General Methods for Alkaloid Synthesis. Total Synthesis of Racemic Lycoramine[1]

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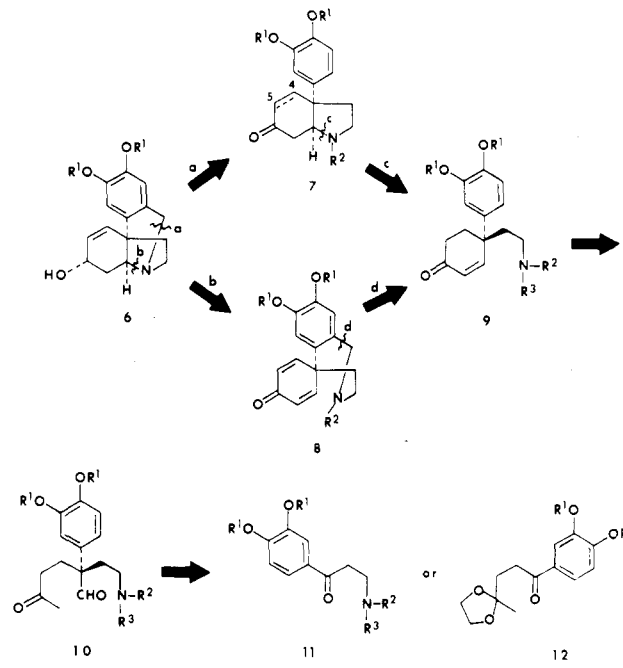
The total synthesis of the Amaryllidaceae alkaloid lycoramine (4) has been completed. The 4-aryl-4-alkylcyclohexenone **24**, which is the key intermediate, was prepared by two independent routes, each of which features an application of a general methodology for the construction of quaternary carbon atoms via the net geminal acylation–alkylation of a carbonyl group. Thus, the protected *o*-vanillin **17** was converted by a standard sequence of reactions to the aryl alkyl ketones **19** and **26** which were then elaborated to the respective metalloenamines **21** and **27** by one-carbon homologation, using the phosphonate **20**. Alkylation of **21** with the β-bromoethyl dioxolane **22** followed by cycloaldolization and dehydration of the intermediate keto aldehyde **23** afforded the cyclohexenone **24** in 32% overall yield from **17**. Alternatively, reaction of **27** with the β-bromoethyl urethane **28** also produced **23** which was cyclized to the cyclohexenone **24** in 40% overall yield from **17**. The synthesis of lycoramine (4) from **24** was effected in 49% overall yield by a straightforward sequence of reactions which culminated with the Bischler–Napieralski cyclization of the formamide **35**.

Introduction

The alkaloids of the Amaryllidaceae family,[3,4] representative members of which include lycorine (**1**),[5] crinine (**2**),[6] pretazettine (**3**),[7] lycoramine (**4**),[8] and galanthamine (**5**),[9] continue to elicit the interests of synthetic organic chemists. In addition to the structural diversity exhibited by this class of alkaloids, the significant biological activity that has been ascribed to lycorine (**1**; inhibitor of the formation of the peptide bond in protein synthesis[10]), pretazettine (**3**; antitumor and antiviral[11]), and galanthamine (**5**; analgesic[9e]) has also provided impetus to the

Scheme I



(1) A preliminary account of a portion of this work has appeared; see Martin, S. F.; Garrison, P. J. *J. Org. Chem.* **1981**, *46*, 3567.

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

(3) For reviews of the chemistry of Amaryllidaceae alkaloids, see (a) Wildman, W. C. In "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1968; Vol. 11, p 307. (b) Fuganti, C. In "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1975; Vol. 15, p 83. (c) Grundon, M. F. In "Specialist Periodical Reports, The Alkaloids"; The Chemical Society, Burlington House: London, 1979; Vol. 9, p 137. See also Vol. 1–8.

(4) For a summary of some recent developments in the syntheses of the Amaryllidaceae alkaloids, see (a) Stevens, R. V. *Acc. Chem. Res.* **1977**, *10*, 193. (b) Stevens, R. V. In "The Total Synthesis of Natural Products"; ApSimon, J. Ed; Wiley-Interscience: New York, 1977; Vol. 3, p 439. (c) Tsuda, Y. *Heterocycles* **1978**, *10*, 555.

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(6) For syntheses of crinine, maritidine, and related alkaloids, see inter alia (a) Muxfeldt, H.; Schneider, R. S.; Mooberry, J. B. *J. Am. Chem. Soc.* **1966** *88*, 3670. (b) Whitlock, H. W., Jr.; Smith, G. L. *Ibid.* **1967**, *89*, 3600. (c) Kametani, T.; Kohno, T.; Charubala, R.; Shibuya, S.; Fukumoto, K. *Chem. Pharm. Bull.* **1972**, *20*, 1488. (d) Stevens, R. V.; DuPree, L. E., Jr.; Loewenstein, P. L. *J. Org. Chem.* **1972**, *37*, 977. (e) Ninomiya, I.; Naito, T.; Kiguchi, T.; *J. Chem. Soc., Perkin Trans. 1* **1973**, 2261. (f) Kotani, E.; Takeuchi, N.; Tobinaga, S. *J. Chem. Soc., Chem. Commun.* **1973**, 550. (g) Tomioku, K.; Koga, K.; Yamada, S. *Chem. Pharm. Bull.* **1977**, *25*, 2681. (h) Schwartz, M. A.; Rose, B. F.; Holton, R. A.; Scott, S. W.; Vishnuvajjala, B. *J. Am. Chem. Soc.* **1977**, *99*, 2571. (i) Kupchan, S. M.; Dhingra, O. P.; Kim, C.-K. *J. Org. Chem.* **1978**, *43*, 4076. (j) Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1978**, *34*, 2579. (k) Fushimi, T.; Ikuta, H.; Irie, H.; Nakadachi, K.; Uyeo, S. *Heterocycles* **1979**, *12*, 1311. (l) Sanchez, I. H.; Mendoza, M. T. *Tetrahedron Lett.* **1980**, 3651. (m) Keck, G. E.; Webb, R. R., II *J. Am. Chem. Soc.* **1981**, *103*, 3173.

(7) For syntheses of pretazettine and related alkaloids, see (a) Tsuda, Y.; Ukai, A.; Isobe, K. *Tetrahedron Lett.* **1972**, 3153. (b) Hendrickson, J. B.; Bogard, T. L.; Fisch, M. E.; Grossert, S.; Yoshimura, N. *J. Am. Chem. Soc.* **1974**, *96*, 7781. (c) Isobe, K.; Taga, J.; Tsuda, Y. *Tetrahedron Lett.* **1976** 2331. (d) Kobayashi, S.; Kihara, M. *Heterocycles* **1979**, *12*, 1547. (e) Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *J. Am. Chem. Soc.* **1980**, *102*, 2838. See also ref 4c.

