Experimental Section

IR spectra were recorded on a JASCO A-3 spectrophotometer. ^{1}H NMR spectra were recorded on a JEOL JNM-FX 90 Q (90 MHz) spectrometer in $CDCl_3$, and chemical shifts are expressed in δ values relation to Me_4Si as internal standard. Coupling constants (J) are given in hertz. Mass spectra were obtained on a JEOL JMS-DX 300 instrument. GLPC analyses were performed on a JEOL JGC-20K instrument with a 10% SE-30 column (1 m × 3 mm). Microanalyses were performed by the Microanalytical Laboratory in this institute.

2-Isopropylcyclohexanone (3).[7] A mixture of 2-isopropylphenol (**2**) (3.0 g, 22 mmol) and Raney nickel (W-2, 0.5 mL, 300 mg)[18] in ethanol (15 mL) was hydrogenated (initial pressure of H_2 at 20 °C, 110 lb) in an externally heated stainless-steel autoclave at 100 °C for 4 h. The catalyst was removed by filtration through a pad of Celite, and the filtrate was diluted with ether and washed successively with 5% aqueous NaOH, water, and saturated brine. Evaporation of the solvent left an oil, an epimeric mixture of 2-isopropylcyclohexanols, which was submitted to the following oxidation without purification.

To a cold solution of the crude cyclohexanols in acetic acid (23 mL) was added a 10% aqueous sodium hypochlorite solution[8] (19.8 mL, 26.5 mmol) in an ice bath and the mixture was further stirred for 1.5 h in the cold. The reaction mixture was poured into cold water and extracted with ether. The ether extract was successively washed with aqueous $NaHCO_3$, aqueous $NaHSO_3$, water, and saturated brine. Removal of the solvent gave an oil, which was distilled under reduced pressure to give 3.01 g (97%) of **3**: bp 82 °C (12 mmHg) [lit.[7e] bp 90–98 °C (30 mmHg)]; IR (neat) 1708, 1370 cm^{-1}; ^{1}H NMR 0.89 (d, 6 H, J = 7), 1.2–2.4 (m, 10 H).

1-Hydroxy-*c*-2-isopropyl-*r*-1-cyclohexanecarbonitrile and Its 2-Epimer (4a and 4b). To a solution of **3** (362 mg, 2.58 mmol) in ethanol (3.6 mL) was added at 0 °C acetone cyanohydrin (1.65 mL, 18.2 mmol) and K_2CO_3 (107 mg, 0.77 mmol), and the mixture was further stirred at 0–10 °C for 18 h. The mixture was diluted with ether and washed with water and saturated brine. Removal of the solvent gave **4** as an isomeric mixture, which in general was submitted to the following ring expansion without separation. For characterization, however, these compounds were separated by flash column chromatography [silica gel, hexane–ethyl acetate (8:1) as solvent] to give 60 mg (14%) of **4b** and 340 mg (79%) of **4a** as an oil, respectively. **4a:** IR (neat) 3440, 2245, 1455, 1100, 1080, 1070 cm^{-1}; ^{1}H NMR 1.01 (d, 6 H, J = 7), 1.10–2.68 (m, 10 H), 2.9 (br s, 1 H, OH). **4b:** IR (neat) 3430, 2240, 1455, 1158, 978 cm^{-1}; ^{1}H NMR 1.01 (d, 6 H, J = 7), 1.05–2.45 (m, 10 H), 3.08 (s, 1 H, OH). Anal. Calcd for $C_{10}H_{17}NO$: C, 71.81; H, 10.25; N, 8.38. Found: C, 71.57; H, 9.95; N, 8.68.

3-Isopropylcycloheptanone (5) and 2-Isopropylcycloheptanone (6). A mixture of **4** (crude oil, 167 mg, 1 mmol) and platinum(IV) oxide (15 mg) in acetic acid (3 mL) was hydrogenated (initial hydrogen pressure, 8 lb) at room temperature until hydrogen uptake ceased (ca. 17 h). The catalyst was filtered off, and the filtrate was diluted with acetic acid (2 mL). A cold 10% aqueous solution of sodium nitrite (10.3 mL, 1.03 g) was added dropwise to the above amino alcohol solution in an ice bath, and the mixture was stirred for 3 h in the cold. Stirring was further continued for an additional 17 h at room temperature. The reaction mixture was partitioned between methylene chloride and water. The organic layer was successively washed with water, aqueous $NaHCO_3$, water, and saturated brine. Evaporation of the solvent left a volatile oil, whose GLPC showed two main peaks in a ratio of 97:3. Flash column chromatography (silica gel, CH_2Cl_2 as solvent) yielded **6**[4c] (8 mg, 5%) and **5** (103 mg, 68%) in 73% overall yield from **3**. **5:** IR (neat) 1700, 1460, 1445, 1368, 1258 cm^{-1}; ^{1}H NMR 0.88 (d, 6 H, J = 7), 1.0–2.2 (m, 8 H), 2.2–2.7 (br m, 4 H); MS, m/e 154 (M^+). Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.58; H, 11.55. **6**:[4c] ^{1}H NMR 0.88 (d, 6 H, J = 6), 1.0–2.7 (m, 12 H); MS, m/e 154 (M^+).

