Total synthesis of racemic lycoramine

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heptanone (phenylsulfonyl)hydrazide, 61892-20-4; cycloheptanone, 502-42-1; (phenylsulfonyl)hydrazone, 80-17-1; 2-methylcyclohexanone tosylhydrazone, 52826-41-2; 2-methylcyclohexanone, 583-60-8; tosyl hydrazide, 1576-35-8; *trans*-1-decalone tosylhydrazone, 85319-00-2; *trans*-1-decalone, 21370-71-8; 2-(2,5,5-trimethyl-1,3-dioxan-2-yl)ethyl bromide, 87842-52-2; [3,3-(ethylenedioxy)butyl]magnesium bromide, 78078-49-6; 4-(1-methylcycloheptyl)-2-butanone, 87842-60-2; 3-buten-2-ol, 598-32-3.

Total Synthesis of Racemic Lycoramine

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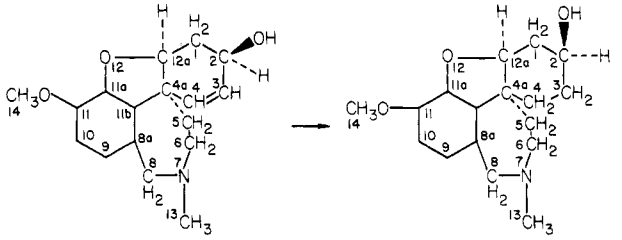
The total synthesis of *d,l*-lycoramine (**2**), an Amaryllidaceae alkaloid, is described. The method utilizes the intermediacy of the biogenetically relevant hydrobenzazepines of type **22**, readily available from cinnamonitrile precursors via a chemospecific cleavage of the more hindered C-6 methoxyl which ensues with concomitant 1,4-addition to the spirocyclic enone system and generates the complete galanthamine-like skeleton. The total synthesis of **2** proceeds in an overall 22% yield from 2,3-dimethoxycinnamonitrile (**3**).

Introduction

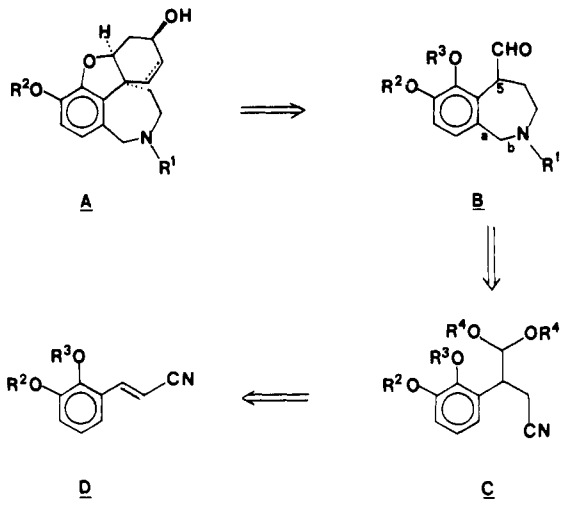
The galanthamine-type alkaloids constitute a group of structurally related bases found in plants from a number of genera within the Amaryllidaceae family.[1] Representative members of this family include galanthamine[2] (**1**) and lycoramine[3] (**2**).



1 **2**

The distinct chemical structure exhibited by these alkaloids, characterized by having a polycyclic system that incorporates a benzylic quaternary carbon atom, and the significant biological activity ascribed[2e,4] to galanthamine (**1**), the parent member of the series, have provided the necessary stimulus for the development of new methodologies and general strategies for the syntheses of these naturally occurring bases.[5] Particularly noteworthy in this respect, is the biomimetic entry to spirocyclic hydrobenzazepines via the intramolecular coupling of phenolic substrates.[2,6]

Scheme I



Close scrutiny of the salient structural features of these alkaloids, such as the presence of a spirocyclic β-oxygenated cyclohexanol system, suggested the utilization of tetrahydrobenzazepine B as a suitable synthetic precursor (Scheme I). Furthermore, if one disconnects bonds a and

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(3) 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*-2953. (b) Misaka, Y.; Mizutani, T.; Sekido, M.; Uyeo, S. *Ibid.* **1968**, *2954*-2959. (c) Schultz, A. G.; Yee, Y. K.; Berger, M. H. *J. Am. Chem. Soc.* **1977**, *99*, 8065-8067. (d) Martin, S. F.; Garrison, P. J. *J. Org. Chem.* **1982**, *47*, 1513-1518.

(4) Cordell, G. A. "Introduction to Alkaloids - A Biogenetic Approach"; Wiley-Interscience: New York, 1981; Chapter 8, pp 551-552.

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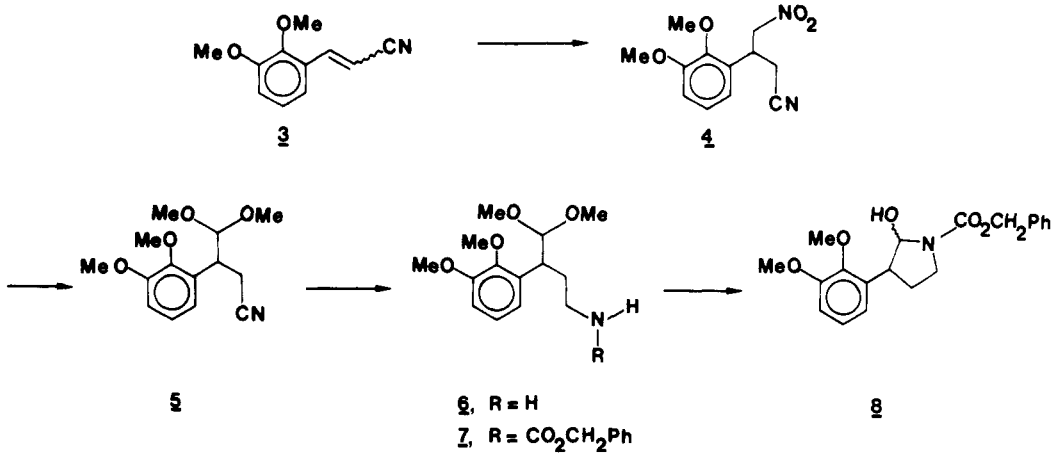
Scheme II



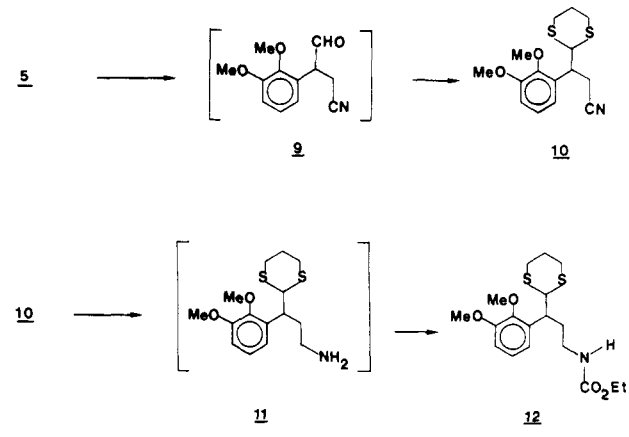
b of the generalized intermediate B, while simultaneously effecting the appropriate functional group interconversions,[7] namely, transformation of the already present formyl and amino functionalities into the more versatile and/or stable acetal and nitrile groups, respectively, one arrives at the β-substituted dihydrocinnamonitrile C. Furthermore, all the required carbon atoms but one of the relevant hydrobenzazepine B are already present in this intermediate, which is readily available[8] by the base-catalyzed conjugate addition of a "formyl anion" equivalent[9] at the β-position of the appropriate cinnamonitrile D.[10] Concurrently, in order to broaden the scope and significance of the general strategy adumbrated in Scheme I, we have also implemented improved procedures for the construction of the 5-substituted hydrobenzazepine ring system[11] and for its efficient conversion into the tetracyclic skeleton characteristic of the galanthamine-like *Amaryllidaceae* alkaloids.