(8) For previous syntheses of lycoramine, see (a) Hazama, N.; Irie, H.; Mizutani, T.; Shingu, T.; Takada, M.; Uyeo, S.; Yoshitake, A. *J. Chem. Soc. C* **1968**, 2947. (b) Misaka, Y.; Mizutani, T.; Sekido, M.; Uyeo, S. *Ibid.* **1968**, 2954. (c) Schultz, A. G.; Yee, Y. K.; Berger, M. H. *J. Am. Chem. Soc.* **1977**, *99*, 8065.

(9) For previous syntheses of galanthamine and related compounds, see (a) Barton, D. H. R.; Kirby, G. W. *J. Chem. Soc.* **1962**, 806. (b) Franck, B.; Lubs, H. J. *Justus Liebigs Ann. Chem.* **1968**, *720*, 131. (c) Kametani, T.; Yamaki, K.; Yagi, H.; Fukumoto, K. *J. Chem. Soc. C* **1969**, 2602. (d) Kametani, T.; Shishido, K.; Hayashi, E.; Seino, C.; Kohno, T.; Shibuya, S.; Fukumoto, K. *J. Org. Chem.* **1971**, *36*, 1295. (e) Kametani, T.; Seino, C.; Yamaki, K.; Shibuya, S.; Fukumoto, K.; Kigasawa, K.; Satoh, F.; Hiiragi, M.; Hayasaka, T. *J. Chem. Soc. C* **1971**, 1043. (f) Kametani, T.; Yamaki, K.; Terui, T.; Shibuya, S.; Fukumoto, K. *Ibid.* **1972**, 1513. (g) Kametani, T.; Yamaki, K.; Terui, T. *J. Heterocycl. Chem.* **1973**, *10*, 35. (h) Shimizu, K.; Tomioka, K.; Yamada, S.; Koga, K. *Chem. Pharm. Bull.* **1978**, *26*, 3765.

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

(11) (a) Papas, T. S.; Sandhaus, L.; Chirigos, M. A.; Furusawa, E. *Biochem. Biophys. Res. Commun.* **1973**, *52*, 88. (b) Suzuki, N.; Tani, S.; Furusawa, S.; Furusawa, E. *Proc. Soc. Exp. Biol. Med.* **1974**, *145*, 771. (c) Furusawa, E.; Suzuki, N.; Furusawa, S.; Lee, J. Y. B. *Ibid.* **1975**, *149*, 771. (d) Furusawa, E.; Furusawa, S.; Lee, J. Y. B.; Patanavanich, S. *Ibid.* **1976**, *152*, 186.

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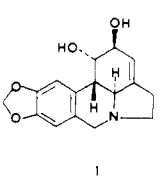
design of general strategies for the syntheses of these naturally occurring bases, and a number of notable achievements have already been recorded.[5-9]



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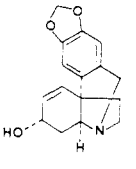

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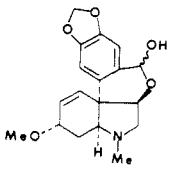

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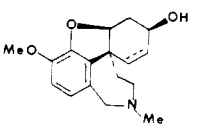


4: 1,2-dihydro
5: $\Delta^{1,2}$

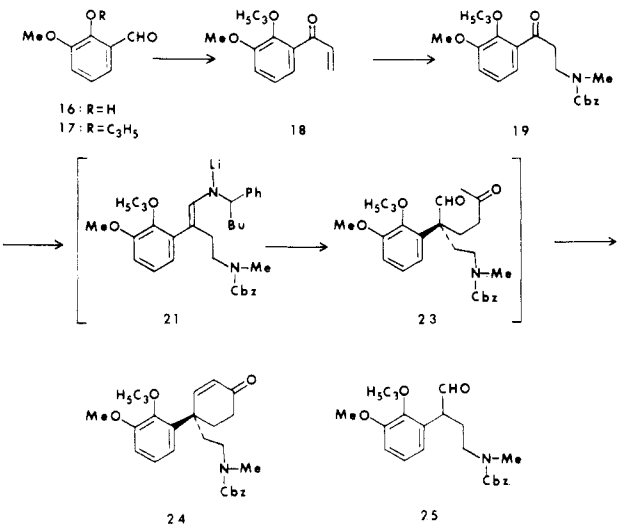
Our analysis of the synthetic problems posed by the Amaryllidaceae alkaloids **2–5**, each of which is characterized by the presence of an oxygenated cyclohexane ring with a geminal aryl–alkyl moiety, is depicted in retrosynthetic format in Scheme I. Disconnection of bond a of the generalized 5,10b-ethanophenanthridine **6** affords the *cis*-3a-arylhydroindole **7** which incorporates the principal skeletal features of pretazettine (**3**). Alternatively, rupture of bond b of **6** produces the spirocyclic hydrobenzazepine **8** which possesses most of the molecular framework found in lycoramine (**4**) and galanthamine (**5**).

It should not escape unnoticed that compounds related to **7** and **8** are frequently employed as the key intermediates in the reported syntheses of crinine (**2**) and related alkaloids. In this regard, the elegant approaches to *cis*-3a-arylhydroindoles **7** that have been developed by Stevens[4a] and Tsuda[7a,c] are particularly noteworthy as is the biomimetic entry to spirocyclic hydrobenzazepines **8** via the intramolecular coupling of phenolic substrates.[6c,e-i,9] On the other hand, the formulation of our own strategy for the synthesis of the Amaryllidaceae alkaloids related to **2–5** was guided by the observation that scission of either bond c in **7** or bond d in **8** afforded the 4-aryl-4-(β-aminoethyl)cyclohexenone **9**. Although the synthesis of **9** from the δ-keto aldehyde **10** is straightforward, the preparation of **10** from readily available starting materials such as the ketones **11** and **12** requires the generation of a quaternary carbon atom by the net replacement of the two carbon–oxygen bonds of the carbonyl function with a geminal acyl–alkyl array and represents a significant challenge to existing methodology.[12]

In our recent synthesis of mesembrine (e.g., **7**, $R^1 = R^2$ = Me; 4,5-dihydro),[13] we unveiled a solution to the problem of constructing *cis*-3a-arylhydroindoles **7** from carbonyl precursors related to **11** and **12**. The featured step in this synthesis entailed the construction of the critical quaternary carbon atom by exploiting a general procedure for effecting the geminal acylation–alkylation at a carbonyl center as required by the conversion **11** or **12** → **10**.[14] In order to establish that compounds related to the spirocyclic hydrobenzazepine **8** may also be elaborated according to the strategy adumbrated in Scheme I, we embarked upon the total synthesis of lycoramine (**4**). We now disclose the details of this investigation.[1]

(12) For a review of methodology for the construction of quaternary carbon atoms, see Martin, S. F. *Tetrahedron* **1980**, *36*, 419.
(13) Martin, S. F.; Puckette, T. A.; Colapret, J. A. *J. Org. Chem.* **1979**, *44*, 3391.
(14) Martin, S. F.; Phillips, G. W.; Puckette, T. A.; Colapret, J. A. *J. Am. Chem. Soc.* **1980**, *102*, 5866.