Deuteriation of 5. A solution of **5** (15 mg) in methanol-d_1 (0.5 mL) was added to a sodium methoxide solution prepared from sodium (20 mg) and methanol-d_1 (0.5 mL), and the mixture was refluxed for 1 h under argon. Deuterium oxide (3 drops) was added, and the solvent was removed. The residue was dissolved in ether and dried ($MgSO_4$). Evaporation of the solvent left an oil, which showed m/e 158 (M^+) in its mass spectrum.

4-Isopropylcycloheptane-1,2-dione (7). A mixture of **5** (123 mg, 0.80 mmol) and selenium dioxide (177 mg, 1.6 mmol) in 95% ethanol (0.8 mL) was stirred at 90 °C (bath temperature)[17] for 2 h. Precipitated selenium was filtered off, and the filtrate was diluted with ether (10 mL). The ethereal solution was washed with saturated brine and evaporated in vacuo to give oily **7** as a tautomeric mixture: IR (neat) 3465, 1715, 1065 cm^{-1}; ^{1}H NMR 0.84 and 0.92 (each d, 6 H in total, J = 7), 1.2-3.0 (m, 10 H). This dione was immediately submitted to the following reaction.

***β*-Thujaplicin (Hinokitiol) (1).** A mixture of **7** (the above crude oil, 0.80 mmol) and phenyltrimethylammonium tribromide[16] (752 mg, 2 mmol) in THF (10 mL) was stirred at room temperature for 1.75 h under nitrogen. The reaction mixture was poured into 0.1 M aqueous $Na_2S_2O_3$ and extracted with ether. The ethereal extract was washed with water and saturated brine, and dried ($MgSO_4$). After removal of the solvent, the residue of dibromo dione was dissolved in DMF (4 mL) and heated with dry LiCl (160 mg) and Li_2CO_3 (160 mg) at 120 °C for 45 min. The cooled reaction mixture was partitioned between ether and water, and the organic layer was extracted with 5% aqueous NaOH. The combined aqueous extracts were acidified with 10% HCl, and the acidic product was thoroughly extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water and saturated brine. Evaporation of the solvent gave **1** (80 mg, 61% overall yield from **5**). Both H_3PO_4-impregnated paper chromatography (benzene as solvent) and silica gel TLC [ether–hexane (5:1) as solvent] of the crude tropolone showed a single spot (detection by $FeCl_3$) whose R_f value was identical with that of authentic β-thujaplicin. Its spectra were also superimposable with those of the authentic specimen. None of the α-isomer was detected on H_3PO_4-impregnated paper chromatography.

The crude cycloheptanone **5** which contains 5% of **6** gave quite similar results by the same sequence of reactions, although a trace of α-thujaplicin was detected on TLC.

Acknowledgment. We thank Professors K. Takase and M. Yasunami (Tohoku University) for providing us with the authentic α-thujaplicin. We also acknowledge Professor T. Asao (Tohoku University) for kind discussions.

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Hofmann Degradation of β-Hydroxy Ammonium Salts. 2.[1] 4-Hydroxybenzylisoquinolines and 4-Hydroxyaporphines

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Introduction

The in vivo late-stage introduction of oxygen, often accompanying further structural modification in alkaloids, is thought to be involved in their subsequent degradation

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(3) Taken, in part, from the Ph.D. Thesis of A. B. Cardis, Temple University, 1977.

(4) Taken, in part, from the Ph.D. Thesis of J. K. Crelling, Temple University, 1977.

(5) Taken, in part, from the Ph.D. Thesis of S. I. Miller, Temple University, 1971.

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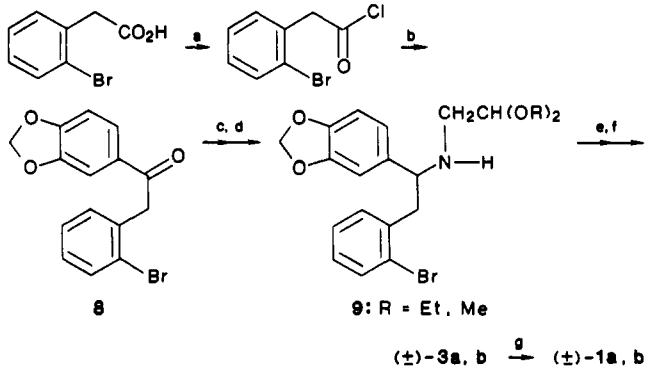
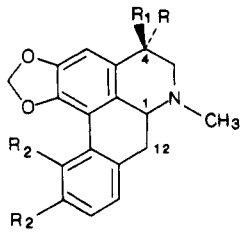
Scheme I. The Preparation of the Racemic Enantiomers of 3a,b and 1a,b[a]

