Synthetic Approaches toward Spiro[2,3-dihydro-4*H*-1-benzopyran-4,1′-cyclohexan]-2-one Derivatives via Radical Reactions: Total Synthesis of (±)-Lycoramine

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Received January 25, 1993

Syntheses of spiro[2,3-dihydro-4*H*-1-benzopyran-4,1′-cyclohexan]-2-one derivatives by reaction sequences including a radical reaction and a total synthesis of (±)-lycoramine (**2**) are described. Radical reactions (Bu_3SnH, AIBN) of 1-[(1′-cyclohexenylmethyl)oxy]-2-halobenzenes **23b–d** in boiling benzene gave the corresponding spiro[2,3-dihydrobenzofuran-3,1′-cyclohexanes] **26a,b** in good yields, whereas the reaction of 1-(1′-cyclohexenylethoxy)-2-bromobenzene (**25**) under similar conditions afforded a mixture of spiro[2,3-dihydro-4*H*-1-benzopyran-4,1′-cyclohexane] **27** and benzoxepin **28**. Furthermore, the radical reaction of ethyl 2-[(2′-bromoaryl)oxy]-1-cyclohexenylacetate **37a** produced ethyl 2-spiro[2,3-dihydrobenzofuran-3,1′-cyclohexane]carboxylate **38** in good yield. Compound **38** was converted to spiro[2,3-dihydro-4*H*-1-benzopyran-4,1′-cyclohexane]-2,4′-dione **40** by treatment with SmI_2 and then with 3 N HCl. Spiro[2,3-dihydro-4*H*-1-benzopyran-4,1′-cyclohexane]-2,4′-dione **40** was transformed to (±)-lycoramine (**2**) in four steps and 43% overall yield.

Introduction

Many synthetic studies of galanthamine-type *Amaryllidaceae* alkaloids[1] galanthamine (**1**)[2] and lycoramine (**2**)[3] have been reported because of their unique spiro seven-membered ring system and their pharmacological activities.[4] Of these reports, only two[3c,h] have dealt with a synthesis of (±)-lycoramine (**2**) involving the application of a radical reaction (other than an oxidative phenol coupling) to the construction of the quarternary carbon skeleton.[5] Because radical reactions are useful in organic synthesis,[6] the synthesis of (±)-**2** by the use of a radical reaction[7] was an attractive project for us. In this paper, we describe the synthesis of a spiro[2,3-dihydro-4*H*-1-benzopyran-4,1′-cyclohexan]-2-one ring system, which could serve as a potent intermediate for the synthesis of (±)-**2** by means of a radical reaction followed by treatment with SmI_2. We also describe a total synthesis of (±)-**2**.

A retrosynthetic analysis for (±)-lycoramine (**2**) is shown in Scheme I. We thought that a spiro[2,3-dihydro-4*H*-1-benzopyran-4,1′-cyclohexan]-2-one derivative such as **B** or **C** might be a potent intermediate for the construction of hexahydrodibenzofuran skeleton **A**, which could be converted to (±)-lycoramine (**2**). With this in mind, three radical-mediated approaches (routes a, b, and c) to **B** or **C** from radical precursors **E**, **F**, or **G**, which could be readily prepared from 6-bromoguaiacol, were planned.

Results and Discussion

Synthesis of the Spiro Lactones. First, for route a, radical precursors **8–11** were prepared. Regioselective *ortho*-bromination[8] of guaiacol (**3**) gave 6-bromoguaiacol (**4**)[9] in 87% yield. Benzylation of **4** afforded benzyl ethyl **5** in 71% yield. The reaction of 3-ethoxycyclohexenone with the Grignard reagent derived from **5** in THF followed by treatment with 1 N hydrochloric acid gave enone **6** in 87% yield. Debenzylation of **6** with $TiCl_4$ in CH_2Cl_2 afforded phenol **7** in 93% yield. Acylation of **7** with halogenoacetyl chlorides afforded **8–11**[10] in 89–100% yield. Unfortunately, the radical reactions[11] of **8–11** with Bu_3SnH (1.05 equiv) in the presence of AIBN (0.1 equiv) in

(1) Martin, S. F. In *The Alkaloids*; Brossi, A. R., Ed.; Academic Press: New York, 1987; Vol. 30, Chapter 2, and references cited therein.

(2) (a) Barton, D. H. R.; Kirby, G. W. *Proc. Chem. Soc.* **1960**, 392. (b) Barton, D. H. R.; Kirby, G. W. *J. Chem. Soc.* **1962**, 806. (c) Kametani, T.; Shishido, K.; Hayashi, E.; Seino, C.; Kohno, T.; Shibuya, S.; Fukumoto, K. *J. Org. Chem.* **1971**, *36*, 1295. (d) Kametani, T.; Yamaki, K.; Terui, T.; Shibuya, S.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1513. (e) Kametani, T.; Yamaki, K.; Terui, T. *J. Heterocycl. Chem.* **1973**, *10*, 35. (f) Shimizu, K.; Tomioka, K.; Yamada, S.; Koga, K. *Heterocycles* **1977**, *8*, 277. (g) Shimizu, K.; Tomioka, K.; Yamada, S.; Koga, K. *Chem. Pharm. Bull.* **1978**, *26*, 3765. (h) Vlahov, R.; Krikoriam, D.; Spassov, G.; Chinova, M.; Vlahav, I.; Parushev, S.; Snatzke, G.; Ernst, L.; Kieslich, K.; Abraham, W.; Sheldrick, W. *Tetrahedron* **1989**, *45*, 3329.

(3) (a) Hazama, N.; Irie, H.; Mizutani, T.; Sinagu, T.; Tanaka, M.; Yoshitaka, A.; Uyeo, S. *J. Chem. Soc. C* **1968**, 2947. (b) Misaki, Y.; Mizutani, T.; Sekido, M.; Uyeo, S. *J. Chem. Soc. C* **1968**, 2954. (c) Schultz, A. G.; Yee, Y. K.; Berger, M. H. *J. Am. Chem. Soc.* **1977**, *99*, 8065. (d) Martin, S. F.; Garrison, J. P. *J. Org. Chem.* **1981**, *46*, 3567. (e) Martin, S. F.; Garrison, J. P. *J. Org. Chem.* **1982**, *47*, 1513. (f) Sánchez, I. H.; Sorria, J. J.; Lapez, F. J.; Larraza, M. I.; Flores, H. J. *J. Org. Chem.* **1984**, *49*, 157. (g) Ackaland, D. J.; Pinhey, J. T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2695. (h) Parker, K. A.; Kim, H.-J. *J. Org. Chem.* **1992**, *57*, 752.

(4) (a) Dolgushina, A. T. *Povysh. Rezistentnosti. Organizama* **1973**, 182; *Chem. Abstr.* **1974**, *81*, 72709h. (b) Baraka, A.; Cozanitis, D. *Anesth. Analg.* **1973**, *52*, 831; *Chem. Abstr.* **1974**, *81*, 132979d. (c) Vasilenko, E. T.; Tonkopii, V. D. *Biokhimiya* **1974**, *39*, 701; *Chem. Abstr.* **1975**, *82*, 12913f. (d) Tonkopii, V. D.; Prozorovskii, V. B.; Konstorum, M. G. *Byull. Eksp. Biol. Med.* **1975**, *80*, 120; *Chem. Abstr.* **1975**, *83*, 189728w. (e) Fisenko, V. P.; Mitsov, V. *Farma. Toksikol (Moscow)* **1975**, *38*, 34; *Chem. Abstr.* **1975**, *82*, 22842e. (f) Sweeniey, J. E.; Puttfarcken, P. S.; Coley, J. T. *Pharmacol. Biochem. Behav.* **1989**, *34*, 129. (g) Thomsen, T.; Kewite, H. *Life Sci.* **1990**, *46*, 1553.

(5) Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

(6) For a review on radical reactions in natural products syntheses: Jasperse, C.; Curran, D. P.; Ferig, T. L. *Chem. Rev.* **1991**, *91*, 1237.

(7) For formation of 5,11-methanomorphanthridine ring system by radical reaction: Ishizaki, M.; Kurihara, K.; Tanazawa, E.; Hoshino, O. *J. Chem. Soc., Perkin Trans. 1* **1993**, 101.

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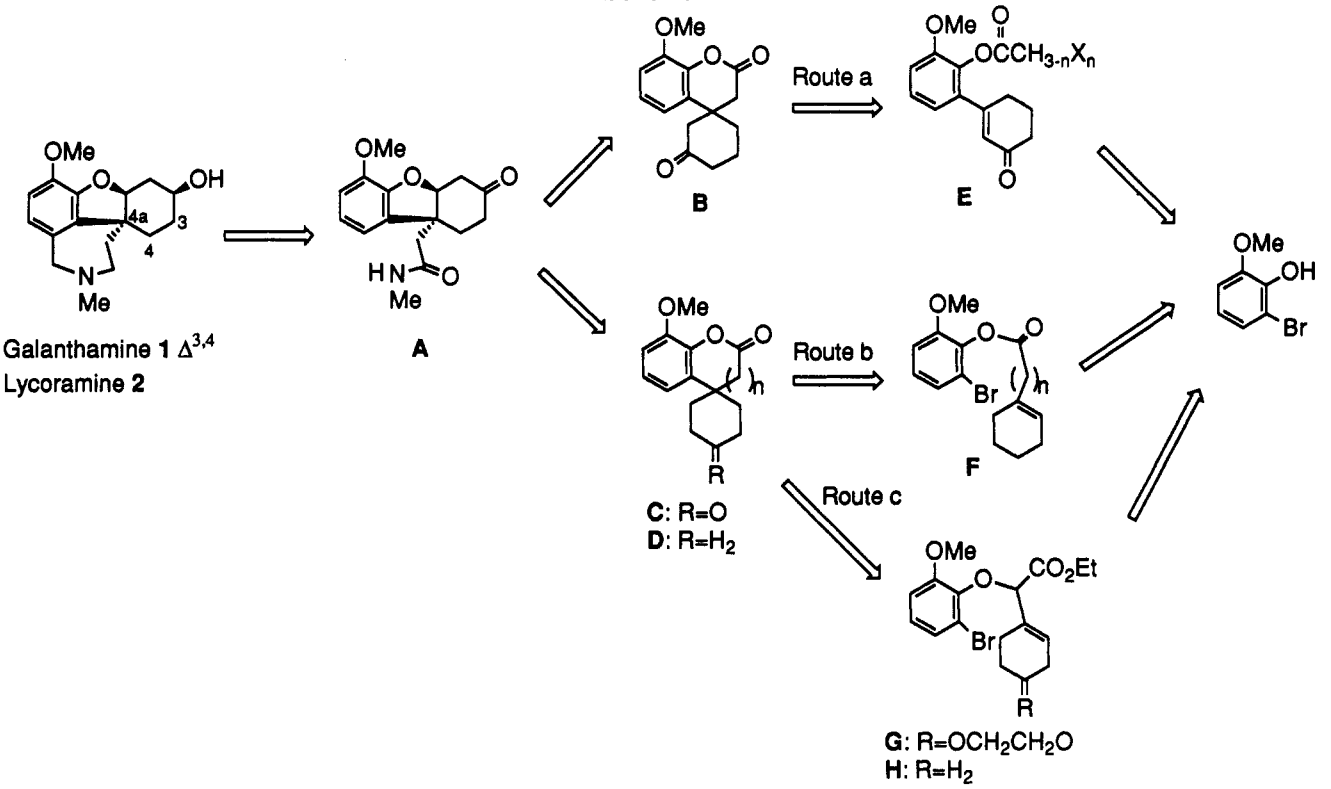
(10) All attempts to synthesize other radical precursors such as bromoacetal and bromomethyl dimethylsilyl ether instead of haloacetates failed. Reports on acetal and methyldimethylsilyl radical reactions have appeared: Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564. Stork, G.; Mook, R. Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741. Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298.

