Pyrroles as Terminators in Cationic Cyclizations. The Preparation of 5,6,7,8-Tetrahydroindolizidines and 6,7,8,9-Tetrahydro-5*H*-pyrrolo[1,2-*a*]azepines

Steven P. Tanis*[1a] and Jeffrey W. Raggon[1b]

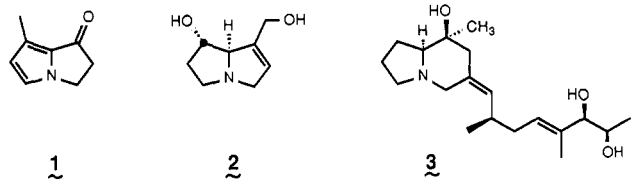
Department of Chemistry, Michigan State University, East Lansing, Michigan 48824

Received July 31, 1986

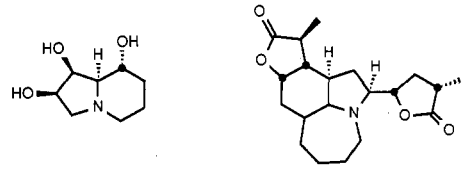
N-(Epoxyalkyl)pyrroles 8–13 are readily prepared either by direct pyrrole N-alkylation with either ω-iodo epoxides or ω-iodo-1,2-alkanediol acetonides followed by conversion to the corresponding epoxides. The cyclizations of these *N*-(epoxyalkyl)pyrroles were examined with a range of Lewis acids providing cyclized products **14** and **16–21** in moderate to excellent yields. The cyclization products **14**, **16**, and **20** are formally the products of "anti-Markovnikov" attack on the less substituted epoxide terminus.

Introduction

The alkaloids present a bewildering array of skeletal and structural types; in addition, a wide variety of potent and interesting biological activities are often associated with such compounds.[2] A common theme displayed by a number of bioactive alkaloids is a five-membered, nitrogen-containing heterocyclic ring fused to five-, six-, or seven-membered rings. This ring system, in the pyrrole or pyrrolidine oxidation state, is an integral part of such molecules as the pyrrolizin-1-one **1**,[3] from the hairpencil secretion of the butterfly *Lycorea ceres*, the pyrrolizidine alkaloid heliotridine **2**,[4] the *dendrobatid* alkaloid pumiliotoxin B (**3**),[5] the α-mannosidase inhibitor swainsonine (**4**),[6] and the insecticide tuberostemonine (**5**).[7]

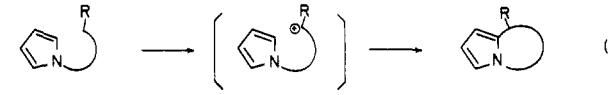


1 **2** **3**



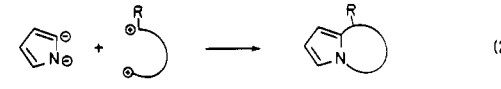
4 **5**

Alkaloids **1–5** exhibit the N–α attachment of the fused system as opposed to α,β-fused observed in indole systems. As a result of our success in preparing fused-ring systems via furan-terminated cationic cyclizations,[8] we became intrigued by the possibility of preparing the fused-ring systems of compounds **1–5** by a pyrrole-terminated cationic cyclization (eq 1). In this sequence, an N-substituted pyrrole with a benign electrophilic center in the side chain should lead to **7** after activation, electrophilic attack at the adjacent α-position, and rearomatization. The obtention



(1)

6 **7**



(2)

7

of **7** from the Lewis acid treatment of **6** would establish pyrrole as the operational equivalent of the pyrrolyl dianion illustrated in eq 2. Variation of the bis-electrophilic moiety (eq 2) would provide compound **7** in which the size of the formed ring can be readily modified and in which the residual functionality from the cyclization initiator might provide sufficient "handles" for the completion of the synthesis.

Design and Synthesis of Cyclization Substrates

Cationic cyclizations have been intensely studied[8,9] and a wide variety of initiator and terminator functions have been examined. However, few examples have appeared

(1) (a) Recipient of a Camille and Henry Dreyfus Foundation Grant for Young Faculty in Chemistry, 1980–1984. Current address: The Upjohn Company, Kalamazoo, MI 49001. (b) Current address: Department of Chemistry, Iowa State University, Ames, IA 50010.

(2) For discussions and reviews of various aspects of alkaloid chemistry, see for example, the review series: *The Alkaloids*; Specialist Periodical Reports 1–13; The Royal Society of Chemistry: London (superceded by Natural Products Reports).

(3) Meinwald, J.; Meinwald, Y. C. *J. Am. Chem. Soc.* **1966**, *88*, 1305.

(4) For an elegant recent synthesis of (+)-heliotridene **2**, see: Chamberlin, A. R.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1983**, *105*, 3653.

(5) For a synthesis of **4**, see: Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192.

(6) For a recent synthesis of **4**, see: Ali, M. H.; Hough, L.; Richardson, A. C. *J. Chem. Soc., Chem. Commun.* **1984**, 447.

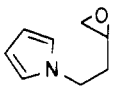
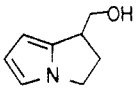
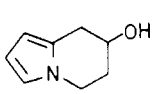
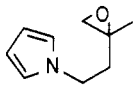
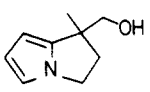
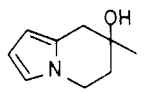
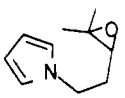
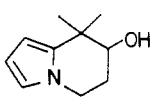
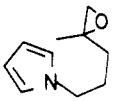
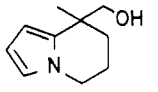
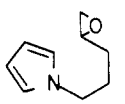
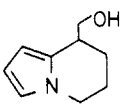
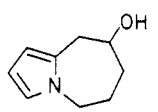
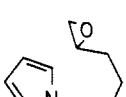
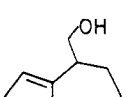
(7) Gotz, M.; Bogri, T.; Gray, A. H. *Tetrahedron Lett.* **1961**, 707. Shingu, T.; Tsuda, Y.; Uyeo, S.; Yamamoto, Y.; Harada, H. *Chem. Ind. (London)* **1962**, 1191.

(8) (a) Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1983**, *48*, 4572. (b) Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1985**, *50*, 3988. (c) Tanis, S. P.; Herrinton, P. M.; Dixon, L. A. *Tetrahedron Lett.* **1985**, *26*, 5347. (d) Tanis, S. P.; Chuang, Y.-H.; Head, D. B. *Tetrahedron Lett.* **1985**, *26*, 6147.

(9) (a) For reviews of polyene cyclization, see: Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1. van Tamelen, E. E. *ibid.* **1975**, *8*, 152. Johnson, W. S. *Bioorg. Chem.* **1976**, *5*, 51. Johnson, W. S. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 9. (b) Groen, M. B.; Zeelen, F. J. *Recl. Trav. Chim. Pays-Bas.* **1978**, *97*, 301. (c) Groen, M. B.; Zeelen, F. J. *J. Org. Chem.* **1978**, *43*, 1961. (d) Peters, J. A. M.; Posthumus, T. A. P.; van Vliet, N. P.; Zeelen, F. J.; Johnson, W. S. *Ibid.* **1980**, *45*, 2208. (e) Johnson, W. S.; McCarry, B. E.; Markezich, R.; Boots, S. G. *J. Am. Chem. Soc.* **1980**, *102*, 352. (f) Gravestock, M. B.; Morton, D. R.; Boots, S. G.; Johnson, W. S. *Ibid.* **1980**, *102*, 800. (g) Johnson, W. S.; McCarry, B. E.; Okorie, D. A.; Parry, R. J. *Ibid.* **1980**, *102*, 800. (h) Johnson, W. S.; Dumas, D. J.; Berner, D. *Ibid.* **1982**, *104*, 3510. (i) van Tamelen, E. E.; Loughhead, D. G. *Ibid.* **1980**, *103*, 869. (j) van Tamelen, E. E.; Zawacky, S. R.; Russell, R. K.; Carlson, J. G. *Ibid.* **1983**, *105*, 142. (k) van Tamelen, E. E.; Hwu, J. R. *Ibid.* **1983**, *105*, 2490. Stereoselective iminium ion cyclizations: (l) Johansen, J. E.; Christie, B. D.; Rapoport, H. *J. Org. Chem.* **1981**, *46*, 4914. (m) Dean, R. T.; Rapoport, H. *Ibid.* **1978**, *43*, 4183. (n) Vlaeminck, F.; Van Binst, G. *Heterocycles* **1979**, *12*, 329. Stereoselective *N*-acyl iminium ion cyclizations: (o) For a review, see: Speckamp, W. N. *Recl. Trav. Chim. Pays-Bas* **1981**, *100*, 345. (p) Maryanoff, B. E.; McComsey, D. F.; Duhl-Emswiler, B. A. *J. Org. Chem.* **1983**, *48*, 5062. (q) Hart, D. J.; Yang, T.-K. *Tetrahedron Lett.* **1982**, *23*, 2761. (r) Nossin, P. M. M.; Hamersma, J. A. M.; Speckamp, W. N. *Ibid.* **1982**, *23*, 3207. (s) Winjberg, B. P.; Speckamp, W. N. *Tetrahedron* **1982**, *38*, 209. (t) Veenstra, S. J.; Speckamp, W. N. *J. Am. Chem. Soc.* **1981**, *103*, 4645. (u) Hart, D. J.; Kanai, K. *J. Org. Chem.* **1982**, *47*, 1555. (v) Hart, D. J. *Ibid.* **1981**, *46*, 3576. (w) Hart, D. J. *Ibid.* **1981**, *46*, 367 and references cited therein.

0022-3263/87/1952-0819$01.50/0

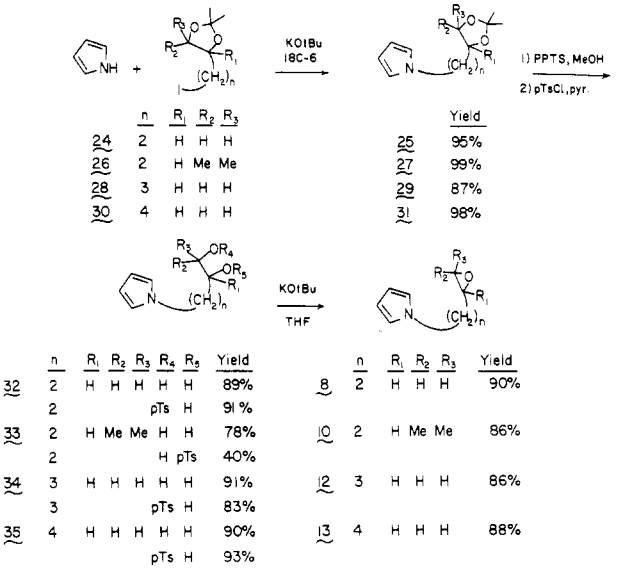
Table I. Cyclization Substrates and Possible Products

designation	(epoxyalkyl)-pyrrole	possible products
5-exo/6-endo	 8	 13  14
5-exo/6-endo	 9	 15  16
6-endo	 10	 17
6-exo	 11	 18
6-exo/7-endo	 12	 19  20
7-exo	 13	 21

in the literature in which the terminator is a pyrrole.[3,9p,10,11] The lack of precedent in this area is likely the result of the reactivity of *N*-alkylpyrrole starting materials and *N*,α-dialkylpyrrole products. Pyrrole and simple alkyl pyrroles have been reported to react readily with oxygen and acids, often providing polymeric products.[12] As a result, careful choice of the initiatory moiety and the reaction conditions will be required to ensure successful cyclizations.

