4.5 g; 33%; ^{1}H NMR δ 7.3–6.8 (m, PhH), 3.7 (broad s, H-8), 3.6–3.1 (m, H-3), 2.65 (broad s, H-1), 2.25 (m, H-4,5), 2.1–1.0 (m, H-6,7), 1.15 (s, *t*-Bu); IR 1735 (CO). A small sample was distilled in a Hickman still (bath 150 °C (0.2 mm)) to obtain an analytical sample.

Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.12; H, 8.87.

The **2,4-dinitrophenylhydrazone** derivative, mp 200–202 °C, was also prepared and analyzed.

Anal. Calcd for $C_{24}H_{28}O_5N_4$: N, 12.38. Found: N, 12.16.

***exo*-3-Phenylbicyclo[3.2.1]oct-8-*anti*-yl *tert*-Butyl Ether (2–O-*t*-Bu).** A mixture of ketone **7** (13.4 g, 50 mmol), potassium hydroxide (85%, 6.7 g), hydrazine hydrate (95%, 45 mL), and triethylene glycol (TEG, 50 mL) was refluxed for 2 h. The excess hydrazine and water were distilled off as the temperature rose to 200 °C. After 4 h at this temperature, the solution was cooled and extracted with ether (4 × 50 mL). The washed and dried ethereal material was concentrated in vacuo and distilled to afford ether 2-O-*t*-Bu as a colorless oil: bp 128–131 °C (0.1 mm); ^{13}C NMR[30] δ 146.1, 128.5–125.0 (Ph), 81.8 (C-8), 72.9 ($OCMe_3$), 42.1 (C-1,5), 39.9 (C-2,4), 35.7 (C-3), 28.7 (C-6,7) 27.1 (CH_3).

***exo*-3-Phenylbicyclo[3.2.1]octan-*anti*-8-ol (2–OH) and Tosylate (2–OTs).** Ether **2**–O-*t*-Bu was converted as described[10] to the corresponding acetate **2**–OAc (75%, ν_{co} 1745 cm^{-1}) and thence to alcohol **2**–OH (75%, methylmagnesium bromide was used to cleave the acetate instead of lithium aluminum hydride in this instance). Alcohol **2**–OH formed white crystals from hexane: mp 124–125 °C; ^{1}H NMR δ 7.2 (s, PhH), 3.8 (s, H-8), 2.2 (m, H-1,5), 2.0–1.4 (m, H-2,3,4,6,7), 1.3 (s, OH); ^{13}C NMR[30] δ 145.8, 130.4–124.0 (Ph), 81.9 (C-8), 42.4 (C-1,5), 39.2 (C-2,4), 35.4 (C-3), 26.4 (C-6,7); IR (KBr) 3290 (OH), 1000 (CO).

Anal. Calcd for $C_{14}H_{18}O$: C, 83.21; H, 8.97. Found: C, 82.95; H, 8.90.

In the customary fashion, alcohol **2**–OH was converted to its tosylate **2**–OTs (5 day reaction time at 25 °C): 83%; mp 128–129 °C (petroleum ether); ^{1}H NMR (partial) δ 4.65 (br s, H-8); IR (KBr) 1340, 1170 (SO_2).

Anal. Calcd for $C_{12}H_{24}O_3S$: C, 70.76; H, 6.79. Found: C, 70.72; H, 6.77.

Solvolysis of Tosylates. The procedure followed has been described in detail.[1] The kinetic and activation parameter data were obtained by computer. The data are collected in Table I. Tosylate *anti*-1–OTs showed no change after 24 h at 84.2 °C or after 1 week at 119–120 °C.

Solvolysis Products. The ampoule contents comprising the titrated aliquots of tosylate *syn*-1–OTs were combined and extracted thoroughly with ether. Chromatography on silica gel led to recoverable starting material and to enriched product samples that were characterized by ^{1}H NMR spectra only. The products observed were: ***syn*-8-phenylbicyclo[3.2.1]oct-3-en-*endo*-2-ol** (8–OH) [86%; ^{1}H NMR (partial) δ 6.3 (m, H-3,4), 4.47 (m, H-2)] and ***syn*-8-phenylbicyclo[3.2.1]oct-2-en-*endo*-4-yl trifluoroethyl ether** (8–TFE) [14%; ^{1}H NMR (partial) δ 6.3 (m, H-2,3), 4.23 (m, H-4), 3.33 (q, J = 9 Hz, CH_2CF_3)]. Tosylate **2**–OTs (73 mg 0.2 mmol) was heated in the solvolysis solvent (10 mL) for 48 h. The solvent was evaporated and the residue was diluted with water and extracted with ether (2 × 25 mL). The washed and dried ethereal extracts were freed of solvent and the residual oil was then chromatographed on Florisil with hexane and ether mixtures as eluants. Although separations were not as desired, resonably pure ***syn*-7-phenyl-*cis*-bicyclo[3.3.0]oct-2-ene (9)** was isolated: 28 mg; 75%; ^{1}H NMR δ 7.2 (s, PhH), 5.65 (m, H-2,3), 3.5–1.7 (series of multiplets, all other H's); ^{13}C NMR see Table II; IR 3090, 2890, 1610, 1510, 1460, 1360, 1280, 1170, 1100, 1080, 1040, 970, 910, 810, 760, 700.

Anal. Calcd for $C_{14}H_{16}$: C, 91.25; H, 8.75. Found: C, 89.68; H, 9.87.

Lack of material prevented further purification, but even so the above analysis served to establish the hydrocarbon nature of **9** (%C + %H observed = 99.55%). Also isolated was an even smaller amount of a poorly resolved mixture of ***syn*-7-phenyl-*cis*-bicyclo[3.3.3]octan-2-ol**, OH configuration unknown (9–OH), and ***syn*-7-phenyl-*cis*-bicyclo[3.3.0]oct-2-yl trifluoroethyl ether**, ether configuration unknown (9–TFE), ca. 25% of product. Several milligrams of the latter were isolated in reasonable purity to observe its spectra: ^{1}H NMR (partial) δ 3.8 (q, J = 9 Hz, CH_2CF_3); ^{13}C NMR (partial) 81.8 (C-3); IR 1340 (CF_3). Insufficient material was available for combustion analysis.

Reaction of **2**–OTs (169 mg, 0.474 mmol) in dioxane–water (80:20 v/v, 2.0 mL) containing distilled 2,6-lutidine (52 mg, 0.485 mmol) in a sealed tube at 110 °C for 70 h led to the isolation of essentially only **9** (75 mg, 86%). Its spectral properties were identical with those of **9** isolated from the kinetic studies.

Acknowledgment. We are indebted to those individuals cited in the article for invaluable assistance. The Loyola University Research Committee is thanked for financial support of a portion of this work.

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[30] Reference 13 lists the ^{13}C NMR spectrum of bicyclo[3.2.1]octan-*anti*-8-ol (the non-phenyl analogue of the 2 system): δ_c 42.2 (C-1,5), 31.3 (C-2,4), 17.1 (C-3), 26.2 (C-6,7), 82.2 (C-8).

