Electrocyclic Ring-Opening/π-Allyl Cation Cyclization Reaction Sequences Involving *gem*-Dihalocyclopropanes as Substrates: Application to Syntheses of (±)-, (+)-, and (−)-γ-Lycorane

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The readily prepared *gem*-dibromocyclopropanes (±)-**13** and (±)-**19** each engage in a silver(I)-promoted electrocyclic ring-opening/π-allyl cation cyclization sequence to deliver the hexahydroindole (±)-**20**, which participates in a Suzuki cross-coupling reaction with arylboronic acid **3** to give the tetracyclic compound (±)-**21**. Catalytic hydrogenation of this last compound proceeds in a completely stereoselective manner to give the saturated analogue (±)-**24**, which undergoes Bischler-Napieralski cyclization on reaction with phosphorus oxychloride. The resulting lactam (±)-**25** is then reduced with lithium aluminum hydride to give (±)-γ-lycorane [(±)-**1**]. By using (−)-menthyl-derived carbamates **27** and **28**, this chemistry has been extended to the synthesis of the (+)- and (−)-modifications of the title compound.

Introduction

Many of the lycorine-type *Amaryllidaceae* alkaloids, which are characterized by the presence of the galanthan ring system,[1] display potentially useful biological properties including antiviral, insect antifeedant, and antineoplastic activity, while others are known to inhibit plant growth and/or disrupt the formation of peptide bonds during protein synthesis.[1] As a consequence of such features, considerable effort has been directed toward the total synthesis of these compounds.[1] Unlike many of its congeners, γ-lycorane (**1**), which was obtained in both enantiomeric forms by Kotera during his degradation studies[2] of lycorine, does not appear to possess any useful pharmacological properties. Nevertheless, it has been a popular synthetic target[3] primarily because its pentacyclic structure provides a means to demonstrate the utility of new synthetic strategies. The racemic modification of compound **1** has been prepared a number of times.[3] Mori has described[3e] an asymmetric synthesis of (+)-γ-lycorane, but the ee obtained in this case was only 46%. More recently Ishibashi and co-workers[3d] have exploited 1-arylethylamine-based chiral auxiliaries in developing a synthesis of (−)-γ-lycorane. It is against this background that we now report short and efficient syntheses of the (±)-, (+)-, and (−)-modifications of the title compound.[4] The work reported herein derives from a general program underway within our laboratories[5] that is designed to exploit electrocyclic ring-opening reactions of readily available halocyclopropanes for the purposes of natural product synthesis.

Our retrosynthetic analysis of the target molecule **1** is shown in Scheme 1 and involves, inter alia, disconnection at the C7−C7a bond, which would be established via Bischler-Napieralski cyclization of carbamate **2**. Compound **2** would, in turn, be constructed via installation of the C12a−C12b bond (lycorane numbering) using a Suzuki cross-coupling reaction between boronic acid **3** and hexahydroindole **4**. It was anticipated that intermediate **4** could be prepared by subjecting the *gem*-dibromocyclopropane **5** to silver(I)-promoted electrocyclic ring opening and intramolecular nucleophilic capture of the incipient π-allyl cation by the nitrogen of the tethered carbamate so as to give the target hexahydroindole.[6,7]

Establishing the required all-*cis* stereochemical relationship between the three mutually fused and saturated rings of γ-lycorane would rely on preferential formation of the *cis*-isomer of hexahydroindole **4** during the cyclization step just mentioned. As a consequence of establishing

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(3) For previous syntheses of γ-lycorane see: (a) Cassayre, J.; Zard, S. Z. *Synlett.* **1999**, 501−503. (b) Hoang-Cong, X.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2125−2126. (c) Cossy, J.; Tresnard, L.; Pardo, D. G. *Eur. J. Org. Chem*. **1999**, 1925−1933. (d) Ikeda, M.; Ohtani, S.; Sato, T.; Ishibashi, H. *Synthesis* **1998**, 1803−1806. (e) Yoshizaki, H.; Satoh, H.; Sato, Y.; Nukui, S.: Shibasaki, M.; Mori, M. *J. Org. Chem*. **1995**, *60*, 2016−2021. (f) Angle, S. R.; Boyce, J. P. *Tetrahedron Lett*. **1995**, *36*, 6185−6188. (g) Grothjahn, D. B.; Vollhardt, K. P. C. *Synthesis* **1993**, 579−605. (h) Pearson, W. H.; Schkeryantz, J. M. *J. Org. Chem*. **1992**, *57*, 6783−6789. (i) Bäckvall, J.-E.; Andersson, P. G.; Stone, G. B.; Gogoll, A. *J. Org. Chem*. **1991**, *56*, 2988−2993. (j) Sugiyama, N.; Narimiya, M.; Iida, H.; Kikuchi, T. *J. Heterocycl. Chem*. **1988**, *25*, 1455−1457. (k) Umezawa, B.; Hoshino, O.; Sawaki, S.; Sashida, H.: Mori, K.; Hamada, Y.; Kotera, K.; Iitaka, Y.; *Tetrahedron* **1984**, *40*, 1783−1790 and references therein. (l) Higashiyama, H.; Honda, T.; Otomasu, H.; Kametani, T. *Planta Med*. **1983**, *48*, 268−271. (m) Iida, H.; Yuasa, Y.; Kibayashi, C. *J. Org. Chem*. **1979**, *44*, 1074−1080.

(4) Aspects of this work have been described previously in communication form: Banwell, M. G.; Wu, A. W. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2671−2672.

(5) See: (a) Banwell, M. G.; Berak, M.; Hockless, D. C. R. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2217−2219. (b) Banwell, M. G.; Gable, R. W.; Peters, S. C.; Phyland, J. R. *J. Chem. Soc., Chem. Commun*. **1995**, 1395−1397. (c) Banwell, M. G.; Cowden, C. J.; Gable, R. W. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3515−3518. (d) Banwell, M. G.; Cowden, C. J. *Aust. J. Chem*. **1994**, *47*, 2235−2254. (e) Banwell, M. G.; Lambert, J. N.; Gulbis, J. M.; Mackay, M. F. *J. Chem. Soc., Chem. Commun*. **1990**, 1450−1452. (f) Banwell, M. G.; Onrust, R. *Tetrahedron Lett.* **1985**, *26*, 4543−4546.

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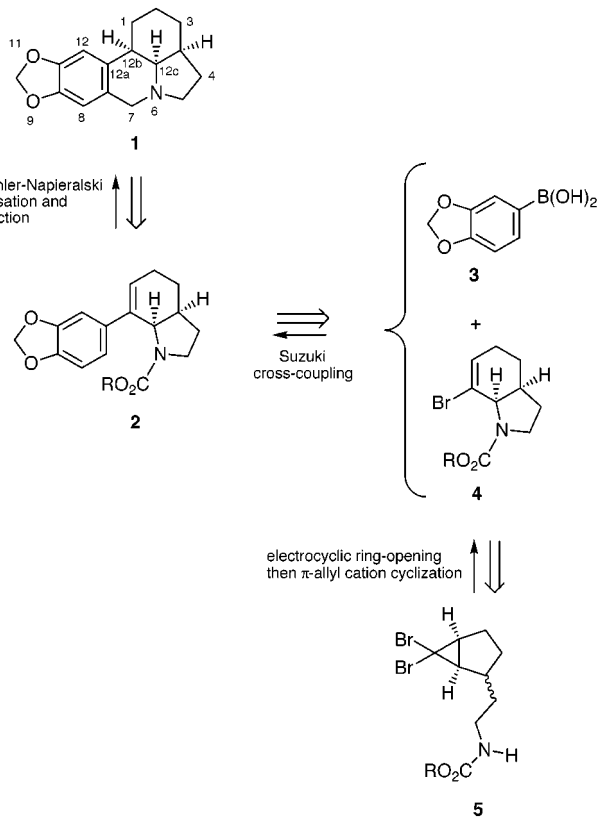
Scheme 1



the latter stereochemical feature, it was anticipated that hydrogenation of the derived 7-arylhexahydroindole **2** should proceed with the desired facial selectivity and thereby allow for installation of the correct (relative) stereochemistry at C12b. The successful implementation of this plan is outlined below.

Results and Discussion

Synthesis of (±)-γ-Lycorane. To establish whether the crucial π-allyl cation cyclization reaction **5** → **4** had any specific stereochemical requirements, both diastereoisomers represented by structure **5** were sought. The synthesis of a relevant congener, compound (±)-**13**, is outlined in Scheme 2 and starts with the commercially available carboxylic acid (±)-**6**. Thus, reduction of the latter compound to the corresponding and previously reported[8] alcohol (±)-**7** was achieved using lithium aluminum hydride. To reduce the possibility of O−H and C−H insertion reactions in the subsequent dibromocarbene addition reaction, compound (±)-**7** was converted into acetate (±)-**8**.

Reaction of compound (±)-**8** with dibromocarbene, generated from bromoform and aqueous sodium hydroxide with triethylbenzylammonium chloride (TEBAC) as phase-transfer catalyst,[9] gave an inseparable and ca. 3:1 mixture of compound (±)-**9** and its C2-epimer. The assignment of compound (±)-**9** as the major product of this reaction was based on the reasonable assumption that dibromocarbene would add, preferentially, to the less hindered face of the double bond within precursor (±)-**8**. Hydrolysis of the mixture of compound (±)-**9** and its C2-epimer was readily effected with potassium carbonate in methanol, and the ensuing alcohols [(±)-**10** and C2-*epi*-(±)-**10**] were converted into the corresponding mesylates, (±)-**11** and C2-*epi*-(±)-**11**, using conditions developed by Crossland and Servis.[10] The major mesylate was readily separated from its less abundant and unstable counterpart by flash chromatography. Reaction of compound (±)-**11** with sodium azide in DMF at 18 °C for 24 h then gave the azide (±)-**12**. Reduction of this latter material to the corresponding amine could be achieved under Staudinger conditions (triphenylphosphine/water) or, preferably, via hydrogenolysis using hydrogen with 10% Pd on C as catalyst. Since the product amine was a labile material, it was reacted in situ with methyl chloroformate. In this manner the target carbamate (±)-**13** was obtained as an oil and characterized by standard spectroscopic methods.

A stereoselective route to the C2-epimer of carbamate (±)-**13**, viz., compound (±)-**19**, is shown in Scheme 3 and starts with the allylic acetate (±)-**14**, which is readily prepared in large quantity from cyclopentadiene.[11] Thus, dibromocarbene addition to compound (±)-**14** afforded a ca. 4:1 mixture of the expected adducts (±)-**15** and C2-*epi*-(±)-**15**, which were hydrolyzed to the corresponding alcohols (±)-**16** and C2-*epi*-(±)-**16** with potassium hydroxide in methanol. Oxidation of the latter compounds with pyridinium chlorochromate (PCC)[12] then gave the previously reported ketone (±)-**17**,[13] which was reacted with the anion derived from diethyl cyanomethylphosphonate,[14] and in this manner a ca. 2:1 mixture of the (*E*)- and (*Z*)-isomers of α,β-unsaturated nitrile (±)-**18** was obtained. Subjection of this mixture to reaction with hydrogen in the presence of PtO_2 and chloroform[15] resulted in formation of the hydrochloride salt of the target amine. This material was immediately subjected to reaction with methyl chloroformate in the presence of pyridine, and the carbamate (±)-**19** was thereby obtained [ca. 32% overall yield from the starting alkene (±)-**14**]. Like isomer (±)-**13**, carbamate (±)-**19** was obtained as an oil and fully characterized by standard spectroscopic methods. While rigorous proof of the stereochemical relationship between the cyclopropane ring and the C2 side chain within this compound could not be obtained, it is reasonable to assume that hydrogenation of the

(6) For some earlier examples of cationic cyclizations initiated by electrocyclic cleavage of *gem*-dibromocyclopropanes see: (a) Gassman, P. G.; Tan, L.; Hoye, T. R. *Tetrahedron Lett.* **1996**, *37*, 439−442. (b) Hemmingsen, T. H.; Svendsen, J. S.; Sydnes, L. K. *Acta Chem. Scand.* **1988**, *B42*, 651−661. (c) Brocksom, T. J.; Canevarolo, E. T.; Lopes, F. T. *An. Acad. Bras. Cienc.* **1985**, *57*, 165−168; *Chem. Abs.* **1986**, *105*, 191422. (d) Danheiser, R. L.; Morin, J. M.; Salaski, E. J. *J. Am. Chem. Soc.* **1985**, *107*, 8066−8073. (e) Danheiser, R. L.; Morin, J. M.; Yu, M.; Basak, A. *Tetrahedron Lett.* **1981**, *22*, 4205−4208.