Our earlier work with furan-terminated cyclizations[8] demonstrated the utility of the epoxide function[8a,d] as a cyclization initiator. A wide variety of Lewis acids were examined in that study, and successful ring closure was observed when the Brønsted acidity of the medium was moderated. These relatively mild conditions, coupled with the ease of epoxide introduction, either insertion intact or as the corresponding protected diol, made the epoxide the initiator of choice.

The cyclization substrates examined were designed to permit entry into five-, six-, or seven-membered ring systems. In all of the cases examined, the substitution about



	n	R_1	R_2	R_3	Yield
24	2	H	H	H	
25					95%
26	2	H	Me	Me	
27					99%
28	3	H	H	H	
29					87%
30	4	H	H	H	
31					98%

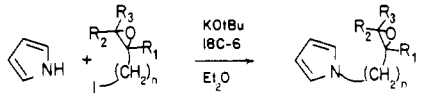
	n	R_1	R_2	R_3	R_4	R_5	Yield
32	2	H	H	H	H	H	89%
	2				pTs	H	91%
33	2	H	Me	Me	H	H	78%
	2				H	pTs	40%
34	3	H	H	H	H	H	91%
	3				pTs	H	83%
35	4	H	H	H	H	H	90%
					pTs	H	93%

	n	R_1	R_2	R_3	Yield
8	2	H	H	H	90%
10	2	H	Me	Me	86%
12	3	H	H	H	86%
13	4	H	H	H	88%

Figure 1. The synthesis of *N*-(epoxyalkyl)pyrroles **8**, **10**, **12**, and **13**.

the oxirane was biased to favor one mode of C–O bond polarization over the alternative bond.[8a,d,13] The initiating moiety was placed within the ring being formed (endocyclic) or outside the forming cycle (exocyclic).[14] The required *N*-(epoxyalkyl)pyrroles and possible reaction products are illustrated in Table I.

Pyrrole lability, in the presence of oxidizing reagents, necessitates the introduction of the epoxide, or its equivalent, intact in lieu of olefin epoxidation. Therefore, the most direct route to the requisite *N*-(epoxyalkyl)pyrroles is the alkylative process depicted in eq 3. Treatment of



(3)

	n	R_1	R_2	R_3	
22	2	Me	H	H	
9					40%
23	3	Me	H	H	
11					34%

pyrrole with KO-*t*-Bu and 18-crown-6 ether followed by epoxy iodide **22**, which is prepared from the commercially available 3-methyl-3-buten-1-ol, provided *N*-(epoxyalkyl)pyrrole **9** in a modest 40% yield. Similarly, iodo epoxide **23**[16] led to *N*-(epoxyalkyl)pyrrole **11** in a disappointing 34% yield. The low yields of **9** and **11** obtained in the alkylation of pyrrole with **22** and **23** caused us to consider introducing the epoxide moiety in a protected form, as the corresponding diol acetonide, in order to complete the syntheses of **8**, **10**, **12** and **13**.

As is shown in Figure 1, the alkylation (KO-*t*-Bu, 18-C-6, Et_2O) of pyrrole with ω-iodo diol acetonide **24**[17] provided the corresponding *N*-pyrrolylalkanediol acetonide **25** in

(10) Trost, B. M.; Reiffen, M.; Crimmin, M. *J. Am. Chem. Soc.* **1979**, *101*, 257.

(11) Thiophenes have been employed as cyclization terminators, see ref 9p and: (a) Heathcock, C. H.; Jennings, R. A.; von Geldern, T. W. *J. Org. Chem.* **1983**, *48*, 3428. (b) Jenssen, C. G. M.; Macco, A. A.; Buck, H. M.; Godefroi, E. F. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 448. (c) Macco, A. A.; de Brouwer, R. J.; Nossin, P. M. M.; Godefroi, E. F.; Buck, H. M. *J. Org. Chem.* **1978**, *43*, 1591. (d) Corvers, A.; Scheers, P. C. H.; deHaan, J. W.; Buck, H. M. *Recl. Trav. Chim. Pays-Bas.* **1977**, *98*, 279. (e) Gourler, J.; Cannone, P. *Can. J. Chem.* **1970**, *48*, 2587.

(12) Jackson, A. H. In *Comprehensive Organic Chemistry*; Sammes, P. E., Ed.; Pergamon: Oxford, 1979; Vol. 4, pp 275–320.

(13) (a) Goldsmith, D. J. *J. Am. Chem. Soc.* **1962**, *84*, 3913. (b) Goldsmith, D. J.; Phillips, C. F. *Ibid.* **1969**, *91*, 5802. (c) van Tamelen, E. E.; Marson, S. A. *J. Am. Chem. Soc.* **1975**, *97*, 5614. (d) Boeckman, R. K., Jr.; Bruza, K. J.; Heinrich, G. R. *Ibid.* **1978**, *100*, 7101.

(14) Baldwin, J. E.; Thomas, R. C.; Bruse, L. I.; Silberman, L. X. *J. Org. Chem.* **1977**, *42*, 3846.

(15) Available from the Aldrich Chemical Co., Milwaukee, WI.

(16) Prepared from 4-methyl-4-penten-1-ol, which is available by the procedure of: Mori, K.; Kobayashi, S.; Matsui, M. *Agric. Biol. Chem.* **1975**, *39*, 1889.

(17) Iodo acetonide **24** was prepared from the corresponding (±)-ω-hydroxy diol acetonide, which has previously been synthesized in the enantiomerically pure *R* form, see: Mori, K.; Takigawa, T.; Matsui, R. *Tetrahedron* **1979**, *35*, 933.

Table II. Cyclization Results

N-(epoxyalkyl)pyrrole	Lewis acid				
	BF_3·OEt_2 (1 equiv)	$EtAlCl_2$ (2 equiv)	Et_2AlCl (2 equiv)	$Ti(O\text{-}i\text{-}Pr)_3Cl$ (3 equiv)	ZnI_2 (3 equiv)
8	**14** (70%)	**14** (23%)	**14** (32%)	**14** (45%)	**14** (33%)
9	**16** (32%)	**16** (42%)	**16** (44%)		**16** (67%)
10	**17** (91%)	**17** (60%)	**17** (61%)	**17** (74%)	**17** (70%)
11	**18** (73%)	**18** (81%)	**18** (81%)	**18** (80%)	**18** (72%)
12	**19** (20%)	**19** (35%)	**19** (37%)	**19** (64%)	**19** (21%)
		20 (45%)	**20** (48%)		**20** (30%)
13	**21** (21%)	**21** (56%)	**21** (56%)	**21** (85%)	**21** (48%, C_6H_6) + iodohydrin (21%)
					21 (26%, Et_2O) + iodohydrin (49%)

95% yield after purification by chromatography. Careful hydrolysis within pyridinium *p*-toluenesulfonate[18] in methanol yielded diol **32** (R_4 = R_5 = H, 89%), which was immediately converted to the monotosylate **32** (R_4 = *p*-Ts, R_5 = H, 91%). Closure to the epoxide ring (KO-*t*-Bu, THF) gave the desired *N*-(epoxyalkyl)pyrrole **8** (90%) in 69% overall yield. In similar fashion, pyrrole alkylation with ω-iodo diol acetonides **26**,[19] **28**,[20] and **30**[21] led to *N*-(epoxyalkyl)pyrroles **10**, **12**, and **13** in 25%, 57%, and 72% overall yields, respectively. With the exception of the formation of the monotosylate of diol **33** (R_4 = R_5 = H), all yields were ≥78% per step. Although the isolation of but 40% of monotosylate **33** (R_4 = H, R_5 = *p*-Ts) was initially disappointing, the remainder of the reaction mixture consisted of unreacted starting material which could be readily recovered and recycled.

Cyclization Studies

With the desired cyclization substrates available, the cyclization sequence was examined. The acid lability of the pyrrole terminator function and the enhanced fragility of the product *N*,α-dialkylpyrroles necessitate the selection of carefully balanced reaction conditions. As in our earlier studies of furan-terminated, epoxide-initiated cyclizations,[8a,d] Lewis acids were selected after considering two factors, (i) the ability to readily modify the potency of a group of Lewis acids with a common metal center and (ii) the possibility of moderating the Brønsted acidity of the medium through the choice of Lewis acid. Protic acid might be scavenged by Lewis acids such as the alkyl aluminum halides[22] possessing a protolyzable carbon–metal bond, thus releasing an alkane. Alternatively, with proper choice of metal, the product metal–alcohol complex should be a much weaker protic acid compared to a BF_3–alcohol complex.

For this study, we examined the ability of the following five Lewis acids to effect pyrrole-terminated cationic cyclizations: $EtAlCl_2$; Et_2AlCl; $Ti(O\text{-}i\text{-}Pr)_3Cl$; ZnI_2; BF_3·OEt_2 and Et_3N. The first four Lewis acids had provided excellent yields of products during our furan studies, but only $Ti(OiPr)_3Cl$ and ZnI_2 gave significant quantities of cyclized compounds; the aluminum-based Lewis acids afforded mainly allylic alcohols. Moderation of BF_3·OEt_2 with ethereal solvents and amine bases was first attempted in this study.

N-(Epoxyalkyl)pyrrole **8** was treated with BF_3·OEt_2 (1 equiv), and Et_3N (1 equiv) in THF (−45 °C) to provide a single product **14** in 70% yield (Table II). The nature of **14** was apparent after an inspection of spectroscopic data (IR; ^1H NMR; EI/MS), and the structure was assigned as the 6-endo cyclization product. The observation of cyclization exclusively at the less-substituted terminus of the epoxide was surprising in light of our experiences with a similar 5-exo, 6-endo furan-terminated cyclization.[8a] In that case, closure to the five-membered ring was not observed, and the ring-opened allylic alcohol was obtained. The failure to form a five-membered ring is likely the result of but two sp^3-carbon atoms in the forming cycle. The "Markovnikov" attack of the pyrrole α-carbon upon the more substituted end of the Lewis acid complexed epoxide would result in severe bond distortion if the essential colinear α-C, C–O arrangement were to be attained.[23] van Tamelen[23b] has examined a polyene cyclization with an identical orientation of the π-system nucleophile relative to monosubstituted epoxide and has obtained the "anti-Markovnikov" cyclization product albeit in 2% yield. The exclusive "anti-Markovnikov" attack in *N*-(epoxyalkyl)-pyrrole **8** to give **14** in 70% yield is indeed noteworthy.[23c] In similar fashion, **8** was exposed to $EtAlCl_2$ (2 equiv, CH_2Cl_2, −78 °C), Et_2AlCl (2 equiv, CH_2Cl_2, −45 °C), $Ti(O\text{-}i\text{-}Pr)_3Cl$ (3 equiv, CH_2Cl_2, 0 °C), and ZnI_2 (3 equiv, PhH, 25 °C), providing **14** in 23%, 32%, 45%, and 33% yield, respectively. The indicated conditions have been optimized for the yield of cyclized product which represents virtually all of the recovered material.

N-(Epoxyalkyl)pyrrole **9**, which has been further biased toward C–O bond rupture at the internal epoxide carbon, was treated with BF_3·OEt_2 in THF containing Et_3N to give the 6-endo product **16** in 32% yield and none of the products of epoxide opening. The aluminum and zinc-based Lewis acids yielded only **16** in 42–67% yields. The generally mild $Ti(O\text{-}i\text{-}Pr)_3Cl$[8a] afforded a complex mixture of unstable products, which apparently did not contain **16**.