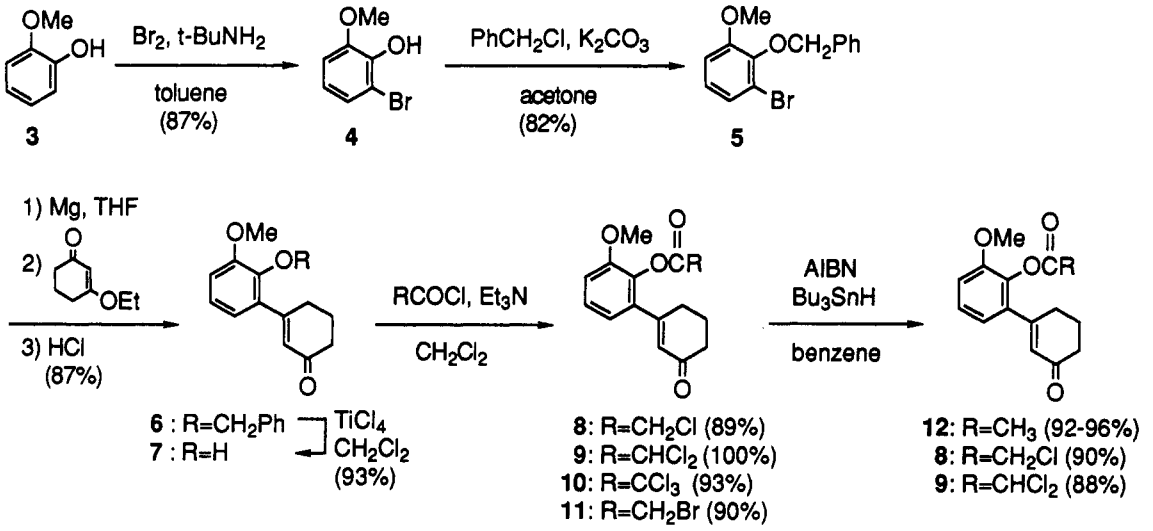
(11) For a review of lactone synthesis by radical chemistry, see: Surzur, J.-M.; Bertrand, M. P. *Pure Appl. Chem.* **1988**, *60*, 1659. Recently, a direct radical cyclization of haloacetates has been reported: Hanessian, S.; Fabio, R. Di.; Marcoux, J.-F.; Prund'homme, M. *J. Org. Chem.* **1990**, *55*, 3436.

0022-3263/93/1958-3877$04.00/0

Scheme I



Scheme II



boiling benzene (0.03–0.2 M) furnished only reduced products. Compound **12** (90–96%) was obtained from **8** and **11**, and **8** (90%) and **9** (88%) were obtained from **9** and **10**, respectively (Scheme II). In these cases, steric repulsion between the halomethyl group and the cyclohexenone ring seemed to force aryl haloacetates **8–11** into unfavorable conformations, thus preventing radical cyclization. Therefore, synthesis of the spiro compound by this route was given up.

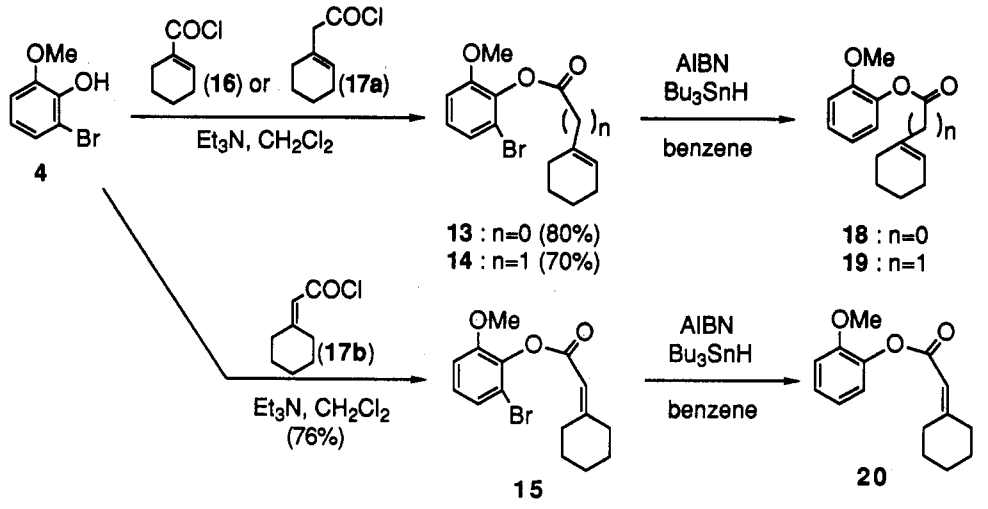
Second, synthesis of the spiro compound via an aryl radical was carried out by means of route b. As model experiments, radical precursors **13–15** were synthesized as follows. The reaction of 6-bromoguaiacol (**4**) and acid chloride **16**[12] gave **13** in 80% yield. Compounds **14** and **15**, homologues of **13**, were prepared in 70% and 76% yields by the reaction of **4** with acid chlorides **17a**[13a] and **17b**.[13b] Radical reactions[14] of **13–15** with Bu_3SnH (1.1–1.5 equiv) in the presence of AIBN (0.5 equiv) in boiling benzene, toluene, or *o*-xylene (0.01–0.04 M) afforded reduced products **18–20** (13–64%), and none of the desired spiro compounds were detected (Scheme III).[15]

To determine whether or not the presence of the ester group in **13–15** retarded the reaction, radical reactions of

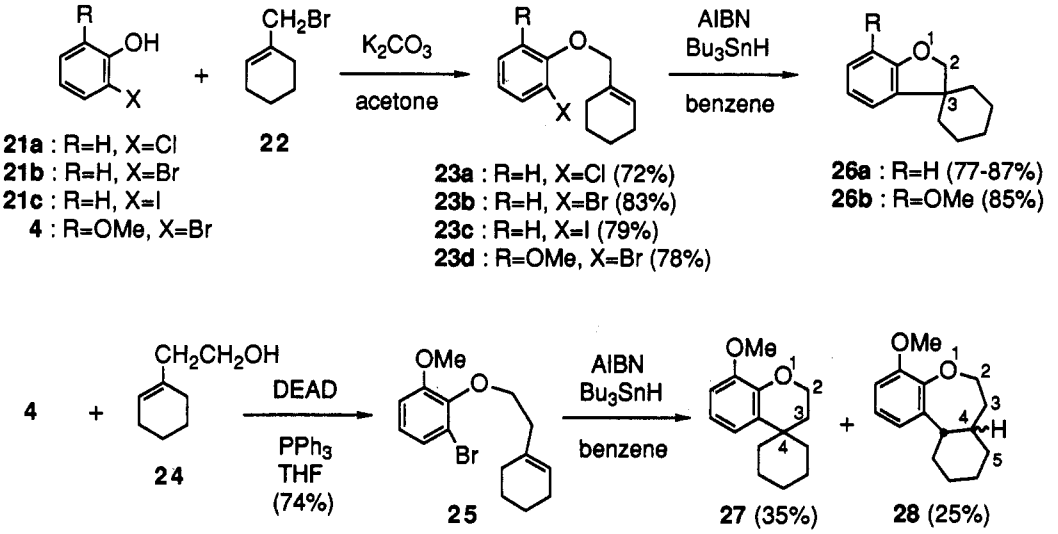
(12) (a) Kidd, D. A. A.; Robins, P. A.; Walker, J. *J. Chem. Soc.* **1953**, 3244. (b) Wheeler, O. H.; Lerner, I. *J. Am. Chem. Soc.* **1956**, *78*, 63.

(13) (a) This compound was prepared by isomerization of **17b** (Et_3N, EtOH, CH_2Cl_2, 75%) followed by hydrolysis and reaction of the hydrolyzed product with $SOCl_2$ in CH_2Cl_2 (77%). *Cf.* Hoye, T. R.; Magee, A. S.; Trumper, W. S. *Synth. Commun.* **1982**, *12*, 183. (b) This compound was prepared by hydrolysis of ethyl cyclohexylideneacetate (96%) (Wadsworth, W. S., Jr.; Emmons, W. D. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. 5, p 547) followed by treatment of the hydrolyzed product with $SOCl_2$ in CH_2Cl_2 (90%). (c) This compound was prepared by reduction of the isomerized ester of **17b** with $LiAlH_4$ (95%).

