (3 H, m), 5.8 (2 H, m), 4.24 (1 H, dd, J = 10, 3.5 Hz), 2.2–3.1 (6 H, m), 1.6–1.9 (2 H, m); exact mass 232.09216 (calcd for $C_{14}H_{16}O_5$: 232.09219).

(9) Characterization, **5**: NMR ($CDCl_3$, δ) 8.0 (2 H, dd, J = 8, 2 Hz), 7.4–7.7 (3 H, m), 6.1 (1 H, m), 5.35 (1 H, ddd, J = 16, 12, 4 Hz), 4.42 (1 H, dd, J = 12, 4 Hz), 1.8–3.3 (8 H, m); exact mass 232.092; ir (neat, cm^{-1}) 1670, 970.

(10) A third isomer is formed in 4% yield. The NMR spectrum indicates a terminal vinyl group and a methine doublet at δ 4.35 (J = 4 Hz), consistent with structure i (Stevens rearrangement):



i

(11) Characterization of **8**: NMR ($CDCl_3$, δ) 7.2–7.5 (5 H, m), 5.88 (1 H, t, J = 7 Hz), 5.74 (1 H, dt, J = 11, 6 Hz), 5.43 (1 H, dt, J = 11, 7 Hz), 3.45 (6 H, s), 3.40 (2 H, s), 2.3–2.9 (6 H, m), 1.5–1.8 (2 H, m); exact mass, 360.13918 (calcd for $C_{20}H_{24}O_4S$: 360.13945).

(12) J. E. Baldwin and J. E. Patrick, *J. Am. Chem. Soc.*, **93**, 3556 (1971).

(13) W. T. Flower, G. Holt, and M. A. Hope, *J. Chem. Soc., Perkin Trans. 1*, 1116 (1974).

(14) Ylide sulfur inversion: D. Darwish and R. L. Tomilinson, *J. Am. Chem. Soc.*, **90**, 5938 (1968). Sulfonium sulfur inversion: D. Darwish and G. Tourigny, *Ibid.*, **88**, 4303 (1966); D. Darwish and C. Scott, *Can. J. Chem.*, **51**, 3647 (1973), and references therein.

(15) D. A. Evans and G. C. Andrews, *Acc. Chem. Res.*, 7, 147 (1974); P. A. Grieco, D. Boxler, and K. Hiroi, *J. Org. Chem.*, **38**, 2572 (1973); P. A. Grieco, *J. Chem. Soc., Chem. Commun.*, 702 (1972).

(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.

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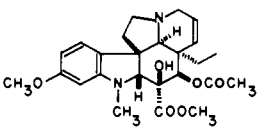
The Total Synthesis of (±)-Vindoline

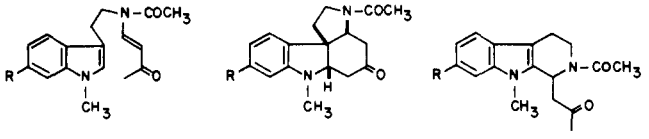
Sir:

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

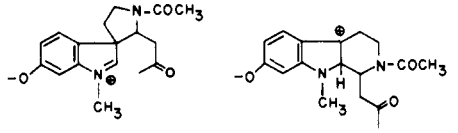
Previous experience[3] with the acid catalyzed cyclization of the vinylogous imide **2** to the tetracyclic isomer **5** suggested the 6-methoxy derivative **3** to be well suited for the synthesis of vindoline (**1**). To our surprise cyclization of **3** afforded only 9% of the tetracyclic ketone **6** 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=$C_7H_7SO_3$

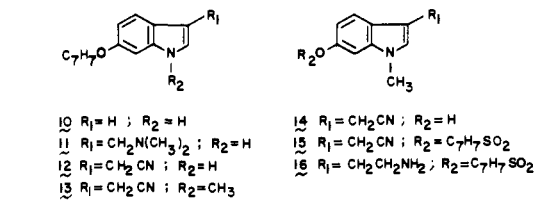
5 R=H
6 R=CH_3O
7 R=$C_7H_7SO_3$

8 R=CH_3O
9 R=$C_7H_7SO_3$



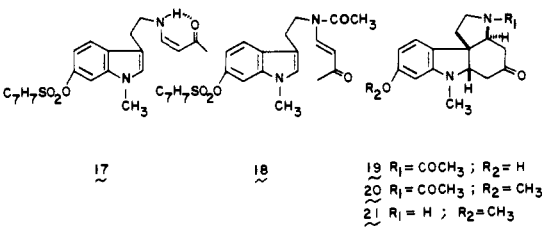
A **B**

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-