The First Asymmetric Total Syntheses of (+)-Lycorine and (+)-1-Deoxylycorine

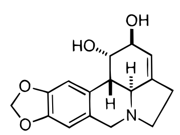
Arthur G. Schultz,* Mark A. Holoboski, and Mark S. Smyth

Contribution from the Department of Chemistry, Rensselaer Polytechnic Institute, Troy, New York 12180-3590

Received February 26, 1996[⊗]

Abstract: The first asymmetric total syntheses of (+)-1-deoxylycorine (**2a**) and (+)-lycorine (**2b**), the unnatural enantiomer of lycorine (**1**), are described. Construction of lactam **12**, a key intermediate in the synthesis of both **2a** and **2b**, began by Birch reduction-alkylation of the chiral benzamide **3** with 2-bromoethyl acetate followed by ester saponification to give the 6-(2-hydroxyethyl)-1-methoxy-1,4-cyclohexadiene **6a** in 96% yield as a single diastereomer. This material was converted to the radical cyclization substrates **11a** and **11b**. Both **11a** and **11b** gave **12** and the reduced enamide **11c** on treatment with AIBN and Bu_3SnH in refluxing benzene solution. Lactam **12** also was obtained by photocyclization of enamide **11c**. The allylic alcohol unit characteristic of the C ring of the lycorine alkaloids was fashioned by a radical induced decarboxylation-epoxide fragmentation of the *N*-hydroxy-2-thiazoline ester **21b**. The resulting (+)-2-*epi*-deoxylycorine (**22**) was subjected to Mitsunobu inversion followed by $LiAlH_4$ reduction to give (+)-1-deoxylycorine (**2a**). The synthesis of (+)-lycorine (**2b**) involved the conversion of **12** to allylic alcohol **32** followed by a Torssell rearrangement of **32** to give the rearranged allylic acetate **35**. Epoxidation of **35** with dimethyldioxirane gave **36a**, which set the stage for a decarboxylation-epoxide fragmentation of carboxylic acid **36b** to give **37** by photolysis of **36b** in the presence of acridine and *tert*-BuSH. Reduction of **37** with $LiAlH_4$ gave (+)-lycorine (**2b**).

Lycorine (**1**) is the most abundant alkaloid in plants of the *Amaryllidaceae*. It is said that as much as 1% of the dry weight of daffodil bulbs may consist of lycorine.[1] From the time of its initial isolation in 1877 lycorine was recognized as a potent emetic;[2] more recent studies have shown that lycorine inhibits protein and DNA synthesis in murine cells and *in vivo* growth of a murine transplantable ascite tumor.[3] Lycorine is a powerful inhibitor of growth and cell division in higher plants, algae, and yeast[4] and has antiviral activity.[5]

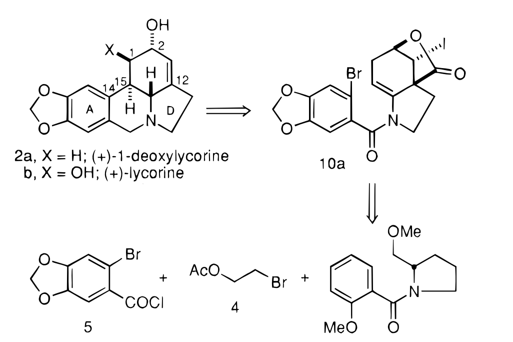


1, (-)-lycorine

Much of the determination of structure for lycorine was accomplished by Kondo and co-workers[2,6] by utilization of classical chemical studies; proof of structure was provided by X-ray crystallographic analysis of dihydrolycorine hydrobromide.[7] Although several syntheses of racemic lycorine alkaloids have been developed,[8] an asymmetric synthesis had not been reported until we communicated the first asymmetric synthesis of (+)-1-deoxylycorine (**2a**).[9] Herein we report the details of the synthesis of **2a** along with the first asymmetric synthesis of (+)-lycorine (**2b**), the unnatural enantiomer of **1**.

Results and Discussion

The lycorine ring system **2** was assembled by utilization of three structural components as shown below. Stereoselective development of the C ring centered on the reductive alkylation of chiral benzamide **3**[10] with the two-carbon alkylation reagent **4** to give a 1,4-cyclohexadiene. It was expected that the C(1) hydroxy group of **2** would be introduced by bis-allylic oxidation of the intermediate 1,4-cyclohexadiene;[11] however, this oxidation was ineffective, and an alternative process had to be developed. Introduction of the hydroxy group at C(2) was accomplished by a halolactonization (see **10a**).



The methoxy group on **3** and the acetoxy group on **4** provided the means to introduce the nitrogen atom in **2**, while the bromine atom on the aroyl component **5** enabled the C(14)−C(15) bond to be fashioned by a completely stereoselective aryl radical

[⊗] Abstract published in *Advance ACS Abstracts,* June 15, 1996.

(1) Dalton, D. R. *The Alkaloids: The Fundamental Chemistry -- A Biogenetic Approach*; Marcel Dekker: New York, 1979.

(2) Cook, J. W.; Loudon, J. D. In *The Alkaloids*; Manske, R. H. F., Holmes, H. L., Eds; Academic Press: New York, 1952; Vol. 2, p 331.

(3) (a) Mineshita, T.; Yayaguchi, K.; Takeda, K.; Kotera, K. *Ann. Rep. Shinogi Res. Lab.* **1956**, *6*, 119. (b) Chattopadhyay, U.; Chaudhuri, L.; Das, S.; Kumar, Y.; Ghosal, S. *Pharmazie* **1984**, *39*, 855.

(4) Leo De, P.; Dalessandro, G.; De Santis, A.; Arigoni, O. *Plant Cell Physiol*. **1973**, *14*, 487.

(5) For a review of the chemistry and biological effects of lycorine and related *Amaryllidaceae* alkaloids, see: Ghosal, S.; Saini, K. S.; Razdan, S. *Phytochem*. **1985**, *24*, 2141.

(6) Kondo, H.; Uyeo, S. *Chem. Ber*. **1935**, *68*, 1756.

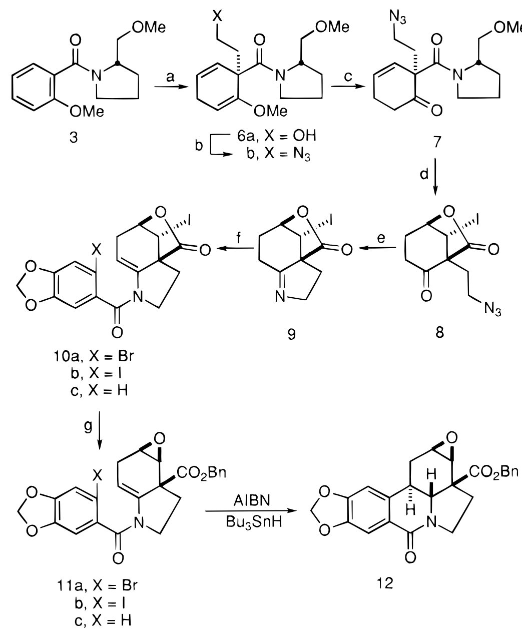
(7) Shiro, M.; Sato, T.; Koyama, H. *Chem. Ind*. **1966**, 1229.

(8) For recent reviews of the *Amaryllidaceae* alkaloids, see: (a) Martin, S. M. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1987; Vol. 30, p 251. (b) Lewis, J. R. *Nat. Prod. Rep*. **1995**, *12*, 339.

(9) Schultz, A. G.; Holoboski, M. A.; Smyth, M. S. *J. Am. Chem. Soc.* **1993**, *115*, 7904.

S0002-7863(96)00644-0 CCC: $12.00

Scheme 1[a]



[a] Reaction conditions: (a) K, NH_3, *tert*-BuOH (1 equiv) −78 °C; $BrCH_2CH_2OAc$ (2 equiv) −78 to 25 °C; KOH, MeOH; (b) DEAD, PPh_3, $(PhO)_2P(O)N_3$, THF; (c) HCl, MeOH; (d) I_2, THF, H_2O; (e) PPh_3, THF, reflux; (f) ArCOCl (1 equiv) Et_3N, CH_2Cl_2; (g) BnOH, THF, *n*-BuLi, −78 to 25 °C.

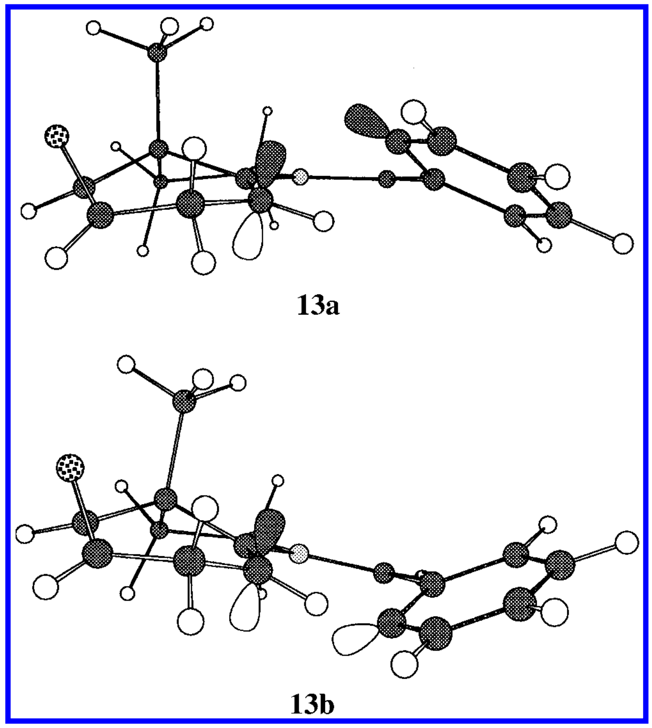


Figure 1. Qualitative transition state structures **13a** and **13b** for the radical cyclization of **12** showing a more favorable orbital overlap in **13a** and a steric interaction resulting from passage of C(14) near the C(15)−H bond during α-facial attack in **13b**.

addition reaction (see **10a**). With the ring system completely assembled, a decarboxylative elimination reaction unveiled the ring C allylic alcohol unit characteristic of the lycorine alkaloids.

Construction of the Lycorine Ring System. The preparation of **12**, a key intermediate in the asymmetric syntheses of both (+)-1-deoxylycorine (**2a**) and (+)-lycorine (**2b**), is shown in Scheme 1. Birch reduction-alkylation of **3**[12] with 2-bromoethyl acetate followed by ester saponification gave the 6-(2-hydroxyethyl)-1-methoxy-1,4-cyclohexadiene **6a** in 96% yield as a single diastereomer. Diastereomeric purity of the product of reductive alkylation of **3** was determined by direct ^{1}H NMR comparison to a 1:1 diastereomeric mixture prepared by reductive alkylation of *o*-anisic acid with 2-bromoethyl acetate and coupling of the resulting cyclohexadienecarboxylic acid to L-prolinol (methyl ether).[13] In comparison, alkylations of the enolate derived from **3** with methyl iodide and ethyl iodide have provided diastereoselectivities of 260:1 as determined by quantitative gas chromatographic analysis.[12a]

Alcohol **6a** was converted to azide **6b**, which was subjected to enol ether hydrolysis to give **7**. Iodolactonization of **7** provided **8**, and treatment of **8** with triphenylphosphine gave the enantiomerically pure imine **9** in ∼50% overall yield from **6a**. The racemate of **9** was prepared (see supporting information), and a chiral HPLC analysis was developed to give near base line resolution of the enantiomers. Examination of **9** prepared from **3** demonstrated that **9** had been prepared with ≥99% ee.

Acylation of imine **9** with 2-bromo- and 2-iodopiperonyloyl chloride gave enamides **10a** and **10b**. Treatment of **10a** and **10b** with the lithium salt of benzyl alcohol afforded radical cyclization substrates **11a** and **11b**. Both **11a** and **11b** underwent cyclization on treatment with AIBN and Bu_3SnH in refluxing benzene solution to give the highly crystalline lactam **12** (53% and 51% yields); a single-crystal X-ray structure determination provided the molecular structure of **12**.[9]

The only other material isolated from the radical cyclizations of **11a** and **11b** was the reduced enamide **11c** (45%). Enamide **11c** might be formed by direct reduction of the radical derived from **11a** and **11b** with Bu_3SnH or by way of an intramolecular α-amidoyl to aryl 1,5-hydrogen atom transfer followed by reduction.[14]

Precedence for formation of a trans BC ring junction in a radical cyclization of an achiral substrate related to **11** is available in the work of Rigby and co-workers.[15] Thus, the most remarkable feature of the conversions of **11a** and **11b** to **12** is the outstanding facial selectivity exhibited by the intermediate aryl radical. Qualitative transition state structures **13a** and **13b** for aryl radical addition to the β- and α-face of the C(15)−C(16) double bond are shown in Figure 1. These models were obtained by minimization of a simplified precursor of the intermediate aryl radical, wherein the benzyl ester was replaced by a methyl group. From inspection of these models, it is clear that the observed β-facial addition is a result of more favorable orbital overlap as shown in **13a** as well as an obvious steric interaction that would result from passage of C(14) near the C(15)−H bond during α-facial attack as shown in **13b**.

Reduction of the intermediate tertiary radical **14** at C(16) by Bu_3SnH also occurs from the β-face despite the presence of the relatively bulky (benzyloxy) carbonyl group at C(12). This

(10) For prior consideration of the development of the C ring of lycorine by way of a Birch reduction, see: (a) Hendrickson, J. B.; Alder, R. W.; Dalton, D. R.; Hey, D. G. *J. Org. Chem.* **1969**, *34*, 2667. (b) Schultz, A. G. *Acc. Chem. Res.* **1990**, *23*, 207.

(11) Schultz, A. G.; Taveras, A. G.; Harrington, R. E. *Tetrahedron Lett.* **1988**, *29*, 3907.