Convenient Synthesis of 3-Methyl-2,3,4,4aα,5,6,7,7aα-octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline

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A new synthesis of 3-methyl-2,3,4,4aα,5,6,7,7aα-octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (**3**) has been developed. The synthesis utilizes the acylation of anion **5** with γ-butyrolactone preferentially at the 4-position. Reduction of the resulting keto alcohol **9** afforded two diastereomeric azabicyclooctanes **11a** and **11b**. Synthetic transformation of both of these compounds gave the desired product **3** in respectable yields. The structure of one of the intermediates (**14a**) was confirmed by single-crystal X-ray diffraction analysis.

The search for potent, nonaddictive analgesics based on the morphine ring system **1** (Scheme I) has been an area of considerable interest for many years.[1] The morphine fragment 2,3,4,4aα,5,6,7,7aα-octahyro-1*H*-benzofuro[3,2-*e*]isoquinoline (**3**), which contains the complete morphine skeleton with the exception of C-10, was synthesized by one of us[2] using the intramolecular Diels–Alder reaction

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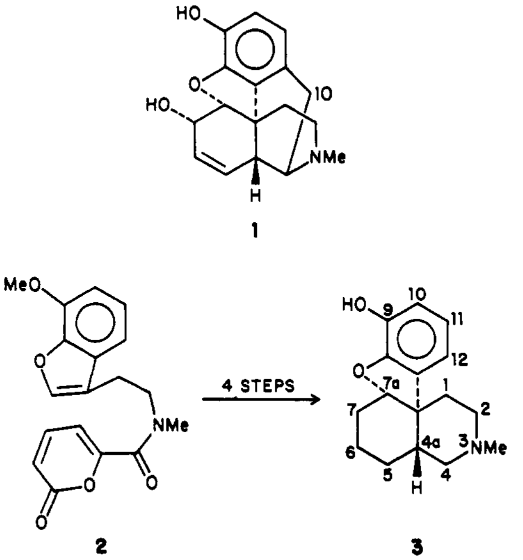
† Contribution No. 3382.

[1] Johnson, M. R.; Michne, G. M. In "Medicinal Chemistry", 4th ed.; Wolff, M. E., Ed.; Wiley Interscience: New York, 1981; Part III, p 699.

0022-3263/84/1949-2942$01.50/0 © 1984 American Chemical Society

Scheme I



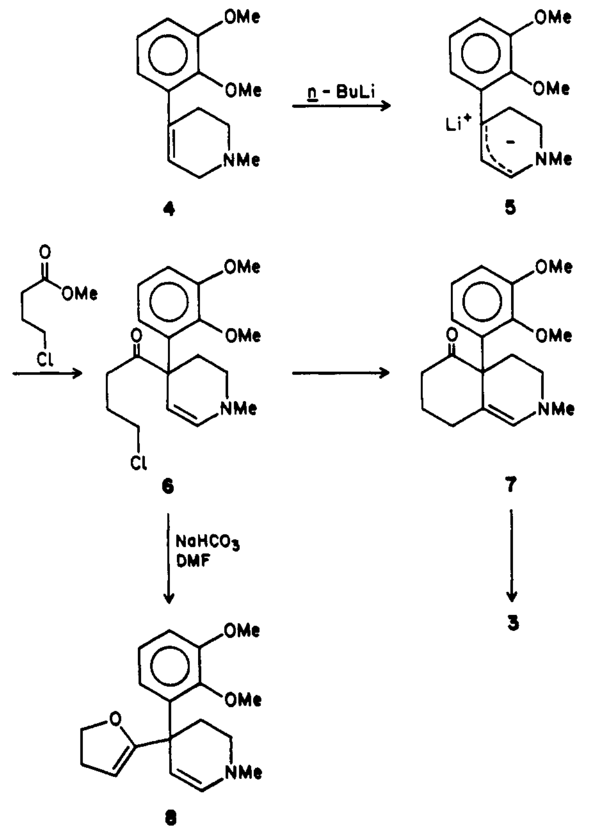
of *N*-[2-(7-methoxy-3-benzofuranyl)ethyl]-*N*-methyl-6α-pyronecarboxamide (2).[3] Compound 3 and its N-substituted analogues were found to have potent analgesic activity.[2]

Despite the respectable yields of 3, the preparation of larger amounts of this compound using the aforementioned synthetic route was deemed cumbersome because of the low concentration of 2 needed for the intramolecular Diels–Alder reaction. We herein report an alternate and more convenient synthesis of 3.

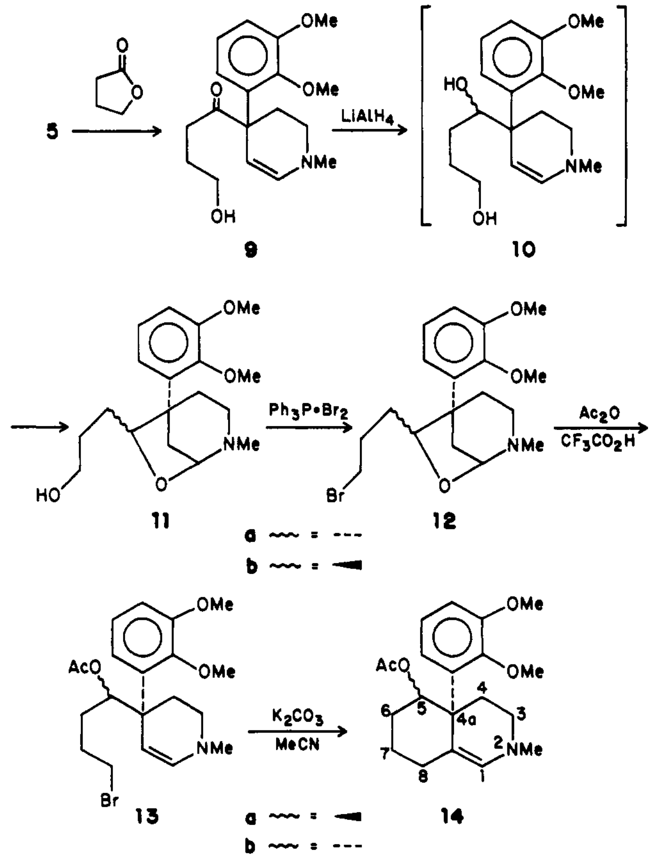
Results and Discussion

The general synthetic strategy envisaged for the preparation of 3 is depicted in Scheme II.[4] It was hoped that cyclization of the enamine 6 prepared from the enamine anion 5[5] would afford the tricyclic compound 7 which could then be transformed to the desired material 3. Indeed, addition of enamine anion 5, prepared by the treatment of the tetrahydropyridine 4[6] with *n*-butyllithium, to ethyl 4-chlorobutyrate afforded the keto enamine 6. However, attempted cyclization of the latter in dimethylformamide in the presence of sodium bicarbonate produced the undesired furan 8 (Scheme II). The identity of 8 was determined by spectral methods and by hydrolysis to the keto alcohol 9 (see below). Modification of the keto group in compound 6 was thus necessary. Treatment of the enamine anion 5 with γ-butyrolactone afforded keto alcohol 9 (Scheme III) in 99% crude yield. Reduction of 9 with lithium aluminum hydride afforded the bicyclic alcohols 11a and 11b in 99% crude yield, presumably via alcohol 10[5,7] and its immonium form. Alcohols 11 were formed even with basic workup; their structures were established by IR, NMR, and MS.