Results

In accordance with the general synthetic strategy shown in Scheme I, we decided on 2,3-dimethoxycinnamonitrile (3) as a most convenient starting material, provided of course that a suitable chemospecific[12] cleavage of the more hindered methoxyl group could be effected at the appropriate stage of the synthesis.

Therefore, we proceeded to attempt the introduction of a "formyl anion" equivalent[9] at the β-position of nitrile 2. Although various systems were studied (e.g., 1,3-dithiane/*n*-butillithium,[13] methyl (methylsulfinyl)methyl sulfide/lithium diisopropylamide[14]), it soon became apparent that the Triton B-catalyzed conjugate addition of nitromethane[8] was the reaction of choice, both in yield and expedience. In this manner, the oily nitromethyl derivative 4 was obtained in 96% yield. Hydrolysis of the latter

Scheme III



functionality according to Jacobson's modification[15] of the Nef reaction[16] furnished the corresponding acetal 5 in 90% yield.

The next stage of the synthesis involved first the transformation of the nitrile group into a protected amine prior to the introduction of the functionalized one-carbon unit required for cyclization to hydrobenzazepine B. Accordingly, acetal 5 was reacted with sodium borohydride in the presence of various transition metal halides.[17] After some experimentation it was found that by using cobalt(II) chloride moderate yields of the desired amine 6 were obtained. Although the carbobenzyloxy (Cbz) moiety appeared at the outset to be eminently suited as a protecting group for nitrogen, in practice it proved best to routinely react the crude reduction mixture with benzyl chloroformate in the presence of excess triethylamine to afford urethane 7 in 37% overall yield. However, the attempted one-pot *N*-methoxymethylation–aromatic amidoalkylation in the presence of chloromethyl methyl ether[18] resulted

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(11) For a comprehensive review of the chemistry of benzazepines, see: Kasparek, S. *Adv. Heterocycl. Chem.* **1974**, *17*, 45–98. For an alternative synthesis of the tetrahydrobenzazepine system, see: Sánchez, I. H.; Mendoza, M. T. *Tetrahedron Lett.* **1980**, 3651–3654.
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(14) Herrman, J. L.; Richman, J. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, 3271–3274.
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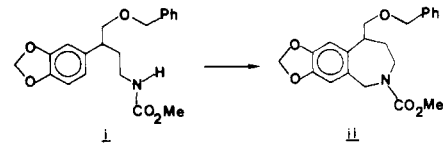
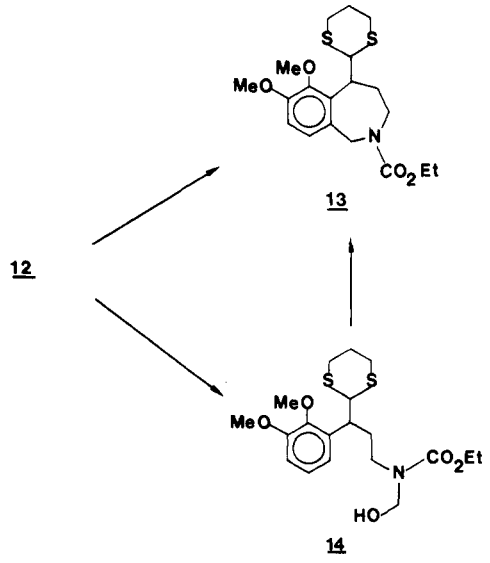
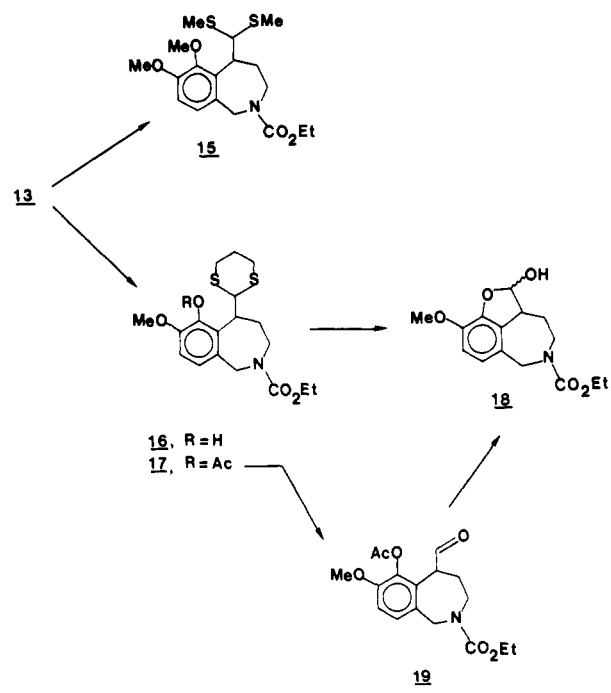
(16) Noland, W. E. *Chem. Rev.* **1955**, *55*, 137–155.
(17) Satoh, T.; Suzuki, S.; Suzuki, Y.; Miyaji, Y.; Imai, Z. *Tetrahedron Lett.* **1969**, 4555–4558.
(18) We have previously observed that under certain conditions the hydriodic acid-catalyzed reaction of *i* with chloromethyl methyl ether affords directly the corresponding 5-substituted hydrobenzazepine *ii* in 78% yield. Sánchez, I. H.; Yañez, R.; Linzaga, I., unpublished results.



Scheme IV



Scheme V



instead in a complex reaction mixture from which the oily hydroxypyrrolidine **8**,[19] resulting from intramolecular attack of the urethane moiety on the liberated aldehyde grouping, could be isolated in low yield (Scheme II).

Therefore, in order to avoid the formation of side products, it became necessary to find a better protecting group for the aldehyde functionality. Acid treatment of acetal **5** quantitatively furnished free cyano aldehyde **9** which was immediately transformed, under the standard conditions,[20] into the stabler dithioacetal derivative **10** in 98% yield (Scheme III). The latter can also be obtained by direct treatment of **5** with 1,3-propanedithiol and boron trifluoride, albeit in lower yield (45%). As before, reduction of **10** with the $NaBH_4/CoCl_2$ system[17] resulted in a 42% yield of amine **11**. However, reduction with the 1:1 lithium aluminum hydride–aluminum trichloride reagent,[21] followed by reaction with excess ethyl chloroformate provided the expected urethane **12** in 98% overall yield.

Next, we attempted again the one-pot formation of the hydrobenzazepine ring system via the acid-catalyzed reaction of **12** with chloromethyl methyl ether.[18] Unfortunately, this resulted only in a low 25% yield of **13**. Spectroscopic analysis of the various byproducts revealed that deprotection of the urethane moiety had occurred to a large extent. Therefore, since our synthetic strategy called for the ethoxycarbonyl grouping to be maintained throughout the synthetic sequence and eventually transformed, at a later stage, into the required *N*-methyl substituent,[22] we turned our attention to the Pictet–Spengler reaction,[23] or a modification thereof. After some experimentation, an extremely interesting alternative was found via a modified two-step Tscherniac–Einhorn-like[24] aromatic amidoalkylation involving initial base-catalyzed condensation of **12** with 40% aqueous formaldehyde to provide, in quantitative yield, the *N*-hydroxymethyl derivative **14**, which cleanly cyclized (90%) to the desired tetrahydrobenzazepine **13**, mp 146–147 °C upon heating with *p*-toluensulfonic acid (Scheme IV).