(12) (a) Schultz, A. G.; Macielag, M.; Sundararaman, P.; Taveras, A. G.; Welch, M. *J. Am. Chem. Soc.* **1988**, *110*, 7828. (b) Benzamide **3** is prepared by procedures described in ref 12a or may be purchased from Aldrich Chemical Co. (34,836−8).

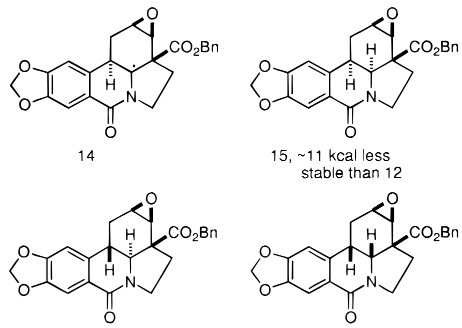
(13) For the genesis of this procedure, see ref 12a.

(14) (a) Cohen, T.; McMullen, C. H.; Smith, K. *J. Am. Chem. Soc.* **1968**, *90*, 6866. (b) Snieckus, V.; Cuevas, J.-C.; Sloan, C. P.; Liu, H.; Curran, D. P. *J. Am. Chem. Soc.* **1990**, *112*, 896.

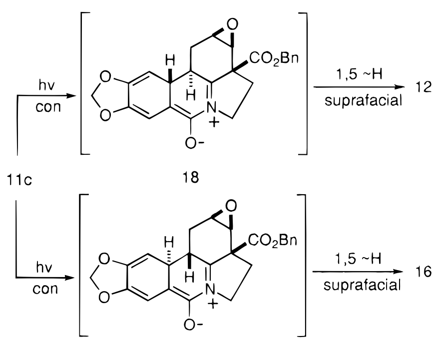
(15) Rigby, J. H.; Qabar, M. *J. Am. Chem. Soc.* **1991**, *113*, 8975.

(16) Molecular modeling studies were carried out with MacroModel (MM2, Version 3.0).

stereoselectivity reflects the greater stability of the product **12**, which has a trans BC ring fusion and a cis CD ring fusion compared to the epimer **15** which has cis BC and trans CD ring fusions; molecular modeling[16] demonstrated that **15** is ~11 kcal/mol less stable than **12**. Radical transfer reactions are generally considered to occur by way of early transition states. Thus, it is believed that radical **14** has geometry at C(16) analogous to **12** and that inversion to a radical resembling **15** is virtually impossible because of ring strain. On the basis of this analysis, it is noteworthy that aryl radical addition to the α-face of the enamide double bond followed by reduction of the tertiary radical corresponding to **14** would have generated **17** with cis BC and CD ring fusions (overall trans radical addition) rather than the less stable epimer **16** required for a lycorine synthesis.[17]

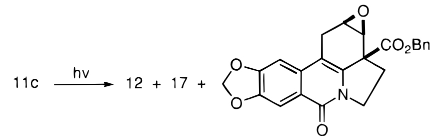


We have examined the photochemistry of enamide **11c**.[18] Related enamides undergo photocyclization to six-membered nitrogen heterocycles[19] by conrotatory cyclization of the enamide to an intermediate zwitterion which undergoes a suprafacial 1,5-hydrogen atom migration.[20] As shown for enamide **11c**, a conrotatory photocyclization would generate zwitterion **18**, from which suprafacial 1,5-hydrogen migration would give **12**. Alternative facial selectivity for the conrotatory photocyclization was expected to provide the diastereomeric trans-dihydro **16** via zwitterion **19**.



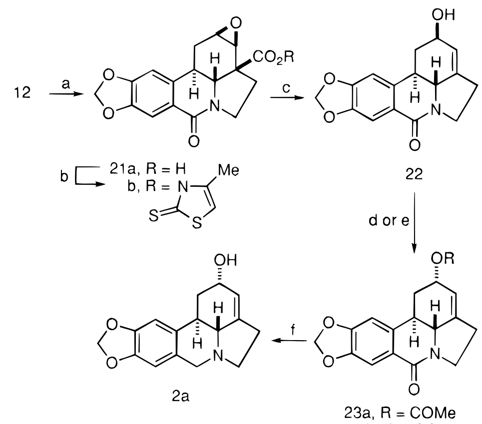
Irradiation of **11c** in deoxygenated benzene solution (0.02 *M*) through Pyrex glass gave a mixture of **12, 20**, and **17** (1.1:2.7:1.0) in 80% yield (Scheme 2). Characteristic doublets in

Scheme 2



20

Scheme 3[a]



[a] Reaction conditions: (a) 10% Pd/C, H_2, EtOH (1 atm); (b) DCC, 4-pyrrolidinopyridine, $HONC_4H_4S_2$, CH_2Cl_2; (c) AIBN, Bu_3SnH, PhH, reflux; (d) DEAD, PPh_3, AcOH, THF; (e) DEAD, PPh_3, $PhCO_2H$, THF; (f) $LiAlH_4$, THF, reflux.

the ^{1}H NMR spectra of crude photoreaction mixtures indicated that regioisomeric photoproducts also had formed. In an attempt to eliminate the formation of the dehydrogenated photoproduct **20**, irradiation of **11c** was carried out in the presence of 5.5 equiv of thiophenol. Inhibition of the oxidative pathway leading to **20** occurred and a 2:1 mixture of **12** and **17** was obtained in 60% yield. Control experiments demonstrated that **20** did not convert to **12** or **17** on irradiation in the presence of thiophenol.

Thus, the byproduct from radical cyclizations of **11a** and **11b** also can be converted to **12**, although the facial selectivity for the photocyclization of enamide **11c** is poor. The unexpected formation of cis-dihydro **17** rather than **16** may be a result of the relative instability calculated for **16** compared to **17** (~6 kcal/mol). Perhaps another mechanism for hydrogen atom transfer in zwitterion **19** competes with the expected suprafacial 1,5-hydrogen migration to give the more stable product.[21] It is noteworthy that thiophenol was found to be an effective additive to avert the formation of **20**.

The Synthesis of (+)-1-Deoxylycorine (2a). The radical cyclization **11** → **12** effectively transfers the stereogenicity developed at *pro*-C(12) during reductive alkylation of the chiral benzamide **3** to C(15) of **12**. With this transfer accomplished, the synthesis of (+)-1-deoxylycorine (**2a**) was completed as shown in Scheme 3.

Successful debenzylation of the benzyl ester in **12** depended on the source of palladium catalyst. Utilization of Johnson-Matthey 10% Pd/C (steam reduced) gave carboxylic acid **21a** in 84% yield. Attempts to decarboxylate **21a** directly by photolysis in the presence of acridine and *tert*-BuSH in benzene solution[22] resulted in decomposition. It is unclear why this method for decarboxylation is ineffective, especially in light of

(17) For a more complete discussion of the facial, regio- and stereoselectivity of radical cyclizations of chiral enamides, see: Schultz, A. G.; Guzzo, P. R.; Nowak, D. M. *J. Org. Chem.* **1995**, *60*, 8040.

(18) Enamide **11c** also was prepared via acylation of **9** with piperonyloyl chloride to give **10c**.

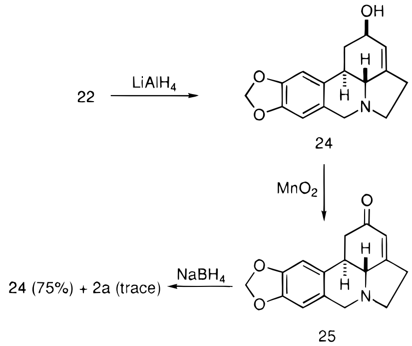
(19) (a) Lenz, G. R. *Synthesis* **1978**, 489. (b) Ninomiya, I.; Naito, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1983; Vol. 22, p 189.

(20) For an approach to the lycorine alkaloids involving photocyclizations of enamides to dehydrogenated photoproducts, see: Iida, H.; Aoyagi, S.; Kibayashi, C. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2502.

(21) For an alternative mechanism involving intermolecular hydrogen atom migration, see (a) Schultz, A. G.; Lucci, R. D. *J. Chem. Soc., Chem. Commun.* **1976**, 925. (b) Schultz, A. G.; Lucci, R. D.; Fu, W. Y.; Berger, M. H.; Erhardt, J.; Hagmann, W. K. *J. Am. Chem. Soc.* **1978**, *100*, 2150.

(22) (a) Okada, K.; Okubo, K.; Oda, M. *J. Photochem. Photobiol. A: Chem.* **1991**, *57*, 265. (b) Okada, K.; Okubo, K.; Oda, M. *Tetrahedron Lett.* **1989**, *30*, 6733.

Scheme 4



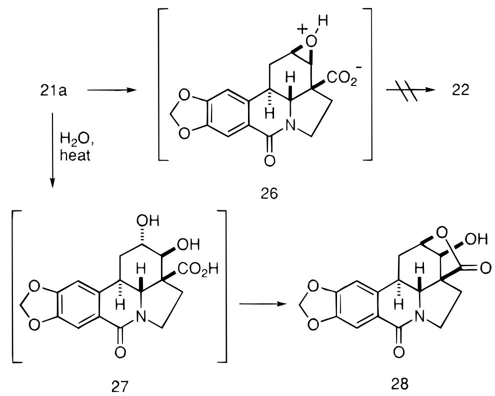
a related successful conversion (*vide infra*). In any event, conversion of **21a** to either the *N*-hydroxy-2-thiopyridone ester[23a] (not shown) or the *N*-hydroxy-2-thiazoline thione ester **21b**[23b] with DCC[24] and treatment of either ester with AIBN and Bu_3SnH in refluxing benzene solution provided the crystalline (+)-2-*epi*-1-deoxylycorine (**22**).[25,26]

Inversion of the allylic alcohol of **22** under classic Mitsunobu conditions with glacial acetic acid gave a 50% yield (44% recovered starting material) of acetate **23a** which was identical (TLC, ^1H NMR, ^{13}C NMR, CIMS) to authentic racemic material prepared from (±)-1-deoxylycorine-7-one[27] provided by Professor Kurt Torssell. A higher yield of ester **23b** (73%) was obtained when benzoic acid was used in the Mitsunobu inversion. Reduction of either **23a** or **23b** with $LiAlH_4$ provided (+)-1-deoxylycorine (**2a**) in good yield, identical to racemic material prepared from (±)-1-deoxylycorine-7-one (TLC, ^1H NMR).

Although the relative configuration of **2a** was known for certain, the absolute configuration was not. Reduction of 2-*epi*-1-deoxylycorin-7-one (**22**) with $LiAlH_4$ gave **24** in 77% yield (Scheme 4). Oxidation of **24** with MnO_2[28] provided 1-deoxylycorin-2-one (**25**) which exhibited an optical rotation ($[\alpha]^{24}_D$ +164° with mp 157−8 °C) opposite to that of **25** ($[\alpha]^{24}_D$ −169° with mp 157−8 °C) prepared from natural lycorine (**1**) by Kotera.[29] These data confirm that **2a** has absolute configuration opposite to that of the natural lycorine alkaloids. In addition, the stereochemical sense of alkylation of the enolate derived from **3** with 2-bromoethyl acetate is confirmed to be the same as that observed under identical reaction conditions for less highly functionalized alkylation reagents.[12]

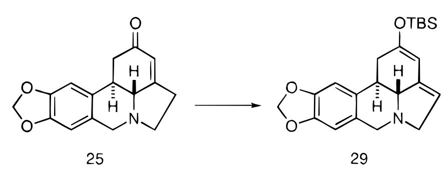
It is of interest to note that 1-deoxylycorin-2-one (**25**) provides 2-*epi*-1-deoxylycorine (**24**) with only a trace of **2** upon reduction with sodium borohydride in ethanol (Scheme 4). This is significant considering that independent syntheses of racemic **25** have been reported by Muxfeldt[30] and Seebach[31] and that the assignment of structure for the reduction product had not been previously determined.[32]

One additional observation deserves comment. It was thought that carboxylic acid **21a** might undergo a decarboxylative fragmentation to allylic alcohol **22** via the hypothetical zwitterionic intermediate **26**. Instead, **21a** rearranged to the lactone alcohol **28** in 80% yield on heating a solution of **21a** in water to reflux. This rearrangement may occur by way of trans diaxial hydrolysis of the epoxide ring in **26** to give diol **27** initially in a chair conformation followed by relaxation to a boat conformation and lactonization involving displacement of the C(2) alcohol group.



The Synthesis of (+)-Lycorine (2b). The remaining challenge to development of the first asymmetric synthesis of **2b** was the incorporation of the C(1) hydroxy substituent. This substitution proved to be somewhat more difficult than initially expected.

Introduction of C(1) oxygenation prior to radical or photochemical formation of the C(14)−C(15) bond could not be accomplished.[33] As a first alternative, the hydroxylation of an enolate derived from (+)-1-deoxylycorin-2-one (**25**) was examined. Unfortunately, treatment of **25** with either *tert*-butyldimethylsilyl triflate at 0 °C in CH_2Cl_2[34] or sodium hexamethyldisilylamide followed by *tert*-butyldimethylsilyl chloride gave dienol silyl ether **29** rather than the desired C(1) analogue.[35]



An effective solution to the C(1)-oxidation problem is shown in Schemes 5 and 6. The conversion of epoxide **12** to selenide **30** was carried out by utilization of standard Sharpless conditions at room temperature.[36] Prolonged reaction or elevated temperatures resulted in transesterification by the solvent (ethanol). Oxidation with hydrogen peroxide produced epoxide **31** rather

(23) (a) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901. (b) Barton, D. H. R.; Crich, D.; Kretzschmar, G. *J. Chem. Soc., Perkin Trans. 1* **1986**, 39.

(24) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475.