Pyrrole **10**, which is expected to give only 6-endo product **17** by analogy to our earlier work,[8a] was exposed to moderated BF_3·OEt_2 (Et_3N, THF), providing cyclized alcohol **17** in an excellent 91% yield as a white crystalline solid (mp 79–81 °C). Good yields of **17** were realized (60–74%) with the remaining Lewis acids (Table I). Similarly, *N*-(epoxyalkyl)pyrrole **11** led to uniformly high (72–81%) yields of 6-exo alcohol **18** after treatment with the Lewis acids of Table II.

N-(Epoxyalkyl)pyrrole **12**, precursor to 6-exo **19** and 7-endo alcohol **20**, was then the next substrate examined. The analogous 5-(3-furyl)-1,2-epoxypentane provided exclusively the corresponding 6-exo-cyclized product with a

(18) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3772.
(19) Compound **26** was prepared from 5-methyl-3-penten-1-ol by: Moppett, C. E.; Sutherland, J. K. *J. Chem. Soc.* **1968**, 3040.
(20) Compound **28** was prepared from 1,2,5-pentanetriol: Cervinka, O.; Hub, L. *Collect. Czech. Chem. Commun.* **1968**, *38*, 2927.
(21) Compound **30** was prepared from commercially available 1,2,6-hexanetriol. The diol acetonide of 1,2,6-hexanetriol has been previously prepared: Landini, D.; Montanari, F.; Rolla, F. *Synthesis* **1979**, 134.
(22) (a) Snider, B. B.; Rodini, D. J.; Karras, M.; van Straten, J. *Tetrahedron* **1981**, *37*, 3927. (b) Snider, B. B.; Rodini, D. J.; van Straten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5872.
(23) (a) Stork, G.; Cohen, J. F. *J. Am. Chem. Soc.* **1974**, *96*, 5270. (b) van Tamelen, E. E.; Leiden, T. M. *Ibid.* **1982**, *104*, 2061. (c) Livinghouse has recently observed "anti-Markovnikov" attack in aryl-terminated, episulfonium ion initiated cyclizations, see: Edstrom, E.; Livinghouse, T. *J. Chem. Soc., Chem. Commun.* **1986**, 279.

variety of Lewis acids,[8a] leading us to expect similar behavior in the pyrrole series. In the event, reaction of **12** with BF_3·OEt_2 (THF, Et_3N, −78 °C) afforded a 6-exo **19** in 20% yield. The treatment of **12** with $EtAlCl_2$ (CH_2Cl_2, −78 °C) provided a mixture of two compounds, the expected **19** (35%) and the heretofore unobserved 7-endo alcohol **20** (45%). The isolation of the 7-endo product **20** as the major cyclized product suggests that the more nucleophilic pyrrole terminator and the relatively mild reaction conditions are conspiring to produce products of assisted S_N2 substitution[24] at the less sterically hindered epoxide carbon when ring size and geometric constraints do not interfere. Exposure of **12** to Et_2AlCl gave a mixture of **19** (37%) and **20** (48%). Employing Ti(O-*i*-Pr)$_3$Cl as the Lewis acid afforded *only* the 6-exo alcohol **19** (64%). The heterogenous ZnI_2 reaction conditions, again, yielded a mixture of 6-exo **19** (21%) and 7-endo **20** (30%) alcohols.

The final cyclization substrate **13** provided the 7-exo alcohol as anticipated as the only cyclized product with all the Lewis acids employed. The yield of **21** ranged from a low of 21% (BF_3·OEt, THF, Et_3N) to a high of 85% (Ti(O-*i*-Pr)$_3$Cl). However, exposure of **13** to ZnI_2 provided an additional product, the corresponding iodohydrin, in yields which were dependent upon the reaction solvent (PhH, 21%; Et_2O, 49%).

In conclusion, the pyrrole moiety has proved to be an excellent cationic cyclization terminator in epoxide-initiated cyclizations. The ring size obtained is generally predictable, providing mixtures only in the case of *N*-(epoxyalkyl)pyrrole **12**. It is noteworthy that the exclusive products obtained from pyrroles **8** and **9** are the "anti-Markovnikov" cyclized materials and that the 7-endo mode of closure can compete with the expected 6-exo path with compound **12**. The yields of cyclized products obtained ranged from fair to excellent; however, an inspection of Table II does not reveal trends that would assist in the selection of general "optimum" reaction conditions. The most favorable reaction conditions must be determined on a case-by-case basis. The products obtained in this study are closely related to 5,6,7,8-tetrahydroindolizidines and 6,7,8,9-hexahydro-5*H*-pyrrolo[1,2-*a*]azepines which have been implicated in the development of certain nonsteroidal, antiinflammatory agents[25] and possess functional groups amenable to further elaboration. An extension of this work to additional initiator functions, pyrrole α- to β- and β- to α-cyclizations, and the conversion of these products to other ring systems and bioactive alkaloids are in progress and will be reported in due course.

Experimental Section

General. Tetrahydrofuran (THF) and benzene were dried by distillation under argon from sodium–benzophenone ketyl; methylene chloride was dried by distillation under argon from calcium hydride; triethylamine (TEA) was dried by distillation under argon from calcium hydride; *tert*-butyl alcohol was dried by distillation under argon from sodium; pyridine was dried by distillation under argon from calcium hydride; acetone was dried over calcium chloride. Boron trifluoride etherate (BF_3·OEt_2) was purified by distillation at reduced pressure from calcium hydride. Petroleum ether refers to the 35–60 °C boiling point fraction of petroleum benzin. Diethyl ether was purchased from Columbia Chemical Industries, Inc., Columbus, WI, and was used as received. Osmium tetraoxide was purchased from Aldrich Chemical Company, Milwaukee, WI, and prepared as a 0.5 M solution in *tert*-butyl alcohol. Ethylaluminum dichloride and diethylaluminum chloride were purchased as hexane solutions from Alfa Products, Danvers, MA and used as received. All other reagents were used as received unless otherwise stated; all reactions were performed under argon with the rigid exclusion of moisture from all reagents and glassware unless otherwise mentioned.

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Pye-Unicam SP-1000 infrared spectrometer or a Perkin-Elmer Model 167 spectrometer with polystyrene as standard. Proton magnetic resonance spectra (^1H NMR) were recorded on a Varian T-60 at 60 MHz, a Varian CFT-20 at 80 MHz, or a Bruker WM-250 spectrometer at 250 MHz as mentioned in deuteriochloroform unless otherwise indicated. Chemical shifts are reported in parts per million (δ scale) from internal tetramethylsilane. Data are reported as followed: chemical shifts [multiplicity (s = singlet, br s = broad singlet, dd = doublet of doublets, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), integration). Electron impact (EI/MS, 70eV) mass spectra were recorded on a Finnigan 4000 with an INCOS 4021 data system. High-resolution EI/MS were obtained at the Michigan State University Regional Mass Spectroscopy Facility, Department of Biochemistry, East Lansing, MI.[26]

Flash column chromatography was performed according to the procedure of Still[27] et. al. by using the Merck silica gel mentioned and eluted with the solvents mentioned. The column outer diameter (o.d.) is listed in millimeters.

General Procedure for the N-Alkylation of Pyrroles with ω-Iodo Epoxides. 2-Methyl-5-*N*-pyrrolyl-1,2-epoxypentane (11). To anhydrous ether (40 mL) at room temperature under argon was added 18-crown-6 ether (0.53 g, 2.0 mmol) and potassium *tert*-butoxide (2.58 g, 23.0 mmol) followed immediately by pyrrole (1.34 g, 1.39 mL, 20.0 mmol). The resulting off-white suspension was stirred for 15 min. To this mixture was added a solution of **23** (5.20 g, 23.0 mmol) in ether (18 mL) over 15 min. The mixture was stirred at room temperature for 20 h, diluted with H_2O (100 mL), and cast into ether (100 mL) and H_2O (100 mL). The aqueous layer was separated and extracted with ether (2 × 80 mL). The combined ether layers were washed with brine (200 mL), dried (Na_2SO_4), and concentrated in vacuo to afford a yellow liquid. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 200 g, 60 mm o.d., ether–petroleum ether (30:70), 60-mL fractions) with the flash technique. Fractions 24–32 provided 1.13 g, 34%, of **11** as a pale yellow, free-flowing liquid: ^1H NMR (250 MHz, C_6D_6) δ 6.45 (m, 2), 6.35 (m, 2), 3.29 (t, J = 6 Hz, 2), 2.10 (s, 2), 1.38 (m, 2), 1.10 (m, 2), 0.93 (s, 3); IR (neat) 3100, 3040, 2920, 1290, 1090, 720 cm^{-1}; EI-MS (70 eV); m/z (relative intensity) 165 (M^+, 73.3), 148 (37.7), 134 (38.7), 120 (60.5), 81 (53.5), 80 (base), 68 (60.7).

2-Methyl-4-*N*-pyrrolyl-1,2-epoxybutane (9). According to the general procedure for N-alkylation of pyrroles with ω-iodo epoxides, 0.34 g (5 mmol) of pyrrole, KO-*t*-Bu (0.56 g, 5 mmol), and 18-crown-6 ether (44 mg, 0.17 mmol) in benzene (8 mL) followed by the addition of ω-iodo epoxide **22**[8,16] gave 0.302 g (40%) of **9** after purification by chromatography on a column of silica gel: ^1H NMR (60 MHz) δ 6.43 (t, J = 1.5 Hz, 2), 5.90 (br t, J = 1.5 Hz, 2), 3.88 (t, J = 6.5 Hz, 2), 2.3 (m, 2), 1.85–2.20 (m, 2), 1.22 (s, 3); IR (neat) 3100, 3020, 2930, 2870, 1500, 1450, 1380 (br), 1285, 1090, 905, 800, 730 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 151 (M^+, 68), 120 (33), 106 (14), 95 (12.8), 80 (base); exact mass calcd for $C_9H_{13}NO$ 151.0997, found 151.0995.

1-(Benzyloxy)-4-methylpent-3-ene. To a suspension of oil-free NaH (1.42 g, 59 mmol) in dry THF (100 mL), chilled in an ice–H_2O bath, was added 4-methylpent-3-en-1-ol[28] (5.78 g, 57.8 mmol) over 30 min. The mixture was warmed to 25 °C, stirred for 30 min, and then a catalytic amount of tetrabutylammonium iodide (214 mg, 0.578 mmol) was added, followed by the addition

(24) See: Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693 and references cited therein.

(25) Carpio, H.; Galeazzi, E.; Greenhouse, R.; Guzman, A.; Velarde, E.; Antonio, Y.; Franco, F.; Leon, A.; Perez, v.; Salas, R; Valdes, D.; Ackrell, J.; Cho, D.; Gallegra, P.; Halpern, O.; Koehler, R.; Maddox, M. L.; Muchowski, J. M.; Prince, A.; Tegg, D.; Thurber, T. C.; Van Horn, A. R.; Wren, D. *Can. J. Chem.* **1982**, *60*, 2295.

(26) Numerous attempts to obtain combustion analyses for the compounds described herein were unsuccessful. In every instance, the unstable pyrroles decomposed in transit or after receipt at the site of analysis.

(27) Still, W. C.; Mitra, A.; Khan, M. *J. Org. Chem.* **1978**, *41*, 2923.