Scheme III



Scheme IV



the corresponding ethers were attempted. Radical precursors **23a–d** were synthesized in 72–83% yield by the reaction of 1-(bromomethyl)cyclohex-1-ene (**22**)[16] and either 2-halophenols **21a–c** or 6-bromoguaiacol (**4**) in acetone containing K_2CO_3 at room temperature. Compound **25**, a homologue of **23b**, was obtained in 74% yield by the Mitsunobu reaction[17] of **4** with 2-(1-cyclohexenyl)-ethanol (**24**).[13c]

Although the radical reaction (0.5 equiv of AIBN, 1.2 equiv of Bu_3SnH) of chloride **23a** in refluxing benzene (0.02 M) failed, the reactions of bromide **23b** and iodide **23c** under conditions similar to those for **23a** (0.02 M, 2 h for **23b** and 0.5 h for **23c**) gave spiro compound **26a** in 87% and 77% yields, respectively, and no reduced product was detected in either case (Scheme IV). Similarly, the reaction of **23d** in refluxing benzene (0.02 M) gave **26b** in 85% yield. The structures of **26a** and **26b** were determined by ^{13}C NMR spectroscopy, which showed the presence of singlet peaks (δ 46.0 for **26a** and 46.9 ppm for **26b**) due to C_3. In contrast to the reaction of **23d**, the radical reaction of **25** in refluxing benzene (0.02 M) in a manner similar to that described for **23b,c** produced **27** and **28** in 35% and 25% yields, respectively.[18] The structures of **27** and **28** were also determined by ^{13}C NMR spectroscopy. The spectrum for **27** showed a singlet peak (δ 34.0 ppm) for C_4, whereas that for **28** showed three doublet peaks (δ 39.3, 42.5, and 50.0 ppm) for C_4 and C_5, indicating a mixture of diastereomers. The ratio of the diastereomers of **28** was estimated to be 1.2:1 by the height of peaks due to the methoxyl group in the ^1H NMR spectrum. The aforementioned results suggested that the conformations of esters **13–15** as well as those of haloacetates **8–11** play an important role in the cyclization. An O–CO bond in the esters may be in s-cisoid conformation[19] owing to steric

(14) A radical reaction of the corresponding amides has been reported. (a) Jones, K.; Thompson, M.; Write, C. *J. Chem. Soc., Chem. Commun.* **1986**, 115. (b) Clark, A. J.; Jones, K. *Tetrahedron Lett.* **1989**, *30*, 5485. (c) Jones, K.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.* **1992**, 1766.

(15) Radical reaction of **13** in catalytic tin hydride method (0.1 equiv of AIBN, 0.1 equiv of Bu_3SnCl, 2 equiv of $NaBH_3CN$, *t*-BuOH, 0.02 M, reflux 3 h) gave reduced product **18** in 70% yield. *Cf.* Stork, G.; Sher, P. M. *J. Am. Chem. Soc.* **1986**, *108*, 303.

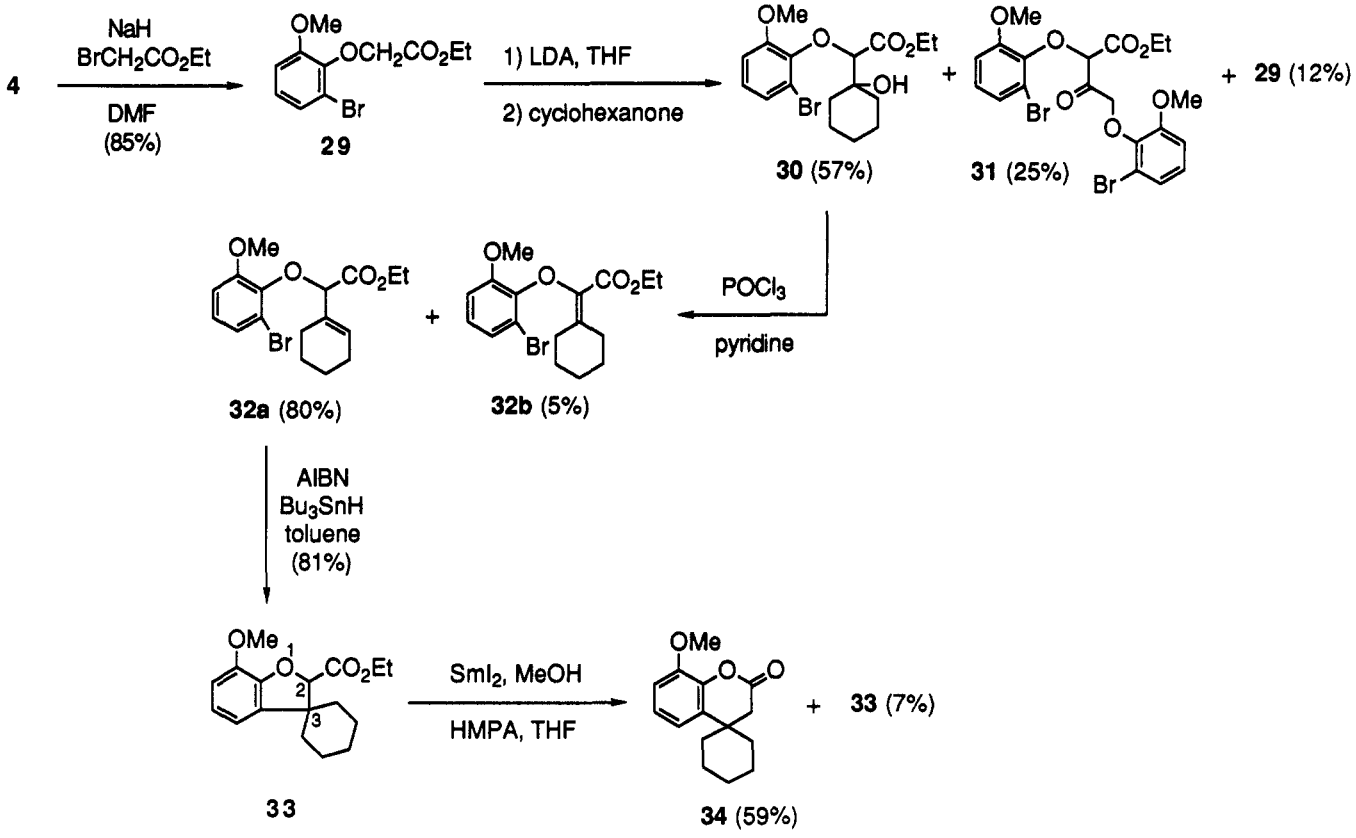
(16) Lythgoe, B.; Trippett, S.; Watkins, J. W. *J. Chem. Soc.* **1956**, 4060.

(17) *Cf.* Manhas, M. S.; Hoffman, W. H.; Lal, B.; Bose, A. K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 461.

(18) For the 5-hexenyl radical, 5-exo cyclization is 50 times faster than 6-endo cyclization, but for the 7-heptenyl radical, 6-exo cyclization is only six times faster than 7-endo cyclization. Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron Lett.* **1985**, *26*, 373; *Tetrahedron* **1985**, *41*, 3925. Houk, K. N.; Paddon-Row, M. N.; Spellmeyer, D. C.; Rondan, N. G.; Nagase, S. *J. Org. Chem.* **1986**, *51*, 2874. Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.

(19) (a) Wu, L.; Fischer, H. *Helv. Chim. Acta* **1983**, *66*, 138. (b) Beckwith, A. L. J.; Brumby, S. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1801. (c) Stork, G.; Mah, R. *Heterocycles* **1989**, *28*, 723.

Scheme V



repulsion between the aryl group and the cyclohexene ring. Consequently, the reduction of the intermediate radical is faster than its cyclization. In **23b–d**, such a restriction does not exist, and the cyclization proceeds readily.

The successful cyclization of ethers **23b–d** encouraged us to synthesize lactone intermediate **34** (Scheme V). We expected that the introduction of an ester group α to the ether group would be useful because, when the ethers were cleaved,[20] the resulting phenol group could react with the ester group to afford a lactone. Therefore, route c was explored. As a model experiment, radical precursor **32a** was synthesized as follows. Reaction of 6-bromoguaiacol (**4**) with ethyl bromoacetate in DMF in the presence of NaH gave phenoxyacetate **29** in 85% yield. Reaction of the lithiated intermediate generated by treatment of **29** with LDA in THF at 0 °C with cyclohexanone at −78 °C afforded alcohol **30**, dimer **31**, and unchanged **29** in 57, 25, and 12% yields, respectively. Attempts to prevent the formation of dimer **31** were unsuccessful. Dehydration of **30** with $POCl_3$ in pyridine furnished predominantly β,γ-unsaturated ester **32a** in 80% yield along with conjugated ester **32b** (5%).

The radical reaction of **32a** with AIBN (0.5 equiv) and Bu_3SnH (1.2 equiv) in boiling benzene (0.02 M) afforded the desired spiro compound **33** in 56% yield as the sole product. The structure of **33** was confirmed by the presence of a singlet peak for C_3 at 50.2 ppm in the ^{13}C NMR spectrum. Similarly, the radical reaction of **32a** in boiling toluene gave **33** in 81% yield. This remarkable temperature effect demonstrated that the transition state for the radical reaction of **32a** to **33** required a high activation energy.[21]

Cleavage of the α-phenoxy group in **33** was accomplished with SmI_2[22] in THF–HMPA–MeOH to give spiro[2,3-dihydro-4*H*-1-benzopyran-4,1′-cyclohexan]-2-one **34** and unchanged **33** in 59 and 7% yields, respectively. As anticipated, **34** was produced by ether cleavage and spontaneous reaction of the resulting phenol and ester groups. Thus, we could synthesize spiro lactone **34** in 19% overall yield from 6-bromoguaiacol (**4**) by means of route c.

Total Synthesis of (±)-Lycoramine (2). A total synthesis of (±)-lycoramine (**2**) was achieved starting with **38**, prepared from radical precursor **37a** in a manner similar to that described for **32a**. Thus, the reaction of **29** with cyclohexane-1,4-dione monoketal **35**[23] in the manner described for **30** afforded alcohol **36**, dimer **31**, and unchanged **29** in 71%, 11%, and 11% yields, respectively. Dehydration of **36** with $POCl_3$ in pyridine gave **37a** and **37b** in 72% and 7% yields, respectively (Scheme VI). Compound **37b** could not be transformed to **37a** under basic conditions.

With radical precursor **37a** in hand, the radical reaction of **37a** with AIBN (0.5 equiv) and Bu_3SnH (1.3 equiv) in boiling toluene (0.02 M) was carried out to afford the desired spiro compound **38** in 48% yield (Scheme VII). The structure of **38** was confirmed by the presence of a singlet peak for C_3 at 49.4 ppm in the ^{13}C NMR spectrum. As expected, the radical reaction of **37a** in boiling *o*-xylene increased the yield of **38** to 91%. In contrast with the reaction of **37a**, the reaction of **37b** in boiling *o*-xylene

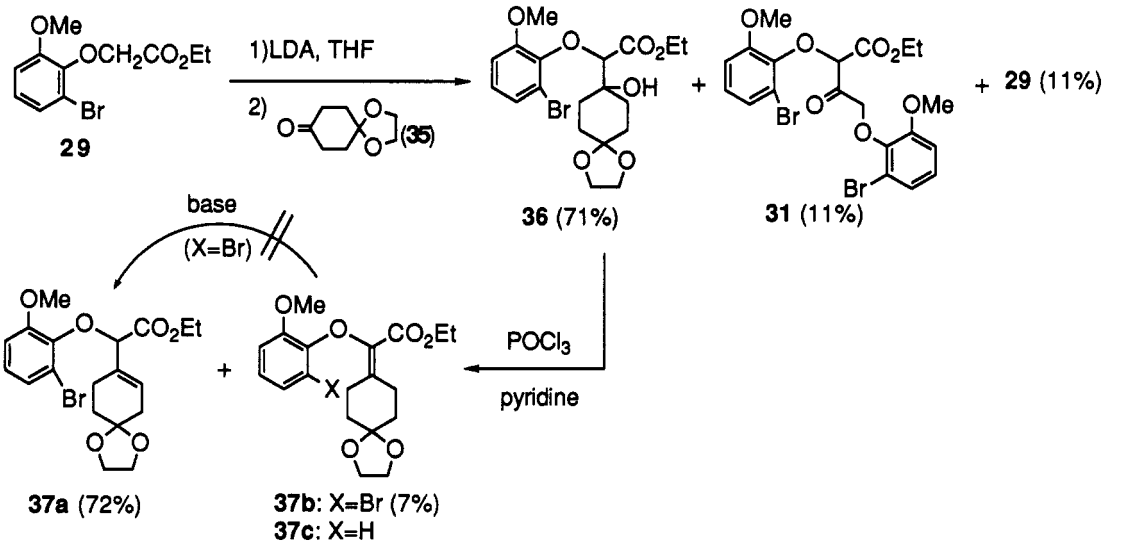
(20) For a review on cleavage of ethers; Bhatt, M. V.; Kulkarni, S. U. *Synthesis* **1983**, 249.