(25) For earlier examples of radical-induced epoxide fragmentations, see: (a) Sabatino, E. C.; Gritter, R. J. *J. Org. Chem.* **1963**, *28*, 3437. (b) Barton, D. H. R.; Motherwell, R. S. H.; Motherwell, W. B. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2363. (c) Rawal, V. H.; Newton, R. C.; Krishnamurthy, V. *J. Org. Chem.* **1990**, *55*, 5181. (d) Kim, S.; Lee, S.; Koh, J. S. *J. Am. Chem. Soc.* **1991**, *113*, 5106. (e) Rawal, V. H.; Krishnamurthy, V. *Tetrahedron Lett.* **1992**, *33*, 3439. (f) Rawal, V. H.; Iwasa, S. *Tetrahedron Lett.* **1992**, *33*, 4687. (g) Dang, H.-S.; Roberts, B. P. *Tetrahedron Lett.* **1992**, *33*, 6169.

(26) For a nonstereoselective synthesis of racemic **22**, see: Torssell, K. *Tetrahedron Lett.* **1974**, 623.

(27) Moller, O.; Steinberg, E.-M.; Torssell, K. *Acta Chem. Scand. B* **1978**, *32*, 98.

(28) Salmond, W. G.; Barta, M. A.; Havens, J. L. *J. Org. Chem.* **1978**, *43*, 2057.

(29) Kotera, K. *Tetrahedron* **1961**, *12*, 240.

(30) Muxfeldt, H.; Bell, J. P.; Baker, J. A.; Cuntze, U. *Tetrahedron Lett.* **1973**, 4587.

(31) Weller, T.; Seebach, D. *Tetrahedron Lett.* **1982**, *23*, 935.

(32) Baker, J. A. Ph.D. Thesis, Cornell University, 1970.

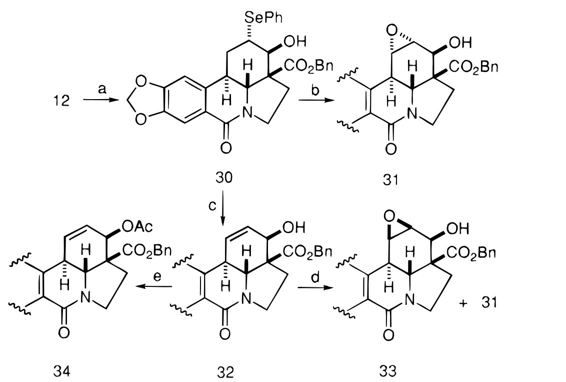
(33) Holoboski, M. A. Ph.D. Thesis, Rensselaer Polytechnic Institute, 1995.

(34) Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Gotz, A.; Hergott, H. H.; Hofmann, K.; Kober, W.; Krageloh, K.; Oesterle, T.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1.

(35) Unexpected problems associated with the oxidation of **22** with MnO_2 to the corresponding enone made the study of dienol silyl ether formation impractical; see ref 33.

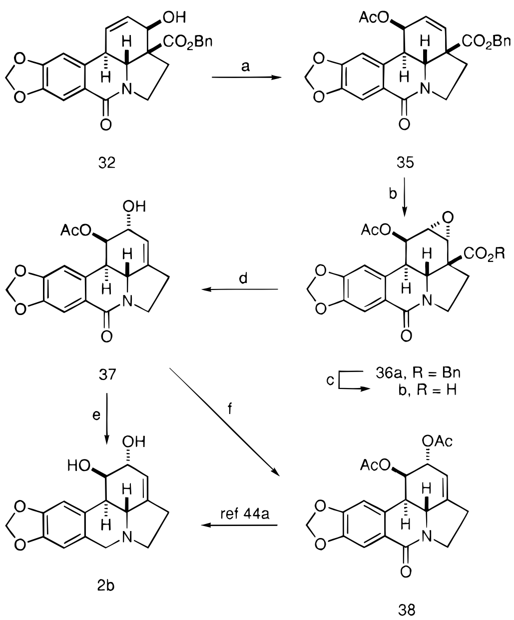
(36) Sharpless, K. B.; Lauer, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 2697.

Scheme 5[a]



[a] Reaction conditions: (a) $NaBH_4$, EtOH, PhSeSePh; (b) 30% H_2O_2, THF; (c) $NaIO_4$, H_2O, THF; (d) TFAA, UHP, CH_2Cl_2; (e) Ac_2O, DMAP.

Scheme 6[a]



[a] Reaction conditions: (a) AcOH, Ac_2O, H_2SO_4, 50 °C; (b) dimethyldioxirane, acetone, 0 °C; (c) 10% Pd/C, H_2 (1 atm) EtOH; (d) h*ν*, Pyrex, acridine, PhH, *tert*-BuSH; (e) $LiAlH_4$, THF, reflux; (f) Ac_2O, DMAP.

than the desired allylic alcohol **32**.[37] Oxidation of selenide **30** with sodium periodate gave allylic alcohol **32** in 81% overall yield from **12**.

Epoxidation of allylic alcohol **32**[38] with trifluoroperacetic acid[39] generated from the reaction of trifluoroacetic anhydride and urea hydrogen peroxide complex[40] gave a 1:1 mixture of **31** and **33**. Epoxidation of **32** with *m*-chloroperbenzoic acid or $VO(acac)_2$/*tert*-BuOOH provided even less of the desired epoxide **33**. Molecular models of **32** show that the pseudoequatorial C(3) hydroxyl group on the boat cyclohexene C ring is poorly oriented for stereodirected peracid and $VO(acac)_2$/*tert*-BuOOH epoxidations.[41]

Although the conversion of epoxide **33** to (+)-lycorine (**2b**) might be possible, the absence of stereocontrol for its formation represented an unfortunate turn of events in an otherwise completely stereoselective synthesis. For this reason, a study of an allylic substitution[42] of alcohol **32** or acetate **34** gained considerable appeal. Esterification of **32** with acetic anhydride, triethylamine, and 4-dimethylaminopyridine gave the allylic acetate **34** in 92% yield.

Effective reaction conditions for the rearrangement of **34** to **35** (Scheme 6) could not be found; however, treatment of allylic alcohol **32** with a mixture of acetic acid, acetic anhydride, and sulfuric acid at 50 °C, conditions first described by Torssell and co-workers[27] for rearrangement of a closely related analogue of **32**, provided a mixture consisting of the desired allylic acetate **35**, the unrearranged allylic acetate **34**, and a minor amount of a substance tentatively identified as the C(1) diastereomeric allylic acetate corresponding to **35**. Chromatography on silica gel provided crystalline **35** in 34% yield. The overall yield of **35** could be considerably improved by recycling operations that involved hydrolysis of the recovered mixture of isomeric allylic acetates followed by re-exposures to the Torssell reaction conditions.

Allylic acetate **35** was converted to epoxide **36a** on treatment with dimethyldioxirane.[43] It is noteworthy that *m*-chloroperbenzoic acid did not react with **35** and that CF_3CO_3H gave only a trace of **36a** after an extended reaction period. The stereoselectivity of epoxidation was determined by observation of a coupling constant of 2.7 Hz for H(1) and H(2). A coupling of ~6 Hz would have been expected had the epoxidation of **35** occurred syn to the benzyl ester group; cf., epoxide **12**.

Debenzylation of ester **36a** occurred uneventfully to give carboxylic acid **36b**. While preparation of the desired ester for radical fragmentation proved to be problematic, Okada's direct procedure for photochemical decarboxylation cleanly afforded allylic alcohol **37**.[22] Acetylation of **37** gave diacetate **38** (mp 114 °C) for which the IR, ^1H NMR, and mass spectra agreed with data published for the racemate.[44] Reduction of **37** with $LiAlH_4$ gave (+)-lycorine (**2b**) which was identical to a sample of natural (−)-lycorine provided by Professor George Pettit (TLC, ^1H NMR). Because of general insolubility of lycorine in organic solvents, **2b** was converted to its diacetate [mp 207−9 °C dec, $[\alpha]^{23}_D$ −25° (*c* 0.16, $CHCl_3$)] which was identical (TLC, ^1H NMR, CIMS, IR, HPLC) to the diacetate (mp 207−13 °C)[44a] prepared from natural (−)-lycorine (**1**) [$[\alpha]^{23}_D$ +25.6° (*c* 0.39, $CHCl_3$)].

Conclusion

The first asymmetric total syntheses of (+)-1-deoxylycorine (**2a**) and (+)-lycorine (**2b**) have been achieved. The synthesis of **2a** required 13 steps from the readily available chiral benzamide **3**,[12b] while (+)-lycorine (**2b**) was obtained in 15 steps. Both **2a** and **2b** were prepared in enantiomerically pure form via Birch reduction-alkylation of **3**. The iodolactonization **7** → **8** accomplished the dual functions of introduction of the hydroxy group at C(2) with complete stereocontrol and release of the chiral auxiliary.

A key step in the synthesis of both **2a** and **2b** is the completely regio- and stereoselective radical cyclization reaction to give **12**. Companion studies[17] suggest that this type of chiral

(37) For a discussion of this type of oxidation, see: Hori, T.; Sharpless, K. B. *J. Org. Chem*. **1978**, *43*, 1689.

(38) Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc*. **1959**, 1958.

(39) McKittrick, B. A.; Ganem, B. *Tetrahedron Lett*. **1985**, *26*, 4895.

(40) Cooper, M. S.; Heaney, H.; Newbold, A. J.; Sanderson, W. R. *Synlett*. **1990**, 533.

(41) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev*. **1993**, *93*, 1307.

(42) Stork, G.; White, W. N. *J. Am. Chem. Soc*. **1956**, *78*, 4609.

(43) (a) Adam, W.; Chan, Y.; Cremer, D.; Gauss, J.; Scheutzow, D.; Schindler, M. *J. Org. Chem*. **1987**, *52*, 2800. (b) Adam, W.; Curci, R.; Edwards, J. O. *Acc. Chem. Res*. **1989**, *22*, 205. (c) Murray, R. W. *Chem. Rev*. **1989**, *89*, 1187.

(44) (a) 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. (b) Kotera, K.; Hamada, K.; Tori, Y.; Aono, K.; Kuriyama, K. *Tetrahedron Lett*. **1966**, 2009.

enamide cyclization will have substantial application to the stereocontrolled synthesis of other alkaloids.

While our earlier applications of the Birch reduction-alkylation to asymmetric synthesis focused on target structures with a quaternary stereocenter derived from C(1) of the starting benzoic acid derivative,[10b] the syntheses of **2a** and **2b** rather convincingly demonstrate that the methodology is applicable to the synthesis of chiral six-membered rings containing only tertiary and trigonal carbon atoms. The development of synthetic strategies that illustrate a more versatile Birch reduction-alkylation will continue to be the subject of future publications from this laboratory.

Experimental Section

^{1}H and ^{13}C NMR spectra were obtained on either a Varian XL-200 (200 MHz) or Unity 500 (500 MHz) spectrometer employing tetramethylsilane as an internal standard. Infrared spectra were recorded on a Perkin-Elmer 298 Model spectrometer. Mass spectral data were obtained on a Hewlett-Packard Model 5987-A GC-MS system employing methane or isobutane as chemical ionization gases or utilizing direct electron impact. Optical rotations were taken on a Perkin-Elmer Model 241 polarimeter with a 0.5 mL (L = 0.1 dm) cell. Elemental analyses were performed by either Spang Microanalytical Laboratories, Eagle Harbor, MI or Quantitative Technologies Inc., Whitehouse, NJ. Melting points were determined in open capillary tubes on a Thomas Hoover apparatus and were uncorrected. Column chromatography was performed on Baker 40 μm silica gel. Radial chromatography was performed with EM Science silica gel 60 (PF_{254}) containing Gypsum. All reactions were performed under an inert atmosphere of nitrogen unless otherwise noted. HPLC analyses were performed on a Waters Associates Model 6000A instrument equipped with a Model R401 differential refractometer and a Hewlett Packard Model HP3394 integrator using a 25 cm Daicel OD or a 25 cm Partisil 5 column. The 300 nm light source was a medium pressure 450W Hanovia mercury arc lamp.

6-Bromopiperonylic acid was prepared[45] and recrystallized from water. 6-Iodopiperonal was prepared according to a literature procedure[46] and oxidized to 6-iodopiperonlyic acid.[47] The corresponding acid chlorides were prepared with thionyl chloride.

(2′*S*,6*R*)-1-Methoxy-6-(2-hydroxyethyl)-6-[[2′-(methoxymethyl)-pyrrolidinyl]carbonyl]-1,4-cyclohexadiene (6a). A solution of **3**[12] (7.08 g, 0.0284 mol) in THF (40 mL) was cooled to −78 °C and ammonia (400 mL) and *tert*-butyl alcohol (2.11 g, 0.0284 mol) were added. Potassium was added in small pieces until a blue color persisted for 15 min. 2-Bromoethyl acetate (12.0 g, 0.071 mol) was added, and the yellow solution was stirred 0.5 h. After evaporation of the ammonia, methanol (42 mL) and 10% potassium hydroxide (14 mL) were added, and the resulting solution stirred 6 h at room temperature. The mixture was concentrated, CH_2Cl_2 (50 mL) and water (20 mL) were added, the layers separated, and the aqueous solution was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine and dried ($MgSO_4$), and the solvent was removed *in vacuo* to afford a yellow oil. Chromatography over silica gel (1:1 hexanes/ethyl acetate; then ethyl acetate) provided pure **6a** (8.05 g, 96%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 5.91 (dt, 1 H, J = 9.8, 3.7, 1.2 Hz), 5.61 (d, 1 H, J = 9.88 Hz), 4.72 (t, 1 H, J = 3.50 Hz), 4.30 (m, 1 H), 3.70−3.56 (m, 4 H), 3.53 (s, 3 H), 3.35 (s, 3 H), 3.38−3.20 (m, 3 H), 2.99−2.75 (m, 2 H), 2.33 (m, 1 H), 2.08 (m, 1 H), 1.95−1.70 (m, 4 H); IR ($CHCl_3$) 3360, 3000, 1610 cm^{-1}; CIMS, m/z (rel intensity) 296 (M$^+$ + 1, 100). An acceptable elemental analysis could not be obtained.