The next step of the synthesis needed a suitable chemospecific[12] cleavage of the more hindred C-6 methoxyl in order to form the ring B hydrobenzofuran system. During the early stages of this study it was found that, under the standard conditions, Lewis acids alone were not selective enough to effect such cleavage. However, under much milder experimental conditions and upon the addition of a large excess of various alkanethiols[25] some interesting results were obtained (Scheme V). Thus, reaction of **13** with boron trifluoride in the presence of methanethiol resulted simply in thioacetal exchange to give **15** in 80% yield. At this point we reasoned that, if the *initial* Lewis acid–base interaction occurred predominantly at the dithioacetal sulfur atoms, as evidenced by the latter transformation (**13** → **15**), thus placing the Lewis acid much nearer the more hindered methoxyl, one could expect a considerable rate enhancement for the desired cleavage (e.g., the one with the required "chemospecificity") by the use of a larger Lewis acid and a relatively weaker sulfur nucleophile. In thus manner, treatment of **13** with aluminum trichloride–ethanethiol at room temperature produced a nearly quantitative yield of a phenolic derivative, which was further characterized as its oily monoacetate. The ^1H NMR spectrum of the phenolic product in pyri-

(19) As part of our studies dealing with the total synthesis of *Amaryllidaceae* alkaloids we have recently prepared similar intermediates by an alternative route, see Sánchez, I. H.; López, F. J.; Flores, H. J.; Larraza, M. I. *Heterocycles* **1983**, *20*, 247–254.

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(21) Nystrom, R. F. *J. Am. Chem. Soc.* **1955**, *77*, 2544–2545.

(22) Friedman, O. M.; Parameswaran, K. N.; Burstein, S. *J. Med. Chem.* **1963**, *6*, 227–229. For a similar transformation, see: Weiss, B. *J. Org. Chem.* **1965**, *30*, 2483–2485.

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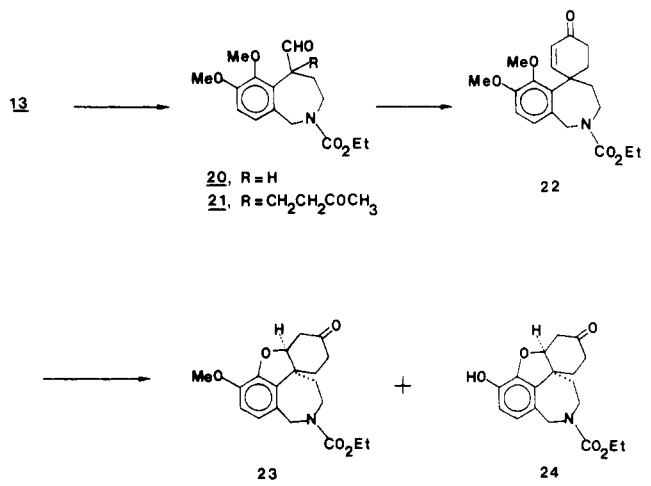
(24) For a recent review of the Tscherniac–Einhorn aromatic amidoalkylation reaction, see: Zaugg, H. E.; Martin, W. B. *Org. React. (NY)* **1965**, *14*, 52–269 and references cited therein. For a related process, see: Wittekind, R. R.; Lazarus, S. *J. Heterocycl. Chem.* **1971**, *8*, 495–501. For recent examples of the closely related Ben-Ishai's intramolecular amidoalkylation reaction, see: (a) Ben-Ishai, D.; Peled, N.; Sataty, I. *Tetrahedron Lett.* **1980**, *21*, 569–572. (b) Danishefsky, S.; Berman, E.; Cvetovich, R.; Minamikawa, J. I. *Tetrahedron Lett.* **1980**, *21*, 4819–4822.

(25) For the use of the alkanethiol or alkyl sulfide–Lewis acid system for the cleavage of ethers and esters, see: (a) Fuji, K.; Kawabata, T.; Fujita, E. *Chem. Pharm. Bull.* **1980**, *28*, 3662–3664. (b) Node, M.; Nishide, K.; Sai, M.; Ichikawa, K.; Fuji, K.; Fujita, E. *Chem. Lett.* **1979**, 97–98. (c) Node, M.; Nishide, K.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1980**, *45*, 4275–4277.

Scheme VI



dine-d_5[26] (see Experimental Section) suggested that the expected reaction had actually taken place. However, in order to fully ascertain the position where cleavage had occurred, we proceeded next ot hydrolyze its dithioacetal grouping under Vedejs' conditions[27] (red mercuric oxide–boron trifluoride). The isolation of lactol **18** (73% yield) left no doubt as to the site of O-dealkylation. Therefore, the isolated phenol corresponds to **16** and its acetate to **17** (Scheme V). Moreover, **17** was also hydrolyzed[27] (73%) to the corresponding acetoxy aldehyde **19**, which readily cyclized to **18** (82%) upon acid hydrolysis. Unfortunately, further progress along the lines of our original strategy (Scheme I) was not forthcoming, since the attempted Robinson annulation[28] of **18** failed to yield the expected tetracyclic skeleton.

Therefore, we turned our attention to the modification depicted in Scheme VI. Initial hydrolysis[27] of the dithioacetal moiety of **13** produced (81% yield) aldehyde **20**, which underwent facile base-catalyzed[8] 1,4-addition with methyl vinyl ketone to yield **21**. Further treatment of (crude) **21** with 0.03 N ethanolic sodium ethoxide[29] effected the required cycloaldolization and dehydration reactions to furnish enone **22**,[30] mp 135.5–136.5 °C, in 65% overall yield.

At this point we envisaged that, concomitantly with the Lewis acid mediated[31] formation of an electron deficient enone system, an intramolecular 1,4-addition of the C-6 methoxyl should ensue, favored by the alkyl sulfide-assisted[25] nucleophilic cleavage of the resulting oxonium ion, thus terminating the elaboration of the complete lycoramine skeleton. To our satisfaction, the aluminum trichloride catalyzed reaction of **22** with ethyl sulfide,[25] to avoid thioketal formation, afforded the desired tetracyclic ketone **23** in 75% yield, accompanied with a small amount (15%) of the phenolic derivative **24**, mp 179–180 °C. Conversion of **24** into its corresponding methyl ether **23** was accomplished in quantitative yield under the standard O-methylation conditions.

Finally, the synthesis of (±)-lycoramine (**2**) was completed by the controlled (76% yield) lithium aluminum hydride reduction[3d] of ketone **23** with concomitant transformation[22] of the ethoxycarbonyl protecting group into the required *N*-methyl substituent. Our synthetic sample proved identical by spectral comparison[32] with authentic (±)-lycoramine (**2**). The present total synthesis of **2** proceeds in an overall 22% yield from 2,3-dimethoxycinnamonitrile (**3**).

Experimental Section

General Procedures. Melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra were recorded on Perkin-Elmer 681 or 283-B spectrophotometers. Ultraviolet spectra were obtained in methanol solution on a Perkin-Elmer 552 spectrophotometer. ^{1}H NMR spectra were obtained in deuteriochloroform, unless otherwise indicated, on Varian EM-390 (90 MHz) or FT-80A (80 MHz) instruments. 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; quint, quintet; m, multiplet; b, broad, and comp, complex multiplet. Coupling constants are given in hertz (Hz). Low-resolution mass spectra were obtained on a Hewlett-Packard 5985-B spectrometer. Elemental analyses were performed at the Instituto de Investigaciones Eléctricas, Cuernavaca, Mor., México. All yields reported refer to isolated materials homogeneous by TLC and NMR spectroscopy.