(21) For discussions of the effect of temperature on radical reactions, see: (a) Wu, L.; Fischer, H. *Helv. Chim. Acta* **1983**, *66*, 138. (b) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746.

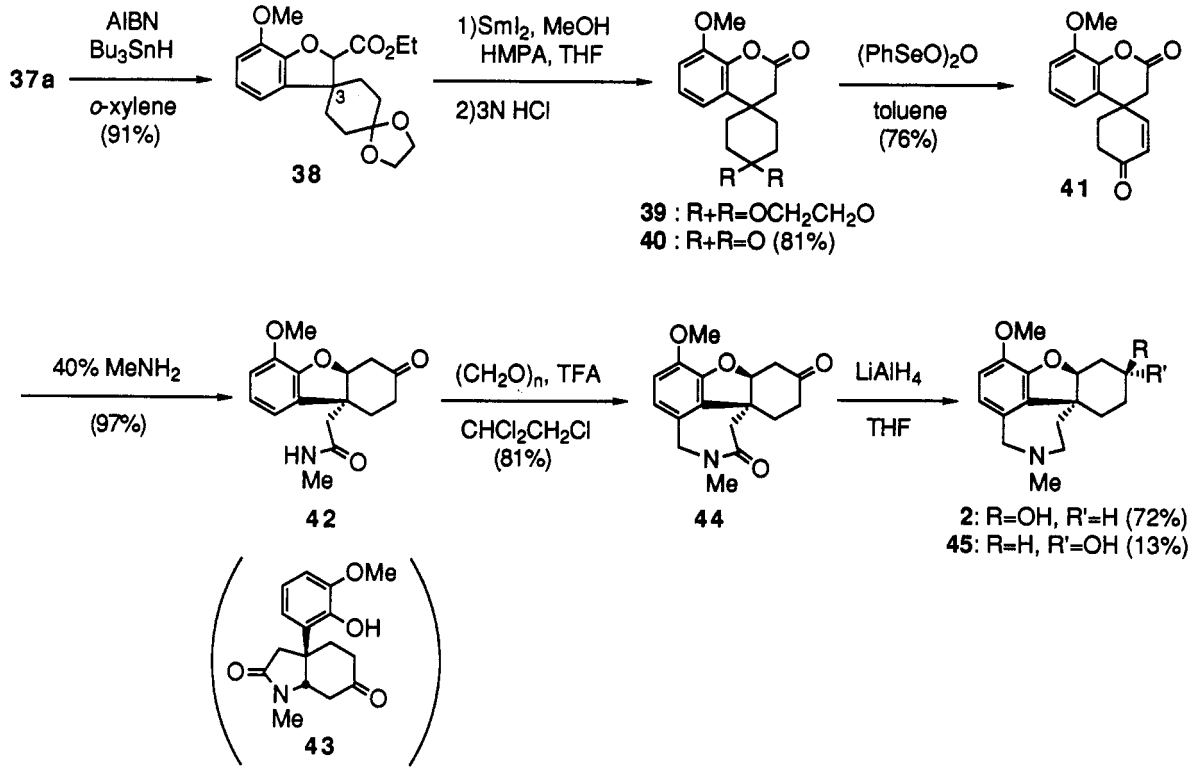
(22) Kusuda, K.; Inanaga, J.; Yamaguchi, M. *Tetrahedron Lett.* **1989**, *30*, 2945.

(23) Haslanger, M.; Lawton, R. G. *Synth. Commun.* **1974**, 155.

Scheme VI



Scheme VII



afforded **38** (23%),[24] reduced product **37c** (55%), and unchanged **37b** (5%).

Reaction of **38** with SmI_2 in THF–HMPA–MeOH in the manner described for **33** gave spiroacetal lactone **39** and spiroketo lactone **40** in 25% and 35% yields, respectively. Spiroketo lactone **40** may be produced by hydrolysis of the acetal group of **39** during the reaction. Reductive cleavage of **38** with SmI_2 followed by treatment with 3 N HCl furnished **40** in 81% yield. Spiroketo lactone **40** was converted to enone **41**[25] in 76% yield by the reaction of **40** with benzeneselenenic anhydride [$(PhSeO)_2O$][26] in refluxing toluene; the oxidation of **40** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave **41** in only 15% yield. Attempts at further transformation of **40** and **41** to a dienone with excess $(PhSeO)_2O$ or DDQ were unsuccessful.

Next, the introduction of an amino group to **41** was carried out. Reaction of **41** with 40% aqueous $MeNH_2$ at room temperature resulted in spontaneous Michael addition of the resulting phenol to cyclohexenone to afford in 97% yield keto amide **42** as the sole product.[27]

(24) Recently, 5-endo radical cyclization of α-halo- or α-thio-substituted *N*-(1-arylethenyl)acetamides has been reported. (a) Sato, T.; Machigashira, N.; Ishibashi, H.; Ikeda, M. *Heterocycles* **1992**, *33*, 139. (b) Sato, T.; Nakamura, N.; Ikeda, K.; Okada, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2399.

(25) Bromination of **40** with phenyltrimethylammonium perbromide in AcOEt followed by treatment with DBU afforded **41** in 48% yield.

(26) Barton, D. H. R.; Lester, D. J.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2209.

(27) For controlling the stereochemistry of the ring junction in hexahydrobenzofurans, see: Rupprecht, K. M.; Boger, J.; Hoogsteen, K.; Nachbar, R. B.; Springer, J. P. *J. Org. Chem.* **1991**, *56*, 6180.

Aminolysis of 41 followed by acid treatment gave phenol 43 in 51% yield along with 42 (16%).

Although the cyclization of 42 in two steps [paraformaldehyde, saturated aqueous Na_2CO_3; trifluoroacetic acid (TFA)][28] was unsuccessful, a modified Pictet–Spengler reaction of 42 and paraformaldehyde with either $MeSO_3H$[29,30] or TFA at ambient temperature smoothly proceeded to give 44 in 40% or 81% yield, respectively.

Finally, reduction of 44 with $LiAlH_4$ in THF (−78 to 0 °C for 1 h, then reflux for 2 h) instead of DME[3f] afforded (±)-2 and (±)-45 in 72% and 13% yields, respectively.[31] The ^1H and ^{13}C NMR spectra of synthetic (±)-lycoramine (2) were identical with those of authentic sample provided by Prof. K. A. Parker.

Thus, a synthesis of spiro[2,3-dihydro-4*H*-1-benzopyran-4,1′-cyclohexan]-2-one derivatives by means of a radical reaction followed by treatment with SmI_2 and a total synthesis of (±)-lycoramine (2) in nine steps and 13% overall yield from 6-bromoguaiacol (4) were achieved.

Experimental Section

General.[30d] All melting points are uncorrected. Unless otherwise indicated, IR spectra were recorded in $CHCl_3$ solution, and NMR spectra were measured in $CDCl_3$ solution with tetramethylsilane as an internal standard. Preparative TLCs were run of Merck 5744 or Merck 7730 plates.

Materials. THF, ether, dioxane, toluene, and *o*-xylene were distilled from $LiAlH_4$ prior to use. DMSO, DMF and diisopropylamine were distilled from CaH_2 prior to use. Benzeneselenenic anhydride was prepared according to the reported method.[26]

6-Bromoguaiacol (4). Br_2 (51.3 g, 0.321 mol) was added dropwise to a solution of *tert*-butylamine (68 mL, 0.322 mol) in toluene (600 mL) at −30 °C. After being stirred for 0.5 h, the reaction mixture was cooled to −60 °C. A solution of guaiacol (40.0 g, 0.322 mol) in CH_2Cl_2 (40 mL) was added dropwise to the reaction mixture, and the mixture was warmed to rt over a period of 5 h. The reaction mixture was treated with 10% $Na_2S_2O_3$, washed with brine, and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure gave an oily residue, which was distilled under reduced pressure (146 °C/4 mmHg) to produce 4 (57.2 g, 87%) as colorless crystals: mp 60–62 °C. [lit.[9] mp 63 °C]; ^1H NMR δ 7.06 (1 H, dd, J = 2.9, 6.8 Hz, arom H), 6.60–6.84 (2 H, m, arom H × 2), 5.90 (1 H, s, OH, exchangable with D_2O), 3.78 (3 H, s, OMe); IR 3500, 1590 cm^{-1}; MS m/z 202 (M^+), 204 ($M^+ + 2$). Anal. Calcd for $C_7H_7O_2Br$: C, 41.35; H, 3.47. Found: C, 41.24; H, 3.54.

General Procedure for Preparation of Radical Precursors 23a–d. A mixture of 2-halophenol, 1-bromomethylcyclohex-1-ene, and K_2CO_3 in acetone (8 mL) was stirred at rt overnight. After filtration of the precipitate, the filtrate was evaporated under reduced pressure. The residue was taken up in ether. The ether extract was washed with 10% NaOH and brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave an oily residue.