(2′*S*,6*R*)-1-Methoxy-6-(2-azidoethyl)-6-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-1,4-cyclohexadiene (6b). To a solution of **6a** (7.72 g, 0.0261 mol) in THF (130 mL) at 0 °C was added triphenylphosphine (6.86 g, 1 equiv) and diethyl azodicarboxylate (4.55 g, 0.0261 mol), and stirring was continued for 20 min. Then a solution of diphenylphosphoryl azide (7.18 g, 0.0261 mol) in THF (33 mL) was added slowly, and the mixture was allowed to warm to room temperature overnight. Evaporation of the solvent provided a dark brown oil (27.75 g) which was flash chromatographed (hexanes/ethyl acetate 2:1) to afford **6b** (6.15 g, 73%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 5.93 (m, 1 H), 5.41 (dt, 1 H, J = 10.0 Hz, 2.0 Hz), 4.80 (t, 1 H, J = 3.20 Hz), 4.30 (m, 1 H), 3.61−3.55 (m, 2 H), 3.53 (s, 3 H), 3.35−3.32 (m, 1 H), 3.34 (s, 3 H), 3.27−3.09 (m, 3 H), 2.95−2.79 (m, 2 H), 2.41 (m, 1 H), 2.03 (m, 1 H), 1.93−1.70 (m, 4 H); IR ($CHCl_3$) 2940, 2110, 1610 cm^{-1}; ^{13}C NMR ($CDCl_3$) 169.15, 152.14, 126.51, 125.74, 92.91, 71.72, 58.71, 58.08, 54.02, 50.48, 47.66, 45.77, 34.88, 26.49, 26.12, 24.73; CIMS, m/z (rel intensity) 321 (M$^+$ + 1, 100). Anal. Calcd for $C_{16}H_{24}N_4O_3$: C, 59.98; H, 7.55. Found: C, 59.71; H, 7.41.

(2′*S*,2*R*)-2-(2-Azidoethyl)-2-[[2′-(methoxymethyl)pyrrolidinyl]carbonyl]-3-cyclohexen-1-one (7). To **6b** (6.15 g, 0.0191 mol) in MeOH (192 mL) was added 6 *M* HCl (71 mL), and the clear yellow solution was stirred at room temperature overnight. After removing the MeOH under reduced pressure, water was added (30 mL), and the mixture was extracted with methylene chloride (5 × 50 mL). The combined organic layers were washed with $NaHCO_3$ (saturated), dried ($MgSO_4$), and concentrated. Flash chromatography (hexanes/ethyl acetate, 1:1) afforded **7** (5.57 g, 95%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ 6.04 (dt, 1 H, J = 9.8 Hz, 4.2 Hz), 5.67 (d, 1 H, J = 9.6 Hz), 4.27 (m, 1 H), 3.62 (dd, J = 9.5, 3.1 Hz, 1 H), 3.48 (m, 1 H), 3.39−3.30 (m, 3 H), 3.36 (s, 3 H), 3.10−3.05 (m, 1 H), 2.66−2.60 (m, 3 H), 2.54 (m, 1 H), 2.31 (m, 1 H), 2.02 (m, 1 H), 1.75 (m, 1 H), 1.95−1.86 (m, 3 H); IR ($CHCl_3$) 2950, 2110, 1710, 1625 cm^{-1}; ^{13}C NMR ($CDCl_3$) 207.12, 167.59, 128.43, 128.29, 71.55, 59.87, 58.83, 57.84, 47.68, 46.53, 36.15, 35.48, 26.48, 25.57, 24.34. CIMS, m/z (rel intensity) 307 (M$^+$ + 1, 100). Anal. Calcd for $C_{15}H_{22}N_4O_3$: C, 58.81; H, 7.24. Found: C, 58.83; H, 7.25.

(2*R*,3*R*,4*R*)-1-Oxo-2-(2-azidoethyl)-3-iodocyclohexane-2,4-carbolactone (8). To a solution of amide **7** (2.22 g, 7.25 mmol) and THF (45 mL) were added H_2O (45 mL) and iodine (11 g, 43 mmol). The reaction was stirred 12 h and $Na_2S_2O_3$ (sat) was added until the black reaction turned yellow. The THF was evaporated and the aqueous phase was washed with CH_2Cl_2 (5 × 20 mL). The combined organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (EtOAc/hexanes; 1:2) afforded lactone **8** as a colorless solid (2.0 g, 82%). Mp 69−72 °C; $[\alpha]^{18}_D$ −161.5° (c 6.76, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 2.05 (m, 1 H), 2.25 (m, 1 H), 2.46 (m, 1 H), 2.56−2.77 (m, 3 H), 3.41 (m, 2 H), 4.96 (d, J = 1.4 Hz, 1 H), 5.00 (m, 1 H). ^{13}C NMR ($CDCl_3$) 197.13, 169.27, 77.46, 62.46, 46.28, 32.73, 27.26, 23.87, 23.82. IR ($CDCl_3$) 2120, 1780, 1725 cm^{-1}. CIMS m/z (rel intensity) 336 (M$^+$ + 1, 100), 308 (50). Anal. Calcd for $C_9H_{10}N_3O_3I$: C, 32.26; H, 3.01; N, 12.54. Found: C, 32.63; H, 2.95; N, 12.49.

(3a*R*,4*R*,5*R*)-4-Iodo-2,3,6,7-tetrahydroindole-3a,5-carbolactone (9). To a solution of lactone **8** (6.35 g, 19.0 mmol) in THF (250 mL) was added triphenylphosphine (5.0 g, 19 mmol), and the reaction was refluxed (9 h), cooled, and concentrated. Flash chromatography (Et_2O/hexane; 1:1) afforded imine **9** (4.97 g, 90%) as a colorless solid. Mp 130 °C; $[\alpha]^{20}_D$ −170.6° (c 2.18, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.91 (m, 1 H), 2.50 (m, 4 H), 2.83 (dd, J = 16.5, 7.5 Hz, 1 H), 4.00 (m, 2 H), 4.70 (d, J = 5 Hz, 1 H), 4.90 (s, 1 H); ^{13}C NMR ($CDCl_3$) 170.33, 167.00, 77.93, 65.20, 60.23, 28.67, 25.42, 24.66, 22.63; IR ($CHCl_3$) 2940, 1785, 1665 cm^{-1}; CIMS m/z (rel intensity) 292 (M$^+$ + 1, 100), 166 (66). Anal. Calcd for $C_9H_{10}NO_2I$: C, 37.14; H, 3.46. Found: C, 37.20; H, 3.46.

(3a*R*,4*R*,5*R*)-*N*-(6-Bromopiperonyloyl)-5,6-dihydro-4*H*-indoline-3a,5-carbolactone (10a). A solution of imine **9** (0.526 g, 1.81 mmol) and Et_3N (0.37 g, 3.6 mmol) in CH_2Cl_2 (50 mL) was cooled to 0 °C, and then a solution of 6-bromopiperonyloyl chloride (0.477 g, 1.81 mmol) in CH_2Cl_2 (25 mL) was added slowly. The reaction was allowed to gradually warm to room temperature while stirring (12 h). The mixture was washed with 10% HCl (20 mL), saturated $NaHCO_3$ (30 mL), and dried (Na_2SO_4); solvent evaporation and flash chromatography (EtOAc/hexane; 1:4) provided enamide **10a** (0.915 g, 98%) as a colorless solid. Mp 131 °C; $[\alpha]^{25}_D$ −4.3° (c 0.46, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.10 (m, 1 H), 2.25 (m, 1 H), 2.77 (d, J = 19 Hz, 1 H), 2.97 (d, J = 19 Hz, 1 H), 3.50 (m, 2 H), 4.64 (d, J = 4.9 Hz, 1 H), 4.82 (m, 1 H), 6.03 (s, 2 H), 6.60 (s, 1 H), 6.78 (s, 1 H), 7.01 (s, 1 H). IR ($CDCl_3$) 1780, 1640 cm^{-1}; CIMS m/z (rel intensity) 520 (M$^+$ + 1, 21),

(45) Auerbach, J.; Weissman, S. A.; Blacklock, T. J.; Angeles, M. R.; Hoogsteen, K. *Tetrahedron Lett*. **1993**, *34*, 931.
(46) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507.
(47) CA 55:3594c.

518 ($M^+ + 1$, 22), 248 (100). Anal. Calcd for $C_{17}H_{13}NO_5BrI$: C, 39.41; H, 2.53; N, 2.70. Found: C, 39.26; H, 2.70; N, 2.55.

(3a*R*,4*R*,5*R*)-*N*-(6-Iodopiperonyloyl)-5,6-dihydro-4*H*-indoline-3a,5-carbolactone (10b). A solution of imine **9** (1.76 g, 6.06 mmol) and Et_3N (1.23 g, 12.1 mmol) in CH_2Cl_2 (150 mL) was cooled to 0 °C, and then a solution of 6-iodopiperonyloyl chloride (1.88 g, 6.06 mmol) in CH_2Cl_2 (50 mL) was added slowly. The reaction was allowed to gradually warm to room temperature while stirring (12 h). The mixture was washed with 10% HCl (70 mL) and saturated $NaHCO_3$ (100 mL) and dried (Na_2SO_4); solvent evaporation and flash chromatography (EtOAc/hexane; 1:4) provided enamide **10b** (3.4 g, 99%) as a colorless solid, mp 200−202 °C; $[\alpha]^{24}_D$ −0.3° (*c* 3.26, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.10 (m, 1 H), 2.25 (m, 1 H), 2.76 (d, J = 19 Hz, 1 H), 2.96 (d, J = 19 Hz, 1 H), 3.50 (m, 2 H), 4.63 (d, J = 5 Hz, 1 H), 4.82 (m, 1 H), 6.01 (s, 2 H), 6.59 (s, 1 H), 6.76 (s, 1 H), 7.21 (s, 1 H). IR ($CDCl_3$) 1780, 1640 cm^{-1}; CIMS *m/z* (rel intensity) 566 ($M^+ + 1$, 14), 440 (37), 394 (94), 314 (98), 312 (80).

(3a*S*,4*S*,5*R*)-*N*-(6-Bromopiperonyloyl)-4,5-epoxy-5,6-dihydro-4*H*-3a-(benzyloxycarbonyl)indoline (11a). A solution of BnOH (1.03 g, 9.61 mmol) in THF (60 mL) was cooled to −78 °C and a 2.5 *M* solution of BuLi (2.60 mL, 6.5 mmol) in hexanes was added. The mixture was allowed to stir for 5 min, and then enamide **10a** (3.33 g, 6.43 mmol) in THF (20 mL) was added. The reaction was stirred at −78 °C (5 min), 0 °C (3 h), and room temperature (2 h). The reaction was quenched with excess NH_4Cl (saturated) and concentrated *in vacuo*. The aqueous phase was washed with CH_2Cl_2 (5 × 25 mL), and the combined organic phase was dried (Na_2SO_4). Flash chromatography (EtOAc/hexane; 1:4) afforded benzyl ester **11a** (2.29 g, 73%) as a colorless solid. Mp 68−72 °C; $[\alpha]^{24}_D$ +85° (*c* 2.0, $CHCl_3$). ^1H NMR δ 2.05 (m, 1 H), 2.45 (m, 1 H), 2.65 (m, 2 H), 3.35 (m, 1 H), 3.45 (m, 1 H), 3.62 (m, 1 H), 3.92 (m, 1 H), 4.52 (s, 1 H), 5.22 (d, J = 12.2 Hz, 1 H), 5.26 (d, J = 12 Hz, 1 H), 6.0 (m, 2 H), 6.70−7.50 (m, 7 H). IR ($CHCl_3$) 1730, 1630 cm^{-1}. CIMS *m/z* (rel intensity) 500 and 498 ($M^+ + 1$, 4), 420 (5), 266 (15), 133 (40), 107 (45), 91 (100). Anal. Calcd for $C_{24}H_{20}NO_6Br$: C, 57.85; H, 4.05; N, 2.81. Found: C, 57.86; H, 4.39; N, 2.65.

(3a*S*,4*S*,5*R*)-*N*-(6-Iodopiperonyloyl)-4,5-epoxy-5,6-dihydro-4*H*-3a-(benzyloxycarbonyl)-indoline (11b). A solution of BnOH (1.90 g, 17.7 mmol) in THF (75 mL) was cooled to −78 °C and a 2.5 *M* solution of BuLi (5.20 mL, 13 mmol) in hexanes was added. The mixture was allowed to stir for 5 min and then enamide **10b** (6.67 g, 11.8 mmol) in THF (35 mL) was added. The reaction was stirred at −78 °C (5 min), 0 °C (3 h), and room temperature (2 h). The reaction was quenched with excess NH_4Cl (saturated) and concentrated *in vacuo*. The aqueous phase was washed with CH_2Cl_2 (5 × 25 mL), and the combined organic phase was dried (Na_2SO_4). Flash chromatography (EtOAc/hexane; 1:4) afforded benzyl ester **11b** (5.92 g, 92%) as a colorless solid. Mp 57−63 °C; $[\alpha]^{23}_D$ +73.5° (*c* 2.45, $CHCl_3$). ^1H NMR δ 2.05 (m, 1 H), 2.45 (m, 1 H), 2.65 (m, 2 H), 3.35 (m, 1 H), 3.45 (m, 1 H), 3.62 (m, 1 H), 3.92 (m, 1 H), 4.49 (s, 1 H), 5.23 (d, J = 12 Hz, 1 H), 5.26 (d, J = 12.5 Hz, 1 H), 5.99 (s, 2 H), 6.70−7.50 (m, 7 H). IR ($CDCl_3$) 1739, 1630 cm^{-1}. CIMS *m/z* (rel intensity) 546 ($M^+ + 1$, 4), 420 (25), 266 (40), 133 (55), 107 (70), 91 (100).