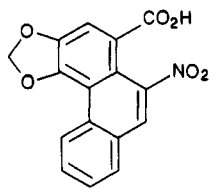


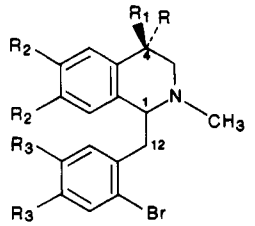
[a] (a) $SOCl_2$; (b) (methylenedioxy)benzene, anhydrous stannic chloride; (c) aminoacetaldehyde diethyl acetal or dimethyl acetal, toluene; (d) sodium borohydride, methanol; (e) HOOCH, formaldehyde, DMF; (f) 6 N HCl, CH_3CN; (g) photolysis, Corex filter, 450-W Hanovia lamp.

or rearrangement.[6,7] For example, 4-hydroxyaporphines, e.g., **1a,b**, have been postulated as potential intermediates



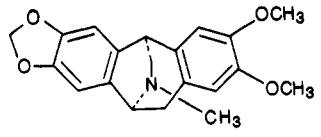
1a: R = OH; R_1, R_2 = H
1b: R_1 = OH; R, R_2 = H
1c: R, R_1 = H; R_2 = OCH_3





3a: R = OH; R_1, R_3 = H; R_2 = OCH_2O
3b: R_1 = OH; R, R_3 = H; R_2 = OCH_2O
3c: R, R_1 = H; OH; R_2 = OCH_2O; R_3 = OCH_3; Br = H
3d: R, R_1 = H; OH, R_2, R_3 = OCH_3; Br = H
3e: R, R_1 = H; R_2, R_3 = OCH_3; Br = H

in the biosynthesis of aristolochic acids, e.g., aristolochic acid II (**2**),[8] and 4-hydroxytetrahydroisoquinolines, e.g., **3c,d**, or species in the same oxidation state may lie along the path from tetrahydroisoquinolines to the isopavines, e.g., (−)-amurensinine (**4**) and the pavines, e.g., (−)-argemonine (**5**).[9] While it does not appear that any 4-hydroxylated tetrahydroisoquinolines themselves have been isolated from plant sources, at least nine 4-hydroxyaporphines have and several, including (±)-stepporphine (**1a**), have been synthesized.[10]



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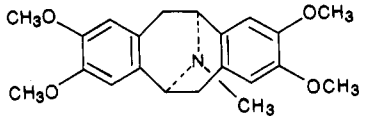
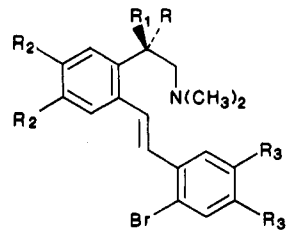
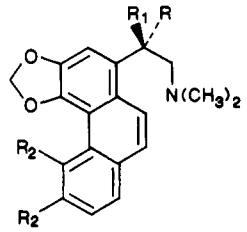


5

As expected for benzylisoquinoline and aporphine alkaloids *lacking* a β-hydroxyl, e.g., laudanosine (**3e**) and *O*-methylbulbocapnine (**1c**), respectively, Hofmann degradation of the corresponding methiodides generates the corresponding stilbenes and phenanthrenes, e.g., **6a** [both the *E* (major) and *Z* (minor) isomers] and **7a**, respectively.[11,12] However, since both the 4-hydroxytetrahydroisoquinolines and the 4-hydroxyaporphines possess an oxygen β to nitrogen they could, in principle, undergo Hofmann elimination with formation of either epoxides or ketones as an early step in their oxidative elaboration.[1,13,14] Interestingly, for other similarly constituted β-hydroxy amines, when the quaternary nitrogen is part of the ring, laboratory experience does not support this speculation; Hofmann elimination not involving the oxygen, unusual cleavage reactions, dehydration, and/or oxidation occurs instead.[1]



6a: R, R_1 = H; R_2, R_3 = OCH_3; Br = H
6b: R, R_1 = H; OH; R_2, R_3 = H



7a: R, R_1 = H; R_2 = OCH_3
7b: R, R_1 = H; OH; R_2 = H

As the 4-hydroxytetrahydroisoquinoline and 4-hydroxyaporphine bases had not been investigated in this regard, we undertook Hofmann elimination of their respective quaternary methiodides to test laboratory emulation of the biogenetic speculations and to complete our examination of the series of such bases.[1]

Methods

(A) Preparation of the Racemic Amines 1a,b and 3a,b. (i) The C-4 Epimers of Racemic 1-(*o*-Bromobenzyl)-4-hydroxy-2-methyl-6,7-(methylenedioxy)-1,2,3,4-tetrahydroisoquinoline (3a,b). The racemic amines **3a,b** were prepared by a modification of previously reported work.[10,15] *o*-Bromophenylacetyl chloride, under very carefully controlled Friedel–Crafts conditions gave the ketone **8** on reaction with (methylenedioxy)benzene (51%, Scheme I). This ketone, typical of its kind, reacted only sluggishly with aminoacetaldehyde diethyl (or dimethyl) acetal and the imine thus formed was reduced directly with sodium borohydride in methanol to the amine

