# Intramolecular [4 + 2] Cycloadditions as a General Strategy for Alkaloid Synthesis. A Novel Formal Synthesis of Lycorine[1]

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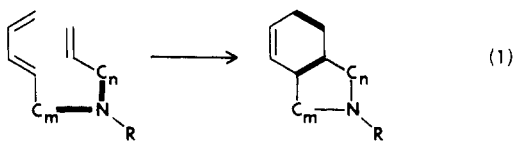
The intramolecular [4 + 2] cycloadditions of the aryl-substituted enamido dienes that were produced upon thermal, cheletropic extrusion of sulfur dioxide from the enamides **8**, **15**, and **26** were examined. Whereas thermolysis of **8** in refluxing xylene in the presence of bis(trimethylsilyl)acetamide (BSA) and bis(3-*tert*-butyl-4-hydroxy-5-methylphenyl) sulfide (**10**) cleanly produced the *cis*-hydroindole **11** in 48% yield, heating **15** under identical conditions produced a 1:1.5 mixture of the *cis*-and *trans*-hydroindoles **17a** and **17b** (45–50%), together with trace amounts of **17c** and **18**. Thermolysis of **8** and **15** under several different conditions afforded various mixtures of the respective cycloadducts **11** and **12** or **17a–c** and **18**. The structures of **17a–c** were unequivocally established by their conversion to the corresponding α-, β-, and δ-lycoranes **19a–c**. The enamide **26**, which is closely related to **15**, underwent thermolysis in refluxing xylene in the presence of BSA and the sulfide **10** to give 1:1.4 mixture of the *cis*- and *trans*-hydroindoles **27a** and **27b** (47% yield) together with a small amount of **28**. The *cis*-hydroindole **27a** was then converted in three steps to the lycorane **4**. Since **4** has been previously converted to the Amaryllidaceae alkaloid lycorine (**3**), its preparation represents an extraordinarily facile, formal synthesis of the title alkaloid.

## Introduction

Central to the design of a general strategy for the synthesis of alkaloids is the development of a practical methodology for the construction of substituted hydroindoles, hydroquinolines, and hydroisoquinolines, which are important structural elements common to a diverse array of these naturally occuring bases. Several years ago we became intrigued with the potential of exploiting the intramolecular [4 + 2] cyloadditions[3] of azatrienes of the general structure **1** for the assemblage of these heterocyclic synthons (eq 1). Prior to our own investigations, Oppolzer



(1)

**1** **2**

m = 0-3; n = 0-2

and others[4] had elegantly demonstrated that hydroindoles **2** ($m = 0$, $n = 2$) and hydroquinolines **2** ($m = 0$, $n = 3$) were produced by the thermal cyclizations of olefinic dienamides and dienamines **1** ($m = 0$, $n = 2$ and 3, respectively). We then established that the isomeric hydroindoles **2** ($m = 2$, $n = 0$) and hydroquinolines **2** ($m = 3$, $n = 0$) could be readily obtained via the intramolecular [4 + 2] cycloadditions of the corresponding enamido dienes **1** ($m = 2$ and 3, $n = 0$).[1,5a] Subsequent investigations in our laboratory[6] have revealed that substituted hydroisoquinolines **2** ($m = 1$, $n = 2$; $m = 2$, $n = 1$) may be readily elaborated by thermolyses of the respective azatrienes **1** ($m = 1$, $n = 2$; $m = 2$, $n = 1$).[7] When an orthoquinodimethane is employed as the diene in such reactions, hydrobenzisoquinolines are formed.[8] Further important variants of this general strategy for alkaloid synthesis have been described that involve the intramolecular [4 + 2] cycloadditions of other isomeric azatrienes to provide hydroisoindoles,[8b,9] indolizidines,[10] and quinolizidines.[10a]

There are several tactical advantages that attend the design of a general strategy for the elaboration of functionalized hydroindoles, hydroquinolines, and hydroisoquinolines by a protocol that features the intramolecular [4 + 2] cycloaddition of an azatriene **1** as the key step. For example, since there are two possible connective modes (darkened bonds in **1**) for coupling the dienic and dienophilic moieties via either N-acylation or N-alkylation, there is considerable flexibility in formulating synthetic pathways to the requisite azatrienes **1**. Thus, the facile construction of a carbon–nitrogen bond in a bimolecular reaction serves to expedite the subsequent formation of two new carbon–carbon bonds (darkened in **2**) by an entropically favored, intramolecular process. Another important aspect of the thermal cyclizations of substrates **1** possessing an *E* internal double bond and three or four atoms in the

(1) For a preliminary account of a portion of this work, see Martin, S. F.; Tu, C. *J. Org. Chem.* **1981**, *46*, 3763.

(2) Recipient of a National Insitutes of Health (National Cancer Institute) Research Career Development Award, 1980–1985.

(3) For excellent reviews of intramolecular [4 + 2] cycloaddition reactions, see (a) Oppolzer, W. *Angew. Chem., Int Ed. Engl.* **1977**, *16*, 10; *Synthesis*, **1978** 793; *Heterocycles* **1980**, *14*, 1615. (b) Brieger, G.; Bennett, J. N. *Chem. Rev.* **1980**, *80*, 63.

(4) (a) Oppolzer, W. *J. Am. Chem. Soc.* **1971**, *93*, 3834. (b) Greuter, H.; Schmid, H. *Helv. Chim. Acta* **1974**, *57*, 1204. (c) Oppolzer, W.; Fröstl, W. *Ibid.* **1975**, *58*, 590. (d) Oppolzer, W.; Fröstl, W.; Weber, H. P. *Ibid*, **1975**, *58*, 593. (e) Oppolzer, W.; Flaskamp, E. *Ibid.* **1977**, *60*, 204. (f) Stork, G.; Morgans, D. J., Jr, *J. Am. Chem. Soc.* **1979**, *101*, 7110. (g) Keck, G. E.; Boden E.; Sonnewald, U. *Tetrahedron Lett.* **1981**, *22*, 2615. (h) Witiak, D. T.; Tomita, K.; Patch, R. J.; Enna, S. J. *J. Med. Chem.* **1981**, *24*, 788. (i) Gallagher, T.; Magnus, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 1140.

(5) (a) Martin, S. F.; Desai, S. R.; Phillips, G. W.; Miller, A. C. *J. Am. Chem. Soc.* **1980**, *102*, 3294. (b) For related examples, see Stork, G.; Morgans, D. J., Jr. *Tetrahedron Lett.* **1979**, 1959 and Kuehne, M. E.; Okuniewicz, F. J.; Kirkemo, C. L.; Bohnert, J. C. *J. Org. Chem.* **1982**, *47*, 1335 and previous work.

(6) Martin, S. F.; Williamson, S. A.; Gist, R. P., unpublished results.

(7) Dr. E. Ciganek (Central Research and Development Department, E. I. du Pont de Nemours & Co.) has recently informed us that he has prepared certain isoquinoline derivatives by intramolecular Diels–Alder reactions. For example, see U.S. Patent 4 243 668; *Eur Pat. Appl 9780* (1980); *Chem. Abstr.* **1980**, *93*, 220720v. *J. Am. Chem. Soc.* **1981**, *103*, 6261.

(8) (a) Oppolzer, W.; Keller, K. *J. Am. Chem. Soc.* **1971**, *93*, 3836. (b) Cox, M. T. *J. Chem. Soc., Chem. Commun.* **1975**, 903. (c) Cannon, J. G.; Lee, T.; Hsu, F.-L.; Long, J. P.; Flynn, J. R. *J. Med. Chem.* **1980**, *23*, 502. (d) For a novel variant, see Oppolzer, W.; Francotte, E.; Bättig, K. *Helv. Chim. Acta*, **1981**, *64*, 478.

(9) (a) Oppolzer, W. *J. Am. Chem. Soc.* **1971**, *93*, 3833. (b) Gschwend, H. W.; Lee, A. O.; Meier, H.-P. *J. Org. Chem.* **1973**, *38*, 2169. (c) Oppolzer, W. *Helv. Chim Acta* **1974**, *57*, 2610. (d) Gschwend, H. W.; Hillman, M. J.; Kisis, B.; Rodebaugh, R. K. *J. Org. Chem.* **1976**, *41* 104. (e) Oppolzer, W.; Achini, R.; Pfenninger, E.; Weber, H. P. *Helv. Chim. Acta*, **1976**, *59*, 1186. (f) Fráter, G. *Tetrahedron Lett.* **1976**, 4517. (g) Parker, K. A.; Adamchuk, M. R. *Ibid.* **1978**, 1689. (h) Mukaiyama, T.; Tsuji, T.; Iwasawa, N. *Chem. Lett.* **1979**, 697. (i) Mukaiyama, T.; Takebayashi, T. *Ibid*, **1980**, 1013. (j) Pyne, S. G.; Hensel, M. J.; Byrn, S. R.; McKenzie, A. T.; Fuchs, P. L. *J. Am. Chem. Soc.* **1980**, *102*, 5960. (k) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1981**, 29.

(10) (a) Cheng, Y.-S.; Fowler, F. W.; Lupo, A. T., Jr. *J. Am Chem. Soc.* **1981**, *103*, 2090. (b) Khatri, N. A.; Schmitthenner, H. F.; Shringarpure, J.; Weinreb, S. M. *Ibid.* **1981**, *103*, 6387.

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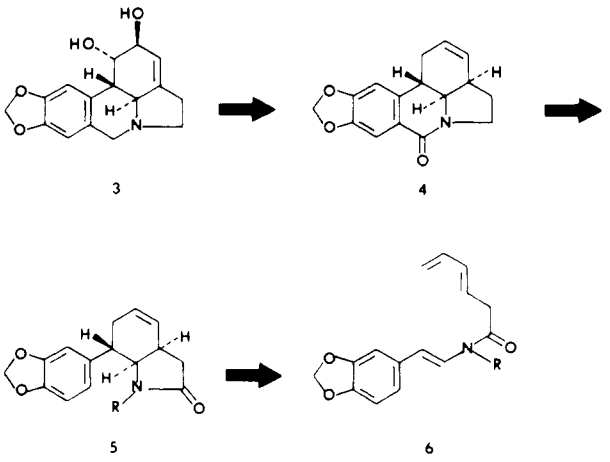
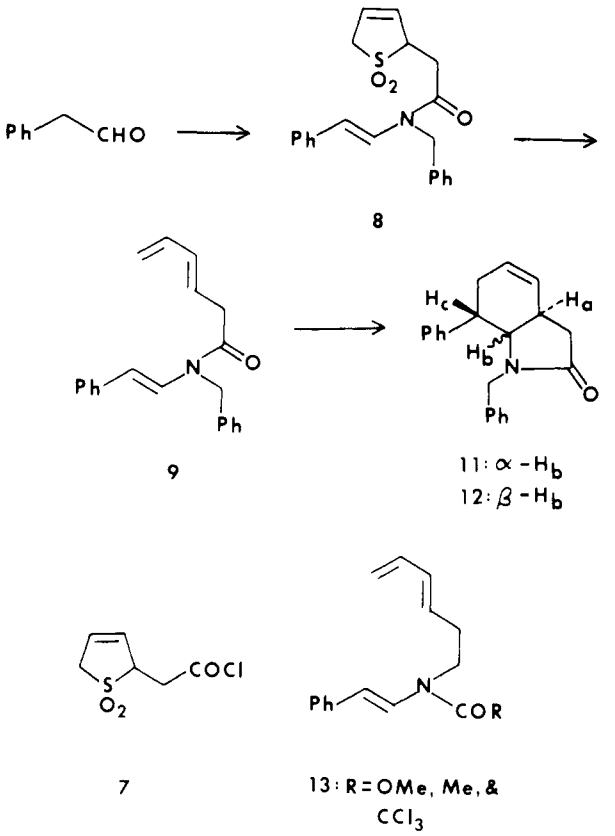
Scheme I



