# A Novel Straightforward Synthesis of Enantiopure Tetrahydroisoquinoline Alkaloids

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A novel, direct, and high-yielding stereoselective method for enantiopure 1-substituted tetrahydroisoquinolines (THIQ) is described. The successful approach, which creates the stereocenter during the formation of the THIQ nucleus is based on (i) formation of chiral 2,3-substituted perhydro-1,3-benzoxazines derived from (−)-8-aminomenthol, (ii) diastereoselective intramolecular ring opening of the *N*,*O*-acetal moiety by an arylmetal generated from the substituent at the nitrogen atom in the perhydrobenzoxazine ring, and (iii) removal of the chiral auxiliary appendage. The starting perhydrobenzoxazines are easily prepared from (−)-8-aminomenthol and two different aldehydes, and the intramolecular opening is stereospecific, leading to a single stereoisomer. The method allows the preparation of a wide variety of enantiopure 1-substituted THIQ, with different substituents at C-1, by changing the nature of the starting aldehydes.

## Introduction

1,2,3,4-Tetrahydroisoquinolines (THIQ), specially 1-substituted-THIQ, are compounds of great interest due to their biological and pharmacological properties. For instance, 1-methyl- and 1-phenyl-THIQ are involved in the treatment of Parkinson's and other nervous diseases,[1] and derivatives with alkoxy substituents at the aromatic rings comprise the widest group of naturally occurring alkaloids. Preparation of these compounds has received much attention, especially efforts directed to the enantioselective synthesis.[2] The most remarkable synthetic methods are the Pictet−Spengler cyclization,[3] the reduction of 3,4-dihydroisoquinolines,[4] the Pomeranz−Fristch reaction,[5] and more recently, α-alkylation of chiral formamidines,[6] organolithium additions to imines followed by condensation,[7] and metal-catalyzed cyclization reactions.[8] These methods allow the synthesis of enantiopure 1-substituted-THIQ in two steps: cyclization and creation of the stereocenter, although only the Pictet−Spengler reaction creates the stereogenic carbon at C-1 simultaneous with the ring closure.

We have recently reported[9] that the diastereoselective ring opening of the *N*,*O*-acetal moiety in perhydrobenzoxazines derived from (−)-8-aminomenthol affords enantiopure amines. In this way, the perhydrobenzoxazine acts as chiral inductor and as a source of the nitrogen atom, and both the stereochemistry of the final amines and the stereochemical course of the reactions depend on the nature of the organometallic nucleophile.

These facts intrigued us to develop a novel, direct way to enantiopure 1-substituted THIQ, including some alkaloids, by diastereoselective intramolecular ring opening of perhydrobenzoxazines derived from (−)-8-aminomenthol. THIQ could be prepared from 2-substituted perhydro-1,3-benzoxazines bearing the aryl group attached to the nitrogen through an ethylene tether. The saturated heterocycle of the THIQ nucleus could be created by intramolecular nucleophilic attack of the *o*-arylmetal to C-2, while the stereochemistry and the nature of the substituent at C-1 in the final heterocycle were determined by the stereochemical outcome of the reaction and the nature of the substituent at C-2 in the starting perhydrobenzoxazine (Figure 1).

This strategy afforded different enantiopure 1-substituted THIQ simply by changing both the nature of the aryl nucleus on the substituent at the nitrogen atom, and the substituent at C-2 of the initial chiral *N*,*O*-acetal.

## Results and Discussion

The preparation of the starting perhydrobenzoxazines **7a**,**b** and **8a**−**f** was carried out in three steps in 82−90% overall yield as shown in Scheme 1. Condensation of (−)-8-aminomenthol with 2-bromophenylacetaldehyde (**1**) or 2-bromo-4,5-dimethoxyphenyl acetaldehyde (**2**), in me-

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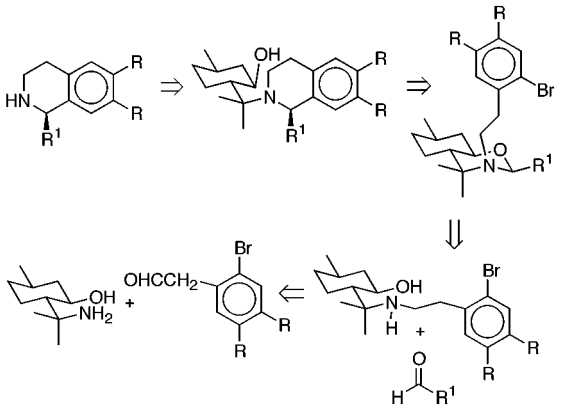
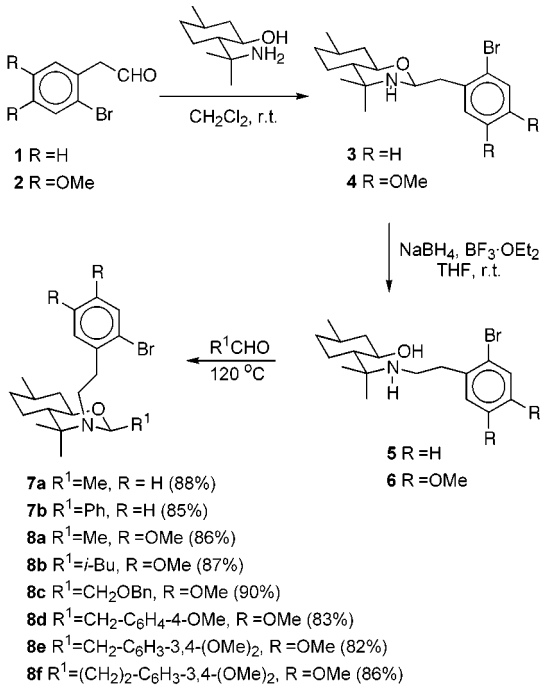


**Figure 1.**

**Scheme 1**




thylene chloride at rt afforded quantitatively perhydrobenzoxazines **3** or **4**, respectively. These compounds were transformed into phenethylaminomenthols **5** or **6** by reduction[10] with sodium borohydride and boron trifluoride etherate in THF at rt. Perhydrobenzoxazines **7a**,**b** and **8a**−**f** were obtained in excellent overall yields by heating, in a sealed tube at 120 °C, a mixture of **5** or **6** with the corresponding aldehyde, prepared by homologation[11] of benzaldehyde derivatives or by oxidation[12] of the corresponding alcohols with PCC.

The formation of the arylmetal was tested by treatment of **7a** with *t*-BuLi (2.2 equiv) in dry, degassed diethyl ether at −90 °C and then warming the reaction mixture to rt. Under these conditions, the debromination product **H-7a** was detected as the only product, indicating that the aryllithium intermediate was formed but the intramolecular ring opening did not take place[13] even after stirring at rt for 24 h. Then, we turned our attention to

**Scheme 2**

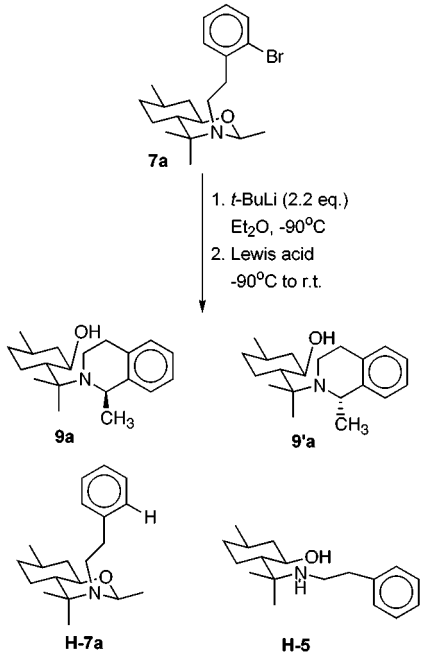



**Table 1. Stereoselective Intramolecular Ring Opening of Perhydrobenzoxazines 7and 8**

| entry | compd | Lewis acid (equiv) | products (ratio)[a] | yield, % |
|---|---|---|---|---|
| 1 | **7a** | none | **H-7a** | 100[b] |
| 2 | **7a** | $ZnCl_2$ (2) | **H-7a** | 100[b] |
| 3 | **7a** | $BF_3{\cdot}OEt_2$ (1) | **H-5** | 100[b] |
| 4 | **7a** | $BF_3{\cdot}OEt_2$ (2) | **H-5** | 100[b] |
| 5 | **7a** | $MgBr_2{\cdot}OEt_2$ (1) | **H-7a** (40) **9a** (48) **9′a** (12) | 100[b] |
| 6 | **7a** | $MgBr_2{\cdot}OEt_2$ (2) | **H-7a** (25) **9a** (60) **9′a** (15) | 100[b] |
| 7 | **7a** | $Et_2AlCl$ (2) | **9a** | 80[c] |
| 8 | **7b** | $Et_2AlCl$ (2) | **9b** | 78[c] |
| 9 | **8a** | $Et_2AlCl$ (2) | **10a** | 83[c] |
| 10 | **8b** | $Et_2AlCl$ (2) | **10b** | 83[c] |
| 11 | **8c** | $Et_2AlCl$ (2) | **10c** | 77[c] |
| 12 | **8d** | $Et_2AlCl$ (2) | **10d** | 81[c] |
| 13 | **8e** | $Et_2AlCl$ (2) | **10e** | 79[c] |
| 14 | **8f** | $Et_2AlCl$ (1) | **10f** | 77[c] |

[a] Determined by integration of the $^1H$ NMR signals in the crude reaction. [b] The referred compounds were the only detected by $^1H$ NMR in the crude of the reaction. [c] Yield of isolated pure product after flash chromatography.

probe other arylmetals prepared from the intermediate aryllithium by transmetalation. To this end, **7a** was treated with 2.2 equiv of *t*-BuLi at −90 °C in dry diethyl ether, and after 10 min, 1 or 2 equiv of the corresponding Lewis acid were added at −90 °C, and the reaction mixture was allowed to reach room temperature. The results are summarized in Scheme 2 and Table 1.