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Table I. A Comparison of Torsional Angles around the Carbon-Carbon Bonds Across Which Elimination Might Be Expected To Occur in the Bases Listed

bond	angle, deg (±)-3a	(±)-3b	(±)-1a
H-C4-C3-N	77	153	168
O-C4-C3-N	163	90	83
H-C1-C12-N	53	79	60
H-C1-C12-N	167	38	68

9 (65% for the two steps). Eschweiler–Clarke methylation[16] (95%) followed by Bobbitt cyclization[17] gave, in contrast to earlier work[10] a 60:40 mixture of racemic **3a**/**3b** (70% total). The assignment of structure (based on ^{1}H NMR) was confirmed by x-ray crystallographic analysis (see supplementary material).

(ii) Racemic Steporphine (1a) and Its Racemic C-4 Epimer (1b). Each of the separated racemic isomers **3a** and **3b** was photolytically converted to the corresponding aporphine in 3% aqueous hydrochloric acid containing some methanol. Racemic **3a** yielded (±)-steporphine (**1a**, 20%) and racemic **3b** yielded the C-4 epimer of (±)-steporphine, racemic **1b** (34%).

B. Hofmann Degradation. (i) The C-4 Epimers of Racemic 1-(*o*-Bromobenzyl)-4-hydroxy-2-methyl-6,7-(methylenedioxy)-1,2,3,4-tetrahydroisoquinoline (3a,b). Each of the racemic amines **3a** and **3b** was converted to its respective methiodide with iodomethane in acetone. Each of the racemic methiodides was suspended in 10% aqueous sodium hydroxide and the suspension heated at reflux for 10 h. Each gave the same racemic (*E*)-stilbene **6b**.

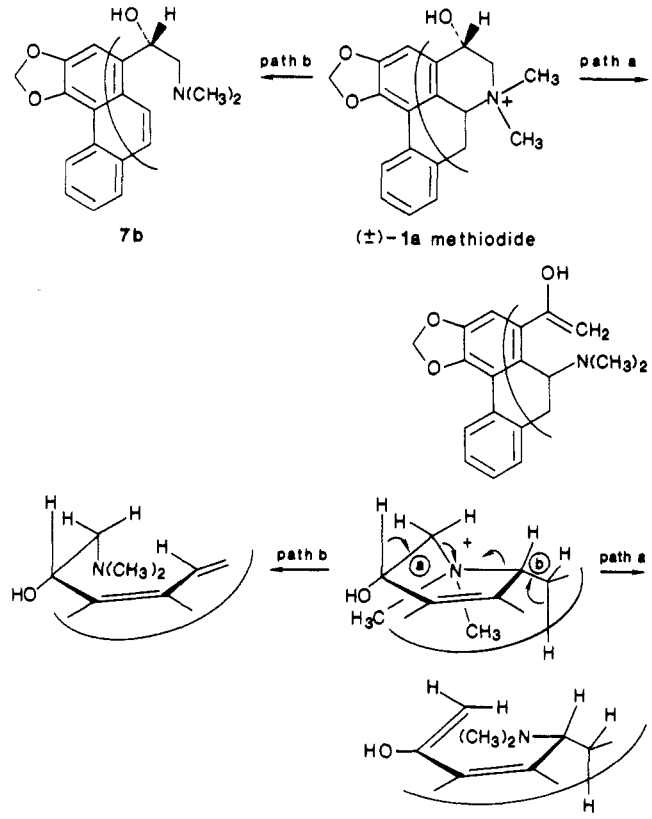
(ii) Racemic Steporphine (1a) and Its Racemic C-4 Epimer (1b). Each of the racemic amines **1a** and **1b** was converted to its respective racemic methiodide and, as above, suspended in 10% aqueous sodium hydroxide and heated at reflux for 10 h. Each gave the same racemic phenanthrene **7b** (95–96% of theory).

Discussion

As described above, both of the racemic 1-benzyl-4-hydroxy-2-methyl-1,2,3,4-tetrahydroisoquinolines **3a** and **3b**, the former with the benzyl and hydroxyl groups cis (or Z) and the latter with the same groups trans (or E), yield only (*E*)-stilbene on further methylation and Hofmann degradation. Similarly, the corresponding epimeric 4-hydroxyaporphines yield only the phenanthrene **7b**. Neither yields epoxide nor (enol leading to) ketone.

X-ray crystallographic data[18] are summarized in Table I for the angles about which elimination has occurred. The structure solution of (±)-**1b** is incomplete because portions of the molecule appear to be disordered over several positions. Despite the more-or-less well established preference for either anti or syn coplanarity[19] in elimination reactions and keeping in mind the usual caveats concerning solution conformations not necessarily being similar to those in the crystalline state and the effect of nitrogen substitution on the conformations available to the 1-benzyl substituent in the methiodides of **3a** and **3b**[20] it is, nevertheless, noteworthy that only the phenanthrene

Scheme II. Idealized Representations of (±)-1a (Based on Single-Crystal X-ray Analysis) and the Products of Hofmann Elimination Generating Enol (Path a) and Phenanthrene (Path b)[a]



[a] Only phenanthrene **7b** is obtained.