Scheme II



chain connecting the diene and dienophile is that such cycloadditions generally proceed with a high degree of regioselectivity to give fused rather than bridged cycloadducts.[11] On the other hand, only a moderate degree of stereoselectivity is sometimes observed in these processes, and mixtures containing significant amounts of cis and trans cycloadducts are often obtained. It presently appears, therefore, that the stereochemical course of these intramolecular [4 + 2] cycloadditions is dependent upon the delicate balance of a number of factors that may affect the relative energies of the two possible transition states, including any nonbonded interactions, together with the angle and torsional strains in the chain linking the diene and the dienophile. The relative importance of each of these various factors may depend upon the extent to which each of the new carbon–carbon $\sigma$ bonds is formed in the transition state.[12]

In order to establish further the viability of employing the intramolecular [4 + 2] cycloadditions of azatrienes (eq 1) as the key step in the design of a practical strategy for the synthesis of alkaloids, we have continued to examine inter alia the thermal cyclizations of enamido dienes in which the dienic moiety is unactivated. One alkaloid that captured our attention as a particularly attractive target for such investigations was lycorine (**3**), the most abundant alkaloid of the Amaryllidaceae family.[13] Lycorine (**3**), which is an inhibitor of plant growth[14] and of the formation of the peptide bond in protein synthesis,[15] has been the object of a number of synthetic efforts,[16,17] but only a few of these have successfully culminated in its synthesis. Our approach to lycorine (**3**) is adumbrated in the retrosynthetic format depicted in Scheme I and features the intramolecular [4 + 2] cycloaddition of the enamido diene **6** to give the hydroindole **5**, which should be eminently suited for facile conversion to the 7-oxo-$\Delta^{2,3}$-$\alpha$-lycorane **4**. Since **4** has been previously converted to lycorine,[16a,b] its preparation would then constitute a formal total synthesis of the title alkaloid. We now reveal the details of this investigation.[1]

## Results and Discussion

**Preliminary Studies of Intramolecular [4 + 2] Cycloadditions.** Since our principal concern was whether an aryl-substituted enamido diene such as **6** would undergo an intramolecular [4 + 2] cycloaddition to produce a 7-arylhydroindole, we initiated a simple model study. Thus, condensation of commercially available phenylacetaldehyde with benzylamine in benzene containing $MgSO_4$ afforded an unstable imine, which was acylated in situ with the acid chloride **7**[11] in the presence of triethylamine to give the enamide **8** in an unoptimized yield of 35%. That the enamide was trans was clearly evident from the coupling constant of 15 Hz for the respective vinyl protons. Brief thermolysis of **8** in refluxing toluene afforded the enamido diene **9** in virtually quantitative yield. Although **9** could also be prepared directly by acylation of the imine

(11) For an interesting exception see Martin, S. F.; Tu, C.; Chou, T. *J. Am. Chem. Soc.* **1980**, *102*, 5274.

(12) For a discussion of some of these factors, cf. (a) White, J. D.; Sheldon, B. G. *J. Org. Chem.* **1981**, *46*, 2273. (b) Roush, W. R.; Hall, S. E. *J. Am. Chem Soc.* **1981**, *103*, 5200. (c) Roush, W. R.; Peseckis, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6696. (d) Boeckman, R. K, Jr.; Ko, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1032.

(13) For reviews of the chemistry of the *Amaryllidaceae* alkaloids, see (a) Wildman, W. C. in "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1968; Vol. XI, p 307. (b) Fuganti, C. *Ibid*, Vol. XV, 1975, Chapter III. (c) Grundon, M. F. In "The Alkaloids", Specialist Periodical Reports; The Chemical Society, Burlington House: London; 1981, Vol. 10, p 135. See also in Vol. 1–9.

(14) (a) Furusawa, E.; Furusawa, S.; Morimoto, S.; Cutting, W. *Proc. Soc. Exp. Biol. Med.* **1971**, *136*, 1168. (b) Furusawa, E.; Suzuki, N.; Ramanathan, S.; Furusawa, S.; Cutting W. *Ibid.* **1972**, *140*, 1034.

(15) Jimenez, A.; Santos, A.; Alonso, G.; Vazquez, D. *Biochem. Biophys. Acta* **1976**, *425*, 342.

(16) For syntheses of lycorine, see (a) Moller, O.; Steinberg, E.-M.; Torssell, K. *Acta Chem. Scand., Ser* B. **1978**, *32*, 98. (b) Tsuda, Y.; Sano, T.; Taga, J.; Isobe, K.; Toda, J.; Takagi, S.; Yamaki, M.; Murata, M.; Irie, H.; Tanaka, H. *J. Chem. Soc., Perkin Trans.* 1 **1979**, 1358. (c) Umezawa, B.; Hoshino, O.; Sowaki, S.; Sashida, H.; Mori, K. *Heterocycles* **1979**, *12*, 1475. (d) Sano, T.; Kashiwaba, N.; Toda, J.; Tsuda, Y.; Irie, H. *Ibid*, **1980**, *14*, 1097.

(17) For synthetic approaches to lycorine, see (a) Hill, R. K.; Joule, J. A.; Loeffler, L. J. *J. Am. Chem. Soc.* **1962**, *84*, 4951. (b) Ueda, N.; Tokuyama, T.; Sakan, T. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 2012. (c) Hendrickson, J. B.; Alder, R. W.; Dalton, D. R.; Hey, D. G. *J. Org. Chem.* **1969**, *34*, 2667. (d) Ganem, B. *Tetrahedron* Lett. **1971**, 4105. (e) Dyke, S. F.; Sainsbury, M.; Evans, J. R. *Tetrahedron* **1973**, *29*, 213. (f) Muxfeldt, H.; Bell, J. P.; Baker, J. A.; Cuntze, U. *Tetrahedron Lett.* **1973**, 4587. (g) Wenkert, E.; Chawla, H. P. S.; Schell, F. M. *Synth. Commun.* **1973**, *3*, 381. (h) Umezawa, B.; Hoshino, O.; Sawaki, S.; Sato, S.; Numao, N. *J. Org. Chem.* **1977**, *42*, 4272. (i) Iida, H.; Yuasa, Y.; Kibayashi, C. *Ibid*, **1979**, *44*, 1074, 1236. (j) See also ref 4f and 5a.

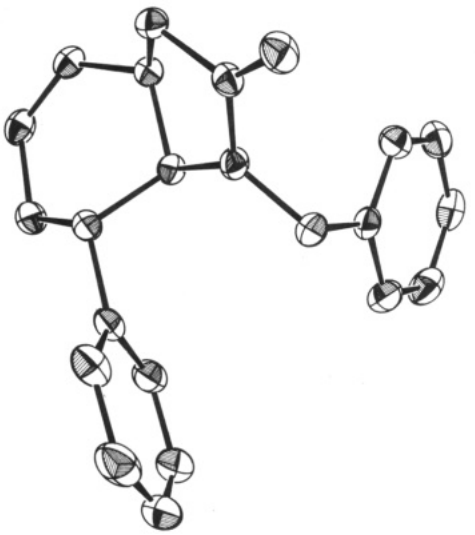


**Figure 1.** ORTEP plot of hydroindole **11** with non-hydrogen atoms shown as 50% thermal ellipsoids.

derived from phenylacetaldehyde and benzylamine with 3,5-hexadienoyl chloride,[11] the yields of **9** by this route were poor. Having established that the thermal unmasking of **8** cleanly afforded diene **9**, we then examined the thermolysis of **8** under reaction conditions in which the azatriene **9** would be liberated in situ. However, as shall become evident, this seemingly innocuous experimental expedient must be exercised with some caution.

When the enamide **8** was heated for 18 h in refluxing xylene (1% solution) containing 1% bis(trimethylsilyl)-acetamide (BSA) and 0.3% bis(3-*tert*-butyl-4-hydroxy-5-methylphenyl) sulfide (**10**), a single cycloadduct was isolated in 48% yield. The same product was formed upon thermolysis of **9** in refluxing xylene in the absence of any additives. The infrared (IR) spectrum of this cycloadduct displayed a carbonyl stretching frequency at 1670 $cm^{-1}$, which is characteristic of a $\gamma$-lactam. Since the proton $H_b$ at C(7a) in the cycloadduct appeared as a doublet of doublets ($J_{ab}$ = 7 Hz; $J_{bc}$ = 11 Hz) centered at $\delta$ 3.61, we tentatively concluded that the structure of this cycloadduct was **11**. This assignment was fully confirmed by an *x*-ray analysis, as shown by the ORTEP plot in Figure 1. The coupling constants between the vicinal protons $H_a$ and $H_b$ of 7 Hz and between $H_b$ and $H_c$ of 11 Hz in the cycloadduct correlate relatively well with those expected from the Karplus curve[18] for the measured dihedral angles of 36 and 179°, respectively. It did not escape unnoticed that the stereochemical outcome of the intramolecular [4 + 2] cycloaddition of the model azatriene **9** augured well for the application of such a process to the synthesis of the lycorane **4** according to Scheme I.

Surprisingly, thermolysis of **8** as a solution in xylene (1%) at 180 °C for 4 h in a sealed glass tube afforded a 41% yield of a 3:1 mixture of the *cis*-hydroindole **11**, together with a new cycloadduct. Once again, a sharp absorption at 1675 $cm^{-1}$ in the IR spectrum of this substance suggested the presence of a $\gamma$-lactam. However, the appearance of the tertiary hydrogen $H_b$ at C(7a) in the 200-MHz $^1H$ NMR spectrum as a doublet of doublets ($J_{ab}$ = 10 Hz; $J_{bc}$ = 4 Hz) centered at $\delta$ 3.41 provided strong evidence that this cycloadduct was the *trans*-hydroindole **12** in which the relative stereochemistry about the original double bond of the enamide had been lost. This structural

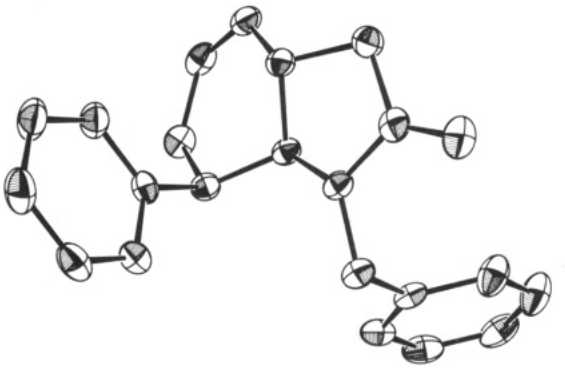
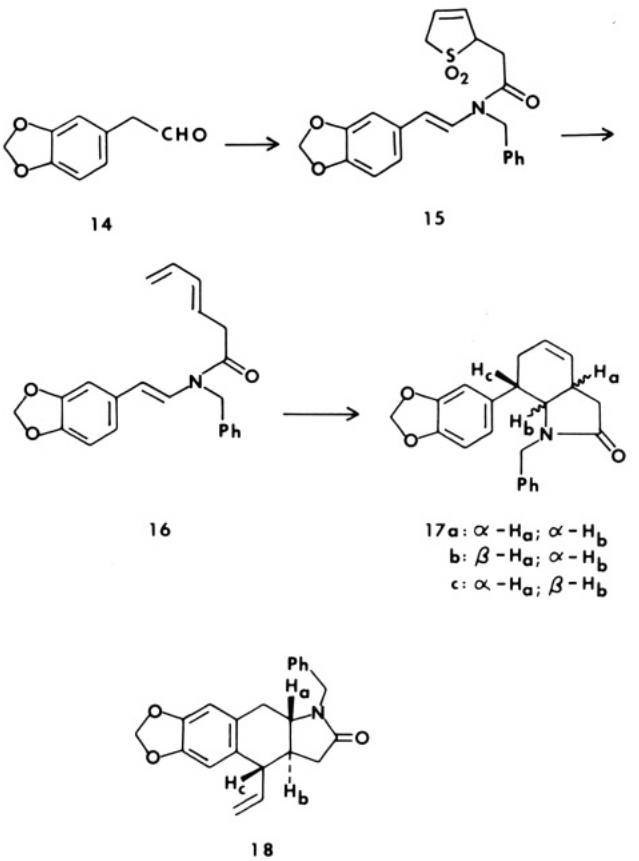


**Figure 2.** ORTEP plot of hydroindole **12** with non-hydrogen atom shown as 50% thermal ellipsoids.

Scheme III




assignment was again unequivocally established by an X-ray analysis, as indicated by the ORTEP plot in Figure 2. The vicinal coupling constants ($J_{ab}$ = 10 Hz and $J_{bc}$ = 4 Hz) are again in good agreement with those expected from the Karplus curve for the measured dihedral angles of 171 and 62°, respectively.