3-(2,3-Dimethoxyphenyl)-4-nitrobutanenitrile (4). A solution of 2,3-dimethoxycinnamonitrile[10] (**3**) (11.0 g, 58.5 mmol) in dry acetonitrile (140 mL) was treated with distilled nitromethane (40 mL, 730 mmol) and benzyltrimethylammonium hydroxide (1.5 mL) and heated to reflux under nitrogen for 24 h. The reaction mixture was diluted with water (100 mL) and 10% aqueous HCl (15 mL) and extracted with EtOAc (3 × 100 mL). Drying (Na_2SO_4) and concentration gave a dark yellow residue (17 g). Purification by column chromatography (600 g of SiO_2, 8:2 hexane–EtOAc) gave pure **4** (14 g, 56 mmol, 96%) as a light yellow oil: IR ($CHCl_3$) 2160, 1515, 1390 cm^{-1}; ^{1}H NMR (90 MHz) δ 7.13 (t, J = 8 Hz, Ar H_5), 6.98 (dd, J = 8, 2 Hz, Ar H_6), 6.76 (dd, J = 8, 2 Hz, Ar H_4), 4.73 (d, J = 7 Hz, CH_2NO_2), 4.2 (quint, J = 7 Hz, Ar CH), 3.93 (s, OCH_3), 3.85 (s, OCH_3), 2.8 (d, J = 7 Hz, CH_2CN). Anal. ($C_{12}H_{14}N_2O_4$) C, H, N.

4,4-Dimethoxy-3-(2,3-dimethoxyphenyl)butanenitrile (5). A solution of **4** (5 g, 20 mmol) in 0.5 N methanolic sodium methoxide (47 mL) was added dropwise to a cold (−35 °C) and stirred solution of concentrated H_2SO_4 (47 mL) in dry methanol (181 mL). After 20 min the reaction mixture was poured into $CHCl_3$ (1 L) and water (200 mL). The extract was washed (H_2O, 3 × 1 N NaOH), dried (K_2CO_3), and evaporated to a yellowish oil (5.4 g). Purification by column chromatography (300 g of SiO_2, 8:2 hexane-EtOAc) furnished pure **6** (4.76 g, 17.96 mmol, 90%) as a colorless oil: IR (neat) 2250 cm^{-1}; ^{1}H NMR (90 MHz) δ 7.13–6.76 (m, 3 × Ar H), 4.5 (d, J = 7 Hz, $CH(OCH_3)_2$), 3.85 (s, Ar OCH_3), 3.81 (s, Ar OCH_3), 3.76 (m, Ar CH), 3.35 (s, OCH_3), 3.26 (s, OCH_3), 2.73 (d, J = 6.5 Hz, CH_aCN), 2.72 (d, J = 8 Hz, CH_bCN). Anal. ($C_{14}H_{19}NO_4$) C, H, N.

4,4-Dimethoxy-3-(2,3-dimethoxyphenyl)butylamine (6) and *N*-(Carbobenzyloxy)-4,4-dimethoxy-3-(2,3-dimethoxyphenyl)butylamine (7). A solution of acetal **5** (360 mg, 1.358 mmol) and cobalt(II) chloride hexahydrate (1.713 g, 7.199 mmol) in methanol (20 mL) was treated portionwise with sodium borohydride (1.36 g, 35.95 mmol). After 1 h stirring at room temperature, the reaction mixture was filtered through Celite, diluted with water (10 mL), and concentrated to a small volume. Ex-

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(28) For excellent reviews of the Robinson annulation reaction, see: (a) Jung, M. E. *Tetrahedron* **1976**, *32*, 3–31. (b) Gawley, R. E. *Synthesis* **1976**, *777–794*.

(29) Sánchez, I. H.; López, F. J.; Soria, J. J.; Larraza, M. I.; Flores, H. J. *J. Am. Chem. Soc.* **1983**, in press.

(30) It has been shown (see ref 1b, pp 178–183, and ref 4, pp 545–551) that spirocyclic hydrobenzazepines of type **22** are indeed the biosynthetic precursors of these alkaloids. For further work dealing with the utilization of such intermediates in the total synthesis of the 5,10b-ethanophenanthridine-like *Amaryllidaceae* alkaloids, see ref 19.

(31) For the reaction of α,β-unsaturated ketones with aluminum trichloride, see: (a) Dippy, J. F. J.; Palluel, A. L. L. *J. Chem. Soc.* **1951**, 1415–1420. (b) Baddeley, G.; Holt, G.; Makar, S. M. *J. Chem. Soc.* **1952**, 3289–3292.

(32) We thank Professors S. F. Martin and A. G. Schultz for kindly providing us with authentic comparison (^{1}H NMR, IR, mass) spectra of racemic lycoramine (**2**).

traction with $CHCl_3$ (2 × 20 mL), washing (H_2O and brine), drying (Na_2SO_4), and evaporation afforded crude **6** (300 mg) as a yellow oily residue, which was taken up in dry CH_2Cl_2 (4 mL), cooled in an ice-water bath, and treated with triethylamine (0.2 mL) and benzyl chloroformate (1 mL of a 10 wt. % solution in toluene). After 20 min the reaction was quenched with saturated NH_4Cl solution (2 mL), diluted with H_2O (20 mL), and extracted with EtOAc (3 × 20 mL). Drying (Na_2SO_4) and evaporation furnished a yellow oil (230 mg). Purification by preparative-layer chromatography (PLC) (SiO_2, 70:30 hexane–EtOAc) afforded pure **7** (200 mg, 0.496 mmol, 37%) as a colorless oil: IR (neat) 3350, 1720 cm^{-1}; ^1H NMR (90 MHz) δ 7.33 (s, C_6H_5), 7.03 (t, J = 8 Hz, Ar H_5), 6.9–6.7 (m, Ar H_4, Ar H_6), 5.26–5.0 (m, NH, exchangeable with D_2O), 5.05 (s, CH_2Ph), 4.45 (d, J = 8 Hz, $CH(OCH_3)_2$), 3.83 (s, 2 × Ar OCH_3), 3.33 (s, OCH_3), 3.23 (s, OCH_3), 3.63–2.6 (comp. Ar CH, CH_2N), 2.26–1.46 (m, CH_2). Anal. ($C_{22}H_{29}NO_6$) C, H, N.

***N*-(Carbobenzyloxy)-3-(2,3-dimethoxyphenyl)-2-hydroxypyrrolidine (8).** A cold and stirred solution of **7** (200 mg, 0.496 mmol) in glacial acetic acid (6 mL) was treated with chloromethyl methyl ether (351 mg, 4.36 mmol) and 57% aqueous hydriodic acid (0.33 mL). After 20 min the dark brown reaction mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 10 mL). The combined extracts were washed ($NaHCO_3$, H_2O, and brine), dried (Na_2SO_4), and evaporated to a dark yellow residue (80 mg). Purification by PLC (SiO_2, 8:2 hexane–EtOAc) afforded **8** (33 mg, 0.098 mmol, 20%) as a yellowish oil: IR (neat) 3450, 1705 cm^{-1}; ^1H NMR (90 MHz) δ 7.33 (s, C_6H_5), 6.96–6.63 (m, Ar H), 6.24 (b t, NCHOH), 5.16 (b s, CH_2Ph), 3.83 (s, 2 × Ar OCH_3), 4.0–3.56 (m, CH_2N), 3.16 (dt, J = 10, 7 Hz, Ar CH), 2.4–1.83 (m, CH_2, OH); MS (EI), m/e (intensity) 357 ($C_{20}H_{23}NO_5$ requires 357, 2), 356 (13), 355 (55), 91 (100).

3-(2,3-Dimethoxyphenyl)-3-formylpropanenitrile (9). Acetal **5** (95 mg, 0.358 mmol) in THF (6 mL) was treated with 10% (v/v) aqueous HCl (2 mL) and stirred at 40 °C for 30 min. The reaction mixture was diluted with water (5 mL) and extracted (EtOAc). The combined extracts were washed ($NaHCO_3$ and brine), dried (Na_2SO_4), and evaporated to furnish a yellow oil (81 mg). PLC purification (SiO_2, 8:2 hexane–EtOAc) afforded pure **9** (78.5 mg, 0.358 m mol, 100%) as a colorless oil: IR (neat) 2250, 1730 cm^{-1}; ^1H NMR (90 MHz) δ 9.6 (s, CHO), 7.09 (t, J = 8 Hz, Ar H_5), 6.91 (dd, J = 8, 2 Hz, Ar H_6), 6.7 (dd, J = 8, 2 Hz, Ar H_4), 4.05 (dd, J = 8, 6 Hz, ArCH), 3.88 (s, 2 × Ar OCH_3), 3.03 (dd, J = 17, 6 Hz, CH_bCN), 2.63 (dd, J = 17, 8 Hz, CH_aCN).