Scheme II



Scheme III



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(2) Ciganek, E. *J. Am. Chem. Soc.* **1981**, *102*, 6261. Ciganek, E. U.S. Patent 4 243 668, January 6, 1981; *Chem. Abstr.* **1981**, *95*, 809241.

(3) For alternate syntheses of this ring system see: Schultz, A. G.; Lucci, R. D. *J. Chem. Soc., Chem., Commun.* **1976**, 925. Schultz, A. G.; Lucci, R. D.; Fu, W. Y.; Berger, M. H.; Erhardt, J.; Hagmann, W. K. *J. Am. Chem. Soc.* **1978**, *100*, 2105. Moos, W. H.; Gless, R. D.; Rapoport, H. *J. Org. Chem.* **1981**, *40*, 5064. Weller, D. D.; Weller, D. L. *Tetrahedron Lett.* **1982**, *23*, 5239.

(4) Alkylation of enamines of type 4[5] is the key step in the synthesis of 4a-aryldecahydroisoquinolines reported by Evans et al. (Evans, D. A.; Smith, C. H.; Thomas, R. C.; Zimmerman, D. M.; Robey, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 5955. Evans, D. A.; Mitch, C. H. *Tetrahedron Lett.* **1982**, *23*, 285).

(5) Levine, R.; Bell, V. U.S. Patent 3 824 242, 1974; (*Chem. Abstr.* **1974**, *81*, 813 691). Martin, S. F.; Du Priest, M. T. *Tetrahedron Lett.* **1977**, 3925.

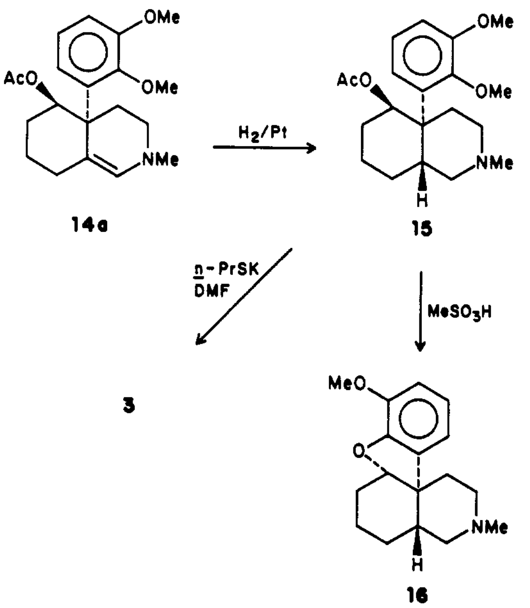
(6) For the preparation of this compound see the Experimental Section; this compound has also been reported in ref 4.

(7) Lewis, J. W.; Mayor, P. A. *J. Chem. Soc. C* **1970**, 1974.

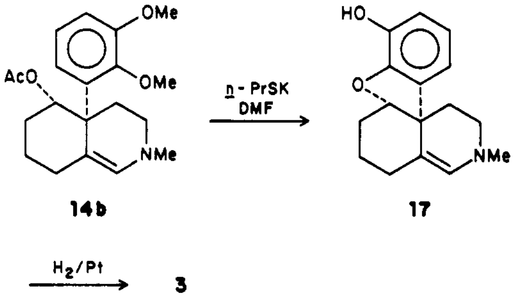
Diastereomer **11a** could be separated from **11b** by crystallization of the hydrochloride salts. Since the formate esters of alcohols **11a** and **11b** showed signals at δ 7.97 and 8.05, respectively, the ratios of these diastereomers in a mixture could be determined by NMR. The stereochemistry of alcohols **11a** and **11b** follows from results of further steps. Attempts to selectively produce one of the diastereomers (**11a** or **11b**) were met with some success.[8] Reduction of **9** with lithium aluminum hydride at 0 °C or with sodium in isopropyl alcohol produced almost equal amounts of **11a** and **11b**. However, lithium aluminum hydride reduction of **9** at −72 °C or that of the lithium salt of **9** (produced by the treatment of anion **5** with γ-butyrolactone) afforded a 1:3 ratio of **11a** and **11b**.

Each of the two diastereomers **11a** and **11b** was transformed to the corresponding bromides **12a** and **12b** in 78% yield by using the triphenylphosphine–bromine complex.[9] When the hydrochloride of **11a** was used, a crystalline hydrobromide salt of the bromide **12a** was isolated, rendering the purification of the product relatively easy. However, the diastereomer **11b** failed to produce a crystalline product, and therefore, the bromide **12b** had to be purified by column chromatography. Having introduced the leaving group, it was necessary to liberate the enamine double bond in compound **12** to effect the cyclization to form the desired isoquinoline ring system. We hoped that under forced esterification conditions the masked alcohol function forming the oxygen bridge in **12** would be esterified, concomitantly liberating the enamine double bond. Indeed, treatment of either **12a** or **12b** with acetic anhydride in the presence of a strong acid such as *p*-toluenesulfonic acid at 60 °C afforded bromo acetates **13a** and **13b**, respectively. Further, it was found that mixed acetic trifluroacetic anhydride[10] produces higher yields ($\simeq$69%) of **13** at ambient temperature. The cyclization of bromo acetate **13a** to isoquinoline **14a** was achieved by treating it with potassium carbonate in refluxing acetonitrile. The isoquinoline **14a** was obtained in 92% yield as a crystalline solid whose IR and MS were as expected. However, its NMR showed a doublet at δ 6.3 and a singlet at 5.9 amounting to one proton each. The singlet at δ 5.9 can be reasonably assigned to the vinyl proton of the enamine double bond, but the doublet at δ 6.3 is at such low field that assignment of this signal to H-5 seemed unwarranted. However, a single-crystal X-ray diffraction analysis[11] confirmed that the product has structure **14a**. As this compound is derived from compound **11a**, it follows that the structure of diastereomer **11a** is also as represented. The cyclization of bromo acetate **13b** under conditions similar to those used for the cyclization of **11a** afforded the acetate **14b**. This material was relatively less stable but showed the expected spectral characteristics.

Scheme IV



Scheme V



The transformation of isoquinoline **14a** to the target compound **3** was achieved by a sequence of reactions shown in Scheme IV. Hydrogenation of **14a** over platinum oxide in ethanol afforded the *trans*-perhydroisoquinoline **15** exclusively in 98% yield.[4] Treatment of this material with various acids afforded the methoxybenzofuroisoquinoline **16**[2] in a low yield ($\simeq$10%). However, when isoquinoline **15** was heated with potassium *n*-propyl mercaptide in dimethylformamide, closure of the furan ring as well as demethylation took place affording the target compound **3**[2] in 90% yield. While the exact mechanism of this interesting transformation is not known, formation of substantial amounts of methoxybenzofuroisoquinoline **16** at shorter reaction time indicates that the closure of the furan ring precedes the second demethylation of the 3-methoxy group on the aromatic ring in compound **15**.