(28) Moppett, C. E.; Sutherland, J. K. *J. Chem. Soc. C* **1968**, 3040.

of a solution of benzyl bromide (9.99 g, 58.4 mmol) in THF (10 mL) over 40 min. The resulting suspension was stirred at 25 °C for 5 h, quenched by cautiously adding water (100 mL), and extracted with Et_2O (3 × 100 mL). The combined Et_2O layers were washed with brine (300 mL), dried ($MgSO_4$), and concentrated in vacuo to 11.0 g, 100%, of the benzyl ether as a pale yellow liquid, which was used without further purification: ^1H NMR (60 MHz) δ 7.38 (s, 5), 5.10 (m, 1), 4.45 (s, 2), 3.48 (t, J = 8 Hz, 2), 2.50–2.0 (m, 2), 1.70 (s, 3), 1.63 (s, 3); EI-MS (70 eV), m/z (relative intensity) 190 (M^+, 1.05), 175 (1.97), 147 (1.48), 132 (8.50), 107 (26.6), 91 (base), 69 (76.7), 41 (76.0).

1-(Benzyloxy)-4-methylpentane-3,4-diol. To a solution of benzyl ether (3.85 g, 20.26 mmol) and *N*-methylmorpholine *N*-oxide hydrate[29] (3.56 g, 26.34 mmol) in acetone (13 mL) and water (5.0 mL) was added at room temperature a solution of osmium tetraoxide[28] (2.02 mL, 1.01 mmol, 0.5 M) in *tert*-butyl alcohol. The resulting deep purple solution faded within minutes to a light maroon color, where it remained for 15 min before returning to a deep purple cast. The mixture was stirred at room temperature for 24 h. A major portion of the solvents were removed at reduced pressure, and the aqueous residue was acidified with cold 2 N aqueous HCl followed by the addition of 10% aqueous sodium bisulfite (10 mL). The aqueous mixture was saturated with sodium chloride and extracted with ethyl acetate (6 × 50 mL). The combined organic phases were washed with 10% aqueous sodium bisulfite (300 mL) and brine (300 mL), dried ($MgSO_4$), and concentrated in vacuo to provide 4.03 g of a pale yellow, viscous liquid. The crude product was purified by chromatography on a column of silica gel (60–230 mesh, 200 g, 60 mm o.d., ethyl acetate, 75–100-mL fractions) with the flash technique to provide 3.50 g, 77%, of monoprotected triol as a water-white viscous liquid, which was immediately converted to the corresponding acetonide: ^1H NMR (60 MHz) δ 7.30 (s, 5), 4.50 (br s, 2), 3.70 (t, J = 6 Hz, 2), 3.50 (m, 1), 3.15 (s, 2), 2.0–1.56 (m, 2), 1.23 (s, 3), 1.15 (s, 3); EI-MS (70 eV), m/z (relative intensity) 224 (M^+, 0.20), 206 (0.18), 188 (0.44), 178 (0.65), 165 (1.32), 148 (0.87), 123 (8.25), 107 (15.1), 91 (base).

1-(Benzyloxy)-4-methyl-3,4-*O*-isopropylidenepentane-3,4-diol. To a solution of the *O*-benzyl diol (3.50 g, 15.62 mmol) in dry acetone (50 mL) were added two drops of concentrated sulfuric acid and solid sodium sulfate (4.0 g). The mixture was stirred at room temperature overnight then quenched by suspending solid sodium bicarbonate in the reaction mixture for 15 min. The mixture was then filtered through a pad of Celite topped with a layer of anhydrous magnesium sulfate and concentrated in vacuo to give 4.0 g, 97%, of the desired acetonide as a water-white viscous liquid: ^1H NMR (60 MHz) δ 7.32 (s, 5), 4.58 (s, 2), 3.69 (m, 3), 1.80 (m, 2), 1.43 (s, 3), 1.37 (s, 3), 1.28 (s, 3), 1.10 (s, 3); EI-MS (70 eV), m/z (relative intensity) 264 (M^+, 0.85), 249 (base), 206 (18.8), 175 (4.46), 147 (25.4), 123 (38.2), 107 (13.8), 91 (73.3), 84 (16.7).

4-Methyl-3,4-*O*-isopropylidenepentane-1,3,4-triol. A solution of benzyl ether acetonide (4.00 g, 15.2 mmol) in ethanol (60 mL) was hydrogenated at 65 psi over 10% palladium on charcoal (0.98 g) for 24 h. The catalyst was removed by filtration, and the solution was concentrated in vacuo to afford 2.54 g, 98%, of the deprotected triol as a water-white viscous liquid: ^1H NMR (60 MHz) δ 3.64 (m, 4), 1.78 (m, 2), 1.41 (s, 3), 1.32 (s, 3), 1.25 (s, 3), 1.10 (s, 3); IR (neat) 3480, 2950, 1460, 1370, 1100, 750, 700 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 174 (M^+, 1.05), 159 (19.3), 117 (14.6), 99 (34.8), 85 (50.8), 71 (23.4), 59 (61.4), 43 (base).

General Procedure for the Tosylation of ω-Hydroxy Acetonides. 2-Methyl-2,3-*O*-isopropylidenepentane-2,3,5-triol 5-*p*-Toluenesulfonate. To a solution of the ω-hydroxy acetonide (2.54 g, 14.60 mmol) in dry pyridine (8 mL), chilled in an ice–water bath, was added *p*-toluenesulfonyl chloride (3.48 g, 18.25 mmol) in one portion. The reaction mixture was stirred at 0 °C for 2 h and then placed in a freezer (−20 °C) overnight. The reaction mixture was allowed to come to room temperature, cast into ice–concentrated HCl (50 g/50 mL), and extracted with ether (100 mL). The ether layer was washed with 1 N aqueous HCl (100 mL), water (100 mL), saturated aqueous sodium bicarbonate (100 mL), and brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to give 4.57 g, 95%, of the acetonide tosylate as a pale yellow, viscous liquid, which was used without further purification.

General Procedure for the Formation of ω-Iodo Acetonides. 5-Iodo-2-methyl-2,3-*O*-isopropylidenepentane-2,3-diol (26). To a solution of the corresponding acetonide tosylate (8.22 g, 25.06 mmol) in acetone (80 mL) was added anhydrous sodium iodide (4.25 g, 27.68 mmol). The resulting yellow-brown mixture was heated under reflux for 5 h, cooled to room temperature, and filtered and the filtrate taken up in ether (150 mL). The organic layer was washed with 10% aqueous sodium thiosulfate (2 × 150 mL), water (150 mL), saturated aqueous sodium bicarbonate (150 mL), and brine (150 mL), dried (Na_2SO_4), and concentrated in vacuo to provide 6.0 g (84%) of **26** as a pale yellow, free-flowing liquid. The crude product was purified by bulb-to-bulb distillation, bp = 78 °C (0.5 mmHg), to yield 5.69 g, 80%, of **26** as a water-white, free-flowing liquid: ^1H NMR (60 MHz) δ 3.45 (m, 1), 3.32 (m, 2), 2.10 (m, 2), 1.50 (s, 3), 1.40 (s, 3), 1.29 (s, 3), 1.18 (s, 3); IR (neat) 2940, 1450, 1400, 1230, 1060, 830 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 284 (M^+, 2.57), 269 (70.5), 239 (5.08), 227 (30.5), 212 (20.5), 127 (4.38), 99 (34.8), 71 (23.4), 59 (61.5), 43 (base).

1,2-*O*-Isopropylidenebutane-1,2-diol 4-*p*-Toluenesulfonate. According to the general procedure for tosylation of ω-hydroxy acetonides, 8.42 g (57.7 mmol) of the ω-hydroxy acetonide gave 15.0 g, 87%, of the corresponding tosylate.

4-Iodo-1,2-*O*-isopropylidenebutane-1,2-diol (24). A solution of the tosylate acetonide (15.0 g, 50 mmol) in acetone (200 mL) was reacted with anhydrous sodium iodide (8.25 g, 55 mmol) according to the general procedure. The crude iodo acetonide **24** was purified by bulb-to-bulb distillation, bp 52 °C (0.7 mmHg), to provide 10.1 g, 79%, of **24** as a water-white, free-flowing liquid: ^1H NMR (60 MHz, CCl_4) δ 4.08 (m, 2), 3.60 (m, 1), 3.22 (t, J = 8 Hz, 2), 2.02 (m, 2), 1.38 (s, 3), 1.31 (s, 3); IR (neat): 2980, 2940, 2880, 1370, 1230, 1160, 1060, 840 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 256 (M^+, 0.87), 241 (base), 218 (6.79), 199 (9.66), 181 (30.9), 101 (13.7), 72 (22.0), 59 (18.7), 43 (95.3).

5-Hydroxy-1,2-*O*-isopropylidenepentane-1,2-diol. To a solution of the 1,2,5-pentanetriol[20] (4.13 g, 34.4 mmol) in acetone (50 mL, dried over $CaCl_2$) at room temperature was added two drops of concentrated HCl together with anhydrous Na_2SO_4 (6.0 g). The reaction mixture was stirred for 3 h at room temperature, then solid $NaHCO_3$ was suspended in the mixture, and stirring was continued for an additional 25 min. The reaction mixture was filtered and concentrated in vacuo to give 4.98 g, 90%, of the hydroxy acetonide as a slightly cloudy, viscous liquid, which was purified by distillation: bp 70 °C (0.1 mmHg); ^1H NMR (60 MHz, CD_3CN) δ 4.10 (m, 2), 3.53 (m, 3), 2.80 (br s, 1), 1.60 (m, 4), 1.40 (s, 3), 1.32 (s, 3); EI-MS (70 eV), m/z (relative intensity) 160 (M^+, 1.00), 145 (6.39), 117 (6.27), 99 (24.5), 101 (15.7), 83 (18.9), 59 (60.1), 43 (base).

1,2-*O*-Isopropylidenepentane-1,2-diol 5-*p*-Toluenesulfonate. According to the general procedure for tosylation of ω-hydroxy acetonides, 2.85 g (17.8 mmol) of the hydroxy acetonide gave 4.08 g (85%) of the corresponding tosylate.

5-Iodo-1,2-*O*-isopropylidenepentane-1,2-diol (28). A solution of the tosylate acetonide (4.23 g, 13.43 mmol) in acetone (50 mL) was reacted with anhydrous sodium iodide (2.32 g, 15.44 mmol) according to the general procedure for the formation of ω-iodo acetonides to provide 2.94 g, 76%, of **28** as a pale yellow, free-flowing liquid. The crude product was purified by Kugelrohr distillation, bp 68–70 °C (0.1 mmHg), to yield a colorless free-flowing liquid: ^1H NMR (60 MHz) δ 4.1 (m, 2), 3.45 (m, 1), 3.20 (t, J = 6 Hz, 2), 2.15 (m, 2), 1.60 (m, 2), 1.35 (s, 3), 1.30 (s, 3); IR (neat): 2960, 1370, 1230, 1180, 1080, 850 cm^{-1}.

1,2-*O*-Isopropylidenehexane-1,2-diol 6-*p*-Toluenesulfonate. According to the general procedure for tosylation of ω-hydroxy acetonides, 11.12 g (63.9 mmol) of the hydroxy acetonide gave 18.95 g (90%) of the corresponding tosylates.

6-Iodo-1,2-*O*-isopropylidenehexane-1,2-diol (30). A solution of the tosylate acetonide (18.84 g, 57.44 mmol) in acetone (180 mL) was reacted with anhydrous sodium iodide (9.48 g, 63.2 mmol) according to the general procedure. The crude iodo acetonide **30** was purified by bulb-to-bulb distillation, bp 87 °C (0.1 mmHg), to give 15.17 g, 93%, of **30** as a water-white liquid: ^1H NMR (60 Hz) δ 4.08 (m, 2), 3.50 (m, 1), 3.20 (t, J = 7 Hz, 2), 1.90 (m, 2),

(29) Van Rheenan, V.; Kelley, R. C.; Cha, P. Y. *Tetrahedron Lett.* **1976**, 1973.