We also briefly examined the thermolyses of the enamido dienes **13** (R = OMe, Me, $CCl_3$), which were readily prepared by the condensation of phenylacetaldehyde with 3,5-hexadienylamine, followed by acylation of the intermediate imine with the appropriate acid chloride.[19] However, no identifiable cycloadducts were obtained under a variety of conditions at temperatures as high as 600 °C, and these studies were abandoned.

Having been encouraged by the preliminary experiments involving the enamides **8** and **9**, we turned our attention

(18) Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11; *J. Am. Chem. Soc.* **1963**, *85*, 2870.

(19) Chou, T. Ph.D. Dissertation, The University of Texas, Austin, Texas, 1979.

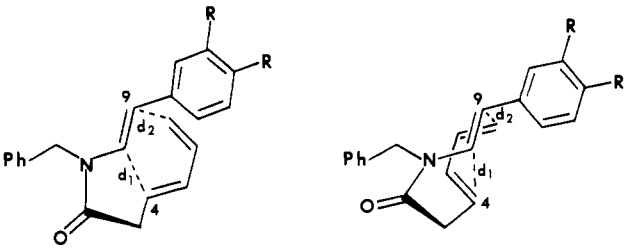
to the thermolyses of substrates more closely related to **6** as summarized in Scheme III. In the event, condensation of homopiperonal (**14**)[20] with benzylamine in toluene containing $MgSO_4$, followed by the acylation in situ of the intermediate imine with the acid chloride **7** in the presence of diethylaniline, afforded the masked enamido diene **15** in 48% yield. The expulsion of sulfur dioxide from **15** occurred upon brief thermolysis at 110 °C to give **16** quantitatively. When a solution containing either the enamide **15** or **16**, BSA, and the aryl sulfide **10** in xylene was heated at reflux, an inseparable mixture of the two hydroindoles **17a** and **17b** in a ratio of 1:1.5[21] was obtained in 45–50% yield, along with trace amounts (<2% of each) of two other cycloadducts. The structures of **17a** and **17b** were convincingly established by their eventual conversion to $\alpha$-lycorane (**19a**) and $\beta$-lycorane (**19b**), respectively (vide infra). Since it was also of interest to determine the structures of these two minor cycloadducts, other conditions for the thermolysis of **15** were examined in the anticipation that larger quantities of these materials might be produced.

Heating the enamide **15** (1% in xylene) in a sealed tube at 150 °C (bath temperature) afforded a 1:1.5 mixture[21] of the cis and trans cycloadducts **17a** and **17b** (27% yield), together with 16% of the isomeric hydroindole **17c** and a trace of another substance. These latter two compounds corresponded by HPLC with the two minor products obtained previously upon the thermolyses of **15** or **16** in the presence of BSA and the aryl sulfide **10**. The relative stereochemistry at the three chiral centers of **17c** is supported by the appearance in the $^1H$ NMR spectrum (200 MHz) of the proton $H_b$ as a doublet of doublets ($J_{ab}$ = 10 Hz; $J_{bc}$ = 4 Hz) centered at $\delta$ 3.33, which is identical with that observed for $H_b$ in the closely related hydroindole **12**. Moreover, the aliphatic portion of the $^{13}C$ NMR spectrum of **17c** is very similar to that of **12**. The conversion of **17c** to a tetracyclic amine (vide infra) whose IR spectrum in the region 2600–3000 $cm^{-1}$ is identical with that of $\delta$-lycorane (**19c**) adds further credibility to this structural assignment.

Interestingly, thermolysis of the enamido diene **16** in either a sealed tube at 150 °C or in refluxing xylene produced a mixture of **17a** and **17b** (1:1.5, 48%), together with 15% of another material, tentatively identified as the hydrobenzindole **18**, which was identical by HPLC with the other minor cycloadduct previously formed by the thermolysis of **15** or **16** in the presence of BSA and aryl sulfide **10**. Only trace amounts of **17c** were detected. Virtually the same results were obtained if the enamide **15** was heated in xylene under vigorous reflux. The structural assignment of **18** is based upon an examination of its IR and NMR spectra. Thus, the IR spectrum of **18** exhibits a strong absorption at 1675 $cm^{-1}$ that is characteristic of a $\gamma$-lactam. Furthermore, the $^1H$ NMR spectrum (200 MHz) of **18** reveals that there are a total of three vinyl protons [$\delta$ 5.60 (m, 1 H), 5.23 (dd, 1 H, $J$ = 2 and 11 Hz), and 5.22 (dd, 1 H, $J$ = 2 and 16 Hz)], thereby signifying the presence of a terminal vinyl group. Confirmation of this fact was readily obtained by catalytic hydrogenation of the double bond to give a dihydro derivative, which displayed an easily discernible triplet ($\delta$ 0.75) for the terminal methyl group. Use of double resonance techniques determined the vicinal coupling constant between $H_b$ and $H_c$ to be 11 Hz, which is indicative of their anti relationship. Owing to overlapping signals, the exact magnitude of the coupling constant between $H_a$ and $H_b$ has been difficult to obtain, but it is approximately 11 Hz, which suggests that the hydroindole ring is trans-fused. This assignment remains somewhat equivocal,[6] however, since large vicinal coupling constants (10–12 Hz) have been observed for the bridgehead protons in related compounds having a *cis*-azabicyclo[4.3.0]nonane ring.[9f,22]

In separate experiments it was established that under the conditions required for the intramolecular [4 + 2] cycloadditions of the enamide **8** (or **9**) or **15** (or **16**) there was no interconversion of **11** and **12** or **17a–c** and **18**. Since no equilibration of the cycloadducts could be observed, it appears that the thermal cyclizations of **9** and **16** are kinetically controlled processes. It should also be noted that care was taken to identify all of the cycloadducts that could be isolated in significant quantity (>5% yield) from these reactions, but it could be misleading to assume that no other cycloadducts were formed in trace amounts.

One striking difference between the intramolecular [4 + 2] cycloadditions of the enamido dienes **9** and **16** is that the thermolysis of **9** in the presence of BSA afforded the *cis*-hydroindole **11** as the sole product, whereas thermolysis of **16** produced a 1:1.5 mixture of the *cis*- and *trans*-hydroindoles **17a** and **17b**, respectively. The stereochemical course of these cyclizations may be interpreted by employing a model of a concerted reaction with an unsymmetrical transition state having either biradical or zwitterionic character. The consequence of an unsymmetrical pathway for a concerted Diels–Alder reaction, a concept which has been previously suggested for both intermolecular[23] and intramolecular processes,[12] is that the relative rates of the formation of the two new carbon–carbon $\sigma$ bonds, and hence the relative distances $d_1$ and $d_2$ in the exo and endo transition states I and II, become important.




I II

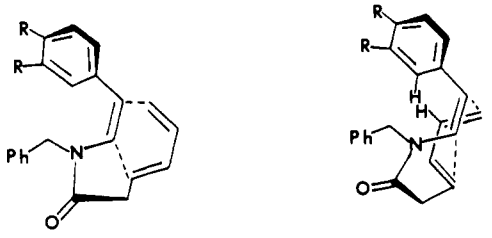
R,R = $H_2$; $OCH_2O$

Thus, in the transition state for the cyclization of these enamido dienes, if nitrogen stabilization of a developing radical or cationic center at C(8) dominates aryl stabilization of such a center at C(9), bond formation between C(1) and C(9) should precede that between C(4) and C(8). Since the nonbonded interactions between the aromatic ring and the diene would be greater in the exo transition state I ($d_1 > d_2$) than in the endo transition state II ($d_1 > d_2$), the cis cycloadduct should be favored, as is observed for the cyclization of **9**. However, if the stabilization of a developing radical or cationic center at C(9) by the aryl group dominates that of nitrogen stabilization of such a center at C(8), the bonding interaction between C(4) and C(8) will increase at the expense of bonding between C(1) and C(9). As bonding in the transition state between C(4) and C(8) becomes more significant, the formation of in-

(20) Howell, F. H.; Taylor, D. A. H. *J. Chem. Soc.* **1956**, 4252.
(21) This ratio was determined by a comparison of the relative intensities of the carbonyl carbons in the $^{13}C$ NMR spectrum of the mixture.
(22) See Ban, Y.; Iijima, I.; Inoue, I.; Akagi, M.; Oishi, T. *Tetrahedron Lett.* **1969**, 2067, and refs 3 and 4 therein.
(23) See (a) Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 4092. (b) Dewar, M. J. S.; Olivella, S.; Rzepa, H. S. *Ibid.* **1978**, *100*, 5650.

creased amounts of the trans cycloadduct, as observed for the cyclization of **16**, might be expected, since the trans orientation of the side chains in the incipient γ-lactam (e.g., I, $d_1 < d_2$) appears subject to less torsional and steric strain than the corresponding cis orientation (e.g., II, $d_1 < d_2$). Our experimental results are in qualitative agreement with this model.

There remains the question of the origin of the cycloadducts **12** and **17c**, which were isolated whenever the corresponding enamides **8** and **15** were heated in sealed tubes in the absence of BSA. Since only traces of **12** and **17c** were detected upon thermolyses of the enamido dienes **9** and **16** under numerous conditions, it appears that the presence of sulfur dioxide affects the stereochemical course of these intramolecular cycloadditions. A reasonable interpretation of these observations is that sulfur dioxide, a Lewis acid, induces isomerization of the trans-enamido dienes **9** and **16** to give the isomeric *cis*-enamido dienes, which then undergo the intramolecular [4 + 2] cycloaddition. Examination of molecular models of the exo and endo transition states III and IV for this process reveals



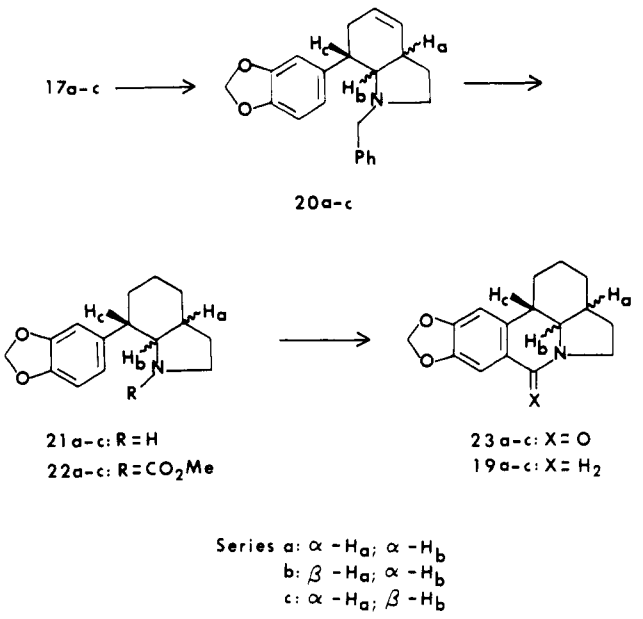
III IV

R,R = $H_2$; $OCH_2O$

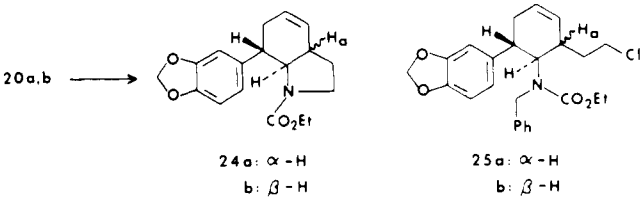
that the former, which leads to a *trans*-hydroindole, involves less severe nonbonded interactions and should be preferred. Inasmuch as *cis*-enamido dienes were not detected in the reaction mixture, this explanation must, however, be considered tentative.