Attempted reduction of **14b** (Scheme V) by catalytic hydrogenation or with sodium borohydride produced a material that indicated the loss of the acetoxy group. However, when isoquinoline **14b** was subjected to the demethylation conditions described above, the benzofuroisoquinoline **17** was obtained[12] in 65% yield. This material was identical with the product obtained from **14a** under similar reaction conditions. Catalytic hydrogenation of **17** over platinum oxide afforded the desired product **3** in 62% yield.[13]

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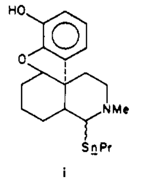
(8) We thank W. Seibel for some of these studies.

(9) Horner, L.; Oediger, H.; Hoffmann, H. *Liebigs Ann. Chem.* **1959**, *626*, 26. Wiley, E. A.; Hershkowitz, R. L.; Rein, B. M.; Chung, B. C. *J. Am. Chem. Soc.* **1964**, *86*, 964. Wiley, G. A.; Rein, B. M.; Hershkowitz, R. L. *Tetrahedron Lett.* **1964**, 2509.

(10) Tedder, J. M. *Chem. Rev.* **1955**, *55*, 787. Almirante, L.; Tasolini, G. *J. Org. Chem.* **1961**, *26*, 177. Parish, R. C.; Stock, L. M. *Ibid.* **1965**, *30*, 927.

(11) We thank Dr. J. F. Whitney for carrying out this determination. See paragraph at the end of the paper about supplementary material.

(12) This product was contaminated with another material whose molecular weight as shown by MS was 333, consistent with the structure i.



i

Experimental Section

General Methods. Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM-390 or Varian HR-220 spectrometer with $CDCl_3$ as solvent and Me_4Si as an internal standard. ^{13}C NMR spectra were recorded on a Bruker WH-90 spectrometer. Chemical shifts are reported in δ units in parts per million downfield from internal standard. IR spectra were obtained on a Nicolet 7199 FT-IR spectrometer. Mass spectra were obtained at 700 V on a VG-Micromass 70-70H double-focusing high-resolution spectrometer or by using isobutene as ion source on a Du Pont 491 low-resolution spectrometer. Thin-layer chromatography was performed on 0.25 mm thick silica gel plates; spots were visualized by dipping the plates in 10% ethanolic solution of phosphomolybdic acid and baking at 180 °C for 5 min. High-pressure liquid chromatography (HPLC) was performed by using a Waters Associates 500 liquid chromatograph equipped with a UV absorbance detector on a Prep Pack 500 silica column. *n*-Butyllithium was used as a solution in hexane. Unless otherwise indicated the reactions were performed under positive pressure of nitrogen. All asymmetric substances described in this section are racemic mixtures.

4-(2,3-Dimethoxyphenyl)-1,2,3,6-tetrahydro-1-methylpyridine (4). A solution of 138 g (1.0 mol) of veratrole in 400 mL of dry tetrahydrofuran was cooled in a dry ice/acetone bath and treated with 500 mL of a 1.6 M solution (0.8 mol) of *n*-butyl lithium at such a rate that the temperature of the reaction mixture remained at 0 °C. After the addition was complete the reaction mixture was stirred at room temperature for 3 h. The resulting white slurry was cooled in a dry ice/acetone bath and 90.4 g (0.8 mol) of 1-methyl-4-piperidone was added at such a rate that the temperature of the reaction mixture remained below −10 °C. After the addition was complete the reaction mixture was stirred at 0 °C for 2 h, quenched with 400 mL of water, and diluted with 400 mL of ether. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 400 mL). The combined organic layers were dried (K_2CO_3) and concentrated under reduced pressure to afford 270.9 g of an oil. This oil was heated under reduced pressure to remove all the material boiling below 150 °C (0.025 torr). The remaining residue, 97.55 g, was dissolved in 292 mL of concentrated hydrochloric acid and the solution was heated to 65 °C for 3 h. The reaction mixture was cooled to room temperature and made basic with 20% sodium hydroxide solution. Extraction with dichloromethane (3 × 200 mL), drying (K_2CO_3), and concentration under reduced pressure afforded an oil. This oil was distilled under reduced pressure to afford 67.30 g (36%) of the product **4**: bp 120–125 °C (0.1 torr); IR (film) 2940, 1570 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) 2.4 (s, 3 H), 2.60 (s, 4 H) 3.1 (d, J = 3 Hz, 2 H), 3.76 (s, 3 H), 3.83 (s, 3 H), 5.8 (t, J = 3 Hz, 1 H), 6.7–7.1 (m, 3 H); ^{13}C NMR (22.6 MHz, $CDCl_3$) 30.02, 45.81, 52.44, 54.98, 55.56, 60.31, 111.32, 121.33, 123.67, 123.93, 134.72, 136.99, 146.74, 152.85; HRMS calcd, m/z 233.1416; found, m/z 233.1414. Anal. Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.11; H, 7.96; N, 5.66.

4-(4-Chlorobutyroyl)-4-(2,3-dimethoxyphenyl)-1-methyl-1,2,3,4-tetrahydropyridine (6). To a solution of 14.85 g (0.02 mol) of tetrahydropyridine **4** in 50 mL of dry tetrahydrofuran at −10 °C was added 21 mL of a 1.50 M solution (0.03 mol) of *n*-butyl lithium. The resulting red solution was transferred under nitrogen into a solution of 16.12 g (0.11 mol) of ethyl 4-chlorobutyrate in 30 mL of tetrahydrofuran kept at −75 °C. After the addition was complete, the reaction mixture was stirred at −75 °C for 5 min and then quenched with 5% hydrochloric acid. After allowing the solution to come to 0 °C, the reaction mixture was extracted repeatedly with ether. The aqueous phase was made basic with 10% sodium hydroxide solution and extracted with methylene chloride to afford 6.47 g of crude product. Purification by HPLC gave a pure sample of **6**: IR (film) 2940, 1700, 1630 cm^{-1}; ^{1}H NMR (220 MHz, $CDCl_3$) 2.60 (s, 3 H), 3.5 (td, J = 6.5, 2.5 Hz, 2 H), 3.7 (s, 3 H), 3.8 (s, 3 H), 4.3 (d, J = 8 Hz, 1 H) 6.1 (d, J = 8 Hz, 1 H), 6.4 (dd, J = 8, 2 Hz, 1 H) and 6.8 (m, 2 H); MS calcd, m/z 337.1443; found, 337.1431.