(2*R*,3*S*,12*S*,15*R*,16*R*)-2,3-Epoxy-12-(benzyloxycarbonyl)-9,10-[methylenebis(oxy)]galanthan-7-one (12). A solution of ester **11a** (1.10 g, 2.2 mmol), Bu_3SnH (960 mg, 3.30 mmol), AIBN (40 mg, 0.24 mmol), and benzene (240 mL) was degassed for 15 min and then refluxed for 16 h (until the complete disappearance of starting material was observed by TLC). The solvent was evaporated, and the organic residue was partitioned between MeCN and hexane. The MeCN layer was washed with hexane (four times) and after solvent removal, flash chromatography (EtOAc/hexane; 1:1) afforded lactam **12** (490 mg, 53%) as a colorless solid (mp 203 °C, recrystallized from EtOAc/hexane) and enamide **11c** (45%). (**12**): $[\alpha]^{24}_D$ +86° (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.66 (dd, J = 15.1, 14.7 Hz, 1 H, H_{1ax}), 2.12 (ddd, J = 12.5, 12.2, 7.3 Hz, 1 H, H_4), 2.47 (dd, J = 4.9, 12.7 Hz, 1 H, H_4), 2.66 (m, 2 H, H_{15}, H_{1eq}), 3.21 (ddd, J = 12.5, 11.2, 4.9 Hz, 1 H, H_5), 3.45 (d, J = 3.9 Hz, 1 H, H_3), 3.58 (m, 1 H, H_2), 4.09 (d, J = 12.2 Hz, 1 H, H_{16}), 4.16 (dd, J = 7.3, 11.7 Hz, 1 H, H_5), 5.25 (d, J = 12.2 Hz, 1 H), 5.30 (d, J = 12.2 Hz, 1 H), 6.01 (s, 2 H), 6.64 (s, 1 H), 7.25−7.38 (m, 5 H), 7.44 (s, 1 H). ^{13}C NMR ($CDCl_3$) 172.26, 162.65, 150.59, 146.83, 135.38, 135.11, 128.60, 128.42, 128.10, 124.82, 108.46, 103.62, 101.60, 67.57, 60.04, 53.96, 53.81, 53.44, 43.80, 36.57, 32.50, 25.05. IR ($CHCl_3$) 1732, 1641 cm^{-1}. CIMS *m/z* (rel intensity) 420 ($M^+ + 1$, 100), 330 (24), 286 (25). Anal. Calcd for $C_{24}H_{21}NO_6$: C, 68.73; H, 5.05; N, 3.34. Found: C, 68.38; H, 5.14; N, 3.10.

(3a*S*,4*S*,5*R*)-*N*-(Piperonyloyl)-4,5-epoxy-5,6-dihydro-4*H*-3a-(benzyloxycarbonyl)indoline (11c). ^1H NMR ($CDCl_3$) δ 1.98 (ddd, J = 9.5, 11, 20.5 Hz, 1 H), 2.50 (m, 2 H), 2.66 (dd, J = 7, 12.5 Hz, 1 H), 3.38 (m, 1 H), 3.47 (d, J = 4 Hz, 1 H), 3.50 (m, 1 H), 3.88 (m, 1 H), 5.24 (d, J = 12 Hz, 1 H), 5.29 (d, J = 12.5 Hz, 1 H), 5.97 (s, 2 H), 6.65 (d, J = 8 Hz, 1 H), 7.1−7.5 (m, 7 H). γ = 300 nm (ϵ = 5246, PhH) γ_{max} = 295 nm (ϵ = 5485, PhH). IR ($CHCl_3$) 1730, 1630 cm^{-1}. CIMS *m/z* (rel intensity) 420 ($M^+ + 1$, 100), 149 (16). CI HRMS (methane) m/z 420.1444 (M + 1). Calcd for $C_{24}H_{22}NO_6$: 420.1447.

Alternate Procedure. A solution of ester **11b** (600 mg, 1.10 mmol), Bu_3SnH (476 mg, 1.65 mmol), AIBN (18 mg, 0.11 mmol), and benzene (120 mL) was degassed for 15 min and then refluxed for 5 h (until the complete disappearance of starting material was observed by TLC). The solvent was evaporated, and the organic residue was partitioned between MeCN and hexane. The MeCN layer was washed with hexane (four times), and after solvent removal, flash chromatography (EtOAc/hexane; 1:1) afforded lactam **12** (235 mg, 51%) as a colorless solid. ^1H NMR analysis of the crude reaction mixture indicated that **12** and **11c** were present in a ratio of ∼1:1.

Photolysis of Enamide 11c. A solution of enamide **11c** (50 mg, 0.12 mmol) and benzene (6 mL) in a Pyrex test tube was degassed with nitrogen for 15 min. The mixture was irradiated (7 h) and then concentrated. Flash chromatography (EtOAc/hexanes, 1:1) afforded a colorless solid (40 mg, 80%) which consisted of lactams **12**, **20**, and **17** (1.1:2.7:1 ratio by 500 MHz ^1H NMR). Analytical samples were obtained by radial chromatography (EtOAc/hexanes, 1:1).

(2*R*,3*S*,12*S*)-2,3-Epoxy-12-(benzyloxycarbonyl)-15,16-didehydro-9,10-[methylenebis(oxy)]galanthan-7-one (20). Mp 118 °C. ^1H NMR ($CDCl_3$) δ 2.30 (m, 1 H), 2.92 (m, 2 H), 3.20 (dd, J = 5.8, 17.6 Hz, 1 H), 3.60 (d, J = 3.1 Hz, 1 H), 3.70 (m, 1 H), 3.78 (ddd, J = 5.6, 12, 12 Hz, 1 H), 4.39 (dd, J = 8.5, 12.5 Hz, 1 H), 5.18 (d, J = 12.2 Hz, 1 H), 5.22 (d, J = 12.2 Hz, 1 H), 6.1 (m, 2 H), 6.93 (s, 1 H), 7.82 (s, 1 H), 7.32 (m, 5 H). IR (CH_2Cl_2) 1730, 1675, 1600 cm^{-1}. CIMS *m/z* (rel intensity) 418 ($M^+ + 1$, 55), 266 (65), 147 (25), 91 (100). CI HRMS (methane) *m/z* 418.1291(M + 1). Calcd for $C_{24}H_{20}NO_6$: 418.1291.

2*R*,3*S*,12*S*,15*S*,16*R*)-2,3-Epoxy-12-(benzyloxycarbonyl)-9,10-[methylenebis(oxy)galanthan-7-one (17). ^1H NMR ($CDCl_3$) δ 1.78 (dd, J = 11, 15 Hz, 1 H, H_{1ax}), 2.20 (ddd, J = 2.5, 6, 16 Hz, 1 H, H_{1eq}), 2.32 (m, 2 H), 3.03 (m, 1 H, H_{15}), 3.34 (d, J = 4 Hz, 1 H, H_3), 3.38 (m, 1 H, H_2), 3.60 (m, 1 H, H_5), 3.93 (m, 1 H, H_5), 4.35 (d, J = 3 Hz, 1 H, H_{16}), 5.25 (d, J = 12.5 Hz, 1 H), 5.29 (d, J = 10.5 Hz, 1 H), 6.00 (s, 1 H), 6.01 (s, 1 H), 6.61 (s, 1 H), 7.47 (s, 1 H), 7.38 (m, 5 H). CIMS *m/z* (rel intensity) 420 ($M^+ + 1$, 100), 330 (12), 286 (20). CI HRMS (methane) *m/z* 420.1442 (M + 1). Calcd for $C_{24}H_{22}NO_6$: 420.1447.

Photolysis of Enamide 11c in the Presence of Thiophenol. A solution of enamide **11c** (70 mg, 0.17 mmol), benzene (8.5 mL), and thiophenol (0.1 mL) in a Pyrex test tube was degassed with nitrogen for 15 min. The mixture was irradiated (7 h) and then concentrated. Flash chromatography (EtOAc/hexanes, 1:1) afforded a colorless solid (42 mg, 60%) which consisted of lactams **12** and **17** (2:1 ratio by 500 MHz ^1H NMR).

(2*R*,3*S*,12*S*,15*R*,16*R*)-2,3-Epoxy-12-(hydroxycarbonyl)-9,10-[methylenebis(oxy)]galanthan-7-one (21a). A mixture of lactam **12** (260 mg, 0.62 mmol), abs. EtOH (26 mL) and 10% Pd/C (260 mg; Alfa) was stirred under (1atm) H_2 for 3 h. The mixture was filtered through Celite, and the Celite was rinsed with CH_2Cl_2. The combined filtrate was concentrated to give acid **21a** (172 mg, 84%) as a colorless solid (mp 214−219 °C, $-CO_2$), which was used without further purification. ^1H NMR ($CDCl_3$) δ 1.65 (dd, J = 15.9, 14.2 Hz, 1 H), 2.17 (ddd, J = 7.8, 11.0, 12.4 Hz, 1 H), 2.55 (dd, J = 5.2, 12.5 Hz, 1 H), 2.67 (m, 2 H), 3.34 (ddd, J = 5.6, 12.2, 11.2 Hz, 1 H), 3.47 (d, J = 3.4 Hz, 1 H), 3.60 (dd, J = 3.4, 6.4 Hz, 1 H), 4.03 (d, J = 12.7 Hz, 1 H), 4.20 (dd, J = 7.8, 11.2 Hz, 1 H), 6.01 (s, 2 H), 6.63 (s, 1 H), 7.42 (s, 1 H); IR (KBr) 3420, 1715, 1625 cm^{-1}; CIMS *m/z* (rel intensity) 330 ($M^+ + 1$, 16), 315 (40), 262 (80), 232 (100).

(2*R*,3*S*,12*S*,15*R*,16*R*)-2,3-Epoxy-12-(3-hydroxy-4-methyl-2(3*H*)-thiazolethione)carbonyl-9,10-[methylenebis(oxy)]galanthan-7-one (21b). The acid **21a** (266 mg, 0.809 mmol) was combined with DCC (253 mg, 1.23 mmol), 4-pyrrolidinopyridine (61 mg, 0.41 mmol), 3-hydroxy-4-methyl-2(3*H*)-thiazolethione (180 mg, 1.2 mmol), and CH_2Cl_2 (50 mL) and stirred for 12 h in the dark. The mixture was concentrated and flash chromatography (EtOAc/hexane; 1:1) afforded ester **21b** (318 mg, 86%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 1.69 (m, 1 H, H_{1ax}), 2.25 (s, 3 H), 2.40 (m, 1 H, H_4), 2.74 (m, 2 H, H_{15}, H_{1eq}), 3.36 (dd, J = 5.4, 12.9 Hz, 1 H, H_4), 3.59 (ddd, J = 4.9, 12.5, 11.2 Hz, 1 H, H_5), 3.65 (d, J = 3.5 Hz, 1 H, H_3), 3.69 (m, 1 H, H_2), 4.04 (d, J = 12.5 Hz, 1 H, H_{16}), 4.28 (dd, J = 8.1, 12.5 Hz, 1 H, H_5), 6.02 (s, 2 H), 6.26 (m, 1 H), 6.65 (s, 1 H), 7.47 (s, 1 H).

(2*R*,15*R*,16*R*)-2-Hydroxy-3,12-didehydro-9,10-[methylenebis(oxy)]galanthan-7-one (22). To ester **21b** (318 mg, 0.694 mmol) were added benzene (56 mL), Bu_3SnH (303 mg, 1.03 mmol), and AIBN (11 mg, 0.067 mmol). The mixture was purged with nitrogen gas and then refluxed for 2 h. The reaction was recharged with Bu_3SnH (202 mg, 0.69 mmol) and AIBN (11 mg, 0.067 mmol), refluxed for 1 h, and then the solvent was evaporated. The organic residue was partitioned between MeCN and hexane, and the MeCN layer was washed with hexane (five times). The combined MeCN solution was concentrated and flash chromatography (MeOH/EtOAc; 1:9) afforded alcohol **22** as a colorless solid (98 mg, 50%). Mp 231 °C. $[\alpha]^{27}_{D}$ +80.6° (*c* 1.65, THF). ^{1}H NMR ($CDCl_3$) δ 1.52 (ddd, J = 9.5, 12.5, 12.5 Hz, 1 H, H_{1ax}), 1.76 (d, J = 6.8 Hz, 1 H, *OH*), 2.75 (m, 4 H, H_{15}, H_4, H_4, H_{1eq}), 3.73 (m, 1 H, H_5), 3.82 (m, 1 H, H_5), 3.89 (d, J = 12 Hz, 1 H, H_{16}), 4.67 (m, 1 H, H_2), 5.66 (m, 1 H, H_3), 6.02 (s, 2 H), 6.72 (s, 1 H), 7.55 (s, 1 H). ^{13}C NMR ($CDCl_3$, MeOH; 9:1) 163.42, 150.67, 146.60, 140.30, 135.86, 125.29, 122.67, 108.31, 103.36, 101.60, 68.55, 60.23, 43.31, 39.99, 32.15, 28.08. IR ($CHCl_3$) 3600, 1640 cm^{-1}. CIMS *m/z* (rel intensity) 286 (M^+ + 1, 100), 268 (40).