1.60 (m, 2), 1.42 (s, 3), 1.39 (s, 3); IR (neat) 2920, 1450, 1370, 1225, 1170, 1060, 850 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 284 (M^+, 11.9), 269 (base), 227 (8.85), 209 (22.6), 127 (4.38), 101 (13.5), 81 (76.3), 72 (37.8), 43 (89.3).

General Procedure for the N-Alkylation of Pyrroles with ω-Iodo Acetonides. 1,2-*O*-Isopropylidene-6-*N*-pyrrolylhexane-1,2-diol (31). To anhydrous ether (60 mL) at room temperature under argon were added 18-crown-6 ether (0.793 g, 3.0 mmol) and potassium *tert*-butoxide (3.82 g, 34.0 mmol), followed immediately by pyrrole (2.08 mL, 30.0 mmol). The resulting off-white suspension was stirred at room temperature for 15 min. A solution of **30** (9.37 g, 33.0 mmol) in ether (22 mL) was then added over 20 min. The reaction mixture was stirred at room temperature for 24 h, diluted with water (100 mL), and cast into ether (100 mL) and water (50 mL). The aqueous layer was separated and extracted with ether (2 × 75 mL). The combined ether layers were washed with brine (200 mL), dried (Na_2SO_4), and concentrated in vacuo to provide a yellow liquid. The crude product was purified by chromatography on a column of silica gel (60–230 mesh, 120 g, 50 mm o.d., ether–petroleum ether (1:1), 75-mL fractions) with the flash technique. Fractions 7–14 yielded 6.56 g, 98%, of **31** as a pale yellow, free-flowing liquid: ^1H NMR (250 MHz, C_6D_6) δ 6.46 (t, J = 1 Hz, 2), 6.34 (t, J = 1 Hz, 2), 3.70 (m, 2), 3.27 (m, 1), 3.25 (t, J = 8 Hz, 2), 1.42 (s, 3), 1.32 (s, 3), 1.65–0.9 (m, 6); IR (neat: 2940, 1370, 1240, 1060, 720 cm^{-1}; EI-MS (70 eV); 223 (M^+, 26.1), 208 (8.21), 165 (18.6), 148 (55.2), 81 (base), 72 (35.3), 43 (53.5).

General Procedure for the Deprotection of the Pyrrole Acetonides. 6-*N*-Pyrrolylhexane-1,2-diol (35). To a solution of the pyrrole acetonide **31** (1.045 g, 4.69 mmol) in methanol (250 mL) at 25 °C was added *p*-toluenesulfonic acid (0.095 g, 0.50 mmol). The mixture was allowed to stir for 2 h then quenched by suspending solid $NaHCO_3$ for 5 min in the reaction mixture. The mixture was filtered and concentrated in vacuo to provide a yellow viscous liquid together with some solid $NaHCO_3$. The crude diol was purified by chromatography on a column of silica gel (60–230 mesh, 100 g, 50 mm o.d., EtOAc, 75-mL fractions) with the flash technique. Fractions 7–15 yielded 0.775 g, 90%, of **35** as a yellow viscous liquid: ^1H NMR (250 MHz, C_6D_6) δ 6.51 (t, J = 2 Hz, 2), 6.35 (t, J = 2 Hz, 2), 3.81 (br s, 1), 3.55 (m, 2), 3.41 (m, 1), 3.34 (t, J = 7 Hz, 2), 3.30 (br s, 1), 1.25 (m, 6); IR (neat) 3360 (br), 2920, 1280, 1070, 730 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 183 (M^+, 44.4), 166 (7.34), 152 (12.3), 134 (15.2), 81 (base), 80 (78.2), 41 (44.3).

General Procedure for the Monotosylation of the Pyrrolyl 1,2-Diols. Preparation of 6-*N*-Pyrrolylhexane-1,2-diol 1-*p*-Toluenesulfonate (35, R_4 = *p*-Ts, R_5 = H). To a solution of diol **35**, $R_4 = R_5 = H$ (0.75 g, 4.10 mmol), in dry pyridine (18 mL), chilled in an ice–water bath, were added in one portion *p*-toluenesulfonyl chloride (0.90 g, 4.72 mmol) and a crystal of 4-(dimethylamino)pyridine. The resulting deep red colored mixture was stirred at room temperature for 48 h. The mixture was then cast into ice–concentrated HCl (100 g/100 mL) and extracted with ether (150 mL). The ether layer was washed with 1 N aqueous HCl (100 mL), water (100 mL), and brine (100 mL), dried (Na_2SO_4), and concentrated in vacuo to provide a green viscous liquid (1.4 g). The crude tosylate was purified by chromatography on a column of silica gel (60–230 mesh, 100 g, 50 mm o.d., EtOAc, 40-mL fractions) with the flash technique. Fractions 3–7 yielded 1.28 g, 93%, of **35** as an orange viscous liquid: ^1H NMR (60 MHz, C_6D_6) δ 7.70 (d, J = 8 Hz, 2), 6.70 (d, J = 8 Hz, 2), 6.40 (m, 2), 6.27 (m, 2), 3.95 (br s, 1), 3.74 (m, 2), 3.30 (m, 3), 1.89 (s, 3), 1.10–1.70 (m, 6); IR (neat) 3500, 3100, 2920, 1600, 1360, 1180, 970, 730 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 337 (M^+, 0.81), 182 (1.43), 166 (5.20), 165 (19.7), 134 (10.2), 122 (16.7), 107 (20.5), 91 (46.9), 81 (base).

General Procedure for the Formation of the Pyrrolyl Epoxides. 6-*N*-Pyrrolyl-1,2-epoxyhexane (13). To a suspension of potassium *tert*-butoxide (0.775 g, 6.91 mmol) in dry THF (40 mL), cooled in a dry ice–CCl_4 bath to −23 °C, was added dropwise over 15 min a solution of **35** (2.025 g, 6.01 mmol) in dry THF (20 mL). The resulting magenta-colored mixture was stirred at −23 °C for 15 min, warmed to room temperature, diluted with water (24 mL), and cast into ether (200 mL) and water (100 mL). The organic layer was separated, washed with brine (200 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a pale yellow, free-flowing liquid. The crude product was purified by chromatography on a column of silica gel (60–230 mesh, 100 g, 50 mm o.d., Et_2O–petroleum ether (30:70), 50-mL fractions) with the flash technique. Fractions 7–13 provided 0.87 g, 88%, of **13** as a pale yellow, free-flowing liquid: ^1H NMR (250 MHz) δ 6.61 (t, J = 1 Hz, 2), 6.10 (t, J = 1 Hz, 2), 3.85 (t, J = 6 Hz, 2), 2.75 (m, 1), 2.69 (t, J = 3 Hz, 1), 2.40 (m, 1), 1.78 (m, 2), 1.45 (m, 4); IR (neat) 3100, 3050, 2920, 1500, 1290, 1100, 730 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 165 (M^+, 15.5), 147 (1.98), 134 (13.2), 120 (13.8), 106 (14.6), 94 (15.9), 81 (base), 80 (78.6), 53 (40.1); exact mass calcd for $C_{10}H_{15}NO$ 165.1153, found 165.1090.

1,2-*O*-Isopropylidene-4-*N*-pyrrolylbutane-1,2-diol (25). According to the general procedure for the preparation of pyrrole acetonides, 1.38 g (20 mmol) of pyrrole, 0.53 g (2.0 mmol) of 18-crown-6-ether, 5.76 g (22.5 mmol) of **24**, and 2.58 g (23 mmol) of potassium *tert*-butoxide were combined to afford crude **25** as a pale yellow liquid. Flash chromatograpy on a column of silica gel provided 3.73 g, 95%, of **25** as a pale yellow liquid: ^1H NMR (60 MHz, CCl_4) δ 6.41 (t, J = 2 Hz, 2), 5.87 (t, J = 2 Hz, 2), 3.83 (m, 4), 3.28 (m, 1), 1.80 (m, 2), 1.28 (s, 3), 1.20 (s, 3); IR (neat) 3100, 2980, 2940, 2880, 1500, 1370, 1290, 1250, 1220, 1160, 1090, 1065, 860, 730 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 196 (M + 1, 2.97), 195 (M^+, 24.4), 180 (1.17), 137 (10.4), 120 (43.0), 106 (4.34), 94 (30.1), 81 (base), 80 (73.9), 43 (36.0).

4-*N*-Pyrrolylbutane-1,2-diol (32, $R_4 = R_5$ = H). According to the general procedure for the deprotection of pyrrole acetonides, 0.14 g (0.77 mmol) of **25** and 0.015 g (0.06 mmol) of pyridinium *p*-toluenesulfonate afforded 0.11 g of crude **32** as a viscous yellow liquid. Flash chromatography on a column of silica gel gave 0.10 g (89%) of pyrrole diol **32** as a pale yellow, viscous liquid: ^1H NMR (60 MHz, CCl_4) δ 6.38 (t, J = 2 Hz, 2), 5.83 (t, J = 2 Hz, 2), 3.89 (t, J = 7 Hz, 2), 3.50 (m, 2), 3.26 (m, 3), 2.62 (m, 2); IR (CCl_4) 3400, 2930, 2870, 1500, 1280, 1240, 1090, 1060, 720 cm^{-1}; EI-MS (70 eV), (relative intensity) 156 (M + 1, 4.24), 155 (M^+, 38.3), 137 (1.78), 124 (4.17), 120 (5.60), 106 (2.44), 94 (6.40), 81 (base), 80 (80.0), 68 (15.1), 53 (22.2).

4-*N*-Pyrrolylbutane-1,2-diol 1-*p*-Toluenesulfonate (32, R_4 = *p*-Ts, R_5 = H). According to the general procedure for the tosylation of pyrrole diols, 0.098 g (0.632 mmol) of **32** ($R_4 = R_5$ = H) and 0.132 g (0.692 mmol) of *p*-toluenesulfonyl chloride were combined in pyridine (4 mL), chilled to 0 °C in an ice–water bath, and reacted with *p*-toluenesulfonyl chloride to give the crude monotosylate **32** as a viscous yellow-green oil. Flash chromatography on a column of silica gel yielded 0.177 g, 91%, of the glycol monotosylate **32** (R_4 = *p*-Ts, R_5 = H) as a pale yellow, viscous liquid: ^1H NMR (60 MHz, CCl_4) δ 7.72 (d, J = 8 Hz, 2), 6.73 (d, J = 8 Hz, 2), 6.42 (t, J = 2 Hz, 2), 6.28 (t, J = 2 Hz, 2), 3.97 (br s, 1), 3.77 (t, J = 6 Hz, 2), 3.30 (m, 3), 1.87 (s, 3), 1.32 (m, 2); EI-MS (70 eV), m/z (relative intensity) 309 (M^+, 0.41), 172 (1.08), 155 (2.72), 137 (35.5), 120 (11.3), 106 (2.92), 94 (43.3), 81 (22.2), 80 (base), 68 (9.61), 67 (14.0), 53 (22.2).