(7) For other examples of intramolecular alkylation at carbamate nitrogen see: (a) see ref 3i. (b) Abelman, M. M.; Overman, L. E.; Tran, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 6959−6964. (c) Knapp, S.; Kukkola, P. J.; Sharma, S.; Murali Dhar, T. G.; Naughton, A. B. J. *J. Org. Chem.* **1990**, *55*, 5700−5710 and references therein. For an excellent recent review on "the tethered nitrogen in natural product synthesis" see: Knapp, S. *Chem. Soc. Rev.* **1999**, *28*, 61−72.

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(11) Alder, K.; Flock, F. H. *Chem. Ber.* **1956**, *89*, 1732−1737.

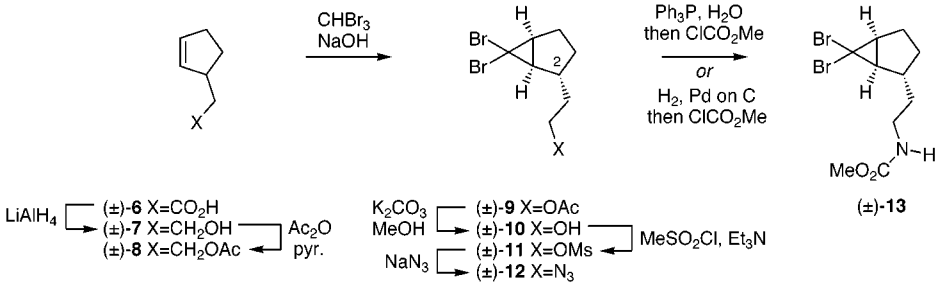
(12) Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis* **1982**, 245−258.

(13) Washburn, W. N.; Zahler, R.; Chen, I. *J. Am. Chem. Soc.* **1978**, *100*, 5863−5874.

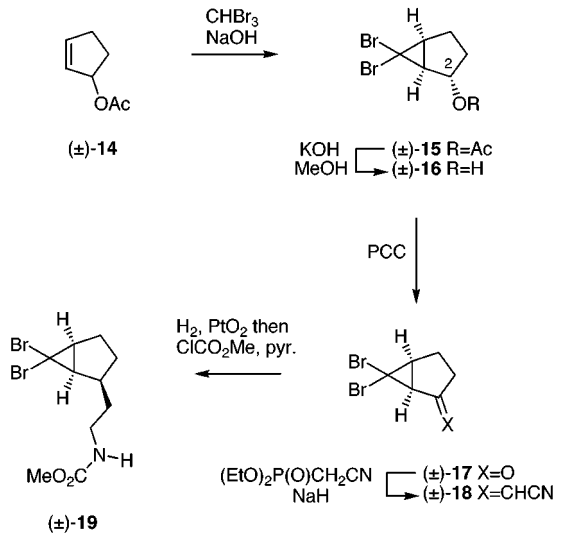
(14) Fieser, M.; Fieser, L. F. *Reagents for Organic Synthesis*; John Wiley and Sons: New York, 1974; Vol. 4, p 150 and references therein.

(15) Secrist, J. A.; Logue, M. W. *J. Org. Chem.* **1972**, *37*, 335−336.

Scheme 2



Scheme 3



carbon−carbon double bond within precursors (±)-**18** should occur from the less hindered α-face and thereby establish the illustrated *syn*-relationship between the cyclopropane ring and the side chain.

The critical π-allyl cation cyclization reaction foreshadowed in Scheme 1 proved to be a rather facile process and was initially effected using trifluoroethanol (TFE) as solvent and silver acetate to promote electrocyclic ring opening of the halocyclopropane unit (Scheme 4). Under such conditions, substrate (±)-**19** was readily converted into desired hexahydroindole (±)-**20**, which was obtained in 87% yield. Under the same conditions, the isomeric *gem*-dihalocyclopropane (±)-**13** also gave compound (±)-**20** (44%). However, the reaction was not as clean, and ^{1}H NMR and MS analysis of the reaction products suggested formation of uncyclized products, each incorporating either an acetate or trifluoroethoxy group. The formation of such byproducts could be suppressed dramatically by using silver perchlorate in TFE at 18 °C to effect the π-allyl cation cyclization, and under such conditions substrates (±)-**13** and (±)-**19** gave product (±)-**20** in yields of 95% and 91%, respectively.

These results clearly suggest that, under optimal conditions, the stereochemical relationship between the *gem*-dihalocyclopropane and the tethered nucleophile is not important in determining the success of this type of electrocyclic ring-opening/cyclization process. Indeed, on the basis of the latter observations it could be argued that the conversions described here are not concerted but involve a common cationic intermediate. The exclusive formation of the *cis*-fused cyclization product (±)-**20**, the structure of which follows from its successful conversion into target (±)-**1**, is a consequence of the short length of the tether linking the reacting centers in precursors (±)-**13** and (±)-**19**.

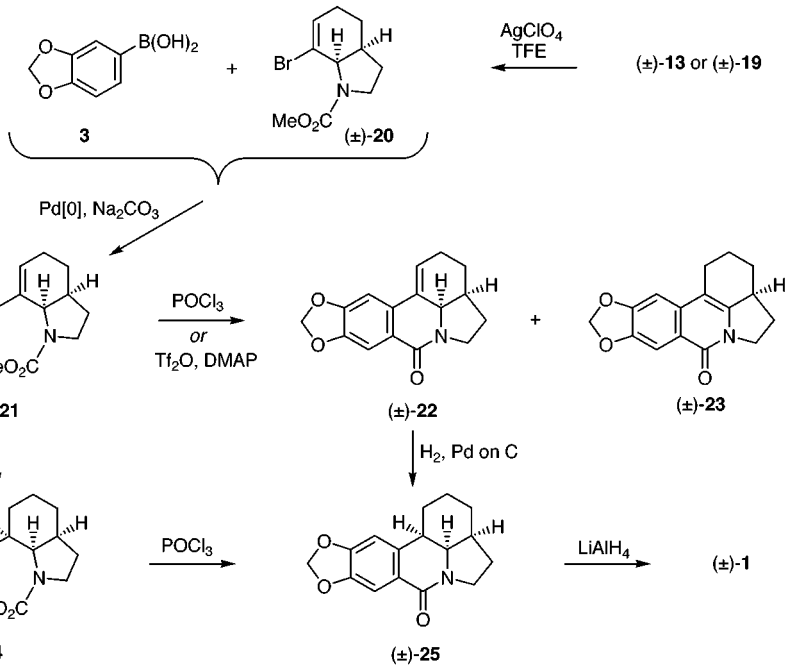
With the pivotal hexahydroindole (±)-**20** in hand, completion of the synthesis of the racemic modification of γ-lycorane proved relatively straightforward. Thus, Suzuki cross-coupling of this compound with the readily available arylboronic acid **3**[5d] proceeded uneventfully to give the 7-arylated hexahydroindole (±)-**21** in 87% yield. When this latter compound was subjected to a Bischler-Napieralski reaction with $POCl_3$ at 80 °C for 30 h, the previously reported[16] cyclization product (±)-**23**, containing a rearranged double bond, was obtained in 56% yield. When the same reaction was conducted for 16 h, a 1:1 mixture of cyclization products (±)-**22** and (±)-**23** was obtained in a combined yield of 92%, thus suggesting that the double-bond isomerization process leading to the latter product occurs after the cyclization reaction. While compound (±)-**22** was readily hydrogenated, in excellent yield, to give the known lactam (±)-**25**,[3i] isomer (±)-**23** was quite resistant to such a conversion even when ionic hydrogenation conditions were employed. The difficulties created by the double-bond migration process accompanying the $POCl_3$-promoted cyclization reaction could be overcome by using a combination of triflic anhydride (Tf_2O)/*N*,*N*-(dimethylamino)pyridine (DMAP)[17] to effect this conversion, and under appropriate conditions lactam (±)-**22** was the exclusive product of reaction. Another serviceable route to compound (±)-**25**, a proven precursor[3i] to the target γ-lycorane, involved reversing the order of hydrogenation and Bischler-Napieralski cyclization steps. Thus, compound (±)-**21** was readily hydrogenated under standard conditions, and the resulting product (±)-**24** (95%) underwent a smooth reaction with $POCl_3$ to give lactam (±)-**25** in 79% yield. Using the conditions reported by Bäckvall,[3i] this last compound was reduced with $LiAlH_4$ to give (±)-γ-lycorane [(±)-**1**] in 84% yield. The ^{1}H and ^{13}C NMR spectra of this material matched those derived from an authentic sample kindly provided by Professor W. Pearson (University of Michigan).

Synthesis of (+)- and (−)-γ-Lycorane. Previous work from our laboratories[5d] suggested that replacing, in the synthetic sequences outlined in Scheme 4, methyl carbamates such as (±)-**13** and (±)-**19** with the corresponding (−)-menthyl carbamates should enable preparation of the (+)- and (−)-forms of γ-lycorane. This could be done without any need to increase the number of synthetic steps, since the use of such a chiral auxiliary would only entail a separation of diastereoisomers at an appropriate stage. To these ends, the *E*/*Z* mixture of α,β-

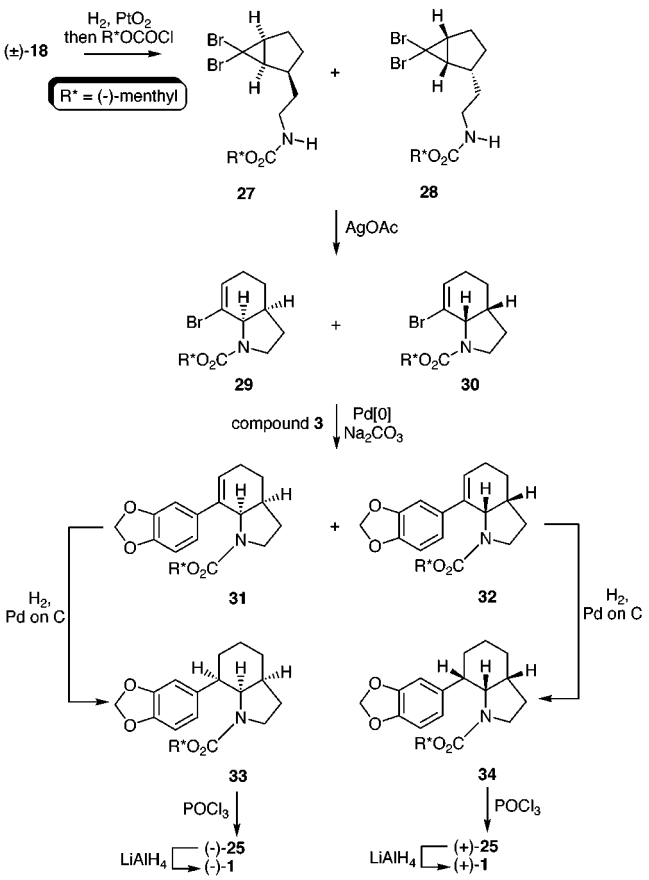
(16) Iida, H.; Aoyagi, S.; Kibayashi, C. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2502−2506.