3-(2,3-Dimethoxyphenyl)-3-(1,3-dithian-2-yl)propanenitrile (10). The purified aldehyde **9** (78.5 mg, 0.358 mmol) in dry CH_2Cl_2 (5 mL) was treated under ice-bath cooling with 1,3-propanedithiol (54 mg, 0.5 mmol) and boron trifluoride etherate (3 drops). The reaction was allowed to proceed at room temperature for 3 h, then poured into an ice-cold 1 N NaOH solution (10 mL), and extracted with $CHCl_3$ (3 × 10 mL). Evaporation afforded a nearly colorless oily residue, which upon PLC purification (SiO_2, 7:3 hexane–EtOAc) afforded pure **10** (108.5 mg, 0.351 mmol, 98%) as a colorless oil: IR (neat) 2240 cm^{-1}; ^1H NMR (90 MHz) δ 7.2–6.83 (m, Ar H), 4.33 (d, J = 9 Hz, SCHS), 3.93 (s, Ar OCH_3), 3.86 (s, Ar OCH_3), 3.93–3.66 (m, Ar CH), 3.0–2.73 (comp, 2 × CH_2S, CH_2CN), 2.06–1.83 (m, CH_2). Anal. ($C_{15}H_{19}NO_2S_2$) C, H, N.

3-(2,3-Dimethoxyphenyl)-3-(1,3-dithian-2-yl)propylamine (11). Method A. A solution of aluminum trichloride (174 mg, 1.3 mmol) in dry THF (10 mL) was added in one portion to a magnetically stirred suspension of lithium aluminum hydride (49.5 mg, 1.3 mmol) in dry THF (5 mL). After 5 min stirring at 5 °C, a solution of **10** (200 mg, 0.647 mmol) in THF (10 mL) was added dropwise, and the mixture heated at 40 °C (oil bath) for 1.5 h. After the mixture had cooled (ice bath), saturated sodium sulfate solution (3 mL) was carefully added. The resulting suspension was thoroughly extracted with ethyl ether. The combined extracts were washed (H_2O, brine), dried (Na_2SO_4), and evaporated to a reddish oil (210 mg). Purification by column chromatography (Grade III neutral Al_2O_3, 9.95:0.05 $CHCl_3$–MeOH) afforded pure **11** (200 mg, 0.638 mmol, 99%) as a nearly colorless oil: IR (neat 3400 cm^{-1}; ^1H NMR (90 MHz) δ 7.02 (t, J = 8 Hz, Ar H_5), 6.86–6.7 (m, Ar H_4, Ar H_5), 4.26 (d, J = 8 Hz, SCHS), 3.86 (s, Ar OCH_3), 3.83 (s, Ar OCH_3), 3.5 (ddd, J = 12, 8, 3 Hz, Ar CH), 2.86–2.66 (m, 2 × CH_2S), 2.53–2.26 (m, CH_2N), 2.03–1.56 (m, CH_2), 1.43 (s, NH_2, exchangeable with D_2O).

Method B. Sodium borohydride (1.1 g, 29.1 mmol) was added in small portions to a stirred solution of **10** (900 mg, 2.91 mmol) and cobalt(II) chloride hexahydrate (1.385 g, 5.82 mmol) in reagent grade methanol (35 mL). After 1 h, the reaction was carefully treated with 3 N HCl (15 mL) and concentrated to a small volume. The mixture was neutralized with NH_4OH and extracted with $CHCl_3$. The extracts were washed (H_2O and brine), dried (Na_2SO_4), and evaporated to give a yellow-brown oil. Purification by column chromatography as before furnished pure **11** (380 mg, 1.21 mmol, 42%).

***N*-(Carboethoxy)-3-(2,3-dimethoxyphenyl)-3-(1,3-dithian-2-yl)propylamine (12).** To a cold and stirred solution of **11** (200 mg, 0.638 mmol) and triethylamine (77.26 mg, 0.765 mmol) in dry dichloromethane (7 mL) was added dropwise a solution of ethyl chloroformate (138.6 mg, 1.27 mmol) in CH_2Cl_2 (3 mL). After 30 min, the reaction mixture was diluted with water (3 mL) and saturated NH_4Cl solution (5 mL) and extracted with EtOAc. The extracts were washed ($NaHCO_3$ and H_2O), dried (Na_2SO_4), and evaporated. The residue (254 mg) was purified by PLC (SiO_2, 7:3 hexane–EtOAc) to yield pure **12** (245.5 mg, 0.637 mmol, 100%) as a colorless oil: IR (neat) 3350, 1710 cm^{-1}; ^1H NMR (90 MHz) δ 7.03 (t, J = 8 Hz, Ar H_5), 6.9–6.7 (m, Ar H_4, Ar H_6), 5.06–4.07 (br, NH, exchangeable with D_2O), 4.31 (d, J = 8 Hz, SCHS), 4.05 (q, J = 7 Hz, CH_2O), 3.92 (s, Ar OCH_3), 3.86 (s, Ar OCH_3), 3.46 (ddd, J = 12, 8, 3 Hz, Ar CH), 3.3–2.86 (m, CH_bN), 2.9–2.7 (m, 2 × CH_2S), 2.5–2.1 (m, CH_aN), 2.0–1.6 (comp, 2 × CH_2), 1.2 (t, J = 7 Hz, CH_3). Anal. ($C_{18}H_{27}NO_4S_2$) C, H, N.

2-(Carboethoxy)-5-(1,3-dithian-2-yl)-6,7-dimethoxy-2,3,4,5-tetrahydro-1*H*-2-benzazepine (13). Method A. A solution of **12** (135 mg, 0.35 mmol) in glacial acetic acid (5 mL) was cooled to 5 °C and treated dropwise with chloromethyl methyl ether (244.6 mg, 3.03 mol) and hydriodic acid (0.23 mL of a 57% aqueous solution). After 20 min stirring, the dark brown mixture was diluted with water (10 mL) and extracted with EtOAc (4 × 10 mL). The extracts were washed ($NaHCO_3$, H_2O, and brine), dried (Na_2SO_4), and evaporated to a dark brown gum (100 mg). PLC purification (SiO_2, 8:2 hexane–EtOAc) afforded **13** (35 mg, 0.09 mmol, 25%) as a yellowish oil: IR (neat) 1700 cm^{-1}; ^1H NMR (90 MHz) δ 7.13–6.8 (m, H_9), 6.73 (d, J = 8 Hz, H_8), 4.66 (d, J = 11 Hz, SCHS), 4.9–4.5 (b d, J = 15 Hz, H_{1ax}), 4.26 (d, J = 15 Hz, H_{1eq}), 4.06 (q, J = 7 Hz, CH_2O), 4.13–3.87 (m, H_5), 3.86 (s, OCH_3), 3.83 (s, OCH_3), 3.76–3.23 (m, H_{3ax}), 2.93–2.7 (comp, 2 × CH_2S), 2.6–2.2 (m, H_{3eq}), 2.13–1.6 (comp, 2 × CH_2), 1.2 (t, J = 7 Hz, CH_3); MS (EI), m/e (relative intensity) ($C_{19}H_{27}NO_4S_2$ requires 397, 6) 177 (9), 121 (10), 119 (100).