2′-Chlorophenyl Cyclohex-1-enylmethyl Ether (23a). 2-Chlorophenol (0.404 g, 3.14 mmol), 1-(bromomethyl)cyclohex-1-ene (0.499 g, 2.85 mmol), and K_2CO_3 (0.472 g, 3.42 mmol)–acetone (8 mL) were used. **23a** (0.454 g, 72%): oil; ^1H NMR δ 7.81, 6.89 (each 1 H, dd, J = 1.7, 7.1 Hz, arom H × 2), 7.14, 6.82 (each 1 H, dt, J = 1.7, 7.1 Hz, arom H × 2), 5.81 (1 H, brs, $W_{1/2}$ = 6.3 Hz, olefinic H), 4.41 (2 H, s, OCH_2), 1.87–2.19 (4 H, m, H-3 × 2, H-6 × 2), 1.40–1.84 (4 H, m, H-4 × 2, H-5 × 2); MS m/z 222 (M^+), 224 ($M^+ + 2$); high-resolution mass m/z calcd for $C_{13}H_{15}OCl$ (M^+) 222.0810, found 222.0803.

2′-Bromophenyl Cyclohex-1-enylmethyl Ether (23b). 2-Bromophenol (0.812 g, 4.68 mmol), 1-(bromomethyl)cyclohex-1-ene (0.683 g, 3.90 mmol), and K_2CO_3 (0.811 g, 5.85 mmol)–acetone (8 mL) were used. **23b** (Kugelrohl distillation; bp 130 °C/2 mmHg) (0.864 g, 83%): oil; ^1H NMR δ 7.49, 6.85 (each 1 H, dd, J = 1.4, 7.1 Hz, arom H × 2), 7.16, 6.76 (each 1 H, dt, J = 1.4, 7.1 Hz, arom H × 2), 5.82 (1 H, brs, $W_{1/2}$ = 6.3 Hz, olefinic H), 4.41 (2 H, s, OCH_2), 1.88–2.02 (4 H, m, H-3 × 2, H-6 × 2), 1.40–1.84 (4 H, m, H-4 × 2, H-5 × 2); MS m/z 266 (M^+), 268 ($M^+ + 2$); high-resolution mass m/z calcd for $C_{13}H_{15}OBr$ (M^+) 266.0305, found 266.0303.

Cyclohex-1-enylmethyl 2′-Iodophenyl Ether (23c). 2-Iodophenol (0.484 g, 2.19 mmol), 1-(bromomethyl)cyclohex-1-ene (0.350 g, 1.99 mmol), and K_2CO_3 (0.414 g, 2.98 mmol)–acetone (6 mL) were used. **23c** (Kugelrohl distillation; bp 134–137 °C/6 mmHg) (0.495 g, 79%): oil; ^1H NMR δ 7.73, 6.77 (each 1 H, dd, J = 1.4, 7.1 Hz, arom H × 2), 7.23, 6.66 (each 1 H, dt, J = 1.4, 7.1 Hz, arom H × 2), 5.84 (1 H, brs, $W_{1/2}$ = 7.7 Hz, olefinic H), 4.40 (2 H, s, OCH_2), 1.91–2.23 (4 H, m, H-3 × 2, H-6 × 2), 1.54–1.84 (4 H, m, H-4 × 2, H-5 × 2); MS m/z 314 (M^+); high-resolution mass m/z calcd for $C_{13}H_{15}OI$ (M^+) 314.0168, found 314.0168.

2′-Bromo-6′-methoxyphenyl Cyclohex-1-enylmethyl Ether (23d). 6-Bromoguaiacol (0.321 g, 1.58 mmol), 1-(bromomethyl)cyclohex-1-ene (0.291 g, 1.66 mmol), and K_2CO_3 (0.327 g, 2.37 mmol)–acetone (6 mL) were used. **23d** (Kugelrohl distillation; bp 114 °C/2 mmHg) (0.385 g, 78%): oil; ^1H NMR δ 7.09, 6.77 (each 1 H, dd, J = 2.8, 7.1 Hz, arom H × 2), 6.87 (1 H, t, J = 7.1 Hz, arom H), 5.79 (1 H, brs, $W_{1/2}$ = 8 Hz, olefinic H), 4.31 (2 H, s, OCH_2), 3.82 (3 H, s, OMe), 1.88–2.41 (4 H, m, H-3 × 2, H-6 × 2), 1.44–1.83 (4 H, m, H-4 × 2, H-5 × 2); MS m/z 296 (M^+), 298 ($M^+ + 2$); high-resolution mass m/z calcd for $C_{14}H_{17}O_2Br$ (M^+) 296.0410, found 296.0393.

2″-Bromo-6″-methoxyphenyl 2-(Cyclohex-1′-enyl)ethyl Ether (25). To a solution of 6-bromoguaiacol (4) (1.26 g, 6.23 mmol), alcohol 24[13c] (0.786 g, 6.23 mmol), and Ph_3P (1.63 g, 6.23 mmol) in THF (150 mL) at ambient temperature was added diethyl azodicarboxylate (0.98 mL, 6.23 mmol). After the reaction mixture was stirred for 2 days, the solvent was evaporated under reduced pressure. Ether was added to the residue, and the precipitate was filtered off. The filtrate was washed with 10% NaOH, water, and brine, successively, and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give an oily residue. Silica gel column chromatography of the residue with hexane/AcOEt (15:1) produced **25** (1.43 g, 74%): oil; ^1H NMR δ 7.09, 6.77 (each 1 H, dd, J = 2.9, 7.1 Hz, arom H × 2), 6.87 (1 H, t, J = 7.1 Hz, arom H), 5.51 (1 H, brs, $W_{1/2}$ = 7.1 Hz, olefinic H), 4.04 (2 H, t, J = 7.1 Hz, OCH_2CH_2), 3.83 (3 H, s, OMe), 2.47 (2 H, t, J = 7.1 Hz, OCH_2CH_2), 1.80–2.11 (4 H, m, H-3′ × 2, H-6′ × 2), 1.40–1.77 (4 H, m, H-4′ × 2, H-5′ × 2); MS m/z 310 (M^+), 312 ($M^+ + 2$); high-resolution mass m/z calcd for $C_{15}H_{19}O_2Br$ (M^+) 310.0568, found 310.0570.

General Procedure for Radical Reactions of 23a–d. A mixture of olefin **23a–d** (0.30–0.36 mmol), AIBN (0.5 equiv), and Bu_3SnH (1.5 equiv) in benzene (0.02 M) was refluxed for 0.5–1 h. The solvent was evaporated under reduced pressure to give an oily residue, which was taken up in ether. The ether layer was washed with 10% aqueous KF and brine, successively, and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give an oily residue. Preparative TLC of the residue with hexane followed by hexane/AcOEt (20:1) afforded **26a** or **26b** as a colorless oil. Olefin **23a** was recovered unchanged in quantitative yield.

Spiro[2,3-dihydrobenzofuran-3,1′-cyclohexane] (26a): oil; ^1H NMR δ 6.64–7.19 (4 H, m, arom H × 4), 4.33 (2 H, s, H-2 × 2), 1.12–1.92 (10 H, m); ^{13}C NMR δ 159.3 (s, C-7a), 136.2 (s, C-3a), 127.2 (d, C-6), 122.8 (d, C-5), 120.3 (d, C-4), 109.6 (d, C-7), 80.9 (t, C-2), 46.0 (s, C-3), 36.8 (t, C-2′, C-6′), 25.4 (t, C-4′), 23.3 (t, C-3′, C-5′); MS m/z 188 (M^+); high-resolution mass m/z calcd for $C_{13}H_{16}O$ (M^+) 188.1200, found 188.1207.

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(31) Reduction of 44 with $LiAlH_4$ in DME[3f] (−78 to 0 °C for 1.5 h, then reflux for 1 h) gave (±)-lycoramine (2) and its isomer 45 in 33% and 34% yields, respectively. The lower stereoselectivity of the ketone reduction may have been the result of the elevated reaction temperature that was required because of the poor solubility of 44 in DME. The reduction of 44 with either $LiAlH_4$ in THF (0 °C for 0.5 h, then reflux for 2.5 h) or BH_3·THF (0 °C for 0.5 h, then reflux for 2.5 h) gave 2 (67% or 33%) and 45 (28% or 14%).

Spiro[2,3-dihydro-7-methoxybenzofuran-3,1′-cyclohexane] (26b): oil; ^{1}H NMR δ 6.60–6.91 (3 H, m, arom H × 3), 4.40 (2 H, s, H-2 × 2), 3.85 (3 H, s, OMe), 1.14–1.87 (10 H, m); ^{13}C NMR δ 147.4 (s, C-7a), 144.6 (s, C-7), 137.5 (s, C-3a), 121.0 (d, C-4), 115.1 (d, C-5), 111.2 (d, C-6), 96.2 (t, C-2), 75.8 (q, OMe), 55.9 (s, C-3), 36.7 (t, C-2′, C-6′), 25.4 (t, C-4′), 23.3 (t, C-3′, C-5′); MS *m/z* 218 (M$^+$); high-resolution mass *m/z* calcd for $C_{14}H_{18}O_2$ (M$^+$) 218.1306, found 218.1306.

Radical Reaction of 25. A mixture of olefin **25** (0.100 g, 0.32 mmol), AIBN (26.4 mg, 0.16 mmol), and Bu_3SnH (0.11 mL, 0.384 mmol) in benzene (16 mL) was refluxed for 3 h. A workup similar to that described above afforded a crude oil. Two silica gel preparative TLCs with hexane followed by hexane/AcOEt (10:1) gave **27** (0.0263 g, 35%) and **28** (0.0183 g, 25%). Compound **28** was obtained as a 1.2:1 mixture of diastereomers (ratio estimated by the height of peaks due to methoxyl group in the ^{1}H NMR spectrum).

Spiro[2,3-dihydro-8-methoxy-4*H*-1-benzopyran-4,1′-cyclohexan]-2-one (27): mp 105–106 °C (hexane); ^{1}H NMR δ 6.94, 6.64 (each 1 H, dd, *J* = 2.9, 7.1 Hz, arom H × 2), 6.80 (1 H, t, *J* = 7.1 Hz, arom H), 4.20 (2 H, t, *J* = 5.7 Hz, H-2 × 2), 3.84 (3 H, s, OMe), 1.99 (2 H, t, *J* = 5.7 Hz, H-3 × 2), 1.20–1.89 (10 H, m); ^{13}C NMR δ 148.3 (s, C-8a), 143.9 (s, C-8), 133.1 (s, C-4a), 119.6 (d, C-5), 118.8 (d, C-6), 108.5 (d, C-7), 63.2 (t, C-2), 55.8 (q, OMe), 38.3 (t, C-3), 34.0 (s, C-4), 30.4 (t, C-2′, C-6′), 25.9 (t, C-4′), 21.8 (t, C-3′, C-5′); MS *m/z* 232 (M$^+$). Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.86. Found: C, 77.47; H, 8.80.