Scheme II



16: R=H
17: R=C_3H_5

18

19

21

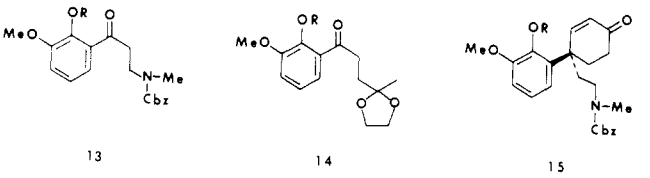
23

24

25

Results

In accordance with the general strategy depicted in Scheme I, we envisioned that the synthesis of lycoramine (**4**) would proceed via the key intermediate cyclohexenone **15**, which should be accessible from either of the ketones **13** and **14**. Since the carbobenzyloxy (Cbz) moiety ap-



13

14

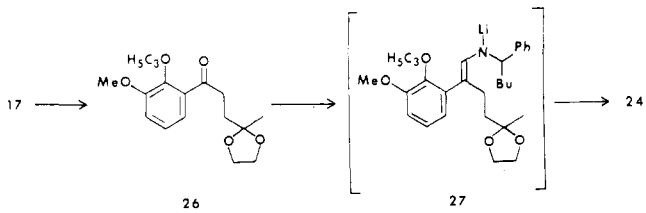
15

peared at the outset to be eminently suitable as a protecting group for nitrogen, it merely remained to select a protecting group for the phenolic oxygen. In the early stages of the investigation, we examined the feasibility of employing the benzyl and the methoxymethyl ether protecting groups, but it soon became apparent that there were serious problems associated with both. For example, the selective removal of the *O*-benzyl group from **15** (R = CH_2Ph) was not possible under a variety of conditions. Although trityl tetrafluoroborate[15] did selectively cleave the *O*-benzyl group of **13** (R = CH_2Ph), the cyclohexenone **15** (R = CH_2Ph) was recovered unchanged after prolonged treatment with the reagent. In contrast, the methoxymethyl ether group proved too labile. Repeated attempts to prepare the aryl ketone **13** (R = CH_2OMe) were unsuccessful since the propitious carbonyl function appears to facilitate both the Lewis and protic acid catalyzed cleavage of the neighboring methoxymethyl ether moiety. In the end, the allyl group emerged as the most suitable protecting group for the phenolic oxygen.

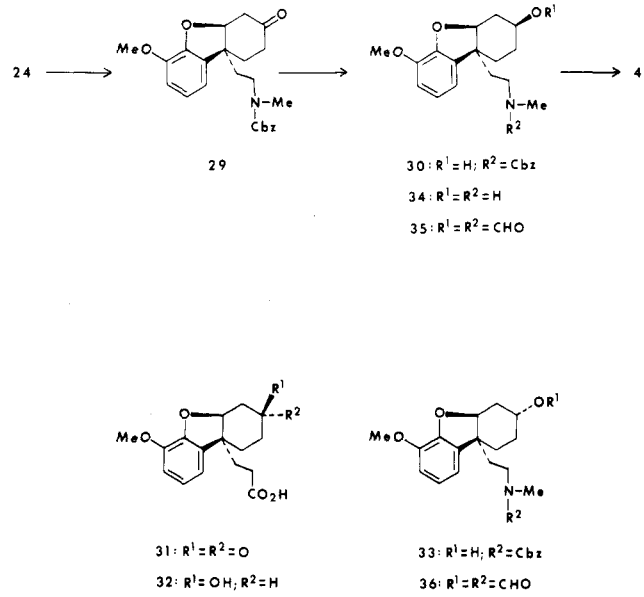
The preparation of the requisite ketone **19** was readily achieved by a straightforward sequence of reactions (Scheme II). Deprotonation of commercially available *o*-vanillin (**16**) with sodium hydride in dimethylformamide followed by alkylation of the intermediate phenoxide anion with allyl bromide provided *O*-allyl-*o*-vanillin (**17**) in 92% yield. The subsequent conversion of **17** to the vinyl ketone **18** was then conveniently effected in 81% yield by the addition of vinylmagnesium bromide (4 equiv) to **17** followed by Jones oxidation of the intermediate alcohol. When the enone **18** was allowed to react neat with benzyl

(15) Barton, D. H. R.; Magnus, P. D.; Smith, G.; Streckert, G.; Zurr, D. *J. Chem. Soc., Perkin Trans. 1* **1972**, 542.

Scheme III



Scheme IV



N-methylcarbamate in the presence of camphorsulfonic acid, the protected β-aminoethyl aryl ketone **19** was obtained in 91% yield.[16]

The next stage of the synthesis involved the transformation of the ketone **19** into the 4,4-disubstituted cyclohexenone **24** and was readily achieved by exploiting our one-pot procedure for effecting the annelation of a cyclohexenone ring at a carbonyl carbon.[14] In the event, olefination of **19** with diethyl [(benzylideneamino)lithiomethyl]phosphonate (**20**) produced an intermediate 2-azadiene which underwent selective addition of *n*-butyllithium to the carbon–nitrogen double bond to afford the metalloenamine **21**. Alkylation of **21** in situ with carefully purified 2-(2-bromoethyl)-2-methyl-1,3-dioxolane (**22**)[17] and subsequent acid-catalyzed hydrolysis of the intermediate imino ketal provided the δ-keto aldehyde **23**. Upon treatment with potassium hydroxide in aqueous methanol, **23** underwent facile base-catalyzed cycloaldolization and dehydration to give **24** in 43% overall yield from **19**. Unfortunately, variable amounts (10–20%) of the unalkylated aldehyde **25** accompanied the desired ketone **24**. Despite numerous attempts, reaction conditions that would allow the complete alkylation of the metalloenamine **21** could not be found. The use of the corresponding alkyl iodide[18] as the alkylating agent provided no advantage.