Method B. (a) *N*-(Carboethoxy)-3-(1,3-dithian-2-yl)-3-(2,3-dimethoxyphenyl)-*N*-(hydroxymethyl)propylamine (14). A solution of **12** (190 mg, 0.493 mmol) in methanol (5 mL) was treated with formaldehyde (0.5 mL of a 37 wt % aqueous solution) and a catalytic amount of 25% aqueous NaOH (3 drops). After 12 h stirring at room temperature, the reaction mixture was diluted with water (5 mL) and saturated NH_4Cl solution (5 mL) and concentrated to a small volume. The resulting suspension was extracted with $CHCl_3$ (3 × 10 mL), washed (brine), dried (Na_2SO_4), and evaporated to a light yellow residue (215 mg). Purification by PLC (SiO_2, 7:3 hexane–EtOAc) afforded pure **14** (204 mg, 0.492 mmol, 100%) as a colorless oil: IR (neat) 3450, 1710 cm^{-1}; ^1H NMR (90 MHz) δ 7.04 (t, J = 8 Hz, Ar H_5), 6.93–6.73 (m, Ar H_4, Ar H_6), 4.76–4.53 (m, NCH_2O, OH), 4.26 (d, J = 8 Hz, SCHS), 4.06 (q, J = 7 Hz, CH_2O), 3.86 (s, Ar OCH_3), 3.83 (s, Ar OCH_3), 3.4 (ddd, J = 12, 8, 3 Hz, Ar CH), 3.2–2.96 (m, CH_aN), 2.9–2.7 (comp, 2 × CH_2S), 2.36 (ddd, J = 15, 8, 3, Hz, CH_bN), 2.16–1.6 (m, 2 × CH_2), 1.2 (t, J = 7 Hz, CH_3).

(b) Hydrobenzazepine 13. A small amount of *p*-toluenesulfonic acid monohydrate (5 mg) was added to a solution of **14** (114 mg, 0.274 mmol) in dry benzene (10 mL), and the mixture was heated to reflux for 30 min using a water separator (Dean–Stark). The reaction mixture was washed ($NaHCO_3$, H_2O, and brine), dried (Na_2SO_4), and evaporated. Purification of the residue (122 mg) by PLC (SiO_2, 7:3 hexane–EtOAc) afforded pure **13** (99 mg, 0.249 mmol, 90%) as colorless prisms, mp 146–147 °C (EtOAc–hexane). Anal. ($C_{19}H_{27}N\,O_4S_2$) C, H, N. It proved identical by spectroscopic and TLC comparison with the sample isolated from previous experiments.

2-(Carboethoxy)-6,7-dimethoxy-5-formyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine Dimethyl Dithioacetal (15). An

ice-cold solution of **13** (90 mg, 0.226 mmol) in dry CH_2Cl_2 (8 mL) was treated successively with boron trifluoride etherate (356 mg, 2.5 mmol) and methanethiol (1 mL). After 1 h stirring, the reaction mixture was poured into ice–1 N NaOH (10 mL) and extracted with $CHCl_3$. The combined extracts were washed (0.5 N NaOH and water), dried (Na_2SO_4), and evaporated. The oily residue (78 mg) was purified by PLC (SiO_2, 7:3 hexane–EtOAc) to afford pure **15** (69.7 mg, 0.181 mmol, 80%) as a colorless oil: IR (neat) 1705 cm^{-1}; ^1H NMR (80 MHz) δ 7.1–6.86 (m, H_9), 6.7 (d, J = 8 Hz, H_8), 4.69 (b d, J = 15 Hz, H_{1eq}), 4.3 (d, J = 11 Hz, SCHS), 4.23 (d, J = 15 Hz, H_{1ax}), 4.03 (q, J = 7 Hz, CH_2O), 4.03–3.73 (m, H_5), 3.82 (s, OCH_3), 3.8 (s, OCH_3), 3.6–3.23 (m, H_{3ax}), 2.6–2.23 (m, H_{3eq}), 2.1 (s, SCH_3), 2.05 (s, SCH_3), 2.0–1.5 (m, 2 × H_4), 1.2 (t, J = 7 Hz, CH_3). Anal. ($C_{18}H_{23}NO_4S_2$) C, H, N.

2-(Carboethoxy)-5-(1,3-dithian-2-yl)-6-hydroxy-7-methoxy-2,3,4,5-tetrahydro-1*H*-2-benzazepine (16). A solution of **13** (150 mg, 0.377 mmol) in dry CH_2Cl_2 (3 mL) was added dropwise to a solution of aluminum trichloride (151 mg, 1.13 mmol) and ethyl sulfide (418 mg, 4.63 mmol) in CH_2Cl_2 (5 mL). After 20 min stirring at room temperature, the resulting mixture was diluted with H_2O (10 mL) and extracted with $CHCl_3$. The combined extracts were washed ($NaHCO_3$, H_2O, and brine), dried (Na_2SO_4), and evaporated. The oily residue was percolated through a small silica gel column using 1:1 hexane–EtOAc to give **16** (144 mg, 0.376 mmol, 100%) as a colorless oil: IR (neat) 3370, 1700 cm^{-1}; ^1H NMR (80 MHz) δ 6.9–6.56 (m, H_8, H_9), 5.98 (s, OH, exchangeable with D_2O), 4.52 (d, J = 11 Hz, SCHS), 4.66 (b d, J = 15 Hz, H_{1eq}), 4.23 (d, J = 15 Hz, H_{1ax}), 4.2–3.73 (m, H_5), 4.03 (q, J = 7 Hz, CH_2O), 3.83 (s, OCH_3), 3.63–3.2 (m, H_{3ax}), 2.96–2.66 (comp, 2 × CH_2S), 2.6–2.16 (m, H_{3eq}), 2.16–1.6 (comp, 2 × H_4, CH_2), 1.2 (t, J = 7 Hz, CH_3). Anal. ($C_{18}H_{25}NO_4S_2$) C, H, N. ^1H NMR (80 MHz, C_5D_5N) δ 6.9–6.6 (m, H_8, H_9), 5.07 (d, J = 12 Hz, SCHS), 4.95–4.5 (m, H_{1eq}, OH), 4.35 (d, J = 15 Hz, H_{1ax}), 4.1 (q, J = 7 Hz, CH_2O), 4.0–3.75 (m, H_5), 3.7–3.2 (m, H_{3ax}), 3.65 (s, OCH_3), 2.95–2.35 (m, 2 × CH_2S), 2.25–1.65 (comp, H_{3eq}, 2 × H_4, CH_2), 1.12 (t, J = 7 Hz, CH_3).

6-Acetoxy-2-(carboethoxy)-5-(1,3-dithian-2-yl)-7-methoxy-2,3,4,5-tetrahydro-1*H*-2-benzazepine (17). A solution of phenol **16** (100 mg, 0.26 mmol) in acetic anhydride (1 mL) and dry pyridine (1 mL) was stirred at room temperature under nitrogen atmosphere for 5 h. The mixture was poured into ice-water (20 mL), acidified to Congo paper with 0.1 N HCl, and extracted with EtOAc (3 × 10 mL). The extracts were washed ($NaHCO_3$, H_2O, and brine), dried (Na_2SO_4), and evaporated to a yellow oil (116 mg). Purification by PLC (SiO_2, 8:2 hexane–EtOAc) afforded pure **17** (110 mg, 0.258 mmol, 100%) as a colorless oil: IR (neat 1775, 1700 cm^{-1}; ^1H NMR (80 MHz) δ 7.16–6.93 (b, H_9), 6.75 (d, J = 8 Hz, H_8), 4.7 (b d, J = 15 Hz, H_{1eq}), 4.62 (d, J = 12 Hz, SCHS), 4.3 (d, J = 15 Hz, H_{1ax}), 4.03 (q, J = 7 Hz, CH_2O), 3.76 (s, OCH_3), 3.56 (ddd, J = 12, 8, 3 Hz, H_5), 3.33–3.0 (m, H_{3ax}), 2.93–2.66 (comp, 2 × CH_2S), 2.42–2.13 (m, H_{3eq}), 2.33 (s, CH_3CO), 2.1–1.56 (comp, 2 × H_4, CH_2), 1.2 (t, J = 7 Hz, CH_3). Anal. ($C_{20}H_{27}NO_5S_2$) C, H, N.