***cis*- and *trans*-Cyclohexo[1,2-*c*]-2,3,4,5-hexahydro-9-methoxy-1-benzoxepine (28)**: mp 64–65 °C (hexane); ^{1}H NMR δ 6.60–6.99 (3 H, m, arom H × 3), 4.27–4.60 (1 H, m), 3.82, 3.81 (1:1.2) (3 H, s, OMe), 3.63 (1 H, dt, *J* = 2.9, 11.4 Hz), 2.36–2.90 (2 H, m), 1.14–2.20 (10 H, m); ^{13}C NMR δ 151.8 (s), 149.3 (s), 139.4 (s), 138.2 (s), 123.1 (d), 122.9 (d), 118.1 (d), 110.2 (d), 110.0 (d), 96.1 (s), 73.7 (t), 70.0 (t), 56.0 (q, OMe), 50.0 (d), 42.5 (d), 39.3 (d), 36.1 (m), 35.7 (m), 34.4 (m), 33.0 (m), 32.1 (m), 30.8 (m), 27.2 (m), 26.4 (m), 20.4 (m); MS *m/z* 232 (M$^+$); high-resolution mass *m/z* calcd for $C_{15}H_{20}O_2$ 232.1461, found 232.1461.

Ethyl (2-Bromo-6-methoxyphenoxy)acetate (29). To a suspension of NaH (60% dispersion in mineral oil, 2.56 g, 63.7 mmol) in DMF (80 mL) at rt under an argon atmosphere was added a solution of 6-bromoguaiacol (**4**) (10 g, 49.3 mmol) in DMF (10 mL). After the reaction mixture was stirred for 1 h, a solution of ethyl bromoacetate (8.23 g, 54.2 mmol) in DMF (8 mL) was added over a period of 20 min, and stirring was continued for 1.5 h. After being quenched with water, the reaction mixture was extracted with ether. The extract was washed successively with 10% NaOH, water, and brine and dried ($MgSO_4$). Removal of the solvent under reduced pressure gave an oily residue, which was distilled under reduced pressure (150–153 °C/4 mmHg) to afford **29** (12.07 g, 85%): oil; ^{1}H NMR δ 7.11, 6.80 (each 1 H, dd, *J* = 2.5, 7.9 Hz, arom H × 2), 6.91 (1 H, t, *J* = 7.9 Hz, arom H), 4.60 (2 H, s, C*H*$_2$CO$_2$Et), 4.27 (2 H, q, *J* = 6.8 Hz, C*H*$_2$CH$_3$), 3.81 (3 H, s, OMe), 1.31 (3 H, t, *J* = 6.8 Hz, CH$_2$C*H*$_3$); IR 1760 cm^{-1}; MS *m/z* 288 (M$^+$), 290 (M$^+$ + 2); high-resolution mass *m/z* calcd for $C_{11}H_{13}O_4Br$ (M$^+$) 287.9997, found 288.0005.

Ethyl α-(2′-Bromo-6′-methoxyphenoxy)-α-(1-hydroxycyclohexyl)acetate (30) and Ethyl 2,4-Bis(2′-bromo-6′-methoxyphenoxy)-3-oxobutyrate (31). To an ice-cooled, stirred solution of diisopropylamine (4.8 mL, 34.6 mmol) in THF (15 mL) was added n-BuLi (21 mL, 34.6 mmol, 1.64 M in hexane) under an argon atmosphere. The reaction mixture was stirred at 0 °C for 1 h and then cooled to −78 °C. A solution of ester **29** (5.00 g, 17.3 mmol) in THF (2 mL) was added to the mixture over a period of 8 min. The mixture was stirred for 10 min, and a solution of cyclohexenone (2.04 g, 20.8 mmol) in THF (1.5 mL) was added over a period of 6 min. After being stirred for 5 min, the reaction mixture was quenched with water and extracted with ether. The extract was washed with 10% HCl, water, and brine, successively, and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give an oily residue, which was purified by silica gel column chromatography with hexane/AcOEt (8:1) to afford **30** (3.81 g, 57%), **31** (1.13 g, 25%), and **29** (0.61 g, 12%). **30**: mp 89–90 °C (EtOH); ^{1}H NMR δ 7.11 (1 H, dd, *J* = 2.9, 7.1 Hz, arom H), 6.71–6.98 (2 H, m, *J* = 6.3 Hz, arom H × 2), 4.60 (1 H, s, C*H*CO$_2$Et), 4.11 (2 H, q, *J* = 7.7 Hz, C*H*$_2$CH$_3$), 3.77 (3 H, s, OMe), 3.14 (1 H, s, OH), 1.36–1.99 (10 H, m, cyclohexyl), 1.24 (3 H, t, *J* = 7.7 Hz, CH$_2$C*H*$_3$); IR 3250–3650, 1745 cm^{-1}; MS *m/z* 386 (M$^+$), 388 (M$^+$ + 2). Anal. Calcd for $C_{17}H_{23}O_5Br$: C, 52.72; H, 5.99. Found: C, 52.89; H, 6.02. **31**: oil; ^{1}H NMR δ 6.72–7.20 (6 H, m, arom H × 6), 5.32, 5.08 (each 1 H, d, *J* = 16 Hz, OC*H*$_2$CO$_2$), 5.28 (1 H, s, OC*H*CO$_2$Et), 4.26 (2 H, q, *J* = 6.6 Hz, C*H*$_2$CH$_3$), 3.80 (6 H, s, OMe × 2), 1.31 (3 H, t, *J* = 6.6 Hz, CH$_2$C*H*$_3$); IR 1750, 1740 cm^{-1}; MS *m/z* 530 (M$^+$), 532 (M$^+$ + 2), 534 (M$^+$ + 4); high-resolution mass *m/z* calcd for $C_{20}H_{20}O_7Br_2$ (M$^+$) 529.9576, found 529.9587.

Ethyl α-(2′-Bromo-6′-methoxyphenoxy)-α-cyclohex-1-enylacetate (32a) and Ethyl α-(2-Bromo-6-methoxyphenoxy)-α-cyclohexylideneacetate (32b). A solution of alcohol **30** (0.200 g, 0.52 mmol) and $POCl_3$ (0.1 mL, 1.04 mmol) in pyridine (2 mL) was refluxed for 0.5 h. Then the mixture was poured onto crushed ice. The product was taken up in ether, and the organic extract was washed successively with water, 10% HCl, water, saturated aqueous $NaHCO_3$, and brine and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give an oily residue, which was purified by silica gel column chromatography with hexane/AcOEt (1:1) to afford **32a** (0.152 g, 80%) and **32b** (0.009 g, 5%). **32a**: oil; ^{1}H NMR δ 7.09 (1 H, dd, *J* = 2.9, 6.3 Hz, arom H), 6.67–6.94 (2 H, m, arom H × 2), 5.74 (1 H, brs, $W_{1/2}$ = 6.6 Hz, olefinic H), 5.00 (1 H, s, OC*H*CO$_2$Et), 4.24 (2 H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 3.77 (3 H, s, OMe), 1.40–2.16 (8H, m), 1.27 (3 H, t, *J* = 7.1 Hz, CH$_2$C*H*$_3$); IR 1740 cm^{-1}; MS *m/z* 368 (M$^+$), 370 (M$^+$ + 2); high-resolution mass *m/z* calcd for $C_{17}H_{21}O_4Br$ (M$^+$) 368.0623, found 368.0639. **32b**: oil; ^{1}H NMR δ 7.09 (1 H, dd, J = 3.4, 7.1 Hz, arom H), 6.64–6.86 (2 H, m, arom H × 2), 4.03 (2 H, q, *J* = 6.7 Hz, C*H*$_2$CH$_3$), 3.72 (3 H, s, OMe), 2.54–2.77, 2.28–2.76 (each 2 H, m, H-2 × 2, H-6 × 2), 1.43–1.76 (6H, brs, H-3 × 2, H-4 × 2, H-5 × 2), 1.03 (3 H, t, *J* = 6.7 Hz, CH$_2$C*H*$_3$); IR 1740 cm^{-1}; MS *m/z* 368 (M$^+$), 370 (M$^+$ + 2); high-resolution mass *m/z* calcd for $C_{17}H_{21}O_4Br$ (M$^+$) 368.0623, found 368.0628.

Radical Reaction of 32a. A mixture of olefin **32a** (1.123 g, 3.31 mmol), AIBN (0.272 g, 1.66 mmol), and Bu_3SnH (1.1 mL, 4.09 mmol) in toluene (156 mL) was refluxed for 2 h. The solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography with hexane followed by hexane/AcOEt (10:1) to give **33** (0.781 g, 81%): oil; ^{1}H NMR δ 6.61–6.88 (3 H, m, arom H × 3), 5.89 (1 H, s, OC*H*CO$_2$Et), 4.21 (2 H, q, *J* = 7.1 Hz, C*H*$_2$CH$_3$), 3.86 (3 H, s, OMe), 1.43–1.85 (10 H, m), 1.26 (3 H, t, *J* = 7.1 Hz, CH$_2$C*H*$_3$); ^{13}C NMR δ 169.5 (s, *C*O$_2$Et), 146.6 (s, C-7a), 144.4 (s, C-7), 135.8 (s, C-3a), 121.4 (d, C-4), 115.8 (d, C-5), 111.7 (d, C-6), 89.0 (d, C-2), 60.8 (t, *C*H$_2$CH$_3$), 55.9 (q, OMe), 50.2 (s, C-3), 38.0 (t, C-2′ or C-6′), 31.9 (t, C-2′ or C-6′), 25.3 (t, C-4′), 22.5 (t, C-3′ or C-5′), 22.2 (t, C-3′ or C-5′), 14.0 (q, CH$_2$CH$_3$); IR 1745 cm^{-1}; MS *m/z* 290 (M$^+$); high-resolution mass *m/z* calcd for $C_{17}H_{22}O_4$ (M$^+$) 290.1517, found 290.1519.

Spiro[2,3-dihydro-8-methoxy-4*H*-1-benzopyran-4,1′-cyclohexan]-2-one (34). SmI_2 (6 mL, 6 mmol, 0.1 M in THF, purchased from Aldrich) was added to a mixture of **33** (58.3 mg, 0.29 mmol), HMPA (0.3 mL, 1.81 mmol), and MeOH (12 μL, 0.30 mmol) under an argon atmosphere. After the reaction mixture was stirred for 0.5 h, brine was added. The solvent was evaporated under reduced pressure, and the aqueous layer was extracted with ether. The extract was washed with saturated aqueous $NaHCO_3$ and brine, successively, and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure produced a crude residue, which was purified by silica gel preparative TLC with hexane/AcOEt (6:1) to afford **34** (29.4 mg, 60%) and **33** (4.1 mg, 7%). **34**: mp 108–109 °C (MeOH); ^{1}H NMR δ 7.08 (1 H, t, *J* = 8.0 Hz, arom H), 6.91, 6.88 (each 1 H, dd, *J* = 2.6, 8.0 Hz, arom H × 2), 3.87 (3 H, s, OMe), 2.77 (2 H, s, H-3 × 2), 1.40–1.89 (10 H, m); IR 1775 cm^{-1}; MS *m/z* 246 (M$^+$). Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: 73.18; H, 7.10.