4-*N*-Pyrrolyl-1,2-epoxybutane (8). According to the general procedure for the formation of *N*-(epoxyalkyl)pyrroles, 0.076 g (0.68 mmol) of potassium *tert*-butoxide and 0.174 g (0.567 mmol) of **32** (R_4 = *p*-Ts, R_5 = H) were combined to afford the crude *N*-(epoxyalkyl)pyrrole **8** as a pale yellow liquid. Flash chromatography on a column of silica gel provided 0.070 g, 90%, of **8** as a pale yellow, free-flowing liquid: ^1H NMR (60 MHz) δ 6.62 (t, J = 2 Hz, 2), 6.10 (t, J = 2 Hz, 2), 4.00 (t, J = 7 Hz, 2), 2.78 (m, 2), 2.37 (m, 1), 1.91 (m, 2); IR (neat) 3040, 2985, 2920, 2860, 1500, 1350, 1285, 1090, 1065, 910, 720 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 137 (M^+, 48.4), 120 (3.71), 106 (14.0), 94 (12.7), 81 (20.3), 80 (base), 67 (13.9), 53 (29.3), 39 (26.4); exact mass calcd for $C_8H_{11}NO$ 137.0840, found 137.0869.

2-Methyl-2,3-*O*-isopropylidene-5-*N*-pyrrolylpentane-1,2-diol (27). According to the general procedure for the preparation of pyrrole acetonide, 0.67 g (10 mmol) of pyrrole, 0.264 g (1.0 mmol) of 18-crown-6-ether, 3.00 g (10.56 mmol) of **26**, and 1.23 g (11.0 mmol) of potassium *tert*-butoxide were combined to yield crude **27** as a pale yellow liquid. Flash chromatography on a column of silica gel yielded 2.21 g, 99%, of **27** as a pale yellow liquid: ^1H NMR (80 MHz, $CDCl_3$) δ 6.70 (br s, 2), 6.25 (br s, 2), 4.10 (m, 2), 3.60 (m, 1), 1.90 (m, 2), 1.50 (s, 3), 1.38 (s, 3), 1.22 (s, 3), 1.12 (s, 3); IR (neat) 3100, 2980, 2930, 2860, 1500, 1450, 1370, 1280, 1220, 1120, 1000, 730 cm^{-1}; EI-MS (70 eV) m/z (relative intensity) 224 (M + 1, 4.80), 223 (M^+, 17.1), 208 (6.09), 178 (5.65),

166 (14.5), 148 (16.5), 81 (base), 80 (37.8), 59 (13.5), 43 (32.4).

2-Methyl-5-*N*-pyrrolylpentane-2,3-diol (33, $R_4 = R_5 = H$). According to the general procedure for the deprotection of pyrrole acetonides, 1.10 g (4.83 mmol) of **27** and 0.0938 g (0.493 mmol) of *p*-toluenesulfonic acid provided crude **33** ($R_4 = R_5 = H$) as a viscous yellow liquid. Flash chromatography on a column of silica gel yielded 0.708 g, 78%, of **33** ($R_4 = R_5 = H$) as a yellow viscous liquid: ^1H NMR (60 MHz, CCl_4) δ 6.40 (t, J = 2 Hz, 2), 5.83 (t, J = 2 Hz, 2), 3.90 (t, J = 6 Hz, 2), 3.60 (t, J = 7 Hz, 1), 3.20 (br s, 1), 1.95–1.55 (m, 3), 1.25 (s, 3), 1.15 (s, 3); IR (neat) 3400, 2940, 2860, 1500, 1450, 1370, 1280, 1110, 1050, 720 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 166 (M − 17, 6.86), 165 (M − 18, 33.8), 150 (49.8), 148 (14.6), 121 (21.8), 106 (21.6), 81 (base), 80 (52.7), 59 (36.0), 43 (28.1).

2-Methyl-5-*N*-pyrrolylpentane-2,3-diol 3-*p*-Toluenesulfonate (33, $R_4 = H$, $R_5 = p$-Ts). According to the general procedure for the tosylation of pyrrole diols, 0.708 g (3.87 mmol) of **33** ($R_4 = R_5 = H$) and 0.848 g (4.45 mmol) of *p*-toluenesulfonyl chloride were combined in pyridine (17 mL) to give **33** ($R_4 = H$, $R_5 = p$-Ts) as an orange liquid. Flash chromatography on a column of silica gel gave 0.522 g, 40%, of **33** ($R_4 = H$, $R_5 = p$-Ts) as an orange viscous liquid and 0.389 g, 55%, of recovered **33** ($R_4 = R_5 = H$): ^1H NMR (60 MHz, C_6D_6) δ 7.68 (d, J = 8 Hz, 2), 6.73 (d, J = 8 Hz, 2), 6.53 (t, J = 2 Hz, 2), 6.20 (t, J = 2 Hz, 2), 4.50 (t, J = 4 Hz, 1), 3.82 (t, J = 6 Hz, 2), 2.39 (br s, 1), 1.92 (s, 3), 1.70 (m, 2), 1.00 (s, 3), 0.98 (s, 3); EI-MS (70 eV), m/z (relative intensity) 337 (M^+, 1.12), 182 (2.95), 165 (63.8), 150 (100), 132 (9.49), 121 (44.6), 106 (40.8), 80 (34.4).

2-Methyl-5-*N*-pyrrolyl-2,3-epoxypentane (10). According to the general procedure for the preparation of *N*-(epoxyalkyl)-pyrroles, 0.125 g (0.371 mmol) of **33** ($R_4 = H$, $R_5 = p$-Ts) and 0.049 g (0.44 mmol) of potassium *tert*-butoxide were combined to yield crude **10** as a yellow liquid. Flash chromatography on a column of silica gel provided 0.053 g, 86%, of **10** as a pale yellow, free-flowing liquid: ^1H NMR (60 MHz) δ 6.52 (t, J = 2 Hz, 2), 6.02 (t, J = 2 Hz, 2), 4.12 (t, J = 7 Hz, 2), 2.82 (t, J = 7 Hz, 2), 1.70 (br s, 1), 1.10 (s, 3), 0.99 (s, 3); IR (CCl_4): 3050, 2980, 2920, 2860, 1500, 1280, 1090, 910, 720 cm^{-1}; EI-MS (70 eV), 166 (M + 1, 4.70), 165 (M^+, 36.9), 150 (47.3), 135 (5.40), 121 (25.7), 106 (63.6), 94 (21.3), 81 (50.6), 80 (88.7), 71 (32.0), 68 (45.3), 43 (base); exact mass calcd for $C_{10}H_{15}NO$ 165.1153, found 165.1179.

1,2-*O*-Isopropylidene-5-*N*-pyrrolylpentane-1,2-diol (29). According to the general procedure for the preparation of pyrrole acetonides, 0.67 g (10 mmol) of pyrrole, 0.264 g (1.0 mmol) of 18-crown-6-ether, 2.85 g (10.56 mmol) of **28**, and 1.29 g (11.5 mmol) of potassium *tert*-butoxide were combined to afford crude **29** as a yellow liquid. Flash chromatography on a column of silica gel gave 1.82 g, 87%, of **29** as a pale yellow, free-flowing liquid: ^1H NMR (60 MHz, CCl_4) δ 6.52 (t, J = 2 Hz, 2), 6.00 (t, J = 2 Hz, 2), 3.88 (m, 4), 3.38 (m, 1), 2.15–1.50 (m, 4), 1.32 (s, 3), 1.25 (s, 3); IR (CCl_4) 3100, 2880, 2940, 2870, 1500, 1450, 1380, 1280, 1230, 1160, 1060, 850, 730 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 210 (M + 1, 3.91), 209 (M^+, 26.4), 194 (2.41), 166 (0.55), 151 (24.5), 134 (53.0), 93 (36.7), 81 (base), 80 (62.4), 72 (30.2), 43 (54.4).

5-*N*-Pyrrolylpentane-1,2-diol (34, $R_4 = R_5 = H$). According to the general procedure for the deprotection of pyrrole acetonides, 1.00 g (4.78 mmol) of **29**, and 0.12 g (0.478 mmol) of pyridinium *p*-toluenesulfonate gave crude **34** ($R_4 = R_5 = H$) as a viscous yellow liquid. Flash chromatography on a column of silica gel provided 0.735 g, 91%, of **34** ($R_4 = R_5 = H$) as a pale yellow, viscous liquid: ^1H NMR (60 MHz) δ 6.67 (t, J = 2 Hz, 2), 6.15 (t, J = 2 Hz, 2), 3.94 (t, J = 7 Hz, 2), 2.72 (t, J = 4 Hz, 2), 2.43 (m, 1), 2.12–1.20 (m, 4); IR (neat) 3360, 2920, 2860, 1500, 1450, 1280, 1090, 1060, 730 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 170 (M + 1, 8.20), 169 (M^+, 85.5), 152 (10.2), 149 (12.6), 138 (10.9), 134 (11.8), 120 (54.1), 95 (25.7), 85 (45.1), 81 (99), 80 (base), 68 (64.1), 53 (27.4), 43 (45.8).

5-*N*-Pyrrolylpentane-1,2-diol 1-*p*-Toluenesulfonate (34, $R_4 = p$-Ts, $R_5 = H$). According to the general procedure for the tosylation of pyrrole diols, 0.29 g (1.74 mmol) of **34** ($R_4 = R_5 = H$) and 0.393 g (2.06 mmol) of *p*-toluenesulfonyl chloride were combined in pyridine (7 mL) to provide crude **34** ($R_4 = p$-Ts, $R_5 = H$) as a viscous yellow oil. Flash chromatography on a column of silica gel yielded 0.462 g, 83%, of **34** ($R_4 = p$-Ts, $R_5 = H$) as a yellow viscous liquid: ^1H NMR (250 MHz, C_6D_6) δ 7.75 (d, J = 8 Hz, 2), 6.72 (d, J = 8 Hz, 2), 6.43 (t, J = 2 Hz, 2), 6.30 (t, J = 2 Hz, 2), 4.02 (br s, 1), 3.81 (m, 2), 3.54 (m, 1), 3.31 (t, J = 7 Hz, 2), 1.84 (s, 3), 1.60 (m, 1), 1.40 (m, 1), 1.02 (m, 2); IR (neat) 3100, 3050, 2930, 2885, 1500, 1280, 1090, 1070, 730 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 152 (M + 1, 20.4), 151 (M^+, 64.9), 134 (38.4), 120 (44.1), 106 (12.6), 93 (19.0), 81 (48.9), 80 (base), 68 (32.5), 53 (14.3).

5-*N*-Pyrrolyl-1,2-epoxypentane (12). According to the general procedure for the preparation of *N*-(epoxyalkyl)pyrroles, 0.672 g (2.08 mmol) of **34** ($R_4 = p$-Ts, $R_5 = H$) and 0.280 g (2.50 mmol) of potassium *tert*-butoxide were combined to yield **12** as a yellow liquid. Flash chromatography on a column of silica gel afforded 0.271 g, 86%, of **12** as a pale yellow, free-flowing liquid: ^1H NMR (60 MHz, $CDCl_3$) δ 6.52 (t, J = 2 Hz, 2), 6.25 (t, J = 2 Hz, 2), 4.698 (br s, 2), 3.44 (m, 5), 2.00–1.40 (m, 2), 1.30 (m, 2); IR (neat) 3100, 3050, 2930, 2885, 1500, 1280, 1090, 1070, 730 cm^{-1}; EI/MS (70 eV), m/z (relative intensity) 152 (M + 1, 20.94), 151 (M^+, 64.9), 134 (38.4), 120 (44.1), 106 (12.6), 93 (19.0), 81 (48.9), 80 (base), 68 (32.5), 53 (14.3); exact mass calcd for $C_9H_{13}NO$ 151.0997, found 151.0977.