7b results from the methiodides **1a,b** where solution conformers cannot differ dramatically from what is found in the solid state. As indicated in Table I and as shown in Scheme II. Hofmann elimination from **1a** involving the quaternary nitrogen and the hydrogen at C-4 via path a (where a 168° dihedral angle is subtended) is *not* preferred over the path (path b) utilizing one of the two benzylic hydrogens at C-12, where the angles between nitrogen and the hydrogens are 60° and 68°.

We suggest, therefore, that formation of carbanions which do not lie on the traditional E2[21] pathway provide phenanthrene (or, indeed, (*E*)-stilbene) either because the (benzylic) carbanion geometry differs markedly from the undeprotonated ground state or because of a dramatically lower energy barrier leading to an aromatic system.

Experimental Section[22]

***β*-(*o*-Bromophenyl)-3,4-(methylenedioxy)acetophenone (8).** To a solution of (methylenedioxy)benzene (1,3-benzodioxole, 1.22 g, 10 mmol) in dry dichloromethane (50 mL) cooled to 0 °C with an ice–salt bath was added anhydrous stannic chloride (1.53 mL). The solution was stirred for a few minutes under an atmosphere of nitrogen, while a pressure-equilibrated dropping funnel containing a solution of the acid chloride of 2-bromophenylacetic acid

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(18) Information provided in the supplementary material.
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(21) (a) Breslow, R. *Tetrahedron Lett.* **1964**, 399. (b) Saunders, W. H. *Acc. Chem. Res.* **1976**, *9*, 19.
(22) Infrared spectra were recorded on a Beckman IR 5A or a Perkin-Elmer 227 infrared spectrophotometer. NMR spectra were taken in $^2HCCl_3$ for ^{1}H on a Perkin-Elmer R-32 and for ^{13}C on Varian XL-100-15 spectrometers and values are reported as ppm (δ) from tetramethylsilane (Me_4Si): s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra were obtained on an Hitachi RMU6H spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN, or Schwarzkopf Microanalytical Laboratory, Woodside, NY. Melting points are uncorrected.

(prepared from 2.0 g, 9.2 mmol of acid) in dichloromethane (50 mL) was put in place. The addition of the acid chloride was effected over a period of 1 h while the temperature of the reaction mixture was maintained at 0 °C. Stirring was continued for an additional 24 h, while the temperature of the reaction mixture gradually rose to ambient. Concentrated HCl (10 mL) was added to the stirred reaction mixture over 30 min and stirring continued for an additional 24 h. The reaction mixture was diluted with fresh dichloromethane to a total volume of 150 mL, washed with water (1 × 150 mL), 10% aqueous NaOH (3 × 300 mL), and water (2 × 300 mL), dried over anhydrous potassium carbonate, and filtered through a plug of glass wool and the solvent removed at reduced pressure to yield a tan solid. The solid was chromatographed on silica gel (Woelm, Activity I, 200 g) using a column 3 cm in diameter, with chloroform as eluent. The product (8) was a pale yellow solid (1.5 g, 4.7 mmol, 51%, mp 94–95 °C). Anal. Calcd for $C_{15}H_{11}O_3Br$: C, 56.43; H, 3.45; Br, 25.08. Found: C, 56.73; H, 3.41; Br, 24.97. Recrystallization is best effected from cyclohexane: IR λ_{max} 1680 cm^{-1} (C=O); ^1H NMR δ 4.3 (2 H, s), 5.9 (2 H, s), 6.8–7.6 (7 H, m); ^{13}C NMR δ 194.0 (C=O), 151.8, 148.2, 135.3, 132.6, 128.4, 127.3, 124.4, 107.8, 101.8 (OCH_2O), 45.3 (CH_2).