**Synthesis of α-, β-, and δ-Lycoranes (19a–c).** The structures of the cycloadducts **17a–c** were unequivocally established by their respective conversion to α-, β-, annd δ-lycoranes (**19a–c**) employing a straightforward sequence of reactions (Scheme IV). Thus, treatment of the mixture of lactams **17a** and **17b** with lithium aluminum hydride afforded a mixture of the corresponding tertiary amines **20a** (32%) and **20b** (51%), which could be separated by HPLC. Catalytic hydrogenation of the double bond of the *cis*-hydroindole **20a** ($H_2$, 5% Pd/C, HOAc) proceeded with concomitant N-debenzylation to provide the secondary amine **21a**, which was treated with methyl chloroformate to give the carbamate **22a** in 71% overall yield. Upon heating in phosphorus oxychloride **22a** underwent facile cyclization in 82% yield to provide 7-oxo-α-lycorane (**23a**), which was reduced in 84% yield to α-lycorane (**19a**) by reaction with lithium aluminum hydride. Both of the lycoranes **19a** and **23a** thus obtained exhibited spectral properties identical with those of authentic samples.[24-26] The *trans*-hydroindole **20b** was then converted by the same sequence of reactions in 50% overall yield into β-lycorane (**19b**), whose IR spectrum was identical with that of an authentic sample.[26] In a similar fashion, the cycloadduct **17c** was converted to δ-lycorane (**19c**) in 36% overall yield. Unfortunately, it has not been possible to correlate rigorously this synthetic δ-lycorane with an authentic sample, since the IR spectrum of (−)-δ-lycorane has been reported[27] only in the region of 2600–3000 $cm^{-1}$. Nevertheless, in that region the IR spectrum of our racemic δ-lycorane (**19c**) corresponds with that published.

Scheme IV




**Formal Synthesis of Lycorine (3).** Having established the structure of the cycloadduct **17a** and the derived tertiary amine **20a**, our attention was then directed toward the conversion of **20a** to **4** in order to complete the formal synthesis of lycorine (**3**). Surprisingly, the reaction of **20a**




with ethyl chloroformate[28] in refluxing benzene containing $NaHCO_3$ resulted not only in the formation of the desired urethane **24a** in 76% yield by removal of the *N*-benzyl group, but **25a**, which results from cleavage of the pyrrolidine ring, was also isolated in 18% yield. It is of interest to note that the more highly strained *trans*-hydroindole **20b** suffered exclusive rupture of the pyrrolidine ring to give **25b** when heated with ethyl chloroformate under identical conditions. Since the regiochemical course of these *N*-dealkylations could not be significantly altered by changing the reaction conditions or by employing other chloroformates, an alternate route to **24a** was examined. This modification of the original synthetic plan was founded upon the prediction that mere replacement of the *N*-benzyl group of **20a,b** with a *N*-*p*-methoxybenzyl moiety

(24) We thank Professor G. Stork for a $^1H$ NMR spectrum and IR spectrum of 7-oxo-α-lycorane (**23a**).[4f]

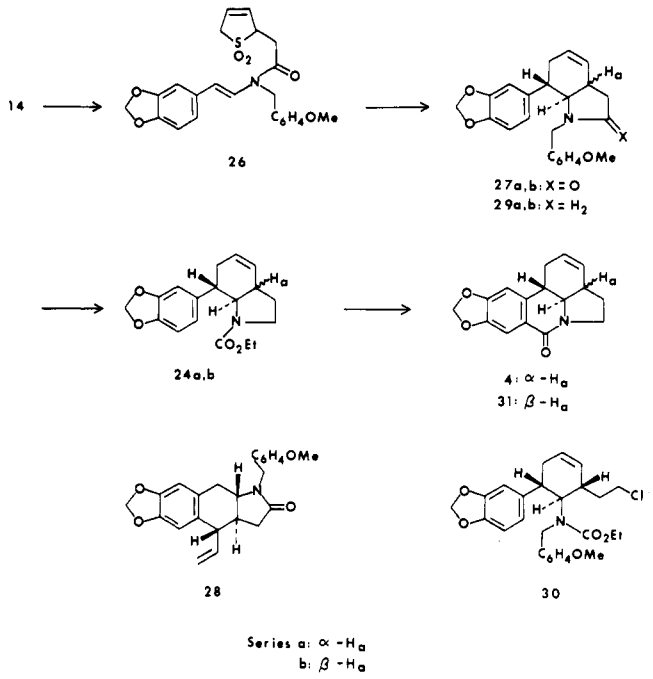
(25) We thank Professor B. Umezawa for providing an authentic sample of racemic α-lycorane (**19a**) and its $^1H$ NMR spectrum.

(26) We thank Professor R. K. Hill and Dr. Y. Hamada[27] (Shionogi Research Laboratories, Osaka, Japan) for IR spectra of α-, β-, and γ-lycorane.

(27) Cf., Kotera, K. *Tetrahedron* **1961**, *12*, 248.

(28) For example, see (a) Wright, W. B., Jr.; Brabander, H. J. *J. Org. Chem.* **1961** *26*, 4057. (b) Hobson, J. D.; McClusky, J. G. *J. Chem. Soc. C* **1967**, 2015. (c) Montzka, T. A.; Matiskeller, J. D.; Partyka, R. A. *Tetrahedron Lett.* **1974**, 1325. (d) Banholzer, R.; Heusner, A.; Schulz, W. *Liebigs Ann. Chem.* **1975**, 2227. (e) Brine, G. A.; Boldt, K. G.; Hart, C. K.; Carroll, F. I. *Org. Prep. Proced. Int.* **1976**, *8*, 103. (f) Olofson, R. A.; Schnur, R. C.; Bunes, L.; Pepe, J. P. *Tetrahedron Lett.* **1977**, 1567, 1571.

Scheme V




should greatly enhance the cleavage of the benzylic carbon–nitrogen bond relative to opening of the pyrrolidine ring. To our immense gratification, this proved to be precisely the case.

The requisite *cis*-hydroindole **29a** was readily prepared from homopiperonal (**14**) by a simple adaptation of previously established procedures (Scheme V). Thus, condensation of **14** with *p*-methoxybenzylamine in toluene containing $MgSO_4$, followed by acylation of the intermediate imine with the acid chloride **7** in the presence of diethylaniline, afforded the latent enamido diene **26** in 68% yield. When a 1% solution of **26** in xylene containing aryl sulfide **10** (0.3%) and BSA (1%) was heated at reflux for 18 h, a 47% yield of an inseparable mixture of the *cis*- and *trans*-hydroindoles **27a** and **27b** (1:1.4[21]) was obtained. In addition to the cycloadducts **27a,b**, a small amount (~2%) of a substance was also isolated which, based upon its spectral data, has been tentatively identified as the hydrobenzindole **28**. Since prior experience had adequately demonstrated that the use of these conditions for thermolysis resulted in the highest yields of *cis*- and *trans*-hydroindoles without the formation of side products, no other thermolyses of **26** were undertaken. Reduction of the mixture of lactams **27a,b** with lithium aluminum hydride provided the corresponding tertiary amines **29a** (35%) and **29b** (50%), which were readily separated by preparative HPLC. Upon reaction with ethyl chloroformate in refluxing benzene containing $NaHCO_3$, the *cis*-hydroindole **29a** underwent smooth N-debenzylation to give a 91% yield of the urethane **24a** as the only isolable product. Attempts to cleave the *N*-*p*-methoxybenzyl group from **29a** (or **27a,b**) under a variety of acidic conditions were much less satisfactory. Subsequent cyclization of **24a** with $POCl_3$ proceeded without event to afford 7-oxo-$\Delta^{2,3}$-$\alpha$-lycorane (**4**) in 86% yield, thereby completing a novel, formal synthesis of lycorine (**3**). The racemic **4** thus obtained was identical in all respects ($^1H$ NMR, IR, low-resolution mass spectrum, TLC, mp, mmp) with an authentic sample.[29] Moreover, catalytic hydrogenation of **4** gave **23a**, which was identical with the sample previously prepared independently from **22a**.

When the *trans*-hydroindole **29b** was allowed to react with ethyl chloroformate in the usual fashion, the hydroindole **24b** was obtained in 61% yield, but the urethane **30**, which is the product of cleavage of the strained pyrrolidine ring, was also isolated in 34% yield. The hydroindole **24b** was readily converted in 90% yield to 7-oxo-$\Delta^{2,3}$-$\beta$-lycorane (**31**) by heating in $POCl_3$. Reduction of **31** via catalytic hydrogenation provided 7-oxo-$\beta$-lycorane (**23b**), which was completely identical with that prepared earlier from **22b**.

## Conclusions

The facile elaboration of lycorane **4** in only five steps from homopiperonal (**14**) completes a novel, formal synthesis of the Amaryllidaceae alkaloid lycorine (**3**) and further establishes the practical utility of employing the intramolecular [4 + 2] cycloadditions of enamido dienes as a key step in the syntheses of alkaloids containing hydroindole rings. We are currently in the process of further exploring the intramolecular [4 + 2] cycloadditions of other azatrienes to give functionalized hydroindoles, hydroquinolines, and hydroisoquinolines in order to develop better models for predicting the stereochemistry of these processes. These studies, together with new applications of these thermal cyclizations to the total syntheses of alkaloids, will be reported in due course.

## Experimental Section

**General.** Unless noted otherwise, all starting materials were obtained from commercial suppliers and were used without further purification. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. All boiling points are uncorrected. Ether, tetrahydrofuran (THF), benzene, toluene, and xylene were distilled from either sodium or potassium benzophenone immediately prior to use. Hexamethylphosphoramide (HMPA) was distilled from potassium under reduced pressure. Phosphorus oxychloride was freshly distilled under dry nitrogen, and methyl and ethyl chloroformate were distilled from calcium hydride. All reactions involving organometallic reagents and $LiAlH_4$ were executed under an atmosphere of dry nitrogen or argon using oven-dried glassware. IR spectra were determined as solutions in chloroform unless otherwise specified on Beckman Acculab 8 infrared recording spectrophotometer. $^1H$ NMR spectra were determined as solutions in $CDCl_3$ as indicated on either a Varian EM 390 (90 MHz) or a Nicolet NT 200 (a superconducting 200-MHz FT instrument). Chemical shifts are expressed in parts per million ($\delta$) downfield from internal tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; and comp, complex multiplet. Coupling constants are given in hertz (Hz). The $^{13}C$ NMR spectra were determined on either a Bruker WH-90 FT or Varian FT-80A, and the chemical shifts are reported in parts per million ($\delta$ units) downfield from internal tetramethylsilane. Low-resolution mass spectra were obtained on a DuPont (CEC) 21-491 instrument at an ionizing voltage of 70 eV, and exact mass determinations were obtained on a DuPont (CEC) 21-110 instrument. Preparative high-performance liquid chromatography (HPLC) was done on either a Waters Prep LC 500 instrument using two Prep PAK columns (sample size >500 mg) or a Waters 6000A solvent delivery system with a Model U6K injector and two Porasil A columns (0.6 m × 7.8 mm) (sample size <500 mg).