The dehalogenation product **H-7a** was the only one detected in the reaction with $ZnCl_2$, whereas the reaction with boron trifluoride etherate (entries 3, 4) afforded the debrominated amino alcohol **H-5** and acetaldehyde resulting from the hydrolysis of the *N*,*O*-acetal. The addition of 1 equiv of $MgBr_2{\cdot}OEt_2$ to the preformed aryllithium intermediate gave a mixture of debrominated perhydrobenzoxazine **H-7a** (40%) and the aminomenthol derivative resulting from the intramolecular nucleophilic ring opening as a mixture (4:1) of diastereomers **9a** and

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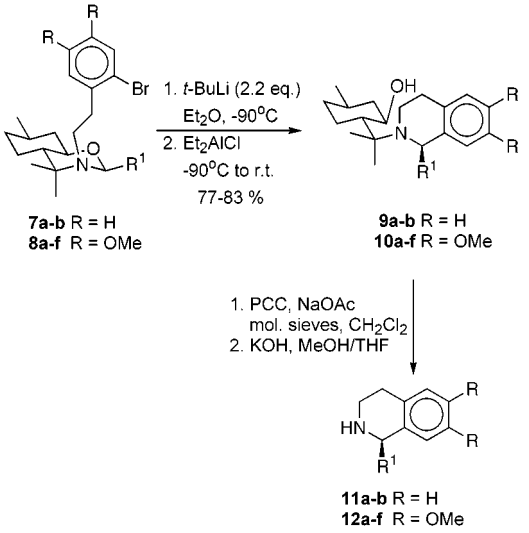
(11) Gibson, S. E.; Guillo, N.; Middleton, R. J.; Thuilliez, A.; Tozer, M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 447.
(12) For experimental details of preparation and analytical and spectroscopical data for aldehydes, see Supporting Information.
(13) This result contrasts with the easy ring opening of oxazolidines; see: Takahashi, H.; Suzuki, Y.; Kametani, F. *Heterocycles* **1983**, *20*, 607.

**Scheme 3**




**9′a**. When the ratio of the magnesium salt increased to 2 equiv, tetrahydroisoquinoline derivatives **9a** and **9′a** (4:1 ratio) were isolated in 75% yield and the amount of **H-7a** decreased to 25% yield.

The best results were obtained when 2 equiv of diethylaluminum chloride were added (entry 7). In this case, the transmetalation and subsequent *N*,*O*-acetal opening with concomitant formation of the tetrahydroisoquinoline nucleus is the only process observed. This protocol was then applied to perhydrobenzoxazines **7b** and **8a**−**e** directed to the synthesis of enantiopure tetrahydroisoquinoline alkaloids. Thus, a solution of the substrate in dry ether was treated with *t*-BuLi (2.2 equiv) at −90 °C, and after 5 min, 2 equiv of diethylaluminum chloride were added, the mixture was allowed to reach room temperature and stirred for 16 h. Isolation and purification by flash chromatography, after the corresponding hydrolysis, afforded tetrahydroisoquinoline derivatives **9a**,**b** and **10a**−**e** in 77−83% yield as single diastereomers (entries 8−14 in Table 1 and Scheme 3). The only exception to this general method was for compound **8f**. In this case, only 1 equiv of *t*-BuLi was used in the aryllithium formation because the reaction with 2 equiv of *t*-BuLi yielded the reductive ring opening as major product.

The final tetrahydroisoquinolines **11a**,**b** and **12a**−**f** were obtained in 55−82% yield from **9a**,**b** and **10a**−**f** by removal of the menthol appendage using a two-step procedure. **9a**,**b** and **10a**−**f** were oxidized to the corresponding 8-aminomenthone derivatives by a modified published procedure.[14] In this case the oxidation of aminomenthol derivatives must be carried out with PCC and molecular sieves in a solution buffered with NaOAc; otherwise the formation of 3,4-dihydroisoquinoline derivative was observed. The crude 8-aminomenthones, without isolation, were then transformed into enantiopure **11a**,**b** or **12a**−**f** by treatment with a KOH solution in MeOH/THF (Scheme 3).

The absolute configuration at C-1 in the tetrahydroisoquinolines **11a**,[15] **11b**,[7,16] **12a**,[4a,15,17] and **12e**[4a,18] was assigned as *R* and **12c**[19] as *S* by comparison of the sign of the optical rotations with those previously described. However, compounds **12d**, **12e**, and **12f** were transformed into the enantiopure known alkaloids (*R*)-*O*-methylarmepavine[20] (**13d**), (*R*)-laudanosine[20] (**13e**), and (*R*)-homolaudanosine[21] (**13f**) respectively, by methylation with dimethylpyrocarbonate followed by carbamate reduction with $LiAlH_4$ (Scheme 4). This method allowed the first preparation of enantiopure (*R*)-*O*-methyllophocerine (**13b**) from **12b**. In this case the assignment of *R* configuration at C-1 was made by generalization of the stereochemical outcome of the intramolecular ring opening. (*S*)-Calycotomine[19] (**13c**) was obtained from **12c** by debenzylation with Pearlmann's catalyst.

**Scheme 4**

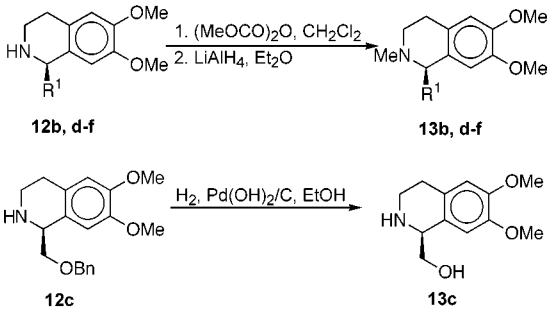



**Table 2. Experimental Conditions and Retention Times for Chiral-HPLC of Racemates 11, 12, and 13**

| compd | eluent (*i*-PrOH/hex) | flow rate (mL/min) | $t_R$ (min) *R* | $t_R$ (min) *S* |
|---|---|---|---|---|
| **11a** | 5/95 | 0.3 | 33.48 | 32.20[a] |
| **11b** | 30/70 | 0.7 | 9.99 | 6.96 |
| **12a** | 20/80 | 0.7 | 14.88 | 11.83 |
| **12b** | 20/80 | 0.3 | 23.21 | 25.35 |
| **13b** | 20/80 | 0.2 | 23.24 | 20.42 |
| **12c** | 30/70 | 0.7 | 12.04 | 15.72 |
| **12d** | 20/80 | 0.9 | 25.77 | 17.91 |
| **13d** | 20/80 | 0.5 | 22.34 | 12.43 |
| **13e** | 30/70 | 0.7 | 19.30 | 9.38 |
| **12f** | 30/70 | 1 | 16.63 | 10.79 |
| **13f** | 20/80 | 0.5 | 23.59 | 16.18 |

[a] Peaks not completely resolved at the baseline.

The enantiomeric purity of the final compounds was studied by HPLC on a chiral stationary phase using mixtures of *i*-PrOH/hexane as eluent. To this end, racemates of the tetrahydroisoquinolines were prepared by Bischler−Napieralski cyclization[4a] of the intermediate amides followed by $NaBH_4$ reduction of the dihydroisoquinolines. Our synthetic products were studied by HPLC and coinjected with the corresponding racemate showing ee >99% in all the cases. Table 2 summarizes the experimental conditions for the resolution of racemates and the retention times for both enantiomers of compounds **11**, **12**, and **13**.

It is noteworthy that, in the experimental conditions used, the *S* enantiomer eluted before than *R* except for compound **12b**, although *O*-methyllophocerine **13b**, resulting from the methylation of **12b**, fits in with the

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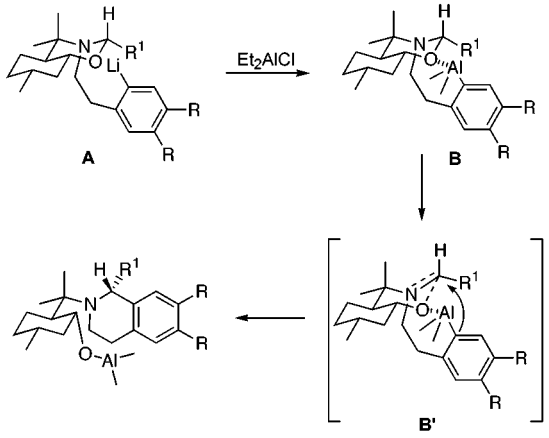
**Scheme 5**




general tendency. **12c** was not an exception to this behavior because the priority of the substituents is different.

The stereochemical outcome of the intramolecular ring opening for 1,3-perhydrobenzoxazine system is in agreement with that previously described for intermolecular reactions.[9a] The stereodiscrimination is better for organoaluminum derivatives because they have a greater nucleophilic character than magnesium derivatives.[22] Taking into account the configuration of the stereocenter created in the reaction, we can rationalize the results as summarized in Scheme 5.

The lithiated intermediate **A** formed by reaction of the initial bromo derivative with *t*-BuLi will be transformed into the arylaluminum reagent **B** by transmetalation with $Et_2AlCl$. The tetrahydroisoquinoline derivative should be formed by both intramolecular transfer of the aryl group from the aluminum atom while complexed to the oxygen in **B′** to the *si* face of the incipient iminium ion or by synchronous intramolecular arylation in the early transition state **B′**. The formation of the minor diastereomer with the arylmagnesium is a consequence of the lesser reactivity of this organometallic and can be interpreted by intramolecular arylation of the late iminium ion to the *re* face.