(17) Banwell, M. G.; Bissett, B. D.; Busato, S.; Cowden, C. J.; Hockless, D. C. R.; Holman, J. W.; Read, R. W.; Wu, A. W. *J. Chem. Soc., Chem. Commun.* **1995**, 2551−2553.

Scheme 4



Scheme 5



unsaturated nitriles (±)-**18** was hydrogenated under the previously described conditions, and the resulting amine was reacted with (−)-menthyl chloroformate.

The ensuing 1:1 mixture of diastereoisomeric carbamates **27** and **28** was subjected to reaction with silver acetate in TFE. Under such conditions the expected hexahydroindoles **29** and **30** were formed in 94% combined yield. In an alternate and equally high yielding route to these compounds, methyl carbamate (±)-**20** was treated with potassium hydroxide and hydrazine hydrate in ethylene glycol, and the resulting (racemic) amine was reacted with (−)-menthyl carbamate. As with precursors **27** and **28**, compounds **29** and **30** could not be separated from one another by conventional means, so the mixture was subjected to palladium-catalyzed Suzuki cross-coupling with the boronic acid **3**. The products **31** and **32** so formed were now easily separated by HPLC techniques, and each was obtained as an oil in 49% yield. The absolute stereochemistry of these compounds follows from their successful conversions into (+)- and (−)-γ-lycorane. Thus, each was converted, quantitatively, into the corresponding saturated analogues, **33** and **34**, under standard hydrogenation conditions. The ^{1}H and $\{^1H\}^{13}$C NMR spectra of diastereoisomers **33** and **34** were in stark contrast to those of their unsaturated precursors. Thus, the extensive line broadening observed in the precursors was no longer as severe, with the result that the signals (in both spectra) were sharper. The removal of the double bond seemingly results in more ready interconversion of the carbamate rotamers.[18]Compounds **33** and **34** were each subjected to Bischler-Napieralski cyclization with $POCl_3$, and the lactams (−)-**25** and (+)-**25**, respectively, were thereby obtained (95% in each case). Each of these products had identical physical and spectroscopic properties save for the fact that the specific rotations were of opposite sign (although of equal magnitude). Compound (+)-**25** was subjected to single-crystal X-ray analysis, and the resulting structure is shown in Figure 1.[19]

Lithium aluminum hydride promoted reduction of compounds (+)- and (−)-**25** then gave the corresponding (+)- and (−)-forms of γ-lycorane, and the physical and spectroscopic properties of each of these materials matched those reported previously. The enantiomeric purity of

(18) Cox, C.; Lectka, T. *J. Org. Chem*. **1998**, *63*, 2426−2427.

(19) Crystal data for compound (+)-**25**: $C_{16}H_{17}NO_3$ = 411.38, orthorhombic, $P2_12_12_1$ (no. 19) with a = 7.006(2), b = 12.782(2), c = 29.395(2) Å, V = 2632.4(8) Å^3, Z = 8, D_c = 1.038 g cm^{-1}, R = 0.027 and R_w = 0.030 with 2062 reflections having $I > 3\sigma(I)$ (from a total of 2305 reflections).

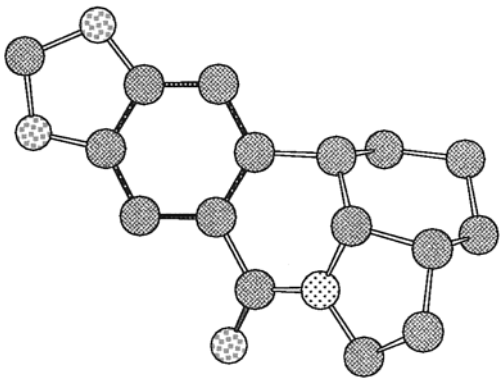


Figure 1. CS Chem3D Pro drawing of compound (+)-**25** generated using data derived from an X-ray crystallographic study (hydrogen atoms omitted for clarity).

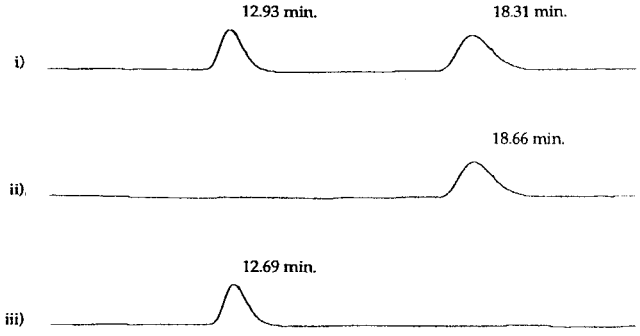


Figure 2. Chiral HPLC analysis of (i) (±)-(**1**), (ii) (+)-(**1**), and (iii) (−)-(**1**). Analyses conducted using a Chiralcel OD analytical column (4.6 cm × 25 cm) with 1:9 EtOH/hexane as eluting solvent and a flow rate of 1 mL/min; limits of detection, ±5%.

these compounds was confirmed using a chiral HPLC column, and under appropriate conditions baseline separation of the two enantiomers could be achieved (Figure 2).

Conclusion

The concise syntheses of the (±)-, (+)-, and (−)-modifications of γ-lycorane outlined above serve to highlight the potential utility of the title reaction sequences for the synthesis of polycyclic frameworks, including those associated with alkaloids. The capacity to vary the internal nucleophile, which captures the pivotal π-allyl cation intermediate, and the length of the tether connecting such reacting centers would seem to offer considerable potential for the synthesis of a wide range of carbo- and heterocyclic frameworks. This potential is further enhanced by the ease of production of the requisite *gem*-dihalocyclopropane-containing substrates via phase-transfer generated dihalocarbene addition to the corresponding alkene. Work aimed at extending this type of chemistry is currently underway in our laboratories and the results will be reported in due course.

Experimental Section

Unless otherwise specified, all NMR spectra were recorded in $CDCl_3$ on a Varian Unity 300 spectrometer. General experimental procedures have been described elsewhere.[5d,20]

2-Cyclopentene-1-ethanol [(±)-7]. $LiAlH_4$ (13.3 mL of a 1.0 M solution in THF, 13.3 mmol) was slowly added to a magnetically stirred solution of acid **6** (2.0 mL, 16.6 mmol, Aldrich) in anhydrous THF (5.0 mL) at such a rate so as to maintain gentle reflux. The resulting mixture was allowed to cool to 18 °C, stirred at this temperature for 21 h, cooled on an ice−water bath, and treated, dropwise, with ethyl acetate (1.1 mL), NaOH (1.2 mL of a 15% w/v aqueous solution), and water (3.0 mL). The resulting suspension was stirred at 0 °C for 3 h and then filtered through a no. 3 porosity sintered-glass funnel. The solids thus retained were washed with diethyl ether (20 mL), and the combined filtrates were concentrated under reduced pressure. The residue was cooled on an ice−water bath and treated with HCI (120 mL of a 2 M aqueous solution), and the resulting mixture was extracted with diethyl ether. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give alcohol (±)-**7**[8] (1.80 g, 97%) as a pungent yellow liquid, which was immediately used in the next step of the reaction sequence. A spectroscopically pure sample of this material was obtained by vacuum distillation (bp 79 °C, 2 mmHg) of the crude material: found $(M - H)^+$ 111.0809, $C_7H_{12}O$ requires $(M - H)^+$ 111.0810; IR (KBr) 3326, 1613 cm^{-1}; ^1H NMR δ 5.73 (m, 1H), 5.68 (m, 1H), 3.69 (m, 2H), 2.76 (m, 1H), 2.42−2.21 (complex m, 2H), 2.06 (m, 1H), 1.69 (m, 1H), 1.58 (s, 1H), 1.58 (partially obscured m, 1H), 1.43 (m, 1H); ^{13}C NMR δ 134.6 (CH), 130.7 (CH), 61.8 (CH_2), 42.1 (CH), 38.9 (CH_2), 31.9 (CH_2), 29.8 (CH_2); MS (EI, 70 eV) *m*/*z* (rel intensity) 111 [$(M - H^+$, 25], 95 [$(M - OH)^+$, 100].

2-Cyclopentene-1-ethanol Acetate [(±)-8]. A magnetically stirred solution of alcohol (±)-**7** (1.83 g, 16.3 mmol) in anhydrous pyridine (2.65 mL, 32.8 mmol) maintained under a nitrogen atmosphere at 18 °C was treated with acetic anhydride (3.10 mL, 32.9 mmol). The reaction mixture was stirred at 18 °C for 20 h and then subjected to flash chromatography (silica, 1:19 EtOAc/hexane elution). Concentration of the appropriate fractions ($R_f = 0.3$) gave a pale-yellow oil, which was subjected to short path distillation under reduced pressure. Collection of the appropriate fractions then gave the title compound (±)-**8**[21] (2.30 g, 92%) as a clear colorless oil (bp 89 °C, 3 mmHg): IR (KBr) 1745 cm^{-1}; ^1H NMR δ 5.72 (m, 1H), 5.64 (m, 1H), 4.09 (m, 2H), 2.71 (m, 1H), 2.38−2.19 (complex m, 2H), 2.05 (m, 1H), 2.02 (s, 3H), 1.74 (m, 1H), 1.58 (m, 1H), 1.46−1.35 (complex m, 1H); ^{13}C NMR δ 171.1 (CO), 134.1 (CH), 130.9 (CH), 63.4 (CH_2), 42.3 (CH), 34.6 (CH_2), 31.8 (CH_2), 29.7 (CH_2), 21.0 (CH_3); MS (EI, 70 eV) *m*/*z* (rel intensity) 94 (75) [$(M - CH_3CO_2H)^+$], 79 (100).

[1α,2α,5α]-6,6-Dibromo-2-(2′-hydroxyethyl)bicyclo[3.1.0]-hexane Acetate [(±)-9] and [1α,2β,5α]-6,6-Dibromo-2-(2′-hydroxyethyl)bicyclo[3.1.0]hexane Acetate [C2-*epi*-(±)-9]. NaOH (5.5 g of a 44% w/w aqueous solution) was added dropwise to a magnetically stirred solution of alkene (±)-**8** (409 mg, 2.65 mmol), bromoform (2.60 mL, 29.8 mmol), and TEBAC (64 mg, 0.28 mmol) in benzene (7.2 mL) maintained at 0 °C (ice bath). The resulting two-phase mixture was allowed to warm to 18 °C, stirred vigorously for 66 h, and then poured into a mixture of hexane (40 mL) and water (40 mL). The separated aqueous phase was extracted with hexane, and the combined organic fractions were washed with brine, dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a pale-yellow oil. This material was subjected to flash chromatography (silica, 1:24 EtOAc/hexane elution), and after concentration of the appropriate fractions ($R_f = 0.2$), a ca. 3:1 mixture of compound (±)-**9** and C2-*epi*-(±)-**9** (606 mg, 70%) was obtained as a pale-yellow oil: found $(M + H^+)$ 326.9417; $C_{10}H_{14}{}^{79}Br^{81}BrO_2$ requires $(M + H^+)$ 326.9418; IR (KBr) 1740 cm^{-1}; ^1H NMR δ [(±)-**9**] 4.11 (m, 2H), 2.29−2.21 (complex m, 2H), 2.15−1.60 (complex m, 6H), 2.06 (s, 3H), 1.47 (m, 1H); δ [C2-*epi*-(±)-**9**] 4.21 (m, 2H), 2.53 (broad m, 1H), 2.12−1.60 (complex m, 7H), 2.09 (s, 3H), 1.47 (m, 1H); ^{13}C NMR δ [(±)-**9**]

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δ 171.1 (CO), 62.8 (CH_2), 44.1 (CH), 40.0 (CH), 39.4 (CH), 38.6 (CBr_2), 34.5 (CH_2), 32.9 (CH_2), 28.3 (CH_2), 21.0 (CH_3); δ [C2-*epi*-(±)-**9**] 171.2 (CO), 63.9 (CH_2), 41.9 (CH), 41.3 (CH), 36.2 (CH), 29.4 (CH_2), 28.7 (CH_2) (three signals obscured/overlapping); MS *m*/*z* (EI, 70 eV) (rel intensity) 329 (1.5) 327 (2.7) 325 (1.4) ($M + H^+$), 149 (100).