6-Acetoxy-2-(carboethoxy)-5-formyl-7-methoxy-2,3,4,5-tetrahydro-1*H*-2-benzazepine (19). A solution of **17** (110 mg, 0.258 mmol) in THF (2 mL) was added dropwise to a magnetically stirred suspension of boron trifluoride etherate (73 mg, 0.516 mmol) and red mercuric oxide (112 mg, 0.516 mmol) in 15% aqueous THF (3 mL). After 5 min, the resulting suspension was diluted with ethyl ether (10 mL) and filtered through Celite. The filtrate was washed ($NaHCO_3$, H_2O, and brine), dried (Na_2SO_4), and evaporated. Purification of the residue (97 mg) by PLC (SiO_2, 8:2 hexane–EtOAc) afforded pure **19** (80 mg, 0.238 mmol, 93%) as a colorless oil: IR (neat) 2730, 1750, 1720 cm^{-1}; ^1H NMR (90 MHz) δ 9.68 (s, CHO), 7.2–7.06 (m, H_9), 6.85 (d, J = 8 Hz, H_8), 4.58 (d, J = 15 Hz, H_{1eq}), 4.1–3.9 (m, H_{1ax}), 4.05 (q, J = 7 Hz, CH_2O), 3.82 (s, OCH_3), 3.63–3.3 (m, H_5), 2.73–2.3 (m, H_{3ax}), 2.3 (s, CH_3CO), 2.06–1.76 (m, 2 × H_4, H_{3eq}), 1.2 (t, J = 7 Hz, CH_3). Anal. ($C_{17}H_{21}NO_6$) C, H, N.

Lactol 18. Method A. Boron trifluoride etherate (92 mg, 0.648 mmol) was rapidly added to a magnetically stirred suspension of red mercuric oxide (140 mg, 0.648 mmol) in 15% aqueous THF (3 mL). The mixture was stirred under nitrogen for 3 min and treated dropwise with a solution of **16** (123 mg, 0.321 mmol) in THF (2 mL). After 5 min stirring, the reaction mixture was diluted with commercial ethyl ether (10 mL) and filtered through Celite. The filtrate was washed ($NaHCO_3$, H_2O, and brine), dried (Na_2SO_4), and evaporated to a yellow oil (75 mg). Purification by PLC (SiO_2, 7:3 hexane–EtOAc) furnished pure **18** (69 mg, 0.235 mmol, 73%) as a colorless oil: IR (neat) 3380, 1700 cm^{-1}; ^1H NMR (80 MHz) δ 6.83–6.53 (m, H_8, H_9), 6.03 and 5.77 (2 d, J = 5 Hz and J = 7 Hz, respectively, OCHO), 5.36–4.86 (b, OH), 4.63 (d, J = 15 Hz, H_{1eq}), 4.46–3.8 (m, H_{1ax}, H_5), 4.0 (q, J = 7 Hz, CH_2O), 3.8 (s, OCH_3), 3.42 (dt, J = 16, 5 Hz, H_{3eq}), 3.23–2.86 (m, H_{3ax}), 2.16–1.5 (m, 2 × H_4), 1.16 (t, J = 7 Hz, CH_3). Anal. ($C_{15}H_{19}NO_5$) C, H, N.

Method B. A solution of **19** (100 mg, 0.235 mmol) in 10 wt % ethanolic hydrogen chloride (3 mL) was stirred at room temperature under nitrogen for 2 h. The reaction mixture was taken up in $CHCl_3$ (20 mL), washed ($NaHCO_3$, H_2O, and brine), dried (Na_2SO_4), and evaporated to a yellow oil (115 mg). Purification by PLC (SiO_2, 7:3 hexane–EtOAc) afforded pure **18** (63.0 mg, 0.215 mmol, 92%), identical in all respects with the sample isolated by Method A.

2-(Carboethoxy)-6,7-dimethoxy-5-formyl-2,3,4,5-tetrahydro-1*H*-2-benzazepine (20). A solution of **13** (300 mg, 0.75 mmol) in THF (2 mL) was added dropwise to a previously prepared (3 min) suspension of boron trifluoride etherate (230 mg, 1.62 mmol) and red mercuric oxide (327 mg, 151 mmol) in 15% aqueous THF (5 mL). After 5 min stirring, the mixture was diluted with ethyl ether (15 mL) and filtered through Celite. The filtrate was washed ($NaHCO_3$, H_2O, and brine), dried (Na_2SO_4), and evaporated. The residue (192 mg) was purified by PLC (SiO_2, 7:3 hexane–EtOAc) to furnish **20** (188 mg, 0.612 mmol, 81%) as a colorless oil: IR (neat) 2730, 1730, 1710 cm^{-1}; ^1H NMR (80 MHz) δ 9.77 (s, CHO), 6.96 (d, J = 8 Hz, H_9), 6.8 (d, J = 8 Hz, H_8), 4.5 (d, J = 17 Hz, H_{1eq}), 4.03 (q, J = 7 Hz, CH_2O), 3.93 (d, J = 17 Hz, H_{1ax}), 3.86 (s, OCH_3, 3.75 (s, OCH_3), 4.0–3.7 (m, H_5), 3.46 (ddd, J = 15, 10, 3 Hz, H_{3ax}), 2.43 (dt, J = 15, 4 Hz, H_{3eq}), 2.2–1.76 (m, 2 × H_4), 1.2 (t, J = 7 Hz, CH_3). Anal. ($C_{16}H_{21}NO_5$) C, H, N.

2-(Carboethoxy)-6,7-dimethoxy-2,3,4,5-tetrahydrospiro-[1*H*-2-benzazepine-5,4′-cyclohexenone] (22). A solution of **20** (225 mg, 0.732 mmol) in dry THF (5 mL) was cooled to 0 °C, and treated with freshly distilled methyl vinyl ketone (65.5 mg, 1.464 mmol) and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN, 3 drops). After 3.5 h stirring, the reaction mixture was diluted with water (5 mL) and saturated NH_4Cl solution (3 mL) and extracted with EtOAc. The combined extracts were washed (H_2O and brine), dried (Na_2SO_4), and evaporated to a yellow oil. The crude residue (**21**, 300 mg) was taken up in 0.03 N ethanolic sodium ethoxide (20 mL) and heated to reflux under nitrogen for 45 min. The brownish reaction mixture was diluted with water (15 mL) and saturated NH_4Cl solution (15 mL) and concentrated to a smaller volume. The residue was thoroughly extracted with EtOAc, and the extracts were washed (H_2O, brine), dried (Na_2SO_4), and evaporated to a dark oil (220 mg). Purification by PLC (SiO_2, 8:2 hexane–EtOAc) furnished pure **22** (170 mg, 0.473 mmol, 65%) as colorless prisms: mp 135.5–136.5 °C (AcOEt–hexane); UV (MeOH) λ_{max} (log ϵ) 236 (4.22), 285 nm (3.34); IR ($CHCl_3$) 1705, 1685 cm^{-1}; ^1H NMR (80 MHz) δ 7.03 (dd, J = 10, 1.5 Hz, $H_{3'}$), 6.93–6.83 (m, H_9), 6.78 (d, J = 8 Hz, H_8), 5.88 (d, J = 10 Hz, $H_{2'}$), 4.63 (b d, J = 16 Hz, H_{1eq}), 4.23–3.86 (comp, CH_2O, H_{1ax}), 3.81 (s, OCH_3), 3.73 (s, OCH_3), 3.6–3.23 (m, H_{3ax}), 2.73–1.86 (comp, 2 × $H_{5'}$, 2 × H_6, 2 × H_4), 1.23 (t, J = 7 Hz, CH_3); MS (EI), m/e (intensity) 359 (83), 330 (100), 151 (71), 115 (69). Anal. ($C_{20}H_{25}NO_5$) C, H, N.