[*N*-(1-(3,4-(Methylenedioxy)phenyl)-2-(2-bromophenyl)-ethyl)amino]acetaldehyde Diethyl Acetal (9, R = Et). The ketone 8 (3.2 g, 10 mmol) was dissolved in dry toluene (40 mL), and the solution was degassed by bubbling dry nitrogen through it for 15 min. Activated molecular sieves (Linde type 5A, 40 g) were added together with excess aminoacetaldehyde diethyl acetal (3.7 g, 4.0 mL, 27.5 mmol). The reaction mixture was heated just below the reflux temperature under an atmosphere of nitrogen for 2 weeks. After the reaction mixture was cooled to room temperature and while the nitrogen atmosphere was maintained, the mixture was rapidly filtered through a thin Celite mat into a flask containing methanol (50 mL) and excess sodium borohydride (1 g, 26 mmol). Additional fresh methanol (50 mL) was used to wash the sieves and Celite, and after being stirred overnight, the reaction mixture was acidified with 10% aqueous HCl (pH ca. 6). The two-phase reaction mixture was transferred to a separatory funnel and washed with ether (2 × 50 mL). The aqueous layer was basified with 10% aqueous NaOH and the basic solution extracted with ether (3 × 50 mL). The combined ether extracts were washed with water (2 × 75 mL), dried over anhydrous potassium carbonate, filtered through a plug of glass wool, and evaporated under reduced pressure to yield a brown gum that was subsequently chromatographed on neutral alumina (200 g, Woelm Activity III) using a column whose dimensions were 3 × 48 cm with benzene as eluent. The oily amine (2.8 g, 65 mmol, 65% of theory) could not be induced to crystallize. **9**: mass spectrum, *m/e* 434 and 436 ($M^+ - 1$); IR λ_{max} 3400, 3330, 1480, 1425 cm^{-1}; ^1H NMR δ 1.1 (6 H, t), 1.7 (1 H, s), 2.5 (2 H, d), 3.3–3.6 (4 H, m), 3.9 (1 H, t), 5.8 (2 H, s), 6.7–7.5 (7 H, m). The hydrobromide salt **9**·HBr (R = Me) was prepared as above by using aminoacetaldehyde dimethyl acetal and treating a solution of the amine product in methanol with 1 equiv of 48% hydrobromic acid. The hydrobromide was recrystallized from methanol, mp 135 °C. Anal. Calcd for $C_{19}H_{23}NO_4Br_2$: C, 46.63; H, 4.70; N, 2.86. Found: C, 46.62; H, 4.50; N, 2.90.

Eschweiler–Clarke Methylation of 9.[16] To a cooled solution of **9** (1.0 g, 2.3 mmol) in dry dimethylformamide (10 mL) was added formic acid (88%, 0.26 mL) and formaldehyde (37%, 0.2 mL). The reaction mixture was heated on a steam bath for 2.5 h, allowed to cool to room temperature, and made basic with 20% aqueous NaOH (ca. 50 mL). The aqueous solution was extracted with ether (3 × 50 mL) and dried over anhydrous potassium carbonate and the ether removed under reduced pressure to give a brown oil, which was chromtographed on neutral alumina (40 g, Woelm Activity Grade III, 3 cm diameter column). Elution with 9:1 (v/v) cyclohexane/ethyl acetate yielded the *N*-methyl derivative (0.98 g, 2.2 mmol, 95% of theory): ^1H NMR δ 1.1 (6 H, t), 2.3 (3 H, s), 2.6 (2 H, d), 2.9 (2 H, m), 3.3–3.6 (4 H, m), 3.9 (1 H, t), 4.5 (1 H, t), 5.8 (2 H, s), 6.6–7.5 (7 H, m). This material was not characterized further but was used directly in the preparation of the tetrahydroisoquinoline as described below.

The Racemic C-4 Epimers of 1-(*o*-Bromobenzyl)-4-hydroxy-2-methyl-6,7-(methylenedioxy)-1,2,3,4-tetrahydroisoquinoline (3a,b). The Bobbitt Cyclization.[17] The *N*-methyl derivative obtained above via the Eschweiler–Clarke method (0.5 g, 1.1 mmol) was dissolved in acetonitrile (2.5 mL) and the solution cooled to 0 °C. Ice-cold 6 N HCl (5.5 mL) was added and the reaction mixture stirred for 1 h at 0 °C and then for 14 h at ambient. The reaction mixture was concentrated in vacuo *without heating*. Cold concentrated ammonium hydroxide (20 mL) was added and the reaction mixture extracted with chloroform (3 × 25 mL). The combined chloroform extracts were washed with water (3 × 25 mL), dried over anhydrous potassium carbonate, filtered through a plug of glass wool, and evaporated under reduced pressure to give a brown residue. Flash chromatography [silica gel, ethyl acetate/cyclohexane (9:1, v/v)] yielded 0.18 g of **3a** closely followed by 0.12 g of **3b**. The total yield was 70% of theory. **3a**: mp 134–135 °C (methanol) (lit.[10] mp 134–135 °C); ^1H NMR δ 2.5 (3 H, s), 4.5 (1 H, t), 5.8 (2 H, s), 6.2 (1 H, s), 6.8–75 (5 H, m). The X-ray crystal structure is given in the supplementary material. **3b**: mp 114–115 °C (methanol); ^1H NMR δ 2.5 (3 H, s), 4.5 (1 H, t), 5.6 (1 H, s), 5.8 (2 H, s), 6.8–7.5 (5 H, m). Anal. Calcd for $C_{18}H_{18}O_3NBr$: C, 57.45; H, 4.79. Found: C, 57.54; H, 4.77. The X-ray structure of **3b** is given in the supplementary material.