[1α,2α,5α]-6,6-Dibromo-2-(2′-hydroxyethyl)bicyclo[3.1.0]-hexane [(±)-10] and [1α,2*β*,5α]-6,6-Dibromo-2-(2′-hydroxyethyl)bicyclo[3.1.0]hexane [C2-*epi*-(±)-10]. A solution of a ca. 3:1 mixture of compound (±)-**9** and its C2-epimer (606 mg, 1.86 mmol) in methanol (4.0 mL) was treated with potassium carbonate (688 mg, 4.98 mmol), and the resulting suspension was stirred at 18 °C for 24 h and then poured into brine (100 mL). The ensuing mixture was extracted with dichloromethane, and the combined organic layers were then washed with water before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a pale-yellow oil. Subjection of this material to flash chromatography (silica, 1:4 EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.2) afforded a ca. 3:1 mixture of alcohol (±)-**10** and its C2-*epi*-(±)-**10** (329 mg, 62%) as a clear, colorless oil: found $(M - H_2O)^+$ 263.9153; $C_8H_{12}{}^{79}Br_2O$ requires $(M - H_2O)^+$ 263.9149; IR (KBr) 3332 cm^{-1}; ^1H NMR δ [(±)-**10**] 3.70 (m, 2H), 2.26 (m, 2H), 2.17−1.72 (complex m, 6H), 1.62 (m, 1 H), 1.50−1.40 (complex m,1H); δ [C2-*epi*-(±)-**10**] 3.75 (m, 2H), 2.60 (broad m, 1H), 2.26 (m, 2H), 2.17−1.72 (complex m, 6H), 1.62 (m, 1 H); ^{13}C NMR δ [(±)-**10**] 61.2 (CH_2), 44.3 (CH), 39.8 (CH), 39.7 (CBr_2), 39.3 (CH), 38.6 (CH_2), 33.0 (CH_2), 28.3 (CH_2); δ [C2-*epi*-(±)-**10**] 62.2 (CH_2), 42.0 (CH), 40.7 (CH), 38.4 (CH), 36.6 (CBr_2), 33.5 (CH_2), 29.3 (CH_2), 28.8 (CH_2); MS *m*/*z* (EI, 70 eV) (rel intensity) 286 (0.2) 284 (0.5) 282 (0.3) (M^+), 105 (100).

[1α,2α,5α]-6,6-Dibromo-2-(2′-hydroxyethyl)bicyclo[3.1.0]-hexane Methanesulfonate [(±)-11]. A chilled (0 °C) and magnetically stirred mixture of a solution of a ca. 3:1 mixture of compound (±)-**10** and C2-*epi*-(±)-**10** (88 mg, 0.31 mmol) in anhydrous dichloromethane (400 μL) maintained under a nitrogen atmosphere was treated, dropwise, with triethylamine (60 μL, 0.43 mmol) and then methanesulfonyl chloride (30 μL, 0.338 mmol). The resulting solution was stirred at 0 °C for 10 h and then at 18 °C for 14 h before being poured into brine (20 mL) and extracted with dichloromethane. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a ca. 3:1 mixture of compound (±)-**11** and C2-*epi*-(±)-**11** as a pale-yellow oil. Subjection of this mixture of mesylates to flash chromatography (silica, 1:4 EtOAc/hexane elution) afforded, after concentration of the appropriate fractions (R_f = 0.2), the mesylate (±)-**11** (80 mg, 72%) as a pale-yellow oil: IR (KBr) 1354, 1175 cm^{-1}; ^1H NMR δ 4.27 (m, 2H), 3.04 (s, 3H), 2.29 (m, 2H), 2.17−1.93 (m, 4H), 1.88−1.77 (m, 2H), 1.52−1.44 (m, 1H); ^{13}C NMR δ 68.0 (CH_2), 43.8 (CH), 39.6 (CH or CH_3), 39.4 (CH or CH_3), 39.0 (CBr_2), 37.5 (CH or CH_3), 34.9 (CH_2), 33.1 (CH_2), 28.3 (CH_2).

[1α,2α,5α]-2-(2′-Azidoethyl)-6,6-dibromobicyclohexane [(±)-12]. A magnetically stirred solution of mesylate (±)-**11** (110 mg, 0.30 mmol) in anhydrous DMF (3.0 mL) maintained under a nitrogen atmosphere was treated, in one portion, with NaN_3 (398 mg, 6.12 mmol). The resulting mixture was protected from light and stirred at 18 °C for 24 h, and then the DMF was removed under reduced pressure. The white solid thus obtained was partitioned between hexane (60 mL) and water (60 mL), and the separated aqueous layer was extracted with hexane. The combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a pale-yellow oil, which was subjected to flash chromatography (silica, 1:19 CH_2Cl_2/hexane elution). Concentration of the appropriate fractions (R_f = 0.3) gave the title azide (±)-**12** (72 mg, 77%) as a clear, colorless oil: found $(M - N_2 - H)^+$ 281.9142; $C_8H_{11}{}^{81}Br_2N_3$ requires $(M - N_2 - H)^+$ 281.9139; IR (KBr) 2095 cm^{-1}; ^1H NMR δ 3.33 (m, 2H), 2.25 (m, 2H), 2.15−1.75 (complex m, 5H), 1.64 (m, 1H), 1.44 (m, 1H); ^{13}C NMR δ 49.8 (CH_2), 44.0 (CH), 40.5 (CH), 39.3 (CH), 39.1 (CBr_2), 34.7 (CH_2), 32.9 (CH_2), 28.3 (CH_2); MS *m*/*z* (EI, 70 eV) (rel intensity) 283 (0.2) 281 (0.6) 279 (0.3) $[(M - N_2)^+]$, 55 (100).

Methyl (1′α,2′α,5′α)-{2-(6′,6′-Dibromobicyclo[3.1.0]hex-2′-yl)ethyl}carbamate [(±)-13]. Method A. A solution of triphenylphosphine (51 mg, 0.19 mmol) in THF (250 μL) maintained under a nitrogen atmosphere was treated with a solution of azide (±)-**12** (52 mg, 0.168 mmol) in THF (400 μL). The reaction mixture was protected from light and stirred at 18 °C for 1.5 h and then treated with water (30 mg, 1.67 mmol). The resulting two-phase mixture was stirred at 18 °C for a further 6.5 h and then concentrated under reduced pressure. The residue was dissolved in anhydrous dichloromethane (0.80 mL), and the resulting magnetically stirred solution was cooled to 0 °C and treated, dropwise, with pyridine (61 μL, 0.754 mmol) and methyl chloroformate (147 μL, 1.90 mmol). Stirring was continued for 2 h at 0 °C followed by 14 h at 18 °C, and then the reaction mixture was diluted with dichloromethane (5 mL) and washed with water followed by brine. The separated organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a pale-yellow oil, which was subjected to flash chromatography (silica, 1:4 EtOAc/hexane elution). Concentration of the appropriate fractions (R_f = 0.2) then gave the title carbamate (±)-**13** (25 mg, 43%) as a pale-yellow oil: found M^+ 338.9466; $C_{10}H_{15}{}^{79}Br_2NO_2$ requires M^+ 338.9470; IR (KBr) 3332, 1701 cm^{-1}; ^1H NMR δ 4.74 (s, 1H, NH), 3.67 (s, 3H), 3.21 (m, 2H), 2.27 (m, 1H), 2.22−1.77 (complex m, 5H), 1.71 (m, 1H), 1.62−1.41 (complex m, 2H); ^{13}C NMR δ 157.0 (CO), 52.1 (CH), 44.1 (CH or CH_3), 40.6 (CH or CH_3), 39.5 (CH_2), 39.3 (CH or CH_3), 36.1 (CH_2), 32.9 (CH_2), 28.4 (CH_2) (one signal obscured/overlapping); MS *m*/*z* (EI, 70 eV) (rel intensity) 343 (0.4) 341 (0.8) 339 (0.4) (M^+), 88 (100) $[(CH_2NHCO_2CH_3)^+]$.

Method B. A chilled (0 °C) and magnetically stirred solution of azide (±)-**12** (65 mg, 0.21 mmol) in THF (5.0 mL) was treated with 10% palladium on charcoal (67 mg), and an atmosphere of hydrogen was established above the reaction mixture. After 0.66 h methyl chloroformate (81 μL, 1.1 mmol) and then triethylamine (58 μL, 0.42 mmol) were introduced, and stirring was continued under a hydrogen atmosphere at 0 °C for 2 h. The reaction mixture was then filtered through a 1 cm deep pad of Celite contained in a sintered-glass funnel. The pad was washed with EtOAc (30 mL), and the combined filtrates were concentrated under reduced pressure to give a light-yellow oil, which was subjected to flash chromatography (silica, 1:4 EtOAc/hexane elution). Concentration of the appropriate fractions (R_f = 0.3) then gave the title carbamate (±)-**13** (61 mg, 85%) as a clear colorless oil, which was identical, in all respects, with the material obtained via Method A (above).

(1α,2α,5α)-6,6-Dibromobicyclo[3.1.0]hexan-2-ol acetate [(±)-15] and (1α,2*β*,5α)-6,6-dibromobicyclo[3.1.0]hexan-2-ol acetate [C2-*epi*-(±)-15]. NaOH (85 mL of a 50% w/v aqueous solution) was added in portions to a magnetically stirred solution of 3-acetoxycyclopentene (±)-**14**[11] (8.0 g, 63.5 mmol), bromoform (55 mL, 0.698 mol), and TEBAC (170 mg, 0.75 mmol) in benzene (150 mL), which was maintained at 0 °C on an ice bath. After addition was complete the resulting mixture was allowed to stir vigorously for a further 16 h at 18 °C and then poured into water (200 mL) and hexane (200 mL). The aqueous layer was extracted with hexane, and the combined organic fractions were washed with brine before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a brown oil. This material was subjected to dry-column flash chromatography (silica, 1:19 EtOAc/hexane elution) to give a ca. 4:1 mixture of diastereoisomeric adducts (±)-**15** and C2-*epi*-(±)-**15** (15.2 g, 81%) as a pale-yellow oil. For the purposes of spectroscopic characterization a small amount of this material was resubjected to dry-column flash chromatography (silica, 1:19 EtOAc/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.3) afforded (±)-**15** as a clear colorless oil: found M^+ 295.9058; $C_8H_{10}{}^{79}Br_2O_2$ requires M^+ 295.9047; IR (NaCl) 1733 cm^{-1}; ^1H NMR δ 5.16 (m, 1H), 2.41 (m, 2H), 2.31−2.16 (complex m, 2H), 2.06 (s, 3H), 1.92 (m, 1H), 1.72 (m, 1H); ^{13}C NMR δ 170.0, 77.9, 42.8, 39.0, 33.7, 32.8, 27.5, 21.1; MS *m*/*z* (EI, 70 eV) (rel intensity) 300 (3) 298 (5) 296 (3) (M^+), 77 (100). Concentration of fraction B (R_f = 0.25) afforded C2-*epi*-(±)-**15** as a clear colorless oil: found M^+

295.9052; $C_8H_{10}{}^{79}Br_2O_2$ requires M^+ 295.9047; IR (NaCl) 1733 cm^{-1}; ^1H NMR δ 5.45 (dd, J = 9.3 and 5.9 Hz, 1H), 2.57 (dd, J = 7.4 and 5.9 Hz, 1H), 2.27 (m, 1H), 2.17−2.11 (complex m, 1H), 2.10 (s, 3H), 2.09−2.03 (complex m, 2H), 1.90−1.80 (complex m, 1H); ^{13}C NMR δ 171.0, 77.8, 40.0, 38.3, 32.5, 28.6, 26.6, 21.1; MS m/z (EI, 70 eV) (rel intensity) 300 (3) 298 (7) 296 (4) (M^+), 77 (100).