**X-ray Analysis.** The X-ray investigations of hydroindoles **11** and **12** were carried out with a Syntex $P2_1$ diffractometer. Unit cell dimensions were determined by least-squares refinement using the Bragg angles of 45 and 30 reflections, respectively, ($25° < 2\theta < 30°$, Mo $K\alpha$ radiation, $\lambda = 0.791069$ Å) at 180 K. Intensity data were collected at 180 K by the $\omega$-scan technique using Mo $K\alpha$ radiation monochromatized by a graphite crystal. Scans of 1.0° were used with scan rates that varied from 2.0 to 5.0° $min^{-1}$ depending directly upon the number of counts obtained in a short preliminary count of the peak height. Backgrounds were measured

(29) We thank Professor K. Torssell for the $^1H$ NMR and IR spectra, and a generous sample of the unsaturated lactam **4**.

by a stationary counter with $\omega$ displaced ±1.0° from $K\alpha$ peak position; the time of each background measurement was one-half the scan time. Four standard reflections, measured after every 96 reflections, showed no significant variation during intensity measurements of the two crystals. Lorentz and polarization corrections were applied to the intensities, but no absorption corrections were made. Standard deviations of the intensities, $\sigma(I)$, and of the structure amplitudes, $\sigma(F)$, were derived directly from counting statistics and an "ignorance factor" $p$ of 0.040.[30] The structures were solved by direct methods using MULTAN78.[31] The observed reflections [$I > 3\sigma(I)$] were used in a full-matrix least-squares refinement of positional and thermal parameters in which the function minimized was $\sum w(|F_o| - |F_c|)^2$, where $w = 1/\sigma^2(F_o)$. The agreement index, $R$, = $\sum\langle|F_o| - |F_c|\rangle/\sum|F_o|$, and $R_w = (\sum w(|F_o| - |F_c|)^2/\sum w|F_o|^2)^{1/2}$. Hydrogen atoms were located in difference Fourier maps after convergence of isotropic refinement. Non-hydrogen atoms were then refined anisotropically, and the hydrogen atoms were refined isotropically. Final difference maps revealed no electron density above the noise level. For C, N, and O, scattering factors were taken from the International Tables for X-Ray Crystallography,[32] and for hydrogen scattering factors of Stewart et al.[33] were used. Mathematical and computational details are noted elsewhere.[34]

A crystal of hydroindole **11**, dimensions of 0.40 × 0.40 × 0.35 mm, obtained from Skelly B was monoclinic, space group $P2_1/c$, $a$ = 14.223 (3), $b$ = 8.621 (2), $c$ = 14.853 (4) Å, $\beta$ = 116.96 (2)°, $V$ = 1623.3 Å$^3$, $Z$ = 4, $d_{calcd}$ = 1.18 g cm$^{-3}$, $\mu$ = 1.11 cm$^{-1}$. Of 3723 unique reflections measured in the range $4° < 2\theta < 55°$, 2650 were considered to be observed. An extinction coefficient was included in the refinement, which converged to a final $R$ = 0.038 and $R_w$ = 0.045.

A crystal of hydroindole **12**, of dimensions 0.30 × 0.35 × 0.40 mm obtained from EtOAc–Skelly B (1:1, v/v) was selected for data collection. The crystal was triclinic, space group $P\bar{1}$, with $a$ = 9.415 (4), $b$ = 11.815 (4), $c$ = 8.858 (2) Å, $\alpha$ = 96.85 (2), $\beta$ = 107.55 (3), $\gamma$ = 114.66 (2)°, $V$ = 818.8 Å$^3$, $Z$ = 2, $d_{calcd}$ = 1.17 g cm$^{-3}$, $\mu$ = 1.10 cm$^{-1}$. Of 3753 unique reflections measured in the range $4° < 2\theta < 55°$, 2695 reflections were considered to be observed. Final $R$ = 0.039 and $R_w$ = 0.048.

**(*E*)-*N*-Benzyl-*N*-(benzylidenemethyl)-2-(2,5-dihydro-1,1-dioxothienyl)acetamide (8).** To a solution of benzylamine (450 mg, 4.2 mmol) in anhydrous benzene (6 mL) containing magnesium sulfate (2 g) at 5 °C under dry nitrogen was added dropwise phenylacetaldehyde (500 mg, 4.2 mmol), and the mixture was stirred at 5 °C for 1 h. A solution of the acid chloride **7** (815 mg, 4.2 mmol) in anhydrous benzene (6 mL) was then added, and the mixture was stirred at 5 °C for another 0.5 h, at which time triethylamine (455 mg, 4.5 mmol) was added. The resulting mixture was stirred at 5 °C for 1 h and then allowed to warm to room temperature. The solid was removed by suction filtration and washed with anhydrous benzene (3 × 20 mL). The combined filtrates and washings were concentrated under reduced pressure, and the residue was purified by preparative HPLC using ethyl acetate/hexane (1:1) as the eluting solvent. The crude product was recrystallized from ethyl acetate/hexane (1:2) to give 538 mg (35%) of pure **8** as a white amorphous solid: mp 144–145 °C dec; IR 1665, 1640 cm$^{-1}$; NMR (200 MHz) $\delta$ 8.17 (d, 0.4 H, $J$=15 Hz), 7.27 (m, 10.6 H), 6.12 (m, 2.6 H), 5.92 (d, 0.4 H, $J$ = 15 Hz), 5.04 (s, 1.2 H), 4.93 (s, 0.8 H), 4.40 (m, 1 H), 3.79 (m, 2 H), 3.36 (dd, 0.6 H, $J$ = 6 and 17 Hz), 3.12 (dd, 0.4 H, $J$ = 6 and 17 Hz), 2.93 (dd, 0.6 H, $J$ = 6 and 17 Hz), 2.69 (dd, 0.4 H, $J$ = 6 and 17 Hz); mass spectrum, $m/e$ 303, 212, 209, 91 (base), 67.

Anal. Calcd for $C_{21}H_{21}NO_3S$: C, 68.63; H, 5.76; N, 3.81. Found: C, 68.46; H, 5.71; N, 3.93.

**(*E*)-*N*-Benzyl-*N*-[[3,4-(methylenedioxy)benzylidene]-methyl]-2-(2,5-dihydro-1,1-dioxothienyl)acetamide (15).** To a stirred solution of benzylamine (530 mg, 5 mmol) in anhydrous toluene (8 mL) containing magnesium sulfate (3 g) at 0 °C under dry nitrogen was added dropwise a solution of homopiperonal[20] (**14**) (980 mg, 6 mmol) in dry toluene (2 mL), and the resulting mixture was stirred at 0 °C for 1 h and then at room temperature for another 0.5 h. The magnesium sulfate was removed by suction filtration, and the filtrate was added dropwise to a mixture of the acid chloride **7** (970 mg, 5 mmol) and *N*,*N*-diethylaniline (931 mg, 6.25 mmol) dissolved in dry toluene (8 mL) at −78 °C under nitrogen. The resulting mixture was stirred at −78 °C for 2 h and then at room temperature for 2 h. The solid was removed by suction filtration and washed with ethyl acetate/hexane (5:1) (60 mL). The filtrate was concentrated under reduced pressure, and the residue was passed through a column of silica gel (10 g) using ethyl acetate/hexane (5:1) as the eluent. The solvent was evaporated under reduced pressure, and the crude product was recrystallized from ethyl acetate/hexane (1:2) to give 986 mg (48%) of the enamide **15** as a white amorphous solid: mp 121–122 °C dec; IR 1665, 1640 cm$^{-1}$; NMR (200 MHz) $\delta$ 8.01 (d, 0.4 H, $J$ = 15 Hz), 7.30 (m, 5 H), 7.07 (d, 0.6 H, $J$ = 15 Hz), 6.74 (m, 3 H), 6.09 (m, 2.6 H), 5.93 (s, 1.2 H), 5.92 (s, 0.8 H), 5.85 (d, 0.4 H, $J$ = 15 Hz), 5.00 (s, 1.2 H), 4.90 (s, 0.8 H), 4.39 (m, 1 H), 3.77 (m, 2 H), 3.33 (dd, 0.6 H, $J$ = 6 and 17 Hz) 3.11 (dd, 0.4 H, $J$ = 6, and 17 Hz), 2.90 (dd, 0.6 H, $J$ = 6 and 17 Hz), 2.68 (dd, 0.4 H, $J$ = 6 and 17 Hz); mass spectrum, $m/e$ 347 (base), 254, 174, 91, 67.

Anal. Calcd for $C_{22}H_{21}NO_5S$: C, 64.21; H, 5.14; N, 3.40; S, 7.79. Found: C, 63.34; H, 5.31; N, 3.46; S, 8.09.

**(*E*)-*N*-(*p*-Methoxybenzyl)-*N*-[[3,4-(methylenedioxy)-benzylidene]methyl]-2-(2,5-dihydro-1,1-dioxothienyl)acetamide (26)** was prepared in 68% yield according to the previous procedure above using *p*-methoxybenzylamine (0.94 g, 7.3 mmol), homopiperonal (**14**) (1.12 g, 7.3 mmol), acid chloride **7** (1.41 g, 7.3 mmol), and diethylaniline (1.19 g, 8.0 mmol). The crude product was purified by preparative HPLC using ethyl acetate/hexane (1:1) as the eluting solvent to produce 2.20 g (68%) of **26** as pale yellow flakes: mp 73–76 °C dec; IR 1662, 1635 cm$^{-1}$; NMR (200 MHz) $\delta$ 7.97 (d, 0.4 H, $J$ = 15 Hz), 7.17 (d, 1 H, $J$ = 8 Hz), 7.12 (d, 1 H, $J$ = 8 Hz), 7.03 (d, 0.6 H, $J$ = 15 Hz), 6.77 (m, 5 H), 6.08 (m, 2.6 H), 5.93 (s, 1.2 H) , 5.91 (s, 0.8 H), 5.87 (d, 0.4 H, $J$ = 15 Hz), 4.92 (s, 1.2 H), 4.83 (s, 0.8 H) , 4.38 (m, 1 H), 3.79 (s, 1.2 H), 3.77 (s, 1.8 H), 3.74 (m, 2 H), 3.29 (dd, 0.6 H, $J$ = 6 and 17 Hz), 3.10 (dd, 0.4 H, $J$ = 6 and 17 Hz), 2.88 (dd, 0.6 H, $J$ = 6 and 17 Hz), 2.70 (dd, 0.4 H, $J$ = 6 and 17 Hz); mass spectrum, $m/e$, 377, 121 (base).

Anal. Calcd for $C_{23}H_{23}NO_6S$: C, 62.57; H, 5.25; N, 3.17. Found: C, 62.48; H, 5.17; N, 3.28.

**(*E*)-*N*-Benzyl-*N*-[[3,4-(methylenedioxy)benzylidene]-methyl]-3(*E*),5-hexadienamide (16).** A 1% solution of the enamide **15** (500 mg) in dry, degassed toluene (100 mL) under dry nitrogen was heated at reflux for 2 h. The solvent was removed under reduced pressure to give 410 mg (97%) of the enamido diene **16** as a light yellow oil: NMR $\delta$ 7.97 (d, 0.4 H, $J$ = 15 Hz), 7.17 (m, 5.6 H), 6.67 (m, 3 H), 6.00 (m, 4 H), 5.83 (s, 2 H), 5.00 (m, 4 H), 3.27 (m, 2 H); mass spectrum, $m/e$ 347.1517 (base) ($C_{22}H_{21}NO_3$ requires 347.1521, 254, 174, 91.

**Thermolyses of Enamides 8, 15, 16, and 26. General Procedures. Method A.** A 1% solution of the appropriate enamide **8**, **15**, **16**, or **26** (weight given) in dry, degassed xylene containing *O*,*N*-bis(trimethylsilyl)acetamide (1%) and bis(3-*tert*-butyl-4-hydroxy-5-methylphenyl) sulfide (0.3%) under dry nitrogen was heated at reflux for 18 h. The solution was cooled, washed with saturated NaCl, and dried ($MgSO_4$), and the crude product was purified by preparative HPLC with ethyl acetate/hexane (ratio given). Yield, physical properties, and spectral data are given.

**Method B.** A 1% solution of the appropriate enamide **8**, **15**, or **16** (weight given) in dry, degassed xylene was heated under dry nitrogen at reflux for 18 h. The solvent was evaporated under reduced pressure, and the crude product was purified by preparative HPLC using ethyl acetate/hexane (ratio given). Yield, physical properties, and spectral data are given.