Since complete alkylation of the metalloenamine **21** could not be achieved, an alternate route to the key intermediate cyclohexenone **24** was examined (Scheme III) in the hope that the overall yield might be improved. This sequence commenced with the monoprotected 1,4-dione **26** which was readily prepared in 72% overall yield by the addition of the Grignard reagent derived from 2-(2-bromoethyl)-2-methyl-1,3-dioxolane[19] to *O*-allyl-*o*-vanillin (**17**) followed by oxidation of the intermediate benzylic alcohol with pyridinium dichromate[20] in dimethylformamide. The ketone **26** was converted to the metalloenamine **27** in the usual fashion by sequential reaction of **26** with diethyl [(benzylideneamino)lithiomethyl]phosphonate (**20**) and then *n*-butyllithium. The metalloenamine **27** thus generated was alkylated in situ with benzyl *N*-(2-bromoethyl)-*N*-methylcarbamate (**28**) followed by acid-catalyzed hydrolysis of the intermediate imino ketal to afford the δ-keto aldehyde **23** which was smoothly converted to the cyclohexenone **24** upon treatment with potassium hydroxide in aqueous methanol. The yield of **24** from the monoprotected dione **26** was 55%. Since no α,α-disubstituted aldehyde was isolated, the alkylation of the metalloenamine **27** with **28** appears to have proceeded efficiently.

The overall yield of the key intermediate cyclohexenone **24** from *O*-allyl-*o*-vanillin (**17**) by this second route (Scheme III) was 40% and represents a significant improvement over that of 32% which was previously obtained by the route depicted in Scheme II. The applicability of our procedure for effecting the net geminal acylation–alkylation of the carbonyl function[14] to the synthesis of polyfunctional substrates is clearly evidenced by these conversions (e.g., **19** or **26** → **23** → **24**). It is particularly significant that a variety of functionalities in both the starting ketones (e.g., **19** and **26**) and the alkylating agents (e.g., **22** and **28**) are compatible with the reaction conditions.

With the protected 4-aryl-4-(β-aminoethyl)cyclohexenone **24** now readily available, the stage was set for the completion of the synthesis of lycoramine (**4**) (Scheme IV). Having served its purpose, the *O*-allyl group was cleaved by heating **24** in refluxing ethanol containing a catalytic amount (7%) of rhodium trichloride,[21] whereupon spontaneous cyclization of the intermediate phenol ensued to afford the *cis*-hydrodibenzofuran **29** in 86% yield.

Although the obtention of the cis B/D ring juncture was anticipated on the basis of available precedent in a closely related system,[8b] it was nevertheless deemed desirable to confirm this stereochemical assignment prior to the execution of further transformations. Whereas the 200-MHz ^{1}H NMR spectrum of **29** at 25 °C is difficult to interpret owing to the hindered rotation about the carbon–nitrogen bond of the urethane moiety, all protons are well resolved in the spectrum at 85 °C, and the proton α to the ether oxygen appears as a broadened triplet (J = 3.5 Hz) at δ 4.92 having a width at half-height (W_H) of 8 Hz. In rigid cyclohexanes, this value of W_H is normally indicative of an equatorial proton.[22] Since these data clearly establish that the proton α to the ether oxygen is equatorial, the B/D ring juncture is necessarily cis.

The next step of the synthesis requires the stereoselective reduction of **29** from the less hindered, equatorial face of the carbonyl function to give the endo alcohol **30**. Although it had been previously reported that **31** underwent stereoselective reduction with sodium borohydride in aqueous tetrahydrofuran to give **32**,[8b] subjection of **29** to the identical conditions afforded a mixture (3.5:1) of the desired alcohol **30** together with its epimer **33**. A variety of conditions were then examined in order to improve the stereoselectivity of the reduction, and these data are

(16) Cf. Mohrle, H.; Engelsing, R. *Monatsch. Chem.* **1971**, *102*, 233.
(17) Brown, E.; Dhal, R. *Bull. Soc. Chim. Fr.* **1972**, 4292.
(18) Trost, B. M.; Kunz, R. A. *J. Am. Chem. Soc.* **1975**, *97*, 7152.
(19) Ponaras, A. A. *Tetrahedron Lett.* **1976**, 3105.
(20) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.
(21) (a) Corey, E. J.; Suggs, J. W. *J. Org. Chem.* **1973**, *38*, 3224. (b) Grieco, P. A.; Nishizawa, M.; Marinovic, N.; Ehmann, W. J. *J. Am. Chem. Soc.* **1976**, *98*, 7102.
(22) Cf. Hassner, A.; Heathcock, C. *J. Org. Chem.* **1964**, *29*, 1350.

Table I. Hydride Reduction of 29

entry	reducing agent	solvent	temp, °C	30/33	% yield
1	$NaBH_4$	THF/H_2O	0 → 25	3.5:1	85
2	$LiAlH_4$	Et_2O	−78 → −40	3.5:1	86
3	$LiAlH_4$	THF	0	4:1	91
4	$LiAlH_4$	THF	−78 → −40	5:1	89
5	$LiAlH_4$	glyme	−78 → −40	20:1	90
6	$LiAlH_4/AlCl_3$	Et_2O	reflux	20:1	52
7	$LiBH(sec\text{-}Bu)_3$	THF	−78	>40:1	88

summarized in Table I. As is evident upon examination of these results, the stereochemical outcome of the reduction of **29** is primarily dependent upon the nature of the hydride reducing agent and the solvent. When lithium aluminum hydride was employed, the stereoselectivity of the reduction increased with Lewis basicity of the solvent. The most sterically demanding reagent L-Selectride (entry 7) gave in 88% yield the desired alcohol **30** as the only product detectable by NMR (^1H and ^{13}C) and HPLC.

The N-protected amino alcohol **30** was smoothly converted to the amino alcohol **34** by catalytic hydrogenolysis (H_2, 5% Pd–C, EtOH/HCl). At the outset of the synthesis, it seemed likely that it would be feasible to convert **34** directly into lycoramine (**4**) by a classical Pictet–Spengler reaction, but it soon became apparent that such optimism was unjustified.[23] Repeated attempts to effect the cyclization of **34** with formaldehyde under a wide variety of acidic reaction conditions utterly failed to produce significant quantities of lycoramine. Consequently, we turned our attention to the transformation of **34** to lycoramine (**4**), using a Bischler–Napieralski reaction.[24]

In the event, reaction of the amino alcohol **34** with excess acetic formic anhydride in pyridine at 80 °C afforded **35** in 95% overall yield from **30**. At this juncture it is relevant to mention that **35** could be more expeditiously prepared by the initial catalytic hydrogenation of **29** (H_2, PtO_2, HOAc) to give the crude amino alcohol **34** which was directly formylated as before to give **35**, albeit in 80% yield from **29**. None of the epimeric formate ester **36** could be detected by either NMR or HPLC.

The final conversion of **35** to racemic lycoramine (**4**) was then readily achieved in 68% yield by the cyclization of **35** with $POCl_3$ at 85 °C followed by the reduction of the intermediate iminium salt, which proceeded with concomitant hydrolysis of the formate ester, using methanolic sodium borohydride. The synthetic lycoramine (**4**) thus obtained exhibited spectral and physical properties (90-MHz ^1H NMR, solution IR, low-resolution mass spectra, TLC, VPC) identical with an authentic sample.[25,26]

Conclusions

The facile total synthesis of lycoramine (**4**), which was obtained in 18% overall yield from commercially available *o*-vanillin (**16**), further establishes the viability of the general strategy formulated in Scheme I for the synthesis of Amaryllidaceae alkaloids related to **2–5**. We have now convincingly demonstrated that both *cis*-3a-hydroindoles **7** and spirocyclic hydrobenzazepines related to **8** are readily available from ketones such as **11** and **12** via the common intermediate cyclohexenone **9** by exploiting our general methodology for effecting the geminal acylation–alkylation of carbonyl compounds. The application of this strategy to the syntheses of other alkaloids of the Amaryllidaceae family are in progress and will be the subject of further reports.