4-(2,3-Dihydro-5-furyl)-4-(2,3-dimethoxyphenyl)-1-methyl-1,2,3,4-tetrahydropyridine (8). A mixture of 0.48 g (1.4 mmol) of chlorobutyroyltetrahydropyridine **6**, 0.78 g (9.3 mmol) of sodium bicarbonate, and 10 mL of dimethylformamide was stirred at 105 °C for 15 h. The solvent was removed, the residue was taken up in methylene chloride, and the filtered solution was concentrated. Short-path distillation of the residue gave 0.31 g (74%) of product, bp 140–180 °C (0.002 torr), consisting of the title compound and minor amounts of an impurity: ^{1}H NMR (220 MHz, $CDCl_3$) 3.8 (2 s, 6 H), 4.2 (td, J = 9, 2 Hz, 2 H), 4.6 (dd, J = 8, 1.5 Hz, 1 H), 4.7 (t, J = 2.5 Hz, 1 H), 5.9 (d, J = 8 Hz, 1 H), 6.8 (dd, J = 8, 2 Hz, 1H) and 7.0 (m, 2 H) among others; MS calcd, m/z 301.1677; found, 301.1657. Anal. Calcd for $C_{18}H_{23}NO_3$: C, 71.73; H, 7.69; N, 4.65. Found: C, 71.13; H, 7.48; N, 4.40. Hydrolysis of this product with 5% hydrochloric acid at room temperature for 15 min, followed by treatment with 5% sodium carbonate solution gave 1-[4-(2,3-dimethoxyphenyl)-1,2,3,4-tetrahydro-1-methylpyrid-4-yl]-4-hydroxy-1-butanone (**9**), identical by NMR with the product described below.

1-[4-(2,3-Dimethoxyphenyl)-1,2,3,4-tetrahydro-1-methylpyrid-4-yl]-4-hydroxy-1-butanone (9). A solution of 9.32 g (0.04 mol) of the tetrahydropyridine **4** in 75 mL of dry tetrahydrofuran was cooled to −10 °C and treated with 40 mL of a 1.65 M solution (0.066 mol) of *n*-butyllithium. The resulting red solution was stirred at −10 °C for 15 min and transferred over a period of 5 min, under nitrogen, into a solution of 18.4 g (0.21 mmol) of γ-butyrolactone in 40 mL of dry tetrahydrofuran kept at −72 °C. After the addition was complete, the reaction mixture was stirred at −70 °C for 15 min, then quenched with 100 mL of 20% sodium hydroxide solution, and stirred at room temperature for 1 h. At the end of this period, the reaction mixture was diluted with 200 mL of dichloromethane and the organic layer was separated. The aqueous layer was extracted with an additional 200-mL portion of dichloromethane. The organic layers were washed with brine, dried (K_2CO_3), and concentrated under reduced pressure to afford 12.6 g of the product (99%), which was used for the next step without further purification. Pure 1-[4-(2,3-dimethoxyphenyl)-1,2,3,4-tetrahydro-1-methylpyrid-4-yl]-4-hydroxy-1-butanone (**9**) was obtained by HPLC purification of this material: IR (film) 3440, 2940, 1700, 1630 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) 2.63 (s, 3 H), 3.45 (m, 3 H), 3.73 (s, 3 H), 3.88 (s, 3 H), 4.3 (d, J = 8 Hz, 1 H), 6.15 (d, J = 8 Hz, 1 H), 6.7–7.2 (m, 3 H). Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.54; H, 7.99; N, 4.67.

(1*R,5*R**,6*S**)-5-(2,3-Dimethoxyphenyl)-2-methyl-6-(3-hydroxypropyl)-7-oxa-2-azabicyclo[3.2.1]octane Hydrochloride (11a Hydrochloride Salt).** A solution of 124.55 g (0.39 mol) of **9** in 250 mL of dry tetrahydrofuran was added to a suspension of 20 g (0.51 mol) of lithium aluminum hydride in 200 mL of dry tetrahydrofuran at −10 to 0 °C. After the addition was complete, the reaction mixture was stirred at 0 °C for 1 h and then treated sequentially with 20 mL of water, 20 mL of 20% sodium hydroxide solution, and 60 mL of water. The resulting slurry was filtered, and the residue was washed with dichloromethane. The combined filtrates were concentrated under reduced pressure to afford 125 g (99.8% yield) of crude product. This material was dissolved in 200 mL of ether and treated with 100 mL of methanol saturated with hydrogen chloride. Part of the solvent was removed from the resulting mixture under reduced pressure, and the slurry thus generated was diluted with 25 mL of methanol. Upon filtration, 55 g of a solid was obtained which was recrystallized from 200 mL of methanol to afford 26.7 g of a solid, mp 209–212 °C. The mother liquor from the recrystallization afforded an additional 3.0 g of a solid. The total yield of the solid hydrochloride was 29.7 g (21.4%): IR (KBr) 3380, 2940, 2600, 1580 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) 3.80 (s, 3 H), 3.90 (s, 3 H), 4.66 (dd, J = 9, 3 Hz, 1 H), 5.05 (d, J = 6 Hz, 1 H), 6.6 (dd, J = 6, 3 Hz, 1 H), 6.7–7.1 (m, 3 H); ^{13}C NMR (22.6 MHz, D_2O) 27.68, 28.27, 33.53, 37.85, 38.92, 46.53, 47.50, 55.63, 60.37, 61.02, 86.56, 90.40, 113.14, 119.51, 124.13, 133.35, 146.16, 152.07; MS calcd, 321.1940 (M − HCl); found, 321.1930. Anal. Calcd for $C_{18}H_{28}NO_4Cl$: C, 60.41; H, 7.88; N, 3.91, Cl, 9.90. Found: C, 60.34; H, 7.88; N, 3.70; Cl, 10.01. A sample of the hydrochloride dissolved in dichloromethane was treated with saturated sodium carbonate solution and the organic layer was dried and evaporated to give the free (1*R**,5*R**,6*S*)-5-(2,3-dimethoxyphenyl)-2-methyl-6-(3-

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(13) The subject matter described in this paper has been claimed: Ciganek, E.; Shenvi, A. B. U.S. Patent 4415736, November 15, 1983. Shenvi, A. B. U.S. Patent 4421916, December 20, 1983.

hydroxypropyl)-7-oxo-2-azabicyclo[3.2.1]octane (1*R**,5*S**,6*R**)-5-(2,3-dimethoxyphenyl)-2-methyl-6-(3-hydroxypropyl)-7-oxo-2-azabicyclo[3.2.1]octane (**11a**): IR (KBr) 3400, 2940, 1580 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) 2.36 (s, 3 H), 3.5 (t, $J = 6$ Hz, 2 H), 3.86 (s, 3 H), 3.90 (s, 3 H), 4.40 (dd, $J = 9$, 3 Hz, 1 H), 4.70 (d, $J = 6$ Hz, 1 H), 6.57–7.03 (m, 3 H); ^{13}C NMR (22.6 MHz, $CDCl_3$) 29.84, 30.43, 36.54, 40.50, 42.46, 47.97, 48.69, 55.58, 60.19, 62.60, 82.87, 90.71, 111.79, 119.46, 123.23, 136.95, 146.89, 152.41; MS calcd, m/z 321.1945; found, 321.1940 Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.26; H, 8.38, N, 4.30.