**Method C.** A 1% solution of the appropriate enamide **8**, **15**, and **16**, (weight given) in dry, degassed xylene in a resealable glass bomb was heated at (oil bath temperature given) for (time given). The solvent was evaporated under reduced pressure, and the crude

(30) Corfield, P. W. R.; Doedens, R. J.; Ibers, J. A. *Inorg. Chem.* **1967**, *6*, 197.
(31) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr. Sect. A.* **1971**, *A27*, 368.
(32) "International Tables for X-Ray Crystallography"; Kynoch Press: Birmingham, England 1974; Vol. IV, p 72.
(33) Stewart, R. F.; Davidson, E. R.; Simpson, W. T *J. Chem. Phys.* **1965**, *42*, 3175.
(34) Harlow, R. L.; Simonsen, S. H. *Acta Crystallogr., Sect. B* **1976**, *B32*, 466.

cycloadducts were purified by preparative HPLC using ethyl acetate/hexane (ratio given) as the eluting solvent. Yield, physical properties, and spectral data are given.

**Thermolysis of (*E*)-*N*-Benzyl-*N*-(benzylidenemethyl)-2-(2,5-dihydro-1,1-dioxothienyl)acetamide (8). Preparation of (3a*R**,7*R**,7a*R**)- and (3a*R**,7*R**,7a*S**)-*N*-Benzyl-2-oxo-7-phenyl-2,3,3a,6,7,7a-hexahydroindoles (11 and 12). Method A:** 8 (500 mg); preparative HPLC using ethyl acetate/hexane (1:2.5) afforded 185 mg (45%) of the *cis*-hydroindole 11 as the sole product; colorless cubes from hexane; mp 155–156 °C; IR 1670 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 7.30 (m, 8 H), 6.87 (m, 2 H), 5.87 (m, 1 H), 5.75 (m, 1 H), 4.92 (d, 1 H, $J$ = 16 Hz), 3.61 (dd, 1 H, $J$ = 7 and 11 Hz), 2.87 (m, 2 H), 2.68 (m, 1 H), 2.66 (d, 1 H, $J$ = 16 Hz), 2.43 (dd, 1 H, $J$ = 11 and 16 Hz), 2.26 (m, 2 H); $^{13}C$ NMR $\delta$ 174.7, 60.8, 45.4, 43.8, 37.5, 35.5, 32.2; mass spectrum, $m/e$ 303.1631 ($C_{21}H_{21}NO$ requires 303.1623), 212 (base), 91.

Anal. Calcd for $C_{21}H_{21}NO$: C, 83.12; H, 6.98; N, 4.62. Found: C, 82.64; H, 7.00; N, 4.60.

**Method C:** 8 (1.00 g); 170 °C; 4 h; ethyl acetate/hexane (1:2.5) to give 11 (310 mg, 36%) and 12 (100 mg, 12%).

For 12: colorless cubes from hexane, mp 130–131 °C; IR 1675 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 7.26 (m, 10 H), 5.88 (br d, 1 H, $J$ = 11 Hz), 5.77 (m, 1 H), 5.26 (d, 1 H, $J$ = 15 Hz), 4.13 (d, 1 H, $J$ = 15 Hz), 3.51 (m, 1 H), 3.41 (dd, 1 H, $J$ = 4 and 10 Hz), 2.53 (comp, 4 H), 2.15 (dd, 1 H, $J$ = 13 and 15 Hz), $^{13}C$ NMR $\delta$ 177.0, 63.2, 45.3, 38.7, 36.3, 32.8 (2 C); mass spectrum, $m/e$ 303.1631 ($C_{21}H_{21}NO$ requires 303.1623), 212 (base), 91.

Anal. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.32; H, 6.91; N, 4.78.

**Thermolysis of Enamides 15 and 16. Preparation of (3a*R**,7*R**,7a*R**)-, (3a*R**,7*S**,7a*S**)-, and (3a*R**,7*R**,7a*S**)-*N*-Benzyl-2-oxo-7-[3,4-(methylenedioxy)-phenyl]-2,3,3a,6,7,7a-hexahydroindoles (17a–c) and (3a*R**,4*R**,9a*S**)-*N*-Benzyl-2-oxo-4-vinyl-2,3,3a,4,9,9a-hexahydro-6,7-(methylenedioxy)benz[*f*]indole (18). Method A:** 15 or 16 (2.00 g); preparative HPLC using ethyl acetate/hexane (1:2) gave 760 mg (46%) of an inseparable mixture (1:1.5) of hydroindoles **17a** and **17b** as the major products.

**Method B:** 15 or 16 (1.00 g); reflux; 18 h; preparative HPLC as in method A afforded 125 mg (15%) of the hydrobenzindole 18 and 285 mg (34%) from 15 or 377 mg (45%) from 16 of an inseparable mixture (1:1.5) of the hydroindoles **17a,b**.

For 18: mp 252–254 °C; as white needles from hexane; IR 1675 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 7.30 (m, 5 H), 6.68 (s, 1 H), 6.53 (s, 1 H), 5.88 (s, 2 H), 5.60 (m, 1 H), 5.23 (dd, 1 H, $J$ = 2 and 11 Hz), 5.22 (dd, 1 H, $J$ = 2 and 16 Hz), 4.92 (d, 1 H, $J$ = 15 Hz), 4.16 (d, 1 H, $J$ = 15 Hz), 3.30 (dt, 1 H, $J$ = 5 and 11 Hz), 3.19 (br t, 1 H, $J$ = 11 Hz), 2.96 (dd, 1 H, $J$ = 5 and 15 Hz), 2.66 (m, 1 H), 2.56 (dd, 1 H, $J$ = 7 and 16 Hz), 2.18 (m, 1 H), 2.01 (dq, 1 H, $J$ = 6 and 11 Hz); $^{13}C$ NMR $\delta$ 175.6, 58.7, 49.4, 44.5, 43.7, 36.4, 35.2; mass spectrum $m/e$ 347.1534 (base) ($C_{22}N_{21}NO_3$ requires 347.1521), 212, 173, 115, 91.

**Method C:** 15 (1.00 g); 150 °C; 3.5 h; preparative HPLC as in method A gave 139 mg (16%) of the hydroindole **17c** and 223 mg (27%) of an inseparable mixture (1:1.5) of the hydroindoles **17a** and **17b**.

For 17c: mp 156–157 °C as colorless cubes from hexane: IR 1680 $cm^{-1}$; $^1H$ NMR (200 MHz) $\delta$ 7.32 (m, 5 H), 6.73 (m, 3 H), 5.96 (s, 2 H), 5.86 (br d, 1 H, $J$ = 9 Hz), 5.74 (m, 1 H), 5.20 (d, 1 H, $J$ = 15 Hz), 4.06 (d, 1 H, $J$ = 15 Hz), 3.42 (m, 1 H), 3.33 (dd, 1 H, $J$ = 4 and 10 Hz), 2.27–2.73 (comp, 4 H), 2.12 (dd, 1 H, $J$ = 13 and 15 Hz); $^{13}C$ NMR $\delta$ 177.0, 63.1, 45.1, 38.2, 36.1, 32.8, 32.7; mass spectrum, $m/e$ 347.1525 ($C_{22}N_{21}NO_3$ requires 347.1521), 212, 202, 149, 121, 91 (base).

Anal. Calcd for $C_{22}N_{21}NO_3$: C, 76.06; H, 6.09; N, 4.03. Found: C, 76.24; H, 6.21; N, 4.35.

**(3a*R**,7*R**,7a*R**)- and (3a*R**,7*S**,7a*S**)-*N*-(*p*-Methoxybenzyl)-2-oxo-7-[3,4-(methylenedioxy)phenyl]-2,3,3a,6,7,7a-hexahydroindoles (27a and 27b). Method A:** 26 (1.00 g); preparative HPLC using ethyl acetate/hexane (1:1) provided 400 mg (47%) of an inseparable mixture (1:1.4) of the hydroindoles **27a** and **27b**.

**(3a*R**,7*R**,7a*R**)- and (3a*R**,7*S**,7a*S**)-*N*-Benzyl-7-[3,4-(methylenedioxy)phenyl]-2,3,3a,6,7,7a-hexahydroindoles (20a and 20b).** A solution of the lactams **17a** and **17b** (300 mg, 0.86 mmol) in dry ether (2 mL) was added dropwise (5 min) to a suspension of $LiAlH_4$ (95 mg) in dry ether (20 mL), and the mixture was stirred at room temperature for 2 h. The excess $LiAlH_4$ was destroyed by the sequential addition of $H_2O$ (0.1 mL), 4 N NaOH (0.1 mL), and $H_2O$ (0.3 mL), and the precipitated solids were removed by suction filtration and washed with $CH_2Cl_2$ (50 mL). The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure. The isomeric amines were separated by preparative HPLC using ethyl acetate/hexane/triethylamine (14:85:1) as the eluting solvent to give 86 mg (30%) of **20a** and 147 mg (51%) of **20b** as pale yellow oils.

For **20a**: NMR $\delta$ 7.14, (m, 5 H), 6.77 (m, 3 H), 5.84 (s, 2 H), 5.73 (overlapping AB q, 2 H, $J$ = 12 Hz), 3.53 (d, 1 H, $J$ = 14 Hz), 3.13 (d, 1 H, $J$ = 14 Hz), 1.33–3.00 (comp, 9 H); mass spectrum, $m/e$ 333.1740 ($C_{22}H_{23}NO_2$ requires 333.1729), 198 (base), 91.

For **20b**: NMR $\delta$ 7.10 (m, 5 H), 6.69 (m, 3 H), 5.80 (s, 2 H), 5.79 (d, 1 H, $J$ = 10 Hz), 5.57 (m, 1 H), 3.20 (d, 1 H, $J$ = 14 Hz), 2.67 (d, 1 H, $J$ = 14 Hz), 1.10–3.20 (comp, 9 H); mass spectrum, $m/e$ 333.1737 ($C_{22}H_{23}NO_2$ requires 333.1729), 198 (base), 91.

**(3a*R**,7*R**,7a*S**)-*N*-Benzyl-7-[3,4-(methylenedioxy)phenyl]-2,3,3a,6,7,7a-hexadroindole (20c).** The lactam **17c** (100 mg, 0.29 mmol) was reduced with $LiAlH_4$ (50 mg) in dry ether (10 mL) according to the above procedure to give 88 mg (91%) of the amine **20c** as a light yellow oil: NMR $\delta$ 7.27 (m, 5 H), 6.75 (m, 3 H), 5.90 (s, 2 H), 5.80 (overlapping AB q, 2 H, $J$ = 12 Hz), 4.42 (d, 1 H, $J$ = 14 Hz), 3.43 (m, 1 H), 3.09 (d, 1 H, $J$ = 14 Hz), 2.90 (m, 1 H), 1.33–2.73 (comp, 7 H); mass spectrum, $m/e$ 333.1734 ($C_{22}H_{23}NO_2$ requires 333.1729), 198, 120, 91 (base).

**(3a*R**,7*R**,7a*R**)- and (3a*R**,7*S**,7a*S**)-*N*-(*p*-Methoxybenzyl)-7-[3,4-(methylenedioxy)phenyl]-2,3,3a,6,7,7a-hexahydroindole (29a and 29b).** A mixture of the lactams **27a** and **27b** (300 mg, 0.79 mmol) was reduced with $LiAlH_4$ (73 mg) in dry ether (20 mL) as described above to give a mixture of amines **29a** and **29b**. Purification by preparative HPLC using ethyl acetate/hexane/triethylamine (14:85:1) as the eluting solvent afforded 90 mg (32%) of the *cis*-hydroindole **29a** and 145 mg (51%) of the *trans*-hydroindole **29b** as amber oils.