(2*S*,15*R*,16*R*)-2-Acetyloxy-3,12-didehydro-9,10-[methylenebis(oxy)]galanthan-7-one (23a). To a solution of alcohol **22** (9 mg, 0.03 mmol) and THF (1.5 mL) were added PPh_3 (12 mg, 0.045 mmol), AcOH (3 mg, 0.05 mmol) and DEAD [(8 mg, 0.05 mmol) in THF (0.5 mL)]. The mixture was stirred (24 h) and concentrated, and flash chromatography (EtOAc/hexane; 1:1) afforded acetate **23a** (5 mg, 50%) as a colorless solid (mp 223 °C) and recovered starting material (44%). ^{1}H NMR ($CDCl_3$) δ 1.84 (ddd, J = 5.2, 13.2, 13.1 Hz, 1 H, H_{1ax}), 2.08 (s, 3 H), 2.43 (dd, J = 14.6, 1.7 Hz, 1 H, H_{1eq}), 2.80 (m, 2 H, H_4, H_4), 2.85 (ddd, J = 2.9, 12.7, 12.5 Hz, 1 H, H_{15}), 3.72 (d, J = 12.3 Hz, 1 H, H_{16}), 3.82 (m, 2 H, H_5, H_5), 5.57 (m, 1 H, H_2), 5.65 (m, 1 H, H_3), 6.02 (s, 2 H), 6.70 (s, 1 H), 7.56 (s, 1 H). IR ($CHCl_3$) 1720, 1640 cm^{-1}. ^{13}C NMR ($CDCl_3$) 170.44, 163.01, 150.56, 146.74, 143.68, 135.52, 126.04, 117.48, 108.80, 103.51, 101.65, 67.87, 60.50, 43.53, 35.83, 29.05, 28.60, 21.31. CIMS *m/z* (rel intensity) 328 (M^+ + 1, 100), 268 (80).

(2*S*,15*R*,16*R*)-2-Benzyloxy-3,12-didehydro-9,10-[methylenebis(oxy)]galanthan-7-one (23b). To a solution of alcohol **22** (27 mg, 0.095 mmol) and THF (4 mL) were added PPh_3 (35 mg, 0.13 mmol), BzOH (16 mg, 0.13 mmol) and DEAD [(24 mg, 0.13 mmol), in THF (2 mL)]. The mixture was stirred (24 h) and concentrated, and flash chromatography (EtOAc/hexane; 1:1) afforded benzoate **23b** (27 mg, 73%) as a colorless solid (mp 199−203 °C). $[\alpha]^{24}_{D}$ −195° (*c*, 0.22, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.96 (ddd, J = 5.4, 13.2, 13.2 Hz, 1 H, H_{1ax}), 2.59 (dd, J = 14.7, 2.9 Hz, 1 H, H_{1eq}), 2.84 (m, 2 H, H_4, H_4), 2.98 (ddd, J = 2.6, 12.7, 12.4 Hz, 1 H, H_{15}), 3.79 (d, J = 12.4 Hz, 1 H, H_{16}), 3.85 (m, 2 H, H_5, H_5), 5.78 (m, 1 H, H_2), 5.84 (m, 1 H, H_3), 6.01 (s, 1 H), 6.02 (s, 1 H), 6.72 (s, 1 H), 7.4−8.1 (m, 6 H). IR ($CHCl_3$) 1710, 1640 cm^{-1}. ^{13}C NMR ($CDCl_3$) 165.91, 163.03, 150.58, 146.74, 143.85, 135.52, 133.19, 130.07, 129.65, 128.40, 126.03, 117.51, 108.80, 108.73, 103.57, 103.50, 101.63, 68.34, 60.58, 43.53, 35.94, 29.15, 28.59. CIMS *m/z* (rel intensity) 390 (M^+ + 1, 2), 268 (6), 266 (28), 123 (100). Anal. Calcd for $C_{23}H_{19}NO_5 \cdot 0.5\ H_2O$: C, 69.34, H. 5.06, N, 3.52. Found: C, 69.72; H, 4.90; N, 3.40.

(±)-1-Deoxylycorine (2a). (±)-1-Deoxylycorin-7-one (10 mg, 0.04 mmol) was dissolved in CH_2Cl_2 (1 mL), and 4-(dimethylamino)pyridine (1 mg, 0.008 mmol), triethylamine (4 mg, 0.04 mmol), and acetic anhydride (4 mg, 0.04 mmol) were added. The solution was stirred at room temperature for 1 h and was washed with 10% HCl followed by $NaHCO_3$ (sat). The organic phase was dried (Na_2SO_4) and the solvent was evaporated. Flash chromatography (EtOAc/hexanes, 1:4 then 1:1) afforded (±)-**23a** as a colorless solid (12 mg, 91%). A solution of (±)-**23a** (11 mg, 0.034 mmol), $LiAlH_4$ (13 mg, 0.34 mmol), and THF (2 mL) was refluxed for 3 h and then quenched by sequential dropwise addition of H_2O (0.013 mL), 15% NaOH (0.013 mL), and H_2O (0.039 mL). Filtration of the mixture followed by flash chromatography of the concentrated filtrate (10% MeOH/EtOAc) afforded (±)-1-deoxylycorine (**2a**) (7 mg, 76%) as a colorless solid, mp 153 °C.

(+)-1-Deoxylycorine (2a). A solution of acetate **23a** (15 mg, 0.046 mmol), $LiAlH_4$ (15 mg, 0.39 mmol), and THF (1 mL) was refluxed for 3 h and then quenched by sequential dropwise addition of H_2O (0.015 mL), 15% NaOH (0.015 mL), and H_2O (0.045 mL). Filtration of the mixture followed by flash chromatography of the concentrated filtrate (10% MeOH/EtOAc) afforded (+)-1-deoxylycorine (**2a**) (9 mg, 73%) as a colorless solid, which was recrystallized from $CH_2Cl_2/CHCl_3/$hexanes. Mp 155 °C; $[\alpha]^{25}_{D}$ +48° (*c* 0.46, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.64 (ddd, J = 4.9, 13.4, 13.4 Hz, 1 H, H_{1ax}), 2.35 (m, 2 H, H_{15}), 2.44 (d, J = 13.9 Hz, 1 H, H_{1eq}), 2.58 (m, 2 H), 2.63 (m, 1 H, H_{15}), 3.32 (m, 1 H), 3.53 (d, J = 14.1 Hz, 1 H, H_7), 4.14 (d, J = 13.9 Hz, 1 H, H_7), 4.41 (s, 1 H, H_2), 5.56 (s, 1 H, H_3), 5.92 (s, 1 H), 5.93 (s, 1 H), 6.57 (s, 1 H), 6.75 (s, 1 H). ^{13}C NMR ($CDCl_3$) 146.38, 145.95, 143.93, 130.99, 128.69, 119.73, 107.14, 105.14, 100.88, 67.43, 66.30, 56.84, 53.63, 34.87, 34.00, 28.62. IR ($CHCl_3$) 3600 cm^{-1}. CIMS *m/z* (rel intensity) 272 (M^+ + 1, 100), 254 (90).

Alternate Procedure. A solution of benzoate **23b** (20 mg, 0.05 mmol), $LiAlH_4$ (12 mg, 0.31 mmol), and THF (1 mL) was refluxed for 3 h and then quenched by sequential dropwise addition of H_2O (0.012 mL), 15% NaOH (0.012 mL) and H_2O (0.036 mL). Filtration of the mixture followed by flash chromatography of the concentrated filtrate (10% MeOH/EtOAc) afforded (+)-1-deoxylycorine (**2a**) (10.2 mg, 76%).

(+)-2-*epi*-1-Deoxylycorine (24). A solution of alcohol **22** (143 mg, 0.502 mmol), $LiAlH_4$ (0.19 g, 5.0 mmol), and THF (25 mL) was refluxed for 6 h and then quenched by sequential dropwise addition of H_2O (0.19 mL), 15% NaOH (0.19 mL), and H_2O (0.57 mL). Filtration of the mixture followed by flash chromatography of the concentrated filtrate (10% MeOH/EtOAc) afforded (+)-2-*epi*-1-deoxylycorine **24** (105 mg, 77%) as a colorless solid. Mp 60−64 °C; $[\alpha]^{23}_{D}$ +105° (*c* 0.21, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ 1.41 (ddd, J = 9.1, 12.2, 12.2 Hz, 1 H, H_{1ax}), 2.43 (m, 1 H), 2.60 (m, 4 H, H_{15}), 2.73 (m, 1 H, H_{1eq}), 3.26 (m, 1 H), 3.56 (d, J = 14.1 Hz, 1 H, H_7), 4.08 (d, J = 13.9 Hz, 1 H, H_7), 4.64 (m, 1 H, H_2), 5.52 (s, 1 H, H_3), 5.92 (d, J = 1.2 Hz, 1 H), 5.93 (d, J = 1.5 Hz, 1 H), 6.57 (s, 1 H), 6.73 (s, 1 H). IR ($CHCl_3$) 3600 cm^{-1}. ^{13}C NMR ($CDCl_3$) 146.28, 145.87, 142.91, 130.56, 128.53, 121.28, 107.12, 104.89, 100.80, 69.59, 66.90, 56.63, 53.65, 39.82, 34.59, 28.30. CIMS *m/z* (rel intensity) 272 (M^+ + 1, 50), 254 (100).

(+)-1-Deoxylycorin-2-one (25). A solution of alcohol **24** (104 mg, 0.38 mmol), MnO_2 (330 mg, 3.80 mmol), and $CHCl_3$ (25 mL) was stirred at room temperature for 6 h. The mixture was filtered through Celite, and the filtrate was concentrated and chromatographed (EtOAc) to give enone **25** as a colorless solid (65 mg, 63%). Mp 157−8 °C (dec); $[\alpha]^{24}_{D}$ +164° (*c* 0.33, dioxane). Reported for (−)-**25**: mp 157−8 °C; $[\alpha]_{D}^{24}$ −169° (*c* 0.490, dioxane).[29] ^{1}H NMR ($CDCl_3$) δ 2.28 (dd, J = 13.5, 16.4 Hz, 1 H, H_{1ax}), 2.53 (dd, J = 8.5, 17.1 Hz, 1 H, H_4), 2.84 (m, 3 H, H_{16}, H_4, H_5), 3.05 (dd, J = 4.4, 16.6 Hz, 1 H, H_{1eq}), 3.12 (m, 1 H, H_{15}), 3.43 (m, 1 H, H_5), 3.63 (d, J = 13.9 Hz, 1 H, H_7), 4.18 (d, J = 13.9 Hz, 1 H, H_7), 5.94 (s, 1 H), 5.94 (s, 1 H), 5.97 (m, 1 H, H_3), 6.59 (s, 1 H), 6.64 (s, 1 H). ^{13}C NMR ($CDCl_3$) 198.63, 167.73, 146.47, 146.31, 129.48, 128.06, 122.14, 107.09, 104.90, 100.97, 67.28, 56.19, 53.20, 40.40, 39.97, 29.70. IR ($CHCl_3$) 1655 cm^{-1}.

Alternate Procedure. A solution of (+)-1-deoxylycorine (**2a**) (4.0 mg, 0.015 mmol), MnO_2 (13 mg, 0.15 mmol), and $CHCl_3$ (2 mL) was stirred at room temperature for 6 h. The mixture was filtered through Celite, and the filtrate was concentrated and chromatographed (EtOAc) to give enone **25** as a colorless solid (2.6 mg, 63%). Mp 157−8 °C.

Reduction of (+)-1-Deoxylycorin-2-one (25). A solution of enone **25** (4 mg, 0.015 mmol), $NaBH_4$ (2 mg, 0.053 mmol), and EtOH (2 mL) were stirred at room temperature for 30 min. The reaction was quenched by dropwise addition of NH_4Cl (saturated), concentrated in vacuo, diluted with $NaHCO_3$ (5 mL, saturated), and extracted with CH_2Cl_2 (5 × 2 mL). The combined organic phase was dried (Na_2SO_4), concentrated, and chromatographed (10% MeOH/EtOAc) to give (+)-

2-*epi*-1-deoxylycorine (**24**) and **2a** as a 10:1 mixture of diastereomers by 500 MHz ^{1}H NMR (3 mg, 75%). Mp 98 °C.

(2*R*,3S,12S,15*R*,16*R*)-3-Hydroxy-7-keto-9,10-[methylenebis(oxy)]-galanthan-12,2-carbolactone (28). A solution of acid **21a** (5 mg, 0.02 mmol) and water (10 mL) was refluxed for 5 h. The solution was cooled to room temperature and extracted with CH_2Cl_2 (5×). The organic phase was dried (Na_2SO_4) and concentrated to afford lactone **28** as a colorless solid (4 mg, 80%). Mp 144 °C. ^{1}H NMR ($CDCl_3$) δ 2.09 (dd, J = 12.7, 15.1 Hz, 1 H, H_{1ax}), 2.38 (m, 1 H, H_4), 2.61 (m, 2 H, H_4, H_{1eq}), 3.21 (ddd, J = 6.8, 13.2, 13.2 Hz, 1 H, H_{15}), 3.67 (d, J = 13.7 Hz, 1 H, H_{16}), 3.82 (m, 1 H, H_5), 3.92 (m, 1 H, H_5), 4.71 (s, 1 H, H_3), 4.88 (d, J = 5.9 Hz, 1 H, H_2), 6.02 (s, 2 H), 6.53 (s, 1 H), 7.48 (s, 1 H). IR (film) 3350, 1775, 1625 cm^{-1}. CIMS *m*/*z* (rel intensity) 330 (M$^+$ + 1, 68), 286 (30), 156 (100).

(15*R*,16*R*)-2-(*tert*-Butyldimethylsilyloxy)-2,3,4,12-tetrahydro-9,10-[methylenebis(oxy)]galanthan (29). To a solution of enone **25** (20 mg, 0.07 mmol), triethylamine (0.24 g, 2.4 mmol), and CH_2Cl_2 (5 mL) was added *tert*-butyldimethylsilyl triflate (0.26 g, 1.2 mmol) at 0 °C. The reaction was allowed to warm and stirred for 1 h at room temperature. The solvent was evaporated, and the residue was partitioned between Et_2O and $NaHCO_3$ (aq). The aqueous layer was extracted (3×) with Et_2O, and the combined organic phase was dried (Na_2SO_4). Evaporation of the solvent and flash chromatography (EtOAc) of the residue afforded enol ether **29** (26 mg, 93%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.22 (s, 3 H), 0.21 (s, 3 H), 0.96 (s, 9 H), 2.40 (dd, J = 12.7, 15.2 Hz, 1 H, H_{1ax}), 2.67 (dd, J = 16.8, 5.1 Hz, 1 H, H_{1eq}), 2.90 (ddd, J = 5.1, 11.5, 11.5 Hz, 1 H, H_{15}), 3.14 (m, 1 H, H_{16}), 3.66 (m, 1 H), 3.83 (d, J = 13.4 Hz, 1 H), 3.89 (d, J = 13.4 Hz, 1 H, H_7), 3.97 (d, J = 13.2 Hz, 1 H, H_7), 5.31 (s, 1 H, H_4), 5.61 (d, J = 5.31 Hz, 1 H, H_4), 5.61 (d, J = 1.7 Hz, 1 H, H_3), 5.92 (s, 1 H), 5.93 (s, 1 H), 6.65 (s, 1 H), 6.68 (s, 1 H).