(1*R,5*R**,6*R**)-5-(2,3-Dimethoxyphenyl)-2-methyl-6-(3-hydroxypropyl)-7-oxa-2-azabicyclo[3.2.1]octane (11b).** A solution of 67.30 g (0.28 mol) of **4** in 450 mL of dry tetrahydrofuran was cooled to −10 °C and treated with a slow stream of 198 mL of a 1.6 M solution (0.31 mol) of *n*-butyllithium so that the temperature of the reaction mixture remained below 5 °C. After the addition was complete, the resulting red solution was stirred at −10 °C for 15 min and then added under nitrogen to a solution of 40.86 g (0.475 mol) of γ-butyrolactone in 100 mL of dry tetrahydrofuran which had been cooled to −72 °C. The resulting pale brown solution was stirred at −72 °C for 1 h and then transferred into a suspension of 18.05 g (0.47 mol) of lithium aluminum hydride in 150 mL of dry tetrahydrofuran cooled to −72 °C. After the addition was complete, the reaction mixture was stirred at −10 °C for 1 h, warmed to room temperature, and quenched with 18 mL of water followed by 54 mL of 20% sodium hydroxide. The resulting slurry was filtered, and the residue was washed with four 200-mL portions of dichloromethane. The filtrates were dried (K_2CO_3) and concentrated under reduced pressure to give 109.9 g of crude product. This material was heated to 80 °C at 0.2 torr pressure to remove any volatile impurities; 103.6 g of an oil containing the desired product **11b** was obtained. It was used in the next step without further purification. The ratio of the two diastereomers **11a** and **11b** in the product was estimated by NMR to be approximately 1:3. A sample prepared in a similar experiment was purified by chromatography to afford a sample of the diastereomer (1*R**,5*R**,6*R**)-5-(2,3-dimethoxyphenyl)-2-methyl-6-(3-hydroxypropyl)-7-oxa-2-azabicyclo[3.2.1]octane (**11b**): ^{1}H NMR (90 MHz, $CDCl_3$) 2.33 (s, 3 H), 3.83 (s, 6 H), 4.1–4.4 (m, 1 H) 4.70 (d, $J = 6$ Hz, 1 H), 6.6–7.1 (m, 3 H).

Synthesis of the Formate Esters of 11. A solution of approximately 0.10 g (0.3 mmol) of the alcohols **11** in 5 mL of formic acid and about 3 drops of trifluoroacetic acid was stirred at room temperature for 2 h. At the end of this period, the reaction mixture was made basic with saturated sodium carbonate solution and extracted with 100 mL of dichloromethane. The organic layer was dried (K_2CO_3) and concentrated under reduced pressure to afford the formate esters whose NMR was used for the estimation of the relative ratios of **11a** and **11b**. The NMR spectrum showed the presence of two peaks, one at 7.97 ppm and the other at 8.03 ppm corresponding to **11a** and **11b**, respectively. A sample purified by column chromatography showed the following: IR (film) 2940, 1720, 1580 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) 2.33 (2 s, 3 H), 3.8 (2 s, 6 H), 3.9–4.5 (m, 3 H), 4.7 (t, $J = 6$ Hz, 1 H), 6.6–8.1 (m, 3 H), 8.00 (2 s, 1 H).

(1*R,5*R**,6*S**)-6-(3-Bromopropyl)-5-(2,3-dimethoxyphenyl)-2-methyl-7-oxa-2-azabicyclo[3.2.1]octane Hydrobromide (12a Hydrobromide).** A suspension of 11.60 g (0.032 mol) of **11a** hydrochloride salt in 100 mL of dry tetrahydrofuran was treated with 10.20 g (0.039 mol) of triphenylphosphine and cooled in water. To this suspension was added 6.22 g (0.0329 mol) of bromine. After the reaction mixture was stirred for 15 min, 10 mL of methanol was added, and the reaction mixture was concentrated under reduced pressure; the solid product was suspended in 200 mL of toluene and filtered to obtain 9.15 g of a solid. The toluene from the mother liquor was removed under reduced pressure, and the resulting residue was treated with 25 mL of toluene. The resulting slurry was filtered, and the residue was washed with 25 mL of toluene. The solid thus obtained was again suspended in 25 mL of toluene and filtered to afford 2.61 g of the hydrobromide salt of **12a**. The combined total yield of the desired (1*R**,5*R**,6*S**)-6-(3-bromopropyl)-5-(2,3-dimethoxyphenyl)-2-methyl-7-oxa-2-azabicyclo[3.2.1]octane hydrobromide **12a** was 11.78 g (78%). This hydrobromide salt can be used for the next reaction without further purification or liberation of the free amine. A sample crystallized from methanol–ether: mp 162–164 °C; IR (KBr) 2940, 2600, 1580 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) 2.77 (s, 3 H), 3.83 (s, 3 H) 3.9 (s, 3 H), 4.66 (dd, $J = 9$, 3 Hz, 1 H), 5.16 (d, $J = 6$ Hz, 1 H), 6.66 (dd, $J = 6$, 3 Hz, 1 H), 6.8–7.1 (m, 2 H); ^{13}C NMR (22.6 MHz, D_2O) 27.68, 28.27, 33.53, 37.83, 38.52, 46.53, 47.50, 55.63, 60.37, 61.02, 86.56, 90.40, 113.13, 119.51, 124.13, 133.35, 146.16, 157.07. Anal. Calcd for $C_{18}H_{27}NO_3Br_2$: C, 46.47; H, 5.85; N, 3.01; Br, 34.43. Found: C, 46.67; H, 5.88; N, 2.85; Br, 30.31.

(1*R,5*R**,6*R**)-6-(3-Bromopropyl)-5-(2,3-dimethoxyphenyl)-2-methyl-7-oxa-2-azabicyclo[3.2.1]octane (12b).** A solution of 4.9 g (15.2 mmol) of the free base **11b** in 40 mL of dry tetrahydrofuran and 4.78 g (18.2 mmol) of triphenylphosphine was treated with 2.9 g (18.2 mmol) of bromine. The reaction mixture was stirred for 15 min, diluted with 40 mL of toluene, and extracted with 10% hydrochloric acid (3 × 75 mL). The aqueous layers were made basic with a saturated solution of sodium carbonate and extracted with dichloromethane (5 × 50 mL). The organic layers were dried, combined, and concentrated under reduced pressure to afford 7.00 g of an oil. This oil contained substantial amounts of phosphorous-containing materials. However, for preparative purposes, the crude material was used directly in the next step without further purification.