In conclusion, the described method allows preparation, in a short, highly efficient way, enantiopure 1-substituted tetrahydroisoquinolines from two different aldehydes by using (−)-8-aminomenthol as chiral template. The general method allows alkyl, aryl, benzyl, or homobenzyl substituents to be introduced at C-1 in the final THIQ by changing the structure of the aldehyde employed in the formation of the starting perhydrobenzoxazine.

## Experimental Section

All solvents employed were dried and distilled prior to use. *t*-BuLi was used as 1.5 M solution in pentane and $Et_2AlCl$ as 1 M solution in hexanes. TLC was performed with silica gel 60 F254 plates, and flash chromatography using 240−300 mesh silica gel. Melting points were measured in a capillary tube and are uncorrected. Optical rotation measurements are obtained on a digital polarimeter with a sodium lamp (254 nm). The $^1$H NMR and $^{13}$C NMR were recorded at 300 MHz and 75.2 MHz using $CDCl_3$ as solvent; chemical shifts ($\delta$) are given in ppm related to tetramethylsilane (TMS) as internal reference ($\delta$ = 0 for TMS) and *J* values are given in hertz. Some methylene signals in $^1$H NMR and $^{13}$C NMR for **9a**,**b** and **10a**−**f** appeared unresolved at 298 K, and then the spectra for these compounds were registered at 333 K. Analytical HPLC was done on a Chiralcel OD column (0.46 × 25 cm) equipped with a precolumn (0.46 × 5 cm) using a UV detector at 220 nm wavelength. The eluents were mixtures 2-propanol/*n*-hexane, as indicated in Table 2. Mass spectra were obtained by chemical ionization (MSCI), and infrared spectra were registered neat or as Nujol dispersion.

**Synthesis of Perhydrobenzoxazines 3 and 4.** A mixture of (−)-8-aminomenthol (5 g, 29.2 mmol) and the corresponding aldehyde (32 mmol) in $CH_2Cl_2$ (50 mL) was stirred at room temperature until disappearance of the amino alcohol (TLC). Then, anhydrous $MgSO_4$ (2 g) was added and the mixture stirred for 10 min. The solid was filtered off and the solvent removed under vacuo. The oily residue was purified by flash chromatography (silica gel ethyl acetate/hexanes 1:15 v/v).

**2α-(2′-Bromophenylmethyl)-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 3.** 97%. White solid, mp 61−62 °C (from ethanol). $[\alpha]^{25}_D = -18.6$ ($c$ = 0.9, $CHCl_3$). $^1$H NMR $\delta$: 0.80−1.10 (4H, m); 0.88 (3H, d, $J$ = 6.5); 1.03 (3H, s); 1.05 (3H, s); 1.30−1.50 (2H, m); 1.55−1.70 (2H, m); 1.79−1.89 (1H, m); 2.89 (1H, dd, $J$ = 6.6, 14.2); 2.98 (1H, dd, $J$ = 4.8, 14.2); 3.30 (1H, dt, $J$ = 4.1 Hz, 10.4); 4.56−4.60 (1H, m); 6.97−7.49 (4H, m). $^{13}$C NMR $\delta$: 19.7; 22.3; 25.5; 29.9; 31.3; 35.0; 41.6; 42.4; 51.3; 51.6; 74.9; 81.9; 125.0; 126.9; 127.7; 131.7; 132.4; 137.4. IR (neat): 3050, 2940 cm$^{-1}$. MSCI (*m*/*z*, %): 352 (M + 1, 100), 354 (M + 3, 95). Anal. Calcd for $C_{18}H_{26}BrNO$: C, 61.36; H, 7.44; N, 3.98. Found C, 61.25; H, 7.35; N, 4.15.

**2α-(2′-Bromo-3′,4′-dimethoxyphenylmethyl)-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 4.** 95%. Colorless oil. $[\alpha]^{25}_D = -9.6$ ($c$ = 0.4, $CHCl_3$). $^1$H NMR $\delta$: 0.80−1.05 (4H, m); 0.87 (3H, d, $J$ = 6.5); 1.04 (3H, s); 1.05 (3H, s); 1.32−1.52 (1H, m); 1.55−1.70 (3H, m); 1.80−1.89 (1H, m); 2.80 (1H, dd, $J$ = 6.5, 14.3); 2.91 (1H, dd, $J$ = 4.8, 14.3); 3.32 (1H, dt, $J$ = 4.1 Hz, 10.6); 3.82 (6H, s); 4.52 (1H, dd, $J$ = 4.8, 6.5); 6.93 (1H, s); 6.96 (1H, s). $^{13}$C NMR $\delta$: 19.7; 22.2; 25.4; 29.9; 31.2; 34.9; 41.5; 41.7; 51.3; 51.5; 55.8; 55.9; 74.8; 82.1; 114.3; 114.6; 114.9; 129.3; 147.7; 147.8. IR (neat): 3050, 2940 cm$^{-1}$. MSCI (*m*/*z*, %): 412 (M + 1, 100), 414 (M + 3, 94). Anal. Calcd for $C_{20}H_{30}BrNO_3$: C, 58.25; H, 7.33; N, 3.40. Found C, 58.39; H, 7.36; N, 3.28.

**Reduction of 3 and 4 to 8-Aminomenthols 5 and 6.** To a cooled (0 °C) mixture of $NaBH_4$ (2.85 g, 75 mmol) and $BF_3$·$OEt_2$ (150 mL of 1 M solution, 15 mmol) in THF (80 mL) was added a solution of the corresponding perhydrobenzoxazine (35 mmol) in THF (40 mL). The mixture was allowed to reach rt, stirred for 2 h, and then quenched by slow addition of methanol (30 mL), and the sttirring was continued for additional 30 min. The solvents were eliminated under vacuo, the residue was treated with 20% solution of NaOH (30 mL) and solid NaOH (2 g), and the mixture was refluxed for 1 h. The reaction mixture was cooled and extracted with $CHCl_3$ (5 × 75 mL), the organic layer washed with brine and dried over anhydrous $Na_2SO_4$, and the solvent was eliminated under vacuo. The amino alcohols were purified by flash chromatography (silica gel ethyl acetate/hexanes 1/3).

***N*-[(2′-Bromophenyl)ethyl]-8-aminomenthol 5.** 90% from **3**. Colorless oil. $[\alpha]^{25}_D = -15.8$ ($c$ = 0.8, $CHCl_3$). $^1$H NMR $\delta$: 0.80−1.05 (3H, m); 0.90 (3H, d, $J$ = 6.5); 1.04 (3H, s); 1.08 (3H, s); 1.22−1.31 (1H, m); 1.32−1.51 (1H, m); 1.57−1.68 (2H, m); 1.91−2.01 (1H, m); 2.81−2.88 (4H, m), 3.60 (1H, dt, $J$ = 3.8, 10.1), 7.03−7.53 (4H, m). $^{13}$C NMR $\delta$: 21.5; 22.1; 25.7; 26.1; 30.9; 34.9; 37.1; 40.7; 44.4; 49.5; 56.6; 72.5; 124.4; 127.4; 128.0; 130.8; 132.8; 138.7. IR (neat): 3320, 3050, 2940 cm$^{-1}$. MSCI (*m*/*z*, %): 354 (M + 1, 100), 356 (M + 3, 94). Anal. Calcd for $C_{18}H_{28}BrNO$: C, 61.02; H, 7.97; N, 3.95. Found C, 60.88; H, 8.06; N, 3.99.

***N*-[(2′-Bromo-4′,5′-dimethoxyphenyl)ethyl]-8-aminomenthol 6.** 90% from **4**. Colorless oil. $[\alpha]^{25}_D = -9.2$ ($c$ = 0.6, $CHCl_3$). $^1$H NMR $\delta$: 0.80−1.10 (3H, m); 0.91 (3H, d, $J$ = 6.5); 1.07 (3H, s); 1.10 (3H, s); 1.18−1.47 (2H, m); 1.6−1.59 (2H, m); 1.88−1.97 (1H, m); 2.74−2.90 (4H, m); 3.61 (1H, dt, $J$ = 3.9, 10.2); 3.84 (3H, s); 3.87 (3H, s); 6.75 (1H, s); 6.99 (1H, s). $^{13}$C NMR $\delta$: 21.4; 22.0; 25.6; 25.9; 30.9; 34.8; 36.6; 40.8; 44.3;

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49.3; 56.0 (2C); 56.7; 72.4; 113.3; 113.9; 115.4; 130.4; 148.0; 148.2. IR (neat): 3320, 3050, 2940 $cm^{-1}$. MSCI (*m*/*z*, %): 414 (M + 1, 100), 416 (M + 3, 96). Anal. Calcd for $C_{20}H_{32}BrNO_3$: C, 57.97; H, 7.78; N, 3.38. Found C, 58.02; H, 7.61; N, 3.56.

**Synthesis of Perhydrobenzoxazines 7 and 8. General Procedure.** A mixture of (−)-8-aminomenthol derivative **5** or **6** (1.5 mmol) and the corresponding aldehyde (3 mmol) was heated, without solvent, in a sealed tube at 120 °C in an oil bath. When the reaction was finished (TLC), the mixture was diluted with EtOH (50 mL), and the solvents were evaporated under vacuum. The residue was purified by flash chromatography (silica gel, EtOAc/hexane).