Experimental Section

General Procedures. Unless noted otherwise, all starting materials were obtained from commercial suppliers and were used without further purification. Ether and tetrahydrofuran (THF) were distilled from either sodium- or potassium–benzophenone immediately prior to use. Hexamethylphosphoramide (HMPA) was distilled from potassium under reduced pressure. Dimethylformamide (DMF) was distilled from calcium hydride. Allyl bromide and 2-(2-bromoethyl)-2-methyl-1,3-dioxolane[17] were freshly distilled from K_2CO_3 and filtered through basic alumina. All reactions involving organometallic reagents were executed under an atomosphere of dry nitrogen or argon, using oven-dried glassware. All yields reported are isolated yields of material judged to be homogeneous by TLC and NMR spectroscopy. IR spectra were determined on a Beckman Acculab 8 infrared recording spectrophotometer. ^1H NMR spectra were determined as indicated on either a Varian EM 390 (90 MHz) or a Nicolet NT 200 (a superconducting 200-MHz FT instrument) spectrometer. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; and comp, complex multiplet. Coupling constants are given in hertz (Hz). Low-resolution mass spectra were obtained on a DuPont (CEC) 21-491 instrument at an ionizing voltage of 70 eV, and exact mass determinations were obtained on a DuPont (CEC) 21-110 instrument. Preparative high-performance liquid chromatography (HPLC) was done on either a Waters Prep LC 500 instrument using two Prep PAK columns (sample size >500 mg) or a Waters 6000A solvent delivery system with a Model U6K injector and two Porasil A columns (0.6 m × 7.8 mm; sample size <500 mg).

2-(Allyloxy)-3-methoxybenzaldehyde (17). To a stirred suspension of sodium hydride (5.50 g, 0.229 mol of a 55% dispersion in mineral oil), which had been washed with hexane to remove the mineral oil, in anhydrous DMF (200 mL) at 0 °C was added a solution of *o*-vanillin (**16**; 30.0 g, 0.197 mol) in anhydrous DMF (50 mL), and the resulting solution was stirred at room temperature for 2 h. The solution was again cooled to 0 °C, allyl bromide (47.7 g, 0.394 mol) was added, and the stirring was continued at room temperature overnight. The reaction mixture was then poured into saturated brine (1 L), and the aqueous layer was extracted with ether (4 × 150 mL). The organic phases were combined and washed with 10% KOH (2 × 75 mL) and saturated brine (75 mL) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure yielded **17** as a yellow oil which was purified by distillation to give 34.9 g (92%) of **17** as a pale-yellow solid: mp 10–11 °C, bp 93–95 °C (0.01 mm); IR ($CHCl_3$) 1690 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 10.38 (s, 1 H), 7.35 (m, 1 H), 7.07 (m, 2 H), 6.00 (m, 1 H), 5.23 (m, 2 H), 4.60 (dd, 2 H, J = 6, 1 Hz), 3.87 (s, 3 H); mass spectrum, m/e 192.0791 ($C_{11}H_{12}O_3$ requires 192.0786), 163, 151 (base).

1-[2-(Allyloxy)-3-methoxyphenyl]-2-propenone (18). To a stirred suspension of magnesium turnings (2.27 g, 93.6 mmol) in anhydrous THF (50 mL) at room temperature was added in one portion a solution of vinyl bromide (2.23 g, 20.8 mmol) in THF (2 mL). After the initial reaction had subsided, an additional portion of vinyl bromide (4.45 g, 41.6 mmol) in THF (4 mL) was added dropwise at a rate that maintained a gentle reflux. Upon completion of the addition, the reaction mixture was heated at reflux for an additional 2 h. The reaction was then cooled to 10 °C, and a solution of the aldehyde **17** (3.00 g, 15.6 mmol) in THF (10 mL) was added dropwise (10 min) with stirring. After the

(23) We are aware of only one example of the formation of a seven-membered ring by a Pictet–Spengler reaction: Kametani, T.; Terui, T.; Ogino, T.; Fukumoto, K. *J. Chem. Soc. C* **1969**, 874. For a related process, see Wittekind, R. R.; Lazarus, S. *J. Heterocycl. Chem.* **1971**, *8*, 495.

(24) There are several examples of the use of a Bischler–Napieralski reaction for the construction of hydrobenzazepines. Cf. (a) Minami, S.; Uyeo, S. *Chem. Pharm. Bull.* **1964**, *12*, 1012. (b) Kanaoka, Y.; Sato, E.; Yonemitsu, O.; Ban, Y. *Tetrahedron Lett.* **1964**, 2419. See also ref 6k and 6l.

(25) We thank Professor A. G. Shultz for the 90-MHz ^1H NMR and IR spectra and also an authentic sample of racemic lycoramine.

(26) The observed melting point of our synthetic *dl*-lycoramine (as needles, mp 101–102 °C) was also in accordance with the values reported in the literature (e.g., 98–99 °C[8a] and 94–97 °C[8c]). However, the crystals of racemic lycoramine obtained from Professor Shultz were cubes (from ether/methylene chloride), instead of needles, and had mp 107–108 °C.[27]

addition had been completed, the reaction mixture was stirred for 10 min and cooled to 0 °C, and water (1.5 mL) was then carefully added to quench the excess Grignard reagent. The resulting slurry was filtered through a Celite pad, and the residual magnesium salts were thoroughly washed with ether (3 × 40 mL). The organic fractions were combined and washed with 10% KOH (2 × 40 mL) and saturated brine (40 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford 3.27 g (95%) of crude benzylic alcohol which appeared pure by TLC and ^1H NMR. The crude alcohol (3.27 g, 14.8 mmol) was immediately dissolved in acetone (50 mL) at 0 °C, and Jones reagent [CrO_3 (1.85 g, 18.5 mmol) and H_2SO_4 (1.47 mL, 27.8 mmol) in H_2O (10 mL)] was added over 15 min. After the addition had been completed, the reaction mixture was stirred an additional 30 min at 0 °C, whereupon 2-propanol (5 mL) was added. The excess solvents were removed under reduced pressure, and water (30 mL) was added to the green residue. The resulting mixture was thoroughly extracted with ether (5 × 30 mL), and the combined extracts were washed with 10% KOH (2 × 30 mL) and saturated brine (30 mL) and dried ($MgSO_4$). Evaporation of the excess solvent under reduced pressure followed by purification of the crude product by HPLC (Prep LC 500), using Skelly B/EtOAc (1:1) as the eluent, yielded 2.76 g (81%) of pure **18** as a yellow oil: IR ($CHCl_3$) 1675 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 6.96 (m, 4 H, 5.95 (m, 3 H), 5.18 (m, 2 H), 4.39 (dd, 2 H, J = 6.0, 1.0 Hz), 3.82 (s, 3 H); mass spectrum, m/e 218.0952 ($C_{13}H_{14}O_3$ requires 218.0943), 177, 151, 55 (base).