Ethyl α-(2′-Bromo-6′-methoxyphenoxy)-α-(4,4-(ethylenedioxy)-1-hydroxycyclohexyl)acetate (36). To an ice-cooled, stirred solution of diisopropylamine (5.1 mL, 36.3 mmol) in THF (10 mL) was added n-BuLi (22.4 mL, 36.3 mmol, 1.64 M in hexane) under an argon atmosphere. The reaction mixture was stirred for 1 h at the same temperature and then cooled to −78 °C. A solution of ester **29** (5.25 g, 18.2 mmol) in THF (8 mL) was added to the mixture over a period of 15 min at −78 °C under an argon atmosphere. After 15 min, a solution of cyclohexane-1,4-dione monoketal **35**[22] (3.40 g, 21.8 mmol) in THF (5 mL) was added to the mixture over a period of 10 min. After being stirred for an

additional 15 min, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The product was taken up in ether. The ether extract was washed with 5% HCl, water, saturated $NaHCO_3$, and brine, successively, and dried (K_2CO_3). The solvent was evaporated under reduced pressure to give an oily residue, which was purified by silica gel column chromatography with CH_2Cl_2/AcOEt (3:1) to afford **36** (5.73 g, 71%), **31** (0.517 g, 11%), and **29** (0.595 g, 11%). **36**: mp 89–91 °C (EtOH); ^1H NMR δ 7.10, 6.82 (each 1 H, dd, J = 2.9, 6.6 Hz, arom H × 2), 6.84 (1 H, t, J = 6.6 Hz, arom H), 4.66 (1 H, s, OC*H*CO_2Et), 4.20 (2 H, q, J = 7.5 Hz, C*H*$_2CH_3$), 3.92 (4H, s, OCH_2CH_2O), 3.77 (3 H, s, OMe), 3.22 (1 H, s, OH, exchangable with D_2O), 1.49–2.17 (8 H, m), 1.24 (3 H, t, J = 7.5 Hz, CH_2CH_3); IR 3300–3650, 1745 cm^{-1}; MS m/z 444 (M^+), 446 ($M^+ + 2$). Anal. Calcd for $C_{19}H_{25}O_7Br$: C, 51.24; H, 5.66. Found: C, 51.26; H, 5.67.

Ethyl α-(2′-Bromo-6′-methoxyphenoxy)-α-(4,4-(ethylenedioxy)cyclohex-1-enyl)acetate (37a) and Ethyl α-(2′-Bromo-6′-methoxyphenoxy)-α-(4,4-(ethylenedioxy)cyclohexylidene)-acetate (37b). A solution of alcohol **36** (5.42 g, 12.2 mmol) and $POCl_3$ (2.3 mL, 25.6 mmol) in pyridine (40 mL) was heated at 90 °C for 1 h. The reaction mixture was poured onto crushed ice and worked up in a manner similar to that described for **30**. The oily residue was purified by silica gel column chromatography with hexane/AcOEt (3:1) to afford **37a** (3.74 g, 72%) and **37b** (0.37 g, 7%). **37a**: oil; ^1H NMR δ 7.10, 6.80 (each 1 H, dd, J = 3.1, 7.1 Hz, arom H × 2), 6.86 (1 H, t, J = 7.1 Hz, arom H), 5.67 (1 H, brs, $W_{1/2}$ = 8.6 Hz, olefinic H), 5.06 (1 H, s, OC*H*CO_2Et), 4.24 (2 H, q, J = 6.6 Hz, C*H*$_2CH_3$), 3.94 (4 H, s, OCH_2CH_2O), 3.77 (3 H, s, OMe), 2.08–2.90 (4 H, m), 1.78 (2 H, t, J = 5.7 Hz, H-5 × 2), 1.28 (3 H, t, J = 6.6 Hz, CH_2CH_3); IR 1750 cm^{-1}; MS m/z 426 (M^+), 428 ($M^+ + 2$); high-resolution mass m/z calcd for $C_{19}H_{23}O_6Br$ (M^+) 426.0678, found 426.0674. **37b**: oil; ^1H NMR δ 7.11, 6.79 (each 1 H, dd, J = 2.9, 7.6 Hz, arom H × 2), 6.93 (1 H, t, J = 7.6 Hz, arom H), 4.01 (2 H, q, J = 6.9 Hz, C*H*$_2CH_3$), 3.97 (4 H, s, OCH_2CH_2O), 3.71 (3 H, s, OMe), 2.84, 2.63 (each 2 H, t, J = 5.7 Hz, H-2 × 2, H-6 × 2), 1.63–1.89 (4 H, m, H-3 × 2, H-5 × 2), 1.03 (3 H, t, J = 6.9 Hz, CH_2CH_3); IR 1720 cm^{-1}; MS m/z 426 (M^+), 428 ($M^+ + 2$); high-resolution mass m/z calcd for $C_{19}H_{23}O_6Br$ (M^+) 426.0678, found 426.0670.

Radical Reaction of 37a and 37b. (a) **37a**. A mixture of olefin **37a** (5.84 g, 13.7 mmol), AIBN (1.12 g, 6.38 mmol), and Bu_3SnH (4.9 mL, 18.2 mmol) in *o*-xylene (680 mL) was refluxed for 1.5 h. The solvent was removed under reduced pressure. Silica gel column chromatography of the residue with hexane followed by hexane/AcOEt (3:1) gave **38** (4.34 g, 91%): oil; ^1H NMR δ 6.63–6.90 (3 H, m, arom H × 3), 4.92 (1 H, s, OC*H*CO_2Et), 4.21 (2 H, q, J = 6.9 Hz, C*H*$_2CH_3$), 3.96 (4 H, s, OCH_2CH_2O), 3.86 (3 H, s, OMe), 1.68–2.08 (8 H, m, $-CH_2CH_2-$ × 2), 1.27 (3 H, t, J = 6.9 Hz, CH_2CH_3); ^{13}C NMR δ 169.4 (s, *C*O_2Et), 146.8 (s, C-7a), 144.6 (s, C-7), 134.9 (s, C-3a), 121.8 (d, C-4), 115.5 (d, C-5), 112.1 (d, C-6), 107.9 (s, C-4′), 88.3 (d, C-2), 64.3 (t, OCH_2CH_2O), 61.1 (t, CH_2CH_3), 56.1 (q, OMe), 49.4 (s, C-3), 35.5 (t, C-2′ or C-6′), 31.5 (t, C-2′ or C-6′), 29.5 (t, C-3′, C-5′), 14.2 (q, CH_2CH_3); IR 1750 cm^{-1}; MS m/z 348 (M^+); high-resolution mass m/z calcd for $C_{19}H_{24}O_6$ (M^+) 348.1571, found 348.1568.

(b) **37b**. A mixture of olefin **37b** (0.128 g, 0.3 mmol), AIBN (24.5 mg, 6.38 mmol), and Bu_3SnH (0.1 mL, 0.36 mmol) in *o*-xylene (15 mL) was refluxed for 2 h. A workup similar to that described above afforded an oily residue. Silica gel column chromatography of the oily residue with hexane followed by hexane/AcOEt (3:1) gave a mixture of **37b**, **37c**, and **38** (92.5 mg) as a colorless oil. GLC analysis of the reaction mixture showed the ratio of **38**, **37b**, and **37c** to be 1.0:5.7:11.5. Analytical conditions: 1% OV-1 on Shimalite W, 3.5-mm i.d. × 3-m glass column; column temperature, 280 °C; flame ionization detector; t_R min, 11.8 for **37c**, 13.8 for **38**, and 20.0 for **37b**.

Spiro[2,3-dihydro-4*H*-1-benzopyran-4,1′-(4′,4′-ethylenedioxy)cyclohexan]-2-one (39) and Spiro[2,3-dihydro-8-methoxy-4*H*-1-benzopyran-4,1′-cyclohexane]-2,4′-dione (40). (a) With 3 N HCl. To Sm powder (2.839 g, 18.9 mg atom) was added a solution of 1,2-diiodoethane (5.155 g, 18.3 mmol) in THF (92 mL) over a period of 0.5 h at rt under an argon atmosphere. The reaction mixture was stirred for 1 h at the same temperature. HMPA (11.5 mL, 66.1 mmol) was added to this solution, and the mixture was stirred for 15 min. A solution of ester **38** (1.403 g, 3.65 mmol) and MeOH (0.6 mL, 14.8 mmol) in THF (20 mL) was added to the reaction mixture over a period of 5 min, and the mixture was stirred for 1 h 20 min. Then 3 M HCl (40 mL) was added, and the mixture was stirred for an additional 1 h. The solvent was removed under reduced pressure. The aqueous layer was extracted with ether. The extract was washed with brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure produced a crude residue. When ether was added to the residue, a precipitate formed. Filtration by suction afforded **40** (0.740 g, 71%) as colorless crystals. Purification of the filtrate by silica gel preparative TLC with hexane/AcOEt (1:1) afforded additional **40** (0.109 g, 10%): mp 175–176 °C (MeOH); ^1H NMR δ 6.80–7.24 (3 H, m, arom H × 3), 3.88 (3 H, s, OMe), 2.96 (2 H, s, CH_2CO_2), 1.84–2.64 (8 H, m); IR 1765, 1705 cm^{-1}; MS m/z 260 (M^+). Anal. Calcd for $C_{15}H_{16}O_4$: C, 69.23; H, 6.15. Found: C, 69.10; H, 6.10.

(b) Without 3 N HCl. To Sm powder (1.466 g, 9.98 mg atom) was added a solution of 1,2-diiodoethane (2.537 g, 9.0 mmol) and THF (45 mL) over a period of 0.5 h at rt under an argon atmosphere. The reaction mixture was stirred for 1 h at the same temperature. HMPA (5.9 mL, 33.9 mmol) was added to this solution, and the mixture was stirred for 10 min. A solution of ester **38** (0.5227 g, 1.5 mmol) and MeOH (0.25 mL, 6.2 mmol) in THF (4 mL) was added to the reaction mixture over a period of 5 min, and the mixture was stirred for 1 h. The solvent was removed under reduced pressure. After extraction with ether, the extract was washed with brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure produced a crude residue, which was purified by silica gel column chromatography with AcOEt/hexane (1:5) to afford **39** (0.132 g, 25%) and **40** (0.1372 g, 35%). The latter was identical in all respects with **40** obtained from procedure a. **39**: mp 148–149 °C (MeOH); ^1H NMR δ 7.11–7.67 (3 H, m, arom H × 3), 3.94 (4 H, s, OCH_2CH_2O), 3.89 (3 H, s, OMe), 2.80 (2 H, s, H-3), 1.47–2.26 (8 H, m); IR 1765 cm^{-1}; MS m/z 304 (M^+). Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.02; H, 6.62. Found: C, 66.83; H, 6.63.