***N*-(Carboethoxy)-*N*-demethyllycoraminone (23) and *N*-(Carboethoxy)-*N*,*O*-didemethyllycoraminone (24).** Aluminum trichloride (190 mg, 1.42 mmol) and ethyl sulfide (502 mg, 5.56 mmol) were dissolved at 0 °C in dry dichloromethane (5 mL). The resulting solution was allowed to warm up to room temperature and enone **22** (170 mg, 0.473 mmol) in dry CH_2Cl_2 (3 mL) was added dropwise. After 24 h stirring, the reaction mixture was diluted with H_2O (10 mL) and extracted with $CHCl_3$ (3 × 10 mL). The combined extracts were washed (H_2O and brine), dried (Na_2SO_4), and evaporated. The oily residue (150 mg) was purified by PLC (SiO_2, 7:3 hexane–EtOAc) for furnish **23** (122.5 mg, 0.355 mmol, 75%) as a colorless oil: IR (neat) 1735, 1700 cm^{-1}; ^1H NMR (80 MHz) δ 6.71 (b s, H_7, H_8), 4.85 (b d, J = 15 Hz, H_{9eq}), 4.7 (t, J = 3 Hz, H_{4a}), 4.23–3.86 (m, CH_2O, H_{9ax}), 3.82 (s, OCH_3), 3.43–3.03 (m, H_{11ax}), 2.98 (dd, J = 18, 3 Hz, H_{4ax}), 2.56 (dd, J = 18, 3 Hz, H_{4eq}), 2.4–1.6 (comp, 2 × H_1, 2 × H_2, H_{11eq}, 2 × H_{12}), 1.18 (t, J = 7 Hz, CH_3). Anal. ($C_{19}H_{23}NO_5$) C, H, N. Phenol **24**

(23.5 mg, 0.07 mmol, 15%), a colorless powder, mp 179–180 °C ($CHCl_3$–hexane), was identified as the more polar product: IR (KBr) 3290, 1735, 1695 cm^{-1}; ^1H NMR (80 MHz) δ 6.66 (s, H_7, H_8), 5.0–4.7 (m, H_{9eq}), 4.7 (t, J = 3 Hz, H_{4a}), 4.56–3.9 (comp, CH_2O, H_{9ax}, OH), 3.5–3.06 (m, H_{11ax}), 2.93 (dd, J = 17, 3 Hz, H_{4ax}), 2.63 (dd, J = 17, 3 Hz, H_{4eq}), 2.46–1.63 (comp, 2 × H_1, 2 × H_2, H_{11eq}, 2 × H_{12}), 1.2 (t, J = 7 Hz, CH_3); MS (EI), m/e (intensity) ($C_{18}H_{21}NO_5$ requires 331) 331 (41), 303 (20), 302 (100), 258 (9).

Conversion of 24 → 23. To a magnetically stirred solution of **24** (20 mg, 0.06 mmol) in dry acetone (2 mL) were added anhydrous potassium carbonate (20 mg) and iodomethane (42.5 mg, 0.3 mmol). After 14 h, the mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3 × 5 mL). The combined extracts were washed (H_2O and brine) and evaporated. The residue (25 mg) was percolated through a small SiO_2 column using 1:1 hexane–EtOAc to afford **23** (21.7 mg, 0.06 mmol, 100%) identical with the previous sample.

Lycoramine (2). A solution of **23** (90 mg, 0.26 mmol) in dry dimethoxyethane (DME, 1.5 mL) was added dropwise to a cold (−78 °C) and stirred suspension of lithium aluminum hydride (39 mg, 1.02 mmol) in dry DME (5 mL). After 30 min stirring at −78 °C, the reaction mixture was allowed to warm up to temperature and eventually heated to reflux under nitrogen for 15 min. After this time, a saturated solution of $Na_2SO_4 \cdot 10H_2O$ (0.5 mL) was carefully added dropwise with external cooling (ice-water bath), the mixture diluted with 0.5 N NaOH (3 mL), and the whole extracted exhaustively with ethyl ether (5 × 10 mL). The combined extracts were washed (H_2O and brine), dried (Na_2SO_4), and evaporated. The oily residue (66 mg) was purified by PLC (SiO_2, 95:5 $CHCl_3$–15% (v/v) methanolic trimethylamine) to furnish pure lycoramine (**2**) (57 mg, 0.197 mmol, 76%), mp 96–98 °C (CH_2Cl_2) (lit.[3d] mp 101–102 °C, lit.[3a] 98–99 °C, lit.[3c] 94–97 °C). Our synthetic sample proved identical with authentic[32] (±)-lycoramine by comparison (IR, ^1H NMR, mass) of spectra.

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Registry No. (±)-**2**, 18797-70-1; **3**, 81011-95-2; (±)-**4**, 87783-38-8; (±)-**5**, 87783-39-9; (±)-**6**, 87783-40-2; (±)-**7**, 87783-41-3; **8**, 87783-42-4; (±)-**9**, 87783-43-5; (±)-**10**, 87783-44-6; (±)-**11**, 87783-45-7; (±)-**12**, 87783-46-8; (±)-**13**, 87783-48-0; (±)-**14**, 87783-47-9; (±)-**15**, 87783-49-1; (±)-**16**, 87783-50-4; (±)-**17**, 87783-51-5; **18**, 87783-53-7; (±)-**19**, 87783-52-6; (±)-**20**, 87783-54-8; (±)-**21**, 87783-56-0; (±)-**22**, 87783-55-9; (±)-**23**, 87801-03-4; (±)-**24**, 87801-04-5; nitromethane, 75-52-5; chloromethyl methyl ether, 107-30-2; 1,3-propanedithiol, 109-80-8; methanethiol, 74-93-1; methyl vinyl ketone, 78-94-4.

Notes

Transfer of Hydrogen from Tin Formates. Reduction of Aldehydes and Ketones

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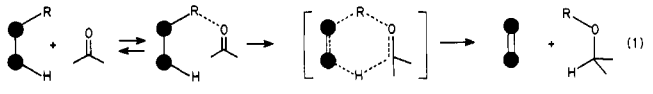
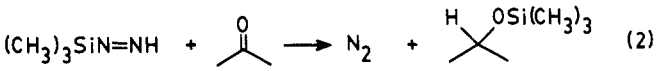
Reagents specifically designed to reduce carbon–oxygen double bonds should incorporate a binding site that recognizes and activates carbonyl groups and an adjacent site that serves as a formal source of hydride. A very simple reagent of this kind is represented by structure **1**. Binding and activation of a substrate at the receptor R in complex **2**, followed by transfer of hydrogen in transition state **3**, would yield the product of reduction **4** and an unsaturated fragment, ●═● (eq 1). Formally analogous transfers of



1 2 3 4

hydrogen occur during Meerwein–Ponndorf–Verley reductions,[1] Cannizzaro reactions,[2] Grignard reductions,[3] and other related processes.[4] In addition, we have recently shown that aryl ketones can be reduced in a similar way (eq 2) by a reagent tentatively identified as (trimethylsilyl)diazene (**5**).[5]



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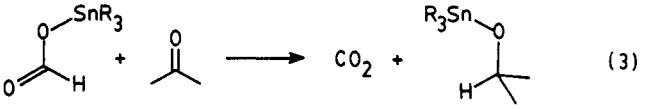
Encouraged by these precedents, we decided to study the hypothetical reaction in eq 3, in which the transfer of



hydrogen from tin formates to carbonyl compounds produces stannyl ethers and carbon dioxide. The results summarized in Table I confirm that a variety of aldehydes are slowly but efficiently reduced by triphenyltin formate.[6]

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