**3-[(2′-Bromophenyl)ethyl]-2α,4,4,7α-tetramethyl-*trans*-octahydro-1,3-benzoxazine 7a.** 88% from **5** and acetaldehyde. Colorless oil. $[\alpha]^{25}_D = -34.7$ (*c* = 1.3, $CHCl_3$). $^1$H NMR *δ*: 0.80−1.08 (3H, m); 0.89 (3H, d, *J* = 6.5); 1.11 (3H, s); 1.20−1.51 (2H, m); 1.22 (3H, s); 1.37 (3H, d, *J* = 5.9); 1.53−1.71 (2H, m); 1.81−1.91 (1H, m); 2.54−2.64 (1H, m); 2.78−2.97 (3H, m); 3.41 (1H, dt, *J* = 4.0, 10.5); 4.68 (1H, q, *J* = 5.9); 7.00−7.53 (4H, m). $^{13}$C NMR *δ*: 19.1; 20.9; 22.2; 25.1; 26.8; 31.3; 34.9; 40.8; 41.4; 43.6; 46.6; 57.0; 75.5; 83.1; 124.2; 127.3; 127.6; 131.0; 132.6; 140.1. IR (neat): 3050, 2940, 745 $cm^{-1}$. MSCI (*m*/*z*, %): 380 (M + 1, 100), 382 (M + 3, 95). Anal. Calcd for $C_{20}H_{30}BrNO$: C, 63.15; H, 7.95; N, 3.68. Found C, 63.26; H, 8.08; N, 3.77.

**3-[(2′-Bromophenyl)ethyl]-2α-phenyl-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 7b.** 85% from **5** and benzaldehyde. Colorless oil. $[\alpha]^{25}_D = +11.0$ (*c* = 1.2, $CHCl_3$). $^1$H NMR *δ*: 0.90−1.05 (2H, m); 0.92 (3H, d, *J* = 6,4); 1.05−1.16 (1H, m); 1.26 (3H, s); 1.30 (3H, s); 1.40−1.55 (2H, m); 1.60−1.72 (2H, m); 1.92−2.00 (1H, m); 2.25 (1H, m); 2.37−2.53 (2H, m); 2.64−2.75 (1H, m); 3.57 (1H, dt, *J* = 4.0, 10.5); 5.56 (1H, s); 6.35 (1H, d, *J* = 7.4); 6.88−7.56 (8H, m). $^{13}$C NMR *δ*: 19.7; 22.4; 25.2; 27.0; 31.4; 35.1; 39.9; 41.5; 44.4; 46.5; 57.1; 75.9; 87.9; 124.1; 127.2; 127.4; 127.6; 127.7 (2C); 127.9 (2C); 130.9; 132.3; 140.3; 140.9. IR (neat): 3020, 2920, 750 $cm^{-1}$. MSCI (*m*/*z*, %): 442 (M + 1, 100), 444 (M + 3, 93). Anal. Calcd for $C_{25}H_{32}BrNO$: C, 67.87; H, 7.29; N, 3.17. Found C, 67.69; H, 7.26; N, 3.27.

**3-[(2′-Bromo-4′,5′-dimethoxyphenyl)ethyl]-2α,4,4,7α-tetramethyl-*trans*-octahydro-1,3-benzoxazine 8a.** 86% from **6** and acetaldehyde. Colorless oil. $[\alpha]^{25}_D = -32.3$ (*c* = 0.2, $CHCl_3$). $^1$H NMR *δ*: 0.83−1.09 (3H, m); 0.90 (3H, d, *J* = 6.5); 1.12 (3H, s); 1.22 (3H, s); 1.23−1.55 (2H, m); 1.37 (3H, d, *J* = 5.8); 1.57−1.73 (2H, m); 1.80−1.90 (1H, m); 2.54−2.63 (1H, m); 2.69−2.97 (3H, m); 3.42 (1H, dt, *J* = 4.0, 10.5); 3.83 (3H, s); 3.85 (3H, s); 4.69 (1H, q, *J* = 5.8); 6.69 (1H, s); 6.98 (1H, s). $^{13}$C NMR *δ*: 19.2; 20.9; 22.2; 25.0; 26.8; 31.2; 34.9; 40.4; 41.4; 43.5; 46.5; 55.9; 56.0; 56.9; 75.4; 83.0; 113.5; 113.9; 115.3; 132.0; 147.8; 148.2. IR (neat): 3020, 2920, 745 $cm^{-1}$. MSCI (*m*/*z*, %): 440 (M + 1, 100), 442 (M + 3, 94). Anal. Calcd for $C_{22}H_{34}BrNO_3$: C, 60.00; H, 7.78; N, 3.18. Found C, 60.12; H, 7.69; N, 3.36.

**3-[(2′-Bromo-4′,5′-dimethoxyphenyl)ethyl]-2α-isobutyl-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 8b.** 87% from **6** and isovaleraldehyde. Colorless oil. $[\alpha]^{25}_D = -37.1$ (*c* = 0.1, $CHCl_3$). $^1$H NMR *δ*: 0.89 (3H, d, *J* = 6.5); 0.90−1.10 (3H, m); 0.94 (3H, d, *J* = 6.5); 0.95 (3H, d, *J* = 6.5); 1.19 (3H, s); 1.24 (3H, s); 1.30−1.40 (1H, m); 1.42−1.75 (5H, m); 1.78−1.90 (2H, m); 2.62−2.99 (4H, m); 3.41 (1H, dt, *J* = 3.9, 10.6); 3.83 (3H, s); 3.85 (3H, s); 4.64 (1H, s); 6.68 (1H, s); 6.98 (1H, s). $^{13}$C NMR *δ*: 21.3; 22.2; 22.6; 23.1; 24.9; 25.1; 26.8; 31.3; 35.0; 40.3; 41.5; 42.9; 43.6; 45.7; 55.9; 56.0; 57.0; 76.1; 85.6; 113.3; 113.9; 115.3; 132.3; 147.8; 148.2. IR (neat): 3040, 2940, 750 $cm^{-1}$. MSCI (*m*/*z*, %): 482 (M + 1, 100), 484 (M + 3, 89). Anal. Calcd for $C_{25}H_{40}BrNO_3$: C, 62.23; H, 8.36; N, 2.90. Found C, 62.29; H, 8.45; N, 2.74.

**2α-Benzyloxymethyl-3-[(2′-bromo-4′,5′-dimethoxyphenyl)ethyl]-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 8c.** 90% from **6** and benzyloxy acetaldehyde. Colorless oil. $[\alpha]^{25}_D = -20.8$ (*c* = 0.1, $CHCl_3$). $^1$H NMR *δ*: 0.88 (3H, d, *J* = 6.4); 0.85−1.10 (3H, m); 1.16 (6H, s); 1.22−1.48 (2H, m); 1.53−1.70 (2H, m); 1.85−1.96 (1H, m); 2.67−2.88 (4H, m); 3.47 (1H, dt, *J* = 3.5, 10.4); 3.61−3.64 (2H, m); 3.71 (3H, s); 3.78 (3H, s); 4.55 (1H, d, *J* = 12.1); 4.64 (1H, d, *J* = 12.1); 4.83 (1H, t, *J* = 5.0); 6.59 (1H, s); 6.94 (1H, s); 7.22−7.37 (5H, m). $^{13}$C NMR *δ*: 20.7; 22.3; 25.0; 26.5; 31.2; 35.0; 39.7; 41.3; 43.7; 46.1; 55.8; 56.0; 56.9; 71.9; 73.5; 75.8; 86.0; 113.7; 113.9; 115.1; 127.6; 127.9 (2C); 128.3 (2C); 131.9; 138.0; 147.8; 148.1. IR (neat): 3020, 2920 $cm^{-1}$. MSCI (*m*/*z*, %): 546 (M + 1, 100), 548 (M + 3, 94). Anal. Calcd for $C_{29}H_{40}BrNO_4$: C, 63.73; H, 7.38; N, 2.56. Found C, 63.86; H, 7.47; N, 2.37.

**3-[(2′-Bromo-4′,5′-dimethoxyphenyl)ethyl]-2α-(*p*-methoxybenzyl)-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 8d.** 83% from **6** and 4-methoxyphenylacetaldehyde. Colorless oil. $[\alpha]^{25}_D = -26.4$ (*c* = 0.3, $CHCl_3$). $^1$H NMR *δ*: 0.85−1.10 (3H, m); 0.88 (3H, d, *J* = 6.5); 1.25 (3H, s); 1.30 (3H, s); 1.30−1.50 (2H, m); 1.55−1.75 (2H, m); 1.79−1.89 (1H, m); 2.75−3.20 (6H, m); 3.37 (1H, dt, *J* = 4.0, 10.5); 3.77 (3H, s); 3.82 (3H, s); 3.84 (3H, s); 4.76−4.79 (1H, m); 6.69 (1H, s); 6.83 (2H, d, *J* = 8.6); 6.98 (1H, s); 7.25 (2H, d, *J* = 8.6). $^{13}$C NMR *δ*: 20.4; 22.1; 24.8; 26.4; 31.2; 34.8; 39.2; 39.4; 41.1; 43.9; 45.6; 55.1; 56.1 (2C); 58.6; 76.0; 88.4; 113.5 (3C); 113.9; 115.4; 130.3 (2C); 130.6; 131.7; 148.0; 148.3; 158.0. IR (neat): 3020, 2930 $cm^{-1}$. MSCI (*m*/*z*, %): 546 (M + 1, 100), 548 (M + 3, 95). Anal. Calcd for $C_{29}H_{40}BrNO_4$: C, 63.73; H, 7.38; N, 2.56. Found C, 63.58; H, 7.51; N, 2.51.