(1α,2α,5α)-6,6-Dibromobicyclo[3.1.0]hexan-2-ol [(±)-16] and (1α,2*β*,5α)-6,6-dibromobicyclo[3.1.0]hexan-2-ol [C2-*epi*-(±)-16]. The ca. 4:1 mixture of acetates (±)-**15** and C2-*epi*-(±)-**15** (9.10 g, 30.7 mmol), prepared as described above, was added dropwise to a magnetically stirred solution of KOH (20.0 g, 0.357 mol) in MeOH (100 mL) maintained at 0 °C. After addition was complete the resulting mixture was allowed to warm to 18 °C, and stirring was continued for a further 16 h. The reaction mixture was then poured into brine (200 mL) and extracted with CH_2Cl_2. The combined organic fractions were washed with water before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow residue. Subjection of this material to dry-column flash chromatography (silica gel, 1:4 EtOAc/hexane elution) afforded a ca. 4:1 mixture of diastereoisomeric alcohols (±)-**16** and C2-*epi*-(±)-**16** (7.5 g, 96%) as a clear, colorless oil, which could be used in the next step of the reaction sequence. For the purposes of spectroscopic characterization a small amount of this material was resubjected to dry-column flash chromatography to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.5) afforded alcohol (±)-**16**[13] as a clear colorless oil: found $(M - HO)^+$ 236.8920; $C_6H_8{}^{79}Br_2O$ requires $(M - HO)^+$ 236.8914; IR (NaCl) 3333 cm^{-1}; ^1H NMR δ 4.35 (m, 1H), 2.42−2.12 (complex m, 4H), 1.92−1.63 (complex m, 3H); ^{13}C NMR δ 76.0, 45.6, 39.0, 36.4, 33.9, 27.3; MS m/z (EI, 70 eV) (rel intensity) 240 (0.3) 238 (0.5) 236 (0.3) $(M - HO)^+$, 214 (39) 212 (80) 210 (42) $[(M - H_2O - C_2H_2)^+]$, 67 (100). Concentration of fraction B (R_f = 0.35) afforded alcohol C2-*epi*-(±)-**16**[13] as a clear colorless oil: found $(M - H)^+$ 252.8868; $C_6H_8{}^{79}Br_2O$ requires $(M - H)^+$ 252.8864; IR (NaCl) 3366 cm^{-1}; ^1H NMR δ 4.78 (broad s, 1H), 2.46 (dd, J = 7.3 and 5.9 Hz, 1H), 2.26−2.00 (complex m, 4H), 1.81−1.71 (complex m, 1H), 1.54 (broad s, 1H); ^{13}C NMR δ 77.7, 42.1, 38.8, 33.8, 32.2, 27.0; MS m/z (EI, 70 eV) (rel intensity) 255 (0.3) 253 (0.2) $[(M - H)^+]$, 67 (100).

(1α,5α)-6,6-Dibromobicyclo[3.1.0]hexan-2-one [(±)-17]. Pyridinium chlorochromate (12.0 g, 55.7 mmol) was added, in portions, to a magnetically stirred solution of a ca. 4:1 mixture of alcohols (±)-**16** and C2-*epi*-(±)-**16** (7.70 g, 30.3 mmol) in CH_2Cl_2 (200 mL) maintained at 0 °C under a nitrogen atmosphere. The resulting mixture was stirred in the dark for 8 h and then filtered through a 2 cm deep pad of TLC-grade silica gel, which was eluted with ether (400 mL). The combined filtrates were concentrated under reduced pressure to give a brown oil, which was subjected to dry-column flash chromatography (silica gel, 1:9 EtOAc/hexane elution). Concentration of the appropriate fractions (R_f = 0.3) afforded the title ketone (±)-**17**[13] (6.88 g, 90%) as a pale-yellow and low melting solid: found M^+ 251.8782; $C_6H_6{}^{79}Br_2O$ requires M^+ 251.8785; IR (NaCl) 1727 cm^{-1}; ^1H NMR δ 2.77 (m, 1H), 2.71 (dd, J = 6.4 and 0.5 Hz, 1H), 2.42−2.12 (complex m, 4H); ^{13}C NMR δ 207.9, 45.5, 39.8, 36.3, 28.1, 22.8; MS m/z (EI, 70 eV) (rel intensity) 256 (0.4) 254 (0.8) 252 (0.5) (M^+), 214 (49) 212 (100) 210 (52).

(*E*)-(1′α,5′α)-{6′,6′-Dibromobicyclo[3.1.0]hex-2′-ylidene}-acetonitrile [(*E*)-(±)-18] and (*Z*)-(1′α,5′α)-{6′,6′-Dibromobicyclo[3.1.0]hex-2′-ylidene}acetonitrile [(*Z*)-(±)-18]. A magnetically stirred suspension of NaH (822 mg, 34.3 mmol) in anhydrous 1,2-dimethoxyethane (DME) (80 mL) maintained under a nitrogen atmosphere at 0 °C was treated with diethyl cyanomethylphosphonate (6.07 g, 34.3 mmol, Aldrich). After the evolution of hydrogen had ceased (ca. 20 min) a solution of ketone (±)-**17** (7.2 g, 28.6 mmol) in anhydrous DME (15 mL) was added dropwise, and the resulting mixture was allowed to stir at 0 °C for 1.5 h. The reaction mixture was then filtered through a 2 cm deep pad of TLC-grade silica gel, which was eluted with ether (400 mL). Concentration of the combined filtrates gave a yellow oil, which was subjected to flash chromatography (silica gel, 1:9 EtOAc/hexane elution) to afford a ca. 2:1 mixture of the title compounds (*E*)-(±)-**18** and (*Z*)-(±)-**18** (7.86 g, 100%) as a clear, colorless oil, which could be used without purification in the next step of the reaction sequence. For the purposes of spectroscopic characterization a portion of this mixture was resubjected to flash column chromatography (silica gel, 1:9 EtOAc/hexane elution) to afford two fractions, A and B.

Concentration of fraction A (R_f = 0.4) gave a white solid, which was recrystallized (diethyl ether/hexane) to give compound (*E*)-(±)-**18** as white prisms, mp 72−73 °C: found C, 34.8; H, 2.2; N, 5.1; Br, 57.6; M^+ 274.8936; $C_8H_7{}^{79}Br_2N$ requires C, 34.7; H, 2.5; N, 5.1; Br, 57.7; M^+ 274.8945; IR (KBr) 2210, 1604 cm^{-1}; ^1H NMR δ 5.50 (t, J = 2.7 Hz, 1H), 2.90 (d, J = 6.8 Hz, 1H), 2.84−2.75 (complex m, 1H), 2.70 (dt, J = 6.8 and 0.7 Hz, 1H), 2.65−2.55 (complex m, 1H), 2.37−2.67 (complex m, 1H), 2.14−2.07 (complex m, 1H); ^{13}C NMR δ 167.8, 116.5, 94.7, 45.1, 42.8, 33.7, 33.1, 27.3; MS m/z (EI, 70 eV) (rel intensity) 278 (0.6) 276 (1) 274 (0.5) $[(M - H)^+]$, 117 (100), 116 (54). Concentration of fraction B (R_f = 0.3) gave compound (*Z*)-(±)-**18** as a clear, colorless oil: found M^+ 274.8947; $C_8H_7{}^{79}Br_2N$ requires M^+ 274.8945; IR (NaCl) 2216, 1630 cm^{-1}; ^1H NMR δ 5.37 (t, J = 2.3 Hz, 1H), 3.18 (d, J = 6.6 Hz, 1H), 2.70 (t, J = 6.7 Hz, 1H), 2.59−2.54 (m, 2H), 2.34−2.25 (m, 1H), 2.11−2.04 (m, 1H); ^{13}C NMR δ 167.5, 116.8, 94.6, 44.3, 42.5, 33.6, 33.2, 27.5; MS m/z (EI, 70 eV) (rel intensity) 278 (1) 276 (2) 274 (1) $[(M - H)^+]$, 198 (97) 196 (100) $[M - Br)^+]$.

Methyl (1′α,2′*β*,5′α)-{2-(6′,6′-Dibromobicyclo[3.1.0]hex-2′-yl)ethyl}carbamate [(±)-19]. A solution of a ca. 2:1 mixture of compounds (*E*)-(±)-**18** and (*Z*)-(±)-**18** (550 mg, 2.0 mmol) and $CHCl_3$ (1.0 mL) in EtOH (40 mL) containing PtO_2 (50 mg) was placed in a Parr apparatus, which was pressurized to 3 atm with hydrogen. The vessel was shaken for 3 h at 18 °C, the pressure was released, and the reaction mixture was filtered through a pad of Celite. The solids thus retained were washed with EtOAc (80 mL), and the combined filtrates were concentrated under reduced pressure to give a white crystalline solid (amine salt). This material was partitioned between HCl (30 mL of a 1 M aqueous solution) and CH_2Cl_2 (30 mL), and the separated aqueous layer was basified with $NaHCO_3$ (saturated aqueous solution) to pH 12 and then extracted with CH_2Cl_2. The organic fractions were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a light-yellow oil (free amine), which was immediately dissolved in CH_2Cl_2 (30 mL) containing pyridine (0.5 mL, 6.18 mmol). The resulting solution was cooled to 0 °C and while being magnetically stirred and maintained under a nitrogen atmosphere was treated, dropwise, with methyl chloroformate (0.46 mL, 5.95 mmol). The resulting yellow solution was warmed to 18 °C, stirred for a further 12 h, diluted with CH_2Cl_2 (20 mL), and washed with water and then brine. The organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. Subjection of this material to dry-column flash chromatography (silica gel, 3:7 EtOAc/hexane elution) and concentration of the appropriate fractions (R_f = 0.4) afforded the title compound (±)-**19** (529 mg, 78%) as a clear, colorless oil: found $(M - H)^+$ 337.9394; $C_{10}H_{15}{}^{79}Br_2NO_2$ requires $(M - H)^+$ 337.9391; IR (NaCl) 1696 cm^{-1}; ^1H NMR δ 4.72 (broad s, 1H), 3.67 (s, 3H), 3.27 (m, 2H), 2.51 (m, 1H), 2.21 (m, 2H), 2.07−1.92 (complex m, 3H), 1.85−1.70 (complex m, 2H), 1.67−1.45 (complex m, 1H); ^{13}C NMR δ 157.1, 52.0, 41.9, 41.7, 40.5, 38.6, 36.3, 31.0, 29.3, 28.8; MS m/z (EI, 70 eV) (rel intensity) 340 (0.3) 338 (0.2) $[(M - H)^+]$, 88 (100).