For **29a**: NMR (200 MHz) $\delta$ 7.05 ( br d, 2 H, $J$ = 8 Hz), 6.79 (m, 5 H), 5.91 (s, 2 H), 5.75 (m, 2 H), 3.78 (s, 3 H) 3.50 (d, 1 H, $J$ = 13 Hz), 3.19 (br d, 1 H, $J$ = 13 Hz), 2.95 (m, 1 H), 2.70 (m, 1 H), 1.89–2.40 (comp, 6 H), 1.62 (m, 1 H); mass spectrum, $m/e$ 363.1835 ($C_{23}H_{25}NO_3$ requires 363.1834), 228, 121 (base).

For **29b**: NMR (200 MHz) $\delta$ 7.04 (m, 2 H), 6.81 (m, 5 H), 5.91 (s, 2 H), 5.80 (br d, 1 H, $J$ = 9 Hz), 5.65 (m, 1 H), 3.75 (s, 3 H), 3.21 (d, 1 H, $J$ = 13 Hz), 2.98 (m, 1 H), 2.68 (d, 1 H, $J$ = 13 Hz), 1.79–2.68 (comp, 7 H), 1.46 (m, 1 H); mass spectrum, $m/e$ 363.1828 ($C_{23}H_{25}NO_3$ requires 363.1834), 228, 121 (base).

**(3a*R**,7*R**,7a*R**)-7-[3,4-(Methylenedioxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydroindole (21a).** A solution of the amine **20a** (45 mg, 0.13 mmol) in glacial acetic acid (1.5 mL) containing 5% Pd/C (30 mg) was stirred under $H_2$ (1 atm) at room temperature for 48 h. The catalyst was removed by suction filtration and washed with hot ethanol (30 mL). The filtrate and washings were concentrated under reduced pressure, and the residue was dissolved in $CH_2Cl_2$ (10 mL). The solution was washed with saturated aqueous $NaHCO_3$ (2 × 5 mL) and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to give 28 mg (85%) of pure **21a**: NMR $\delta$ 6.65 (m, 3 H), 5.87 (s, 2 H), 2.99 (m, 3 H), 1.13–2.53 (comp, 11 H); mass spectrum, $m/e$ 245.1421 ($C_{15}H_{19}NO_2$ requires 245.1416), 82 (base).

**(3a*R**,7*S**,7a*S**)-7-[3,4-(Methylenedioxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydroindole (21b).** The amine **20b** (97 mg, 0.29 mmol) dissolved in glacial acetic acid (3 mL) containing 5% Pd/C (40 mg) was hydrogenated and worked up as described above to produce 53 mg (74%) of pure **21b**: NMR $\delta$ 6.67 (br s, 3 H), 5.84 (s, 2 H), 2.90 (m, 2 H), 2.39 (m, 2 H), 1.00–2.10 (comp, 10 H); mass spectrum $m/e$ 245.1421 ($C_{21}H_{19}NO_2$ requires 245.1416), 82 (base).

**(3a*R**,7*R**,7a*S**)-7-[3,4-(Methylenedioxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydroindole (21c).** The amine **20c** (60 mg, 0.18 mmol) dissolved in glacial acetic acid (2 mL) containing 5% Pd/C (30 mg) was hydrogenated and worked up as described above to give 35 mg (79%) of pure **21c**: NMR $\delta$ 6.79 (m, 3 H), 5.88 (s, 2 H), 3.38 (m, 1 H), 2.83 (d, 1 H, $J$ = 6 Hz), 2.74 (d, 1 H, $J$ = 6 Hz), 2.43 (dd, 1 H, $J$ = 6 and 9 Hz), 1.00–2.23 (comp, 10 H); mass spectrum, $m/e$ 245.1423 ($C_{15}H_{19}NO_2$ requires 245.1416), 120, 91, 82 (base).

**(3a*R**,7*R**,7a*R**)-*N*-Carbomethoxy-7-[3,4-(methylenedioxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydroindole (22a).** To a solution of **21a** (25 mg, 0.10 mmol) and triethylamine (15 mg, 0.15 mmol) in dry $CH_2Cl_2$ (2 mL) at 0 °C under dry nitrogen was added methyl chloroformate (30 mg, 0.30 mmol), and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with $CH_2Cl_2$ (5 mL), and the resulting solution was washed with 1 N HCl (5 mL) and saturated aqueous $NaHCO_3$ (5 mL) and then dried ($MgSO_4$). The excess solvents were removed under reduced pressure to afford 25 mg (83%) of the urethane **22a** as a colorless oil: IR 1675 $cm^{-1}$; NMR $\delta$ 6.62 (m, 3 H), 5.87 (s, 2 H), 3.77 (m, 1 H), 3.45 (m, 2 H), 3.07 (br s, 3 H), 1.33–2.53 (comp, 10 H); mass spectrum, *m/e* 303.1470 (base) ($C_{17}H_{21}NO_4$ requires 303.1470), 228, 201, 140.

**(3a*R**,7*S**,7a*S**)-*N*-Carbomethoxy-7-[3,4-(methylenedioxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydroindole (22b).** The amine **21b** (45 mg, 0.18 mmol) was treated with methyl chloroformate (52 mg, 0.55 mmol) in the presence of triethylamine (22 mg, 0.22 mmol) as described above to give 48 mg (88%) of the urethane **22b** as a colorless oil: IR 1677 $cm^{-1}$; NMR $\delta$ 6.67 (m, 3 H), 5.84 (s, 2 H), 3.70 (m, 1 H), 3.28 (m, 1 H), 3.03 (s, 3 H), 2.60 (m, 1 H), 1.00–2.07 (comp, 10 H); mass spectrum, *m/e* 303.1478 (base) ($C_{17}H_{21}NO_4$ requires 303.1470), 228, 201, 176, 140.

**(3a*R**,7*R**,7a*S**)-*N*-Carbomethoxy-7-[3,4-(methylenedioxy)phenyl]-2,3,3a,4,5,6,7,7a-octahydroindole (22c).** The amine **21c** (35 mg, 0.14 mmol) was treated with methyl chloroformate (40 mg, 0.42 mmol) in the presence of triethylamine (16 mg, 0.16 mmol) as described above to give 39 mg (90%) of the urethane **22c** as a colorless oil: IR 1680 $cm^{-1}$; NMR $\delta$ 6.75 (m, 3 H), 5.89 (s, 2 H), 3.93 (m, 1 H), 3.73 (s, 3 H), 3.63 (m, 1 H), 3.32 (dd, 1 H, *J* = 5 and 10 Hz), 2.96 (m, 1 H), 1.07–2.33 (comp, 9 H); mass spectrum, *m/e* 303.1464 ($C_{17}H_{21}NO_4$ requires 303.1470), 228, 140.

**7-Oxo-α-lycorane (23a).** The urethane **22a** (23 mg, 0.07 mmol) was dissolved in freshly distilled $POCl_3$ (0.5 mL) and heated at 90 °C (bath temperature) for 20 h in a sealed glass tube. The mixture was cooled to room temperature and slowly poured into cold water (2 mL) with stirring. The aqueous solution was made slightly allkaline with external cooling using sodium hydroxide pellets, and the aqueous mixture was then extracted with $CH_2Cl_2$ (3 × 10 mL). The combined extracts were dried ($MgSO_4$), and the excess solvent was evaporated under reduced pressure to give 17 mg (83%) of pure 7-oxo-α-lycorane (23a) as white prisms from hexane: mp 168–169 °C (lit.[4f] 169–171 °C); IR 1648, 1617, 1370 $cm^{-1}$; NMR (200 MHz) $\delta$ 7.45 (s, 1 H), 6.65 (br s, 1 H), 5.98 (s, 2 H), 4.14 (dd, 1 H, *J* = 7 and 12 Hz), 3.48 (dd, 1 H, *J* = 8 and 13 Hz), 3.26 (dt, 1 H, *J* = 5 and 12 Hz), 2.67 (dt, 1 H, *J* = 5 and 13 Hz), 2.45 (m, 1 H), 1.58–2.23 (comp, 7 H), 1.34 (m, 1 H); mass spectrum, *m/e* 271.1206 ($C_{16}H_{17}NO_3$ requires 271.1208), 85, 57 (base). The spectral data (IR, $^1H$ NMR) were identical with those of an authentic sample.[24]

**7-Oxo-β-lycorane (23b).** The urethane **22b** (48 mg, 0.16 mmol) was treated with $POCl_3$ (0.5 mL) as described above to give 37 mg (86%) of 7-oxo-β-lycorane (**23b**) as white prisms from hexane: mp 157–158 °C; IR 1640, 1602, 1380, 1357 $cm^{-1}$; NMR (200 MHz) $\delta$ 7.58 (s, 1 H), 6.68 (s, 1 H), 5.99 (s, 2 H), 3.80 (dd, 1 H, *J* = 9 and 12 Hz), 3.58 (dt, 1 H, *J* = 5 and 12 Hz), 2.82 (dd, 1 H, *M* = 9 and 13 Hz), 2.69 (dt, 1 H, *J* = 4 and 13 Hz), 2.35 (m, 1 H), 1.20–2.23 (comp, 8 H); mass spectrum, *m/e* 271.1204 ($C_{16}H_{17}NO_3$ requires 271.1208), 84 (base).

**7-Oxo-δ-lycorane (23c).** The urethane **22c** (30 mg, 0.1 mmol) was treated with $POCl_3$ (0.5 mL) as described above to provide 16 mg (62%) of 7-oxo-δ-lycorane (**23c**): IR 1644, 1614 $cm^{-1}$; NMR $\delta$ 7.67 (s, 1 H), 6.77 (br s, 1 H), 5.97 (s, 2 H), 4.20 (m, 1 H), 3.50 (m, 1 H), 2.80–3.33 (comp, 2 H), 2.39 (br d, 1 H, *J* = 15 Hz), 1.03–2.17 (comp, 8 H); mass spectrum, *m/e* 271.1204 ($C_{16}H_{17}NO_3$ requires 271.1208), 270 (base).

**α-Lycorane (19a).** A solution of the lactam **23a** (50 mg, 0.16 mmol) in dry ether/THF (1:1) (10 mL) containing $LiAlH_4$ (23 mg) was stirred at room temperature for 3 h, whereupon the excess $LiAlH_4$ was destroyed by the sequential addition of $H_2O$ (0.03 mL), 4 N NaOH (0.03 mL), and $H_2O$ (0.1 mL). The precipitated solids were removed by suction filtration and washed with $CH_2Cl_2$ (50 mL). The filtrate was dried ($MgSO_4$) and concentrated under reduced pressure to give 39 mg (84%) of the crude product, which was recrystallized from hexane to give α-lycorane (**19a**) as white prisms: mp 92–94 °C (lit. mp 93–94 °C,[17a] 95.5–97 °C[17b]). The spectral data ($^1H$ NMR, IR, MS) and TLC were identical with those of an authentic sample.[25]

**β-Lycorane (19b).** The lactam **23b** (54 mg, 0.2 mmol) was reduced with $LiAlH_4$ (22 mg) as described above to give 46 mg (89%) of β-lycorane (**19b**), which was recrystallized from hexane to afford **19b** as white prisms: mp 86–88 °C (lit.[17a] mp 88 °C). The IR spectrum was identical with that of an authentic sample:[26] NMR $\delta$ 6.70 (s, 1 H), 6.50 (s, 1 H), 5.88 (s, 2 H), 4.07 (d, 1 H, *J* = 15 Hz), 3.33 (d, 1 H, *J* = 15 Hz), 3.32 (m, 1 H), 1.03–2.63 (comp, 12 H); mass spectrum, *m/e* 257.1240 ($C_{16}H_{18}NO_2$ requires 257.1413), 256 (base).