**3-[(2′-Bromo-4′,5′-dimethoxyphenyl)ethyl]-2α-(3′,4′-dimethoxybenzyl)-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 8e.** 82% from **6** and 3,4-dimethoxyphenylacetaldehyde. Colorless oil. $[\alpha]^{25}_D = -28.7$ (*c* = 0.6, $CHCl_3$). $^1$H NMR *δ*: 0.88 (3H, d, *J* = 6.5); 0.90−1.10 (3H, m); 1.18 (3H, s); 1.25 (3H, s); 1.32−1.48 (2H, m); 1.52−1.71 (2H, m); 1.79−1.88 (1H, m); 2.70−3.10 (6H, m); 3.36 (1H, dt, *J* = 3.9, 10.6); 3.84 (3H, s); 3.85 (3H, s); 3.86 (3H, s); 3.88 (3H, s); 4.70−4.73 (1H, m); 6.67 (1H, s); 6.80−6.99 (4H, m). $^{13}$C NMR *δ*: 20.8; 22.2; 25.0; 26.8; 31.2; 35.0; 40.1; 40.3; 41.4; 43.7; 45.8; 55.7; 56.0 (2C); 57.3 (2C); 75.9; 88.2; 110.7; 112.7; 113.5; 114.0; 115.3; 121.1; 131.8; 132.1; 147.2; 147.9; 148.2; 148.4. IR (neat): 3020, 2930 $cm^{-1}$. MSCI (*m*/*z*, %): 576 (M + 1, 100), 578 (M + 3, 90). Anal. Calcd for $C_{30}H_{42}BrNO_5$: C, 62.49; H, 7.34; N, 2.43. Found C, 62.71; H, 7.41; N, 2.32.

**3-[(2′-Bromo-4′,5′-dimethoxyphenyl)ethyl]-2α-(3′,4′-dimethoxyphenethyl)-4,4,7α-trimethyl-*trans*-octahydro-1,3-benzoxazine 8f.** 86% from **6** and 3-(3′,4′-dimethoxyphenyl)-propionaldehyde. White solid, mp 113−114 °C (from ethanol). $[\alpha]_D^{25} = -29.1$ (*c* = 0.3, $CHCl_3$). $^1$H NMR *δ*: 0.88−1.10 (3H, m); 0.90 (3H, d, *J* = 6.5); 1.11 (3H, s); 1.22 (3H, s); 1.30−1.55 (2H, m); 1.55−1.70 (2H, m); 1.80−2.01 (3H, m); 2.58−2.90 (5H, m); 2.92−3.00 (1H, m); 3.38 (1H, dt, *J* = 4.0; 10.6); 3.76 (3H, s); 3.80 (3H, s); 3.84 (3H, s); 3.85 (3H, s); 4.51 (1H, dd, *J* = 4.9; 7.1); 6.64 (1H, s); 6.72−6.80 (3H, m); 6.95 (1H, s). $^{13}$C NMR *δ*: 20.7; 22.0; 25.1; 26.8; 31.4; 31.7; 35.1; 35.8; 40.3; 41.6; 43.7; 46.3; 55.9; 56.0; 56.1; 56.2; 57.0; 76.1; 86.6; 111.9; 112.5; 114.1; 114.2; 116.1; 120.4; 132.5; 135.1; 147.4; 148.3; 148.6; 149,1. IR (neat): 3020, 2940 $cm^{-1}$. MSCI (*m*/*z*, %): 590 (M + 1, 100), 592 (M + 3, 94). Anal. Calcd for $C_{31}H_{44}BrNO_5$: C, 63.04; H, 7.51; N, 2.37. Found C, 63.19; H, 7.53; N, 2.49.

**General Method for Intramolecular Opening of Perhydrobenzoxazines 7a,b and 8a−f.** A solution of the corresponding perhydrobenzoxazine **7a**,**b** or **8a**−**f** (3.5 mmol) in anhydrous $Et_2O$ (35 mL) under argon and cooled to −90 °C was treated with 1.5 M solution of *t*-BuLi in pentane (4.12 mL, 7.7 mmol) for 10 min and then was added 1 M solution of $Et_2$-AlCl in hexane (7 mL, 7 mmol) at that temperature. The cooling bath was removed, and the reaction was allowed to reach rt and stirred overnight. The reaction was quenched by addition of 2 M NaOH solution (4 mL) and extracted first with EtOAc (3 × 25 mL) and then with $CHCl_3$ (3 × 25 mL). The organics were washed with brine and water and dried over anhydrous $Na_2SO_4$. The solvents were removed, and the residue was purified by flash chromatography (silica gel, EtOAc/hexane).

**(1*R*)-*N*-(8-Menthyl)-1-methyl-1,2,3,4-tetrahydroisoquinoline 9a.** 80% from **7a**. White solid, mp 138−139 °C (from EtOAc/hexane). $[\alpha]^{25}_D = -6.4$ (*c* = 0.8, $CHCl_3$). $^1$H NMR (333 K) *δ*: 0.85−1.05 (3H, m); 0.92 (3H, d, *J* = 6.5); 0.95 (3H, s); 1.34 (3H, s); 1.40−1.50 (1H, m); 1.44 (3H, d, *J* = 6.8); 1.53−1.75 (3H, m); 1.88−1.97 (1H, m); 2.63−2.70 (1H, m); 2.89−3.18 (2H, m); 3.20−3.26 (1H, m); 3.61 (1H, dt, *J* = 4.0, 10.0);

4.37 (1H, q, $J$ = 6.8); 6.99−7.12 (4H, m). $^{13}$C NMR (333 K) $\delta$: 19.6; 21.9 (2C); 23.7; 25.9; 28.0; 31.0; 35.4; 37.2; 45.2; 48.6; 51.6; 60.8; 72.4; 125.6; 125.8; 126.8; 128.7; 133.9; 141.6. IR (Nujol): 3240, 2920 cm$^{-1}$. MSCI (*m*/*z*, %): 302 (M + 1, 100). Anal. Calcd for $C_{20}H_{31}NO$: C, 79.68; H, 10.36; N, 4.65. Found C, 79.77; H, 10.40; N, 4.63.

**(1*R*)-*N*-(8-Menthyl)-1-phenyl-1,2,3,4-tetrahydroisoquinoline 9b.** 78% from **7b.** White solid, mp 184−185 °C (from EtOAc). $[\alpha]^{25}_D$ = −124.5 ($c$ = 0.7, $CHCl_3$). $^1$H NMR (333 K) $\delta$: 0.74 (3H, s); 0.92−1.14 (3H, m); 0.93 (3H, d, $J$ = 6.9); 1.38−1.55 (1H, m); 1.44 (3H, s); 1.56−1.78 (2H, m); 1.80−1.92 (1H, m); 1.93−2.03 (1H, m); 2.75−2.80 (1H, m); 3.00−3.12 (1H, m); 3.25−3.35 (2H, m); 3.63 (1H, dt, $J$ = 4.1, 10.5); 5.37 (1H, s); 6.81−7.22 (9H, m); 7.55 (1H, broad s). $^{13}$C NMR (333 K) $\delta$: 20.2; 21.9; 24.2; 26.2; 27.1; 31.0; 35.4; 37.4; 45.4; 48.8; 59.7; 61.8; 72.6; 125.9; 126.3; 126.9; 127.8 (2C); 128.2; 128.7; 130.2 (2C); 134.3; 138.3; 143.4. IR (Nujol): 3200, 2940 cm$^{-1}$. MSCI (*m*/*z*, %): 364 (M + 1, 100). Anal. Calcd for $C_{25}H_{33}NO$: C, 82.60; H, 9.15; N, 3.85. Found C, 82.71; H, 9.23; N, 3.88.

**(1*R*)-*N*-(8-Menthyl)-1-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 10a.** 83% from **8a.** White solid, mp 66−67 °C (from EtOAc/hexane). $[\alpha]^{25}_D$ = −24.2 ($c$ = 1.0, $CHCl_3$). $^1$H NMR (333 K) $\delta$: 0.85−1.10 (6H, m); 0.93 (3H, d, $J$ = 6.5); 1.34 (3H, s); 1.40−1.53 (1H, m); 1.44 (3H, d, $J$ = 6.7); 1.55−1.75 (3H, m); 1.89−1.99 (1H, m); 2.51−2.61 (1H, m); 2.82−3.18 (2H, m); 3.21−3.31 (1H, m); 3.61 (1H, dt, $J$ = 4.0, 10.2); 3.81 (3H, s); 3.83 (3H, s); 4.30 (1H, q, $J$ = 6.7); 6.54 (2H, s); 8.10 (1H, broad s). $^{13}$C NMR (333 K) $\delta$: 19.5; 21.9 (2C); 23.7; 25.8; 27.2; 30.9; 35.3; 37.6; 45.2; 48.5; 53.2; 55.8; 56.0; 60.7; 72.3; 110.5; 112.0; 125.9; 133.7; 147.5; 147.7. IR (Nujol): 3200, 2920 cm$^{-1}$. MSCI (*m*/*z*, %): 362 (M + 1, 100). Anal. Calcd for $C_{22}H_{35}NO_3$: C, 73.09; H, 9.76; N, 3.87. Found C, 73.22; H, 9.64; N, 3.91.