1-[2-(Allyloxy)-3-methoxyphenyl]-3-[(carbobenzyloxy)-methylamino]propan-1-one (19). A mixture of **18** (2.76 g, 12.7 mmol), benzyl *N*-methylcarbamate (2.09 g, 12.7 mmol), and a catalytic amount of camphorsulfonic acid (ca. 200 mg) was stirred at room temperature for 36 h. The crude product was then purified by HPLC (Prep LC 500), using Skelly B/EtOAc (1.5:1) as the eluting solvent, to afford 4.36 g (90%) of pure **19** as a viscous pale yellow oil:[28] IR ($CHCl_3$) 1690 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 7.26 (br s, 5 H), 7.00 (m, 3 H), 5.93 (m, 1 H), 5.17 (m, 2 H), 5.06 (s, 2 H), 4.48 (br d, 2 H, J = 6 Hz), 3.78 (s, 3 H), 3.59 (br t, 2 H, J = 6 Hz), 3.20 (br t, 2 H, J = 6 Hz), 2.89 (s, 3 H); mass spectrum, m/e 383.1740 ($C_{22}H_{25}O_5N$ requires 383.1732), 342, 292, 218, 191, 177, 151, 91 (base).

2-Methyl-2-[3-(2-(allyloxy)-3-methoxyphenyl)-3-oxopropyl]-1,3-dioxolane (26). To a stirred suspension of magnesium turnings (7.20 g, 0.30 mol) in anhydrous THF (100 mL) was added 1,2-dibromoethane (3.53 g, 0.019 mol). After the initial reaction had subsided, a solution of 2-(2-bromoethyl)-2-methyl-1,3-dioxolane (**22**;[17] 22.6 g, 0.12 mol) and 1,2-dibromoethane (3.53 g, 0.019 mol) in anhydrous THF (100 mL) was added dropwise at a rate which kept the temperature in the reaction vessel between 22 and 24 °C (ca. 2 h). After the addition was completed, the mixture was stirred for 0.5 h at room temperature and then slowly transferred via cannula (30 min) into a stirred solution of the aldehyde **17** (7.00 g, 0.036 mol) in anhydrous THF (100 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h and then poured into saturated NH_4Cl (100 mL). Water (75 mL) was added, and the aqueous layer was extracted with ether (3 × 100 mL). The combined organic phases were washed with H_2O (50 mL), saturated $NaHCO_3$ (50 mL), and saturated brine (50 mL) and then dried ($MgSO_4$). Removal of the excess solvents under reduced pressure yielded the crude alcohol which was immediately dissolved in DMF (20 mL). The solution was then added in one portion with stirring to an ice-cooled solution of pyridinium dichromate[20] (27.0 g, 0.073 mol) in DMF (75 mL). After being stirred for 0.5 h at 0 °C, the reaction mixture was allowed to warm to room temperature, stirred for 4 h, and then poured into H_2O (300 mL). Ether (150 mL) was added, and the layers were separated. The aqueous layer was extracted with ether (4 × 150 mL), and the combined organic phases were washed with H_2O (5 × 100 mL) and saturated brine (100 mL) and dried ($MgSO_4$). Removal of the excess solvents under reduced pressure gave the crude monoprotected dione **26** which was purified by HPLC (Prep LC 500), using Skelly B/EtOAc (5:1) as the eluting solvent, to afford 8.00 g (72%) of pure **26** as a yellow oil: IR ($CHCl_3$) 1685 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 7.02 (m, 3 H), 6.00 (m, 1 H), 5.23 (m, 2 H), 4.51 (dd, 2 H, J = 6, 1 Hz), 3.88 (s, 3 H), 3.86 (s, 4 H), 3.05 (t, 2 H, J = 7 Hz), 2.05 (t, 2 H, J = 7 Hz), 1.30 (s, 3 H); mass spectrum, m/e 306.1468 ($C_{17}H_{22}O_5$ requires 306.1470), 291, 191, 151 (base).

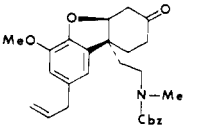
Benzyl *N*-(2-Bromoethyl)-*N*-methylcarbamate (28). A solution of *N*-methylethanolamine (14.0 g, 0.25 mol) in 48% aqueous HBr (85.0 g, 0.52 mol) was heated at 160–180 °C (oil bath temperature) for 9 h. During the course of the reaction, water (45 mL) was removed by distillation at a rate which prevented the head temperature from exceeding 110 °C. The residue was cooled and poured into cold acetone (10 mL), whereupon 38.2 g of 1-(methylamino)-2-bromoethane hydrobromide precipitated. Concentration of the mother liquor yielded an additional 6.5 g of the hydrobromide salt (82%) which was used without further purification. A portion of this salt (15.0 g, 0.069 mol) was dissolved in 2 N NaOH (35 mL) at 0 °C, and benzyl chloroformate (13.9 g, 0.082 mol) and 4 N NaOH (17 mL) were added simultaneously with vigorous stirring. After 0.5 h, the aqueous mixture was poured into ether (50 mL), and the layers were separated. The aqueous layer was extracted with ether (3 × 50 mL), and the combined organic phases were washed with 1 N HCl (30 mL), saturated $NaHCO_3$ (30 mL), and saturated brine (30 mL). The solution was dried ($MgSO_4$), and the excess solvents were removed under reduced pressure. The crude product was purified by HPLC (Prep LC 500), using Skelly B/EtOAc (5:1) as the eluent, to give 13.6 g (72%) of pure **28** as a colorless oil: IR ($CHCl_3$) 1705 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 7.26 (s, 5 H), 5.07 (s, 2 H), 3.50 (m, 4 H), 2.93 (s, 3 H); mass spectrum, m/e 271.0214 ($C_{11}H_{14}BrNO_2$ requires 271.0208), 136, 91(base).