[1*S,(4*R**)]-4-Bromo-1-(4-[2,3-dimethoxyphenyl]-1,2,3,4-tetrahydro-1-methylpyrid-4-yl)-1-butanol Acetate (13a).** A solution of 11.78 g (0.025 mol) of the hydrobromide of **12a** in 50 mL of a 1:1 mixture of acetic anhydride and trifluoroacetic acid was stirred at 25 °C for 16 h. The reaction mixture was cooled to room temperature, and the solvent was removed under vacuum. The resulting oil was stirred with 100 mL of water for 15 min, made basic with a saturated solution of sodium carbonate, and extracted with dichloromethane (3 × 100 mL). The combined organic layers were dried (K_2CO_3) and concentrated under reduced pressure to afford 7.4 g (69%) of the product as an oil. As this material was unstable, it was used immediately for the next step. A sample prepared in a similar experiment was purified by column chromatography to afford pure [1*S**,(4*R**)]-4-bromo-1-(4-[2,3-dimethoxyphenyl]-1,2,3,4-tetrahydro-1-methylpyrid-4-yl)-1-butanol acetate (**13a**): IR (film) 2940, 1725, 1635, 1575 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) 2.03 (s, 3 H), 2.53 (s, 3 H), 3.85 (s, 3 H), 3.93 (s, 3 H), 4.7 (d, $J = 9$ Hz, 1 H), 5.9 (m, 1 H), 6.03 (d, $J = 9$ Hz, 1 H), 6.8–7.1 (m, 3 H).

[1*R,(4*R**)]-4-Bromo-1-(4-[2,3-dimethoxyphenyl]-(1,2,3,4-tetrahydro-1-methylpyrid-4-yl)-1-butanol Acetate (13b).** A solution of 7.0 g of the material prepared as above containing **12b** in 20 mL of a 1:1 mixture of acetic anhydride and trifluoroacetic acid (V:V) was stirred at room temperature for 1 h. At the end of this period, the volatile material from the reaction mixture was removed by distillation under reduced pressure, and the residue was dissolved in dichloromethane. This solution was shaken with a solution of sodium carbonate, and the organic layer was separated. The aqueous layer was extracted with portions of dichloromethane (3 × 100 mL). The combined organic layers were dried and concentrated under reduced pressure to yield a product which was chromatographed on a silica gel column. Elution with 9:1 hexane:acetone (v:v) containing 5% of triethylamine afforded 3.80 g (59% yield) of [1*R**,(4*R**)]-4-bromo-1-(4-[2,3-dimethoxyphenyl]-1,2,3,4-tetrahydro-1-methylpyrid-4-yl)-1-butanol acetate (**13b**): IR (film) 2980, 1720, 1630, 1575 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) 1.90 (s, 3 H), 2.53 (s, 3 H), 3.8 (s, 3 H), 3.9 (s, 3 H), 4.83 (d, $J = 6$ Hz, 1 H), 5.63 (t, $J = 6$ Hz, 1 H), 5.9 (d, $J = 9$, 1 H), 6.7–7.1 (m, 2 H). This material was unstable and therefore was used immediately for the next transformation.

(4a*R,5*S**)-4a-(2,3-Dimethoxyphenyl)-2,3,4,4a,5,6,7,8-octahydro-2-methyl-5-isoquinolinol Acetate (14a).** A solution of 7.40 g (0.017 mol) of the bromo acetate **13a** in 75 mL of acetonitrile was heated under reflux for 16 h in the presence of 7.4 g of potassium carbonate. The reaction mixture was cooled to room temperature, diluted with 75 mL of acetone, and filtered, and the solid was washed with acetone (3 × 50 mL). The combined filtrates were evaporated to give 6.50 g of an oil which on crystallization from 50 mL of ethanol afforded 5.53 g (92%) of (4a*R**,5*S**)-4a-(2,3-dimethoxyphenyl)-2,3,4,4a,5,6,7,8-octahydro-2-methyl-5-isoquinolinol acetate (**14a**) as a crystalline solid: mp 140–142 °C; IR (KBr) 2925, 1725, 1655, 1575 cm^{-1}; ^{1}H NMR (90

MHz, $CDCl_3$) 2.10 (s, 3 H), 2.50 (s, 3 H), 3.83 (s, 3 H), 3.93 (s, 3 H), 5.9 (s, 1 H), 6.29 (d, J = 3 Hz, 1 H), 6.7–6.9 (m, 3 H); ^{13}C NMR (22.6 MHz, $CDCl_3$) 20.48, 21.39, 27.11, 29.78, 31.40, 42.71, 46.03, 46.29, 55.64, 60.13, 72.28, 109.39, 111.14, 122.26, 125.25, 135.65, 137.53, 147.21, 153.39, 170.74; MS calcd, m/z 345.194; found, 345.1935. Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.05. Found: C, 69.62; H, 7.92; N, 3.90. The single crystals grown from ethanol were monoclinic belonging to the space group $P21/c$. A single crystal was subjected to X-ray diffraction analysis and shown to have structure **14a**.[11]

(4a*R,5*R**)-4a-(2,3-Dimethoxyphenyl)-2,3,4,4a,5,6,7,8-octahydro-2-methyl-5-isoquinolinol Acetate (14b).** A solution of 1.00 g (2.34 mmol) of **13b** in 20 mL of acetonitrile was heated under reflux for 1 h in the presence of 1.0 g of potassium carbonate. The reaction mixture was cooled to room temperature, diluted with dichloromethane, and filtered. The filtrate was evaporated to give 0.74 g of a solid which was purified by chromatography over silica gel. Elution with a 9:1 mixture of hexane and acetone (v:v) containing 5% of triethylamine afforded 0.42 g (52% yield) of (4a*R**,5*R**)-4a-(2,3-dimethoxyphenyl)-2,3,4,4a,5,6,7,8-octahydro-2-methyl-5-isoquinolinol acetate (**14b**) which decomposes to a dark red material within 5 min at room temperature. A sample prepared in a similar experiment showed the following: IR (film) 2980, 1730, 1655, 1575 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) 1.91 (s, 3 H), 2.60 (s, 3 H), 3.76 (s, 3 H), 3.83 (s, 3 H), 5.36 (dd, J = 6, 3 Hz, 1 H), 5.8 (s, 1 H), 6.7–7.31 (m, 3 H).

(4a*R,5*S**,8a*S**)-4a-(2,3-Dimethoxyphenyl)-1,2,3,4,4a,5,6,7,8,8a-decahydro-2-methyl-5-isoquinolinol Acetate (15).** A solution of 1.2 g (3.46 mmol) of **14a** in 25 mL of anhydrous ethanol was hydrogenated over PtO_2 at a hydrogen pressure of 40 psi for 16 h. At the end of this period, the catalyst was filtered off and the solvent was removed under reduced pressure to afford 1.18 g (98%) of (4a*R**,5*S**,8a*S**)-4a-(2,3-dimethoxyphenyl)-1,2,3,4,4a,5,6,7,8,8a-decahydro-2-methyl-5-isoquinolinol acetate (**15**): mp 116–117 °C; IR (KBr) 2940, 1735, 1580 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) 2.13 (s, 3 H), 2.27 (s, 3 H), 3.8 (s, 3 H), 3.9 (s, 3 H), 5.8–5.9 (m, 1H), 6.8–7.5 (m, 2 H), 7.3 (dd, J = 9, 2 Hz, 1 H); ^{13}C NMR (22.6 MHz, $CDCl_3$) 20.09, 21.20, 26.53, 26.76, 32.90, 39.46, 44.98, 45.96, 52.33, 55.5, 58.24, 67.19, 72.28, 110.95, 121.54, 125.12, 134.74, 148.51, 153.91, 170.42; MS calcd, m/z 347.2096; found, 347.2065. Anal. Calcd for $C_{20}H_{29}NO_4$: C, 69.14; H, 8.41; N, 4.03. Found: C, 69.31; H, 8.55; N, 3.89.