**(1*R*)-*N*-(8-Menthyl)-1-isobutyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 10b** 83% from **8b.** Colorless oil. $[\alpha]^{25}_D$ = −18.2 ($c$ = 1.1, $CHCl_3$). $^1$H NMR (333 K) $\delta$: 0.92 (3H, s); 0.97−1.09 (3H, m); 0.99 (3H, d, $J$ = 2.7); 1.01 (3H, d, $J$ = 2.4); 1.15 (3H, d, $J$ = 6.1); 1.37 (3H, s); 1.40−1.72 (4H, m); 1.75−1.95 (3H, m); 2.00−2.08 (1H, m); 2.63−2.72 (1H, m); 2.78−2.89 (1H, m); 3.23−3.37 (2H, m); 3.67 (1H, dt, $J$ = 4.0, 10.3); 3.90 (3H, s); 3.91 (3H, s); 4.10 (1H, dd, $J$ = 4.8, 8.5); 6.61 (1H, s); 6.63 (1H, s). $^{13}$C NMR (333 K) $\delta$: 20.0; 21.9; 22.2; 23.5; 24.1; 24.9; 26.1; 26.8; 31.0; 35.5; 38.9; 45.3; 47.5; 48.5; 53.6; 55.8; 56.1; 61.4; 72.7; 111.0; 112.1; 126.6; 133.2; 147.2; 147.7. IR (Nujol): 3200, 2940 cm$^{-1}$. MSCI (*m*/*z*, %): 404 (M + 1, 100). Anal. Calcd for $C_{25}H_{41}NO_3$: C, 74.40; H, 10.24; N, 3.47. Found C, 74.27; H, 10.28; N, 3.59.

**(1*S*)-*N*-(8-Menthyl)-1-(benzyloxymethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 10c.** 77% from **8c.** Colorless oil. $[\alpha]^{25}_D$ = −36.5 ($c$ = 0.5, $CHCl_3$). $^1$H NMR (333 K) $\delta$: 0.85−1.10 (9H, m); 1.31 (3H, s); 1.33−1.50 (1H, m); 1.55−1.70 (3H, m); 1.88−1.95 (1H, m); 2.49−2.59 (1H, m); 2.71−2.86 (1H, m); 3.08−3.21 (2H, m); 3.54−3.62 (2H, m); 3.74 (3H, s); 3.81 (3H, s); 3.96 (1H, dd, $J$ = 5.2, 9.2); 4.20−4.25 (1H, m); 4.41 (1H, d, $J$ = 11.8); 4.46 (1H, d, $J$ = 11.8); 6.54 (1H, s); 6.70 (1H, s); 7.21−7.27 (5H, m). $^{13}$C NMR (333 K) $\delta$: 19.9; 21.9; 23.7; 26.1; 27.7; 31.0; 35.3; 39.8; 45.2; 48.5; 55.5; 55.8 (2C); 61.3; 72.7; 73.3; 74.3; 111.6; 111.7; 127.2; 127.3; 127.5 (2C); 128.1 (2C); 129.7; 138.3; 147.2; 148.0. IR (neat): 3200, 2920 cm$^{-1}$. MSCI (*m*/*z*, %): 468 (M + 1, 100). Anal. Calcd for $C_{29}H_{41}NO_4$: C, 74.48; H, 8.84; N, 3.00. Found C, 74.53; H, 8.77; N, 3.08.

**(1*R*)-*N*-(8-Menthyl)-1-(*p*-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 10d.** 81% from **8d.** Colorless oil. $[\alpha]^{25}_D$ = −48.2 ($c$ = 0.5, $CHCl_3$). $^1$H NMR (333 K) $\delta$: 0.89−1.10 (9H, m); 1.35−1.60 (1H, m); 1.36 (3H, s); 1.65−1.80 (3H, m); 1.95−2.05 (1H, m); 2.55−2.63 (1H, m); 2.75−2.85 (2H, m); 3.14−3.22 (2H, m); 3.31 (1H, dd, $J$ = 3.7, 12.8); 3.40 (3H, s); 3.63 (1H, dt, $J$ = 4.0, 10.1); 3.73 (3H, s); 3.78 (3H, s); 4.17 (1H, dd, $J$ = 3.2, 9.8); 5.68 (1H, s); 6,52 (1H, s); 6.77 (2H, d, $J$ = 8.6); 6.86 (2H, d, $J$ = 8.6). $^{13}$C NMR (333 K) $\delta$: 20.0; 21.9; 23.9; 26.0; 27.2; 30.9; 35.4; 39.0; 42.8; 45.3; 48.7; 55.1; 55.2; 55.7; 58.1; 61.4; 72.6; 111.5; 113.7 (2C); 126.2; 127.5; 130.6; 130.8 (2C); 131.7; 146.0; 147.5; 158.2. IR (neat): 3200, 2920 cm$^{-1}$. MSCI (*m*/*z*, %): 468 (M + 1, 100). Anal. Calcd for $C_{29}H_{41}NO_4$: C, 74.48; H, 8.84; N, 3.00. Found C, 74.51; H, 8.89; N, 2.89.

**(1*R*)-*N*-(8-Menthyl)-1-(3′,4′-dimethoxyphenylmethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 10e.** 79% from **8e.** Colorless oil. $[\alpha]^{25}_D$ = −44.3 ($c$ = 0.5, $CHCl_3$). $^1$H NMR (333 K) $\delta$: 0.80−1.10 (3H, m); 0.90 (3H, s); 0.93 (3H, d, $J$ = 6.5); 1.36 (3H, s); 1.40−1.50 (1H, m); 1.60−1.75 (3H, m); 1.95−2.05 (1H, m); 2.55−2.62 (1H, m); 2.75−2.86 (2H, m); 3.10−3.22 (2H, m); 3.30 (1H, dd, $J$ = 3.5, 12.9); 3.47 (3H, s); 3.64 (1H, dt, $J$ = 4.0, 10.2); 3.73 (3H, s); 3.80 (3H, s); 3.82 (3H, s); 4.16−4.20 (1H, m); 5.80 (1H, s); 6.54−6.58 (2H, m); 6.75 (2H, d, $J$ = 8.1). $^{13}$C NMR (333 K) $\delta$: 20.0; 21.9; 23.8; 26.0; 27.0; 30.9; 35.4; 39.1; 43.3; 45.4; 48.7; 55.4; 55.8 (2C); 56.0; 58.1; 61.4; 72.5; 111.6; 111.7; 111.8; 114.0; 122.1; 126.3; 130.7; 132.4; 146.2; 147.6; 147.8; 148.9. IR (neat): 3200, 2920 cm$^{-1}$. MSCI (*m*/*z*, %): 498 (M + 1, 100). Anal. Calcd for $C_{30}H_{43}NO_5$: C, 72.40; H, 8.71; N, 2.81. Found C, 72.59; H, 8.77; N, 2.69.

**(1*R*)-*N*-(8-Menthyl)-1-(3′,4′-dimethoxyphenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 10f.** 77% from **8f.** Colorless oil. $[\alpha]^{25}_D$ = −30.2 ($c$ = 0.1, $CHCl_3$). $^1$H NMR (333 K) $\delta$: 0.79 (3H, s); 0.86−1.12 (3H, m); 0.93 (3H, d, $J$ = 6.4); 1.28 (3H, s); 1.37−1.48 (1H, m); 1.50−1.62 (2H, m); 1.64−1.73 (1H, m); 1.90−2.05 (2H, m); 2.23−2.38 (1H, m); 2.55−2.83 (4H, m); 3.12−3.28 (2H, m); 3.60 (1H, dt, $J$ = 4.0, 10.3); 3.81 (3H, s); 3.82 (3H, s); 3.84 (3H, s); 3.86 (3H, s); 3.95−3.99 (1H, m); 6.46 (1H, s); 6.57 (1H, s); 6.78 (1H, s); 6.81 (2H, s); $^{13}$C NMR (333 K) $\delta$: 20.1; 21.9; 23.8; 26.0; 26.9; 30.9; 32.9; 35.3; 39.6 (2C); 45.2; 48.3; 54.9; 55.8; 56.0 (2C); 56.1; 61.4; 72.8; 111.1; 112.0 (2C); 112.8; 120.5; 126.9; 132.4; 134.8; 147.2; 147.5; 147.8; 149.3. IR (neat): 3200, 2940 cm$^{-1}$. MSCI (*m*/*z*, %): 512 (M + 1, 100). Anal. Calcd for $C_{31}H_{45}NO_5$: C, 72.76; H, 8.86; N, 2.74. Found C, 72.88; H, 8.98; N, 2.68.

**Elimination of the Chiral Auxiliary.** To a stirred solution of the corresponding aminomenthol (0.55 mmol) in dichloromethane (15 mL) were added PCC (2.1 mmol), NaOAc (0.55 mmol), and 3 Å molecular sieves, and the mixture was stirred at room temperature for 2 h. The reaction was quenched with 2 M NaOH solution (20 mL) in an ice bath and stirred at 0 °C for 15 min. The organic layer was decanted and the aqueous phase extracted with chloroform (5 × 25 mL). The organic extracts were washed with brine and dried over anhydrous $Na_2SO_4$, and the solvent was removed. The residue was redissolved in THF (6 mL), MeOH (2 mL), and 2.5 M KOH solution (2 mL), and the mixture was stirred overnight. The volatiles were eliminated, and the residue was acidified with 1 N solution of HCl and extracted with ether (2 × 25 mL). The aqueous layer was then made alkaline by careful addition of 2 M NaOH solution and extracted with chloroform (5 × 25 mL). The organic phase were washed, dried, and concentrated, and the residue was purified by flash chromatography (silica gel, $CHCl_3$/EtOH) to give enantiopure THIQ.