Spiro[2,3-dihydro-8-methoxy-4*H*-1-benzopyran-4,1′-cyclohex-2′-ene]-2,4′-dione (41). A mixture of ketone **40** (0.200 g, 0.77 mmol) and benzeneselenenic anhydride[26] (0.305 g, 0.85 mmol) in toluene (10 mL) was refluxed for 0.5 h. After the addition of saturated aqueous $NaHCO_3$, the mixture was extracted with AcOEt. The extract was washed with brine and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to produce a crude residue. Silica gel column chromatography of the residue with hexane, 3:1 hexane/AcOEt, and then 3:2 hexane/AcOEt gave **41** (0.152 g, 76%) as colorless crystals: mp 130.5–131.5 °C (MeOH); ^1H NMR δ 7.11 (1 H, t, J = 8 Hz, arom H), 6.94, 6.69 (each 1 H, dd, J = 1.6, 8 Hz, arom H × 2), 6.67, 6.27 (each 1 H, d, J = 10 Hz, olefinic H × 2), 3.90 (3 H, s, OMe), 2.88 (2 H, s, H-3 × 2), 2.30–2.54 (2 H, m, H-6′ × 2), 2.04–2.30 (2 H, m, H-5′ × 2); IR 1765, 1675 cm^{-1}; MS m/z 258 (M^+). Anal. Calcd for $C_{15}H_{14}O_4$; C, 69.77; H, 5.43. Found: C, 69.97; H, 5.45.

1,2,3,4,4a,9b-Hexahydro-6-methoxy-9b-(((*N*-methylamino)carbonyl)methyl)dibenzofuran-3-one (42) and 3a-(2-Hydroxy-3-methoxyphenyl)octahydro-1-methyl-6*H*-indole-2,6-dione (43). (a) Without 3 N HCl. A solution of enone **41** (0.258 g, 1 mmol) and 40% aqueous $MeNH_2$ (0.3 mL) in THF (4 mL) was stirred at rt for 20 min. The solvent was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$, and the organic phase was washed with brine and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure gave **42** (0.281 g, 97%) as colorless crystals: mp 119–120 °C (AcOEt–hexane); ^1H NMR δ 6.60–6.88 (3 H, m, arom H × 3), 5.54 (1 H, brs $W_{1/2}$ = 18.6 Hz, NH), 5.32 (1 H, t, J = 3.2 Hz, H-4a), 3.84 (3 H, s, OMe), 3.06 (1 H, dd, J = 3.2, 8 Hz), 2.78 (3 H, d, J = 5.2 Hz, NH*Me*), 2.71 (2 H, s, C*H*$_2$CONH), 1.52–2.60 (6 H, m, H-1 × 2, H-2 × 2, H-4 × 2); IR 3450, 1715, 1680 cm^{-1}; MS m/z 289 (M^+). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.44; H, 6.57; N, 4.84. Found: C, 66.37; H, 6.84; N, 4.66.

(b) With 3 N HCl. A solution of enone **41** (0.050 g, 0.2 mmol) and 40% aqueous $MeNH_2$ (50 μL) in THF (1 mL) was stirred at rt for 20 min. Then 3 N HCl (1 mL) was added to the mixture. After the reaction mixture was stirred at rt for 20 min, a workup similar to that described above afforded a residue, which was purified by silica gel preparative TLC with $CHCl_3$/MeOH (20:1) to afford **42** (9.2 mg, 16%) and **43** (28.4 mg, 51%). **43**: mp 210–211 °C; ^1H NMR δ 6.83 (3 H, s, arom H × 3), 6.11 (1 H, s, OH),

4.38 (1 H, t, J = 3.8 Hz, H-7a), 3.90 (3 H, s, OMe), 2.68–3.00 (3 H, m), 2.80 (3 H, s, NMe), 2.00–2.64 (5 H, m); IR 3520, 1715, 1670 cm^{-1}; MS m/z 289 (M^+); high-resolution mass m/z calcd for $C_{16}H_{19}NO_4$ (M^+) 289.1313, found 289.1315.

Pictet-Spengler Cyclization of 42. (a) With TFA. A mixture of amide **42** (0.150 g, 0.52 mmol), paraformaldehyde (0.0474 g, 1.56 mmol), and TFA (0.5 mL, 6.5 mmol) in CH_2ClCH_2Cl (5 mL) was stirred at rt for 1 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$ and brine, successively, and dried (Na_2SO_4). The solvent was evaporated under reduced pressure to produce a crude residue. Silica gel preparative TLC of the residue with $CHCl_3$/MeOH (20:1) afforded **44** (0.126 g, 81%): mp 150 °C (AcOEt); ^1H NMR δ 6.74, 6.64 (each 1 H, d, J = 8 Hz, arom H × 2), 4.83 (1 H, t, J = 3.8 Hz, H-12a), 4.41 (2 H, s, H-8 × 2), 3.84 (3 H, s, OMe), 3.02 (3 H, s, NMe), 2.72–3.20 (4 H, m), 2.24–2.44 (2 H, m), 1.92–2.12 (2 H, m); IR 1720, 1635 cm^{-1}; MS m/z 301 (M^+). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.77; H, 6.31; N, 4.65. Found: C, 67.66; H, 6.21; N, 4.34.

(b) With $MeSO_3H$. A mixture of amide **42** (28.9 mg, 0.1 mmol), paraformaldehyde (9 mg, 0.3 mmol), Ac_2O (20.5 mg, 0.2 mmol), and $MeSO_3H$ (48 mg, 0.5 mmol) in CH_2ClCH_2Cl (1 mL) was stirred at 0 °C for 2 h. A workup similar to that described above afforded **44** (13.0 mg, 43%), which was identical in all respects with **44** obtained from procedure a.

(±)-Lycoramine (2) and (±)-2-Epilycoramine (45). To a suspension of $LiAlH_4$ (19.4 mg, 0.51 mmol) in THF (3 mL) at −78 °C under argon was added a solution of **44** (30.1 mg, 0.1 mmol) in THF (2 mL). The reaction mixture was warmed to rt over a period of 1 h and refluxed for 2 h. $LiAlH_4$ (9.7 mg, 0.26 mmol) was added, and the mixture was refluxed for an additional 1 h. The reaction mixture was quenched with saturated aqueous Na_2SO_4 under cooling. Then 3 N NaOH was added to this mixture, and the mixture was extracted with AcOEt. The extract was washed with brine and dried (K_2CO_3). Evaporation of the solvent under reduced pressure produced a crude residue, which was purified by silica gel preparative TLC with $CHCl_3$/MeOH (100:12) to afford **2** (20.9 mg, 72%) and **45** (3.7 mg, 13%). (±)-**2**: mp 98–100 °C; ^1H NMR (500 MHz) δ 6.65 (1 H, d, J = 8 Hz, H-10), 6.60 (1 H, d, J = 8 Hz, H-11), 4.37 (1 H, t, J = 3 Hz, H-12a), 4.07–4.10 (1 H, m, H-2), 4.00 (1 H, d, J = 14.5 Hz, H-8), 3.86 (3 H, s, OMe), 3.61 (1 H, d, J = 14.5 Hz, H-8), 3.21 (1 H, ddd, J = 1.5, 12.5, 14 Hz, H-6), 3.04 (1 H, dt, J = 3, 14 Hz, H-6), 2.50 (1 H, ddd, J = 3, 4, 16 Hz, H-1), 2.37 (3 H, s, NMe), 1.96 (1 H, dt, J = 3, 14 Hz, H-5), 1.89 (1 H, ddd, J = 3, 5, 16 Hz, H-1), 1.75–1.85 (2 H, m, H-4 × 2), 1.72 (1 H, dt, J = 4, 14 Hz, H-3), 1.65 (1 H, ddd, J = 1.5, 3, 14 Hz, H-5), 1.54–1.60 (1 H, m, H-3); ^{13}C NMR (125 MHz) δ 145.9, 144.1, 136.3, 128.9, 121.8, 110.7, 90.0, 65.4, 60.5, 50.9, 54.1, 46.7, 41.8, 31.5, 31.1, 27.7, 23.7; IR 3250–3600, 2925, 1620, 1585, 1500 cm^{-1}; MS m/z 289 (M^+); high-resolution mass m/z calcd for $C_{17}H_{23}NO_3$ (M^+) 289.1676, found 289.1673. ^1H and ^{13}C NMR spectra of (±)-**2** were identical with those of authentic sample provided us by Prof. K. A. Parker. **45**: mp 182–183 °C; ^1H NMR (500 MHz) δ 6.64 (1 H, d, J = 8 Hz, H-10), 6.56 (1 H, d, J = 8 Hz, H-11), 4.07–4.40 (1 H, t, J = 3.5 Hz, H-12a), 4.07 (1 H, tt, J = 5, 10 Hz, H-2), 3.95 (1 H, d, J = 15 Hz, H-8), 3.85 (3 H, s, OMe), 3.18 (1 H, dt, J = 2, 14.5 Hz, H-6), 3.05 (1 H, dt, J = 3, 14.5 Hz, H-6), 2.65 (1 H, ddd, J = 3.5, 5, 15 Hz, H-1), 2.37 (3 H, s, NMe), 2.17 (1 H, ddd, J = 2.5, 4.5, 13.5 Hz, H-4), 1.94 (1 H, dt, J = 3, 14 Hz, H-5), 1.79 (1 H, ddd, J = 2, 3, 14 Hz, H-5), 1.72–1.83 (1 H, m, H-3), 1.62 (1 H, ddd, J = 3.5, 10, 15 Hz, H-1), 1.45 (1 H, dt, J = 2.5, 13.5 Hz, H-4), 1.33 (1 H, ddt, J = 2.5, 10, 12.8 Hz, H-3); IR 3100–3650, 2930, 1625, 1595, 1500 cm^{-1}; MS m/z 289 (M^+); high-resolution mass m/z calcd for $C_{17}H_{23}NO_3$ (M^+) 289.1676, found 289.1668.

Acknowledgment. We are grateful to Professor K. A. Parker, Brown University, for providing us with copies of the ^1H and ^{13}C NMR spectra of (±)- and (−)-lycoramine. Thanks are also due to Miss N. Sawabe, Mrs. F. Hasegawa, and Mr. H. Igarashi of this faculty for ^1H-NMR and mass spectral measurements and elementary analyses.

Supplementary Material Available: NMR spectra (29 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.