General Procedure for Cyclization of Pyrrole Epoxides with $BF_3{\cdot}OEt_2$ and Et_3N. Preparation of 8-(Hydroxymethyl)-8-methyl-5,6,7,8-tetrahydroindolizidine (18). To a solution of **11** (0.1 g, 0.6 mmol) in dry THF (15 mL), cooled to −42 °C in a dry ice–CH_3CN bath, was added Et_3N (0.083 mL, 0.6 mmol), followed by freshly distilled $BF_3{\cdot}OEt_2$ (0.074 mL, 0.6 mmol). The reaction was allowed to slowly warm to room temperature overnight and then was quenched with saturated aqueous $NaHCO_3$ (10 mL). The mixture was cast into ether (75 mL) and saturated aqueous $NaHCO_3$ (50 mL). The organic layer was separated, washed with 1 N aqueous HCl (50 mL), water (50 mL), and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to provide a yellow viscous liquid. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 25 g, 30 mm o.d., Et_2O–petroleum ether (30:70), 15-mL fractions) with the flash technique. Fractions 15–20 provided 0.073 g, 73%, of **18** as a pale yellow, viscous liquid, which solidified upon cooling: ^1H NMR (250 MHz, C_6D_6) δ 6.35 (m, 1), 6.31 (t, J = 2 Hz, 1), 6.05 (m, 1), 3.55 (d, J = 11 Hz, 1), 3.42 (d, J = 11 Hz, 1), 3.31 (t, J = 6 Hz, 2), 2.62 (br s, 1), 1.75 (m, 1), 1.48 (m, 2), 1.27 (m, 1), 1.20 (s, 3); IR (neat) 3280, 2940, 1450, 1350, 1050, 720 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 165 (M^+, 12.7), 147 (6.56), 134 (base), 118 (9.97), 80 (8.30), 44 (54.4), 40 (88.2); exact mass calcd for $C_{10}H_{13}NO$ 165.1153, found 165.1183.

General Procedure for Cyclization of Pyrrole Epoxides with $EtAlCl_2$. Preparation of 18. To a solution of **11** (0.1 g, 0.606 mmol) in dry CH_2Cl_2 (5 mL), chilled in a dry ice–CCl_4 bath, was added $EtAlCl_2$ (0.82 mL, 1.21 mmol, 1.47 M in hexane) over 2 min. The reaction mixture was stirred for 25 min at −24 °C and then quenced with saturated aqueous NH_4Cl (5 mL). The mixture was cast into Et_2O (50 mL) and 1 N aqueous HCl (50 mL). The organic layer was separated, washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a pale yellow, viscous liquid. The crude product was purified by chromatography on a column of silica gel with the flash technique to provide 0.081 g, 81%, of **18**.

General Procedure for Cyclization of Pyrrole Epoxides with Et_2AlCl. Preparation of 18. To a solution of **11** (0.104 g, 0.63 mmol) in dry CH_2Cl_2, cooled to −40 °C in a dry ice–CH_3CN bath, was added Et_2AlCl (0.86 mL, 1.26 mmol, 1.47 M in hexane). The mixture was stirred at −40 °C for 10 min and then quenched by cautiously adding 1 N aqueous HCl (10 mL). The mixture was cast into Et_2O (50 mL) and 1 N aqueous HCl (50 mL). The organic layer was separated, washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a yellow viscous liquid. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 25 g, 30 mm o.d., EtOAc–petroleum ether (40:60), 15-mL fractions) with the flash technique. Fractions 5–10 provided 0.084 g, 81%, of **18**.

General Procedure for Cyclization of Pyrrole Epoxides with $Ti(O\text{-}i\text{-}Pr)_3Cl$. Preparation of 18. To a solution of **11** (0.142 g, 0.861 mmol) in dry CH_2Cl_2 (20 mL), chilled in an ice–water bath, was added $Ti(O\text{-}i\text{-}Pr)_3Cl$[30] (3.44 mL, 2.58 mmol, 0.75 M in CH_2Cl_2). The mixture was stirred for 15 min and then

(30) See ref 8a and: Feld, R.; Cowe, D. L. In *The Organic Chemistry of Titanium*, Butterworths: Washington, DC, 1965.

quenched with saturated aqueous NH_4Cl (15 mL). The solution was cast into Et_2O (75 mL) and saturated aqueous NH_4Cl (75 mL). The organic layer was separated, washed with 1 N aqueous HCl (75 mL), water (75 mL), and brine (75 mL), dried (Na_2SO_4), and concentrated in vacuo to give an orange viscous liquid. The crude product was purified by chromatography on a column of silica gel with the flash technique to give 0.115 g, 80%, of **18**.

General Procedure for Cyclization of Pyrrole Epoxides with ZnI_2·OEt_2. Preparation of 18. To a solution of **11** (0.1 g, 0.6 mmol) in dry benzene (15 mL) at room temperature was added freshly prepared ZnI_2·OEt_2[31] (0.472 g, 1.2 mmol) in one portion. Within 5 min, the colorless suspension became orange in color, and the reaction was complete. The mixture was quenched with saturated aqueous NH_4Cl (10 mL) and was cast into Et_2O (50 mL) and saturated NH_4Cl (50 mL). The organic layer was separated, washed with 10% aqueous $Na_2S_2O_3$ (50 mL), water (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to provide a pale orange viscous liquid. The crude product was purified by chromatography on a column of silica gel with the flash technique to give 0.072 g, 72%, of **18**.

Cyclization of 8 with Et_2AlCl. Preparation of 7-Hydroxy-5,6,7,8-tetrahydroindolizidine (14). To a solution of **8** (0.1 g, 0.73 mmol) in dry CH_2Cl_2 (5 mL), chilled to −23 °C in a dry ice–CCl_4 bath, was added Et_2AlCl (1.0 mL, 1.47 mmol, 1.47 M in hexane). The mixture was stirred at −23 °C for 30 min and then quenched by cautiously adding 1 N aqueous HCl (5 mL). The reaction mixture was worked up according to the general procedure for the cyclization of pyrrole epoxides with Et_2AlCl. The crude product was purified by chromatography on a column of silica gel (60–230 mesh, 30 g, 30 mm o.d., EtOAc–petroleum ether (1:1), 20-mL fractions) with the flash technique. Fractions 6–12 provided 0.032 g, 32%, of **14** as a pale yellow, viscous liquid: ^1H NMR (250 MHz) δ 6.54 (br s, 1), 6.14 (m, 1), 5.84 (br s, 1), 4.15 (m, 1), 3.96 (m, 2), 3.13 (dd, J = 16.6, 4.2 Hz, 1), 2.77 (dd, J = 16.6, 8.3 Hz, 1), 2.03 (m, 2); IR (CCl_4) 3380, 3100, 2940, 1490, 1430, 1320, 1200, 1070, 980, 700 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 137 (M^+, 2.31), 118 (0.31), 108 (1.51), 93 (2.79), 44 (16.8), 40 (base); exact mass calcd for $C_8H_{11}NO$ 137.0840, found 137.0842.

Cyclization of 9 with Et_2AlCl. Preparation of 7-Hydroxy-7-methyl-5,6,7,8-tetrahydroindolizidine (16). To a solution of **9** (0.085 g, 0.566 mmol) in dry CH_2Cl_2 (5 mL), cooled to −78 °C in a dry ice–*i*-PrOH bath, was added Et_2AlCl (0.76 mL, 1.13 mmol, 1.47 M in hexane). The mixture was stirred at −78 °C for 2 h and then quenched by cautiously adding 1 N aqueous HCl (5 mL). The reaction mixture was worked up according to the general procedure for the cyclization of pyrrole epoxides with Et_2AlCl. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 30 g, 30 mm o.d., EtOAc–petroleum ether (30:70), 15-mL fractions) with the flash technique. Fractions 8–13 provided 0.038 g, 44%, of **16** as a pale yellow, viscous liquid: ^1H NMR (250 MHz, C_6D_6) δ 6.42 (m, 1), 6.37 (t, J = 2 Hz, 1), 6.01 (br s, 1), 3.65 (m, 1), 3.32 (m, 1), 2.50 (s, 2), 1.34 (m, 3), 0.97 (s, 3); IR (neat) 3420, 2900, 1450, 1380, 1330, 1120, 700 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 151 (M^+, 61.9), 136 (6.72), 120 (8.70), 108 (23.2), 93 (base), 80 (52.5), 66 (18.0), 43 (31.6); exact mass calcd for $C_9H_{13}NO$ 151.0997, found 151.0977.

Cyclization of 10 with Et_2AlCl. Preparation of 7-Hydroxy-8,8-dimethyl-5,6,7,8-tetrahydroindolizidine (17). To a solution of **10** (0.023 g, 0.139 mmol) in dry CH_2Cl_2 (1.0 mL), cooled to −78 °C in a dry ice–*i*-PrOH bath, was added Et_2AlCl (0.19 mL, 0.279 mmol, 1.47 M in hexane). The mixture was stirred at −78 °C for 20 min and then quenched by the addition of saturated aqueous NH_4Cl (3 mL). The reaction mixture was worked up according to the general procedure for the cyclization of pyrrole epoxides with Et_2AlCl. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 15 g, 20 mm o.d., EtOAc–petroleum ether (30:70), 15-mL fractions) with the flash technique. Fractions 7–12 provided 0.014 g, 61%, of **17** as a pale yellow, viscous liquid, which solidified on cooling: mp 79–81 °C; ^1H NMR (250 MHz, C_6D_6) δ 6.34 (m, 1), 6.30 (m, 1), 6.07 (m, 1), 3.55 (m, 1), 3.30 (m, 2), 1.56 (m, 2), 1.45 (br s, 1), 1.20 (s, 3), 1.18 (s, 3); IR (CCl_4) 3460, 2920, 1450, 1370, 1190, 1180, 1080, 1050, 850, 700 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 165 (M^+, 48.9), 150 (base), 132 (9.12), 121 (47.0), 106 (38.1), 80 (13.7); exact mass calcd for $C_{10}H_{15}NO$ 165.1153, found 165.1168.

Cyclization of 12 with Ti(O-*i*-Pr)$_3$Cl. Preparation of 8-(Hydroxymethyl)-5,6,7,8-tetrahydroindolizidine (19). To a solution of **12** (0.050 g, 0.33 mmol) in dry CH_2Cl_2 (5 mL), chilled in an ice–water bath, was added Ti(O-*i*-Pr)$_3$Cl (0.50 mL, 1.0 mmol, 2.0 M in CH_2Cl_2). The mixture was stirred at 0 °C for 1 h, warmed to room temperature, and allowed to stir for additional 45 min. The reaction mixture was worked up according to the general procedure for the cyclization of pyrrole epoxides with Ti(O-*i*-Pr)$_3$Cl. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 20 g, 200 mm o.d., EtOAc–petroleum ether (30:70), 10-mL fractions) with the flash technique. Fractions 10–14 provided 0.032 g, 64%, of **19** as a pale yellow, viscous liquid: ^1H NMR (250 MHz, CD_3CN) δ 6.51 (m, 1), 6.00 (t, J = 2.5 Hz, 1), 5.88 (m, 1), 4.0–3.80 (m, 3), 3.74 (dd, J = 10, 5.4 Hz, 1), 3.50 (dd, J = 10, 8.3 Hz, 1), 2.88 (m, 1), 2.00 (m, 2), 1.81 (m, 1), 1.58 (m, 1); IR (CCl_4): 3460, 2930, 2860, 1450, 1330, 1080, 1030, 700 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 151 (M^+, 22.4), 120 (base), 118 (17.2), 105 (3.17), 91 (4.43), 80 (3.88), 65 (3.54), 41 (3.40); exact mass calcd for $C_9H_{13}NO$ 151.0997, found 151.1015.