***π*-Allyl Cation Cyclization Reactions of Compounds (±)-13 and (±)-19. Formation of Methyl *cis*-7-Bromo-2,3,-3a,4,5,7a-hexahydro-1*H*-indole-1-carboxylate [(±)-20].** A magnetically stirred solution of carbamate (±)-**13** (28 mg, 0.082 mmol) in 2,2,2-trifluoroethanol (TFE) (1.0 mL), maintained under a nitrogen atmosphere and protected from light, was treated with $AgClO_4$ (38 mg, 0.18 mmol). The resulting suspension was stirred at 18 °C for 5 h and then filtered through a pad of Celite, which was washed with EtOAc (10 mL). The combined filtrates were concentrated under reduced pressure, and the resulting yellow solid was subjected to flash chromatography (silica, 1:4 EtOAc/hexane elution). Concentration of the appropriate fractions (R_f = 0.3) afforded a solid,

which was recrystallized (diethyl ether/hexane) to give the title compound (±)-**20** (20 mg, 95%) as a white crystalline solid, mp 55−56 °C: found C, 46.2; H, 5.5; N, 5.5; Br, 30.6; $C_{10}H_{14}BrNO_2$ requires C, 46.2; H, 5.4; N, 5.4; Br, 30.7; IR (KBr) 1696, 1638 cm^{-1}; ^1H NMR δ 6.12 (m, 1H), 4.61 (broad s, 1H), 3.73 (s, 3H), 3.53 (broad s, 1H), 3.38 (m, 1H), 2.51 (broad s, 1H), 2.21−2.00 (complex m, 2H), 1.94−1.73 (complex m, 4H); ^{13}C NMR δ 156.3 (CO), 131.2 (CH), 124.1 (C), 60.2 (CH or CH_3), 52.4 (CH or CH_3), 44.9 (CH_2), 38.6 (CH, broad), 25.7 (CH_2, broad), 22.8 (CH_2), 21.5 (CH_2); MS *m*/*z* (EI, 70 eV) (rel intensity) 261 (0.3) 259 (0.3) (M^+), 180 (100) [$(M - Br)^+$].

Subjection of carbamate (±)-**19** (42 mg, 0.12 mmol) to the same conditions afforded compound (±)-**20** (29 mg, 91%), which was identical, in all respects, to the material obtained as described above.

Methyl *cis*-7-(1′,3′-Benzodioxol-5′-yl)-2,3,3a,4,5,7a-hexahydro-1*H*-indole-1-carboxylate [(±)-21]. A magnetically stirred mixture of hexahydroindole (±)-**20** (287 mg, 1.11 mmol), boronic acid **3**[5d] (204 mg, 1.23 mmol), benzene (25 mL), EtOH (3.0 mL), Na_2CO_3 (7.0 mL of a 2 M aqueous solution), and $Pd(PPh_3)_4$ (128 mg, 0.111 mmol) was heated at reflux for 6 h while being maintained under a nitrogen atmosphere and protected from light. The cooled reaction mixture was diluted with diethyl ether (40 mL) and $NaHCO_3$ (40 mL of a saturated aqueous solution), and the separated aqueous layer was extracted with diethyl ether. The combined organic fractions were washed with $NaHCO_3$ (saturated aqueous solution) and brine before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. Subjection of this material to dry-column flash chromatography (silica gel, 3:7 EtOAc/hexane elution) afforded, after concentration of the appropriate fractions ($R_f = 0.3$), a white solid. Recrystallization (diethyl ether/hexane) of this material gave the title compound (±)-**21** (307 mg, 92%) as white prisms, mp 81−83 °C: found C, 67.9; H, 6.4; N, 4.7; $C_{17}H_{19}NO_4$ requires C, 67.8; H, 6.4; N, 4.7; IR (KBr) 1692 cm^{-1}; ^1H NMR δ 6.75−6.69 (m, 3H), 5.90 (t, $J = 1.7$ Hz, 2H), 5.69 (broad s, 1H), 4.84 (broad s, 1H), 3.51 (m, 1H), 3.44 (broad s, 3H), 3.23 (m, 1H), 2.47 (m, 1H), 2.28−2.07 (complex m, 2H), 2.01−1.74 (complex m, 4H); ^{13}C NMR δ 156.0, 146.7, 146.1, 138.5, 135.8, 127.6, 121.1, 108.6, 107.4, 100.7, 57.5, 52.0, 44.6, 36.6, 25.4, 22.0, 20.8; MS *m*/*z* (EI, 70 eV) (rel intensity) 301 (100) (M^+).

1,15-Didehydro-9,10-[methylenebis(oxy)]-galanthan-7-one [(±)-22] and 1,2,3,3a,4,5-Hexahydro-7*H*-[1,3]dioxolo-[4,5-*j*]pyrrolo[3,2,1-*de*]phenanthridin-7-one [(±)-23]. Method A. A solution of compound (±)-**21** (50 mg, 0.166 mmol) in freshly distilled $POCl_3$ (4.0 mL, 0.043 mol) was placed in an Ace Glass pressure tube (Aldrich) containing a magnetic stirring bar. The tube was sealed and then placed in an oil bath maintained at 80 °C, and the contents were stirred magnetically for 30 h while being protected from light. The resulting yellow reaction mixture was cooled to 0 °C and basified (**CAUTION**) to pH 12 using NaOH (2 M aqueous solution). Water (15 mL) was then added, and the resulting mixture was extracted with EtOAc. The combined organic fractions were washed with water and brine and then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to provide a yellow oil. Subjection of this material to dry-column flash chromatography (silica gel, EtOAc elution) afforded, after concentration of the appropriate fractions ($R_f = 0.3$), a white solid which was recrystallized (acetone/hexane) to give the title compound (±)-**23** (25 mg, 56%) as colorless plates, mp 170−172 °C (lit.[16] mp 166−168 °C): found M^+ 269.1042; $C_{16}H_{15}NO_3$ requires M^+ 269.1052; IR (KBr) 1673, 1602 cm^{-1}; ^1H NMR δ 7.82 (s, 1H), 6.89 (s, 1H), 6.06 (s, 2H), 4.37 (dd, $J = 12.2$ and 8.5 Hz, 1H), 3.82 (td, $J = 11.9$, 11.9 and 5.8 Hz, 1H), 3.00 (m, 1H), 2.72 (dd, $J = 16.1$ and 6.9 Hz, 1H), 2.52−2.43 (complex m, 1H), 2.43−2.33 (complex m, 1H), 2.26−2.16 (complex m, 1H), 1.84−1.63 (complex m, 3H), 1.40−1.28 (complex m, 1H); ^{13}C NMR δ 160.0, 151.7, 146.6, 141.2, 135.1, 121.1, 106.5, 106.0, 101.6, 99.9, 46.8, 40.3, 31.1, 28.1, 22.8, 22.1; MS *m*/*z* (EI, 70 eV) (rel intensity) 269 (100) (M^+).

Method B. Treatment of compound (±)-**21** (25 mg, 0.08 mmol) with $POCl_3$ (4.0 mL, 0.043 mol) under the conditions defined above but using a reaction time of 16 h afforded a light yellow oil on workup. Subjection of this material to dry-column flash chromatography (silica gel, EtOAc elution) afforded two fractions, A and B.

Concentration of fraction A ($R_f = 0.4$) gave a white solid which was recrystallized (CH_2Cl_2/hexane) to afford compound (±)-**22** (10 mg, 46%) as colorless prisms, mp 149−151 °C (lit.[22] 145−147 °C): found M^+ 269.1037; $C_{16}H_{15}NO_3$ requires M^+ 269.1052; IR (KBr) 1639, 1610 cm^{-1}; ^1H NMR δ 7.46 (s, 1H), 6.82 (s, 1H), 6.11 (dt, $J = 6.6$ and 2.4 Hz, 1H), 5.98 (dd, $J = 1.5$ and 1.2 Hz, 2H), 4.10 (d, $J = 7.1$ Hz, 1H), 3.68 (m, 2H), 2.50 (m, 1H), 2.35−1.99 (complex m, 3H), 1.87−1.72 (complex m, 2H), 1.32−1.18 (complex m, 1H); ^{13}C NMR δ 162.6, 150.5, 147.4, 134.1, 132.2, 125.9, 124.0, 107.5, 102.5, 101.5, 56.5, 43.3, 37.4, 29.3, 25.5, 24.6; MS *m*/*z* (EI, 70 eV) (rel intensity) 269 (100) (M^+).

Concentration of fraction B ($R_f = 0.3$) afforded compound (±)-**23** (10 mg, 46%), which was identical in all respects with the material obtained by Method A detailed above.

Method C. A solution of Tf_2O (210 μL, 1.25 mmol) in anhydrous CH_2Cl_2 (2.0 mL) was added, dropwise, to a magnetically stirred solution of compound (±)-**21** (74 mg, 0.25 mmol) and DMAP (95 mg, 0.78 mmol) in anhydrous CH_2Cl_2 (10 mL) maintained at 0 °C under a nitrogen atmosphere. The resulting yellow mixture was stirred for a further 2 h at 0 °C and then diluted with ether (20 mL). The organic layer was washed with Na_2CO_3 (saturated aqueous solution) and HCl (1 M aqueous solution), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a pale-yellow oil. Subjection of this material to dry-column flash chromatography (silica gel, EtOAc elution) afforded, after concentration of the appropriate fractions (Rf = 0.4), a white solid. This solid was recrystallized (CH_2Cl_2/hexane) to give compound (±)-**22** (56 mg, 85%), which was identical in all respects with the material obtained by Method B detailed above.

Methyl (3aα,7*β*,7aα)-7-(1′,3′-benzodioxol-5′-yl)octahydro-1*H*-indole-1-carboxylate [(±)-24]. A solution of compound (±)-**21** (66 mg, 0.22 mmol) in EtOAc (5.0 mL) containing 10% Pd on C (15 mg) and maintained at 18 °C was stirred under an atmosphere of hydrogen for 16 h. The catalyst was then removed by filtration through a pad of Celite, and the solids thus retained were washed with EtOAc (15 mL). The combined filtrates were concentrated under reduced pressure to give a yellow oil, which was subjected to dry-column flash chromatography (silica gel, 3:7 EtOAc/hexane elution). Concentration of the appropriate fractions ($R_f = 0.4$) then afforded the title compound (±)-**24** (66 mg, 100%) as a clear, colorless oil: found M^+ 303.1474, $C_{17}H_{21}NO_4$ requires M^+ 303.1470; IR (NaCl) 1693 cm^{-1}; ^1H NMR δ 6.75 (s, 1H), 6.69 (s, 2H), 5.89 (q, $J = 1.3$ Hz, 2H), 4.12 (t, $J = 7.1$ Hz, 1H), 3.42 (s, 3H), 3.13 (m, 1H), 3.05−2.97 (complex m, 1H), 2.42−2.34 (complex m, 1H), 1.96−1.52 (m, 9H); ^{13}C NMR δ 156.3, 147.0, 145.4, 138.3, 121.4, 108.9, 107.6, 100.6, 59.7, 52.0, 46.5, 41.2, 37.4, 29.1, 26.2, 25.1, 19.3; MS *m*/*z* (EI, 70 eV) (rel intensity) 303 (65) (M^+), 140 (100).

(15α)-(±)-9,10-[Methylenebis(oxy)]galanthan-7-one [(±)-25]. Method A. Treatment of compound (±)-**24** (95 mg, 0.08 mmol) with $POCl_3$ (3.0 mL, 0.043 mol) under the conditions defined for the conversion (±)-**21** → (±)-**22** (but using a reaction time of 22 h) afforded a light-yellow oil on workup. Subjection of this material to dry-column flash chromatography (silica gel, EtOAc elution) and concentration of the appropriate fractions ($R_f = 0.4$) gave a white solid. Recrystallization (EtOAc/diethyl ether) of this material then afforded the title compound (±)-**25** (69 mg, 81%) as colorless prisms, mp 125−126 °C (lit.[3h] 126−127 °C): found M^+ 271.1214; $C_{16}H_{17}NO_3$ requires M^+ 271.1208; IR (NaCl) 1647, 1605 cm^{-1}; ^1H NMR δ 7.52 (s, 1H), 6.61 (s, 1H), 5.98 (d, $J = 2.2$ Hz, 2H), 3.84 (t, $J = 4.7$ Hz, 1H), 3.75 (m, 1H), 3.62 (dt, $J = 11.5$ and 7.6 Hz, 1H), 2.79 (dt, $J = 12.0$ and 4.9 Hz, 1H), 2.26 (sextet, $J = 5.6$ Hz, 1H), 2.00−1.87 (complex m, 1H), 1.78−1.60 (complex m, 4H), 1.37−1.02 (complex m, 3H); ^{13}C NMR δ 162.7, 150.2,

(22) Hwang, G.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1983**, 693−694.