Alternate Procedure. A flask was cooled to −78 °C and charged with $NaN(SiMe_3)_2$ (1 *M* in THF; 0.1 mL). Enone **25** (8 mg, 0.03 mmol) was dissolved in THF (1 mL) and added to the flask via syringe. The reaction stirred at −78 °C for 10 min, and then a solution of TBDMSCl (7 mg, 0.05 mmol) in THF (1 mL) was rapidly added. The reaction was allowed to warm to room temperature and was quenched with NH_4Cl (saturated). The solvent was evaporated, and the mixture was partitioned between CH_2Cl_2 and $NaHCO_3$ (saturated), and the aqueous layer was extracted with CH_2Cl_2 (3×). The combined organic phase was dried (Na_2SO_4) and concentrated. ^{1}H NMR (500 MHz) analysis of the crude reaction mixture showed enol ether **29** as the only product.

(2*S*,3*S*,12*S*,15*R*,16*R*)-2-Phenylseleno-3-hydroxy-12-(benzyloxycarbonyl)-9,10-[methylenebis(oxy)]galanthan-7-one (30). Epoxide **12** (50 mg, 0.1 mmol) was stirred as a suspension in absolute EtOH (25 mL). Diphenyldiselenide (93 mg, 0.30 mmol) was added in one portion, and stirring continued for 15 min at room temperature. Sodium borohydride (23 mg, 0.61 mmol) was added slowly [CAUTION, exothermic], and the mixture was stirred for 1 h at room temperature. The reaction was quenched with NH_4Cl (aq), and the EtOH was evaporated. The aqueous layer was extracted with CH_2Cl_2 (3×) and the combined organic phase was dried (Na_2SO_4). Evaporation of the solvent and flash chromatography (EtOAc/hexanes, 1:3) afforded selenide **30** as a colorless solid (64 mg, 93%). Mp 124 °C. ^{1}H NMR ($CDCl_3$) δ 1.88 (ddd, J = 8.3, 10.7, 11.9 Hz, 1 H), 2.38 (m, 1 H, H_{1ax}), 2.59 (m, 1 H, H_{1eq}), 2.71 (ddd, J = 5.8, 13.1, 13.1 Hz, 1 H, H_{15}), 3.05 (dd, J = 5.4, 13 Hz, 1 H), 3.23 (ddd, J = 5.6, 12.2, 12.2 Hz, 1 H), 3.87 (m, 1 H, H_2), 3.95 (d, J = 13.5 Hz, 1 H, H_{16}), 4.15 (dd, J = 7.5, 11.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$) 172.59, 161.83, 150.64, 146.74, 135.64, 135.52, 135.18, 129.41, 128.66, 128.46, 128.11, 126.28, 124.46, 108.39, 103.93, 101.61, 75.97, 67.51, 64.07, 57.50, 44.47, 43.54, 35.61, 34.44, 30.86. IR ($CHCl_3$) 3450, 1720, 1640 cm^{-1}. CIMS *m*/*z* (rel intensity) 578 (M$^+$ + 1, 1), 420 (2), 330 (4), 286 (8), 315 (17), 313 (15), 213 (16), 215 (15), 159 (30). Anal. Calcd for $C_{30}H_{27}NO_6Se$: C, 62.50; H, 4.72; N, 2.43. Found: C, 62.53; H, 5.09; N, 2.32.

(1*S*,2*S*,3*S*,12*S*,15*R*,16*R*)-1,2-Epoxy-3-hydroxy-12-(benzyloxycarbonyl)-9,10-[methylenebis(oxy)]galanthan-7-one (31). A solution of selenide **30** (91 mg, 1.6 mmol), THF (50 mL), and 30% H_2O_2 (17 mL) was stirred at room temperature for 2 h. The solution was concentrated and partitioned between H_2O and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2 (3×) and the combined organic phase was dried (Na_2SO_4). Concentration and flash chromatography afforded epoxide **31** as a colorless solid (45 mg, 67%). ^{1}H NMR ($CDCl_3$) δ 1.87 (ddd, J = 8.3, 12.4, 12.4 Hz, 1 H), 2.63 (dd, J = 4.6, 14.4 Hz, H_{15}), 2.88 (dd, J = 5.6, 12.7 Hz, 1 H), 3.41 (ddd, J = 5.6, 11.7, 12 Hz, 1 H), 3.46 (m, 2 H, H_3, H_2), 3.78 (d, J = 3.4 Hz, 1 H, H_1), 4.12 (d, J = 14.4 Hz), 4.19 (dd, J = 7.8, 11.7 Hz, 1 H), 5.18 (d, J = 12.4 Hz, 1 H), 5.23 (d, J = 12.2 Hz), 6.03 (s, 2 H), 6.92 (s, 1 H), 7.31 (m, 5 H), 7.45 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ 173.19, 161.54, 151.04, 147.39, 134.95, 133.06, 128.74, 128.61, 128.19, 124.24, 108.69, 105.13, 101.89, 78.36, 67.72, 64.74, 59.68, 57.43, 52.41, 45.85, 41.82, 34.19. IR ($CHCl_3$) 3370, 1725, 1645, 1260 cm^{-1}.

(3*R*,12*S*,15*R*,16*R*)-1,2-Didehydro-3-hydroxy-12-(benzyloxycarbonyl)-9,10-[methylenebis(oxy)]galanthan-7-one (32). To a solution of selenide **30** in THF/water (1.2:1, 25 mL) was added sodium periodate (0.47 g, 0.22 mmol), and the mixture was stirred at room temperature for 12 h. The THF was evaporated, and the aqueous remains were extracted with CH_2Cl_2 (3×). The combined organic phase was dried (Na_2SO_4), the solvent evaporated, and flash chromatography (EtOAc/hexanes, 1:3, then EtOAc) of the residue afforded alcohol **32** as a light tan solid (40 mg, 87%). Mp 138−140 °C. ^{1}H NMR ($CDCl_3$) δ 2.10 (ddd, J = 8.3, 11.7, 11.7 Hz, 1 H, H_4), 2.76 (dd, J = 5.9, 12.9 Hz, 1 H, H_4), 3.36 (dd, J = 1.5, 12 Hz, 1 H, H_{15}), 3.54 (ddd, J = 5.9, 11.5, 11.5 Hz, 1 H, H_5), 3.79 (d, J = 12 Hz, 1 H, H_{16}), 4.25 (dd, J = 8.1, 11.7 Hz, 1 H, H_5), 4.30 (m, 1 H, H_2), 5.13 (d, J = 12.2 Hz, 1 H), 5.20 (d, J = 12.5 Hz, 1 H), 6.03 (s, 2 H), 6.26 (dt, J = 2.7, 9 Hz, 1 H), 6.31 (dt, J = 2.7, 9.5 Hz, 1 H), 6.31 (dt, J = 2.7, 9.5 Hz, 1 H), 6.88 (s, 1 H), 7.24−7.38 (m, 5 H), 7.53 (s, 1 H). ^{13}C NMR (1:9 $CD_3OD/CDCl_3$) 173.36, 162.25, 150.85, 146.82, 138.13, 135.15, 134.08, 128.42, 128.15, 127.80, 124.18, 123.23, 108.59, 104.13, 101.67, 75.48, 67.14, 65.22, 60.68, 45.35, 39.17, 34.08. IR ($CHCl_3$) 3400, 1710, 1640 cm^{-1}; CIMS (*m*/*z*) 420 (M$^+$ + 1, 13), 402 (2), 330 (2), 315 (1), 286 (5), 266 (14). FAB HRMS *m*/*z* 420.1439 (M + H)$^+$. Calcd for $C_{24}H_{22}NO_6$: 420.1447.

(1*R*,2*R*,3S,12*S*,15*R*,16*R*)-1,2-Epoxy-3-hydroxy-12-(benzyloxycarbonyl)-9,10-[methylenebis(oxy)]galanthan-7-one (33). To a stirred mixture of allylic alcohol **32** (4 mg, 0.01 mmol), urea hydrogen peroxide complex (10 mg, 0.1 mmol), and Na_2HPO_4 (13 mg, 0.09 mmol) in CH_2Cl_2 (2 mL) was added trifluoroacetic anhydride (6 mg, 0.03 mmol). The reaction was stirred 1.5 h and water was added. The aqueous layer was extracted with CH_2Cl_2 (3×) the combined organic phase was dried (Na_2SO_4), and the solvent evaporated. Flash chromatography (EtOAc) afforded epoxide **31** (1.6 mg, 40%) and epoxide **33** (1.8 mg, 45%) as colorless solids. Mp 128 °C. (**33**): ^{1}H NMR ($CDCl_3$) δ 2.27 (m, 1 H), 2.41 (dd, J = 6.6, 13.7 Hz, 1 H), 3.20 (d, J = 12.7 Hz, 1 H, H_{15}), 3.45 (ddd, J = 6.6, 11.7, 11.7 Hz, 1 H), 3.61 (d, J = 4.7 Hz, 1 H), 3.80 (d, J = 4.7 Hz, 1 H), 4.09 (d, J = 12.9 Hz, 1 H, H_{16}), 4.08 (m, 1 H), 4.13 (m, 1 H, H_3), 5.09 (d, J = 12.2 Hz, 1 H), 5.31 (d, J = 12.2 Hz, 1 H), 6.04 (s, 2 H), 6.95 (s, 1 H), 7.24−7.38 (m, 5 H), 7.52 (s, 1 H). ^{13}C NMR ($CDCl_3$) 175.34, 162.13, 150.79, 147.21, 134.73, 133.22, 128.80, 128.72, 128.23, 125.01, 109.10, 103.12, 101.87, 76.45, 67.53, 61.05, 55.11, 53.15, 48.38, 43.75, 38.11, 35.94. IR ($CHCl_3$) 3450, 1705, 1640, 1275 cm^{-1}. CIMS *m*/*z* (rel intensity) 436 (M$^+$ + 1, 2), 420 (1), 374 (4), 343 (1), 137 (4), 107 (25), 91 (100). Anal. Calcd for $C_{24}H_{21}NO_7$: C, 66.20; H, 4.86; N, 3.22. Found: C, 66.02; H, 5.57; N, 2.81.

(3*R*,12*S*,15*R*,16*R*)-1,2-Didehydro-3-acetyloxy-12-(benzyloxycarbonyl)-9,10-[methylenebis(oxy)]galanthan-7-one (34). Alcohol **32** (35 mg, 0.084 mmol) was dissolved in CH_2Cl_2 (10 mL), and 4-(dimethylamino)pyridine (1 mg, 0.008 mmol), triethylamine (29 mg, 0.25 mmol), and acetic anhydride (22 mg, 0.17 mmol) were added. The solution was stirred at room temperature for 1 h and was washed with 10% HCl followed by $NaHCO_3$ (saturated). The organic phase was dried (Na_2SO_4), and the solvent was evaporated. Flash chromatography (EtOAc/hexanes, 1:4 then 1:1) afforded acetate **34** as a colorless solid (36 mg, 92%). Mp 133−7 °C. ^{1}H NMR ($CDCl_3$) δ 1.88 (s, 3 H), 1.98 (ddd, J = 7.5, 12.5, 12.5 Hz, 1 H, H_4), 2.93 (dd, J = 5.5, 13 Hz, 1 H, H_4), 3.27 (ddd, J = 5.5, 12, 12 Hz, 1 H, H_5), 3.39 (dd, J = 1.5, 12 Hz, H_{15}), 3.96 (d, J = 12 Hz, 1 H, H_{16}), 4.21 (dd, J = 7.5, 11.5 Hz, 1 H, H_5), 5.07 (d, J = 12 Hz, 1 H), 5.25 (d, J = 12 Hz, 1 H), 5.43 (m, 1 H, H_3), 6.02 (s, 2 H), 6.08 (dt, J = 2.5, 9.5 Hz, 1 H), 6.36 (dt, J = 3, 9.5 Hz, 1 H), 6.90 (s, 1 H), 7.2−7.4 (m, 5 H), 7.50 (s, 1 H). ^{13}C NMR ($CDCl_3$) 171.34, 169.99, 161.70, 150.82, 147.02, 135.34, 133.63, 133.48, 128.56, 128.42, 128.31, 125.04, 124.85, 109.04, 104.15, 101.74, 75.69, 67.36, 64.56, 59.60, 45.24, 39.56, 34.29, 20.54. IR ($CHCl_3$) 1740, 1730, 1640 cm^{-1}. CIMS *m*/*z* (rel intensity)

462 (M^+ + 1, 13), 266 (23), 223 (3), 191 (13), 177 (10), 123 (20). Anal. Calcd for $C_{26}H_{23}NO_7$. C, 67.67; H, 5.02; N, 3.04. Found: C, 66.76; H, 5.01; N, 2.98.