**δ-Lycorane (19c).** 7-Oxo-δ-lycorane (**23c**; 12 mg, 0.04 mmol) was reduced with $LiAlH_4$ (6 mg) as described above to give 8 mg (81%) of δ-lycorane (**19c**). The IR in the region 2600–3000 $cm^{-1}$ was identical with that of an authentic sample:[27] IR ($CS_2$) 2938, 2868, 1268, 1242 $cm^{-1}$; NMR $\delta$ 6.82 (s, 1 H), 6.60 (s, 1 H), 5.90 (s, 2 H), 3.94 (d, 1 H, *J* = 15 Hz), 3.32 (d, 1 H, *J* = 15 Hz), 1.07–3.37 (comp, 13 H); mass spectrum, *m/e* 257.1410 ($C_{16}H_{19}NO_2$ requires 257.1416), 256 (base).

**(3a*R**,7*R**,7a*R**)-*N*-Carbethoxy-7-[3,4-(methylenedioxy)phenyl]-2,3,3a,6,7,7a-hexahydroindole (24a).** A mixture of the *cis*-*N*-(*p*-methoxybenzyl)hydroindole **29a** (100 mg, 0.28 mmol), sodium bicarbonate (250 mg), and ethyl chloroformate (200 mg, 2.0 mmol) in dry benzene (5 mL) was heated at reflux for 24 h. The sodium bicarbonate was removed by suction filtration and washed with $CH_2Cl_2$ (20 mL), and the combined filtrate and washings were then washed with 1 N HCl (5 mL), saturated aqueous $NaHCO_3$ (5 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by preparative HPLC using ethyl acetate/hexane (1:2.5) as the eluting solvent to give 78 mg (89%) of the urethane **24a** as a colorless oil: IR 1675 $cm^{-1}$; NMR $\delta$ 6.70 (m, 3 H), 5.87 (s, 2 H), 5.76 (overlapping AB q, 2 H, *J* = 12 Hz), 1.47–4.13 (comp, 11 H), 1.05 (br t, 3 H, *J* = 7 Hz); mass spectrum, *m/e* 315.1470 ($C_{18}N_{21}NO_4$ requires 315.1470), 180 (base).

**(3a*R**,7*S**,7a*S**)-*N*-Carbethoxy-7-[3,4-(methylenedioxy)phenyl]-2,3,3a,6,7,7a-hexahydroindole (24b).** The *trans*-*N*-(*p*-methoxybenzyl)hydroindole **29b** (80 mg, 0.22 mmol) was treated with ethyl chloroformate (150 mg, 1.4 mmol) in the presence of sodium bicarbonate (184 mg, 2.2 mmol) in refluxing benzene as described above to give 42 mg (61%) of the desired urethane **24b** together with 35 mg (34%) of the *N*-(*p*-methoxybenzyl)urethane **30**.

For **24b**: IR 1675 $cm^{-1}$; NMR (200 MHz) $\delta$ 6.71 (m, 3 H), 5.92 (m, 2 H), 5.88 (m, 1 H), 5.73 (m, 1 H), 3.79 (m, 2 H), 3.45 (m, 3 H), 3.18 (dt, 1 H, *J* = 6 and 10 Hz), 2.27–2.71 (comp, 2 H), 1.99, (m, 1 H), 1.52 (m, 1 H), 1.27 (m, 1 H), 0.93 (t, 3 H, *J* = 7 Hz); mass spectrum, *m/e* 315.1470 ($C_{18}H_{21}NO_4$ requires 315.1470), 180 (base).

For **30**: IR 1680 $cm^{-1}$; NMR $\delta$ 6.57–7.23 (comp, 7 H), 7.01 (s, 2 H), 5.62 (AB q, 2 H, *J* = 11 Hz), 4.13 (m, 4 H), 3.77 (s, 3 H), 1.47–3.53 (comp, 9 H), 1.33 (t, 1.5 H, *J* = 7 Hz), 1.10 (t, 1.5 H, *J* = 7 Hz); mass spectrum, *m/e* 471.1817 ($C_{26}H_{30}NO_5Cl$ requires 471.1812), 355, 262, 121 (base).

**7-Oxo-$\Delta^{2,3}$-α-lycorane (4).** The urethane **24a** (100 mg, 0.45 mmol) was dissolved in freshly distilled $POCl_3$ (1.5 mL) and heated in a sealed glass tube at 90 °C (oil bath temperature) for 20 h. The mixture was cooled to room temperature and slowly poured into cold water (5 mL) with stirring. The aqueous solution was made slightly alkaline using sodium hydroxide pellets with external cooling. The aqueous mixture was then extracted with $CH_2Cl_2$ (3 × 25 mL), and the combined extracts were dried ($MgSO_4$). The solvent was evaporated under reduced pressure, and the crude product was recrystallized from ethyl acetate/hexane (1:4) to give 73 mg (84%) of pure **4** as white needles: mp 195–196 °C (lit.[16a] mp 196–198 °C), mmp 195–197 °C; IR, $^1H$ NMR, and MS were identical with those of an authentic sample.[16a,29]

**7-Oxo-$\Delta^{2,3}$-β-lycorane (31).** The urethane **24b** (42 mg, 0.13 mmol) was treated with $POCl_3$ (0.6 mL) as described above to give, after recrystallization from ethyl acetate/hexane (1:4), 33 mg (92%) of the lactam **31** as white prisms: mp 230–232 °C; IR 1640, 1601 $cm^{-1}$; NMR (200 MHz) $\delta$ 7.62 (s, 1 H), 6.64 (s, 1 H), 6.01 (s, 2 H), 5.96 (m, 1 H), 5.74 (m, 1 H), 3.87 (dd, 1 H, *J*= 8 and 11 Hz), 3.71 (dt, 1 H, *J* = 7 and 11 Hz), 3.12 (m, 1 H), 2.86 (m, 1 H), 2.54 (m, 1 H), 2.24 (m, 1 H), 1.68 (m, 3 H); mass

spectrum, $m/e$ 269.1044 ($C_{16}H_{15}NO_3$ requires 269.1052) 268 (base).

**7-Oxo-α-lycorane (23a).** A solution of the lactam **4** (15 mg, 0.05 mmol) in glacial acetic acid (1.5 mL) containing 10% Pt/C (10 mg) was stirred under $H_2$ (1 atm) at room temperature for 4 h. The catalyst was removed by suction filtration and washed with hot ethanol (20 mL). The combined filtrates were concentrated under reduced pressure, and the residue was dissolved in $CH_2Cl_2$ (10 mL). The solution was then washed with saturated aqueous $NaHCO_3$ (2 × 5 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was recrystallized from hexane to give 14 mg (94%) of **23a** which was identical in all respects with that obtained previously.

**7-Oxo-β-lycorane (23b).** The lactam **31** (20 mg, 0.08 mmol) was hydrogenated as described above to give 19 mg (95%) of **23b**, which was identical in all respects with that obtained previously.

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**Registry No.** **4**, 53951-02-3; **8**, 82281-20-7; **11**, 82281-21-8; **12**, 82281-22-9; **15**, 82281-23-0; **16**, 82293-68-3; **17a**, 82281-24-1; **17b**, 82281-25-2; **17c**, 82281-26-3; **18**, 82281-27-4; **19a**, 63814-02-8; **19b**, 71630-03-0; **19c**, 10313-53-8; **20a**, 82281-28-5; **20b**, 82281-29-6; **20c**, 82281-30-9; **21a**, 82281-31-0; **21b**, 82281-32-1; **21c**, 82281-33-2; **22a**, 82281-34-3; **22b**, 82281-35-4; **22c**, 82281-36-5; **23a**, 66816-53-3; **23b**, 78512-55-7; **23c**, 82398-31-0; **24a**, 78456-83-4; **24b**, 78456-84-5; **26**, 78456-78-7; **27a**, 78479-41-1; **27b**, 78456-80-1; **29a**, 78456-81-2; **29b**, 78456-82-3; **30**, 78456-85-6; **31**, 78512-54-6; benzylamine, 100-46-9; phenylacetaldehyde, 122-78-1; homopiperonal, 6543-34-6; *p*-methoxybenzylamine, 2393-23-9.

**Supplementary Material Available:** Tables of positional and thermal parameters and bond lengths and angles (7 pages). Ordering information is given on any current masthead page.

# Reactions of the Formaldehyde–Trimethylaluminum Complex with Alkenes

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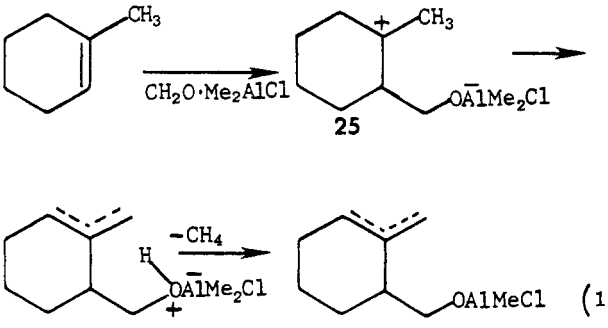
Reaction of $CH_2O{\cdot}Me_3Al$ with electron-rich alkenes gives a zwitterion that reacts further to give homoallylic alcohols (ene adducts), allylic alcohols, and the product of cis addition of a hydroxymethyl and a methyl group to the double bond. The stereochemistry and effect of alkene structure on the nature of the reaction are examined.

The acid-catalyzed addition of aldehydes to alkenes, the Prins reaction, has been extensively investigated over the past 60 years.[2] 1,3-Diols and *m*-dioxanes are the major products in aqueous media. Homoallylic alcohols resulting from a stepwise or concerted ene reaction are the major products from the Lewis acid catalyzed reaction of electron-deficient aldehydes, e.g., chloral and formaldehyde, with electron-rich alkenes, i.e., those that can give a tertiary carbenium ion.

We have recently found the use of $Me_2AlCl$ as the Lewis acid extends the scope of this reaction.[3] Ene adducts can now be obtained in good yield from aliphatic and aromatic aldehydes and reactive alkenes that give a tertiary carbenium ion. With $Me_2AlCl$ as a catalyst, formaldehyde also reacts with alkenes that give a secondary carbenium ion to give ene adducts and varying amounts of chloro alcohol resulting from the cis addition of hydroxymethyl and chloride groups to the double bond. The success of these reactions is due to the fact that $Me_2AlCl$ is a proton scavenger as well as a Lewis acid.[4]

The reactions of $CH_2O{\cdot}Me_3Al$ with alkenes were explored to determine the suitability of a weaker Lewis acid as the catalyst and to prevent the formation of chloride-containing byproducts. To our surprise, the reaction of $CH_2O{\cdot}Me_3Al$ with 1-methylcyclohexene (see Table I) gave only 5% of ene adducts **4a** and **5a**, the exclusive products with $CH_2O{\cdot}Me_2AlCl$[3b] (see eq 1). The major products were




(1)

the alcohol **2a**, resulting from cis addition of the hydroxymethyl and methyl groups to the double bond, and the allylic alcohol **3a**. Both of these products appear to result from a common zwitterionic intermediate that can undergo a 1,5 methyl shift to give **2a**[5] or a 1,5 proton shift with loss of methane to give **3a** (see eq 2). The enhanced basicity and nucleophilicity of the methyl groups of **26** as compared to those for **25** are apparently responsible for the difference between these reactions. The product mixtures obtained from a variety of alkenes are shown in Table I.

1-Phenylcyclohexene (run 3) gives a single adduct **7**, which results from methyl addition to the zwitterion. Formation of the allylic alcohol would require that the oxyalkyl group be equatorial so that the hydrogen being

(1) (a) Brandeis University. (b) Princeton University.
(2) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661.
(3) (a) Snider, B. B.; Rodini, D. J. *Tetrahedron Lett.* **1980**, *21*, 1815. (b) Snider, B. B.; Rodini, D. J.; Kirk, T. C.; Cordova, R. *J. Am. Chem. Soc.* **1982**, *104*, 555.
(4) Snider, B. B.; Rodini, D. J.; Karras, M.; Kirk, T. C.; Deutsch, E. A.; Cordova, R.; Price, R. T. *Tetrahedron* **1981**, *37*, 3927.
(5) For related reactions see: Yamamoto, H.; Nozaki, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 169.

0022-3263/82/1947-3643$01.25/0 