146.7, 138.5, 122.9, 107.5, 106.9, 101.4, 57.9, 42.7, 39.1, 38.1, 29.9, 28.9, 26.2, 23.7; MS *m*/*z* (EI, 70 eV) (rel intensity) 271 (37) (M^+), 83 (100).

Method B. Treatment of compound (±)-**22** (25 mg, 0.093 mmol) with hydrogen (1 atm) under the conditions defined for the conversion (±)-**2** → (±)-**24** afforded a light-yellow oil on workup. Subjection of this material to dry-column flash chromatography (silica gel, EtOAc elution) and concentration of the appropriate fractions (R_f = 0.4) gave a white solid. Recrystallization (EtOAc/diethyl ether) of this material then afforded compound **22** (24 mg, 95%), which was identical in all respects with the material prepared via Method A.

(15α)-(±)-9,10[Methylenebis(oxy)]galanthan [(±)-γ-lycorane, (±)-1]. $LiAlH_4$ (34 mg, 0.89 mmol) in anhydrous THF (1.0 mL) was added to a magnetically stirred solution of lactam (±)-**25** (40 mg, 0.15 mmol) in anhydrous THF (6.0 mL) maintained under a nitrogen atmosphere. The resulting mixture was heated at reflux for 3 h then cooled to room temperature and treated (**CAUTION**) with water (0.15 mL). The resulting slurry was filtered through a plug of Celite, and the filtrate was concentrated under reduced pressure to afford a yellow oil. Subjection of this material to dry-column flash chromatography (silica gel, EtOAc elution) and concentration of the appropriate fractions (R_f = 0.4) afforded (±)-γ-lycorane [(±)-**1**] (32 mg, 84%) as white prisms, mp 98−99 °C (lit.[2c] 101−102 °C): found $(M - H)^+$ 256.1341; $C_{16}H_{19}NO_2$ requires $(M - H)^+$ 256.1337; ^{1}H NMR δ 6.61 (s, 1H), 6.49 (s, 1H), 5.89 (q, *J* =1.5 Hz, 2H), 4.02 (d, *J* = 14.4 Hz, 1H), 3.38 (dt, *J* = 9.2 and 3.9 Hz, 1H), 3.21 (d, *J* = 14.4 Hz, 1H), 2.74 (dt, *J* = 11.7 and 5.3 Hz, 1H), 2.37 (t, *J* = 4.8 Hz, 1H), 2.23−2.08 (complex m, 2H), 2.07−1.95 (complex m, 1H), 1.78−1.60 (complex m, 3H), 1.53−1.21 (complex m, 4H); ^{13}C NMR δ 146.0, 145.6, 133.2, 127.3, 108.3, 106.2, 100.6, 62.9, 57.2, 53.7, 39.5, 37.4, 31.7, 30.4, 29.3, 25.2; MS *m*/*z* (EI, 70 eV) (rel intensity) 257 (35) (M^+), 256 (100) $[M - H]^+$.

A small sample of amine (±)-**1** was dissolved in HCl (1 M aqueous solution), and the resulting mixture was concentrated under reduced pressure to give a white solid. This material recrystallized (water) to give (±)-γ-lycorane hydrochloride as white needles, mp 255−256 °C (dec) [lit.[2c] 255−256 °C (dec)].

[1α(*R),2β,5α]-5-Methyl-2-(1′-methylethyl)cyclohexyl-(1′*R*,2′*S*,5′*S*)−(±)-{2-(6′,6′-dibromobicyclo[3.1.0]hex-2′-yl)-ethyl}carbamate (27) and [1α(*R**),2β,5α]-5-Methyl-2-(1′-methylethyl)cyclohexyl-(1′*S*,2′*R*,5′*R*)−(±)-{2-(6′,6′-dibromobicyclo[3.1.0]hex-2′-yl)ethyl}carbamate (28).** A ca. 2:1 mixture of nitriles (*E*)-(±)-**18** and (*Z*)-(±)-**18** (400 mg, 1.45 mmol), anhydrous $CHCl_3$ (1.0 mL), and PtO_2 (50 mg) were added to absolute EtOH (50 mL), and the resulting mixture was hydrogenated, with continuous agitation, in a Parr apparatus at 3 atm and 18 °C for 3 h.[15] The reaction mixture was then filtered through a pad of Celite, and the solids thus retained were washed with EtOAc (80 mL). Concentration of the combined filtrates gave a white crystalline solid, which was treated with HCl (30 mL of a 1 M aqueous solution) and CH_2Cl_2 (30 mL). The organic layer was discarded, and the aqueous layer basified to pH 12 with $NaHCO_3$ (saturated aqueous solution) and then extracted with CH_2Cl_2. The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give an unstable yellow oil (free amine), which was immediately dissolved in anhydrous CH_2Cl_2 (15 mL) containing pyridine (0.234 mL, 2.90 mmol). The resulting solution was stirred magnetically, cooled to 0 °C, and then treated dropwise with (−)-menthyl chloroformate (620 μL, 2.90 mmol). The resulting clear yellow solution was allowed to warm to 18 °C, stirred for a further 16 h, and then diluted with CH_2Cl_2 (20 mL) and water (20 mL). The separated aqueous phase was extracted with CH_2Cl_2, and the combined organic fractions were washed with water and brine before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The yellow oil obtained in this manner was subjected to dry-column flash chromatography (silica gel, 3:17 EtOAc/hexane elution). Concentration of the appropriate fractions (R_f = 0.4) gave a 1:1 mixture of compounds **27** and **28** (430 mg, 64%) as a clear, colorless oil: found $(M - Br)^+$ 384.1534; $C_{19}H_{31}{}^{79}Br_2NO_2$ requires $(M - Br)^+$ 384.1538; IR (NaCl) 1685 cm^{-1}; ^{1}H NMR δ 4.54 (m, 2H), 3.31−3.17 (complex m, 2H), 2.55−2.47 (complex m, 1H), 2.25−2.17 (complex m, 2H), 2.07−1.42 (complex m, 13H), 1.37−1.25 (complex m, 1H), 1.12−0.94 (complex m, 2H), 0.89 (d, *J* = 6.5 Hz, 6H), 0.79 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 156.5, 74.4, 47.4, 42.0, 41.5, 40.5, 38.5, 34.3, 33.2, 32.4, 31.4, 31.1, 29.4, 28.8, 27.8, 26.5, 26.3, 25.7, 23.5, 22.1, 20.8, 16.5 (sixteen signals obscured/overlapping); MS *m*/*z* (EI, 70 eV) (rel intensity) 386 (0.3) 384 (0.3) $[(M - Br)^+]$, 166 (100).

[1α(*R),2β,5α]-5-Methyl-2-(1′-methylethyl)cyclohexyl-(3a*S*,7a*R*)-7-bromo-2,3,3a,4,5,7a-hexahydro-1*H*-indole-1-carboxylate (29) and [1α(R*),2β,5α]-5-Methyl-2-(1′-methylethyl)cyclohexyl-(3a*R*,7a*S*)-7-bromo-2,3,3a,4,5,7a-hexahydro-1*H*-indole-1-carboxylate (30). Method A.** Silver acetate (80 mg, 0.479 mmol) was added to a magnetically stirred solution of a 1:1 mixture of carbamates **27** and **28** (150 mg, 0.324 mmol) in anhydrous TFE (50 mL). The resulting mixture was protected from light and allowed to stir, under an atmosphere of nitrogen, at 18 °C for 10 h. The precipitated silver salts were then removed by filtration through a plug of Celite, and the solids thus retained were washed with EtOAc (60 mL). Concentration of the combined filtrates afforded a pale-yellow oil, which was subjected to dry-column flash chromatography (silica gel, 1:4 EtOAc/hexane elution). Concentration of the appropriate fractions (R_f = 0.4) gave an inseparable 1:1 mixture of the diastereoisomeric hexahydroindoles **29** and **30** (116 mg, 94%) as a clear, colorless oil: found $(M - Br)^+$ 304.2265; $C_{19}H_{30}BrNO_2$ requires $(M - Br)^+$ 304.2276; IR (NaCl) 1687 cm^{-1}; ^{1}H NMR δ 6.09 (broad s, 1H), 4.64−4.55 (complex m, 2H), 3.61−3.36 (complex m, 2H), 2.50 (m, 1H), 2.13−1.95 (complex m, 4H), 1.93−1.73 (complex m, 5H), 1.66−1.61 (complex m, 2H), 1.47−1.32 (complex m, 2H), 1.11−0.94 (complex m, 2H), 0.87 (d, *J* = 6.9 Hz, 6H), 0.76 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR δ 155.7, 130.8, 124.5, 75.0, 60.1, 59.8, 47.3, 44.7-(4), 44.6(6), 41.8, 38.0, 34.4, 34.3, 31.4, 26.5, 25.7, 24.8, 23.9, 22.8, 22.0, 21.5, 21.0, 20.7, 16.8 (fourteen signals obscured/overlapping; MS *m*/*z* (EI, 70 eV) (rel intensity) 304 (9) $[(M - Br)^+]$, 166 (100).

Method B. A solution of carbamate (±)-**20** (500 mg, 1.93 mmol), KOH (2.7 g, 48.2 mmol) and hydrazine hydrate (0.6 mL, 19.3 mmol) in ethylene glycol (30 mL) was heated at reflux under a nitrogen atmosphere for 2 h. The cooled reaction mixture was poured into water (100 mL) and extracted with CH_2Cl_2. The combined organic fractions were acidified with HCl (40 mL of a 2 M aqueous solution), and the separated aqueous phase was basified to pH 12 using NaOH (2 M aqueous solution) and then extracted with CH_2Cl_2. The combined organic fractions were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give *cis*-(±)-7-bromo-2,3,3a,4,5,7a-hexahydro-1*H*-indole (380 mg, 98%) as an unstable, volatile and colorless oil. ^{1}H NMR δ 6.17 (t, *J* = 4.3 Hz, 1H), 3.59 (d, *J* = 6.3 Hz, 1H), 3.07−2.99 (complex m, 1H), 3.95−2.87 (complex m, 1H), 2.44−2.32 (complex m, 1H), 2.18−1.90 (complex m, 4H), 1.75−1.65 (complex m, 1H), 1.63−1.45 (complex m, 2H); ^{13}C NMR δ 131.1, 125.9, 62.5, 44.2, 38.0, 30.2, 25.6, 24.3.

A magnetically stirred solution of *cis*-(±)-7-bromo-2,3,-3a,4,5,7a-hexahydro-1*H*-indole (380 mg, mmol) and pyridine (320 μL, 3.96 mmol) in anhydrous CH_2Cl_2 (25 mL) maintained at 0 °C was treated, dropwise, with (−)-menthyl chloroformate (830 μL, 3.87 mmol). The resulting mixture was stirred at room temperature for 10 h and then diluted with CH_2Cl_2 (25 mL) and water (30 mL). The separated aqueous phase was extracted with CH_2Cl_2, and the combined organic fractions were washed with water and then brine before being dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting oil was subjected to dry-column flash chromatography (silica gel, 1:4 EtOAc/hexane elution), and concentration of the appropriate fractions (R_f = 0.4) gave an inseparable 1:1 mixture of the carbamates **29** and **30** (665 mg, 92%) as a clear, colorless oil. This material was identical, in all respects, with that obtained by Method A as described above.