9-Methoxy-3-methyl-2,3,4,4a*α*,5,6,7a*α*-octahydro-1*H*-benzofuro[3,2-*e*]isoquinoline (16). A solution of 1.4 g (4.03 mmol) of **15** in a mixture of 25 mL of dichloromethane and 2.5 mL of methanesulfonic acid was stirred at room temperature for 20 h and then heated at reflux for 6 h. The reaction mixture was diluted with dichloromethane and made basic with a solution of sodium carbonate. The aqueous layer was extracted with 3 × 50 mL of dichloromethane, and the organic layers were dried (K_2CO_3). Concentration under reduced pressure afforded 1.32 g of the product which was subjected to chromatography over silica gel. Fractions containing a total of 0.120 g of the desired product were collected (11%). The NMR of this sample was identical with the material prepared previously.[2]

2,3,5,6,7,7a*α*-Hexahydro-3-methyl-1*H*-benzofuro[3,2-*e*]isoquinolin-9-ol (17). A. From 14a. A solution of 0.345 g (1.00 mmol) of octahydroisoqinolinol acetate **14a** in 10 mL of dimethylformamide was treated with 0.38 g (5.00 mmol) of *n*-propyl mercaptan followed by 0.28 g (2.5 mmol) of potassium *tert*-butoxide. The reaction mixture was heated at a temperature of 140 to 150 °C for 3 h, cooled to room temperature, and all volatiles were removed under reduced pressure. The residue was suspended in a saturated solution of sodium carbonate and extracted with dichloromethane (3 × 25 mL). The organic layers were dried (K_2CO_3) and concentrated under reduced pressure. The residue was chromatographed to yield 0.245 g (95%) 2,3,5,6,7,7a*α*-hexahydro-3-methyl-1*H*-benzofuro[3,2-*e*]-isoquinolin-9-ol (12b*R**)-2,3,5,6,7,7a*α*-hexahydro-3-methyl-1*H*-benzofuro[3,2-*e*]isoquinolin-9-ol (**17**): IR (film) 2960, 1650, 1600 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) 2.6 (s, 3 H), 4.5 (dd, J = 9, 6 Hz, 1 H), 5.93 (s, 1 H), 6.66–6.83 (m, 3 H), 6.9 (s, 1 H); ^{13}C NMR (22.6 MHz, $CDCl_3$) 22.50, 29.06, 29.52, 36.67, 42.85, 45.89, 46.87, 90.93, 107.70, 115.56, 116.02, 120.89, 134.09, 137.73, 141.17, 144.55; MS calcd, m/z 257.1414; found, 257.1415. Anal. Calcd for $C_{16}H_{19}O_2N$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.39, H, 7.35; N, 5.48.

B. From 14b. A procedure as in **A** was used to produce, after chromatography, two fractions, both containing the desired material **17**[12] (combined yield 77%) as shown by IR, NMR, and MS. Both of the fractions were used in the next step.

2,3,4,4a*α*,5,6,7,7a*α*-Octahydro-3-methyl-1*H*-benzofuro[3,2-*e*]isoquinolin-9-ol (3). A. From 15. A solution of 47.00 g (0.136 mol) of **15** in 470 mL of dimethylformamide was treated with 51.79 g (0.664 mol) of *n*-propyl mercaptan followed by 52.31 g (0.467 mol) of potassium *tert*-butoxide. The mixture was heated under nitrogen atmosphere at 150–165 °C for 4.5 h and cooled to room temperature, and the volatile materials were removed under vacuum. The residue was suspended in 100 mL of water, and the suspension was acidified with 50 mL of concentrated hydrochloric acid and then extracted with 150 mL of toluene. The toluene layer was washed with 50 mL of 10% hydrochloric acid, and the combined aqueous layers were made basic with sodium carbonate solution. The resulting precipitate was collected by filtration, washed with 50 mL of water, and dried under reduced pressure for 16 h to yield 32.00 g (91%) of the desired material, mp 210–213 °C. This material was crystallized from ethanol: mp 220–222 °C; IR (KBr) 3420, 2920, 2850, 1600 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$) 1.3–1.6 (m, 5 H), 1.8–2.1 (m, 4 H), 2.4 (s, 3 H), 2.5–2.9 (m, 4 H), 4.43 (t, j = 6 Hz, 1 H), 5.96 (m, 1 H), 6.7–6.8 (m, 2 H), 6.9–7.1 (br, 1 H); ^{13}C NMR (22.6 MHz, $CDCl_3$) 20.14, 24.69, 28.40, 39.12, 39.31, 46.01, 48.61, 50.95, 57.32, 89.68, 115.22, 118.93, 120.10, 132.90, 141.87, 147.093; HRMS calcd, m/z 259.1572; found, 259.1571. This product was identical with the material prepared previously.[2]

B. From 17. A solution of 0.52 g (2.0 mmol) of the enamine **17** in 10 mL of ethanol was hydrogenated over 50 mg of PtO_2 at a hydrogen pressure of 40 psi for 48 h. An additional 50 mg of PtO_2 was added and the hydrogenation was continued for an additional 72 h. The mixture was filtered, and the solvent was removed under reduced pressure to afford 0.51 g of a brown oil which upon dilution with acetone deposited 0.32 g (62%) of **3**, mp 212–216 °C, identical by NMR with the material prepared previously.[2]

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Registry No. **3**, 87828-49-7; **4**, 82359-63-5; **6**, 89998-48-1; **8**, 89998-49-2; **9**, 87766-67-4; **11a**, 87766-69-6; **11a**·HCl, 87766-70-9; **11a** formate ester, 89998-50-5; **11b**, 87766-68-5; **11b** formate ester, 89998-51-6; **12a**, 87766-72-1; **12b**, 87766-73-2; **13a**, 87766-74-3; **13b**, 87766-75-4; **14a**, 87766-76-5; **14b**, 87766-77-6; **15**, 87766-78-7; **16**, 90079-79-1; **17**, 87766-80-1; $Cl(CH_2)_3C(O)OEt$, 3153-36-4; veratrole, 91-16-7; 1-methyl-4-piperidone, 1445-73-4; 3-(1-methyl-4-hydroxypiperidin-4-yl)veratrole, 82359-62-4; γ-butyrolactone, 96-48-0.

Supplementary Material Available: Full crystallographic information and tables listing selected bond distances, bond angles, and positional and thermal parameters (10 pages). Ordering information is given on any current masthead page.