4-[2-((Carbobenzyloxy)methylamino)ethyl]-4-[2-(allyloxy)-3-methoxyphenyl]-2-cyclohexenone (24). Method A. To a stirred solution of *n*-butyllithium (9.40 mmol, 3.3 N in hexane) in anhydrous THF (40 mL) at −78 °C was added dropwise a solution of diethyl [(benzylideneamino)methyl]phosphonate[14] (2.40 g, 9.40 mmol) in anhydrous THF (5 mL). After 1 h, a solution of the ketone **19** (3.00 g, 7.83 mmol) in anhydrous THF (5 mL) was added dropwise (5 min). The reaction mixture was allowed to warm to room temperature and then heated at reflux for 2 h, whereupon it was again cooled to −78 °C and *n*-butyllithium (9.40 mmol, 3.3 N in hexane) added dropwise. After 1 h at −78 °C, HMPA (15 mL) and then carefully purified 2-(2-bromoethyl)-2-methyl-1,3-dioxolane (**22**;[17] 4.59 g, 23.4 mmol) were added, and the reaction mixture was permitted to warm slowly to room temperature (ca. 3 h) and then stirred overnight. The mixture was poured into an equal volume of 1 N HCl and stirred vigorously at room temperature for 6 h. Ether (100 mL) was added, and the layers were separated. The aqueous layer was extracted with ether (3 × 50 mL), and the combined organic portions were washed with saturated $NaHCO_3$ (50 mL) and saturated brine (50 mL) and dried ($MgSO_4$). Removal of the excess solvents under reduced pressure yielded the crude keto aldehyde **23** which was immediately dissolved in methanol (30 mL) at 0 °C, and 10% KOH (20 mL) was added. The resulting mixture was then stirred for 2 h at room temperature. The methanol was removed under reduced pressure, and ether (40 mL) was added to the aqueous mixture. The layers were separated, and the aqueous layer was extracted with ether (3 × 30 mL). The combined organic phases were washed with saturated brine (30 mL) and dried ($MgSO_4$), and the excess solvent was removed under reduced pressure. The crude **24** was purified by HPLC (Prep LC 500), using Skelly B/EtOAc (3:1) as the eluting solvent, to give 1.51 g (43%) of pure cyclohexenone **24** as a pale-yellow oil:[29] IR ($CHCl_3$) 1685 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 7.31 (br s, 6 H), 6.84 (m, 3 H), 5.97 (m,

(27) Lee, Y. K. Ph.D. Dissertation, Cornell University, Ithaca, NY, 1978.

(28) Attempted purification of **19** by bulb-to-bulb distillation (Kügelrohr) led to extensive reversion to starting material.

(29) Upon attempted distillation (Kügelrohr) of **24** at 200 °C (oven temperature; 0.1 mm), **24** underwent a Claisen rearrangement followed by a Cope rearrangement to give i.



2 H), 5.23 (m, 2 H), 5.03 (s, 2 H), 4.53 (m, 2 H), 3.79 (br s, 3 H), 3.17 (m, 2 H), 2.79 (s, 3 H), 1.83–2.36 (comp, 6 H); mass spectrum, m/e 449.2194 ($C_{27}H_{31}O_5N$ requires 449.2202), 314, 257, 217, 91 (base).

Method B. To a stirred solution of *n*-butyllithium (9.80 mmol, 2.8 N in hexane) in anhydrous THF (50 mL) at −78 °C was added drowise a solution of diethyl [(benzylideneamino)methyl]-phosphonate (2.50 g, 9.80 mmol) in anhydrous THF (5 mL). After 1 h at −78 °C, a solution of monoprotected 1,4-dione **26** (2.00 g, 6.50 mmol) in anhydrous THF (5 mL) was added dropwise (ca. 5 min), and the solution was allowed to warm to room temperature (ca. 1 h) and then heated at reflux for 2 h. The resulting solution was again cooled to −78 °C, and *n*-butyllithium (9.80 mmol, 2.8 N in hexane) was added dropwise. After 1 h, a solution of benzyl *N*-(2-bromoethyl)-*N*-methylcarbamate (**28**; 7.15 g, 26.1 mmol) in THF (10 mL) was added dropwise (5 min). The reaction mixture was permitted to warm slowly to room temperature (ca. 3 h) and then stirred overnight. An equal volume of 1 N HCl was added, and the resulting mixture was stirred vigorously at room temperature for 6 h. Ether (100 mL) was added, and the layers were separated. The aqueous layer was extracted with ether (3 × 50 mL), and the combined organic portions were washed with saturated $NaHCO_3$ (50 mL) and saturated brine (50 mL) and dried ($MgSO_4$). The excess solvents were removed under reduced pressure to give crude **23** which was immediately dissolved at 0 °C in a mixture of methanol (30 mL) and 10% KOH (20 mL), and the resulting solution was then stirred for 2 h at room temperature. The methanol was removed under reduced pressure, and ether (50 mL) was added to the aqueous residue. The layers were separated, and the aqueous layer was extracted with ether (3 × 30 mL). The combined organic phases were washed with saturated brine (30 mL) and dried ($MgSO_4$). After the excess solvents were removed under reduced pressure, the crude **24** was purified by HPLC (Prep LC 500), using Skelly B/EtOAc (3:1) as the eluting solvent, to afford 1.61 g (55%) of pure **24** as a pale-yellow oil which exhibited spectral properties (^1H NMR, IR, and low-resolution mass spectrum) identical with that of the material prepared by method A.

9b-[2-((Carbobenzyloxy)methylamino)ethyl]-1,4,4a-(*R),9b(*R**)-tetrahydro-6-methoxy-3(2*H*)-dibenzofuranone (29).** A solution of the cyclohexenone **24** (1.50 g, 3.34 mmol) in absolute ethanol (25 mL) containing a catalytic amount of rhodium trichloride trihydrate (61 mg) was heated at reflux under N_2 for 8 h. The ethanol was then removed under reduced pressure, and the residue was purifed by HPLC (Prep LC 500), using Skelly B/EtOAc (1:1) as the eluting solvent, to afford 1.17 g (86%) of **29** as a pale yellow oil. An analytical sample was obtained by bulb-to-bulb (Kügelrohr) distillation at 200 °C (bath temperature; 0.01 mm): IR ($CHCl_3$) 1711, 1685 cm^{-1}; NMR (C_5Cl_6, 200 MHz, 85 °C) δ 7.32 (m, 5 H), 6.74 (m, 3 H), 5.13 (s, 2 H), 4.93 (br t, 1 H, J = 3.5 Hz), 3.85 (s, 3 H), 3.42 (m, 1 H), 3.17 (m, 1 H), 2.87 (s, 3 H) 2.82 (m, 1 H), 2.57 (m, 1 H), 1.87–2.22 (comp, 6 H); mass spctrum, m/e 409, 274, 217, 91 (base). Anal. ($C_{24}H_{27}O_5N$) C, H, N.