Racemic Steporphine (1a) and Its Racemic C-4 Epimer (1b). The separated racemic C-4 epimers **3a** and **3b** were converted to the racemic aporphines **1a** and **1b**, respectively, in an identical fashion. For **3a** (or **3b**), 0.2 g (0.53 mmol) of the base was dissolved in methanol (15 mL), 3% aqueous HCl (350 mL) was added, and the solution was irradiated for 1 h with a 450-W Hanovia type lamp using a Corex filter. The resulting yellow reaction mixture was made basic with ice-cold ammonium hydroxide and extracted continuously with ether. After 24 h, the cooled ether extract was dried over anhydrous potassium carbonate and filtered through a plug of glass wool and the solvent removed under reduced pressure to yield a brown gum. Preparative thin-layer chromatography (silica gel, 1000 μm) with ethyl acetate as eluent generated three mobile bands. The fastest moving band from the photolysis of **3a** (R_f 1.0, 53 mg) consisted of a complex mixture of as yet unidentified materials. The second band (R_f 0.46, 26 mg) contained unreacted starting material, **3a**. The third band (R_f 0.25, 27 mg) was the desired steporphine, (±)-**1a** (20% of theory based on recovered starting material), mp 172–173 °C (lit.[10] mp 172–173 °C). Spectroscopic data were identical with those reported.[23] The X-ray crystal structure of **1a** as the methiodide salt is given in the supplementary material. The fastest moving band from the photolysis of **3b** (R_f 1.0, 54 mg) was comparable to the material obtained from **3a**. The second band (R_f 0.37, 22 mg) contained unreacted starting material, **3b**. The third band (R_f 0.18, 47 mg) was the desired C-4 epimer of steporphine, (±)-**1b** (34% of theory, based on recovered starting material) as a waxy solid: mp 135–136 °C; IR (KBr) 3340, 1350, 1050, 940 cm^{-1}; ^1H NMR δ 2.5 (3 H, s), 4.9 (1 H, t), 5.95 and 6.05 (2 H, 2 d), 7.0 (1 H, s), 7.2–8.1 (4 H, m); ^{13}C NMR (undecoupled) δ 147.2 (s), 143.5 (s), 135.2 (s), 131.0, 130.8, 128.1, 127.6, 126.9, 115.9 (s), 105.3 (d), 100.8 (OCH_2O, t), 66.4 (d, C-4), 62.2 (d, C-1), 61.6 (t, C-3), 43.0 (q, NCH_3), 34.3 (t, C-12); MS, *m/e* 295 (M^+). For the methiodide, mp 235–236 °C dec: Anal. Calcd for $C_{19}H_{20}O_3NI$: C, 52.17; H, 4.58. Found: C, 51.96; H, 4.50. Crystals suitable for X-ray analysis could not be obtained as significant disorder was evident.

Hofmann Degradation of the Racemic C-4 Epimers of 1-(*o*-Bromobenzyl)-4-hydroxy-2-methyl-6,7-(methylenedioxy)-1,2,3,4-tetrahydroisoquinoline (3a,b). The racemic C-4 epimers **3a** and **3b** were each, individually, converted to their corresponding methiodides with excess methyl iodide in acetone at reflux. From **3a**, the methiodide had mp 230–231 °C dec, and from **3b**, the methiodide had mp 205–207 °C dec. Recrystallization was effected from benzene–ethanol. The respective methiodides (500 mg, 0.97 mmol) were suspended in 10% aqueous NaOH (25 mL) and the suspension heated at reflux for 10 h, by which time all of the solid initially present had disappeared and had been replaced by an oil on the surface of the aqueous solution. After the mixture was cooled, additional water (20 mL) was added and the aqueous suspension extracted with chloroform (4 × 25 mL). The combined chloroform extracts were dried over potassium carbonate and filtered and the solvent removed at reduced

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pressure to give a pale yellow oil, which was purified by passing it through a small silica gel column (Woelm Activity I) in 10% MeOH/$CHCl_3$ (v/v) to yield 343 g (91%) of **6a**: ^1H NMR δ 2.3 (6 H, s), 4.2 (1 H, s), 5.1 (1 H, t), 5.9 (2 H, s), 6.9-7.6 (8 H, m); ^{13}C NMR (undecoupled) δ 45.3 (q, NCH_3), 66.4 (t, CH_2N), 66.7 (d, COH), 101.0 (t, OCH_2O), 106.1 (d, CH=), 106.3 (d, CH=), 123.8, 126.4, 127.9, 128.4, 133.0, 134.6, 137.3, 147.0, 147.9; IR (neat) 3330, 1470, 1240 cm^{-1}; MS, *m/e* 389 and 391 (M^+). Anal. [as HCl salt (mp 228-229 °C dec and 240-241 °C dec; polymorphs] Calcd for $C_{19}H_{21}O_3NBrCl$: C, 53.46; H, 4.92. Found: C, 53.29; H, 4.70.