[1α(*R),2β,5α]-5-Methyl-2-(1′-methylethyl)cyclohexyl-[3a*S*,7a*R*]-7-(1′,3′-benzodioxol-5′-yl)-2,3,3a,4,5,7a-hexahydro-1*H*-indole-1-carboxylate (31) and [1α(*R**),2β,5α]-5-**

Methyl-2-(1′-methylethyl)cyclohexyl-[3a*R*,7a*S*]-7-(1′,3′-benzodioxol-5′-yl)-2,3,3a,4,5,7a-hexahydro-1*H*-indole-1-carboxylate (32). A solution of a 1:1 mixture of carbamates **29** and **30** (374 mg, 0.98 mmol) and boronic acid **3**[5d] (205 mg, 1.23 mmol) in EtOH (6.0 mL) and benzene (50 mL) was treated with Na_2CO_3 (14 mL of a 2 M aqueous solution) and $Pd(PPh_3)_4$ (113 mg, 0.098 mmol). The resulting mixture was heated at reflux for 16 h under a nitrogen atmosphere while being protected from light. The cooled reaction mixture was then diluted with diethyl ether (40 mL) and washed with $NaHCO_3$ (saturated aqueous solution) and then brine. The separated organic phase was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil, which was subjected to dry-column flash chromatography (silica gel, 3:17 EtOAc/hexane elution). Concentration of the appropriate fractions (R_f = 0.4) then gave a clear, colorless oil, which was subjected to semipreparative HPLC (Waters μ-Porasil column, 3:17 EtOAc/hexane elution, flow rate 2 mL/min), and in this manner two fractions, A and B, were obtained.

Concentration of fraction A (R_t = 9.6 min) afforded carbamate **31** (203 mg, 49%) as a clear, colorless oil: found M^+ 425.2555; $C_{26}H_{35}NO_4$ requires M^+ 425.2566; IR (NaCl) 1688 cm^{-1}; ^1H NMR δ 6.70 (m, 3H), 5.89 (s, 2H), 5.67 (broad s, 1H), 4.85 (broad s, 1H), 4.40−4.34 (complex m, 1H), 3.51 (broad s, 1H), 3.27−3.19 (complex m, 1H), 2.45 (broad s, 1H), 2.27−2.06 (complex m, 2H), 1.98−1.56 (complex m, 8H), 1.46−1.31 (complex m, 1H), 1.23 (broad s, 1H), 1.04−0.60 (complex m, 6H), 0.84 (d, J = 6.8 Hz, 6H); ^{13}C NMR δ 155.6 146.7, 146.2, 138.5, 135.9, 127.0, 121.2, 108.7, 107.5, 100.6, 74.6, 57.5, 47.0, 44.4, 41.3, 36.4, 34.3, 31.2, 25.7, 23.3, 22.0, 20.9(1), 20.8(6), 16.2, (two signals obscured/overlapping); MS *m*/*z* (EI, 70 eV) (rel intensity) 425 (5) (M^+), 54 (100).

Concentration of fraction B (R_t = 10.3 min) gave carbamate **32** (203 mg, 49%) as a colorless oil: found $(M - H)^+$ 424.2468; $C_{26}H_{35}NO_4$ requires $(M - H)^+$ 424.2488; IR (NaCl) 1688 cm^{-1}; ^1H NMR δ 6.78−6.56 (complex m, 3H), 5.88 (s, 2H), 5.65 (broad s, 1H), 4.92−4.73 (complex m, 1H), 4.39−4.30 (dt, J = 10.8 and 4.0 Hz, 1H), 3.61−3.45 (complex m, 1H), 3.22 (broad s, 1H), 2.52−2.41 (complex m, 1H), 2.31−2.07 (complex m, 2H), 2.00−1.71 (complex m, 6H), 1.62−1.58 (complex m, 3H), 1.37 (broad s, 1H), 1.27−1.21 (complex m, 1H), 1.18−0.74 (complex m, 10H), 0.56 (broad s, 1H); ^{13}C NMR δ 155.3, 146.6, 146.2, 138.7, 136.2, 127.9, 121.2, 108.9, 107.6, 100.6, 74.5, 57.5, 47.1, 44.5, 41.7, 40.2, 36.9, 36.1, 34.3, 31.1, 26.0, 25.2, 23.8, 22.0, 20.8, 16.8; MS *m*/*z* (EI, 70 eV) (rel intensity) 425 (1) (M^+), 174 (100).

[1α(*R),2*β*,5α]-5-Methyl-2-(1′-methylethyl)cyclohexyl-[3a*S*,7*S*,7a*R*]-7-(1′,3′-benzodioxol-5′-yl)octahydro-1*H*-indole-1-carboxylate (33)**. A magnetically stirred solution of compound **31** (72 mg, 0.17 mmol) in EtOAc (10 mL) containing 10% Pd on C (15 mg) maintained at 18 °C was stirred under an atmosphere of hydrogen for 16 h. The catalyst was then removed by filtration through a pad of Celite, and the solids thus retained were washed with EtOAc (15 mL). The combined filtrates were concentrated under reduced pressure to give a yellow oil, which was subjected to dry-column flash chromatography (silica, 3:17 EtOAc/hexane elution). Concentration of the appropriate fractions (R_f = 0.5) afforded the title compound **33** (72 mg, 100%) as a clear, colorless oil: found M^+ 427.2703; $C_{26}H_{37}NO_4$ requires M^+ 427.2722; IR (NaCl) 1688 cm^{-1}; ^1H NMR δ 6.81−6.75 (complex m, 2H), 6.67 (d, J = 8.0 Hz, 1H), 5.89 (s, 2H), 4.48 (dt, J = 10.7 and 4.1 Hz, 1H), 4.17 (t, J = 7.1 Hz, 1H), 3.36−3.22 (complex m, 2H), 2.85 (m, 1H), 2.35 (m, 1H), 2.10−1.40 (complex m, 12H), 1.37−1.28 (complex m, 1H), 1.10−0.80 (complex m, 4H), 0.91 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H), 0.76 (d, J = 6.9 Hz, 3H); ^{13}C NMR δ 155.3, 147.1, 145.4, 138.1, 121.8, 109.3, 107.6, 100.6, 74.5, 59.3, 47.2, 45.9, 41.6, 39.9, 37.2, 34.4, 31.3, 28.8, 26.7, 26.2, 25.2, 23.3, 22.1, 20.9, 18.7, 16.2; MS *m*/*z* (EI, 70 eV) (rel intensity) 427 (32) (M^+), 289 (100).

[1α(*R),2*β*,5α]-5-Methyl-2-(1′-methylethyl)cyclohexyl-[3a*R*,7*R*,7a*S*]-7-(1′,3′-benzodioxol-5′-yl)octahydro-1*H*-indole-1-carboxylate (34).** Hydrogenation of the unsaturated carbamate **32** (72 mg, 0.17 mmol) under the same conditions as used for isomer **31** gave, after work up and dry-column flash chromatography (silica gel, 3:17 EtOAc/hexane elution, R_f = 0.5), the title compound **34** (72 mg, 100%) as a clear, colorless oil: found M^+ 427.2699; $C_{26}H_{37}NO_4$ requires M^+ 427.2722; IR (NaCl) 1688 cm^{-1}; ^1H NMR δ 6.77−6.64 (complex m, 3H), 5.89 (s, 2H), 4.44 (dt, J = 10.7 and 4.2 Hz, 1H), 4.16 (t, J = 8.3 Hz, 1H), 3.29 (broad s, 1H), 3.22 (broad s, 1H), 2.94 (broad s, 1H), 2.37 (broad s, 1H), 2.01−1.50 (complex m, 12H), 1.46 (broad s, 1H), 1.28−1.21 (complex m, 1H), 1.09−0.66 (complex m, 3H), 0.89 (d, J = 7.4 Hz, 3H), 0.87 (d, J = 7.5 Hz, 3H), 0.78 (d, J = 6.9 Hz, 3H); ^{13}C NMR δ 155.5, 147.1, 145.5, 138.2, 121.8, 109.3, 107.6, 100.6, 74.4, 59.5, 47.2, 46.2, 41.4, 40.3, 37.4, 34.4, 31.3, 29.0, 26.4, 26.3, 25.0, 23.6, 22.1, 20.9, 18.7, 16.5; MS *m*/*z* (EI, 70 eV) (rel intensity) 427 (17) (M^+), 83 (100).

(12α,15α,16α)-9,10-[Methylenebis(oxy)]galanthan-7-one [(−)-25]. Treatment of compound **33** (50 mg, 0.08 mmol) with $POCl_3$ (8.0 mL, 0.043 mol) under the conditions defined for the conversion (±)-**24** → (±)-**25** above but using a reaction time of 24 h afforded a light-yellow oil on workup. Subjection of this material to dry-column flash chromatography (silica, EtOAc elution) and concentration of the appropriate fractions (R_f = 0.4) gave a white solid, which was recrystallized (EtOAc/diethyl ether) to afford the title compound (−)-**25** (30 mg, 95%) as colorless prisms, mp 152−153 °C: found C, 70.4; H, 6.3; N, 5.1; $C_{16}H_{17}NO_3$ requires C, 70.8; H, 6.3; N, 5.2; $[\alpha]_D$ −41.5 (*c* 0.2). This material was identical, by IR, ^1H NMR, and ^{13}C NMR spectroscopy, with the racemic modification obtained earlier.

(12α,15α,16α)-9,10-[Methylenebis(oxy)]galanthan-7-one [(+)-25]. Treatment of compound **34** (48 mg, 0.08 mmol) with $POCl_3$ (8.0 mL, 0.043 mol) under the conditions defined for the conversion (±)-**24** → (±)-**25** above but using a reaction time of 24 h afforded a light-yellow oil on workup. Subjection of this material to dry-column flash chromatography (silica, EtOAc elution) and concentration of the appropriate fractions (R_f = 0.4) gave a white solid, which was recrystallized (EtOAc/diethyl ether) to afford the title compound (+)-**25** (29 mg, 95%) as colorless prisms, mp 152−153 °C: found C, 70.7; H, 6.0; N, 5.2; $C_{16}H_{17}NO_3$ requires C, 70.8; H, 6.3; N, 5.2; $[\alpha]_D$ +41.5 (*c* 0.2). This material was identical, by IR, ^1H NMR, and ^{13}C NMR spectroscopy, with the racemic modification obtained earlier.

(12α,15α,16α)-9,10-[Methylenebis(oxy)]galanthan [(−)-γ-lycorane, (−)-1]. Treatment of compound (−)-**25** (30 mg, 0.11 mmol) with $LiAlH_4$ (26 mg, 0.684 mol) in THF (1 mL) under the conditions defined for the conversion (±)-**25** → (±)-**1** afforded, after workup and flash chromatography (silica, EtOAc elution, R_f = 0.4), the title compound (−)-**1** (24.5 mg, 86%) as a clear colorless oil, $[\alpha]_D$ −16.7 (*c* 1.2) {lit.[2] $[\alpha]_D$ −17.0 (*c* 0.25)}. This material was identical, by IR, ^1H NMR, and ^{13}C NMR spectroscopy, with the racemic modification obtained earlier.

(12*β*,15*β*,16*β*)-9,10-[Methylenebis(oxy)]galanthan [(+)-γ-lycorane, (+)-1]. Treatment of compound (+)-**25** (28 mg, 0.103 mmol) with $LiAlH_4$ (25 mg, 0.658 mol) under the conditions defined for the conversion (±)-**25** → (±)-**1** afforded, after workup and flash chromatography (silica, EtOAc elution, R_f = 0.4), the title compound (+)-**1** (22.5 mg, 85%) as a clear colorless oil, $[\alpha]_D$ +17.0 (*c* 1.2) {lit.[2] $[\alpha]_D$ = +16.3 (*c* 0.30)}. This material was identical, by IR, ^1H NMR, and ^{13}C NMR spectroscopy, with the racemic and levorotatory modifications obtained earlier.

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Supporting Information Available: ^1H or ^{13}C NMR spectra for the mixtures of compounds (+)-**9**/C2-*epi*-(+)-**9**, (+)-**10**/C2-*epi*-(+)-**10**, **27**/**28**, **29**/**30** and ^1H or ^{13}C NMR spectra for compounds (±)-**11**, (±)-**12**, (±)-**13**, (±)-**15**, C2-*epi*-(±)-**15**, (*Z*)−(±)-**18**, (±)-**19**, (±)-**24**, **31**, **32**, **33** and **34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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