9b-[2-((Carbobenzyloxy)methylamino)ethyl]-1,2,3-(*R),4,4a(*R**),9b(*R**)-hexahydro-6-methoxy-3-dibenzofuranol (30).** To a stirred solution of L-Selectride (1.80 mmol, 1 N in THF) in anhydrous THF (10 mL) at −78 °C was added dropwise a solution of ketone **29** (500 mg, 1.20 mmol) in THF (10 mL). The reaction mixture was stirred at −78 °C for 2 h and then allowed to warm to 0 °C. After 2 h at 0 °C, methanol (0.2 mL) was added and the solution allowed to warm to room temperature (ca. 15 min), whereupon the solvent was removed under reduced pressure. Hexane (20 mL), 10% NaOH (0.8 mL), and 30% H_2O_2 (2 mL) were then added to the residue at 0 °C, and the resulting mixture was stirred overnight at room temperature. Water (5 mL) was added, and the aqueous layer was extracted with ether (3 × 25 mL). The combined organic portions were washed with saturated brine (10 mL) and dried ($MgSO_4$), and the excess solvent was removed under reduced pressure. The crude alcohol was purified by HPLC (Waters 6000A, Porasil A), using Skelly B/EtOAc (1:3) as the eluting solvent, to give 442 mg (88%) of pure **30**: IR ($CHCl_3$) 1690 cm^{-1}; NMR (C_5Cl_6, 200 MHz, 85 °C) δ 7.29 (m, 5 H), 6.72 (m, 3 H), 5.11 (s, 2 H), 4.53 (br t, 1 H, J = 5.5 Hz), 3.87 (s, 3 H), 3.73 (br s, 1 H), 3.20 (m, 2 H), 2.83 (s, 3 H), 1.65–2.15 (comp, 6 H), 1.25–1.57 (comp, 3 H); mass spectrum, m/e 411.2051 ($C_{24}H_{29}O_5N$ requires 411.2045), 276, 219, 201, 91 (base). Anal. ($C_{24}H_{29}O_5N$) C, H, N.

9b-[2-(Formylmethylamino)ethyl]-1,2,3(*R),4,4a(*R**),9b-(*R**)-hexahydro-6-methoxy-3-(formyloxy)dibenzofuran (35). Method A.** A solution of **30** (200 mg, 0.49 mmol) in ethanol (10 mL) containing concentrated HCl (0.2 mL) and 5% Pd–C (40 mg) was stirred under hydrogen (1 atm) at room temperature for 18 h. The reaction mixture was then filtered through a plug of glass wool, and the ethanol was removed under reduced pressure to provide 152 mg of the crude hydrochloride salt of **34** which was dissolved in dry pyridine (10 mL) containing acetic formic anhydride (1.0 mL). The resulting solution was heated at 80 °C (bath temperature) under nitrogen for 6 h, and the pyridine was removed under reduced pressure. The residue was dissolved in EtOAc (10 mL) which was then sequentially washed with 1 N HCl (2 mL), saturated $NaHCO_3$ (2 mL), and saturated brine (2 mL). The solution was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The crude product was purified by HPLC (Waters 6000A, Porasil A), using EtOAc as the eluent, to provide 136 mg (95%) of **35**: IR ($CHCl_3$) 1730, 1680 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 7.98 (s, 0.5 H), 7.97 (s, 0.5 H), 7.95 (s, 0.5 H), 7.87 (s, 0.5 H), 6.68–6.97 (m, 3 H), 4.95 (m, 1 H), 4.67 (t, 0.5 H, J = 7.5 Hz) 4.64 (t, 0.5 H, J = 7.5 Hz), 3.90 (s, 1.5 H), 3.89 (s, 1.5 H), 2.90–3.31 (m, 2 H), 2.81 (s, 1.5 H), 2.74 (s, 1.5 H), 2.26 (m, 2 H), 1.50–2.01 (comp, 6 H); mass spectrum, m/e 333.1568 ($C_{18}H_{23}O_5N$ requires 333.1576), 228, 201 (base).

Method B. A mixture of **29** (45 mg, 0.11 mmol) and PtO_2 (12 mg) in acetic acid (3 mL) was stirred under an atmosphere of hydrogen at room temperature for 18 h, whereupon the reaction mixture was filtered through a plug of glass wool to remove the catalyst. The solvent was removed under reduced pressure, and the residue was dissolved in anhydrous pyridine (5 mL) containing acetic formic anhydride (0.5 mL). The resulting mixture was heated at 80 °C (bath temperature) under nitrogen for 6 h, whereupon the pyridine was removed under reduced pressure. The residue was dissolved in EtOAc (5 mL) which was washed sequentially with 1 N HCl (1 mL), saturated $NaHCO_3$ (1 mL), and saturated brine (1 mL). The solution was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. Crude **35** was then purified by HPLC (Waters 6000A, Porasil A), using EtOAc as the eluent, to give 29 mg (80%) of **35** which was identical in all respects with that obtained in method A above.

Lycoramine (4). A solution of **35** (120 mg, 0.360 mmol) in freshly distilled $POCl_3$ (0.75 mL) was sealed in a glass tube under N_2 and heated at 85 °C (bath temperature) for 20 h and then cooled. The mixture was concentrated to a thick syrup under reduced pressure, the residue was dissolved in methanol (5 mL), and the resulting solution was cooled to −78 °C. Excess $NaBH_4$ (68 mg, 1.80 mmol) was added in one portion, and the reaction was permitted to warm slowly to room temperature over about 3 h. After an additional 12 h at room temperature, the methanol was removed under reduced pressure, and the residue was partioned between 1 N HCl (2 mL) and ether (2 mL). After the layers were separated, the aqueous layer was washed with ether (2 mL) and then basified to pH 8–10 by the addition of solid KOH. The aqueous layer was then extracted with EtOAc (3 × 5 mL), and the combined organic layers were washed with saturated brine (5 mL) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure yielded crude lycoramine (**4**) which was recrystallized from methylene chloride to yield 68 mg (68%) of pure, racemic lycoramine as colorless needles: mp 101–102 °C (lit. mp 98–99 °C,[8a,b] 94–97 °C.[8c] The synthetic lycoramine had spectral properties (90-MHz ^1H NMR, IR, low-resolution mass spectra, TLC, VPC) identical with an authentic sample of racemic lycoramine.[25,26]

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Registry No. **4**, 18797-70-1; **16**, 23343-06-8; **17**, 148-53-8; **18**, 78166-98-0; **19**, 78166-99-1; **22**, 37865-96-6; **23**, 80754-81-0; **24**, 80754-82-1; **26**, 80754-83-2; **28**, 80754-84-3; **29**, 80754-85-4; **30**, 80754-86-5; **34**·HCl, 80794-98-5; **35**, 78167-06-3; allyl bromide, 106-95-6; vinyl bromide, 593-60-2; benzyl *N*-methylcarbamate, 30379-59-0; *N*-methyl ethanolamide, 109-83-1; 1-methylamino-2-bromoethane hydrobromide, 40052-63-9; benzyl chloroformate, 501-53-1.