(1*S*,12*R*,15*R*,16*R*)-1-Acetyloxy-2,3-didehydro-12-(benzyloxycarbonyl)-9,10-[methylenebis(oxy)]galanthan-7-one (35). Alcohol **33** (10 mg, 0.02 mmol) was dissolved in glacial AcOH (2 mL) and heated to 50 °C. A solution of acetic anhydride (2 mL) and H_2SO_4 (4 drops) was added dropwise and heating continued for 15 min. The solution was neutralized with $NaHCO_3$ (saturated) and extracted with CH_2Cl_2 (3×). The solvent was dried (Na_2SO_4) and evaporated, and the residue was passed through a short column of silica gel (EtOAc/hexanes, 1:1) to remove polar impurities. Radial chromatography (EtOAc/hexanes, 2:3) afforded the acetate **35** (3.1 mg, 34%) as a colorless solid. ^{1}H NMR ($CDCl_3$) δ 1.87 (s, 3 H), 1.93 (ddd, J = 12.5, 12.5, 7.8 Hz, 1 H), 2.61 (dd, J = 5.4, 12.7 Hz, 1 H), 2.97 (dd, J = 2.7, 13.2 Hz, 1 H, H_{15}), 3.32 (ddd, J = 5.1, 11.9, 11.9 Hz, 1 H), 4.17 (dd, J = 7.6, 12 Hz, 1 H), 4.69 (d, J = 13.2 Hz, 1 H, H_{16}), 5.14 (d, J = 12.4 Hz, 1 H), 5.25 (d, J = 12.2 Hz, 1 H), 5.59 (dd, J = 2.9, 6.1 Hz, 1 H, H_1), 6.01 (d, J = 1.5 Hz, 1 H), 6.02 (d, J = 1.5 Hz, 1 H), 6.16 (d, J = 9.8 Hz, 1 H, H_3), 6.32 (dd, J = 6.1, 9.8 Hz, 1 H, H_2), 6.55 (s, 1 H), 7.3−7.4 (m, 5 H), 7.50 (s, 1 H). ^{13}C NMR ($CDCl_3$) 172.42, 170.68, 162.10, 150.75, 147.00, 135.23, 132.54, 131.68, 128.69, 128.56, 128.08, 126.46, 125.23, 108.86, 103.93, 101.66, 67.71, 62.40, 57.08, 54.90, 44.26, 40.92, 34.55, 20.64. IR (CH_2Cl_2) 1730, 1640 cm^{-1}. CIMS m/z (rel intensity) 462 (M^+ + 1, 50), 404 (25), 314 (20), 268 (100). FAB HRMS m/z 462.1543 (M + H)$^+$. Calcd for $C_{26}H_{24}NO_7$: 462.1553.

(1*R*,2*R*,3*R*,12*S*,15*R*,16*R*)-1-Acetyloxy-2,3-epoxy-12-(benzyloxycarbonyl)-9,10-[methylenebis(oxy)]galanthan-7-one (36a). Acetate **35** (13 mg, 0.028 mmol) was added to a solution of dimethyldioxirane in acetone (11 mL, 0.1 *M*), and the reaction was stirred at 0 °C for 96 h. The solution was concentrated and passed through a short column of silica gel (EtOAc/hexanes, 1:1). Radial chromatography (ethyl acetate/hexanes, 1:1) afforded epoxide **36a** as a colorless solid (6.0 mg, 46%). Recovered acetate **35** was resubjected to epoxidation to provide an additional 2.5 mg (19%) of epoxide **36a**. Mp 110−112 °C. ^{1}H NMR ($CDCl_3$) δ 1.88 (s, 3 H), 2.31 (ddd, J = 8.3, 12.7, 12.7 Hz, 1 H), 2.52 (dd, J = 5.7, 12.7 Hz, 1 H), 3.26 (dd, J = 2.2, 13 Hz, 1 H, H_{15}), 3.40 (ddd, J = 5.9, 12.2, 12.2 Hz, 1 H), 3.63 (m, 2 H, H_2, H_3), 4.13 (dd, J = 8, 12.2 Hz, 1 H), 4.23 (d, J = 13.2 Hz, 1 H, H_{16}), 5.21 (d, J = 12.2 Hz, 1 H), 5.25 (d, J = 12.2 Hz, 1 H), 5.97 (dd, J = 2.5, 2.4 Hz, 1 H, H_1), 6.00 (s, 1 H), 6.01 (s, 1 H), 6.53 (s, 1 H), 7.3−7.4 (m, 5 H), 7.48 (s, 1 H). IR ($CHCL_3$) 1723, 1642 cm^{-1}. ^{13}C NMR ($CDCl_3$) 172.34, 170.63, 161.87, 150.81, 146.98, 134.97, 132.36, 128.81, 128.77, 128.28, 125.50, 108.94, 103.25, 101.70, 67.87, 64.68, 57.12, 54.12, 52.60, 51.30, 43.68, 36.62, 31.88, 20.52. CIMS m/z (rel intensity) 478 (M^+ + 1, 0.5), 452 (0.5), 266 (3). FAB HRMS m/z 478.1491 (M + H)$^+$. Calcd for $C_{26}H_{24}NO_8$: 478.1501.

(1*R*,2*R*,3*R*,12*S*,15*R*,16*R*)-1-Acetyloxy-2,3-epoxy-12-hydroxycarbonyl-9,10-[methylenebis(oxy)]galanthan-7-one (36b). Benzyl ester **36a** (6 mg, 0.01 mmol), absolute EtOH (1 mL), and 10% Pd/C (2 mg) were stirred under 1 atm of H_2 for 2 h. The mixture was filtered through Celite, the retained solid was rinsed with CH_2Cl_2, and the combined solvent was evaporated to provide acid **36b** as a colorless solid (3.5 mg, 90%). Mp 225 °C (dec). ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3 H), 2.33 (m, 1 H), 2.53 (m, 1 H), 3.26 (d, J = 13.2 Hz, 1 H, H_{15}), 3.43 (m, 1 H), 3.65 (dd, J = 3.1, 3.0 Hz, 1 H, H_2), 3.72 (d, J = 3.1 Hz, 1 H, H_3), 4.09 (m, 1 H), 4.31 (d, J = 13.1 Hz, 1 H, H_{16}), 5.98 (m, 1 H, H_1), 6.00 (m, 2 H), 6.55 (s, 1 H), 7.41 (s, 1 H). IR (CH_2Cl_2) 3500, 1727, 1640 cm^{-1}. CIMS m/z (rel intensity) 388 (M^+ + 1, 2), 344 (65), 284 (25), 266 (65).

(1*R*,2*R*,15*R*,16*R*)-1-Acetyloxy-2-hydroxy-3,12-didehydro-9,10-[methylenebis(oxy)]galanthan-7-one (37). A solution of carboxylic acid **36b** (13 mg, 0.034 mmol), benzene (10 mL) *tert*-butyl thiol (0.2 mL), and acridine (12 mg, 0.068 mmol) in a 25 mL Pyrex flask was degassed (N_2) for 5 min and then irradiated (300 nm) for 105 min. The flask was 6 inches from the light source and the contents were stirred during the irradiation. The benzene was evaporated, and the residue was dissolved in CH_2Cl_2 and washed with 10% HCl. The organic phase was dried (Na_2SO_4) and concentrated. Flash chromatography (EtOAc) afforded alcohol **37** (6 mg, 50%) as a colorless solid; mp 236 °C (dec). The remaining material was judged to be decomposition material by 500 MHz ^{1}H NMR analysis of the crude reaction mixture. $[\alpha]^{23}_D$ +130° (c 0.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 3 H), 2.81 (m, 2 H), 3.02 (dd, J = 1, 12.4 Hz, 1 H, H_{15}), 3.80 (m, 2 H), 4.19 (d, J = 12.3 Hz, 1 H, H_{16}), 4.31 (m, 1 H, H_2), 5.62 (m, 1 H, H_1), 5.66 (m, 1 H, H_3), 6.01 (s, 1 H), 6.02 (s, 1 H), 6.60 (s, 1 H), 7.55 (s, 1 H). ^{13}C NMR ($CDCl_3$) 170.62, 162.72, 150.79, 147.01, 141.99, 132.38, 128.24, 118.68, 108.94, 103.38, 101.73, 70.66, 69.39, 55.34, 43.60, 39.40, 28.52, 20.93. IR ($CHCl_3$) 3590, 1730, 1643 cm^{-1}. CIMS m/z (rel intensity) 344 (M^+ + 1, 100), 284 (50), 266 (44). CI HRMS m/z 344.1128 (M^+ + 1) calcd for $C_{18}H_{18}NO_6$: 344.1134.

(1*R*,2*R*,15*R*,16*R*)-1,2-Bis(acetyloxy)-3,12-didehydro-9,10-[methylenebis(oxy)]galanthan-7-one (38). A solution of alcohol **37** (2.0 mg, 0.0058 mmol), acetic anhydride (3 mg, 0.029 mmol), triethylamine (3 mg, 0.029 mmol), and CH_2Cl_2 (2 mL) were stirred at room temperature for 3 h. The mixture was washed with 10% HCl followed by $NaHCO_3$ (saturated). The organic layer was dried (Na_2SO_4) and concentrated, and flash chromatography afforded diacetate **38** (2.2 mg, 100%) as a colorless solid. Mp 114 °C. $[\alpha]^{23}_D$ −27° (c 0.22, CH_2Cl_2). Reported: mp 114 °C.[44] ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 3 H), 2.10 (s, 3 H), 2.82 (m, 2 H), 3.06 (ddd, J = 12.4, 2.2, 1.3 Hz, 1 H, H_{15}), 3.81 (m, 2 H), 4.24 (d, J = 12.5 Hz, 1 H, H_{16}), 5.29 (m, 1 H, H_2), 5.63 (m, 1 H, H_3), 5.76 (m, 1 H, H_1), 6.02 (m, 2 H), 6.69 (s, 1 H), 7.57 (s, 1 H). ^{13}C NMR ($CDCl_3$) 169.86, 169.52, 162.60, 150.83, 147.10, 143.70, 131.88, 126.38, 115.46, 109.04, 103.55, 101.75, 70.22, 67.37, 55.17, 43.54, 40.46, 28.58, 21.01, 20.84. IR ($CHCl_3$) 1735, 1643 cm^{-1}. CIMS m/z (rel intensity) 386 (M^+ + 1, 96), 326 (32), 266 (100).

(+)-Lycorine (2b) and Its Diacetate. Alcohol **38** (5 mg, 0.01 mmol), $LiAlH_4$ (30 mg, 0.8 mmol), and THF (3 mL) were refluxed 4 h. Dropwise addition of H_2O (0.03 mL), 15% NaOH (0.03 mL), and H_2O (0.09 mL) followed by filtration and concentration afforded (+)-lycorine (**2b**) (3 mg, 70%). R_f 0.5 EtOAc/CH_2Cl_2/MeOH (2:2:1). Reported: R_f 0.35 EtOAc/CH_2Cl_2/MeOH (2:2:1). ^{1}H NMR (DMSO-d_6) 2.22 (m, 1 H), 2.44 (m, 1 H), 2.60 (m, 1 H), 3.19 (m, 1 H), 3.32 (d, J = 11.5 Hz, 1 H), 3.97 (m, 1 H), 4.02 (d, J = 14.2 Hz, 1 H), 4.27 (m, 1 H), 4.79 (m, 1 H), 4.89 (m, 1 H), 5.37 (m, 1 H), 5.94 (s, 1 H), 5.96 (s, 1 H), 6.68 (s, 1 H), 6.81 (s, 1 H). (+)-Lycorine (**2b**) in DMSO-d_6 (0.5 mL), acetic anhydride (0.5 mL), CH_2Cl_2 (2 mL), and 4-(dimethylamino)pyridine (2 mg, 0.02 mmol) was stirred at room temperature for 3 h. $NaHCO_3$ (saturated) was added and stirred for 30 min. The mixture was partitioned and the organic layer was washed with water (5×). The organic layer was dried (Na_2SO_4) and concentrated, and flash chromatography (EtOAc/hexane; 1:1 then 1:0) afforded lycorine diacetate (2 mg, 54%) as a colorless solid. $[\alpha]_D^{23}$ −25° (c 0.16, $CHCl_3$), mp 207−209 °C (dec). Reported mp 207−13 °C.[44a] ^{1}H NMR ($CDCl_3$) δ 1.95 (s, 3 H), 2.08 (s, 3 H), 2.42 (dd, J = 9, 17.6 Hz, 1 H), 2.66 (m, 2 H), 2.79 (d, J = 11.4 Hz, 1 H, H_{16}), 2.88 (d, J = 10.3 Hz, 1 H, H_{15}), 3.38 (m, 1 H), 3.54 (d, J = 14.1 Hz, 1 H, H_7), 4.17 (d, J = 13.9 Hz, 1 H, H_7), 5.25 (m, 1 H, H_2), 5.53 (m, 1 H, H_3), 5.74 (m, 1 H, H_1), 5.92 (s, 2 H), 6.58 (s, 1 H), 6.75 (s, 1 H). IR ($CHCl_3$) 1735 cm^{-1}; CIMS m/z (rel intensity) 372 (M^+ + 1, 18), 312 (52), 252 (100).

Lycorine Diacetate from Natural (−)-Lycorine. (−)-Lycorine (**1**) (4 mg, 0.014 mmol) in DMSO (0.5 mL), acetic anhydride (0.5 mL), CH_2Cl_2 (2 mL), and 4-(dimethylamino)pyridine (2 mg, 0.02 mmol) was stirred at room temperature for 3 h. $NaHCO_3$ (saturated) was added and stirred for 30 min. The mixture was partitioned, and the organic layer was washed with water (5×). The organic layer was dried (Na_2SO_4) and concentrated, and flash chromatography (EtOAc/hexane; 1:1 then 1:0) afforded lycorine diacetate (4 mg, 80%) as a colorless solid. $[\alpha]_D^{23}$ +25.6° (c 0.39, $CHCl_3$), mp 207−209 °C (dec).

Acknowledgment. This work was supported by the National Institutes of Health (GM 26568). We thank Professor Kurt Torssell for a sample of (±)-1-deoxylycorine-7-one, Professor George Pettit for a sample of (−)-lycorine together with ^{1}H and ^{13}C NMR spectra, and Degussa AG for a generous gift of L-proline.

Supporting Information Available: Procedures for preparation of *rac*-**9** and a description of the enantiomer assay for (−)-**9** (6 pages). See any current masthead page for ordering and Internet access instructions.

JA9606440