**(*R*)-1-Methyl-1,2,3,4-tetrahydroisoquinoline 11a.** 71% from **9a.** Colorless oil. $[\alpha]^{25}_D$ = +72.2 ($c$ = 1.1, $CHCl_3$). Lit.[15] $[\alpha]^{25}_D$ = −71.3 ($c$ = 0.6, $CHCl_3$) for the *S* enantiomer. $t_R$: 33,-48 min (*i*-PrOH/hexane 5/95; 0,3 mL/min). $^1$H NMR $\delta$: 1.42 (3H, d, $J$ = 6.6); 2.41 (1H, broad s); 2.68 (1H, dt, $J$ = 4.0, 16.0); 2.78−2.88 (1H, m); 2.92−3.00 (1H, m); 3.20 (1H, dt, $J$ = 5.0, 12.2); 4.05 (1H, q, $J$ = 6.6); 7.03−7.11 (4H, m). $^{13}$C NMR $\delta$: 22.7; 30.0; 41.8; 51.5; 125.8 (2C); 125.9; 129.2; 134.7; 140.5. IR (Nujol): 3300 cm$^{-1}$. MSCI (*m*/*z*, %): 148 (M + 1, 100). Anal. Calcd for $C_{10}H_{13}N$: C, 81.59; H, 8.90; N, 9.51. Found C, 81.62; H, 8.96; N, 9.39.

**(*R*)-1-Phenyl-1,2,3,4-tetrahydroisoquinoline 11b.** 82% from **9b.** White solid, mp 78−79 °C (from EtOAc/hexane). $[\alpha]^{25}_D$ = − 10.9 ($c$ = 1.1, $CHCl_3$). lit.[16] $[\alpha]^{25}_D$ = −12.3 ($c$ = 1.5, $CH_2Cl_2$); lit.[7] $[\alpha]^{25}_D$ = −10.2 ($c$ = 0.2, $CHCl_3$); $[\alpha]^{25}_D$ = +12.7 ($c$ = 0.5, $CHCl_3$) for the *S* enantiomer.[16] $t_R$: 9.99 min (*i*-PrOH/hexane 30/70; 0.7 mL/min). $^1$H NMR $\delta$: 2.10 (1H, broad s); 2.79−2.89 (1H, m); 2.99−3.14 (2H, m); 3.23−3.31(1H, m); 5.11 (1H, s); 6.74−7.35 (9H, m). $^{13}$C NMR $\delta$: 29.7; 42.2; 62.0; 125.6; 126.2; 127.4; 128.1; 128.4 (2C); 129.0 (3C); 135.4; 138.2; 144.8. IR (Nujol): 3300 cm$^{-1}$. MSCI (*m*/*z*, %): 210 (M + 1, 100). Anal. Calcd for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found C, 86.19; H, 7.12; N, 6.73.

**(*R*)-1-Methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (*R*)-Salsolidine 12a.** 60% from **10a.** Colorless oil. $[\alpha]^{25}_D$ = +59.5 ($c$ = 0.9, EtOH). lit.[17] $[\alpha]^{25}_D$ = −59.5 ($c$ = 4.4, EtOH);

lit.[4a] $[\alpha]^{25}_D = -58$ ($c = 2.4$, EtOH); lit.[15] $[\alpha]^{25}_D = -56.5$ ($c = 4.1$, EtOH), all of them referred to the *S* enantiomer. $t_R$: 14.88 min (*i*-PrOH/hexane 20/80; 0.7 mL/min). $^1$H NMR $\delta$: 1.46 (3H, d, $J = 6.7$); 2.10 (1H, broad s); 2.64−2.70 (1H, m); 2.71−2.86 (1H, m); 2.97−3.05 (1H, m); 3.23−3.28 (1H, m); 3.84 (3H, s); 3.85 (3H, s); 4.07 (1H, q, $J = 6.7$); 6.57 (1H, s); 6.62 (1H, s). $^{13}$C NMR $\delta$: 22.5; 29.1; 41.4; 51.1; 55.8; 55.9; 108.9; 111.6; 126.4; 131.8; 147.2; 147.3. IR (neat): 3300 cm$^{-1}$. MSCI (*m*/*z*, %): 208 (M + 1, 100). Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found C, 69.66; H, 8.32; N, 6.63.

**(*R*)-1-Isobutyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 12b.** 61% from **10b.** Colorless oil. $[\alpha]^{25}_D = +45.4$ ($c = 1.0$, $CHCl_3$). $t_R$: 23.21 min (*i*-PrOH/hexane 20/80; 0.3 mL/min). $^1$H NMR $\delta$: 0.98 (3H, d, $J = 6.6$); 1.02 (3H, d, $J = 6.5$); 1.52 (1H, ddd, $J = 3.6$, 10.3, 13.9); 1.66 (1H, ddd, $J = 3.8$, 10.3, 13.9); 1.83−1.94 (1H, m); 2.05 (1H, broad s); 2.62−2.79 (2H, m); 2.92−3.00 (1H, m); 3.17−3.25 (1H, m); 3.84 (3H, s); 3.86 (3H, s); 3.91−3.96 (1H, m); 6.56 (1H, s); 6.58 (1H, s). $^{13}$C NMR $\delta$: 21.3; 24.0; 24.7; 29.4; 40.6; 46.0; 53.0; 55.7; 55.9; 109.1; 111.7; 126.9; 132.1; 147.0; 147.1. IR (neat): 3300 cm$^{-1}$. MSCI (*m*/*z*, %): 250 (M + 1, 100). Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found C, 72.36; H, 9.38; N, 5.55.

**(*S*)-1-Benzyloxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 12c.** 59% from **10c.** Colorless oil. $[\alpha]^{25}_D = +20.2$ ($c = 0.6$, EtOH). lit.[19] $[\alpha]^{25}_D = +19.3$ ($c = 1.2$, EtOH). $t_R$: 15.72 min ($^i$PrOH/hexane 30/70; 0.7 mL/min). $^1$H NMR $\delta$: 2.50 (1H, broad s); 2.70−2.73 (2H, m); 2.90−2.97 (1H, m); 3.10−3.18 (1H, m); 3.63−3.75 (2H, m); 3.78 (3H, s); 3.82 (3H, s); 4.14 (1H, dd, $J = 3.8$, 8.1); 4.55 (1H, d, $J = 11.9$); 4.60 (1H, d, $J = 11.9$); 6.57 (1H, s); 6.59 (1H, s); 7.26−7.34 (5H, m). $^{13}$C NMR $\delta$: 29.2; 40.1; 55.1; 55.7; 55.9; 73.1; 73.2; 109.3; 111.8; 127.1; 127.6; 127.7 (2C); 127.9; 128.3 (2C); 138.1; 147.0; 147.5. IR (neat): 3300 cm$^{-1}$. MSCI (*m*/*z*, %): 314 (M + 1, 100). Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found C, 72.97; H, 7.37; N, 4.58.

**(*R*)-1-(4′-Methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 12d.** 55% from **10d.** Colorless oil. $[\alpha]^{25}_D = +15.7$ ($c = 0.4$, $CHCl_3$). $t_R$: 25.77 min (*i*-PrOH/Hexane 20/80; 0.9 mL/min). $^1$H NMR $\delta$: 2.22 (1H, broad s); 2.70−2.76 (2H, m); 2.80−2.96 (2H, m); 3.12−3.25 (2H, m); 3.80 (3H, s); 3.82 (3H, s); 3.86 (3H, s); 4.11 (1H, dd, $J = 4.2$, 9.3); 6.59 (1H, s); 6.63 (1H, s); 6.87 (2H, d, $J = 8.5$); 7.16 (2H, d, $J = 8.5$). $^{13}$C NMR $\delta$: 29.4; 40.6; 41.7; 55.2; 55.8; 55.9; 56.8; 109.3; 111.7; 113.9 (2C); 127.2; 130.3 (2C); 130.9; 145.8; 146.9; 147.3; 158.2. IR (neat): 3300 cm$^{-1}$. MSCI (*m*/*z*, %): 314 (M + 1, 100). Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found C, 72.96; H, 7.36; N, 4.57.

**(*R*)-1-(3′,4′-Dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. (*R*)-Norlaudanosine 12e.** 58% from **10e**. Colorless oil. $[\alpha]^{25}_D = +21.5$ ($c = 0.6$, $CHCl_3$). lit.[4a] $[\alpha]^{25}_D = -28.8$ ($c = 1.1$, $CHCl_3$); lit.[18] $[\alpha]^{25}_D = -21$ ($c = 1$, $CHCl_3$), both of them for the *S* enantiomer. $^1$H NMR $\delta$: 2.59 (1H, broad s); 2.62−2.83 (2H, m); 2.84−2.96 (2H, m); 3.14−3.25 (2H, m); 3.83 (3H, s); 3.85 (3H, s); 3.86 (3H, s); 3.87 (3H, s); 4.15 (1H, dd, $J = 4.5$, 9.1); 6.59 (1H, s); 6.65 (1H, s); 6.76 (1H, s); 6.77−6.85 (2H, m). $^{13}$C NMR $\delta$: 29.3; 40.8; 42.1; 55.8 (2C); 55.9; 56.0; 56.7; 109.3; 111.2; 111.7; 112.3; 121.4; 127.3; 130.2; 131.2; 146.9; 147.4; 147.6; 148.8. IR (neat): 3300 cm$^{-1}$. MSCI (*m*/*z*, %): 344 (M + 1, 100). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found C, 70.09; H, 7.46; N, 4.14.