Hofmann Degradation of Racemic Steporphine (1a) and Its Racemic C-4 Epimer (1b). The racemic C-4 epimers (±)-**1** and (±)-**1b** were each, individually, converted to their corresponding methiodides with excess methyl iodide in acetone at reflux. From (±)-**1a**, the racemic methiodide had mp 249-250 °C dec, and from (±)-**1b**, the methiodide had mp 235-236 °C dec. Recrystallization was effected from benzene-ethanol. The respective racemic methiodides (65 mg, 0.22 mmol) were suspended in 10% aqueous NaOH (25 mL), and the respective suspensions were heated at reflux for 10 h, during which the suspended material disappeared and was replaced by a white precipitate, which was collected from the cool solution by such filtration and repeatedly washed with distilled water until the washings were no longer basic to litmus. The precipitate was dried, in vacuum, at 80 °C for 14 h to yield 52 mg, 0.17 mmol (94% of theory), of **7b**: mp 130-131 °C (ethanol) IR (KBr) 3330, 2850, 1600, 1450 cm^{-1}; ^1H NMR δ 2.3 (6 H, s), 4.8 (1 H, s), 5.5 (1 H, t), 6.1 (2 H, s), 7.2-9.0 (7 H, m); ^{13}C NMR (undecoupled) δ 45.9 (q, NCH_3), 67.7 (t, CH_2N), 67.9 (d, HCOH), 102.2 (t, OCH_2O), 108.2 (d), 117.4, 123.0, 125.7, 125.8, 127.1, 127.7, 128.1, 128.6, 132.9, 135.3, 143.5, 146.6; MS, *m/e* 309 (M^+). Anal. Calcd for $C_{19}H_{19}O_{13}N$: C, 73.79; H, 6.15. Found: C, 74.00; H, 6.04.

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Supplementary Material Available: ORTEP drawings, details of the X-ray crystallographic procedures, and atomic coordinates for racemic steporphine methiodide, (±)-**1a**, and for the C-4 epimers of racemic 1-(*o*-bromobenzyl)-4-hydroxy-2-methyl-6,7-(methylenedioxy)-1,2,3,4-tetrahydroisoquinoline, (±)-**3a** and (±)-**3b** (13 pages). Ordering information is given on any current masthead page.

Enzymatic Routes to Enantiomerically Enriched 1-Butene Oxide[1]

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This paper compares several routes to enantiomerically enriched 1-butene oxide (**1**) in which resolution is achieved by using an enzymatic reaction (Scheme I). This research had two objectives: to enumerate several general strategies that can be followed in practical, enzyme-based routes to enantiomerically enriched epoxides and to compare the utility of these routes in the particular case of compound **1**. In general, we restrict our account to reactions that proceed with high values of enantiomeric excess (ee) and that have the potential for preparing 50-g quantities of product. Enantiomerically enriched epoxides are useful synthons in chiral synthesis. General routes are now available to only epoxy alcohols and analogues of these substances.[2,3]

All reactions were conducted on scales that generated 1-5 g of **1** as product. The chemical yields reported in Scheme I are *overall* yields for conversion of the substrate for the enzymatic reaction to **1**; these yields are not optimized. We established the optical purity of **1** by ^1H NMR analysis in the presence of $Eu(hfc)_3$.[4] With careful calibration, this method can detect a 1% enantiomeric impurity (i.e., 98% ee).

Acylase I (EC 3.5.1.14) is commercially available, inexpensive, and stable. It hydrolyzes a range of *N*-acyl-α-amino acids with high (>99% ee) enantioselectivity.[5] Both enantiomers are easily recovered, and the reaction can be run virtually to completion. In resolutions of 2-aminobutanoic acid, the reaction stops spontaneously after hydrolysis of the *S* enantiomer is complete, and losses of material occur entirely in the recovery and purification of product. Conversion of the 2-amino acid via the corresponding 2-chloro acid and chlorohydrin to the epoxide preserves chirality well.[6]

Lipase (porcine pancreas, EC 3.1.1.3) and **cholesterol esterase** (CE, EC 3.1.1.13) are broad-specificity enzymes showing substrate-dependent enantioselectivity.[3,7] For the hydrolysis of 2-bromobutyl butyrate, without extensive optimization, the best ee was obtained with CE and was 80% at 77% conversion of the racemic starting material. Although this number could, in principle, be improved by carrying the reaction to higher conversion, and probably also by varying temperature and pH, we have not done so since alternative procedures seemed preferable. We note, however, that high values of ee can be obtained in kinetic resolutions of other halohydrins (e.g. 2-bromopropyl butyrate: ≥98% ee at 60% conversion) and that this method provides a good route to certain optically active epoxides.

L-**Lactate dehydrogenase** (L-LDH, EC 1.1.1.27) and D-**lactate dehydrogenase** (D-LDH, EC 1.1.1.28) are both highly enantioselective.[8] The L enzyme accepts a broad range of small and medium-size unhindered α-keto acids; the D enzyme is more restrictive toward its substrates.[9] The LDH enzymes are interesting in asymmetric synthesis because they comprise one of the few systems in which enzymes catalyzing reactions having opposite enantioselectivities are both commercially available. Unfortunately, the range of products available by this method in both D and L forms is limited by the range of substrates accepted by both enzymes. The LDH-catalyzed reactions (coupled with formate/formate dehydrogenase (FDH) for in situ regeneration of NADH[10]) can be run to completion with high enantioselectivities (>99% ee) and good isolated yields (84-99%).

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