Cyclization of 12 with Et_2AlCl. Preparation of 19 and 6-Hydroxy-6,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine (20). A solution of **12** (0.055 g, 0.36 mmol) in dry CH_2Cl_2 (1 mL) was reacted with Et_2AlCl (0.49 mL, 0.72 mmol, 1.47 M in hexane) according to the general procedure for cyclization of pyrrole epoxides with Et_2AlCl. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 20 g, 20 mm o.d., EtOAc–petroleum ether (40:60), 15-mL fractions) with the flash technique. Fractions 6–8 provided 0.020 g, 37%, of **19**, and fractions 10–13 yielded 0.026 g, 48%, of **20** as a water-white liquid: ^1H NMR (250 MHz, C_6D_6) δ 6.31 (br s, 1), 6.18 (t, J = 1.5 Hz, 1), 6.10 (br s, 1), 3.32 (br s, 1), 3.20 (t, J = 6.0 Hz, 2), 3.16 (m, 1), 2.69 (br d, J = 15.4 Hz, 1), 2.63 (dd, J = 15.4, 9.4 Hz, 1), 1.41 (m, 2), 1.09 (m, 2); IR (CCl_4) 3460, 2920, 1430, 1350, 1280, 1020, 700 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 151 (M^+, base), 150 (49.3), 134 (6.55), 122 (18.7), 106 (20.6), 94 (75.3), 80 (36.5), 53 (9.77), 41 (10.4); exact mass calcd for $C_9H_{13}NO$ 151.0997, found 151.1024.

Cyclization of 13 with Ti(O-*i*-Pr)$_3$Cl. Preparation of 5-(Hydroxymethyl)-5,7,8,9-tetrahydro-5*H*-pyrrolo[1,2-*a*]azepine (21). To a solution of **13** (0.104 g, 0.630 mmol) in dry CH_2Cl_2 (15 mL), chilled in an ice–water bath, was added Ti(O-*p*-Pr)$_3$Cl (0.945 mL, 1.89 mmol, 2.0 M in CH_2Cl_2). The mixture was stirred at 0 °C for 1 h, then warmed to room temperature, and stirred for an additional 3 h. The reaction mixture was worked up according to the general procedure for the cyclization of pyrrole epoxides with Ti(O-*i*-Pr)$_3$Cl. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 30 g, 30 mm o.d., EtOAc–petroleum ether (30:70), 25-mL fractions) with the flash technique. Fractions 8–13 yielded 0.088 g, 85%, of **21** as a pale yellow, viscous liquid: ^1H NMR (250 MHz, C_6D_6) δ 6.35 (m, 1), 6.18 (t, J = 2 Hz, 1), 5.99 (br s, 1), 3.85 (dd, J = 10.8, 6.7 Hz, 1), 3.58 (dd, J = 10.8, 7.5 Hz, 1), 3.31 (br q, J = 7.7 Hz, 2), 2.61 (m, 1), 1.74 (m, 1), 1.60 (m, 1), 1.32 (m, 2), 1.15 (m, 2); IR (CCl_4) 3580, 2920, 2860, 1480, 1290, 1110, 1080, 1030, 700 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 165 (M^+, 19.4), 134 (base), 118 (5.85), 106 (7.02), 93 (3.00), 80 (17.8); exact mass calcd for $C_{10}H_{15}NO$ 165.1153, found 165.1161.

Cyclization of 13 with ZnI_2·OEt_2. Preparation of 21 and 1-Iodo-2-hydroxy-6-*N*-pyrrolylhexane. A solution of **13** (0.105 g, 0.636 mmol) in anhydrous ether (10 mL) was reacted with freshly prepared ZnI_2·OEt_2 (0.477 g, 1.212 mmol) for 3 h at room temperature according to the general procedure for cyclization of pyrrole epoxides with ZnI_2·OEt_2. The crude product was purified by chromatography on a column of silica gel (230–400 mesh, 30 g, 30 mm o.d., EtOAc–petroleum ether (30:70), 20-mL fractions) with the flash technique. Fractions 9–13 provided 0.273 g, 26%, of **21** as a pale yellow, viscous liquid. Fractions 5 and 6 gave 0.091 g, 49%, of 1-iodo-2-hydroxy-6-*N*-pyrrolylhexane as a pale yellow, viscous liquid: ^1H NMR (250 MHz, C_6D_6) δ 6.46 (t, J = 1 Hz, 2), 6.34 (t, J = 1 Hz, 2), 3.27 (t, J = 6 Hz, 2), 2.92 (m, 1), 2.75 (t, J = 4 Hz, 1), 2.64 (t, J = 6 Hz, 1), 1.45 (br s, 1), 1.24 (m, 2), 1.00

(31) See ref 8a and: Marshall, J. A.; Wuts, P. G. M. *J. Org. Chem.* **1977**, *42*, 1794. Reetz, M. T.; Huttenhain, S.; Hubner, F. *Synth. Commun.* **1981**, *11*, 217.

(m, 4); IR (neat) 3440, 2920, 1290, 1100, 730 cm^{-1}; EI-MS (70 eV), m/z (relative intensity) 166 (M - 1, 8.07), 151 (5.80), 134 (4.54), 81 (8.11), 61 (13.8), 43 (base).

Acknowledgment. We gratefully acknowledge support of this research by the Camille and Henry Dreyfus Foundation, The Research Corporation, and the donors of the Petroleum Research Fund, administered by the American Chemical Society. We thank Kathleen Kayganich of the Michigan State University Chemistry Department for high-resolution mass spectra.

Rothemund and Adler–Longo Reactions Revisited: Synthesis of Tetraphenylporphyrins under Equilibrium Conditions

Jonathan S. Lindsey,* Irwin C. Schreiman, Henry C. Hsu, Patrick C. Kearney, and Anne M. Marguerettaz

Department of Chemistry, Carnegie-Mellon University, Pittsburgh, Pennsylvania 15213

Received July 30, 1986

We present a new synthetic strategy for preparing tetraphenylporphyrins that should greatly expand synthetic entries into porphyrin containing model systems. Pyrrole and the desired benzaldehyde react reversibly at room temperature with trace acid catalysis to form the cyclic tetraphenylporphyrinogen at thermodynamic equilibrium. An oxidant is then added to irreversibly convert the porphyrinogen to the porphyrin. The greater stability of the cyclic porphyrinogen over the open-chain polypyrrylmethanes occurs when the reaction is performed at moderate dilution (10^{-2} M). The reaction at high dilution or high concentration affords a negligible yield of the cyclic porphyrinogen. Porphyrinogen exchange reactions provide proof of equilibrium. This methodology is complementary to the Adler–Longo procedure, allowing small quantities of porphyrins to be prepared from sensitive aldehydes in 30–40% yield without difficult purification problems. This methodology is also extended to the preparation of *meso*-tetraalkylporphyrins and one hybrid porphyrin containing both aryl and alkyl substituents. The mild reaction conditions and convenience of this method permit consideration of new design strategies in preparing complex porphyrins.

The porphyrins lie at the focal point formed from divergent fields of research, including solar energy conversion, catalysis, spectroscopy, and the development of organic metals. A constant theme among these diverse areas is the creation of structured assemblies containing porphyrins located in well-defined chemical environments. The precise sculpturing of the porphyrin environment requires the synthesis of porphyrin derivatives carrying functional groups attached at the periphery of the macrocycle. The *meso*-tetraphenylporphyrins offer attractive features in this context and have been used in a wide variety of model studies.[1,2]

Tetraphenylporphyrin was first synthesized 50 years ago by Rothemund, who caused benzaldehyde and pyrrole in pyridine to react in a sealed bomb at 150 °C for 24 h.[3] The yields were low and the conditions so severe that few substituted benzaldehydes could be converted to the corresponding porphyrin. The Rothemund conditions were obviously based on the premise that the porphyrin is aromatic, aromatic compounds are stable, and therefore merely cracking the initially formed adducts of benzaldehyde and pyrrole at high temperatures should give the porphyrin. Adler and Longo modified the Rothemund reaction by allowing benzaldehyde and pyrrole to react for 30 min in refluxing propionic acid (141 °C) open to the air.[4] These comparatively milder reaction conditions have allowed a wider selection of substituted benzaldehydes to be converted to the corresponding porphyrins in yields of up to 20%.[5-7] The reaction is also amenable to large-scale syntheses and multigram quantities of many porphyrins have been prepared.

Nonetheless, the Adler–Longo methodology is beset with certain vexing problems. First, the harsh reaction conditions result in complete failure with benzaldehydes bearing sensitive functional groups. Second, the high level of tar produced presents purification problems in many instances, especially with those porphyrins that do not crystallize or precipitate at the end of the reaction. Third, the batch-to-batch reproducibility of the reaction is often rather poor.

The current synthetic needs of porphyrin chemistry are thus only partially satisfied by this methodology. Of at least comparable necessity is the ability to prepare small quantities of porphyrins from sensitive aldehydes in high yield without encountering difficult purification problems. This paper describes in detail a procedure that achieves the latter goals and is therefore complementary in nature to the Adler–Longo procedure.[8]

The development of our procedure began from a vantage point fundamentally different from that of Rothemund, Adler, and Longo. Our strategy, based on studies of

(1) Lindsey, J. S.; Mauzerall, D. C.; Linschitz, H. *J. Am. Chem. Soc.* **1983**, *105*, 6528. Wasielewski, M. R.; Niemczyk, M. P.; Svec, W. A.; Pewitt, E. B. *J. Am. Chem. Soc.* **1985**, *107*, 5562. Moore, T. J.; Gust, G.; Mathis, P.; Mialocq, J. C.; Chachaty, C.; Bensasson, R. V.; Land, E. J.; Doizi, D.; Liddell, P. A.; Lehman, W. R.; Nemeth, G. A.; Moore, A. L. *Nature (London)* **1984**, *307*, 630.

(2) Bogatskii, A. V.; Zhilina, Z. I. *Russ. Chem. Rev.* **1982**, *51*, 592.

(3) Rothemund, P. *J. Am. Chem. Soc.* **1936**, *58*, 625. Rothemund, P. *J. Am. Chem. Soc.* **1939**, *61*, 2912.

(4) Adler, A. D.; Longo, F. R.; Finarelli, J. D.; Goldmacher, J.; Assour, J.; Korsakoff, L. *J. Org. Chem.* **1967**, *32*, 476. Kim, J. B.; Adler, A. D.; Longo, F. R. In *The Porphyrins*; Dolphin, D., Ed.; Academic Press: New York, 1978; Vol. 1, pp 85–100.

(5) For reports of yields greater than 20% in the Adler–Longo procedure, see ref 6 and 7. The frequent absence of yield data in the tetraphenylporphyrin literature suggests that for a variety of benzaldehydes the actual yields are in fact much less than 20%.

(6) Dolphin, D. *J. Heterocycl. Chem.* **1970**, *7*, 275.

(7) Adler, A.; Longo, F. R.; Shergalis, W. *J. Am. Chem. Soc.* **1964**, *86*, 3145.

(8) Presented in part at the 20th Meeting of the American Chemical Society, Great Lakes Region, Milwaukee, June, 1986, and the 192nd National Meeting of the American Chemical Society, Anaheim, CA, Sept. 1986. Lindsey, J. S.; Schreiman, I. C.; Hsu, H. C. *Tetrahedron Lett.* **1986**, *27*, 4969.

0022-3263/87/1952-0827$01.50/0