**(*R*)-1-(3′,4′-Dimethoxyphenethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline 12f.** 57% from **10f.** Colorless oil. $[\alpha]^{25}_D = +13.0$ ($c = 0.4$, $CHCl_3$). $t_R$: 16.63 min (*i*-PrOH/hexane 30/70; 1 mL/min). $^1$H NMR $\delta$: 1.84 (1H, broad s); 1.91−2.18 (2H, m); 2.62−2.84 (4H, m); 2.94−3.03 (1H, m); 3.19−3.27 (1H, m); 3.82 (3H, s); 3.83 (3H, s); 3.84 (3H, s); 3.86 (3H, s); 3.89−3.96 (1H, m); 6.57 (1H, s); 6.59 (1H, s); 6.76−6.82 (3H, m). $^{13}$C NMR $\delta$: 29.4; 32.0; 38.4; 41.0; 55.0; 55.7 (2C); 55.8; 55.9; 109.1; 111.2; 111.7 (2C); 120.1; 127.2; 131.2; 134.9; 147.1(2C); 147.2; 148.7. IR (neat): 3300 cm$^{-1}$. MSCI (*m*/*z*, %): 358 (M + 1, 100). Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found C, 70.68; H, 7.69; N, 3.84.

***N*-Methylation of THIQ.** To a solution of the corresponding THIQ (0.6 mmol) in $CH_2Cl_2$ (10 mL) was added dimethylpyrocarbonate (0.9 mmol) and the mixture stirred for 20 min. at room temperature. The solvent was removed by evaporation and the residue redissolved in anhydrous diethyl ether (10 mL) and slowly added to a suspension of $LiAlH_4$ (0.14 g., 3.6 mmol) in the same solvent at 0 °C. After stirring at that temperature for 20 min., the reaction was quenched by addition of $H_2O$ (0.14 mL), 20% NaOH solution (0.14 mL) and $H_2O$ (0.42 mL), and the mixture was stirred for 1 h. The mixture was filtered off. The solids were washed with EtOAc and the solution was dried over anhydrous $Na_2SO_4$. The solvents were evaporated and the mixture was purified by flash chromatography (silica gel, EtOAc/hexane).

**(*R*)-1-Isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. (*R*)-O-Methyllophocerine. 13b.** 77% from **12b.** Colorless oil $[\alpha]^{25}_D = +0.7$ ($c = 0.9$, $CHCl_3$); $[\alpha]^{25}_D = -5.4$ ($c = 0.7$, EtOH). $t_R$: 23.24 min (*i*-PrOH/hexane 20/80; 0.2 mL/min). $^1$H NMR $\delta$: 0.92 (3H, d, $J = 6.6$); 0.99 (3H, d, $J = 6.6$); 1.37 (1H, ddd, $J = 4.8$, 8.8, 14.0); 1.70 (1H, ddd, $J = 5.2$, 8.8, 14.0); 1.81−1.92 (1H, m); 2.44 (3H, s); 2.45−2.53 (1H, m); 2.74−2.91 (2H, m); 3.14−3.25 (1H, m); 3.45 (1H, dd, $J = 4.8$, 8.6); 3.84 (3H, s); 3.85 (3H, s); 6.53 (1H, s); 6.55 (1H, s). $^{13}$C NMR $\delta$: 22.2; 23.0; 23.4; 25.1; 41.8; 45.4; 45.5; 55.7; 55.8; 60.6; 110.5; 111.3; 125.5; 130.8; 147.1 (2C). IR (neat): 3020, 2940 cm$^{-1}$. MSCI (*m*/*z*, %): 264 (M + 1, 100%). Anal. Calcd for $C_{16}H_{25}NO_2$: C, 72.96; H, 9.57; N, 5.32. Found C, 72.87; H, 9.45; N, 5.28.

**(*R*)-1-(4′-Methoxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. (*R*)-*O*-Methylarmepavine 13d.** 78% from **12d.** Colorless oil. $[\alpha]^{25}_D = -69.9$ ($c = 0.8$, $CHCl_3$). Lit.[20] $[\alpha]^{25}_D = -81$ ($c = 1.2$, $CHCl_3$); $[\alpha]^{25}_D = +85.0$ for the *S* enantiomer. $t_R$: 22.34 min (*i*-PrOH/hexane 20/80; 0.5 mL/min). $^1$H NMR $\delta$: 2.53 (3H, s); 2.53−2.62 (1H, m); 2.72−2.89 (3H, m); 3.11−3.22 (2H, m); 3.55 (3H, s); 3.68 (1H, dd, $J = 5.2$, 7.7); 3.77 (3H, s); 3.83 (3H, s); 6.00 (1H, s); 6.55 (1H, s); 6.80 (2H, d, $J = 8.5$); 7.00 (2H, d, $J = 8.5$). $^{13}$C NMR $\delta$: 25.4; 40.3; 42.6; 46.7; 55.2; 55.4; 55.7; 64.9; 110.9; 111.0; 113.5 (2C); 125.8; 129.1; 130.7 (2C); 131.9; 146.1; 147.1; 157.8. IR (neat): 3020, 2920 cm$^{-1}$. MSCI (*m*/*z*, %): 328 (M + 1, 100). Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28. Found C, 73.48; H, 7.77; N, 4.39.

**(*R*)-1-(3′,4′-Dimethoxybenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. (*R*)-Laudanosine 13e.** 77% from **12e.** White solid, mp 114−115 °C, (from EtOAc/hexane). $[\alpha]^{25}_D = -45.2$ ($c = 0.6$, $CHCl_3$); $[\alpha]_D = -85$ ($c = 0.4$, EtOH). Lit.[20] $[\alpha]_D = +103$ (EtOH); $[\alpha]_D = +52$ ($CHCl_3$) for the *S* enantiomer. $t_R$: 19.30 min (*i*-PrOH/hexane 30/70; 0.7 mL/min). $^1$H NMR $\delta$: 2.55 (3H, s); 2.55−2.62 (1H, m); 2.73−2.88 (3H, m); 3.11−3.23 (2H, m); 3.57 (3H, s); 3.70 (1H, dd, $J = 4.9$, 7.7); 3.79 (3H, s); 3.84 (3H, s); 3.85 (3H, s); 6.05 (1H, s); 6.56 (1H, s); 6.60−6.65 (2H, m); 6.76 (1H, d, $J = 8.1$). $^{13}$C NMR $\delta$: 25.4; 40.8; 42.6; 46.9; 55.5; 55.7 (2C); 55.8; 64.8; 110.8; 110.9; 111.0; 112.9; 121.8; 125.9; 129.1; 132.4; 146.0; 146.2; 147.2; 148.4. IR (Nujol): 3040 cm$^{-1}$. MSCI (*m*/*z*, %): 358 (M + 1, 100). Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found C, 70.68; H, 7.71; N, 3.85.

**(*R*)-1-(3′,4′-Dimethoxyphenethyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. (*R*)-Homolaudanosine 13f.** 75% from **12f.** Colorless oil. $[\alpha]^{25}_D = -3.2$ ($c = 1.0$, $CHCl_3$); $[\alpha]^{25}_D = -10.9$ ($c = 1.0$, EtOH). lit.[21] $[\alpha]^{25}_D = +11$ ($c = 0.2$, EtOH) for the *S* enantiomer. $t_R$: 23.59 min (*i*-PrOH/hexane 20/80; 0.5 mL/min). $^1$H NMR $\delta$: 2.00−2.08 (2H, m); 2.48 (3H, s); 2.50−2.57 (1H, m); 2.63−2.84 (4H, m); 3.11−3.22 (1H, m); 3.43 (1H, t, $J = 5.4$); 3.83 (3H, s); 3.84 (3H, s); 3.85 (3H, s); 3.86 (3H, s); 6.54 (1H, s); 6.58 (1H, s); 6.71 (1H, s); 6.72−6.80 (2H, m). $^{13}$C NMR $\delta$: 25.3; 31.2; 37.0; 42.6; 47.9; 55.7 (2C); 55.8; 55.9; 62.5; 109.9; 111.1; 111.2; 111.7; 120.1; 126.6; 129.7; 135.5; 146.9; 147.1; 147.2; 148.6. IR (neat): 3020, 2900 cm$^{-1}$. MSCI (*m*/*z*, %): 372 (M + 1, 100). Anal. Calcd for $C_{22}H_{29}NO_4$: C, 71.13; H, 7.87; N, 3.77. Found C, 71.17; H, 7.96; N, 3.89.

**(*S*)-1-Hydroxymethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. (*S*)-Calycotomine 13c.** Debenzylation of **12c**[19] afforded *S*-calycotomine in 90% yield. White solid, mp 140 °C (dec) (from toluene) $[\alpha]^{25}_D = +37.9$ ($c = 0.2$, $H_2O$); $[\alpha]^{25}_D =$

−13.1 ($c$ = 0.38, $CHCl_3$); lit.[23] $[\alpha]^{25}_D$ = +33.7 ($c$ = 1.1, $H_2O$); $[\alpha]^{25}_D$ = +36 ($c$ = 1, $H_2O$). $^1$H NMR $\delta$: 2.66−2.75 (2H, m); 2.94−3.02 (1H. m); 3.07−3.14 (1H, m); 3.24 (2H, broad s); 3.60−3.67 (1H, m); 3.77 (1H, dd, $J$ = 3.9, 10.9); 3.82 (3H, s); 3.83 (3H, s); 3.96 (1H, dd, $J$ = 3.8, 8.8); 6.57 (1H, s); 6.58 (1H, s). $^{13}$C NMR $\delta$: 28.9; 39.0; 55.7; 55.9; 56.3; 64.1; 109.1; 111.8; 126.9; 127.5; 147.2; 147.6. IR (Nujol): 3300 $cm^{-1}$. MSCI (*m*/*z*, %): 224 (M + 1, 100). Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found C, 64.63; H, 7.76; N, 6.31.

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**Supporting Information Available:** Synthesis and spectroscopic data for starting aldehydes, and $^{13}$C NMR spectra for compounds **7a**,**b**, **8a**−**f**, **9a**,**b**, and **10a**−**f**.

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